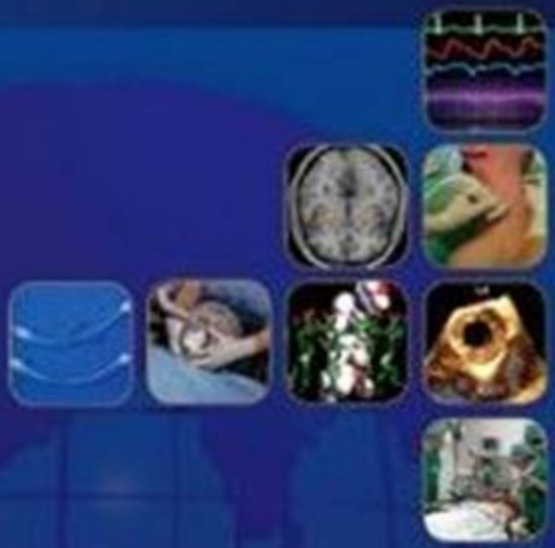
Miller's Anesthesia

SEVENTH EDITION



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Preface to the Seventh Edition

For over 25 years, *Miller's Anesthesia* has been recognized as the most complete and thorough resource on the global scope and practice of contemporary anesthesiology. The seventh edition continues that tradition and represents the most extensive revision we have ever undertaken. These advances include 13 new chapters, more than 30 new authors, and 1500 full-color illustrations. All existing chapters were meticulously revised and updated. The extensive scope of the revision was greatly facilitated by a team of expert and dedicated associate editors: Lee A. Fleisher, MD, Professor and Chair of the Department of Anesthesiology and Critical Care at the University of Pennsylvania; Jeanine P. Wiener-Kronish, MD, Anesthetist-in-Chief, Massachusetts General Hospital and Professor of Anaesthesia at the Harvard Medical School; William L. Young, MD, Professor and Vice Chair of the Department of Anesthesia and Perioperative Care, University of California, San Francisco; and Lars I. Eriksson, MD, PhD, Professor and Academic Chair of Anesthesiology and Intensive Care Medicine at the Karolinska University Hospital in Stockholm.

The 13 new chapters were added in response to an intense analysis of the changes in the scope of anesthesiology. The increasing importance of critical care medicine dictated five separate chapters on nitric oxide, clinical critical care protocols, neurocritical care, renal replacement therapy in the critically ill patient, and prehospital emergency and trauma care, which complements the existing chapter on anesthesia for trauma. The entire state of anesthesia for surgery and other procedures is being examined in more depth in two new chapters on sleep, memory, and consciousness, and perioperative cognitive dysfunction and other long-term implications of anesthetics, the implications being that general anesthesia may have impact long after its administration has been completed. Some rapidly evolving and important subjects in anesthesia are detailed in new chapters on anesthesia for correction of cardiac arrhythmias and anesthesia for bariatric surgery, given that obesity is a major health care issue in many areas of the world, particularly in the United States. The multiple opportunities to interfere with or correct abnormalities in coagulation dictated a separate chapter.

Ultrasound guidance has become a standard of care in the modern practice of regional anesthesia; thus, a dedicated chapter focused on the technique of ultrasound-guided regional anesthesia was clearly warranted. The philosophic question is whether non-ultrasound-guided techniques should continue to be taught, given that many clinicians practice in countries and regions that cannot afford ultrasound technology. Likewise, information technology has become increasingly dominant in medicine as a whole, but especially in anesthesia, necessitating a focused analysis in a dedicated chapter. An ever-growing number of medical centers rely on paperless communication and record keeping, including the anesthetic record. Information technology also allows formation of databases, which can answer important questions related to the institution or individual health care delivery. Chapter 2, entitled Scope of Modern Anesthetic Practice, covers the scope of anesthesia as we know it now with use of modern technology. Lastly, *Miller's Anesthesia* now incorporates the scope and historical development of anesthesia practice in many areas of the world. In Chapter 3, entitled The International Scope and Practice of Anesthesia, the individual contributions from numerous leaders of anesthesia worldwide were compiled into a synopsis of international anesthesia from its origin to the present. Further attesting to the book's global perspective, *Miller's Anesthesia* features contributions from anesthesiologists from all over the world, with 45 contributors to this new edition practicing outside of North America.

Each 2-volume set of the 7th edition of *Miller's Anesthesia* is now accompanied by access to a dedicated *Expert Consult website*, either basic or premium edition. The *basic edition* includes complete, fully searchable online text. The *premium edition* includes all of the above plus additional high-value features such as regular content updates, references linked to Medline abstracts and full-text articles, downloadable image library, drug database, self-assessment questions, and, most importantly, an extensive video library featuring full-length video presentations of anesthesia procedures including airway and ultrasound-guided regional anesthesia techniques.

We wish to acknowledge the long-time participation of Roger A. Johns, MD, and John J. Savarese, MD, who served as consulting editors on the previous edition. We are grateful for the tireless help of Tula Gourdin, who managed all communication with contributors and the publisher, facilitated the flow of manuscripts and page proofs, and checked every detail to make sure the chapters are as accurate and consistent as possible. We also wish to acknowledge our publisher, Elsevier, and the help and dedication of their staff, in particular executive publisher Natasha Andjelkovic, senior developmental editor Heather Krehling, and project manager Fran Gunning.

Ronald D. Miller, MD

Merlin D. Larson

1 History of Anesthetic Practice

Key Points

1. Methods to safely alleviate severe pain are relatively recent discoveries, as viewed within the time span of human history.
2. The public demonstration of ether anesthesia on October 16, 1846, ranks as one of the most significant events in the history of medicine.
3. No single individual can be said to have discovered anesthesia.
4. The specialty of anesthesia rests on discoveries made from several scientific disciplines.
5. Major discoveries were often made by small groups of curious individuals with diverse backgrounds.
6. Techniques in common use at any one time often seem dangerous to subsequent generations of anesthesiologists.
7. Major innovations were sometimes ignored until their rediscovery several decades later.
8. Developments in anesthesia often arose to meet the needs of patients with severe comorbid conditions that required complex surgical procedures. Consequently, advances within the specialties of surgery and anesthesia are closely integrated.

The first anesthetics were given to ameliorate the pain associated with dental extractions and minor surgery. As the complementary fields of surgery and anesthesiology matured together, new skills were required of the anesthesiologist, including expertise in resuscitation, fluid replacement, airway management, oxygen transport, operative stress reduction, and postoperative pain control. Today, personnel from the anesthesiology department are located throughout the hospital, ranging from the ambulatory care center to the intensive care unit. Organizing a coherent historical document is therefore complicated by the diverse roles of anesthesiologists, in the modern hospital, especially in perioperative medicine.

One approach to the history of anesthesiology is to relate in detail the events surrounding the 1846 public demonstration of ether anesthesia by William T. G. Morton (1819-1868).[1,2] This event represents the starting point from which anesthesiology emerged as a specialty. Although the ether demonstration was dramatic and enacted by interesting personalities, it was just the opening act of the pain control story. Since 1846, there has been enormous progress and change in the specialty of medicine that has become known as anesthesiology, and these changes have often occurred in small, incremental steps that are hardly noteworthy on their own. Most operations in the modern operating room could not have been performed before the great progress in anesthetic practice that took place in the years between 1925 and 1960, but historians often overlook these advances because they were introduced without the drama and spectacle of previous developments.

In addition to examining the advancements of the 20th century, the mid-19th century provided the groundwork laid by inquisitive individuals who sought scientific understanding of cardiopulmonary physiology and pain. These fundamental discoveries provide the physiologic foundation for safe anesthetic practice. A brief survey of these early developments is provided in the opening sections of this chapter. Dentists, priests, musicians, pediatricians, engineers, ophthalmologists, neurophysiologists, pharmacologists, urologists, otolaryngologists, surgeons, ministers, dilettantes, philosophers, physiologists, missionaries, chemists, South American Indians, and anesthesiologists all had a role in shaping the practice of contemporary anesthesiology, one of the most fascinating stories in the history of medicine.

I have attempted to describe and reference the origins of ideas related to modern anesthetic practice, but the issue of priority is vague on some topics and may be open to question by other historians of specific subjects.

Cardiopulmonary Physiology

Respiration

Although volatile anesthetics have changed over the past 150 years, there are two gases that will always be part of anesthetic practice. How oxygen and carbon dioxide are consumed and produced and how they interact with the body have been the subject of intense research over the past 400 years. The ability to manipulate the pressure of these gases in tissues has contributed a great deal to the success of intensive care medicine. Because of the importance that carbon dioxide and oxygen have in the practice of anesthesiology, it is worthwhile to consider how our understanding of respiration came about.

Aristotle (384-322 BC) and Galen (120-200 AD) both thought that the air moving in and out of the lungs served merely to cool the heart, which otherwise became overheated in working to sustain life.[3] In 1678, Robert Hook (1635-1703) attached a bellows to the trachea of a dog with an open chest and demonstrated that the animal could be kept alive by rhythmic and sustained contraction of the bellows. Hook proved that movement of the chest wall was not the essential feature of respiration but instead it was exposure of fresh air to blood circulating through the lungs.[4] Richard Lower (1631-1691), who was the first to transfuse blood from one animal to another, demonstrated in 1669 that blood absorbed a definite chemical substance necessary for life that changed venous blood from dark blue to red and that the process was the chief function of the pulmonary circulation.[5]

Joseph Priestley (1733-1804) (Fig. 1-1A), a complex individual who was a dissenting minister in Leeds, England, and later the "resident intellectual" to the Earl of Shelburne, observed that respiration and combustion had many similarities[6] in that a candle flame would go out and an animal would die if left within a closed space. He thought this effect occurred because the air was putrefied with phlogiston. Priestley discovered photosynthesis by showing that placing plants that imbibed the "phlogistic matter" within the contained space could restore this "bad air." By heating mercuric oxide, he generated a gas that would make flames brighter and keep mice alive longer in a closed space. Priestley called it *dephlogisicated* air, and Carl Scheele[7] (1742-1786) in Sweden, who detected it earlier but failed to publish, called it *feuer luft* ("fire air"). Priestley thought that this process absorbed phlogiston and informed the French chemist Antoine-Laurent Lavoisier (1743-1794) (Fig. 1-1B) of his discovery. Lavoisier then outlined the great facts of respiration: absorption of oxygen through the lungs with liberation of carbon dioxide.

Lavoisier thought that the change from oxygen to carbon dioxide was accomplished in the lungs, but Humphry Davy (1778-1829) (Fig. 1-1C), an English teenager who dropped out of school at the age of 16 years, read the works of Lavoisier and designed his own experiments to study the site of metabolism. Davy heated blood and collected the gases that were produced. By showing that these gases were oxygen and carbon dioxide, he surmised that metabolism takes place in tissues.[8] Davy also estimated rates of oxygen consumption and carbon dioxide production and measured the total and residual volumes

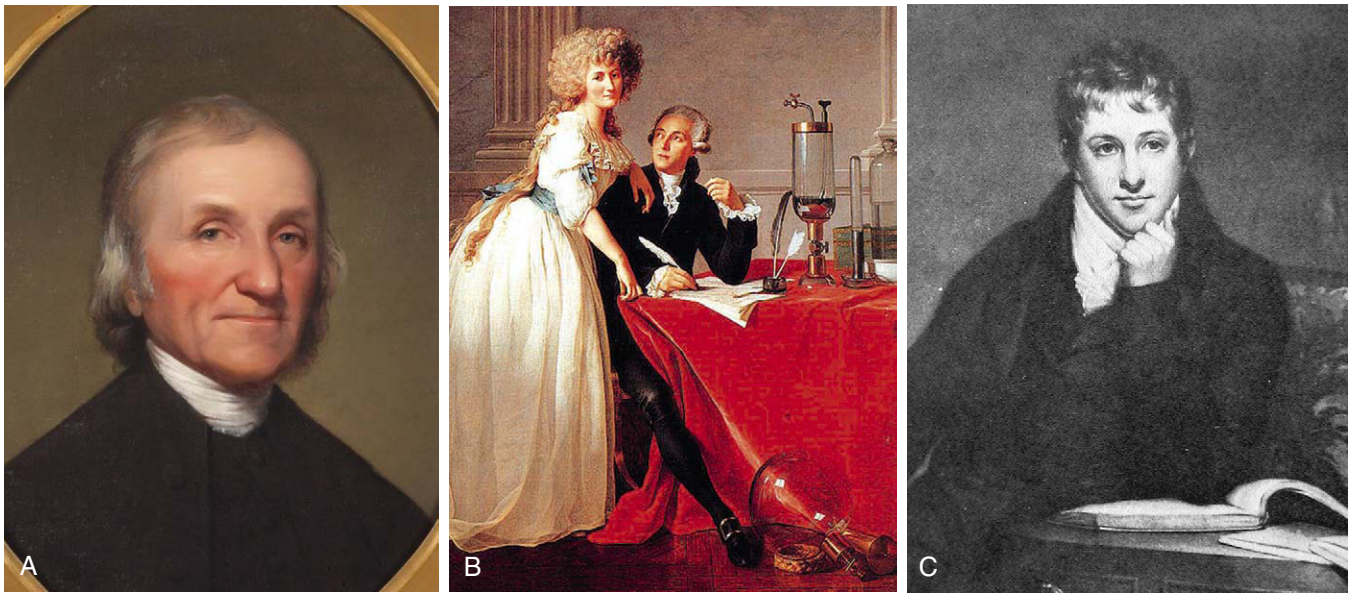


Figure 1-1 A, Joseph Priestley was born in Fieldhead, England, and educated as a minister. His early career was spent as a schoolmaster in Leeds, England. In 1780 he accepted an appointment in Birmingham as minister, where he joined Erasmus Darwin and James Watt in forming the Lunar Society, which met to discuss the new ideas in chemistry and physics emerging at that time. Because of his political views, his chapel and home were vandalized in 1789. Five years later, he joined his sons in Pennsylvania in the United States, where he died in 1804 at the age of 70. **B,** This portrait of Lavoisier and his wife Marie Anne Pierrette Paulz was painted in 1788 by the famous French artist Jacques Louis David. Marie Paulz, who married Lavoisier when she was only 14 years old, was taught to draw by David, and she drew many of the illustrations in Lavoisier's magnum opus *Traite Elementaire de Chimie*. Several experimental devices and gasometers are shown on and below the table. **C,** Humphry Davy was born in Cornwall, England, and became apprenticed to a surgeon, J. B. Borlase of Penzance, at age 17. At 20 years of age he was appointed superintendent of the Beddoe's Pneumatic Institute, where he studied the effects of nitrous oxide inhalation. His later career in chemistry gained him fame and honors. He directed the Royal Institute and was made a baronet in 1818 at the age of 40. *(Courtesy of the Wood Library-Museum of Anesthesiology, Park Ridge, IL.)*

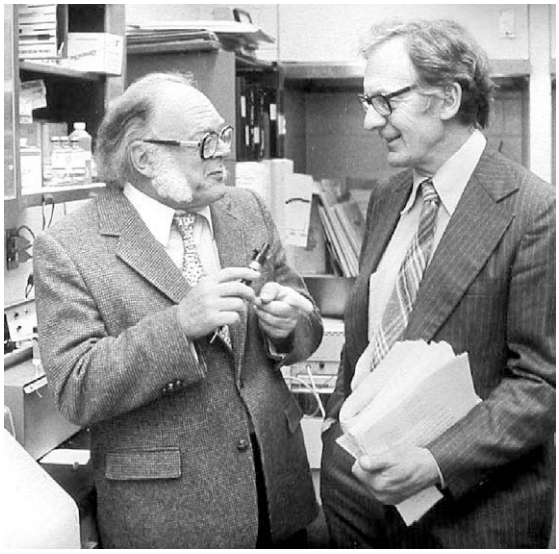


Figure 1-2 This photograph of Leland Clark and John Severinghaus, whose contributions led to modern techniques of blood gas analysis, was taken in Clark's laboratory at the Cincinnati Children's Hospital in 1982. *(From Severinghaus JW, Astrup PB: History of blood gas analysis. Int Anesthesiol Clin 25:1-224, 1987.)*

of the lungs. John S. Haldane (1860-1936) was a pioneer investigator in the study of respiration a century ago. His apparatus for measurement of blood gases was described in 1892.[9] He was the first to promote oxygen therapy for respiratory disease,[10] and in 1905 he discovered that the carbon dioxide tension of blood was the normal stimulus for the respiratory drive.[11] Haldane experimented with self-administration of hypoxic mixtures and coined the ominous phrase that lurks within the inner recesses of the anesthesiologist's mind: "Anoxemia not only stops the machine but wrecks the machinery." He believed until his death, despite experimental evidence, that the lung actively secreted oxygen into the blood from the air. His landmark monograph *Respiration*, published in 1922,[12] summarized his studies on the respiratory system.

At the end of the 19th century it was known that hemoglobin had a vital role in the transport of oxygen to tissues. In 1896, Carl Gustav von Hufner (1840-1908) showed that the presence of hemoglobin in blood greatly enhanced its oxygen-carrying capacity and quantified that 1 g of hemoglobin carried 1.34 mL of oxygen.[13] It was soon observed that delivery of high concentrations of oxygen to patients with advanced pulmonary disease was often inadequate to fully maintain tissue respiration and saturate hemoglobin completely. Gradients for inspired, alveolar, and arterial oxygen partial pressures became apparent after development of the oxygen electrode by Leland C. Clark[14] (1918-) (Fig. 1-2) in 1953. The Clark electrode consisted of a platinum cathode and a silver anode separated from blood by a polyethylene membrane. The platinum was negatively charged to react with any oxygen reaching it through the membrane and was sensitive to the oxygen pressure outside the membrane (i.e., the oxygen tension in blood).

Further understanding of respiratory physiology arose because of the worldwide polio epidemic that occurred roughly between the years of 1930 and 1960. Thousands of afflicted patients were kept alive with mechanical respirators, but the adequacy of ventilation could not be assessed without some measure of carbon dioxide tension (P_{CO_2}) in the blood. Several methods to measure P_{CO_2} indirectly were made by Donald D. Van Slyke[15] (1883-1971) and Paul B. Astrup (1915-2000), but the modern solution rested on development of the carbon dioxide electrode. This problem was solved in 1958, when John W. Severinghaus (1922-) (see Fig. 1-2) improved the accuracy of a prototype carbon dioxide electrode produced by Richard Stow (1916-) that measured the pH of a thin film of electrolyte separated from blood by a Teflon membrane through which carbon dioxide could diffuse and equilibrate. Severinghaus and A. F. Bradley[16] (1932-) constructed the first blood gas apparatus by mounting the carbon dioxide electrode and Clark's oxygen electrode in cuvettes in a bath heated to 37°C. To measure blood P_{O_2} accurately, Severinghaus found it necessary to rapidly stir the blood in contact with Clark's electrode because of its high oxygen consumption rate. A pH electrode was added in 1959. Blood gas analysis made possible rapid assessment of respiratory exchange and acid-base balance. The use of blood gas analysis was rapidly adopted by the anesthesia community and has become one of the most common laboratory tests performed in the modern hospital. The impact of a more in-depth understanding of gas exchange on the practice of anesthesia is summarized by John Nunn in his book *Applied Respiratory Physiology*.[17]

Until the mid-20th century, hemoglobin saturation could be determined only by directly measuring a sample of arterial blood, a technique that required arterial puncture. Oximetry achieves the same measure noninvasively through a finger or ear probe by using optical measures of transmitted light. Glenn Millikan (1906-1947), working in the Johnson Foundation for Medical Physics at the University of Pennsylvania, devised the first ear oximeter in 1942, and it was used to detect hypoxia in pilots, who flew in open cockpits during World War II. Its introduction into anesthesia practice was delayed until the discovery of pulse oximetry by a Japanese engineer, Takuo Aoyagi (1936-).[18] Pulse oximetry added the additional measure of heart rate, and it provided assurance that the signal was actually measuring a biologic parameter. A highly successful commercial product, the Nellcor pulse oximeter was introduced in 1983 and had the unique feature of lowering the pitch of the pulse tone as saturation dropped.

Intravascular Pressures

The first measurement of blood pressure was made by Stephen Hales (1677-1761) (Fig. 1-3A), the curate of Middlesex, England, who occupied himself between sermons with experiments on mechanics of the circulation. He described one of his experiments[19] performed (1733) on an "old mare who was to be killed, as being unfit for service":

> *I fixed a brass pipe to the carotid artery of a mare . . . the blood rose in the tube till it reached to nine feet six inches in height. I then took away the tube from the artery and let out sixty cubic inches of blood, and then replaced the tube to see how high the blood would rise after each evacuation; this was repeated several times until the mare expired. In the three horses, death occurred when the height of the blood in the tube was about two feet.*

Hales also discovered that the resistance of a vascular bed could change by mixing alcohol in the blood, which he observed





Figure 1-3 Two scientists of the Enlightenment era. **A,** Stephen Hales (1677-1761): detail of an oil painting by T. Hudson, 1759, in the National Portrait Gallery, London. Hales was educated at Cambridge University, England, and ordained as a minister in 1703. He spent his career as minister to the parish of Teddington, England. His rudimentary studies on the gas produced by mixing Walton pyrites (i.e., ferric disulfide) and spirit of nitre (i.e., nitric acid) was the spark that prompted Priestley to pursue his studies on nitric oxide, which led to the discovery of nitrous oxide in 1773. Hales was the first to measure blood pressure and cardiac output. He also developed ventilators that brought fresh air into prisons and granaries. **B,** Albrecht von Haller (1708-1777): detail of an engraving by Ambroise Tardieu. Haller was born in Bern, Switzerland. He served as professor of medicine and surgery at the University of Göttingen, Germany, where he began his encyclopedic work, *Physiological Elements of the Human Body*, published in eight volumes between 1757 and 1766. His demonstration that "irritability" was a property of muscle and "sensitivity" was a property of nerves was derived from nearly 600 experiments on live animals. He returned to Bern in 1753, and while there he published a catalog of the scientific literature containing 52,000 references. *(Portraits courtesy of the National Library of Medicine, Bethesda, MD.)*

could account for changes in blood pressure brought about by diverse ingested agents. In 1828, Jean L. Poiseuille[20] (1799-1869) repeated these experiments and devised a hemomanometer that used mercury instead of the long blood-filled tubes used by Hales. Poiseuille also showed that blood pressure varied with respiration.

In 1854, Karl Vierordt[21] (1818-1884) invented a sphygmograph that acted on the principle that indirect estimation of blood pressure could be accomplished by measuring the counterpressure necessary to obliterate the arterial pulsation. Scipione Riva-Rocci's (1863-1937) sphygmomanometer, described in 1896,[22] involved the same principle but used a rubber cuff that occluded a major arterial vessel and then slowly deflated. In 1905, Nikolai Korotkov[23] (1874-1920) described the sounds produced during auscultation over a distal portion of the artery as the cuff was deflated. These Korotkoff sounds resulted in more accurate determination of systolic and diastolic blood pressure. Oscillometric blood pressure measurement relied on a cuff that sensed changes in arterial pulsations and was described by H. von Recklinghausen in 1931.[24] Automatic blood pressure devices based on the oscillometric method were developed in the 1970s and have become the standard noninvasive measure of arterial pressure in most hospitals.

Venous pressure was of less interest to anesthesiologists until convenient methods for placing cannulas into central vascular structures were described more than 50 years ago by Sven Seldinger.[25] Werner Forssman (1904-1979), a urologist, described methods for central venous access and right heart catheterization in humans in 1929[26]; he originally experimented on himself and was awarded the Nobel Prize in Physiology and Medicine for his work on venous pressure in 1956. The introduction of plastic catheters[27] gradually made it possible to measure central pressure in the clinical setting. Although arm and femoral veins were used initially, subclavian and internal jugular vein cannulation eventually replaced the peripheral sites. Pulmonary artery catheterization with a balloon-tipped, flow-directed catheter was described in 1970[28] and has been used extensively since then by anesthesiologists to measure pulmonary artery pressure and cardiac output via the Fick[29] (Adolf E. Fick—1829-1901) principle. The pulmonary artery catheter also allowed clinicians to use the well-known pressure-volume relationships of the heart described by Ernest H. Starling (1866-1927) in 1918 to maximize cardiac output and oxygen delivery to tissues.

Transesophageal echocardiography (TEE) was described in 1976[30] and used in anesthesia practice a few years later. One of the original probes used during anesthesia was fashioned from an esophageal stethoscope combined with an M-mode echocardiographic probe and was used to calculate cardiac output and ejection fraction in a 65-year-old woman undergoing mitral valve repair.[31] An improved electronic phased-array transducer was initially applied at the University of California, San Francisco, for monitoring regional myocardial function in high-risk surgical patients.[32] Biplane TEE and color flow mapping were introduced in the 1980s and resulted in an explosive growth in TEE applications.[33] With experience and training in TEE, the anesthesiologist can quickly evaluate filling pressures of the heart, as well as obtain measures of myocardial contractility and valvular function. TEE has become a routine monitor for certain surgical procedures.

Autonomic Nervous System and Neurohumoral Transmission

The first hint of involuntary control of glandular and vascular function occurred in the 18th century. In a classic paper written in 1751, Robert Whytt (1714-1766) described the reflex nature of many involuntary activities.[34] Thomas Willis[35] (1621-1675) had described the sympathetic chain as early as 1657. He called it the intercostal nerve because it received segmental branches from the spinal cord at each level.

Pourfour du Petit (1664-1741) observed that there was a corresponding miosis and retraction of the nictitating membrane when this "intercostal" nerve was unilaterally cut in the neck of a cat.[36] Jacob B. Winslow (1669-1760) gave the intercostal nerve the name grand sympathique to stress that this nerve brought the various organs of the body into sympathy,[37] a term that was originally coined by the Greek physician Soranus of Ephesus (98-138) in the first century AD (*sym*, "together," and *pathos*, "feeling"). Claude Bernard (1813-1878) observed vasoconstriction and pupillary dilation after stimulation of the same intercostal (now called the sympathetic) nerve and then described the vasomotor nerves arising between the cervical and lumbar enlargements of the spinal cord.[38]

In 1889, John N. Langley (1852-1925) began his work on sympathetic transmission in autonomic ganglia. He blocked synaptic transmission in the ganglia by painting them with nicotine and then mapped the distribution of the presynaptic and postsynaptic autonomic nerves.[39] He observed a similarity between the effects of injection of adrenal gland extracts and stimulation of the sympathetic nerves.[40] The active principle of adrenal medullary extracts was called epinephrine by John J. Abel[41] (1837-1938) in 1897. Abel was one of the first pharmacologists in the United States, and with his discovery of the hormone epinephrine, he uncovered one of the most commonly used lifesaving agents in the anesthesiologist's pharmacopoeia.

Thomas R. Elliott (1877-1961) postulated that sympathetic nerve impulses release a substance similar to epinephrine and considered this substance to be a chemical step in the process of neurotransmission.[42] George Barger (1878-1939) and Henry H. Dale (1875-1968) then studied the pharmacologic activity of a large series of synthetic amines related to epinephrine and called these drugs sympathomimetic.[43] The different effects on end organs produced by adrenal extracts and sympathetic stimulation were analyzed by Walter B. Cannon (1871-1945) and by Ulf Svante von Euler (1905-1983). In a series of papers, these authors demonstrated that the sympathetic nerves released norepinephrine, whereas the adrenal gland released both epinephrine and norepinephrine.

In 1907, Walter E. Dixon[44] (1871-1931) observed that the alkaloid muscarine had the same effect as stimulation of the vagus nerves on various end organs. He proposed that the nerve liberated a muscarine-like chemical that acted as a chemical mediator. In 1914, Henry H. Dale[45] investigated the pharmacologic properties of acetylcholine and was impressed that its effects reproduced the same effects as stimulation of the craniosacral fine myelinated fibers that Walter H. Gaskell[46] (1847-1914) had called the bulbosacral involuntary nerves and had by then been called parasympathetic by Langley.

The final proof of neurotransmission by acetylcholine was provided through the elegant experiments of Otto Loewi (1873-1961). He stimulated the neural innervation of the frog heart and then allowed the perfusion fluid to come in contact with a second isolated heart preparation.[47] The resulting bradycardia provided evidence that some substance was released from the donor nerves that slowed the heart rate of the second organ.[47] Loewi and Navrail presented evidence that this substance was acetylcholine, as Dale had suggested. Loewi and Dale were jointly awarded the Nobel Prize in 1936 for their work on chemical neurotransmission.

Theodore Tuffier (1857-1929) first demonstrated the relevance of the sympathetic nervous system to the practice of anesthesia in 1900. In a series of experiments on dogs, he demonstrated the sympatholysis that occurs after spinal anesthesia.[48] Further studies on the sympathectomy resulting from neuraxial blockade were performed by G. Smith and W. Porter in 1915.[49] Working with cats, they concluded that the decrease in arterial blood pressure was secondary to sympathetic paralysis of the vasomotor fibers in the splanchnic vessels. Gaston L. Labat[50] (1877-1934) encouraged the use of sympathetic stimulants such as ephedrine to counter the hypotensive effects of spinal anesthesia.

Reversal of neuromuscular blockade rests on a fundamental understanding of two types of cholinergic receptors, muscarinic and nicotinic, originally described in 1914 by Dale.[45] Neostigmine, synthesized in 1931,[51] when given alone during reversal of neuromuscular blockade had produced cardiac arrest in several instances before it was learned that previous administration of an antimuscarinic drug would prevent this complication.[52] Atropine, isolated from the plant *Atropa belladonna* by A. Mein[53] in 1831, blocked peripheral and central nervous system muscarinic receptors. Glycopyrrolate was synthesized in 1960 as an antimuscarinic agent that did not pass the blood-brain barrier.[54] Glycopyrrolate is more titratable, has fewer central nervous system side effects, and has gradually replaced atropine as the preferred anticholinergic during reversal of neuromuscular blockade.

Crucial to the control of arterial blood pressure and heart rate in the perioperative period was the realization that there was more than one type of adrenergic receptor. In 1948, Raymond P. Ahlquist (1914-1983) proposed the designations α- and β-adrenergic receptors,[55] and various subtypes of these two main classes have been characterized since then. Esmolol was introduced in 1985 as a short-acting β-adrenergic antagonist that effectively controls the heart rate during anesthesia. Labetalol, a unique agent introduced in 1976, antagonizes α- and β-adrenergic receptors. α_2-Adrenergic agonists such as clonidine and dexmedetomidine have been shown to be useful agents in certain clinical settings. The α_2-adrenergic agonist effects produce sedation and analgesia through a central effect and, because they do not induce respiratory depression, they may have some advantages over opioids as sedatives in awake subjects.[56]

Manipulation of blood pressure can be achieved rapidly by intravenous nitrates such as nitroglycerin and nitroprusside. These drugs act directly on smooth muscle to allow rapid and more precise control of hemodynamics. Nitroglycerin was synthesized in 1846 by the Italian chemist Ascanio Sobrero (1812-1888) by combining nitric acid and glycerol. The first practical use of the drug was made by Alfred Nobel (1833-1896), who mixed the agent with silica to make dynamite, a highly successful explosive used in building tunnels and canals. A portion of the

vast wealth of Nobel was directed by his will to be distributed annually in the form of Nobel Prizes beginning in 1901.[57,58] William Murrell[59] (1853-1912) reported the use of sublingual nitroglycerin in 1879 to treat angina. Intravenous use of the nitrovasodilators during anesthesia was not feasible until the development of continuous arterial monitoring, but for the past 30 years these drugs have been popular for rapid control of hypertensive crises in the operating room.[60] The mechanism of action of nitrates on smooth muscle, through the release of nitric oxide, was demonstrated by Ferid Murad (1936-) in 1986.[61] Nitric oxide, considered a toxic gas by Priestley who discovered it and by Humphry Davy who breathed it, has been shown to be a useful inhaled agent when used in a very low dose of 5 to 10 ppm in cases of life-threatening pulmonary hypertension.[62]

Historical Development of Theories of Pain

An understanding of the mechanism of pain production was not required by the physicians who developed the use of general anesthesia in the second half of the 19th century. Although inhalation of vapors produced a lack of awareness during surgery, anesthesiologists learned that control of perioperative nociception would require a more thorough understanding of pain. Fortunately, by the beginning of the 20th century, there was already a large body of knowledge on pain mechanisms dating from the earliest days of medical inquiry.

In antiquity, pain was thought to be an emotion rather than a sensory modality. Pain control was a function of religious authorities and shamans in primitive cultures, and relief of pain was sought through incantations and prayers. Pain was then often considered to be a punishment for committed sins or a form of religious suffering. The word *pain* is derived from the Greek term *poine* ("penalty"). Aristotle thought that pain was an emotion emanating from the heart, but Galen correctly observed that the brain was required for pain to be manifested in animals. Galen also proposed that sensation was a property of nervous tissue, but his physiologic system was altogether hampered by his idea that an invisible psychic pneuma traveled within hollow nerves.[3]

The 18th and 19th centuries witnessed considerable progress in understanding the mechanisms of pain. Albrecht von Haller[63] (1708-1777) (see Fig. 1-3B) observed that some tissues in the body have a property that he called sensibility: "I call those parts sensible, if the irritation occasions evident signs of pain and disquiet in the animal." Other tissues were insensible, which "if touched occasioned no sign of pain nor convulsion." Some tissues were irritable. "I call that part of the human body irritable, if it becomes shorter upon being touched." von Haller's landmark contribution in 1752[64] concluded that only parts of the body supplied with nerves possess sensibility, whereas irritability is a property of muscular fibers.

The idea of specific neural pathways for painful sensations began with Charles Bell[65] (1774-1842) and François Magendie[66] (1783-1855), who both demonstrated that the dorsal roots transmitted sensory information and that the ventral roots contained the motor nerves. Johannes Müller (1801-1858), in his 1826 paper titled "Of the Peculiar Properties of Individual Nerves," proposed that each sense organ gave rise to its own characteristic sensation and to no other; electrical or mechanical stimulation of the optic nerve, for example, gives rise to only a sensation of light.[67] The evidence that pain was a separate and distinct sense with separate end organs was formulated in 1858 by Moritz S. Schiff (1823-1896).

By the end of the 19th century, the idea was firmly established that acute pain was a distinct sensory modality that was susceptible to interruption through a conduction block initiated with local anesthetics. Pain as a separate sensation that was transmitted through separate neural fiber tracts was supported by clinical observations after neural blockade. Several investigators found, for example, that acute pain could be abolished with cocaine injections, which left some sensory modalities unaffected.[68]

There is evidence that operations undertaken on the battlefield may be associated with less pain than occurs with similar elective operations performed without anesthesia. The amputation of Lord Horatio Nelson's right arm in the battle at Tenerife, Canary Islands, was performed aboard ship after he sustained a musket shot above the elbow that divided the artery and shattered the humerus. Nelson complained only that the knife felt cold and thereafter ordered that all knives on board be heated before entering into conflict because his personal experience had indicated that a warm knife would produce almost no discomfort.[69] Henry Beecher[70] (1904-1976) confirmed during World War II that wounded soldiers had surprisingly little pain.

To further explain some of these central influences on nociception, Ronald Melzack (1929-) and P. D. Wall proposed the gate control theory of pain in 1965.[71] This theory suggested that the nociceptive afferent pain fibers were subjected to the modulating influence of a "gate" at the first synaptic contact in the spinal cord. Whereas large-fiber input tends to close the gate (i.e., inhibit nociceptive transmission), small-fiber input opens it, and descending influences from the cortex and midbrain[72] also profoundly influence the gate. Endogenous opioids, first discovered in 1974 by A. Goldstein[73] and later confirmed by J. Hughes[74] in 1975 and S. H. Snyder and coworkers[75] in 1977, are located at diverse sites in the pain pathway, including the dorsal horn, and they can influence the rostral transmission of pain sensations. Several modalities of pain therapy, such as acupuncture and biofeedback, attempt to activate these endogenous systems to suppress chronic pain syndromes.

The gate theory of pain has had considerable influence on the anesthesiologist's management of pain by focusing attention on the unique pharmacology of the dorsal horn of the spinal cord. By using intrathecal and epidural injections,[76] anesthesiologists have learned to suppress nociceptive transmission at the first synaptic relay in the spinal cord. The technique has implications in acute and chronic pain therapy because neuraxially administered drugs can provide analgesia without some of the systemic side effects of intravenously administered drugs. A typically modern view of perioperative pain is to view it as an impediment to recovery. Aggressive methods are often used to minimize pain and facilitate rapid return to normal functional activity.[77]

Surgical Procedures Before 1846

Greek and Roman surgeons used a variety of surgical instruments that we would recognize today. Drills, saws, syringes, cannulas, probes, and scalpels can all be viewed in the excavations at Her-

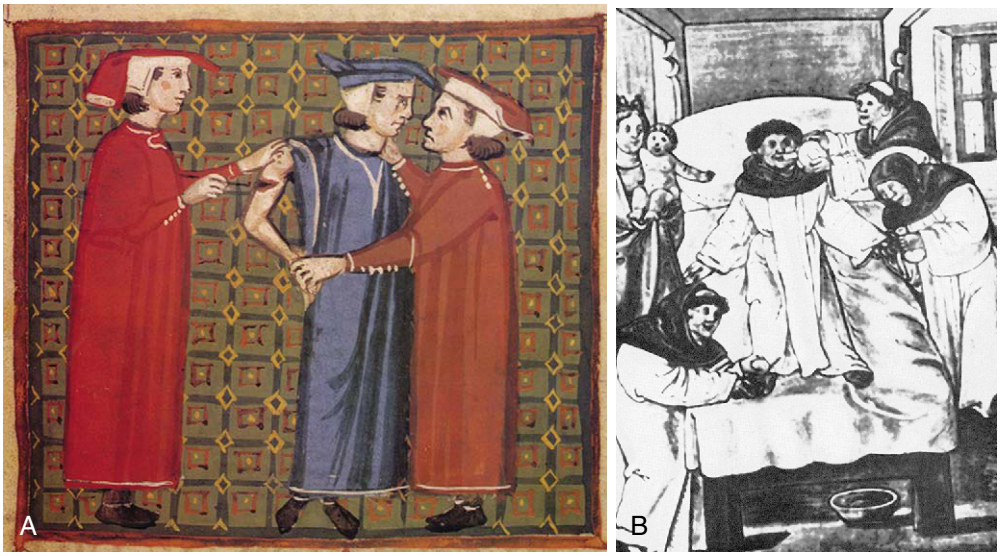


Figure 1-4 A, "Operating on the Upper Arm" is taken from the textbook titled *Chirurgia* by Theodoric of Cervia. It is noteworthy because it shows an intense focus by the patient directly into the gaze of an assistant. Although hypnosis is a 19th century term and its use for pain relief during surgery was not widely promoted until then, induction of trances and altered states of being was known to the ancients. Theodoric apparently realized the value of diverting the patient's attention away from the pain of surgery. **B,** Inhalation of the vapor of alcohol was tried in the Middle Ages as a method for pain relief during surgery. The inhaler shown here is remarkably similar to that used by William T. G. Morton on October 16, 1846, which used ether as the volatile agent (compare with Fig. 1-6).

culaneum, Pompeii, and Rheims. Hippocrates (460-377 BC) wrote a treatise on surgery, but it provided little sympathy for the patient. His advice to the patient was "to accommodate the operator . . . and maintain the figure and position of the part operated on . . . and avoid sinking down, and shrinking from or turning away."[78] The most famous Roman surgeon was Pedanius Dioscorides (40-90 AD), a Greek physician who served in the armies of Nero. His *Materia Medica*, written in 77 AD, was the authoritative work on pharmacology for more than 15 centuries. In this book he described the effects of mandragora and wine to produce "anesthesia" in a patient being cut or cauterized. He also described local anesthesia produced by the "stone of Memphis," which "being cut small, and smeared upon the places to be cut or cauterized, produces anesthesia without danger."[3]

During the Middle Ages, attempts were made to use alcohol fumes as an analgesic during surgery (Fig. 1-4B). Another inhaled technique, the soporific sponge, is mentioned in numerous manuscripts written in the Middle Ages. One example[3] from the 9th century comes from a Benedictine monastery at Monte Cassino, near Salerno, Italy:

> *A hypnotic aid, that is a soporific suitable for those who are treated by surgery, so that asleep, they do not feel the pain of cutting. Rx: opium one half ounce, mandragora the juice from the leaves, eight ounces, the juice of fresh hemlock, hyposcyanus three ounces of the juice together with sufficient water so that it forms a liquor, and then absorb in a fresh dry sponge and dry it carefully. And when thou wouldst employ this sponge, dip it in warm water, place it over the nose and cause the patient to breathe deep until he sleeps. And when thou wouldst wake him up, apply to his nose another sponge well soaked with vinegar and thou willst end the sleep.*

The sponge used by Theodoric of Cervia (1205-1296), a member of the Dominican order who practiced in Bologna, contained the same ingredients as the Salernitan sponge.

The effective agents in this sponge were very likely opium and scopolamine.[3] Theodoric was one of the first surgeons to promote methods to ablate pain during surgery (see Fig. 1-4A). One of the great physicians of the Renaissance, Theophrastus Bombastus von Hohenheim, otherwise known as Paracelsus (1493-1541), was familiar with the soporific action of sulfuric ether, a compound that had been synthesized from sulfuric acid and alcohol by the chemist Valerius Cordus (1515-1544). Cordus called the flammable, volatile liquid "sweet vitriol," and in 1740, Frobenius named it ether (from the Greek word for "ignite" or "blaze"). Paracelsus described the effect of ether on chickens and stated that it "quiets all suffering without harm, and relieves all pain." Although he was appointed "surgeon to the Danish army" when they besieged Stockholm in 1518, he had little interest in surgery, and these ideas were not developed clinically.

The suffering associated with surgery is found by examining accounts written by patients who survived major surgical procedures before that time. One comes from Fanny Burney[79] (1752-1840), a novelist and celebrity of the early part of the 19th century. Here is an abbreviated account of her mastectomy for breast cancer by the surgeon Dominique J. Larrey (1766-1842), the celebrated military surgeon in Napoleon's army, on September 30, 1811:

> *I mounted the bed and a cambric handkerchief was placed upon my face. The bed was then surrounded by 7 men and my nurse. Through the cambric I saw the glitter of the polished steel knife. A silence ensued. . . . Oh what a horrible suspension! . . . When the dreadful steel was plunged into the breast, I needed no*

injunctions not to restrain my cries. I began a scream that lasted unintermittently during the whole time of the incision and I almost marvel that it rings not in my ears still, so excruciating was the agony.

Although Fanny Burney lived for another 29 years after this operation, she observed that anything that would recall the surgery to her mind would reactivate the terror of the horrible experience. Apparently, operations performed without anesthesia produced long-lasting emotional and painful side effects. A modern interpretation of this phenomenon could conclude that these patients lacked any form of "preemptive analgesia"[80] and that they therefore experienced lingering side effects after their surgical wounds had healed.

Even though thousands of patients experienced the terror of an operation, countless others suffered with chronic ailments because the risk associated with surgery was too high or because they feared death or severe pain during the operation. For example, even after the introduction of anesthesia in 1846, textbooks on the treatment of hernia continued to have extensive descriptions of hernia belts and trusses.[81]

Introduction of General Anesthesia

Background

Although surgical technique was in development, the patient presented a problem to the surgeon, chiefly because of active physical resistance and because the cries and screams were distracting and often left the patient emotionally and physically exhausted. These factors, combined with the inevitable sepsis, resulted in high mortality rates. No wonder that by the middle of the 19th century there was greater determination by some surgeons to devise ways of improving operating conditions so that these appalling surgical mortality figures could be decreased, which in some reports reached nearly 50%. Bold approaches and risks were required, and these factors came together in Boston, Massachusetts, on October 16, 1846, when William T. G. Morton demonstrated the use of ether inhalation for surgical anesthesia.

Gas Inhalation

As a result of the growing scientific interest in various types of "airs," popular medical treatments involving gas inhalation evolved. Health resorts were popular attractions and financially successful because of their use by prominent members of society. One important "pneumatic" spa was located at Clifton, near Bristol, England, where Thomas Beddoes[82] (1760-1808) furnished airs for therapeutic use and funded research on the manufacture and use of gases. Nitrous oxide, a gas codiscovered by Priestley and Joseph Black, was by then considered to be a dangerous gas after a pronouncement by the influential American physician and U.S. Senator Samuel Latham Mitchill (1764-1831) that the gas was the "principle of contagion" and if breathed would "spread plague." The young scientist Humphry Davy conducted research on nitrous oxide at the Beddoes institute and, undaunted by these pronouncements, made several important observations. He inhaled nitrous oxide and noticed that it provided relief from the pain caused by an erupting wisdom tooth. In 1800 he wrote: "As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place."[83]

Davy was not a surgeon, and clinicians overlooked his suggestion at the time. He resigned his position at the Beddoes Medical Pneumatic Institute in 1801 and moved to London to lecture at the newly founded Royal Institution of Great Britain. Davy was just 20 years old when he performed his studies on nitrous oxide, and his subsequent, highly successful career took him into other areas of scientific study that led to discovery of the elements potassium, sodium, calcium, barium, magnesium, strontium, and chlorine. He was knighted in 1812, became President of the Royal Society in 1820, and never returned to develop his promising early thoughts on nitrous oxide analgesia. Regrettably, he left no students to continue these studies, although his successor at the Royal Institute, Michael Faraday (1791-1867), briefly experimented with ether inhalation and observed that its "effects were similar to those occasioned by nitrous oxide."[84]

The first research specifically directed toward an effective method of providing pain-free surgery was made by a physician working in the village of Ludlow, Shropshire, in northern England. Henry Hill Hickman (1800-1830) was a practicing surgeon who investigated the use of carbon dioxide to induce insensibility in animals. Because of the widespread interest in inhalation therapy at the beginning of the 19th century, it is not surprising that Hickman used an inhaled gas. Unfortunately for him, he used the wrong gas; if he had selected nitrous oxide, which was known to produce analgesia, his results might have achieved further attention. Although he published his work in 1824 in a private letter to T. A. Knight,[85] Hickman failed to find any support from his colleagues in England or France, and he died at an early age without recognition.

Beginning of Inhaled Anesthesia

The story of anesthesia continues with another amateur and itinerant chemist, Gardner Quincy Colton (1814-1898) (Fig. 1-5A). Colton had attended 2 years of medical school at the Crosby Street College of Physicians and Surgeons in New York. While in school, he perfected the manufacture of nitrous oxide by heating ammonium nitrate, and after 2 years of study, he proclaimed himself to be a "Professor of Chemistry" and went on the road to lecture on chemistry and present "scientific exhibitions."

On the night of December 10, 1844, Professor Colton presented his exhibit featuring inhalation of nitrous oxide at Union Hall in Hartford, Connecticut. It was at the Colton exhibit that the dentist Horace Wells (1815-1848) originated an idea that culminated in the first successful demonstration of inhalation anesthesia 22 months later. Wells had experimented with mesmerism to relieve the pain of dental extractions and was aware of the work of Humphry Davy. He attended the Colton demonstration and observed a young man, Samuel A. Cooley, sustain a significant leg injury without pain after nitrous oxide inhalation. Here was the answer to the problem of painful tooth extractions that had occupied his mind. He arranged for Colton to administer nitrous oxide to him on the following day for extraction of one of Wells' own teeth by fellow dentist John M. Riggs. Only a slight tinge of pain was felt, and Wells proceeded to manufacture nitrous



Figure 1-5 A, Gardner Q. Colton was born in Georgia, Vermont, and studied medicine briefly at the College of Physicians and Surgeons in New York City. His demonstrations of nitrous oxide inhalation were the spark that prompted Horace Wells and William T. G. Morton to use gas inhalation for relief of surgical pain. After a long and adventurous career, he died at age 84 in Rotterdam, Holland. **B,** William T. G. Morton was born in 1819 on a farm near Charlton, Massachusetts. After several business failures, he studied at the Baltimore College of Dental Surgery and, in 1842, entered into a partnership in Boston with another dentist, Horace Wells. This partnership was dissolved within a year on amicable terms. During this association, the two dentists had devised a new method for fitting dentures that required removal of all the diseased teeth, a prohibitively painful procedure for most patients. Morton experimented with laudanum and opium without success, and in proceeding with his investigations, he realized that greater knowledge of medicine was essential for further success. He briefly entered Harvard Medical School while continuing a part-time dental practice. During the summer of 1844, Morton, on the advice of Charles T. Jackson, used sulfuric ether for painless tooth extractions, and study of this agent eventually led to his successful demonstration of ether anesthesia at Massachusetts General Hospital on October 16, 1846. The remainder of Morton's life was spent in efforts to patent and receive monetary recognition for the discovery of ether anesthesia. Broken and despondent, he died of a cerebral hemorrhage in New York City in July 1868. *(Images courtesy of the Wood Library-Museum of Anesthesiology, Park Ridge, IL.)*

oxide according to Colton's instructions and use it for extractions of teeth. He recognized the enormous potential of his discovery and used his connections in Boston to arrange a date at the Harvard Medical School to demonstrate the technique of painless surgery.

Wells' appointment was to administer the gas for a leg amputation. The patient scheduled for this procedure refused to proceed with the anesthesia, and a young male student agreed to breathe nitrous oxide for extraction of a wisdom tooth. During the extraction the subject moved and groaned, only later to proclaim that little pain was actually felt. Nevertheless, Wells was discredited and became despondent, eventually withdrawing from further public promotions of his methods.

William T. G. Morton (see Fig. 1-5B), a young dentist from Boston, was acquainted with Wells, having been a former student and colleague of his, and had attended the failed demonstration at Harvard. Morton had lingering thoughts about a more suitable agent, in part arising from his interest in promoting his business of selling dentures. He had invented a new method for fitting dentures, but the process was prohibitively painful, and few patients would submit to the procedure. An adequate analgesic could accelerate his business.

Morton was initially trained as a dentist but had enrolled briefly at Harvard Medical School. Because of financial difficulties, he abandoned these studies and returned to dentistry. In the course of his education he became acquainted with Charles A. Jackson, a professor of chemistry at Harvard Medical School. On Morton's queries, Jackson advised a trial of sulfuric ether as an alternative to nitrous oxide. Later, Jackson was to claim priority in the discovery of anesthesia based on these consultations, but Morton countered that Jackson's role was negligible. Morton obtained the ether and, after performing experiments on himself and his pet animals, administered the agent successfully on September 30, 1846, to Eben Frost for extraction of an upper bicuspid tooth. Prompted by this success, he promoted use of the agent in his dental practice, thereby gaining the attention of another key figure, Henry J. Bigelow (1818-1890), in the unfolding drama. Bigelow, a prominent young surgeon at Massachusetts General Hospital, privately witnessed Morton's success with ether and arranged the time and date for its public demonstration.

The events of October 16, 1846, a complete triumph for Morton, have been recounted several times by others, but certain points are of special interest. The patient, Edward Gilbert Abbott, whom Morton apparently had never met, was to have a vascular tumor of the neck with large tortuous veins excised in the sitting position by 68-year-old Chief Surgeon John Collins Warren (1778-1856). Fearing a difficult airway or air embolism, a modern anesthesiologist might seek special equipment for this case, perhaps a special laryngoscope and central venous catheters. Morton, however, had only a poorly designed inhaler and no intravenous access. Close examination of the circumstances surrounding administration of this anesthetic indicates how dangerous this bold endeavor by Morton actually was and how likely it was to fail miserably. With the inhaler that he used, it seems unlikely that the vapor could be administered during the surgical procedure. Fortunately for Morton, the kinetic properties of ether result in prolonged emergence, and Mr. Abbott responded only briefly at the end of the procedure (Fig. 1-6).

Morton, intending to profit from his discovery, withheld identification of the ether that he used and called it Letheon. He

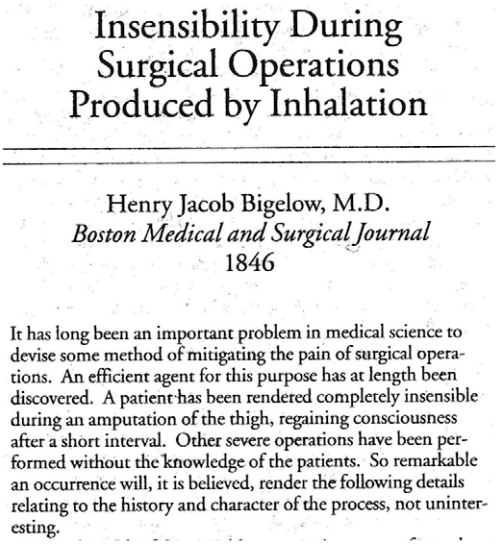


Figure 1-6 Drawing by H. H. Hall in *Rice's Trials of a Public Benefactor* illustrates the first public demonstration of ether anesthesia at Massachusetts General Hospital on October 16, 1846. From the left are Henry J. Bigelow (1818-1890), the earliest advocate and sponsor of William T. G. Morton at the hospital, who also wrote the classic article describing the first experiences with ether anesthesia in the *Boston Medical and Surgical Journal*; Augustus A. Gould, with whom Morton and his wife were boarding and who suggested the design of the first inhaler (Gould also suggested the name Letheon); Jonathan Mason Warren (1811-1867), son of John Collins Warren, who later devised new surgical procedures for nasal deformity and cleft lip (Hall erroneously places him at this event; others [not shown] who were present are George Heywood, house officer, and Eben Frost, who had a tooth pulled by Morton after ether administration on September 30, 1846); John Collins Warren (1778-1856), 68-year-old Chief of Surgery at Massachusetts General Hospital, who performed the operation that day; William T. G. Morton, to whom credit is given for introducing ether anesthesia to the world; Gilbert Abbott, a 28-year-old house painter and printer with a congenital vascular tumor, visible in the drawing as a tumor below the left mandible; and Samuel Parkman, Morton's anatomy instructor at Harvard Medical School; and George Hayward (1791-1863), 53-year-old senior surgeon at Massachusetts General Hospital, who excised an arm mass under ether anesthesia the following day, October 17, 1846. His operation for vesicovaginal fistula is considered to be an original procedure. Also present was Solomon D. Townsend, one of the prominent surgeons at Harvard Medical School. *(Courtesy of the Wood Library-Museum of Anesthesiology, Park Ridge, IL.)*

masked the aroma and appearance of ether by adding a colored dye and additional scents. For a fee, he intended to provide instruction on its safe use. The surgeons at Massachusetts General Hospital then denied continued use of the agent until its true nature was identified. After Morton disclosed its chemical nature, further operations were performed with success. Bigelow read his manuscript describing the use of ether for operative surgery on November 3, 1846, before the American Academy of Arts and Sciences and published it (Fig. 1-7) in the November 18, 1846, issue of the *Boston Medical and Surgical Journal*.[86] The name anesthesia (Greek *an*, "without," and *esthesia*, "sensation") was suggested by Oliver Wendell Holmes (1809-1894) in a private letter to Morton dated November 21, 1846. Holmes also considered the words antineurotic, aneuric, neuroleptic, neurolepsia, and neurostasis, but he rejected these as being "too anatomical" because the change induced by ether was physiologic.

Aftermath

It is remarkable that without more explicit instructions or actual demonstration by one of the Boston group, ether anesthesia was adopted so rapidly around the world. Only 63 days after the Morton demonstration, ether was administered in England by



Insensibility During Surgical Operations Produced by Inhalation

Henry Jacob Bigelow, M.D.
Boston Medical and Surgical Journal
1846

It has long been an important problem in medical science to devise some method of mitigating the pain of surgical operations. An efficient agent for this purpose has at length been discovered. A patient has been rendered completely insensible during an amputation of the thigh, regaining consciousness after a short interval. Other severe operations have been performed without the knowledge of the patients. So remarkable an occurrence will, it is believed, render the following details relating to the history and character of the process, not uninteresting.

Figure 1-7 Title and opening paragraph of Henry J. Bigelow's description of the first ether anesthetics. *(From Bigelow HJ: Insensibility during surgical operations produced by inhalation. Boston Med Surg J 35:309-317, 379-382, 1846.)*

James Robinson (1813-1862), a prominent London dentist, for extraction of a deep-seated molar in a 13-year-old girl. Robinson had learned of ether anesthesia through a letter shown to him by a neighboring friend, Francis Boott (1792-1863), who had received the letter from Jacob Bigelow (1786-1879), father of Henry Bigelow, in which the effects of ether inhalation were described. Robinson devised a new inhaler and wrote the first textbook on anesthesia, published in London on March 1, 1847.[87] Two days after Robinson's use of ether, Robert Liston (1794-1847) performed the first operation in England—a leg amputation at University College Hospital, London—with ether as the anesthetic delivered by William Squire. Within a few months, ether anesthesia had spread to the European continent. Nikolai Ivanovitch Pirogoff (1810-1881) used ether in St. Petersburg as early as February 1847, and he wrote a treatise on the subject. Of significant importance for the widespread use of ether was the prestige of the Boston surgeons, who firmly supported its legitimacy.

Many who tried to administer the anesthetic did so without proper preparation, and failures were common. Several questions remained unanswered. Bigelow's article was vague about how it should be administered and simply described a number of cases with the use of Morton's inhaler. How the ether was supposed to be administered after loss of consciousness was not addressed. Nasal breathing or failure to purse the lips around the mouthpiece must have placed a limit on the duration of effective vapor administration. It was another lucky circumstance for Morton that ether was chosen as his agent. Subsequent studies with ether have revealed that it stimulates the sympathetic nervous system at deep levels of anesthesia.[88] This unique property of the drug and its high blood solubility result in a remarkably safe agent that requires only marginal skills to avoid overdose.

Priority for Discovery

Claims of priority for the discovery of ether anesthesia arose quickly. Wells, Morton, and Jackson all claimed to have discovered anesthesia. The issue of priority was further complicated by

a report that a surgeon in Jefferson, Georgia, had used ether anesthesia as early as 1842. Crawford Long (1815-1878) published a manuscript in the *Southern Medical and Surgical Journal* in December 1849 describing his use of ether on March 30, 1842, to excise a tumor from the neck of a young man, James M. Venable.[89]

Numerous monuments have been erected to commemorate the man "who discovered anesthesia." At least 15 have been erected for the group of Morton, Wells, and Long. A chair that Charles Jackson sat in while experimenting with ether inhalation is on display in the Pilgrim Memorial Hall in Plymouth, Massachusetts, with the label "Seated in this chair, Dr. Charles T. Jackson discovered etherization February, 1842." In the Public Gardens of Boston, a monument without a name has been erected to those who discovered anesthesia, thus suggesting that the introduction of ether anesthesia was the product of several individuals. Howard R. Raper, in his book *Man Against Pain*, analyzed the controversy about "who discovered anesthesia" and suggested that Crawford Long was the discoverer if only the issue of priority is considered. However, Long continued to use whiskey and other ineffective means after 1842, indicative of his apparent lack of enthusiasm for ether. Wells was the discoverer if the idea of inhalation anesthesia is considered, and Morton was the discoverer if the primary consideration is who introduced inhalation anesthesia to the world. Historians have generally credited the personality who produces the actual change in medical practice, and that individual was William Thomas Green Morton.

Neither honors nor monetary awards were forthcoming during the remaining lives of Wells or Morton. Wells committed suicide in 1848, unaware that the French Academy of Sciences had just named him as the true discoverer of anesthesia. Morton was unsuccessful in his effort to profit from a patent on his discovery or to secure a financial award from the U.S. government and died, broken and despondent, at age 49. Jackson was committed to a hospital for the mentally ill at the age of 68 years, where he died 7 years later. Morton was 27 years old when he demonstrated ether anesthesia. The ages of the other participants at the time of their discoveries were as follows: Wells (1815-1848) was 29; Davy (1778-1829) was 22; Hickman (1800-1830) was 24; Jackson (1804-1880) was 41; Long (1815-1878) was 27; and Colton (1814-1898) was 30 years old.

Development of Inhaled Anesthetics

Chloroform

Within a year after the introduction of ether anesthesia, the search had already begun for other agents that could anesthetize without some of the problems associated with ether. Although ether was a remarkably safe anesthetic, even when administered by untrained hands, there were disadvantages, including flammability, prolonged induction, an unpleasant odor that was persistent, and a high incidence of nausea and vomiting. James Young Simpson (1811-1870), an obstetrician from Edinburgh, Scotland, used ether in 1846 but was determined to find a better anesthetic. As early as January 1847, he began experimenting with a variety of different solvents and volatile liquids.[90]

Marie Jean Flourens (1794-1867) had used chloroform in dogs while studying stages in depression of the central nervous system by chloroform and ether. Simpson and a group of friends learned of the surprising potency of chloroform at a dinner party hosted by Simpson on September 4, 1847. Dinner was followed by the experimental inhalation of volatile drugs, and the use of chloroform was followed by stupor and coma in several participants, including Simpson. Simpson promoted chloroform vigorously, and its use was widely accepted in England. As an obstetrician, he advocated its use during labor and promoted, along with others,[91] the use of analgesics during parturition. Initially, his views conflicted with those of medical authorities, who considered it unsafe during labor, and with those of religious authorities, who opposed it on theologic grounds. Edinburgh had a black history on the issue of pain relief during childbirth. In 1591, a young woman named Euphanie Macalyane was burned alive as punishment for seeking pain relief during labor. Her sentence was on a direct order from the King of Scotland, James VI (1567-1625). Simpson was not a timid man and met the religious controversy with direct quotations from the Bible that appeared to support his views (Genesis 2, 21: "and the Lord God caused a deep sleep to fall upon Adam, and he slept: and he took one of his ribs, and closed up the flesh instead thereof.").

Chloroform was used widely in England, but controversy developed about its safety, particularly in otherwise healthy subjects, those in whom a physician would not anticipate any difficulties. Various commissions and committees were formed, notably the two Hyderabad commissions (1888 and 1890),[92] to investigate the relative safety of chloroform. In the late 19th century, Hyderabad, a city in the middle of the Indian subcontinent, was the capital of the independent state of Hyderabad, ruled by the Nizam Mir Mehboob Ali Khan. The Nizam was persuaded to underwrite an animal investigation into the safety of chloroform anesthesia by Major Edward Lawrie (1846-1915), principal of the Indian Medical School in Hyderabad. Lawrie had a preconceived belief in the safety of chloroform, and the results of his studies understandably concluded that chloroform was entirely safe if given according to his methods. The agent continued in use for several decades, but its slow demise was initiated in 1894, when Leonard G. Guthrie[93] reported several cases of delayed chloroform hepatotoxicity in children. The future use of chloroform anesthesia was doomed after the studies of A. Goodman Levy[94] (1856-1954), who demonstrated that the combination of light chloroform anesthesia and adrenalin produced fatal ventricular fibrillation in experimental animals, thereby explaining the perplexing sudden demise of several healthy subjects who were administered chloroform anesthetics.

Nitrous Oxide

Because of the embarrassing public demonstration by Wells in 1863, revival of nitrous oxide as a surgical anesthetic was delayed until its reintroduction by the same man, Gardner Q. Colton, whose lecture and demonstration Wells had attended in 1844 and from whom he obtained the gas used in his first experiments with inhalation analgesia. Soon after the Wells debacle in 1844, Colton abandoned nitrous oxide demonstrations and joined his brother in California, where he unsuccessfully panned for gold and served briefly as Justice of the Peace for San Francisco. His stay in San Francisco terminated when he was involved in controversial land sales, and he moved to Boston and took a job as a writer for the

Boston Transcript.[95] Colton also resumed his "laughing gas" exhibitions, and in 1863 he joined into a partnership with Joseph H. Smith, a dentist in New Haven, Connecticut, for the "painless extraction of teeth." The business thrived, and between 1864 and 1897, the Colton Dental Association had treated nearly 200,000 patients without a fatality. Colton demonstrated nitrous oxide inhalation in Paris at the First International Congress of Medicine in June 1867, and its wider use in Europe originates from that time. Colton was a unique individual who promoted the continued use of a valuable agent, but he remained ignorant of its true chemical nature. In his writings,[96] he states, for example, the following:

> *The gas is composed of half nitrogen and half oxygen and because oxygen is the life giving principle of the air, a person lives a little faster while under its influence. It acts as an exhilarant, as by supplying an extra supply of oxygen to the lungs, the pulse is increased 15 to 20 beats to the minute.*

Until 1870, nitrous oxide was administered with air, and the livid appearance of many patients raised the question about whether the analgesic properties of the gas were primarily caused by lack of oxygen. The idea of using nitrous oxide with oxygen is usually credited to Edmund Andrews[97] (1824-1904), a Chicago surgeon who was able to provide analgesia without cyanosis, thereby confirming the inherent analgesic properties of nitrous oxide. Andrews noticed that the nitrous oxide provided to dentists in gaseous form was often impure and instead advocated the use of liquid nitrous oxide contained in iron flasks. This pure nitrous oxide, when combined with oxygen, provided satisfactory anesthesia without cyanosis for short procedures. Paul Bert (1833-1886), a French physiologist who contributed significantly to the understanding of blood gas tensions at altered barometric pressures, demonstrated that nitrous oxide and oxygen mixtures produced highly satisfactory surgical anesthesia without hypoxia when delivered at pressures greater than 1 atm. Frederick Hewitt[98] (1857-1916) devised the first anesthesia machine to deliver variable portions of nitrous oxide and oxygen. Johnson demonstrated that the pupillary dilation, lividity, jactitation, and clonic movements of the extremities after the administration of nitrous oxide and air were caused by extreme hypoxia because they could be reproduced exactly by administering nitrogen with only 0.5% oxygen.[99]

These developments led to reintroduction of nitrous oxide into the operating room, where Horace Wells had predicted it would be used with success. Nitrous oxide and oxygen anesthesia was promoted in the United States by Elmer I. McKesson[100] (1881-1935), Paluel J. Flagg (1886-1970), and F. W. Clement (1892-1970). McKesson's method for induction of anesthesia with 100% nitrous oxide did not survive into the latter part of the 20th century. A landmark publication by C. B. Courville described the neuropathologic findings in patients who had sustained hypoxic insults during anesthesia with high concentrations of nitrous oxide.[101] W. D. A. Smith recounts the revival of nitrous oxide after Colton's reintroduction of the agent in an entertaining and informative book on the subject.[102]

Unsatisfactory Inhaled Anesthetics

During the first few decades of the 20th century, practitioners were searching for new and improved anesthetics. An American anesthesia textbook written by James T. Gwathmey (1865-1944) (see Fig. 1-18D) was published in 1914 and briefly discussed more than 600 possible anesthetic agents for the reader to consider. By 1930, all successful anesthetic agents except chloroform and nitrous oxide were explosive. Chloroform by then was thought to be dangerous, and the popularity of nitrous oxide was curtailed by the need for a nearly hypoxic mixture to provide adequate anesthesia. Ethyl chloride was the last agent to be introduced in the 19th century, and like ether, it was flammable. It was a unique agent that was first used as a spray to induce local anesthesia, but if inhaled, it also produced general anesthesia.

In the early 20th century, several unsatisfactory volatile anesthetics were introduced. Ethylene was used clinically in 1923. This agent required high concentrations to achieve anesthesia, had an unpleasant smell, and was explosive. Divinyl ether, developed by Chauncey Leake[103] (1896-1978), had some advantages over ether for induction of anesthesia, but it was also flammable and never widely used. Cyclopropane was introduced in 1934 by Ralph Waters (1884-1979) and was briefly popular, but it was violently explosive. The flammable anesthetics prevented the use of surgical cautery and electronic monitoring. One attempt to produce a nonflammable alternative to ether and cyclopropane was made in 1935, when trichloroethylene was introduced. It was promoted by Christopher L. Hewer[104] (1896-1986) as a nonexplosive agent, but it was eventually withdrawn when it was shown to decompose to the toxic nerve poison dechloroacetylene in the presence of soda lime and to produce phosgene, a severe respiratory irritant, when electrocautery was used. Clearly, new directions were needed.

Fluorinated Anesthetics

In the early 1930s, progress was made in attempts to fluorinate hydrocarbons, and many fluorinated compounds became available commercially, primarily as refrigerants. From a theoretical analysis of hydrocarbon chemistry, it was known that halogenation of the parent hydrocarbon compound would decrease its flammability. One early approach to produce a nonflammable anesthetic was to select a flammable agent and partially fluorinate it. With this in mind, John C. Krantz, Jr., of the University of Maryland, took the flammable anesthetic vinamar, which is ethyl vinyl ether, and produced trifluoroethyl vinyl ether,[105] or fluroxene.

The circumstances surrounding the first anesthesia with fluroxene illustrate the lure of self-experimentation in research related to the advancement of anesthetic practice. Max S. Sadove (1914-1997), an anesthesiologist at the University of Illinois, was a member of the Walter Reed Society, a group of scientists who, following the example of Walter Reed, allowed themselves to be administered the first dose of investigational drugs. Sadove, a close acquaintance of Krantz, insisted that he be given the first fluoride-containing anesthetic, fluroxene, in 1953. Krantz, who had synthesized the drug, was a pharmacologist with no training in anesthesia. Krantz advised Sadove that there was danger that the agent might be administered improperly or might be metabolized to a toxic by-product. Nevertheless, Sadove was insistent, and on April 10, 1953, Krantz administered open-drop fluroxene to Sadove, and recovery was rapid and uneventful.[106]

Fluroxene had marginal success but was eventually withdrawn because of questions about toxicity and the frequent occurrence of postanesthetic nausea and vomiting. Charles Suck-

ling, a chemist at Imperial Chemical Industries, synthesized halothane in 1954 after a theoretical analysis of possible anesthetic halogenated drugs. The pharmacologic properties of halothane were studied by James Raventós[107] (1905-1983), and it was introduced clinically in 1956 by Michael Johnstone.[108] Halothane had definite advantages over ether and cyclopropane because of its more pleasant odor, higher potency, favorable kinetic characteristics, nonflammability, and low toxicity, and it gradually replaced the older agents. Halothane was a highly successful drug that achieved worldwide acceptance, but its unblemished record lasted only a few years before controversy appeared.

In 1958, a case report described a 39-year-old woman who died of fulminant hepatic necrosis 11 days after cholecystectomy with halothane anesthesia.[109] This was followed in 1963 by nine case reports of patients in whom hepatic necrosis developed after halothane anesthesia (also see Chapter 24).[110] The cases were unique in that hepatic failure often followed minor operations in which other causes of hepatic failure were not apparent. Eventually, the term "halothane hepatitis" became a common clinical diagnosis for patients with postoperative liver failure, even when halothane was not used as the anesthetic. A national study formally titled "The National Halothane Study" was established in 1964 and reported that the incidence of liver failure after halothane anesthesia was no more frequent than that reported with other anesthetics.[111] Nevertheless, halothane was extensively metabolized in the body, and in some individuals it seemed that a toxic metabolite might produce liver necrosis. Other halogenated anesthetics were also extensively metabolized, and in the case of methoxyflurane, such metabolism resulted in high levels of fluoride ions. High-output renal failure was an infrequent but potentially morbid side effect of methoxyflurane[112] that was related to increased blood fluoride ion concentrations.

Beginning in 1960, the pharmaceutical industry launched new efforts to synthesize the "ideal anesthetic." Ross C. Terrell at Ohio Medical Products synthesized more than 700 potential anesthetic compounds between 1960 and 1980. During the same period, Edmund I. Eger II (1930-) began a series of studies that significantly enhanced the rational use of inhaled anesthetics. Eger drew on the work of Seymore S. Kety[113] (1915-2000) and Severinghaus,[114] which had previously demonstrated that the end-tidal partial pressure of anesthetic gases at steady state was the same as the brain cerebral partial pressure of those gases. By correlating the end-tidal (alveolar) concentration with the movement response to supramaximal nociceptive stimulation, the concept of minimum alveolar concentration (MAC) was born (also see Chapter 19). By definition, MAC represents the end-tidal concentration of any anesthetic agent at which 50% of patients move in response to a supramaximal stimulus.[115] With this standard measure of potency, new agents could easily be introduced to the anesthesia community. Several further studies by Eger and others on the pharmacokinetics of inhaled anesthetics and factors that alter MAC[116] accelerated an understanding of volatile anesthetic requirements and significantly enhanced the safe use of these drugs.

Two of the anesthetics developed by Ohio Medical Products, enflurane and isoflurane, were introduced about 40 years ago.[117,118] Isofluorane has been highly successful and used extensively since that time. Desflurane was one of the last volatile anesthetics to be synthesized and required a potentially dangerous explosive method of synthesis. Desflurane had a high vapor pressure and the added limitation of requiring more than five times the quantity of vapor to produce anesthesia than needed with isoflurane. Although desflurane was initially overlooked because of these problems, it was studied thoroughly in animals[119] and first used in humans in 1990.[120] Because of its favorable kinetic properties, recovery is more rapid with desflurane than with isoflurane or enflurane.

Sevoflurane was synthesized more than 40 years ago at Travenol Laboratories. Recovery is rapid with this agent, but because the compound is unstable in soda lime, it was not introduced until the late 1980s,[121] first in Japan and then in the United States. The decision to introduce the product was, as with desflurane, spurred by the emphasis on early discharge after anesthesia. Anesthesia has been induced with sevoflurane several million times without apparent complications resulting from the potential by-products arising from contact with carbon dioxide absorbents. Since the introduction of sevoflurane, there have been no additional inhaled anesthetics introduced for clinical use. The inert gas xenon has been under investigation as an anesthetic for several years, but it is expensive and, like nitrous oxide, requires high concentrations to produce anesthesia.

Needles and Syringes

In an attempt to find another parenteral route of drug administration, some physicians raised blisters or excoriated the skin and then deposited drugs on the exposed surface of the wound. Francis Rynd[122] (1801-1861) used a lancet to pierce the skin and devised a syringe to insert medication into the wound by gravity. Alexander Wood[123] (1817-1884) invented a hollow needle that would fit on the end of a piston-style syringe made for him by Daniel Ferguson, an instrument maker from London. Wood used the syringe and needle combination to successfully treat painful neuralgias by local injections of morphine. The syringe and needle combination became a popular item after these reports, and many practitioners used the device to inject morphine subcutaneously for pain relief. The term *hypodermic injection* was coined by Charles Hunter, who argued with Wood that morphine could be injected into the body at any place and achieve the same analgesic effect as that obtained by injection at the site of pain.

The early syringes were inadequate for the work of the developing specialty of regional anesthesia (Fig. 1-8). The rubber or leather plunger cracked or deteriorated after repeated sterilization. During use, the drug contents accumulated proximal to the plunger, or the plunger itself jammed inside the glass barrel. To achieve the fine control required for identification of the epidural space, a more carefully tooled instrument was required. H. Wulfing Luer of Paris introduced the first all-glass syringe in 1896. He sold the patent to partners Maxwell W. Becton and Fairleigh S. Dickinson (Becton, Dickinson and Company) in 1898. The Record syringe was made by Dewitt and Herz of Berlin, Germany, in 1906, and it consisted of an all-metal plunger with a finely ground glass barrel. The fit between the barrel and plunger was precise and sturdy, and Record syringes nearly 100 years old can still be used for identification of the epidural space.

The first hypodermic needles were made of tempered steel, a metal that rusted easily when in contact with water. A small rusted area might not be observed visually, and defective needles sometimes broke below the skin. Meticulous care was taken to



Figure 1-8 Drawing by an unknown artist appearing in *Clysmatica Nova*, a book written by Johan S. Elsholtz (1623-1688) and dated 1667. The artist clearly shows that syringes and rudimentary hollow intravenous tubes were used before the 19th century. Although this book was published in Cologne, Germany, most historians credit the first intravenous injections of pharmaceuticals to Christopher Wren and Timothy Clarck in England. *(Courtesy of the National Library of Medicine, Bethesda, MD.)*

dry each needle after steam sterilization. Specially designed introducers, called rimmers, were used for storage of the needles to prevent rust from developing inside the needle. To avoid the problem with needle breakage, platinum or gold needles were used occasionally. These needles were highly flexible and expensive and never became popular. Stainless steel was produced commercially in 1918 and essentially eliminated the problem with rust. Modern needles are usually disposable stainless steel needles, which has minimized complications resulting from infection and breakage.

The bevel of the needle was a topic of great discussion in the early 20th century. A long bevel produced less trauma to tissues, but it allowed a small portion of the needle to lie in the intrathecal space with the proximal portion of the bevel in the epidural space. To increase the success of spinal anesthesia and minimize side effects, short-beveled needles and pencil-point needles were developed by several regional anesthesia specialists, a process that continues to this day. Fine, 25-gauge spinal needles, designed to produce minimal trauma to the dura, have reduced the incidence of post–dural puncture headache.

Intravenous Fluid Therapy

Awareness of fluid balance had its beginnings in the writings of Claude Bernard, who in his final published work emphasized the importance of extracellular fluid in the support of vital functions.[124] In these writings he stressed that blood and lymph bathe the cells of the body and that these fluids constitute the *milieu interne*, later called the *fluid-matrix* by Walter B. Cannon. These researchers pointed out that an organism's freedom from external disturbances such as hunger, thirst, and cold is brought about by mechanisms that maintain uniformity of body fluids. The concept of the steady state maintained in this internal environment became known as *homeostasis* in the Cannon doctrine. During anesthesia, many of the homeostatic mechanisms are abolished or severely blunted, and the anesthesiologist must assume the role of maintaining a favorable *milieu interne*.

Crystalloids

In the late 19th century, the sodium content of serum was found to be roughly equivalent to an aqueous solution of 0.9% sodium chloride, and this became known as physiologic salt solution. Hartog J. Hamburger (1856-1924) showed a change in the volume of red blood cells at concentrations above and below 0.9% saline.[125] As a result of these experiments, the value of sodium ions in maintenance of osmotic pressure in serum was realized. Ernest H. Starling[126] (1866-1927) extended these observations to explain edema formation on the basis of hydrostatic and colloidal osmotic pressure.

Maintenance of fluid balance was not a priority or even a possibility for those who administered anesthetics during the 19th century. Without intravenous access, there was little that the anesthesia provider could do if the surgeon was recklessly losing blood. The importance of intravenously administered salt to patients with dehydration from cholera was observed in 1831 by William B. O'Shaughnessy[127] (1804-1889). Although there were isolated successful attempts to treat the dehydration of cholera with saline infusions, such treatment did not flourish, and the victory over cholera was finally won only through improved sanitary conditions.

The experimental introduction of saline infusions after surgery was based on work performed by Emil Schwarz[128] (1852-1918), who observed that saline infusions could save the lives of bled rabbits. This work was recognized by Johann J. Bischoff[129] (1841-1892), who reported that a salt infusion saved the life of a woman with severe postpartum hemorrhage. Treatment with salt infusions was generally adopted after surgical hemorrhage, but sepsis and failed attempts to revive the bleeding patient soon became apparent.

Alternative solutions to saline originated with Sydney Ringer[130] (1835-1910), Professor of Medicine at University College, London. Ringer observed that saline prepared from distilled water was not as effective as saline made from pipe water in maintaining contractility of the isolated frog heart. After careful analysis of the pipe water, he learned that it contained calcium and potassium impurities. Adding these cations to the saline made from distilled water proved his hypothesis that these ions played an important role in maintaining normal cardiac function.

In the first decades of the 20th century there were substantial barriers to the successful use of parenteral electrolyte solutions during surgery. Closed sterile administration sets and intravenous cannulas were slow to develop, and alternative methods were therefore used. Most patients received several liters of fluid, usually administered rectally; however, salt was administered, if possible, orally or by subcutaneous injection. With these ineffectual methods, the use of saline in the perioperative period fell into decline. In 1944, a syndrome described as postoperative salt intolerance was caused ostensibly by failure of the kidney to excrete a salt load.[131] These ideas had the support of the influential Francis D. Moore, Chief of Surgery at Peter Bent Brigham Hos-

pital in Boston. When intravenous therapy became more widely available, patients were often administered dextrose and water or dilute sodium-containing solutions. Carl Moyer[132] (1908-1970) presented evidence in 1950 that sodium was avidly retained postoperatively and argued against the use of saline for perioperative fluid maintenance.

The reintroduction of perioperative saline therapy began in 1959, when G. Shires and associates[133] reported the redistribution of extracellular fluid into "third space" compartments during extensive surgical procedures. These reports encouraged preoperative administration of fluid to compensate for the lack of oral intake and intraoperative administration of sodium-containing fluid to replace translocation of extracellular fluid into edematous spaces such as the gut and peritoneum. The increased use of saline reduced the incidence of postoperative renal failure and decreased the requirement for blood transfusions. As a result of these studies, fluid replacement today consists of saline-containing fluids, with the addition of colloid and blood when excessive blood loss occurs. These concepts of fluid management were vigorously promoted by M. T. Jenkins (1917-1994).[134]

Blood Transfusions

The first blood transfusions were not performed as treatment of blood loss. Jean Baptiste Denis (1625-1704) from Montpellier, France, administered lamb's blood[135] to a demented patient with the idea of transferring the attributes of the donating animal to the recipient. Although the first patient survived, a subsequent transfusion resulted in death. Denis was tried for murder, and although he was acquitted, the procedure was condemned and prohibited by the Faculty of Medicine in Paris. Physicians in the 18th and 19th centuries were more prone to remove rather than administer blood.

Successful blood transfusions were performed by James Blundell[136] (1790-1877), who experimented with blood transfusions in animals and rejected the idea of animal-to-human transfusions. Blundell recorded 10 human-to-human transfusions between 1818 and 1828 and recognized that acute blood loss was the primary reason for transfusion. Five of these 10 patients died after the transfusion, possibly as a result of incompatible blood.

In 1900, Karl Landsteiner[137] (1868-1943) described three blood groups: A, B, and O; the fourth blood group (AB) was described by A. V. Decastello[138] 2 years later. George W. Crile (1865-1943) performed the first transfusion of human blood after a preceding compatibility test in 1906. Discovery of the Rh antigens was delayed until 1939.

One hundred years ago, the accepted method of transfusing blood was to surgically anastomose the artery of the donor to the vein of the patient. This method required a long and delicate operation, and there was no way to measure the amount of blood transfused. Blood could not be removed from the body without defibrination, a process that often produced serious reactions and air embolization. In 1914, Albert Hustin[139] (1882-1967) noticed that when sodium citrate was added to blood, it prevented coagulation, and with the addition of dextrose by P. Rous and J. R. Turner in 1916,[140] storage of blood products for up to 21 days became a reality.[141] The familiar drip chamber for estimating infusion rates was devised by R. Laurie in 1909. The effect of these advancements in the use of blood products on the practice of anesthesia is apparent by comparing the American textbook by Gwathmey, dated 1914, in which there is no mention of blood administration, with that of John S. Lundy[142] (1894-1972), dated 1945, which contains an extensive chapter on the subject. Lundy was an early proponent of blood transfusions and opened the first blood bank in the United States at the Mayo Clinic in 1935. The effect of two world wars on the practice of anesthesia in the United States can be appreciated by comparing these two books.

With the increased frequency of contamination of homologous blood by hepatitis virus and human immunodeficiency virus, a new look at an old technique,[143] autologous transfusion, was begun in 1970 (also see Chapter 57). In that year, G. Klebanoff described a disposable autologous transfusion system manufactured by Bentley Laboratories. Klebanoff reported[144] on its use in 53 patients with no deaths if the total volume of blood replaced was less than 3500 mL. Malcolm D. Orr first reported cell-washing techniques in 1975 with the Haemonetics cell-washing system.[145] This system obviated some of the problems when blood was filtered, but not washed after retrieval from the surgical wound. From these early reports it became apparent that washed and concentrated red cells obtained from the surgical site could provide safe alternatives to homologous transfusion. The "cell saver" method of autologous blood transfusion has become an integral part of intraoperative fluid management when large volumes of blood loss are anticipated.

Coagulopathies often develop during large-volume blood transfusions, and their diagnosis and prompt treatment significantly contribute to survival during major surgery. Ronald D. Miller (1939-) and colleagues[146] recognized thrombocytopenia as one of the earliest defects in coagulation after massive blood loss (also see Chapter 55). Advances in specific blood component therapy[147,148] have also contributed to maintenance of normal blood coagulability during large-volume blood loss.

Introduction of Regional Anesthesia

Early Attempts at Local Anesthesia

The first written account of the coca plant being used as a local anesthetic was by the Spanish Jesuit Bernabe Cobo (1582-1657), who chewed the plant to relieve a toothache and wrote about it in 1653.[149] Albert Niemann (1834-1861) of Göttingen, Germany, who isolated the alkaloid from the dried leaves in 1856 (Fig. 1-9B), gave the name *cocaine* to the active drug. Interest in cocaine in Europe and America was directed initially toward the central effects of the drug when taken systemically. Vasili von Anrep[150] (1852-1918) was the first to remark on its local anesthetic properties, and after animal experiments, he suggested its use as a local anesthetic during surgery. This suggestion went unnoticed, and the drug remained a curiosity. A comprehensive pharmacology textbook from 1883 does not mention cocaine or the plant *E. coca*.

Sigmund Freud (1856-1939), a young house officer at the prestigious Allgemeines Krankenhaus in Vienna, had a unique interest in cocaine and tested the drug as a substitute for opioids on a colleague who was addicted to morphine. Although this research met with little success, he had also noticed its ability to

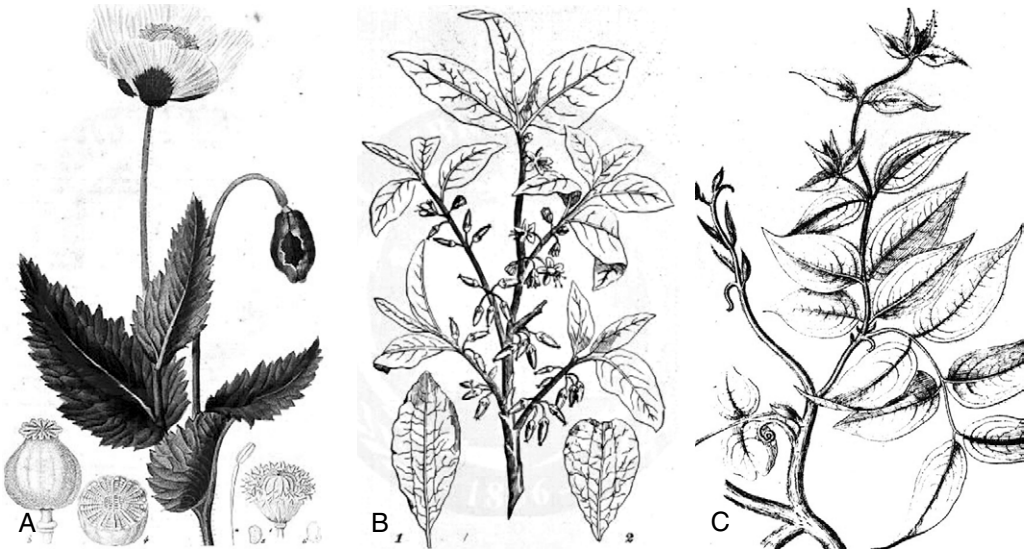


Figure 1-9 Botanical origins of adjuvants used in anesthesiology. **A,** *Papaver somniferum*, from which opium is obtained. The word *opium* is derived from the ancient Greek word for juice because the active alkaloids, which include morphine and codeine, are obtained from juice squeezed from the unripe seed pods. The first undisputed reference to poppy juice is from the writings of Theophrastus (372-287 BC) in the third century BC. **B,** *Erythroxylon coca*, a shrub native to Peru and Bolivia from which cocaine was isolated in 1856. Although the native people of Peru have used the drug for centuries to increase endurance, they may have also used it as a local anesthetic. **C,** *Strychnos toxifera*, a source of curare, as drawn by Robert Schomburgk in 1841. Schomburgk used maps drawn by Waterton to travel into Guiana and obtain several species containing the active drug. Richard Gill's curare was obtained primarily from Ecuador, and the arrow poisons there were made from *Chondodendron tomentosum*. Other botanical drugs that have been used in anesthesia include atropine (*Atropa belladonna*) , scopolamine (*Atropa mandragora*), physostigmine (*Physostigma venenosum*), ether (*Vitus vinifera*), gramine (*Hordeum vulgare*, from which lidocaine was derived), strychnine (*Strychnos toxifera*), ephedrine (*Ephedra sinica*), picrotoxin (*Anamirta cocculus*), theophylline (*Camellia sinensus*), and digitalis (*Digitalis purpurea*). *(Courtesy of the National Library of Medicine, Bethesda, MD.)*

produce numbness of the tongue and provided a small sample to his junior colleague Carl Koller[151] (1858-1944), an intern who was interested in producing local anesthesia for operations on the eye.

Koller had anticipated a career as a scientist in Vienna. He had taken up this question for his research project because the anesthetic methods of the time were highly unsatisfactory for ophthalmic surgery. General anesthetics presented numerous difficulties for the surgeon, and refrigeration anesthesia, although marginally successful for surgery on the extremities, was clearly inappropriate for the eye. Koller observed that after topical application of cocaine he was able to pinch and prick the cornea of dogs without discomfort to the animals. Self-experimentation confirmed complete analgesia of the corneal surface, and he proceeded to use the agent for superficial surgery on the eye.

Koller arranged to demonstrate the use of topical cocaine analgesia at the Ophthalmologic Congress in Heidelberg, Germany, on September 15, 1884. As the time for this presentation approached, he was unable to afford the travel expenses from Vienna, and a colleague from Trieste, Josef Brettauer (1835-1905), presented the three-page manuscript in his absence.[152] The presentation and demonstration were followed by an enthusiastically favorable response. Priority for the discovery was briefly confounded by a report on topical cocaine analgesia at an ophthalmologic meeting in October 1884 by Leopold Koenigstein, who did not mention Koller's previous paper, and by other comments that Sigmund Freud had actually originated the idea of cocaine analgesia. Koenigstein later conceded full credit for the discovery to Koller, and Freud eventually rejected all claims to the idea of topical analgesia with cocaine, although many concede that with his earlier publication on the subject,[153] he was instrumental in reviving interest in a drug that before 1884 was of no interest to pharmacologists.

Koller's career in Vienna seemed secure, but a disagreement arose with another house officer in January 1885. The altercation escalated into a duel with sabers, an activity that was banned in Austria at that time. Koller emerged unscathed from the duel, but the offending party suffered two saber cuts to the face. After this episode, Koller became depressed and ultimately decided to leave Austria. He first immigrated to Holland and then settled in New York City in 1886. There he built a successful private practice while continuing to contribute occasional clinical articles to the ophthalmologic literature. He died in New York City in 1944 after modestly receiving several awards for his seminal role in the development of local and regional anesthesia.[151]

Regional Blocks

It was not obvious that cocaine would produce blockade of sensation if injected directly into peripheral nerves. In 1880, von Anrep had injected cocaine under the skin of his arm and discovered that it produced insensitivity, but this information did not attract attention. At least one Viennese surgeon, Anton Wölfler, first assistant to Theodore Billroth, had attempted hypodermic cocaine injections without producing analgesia and was convinced that it was effective only on the mucous membranes. The idea of injecting cocaine into nerve trunks is credited to William Halsted (1852-1922) and Alfred Hall, who began their injection experiments as early as 8 weeks after the Heidelberg announcement.

Halsted and Hall had studied in Vienna during 1879 and 1880, but it is unlikely that they met Koller during those years because Koller did not finish his medical school training until 1882. During those years Koller was working on a paper about development of the mesoderm and had not developed his interest in cocaine. In 1884, Halsted was occasionally performing operations in the bedroom of his own house in New York City, and it was there that the two surgeons began their work on regional anesthesia. The first report of their success with injection appeared on December 6, 1884, in the *New York Medical Journal* in a letter written by Hall.[154] In this letter, Hall reported that they first injected 4% cocaine (15 mg) into the forearm and concluded that it blocked transmission in the cutaneous nerves because it provided analgesia below but not above the point of injection. They then injected 2 mL (80 mg) into the ulnar nerve at the elbow and produced a block of the entire ulnar distribution distal to the point of injection. Additional blocks were then performed on the brachial plexus and the infraorbital nerves, inferior dental nerves, and the sciatic nerve, all for operative surgery.[155]

With these large doses, it is not surprising that constitutional symptoms developed. Hall described dizziness and nausea. Both Halsted and Hall became addicted to cocaine; Halsted lived with an occult cocaine or morphine addiction the rest of his life. Hall took a position at Columbia University in New York City, but he later moved to Santa Barbara, California, where he died in 1924.

Carl Schleich[156] (1859-1922) introduced infiltration local anesthesia in 1892 as an alternative to direct injection of nerve trunks. His method was to infiltrate cocaine in dilute concentrations (0.01% to 0.2%) directly into subcutaneous tissues. James Leonard Corning[157] (1855-1923), a neurologist from New York, observed that placing a tourniquet on the limb could prolong the analgesic effect of infiltration analgesia, and he reasoned that the tourniquet prevented the blood from removing cocaine from its active site. Heinrich F. Braun[158] (1862-1934) achieved the same prolonged effect of cocaine by adding epinephrine to the solution and producing a "chemical tourniquet." Braun became the pioneer of the new drug procaine, introduced in 1905 as a less toxic drug than cocaine. Braun's textbook,[158] initially published in 1907, was one of the first devoted to regional anesthesia and went through eight editions, with the last one published in 1933.

Although Halsted was the first to block the brachial plexus, he did not use a percutaneous technique. His method in 1884—and that used by George Crile 13 years later—was to surgically expose the roots and then inject each nerve directly. G. Hirschel[159] produced the first percutaneous brachial plexus block in 1911 through an axillary approach (Fig. 1-10A). The axillary brachial plexus block has been modified by several surgeons, including George Pitkin and R. H. de Jong,[160] and remains a popular technique today.

D. Kulenkampff introduced the supraclavicular brachial plexus block[161] a few months after Hirschel described the axillary approach (see Fig. 1-10B). Kulenkampff injected his own plexus with 10 mL of procaine at the midclavicular position, lateral to the subclavian artery, and achieved complete anesthesia of the arm. Early reports indicated a frequent incidence of success with this block, but other practitioners soon reported complications such as pneumothorax and mediastinal emphysema. Several modifications of the supraclavicular block have emerged in an effort to avoid pneumothorax. Infraclavicular approaches to the brachial plexus were described by L. Bazy and V. Pauchet in 1917 and later popularized by P. Raj[162] in 1973 (see also Chapter 52).

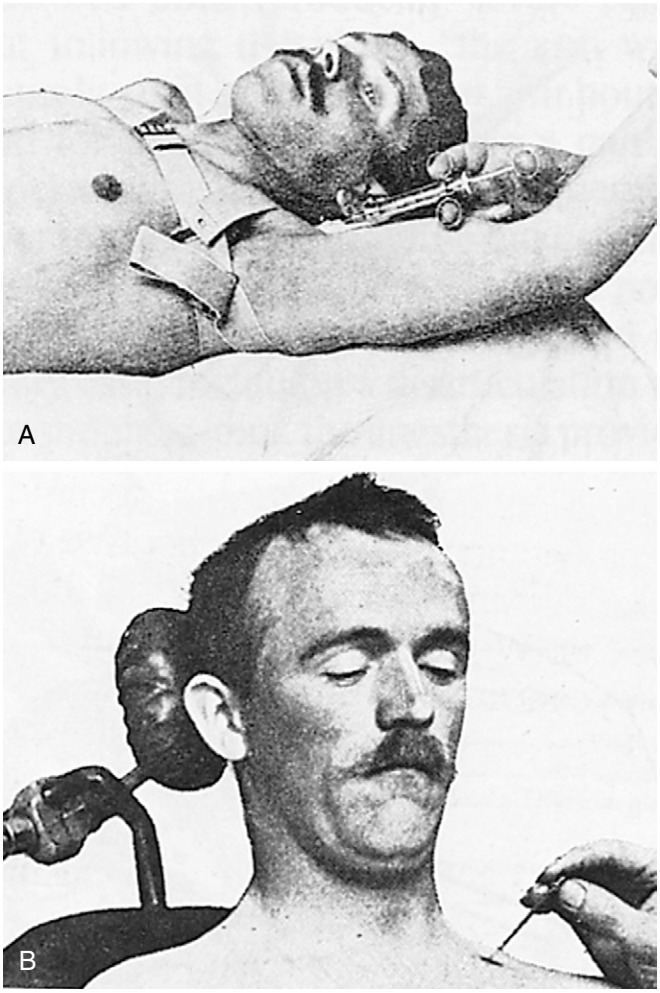


Figure 1-10 **A,** Hirschel performed the first percutaneous axillary block with 20 mL of 2% procaine in 1911. He forced a rubber ball under the pectoral muscles and fixed it with elastic bandages to prevent rapid absorption of anesthetic solution, a maneuver that he later abandoned as unnecessary. **B,** Kulenkampff approached the brachial plexus above the clavicle, just lateral to the subclavian artery. The patients were positioned in the sitting position for the block. An injection of 10 mL of 2% procaine with epinephrine was given only after paresthesia had been achieved. If the first rib was contacted, the injection was directed more medially. (***A,*** *From Hirschel G: Die Anasthesierung de Plexus Brachialis fur die Operationen an der oberen Extremitat, Much Med Wochenschr 58:1555-1556, 1911;* ***B,*** *from Kulenkampff D: Anesthesia of the brachial plexus. Zentrabl Chr 38:1337-1340, 1911.)*

In an attempt to approach the brachial plexus in the neck and thereby avoid pulmonary complications, M. Kappis[163] in 1912 attempted to perform the block through a posterior paravertebral approach. Because of a high incidence of failures with the posterior approach, several investigators, including J. Etienne, V. Pauchet, and G. Pitkin, used various anterior approaches to the brachial plexus in the neck. In 1970, Alon P. Winnie[164] introduced the interscalene brachial plexus block and emphasized that the scalene muscles are more accurate landmarks to the nerves than the subclavian artery or the midclavicular line is. The block has remained popular for operations on the shoulder and upper part of the arm; the nerves are located by paresthesias or direct nerve

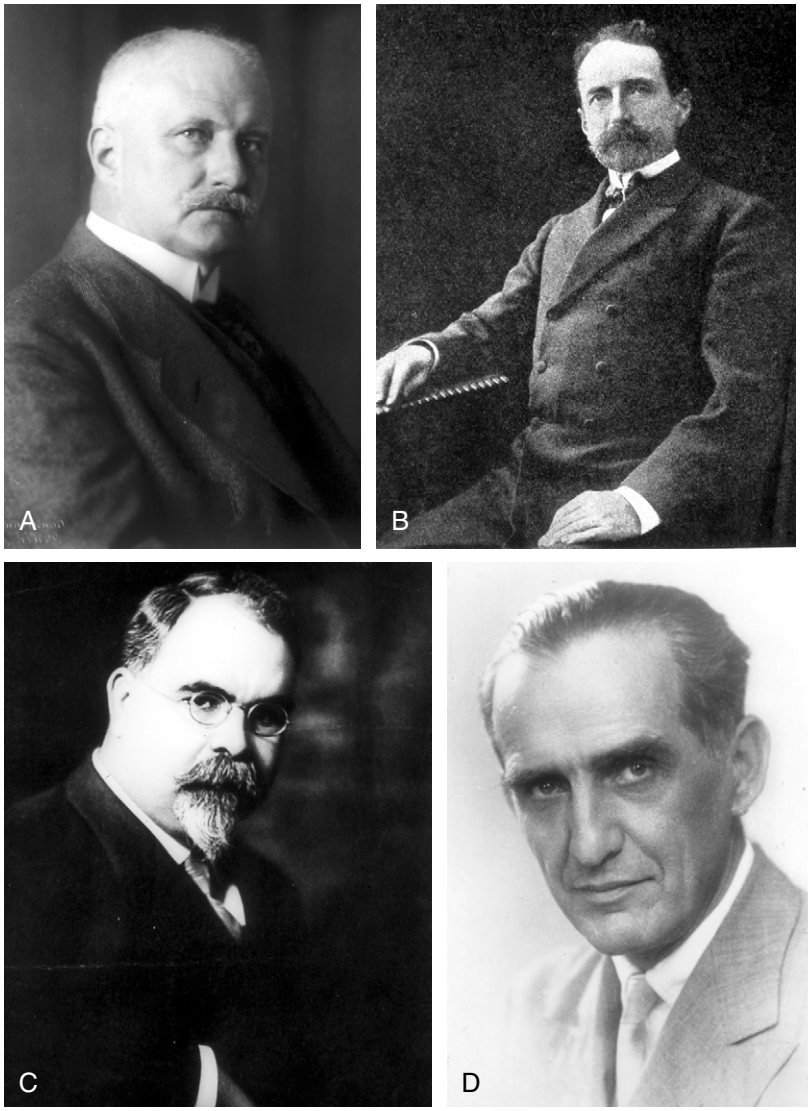


Figure 1-11 Pioneers of the neuraxial block. **A,** August K. G. Bier. **B,** Theodore Tuffier. **C,** Rudolph Matas. **D,** Achille M. Dogliotti. *(Courtesy of the National Library of Medicine, Bethesda, MD.)*

stimulation. Continuous infusion into the roots of the brachial plexus has been introduced and can provide long-lasting analgesia after operations on the arm and shoulder.

A novel method of producing regional analgesia for operations on the extremities was described by August Bier (1861-1949) (Fig. 1-11A) in 1908.[164,165] Bier first exsanguinated the arm with an Esmarch wrap and, after placement of two tourniquets, injected a dilute solution of procaine intravenously. Analgesia was found to develop within minutes and persist until release of the tourniquet. The technique, known now as intravenous regional anesthesia, has been modified with new agents and remains a useful anesthetic technique for surgery on the extremities when a tourniquet is used.

The development of regional anesthesia in the United States was accelerated with the arrival of Gaston Labat at the Mayo Clinic in 1924. Labat had learned regional anesthetic methods from the French authority on injection techniques, Victor Pauchet (1869-1936), and expanded on his work while in Rochester, Minnesota. Labat founded the American Society of Regional Anesthesia and was active during its formative years. John Lundy adopted many of the regional techniques introduced by Labat at the Mayo Clinic and continued their use after Labat relocated to Bellevue Hospital in New York City. Labat's 1922 textbook[50] was one of the first English texts on regional anesthesia and has been followed by several authoritative works on the subject. Labat's influence was also evident in New York City, where Emery A. Rovenstine (1895-1960), his successor as Chairman of the Department of Anesthesiology at Bellevue Hospital, established the first chronic pain clinic. The commitment of anesthesiologists to chronic pain therapy arose as a natural sequel to their emerging expertise in neuraxial and peripheral nerve blocks. Chronic pain clinics today are often modeled after the multidisciplinary clinic established by John J. Bonica (1917-1994) at the University of Washington in Seattle.[166]

The continued success of regional anesthetic techniques can be partially credited to ultrasound techniques for localization of the nerves and also to improved local anesthetics with lower toxicity and longer duration of action. Cocaine was highly toxic, addictive, and of short duration. Procaine was synthesized in 1905 by Alfred Einhorn[167] (1856-1917) and was the most commonly used agent until 1932, when tetracaine, a longer-acting agent, became available. Lidocaine, introduced in 1948 by Torsten

Gordh[168] (1907-), had several advantages, including lower toxicity and intermediate duration of action, and it is still widely used. Other local anesthetics include chloroprocaine (introduced in 1952), mepivacaine (1957), and bupivacaine (1963). Concern about therapy-resistant cardiovascular toxicity with bupivacaine[169] led to introduction of the newer agents ropivacaine (1996) and levobupivacaine.[170] Bupivacaine, ropivacaine, and levobupivacaine are popular agents in low concentration for control of postoperative pain and for obstetric anesthesia because of their long duration of action.

Neuraxial Block and Acute Pain Service

The first neuraxial block was performed 8 months after the demonstration in Heidelberg of the local anesthetic properties of cocaine (see Chapter 87). James Leonard Corning (1855-1923) was a neurologist who had learned of the action of cocaine possibly from observation of Halsted's work in New York City. Corning was interested to know whether the blood could carry cocaine to the spinal cord, similar to what had been demonstrated to occur after the injection of strychnine between the spinous processes. On October 12, 1885, Corning injected a total of 120 mg of cocaine between the T11 and T12 spinous processes in a 45-year-old man and obtained loss of sensation of the legs and perineum. He concluded that this proved cocaine's action on the spinal cord and suggested its use in certain cases of spinal spasticity and for operations on the genitourinary system.

The consensus is that Corning produced an epidural injection of the drug[171] because 120 mg (60 mg initially and then 60 mg 8 minutes later) of intrathecal cocaine would be expected to produce a total spinal anesthetic or a block extending into the cervical dermatomes. It is not surprising that Corning's method of neuraxial blockade was not repeated because the technique of consistently injecting into the epidural space had not yet been described. If any investigators had attempted to repeat the Corning experiment with the dose that he used, it might have ended in disaster and thereby have delayed the development of neuraxial blockade by several years.

Spinal Analgesia (also see Chapter 51)

In Kiel, Germany, during the last decade of the 19th century, preparations were being made for the next major advance in anesthetic practice. At the Kiel University Medical School, Friederich von Esmarch (1823-1908) was the senior surgeon and August Bier one of the junior surgeons. Heinrich I. Quincke (1842-1922) was the leading internist in Kiel and had already contributed several useful clinical observations, among them the Quincke pulse and Quincke edema, to the medical literature. In 1891, Quincke observed that the dural sac, described by Domenico Cotugno (1736-1822) in 1787, could be punctured by inserting a needle between the lumbar spinous processes.[172] This procedure, independently reported by Walter Wynter (1860-1945) of Leeds, England, in the same year, at first was a curiosity without any real purpose. Quincke unsuccessfully attempted to treat hydrocephalus by draining fluid from the dural sac. Microscopic examination of the fluid did have some diagnostic value in cases of inflammation of the central nervous system.

On August 15, 1898, August Bier and his assistant August Hildebrandt (1868-1854) used the Quincke method of entering the intrathecal space and injected between 5 and 15 mg of cocaine to produce spinal anesthesia in six cases for operations on the lower part of the body. They also reported the results of spinal anesthesia given to each other in what has become one of the classic clinical papers in medical literature.[173] Bier thought that it would not replace general anesthesia because of the severity of side effects such as nausea, vomiting, dizziness, and headache. He proposed that these undesirable side effects were caused by escape of cerebrospinal fluid from the dural sac. The method whereby Bier arrived at the correct intrathecal dose of cocaine on the first attempt remains a mystery.

After Bier's report, interest in spinal anesthesia spread rapidly. J. B. Seldowitsch[174] successfully provided spinal anesthesia in St. Petersburg on May 11, 1899; Frederick Dudley Tait (1862-1918) and Guido Caglieri[175] (1871-1951) in San Francisco on October 26, 1899; Theodore Tuffier[176] (see Fig. 1-11B) in Paris on November 9, 1899; and Rudolph Matas[177] (1860-1957) (see Fig. 1-11C) in New Orleans on November 10, 1899. By one report, more than 1000 manuscripts relating to spinal anesthesia had been published within 2 years of the original paper by Bier.

Not all researchers agreed on the technique and indications for spinal anesthesia. Tait and Caglieri suggested the use of cervical intrathecal injections for operating on the upper extremities. A. W. Morton[178] reported success with total spinal anesthesia after lumbar puncture for operations on all parts of the body. Thomas Jonnesco[179] reported no adverse effects from 398 spinal anesthetics administered between vertebrae at the thoracic and lumbar levels with a novocaine and strychnine mixture. Jonnesco called the method general spinal anesthesia. Remarkably, in his series there were 14 operations on the skull, 45 on the face, and 25 on the neck. In 1909, Bier[180] claimed that to be successful with spinal anesthesia, the anesthetist should inject the solution only at body temperature and that tropacocaine was preferable to cocaine.

The early reports of cocaine spinal anesthesia mentioned that after injection, patients frequently became restless and excitable, often exhibiting a significant rise in body temperature. One of the first physicians to specialize in anesthesia, S. Ormond Goldan, maintained accurate anesthesia records from several cases of spinal anesthesia with cocaine.[181] His records reveal a typical increase in heart rate, pupil size, and body temperature after cocaine spinal anesthesia. Matas reasoned that these effects were secondary to an action of cocaine on the central nervous system. He learned that mixing 1.5 mg of morphine with cocaine was useful in mitigating these symptoms. In his 1900 report on spinal anesthesia, he regarded a mixture of cocaine and morphine as his standard agent. This report by Matas appears to be among the first attempts to use spinal opioids to enhance neuraxial analgesia.[177] The Japanese anesthesiologist Otojiro Kitagawa[182] (1864-1922) used intrathecal morphine (10 mg) in the same year to treat the chronic painful conditions of two patients.

It is not surprising that serious complications from the spinal technique were soon observed. F. Gumprecht[183] reported 15 cases of sudden death from lumbar puncture in 1900. Several investigators observed respiratory arrest after high spinal injections. After the introduction of routine blood pressure measurements by Cushing in 1903, it was observed that severe hypotension could occur after spinal anesthesia.

The scientific study of spinal anesthesia began within a few years after its introduction. Investigations were undertaken by Arthur E. Barker[184] (1850-1916) to determine factors involved in spread of the local anesthetic within the subarachnoid space. Barker advised meticulous sterile technique and introduced the use of dextrose to produce hyperbaric solutions. His emphasis on gravity as an essential determinant of local anesthetic spread remains an important facet of the spinal technique today.[185] Several researchers reported the dangers of total spinal anesthesia. Gaston Labat[50] and George P. Pitkin contributed clinical observations that improved the safety of spinal anesthesia.

A widely publicized malpractice trial in 1953 had a negative impact on the use of spinal anesthesia.[186] Albert Woolley and Cecil Roe were healthy subjects who received dibucaine spinal anesthetics on the same day in 1947 at the Chesterfield Royal Hospital in England. Permanent painful spastic paraparesis developed in both patients. Although the cause of the paresis was inconclusive, it was thought that the injuries were caused by contamination of the spinal solution by phenol, in which the dibucaine ampules had been immersed for sterilization. The Wooley and Roe case was followed by other reports of paralysis after spinal anesthesia.[187] However, in 1954, a reassuring study of 10,098 spinal anesthetics with only 71 minor neuropathies, most unrelated to the block itself, was published in a widely circulated medical journal.[188] Spinal anesthesia then re-emerged as a safe anesthetic method, provided that attention was directed to meticulous technique.

Consideration has been given to a syndrome characterized by transient paresthesias after lidocaine spinal anesthesia.[189] However, with the introduction of disposable spinal kits and improved techniques, the spinal route of drug administration is now firmly established. Research is continuing on new drugs and methods of delivery. Reports of cauda equina syndrome after the introduction of lidocaine through spinal microcatheters[190] emphasize the importance of careful clinical observations when new methods of spinal delivery are introduced.

Post–dural puncture headache was an annoying problem for the first practitioners and their patients. The exact cause of this reaction was not agreed on for several years. As late as 1924, Labat had suggested removal of cerebrospinal fluid for the treatment of spinal headache. However, an extensive study by Leroy D. Vandam (1914-2004) and Robert Dripps (1911-1974) confirmed Bier's original suggestion that leakage of cerebrospinal fluid through the dural rent was the causative factor.[191]

The use of small-diameter spinal needles has decreased the incidence of spinal headache after spinal anesthesia. However, inadvertent dural puncture with larger needles can sometimes occur during the placement of epidural catheters. An innovative treatment of headache after dural puncture, the epidural blood patch, was suggested by James B. Gormley[192] in 1960 and further described by Anthony J. DiGiovanni and Burdett S. Dunbar[193] in 1970. The blood patch has been reported to be successful in a high percentage of cases and has withstood the test of time as an effective treatment of this condition.

Epidural Analgesia (also see Chapter 51)

Jean Enthuse Sicard (1872-1929) and Fernand Cathelin (1873-1945) independently introduced cocaine through the sacral hiatus in 1901, thereby becoming the first practitioners of caudal (epidural) anesthesia. Sicard was a neurologist and used the technique to treat sciatica and tabes, but Cathelin used the technique for surgical anesthesia. Arthur Läwen[194] (1876-1958), a pupil of Heinrich Braun (1862-1934) and an early proponent of regional anesthesia, successfully used caudal anesthesia with large volumes of procaine for pelvic surgery. It soon became apparent that caudal anesthesia was sufficient for operations on the perineum, but the drug would have to be deposited into the epidural space at higher levels if the surgeon anticipated operating on the abdomen or thorax. Initial attempts to provide epidural anesthesia through needles placed at higher levels were unsuccessful. B. Heile[195] published an extensive study of the epidural space in 1913, but the focus of his final report was on the treatment of neurologic conditions with epidural injections. His unique approach was to enter the epidural space through the intervertebral foramina (a technique that has recently been revived). Tuffier[196] was aware of the need for entry at higher levels but was unable to perfect a reliable technique for lumbar or thoracic epidural injections.

In 1921, Fidel Pagés[197] (1886-1923), a Spanish military surgeon, devised a technique to introduce epidural procaine at all levels of the neuraxis. His method was to use a blunt needle and then feel and hear entry of the needle through the ligamentum flavum. His report of 43 cases of lumbar and thoracic epidural anesthesia represents a landmark article that went unnoticed because of its publication in an obscure medical journal. Pagés died in an automobile accident soon after his report on epidural analgesia, and no students at the time had learned his technique. Pagés had the idea of producing segmental anesthesia through epidural injections, thereby avoiding some of the side effects of complete neuraxial blockade, which occurred after high subarachnoid administration of local anesthetics. He provided the anesthetics himself and then performed the operations, noting that much time was saved with the epidural technique as compared with general anesthesia. Of the 43 cases, it appears that one subject experienced total spinal anesthesia but survived after assisted ventilation.

Achille Mario Dogliotti[198] (1897-1966) (see Fig. 1-11D) described epidural injections of local anesthetics in 1931, apparently without previous knowledge of the work of Pagés. Dogliotti performed extensive studies to determine the spread of solutions within the epidural and paravertebral space after injection. His work launched one of the most valuable techniques in the modern practice of anesthesiology. An important innovation was Dogliotti's method of identification of the epidural space. His 1939 textbook illustrates the use of continuous pressure on the plunger of a saline-filled syringe as the needle is advanced through the ligamentous structures. In contrast to the methods of Corning and Pagés, the Dogliotti technique was reproducible and easily learned. Dogliotti also observed the extent and duration of analgesia after injection into various spinal interspaces.

Initial acceptance of epidural analgesia was slow to develop in North America, although it gained early acceptance in Europe and South America. A. Gutierrez of Argentina became an enthusiastic advocate for the epidural method and collected valuable data on a large series of successful epidural anesthesia. He also developed the "hanging drop" sign, which is still used by some anesthesiologists to identify the epidural space. Dogliotti's anesthesia textbook was translated into English in 1939 and contained an extensive chapter on epidural analgesia. Textbooks by American authors several years later[142,199] contained only a short

description of the technique and considered it a novelty practiced only by those with special expertise. There were some early practitioners of epidural anesthesia in North America. Charles B. Odom of New Orleans published 285 cases of lumbar epidural anesthesia in 1936 and introduced the concept of a test dose to detect intrathecal injection.[200] In Odom's series there was one death attributed to the poor condition of the patient. John R. Harger and coworkers[201] of Cook County Hospital in Chicago reported 1000 cases without a fatality when using single injections of 45 to 50 mL of 2% procaine. Oral Crawford and colleagues[202] reported more than 600 cases of thoracic epidural analgesia for thoracic surgery in 1951, with two deaths.

One major limitation of the neuraxial techniques was the short duration of action of procaine. Bier experimented with the addition of rubber and latex to the spinal anesthetic solution in an attempt to prolong the duration of blockade.[180] These ideas were not expanded on because of complications or lack of effect. To deal with the same problem, William T. Lemmon (1896-1974) used a 17-gauge, malleable, silver needle that was connected through a hole in the operating room table to rubber tubing and a syringe. Injections could then be made at intervals to maintain the spinal block for several hours. Edward B. Tuohy[203] (1908-1959) used a ureteral catheter threaded through a large Huber-tipped spinal needle to provide continuous spinal anesthesia. The Tuohy needle, a simple modification of the Huber needle, was used by him to thread the catheter into the subarachnoid space. Beginning in 1947, Manuel Martinez Curbelo[204] of Havana, Cuba, used the Tuohy needle and a small ureteral catheter to provide continuous lumbar epidural analgesia. He reported 59 successful cases, and in one patient the catheter remained in place for 4 postoperative days with intermittent injections of local anesthetic.

Caudal anesthesia experienced a resurgence in popularity after the report by W. B. Edwards and Robert A. Hingson (1918-1996)[205] in 1942 that analgesia for labor and delivery could be achieved with caudal injections of tetracaine through a malleable needle left in situ within the sacral canal. Their report was widely publicized, and within months the technique was adopted by several hospitals. Although caudal epidural injections had been used for obstetric analgesia for many years, it became apparent that the lumbar approach to the epidural space was more consistent, and it eventually replaced the caudal approach.

Beginning in 1960, coincident with its rising popularity in obstetric anesthesia, the epidural method was taken up by several practitioners in North America. Philip R. Bromage and John J. Bonica performed several studies on epidural dose-response relationships and the hemodynamic changes that followed initiation of the block. Textbooks soon followed that introduced epidural analgesia into the operating room.[206] Although Dogliotti thought that general anesthesia was contraindicated after the initiation of epidural blockade, Massey Dawkins (1905-1975), Philip R. Bromage, and later Michael Cousins[207] discussed the advantages of providing general anesthesia during prolonged surgery while extending epidural analgesia throughout the surgical procedure and into the postoperative period. Although lumbar epidurals were widely used for postoperative pain relief, problems with ambulation and inadequate analgesia led to the current practice of placing epidural catheters between the appropriate interspaces to provide selective antinociception along the surgical incision site.

A report in 1979 by J. Wang and associates[208] demonstrated long-lasting analgesia from the intrathecal administration of morphine in eight patients with cancer pain. This clinical study had firm groundwork from previous basic studies on the spinal effects of opioids in animals. In 1976, Yaksh and Rudy[209] reported that intrathecal morphine produced spinal analgesia in rats. Duggan and North[210] demonstrated evidence of spinal analgesia after iontophoretic application of morphine into the dorsal horn region of the spinal cords of animals. Autoradiographic studies demonstrated a high density of opioid receptors in the substantia gelatinosa of the spinal cord.[211]

The use of spinal opioids spread rapidly after the initial report by Wang and coworkers.[208] Samii and colleagues[212] confirmed that selective opioid spinal analgesia occurs in humans. Cousins and associates[213] noticed that 1 to 2 mg of intrathecal morphine injected into the thoracic intrathecal region relieved the pain of breast or lung cancer for more than 24 hours. Behar and collaborators[214] reported epidural opioid therapy in 1979. The explosive interest in neuraxial opioids that followed these reports was equal to the enthusiasm after the initial report of cocaine spinal anesthesia. The use of epidural catheters to provide long-lasting pain relief after surgery led to the formation of acute pain services.[215] With special attention to drug concentrations and rates of infusion, patients were able to recuperate without pain and ambulate on the first postoperative day, even after extensive thoracic, abdominal, and orthopedic operations. The special advantage of epidural opioids was the synergistic effect that they exhibited with local anesthetics, which allowed a marked decrease in the dose of both drugs to achieve the same level of analgesia.[216]

Intravenous Anesthetics

The development of intravenous anesthetics has been an important component of anesthetic management for more than 70 years (see Chapters 26 and 27). Before the introduction of rapidly acting intravenous agents, induction of general anesthesia necessarily required inhalation of gases or vapors, an unpleasant experience for some patients.

Pierre-Cyprien Oré (1828-1891) performed the first successful attempt at intravenous anesthesia in 1872 by using chloral hydrate to anesthetize a human subject. Although he believed it was superior to chloroform, his contemporaries did not adopt the method. Intravenous paraldehyde was briefly used as an anesthetic during and after World War I. At the same time, the combination of intravenous morphine and scopolamine gained wide popularity, particularly in obstetric anesthesia. The method became known as twilight sleep, but this drug combination was slowly abandoned because of unpredictable side effects when given to some patients. Tribromoethanol (Avertin) was originally promoted as a full anesthetic agent to be administered rectally. Although rectal administration of agents had been promoted by Pirogoff, Gwathmey, and others, the use of rectal tribromoethanol fell into disfavor when rectal ulcerations were reported after use of the agent. Thereafter, tribromoethanol was used briefly as an intravenous agent, but because it had a prolonged duration of action and produced profound respiratory depression and probable hepatotoxicity, other suitable intravenous agents were sought.

Adolf von Baeyer discovered the first barbiturate, barbituric acid, in 1864, but the drug had no sedative properties. It is said

that Baeyer celebrated discovery of the compound on Saint Barbara's Day, and he coined the word barbiturate as a combination of Barbara with urea because barbituric acid results from the combination of malonic acid and urea. The first sedative barbiturate was synthesized in 1903 by Emil Fischer (1852-1919) of Berlin, but short-acting intravenous agents such as hexobarbital were not introduced until nearly 30 years later. Helmut Weese[217] (1897-1954), considered by many to be the originator of successful intravenous anesthetic methods, reported several thousand cases of hexobarbital use in 1932. Sodium thiopental followed hexobarbital in 1934, and the first detailed analysis of its use was described by John Lundy of the Mayo Clinic.[218] The use of thiopental was a further refinement of his earlier concept of balanced anesthesia, whereby anesthesia is achieved with the use of multiple agents. According to Lundy, general anesthesia was safer with the use of multiple agents because the dose of any one particular agent was smaller and fewer side effects were observed.

It was soon learned that thiopental could be dangerous to administer in certain circumstances. When the drug was used for induction of anesthesia in injured personnel after the bombing of Pearl Harbor in 1941, the frequent occurrence of sudden death emphasized the profound depressant effect that this drug has on the cardiovascular system.[219] Later analysis of the use of thiopental at Pearl Harbor, however, did not implicate the drug as the cause of the high mortality rate observed at that time.[220] The only other commonly used short-acting barbiturate is methohexital, an oxybarbiturate that has similar depressant effects on the circulation. Because of its unique proconvulsive effect, methohexital is used as an anesthetic for electroshock therapy.

There have been several attempts to replace the barbiturates with shorter-acting drugs that have less cardiovascular depression. Some of these drugs, such as althesin,[221] propanidid, and eltanolone, were withdrawn from clinical use because of unwanted side effects. Etomidate, an intravenous anesthetic introduced in 1973 that was used to induce anesthesia, produces only minimal hemodynamic depression and has found use in patients with hypovolemia and those with significant cardiovascular disease.[222] Etomidate can cause undesirable myoclonic movements during induction in some patients.

The benzodiazepines midazolam, diazepam, and lorazepam are useful intravenous agents that relieve anxiety without the same degree of sedation produced with the barbiturates. Experimental studies on this class of drugs began in 1933 at the University of Cracow in Poland, with the first clinically useful drug, chlordiazepoxide (Librium), introduced in 1960. Diazepam (1963) and midazolam (1978) followed. A specific antagonist can be used to treat overdosage.[223]

Ketamine was synthesized in 1962 as an alternative to phencyclidine, a drug that resulted in severe psychological effects in the postoperative period. Ketamine was one of 200 phencyclidine derivatives that were studied, and it was introduced as an anesthetic in 1966.[224] It was initially used intravenously or intramuscularly as a complete agent by itself, but reports of postoperative hallucinations led to re-evaluation of its use, and it is now typically used only in combination with other sedative agents. Ketamine is a unique agent in the armamentarium of the anesthesiologist because it does not depress the cardiovascular system, even when used in full anesthetic doses.

Propofol, introduced clinically[221,225] in 1977, is an alkylphenol compound that has some advantages over thiopental. It appears to have antiemetic properties and suppresses laryngeal reflexes to a greater extent than thiopental does, thus allowing easy placement of supraglottic airways. It has achieved widespread use since its introduction, partially because of its rapid recovery profile. Propofol is often administered as a continuous infusion for general anesthesia, with or without the addition of inhaled anesthetics. When combined with analgesic agents such as opioids, propofol can provide all the components of satisfactory general anesthesia. This method, often called total intravenous anesthesia (TIVA), can eliminate the need for any gaseous or volatile agents. Propofol is a profound cardiovascular depressant, and it can produce significant pain on injection.

Although intravenous opioids were once considered unsafe in the private rooms of hospitals, a modality of administration called patient-controlled analgesia (PCA) is now routinely used in most hospitals. The rationale is that because pain is a subjective experience, only patients can assess the need for analgesics and balance that with their experience of side effects. Overdose is obviated by lock-out intervals and by the inability to perform the task of drug administration as somnolence ensues. Methods for intravenous PCA therapy in the postoperative setting were developed by anesthesiologists more than 30 years ago,[226] but they are now used by several specialty groups within the hospital.

Muscle Relaxants

Neuromuscular blocking drugs or muscle relaxants are firmly entrenched as an integral part of everyday anesthetic practice (see Chapter 29). Anesthesia providers practiced for nearly 100 years without these drugs, but it would be difficult to provide the same level of anesthetic service today without their use.

Initial Contact with Arrow Poison

Homer (*Odyssey*, I, 260) and Virgil (*Aeneid*, IX, 772) mention poisoned arrows. The word *toxin* is derived from the Greek root *toxon* ("bow"). Medical fascination with the specific arrow poison now called curare began nearly 500 years ago when the first returning explorers from South America told of a poisoned arrow that was used in warfare and to kill game. In 1505, Pietro Martyr d'Anghiera (1457-1525), an Italian monk who visited South America in the early 16th century, wrote the following:

> *This Indian King layd wait for oure men . . . set on them with about seven hundred men armed after theire maner, although they were naked. For only the King and his noblemen were appareled . . . So fiercely assayling oure men with theire venomous arrowes that they slewe of them fortie and seven . . . for that poyson is of such force, that albeit the wounds were not great, yet they dyed thereof immediately.*

Sir Walter Raleigh[227] (1552-1618) was one of the first to report on the wonders of the drug, which his first lieutenant, Laurence Keymis, called ourari, the first English attempt to reproduce the Macusi Indian pronunciation of the poison. Remarkably, the flesh of the poisoned animal was eaten with impunity. The native inhabitants were greatly impressed with gunpowder but noticed that the noise from guns frightened the game, and they

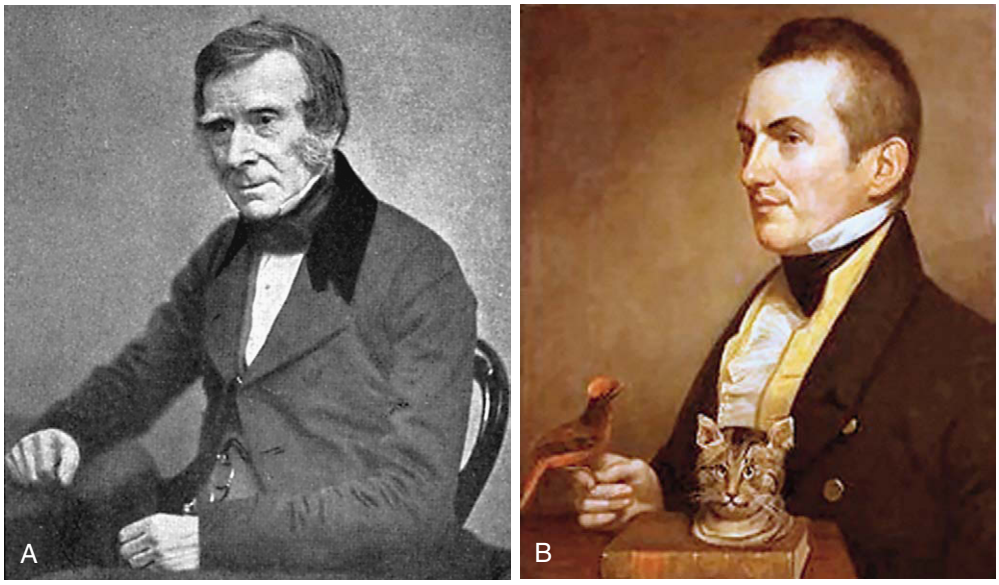


Figure 1-12 Benjamin Brodie (**A**) and Charles Waterton (**B**) collaborated in demonstrating that animals could survive curare poisoning if artificial ventilation was provided. *(Courtesy of the National Library of Medicine, Bethesda, MD.)*

preferred a poison-tipped arrow that was sent quietly from a blowgun. Initial reports indicated that the poison was made from a mixture of rat bones and bark.

Charles-Marie de la Condamine (1701-1774) was the first to bring creditable samples back to Europe. His samples were used by Richard Brocklesby (1722-1797) to demonstrate that the heart of a cat continued to beat for 2 hours after it was apparently dead from curare poisoning. The Florentine Abbot Felix Fontana (1720-1805) injected the drug directly into the exposed sciatic nerve and observed no effect. He concluded that the curare impaired irritability of the muscle.[228]

Mechanism of Action

The collaborative project of Benjamin Brodie (1783-1862) (Fig. 1-12A) and Charles Waterton (1783-1865) (see Fig. 1-12B) initiated our modern understanding of muscle relaxants.[229] Benjamin Brodie was the principal figure of English surgery at that time, and Waterton was the eccentric Squire of Walton Hall, near Wakefield, England. Waterton had traveled extensively, including several expeditions into British Guiana, where he owned property and eventually obtained several samples of the arrow poison.

In 1814, Brodie and Waterton demonstrated that an animal could survive an injection of curare provided that ventilation was continued after injection. For this famous experiment, it seems that Waterton supplied the curare and the animal—a donkey—and Brodie supplied the experimental idea. They injected the donkey with poison in the shoulder, and it was immobilized within 10 minutes.

> *An incision was then made in its windpipe, and through it the lungs were inflated for two hours, with a pair of bellows. The ass held up her head, and looked around, but the inflating being discontinued, she sunk once more in apparent death. The artificial respiration was immediately recommenced and continued without intermission for two hours. This saved the ass from final dissolution: she rose up and walked about; she seemed neither in agitation nor pain.*

Waterton named the donkey Wouralia and nurtured her on his estate, where she died 25 years later. Curiously, in their later correspondence, neither partner mentions the collaboration of the other individual. Waterton's book, titled *Wanderings in South America* and dated 1879, contains an extensive description of the preparation and use of curare, as well as the manner of use of the blowpipe, which he called the "extraordinary tube of death."

The experiment performed by Claude Bernard[230] (1813-1878) demonstrating the action of curare at the junction between the nerve and muscle was deceptively simple (Fig. 1-13). In his studies with curare, Bernard used the drug to open a new area of investigation, the physiology and pharmacology of the junction between the nerve and muscle. Experiments on the specialized apparatus where the action of curare is primarily located, the neuromuscular junction, were begun by one of Bernard's students, Willy Kuhne (1837-1900).

Introduction into Clinical Medicine

Waterton suggested the use of his woraria for the treatment of tetanus and rabies, and the few successful trials of the small samples of curare that were available then were used to treat these conditions.[231] For the next 175 years in Europe and North America, the drug remained a curiosity with no definite purpose. The medical community ignored an early report from 1912 suggesting its use to provide muscular relaxation during closure of the abdomen:

> *Thus far I have used solution of curarine up to 2% by intramuscular injection. With this dose, closure of the abdominal wall was achieved readily. There is not sufficient curare available, so I have not yet been able to ascertain the correct dose for this purpose.*

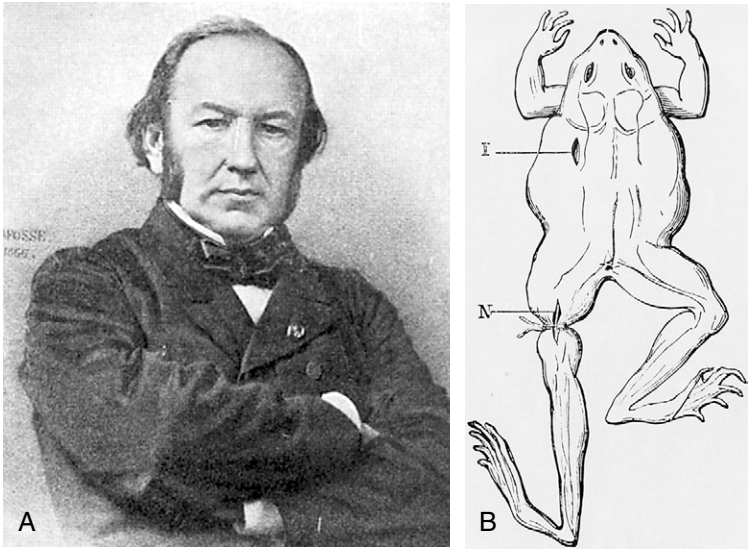


Figure 1-13 A, Claude Bernard (1813-1878) was one of the greatest physiologists of all time and made several contributions to the anesthesia literature. Bernard was born in Saint Julien, France, and educated in Paris. After medical training, he became an assistant to François Magendie, the leading physiologist of that era. He never practiced medicine, but his research contributions pervade every field of modern medicine. In 1855, he succeeded Magendie as Professor of Physiology at the College de France. A special Chair of General Physiology was created for him at the Sorbonne. **B,** Experiment by Claude Bernard illustrating the site of action of curare at the junction of the nerve and muscle. A ligature prevented injected curare (I) from reaching the muscle of the frog's hind limb. After systemic injection of curare, Bernard observed that the limb contracted in response to a neural stimulus (N) applied above the ligature. The opposite limb would contract only to direct electric stimulation of the muscle but not to a neural stimulus. He showed that the nerve and muscle were unaffected but that the connection between the nerve and muscle was blocked.[230] *(Courtesy of the National Library of Medicine, Bethesda, MD.)*

The active principle was eventually found in several plant species, primarily *Chondodendron tomentosum* and *Strychnos toxifera* (see Fig. 1-9C). King isolated the active compound from the *Chondodendron* species that he called D-tubocurarine in 1935.

Curare was initiated into clinical practice by several individuals, beginning with Richard C. Gill[232] (1901-1958), whose contributions, like those of Waterton, arose out of a strong sense of wanderlust, combined with an interest in primitive medicine. As a young man growing up in Washington, D.C., Gill was expected to follow his father and older brother into the practice of medicine. Instead, his degree in 1929 from Cornell University was in English, and his career as a teacher was brief. He took a position with a rubber company in Lima, Peru, but with the stock market crash of 1929, he consolidated his savings and, together with his wife Ruth, purchased 750 acres of land in the Ecuadorian jungle. By 1930, Richard and Ruth Gill were the proud owners of a large hacienda on the Eastern slopes of the Andes,[233] where they raised tropical fruits and vegetables and studied the local Indian customs.

While returning to the United States in 1932 for a brief holiday, Gill fell from his horse and a neurologic syndrome, initially thought to be multiple sclerosis, developed and eventually progressed to a painful spastic disorder. His neurologist Walter Freeman (1895-1972) advised him that the arrow poison from South America might help cure his painful spasms, but it was nearly impossible to obtain the drug. Procuring curare and other herbal remedies thereafter became the focus of Gill's life until his death in 1958 at 57 years of age. Gill obtained funding from Sayre Merrill, a wealthy Massachusetts businessman, for an expedition to retrieve indigenous medicinal plants from the Ecuadorian jungle. The primary aim was to retrieve adequate amounts of the crude curare preparation to begin clinical trials with the drug in cases of spasticity. It is noteworthy that Gill was in a unique position to obtain large quantities of curare because the Indian "medicine men," who jealously guarded the secrets of making the poisonous darts, trusted him.

After 4 years of planning, Gill's neurologic condition had improved, and the expedition was launched. In 1938, Richard and Ruth Gill returned with 11 kg of a crude curare mixture and 75 other indigenous medicinal preparations obtained from the Indian shamans. Sadly for the Gills, there was no interest in their jungle remedies. Initially, even the curare failed to generate any interest. Freeman was acquainted with Abram E. Bennett, a psychiatrist at the University of Nebraska who had expressed interest in the drug. Bennett had the crude concoction standardized by the pharmacologist A. R. McIntyre but failed to find any prolonged benefit for it in cases of spasticity (Fig. 1-14A).

Bennett then turned his attention to the use of curare during Metrazol convulsive therapy, which at that time was thought to be therapeutic for depression and mania but was complicated by a high incidence of bone fractures and joint dislocations. By then, E. R. Squibb and Sons had taken the remainder of Gill's curare and was distributing a small quantity of the drug as Intocostrin, an unpurified form of D-tubocurarine. Bennett[234] reported on the successful use of Intocostrin in cases of Metrazol convulsive therapy in 1940. His method was to administer Intocostrin until a head lift was impossible and then give Metrazol. Surprisingly, he reported no respiratory embarrassment and no complications and thought that patients preferred his new method.

E. R. Squibb and Sons, together with their anesthesiologist consultant Lewis H. Wright (1894-1974), were convinced that the true home for curare was with the anesthesiologist, and in 1940, with some urging, Wright convinced Harold R. Griffith (1894-1985) (see Fig. 1-14B) of Montreal, Canada, to use the drug during general anesthesia when muscular relaxation was required by the surgeon. Previous attempts by Wright to generate interest in the drug had failed until Griffith agreed to use Intocostrin during cyclopropane anesthesia. Griffith and his junior colleague Enid Johnson reported the successful use of curare in 43 patients to provide muscular relaxation during surgical anesthesia in 1942.[235] They concluded that the agent provided relaxation without interfering with respiration. This was followed by a study in Iowa by Stuart Cullen[236] (1909-1979), who enthusiastically supported use of the drug to provide muscular relaxation without the need for deep levels of general anesthesia. T. Cecil Gray[237] (1913-) of Liverpool popularized the drug in England and developed an anesthetic technique consisting of profound muscular paralysis and nitrous oxide–oxygen anesthesia. Phyllis Harroun[238,239] used

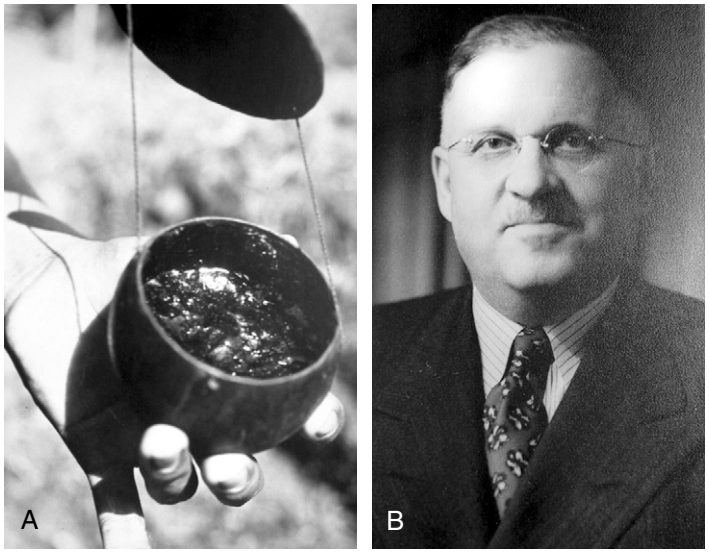


Figure 1-14 A, Richard Gill returned from Ecuador in 1938 with 11 kg of a dark tarlike paste from which Squibb and Sons, Inc., prepared the sterile, injectable solution Intocostrin. **B,** Harold Griffith and Enid Johnson (not shown) used Intocostrin in 43 abdominal surgeries with success in 1942. *(Courtesy of the Guedel Memorial Anesthesia Center, San Francisco, CA.)*

high-dose curare, nitrous oxide, and morphine for thoracic surgery, thereby providing muscular relaxation without the use of flammable agents, a novel technique at the time. In 1947, William Neff used nitrous oxide and oxygen supplemented with meperidine and curare and reported favorable anesthetic conditions. Although Griffith and Cullen had both maintained spontaneous respiration, the technique of Harroun, Gray, and Neff provided profound muscular paralysis with controlled respiration.

In a report from 1954, Henry K. Beecher (1907-1976) and D. P. Todd[240] concluded that the use of curare led to a nearly sixfold increase in postoperative complications and deaths. Similar cautionary articles followed their report but were refuted by others. Churchill-Davidson and Richardson[241] advised in 1952 that a useful technique for monitoring the degree of neuromuscular blockade was to stimulate a peripheral nerve and observe the resulting muscular contraction. Specific devices designed to stimulate the ulnar nerve were promoted in the 1960s.[242,243] Various modifications of the stimulus array to ensure complete return of neuromuscular function before allowing the patient to breathe unassisted have been described since that time.[244]

Since the introduction of curare into anesthesia practice, numerous additional neuromuscular blocking agents have been developed. Gallamine triethiodide was introduced in 1947, but like curare, it had undesirable effects on the autonomic nervous system, which prompted a search for other drugs. Exploration of the structure-activity relationships of plant alkaloids led to development of the methonium compounds. In 1949, the neuromuscular blocking activity of one of this class of drugs, succinylcholine, was recognized,[245] and it was introduced clinically soon thereafter.[246] Daniel Bovet (1907-1992) won the Nobel Prize in 1957, in part related to his discovery of gallamine and succinylcholine. Succinylcholine and other similar agents were shown to depolarize the end plate, thereby preventing additional motor contractions as a result of activity in the motor nerve. Advances in chemistry allowed the synthesis of neuromuscular blocking agents that lacked the autonomic effects of curare. Since the discovery of curare, nearly 50 neuromuscular blocking agents have been introduced, but many of these drugs have been abandoned because of undesirable side effects. Drugs that have maintained favorable safety records are steroid-based synthetic neuromuscular blocking agents such as pancuronium (1966),[247] vecuronium (1980),[248,249] and rocuronium (1991),[250] and they have replaced older drugs such as curare and gallamine in the modern drug armamentarium.

Anesthesia Apparatus

Early Delivery Systems

For the first public demonstration of ether anesthesia, Morton used a specially constructed glass bottle with an attached mouthpiece (see Chapter 25). In England, John Snow developed a new type of ether inhaler and took up the practice of ether anesthesia as a full-time endeavor. His apparatus provided valves to prevent rebreathing, and although he experimented with methods for absorption of carbon dioxide, he did not develop it into a clinically useful technique. John Snow was aware of the difficulties associated with the simple mouthpiece that was used with a noseclip by Wells and Morton. In his book on ether published in 1847, he states the following:

> *For some of the adult patients, after they lost their consciousness, made such strong instinctive efforts to breathe by the nostrils, that the air was forced through the lachrymal ducts, and occasionally they held the breath altogether for a short time, and were getting purple in the face, when the nostrils had to be liberated, for a short time, to allow respiration of the external air, and thus a delay was occasioned.*

Many types of anesthesia machines were developed to provide anesthesia via the insufflation method, whereby a small catheter was placed with its tip near the carina to deliver air and ether or chloroform. These continuous-flow machines did not rely on respiratory movement for oxygenation and were based on the work of Samuel Meltzer (1851-1920) and John Auer (1875-1948), who demonstrated their safe use in animals.[251] It was one

solution to the problem of pneumothorax and respiratory decompensation during thoracic surgery. C. A. Elsberg's (1871-1948) continuous-flow machine was described in 1911 and went through several modifications.[252] The popular Shipway model was used by Francis E. Shipway (1875-1968) to provide anesthesia to King George V of England for rib resection and drainage of empyema, a feat for which Shipway was knighted. In retrospect, it is clear that these continuous-flow machines were not capable of eliminating carbon dioxide in all cases,[253] and anesthesia machines eventually were developed that allowed to-and-fro respiration through one large-bore endotracheal tube.

Compressed Gases and Reducing Valves

Of major importance in design of the modern anesthesia machine was compression of gases in metal cylinders. Oxygen and nitrous oxide were available under compression as early as 1885 through the manufacturers S. S. White of Philadelphia and Messrs. Coxeter of London. This allowed the development of compact machines capable of prolonged delivery of anesthetics without the cumbersome feature of low-pressure reservoirs. Frederick Hewitt's first anesthetic gas machine designed for administering oxygen and nitrous oxide mixtures had two nitrous oxide cylinders and one oxygen cylinder; the mixture was fed into a large breathing bag through a double cylinder yoke.[98] Oxygen concentrations could be adjusted at the stopcock near the mask. His preferred oxygen concentrations were 5% to 8%. With the addition of oxygen, he attempted to "dispense with cyanosis, jerky and irregular breathing, deep stertor and clonic movements of the extremities."

Invention of the reducing valve is accredited to Jay Albion Heidbrink (1857-1957), an anesthesiologist from Minneapolis who observed that the opening from high-pressure cylinders often froze closed as the gases were released. He described a valve that reduced the high tank pressures to working pressures and incorporated this device into his Heidbrink Anesthetizer. In Germany, Heinrich Drager (1847-1917) and his son Bernhard Drager (1870-1928) developed reducing valves to control an even, accurate flow of carbon dioxide gas drawn from beer cylinders, and these valves were later used in the early anesthesia machines. Further refinements to the early machines were added by James T. Gwathmey and H. Edmund G. Boyle (1875-1941), chiefly through the addition of bubble-through heated water baths for estimation of gas flow. The Boyle machine passed various amounts of oxygen through ether with a "water-sight" meter. This flow meter estimated the flow through the vaporizer from how many of the holes were generating bubbles. Heidbrink further improved the flow meter by using an inverted float in a tube of varying taper with calibrations marked on the side. Rotating floats, also called rotameters, have slanted grooves cut into the rim that cause them to rotate, and they are more accurate than ball or nonrotating floats. Rotameters were introduced in 1908 by Karl Kuppers and first used in anesthesia in 1910.

Carbon Dioxide Absorption

Anesthesiologists from the first half of the 20th century were not privileged to visit just one hospital during a day's work. Visits to several institutions might take place in a single day, with the practitioners bringing their own delivery systems and drugs with them as they traveled. Understandably, portability and elimination of waste were a priority because these anesthesiologists paid for the agents themselves. One development that conserved gases and vapors was the use of systems that absorbed expired carbon dioxide and allowed rebreathing of expired gases.

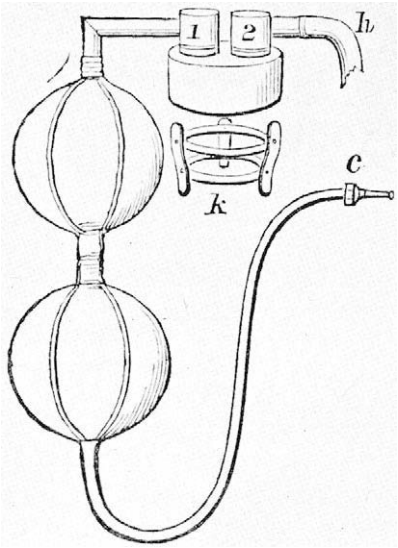


Figure 1-15 Alfred Coleman's economizing device. The anesthetic gases entered the lower bag and passed into the upper bag through a one-way valve. Gases were inhaled and exhaled through the tube (h) and passed over a lime container (1, 2) held in a frame (k) that eliminated carbon dioxide; c, gas inlet. The conserved gas in the upper bag was used during a later anesthetic administration. *(From Coleman A: Mr. Coleman's economizing apparatus for re-inhaling the gas. Br J Dent Sci 12:443, 1869.)*

Several ineffectual attempts were made to introduce carbon dioxide absorption methods in the 19th century. John Snow and Alfred Coleman (1828-1902) were motivated to conserve anesthetic gases that escaped into the atmosphere through nonrebreathing valves. Coleman devised a system of absorbing carbon dioxide by passing the expired gases over slaked quick lime.[254] The recovered gases were then used for subsequent anesthetics (Fig. 1-15). Franz Kuhn (1866-1929) described soda lime absorption of exhaled carbon dioxide in 1905, but the report did not attract attention.

Dennis E. Jackson (1878-1980) demonstrated the use of soda lime absorption to maintain stable levels of anesthesia for several hours in animals with minimal ether consumption.[255] The animals were given additional oxygen to meet metabolic needs, but the anesthetic gases were rebreathed, thereby resulting in economy and improved maintenance of body temperature and airway humidity. In 1923, Ralph Waters (1884-1979) (see Fig. 1-18B), then working as an anesthesia practitioner in Sioux City, Iowa, contacted Jackson and devised a soda lime canister for clinical use.[256] The canister was attached to a breathing hose close to the face, and although it was cumbersome to use, the device was widely distributed. The in-line soda lime canister launched the academic career of Waters, who later became one of the most prominent figures in anesthesiology during the first half of the 20th century. In 1930, Brian C. Sword[257] altered the Waters canister by attaching it to the chassis of a movable cart with two hoses directed to the airway, one for inspired gases and one for exhaled gases.

Controlled Vaporizers

With the introduction of more potent volatile anesthetics such as halothane it became important to control the concentration of inspired vapor carefully. To solve this problem, Lucien Morris[258] invented the copper kettle to vaporize liquid anesthetics. Its advantage rested on the fact that as the agent was vaporized, there was little change in the temperature of the anesthetic liquid. The copper kettle could be used with any agent provided that the practitioner was cognizant of the vapor pressure of the agent and the flow rates of the inspired gases. Without the addition of diluent gases such as nitrous oxide or oxygen, the copper kettle could deliver lethal concentrations of vapor. The vaporizers in common use today use bimetallic strips that bend as the temperature drops and permit more fresh gas to enter the vaporizing chamber. Vaporizers have been designed for all the agents in use today, including halothane, enflurane, isoflurane, desflurane, and sevoflurane. Modern anesthesia machines are also equipped with scavenging systems designed to minimize escape of anesthetic vapors and nitrous oxide into the operating room. Although controversial, some studies have shown that daily exposure to anesthetic vapors in low concentrations can have deleterious side effects.

Ventilators in the Intensive Care Unit

The earliest ventilator, the Fell-O'Dwyer apparatus, was described in 1892.[259] It was used as early as 1896 to provide respiratory support in cases of opium poisoning. Rudolph Matas, a surgeon in New Orleans who contributed significantly to the early development of regional anesthesia in the United States, was one of the first to use the Fell-O'Dwyer ventilator during thoracic surgery.[260] During the polio epidemic, thousands of afflicted patients were kept alive with the Drinker respirator,[261] often referred to as the *iron lung*, a negative-pressure device that surrounded the patient and provided air movement into and out of the lungs. A Swedish ventilator called the Spiropulsator was introduced in 1934 and modified in 1947 by E. Trier Moerch (1908-1995).[262] This ventilator used a piston pump to deliver a fixed volume of gas. Ventilators today are usually an integral part of the anesthesia machine and direct compressed air into a rigid container containing a bellows that inflates the lungs. Bjørn Ibsen[263] (1915-), a Danish anesthesiologist, initiated the concept of intensive care units in the early 1950s to care for polio patients and guided the transition from iron lungs to modern ventilators. Intensive care units have since become an integral part of the modern hospital, with anesthesiologists actively involved in their daily operation.

Stress-Free Anesthesia

Procedures before the discovery of anesthesia were necessarily of short duration. Raper relates that surgical cases lasting longer than 20 minutes would usually result in death of the patient because the stress associated with such intense nociception would exhaust the patient's reserves. Highly stressful procedures such as abdominal surgery were rarely attempted before 1846. Ephraim McDowell[264] (1771-1830), a rural surgeon from Kentucky, performed the first successful intraperitoneal procedure when he excised a 10-kg ovarian cyst from Mrs. Jane Todd Crawford in 1809. McDowell's publication of the case achieved for him a small measure of fame, unusual for a rural practitioner. However, intraperitoneal procedures are among the most highly stressful operations, and McDowell's accomplishment was rarely repeated. The first successful upper abdominal procedure occurred only after the advent of general anesthesia. Theodor Billroth (1829-1894) performed the first gastrectomy with chloroform anesthesia on January 29, 1881.

The idea that reduction of perioperative stress had a beneficial effect on recovery was championed by George W. Crile (1864-1943), chief surgeon at the Cleveland Clinic at the beginning of the 20th century. Crile's operative technique was to infiltrate all tissues with dilute procaine before incision. Patients were lightly anesthetized by mask inhalation of nitrous oxide and oxygen.[265] He describes these concepts of stress-free anesthesia in his book *Anoci-Association*, published in 1914.[266]

An early devotee of Crile's ideas was the prominent neurosurgeon Harvey Cushing[267] (1869-1939), who promoted the use of regional blocks before emergence from ether anesthesia to ensure a smooth postoperative course. Cushing was the first surgeon to use blood pressure measurements on his patients after he learned the Rovi-Rocci method in Italy (Fig. 1-16). Accurate anesthetic records were maintained during Cushing's cases and confirmed his opinion that shock could be prevented by careful attention to avoiding the stresses associated with surgery.

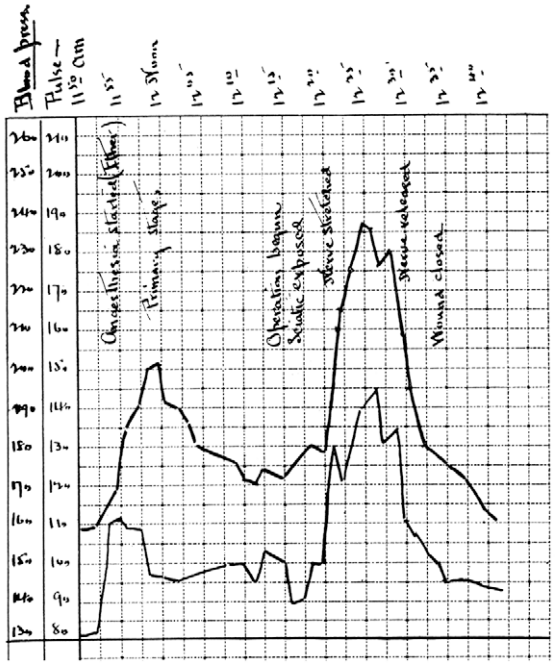


Figure 1-16 One of Harvey Cushing's early anesthesia records shows systolic blood pressure (*top tracing*) and pulse rate (*bottom tracing*). The first rise in blood pressure occurred during the excitement phase of ether induction, and the second rise occurred during the release of adhesions of the sciatic nerve. *Vertical lines* take place 2.5 minutes apart. Systolic blood pressure rose to greater than 230 mm Hg during the operation. Cushing was an early proponent of regional anesthesia, possibly stemming from his observations on blood pressure and heart rate.[267] *(From Cushing H: On routine determination of arterial tension in operating room and clinic. Boston Med Surg J 148:250-256, 1903.)*

Crile's ideas have had a significant impact on how the modern anesthesiologist defines general anesthesia. In 1957, P. Woodbridge[268] defined general anesthesia as consisting of four components: (1) sleep or unconsciousness, (2) blockade of undesirable reflexes, (3) motor blockade, and (4) sensory blockade. These ideas have been discussed and modified by M. Pinsker[269] into three components: (1) paralysis, (2) unconsciousness, and (3) attenuation of the stress response. Lundy's balanced anesthesia is another formulation of the idea that several drugs can be used in combination to produce the state of unconsciousness and analgesia that we define as general anesthesia.

An enduring question during the past century, since Crile's introduction of the concept of stress-free anesthesia, has been how to evaluate the analgesic component of the ideal general anesthetic. Michael Roizen[270] (1947-) observed in 1981 that general anesthetics did not prevent the increase in sympathetic activity in response to a skin incision, even in concentrations that prevented movement. Surgical stimulation often results in intraoperative hypertension and tachycardia, with the corollary that interventions that prevent these hemodynamic reflexes provide "analgesia." Hemodynamic instability was of marginal significance until surgeons began to operate on patients with significant ischemic heart disease. Studies have demonstrated that perioperative β-adrenergic blockade reduces the risk for perioperative myocardial infarction in patients at risk for this complication.[271]

It became apparent that intravenous opioids were highly successful in ablating the hemodynamic markers of stress. Edward Lowenstein and coworkers[272] used large doses of morphine to stabilize the heart rate and blood pressure during cardiac surgery. In 1967, the short-acting opioid fentanyl was introduced to provide intraoperative hemodynamic stability. Theodore H. Stanley and colleagues[273] reported its successful use in large doses for cardiac surgery without the side effect of histamine release that sometimes occurs after administration of morphine. Other short-acting opioids tailored for the anesthesiologist have been added since that time. Alfentanil, sufentanil, and remifentanil have different pharmacokinetic profiles that make them suitable agents for selected procedures. Naloxone, a specific antagonist for this class of drugs, was first used clinically in 1971.[274] Increased understanding of opioid pharmacology has opened up a new role for anesthesiologists, including acute pain management. Rapid detoxification of opioid addiction by using general anesthesia combined with opioid antagonism is a new technique that if combined with judicious follow-up, can be a useful treatment of this condition.[275]

The combination of opioids with tranquilizers such as phenothiazines and butyrophenones provides a form of anesthesia called neuroleptanesthesia, which was introduced by DeCastro and Mundeleer[276] in 1959. Patients administered this form of anesthesia are immobile and tranquil and have stable hemodynamics, even during major surgical procedures. One goal of this technique is to block the autonomic and endocrine response to stress. This unique method of providing anesthesia is another technique for ablating the stress response, but unless other agents such as nitrous oxide or other intravenous agents are administered, there can be a high incidence of awareness. Side effects from dopamine antagonism, such as dysphoria and uncontrolled extrapyramidal motor movements, have limited the widespread use of neuroleptanesthesia.

During the past 30 years, several investigators began a series of studies to measure markers of the stress response during and after surgery. It was learned that during major surgery, patients anesthetized with traditional vapor anesthetics, with or without opioids, displayed increased levels of catabolic hormones postoperatively.[77] Significant elevations in catecholamines and in adrenocorticotropic hormone, cortisol, antidiuretic hormone, and growth hormone were observed. Various methods of preventing postoperative catabolism have been under investigation for several years. The resulting catabolic state is thought by some to delay recovery and, with some operations, can be prevented with the use of neuraxial blockade.[77,277,278] It is apparent from recent reviews on this subject that the formulations of George Crile are still valid 100 years after he promoted them and are likely to be the subject of further studies in the future.

Airway Management and Resuscitation

Masks and Airways

Ventilation during anesthesia was managed without specialized airway devices for more than 50 years after Morton's discovery, and a survey of anesthetic complications during this era attests to the relative safety of inhalation techniques in spontaneously breathing patients (see Chapters 50 and 93). Deaths occurred during this era, and in some reports the anesthetic death rate was alarmingly high, but an obstructed airway was rarely mentioned as the primary cause of death. Friedrich von Esmarch[279] described the jaw thrust (Fig. 1-17) as a lifesaving maneuver in some cases of airway obstruction that resulted from chloroform or asphyxia:

> *Press the lower jaw forwards with both hands by placing the forefingers behind the ascending ramus . . . by this movement the hyoid bone and root of the tongue, and the epiglottis are drawn forwards, and the entrance to the larynx is thus freed from obstruction.*

In 1874 the same maneuver had been previously described, but not popularized by J. Heiberg, a Norwegian surgeon.

Various problems with the Morton inhaler in the United States led to abandonment of inhalers in favor of a simple towel or sponge saturated with ether. In 1850, John Warren,[280] in his

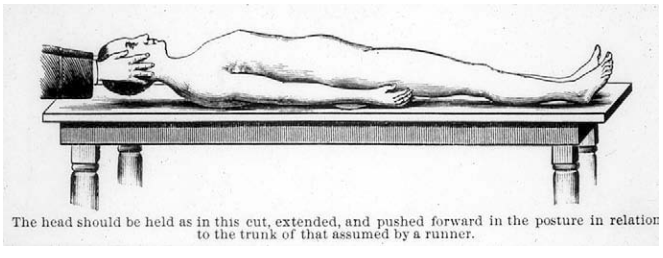


Figure 1-17 Illustration in a treatise by von Esmarch[279] showing the technique of maintaining an open airway in an unconscious patient. *(From von Esmarch F: Handbuch der kriegschirurgischen Technik. Hanover, Carl Rumpler, 1877.)*

address to the American Medical Association, described his preferred technique for administration of ether at the Massachusetts General Hospital: (1) no oral intake for at least 3 hours before surgery, (2) a horizontal position for induction, (3) bleeding the patient before surgery for bloodless operations, (4) pulse and respiration watched carefully by an assistant to the anesthetist, (5) ether applied with a large sponge soaked with ether, and (6) avoidance of cautery.

Several wire frame masks were devised to replace the sponge or folded towel. The popular mask devised by Curl Schimmelbusch (1860-1895) had a trough-shaped rim to prevent liquid chloroform or ether from dropping onto the patient's face. Friederich von Esmarch[279] used a wire mask with a clip that enabled it to be strapped to the patient. The advantages of these masks were low cost, simplicity, and portability. Disadvantages included delivery of vapor throughout the operating room, cooling of the patient, and waste of anesthetic agent.

Development of the modern facemask originated with Francis Sibson[281,282] (1814-1876), who devised a mask made of pliable tinned iron and covered with glove leather. The mask covered the mouth and nose and therefore eliminated the need for noseclips. Snow quickly recognized the superiority of the Sibson mask and incorporated it into his practice.

The first anesthetics were of short duration and rarely required special devices to maintain patency of the airway. With the increasing complexity and duration of surgical procedures, special devices were fashioned to facilitate an open airway. Frederick Hewitt promoted a simple metal tube that projected through the mouth into the hypopharynx. The commonly used Guedel rubber curved airway was described in 1933.[283] At the same time, cuffs were sometimes used on oral airways, a design that has been resurrected in the form of a modern product, the cuffed oral pharyngeal airway (COPA).

Tracheal Tubes

In the 18th century, tubes were passed into the trachea during resuscitation from drowning, but these tubes were passed without direct visualization and were not used for delivery of anesthetic agents. Similarly, the intubations of pediatrician Joseph O'Dwyer (1841-1898) in cases of diphtheria were performed with metal tubes passed blindly.[284] The O'Dwyer metal tube was later attached to a bellows by George Fell (1850-1918) for the treatment of opioid respiratory depression. Placement of tracheal tubes was vigorously opposed by the influential Parisian surgeon Armand Trousseau (1801-1867), who quoted the failures experienced by M. Bouchut in attempting to pass metal tubes for airway obstruction. Bouchut had lost five of seven patients during his procedure, called *le tubage du larynx*, and the other two were rescued only by tracheotomy.[285] Trousseau was the first to perform a tracheotomy in Paris and wrote a treatise promoting its use during airway compromise in 1851.

John Snow had administered chloroform through tracheotomy tubes in animals, and Friedrich Trendelenburg (1844-1924) used the same technique in humans.[286] Sir William Macewen (1848-1924) was the first physician to intubate the trachea orally for the sole purpose of administering anesthesia, and it was done to permit continued administration of chloroform during an operation in the mouth. On July 5, 1878, Macewen[287] performed a blind oral intubation on an awake patient with an ulcerating epithelioma of the tongue. An extensive operation was performed, and the results were excellent. Subsequently, Macewen tracheally intubated three other patients, two for edema of the larynx, and a fourth for another surgical procedure in the mouth. In the fourth case, the pulse was suddenly lost after chloroform was administered, and the patient died on the table.

The use of tracheal intubation was accelerated to meet the needs of surgeons operating on the face and in the thoracic cavity. To operate within the thoracic cavity, some means was required to avoid respiratory compromise, which followed the inevitable pneumothorax when the chest was opened. Ernst Ferdinand Sauerbruch[288] (1875-1951) studied the problem as a young assistant to Johann von Mickulicz-Radecki (1850-1905) in Breslau, Germany, and his solution, the Sauerbruch Box, elevated him into a position of international prominence at a young age. The Sauerbruch Box was a cumbersome solution to the problem of pneumothorax and entailed placing the surgeon and the patient (below the neck) in a negative-pressure chamber while the head of the patient and the anesthetist were outside the box at normal atmospheric pressure. The use of such an awkward construction indicates that surgeons were determined to solve this problem at any cost. The modern solution, endotracheal intubation and controlled ventilation, as it unfolded was relatively simple, but it took several years to become established.

Franz Kuhn (1866-1929) perfected a flexible metal tube and used blind oral or nasal intubation for anesthetic purposes when the surgeon operated in the mouth. Kuhn's first report on tracheal intubation was in 1905 and included an extensive description of a technique using carbon dioxide absorption cartridges. He proposed but did not use inflatable pharyngeal cuffs to prevent air leaks. Insertion of catheters directly into the trachea to insufflate anesthetic agents was begun in the first decades of the 20th century. With this method, gases were introduced under continuous pressure through catheters that allowed exhalation through the space between the catheter and tracheal wall.

The use of to-and-fro respiration through one large-bore endotracheal tube is credited to Ivan W. Magill[289] (1888-1986) (Fig. 1-18A) and Edgar S. Rowbotham[290] (1890-1979) to meet the demands of the maxillofacial surgeon. Their technique of blind nasal intubation was to position patients as if they were "sniffing the morning air." Occasional failures of blind intubation were solved with a special instrument designed by Magill to lift the tube off the posterior wall of the pharynx into the glottic opening. The so-called Magill tubes were formed to fit the airway and were made of red mineralized rubber. The cuffed endotracheal tube was promoted by Arthur Guedel (1883-1956) (Fig. 1-19) and Ralph M. Waters (1883-1979) (see Fig. 1-18B) in 1928,[291] and this refinement allowed the use of intermittent, controlled, positive-pressure ventilation and the potential for one-lung ventilation, introduced by Gale and Waters in 1932.[292] Four years later, Magill introduced the bronchial blocker to confine the secretions of an infected lung to one side. Magill's technique was to pass the blocker before induction of anesthesia with a specially designed bronchoscope.[293] Double-lumen tubes for bronchospirometry were introduced by Carlens in 1949,[294] but the small lumen size made these tubes inconvenient for anesthetized subjects. The commonly used disposable double-lumen tubes in use today are modeled after the Robertshaw tube[295] for the left side and after the Green-Gordon tube[296] for the right side. An opening called the Murphy eye, on the side of the standard endotracheal tube,

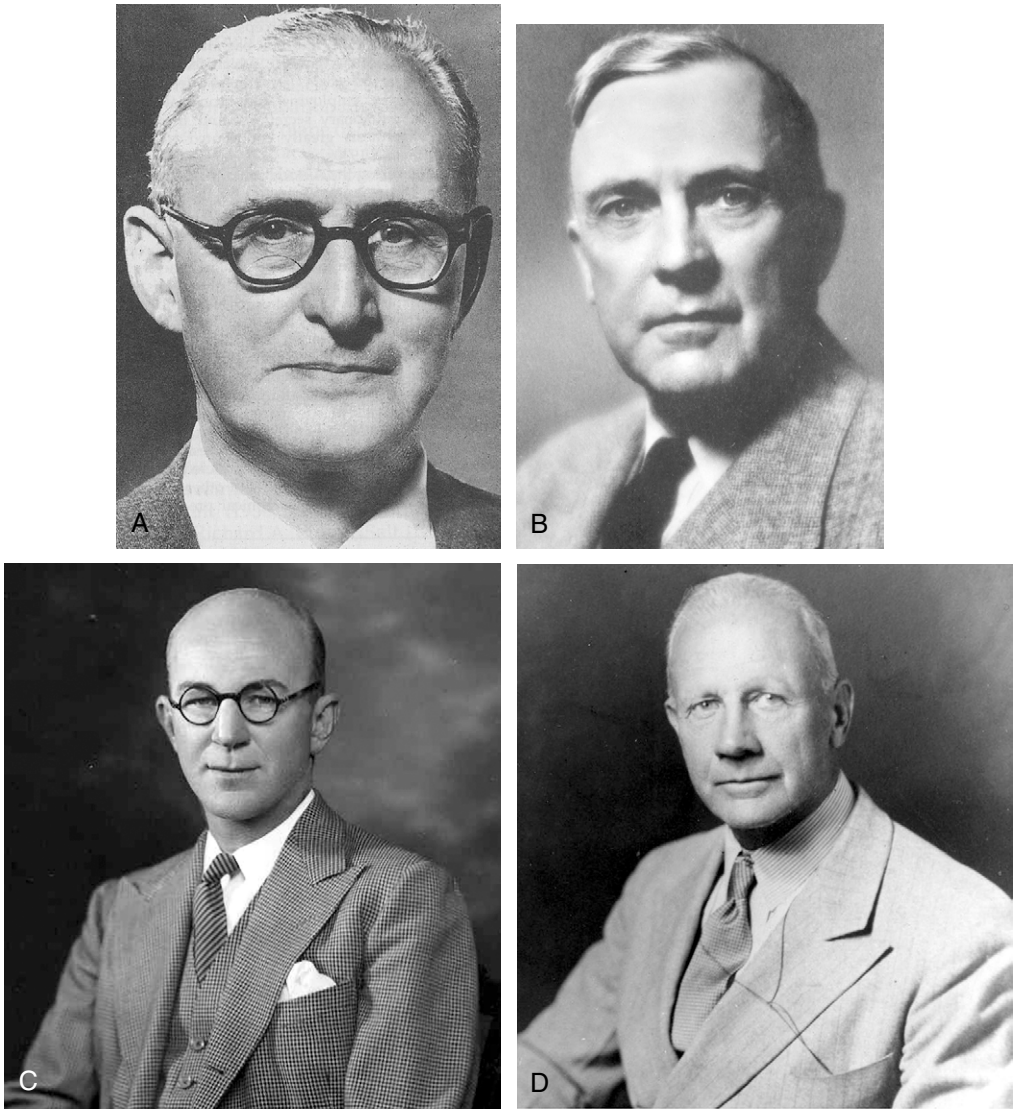


Figure 1-18 Prominent anesthesiologists of the 20th century. **A,** Sir Ivan Whiteside Magill (1888-1986) was born in Larne, Northern Ireland. He obtained a medical degree from Queen's University, Belfast, in 1913. During World War I, he served with the Irish Guards in the Medical Corps. After the war, he and Stanley Rowbotham (1890-1979) pioneered the use of large-bore endotracheal tubes to allow plastic surgeons to operate on the facial injuries of wounded soldiers. He designed many pieces of equipment for the anesthesiologist, some of which are still used today. Before his death at the age of 98 years, he received many awards, including a knighthood awarded personally by the Queen of England in 1960 and the Henry Hill Hickman Award. **B,** Ralph M. Waters was born in North Bloomfield, Ohio, and obtained his medical degree from Western Reserve University in Cleveland. He began his career in general practice in Sioux City, Iowa, and specialized in delivering anesthesia in 1916. Waters established the first academic program of anesthesiology in Madison, Wisconsin, in 1927. His contributions were many and included the carbon dioxide absorption method, endobronchial anesthesia for thoracic surgery, and introduction of cyclopropane. His chief legacy is the many residents he trained who then became leaders within the specialty in the following generation. **C,** Sir Robert R. Macintosh (1897-1989) was born in New Zealand and was a prisoner of war during World War I. He finished medical training in London after the war and began the practice of anesthesia there. In 1937, he was appointed the first Nuffield Professor of Anaesthetics at Oxford University. He was primarily a clinician, and his innovative techniques of airway management were eventually accepted worldwide. He received honorary degrees from universities in several countries and was knighted in 1955. **D,** James T. Gwathmey was born in Roanoke, Virginia, in 1865 and graduated from the Vanderbilt School of Medicine in 1899. In 1903, he limited his practice to the administration of anesthetics, and he is considered one of the first full-time private practice physician-anesthesiologists in the United States. He devised several innovations for the delivery of anesthetic gases and introduced these machines to his European colleagues during World War I. He was an original member of the Long Island Society of Anesthetists, which eventually evolved into the American Society of Anesthesiologists. *(Courtesy of the Wood-Library Museum of Anesthesiology, Park Ridge, IL.)*



Figure 1-19 Photograph of Arthur Guedel while he was serving in the American Expeditionary Forces in France during World War I. During the war, he was responsible for the safe administration of thousands of anesthetics, often delivered without properly trained personnel. As a guide for teaching nurses and orderlies to administer ether, he devised a wall chart describing the various stages and planes of ether anesthesia that eventually resulted in his classic publication on this topic in 1919. He used a drug sequence of ethyl chloride, chloroform, and ether, which prepared the patient for surgery within 2 minutes.[353] *(Courtesy of the Guedel Memorial Anesthesia Center, San Francisco, CA.)*

was suggested in 1941 as an alternative air passage in the event of distal tip occlusion.[297]

Laryngoscopes

Although blind or tactile tracheal intubation of awake patients could be mastered with extensive practice, an improved technique to accomplish tracheal intubation was developed by Alfred Kirstein[298,299] (1863-1922), Chevalier Jackson[300] (1865-1958), and Gustav Killian (1898-1912), all contributors to the introduction of the hand-held laryngoscope. Before the pioneering efforts of these innovators, the only way to visualize the larynx was by indirect laryngoscopy, a technique introduced by the Spanish singing instructor Manuel Garcia (1805-1868). In 1854, Garcia read a paper before the Royal Society titled "Observations on the Human Voice," wherein he described his use of mirrors to view his student's and his own larynx during vocalization.[301] Alfred Kirstein was charting unknown territory in 1895 when he boldly suggested that the larynx could be directly visualized with instruments similar to the commonly used esophagoscope.[298] Although he abandoned the procedure after 1 year, it was revived 3 years later by Gustav Killian,[302] whose portable laryngoscope was remarkably like the current instrument, but with no light attached.

Direct laryngoscopy did not gain in popularity among anesthesiologists until Chevalier Jackson promoted the use of his hand-held laryngoscope for insertion of tracheal insufflation catheters. Even then, the technique was slow to gain acceptance, but the accelerated use of muscle relaxants eventually required the anesthesiologist to be adept at rapid placement of tubes within the trachea. The first hand-held laryngoscopes, as perfected by Jackson, were U shaped and had no curve at the tip. A light at the end of the blade was a unique contribution by Jackson that has been retained, with the modification that some instruments today use a fiberoptic bundle in the blade.

Anesthesiologists soon began to design their own laryngoscopes that were more suitable for insertion of endotracheal tubes. Robert A. Miller[303] designed a new blade that was remarkably similar to Killian's instrument, except for a slight curve at the distal end. Robert R. Macintosh's (1897-1989) (see Fig. 1-18C) improved laryngoscope featured a short, curved blade that elevated instead of retracted the epiglottis.[304] This promoted a new concept in laryngoscopy specifically designed with the anesthesiologist in mind for timely tracheal intubation. Many intubations were then performed without muscle relaxants, and the Macintosh blade was able to expose the glottis without coming into contact with the sensitive posterior surface of the epiglottis. By this time a detachable joint had been placed between the blade and the handle. The batteries were located in the handle, thereby conveniently avoiding the trailing wires attached to the distal bulb.

Alternatives to the Laryngoscope

Unfortunately, not all patients could be successfully intubated with the hand-held laryngoscope. Several new blades were developed in the 1940s and 1950s to solve the problem of a difficult airway, but none were 100% successful, and it soon became apparent that some airways could not be intubated with any hand-held instrument. In such cases, the few remaining members of the hospital staff who had been trained in blind tactile intubations were called in to secure the airway.

The problem of a difficult or impossible intubation is now solved with a variety of tools, including various modifications of the laryngeal mask airway (LMA) and the flexible laryngoscope, both established tools in the modern anesthesia department. The LMA was developed by A. J. Brain of the Royal Berkshire Hospital, Reading, England, with the commercial product first appearing in 1983.[305] This device is well named, for it is indeed a small mask that covers the glottic opening. The LMA eliminates the need for tracheal intubation in many cases and is useful in managing a difficult airway.

The beginnings of flexible laryngoscopy were rooted in the 19th century. John Tyndall (1820-1893) succeeded the more famous Michael Faraday as Superintendent of the Royal Institution in London in 1867 and published his observation in 1854 that light could follow a curved path through a water tube. In 1930, H. Lamm[306] used this property of light when he introduced the flexible gastroscope, with glass fibers used instead of water. S. Ikeda[307] transferred the same technology to a smaller-diameter instrument and thereby introduced flexible bronchofiberoscopy in 1968. The definitive work followed in 1971.[308]

Resuscitation (see Chapter 97)

Resuscitation from drowning was successfully accomplished by a variety of methods as early as 1792, when James Curry used digital intubation of the trachea and forced air into the lungs with a bellows (see Chapters 93 and 97). J. Leroy criticized the use of

positive pressure with bellows as a dangerous procedure in 1827 by showing that it could rupture the alveoli and produce fatal tension pneumothorax. Consequently, several ineffectual techniques developed, such as administration of stimulating vapors, swinging the arms up and down, and pulling the tongue forward in a rhythmic motion, and these futile techniques were slow to dissipate. Largely through the work of O'Dwyer, Tuffier, and Matas, positive-pressure methods were reintroduced in the first few decades of the 20th century. James O. Elam (1918-1995) instinctively demonstrated the efficacy of mouth-to-mouth ventilation in 1946 when ventilators were in short supply during the polio epidemic. Peter Safar (1924-2003) and Elam were influential in converting teaching of the ineffectual arm-lift method to mouth-to-mouth breathing techniques by demonstrating the proficiency of the later technique on volunteer medical students.[309,310]

Rational methods of resuscitation from full cardiac arrest awaited development of the electrocardiogram and its interpretation. Augustus Waller[311] (1856-1922) first produced tracings of the electrical activity of the heart in 1887, but Willem Einthoven[312] (1860-1927) is credited with producing the first modern electrocardiogram by using a string galvanometer in 1903. Tracings compatible with occlusion of the main coronary vessels were demonstrated first in animals and then confirmed in patients by James B. Herrick[313] (1861-1954) of Chicago. John MacWilliam[314] (1857-1937) described ventricular fibrillation in 1887 and provided a case report showing it to be the cause of death in one subject.[315] In 1899, J. L Prevost and F. Battelli[316] showed that small electrical currents passed across the heart could induce ventricular fibrillation and that larger currents could convert fibrillation to a normal rhythm. Claude Beck[317] (1894-1971) performed the first successful use of electric defibrillation in a patient in 1947.

Open cardiac massage was first performed in Norway in 1901[310] and in the following year by Starling,[318] and external massage over the chest was described by W. W. Keen (1837-1932) in 1904.[319] Brief anecdotal reports had been presented on closed chest massage as early as 1883 by Franz Koenig of Göttingen, Germany.[320] William B. Kouwenhoven (1886-1975), Dean of the School of Engineering at Johns Hopkins from 1939 to 1953, began his studies on resuscitation from cardiac arrest in 1929 and 31 years later published the full sequence of external cardiac massage, combined with electric countershock, to restore cardiac rhythm.[321] These methods of resuscitation have been promoted by the American Heart Association and, with some modifications, have become the basis for the widely disseminated educational programs of advanced cardiac life support (ACLS).

Anesthetic Accidents and Complications—Preventive Measures

Anesthetic accidents have occurred since the early days of administration of ether and nitrous oxide. Wells and Morton described patients who required resuscitative measures during anesthesia. Several near deaths were reported after the October 1846 demonstration. Bigelow's first description of ether anesthesia provides a case report of a patient who nearly died after ether administration and was resuscitated by cold effusions, ammonia inhalation, and syringing of the ears.[86] Two other patients "failed to be affected by ether." George Hayward (1791-1863) reported a death occurring after ether inhalation in August 1847. Snow's book on chloroform appeared in 1858 and discusses a number of frightening cases and deaths during administration of anesthesia. The first such tragedy with chloroform struck in 1848, when an anesthetic was given to a 12-year-old girl, Hannah Greener, for a minor surgical procedure. The postmortem examination of this young girl was inconclusive, but the anesthetic was thought to have been administered properly. The controversy surrounding this death has occupied the minds of numerous anesthesiologists for the past 150 years.[322,323]

Most anesthetic deaths were not attributed to the agent or the method of administration but resulted simply from "the patient not taking the anesthetic well." A frequent diagnosis after death during anesthesia was the vague syndrome of "status lymphaticus."[324] Although this phrase was convenient for the anesthesiologist to use, it thwarted a review of causes that might help prevent future disasters. A major change occurred in anesthetic practice with the introduction of morbidity and mortality conferences to examine causes of anesthetic accidents. Originally introduced by Ralph Waters in Madison, Wisconsin, these meetings sought to carefully scrutinize anesthetic complications, thereby shifting the focus of investigation from the patient to the provider and the equipment used to deliver the anesthetic. The postanesthesia care unit, originally designated the recovery room, was promoted for safety reasons by two anesthesiologists from Washington, D.C., in an influential paper in 1951,[325] and these units are now mandated by the accreditation process for all hospitals.

Curtis L. Mendelsohn, an obstetrician from New York City, presented one of the early useful reports of anesthetic complications. In 1945, he reported 66 cases of aspiration of stomach contents during general anesthesia for labor and delivery.[326] He further observed that aspiration of even small volumes of low-pH stomach contents in rabbits would result in fatal pulmonary edema. Since his classic descriptions, the syndrome of acid aspiration is often called the Mendelsohn syndrome.

The cuffed endotracheal tube was one solution to the problem of acid aspiration. Authur Guedel and Ralph Waters were motivated to devise a truly closed system of anesthetic administration with carbon dioxide absorption that would conserve anesthetic gases and body heat. Their 1928 report of the cuffed endotracheal tube[291] achieved these goals with the added benefit of protection of the tracheobronchial tree from aspiration. Others had devised cuffed endotracheal tubes before them,[327] but Guedel and Waters used a novel method to demonstrate and promote the safety features of the cuffed tube. Guedel anesthetized and then intubated his pet dog, appropriately named Airway, with a cuffed endotracheal tube. The dog was submerged in a water tank for several minutes and then removed and awakened unharmed. The demonstration was repeated at several meetings, and this publicity enhanced rapid acceptance of the new endotracheal tube. The cuffed tube is regarded today as an effective measure for preventing acid aspiration.

In 1961, Brian A. Sellick[328] (1918-1996) described rapid-sequence induction for prevention of acid reflux. The method involves the application of firm pressure over the cricoid cartilage to occlude the esophagus during endotracheal intubation. John Hunter[329] had previously described the technique in 1776 for use in resuscitation of individuals "apparently drowned." Rapid-

sequence induction remains a popular technique for induction of patients at risk for acid aspiration.

Although few defects in apparatus could occur while applying ether onto a folded towel, the increasing complexity of the anesthetic delivery system brought with it the unfortunate side effect of equipment failure. One of the earliest equipment defects occurred with the simple Morton inhaler. George Hayward reported that a defective intake port led to restricted breathing, lividity, and convulsions in an elderly woman having a leg amputated in January 1847. Wrong gas, wrong agent, wrong concentration, sticky or jammed valves, contaminated agents, and hypoxic mixtures—all of these and others were reported as routes to disaster.

Open discussions of these complications led to adjustments in equipment design.[330] Pin indexing of gas cylinders and hoses eliminated the possibility of introducing air or nitrous oxide into the oxygen lines of the gas machine. In-line oxygen analyzers were placed on the inspiratory limb of the breathing circuit. Fail-safe devices prevented the use of any machine that was not supplied with oxygen. Uniform connectors were adopted, thereby providing rapid assembly of breathing circuits. The American Society of Anesthesiologists (ASA) initiated formation of the Z-79 Committee of the American Standards Institute. This committee recommended safe construction of endotracheal tubes, needles, and connectors. The American Society for Testing and Materials (ASTM), a not-for-profit organization that writes standards for materials and products (through their committee designated F-29), describes the requirements used in the design of safe anesthetic gas machines. The International Standards Organization is also developing global standards for anesthesia equipment.

Further progress in reducing anesthetic-related complications resulted from the formation of professional societies, specialty journals, and certification boards. One of the earliest journals limited exclusively to anesthesiology was *Current Research in Anesthesia and Analgesia*, founded in 1922 largely through the efforts of Francis Hoffer McMechan (1879-1939).[331] McMechan was an anesthesiologist who had retired at an early age for health reasons and devoted the remainder of his career to promoting organizational and political causes of anesthesiologists. An independent American Board of Anesthesiology was formed in 1940 and, through its examination process, continues to elevate standards of anesthetic care. Specialty societies of professional anesthesiologists have formed in most countries practicing modern anesthetic techniques. The ASA was founded as the American Society of Anesthetists in 1936 and currently has approximately 38,000 members. *Anesthesiology*, the official journal of the ASA, began publication in 1940. National anesthesia societies promote safe anesthetic practice through annual meetings, refresher courses, and direct communication with members. Practice guidelines for general anesthesia, obstetric anesthesia, and ambulatory surgery are sent annually to each member of the ASA. Subspecialty societies in cardiac, ambulatory, transplant, pediatric, neurosurgical, and obstetric anesthesia have been formed and strive to improve the anesthetic management of patients within their respective groups.

The Anesthesia Patient Safety Foundation (APSF) was conceived in October 1985, largely through the organizational efforts of Ellison C. Pierce, Jr. This highly successful organization promotes safe anesthesia practice through research grants and periodic mailings to members. As a result of these efforts, anesthesiologists have been recognized as forerunners in promoting agendas that enhance patient safety.[332,333]

Improved monitors have provided the anesthesiologist with methods to fine-tune anesthetic delivery and detect early signs of danger. Auscultation of the chest, an obligatory skill in the current era, had its beginnings in the early 19th century when Rene T. Laennec[334] (1781-1826) used a cylindrical paper tube to listen to the chest. The term *stethoscope* was a combination of the Greek words *stetho* ("chest") and *scope* ("I see") and was used by anesthesia providers as early as 1896 to monitor cardiac and respiratory sounds. The esophageal stethoscope, introduced in 1954 by C. Smith,[335] has been used extensively to detect breathing circuit disconnects, airway obstruction, and bronchospasm in anesthetized patients.

A. E. Codman (1869-1940) of Boston introduced the first anesthetic records in 1894, and the practice was encouraged by Harvey W. Cushing (1869-1939), who promoted recordings of blood pressure, pulse, and respiratory rate on all of his cases.[336] Practice guidelines for minimal monitoring standards were first issued[337] at the nine teaching hospitals of Harvard Medical School, and 2 years later, the ASA issued similar standards that included measures of oxygenation, ventilation, circulation, and body temperature. Electronic monitoring has contributed to the safe practice of anesthesiology significantly. Continuous electrocardiography displays, often with ST-segment analysis, are attached to most anesthesia machines. End-tidal gas analysis using infrared technology developed in the 1940s is in common use. Thermistors offer a continuous measure of core body temperature, thereby providing an early warning of the rare, but potentially lethal syndrome of malignant hyperthermia.[338] Awareness of complications associated with hypothermia in anesthetized patients and the use of methods to prevent its occurrence have contributed significantly to a safer environment for surgical patients.[339,340]

Some complications that may seem trivial to the provider can be highly significant for the patient. Surveys have shown, for example, that postoperative nausea and vomiting are feared complications in a large percentage of patients contemplating surgery.[341] Progress has been made in eliminating this complication through the use of agents with less emetogenic potential. Increased understanding of the neurochemical substrates that regulate the vomiting reflex has resulted in specific therapies to prevent or lessen the gastrointestinal side effects of general anesthetics and opioids.[342] Dopamine antagonists and serotonin 5-HT_3 antagonists have been particularly cost effective.[343]

The increasing use of muscle relaxants by anesthesia providers has led to the terrifying complication of an awake, paralyzed patient who is fully aware of surgical pain. Although early pharmacologic studies of muscle relaxants suggested a central depressant effect of these drugs, this issue was settled when Scott M. Smith[344] (1912-) allowed himself to receive curare without other agents and reported that no sedation or analgesia was present during complete paralysis. R. S. Blacher[345] noticed that complete paralysis with awareness during surgery could sometimes lead to a postoperative traumatic neurotic syndrome characterized by anxiety, irritability, and repetitive nightmares. Various monitors have been used to avoid this rare, but dreaded complication. Tunstall[346] described the isolated arm technique whereby one arm is excluded from the circulation, thereby allowing an awake, paralyzed patient to follow commands by moving that extremity. The electroencephalogram was described in 1929 by Johannes Hans Berger[347] (1873-1941) and first used during

administration of anesthesia by Albert Falconer, Jr.[348] (1911-1985). Within the past 30 years, new technologies have been developed that process the electroencephalographic raw signals and provide a number that is indicative of anesthetic depth. The bispectral index (BIS) monitor is a recent commercial product that analyzes the electroencephalographic pattern and provides some assurance that the paralyzed patient is also asleep.[349] Some exceptions have occurred with this device, with paradoxically low BIS numbers being associated with awareness, and solutions to the problem of awake and paralyzed patients continue to evolve.

Allergic reactions to drugs can be life threatening. Anaphylaxis (meaning "without protection") is appropriately named, especially for anesthetized patients, because the symptoms of hypotension and bronchospasm can have many causes and specific treatment can often be delayed. The syndrome was described in 1913 by Charles R. Richet[350] (1850-1935), who was studying the toxicology of various fish poisons and observed the rapid onset of death in dogs that more than 15 days earlier had withstood a much larger dose of the toxin. Richet postulated that an immune response had developed in the interim and produced a fatal reaction to the injection. The role of histamine and vasomotor instability was described in 1932,[351] and this understanding led to the role of vasopressors and antihistamines as treatment.

Even though enormous progress has been achieved toward the goal of zero anesthetic-related morbidity and mortality, no such claim can yet be made at any institution. In part, this is because more extensive procedures are being performed on sicker patients than was the case 100 years ago. In 1914, Gwathmey (see Fig. 1-18D) reported a 0.01% anesthetic-related mortality rate with ether anesthesia, a surprisingly low figure in view of the anesthetic methods in use at the time. However, in 1914 they did not perform extensive procedures such as liver and heart transplantation on patients with life expectancies (without surgical intervention) of only a few weeks. Anesthesiologists have recently focused on postoperative as well as intraoperative pain, and this extension carries with it additional risks to anesthesia providers.

The quest for improving the perianesthetic experience is far from over. A physician has only to ask patients about the experience of having a major surgical procedure to conclude that it is far from pleasant, even in the absence of complications. It is futile to attempt to summarize the current hardships that a surgical patient must undergo in the modern hospital or even attempt possible solutions. Change will occur—that is certain—and if we can learn anything from the past 150 years, there are possibilities for improvement and modalities of practice that we cannot even imagine today. Some methods in use today will appear nonsensical to future practitioners. As portions of the preceding historical survey demonstrate, one barrier to progress is failure by those entrenched in their routines and biases to recognize a breakthrough when it occurs. Perhaps the smarter we are, the more we fail to see our failures. In 1775, while Joseph Priestley[352] was hopelessly lost in the phlogiston theory of combustion, we find these words written in his classic manuscript *Experiments and Observations of Different Kinds of Air*: "The more ingenious a man is, the more effectually he is entangled in his errors; his ingenuity only helping him to deceive himself, by evading the force of truth."

Truth in clinical medicine is perhaps even more difficult to recognize than answers to the questions that chemists were contemplating at the end of the 18th century. However, anesthesiology has made remarkable progress in the more than 150 years since the public demonstration of ether anesthesia, and this progress should continue until safe elimination of all unwanted pain from human experience has been attained.

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2 Scope of Modern Anesthetic Practice

Key Points

1. With the increase in the elderly population, more of the surgeries performed will be procedures required by elderly patients.
2. Minimally invasive procedures are increasing; anesthesiologists will be performing more anesthetic procedures outside operating rooms. Anesthesia may be the major risk to patients as the surgical procedures become more minimal.
3. The mandates for quality, competency, and uniform process will change the way anesthesia is delivered. More standardization and protocols will be used; this will allow more evaluation and research as to what optimal anesthesia is and what competent anesthesiologists are required to do.
4. The increase in nurses with degrees will change the number of anesthetics delivered by physicians. Team management and relationships between physicians and nurses will become more crucial, and the demand for skills in personnel management will increase.
5. Not enough research is being done by anesthesiologists. Anesthesiologists will need to engage in research to maintain an academic foothold. Opportunities for multidisciplinary research are increasing, and they need to be embraced to increase the number of research-trained anesthesiologists.

Forces That Will Change Anesthetic Practice

Multiple changes are occurring that will affect the role of the anesthesiologist in the United States and perhaps globally. The population of industrialized nations is *aging* so that many more operations are performed on elderly patients; this dictates which operations are being performed. The *cost of medical care* is increasing globally, and perhaps most rapidly in the United States. The increased cost will lead to more scrutiny regarding the need for operations, increased focus on quality and use of care that has documentation by research, changes in Medicare reimbursement, changes in the ability of patients to pay, and a demand for the use of less costly health care providers whenever possible. Technologic advances are leading to less invasive procedures that can be done on patients who heretofore would be denied routine surgical procedures. The mandates for *quality metrics* and *evaluation of processes* will change the way we practice medicine. Changes in *personnel* also will affect the workforce in practices. We can only speculate as to what the practice of anesthesia will be like in the next 10 years, but these forces will likely have a major effect (Fig. 2-1).

Aging of Society

With the aging of the population and improvements in anesthetic and surgical methods, the fraction of the elderly population undergoing surgical procedures is increasing in the United States (see Chapter 71). Use of surgical services in older patients is not unexpectedly higher than in younger patients. In the Centers for Disease Control and Prevention report of inpatient hospitalizations for 2005, there were 45 million procedures performed on inpatients with a similar number of outpatient procedures. From 1995 through 2004, the rate of hip replacements for patients 65 years old and older increased 38%, and the rate of knee replacements increased 70%. There seems to be a direct correlation between age and use of surgical services.[1]

Changes in Location of Care Delivery

Because of the high costs to the insurance industry, the pressure to move less invasive surgical procedures to locations remote from the hospital setting will continue, frequently motivated by changes in reimbursement.[2] Providing anesthesia in ambulatory surgical settings and offices has increased dramatically over the



Figure 2-1 Changing scope and settings of anesthesia and perioperative medicine. **A,** *The Cure of Folly,* by Hieronymus Bosch (c. 1450-1516), depicting the removal of stones in the head, thought to be a cure for madness. **B,** Friedrich Esmarch amputating with the use of anesthesia and with antisepsis. Woodcut from Esmarch's *Handbuch der Kriegschirurgischen Technik* (1877). **C,** Harvey Cushing performing an operation, with the Harvey Cushing Society observing, 1932. **D** and **E,** Placement of deep brain stimulator for the treatment of Parkinson's disease using a real-time magnetic resonance imaging technology (MR fluoroscopy). The procedure takes place in the MR suite of the radiology department. The patient is anesthetized (**D**) and moved into the bore of the magnet (**E**). **F** and **G,** A sterile field is created for intracranial instrumentation (**F**), and placement of electrodes is done using real-time guidance (**G**). (***A,*** *Courtesy of Museo del Prado, Madrid;* ***B,*** *courtesy of Jeremy Norman & Co, Inc;* ***C,*** *photograph by Richard Upjohn Light [Boston Medical Library];* ***D-G,*** *courtesy of Paul Larson, MD, UCSF/SF Veterans Administration Medical Center.)*

last several decades (see Chapter 78). As procedures become less invasive than those currently performed in the operating room, they will be performed in procedure units. It will be important to determine the need for anesthesiologists to provide traditional anesthesia and moderate to deep levels of conscious sedation in these settings. Postoperative care has been shifted from the medical setting to the families, which may present difficulties in elderly patients. Anesthesiologists must be involved in determining which patients are appropriate candidates to have different procedures in these different locations of care, and the level of monitoring needed to perform these procedures safely.[3]

Cost of Medical Care

As the cost of health care in the United States approaches 15% of the gross national product, there has been increased interest in determining the factors that are increasing the costs, attempting to find methods to decrease the cost, and obtaining more valuable health care for the money spent. The primary driver of cost in the United States apparently is technical progress, as health care costs are increasing throughout the world, regardless of the insurance system.[4-6] The increase in elderly patients and patients with chronic disease in the population also is increasing health care costs.[7]

The increase in cost has led to a movement to get more value for the money spent. Pay-for-performance programs have been created (i.e., rewarding medical care that is consistent with published evidence and not paying for care that is inconsistent with evidence).[8-10] The concept and reality of pay-for-performance programs has now moved to other countries, including the United Kingdom.[11]

In the nonsurgical arena, the concept of pay-for-performance has been studied for several years.[12,13] In addition to paying for performance, in the United States, there is increasing emphasis on not paying for "never" events, such as decubitus ulcers or urinary tract infections, unless they are present on admission to the hospital. Because of the role of anesthesiologists in the entire continuum of perioperative care, including postoperative intensive care and pain management, we have an opportunity to influence many of the practices that can be associated with poor outcomes and increased cost, but that traditionally have not been considered under our domain of care.

Appropriate and timely administration of antibiotics has a significant impact on surgical site infection, but before the initiation of the Surgical Care Improvement Project, many anesthesiologists were arguing that control of antibiotics was not within

their domain (see Chapter 5).[14] Anesthesiologists tend to focus on intraoperative cardiac arrests and other short-term outcomes, such as postoperative nausea and vomiting (see Chapters 33 and 86). Anesthesiologists will need to rethink this approach for other "never" conditions, such as urinary tract infections because they help determine the need for Foley catheters. Anesthesiologists and intensivists also can have a significant impact on the rate of ventilator-associated pneumonia. Some of these proposed measures, particularly the use of ventilator-associated pneumonia as a quality measure, have become quite controversial, however.[15] Pain is considered the fifth vital sign, and the management of postoperative pain is another area in which anesthesiologists can have a significant impact with respect to cost and potential interaction with other members of the hospital team.

Process Assessment and Quality Metrics

Anesthesiology was among the first professions to focus on reducing the risk of complications, and anesthesiologists were among the first groups to develop evidence-based guidelines and standards, as shown by the American Society of Anesthesiologists standards and practice parameters (see Chapter 5).[16] It will be important to continue to be involved in multidisciplinary approaches to surgical care. Examples where anesthesiologists were initially less involved include the Society of Thoracic Surgeons database and the National Surgical Quality Improvement Project.[17,18] More recently, anesthesiologists have become involved in both groups, and the Society of Cardiovascular Anesthesiologists have begun discussions with the Society of Thoracic Surgeons. Anesthesiologists have been involved from an early stage in quality initiatives with the Institute of Healthcare Improvement and the Surgical Care Improvement Project.[19]

Other quality measures that will have an impact on anesthesiologists include the new demand for metrics of competency, to be measured on a focused and an ongoing basis. Defining competency will demand that anesthesiologists adhere to more protocols, and that the concept of safe anesthesia be standardized. Rather than stifling medical innovation, standardization should be viewed as a mechanism for evaluating process and outcomes because comparisons cannot be made without standardization. Anesthesiologists will need to engage in creating quality and competency metrics, or these instruments will be created by others. This is an opportunity to formulate meaningful metrics that can be used in training physicians. Metrics also will be sought for nurse anesthetists and other health care professionals.

Changing processes has become a cottage industry in medical care, with courses being offered on how to change behaviors and processes in medical care. These mandates offer the opportunity for more research as to whether changing processes leads to improved patient outcomes. These mandates also allow anesthesiologists to assume a leadership role in team management. For anesthesiologists to accomplish this role, new skills need to be taught, including leadership training, improved communication skills, and improved relationship training.

One advantage that anesthesiologists have is a long tradition and training in system approaches to care. These date back to the original checklists for the anesthesia machine. It is crucial that this skill set be disseminated beyond the intraoperative setting. Many ambulatory surgery centers are directed by anesthesiologists.

Changes in Personnel

There are approximately 250,000 active physicians, one third of whom are older than 55 years old and likely to retire by 2020.[20] Although in the 1960s enrollment in U.S. medical schools doubled, during the years 1980 through 2005, the enrollment has been flat. There has been zero growth in U.S. medical school graduates. In this same interval, the U.S. population grew by more than 70 million, creating a discrepancy between the supply of medical school graduates and the demand for physician-associated care.

There also has been a significant increase in the number of women in medical schools, so that about 50% of medical students are now women.[21] Women tend not to work as many hours as their male counterparts, even when part-time status is taken into consideration.[22] Also, today's younger physicians choose to work fewer hours than their older counterparts, regardless of gender.[20,23]

There has been a steady use of international medical graduates; 60,000 international medical graduates are used as residents and constitute 25% of all residents in training.[24] There also has been an increase in the number of osteopath schools and schools offering advanced degrees in nursing, including training of nurses to become nurse anesthetists.[20] Given the increase in demand for medical care resulting from the increase in the geriatric population, this need will most likely be met by a combination of physicians and nonphysician personnel.

Research

In terms of creative new investigations, most benchmarks suggest that the specialty of anesthesiology fares poorly compared with other disciplines, especially clinical disciplines. Using data gleaned from publicly available National Institutes of Health (NIH) sources, Reves[25] produced a troubling figure showing that anesthesiology ranked second to the last for many medical disciplines. The exact position on any such figure would undoubtedly change from year to year. The fact that U.S. anesthesiology inhabits the lowest quartile is of concern, however, because the external forces on the practice components are generally applicable to all specialties.

NIH is not the only source of funding that may influence the specialty of anesthesiology; it is not even the largest portion of total research funding in the United States (Fig. 2-2).[26] For all sources, there has been a doubling over the last decade in research expenditures for health and biomedical science research, although compared with biologically based disciplines, health services research is considerably less well funded. In anesthesiology journals, the fraction of non-U.S., original peer-reviewed articles has increased dramatically. This increase does not seem to be attributable directly to research support. Adjusted per capita, research support in Europe is only 10% of that in the United States, even though the proportion of scientists in the population is similar.[27]

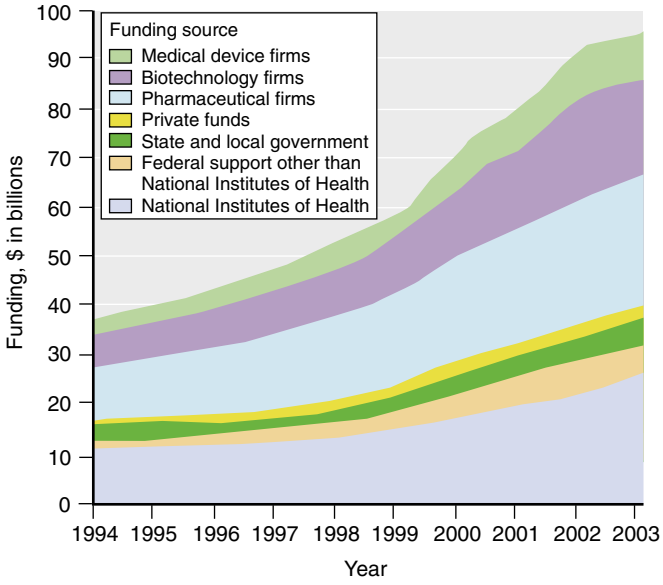

Figure 2-2 Research expenditures in the United States, 1994 to 2003, by funding source (see text).

There is no a priori reason why anesthesiology should differ from any other medical specialty in terms of research output. In our opinion, it should excel. One might argue that practitioners at academic institutions might be better compared in terms of surgical versus medical specialties, but even in that comparison we fare poorly. One line of remedy is to develop clinician-scientist training programs further, such as the NIH T-32 model. This approach is limited, however, by the fact that *selection* of individuals entering the specialty has already occurred.

One of the most exciting and promising developments in this regard has been the initiative by several programs in the United States to construct a special residency track that allows training for scientific independence to occur roughly in parallel with clinical residency training over the course of a 4-year track after internship. Such an approach recognizes that, to change the culture of the specialty, we must build from the ground up. Not all physicians who enter anesthesiology training go on to participate in the research/academic sector. Similar to other highly visible specialties, however, a sufficiently large cadre will be available to replenish those who leave active practice and further build up intellectual capital for future generations.

One of the challenges in training is the inherent and increasingly diverse nature of the disciplines involved in any one-subject area. The term "interdisciplinary research" has become a tautology. Practically all new frontiers lie at the boundaries of established departmental or specialty divisions, which are largely a historical relic of 19th century or early 20th century conceptualizations. A look at any large institution's roster of academic divisions yields a growing number of "centers," "programs," and "institutes," reflecting the ever-increasing interdependency of branches in biomedical knowledge.[28,29] In basic science departments, with conjugate names such as "Physiology and Cellular Biophysics," "Anatomy and Cell Biology," "Biochemistry and Biophysics," and "Cellular and Molecular Pharmacology," it is becoming increasingly difficult to differentiate one faculty research program from another, solely on the basis of the topics and methods of study. Although this differentiation is clearly less complicated for domains that do not involve patient care, the trend is evident. One might cite the example of endovascular surgery as an example in the collision of science, technology, and historical boundaries of medical specialties.[30]

Medical research is at one level original creative work that involves systemic investigation of medical phenomena with the direct or indirect consequence of improving health care. Activity that might be subsumed under "medical research" is scholarly synthesis of available data to generate new insights into phenomena. Scholarship that involves this synthesis is perhaps underappreciated and underemphasized. The most common type of publication in this category is the review article. Although often review articles are written by the individuals performing the original research, this is neither a necessary nor a sufficient precondition for a meaningful review. Especially for clinically oriented reviews, a broad perspective on a particular clinical practice may not only be sufficient, but also desirable.

Ramachandran[31] quotes Medwar: "An imaginative conception of what might be true is the starting point of all great discoveries in science." Ramachandran says that if he would show the reader a talking pig, it is unlikely that he or she would respond: "Ah, but that's just one pig. Show me a few more, and then I might believe you!" In this regard, an unintended consequence of moving toward quantitative indices for impact of biomedical journals has led to the demise of the case report. The case report is just such a Medwarian "imaginative conception of what might be true." It is also an ideal setting in which to perform a synthesis of available knowledge on a particular topic. Well-written and timely case reports can add significantly to the medical literature and provide an "early warning" function before laborious efforts are undertaken to conduct larger scale efforts to characterize a particular complication or phenomenon. Finally, case reports are "entry-level" scholarly activities that students, residents, and junior faculty can use as a stairstep to more complex modes of writing.

An area of potentially increasing contribution of anesthesia and perioperative care is in the realization of clinical trials for efficacy of surgical therapy. It is not unreasonable to assume that reimbursement for delivery of clinical care in the future may be increasingly tied to participation in some form of organized assessment of efficacy, such as a randomized controlled trial (e.g., the case of lung reduction surgery).[32] Such considerations are especially pertinent for procedures that are highly reimbursed, but controversial in terms of efficacy, as in the case of minimally symptomatic cerebrovascular diseases.[30,33] Perverse incentives can drive clinical practice and influence expert opinion. In addition to insights into the delivery of perioperative medical care, anesthesiologists can help provide an "honest broker" function in such settings.

In the clinical and policy research domain, anesthesiologists have an opportunity to study all aspects of surgical care. By joining or leading multidisciplinary teams, they can ask questions relevant to the patient undergoing surgery and not just undergoing anesthesia. Anesthesiologists must take leading roles in helping to define best surgical practice.

Why is it important that anesthesiology maintain the strongest possible profile in research and scholarly contributions to medical knowledge? Besides the intuitive sense that medical specialties must strive for advancing their domains, there is a strategic necessity of significant proactive involvement in scholarly and investigative pursuits. In the modern medical market-

place, physicians are not the only stakeholders in the delivery of health care. Physicians, particularly those in professorial tracks, traditionally conduct the bulk of investigative research, however. The advent of higher-level, doctoral degrees in nursing could significantly change this dynamic. The public that we serve, and the various governmental and institutional bodies that regulate health care delivery, should have a clear vision of our mission and approach.

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Ronald D. Miller with Andrew Schwartz, Editors

3 The International Scope and Practice of Anesthesia

Outline

The Early History of International Anesthesia
- India (Deepak K. Tempe)
- The Middle East (Anis Baraka and Fouad Salim Haddad)
- Russia (Olga Afonin)

The Cross-Pollination Period: 1920-1980
- India (Deepak K. Tempe)
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- South America (Guillermo Lema)
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- Uganda/Sub-Sharan Africa (D.G. Bogod)
- Japan (Akiyoshi Namiki and Michiaki Yamakage)

The Modern Period: Essentials of Modern Anesthesia around the World
- Roles and Responsibilities of Anesthesia Providers
- Facilities and Equipment
- Education, Accreditation, and Availability of Practitioners
- Subspecialization
- Professional and Research Activity

Conclusion

At a recent international anesthesia conference, an American anesthesiologist spoke about the value of using modern electronic monitoring devices in the operating room. Believing that they are essential for improved patient safety, the presenter expressed a hope that hospitals worldwide would adopt and use these devices. During the question and answer session, however, a physician from another country—one whose hospitals have considerably fewer resources than those in the United States—stood to express his frustration with this argument. In his country, he believed, there were other priorities and the sheer cost of monitoring equipment prohibited its widespread adoption. Another physician, also from a country whose hospitals do not have a wealth of resources, disagreed; by understanding what monitoring devices were available, he would pick the most effective monitoring device or devices in accordance with the resources available. A spirited exchange followed. Of course, there is no one right way for hospitals to spend their limited resources. There was, however, enormous value in this exchange among physicians from different countries with different cultures, different resources, and different perspectives. It is through these discussions that the profession can create fully informed baseline standards that foster greater levels of patient safety and improved outcomes worldwide.

Such discussions, which occur with increasing frequency, also inspired this chapter on the global scope and practice of anesthesia. Throughout his career, this book's editor, Ronald D. Miller, has had the privilege and pleasure of speaking and working with leading anesthesiologists from all over the world. His work and discussions with international colleagues spurred a desire to recognize and honor the growth and practice of anesthesia outside North America. He wanted to describe the different ways that anesthesia began from place to place and to follow the regions through time so that we can better understand how the various regions influence each other today.

This chapter is the first step in realizing his hope. Work on this chapter began in earnest when he invited a number of colleagues whom he had met over the years—prominent anesthesiologists in their parts of the world and beyond—to contribute a short summary describing the growth and practice of anesthesia in their country or region. When the contributions arrived, they proved to be a fascinating read: creative, informative, and inspirational. Yet for all their rich content, they also posed an editorial challenge in that the unique cultures, politics, economics, and developments in various regions prompted the contributors to emphasize different ideas, discoveries, or time periods. These differences in emphasis and coverage reflect the freedom that the contributors were given to describe their country or region. In the future we hope to expand on this topic by covering other areas of practice and including world regions not featured in this chapter.

It was in the face of this challenge that Dr. Schwartz was asked to integrate the short individual contributions into a single chapter without compromising their integrity. Dr. Miller and Dr. Schwartz chose to create a chronologic narrative that progresses through three distinct time periods. Each period is broken up by region; each regional narrative draws directly from the work of the international contributors. Our intent was to always acknowledge and document the sources and wherever possible maintain

each contributor's individual voice, and we hope that we have achieved that goal.

Dr. Miller is deeply grateful to all the colleagues who contributed to this chapter, for their insightful writing and the time that they devoted to their tasks, and regrets that because of time and space constraints not more contributions of this kind could be included in this edition. He recognizes that the pages you are about to read are only a first step and by no means a comprehensive look at the development of anesthesia around the world. Future editions will deepen and broaden the international focus.

The first section of this chapter is a sprint through a vast stretch of history, from ancient times through the early 20th century. Over these two thousand or so years, with a few notable exceptions, the practice of anesthesia grew independently by region in response to the need for pain relief during medical procedures.

The second section covers the period from the 1920s through the early 1980s. This was a time when modern communications and international travel expanded dramatically, leading to increased cross-pollination of anesthesia techniques. Physicians and researchers began to regularly travel to foreign countries, receive training and education abroad, and hear others speak at conferences. As international journals grew, knowledge about emerging practices in anesthesia spread further.

The third section covers the time from the early 1980s through the present. This has been an exciting period because today nearly all anesthesiologists, no matter where they practice in the world, can gain access to the information necessary to deliver safe anesthesia at the most basic level. Even though significant differences in resource levels still remain, some of which undermine the practice of safe anesthesia, at least all anesthesiologists worldwide today know how to avoid the common complications of anesthesia that can endanger patients' lives. This section details the state of anesthesia in the regions covered—from education, accreditation, professional exchanges, and actual practice to available facilities and equipment.

The chapter concludes by raising questions about what is next in terms of the way various countries and regions practice anesthesia. How integrated should the practice of anesthesia become? What can we do to raise levels of care worldwide? Again, there are no simple answers, but it is a future that anesthesiologists face together.

The Early History of International Anesthesia

Before the early 20th century, those interested in analgesia during surgery rarely had the advantage of being able to learn from what their colleagues around the world were doing. Rather, in response to patient need, physicians from various regions came to different, but often similar conclusions about how to relieve pain. In many, if not most places, herbs, opium, and alcohol were the mainstays of pain relief medication.

Regions were not completely isolated, however. As the narratives herein describe, the traditional ways of spreading culture and information, such as war and trade, enabled at least some sharing of anesthesia techniques. In particular, the first published account of ether used as an anesthetic in 1846 seems to have been anesthesia's "shot heard 'round the world."

India (Deepak K. Tempe)

The history of anesthesia in India dates back to the era of Susruta, the great surgeon of ancient India. During his time, around 600 BC, operations were performed with the use of opium, wine, and Indian hemp (an herb). Surgical science was called "salya-tantra" (*salya*: broken parts of an arrow and other sharp weapons; *tantra*: maneuver).[1]

Much later, in 980 AD, Pandit Ballala mentioned in *Bhoj Prabandh* that Raja (King) Bhoj underwent a cranial operation under the anesthetic influence of a plant called "sammohini." The same plant was applied as healing balm to surgical wounds. A drug called "sanjivan" was administered to revive the Raja and help him regain consciousness.[2]

Nearly 900 years later, after the first widely publicized demonstration of ether anesthesia in the United States in 1846, India quickly followed suit by administering ether anesthesia on March 22, 1847, in Calcutta under the supervision of a surgeon named Dr. O'Shaughnessy.[3] Later, chloroform was also used but fell into disrepute because of the high morbidity associated with it. Despite this—and the fact that the world began to discard chloroform in preference for ether by 1890—India continued to use chloroform until 1928.

Among the several interesting case reports related to anesthetic practice is the emergency appendectomy performed on Mahatma Gandhi on January 12, 1925, at Sassoon Hospital, Pune. During an electricity failure, the mahatma was administered open-drop chloroform anesthesia, with the surgery being completed by the light of a kerosene lamp and battery-operated torch.[4]

The Middle East (Anis Baraka and Fouad Salim Haddad)

With the decline of the Greco-Roman Empire in the fifth century AD, the Middle East witnessed the rise of an Arab/Islamic civilization that within a hundred years (632-732 AD) expanded over a 3000-mile stretch extending from the western borders of India, through north Africa and Sicily, to Andalusia on the Atlantic coast of Spain. This civilization interacted with the ancient Egyptian, Hellenistic, Byzantine, Syrian, Persian, and Indian cultures. Many Arab/Islamic, Christian, and Jewish scholars translated, refined, and augmented the knowledge contained in these cultures. The new civilization that evolved lasted for around 1000 years, carried the torch of knowledge in the Middle Ages, and through its transmission via Spain and Sicily, contributed to the European Renaissance.

In this epoch, some prominent Arab/Islamic, Christian, and Jewish scholars made important contributions in the fields of medicine, philosophy, astronomy, mathematics, and chemistry. A wealth of knowledge was thus inherited by several succeeding ages. Of special interest, the following scholars made contributions to the field of anesthesia: (1) Al-Rhazi (865-925 AD), born in Ray, Persia, described the pupillary reaction to light and the laryngeal branch of the recurrent laryngeal nerve[5]; (2) Avicenna (980-1037 AD), born near Bukhara, Persia, enumerated agents that

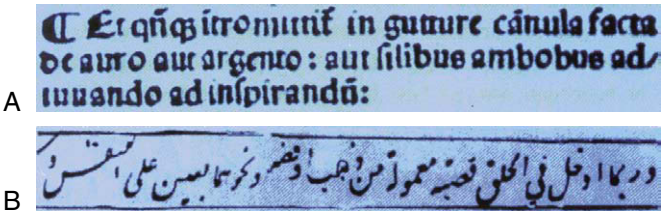

Figure 3-1 **A,** The Latin version of oral intubation: *Et quandoque intromittiture in gutture canula facta de auro aut argento: aut silibus ambobus, adjuvando ad inspirandu*. **B,** The Arabic version of oral intubation: When necessary, a cannula made of gold, silver, or another suitable material is advanced down the throat to support inspiration. *(From Haddad FS: Ibn Sina [Avicenna] advocated orotracheal intubation 1000 years ago: Documentation of Arabic and Latin originals. Middle East J Anesthesiol 17:155-162, 2000.)*

alleviate pain: opium, henbane, and mandrake; in his *Canon of Medicine*, he advocated oral intubation: "When necessary, a cannula of gold, silver, or another suitable material is advanced down the throat to support inspiration" (Fig. 3-1)[6,7]; (3) Ibn Al Nafis (1208-1288 AD), born in Quresh, near Damascus, Syria, criticized in his *Sharh Tashrih Al Qanou* Galen's theory of blood movement, which said that blood from the right ventricle passes into the left ventricle through small invisible pores in the septum (Fig. 3-2A); Ibn Al Nafis asserted that there is no direct pathway between the chambers and the thick septum of the heart is not perforated, and he described the pulmonary circulation as we know it today (see Fig. 3-2B)[8,9]; and (4) Al-Khawarizmi (died 840 AD), born in Balkh, Persia, who was a famed mathematician; the word "algorithm," a mathematical tool, is attributed to him. Algorithm is defined as "a step-by-step problem-solving procedure."[10]

THE USE OF SPONGIA SOMNIFERA. In the Middle Ages, the concept of inhalation to induce sedation before surgery with use of the sleeping sponge, or *spongia somnifera*, is attributed to Arab origins.[11,12] With the Arab conquest of Sicily in the ninth century and the Latin translations of Arabic medical books that followed, Arabic medicine, including the soporific sponge, took hold in southern Italy (Salerno, Monte Cassino). From there it spread to other parts of Europe and was used in the Middle Ages.[12] A probability also exists that it was carried from the Andalus of Spain by Michael Scot, who in the 13th century transmitted scientific culture from Toledo to Bologna via the Court of Frederick II Hohenstaufen in Sicily.[13,14]

After the Middle Ages, major political events in the 19th century affected the development of medicine throughout the countries of the Middle East. First, with Napoleon's invasion of Egypt in 1798, the medical awakening of Middle Eastern countries to western medicine can be said to have started. To win the cooperation of the Egyptian people, Napoleon brought with him men of all specialties.[15] After Napoleon's departure from Egypt and the assumption of power by Mohammad Ali in 1805, efforts to propagate knowledge and education continued. Mohammad Ali brought doctors from Europe and France to take care of the health of his army. Of those, the most remarkable was Dr. Antoine Berthelemy Clot (later Clot Bey) (1793-1868), who was brought to Egypt in 1825. In 1835 Bey established a medical school in Kasr Al Aini Hospital in Cairo, the only Arab medical school in the Middle East at the time.[15]

The developing renovation of Egypt then influenced other regions of the Middle East, either through students flocking to

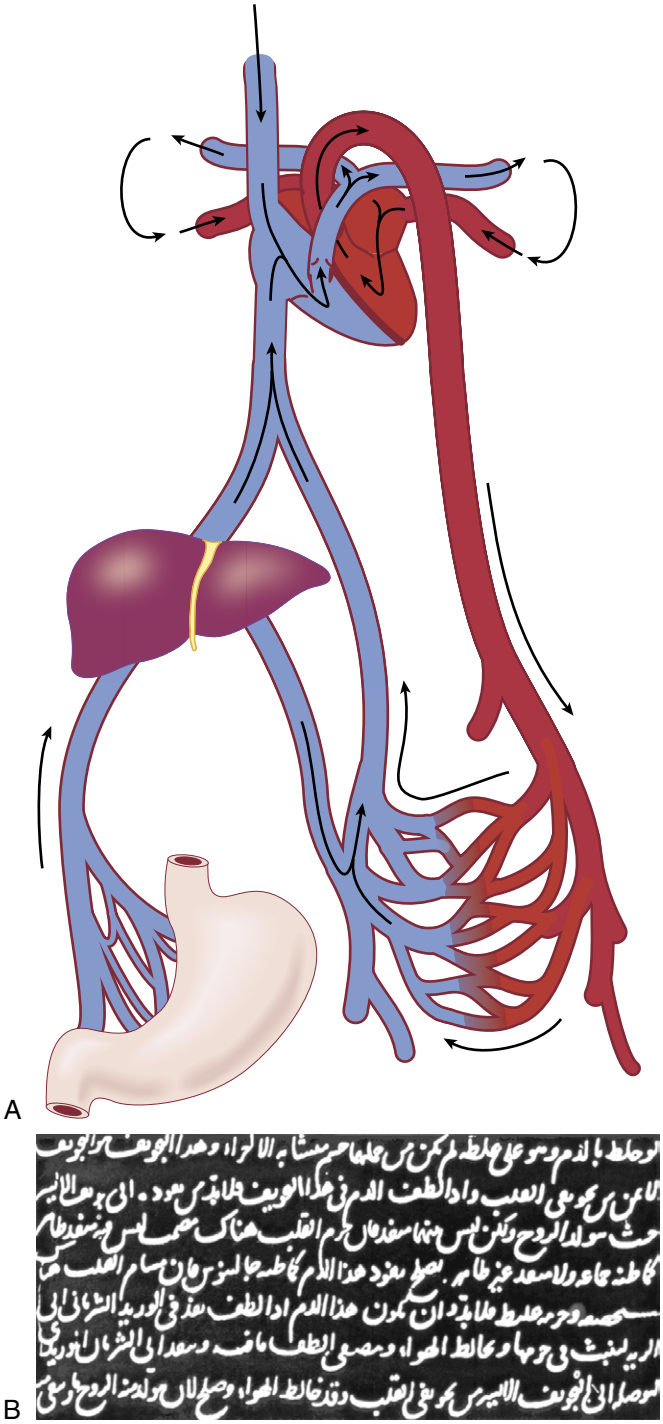

Figure 3-2 **A,** Galen's theory of blood movement. According to Galen, blood reached the periphery through the veins (most of it departing from the liver), as well as through the arteries (departing from the heart). Little blood went to the lungs from the right ventricle of the heart. He thought that most of the blood passed from the right to the left ventricle through pores in the intraventricular septum. **B,** Photographic reproduction of the original manuscript of Ibn al-Nafis denying the presence of intraventricular pores and describing the pulmonary circulation as we know it today.

study medicine in Kasr Al Aini Hospital or through the influence of the Egyptian military campaign (Ibrahim Pasha, son of Mohammad Ali) against the then known Syria (1831-1840). Graduates from the medical school in Cairo practiced in all big cities of the Middle East: Beirut, Damascus, Allepo, Jerusalem, Safad, Nablus, Haifa, and Nazareth. It is assumed that the analgesia practiced in major cities of the Middle East was the same technique used in Cairo. Relief of surgical pain in Cairo then consisted of herbal medications and antispasmodics.[15] No kind of inhaled anesthesia was known.

After the invasion of Syria by Ibrahim Pasha from 1831 to 1840, the Egyptians, with the influence of Western missionaries, built two military hospitals—one in Allepo and one in Damascus—and established free medical clinics.[15,16] The presence of Clot Bey in the campaign was instrumental in sending the first five Lebanese students to study medicine at Kasr Al Aini Hospital.[15]

Finally, after massacres in 1860, western powers (American, French, and British) intervened in Lebanon, and with the inflow of missionaries, more medical schools and hospitals were established. In 1866, the Americans founded the Syrian Protestant College, which in 1920 became the American University of Beirut. In 1883, the French founded their medical school (Faculté Française de Médecine).[15]

Introduction of Modern Anesthesia to the Middle East. In 1846, the first published account of the use of ether anesthesia for a surgical operation appeared, and the innovation spread rapidly,[17,18] including to London in December 1846 and Paris in January 1847. Twenty-seven years later, in 1873, it arrived in Beirut[15] with the help of an American surgeon, Dr. George Post.

In 1863, Dr. Post had arrived in Lebanon to assist in missionary work. In 1867, he and others established the medical school of the then Syrian Protestant College, and in 1873, Dr. Post wrote a book on surgery in the Arabic language, which included a chapter on general anesthesia, the first of its kind in the Middle East. It was in this book that for the first time mention was made of administering chloroform to reduce a dislocated shoulder of a patient, which was performed at the Syrian Protestant College's Johanniter Hospital in Beirut. To describe this action, Dr. Post coined the word "kulfera," an Arabization of the word chloroform. Dr. Post rightly deserves the title of the First Pioneer of Modern Anesthesia in Lebanon and the Middle East.[15]

Graduates of the Syrian Protestant College in Lebanon and other graduates of medical schools in the Middle East probably administered open-drop ether or chloroform along with local and spinal anesthesia through the rest of the 19th century and middle of the 20th century. Physicians, students, nurses, nuns, and technicians were most likely also involved.

Russia (Olga N. Afonin)

The history of Russian medicine has its roots in the history of medieval European medicine. Right through the 18th and 19th centuries, much of the information about anesthetic techniques—applying "snow" 15 minutes before surgical procedures and analgesics for the cardiovascular and respiratory systems and wound healing, as well as the use of bellows for lung ventilation—came from various leaders in European medicine. In addition, like their colleagues in the Middle East and India, Russian physicians of course heard of the use of ether on October 16, 1846; that day is still a professional holiday for anesthesiologists in Russia. A brief 4 months later, Dr. F. I. Inozemtzev of Moscow became the first in Russia to use ether for anesthesia during surgery.

Around the same time, the art of local anesthesia was developing rapidly after the publication of an article by the Russian doctor Vassili von Anrep. He described the effects of cocaine as a topical and subcutaneous local anesthetic in 1879. Isolated by the German chemist Friedrich Gaedcke in 1855 and purified by University of Gottingen student Albert Niemann in 1859, cocaine was first given to a patient in 1884. It was the only local anesthetic until 1904, when procaine was synthesized.

von Anrep's ideas of local anesthesia were very popular. Famous physicians of Europe and Russia (Shleich, Lukashevich, Vishnevskiy, Bier) were developing the knowledge of local anesthesia, which gave rise to new methods of preventing pain: local field anesthesia, local infiltration anesthesia, nerve blocks, plexus anesthesia, intravenous anesthesia, and neuraxial anesthesia.

In general anesthesia, the Russian physician Nikolay Pirogov (1810-1881) was a prominent physician and surgeon, well known in Europe. He was the first to describe the negative effects of general anesthesia and the possibility of severe complications. He postulated the necessity of acquiring detailed knowledge of the physiologic and clinical effects of anesthetics and requiring a separate course on anesthesia during medical education. He also described many of the modern methods of anesthesia, including inhaled endotracheal anesthesia, intravenous anesthetics, rectal use of anesthetics, and spinal anesthesia. This had a huge impact on the analgesia provided to wounded soldiers in terms of increasing surgical success and rates of survival.

In 1904, the Russian physicians S. P. Feodorov and N. P. Kravkov described and demonstrated total intravascular anesthesia with the intravenous anesthetic Gedonal. They were also the first to use combined narcosis through induction with Gedonal and maintenance with inhaled chloroform.

Another area in which Russian physicians made advances was in the field of blood transfusions. In 1901, Karl Landsteiner reported his discovery of the possible existence of blood types. In 1909 he expanded his initial discovery by establishing the A, B, AB, and O blood types. He demonstrated that transfusions between individuals with the same blood group do not result in the destruction of new blood cells and that this catastrophe occurs only when a person is transfused with the blood of a person belonging to a different group. In 1930, Landsteiner received the Nobel Prize for his work. In 1907, Russian physician Yanskiy had described four blood types and created the basics of blood transfusion. His work, however, went unnoticed.

Just a few short years later, World War I began, followed by the October Revolution in 1917, which destroyed the monarchy in Russia. Civil war, general poverty, and empowerment of the Communist Party in the early 1920s led to dramatic changes in Russia's political philosophy, economics, and technical and scientific progress, all of which affected the development of medicine. With Joseph Stalin coming to power in the 1920s, communication with other countries in Europe was terminated, exchange of information stopped, and Russian physicians had to continue treating their patients while developing the art of medicine separate from the knowledge and advances in the rest of the world. On the other hand, advances in Russian medicine were not known to the world and, frequently, had to be reinvented.

The Cross-Pollination Period: Approximately 1920-1980

In the late 1970s, the editor took a sabbatical in Holland, during which time he lectured at a local university hospital. Also there at the time was a young anesthesiologist from Ecuador. Over time, the two physicians became friends as they shared ideas about the practice of anesthesiology and its future. This rich exchange about their profession continues to this day. This was the beginning of the editor's understanding of the interesting and varied approaches in different parts of the world to achieve the status of anesthesiology as it now stands.

Their cross-cultural exchange, however, is no aberration. Over the approximately 60 years from the end of World War I through the early 1980s, anesthesiologists from around the world began to meet in a variety of forums facilitated by the advent of air travel and modern communications.

Physicians received training and education abroad. Lecturers from diverse nations spoke frequently outside their home country and brought in new ideas and techniques. Academic and research journals proliferated, as did international congresses and access to textbooks, thereby laying the groundwork for a common understanding about how to practice anesthesia.

India (Deepak K. Tempe)

Up to about 30 years ago, anesthetic equipment in Indian operating rooms often consisted solely of a simple anesthesia machine, a suction unit, and perhaps an electrocardiographic monitor. Even the oxygen supply was mainly via cylinders, with very few hospitals having a centralized medical gas supply. The first medical pipeline system was installed in Vellore in 1954.

Today it is widely accepted that postoperative care is crucial for the success of surgery, but in previous days, many patients were sent back to the ward directly after surgery and only a few would go to the recovery room. In recognition of the fact that surgical patients often need to be observed in a specialized area, India commissioned its first intensive care unit (ICU) in 1963 in an Army hospital in Delhi. Interestingly, that was the same year that an ICU was first established by an anesthesiologist at the University of California, San Francisco.

During this stretch of the 20th century, Indian anesthesiologists also recognized the need for professional societies. The idea of an Indian Society of Anaesthesiologists (ISA) was conceived in 1946; the group was established in 1947. The first ISA meeting was held in 1949 during a surgeons' conference in Mumbai, and the first independent ISA conference was held in Hyderabad in 1965. Professors Macintosh and Gray were the distinguished guests during the conference. The ISA published its first official journal in July 1953 and joined the World Federation of Societies of Anesthesiologists (WFSA) in 1956. The group has grown from 19 members when it began to nearly 12,000 members in 2007.

The Middle East (Anis Baraka and Fouad Salim Haddad)

At the end of World War I, the Middle East was divided by Western powers into small countries that were placed under British and French mandate. The major pattern in the practice of anesthesia was complete dependence on foreign surgeons, who could administer anesthetics, as well as on local and foreign nurses or nonanesthesiologists and technicians, who administered ether or chloroform. This period also witnessed the foundation of faculties of medicine in some countries of the Middle East (Syria, Sudan, and Iraq).[16]

By the end of World War II, the beginning of oil production contributed to an improving economy, which meant more funds available for anesthesia machines, endotracheal tubes, and thiopental, all of which began to appear in many countries of the Middle East. An influx of newly trained surgeons increased the demand for qualified anesthesiologists, thus prompting anesthesia residencies. In addition, in response to a manpower shortage in many countries of the Middle East, nurse and technician training began as well, although this was gradually phased out as locally and internationally trained and certified anesthesiologists began arriving in many countries of the Middle East.

During the second half of the 20th century, all countries of the Middle East were striving to attain state-of-the-art anesthesia. The World Health Organization (WHO) played a great role in encouraging and sponsoring graduate physicians for training in anesthesia at the World Anesthesiology Training Center in Copenhagen.

Raising the Professional Profile of Anesthesia. As in many other places in the world, the status of anesthesia in the Middle East depends partly on the establishment of fully independent departments of anesthesia that have their own structure, staff, residency training, research, and certification by international academic institutions and that offer fellowships in cardiovascular, obstetric, and pediatric anesthesia, as well as pain management. To that end, certain landmark strides were taken during this period.

In 1966, the *Middle East Journal of Anesthesiology* (ISSN 0544-0440) was founded; it continues to thrive to this day. Its main objectives are to act as a forum for education and exchange of opinions and to promote research and publication of Middle Eastern medicine and anesthesia. The journal is accepted for inclusion in the Index Medicus and MEDLARS system.

In addition, in the 1960s and 1970s, many Middle Eastern countries founded their own national societies of anesthesia, which promoted the practice and image of the specialty. In 1990, The Pan Arab Society of Anesthesia and Intensive Care was founded and became a member of the WFSA. Every 2 years, the Pan Arab Society holds The Pan Arab Congress of Anesthesia and Intensive Care in one of the member countries.

Russia (Olga N. Afonin)

In the midst of the economic difficulties and political upheaval after the Russian civil war, medical services underwent dramatic reorganization and expansion, and some positive developments ensued. Campaigns were carried out against diseases and poor hygiene. Thousands of unpaid men and women underwent short courses in nursing. They went all over the country to educate people and treat deadly diseases, often risking their own lives. This remarkable effort was rewarded in just a few years. The epidemics were stopped, and control of many diseases was established. This

experience emphasized the importance of preventive measures, including vaccinations, and Soviet physicians began working on preventive medicine.

Meanwhile, in Moscow, Dr. Yurevich was first in the world to begin using citrate for blood conservation. His colleague Dr. Shamov was first to use cadaveric blood for transfusion in 1928, thus giving birth to a new field of medicine—transplantation.

The very first Institute of Blood Transfusion, a scientific center for study and development of the science of blood and blood component use and storage, was formed in 1926 in Moscow by Professor A. A. Bogdanov. Physicians of the institute developed and published the first systematic approach to the treatment of shock, including traumatic, hypovolemic, and "burn related." Another dramatically important innovation of Russian physicians was the introduction of methods of diagnosis and treatment of electrolyte and acid-base imbalances with complex salt solutions, blood substitutes, and total parenteral nutrition solutions.

In 1924, the Russians S. S. Bryuchonenko and S. I. Chechulin constructed and used the very first artificial heart machine in the world, the parent of what is now known to us as a cardiopulmonary bypass machine. Surgical procedures were becoming more complex and required more advanced methods of exposure of the abdominal and thoracic organs. The bellows of Dr. Henry Hickman was transformed into many different machines to provide artificial ventilation, including the famous "iron lung" of Harvard, used first in Boston in 1928.

In 1939, N. L. Gurevich and G. S. Yun'ev developed the physiologic basis and methods of indirect heart massage and electrical defibrillation. These methods were used successfully on patients requiring complicated cardiothoracic surgeries in Russia.

As all these developments grew into complex surgical procedures and as the use of neuromuscular blocking drugs spread, it became necessary in Russia to develop a new kind of subspecialty in medicine: anesthesiology. This would require extensive and detailed knowledge of many disciplines, including physiology, biochemistry, surgery, medicine, neurology, pharmacology, traditional anesthesia, and critical care.

The first Department of Anesthesiology in Russia branched out of the Department of Cardiothoracic Surgery (now the Russian Medical Academy of Physicians Postgraduate Education) in 1959 in Moscow (this is also the same year that the current Department of Anesthesia was formed at the University of California, San Francisco). The first postgraduate courses for physicians to become anesthesiologists lasted 4 months. Later, there were additional courses of anesthesiology that included the basics of intensive care and another couple of months of additional training. The broad variety of topics covered and the complexity of the potential patient care issues meant that the new specialists needed more time to properly prepare for their careers. These careers were in demand as newly formed anesthesiology and intensive care departments required more and more anesthesiologists to teach and take care of patients.

It was in 1969 when the Ministry of Health of the Soviet Union released the "Order of improvement of anesthesiologic and reanimatologic (intensive care) services in the country." That was when anesthesiology finally received the financial and administrative support required at that time for any significant changes to take place.



Figure 3-3 The Ombrédanne anesthesia delivery device.

South America (Guillermo Lema)

The main influences on the South American practice of medicine in general, and anesthesia and surgery in particular, come from Europe. For many years and particularly during the first 6 decades of the 20th century, many doctors were trained in different parts of Europe: France, Germany, and Scandinavian countries among others. The European influence was as strong in medicine as it was in other aspects of daily life.

One example of Europe's influence was South Americans' wide use of the Ombredanne (Fig. 3-3). This device, used to deliver anesthesia, was invented in France in 1908 by the surgeon Dr. Louis Ombrédanne (1871-1956). It is believed that South America is the only continent where this particular equipment was clinically acceptable and used widely.

Of course, ether was not the only anesthetic used during this time. Cyclopropane was another, although Chile had a dramatic experience with this gas that eventually caused it to be banned. In 1963 at the Manuel Arriarán Hospital in Santiago, a cyclopropane tank exploded in a pediatric operating room. Two small boys and four physicians—two of them anesthesiologists—died. This remains one of the worst anesthesia-related accidents ever to happen in the world. New standards, including the banning of cyclopropane, were imposed to avoid further accidents.

China (Yuguang Huang)

In the early 20th century, with the introduction of Western medicine into China, modern anesthesia began to be applied in clinics. At that time, anesthesia was implemented mainly by nurses or surgeons. Only a few Western professional anesthesiologists, such as Mr. Yueqing Ma from the Peking Union Medical College, could undertake clinical anesthesia in China.

After the foundation of the People's Republic of China in 1949, some early pioneers—such as Jue Wu and Xingfang Li from Shanghai and Rong Xie, Deyan Shang, and Huiying Tan from Beijing—returned from the United States and Europe to help modern anesthesia take shape in China.

In the 1950s, only simple anesthesia was available in China, such as the ether open-drop method, inhaled tracheal intubation anesthesia, and single procaine spinal anesthesia. Peripheral nerve block and continuous epidural anesthesia were introduced gradually.

From the 1950s to the 1980s, intravenous procaine combined anesthesia and continuous epidural anesthesia were the most common methods in China. When anesthetic drugs and monitoring tools became scarce in the 1960s, Chinese anesthesiologists tried to develop acupuncture anesthesia based on the pain-relieving mechanisms of traditional Chinese acupuncture. In addition, in the 1970s Chinese anesthesiologists investigated the anesthetic effect of Chinese herbal medicine. However, beginning in the late 1970s, because of the success of reform and the government's opening-up policy, many new anesthetic drugs and instruments were introduced into China. At that time, acupuncture anesthesia and herbal anesthesia stepped down from the clinical stage as a result of their unsatisfying anesthetic efficacy and adverse effects.

Raising the Professional Profile of Anesthesia. Chinese anesthesiologists also began raising their profile as early as the 1950s, when they took part in the rescue of critically ill patients via cardiopulmonary resuscitation. For example, in 1959, Professor Yuanchang Wang from Tianjin Medical College shared his experience in the *Chinese Journal of Surgery* by reporting that a woman whose life was in danger during cesarean section was saved by chest compressions. Partly because of the influence of anesthesiologists, since the 1970s ICUs and postanesthesia care units (PACUs) have gradually been established in many domestic hospitals.

China has also participated in numerous international conferences and professional groups (Fig. 3-4). The First National Conference on Anesthesia was held in Nanjing in 1964, during which the development and achievements of Chinese anesthesiology were systematically reviewed. In 1979, the Chinese Society of

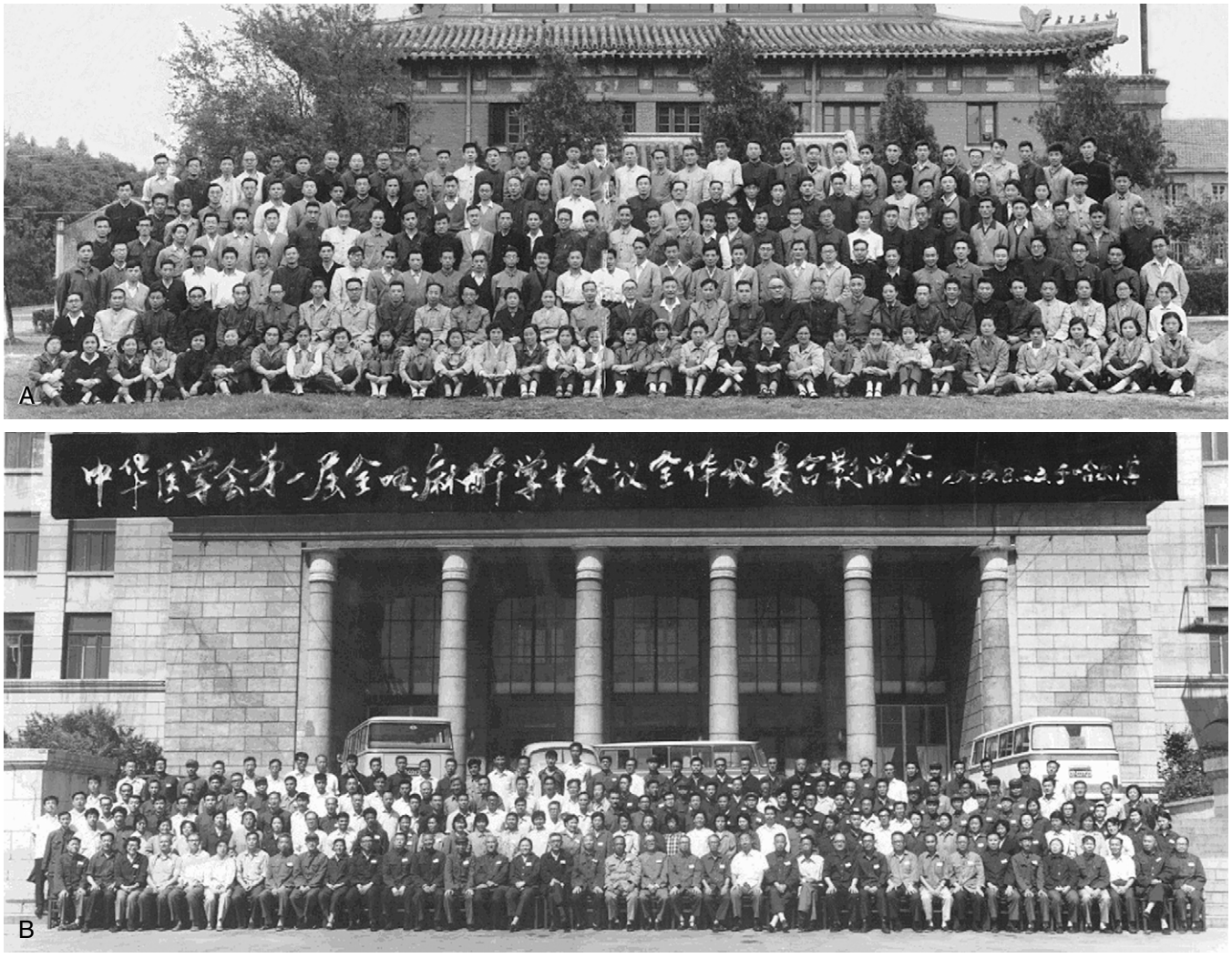

Figure 3-4 A, Participants of the First National Conference on Anesthesia, Nanjing, 1964. **B,** Participants of the Second National Conference on Anesthesia, Harbin, 1979, during which the Chinese Society of Anesthesiology was founded.

Anesthesiology (CSA) was founded during the Second National Conference on Anesthesiology held in Harbin. Professor Deyan Shang was elected as president of the first CSA committee. Since then, national CSA conferences have been held every 3 or 4 years.

During this period there was also a foray into professional publications, most notably Professor Jue Wu, the leader of Chinese anesthesia, who was the lead editor of *Clinical Anesthesiology* in 1954 and *Practical Anesthesiology* in 1976.

Western medicine introduced by the United States also helped promote the development of modern medicine in China. A good example is Peking Union Medical College (PUMC) Hospital, which was founded by the Rockefeller Foundation in 1917. Even today, PUMC Hospital is still regarded as an "ivory tower" of Chinese medicine. Some professors from PUMC Hospital moved to Taiwan in 1949, and some of them changed their specialization from surgery to anesthesiology and became the early practitioners of anesthesiology there. They made important contributions to the foundation and development of modern anesthesiology in Taiwan.

The Modern Period: The Essentials of Modern Anesthesia Around the World

The last 25 years has been an exciting period for anesthesia, largely because the ability to share clinical and research experience has made the practice safer and better than it ever has been.

Today, all anesthesiologists, no matter where they practice in the world, can gain access to the information necessary to deliver safe anesthesia. However, there are still places in the world that do not have access to the equipment or supplies needed to implement that knowledge. This section details the essentials: the roles and responsibilities, the facilities and equipment available, the education and accreditation, the professional societies, and the research conducted by anesthesiologists around the world.

Roles and Responsibilities of Anesthesia Providers

India (Deepak K. Tempe)

In India, anesthesia can be administered only by a qualified anesthesiologist or by a trainee anesthesiologist under the supervision of a qualified anesthesiologist. In some states, such as Delhi, a directive from the government has been issued that states, "Anesthesia must be administered by a qualified anesthesiologist, i.e., an anesthesiologist with a postgraduate qualification and who has been actively working."

The duties and responsibilities of anesthesiologists have been evolving, but they have not yet been clearly defined by the ISA or health care officials (Ministry of Health). Nevertheless, it is now well recognized that an anesthesiologist's work is not limited to the operating room (OR). Typically, anesthesiologists in India are involved in the following types of care: (1) preoperative assessment and preparation of patients; (2) perioperative care of patients; (3) pain relief during the perioperative period; (4) management of critically ill patients; (5) management of acute, chronic, and cancer-related pain; (6) management and teaching of resuscitation skills; (7) provision of outpatient anesthesia services; (8) administrative involvement in setting up and managing health care organizations; (9) disaster management coordinator in the hospital; and (10) teaching and training of the medical and paramedical staff.

In addition to the duties just listed, both natural and man-made disasters have provided an extra challenge for anesthesiologists. By virtue of their ability to administer emergency life support measures, as well as their perioperative management skills, anesthesiologists were at the forefront during the Gujrat earthquake and tsunami disasters and actively participated in setting up operating theaters on site and providing care to victims. Likewise, during the Mumbai and Delhi bomb blasts, anesthesiologists played a leading role in carrying out emergency surgery and perioperative management.

Preoperative Evaluation. Despite preoperative evaluation and preparation of the patient being integral components of safe surgery, there were no dedicated preoperative anesthesia clinics (PACs) in India until recently. That began to change in the early 1980s, and today almost all hospitals have a dedicated PAC in which all patients are screened before surgery (including outpatient day surgery). PACs have become increasingly important because of a growing incidence of cardiovascular and other systemic diseases in patients undergoing surgery. In PACs anesthesiologists review and optimize the treatment of other systemic diseases, as well as detect new diseases and health concerns. In addition to improving patient outcomes, PACs help develop the patient-physician relationship and patient awareness about anesthesia. A few hospitals have started awareness programs wherein a lecture is delivered (with illustrations) on a monthly basis to patients and their relatives to make them familiar with the anesthetic techniques and procedures that they will undergo.

Operating Room. The OR continues to be the mainstay of anesthetic practice, but because ORs are the major consumers of hospital resources, as well as a major source of income for private hospitals, it is imperative that ORs be managed in the most efficient manner. However, there is no consensus on an ideal system to ensure efficiency in this area. The anesthesiologist is actively involved in trying to improve efficiency, especially with triage and scheduling of urgent and emergency cases. Safety is another concern. The professional risks (especially those related to needlestick injuries) of anesthesiologists, as well as other workers in the OR, are well recognized, and preventing such health care hazards has become an important consideration.

Recovery Room and Postoperative Intensive Care Units. Appropriate postoperative care is crucial for the success of surgery. Today in India, depending on the nature of the surgery and the patient's condition, the patient is transferred to either a recovery room or an ICU; some version of an ICU or recovery room exists in almost all major hospitals in India today. The nomenclature of these areas is not uniform, though, so terms that include postoperative ward, recovery room, high-dependence unit, critical care unit, and PACU are often used to describe the same facility. At some hospitals, especially those in which major and complex surgery requiring postoperative ICU management is not performed regularly, there is no demarcation between an

ICU and the recovery room. A single area designated as a recovery room is used for both purposes.

Where there is a distinction, the decision about where a postsurgical patient belongs is governed by the degree of morbidity. If a patient is very sick and requires ventilation and careful hemodynamic monitoring, the patient is transferred to an ICU. If mechanical ventilation and continuous hemodynamic monitoring are not required, the patient is transferred to a recovery room, which is perhaps the equivalent of the PACU. Patients undergoing daycare surgery (if practiced in a given hospital) are also transferred to the recovery room before discharge.

Most recovery rooms are under the charge of an anesthesiologist; in the case of ICUs, sometimes the anesthesiologist is in charge and sometimes not. Practice varies from place to place and is generally governed more by the logistics involved in a particular hospital than by any definite norms.

Ambulatory Care and Other Areas. Although it is recognized and appreciated that ambulatory care is a distinct possibility in a substantial number of patients, it is not practiced as much as it should be. It is difficult to provide exact figures in this matter, but in general, it is the private/corporate hospitals that practice ambulatory care. The number of government hospitals practicing ambulatory care is relatively small, mainly because of logistic reasons. That is likely to change, however, with the increasing availability of short-duration anesthetic drugs and modern surgical facilities (tools for minimally invasive surgery). Saving cost to the patient and the hospital and increasing patient turnover have been the major factors influencing interest in ambulatory care. The safety issues related to ambulatory care are well recognized, but there are no guidelines or recommendations from the ISA or any other regulatory body on this matter.

Anesthesia services are also frequently required in several other areas outside the OR. These areas tend to be less familiar to most anesthesiologists and provide less access to the facilities typically available in an OR. Their proliferation, however, has increased the demands on our profession. Areas where anesthesia is playing an increasingly prominent role include radiology suites (computed tomography, magnetic resonance imaging [MRI], and interventional radiology), the cardiac catheterization laboratory, electrophysiologic laboratories, the endoscopy room, and the electroconvulsive therapy room. In most of these areas patients require sedation, but with some lengthy procedures—such as MRI, electrophysiologic studies, and some interventional procedures—patients tend to get restless and may require general anesthesia. In addition, special considerations such as long breathing circuits or MRI-compatible equipment may be necessary. The anesthesiologist should be familiar with these requirements to maintain safety standards.

Critical Care Medicine. In the beginning, the anesthesiologist's focus on critically ill patients was ventilatory care because anesthesiologists are well versed in cardiorespiratory physiology and ventilatory management. Furthermore, managing a critically ill patient was considered an extension of the job that anesthesiologists performed in the OR. Therefore, the anesthesiologist managed patients receiving controlled ventilation via a ventilator and, ultimately, weaned the patient from mechanical ventilation.

Subsequently, however, it became obvious that respiratory function was only one aspect (albeit a crucial one) of the care of the critically ill. Anesthesiologists therefore became well informed about cardiovascular support, nutrition, infection, and various other diagnostic procedures. However, the interest of anesthesiologists in critical care medicine has been waxing and waning, and other specialists have entered this field. Currently, management of critical care units in India tends to be split: some are managed by physicians not trained in anesthesia, others by anesthesiologists.

There is widespread agreement that a critical care specialist who is devoted full-time to the care of critically ill patients should manage a critical care unit. The consensus includes three key items: (1) a dedicated expert irrespective of the specialty (if not holding a critical care qualification) should be in charge of the critical care unit; (2) each hospital can follow practices according to the availability of trained or experienced personnel with the primary aim of giving the best possible care; and (3) care of critically ill patients is always a team-based process, and the practice of taking the advice of different experts in managing a particular case is encouraged to achieve better outcomes.

Critical care training has long been part of the anesthesia residency program in India, but in 2001 the National Board of Examinations initiated a full-fledged 2-year training program in critical care medicine with 6 seats throughout India; the number has now increased to 25. Anesthesiologists, chest physicians, and general physicians are eligible to seek admission to this program. Clearly, the number of these specialized intensivists is not sufficient to cater to the critical care units that have mushroomed all over the country, so some disparities exist in the personnel involved in the management of critically ill patients.

In summary, critical care medicine has emerged as a new specialty but is still evolving in India. Because the number of persons having a qualification in the critical care area is not sufficient to fill current needs, anesthesiologists and physicians with interest in the specialty continue to practice critical care medicine. Out of a total of around 25 training seats, anesthesiologists account for about half, followed by general physicians (30%) and chest physicians (20%). The fact that all the seats in this program get filled suggests the growing interest in this specialty area.

Pain Management. Interest in managing pain, both acute and chronic, has been growing over the last 2 decades. Nevertheless, the specialty is in its infancy in India, the number of pain clinics is limited, and there is no formal training program. The focus has largely been on the treatment of chronic pain, including cancer pain. Most anesthesiology departments perform nerve blocks, with a few even practicing acupuncture. There are, however, very few departments that have the facilities to conduct procedures such as radiofrequency ablation, implantation of intrathecal pumps, or spinal cord stimulation. The thrust now is toward treating pain as a disease, especially in patients suffering from nervous disorders or in terminal cancer patients where the only possible form of management is alleviation of pain.

There is also growing awareness of the management of acute pain, including the possibility of providing the patient with a totally pain-free surgical experience. After all, the WHO now recognizes pain as the fifth vital sign, and alleviation of pain is regarded as a basic human right. Various forms of medicine and equipment (patient-controlled analgesia pumps; intrathecal, epidural, and intrapleural techniques) can now offer the possibility of a relatively pain-free course of surgical treatment. Indeed, management of acute pain during the entire perioperative period is a leading concern of all anesthesia departments and is also actively practiced in recovery rooms or PACUs. However, much needs to be done regarding pain management in India. The Indian Society

for the Study of Pain was formed in the late 1980s and currently has about 3200 members. The society is working toward improving pain management, but it is facing tough challenges, mainly because of lack of awareness. One looks forward to improving pain relief facilities in the country.

Russia (Olga Afonin)

Until the 1980s, Russia's anesthesia educational system was unified and structured into courses for nurse anesthetists and postgraduate education for physicians that included either a 1-year anesthesiology internship or a 2-year "Orditatura" (analogue of residency). All the programs included intensive care (reanimatology) as an obligatory part of the education. Participants were working in operating rooms and ICUs under the supervision of attending physicians and had a required course of lectures. Self-education was encouraged as well. After completion of training, graduates had to pass an oral qualification examination and were granted a Diploma of a Physician Anesthesiologist-Reanimatologist.

The quality of the education and the amount of experience varied significantly from program to program, and there were no universally accepted standardized examinations. Many conscientious anesthesiologists took additional courses on "qualification improvements" from the Academy of Physicians Postgraduate Education. However, there were also "specialists" whose education was finalized on completion of the courses.

By the end of the 1980s it became clear that the quality of education had to be monitored and the need for standardized examinations was debated to acceptance. Meanwhile, the Iron Curtain had become partially permeable to some of the information about accepted standards of education and care in the other countries. The future promised improvements, but not for long. The "era of stagnation" of the 1980s led to economic imbalance and a gradual decline in political structures. By the end of the 1980s, Communist leaders embarked on major reforms in an effort to revive the country's economics, which led to the collapse of the Soviet Union.

In turn, the continued financial support from the government for the entire medical structure became very thin and eventually disappeared. All the financially unsound programs, such as research, education, and development of new technologies or educational methods, were frozen. The government-funded health care system did not exist any more. Many professionals had to quit their careers for their families to survive. The private sector was in the very beginning of its development, and the great majority of the population could not afford private health care. It was not uncommon for patients to be asked to bring supplies for the medical care that they required, even for surgeries, and it was not uncommon for people to die as a result of the lack of proper medications or proper medical care. This continued until the mid-1990s, when things began to turn around. The damage, however, has not been completely overcome, even now.

As of today, anesthesiology education in Russia still requires revision and improvements. There is a need for structured residency programs that would teach the standards accepted around the world, which are based on decades of experience in the safe practice of anesthesiology. The Academy of Postgraduate Education recently introduced new standardized tests, comparable to internationally accepted graduation examinations, that would permit objective measurement of the knowledge of newly graduated anesthesiologists.

That said, with the exception of very few medical centers, most anesthesiologists have to practice their art of extremely invasive and possibly dangerous science without sufficient monitoring. Pulse oximeters, gas analyzers, and capnographs are still a luxury in many medical centers. Medical science is again government financed, but it is often still subject to the good will of the physicians who carve out time for research from their private lives. Russian anesthesiologists, as well as medics in other specialties, have been raising their concerns to the government. The Ministry of Health recently accepted a new national program for improvement in medical services, but it will take dramatic measures and significant investments in the health of Russian citizens for the country to achieve the goal of a safe and effective health care system in compliance with international standards. Statistics and the experience of multiple countries prove that the huge initial investments are returned as improvements in population health decrease medical and illness-related costs. It would be great to see Russia, the country that contributed so much to the growth and development of medicine and anesthesiology, return to the international scene as a partner in health promotion in all forms of medical science and art.

South America (Guillermo Lema)

For the past 50 years, anesthesiologists have been involved in PACUs and more recently have been responsible for them, including determination of the standards of care for these areas. Pediatric and cardiovascular anesthesia is generally performed by physicians with subspecialty training in these areas. Pain management and critical care reflect important areas where the influence of the anesthesiologist has been important. Anesthesia-trained personnel run most of these units.

Another area of interest is the choice that many physicians, including anesthesiologists, must make between public and private hospitals. For many years, anesthesiologists worked in public hospitals. Private practice came about afterward, in small clinics and in other institutions, with anesthesiologists generally continuing to work in public hospitals in the mornings. Nowadays, anesthesiologists tend to work solely in one hospital, either public or private.

Economic groups own most of the private clinics and run them under strict financial criteria. There are very strict professional duties, and the cost containment issue features heavily. Anesthesiologists, as well as other specialties, have lost control of these institutions, although a few have dedicated their time to administrative duties.

The resources given to public hospitals are increasing, but the benefit of these resources is less than one might expect, probably because of central and nonprofessional administration. Thus, economic restraints and inadequate conditions for anesthesiologists make posts in public practice less attractive than in private institutions.

Southeast Asia (Florian R. Nuevo)

The Association of Southeast Asian Nations (ASEAN) includes Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam. While maintaining their operating room presence, anesthesiologists in this region are beginning to assume duties outside the operating room.

First, having gained the respect of their medical colleagues, anesthesiologists have become an important part of perioperative

care and critical care management teams. Many are also moving toward pain management, which has paved the way to the Association of Southeast Asian Pain Societies, with the main goal of promoting further advancement in the study of pain in the region. Some anesthesiologists also practice anesthesia in conjunction with intensive care medicine. Hospice care and palliative medicine are also areas where anesthesiologists are now part of the team. In addition, ASEAN anesthesiologists have emerged as leaders in their national medical organizations and have become essential stakeholders in almost every aspect of medical and surgical care.

However, as we enter areas outside the delivery and operating suites, we must caution ourselves to slow down. ASEAN anesthesiologists must remain focused in our work, within that small space in operating theaters, where we remain the unsung heroes. Physician anesthesiologists should take full responsibility for safeguarding all patients who entrust their whole being to us while undergoing a diagnostic or therapeutic procedure—asleep, immobilized, unable to protect himself from harm—with the hope that as patients regain consciousness, they will not only be healed but comforted as well.

Europe (Lars I. Eriksson and Peter Simpson)

The main areas of work in European anesthesia departments are delivery of operating room anesthesia, postoperative care, critical care medicine, pain medicine, emergency medicine, and prehospital care. In some countries, such as Italy, Germany, Norway, and the United Kingdom, more than 30% of the daily activity of anesthesiologists is devoted to critical care medicine, and in some countries a large proportion of anesthesiologists are also involved in acute and chronic pain medicine.[18]

Delivery of anesthesia in the operating room is most often performed by anesthesiologists and nurse anesthetists, although the number of operating rooms staffed by nurse anesthetists and supervised by a certified anesthesiologist varies between countries. A recent survey has indicated that Greece, Ireland, Italy, Spain, the United Kingdom, Lithuania, Bosnia-Herzegovina, and Israel do not have programs for nurse anesthetists.[18] In all remaining countries, the number of nurse anesthetists per 100,000 population varies largely, from 0.7 in Albania and 4.9 in Turkey to 106.4 in Luxembourg. In most Western European countries (except Luxembourg and Switzerland), nurse anesthetists have undergone formal examination before graduation.

In Western European countries, surveys estimate that more than 70% of an average clinician's time is spent providing operating room anesthesia, with about 20% being spent in critical care medicine, 5% in pain control, and 5% in prehospital care.[18] A similar distribution of working time is found among non–European Union (EU) member countries from all parts of Europe, including the former Eastern Europe. Although most critical care units are staffed by anesthesiologists who have an interest and training in critical care medicine and who are associated with departments of anesthesia, in some countries an increasing number of departments of critical care medicine are staffed by dedicated specialists in critical care medicine.

Facilities and Equipment

India (Deepak K. Tempe)

In India, the journey from open-drop chloroform and ether anesthesia to the present-day high-tech operating theaters with anesthesia workstations and monitors, ICUs, PACUs, pain clinics, and preanesthetic checkup clinics is nearly complete. In fact, the ORs in India have undergone huge change during the last 2 to 3 decades. The present day OR is totally modular in structure with high-tech anesthesia workstations, monitoring systems, and online networking of the various equipment that is used. Such a change has been largely due to the arrival of private investment and management in the health care business. These corporate hospitals have built state-of-the-art ORs that match the best of the ORs in the rest of the world.

One should remember, however, that like many other things in India, diversity is also a hallmark of the health care system. Although corporate and other private hospitals have state-of-the-art ORs, government hospitals—other than those in cities such as Delhi and Mumbai—may not. In general, government hospitals cater to the general population and are overcrowded with long waiting lists. The situation in rural areas in particular is not up to the mark because these places typically have only primary health centers with basic facilities and the ORs are equipped to deal with just minor surgical procedures. Thus, ORs of several varieties can still be seen in India, and one hopes that this diversity gradually changes to uniformity in times to come.

It has been quite a challenging and turbulent journey from the days when Mahatma Gandhi was operated on with the open-drop chloroform technique to today. However, it is satisfying to see that developments in anesthesia have kept pace with time in India. Consider that recently the present Prime Minister Dr. Manmohan Singh underwent prostatectomy at the All India Institute of Medical Sciences (AIIMS). During that procedure, anesthesiologists used a balanced general anesthesia with drugs such as fentanyl, midazolam, sevoflurane, and atracurium and full-fledged monitoring. In addition, they used a patient-controlled analgesia pump for postoperative analgesia.

The Middle East (Anis Baraka)

The anesthetic machinery, monitoring equipment, and anesthetics used match the international standards that are approved by international societies, such as the American Society of Anesthesiologists. Figure 3-5 shows the operating room and illustrates monitoring of a patient undergoing coronary artery bypass grafting at the American University of Beirut Medical Center, which has updated anesthesia equipment.

South America (Guillermo Lema)

In South America, as in other places in the world, the economic resources invested in medicine and anesthesia depend on the economic situation of the country. The huge disparity in economic growth among countries in the region has produced an enormous difference in public resources allocated to health care, which has created diverse conditions for public health management. Moreover, anesthesia has been a relatively low government priority in many countries because governments often perceive anesthesia as having high cost (because of the technology) and little impact on the improvement of health care.

Nevertheless, countries with anesthesia as a mature specialty (Argentina, Brazil, Colombia, Chile, and Uruguay) have modern equipment, advanced monitoring technology, and access to all types of anesthetics and ancillary drugs, comparable to the United States and Europe. Anesthesia techniques vary, and many different types are being practiced. Anesthesia with volatile anesthetics has been used widely for many years and in all of these



Figure 3-5 The operating room at the American University of Beirut Medical Center, which shows the updated anesthesia equipment and monitoring of a patient undergoing coronary artery bypass grafting.

countries. Total intravenous anesthesia is also common these days, and the use of regional anesthesia has been widespread. Other countries, because of resource constraints, practice a more basic form of anesthesia. Regardless of resources, however, all anesthesiologists in South America need to have a strong focus on cost containment. Indeed, this situation is common globally.

Uganda/Sub-Saharan Africa (D.G. Bogod)

In a 2007 survey of more than a quarter of Uganda's anesthetic practitioners, 23% thought that their facilities met all of the widely accepted minimal standards for the practice of safe, adult anesthesia. Categories surveyed included access to updated information, basic operating room equipment, and the most basic supply of anesthetic drugs. For safe pediatric anesthesia, only 13% thought that their facility met the basic requirements.[19]

For spinal anesthesia techniques, more than half of the anesthesiologists surveyed did not have regular access to the necessary local anesthetics, and others did not have a ready supply of spinal needles. Only 23% could guarantee being able to find a brush to clean their tracheal tube between procedures.[19]

For cesarean sections in women during childbirth, nearly all of the respondents (94%) said that they did not have the facilities to perform this procedure safely. More than three quarters did not have reliable access to magnesium sulfate, and half of them said that they could never get it.[19]

As D. G. Bogod, editor-in-chief of *Anaesthesia*, wrote in the editorial of the issue in which these numbers were published:

> *The figures revealed by this survey show that despite the best efforts of all involved, 27 million Ugandans essentially enter a lottery every time they undergo anaesthesia—a lottery with poor odds of a happy outcome. What the authors cannot tell us is whether this problem is confined to Uganda alone . . . it would be foolish to try to extrapolate from one country to another, but it is unlikely that Uganda data differ wildly from most of sub-Saharan Africa. . . . If the situation in Uganda is bad, it is likely to be far worse in Ethiopia, Somalia, Tanzania and many other neighbouring countries.*[19]

Japan (Michiaki Yamakage)

The following summary of the practice and scope of anesthesia in Japan was excerpted, with permission, from the *Journal of Anesthesia*.[20]

> *In the 1980s, general anesthesia was mainly conducted using halothane or enflurane with nitrous oxide (laughing gas). Fentanyl, an opioid analgesic, was also available, but was rarely used because it was believed to cause delay in awakening. Epidural anesthesia was used more frequently then than it is now. For example, cervical epidural anesthesia was generally used in surgery on upper limbs or for breast cancer. The only intravenous anesthetics available at that time were thiamylal and ketamine, which was administered to asthma patients despite its known secretion-promoting effects. The depolarizing neuromuscular blocking drug (NMBA) succinylcholine was used for induction of anesthesia and the nondepolarizing NMBA pancuronium was the only NMBA available for maintenance of anesthesia. During the 1980s, there was no awareness of the progression of acute renal failure during emergency surgery, and some patients did not awake from anesthesia for a long time after surgery due to the prolonged effect of pancuronium.*
>
> *Since the 1980s, various anesthetic agents have become available in Japan. The availability of a large range of anesthetic agents together with the development of anesthetic monitors has made anesthesia a much safer and more comfortable procedure for patients. However, Japan (maybe due to its unique medical system) lags behind the US and Europe with regard to the use of anesthetic agents other than sevoflurane. The ultrashort-acting opioid analgesic remifentanil has finally been launched in Japan, and the fast-onset nondepolarizing NMBA rocuronium is expected to become available soon. The selective relaxant binding agent sugammadex that is currently being used in phase III clinical trials throughout the world is also expected to be approved for clinical use in the near future.*
>
> *General anesthesia with airway management using a laryngeal mask is increasing in Japan due to the promotion of this device and the widespread use of ProSeal (Laryngeal Mask, Jersey, UK), which has high sealability. The indication for this method of anesthesia depends on the anesthesiologist, although it is generally not used for laparotomy, thoracotomy, or for prolonged general anesthesia. If the device has high sealability and can withstand positive pressure ventilation, anesthetic management is sometimes performed under artificial ventilation with the use of NMBAs. The use of the laryngeal mask is expected to increase further.*
>
> *In the US and Europe, day surgery has become popular due to the high costs of hospitalization. Day surgery in Japan, however, is rare as most patients have national and private medical insurance. However, the duration of hospitalization is expected to become shorter with the introduction of a comprehensive medical system, though it is impossible to predict at present whether this will have an effect on the methods of anesthesia used.*

Methods used for postoperative analgesia differ greatly between countries, and between institutions in Japan. In the US and Europe, patient-controlled analgesia is popular, and intravenous opioids alone are used in about two-thirds of patients. The combination of intravenous opioids with epidural analgesia appears to be used only for patients who have undergone upper abdominal surgery or thoracotomy. In Japan, epidural analgesia with or without intravenous opioids is used for postoperative pain control in almost 50% of patients. When delivery of fentanyl by iontophoresis (Ionsys; Ortho-McNeil, Titusville, NJ, US), which is currently being tested in trials, becomes applicable for clinical use, the methods used for postoperative analgesia might undergo great change.

Finally, . . . the number of surgery cases in specialized hospitals, including university hospitals, is expected to continue to rise in Japan. Due to the increasingly advanced age of patients and an increase in incompatibility complications, the number of cases anesthetically managed by neural block or general anesthesia alone is also growing.

In Japan, with the launch of remifentanil, the anticipated approval of rocuronium, and when sugammadex and the fentanyl iontophoretic transdermal system become available, the methods used for anesthesia will continue to change significantly in the future.

Clinical use in Japan of xenon, an ideal anesthetic, and dexmedetomidine, a respiratory-sparing sedative, is unknown and controversial due to their high cost and prolonged effect/"off label" use, respectively.

Education, Accreditation, and Availability of Practitioners

India (Deepak K. Tempe)

In India, there are mainly two types of postgraduate qualifications that one can obtain in the field of anesthesiology. The first, provided by medical colleges (MD in anesthesiology, a 3-year degree program), is governed by the Medical Council of India (MCI), which oversees the syllabus and other teaching and training standards. The second one is provided by the National Board of Examinations, which awards a degree called Diplomate of National Board (DNB). In addition, the MCI also regulates the "diploma in anaesthesiology (DA)," which is a 2-year training program that is available at medical colleges.

In 1992 it was determined that no new medical college or postgraduate course could be started without the prior approval of the MCI, and the recommendations of the MCI became mandatory for all medical colleges. Thus, it was only after the addition of this section, known as 10a, that teaching and training in the medical field in India were standardized and minimum standards were enforced. The strength of the MCI as a regulatory body was further reinforced in 1998 by a Supreme Court judgment, which ruled that the regulations of the MCI are mandatory and must be applied to all medical colleges in India. As of now, the recognition awarded by the MCI for undergraduate courses must be reviewed every 5 years by an inspection team of the MCI.

However, this is not so for postgraduate courses. Institutions conducting a postgraduate course today can enjoy the benefit of one-time MCI recognition, but the MCI will soon implement a review process every 5 years for postgraduate courses. Thus, teaching and training in anesthesiology in India are standardized through the setting of minimum standards throughout the country in terms of the facilities (space, equipment, manpower, and infrastructure) and the syllabus.

Growth of the Specialty. The interest of Indian medical students in the specialty of anesthesiology has shown a dramatic increase during the last decade. Candidates for a postgraduate course in anesthesiology used to be admitted on the basis of scores obtained on the MBBS examination. This practice has now changed to conducting a common entrance examination, and admission to a given subject area is decided on the basis of the rank obtained by the student. In a few states such as Delhi, this has been the practice for approximately 20 years.

Table 3-1 shows the top and bottom ranks that were admitted to an MD anesthesiology program between 2002 and 2007 in the states of Maharashtra and Delhi. The table indicates that interest among students to learn and practice anesthesia is increasing. Reasons for the growing interest in anesthesia among students could be related to the increasing scope of anesthesia (as discussed earlier) and better job prospects. It may also be related to resistance to pursuing other fields, such as general surgery and general medicine, which require further subspecialty training. In Delhi, anesthesiology is among the top six specialties preferred by medical students, along with radiology, dermatology, pediatrics, orthopedics, and gynecology. This is in sharp contrast to the situation about 10 to 15 years ago, when anesthesiology was among the last five choices.

There are a total of 269 medical colleges in India with 30,000 undergraduate and 9100 postgraduate seats. Of these, there are 612 seats in MD anesthesia and 528 in DA anesthesia. In addition, the Ministry of Health and Family Welfare of India recognizes the DNB as a qualification in the given field and equates it with the postgraduate degrees awarded by other Indian universities; there are approximately 205 DNB seats in anesthesiology.

One challenge is assigning seats, especially because it remains unclear just how many anesthesiologists India needs. According to one estimate, there are approximately 28,000 anesthesiologists in India and the country requires about 7000

Table 3-1 Overall Rankings of Postgraduate Students Enrolled in Anesthesiology Programs in Maharashtra and Delhi (2002-2007)

	Maharashtra		Delhi	
Year	Top Rank	Bottom Rank	Top Rank	Bottom Rank
2002	228	854	65	98
2004	No exam		53	96
2005	405	642	32	96
2006	160	606	33	99
2007	106	504	61	85

Note: The total number of postgraduate seats in all subjects is 140 in Delhi and 450 in Maharashtra. The students often sit for entrance examinations in several states, which probably explains why the last rank exceeds the number of seats in Maharashtra.

more (data provided by the current president of the ISA at the Uttar Pradesh chapter congress in November 2007).

The Middle East (Anis Baraka)
The departments of anesthesia in the different Middle East countries consist of highly academic staff certified either by the Arab Board or foreign academic bodies, such as the American Board of Anesthesiology of the United States and the Faculty of the Royal College of Anaesthetists of the United Kingdom.

South America (Guillermo Lema)
Training of anesthesiologists is a contentious issue in South America. First, there is a large discrepancy between the views of anesthesia societies and the government with regard to the number of anesthesiologists needed. All countries on the continent have anesthesia training programs of different quality. The governments run a few, but universities conduct most of them.

There is no dispute about the length of time needed for training; regardless of who runs the program, 3 years is required to complete the training. Some countries also have specific scientific organizations run by universities and scientific societies to certify the various places where anesthesia is being taught. There are still places without proper certification that teach residents, but they are gradually being restricted from teaching.

Requirements for anesthesiologists are viewed differently by governments and scientific societies. Governments push for increased numbers of practitioners, whereas universities prefer better trained ones. Despite such difficulties, anesthesiologists and their scientific societies have campaigned for greater influence in the processes of accreditation. To the author's knowledge, only two countries have an anesthesia training program conducted by anesthesia societies; however, in those countries conflict with the government is even greater.

Further training of anesthesiologists is performed abroad, usually in Europe, the United States, or some prominent anesthesia departments in South America: Buenos Aires (Argentina), San Paulo (Brazil), and Santiago (Chile).

China (Yuguang Huang)
In Chinese medical universities, there currently exist 8-year, 7-year, and 5-year options for training in anesthesiology. Specialists in anesthesiology come mostly from undergraduate and postgraduate programs. The system of nurse anesthesiologists is not popular in China. More than 80,000 anesthesia professionals are available in mainland China, based on data from Dr. Shuren Li, Emeritus President of the CSA in 2007.

Southeast Asia (Florian R. Nuevo)
In the Philippines, the certification process for anesthesia includes three phases: a written examination, an oral examination, and practical examinations. Every year, a national anesthesia in-service examination is conducted that gives a percentile assessment of the standing of each trainee. However, even though our medical education has an American flavor, there is no reciprocity with the United States. Everybody must still comply with the licensure requirements or examinations prescribed by the United States to be able to pursue fellowships in anesthesia subspecialties. Thailand, Singapore, Malaysia, and Indonesia have their own framework of certification, one that is more European in context and process.

For basic training on the fundamentals of anesthesiology, many Indonesians prefer to go to the Philippines. In addition, the WFSA supports a regional training center for Southeast Asian countries in Bangkok, Thailand. It is called the Bangkok Anesthesia Regional Training Center and has graduated anesthesiologists from Laos, Myanmar, Cambodia, and Mongolia.

The Anesthesiology Center for the Western Pacific in Manila, Philippines, is a joint activity of the WHO Regional Office for the Western Pacific, the University of the Philippines, the China Medical Board, and the WFSA. It is an 11-month course in anesthesia that was initiated in January 1970. The rationale for this center was to help alleviate the shortage of reliable anesthesiologists in the region and to underscore the importance of administering safe anesthesia. The center does not seek to provide a complete training program, but rather its purpose is to emphasize the basic sciences in anesthesiology. It creates a foundation for students to build on so that they can eventually qualify, through further training, as specialist anesthesiologists. Students come to the center from the Pacific Islands, Southeast Asia, southern Asia, Hong Kong, Taiwan, Korea, Japan, Iraq, Russia, and Sudan. The program has served the region for 16 consecutive years, and many of its graduates have become respected anesthesiologists and contributed to the development of anesthesia programs and safe anesthesia care in their respective countries. If further studies or a fellowship in anesthesia specialties is desired, Singapore and Malaysia are two countries that can offer these particular courses.

At present, only the societies of Malaysia, Singapore, and Philippines have a written monograph on the guidelines for minimum requirements in delivering safe anesthesia practice. The government of Malaysia supports the activity of a national medical audit system and includes respectable physicians from all specialties. Apart from Singapore, most ASEAN anesthesia programs have not developed a quality assurance program. In effect, we have no factual regional database to document and monitor anesthesia-related morbidity and mortality.

Organizations, certification requirements, and recognition of anesthesiologists in Southeast Asian countries are summarized in Table 3-2. Workforce, scope, and type of anesthesiology practice are summarized in Table 3-3.

A shortage of physician anesthesiologists has become a persistent problem in densely populated Southeast Asian countries such as Indonesia, Philippines, and Thailand. The Philippines has the largest number of physician anesthesiologists in this region but is beset by maldistribution of qualified anesthesiologists, with more found in urbanized areas and the majority electing to engage in private (not public) hospital practice.

One strategy to address this personnel shortage is to formally conduct training of nurse anesthesiologists. Unlike the situation in the United States, where nursing programs independently train nurse anesthesiologists, both Indonesia and Thailand have developed formal courses for nurse anesthesiologists. These nurse anesthesiologists are supervised by physician anesthesiologists—and there is a clearly defined demarcation of responsibilities between physician anesthesiologists and nurse anesthesiologists. Hence, through an anesthesia care team composed of physicians and nurses working together, they found the answer to the crying need for anesthesia services in Indonesia and Thailand.

In the Philippines, nurse anesthesia practice is considered illegal. It is not allowed under the Nursing Act of the country. Moreover, the Philippine Society of Anesthesiologists maintains

Table 3-2 Organizations, Certification Requirements, and Recognition of Anesthesiologists in Southeast Asian Countries

	Indonesia	Malaysia	Philippines	Singapore	Thailand
Training	4 years' medicine 1.5 years' internship 3.5 years' residency	Patterned after the British Stringent examination and promotion requirements	Patterned after the United States 3 years' residency	Patterned after the British Stringent examination and promotion requirements	3 years' residency
Certification/certifying organization/continuing medical education	Collegium of Indonesian Anesthesiologist		Philippine Board of Anesthesiology	Singapore Society of Anesthesiologists	Royal College of Anesthesiologists in Thailand
Societies	Indonesian Society of Anesthesiologists & Reanimateurs	Malaysian Society of Anaesthesiologists	Philippine Society of Anesthesiologists	Singapore Society of Anesthesiologists	
Roles outside the operating room			Critical care Pain management	Critical care Pain management	
Recognition by peers/accomplishment	Neuroanesthesia fellowship	National Anesthesia Day		Head of critical care	

that anesthesiology is a practice of medicine and will not allow nurses to deliver anesthesia care.

It is rather sad that the practice of medicine in Philippine government hospitals is not able to provide decent remuneration for the majority of its health care providers, including physician anesthesiologists. Migration of physicians to seek better alternatives in greener pastures is a reality. With the high demand for nurses worldwide, it is also not unusual for some physicians to take a 4-year bachelor's degree in nursing and decide to migrate abroad to work professionally as nurses.

Uganda/Sub-Saharan Africa (D.G. Bogod)

In a survey by Hodges and colleagues, there was only 1 medical anesthesiologist among the 91 anesthesia practitioners who participated in the survey, which means that as is so often the case, many trained physicians in Uganda probably traveled to the West to find a better life for their families. In addition, based on the survey, access to up-to-date textbooks seems iffy at best—fewer than half of those surveyed have access to such texts.[18]

Europe (Lars I. Eriksson and Peter Simpson)

As a geographic area, Europe consists of more than 30 countries, a number of which, during the last decade, have undergone the dynamic process of integration into the EU. Although a core of European countries has had a strong impact for many years on development of the EU, several other countries, many of them belonging to the former Eastern Europe, are still candidates or potential candidates for entry into the EU. Europe is therefore a heterogeneous region and group of countries, which is reflected in the large variation in medical systems, research, and education, as well as language and culture. Over the years, continuous expansion of the number of countries associated with the EU has inevitably affected financial, monetary, labor, and educational systems in the other member states. Inevitably, this has also changed health care systems and provided a new impetus for increased migration of qualified health care workers and academic personnel between member states. Partly because of the large variation in social welfare and financial systems between parts of Eastern Europe and the traditional Western European countries, the net

Table 3-3 Workforce, Scope, and Type of Anesthesiology Practice in Southeast Asian Countries

	Indonesia	Malaysia	Philippines	Singapore	Thailand
Workforce					
Physician anesthesiologist	Yes	Yes	Yes	Yes	Yes
Nurse anesthesiologist	Yes	No	No	None	Yes
Scope of Practice					
Operating room*	Yes	Yes	Yes	Yes	Yes
Intensive care	Yes	Yes	Slowly developing	Yes	Yes
Pain management	Yes	Yes	Yes	Yes	Yes
Type of Practice					
Anesthesia care team (physician, nurse, technician)	Yes (physician has a supervisory role)	No	Limited group practice (consisting of physicians)	No	Yes (physician has a supervisory role)

*Includes anesthesia services for inpatient, ambulatory/office-based, and diagnostic procedures.

migration of health care workers has deprived many low-income countries of their own medical staff. In addition, new working time directives in Western European countries have led to increased demand for physicians, and taken together, these two issues have encouraged emigration from Eastern European countries. In general, the many changes brought about by the integration of new countries into the EU continue to have an impact on the practice of medicine in Europe, and in this context the practice of anesthesiology is no exception.

The average number of anesthesiologists within Western European countries has increased over the last decade from 10.8 to 14.5 per 100,000 population.[18,21] In contrast, among non-EU Eastern European countries, the average number of anesthesiologists is currently 6.1 per 100,000 population.[18] Hence, there is large variation in both the supply and demand of anesthesiologists between parts of Europe.

In most European countries, health care is funded by the government, although local exceptions to this rule exist. Whereas more than 50% of anesthesiologists in some Western European countries (Luxembourg, The Netherlands) are involved in private practice, anesthesiologists within Scandinavia and the United Kingdom rarely (less than 5%) work in private practice.

The European Diploma in Anesthesiology and Intensive Care (EDA). The EDA, introduced in 1984, is a two-part examination intended as a comprehensive test of knowledge of anesthesiology, critical care, and pain management. It provides an international European standard that allows harmonization of training and assessment of knowledge across all European countries and is used by some (Switzerland, Austria, Hungary, and Poland) as part of their internal examination structure. Both parts of the examination take place in designated centers across Europe, depending on demand. Part 1 consists of multilingual, multiple-choice questions available in English, French, German, Italian, Spanish, and Russian. It consists of two multiple-choice sections, one on basic physiology, pharmacology, physics, clinical measurement, and statistics and the other on clinical practice associated with anesthesia and its subspecialty areas. It is intended to be taken after approximately 2 years of anesthesia training. Part 2 consists of four oral examinations, each with two examiners moderating each other. Guidelines for the content of these oral examinations are determined by the examination committee, and each examination is divided again into clinical practice, intensive care medicine, and general anesthesia. Candidates may choose the language in which they wish to be examined within the constraints available at the examination center.

Success in Part 2, which is an end-of-training examination, qualifies the candidate to receive the EDA. Because the EDA is an assessment of anesthetic knowledge, it can in no way substitute for the local assessment of skills and professional attitudes or behavior that takes place in each country according to local systems and is a requirement before an individual can be placed on the specialist register of their country. Because entry onto a person's national specialist register is necessary before award of the EDA, it follows that anyone passing the Part 2 examination also has to provide evidence of specialist registration before receiving the EDA itself. Thus, the EDA examination is a test of knowledge, embedded in and dependent on assessment of clinical skills and attitudes, that is provided by the national training program.

In addition to the examination itself, there is also the option for those wishing to assess their level of knowledge to take the Part 1 EDA as an in-training examination at a much reduced fee. This not only allows personal assessment of one's knowledge but also includes detailed feedback so that candidates can assess their own performance—both in comparison to those in their national peer group and in comparison to candidates in other parts of Europe—in areas as detailed as cardiovascular physiology and other fields.

The ESA/EBA Joint Hospital Visiting and Accreditation Program (HVAP). The HVAP has been in place since January 1996 as a joint permanent committee of the European Society of Anaesthesiology (ESA, formerly the European Academy) and the European Board of Anesthesiology (EBA), its main goal being to encourage and enhance training standards across Europe and to ensure that an academic institution meets the prerequisites of training in anesthesia as set out in the EBA training guidelines (1996). Together with the EDA, the HVAP serves to improve the overall quality of the specialty of anesthesia and to harmonize its activities throughout Europe. The visit consists of a detailed presentation of the staffing and organization of the hospital, the department (or the institute), and the structure of training. This forms the basis for discussion and evaluation of all aspects of the teaching and training process with the staff members involved for the purpose of complementing and building on strengths and encouraging development and change to address areas of weakness. A subsequent comprehensive report of the visit, together with recommendations for improvement or accreditation (or both), is presented by the program committee.

Standardizing the Quality of Patient Care in Anesthesiology and Intensive Care. In recent years the opportunity for accredited specialists in anesthesiology and intensive care to work and move between different European countries has increased considerably. EU legislation allows such free movement of specialists, which in many ways is beneficial to everyone. In such circumstances, it is essential to ensure that the quality and safety of care that patients receive is sustained and enhanced. Training and accreditation programs inevitably vary between member states and even within countries that lack a single national organization. The EBA is uniquely placed to ensure that appropriate standards are set to achieve harmonization in the quality and safety of patient care, and two important areas of standardization are already in place: the joint HVAP and the EDA.

At the present time, although the standards of well-established training and accreditation programs are known and thus acknowledged across many European states, others are not, particularly in some of the countries that have recently joined the EU. As a result, those trained in these countries are potentially unfairly disadvantaged. Their specialists wish to move freely as much as others and should be able to do so. Equally, those appointing them to specialist posts need a uniform quality standard to ensure the delivery of high-quality and safe patient care. Individual countries' specialist qualifications do vary, and an international assessment standard to facilitate free movement of specialists is needed. New proposals for EBA membership and fellowship have been developed and agreed on and build on the initiatives and programs already in place. These proposals are in addition to—but do not replace—national qualifications or competence in discourse or dialogue and allow those who desire to clearly demonstrate their ability to deliver anesthetic care of a uniformly high standard to patients. They are marks of individual

excellence in the specialty and can be awarded only after European national accreditation as a medical specialist in anesthesiology is achieved. They will be open to anesthesiologists who are nationals of any country in the world and who are on the specialist anesthesiology register of a European country. They will be strictly awarded to individuals in recognition of their personal achievement and not automatically to all those working in a particular hospital or anesthesiology department. However, they will have no legal standing and do not in themselves confer a right to practice in a country of the EU.

Subspecialization

India (Deepak K. Tempe)
For more than 2 decades, anesthesiologists have recognized the need for dedicated practice in the field of cardiac anesthesia and neuroanesthesia. There are anesthesiologists who are working exclusively in these specialties, but there are no separate departments of cardiac anesthesia and neuroanesthesia. AIIMS is an exception in this respect because it created two such departments in 1986. Postdoctoral courses in these specialties have been started in the country. AIIMS has conducted the courses in both specialties since 2002, whereas the Sri Chitra Tirunal Institute of Medical Sciences, Thiruvananthpuram, has offered a course in cardiac anesthesia since 2003. The number of seats, however, is grossly inadequate, with four seats in cardiac anesthesia and two in neuroanesthesia. The National Board of Examinations started a DNB fellowship program (2 years) in cardiac anesthesia in 2002; it began with four seats, and the number has increased to 18.

South America (Guillermo Lema)
In South America, only Colombia has a specialty law. In all other countries, physicians can perform professional actions without a law to certify the proficiency and quality of care and protect patients. In fact, physicians with a very low level of training have practiced anesthesia for many years; in most of the countries, paramedical personnel have performed anesthesia because of lack of sufficient medical personnel or interest in the specialty. In some countries, surgeons perform both anesthesia and surgery with the help of technical personnel. This practice has been abandoned in most countries, but in a few—Bolivia, Ecuador, Paraguay, Peru, and Venezuela—this situation persists, with government authorization.

Nowadays, the law in most countries specifies that only physicians can provide anesthesia. The problem is a shortage of trained physicians, so some countries are left with inadequately trained ones. Nevertheless, the process of certification of specialties, including anesthesia, is on the way. Most countries have medical organizations and anesthesia societies demanding proper certification methods. In some countries these medical organizations have obtained the support of the government. So even though a law does not exist, there is an intense effort to gain official certification. Medicolegal issues and increased concern from patients have helped. It is interesting that most anesthesiologists are willing to obtain certification; clinics and hospitals are also requiring certification for physicians to work in these institutions.

Professional and Research Activity

India (Deepak K. Tempe)
Since its inception in 1947, the ISA has grown from 19 members in 1947 to nearly 12,000 in 2007. Today, there are also separate Indian associations of cardiothoracic anesthesia and neuroanesthesia. The Indian Association of Cardiovascular and Thoracic Anesthesiologists (IACTA) is 10 years old and holds an annual meeting. IACTA also publishes the journal *Annals of Cardiac Anaesthesia*, which is now in the 10th year of publication and is the first Indian journal in anesthesia to be indexed in the National Library of Medicine and included in the MEDLINE database. In addition, there are societies of critical care medicine (founded in 1992) and for the study of pain.

The Middle East (Anis Baraka)
Most anesthesiologists in the Middle East are in close contact with developments in anesthesia throughout the world through attending congresses and lectures, publications, subscriptions to various international anesthesia journals, and building of worldwide friendships.

Some anesthesiologists in the Middle East, including those who have emigrated abroad, have become leaders in the specialty and have made original contributions in the fields of muscle relaxants,[22-24] semiopen systems, obstetrics,[25] pediatric anesthesia,[26,27] and the pathophysiology of open heart surgery.[28]

South America (Guillermo Lema)
Time, funding, and expertise are the basic requirements for research of sufficient quality to support publications or communications internationally. These requirements are not found widely in South America. Only a few university anesthesia departments have the capability of producing clinical research of high enough quality to be published in esteemed journals such as the Institute for Scientific Information (ISI), most notably in Chile. Some colleagues have argued that research is not important in a continent that has more pressing priorities. I do not agree.

Research is also a tool for learning and it should be encouraged, at least at university-based anesthesia residencies. Unfortunately, research does not generate income, so most of the clinical groups are not willing to dedicate time to this particular activity. Funding is lacking, and although some countries have national research grants to support clinical research, most do not. Support from drug companies is weak and usually depends on the impact that their drugs have in our clinical setting. Because of economic constraints, a large number of generic drugs are used, so major pharmaceutical companies are not willing to support research activities. In short, basic research in anesthesia virtually does not exist in South America.

Anesthesia meetings achieve the goal of educating residents and older generations of anesthesiologists. Anesthesia journals are in existence, and although none of them are ISI, effort is being made to enter the international medical databases.

China (Yuguang Huang)
The CSA was founded in 1979 at the Second National Conference held in Harbin. Professor Deyan Shang was elected president of the first CSA committee. Since then, a national CSA conference has been held every 3 or 4 years. In 1986, the Beijing International Conference on Anesthesia was held successfully. Many famous

experts from abroad, including Professor Ronald Miller (this textbook's editor), were invited to join as keynote speakers.

From that point on, Chinese anesthesiologists began to communicate more with international professionals. At the first Sino-Japanese Clinic Anesthesia Symposium held in 1986, the CSA and Japan Society for Clinical Anesthesia agreed to hold a symposium every 2 years. Professor Ailun Luo, after being selected president of CSA in 1997, advocated China's integration into the world anesthesia community. The National Conference on Anesthesia is held annually on the second weekend of every September.

Regarding professional publications, Professor Rong Xie was chief editor of the *Encyclopedia of Chinese Anesthesia Medicine* in 1986. Professor Jun Zhao was the chief editor of *Modern Anesthesiology* in 1987. These books have contributed to the development of clinical and research anesthesiology in China. Two academic journals, *Chinese Journal of Anesthesiology* and *Journal of Clinical Anesthesiology*, were launched in 1981 and 1982 by the Chinese Medical Association. Besides these two journals, the *International Journal of Anesthesiology and Resuscitation* and the *Chinese Journal of Pain Medicine* have formed a good platform for rapid communication among Chinese anesthesiologists.

From the 1990s until today, research in Chinese anesthesiology has moved as fast as the economy of China. The CSA has built good cooperative relationships with many international associations, such as the American Society of Anesthesiologists, the International Anesthesia Research Society, and the Association of Anaesthetists of Great Britain and Ireland, among others. Many well-known journals including, *Anesthesia & Analgesia*, *Anesthesiology*, and *Anaesthesia*, have been published with Chinese editions, which has extended their influence among Chinese professionals. These localized journals will become the window for communication in anesthesiology between China and the world.

Southeast Asia (Florian R. Nuevo)

To lessen the variability in medical practice and anesthesia care—and with the vision of fostering more understanding and cooperation among ASEAN anesthesiologists—two pioneering anesthesiologists (Professor Quintin J. Gomez of the Philippines and Dr. Saywan Lim of Malaysia) conceived of the Confederation of ASEAN Societies of Anesthesiologists (CASA). This took place in Kuala Lumpur in September 1974 during a meeting after the Fourth Asian Australasian Congress of Anaesthesiologists, a regional congress of the WFSA.

The main objective of CASA is to enhance and promote the specialty of anesthesiology in the region by hosting biennial congresses of anesthesia called the ASEAN Congress of Anaesthesiologists. These congresses serve as a venue for ASEAN anesthesiologists to meet experts from the United States and Europe, as well as other international anesthesia leaders, and to learn current practices in anesthesia from them. They also inspire trainees and younger anesthesiologists in Southeast Asia to present their clinical trials and modest research activity and participate in scientific activities as resource speakers or workshop facilitators.

The first such congress was held in December 1979 in Manila, Philippines, under the leadership of Professor Gomez, who was then the incumbent president of the WFSA (1976-1980). More than 400 delegates came from Indonesia, Malaysia, Philippines, Singapore, Thailand, Japan, Taiwan, Hong Kong, and the United States. Professor John Bonica (United States) was the guest of honor and main invited speaker; Professor Bonica would later become president of the WFSA.

Over time, the objectives of CASA have grown. The group has strived to promote closer ties among member societies, to enhance the image of the specialty in the region, and to upgrade the specialty through exchange of information between local and international experts in anesthesia. Indeed, through CASA there has been an information avalanche that has paved the way to further upgrade and develop the practice of anesthesia and anesthesiologists themselves.

Unfortunately, of late, economic depression and terrorism—as well as health threats such as bird flu and severe acute respiratory syndrome (SARS)—have threatened these academic activities. Nevertheless, the ASEAN confederation has persisted in hosting its biennial congress. The five founding members take turns, with much enthusiasm and camaraderie, in hosting these meetings. Attendance has grown from 400 to almost a thousand anesthesiologists coming from ASEAN and non-ASEAN countries, such as Japan, Korea, China, Saudi Arabia, Mongolia, Canada, and the Middle East. The faculty of speakers includes local ASEAN and international anesthesia experts from the United States, Europe, Canada, Australia, and New Zealand, some of whom were supported by the WFSA, by industry, by respective anesthesia societies, and by the faculty themselves.

Currently, each of the CASA member organizations is conducting clinical research activities in anesthesia, but there is much room for improvement. Most research studies involve clinical drug trials funded by pharmaceutical companies, but there is a paucity of published papers in peer-reviewed anesthesiology. What is lacking is translating the research activities into well-written research papers.

The *ASEAN Journal of Anesthesiology* (AJA) is only 8 years old. Thus far it has served as an avenue to publish all of these research endeavors in the region. We encourage all member societies to submit their research papers for publication. The current seat of editorship of the AJA is located in Singapore. Perhaps to encourage more output, future ASEAN Congress of Anaesthesiologists meetings may provide incentives for participation in free papers and poster discussion sessions.

Europe (Lars I. Eriksson and Peter Simpson)

Before formation of the European Academy of Anaesthesiology in 1978 there was no formal representative structure for the specialty within Europe. The five statutory aims of the academy were to (1) raise the scientific level of the discipline; (2) improve the training of anesthetists, their clinical and theoretical education, and their competence at the completion of the training period by holding examinations; (3) hold scientific meetings, conferences, and seminars; (4) facilitate research in anesthesia and its associated disciplines; and (5) promote exchange among anesthetists and discussion of all matters concerning their profession.

The European Academy of Anaesthesiology had a limited number of members and academicians and, as European anesthesiology grew, was perceived by many to be an exclusive organization. In 1992, the ESA was formed and was open to everyone. Its chief aims were to conduct an annual Euroanesthesia meeting to replace the European Congress, which had formerly run on a 4-year cycle alternating with the World Congress, and to support educational and research activities by awarding grants and fellow-

ships. Whereas the ESA was concerned with the practice of clinical anesthesia and supporting its membership, the European Academy of Anaesthesiology had developed formal initiatives such as the EDA, the *European Journal of Anaesthesiology* (EJA), and a system of hospital visiting and accreditation training in conjunction with the Anesthesiology Board and Section of the UEMS (Union Européenne des Médecins Spécialistes or European Union of Medical Specialists).

The fourth organization that existed at that time was the Confederation of European National Societies of Anesthesiology (CENSA), which was effectively the European section of the WFSA.

For some years, the roles of all the various organizations were increasingly complementary, thus making it necessary for an individual anesthesiologist to be a member of more than one body to participate in and benefit from all the variety of activities. As a result, in 1998 a decision was made to amalgamate the former ESA, the European Academy, and CENSA into one organization. A temporary organization, the European Federation of Anaesthesiologists, was established in 2001, under which amalgamation was successfully achieved, and the new European Society of Anaesthesiology, which thus represents every anesthesiologist in Europe, was launched in January 2005 in its interim form before becoming fully established in January 2006. Moreover, because the formal, declared responsibilities of the parent organizations were essentially different and there was very little overlap between them, a strong and comprehensive organization could be established right from the start. Under this new organizational structure, CENSA became the ESA's National Anaesthesiology Societies Committee, now ESA National. Each country has a number of delegates to ESA National, depending on the number of members of its National Society.

The ESA now provides a comprehensive range of activities to support European anesthesiology, primarily aimed at sustaining and enhancing the safety, efficacy, and quality of care of patients. Through publication of the EJA and the Euroanaesthesia organization and other meetings, it supports the interests of its members and facilitates the exchange and dissemination of information related to anesthesiology, critical care, pain, and emergency medicine. It encourages research and scientific progress both by conducting academic meetings and by awarding grants and fellowships and has a key role in raising and harmonizing the standards of anesthesiology. This is achieved by delivering education, training, continuous medical education, and accreditation of anesthetists through educational programs, the EDA, and in-service training examinations, as well as through the HVAP run jointly with UEMS.

UEMS represents national associations of medical specialists in the EU and its associated countries. UEMS provides general and specialist medical advice to ministers. It is also responsible for the European Accreditation Council for Continuing Medical Education. Each specialty has its own board and section, the members of which are drawn from all the EU member states together with Norway and Switzerland. The EBA has two delegates per country, one professional and one academic. UEMS itself is a nonprofit organization concerned with (1) the study, promotion, and harmonization of the highest level of training of medical specialists, medical practice, and health care within the EU; (2) study and promotion of free movement of specialist doctors within the EU; (3) representation, within this framework of medical specialists in the member states of the EU, to EU authorities and to any other authority with similar responsibility; and (4) protection of the professional interests of European medical specialists. UEMS defines a medical specialist as a physician who has satisfactorily completed a specialist training program in a recognized specialty that conforms to the UEMS charter on specialist training.

Thus, European anesthesiologists are represented in several ways. Those in EU member states, together with Norway and Switzerland, are represented nationally through their country's membership in the UEMS Anesthesiology Board and Section. Additionally, anesthesiologists in all European countries are represented nationally as members of their respective national society through that society's delegates to the ESA, through the ESA council via their national elected council member, and individually as active members of ESA.

THE *EUROPEAN JOURNAL OF ANESTHESIOLOGY*. The EJA is the official journal of the ESA and is distributed to all ESA members. It is published and owned by the ESA. The EJA is also the official journal of a variety of organizations (EACTA, UEMS, FEEA) and is distributed to all members of these societies. It is published monthly and run by an editorial board that is not directly involved in any editing or editorial work and by a 19-member "group of editors" who are responsible for the content of the journal itself. The EJA has two main functions: to publish peer-reviewed original articles and reviews in the field of anesthesia, pain, emergency medicine, and critical care, together with correspondence pertaining to these articles, and to provide educational material with appropriate methods of self-assessment for ESA members. The ESA also publishes a newsletter four times a year, separately from the EJA, that contains items of interest to ESA members together with information and formal announcements.

Conclusion

As demonstrated in this chapter, anesthesiology as a discipline and a profession has grown dramatically around the world. Differences in the rate of growth and scope of practice exist for a variety of reasons, largely because of disparities in resources and socioeconomic and political factors. Nevertheless, regardless of country of residence, patients can feel much safer today with regard to receiving anesthesia than even 20 or 30 years ago. As noted repeatedly throughout this chapter, some of the most powerful advances are the spread of knowledge, professional integrity, curiosity, and the utmost desire to practice anesthesiology at the highest possible level. This means that anesthesiologists not only can learn of the advances of their colleagues elsewhere but can also better understand and respond to the needs of others.

So where do we go from here? Some authorities suggest that we take advantage of the latest advances to further the interconnectedness of our profession, such as conducting more in-depth comparisons of the effectiveness of various techniques from country to country and engaging in more joint research. Others believe that such comparisons would serve no useful purpose given the disparities in resources and different approaches to care. The editor has dreamed of the day that anesthesiologists worldwide would form global think tanks to ask and answer the most important questions to advance our intellectual foundations and benefit society.

As is noted in the opening paragraph, the purpose of this chapter is not to invite comparisons or highlight differences in the practice of anesthesiology around the world, but rather to encourage and invite anesthesiologists globally to keep talking to each other. The editor was thrilled and honored that his invitation to contribute to this chapter has resulted in so many interesting contributions from leaders of anesthesia worldwide. When viewed together, the journey of anesthesiology has been an amazing story worldwide.

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C. William Hanson

4 Medical Informatics

Key Points

1. A computer's hardware serves many of the same functions as those of the human nervous system, with a processor acting as the brain and buses acting as conducting pathways, as well as memory and communication devices.
2. The computer's operating system serves as the interface or translator between its hardware and the software programs that run on it, such as the browser, word processor, and e-mail programs.
3. The hospital information system is the network of interfaced subsystems, both hardware and software, that coexist to serve the multiple computing requirements of a hospital or health system, including services such as admissions, discharge, transfer, billing, laboratory, radiology, and others.
4. An electronic health record is a computerized record of patient care.
5. Computerized provider order entry systems are designed to minimize errors, increase patient care efficiency, and provide decision support at the point of entry.
6. Decision support systems can provide providers with best-practice protocols and up-to-date information on diseases or act to automatically intervene in patient care when appropriate.
7. The Health Insurance Portability and Accountability Act is a comprehensive piece of legislation designed in part to enhance the privacy and security of computerized patient information.
8. Providers are increasingly able to care for patients at a distance via the Internet, and telemedicine will continue to grow as the technology improves, reimbursement becomes available, and legislation evolves.

Computer Hardware

Central Processing Unit

The central processing unit (CPU) is the "brain" of a modern computer. It sits on the motherboard, which is the computer's skeleton and nervous system, and communicates with the rest of the computer and the world through a variety of "peripherals." Information travels through the computer on "buses," which are the computer's information highways or "nerves," in the form of "bits." Bits are aggregated into meaningful information in exactly the same way that dots and dashes are used in Morse code. Bits are the building blocks for both the instructions, or programs, and the data, or files, with which the computer works.

Today's CPU is a remarkable piece of engineering, totally comparable in scope and scale to our great bridges and buildings, but so ubiquitous and hidden that most of us are unaware of its miniature magnificence. Chip designers essentially create what can be thought of as a city, complete with transportation, utilities, housing, and a government, every time they create a new CPU. With each new generation of chips, the "cities" grow substantially and yet remain miniaturized to the size of a fingernail.

For the purposes of this text, the CPU can be treated as a black box into which flow two highways: one for data, the other for instructions. Inside that black box, the CPU (Fig. 4-1) uses the instructions to determine what to do with data—for example, how to create this sentence from my interaction with the computer's keyboard. The CPU's internal clock is like a metronome pacing the speed with which the instructions are executed.

Most people think that the clock speed of the CPU, which is measured in megahertz, or millions of instructions per minute, determines the performance speed of the unit. In reality, the performance of a CPU is a function of several factors that should be intuitive to anesthesiologists when an operating room (OR) analogy is used. Let us compare the clock speed to surgical speed, where a fast clock is comparable to a fast surgeon and vice versa. CPUs also have what are called caches, which are holding areas

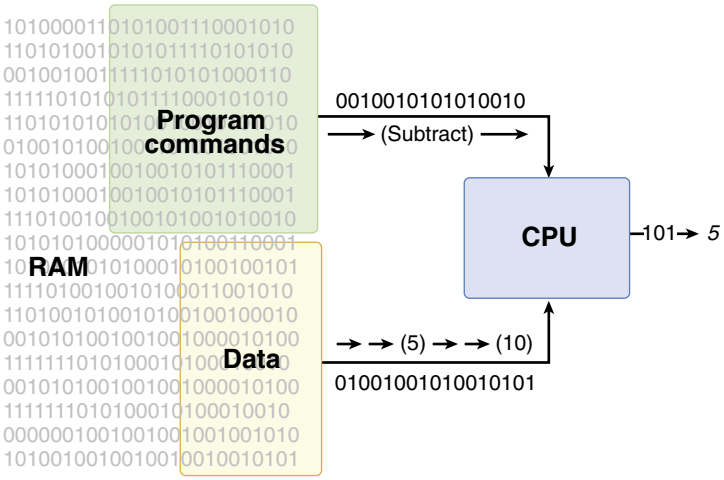

Figure 4-1 Programs and data are stored side by side in memory in the form of single data bits—the program tells the central processing unit (CPU) what to do with the data. RAM, random-access memory.

for data and instructions, quite comparable to preoperative holding areas. Information is moved around in the CPU on buses, which can be likened to the number of ORs. In other words, it is possible to have a CPU that is limited because it has a slow or small cache, in the same way that OR turnover is limited by the lack of preoperative preparation beds or too few ORs for the desired caseload.

The speed of a processor is a function of the width of its internal buses, clock speed, the size and speed of internal caches, and the effectiveness with which it anticipates the future. Although this last concept may seem obscure, an OR analogy would be an algorithm that predicts a procedure's length based on previous operations of the same type by the same surgeon. Without going into detail, modern processors use techniques called *speculation*, *prediction*, and *explicit parallelism* to maximize efficiency of the CPU.

True general-purpose computers are distinct from their predecessor calculating machines in that regardless of whether they are relatively slow and small, as in dedicated devices such as smart phones, or highly streamlined and fast, as in supercomputers, they can perform the same tasks given enough time. This definition was actually formalized by Alan Turing, who is one of the fathers of computing.

Each type of CPU has its own instruction set, which is essentially its language. Families of CPUs, such as Intel's processors, tend to use one common language, albeit with several dialects, depending on the specific chip. Other CPU families use a very different language. A complex–instruction set computer (CISC) has a much more lush vocabulary than a reduced–instruction set computer (RISC), but the latter may have certain efficiencies relative to the former. It is the fact that both types of computer architecture can run exactly the same program (i.e., any windowed operating system) that makes them general-purpose computers.

Memory

Computers have a variety of different kinds of memory ranging from very small, very fast memory in the CPU to much slower, typically much larger memory storage sites that may be fixed (hard disk) or removable (compact disk, flash drive).

Ideally, we would like to have an infinite amount of extremely fast memory immediately available to the CPU, just as we would like to have all of the OR patients for a given day waiting in the holding area ready to roll into the OR as soon as the previous case is completed. Unfortunately, this would be infinitely expensive. The issue of ready data availability is particularly important now, as opposed to a decade ago, because improvements in central processing speed have outpaced gains in memory speed such that the CPU can sit idle for extended periods while it waits for a desired chunk of data from memory.

Computer designers have come up with an approach that ensures a high likelihood that the desired data will be close by. This necessitates the storage of redundant copies of the same data in multiple locations at the same time. For example, the sentence I am currently editing in a document might be stored in very fast memory next to the CPU, whereas a version of the complete document, including an older copy of the same sentence, could be stored in slower, larger-capacity memory (Fig. 4-2). At the conclusion of an editing session, the two versions are reconciled and the newer sentence is inserted into the document.

The very fast memory adjacent to the CPU is referred as cache memory, and it comes in different sizes and speeds. Cache memory is analogous to the preoperative and postoperative holding areas in an OR in that both represent rapidly accessible buffer space. Modern computer architectures have primary and secondary caches that can either be built into the CPU chip or be situated adjacent to it on the motherboard. Cache memory is typically implemented in static random-access memory (SRAM), whereas the larger and slower "main memory" consists of dynamic random-access memory (DRAM) modules. RAM has several characteristics, including the facts that it can be read or written (in contrast with read-only memory), it disappears when the electricity is turned off, and it is much faster than the memory on a disk drive.

To understand the impact of the mismatch in memory access times and CPU speed, consider the following. Today's fastest hard disks have access times measuring about 10 milliseconds (to get a random chunk of information). If a 200-mHz CPU had to wait for 10 milliseconds between each action requiring new data from a hard disk, it would sit idle for 2 *million* clock cycles between each clock cycle used for actual work. Furthermore, it takes 10 times longer for the computer to get data from a compact disk or digital video disk than it does for data from a hard disk.

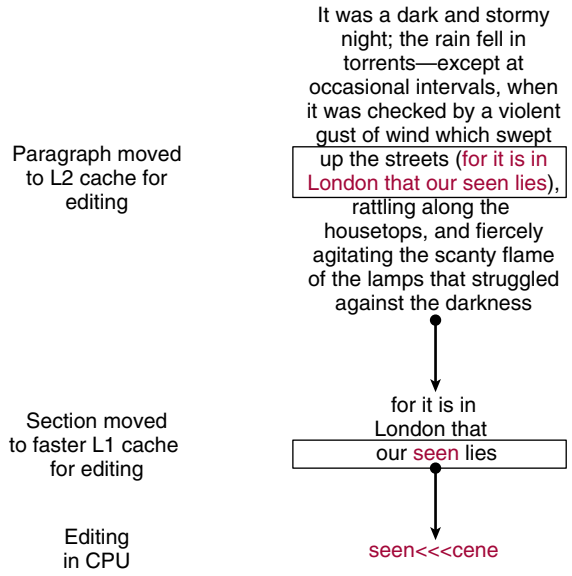

Figure 4-2 Processing of text editing using several "memory" caches in which duplicate copies of the same text may be kept nearby for ready access.

Communications

There are many functionally independent parts of a computer that need to communicate seamlessly and on a timely basis. The keyboard and mouse have to be able to signal their actions, the monitor must be refreshed continuously, and the memory stores have to be read and written correctly. The CPU orchestrates all of this by using various system *buses* as communication and data pathways. Whereas some of the buses are dedicated to specific tasks on newer computers, such as communication with the video processor over a dedicated video bus, others are general-purpose buses.

Buses are analogous to highways traveling between locations in the computer (Fig. 4-3). In most computers, the buses vary in width, with the main bus typically being the widest and other buses narrower and therefore of lower capacity. Data (bits) travel along a bus in parallel, like a rank of soldiers, and at regular intervals determined by the clock speed of the computer. Older computers had main buses 8 bits wide, whereas newer Pentium-class computers use buses as wide as 64 bits.

Input-output buses link "peripherals" such as the mouse, keyboard, removable disk drives, and game controllers to the rest of the computer. These buses have become faster and increasingly standardized. The universal serial bus (USB) is a current widely accepted standard, as is Apple's proprietary Firewire bus. These buses allow "on-the-fly" attachment and removal of peripherals via a standardized plug, and a user can expect that a device plugged into one of these ports will identify itself to the operating system and function without the need for specific configuration. This is a distinct improvement over the previous paradigm, in which a user typically needed to open the housing of the computer to attach a new peripheral and then configure a specific software driver to permit communication between the device and the computer.

In addition to their local computing function, modern personal computers have become our conduits to networks and must therefore act as terminal points on the Internet. As with houses or phones, each computer must have an individual identifier (address, phone number) to receive communications uniquely intended for it. Examples of these kinds of specific addresses are the IP (Internet protocol) address and the MAC (media access control) address. The IP address is temporarily or permanently assigned to a device on the Internet (typically a computer) to uniquely identify it among all of the other devices on the Internet. The MAC address is used to specifically identify the network interface card for the computers that assign IP addresses.

The computer must also have the right kind of hardware to receive and interpret Internet-based communications. Wired and wireless network interface cards are built into all new computers and have largely replaced modems as the hardware typically used

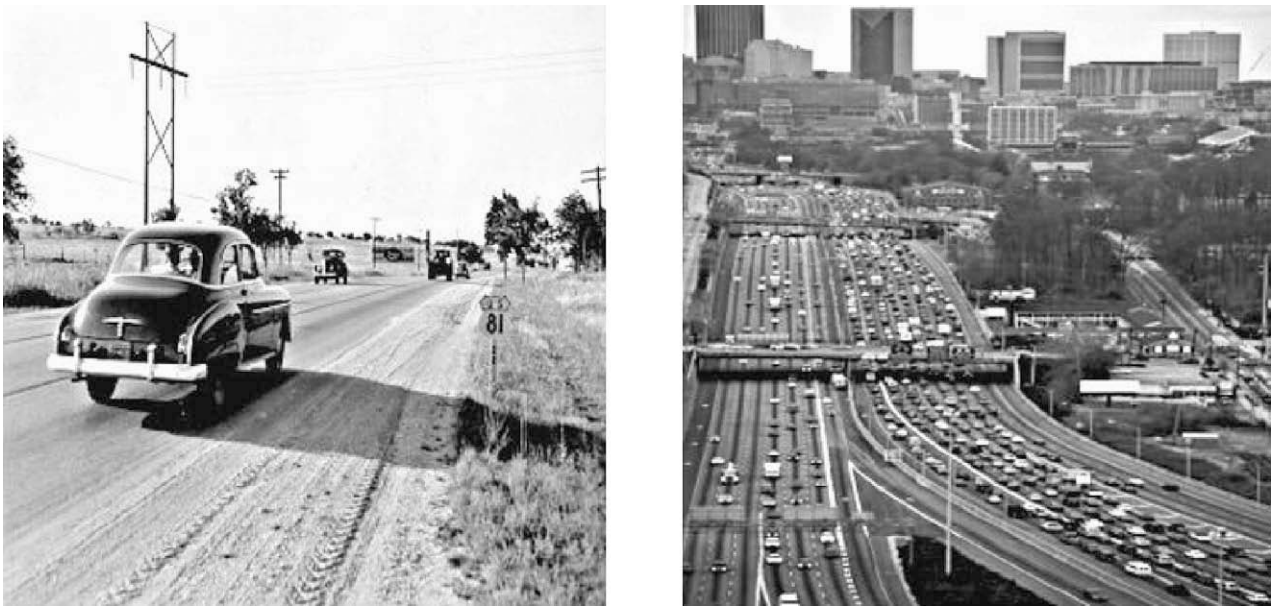

Figure 4-3 Buses are like highways, where the number of available "lanes" relates to bus capacity.

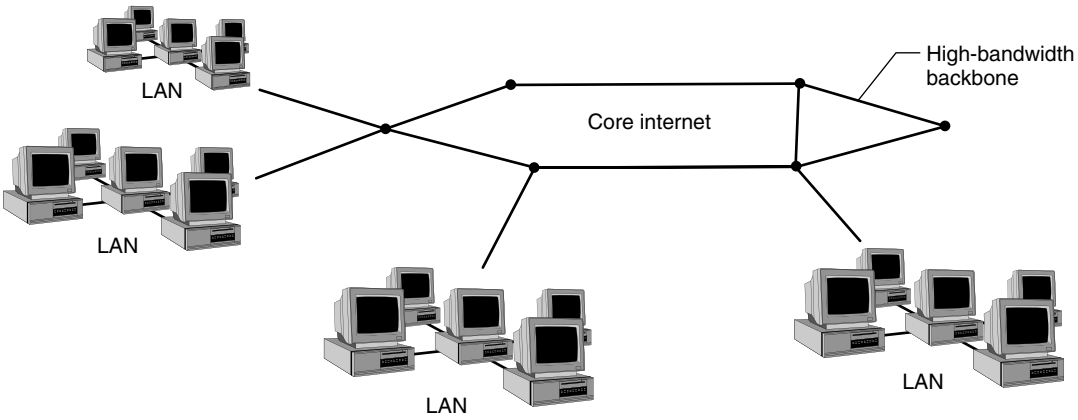

Figure 4-4 Lower-speed networks are attached to high-speed "core" networks that span the globe. LAN, local area network.

for network communications. Whereas a modem communicates over existing phone lines also used for voice communication, network cards communicate over channels specifically intended for computer-to-computer communications and are almost invariably faster than modems.

Although we commonly think of the Internet as being one big network, it is instructive to understand a little bit about the history of computer networking. In the beginning there were office networks and the progenitor Internet. The first office network was designed at the Palo Alto Research Center, which is the Xerox research laboratory where a number of major computer innovations were developed. That office network was called Ethernet and was designed as part of the "office of the future," where word-processing devices and printers were cabled together. Separately, the ARPAnet was the Defense Advanced Research Project Agency's creation and linked mainframe computers at major universities. Over time, the two networks grew toward one another almost organically, and today we have what seems to be a seamless network that links computers all over—and above—the world.

Networking technology has evolved almost as rapidly as computer technology. As with buses in a computer, the networks that serve the world can be likened to highways. Backbone networks (Fig. 4-4) are strung across the world and have tremendous capacity, like interstate highways. Lower-capacity systems feed into the backbones, and traffic is directed by router computers. To facilitate traffic management, before transmission messages are cut up into discrete packets, each of which travels autonomously to its destination, where they are reassembled. Internet packets may travel over hard-wired, optical, or wireless networks en route to their destination.

Computer Software

Operating System and Programming

The operating system (OS) is the government of the computer. As with a municipal government, the OS is responsible for coordinating the actions of disparate components of a computer, including its hardware and various software programs, to ensure that the computer runs smoothly. Specifically, it controls the CPU, memory, interface devices, and all the programs running on the machine at any given time. The OS also needs to provide a consistent set of rules and regulations to which new programs must adhere to participate.

Although most of us think of Apple and Windows synonymously with OSs, there are other OSs that deserve mention. Linux is an open-source, meaning nonproprietary, OS for personal computers that is distributed by several different vendors but continuously maintained by a huge community of passionate programmer devotees who contribute updates and new programs. In addition, every cell phone and smart device has its own OS that performs exactly the same role as for a personal computer OS.

OSs can be categorized into four broad categories (Fig. 4-5). A real-time OS is typically used to run a specific piece of machinery, such as a scientific instrument, and is dedicated solely to that task. A single-user, single-task OS is like that found on a cell phone, where a single user does one job at a time, such as dialing, browsing, or e-mail. Most of today's laptop and desktop computers are equipped with single-user, multitasking OSs, whereby a single user can run several "jobs" *simultaneously*, such as word processing, e-mail, and a browser. Finally, multi-user, multitasking OSs are usually found on mainframe computers and run many jobs for many users concurrently.

All OSs have a similar core set of jobs: CPU management, memory management, storage management, device management, application interfacing, and user interfacing. Without getting into detail beyond the scope of this chapter, the OS breaks a given software job down into manageable chunks and orders them for sequential assignment to the CPU. The OS also coordinates the flow of data among the various internal memory stores, as well as determines where that data will be stored for the long term and keeps track of it from session to session. The OS provides a consistent interface for applications so that the third-party program that you buy at a store will work properly on a given OS. Finally, and of most importance for many of us, the OS manages its interface to you, the user. Typically, today that takes the form of a graphic user interface (GUI).

E-mail

E-mail communication over the Internet antedated the browser-based World Wide Web by decades. In fact, the earliest e-mail

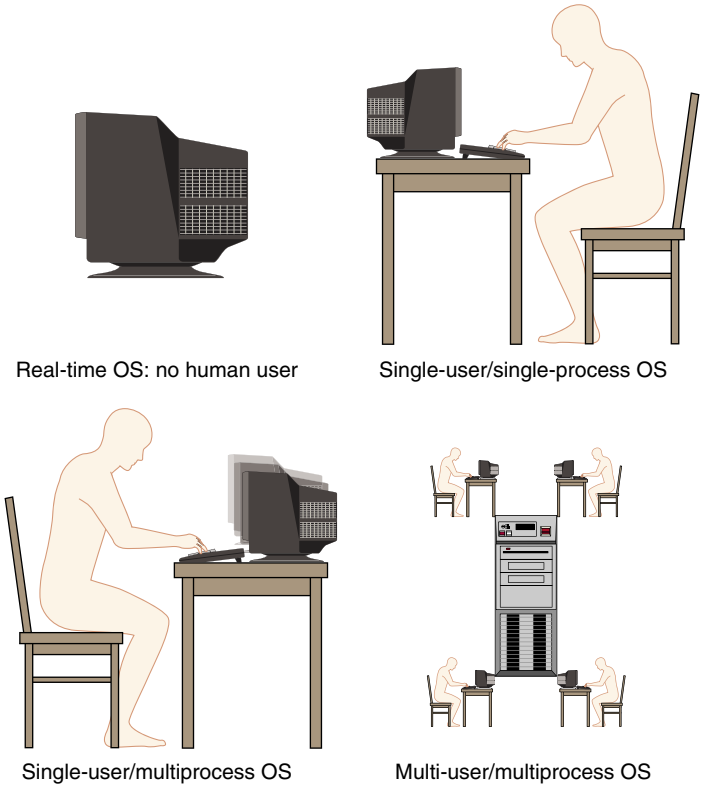

Figure 4-5 Several operating system configurations.

was designed for communication among multiple users in a "time-sharing," multi-user environment on a mainframe computer. E-mail was used for informal and academic communications among the largely university-based user community. Without going into great detail, an e-mail communication protocol was designed so that each message included information about the sender, the addressee, and the body of the message. The protocol is called the Simple Mail Transfer Protocol (SMTP), and the process of message transmission proceeds as follows. The sender composes a message via a software-based messaging program (such as Outlook, Gmail). The sender then applies the recipient's address and dispatches the message. The message travels through a series of mailboxes, much as a regular letter does, and eventually arrives at the addressee's mailbox, where it sits awaiting "pickup."

Although e-mail has had dramatic and largely positive implications for the connectedness of organizations and people, it has also created hitherto unimagined problems, including spam, privacy issues, and the need for new forms of etiquette.

The term *spam* is said to have come from a Monty Python skit. Spam is such a ubiquitous problem that most e-mail crossing the Internet is spam at this point. Spam is essentially bulk e-mail and was never envisioned by the creators of SMTP. Spam is a generic problem with e-mail communications, but the issues of privacy and etiquette are of much greater relevance for medically oriented e-mail.

The American Medical Informatics Association has taken a lead role in defining the issues associated with e-mail in the medical setting. The organization defined patient-provider e-mail as "computer based communication between clinicians and patients within a contractual relationship in which the health care provider has taken on an explicit measure of responsibility for the client's care."[1] A parallel set of issues relates to medically oriented communications between providers.[2-5] Another category of medically oriented communications is that in which a provider offers medical advice in the absence of a "contractual relationship." An egregious example of the latter is the prescription of erectile dysfunction remedies by physicians who review a Web-based form submitted by the "patient" and then prescribe a treatment for a fee.

In theory, e-mail is a perfect way to communicate with patients.[6-9] Because of its asynchronous nature, it allows two parties who may not be available at the same time to communicate efficiently (Fig. 4-6), and it represents the middle road between two other types of asynchronous communication: voice mail and traditional mail. E-mail can also be tailored to brief exchanges, more structured communications, and information broadcasts (such as announcements). As such, a patient could send interval updates (blood pressure, blood sugar) to the physician. Alternatively, the physician could follow up on an office visit by providing educational material about a newly diagnosed condition or planned procedure.

Even though e-mail has many advantages in medicine, there are a variety of risks associated with its use, which has slowed adoption.[10] Some of the problems are generic to any e-mail exchange. Specifically, it is a more informal and often unfiltered form of communication than a letter and often has the immediacy of a conversation but lacks its visual and verbal cues. Emoticons (such as the use of ":)" to indicate that a comment was sent with a "smile") evolved as a remedy for this problem.

E-mail is also permanent in the sense that copies of it remain in mailbox backups even after deletion from local files (Fig. 4-7). Every e-mail should therefore be thought of as discoverable from both a liability and recoverability standpoint. Before dispatch e-mail should be scrutinized for information or content that might be regretted at a later date.

E-mail is also vulnerable to inadvertent or malicious breaches in privacy or disclosure through improper handling of data at any point along the "chain of custody" between the sender and the recipient. Alternatively, a hacker could potentially acquire sensitive medical information from unsecured e-mail or possibly even alter medical advice and test results in an e-mail from physician to patient.

The Healthcare Insurance Portability and Accountability Act (HIPAA) legislation mandates secure electronic communication in correspondence regarding patient care. Three prerequisites for secure communication include authentication (that the

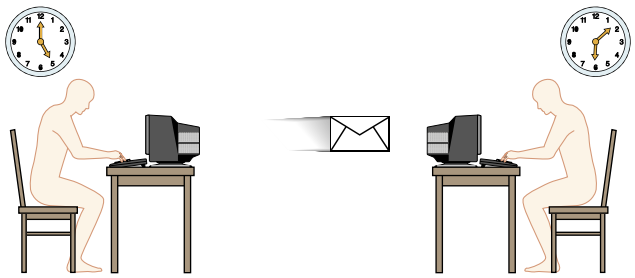

Figure 4-6 E-mail is an effective form of communication between a patient and a physician because it does not require both parties to be present at the same time.

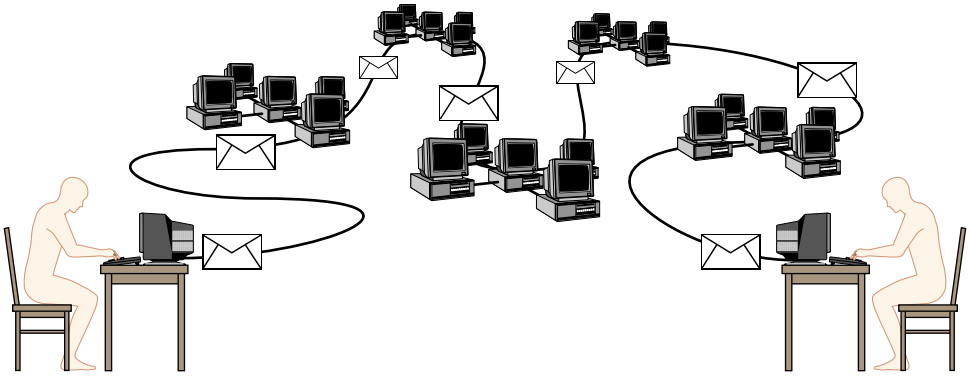

Figure 4-7 E-mail leaves copies of itself as it travels across the Internet.

message sender and recipient are who they say they are), encryption (that the message arrived unread and untampered with), and time/date stamping (that the message was sent at a verifiable time and date), although these techniques are not yet widely deployed in the medical community.

It is beyond the scope of this chapter to go into great detail about the methods used to authenticate, encrypt, and time-stamp e-mail. However, it is possible to ensure that each of these elements by using mathematically linked pairs of numbers (keys), in which an individual's public key is published and freely available through a central registry (like a phone book) whereas a linked private key is kept secret (Fig. 4-8). Public key encryption combined with traditional encryption is used to transmit messages securely across public networks, ensure that messages can be read only by a specific individual, and digitally sign the message.

Although the use of e-mail for medical patient-provider and provider-provider communications is growing, it is not yet universally adopted for several reasons, including physician distrust of the medium, unfamiliarity with software, lack of standards, and lack of clear methods for reimbursement for time spent in e-mail communications. Nevertheless, several professional societies have published consensus recommendations about the management of e-mail in medical practice. Common consensus-based elements are enumerated in (Box 4-1).

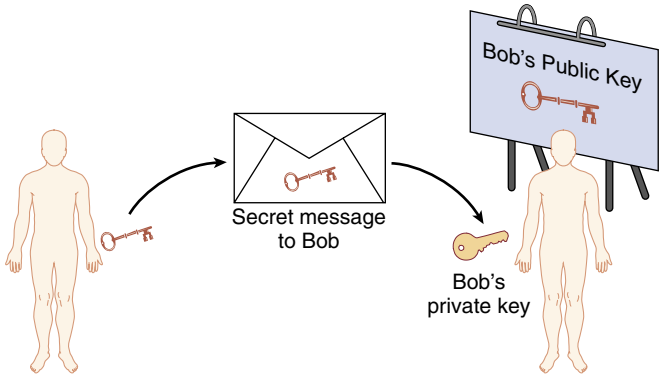

Figure 4-8 Public/private key encryption in which Joe sends a message intended only for Bob by using Bob's public key—the message remains encrypted until Bob decrypts it with his private key.

Box 4-1 Suggested Rules for E-mail Correspondence in a Medical Setting

All patient-provider e-mail should be encrypted.

Correspondents should be authenticated (guarantee you are who you say you are).

Patient confidentiality should be protected.

Unauthorized access to e-mail (electronic or paper) should be prevented.

The patient should provide informed consent regarding the scope and nature of electronic communications.

Electronic communications should (ideally) occur in the context of a preexisting physician-patient relationship.

On-line communications are to be considered a part of the patient's medical record and should be included with the same.

Browser

Many people think of the Internet and the World Wide Web as one and the same. The Internet is the worldwide network, whereas the Web is one of its applications characterized by the browsers with which its users interact. The browser was invented by Tim Berners Lee at the European Organization for Nuclear Research, commonly known as CERN, in 1990. Marc Andreessen wrote the Mosaic browser and subsequently the Netscape browser, which like all subsequent browsers, has a GUI and uses a specific "language" called hypertext markup language (HTML). Microsoft eventually developed its own version of the browser, Internet Explorer, after recognizing the inevitability of the Web.

The browser is a computer program, just like a word-processing or e-mail program, with a GUI. It can be thought of as a radio or television insofar is it serves as an interface to media that do not originate within it. The address of a webpage is analogous to the channel or frequency of a television or radio, and the browser "tunes in" to that address. In actuality, the local browser on your machine communicates with a server somewhere on the Internet (at the address specified in the address line) and uses a communication protocol called HTML as its language. The webpage displayed on your local browser was first constructed on the server and then sent to you.

The original HTML was extremely spare and permitted the construction of very simple webpages. A variety of new "languages" and protocols have subsequently come into existence, such as Java, Javascript, ActiveX, Flash, and others, that allow enhancements to HTML. New browsers support interactivity, security, display of audio and video content, and other functions. Even though the scope of topics that could be covered in discussing browser communications far exceeds that of this chapter, certain issues deserve mention.

"Cookies" is the term used for short lines of text that act like laundry tickets and are used by an Internet server (such as a Google search engine server) to "remember" things about the client computers with which it interacts. Cookies allow the server to keep track, for example, of the items that you have put in your virtual shopping cart as you shop (Fig. 4-9). Although cookies are not inherently risky, there are other risks to the use of a browser.

Like a television, the browser acts like a window on the Internet, and for a long time it was safe to think of that window as being made of one-way glass. Unfortunately, many of the new innovations that allow us to function interactively with websites also have built-in flaws that permit malicious programmers to gain access to your computer. The best way to protect a computer involves timely application of all updates and patches issued by software manufacturers and the use of antivirus software with up-to-date definitions.

Computers and Computing in Medicine

Hospital Information Systems

Modern hospital information systems invariably fall somewhere on the spectrum between a monolithic single comprehensive system design, wherein a single vendor provides all of the components of the system, and a "best-in-breed" model consisting of multiple vendor-specific systems interacting through interfaces or, more typically, an interface "engine."[11-14] The monolithic system has the advantage of smooth interoperability, but some of the component elements may be substantially inferior to those offered by best-in-breed vendors.

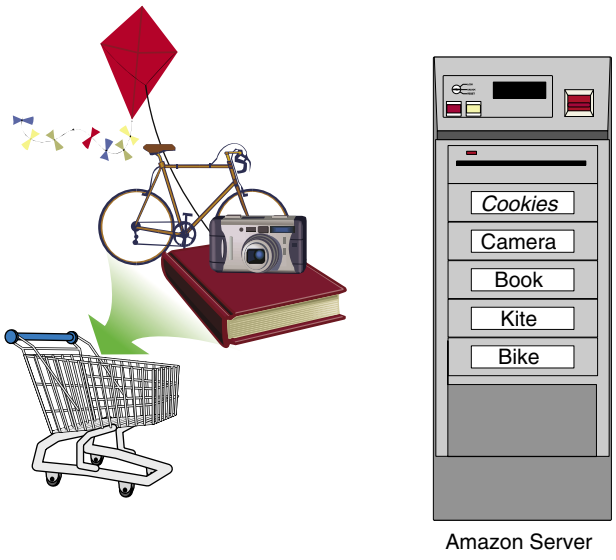

Figure 4-9 Cookies are used by a website, for example, to keep track of the items that a user has put in the "shopping cart."

Component elements of a hospital information system include administrative, clinical, documentation, billing, and business systems.[15-17] Medical information technology is increasingly subject to governmental regulation, security concerns, and standards. Standards are essential for interoperability among systems and to ensure that systems use uniform terminology.[18]

Health Level 7 (HL7) is an accepted set of rules and protocols for communication among medical devices. Clinical Context Management Specification (also known as CCOW) is a method to enable end users to seamlessly view results from disparate "back-end" clinical systems as though they were integrated. Some of the common medical terminologies or vocabularies include the Systematized Nomenclature of Medicine (SNOMED) and the International Classification of Diseases (the ICD family of classifications).[19]

Modern complicated medical information systems often weave a host of disparate systems at geographically dispersed locations into an extended "intranet." A core hospital, for example, may share an intranet with a geographically remote outpatient practice, or several hospitals in the same health system may coexist within the same intranet. Some of the elements may be physically connected (Fig. 4-10) along a network "backbone," whereas others may use virtual private network (VPN) connections that allow the user to appear to be part of the network while at a remote location.[16]

Electronic Health Record

The electronic record (see Chapter 99) has been described variously as a computerized medical record, computerized patient record, electronic medical record, and electronic health record (EHR).[20-23] It is clear that various settings require radically different EHRs and that EHRs will eventually need to interface seamlessly.[24,25]

The current evolution of software-based EHRs is recapitulating the evolution of hospital information systems as it occurred over the 1980s and 1990s. Best-in-breed commercial systems or "home-grown" site-specific systems are evolving, such as automated anesthesia EHRs[26,27] and intensive care unit (ICU) EHRs (Fig. 4-11). At the same time, large vendors have developed generic inpatient and outpatient EHRs. Health systems will inevitably be faced with the same choices about whether to go with monolithic or best-in-breed EHR software that they have with clinical systems.

The Institute of Medicine issued a recent report characterizing key aspects of an EHR, including an integrated, longitudinal view of patient data; concurrent access to the body of knowledge pertaining both to the patient's condition and to the rules and regulations associated with reimbursement in this age of managed care; order and data entry; and decision support tools that provide current knowledge about diseases, treatments, drug interactions, and risk profiles.

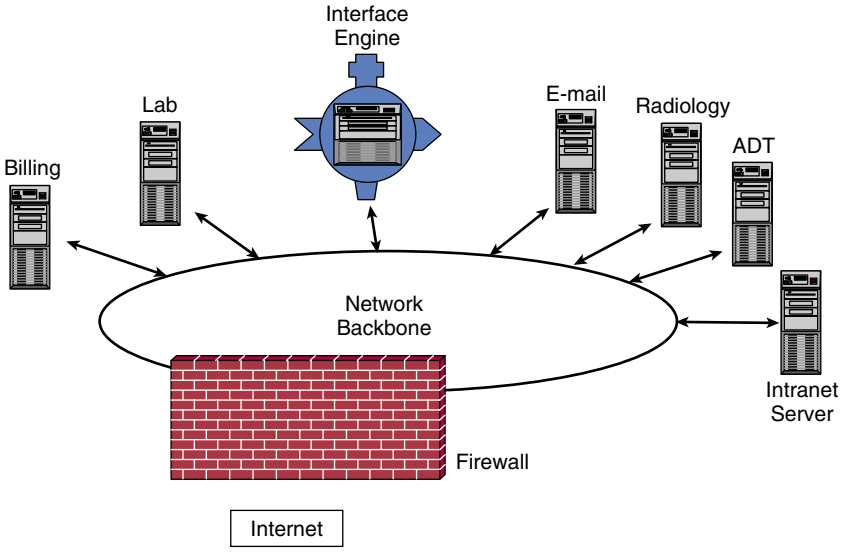

Figure 4-10 Modern health care information systems consist of elements attached to a backbone. ADT, admission, discharge, and transfer.

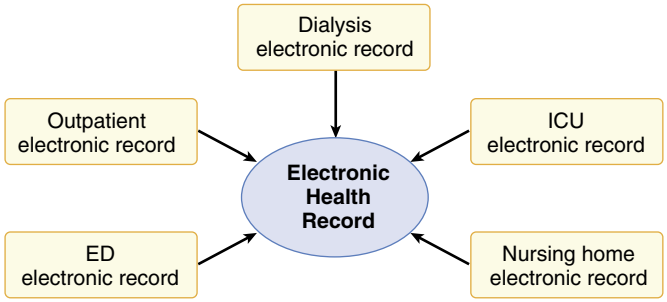

Figure 4-11 Vendors have developed specialty electronic health records. ED, emergency department; ICU, intensive care unit.

Ideally, the electronic record will provide tools for communication among providers. The EHR should also provide immediate access to population-level information for administrative and research applications.

The Veteran's Health Administration of the United States is an example of a very successful EHR implementation; however, in most hospitals, orders, notes, and reports are still maintained on paper. Additionally, very few small-practice environments have undergone any degree of computerization because the barriers to computerization are formidable.

Technical obstacles to computerization of the medical record are relatively obvious, but there are also organizational, financial, and policy obstacles.[28-30] Adoption of an EHR implies a fundamental reorganization of the way that medicine is practiced in a clinical environment.[31,32] For example, many older physicians have had little occasion to use a computer and are likely to be slowed in their performance of formerly routine tasks, which is a major barrier at a time when demands for efficiency are increasing substantially (Fig. 4-12).

Despite the barriers, governmental and private stakeholders are developing incentives, bonuses, and low-cost capital to encourage use of the EHR. Providers may eventually mandate EHR systems as a condition of participation in certain U.S. insurance plans, such as Medicare.

The EHR is designed to automate the medical record, but once that process occurs, a number of follow-on opportunities become available, such as enhanced patient care delivery, improved efficiency of support processes (e.g., laboratory, radiology, housekeeping, transport), and automated administrative functions (e.g., billing and reimbursement). The EHR can also be used as a vehicle for education, provider regulation, research, public health, and policy support (see Fig. 4-12).

The core functions expected of EHRs fall into eight general categories. The first is management of patient health information and data. Second is presentation of results acquired from patient testing. The third function of EHRs is computerized order entry (CPOE). A fourth key benefit of EHRs is decision support, whereby automatically generated reminders and prompts are used to inform the behavior of clinicians. EHRs may be equipped

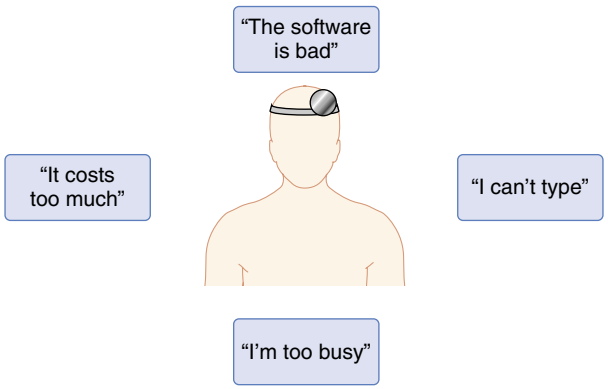

Figure 4-12 Various barriers to adoption of electronic health records.

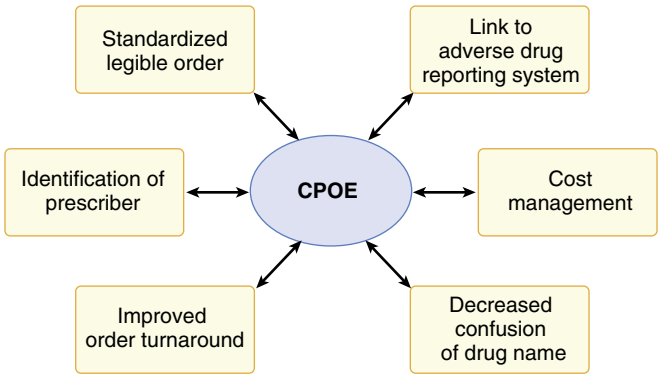

Figure 4-13 Various benefits of a computerized order entry (CPOE).

with communication tools. Patient support tools such as pamphlets describing a disease or discharge directions can be generated automatically. Administrative processes can be integrated into EHRs, including scheduling systems, billing management, and insurance validation. Finally, internal and external reporting requirements can be simplified by using reporting systems built into EHRs.

The concept of a universal medical record deserves specific attention. It has always been desirable for providers in one location to have access to data from a medical record generated at another location, and although there are many models of a universal medical record, such as a record owned and kept by the patient on a piece of hardware such as a flash drive, there are a variety of problems with this approach. A more practical approach is currently being deployed by large vendors such as Microsoft and Google, which now offer patient medical "vaults" that are maintained on line and over which the patient has read-write and access control.

Computerized Order Entry

CPOE systems have begun to gain a foothold in the provision of care at many hospitals, although 50% of American hospitals still lack one. Prescribing errors are the most common source of adverse drug event, and CPOEs, with or without decision support tools, are widely viewed as being integral to reduction in errors and formulary control. CPOEs came into the spotlight after the Institute of Medicine's 1999 report "To Err Is Human: Building a Safer Health System," in which 44,000 to 98,000 deaths per year were attributable to medical errors; however, although CPOE has great potential, poorly designed or deployed systems will either not be adopted or potentially cause errors.

Broadly, the term CPOE is used to refer to computer-based ordering systems designed to automate the ordering process, be it for drugs or for requesting pathologic or radiologic tests. Benefits include the output of standardized, complete, legible orders consistent with the hospital's formulary and automatically sent to the pharmacy (Fig. 4-13). CPOE is also almost invariably associated with a decision support system (DSS), which will be discussed in more detail in the next section.

Successful deployment of CPOE will occur only when the system is deployed as part of a fundamental redesign in the delivery of patient care. The organizational aspects of CPOE deployment have been described by a recent consensus panel from the American Medical Informatics Association in which nine elements of successful systems were highlighted. The first is the development of a clear understanding of all of the institution-specific drivers for implementation of a CPOE system, be they regulatory, regional competition for patients, or internal. A second critical element is sustained internal leadership-level support during implementation of the CPOE system. Third, the CPOE system must be adequately funded in all respects, including training of personnel. A fourth and critical element is prospective understanding of the way in which CPOE will affect workflow at all sites in the organization (Fig. 4-14). A corollary to this element is the fifth, which is ensuring a positive "cost-benefit" ratio for each of the providers who use the system by the creation of time savers such as order sets. The sixth element of successful CPOE systems is the selection of an appropriate deployment strategy, whether it be an all-at-once or a staged approach. The seventh consideration relates to the technical details of CPOE implementation, such as the replacement of legacy systems. Training and support must be comprehensive and is the eighth element. The ninth and final critical aspect is the design of a plan for continuous quality improvement after implementation of the system.

Decision Support Systems/Artificial Intelligence

Decision support tools integrated into the EHR and CPOE can provide immediate access to current medical knowledge, institutional best practices, billing compliance information, and administrative functions and can facilitate cost control. Although there is a wide range of architectures, DSSs fall somewhere on the spectrum between expert systems, in which rules developed by domain experts are used to drive decision support, and autonomous systems that have the ability to "learn" and make observations about large data sets. An example of the latter might be a system that automatically culls through a physician's orders to develop a profile of prescribing patterns.

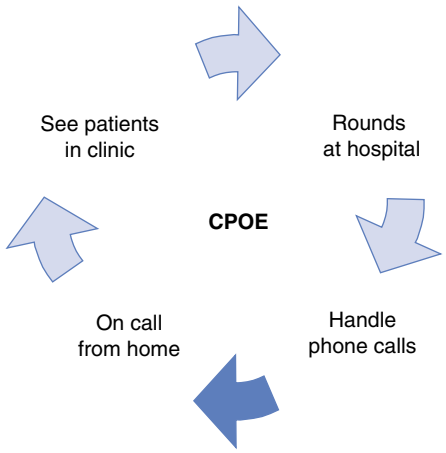

Figure 4-14 Integration of computerized order entry (CPOE) into the workflow of an organization.

A DSS can "act" in one of three ways. It may be a passive system that responds with information when asked. Alternatively, it may be semiactive and provide alerts or alarms only when certain conditions are met. Finally, a system may be active and autonomous and generate an order set or manage a medical process automatically, such as automated weaning of mechanical ventilation according to built-in rules.

Clinicians want certain functions from a DSS, such as access to national consensus guidelines when available, concurrent presentation of relevant patient information when ordering, intelligent alerts, reminders to engage in patient-specific activities (such as immunizations), and the ability to measure their performance versus that of peers in a way that results in continuous improvement in performance.

HIPAA and Data Security

Enacted in 1996, the HIPAA was initially designed to protect workers from losing their health insurance (portability) during job transition and to protect the integrity, confidentiality, and availability of their medical information (accountability). HIPAA covers three critical aspects of automated health care information: privacy, universal coding formats, and security.[33-38]

The target of the privacy element is what is known as protected health information, and the bill ensures a patient's right to control the use of that information as it relates to health care, the business of health care, and research. The HIPAA mandates the creation of universal code sets that cover, for example, the classification of diseases and describes both a national provider and national patient identification number. There are a variety of concerns about the latter that have prevented its adoption to date. The security aspect of the legislation relates to the physical and electronic aspects of ensuring the protection of patient health information (Fig. 4-15).

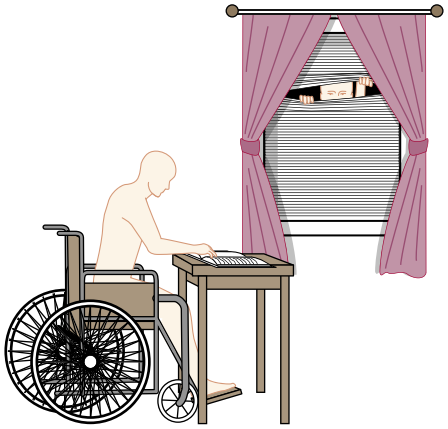

Figure 4-15 Security aspects of the HIPAA legislation relate to the physical aspects protecting unauthorized access to protected health information.

Telemedicine

Telemedicine and telehealth are the application of health care services across space, time, and social and cultural barriers. Telemedicine has been demonstrated in a variety of disciplines, including surgery, emergency medicine, cardiology, dermatology, ophthalmology, neurology, gastroenterology, rehabilitation, and critical care medicine.[26,39-50] However, although telemedicine has already had an enormous impact on the ability of patients to access medical information, there are a variety of barriers to widespread implementation of clinical care at a distance, including licensure, credentialing, malpractice, and reimbursement.

Telemedicine holds great promise as a means of making medical care available to underserved areas, providing access to specialists at remote locations, and allowing patients to receive medical attention in their home when physical contact is not a critical element of an encounter. In addition, new technologies are currently under development, including teleimmersion and telepresence. Teleimmersion permits geographically dispersed people to collaborate in a shared virtual space, whereas telepresence refers to a system in which the human practitioner may have visual and mechanical actuators and sensors permitting them to "see," "feel," and "move" objects in a remote environment (Fig. 4-16).

Telesurgery demonstration projects have been done, for example, with both laparoscopic and robotic instruments to operate at a distance. A number of other demonstration projects are under way in various fields of medicine, and reimbursement agencies are beginning to develop methods of reimbursement for

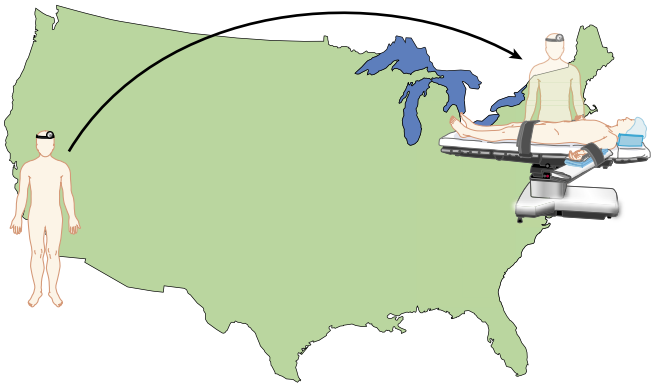

Figure 4-16 Telepresence relates to the ability to be virtually present at a patient's bedside.

telemedicine-based activities. In addition, there are a few commercially available models for delivery of telemedicine, including remote radiographic interpretation, in some cases from appropriately credentialed radiologists interpretation from international locations, and critical care coverage from remote, virtual ICUs.

Telemedicine will eventually change the way that medicine is practiced in many fundamental ways. It is equally certain that the speed of technologic change will outstrip that of regulatory, reimbursement, and legislative change.[51]

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5 Quality Improvement

Key Points

1. Quality is a characteristic of the system in which care is delivered, and every system is perfectly designed to achieve the results that it achieves. If we want to improve the quality of care that we provide, we need to reorganize the way that we work.
2. The growing demand for improved quality and safety in health care from patients, providers, insurers, regulators, accreditors, and purchasers calls for anesthesiologists to evaluate the quality of care that they provide.
3. Improving quality of care entails measuring performance. However, health care providers have limited ability to obtain feedback regarding performance in their daily work, in part because of a lack of information systems and lack of agreement on how to measure quality of care.
4. The goal of measurement is to learn and improve. The measurement system must fit into an improvement system; caregivers must have the will to work cooperatively to improve, they must have ideas or hypotheses about changes in the current system of care, and the team must have a model for testing changes and implementing those that result in improvements.
5. Previous efforts to measure performance have focused predominantly on outcome measures, including in-hospital mortality rates. Although important, hospital mortality alone provides an incomplete picture in that it does not provide insight into all domains of quality. A balanced set of structures (how care is organized), processes (what we do), and outcome measures (results we achieve) is needed to obtain a more accurate picture of the quality of care.
6. Future efforts to improve quality of care in the field of anesthesiology should focus on the development of valid, reliable, and practical measures of quality.
7. Developing a quality measure requires several steps: prioritize the clinical area to evaluate; select the type of measure; write definitions and design specifications; develop data collection tools; pilot-test data collection tools and evaluate the validity, reliability, and feasibility of measures; develop scoring and analytic specifications; and collect baseline data.
8. One of the greatest opportunities to improve quality of care and patient outcomes probably will not come from discovering new therapies but from discovering how to better deliver therapies that are known to be effective.
9. Strategies that have been used successfully in the aviation industry to improve performance include interventions to reduce complexity and the creation of redundancies in the system to ensure that critical processes occur. These strategies have not been fully evaluated in the practice of anesthesia.
10. Health care providers can organize their patient safety and quality improvement efforts around three key areas: translating evidence into practice, identifying and mitigating hazards, and improving culture and communication. Although each of these areas requires different tools, they all help health care organizations to evaluate progress in patient safety and quality.

Quality improvement (QI) programs have become a compelling force in virtually all branches of medicine. The Centers for Medicare and Medicaid Services (CMS) and The Joint Commission have put forth regulatory policies to further ensure that patients receive interventions that are evidence based and are broadly accepted as the standard of care. The Agency for Healthcare Research and Quality (AHRQ), the health services research arm of the U.S. Department of Health and Human Services, maintains a website that contains information on clinical practice guidelines and QI initiatives along with data to support their use. These

guidelines and initiatives are increasingly being used to maintain accreditation of facilities, achieve optimal reimbursement, and provide quality patient care.

The goal of this chapter is to present a practical framework for developing and implementing QI programs in anesthesiology and critical care medicine that are both scientifically sound and feasible. To accomplish this goal, we review the science of QI, present measures that help evaluate whether QI programs are valid, and offer examples of successful QI efforts.

What Is Quality?

The word *quality* is used to describe the degree or grade of excellence of a trait or characteristic of a system. It is a key word used ubiquitously by many professions and businesses. "Quality is job one" was once the well-known slogan of the Ford Motor Company. It implied that they got it right. However, the recalls on their cars and trucks revealed that such was not always the case. In health care, our "recall" was the 1999 Institute of Medicine (IOM) report *To Err Is Human*.[1] By estimating the number of preventable deaths per year caused by medical errors, the report showed that the need to improve quality in health care was substantial. It still is.

The medical profession has been working for more than a century to improve health care quality. In the early 1900s, Dr. Ernest Codman, a surgeon at Massachusetts General Hospital, began his lifelong pursuit of tracking patient outcomes to serve as a foundation for improving the care of future patients.[2] He went on to lead the founding of the American College of Surgeons and its Hospital Standardization Program, which has become what is known today as The Joint Commission. Over time, quality assurance programs were developed whereby selected indicators were monitored by retrospective chart review to measure compliance with recommended practices. However, we learned that this did not necessarily ensure quality and that it led to fears of punitive action for the health care worker. The intention of monitoring quality of care was, and still is, to learn and improve, not to judge or punish. With this realization, quality assurance became quality improvement. Today, the focus of health care quality is on continuous QI programs.

QI is better facilitated when an interdisciplinary group of health care providers and administrators regularly reviews performance, designs interventions to improve, and creates a team to implement the interventions.[3] It is common to describe "quality improvement" in terms of "patient safety." At times, it is difficult to separate the two. The 2001 IOM report *Crossing the Quality Chasm* classified safety as a component of the broader concept of quality.[4] However, the boundaries between the two remain poorly defined. Among the domains of quality, patient safety generally includes efforts to translate evidence into practice, identify and mitigate hazards, and improve safety culture and communication.

A growing demand continues for improved quality and safety in health care from patients, providers, insurers, regulators, and accreditors. This demand is warranted; evidence suggests that safety and quality of care in hospitals can be improved.[5-7] Improvement is not limited just to programs developed to prevent mistakes of *commission*—things we do to patients—but also includes programs to prevent mistakes of *omission*, whereby patients do not receive the therapies that they should.[8]

Historical Methods of Quality Assessment

Before QI, there was quality assurance. Review of adverse events or defects—peer review, morbidity and mortality conferences, isolated liability claims, and incident reports—has been used historically for quality assurance programs. However, the information provided by these sources is often haphazard and biased. Typically, these adverse events are rare for any given practitioner and are not linked to denominators, thereby limiting the ability to estimate rates and risk, nor do they necessarily reflect quality of care or progress made by QI programs. Moreover, these efforts generally focus on assigning blame (who made the error) rather than on how to reduce the risk for future patients (learning from the mistake).

In an effort to encompass a larger group of adverse events, the American Society of Anesthesiology (ASA) began a Closed Claims Database in 1985.[9] Closed malpractice claims against anesthesiologists provided an enriched environment for collecting information about rare but often catastrophic events. The database provided an opportunity to examine a large set of rare events that might reveal hazards that were common in hospitals and insights that would be otherwise difficult to discern. To be certain, these events represent a biased sample. Most adverse events do not result in claims, and many claims are not the result of preventable adverse events.[10] The information derived from the ASA Closed Claims Database was the impetus for development of QI safety and educational programs with the goal of reducing risk to patients. As an example, a review of adverse respiratory events in the Closed Claims Database, published by Caplan and colleagues in 1990,[11] was followed by organization of an ASA taskforce that established practice guidelines for the difficult airway,[12,13] founding of a Difficult Airway Society in 1995 (http://www.das.uk.com) with its difficult airway guidelines,[14] and development of multidisciplinary difficult airway programs.[15]

Voluntary incident reporting that identifies hazardous systems has been used successfully to improve patient care and foster QI programs.[16] As the potential of voluntary incident reporting is being realized in health care, reporting has become less punitive and more focused on systems rather than individuals. Voluntary incident reporting, when appropriately applied, helps identify hazards to patients, which can then become the focus of QI efforts that seek to mitigate these hazards.[17] Unlike other methods that evaluate harmed patients, voluntary incident reporting provides the potential to also learn from near misses—incidents that did not lead to harm but could have. Although voluntary reporting systems are growing rapidly, most of the effort has been focused on encouraging the actual reporting of events; even more important is the need to focus on learning from these events and reducing risks to patients.

The Intensive Care Unit Safety Reporting System (ICUSRS) project is an example of such an incident reporting system.[18] In the ICUSRS, researchers and caregivers created a web-based, anonymous reporting system that sought to uncover unsafe conditions that could lead to patient harm. They partnered with the Society for Critical Care Medicine to provide expert analysis and feedback to members on lessons learned regarding how to improve patient safety. The ICUSRS has assembled a large community of intensive care units (ICUs) across the United States and is realiz-

ing the potential for incident reporting to improve patient care.[19,20] This type of reporting system could be widely applied by anesthesiology to develop QI programs and evidence-based practice.

Measures of Quality Improvement

Key to improving quality in patient care is the ability to measure the progress made. Health care currently has few scientifically sound, feasible measures, and significant effort is necessary to further develop such measures. Health care has borrowed tools from other disciplines (e.g., organizational psychology, sociology, and human-factors engineering) that have developed basic quality and safety-related principles. As Brennan and coworkers noted, other disciplines can be considered the basic science of quality.[21]

At the end of World War II, W. Edwards Deming, an American statistician, introduced the concept of QI in industry, thereby heralding the advent of the modern-day science of improvement. Deming's work helped improve productivity in the United States but made an even bigger impact in Japan, where implementation of his QI methods resulted in Japan becoming renowned for producing innovative, high-quality products.[22] Deming's components for improvement were summarized by Langley and associates[23] as (1) appreciation of a system (people, procedures, equipment), (2) understanding of variation (is a change in outcome a result of a change in practice or simply due to luck?), and (3) theory of knowledge and psychology of change (how people react to change, why they resist, and how to overcome the resistance).

Japan's increased productivity, plus the subsequent adoption of these techniques globally, was a clear measure of the validity of Deming's methods. These methods are rooted in science and depend on robust evaluation. Developing similar measures of quality in health care was (and still is) a challenge. Although patient care cannot necessarily be equated with industry, some similarities exist. Avedis Donabedian was one of the masters of designing measures of health care improvement programs. In the 1980s, Donabedian proposed that we measure the quality of health care by observing its structure (the attributes of the settings where care is delivered), process (whether good medical practices are being followed), and outcome (the impact of the care on health status); this is known as the Donabedian Quality-of-Care Framework.[24,25] This framework may be applied to the clinical setting as follows: First, caregivers must have the will to work cooperatively to improve. Second, the group must have ideas or hypotheses about making changes in the current system of care that are based on scientific fact or expert consensus. Third, the team must have a model for testing changes and implementing those that result in improvement.[23] This ability to measure change in terms of improvement is fundamental to any QI program.[26]

Process and Outcome Measures

As stated earlier, QI measures can be an outcome (morbidity, mortality, length of stay, quality of life, or perceptions of care), a process (β-blockers for patients with coronary artery disease), or a structural measure (ICU physician or nurse staffing ratio).[27,28] Each of these measures has advantages and limitations.[29] Process measures are readily accepted by health care providers because they demonstrate the degree to which caregivers can influence a process, with the intention of improving patient outcomes. Providers generally feel more accountable for the process of care than for its outcomes because outcomes may be affected by many other variables.[29] An obstacle to using process as a measure of quality is sustainability; frequent updating is required as the science of medicine advances.

Process measures that evaluate how care is delivered may be easier to measure and implement and can provide important insight into care.[30] Process measures can provide immediate feedback regarding performance, thereby allowing rapid improvements in care. Additional important advantages of evaluating process measures are (1) that they generally have face validity for providers, which means that providers believe that they can use the data to improve care, and (2) because risk adjustment is less important, broad implementation is feasible. Moreover, joint efforts among providers, professional societies, and external government or payer agencies have made them more feasible.[30]

To be valid, process measures should have causal links to important outcomes; a change in the process should produce a desired change in outcome. One of the greatest opportunities to improve patient outcome may well come from discovering how to deliver therapies (processes) that are known to be effective in producing a desired outcome.[31] For example, prior hand washing and application of chlorhexidine to sterilize the skin site before insertion of a central venous catheter (CVC) are two of five processes known to reduce catheter-related bloodstream infections (CRBSIs).[32] Process measures such as these are indicators of whether patients reliably receive evidence-based interventions known to prevent complications.

When measuring processes, it is essential to remember that patient factors, bias in measurement, and interventions already in place as part of standard practice all play a role in outcomes. The linkage of process to outcomes must be previously demonstrated scientifically or must be widely accepted by peers, although the latter risks being accepted but wrong. In general, a balanced set of process and outcome measures helps to inform improvement efforts and provides evidence that such efforts have made a difference in the lives of patients.

The need for risk adjustment and long-term follow-up is complex. If an outcome occurs infrequently, it will take considerable time before providers can obtain meaningful feedback. For example, evidence of improved rates of CRBSI (an outcome measure) may require 3 months of data (because infections develop in few patients), whereas improved adherence to evidence-based practices to reduce infections (process measures) may be observed within a week (because all patients can be evaluated to determine whether they received the intervention). Nevertheless, consumers and employers are increasingly requesting outcome measures. The relative focus on outcome and process measures will depend on finding the balance between collecting data that are scientifically sound yet feasible.

Analysis of Quality Improvement Data

The QI team must decide how the data will be analyzed and how clinical and statistical significance will be determined. A common feature of a well-run QI project is correlation of several measures

over time. The horizontal (*x*) axis can represent time in days, weeks, or months, and the vertical (*y*) axis can represent the performance measure (Fig. 5-1). The analyst annotates the plots with the timing of the interventions or other significant events such as, in this example, implementation of an educational program for the appropriate timing of administering antibiotics preoperatively.

Although analysis of rates or proportions is generally clear, analysis of continuous data, such as time, is less clear. There is often uncertainty regarding the unit of analysis when plotting data over time (commonly called a *control chart*). Should the unit of time be days, weeks, months, or years? The unit of analysis should be selected so that learning is optimized; it is influenced by sample-size requirements and by the frequency with which the investigator plans to provide feedback or launch interventions, or both.[33] In general, feedback regarding process measures can be provided more frequently than feedback for outcome measures can. Scales and units of measure should be chosen to optimize learning of the user.[34] Therefore, the user of the information should be involved in deciding which unit of measure to use.

Time series consisting of data from small samples collected continually over time is the standard for QI work. It is less costly to implement than measurements associated with the large, one-time data collection of controlled trials. Study of the patterns of variation in the measures over time determines the performance of the system and its stability. The patterns in time series data contain important information; other methods that rely on averages or other summary statistics can hide this information (e.g., comparing results across the arms of a randomized, controlled trial).

Uncontrolled observational measurement holds higher risk for unrecognized bias and incorrect conclusions about cause and effect than more rigorous designs do. However, unlike these designs, in which measurement ends when the researchers leave, in a health care setting, time series measurement continues to determine whether the perceived improvement is sustainable. This is contingent on having a system to collect, analyze, and report back data. Incorrect claims of improvement that result from faulty inference become apparent in time.

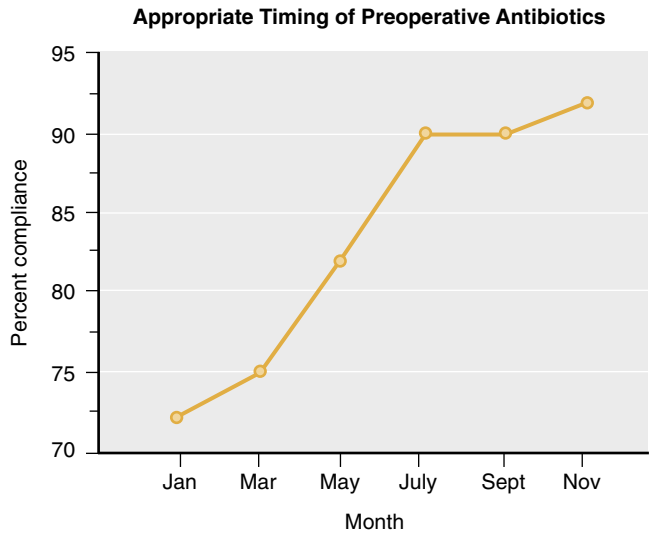

Figure 5-1 Example of a plot of a performance measure over time. The horizontal (*x*) axis represents time in months, and the vertical (*y*) axis represents the performance measure—percent compliance with the timing of administration of preoperative antibiotics.

Periodic measurement can be built into daily work and allows the clinical team to continually evaluate performance. Any decline in performance is evident, and a clinical team can quickly respond. If properly planned and coordinated, such local outcomes tracking, when combined with descriptions of evolved systems of care, can enhance learning at both the local and regional level, as well as the national level. This widespread learning and improvement are consistent with the "call for action" issued in 1997 by Lundberg and Wennberg.[35]

Examples of Quality Improvement Programs and Tools

Voluntary Incident Reporting

Providers who are given a readily available means of reporting incidents can be an excellent source of information for the development of QI programs. However, data from these voluntary reporting systems should not be interpreted as rates or be used to evaluate progress in patient safety. The following is an example of a self-reported medication error and the actions that were taken after a detailed (root cause) analysis of the factors that led to the error.

An ICU patient was administered Zosyn (piperacillin/tazobactam) intravenously despite a documented allergy to penicillin. On cursory review, the physician who wrote the order and the nurse who administered the medication appeared to be at fault because they failed to note the penicillin allergy. An in-depth investigation of this medication error was undertaken, with appropriate scrutiny to identify the system failures that resulted in this error. First, we will review the circumstances that led to the error through the eyes of the caregivers involved.

The patient was exhibiting signs of pneumonia. The physician was interrupted (distracted) while writing the order for Zosyn and failed to review the patient's allergies. The bedside nurse did not realize that Zosyn contained piperacillin and was contraindicated for a patient with an allergy to penicillin. The bedside nurse did know that administering the antibiotic within 1 hour of the diagnosis of pneumonia would dramatically improve the patient's outcome and that the 1-hour rule was a core measure for pneumonia therapy. On further discussion with staff, investigators discovered that the nurse's concern over administering the antibiotic quickly was perpetuated by a broken fax machine and a nonfunctioning pneumatic tube transport system. Orders were normally faxed to the pharmacy, and medications were then dispensed through the pneumatic tube system for a quick turnaround. Because the system for quickly obtaining medications failed, the nurse borrowed the Zosyn from floor stock.

This case is a powerful example of how each step aligned to achieve a catastrophic outcome. By borrowing the antibiotic from floor stock, a crucial safety check of potential medication allergies by the pharmacist was bypassed. The root-cause analysis demonstrated the frontline caregivers' commitment to quality, uncovered several defects that resulted in the event (the drug name Zosyn was unfamiliar and did not indicate that the drug

contained piperacillin, the fax machine was broken, the pneumatic tube transport system was broken, and the pharmacy safety check was bypassed), and provided solutions to fix the problem (ongoing preventive maintenance to ensure the functionality of equipment, electronic provider order entry, and possibly hiring staff for transport backup to ensure that medications come from the pharmacy and not floor stock).

It is important to recognize that QI projects often require resources. In this case example, a QI project was undertaken by senior leaders in the organization to intensively evaluate the pneumatic tube used for transport to identify sources of malfunction and reduce defects, develop protocols for handling transport capsules, and determine whether adding staff for transport backup was needed. A plan for electronic order entry was being developed. Each step required measurement and analysis, with the understanding that changes made in a system may introduce new hazards that must be guarded against.

Collaboratives

A collaborative involves the participation of multidisciplinary care providers within a clinical area, across clinical areas, or across multiple health care organizations to improve care. It incorporates a structured program with a shared goal. The team leading the collaborative will (1) determine the evidence-based interventions to be used and, if none are available, generate interventions based on local and broad expert consensus and (2) establish the data collection approach (define measures, collection methods, and feedback mechanisms).

As with all successful QI projects, baseline compliance and change over time are key data points to collect. Collaboratives are successful when they involve a sharing process of interventions and obstacles. Through group discussions (meetings, conference calls), teams can learn about best practices and innovative methods used by other teams to approach a problem. In addition, collaboratives bring a shared momentum that can increase sustainability.[26,36]

Multicentered and single-hospital projects can fail because of inadequate resources, lack of support by leadership, vague expectations and objectives for team members, poor communication, complex study plans, inadequate management of data collection, and wasted effort to "reinvent the wheel" rather than adopting practices proven to be effective. Successful collaboratives require a local culture (the set of values, attitudes, and beliefs of the group) that is ready for change and participants with a shared view of safety, who understand the science of patient quality and safety (i.e., the technical components of how care is organized and delivered). Pronovost and colleagues reported the reproducible success of a collaborative that has adhered to the following steps, which have been validated in several large collaborative efforts.[37,38]

1. Identify evidence-based interventions associated with improved outcome through review of peer-reviewed publications.
2. Select goal-oriented interventions that have the biggest impact on outcomes and transform them into behavior. In selecting behavior, focus on interventions with the strongest treatment effect (lowest number needed to treat) and the lowest barrier to use.
3. Develop and implement measures that evaluate either the interventions (processes) or the outcomes.
4. Measure baseline performance and establish databases to facilitate accurate data management and timely feedback to teams.
5. Ensure that patients receive evidence-based interventions through four basic steps: engagement, education, execution, and evaluation (Table 5-1).

Table 5-1 Four Steps to Ensure That Patients Receive Evidence-Based Interventions through a Collaborative As Illustrated by the Example of Catheter-Related Bloodstream Infections

Step	Action	Example
Engage	Make the problem real	Share information of the local CRBSI rate vs. the national rate
Educate	Develop an educational plan to reach *all* members of the caregiver team	Present evidence-based practices at Grand Rounds and multidisciplinary team meetings Present plans to improve care and measure outcome
Execute	Develop a safety culture Reduce complexity of the processes Introduce redundancy in processes Hold regular team meetings	Develop a culture of intolerance for CRBSI Make certain that all equipment and supplies for sterile CVC insertion are in one place and easily available Use checklists that identify key steps to reduce CRBSI Focus on 1-2 tasks per week and identify team member responsible for the tasks
Evaluate	Measurement and feedback	Develop a data collection plan and database to track progress Give staff real-time feedback; post the progress in a highly visible location Identify causes of defects

CRBSI, catheter-related bloodstream infection; CVC, central venous catheter.

Comprehensive Unit–Based Safety Program: A Strategy To Learn from Mistakes and Improve Culture

The Comprehensive Unit–Based Safety Program (CUSP) is a six-step program that has been tested and successfully used to improve quality and safety in ICUs (Table 5-2).[39,40] It provides a structured approach to improve safety culture and mitigate hazards (i.e., learn from mistakes).[39,41]

Safety culture is assessed in the first step of CUSP and reassessed after 1 year to evaluate the impact of the program. The Safety Attitudes Questionnaire—valid, reliable, and widely recognized—is the survey tool used to assess safety culture.[42,43] The initial measure provides a baseline assessment of staff perceptions of safety culture in their clinical areas and their perceptions of the organization's commitment to patient safety.

Education is a crucial aspect of CUSP; it provides staff with a new set of lenses through which to identify hazards and recommend system changes to improve care. The objectives of

Table 5-2 Six-Step Comprehensive Unit–Based Safety Program

Step	Description
1. Measure safety culture	Assess safety culture by all staff members in each clinical area through the Safety Attitudes Questionnaire
2. Present educational material	Educate staff on the science of safety though lectures and other educational material
3. Complete forms identifying patient safety issues	Ask the following questions: How will the next patient be harmed? How can this harm be prevented? Establish voluntary incident reporting
4. Assign a senior executive responsible for a specific area	The senior executive meets with all staff members of the clinical area to: Help prioritize safety efforts Remove barriers for system changes Provide resources Demonstrate hospital commitment to patient safety Foster relationship between senior leadership and staff
5. Implement projects	Focus on two to three safety issues Keep goals simple: Reduce complexity in the process Create independent redundancies to ensure that critical steps are being accomplished
6. Repeat measure of safety culture	Remeasure safety culture; determine whether scores improve

these educational efforts are to ensure that staff members (1) understand that safety is a system property, (2) learn concepts for reliable health care design, and (3) understand the basics of change management. After an educational lecture on the science of safety, staff members are requested to identify patient safety hazards in their clinical areas and suggest interventions for improvement. For this phase, staff members review incident reports, liability claims, and sentinel events from their unit. In addition, two questions are asked: "How do you think the next patient will be harmed?" and "How can we prevent it from happening?"

After completion of the survey and educational component, a senior leader of the institution (e.g., hospital president, vice-president, director) is partnered with a unit or clinical area and attends monthly rounds on the unit with the staff to help them prioritize safety efforts, ensure that they have the resources to implement improvements, and hold staff accountable for evaluating whether safety has improved. Staff members are asked to learn from one defect per month and implement one tool per quarter that is designed to improve delivery of care, such as a daily goals sheet (see later) to improve communication and teamwork.[44,45]

Our institution pilot-tested CUSP in its ICUs and subsequently implemented it throughout the hospital. In the pilot test, a patient safety team that consisted of staff from the clinical area was responsible for oversight of the program. To be most effective, this team included the ICU director as the ICU physician safety champion, the nurse manager, another ICU physician and nurse, a risk manager or patient safety officer, and a senior executive from the institution. We found that the program worked best if the physician and nurse who led the program dedicated at least 20% of their time to improving patient safety and QI. The first unit was the beta site; subsequent teams from other clinical areas would learn from their successes and failures. The ultimate goal was to have every area in the hospital organizing and managing safety through CUSP.

CUSP has been associated with significant improvements in safety culture. The proportion of staff members reporting a positive safety climate increased from 35% before CUSP to 60% after CUSP.[39,41] In addition, teams identified and mitigated several specific hazards through CUSP. As a result of asking staff how the next patient will be harmed, the ICU created a dedicated ICU transport team, implemented point-of-care pharmacists, put into practice a daily goals sheet, clearly labeled epidural catheters to prevent inadvertent intravenous connection, and standardized the equipment in transvenous pacing kits.[46] Moreover, the use of CUSP was associated with a reduction in patient length of stay and nurse turnover.

In summary, CUSP provides several benefits for improving safety culture and is a primer for compliance of staff in implementing any safety or QI intervention or project. It provides enough structure to convert the often vague goals of improving safety into a focused strategy yet is malleable enough to allow units to work on issues most important to them. CUSP provides a venue to introduce rigorous research methods, acts as a learning laboratory to identify and mitigate hazards, and has the potential to improve patient outcomes.

Quality Improvement Tools

Efforts in QI and patient safety have produced tools with which to reorganize the way that care is delivered. Some of these tools are described briefly in the following sections.

Daily Goals Sheet

The daily goals sheet has been used since July 2001 during multidisciplinary rounds in the ICU at Johns Hopkins to improve communication.[44] A one-page checklist, this tool is completed every morning to establish the care plan, set goals, and review potential safety risks for each patient (Fig. 5-2). The goals sheet stays with the patient, is updated as needed, and is used as an information sheet for all staff involved in the patient's care. It can be modified for use in other nursing units or during operating room sign-out or emergency department rounds.

On initial survey it was found that care team members were unable to answer two simple questions after rounds at each patient's bedside: "Do you understand the patient's goals for the day? and "Do you understand what work needs to be accomplished on this patient today?" The team's inability to answer these questions became the impetus to develop the daily goals sheet. Before implementation of the daily goals sheet, a survey showed that fewer than 10% of the residents and nurses knew the care

	Room Number _____	Shift: ❒ AM / ❒ PM
Safety	What needs to be done to d/c patient from the ICU?	
	Patient's greatest safety risk? How can we ↓ risk?	
	What events or deviations need to be reported? ICUSRS issues?	
Patient Care	Pain & Sedation Management	Pain goal ____ /10
	Cardiac Review ECGs	HR goal ____ ❒ at goal ❒ ↑ ❒ ↓ beta-blockade
	Volume status Net goal for midnight	Even ❒ Pos ❒ Neg ___ Net ___ (cc) ❒ Patient determined
	Pulmonary: Ventilator, ventilator bundle, HOB ↑, wean	❒ OOB/pulmonary toilet/ambulation
	SIRS/Infection/Sepsis evaluation Temp >38°C or <36°C; HR >90 RR >20 or $Paco_2$ <32 WBC >12000 < 4000 or >10% bands	❒ No current SIRS/sepsis issues ❒ Known/suspected infection ❒ Culture blood ×2/urine/sputum ❒ Antibiotic changes ❒ Discontinue sepsis bundle
	Can catheters/tubes be removed?	Y/N
	GI/Nutrition/Bowel regimen: TPN catheter, ND tube PEG needed?	❒ TPN ❒ NPO/Advance diet
	Is patient receiving DVT/PUD prophylaxis?	Y/N
	Can meds be discontinued, changed to PO, adjusted?	
To Do	Tests/Procedures today	
	Scheduled labs	
	AM labs needed/CXR?	
	Consultations	
Description	Has primary service been updated?	
	Has family been updated? Social issues addressed? Long-term/Palliative care	

Figure 5-2 Example of an intensive care unit (ICU) daily goals sheet. CXR, chest radiograph; d/c, discharge; DVT, deep venous thrombosis; ECG, electrocardiogram; GI, gastrointestinal; HOB, head of bed; HR, heart rate; ICUSRS, ICU self-reporting system; ND, nasoduodenal; NPO, nothing by mouth; OOB, out of bed; PEG, percutaneous endoscopic gastrostomy; PUD, peptic ulcer disease; RR, respiratory rate; SIRS, severe infectious respiratory syndrome; temp, temperature; TPN, total parenteral nutrition; vent, ventilator; WBC, white blood cell count.

plan for the day—a finding that is not surprising because traditional bedside rounds tended to focus on teaching staff about the disease rather than the work that was necessary to treat the patient. Approximately 4 weeks after implementing the daily goals sheet, 95% of the residents and nurses understood the goals for each patient. Moreover, after implementing the daily goals sheet, length of stay in a surgical ICU at Johns Hopkins Hospital decreased from a mean of 2.2 days to just 1.1 days.[44]

Briefings and Debriefings

Similar to the daily goals sheet, briefing and debriefing tools are designed to promote effective interdisciplinary communication and teamwork. Both have been used in the operating room, in sign-out from the ICU nursing staff to the intensivist, and between operating room nursing and anesthesia coordinators.[45,47,48] A briefing is a structured review of the case at hand for all team members before the start of an operative procedure. A debriefing occurs after the procedure; the team reviews what worked well, what failed, and what could be accomplished better in the future (Fig. 5-3).

An example of an operating room briefing includes introduction by name (first and last) and the role of each team member; confirmation of the correct patient, site/side, and procedure ("time-out"); and verbal assurance that all team members agree that they understand the procedure and what is required to ensure its success. A check of all necessary equipment (e.g., electrocautery), medications (e.g., appropriate antibiotic), and blood availability is performed. The question "If something were to go wrong, what would it be?" is asked, and plans to mitigate or respond to the potential hazard are discussed.

Checklists

Checklists have been used in health care and in industry in an effort to ensure that important steps in a process are not forgotten. The Food and Drug Administration recommends that a checklist be used when performing checkout and inspection of an anesthesia machine before use to ensure that the equipment and monitors are functioning properly.[49] As part of a QI project to reduce CRBSI, a checklist was one of several interventions implemented

	Briefing: Before Every Procedure
	Team introductions: First and last names, including roles; write names on board
	Verify: Patient ID band, Informed Consent (read out loud), site marking, OR posting, patient's verbalization of procedure (if patient awake), H&P or clinic note
	Are there any safety, equipment, instrument, implant, or other concerns?
	Have antibiotics been given, if indicated?
	What are the anticipated times of antibiotic redosing?
	Is glucose control or beta-blockade indicated?
	Is the patient positioned to minimize injury?
	Has the prep solution been applied properly, without pooling, and allowed to dry?
	Have the goals and critical steps of the procedure been discussed?
	Is the appropriate amount of blood available?
	Is DVT prophylaxis indicated? If yes, describe.
	Are warmers on the patient?
	Is the time allotted for this procedure an accurate estimate?
	Have the attendings reviewed the latest laboratory and radiology results?
	Debriefing: After Every Procedure
	Could anything have been done to make this case safer or more efficient?
	Has the Surgical Site Infection data collection form been completed?
	Are the patient's name, history number, surgical specimen name, and laterality on the paper work? (must be independently verified by the surgeon)
	Did we have problems with instruments? Were they reported?
	Plan for transition of care to postop unit discussed? ❒ Fluid management? ❒ Blood transfusion paperwork in chart? ❒ Antibiotic dose and interval to be continued postop? ❒ Pain management/PCA plan? ❒ New medications needed immediately postop? ❒ Beta-blockers needed? ❒ Glucose control? ❒ DVT prophylaxis?

Figure 5-3 Example of a checklist for operating room (OR) briefing and debriefing. DVT, deep venous thrombosis; H&P, history and physical examination; ID, identification.

to reduce complexity and introduce a redundant safety check. The checklist, typically completed by a nurse, was attached to the CVC insertion cart to ensure compliance with the best practices for CVC placement. The nurse was empowered to stop the procedure if the checklist was not followed or if sterile technique was compromised. This intervention resulted in a 66% reduction in the overall CRBSI rate, with the median rate reduced from 2.7 per 1000 catheter-days before the intervention to 0 by month 3 and through month 18 of the postintervention period.[50,51] In general, these QI tools seek to standardize communication and technical work.

Sources of Quality Improvement Information

Multiple sources of QI data that span both the clinical and administrative arenas include evidence-based medicine and evidence-based clinical practice guidelines, alerts from accrediting agencies and nonprofit safety organizations, standards and guidelines put forth by medical specialty associations, and administrative (such as those maintained by CMS) and claims databases. U.S. governmental agencies, including AHRQ, CMS, and the National Quality Forum (NQF), promote the development and reporting of health care quality measures.[52]

Peer-reviewed journals have published the results of studies that support evidence-based clinical practice guidelines, as well as individual QI programs, and can be a rich source of ideas to improve clinical decision making and patient care by incorporating the best available evidence with patient values and provider preferences.[53,54] In anesthesiology and critical care medicine, guidelines and protocols have been successful in improving performance in some care processes. Sedation and ventilator weaning protocols in ICUs have been shown to decrease the duration of mechanical ventilation and length of stay in the ICU.[55,56] Moreover, individual QI programs have been used to improve delivery of care and have been shown to have a positive effect on job satisfaction and organizational commitment.[57]

National Programs in Quality Improvement

A growing number of regional and national organizations are developing initiatives that are driving the reporting of specific evidence-based practices and outcomes and determining the local selection of areas for QI (Table 5-3).

The Joint Commission has developed quality measures for several areas (www.jcaho.org). Their ORYX initiative was devel-

Table 5-3 Nonprofit and Government Quality Improvement Organizations Pertinent to Anesthesia

Quality Improvement Organization	Website	Description
Agency for Healthcare Research and Quality (AHRQ)	www.ahrq.gov	Lead federal agency charged with improving the quality, safety, efficiency, and effectiveness of health care
American Health Quality Association (AHQA)	www.ahqa.org	Represents quality improvement organizations and professionals working to improve the quality of health care
Anesthesia Patient Safety Foundation (APSF)	www.apsf.org	Promotes investigations and programs that will provide a better understanding of anesthetic injuries
Centers for Disease Control and Prevention (CDC)	www.cdc.gov	One of the major operating components of the Department of Health and Human Services
Emergency Care Research Institute (ECRI)	www.ecri.org	Uses applied scientific research to discover which medical procedures, devices, drugs, and processes are best
Institute for Healthcare Improvement (IHI)	www.ihi.org	Health care improvement organization based in Cambridge, Massachusetts
Institute for Safe Medication Practices (ISMP)	www.ismp.org	The nation's only 501(c)(3) organization devoted entirely to prevention of medication errors and safe medication use
Medicare Quality Improvement Community (MedQIC)	www.medquic.org	A national knowledge forum for health care and quality improvement professionals
National Quality Forum	www.qualityforum.org	Created to develop and implement a national strategy for health care quality and reporting
National Patient Safety Foundation (NPSF)	www.npsf.org	An independent 501(c)(3) organization, the mission of which is to improve the safety of patients

oped to integrate performance measurement data into the accreditation process and to permit rigorous comparison of the actual results of care across hospitals. In 2004, The Joint Commission partnered with CMS to align measures common to both organizations, called "Hospital Quality Measures." These measures are also endorsed by the NQF.

The NQF is a private, nonprofit membership organization created to develop and implement a national strategy for health care quality measurement and reporting (www.qualityforum.org). One of its functions is to endorse certain quality and safety measures (consensus standards), which are then incorporated into other national quality initiatives. The goal is for NQF-endorsed standards to become the primary standards used to measure the quality of health care in the United States. Anesthesia programs are increasingly focusing on standards that are relevant to them because facilities are being evaluated on their compliance and are required to report their performance regarding these standards to the governing bodies.

The Surgical Care Improvement Project

The Surgical Care Improvement Project (SCIP), a national collaborative of public and private entities that has outlined perioperative QI goals (www.medqic.org) and is in partnership with The Joint Commission and CMS national initiative, was initiated in 2003. This multidisciplinary group uses both process and outcome measures (Box 5-1) to focus on key clinical areas that include preventing surgical-site infections, perioperative myocardial infarctions, venous thromboembolism, and mortality and readmission, as well as increasing the use of fistulas in providing hemodialysis for Medicare beneficiaries with kidney failure.

Private Insurers

Many private insurers now collect data on certain quality elements. The Leapfrog group is one such entity. The Leapfrog Hospital Quality and Safety Survey assesses hospital performance according to four evidence-based safety practices: (1) use of computerized physician order entry, (2) evidence-based hospital referral, (3) ICU physician staffing, and (4) a Leapfrog Safe Practices score, which is based on the level of performance of other NQF-endorsed practices (www.leapfroggroup.org). Leapfrog not only reports the results and rankings of its survey but also uses them as a basis for their selection of hospitals to be covered by the plan for the employees of participating companies.

Pay for Performance

Public and private insurers are demanding increased accountability as a result of rising health care costs and threatened budgets. In response, pay for performance (P4P) has been proposed and implemented as a means of improving quality based on successful examples in business. P4P has been defined as the use of incentives to encourage and reinforce the delivery of evidence-based practices and health care system transformations that promote better outcomes as efficiently as possible. Measures that are incorporated into P4P must be evidence based, consistent with national goals, and based on consensus in the absence of evidence (www.jointcommission.org). Furthermore, it is important that measures be reliable, valid, and feasible and that the programs be voluntary. Although the strategy of P4P is to align quality of care and payment, the impact of P4P on quality of care has thus far been modest.

Box 5-1 Process and Outcome Measures of the Surgical Care Improvement Project

Infection
Prophylactic antibiotics:
- Received within 1 hr before the surgical incision
- Appropriately selected for surgical patients
- Discontinued within 24 hr after the surgical end time (48 hr for cardiac patients)

Cardiac surgery patients with controlled 6 AM postoperative serum glucose

Postoperative wound infection diagnosed during the index hospitalization (***outcome***)

Surgery patients with appropriate hair removal

Colorectal surgery patients with immediate postoperative normothermia

Cardiac
Noncardiac vascular surgery patients with evidence of coronary artery disease who received β-blockers during the perioperative period

Surgery patients who had already received a β-blocker before arrival and then during the perioperative period

Intraoperative or postoperative acute myocardial infarction diagnosed during the index hospitalization and within 30 days of surgery (***outcome***)

Venous Thromboembolism (VTE)
Surgery patients with recommended VTE prophylaxis ordered

Surgery patients who received appropriate VTE prophylaxis within 24 hr before surgery to 24 hr after surgery

Intraoperative or postoperative pulmonary embolism diagnosed during the index hospitalization and within 30 days of surgery (***outcome***)

Intraoperative or postoperative deep venous thrombosis diagnosed during the index hospitalization and within 30 days of surgery (***outcome***)

Respiratory
Number of days ventilated surgery patients had documentation of the head of the bed being elevated from the recovery end date (day 0) through postoperative day 7

Patients in whom postoperative ventilator-associated pneumonia is diagnosed during the index hospitalization (***outcome***)

Number of days ventilated surgery patients had documentation of stress ulcer disease prophylaxis from the recovery end date (day 0) through postoperative day 7

Surgery patients whose medical record contained an order for a ventilator weaning program (***protocol* or *clinical path***)

Global
Mortality within 30 days of surgery

Readmission within 30 days of surgery

Vascular Access
Proportion of permanent hospital end-stage renal disease vascular access procedures that involve autogenous arterial venous fistulas

The Physician Quality Reporting Initiative is a program in which anesthesiologists can earn a 1.5% bonus from CMS by reporting their compliance with appropriate timing of perioperative antibiotics. Initial steps in this program are payment for participation, with the ultimate goal that successful compliance with the clinical measures will be the basis for bonus payments. The ASA has identified five "quality incentives" or P4P measures to date (www.asahq.org, accessed September 9, 2007):

1. Timely administration of antibiotic prophylaxis
2. Maintenance of normothermia
3. Comprehensive planning for chronic pain management
4. Prevention of ventilator-associated pneumonia
5. Prevention of CRBSIs

All but the chronic pain measure are adaptations of national quality measures. The chronic pain measure was drafted by the ASA Committee on Pain Medicine and subsequently endorsed by five additional specialty organizations representing pain physicians. Additional measures are being evaluated, and the methods by which they will be incorporated into national initiatives or P4P (or both) will continue to evolve.[51,58]

The Future: Research, Education, and Ethics

Much remains to be accomplished in QI research and practice. The opportunity to improve patient care is substantial, and the pressure to improve the quality of perioperative care will continue to increase. Improving quality of care requires the ability to measure and improve performance. Research is needed to develop measures of quality that clinicians believe are valid and to learn how to ensure that all patients reliably receive the recommended interventions. Innovation is needed to develop information systems that can be used by multiple disciplines. Anesthesiologists and professional societies may need to partner with experts in quality measurement to develop and implement quality measures. Future efforts should balance the feasibility and validity of quality measures and develop integrated approaches to improving quality, including strategies to develop care bundles, decrease complexity, and create independent redundancies.

Providers need to be educated in the skills necessary to improve quality. Health care will cross the quality chasm only

Table 5-4 Six Core Competencies of the Accreditation Council of Graduate Medical Education and Six Aims for Improvement of the Institute of Medicine

ACGME Core Competencies	IOM Aims for Improvement
1. Patient Care	Safe
2. Medical Knowledge	Timely
3. Interpersonal and Communication Skills	Effective
4. Professionalism	Efficient
5. System-based Practice	Equitable
6. Practice-based Learning and Improvement	Patient centered

when all view quality and safety as what they do primarily rather than as an added activity and when health care organizations provide the infrastructure to monitor and improve performance. Frontline caregivers must understand the science of quality and safety and evaluate safety risks with lenses that see hazardous systems, not incompetent people.

Anesthesiologists need to train providers in the methodology of improvement. Integral to this goal is the education of our anesthesia resident trainees. Continuous QI has been touted in anesthesia residency training programs for well over a decade.[59] In recent years, residents in training were presented with six core competencies to master, as mandated by the Accreditation Council of Graduate Medical Education (ACGME),[60] and the IOM put forth their six Aims for Improvement[4] (Table 5-4). In an effort to link these two sets of goals and apply them to the clinical setting for training purposes, Bingham and associates developed a framework called a "Healthcare Matrix" that can be used as an educational tool and a research tool for improvement.[61]

With the increasing amount of intellectual focus and health care resources being directed toward QI programs, the ethics of QI have come to light. QI projects have generally been exempt from the rigorous review of human subject research. However, a Hastings Center Report on the ethics of using QI methods to improve health quality and safety suggests that some QI projects may involve risk to patients and should undergo a formal review.[62] This report lists QI initiatives that may trigger the need for a review, such as those with a randomized design, novel treatments, involvement of researchers, or delayed feedback of monitoring or those funded by external sources. Reporting of QI activities should be encouraged, and requiring approval by an internal review board in addition to having a standardized format for reporting the results supports the premise that delivery of quality care is a science as well as an art.

Summary

Health care organizations need a systematic approach to three areas of patient safety: (1) translating evidence into practice, (2) identifying and mitigating hazards, and (3) improving culture and communication. The underlying principle for all of the approaches discussed is that to improve the quality of care that they provide, providers must be able to measure their performance. Health care providers have traditionally had limited ability to obtain feedback regarding performance in their daily work, in part because of a lack of information systems and lack of agreement on how to measure quality of care.[63] As a result, many in health care do not have access to performance data and consequently do not know the results that they achieve (or fail to achieve). As consumers, payers, regulators, and accreditors require evidence regarding quality of care, the demand for quality measures will probably grow. To meet these demands, anesthesiologists must be able to evaluate the quality of care that they provide with valid measures and implement evidence-based best practices in the perioperative care of patients.

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6 Human Performance and Patient Safety

Key Points

1. Clinical excellence is not achieved by the use of sound medical knowledge alone. Human factors and the interaction of team members, as well as organizational conditions in the system of care, also play major roles. Therefore, the study of human performance and related organizational matters is very important.
2. The health care system in general and clinical institutions in particular must provide appropriate organizational characteristics to allow and foster safe patient care practices (e.g., improve safety culture, integrate effective incident reporting and analysis systems).
3. High-reliability organization theory describes the key features of systems that conduct complex and hazardous work with very low failure rates. Errors do occur in such organizations, but their systems make them more impervious to errors and their sequelae (resilience).
4. In dynamic domains such as anesthesia, continuous decision-making, as described in the cognitive process model, is critical to achieving safe patient care.
5. Several error mechanisms have been demonstrated through human factors research. Understanding these psychological "traps" (for example, "fixation errors") can help anesthetists avoid or mitigate them.
6. The introduction and spread of crisis resource management training, including the application of realistic simulation exercises, is likely to improve patient safety in anesthesia and other acute care domains.
7. Like all human beings, the performance of individual anesthetists can be adversely influenced by "performance-shaping factors," including noise, illness, aging, and especially sleep deprivation and fatigue.
8. A particular technique of human factors research called "task analysis" has been useful in understanding the work of anesthetists.
9. Observation of anesthetists during routine operations or in the handling of adverse events (using realistic patient simulators) has improved our knowledge of critical decision-making and team interactions.
10. Future progress on patient safety in anesthesia will require interdisciplinary research and training, improvements in systems safety and organizational learning, and the involvement of all levels of the health care industry.

Impact of Human Performance on Patient Safety

The most important component of every anesthetic regimen is the human performance of the anesthetist and its relationship to patient safety. More than 70% of accidents are due to "human factors." Because the performance of the anesthetist—embedded in a larger system of care—is such a critical and most determining aspect of patient safety, education and training of health care professionals in this area need improvement. This chapter aims to provide an overview of the importance of human performance and systems safety in anesthesia and to provide start-up knowledge of key safety factors and methods.

Anesthesia is an intrinsically hazardous undertaking, but as hazardous activities go, its track record is indeed a model of patient safety for the rest of health care.[1,2] The Institute of Medicine (IOM) asserts: "Anesthesia is an area in which very impressive improvements in safety have been made."[3,4] However, the theory of organizational safety teaches us that safety is a never-ending process; any patient harmed by an anesthetic is one patient too many (in concert with the "zero vision" statement of the U.S. Anesthesia Patient Safety Foundation [APSF]: "That no patient shall be harmed by anesthesia"). Cooper and Gaba[1] wrote: "Anesthesiologists should remain aware of the hazards they still face, take pride in having been the leaders in patient safety efforts, and stay motivated to continue the pursuit of 'no harm from anesthesia' with the passion it still demands."

Because most of the work on human performance (and also on simulation) has been started and has focused on anesthesiology in the operating room (OR), this chapter deals primarily with aspects of performance and safety in the OR setting. Nevertheless, most of the same principles and issues are relevant to the

postanesthesia care unit (PACU), the intensive care unit (ICU), emergency medicine, and to a lesser degree, pain therapy and other domains of importance to anesthesiologists. For readers with a special interest in the ICU, a selection of references is given as a starting point.[5-17]

Safe conduct of anesthesia depends on the appropriate application by skilled anesthetists of knowledge concerning surgical procedures, the physiology of patients during and after anesthesia, the characteristics of anesthetic and adjuvant drugs, and the means of monitoring the patient and the life support equipment throughout the perioperative period. In this chapter the term *anesthetist* refers to any anesthesia professional taking care of a patient, whether a physician, certified registered nurse anesthetist (CRNA), or anesthesia assistant.

Traditionally, an adequately trained anesthetist automatically was assumed to perform appropriately. Deviations from optimal outcomes were understood to be due to imperfections in the art and science of anesthesia, which led to heavy emphasis on the scientific and technical aspect of anesthesia training and care. More rarely, adverse outcomes were ascribed to negligence or incompetence on the part of the anesthetist. Today, there is a more complete understanding that anesthetists themselves, both as a profession and as individuals, have strengths and vulnerabilities pertaining to their work environment. The performance of human beings is incredibly flexible and powerful in some aspects, but is very limited in others. They are vulnerable to distractions, biases, and errors. This chapter surveys some of the human characteristics that define the performance of anesthetists. These characteristics (also termed human factors) are by no means constant; for example, a person may communicate very effectively in one instance and fail to close the loop in the next challenging communication role.

The domain of the anesthetist is very challenging; it is as difficult or more so than other domains that more readily capture the public's imagination, such as aviation. The past 25 years has seen new research on the nature and limitations of professional judgment and decision-making in this dynamic and complex world. Chapter 7, "Patient Simulation," explores developments in the methods of using simulations and simulation technologies that have contributed to this research and that may open new opportunities to prepare anesthetists to handle the challenges that they face in their work.

The literature related to human performance and patient safety is vast (standard reference works are available[18-26]), and this chapter samples only a portion of it as it most closely relates to the work of anesthetists. Moreover, this chapter does not deal to any great extent with human-machine interactions and the physical design of the work environment. These aspects of human factors, or ergonomics, in anesthesia have considerable importance in their own right. The reader is referred to several publications that review these issues in detail.[27-38]

Nature of the Operational Domain of Anesthesiology

The operational domain of anesthesia is a complex, dynamic world that presents a cognitive profile common to many real-world task domains. Analysis of complex dynamic worlds in the last decade has departed sharply from previous conceptions of decision-making.[39] Classic decision-making approaches, such as decision theory and multi-attribute utility theory, are mathematical techniques that were traditionally used as the dominant framework for understanding human performance. They worked well in simplified laboratory experiments on decision-making and action, yet a number of investigators had significant difficulty in applying them to real-world decision and action settings.[39] Orasanu and colleagues[39] identified eight factors that characterize such naturally occurring complex dynamic worlds. They apply to anesthesia as follows:

1. **Ill-structured problems.** Unlike traditional decision experiments, there is not just a single decision to be made. Rather, a variety of interrelated decisions must be made by the anesthetist and surgeon. The patient's physiologic behavior is not an independent random variable but is causally linked to previous decisions and actions.
2. **Uncertain dynamic environment.** Dynamism stems from the frequency of routine and anomalous changes or events, the rapidity with which they evolve, and the unpredictability of the patient's physiology and response to interventions. An anesthetized patient is in a constant state of change during surgery, with many events outside the anesthetist's control. Although preventive measures can reduce the likelihood of some events, others cannot be avoided because they are inevitable side effects of medically necessary procedures (e.g., surgical blood loss). Unpredictable and dynamic occurrences compete with the preplanned aspects of the case and drive the anesthetist's actions. The true state of the patient cannot usually be measured directly. It must be inferred from ambiguous patterns of clinical observations and data from electronic monitors. These data are imperfect because unlike industrial systems that are designed and built with sensors in key areas to measure the most important variables, patients are typically instrumented to measure the variables that are easiest to monitor, predominantly with the use of noninvasive methods. Most physiologic functions are observed indirectly through weak signals available at the body surface and thus are prone to various types of electrical and mechanical interference. Invasive measurements are also vulnerable to artifacts and uncertainties of interpretation. Even if the anesthetist knew the exact state of the patient, the patient's response to interventions would be unpredictable.
3. **Time stress.** Because the OR is a scarce resource, there is an incessant overall time pressure to use it efficiently. There is an even more intense immediate time stress within each case generated by dynamic situations that evolve rapidly and must be dealt with in timely fashion.
4. **Shifting, ill-defined, or competing goals.** Multiple goals of case management (e.g., hemodynamic stability, good operating conditions for the surgeon, rapid emergence from anesthesia) may compete with each other. The surgeon's goals may sometimes compete with those of the anesthetist. All these goals shift as the patient's situation changes dynamically throughout the procedure.
5. **Action/feedback loops.** The time constants of actions and their effects are very short, on the order of seconds to minutes. There is complete intermixing of decision-making and action; these functions are not performed in separate

cycles. Most decisions and actions are implemented and evaluated incrementally, with the effect of one cycle assessed before deciding on further possible actions.

6. **High stakes.** The stakes are high because even for elective surgery in healthy patients, there is an ever-present and very real risk of injury, brain damage, or even death. A catastrophe is often the end result of many pathways that begin with seemingly innocuous triggering events. Each intervention, even if appropriate, is associated with side effects, some of which are themselves serious. Some risks cannot be avoided. Unlike an event such as a commercial flight, which can be delayed or aborted if a problem occurs, during an event in the OR this is not usually possible, and immediate surgery may be necessary to treat a medical problem that is itself life threatening. Analogous to military aviation, balancing the risks of action (anesthesia and surgery) against those of inaction is often extremely difficult.
7. **Multiple players.** Anesthesia domains involve multiple players from different professional backgrounds. Each individual has a set of goals, abilities, and limitations. In some situations, interpersonal interactions, among anesthesia personnel and between them and other OR team members, will dominate the work environment.
8. **Organizational goals and norms.** The anesthetist works within the stated and unstated norms of the OR suite, the anesthesia department, the institution, and the profession as a whole. Decisions are sometimes made to conform to these norms even though they are not wholly subscribed to by the anesthetist.

Although many of these features apply to other domains of medicine, anesthesiology is unique in that all eight factors are prominent. In particular, what sets anesthesia apart from clinic- or ward-based medicine is the intensity of the dynamism, time pressure, and uncertainty, with danger lurking just below the surface.

Safety Culture of the Operating Room and Intensive Care Environment (See Chapters 99-101)

Analyzing the Anesthetist's Domain: The Operational World Versus the Organizational World

Psychologists and cognitive engineers who study real work environments describe each field as a domain. Each domain has specific characteristics that set it apart from others, including the nature of the tasks to be performed, the relationships among the tasks, the time scale over which they must be executed, and the criteria for their successful performance. This chapter deals mainly with the operational domains in which anesthesia care is delivered, primarily the OR, the PACU, and the ICU. However, as pointed out by Reason,[40-43] as well as by Cook, Woods, and McDonald,[44] what goes on in the operational domain is extensively shaped by the organizational and managerial environment in which it is located, even to the point that operational personnel believe themselves to be the "victims" of problematic decisions further back in the system.

In everyday practice, these distinctions are hidden or blurred. The positive and negative contributions of the organizational and management elements are often so embedded in the normal routine that they are difficult to isolate. Interesting information about the system often comes from considering abnormal situations, accidents, or near misses instead of normal events. For example, investigation of the loss of the space shuttle Columbia revealed a variety of latent errors within the procedures and safety culture at the National Aeronautics and Space Administration (NASA):

> *The accident was probably not an anomalous, random event, but rather likely rooted in NASA's history and the space flight program's culture.*[45]

The report placed as much weight on these factors as on the direct technical causes of the accident. Traditionally, one speaks of errors arising in decisions and actions that lead to a mishap. However, the term "error" is increasingly considered an inappropriate way to categorize behavior (being a judgment of attribution and blame) and should be thought of merely as a way to identify behavior at the locus of a critical situation. In this context it must be understood that "errors are not the cause of an accident." Rather, errors are usually the consequence of a combination of several underlying factors. Beyond that, errors must combine with other circumstances to result in an accident or adverse outcome.[46] This concept is illustrated in Figure 6-1. Some errors are actively produced in the operational domain, whereas others are introduced by the organizational environment. James Reason, a psychologist at the University of Manchester, England, described the latter by using the concept of "latent errors"[46]:

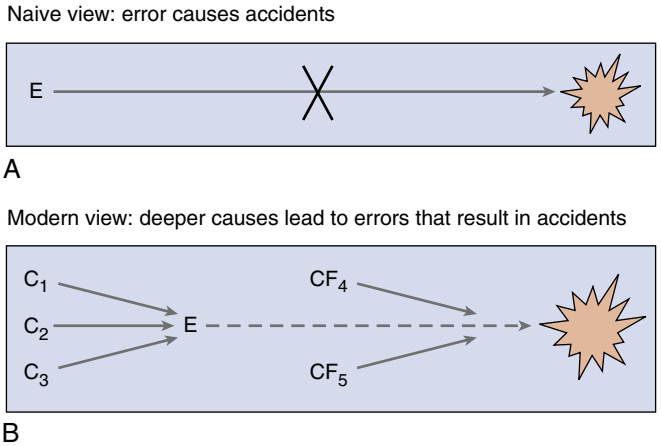

Figure 6-1 Relationship between errors (E) and adverse events. **A,** Errors are not the cause of accidents but in rare cases they lead directly to the adverse event. Multiple root causes (C_1, C_2, C_3) lead to the error (**B**). For the most part, additional contributing factors (CF_4, CF_5) are necessary to allow the error to evolve into an adverse event. Incident reporting systems should try to identify as many of the root causes and contributing factors before an accident happens and try to influence these factors in such a way that no accident will happen. *(Adapted from Rall M, Manser T, Guggenberger H, et al: [Patient safety and errors in medicine: Development, prevention and analyses of incidents.] Anästhesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie 36:321-330, 2001, with permission.)*

errors whose adverse consequences may lie dormant within the system for a long time, only becoming evident when they combine with other factors to breach the system's defenses. [They are] most likely to be spawned by those whose activities are removed in both time and space from the direct control interface: designers, high-level decision makers, construction workers, managers and maintenance personnel.

Latent errors probably exist in all complex systems, and Reason adopted a medical metaphor to describe them as "resident pathogens." Like microorganisms in the body, the resident pathogens remain under control until sets of local circumstances "combine with these resident pathogens in subtle and often unlikely ways to thwart the system's defenses and bring about its catastrophic breakdown" (Fig. 6-2). This "threat and error model" has also been articulated by the noted aviation-oriented psychologist Robert Helmreich at the University of Texas (Fig. 6-3).[47]

A variety of latent failures can exist in the anesthesia environment. They may include such issues as how surgical cases are booked, how cases are assigned to specific anesthetists, what provisions are made for preoperative evaluation of outpatients, and what relative priority is given to rapid turnover between cases or avoiding cancellation of cases as opposed to avoidance of risk. Latent errors can also result from the design of anesthesia equipment and its user interfaces, which in some cases lead clinicians to err or are unforgiving of errors. Manufacturing defects and routine maintenance failures are also types of latent failure.

Investigation of untoward events must address both latent and active failures and both the organizational and managerial environment and the operational domain. One risk of focusing solely on active failures is that operational personnel may be "victims of the system" in a "Catch-22"–type situation and be pushed to maximize production while admonished to "be safe." Addressing only their actions—and not the latent pressures under which they must work—can make them defensive and uncooperative. Cook, Woods, and McDonald[44] pointed out that if one looks at the chain of events in an accident sequence, one can always find a failure on the part of an operator. If the analysis stops at this point, the operator (i.e., the anesthetist) may be wrongly blamed for a failure, the real roots of which go back to latent failures in the organization. If the underlying latent errors are never identified or never fixed, they remain in the system and

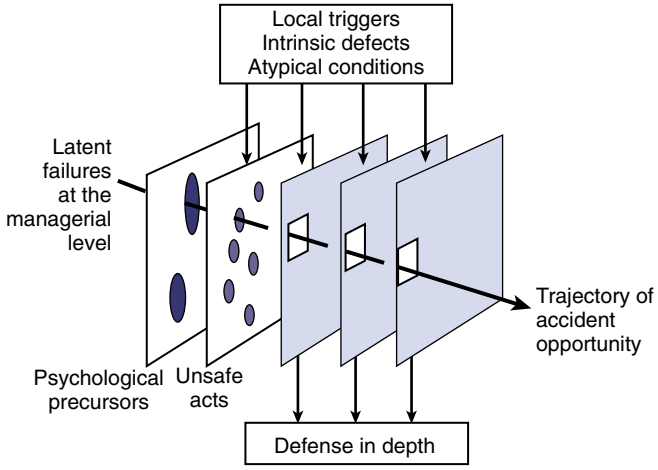

Figure 6-2 James Reason's model of the causation of accidents. Latent failures at the managerial level may combine with psychological precursors and event triggers at the operational level to initiate an accident sequence. Most accident sequences are trapped at one or more layers of the system's defenses. The unforeseen combination of organizational or performance failures with latent errors and triggers may lead to breach of the system's defenses and allow the accident to take place. The diagram should be envisioned as being three-dimensional and dynamic—with "shields" moving around and holes in the defense's opening and closing. *(Redrawn from Reason JT: Human Error. Cambridge, Cambridge University Press, 1990.)*

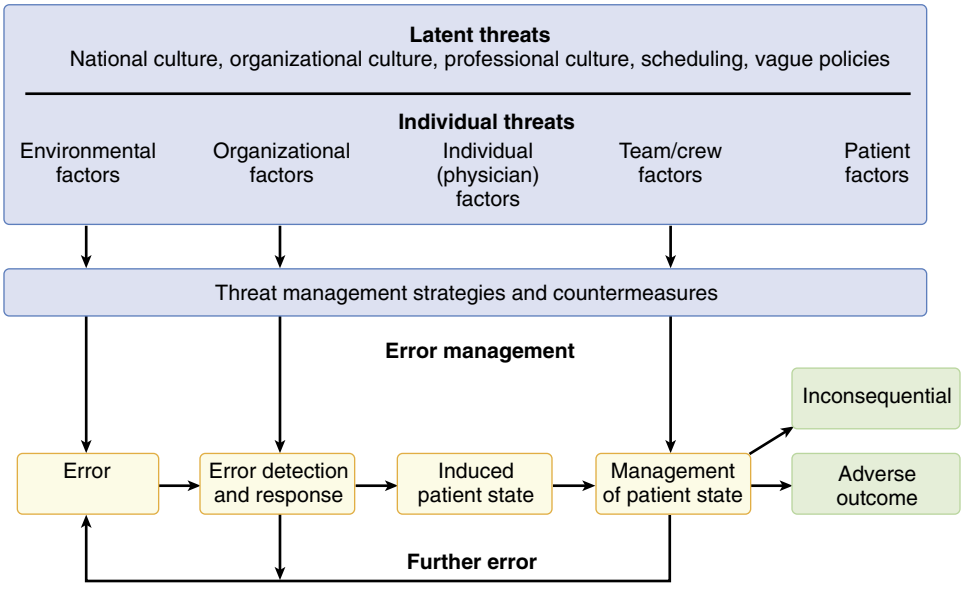

Figure 6-3 University of Texas threat and error model. This model, which illustrates the evolution of errors, is used in the analysis of incidents and accidents (a detailed example is available at http://bmj.bmjjournals.com/misc/bmj.320.7237.781/sld001.htm).

Table 6-1 Asymmetry of Signals of Safety Versus Signals of Production

Production	Safety
Feedback about production is easy to measure reliably and nearly continuously ("revenue,""earnings,"" expenses") and indicates success in a positive fashion	Traditional measures of "safety" are indirect and discontinuous, thus making them noisy and difficult to interpret or even deceptive
Success is indicated "positively" (e.g., increasing earnings), is obviously reinforcing, and has high salience (the bottom line is the "bottom line" for a firm)	Feedback is provided "negatively" (fewer accidents or incidents) and has little reinforcement value in itself. High salience is achieved only after an accident or a scary near miss
The relationship between the application of resources (money, effort, time) and production goals is relatively certain, thus making it easy to use feedback	Even when interpreted correctly, the relationship between application of resources and safety goals is relatively uncertain, thus making it hard to use the feedback

Adapted from Reason JT: Human Error. Cambridge, Cambridge University Press, 1990.

will probably induce another accident chain in the future. This is visualized in Reason's accident trajectory, shown in Figure 6-2.

Asymmetry Between Safety and Production

An additional difficulty in achieving optimal safety is an inherent asymmetry of information and concern about safety versus production (Table 6-1).[46] Investments for production are easy to plan for and measure; feedback about production is easy to obtain and to interpret. Investments for safety are harder to plan for, and the costs are harder to measure. Most importantly, feedback about safety is inherently weak and ambiguous. How can one measure the accidents that could have occurred but did not? Only after a catastrophe takes place do the costs of a safety failure become apparent.

Organizational Safety

Over the last few years there have been many landmark publications and activities concerned with patient safety and the organizational aspects of reducing errors.[3,25,42,48-52] The report of the IOM in 1999, "To Err Is Human,"[3] was a highly publicized awakening in the United States about the problems of patient safety. Summarizing the primary literature, the report stated that "tens of thousands die each year from errors in their care and hundreds of thousands suffer or barely escape from nonfatal injuries that a truly high-quality care system would largely prevent." The most important recommendations of this report, which led to nationwide activities to promote patient safety, are shown in Box 6-1.

The subsequent report of the IOM Committee on Quality of Health Care in America, titled "Crossing the Quality Chasm—A New Health System for the 21st Century,"[48] took a systematic approach to improvement of the entire health care system. It stated that "between the healthcare we have and the care we could have, lies not just a gap, but a chasm" because the health care system today harms too frequently yet routinely fails to deliver its potential benefits. The report concluded: "The current care system cannot do the job. Trying harder will not work. Changing the systems of care will." In the following text we consider the organizational and systems aspects of anesthesia care and patient safety.

There are several schools of thought about organizational safety in highly hazardous activities. Two theories, normal accident theory (NAT) and high-reliability organization theory (HROT), have dominated the discussion of safety in many domains and have been applied individually to health care with increasing frequency over the last 20 years.[43-52,60] NAT was originally promulgated by the sociologist Charles Perrow[57] in the wake of the Three Mile Island nuclear accident and has been applied by him and others to such diverse fields as commercial aviation, maritime transport, and the handling of nuclear weapons. HROT was promulgated initially by a group of researchers at the University of California at Berkeley. It has also been applied to diverse domains, including aircraft carrier flight decks, offshore oil platforms, air traffic control, nuclear power production, and the financial transaction industry (personal communication, Karlene Roberts).

These workers' complementary views of organizational safety are summarized briefly here and in Table 6-2.

Normal Accident Theory (NAT)

NAT focuses primarily on two features of a system: (1) the complexity of interactions among the system's elements and (2) the presence of tight coupling among the system's elements. A system is tightly coupled when a change in one part of the system rapidly alters other parts of the system. For example, some physiologic systems are buffered from changes in others, whereas certain core components, such as oxygen delivery and blood flow, are tightly coupled together and interact strongly. The patient's physiology may become tightly coupled to external systems such as ventilators and infusions of hemodynamically active drugs. When complexity and tight coupling coexist, abnormal sequences of events can sometimes be hidden and have complex or unpredictable consequences. Typically, active errors in the system do not result

Box 6-1 Recommendations of the Institute of Medicine Report "To Err Is Human"

Make patient safety a declared and serious aim.

Provide strong, clear, and visible attention to safety.

Implement nonpunitive systems for reporting and analyzing errors.

Incorporate well-understood safety principles, such as standardizing and simplifying equipment, supplies, and processes.

Establish interdisciplinary programs to improve teamwork and communication by using modalities proven in other industries, including simulation.

Table 6-2 Complementary Views of High-Reliability Organization Theory (HROT) Versus Normal Accidents Theory (NAT)

HROT	NAT
Accidents can be prevented through good organizational design and management	Accidents are inevitable in complex and tightly coupled systems
Safety is the priority organizational objective	Safety is one of a number of competing objectives
Redundancy enhances safety; duplication and overlap can make a reliable system out of unreliable parts	Redundancy often causes accidents because it increases interactive complexity and opaqueness and encourages risk taking by social-shirking and cue-taking behavior
Decentralized decision-making is needed to permit prompt and flexible field-level responses to surprises	Organizational contradiction: decentralization is needed to handle the distributed complexity, but centralization is needed to manage tightly coupled systems
A "culture of reliability" will enhance safety by encouraging uniform and appropriate responses by field-level operators	A military model of intense discipline, socialization, and isolation is incompatible with democratic values
Continuous operations, training, and simulations can create and maintain high-reliability operations	Organizations cannot train for unimagined, highly dangerous, or politically unpalatable operations
Trial-and-error learning from incidents (through effective incident reporting) can be effective and supplemented by anticipation and simulations	Denial of responsibility, faulty reporting, and biased reconstruction of history frequently cripple learning efforts

Modified from Sagan SD: The Limits of Safety. Princeton, NJ, Princeton University Press, 1993.

in an accident because they are trapped at some point by the system's multiple layers of checks and defenses (see Fig. 6-2). Even a minor perturbation can cause normal system behavior to be out of control when there are complex interactions and tight coupling. Perrow called this a "normal accident" because the perturbations are common and arise out of otherwise normal system operations.[57] He suggested that attention should be directed at strengthening the recovery pathways by which small events can be properly handled before they evolve into a serious accident.

Complexity and Tight Coupling: Latent Errors in Anesthesia

Clearly, the anesthesia domain involves complex interactions with tight coupling.[58] The complexity stems to some degree from the variety of devices in use and their interconnections, but these are, in truth, vastly simpler than those found in an oil refinery, a 747 aircraft, or a space shuttle. A more important source of complexity is the "uncertainty complexity" of the patient.[58] The human body is an incredibly complex system containing numerous components, the interactions of which are only vaguely understood. Because many body systems affect each other, the patient is a major site of tight couplings. Furthermore, the anesthetic state tends to ablate the buffers between some of these interconnected systems, thereby strengthening the coupling between them and between the patient and external mechanical supports. Galletly and Mushet[59] studied anesthesia "system errors" and observed tight coupling associated with "the use of neuromuscular blocking drugs, the presence of cardiorespiratory disease, certain types of surgical procedures, and the effect of general anesthetic agents. Looser coupling was observed with the use of high concentrations of oxygen and air mixtures, preoxygenation, and spontaneous breathing techniques."

According to the NAT view, we delude ourselves by believing that we can control our hazardous technologies and forestall disaster; in reality, many of the efforts we make at management and design tend to only increase the opacity and complexity of the system (making more holes in the barriers), thereby increasing the likelihood of accidents. The combination of these factors provides fertile ground for the occurrence of accidents—indeed, according to NAT it makes it inevitable that some of the "normal" everyday faults, slips, and incidents will evolve into tragic accidents. NAT is often considered a "pessimistic" view of the ability of organizations to conduct highly hazardous operations without harmful errors.

The very concept of risk is constructed and negotiated. This was perhaps expressed most clearly by Dianne Vaughan in her powerful analysis of the explosion of the Challenger space shuttle:

> *Risk is not a fixed attribute of some object, but constructed by individuals from past experience and present circumstance and conferred upon the object or situation. Individuals assess risk as they assess everything else—through the filtering lens of individual worldview.*

Vaughan's main thesis is that the Challenger exploded not because "risk-taking" managers "broke the rules" but because the system evolved to make excessive risk a part of "following the rules." This happened because the system had a "culture of production" with ingrained production pressure; it was a regular occurrence that aberrant findings be explained away ("normalization of deviance"), and "structural secrecy" was enforced between departments, between manufacturers and NASA, and between engineers and managers. Sadly, many of these same phenomena occurred yet again and led to the Columbia accident.[45] Unfortunately, each of these system characteristics is also operative in perioperative settings.

High-Reliability Organization Theory

In contrast to these rather pessimistic views of the organizational challenges to safety is the HROT view that although not easy, proper organization of people, technology, and processes can handle complex and hazardous activities at acceptable levels of performance. Even though accidents can never be totally eliminated, high-reliability organizations (HROs) must be judged by the benefits that we derive from their activities and their small absolute risk of failure. This view seems particularly appropriate in anesthesiology because forgoing surgical treatment is not a

Box 6-2 Elements of a Culture of Safety (part of HROT in Box 6-3)

Values
- Safety as the most important goal, overriding production or efficiency
- Preoccupation with possible "failures" rather than past "successes"
- Necessary resources, incentives, and rewards provided for optimal safety, not only for optimal production

Beliefs
- Safety must be actively managed
- Processes and routines of care are as (or more) important to safety as individual dedication, skill, or effort
- Openness about safety and errors is essential; learning from normal and adverse events should be thorough

Norms
- Low-ranking personnel raise safety issues and challenge ambiguity regardless of hierarchy or rank
- Calling for help is encouraged and occurs frequently, even (or especially) by experienced personnel
- Explicit communication is frequent
- The hierarchy is flat—leaders listen to juniors; juniors speak up; and calling for help is routine regardless of rank
- People are rewarded for rationally erring on the side of safety, even when their credible concerns turn out to be wrong

Adapted from Weick KE: Organizational culture as a source of high reliability. Calif Manage Rev 29:112-127, 1987.

viable option for many patients and challenges to safety must often be met head-on. Although the concepts of HROT have varied over the years, the core characteristics of HROs are shown in Boxes 6-2 and 6-3.

A key aspect of HROT is that of a culture of safety (or "safety culture"). Since publication of the reports from the IOM, health care has begun paying attention to certain elements of "culture." However, most of the attention has been devoted to the "culture of blame" in a system whereby problems are addressed largely in terms of who is to blame rather than what can be done to prevent them. Safety culture goes beyond these issues by dealing with how individuals and groups conduct their work. Culture is made up of values (what is important), beliefs (how things should work), and norms (the way things work). These elements are shown in Box 6-2. It is equally important that the culture is highly uniform throughout the organization and be continually reinforced by peers, more so than by enforcement of rules.

High-Reliability Organization Theory in Anesthesiology

Anesthesiology has traditionally been strong at some elements of an HRO, particularly in redundancy and technical safety measures. There is a growing movement in anesthesia to more fully implement HRO philosophies and techniques.[60] In fact, anesthesiologists have not only been promoters of the patient safety movement in general but have also been leaders at applying HROT principles to health care. In 2003, the APSF began initiatives in high-reliability perioperative health care (see Special

Box 6-3 Key Elements of a High-Reliability Organization (HRO) in Medicine

Established Culture of Safety (see Box 6-2)

Optimal Structures and Procedures

Decision-making rests with those with greatest knowledge or experience about specific issues regardless of rank or job type.

The unit integrates crews from different departments (e.g., cardiac surgery, cardiac anesthesia, OR nursing, perfusion, ICU) into a coherent clinical team. Teamwork and resiliency are emphasized.

There are formal procedures to maximize transfer of information to all team members before a case (e.g., briefings or time-out procedures).

Schedules are designed to keep work hours and duty periods at reasonable levels to avoid undue fatigue. Personnel under excessive stress are supported or replaced as needed.

Standardized procedures, techniques, and equipment are adopted whenever possible so that similar tasks or operations are performed similarly regardless of the personnel involved; conversely, when necessary (in an emergency or adverse event), the team is resilient and responds as needed to the situation without slavish dependence on standard routines.

The use of preplanned algorithms, checklists, and cognitive aids is actively encouraged.

Easy access to current information systems is available at all times and all locations.

Training and Practice in Routine Procedures and Simulations

Debriefings are conducted after each case.

Nonpunitive assessment instruments are used on a regular basis to provide current feedback and identify elements requiring special training.

There is initial and recurrent simulation-based single-discipline and multidisciplinary training in crew resource management (see Chapter 7).

Actual clinical crews and teams conduct periodic drills or simulations of critical situations in the real OR, PACU, and ICU.

Resident training uses a guided curriculum; training goals and the level of responsibility assigned to a resident match the current proficiency level of the trainee with the complexity of the procedure.

Organizational Learning

Robust mechanisms are in regular use for organizational learning, both prospectively (considering in advance how to optimize protocols and procedures, such as failure mode and analysis of effects) and retrospectively (from analyzing reports of adverse events, near misses, or problems such as root cause analysis).

Problems are analyzed primarily to determine what can be improved rather than whom to blame. Altered procedures are assessed and adopted as appropriate. Process changes reflect appropriate analysis.

ICU, intensive care unit; OR, operating room; PACU, postanesthesia care unit.

Issue of APSF Newsletter, Summer 2003, at www.apsf.org). Box 6-3 summarizes key elements of an HRO adapted to health care.

Teams and Communication

Unlike teams in aviation, the military, and police and fire services, the OR team is unusual in that the command structure is ambiguous. Physicians (surgeon and anesthesiologist) are nominally superior to nursing and technical staff, but physicians are coequally responsible for the patient during the immediate perioperative period. Surgeons were historically considered the "captain of the ship," with even a legal doctrine giving them responsibility for the actions of all other OR team members. Although this legal doctrine has formally fallen by the wayside, remnants of it still remain in aspects of the organizational structure and culture of OR environments. Nonetheless, when both an anesthesiologist and surgeon are caring for a patient, they are coequally responsible, which can lead to complex issues of command authority, hierarchy, and control.

Each physician, as well as the nurses and technicians, has a primary territory of knowledge, skill, and responsibility, but there is considerable overlap among them.

Strictly speaking, a team is defined as "a distinguishable set of two or more people who interact, dynamically, interdependently, and adaptively toward a common and valued goal/objective/mission, who have each been assigned specific roles or functions to perform, and who have a limited life-span of membership." A team is distinct from a group in that a group is an ad hoc collection of individuals without a specific mission and without specific roles. In the OR, all team members have the common goal of a good outcome for the patient. However, there can be considerable disagreement about how to achieve this goal and which elements of patient care have the highest priority. These differences are probably traceable to the fact that the OR team is itself made up of several "crews" (i.e., surgery, anesthesiology, nursing, perfusionist, radiology), each of which has its own command hierarchy, its own global properties (professional standing, culture, traditions, and history), and its own set of local goals and objectives for management of the patient. The differences among the crews can be so striking that some investigators refer to them as separate tribes (transcript of Conference on Human Error in Anesthesia, Asilomar, CA, 1991).

Each "crew" has one or more members who must work effectively together, and crews combine to form a team. A critical component of the success of this process is the establishment and maintenance of a shared mental model of the situation. To the degree that this can be accomplished, the different individuals will be able to tailor their efforts toward a common goal. Experience working together as a crew or team will improve the likelihood of generating a shared mental model.

Cooke and Salas[61,62] made some interesting statements on teams and team knowledge (Box 6-4). In their view, "team knowledge" is more than the sum of individual team members' knowledge, and they demonstrate the need for new methods to elicit team knowledge (e.g., a collective holistic approach). In team knowledge they distinguish between "team mental model" and "team situation model." To judge team knowledge, information is also needed on the broader aspect of "team cognition," which involves team knowledge itself, team decision-making, team situation awareness, and team perception. Figure 6-4 reflects these components of team cognition and team knowledge.[61]

Box 6-4 Teamwork Principles

Team leadership matters.

Team members must have clear roles and responsibilities.

Shared understanding of the task, teammates, and objectives goes a long way.

Take time to develop a discipline of prebriefing, performance, and postbriefing.

Teamwork effects matter.

Clinical expertise is necessary but insufficient for patient safety; cooperation, communication, and coordination skills matter.

Teams must have clear and valued visions.

Learning from mistakes, self-correction, and adaptability are the hallmarks of high-performance teams.

From Salas E, Rosen MA, King H: Managing teams managing crises: Principles of teamwork to improve patient safety in the emergency room and beyond. Theoret Issues Ergonomics Sci 8:381-394, 2007.

Status and Hierarchy Effects

Status and hierarchy effects are important in team performance. Especially in crisis situations, the lower-status crew member tends to defer to the higher-status individual, even if that individual is performing poorly. In aviation, some airplane crashes have occurred in which overbearing captains were combined with unassertive subordinates (first officer copilot and flight engineers). The team was not able to respond effectively, even when the subordinates knew that something was wrong.

In aviation, as in academic anesthesia, training is an ongoing activity in the domain. Although the captain is in charge of the flight, the captain and the first officer (who is essentially in training to become a captain) traditionally alternate the roles of "pilot flying" and "pilot not flying" on each leg of a flight. Each of these roles is carefully defined and involves separate but interrelated tasks (the pilot flying handles the flight controls, whereas the pilot not flying handles radio communications and other tasks). In anesthesiology, the roles of the trainee and the faculty member during patient care are rarely made explicit. The trainee is often expected to do all tasks with only occasional assistance from the supervisor (part of a training method known as cognitive scaffolding). The exact responsibility for different tasks in a crisis is not predefined. It is interesting that two factors frequently found to be associated with critical incidents in anesthesia have been "teaching in progress" and "inadequate supervision."[63]

A particular issue of hierarchy is known as "cue giving" and "cue taking," in which people give off "cues" (often without even knowing it) that are taken up by others.[64] Those not at the top are very sensitive to cues emitted by their superiors. The cues sent by high-status personnel can inhibit action or even questions from lower-status people. One effect of this phenomenon is that dyads and teams that expect to have redundancy from "multiple sets of eyes" on a patient may not achieve this goal because the views of a single person dominate the thinking of the group.

<table>
<tr><td rowspan="4">Team cognition</td><td>Team decision-making</td><td colspan="2" rowspan="3">Model and structure of embedded team knowledge in the broader concept of team cognition</td></tr>
<tr><td>Team situation awareness/ vigilance</td></tr>
<tr><td>Team perception</td></tr>
<tr><td>Team knowledge</td><td>Team mental model</td><td>Team situation model</td></tr>
<tr><td colspan="2">• Long lasting, prior to task
• Through training, experience
• Collective knowledge base, common expectations</td><td>• Fleeting, dynamic
• Through task situation specific
• Interpret situation</td></tr>
</table>

Figure 6-4 Components of team cognition and team knowledge.

Production Pressure

The social and organizational environment may also act as a source of production pressure on anesthetists. Production pressure encompasses the economic and social pressures placed on workers to consider production, not safety, their primary priority.[57] In anesthesiology, this typically means keeping the OR schedule moving speedily, with few cancellations and minimum time between cases. In principle, safety and efficiency can go hand in hand. Many aspects of high reliability, such as standard operating procedures, preprocedure briefings, and flattening the hierarchy, may smooth operation of the system, as well as make it safer. Frequently, however, the pressure for throughput can erode safety.

For example, when anesthetists succumb to these pressures, they may skip appropriate preoperative evaluation and planning or they may fail to perform adequate pre-use checkout of equipment. Even when preoperative evaluation does take place, overt or covert pressure from surgeons (or others) can cause anesthetists to proceed with elective cases despite the existence of serious or uncontrolled medical problems. Production pressure can cause anesthetists to choose techniques that they otherwise believe to be inadvisable.

Gaba and associates[65] reported on a randomized survey of California anesthesiologists concerning their experience with production pressure. They found that 49% of respondents had witnessed a situation in which patient safety was compromised by pressure on the anesthesiologist. Thirty percent reported strong to intense pressure from surgeons to proceed with a case that they wished to cancel. Notably, 20% agreed with the statement that "If I cancel a case, I might jeopardize working with that surgeon at a later date."

Production pressure also leads to haste by the anesthetist, a psychological precursor to the commission of unsafe acts. In the survey, 20% of respondents answered "sometimes" to the statement that "I have altered my normal practices in order to speed the start of surgery," whereas 5% answered "often" to this statement. Twenty percent of respondents rated pressure by surgeons to hasten anesthetic preparation or induction as strong or intense. Repeated exposure to these conflicts can cause the anesthetist to internalize pressures; 38% of survey respondents felt strong to intense internal pressure to "get along" with surgeons, and 48% reported strong internal pressure to avoid delaying cases. Anesthetists may then feel impelled to go ahead with cases against their better judgment, even in the absence of overt pressure.

Investigating these aspects of the work environment is difficult because such relationships are driven by economic considerations, as well as by the complex organizational and interpersonal networks linking the different medical cultures. Changing the environment will be equally challenging.

Assessing Risk Factors in Anesthesia

An innovative attempt was made by a team of engineers and anesthesiologists to apply a technique called "probabilistic risk analysis" (PRA) to model cascading risks and the effects of different types of organizational interventions.[66,67] PRA has been used extensively in nuclear power and other highly hazardous industries (for example, it was used for analysis of the risks to the space shuttle from thermal tile failure). Complete PRA models are very complex and extensive. In the anesthesiology study, a highly simplified PRA model was used to assess the feasibility of applying this technique to health care. The PRA analysis of organizational changes in anesthesia suggested that patient risk could be reduced best by closer supervision of residents, the use of patient simulators for training and periodic recertification, and regular medical examination of anesthetists for fitness for duty. As yet it has not been possible to develop comprehensive PRA models of anesthesia risk because the number of decision and action elements is very large and knowledge of the probability of success or failure for each of the decisions or actions is very limited. The PRA approach might be a useful heuristic to help clinicians lay out critical decision-making and therapy issues, but it may never make any meaningful contribution as a quantitative safety management technique.

There has been growing interest in applying process-oriented systems analysis to patient care flows and processes. For example, a group in Tübingen, Germany, performed a process-oriented systems analysis at a medical university hospital

to assess the anesthesia work system's ability to regulate variances and disturbances in the work process.[68] These investigators showed that the internal work process can be regulated well but that the high interdependence of the anesthesia work system with other systems requires extensive coordination activities.

Characteristics of Successful Incident Reporting Systems

Incident Reporting Systems for Learning from Problems

An important strategy for improving patient safety (and a core tenet of HROT) is "organizational learning." Such learning can be both prospective (deliberating in advance of process changes how they might affect safety) and retrospective (learning from events that have already transpired). Most high-hazard and high-reliability industries have made special efforts to create systems for retrospective organizational learning, often concentrating on the reporting, investigation, and analysis of both frank accidents or errors and near-miss events with no negative outcome.[25,46,47,69-72] The details of successful incident reporting systems (IRSs) are covered in a number of publications.[5,7,42,52,73-90]

Historically, investigation of errors in the health care system has been hindered by a "culture of blame"[90-92] in which naming, blaming, and shaming are the main features of event reporting and review rather than analysis by experts and focus on the development of systematic countermeasures. A culture of blame in which it is posited that errors, accidents, and near misses are due primarily to a lack of knowledge, a bad attitude, or a lack of commitment to patients leads to a heavy burden on those involved in adverse events. It may also compound internalized negative feelings over having contributed to patient harm.[92,93]

Anesthesiology as a specialty has played a leading role in the attempt to turn this culture of blame into a safety culture—putting safety first[1,2] and trying to understand how errors, incidents, and adverse events evolve.[5,25,42,60,72,73,75,76,94-103]

Errors Per Se Are Not the Cause of Accidents

Only a minor fraction of errors lead to a negative patient outcome. However, the "harmless" error may well point to a systematic weakness (latent problem) in the system, which if investigated further can lead to a systematic change. Unfortunately, the reverse is often true. The lack of a negative outcome is interpreted as "success" of the system, and the underlying vulnerabilities are ignored. In most cases, errors in complex systems are not the sole causes of accidents and rarely lead inevitably to an adverse event (see Fig. 6-1A). In actuality, first hand there are probably underlying reasons (C_1 to C_3 in Fig. 6-1B) that someone commits an error, and then additional contributing factors (CF_4, CF_5) are "needed" to allow an accident to develop. The main idea of modern IRSs is to identify the factors that make errors more likely to occur, as well as additional factors that allow a negative outcome to ensue. By reporting and analyzing factors C_1 to C_3 and CF_4 and CF_5 in Figure 6-1 regardless of the outcome, it might be possible to eliminate or reduce the probability or the harm potential of the accident long before it ever happens.

"If reporting is safe and provides useful information from expert analysis, it can measurably improve safety."[80]

IRSs, if well structured and operated, can make substantial difference in system safety (Fig. 6-5). The present knowledge about weaknesses and strengths of the health care system that is

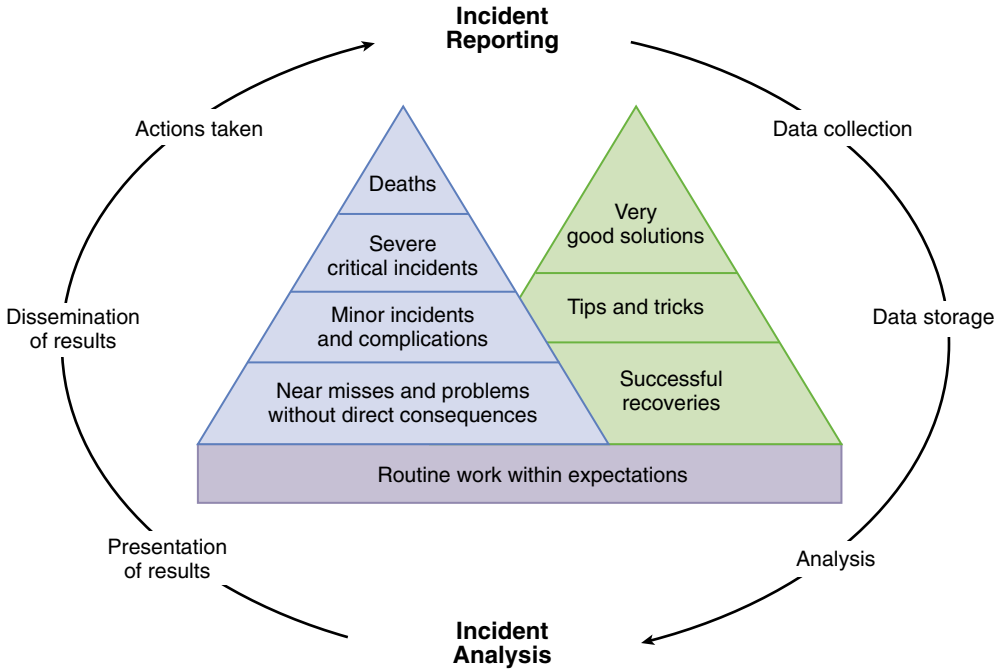

Figure 6-5 Process model of an incident reporting system that is constructed as a complete system. The data need to be collected, saved securely, analyzed independently, and the results need to be visualized in a relevant way, distributed to stakeholders in an applicable way, and result in concrete action by the reporting organization. It should be possible to report all incidents and errors, independent of the outcome. Innovative systems should even include positive reports. (Figure by P. Dieckmann.)

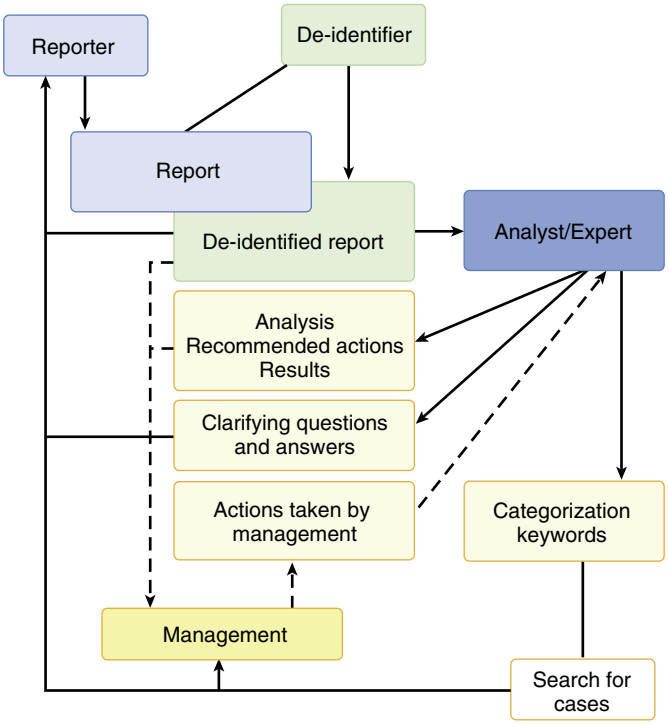

Figure 6-6 Data handling in a modern incident reporting system with de-identification. The incoming reports are first completely de-identified by a trained de-identifier. Only after this step is the report ready to be analyzed. It is important that the reports are analyzed by a multiprofessional team and that recommendations be fed back to the management of the organization from which the report came. The analysis and feedback should be transparent for all stakeholders.

"out there" already can finally be extracted and made available for others. IRSs are often referred to as "learning systems," similar to the National Reporting and Learning System of the National Patient Safety Agency in the National Health Service of the United Kingdom.

Effective IRSs allow insights into the health care system that are otherwise very hard to acquire. In this sense IRSs can open "windows to the system."[94]

Merely having a reporting form or a database of information does not constitute an effective reporting system. They can be effective only when they are constructed, established, and maintained as an entire system (Fig. 6-6; also see Fig. 6-5) and are successfully embedded in the organization or industry. Omission of or faults in any of the requirements in Box 6-5 will limit the success of the system.[88]

What Should Be Reported?

Uncertainty about *what* should be reported is one of the barriers for an IRS.[105] In aviation, it has been necessary to create a reporting system for "incidents" (without negative outcome) that is distinct from systems for reporting or analyzing accidents. Of course, in aviation the occurrence of an accident is usually known immediately, and such events are never "supposed to happen." Yet in health care every human being will get sick and will die; in fact, most people will die in proximity to medical care. Thus, negative outcomes are inherent to the progression of disease, so determining what outcomes are due to "errors" or "accidents" is much harder in health care settings. For this reason many believe that for health care event reporting systems, it should be possible to report all critical incidents, with or without a negative outcome. In fact, the system may also solicit reports of "positive events" in which the outcome was good despite challenging clinical circumstances. In general, the invitation to report should be very broad and cast a "wide net" to find all interesting occurrences.

What Should Report Forms Look Like?

Reporting systems that rely primarily on an array of checkboxes for the reporter to choose from regarding the "causes" of the incident have not proved to be useful. In fact, it is thought in the Aviation Safety Reporting System (ASRS), for example, that "Counting incidents is a waste of time" (quote from Charles

Box 6-5 Important Characteristics of Effective Incident Reporting Systems

Integration of the incident reporting system into the organization and full support by management

No negative sanctions for reporters and people involved

Confidential or anonymous reporting option, with active de-identification (domain expertise required)

Legal protection and state-of-the-art data security

Independence of the organizational hierarchy: reports are sent to a trusted subunit outside the hierarchy of the organization or outside the organization (external trust center, e.g., NASA for the ASRS)

Orientation to a system that enables all stakeholders of patient safety to easily file reports, including physicians, nurses, and technicians

Easy and fast reporting

Training of stakeholders to file valuable reports (e.g., focusing on human factors issues, as well as medical-technical aspects)

Timely feedback about reception of the report, its analysis, and proposed measures to be taken from it

Analysis of each report by experts (a multiprofessional team that has a background not only in the medical domain but also in issues of human performance and analysis methods)

Deep analysis of selected cases using root cause analyses or failure modes and effect analyses with the aim of improving systems safety in the future

Timely implementation of improvements to confirm the "reactivity" of the system and to *make a difference*

Evaluation of improvements and special care to avoid "improvements for the worse" (quick fixes without improving the underlying latent dangers)

Organizational support of reporting and analysis of cases, as well as the implementation of improvements

Supports continuous improvement of the positive proactive safety culture in the department (systems perspective!)

ASRS, Aviation Safety Reporting System; NASA, National Aeronautics and Space Administration.

Data from references 25, 77, 80, 104.

Billings, a founder of the ASRS). In a voluntary reporting system one has no way to estimate the true number of specific problems. Similarly, trend analysis is not feasible because the frequency of events and the frequency of reporting are confounded. A free-text description of the reported incident has been more helpful in identifying what can be learned from the report. This view is also supported by the World Health Organization's Guidelines for Incident Reporting[77]:

> *However, much of what promotes learning in patient safety lacks crisply defined data elements, so most authorities believe it is important for reports to include narrative to convey meaning. Narrative reports provide the opportunity to capture the rich context and storyline that allow the conditions that contributed to the error to be explored and understood.*
>
> *Indeed, some believe that only narrative reports are capable of providing information that provides meaningful insight into the nature of the underlying systems defects that caused the incident (Richard Cook, personal communication).*

Clearly, no reporting system can detect all the problems in a clinical institution, even ones that create a severe vulnerability. For one thing, it is known that between 50% and 96% of critical incidents are not reported[106,107] with current systems, although new thrusts in incident reporting hope to increase the fraction of events that are reported.

Legal Issues of Reporting Systems

Especially in jurisdictions for which medical liability litigation is common, there will be a number of legal issues that affect reporting systems. First, for some kinds of events in some settings there will be legal requirements to report the event to a governmental body. This is true in the United States for certain kind of adverse drug events or for certain failures of medical devices. Moreover, some states have started mandatory reporting programs about so-called never events that are thought should never occur in the absence of a systems failure. In general, voluntary IRSs operate completely in parallel with any other types of reporting systems.

An important question for most reporters is whether the report will be confidential or anonymous and whether the report will confer any immunity to the reporter. Anonymous reporting provides maximum protection for reporters but limits the amount of information that can be acquired about any given event and the cogency of that information. Confidential reporting can allow confidential interaction between analysts and the reporter to acquire all the information and context needed concerning the event, but the linkage between the report and the identity of the reporter exposes a risk even if confidentiality is formally provided. Of note, the ASRS—on which many reporting systems have been modeled—operates as a confidential system but with subsequent de-identification of the reports to make them anonymous. Furthermore, the ASRS was able to offer limited immunity from administrative actions for those who filed a report. This was a major incentive for reporting events. In health care, physicians largely fear malpractice litigation, and it is not possible to offer immunity from litigation to reporters, although offering immunity from administrative action (e.g., an official reprimand) within the hospital itself could be an incentive to report.

Statutory Protection

In the United States there is now both federal and state statutory protection (shield) from discovery of any voluntary event reports that may be available (depending on the locale and many other circumstances). In the United States, Congress passed the Patient Safety and Quality Improvement Act of 2005 (Public Law 109-41). This authorized the Department of Health and Human Services to certify patient safety organizations (PSOs) to collect confidential reports about events and to analyze the information. The act provides strong legal protection (privilege) from any compelled release of the information, as in the process of discovery in a lawsuit. At the time of this writing, rules were in the process of being formulated to govern the certification process for PSOs, so no data have yet been collected that are protected under the act.

Internal reporting systems within hospitals may be protected as quality improvement activities in states that provide privilege from discovery of such reports and deliberations. State laws vary widely on this matter. In addition, the quality improvement protections are often questioned during litigation, and whether the privilege will be applied depends on the ruling of a judge in each individual case.

Reporting systems in other countries have used other strategies. For example, the Center for Patient Safety and Simulation, which runs a national IRS in Germany called PaSOS, has constituted itself as a "press office" (informing the anesthesia public as a journal would); this then brings it under the protection of the "free press act and rights" and makes it almost impossible to use its data in litigation.

De-identification before Information

A common strategy of confidential reporting systems is to quickly convert the data to anonymous status by "de-identification." To do this, it is necessary to edit the reports and delete all information that might be used to identify persons or organizations. Systems vary by what stage of analysis they conduct de-identification and where they set the balance between acquiring needed information versus deleting possibly identifying data. One issue in all reporting systems, especially in health care, is that the key facts of many events might be relatively unique and thereby lead to a high risk of "intrinsic identification" even when all objective identifiers are stripped.

There are now IRSs in many countries with various designs and operational processes (see Appendix 1).[5,7,42,52,73-90] Many systems are installed locally, but more and more national systems, or at least systems with a national common data set, are being installed.[108] Box 6-6 shows some of the features of and lessons learned from the national anesthesia system PaSOS (available at www.pasos-ains.de) in Germany, which is directed by one of this chapter's authors (M.R.).

Human Factors

This part of the chapter deals with human factors in the broadest sense of the meaning. In contrast to the previous part of the chapter, which covered aspects of the health care system and organizational matters, the human factors portion is related to the performance of individuals and teams and to factors influencing their performance and promoting or preventing active or passive errors. Because more than 70% of all errors in medicine can be

Box 6-6 Characteristics of the German National Anesthesia and Intensive Care Incident Reporting System PaSOS (www.pasos-ains.de)

The system is provided by the two German anesthesia societies and run by a professional interdisciplinary group.

Every anesthesia department and ambulatory anesthesia unit in Germany is entitled to take part. The basic functionality, software, server storage, and updates are free of charge (a service by the societies).

The system is Web-based with an anonymous secure login (SSL). No data are stored locally in the hospitals, but users work directly on the central secure server with php technology.

The reports are primarily sent outside one's own institution for de-identification by our independent and interdisciplinary patient safety group (TuPASS), which increases trust of employees in the safety of the system.

All reports undergo a professional four-eye active anonymization and de-identification process by domain experts trained in incident reporting and using checklist protocols to prevent any lapses in de-identification.

After de-identification, most reports can be read in full text by all employees. This is meant to sensitize all by reading all the cases and to stimulate discussion about patient safety in the department and to report your own cases. It also provides very powerful feedback to the reporter, who can read "his" report in the Web.

Every department gets a unique department login that is provided to all employees (physicians, nurses, technicians, etc). This login allows you to separate "your" reports from the national reports. So every department has its own "local" incident reporting system inside the big national system. There are no personal logins because the system is anonymous.

Most reports are readable in the national IRS, open to all anesthesiologists. This should contribute to the national spread of important critical safety information. Of course, on this level, nobody can see where the reports came from. (You can select "your" reports with your department login, but you cannot identify the origin of reports once they are in the national database).

All reports are manually tagged with key words for meaningful search results; they are classified according to the U.K. NHS NPSA contributory factors framework[52,94,95] and also categorized with the CRM key points (see text).[60,109]

A local de-identifier does not exist and can therefore not be interviewed by any legal authorities.

An optional module, "feedback and analysis suggestions," is available on request; it provides expert feedback about every report from the IRS provider team back to the organization's risk management, including systems safety analysis and suggestions for countermeasures.

Several organizational prerequisites need to be fulfilled by departments to take part (organizational embedding before starting to report). For example, all departments have to send their PaSOS representatives to an initial workshop to get briefed about the do's and don'ts of IRS. They also get a set of slides and information material to spread the messages in their local departments (snowball effect).

Departments that do not comply with the minimal requirements, especially prerequisites such as the written "no-blame assurance" to their employees, are not allowed to take part or may even be excluded from the system.

IRS, incident reporting system.
Data from references 60, 104, 108, 110.

attributed to problems with human factors rather than problems with knowledge or practical skills, the impact of human factors cannot be overestimated. On this basis perhaps human factors should take 70% of the whole book! Given that this chapter cannot deal with human factors in a comprehensive way, many topics can be touched on only briefly, and the reader is directed to the available literature. We focus on the most important aspects of human factors that are directly relevant to practicing anesthetists.

Nontechnical Skills in Anesthesia

Over the last 20 years, the health care professions have become more aware of the importance of "nontechnical" skills in the delivery of safe, high-quality medical care. This recognition has brought an increased need for assessment, evaluation, and training of these skills. Patient simulators were perhaps the first opportunity to show and train these skills under realistic stressful conditions.[109,111-113] The introduction of simulators and the associated training concepts accelerated understanding of these human factors by the medical community.[2] Some of the needed "crisis management skills"[20,114] can be trained without the use of simulators, as shown in other domains (aviation, oil platforms, military).[71,115-117] The baseline level of crisis resource management (CRM) performance is somewhat low.[118] Helmreich states that as a first step in establishing error management programs, it is necessary to provide formal training in teamwork, the nature of error, and the limitations of human performance.[47]

There are different ways to group the nontechnical skills that are at the heart of CRM training. One approach is to distinguish between two categories of nontechnical skills: (1) cognitive and mental skills, including decision-making, planning, and situation awareness (Table 6-3), and (2) social and interpersonal skills, including aspects of teamwork, communication, and leadership. Another approach is to split nontechnical skills into five major groups as shown in Figure 6-7.

Crisis Resource Management

What Exactly Is Crisis Resource Management?

Cockpit (later "crew") resource management was introduced in aviation in the mid-1980s and is considered to be successful in

Table 6-3 Nontechnical Skills in Anesthesia: Classification, Markers, and Teaching Points

	Anesthesia Nontechnical Skills (Fletcher et al.[146])		Performance Markers (Gaba et al.[130])	Key Teaching Points in Anesthesia Crisis Resource Management (Gaba et al.[147,148])
Concepts	**Elements**	**Categories**	**Markers**	**Reminders**
Cognitive and mental skills	Planning and preparing	Task management	Orientation to case	Anticipate and plan Know your environment
	Prioritizing		Leadership (also a social and interpersonal skill)	Exercise leadership Set priorities dynamically
	Providing and maintaining standards		Planning	Use cognitive aids
	Identifying and using resources		Workload distribution	Distribute the workload Mobilize all available resources
	Gathering information	Situation awareness	Anticipation	Use all available information
	Recognizing and understanding		Vigilance	Allocate attention
	Anticipating			Anticipate and plan
	Identifying options	Decision-making	Preparation	
	Balancing risks and selecting options		Re-evaluation	Prevent and manage fixation errors
	Re-evaluating			Re-evaluate repeatedly
Social and interpersonal skills	Coordinating activities with team	Team working	Inquiry/assertion	Communicate effectively Teamwork
	Exchanging information		Communication feedback	Communicate effectively
	Using authority and assertiveness		Group climate	Exercise leadership and followership
	Assessing capabilities		Followership	Exercise followership
	Supporting others			
Overall assessment	Not applicable Assessments are made only at the element and category level		Overall nontechnical performance of the primary anesthetist Overall nontechnical performance of the whole team	Teamwork! Concentrate on what is right, not who is right

that industry and other industrial and military settings (although admittedly, there is not what evidence-based medicine would call "level 1 evidence" for this success).[24,25,41,119-122] Crew resource management is now taught systematically to crew members of all major U.S. airlines and at many airlines around the world.[123] A similar program in anesthesiology was first developed by Gaba, Howard, and associates at the Veterans Affairs (VA) Palo Alto Health Care System and Stanford School of Medicine[4,105,109,113,124] originally as anesthesia crisis resource management (ACRM). The ACRM curriculum and its variants have since been adopted by training centers worldwide. A detailed description of the ACRM course is provided.

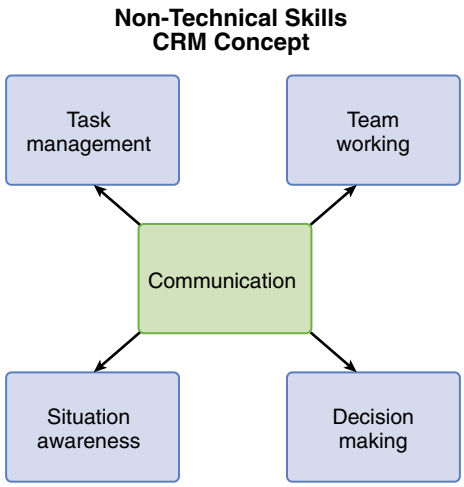

Figure 6-7 Five main groups of nontechnical skills. In this approach, effective communication is like the glue that holds all the other components together.

In overview, CRM means to coordinate, use, and apply all available resources to protect and help the patient as best as possible. Resources include all the personnel involved, along with all their skills, abilities and attitudes—albeit also with their human limitations. Machines, devices, and information sources, including cognitive aids, are also critical resources.

Though termed "crisis management," CRM principles actually also apply before a crisis ensues. CRM includes preventing and intercepting threats and errors and minimizing their negative consequences to the patient.

The key points of CRM as they apply to anesthesia care have been steadily updated and expanded over time (see Box 6-7). Some of the principles might seem obvious or self-evident. However, from our experience in simulation training, it is in fact *not* trivial to actually apply these principles whether during routine work or during crises. More theoretical background on the principles can be found in the textbook on ACRM by Gaba, Fish, and Howard,[125] as well as in related safety literature.[25,41,43,46,47,70,71,72,126-130]

Box 6-7 CRM—Key Points in Healthcare

1. Know the environment.
2. Anticipate and plan.
3. Call for help early.
4. Exercise leadership and followership with assertiveness.
5. Distribute the workload (10-seconds-for-10-minutes principle).
6. Mobilize all available resources.
7. Communicate effectively—speak up.
8. Use all available information.
9. Prevent and manage fixation errors.
10. Crosscheck and double-check (never assume anything).
11. Use cognitive aids.
12. Re-evaluate repeatedly (apply the 10-seconds-for-10-minutes principle).
13. Use good teamwork—coordinate with and support others.
14. Allocate attention wisely.
15. Set priorities dynamically.

Adapted from Rall M, Gaba DM: Human performance and patient safety. *In* Miller RD (ed): Miller's Anesthesia, 6th ed. Philadelphia, Elsevier Churchill Livingstone, 2005.

Like nearly all principles of sound human factors, application of CRM key points to patient care must be supported by top leadership and reinforced in the actual work environment. It is of no worth to study these principles (or even practice them in simulations) only to find that the pressures and culture of the "real OR" make them impossible to implement for real patients. Fully integrating these key points into the structures and processes of clinical practice has proved to be a significant challenge.

Know the environment! (CRM key point 1)

CRM begins before the crisis starts. One of the prerequisites for CRM is to *know the available resources and the details of the specific working environment*. Resources are *personnel*, *equipment* (software, hardware, or cognitive aids), and supplies. It is important to know who can be asked for help, who is available at different times of the day, how to call those helpers quickly, and how long it will take them to arrive. Regarding equipment, it is necessary to not only know *what* is available and *where to find it* but also *how* to operate it. The anesthesiologist is responsible for being well versed in the operation of all relevant equipment and should also use manuals and other cognitive aids to learn to use the gear and as a backup source of information during patient care.

Anticipate and plan (CRM key point 2)

Anticipation is key for goal-oriented behavior. Anesthetists must consider the requirements of a case in advance and plan for the key milestone. They must imagine what could go wrong and plan ahead for each possible difficulty. Savvy anesthetists expect the unexpected, and when it does strike, they then anticipate what could happen next and prepare for the worst. People often talk about "staying ahead of the game" or, conversely, "falling behind" or "being behind the eight ball."

Call for help early (CRM key point 3)

Knowing one's own limitations and calling for help is a sign of a strong character and a competent person. Trying to handle everything alone or toughing out a critical situation is dangerous and unfair for the patient, who should not suffer to protect the anesthetist's pride or ego. In case of an emergency or even a suspected emergency, help should be called early rather than late. Some typical triggers for calling for help that apply to any anesthetist at any level are (1) when there are too many tasks to do, (2) when the situation is already catastrophic (e.g., cardiac arrest, difficulty securing the airway), (3) when serious problems are getting worse or not responding to the usual maneuvers (or both), and (4) when you do not know what is going on. It is important to know in advance who is available and how to call for help and to plan for how best to use the help when it arrives.

Exercise leadership and followership with assertiveness (CRM key point 4)

A team needs a leader. Someone has to take command, distribute tasks, collect information, and make key decisions. Leadership rarely means knowing more than everybody else, doing everything alone, or putting other people down. Leadership is about planning, deciding, and distributing tasks by clear communication. Followership is also an important skill. Followers are key members of the team who listen to what the team leader says and do what is needed. However, it does not mean shutting off their own brains. Followers should be assertive if they think that the team leader is making wrong decisions. It is their responsibility to make sure that the leader is aware of their concerns. Whenever people work together, conflict can ensue; anyone on the team may need to diffuse conflicts to focus the team on care of the patient. Get everyone to concentrate on *what* is right, not on *who* is right.

Distribute the workload "10-seconds-for-10-minutes principle" (CRM key point 5)

One of the main tasks of a team leader is distribution of the workload. Someone is needed to define the necessary tasks and ensure that they are fulfilled properly and that everything fits together. If possible, the team leader should remain free of manual tasks to observe, gather information, and delegate tasks. Team members should also look actively for things that need to be done. It is not a good team if the team leader has to express every idea and nothing is done before it is explicitly ordered.

A corollary is known as the "10-seconds-for-10-minutes principle", which posits that if a team can slow its activities down just a little, it can gain more than enough benefit in rational decision-making and planning to offset the delay. The need to slow down appears to be greatest in critical situations such as the beginning of the diagnosis and treatment planning or when the team "feels stuck" because the usual treatment is not working (Fig. 6-8).

Mobilize all available resources (CRM key point 6)

Everyone and everything that could help deal with the problem at hand should be mobilized, including humans and technology embedded in organizational processes. On the human side, the anesthetist's knowledge and skills (mitigated by knowledge of one's human deficiencies) are the most important resource, com-

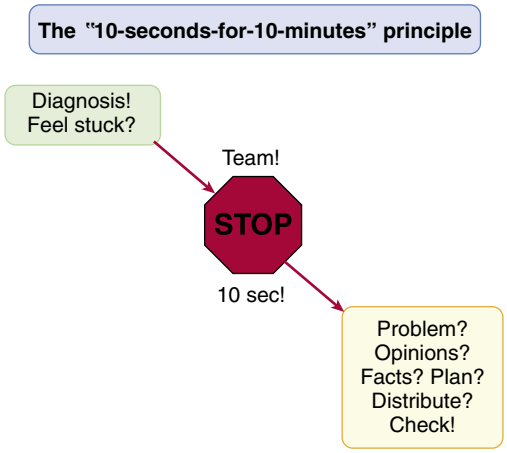

Figure 6-8 The "10-seconds-for-10-minutes principle." When making a *diagnosis* or *feeling stuck*, perform the 10-second team timeout and check to see "what the biggest problem is (the most dangerous aspect right now)" (*Problem*). Clarify this with all available team members (*Opinions*). Gather the information available (*Facts*). *Plan* the treatment, including the desired sequence of actions. *Distribute* the workload by assigning tasks and responsibilities. *Check* with all team members about any further concerns or suggestions.

plemented by the human helpers who can be brought to bear. Equipment and supplies are the means by which knowledge is translated into action. Some equipment will be readily available, but others will need time to be mobilized.

Communicate effectively—speak up (CRM key point 7)

Communication is key in crisis situations. Good team work depends on everybody being on the same page and coordinating their efforts; communication is the glue that holds the disparate members together (see Fig. 6-7). Effective communication is challenging to accomplish. Several aspects make communication difficult sometimes; for example, saying something is meaningful communication only if the messages are received and understood (Fig. 6-9).

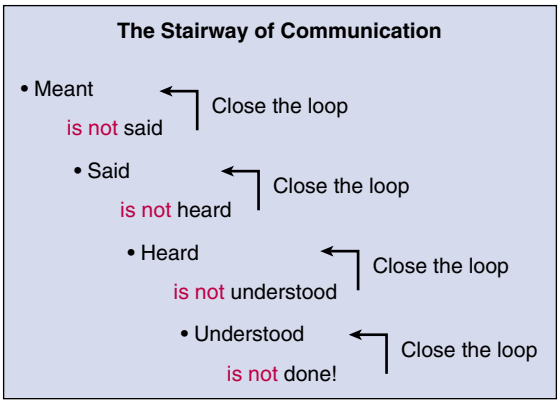

Figure 6-9 Model showing the importance of proper communication. When dealing with complex situations under time pressure, people tend to "mean" a lot but "say" little. It is important to let other team members know what you think (mental model). Not everything that is said is necessarily heard by those who should hear. This is often not the "fault" of the receiving end; acoustic hearing and mental understanding are not the same. It is important for the sender and receiver of a message to close the communication loop. Some tasks need time to be completed and may fail. Let the team know.

Use all available information (CRM key point 8)

Anesthesiology is particularly complex because information must be integrated from many different sources. Every bit of information can assist in understanding a patient's status better and arriving at the correct diagnosis. Information sources include those immediately at hand (the patient, monitors, the anesthesia record), secondary sources such as the patient's chart, and external sources such as cognitive aids (see later) or even the Internet.

Prevent and manage fixation errors (CRM key point 9)

Human actions are based on an instantaneous mental model of the current situation. If the model of the situation is erroneous, the actions will probably be wrong.

The term "fixation error" describes a model that is persistently faulty despite sufficient evidence to correct it. A fixation error is the persistent failure to revise a diagnosis or plan in the face of readily available evidence suggesting that a revision is necessary. This type of error is extremely common in dynamic situations. There are three main types of fixation errors.[131,132]

One type of fixation error is called "**this and only this**"—sometimes also called "cognitive tunnel vision." In this type of error, attention is focused on only one possibility and other (possibly or actually correct) alternatives are not taken into account. Another fixation error is "**everything but this**," the persistent search for irrelevant information and failure to treat a probable cause with serious consequences.

Perhaps the most insidious fixation error is the persistent claim that "**everything is OK**," in which all information is attributed to artifact and possible signs of a catastrophic situation are otherwise dismissed. Another form of "everything is OK" is the failure to transition from "routine mode" to "emergency mode" when the situation demands it.

One principle of managing fixation errors is to get a new view—a second opinion—on the situation from someone unaware of the faulty previous assumptions. Although it is appropriate to brief the new person on the situation, it is best to avoid biasing the person with the conclusions already drawn. Even when working alone the anesthetist can deliberately change perspectives (physically or mentally) and look for information not fitting the picture of the situation, as though entering the room for the first time.

The aforementioned 10-for-10 principle (CRM key point 5) might also be helpful in managing fixation errors. More information on fixation error is provided later in the section "Core Process."

Crosscheck and double-check—(never assume anything) (CRM key point 10)

Crosschecking means to correlate information from different sources. There are often three independent sources of information about the patient's heart rate (electrocardiogram [ECG], pulse oximetry, and blood pressure monitor), for example, and two about the rhythm (ECG and pulse oximetry).

Another aspect of crosschecking involves reviewing the status of actions that have been done or are under way. Human memory about actions performed is vulnerable, especially when interruptions have occurred. Moreover, although we often attempt to check things "at a glance," such fleeting observations are prone to error. Checking numbers and settings on equipment by actually touching them and looking carefully may be worth the effort.

In general it is best to "never *assume* anything"; make sure and double-check important information.

Use cognitive aids (CRM key point 11)

Cognitive aids—such as checklists, handbooks, calculators, and advice hotlines—come in different forms but serve similar functions. They make knowledge "explicit" and "in the world" rather than only being implicit, in someone's brain. Memory and cognitive functioning are vulnerable to error or complete failure, especially in stressful situations. Cognitive aids offload memory and safeguard the recall of critical items. They also help ensure the use of current best practices because during a crisis, people sometimes revert to what they originally learned as the best, not what is the latest recommendation. The use of cognitive aids rather than memory alone is another sign of strength.

Re-evaluate repeatedly (apply the 10-seconds-for-10-minutes principle) (CRM key point 12)

Acute medicine is dynamic. What is correct now might be wrong in the next minute. Some parameters might change slowly over time, and subtle changes can be hard to perceive. Trend monitoring can be helpful to detect slow, but insidious changes.

Furthermore, the dynamic nature of critical events makes it necessary to repeatedly re-evaluate the situation. Box 6-8 shows a set of questions that should be raised repeatedly to check whether one is still treating the most serious problem most effectively.

Implement principles of good teamwork—coordinate with and support others (CRM key point 13)

Teamwork in multidisciplinary teams is at the heart of much patient management in the OR and ICU. Key principles of teamwork in dynamic situations have been delineated, especially in the work of Eduardo Salas and colleagues at University of Central Florida (see Fig. 6-4). Coordination within a team ideally begins before a team gathers. If all members know about the tasks to be done and their roles during these tasks, coordination is easier. Short briefings at the beginning of a task are common in aviation and are worth the time spent. During the acute phase of a crisis situation, it is worth a small amount of time to coordinate the team's activities (see 10-for-10 earlier in CRM key point 5). "Dream teams" support each other continuously, with everybody looking after each other.

Box 6-8 Re-Evaluation Questions—Maintaining Situation Awareness

- Was the initial assessment of the situation or diagnosis correct?
- Did the actions have any effect? (e.g., did the drug reach the patient?)
- Is the problem getting better, or is it getting worse?
- Are there any side effects resulting from previous actions?
- Are there any new problems or other problems that were missed before?
- What further developments can be expected in the (near) future?

Allocate attention wisely (CRM key point 14)

Human attention is very limited and multitasking is very difficult. Attention must be dynamically allocated where it is needed. One can develop rhythms and scan patterns to do this. The "ABC equals airway, breathing, circulation" mnemonic is based on this principle. Other strategies are to alternate between focusing on details and focusing on the big picture and to offload certain responsibilities, tasks, or information streams to other qualified team members, provided that they periodically update the team leader about the situation.

Set priorities dynamically (CRM key point 15)

Dynamic situations demand dynamic measures with decisive, purposeful preliminary decisions and actions that are constantly re-evaluated and modified as new information becomes available or the results of treatment are apparent. What was not a right move at one time may become the right move at another. In addition, having one solution to an obvious problem does not guarantee that it is the best solution to the one problem or that there is only that one problem to deal with. However, one priority is always paramount—ensuring adequate oxygenation and perfusion of critical organs.

How Can CRM Skills Be Learned and Trained

CRM is taught in many different ways. Seminar-based training on human factors and CRM principles has become popular in health care (e.g., programs called "MedTeams," "Medical Team Training," "LifeWings"),[133-140] although the role of such activities versus simulation-based CRM approaches has not yet been fully delineated. Seminars use didactic sessions, group exercises, and sometimes discussion and analysis of "trigger videos." Such training is probably useful for first learning about CRM principles and articulating how they might apply to anesthetists' work environments. Given the experience in the airline industry, it is likely that to completely address CRM skills for both trainees and experienced personnel, a combination of seminars and simulation-based exercises will be needed. We believe that to really practice the execution of CRM skills requires exposure to challenging clinical situations in realistic simulation scenarios, followed by detailed group debriefings (often using video of the simulations) to analyze what transpired. As detailed in Chapter 7, such CRM-oriented simulation training may be available in dedicated simulation centers or as in situ simulation training in actual work environments. Many simulation centers also offer "mobile training," which means that they can bring the simulator and everything else needed (e.g., audio/video equipment) to any facility to train the staff in institutions that do not have a simulator or staff capable of conducting the training.

How Can CRM Skills Contribute to Patient Safety

Although 70% of all errors in anesthesia may be attributable to human factors, interventions to improve this picture have only

partially penetrated the fabric of the industry. CRM-oriented training is one component of a comprehensive approach to addressing human factors issues in anesthesia safety, but it is not yet a standard part of clinical training. There is not yet definitive evidence that CRM training in anesthesia improves patient outcomes, and many believe that it may be functionally impossible to acquire such evidence. Nevertheless, CRM training is an integral and accepted part of training in aviation, nuclear power, and other industries in which human errors can lead to catastrophic events. There is no reason to assume that doctors would be less error prone or would benefit less from human factors–based CRM training than the professionals in other high-hazard industries.

Assessing Nontechnical Skills Is More Subjective Than Assessing Technical Skills

A study by Morgan and Cleave-Hogg concluded that "the simulator environment is somehow unique and allows different behaviors to be assessed."[141] As Glavin and Maran stated, "Any scoring system that attempts to address the assessment of clinical competence clearly has to address both technical and non-technical skills"[142]; consequently, there is still a long road ahead in measuring performance.

Two research groups (VA-Stanford and the University of Basel) have studied adaptations of the anchored subjective rating scales developed by the NASA/University of Texas Aerospace Crew Performance Project. The VA-Stanford group published preliminary data reviewing the inter-rater reliability of subjective ratings of behavior on five-point anchored scales.[130,143] Using a fairly stringent test of inter-rater reliability (the topic is quite complex in the statistical literature), they found only moderate reliability when five trained raters used a five-point scale to score 14 anesthesia teams, each managing two different complex critical events in the simulator (malignant hyperthermia and cardiac arrest). Despite some difficulty in agreement on the operational definitions of each type of behavior, the investigators stated that the largest problem in achieving agreement was the high variability of each behavior over the course of a simulation. For example, an anesthesia crew could show evidence of good communication at one instant, only to be shouting ambiguous orders into thin air at the next instant. Aggregating such behavior into a single rating was extremely difficult, even for bounded time segments of the scenario. These data demonstrate the importance of evaluating performance by more than one rater, who no matter how well trained, may produce scores that differ significantly from another single rater. The investigators suggested combining scores from a minimum of a pair of raters inasmuch as it was shown that the mean of scores from two raters had a very low probability of differing from the mean of five raters by more than a single rating point.

The behavioral markers of their score are shown in Table 6-3 and compared with Fletcher's "anesthesia nontechnical skills (ANTS)" score and the ACRM key teaching points (see Box 6-7).

The ANTS System

Fletcher, from the Industrial Psychology Group of Aberdeen (headed by Rhona Flin) and working with clinicians from the Scottish Clinical Simulation Centre (Glavin and Maran), performed an in-depth review of the role of nontechnical skills in anesthesia. Fletcher stated that nontechnical skills have not been explicitly addressed in the traditional education and training of anesthesiologists, even though they have always been demonstrated and used during clinical work. The group analyzed incident reports and observations of real cases, as well as attitude questionnaires and theoretical models.[144] Like others, they recognized that simulation offers the opportunity to identify, develop, measure, and train nontechnical skills in a safe learning environment, so they also included significant observations during realistic simulations.[145]

Incident reports proved very limited because they did "not provide the finer-grained level of information necessary to understand where the skills broke down."[146] They defined nontechnical skills as "attitudes and behaviours not directly related to the use of medical expertise, drugs or equipment." Although nontechnical skills can be seen under the heading of "human factors," it is preferred that they be addressed as "nontechnical skills," which is more specific.

As in the ACRM instructional paradigm,[109,147,148] Fletcher and colleagues identified two categories of nontechnical skills:

- Cognitive and mental skills, including decision-making, planning, and situation awareness
- Social and interpersonal skills, including aspects of team working, communication, and leadership

Fletcher's ANTS scheme is shown in Table 6-4, along with the behavioral markers of Gaba's team and the ACRM key teaching points. A description of the ANTS categories and elements, including examples of good practice and poor practice, is presented in Table 6-4.

The structure of the new ANTS scheme was derived from a system of behavioral markers that had been developed for aviation in an European project called "NOTECHS," which itself was an evolution of the UT-Markers of the University of Texas (Helmreich). A summarized comparison of the aviation systems and explanations about using nontechnical markers for training and evaluation can be found in the downloadable documentation of the "Group Interaction in High Risk Environments" created by an international group of human factors specialists (available at http://www2.hu-berlin.de/gihre/Download/Publications/GIHRE2.pdf). Several comments about the ANTS approach are appropriate.

ANTS' intent is to score only those skills that can be identified unambiguously through observable behavior. Such restriction may enhance the reliability of the scoring but could exclude relevant personal factors such as self-presentation, stress management, and maintaining perspective. ANTS assumes that "communication" is included or "even pervades" all other categories and does not score communication as a separate skill. This approach is in contrast to that of others who believe that communication is a specific skill that should be rated separately.[115,149] The category "task management" of the ANTS includes the element "providing and maintaining standards," which might be a point of discussion if it can be an observable behavior "not directly related to medical expertise" as stated in the definition. In addition, there might be a problem because there are not so many well-accepted standards in medicine (in strong contrast to, e.g., aviation).

Table 6-4 Example of a Description of the Anesthesia Nontechnical Skills System (ANTS System—V1.0)

Task Management—skills for organizing resources and required activities to achieve goals, be they individual case plans or longer-term scheduling issues. It has four skill elements: planning and preparing, prioritizing, providing and maintaining standards, and identifying and using resources.

Planning and preparing—developing primary and contingency strategies in advance for managing tasks, reviewing these tasks, and updating them if required to ensure that goals will be met; making necessary arrangements to ensure that plans can be achieved.

Behavioral Markers for Good Practice	*Behavioral Markers for Poor Practice*
Communicates plan for case to relevant staff	Does not adapt plan in light of new information
Reviews case plan in light of changes	Does not ask for drugs or equipment until the last minute
Lays out drugs and equipment needed before starting case that are suitable for the patient	Does not have emergency/alternative drugs available
Makes postoperative arrangements for patient	Fails to prepare postoperative management plan

Prioritizing—scheduling tasks, activities, issues, information channels, etc., according to importance (e.g., because of time, seriousness, plans); being able to identify key issues and allocate attention to them accordingly; and avoiding being distracted by less important or irrelevant matters

Behavioral Markers for Good Practice	*Behavioral Markers for Poor Practice*
Discusses priority issues in case	Becomes distracted by teaching trainees
Negotiates sequence of cases on list with surgeon	Fails to allocate attention to critical areas
Conveys order of actions in critical situations	Fails to adapt list to changing clinical conditions

Providing and maintaining standards—supporting safety and quality by adhering to accepted principles of anesthesia; following, when possible, codes of good practice, treatment protocols or guidelines, and mental checklists

Behavioral Markers for Good Practice	*Behavioral Markers for Poor Practice*
Follows published protocols and guidelines	Does not adhere to emergency protocols or guidelines
Cross-checks drug labels	Does not check blood with patient and notes
Checks machine at beginning of each session	Breaches guidelines such as minimum monitoring standards
Maintains accurate anesthetic records	Fails to confirm patient identity and consent details

From Fletcher GCL, Flin R, Glavin RJ, Maran NJ: Framework for Observing and Rating Anaesthetists' Non-Technical Skills—Anaesthetists' Non-Technical Skills (ANTS) System V1.0, 22nd version. Aberdeen, Scotland, University of Aberdeen, 2003.

Flin's group, meanwhile, adapted nontechnical skills scoring systems for several other medical fields, such as for surgeons and ICU care.[25,72,123,128-130,150-152] They have not yet made adaptations that fully describe multidisciplinary crews and teams.

Not all nontechnical skills will be expected to be observed during every scenario or clinical situation. It is important to delineate between "required behaviors" in a given scenario and the generic set of behaviors. If a required behavior is not observed, the rating system advises that one rate that behavior as poor nontechnical skills, whereas the absence of a given nontechnical skill behavior otherwise has no particular meaning and should be rated as "not observed." As in all subjective nontechnical performance systems, training plus calibration of raters is necessary.

Fletcher and coworkers evaluated ANTS by using scripted videotapes taken in a realistic simulator. Fifty consultant anesthetists were given 4 hours of training as raters and then rated eight test scenarios ranging from 4 to 21 minutes each. They rated performance at the level of specific elements and also at the broader level of category (see Table 6-3) by using a four-point scale (they could also enter "not observed"). Three investigator anesthetists also rated the scenarios and agreed on a "reference rating" to be used as the benchmark for the study. In questionnaires the ANTS system was evaluated by raters as relatively complete, possibly with superfluous elements. Raters found that nontechnical skills were usually observable, and most thought that it was not difficult to relate observed behavior to ANTS elements. The inter-rater reliability, accuracy, and internal consistency of the ratings were good to acceptable and are presented in Table 6-5.

Although well performed, there are some caveats about these data. Because scripted videos were used as the basis for

Table 6-5 Results of an Evaluation Study of Anesthesia Nontechnical Skills by Fletcher and Colleagues

Measure	Score	Range	Max/Min	Element/Category
Inter-rater agreement	Element level	0.55-0.67	Highest element	Identifying/using resources
			Lowest element	Recognizing/understanding
	Category level	0.56-0.65	Highest category	Task management
				Team working
			Lowest category	Situation awareness
Accuracy relative to the reference rater's score	% within ±1 point	88%-97%	Highest element	Identifying options
			Lowest element	Assessing capabilities
	Mean absolute deviation	0.49-0.84, depending on elements	Highest element	Authority/assertiveness
			Lowest element	Provide standards

From Fletcher R, Flin P, McGeorge R, et al: Anaesthetists' non-technical skills (ANTS): Evaluation of a behavioural marker system. Br J Anaesth 90:580-588, 2003.

ratings, it is possible that the observability or scorability of the desired sets of behavior was greater than in actual simulation scenarios. The scripted scenarios were rather short (4 to 21 minutes), which perhaps made it relatively easy to remember certain aspects of the performance and reduced the likelihood of raters encountering the problem of aggregating a score from fluctuating behavior over time. The window of "accuracy" as "±1 point" on a 4-point scale seems to be rather wide.

On the whole, the ANTS system appears to be a useful tool to further enhance assessment of nontechnical skills in anesthesia and other medical fields, and its careful derivation from a current system of nontechnical assessment in aviation (NOTECHS) may even allow some interdomain comparisons.

Performance-Shaping Factors

With a few exceptions, the foregoing discussion of the performance of skilled anesthetists has assumed that they are normally fit, rested, and acting in a standard working environment. Experience in human performance in the laboratory and other domains suggests that internal and external performance-shaping factors exert profound effects on the ability of even highly trained personnel. The degree to which performance-shaping factors affect the overall performance of anesthetists and the outcome of patients is highly uncertain. In extreme cases, such as profound fatigue, there is no question that these factors can result in severe degradation of the anesthetist's performance or even complete incapacitation. However, these extreme conditions are quite unusual, and it is unclear whether the levels of performance decrement likely to be induced in typical work situations have any significant effect. Although the practice of anesthesia does require an attentive and skilled individual, it does not require peak human performance. It would be unrealistic to expect peak performance for every anesthetic regimen because on the order of 60,000 anesthetic regimens are administered each day in the United States by a total of approximately 40,000 to 60,000 anesthetists. Although it is unrealistic to expect peak performance for every case, society expects anesthesiologists to come to work prepared—not impaired. As stated in the American Society of Anesthesiologists (ASA) guidelines for the ethical practice of anesthesiology, anesthesiologists have ethical responsibilities to themselves. The guideline goes further by stating that "the practice of quality anesthesia care requires that anesthesiologists maintain their physical and mental health and special sensory capabilities. If in doubt about their health, then anesthesiologists should seek medical evaluation and care. During this period of evaluation or treatment, anesthesiologists should modify or cease their practice."

With these caveats in mind, however, there are several performance-shaping factors that are potentially of sufficient magnitude to be of concern. Ambient noise, music, fatigue and sleep deprivation, aging, illness, drug use, and attitudes are discussed later. Several other issues that are not discussed include the level of illumination and environmental temperature. These factors can be shown to have a performance-shaping effect in the laboratory, but it is uncertain how much they affect performance in the OR. Currently, the responsibility for ensuring fitness for duty rests solely with the individual clinician. In HROs, the institution implements measures to mitigate performance-shaping factors.

Ambient Noise and Music in the Operating Room

The OR is a relatively noisy work environment.[153-156] Mean sound levels are considerably higher than in most offices or control rooms (continuous movement of air through an open surgical suction tip is a common source of continuous noise), and peak sound levels can be quite high. Some sources of noise are uncontrollable, such as surgical drills, monitor alarms, and inadvertently dropped instrument pans; other sources are controllable, such as conversation and music (see later). There is evidence in the general literature that noise can adversely affect human performance.[153] Furthermore, studies by Murthy and colleagues[157,158] demonstrated that volume-accurate replay of recordings of OR noise significantly interfered with the speech discrimination ability of anesthesia residents during laboratory testing. The OR noise also caused a significant reduction in residents' performance on psychometric tests of mental efficiency and short-term memory.[157] The potential interference of noise with communication and situation awareness among personnel in the OR is particularly worrisome to those concerned with optimizing teamwork in this complex work environment.

The use of music in the OR is now widespread. Many health care professionals believe that music enlivens the workday and can build team cohesiveness when all team members enjoy the music. A controversial study by two social psychologists, Allen and Blascovich,[159] suggested that surgeon-selected music improved surgeons' performance on a serial subtraction task and reduced their autonomic reactivity (i.e., "relaxed" them) when compared with control conditions consisting of experimenter-selected music or no music at all. The methodology of this study has been criticized.[160]

In response to Allen and Blascovich, several anesthesiologists challenged the notion that the surgeon's preference for the type or volume of music can or should override the needs of other members of the team.[160,161] This issue generated considerable controversy among surgeons and anesthesiologists. In a reply to some of the letters to the editor commenting on their study, Allen and Blascovich[162] stated: "The letters here suggest that not everyone on the surgical team always appreciates the type of music chosen by the surgeon, and anesthesiologists in particular appear to prefer silence in surgery. When we asked the surgeons in our study about this issue, we were told that the environment of surgery does not lend itself to the democratic process, and music was part of the environment in which they felt most comfortable."

Murthy and colleagues studied the effect of OR noise (80 to 85 dB) and music on knot-tying ability in a laparoscopic skill simulator. They found no difference in time or knot quality in the conditions tested and concluded that surgeons can effectively block out noise and music. Invited commentary that accompanied the article brings up important issues: what impact does noise have on other members of the surgical team, how does noise affect communication between team members, does noise affect judgment, and other unanswered questions.

There is no simple answer to the question of the proper role of music in the OR. Clearly, optimal patient care is the primary goal. Some surgical and anesthesia personnel explicitly forbid any type of music in the OR. A more common approach of many OR teams is to allow any team member to veto the

choice or volume of music if they believe that it interferes with their work.

Reading in the Operating Room

The observation that some anesthetists were observed to read journals or books casually during patient care led to a vigorous debate of the appropriateness of such activity.[163] Although it is indisputable that reading can distract attention from patient care, there are no data at present to determine the degree to which reading does distract attention, especially if the practice is confined to low-workload portions of a case. Furthermore, many anesthetists pointed out that reading as a distraction is not necessarily any different from many other kinds of activities not related to patient care that are routinely accepted, such as idle conversation among personnel. Many comments about the issue were related not to the actual decrement in vigilance induced by reading but rather to the impact of the negative perception of the practice (and of those who do it) by surgeons and by patients (if they were aware of it).

A noted researcher on human performance in anesthesia, Matt Weinger, was asked to comment on the practice of reading in the OR.[164,165] He pointed out that reading can combat boredom, which can be a significant distractor in its own right. He concluded that in the absence of data specifically on the topic, it is unscientific to condemn the practice outright, but that reading—like all other distractions—should not be allowed to impair vigilance and patient care.

In our training course on ACRM, we teach that the anesthetist is responsible for modulating all controllable distractions—for example, allowing music during routine work (if all agree) but eliminating it when the situation becomes complex or urgent. Similarly, although our own institutions do not have a policy against reading in the OR (or against casual conversation for that matter), we do expect the anesthetist to terminate all incidental activities when necessary and to have a very low threshold for abandoning potential distractions.

Sleep Deprivation and Fatigue*

General Principles

Scientists are discovering the importance of adequate sleep to allow normal human performance. A consensus report[166] by leaders in the field of sleep medicine stated the following:

> *[we] evaluated scientific and technical reports on the distribution throughout the 24-h day of medical incidents (such as heart attack and stroke) and performance failures (such as vehicular accidents and human errors in industrial and technical operations that can affect public safety). We found that these events occur most often at times of day coincident with the temporal pattern of brain processes associated with sleep. It thus appears that the occurrence of a wide range of catastrophic phenomena are influenced by sleep-related processes in ways heretofore not fully appreciated.*

This report goes on to give many examples of catastrophes that have occurred at least in part because of the effects of sleep deprivation and fatigue.

Investigations in other complex industries (aviation, nuclear power, maritime, long-haul trucking) have identified fatigue as the probable cause of or a contributing factor in many accidents. Unlike health care, the transportation industries have a body—the National Transportation Safety Board (NTSB)—that actively evaluates accident causation, including performance-shaping factors such as fatigue and sleep deprivation. By formal analysis, fatigue has been implicated in many famous accidents. For example, fatigue was a contributing factor in the Exxon Valdez grounding, the nuclear disasters at Three Mile Island and Chernobyl, and the decision-making process that led to explosion of the space shuttle Challenger. We have no such mechanism for evaluating fatigue causation in medical error, so what is not looked for will not be found.

Based on these findings, however, it is likely that chronic sleep deprivation, circadian rhythm abnormalities, and fatigue can be blamed for some iatrogenic adverse patient outcomes. As previously mentioned, the IOM report published in 1999 revealed that thousands of patients are harmed each year by preventable error. Some of these errors may have fatigue as a causative factor, and this should be an area of active study. However, it is difficult to determine the degree to which this is true because there is no blood test equivalent for level of impairment secondary to fatigue. Although these factors have long been minimized or ignored by health care professionals, an understanding of them is critical to maximize patient safety, as reflected in recently published reviews.[167,168]

Normal Sleep

Carskadon and coworkers[169] referred to sleep as a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment that is usually accompanied by postural recumbency, quiescence, closed eyes, and other indicators commonly associated with sleeping. Sleep can be thought of as a physiologic drive state similar to hunger or thirst and is necessary for maintenance of alertness, performance, and overall well-being. The intensity of this drive can be inferred by noting how quickly an individual falls asleep. Just as eating and drinking satiate hunger and thirst states, sleeping reverses the desire to sleep.

The amount of sleep required by any individual is genetically determined and is the amount that allows that individual to be awake and alert throughout the day. The average sleep time for young adults is 7 to 8 hours per 24-hour period, with an approximately 15% inter-individual variation. These sleep requirements do not change with age, and humans can do little to train their physiology to function optimally on less sleep than what is required.

Sleep Debt

If adequate sleep is not obtained for whatever reason, daytime sleepiness and impaired performance ensue. Sleep loss is cumulative and results in what is referred to as sleep debt. An individual who has obtained an optimal amount of sleep is better prepared to perform long periods of sustained work than one who is operating from a sleep debt.

*This section was co-written by Steven K. Howard, M.D., staff anesthesiologist, Veterans Administration Palo Alto Health Care System, and associate professor, Stanford University School of Medicine, Stanford, California.

Because of the additive effects of chronic partial sleep loss, even minor sleep restriction on a nightly basis can insidiously accumulate into a substantial sleep debt.[170] It is important that the only way to pay back a sleep debt is with sleep.

Sleep debts are commonplace in our culture. The National Sleep Foundation's annual survey continues to reveal that Americans chronically undersleep by 60 to 90 minutes each day (website: http://www.sleepfoundation.org/site/c.huIXKjM0IxF/b.3933533/). Shift work, long and irregular work hours, and the demands of family and recreation lead to irregular sleep patterns and prevent restful sleep. This is particularly true for physicians, who often work in shifts, have long duty periods, and must frequently care for patients for long periods.

Circadian Rhythms

Rhythms that fluctuate on a 24-hour time scale are known as circadian rhythms. The biologic clock that is responsible for these rhythms is located in the suprachiasmatic nucleus in the human brain. The best-known circadian rhythms are those of body temperature, hormone secretion, metabolism, and the sleep/wake cycle. The circadian system is synchronized to the 24-hour day by external stimuli referred to as "zeitgebers," the most influential of which is the light/dark cycle of day and night.

The circadian system is biphasic in that it produces a state of increased sleep tendency and decreased performance capacity during two periods throughout the 24-hour day—from 2 AM to 6 AM and from 2 PM to 6 PM. These periods are sometimes referred to as circadian lulls. The circadian clock is very resistant to alterations, and it does not adjust rapidly to changes such as those produced by jet lag or shift work. Disruption of the normal circadian rhythm or incomplete circadian adaptation leads to acute and chronic sleep deprivation, decreased alertness, increased subjective fatigue, and decreased physical and mental performance.[171]

Sleepiness and Alertness

Sleepiness and alertness are at opposite ends of a continuum. Daytime sleepiness is the most obvious effect of failing to obtain adequate sleep. Healthy adults are maximally alert by midmorning. This is sequentially followed by a circadian lull in the early afternoon (causing some cultures to incorporate an afternoon "siesta"), increased alertness in the early evening, and finally increased sleepiness that normally results in falling asleep at night.

The most extreme periods of sleepiness become manifest when one is out of sync with the circadian clock (either staying awake and working when our clock is pressuring sleep or attempting to sleep when our clock is pressuring wakefulness). Data from the U.S. Department of Transportation reveal that the greatest number of single-vehicle accidents takes place during the early morning hours when people are at a circadian lull of alertness. These accidents are thought to be due to inadvertent lapses in driver attention brought about by extremes of sleepiness.[172]

Determinants of Sleepiness

The major factors causing sleepiness are decreased quantity of sleep, poor quality of sleep (sleep fragmentation resulting from multiple awakenings or abnormal progression of sleep states and stages), disrupted circadian rhythms, and the use of certain medications. The amount of sleep obtained is directly related to daytime sleepiness. If sleep is restricted in healthy adults, daytime sleepiness can be demonstrated the following day.[170] If one is allowed to extend sleep beyond the usual sleep time, increased alertness can be demonstrated in the laboratory.[4] Sleep quality is affected by many factors. Sleep fragmentation affects the elderly and patients with sleep disorders such as sleep apnea and periodic limb movements. Sleep fragmentation commonly occurs in physicians who are awakened from sleep to care for patients while in the hospital.

Caffeine[173] and other stronger stimulants are known to reduce nocturnal sleep if ingested close to bedtime, hence decreasing sleep quantity and quality. Potent stimulants such as amphetamines do produce increased alertness and performance, but they have significant side effects and are not an option for health care personnel (e.g., the individual must undergo a substantial amount of recovery sleep ["crash"] after their effect is gone). Newer, nonamphetamine alertness-enhancing drugs (e.g., modafinil) are currently under study and being used in shift workers, including health care workers (see "Fatigue Countermeasures").

Mood

Long work hours, fatigue, and sleep deprivation have also been shown to bring about consistent and dramatic changes in mood and emotions.[174,175] Depression, anxiety, irritability, anger, and depersonalization have all been shown to increase during testing of chronically fatigued house staff. These emotions are an obvious source of stress between anesthetists and their coworkers, patients, and families. The relationship of mood, performance, and patient safety has yet to be determined.

Vigilance

Vigilance, the centerpiece of the ASA logo, is defined as "alert watchfulness." Vigilance is critical, although studies of the performance of anesthesiologists make it clear that vigilance is not the only key characteristic of careful anesthesiologists. Vigilance is a necessary, but not sufficient condition to permit the safe passage of a patient through the perioperative period. If vigilance and other aspects of decision-making are impaired by performance-shaping factors such as sleep deprivation and fatigue, there is a greater likelihood of an adverse patient outcome.

Monitoring of slowly changing stimuli is a classic vigilance task that makes up a significant proportion of the anesthetist's work. This type of task is most sensitive to the degrading effects of sleepiness and fatigue. During the performance of lengthy vigilance tasks, the most common types of decrements include increased reaction time, lapses (transient periods of unawareness), and a reduction in the probability of detecting an alarm. This type of performance impairment has been documented after as little as 30 minutes of time on a task, and the decrement is even more pronounced if the individual is physiologically sleepy at the beginning of the task.

Microsleep Events

The most extreme cause of impaired vigilance is the occurrence of actual sleep episodes (microsleeps) encroaching into periods of wakefulness. Microsleep events typically last a few seconds to a few minutes. They are intermittent in onset, and their impending occurrence is difficult for the individual to predict. Most individuals underestimate their level of sleepiness when they can be objectively shown to be extremely sleepy, thus making this problem even more insidious. In other words, one can fall asleep and not be perceptually aware of it. This has significant meaning in the workplace and when driving home after long work periods. Microsleep episodes are the probable cause of many single-vehicle crashes.

Microsleeps are a sign of extreme sleepiness and are harbingers of the onset of longer sleep periods. Typically, they occur during periods of low workload or stimulation and when an individual is maximally sleepy. In addition, an individual's performance between microsleep episodes is impaired. Frequent and longer microsleeps increase the number of errors of omission.

Driving while drowsy may be less forgiving than practicing medicine while drowsy. It is easy to imagine that if a driver has a microsleep for only seconds while traveling at 60 miles per hour, there is a high likelihood of an accident. Although the anesthetist's work environment does not (usually) evolve as fast as that of the driver, the safety implications of falling asleep while providing care are similarly obvious.[176]

Scientists at the NASA Ames Research Center studied the occurrence of microsleep episodes in pilots during transmeridian flights.[177] These flights involve multiple time zone changes with long, irregular work schedules and resultant disruption of circadian rhythms. This situation causes fatigue, sleepiness, and decreased performance, which are believed to have an impact on flight safety. This particular protocol compared two pilot groups flying equivalent flights: a control (non-nap) group and a nap group. Electroencephalographic monitoring of the pilots was performed to determine the extent of microsleep episodes and also to document whether pilots were actually able to nap if given the opportunity. In brief, the study revealed that (1) crew members were able to nap seated in the cockpit if given the opportunity, (2) the non-nap crew had significantly more microsleep episodes during critical phases of flight than the crew that had napped did, and (3) performance on a standardized test of visual reaction time was worse in the non-nap group than in the group that had napped. This study demonstrated that microsleeps do occur even in a work environment in which sleep is strictly forbidden and in which work hours are tightly regulated. Napping appears to be a reasonable countermeasure to decrease the likelihood of microsleeps and improve performance. Other work on napping supports these conclusions.

Do anesthetists suffer microsleep events? The answer almost certainly is yes. Anecdotal evidence, as well as unpublished reports from our own surveys, suggests that these events do occur from time to time. Microsleeps occurred in a study of anesthesiologists performing work in a simulated environment.[178]

Shift Work

From a practical standpoint, shift work will remain a common method to provide 24-hour care in the hospital setting.[179-181] Workers and managers should learn how circadian factors, sleep-related factors, and social factors affect the lives of workers and their families. Hospital organizations should make it a priority to establish that workers are appropriately rested, just as they try to ensure that workers are not impaired by drugs or alcohol on the job. Given current knowledge concerning shift work and the many factors that affect an individual's ability to cope, there is no single "best" schedule for shift work. Some workers tolerate systems that others find excessively onerous. If given a choice, many workers choose suboptimal shift work rotations when doing so gives them increased pay or more time off work.

Methodologies for Assessing Sleepiness

There are various methods for assessing an individual's level of sleepiness, including behavioral indicators, subjective measures, and physiologic measures. Behavioral indicators of sleepiness include yawning, ptosis, decreased social interaction, and microsleep events. Many of these behaviors are difficult to quantify.

Subjective measures include various types of numeric or visual analog scales that attempt to measure how sleepy the individual feels. These methods are used frequently in studies of sleepiness because they are very easy to implement; however, subjective feelings of fatigue and sleepiness are often underestimated by individuals in comparison to their level of physiologic sleepiness. Both behavioral and subjective sleepiness can be masked by a stimulating environment, even though the individual remains physiologically sleepy. When environmental stimuli wane, physiologic sleepiness manifests itself as an overwhelming propensity to fall asleep. A person who is physiologically alert does not experience sleepiness as environmental stimuli decrease. For example, without physiologic sleepiness, an individual may become bored during a lecture but does not fall asleep.

Physiologic (objective) measures of sleepiness have been used extensively in sleep research and sleep medicine. Carskadon, Dement, and colleagues[182,183] developed the Multiple Sleep Latency Test (MSLT), which is now the standard method for quantifying daytime sleepiness. The MSLT tests the propensity of an individual to fall asleep in a sleep-inducing environment during the daytime. A short sleep latency (i.e., falling asleep quickly) is a sign of increased sleepiness, whereas a long sleep latency is a sign of decreased sleepiness. A normal MSLT score is greater than 10 minutes, whereas pathologic daytime sleepiness is defined as 5 minutes or less. Pathologic levels correspond to the daytime sleepiness typically seen in patients with narcolepsy or sleep apnea or in healthy individuals deprived of sleep for 24 hours.

Evaluation of Physiologic Sleepiness in Anesthesia Residents

Using the MSLT, Howard and colleagues[168,184] evaluated the physiologic daytime sleepiness of anesthesia residents under three different conditions: (1) "baseline" (daytime shift, no on-call duty period in the previous 48 hours), (2) "post-call" (immediately after a 24-hour work and in-house on-call period), and (3) "sleep extended." In the sleep-extended condition, residents were told to maximize sleep and were allowed to arrive for work at 10 AM (3 to 4 hours later than normal) for 4 consecutive days before testing. They were not on call during this time. The sleep-extended condition was included to provide a true control state of maximal rest and optimum alertness.

In this study, anesthesia residents had an MSLT score of 6.7 ± 5.3 minutes in the "baseline" condition and 4.9 ± 4.7 minutes in the "post-call" condition, both scores revealing the nearly pathologic levels of daytime sleepiness seen in patients with narcolepsy or sleep apnea. The "baseline" group slept an average of 7.1 ± 1.5 hours per night, whereas the "post-call" group reported an average of 6.3 ± 1.9 hours of sleep during their night on call. Ironically, although the on-call periods occurred during rotations that often have very busy call nights, only a few subjects were, in fact, awake most of the night. In the "sleep-extended" condition, the subjects extended their sleep to an average of more than 9 hours per night, and MSLT scores were in the normal range (12.0 ± 6.4 minutes). These results clearly demonstrate that medical personnel who have not been on call cannot be assumed to be "rested" when compared with "fatigued" post-call residents. These data also indicate that under "normal" working conditions, the resident physicians studied were physiologically sleepy to nearly

pathologic levels. This finding documents a previously unknown level of chronic sleep deprivation in this population. Notably, these data cast substantial doubt on previous studies of the performance of medical personnel that have relied on the assumption that individuals working under "normal" conditions are truly rested.

Evaluation of Subjective Sleepiness

In the previously discussed study, Howard and colleagues also investigated the degree of discrepancy between the residents' subjective sleepiness (how sleepy they felt) and their physiologic sleepiness (how easily they fell asleep). Subjective sleepiness was measured with a validated numeric scale (Stanford Sleepiness Scale); physiologic sleepiness was measured with the MSLT, as described earlier. Subjects' self-reported sleepiness immediately before each sleep opportunity during the MSLT did not, in general, correlate with their MSLT score. As in previous studies, subjective sleepiness correlated better with physiologic sleepiness when subjects were extremely alert or extremely sleepy.

The authors also found that subjects demonstrated little ability to determine whether they had actually fallen asleep during the MSLT sleep opportunities. For example, in 51% of trials in which the electroencephalographic/electro-oculographic measurements showed that the subject had fallen asleep, the subjects thought they had remained awake throughout the test. These results support the contention that medical personnel are physiologically vulnerable to degraded alertness yet are unable to perceive this decrement. Thus, an anesthetist could, in fact, fall asleep during a case, awaken, and be totally unaware of the lapse in vigilance.

Sleep Deprivation and Fatigue in Medical Personnel

Human error represents a significant risk to hospitalized patients,[3] and it has been estimated to play a role in more than 70% of anesthesia mishaps.[185] This is similar to the error rate seen in cognitively similar work environments such as aviation.[186] Clearly, the physiologic capabilities and limitations of the human operator in complex work environments remain central to safe and productive performance. The 24-hour demands of medical care parallel the physiologic challenges present in other operational domains; nevertheless, minimal data are available to quantify the fatigue-related risk to performance and alertness in medical personnel.

Providing quality health care requires physicians to attend to details critical for life, such as monitoring of changing vital signs, administering the correct type and dose of medications, and in general, making crucial decisions to achieve optimal patient care. Physicians, like other workers, are affected by all the physiologic, psychological, and behavioral demands that characterize work environments requiring continuous, around-the-clock operation. However, whereas much of the health care system (e.g., nursing) relies on multiple work shifts to cover the 24-hour day (which is also not a perfect system), physicians more typically work long duty periods and frequently experience sleep loss, circadian disruption, and fatigue. Even minimal levels of sleep loss (for example, obtaining as little as 2 hours less sleep than an individual requires) can lead to lapses in performance, increased physiologic sleepiness during the daytime (including microsleeps), and altered moods.[187] This level of degraded performance and alertness almost certainly contributes to medical error and health care mishaps.[167]

Work Hour Regulations

In July 2003, The Accreditation Council for Graduate Medical Education in the United States instituted common duty hour requirements for all accredited residency training programs. The requirements can be found at www.acgme.org and are as follows:

- Eighty hours per week, averaged over a period of 4 weeks (including all in hospital call)
- One day (continuous 24-hour period) in 7 free of all duties (clinical and educational) averaged over a 4-week period
- In-hospital call occurring no more frequently than every third night averaged over 4 weeks
- In-hospital call not to exceed 24 hours; residents may remain on duty for 6 additional hours to participate in educational activities, transfer care of patients to another team, conduct outpatient clinics, and maintain continuity of care
- No new patients accepted after 24 hours of continuous duty
- Provision of a 10-hour period between all daily duty periods and after in-hospital call
- Moonlighting hours to be included as part of the 80-hour limit
- Exceptions: a residency review committee may grant exceptions for up to a 10% increase in the 80-hour limit to individual programs on a case-by-case basis

Training programs were given little direction on how to accomplish the work hour restrictions, but most anesthesiology training programs have been able to successfully adopt them. Interestingly, there are no work hour restrictions for practitioners or any other care providers beyond residency training. There is no proof that the change has had a positive or negative impact on patient or provider safety, although pundits continue to debate both sides of the issue.[188,189] Recent studies show that the number of hospital-wide adverse drug events remained constant after the limitations[190] and that postoperative outcomes were not affected in the programs studied.[191]

Compliance rates for the common program requirements have been tracked by Landrigan and coworkers.[192] In a survey of interns, they found that more than 80% reported some kind of work hour violation during 1 or more months of the study. Average work duration decreased and sleep time increased when compared with an equivalent time before duty hour limits. Reporting of compliance by individual residents is complicated by many factors, so the true amount of work being performed is not known. Many surgical programs have requested and been given a 10% work hour extension, but it is not known how many of these requests have been turned down.

European and Australian Regulations

Work hours regulations in the European Union and in Australia/New Zealand are much more stringent than they are for trainees

in the United States. In 2009, the maximum hours that junior medical staff in the National Health Service (NHS) in the United Kingdom work will be reduced from 58 to 48 under European law. This is a major challenge for the health service and will require new ways of working to be adopted. The NHS National Workforce Projects has been appointed as the lead organization to help support the NHS in finding and implementing solutions to the changes in the work environment (http://www.healthcareworkforce.nhs.uk/). The results of these restrictions on patient and provider safety are still being evaluated, and these findings may have an impact on any further restrictions that may occur in the U.S. system. Empirical studies documenting the effect of the European Union changes are lacking, although there are several argumentative pieces for and against the directive.[193,194]

Harvard Work Hours, Health, and Safety Group Studies

A series of interesting studies has been published recently by a group from the Brigham and Women's Hospital.[195,196] The investigators conducted a randomized study comparing interns working in an ICU on a traditional schedule (every third night on call with shifts longer than 24 hours in duration) and an intervention schedule that reduced work shift duration (to less than 17 hours) and the number of hours worked per week. Interns made 35.9% more serious medical errors and had twice as many attentional failures (microsleeps) during the traditional schedule. Those on the traditional schedule worked more hours per week (85 versus 65 hours) and slept less (5.8 hours), which led the investigators to conclude that elimination of long work shifts reduced errors and decreased manifest sleepiness.

This group also conducted a monthly prospective nationwide survey of interns' first postgraduate year to evaluate the risk for motor vehicle accidents with extended work shifts.[197] They found an increased likelihood of motor vehicle accidents and near-miss accidents after extended work shifts and an increased monthly risk with increasing number of shifts.

Sleep and Performance

Previous studies addressed the effects of sleep deprivation and fatigue on physician performance and well-being. Major reviews of this literature identified little consensus.[198,199] There are several methodologic flaws in the existing literature:

1. The degree of acute sleep deprivation of subjects was poorly defined, and no assessment of chronic fatigue was made. Typically, studies relied on only the previous night's sleep as a level of "fatigue," and subjects could well have been chronically fatigued during baseline (control) trials, which could mask the degree of impairment resulting from the acute fatigue of being on call. This continues to be the greatest weakness in studies of fatigued health care providers.
2. Measuring actual clinical performance is difficult and was not attempted. Most studies had to rely on simple cognitive tasks that probed only short-term memory, immediate recall, and simple reaction time; the validity of using such simple tests to probe complex performance has been challenged because these simple tests do not assess the higher-level cognitive functions most critical to skilled medical care.
3. Most of the performance tests were of very short duration (3 to 5 minutes). Studies have shown that if sufficiently motivated, even fatigued subjects can perform well on short-duration tasks.
4. Practice effects were not adequately accounted for. If subjects have not learned a particular performance test sufficiently to achieve maximum performance, subsequent trials will almost certainly show improvement in performance because of further learning of the task.

Some studies requiring subjects to perform sustained vigilance tasks of long duration have, in fact, shown an impairment in the performance of fatigued physicians. Tasks of this type, which require sustained attention to detail, are highly relevant to the anesthetist's tasks, and they are the most sensitive to the effects of sleep loss and fatigue.

Do Anesthesiologists Perceive Fatigue As a Problem?

The survey by Gaba and associates[200] revealed that more than 50% of respondents believed that they had made an error in clinical management that they thought was related to fatigue. In another survey of anesthesiologists and CRNAs, the majority (61%) of respondents recalled having made an error in the administration of anesthesia that they attributed to fatigue.[201] Data from these surveys and others[202] reveal that issues of sleepiness and fatigue are perceived by anesthesia practitioners as being important causative factors in reducing anesthesia-related patient safety.

Howard and colleagues[178] conducted a study of rested versus sleep-deprived anesthesiology residents using a realistic patient simulator. Multiple measures of performance were collected during this 4-hour experiment (e.g., psychomotor tests, reaction to secondary task probes, response to clinical events). In the rested condition, subjects had 4 consecutive days of sleep extension (showing up at work at 10:00 AM), whereas in the sleep-deprived condition they had remained awake for 25 hours (during a "pseudo"–on-call period) before performing the simulated anesthetic. Subjects in the rested condition were able to increase their total sleep time more than 2 hours from baseline. Psychomotor tests revealed progressive impairment of alertness, mood, and performance over the course of the pseudo–on-call period, as well as on the experimental day, when compared with the well-rested condition. Secondary task probe response times were slower after being sleep deprived, although this reached statistical significance in just one of three probe types. There was no statistical difference in case management between conditions—in fact, subjects in both conditions made significant errors. The behavioral alertness scores in the sleep-deprived condition were different from those of subjects who had increased their sleep time. Even when well rested, the subjects in this experiment did not perform perfectly; however, they did not show any of the behavior indicative of being sleepy (e.g., head nodding, eyes closing). Sleep-deprived subjects cycled (often rapidly) in and out of sleepy behavior, and the most impaired individuals showed such behavior for more than 25% of the experiment (60 minutes).

Fatigue Countermeasures

Studies such as the ones described previously are establishing the true picture of sleepiness and fatigue in medical personnel. From studies of the performance of fatigued individuals in other domains, we know that professionals become increasingly vulnerable to the degrading effects of sleepiness as the sleep debt accumulates. It may be difficult to determine a causal relationship between anesthetist fatigue and patient outcome. However, it is clear that if anesthetists are not awake, they cannot possibly be aware. Such a lapse in vigilance is unacceptable. Furthermore, anesthetists cannot prevent sleep by willpower alone because it is a fundamental physiologic drive. Demands for clinical services must be balanced against the potential for reduced vigilance and error by seriously fatigued practitioners, anesthetists, and surgeons alike.

Because fatigue is such a widespread and insidious problem, it is important to determine ways to counteract its effects. Strategies that institutions or practitioners can use to minimize the negative effects of sleepiness and fatigue on performance, include

- Education
- Improved sleep habits
- Rest breaks at work
- Strategic napping
- Medications
- Light therapy

Education

The first step in addressing sleepiness and fatigue of medical personnel is to educate practitioners and the administrators of health care institutions about the impact of sleep issues on work performance, mood, job satisfaction, and health (see Chapter 8). Education is a relatively simple and inexpensive countermeasure that can be implemented immediately. Educational programs covering sleep deprivation, circadian disruption and fatigue, and countermeasures have been enthusiastically adopted by an increasing fraction of the aviation community.[203,204] Similar programs should be developed for the health care community. Education alone is sufficient for some individuals and institutions to change their work and sleep habits or their organizational and scheduling procedures. However, it is clear at both the individual and organization level that education will not be sufficient to address this issue fully. Other competing forces (e.g., measures of production versus safety) are very powerful and difficult for practitioners to manage.

Improved Sleep Habits

Good sleep habits include the following: regularity of bedtime and wake-up time; sufficient time for sustained and individually adequate sleep; restriction of alcohol, caffeine, and nicotine before bedtime; and use of exercise, nutrition, and environmental factors so that they enhance rather than disturb sleep. A regular sleep schedule is an important part of optimal sleep hygiene, but it is often not possible for medical personnel, given the requirement to cover clinical needs on a 24-hour basis. Medical personnel should make greater effort to maintain as constant a sleep schedule as possible and to maximize sleep opportunities before and after periods of reduced sleep.

Social drug use can have profound effects on sleep. Physicians frequently use caffeine to stay awake during on-call periods, but often its use could be more strategic. Strategic use (i.e., use when its alerting effects are needed) of caffeine requires knowledge about its onset and duration of action. Besides its alerting effects, caffeine produces an increase in awakenings and decreases the total nocturnal sleep time if ingested close to sleep opportunities. Individuals who ingest large amounts of caffeine and who have nocturnal sleep disturbances should limit or cease their intake of caffeine. Chronic use of caffeine, common in our culture, produces tolerance to the alerting effect of the drug, and hence it should be avoided when using it strategically. Nicotine is a stimulant that produces effects similar to those of caffeine. Alcohol is often used successfully to initiate sleep, but its effect on sleep architecture after sleep onset can be devastating. After ingestion of alcohol, frequent awakenings from sleep occur that can be associated with increased sympathetic nervous system activity, often manifested as headache, sweating, and tachycardia. Clearly, use of these substances should be restricted near bedtime.

Physicians often lack good nutritional habits, especially during long duty periods. Meals may be skipped or ingested quickly whenever there is adequate time. If one is hungry before bedtime, it is best to avoid eating or drinking heavily because this, too, can disturb sleep.

The effects of age can make optimum sleep habits difficult to achieve because sleep requirements do not change once reaching adulthood. The number of awakenings per night rises after the age of 45 years and results in decreased sleep efficiency (time in bed versus total sleep time). The ability to initiate sleep at any time during a 24-hour day is diminished after the age of 25 years, and "sleeping in" to make up for lost sleep is more difficult as individuals grow older. Sleep-related disorders such as breathing disruptions (obstructive sleep apnea) and periodic limb movements also become more common with age.

Ideally, the sleep setting should be a dark, quiet room devoid of sources of interruption such as pets, telephones, pagers, and children. The sleeping surface and environmental temperature should be comfortable. Psychological stressors increase baseline physiologic arousal and can impair the quality and quantity of sleep. For example, reviewing the previous day's events or attempting to plan tomorrow's activities while trying to fall asleep is not conducive to sleep. Effort should be made to separate the work of the day with a period of relaxation before attempting to initiate sleep.

Rest Breaks at Work

Although other industries have openly recognized the reality of decrements in vigilance resulting from fatigue and sleepiness, the health care system has not. Rest breaks and rotation of task duties are mandatory for air traffic controllers and are part of naval ship command procedures in an attempt to prevent potential lapses in vigilance. Short breaks have been shown to increase productivity and job satisfaction, and they probably also help alleviate boredom. In anesthesia training programs, residents are frequently given rest breaks during the daytime, but this is often not the case with private practitioners. Private practice anesthesia typically does not provide the mechanisms for rest breaks or task duty rotation, in part because of fiscal issues. An "extra" anesthetist would be necessary to provide these opportunities on a regular basis.

The optimal timing and length of breaks are unknown, but periodic relief from duty should be taken when possible. Cooper and coworkers[205,206] studied the effects of intraoperative exchange of anesthesia personnel. Although in some cases the process of relieving OR personnel caused a problem, it more frequently was

associated with the discovery of a preexisting problem. The positive effect of relief of personnel probably depends on the quality of the handover briefing conducted by anesthetists. Studies are currently being performed to address standardized handover of intraoperative care of patients.

If anesthetists are unable to obtain a break during long work periods, there are other measures that they can take to remain alert. They can engage other OR personnel in conversation (although this, too, can be distracting), thereby increasing the level of stimulation in the environment. Walking around and standing up are also techniques that decrease subjective (but not physiologic) sleepiness. If anesthetists are having microsleep events, which may be noticed by other personnel rather than by the anesthetists themselves, fatigue is already very severe, and complete sleep is imminent. In such a situation the practitioner must secure additional assistance in surveillance of the patient and, if necessary, obtain relief to allow time for sleep.

Strategic Napping

If adequate sleep during the night cannot be obtained, naps can be used to decrease sleepiness and improve performance. The optimal nap length for most individuals is about 45 minutes; this duration acutely improves alertness, allows improved performance, and minimizes the possibility of sleep inertia on awakening. Naps as short as 10 minutes have beneficial effects on alertness. A nap of 90 to 120 minutes allows a full sleep cycle and can additionally boost alertness and performance over that of shorter nap periods. Data from NASA studies of flight crews demonstrate that on the whole, napping is a useful countermeasure to fatigue and sleep deprivation.[177]

Smith-Coggins and associates studied the effect of naps during the night shift on health care providers working in a busy suburban university emergency department.[204] Workers were randomized to work a night shift without rest (as was the norm in this facility) or to receive a 40-minute nap opportunity at 3 AM. They found that a nap taken at this time improved performance on some (but not all) measures. The most important result of this study may be the fact that the subjects were able to (1) successfully use this strategy in the real workplace and (2) improve alertness and performance.

Investigators in the Veteran's Hospital at Palo Alto, California, have developed a Strategic Nap Program that has been successfully piloted at two sites within the Veterans' Administration system. This program has been implemented in ICU settings but is equally applicable to other high-risk, dynamic domains such as the OR. Components of the program include a formal educational program, program guidelines for the individual practitioner and the facility, and other guidance for implementation.

There are issues that complicate the appropriate use of naps by medical professionals. Physicians have an individual and cultural tendency to ignore or to minimize the effect of fatigue and sleep deprivation. The culture of medicine views work breaks and naps as signs of weakness. The military has addressed similar attitudes with the concept of "power napping." Troops are strongly encouraged to take naps of 10 minutes to 1 hour when the situation permits to increase their strength and performance. This approach appropriately presents the idea of napping in a positive light as a sign of wisdom and strength rather than one of cowardice and frailty.

Sleep Inertia

Sleep inertia corresponds to the period of reduced ability to function optimally immediately on awakening.[190,207] This phenomenon usually occurs when individuals are awakened out of slow-wave sleep and is manifested as grogginess and impaired performance lasting as long as 15 to 30 minutes after awakening. Sleep inertia can also occur after being awakened from normal sleep and is most common during the early morning circadian trough (2 to 6 AM). Depending on the preexisting level of sleepiness, individuals who take naps longer than 40 minutes are at greater risk for sleep inertia on awakening. Sleep inertia can be important to health care professionals who may be awakened out of deep sleep to provide emergency care to patients (e.g., emergency cesarean section or emergency intubation). If urgent work can be anticipated, the sleeping individual should be awakened with sufficient time (at least 15 minutes) to minimize the fogginess and decrement in performance associated with sleep inertia. If sleep inertia is unavoidable, it would be wise for the affected person to ask for help until the grogginess dissipates.

Medications

A few studies have evaluated the use of sedative-hypnotics for promotion of sleep during nonduty hours by nonmedical personnel (e.g., to assist in daytime sleep after a night shift). Many questions remain unanswered regarding the quality of sleep obtained after using hypnotics, the severity of hangover effects, and the potential risk of abuse. Melatonin, which is a hormone secreted by the pineal gland, may have promise as a nonaddictive daytime sleep-inducing agent, but the results of existing studies are controversial.

Stimulants may have a role in the maintenance of alertness during periods of extreme sleepiness. Modafinil is a nonamphetamine alertness-enhancing drug that has been approved for use in narcolepsy and shift work sleep disorder.[208] The side effect profile of this drug is so promising that it has been studied extensively by the military and shift workers as a nonaddicting adjunct for alertness management. Its use in health care is also being studied but cannot be sanctioned at this point.[209] The use of sedatives and potent stimulants to manipulate sleep is not considered an appropriate option for anesthetists. Caffeine is used frequently to increase alertness temporarily, but there are caveats about its use, as discussed earlier. Caffeine should be used strategically to maximize its effect when needed. Strategic use of caffeine includes (1) knowledge of its onset (15 to 30 minutes) and duration of action (3 to 4 hours) and (2) use when alertness is required and the opportunity to sleep is minimal.

Countermeasures should be studied and implemented in health care. There are major financial incentives to maintain the status quo.[167] If anesthesiologists know that they are impaired (from fatigue or for any other reason), the assistance of a colleague should be enlisted so that patient safety is not negatively affected.

Light Therapy

Timed cycles of bright light and darkness have been used in certain circumstances to facilitate adaptation to shift work. Exposure to bright light (>7000 to 12,000 lux) and darkness at the appropriate points in the circadian cycle has been shown to reset the circadian pacemaker by 12 hours over a period of 2 to 3 days.[210] This important finding demonstrates the ability to make significant changes in the circadian system relatively quickly. However, resetting the circadian timekeeper is critically dependent on the timing, intensity, and duration of exposure to light and to "total" darkness. Being off by only an hour can prevent the desired effect. Adhering to such time-critical schedules for this

treatment is probably impractical for anesthetists given the many work-related and social factors that affect their activities. Research on light treatment continues and may eventually result in more practical treatment regimens.

Aging

All individuals understand that their abilities cannot be maintained indefinitely as they age. On average, performance on laboratory tests of discrete sensory-motor and cognitive skills can be shown to decrease with increasing age.[211] However, there are large differences among individuals. Again, except at extreme points of performance failure (e.g., severe impairment of vision or hearing), the contribution of isolated changes in physiologic or cognitive performance is difficult to relate to real work situations.[212] For one thing, the work environment is often rich with redundant cues involving multiple sensory modalities. For another, technologic compensation may be possible, as with the use of hearing aids or glasses. Finally, along with possible physiologic changes of age typically comes greater experience with a variety of situations. For many individuals, the lessons learned from experience more than offset the modest degree of physiologic impairment that they face as they grow older. This compensation has, in fact, been documented for skilled typists, chess players, and bridge players. Middle-aged individuals can use their experience to solve everyday problems better than young individuals can; however, for the elderly (on average), compensation by experience is no longer sufficient to offset cognitive slowing.[212] Age takes a toll on short-term (or "working") memory,[213] and there is evidence that aged workers are more sensitive to the interruptions in attention that are so prevalent in dynamic environments. Nevertheless, few of these deficits have been documented in complex work settings, largely because it is so difficult to measure performance in these domains. The issue of the aging anesthesiologist has raised considerable controversy among anesthesiologists.

What do other industries do about this issue? From 1959 until the end of 2007, U.S. and aviation regulations forced airline pilots to retire at age 60 regardless of their health or competence. When the "Age 60 Rule" was put in force, the rationale was that the "increased speeds and passenger loads of commercial airliners placed greater demands on pilots with respect to their physical fitness and piloting skills." Some may argue that the increasingly challenging nature of anesthesia practice also places greater demands on anesthetists than ever before.

After intense debate and many studies over the last 30 years,[54,214] with partially contradictory studies and little data suggesting that pilots between the ages of 60 and 65 are at greater risk, the Age 60 Rule was modified by law (HR 4343) at the end of 2007. The new rule allows airline pilots to continue flying until age 65, although for captains in international operations, a pilot younger than 60 years must be the copilot.

Federal Aviation Administration (FAA) regulations do require air transport pilots to pass "class I" medical examinations every 6 months. However, the medical examination process appears to be largely aimed at identifying individuals with chronic medical conditions that place them at risk for sudden incapacitation (such as significant coronary heart disease). Pilot incapacitation during high-workload phases of flight has been shown in simulator testing to lead to a significant rate of crashes, even when there is a second pilot at the controls. These physical examinations may weed out pilots with severe cognitive or sensory-motor deficiencies, but they are not designed to assess subtle aspects of changes in performance resulting from age. Of course, there are no requirements whatsoever for medical examination or certification of anesthetists, nor is there any limitation on the practice of anesthesia at any age.

It is likely that age alone does not independently cause a significant decrement in performance, but age correlates with other factors that are likely to affect performance. The concern about aging professionals revolves more around the loss of knowledge and skill as one gets farther from initial training rather than the loss of fundamental mental capacity. Thus, the originally well-trained practitioner who keeps abreast of the changing standard of care and who exercises emergency skills frequently is less likely to be affected by advancing age than is a marginal practitioner whose knowledge and skills were frozen immediately after completion of training and who practices in a low-complexity environment. The FAA regulations deal with this issue for air transport pilots by requiring frequent (every 6 months) evaluation of performance by FAA-certified check pilots. These evaluations are performed during actual flights and in realistic simulators, and they, in essence, check fitness for duty regardless of age. There is currently no similar program in anesthesia to assess the competency of practitioners at any age, except for initial board certification, which is voluntary. Periodic maintenance of certification in anesthesiology is now required by the American Board of Anesthesiology for diplomats attaining certification after the year 2000, but it is not mandatory to be board-certified to practice anesthesia, and the recertification examinations are not as intense, as thorough, or as frequent as those required for air transport pilots. Thus, the issue of age-related effects on anesthetist performance is likely to continue to be raised periodically for the foreseeable future.

Illness and Drug Use

Every anesthetist is vulnerable to transient illnesses, which in some cases probably reduce performance ability (see Chapter 101). All personnel are vulnerable to chronic medical conditions that could directly or indirectly affect their fitness and performance capability. The culture of the caring professions often leads individuals to continue to work with illnesses that would cause other professionals to stay at home or to seek medical advice. The performance-shaping effects of the illness can be exacerbated by the use of either over-the-counter or prescribed medications. The degree to which illness and medications affect anesthetist performance is unknown.

A serious problem for anesthetists is that of drug abuse (see Chapter 101).[55,56,215-218] It is estimated that up to 8% of physicians could be classified as alcoholics. In an anonymous survey of anesthesia personnel from one institution, 75% of respondents reported drinking alcohol on a regular basis. They reported drinking an average of 1.6 drinks per day 2.7 days per week. Just less than 10% of subjects reported having been "hung over" while conducting anesthesia, and 40% reported having given anesthesia within 12 hours of alcohol consumption; 84% stated that alcohol use never adversely affected their clinical performance.

The degree to which small doses of alcohol or hangovers affect the performance of complex, real-world tasks is uncertain. Some studies of general aviation and navy pilots[54,219-221] suggested that hangover effects can degrade performance even when more than 8 hours has elapsed since alcohol consumption and there is no detectable blood alcohol level. Nonetheless, though statistically significant, the changes in performance seen in these studies

may not have been functionally significant. These studies[54,219-221] also suggested an interaction among age, workload, and hangover in causing decrements in performance. However, the "aged" cohort was defined as 31 years or older and was compared with a cohort of pilots in their early 20s. Extrapolating these results to the anesthesia domain is difficult.

Nevertheless, the natural history of serious abuse of alcohol, cocaine, sedatives, or narcotics by anesthetists is such that cognitive performance will at some point be seriously compromised. However, addiction specialists frequently report that job performance is one of the last areas of life to become impaired.[222,223] For this reason, the period of time in which an addicted anesthetist's performance in the OR is significantly impaired is a relatively small fraction of the total time during which drugs are abused. Although this in no way excuses the practice of conducting anesthesia while under the influence of drugs, it may account for the fact that reports of addicted anesthesiologists are, unfortunately, common whereas reports of overt patient risk or harm resulting from an addicted physician's errors are unusual.

Anesthesiology has been at the forefront in dealing with impaired medical personnel. Management of those discovered with a drug impairment is fairly standardized,[216,224] but the question of whether to return these individuals to anesthesia practice is increasingly controversial, even when they return under carefully monitored reentry protocols.[216] The main risk appears to be to the addict's own safety, although questions about patient safety can never be eliminated.

Ultimately, in the current medical system the responsibility rests with anesthetists to ensure that their own performance level is sufficient for the work at hand. Pilots use a mnemonic checklist to review the effects of potential performance-shaping factors and are instructed not to fly if they are impaired for any reason. The difficulty in anesthesiology (and to some degree in aviation) is that the real-world organization and incentives of many practice settings do not provide mechanisms for personnel to excuse themselves if they are temporarily impaired. Ironically, there may now be better means to identify and support a practitioner with a serious addiction than there are for the more common occurrences of profound sleep deprivation or impairment by a transient or chronic illness.

The Study of Human Performance

Study of human performance involves research paradigms that are different from those typically used in the science of anesthesia. There are many obstacles to obtaining hard, statistically valid data on human performance. There are no animal models for expert human performance, no "Sprague-Dawley anesthesiologists" to be studied in detail, nor can studies of professional performance be conducted with the psychologist's typical experimental subject, the university undergraduate student. Recruiting expert anesthetists to be the subjects of study is difficult and raises issues of selection bias concerning those who do volunteer. Especially if conducted during actual patient care, investigations of human performance are strongly influenced by concerns about litigation, credentialing, and confidentiality, thus making it difficult to execute optimal studies.

Furthermore, variability among individual anesthetists is quite striking because different anesthetists respond to the same situation in different ways and each individual may act differently on different days or at different times of the same day. The magnitude of this intra-individual variability is often nearly the same as the inter-individual variability.

"Performance" itself is an intuitively meaningful concept that is difficult to define precisely. There are no universal standards for the clinical decisions and actions of anesthetists. They depend heavily on the context of specific situations. In addition, determining how anesthetists perform their jobs, whether successfully or unsuccessfully, means delving into their mental processes. This cannot be measured easily. On the one hand, experimental designs can be used that involve artificial laboratory tasks for which performance can be objectively measured. These tasks will then be far removed from the real world of administering anesthesia. On the other hand, investigating the actual performance of trained practitioners in the real world yields primarily subjective and indirect data. Understanding the anesthetist's performance must be seen as analogous to solving a jigsaw puzzle. Pieces of the puzzle probably come from a variety of sources, none of which by itself captures the entire picture. These pieces include objective data from artificial laboratory tasks, prospective observation of routine patient care, analysis of retrospective reports of near misses or anesthetic mishaps, and prospective observation of the response to simulated events. To achieve the best possible understanding of the situation, it is necessary to accept many data that seem uncomfortably subjective to the physical or biologic scientist. Because the research methodologies may be unfamiliar to anesthetists, some pioneering studies of anesthetist performance are described in detail in this chapter.

Why Study Human Performance in Anesthesia?

How can improved understanding of the human performance of anesthetists help them provide patient care more safely, in a wider variety of clinical situations, with greater efficiency, and with increased satisfaction to both patients and practitioners? The possibilities include the following:

1. Improved operational protocols and enhanced training of anesthetists. The way in which individuals conduct anesthesia is based, in part, on knowing the limits of their performance envelope. Anesthetic techniques and OR practices should draw on anesthetists' abilities and should mitigate their weaknesses. Anesthetists' abilities are strongly affected by training. Understanding the required performance characteristics and inherent human limitations will lead to improved training, which will most fully develop the strengths and counter the existing vulnerabilities of the anesthetist. This process should make patient care safer, less stressful, and more efficient.
2. A more rational view of professional work and legal responsibility (see Chapter 9). Modern medicine, especially in the United States, is strongly influenced by medicolegal concerns. The litigation system has a major selection bias in that every case that comes before it involves an adverse outcome for a patient. The duty of the practitioner is to render care as a "reasonable and prudent" specialist in the area of anesthesia. What is reasonable and prudent? What

type of performance is to be expected from appropriately trained human beings in a complex and dynamic environment? By understanding human performance, it may be possible to generate a more rational view of what is and is not within the standard of care.
3. A more effective work environment. Anesthetists now perform their tasks by using an array of technologies, most of which have not been designed to support the anesthetist's work optimally. By understanding the anesthetist's tasks and performance requirements, the workspace and tools could be improved to better support the most difficult tasks. This, too, can lead to greater safety and to greater efficiency and work satisfaction.
4. A more efficient organizational system (see Chapter 99). Anesthesia is embedded within a larger system of organized medical care that involves interactions among numerous institutions, organizations, and professional domains. Understanding how the anesthetist's work relates to the larger system may enable the development of more rational and efficient flow of information and organizational control.

Although anesthesiologists have been basing analysis of human performance on individual actions, decisions, and mental models and the influence of organizational factors and safety culture for some time (see survey papers[1,2,225]), their importance to health care in general has only recently been appreciated.[3,48]

Cognitive Process Model of the Anesthetist

The empirical data can best be interpreted in accordance with an explicit model of the cognition involved in an anesthetist's performance. Several investigators[44,58,113,144,226-232] have written about the cognitive elements in anesthesiology.[113,144,226,233-235] The model developed here is explicit, comprehensive, and specific to anesthesia. It is described in detail as a framework for understanding the empirical data and provides a vocabulary for discussing the elements of both successful and unsuccessful performance by anesthetists. This model draws heavily on the work of a number of other investigators[126,235-238] who studied human performance in a variety of complex, dynamic worlds.

Decision-Making Involves Multiple Levels of Mental Activity

The entire model, which is shown in Figure 6-10, depicts the anesthetist as working at five different interacting cognitive levels to implement and control a core process (see Box 6-9) of observation, decision-making, action, and re-evaluation. The core process must then be integrated with the behavior of other team members and with the constraints of the work environment.

The division of mental activities into levels follows the work of Rasmussen and Reason.[237,239,240] Having multiple levels supports parallel processing (performing more than one task at a time) and multitasking (performing only one task at a time but switching very rapidly from one task to another). The anesthesia task analyses[241-245] and the direct observations of anesthetists in Toronto[268] and Tübingen[246-249] have provided clear evidence for the occurrence of parallel processing and multitasking. Table 6-6 gives an overview of the mental activity levels.

Box 6-9 Elements of the Core Mental Process

1. Observation
2. Verification
3. Problem recognition
4. Prediction of future states
5. Decision-making
   a. Application of precompiled responses (recognition-primed decision-making)
   b. Decision-making using heuristics and probability
   c. Decision-making including abstract reasoning
6. Action implementation
7. Re-evaluation (avoiding fixation errors)
8. Start again with 1 (loop continues)

At the sensorimotor level, activities involving sensory perception or motor actions take place with minimal conscious control; they are smooth, practiced, and highly integrated patterns of behavior. At the procedural level, the anesthetist performs regular routines in a familiar work situation. These routines have been derived and internalized from training and from previous work episodes. A level of abstract reasoning is used during preoperative planning, and intraoperatively it is used in unfamiliar situations for which no well-practiced expertise or routine is available from previous encounters.

Dynamic Adaptation of the Anesthetist's Thought Processes

Rasmussen's model[237] was extended by the explicit addition of two additional levels of mental activity that provide for dynamic adaptation of the anesthetist's own thought processes. This ability to "think about thinking" in order to control one's own mental activities strategically is called metacognition by psychologists, and it is thought to be an important component of working in complex, dynamic domains. Supervisory control is concerned with dynamically allocating finite attention between routine and nonroutine actions, among multiple problems or themes, and among the five cognitive levels. Resource management deals with the command and control of available resources, including teamwork and communication.

Core Process

An overview of the core process and its elements is given in Box 6-9. The elements are explained in detail in the following sections.

Observation

Management of rapidly changing situations requires the anesthetist to assess a wide variety of information sources, including visual observation of the patient and the surgical field, visual inspection of a multitude of displays from electronic monitors, visual observation of the activities of nurses and the contents of

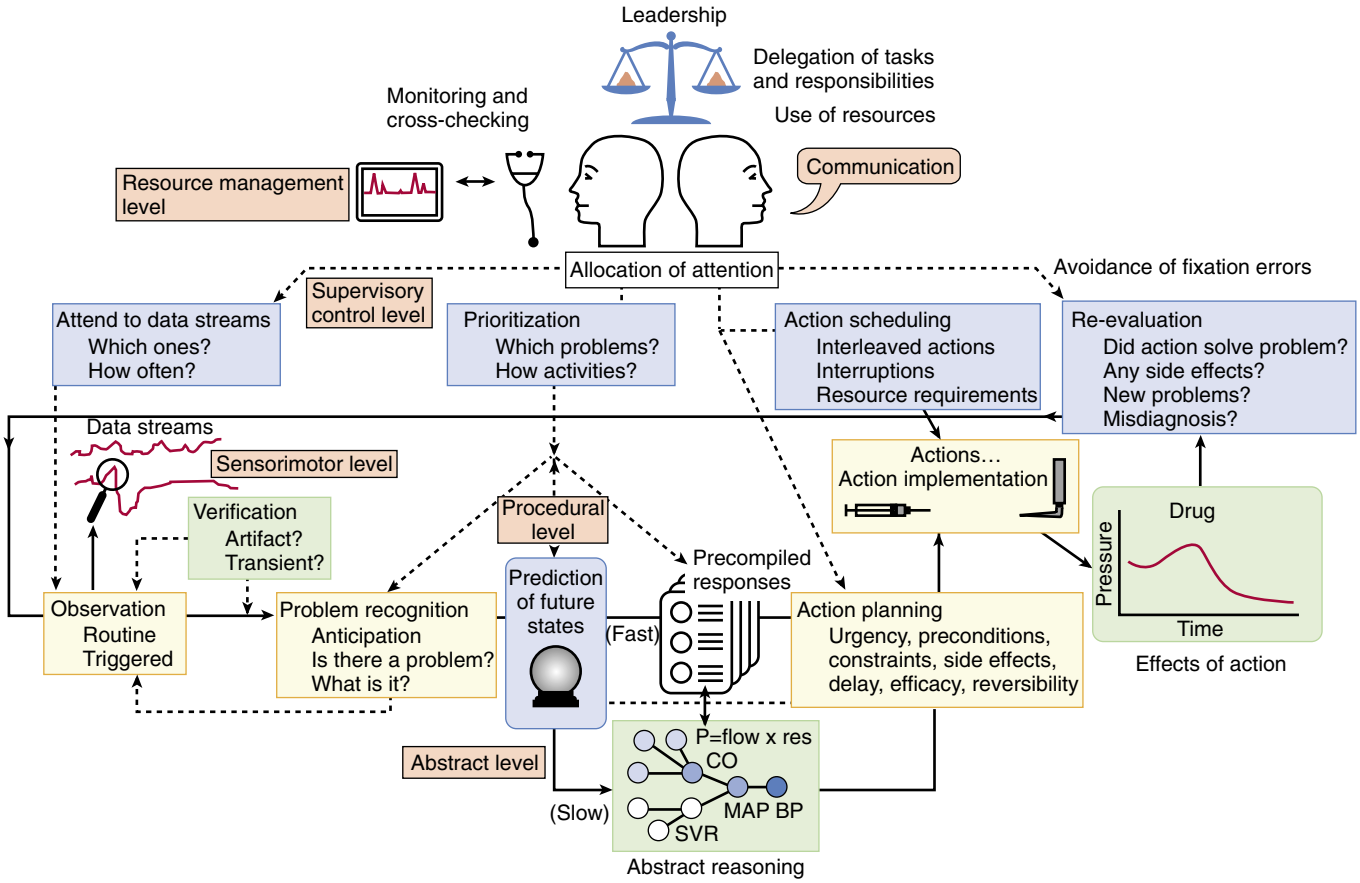

Figure 6-10 Cognitive process model of the anesthetist's real-time problem-solving behavior (see text for a detailed description). Five levels of cognition operate in parallel. The core process involves a main loop (*arrows*) of observation, decision, action, and re-evaluation. The core process is managed by two levels of metacognition that involve supervisory control, allocation of attention, and resource management (above the core process). Each component of the model requires different cognitive skills, and each component is vulnerable to a different set of performance failures or "errors." BP, blood pressure; CO, cardiac output; MAP, mean arterial pressure; SVR, systemic vascular resistance. *(From Gaba DM, Fish KJ, Howard SK: Crisis Management in Anesthesiology. New York, Churchill Livingstone, 1994.)*

Table 6-6 Levels of Mental Activity

Level of Control	Explanation	Comments
Resource management level	Command and control of all resources, including teamwork and communication	Incident analysis shows a huge contribution of lack of resource management and communication skills to the development of incidents and accidents; the importance of these factors is reflected in the ACRM principles and simulation training courses (see Chapter 7)
Supervisory control level	Metacognition: think about thinking	Dynamic adaptation of the thought process, decision-making (e.g., avoiding fixation errors), scheduling, and remembering actions (e.g., prospective memory tasks)
Abstract reasoning level	Use of fundamental medical knowledge, search for high-level analogies, deductive reasoning	Often in parallel with other levels; in emergency situations often too slow and too sensitive to distractions in high-workload situations
Procedural level	Precompiled responses, following algorithms, heuristics, "reflexes"	Recognition-primed decision-making—experts are more often on this level; special errors may occur as a result of not checking for the appropriateness of the "procedure"; less experienced may misuse this level for not-well-considered, unadapted "cookbook medicine"
Sensorimotor level	Use of all senses and manual actions; "feeling, doing, hearing"; sometimes subconscious control of actions	Experts perform smooth action sequences and control their actions by direct feedback from their senses (e.g., action sequences of placing an intravenous line or endotracheal intubation; skill-based errors such as slips and lapses may occur)

ACRM, Anesthesia Crisis Resource Management.

suction canisters and sponges, listening for normal and abnormal sounds from the patient and equipment, interpreting radiographs, and reading the reports of laboratory test results. Because the human mind can attend closely to only one or two items at a time, the anesthetist's supervisory control level must decide what information to attend to and how frequently to observe it.

The multitasking involved in observing multiple data streams was probed by experiments measuring secondary task performance and vigilance. The realistic simulation studies demonstrated the large number of information sources actually used during the response to a critical event. Routine parts of the core process operate primarily at the sensory, motor, and procedural levels and are executed repetitively throughout the course of an anesthetic regimen. Results from the University of California, San Diego (UCSD), and from the Department of Veterans Affairs and Stanford University (UCSD/VA-Stanford group) concerning the vigilance of experienced anesthetists versus novices suggested that novices had not fully developed their core process as a highly automated function and thus were required to devote more mental resources to routine activities.

Verification

In the OR environment, the available information is not always reliable. Most monitoring is noninvasive and indirect and is susceptible to artifacts (false data). Even direct clinical observations such as vision or auscultation can be ambiguous. Brief transients (true data of short duration) can occur that quickly correct themselves. To prevent them from triggering precipitous actions that may have significant side effects, critical observations must be verified before the clinician acts on them. Verification uses a variety of methods, shown in Table 6-7.

It should be noted that if in doubt, it should always be assumed that the patient is at risk and that the parameter in question is real ("rule out the worst case"). The assumption of a technical artifact should be the last step.

Knowing when and how to verify data is a good illustration of strategic knowledge (metacognition). For example, the anesthetist must decide under what conditions it is useful to invest time, attention, and energy in establishing a new information source (e.g., a pulmonary artery catheter) in the middle of a case rather than relying on more indirect information sources that are already in place.

Table 6-7 Methods for Verification of Critical Observations

Method	Explanation, Example
Repeating	The observation or measurement is repeated to rule out a temporary wrong value (e.g., motion artifacts during noninvasive blood pressure measurement)
Checking trend information	The short-term trend is observed for plausibility of the actual value. Trends of physiologic parameters almost always follow curves, not steps
Observing a redundant channel	An existing redundant channel is checked (e.g., invasive arterial pressure and cuff pressure are redundant, or heart rate from an ECG and pulse oximeter)
Correlating	Multiple related (but not redundant) variables are correlated to determine the plausibility of the parameter in question (e.g., if the ECG monitor shows a flat line and "asystole" but the invasive blood pressure curve shows waves)
Activating a new monitoring device	A new monitoring modality is installed (e.g., placing a pulmonary artery catheter). This also adds another parameter for the method of "correlating"
Recalibrating an instrument or testing its function	Checking the quality and reliability of a measurement and testing its function (e.g., if the CO_2 detector shows no values, the anesthetist can exhale through it to see whether the device works). Observation of redundant channels can also help verify a value (see above)
Replacing an instrument	If there is doubt about the function of a device, an entirely new instrument or an alternative backup device may be installed
Asking for help	If the decision on the values remains unclear, help should be sought early to obtain a second opinion from other trained personnel

ECG, electrocardiogram.

Problem Recognition

Anesthetists are taught the importance of scanning their instruments and environment, but they must use these observations to decide whether the patient's course is "on track" or whether a problem is occurring. If a problem is found, a decision must be made regarding its identity and its importance. This process of problem recognition (also known as situation assessment) is a central feature of several theories of cognition in complex, dynamic worlds.[144,250-252]

Problem recognition involves matching sets of environmental cues to patterns that are known to represent specific types of problems. Given the high uncertainty seen in anesthesia, the available information sources cannot always disclose the existence of a problem, and even if they do, they may not specify its identity or origin. Westenskow and colleagues'[253] experiment with the intelligent alarm system mainly probed these parts of problem recognition. In this experiment, subjects were already alerted to the existence of a problem by an alarm, so they could immediately focus their attention specifically on information sources concerning ventilation. In 11 cases, the fault could not be identified, but there was successful compensation for the fault, as described in the next paragraphs.

The supervisory control level mediates the decision when a clear-cut match or "diagnosis" cannot be made. Anesthetists and other dynamic decision-makers use approximation strategies to handle these ambiguous situations; psychologists term such strategies *heuristics*.[254] One heuristic is to categorize what is happening as one of several "generic" problems, each of which encompasses many different underlying conditions. Another is to gamble on a single diagnosis (frequency gambling[239]) by initially choosing the single most frequent candidate event. During preoperative planning, the anesthetist may adjust a mental "index of suspicion" for recognizing certain specific problems anticipated for that particular patient or surgical procedure. The anesthetist must also decide whether a single underlying diagnosis explains all the data or whether these data could be due to multiple causes. This decision is important because excessive attempts to refine the diagnosis

can be very costly in terms of allocation of attention. By contrast, a premature diagnosis can lead to inadequate or erroneous treatment.

The use of heuristics is typical of expert anesthetists and often results in considerable time savings in dealing with problems. However, it is a double-edged sword. Both frequency gambling and inappropriate allocation of attention solely to expected problems can seriously undermine problem solving when these gambles do not pay off if the re-evaluation component of the core process does not correct the situation.

Prediction of Future States

Problems must be assessed in terms of their significance for the future states of the patient.[144,250] Problems that are already critical or that can be predicted to evolve into critical incidents receive the highest priority. Prediction of future states also influences action planning by defining the timeframe available for required actions. Cook and colleagues[255] described "going sour" incidents in which the future state of the patient was not adequately taken into account when early manifestations of problems were apparent. It is also known from research in psychology that the human mind is not very well suited to predict future states, especially if things are changing in a nonlinear fashion. Under such circumstances, which are not uncommon for natural systems such as the human body, the rate of change is almost invariably underestimated and the people are surprised at the outcome.[43] Slow but steady and sustained blood loss in a child during surgery may result in few or subtle changes in hemodynamics for some time until rapid decompensation occurs. If the weak signs of the developing problem were not detected, the ensuing catastrophe may seem to have occurred "suddenly."

Decision-making

Having recognized a problem, how does an expert anesthetist respond? The classic paradigm of decision-making posits a careful comparison of the evidence with various causal hypotheses that can explain them.[39] This is then followed by a careful analysis of all possible actions and solutions to the problem. This approach, though powerful, is relatively slow and does not work well with ambiguous or scanty evidence. In complex, dynamic domains such as anesthesia, many problems require "decisions under uncertainty"[233,256] with quick action to prevent a rapid cascade to a catastrophic adverse outcome. For these problems, deriving a solution through formal deductive reasoning from "first principles" is too slow.

Precompiled Responses and Abstract Reasoning

In complex, dynamic domains, the initial responses of experts to the majority of events stem from precompiled rules or response plans for dealing with a recognized event.[239] This method is referred to as recognition-primed decision-making[236,257] because once the event is identified, the response is well known. In the anesthesia domain, these responses are usually acquired through personal experience alone, although there is a growing realization that critical response protocols need to be codified explicitly and taught systematically. Experienced anesthetists have been observed to rearrange, recompile, and rehearse these responses mentally based on the patient's condition, the surgical procedure, and the problems to be expected.[268] Ideally, precompiled responses to common problems are retrieved appropriately and executed rapidly. When the exact nature of the problem is not apparent, a set of generic responses appropriate to the overall situation may be invoked. For example, if a problem with ventilation is detected, the anesthetist may switch to manual ventilation at a higher F_{IO_2} while considering further diagnostic actions.

However, experiments involving screen-only[258] and realistic[109,143,259,260] simulators have demonstrated that even experienced anesthetists show great variability in their use of response procedures to critical situations. This finding led these investigators to target simulator-based training in the systematic training of responses to critical events.[109,226,261-263]

Even the ideal use of precompiled responses is destined to fail when the problem does not have the suspected cause or when it does not respond to the usual actions. Anesthesia cannot be administered purely by precompiled "cookbook" procedures. Abstract reasoning about the problem through the use of fundamental medical knowledge still takes place in parallel with precompiled responses, even when quick action must be taken. This seems to involve a search for high-level analogies[239] or true deductive reasoning using deep medical and technical knowledge and a thorough analysis of all possible solutions. Anesthetists managing simulated crises have linked their precompiled actions to abstract medical concepts.[258] It is unclear whether this represents merely self-justification as opposed to true abstract reasoning, in part because the particular simulated crises they faced did not require novel abstract solutions. At this time, the degree to which abstract reasoning is necessary for optimal intraoperative crisis management is unknown.[113,226,256]

Taking Action

A hallmark of anesthesia practice is that anesthetists do not just write orders in a patient's chart; they are directly involved in implementing the desired actions.

Although such direct involvement has many benefits in timeliness and flexibility of action, it also poses risks. Implementation of action can usurp a large amount of the anesthetist's attention and can be distracting. This is particularly an issue when other tasks have been interrupted or temporarily suspended. The "prospective memory" to complete these tasks can be erased. (For a more detailed explanation of prospective memory, see later.) In addition, anesthetists engaged in a manual procedure are strongly constrained from performing other manual tasks, as demonstrated in several of the mental workload and vigilance studies described earlier.

Errors in executing a task are termed *slips*, as distinguished from errors in deciding what to do, which are termed *mistakes*.[238] Slips are actions that do not occur as planned, such as turning the wrong switch or making a syringe swap. Thus, when critical incident[185,264] and quality assurance studies described "technical errors" in using equipment, they were referring to slips, whereas "judgment errors" referred to mistakes. One particular type of execution error, termed a *mode error*,[238] is becoming more frequent in all domains with the increased use of microprocessor-based instrumentation and devices.[227] In a mode error, actions appropriate for one mode of a device's operation are incorrect for another mode. An example in anesthesiology is the "bag/ventilator" selector valve in the anesthesia breathing circuit, which selects between two modes of ventilation. Failing to activate the ventilator when in the "ventilator mode" can be catastrophic. Mode errors can also occur with monitoring or drug delivery devices if they assign different functions to the same displays or switches depending on the mode of operation selected.

Particularly dangerous slips of execution can be addressed through the use of engineered safety devices[57] that physically prevent incorrect actions. For example, newer anesthesia machines have interlocks that physically prevent the simultaneous administration of more than one volatile anesthetic drug. Other interlocks physically prevent the selection of a gas mixture containing less than 21% O_2.

Certain very complex issues concerning human-machine interactions and the ways in which technology affects behavior in complex patient care environments are beyond the scope of this chapter. Other publications address these issues.[27,29,31-35,37,38,227,265]

Re-evaluation and Situation Awareness

To cope with the rapid changes and profound diagnostic and therapeutic uncertainties seen during anesthesia, the core process must include repetitive re-evaluation of the situation. Thus, the re-evaluation step returns the anesthetist to the observation phase of the core process, but with specific assessments in mind, as shown in Box 6-7 at CRM key point 12, "Re-evaluate repeatedly").

The process of continually updating assessment of the situation and monitoring the efficacy of chosen actions is termed *situation awareness*.[250-252,266,267] Situation awareness is a very interesting and important topic in analyzing performance and reasons for errors.[144,268,269] There has been a review of situation awareness issues in anesthesiology.[144]

Management and Coordination of the Core Process

Empirical studies have clearly demonstrated that attention sharing is needed among cognitive levels, among tasks, and often among problems. The intensive demands on the anesthetist's attention could easily swamp the available mental resources. Therefore, the anesthetist must strike a balance between acting quickly on every small perturbation (which requires a lot of attention) and adopting a more conservative "wait-and-see" attitude. This balance must be constantly shifted between these extremes as the situation changes. However, during simulated crisis situations, some practitioners showed great reluctance to switch from "business as usual" to "emergency mode" even when serious problems were detected. Erring too far in the direction of "wait and see" is an error that can be particularly catastrophic.

In addition to the attentional demands of the anesthetist's core tasks, the OR environment is full of distractions. Routine events, such as turning the OR table or repositioning the patient, distract attention from the main process of conducting the anesthesia. Noise is prevalent, with peak levels exceeding that of a freeway. Practitioners find false auditory alarms from monitors or other equipment to be extremely distracting.[279-281] Other distractions include teaching in progress,[278] incoming telephone calls, background music, and conversation with OR personnel. Expert anesthetists modulate the distractions by eliminating them when the workload is high and allowing them to occur when the workload is low (to improve morale and team building).

Active Management of Workload

One major aspect of strategic control of attention is the active management of workload. Rather than passively dealing with rising or falling workload, the anesthetist actively manages it. Schneider and Detweiler[163] and Gopher (position paper, Conference on Human Error in Anesthesia, Asilomar, CA, 1991) described the theoretical basis for a variety of strategies of workload management. These strategies have been addressed specifically for anesthesiology by several investigators.[226,228] The anesthetist actively manages workload by the following techniques.

Avoiding High-Workload Situations

Experts may choose techniques and plans that reduce the workload (especially when their individual and team resources are limited), even when those plans are marginally inferior from a technical standpoint. For example, a single anesthetist may choose not to use a high-tech, high-workload monitor such as transesophageal echocardiography (TEE) because of the high workload required to use it properly.

Distributing Workload over Time

The anesthetist can prepare for future tasks when the current load is low (preloading) and can delay or shed low-priority tasks when the workload is high (offloading). Resources that require a significant amount of workload to prepare, such as intravenous infusions, are often made ready before the case starts. Multitasking is also a way to distribute work over time. Every task is made up of several subtasks, each of which has a finite duration. Because close attention may not be required during each of these subtasks, they can be interleaved with a fixed amount of attention (multiplexing). Multiplexed tasks must be scheduled and coordinated in real time at the supervisory control level.

Distributing Workload over Personnel

When workload cannot be distributed over time and when additional resources are available, tasks can be distributed to them. Some resources are internal to the individual anesthetist, whereas others require additional personnel. For example, a single anesthetist can simultaneously ventilate the patient by hand, assess cardiac rhythm, and discuss patient care with the surgeon. A single anesthetist cannot simultaneously insert a pulmonary artery catheter and ventilate the patient's lungs by hand. If these tasks are to be performed at the same time, they must be assigned to different individuals.

Changing the Nature of the Task

The nature of a task is not fixed. Surgery and anesthesia can sometimes be postponed or aborted. Tasks can be executed to different standards of performance; as standards are loosened, the workload required to perform them is reduced. For example, during periods of massive blood loss, the anesthetist focuses primarily on administering blood and fluids and on monitoring blood pressure. In such cases, less critical tasks such as writing on the anesthesia record are offloaded to lessen the workload. The acceptable limits of blood pressure will also be widened.

Action Selection and Scheduling

At any time during an anesthetic regimen there may be multiple things to do, each of which is intrinsically appropriate, yet they cannot all be done at once. Simulator experiments have shown that anesthetists sometimes have difficulty selecting, planning, and scheduling actions optimally. The anesthetist must consider the following factors:

1. Preconditions are necessary for carrying out the actions (e.g., it is impossible to measure a thermodilution cardiac output if there is no pulmonary artery catheter in place).
2. Constraints are placed on the proposed actions (some actions are incompatible with other aspects of the situation; e.g., it is impossible to check the diameter of the pupils when the head is fully draped in the surgical field).
3. Side effects of the proposed actions often play a controlling role in choosing among possible drug therapies.
4. The rapidity and ease of implementation of proposed actions are factors; those that are easily and rapidly performed are preferred over those that require more time, attention, and skill.
5. Certainty of success of the actions is often traded off against rapidity and ease of implementation (under some circumstances, the higher certainty of success of a set of actions justifies the investment of time, attention, and resources needed to implement them).
6. Reversibility of the action and the cost of being wrong are considered, with rapidly reversible actions preferred over those that cannot be reversed, especially when potential side effects are significant.
7. Cost of the action in terms of attention, resources, and money is taken into account.

Experts in other complex, dynamic domains (specifically tank commanders and fire chiefs) have been observed[282] to conduct a mental simulation of the actions that they are contemplating to determine whether there are hidden flaws in their plans. Anesthetists have been observed[228] to rehearse a plan mentally in advance of a case, but the degree to which this is done in real time is not known. Because most actions can be executed incrementally, as in titrating a drug in small aliquots, adverse consequences can often be discovered through repetitive re-evaluation.

Resource Management

The ability of the anesthetist to command and control all the resources at hand to execute the anesthetic regimen as planned and to respond to problems that arise is termed *resource management* (another concept first described in aviation that applies equally well to anesthesiology; see the earlier section on CRM key points). Resource management involves translating the knowledge of what needs to be done into effective team activity by taking into account the limitations of the complex and ill-structured OR, PACU, or ICU domain. Resource management explicitly requires teamwork and crew coordination. It is not enough for the anesthetist to know what to do or even to be able to do each task alone. The anesthetist can accomplish only so much in a given time, and there are some tasks that can be performed only by other skilled personnel (e.g., laboratory tests, taking radiographs). When the task load exceeds the resources available, the anesthetist must mobilize help and distribute the tasks among those present. Many issues concerning optimum resource management and crew coordination are not yet well understood and are the focus of active research by cognitive scientists and experts in many complex and dynamic domains.[24,115-117,283-285] Research in aviation has already demonstrated that a large proportion of aircraft accidents are linked to failures on the part of crews with appropriate technical skills to manage the flight deck effectively.[186] The hallmarks of resource management derived from these studies are discussed in detail in the earlier section on CRM key points.

Dynamic Prioritization of Tasks

Complex multiple personnel simulations of anesthetic crises have been used to address the issue of resource management. Although the data from these simulations are still preliminary, it appears that poor supervisory control and resource management were substantial components of suboptimal management of the simulated crises.[260] In other words, like the pilots, anesthetists had the knowledge and technical skill to manage the patient, but they failed to manage their environment properly to achieve success (hence termed CRM skills or nontechnical skills). (In aviation, such situations have often resulted in what is called "controlled flight into terrain.")

Prospective Memory

Prospective memory describes one's ability to remember in the future to perform an action.[270] It is particularly prone to disruption by concurrent tasks or interruptions. Disruption of intentions or on-going tasks is common in everyday life and has also been described in pilots and air traffic controllers.[271-275] In anesthesia, for example, if the anesthetist suspends ventilation temporarily (say to allow a radiograph to be taken), the intention to restart the ventilator depends on prospective memory and can be easily forgotten. Chisholm and associates performed a study in an emergency department and looked for "interruptions" and "breaks in task." They found that during a 3-hour period, the emergency physician was faced with more than 30 interruptions and more than 20 breaks in task. It is likely that similar results would be found in the ICU.[276]

A variety of methods may preserve prospective memory of intentions. Visual or auditory reminders can be used (physiologic monitor alarms often serve this purpose whether intended or not), although the effectiveness of such methods seems to be less than one would expect. Special actions—such as leaving one's finger on the ventilator switch—can be used to indicate that an important intention is pending.

Fixation Errors

Faulty re-evaluation, inadequate adaptation of the plan, or loss of situation awareness can result in a type of human error termed a *fixation error*.[131,132] Fixation errors have been described by all the investigators conducting experimental studies of responses of anesthetists to abnormal situations.[259,260,277] Avoiding fixation errors in the field of anesthesia is CRM key point 9 and is covered in the section on CRM key points.

Hazardous Attitudes

Attitudes are an important component of ability that can affect performance as strongly as physiologic performance-shaping factors can. Psychologists studying judgment in aviators have identified five types of attitude as being particularly hazardous, and they have developed specific antidote thoughts for each hazardous attitude.[195] These attitudes as related to anesthesia are shown in Table 6-8. Aviation psychologists instruct pilots to

Table 6-8 Examples of Hazardous Attitudes and Their Antidote Thoughts

Hazardous Attitude	Antidote Thoughts
Antiauthority: "Don't tell me what to do. The policies are for someone else."	"Follow the rules. They are usually right.
Impulsivity: "Do something quickly—anything!"	"Not so fast. Think first."
Invulnerability: "It won't happen to me. It's just a routine case."	"It *could* happen to me. Serious problems can develop even in routine cases."
Macho: "I'll show you I can do it. I can intubate the trachea of anyone."	"Taking chances is foolish. Plan for failure."
Resignation: "What's the use? It's out of my hands. It's up to the surgeon."	"I'm not helpless. I can make a difference. There is always something else to try that might help."

physically verbalize the antidote thought whenever they find themselves thinking in a hazardous way.

The *invulnerable* and *macho* attitudes are particularly hazardous for anesthetists. They are compounded by production pressures to handle more cases in less time with fewer cancellations and less opportunity for preoperative evaluation. The feeling that a catastrophe "cannot happen to me" and that perfect performance can always be called on to avert a disaster can lead to cavalier behavior and poor planning. It can alter thresholds for believing that abnormal data represent a problem, thereby leading to the fixation error of "everything's OK." In 1984, Cooper[278] wrote the following about studies of critical incidents in anesthesia:

> *Perhaps the most insidious hazard of anesthesia is its relative safety. The individual anesthetist rarely, on average, will be responsible for a serious iatrogenic complication. It is our impression from the process of collecting incidents, that most seemingly minor errors are not taken seriously and that risk management depends almost solely on the anesthetist's ability to react instinctively and flawlessly every time a problem arises.*

Expert human performance is the anesthetist's most powerful tool to safeguard the patient. However, planning to avoid catastrophe is likely to be more successful than battling to avert it.

The Anesthetist's Tasks

Investigation of a complex work environment typically starts with task analysis (reviews of this technique were published in the journal *Human Factors*[286]). One can perform an abstract analysis of the work goals and constraints and then derive the tasks required to achieve the goals. Alternatively, one can observe what skilled practitioners actually do in their work and classify these actions into task elements. Often the techniques are combined. In this section the anesthetist's tasks are examined in the abstract and then the empirical task analysis approach is reviewed. There are two distinct phases of anesthetic care: (1) preoperative evaluation, planning, and preparation and (2) conduct of the anesthetic regimen and immediate postoperative care.

Preoperative Evaluation and Planning

There are few data on how well anesthetists identify important patient conditions through history taking and physical examination (see Chapter 34). A frequent organizational obstacle to the anesthetist's evaluation task is difficulty obtaining the patient's previous medical records. The performance of anesthetists in selecting appropriate laboratory tests has been found to be relatively poor. Roizen and associates[287] state the following:

> *Even when physicians agree to reduce testing by using specific, agreed upon criteria for selectively ordering tests based on history and physical examination, they still make a surprising number of mistakes when ordering tests. Approximately 30% to 40% of patients who should have certain tests do not get them, and 20% to 40% of patients who should not have tests are subjected to them.*

Roizen has argued for automation of routine patient questioning and selection of laboratory tests and has participated in the development of commercial devices to do so. Whether these devices, in combination with human follow-up for patients with medical problems, will improve the efficiency and accuracy of preoperative evaluation remains to be determined. The performance of anesthetists in interpreting ECGs and chest radiographs also appears to be poor relative to specialists in these fields. The extent to which this factor influences the design of anesthetic plans or patient outcomes is unknown.

Anesthetic Plan

In constructing the plan, the anesthetist uses the preoperative evaluation of the patient to match the technical requirements of the surgical procedure and the physiologic characteristics of the patient to the mental, physical, and technologic resources available. A typical anesthetic plan contains several elements. For example, the plan for general anesthesia includes choices for the means of inducing anesthesia, securing the airway and ensuring proper ventilation, maintaining anesthesia, conducting emergence from anesthesia, and controlling postoperative pain. Skilled planning is as critical as skilled execution in safe patient care. If a significant feature of the situation is missed in formulating the plan, it can leave the patient vulnerable, regardless of how adeptly the plan is implemented.

The technical requirements of most surgical procedures are well known. Most patients do not have medical problems that could significantly alter the anesthetic plan, although Gibby and associates[288] found that 20% of outpatients, most of them with ASA physical status 1 or 2, had conditions identifiable through an anesthetist's history and examination that required changes from a "standard" anesthetic plan. When a procedure is new or challenging, when the patient has significant underlying disease, or when needed resources are not available, creative planning may be needed to identify a set of physiologic goals for the anesthetic regimen. Routine anesthetic plans can be modified or com-

bined to produce a compromise plan that best fits the goals and constraints of the situation.

Although faculty anesthetists routinely critique the anesthetic plans of residents and planning is explicitly probed during the oral examination of the American Board of Anesthesiologists, the process of constructing anesthetic plans has been studied very little. Most of the existing literature on preoperative planning concentrates only on the medical and physiologic aspects of underlying diseases and their anesthetic ramifications.

Pre-use Preparation and Checkout of Equipment

After the plan is established, the anesthetist must prepare the work environment. This involves obtaining the necessary equipment and supplies, assembling infusions, preparing syringes of needed drugs, and conducting pre-use checkouts of life support equipment (see Chapter 38). The performance of anesthetists at these tasks is not optimal. Buffington and coworkers[289] demonstrated that only 3% of anesthetists examining an anesthesia machine could identify all five faults with which it had been rigged; most practitioners found only two of the five. Nearly 30% missed such major faults as complete absence of both unidirectional valve disks in a circle anesthesia breathing system and swap of the nitrous oxide and oxygen cylinders (made possible by a fault in the pin-indexing system).

The Food and Drug Administration (FDA), in cooperation with the ASA, the APSF, and experts from academics and industry, developed a set of recommendations for the checkout of anesthesia apparatus.[290] This checklist was widely disseminated by the ASA and the APSF. However, it was found that use of the checkout procedure was minimal and that the extent of pre-use checkout by practitioners was extremely variable. A newer study[291] was conducted to compare the checkout of anesthesia machines by practitioners with and without use of the FDA checkout procedure. Most of the faults were detected by 50% or fewer participants, regardless of the checkout procedure used. Only for one fault, failure of the oxygen–nitrous oxide ratio protection system, did the FDA checklist offer significant advantages; when using it, the detection rate increased to 65%. Interestingly, 34% of the faults that were not detected were missed by practitioners who had in fact correctly answered three out of three written test questions concerning that fault. This suggests that although some of the performance deficit may be related to lack of knowledge, a substantial proportion are due to the inability to apply abstract knowledge to the practical performance of equipment checkout.

There were many criticisms of the original checklist, particularly its complexity.[292] A streamlined version of the original checklist was published by the FDA in 1994.[293] A study of the new checklist, however, showed no significant benefit from its use and a disturbingly low rate of detection of machine faults (around 50%).[294] In another study, anesthetists using a highly interactive electronic checklist (developed by Blike and Biddle) improved their detection of "easy faults" but still missed a high proportion of difficult faults.[295] A study performed more recently to measure the influence of fatigue on performance in a simulator showed that subjects in both the rested and fatigued conditions left out significant portions of the machine checkout.[178]

Emergency Checklists

One aspect of preparedness is to consider possible emergencies and to mentally rehearse their management. Another approach is the readiness and ability to use critical incident checklists. For example, the Veterans Health Administration has placed a set of emergency checklists on plastic laminated sheets in every OR of 105 hospitals (Fig. 6-11 and Box 6-10 for an example of "anaphylaxis"). Other emergency checklists have been made available electronically.[296,297] Despite these advances, the use of emergency checklists has still not become a regular part of the culture of medical work.

Execution and Adaptation of Plans

Anesthetic plans are dynamic. The anesthetist must monitor the plan as it is executed and must adapt it in response to dynamically changing events. The key features of this task are (1) checking for the achievement of milestones and (2) reactive plan adaptation. These are shown schematically in Figure 6-12. At various points of a procedure there are critical milestones that must be achieved to keep the original plan unaltered. If a milestone is not achieved, the anesthetist must decide whether to delay the next action in the sequence, modify the plan, or suspend or abort the procedure. On some occasions, the milestones are explicitly identified in advance, whereas in others the milestones are implicit.

The anesthetist must also react to a large number of other contingencies, some of which can be predicted in advance based

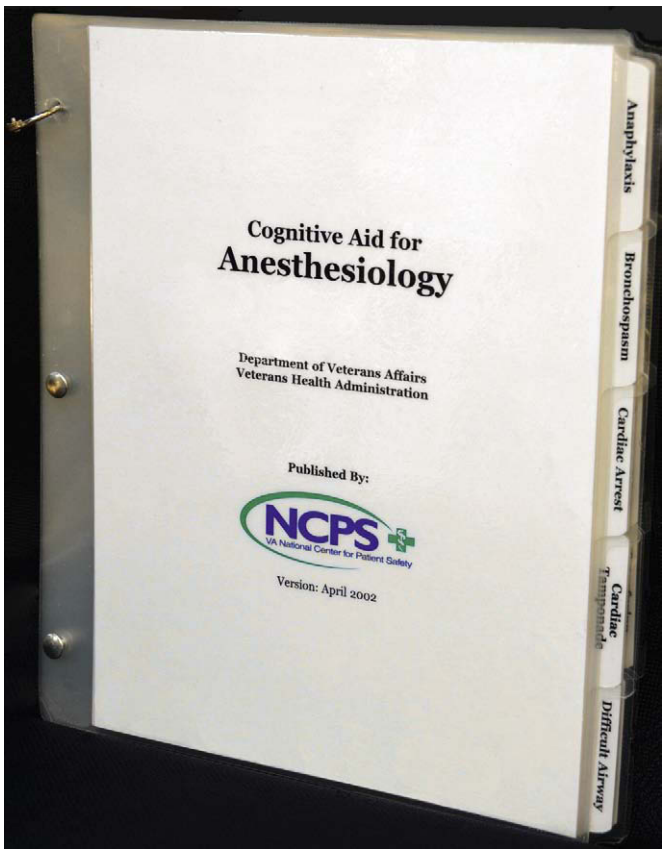

Figure 6-11 Department of Veterans Affairs checklist by NCPS. An example of the cognitive aid is given by Anaphylaxis in Box 6-10.

Box 6-10 VA NCPS Checklist Example (Anaphylaxis)

MANIFESTATIONS

Cardiac

- Hypotension (may be the only sign of anaphylaxis in an anesthetized patient)
- Cardiovascular collapse
- Pulmonary hypertension
- Arrhythmias/tachycardia

Respiratory

- Bronchospasm
- Increased peak inspiratory pressure (high PIP)
- Hypoxemia
- Pulmonary edema
- Stridor, laryngeal edema

Cutaneous

- Rash, flush, hives, angioedema
- In an awake patient, signs and symptoms include
  - Dizziness, decreased level of consciousness, dyspnea and/or chest tightness, pruritus

IMMEDIATE ACTION

- Stop administration of any possible antigen (e.g., antibiotics, muscle relaxants, blood) (transfusion reaction)
- In the absence of any other likely cause, consider *latex allergy*
  - Remove all latex products in contact with the patient
    - Surgical gloves
    - Medications drawn up through a latex stopper
    - Urinary catheter
- Maintain the patient's airway and support oxygenation and ventilation
  - Increase F_{IO_2} to 100%
- Intubate early if the allergic reaction is severe
  - The airway and larynx can become very edematous
- Inform the surgeons
  - Consider terminating the surgical procedure
- Expand circulating fluid volume; ensure adequate intravenous access
  - Immediate fluid needs may be massive (many liters of crystalloid)
- Administer epinephrine intravenously
  - Epinephrine is the drug of choice for the treatment of severe anaphylaxis
    - For hypotension or bronchospasm, 10- to 50-∝g increments; repeat as necessary with escalating doses
    - For cardiovascular collapse, use ACLS doses, 500- to 1000-∝g boluses; repeat as necessary with escalating doses
- Treat bronchospasm if present
  - Administer inhaled bronchodilators
    - Albuterol: initial dose, 4 to 8 metered puffs
    - Depending on the delivery system, a larger dose of any aerosolized medication may be required when administered via the endotracheal tube

ACLS, advanced cardiac life support.

on the patient's history and the type of surgery, whereas others cannot be anticipated. Incoming data streams must be constantly scrutinized (see the "police cars" in Fig. 6-12) to determine whether an expected or unexpected contingency is occurring. If so, the existing plan may have to be modified. As plans are changed, actions may be taken that invalidate other aspects of the previous plan, thereby requiring further adaptation of the plan. In some cases, even the original goals of the anesthetic plan may need to be adapted.

Frequency of Events Requiring Active Intervention by the Anesthetist

The preceding analysis of Figure 6-12 suggests that anesthetists must be prepared to react dynamically to changing events. How frequent is this requirement? In the Multicenter Study of General Anesthesia,[298] 86% of patients had at least one undesirable outcome. Although most events were minor and caused no injury to the patient, more than 5% of patients had one or more severe events requiring "significant therapy, with or without full recovery." This incidence is probably a lower limit for severe events because the entry criteria of the study precluded the enrollment of critically ill patients or emergency surgeries, for which the likelihood of severe problems requiring intervention would be expected to be high.

In another study by Cooper and associates,[299] impact events, defined as "undesirable, unexpected, and which could cause at least moderate morbidity," occurred in 18% of patients either in the OR or in the PACU, and 3% of all cases involved a "serious" event. These figures are also probably lower limits because for technical reasons the study excluded patients going directly from surgery to an ICU.

Moller and coauthors[300] reported 4439 "impact events" in 10,312 patients either in the OR (2441) or in the PACU (1998). Here again, some patients had several events, whereas others had none. The investigators did not compute the frequency of severe events, but overall, these data appear to be consistent with those from earlier studies.

Model of Event Evolution

The findings just discussed, as well as the larger system issues raised by Reason and Perrow, can be summarized in a model of event evolution (Fig. 6-13).[58,113,226]

Similar models incorporating some of the same features have also been described.[59,301] Underlying aspects of the system can gen-

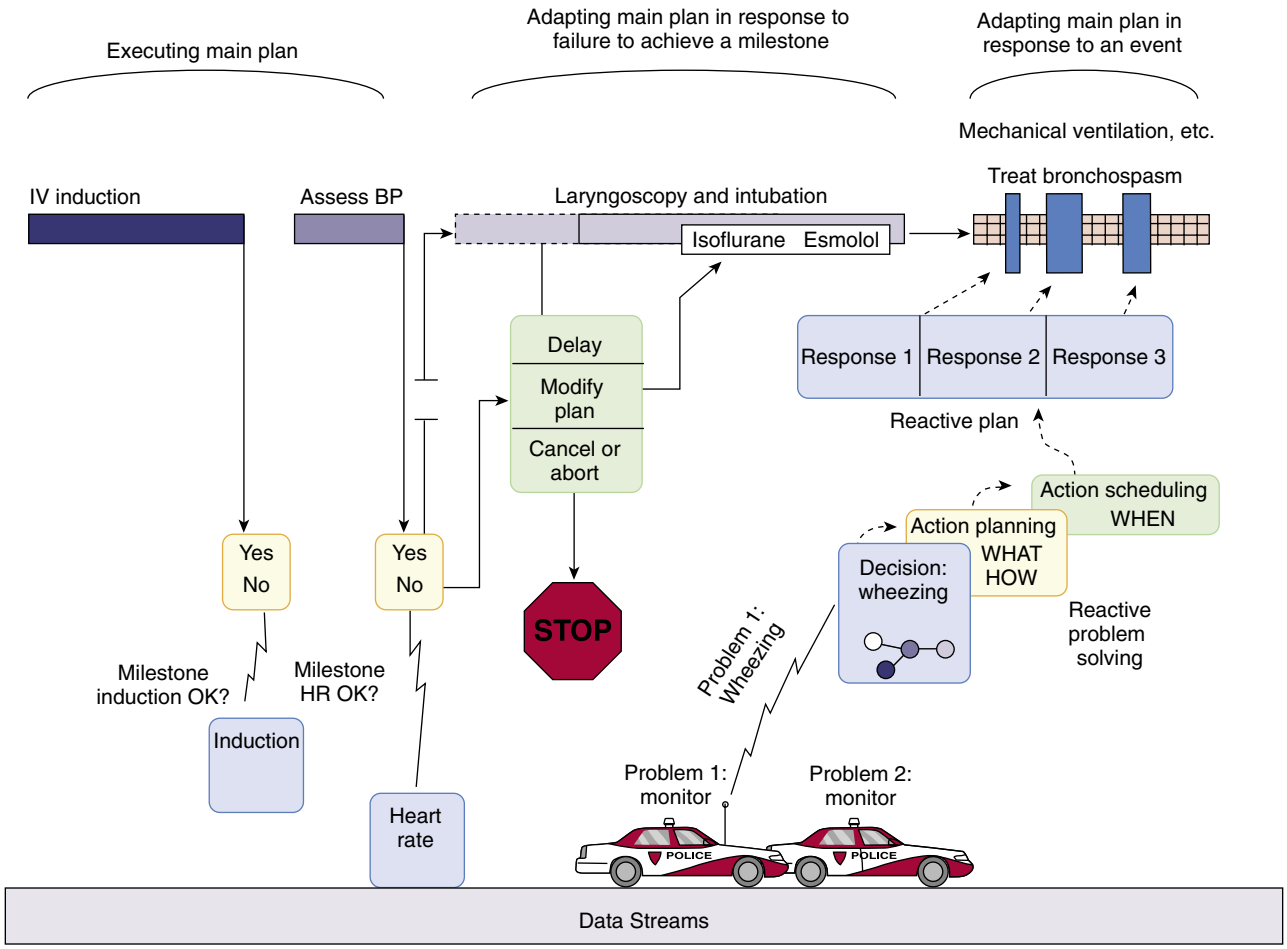

Figure 6-12 Schematic diagram of the dynamic adaptation of preoperative plans. The anesthetist begins with intravenous (IV) induction of anesthesia as planned (*top left*). On achieving the milestone of successful induction of anesthesia, blood pressure (BP) is checked before proceeding with laryngoscopy and intubation (*center*). If BP is not satisfactory, the next step may be delayed and the plan amended to optimize BP. If necessary, the procedure may even be aborted at this stage. Throughout the procedure, the anesthetist is vigilant for the occurrence of new problems ("police cars"). If a problem is detected, a process of reactive problem solving takes place, which may result in new adaptations to the plan (in this case, treatment of bronchospasm). *(From Gaba DM: Human Error in Dynamic Medical Environments. Hillsdale, NJ, Lawrence Erlbaum, 1994, pp 197-224.)*

erate latent failures. Either by random chance or because of interactions between the latent failures, an event may be triggered by one of four components of the operational system in the OR: the anesthetist, the surgeon, the patient, or the equipment. Anesthetists have traditionally been most interested in events that they trigger themselves (such as esophageal intubation), but in fact, most events are initiated by a combination of underlying patient disease and another of the triggering factors. Most problems are not directly harmful to the patient unless they evolve further. Possibilities for evolution of the problem include the following:

1. A single problem worsens and by itself evolves into an adverse outcome.
2. The problem begins to evolve but remains self-limited without any intervention.
3. Multiple small problems combine to trigger a problem that can evolve into an adverse outcome; the original problems by themselves would not have evolved further.
4. A single problem triggers another problem that evolves into an adverse outcome.
5. An evolving problem should be able to be stopped, but the recovery pathway is faulty.
6. Two problems are triggered. Attention focused on one (minor) problem distracts attention from the (serious) evolution of another.

The system has a variety of interruption points at which the occurrence of problems can be prevented (preoperative evaluation of patients and pre-use checkout of equipment). Moreover, although anesthesiology is far more dynamic than many medical domains, it is relatively slow in comparison to many human activities such as sports, driving, and combat flying. Thus, events often evolve slowly enough that the process of accident evolution can be thwarted before an adverse patient outcome actually occurs. The interruption of accident evolution corresponds to the "defense-in-depth" in Reason's "Swiss cheese" model[70] and to recovery from a normal accident in Perrow's paradigm (see Figs. 6-2 and 6-3 and the overview on NAT in Table 6-2).

In the prospective studies of intraoperative events cited earlier, there was a surprisingly high incidence of undesirable situations, whereas the rate of actual patient harm was quite low. The patient's safety was frequently protected only by the skilled intervention of a trained anesthetist. Note that this is a markedly different picture from that in commercial aviation, although the

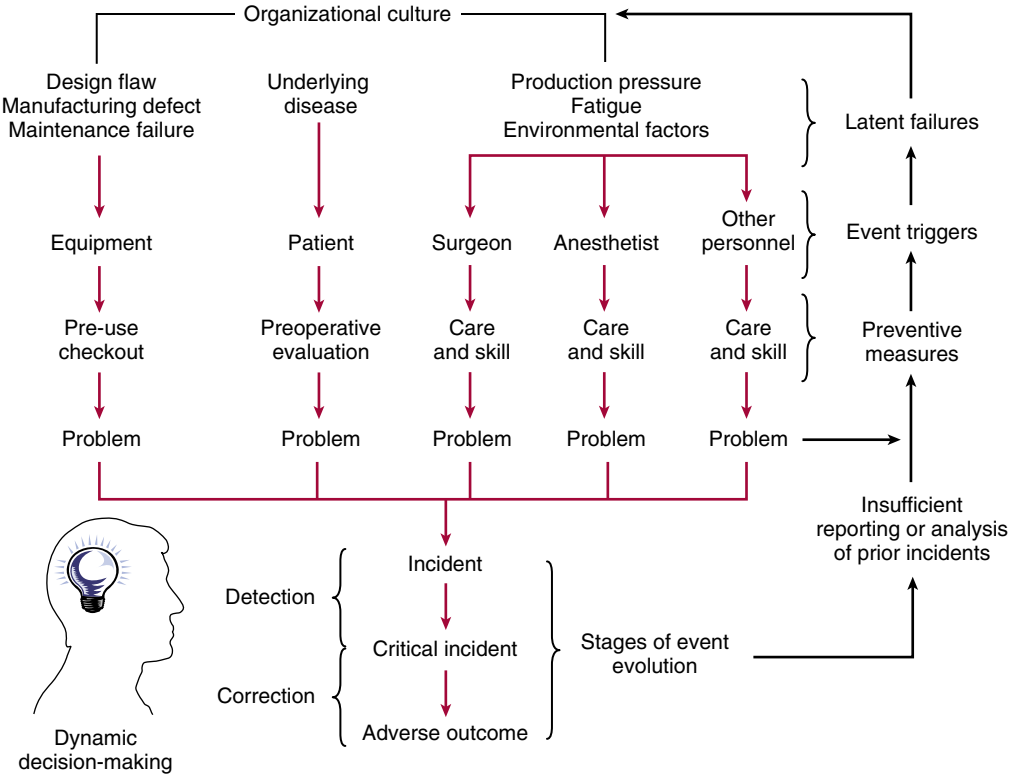

Figure 6-13 Chain of accident evolution in anesthesia. As in Reason's model, underlying latent failures (and the organizational culture) predispose to triggering of an accident sequence by equipment, the patient, the surgeon, the anesthesiologist, and other personnel. This sequence can be prevented by prophylactic measures such as preoperative evaluation and treatment of patient diseases or pre-use checkout of life support equipment. Once a problem occurs, it may remain self-limited or evolve further down the accident chain. Using dynamic decision-making, the anesthetist must detect and correct the problems that do occur at the earliest possible point in the chain of evolution. Interruption of the accident chain is made more difficult when there is tight coupling within the system, when multiple interacting problems are present, or when problems disrupt recovery processes. Efficient use of incident analysis may make it easier in the future to prevent or interrupt problem evolution. *(Redrawn with modification from Gaba DM, Fish KJ, Howard SK: Crisis Management in Anesthesiology. New York, Churchill Livingstone, 1994.)*

accident rate in aviation is very low. About 30,000 airline flights take place each day in the United States, and there are very few serious incidents or accidents, although the exact number is unknown. The total accident rate from all causes (not counting terrorist acts) for major airline flights between 1982 and 2001 was 0.38 per 100,000 departures. Air carrier accidents with one or more fatalities occurred at a rate of 0.045 per 100,000 departures. In 2002 there were no fatalities in U.S. airline or commuter aviation (NTSB website: www.ntsb.gov/aviation/Stats.htm).

The actual number of events in aviation matching the "impact event" criteria given earlier is not known, but it is probably at least 100 times greater than the number of accidents. Even so, this still makes aviation incidents far less frequent than the 3% to 5% rate of "significant" impact events in anesthesia. Based on these data, it is clear that the intraoperative management of abnormal, dynamically changing events remains the critical locus of anesthesia skill.

Empirical Studies of Anesthetists' Tasks

Over the past 20 years there have been a number of studies[31,35-38,40,178,198,235,302-305] of anesthetists' intraoperative activities. In addition, an increasing number of studies have been performed in realistic simulator environments.[2,19,184,306-319]

The earliest studies used time-lapse photography of a handful of anesthetic cases with a frame-by-frame analysis of tasks. One major finding of the first task analysis, by Drui and associates in 1973,[320] was that "the anesthesiologist's attention was often directed away from the patient-surgical field." In subsequent studies,[241-243] it was found that about 40% to 50% of the time the anesthetist's gaze was directed away from the patient or surgical field. McDonald and Dzwonczyk,[242] studying cases from 1981, classified direct patient activity as "one during which the anesthetist had contact with the patient and a view of the surgical field." These investigators explicitly noted "observation of skin color," "palpation of pulse," and "auscultation of heart and breath sounds" as direct patient activities. Observing arterial pressure or the ECG and observing or adjusting the anesthesia machine or intravenous infusions were classified as indirect patient activities. In this study 83% of the anesthetist's time was spent on activities that were not direct patient activities. The same group[243] repeated its study for cases from 1985 and demonstrated a much higher rate of direct patient monitoring than obtained in 1981 (44.8% versus 16.8%). This group attributed the difference to the change from manual ventilation in 1981, which took up much of the anesthetist's visual attention, to the use of mechanical ventilators in 1985, which freed the anesthetist to watch the patient.

It is true that looking at the patient and at the surgical field is a hallmark of an excellent clinician. Opponents of technology

decry the degree to which monitors and therapeutic devices distract the anesthetist's gaze from the patient. However, an important distinction has to be made between the anesthetist's attention, which surely must be directed to the patient's needs, and the anesthetist's gaze, which in fact may best serve the patient by being directed elsewhere. Many of the tasks cited in the study by McDonald and Dzwonczyk[243] were highly related to management of the patient, even though they did not involve direct visualization of or contact with the patient. The critical question, which task analysis by itself cannot answer, is when anesthetists gaze at the surgical field, how often are they gathering information, and how often are they just "watching the scenery"? Put more generally, what is the information content of the various observations being made and what is their relationship to action tasks and to the goals of conducting a safe anesthetic regimen?

Intriguingly, Drui and associates[320] had asked physicians who were helping code their films, "What information, if any, do you gain from the direct performance of this activity?" However, these investigators never described what information was available from each activity, although they seem to have assumed that turning the anesthesiologist's gaze away from the patient and surgical field was bad. Boquet and coworkers[241] not only studied the gaze of anesthetists (using a sophisticated eye-tracking system) but also asked consultant anesthetists to grade the importance of different visual targets and manual tasks. "The patient" was assigned the maximal importance on the scale. However, "the surgical field," which occupied 25% of the anesthetist's time, was apparently not listed by the consultants. Perhaps, in their minds, the surgical field was lumped together with the patient.

Another key finding of the study by Drui and coworkers[320] was that 40% of the anesthetist's time was coded as "idle," meaning that no obvious task was seen on that frame of film. In 1988, McDonald and Dzwonczyk[242] stated that this and other "studies showed that the anaesthetist spends most time performing tasks that are either secondary or unrelated to patient care." However, in their original article, Drui and associates[320] correctly recognized that absence of visually apparent activity did not mean that the anesthetist was truly idle; in fact, they hypothesized that this time was used by anesthetists to make the decisions on which the observable tasks were based.

The most detailed task analyses have taken place in a series of studies[198,235,244,245,304,321] carried out by the UCSD/VA-Stanford group. These analyses have used progressively more task categories (11 to 28 to 32) to analyze the activities of novice and experienced anesthetists in day surgery cases and the activities of senior residents during cardiac surgery. The studies have shown that a small number of tasks, repeated frequently, occupy the majority of case time. In one study, four tasks (observing monitors, recording, conversing with attending staff [for novice residents], and adjusting monitors) accounted for 50.1% of the total case time. Specific activities such as airway management (e.g., bag ventilation, laryngoscopy) occurred in brief, but intense clusters (Fig. 6-14). Given the larger number of task categories, the anesthetist was rarely seen to be idle.

Studies by this group have attempted to determine whether there is a difference between the task patterns of novice versus experienced anesthetists. Confirming a priori expectations, the investigators found that novices perform many of the same tasks as experienced personnel do at specific phases of an anesthetic regimen; however, the novices had a longer dwell time, on average, for each task. These studies also showed that experienced providers had lower heterogeneity of tasks and greater efficiency of tasks per unit time.[322]

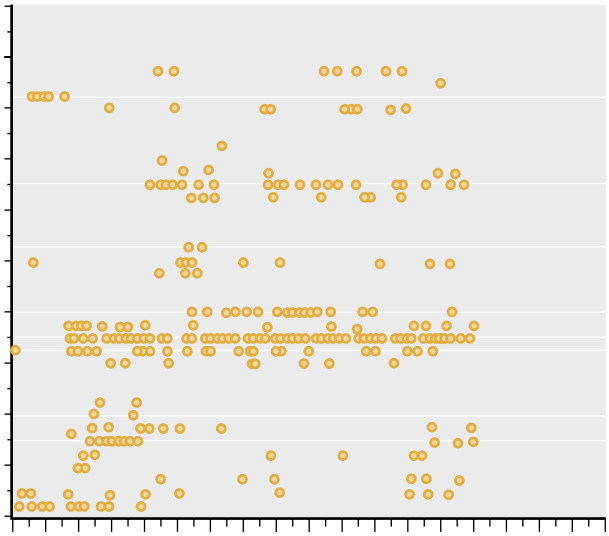

Figure 6-14 Distribution of the anesthetist's tasks during an actual ambulatory surgery procedure. The anesthetist was directly observed by an investigator who recorded a code number for each task as it was performed (there were 28 task codes). Certain tasks, such as bag ventilation, were clustered in specific phases of the case, whereas others, such as observing monitors, were repeated frequently throughout the procedure.

Of note (but also not unexpected), novice residents spent more time speaking to their attending staff (11% of preintubation time) than experienced residents or CRNAs did. Of interest, experienced personnel observed the surgical field more than the novices did. The implications of this finding are not clear. Novices did take longer to complete patient preparation and induction of anesthesia, but it appeared that some of the extra time taken by novices working under supervision was offset by the efficiency of offloading other concurrent tasks to the attending anesthesiologist such that preintubation time was increased by only 6 minutes for novices.[322] This group also reported that as the density of tasks per unit time increased, the dwell time on each task decreased, and vice versa. This finding has important implications for how anesthetists allocate their attention (see "Management and Coordination of the Core Process").

Task Analysis and Action Density

An interdisciplinary research group consisting of the Work and Organisational Psychology Department of the Swiss Federal Institute of Technology in Zurich and the Center for Patient Safety and Simulation of the Department of Anaesthesiology of the University of Tübingen performed several task analysis studies using the Flexible Interface Technique (FIT) system[323] (Fig. 6-15), which facilitates analysis of multiple parallel and overlapping actions.[246] The group produced a set of 41 observation codes—representing a single action (Table 6-9). Because the method allowed true capture of overlapping actions, it was possible to describe a valid task density in the analysis of anesthetists' action sequences.

Figures 6-16 and 6-17 show examples of observations of 24 real OR studies. The observation data contain many short-term fluctuations (dots); the moving average of action density of the previous 5 minutes was charted as well (line). Figure 6-16 shows a complete anesthesia procedure with obvious increases in action

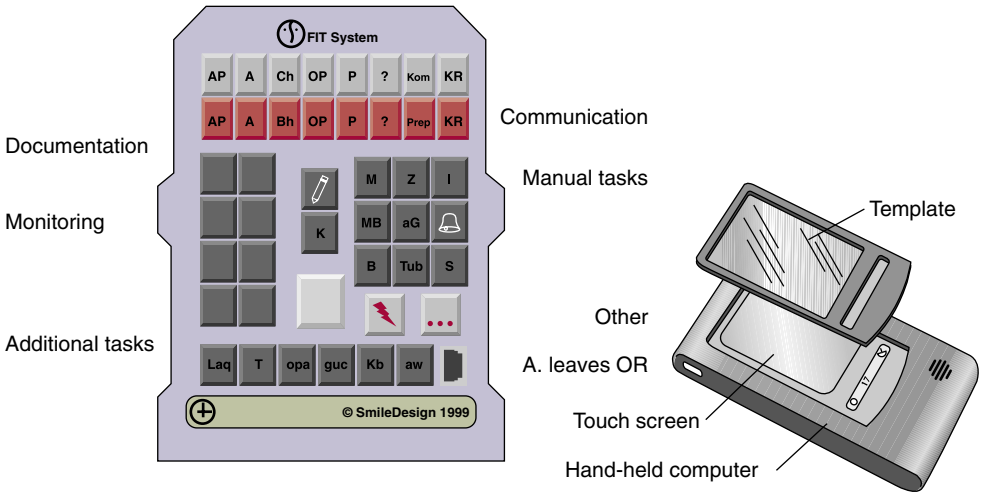

Figure 6-15 Flexible Interface Technique system. The system allows easy reorganization of task analysis items and categories and can properly resolve overlapping actions. OR, operating room.

density during induction and emergence from anesthesia. Figure 6-17 shows two final phases of cardiac cases involving cardiopulmonary bypass. The described task analysis technique was also used successfully by the Tübingen group to study action sequences in a simulator and compare them with findings in the real OR to demonstrate and evaluate the ecologic validity of simulators (see Chapter 7).

Automation

Early task analyses identified repetitive tasks that did not appear to offer substantial information content or therapeutic benefit as candidates for automation. Drui and associates[320] identified filling out anesthesia records, measuring blood pressure, and adjusting intravenous infusions. Kennedy and colleagues[324] identified data display and trend plotting. Many of these tasks have in fact been automated in the past 20 years. Loeb,[325] from University of California, Davis (UCD) showed that anesthesiologists typically observed monitors for about 1 to 2 seconds every 10 to 20 seconds and that it usually took several observing cycles before they detected a subtle cue on the monitor. Gurushanthaiah and coworkers[326] studied the effect of more sophisticated display modalities on detection of signals by anesthesiologists and found that histogram and polygon formats improved response latency in the laboratory setting over formats using raw numbers only. However, the applicability of these laboratory finding to the more complex signal detection that must occur in the midst of patient care is uncertain. Incidentally, the experience in the field of aviation suggests that automation of both monitoring and therapeutic devices produces its own problems in human-machine interactions and may well be a causative or contributing factor in some adverse anesthetic events. Some of the same types of automation-related adverse events seen in aviation are now being observed in anesthesiology.[227]

The impact of automation on task distribution is uncertain. The change to mechanical ventilation did affect the analyses of McDonald and Dzwonczyk,[242] as detailed earlier. A study by Allard and coworkers[327] showed no reduction in time spent recording when automated record-keeping devices were used. However, the UCSD/VA-Stanford collaboration published data demonstrating a 20% reduction in the time spent record keeping when automated record keeping was in use during cardiac anesthesia.[322] There was a slight, but not significant increase in time spent on direct patient care activities when electronic record keeping was in use. There is no clear evidence that electronic record keeping will yield a marked enhancement of the anesthetist's ability to perform other patient care tasks, although automated record keeping may yield other benefits. The UCD and UCSD/VA-Stanford groups demonstrated that electronic automated record keeping does not significantly reduce the vigilance of anesthetists.[328,329]

Table 6-9 Observation Codes Used to Classify Tasks and Actions

Task Group	Actions
Monitoring	Read patient record, observe patient, observe patient monitors, observe anesthesia machine, observe intravenous drip, observe syringe pumps, measurement, scan area
Measures	Placing IV, give drugs, adjust IV, mask ventilation, intubation/extubation, adjust anesthesia machine, use of other equipment, quitting alarms, suctioning
Communication	(1) Active conversation with nurse anesthetist, attending anesthetist, surgeon, OR nurse, patient, others; (2) responsive conversation with nurse anesthetist, attending anesthetist, surgeon, OR nurse, patient, others; and (3) response to pager
Documentation	Patient chart labeling (drugs, drips, laboratory results)
Additional operations	Positioning of patient, patient transfer, tasks of others (circulating nurse, orderly), arrange workplace, conversation with observer ("just looking"), miscellaneous, leaving OR (with possible audiovisual contact with OR)

IV, intravenous line; OR, operating room.

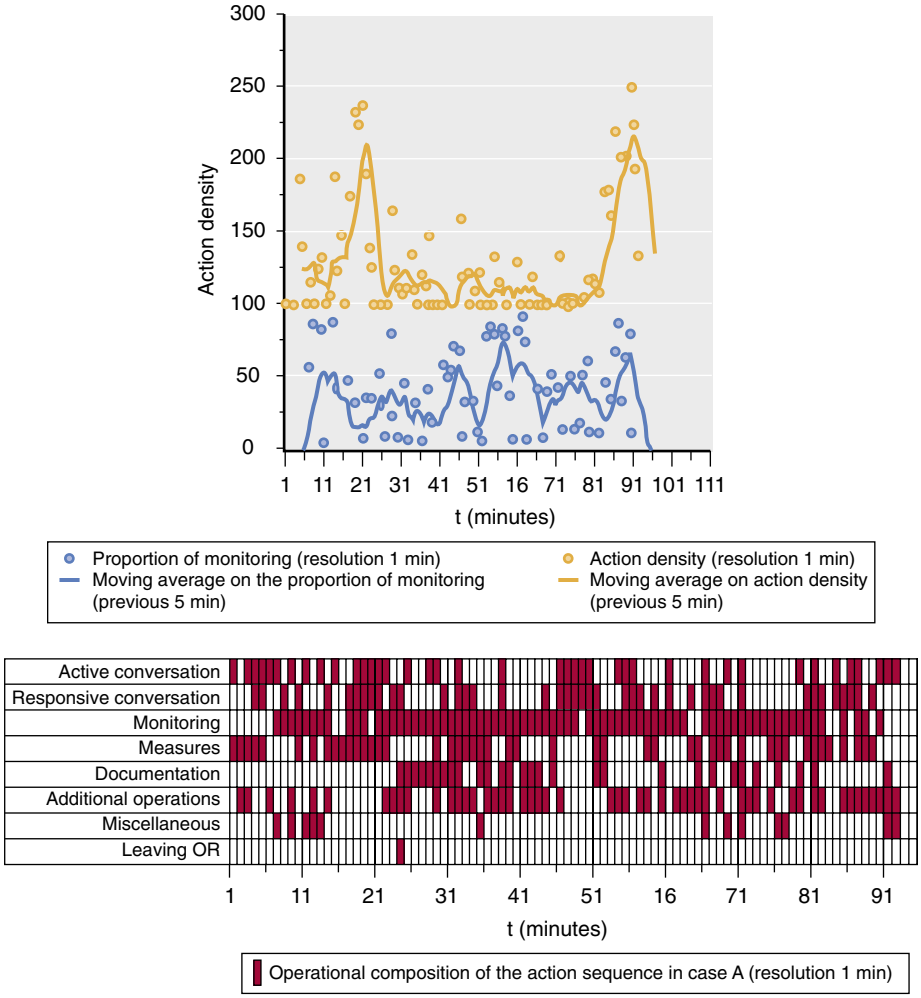

Figure 6-16 Action density diagram illustrating the derived parameter "action density" from induction of anesthesia to emergence in a real anesthetic case. The *top line* in the graph shows the overall action density and the *dots* show the moving average of the density. The *bottom line* shows the contribution of one task group "monitoring" as an example. The table in the lower graph shows the composition of the data for all eight task groups from the same case.

Mental Workload of Administering Anesthesia

The observable tasks do not tell the whole story of what the anesthetist is doing. As Drui and coworkers[320] suggested, mental activity is going on even when the anesthetist appears idle. What, then, is the mental workload of administering anesthesia? Mental workload is another concept that is readily understood but difficult to define precisely. There are various ways to measure workload, none of which are ideal.

Primary Task Performance Measure

The primary task performance measure assesses the subject's performance on standard work tasks as they are made progressively more difficult by increasing the number of tasks, task density, or task complexity. At first the subject is able to keep up with the increasing task load, but at some point the workload exceeds the ability to manage it, and performance on the standard tasks decreases. The disadvantage of the primary task performance measure is that in many complex task domains there is no accepted way to objectively measure the subject's performance on the primary work tasks except by loading to the point of catastrophic performance failure, which is easily detected. In actual high-risk domains, one cannot allow primary task performance to degrade, and one certainly cannot allow it to fail catastrophically. Although experiments of this type are in principle feasible with anesthesia simulators, they have not yet been attempted.

Secondary Task Probing

A more useful technique, secondary task probing, tests the subject with a minimally intrusive secondary task that is added to the primary work tasks. The secondary task is a simple one for which performance can be objectively measured, and the subject is instructed that the primary tasks of patient care take absolute precedence over the secondary task. Therefore, assuming that the secondary task requires some of the same mental resources as the primary task, the performance of the subject on the secondary task is an indirect reflection of the spare capacity available to deal with it; thus, it is an inverse measure of primary task workload (the greater the spare capacity, the lower the primary workload). Secondary tasks such as reaction time (with or without choice), finger tapping, and mental arithmetic have been used for this

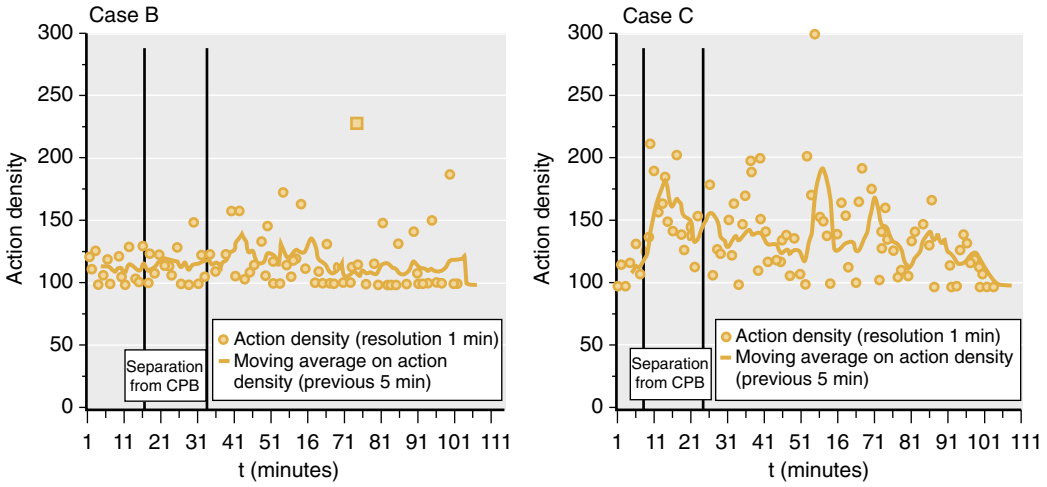

Figure 6-17 Action density during separation from cardiopulmonary bypass (CPB) without and with complications. The graph on the *left* is the density diagram of an uncomplicated case (case B) with a "flat" action density diagram during (between the two *vertical lines*) and after separation from CPB. In contrast, case C, shown in the graph on the *right*, had a complicated weaning from CPB; a very high action density is followed by an elevated density with further peaks after separation.

technique in the psychology laboratory, in high-fidelity simulators, and in some field studies of actual work situations.

Gaba and Lee[330] presented two-digit addition problems on a computer screen placed in the anesthesia workspace at random approximately every 45 seconds. The delay in responding to problems and the number of problems skipped were logged over time and correlated with a concurrent six-category task analysis. The dynamic ebb and flow of mental workload during cases of varying complexity was documented. For example, cardiopulmonary bypass was confirmed as a time of very low workload for the anesthetist, whereas induction of anesthesia was confirmed as a period of high workload. Manual tasks and conversing with the attending physician were correlated with a delayed or absent response to the secondary task.

Subsequent studies by the UCSD/VA-Stanford group[244,245] and the UCD group[325,329,331] used the reaction time to a changing display in or around the clinical monitors as a secondary task to assess mental workload, vigilance, or both. For the UCSD/VA-Stanford group, the display was a red light placed next to the main physiologic monitor. This secondary task was analogous to but totally separate from the standard tasks of clinical work. When the secondary task was embedded in the regular work tasks, it was called an embedded task. The UCD group used a secondary task involving recognition of changes in the alphanumeric display of an unused channel of an actual clinical monitor (a parameter labeled "Vig" on the monitor changed values from "5" to "10"). This task was only partially embedded because although it did involve an actual clinical monitor, it displayed on an otherwise unused channel and was not of clinical significance. The VA-Stanford group has been experimenting with fully embedded secondary tasks during simulator anesthetic cases in which the values of actual clinical variables can be manipulated at will to evaluate the subject's response time to the excursion of data values beyond predefined reporting thresholds.

The mean response time to the red light used by the UCSD/VA-Stanford group was markedly less than 60 seconds for experienced subjects in both the induction and postinduction (maintenance) phases, but it was much higher for novice residents during the induction phase (Fig. 6-18). The probe was not given frequently enough to track the ebb and flow of workload. The response to the UCD task typically (56%) occurred within 60 seconds, but 16% of stimuli overall (27% during the induction period) were not responded to within 5 minutes. The conclusion was that spare capacity may be limited by the workload of the case during certain periods of anesthesia care.

There are several problems with these workload studies. One is interference with the "response channel." If responding to the probe requires manual activity with a mouse or keyboard (as in the studies of Gaba and Lee and the UCD group), it cannot be performed whenever the subject is occupied with a manual task. This is especially true during a sterile procedure. Therefore, it may

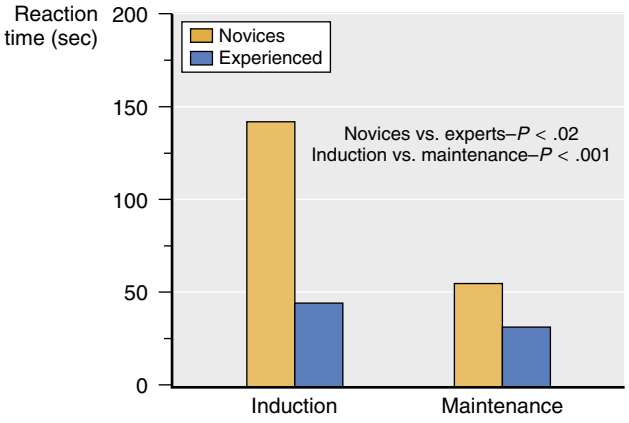

Figure 6-18 A test of the anesthetist's vigilance. Shown is the mean reaction time of novice residents and experienced anesthetists in response to the illumination of a red light placed next to the electrocardiogram monitor display during actual ambulatory surgery procedures. In both groups the reaction was faster in the maintenance phase than during induction of anesthesia. Novices reacted significantly more slowly than experienced anesthetists did. Because the distribution of reaction times was skewed and nongaussian, error bars are not shown and nonparametric statistics were used for hypothesis testing.

be impossible to distinguish between a high primary task load (i.e., no spare capacity to address the secondary task) and a low primary task load that happens to usurp the manual response channel. However, in the Gaba and Lee study,[330] 37% of the problems that were skipped for lack of spare capacity did not occur during a manual task. All of the UCSD/VA-Stanford studies have allowed multiple response channels (manual, voice, and gesture), so there was no response channel interference; however, the potential for interference remains in the UCD studies.

An additional problem with these studies is that even these simple secondary tasks were intrusive when repeated frequently. Thus, there was a tradeoff between temporal resolution of the measurement and its intrusiveness. There is also controversy about whether these probes measure "vigilance" or "workload," although the same techniques probably measure both aspects of performance. When probes occur infrequently, are subtle, have multiple response channels, and are performed with a low level of existing workload, they are more likely to measure vigilance; when they are frequent, readily detectable, require a manual response, and are performed during a high-workload period, they probably are more indicative of spare capacity and workload.

Slagle and colleagues[303] carried out an assessment of an established clinical task analysis methodology regarding intra- and inter-rater reliability. These investigators had one trained observer rating 20 routine anesthesia cases, first rating cases in the OR and then rating the same cases from a videotape, with another observer rating the same videotapes twice. A computerized task analysis program with 38 task categories was used. The results showed good intra-rater reliability and also high concordance between real-time and video analyses. This finding is important because real-time observation is unfeasible in many circumstances. This study had problems in analyzing parallel tasks because the technique of "toggling between the task categories at a rate proportional to the time spent on each task" resulted in big differences in "task duration" and "task occurrences" between the two raters. This problem of recording parallel tasks (two or more) was solved by Manser and colleagues in Tübingen.[246,247,332]

Subjective Measures

A third modality of workload assessment consists of subjective measures in which individuals are asked, either in retrospect or in real time, how much load they were or are under during actual work situations. Subjective measures complement objective measurements because the subjective perceptions of the anesthetist may be an important source of stress and anxiety; conversely, an anesthetist may subjectively underestimate the workload in settings in which objective measurements demonstrate a marked reduction in spare capacity.

Various scales have been proposed to measure dimensions of mental workload that are, in theory, different. However, Gaba and Lee[330] adapted a set of workload scales from those used at NASA and showed that workload ratings on each of the scales were highly correlated. In subsequent studies by the UCSD/VA-Stanford group, a single dimension of overall load was assessed by using an asymmetric numeric scale that minimized biases caused by a tendency to group responses at the middle and extremes of symmetric scales. This group demonstrated that a neutral observer can estimate the subjective workload of the anesthetist in real time with high correlation to the self-rated workload of the subject.[244] Again, as could be expected, subjective workload was highest during induction and emergence from anesthesia, especially for novices.

Physiologic Measures

The final set of techniques for assessing workload consists of physiologic measures. Visual or auditory evoked potentials have been used successfully to assess mental workload, but this technique can be used only in a static laboratory environment. Heart rate is a relatively easily measured variable that may be altered by mental workload. Toung and associates[333] showed that the anesthetist's heart rate increases at the time of intubation and that the amount of increase is inversely related to the amount of overall medical training. Azar and coworkers[334] found that anesthesia faculty members' heart rate and blood pressure increased during induction of anesthesia and that significant ST-segment depression developed in one individual. Bitetti and colleagues[335] confirmed that heart rate changes occurred during anesthesia but did not always correlate with contemporaneous self-recordings of "stress."

Because of the many factors that affect heart rate, the beat-to-beat variability of the heart rate is thought to be a better indicator of mental workload. The frequency components of heart rate variability can be separated by spectral analysis; a component at 0.1 Hz has been linked to mental workload. Although several groups have acquired heart rate data on anesthesiologists, none has reported an analysis of the workload-related frequency components.

Applications of Task Analysis and Workload Methodologies

The results of task analyses and workload measurements have primarily provided objective confirmation of a number of intuitive beliefs about anesthesia practice. The real importance of these studies is that a coherent methodology has been developed that may be useful for studying a variety of interesting questions.[247,336] The question of the impact of electronic automated record-keeping systems was addressed earlier. Another question concerns TEE. This newer monitoring modality has become commonplace during cardiac anesthesia and anesthesia for other patients with cardiovascular disease who undergo complex operations. It is widely recognized that evaluating TEE images and manipulating the TEE probe require substantial visual and mental attention.

The UCSD/VA-Stanford group has published data suggesting that vigilance (as measured by response latency to illumination of a red light) was substantially lower when the anesthesiologist was involved in manipulating, adjusting, or examining the TEE images than when other patient care tasks were being performed (Fig. 6-19).[328] This may be due, in part, to the layout of the workspace. The TEE machine is large and is often placed near the left side of the head of the OR table, whereas the anesthesia machine and attendant monitors, by convention, are typically placed near the right side of the head of the table. Remote displays slaved to the primary monitor are also more likely to be on the patient's right side. This arrangement makes it physically difficult to glance from one modality to another. The degree to which the mental concentration required to use TEE itself detracts from vigilance for other signals remains to be determined explicitly.

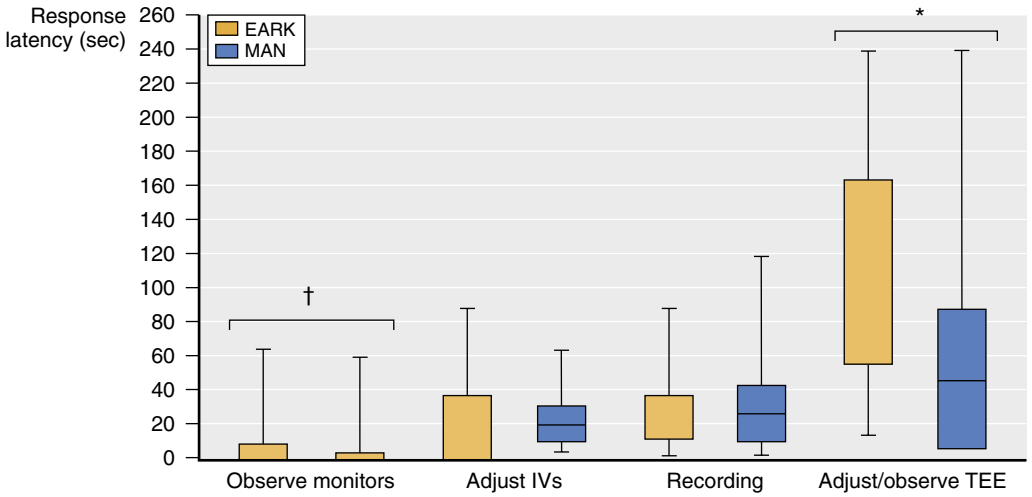

Figure 6-19 Vigilance test data during anesthetic tasks with and without automated record keeping. The range of data is shown for each of four task categories in electronic automated record keeping (EARK) and manual record keeping (MAN). Each box contains 50% of the data for that subgroup (the upper limit of the box is the 75th percentile; the lower limit is the 25th percentile), whereas the maximum and minimum are shown by the upper and lower *horizontal bars*. The response latency during record keeping was not significantly different between EARK and MAN. In both record-keeping groups, subjects had significantly slower responses when observing or adjusting the transesophageal echocardiogram (TEE) than when recording, observing monitors, or adjusting intravenous lines (IVs). Subjects in both groups had faster response latency when observing the monitoring array, which contained a red light, than when performing the other three tasks. *$P < .05$; †$P < .05$. *(From Weinger MB, Herdon OW, Gaba DM: The effect of electronic record keeping and transesophageal echocardiography on task distribution, workload, and vigilance during cardiac anesthesia. Anesthesiology 87:144-145, 1997.)*

It is important to differentiate the various uses of TEE. When it is used to answer specific clinical questions triggered by events or milestones during the procedure, the value of the information may be worth an investment of effort even though there is a reduction in overall vigilance. When it is used as a continuous monitor for myocardial ischemia or when conducting a detailed routine examination, the reduction in vigilance must be considered when evaluating the potential benefits of the technology. Some practitioners describe special ways to handle the attention required for TEE, including tightening alarm thresholds (to provide audio warnings of changed values) and assigning specific patient monitoring functions to another individual while conducting the initial TEE placement and examination.

Many other interesting questions on the performance of anesthetists are still unanswered and can be addressed with the techniques of task analysis and workload and vigilance assessment, including the following:

1. How do task load and task density differ between private practice settings and academic settings?
2. Are there characteristic "patterns" for experts and novices (or should we say for "good" and "bad" anesthesiologists?) in the analysis of tasks and their densities? And if yes,
   a. How do the work patterns of novices change to become those of "experts"? How can the training of novices be focused to support these changes best? Is suboptimal performance of novices detectable through analysis of task distributions and mental workload?
   b. Can work patterns be linked to safe anesthetic practice, or can special patterns be linked to unsafe behavior? Perhaps this could be done by assessing high-workload simulator scenarios. In a proactive safety culture, this would allow us to identify such colleagues and train them individually.
3. How much task load can the average anesthetist handle? How are tasks distributed among personnel (e.g., between resident and faculty, between CRNA and supervisor, and among staff anesthetists) during the high-workload periods of patient care? This question is just beginning to be addressed by applying the task analysis techniques described earlier to videotapes of actual anesthetic cases. With use of these tapes, the task sequences of multiple anesthesia personnel can be elicited separately, as can the communications used to coordinate their activities.

Ability Requirements for Anesthetists

Unlike the situation in military aviation, there are few formal selection criteria for entry into anesthesia practice. Instead, the criteria are decided on by each department's trainee selection committee. Nearly every student who chooses anesthesia as a specialty will be accepted by some training institution. Moreover, few residents are terminated from their anesthesia training—and then usually only because of drug abuse or too persistent or egregious lack of normal or technical skill.

There has been recent work on defining the underlying ability characteristics of a successful anesthetist. Greaves and Grant[21] presented an inventory of 16 characteristics of "good" anesthetic practice—knowledge, skill, perception, confidence, prudence, vigilance, fluency, decisiveness, anticipation, organization, flexibility, responsiveness, good manner, assertiveness, good management, and good communication. This inventory can serve as a basis for discussion of anesthetists' education and training. The authors of the inventory recommended its use for a formalized consultant feedback to trainees, although they pointed out its unproven validity and reliability.

An interdisciplinary group in Germany conducted an evaluation of another list of critical abilities for anesthetists published in German.[337]

Other Studies of "Vigilance" and Decision-Making by Anesthetists

Studies of "Vigilance"

The dominant metaphor for the mental activity of the anesthetist has been that of a vigilance task. "Vigilance" is the motto on the seal of the ASA. What is vigilance and to what degree does it capture the complex nature of the anesthetist's work? "Vigilance, or sustained attention, refers to the ability of observers to maintain their focus of attention and to remain alert to stimuli for prolonged periods of time" (J. Warm, presentation at the Panel on Vigilance, ASA annual meeting, 1992). There is an abundance of literature concerning vigilance. Many laboratory studies have demonstrated decrements in vigilance during prolonged vigilance tasks that are exacerbated or ameliorated by a variety of factors. These studies have generated considerable controversy. Some psychologists believe that the results of laboratory studies of vigilance have little application to complex real-world task domains.[338,339] Certainly, the anesthetist's work involves vigilance as a necessary component because if new stimuli are not perceived, no meaningful work can be accomplished. However, the anesthetist's task is much more complex than just vigilant alertness to stimuli. Therefore, vigilance is a necessary but not sufficient condition for appropriate performance.[58]

Several studies have attempted to quantitate the vigilance of anesthetists to changes in clinically important variables by using low-fidelity simulation. Beatty and associates[340] had anesthetists watch for changes in displays of six vital signs on a video monitor. Denisco and colleagues[341] used videotapes containing abnormal changes in anesthesia flow meter settings and physiologic monitor displays. The raw reaction times were not reported—only the "vigilance scores." Such studies purported to demonstrate a degradation in performance for sleep-deprived and fatigued residents, but there were methodologic flaws. For example, in the study of Denisco and coworkers,[341] the subjects were never told the threshold of change for them to report.

In addition, the work environment of the anesthetist is much more complex than that presented in these low-fidelity simulations. Although it can be argued that complexity will worsen vigilance, such is not necessarily the case. Complexity can combat boredom, which is a distinct possibility in vigilance experiments. In addition, the real work environment often provides redundant data cues on changes, which offers multiple possibilities for their detection.

A study of rested anesthetists[178] using a realistic anesthesia simulator measured detection times (first awareness of a problem) for a variety of intraoperative events embedded within a realistic case situation. Of interest, an event that caused alarms to sound immediately, such as ventricular tachycardia/fibrillation, was detected in 10 seconds or less (thus confirming its veracity, but acting on it took longer in many instances). Another event, occlusion of the intravenous line, was detectable only by visual observation in the direction opposite the anesthesia machine and monitors. This event took several minutes (on average) to detect, but it was corrected quickly after detection. The redundancy of cues in the task domain was confirmed in that six different observational modalities were used by at least 1 of the 19 residents studied to detect endobronchial intubation initially.

Other vigilance studies have focused on detecting the loss of an existing monitoring modality during actual patient care. In one study,[342] the esophageal stethoscope was occluded with a clamp after a staged distraction (conversation or a loud noise). Subjects most commonly detected the occlusion by observing the clamp rather than by noting a loss of sound. Although this study purported to show a difference in vigilance related to the use of automatic blood pressure measurement devices, the artificial distraction could have biased the results; the subjects typically failed to hear the loss of sounds, and there was a significant result for only one group of residents, arbitrarily stratified by length of training. Another study[343] that evaluated reaction time to loss of esophageal stethoscopy more carefully showed that 13% of occlusions were detected after 1 minute. However, this study required a manual response, and the investigators noted that in some instances of delay, the subject was involved in a manual clinical activity such as administering blood or drugs.

Apparent reductions in vigilance could be due either to a reduction in "spare capacity" to attend to the stimuli immediately or to a reduction in the overall alertness of the anesthetist. Enhancements in the display and annunciation of relevant information would be a useful ameliorative strategy in the first case, whereas this strategy would not be useful if the anesthetist's overall alertness were impaired, as by sleep deprivation or illness. The influence and impact of fatigue and possible countermeasures are covered in the earlier section "Performance-Shaping Factors."

Empirical Studies of Complex Decision-Making and Action by Anesthetists

Traditional concepts of decision-making in medicine have concentrated on relatively static, well-structured decisions. For example, should patient A with an elevated blood pressure be treated for hypertension with drug X, or should no treatment be started? Other investigators have looked only at "diagnosis" as an isolated task (specifically, "diagnostic explanation") both in internal medicine[344-346] and in radiology. These approaches to decision-making have not captured the unique aspects of dynamism, time pressure, and uncertainty seen in anesthesiology. Over the past decade, a paradigm has emerged regarding decision-making and action in complex real-world situations.[39,236,250] The cognitive model of dynamic decision-making was described previously. Several teams from inside the anesthesiology profession and from the human performance community have been striving to develop a more comprehensive understanding of the complex performance of anesthetists. Their work has been based on a small number of new experiments (often involving medium- or high-fidelity anesthesia simulators), reinterpretation of previous experiments, direct and indirect observation of the conduct of anesthesia, and extrapolations from other industries to anesthesiology. Each experiment has probed several aspects of decision-making and action, which are described in the following section.

Responding to Simulated Critical Incidents

Using a realistic hands-on anesthesia simulator, Gaba and DeAnda[111,259,347] studied the response of anesthesia trainees and

experienced anesthesia faculty and private practitioners to six preplanned critical incidents of differing type and severity:

1. Breathing hoses too short to turn the table 180 degrees, as requested by the surgeon
2. Endobronchial intubation (EI) resulting from surgical manipulation of the tube
3. Occlusion of intravenous tubing
4. Atrial fibrillation (AF) with a rapid ventricular response and hypotension
5. Disconnection between the endotracheal tube and the breathing circuit
6. Ventricular tachycardia/fibrillation

These investigators measured the detection time (as described in the section on vigilance) and the correction time (the time from the event's onset until any one of a predefined set of corrective actions was first taken). They assessed the information sources by which subjects detected the incidents and then confirmed and diagnosed the problem. They asked subjects to "think aloud" to permit subjective analysis of their decision-making strategies. A summary of the data is shown in Figure 6-20. Major findings from this set of studies included the following:

1. Events differed from each other in their inherent ease of solution. Some events (e.g., airway disconnection) were

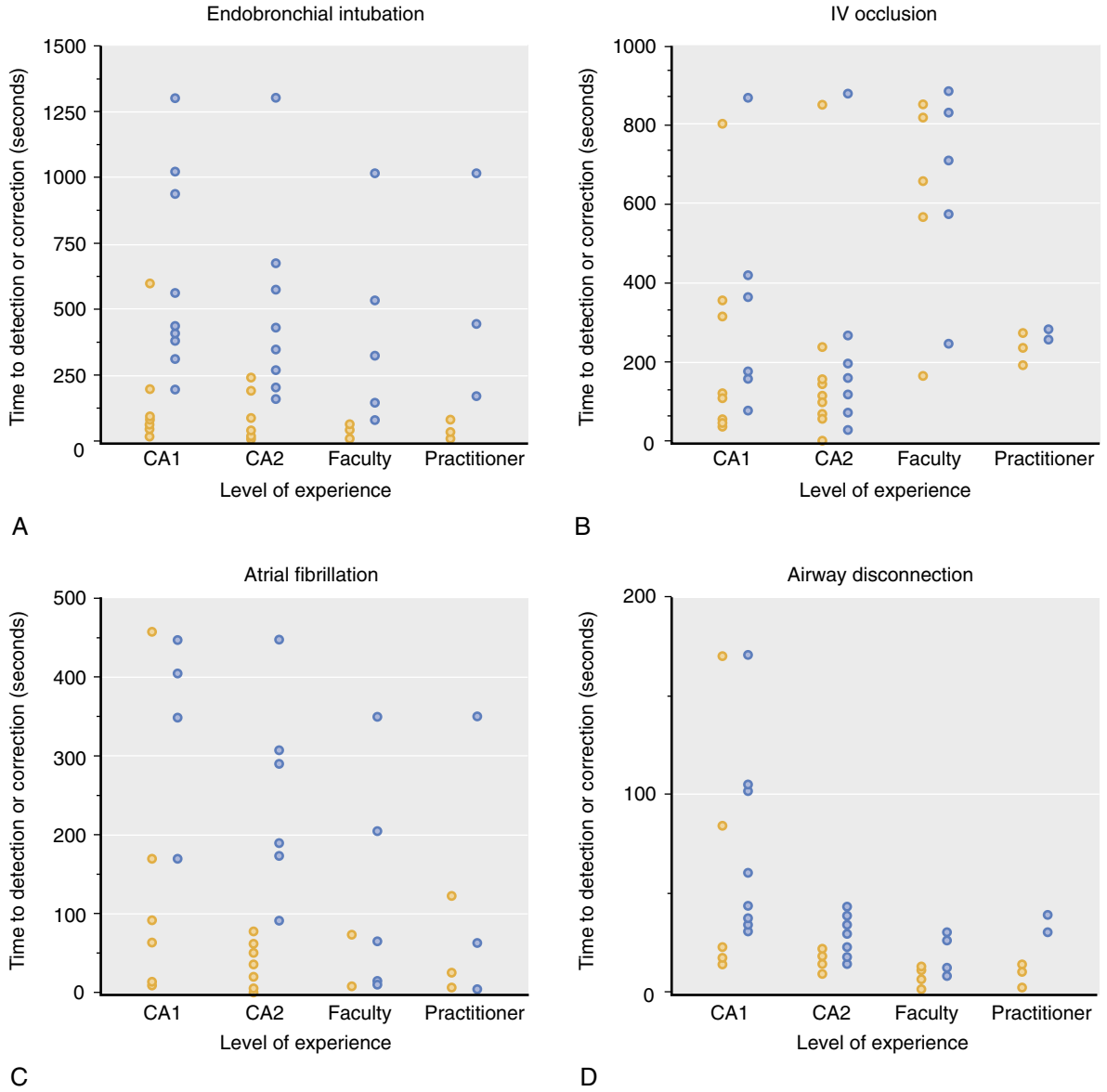

Figure 6-20 Response times of anesthesiologists with different levels of experience to four simulated critical incidents: **A,** endobronchial intubation; **B,** intravenous occlusion (IV); **C,** atrial fibrillation; and **D,** airway disconnection. Detection time is represented by *yellow circles* and correction time by *blue circles* (see text for definitions of these times). Unless there is overlap between response times, each circle represents a single individual. The scale of response times is different for each event. There is substantial variability among incidents and among individuals. Despite a trend to better performance with increased experience, major errors were made by individuals in all groups. *(From DeAnda A, Gaba DM: Role of experience in the response to simulated critical incidents. Anesth Analg 72:308-315, 1991.)*

detected rapidly and corrected. Some problems (e.g., intravenous occlusion) were difficult to detect, but once they were detected, diagnosis and therapy were achieved rapidly. Other problems (EI, AF) were easy to detect by using one of several redundant information sources as the first clue (six for EI, four for AF), but they required additional time (7 to 8 minutes for EI; 1.5 to 4.5 minutes for AF) to confirm the abnormality, establish a diagnosis, and initiate appropriate therapy. Diagnosis and planning and monitoring of therapy used a large number of information sources (11 for EI; 9 for AF).

2. For each incident there was considerable inter-individual variability in detection and correction times, in information sources used, and in the actions taken. In each experience group there were some who required excessive time to solve the problem or who never solved it. In addition, in each experience group at least one individual made major errors that could have had a substantial negative impact on a patient's clinical outcome. For example, one faculty member never used electrical countershock to treat ventricular fibrillation. One private practitioner treated the EI as though it were "bronchospasm" and never assessed the symmetry of ventilation. One resident never found the airway disconnection.
3. The average performance of the anesthetists tended to improve with experience, although this varied by incident. The performance of the experienced groups was not definitively better than that of the second-year residents (who were in their final year of training at that time). Many (but not all) novice residents performed indistinguishably from more experienced subjects.
4. The elements of suboptimal performance were both technical and cognitive. Technical problems included choosing defibrillation energies appropriate for internal paddles when using external paddles, ampule swap, and failure to inflate the endotracheal tube cuff that resulted in a leak. Cognitive problems included failure to allocate attention to the most critical problems and fixation errors.

Schwid and O'Donnell,[258] from the University of Washington, used the Anesthesia Simulator Consultant (ASC) screen-only simulator (Anesoft Corp., Issaquah, WA) (Table 6-10) to perform an experiment similar to those of Gaba and DeAnda with a realistic simulator. This method enabled them to evaluate some elements of anesthetist behavior more carefully, albeit with the limitations imposed by presenting the OR "on the screen." After working on several practice cases without critical incidents, each subject was asked to manage three or four cases involving a total of four serious critical events (esophageal intubation, myocardial ischemia, anaphylaxis, and cardiac arrest). The progression of each event was mediated by the interaction of physiologic and pharmacologic models with the actions taken by the subject. The anesthesiologists studied had varying experience levels. One group was made up of 10 anesthesia residents with at least 1 year of anesthesia training, whereas the other two groups contained 10 anesthesia faculty members and 10 private practitioners, respectively.

Major findings of the study included the following:

1. Significant errors in diagnosis or treatment were made in every experience group. The errors occurred in both diagnosis of problems and in deciding on and implementing appropriate treatment. For example, 60% of subjects did not make the diagnosis of anaphylaxis despite available information on heart rate, blood pressure, wheezing, increased peak inspiratory pressure, and the presence of a rash. In managing myocardial ischemia, there were multiple failures (Table 6-11).
2. Thirty percent of subjects did not compensate for severe abnormalities while considering diagnostic maneuvers.
3. Fixation errors in which initial diagnoses and plans were never revised were frequent, even when they were clearly wrong.

Westenskow and colleagues[253] used a test lung and remotely activated faults in the breathing circuit to test the anesthetist's ability to identify faults related to ventilation and the anesthesia breathing circuit after hearing an alarm. One group of subjects used standard alarms, set to factory defaults, on an anesthesia machine, which included a capnograph. The other group used the same anesthesia machine with the alarms disabled along with a neural network–based intelligent alarm and fault identification system. The mean "human response time," which was the time between sounding of the first alarm and identification of the event, ranged from approximately 15 seconds for airway disconnection to approximately 90 seconds for an endotracheal tube cuff leak. The 10 anesthesiologists tested with the standard alarm setup were unable to identify the fault within 2 minutes on 11 occasions—5 cuff leaks, 3 airway obstructions, and 3 stuck-open expiratory valves. However, in such circumstances they did take appropriate compensatory actions while continuing to search for the cause (e.g., increasing fresh gas flow to compensate for a cuff leak).

The intelligent alarm apparatus used data from three sensors (in-line capnograph, spirometer, and airway pressure). A neural network determined whether any of seven faults was present and, if so, displayed a text message specifying the fault, as well as an animated diagram of the lung, airway, and anesthesia

Table 6-10 Incidence of Totally Correct Diagnosis or Treatment of Simulated Critical Incidents with Use of the Anesthesia Simulator Consultant

Incident	Anesthesia Residents (%)	Anesthesia Attendings (%)	Anesthesiologists in Practice (%)
Diagnosis of esophageal intubation	80	100	100
Treatment of myocardial ischemia	20	40	20
Diagnosis of anaphylaxis	20	60	40
Treatment of cardiac arrest	40	30	20

From Schwid HA, O'Donnell D: Anesthesiologists' management of simulated critical incidents. Anesthesiology 76:495-501, 1992.

Table 6-11 Failure Rate in the Management of Simulated Myocardial Ischemia with the Anesthesia Simulator Consultant

Incident	Anesthesia Residents (%)	Anesthesia Attendings (%)	Anesthesiologists in Practice (%)
Untreated tachycardia	30	50	70
Untreated hypotension	40	60	20
Inappropriate drug	20	10	0
Unable to recall infusion dose	50	20	10
Unable to calculate infusion rate	70	40	40

From Schwid HA, O'Donnell D: Anesthesiologists' management of simulated critical incidents. Anesthesiology 76:495-501, 1992.

breathing circuit with the faulty component highlighted in red. It is interesting that the smart alarm system took slightly longer on average to detect a fault than the conventional alarm system did (25 versus 21 seconds), but the human response time was markedly reduced for three of the seven faults. There were no statistically significant differences between anesthesia residents and faculty members with either alarm system.

The investigators suggested that the more specific alarm messages in their intelligent alarm system could direct the attention of the anesthetist to the occurrence of specific problems and in so doing would decrease workload and reduce the likelihood of fixating on inappropriate information. They stated that such a system's advantages would be even greater in a more realistic clinical environment in which the anesthetist has multiple complex tasks and not just detection and identification of ventilation-related events.

Loeb and Fitch[348] developed and tested an auditory display of six physiologic variables. Encouraged by the popularity of the pulse oximeter's pulse tone,[349-351] they investigated whether the addition of auditory cues would enhance the rate and speed of detection of predefined events. The results showed that the combined display (visual and auditory) lead to faster detection of events, even though the rate for correct identification of the event was slightly higher in the "visual only" display (80% versus 88%). It seems that there is a potential to improve the rate of detection of changes in physiologic variables with more sophisticated display modalities, thereby enhancing the "effective vigilance" of anesthetists.

Complex, Multiple Personnel Simulations of Anesthetic Crises

In the process of evaluating a new type of training for anesthetists involving crisis management, Howard and colleagues[109] collected anecdotal data on the responses of teams of anesthetists, surgeons, and nurses to planned (and unplanned) critical events. These experiments largely confirmed the results of the studies described earlier and extended them to include more complex management issues and team interactions. Howard and colleagues found a substantial incidence of difficulties managing multiple problems simultaneously, applying attention to the most critical needs, acting as team leader, communicating with personnel, and using all available OR resources to best advantage.

Botney and associates[352] analyzed similar videotapes from 18 different simulator training sessions on crisis management. In one event, a volatile anesthetic vaporizer had been left on at 4% and was hidden beneath a printout from the noninvasive blood pressure monitor. Simultaneously, there was a mechanical failure of the capnograph, making it impossible to confirm endotracheal intubation with CO_2 measurements. This event purposefully presented an invitation to become fixated on the endotracheal tube while ignoring other relevant information. Five of 18 subjects never discovered the volatile anesthetic overdose despite catastrophic effects on blood pressure and heart rate and clear evidence that the endotracheal tube was correctly placed. Of those who did detect the vaporizer setting, the average time to detection was nearly 4 minutes, with some subjects taking longer than 12 minutes.

In the second event studied, there was a loss of pipeline O_2 supply while an anesthetist was assuming the care of a critically ill patient who required an F_{IO_2} of 100% to achieve satisfactory blood oxygenation. The O_2 cylinder on the machine was empty (i.e., it had not been checked by the initial anesthetist, who had left the case after becoming ill). The pipeline failure was quickly detected (19 seconds), but the responses to it were extremely variable and showed a variety of problems. Five of 18 anesthetists closed the anesthesia circuit (which preserves the existing oxygen in the circuit), but all 5 subsequently switched to ventilation with a self-inflating bag using room air or to mouth-to-tube ventilation. Five of 18 could not open the reserve oxygen cylinder because they could not locate the tank wrench attached to the machine (it tended to rest between two gas cylinders). Several teams had trouble mounting a new oxygen tank on the anesthesia machine; problems with the gasket disk were frequent. The individuals did not appear to have a well-formulated plan for managing this event, and they did not optimally coordinate their actions with their assistants or with the other OR personnel.

A study by Byrne and Jones[310] looked at differences in the performance of experienced and less experienced anesthetists. Using a self-developed patient simulator system, they measured time to treatment and deficiencies in patient care in 180 simulations. The results showed significant differences only between the first and second year. As seen in other studies,[319] significant errors occurred at all levels of experience, and most of the anesthetists deviated from established guidelines. These studies underscore the importance of recurrent training for experienced anesthetists and the truism that experience is not a substitute for excellence.

The reader is referred to Chapter 7 for discussion of newer studies with the use of patient simulators and performance assessment as such.[17,20,142,148,312,319,353-357]

Indirect Observation of Anesthetists Involved in Difficult Cases

An unusual approach involving indirect observation of actual cases was used by Cook and colleagues[255] at the Ohio State University. Rather than collecting data on the case itself, these investigators transcribed the discussions of interesting cases occurring

at a weekly quality assurance conference. They argued that this approach allowed them to apply a "neutral observer criterion" to the behavior of the anesthetist. The investigators acknowledged the risks of hindsight bias and selection bias with this methodology, but they suggested that their technique provided a unique window on human performance issues.

Fifty-seven cases were analyzed, 21 of which had a full cognitive analysis in the final report. From the presentation and discussion of a case, the investigators classified evolution of the events into one of five categories: acute incident, going-sour incident, inevitable outcome incident, difficult-airway incident, and no-incident incident. For each case, the cognitive analysis was "based on using knowledge about the cognitive demands of the task domain and data about practitioner activities to analyze the practitioner's information-processing strategies and goals, given the resources and constraints of the situation." The investigators postulated a cognitive cycle as a component of data-driven activation of knowledge and knowledge-driven observation and action.

Cook and associates[255] called attention to several issues that surfaced in their cognitive analysis of these cases, including the following:

1. Multiple themes. Many cases involved several lines of concern simultaneously, each of which could have interacted with another (e.g., tight coupling). Each theme had multiple means available to deal with it. Maintaining "situation awareness" was important. The multiple themes sometimes generated competing or conflicting goals. Adaptive planning (as described in the section on abstract task analysis) was sometimes required.
2. Unusual situations. The greatest expertise was seen with infrequent or unusual situations rather than with typical situations.
3. Allocation of attention. Allocation of attention to relevant stimuli or to the most important "theme" was an important issue. The attentional shifts were not always well supported by existing alarm and display technologies.
4. Cognitive workload. Anesthetists attempted to reduce their cognitive workload whenever possible.
5. Team interaction. Cooperative work, team interaction, and communications issues were problems in several cases. These stemmed from both individual and organizational failures to coordinate information and efforts from different organizational components (e.g., ICU and OR, surgeons and anesthesiologists).

Direct Observation of Anesthetists

A team of cognitive scientists and anesthesiologists at the University of Toronto[226] conducted direct observations of anesthesiologists and obtained verbal "think aloud" protocols during actual case management. The group in Tübingen also performed direct observations for their task analysis studies.[247,328] Devitt and coworkers performed a study to assess the validity of performance assessment during simulated scenarios.[19]

Video Analysis of Actual Trauma Resuscitation and Anesthesia

Mackenzie and colleagues[358-362] pioneered in the analysis of actual clinical care of anesthetists captured on videotape, with a focus on trauma resuscitation and anesthesia for trauma patients at the Maryland Shock Trauma Unit. Their sophisticated recording system captures audio, video, and vital signs data and requires only that the clinicians insert a videotape to start the whole system.[363] Analysis of these cases has revealed inadequacies in the availability and arrangement of monitoring equipment, as well as nonexistent or ambiguous communication. Meanwhile, a few groups around the world started to use video for task analysis and assessment of performance for research and training, which is not detailed here.[150,178,270,303,332,364-370]

Problems faced by all investigators are the lack of an accepted standard for objective or subjective evaluation of anesthetist performance and the absence of an agreed-on methodology for analyzing and describing anesthetist performance. Several of the previously mentioned groups are working on methodologies for evaluating technical and behavioral aspects of performance.* Measurement of complex performance is a difficult problem, and it is likely to be some time until there is a well-established metric for assessment of performance.

*See references 20, 79, 81, 142, 143, 198, 235, 244-246, 303, 314, and 357.

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Appendix 1

Links and Useful Resources

Links

Links to Patient Safety and CRM Resources

- http://www.npsf.org/
- www.patientsafety.gov (VA)
- http://www.jcaho.org/
- www.npsa.nhs.uk
- http://anesthesia.stanford.edu/VASimulator
- www.medizin.uni-tuebingen.de/psz

Links to Different Incident Reporting Systems

- www.npsa.nhs.uk/health/reporting
- www.pasis.de
- www.pasos-ains.de
- www.cirrnet.ch
- www.cirsmedical.org
- http://psrs.arc.nasa.gov/
- Pronovost's ICUSRS[75]

Valuable Sources

WHO "World Alliance for Patient Safety"

- "WHO Draft Guidelines for Adverse Event Reporting and Learning Systems—From Information to Action" als pdf
- www.who.int/patientsafety/events/05/Reporting_Guidelines.pdf

U.S. Department of Veterans Affairs Patient Safety Reporting System

- http://www.psrs.arc.nasa.gov
- *U.S. Patient Safety and Quality Improvement Act*
- USA http://www.pso.ahrq.gov/psos/overview.htm

Root-Cause Analysis Tools

- www.va.gov/ncps/rca.html. 2005.
- www.npsa.nhs.uk/health/resources/root_cause_analysis/

Failure Modes and Effects Analysis Tools

- www.va.gov/ncps/HFMEA.html. 2005.

Marcus Rall, David M. Gaba, Peter Dieckmann, and Christoph Eich

7 Patient Simulation

Key Points

1. Simulators and the use of simulation have become an integral part of medical education, training, and research. The pace of developments and applications is very fast, and the results are promising.
2. Different types of simulators can be distinguished: computer-based or screen-based microsimulators versus mannequin-based simulators. The latter can be divided into script-based and model-based simulators.
3. The development of mobile and less expensive simulator models allows for substantial expansion of simulator training to areas where this training could not be applied or afforded previously. The biggest obstacles to providing simulation training are not the simulator hardware but are (1) obtaining access to the learner population for the requisite time and (2) providing appropriately trained and skilled instructors to prepare, conduct, and evaluate the simulation sessions.
4. Realistic simulations are a useful method to show mechanisms of error development (human factors) and to provide their countermeasures. The anesthesia crisis resource management (ACRM) course model with its ACRM key points (see Chapter 6 on Crisis Resource Management) is the de facto world standard for human factor–based simulator training. Curricula should use scenarios that are tailored to the stated teaching goals, rather than focusing solely on achieving maximum "realism."
5. Simulator training is being adapted by many other fields outside anesthesia (e.g., emergency medicine, neonatal care, intensive care, medical and nursing school).
6. Simulators have proved to be very valuable in research to study human behavior and failure modes under conditions of critical incidents and in the development of new treatment concepts (telemedicine) and in support of the biomedical industry (e.g., device beta-testing).
7. Simulators can be used as effective research tools for studying methods of performance assessment.
8. Assessment of nontechnical skills (or behavioral markers) has evolved considerably and can be accomplished with a reliability that likely matches that of many other subjective judgments in patient care. Systems for rating nontechnical skills have been introduced and tested in anesthesia; one in particular (Anaesthetists' Non-Technical Skills [ANTS]) has been studied extensively and has been modified for other fields.
9. The most important part of simulator training that goes beyond specific technical skills is the self-reflective (often video-assisted) debriefing session after the scenario. The debriefing is influenced most strongly by the quality of the instructor, not the fidelity of the simulator.
10. Simulators are just the tools for an effective learning experience. The education and training, commitment, and overall ability of the instructors are of utmost importance.

How can clinicians experience the difficulties of patient care without putting patients at undue risk? How can we assess the abilities of clinicians as individuals and teams when each patient is unique? These are questions that have challenged medicine for years. In recent years, these and related questions have begun to be answered in health care by the application of approaches new to medicine, but borrowed from years of successful service in other industries facing similar problems. These approaches focus on *simulation,* a technique well known in the military, aviation, space flight, and nuclear power industries.

Simulation refers to the artificial replication of sufficient elements of a real-world domain to achieve a stated goal. The goals can include understanding the domain better, training personnel to deal with the domain, or testing the capacity of personnel to work in the domain. The fidelity of a simulation refers to how closely it replicates the domain and is determined by the number of elements that are replicated and the discrepancy between each element and the real world. The fidelity required depends on the stated goals. Some goals can be achieved with minimal fidelity, whereas others require very high fidelity.

Simulation has probably been a part of human activity since prehistoric times. Rehearsal for hunting activities and warfare was most likely an occasion for simulating the behavior of prey or enemy warriors. Technologic simulation probably dates back to the dawn of technology itself. Good and Gravenstein[1] pointed to the medieval quintain as a technologic device that crudely simulated the behavior of an opponent during sword fighting. If the swordsman did not duck at the appropriate time after striking a blow, he would be hit by a component of the quintain. In modern times, preparation for warfare has been an equally powerful spur to the development of simulation technologies, especially for aviation, shipping, and the operation of armored vehicles. These technologies have been adopted by their civilian counterparts, but they have attained their most extensive use in commercial aviation.

Simulation in Aviation

Although some aircraft simulators were built between 1910 and 1927, none of them could provide the proper feel of the aircraft because they could not dynamically reproduce its behavior. In 1930, Link filed a patent for a pneumatically driven aircraft simulator. The Link Trainer was a standard for flight training before World War II, but the war accelerated its use and the further development of flight simulators. In the 1950s, electronic controls replaced pneumatic ones through analog, digital, and hybrid computers. The aircraft simulator achieved its modern form in the late 1960s, but it has been continuously refined. Aviation simulators are so realistic now that pilots with experience flying one aircraft are routinely certified to fly totally new or different aircraft, even if they have never flown the actual aircraft without passengers on board. Similar stories of the development of simulators can be told for numerous other industries.

Uses of Simulators

Although simulators originally were used to provide basic instruction on the operation of aircraft controls, the variety of uses of simulators in general has expanded greatly. Table 7-1 lists possible uses of simulators in all types of complex work situations. Simulation is a powerful generic tool for dealing with human performance issues (e.g., training, testing, and research) (see Chapter 6), for investigating human-machine interactions, and for the design and validation of equipment. As described later in this chapter, each of these uses is potentially relevant to anesthesiology. A few books are devoted solely to the topic of simulation and their use in and outside of anesthesia.[2-4]

Twelve Dimensions of Simulation

Current and future applications of simulation can be categorized by 12 dimensions, each of which represents a different attribute of simulation (Fig. 7-1).[5] Some dimensions have a clear gradient and direction, whereas others have only categorical differences. The total number of unique combinations across all the dimensions is very large (on the order of 4^{12} to 5^{12}—4 million to 48 million). Some combinations overlap strongly with others, and some are inappropriate or irrelevant, so the actual number of meaningful combinations is much lower. Nonetheless, although the demonstrated applications of simulation in health care have been quite diverse, the space of possible applications (a large number, although quite a bit smaller than millions) has by no means been fully examined.

Table 7-1 Use of Simulators in Complex Work Environments

Team training, as human factor or CRM training
Training in dynamic plant control
Training in diagnostic skills
Dynamic mockup for design evaluation
Test bed for checking operating instructions
Environment in which task analysis can be conducted (e.g., on diagnostic strategies)
Test bed for new applications (e.g., telemedicine tools such as the "Guardian-Angel-System")
Source of data on human errors relevant to risk and reliability assessment
Vehicle for (compulsory) testing/assessment and recertification of operators

CRM, Crisis resource management.
Adapted from Singleton WT: The Mind at Work. Cambridge, Cambridge University Press, 1989.

Dimension 1: Purpose and Aims of the Simulation Activity

The most obvious application of simulation is to improve the education and training of clinicians, but other purposes also are important. As used in this chapter, *education* emphasizes conceptual knowledge, basic skills, and an introduction to work practices. *Training* emphasizes the actual tasks and work to be performed. Simulation can be used to *assess performance* and competency of individual clinicians and teams, for low-stakes or formative testing and (to a lesser degree as yet) for high-stakes certification testing.[6,7] Simulation *rehearsals* are now being explored as adjuncts to actual clinical practice; for example, surgeons or an entire operative team can rehearse an unusually complex operation in advance using a simulation of the specific patient.[8-10] Simulators can be powerful tools for research and evaluation, concerning *organizational practices* (patient care protocols) and for the *investigation of human factors* (e.g., of performance-shaping factors, such as fatigue,[11] or of the user interface and operation of medical equipment in high hazard clinical settings[12]). Simulation-based empirical tests of the usability of clinical equipment already have been used in designing equipment that is currently for sale; ultimately, such practices may be required by regulatory agencies before approval of new devices.

Simulation can be a "bottom up" tool for changing the culture of health care concerning patient safety. First, it allows hands-on training of junior and senior clinicians about practices that enact the desired "culture of safety."[13] Simulation also can be a rallying point about culture change and patient safety that can

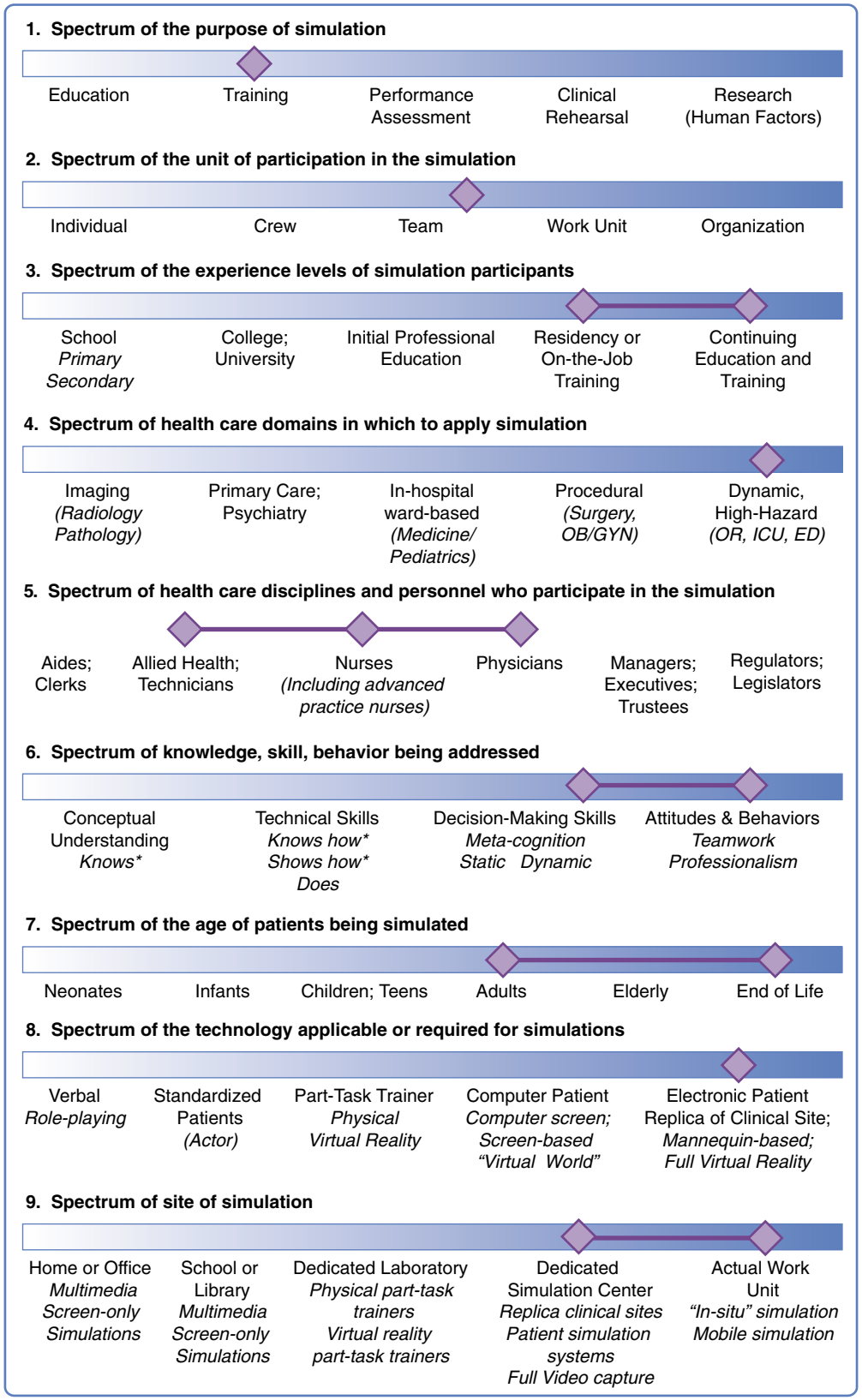


Figure 7-1 The 12 dimensions of simulation applications (10 to 12 shown on next page). Any particular application can be represented as a point or range on each spectrum (shown by *diamonds*). This figure illustrates a specific application—multidisciplinary CRM-oriented decision making and teamwork training for adult intensive care unit personnel. CRM, crises resource management; ED, emergency department; ICU, intensive care unit; OR, operating room. *These terms are used according to Miller's pyramid of learning.

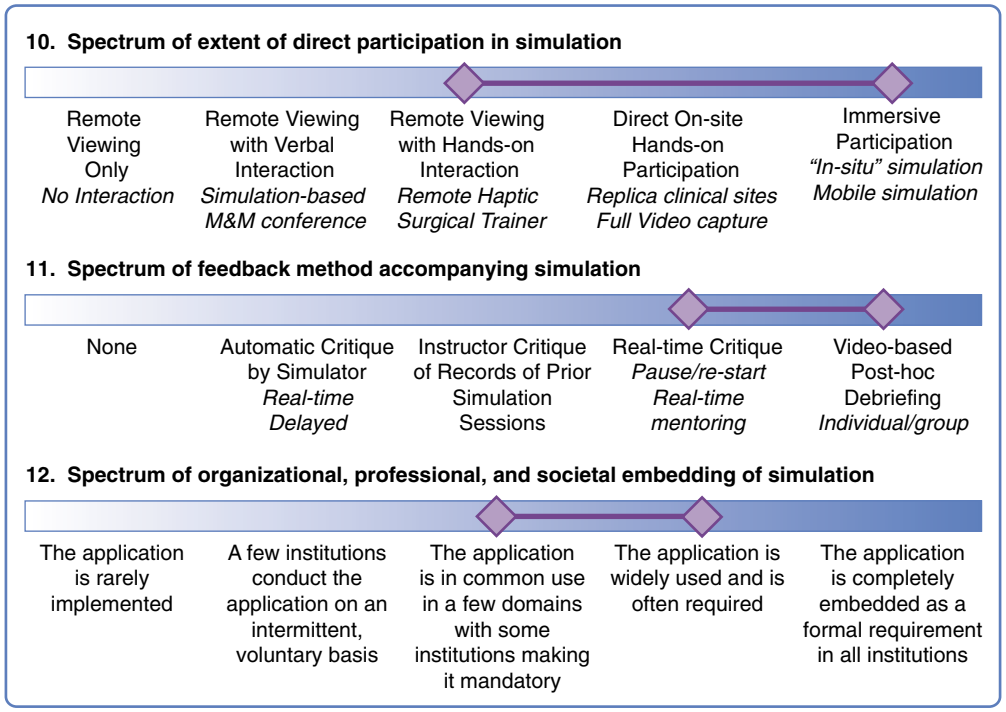


Figure 7-1, cont'd

bring together experienced clinicians from various disciplines and domains (who may be "captured" because the simulations are clinically challenging) along with health care administrators, risk managers, and experts on human factors, organizational behavior, or institutional change.

Dimension 2: Unit of Participation in the Simulation

Many simulation applications are targeted at individuals. These may be especially useful for teaching knowledge and basic skills or for practice on specific psychomotor tasks. As in other high hazard industries, individual skill is a fundamental building block, but a considerable emphasis is applied at higher organizational levels, in various forms of teamwork and interpersonal relations (often summarized under the rubric of *crisis resource management* (CRM) adapted from aviation cockpit resource management) (more on human factors and CRM concepts, see Chapter 6).[14,18] CRM is based on empirical findings that individual performance is not sufficient to achieve optimal safety.[15] Team training may be addressed first to crews (also known as *single discipline teams*), consisting of multiple individuals from a single discipline, and then to teams (or *multidisciplinary teams*).[16] There are advantages and disadvantages to addressing teamwork in the single discipline approach that "trains crews to work in teams" versus the "combined team training" of multiple disciplines together.[21] For maximal benefit, these approaches are used in a complementary fashion.

Teams exist in actual "work units" in an organization (e.g., a specific intensive care unit [ICU]), each of which is its own target for training. There also is growing interest and experience in applying simulation to nonclinical personnel and work units in health care organizations (e.g., to managers or executives)[22] and to organizations as a whole (e.g., entire hospitals or networks).

Dimension 3: Experience Level of Simulation Participants

Simulation can be applied along the entire continuum of education of clinical personnel and the public at large. It can be used with early learners, such as schoolchildren, or lay adults to facilitate bioscience instruction, to interest individuals in biomedical careers, or to explain health care issues and practices. The major role of simulation has been, and will continue to be, to educate, train, and provide rehearsal for individuals actually involved in the delivery of health care. Simulation is relevant from the earliest level of vocational or professional education (students) and during apprenticeship training (interns and residents), and increasingly for experienced personnel undergoing periodic refresher training. Simulation can be applied regularly to practicing clinicians (as individuals, teams, or organizations) regardless of their seniority,[17,18] providing an integrated accumulation of experiences that should have a long-term synergism.

Dimension 4: Health Care Domain in Which the Simulation Is Applied

Simulation techniques can be applied across nearly all health care domains. Although much of the attention on simulation has focused on technical and procedural skills applicable in

surgery,[11,20-22] obstetrics,[23,24] invasive cardiology,[25,26] and other related fields, another bastion of simulation has been recreating whole patients for dynamic domains involving high hazard and invasive intervention, such as anesthesia,[27,28] critical care,[29,30] and emergency medicine.[31-34] Immersive techniques can be used in imaging-intensive domains, such as radiology and pathology, and interactive simulations are relevant in the interventional sides of such arenas.[35] In many domains, simulation techniques have been useful for addressing nontechnical skills and professionalism issues, such as communicating with patients and coworkers, or addressing issues such as ethics or end-of-life care.

Dimension 5: Health Care Disciplines of Personnel Participating in the Simulation

Simulation is applicable to all disciplines of health care, not only to physicians. In anesthesiology, simulation has been applied to anesthesiologists, Certified Registered Nurse Anesthetists, and anesthesia technicians. Simulation is not limited to clinical personnel. It also may be directed at managers, executives, hospital trustees, regulators, and legislators. For these groups, simulation can convey the complexities of clinical work, and it can be used to exercise and probe the organizational practices of clinical institutions at multiple levels.

Dimension 6: Type of Knowledge, Skill, Attitudes, or Behavior Addressed in Simulation

Simulations can be used to help learners acquire new knowledge and to understand conceptual relations and dynamics better. Today physiologic simulations allow students to watch cardiovascular and respiratory functions unfold over time and respond to interventions—in essence making textbooks, diagrams, and graphs "come alive." The next step on the spectrum is acquisition of skills to accompany knowledge. Some skills follow immediately from conceptual knowledge (e.g., cardiac auscultation), whereas others involve intricate and complex psychomotor activities (e.g., catheter placement or basic surgical skills). Isolated skills must be assembled into a new layer of clinical practices. An understanding of the concepts of general surgery cannot be combined only with basic techniques of dissecting and suturing or manipulation of instruments to create a capable laparoscopic surgeon. Basic skills must be integrated into actual clinical techniques, a process for which simulation may have considerable power, especially because it can readily provide experience with even uncommon anatomic or clinical presentations. In the current health care system, for most invasive procedures, *novices at a task typically first perform the task on a real patient,* albeit under some degree of supervision. They climb the learning curve, working on patients with varying levels of guidance. Simulation offers the possibility of having novices practice extensively before they begin to work on real patients as supervised "apprentices."

In this way and others, simulation is applicable to clinicians throughout their careers to support lifelong learning. It can be used to refresh skills for procedures that are not performed often. Knowledge, skills, and practices honed as individuals must be linked into effective teamwork in diverse clinical teams, which must operate safely in work units and larger organizations.[36-38] Perpetual rehearsal of responses to challenging events is needed because the team or organization must be practiced in handling them as a coherent unit.

Dimension 7: Age of the Patient Being Simulated

Simulation is applicable to nearly every type and age of patient literally from "cradle to grave." Simulation may be particularly useful for pediatric patients and clinical activities because neonates and infants have smaller physiologic reserves than most adults.[40,41] Fully interactive neonatal and pediatric patient simulators are now available. Simulation also addresses issues of the elderly and end-of-life issues for every age.

Dimension 8: Technology Applicable or Required for Simulations

To accomplish these goals, various technologies (including no technology) are relevant for simulation. Verbal simulations ("what if" discussions), paper and pencil exercises, and experiences with standardized patient actors[41-43] require no technology, but can effectively evoke or recreate challenging clinical situations. Similarly, very low technology—even pieces of fruit or simple dolls—can be used for training in some manual tasks. Certain aspects of complex tasks and experiences can be recreated successfully with little technology. Some education and training on teamwork can be accomplished with role playing, analysis of videos, or drills with simple mannequins.[44]

Ultimately, learning and practicing complex manual skills (e.g., surgery, cardiac catheterization) or practicing the dynamic management of life-threatening clinical situations that include risky or noxious interventions (e.g., intubation or defibrillation) can only be fully accomplished using either animals—which for reasons of cost and issues of animal rights is becoming very difficult—or a technologic means to recreate the patient and the clinical environment. The different types of simulation technologies relevant to anesthesiology are discussed later in this chapter.

Dimension 9: Site of Simulation Participation

Some types of simulation—those that use videos, computer programs, or the Web—can be conducted in the privacy of the learner's home or office using his or her own equipment. More advanced screen-based simulators might need more powerful computer facilities available in a medical library or learning center. Part-task trainers and virtual reality simulators are usually fielded in a dedicated skills laboratory. Mannequin-based simulation also can be used in a skills laboratory, although the more complex recreations of actual clinical tasks require either a dedicated patient simulation center with fully equipped replicas of clinical spaces or the ability to bring the simulator into an actual work setting (in-situ simulation). There are advantages and disadvantages to doing clinical simulations in situ versus in a dedicated center. Using the actual site allows training of the entire

unit with all its personnel, procedures, and equipment. There would at best be limited availability of actual clinical sites, and the simulation activity may distract from real patient care work. The dedicated simulation center is a more controlled and available environment, allowing more comprehensive recording of sessions, and imposing no distraction on real activities. For large-scale simulations (e.g., disaster drills), the entire organization becomes the site of training.

Video conferencing and advanced networking may allow even advanced types of simulation to be conducted remotely (see dimension 10). The collaborative use of virtual reality surgical simulators in real time already has been shown, even with locations that are separated by thousands of miles (see later for more on Site of Simulator).

Dimension 10: Extent of Direct Participation in Simulation

Most simulations—even screen-based simulators or part-task trainers—were initially envisioned as highly interactive activities with significant direct "on-site" hands-on participation. Not all learning requires direct participation, however. Some learning can occur merely by viewing a simulation involving others, as one can readily imagine being in the shoes of the participants. A further step is to involve the remote viewers either in the simulation itself or in debriefings about what transpired. Several centers have been using videoconferencing to conduct simulation-based exercises, including morbidity and mortality conferences.[45] Because the simulator can be paused, restarted, or otherwise controlled, the remote audience can readily obtain more information from the on-site participants, debate the proper course of action, and discuss with those in the simulator how best to proceed.

Dimension 11: Feedback Method Accompanying Simulation

Similar to real life, one can learn a great deal just from simulation experiences themselves, without any additional feedback. For many simulations, specific feedback is provided to maximize learning. On screen-based simulators or virtual reality systems, the simulator itself can provide feedback about the participant's actions or decisions,[46] particularly for manual tasks where clear metrics of performance are readily delineated.[47,48] More commonly, human instructors provide feedback. This can be as simple as having the instructor review records of previous sessions that the learner has completed alone. For many target populations and applications, an instructor provides real-time guidance and feedback to participants while the simulation is going on. The ability to start, pause, and restart the simulation can be valuable. For the most complex uses of simulation, especially when training experienced personnel, the typical form of feedback is a detailed post-simulation debriefing session, often using audio-video recordings of the scenario. Waiting until after the scenario is finished allows experienced personnel to apply their collective skills without interruption, and then allows them to see and discuss the advantages and disadvantages of their behaviors, decisions, and actions.

Dimension 12: Organizational, Professional, and Societal Embedding of Simulation

Another important dimension is the degree to which the simulation application is embedded into an organization or industry.[19] Being highly embedded may mean that the simulation is a formal requirement of the institution or is mandated by the governmental regulator. Another aspect of embedding would be that—for early learners—the initial (steep) part of the learning curve would be required to occur in a simulation setting before the learners are allowed to work on real patients under supervision. Also, complete embedding of simulation into the workplace would mean that simulation training is a normal part of the work schedule, rather than being an "add-on" activity attended in the "spare time" of clinicians.

Conceptual Issues about Patient Simulation

"The key is the programme, not the hardware," was a truth about simulation learned early in aviation. Using simulators in a goal-oriented way is equally or more about the conceptual aspects of the technique than it is about the technology of the simulation devices. An understanding of the conceptual and theoretical aspects of the use of simulation techniques can be helpful for determining the right applications of the technique and the important matchups that must be made in the design and conduct of simulation exercises to get the best results. When used most effectively, simulation can be—to borrow a line from the band U2—"even better than the real thing."[20] The concepts discussed in this section concern the nature of "realism" and "reality" as they apply to simulation, and the way that these issues relate to the goals of simulation endeavors to generate a complex social undertaking. The ideas and concepts presented here are largely contributed by Peter Dieckmann and his adaptation of broader psychological concepts to simulation in medicine.

Reality and Realism of Simulation

Unless we are dreaming about it or we are an unrepentant solipsist, a simulation exercise is always "real" (it is actually happening), but it may or may not be a "realistic" replication of the reality that is the target of the exercise. Realism addresses the question of how closely a replication of a situation resembles the target. A key distinction is between a *simulator* (a device) and a *simulation* (the exercise in which the device is used). A simulator could be indistinguishable from a real human being (e.g., a standardized patient actor) and yet be used in an implausible and useless fashion. Conversely, certain kinds of realism (see later) can be evoked by simulation exercises that use very simple simulators or even no simulator at all (as in role-playing when the participants in a sense "become the simulator"). Merely creating a realistic simulation does not guarantee that it would have any meaning or utility (e.g., learning).[21,22] A closely related aspect concerns the question of relevance and the social character of simulation.

Three Distinct Dimensions for Simulation Realism

A lot has been written about simulator and simulation realism using a variety of terms and concepts that are subtly different and often overlapping. These include *physical fidelity* (the device replicates physical aspects of the human body), *environmental fidelity* (the simulation room looks like an operating room), *equipment fidelity* (the clinical equipment works like or is the real thing), and *psychological fidelity*[23] (the simulation evokes behaviors similar to the real situation), and a variety of forms of validity, such as *face validity* ("looks and feels" real to participants), *content validity* (the exercise covers content relevant to the target situation), *construct validity* (the simulation can replicate performance or behavior according to predefined constructs about work in real situations), and *predictive validity* (performance during a simulation exercise predicts performance in an analogous real situation).[24,25]

The results of studies trying to investigate roots and effects of simulation "realism" are not conclusive partly because they may each concentrate on a different aspect of this complex whole. It is simply not true that maximum "realism" is either needed or desired for every type of simulation endeavor. For some applications with some target populations, it can be highly advantageous to reduce the realism to heighten the learning experience.[26]

In 2007, we published an article attempting to clarify some issues about realism, reality, relevance, and the purposes of conducting simulations.[21] We applied the model of thinking about reality by the German psychologist Laucken to the realism of simulation.[21] Laucken described three modes of thinking—physical, semantical, and phenomenal, which have been renamed physical, conceptual, and emotional and experiential modes by colleagues in Boston.[27]

Physical Mode

The *physical mode* concerns aspects of the simulation that can be measured in fundamental physical and chemical terms and dimensions (e.g., centimeters, grams, and seconds). The weight of the mannequin, the force generated during chest compressions, and the duration of a scenario all are physical aspects of the simulation reality. Existing simulator mannequins have many "unrealistic" physical elements despite their roughly human shape: they are made of plastic, not flesh and bone; they may have unusual mechanical noises detectable during auscultation of the chest; the "skin" does not change color. Some physical properties are not readily detectable and can be manipulated. Some clinical equipment used in mannequin-based simulation is fully functional and physically identical to the "real thing," although in some cases functional physical limitations may have been introduced for convenience or for safety.[24] Labeled syringes may contain only water instead of opioids, or a real defibrillator may have been modified so that it does not actually deliver a shock (one manufacturer sells a "Hollywood defibrillator"). That certain physical properties and functions have been altered is not usually apparent to participants, at least without special briefings or labels.

Semantical Mode

The *semantical mode* of thinking concerns concepts and their relationships. Within the semantical mode, a simulation of hemorrhage might be described in conceptual terms as "bleeding" of flow rate *X* beginning at time *Y* occurring at site *Z* and associated with a blood pressure of *B* that is a decrease from the prior value of *A*. In this mode of thinking, it is irrelevant how the information is transmitted or represented. The same pieces of *information* could be represented using a vital signs monitor, a verbal description, or the tactile perception of decreasingly palpable pulses. The semantical *recoding* of physical objects is the cornerstone of simulation. It allows the simulation exercise to represent a real situation, and it allows water-filled syringes to be treated as if they contain a drug.

Phenomenal Mode

The *phenomenal mode* deals with the "experience," including emotions and beliefs triggered by the situation. For many purposes, providing high phenomenal realism is the key goal, and the physical realism and semantic realism are merely means to this end.

Relevance versus Reality

A naive view of simulation would suggest that greater realism in all modes would lead to better achievement of the goals of simulation; this view has been criticized repeatedly.[23,28,29] Simulation is a complex social endeavor, conducted with different target populations for different purposes. The relevance of a simulation exercise concerns the match between the characteristics of the exercise and the reasons for which the exercise is conducted. Different elements of realism are emphasized or sacrificed to maximize the relevance of a simulation exercise. When training on invasive procedures, it is typical to forgo phenomenal realism and emphasize physical and semantic realism so that psychomotor skills can be the focus.

Semantic realism may be sacrificed, especially to help early learners. Situations that might become lethal (e.g., trigger a cardiac arrest) very quickly may be slowed down so that inexperienced clinicians can try to think their way out of the problem. If such a situation were allowed to evolve at its normal speed, it would transition to the management of a cardiac arrest before the participants could deal with the original problem. Other realism-sacrificing strategies for early learners include "cognitive scaffolding," providing various forms of assistance or cues to help them as they struggle with decision making and therapy selection. It is important to select which aspects of the simulation are the most relevant to reach the training goal and should be focused on in terms of optimizing their realism in the different modes.

Setting of the Simulation Exercise

Simulation exercises have a purpose and are generally integrated into a larger training context (often a course or a series of exercises), which influences how they are conducted, how they are perceived by participants, and what kind of effects they might have. This context has been called the *simulation setting*. The typical elements of the simulation setting are discussed next and shown graphically in Figure 7-2.

Setting introduction (SI): The introduction delivers general information on how the exercise will be conducted, logistical information, and some of the known pitfalls of the

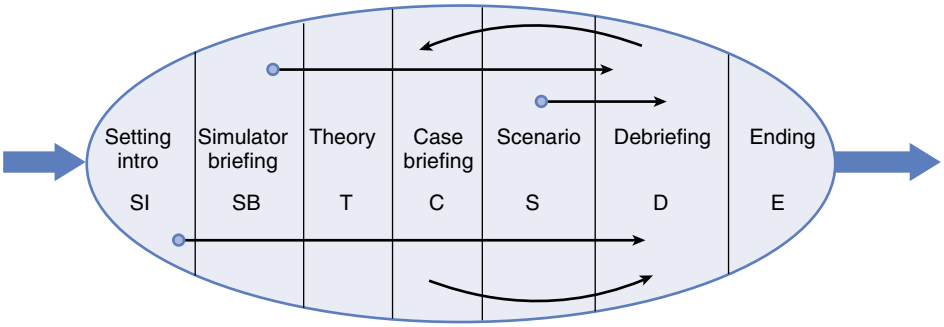


Figure 7-2 The simulator setting. A simulation course consists of different modules or different phases (e.g., setting introduction, simulator familiarization, scenarios, debriefings). This figure shows a typical flow for a course with repeated loops back from debriefing to case briefing for each scenario. The different modules are interrelated, and problems arising in one module can affect other modules (*thin arrows*). For example, it might be difficult to conduct an open, constructive debriefing if the scenario was irrelevant, or the simulator briefing was insufficient, and or the instructor did not succeed in creating an open atmosphere in the beginning of the course. *(Courtesy of Peter Dieckmann.)*

course. Through this introduction and other components of the course, group norms are established explicitly and implicitly.

Simulator briefing (SB) or familiarization: Participants need to be familiar with the simulator and the simulated environment via explanations, demonstrations, and hands-on time. They learn how to use the simulator, what it can and cannot do, what is "normal" (e.g., normal breath sounds), and how they can interact with the environment (e.g., how to call for help, how to request information about the patient that is not directly available in the simulation environment). The familiarization session also is an opportunity for participants to practice the information gathering they must conduct when first entering a new work environment (e.g., for locum tenens practice).

Theory input (T): Most exercises have didactic and theory components on relevant content information. Sometimes this material is made available in advance via readings or online exercises. It may be presented before or after a simulation session. Sometimes there are didactic or group-work modules put in place at different junctures of the course or series.

Breaks (B): For complex courses (e.g., anesthesia crisis resource management [ACRM]), breaks are important for socialization between participants and with instructors. It also is a venue for informal sharing and storytelling.

Case briefing (C): In many simulation scenarios, participants receive a briefing about the upcoming case. Sometimes this is done explicitly before entering the scenario; sometimes it is embedded into a natural "hand-off" of the case from one clinician to another.

Simulation scenario (S): Most simulation exercises involve a scenario that posits a given clinical situation and challenges to be posed for participants to deal with. Commonly, the possible evolutions of the scenario are delineated by instructors in advance, although occasionally an intrinsically challenging situation is started and then allowed to play out naturally depending on how the participants react.

Debriefing (D): Most scenarios are followed by some form of debriefing or feedback. In some courses, there is only minimal feedback, whereas in others there is a dedicated debriefing session (as long or longer than the scenario itself) after each scenario. (See the section on debriefing for more detail.)

Ending (E): Especially for multiple-scenario courses, there may be a separate final session to end the course. This is an opportunity to summarize issues that were covered, to address questions, and to consider how best to apply the principles covered to real patient care.

Components of a course are expected to have a cumulative effect. Similarly, problems in early portions of a course (e.g., inability to create an open learning atmosphere during the introduction) can carry over into later phases. Inadequate familiarization briefings leave participants confused as they try to perform "clinical work" with the patient replaced by a mannequin.

Site of Simulation

Over more than 20 years of experience in simulation, many different variants of simulation have evolved. One particularly rich set of variations is on the site of simulation. The types of "sites" currently in use are described; the advantages and disadvantages of each are summarized in Table 7-2. Many of these variants are not mutually exclusive and can be combined in different hybrids. They are often administratively linked—a simulation group that operates a dedicated center often also conducts in-situ, mobile, and moving patient simulation exercises at various times for different target populations and applications.

Dedicated Simulation Center

One or more simulators are used in a dedicated simulation facility, typically in rooms that can partially or fully replicate, in a relatively generic fashion, various clinical environments (e.g., operating room, ICU, labor and delivery, emergency department). (For more details see the section on Charactistics of Simulation Centers discussed later.)

Table 7-2 Site of Simulation

Site of Simulation	Explanation	Advantages	Disadvantages
Dedicated center	Fixed facility not part of an actual clinical work unit	Equipment permanently installed Facilitates complex audiovisual systems Easy to schedule Personnel not readily "drafted" for clinical work Does not interfere with actual clinical work Multipurpose	Cannot recreate exact work unit, equipment, supplies of diverse target populations May be hard for clinicians to be free to attend training
Temporary in situ	Actual work unit; temporary setup and takedown	Real clinical site Probe or train personnel in their actual work unit, using real equipment and supplies Clinicians can readily attend in proximity to their work	Hard to schedule—may need site for clinical use Interferes with actual clinical work; personnel readily drafted to return to clinical work Great effort of setup and takedown; minimal audiovisual system
Residential in situ	Actual work unit; permanent facility	Same as temporary in situ	Costly to create permanent simulation "bed" in clinical work unit May distract from real clinical work, personnel may be drafted
Patient movement simulations	Transport from site to site is simulated	Transport itself is challenging clinical work Replicates natural flow of patients and handoffs between teams	Requires multiple simulation sites Portable wireless simulators have some technologic limitations
Mobile simulation	Simulation systems and instructor crew travel to client (or neutral) sites	Brings simulation expertise to those who cannot or wish not to invest in it themselves For in-situ use, all advantages thereof	Transport costs can be high (driver, fuel, vehicle) For in-situ use, all disadvantages thereof plus even greater effort for setup and takedown

In-Situ Simulation

In-situ simulation is conducted in an actual clinical workplace; the simulator "replaces" a patient. In-situ simulation is a necessity in the absence of a dedicated center, and can be used in any clinical environment. It is especially useful for unusual workplaces that are difficult to recreate realistically in a simulation center, such as a catheterization laboratory, computed tomography scanner, ambulances, or air rescue aircraft (Figs. 7-3 to 7-9). Most in-situ simulation is performed "mobile" as a temporary setup, but increasingly in-situ simulation is established as "residential simulation," in which a simulator is permanently installed in a clinical workplace (e.g., creating a simulation-specific room in the actual ICU.

Moving Patient Simulation

The advent of completely portable and wireless simulators supports exercises in which the simulated patient can be moved from one clinical site to another. The patient could be brought into the emergency department by ambulance; taken to a computed tomography scanner, interventional radiology, or operating room; and finally transferred to an ICU. Under what circumstances such movements are worth the effort remains to be determined.

Mobile Simulation: "Have Simulator—Will Travel"

Mobile simulation means the simulator and the audiovisual gear are moved (made mobile) outside the originating institution for purposes of the simulation event. In other words, "the simulator comes to the participants." Mobile simulation can be conducted as in-situ simulation in an actual site of a remote client institution, by setting up for simulation in conference rooms or hotel meeting rooms, or by having a simulation facility built into a truck or bus. The built-in mobile facility saves time in setup and takedown, It also is possible to conduct "field exercises" setting up the simulator outside (e.g., in a parking lot or athletic field).

Advantages and Disadvantages of Different Approaches

The advantages and disadvantages of different approaches are summarized in Table 7-2. For sites that lack a dedicated



Figure 7-3 In-situ mobile simulation in a catheterization laboratory. The simulator is placed on the catheterization laboratory tables, surrounded by the x-ray machines, complicating the treatment of the patient by limiting space. The vital sign monitor is connected to the real monitors, providing relevant data to the catheterization laboratory team. The simulator is controlled from the catheterization laboratory control room. Multiple mobile cameras and a scan converter for the vital signs provide a live video transmission to a temporary debriefing area for the nonactive part of the training group and allow for CRM-based debriefings. CRM, crisis resource management. *(Picture by team TuPASS, taken at University Hospital, Tübingen, Germany.)*



Figure 7-5 In-situ mobile simulation team training in an ambulance. The limitations regarding space to work and move around inside an ambulance are very important. This represents a classic need for in-situ training of prehospital teams (in Germany consisting of three paramedics and a prehospital emergency physician). Also, "take-over scenarios" (e.g., the helicopter team is taking over a patient from the ground-based team) are a challenge for CRM expertise (e.g., information transfer and continuous patient treatment). CRM, crisis resource management. *(Picture by team TuPASS, taken at one of the German Air Rescue centers, Germany.)*



Figure 7-4 In-situ mobile simulation in a dentist chair. The simulator was equipped with artificial teeth gum and a chalk tooth preparation to drill, simulating the dentist's procedures (give anesthetic or drilling). Then emergencies developed, and the team response was trained focusing on CRM key points and important medical aspects, including automated external defibrillator use. CRM, crisis resource management. *(Picture by team TuPASS, taken at University Hospital, Tübingen, Germany.)*



Figure 7-6 In-situ mobile simulation team training in a helicopter. The mobile simulation control room with several cameras and microphones is set up outside the helicopter, also providing a multiperspective view inside to monitor the scenario and react to activities performed. *(Picture by team TuPASS at the German Air Rescue/TuPASS training site at Airmed 2008.)*





Figure 7-7 **A,** In-situ mobile simulation training in a simulated apartment for prehospital teams. The apartment (living space) scenarios are very common for prehospital teams, requiring adaptation to the local space availability and other circumstances (e.g., bystanders, dogs). **B,** Emergency department simulation with the prehospital team handing over a patient to the hospital staff—always a phase of high-demand and goal-oriented interactions. From a CRM-training perspective, this scenario is a very good opportunity to highlight problems and unsafe practices (in the sense of high reliability), and to show good team performances using video clips of a scenario. CRM, crisis resource management. (***A,*** *Picture by team TuPASS at a CRM training session with the South Tyrolian White Cross in Bolzano, Italy.* ***B,*** *During an instructor training course at TuPASS, Germany.)*

simulation center, there is no practical alternative to either engage in in-situ simulation or to be a client for mobile simulation. Simulation in the dedicated center facilitates scheduled training and use of complex audiovisual gear. Simulators can be preset, tested, and ready to go. Briefing and debriefing facilities are immediately at hand. In a dedicated center, it is common to use inexpensive discarded, flawed, or outdated clinical equipment and supplies. The major disadvantage to a dedicated center is that regardless of how well equipped it is, it can never replicate the equipment, layout, and clinical processes of actual clinical workplaces. Also, participants know that they are in a simulation center, which may alter their demeanor and reduce the impact of training.

In-situ simulation seems ideal in that it probes and challenges personnel and systems as they actually exist, unmasking real issues of patient care. It is available, in principle, to all sites, even those without a dedicated center, and is conducive to short courses and unannounced mock event drills. In-situ simulation



Figure 7-8 In-situ mobile simulation in an intensive care unit (ICU)/intermediate medical care unit location. The training in actual clinical areas also is especially useful for ICU-like surroundings. CRM-based trainings are very important to highlight the highly complex problems and interactions needed to coordinate high-performing ICU teams. The training also allows for "checking" the local arrangement of equipment and possibilities to react to certain emergencies. There are already a few examples of "residential" in-situ simulation in ICUs (see text). *(Picture by team TuPASS.)*

has disadvantages, however. It is difficult to organize, schedule, and control. The clinical area planned for simulation may not be vacant or may be needed on short notice. The simulations can be distracting to real patient care surrounding them, and the staff engaged in the simulation are prone to being pulled to clinical duty, and there may be constant interruptions of the training sessions. Most clinical supplies must be taken from the stocks of the work unit in order to prevent mix-ups with outdated simulation



Figure 7-9 In-situ mobile CRM-focused simulation team training inside an actual operating room. The figure shows the debriefing room temporarily set up in an induction room. The use of videos for debriefing (here on a 42-inch flat panel placed over the basin) is highly recommended. Training inside a hospital often includes training actual teams and training a large proportion of employees with the same set-up. These mass training sessions seem to offer a much larger impact and longer lasting effects of the lessons learned, including CRM behaviors (see text on subthreshold training). *(Picture by team TuPASS who performed at a full team training of the Anesthesia department at Steinenberg Medical Center, Reutlingen, Germany.)*

supplies, adding expense. There are major limitations to the audiovisual gear that can be deployed in a real clinical site. A permanent in-situ facility could provide the best of both worlds. Such an arrangement offers unique opportunities, such as the ability to "replay" immediately difficult cases in the simulator "next door," the possibility to use low workload times for spur-of-the-moment simulation sessions, and the ability to conduct long-term simulations (team members responsible for a simulated ICU patient over days or weeks). The major drawback to this approach is that to address diverse clinical domains requires such a site in every domain, and this could be extremely costly.

Team Training, Single Discipline, and Crews

Each discipline in health care can be considered a "crew" containing one or more individuals. Several crews may work together closely as a "team." The operating room team consists of an anesthesia crew, a surgery crew, and a nursing crew (and crews of technicians and support personnel).

Further complementarity exists regarding the homogeneity of the target population in simulations. When the simulation is intended to go beyond specific medical and technical skills for individuals (as in crisis resource management–oriented simulations) and to involve nontechnical skills and teamwork, we distinguish between "single-discipline" approaches ("training crews to work in teams") and true "combined-team" (multidisciplinary) training.

The importance of teamwork and team training is widely accepted,[30-35] although it is still not widely implemented. The prerequisites for effective teamwork (e.g., team leadership, mutual performance monitoring, backup behavior, adaptability and team orientation,[35] and the concept of team cognition) are discussed in Chapter 6.

Single Discipline

Training for single-discipline crews (e.g., anesthesiologists) involves curricula in which all participants are from a single discipline, and other crew members' roles are played either by instructors and confederates or by other simulation participants. This approach allows tailoring simulations to challenge skills, knowledge, and situations specific to the discipline, including material that may be of little relevance to other crews and in the context of a wide variety of types of clinical situations (e.g., cardiac, orthopedic, or general surgery; labor and delivery; intensive care). Single-discipline training can emphasize generic skills of dynamic decision making, resource management, leadership, and teamwork applicable to any challenging clinical situation. In the single-discipline approach, scenarios can be designed that present specific types of personalities and behaviors by other crew or team members, rather than relying on the ad-hoc behavior of real personnel from those disciplines. Even without actual personnel from other disciplines, training crews to work in teams also provides a degree of cross-discipline understanding by allowing participants to discuss other team members' views of the same situation.

For dedicated center simulations, single-discipline sessions are simpler logistically because only one discipline needs to be present, rather than scheduling someone from each of the disciplines. In addition, simulations can be applied to some disciplines even in domains where there are not yet credible simulators for the work of each team member. The single-discipline approach may be of particular relevance for trainees who when finished with their training will go on to work in many different settings and with many different kinds of personnel. It also may be of greatest value for individuals who do not work in "fixed" crews or teams and need to acquire generic teamwork skills that can be used with all coworkers.

Combined Team Training

The complementary approach is to conduct *combined team training,* in which all participants of the team, from crews of several different disciplines (e.g., surgeons, nurses, anesthesiologists), undergo training together. Combined team training allows for more natural team interactions and reinforces understanding across disciplines. There are successful examples of such undertakings in many fields, including obstetrics (combining obstetrics, anesthesia, nursing, neonatology/pediatrics) and intensive care (combining physicians from multiple disciplines with nursing, respiratory therapy, and pharmacy).[32,36-46]

Combined team training may be most effective when a specific group of individuals is to work together clinically as a dedicated team. In dedicated simulation centers, combined team training can be hard to schedule, and it may require instructors from several of the disciplines to conduct the debriefings. Combined team simulations may be easiest to organize when they are conducted as unannounced mock events that activate the actual bedside team (e.g., ward or unit team, rapid response team, or code team). In such situations, the real combined team is mobilized as they would be in real life.

Debriefing for Simulation Training

Debriefing refers to a special time and format for talking about an episode of action in the past; it is the counterpoint to a briefing that occurs before an action or task. The term originally came from the military, for after-action reviews of real missions and simulations. In medicine, the debriefing concept was introduced to simulation training by Gaba and colleagues as part of the whole concept of CRM-based simulation training for anesthesia teams.[16,95] This section focuses on debriefings in the context of simulation team training.

Debriefing—Heart and Soul of Simulation Trainings

In aviation and health care simulations, the debriefing after a simulation team training session is a key element—perhaps the most important element—of simulation training.[47] The debriefing offers an unparalleled instance to reflect and discuss openly and understand other team member's intentions, thoughts, and prob-

Table 7-3 Traditional Teaching versus Facilitation in Simulation Training Courses

Traditional Teaching: "Teacher"	Debriefing Facilitation: "Instructor/Facilitator"
Focus on theoretical knowledge	Focus on human factors and CRM aspects
Focus on what	Focus on why and deeper analysis of why it did (not) work
Teacher is the best (expert)	Instructor just moderates, uses knowledge of participants
Teacher tells participants what to do	Instructor helps participants to find what they could have done and what would be the best way
Teacher knows what is important for participants	Instructor helps to self-reflect and gain realistic self-awareness/consciousness Instructor guides toward interesting areas
Talks most	Stimulates discussion among participants
Domain expert	CRM expert
No teaching training	Extensive instructor training
No video	Use of video of own and others' scenarios
Teacher knows what has been learned (or not)	Instructor might not be aware of all aspects that participants take home

CRM, crisis resource management.

lems. Much of the learning occurs in this self-reflective episode. Eventually, these routines will be applied to clinical medicine (e.g., surgical team timeout).

New Way of Teaching

The debriefing as described in aviation and introduced and refined for medicine by Gaba and others[48,49] requires a complete understanding by instructors of their role in promoting learning (see Chapter 8).[50] The philosophy of teaching and learning in a debriefing of a CRM-based simulation course differs from the traditional clinical teaching style (Table 7-3). The instructor's role is to *facilitate* the learning process, *directing the participants* to the most interesting and important areas for consideration, and *stimulating discussion* among participants to *find the underlying issues* and to seek solutions for future events of similar type.

Facilitation is a new way of teaching and often must be learned anew by instructors, even though they have many years of traditional teaching experience. The use of video for debriefing can advance further the self-reflective component of debriefings, but requires additional expertise to integrate it successfully with self-reflection. Generally, faculty intending to be primary debriefers need special training and practice in this teaching method (see section on Instructor Qualification). Several simulation centers conduct instructor training that emphasizes debriefing skills.

Technique of Debriefing

Although debriefing styles and philosophies differ at centers around the world, a common ground is shared by most centers: A debriefing should *stimulate self-reflection,* and analyze *how* something happened, and what the *underlying concepts* for doing so were, rather than merely finding out *what* happened. Usually the debriefing lasts at least as long as the scenario itself.

Detailed discussions about the different techniques appear in the literature.[47,48,50-54] To prepare a good debriefing, the instructor is challenged during the scenario with performing several tasks in the control room, such as listening to trainees, talking to the instructor team, controlling the simulator, and making notes for the debriefing. Figure 7-10 illustrates the different levels of attendance.

Debriefings by nature have different phases, as shown in Table 7-4. The phases are not meant to be followed in this time sequence and order. Often two or more phases are covered regarding one problem of the scenario—especially clinical problems are often covered while discussing the "how" and "when" they happened (analysis). Then another problem is analyzed and discussed according to different phases. Nevertheless, at the end of a good debriefing, all phases should have been covered according to their respective importance. No debriefing style is associated with a proven better learning outcome, and there may never be defini-



Figure 7-10 The multiple levels of work for CRM-based instructors in the control room. The reflections in the one-way mirror of the control room make the multiple levels of activity transparent. The team of instructors has to control the simulation as such, but also make notes for the CRM-based debriefing. The scenario inside and the audio streams (telephone call) need to be monitored. Also, the instructors have to deal with simulation team role players and instructor trainees inside the control room. These complex tasks need some training and good team organization on the side of the simulation center team. CRM, crisis resource management. *(Picture by B. Schaedle, team TuPASS, taken at a PaedSim training at University Hospital, Tubingen, Germany.)*

Table 7-4 Phases of Debriefings: Issues Relevant to CRM-based Simulation Debriefing

Phase of Debriefing	Explanation
Ending the scenario	When possible, the scenario should not be stopped too early. Participants should be allowed to realize the natural end of the scenario. Ideally, it should not be terminated when participants are in the thick of it
Scenario-to-debriefing transition	Most sites use a "hot" debriefing, in which they enter the debriefing room immediately from the simulation room. This allows the instructor to hear and see participants' direct reactions. Another option is to give the participants a few minutes to discuss the scenario itself while the instructor is planning the debriefing
Emotional venting	All participants who were actively involved are given the opportunity to say how they *felt* during the scenario. This vents pent-up feelings, and may be a time to deal with anomalies in the scenario (e.g., simulator malfunction)
Descriptive phase	Participants describe what happened (or portions of the video are replayed). Different points of view (e.g., hot seat versus first responder versus surgeon confederate) are shared
Self-identification of issues	It can be useful, before anyone else including the instructor is allowed to critique the scenario, to allow active participants to say if they themselves detected any errors or actions that they would do differently. It can be painful and rude to critique participants about something they are aware of themselves
Discussion of clinical content	Any major issues of clinical treatment and related CRM points should be covered. A debriefing should not end without discussing and clarifying any significant clinical errors, and ensuring that participants understand the correct management
Analysis	Debriefings should provide considerable "analysis" of *why* things happened vis-à-vis the intentions of all parties, and alternatives and their pros and cons
Opportunities for systems improvement	Based on the analyses, participants can be asked to suggest how the system can be changed to improve the handling of similar situations in the future
Transfer to the "real world"	Participants can discuss how lessons from the scenario or debriefing can be applied in the real clinical world. They should discuss barriers to improvement and ways to overcome them
Providing a "take-home message" from the scenario and debriefing	A summary of the key points of the debriefing can be useful, either by the instructor or the participants themselves
Terminating the debriefing	Debriefings are rich in content and could extend beyond the time available. Marking the end of the debriefing can be a useful transition to preparing for the next scenario or to the end-of-day activities

CRM, crisis resource management.

tive data on the techniques because of the nature of the topic—reflective practice of high-level cognition.

Use of Video for Debriefings

Although the value is not proven, segments of video recordings to support and deepen the debriefing as a learning and self-awareness experience are frequently used. Anesthesia does not allow for much self-reflection and feedback during routine clinical work. Experienced colleagues typically work alone, and there is often little feedback from other anesthesiologists or from other operating room personnel. This situation is now changing, however, with the use of automatic anesthetic records and information technology (see Chapters 2, 4, 5, and 99).

The lack of feedback leaves a large theoretical gap between the way individuals think they perform and how they do act in reality. Video sequences can correct this gap and provide an awareness of how participants have really acted. Also, one's own video recordings can be compared with the recordings of other participants (either their own course co-participants or "trigger videos" meant to stimulate discussion). "Live transmission" of scenarios to participants not actively involved in the scenario also is useful. When this technique is used, the observers can be given special tasks (e.g., look for CRM key points 10 and 11 in Table 7-8). A study in Tübingen evaluated the use of so-called cooperation scripts in the "passive" phase of watching others perform.

The video should be used in the service of the debriefing, rather than the other way around. The authors believe that if the discussion is active and on-target, it is useless to interrupt it just to show video. Video may have a bigger impact for participants' first simulation experiences. Here they are sometimes struck by what can be revealed on seeing themselves and others work. As they gain more experience with simulation, and when debriefers are experienced, they may not need exposure to the video to hone in on key issues to discuss.

Clinical Application of Debriefing Method

The application of the above-described debriefing techniques to the discussion of real world clinical critical incidents seems very promising. Applying the debriefing technique learned in the simulator after a critical incident in short debriefing circles of the involved clinical team has proven quite valuable.[41,50,55-58]

Scenario Design

The design of scenarios for interactive simulation team trainings is demanding and typically differs from preparing training exercises for traditional curricula, such as "mega codes" in advanced life support. Full simulation scenarios are complex enough that

their design is usually an iterative process by which the scenarios are continually improved through experience.

This section can give only an overview of the important aspects of scenario design for realistic simulation team training. The reader is referred to detailed published examples of scenarios in *Simulation in Healthcare*[59] and to more detailed literature about the principles of scenario design.[3,60] The topic also is covered extensively in most of the instructor training curricula that are offered at sites around the world. International and regional simulation meetings often offer workshops on scenario design (IMSH of SSiH, SESAM); the user groups of the major simulator manufacturers also have workshops on the topic. (See section on Simulation Societies discussed later.)

Goal Oriented

Scenarios usually are designed to achieve learning objectives or other goals, such as a formal needs analysis of the relevant target group for training concerning clinical and technical skills or nontechnical CRM skills or both (see Chapter 6). Alternatively, simulation-savvy clinician educators may intuitively know what kinds of scenarios are likely to be valuable for their participant populations, or they may have learned about good examples in their instructor training or in the literature. The cases are not as important as the nature of the underlying challenges that they pose to participants. *Train the causes not the cases.*

Scenarios should be relevant to the trainees. This relevance is more important than realism and depends on many factors, including the trainees' backgrounds and experience, and the method of conducting the scenario and related parts of the simulation course (e.g., familiarization, case briefing, role players).

Constraints and Limitations

It is easy to suggest a scenario on paper but more difficult to translate it into an effective scenario for actual use. There are limitations and constraints to consider, including features and limitations of the simulators available, personnel resources at hand, the props or external systems that would be needed to engage participants, and time available for the proposed scenario. In our experience, most scenarios are first generated with an idea or a "nubbin." The idea is fleshed out by discussion and on paper in an iterative fashion, with limitations addressed either by creative redesign of the proposed situation or by minor technical modifications using the simulator software or simulation environment. The new scenario usually is tested out first by instructors and "simulationists" (the technical staff who operate the simulators and prepare the environment). It can be pilot tested with a volunteer group of participants from the target population. The first one or two sessions typically reveal many problems and flaws in the original scenario layout. After a scenario has been designed and tested, it is advisable to add comments and suggestions for improvement continuously after each training session.

Scenario Templates

Many centers have developed templates for the design of their scenarios. Figure 7-11 is an example of a summary sheet of the template used by TuPASS and taught during their instructor courses. The full version of it is available online (www.tupass.de/scenarioscript.html). Other scenario templates are popular, including the Duke University template (http://simcenter.duhs.duke.edu/SimTemplate1203.doc). The peer-reviewed journal *Simulation in Healthcare* publishes "Simulation Case Reports," which contain detailed scenario descriptions. Some professional societies have created scenario repositories for members; the American Society of Anesthesiologists (ASA) Simulation Committee has a repository for scenarios to be shared between its ASA-endorsed simulation programs.

Instructor Qualification

Teaching with simulation covers a diverse spectrum of applications. In some cases, it is similar to teaching at the bedside, only the patient is a simulator, in which case the skills needed are nearly identical to those used in ordinary clinical supervision and teaching. There are special implications for instructing in courses that involve complex realistic scenarios, with multiple personnel in crews and teams, using video-facilitated debriefings in small groups, and with a focus on human factors and CRM principles and countermeasures. In such courses, the skills needed to be a successful instructor go considerably beyond those typically used by teaching clinicians. Quality of the instructors is *the* key element for any simulation course, captured by the statement "The key is the program, not the hardware."[10] Ensuring instructor competence in using simulation and in debriefing facilitation skills is very important.

Advanced simulation course formats generally reflect very well Kolb's[60a] circle of adult experiential learning: (1) self-experience (participate in the scenario) or vicarious experience (observe scenario live), (2) reflect on experience (debriefing), (3) abstract conceptualization (debriefing, relate to theoretical material), and (4) active experimentation (future scenarios and use of skills in real cases) (Fig. 7-12).

Tasks of Instructors

The tasks of a simulation instructor differ from the tasks of a classic medical educator or a trainer for part-task or skills training. The most prominent differences are the following:

- Need to brief the course participants about an unfamiliar environment
- Creation of relevant, plausible scenarios to reach the intended learning goals
- Theatrical aspects of enacting complex realistic scenarios
- Need for simultaneous control of the simulator, the simulation personnel (instructors, actors, and confederates), and learning objectives during multiperson complex scenarios with built-in problems and challenges and an uncertain flow pathway of action by participants
- Need to provide debriefing and feedback after the scenario, often assisted by replay of video recordings, primarily using a "facilitation style" in small groups; handling group dynamics and individual sensitivities is required

TuPASS Scenario Script Developed by P. Dieckmann & M. Rall, TuPASS, Germany		
Quick reference: Scenario name		
Major problem	Medicine	CRM
Learning goal	Medicine	CRM
Narrative description		
Staffing	Simulator team	Participants
Case briefing	All participants	"Hot seats" only
Simulator setup Mannequin preparation		
Room setup		
Simulator operation		
Scenario lifesavers		
Props needed		

Figure 7-11 The TuPASS Scenario Design Template. The figure shows the summary page of the TuPASS Scenario Design Template, which has more space and details in the full version. The template also includes a script to explain the different fields and their best use. The template is a regular part of the instructor training courses. It can be obtained from the TuPASS webpage (www.tupass.de/scenarioscript.html). *(Template by P. Dieckmann and M. Rall, TuPASS, Germany.)*

- Concentration largely on CRM nontechnical skills of decision making, team management, interpersonal relationships, communication, and professionalism

Instructor Training

For such complex instructor skills, formal training seems warranted. One of the authors (D.G.) pioneered instructor training for CRM-oriented simulation courses in a consortium of the VA–Stanford Simulation Center with the Boston Center for Medical Simulation and the University of Toronto Sunnybrooke Simulation Center. This consortium spread the ideas and format of CRM simulation instructor training around the world. Another author (M.R.) has been running instructor courses in cooperation with a third author (P.D.) for more than 1,000 international participants. Many institutions offer different instructor courses nationally and internationally (ranging from 2 to 6 days in length depending on the course and its scope); the reader is referred to the simulation societies for information about such courses (SSiH, SESAM). The process and impact of instructor training are being evaluated much as the process of simulation training itself is being assessed. Some early evidence is emerging that such courses have value. Also, shorter introductory courses on instructor skills are offered every year at the international health care simulation meetings (e.g., SSH's IMSH conference or the SESAM annual meeting), and there are many workshops at the meeting that cover topics such as debriefing, instructor training, and CRM training.

Table 7-5 presents an example of learning objectives for an instructor training course. For experiences and effects of the instructor course by P. Dieckmann and one of the authors (M.R.), a poster presented at the IMSH 2006 with a short description of the InFacT course and results from a response-shift bias analysis can be downloaded from our website (www.tupass.de/downloads/InFacT.html). The most difficult task for traditional medical teachers is to learn to stop "instructing" and start "facilitating"—guiding participants toward a deep learning experience.

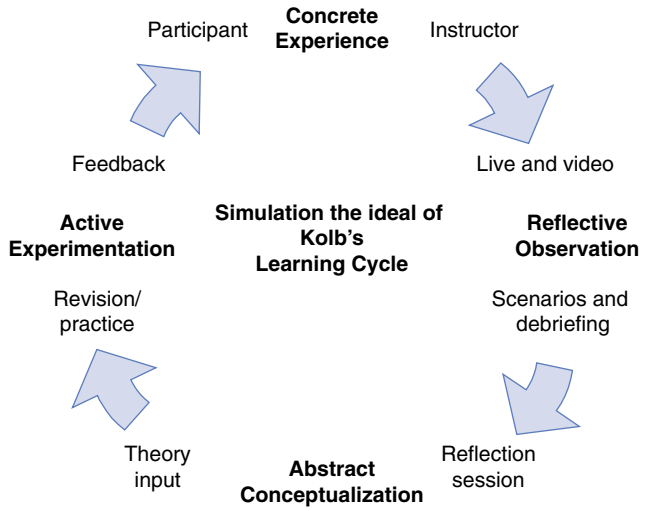


Figure 7-12 Simulation team training with live video transmission as an "ideal" representation of Kolb's learning circle. During the scenario, trainees get a hands-on experience. This is actively reflected in the debriefing. The live video to the nonactive group in the current scenario allows useful reflective observation. During the debriefing, all trainees have a phase of conceptualization, in which the instructor uses generalizations of factors and root causes to show how behavior developed as it did in the scenario (deep learning). During the feedback in the debriefing, but also in the next active scenarios, participants have opportunities to apply and experiment with the newly learned input. *(Figure by P. Dieckmann, modified from Kolb. DA: Experimental learning: Experience as the source of learning and development. Englewood Cliffs, NJ: Prentice Hall, 1984.)*

Certification of Instructors

The original simulation instructors were self-taught in these skills. Should instructors receive documented formal training and certification? CRM-oriented simulation training is probably the most difficult level to achieve. Many institutions have internal systems of levels of training for simulation instructors; they have their own mechanisms for assessing instructor skills and moving instructors up the levels of instructor competency. There is at this time, however, no guideline or agreement regarding criteria for advancement from one level to another.

Certification of instructors is just one piece of a larger puzzle of the certification of simulation centers and programs and the certification of specific simulation-based curricula. The ASA in 2008 started a process to endorse (as opposed to accredit or certify) reputable simulation programs capable of delivering high-quality continuing medical education (CME) to ASA members. The Society for Simulation in Healthcare is planning an accreditation program for simulation centers to be accredited in one or more of the areas of assessment, research, training, and patient safety integration. Various other organizations have started or are considering starting similar programs. Specialty and subspecialty societies within anesthesia (including the ASA Simulation Committee) are considering defining one or more uniform curricula to be offered at accredited or approved programs.

It is likely that the skills and certification needed for an instructor would vary greatly with the particular course or curriculum being taught. Competence in conducting a video-based CRM debriefing would not be needed, and would not help, to teach central line placement using part-task trainers for this procedure, and vice versa. Instructor certification probably would be tied to the specific types of courses each individual is capable of conducting. A tiered instructor certification system also would likely provide for advancement from novice instructor to grand master as experience and special training are acquired.

Table 7-5 Learning Objectives for CRM-oriented Simulation Instructor Courses*

Understand how it feels to be a participant in a simulation scenario, and to be debriefed in a group, seeing oneself on video
Understand the interdependent influence of the different course phases (see Fig. 7-2), and apply this knowledge to a simulation course
Reflect on the changing instructional styles that can be applicable to simulation courses (instruction—facilitation)
Understand basic concepts of human factors, systems theory, and organizational safety
Be able to detect, explain, and discuss CRM key points in the debriefing of scenarios
Use recorded video of scenarios well, selecting the most relevant portions for replay and discussion
Be able to facilitate a debriefing in a nonjudgmental atmosphere with appropriate boundaries
Understand how to manage the individual sensitivities and group dynamics of participants during debriefing
Be able to focus debriefing on the analysis of what happened, why things happened the way they did, and how to apply these lessons to real patient care

*Adapted from the learning objectives of old instructor courses by the authors and P. Dieckmann.

Classification of Patient Simulators

No accepted classification scheme has been devised for the use of patient simulators in anesthesia. Any classification involves some overlapping and gray areas.[19] Cumin and Merry[61] have published a review about available simulators. The following classification and definitions are used in this chapter. In addition to simulators, there are computer-assisted instruction programs and computer-based training devices. Although training devices may replicate certain portions of the clinical domain, they do not attempt to replicate the bulk of the work environment. Some individuals consider the screen-only microsimulator (also known as a screen-based simulator) to be a training device and not a simulator. Computer-assisted instruction programs and training devices are not reviewed in this chapter. This chapter addresses patient simulators in anesthesia that present the overall patient as would be seen by anesthesiologists, intensivists, or others. Devices related purely to emergency medicine (e.g., ResusSim), surgical or procedural simulators that present only the technical work of surgery or invasive manipulations (e.g., bronchoscopy, intravenous access), and partial-task screen-based simulators (e.g., GasMan) are not discussed here.

In this chapter, a *patient simulator* is a system that presents a patient and a clinical work environment of immediate relevance to anesthesiologists (e.g., operating room, postanesthesia care unit, ICU) in one of the following ways:

1. In actual physical reality, defined as a mannequin-based simulator (former and still commonly used synonyms are full-scale simulator, hands-on simulator, realistic simulator, high-fidelity simulator). These simulators can be subdivided in terms of the way that vital signs monitoring is accomplished (interfacing to real clinical monitoring devices or using its own virtual replica of a monitor screen) and in terms of the primary control logic of the simulator (by individual controls and scripts or by using physiologic and pharmacologic modeling).
2. On a computer screen only, defined as a screen-only or screen-based simulator (some prefer the term microsimulator).
3. Using virtual reality, defined as a virtual reality simulator. In such a device, parts or all of the patient and environment are presented to the user by three-dimensional representations with or without "touch" to create a more "immersive" experience. A screen-only simulator could be viewed as a very limited virtual reality simulator.

Components of a Patient Simulator

A patient simulator system contains several components (Fig. 7-13).[19] A set of outputs make up a representation of the patient, the clinical environment, and diagnostic and therapeutic equipment. For screen-only simulators, this representation is generated graphically on the computer screen. For mannequin-based simulators, the representation is generated by using a patient mannequin, plus either actual clinical equipment or virtual replicas of monitor screens, placed (typically) in a recreation of an actual clinical setting. The mannequin and, where appropriate, the clinical equipment are stimulated or actuated by interface hardware. Mannequin-based simulators often use physical stimulation of clinical equipment in addition to electronic stimulation. The mannequin can actually be ventilated with any desired mixture of inspired gases. Carbon dioxide and other gases can be introduced physically by the simulator into the mannequin's lungs to provide the desired elements of gas exchange. A real respiratory gas analyzer can be used to measure the inspired and expired gases. The currently available features of full-scale, mannequin-based patient simulators are presented in Table 7-6.

Any simulator must have control logic by which changes in the simulated patient's condition can be generated, controlled, and sent to the appropriate output of the representation. Originally, the control logic was embedded in the software as a fixed sequence of events, or it consisted largely of continuous input from the instructor working from a script. Some current simulators use upgraded types of manual control logic that allows scripting of combinations of changes in control input. Other current simulators incorporate a more sophisticated technique using mathematical differential equations that model a patient's physiology and pharmacology to provide the bulk of the control logic. These models can be tailored to represent different patients with different pathophysiologic abnormalities.

Not all states or changes in a patient can be modeled by differential equations. Ventricular fibrillation is a totally different state of heart rhythm that does not evolve continuously from normal rhythms. No model can predict exactly when a patient will have a myocardial infarction or when an ischemic heart will begin to fibrillate. A model can only predict factors that increase the likelihood of such events. Most simulators incorporate other modeling techniques in addition to the basic physiologic and pharmacologic mathematical equations, including finite-state

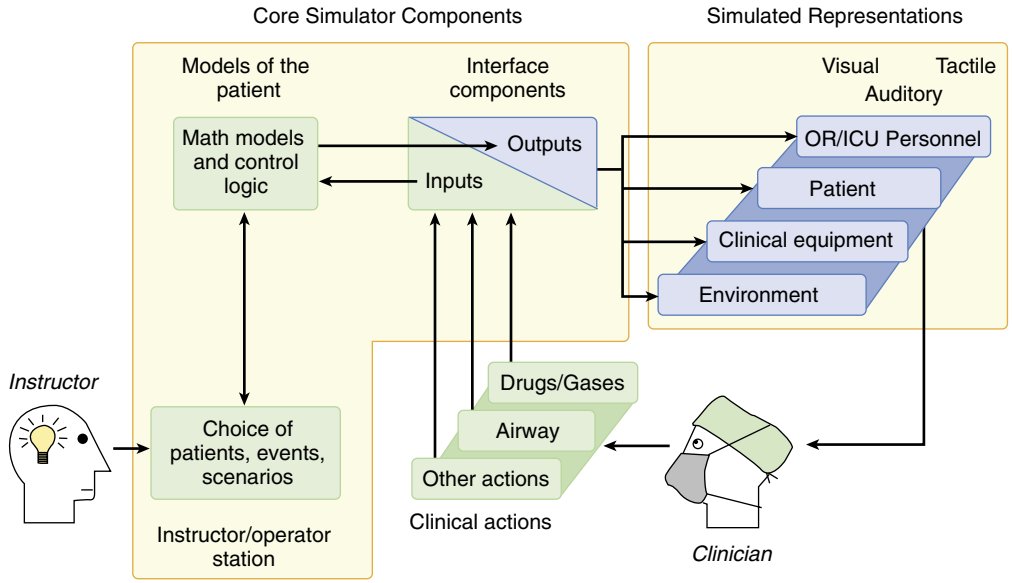


Figure 7-13 Schematic diagram of the generic architecture of patient simulator systems. The simulator generates a representation of the patient and the work environment with appropriate interface hardware, display technologies, or both. The representation is perceived by the anesthesiologist, whose actions are input to the simulator through physical actions or input devices. The behavior of the simulated scenario is manipulated by the instructor or operator through a workstation that allows selection of different patients, abnormal events, and other features of the simulated patient. The control may be manual, script-based, or model-based with manual adaptation to reach optimal learning outcomes. ICU, intensive care unit; OR, operating room. *(Figure by D.M. Gaba, Stanford.)*

Table 7-6 Functionality of Current Mannequin-based Simulator Systems

Clinical Area	Features and Functions	Remarks
Airway	Appropriate pharyngeal and glottic anatomy Placement of facemask, ETT, LMA, LT, Combitube Laryngospasm, tongue and airway swelling, cervical immobility, jaw closure, breakable teeth Cricothyrotomy Transtracheal jet ventilation Bronchial anatomy (to the lobar bronchus level)	Airway often provides acceptable seal for ETT, LMA, Combitube and LT Facemask seal is often difficult as well as placement of ETT
Head	Eyelid movement, pupil dilation, and reaction to light or medications Patient voice and sounds such as coughing and vomiting (through built-in loudspeaker) Palpable carotid pulses Cyanosis by blue light Tearing	Sweating as prototype available The authors prefer "live" voice over prerecorded audio clips, due to higher flexibility in scenarios
Chest	Physiologic and pathophysiologic heart and breath sounds Spontaneous breathing with chest wall movement Bronchospasm Adjustable pulmonary compliance Adjustable airway resistance Pneumothorax Needle thoracotomy and chest tube placement Defibrillation, transthoracic pacing ECG Chest compressions	Breath and heart sounds through loudspeakers; sounds contain artifacts and mechanical noise. Often sound level depends on position of stethoscope relative to loudspeaker
Extremities	Palpable pulses (dependent on arterial pressure) Cuff blood pressure by auscultation, palpation, or oscillometry Modules for fractures and wound modules Intravenous line placement Thumb twitch in response to peripheral nerve stimulation Arm movement Representations of tonic clonic spells	Still very limited movement capabilities at best (as of 2008)
Monitoring (waveforms or numerical readouts)	ECG (including abnormalities in morphology and rhythm) Spo_2 Invasive blood pressure CVP, PAP, PCWP Cardiac output Temperature CO_2 (may be actual CO_2 exhalation) Anesthetic gases (may have actual uptake and distribution of agents) Cardiopulmonary bypass	Simulators interface to actual clinical monitors or provide a simulated virtual vital signs display (or both); may include a virtual heart-lung machine
Automation and sensors	Chest compressions Ventilation rate and volume Defibrillation and pacing (including energy measurement) Gas analyzer (inspired O_2, anesthetics) Drug recognition (drug identification and amount)	Quality of sensors varies greatly from rough ventilation yes/no to almost realistic ventilation loops, etc.

Note: The features listed are each present in some existing simulators, but not all features are present on any single device. Sets of features depend on the device and model.

CVP, central venous pressure; ECG, electrocardiogram; ETT, endotracheal tube; LMA, laryngeal mask airway; LT, larynx tube; PAP, positive airway pressure; PCWP, pulmonary capillary wedge pressure.

Table 7-7 Desirable Features of Future Mannequin-based Simulator Systems

Advanced skin signs such as Change in skin color to cyanotic or pale Diaphoresis Change in skin temperature (e.g., as a result of shock or fever) Rash, hives, or generalized edema
Regurgitation, vomiting, airway bleeding or secretions
Physical coughing (currently only sounds are simulated)
Realistic convulsions
Purposeful movements of extremities
Support for spinal, epidural, or other regional anesthesia procedures
EEG signals (e.g., for BIS, AEP, PSI)
Intracranial pressure
Support for physical central venous and arterial cannulation
Fetal/maternal cardiotocogram

Note: This table shows what features are not currently incorporated (April 2008). Some features may be under development and could be available after publication of this book. In addition, some features are currently available as third-party or homemade add-ons.
AEP, auditory evoked potential; BIS, bispectral index; EEG, electroencephalographic; PSI, patient state index.

models, instructor initiation of abnormal events, and manual modulation of modeled parameters. In finite-state models, different underlying clinical states are defined, each of which has appropriate entry conditions and transition conditions to other states. When an entry or transition condition is met, a new state becomes active, which may directly trigger new observable phenomena (e.g., ventricular fibrillation), or may alter constants in the mathematical models that then evolve in time.[62-64]

The control logic of most simulators is manipulated through an instructor/operator's station that allows the instructor to create specific patients, select and implement abnormal events and faults, and monitor the progress of the simulation session. The system may have a remote-controlled, hand-held instructor/operator's station in addition to the main instructor/operator's station. The instructor/operator's station typically provides logs of physiologic changes and the anesthesiologist's response, and may provide graphics to support the analysis of a simulation run. Some screen-based simulators provide advice and tutorials linked to the management of simulated events. With mannequin-based simulators, especially for applications in which complete work environments are recreated, it is common to obtain detailed records of the simulation and the actions taken from video and audio recording of the personnel working in the replicated clinical environment.

Modern simulators still do not provide many of the desired features listed in Table 7-7. Many different simulator systems are available. No single system is the best choice for all uses, so the decision about the type of simulator required must be based on the objectives and needs of the application. In our experience, the success of a simulator program would not be determined primarily by the type or fidelity of the simulator used, but mostly by the enthusiasm, skill, and creativity of instructors, and the time and effort devoted to preparing and performing credible simulation scenarios.[28]

Virtual Reality Simulators

Virtual reality refers to a set of techniques in which one interacts with a synthetic (*virtual*) environment that exists solely in the computer.[65] In the typical conception of virtual reality, representation of the synthetic environment is fed directly to the eyes (three-dimensional head-mounted displays), the ears, and possibly the hands and limbs (special instrumented "gloves" and sensors). The actions of the user in the environment are translated directly from typical physical activities, not through manipulating a special pointing device. Realization of this ideal is a continuum involving compromises in these input/output modalities. At one end of the continuum, which we call a *complete virtual reality simulation,* the participant is immersed in a virtual world that fully replicates at least three sensory inputs—full three-dimensional vision, hearing, and touch (the last is more technically known as a haptic/kinesthetic system)[65]—and allows complete physical interaction with the world. The "Holodeck" of "Star Trek" would be an example.

At the other extreme of the continuum is a screen-based simulator that generates a limited virtual setting, restricting its output to a screen display, and provides interaction with the virtual world only through a pointing device. Screen-based simulators provide an interface to the human sensory system that is very far from physical reality, whereas a complete virtual reality simulation may be, in its most advanced form, nearly indistinguishable from the real world. A "partial" virtual reality simulator would replicate fewer senses (or less complete replication, such as a three-dimensional visual representation on a two-dimensional screen) or could restrict physical interaction with the world, or both. Finally, one can imagine hybrids of realistic simulators and virtual reality simulators (sometimes called *mixed reality*) in which the virtual reality representation is overlaid onto a real physical environment.

Some surgical and procedural part-task trainers/simulators, such as those used for laparoscopic, endoscopic, or endovascular procedures, might be considered virtual reality because the real procedure is performed only using a two-dimensional television display that can be recreated by the simulator. A comprehensive virtual reality patient simulator would be very complicated, however, because it requires the following:

- Complete computer model of the patient, the environment, and the function of every object in the environment that could be used (e.g., monitoring devices, carts)
- Means of tracking visual, audio, and touch fields of the user to determine what is to be displayed, and to identify what physical actions are being performed
- Appropriate display hardware for every sensory modality and appropriate input hardware for each action pathway (e.g., touch, speech)
- Hardware to compute all the models, to conduct the tracking, and to produce all the output to the display hardware in real time

Immersive virtual reality is a rapidly developing field. It has stimulated intense interest in numerous domains, particularly space flight, the military, and entertainment. Although the potential of this approach is very exciting, virtual reality is still under development. Prototype virtual reality patient simulators in anesthesia or intensive care have been discussed informally, but

as of this writing, there is no published experience with any meaningful immersive virtual reality patient simulation system.

A related type of simulation is the virtual environment or virtual world. According to the Wikipedia, a virtual world is a computer-based simulated environment intended for its users to inhabit and interact via "avatars" (users' graphical [often perspective three-dimensional] representation of their "selves"). Such systems typically allow multiple participants each to control simultaneously over a network their own avatar (including speech) and to interact verbally and by virtual physical actions within a commonly perceived virtual environment. This technology currently portrays the virtual world as perspective three-dimensional images on a computer screen plus sound. Virtual worlds have been commonly used for games (the popular "World of Warcraft" game has 9 million monthly subscribers), whereas other virtual worlds encompass online communities (e.g.,"Second Life," in which the primary activity is socializing, although commerce and education take place).

In a medical virtual world, the patient may be an automated avatar controlled by the computer, or the patient may be an avatar inhabited by a human participant (an unusual case of a standardized patient actor). Virtual worlds are starting to be used in health care, especially concerning acute care settings such as the ICU, the emergency department, or field resuscitation.

Although virtual reality simulators have many theoretical advantages over screen-based and mannequin-based simulators (e.g., more overall realism in some cases, instantaneous reset of the environment), these advantages are currently offset by the immaturity of the field. Despite considerable hype about virtual reality, such systems are now either very limited in capability or very expensive, and in most cases, they are limited and expensive. A true virtual reality *immersion* experience in a patient care setting comparable to that obtainable with a mannequin-based simulator is not yet on the horizon. Nonetheless, it is likely that virtual reality techniques eventually will eclipse other types of simulators. More than 15 years ago, we (D.G.) predicted this would occur by 2020, but the rate of development of immersive virtual reality has been slower than expected.[66,67]

Development of Patient Simulators

The descriptions given in the following sections are very brief, and the introduction of new or upgraded features in all the simulation systems continues steadily. For up-to-date information about any of the current systems, the reader is advised to contact the manufacturers or authors directly.

The history of the development of patient simulators—particularly the mannequin-based simulators that are in wide use—is well covered in several more recent review articles and book chapters.[5,68-70] The history is of some relevance to anesthesiology because of the dominant role played by anesthesiologists in the early developments in mannequin-based simulation. Anesthesiologists continue to play a major role in this field today, far out of proportion to their numbers relative to other medical domains.

In the late 1960s, a mannequin-based simulator—Sim One—was produced by an aerospace company working with anesthesiologists at the University of Southern California. For that era, it was a technologic marvel and was years ahead of its time.[71] The Sim One project drifted into oblivion, however, largely because the medical professions were not ready to understand the applicability of simulation to key issues of training, research, and assessment, especially regarding the importance of human factors.

Several patient simulators were developed and introduced in the mid to late 1980s. Each was an independent development, and none had any direct connection with the Sim One project. Several factors led to these advances. Most prominent was the new availability of powerful (comparable to advanced minicomputers of a decade earlier) personal computers (PCs) at a relatively cheap price. The popularity of various simulators for PCs (e.g., flight simulators, driving simulators) showed that simulation of complex systems was possible with a PC, and a screen-based simulator could give users some degree of "feel" that they had been in the environment. On the applications side, the public and the anesthesia profession had become more aware of the utility of simulation-based training for military and commercial aviation, space flight, automobile driving, shipping, military command and control, and the operation of nuclear power plants. Media coverage of the space program and corrective responses to the Three Mile Island nuclear power plant accident highlighted the role of simulators. Another pivotal factor was growing interest in anesthesiology in studying the anesthesiologist's performance and the human factors and ergonomics of the anesthesia work environment (see Chapter 6).[72-75]

Screen-Based Simulators (Microsimulators)

Beginning in the mid 1980s, several screen-based simulators were developed by anesthesiologists. These included part-task trainers that simulated isolated aspects of anesthesia, such as the uptake and distribution of anesthetic gases in the body given different physiologic and physical chemistry situations (the well-known GasMan simulator has excelled in this role). Other "full" screen-based simulators represented nearly all aspects of the patient and clinical environment. Originally the control logic was based heavily on mathematical models of physiology and pharmacology, some of the screen-based simulators have converted to control largely from scripts and finite-state models. Originally, the patient was represented by drawings or animations, but increasingly in these systems the representation of the patient is by photos or videos. Vital signs appear on virtual monitors that may mimic real clinical devices. Actions are selected typically using a graphical user interface, pointing and clicking on menus and buttons, and using sliders and numerical entry boxes to allow control of most kinds of interventions that clinicians use on a regular basis.

Experience with Patient Simulators in Anesthesia

Several companies now offer mannequin-based patient simulators with a wide range of capabilities (the term *fidelity* is reserved for the apparent veracity of the simulation; the simulator device

has a set of features or capabilities) and with different user interfaces and control logics. The bulk of simulators in use today (coming from several vendors) are considered medium-capability devices. They do approximately 70% as much as a top-of-the-line simulator, but at approximately 15% of the cost of the most expensive simulators. This value proposition has been persuasive to most customers, although for certain applications the high-end simulators still may be required.

The new patient simulators have been in use in anesthesia for more than 20 years, and considerable collective experience with the devices already has been achieved. This section and subsequent sections cover the use of simulators for education, training, evaluation, and research (the last especially in decision making and human factors). The results of simulator studies as regards human performance and patient safety are discussed primarily in Chapter 6.

Simulation for Education and Training of Health Care Personnel

The various available patient simulators offer an unparalleled opportunity for students to experience physiologic and pathophysiologic reactions in a realistic manner. Different objectives are possible for teaching sessions. A study by Morgan and Cleave-Hogg[76] concluded that "the simulator environment is somehow unique and allows different behaviors to be assessed." The objectives of *education* are to provide conceptual understanding and an introduction to skills, whereas the objective of *training* is to implement specific skills and behaviors applicable directly to real-world surroundings. Consistency in objectives is important for evaluating education and training; if we are teaching conceptual understanding, but assessing specific skills, we may obtain misleading results.[77]

A Best Evidence Medical Education (BEME, www.bemecollaboration.org) review by Issenberg and colleagues[25] concluded that high-fidelity medical simulations are educationally effective, but only if the right conditions are met, as follows:

Conditions for the Educational Effectiveness of High-Fidelity Medical Simulations (according to a BEME review by Issenbery[25])

- Educational feedback is provided
- Repetitive practice is used or is allowed
- Simulation is integrated sensibly into the standard curriculum
- The range of task difficulty can be adapted to the level of the learner

Simulation for Education and Training of Medical and Other Health Profession Students

The structured review about simulation effects on simulation-based medical education by Issenberg and colleagues[25] showed that (1) the methodologic quality of educational research is often weak, and (2) in the high-quality studies that were evaluated, there was an effect between hours of simulator practice and learning outcomes equaling a dose-response relationship. Studies by Coates and associates[78] and Gordon and coworkers[79] showed that simulator education for medical students on patient management skills related to dyspnea was superior to problem-based learning.

A variety of curricula exist,[54,77,80-90] including the following:

- Educational sessions and demonstrations concerning basic cardiopulmonary physiology or pharmacology; in some institutions, these sessions replace animal laboratory exercises.[91]
- Introduction to integrated management (i.e., interweaving of diagnosis and treatment) of critically ill patients; this training is offered to immediate preclinical medical students as part of their preparation for clinical medicine courses.
- Anesthesia practicum for clinical students during anesthesia or intensive care clerkships.
- Problem-solving skills training; simulation has been tested as a means of educating and training students in the appropriate response to specific critical events. Morgan and Cleave-Hogg[92] tested simulation versus instructor-facilitated viewing of a videotape for this purpose and found no difference between the two. The generalizability of this finding has been questioned, however.[77]
- Adaptation of curricula originally aimed at experienced trainees or practicing clinicians to students; there is increasing interest in providing early exposure to medical students, and possibly students of nursing or allied health professions, to interdisciplinary team aspects of medical practice. The aim is to inculcate concepts of teamwork and communication at the earliest stages of education and training as a vehicle to implement long-term culture change in the health care system.

A stimulating critical overview of medical education in general was written by Hodges, provocatively titled "Medical education and the maintenance of *incompetence*" (emphasis added).[93] The article points out that any type of education runs a risk of creating or maintaining *incompetence* in certain areas, especially areas that are ignored by the actual educational program. Objective structured clinical examination–style methods in particular are criticized because students may learn to pass the objective structured clinical examination, but still have even gross incompetence in important aspects of real patient care that are not covered by the objective structured clinical examination rating scale. Simulation offers the promise of targeting more thorough integration of different kinds of skills into a better representation of the realities of clinical care. Nonetheless, we recommend that all simulation instructors be especially cognizant of the risks that Hodges articulates.

Anesthesia Crisis Resource Management

In 1989, based on the cognitive process model presented in Chapter 6 and the research results of Cooper and coworkers,[72,94] Howard and associates,[95] and Gaba[73,74] of the VA–Stanford group identified gaps in the training of anesthesiologists regarding

several critical aspects of decision making and crisis management that were not systematically taught during standard residency or postgraduate education. These gaps were (1) inadequate learning of precompiled plans for dealing with perioperative events; (2) inadequate skills of metacognition and allocation of attention; and (3) inadequate skill in resource management behavior, including leadership, communication, workload management, monitoring, and cross-checking of all available information. Historically, it had been assumed that anesthesiologists would acquire these plans and skills "by osmosis," solely by experience and by observing role models who had these qualities. As indicated in a previous section, the aviation field had learned that such skills were not acquired unless specifically taught, and CRM training was created to address these issues for flight crews. The VA–Stanford group modeled their ACRM training[95] after CRM, and this approach has been highly influential. ACRM-like curricula are taught at simulation centers around the world, not only in anesthesia, but also in many other domains of health care, including ICU, emergency medicine, labor and delivery, trauma, and field responders.[16,35,38,41,43,44,54,68,96-113] Figure 7-14 shows a typical ACRM team training scenario.

To target the identified gaps in training, approximately 40% of the emphasis of ACRM is on the medical and technical management of specific high-risk perioperative situations, but at least 60% of the emphasis is on generic principles of crisis management that apply to nearly every complex patient care situation. The key teaching points of ACRM are shown in Table 7-8. These points are emphasized during the ACRM simulation course, and their occurrence or omission is highlighted during the video-assisted debriefing sessions (see more on CRM in Chapter 6).

A working group of the original ACRM centers (VA–Stanford, Boston CMS, Toronto Sunnybrooke) has promulgated a set of criteria to be met by a curriculum to be called "ACRM" or "ACRM-like." Table 7-9 presents an excerpt of the criteria. The full set of criteria is available at http://anesthesia.stanford.edu/VASimulator/ACRM_Criteria.htm.

These criteria delineate that special training is needed for instructors in ACRM-like curricula. Experience suggests that the most difficult aspect of ACRM instructing is debriefing, and new instructors require a significant period of experience, preferably under supervision by more senior instructors, before being ready to be fully independent instructors. Several groups working separately or collectively have developed comprehensive training programs on simulation instruction, including substantial modules on debriefing and scenario design.

Table 7-8 Key Points in Anesthesia Crisis Resource Management

1. Know the environment
2. Anticipate and plan
3. Call for help early
4. Exercise leadership and followership with assertiveness
5. Distribute the workload (10 seconds for 10 minutes)
6. Mobilize all available resources
7. Communicate effectively
8. Use all available information
9. Prevent and manage fixation errors
10. Cross and double check (never assume anything)
11. Use cognitive aids
12. Re-evaluate repeatedly (apply the 10 seconds for 10 minutes concept)
13. Use good teamwork
14. Allocate attention wisely
15. Set priorities dynamically

(Detailed explanation of the CRM Key Points are given in Chapter 6.



Figure 7-14 Anesthesia crisis resource management team training scenario. A full operating room team (enacted surgeons and nurses) is doing a complicated endoscopic surgery case (replayed on screen). The anesthesia team consisting of the trainee ("hot seat") and the nurse has to solve complex problems. Video cameras (ceiling), microphones, and loudspeakers provide the necessary connectivity and debriefing tools. *(Picture by team TuPASS, taken at Center for Patient Safety and Simulation, University Hospital, Tubingen, Germany.)*

ACRM-like curricula use several teaching modalities to achieve these goals, including the following:

- A comprehensive textbook on anesthesia crisis management (*Crisis Management in Anesthesiology*). This book includes didactic material on ACRM principles and a comprehensive catalog of critical incidents in anesthesia that provides guidelines for preventing, recognizing, and managing 83 perioperative situations in a uniform format. The catalog section of the text is intended to provide study material to increase anesthesiologists' stock of precompiled response plans to common and uncommon situations. This textbook has been translated into Japanese and German (by one of this chapter's authors).
- A brief presentation reviewing the principles of CRM and patient safety.
- Analysis of a videotape of an aviation accident.
- Small group exercises analyzing a videotape of an actual patient care mishap or analyzing written or video presentations about difficult cases.
- Several hours of complex multifaceted realistic simulations in which training participants rotate through different roles, including primary anesthesiologist, first responder (called "cold" with no knowledge of the situation), and scrub nurse. Other personnel play the roles of surgeons, nurses, and technicians as in a real operating room. Each situation is followed by a detailed debriefing with video feedback (see earlier discussion of debriefing).

Several publications have detailed the response of participants with varying levels of experience to ACRM training.[95,109] Participants have been extremely positive about their experience in the ACRM course, and most believe that it contributes to their

Table 7-9 Characteristics of Anesthesia Crisis Resource Management–like Simulator Training

Objectives
Learn generic principles of complex problem solving, decision making, resource management, and teamwork behavior
Improve participants' medical/technical, cognitive, and social skills in the recognition and treatment of realistic, complex medical situations
Enhance capacity for reflection, self-discovery, and teamwork and building a personalized tool kit of attitudes, behaviors, and skills
Aim
Prevent, ameliorate, and resolve critical incidents
Setting Characteristics
Realistic simulation environment replicating a relevant work setting (or an actual patient care setting with in-situ simulation)
Personnel to represent individually those found in the typical work environment of the participant, including nurses, surgeons, and technicians
Bulk of the training course consists of realistic simulations followed by detailed debriefings
Primary participant can request and receive help from other participants
Participants may rotate between different roles during different scenarios to gain different perspectives
Simulation scenarios may be supplemented by additional modalities, including activities such as assigned readings, didactic presentations, analysis of videotapes, role playing, or group discussions
Training involves significant time (>4 hours, typically ≥8 hours) and is conducted with a small group of participants
Content Characteristics
Scenarios require participants to engage in appropriate professional interactions
At least 50% of the emphasis of the course is on crisis resource management behavior (nontechnical skills), rather than medical or technical issues (nontechnical skills are discussed in Chapter 6)
Observation only is not equivalent to actual participation in the course
Faculty Characteristics
Training is intense and entails high level of involvement of faculty with the participants and a low participant-to-faculty ratio
Faculty, especially those leading debriefing, have special training or experience in conducting crisis resource management–oriented training
Debriefing Characteristics
Debriefings are performed with the whole group of participants together and use (as appropriate) audio/video recordings of the simulation sessions
Debriefings emphasize constructive critique and analysis in which the participants are given the greatest opportunity possible to speak and to critique and to learn from each other (debriefing facilitation)

safe practice of anesthesia. Table 7-10 shows the results of one of the earliest studies on that topic.

At VA–Stanford, ACRM has been extended to a multilevel course conducted over several years (i.e., ACRM 1, 2, 3). As the course levels progress, the scenarios become more complex and involve subspecialties of anesthesia. In addition, additional teaching modules cover other important aspects of organizational safety, such as "systems thinking" in morbidity and mortality conference settings or peer review settings, follow-up response to severe adverse perioperative events, and disclosure to the patient or family of "bad news" after an adverse event.

ACRM courses and ACRM-like variants are now being offered worldwide and are often mandatory for trainees (and in some cases for experienced personnel). In Denmark, ACRM-like training courses are a legal requirement for nurse anesthetists (3-day course) and first-year (2-day course) and third-year residents (4-day course), in addition to some other simulator training courses (e.g., difficult airway). Further plans are being made to require simulation training for ICU and recovery room nurses and ICU residents.[114-116] Salas and colleagues[33] published an excellent critical overview about prerequisites for effective CRM training.

Simulation for Training of Anesthesia Residents

Simulation is now a widely used technique in the training of anesthesia residents. It is used in various ways—for technical training on particular procedures or patient care protocols (especially for airway management), for supplementing didactic instruction about anesthesia equipment, and for training about issues of decision making and nontechnical skills as outlined earlier concerning ACRM. Nearly every anesthesia residency program in the United States now offers some cogent simulation training experiences, although the scope, frequency, and target content vary.

Other disciplines and other countries may not have adequate simulation training coverage during residency, as evidenced by a study by Hayes and colleagues[117] about the perception of Canadian internal medicine residents to be qualified for their service on the cardiac arrest team: 49% felt inadequately trained, 50% felt that the provided advanced life support course did not prepare enough to lead the arrest team, and almost none got postevent debriefing or feedback.

Table 7-10 Evaluation of Anesthesia Crisis Resource Management (ACRM) Course in Harvard Anesthesia Simulation Training

		Attending Staff (n = 30)		Residents and Fellows (n = 34)	
Rating	**Scale**	**Evaluation of Simulator Environment (%)**	**Value of ACRM Course (%)**	**Evaluation of Simulator Environment (%)**	**Value of ACRM Course (%)**
Less favorable	1	13	3	9	1
	2	10	3	6	2
	3	15	15	11	4
	4	10	25	28	28
More favorable	5	33	54	46	75

Modified from Holzman RS, Cooper JB, Gaba DM, et al: Anesthesia crisis resource management: Real-life simulation training in operating room crises. J Clin Anesth 7:675-687, 1995.

Special Considerations in Pediatric Simulation

A sizable body of international experience with simulation in pediatric settings now exists (see Chapter 82).[43,111,118] A study by Overly and coworkers[119] assessing airway management skills in pediatric residents identified many areas of concern about residents' abilities. The authors concluded that high-fidelity simulation can be used to assess residents' airway management, and that the training program was effective to teach these skills.

Many centers use pediatric simulators predominantly for training of the management of critical incidents and medical emergencies, targeting trainees and specialists in anesthesia and pediatric critical care medicine. Because there is frequent organizational and clinical overlap between personnel engaged in pediatric anesthesia, critical care, and emergency medicine, multispecialty (physician crews from different specialties) and multidisciplinary (crews from different professional disciplines), team training can be particularly helpful to prevent failures of cooperation at treatment interfaces (Figs. 7-15 and 7-16). A review by Eppich and colleagues[35] on team training in pediatric acute care settings underlines the impact and effectiveness of team training addressing pediatric teams. The American Academy of Pediatrics now specifically recommends teamwork and communication training for all health care professionals in pediatric emergency settings, and the American Heart Association has included a team concept video and eight elements of team dynamics in its training programs.[120-122]



Figure 7-16 Neonatal CRM and resuscitation training at a neonatal emergency workplace. All treatment steps need to be performed in the simulation to show the need to coordinate and delegate. The experienced instructor (on the right side of the infant) is taking part as a team member, while another instructor team is in the control room, presiding over simulation control and debriefing videos. CRM, crisis resource management. *(Picture taken at Stanford Simulation Center.)*

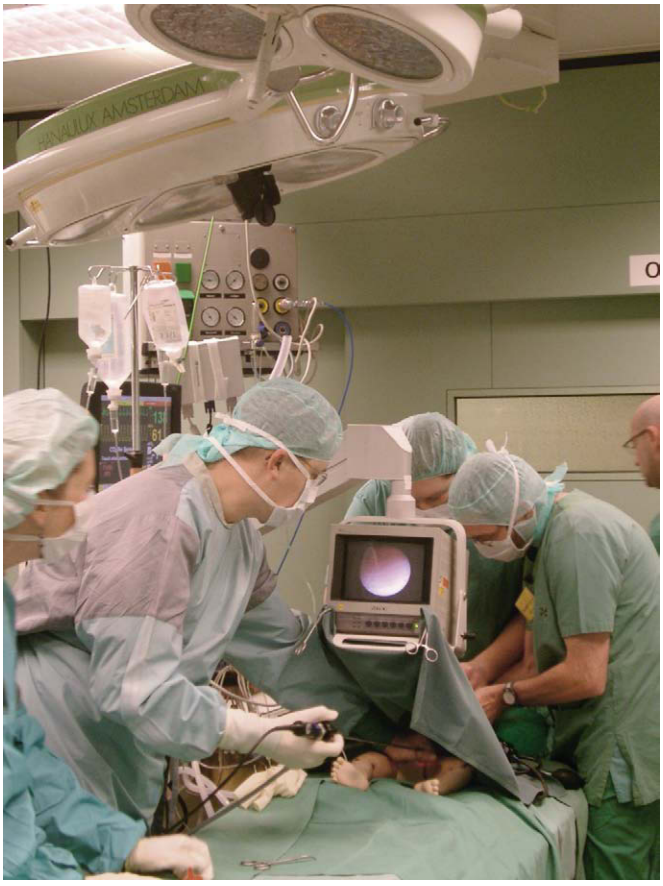


Figure 7-15 Pediatric full team simulation training. The primary trainees (anesthesia) have to solve problems with the infant simulator, while urologic surgical team members perform their procedure. *(Courtesy of C. Eich, University Hospital, Göttingen, Germany.)*

In contrast to adult medicine, the demand in pediatrics for simulation has been largely to address particular points of medical knowledge and technical skill, perhaps because many personnel have little experience with pediatric care, especially for cases involving neonates and infants (Table 7-11).[123] Many simulation courses in pediatric anesthesia or intensive care need extensive involvement by experienced pediatric clinicians. More senior clinical personnel who work regularly in pediatric settings may be comfortable with their pediatric clinical skills, but may be more interested in the generic nontechnical skills that are equally applicable to pediatric and adult care.[120]

There is a positive correlation between the difficulty of pediatric scenarios and the participants' own perception of the learning effect.[123] Scenarios that participants rarely encounter in their clinical practice (e.g., an infant in circulatory shock owing to extensive thermal injury) on the one hand are thought to be threatening, but on the other hand are considered to be particularly beneficial in terms of training effect. A commonplace but interesting aspect inherent in pediatric simulation is the incorporation of role play by family members. Although family members may be present in adult medicine, their presence in pediatrics is nearly ubiquitous.[124] This presence can put further strain and stress on the provider, making it particularly useful to add family role players (either trained actors or instructors or even the participants themselves) to pediatric simulation scenarios.[118]

Continuing Medical Education

Most simulation centers offer CME for experienced practitioners, and nearly all aspects of simulation training for residents (except novice training) can be expanded for this purpose. Several studies

Table 7-11 Unique Aspects of Simulation in Pediatric Anesthesia

Huge discrepancy between high degree of required clinical proficiency and often limited level of expertise
Strong demand for training on medical-technical aspects of management—recommendation to participate in a pediatric advanced life support course before simulation team training course
Need to familiarize with parental presence during pediatric anesthetic care by combination of simulation and role play
The small patient requires an even better organization of the work environment and task responsibilities (in-situ training)
High-impact multidisciplinary team training, including CRM
High level of interest in assessment and certification of trainees and subspecialists for work in pediatric anesthesia

CRM, Crisis resource management.

have shown that experienced anesthesiologists also have deficiencies in the management of critical patient situations and make severe errors comparable to those of anesthesia residents.[64,116,125-129] A study by Jacobsen and associates in Denmark[130] involving 42 specialist anesthesiologists showed major deficiencies in the diagnosis and treatment of anaphylactic shock and in application of the ACRM principles when a score adopted from Gaba and Howard was used.[69,131] Because crisis situations are rare during routine clinical work, these results are not unexpected. In addition, experience in terms of years on the job and hierarchy probably do not correspond to expertise and excellence. It cannot be overemphasized that crisis management training with simulators should be started early in education and training and applied on a recurring basis during practice.

An aspect of CME training in the United States is that it is regulated separately by each of the states, and it is nearly uniformly based only on the number of hours spent in the activity. Reading a short article and answering a handful of questions can generate 1 hour of credit, as can sitting through a lecture. Simulation training is generally much more interactive and much more intensive than other activities. In Australia and Germany, CME requirements are expressed in terms of points to be accrued. Simulation training counts for a large number of points per hour spent, commensurate with its intensity, which might make simulation-based CME financially competitive relative to simpler methods.

The ASA has established a standing Committee on Simulation. The ASA offers an endorsement (analogous to but different from an accreditation) of simulation programs that can show their capability to offer excellent CME curricula to ASA members. The Committee began reviewing applicants for endorsement in 2008.

At the Harvard hospitals, the captive insurer, Harvard Risk Management Foundation, has taken unprecedented steps to link simulation-based CME training to discounts for medical malpractice premium rates for experienced clinicians in anesthesia and in obstetrics (Cooper J: personal communication, 2005). This forward-thinking program is now being adopted by other malpractice carriers. In some jurisdictions, risk managers have chosen to invest directly in simulation activities at their institution, rather than to use the premium discount approach.

Use of Patient Simulation for Training Health Care Personnel outside Anesthesia

Anesthesiology remains a driving force in the use of simulation in health care, but simulation has spread to nearly every discipline and domain. It is proven to be particularly applicable to other areas that share the cognitive profile of anesthesiology—dynamic decision making (played out over seconds, minutes, and hours), with complex teams, wielding highly lethal interventions. ACRM-like training has been performed in settings that include, but are not limited to, intensive care,[113,132] emergency medicine and emergency field responders,[133-138] trauma medicine and surgery, neonatology (neonatal resuscitation and neonatal ICU), labor and delivery (Fig. 7-16),[139,140] cardiac arrest and rapid response teams,[141-143] and radiology. Simulation is such a diverse technique that it is equally applicable—using different modalities of simulation—to nearly all domains. Knudson and colleagues[36] found a significant improvement in overall and teamwork scores in surgical residents when taking care of critically injured simulated trauma patients if they have undergone CRM-like simulation training.

The military and Homeland Security also have been heavy users of simulation in health care, where it has been applied to the initial training of new field medics and to the recurrent training of experienced clinicians and clinical teams.[144] Figure 7-17 shows one room with 10 simulators in a training center for military medics that has more than 100 simulator mannequins altogether.

Simulation is now used more frequently in training for the management of chemical, biologic, or nuclear threats from accidents, weapons of mass destruction, or terrorism. One of our groups in Tübingen, Germany, used their simulator to test the constraints of treating patients in full chemical protection gear (publication of the results is in preparation) to optimize the strategies of the German Ministry of Internal Affairs for dealing with terror attacks or chemical plant disasters (Figs. 7-18 and 7-19) (see Chapter 74). Several investigators have performed multidis-



Figure 7-17 Simulation-based training center for military medics. The room is equipped with 10 SimMan training stations. During training sessions, one instructor team is sitting at each foot of each mannequin. Teaching is provided "on scene" during the sessions.



Figure 7-18 Realistic patient simulation as a test bed for studying the performance of medical rescue teams in full chemical protection gear. Teams wore normal uniforms or full protection suits while performing basic resuscitation actions (e.g., placement of intravenous lines, drawing up drugs, intubation). *(Picture taken at the TuPASS Center for Patient Safety and Simulation, Tübingen, Germany.)*

ciplinary studies with combined simulation modalities (script-based, model-based mannequin simulators, and simulated acted patients) to teach the management of victims of an attack with weapons of mass destruction and terrorism.[59,60] The demand for such training is substantial in nations engaged in active military conflicts or with an ongoing need to prepare for war or terrorist attacks (e.g., the United States and Israel).

Use of Patient Simulation for Research

Research in simulation falls into two categories: (1) research *about* simulation—testing or improving the techniques, technologies, and pedagogy of simulation, and (2) research that uses simulation as a tool to study other things, such as human performance, clinical cognition, or clinical care processes (see Chapter 6). Table 7-12 provides a sampling of these latter types of questions. As a research tool, simulation offers some unique features, and it can be thought of as a complementary window on the clinical world relative to other modalities. One can study clinical work using



Figure 7-19 In rescue situations with full protective gear, communication within the team and with the patient is difficult. *(Picture taken from a video screen at the TuPASS Center for Patient Safety and Simulation, Tübingen, Germany.)*

Table 7-12 Research Issues That Can Be Addressed by Using Simulation

Cognitive Science of Dynamic Decision Making (see Chapter 6)
What is the interaction of precompiled procedural knowledge versus deep medical knowledge and abstract reasoning?
How does supervisory control of observation relate to vigilance, data overload, and visual scanning patterns?
What is the information content of watching the surgical field?
How are optimal action planning and scheduling implemented?
How does re-evaluation fail and result in fixation errors?
Human-Machine Interactions
What is the distraction penalty for false alarms?
Is there an advantage to integrated monitors and displays versus multiple stand-alone devices and displays?
How easy to use are the controls and displays of existing anesthesia equipment in standard case situations and in crisis situations?
Teaching Anesthesia in the Operating Room
How much teaching can be accomplished in the operating room without sacrificing the anesthesia crew's vigilance?
How well can faculty detect and categorize the performance of anesthesia trainees?
What teaching styles are best integrated with case management in the operating room?
Issues of Teamwork
How does an anesthesia crew (attending anesthesiologist plus resident or Certified Registered Nurse Anesthetist) interact during case and crisis management?
How is workload distributed among individuals?
How do crew members communicate with each other, and how do they communicate with other members of the operating room team?
Effects of Performance-Shaping Factors on Anesthesiologist Performance
How do sleep deprivation, fatigue, aging, and the carryover effects of over-the-counter medications, coffee, or alcohol affect the performance of anesthesiologists?
Intelligent Decision Support
Can smart alarm systems or artificial intelligence provide correct and clinically meaningful decision support in the operating room or intensive care unit?
Development of New Devices and Applications: Research Regarding Technique of Simulation
How well do simulators resemble the operating room and provoke the same actions as use in the operating room (ecologic validity of simulators)?
How much does debriefing add to learning from simulation? Are specific techniques of debriefing (e.g., use of video; participant-centered discussion) of significant utility?
How does the setting of simulation scenarios influence aspects of perceived reality, and how does it influence transfer into the real world?
Does simulation training lead to better clinical practice and improved clinical outcomes?

prospective observation of real cases. This has the benefit of being prospective, but by nature, more cases in most domains would be unremarkable, and one would mostly observe the routine and banal. For some purposes, this study would be more than sufficient. Another source of information is in case reports of challenging cases, whether the challenges were expected or unexpected. These also are real cases, and they are out of the ordinary, but the data obtained from such retrospective reports are usually scanty and biased.

Simulation provides an alternative view of clinical work that can be prospective and about challenging cases, albeit simulated cases. The simulation centers around the world probably have the largest experience by far of observing anesthesiologists managing (simulated) malignant hyperthermia. It is hard to imagine how else one might gather systematic data about how clinicians work while managing this uncommon life-threatening situation.

An important milestone for simulation-based research of both types is the publication by the Society for Simulation in Healthcare since 2007 of a peer-reviewed journal titled *Simulation in Healthcare* (one of the authors, D.G., is the founding editor-in-chief of the journal). In addition, for research that is linked tightly to a specific clinical domain, the traditional medical specialty journals have become more welcoming to articles about simulation or that use simulation as an experimental technique.

Cooperation between simulation directors and instructors with psychologists, human factors engineers, or educators has proved to be helpful in research and training. Such collaborations have helped to delineate the theoretical foundations of simulation-based experiential learning, for improving the understanding of debriefing, and for research on work psychology and human performance in health care.[19,21,22,26,27,145,146] Many institutions have integrated psychologists or educators or both into their simulation center staff.[104] Ways to make such collaborations fruitful and rewarding also have been described.

Use of Patient Simulation in Support of Biomedical Industries

Various simulation activities have involved the pharmaceutical or medical equipment industries. Numerous centers (perhaps the University of Florida at Gainesville was the first) offer training to executives and sales representatives of equipment and pharmaceutical manufacturers. The simulator allows these individuals to gain some understanding of the clinician's task demands during patient care and the situations in which their company's drugs or devices could be useful. At the Boston Center for Medical Simulation, this course is dubbed "Anesthesia for Amateurs." Other industrial uses include training personnel in the use of novel pharmaceuticals. Simulators have been featured in a multifaceted approach to launch the opioid remifentanil. Simulators were used to train the manufacturer's representatives and clinicians in safe use of the drug, and it was possible to train anesthesiologists in the application of remifentanil with the simulator before remifentanil was approved by the U.S. Food and Drug Administration (WB Murray: personal communication, 1998.) Besides offering important educational benefits, the industrial activities are an important source of income for simulation centers to help defray the costs of training students and residents.

Simulators have been used to conduct research on human factors issues in the development of new monitoring and therapeutic devices. The simulator also provides a unique test bed and demonstration modality for preprocurement evaluation of the usability of medical devices from different manufacturers. In our own hospitals (Stanford and Tübingen, Germany), simulators enabled us to conduct evaluations of prototype monitoring systems that were not yet approved for clinical use and could not be evaluated in a preprocurement clinical trial.

Other Uses of Simulators

Other unique applications of simulators have surfaced. Some centers use simulators for conducting outreach programs with high school or college students interested in health care. Simulators have been used to help produce educational videotapes on various patient safety issues. It has been suggested that a "legislator day" could be held in a simulator center to familiarize legislators with the demands of dynamic patient care.

Simulators have been used as adjuncts in medicolegal proceedings.[147] Current patient simulators cannot predict the exact physiologic behavior of a specific patient, but they can be used to illustrate typical perioperative situations and the role of different monitors and therapeutic actions, and provide context for the patient management questions of the litigation.

Effectiveness of Simulation Training

Flanagan and associates[148] provide a thorough review on the literature to date on the efficacy of simulation-based training for learning and assessment. The investigators identified more than 3500 articles, of which 458 were included in the review. The conclusion was that "simulation makes a valuable contribution to learning for students, trainees and clinicians. It enables learning of both routine and non-routine procedures and management of patients."[148] They further concluded that simulation is widely used in teaching and learning, is increasingly being used for formative and low-stakes assessments, and is rarely used (but under growing consideration for) high-stakes summative assessment. Flanagan and associates[148] also observed that the range of simulation modalities used for these activities varies widely. Similar to the BEME review by Issenberg[25], they found that many studies lacked a robust design, and that the level of outcome effectiveness as measured with a modified Kirkpatrick scale rarely exceeded 3 out of 6, with most at the level of 2 or below.

The most important question concerning simulator-based training in anesthesia is its cost-effectiveness. This complicated question has two independent components. The first component is the impact and benefit of the training on the performance abilities of participants, and the second is the cost to achieve that impact. In principle, simulation has many advantages as a training tool, as follows[149]:

- There is no risk to a patient.
- Exercises in routine procedures can be repeated intensively, whereas situations and events involving uncommon, but serious problems can be presented at will.
- Participants can learn to use actual complex devices (with a hands-on simulator).
- The same situation can be presented independently to multiple subjects for evaluating individual or group performance.
- Errors can be allowed to occur that in a clinical setting would require immediate intervention by a supervisor.
- The simulation can be frozen to allow discussion of the situation and its management, and it can be restarted or begun anew to show alternative strategies or techniques.
- Recording, replay, and critique of performance are facilitated because patient safety or confidentiality is not an issue.

The fidelity required of the simulator and the choice between screen-only and realistic simulators depend on the intended goals of the training and the relevant target population. A spectrum of computer-based training is possible. Computer-assisted instruction programs and partial-task trainers can be used to teach basic concepts and technical material, such as the uptake and distribution of inhaled anesthetics or the pharmacokinetics of intravenous drugs. These uses are appropriate for students, novices, advanced residents, and experienced practitioners. Screen-only simulators are inexpensive and easy to use. They allow the presentation of and practice with the concepts and procedures involved in managing normal and abnormal case situations. They also are useful for numerous user populations. Realistic simulators can be used to capture the full complexity of the real task domain, including human-machine interactions and the complications of working with multiple personnel. They are most appropriately used for residents and experienced practitioners. Regardless of the device used, the simulator is only a teaching tool that must be coupled with an effective curriculum for its use.[25]

The evaluations conducted so far suggest that simulator-based training is a powerful technique that novice and experienced anesthesiologists believe to be highly beneficial, and that participants and instructors alike believe may improve clinical performance. As the developers of Sim One 7 pointed out, when simulation provides an opportunity to teach material that cannot be taught in another way, as for the systematic instruction of anesthesiologists in handling severe critical events such as cardiac arrest, anaphylaxis, or malignant hyperthermia, there is nothing with which to compare the simulator. Assessing whether the actual outcome of patients can be affected by this or any other training modality would be extremely difficult and expensive. Individuals investigating simulator-based training do not believe that definitive outcome studies of this type are logistically feasible.[150] Determining the impact of a given type of simulator training on the intermediate variables of "performance" and "ability" is feasible, but it would not be easy. The Leiden group provided data supporting the contention that simulation training improves performance in handling a malignant hyperthermia situation. There is a potential, however, for substantial bias when attempting to measure the impact of simulator training by using performance in the simulator as a criterion. The control procedures used by the Leiden group alleviate this bias, but they cannot eliminate it.[151]

Perhaps of even greater importance, no methodology is currently accepted for measuring the clinical performance of anesthesiologists either in the simulator or in actual practice.[152] Ironically, the simulator itself provides a tool for presenting the same calibrated situation to multiple anesthesiologists and may be a crucial tool in developing such performance measures. Many groups around the world are trying to refine performance measurement tools,[107,140,153-172] but no "gold standard" measurement is yet available to assess a simulation's effectiveness (see the later section on evaluation of performance).[152]

How Simulation Can Be More Effective

Health care has not yet scratched the surface of assessing the impact of simulation-based training. Most simulation is currently targeted at students and trainees (i.e., residents), although programs targeting experienced personnel are growing. The assessment of the impact of simulation to date can be seen using the following analogy to drug development and testing. Suppose we wished to test whether a purported antihypertensive drug actually succeeded in reducing blood pressure in patients, and, more importantly, whether it reduced the occurrence of adverse cardiovascular events, such as myocardial infarction and stroke. Imagine then that we proceeded as follows: Administer a relatively small dose of this drug only a few times per year. Acknowledge variable compliance in taking even these few doses of drug. Immerse all subjects in an environment full of stress and other factors predisposing to cardiovascular events. Use only a few patients, and follow them for a very short time.

Using this methodology, would anyone wonder if no significant effect was found even for a drug otherwise known to be effective? Simulation in health care has so far been tested in this way: very small short-term studies of infrequent (often short) simulation sessions, whose lessons are not fully reinforced in real clinical environments full of production pressure and stress. In truth, the question is not "Does one run through a simulation course make a practitioner better?" To follow the lead of other industries of intrinsic hazard, such as commercial aviation or nuclear power production, the real question is: "What is the impact of health care as an industry adopting a comprehensive integrated strategy of intensive simulation-based training and continued performance assessment of clinical personnel, over a long period of time?" This is the approach in aviation, where no matter how senior and how experienced pilots are, they still undergo training and assessment in simulation every year, for the entirety of their careers.

Even so, industries such as aviation do not have anything resembling level 1A evidence for the benefits of simulation, even though such studies could be grafted onto the existing structure of yearly training and testing. It is unlikely that aviation would ever attempt randomized trials. For one thing, as the saying goes, "Pilots are the first ones at the scene of the accident." It seems unlikely that pilots would forgo simulation training and assessment when their own lives are on the line. For another thing, the public has come to expect that there is a regulatory safety floor imposed by the government to ensure the competency of pilots. The regulator is unlikely to forgo its requirement for mandatory training and testing of pilots. If such requirements continue, there may be only two options: conduct them in real airplanes, with the attendant costs (e.g., fuel) and risks, or conduct

them using simulation. With health care heading toward that direction,[37,38,43,46,173-177] we may be able to assess the impact of more effective simulation programs, although we might lose a control group.

Avoiding Subthreshold Training Effects

To date, simulation training has largely been employed in "small doses" given intermittently, not sustained over the long-term, and ignoring many personnel who are crucial in the chain of patient care. When conducted this way, simulation training may not achieve a "critical mass" and may produce a subthreshold effect. It seems likely that a long-term cumulative effect would be achieved only with a long-term comprehensive program of training and performance assessment.

It is possible that it is worth the inherent logistical difficulties and costs to undertake bulk training (>75% of personnel trained in a short time, rather than starting a program of training a few individuals a month and achieving a high penetration rate only in months or years). Where the training is about teamwork and behavioral issues (CRM-focused), this might be especially important so that the lessons taught in the simulator are continuously reinforced by experiences in real patient care. The hope is that creating a critical mass of adherents to CRM principles via simulation would create a self-sustaining reinforcement of safety-oriented behaviors that continues with only occasional refresher sessions of simulation.

An analogy for that effect would be the starting of a fire with wood logs: If you take away the match too early, you do not light the fire, and all you get is a black mark on the wood, but if you keep the match on the wood long enough (similar to activation energy), the fire starts to burn and spread to all logs without any more input—similar to what we would like to see with CRM team behaviors.

Ecologic Validity of Simulators Compared with the Operating Room

The question whether full-scale simulators are an ecologically valid representation of the operating room (i.e., to what extent "the environment experienced by the subjects in a scientific investigation has the properties it is supposed or assumed to have by the experimenter"[178]) has been investigated by an interdisciplinary research group in Tübingen and Zurich.[145] If the actions in the simulator resemble the actions in real operating room environments (*behavioral validity*), it is much more likely that the results of research conducted in a simulator setting or lessons learned in the simulator environment would be transferable to the context of actual patient care. The group developed an improved task analysis method that allows the recording of overlapping activities (41 actions from five categories—monitoring, actions, communication, documentation, and other) to analyze and describe the performance of anesthesia.[179]

This method is described in more detail in Chapter 6. Each of the six anesthesiologists participating in the study was observed during two clinical cases and during three comparable simulator cases (one routine and two involving critical incidents). Analysis of the study showed good comparability of the different action categories (Fig. 7-20). The interpretation of the group is that overall comparability between the operating room and the simulator setting is good, indicating high ecologic validity for simulators in anesthesia. The results of the study also show few, but distinct variations in the task structure of operating room and simulator cases. These variations are mostly due to organizational factors (e.g., fewer "additional tasks" required in the simulator). These studies provide objective confirmation of the favorable sub-

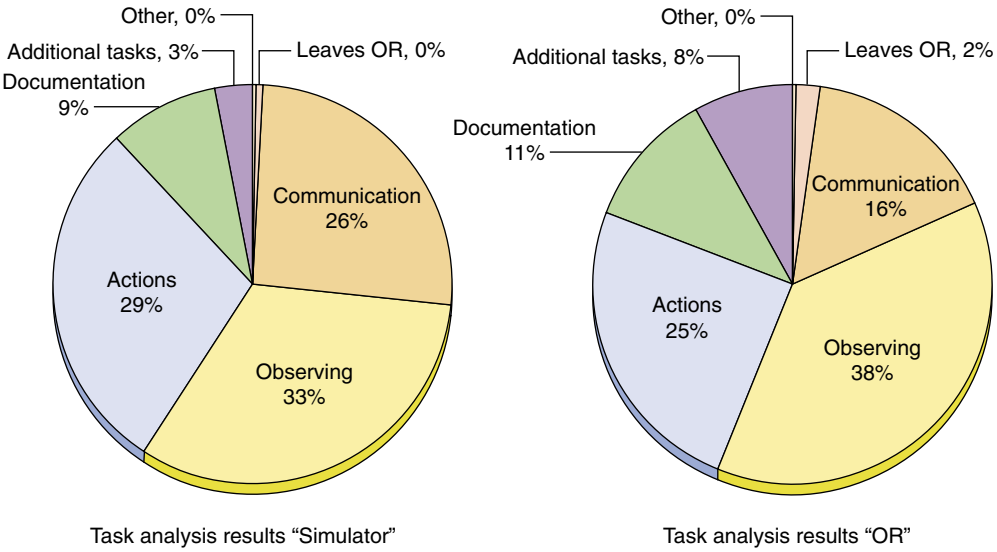


Figure 7-20 Validity of simulator systems versus the operating room (OR). The same anesthesiologists were observed in the OR and the simulator environment with full enactment of the OR personnel, surgical team, and anesthesia nurse. Even though the two settings have some interesting differences, the overall "ecologic validity" of the simulator is good. *(Courtesy of T. Manser, ETH Zurich, and University Hospital, Tübingen, Germany.)*

jective impressions of realistic simulation scenarios by anesthesiologists of varying levels of experience.[126,127,159,161,180-182]

Some differences between simulation and real patient care are inherent to simulation. Subjects realize that they are in a simulator and are likely to be hypervigilant (e.g., many participants neglect documentation in the simulator while waiting for a disaster to happen). In addition, there might be some organizational factors that are usually different in the simulator than in the real operating room (e.g., reflected in fewer "additional tasks" in the simulator compared to the real OR in the study of Manser and Rall). Careful and creative scenario design and introductory briefings may mitigate the hypervigilance and organizational effects.[47,183]

Evaluation of Clinical Performance during Simulation Scenarios

The introduction of patient simulators allowed the study of human performance when responding to critical events (see Chapter 6). Techniques are needed to assess anesthesiologists' performance. Performance can be divided into two components: technical performance, which is the appropriateness and thoroughness of the medical and technical response to the critical event, and behavioral performance, which is the appropriate use of sound crisis management behavior (e.g., leadership, communication, distribution of workload).[184,185] (See Chapter 6 on CRM.) Assessment of medical and technical responses has resulted in "technical scores" suggested by different authors.[151,152,160,161,186-189]

Simulation offers some benefits in assessing performance. Because the nature and cause of the critical incident are known, one can construct in advance a list of essential or appropriate technical activities with relative weights of importance. When assessing technical performance in managing malignant hyperthermia, terminating the trigger agent and administering intravenous dantrolene would be essential items, whereas cooling measures, hyperventilation, and bicarbonate therapy would be among many appropriate (but less critical) technical responses. One also can predict in advance specific technical pitfalls. For malignant hyperthermia, such pitfalls could include diluting dantrolene with the wrong diluent (not sterile water) or an insufficient quantity of diluent. These pitfalls are known to plague clinicians unfamiliar with therapy for malignant hyperthermia.

Can the clinical outcome of the simulator's mathematical physiology predict how a real patient would have fared under that individual's care? This would be possible only where the simulator's control logic used detailed mathematical models of physiology and pharmacology, and not with the script-based control logic. In the latter case, the physiologic state achieved is no different than the checklist of the actions taken that followed the branch points in the script leading to the outcome. The outcome and the actions are essentially the same. Even when mathematical models are used, they are insufficient to predict what would happen to any actual patient after complex sequences of therapy and more subtle patient care judgments. The models have not proven to be robust and have shown a lack of reproducible outcomes even when the same "patient" is given identical perturbations and treatments at exactly the same times.

In extreme cases, the clinical outcome probably does indicate failure or success of performance. A subject who shows totally erroneous decision making (e.g., failure to defibrillate a simulated patient with ventricular fibrillation) unmistakably allows the patient's state to deteriorate quickly. The converse may not be true. Perfect decision making in a resuscitation cannot guarantee that electric countershock would successfully restore a normal cardiac rhythm. We suggest that even with model-driven simulators, the clinical outcome of the simulated patient is at best one datum that can be used to assess the performance of the anesthesiologist on a simulation scenario, but for the foreseeable future, any credible performance measurement technique must involve subjective and semiobjective judgments by clinical experts. In the last few years, there have been many empirical studies attempting to use simulation for different forms of performance assessment in various domains and disciplines.*

Pitfalls of Performance Assessment

Previous trials, experience in other industries, and theoretical analysis suggest that simulation offers substantial opportunities to facilitate performance assessment. Various issues must be resolved, however, to make performance assessment a robust capacity, as follows:

Technical versus nontechnical (CRM) skills. As indicated in previous sections, it is feasible (if difficult) to assess a technical response to specific events and generic nontechnical behaviors (CRM). For which kinds of assessments is it appropriate to measure only technical performance, only nontechnical performance, or some combination of the two?

Number of scenarios. How many different scenarios are needed to achieve robust performance assessment of individuals in all relevant aspects (technical and nontechnical) of patient care? Some emerging results suggest that increasing the number of scenarios is more effective in improving the reliability of ratings than increasing the number of raters is.

Rating individuals versus rating crews or teams. Anesthesiologists work as individuals and in crews and teams with other anesthesiologists and with surgeons, nurses, technicians, and others. Should the performance of individuals working alone be assessed? Should anesthesiologists be able to call for and use help in solving problems? If so, can one still rate the individual when working with a team?

Performance fluctuation. How can performance that fluctuates substantially over time be aggregated into a single rating? This issue was recognized by Gaba and colleagues[185] as a major apparent source of inter-rater disagreement. It is not addressed by the Anaesthetists' Non-Technical Skills (ANTS) system.[162,233] Which techniques would best address this issue, especially as applied to scenarios that represent the actual complexity of clinical practice?

*References 11, 32, 36, 40, 44, 60, 119, 127, 162, 173, 176, 190-215.

Criterion thresholds. What level of performance should be set as criterion thresholds for different purposes? Can benchmarks of performance be established by truly expert clinicians (recognizing that years of experience or hierarchic rank is not a surrogate for expertise or skill)? Similarly, how does the rating system deal with single actions or behaviors that were lethal or harmful in the presence of otherwise good performance? If used for formative assessment, a rating system should indicate the successes of the examinee and the failures. If used for summative or high-stakes assessment, however, it may be critical to ensure that the examinee who risks harming a simulated patient cannot outscore another examinee whose overall performance is less strong, but who at least did not endanger the patient. Not performing chest compressions in a cardiac arrest situation would be such a "knockout" criterion.

Appropriate statistical analysis of validity, inter-rater reliability, and reproducibility of these assessments. Various statistical tests and approaches have been used to evaluate these characteristics. The data on performance show various levels of inter-rater variance and high interindividual (and interteam) variability.[127,151,159-161,180,185,216] As detailed by Gaba and colleagues,[185] some inter-rater reliability statistics are more stringent than others, especially in terms of the nature of the "by chance" benchmark. No firm consensus has been reached regarding which tests are most appropriate to answer key questions about simulation-based performance assessment. Some of the rating systems (including ANTS) have used less stringent tests of inter-rater reliability. Generalizability theory[217,218] offers a set of statistical techniques to sort out the impact of scenario, subject, rater, number of scenarios, and other facets on such assessments. This technique also specifies how comparisons can be made against reference performance levels or as relative comparisons between subjects without a fixed benchmark.

Although simulation should enable performance assessment, a robust set of performance measures of anesthesiologists' skill would be difficult to develop,[219] even if the simulator is used as a tool to present standardized patient scenarios.[220]

Klemola and Norros[221] published a new way of looking at performance that involves anesthesiologists' "habit of actions." These authors distinguish between "reactive habits" (conservative, self-contained, reluctant to construct subjective evaluations) and "interpretative habits" (creative, interactive, continuous integrative reasoning). This article shows that a lot of issues need to be considered when discussing the best method of education and evaluation. Additional issues include defining and assessing professional competence. A more consultant-based method was introduced by Greaves and Grant,[222] who compiled an inventory of characteristics of the anesthesiologist's practice. Epstein and Hundert[223] provide a current review.

Although there are presumed advantages to using simulation as a tool for performance assessment (known scenarios, errors can be allowed to occur and play out, intensive recording and archiving of performance is possible), the anesthesia community should be careful to introduce simulation-based performance evaluation on a slow and measured basis.[224] Performance assessment is expected to be a hot topic for discussion in the simulation and clinical anesthesiology communities in the early 21st century. This controversy should not divert attention from the major application of simulation, which is to improve clinical performance through individual and team training in preventing and managing adverse clinical events.

Can Simulators Be Used for the Evaluation and Testing of Residents or Practitioners?

As discussed previously, patient simulators should be useful tools for evaluating the performance of trainees and others. Scoring or certifying competence by using the simulator is more problematic, however, than using it as a teaching tool.

Anesthesiologists have discussed the possibility of using the simulator as a tool for examinations, either for graduation from a residency or for American Board of Anesthesiologists certification. This use would require independent evaluation of the simulation scenarios and assessment of the predictive power of the subjective judgments made by experts scoring the examinee. An obstacle is the lack of any well-accepted standard for performance evaluation. Another difficulty with using simulation for board certification testing is that the operating room equipment would rarely be the same as that used by the candidate, and the operating room staff's operational protocols could differ from the protocols familiar to the candidate. In the training situation, these difficulties can be overlooked as part of the global suspension of disbelief needed to maximize the benefits of simulator training. In the test situation, these differences potentially could skew the results. This issue could be addressed by allowing candidates preparing to take their examination to undergo sufficient practice sessions to familiarize themselves fully with the standard simulation environment used for the test.

Despite these difficulties, it is likely that if the use of anesthesia simulators does become more widespread, anesthesiologists would become more interested in using them to assist in evaluating performance. The existing system of performance evaluation, which uses a haphazard system of subjective judgment of clinical competency in residency along with written and oral examinations, has itself never been validated. Many believe that the written examination does not correlate well with clinical ability, and the degree to which the oral examination process tests actual clinical skill is unknown. Simulation could offer candidates the opportunity to show their clinical abilities in a controlled clinical domain, while still showing their consulting and language skills through oral examination.

More recently, there have been a few projects on using simulation as a high-stakes test for clinicians.[37,38,96,173,175,197,225,226] Simulation is being used more commonly for "no-jeopardy" formative evaluations of performance in some residencies. This use may then evolve into graded "pass/fail" examinations or demonstrations of skill. Another situation of simulation-based performance assessment would be for the evaluation of residents who have been placed on probation, or for whom dismissal from the residency program is already a distinct possibility. For these residents, the burden of proof is on them to show their skills. The simulator could offer a more controlled environment for them to do so. The same could be true for practitioners who wish to return to clinical work after a hiatus.



Figure 7-21 Multiroom simulation center at the VA–Palo Alto Health Care System and Stanford University. Two control rooms and two audiovisually interconnected lecture rooms provide the opportunity to run three patient simulators at the same time. ER, emergency room; ICU, intensive care unit; OR, operating room.

In Israel, a simulation examination has become part of the Board certification process. In the United States, the American Board of Anesthesiology has been monitoring the progress of simulation for training and performance assessment. As of 2008, however, there is no prospect of simulation-based board examinations in the United States.

Characteristics of Simulation Centers

Although one can install a simulator in a laboratory or conference room, or conduct only in-situ simulation, many institutions have chosen to construct complete simulation centers. Figures 7-21 and 7-22 show floor plans by the authors (D.G. and M.R.) of medium-sized centers (two to four simulation rooms) for mannequin-based simulation. Figure 7-23 shows the equipment of such a center in more detail. Typically, these centers provide a separate control room to allow complex simulations to be presented without an instructor intruding on the simulated case. The center also provides a debriefing room where videotapes of the simulation session can be reviewed. Some centers have elaborate computer-controlled audio-video systems allowing the recording of multiple views with real-time annotation rapid search to annotated portions of the recording. Figure 7-24 shows the simulator control room with advanced audio-video equipment at the TuPASS Center for Patient Safety and Simulation of one of the authors (M.R.) in Tübingen, Germany.

Universities and hospitals or hospital networks are increasingly constructing very large multidisciplinary and multimodal simulation facilities. Often, these facilities combine all the types of simulation and immersive learning in one large unit, including standardized patient actors (usually in clinic settings), mannequin-based simulation, part-task and surgical/procedural trainers, wet and dry work (e.g., plaster casting or procedures on food products), and different forms of virtual reality. Sometimes these also incorporate facilities for dissection of cadavers or the use of anesthetized animals. Having all forms of simulation together also fosters the hybrid techniques, as when a standardized patient actor is combined with a part-task trainer, or when a surgical simulator is combined with a mannequin-based patient simulator. Large multidisciplinary facilities may have anesthesiologists in leadership positions. Figure 7-25 shows an example of such big centers, the floor plan by one of the authors (D.G.) of the new center for immersive learning at Stanford University, currently under construction (2008).

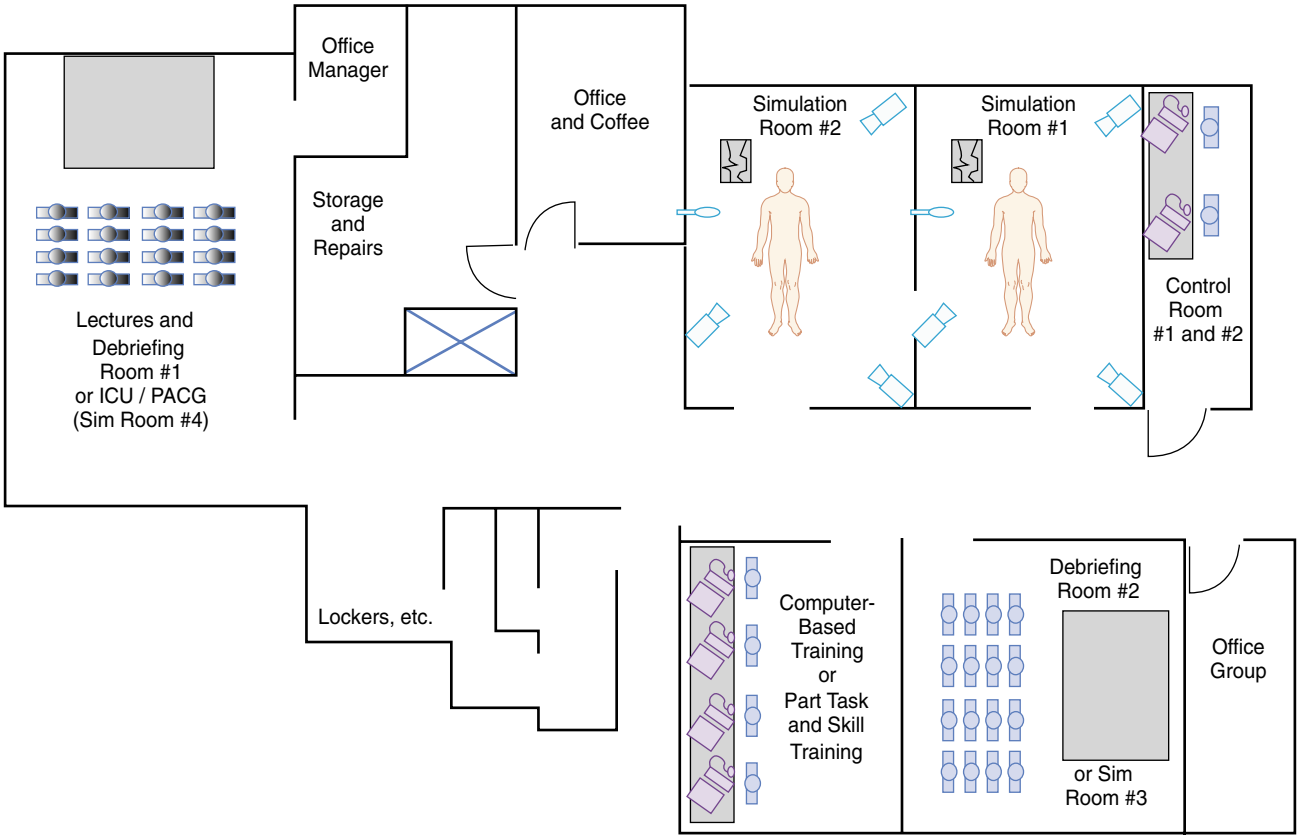
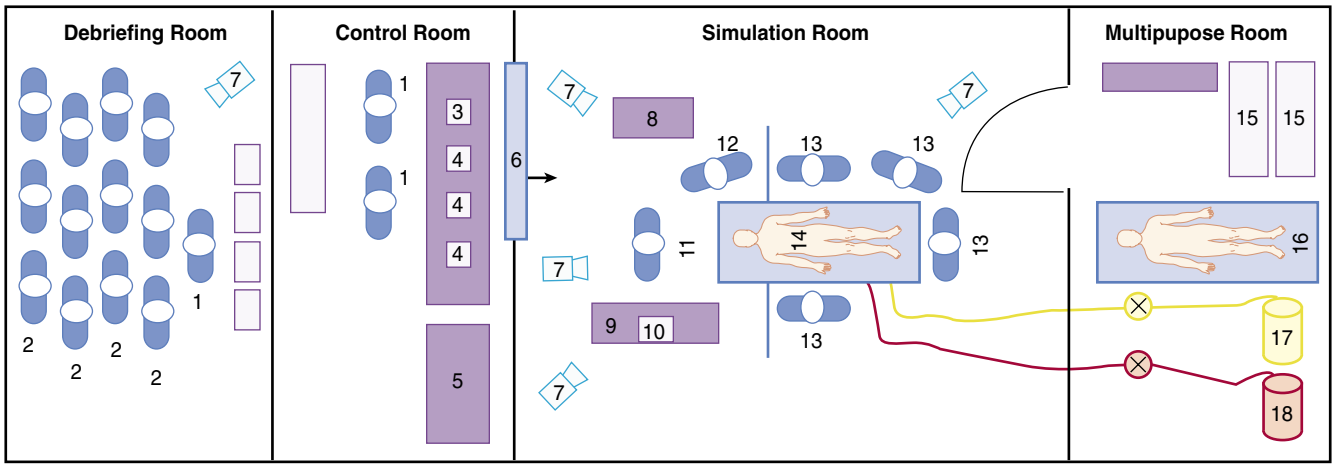


Figure 7-22 An intermediate-sized simulation center with four simulation rooms, a computer-based training room, and several multipurpose rooms, equipped with audio-video patch panels to adjust the room use flexibly to the needs of the different training activities (e.g., the big seminar room also can be used as a big intensive care unit or postanesthesia care unit). *(Picture by E. Stricker from TuPASS Center for Patient Safety and Simulation, Tübingen, Germany.)*



1 Instructor
2 Trainees

1 Instructors
3 Simulator control console
4 Video and computer screens
5 Data storage
6 One-way mirror

7 Video cameras
8 Anesthesia cart
9 Anesthesia machine
10 Vital signs monitor
11 Primary anesthesiologist (trainee)

12 Anesthesia nurse
13 Surgeons (sim. team)
14 Simulator mannequin with linkage to the simulator console

15 Storage (for different scenarios)
16 ICU bed with mannequin
17 Artificial urine and pump
18 Artificial blood and pump

Figure 7-23 Prototypical example of a simulation center (former simulation center at University of Tübingen, Germany). The instructors in the control room look through a one-way mirror into the operating room/intensive care unit (ICU) while they control the "patient" from the simulator workstation and direct the audiovisual recording. Various remote-controllable video cameras, microphones, and loudspeakers in the simulator room provide the best possible view and sound from the "scene." Trainees perform on the simulator mannequin and the vital sign monitors and have to interact with the personnel involved at the same time. Nonactive participants can watch the scenarios live from the adjacent debriefing room, including real-time vital sign transmission, where the video-assisted debriefing session occurs immediately after every scenario. *(From Decker K, Rall M: Simulation in anaesthesia: A step towards improved patient safety. Minim Invasive Ther Allied Technol 9:325-332, 2000.)*



Figure 7-24 Simulator control room. On the left side is the simulator workstation for control of the simulator system itself. In the middle is the audio control desk with integrated control of the simulated patient voice and several wireless headset channels and the remote mixer. On the right are flat screens for selection and control of the multiple views of the video cameras. For anesthesia crisis resource management courses, a multiquad-split view, including the vital sign monitor, is digitally recorded on a hard disk and used for playback. Marks allow jumping to interesting scenes without fast forward or rewind delay. *(Taken at the control room of the TuPASS Center for Patient Safety and Simulation, Tübingen, Germany.)*

The cost structure of a simulation center is a complex issue (see section on Costs). The cost varies greatly depending on the scope of the facility and its programs, the nature of the target populations, and the extent of use by the different possible stakeholder groups. How the costs are allocated to different elements of an institution or consortium is equally complicated and depends highly on local conditions. There is no one formula for success. In some models, the center is wholly responsible for its own costs, but is completely free to generate and retain revenue. At the other extreme is a model whereby the host institution bears all costs of operating a central core facility, but it also collects any and all revenues and may even "tax" components of the institution (e.g., departments) to offset the costs. Perhaps most common are mixed models in which the central authority bears costs of initial construction and outfitting (often funded via philanthropy) and some portion of the ongoing infrastructure (simulation operations personnel, capital refurbishment, utilities), while each user (e.g., department) is responsible for providing instructors and paying for the marginal costs of any specific course or application. To date, few, if any, centers truly generate a profit, but many sites have successfully garnered external funds to offset some of the costs of training their own key target populations.

Costs

What are the costs of simulator-based training? These costs depend on many of the same factors that determine the curriculum, as follows:

Types of training involved, ranging from technology in-service to training in basic anesthesia skills, critical incident management, or CRM

Target populations for the training, whether equipment technicians, medical students, novice residents, experienced residents, nurse anesthetists, teaching faculty, or private practitioners

Organizational and financial characteristics of the institution

The hardware and software costs of the screen-only simulators are quite low (a few hundred dollars), whereas the equivalent cost of a complete hands-on simulator is higher (the prices of commercial simulators range from around $25,000 for intermediate-fidelity simulators to more than $150,000, depending on features; one should contact the manufacturers for detailed information). Cumin and Merry[61] report on available simulators. This cost does not include the necessary clinical equipment (approximately $150,000) and space.[227] Even these large expenditures do not dominate in the cost equation, however, because the capital equipment can be amortized over a relatively long useful life, with appropriate provisions for service and upgrades.

The dominant cost is likely to be the salaries of expert instructors and trainees. An expert must oversee the curriculum, but the type of training and the target population determine the amount of expert instruction required. A single faculty member can review the summaries of exercises performed by residents on a screen-based simulator in a few hours per resident per year. Nonphysician instructors may be suitable for some task training or for drill and practice sessions. A single instructor can use the simulator to show pulmonary or cardiovascular physiology to a whole class of medical students. When training novice residents in basic anesthesia skills, it may be possible to have senior residents or fellows conduct the sessions at a low marginal cost. When training experienced residents and practitioners in complex material, such as the handling of critical events, there is likely to be no substitute for expert instructors. The cost of expert instruction depends on the organizational arrangements of the institution. In a teaching institution where the faculty all have at least some time allocated for teaching or scholarly activities, some of them may choose to fulfill this requirement in simulation-based teaching or scholarship. Where further staffing is needed, payment for clinical release time may be needed.

Another organizational factor that affects the cost has to do with making trainees available for what can be complex, exhausting, and lengthy training sessions. Removing residents from revenue-producing work for training purposes is expensive. If simulator training could allow residents or other anesthesiologists to work more safely and efficiently, the benefit would outweigh the cost. Some residency programs provide protected time for education of residents (e.g., one half day per week). In such cases, residents should be available for educational activities, but faculty time may be even more scarce. Many anesthesia programs have used simulation training as a recruiting tool for residency candidates, although some believe that with the high proportion of programs that already have simulation activities (the scope and quality of which are hard for applicants to judge), the competitive value of simulation has disappeared. Programs that lack such facilities and activities would not be the exception and would likely be seen negatively by applicants.

There is no question that simulation-based training is more costly than exhorting learners to read or putting them in a room with a lecturer. Simulation-based training allows a host of issues to be addressed that cannot be easily tackled in other ways. It is our belief—one that has been borne out by programs "voting with

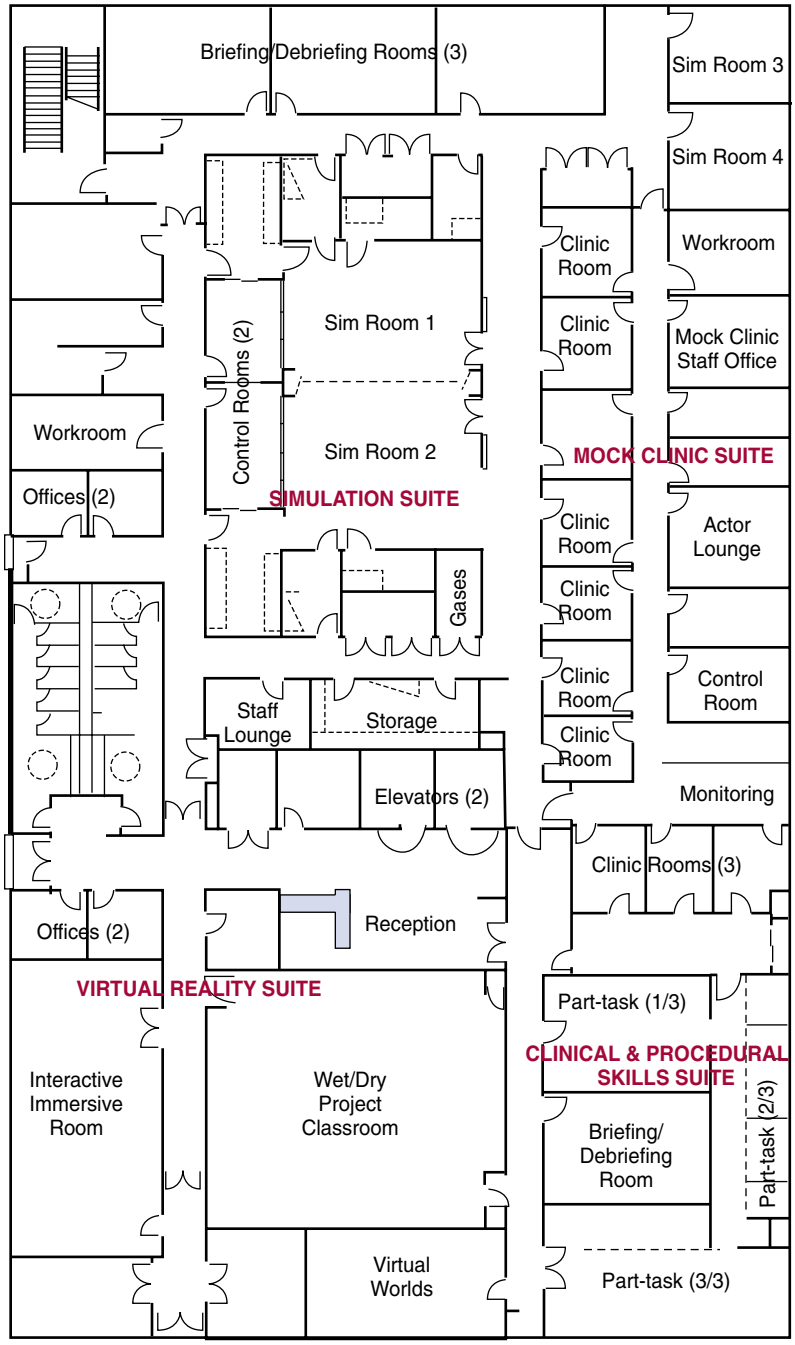


Figure 7-25 Floor plan of a very big interdisciplinary simulation center for multiple domains (anesthesia, surgery, students) with several multipurpose simulation rooms, and skills laboratories. *(Picture by D. M. Gaba, from the Center for Immersive and Simulation-based Learning at Stanford Medical School. Ground floor built as of June 2008.)*

their feet" over the past 15 years—that if simulator-based training is deemed to be desirable, innovative changes in organization would evolve to allow it to occur.

Proliferation of Simulation Centers

Currently, despite the lack of definitive cost-effectiveness data, training with realistic simulators is under way in many sites around the world,[228] with many of them choosing to conduct "high-end" crisis management and critical incident training sessions. Table 7-13 lists useful websites of simulation centers and other resources. These programs have already "voted with their feet" on the issue of cost versus benefit. With so many centers exploring the realities of simulation training, we can expect to see additional data on efficacy and cost within the next few years. A definitive study is in principle possible, but it would require a very large number of subjects evaluated by multiple raters and would be complex and costly.

Still other factors complicate assessment of the effectiveness of simulator-based training. Studying the impact of a single

Table 7-13 Websites of Simulation Centers and Other Useful Resources on Simulation

http://www.ssih.org
Homepage of the Society for Simulation in Healthcare, the largest interdisciplinary society around simulation in Healthcare. Journal Simulation in Healthcare, Elsevier Annual IMSH Meeting (see below).
http://www.hmc.psu.edu/simulation/
Penn State Medical Center, lists of available simulator systems (and links to manufacturers)
www.sesam.ws
Homepage of SESAM (Society in Europe for Simulation Applied to Medicine)
http://www.simulation-users.fsnet.co.uk/
Patient Simulation User's Group, website run by Barts and the London Medical Simulation Centre
http://web.anes.rochester.edu/simulate/simusers.htm
http://web.anes.rochester.edu/simulate/webpages.htm
University of Rochester Medical Center providing lists of and updated links to many simulation centers around the world
http://www.bristol.ac.uk/Depts/BMSC/europe.htm
Bristol Simulation Center, map-based list of simulator sites in Europe and worldwide
http://anesthesia.stanford.edu/VASimulator/simulator.htm
VA–Palo Alto HCS/Stanford University (D. Gaba)
http://www.tupass.de
Center for Patient Safety and Simulation, University of Tübingen (M. Rall)

session of a course that uses a new technology and a new approach to training may underestimate the course's impact when it is used on a regular and repetitive basis. It is widely believed in commercial aviation that CRM training must begin with the initial training of pilots and must be continued throughout their career. Social psychologists Helmreich and Foushee, two of the main architects of CRM training, have written: "Data indicate that even intensive initial CRM training constitutes only an awareness phase and introduction to the concepts, and that continuing reinforcement is essential to produce long-term changes in human factors practice."[229] Similarly, United Airlines states in its CRM manual: "Command/Leadership/Resource management [United's terminology for CRM] cannot be a one-shot approach. It has to be a coordinated long range program. It must therefore be an integral part of the entire training effort: new hire training, transition and upgrade programs, and recurrent training."[230]

Finally, the principles and procedures taught in training must be reinforced within the operational environment. Simulator-based safety training can be totally negated if production pressures or latent failures in the workplace make it impossible to implement its teachings effectively.

It is still too early to make definitive statements about either the benefits or the costs of simulator-based training in anesthesia. To some extent, a "catch 22" is involved. One cannot attempt to determine the true cost-effectiveness until simulation is widespread enough for complex and expensive studies to be undertaken, and until there is more experience on the different organizational aspects of providing the training. Many institutions are likely to shy away from taking the risk until the cost-effectiveness is proven.

Simulation Societies: Society for Simulation in Healthcare and Society in Europe for Simulation Applied to Medicine

One measure of the evolving maturity of simulation in health care is the formation and growth of professional societies focused on this topic. Although anesthesiology was the medical field that initiated work on the fully interactive mannequin-based simulator and that dominated the early developments in the field, simulation is a broad strategy that has now been widely adopted by many different disciplines and domains in health care. For the most part, simulation professional societies have sprung up as explicitly multidisciplinary organizations. Major leadership roles in these societies have been played by anesthesiologists and engineers associated with anesthesiology, however.

The largest simulation organization is the Society for Simulation in Healthcare (SSH; www.ssih.org), which was founded in 2004 as the outgrowth of the group that had operated the International Meeting on Medical Simulation for several years as a satellite to the annual meeting of the Society for Technology in Anesthesia. Under the new auspices of SSH, the meeting was transformed into the International Meeting on Simulation in Healthcare (IMSH), encompassing all health care disciplines and domains, not just medicine. Regular scientific congresses on simulation had been under way since the mid 1990s (the Rochester Conferences on Simulation in Anesthesia). Although they originally had about 100 attendees, Society in Europe for Simulation Applied to Medicine (SESAM) meetings have now around 400 attendees. The IMSH meeting in 2009 is expecting more than 2000 attendees. This puts it in the category of a medium-sized scientific meeting; to put this in the context of anesthesiology, it would rank as the third largest scientific meeting in the United States, falling below only the ASA meeting and the New York Postgraduate Assembly in Anesthesiology (PGA) conference, but ranking ahead of the International Anesthesia Research Society (IARS) annual meeting.

Another sign of the mainstream nature of simulation is that SSH has published a quarterly peer-reviewed journal, *Simulation in Healthcare,* since 2006. It has been integrated in PubMed citations recently (2008). The journal is an official publication of many international professional societies of simulation in health care, including SESAM (www.sesam.ws), the Australian Society for Simulation in Healthcare, and the Association of Standardized Patient Educators. The organizations have become affiliates of the SSH.

Another sign of maturity is the emergence of a trade organization for simulation in health care dedicated to educating and influencing policy makers, primarily concerning federal legislation and health policy. The Advanced Initiatives in Medical Simulation (AIMS) is a 501c6 organization that is allowed to lobby the U.S. government. Supported by universities and industry, AIMS promotes legislation and offers an annual exhibition about simulation in health care on Capitol Hill. What was previously seemingly the province of a few technologically minded anesthesiologists has blossomed into a substantial industry and profession with all the trappings of organizations, meetings, journals, and even lobbyists.

Future of Patient Simulation in Anesthesia

"The future is now—we are it."[231]

Although nearly past 2 decades of consistent development, the field of simulation in health care is still relatively new.[5,16,232] Although there are hundreds to thousands of simulators in use around the world, many targeting anesthesiology and critical care, the fraction of clinicians in these fields who have undergone a meaningful simulation experience is still small.

Simulators have become more sophisticated, and users now can choose from many different models offered by multiple manufacturers. Improvements in simulators depend on the demand for the devices and on the tradeoff between fidelity and cost. Many otherwise desirable improvements may be too costly for the impact that they can be expected to produce. Technologic advances are likely to be targeted at portability and reliability, rather than at supporting increasingly esoteric feature sets. Many users have opted for simpler and cheaper simulators that use direct control, modest scripts, and finite state machines to control the changing state of the simulated patient rather than complex mathematical models. This is partly because the production and use of robust mathematical models has been more difficult than anticipated.

In contrast to aeronautical engineers, physicians do not design and build the system that they wish to model. The fundamental differential equations of fluid mechanics and aerodynamics are firmly established, allowing supercomputers to provide technically meaningful simulations as replacements for many wind tunnel tests. There are still wind tunnel tests, however, and test flights of actual prototype aircraft. Sophisticated instrumentation can be built into test structures to define their behavior accurately. Physicians will never have this type of knowledge about the human body. The advantages and disadvantages of the different types of control logic for different applications is still being sorted out.

There has been growing interest in purely virtual reality simulations, often of a type similar to massive online games or to the popular Second Life system. Participating with others in the same virtual world, linked by the Internet, is appealing for many purposes. Such simulations are only as good as the engines that drive the underlying patients that may be found there, and the quality of the data provided and interventions and choices supported for implementation in these settings. Virtual reality proponents imagine a virtual reality so realistic that it rivals, or is indistinguishable from, the real world. This would approach the Star Trek "Holo-Deck." Although we once predicted that such systems might be in place by 2020, the development of such high-veracity virtual reality has not proceeded as quickly as previously imagined, and it is unclear whether full virtual reality of this nature will be available in the next decade.

Patient simulation has now become a regular part of the initial and recurrent training of most anesthesiologists and many other clinicians in the United States, Australia, and the United Kingdom, and in some European countries. With patient simulation, the human error–based CRM concept was introduced to medicine as ACRM training, revolutionizing the traditional way and content of teaching and learning. The anesthesia community can be proud of its pioneering role in developing patient simulation technology and simulation-based training curricula, and anesthesiologists and others working with them continue to play dominant leadership roles in many settings of simulation, even those devoted to fields outside anesthesia.

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8 Teaching Anesthesia

Key Points

1. Education is an all-encompassing process (not merely a specific activity) that results in a change in behavior on the part of the student/learner. The focus of education is the learner, not the teacher. It is the student who is educated by interacting with an environment that provides experiences. Education is change in behavior based on experiences.
2. Adult learners learn anesthesiology. Adult learners are those with strong motivation to participate in a set of experiences to learn a specific discipline. The discipline that they want to learn is one that they are interested in or need to know, or both. Adult learners participate in life-centered situational learning in the area or areas in which relevance is most likely.

   Adult learners enter the learning activity with a wealth of previous experience and view the current education in light of their background. Adult learners can capitalize on this previous learning; however, the previous learning may color how the current learning takes place.

   Adult learners are self-directed and initiate their own activities. Adult learning is goal oriented toward relevant life-centered needs. An adult learner tends to pick and choose some, not necessarily all, of the educational activities available.

   Inherent differences among people tend to increase with aging. Adult education must provide for differences in style, time, place, and pace of learning among adult learners. The time factor for learning is especially crucial for adults. Adults perceive that time passes more rapidly; that is, there is less time available to learn—or to do anything for that matter. With time perceived to be in short supply, adult learners tend to be selective in their learning to use what time they have more efficiently.
3. In 2006, there were 4970 resident anesthesiologists in 131 accredited American core anesthesiology residency programs and 360 subspecialty residents in 213 accredited American subspecialty anesthesiology programs.
4. Silber and colleagues,[29] in their study of almost 6000 patients undergoing prostate or gallbladder surgery in multiple hospitals, demonstrated that patient recovery or "rescue" from an adverse event correlated with the proportion of board-certified anesthesiologists in the hospital.
5. The Accreditation Council for Graduate Medical Education has defined six educational areas for which residents and fellows must demonstrate competency. These areas additionally are major components of Maintenance of Certification in Anesthesiology:
   a. Patient Care—Residents must be able to provide patient care that is compassionate, appropriate, and effective for the treatment of health problems and the promotion of health.
   b. Medical Knowledge—Residents must demonstrate knowledge of established and evolving biomedical, clinical, epidemiologic, and social-behavioral sciences, as well as the application of this knowledge to patient care.
   c. Practice-Based Learning and Improvement—Residents must demonstrate the ability to investigate and evaluate their care of patients, to appraise and assimilate scientific evidence, and to continuously improve patient care based on constant self-evaluation and lifelong learning.
   d. Interpersonal and Communication Skills—Residents must demonstrate interpersonal and communication skills that result in the effective exchange of information and collaboration with patients, their families, and health professionals.
   e. Professionalism—Residents must demonstrate a commitment to carrying out professional responsibilities and adherence to ethical principles.
   f. Systems-Based Practice—Residents must demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on other resources in the system to provide optimal health care.*
6. Full-time anesthesiology faculty positions in U.S. medical schools in 2006-2007 numbered 5836.[30] Anesthesiologists represent 5.6% of the clinical teachers and 4.7% of all American medical school teaching faculty.[30] The 5836 anesthesia faculty members in medical schools bear the

major responsibility for teaching some or all of the 69,028 enrolled undergraduate medical students, the 4970 graduate trainees in anesthesiology residency training programs, the 360 graduate trainees in anesthesiology subspecialty fellowship programs, and many of the approximately 104,879 physician house-staff trainees.[12,32]

7. Effective clinical teachers who are able to succeed at the bedside teaching encounter display specific actions noted by their students and themselves.[35] These actions include
   a. Allocating time for teaching
   b. Creating a teaching/learning environment of trust and concern
   c. Demonstrating clinical credibility
   d. An initial orientation
   e. A final evaluation
   f. Learners being able to present a case
   g. Teachers managing the case presentation
   h. Didactic sessions being used to enhance clinical case material
   i. Teaching taking place at the bedside so that students can learn physician-patient relationships
   j. Teachers and students discussing psychosocial issues
   k. Attention being paid to transferring the teaching responsibility
8. Teaching content requires attention to increasingly complex cognitive functions. As described by Bloom,[39] teaching/learning in the cognitive domain for any topic addresses the following:
   a. Knowledge—recall
   b. Comprehension—understanding
   c. Application—use of abstractions
   d. Analysis—break down; seeing the relationship of parts
   e. Synthesis—put together; creating a new entity
   f. Evaluation—judgment of value
9. A systematic methodology to develop a psychomotor skill lesson includes the following steps[54]:
   a. Analyze and separate the skill into its component parts and determine which aspects of the skill are most difficult to perform.
   b. Provide students with a model of the skill, effectively demonstrated in its entirety, that they are expected to perform.
   c. Make provisions for students to practice until the expected behavior is mastered.
   d. Provide adequate supervision and an evaluation of the final performance.

*Adapted from ACGME Outcome Project. Available at www.acgme.org/outcome.

"Pedantic" is a description teachers wish to avoid. In the interest of doing so, I offer a fifth grader's biography of the great teacher Socrates[1]:

Socrates was a man.
Socrates was a Greek.
Socrates went around telling people what to do.
They poisoned him!

This chapter on anesthesia education is not intended in such a manner that I risk Socrates' fate, but rather it is meant to be provocative, to give cause for thought on an important subject not often reflected on. All anesthesia education can be easily considered in the following question (Greenhow DE: personal communication, 1982):

How shall who teach what to whom for what purpose now and in the future?!

Anesthesia education is presented by using this question as the framework for consideration. This chapter provides a philosophy of teaching anesthesia rather than a detailed account of the many aspects of anesthesia education (e.g., operating room anesthesia versus critical care medicine versus cardiopulmonary resuscitation versus chronic pain management). Also, this chapter is exclusively directed toward the teaching organization, regulations, and philosophy of teaching that exist in the United States. See Chapter 3 for perspectives on how other countries are teaching anesthesia and their philosophic approaches that parallel their needs.

Teaching and Education

Teaching, in a narrow sense, the way most of us think about it, is an activity by an individual aimed at causing another person to know some new fact or to know how to accomplish some new task. The focus appears to rest on the teacher and the activity of teaching. It does not take long to realize, however, that this way of looking at the teaching/learning activity has misplaced emphasis. If not with the teaching activity, where does the emphasis belong? The answer to this question lies in understanding the definition of education.

Education is an all-encompassing process (not merely a specific activity) that results in a change in behavior on the part of the student/learner. The focus of education is the learner, not the teacher. It is the student who is educated by interacting with an environment that provides experiences. *Education is change in behavior based on experiences.* The experience most often includes the student interacting with a teacher, but it is almost never limited to that alone. The entire milieu defines the total experience (Fig. 8-1). When the milieu changes, so may the education;

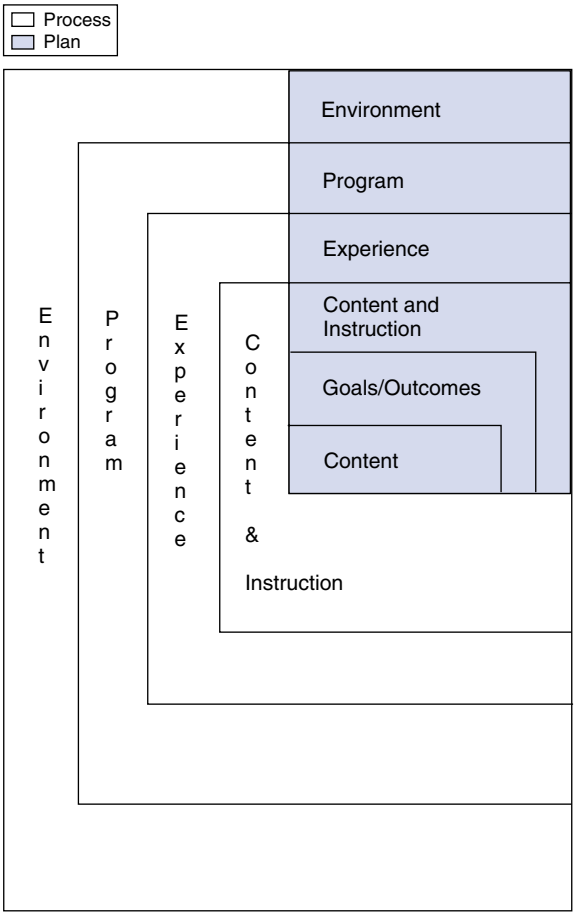

Figure 8-1 Diagrammatic representation of the educational experience. The two major components are the plan for teaching and the process of education that actually occurs. At the core is the content (cognitive, psychomotor, affective, or any combination of the three) to be taught and learned. Growing out of the content are the planned goals of education, the methods and program of instruction, and the environment in which the teaching and learning will occur. In the diagram, each building block of the plan is added to the previous one in an all-encompassing fashion. What is planned as education and what is experienced may or may not be the same. As represented by the diagram, the educational process that actually occurs includes all of the plan and layers on it, both the real environment and the teacher/student interactions that provide the education, that is, the experiences that provide the basis for the ultimate change in student behavior. *(Modified from Atkins E: Curriculum Theorizing as a Scientific Pursuit: A Framework for Analysis [unpublished doctoral dissertation]. University of Pennsylvania, 1982.)*

that is, the change in behavior exhibited by the student may vary dramatically if the milieu is varied.

Picture the educational setting in which an anesthesiology resident is learning how to use epinephrine when weaning a patient from cardiopulmonary bypass. The knowledge and skills that must be learned include application of the pharmacologic principles of catecholamines to the pathophysiology of cardiovascular disease by turning on a mechanical infusion pump to deliver the indicated dose of a medication while technically monitoring for dose response and toxicity. Learning these facts and the skills sufficient to use them is much different when done from a textbook or a preoperative conference with a staff preceptor than when done during the operating room interaction between the surgeon and anesthesiologist, where varied opinions may consider dopamine a more sound physiologic choice or intermittent boluses a better administration technique. The interposition of the concerned surgeon and real-time patient setting between the student and knowledge and skills to be learned changes the learning environment and hence the educational experience for the resident. More is learned than the facts and psychomotor skills. As the attitudes of both the anesthesiologist and the surgeon are displayed during resolution of the question about the "best" drug to use and the "right" way to give it, the resident learns how these two types of practitioners are supposed to relate to one another.

It seems obvious, therefore, that there is more to consider than just teaching. What more is there to the anesthesiologist's responsibility than just teaching those around him or her? The answer is provided by answering the component parts of the question posed at the beginning of this chapter.

Teach to whom?
Why teach?
Who teaches?
What to teach?
How to teach?

Teach to Whom?—The Students

The simplest answer to the question "who learns anesthesiology?" is "those who will provide anesthetic care to patients." Included are the anesthesiologist, nurse anesthetist, and dentist who administers anesthesia for dental procedures.[2] Also to be included are the many varied paramedical personnel who participate in patient care activities related to primary anesthetic care: the anesthesia technician, anesthesia aide, nurse practitioner, postanesthesia recovery room nurse, physician assistant, surgeon assistant, respiratory therapist and aide, intensive care/critical care/emergency room/trauma nurse, perfusionist, emergency medical technician/paramedic, cardiopulmonary technologist, pulmonary function technician, and blood gas laboratory technician.[2] Each of these occupations is intimately related in some way to the body of knowledge that constitutes the practice of anesthesiology.

In a much broader sense, the entire medical community can be considered appropriate learners of anesthesiology. Medical students, for example, are appropriate candidates for learning a core of anesthetic knowledge and skills, specifically those essential for the training of all physicians. Basic central nervous system, cardiovascular, and pulmonary diagnostic monitoring, emergency airway management, and the clinically applied pharmacology of sedative/hypnotic and analgesic medications and local anesthetics are some of these essentials. Medical students, graduate physicians, and paramedical personnel of many types are appropriate learners because all are often faced with the task of educating the lay public about anesthesiology. Who learns anesthesiology, therefore, are those who practice it or perform related duties that require some understanding of the subject.

Another way to address the question of who learns anesthesiology is to answer *adult learners*. What describes an adult learner?[3] How are adult learners unique? Adult learners are those with strong motivation to participate in a set of experiences, such as a curriculum, to learn a specific discipline. The discipline that they want to learn is one that they are interested in, need to know,

or both. The resident actively seeks education in anesthesiology. A sixth grader (a child learner), in contrast, does not seek education in arithmetic. Adult learners participate in life-centered situational learning in the area or areas for which relevance is most likely.

Adult learners enter the learning activity with a wealth of previous experience. They view the current educational experience in light of their background. An internist who enters an anesthesiology residency in preparation for a career in intensive care medicine has a rich resource background in medical practice. Adult learners can capitalize on this previous learning. At the same time, however, the previous learning may color how the current learning takes place. The key for the teacher is to acknowledge the adult learner's expertise and build the new education on it rather than downplay it and, in essence, "reject" the adult learner.

Working together in a mutual peer relationship with the teacher, adult learners are self-directed. Whereas child learners need a set of directions that originate from the teacher, adult learners initiate their own activities. Because adult learning is goal oriented toward relevant life-centered needs, an adult learner tends to pick and choose some, not necessarily all, the educational activities available.

Strong commitment and specific intentional attachments uniquely characterize adulthood. Marriage and child rearing are examples of such commitments and attachments. At the same time that adults make commitments, their lives are evolving and they pass through many critical life stages (e.g., assuming financial responsibility, coping with the illness or death of a parent). These strategic choice points in life have an impact on adult learning. The decision by an anesthesiology resident, for example, to extend education an additional year to learn a subspecialty or to participate in research training may be based on the total financial debt incurred for medical education up to the end of residency and the need to repay that debt, weighed against the acuteness of the family's financial needs.

Inherent differences among people tend to increase with aging. Adult education must provide for differences in style, time, place, and pace of learning among adult learners. The time factor for learning is especially crucial for adults. Adults perceive that time passes more rapidly, that is, there is less time available to learn—or to do anything for that matter. With time perceived to be in short supply, adult learners tend to be selective in their learning so that they use what time they have more efficiently. The anesthesiology resident may devote time to learning in the operating room and weekly departmental case conference but may choose to skip the journal club to spend time with the family.

Recognition of the special traits that adult learners possess allows the anesthesiology educator to provide an educational program embraced by the student rather than one that is rejected. Assessing the needs of the adult learner and using these needs as a springboard from which a curriculum is designed are more likely to result in a good educational outcome than to impose on the learner what the teacher alone thinks is right.

Why Teach?—The Reasons

An obvious reason for teaching anesthesiology is that we as a specialty have defined it as part of our identity (see Chapters 1 and 2)[4]:

> *The American Board of Anesthesiology (ABA) exists in order to . . . maintain the highest standards of practice by fostering educational facilities and training in anesthesiology which the ABA defines as the practice of medicine dealing with but not limited to . . . teaching of cardiac and pulmonary resuscitation, . . . supervision, teaching and evaluation of performance of both medical and paramedical personnel involved in perioperative care, . . . administrative involvement in health care facilities and organizations, and medical schools necessary to implement these responsibilities.*[4]

In addition to our own description, others define anesthesiology in similar terms:

> *[An anesthesiologist] May instruct medical students and other personnel in characteristics and methods of administering various types of anesthetics, signs and symptoms of reactions and complications, and emergency measures to employ.*[2]

Teaching anesthesiology is clearly one component of an anesthesiologist's daily activity. In some instances, it means providing the experience needed for physician trainees to achieve consultant anesthesiologist status. In other settings, it means providing the experience needed for other medical and paramedical professionals to achieve a level of expertise appropriate to their required competencies—as examples, for an internist, the ability to understand anesthesiology sufficiently to relate to anesthesiologists and educate patients about anesthesiology; for a postanesthesia recovery room nurse, the ability to understand anesthesiology sufficiently to care appropriately for patients emerging from anesthesia and to be versed in the critical care aspects of the preanesthesia and postanesthesia periods to provide life support if necessary.

A major purpose of teaching anesthesiology is to provide a common set of learning experiences that when mastered by students, will lead to relatively standardized knowledge and behavior. These standards (minimum standards though they may be) become the criteria by which a student candidate can be evaluated (certified) for entry into a specified mastery level.[4-6]

Becoming a consultant anesthesiologist certified by the ABA depends on being able to demonstrate that one possesses a minimum standard of knowledge of, skills in, and attitudes about anesthesiology.[4] Public trust is gained by this process of specialty certification, which ensures that a certified specialist has met the defined standards of anesthesia practice.[4-6] Although specialty certification in anesthesiology culminates in evaluation mechanisms (achieving clinical competence as attested to by the training program and successfully passing written and oral examinations), the certification process is driven by educational activities focused on teaching the resident how to become a consultant anesthesiologist.[4-6] A key part of this process is establishment of the training curriculum or continuum of education in anesthesiology by the ABA.[4]

A resident trainee in anesthesiology voluntarily enrolls in a graduate medical education program and accepts the ABA's approved curriculum and evaluation (testing) protocol. Coupled with the physician candidate *certification* process is the residency education *accreditation* process.[7] Residency program accreditation is a voluntary process whereby an institution applies for recognition of its anesthesiology graduate medical education as

meeting a minimum set of teaching standards that will support the curriculum. Such recognition is achieved from the Accreditation Council for Graduate Medical Education (ACGME). The ACGME represents the combined "wisdom" of all specialty residency review committees in its publication dealing with institutional requirements of accredited residencies.[7] More focused training guidelines published as program requirements are defined by the Anesthesiology Residency Review Committee (RRC), a group representing the ABA, the American Society of Anesthesiologists (ASA), and the American Medical Association.[8] These guidelines include program requirements for residency education in (1) anesthesiology (the core program) and fellowship education in its accredited subspecialties, (2) adult cardiothoracic anesthesiology, (3) critical care, (4) pain medicine, (5) pediatric anesthesiology, and (6) undersea and hyperbaric medicine.[8,9]

The teaching responsibilities addressed by the candidate certification and the residency and fellowship education program accreditation processes are clearly articulated by the ABA[4]:

Establish and maintain criteria for the designation of a Board certified anesthesiologist.

Inform the Accreditation Council for Graduate Medical Education (ACGME) concerning the training required of individuals seeking certification as such requirements relate to residency training programs in anesthesiology.

Establish and conduct those processes by which the Board may judge whether a physician who voluntarily applies should be issued a certificate indicating that the required standards for certification or recertification as a diplomate of the American Board of Anesthesiology have been met.

A Board certified anesthesiologist is a physician who provides medical management and consultation during the perioperative period, in pain management and in critical care medicine. A diplomate of the Board must possess knowledge, judgment, adaptability, clinical skills, technical facility and personal characteristics sufficient to carry out the entire scope of anesthesiology practice. An ABA diplomate must logically organize and effectively present rational diagnoses and appropriate treatment protocols to peers, patients, their families, and others involved in the medical community. A diplomate of the Board can serve as an expert in matters related to anesthesiology, deliberate with others, and provide advice and defend opinions in all aspects of the specialty of anesthesiology. A Board certified anesthesiologist is able to function as the leader of the anesthesiology care team.

Because of the nature of anesthesiology, the ABA diplomate must be able to manage emergent life-threatening situations in an independent and timely fashion. The ability to independently acquire and process information in a timely manner is central to assure individual responsibility for all aspects of anesthesiology care. Adequate physical and sensory faculties, such as eyesight, hearing, speech and coordinated function of the extremities, are essential to the independent performance of the Board certified anesthesiologist. Freedom from the influence of or dependency on chemical substances that impair cognitive, physical, sensory or motor function also is an essential characteristic of the Board certified anesthesiologist.

Establish and conduct those processes by which the Board may judge whether a physician who voluntarily applies should be issued a certificate indicating that the required standards for subspecialty certification or recertification in an ABA designated subdiscipline of anesthesiology have been met.[4]

The ABA-ACGME model addresses the purpose of education in anesthesiology and clearly outlines the anesthesiologist's responsibilities in teaching colleagues. Other organizational models similar to the ABA-ACGME example serve the same function for teaching physician anesthesiologists outside the United States.

Meeting the teaching responsibilities for nurse anesthesia is standardized in a fashion similar to that of the ABA-ACGME model. For nurses, the Council on Certification of Nurse Anesthetists and the Council on Accreditation of Nurse Anesthesia Educational Programs serve functions similar to those of the ABA-ACGME model. In 2007, 108 nurse anesthesia educational programs of 24 to 36 months' duration (80% are 27/28 months long) graduated nearly 1200 students educated in approximately 1547 clinical training sites staffed by 8248 certified registered nurse anesthetists (CRNAs) and 4689 anesthesiologists serving as faculty (Council on Accreditation of Nurse Anesthesia Educational Programs: personal communication, 2007). After the first 2 years of certification, CRNAs are required to achieve biennial recertification under the auspices of the Council on Recertification of Nurse Anesthetists.

Education of nonphysician health care professionals is coordinated by 26 agencies that accredit/approve training programs in 71 professions.[10,11] These agencies provide guidelines for education in a standardized fashion so that professionals in 71 allied health occupations can gain certification in their respective disciplines.[10,11] More than 50 professional organizations (including the ASA) serve as experts in their fields and work hand in hand with the 26 agencies to accredit/approve the educational programs for health professions.[10,11] The magnitude of this teaching responsibility becomes clear when one realizes that in 2007-2008, 2468 institutions sponsoring 6873 educational programs educated more than 231,000 students.[10,11]

Occupations related to anesthesiology for which standardized educational programs have been defined by the Accreditation Review Commission on Education for the Physician Assistant (www.arc-pa.org), American Society of Health System–Pharmacists (www.ashp.org), Commission on Accreditation for Health Informatics and Information Management Education (www.cahiim.org), Commission on Accreditation of Allied Health Education Programs (www.caahep.org), and Joint Review Committee on Education in Radiologic Technology (www.jrcert.org) (5 of the 26 accrediting agencies referred to earlier) include anesthesiologist assistant, cardiovascular technologist, electroneurodiagnostic technologist, emergency medical technician-paramedic, health information technician, perfusionist, pharmacy technician, physician assistant, radiation therapist, respiratory therapist (entry level and advanced), specialist in blood bank technology, surgical assistant, and surgical technologist.[10,11] In 2006, these occupations were taught in 1572 accredited or approved programs.[10,11] Students enrolled in these training programs during the 2006 academic year numbered 45,285.[10,11]

In contrast to the teaching responsibility for nonphysician health care professionals, in 2006, 4970 physician resident anesthesiologists (5.6% of all residents in the United States) were educated in 131 accredited American core anesthesiology residency programs and 360 physician subspecialty fellows (2.3% of all subspecialty fellows in the United States) in 213 accredited

American subspecialty anesthesiology programs (30 adult cardiothoracic anesthesiology, 49 critical care medicine, 89 pain medicine, and 45 pediatric anesthesiology programs) (Table 8-1A and B).[12,13] A yearly summary of recruitment of graduating medical students into anesthesiology residencies via the National Resident Matching Program (NRMP) process and how these individuals advance through the residency education years is published in the *ASA Newsletter*.[14,15] Adding the tasks of teaching medical and allied health care students, participating in continuing education for anesthesiologists, and teaching other practicing physicians and allied health care professionals increases the educational responsibilities of anesthesiologists in an exponential fashion.

One fundamental reason that we teach anesthesiology is that we recognize the need to provide uniform educational experiences so that students participating in these activities can reach a goal; that is, they will be acknowledged (certified) as competent in their discipline. So important is this process that it has been incorporated into the very definition that we use to describe ourselves. Now more than ever, competence and physician performance are concepts that are key in the minds of the public consuming medical care, the agencies paying for medical care, and the institutions and individuals providing medical education.[16-18] The United States has a system designed to assess medical competence by defining and ensuring the processes of education, licensing, accreditation, and certification.[16-18]

The American Board of Medical Specialties (ABMS) oversees the certification of physician specialists by 24 medical specialty member boards (including the ABA) in more than 130 specialties (residencies) and subspecialties (fellowships) (Table 8-2).

> *The primary function of ABMS is to assist its Member Boards in developing and implementing educational and professional standards to evaluate and certify physician specialists.*[19]

The ABMS states its mission as being

> *. . . the organization that establishes standards for physician specialty certification and Maintenance of Certification (MOC), including performance assessment. ABMS communicates information about these standards to support the public's quest for safe, high-quality healthcare.*[5,19]

The ABMS has eloquently articulated the goal of MOC by stating that

> *. . . ultimately, the measure of physician specialists is not merely that they have been certified, but how well they keep current in their specialty. That's why in 2006, ABMS' 24 Member Boards adopted a program of continuous professional development—ABMS Maintenance of Certification—as a formal means of measuring a physician's continued competency in his or her certified specialty and/or subspecialty. By following MOC, physicians demonstrate their commitment to lifelong learning and ongoing self-assessment to advance specialty practice. They live the standards by which medical care is evaluated and demonstrate leadership in the national movement for healthcare quality and patient safety.*[19]

In 1989, the ABA established a mechanism (continued demonstration of qualifications [CDQ]) for revalidation of an individual's primary board certificate to address the multitude of questions that had been posed about recredentialing and continued "competence" of physicians initially certified as consultants, especially questions related to public trust.[4,20,21] This program allowed anesthesiologists to demonstrate their continuing qualifications through a *voluntary* recredentialing program.[21] The first implementation of CDQ with its two components—documentation of an anesthesiologist's approved practice credentialing and administration of a secure written examination to assess an anesthesiologist's current knowledge of anesthesia practice—took place in 1993. The CDQ certificate allowed anesthesiologists a means to accomplish recredentialing for needs defined by governmental, health care finance reimbursement, hospital, or other regulatory bodies.

The ABA/ABMS has developed more formal recertification processes since implementation of the voluntary CDQ recredentialing mechanism. In 1994-1995, the ABA adopted time-limited certification; all specialty (anesthesiology) certificates issued by the ABA on or after January 1, 2000, were designated valid for only 10 years from the time of completion of the examination for the initial certification and all subsequent recertifications.[4,22] In 1996, the ABA converted the CDQ mechanism to the recertification process containing the same two components described earlier. Anesthesiologists wishing to remain board certified at the end of the time limit on their certification are required to formally recertify and obtain a new board certificate rather than revalidate the primary certificate.[4,22] Current discussion is focusing on shortening the recertification cycle from 10 years to 5 to 7 years from the time of completion of the examination for the initial certification or subsequent recertifications.

The ABA has also had a certification process for its subspecialties (see Table 8-2).[5] A certification process has existed for critical care medicine since 1985. In 1991, the ABA began certification of pain management subspecialists, and in 2006, the ABA began certification of subspecialists in hospice and palliative medicine. In 1998, time-limited certification for subspecialties in anesthesiology was approved. As of January 2000, all newly issued ABA subspecialty certificates in critical care medicine and pain management were designated valid for only 10 years from the time of completion of the examination for the initial certification. Recertification in critical care medicine, pain management, and hospice and palliative medicine is operative in a fashion similar to that described earlier for recertification in anesthesiology. Similar models for continuing medical education and documentation of physician competence are being developed in other countries as well.[23,24]

Maintenance of Certification in Anesthesiology (MOCA) is the

> *. . . program [that] enables ABA diplomates holding non–time limited certificates (issued before 2000) to demonstrate continuing qualifications and those with time-limited certificates to maintain their certification. Each MOCA cycle is a 10-year period of ongoing Lifelong Learning and Self-Assessment; continual assessment of Professional Standing; periodic assessments of Practice Performance; and assessment of Cognitive Expertise. MOCA is an opportunity for physicians to document maintenance of their skills in six general competencies, namely, Medical Knowledge; Patient Care; Practice-Based Learning and Improvement; Professionalism; Interpersonal and Communication Skills;*

Table 8-1 Number of Anesthesiology Specialty and Subspecialty Graduate Medical Education Programs, Residents, Fellows, and U.S. Medical Students and Full-Time Faculty

A. Core Anesthesiology Residencies and Residents in Graduate Medical Education (GME) Programs in the United States Accredited by the Accreditation Council for Graduate Medical Education (ACGME)

Academic Year	Number of Accredited Core Anesthesiology Residency Programs	Total Number of Core Anesthesiology Residents on Duty	Number (%) of Core Anesthesiology Residents on Duty Who Are U.S. Medical Graduates	Number of Residencies/ Residents on Duty in All ACGME-Accredited and Combined Specialty GME Programs
1990	157	4362	3871 (88.7)	4144/69,798
1995	149	5490	4395 (81.1)	4245/85,732
2000	134	3837	1627 (42.4)	4268/85,460
2005	132	4785	3450 (72.1)	4151/86,975
2006	131	4970	3731 (75.1)	4134/89,269

B. Subspecialty Anesthesiology Fellowships and Fellows in ACGME-Accredited GME Programs in the United States

Academic Year	Number of Accredited Subspecialty Anesthesiology Fellowship Programs	Total Number of Subspecialty Anesthesiology Fellows on Duty	Number (%) of Subspecialty Anesthesiology Fellows on Duty Who Are U.S. Medical Graduates	Number of Subspecialty Programs/Fellows on Duty in All ACGME-Accredited GME Programs
1990	Critical care medicine, 27	7	4 (57.1)	2447/8,006
1995	Critical care medicine, 46 Pain medicine, 55	70 112	52 (74.3) 83 (74.1)	3264/12,100
2000	Critical care medicine, 53 Pain medicine, 98 Pediatric anesthesiology, 37	59 215 63	29 (49.2) 100 (46.5) 33 (52.4)	3678/12,529
2005	Critical care medicine, 47 Pain medicine, 95 Pediatric anesthesiology, 43	43 190 91	20 (46.5) 88 (46.3) 43 (47.3)	4095/14,316
2006	Adult cardiothoracic, 30 Critical care medicine, 49 Pain medicine, 89 Pediatric anesthesiology, 45	0 44 206 110	0 (0) 22 (50) 127 (61.7) 78 (70.9)	4368/15,610
2007-2008 Projected	Adult cardiothoracic Critical care medicine Pain medicine Pediatric anesthesiology	0 129 264 166		

C. Number of Medical Students and Full-Time Faculty (Total and Anesthesiology Specific) in U.S. Medical Schools

Academic Year	Number of Medical Students in U.S. Medical Schools	Total Number of Full-Time Faculty in U.S. Medical Schools	Number (% of Total Faculty) of Full-Time Anesthesiology Faculty in U.S. Medical Schools
1990	65,081	72,320	3393 (4.7)
1995	67,030	90,016	4535 (5.0)
2000	66,500	102,446	4979 (4.9)
2005	68,280	119,025	5471 (5.7)
2006	69,028	124,725	5836 (4.7)

Data abstracted from the Journal of the American Medical Association, yearly Medical Education editions: 264, 1990; 274, 1995; 284, 2000; 294, 2005; and 298, 2007; and Warner MA: Residency Review Committee for Anesthesiology. ASA Newsl 71:26-27, 2007.

Table 8-2 American Board of Medical Specialties (ABMS) Certificates Issued

	Before 1997	1997-2006	2000-2006
Anesthesiology*	28,515	12,012	7,592
Critical care medicine†		480	267
Pain medicine‡		1,941	1,233
Hospice and palliative medicine§	—	—	—
All specialties	602,578	242,684	167,656
All subspecialties		76,782	51,057

*First ABMS certificate issued in 1938; first time-limited (10 year) certificate issued in 2000.
†First ABMS certificate issued in 1986; first time-limited (10 year) certificate issued in 2000.
‡First ABMS certificate issued in 1993; first time-limited (10 year) certificate issued in 1993.
§First ABMS certificate to be issued in 2008; first time-limited (10 year) certificate to be issued in 2008.
Data abstracted from 2007 Reference Handbook and Certificate Statistics. Evanston, IL, American Board of Medical Specialties, 2007.

and System-Based Practice. There are four requirements for MOCA:

Professional Standing
Diplomates must hold an unrestricted license to practice medicine . . . no medical license . . . can be revoked, suspended or surrendered. . . .

Lifelong Learning and Self-Assessment (LL-SA) Activities
LL-SA is personalized and self-directed professional development, . . . an assessment of . . . current knowledge and practice of anesthesiology . . . [and] continuing medical education (CME) activities and other learning opportunities that meet . . . professional development needs. . . .

Cognitive Examination
The Cognitive Examination is designed to assess core knowledge of the discipline of anesthesiology. It is very clinically oriented, with an emphasis on customary practice. . . .

Practice Performance Assessment and Improvement (PPAI)
The PPAI process consists of the ABA obtaining attestations and evidence of . . . [an anesthesiologist's] clinical activity and ongoing program of practice assessment and performance improvement. The ABA minimum clinical activity requirement is the practice of anesthesiology or a recognized anesthesiology subspecialty, on average, at least one day per week during one of the previous three years. . . . Evidence of PPAI acceptable to the ABA is a prerequisite for the MOCA Cognitive Examination and is a requirement for maintenance of certification in anesthesiology.[25]

The six general competencies for which anesthesiologists need to document maintenance of their skills for the MOCA program are rooted in the graduate medical education process of residency and fellowship education for anesthesiologists. Being concerned that the full range of learning had not been adequately provided for or ensured by an evaluation process, the ACGME developed its Outcome Project in 1999.[26] The ACGME defined six educational areas for which graduate trainees must demonstrate competency (see Appendix 1).[27] The ACGME Outcome Project places the educational responsibility squarely on the shoulders of the residency programs and their faculty to develop innovative curricula and evaluation methods to ensure that trainees graduate with these competencies.[28]

Anesthesiology education for physicians and other health care professionals is, as described earlier, a specific application of assessing medical competence by process evaluation. An equal, and perhaps even more important, question is how to evaluate the outcome of the education rather than the process by which it is achieved.[16,17] The question of why we teach medicine, specifically anesthesiology, is best answered by saying that we want physicians and other health care professionals to perform the activities of anesthesia patient care at a specific level of achievement. Although we are very good at evaluating knowledge, assessment of patient care outcomes is not easily measured. Outcome assessment, that is, evaluation of the practice aspects of anesthesiology, represents the greatest challenge for the future.[16,17]

One such assessment demonstrates the value of the ABA-ACGME model of educating and certifying physician anesthesiologists. Silber and colleagues,[29] in their study of almost 6000 patients undergoing prostate or gallbladder surgery in multiple hospitals, demonstrated that patient recovery or "rescue" from an adverse event correlated with the proportion of board-certified anesthesiologists in the hospital.

Outcome analysis is also becoming a part of the training process for anesthesiologists.[30] An example of this type of approach has been described in an educational setting that makes use of the quality improvement concepts developed in industry.[30] Such an approach is also appearing in post-training practice settings as a form of continuing medical education, as well as a quality assessment tool.[31] We are seeing more of this type of approach as the pressures of health care economics help restructure our clinical practice.

Who Teaches?—The Teachers

Anesthesiology is taught by physician anesthesiologists, the experts in the field, as well as by other expert individuals in related disciplines, examples of whom include pharmacologists, physiologists, biomedical engineers, pediatricians, and neurosurgeons. Full-time anesthesiology faculty positions in U.S. medical schools in 2006 numbered 5836 (see Table 8-1C).[31] Anesthesiologists represent 5.6% of the clinical teachers and 4.7% of all American medical school teaching faculty (see Table 8-1C).[32] The 5836 anesthesia faculty members in medical schools bore the major responsibility for teaching some or all of the 69,028 enrolled undergraduate medical students, the 4970 graduate trainees in accredited anesthesiology residency training programs, the 360 graduate trainees in accredited anesthesiology subspecialty fellowship programs, and many of the other 104,879 physician house staff trainees (see Table 8-1A to C).[12,32]

Clinical care, teaching, research, and administration are major roles assumed by faculty. For anesthesia faculty, clinical care is a prime activity for obvious reasons. The other functions are attended to as time and resources permit. For this reason, teaching is often relegated to a lower level of priority, not always adequately acknowledged in career advancement decisions. Junior faculty members are frequently expected to take on a large part of the teaching load. This expectation, however, could be viewed as a case of reversal of the proper roles for the junior and senior faculty.[33] Junior faculty members have a heavy teaching load during the phase of their career when they lack experience.[33] Senior faculty members, on the other hand, are responsible for departmental, institutional, and specialty roles that limit their availability for teaching, although these same individuals have vast experience and could teach much.[33] The extreme example of this dichotomy is the expectation that house staff teach the more junior of their ranks and medical students. Perhaps the teaching role for house staff would best be accomplished by making the resident a teaching apprentice who not only receives general medical and anesthesiology specialty education but is also educated about education.

Little specific information exists about the teaching credentials or qualities of anesthesiologists, unlike the situation for other physician groups.[34,35] These descriptions can be used to infer what does or could characterize anesthesiology teachers. Physician teachers in general are not trained as educators.[34] They have not had formal training in educational psychology or methodology.[34] Physicians who teach do not use the educational resources available.[34] When faced with a new or difficult educational assignment, physician teachers rarely read medical education journals, nor do they consult educational experts, as they might consult a cardiologist, for example, when treating a patient with a difficult rhythm disturbance.[34] Physician teachers, for the most part, mimic their own teachers, who also had little or no formal training as educators.[34] It seems curious, for example, that at the same time we would not trust a general surgery resident to perform a complicated neurosurgical dissection and achieve a good outcome for the patient without extensive education, we do entrust an anesthesiology trainee to faculty who have limited educational expertise in the hope of achieving a good learning outcome.

What characterizes a good teacher? Effective clinical teachers who are able to succeed at the bedside teaching encounter display specific actions noted by their students and themselves.[35] Table 8-3 presents a schema that was developed by observing internists teaching internal medicine residents and medical students. The similarity of the attending anesthesiologist teaching at the bedside in the intensive care unit or in the operating room is striking.

A teaching responsibility that anesthesiology faculty might consider is how to blend their "expert" status as anesthesiologists with their "novice" status as teachers. As the experts, teachers of anesthesiology can define educational objectives based on the competencies that they believe newly trained anesthesiologists need. Having set the objectives, the teacher can direct the educational process by selecting the appropriate learning activities and then designing tests that assess the learning. As described, the "authoritarian" teacher, the expert, determines the educational ends that must be met, defines the means to these ends, and requires conformity to these ends by the students.

Table 8-3 Traits of Effective Clinical Teachers

Overall instructional effectiveness depends on	1. Allocating time for teaching 2. Creating a teaching/learning environment of trust and concern 3. Demonstrating clinical credibility
A complete educational experience requires	4. An initial orientation 5. A final evaluation
Teaching rounds are facilitated when	6. Learners are able to present a case 7. Teachers manage the case presentation 8. Didactic sessions are used to enhance clinical case material 9. Teaching takes place at the bedside to allow students to learn physician-patient relationships 10. Teachers and students discuss psychosocial issues
Maintained teaching effectiveness occurs when	11. Attention is paid to transferring the teaching responsibility

Adapted from Mattern WD, Weinholtz D, Friedman CP: The attending physician as teacher. N Engl J Med 308:1129, 1983.

Although anesthesiology faculty provide education with this type of curriculum design, few if any know that they are using Tyler's model, nor do they realize that there might be equally good or better alternatives.[36] Dewey's progressive education offers one such alternative.[37] Dewey's philosophy of education elevates students to a level where they can join in a partnership with the teacher. For students of anesthesiology, the adult learners described previously, this type of student-teacher relationship may make very good sense.

An example of these two philosophies put into action clarifies their differences. Let us consider teaching/learning how to manage a patient who is being mechanically ventilated in the operating room. A Tylerian teacher might lecture to residents on how to use the ventilator. It is hoped that the residents will remember what they heard and be able to put what they have learned into action. In contrast, a teacher using Dewey's approach might create a patient simulation exercise in which residents can "experiment" with differing ventilator setups to infer what might occur clinically. A much more meaningful learning environment might be provided by the simulation—coupled with the anesthesiologist faculty member's reactions to and guidance about how the residents "tinkered" with the ventilator—than might be provided by the lecture format. In addition, a teacher using Dewey's philosophy might be more likely to encourage students with previous experience, such as residents who have used different types of ventilators during their internship, to share their know-how with other, less experienced peers.

This chapter is discussing the component parts of the question "How shall who teach what to whom for what purpose now and in the future?" It should be obvious that individually studying the component parts of the question is an artificial separation for teaching purposes. To fully understand the question, its parts must be linked. The consideration "Who teaches anesthesiology?" is an example of how the blending of the individual parts of the total picture of anesthesia education must occur. It is virtually

impossible to talk about the teacher without bringing the student and the educational needs into the discussion. This key concept, that is, the importance of knowing not only the component parts of education but also how they interrelate, is essential for understanding and implementing anesthesiology education.

The Curriculum—What to Teach?

The table of contents from any standard anesthesiology textbook provides a broad outline of what to teach in anesthesiology. Similar to a medical school course outline, anesthesiology is a mix of the fundamental basic sciences applied to clinical practice as they relate to specific pathophysiologic disease entities. Patients with these problems are encountered in preoperative, intraoperative, and postoperative settings; therefore, the content is taught as it specifically applies to the time progression of their disease process in these different patient environments. This framework of basic and clinical science is used for teaching anesthesiology to all health professionals, with particular emphasis placed on the areas most pertinent to the particular group being taught (e.g., detailed teaching about the mechanics and clinical application of ventilators is provided to student respiratory therapists).

An accepted uniform content outline exists and has been agreed on for teaching physician anesthesiologists.[38] The major outline headings are listed in Appendix 2. Few teachers would be at a loss to define the content of anesthesiology teaching. Anesthesiology education, however, is not limited to content teaching alone.

The three major areas for teaching/learning all subjects are cognitive, psychomotor, and affective. For anesthesiology, it appears that the cognitive teaching/learning area is well defined. It is the responsibility of the anesthesiology teacher, however, to go further than just listing the content topics. Teaching in the content area requires attention to increasingly complex cognitive functions. Described by Bloom,[39] teaching/learning in the cognitive domain for any topic addresses the following:

1. Knowledge—recall
2. Comprehension—understanding
3. Application—use of abstractions
4. Analysis—break down; seeing the relationship of parts
5. Synthesis—put together; creating a new entity
6. Evaluation—judgment of value

Knowing the facts about pulmonary function is obviously much more basic than being able to apply them to the management of a multiple-trauma patient maintained on a ventilator. Teachers of anesthesiology serve students well by considering the more complex aspects of cognitive learning.

A general taxonomy of psychomotor skill teaching/learning for universal application to all educational settings does not exist because of the great variability among disciplines in this type of domain. A broadly accepted, standardized outline of psychomotor skill learning for anesthesiology also does not exist. There are many psychomotor skills that anesthesiologists and other related health care professionals need to learn. Perhaps a major challenge for teachers of anesthesiology is to codify the fundamental and supplemental psychomotor skills that must be taught and learned. This process is beginning to occur with the introduction of practice parameters or practice guidelines developed by medicine in general and anesthesiology in particular.[40-46]

Affective teaching/learning deals with feelings or emotions. The taxonomy of affective learning addresses the following[47]:

1. Receiving
2. Responding
3. Valuing
4. Organizing
5. Value complexing

Although we actively and consciously teach in the cognitive and psychomotor areas, we are much less aware of our affective teaching. Even though we may not be aware of it, we are nonetheless constantly teaching in the affective arena by the role modeling that we perform. Earlier in this chapter, an example of how affective teaching/learning takes place was described. In the real-life setting, the aggressive, passive-aggressive, or passive posture of the anesthesiology teacher interacting with the surgeon provides a lasting lesson in the affective domain for the resident anesthesiology learner.

Thinking about affective learning results in goals for such learning and permits the development of teaching plans to achieve these goals. Only if we decide how we believe we as anesthesiologists and health care professionals in related fields need to behave in relation to others will we be able to teach professionalism and these psychosocial skills to our students.[48]

Another example of the importance of affective learning concerns our approach to the teaching task. When our students sense our own enthusiasm about and commitment to a particular topic, their attitudes about it follow suit. In similar fashion, if we as teachers are negative about some aspect of learning, we can expect our students to mimic these feelings. The charge that teachers of anesthesiology must accept is that they must be conscious of the emotions that they display and prospectively decide on the values that they wish to teach because affective teaching and learning occur all the time.

Defining the areas of learning (i.e., what to teach) makes it possible for the teacher to devise methods to evaluate the success of the teaching endeavor. For anesthesiology education of physicians, the ABA examination and certification protocol evaluates the three areas of learning. The written examination tests cognitive learning, although perhaps at its simpler levels. Psychomotor and affective learning is evaluated in an ongoing manner by the anesthesiology faculty of residency training programs and is attested to by the faculty granting a "certificate of clinical competence" to successful learners.

> *The Board [ABA] requires every residency training program to file . . . an Evaluation of Clinical Competence in January and July on behalf of each resident who has spent any portion of the prior six months in Clinical Anesthesia training in or under the sponsorship of the residency program and its affiliates. . . . Entry into the examination system is contingent upon the applicant having a Certificate of Clinical Competence on file with the Board attesting to satisfactory clinical competence during the final period of Clinical Anesthesia training in or under the sponsorship of each program. . . . The Board, therefore, will deny entry into the examination system until this requirement is fulfilled.*[4]

The oral examination evaluates cognitive learning, one hopes at its more complex levels. In addition, the oral examination may assess affective learning, although such assessment is accomplished in an unsystematic approach. The goal of the ABA oral examination process is to access the candidate's ability to (1) apply knowledge in the development of a treatment plan, (2) exhibit sound medical judgment in making medical/anesthetic decisions, (3) demonstrate adaptability in handling complications and changing medical situations, and (4) communicate logically and in an organized manner the anesthetic issues and plans for anesthesia patient care.[4]

The Methods—How to Teach

When faculty members talk about education, one of their first considerations is how to teach. Although obviously an important aspect of instruction, it is of relatively minor importance when viewed in the entire context of education. Before one can decide whether a lecture is a better method to teach a specific topic than a group discussion or whether slides, a chalkboard, or computer-assisted instructional software should be used to facilitate making a concept clear, it is essential to understand the student, the student's needs, the purpose of the education, and the content to be taught.

Too often, the instructional methodology, which is easy to consider, receives the major emphasis, whereas the difficult questions about education, such as what is its rationale, are glanced over or never even considered. After the fundamental questions about educational philosophy are answered, selection of a particular instructional technique becomes critical. The specific teaching method selected is intended to be the one best suited to the specific educational goal desired.

The use of simulation games is a good example of how the method satisfies the educational goal. In cardiopulmonary resuscitation training, for example, a simulated cardiac arrest is an exercise during which students play the resuscitator roles and use all the real-life equipment in a real-time setting. The involved students, as well as other students and the teacher or teachers who observe the simulation, review and critique the resuscitation to point out correct knowledge, skills, and attitudes displayed and which of these actions could have been performed better. The goal of the exercise is to teach students to coordinate the entire cardiopulmonary resuscitation effort by bringing together the facts and skills in an atmosphere in which reasonable attitudes are exhibited despite the tense nature of the emergency situation, all without jeopardizing any patient. A lecture, a slide show, or even a small group discussion could not achieve this goal.

Simulation is becoming an integral teaching methodology in anesthesia education.[49,50] Borrowed from flight simulation, which is an essential part of the training and certification of commercial and military pilots, anesthesia patient simulators have been developed and used to educate individuals in the discipline of anesthesiology in two major ways: (1) for specific recognition and management of critical events and (2) in the general comprehensive education about all aspects of anesthesia patient care, such as crew resource management. By coupling a mannequin with a computer and anesthesia patient care equipment, a simulation setting is created that so closely mimics real life that it is a virtual reality. Physiology, pharmacology, pathophysiology, and crisis management are a few of the curricular areas that can be most effectively taught by the anesthesia simulator approach, that is, modeling a real patient scenario for students to manage with zero risk to the simulated patient and no real risk to the student (except for the trainee's self-imposed stress to achieve). Use of this technology is limited only by the ability of the educators and students to create and "live" the scenarios.[49-51] Additional advantages of human patient simulators include their use in teaching all types of students (e.g., medical students, student nurse anesthetists, allied health professionals in a wide variety of disciplines, practitioners in continuing education programs) and the ability to conduct educational research and collect "simulated" patient management outcome data.[49-51]

Scientific evaluation of simulation is being conducted, but there are considerable study design difficulties.[52,53] In addition to the difficulty of designing studies to evaluate simulation, the evidenced-based data that are being collected deal with the performance of providers of simulated care and have yet to effectively answer the question about patient benefit related to simulation-educated physicians.[52,53] Undoubtedly, the field of human simulator education and research will continue to grow exponentially in the next few years.

An in-depth study of individual teaching techniques is appropriate after the links between the questions about educational philosophy and rationale and the methods of teaching have been established. At the teacher's disposal for effective use in the proper situation are lectures; small group discussions; the use of questions; clinical problem solving; psychomotor skill learning at the bedside, in the operating room, or in the classroom; and the use of adjunctive educational media such as slides, chalkboard, videotape, audiotape, overhead projector, computer, and teaching models. Each of these techniques can be used more effectively and efficiently when the method is studied and understood.

Effective use of questioning, for example, occurs when the teacher understands the difference between closed and open questions.[54] Closed questions are used when the teacher is interested in having the student remember facts. Because the range of responses to closed questions is limited, students answer with facts and have limited opportunity to delve into more complex cognitive learning (i.e., problem solving). A teacher uses open questions as a teaching device when desirous of directing the teaching/learning activity toward the application of knowledge to new settings or analysis of information for conceptual learning rather than mere regurgitation of facts. There is a considerable difference in the learning that might occur when a question such as "What might explain postanesthetic stupor in a patient operated on for head trauma?" is asked of a student versus asking a question such as "What are the signs and symptoms of increased intracranial pressure?"

Developing a psychomotor skill lesson is another example of how understanding instructional methodology can lead to effective teaching and learning. The old adage about teaching psychomotor skills in medicine is "see one, do one, teach one." The absurd nature of this approach has been highlighted in the following way: "This is akin to a piano instructor playing 'The Minute Waltz' for a beginner and then saying, 'Now, try it yourself.'"[54] Rather than using the repetitive trial-and-error approach to teaching/learning psychomotor skills, systematic methodology can be used.[54]

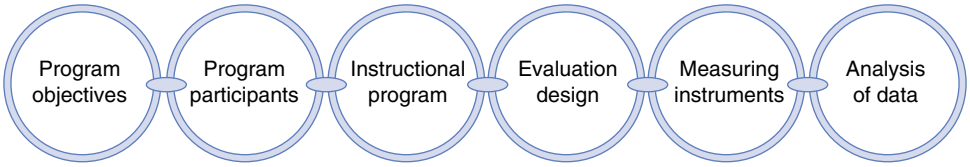

Figure 8-2 Diagrammatic representation of a model to conduct educational outcome analysis. The six components are joined in "chain-link" fashion to signify that the outcome analysis is as strong as its weakest link. Essential to the model, therefore, is sound development and implementation of the educational plan and process. This includes definition of the educational objectives, understanding of both the teaching faculty and student participants, and execution of the instructional activity. Having established the educational experience, its outcome can be assessed by applying an appropriate evaluation design[56] and using the measurement techniques to collect the data for analysis. The final step in the analysis is to apply the results to the program objectives and instructional activities to enhance future desired learner outcomes. *(From Hutchins EB: Unpublished lecture notes: Evaluation Methods in Professional Education. Course ED668, Graduate School of Education. University of Pennsylvania, 1981.)*

1. Analyze and separate the skill into its component parts and determine which aspects of the skill are most difficult to perform.
2. Provide students with a model of the skill, demonstrated effectively in its entirety, that they are expected to perform.
3. Make provisions for students to practice until the expected behavior is mastered.
4. Provide adequate supervision and an evaluation of the final performance.

Anesthesiology instructors need only think of the protocol that they are using to teach, for example, pulmonary artery catheterization by the internal jugular venous route, to assess whether they are expecting their students to perform (learn) with the type of plan just outlined or rather to "learn as they go" on each successive patient as they probe in the neck. The learn-as-you-go method can be quite stressful for both patient and trainee.[55]

A final example of an answer to the question of how to teach comes from review of the effective use of audiovisual aids. Although it is true that "a picture is worth a thousand words," the anesthesiology teacher must be sure that this image is the "text" that the teacher wishes the students to read and absorb. Slides, for example, focus the viewer's attention on an idea or ideas that the lecturer wishes to amplify in some manner. By definition, the entire lecture cannot be put on slides. Only a few important portions of the presentation are conveyed by slides, and these points are emphasized in some specific way by the visual image or images, which add to the verbal presentation. Slides are not the TelePrompTer, although they are often used this way.

Even more basic is the need to understand the proper production formatting of slides so that the message on a 35-mm transparency or a PowerPoint computer image can be seen clearly when projected onto a 12-foot-high screen in a large 800-seat lecture hall. If format is not considered, the slide is not visible and undoubtedly detracts from, rather than enhances, the lecture. Finally, even the best-produced slide is useless if nobody, including the lecturer, knows how to troubleshoot a nonfunctional computer or projector. Surely, the thousands of hours that have been devoted to slide lectures about anesthesiology could have benefitted from teachers taking more responsibility in the preparation of effective visual aids.

Summary

What is the anesthesiologist's responsibility in teaching colleagues and other health care professionals? The answer lies in the answers to the many aspects of the following question:

How shall who teach what to whom for what purpose now and in the future?!

For many, however, this type of review of education is "soft" material that lacks the "hard" research data to prove its validity. Perhaps there is some truth to this. Perhaps by its very nature (i.e., psychosocial) the science of education has its limits. On the other hand, however, enough experimental studies of education may not have been performed. A model to conduct such studies might view the preceding question in terms of educational outcome analysis (Fig. 8-2). Although the educational setting is not a pure, controlled laboratory environment, accepted quasi-experimental design techniques exist for this naturalistic research setting.[56]

What then is the anesthesiologist's responsibility in teaching? It is twofold: to understand all aspects of education and then to scientifically study educational outcome so that future students of anesthesiology will be more effectively taught and better prepared as experts in the field.

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Appendix 1

Common Program Requirements: General Competencies (Abridged) Approved by the Accreditation Council for the Graduate Medical Education Board on February 13, 2007

The program must integrate the following Accreditation Council for Graduate Medical Education (ACGME) competencies into the curriculum:

- **Patient Care**
  Residents must be able to provide patient care that is compassionate, appropriate, and effective for the treatment of health problems and the promotion of health.
- **Medical Knowledge**
  Residents must demonstrate knowledge of established and evolving biomedical, clinical, epidemiologic, and social-behavioral sciences, as well as application of this knowledge to patient care.
- **Practice-Based Learning and Improvement**
  Residents must demonstrate the ability to investigate and evaluate their care of patients, to appraise and assimilate scientific evidence, and to continuously improve patient care based on constant self-evaluation and lifelong learning. Residents are expected to develop skills and habits to be able to meet the following goals:
  Identify strengths, deficiencies, and limits in one's knowledge and expertise
  Set learning and improvement goals
  Identify and perform appropriate learning activities
  Systematically analyze practice by using quality improvement methods, and implement changes with the goal of practice improvement
  Incorporate formative evaluation feedback into daily practice
  Locate, appraise, and assimilate evidence from scientific studies related to their patients' health problems
  Use information technology to optimize learning
  Participate in the education of patients, families, students, residents and other health professionals
- **Interpersonal and Communication Skills**
  Residents must demonstrate interpersonal and communication skills that result in effective exchange of information and collaboration with patients, their families, and health professionals. Residents are expected to
  Communicate effectively with patients, families, and the public, as appropriate, across a broad range of socioeconomic and cultural backgrounds
  Communicate effectively with physicians, other health professionals, and health-related agencies
  Work effectively as a member or leader of a health care team or other professional group
  Act in a consultative role to other physicians and health professionals
  Maintain comprehensive, timely, and legible medical records, if applicable
- **Professionalism**
  Residents must demonstrate a commitment to carrying out professional responsibilities and adherence to ethical principles. Residents are expected to demonstrate
  Compassion, integrity, and respect for others
  Responsiveness to patient needs that supersedes self-interest
  Respect for patient privacy and autonomy
  Accountability to patients, society, and the profession
  Sensitivity and responsiveness to a diverse patient population, including but not limited to diversity in gender, age, culture, race, religion, disabilities, and sexual orientation
- **Systems-Based Practice**
  Residents must demonstrate awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on other resources in the system to provide optimal health care. Residents are expected to
  Work effectively in various health care delivery settings and systems relevant to their clinical specialty
  Coordinate patient care within the health care system relevant to their clinical specialty
  Incorporate considerations of cost awareness and risk-benefit analysis in patient- or population-based care as appropriate
  Advocate for quality patient care and optimal patient care systems
  Work in interprofessional teams to enhance patient safety and improve the quality of patient care
  Participate in identifying system errors and implementing potential systems solutions

Available from http://www.acgme.org/outcome/comp/GeneralCompetenciesStandards21307.pdf.

Appendix 2

Content Outline—Joint Council on In-Training Examinations

I. Basic Sciences
  A. Anatomy
    1. Topographic anatomy as landmarks
    2. Radiologic anatomy
  B. Physics, monitoring, and anesthesia delivery devices
    1. Mechanics
    2. Flow velocity
    3. Properties of liquids, gases, and vapors
    4. Gas laws
    5. Vaporizers
    6. Uptake and distribution of inhalation agents
    7. Physics of the anesthesia machine/breathing system
    8. Monitoring methods
    9. Instrumentation
    10. Ventilators
    11. Alarms and safety features
    12. Defibrillators
    13. Pacemakers
    14. Electrical, fire, and explosion hazards; basic electronics
    15. Drug delivery devices
  C. Mathematics
    1. Simple mathematics
    2. Statistics
    3. Computer
  D. Pharmacology
    1. General concepts
    2. Anesthetics—gases and vapors
    3. Anesthetics—intravenous
    4. Anesthetics—local
    5. Muscle relaxants

II. Clinical Sciences
  A. Anesthesia procedures, methods, and techniques
    1. Evaluation of the patient and preoperative preparation
    2. Regional anesthesia
    3. General anesthesia
    4. Monitored anesthesia care and sedation
    5. Intravenous fluid therapy during anesthesia
    6. Complications (etiology, prevention, treatment)
    7. Special techniques
    8. Postoperative period

III. Organ-Based Basic and Clinical Sciences (Outline for Sections May Include Physiology, Anatomy, Biochemistry, Pharmacology, Clinical Science)
  A. Respiratory system
  B. Cardiovascular system
  C. Central and peripheral nervous systems
  D. Gastrointestinal/hepatic
  E. Renal/urinary
  F. Endocrine/metabolic
  G. Hematologic
  H. Neuromuscular

IV. Clinical Subspecialties
  A. Painful disease states
  B. Pediatric anesthesia
  C. Obstetric anesthesia
  D. Otolaryngologic anesthesia
  E. Anesthesia for plastic surgery
  F. Anesthesia for laparoscopic surgery
  G. Ophthalmologic anesthesia
  H. Orthopedic anesthesia
  I. Trauma, burn management, mass casualty, biological warfare
  J. Anesthesia for ambulatory surgery
  K. Geriatric anesthesia/aging
  L. Critical care

V. Special Problems or Issues in Anesthesiology
  A. Electroconvulsive therapy
  B. Organ donors
  C. Radiologic procedures
  D. Physician impairment or disability
  E. Ethics, practice management and medicolegal issues

Adapted from American Board of Anesthesiology, American Society of Anesthesiologists Joint Council on In-Training Examinations: American Board of Anesthesiology Examination Part I. Revised—September 2006.[38]

Gail A. Van Norman and Stanley H. Rosenbaum

9 Ethical Aspects of Anesthesia Care

Key Points

1. Anesthesiologists have ethical obligations to promote patients' abilities to make medical decisions, as well as obligations to respect those decisions.
2. Competent patients have the right to refuse medical treatments or tests, even if it appears to be a "bad" decision. Coercing or restraining competent patients is unethical.
3. Children should be involved in medical decision-making to the degree that their abilities allow, and their wishes should usually be respected.
4. Advance directives and decisions by surrogate decision-makers are legally binding.
5. Do-not-attempt-resuscitation orders require reconsideration before anesthesia and surgery and cannot be automatically suspended.
6. Withdrawal or withholding of life-sustaining treatments at the end of life requires specialized training or experience.
7. Anesthesiologists play a pivotal role in caring for both brain-dead and non–heart-beating organ donors and must be familiar with the medical, legal, and ethical issues involved.
8. Human and animal research carries special obligations to protect the subjects from inhumane treatment. Whenever possible, alternatives to human and animal research should be sought.
9. "State-sponsored" activities such as executions (1) are not the practice of medicine, (2) undermine the medical profession, and (3) place the physician on dubious moral grounds.
10. Although physicians have a right to withdraw from some situations in which patient care presents them with personal moral conflicts, this right is limited, and professionally accepted standards and obligations usually prevail (e.g., well-established standards, such as informed consent).

History of Ethics in Medicine and Ethical Theory

Medicine is a respected profession with codes of behavior and definite rules of conduct. In modern times, medical practitioners have tremendous powers, recognized social import, and powerful financial interactions that touch nearly everyone's lives. It is in the context of long-held and highly developed rules and practices that we examine the ethical bases of the practice of medicine and its implications for anesthesiologists.

Ethical Theory

Virtue Ethics, Utilitarianism, and Duty-Driven Ethics

The classic style of medical practice, called "paternalism," is derived from "virtue-based ethics." In this view, the physician is a genuinely virtuous person with inherent qualities of competence, sincerity, confidentiality, and altruism who naturally knows and does what is correct for the patient. The patient, who is not knowledgeable in the art of medicine, should trust the physician to decide what is best. Our society and legal system have changed substantially since paternalism flourished, but some patients and physicians still see this style as a desirable component of medicine.

In utilitarian ethics, actions are judged right or wrong on the balance of their good and bad consequences. A "right" action produces the most good, based on a perspective that gives equal weight to the interests of all affected parties. Although utilitarian theory is compelling (who would not want to do the most good and minimize evil?), it falls short in defining which benefits are most important. Is it the "good" that all reasonable people want or the "good" defined by the individual patient? What if the only way to maximize "good" is to commit an entirely immoral act? Suppose, for example, the only way to win a war is to systematically torture children?

Utilitarian theory may be best when applied to analyzing broad-based policies, in decisions regarding rationing of resources, and when attempting to resolve conflicting ethical obligations.

The premise of Kantian-based ethics (also called "deontological theory") is that there are features of actions other than their consequences that make them right or wrong. Intention is more important than outcome. Furthermore, no person should use another exclusively as a means to an end because each person *is* the end for which we should act. Each person is uniquely valuable and should not be used to further the purposes of other persons without their autonomous consent. Kantian philosophy would, for example, forbid killing one innocent person to save another innocent person.

Deontological and utilitarian theories are both applied to varying degrees in modern medical ethics. Individualism and autonomy are highly valued in Western society, and people tend to turn to Kantian philosophy when ethical questions arise that balance the authority of the physician against the goals and values of individual patients. When broad-based social issues are at stake, such as allocation of scarce medical resources, utilitarian arguments are often used. Some of the toughest ethical questions in medical practice occur when the rights and desires of individual patients are in conflict with social policies. Clashes between deontological and utilitarian principles are common in the intensive care unit (ICU), managed care settings, and the care of poor and elderly patients whose medical management is funded by the government. In each of these settings, the will of the individual patient may be in conflict with the broader principles of minimizing expense, fairly allocating scarce resources, and determining where and how society's health care dollars are best spent.[1]

The American political tradition provides a clear underpinning to individual freedom, hence translation of the Jeffersonian "life, liberty, and the pursuit of happiness" into the contemporary interest in physician beneficence and patient autonomy. It was with the background of this political tradition that contemporary bioethics shifted away from paternalism. At the beginning of the 20th century, the concept of autonomy of patients began to emerge.

Clinical Ethics

Informed Consent

Legal and moral imperatives for informed consent are based on the ethical principle of respect for patient autonomy. "Autonomy" refers to the ability to choose without controlling interference by others and without personal limitations that prevent meaningful choices, such as inadequate information or understanding.[1] Individuals have the right to determine what happens to them to the degree that they are capable of doing so. In the United States, this right is rooted in constitutional guarantees of privacy and noninterference. In 1914, the case of *Schloendorff v Society of New York Hospital* established that it was the right of "every human being of adult years and sound mind to determine what shall happen to his own body."[2] In 1957, the term "informed consent" was first used in the case of *Salgo v Trustees of Leland Stanford Hospital*, which established that it is not sufficient for physicians to simply secure consent; physicians have a duty to inform patients about the risks and alternatives to treatment, in addition to the procedures themselves and their consequences.[3]

Respect for patient autonomy requires physicians to respect decisions made by competent patients and to *promote* autonomy by removing barriers to competent participation in making decisions. Such obstacles range from incomplete or inaccurate information to reversible medical conditions that interfere with a patient's ability to understand the information provided.

Competence or Capacity

Autonomy to make medical decisions cannot exist in the absence of competence. Because "competence" is a legal term, most medical experts prefer the term "capacity" to describe the necessary skills to participate in medical decisions.

Impairment of capacity can be temporary or permanent. Examples include some mental illnesses, dementia, immaturity, anxiety, pain, and effects of medications. The elderly, those suffering from mental impairment, and children are particularly vulnerable to having their participation in medical decisions inappropriately curtailed or even denied because their capacity to participate is frequently underestimated. Hearing loss, dysarthria, and expressive aphasia can create the false impression that capacity is impaired. Many children make medical decisions in ways similar to adults but may be mistakenly excluded from the decision-making process solely because of their age. Language barriers can present significant challenges to communication.

Capacity is both relative and task specific. Patients may be able to understand and make decisions about medical issues while being unable to care for themselves in other ways.

Both prejudice and paternalism permeate physician behavior in the informed consent process. Challenges to patient competence rarely occur unless there is a difference of opinion or values between the patient and physician. Patients are often referred for competency evaluation because they refuse medical advice, although refusal of treatment is not by itself evidence of incompetence.[4] Physicians frequently disagree with patient decisions because they regularly ascribe a lower quality of life to impaired and handicapped patients than the patients themselves do. Doctors are mistaken about patients' preferences regarding life-extending therapies in the majority of cases and underestimate older patients' desire for life-extending therapies in up to 30% of cases.[5] Moreover, surveys indicate that physicians and other health care workers are likely to *act* on personal prejudices regarding handicapped or impaired patients.[6]

Functional capacity for decision-making must be judged separately from the perceived quality of the decision itself. Patients have the right to make "bad" decisions if they are competent and have appropriate information. Otherwise, physicians could merely substitute their own judgment for that of the patient, and autonomy in medical decision-making would be nonexistent.

How do we recognize competence? When assessing a patient for anesthesia care, the anesthesiologist should focus on the following concerns: (1) Can the patient formulate and communicate a decision? (2) Can the patient receive and understand the information relevant to the decision? (3) Can the patient understand potential consequences of the decision, including potential risks and benefits, even if in a very simplified way? (4) Can the patient express a decision and communicate values regarding the medical advice being given?

It is the anesthesiologist's ethical duty to treat reversible conditions that interfere with medical decision-making. Elective surgery may have to be postponed until expert consultation for determination of mental capacity or treatment of reversible

conditions can take place. When surgery is urgent or a patient is impaired by an irreversible condition, anesthesiologists may have to rely on a surrogate decision-maker or proceed with their best determination of the patient's interests in mind.

Disclosure

The informed consent process requires honest disclosure of medical information to the patient. U.S. courts currently rely on two standards of disclosure: the reasonable person standard and the subjective standard. A third, "professional standard," in which the physician is obliged to disclose only what other physicians of the same specialty would disclose, was subject to abuse and manipulation and is essentially no longer recognized. In the "reasonable person" standard, the physician must disclose any information that a theoretical "reasonable person" would want to know. This standard does not require an exhaustive recitation of facts and acknowledges that not all information related to the procedure is integral to making a decision about whether to undergo the procedure. The "subjective standard" recognizes that some patients may have special needs for specific information and that when that need is obvious or has been brought to the attention of the physician, the information must be disclosed. For example, a concert violinist may have a specific need to know about the potential for nerve damage from an axillary block. In general, legal and ethical standards now require that (1) the physician accurately discuss the therapy and its potential alternatives—including no therapy—and (2) disclose the common risks (because they are more likely to happen) and the serious risks (because the consequences are severe).

The doctrine of "therapeutic privilege" is sometimes cited to avoid discussing risks under the reasoning that the stress of discussing risks can harm the patient psychologically or physically. Studies of patient stress during the informed consent process *do not* support this concept.[7] Therapeutic privilege is probably invoked in many cases because the physician is uncomfortable with disclosure or wants to curtail discussion. Although it is ethical to forgo or curtail risk discussions at the patient's request, it is not generally ethical for the physician to unilaterally decide to do so.

The physician-patient relationship is an inherently unequal one because of physicians' knowledge and authority and the patient's dependence on them for care. Physicians have ethical obligations to avoid exploiting their influence for the purpose of accomplishing their own ends. Although it is acceptable to offer a rational basis for a medical choice, it is generally unethical to coerce or manipulate patients into decisions by presenting real or implied threats or by omitting or misrepresenting key information.

Legal implications of Informed Consent

The informed consent process does not prevent legal liability when adverse events occur. Flawed informed consent processes have been cited, however, as evidence of a lack of quality of care by the physician. The American Society of Anesthesiologists (ASA) closed claims database reveals that the absence of informed consent is cited in approximately 1% of claims and that cases with inadequate documentation of informed consent are associated with larger monetary awards.[8] Studies repeatedly show that the risk of filing a malpractice claim is directly related to patients' perception of their relationship with the physician.[9] The informed consent process provides one of the few opportunities that anesthesiologists have to establish that relationship, however brief, and should not be underestimated in its medicolegal importance.

Informed Refusal

Informed consent is meaningless if the patient cannot also refuse medical therapy because the consent process is then merely an exercise in patient acquiescence to the physician's will. Examples of informed refusal in anesthesiology include requests to withdraw or withhold life-supporting care in the ICU; do-not-attempt-resuscitation (DNAR) orders in the operating room; cases in which the patient has objections to certain forms of therapy, such as a Jehovah's Witness who refuses blood transfusions; and cases in which a patient refuses preoperative testing, such as human immunodeficiency virus (HIV) or pregnancy testing.

Informed refusal has similar concerns and requirements as informed consent. When patients refuse medical care or insist on what the physician believes is suboptimal care, disclosure of the risks and benefits becomes even more important because these decisions may veer from options that are already widely accepted and for which the risks are believed to be lowest. It is easier to justify agreeing to the unusual preferences of a well-informed patient than to subject a poorly informed patient to unorthodox care.

Despite full information, patients may sometimes request or demand care that is unreasonable, either because it will adversely affect the performance of surgery or because it would be associated with unreasonably high risk. When a patient demands a technique that is inappropriate or outside the realm of reasonable practice, the anesthesiologist is under no ethical obligation to provide that care. No physician can be compelled by a patient to practice negligently.

Special Issues in Informed Consent and Informed Refusal

Jehovah's Witness Patients

The classic example of a patient who refuses therapy in anesthesia practice is that of Jehovah's Witnesses, many of whom believe that accepting a blood transfusion violates a Biblical injunction (also see Chapters 5 and 6). The Jehovah's Witness doctrine has been subject to change over time, which has resulted in inconsistencies in religious practice with regard to which, if any blood components might be acceptable. Individuals interpret religious doctrines in light of their own spiritual contexts, and not all believers hold to the same tenets with equal fervor. Church doctrines, like medical practices, evolve over time, and practices that are acceptable at one time may not be acceptable years later. Anesthesiologists and surgeons have cited individual and doctrinal inconsistencies as justification for ignoring the wishes of Jehovah's Witness patients—but to do so is no more logical than assuming that every hypertensive patient needs or will respond well to identical treatment or that optimal treatments will not evolve over time.[10] Moreover, it is the right of *any* patient to refuse blood transfusion therapy, regardless of whether this desire is founded in a religious preference. Such refusals have become more common in non–Jehovah's Witness patients because blood transfusion

therapy was connected to cases of acquired immunodeficiency syndrome (AIDS) in the 1980s and patients began questioning the value and necessity of transfusion therapy in light of its risks.

Because beliefs differ regarding which, if any, blood replacement therapies are acceptable, it is important to have a thorough and detailed discussion of possible therapies with a Jehovah's Witness patient before surgery, and the conclusions should be documented in the patient's chart. If anesthesiologists believe that they cannot comply with an adult patient's desire to forgo transfusion, they have the ethical obligation to find an alternative caregiver whenever possible.[11]

The courts strongly support the rights of adult patients to refuse blood products for themselves but have been inconsistent and have interfered in the cases of some pregnant patients. Transfusion of pediatric Jehovah's Witness patients by court order is common at this time but may become ethically and legally less acceptable as therapy other than blood transfusion to maintain oxygen-carrying capacity evolves, as the Jehovah's Witness church further defines its doctrines with regard to children, and as the capacity of children to consent to or refuse therapy is better understood.

The Pediatric Patient and Other Patients with Impaired Competence

The ethical practice of medicine weighs heavily toward adherence to respect for autonomy in patients who are competent to make medical decisions (also see Chapter 82) or who have executed advance directives when they were competent to do so. Medical care of individuals who have never been autonomous relies on principles such as respect for human dignity, beneficence, avoidance of harm, and adherence to the principle of justice.

Children are an example of persons who may or may not yet be autonomous. Laws in each state define the age at which children become *legally* competent to make medical decisions (usually age 18), but many younger children have the mental and emotional capacity to make medical decisions. Forcing such individuals to undergo treatments that they do not want is unethical and could be illegal as well.

Decision-making capacity in children is variable. Most 2-year-olds are clearly not able to make medical decisions, but there is a wide range of capability present in children as young as 7 or 8, and studies suggest that the average 14-year-old makes medical decisions similar to adults. In one study, children from 6 through 9 years of age invited to participate in influenza vaccine research asked pertinent questions about individual risks and benefits and whether their community and other children would benefit.[12]

Most states recognize "emancipated minor" status whereby a court determines that minors can legally make medical decisions for themselves. Legal exceptions to the age of consent are recognized in most states when treatment is believed to be in the minor's best interest and a requirement for parental consent would interfere with the child's ability to receive medical help. The law recognizes that tragically, some conditions for which a minor seeks therapy may even be the result of parental abuse and that seeking parental permission for treatment may actually further endanger the minor. Thus, minors are allowed in many states to consent to treatment for substance abuse, sexually transmitted disease, mental illness, and medical care affecting pregnancy, including abortion. In situations in which a minor has decision-making capacity but is not "emancipated," a judge may declare the child to be a "mature minor" with decision-making rights.

Ideally, individuals of any age should be involved in medical decisions to the degree that their capacity allows. A minor who possesses the capacity to make decisions should not be coerced or restrained under most circumstances.[13] Determining whether a minor has such capacity may require formal consultation and assessment. The term "assent" rather than "consent" is used to refer to agreement with treatment by children who do not fall into legal categories awarding them adult rights. The American Academy of Pediatrics has stated that physicians who care for children "should give serious consideration to each patient's developing capacities for participating in decision-making, including rationality and autonomy."[14]

When children dissent to undergo medical care, persistent refusals may be ethically binding, particularly in the case of participation in research. Medical personnel should respect the wishes of patients who withhold assent and try to gain a better understanding of their situation or deal with their fears. "A patient's reluctance or refusal to assent should also carry considerable weight when the proposed intervention is not essential to his or her welfare and/or can be deferred without substantial risk."[14,15]

Consent for Laboratory Tests: HIV and Pregnancy Testing

HIV and pregnancy testing has serious ethical considerations (also see Chapters 69 and 101), has limited, if any beneficial impact in the setting of surgery, may create serious social and economic consequences for the patient beyond the operating room, and may require the patient's informed consent.

HIV tests are usually ordered for the purpose of singling out patients for whom "extra universal precautions" could be taken to reduce transmission in the operating room. Most surgeons and anesthesiologists believe that compulsory AIDS testing would reduce their risk of exposure, and many believe that it is the physician's prerogative and can be done without the patient's consent.[16]

However, HIV testing does not necessarily yield safer anesthetic management and is more costly than diligent application of universal precautions.[17] In low-prevalence populations, testing is more likely to give false-negative results that wrongly reassure operating room workers that a patient is not infected. This may paradoxically increase the risk for transmission of HIV if relaxation in vigilance is the result.

Positive HIV tests can result in loss of employment or insurance coverage, or both. Seropositive women often experience marital breakup, abandonment, verbal abuse, and physical violence if their status is disclosed.[18] The threat of compulsory AIDS testing almost certainly would prevent some patients from seeking needed surgical care.[19]

Routine preoperative pregnancy testing has ethical ramifications analogous to HIV testing. Despite pervasive beliefs to the contrary, large, well-designed population studies do not demonstrate that anesthetics lead to early fetal loss or an increased frequency of fetal malformations.[20,21] Studies have also shown that even adolescent girls generally report the possibility of pregnancy accurately when asked privately.[22] Legal ramifications of not routinely testing for pregnancy preoperatively have been virtually nonexistent, and less than a third of U.S. practices require it.[23] A positive pregnancy test may have extremely negative consequences if a vulnerable patient is in a social situation in which

pregnancy is not accepted. Abandonment, negative family interactions, and violence to the patient or her fetus (or both) all occur. Adolescent pregnancies are sometimes the result of child abuse or rape, and referral of adolescents who are pregnant to Child Protective Services should be considered.[23] In many states it is illegal to disclose or even insinuate a child's pregnancy status to her parents regardless of her age, thus leaving an anesthesiologist who discovers an adolescent pregnancy with few comfortable or legal options.

Many patients may choose not to undergo elective surgery if they know that they are pregnant. However, coercing a female patient to have a test against her wishes and which she may find insulting explicitly violates patient autonomy. Physician self-interest is not a sufficient justification for disregarding patient autonomy or violating a patient's privacy. It was the joint recommendation of the ASA Task Force on Preoperative Testing and the ASA Committee on Ethics that anesthesiologists offer the *choice* of preoperative pregnancy testing to any female patient who might desire one, explain the potential risks and benefits, and obtain informed consent for the test.[24]

Maternal-Fetal Conflicts

In general, the rights of pregnant women to refuse therapy, even if refusal would be detrimental to their fetuses, are protected under right-to-privacy provisions in the U.S. constitution (also see Chapter 69). These rights are weighed against potential harm to the fetus in a decremental fashion as the fetus approaches and surpasses viable age. When the fetus is of nonviable age, mother's rights prevail. Court decisions have consistently upheld the rights of pregnant women to have abortions, to not be subjected to drug testing, and to forgo transfusions early in pregnancy. Attempts to charge women with child abuse, child endangerment, drug trafficking, murder, and attempted murder for activities deemed dangerous to their fetuses have almost uniformly failed.[25] In general, women do not lose their rights to bodily integrity and informed consent when they become pregnant, and neither fetal "rights" nor state interests supersede a pregnant woman's right as medical decision-maker.

The American Academy of Pediatrics Committee on Ethics has outlined conditions that in their view are necessary to override a mother's refusal of care: (1) the fetus *will* suffer irrevocable harm without the treatment, (2) the treatment is *clearly indicated* and likely to be effective, and (3) the risk to the woman is low.[26] However, the American College of Obstetricians and Gynecologists condemns the use of coercion on pregnant women and advocates counseling the patient carefully about risks, in addition to recommending consultation with an ethics committee.[27]

The Uncooperative Patient—Coercion and Restraint

The use of physical restraint to control medical research subjects was first addressed directly in the Nuremberg Code after the Doctor's Trial in 1947-1949 and is a continuing subject of intense scrutiny (also see Chapter 71).[28] For anesthesiologists, chemical restraints often replace physical ones, but the ethical issues are the same. Anesthesiologists are often asked by medical colleagues to chemically restrain uncooperative patients. Use of restraint is antithetical to promotion of autonomy, and anesthesiologists have both ethical and legal obligations to determine whether such extreme intervention is warranted. Coercing or using physical or chemical means to force competent patients to undergo treatment that they are refusing is both unethical and illegal. Refusal of medical care and angry behavior are not proof of incompetence, intoxication, or inability to make medical decisions.[29]

When faced with an uncooperative adult patient, questions to ask include (1) Is the patient clearly incompetent or merely angry and uncooperative? Is there evidence of neurologic impairment, acute intoxication, or severe mental disability? (2) Is the patient in immediate danger? (3) Does the patient pose a direct threat to staff or other patients? (4) Is there a compelling need to treat life-threatening injuries? In the absence of these considerations, the use of coercion or physical or chemical restraint is neither ethical nor legal. Physicians may be forced in some situations to act within a timeframe that does not permit lengthy evaluation of a patient's competence or a protracted search for a surrogate decision-maker. In such cases, the physician must rely on professional judgment in deciding how to care for uncooperative patients who either cannot speak for themselves or appear incompetent to refuse care at a time when a decision must be made. The standard applied here would be to do what a "reasonable" person would wish. Coercion or restraint (or both) in such situations is not ideal but may be necessary and ethically permissible.

An uncooperative child presents special ethical concerns. When a patient who does not have the capacity to make health care decisions dissents to medical care, the anesthesiologist is ethically required to provide care that is most likely to benefit the patient and prevent harm while preserving the dignity and safety of the patient. Although violation of respect for autonomy is technically not possible in a patient who does not have autonomy, violation of the principles of beneficence, nonmaleficence, and respect for dignity certainly is. Indiscriminate use of physical or chemical restraint is not without physical risk, and the fear and anger provoked by such tactics can lead to future aversion toward medical care and mistrust of health care providers. The American Academy of Pediatrics Committee on Child Abuse and Neglect states that restraint should not be used in pediatric care "unless it is necessary for proper diagnosis and treatment in a sick child, as in the case of a child with a high fever and potential ear infection, or in emergency situations."[30]

Behavioral control in an uncooperative child or incompetent adult should focus on alternatives to physical restraint, such as offering choices on how to go to sleep and use of fantasy or hypnotic suggestion. Although there may be many social, economic, and scheduling pressures to the contrary, delaying or rescheduling surgery on a hysterical patient is better than coercion or force. Delaying elective surgery may reduce stress, allow adequate premedication, and promote safer induction conditions. If medical care is urgent or if delay is unlikely to result in better conditions for the patient, the anesthesiologist should proceed in a manner designed to preserve the patient's dignity and safety.

Advance Directives and Surrogate Decision-Makers

Critical decisions regarding medical care often arise when patients are too ill to formulate or express decisions regarding medical interventions. "Advance directives" were developed after several legal decisions affirmed that patients can refuse even lifesaving medical care and that clear and convincing evidence of the patient's wishes is needed to allow surrogate decision-makers to

request withdrawal of life-sustaining therapies.[31] An advance directive is a document executed by patients before incapacity to provide physicians with guidance in medical decision-making when the patients cannot communicate for themselves. Such directives include living wills, which detail which therapies a patient would accept or refuse in the case of terminal incapacity; DNAR orders; and any other information regarding medical care decisions.

A surrogate decision-maker may be someone whom the patient has appointed to make health care decisions for them (a durable power of attorney [POA]) or an individual with other legally recognized authority by virtue of their relationship with the patient.

A durable POA for health care decisions may be given by patients to a specific person whom they designate to make health care decisions for them if they become incapacitated. The authority vested in a POA supersedes most other decision-makers, including family members, except court-appointed guardians.

When the patient has not designated a durable POA, doctors rely on family members to make decisions for the patient. In many states there is no legally defined hierarchy of decision-makers. Usually, the spouse or legally recognized domestic partner is considered the first-line surrogate. Commonly, the surrogate hierarchy after the spouse is the children, if all are in agreement, and then the parents, if both are in agreement, and then the siblings, if all are in agreement. In cases in which there are no advance directives and either a surrogate decision-maker is not available or family members cannot agree, the courts may appoint a guardian ad litem to represent the patient in medical decision-making.

Surrogates explicitly act in "substituted judgment" to provide what the patient would have wanted and, theoretically, are not being asked merely for their own preferences. However, surrogate decision-makers at best only approximate the patient's decisions because their interpretation is subject to their own biases, values, and psychological agendas. Incompetent patients can be emotionally and financially burdensome, and decision-makers may have conflicts of interest that distort their beliefs and testimony about what the patient would have wanted.

Studies demonstrate that patients and their proxies only infrequently discuss issues and values involving life-sustaining technologies. There are often significant discrepancies between patients and proxies in the assessment of patients' emotional health and satisfaction. Neither physicians nor proxies can always accurately predict a patient's preferences for life-sustaining therapy.[32-34] Nevertheless, with all of its imperfections, proxy decision-making may be the only option if a patient has not left specific directives.

Medical Decisions That Cannot Be Made by a Surrogate Decision-Maker

Some medical treatments have intense cultural connotations, may involve limitation on private freedoms such as reproduction, or may have historically been subject to abuse. Decisions regarding such interventions cannot be made by a surrogate decision-maker, even if one is available, and require court review. Examples in some states are sterilization and electroshock therapy.

The anesthesiologist should review the patient record before taking a patient to the operating room and ascertain (1) whether the patient has advance directives, (2) who the patient's surrogate decision-makers are, (3) if the procedure is legally allowed with consent from a surrogate decision-maker, and (4) in special cases, whether an appropriate court order has been obtained.

Special Issues with Advance Directives—Do-Not-Attempt-Resuscitation Orders in the Operating Room

Up to 60% of anesthesiologists incorrectly believe that DNAR orders are automatically suspended during anesthesia and surgery (also see Chapter 97). The ASA,[11] the American College of Surgeons,[35] the Association of Operating Room Nurses,[36] and the Joint Commission on Accreditation of Healthcare Organizations[37] all have published practice guidelines requiring reconsideration, not abandonment, of DNAR orders in the perioperative period.

The DNAR order is, in essence, documentation of the patient's wishes to avoid the medical interventions associated with resuscitation. Because the causes and outcomes expected with cardiac arrest in the operating room are different from what may happen elsewhere and the prognosis is much more favorable, it is very important to reassess the patient's desires when surgery is anticipated.

The ASA has issued guidelines for the management of a patient with DNAR orders and other directives limiting medical care.[11] Although the patient's primary care physician may have introduced the idea of DNAR orders to the patient or surrogate, it is specifically the anesthesiologist's duty to discuss the risks and benefits of resuscitation in the setting of anesthesia and surgery before undertaking the patient's care. The anesthesiologist should include in the discussion the following steps: (1) determine what the patient's goals are regarding surgery and resuscitation; (2) establish exactly what is meant by "resuscitation," in contrast to routine anesthetic care; (3) educate the patient about the risks and benefits of resuscitation in the operating room setting; and (4) document the agreements reached with the patient about which interventions commonly associated with resuscitation are acceptable to the patient. Such interventions might include, but are not limited to, intubation, administration of vasoactive drugs, administration of DC countershock, and institution of chest compressions. Many patients who express reluctance about resuscitation during surgery are fearful of burdensome outcomes, such as permanent neurologic impairment. Education and discussion may reassure them about the favorable outcomes of resuscitation in the operating room and can establish ground rules for discontinuing interventions postoperatively if they do not lead to a chance of meaningful recovery.

Surgery is dependent on the cooperation of many caregivers with differing expertise, each of whom has independent ethical obligations to the patient. It is therefore imperative that resuscitation agreements be discussed with other members of the operating room team. Such a policy prevents crucial disagreements from occurring during a critical event when treatment decisions must be made quickly. It also allows "conscientious objectors" to withdraw from the health care team.

Advance directives are legally and ethically binding. Despite clear, consistent, and forceful legal decisions, many physicians still resist imperatives to respect patient wishes regarding resuscitative care, life-sustaining therapies, or both. Anesthesiologists have ignored DNAR directives under the false assumptions that the legal authority of advance directives and living wills is not binding in the operating room or that the physician has discretion in deciding when to follow or ignore such directives. In response, courts have awarded significant monetary damages for the cost

of continued health care and punitive damages for the pain, suffering, and mental anguish of the patients' survivors when DNAR instructions are ignored.[38]

Finally, DNAR orders must never be construed as an excuse to not "care" for the patient. A patient's decision to forgo resuscitation does not imply a wish to avoid other beneficial interventions. Placement of a pulmonary artery catheter, for example, may help ensure optimal management of a frail patient who has a DNAR order by enabling the anesthesiologist to avoid situations in which the patient's DNAR status becomes pivotal.

End-of-Life Decision-Making

A 1996 review by the American Medical Association showed that end-of-life issues of foremost importance to patients were control over the timing and location of death; management of symptoms such as pain, dyspnea, anxiety, and depression; financial management of medical care; and maintenance of therapeutic options, including physician-assisted suicide.[39,40]

Withdrawal/Withholding of Medical Therapy—*Curing* versus *Caring*

More than 80% of deaths in the United States occur in health care facilities, and the majority of deaths in ICUs take place after an explicit decision to withdraw or withhold treatment.[40] Patients and doctors alike recognize that aggressive medical therapy may not be desired or even appropriate in the face of advancing disease. Continued therapy may not be warranted or desired when quality of life is extremely poor, even if the patient is not suffering from terminal disease.

Before the mid-20th century, the concept of "beneficence" in the eyes of physicians was strongly tied to preventing death. Ethical distinctions between acts of omission ("letting die") and acts of commission ("killing") were and remain confusing at best. Worse, physicians faced threats of criminal punishment if patient death resulted from withdrawal of medical treatment. In 1976, the case of Karen Ann Quinlan[41] established that patients have a right to forgo invasive treatment, even if lifesaving, and that surrogate decision-makers could ask for withdrawal of lifesaving therapies if they could show that the patient would not have wanted them. The right to forgo lifesaving treatment was later extended in the cases of Claire Convoy and Nancy Cruzan to include *any* treatment if patients refused or there was clear and convincing evidence that the therapy would have been refused if the patients could speak for themselves.[31] These decisions were revisited and reconfirmed in the tragic case of Theresa Schiavo in 2005.[42]

Arguments that withdrawing or withholding life-sustaining therapy does not violate rules against killing patients are based on ethical differences between killing and letting die and between acts of commission (e.g., lethal injection) and acts of omission (e.g., withdrawal or withholding of ventilator therapy).[43] Because such distinctions are confusing to physicians and patients alike, a "principle of proportionality" is often applied when withholding or withdrawing treatment.[44] In this principle, treatment is "indicated" to the extent that it is likely to present more benefits than burdens to the patient based on the patient's perception of such medical, social, and psychological benefits and burdens. Of course, competent patients still always have the right to refuse therapy, even if the treatment is lifesaving and otherwise indicated.

Two common scenarios in which anesthesiologists may be involved in withdrawal or withholding of life-sustaining interventions are in the ICU or operating room before organ donation after cardiac death. In both cases, the issues and principles of withdrawing/withholding treatment are the same.

Withdrawal of life-sustaining interventions heralds the final phase of end-of-life care. Terminal care requires special physician knowledge and experience. It requires expertise in medically supportive therapy, problematic symptom management, knowledge about physiologic changes in dying patients, support and counseling of patients and families, understanding and respect for patient autonomy and religious and cultural practices and beliefs, ability to work within complex health care teams, ability to communicate well, and empathy.[45] Anyone intimately involved in care of a dying patient should also be intimately familiar with the ethical and legal standards.

Withdrawal of life-sustaining care begins with an assessment of the individual patient's physiology, level of dependence on therapy, degree of consciousness, preferences regarding sedation and analgesia, and preferences regarding privacy and level of involvement of family and other loved ones. All of the patient's treatment orders should be reviewed to meet the new treatment goals. Treatments promoting patient comfort should generally be continued, whereas those directed only at physiologic maintenance might all be withdrawn. Family members and others attending the patient at the end of life should be educated about the physical and mental changes that they can expect to see as treatments are scaled back, including the possibility that death will not occur imminently once support is withdrawn.[46]

Several interventions have ethical implications and deserve special consideration—fluid and nutritional management, administration of sedatives and narcotics that have the potential to hasten death, and administration of neuromuscular blocking agents.

Fluid and nutritional support is controversial. Burdens associated with continuation of fluid and nutritional support include prolongation of the dying process and complications and suffering from placement and maintenance of intravenous or enteral access (or both). However, feeding and hydration may have important connotations for family and members of the health care team in that they allow a sense of nurturing and mitigate feelings that they are "abandoning" the patient.[47] Pain, dyspnea, and depression are all common symptoms that cause suffering in a dying patient. Alleviating the pain and dyspnea carries the risk of hastening death. Medical, legal, and religious authorities have all clearly accepted the principle of "double effect," in which an action intended to produce a benefit for the patient produces not only the expected benefit but also the potential for significant harm. It is entirely ethical and legal to administer high doses of pain medication and sedatives for the intended effect of relieving suffering, even if the treatment has the side effect of hastening death. However, to administer any medication with the explicit intention of hastening death is euthanasia and not medical therapy.[47]

Neuromuscular blocking agents have no anesthetic, analgesic, or sedative properties and have no role in palliative care. Such drugs should not be initiated if withdrawal of ventilatory support is anticipated. When withdrawal of ventilator support is anticipated in a patient already receiving such agents, they should be withheld in all but extraordinary cases. Paralyzing the patient to comfort *the family* so that they see no disturbing movements

or respirations as the patient dies is not justifiable. Even worse, it can mask symptoms and signs of distress and prevent relief of suffering during the dying process.[46]

Physician-assisted suicide (PAS) involves the provision of medications or prescriptions to patients by specific request for the purpose of ending their life. PAS requires a patient who is both competent and capable of communicating the request. Euthanasia involves the administration of medication by someone other than the patient for the express purpose of causing death in the belief that this would be best for the patient (but not necessarily at a specific request of the patient). Both practices differ ethically from withdrawing or withholding life-supporting medical treatment. In the former, the primary intent is to cause death, which secondarily ends suffering. In the latter, the primary intention is to discontinue treatments that are causing suffering with an understanding that death may or probably will result.

Currently, euthanasia is legal only in the Netherlands. In the United States, euthanasia remains illegal regardless of circumstance, and PAS is legal in the states of Washington and Oregon at the time of this writing.

Supporters of PAS argue that the right to privacy and respect for autonomy support patients' rights to determine the time, location, and circumstance of their own death. Adequate control of pain, anxiety, dyspnea, and other symptoms at the end of life remains a challenge to the medical profession that has fueled the desire for a means to end life when suffering cannot be controlled. Opponents argue that PAS "medicalizes" death, overly idealizes the physician-patient relationship, and ignores any personal and professional conflicts of interest that might occur. Although many ethicists acknowledge that individual circumstances may make assisted suicide an ethically permissible action, most express concern about potential abuse. Vulnerable members of society, such as the poor, elderly, and handicapped, might be pressed by financial and social factors into a suicide option in preference to palliative care.

An additional argument against PAS or legalized euthanasia is that they might provide simpler and less expensive solutions to the medical, social, and economic problems common to elderly and poor patients than seeking and requiring more difficult, but definitive remedies.

Ethical Issues in Organ Transplantation: Brain Death and Donation after Cardiac Death

Two issues critical to vital organ transplantation that confront anesthesiologists are the concept of brain death and linkage of withdrawal of life-sustaining therapies with organ retrieval and transplantation after cardiac death (donation after cardiac death [DCD]).

Brain Death

Before the 1960s, death was defined as the moment when the heartbeat stopped and respirations ceased. Advances in cardiopulmonary resuscitation and mechanical ventilation then made it possible to postpone death, seemingly indefinitely. In 1968, the Ad Hoc Committee of the Harvard Medical School proposed redefining death as the point at which all cardiorespiratory function had irreversibly ceased *or* all function of the whole brain had irreversibly stopped (brain death).[48] The committee gave two explicit reasons for redefining death. The first was to allow patients to be declared dead and not maintained on machines, thereby limiting expense, reallocating medical resources to other salvageable patients, and allowing the social rituals surrounding death to occur. The second was to allow donation of vital organs before the circulation stopped.

The public has been slow to accept brain death, in part because it requires complete trust in physicians and ignores indicators of death that the public already understands. For nonphysicians, brain-dead donors are superficially indistinguishable in many ways from living persons, and they must therefore rely completely on the physician for both accurate and honest information of a loved one's death.

Diagnosing brain death is relatively straightforward. In the United States it requires demonstration that in the absence of drugs, paralytic agents, hypothermia, and other reversible conditions that mimic loss of brain function, cortical and brainstem function is absent. The diagnosis is usually made either clinically by demonstrating that cortical activity and brainstem reflexes are absent or by radiographic studies demonstrating complete absence of cerebral blood flow.

The definition of brain death is *social* rather than *biologic*. Nevertheless, medical, ethical, theologic, and legal experts generally agree that brain death adequately defines a condition in which a person with ethical and legal rights and moral standing ceases to exist and should no longer be treated as an alive being. Expensive medical interventions can be discontinued without legal ramifications, and vital organs can be donated for transplantation if the patient or surrogate agrees.

Before assuming care of a brain-dead organ donor, the anesthesiologist is obliged to review the chart for documentation of the declaration of brain death, as well as the criteria on which it was based. If there are any questions about the diagnosis, organ donation should be postponed until the anesthesiologist is satisfied that these concerns are addressed.

Donation after Cardiac Death

DCD occurs when a patient desires to have life-sustaining medical therapies withdrawn and also wishes to proceed with donation of vital organs after death. Controlling the time and place of death so that the timing of organ donation can be optimized has obvious medical and ethical advantages. The decision to donate organs is made before death so that discussion and informed consent can take place. Ischemia time can be minimized. The dual decision to withdraw life-sustaining interventions and donate vital organs after death can create ethical conflicts, however. When a dying patient becomes an imminent organ donor, there is a risk that patient interests will be minimized or ignored in favor of the organ recipient.

The Institute of Medicine reviewed DCD in 1997[49] and 2000[50] and found that there were serious ethical questions, such as determining how quickly after asystole organ donation can begin and whether medications can ethically be administered to the donor before death that are solely for the purpose of organ preservation.

Ethical, theologic, and legal principles prohibit us from killing one person to benefit another, but the point at which actual death has occurred in DCD patients is unclear. Although expedient donation is the very purpose of DCD, doctors must never

sacrifice any living patient in the process or even take significant risks of doing so—the mistrust that this would engender in the public could place the entire concept of DCD at risk by reducing potential donors and ultimately harming future potential organ recipients.[51-53] Loss of consciousness occurs quickly after asystole, but brain function can continue for some time and irreversible brain injury may not occur for many minutes. Yet many protocols call for organ retrieval to begin only 2 minutes after the circulation has stopped, and in at least one institution, organ donation is allowed to begin within seconds of cardiac arrest.[54] There is both scientific and philosophic uncertainty about when death is complete—this could even lead to accusations of physicians deliberately killing patients to obtain organs for transplantation. Mistakes have occurred in some cases of brain-dead organ donors for which clear clinical criteria exist; DCD is potentially even more prone to error because no such clinical guidelines are universally accepted.[55]

Donation of vital organs after brain death and DCD is both ethical and legal, but the interests of the dying patient must be absolutely protected until death has occurred. Anesthesiologists can play a vital role in the organ donation process by helping hospitals develop reasonable and ethical policies for the management of brain-dead and DCD donors. Every anesthesiologist should be thoroughly familiar with brain death criteria and should review the process of determining brain death before accepting care of a brain-dead donor. Anesthesiologists involved in organ DCD should have appropriate training or expertise in the relevant ethical, legal, and medical issues involved, including end-of-life care.

Research Ethics

Human Subjects Research

The premise that the physician always puts the best interests of the patient first can be jeopardized when research objectives enter the doctor-patient relationship. Human subjects are asked to put aside their own interests to benefit some future, hypothetical group of patients. In extreme cases, the patient becomes a research "object" who will not benefit personally from the experiment at all. Two examples include experiments in healthy subjects and phase I cancer trials in terminally ill patients in which the goal is to determine the toxicity of treatment—not remission, palliation, or cure.

Human subjects research must balance many conflicting interests, such as the needs and rights of the research subject, the hypothetical interests of future patients, and the physician's financial, professional, and personal goals. Academic or corporate advancement, personal prestige, and financial incentives may be disincentives to researchers who are diligently protecting patient interests or remaining objective in designing protocols and analyzing and reporting their findings. Thus, human subjects research is more closely regulated, supervised, and controlled than any other medical endeavor.

Regulation of research began after World War II, with the Nuremburg Code and the Helsinki Declaration outlining the ethical obligations of physicians engaged in human research. The United States was slow to awaken to the parallels between the concentration camp experiments and the sometimes gruesome treatment to which they subjected their own subjects in similar trials.[56] In the years that followed the Doctor's Trial at Nuremburg, Fox[57] and Beecher[58] found that researchers were aware of the standards set at Nuremberg but regularly did not comply with them. In 1974, the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, out of which the modern institutional review board was born.[31]

Ethical conduct of human subjects research follows three principles: (1) respect for autonomy and the obligation to protect subjects with limited autonomy; (2) beneficence, with obligations to minimize risks, maximize benefits, and ensure that the research design is scientifically sound; and (3) justice, the obligation to treat each person with regard to what is morally right and to ensure fair distribution of benefits and burdens.

In addition to comprehensive presentation to research subjects of the risks and benefits of procedures or medications to which they will be subjected, disclosure must include the possibility of commercialization of the results, financial interests of the researchers, and any other actual or perceived conflicts of interest on the part of researchers and their institutions and sponsors. Subjects must be free to refuse or end participation at any time without penalty. "Situational coercion" in which subjects believe that they are not truly free to refuse should be avoided or mitigated. Examples of situational coercion include prisoners whose terms and experiences of incarceration might be affected by their decision to participate or refuse and hospitalized patients who may believe that their care could be compromised if they do not cooperate with researchers.[56]

Monetary or other inducements to participate in research are probably permissible if they do not undermine the freedom of the subject to refuse under reasonable circumstances. Significant monetary awards may have adverse effects on the autonomy of subjects and a negative impact on the scientific quality of the research. If remuneration is high, for example, subjects might conceal factors that would otherwise disqualify them from participating, thereby compromising the research results and exposing themselves to greater risk.

Researchers are obligated to maximize benefit and minimize potential harm, including physical, psychological, social, legal, and financial harm. The research must address a question of sufficient value to justify the level of risk and must follow the approved protocol. Findings must be promptly and accurately reported. The research must be terminated immediately if it is suspected to be harmful to the participants.

Anesthesiology research often involves the treatment or prevention of unpleasant symptoms, such as pain and nausea, for which effective treatments are well established. Such studies should be restricted to comparison of treatments with known efficacy, not placebo-controlled trials, and "escape" analgesics or antiemetics must be provided at the patient's request.[47]

No population group should be unfairly subjected to research without having equal access to its benefits. Finally, in our modern Western research tradition, the interests of the individual subject always prevails over the interests of society.

Children As Research Subjects

Children are particularly vulnerable as research subjects because they may lack the ability to make mature decisions, are subject to the authority of others, may defer to their parents and others in

ways that mask underlying dissent, and may have conditions requiring immediate decisions not consistent with informed consent.[59] Children's rights are frequently undervalued, whereas parental authority may be overvalued. Studies show that even children with decision-making capacity are often excluded from the consent process by both parents and physicians.[60]

If a minor child is "able" to assent, assent must usually be obtained in addition to the consent of any legal surrogate decision-makers. In the United States, federal law requires assent of any minor 7 years and older to participate in medical research. Particularly for research in which no substantive individual benefit is expected, many ethicists believe that a child's dissent *must always be honored*.[60,61]

Ethics of Animal Research

The animal rights movement in the United States has gained significant momentum in the last 25 years, following in the wake of the U.S. civil rights movement and paralleling increasing awareness and concern about the human impact on the environment and other animal species. Federal legislation protecting animal welfare began with the Laboratory Animal Welfare Act of 1966. In 1985, the Health Extension Act and amendments to the Animal Welfare Act required the establishment of Institutional Animal Care and Use Committees to oversee conditions of laboratory animals; review and approve animal research protocols; educate and train investigators in ethical issues and aspects of animal handling such as anesthesia, analgesia, and euthanasia; and act as community liaisons.[62]

Some researchers deny that animal experimentation could be subject to any moral reservations and assert that medical advancements have been and continue to be completely dependent on continued animal research. Many animal welfare activists insist on the moral equivalence of animal and human experimentation and accuse researchers of being blind to or, even worse, of being actually unmoved by the suffering of animal subjects. The simplicity of these polarized views does not do justice to the complexity of the issues.

Advancements in the understanding of animal cognition have led most biologists to now believe that many, if not all animals are capable of feeling pleasure, pain, anticipation, and fear and thus experience both enjoyment and suffering. Many bioethicists accept that the higher animals therefore have sufficient awareness to possess moral standing, although how much moral standing is intensely debated.[63,64] Allowing animal suffering as a result of pain, fear, sickness, or poor standards of care is a moral harm that must be avoided, mitigated, and weighed heavily against the benefits that it produces. Many argue that animals should be protected, not only because they have moral standing but also because people who are cruel to animals are more likely to be cruel to other humans.[65]

Researchers have obligations to provide clean and humane conditions and appropriate veterinary care for animal subjects. Researchers should mind the "3 R's"—replacement, reduction, and refinement—that is, use animal subjects only when necessary, minimize any suffering incurred in the study, and seek nonanimate replacements for animal subjects. Mediocre or repetitive research using animal subjects should not be allowed. It is the responsibility of the medical and scientific community to continue to aggressively seek and promote alternatives to the use of animal subjects.[65]

Physician Participation in Executions

U.S. physician professional organizations have consistently stated that physician participation in executions is unethical, yet many physicians admit that they would agree to be involved. The role of physicians in euthanasia and executions is of particular concern to anesthesiologists, who have been identified as ideal candidates for duties that involve killing because of their particular professional skills. Arguments in favor of physician involvement in executions usually cite the principle of beneficence in allowing a humane death.

Historically, however, beneficence arguments have led to "slippery slope" justifications for physicians to be involved in the killing of persons who have never faced an accuser or had a fair hearing—such killings have included persons with physical or mental handicaps and other "social flaws" for the "benefit" of the individual and society as a whole. Once physicians accept a beneficence argument for participating in executions, it is difficult to draw the ethical line at participation in other dubious state-sponsored activities, such as torture, coercion, and "medical incarceration," because these activities are also usually defended as being beneficial to society.[66]

When physicians agree to participate in an execution, they act as agents of the state while appearing to act on behalf of the "patient." This can lead to eventual erosion of public trust and respect. It also at times undoubtedly leads to physician participation in the killing of innocent persons.[67]

Studies clearly demonstrate that to avoid intolerable self-condemnation, virtually all executioners undergo "moral disengagement" in which they dehumanize the convicts and devalue their lives, thereby deflecting moral responsibility for the execution away from themselves by blaming juries, judges, governors, and "the law," rather than accept the responsibility that they share in ending the prisoner's life.[68] It is difficult to reconcile the medical profession's overt ethical imperatives of valuing human life, respecting individuals, and accepting personal moral responsibility with participation in a process that requires rejection of these very values.

Moral Integrity—Can the Physician Be a Conscientious Objector in Medicine?

Anesthesia care of patients can involve ethical controversy, legitimate disagreement, and moral ambiguity. When a physician's personal values run counter to acceptable ethical standards of care, how should the physician resolve such conflicts? Medical professional societies recognize the right to conscientious objection in

medical practice. The ASA, the British Medical Association, and the Hastings Center have all issued statements recognizing the physician's right to withdraw from situations in which ethical standards of patient care are in serious conflict with their personal values.[69] The ASA specifically recognizes conscientious withdrawal from patient care in the case of patients with DNAR orders or other directives that limit treatment.[11] However, these rights have limitations. Acceptance of moral objections to certain hotly contentious issues such as abortion or physician-assisted suicide may be reasonable, but objections to well-established standards, such as informed consent, are not. Moral objections of physicians are also likely to carry more weight if they involve concepts that physicians believe supports them as ethical doctors—and not just as ethical persons—because these concepts are more likely to be founded in professionally established standards rather than personal beliefs.[69]

Summary

Anesthesiologists face many ethical challenges, including promotion of patient autonomy, resolution of patient-physician conflicts in medical decision-making, ethical obligations in human subjects and animal research, and ethical conflicts during end-of-life care in the ICU and during organ donation. Knowledge about ethical and professional standards in patient care and research is essential in the specialty of anesthesiology, which is more than just the mere provision of technical service on demand. Anesthesiologists may find that at times accepted values in ethical practice conflict with personal values and goals. This is a common challenge to all physicians, but ethical decisions cannot be left to the individual physician's values, and adherence to ethical principles of the medical profession should prevail.

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10 Legal Aspects of Anesthesia Care

Key Points

1. The medical malpractice tort system is intended to improve patient care.
2. Medical negligence occurs when a physician's failure to meet the standard of care directly leads to patient injury.
3. A fully informed attorney is the physician's best advocate.
4. Physicians having their medical competence publicly questioned may feel guilt, failure, anger, shame, isolation, depression, fatigue, denial, and physical symptoms.
5. A detailed, legible anesthesia record strengthens the defense against a malpractice suit.
6. More than half the states have laws prohibiting the admission of apology or sympathy as evidence of wrongdoing.
7. The goal of informed consent is to maximize the ability of the patient to make substantially autonomous informed decisions.
8. Evidence of decision-making capacity (the ability to make a particular decision at a specific time) includes the ability to understand medical problems, proposed treatments, alternatives, options to refuse treatment, and the foreseeable consequences of accepting or refusing proposed treatments, as well as the ability to express a preference based on rational, internally consistent reasoning.
9. A reasonable person standard of disclosure requires that the extent of the disclosure be based on what a reasonable person would consider material for choosing whether to undergo the proposed intervention.
10. Anesthesiologists may refuse to provide care when they ethically or morally disagree with the procedure or if they believe that the patient's choice is too inappropriate or likely to result in harm.
11. Competent patients have a virtually unlimited right to refuse life-sustaining medical treatment.
12. Anesthesiologists are responsible for negligent acts made within the scope of defined duties by trainees and certified registered nurse anesthetists.
13. Physicians have been held liable for inadequate pain control.

Statute law, case law, and regulations affect anesthesiologists (Table 10-1).[1-8] Statute law is the body of prescriptive law created by a legislature to achieve a specific purpose. For example, the National Organ Transplant Act is the law that establishes the Organ Procurement and Transplantation Network and authorizes it to maintain a national registry for organ matching. State legislatures subsequently establish state laws governing organ procurement.

When statute laws need interpretation or clash or when there is no definitive statute law, disagreements may be adjudicated by the judicial system. The aggregate of reported cases, known as case law or common law, is used as the basis for future court decisions. The results of these cases are rarely prescriptive and may lead to a collection of confusing, ambiguous, and even contradictory cases that rest on diverse rulings in different jurisdictions. For example, a widow donated the kidney of her deceased husband to a long-time friend. The transplant surgeon, on receiving and examining the kidney, declared it unsuitable because of a renal artery aneurysm. The transplant surgeon then asked for the donor's second kidney. By then, the donor's second kidney had been allocated to another patient. The plaintiff sued, claiming that the organ procurement organization misappropriated the donor's second kidney and alleging in part that under conversion tort, the organ procurement organization interfered with the plaintiff's right of possession of personal property, in this case the kidney. On appeal, the court ruled for the defendant, the organ procurement organization, because the plaintiff had no common law right to the kidney inasmuch as a person cannot have property rights to a dead body.[9]

Regulations often come from administrative authorities such as executive branch agencies or state medical boards. For example, a U.S. Department of Health and Human Services regulation requires hospitals wishing to participate in Medicare to have written polices that an organ procurement organization is notified of potential donors.[10]

Table 10-1 Laws and Regulations That Affect Medical Practice

Law or Regulation	Comment
Health Insurance Portability and Accountability Act (HIPAA)[1]	HIPAA's privacy rules protect individually identifiable health information held or transmitted in any form, whether electronic, paper, or oral. This includes a patient's past, present, or future health or condition, provision of health care, or payment for the provision of health care and either identifies the individual or provides information through which there is a basis to believe that individual may be identifiable. Privacy rules apply to health plans, to health care clearinghouses, and to any health provider who transmits health information. HIPAA is a complex law that includes many other provisions, including making insurance portable from one employer to another.
Emergency in Medical Treatment and Active Labor Act (EMTALA)[2,3]	EMTALA governs when a patient may be refused treatment and when an unstable patient may be transferred from one hospital to another. More commonly stated, the purpose of EMTALA is to prohibit "dumping" of emergency patients onto other hospitals. Hospitals must perform a screening medical examination to determine whether an emergency condition exists, must provide stabilizing treatment if an emergency condition does exist, and may transfer the patient to another hospital only under certain conditions, such as the patient requesting transfer, the patient being stable and transfer will not worsen the patient's condition, and the receiving hospital having treatment abilities unavailable at presenting hospital. The receiving hospital must accept the transfer. Physicians have a central role in this process inasmuch as they must certify that the patient can be safely transferred. EMTALA also requires assigned on-call physicians to respond to emergency situations.
Controlled Substance Act[4]	This act permits the federal government to regulate the manufacture, importation, possession, and distribution of certain drugs to control the traffic of controlled substances. This act permits the federal government to determine whether a drug should be a controlled substance and into what drug schedule it should be placed. This act does not control the medical use of these drugs.
Employment Retirement Income Security Act (ERISA)[5] (A number of amendments to ERISA are relevant to health benefits, including HIPAA)	ERISA established uniform federal standards to protect private employee benefit plans. The U.S. Department of Labor administers and enforces ERISA and federal courts interpret it. The relevance in medicine is that it regulates health benefit plans. Case law interpretation of ERISA affects how, where, and for what indications members may sue health maintenance organizations.[6-8]

Professional Liability

The medical malpractice tort system is intended to "minimize patient injury, maximize patient safety and compensate injured patients." Unfortunately, the malpractice system may not have the desired effects on physician behavior.[11] Physicians are often uninformed about possible standards from malpractice cases.[11] Jury trials of medical malpractice suits do not reliably inform physicians, in part because of inconsistencies in case law and in part because juries tend to correlate liability with severity of harm and not with physician negligence.[12,13] Nonetheless, to improve patient care, anesthesiologists should vigilantly study the medical malpractice tort system.

Medical Malpractice

The most common cause of medical malpractice is medical negligence (Table 10-2). Negligence is breach of a duty that is the proximate cause of a harm.[14] Expanding on that definition, medical negligence occurs when a physician's failure (breach) to meet the standard of care (duty) directly leads (proximate cause) to patient injury (harm). Proximate cause should be tightly coupled and requires proof of "cause-in-fact" and foreseeability. Cause-in-fact, often known as the "but for" test, means that the harm would not have occurred but for the previous negligent act. Foreseeability suggests that injuries must be of the type that would be foreseen by a reasonable practitioner. For example, "but for" the *absence* of an end-tidal carbon dioxide monitor, esophageal intubation would have been recognized because a reasonable practitioner would foresee that this breach of the standard of care may lead to unrecognized esophageal intubation. There must be a harm for which the individual needs to be compensated. Awards

Table 10-2 Causes of Action Most Relevant to Anesthesiologists

Type	Description
Medical negligence	Breech of a duty of a standard of care causing harm
Wrongful death	One that occurs earlier that it would have otherwise. If negligence causes death, survivors may sue for damages
Lack of informed consent	Obligation to provide information material to a reasonable person
Abandonment	Obligation to provide continuity of care once a physician assumes responsibility for the patient
Vicarious liability	Obligation for reasonable oversight of those working for the physician
Loss of chance of recovery or survival	The patient must show that recovery was likely except for the action of the physician
Battery	Touching a person without express or implied consent. There is no need for the plaintiff to prove harm in battery cases
Assault	The attempt to touch another person. There is no need to prove actual harm

From White C, Rosoff AJ, LeBlang TR: Informed consent to medical and surgical treatment. *In* Sanbar AA, Firestone MH, Fiscina S, et al (eds): Legal Medicine, 7th ed. Philadelphia, Mosby Elsevier, 2007, pp 337-343.

may be conferred for noneconomic losses, for the economic costs of repairing the damage, and for loss of income. The amount of time in which a plaintiff can bring an action is governed by state statutes and typically begins on occurrence or discovery of the allegedly negligent act or the harm.

Medical negligence may be adjudged as criminal medical negligence if it deviates greatly from the standard of care, whether unknowingly (criminal negligence) or knowingly (criminal recklessness).[15] Criminal medical negligence is rarely prosecuted, but characteristics of such cases include failure to modify care based on past similar experiences, hiding errors, and practicing in a way that appears to favor financial and personal gains over patient care. For example, an anesthesiologist was prosecuted (but eventually acquitted) for reckless manslaughter when after more than five documented episodes of falling asleep during anesthesia, he fell asleep during a case in which the child died.[16] The anesthesiologist was convicted for criminal medical negligence, although that conviction was eventually overturned because the prosecutors had not brought the criminal medical negligence charge within the legal time limits.[17]

The Process of Being Sued

Some lawsuits may begin "informally" by a request from a potential plaintiff's attorney to review records or to discuss a case. An attorney should be consulted before engaging in these actions to ensure that proper procedure is followed. Lawsuits officially begin with a document called a Summons and Complaint, which is a notification to respond to allegations by the plaintiff.

After initiation of the suit, the process of discovery begins with exchange of documents and a deposition. The purpose of the deposition is for the other side of a legal action to obtain information or clarification otherwise unavailable, particularly about the reasoning underlying actions.[18] At the deposition, oral testimony is taken under oath and transcribed and may be used as evidence at trial. Experts, consultants, clinicians, witnesses to the event, or defendants may be deposed. Some conversations are privileged and may not be discovered by the plaintiff, including discussions with attorneys, risk management personnel, insurance company representatives, personal clinicians (including psychotherapists, clergy, and a spouse). Conversations with close friends are discoverable.

Before the deposition, the physician should inform the attorney about his or her relationship with the plaintiffs and any problems that may have occurred. The physician should educate the attorney about complex medical components of the case and expected weaknesses. A fully informed attorney is the best advocate.

In addition to the defendant, the defendant's attorney, the plaintiff's attorney, and the court reporter, the plaintiff may also be present at the deposition. After the court reporter administers the oath, the plaintiff's attorney will ask standard questions, including education, licensing, and certification. The defendant's attorney will intercede as appropriate. The same questions may be asked several times over. A goal of a plaintiff's attorney is to develop a causal atmosphere to lower the guard of the defendant before asking more relevant questions. A defendant is best served by not speculating about factual matters that may be found in the medical record and answering only the questions asked and asking for clarification if unclear about the meaning of a question.

Malpractice Defense

Physicians having their medical competence publicly questioned may feel guilt, failure, anger, shame, isolation, depression, fatigue, denial, and physical symptoms.[19] It is important to be forthright about these feelings and to manage them, if for no other reason than to be able to participate fully and positively in the legal defense.

Defendants often rebut claims that the standard of care was not met and that the alleged failure to meet the standard of care was a proximate cause of harm. To help support these arguments, expert witnesses, medical texts, journal articles, practice guidelines, and anesthesia records are often used.

Expert witnesses explain the relevant science and offer professional opinions about the standard of care and causation.[20] Although courts commonly accept the expertise of most expert witnesses, courts and juries do use qualifications to modulate the weight that they give the testimony. An expert witness can support the idea that a different explanation or approach, especially one that other physicians would support, may meet a sufficient standard of care. The obligations of expert witnesses include the following: "expert testimony by anesthesiologists should be readily available, objective and unbiased. To limit uninformed and possibly misleading testimony, experts should be qualified for their role and should follow a clear and consistent set of ethical guidelines" (Box 10-1).[21]

Practice guidelines are being used increasingly as evidence of a standard of care.[22] Although authors of practice guidelines routinely state that the guidelines are not intended to set a standard of care, it is highly likely that juries will be strongly influenced by them.[23] Some authors have even proposed that practice guidelines replace expert opinion.[22]

A detailed, legible anesthesia record often strengthens the defense against a malpractice suit. A goal of documentation should be that uninvolved anesthesiologists would be able to recreate the anesthesia care as if they were in the operating room. Uninvolved anesthesiologists should be able to understand interventions, the reasons for interventions, and the outcomes of interventions. Precise documentation and written explanations of thought processes lead to better understanding. For example, when performing regional anesthesia, an anesthesiologist may want to document the length and type of needle used, nerve stimulator type and settings, number of attempts, strength and location of muscle contractions, whether a paresthesia occurred, and how the paresthesia was managed.[24] Alternatively, consider the effect of documentation on the fairly routine event of decreased urine output. Assume that a patient had no urine output over a certain period in a previously functioning bladder catheter. The anesthesiologist treated the decreased urine output with a fluid bolus. The record would ideally indicate a "0" under urine output and indicate a bolus of fluid under fluid administration. Assume, then, that 30 minutes after the fluid bolus there was still no urine output. At this point, it would be reasonable for the anesthesiologist to write a note on the anesthesia record discussing the decreased urine output, the initial interpretation and treatment of the decreased urine output, the results of that

Box 10-1 Guidelines for Expert Witness Qualifications and Testimony

The physician should be board certified in anesthesiology or hold an equivalent specialist qualification. The physician should be familiar with the clinical practice of anesthesiology at the time of the occurrence and should have been actively involved in clinical practice at the time of the event.

The physician's review of the medical facts should be truthful, thorough, and impartial and should not exclude any relevant information to create a view favoring either the plaintiff or the defendant. The ultimate test of accuracy and impartiality is willingness to prepare testimony that could be presented unchanged for use by either the plaintiff or defendant.

The physician's testimony should reflect an evaluation of performance in light of generally accepted standards, as reflected in the relevant literature, neither condemning performance that clearly falls within generally accepted practice standards nor endorsing or condoning performance that clearly falls outside accepted medical practice.

The physician should make a clear distinction between medical malpractice and adverse outcomes not necessarily related to negligent practice.

The physician should make every effort to assess the relationship of the alleged substandard practice to the patient's outcome. Deviation from a practice standard is not always causally related to a poor outcome.

Fees for expert testimony should relate to the time spent and in no circumstances should be contingent on outcome of the claim.

The physician should be willing to submit such testimony for peer review.

From American Society of Anesthesiologists: Guidelines for expert witness qualifications and testimony. Available at http://www.asahq.org/publicationsAndServices/standards/07.pdf. Accessed November 1, 2007.

Box 10-2 Guidelines for Documentation

Preanesthesia Evaluation

Patient interview

Medical history (medication, allergies, family history of anesthesia problems, pertinent review of systems)

Anesthetic history

Medication history

Appropriate physical examination (including pertinent negatives)

Review of objective diagnostic data (e.g., laboratory, electrocardiogram, radiographs)

Assignment of American Society of Anesthesiologists Physical Status

Formulation of the anesthetic plan and discussion and documentation of the risks and benefits of the plan with the patient

If appropriate, explanations of what may be considered atypical choices of the anesthesiologist or the patient

Intraoperative/Procedural Anesthesia (Time-Based Record of Events)

Immediate review before initiation of anesthetic procedures

Patient re-evaluation

Check of equipment, drugs, and gas supply

Monitoring of the patient

Amounts of drugs and agents used and times of administration

Type and amounts of intravenous fluids used, including blood and blood products, and times of administration

Estimated blood loss and urine output

Specifics about the technique or techniques used

Unusual events during the administration of anesthesia, including explanation of recognition of the event, treatment of the event, and outcome of the event

Status of the patient at the conclusion of anesthesia

Postanesthesia Evaluation

Patient evaluation on admission and discharge from the postanesthesia care unit

Time-based record of vital signs and level of consciousness

Time-based record of drugs administered, their dosages, and routes of administration

Type and amounts of intravenous fluids administered, including blood and blood products

Any unusual events, including postanesthesia or postprocedural complications

Medical interventions

Postanesthesia visits

Data from references 23-25.

treatment, and the current interpretation (including differential diagnoses) and planned treatment of the decreased urine output. The anesthesia record should contain certain information (Box 10-2).[25,26]

Countersuits such as abuse of process, malicious prosecution, and defamation have been consistently rejected by the courts.[27] From a public policy perspective, the courts may be concerned that abuse of countersuits may limit the ability of plaintiffs to seek redress.

Apology and Disclosure

Although often inappropriately conflated, an apology, an expression of regret or sorrow, is distinct from disclosure, which is a revelation about what happened. Apologies and disclosures may occur at the same time.

More than half the states have laws prohibiting an admission of apology or sympathy as evidence of wrongdoing.[19] Some recommendations suggest apologizing for the effect on the patient without admitting fault. Sometimes this may make sense, for example, if a previously acceptable antibiotic caused a rash. However, not to take responsibility may seem stilted, such as when an anesthesiologist errantly administers an antibiotic to a

patient for whom there is clear documentation of an allergy. In the name of good relationships with patients, apologies should not be limited solely to events that may result in a suit. For example, consider a 6-year-old who on initiation of mask induction starts to scream and cry uncontrollably. After a discussion with the father who is present, a decision is made to, in essence, hold her down and apply the mask. A follow-up discussion with the family may include an apology not only for the induction ("I am sorry that was so unpleasant for Becky and you.") but also to acknowledge that this was not the desired reaction ("That is not our goal for induction. We would like it to be smoother." and "Going without sedation turned out to be a mistake."), as well as a recommendation for the future ("In the future, I would recommend giving oral sedation before going to the operating room."). Although this technically seems to admit wrongdoing, it is simply acknowledging what happened and educating the family for the future.

Although it is my belief that it is better to apologize, there are concerns about apologizing. The action for the physician, particularly if the apology is not readily accepted, may be painful. An apology may also embolden an otherwise unsure plaintiff, and it may be construed as admission of error in court.

It is more complicated whether one should admit fault for something that more likely may be medically negligent. Consider, for example, repeated attempts to place an epidural in a patient who is anesthetized and has previously undergone back surgery. The anesthesiologist tries repeatedly without success and without incorporating other methodologies such as fluoroscopy. The patient awakes with a nerve injury consistent with wayward insertion of an epidural needle. Some would suggest that although it is acceptable to express sympathy for the pain and discomfort ("I am sorry for your discomfort."), it would be legally harmful to acknowledge fault and a desire to do it differently ("I am sorry about your injury. In retrospect, although I am not sure what happened, I suspect that it was due to the needle placement. I should have used direct imaging of the back, such as fluoroscopy."). Others would suggest that the second apology with the disclosure is better because it explains what happened, why it happened, and how it may be prevented in the future. Although this combination of disclosure and apology admits culpability, it discloses only information that would eventually be discovered. I would suggest that the potential advantages gained by a genuine apology outweigh the potential harm of admitting culpability.

Full disclosure is gaining favor. From a wholly practical point of view, the patient will eventually learn what was withheld and will wonder, probably with animosity, why such information was not disclosed. Disclosure may have three components.[28] On realization of the problem, the goal is to give as much information as known, but not to speculate about what is not known, particularly about fault. Physicians should clarify the medical implications of the event, any necessary treatment or follow-up, and who will function as a contact for the patient regarding the event. The next step should be to conduct a thorough investigation with an eye toward minimizing problems in the future. Finally, the patient should be informed about what the investigation found, including the cause of the event and how it will be prevented in the future.

It is not unreasonable to consider responding to patient dissatisfaction by waiving part or all of a bill. This is not generally considered an admission of liability, and it may help satisfy a patient.

Legal Aspects of Informed Consent

Until the 1950s, physicians routinely obtained assent, or general agreement of the patient to have a procedure. The 1957 legal case *Salgo v Trustees of Leland Stanford Hospital* codified the modern concept of informed consent. The judge clarified the difference between informed consent and assent by declaring, "A physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form [the] basis of an intelligent consent by the patient to a proposed treatment. . . ."[29]

The goal of informed consent is to maximize the ability of the patient to make substantially autonomous informed decisions. The modifier "substantial" is used because it is unreasonable to expect a patient to be fully informed. The more appropriate goal of substantial informed consent acknowledges that consent may be sufficiently autonomous even if not completely informed. Modern informed consent has seven components.

Components of Informed Consent

Decision-Making Capacity

Decision-making capacity is defined as the ability to make a particular decision at a specific time. Evidence of decision-making capacity includes the ability to understand medical problems, proposed treatments, alternatives, options to refuse treatment, and the foreseeable consequences of accepting or refusing any proposed treatments, as well as the ability to express a preference based on rational, internally consistent reasoning. Decision-making capacity is distinct from the legal concept of competency. Courts determine competency and often make a global determination of competency by declaring that a person is either competent or incompetent for all matters. Adults are presumed to be legally competent unless declared otherwise by a court. On the other hand, anesthesiologists are responsible for assessing decision-making capacity and can make this determination only for specific situations.

Anesthesiologists should permit patients to make decisions to the extent of their ability.[30] For most patients, there are no questions about decision-making capacity. However, anesthesiologists need to actively evaluate the decision-making capacity of patients whose decision-making capacity has been temporarily altered, who do not have legal decision-making authority, or who have preexisting limitations in decision-making capacity. Consider a patient who has received pain medication before giving informed consent. The level of impairment varies depending on the medication, the tolerance of the patient to the medication, and the decision to be made. Indeed, some patients, such as parturients, may have improved decision-making capacity when the pain is decreased. To determine whether a patient has decision-making capacity for a specific decision, anesthesiologists need to balance the medication given and its expected effects with the ability of the patient to show evidence of rational reasoning and understanding. When a patient has temporarily lost decision-making capacity, such as when anesthetized, anesthesiologists should not implement nonemergency care until after the patient regains decision-making capacity and gives consent.

However, in emergencies, anesthesiologists should proceed without obtaining informed consent, based on the presumption that patients want life-sustaining treatment unless they have declared otherwise.[31]

Voluntariness

Physicians should perform procedures only on competent patients who participate willingly. Anesthesiologists compromise voluntariness through manipulation and coercion. Manipulation involves the deliberate distortion or omission of information in an attempt to induce the patient to accept a treatment, such as downplaying or omitting information to influence a patient to make a specific decision. Coercion involves the use of a credible threat to ensure complicity.

Anesthesiologists also hinder voluntariness when they physically restrain or sedate patients who have sufficient decision-making capacity. Competent patients have the legal and moral right to refuse treatment, even in life-threatening emergency situations. It is often hard for physicians to accept that a patient wishes to make what the physician perceives to be a foolish decision. *Shine v Vega* illustrates the complexity of these situations.[32] In 1990, Shine, a competent adult, went to the hospital and received oxygen and an unspecified medication for an asthma attack. Vega, the emergency department attending physician, thought that she was very ill and recommended endotracheal intubation. Shine stated her long-standing refusal of endotracheal intubation (confirmed contemporaneously by her sister and father) and continued to receive oxygen by mask. Later, Shine's sister came into her room in the emergency department and noted that Shine was breathing more easily but was arguing with staff. Shortly thereafter, Shine and her sister attempted to leave but were forcibly detained by a physician and security. Shine was placed in four-point restraints and Vega, choosing to disregard Shine's objection, intubated her trachea. On appeal, the Massachusetts Supreme Court stated that a competent patient has a right to refuse potentially life-sustaining treatment, even if her decision is considered unwise.

Another issue of voluntariness occurs when the interests of a woman and her fetus differ. When a woman refuses a recommended diagnostic or therapeutic procedure, such as cesarean delivery for fetal indications, physicians may choose to respect the patient's autonomy and not proceed, encourage the woman to seek health care elsewhere, or seek judicial involvement. Before seeking judicial involvement, physicians should consider the social, physical, and psychological harm of violating individual liberty and the fallibility and limitations of medical knowledge. Physicians may want to seek judicial involvement only when they are highly confident that the recommended treatment will substantially reduce harm to the fetus, that the risks to the woman are relatively small, and that no comparably effective, less-intrusive option exists.[33] Particularly relevant to anesthesiologists is the American College of Obstetricians and Gynecologists position on forced cesarean section. "Even in the presence of a court order authorizing intervention, the use of physical force against a resistant competent woman is not justified. The use of force will substantially increase the risk to the mother, thereby diminishing the ethical justification of such therapy."[33]

Disclosure

The goal of disclosure is to provide information relevant to the decision-maker and the decision to be made. Skilled disclosure builds trust, helps patients make good decisions, and is a fundamental component of the obligation to respect a patient's autonomy.

Established in 1972, the reasonable person standard requires that the extent of the disclosure be based on what a reasonable person would consider material for choosing whether to undergo the proposed intervention.[34,35] Informed consent discussions should routinely include the specific risks and benefits of reasonable anesthetic options and monitoring techniques, as well as the presence and use of a fallback plan.[31] Anesthesiologists may want to inform patients of common, but less severe risks, such as postoperative nausea and vomiting, and uncommon risks of more long-term significance, such as brain injury and death. If appropriate, the patient should be informed of the quality of the data, such as whether the information has questionable certainty. Anesthesiologists should also inform the patient whether an individual or an anesthesia care team will be providing anesthesia services and, if the latter, the names and specific roles of the team members. It may be appropriate to inform patients if the anesthesiologist is inexperienced in a particular situation.[36] To maintain good relationships with patients, they should be told about other practical matters, such as the probable sequence of events on arrival at the surgical unit, who will be with them at the various stages, what to expect for postoperative pain management, and realistic time estimates.

Exceptions to the obligation to disclose material information include patients who choose not to be informed, emergencies in which a valid informed consent cannot be obtained, and situations of therapeutic privilege. Physicians use therapeutic privilege when they choose to withhold information because they believe that disclosure would cause the patient to become "so ill or emotionally distraught on disclosure as to foreclose a rational decision, or complicate or hinder treatment, or perhaps even pose psychological damage to the patient."[34] Therapeutic privilege has a narrow scope and should be used prudently. Simply because information is undesirable or upsetting to the patient does not mean that such information should be withheld. For example, it may be reasonable to invoke therapeutic privilege when discussing the risk of death with a patient who is having an acute infarction of his myocardium; it would not be reasonable to do the same when discussing the risk of death with the parents of an infant.

Recommendation

Anesthesiologists should offer an opinion about which options are preferable and the advantages and disadvantages of each option. By explaining the value judgments and the quality of data supporting their opinions, anesthesiologists allow the patient not only to receive the benefit of their expertise but also to understand the reasons for the recommendations. Patients can then decide for themselves which choices best fit their priorities.

Understanding

Patients need to understand the risks and benefits of the proposed procedures, the recommendations made, and why those recommendations were made. It is difficult to determine whether a patient fully understands the informed consent discussion, and indeed, many patients may not.[37,38] Pain and distress do not seem to compromise the ability to recall risks, particularly among parturients, and do not preclude obtaining a legally sufficient informed consent.[39-41]

Decision

After considering the information and the anesthesiologist's recommendation, the patient chooses an anesthetic technique. Patients vary in their preferences for participation in decision-making, and anesthesiologists should be sensitive to these preferences. The desire to participate in the decision-making process may be a function of the individual, extent of illness, gender, age, and level of education. Anesthesiologists should attempt to tailor the extent of patient and physician decision-making to the patient and the situation.

When a patient refuses an anesthesiologist's recommendation or requests a technique that the anesthesiologist believes is inappropriate, the focus of conversation moves from informed consent to informed refusal. Informed refusal requirements are similar to informed consent requirements in that the patient should be substantially well versed about the risks, benefits, and alternatives before declining. However, although it may be reasonable to permit a patient agreeing with a recommended or acceptable procedure to refuse extensive information (especially if the likelihood of harm is low), it is more difficult to honor a patient's preference to receive limited information when the patient desires a suboptimal approach.[42] The anesthesiologist may wish to provide additional information about the choice to be sure that the patient has all possible information. If in fact the patient chooses without sufficient information, the anesthesiologist has not fulfilled the obligation of informed refusal. Of course, a patient may still refuse to hear information. In either case, when a patient chooses a technique that the anesthesiologist believes is inappropriate, anesthesiologists are not obligated to provide care in nonemergency situations.

Autonomous Authorization

The informed consent process concludes with the patient intentionally authorizing the anesthesiologist to perform a specific procedure. This authorization is the expression of the patient's self-determination and is the basis of informed consent.

Documentation of Informed Consent

In practice, informed consent for anesthesia may be documented on the surgical consent form, by a handwritten note, or by a separate anesthesia consent form. Use of a surgical consent form is suboptimal because surgeons cannot capably discuss the risks associated with anesthesia and therefore it is unclear what is being documented. Both handwritten notes and anesthesia consent forms may be acceptable. Handwritten notes detail specific discussions with patients. Writing a note for each patient, however, may be impractical and time consuming and may miss key aspects of informed consent. Anesthesia consent forms may act as a prompt for anesthesiologists to discuss key aspects of informed consent. Space for handwritten notes on the consent form will permit additional details to be documented. Having the patient sign the handwritten consent or the consent form gives an indication that some form of communication took place. However, because consent forms by themselves do not fulfill the legal requirement of informed consent, an informed consent discussion must still occur.

Theories of Suit in Informed Consent

Negligence related to the informed consent process may occur if the anesthesiologist provides a disclosure that is insufficient to allow a patient to make an informed decision and an injury subsequently occurs, even if the injury was foreseeable and occured in the absence of a treatment error.[31] To determine whether sufficient information was given, the courts look for materiality and causation. Materiality assesses whether the information given met the standard of care. If the disclosure did not meet the standard of care, it may be considered a breach of duty. Causation then assesses whether sharing the omitted information would have caused the patient to choose a different option.[31] Most jurisdictions use the objective standard, which bases causation on whether a hypothetical reasonable person would have used the additional information to make a different decision. Some jurisdictions use the subjective standard, which is contingent on whether the specific patient involved would have made a different decision. A few jurisdictions combine the two standards by heeding the objective standard while considering factors specific to the patient and situation. Courts also consider how the information was given. The informed consent discussion should occur in a setting conducive to decision-making so that the patient has a chance to ask questions and consider answers.

The disclosure process is not intended to be armor against medical malpractice liability if an adverse event takes place. Informing a patient about a risk does not eliminate liability for its occurrence. Liability is based on negligence theory and depends mainly on whether the standard of care was met and whether failure to meet the standard of care was a proximate cause of the injury.

Refusing to Provide Care

Anesthesiologists may refuse to provide care when they ethically or morally disagree with the procedure or situation, such as elective termination of pregnancy.[43] Although physicians have an obligation to altruistically provide care, this requisite does not always oblige physicians to subjugate their morals. Furthermore, society and medicine have a fundamental interest in preserving the moral fabric of individual physicians. Anesthesiologists should provide care that violates their conscience and possibly weakens their moral constitution only in critical, presumably life-or-death, circumstances. More practically, an anesthesiologist who ethically or morally disagrees with a patient's choice will have difficulty providing the care requested. In a nonemergency situation, such an anesthesiologist should withdraw from or refuse patient care. The anesthesiologist may then be obligated to make a reasonable effort to find a competent and willing replacement.

Physicians may also ethically refuse to provide care if they believe that the patient's choice is too inappropriate or likely to result in harm. Determining that a choice of anesthesia is inappropriate is difficult and should not be invoked lightly or out of convenience. The patient's choice and the resultant risks must be sufficiently extreme that they, say, elicit a similar response from at least several other anesthesiologists. In addition, anesthesiologists may refuse to provide care if they do not feel qualified to provide the needed care.

Legal Aspects of End-of-Life Care

Acknowledgement of patients' rights to refuse life-sustaining treatment began in the mid-20th century with the rise of civil liberties, individual rights, and respect for the importance of self-determination (see Chapters 91 and 98). In 1974, the American Medical Association asserted that "the purpose of cardiopulmonary resuscitation is the prevention of sudden unexpected death. Cardiopulmonary resuscitation is not indicated in cases of terminal irreversible illness where death is not unexpected."[44] Policies acknowledging the need to permit patients to limit resuscitation during terminal illness were prominently published several years later.[45]

Progression of the rights of the individual to refuse potentially life-sustaining care may be seen through case law. The 1976 case of Karen Ann Quinlan first established the right to refuse potentially life-sustaining care. In *Quinlan*, the courts upheld the legality of disconnecting the ventilator from a patient thought to be ventilator dependent and in a permanent vegetative state.[46] The court based this decision on the general constitutional right to privacy. In addition, the court determined that a surrogate had the right to decline medical treatment for an incompetent patient if the surrogate concluded that the patient would have preferred limited care. Quinlan's father thus discontinued his daughter's mechanical ventilation. Quinlan lived for nearly a decade sustained by nasogastric feeding.

The right of a competent person to refuse potentially life-sustaining care was established in the 1984 case of *Bartling v Superior Court*.[47] Bartling was a competent adult patient with an incurable disease who for 6 months received medical therapy against his clear wishes. After pneumothorax from a needle biopsy, Bartling became ventilator dependent. He subsequently received a tracheotomy to facilitate weaning attempts. During this ordeal, Bartling made clear his desire not to receive continued therapy and declared at one point, "While I have no wish to die, I find intolerable the living conditions forced upon me . . . ."[47] Although Bartling died before his case could be adjudicated, the appellate court issued an opinion based on the constitutional right of privacy that supported the right of a competent patient to refuse medical treatment.

The 1990 case of *Cruzan v Director, Missouri Department of Health*, concerned a young woman involved in an automobile accident that left her incapable of expressing a preference.[48] Several years before the accident, Cruzan had expressed to a friend in a somewhat serious conversation a desire not to live in a state of diminished capacity. The Supreme Court of Missouri held that Cruzan's informal statements did not meet Missouri's evidentiary standard of "clear and convincing evidence" of a patient's wish to terminate potentially life-sustaining care and thus mandated continuation of treatment. The case was appealed to the U.S. Supreme Court.[49] Unlike *Quinlan* and *Bartling*, the Supreme Court grounded the right of a competent patient to refuse treatment on the liberty interest of the Fourteenth Amendment, which states, "No State shall make or enforce any law which shall abridge the privileges or immunities of citizens of the United States; nor shall any State deprive any person of life, liberty or property . . . ." The decision also upheld the rights of states to determine standards for the level of certainty required, thereby permitting Missouri to use the "clear and convincing evidence" standard.[48,50]

Competent patients have a virtually unlimited right to refuse life-sustaining medical treatment.[51] For an incompetent patient, three hierarchic levels of judgment direct the decision-making process for end-of-life care. A once-competent patient's previously expressed preferences for end-of-life care should be followed as best as possible. When the patient's declared preferences are not known, substituted judgment, or use of a surrogate's intimate knowledge of the patient's attitudes and beliefs to determine what the patient would have chosen, may be used to direct care. Despite being two distinct categories, both levels require the surrogate to know the patient sufficiently to appropriately choose or interpret the patient's preferences. These standards put significant burdens on decision-makers, who may have legitimate doubts about the appropriateness of their decisions. When a surrogate has to make decisions for a patient who has never been competent, such as a young child or a mentally disabled adult, substituted judgment is impossible, and the surrogate must rely on the best interests standard. The best interests standard requires the surrogate to make decisions based on the surrogate's view of what is best for the patient.

Advanced Care Planning

Advanced care planning permits patients to declare preferences for medical treatment if they become incapacitated. Advance directives are designed to minimize the likelihood of undesired overtreatment and undertreatment. Partially as a result of *Cruzan*, the Patient Self-Determination Act (PSDA) was introduced in 1990 to increase the use of advance directives.[52] The PSDA requires health care institutions, such as hospitals, nursing homes, and hospice programs, to notify individuals about their rights regarding advance directives. Two types of advance directives are living wills and health care proxies (also known as durable power of attorney for health care decisions). Living wills allow patients to declare the extent of desirable interventions, but they may not be able to directly address the subtle differences that characterize clinical situations. The difficulty of applying living wills to clinical situations has led some to prefer the greater flexibility provided by the health care proxy, in which the surrogate decision-maker can consider the specific details when making clinical decisions. Health care proxies permit patients to designate surrogate decision-makers (including non–family members) to make decisions for them should they become unable to make such decisions for themselves. If the patient does not assign surrogacy, most jurisdictions have a hierarchy for assigning surrogacy. Surrogacy is not always effective, particularly for patients who do not make their preferences clearly known to the surrogate before losing their decision-making capacity.[53] Given the strengths and weaknesses of each approach, a combination of the two (a designated proxy with some written form of preferences) may be the best option.

Clinically, advanced care planning should be considered an ongoing process, with the advance directive being used in conjunction with family and friends to help guide the decision-making of patients and surrogates.[54,55] Competent patients may obviously modify their previously declared preferences. Demented patients who previously made an informed choice to limit certain therapy may express an interest in receiving that therapy.[56] If

patients have evidence of decision-making capacity, such as being able to provide internally coherent reasoning, their wishes to receive therapy should be honored. However, the process of resolving this situation in a patient without decision-making capacity and with almost no likelihood of regaining decision-making capacity is more complex. In this situation it is better to base judgment on therapy from multiple sources, including significant others, the type of documentation, and the best interests standard.

Refusal of Cardiopulmonary Resuscitation

The right of a patient to reject unwanted therapy in the operating room is now well accepted. Before proceeding to the operating room, preoperative do-not-resuscitate orders should be re-evaluated in light of the surgical procedures, the anesthetic options, and the patient's overall goals. Anesthesiologists are then prepared to clarify and document the desired resuscitation status in the operating room by using either the goal-directed approach or the procedure-directed approach.[57] The process of obtaining and documenting perioperative refusal of resuscitation should comply with hospital policy and jurisdictional law. Written documentation may include the patient's diagnosis and prognosis, the characteristics of perioperative resuscitation, probable outcomes, and the patient's reasoning. If the decision is being made by a surrogate, the record should note the surrogate's relationship to the patient and the basis of the surrogate's decision. It should be signed by the responsible physician.

Refusal of resuscitation in an emergency situation without time to clarify a patient's wishes is inherently different. The traditional bias of providing treatment in the absence of a clear decision not to treat still holds for the anesthesiologist in an emergency situation. The situation can always be clarified later and the patient withdrawn from the ventilator if it is determined that the patient would have preferred not to receive the interventions. In short, the "inconvenience" of a short period of mechanical ventilation is worth the opportunity to correctly ascertain the patient's desires.

The Demand for Life-Sustaining Therapies

Patients or families may demand therapies that clinicians believe are inadvisable because of burden to the patient, cost, or uncertain benefit. When such situations become irreconcilable, the cases may go to court, often not to determine what therapy should be given but to determine who should be the decision-maker for a noncompetent person. For example, an archetypic case involves Helga Wanglie, an 86-year-old patient in a persistent vegetative state who was receiving mechanical ventilation. The medical center believed that further therapy would be futile for Mrs. Wanglie and wanted to withdraw mechanical ventilation. When Mr. Wanglie refused the medical center's request to stop mechanical ventilation, the medical center sought appointment of an independent guardian to supplant Mr. Wanglie as her guardian. The Court declared that Mr. Wanglie was best able to be Mrs. Wanglie's surrogate.[58,59]

In the 1995 case of *Gilgunn*, a jury supported a unilateral refusal of life-sustaining care. Catherine Gilgunn had multiple medical problems, including severe brain damage, and was in a coma.[60] Her daughter Joan, representing the family, requested that everything be done. The Optimum Care Committee of the hospital agreed with the physicians that providing cardiopulmonary resuscitation would be futile in the sense that it was not a genuine therapeutic option. The legal division approved the do-not-resuscitate order because they believed that the physicians were acting in the patient's best interest. Gilgunn was disconnected from ventilator support and died a few days later. The jury supported the actions of the physician and hospital to impose a unilateral do-not-resuscitate order. There was no appeal.

Despite *Gilgunn*, unilateral physician declarations are insufficiently respectful of patient autonomy and may be legally risky. Evidence indicates that negotiation nearly always resolves these problems without the need to resort to unilateral action. However, being able to resolve differences of opinion about applying treatments with a low likelihood of success is important. Policies for resolution based on a procedural approach in which the process for resolving conflict is described are more practical. Good policies are public, reflect the moral values of the community, and include processes for identifying stakeholders, for initiating and conducting the policy, for commencing appellate mechanisms, and for determining relevant information.[61] In a different approach, the Texas Advance Directives Act permits physicians to unilaterally withhold or withdraw treatments that they regard as "futile," provided that they follow guidelines, including obtaining agreement of the hospital ethics committee.[62]

Physician-Assisted Suicide

Physician-assisted suicide is the act of a physician prescribing lethal quantities of medication for self-administration by the patient. In the United states in the cases of *Washington v Glucksberg*[63] and *Vacco v Quill*,[64] the courts held that there was no constitutional right to physician-assisted suicide. It is important to recognize that the courts followed common ethical opinion in drawing a distinction between the positive right to demand an action, such as physician-assisted suicide, and the more powerful negative right to be free of bodily invasion. Although there was no constitutional right to assisted suicide, individual states may choose to legalize or prohibit it.[65] In 1997, Oregon legalized the Oregon Death with Dignity Act, which permitted terminally ill patients to receive prescriptions in lethal quantities for the purpose of self-administration. It does not permit any other forms of physician aid-in-dying, such as another person administering the medication. From 1998 through 2006, 292 patients used 456 prescriptions authorized by this law. The most common diseases in patients choosing to ingest a lethal dose of medication were malignant neoplasms (81% of patients), amyotrophic lateral sclerosis (8% of patients), and chronic lower respiratory tract diseases (4% of patients).[66] In 2006, 40 physicians wrote 65 such prescriptions. Of these 65 patients, 35 used the prescriptions, 19 died of their underlying disease, and 11 lived throughout the year.[66] The financial and educational status of patients did not seem to play a role in the request for physician-assisted suicide.

Other Legal Aspects of Anesthesiology

Care of Jehovah's Witnesses

Jehovah's Witnesses interpret biblical scripture to prohibit taking in blood because it holds the "life force," and anyone who partakes of it shall be "cut off" from eternal life after death (see Chapter 55).[67] Jehovah's Witnesses have different interpretations about the prohibition of blood transfusions, and anesthesiologists must actively clarify what the patient considers acceptable.

Wholly acceptable anesthetic techniques to reduce blood loss include deliberate hypotension, deliberate hypothermia, and hemodilution. Most Jehovah's Witnesses accept synthetic colloid solutions, dextran, erythropoietin, and preoperative iron. Some Jehovah's Witnesses accept autologous banked blood or cell saver blood, and some accept blood removed at the beginning of surgery and returned in a closed loop. Jehovah's Witnesses will colloquially refer to options that are a matter of individual choice as "matters of conscience." Although blood components, autologous blood, and banked blood are generally unacceptable, these specifics must be discussed with the patient. Documenting acceptable interventions crystallizes the patient's desires and provides legal documentation for the anesthesiologist. Anesthesiologists must be certain that they are capable of fulfilling the patient's requests; otherwise, they should not agree to provide anesthesia. Indeed, the anesthesiologist and surgeon should provide nonemergency care to the patient only if all parties can agree on the approach to blood management.

Case law strongly supports the right of an adult patient to refuse blood products. Case law is in flux for pregnant patients, and in such cases the courts are more likely to intervene and mandate transfusion. The ambiguity in legal rulings results from the fact that issues relating to transfusions in Jehovah's Witnesses are based on case law.

Law Regarding Pediatric Patients

For the most part, parents or other surrogate decision-makers of children make health care decisions for minors (in general, children younger than 18 years) (see Chapters 82 and 84). However, the participation of children should increase as they grow older and depends on both the patient's maturity and the consequences involved in the decision. Informed assent acknowledges that although most pediatric patients cannot legally consent to medical care, they should share in decision-making to the extent that their development permits.

Some minors are permitted to consent for themselves.[68] Emancipated minors are patients younger than 18 who have been given the global right to make their own health care decisions. This status varies by state but is generally awarded to patients who are married, parents, in the military, and economically independent and may include patients who are pregnant. The mature minor doctrine holds that minors who have decision-making capacity are legally and ethically capable of giving informed consent in specific situations as determined by a court. Although particulars vary, the mature minor doctrine in general requires patients to be at least 14 years old and tends to permit decisions of lesser risk. The nearer the child is to the age of majority, the more likely the court is to grant the child the ability to consent. The courts will balance the maturity and decision-making capacity of the minor and the risks associated with honoring the minor's wish. As minors near the age of majority, the likelihood increases that the court will support the right of minors to determine therapy. For example, in a case in 2007 that seemed to be on the margin, a judge ruled that a 14-year-old practicing Jehovah's witness would be permitted to refuse transfusion therapy during treatment for a cancer that had a 70% 5-year survival rate. The patient subsequently died.[69]

Even though pediatric patients who are pregnant may be considered emancipated, many states require some form of parental involvement, such as parental consent or notification, before an elective abortion in an adolescent. If a state requires parental involvement, the ability of the minor to circumvent this regulation by seeking relief from a judge, known as judicial bypass, must be available. Requirements and enforcement of statutes vary from state to state. The need for parental involvement in minors having abortions is not always legally straightforward, and it may be best to consult with hospital counsel when determining such issues.[70,71]

Parents and medical personnel may disagree about what is in the best interests of the child. Based on the legal doctrine of *parens patriae*, or the government's obligation to protect the interests of incompetent patients, parents are not permitted to make decisions that are grossly inappropriate overtreatment or undertreatment.[72,73] One way to decide what is in the best interests of the child is to define which choices fall outside the range of acceptable decision-making. The extent to which one intervenes between a patient and the surrogate's decision depends primarily on how harmful the decision is to the patient. Criteria to make this determination include the amount of harm to the child by the intervention or its absence, the likelihood of success, and the overall risk-to-benefit ratio.[74] Charging a parent of not acting in the child's best interests has significant social, fiscal, and familial ramifications. If, however, after exhausting other options the anesthesiologist believes that the parent has chosen unacceptable treatment, the anesthesiologist should report the situation to the proper child welfare authorities for possible legal action.

For anesthesiologists, this is most frequently seen when courts overrule parental wishes and permit transfusion therapy in the children of Jehovah's Witnesses.[75,76] Anesthesiologists caring for a child of a Jehovah's Witness should inform the patient and family that attempts will be made to limit the need for transfusion therapy and abide by their transfusion preferences but that in a life-threatening situation, the anesthesiologist will seek a court order authorizing the administration of life-sustaining blood. In instances in which the likelihood of requiring blood is high or the local judiciary is not that familiar with case law for Jehovah's Witnesses, the anesthesiologist may choose to obtain the court order before the operation. In crisis situations in which no court order exists, anesthesiologists should initiate emergency transfusion therapy before obtaining a court order. As a child becomes older, the courts become less likely to intervene and often grant the emerging adolescent more decision-making latitude. In elective procedures that may be safely delayed, the patient and family may also consider postponing the procedure until the child is of sufficient age and maturity to decide about transfusion therapy.

Supervision and Professional Associations

Attending physicians may be sued because of resident actions. The question of what is considered acceptable resident supervision is affected by local policies and national guidelines, but again, in any individual case, the standard of care is often determined by a jury. Specific guidelines about what trainees are permitted and not permitted to do may provide some protection for the attending physician if the trainee deviates from these guidelines. In addition, residents are being named in lawsuits with increasing frequency. As a general rule, a resident is held to the same standard of care as a practicing attending physician in that specialty.[77]

Under the doctrine of *respondeat superior* and the theory of *vicarious liability*, anesthesiologists are responsible for negligent acts made within the scope of defined duties by certified registered nurse anesthetists.[78] The fundamental issue of vicarious liability is whether the anesthesiologist is controlling the activities of the certified registered nurse anesthetist. Although the question of vicarious liability may depend on who remunerates the certified registered nurse anesthetist, this is likely to be an ineffective defense because anesthesiologists tend to have full authority to medically direct certified registered nurse anesthetists. The scope of defined duties and whether adequate supervision took place may be affected by societal expectations, medical customs, history, practice, manuals, agreements, actions, expert analysis, and written documentation, but it is ultimately determined by a jury in any individual case. For example, in one case, a certified registered nurse anesthetist did not promptly summon the anesthesiologist for help in managing fatal postoperative laryngospasm and bronchospasm.[78] The anesthesiologist was found vicariously liable for negligence, in part because there was a lack of clear understanding between the professional group and certified registered nurse anesthetist about when the anesthesiologist should be called.[79,80]

Many controlling authorities (e.g., state statutes or hospital bylaws) require physicians to participate in certain aspects of anesthesia care when supervising certified registered nurse anesthetists. It is also the responsibility of the professional association to set forth the expectations in a manner that is consistent with law and regulations. Accepting a standard below medically communicated published standards (such as American Society of Anesthesiologists guidelines) risks liability.

Federal regulations for accreditation of hospital and ambulatory surgery facilities require that a certified registered nurse anesthetist be supervised by the physician performing the procedure or an immediately available anesthesiologist.[81,82] State governors may "opt out" of this supervision requirement if they deem doing so to be in the best interests of their citizens. For the opt-out to have practical consequences, however, state laws must also not require supervision. Health care facilities within states that have opted out may still require supervision. To bill for medically directing certified registered nurse anesthetists, anesthesiologists must participate in specific parts of the case.[83]

Anesthesiology professional associations may be held liable if they do not ensure that members are competent and that appropriate policies are followed.[84] Many agreements between professional associations and hospitals require service that complies with governmental and professional standards.[84] Obligations of professional associations may extend to letters of reference. For instance, an anesthesiologist was terminated with cause secondary to abuse of Demerol.[85] When the anesthesiologist went to a locum tenens company, letters of reference from shareholders of the previous professional association did not mention the abuse or that the anesthesiologist was fired with cause. Subsequent negligent care by this anesthesiologist caused severe brain damage to a patient. The court held that the previous professional association was liable for part of the financial award.

Professional associations are responsible for addressing physician impairment. An impaired physician is one who is unable to perform professional or personal responsibilities. Physicians impaired through alcohol and other addictive disorders are considered to have chronic medical illnesses. The Americans with Disabilities Act forbids discrimination against individuals who are in recovery[86] and government agencies from receiving funding if they engage in discrimination. The treatment records of the physician are confidential.

Legal Issues in Pain Management

Inadequate pain management is a health problem, and part of the problem may be due to the tension inherent in unclear regulations, regulatory scrutiny, and criminal investigation and prosecution by state medical boards and drug enforcement agencies (see Chapters 58 and 87).[87,88] For example, the Drug Enforcement Administration's ability to electronically monitor prescriptions for controlled substances gives them access to physicians' prescription histories. Physicians are concerned that knowledge of prescribing practices, divorced from patient-specific context, will lead to misunderstandings and unwarranted investigations. Physicians' concern about being investigated may affect the doses, quantities, number of refills, or even the type of drug used in the care of chronic pain patients.[88] The Drug Enforcement Administration suggests that there should be no effect and has emphasized that only 0.06% of all physicians had investigations initiated, 0.05% of all physicians had actions taken against them, and 0.01% of all physicians were arrested.[89] However, the 0.06% may be fallaciously low because that percentage is out of all practicing physicians. A more relevant percentage would be based on a population of only physicians who prescribe narcotics for pain control and thus are at risk for investigation. A large percentage of the physicians investigated did have actions taken against them.

The *Gonzales v Oregon* decision should comfort physicians because it limits the effects of the Drug Enforcement Administration on physicians.[90] *Gonzales v Oregon* prohibited the U.S. Attorney General from prohibiting physicians in Oregon from prescribing schedule 2 drugs for terminally ill patients to commit suicide.[90] The point of the case is that Congress can set national drug-prescribing rules through the Controlled Substances Act but cannot affect the ability of states to set medical practice standards.[4] The case turns on the Controlled Substances Act. Although there were a number of reasons, the primary reason was that the Controlled Substances Act does not regulate the practice of medicine and, in fact, that the practice of medicine is to be regulated by the state.

Physicians have been held liable for inadequate pain control.[91,92] For example, an 85-year-old man was admitted to a medical center for 5 days in 1998 before his subsequent death several days later.[91] He received inadequate pain control during

Table 10-3 Data Banks

Data Bank	Purpose	Information	Who Can Query
National Practitioner Data Bank (NDPB)[93]	"To restrict the ability of incompetent physicians to move from State to State without disclosure or discovery of the physician's previous damaging or incompetent performance."[93]	Medical malpractice payments Adverse actions: licensing, clinical privileges, professional society, Medicare and Medicaid exclusions, and U.S. Drug Enforcement Administration actions	Hospitals Health care entities with a review process Professional societies State licensing boards Plaintiff attorneys or plaintiffs Self-query
Healthcare Integrity and Protection Data Bank (HIPDB)[94] Established by federal statute	To stop fraud and abuse in health insurance and health care delivery and to promote quality care	Licensing and certification Civil judgments Criminal convictions Exclusions from federal or state health programs	Government agencies Health plans Self-query Researchers
Federation of State Medical Boards (FSMB)[95]	"Continual improvement in the quality, safety and integrity of health care through the development and promotion of high standards for physician licensure and practice."[95]	Records actions by state medical boards against physicians	Medical boards Individuals

his admission. Although a medical malpractice suit was dismissed and the state medical board did not pursue any action against the physician, the family won a civil suit against the physician under the California's Elder Abuse and Adult Civil Protection Act.

Data Banks

Federal databases are designed to improve health care by tracking performance and flagging suspect health care practitioners and entities (Table 10-3).[93-95] By way of context, from 1991 to 2004, the National Practitioner Data Bank recorded 276,274 medical malpractice payments, 8297 of which were related to anesthesia. Over this time, the number of cases with payments has decreased, whereas the median payment has increased.[96]

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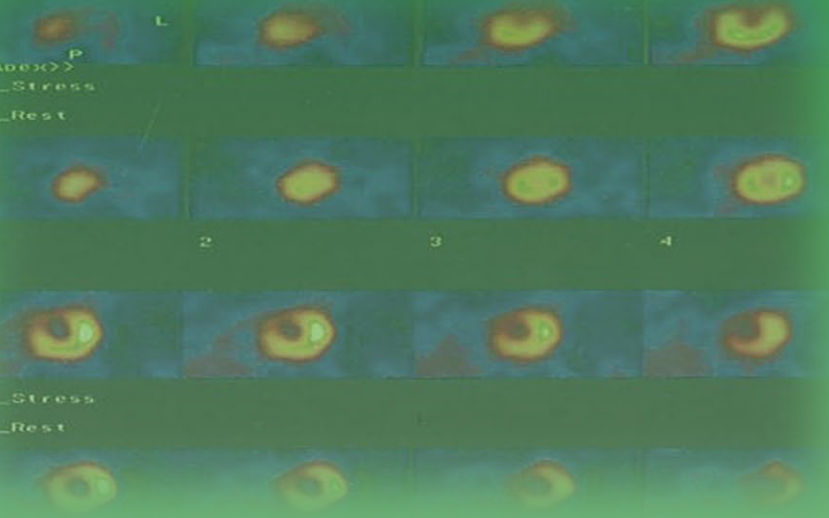
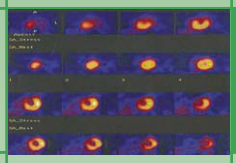


Anesthetic Physiology

Section II



Max B. Kelz, George A. Mashour, Ted G. Abel, and Mervyn Maze

11 Sleep, Memory, and Consciousness

Key Points

1. Sleep is an active process generated in the brain.
2. Structures in the brainstem, diencephalon, and basal forebrain control the sleep-wake cycle and are directly modulated by general anesthetics.
3. Sleep and anesthesia are similar states with distinct traits, with each satisfying neurobiologic features of the other.
4. Distinct memory functions are subserved by distinct neural structures.
5. Limbic system structures such as the hippocampus and amygdala are critical for memory and play a role in anesthetic-induced amnesia.
6. Although brainstem, diencephalon, and basal forebrain structures generate wakefulness, the contents of consciousness are thought to be generated by the cortex.
7. Multiple neural correlates of consciousness are thought to be the targets of general anesthetics.
8. Consciousness and subsequent explicit recall of intraoperative events—known as "awareness during general anesthesia"—occur in 1 to 2 cases per 1000.
9. Monitoring anesthetic depth has evolved to electroencephalographic methods, although limitations still exist.

Within 10 years of Morton's public demonstration of general anesthesia, ether, nitrous oxide, and chloroform were all in widespread use. The existence of three agents with diverse chemical structures led Claude Bernard in 1875 to speculate that the state of general anesthesia must arise through a common mechanism of action. Although decades of research have demonstrated multiple, nonoverlapping molecular targets for individual anesthetics (see Chapters 20 and 26) and appear to refute Bernard's hypothesis, a unitary network theory of anesthetic action remains possible from a systems perspective.

Traditionally, the state of general anesthesia is divided into various behavioral end points, including amnesia, hypnosis (defined as a lack of perceptive awareness to non-noxious stimuli), analgesia, immobility, and blunting of autonomic reflexes. These end points are produced by specific interactions of general anesthetics on discrete neuronal loci. Although volatile anesthetics come closest to being complete and thus capable of producing each of the components of the anesthetized state, the majority of anesthetic drugs fail to satisfy all criteria.

Nonetheless, diverse anesthetics acting at distinct receptor targets might produce common neurophysiologic adaptations in relevant circuits culminating in the behavioral end points that are recognizable as general anesthesia. This chapter considers two distinct anesthetic end points, hypnosis and amnesia. Using sleep as a paradigm to understand the system's neuroscience of control of the arousal state, the first section explores behavioral state transitions, as well as the effects of anesthetics on these circuits. The second section describes the neurophysiology and neurobiology of memory formation and concludes with a discussion of their modulation by anesthetics. Finally, in the last section we address the emerging science of consciousness and discuss how anesthetics reversibly alter its expression.

Neuronal Systems That Regulate Arousal States

Exquisite regulation of the arousal state confers a survival advantage. Predators who fall asleep during the chase may starve, whereas prey caught napping at inopportune times suffer an equally dire fate. Thus, the need to regulate the arousal state seems obvious for all. However, the requirement for sleep in the first place remains mysterious. Prolonged loss of sleep leads to impaired thermoregulation, metabolism, and immune function and, ultimately, to death.[1] Given the tremendous cost of sleep in terms of opportunity—time that might otherwise be spent seeking food or shelter or procreating—one might presume that it offers some as yet unclear selective advantage in an evolutionary sense.[2]

Recent hypotheses about the beneficial effects of sleep include restoration of the neuronal homeostasis essential for

synaptic function, consolidation of memories, and initiation and expression of neuronal plasticity (reviewed elsewhere[3-5]).

Whatever its true role, evolution has exerted a selective pressure on organisms to sleep (Table 11-1). Molecular, neuronal, and behavioral conservation of sleep implies that it also carried a survival advantage in ancestral mammals. Hence, it should not be surprising that the neuronal underpinnings for control of arousal lie in subcortical structures deep within the brainstem, thalamus, and hypothalamus in regions where they are conserved across the animal kingdom.

Table 11-1 Sleep Phylogeny—Hours Spent in Each Arousal State

Species	Waking	NREM	REM
Human	16	6	2
Guinea baboon	14.5	8.5	1
Sheep	18.1	5.3	0.6
Horse	20.5	2.5	0.5
Giraffe	19.5	4	0.5
Bottlenose dolphin	14	9.8	<0.2
Platypus	10	6	8
Thick-tailed opossum	6	11.4	6.6
Ferret	9.5	8.5	6
Cat	11	10	3
European hedgehog	13.9	6.6	3.5
Big brown bat	4.3	15.8	3.9
Armadillo	7	14	3
Rat	11	10.5	2.5

NREM, non–rapid eye movement; REM, rapid eye movement.
Data from McGinty DJ, Sterman MB: Sleep suppression after basal forebrain lesions in the cat. Science 160:1253, 1968; and Siegel JM: The REM sleep-memory consolidation hypothesis. Science 294:1058, 2001.

Passive versus Active Theories of Sleep

The discovery on which the neurobiology of control of the arousal state is built belonged to Frederic Bremer (1892-1982). In 1935, Bremer demonstrated that transection of the caudal medulla, although producing paralysis requiring mechanical ventilation, also produced an animal that remained alert, with normal sleep-wake cycles. Conversely, transection through the mesencephalon, immediately caudal to the nucleus of the third cranial nerve, yielded an animal that breathed spontaneously but was unresponsive and displayed a continuous sleep pattern in its electroencephalogram (EEG) (Fig. 11-1). Bremer's discovery formed the foundation for the passive theory of sleep. However, passive notions of sleep predate Bremer. The roots for this idea exist in the surviving sixth century BC writings of the Greek philosopher Alcemaeon and were known to Aristotle, who expounded on them in his treatise *De Somno et Vigilia* ("On Sleep and Waking"). Bremer's experimental evidence lent credence to the ancient Greek idea that sleep is caused by isolation of the brain from the rest of the body. Bremer hypothesized that sleep results anytime that the brain is deprived of its tonic sensory input. Under this passive view, sleep was nothing more than a default state produced by cessation of the active state—waking. A student of Bremer's, Giuseppe Moruzzi (1910-1986), fortified his mentor's hypothesis in collaboration with the physiologist Horace Magoun (1907-1991). Using electrical stimulation of the brainstem reticular formation (which falls in between Bremer's mesencephalic and caudal medullary lesion sites), Moruzzi and Magoun stimulated wakefulness while suppressing sleep and in so doing made the first description of the ascending reticular activating system.[6] Together, they also narrowed the window for inducing a persist-

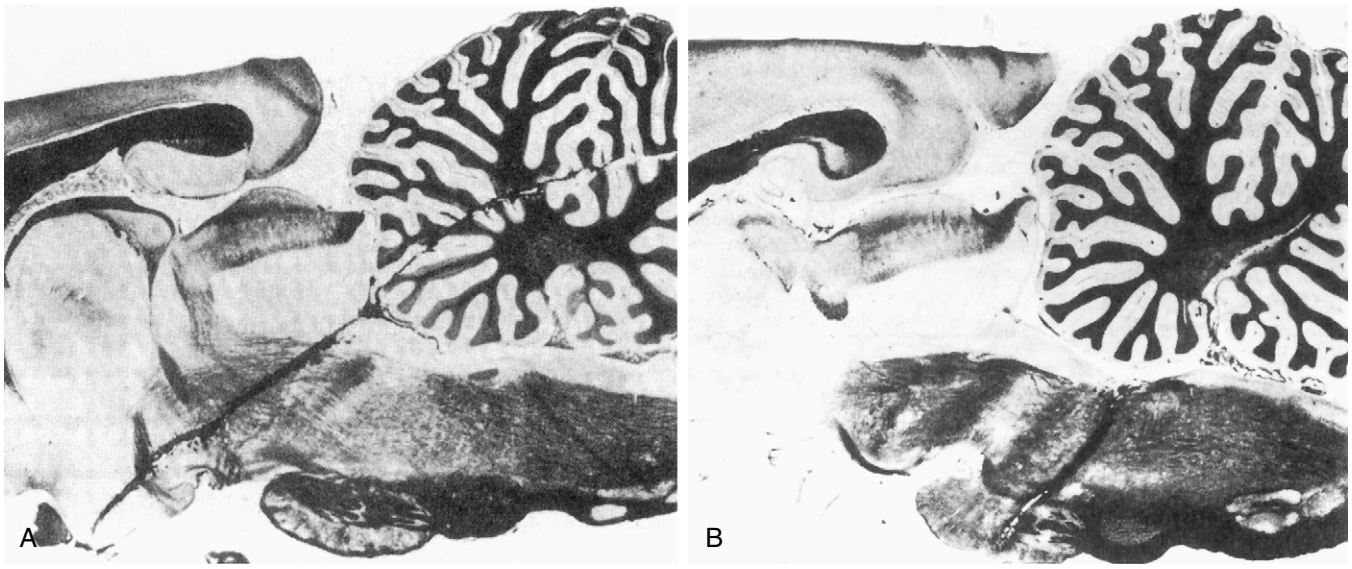


Figure 11-1 Brainstem transections may radically alter the state of arousal. **A,** Bremer's cerveau isole cat in which transection at the collicular level prevents brainstem and hypothalamic arousal-promoting signals from reaching the forebrain, thereby producing a state of deep coma. **B,** This contrasts with the enephale isole cat, in which transection through the caudal medulla disrupts spontaneous ventilation but leaves control of the arousal state intact. *(Modified from Steriade M, Constantinescu E, Apostol V: Correlations between alterations of the cortical transaminase activity and EEG patterns of sleep and wakefulness induced by brain-stem transections. Brain Res 13:177-180, 1969.)*

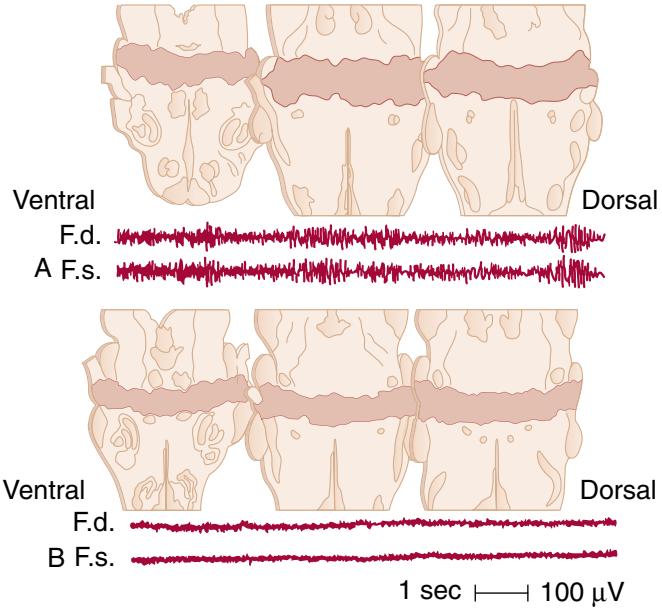


Figure 11-2 Schematic horizontal sections through the cat's brainstem depicting the production of a comatose state resembling continuous sleep in the cat that is immensely similar, if not identical to, the results of barbiturate-induced hypnosis. **A,** Midpontine pretrigeminal lesions that ablate the laterodorsal tegmental (LDT) and pedunculopontine tegmental (PPT) cholinergic neuronal projections to the thalamus and basal forebrain and produce continuous slow-frequency, large-amplitude patterns characteristic of sleep on the electroencephalogram (EEG) in both the right (F.d.) and left (F.s.) frontal EEG leads. **B,** Transections several millimeters more caudad through the rostral pons spare brainstem cholinergic neurons and their projections and lead to preservation of arousal as typified by the fast-frequency low-amplitude patterns on the EEG that characterize normal wakefulness. *(Modified from Batini C, Moruzzi G, Palestini M, et al: Persistent patterns of wakefulness in the pretrigeminal midpontine preparation. Science 128:30-32, 1958.)*

ent state of sleep by demonstrating that lesions through the midpontine pretrigeminal area of the cat did not affect the cyclic nature of control of the arousal state but confirmed that a lesion only a few millimeters more cephalad through the rostral pons at the level of the inferior colliculus produced the identical comatose syndrome as Bremer's (Fig. 11-2).

Nathaniel Kleitman (1895-1999) was another early proponent of the passive theory of sleep genesis. Among his important discoveries was recognition of the paradoxical stage of sleep, termed rapid eye movement (REM) sleep. This state differed dramatically from slow-wave or non-REM (NREM) sleep, as discussed later. For all his careful observations of sleep stages, however, Kleitman pointed out that it was the genesis of wakefulness that required explanation. Before leaving Bremer and the concept of passive sleep, we should return to his studies of the *cerveau isole* cat, in which a mesencephalic lesion deprives the forebrain of all sensory input (save olfactory and visual stimuli, which are carried by cranial nerves I and II). Bremer's insights have direct relevance for anesthetic action. In fact, Bremer's original description of the cerveau isole cat likened the resulting state as being immensely similar, if not identical to barbiturate anesthesia, as well as to natural sleep,[7] a concept to which we shall return in this chapter.

An alternative theory accounting for sleep requires its active genesis. According to the active sleep hypothesis, sleep is generated when specific neuronal systems increase their firing rates and thus inhibit the output of other neuronal structures required for wakefulness. Evidence for an active genesis of sleep has accumulated. During World War I, an outbreak of viral encephalitis reached pandemic proportions. Although many survivors experienced symptoms of profound and prolonged sleepiness (hypersomnolence), a smaller subset of survivors exhibited profound and prolonged insomnia. Based on postmortem neuropathologic observations and correlations with the premortem clinical condition, Baron Constantine von Economo (1876-1931) astutely noticed that the insomniacs had sustained damage within the anterior hypothalamus around the preoptic area, as well as damage to the basal forebrain. Those exhibiting hypersomnolence had sustained posterior hypothalamic damage. von Economo correctly predicted the existence of a sleep-promoting region of brain within the anterior hypothalamus near the optic chiasm, in addition to a wake-promoting region in the posterior hypothalamus.[8] His predictions made more than three quarters of a century ago have withstood the scrutiny of time. Experimental evidence for a hypnogenic center in the preoptic area of the hypothalamus was confirmed in rats and cats inasmuch as insomnia also resulted after lesions to the preoptic area,[9,10] as well as after bilateral microinjection of muscimol, a γ-aminobutyric acid (GABA) agonist, into the preoptic area.[11] Finally, the discovery of a population of inhibitory GABAergic neurons whose activity displays state-dependent firing patterns,[12] with the highest discharge rates occurring during sleep[13] and whose efferent projections inhibit wake-promoting centers (reviewed by Saper and colleagues[14]), fulfills all the criteria for the active generation of sleep.

Although controversy between active and passive mechanisms of the genesis of sleep still remains, these modes need not be mutually exclusive. As we discuss later, the hypnogenic neural substrates that promote sleep antagonize the wake-promoting regions in brain. In the absence of neuropathology, synchronized communication between these sleep- and wake-active neural populations ensures smooth and appropriately timed transitions between arousal states.[15]

Physiologic Patterns of Wakefulness and Sleep

The states of sleep and wakefulness may be characterized physiologically by recording the EEG and electromyogram (EMG). Wakefulness is identified by a fast-frequency, low-amplitude rhythm on the EEG that is "desynchronized," together with the presence of maximal motor activity on the EMG (Fig. 11-3). Broadly speaking, sleep may be subdivided into two distinct patterns, REM sleep and NREM sleep, which is also known as slow-wave sleep. During NREM sleep, the EEG displays large-amplitude, slow frequencies in the δ range of 0.5 to 4 Hz that dominate the power spectrum. Motor tone is lower during NREM sleep than during wakefulness (Fig. 11-3). NREM sleep patterns contrast dramatically with wakefulness, in which the EEG is desynchronized and exhibits low-amplitude, fast frequencies. During REM sleep, the EEG is also desynchronized and is virtually indistinguishable from wakefulness. However, as opposed to wakefulness, EMG activity during REM sleep is minimal to

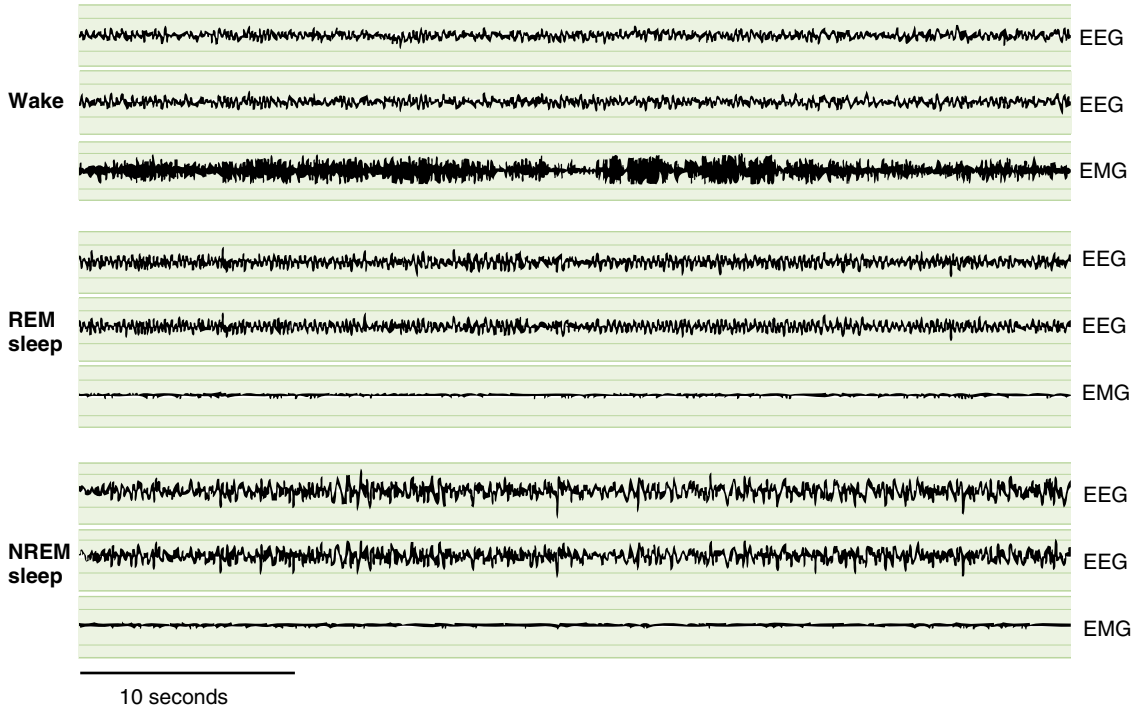


Figure 11-3 Cortical manifestation of wakefulness, rapid eye movement (REM) sleep, and non-REM (NREM) sleep with corresponding muscle tone. Wakefulness is defined by a desynchronized, low-amplitude, fast-frequency electroencephalogram (EEG) with prominent muscle activity. REM sleep shows similar signs of cortical activation with a desynchronized, low-amplitude, fast-frequency EEG in which θ rhythms of 4 to 8 Hz dominate the power spectrum. However, unlike wakefulness, motor activity is minimal in this state. NREM sleep has an EEG appearance that is markedly different from the other two states. During NREM sleep, the EEG displays slow-frequency, large-amplitude oscillations. Motor tone during NREM is dramatically reduced. *(Courtesy of Yihan Chen, University of Pennsylvania, unpublished results.)*

absent. The presence of θ activity (4 to 8 Hz) is also an abundant feature of REM sleep, as is eye movement, which may be recorded with an electro-oculogram (EOG) (for review see Harris[16]).

Wakefulness

Protecting the neural systems responsible for generating wakefulness is so fundamental to survival that evolution has distributed its expression across multiple and partially redundant systems, each contributing in a unique, but nonessential, way to promotion and maintenance of wakefulness. Specific centers in the brain alter their electrical output in proportion to the organism's arousal state. Among these regions, noradrenergic neurons of the locus ceruleus (LC), histaminergic neurons of the tuberomammillary nucleus (TMN), serotonergic neurons of the dorsal and median raphe nuclei (RN), and the newly recognized population of dopaminergic neurons in the ventral periaqueductal gray (vPAG) matter[17] are all monoaminergic centers that display arousal state–dependent firing patterns (Fig. 11-4) (for review see Jones[18]). Their highest discharge rates occur during wakefulness, decrease during NREM sleep, and become virtually quiescent during REM sleep. This pattern contrasts with that of brainstem and basal forebrain cholinergic neurons, which are most active during both wakefulness and REM sleep but decrease their output during NREM sleep, as discussed later. Neurons containing the wake-promoting and wake-sustaining neuropeptide orexin (also known as hypocretin) share similarities with other monoaminergic systems. Although confined to the posterior, lateral, and dorsomedial hypothalamus, orexinergic neurons also innervate the entire neuroaxis of the central nervous system (CNS) from forebrain through the spinal cord. These neurons exhibit maximal activity during wakefulness, reduce their firing during NREM sleep, and become quiescent during REM.[19,20] The orexinergic population positively reinforces wakefulness by stimulating activity in the monoaminergic centers just mentioned. In all mammals studied to date, including humans, impaired orexin signaling causes narcolepsy, a primary disorder affecting the organization of sleep and wakefulness. Although narcoleptics show behavioral state instability and transition to and from sleep at inopportune times, the total amount of sleep and wakefulness remains unchanged. Consistent with this notion, isolated lesion studies in animal models along with pharmacologic and gene knockout experiments have demonstrated that no single monoaminergic, cholinergic, glutamatergic, or orexinergic wake-active center is absolutely required for wakefulness.[21]

Nonetheless, Bremer, Moruzzi, and Magoun demonstrated that complete disruption of the brainstem reticular core, including the laterodorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT), precludes wakefulness. The cholinergic LDT and PPT, the noradrenergic LC, the dopaminergic vPAG, and the serotonergic RN are stimulated by afferent sensory input. Together, these systems ascend through two pathways to stimulate cortical activity and expression of wakefulness (Fig. 11-5). Dorsal fibers synapse in the thalamus, where their input is relayed indirectly to the cortex via glutamatergic thalamocortical afferents. Ventral fibers synapse in the posterior hypothalamus and basal forebrain while communicating with the histaminergic TMN and cholinergic basal forebrain centers on their way to the cortex. Finally, noradrenergic LC and serotonergic RN neurons send afferent input directly to the cortex. Although brainstem and hypothalamic activity modulates wakefulness, the cerebral cortex itself

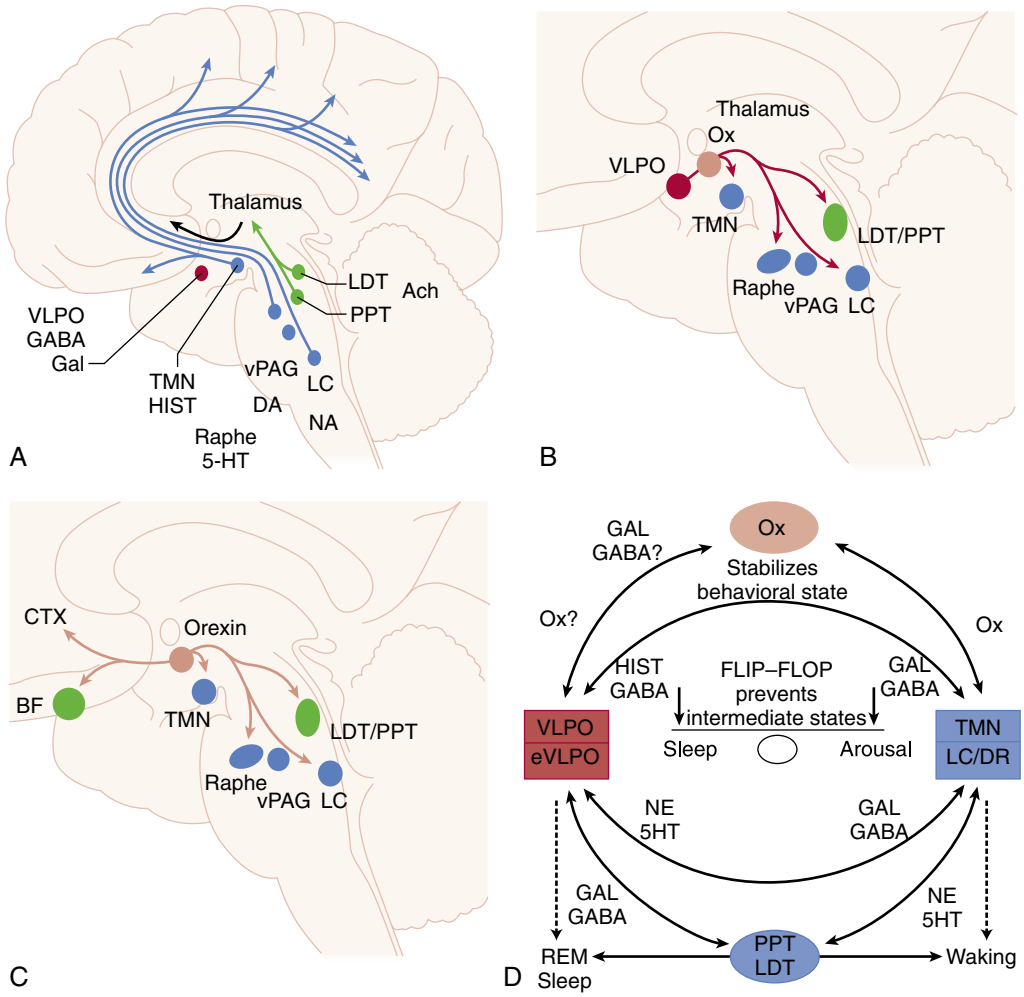


Figure 11-4 Brainstem and hypothalamic regulation of the arousal state. **A,** The ascending arousal system originates in the brainstem and posterior hypothalamus but sends projections throughout the entire central nervous system. Cholinergic neurons of the laterodorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT) project to many forebrain targets, including the thalamus, and are shown in *blue*. Monoaminergic centers (shown in *green*) diffusely project throughout the forebrain and modulate hypothalamic nuclei directly. These wake-active regions include histaminergic neurons of the tuberomammillary nucleus (TMN), serotonergic neurons of the dorsal and median raphe nuclei (Raphe), dopaminergic (DA) neurons of the ventral periaqueductal gray (vPAG) matter, and noradrenergic (NA) neurons of the locus ceruleus (LC). Shown in *red* are the sleep-promoting neurons of the ventrolateral preoptic (VLPO) nucleus, which contain the inhibitory neurotransmitters γ-aminobutyric acid and galanin. **B,** Inhibitory projections from the VLPO antagonize activity in the ascending arousal centers. **C,** Orexinergic (ORX) neurons are confined to the posterior and lateral hypothalamus, yet also communicate with all known arousal centers to promote and reinforce stability of the awake state. **D,** A flip-flop model of control of the arousal state that leads to a bistable circuit in which the individual is predisposed to wakefulness or sleep but should not fluctuate between states of arousal. *(Modified from Saper CB, Chou TC, Scammell TE. The sleep switch: Hypothalamic control of sleep and wakefulness. Trends Neurosci 24:726-731, 2001.)*

contributes to self-awakening through its efferent projections to the thalamus and reticular formation.[22]

NREM Sleep

With a notable exception of the ventrolateral preoptic (VLPO) nucleus, overall electrical activity in most regions of brain is decreased during NREM sleep. This observation correlates with passive notions of sleep in which tonic wake-promoting input dissipates. During NREM sleep, monoaminergic, orexinergic, and cholinergic groups are inhibited by efferent signals emanating from the preoptic anterior hypothalamus, specifically, a cluster of neurons localized to the VLPO nucleus that use the inhibitory neurotransmitters GABA and galanin (see Fig. 11-4). VLPO neurons are sleep active and display increased firing rates and c-Fos immediate early gene expression during sleep.[13,23] Sleep-active VLPO neurons have an antagonistic relationship with wake-active centers such that VLPO activation inhibits firing in wake-active centers. Conversely, rapid firing of wake-active regions inhibits the VLPO nucleus. This network design leads to a bistable behavioral state of arousal favoring either sleep or wakefulness but not rapid transitions between the two. Not surprisingly, destruction of the VLPO nucleus with an excitatory amino acid lesion that destroys cell bodies while leaving fibers of passage intact causes insomnia.[24]

Although preoptic anterior hypothalamic VLPO neurons actively generate NREM sleep, neurons in the thalamus also alter their electrical activity patterns in critical ways during NREM sleep. Thalamic reticular and thalamocortical neurons begin to fire in bursts. This process generates sleep spindles evident on the EEG. Burst firing of thalamocortical neurons transiently causes deafferentation of the cortex by reversibly disconnecting it from sensory stimuli normally conveyed to the cortex from the

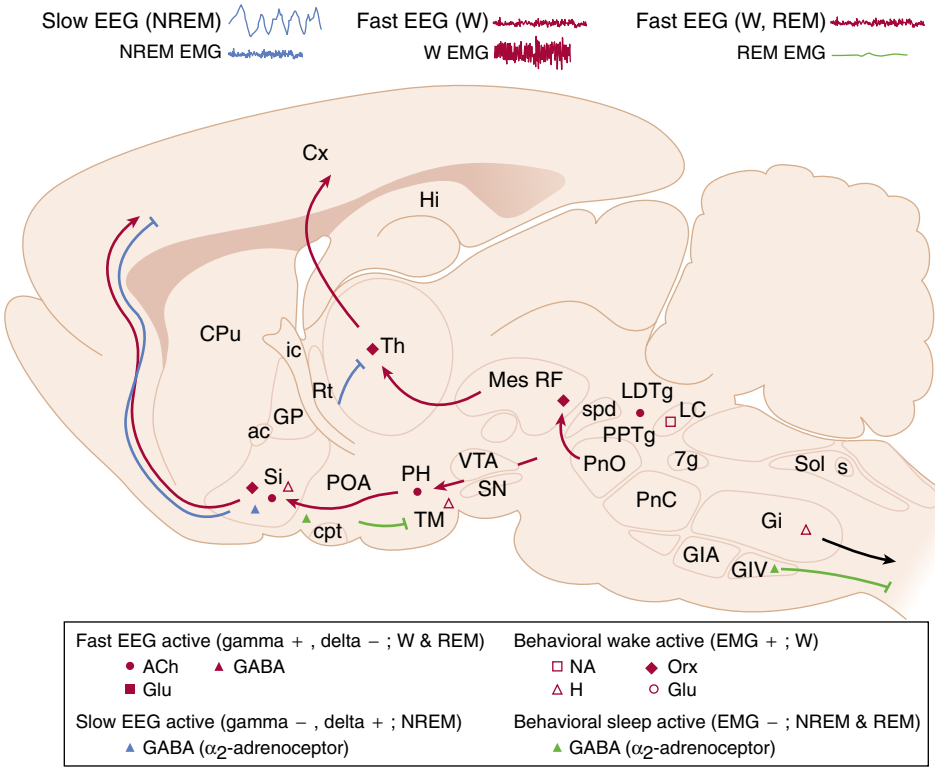


Figure 11-5 Schematic section through a rat brain depicting conserved sleep- and wake-promoting pathways and their corresponding neurotransmitter signaling systems. Neurons that are active during wakefulness (W) include those with ascending projections to the cortex that stimulate a fast-frequency desynchronized EEG (gamma+), along with descending projections to the spinal cord that stimulate the postural muscle tone required for waking behavior. Wake-active neurons display maximal activity during wakefulness, dramatically slow their firing during non–rapid eye movement (NREM) sleep, and become virtually quiescent during rapid eye movement (REM) sleep. Groups shown with *open pink symbols* include noradrenergic neurons (NA), histaminergic neurons (H), orexinergic neurons (Orx), and glutamatergic (Glu) neurons. Additional wake-active neurons shown by *filled pink symbols* are also active during REM sleep. These largely ascending systems include cholinergic (ACh), glutamatergic (Glu), and some γ-aminobutyric acid (GABA)-containing neurons. Sleep-active neurons (*blue* and *green symbols*) include cells whose cortical ascending projections dampen fast cortical activity and those with descending projections to the spinal cord and brainstem, which diminish behavioral arousal and muscle tone. The sleep-active neurons discharge in association with slow EEG activity (gamma–/delta+) during NREM sleep (*blue triangle*) and include some GABAergic neurons in the basal forebrain and preoptic area (POA) that bear α_2-adrenoceptors and are inhibited by NA. Thalamic GABA-containing neurons of the nucleus reticularis discharge in bursts with sleep spindles and slow waves to inhibit and pace thalamocortical relay neurons. In the basal forebrain and preoptic area, α_2-adrenoreceptor–expressing GABAergic neurons with descending projections increase their firing rates as muscle tone decreases (EMG–) during NREM and REM sleep (*green symbols*). Finally, additional GABAergic (and/or possibly glycinergic) neurons of the medulla descend directly into the spinal cord, where they might inhibit motor neurons during sleep. ac, anterior commissure; CPu, caudate putamen; Cx cortex; EEG, electroencephalogram; EMG, electromyogram; 7g, genu of the 7th nerve; Gi, gigantocellular RF; GiA, gigantocellular, alpha part of the RF; GiV, gigantocellular, ventral part of the RF; GP, globus pallidus; Hi, hippocampus; ic, internal capsule; LDTg, laterodorsal tegmental nucleus; Mes RF, mesencephalic RF; opt, optic tract; PH, posterior hypothalamus; PnC, pontine, caudal part of the RF; PnO, pontine oral part of the RF; POA, preoptic area; PPTg, pedunculopontine tegmental nucleus; RF, reticular formation; Rt, reticularis nucleus of the thalamus; s, solitary tract; scp, superior cerebellar peduncle; SI, substantia innominata; SN, substantia nigra; Sol, solitary tract nucleus; Th, thalamus; TM, tuberomammillary nucleus; VTA, ventral tegmental area. *(Modified from Jones BE: From waking to sleeping: Neuronal and chemical substrates. Trends Pharmacol Sci 26:578, 2005.)*

thalamus.[25] Deafferentation of the cortex by intrinsic thalamic activity is reminiscent of Bremer's lesion studies in which permanent deafferentation of the cortex formed the experimental basis of the passive nature of sleep. Together, VLPO and thalamic activity patterns provide mechanistic neuronal network explanations for the active and passive theories of sleep.

REM Sleep

Control of REM sleep is also regulated in the brain. Although several neuroanatomic centers participate in regulation and coordination of REM onset and offset, the main effector responsible for the generation of REM sleep resides in the pontine reticular formation. Transection studies by Michel Jouvet (1925-) in the cat further localized brainstem REM control within the pons to the nucleus pontis oralis (PnO), which appears to be necessary for REM expression. Direct injection of cholinergic agonists into the PnO (which is slightly rostral and just ventral to the LC) produces a state that mimics natural REM sleep.[26] The endogenous cholinergic tone in the brainstem arises from the LDT and PPT, two nuclei located at the junction between the pons and midbrain. Excitotoxic lesions that ablate the LDT and PPT dramatically impair REM sleep.[27] A subset of LDT and PPT neurons fire selectively during REM sleep, whereas other cholinergic LDT and PPT neurons fire during both REM sleep and wakefulness. Notably, the uniquely REM-active subset increases its firing rates prior to the EEG and behavioral features of REM expression,[28,29] thus suggesting that LDT and PPT cholinergic neuronal activity may initiate REM sleep (REM-on neurons). Neurons of the extended VLPO (eVLPO) nucleus also exhibit preferential activation during REM sleep. Because the eVLPO nucleus communicates directly with brainstem cholinergic LDT neurons along with monoaminergic neurons of the LC and RN and because lesions

of the eVLPO nucleus reduce the amount of REM sleep, the eVLPO nucleus appears to play a special role in generation of REM sleep.[30]

The behavioral constellation of REM sleep is dissociable into various components, each with its own specific mechanisms and neuroanatomic controllers. The cardinal signs of REM sleep include rapid eye movement, atonia of all motor groups except for the diaphragm, and activation of a low-voltage, fast-frequency EEG rhythm. Subcortical recordings demonstrate ponto-geniculo-occipital (PGO) waves. This characteristic spiky EEG pattern of REM sleep originates in the pons, is transmitted to the thalamic lateral geniculate, and terminates in the occipital cortex. The REM- and wake-active population of LDT and PPT neurons with rostral projections is important for production of the desynchronized fast-frequency, low-amplitude EEG found in both wakefulness and REM sleep.[26] REM atonia is initiated by a group of pontine reticular neurons that synapse in the bulbar reticular formation before terminating their signal on spinal cord motor neurons. The subset of pontine reticular formation neurons initiating atonia is a non-noradrenergic population of neurons adjacent to the LC, termed either the perilocus ceruleus alpha or subceruleus (SubC) in cats or the sublateral dorsal (SLD) nucleus in rodents.[31,32]

Exit from REM sleep transitions into either NREM sleep or wakefulness and is triggered by "REM-off" groups. The observation that noradrenergic LC neurons decrease their firing rate during NREM sleep and become virtually quiescent during REM sleep, together with pharmacologic and lesion studies, had suggested that inhibition of the LC was a requirement for entry into REM sleep and that LC neurons might serve as REM-off cells. However, genetic studies in noradrenergic-deficient mice have conclusively demonstrated the continued existence of normal, or nearly normal, REM sleep despite the absence of norepinephrine.[33,34] Thus, the adrenergic neurons of the LC cannot be an exclusive REM-off population. Neurons of the ventrolateral periaqueductal gray (vlPAG) matter also serve to terminate REM episodes, as proved by pharmacologic studies during which muscimol inhibition of this region increases REM sleep and also by elegant immunohistochemical mapping combined with vlPAG lesions.[35-37] vlPAG neurons form a mutually antagonistic inhibitory loop with those of the SLD nucleus to efficiently generate or inhibit REM sleep.[35]

Somnogen-Induced Transitions Between Arousal States

Even though cortical EEG and EMG patterns and activity in the sleep- or wake-active centers in the brainstem, hypothalamus, and thalamus are well known during states of sleep or wakefulness, the mechanisms responsible for entry into or exit from a given state remain mysterious. The humoral theory of sleep regulation was independently proposed nearly 100 years ago by French and Japanese neuroscientists. Intrathecal infusion of cerebrospinal fluid (CSF) harvested from sleep-deprived dogs into rested normal dogs caused the recipient dogs to promptly fall asleep.[38,39] This result suggested the existence of an endogenous somnogen, a "hormone" circulating in the CSF whose accumulation could cause the onset of sleep. Over the past century, the list of potential somnogens has grown to include substances as diverse as proteins—δ sleep–inducing peptide (DSIP)[40]; lipids—*cis*-9,10-octadecenoamide[41]; hormones—melatonin; cytokines—interleukin-1; eicosanoids—prostaglandin D_2 (PGD_2); and a nucleoside—adenosine.[42] We shall review data for the latter two putative somnogens, which have been studied most extensively.

Infusion of femtomolar concentrations of PGD_2 into the third ventricle induces both NREM and REM sleep in rats that is indistinguishable from natural sleep.[43] PGD_2 levels fluctuate in the CSF, with circadian frequency paralleling sleep-wake cycles. Sleep deprivation proportionally elevates CSF PGD_2 levels, thus also supporting a role for PGD_2 as an endogenous somnogen. PGD_2 is synthesized by the enzyme prostaglandin D synthetase, which is localized in the arachnoid membrane and choroids plexus (Fig. 11-6), and is secreted directly into CSF, where it is the second most abundant protein. Microdialysis studies confirm a specific sleep-promoting activity of picomolar quantities of PGD_2. However, this somnogenic activity is present only when PGD_2 is infused in the vicinity of the preoptic area of the hypothalamus. The most pronounced activity of PGD_2 is observed when it is

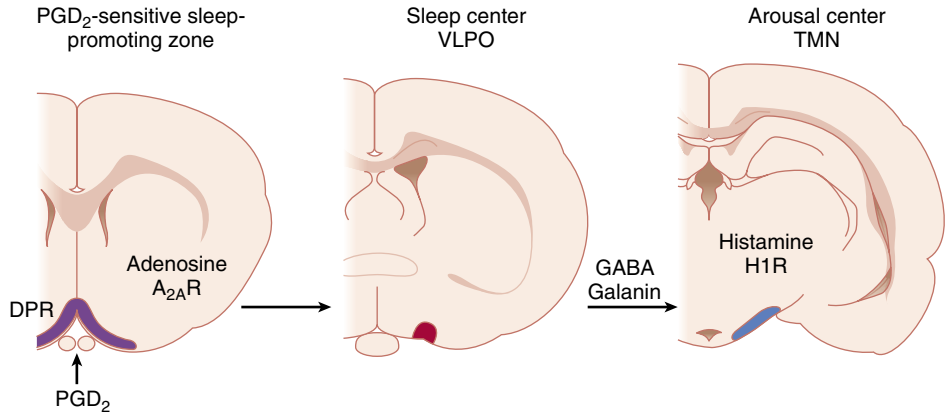


Figure 11-6 Molecular mechanisms of sleep promotion by the endogenous somnogen prostaglandin D_2 (PGD_2). The prostaglandin D_2 receptor (DPR) lines the ventral surface of the basal forebrain and preoptic area (*purple area*). The DPR is thought to transmit the somnogenic PGD_2 signal from cerebrospinal fluid to the ventrolateral preoptic nucleus (VLPO, shown in *red*), with adenosine being used as a signaling molecule. This signal transduction event activates VLPO neurons via the adenosine A_{2A} receptor, which leads to inhibition of wake-active histaminergic groups such as the tuberomammillary nucleus (TMN, shown in *blue*). *(Modified from Hayaishi O, Urade Y: Prostaglandin D_2 in sleep-wake regulation: Recent progress and perspectives. Neuroscientist 8:12, 2002.)*

infused beneath the VLPO nucleus. Infusion of a PGD_2 antagonist into the third ventricle reversibly and dose-dependently inhibits both REM and NREM sleep (for review see Hayaishi and Urade[43]). On binding to the D-type prostanoid receptor (DPR), which is localized to the arachnoid membrane lining the ventral surface of the brain, the somnogenic signal of PGD_2 appears to be transduced indirectly by activation of the VLPO nucleus.[44] The mechanism for VLPO activation after subarachnoid infusion of PGD_2 appears to require adenosine because coadministration of an adenosine receptor A_{2a} antagonist blocks the somnogenic activity of PGD_2. Conversely, administration of an adenosine A_{2a} agonist mimics the somnogenic activity of PGD_2.[45] As adenosine levels accumulate, they activate A_{2a} receptor–expressing neurons to directly or indirectly activate the VLPO nucleus.[46] Hence, it appears that adenosine may function as the neurotransmitter that couples the humoral to the neural mechanisms driving sleep-wake regulation. With this model the homeostatic drive to sleep accumulates proportionally to increases in the endogenous somnogens PGD_2 and adenosine. The existence of such somnogenic substances that accumulate with time argues for active rather than passive generation of sleep.

Anesthesia and Sleep

Anesthesia is a state that shares phenotypic similarities with sleep, and hence the metaphor of "going to sleep" is commonly used to describe induction of general anesthesia in the clinical setting.[47] Not only are anesthesia and sleep similar states, but they also share common neurobiologic traits[48]; indeed, the hypnotic component of anesthesia may result from specific actions of anesthetics on the neural systems that regulate natural sleep. Support for this hypothesis comes from a variety of studies. During sleep and general anesthesia, there is reduced responsiveness to external stimuli. Functional brain imaging during anesthetic-induced unconsciousness has been shown to inhibit thalamic and midbrain reticular formation nuclei.[49] Anesthetic blockade of thalamic information transfer, which disrupts somatosensory input from reaching higher cortical centers, has also been confirmed with more direct microelectrode recordings.[50,51] In both instances, these anesthetic effects on the thalamus resemble the naturally occurring thalamocortical inhibition characteristic of NREM sleep.[25]

Sleep Deprivation

Sleep deprivation potentiates the hypnotic action of anesthetics, including propofol and isoflurane.[52] Moreover, the sleep debt that would otherwise ensue after sleep deprivation dissipates during propofol anesthesia; however, it remains unknown whether other features of sleep deprivation (for example, on immune function) might also be ameliorated by hypnotic doses of propofol.[53] The bispectral index monitor, designed to track the depth of anesthetic-induced hypnosis, also appears to be useful in recording the onset and depth of sleep.[54]

Endogenous Somnogens and Anesthetics

Infusion of adenosine in low doses potentiates the hypnotic actions of intravenous and volatile anesthetics, thereby reducing the amount of anesthetic required to achieve a given depth of anesthesia. This effect is reproduced by 2-chloroadenosine, a potent adenosine analog, and by dipyridamole, an adenosine uptake blocker and adenosine deaminase inhibitor. Conversely, administration of theophylline, an adenosinergic antagonist, produces partial resistance to anesthesia.[55] Mechanistically, these data fit well with an effect of adenosine on activation of the hypothalamic sleep center, the VLPO nucleus (see later discussion). Meanwhile, exposure to anesthetics such as isoflurane affects the levels of endogenous somnogens, with isoflurane altering the balance between prostaglandin E_2, a wake-promoting prostaglandin, and PGD_2, a sleep-inducing prostaglandin, in the hypothalamus.[56]

Effects of Anesthetics on Sleep Circuits

Knowledge of the endogenous arousal systems is an essential prerequisite for any discussion of the mechanisms of action of psychostimulants, sedative-hypnotics, and general anesthetics. Predicted actions of anesthetics based on their known effects at individual cells expressing single recombinant neurotransmitter receptors, including GABAergic, glutamatergic, cholinergic, adrenergic, histaminergic, serotonergic, and orexinergic receptors or voltage-gated calcium, sodium, or potassium channels, allow the generation of testable hypotheses. However, anesthetics distribute throughout the entire brain (Fig. 11-7),[57] and because the majority of sleep- and wake-active nuclei send bidirectional signals that may be either mutually inhibitory, excitatory, or one

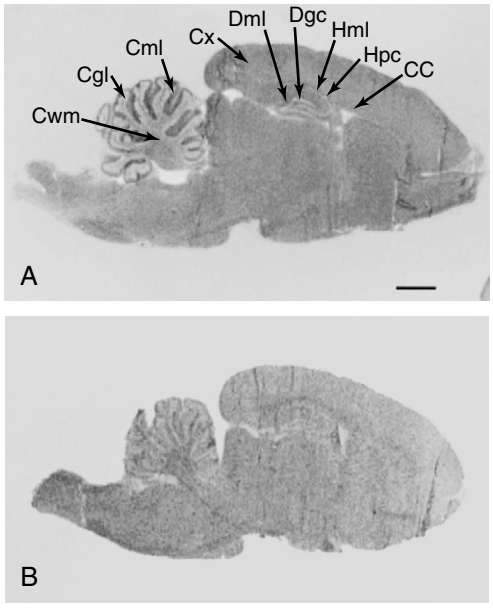


Figure 11-7 Distribution of specific halothane binding throughout the rat brain. **A,** This autoradiogram demonstrates nearly homogeneous binding of the volatile anesthetic halothane at 100 μM by direct photoaffinity labeling with ^{14}C-halothane. Some exceptions to nearly uniform uptake are shown in the cerebellar white matter (Cwm), cerebellar granular layer (Cgl), and subregions of the hippocampus. **B,** Specific binding is competitively inhibited by 2.3 mM nonradioactive halothane. CC, corpus callosum; Cml, cerebellar molecular layer; Cx, cortex; Dgc, dentate granule cell layer; Dml, dentate molecular layer; Hml, hippocampal molecular layer; Hpc, hippocampal pyramidal cell layer. *(Modified from Eckenhoff MF, Eckenhoff RG: Quantitative autoradiography of halothane binding in rat brain. J Pharmacol Exp Ther 285:371, 1998.)*

inhibitory in one direction with an excitatory return, the actual effects of anesthetics on net circuit output must be empirically tested because existing models do not account for all the complexity in the circuits.[58]

Thalamic Sites

The passive theories of sleep set forth by Bremer are similar to many passive concepts of general anesthesia. A central tenet of NREM sleep and anesthesia is that the cortex is deprived of sensory input. Whether by exogenous lesions, as in Bremer's cerveau isole cat, or by endogenous closing of thalamic gates, anesthetics appear to act on NREM sleep circuits, thereby leading to shared mechanisms of action. Within the thalamus, there is a simple architecture of cell types consisting of reticular neurons and thalamocortical neurons that communicate with the cortex while also integrating peripheral input (Fig. 11-8). Activation of the reticular neurons during NREM sleep and anesthesia causes hyperpolarization of thalamocortical relay neurons, which in turn blocks propagation of the action potential through thalamocortical relay neurons. As a result, thalamocortical neurons are prevented from relaying peripheral input to higher cortical centers. This is the mechanism by which the thalamic gates close to transiently, yet reversibly, sever the cortex from the periphery.[25,59,60] Midline thalamic nuclei are thought to play a critical role in generating conscious awareness and appropriately receiving afferent input from most reticular activating arousal-promoting centers.[21] Imaging studies confirm a regionally selective reduction in midline thalamic blood flow, metabolism, and by extension, activity.[49,61] Support for a thalamocortical consciousness switch has recently been strengthened by the finding that microinjection of nicotine into the centromedian nucleus of the thalamus reverses sevoflurane-induced hypnosis (discussed later). These conclusions are mitigated by the fact that administration of nicotine into the centromedian nucleus results in seizures. However, support for the central thalamus as an arousal center that is capable of reversing unconsciousness also comes from literature on the persistent vegetative state. High-frequency stimulation of the central thalamus in the rat has been associated with widespread cortical activation and enhanced cognitive function.[62] Furthermore, deep brain stimulation of the central thalamus has been shown to reverse some of the behavioral deficits in a patient suffering traumatic brain injury.[63]

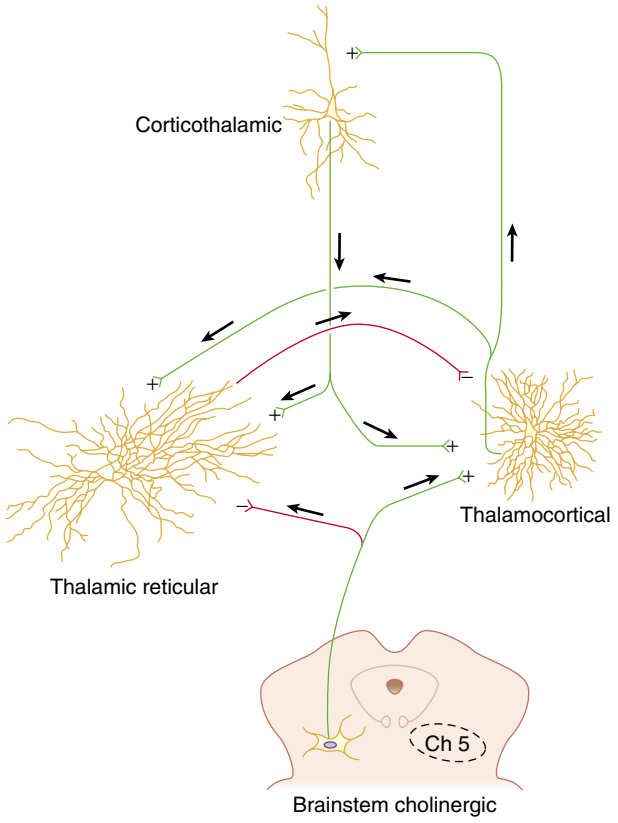


Figure 11-8 The transition from wakefulness to non–rapid eye movement (NREM) sleep is associated with characteristic changes on the electroencephalogram that correlate with underlying changes in the electrical firing patterns of corticothalamic systems. During NREM sleep, thalamocortical neurons are hyperpolarized by thalamic reticular neurons (upper *green* axon). This action prevents incoming peripheral signals from being relayed to corticothalamic neurons in the cortex and transiently, but effectively results in deafferentation of the cortex. Cholinergic input in the brainstem is able to simultaneously hyperpolarize thalamic reticular neurons while depolarizing thalamocortical neurons, thereby returning membrane potential in thalamocortical neurons to baseline and restoring the action potential propagation that transfers peripheral sensory input to corticothalamic neurons. Recent studies suggest that similar changes in the firing properties of corticothalamic loops may also underlie anesthetic-induced hypnosis. Excitatory connections are depicted in *red*, with *plus symbols* at the synapse. Inhibitory connections are displayed in *green*, with *minus signs* at the synapse. *(Modified from Steriade M: The corticothalamic system in sleep. Front Biosci 8:d878, 2003.)*

Because nicotinic acetylcholine receptors are heavily expressed in the thalamus and because many anesthetics inhibit signaling via nicotinic acetylcholine receptors, suppression of the cholinergic arousal system may be one mechanism through which many anesthetics produce unconsciousness.[64] Processed EEG measures of anesthetic depth also reveal an important role for the cholinergic arousal system inasmuch as intracerebroventricular infusions of neostigmine or the muscarinic agonist oxotremorine arouse isoflurane-anesthetized rats.[65]

Hypothalamic Sites

Thalamic nuclei receive input from the ascending brainstem reticular activating system via a dorsal pathway and also receive hypothalamic input from wake-active centers such as histaminergic and orexinergic neurons (see Fig. 11-5). As discussed earlier, the thalamic gates close during NREM sleep and exposure to several anesthetics, and this closure is facilitated by decreased input of monoaminergic, cholinergic, and orexinergic signals during anesthesia. GABAergic anesthetics such as propofol and barbiturates exert their hypnotic effects by inactivating histaminergic neurons of the TMN[66] (see Fig. 11-4). This action may be explained at the molecular level by potentiation of inhibitory GABAergic projection from the sleep center, the VLPO nucleus. Disinhibition of the VLPO nucleus, in turn, shuts down other wake-active groups and further reinforces VLPO activity. This feed-forward mechanism stabilizes the hypnotic state.[14] Blockade of the wake-promoting histaminergic signal is also the mechanism by which the antihistaminergic drug diphenhydramine precipitates sleep. Recovery or emergence from anesthetic hypnosis is facilitated by wake-promoting orexinergic neurons, which are inhibited by volatile anesthetics such as isoflurane and sevoflurane.[67]

Brainstem Sites

One finding that has emerged from studying the hypnotic properties of different anesthetic agents is that there is neither a unitary

molecular target nor an invariant neuronal site of action common to all anesthetics. This point is illustrated by dexmedetomidine, an α_2-adrenergic agonist. The behavioral hypnosis of dexmedetomidine results from the drug's ability to inactivate noradrenergic neurons of the LC (Fig. 11-4). This event disinhibits the VLPO nucleus, which subsequently inactivates other arousal centers via the VLPO's GABAergic and galaninergic inhibitory signaling, as discussed earlier.[68] As with propofol and barbiturates acting on the TMN, the common consequence of VLPO disinhibition is stabilization of the hypnotic state. Pharmacologic and lesion experiments that alter both monoaminergic reticular activating function and anesthetic sensitivity can now be reinterpreted in the framework of integrated arousal network activity. Depletion of CNS catecholamines, including norepinephrine, serotonin, dopamine, and histamine, produces hypersensitivity to anesthetics.[69] Conversely, pretreatment with a monamine oxidase inhibitor or acute exposure to amphetamine, both of which increase catecholamine levels in the brain, produces partial resistance to anesthetics.[70] Focusing once again on noradrenergic neurons of the LC, chemical depletion of norepinephrine with 6-hydroxydopamine[71] and electrolytic destruction of LC neurons[72] both produce hypersensitivity to anesthetics, probably by removing an inhibitory signal to the VLPO nucleus.

These pharmacologic treatments affect other monoaminergic systems in addition to the noradrenergic neurons. Moreover, the action of amphetamines or monoamine oxidase inhibitors on serotonergic or dopaminergic systems might also account for a portion of the anesthetic effects. In support of this concept, destruction of serotonergic RN neurons with the toxin 5,6-dihydroxytryptamine or direct electrolytic lesions of serotonergic RN neurons also cause hypersensitivity to anesthetics.[71,72] Once again, as with lesions of the LC, these actions may be interpreted in the light of partial VLPO disinhibition (see Fig. 11-4).

The discovery that pentobarbital and muscimol, a $GABA_A$ agonist, cause behavioral and EEG signs of hypnosis when microinjected into a discrete upper brainstem site, termed the mesopontine tegmentum (MPTA) in rats, has revealed yet another important anesthetic locus.[73] Neuroanatomic tracing studies have shown that MPTA neurons project to thalamic, hypothalamic, and brainstem sites traditionally recognized as part of the ascending reticular activating system. Like other known wake-active systems, MPTA neurons are spontaneously active during wakefulness and are thought to decrease their firing rates during NREM sleep and under anesthesia.[74] MPTA neurons also project to the septohippocampal system, thus providing a link to yet another anesthetic locus (see later).

Limbic System

Strong emotions such as fear, rage, and joy are accompanied by a heightened state of arousal. Hence, it should not be surprising that the limbic system, which responds to emotional content, connects to arousal circuits. Specifically, within the limbic system the medial septum and hippocampus also participate in modulating awareness. This knowledge of neuroanatomy helps explain how inhibition of the medial septum or hippocampus by local injection of muscimol decreases the doses of propofol and pentobarbital needed for hypnosis.[75] The role of limbic system structures such as the hippocampus and amygdala in memory function and anesthetic-mediated amnesia is discussed later.

Summary

Although once considered a passive process in which the cortex loses afferent input, sleep is now recognized as an actively generated state whose genesis depends on the integrated contribution of multiple neuronal input. Increased understanding of the relevant neuronal circuits controlling sleep and wakefulness has opened a series of investigations into anesthetic-induced hypnosis. These studies suggest that anesthetic-induced unconsciousness may arise in part from selective actions of our drugs on these critical nuclei. One basic principle that appears to tie all the neuroanatomic studies together is that inactivation of structures mediating normal arousal appears to enhance the effects of general anesthetic–induced hypnosis. Conversely, activation of these regions appears to produce partial resistance to anesthetic-induced hypnosis.

Memory

In this portion of the chapter we provide a discussion of the major themes in our understanding of memory as it has developed over the past 100 years. Three major themes are clear.[76] First, there are multiple memory systems that are subserved by specific brain regions and neural circuits. Second, there are multiple stages of memory that are mediated by distinct molecular mechanisms. Third, alterations in the strength of connections between neurons—termed *synaptic plasticity*—is a critical component of the way in which memories are stored in neural circuits. After investigating these three major themes of memory research, we describe the molecular mechanisms by which memories are stored and define potential mechanisms by which anesthetics might induce amnesia. Because the hippocampus and amygdala have been the focus of many studies of memory storage and because modulation of their function may underlie anesthetic-induced amnesia, our discussion will focus on these memory systems.

Over the centuries, memory has fascinated poets, philosophers, and scientists. Memory represents an experience-dependent change in behavior, and it is critical to our sense of self, as well as the development of human society and culture. Thus, it is not surprising that memory remained for centuries the domain of philosophers, many of whom speculated on what memory was and how it might be maintained over a lifetime. In *Theatetus*, Plato proposed that thoughts might be stamped into memory the way a signet ring makes an impression in wax. When he discussed a theory of cognition in *Timaeus*, Plato was among the first to suggest that the brain contains the higher, rational soul that controls our actions, but his idea was that this rational soul interacted with a lower, appetitive soul in the gut to form images on the surface of the liver.[77] Experimental work by scientists on memory had its origins in the 19th century when neurologists and psychiatrists such as Jackson, Ribot, and Alzheimer began to identify patients with memory deficits and psychologists such as Hebbinghaus, Müller, and Pilzecker began to define different types and stages of memory.[78] Importantly, the early clinical work on brain-lesioned patients placed memory into the hands of neuroscientists, who defined the importance of the brain in memory, in contrast to earlier proposals by philosophers, in which it was

suggested that memory was subserved by other organ systems. As this experimental and clinical work was being carried out on memory, anatomists such as Santiago Ramón y Cajal (1852-1934) were identifying the critical cellular components of the nervous system by using histologic stains to identify distinct classes of neurons and glia within the brain. Cajal's "Neuron Doctorine" led him to postulate that it would be these connections between neurons (later called synapses) that might mediate memory storage.[79] With the work of Ivan Pavlov (1849-1936) on the conditioned reflex, the field of memory began to be a central component of the growing field of psychology.[80]

Distinct Memory Systems Subserve Distinct Types of Memory

The field of memory research was revolutionized in the middle part of the 20th century by study of the patient H.M. by Wilder Graves Penfield (1891-1976), Brenda Milner (1918-), and others. Work in the first half of the 20th century that followed on the work of Pavlov had failed to define specific memory systems, as was suggested by the work of Jackson, Ribot, and Alzheimer and popularized by the phrenologist Joseph Gall. Karl Lashley, working at Harvard, suggested that memories might not be localized to specific brain regions inasmuch as his lesion studies in rodents failed to identify such specific circuits. Rather, Lashley proposed his laws of mass action and "equipotentiality," both based on the ideas that the entire cerebral cortex contributes to memory and that other brain regions can compensate for damage to a certain region of the brain.[81] The study of H.M. thus came in striking contrast to these conclusions of Lashley. At 27 years of age, H.M. underwent surgery to remove portions of his temporal lobe in an effort to treat intractable epilepsy that had developed after a childhood accident. As became clear some 40 years later when H.M.'s brain was studied by magnetic resonance imaging techniques, his neurosurgeon Wilder Penfield had removed the bulk of his hippocampus bilaterally and portions of his amygdala[82] (Fig. 11-9). Thus, it is no surprise that H.M. had severe anterograde memory deficits in the ability to acquire new memories.

Neuropsychological evaluation by Brenda Milner and others revealed two surprising aspects of the amnesia that followed H.M.'s surgery.[76,83] First, he also exhibited retrograde amnesia—that is, certain memories of events before his surgery were lost. As this retrograde amnesia was probed in more detail,

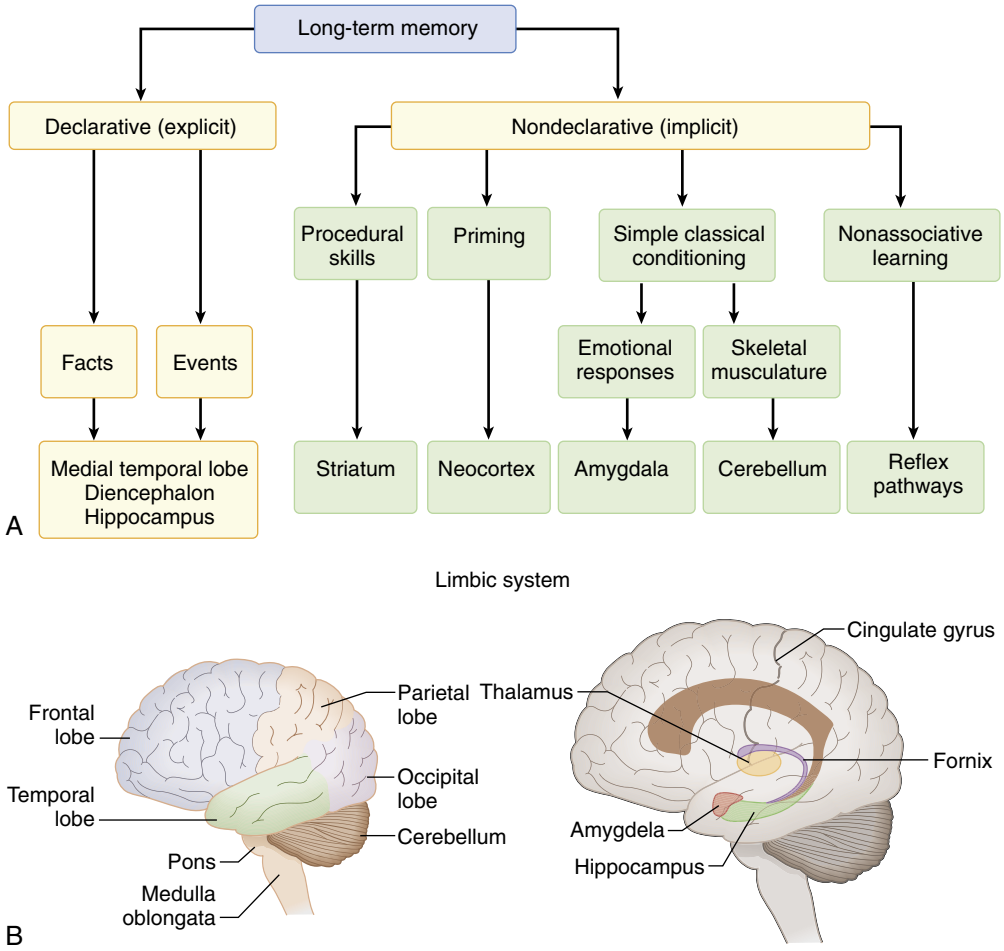


Figure 11-9 There are distinct types of memory (**A**) that are mediated by distinct brain systems (**B**).

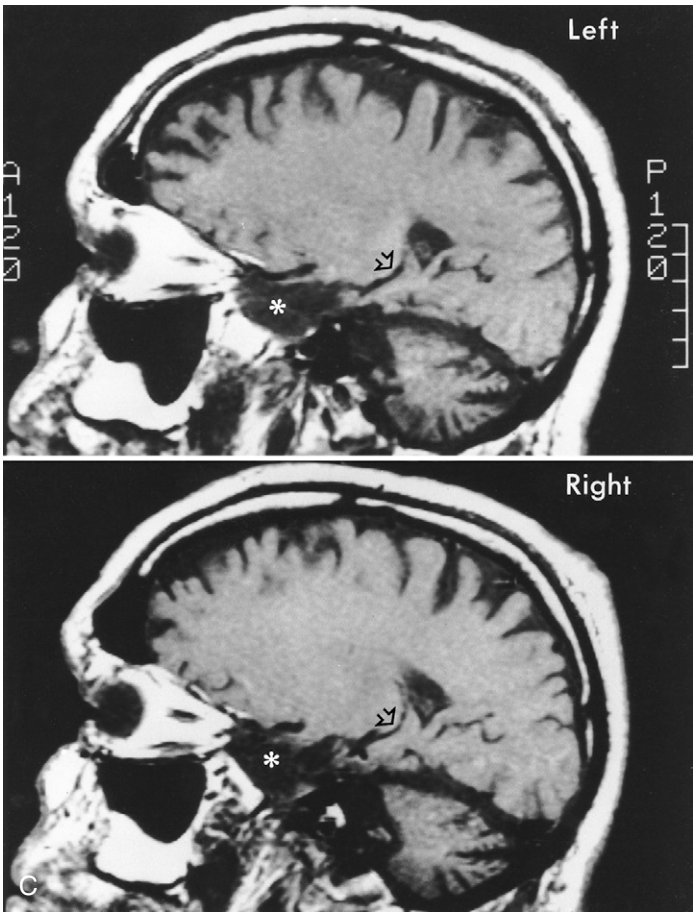


Figure 11-9, cont'd Patient H.M. exhibited selective deficits in declarative memory for facts and events after surgical resection of portions of his medial temporal lobe, including the hippocampus (**C;** the resected portion is marked with an *asterisk*, the remaining portion of the hippocampus is marked with an *arrow*). (**A,** *Modified from Squire LR, Zola SM: Structure and function of declarative and nondeclarative memory systems. Proc Natl Acad Sci U S A 93:13515, 1996;* **C,** *from Corkin S, Amaral DG, Gonzalez RG, et al: H. M.'s medial temporal lobe lesion: Findings from magnetic resonance imaging. J Neurosci 17:3964, 1997.)*

it was found that H.M.'s memory of temporally distinct events was intact, and a "gradient" of retrograde amnesia was revealed that decreased with time. This observation of time-limited retrograde amnesia is in keeping with the "law of regression" proposed by Jackson and Ribot that recent memories are the first to be affected by amnesia.[84,85] This observation also suggests that retrieval and storage of very long-term memories (so-called remote memory) are mediated by neural circuits that were not altered by H.M.'s surgery. We now know that these very long-term memories require the cortex—particularly the anterior cingulate cortex, for storage and retrieval.[86] Second and perhaps most important, H.M. exhibited normal learning and memory for certain tasks, a finding that was first shown for a mirror drawing task. This second aspect of H.M.'s amnesia gave rise to the idea of multiple memory systems, each of which mediate particular types of memory. There appears to be at least two reasons why Lashley did not observe the existence of discrete memory systems. H.M.'s lesions were not precisely focused on specific neural circuits, and his behavioral tasks, which were complex maze tasks, were not configured to probe selectively specific memory systems.

The conclusions from the study of H.M. have been confirmed and extended over the past 50 years, and similar memory deficits have been observed in patients with damage limited to specific subregions of the hippocampus.[83,87,88] A variety of memory systems have been defined by both lesion experiments and functional magnetic resonance imaging studies (Fig. 11-9).

Types of Memory

Memory is divided into two large classes termed *declarative* or *nondeclarative* memories, depending on whether the memory can be consciously recalled or not.[89] Nondeclarative memory includes procedural memory, of which bike riding and mirror drawing represent clear examples. Declarative memory, which is consciously recalled, consists of semantic and episodic memory. The hippocampal formation, lesioned in patient H.M., is a major component of the episodic memory system (see Fig. 11-9). Indeed, H.M. had specific deficits in his ability to store and recall episodic memories—the memory of facts and events that provide most of our conscious recollection of life's experiences. Although much work has focused on the role of the hippocampus in the recollection of episodic memories, recent work has extended the study of the hippocampus to investigate whether patients with hippocampal damage are able to imagine new experiences.[90] Patients with hippocampal damage are impaired at imaging new experience, in

part because their imagined experiences lack spatial coherence and consist of fragmented images in the absence of configural representation of an environmental setting. Beyond its role in our conscious recollection of our past, the hippocampus also makes a critical contribution to our ability to imagine new experiences.

The existence of multiple memory systems provides a critical analytic tool for the analysis of memory deficits observed in patients. A particularly striking example of such a "double dissociation" between types of memory comes from the work of Damasio and colleagues.[91] They examined a patient with bilateral damage to the amygdala and a patient with bilateral hippocampal damage in classic conditioning tasks. The patient with amygdala damage was unable to acquire conditioning of autonomic responses but did acquire declarative knowledge about the conditioning trials. In contrast, the patient with hippocampal damage learned the conditioned autonomic responses but not the facts. One clinical implication of the existence of multiple memory systems is that appropriate neuropsychological testing combined with structural and functional magnetic resonance imaging can be used to identify the basis of memory deficits in patients.

Memory Consolidation and Different Stages of Memory

In 1900, Georg Elias Müller (1850-1934) and his student Alfons Pilzecker (1865-1949), working at the University of Göttingen, Germany, published a seminal 300-page paper describing 40 experiments on the nature of memory.[92] In this work, Müller and Pilzecker presented clear evidence that memory does not immediately develop after learning but instead takes time to be consolidated and stored. Their primary evidence came from two classes of observations termed perseveration and retroactive inhibition. Using lists of nonsense syllables presented as paired associates, Müller and Pilzecker found a strong tendency for syllable pairs to be maintained in a subject's mind for some minutes after learning. Such "perseveration" was interpreted to reflect the persistence of a memory trace that was necessary to encode the memory. In a set of experiments designed to test this idea, they presented subjects with a second list of words at some time interval after the first list. If this second list followed the first list by 30 seconds, "retroactive interference" was observed—subjects showed less retention of the first word list. If learning of the second list was delayed by 6 minutes, such interference was not seen. Müller and Pilzecker concluded: "After all this, there is no alternative but to assume that after reading a list of syllables, certain physiological processes, which serve to strengthen the associations induced during reading of that list, continue with decreasing intensity for a period of time" (quoted by Lechner and colleagues[92]).

With these pioneering experiments, Müller and Pilzecker laid the groundwork for what today is termed memory consolidation—the idea that memories initially persist in a fragile state and are stabilized over time as they are consolidated into long-term memory.[93] Although it was immediately realized that the work on perseveration and retroactive interference provided an explanation for the temporally graded retrograde amnesia observed in patients by Ribot and Jackson, it took some time for this idea to have an impact on animal studies. It was not until 1949 that two papers reported retroactive interference in rodents with the use of electroconvulsive shock to induce retrograde amnesia.[94,95] In theoretical work at the same time, Hebb and Gerard[95,96] proposed that memory consisted of two "traces" of reverberating neural activity that first gives rise to short-term memory and then to long-term memory (Fig. 11-10). An interesting question that is still actively being explored is whether these short-term and long-term memory traces occur in series or in parallel. Although much work assumes that they are serial, some intriguing experiments suggest that they may form independently in parallel. Despite the fact that much work on memory consolidation has focused on impairing memory after training, memory can also be enhanced during the period of consolidation, as revealed by the work of McGaugh.[93] Thus, the existence of periods of memory consolidation provides an evolutionarily important mechanism to modulate our responses to learned experiences.

The concepts of memory consolidation were critically important for the development of biologically based approaches to memory storage. In particular, postulates that structural

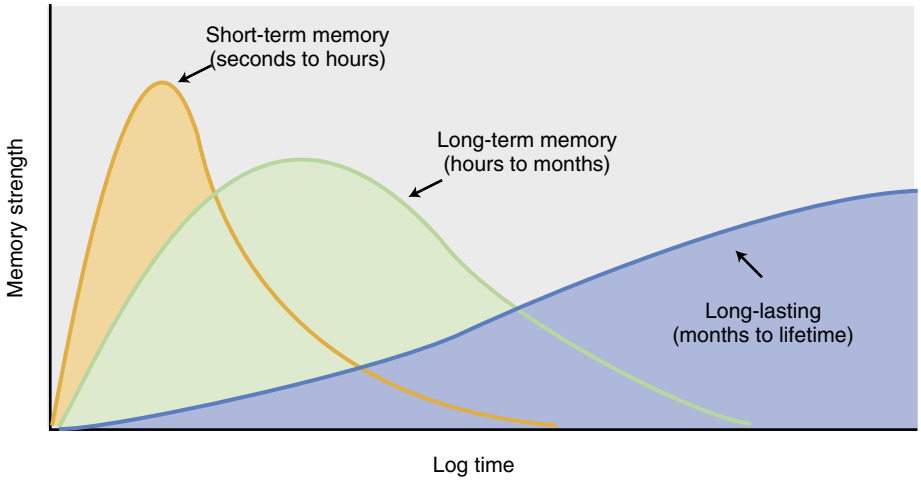


Figure 11-10 Memory consists of distinct phases, including short-term memory, long-term memory, and long-lasting memory. Distinct molecular mechanisms underlie each of these phases. Although these memory phases are shown schematically as though they exist in series, evidence suggests that they may also partially exist in parallel, thus implying that they are mediated by distinct molecular mechanisms acting independently. *(From McGaugh JL: Memory—a century of consolidation. Science 287:248, 2000.)*

changes might underlie memory traces led to development of the idea that proteins might mediate memory storage and then that RNA synthesis was required.[97] With the development of molecular biology, the finding that translation and transcription were critical for memory storage put study of the molecular mechanisms of memory firmly in the realm of the central dogma of molecular biology and led to the use of molecular techniques by many researchers to probe how information is stored in neural circuits. Furthermore, it became clear that it was molecular cascades of signaling molecules, transcription factors, and waves of RNA and protein synthesis that explained the perseveration and retroactive interference observed by experimental psychologists.

Cellular and Molecular Mechanisms of Memory Storage

At the cellular level, the most striking finding about the potential biologic basis of memory came in 1973 when Bliss and Lomo discovered that repeated high-frequency stimulation of input to the hippocampus in vivo resulted in a long-term potentiation (LTP) of synaptic transmission. LTP provides a cellular model of memory.[98,99] Evidence has suggested that processes similar to LTP may mediate memory because induction of LTP impairs ("occludes") subsequent memory formation.[100] LTP is induced after learning.[101] Furthermore, genetic and biochemical manipulations that impair LTP also lead to memory impairment. The development of in vitro slice preparations to study hippocampal LTP and manipulate hippocampal slices pharmacologically and electrophysiologically has been critical for identification of the molecular mechanisms underlying synaptic plasticity and memory.

Like behavioral memory, hippocampal LTP is an experience-dependent process, and extensive evidence suggests that these processes are mediated by similar molecular mechanisms.[98,99] Repeated synaptic stimulation in hippocampal slices, as well as behavioral training, activates the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor, a molecular coincidence detector activated by glutamate and postsynaptic depolarization. When activated, the NMDA receptor becomes permeant to calcium. The resultant influx of calcium into the postsynaptic neuron activates a number of second messenger signaling pathways, including calmodulin kinases (CaMKs), adenylyl cyclase, and mitogen-activated protein kinases (MAPKs)[102] (Fig. 11-11). Synaptic plasticity and behavioral memory are also modulated by neurotransmitters that activate G protein–coupled receptors, such as dopamine and norepinephrine, which in turn also modulate intracellular signaling pathways.

This local synaptic activation mediates plasticity for the first hour or so after induction of LTP. Long-term plasticity, called L-LTP, lasts for many hours and involves the induction of new gene transcription and the synthesis of new proteins.[103] Thus, long-lasting forms of LTP, like long-term memory, are selectively sensitive to inhibition of protein and RNA synthesis. Study of the molecular mechanisms of translational and transcriptional regulation has led to two surprises in recent years. First, the synthesis of new proteins can occur, in part, within the dendrite locally at the synapse, thereby providing a potentially long-lasting synaptic tag to mark synapses that are potentiated.[104] Second, regulation of transcription involves epigenetic mechanisms of chromatin modification, DNA methylation, and chromatin remodeling—mechanisms that were thought to function primarily in a developmental context.[105] It is interesting to suggest that memory may, in part, be stored as epigenetic modifications that alter the expression of select genes.

One important question is how activation of these various signal transduction pathways, changes in gene expression, and epigenetic marks give rise to long-lasting increases in synaptic transmission and memory. The α-amino-3-hydroxy-5-methyl-4-isoxazopropionic acid (AMPA)-type glutamate receptor provides one potential target of these molecular mechanisms. Kinases activated by influx of calcium, such as CaMKII, phosphorylate the GluR1 subunit of the AMPA receptor, which increases its open time and the amount of receptor available on the cell surface at the synapse.[106] Increased levels and activity of the AMPA receptor would increase the depolarization resulting from release of glutamate at the synapse, thereby increasing synaptic strength. Long-lasting forms of LTP activate gene expression and increase transcription of the gene encoding GluR1.[107] Thus, although there are clearly a variety of molecular targets by which synaptic strength can be stably enhanced, the AMPA receptor provides an attractive effector mechanism.

Anesthetic-Induced Amnesia

At larger doses, administration of virtually any anesthetic drug produces loss of consciousness, which in turn results in episodic amnesia. Because monitors capable of assessing memory formation, storage, and retrieval are lacking, one common clinical strategy relies on delivery of hypnotic doses of anesthetics to ensure amnesia. However, anesthetic drugs have the capacity to produce amnesia at subhypnotic doses. The engrams (physical alterations in neural tissue thought to be the substrate for memory) most readily impaired by anesthetic drugs involve episodic memories. Although multiple mechanisms might account for anesthetic-induced amnesia, at subhypnotic doses, benzodiazepines such as midazolam and intravenous anesthetics such as propofol primarily affect either long-term memory storage or its retrieval. At plasma concentrations of 40 ng/mL of midazolam or 0.9 μg/mL of propofol, humans are able to encode and retain memories over a period of 15 to 30 minutes. However, these memories are lost before consolidation.[108]

Even though the circuit-level, neuronal, and molecular mechanisms of anesthetic-induced amnesia remain incompletely understood, animal studies suggest that amnestic doses of anesthetics have the capacity to interfere with memory formation at multiple points. For the volatile anesthetics, memory formation is impaired at drug concentrations between a 25% and 50% the minimum alveolar concentration (MAC) in humans[109] and rodents,[110] with individual agents differing slightly in their amnestic potency relative to their MAC (immobilizing dose).[111]

LTP is a form of synaptic plasticity thought to contribute to memory and it represents a cellular model of memory as discussed earlier. In addition to impairing memory at the behavioral level, anesthetics such as isoflurane may also impair or completely abolish LTP in hippocampal slice preparations.[112] Other anesthetics such as barbiturates, benzodiazepines, and propofol likewise alter the expression of LTP and long-term depression in hippocampal slice preparations, thereby providing cellular correlates of their amnestic properties.[113-115] In these instances, anesthetics are

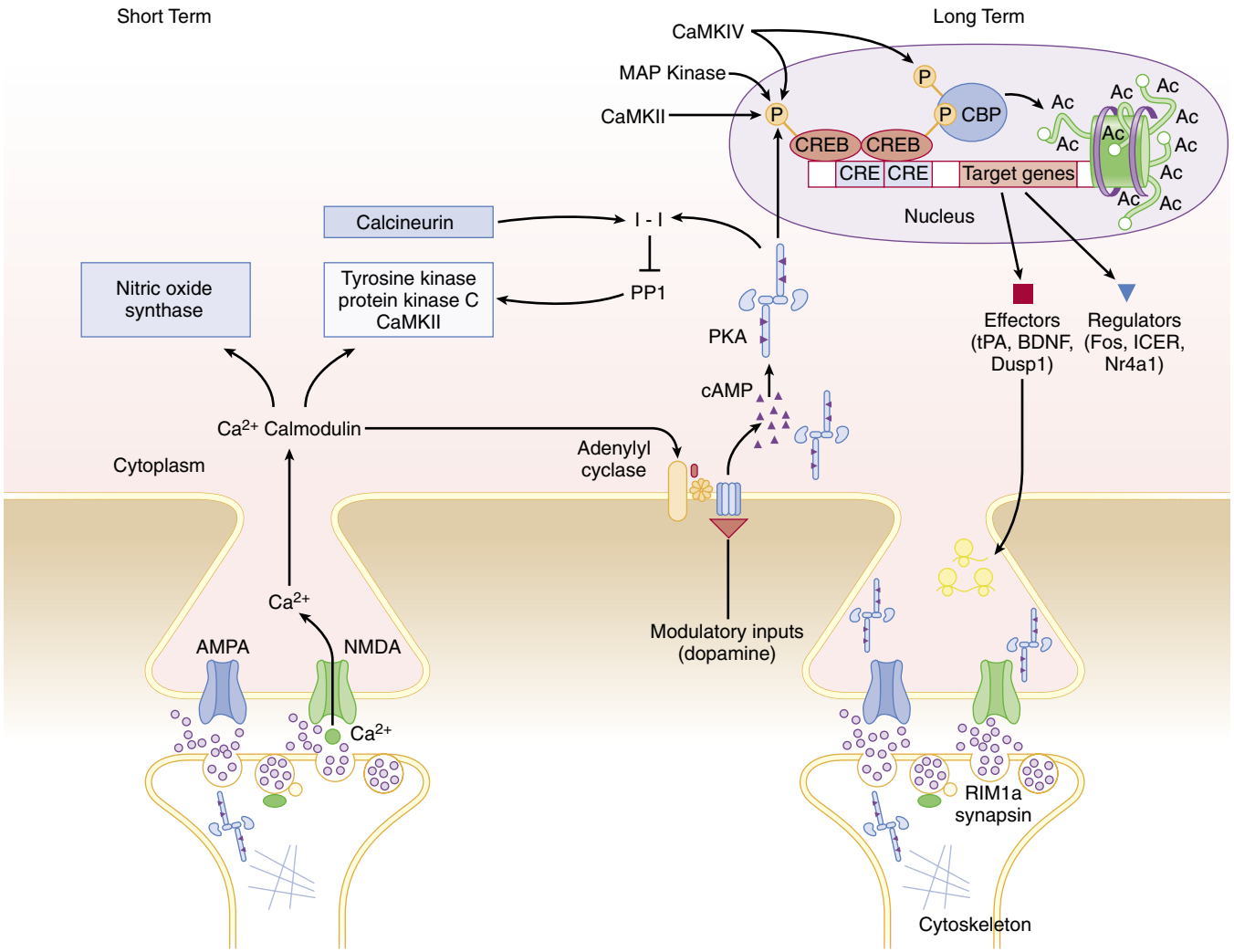


Figure 11-11 Long-term potentiation and long-term memory are mediated by similar molecular mechanisms involving calcium influx through the *N*-methyl-D-aspartate receptor and activation of intracellular signaling pathways that lead to activation of gene expression and synthesis of new proteins. *(Modified from Abel T, Nguyen PV, Barad M, et al: Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based long-term memory. Cell 88:615-626, 1997.)*

thought to impair LTP via GABAergic mechanisms.[112] α_5 Subunit–containing $GABA_A$ receptors are highly sensitive to amnestic concentrations of isoflurane.[116] However, other receptor signaling systems are certainly involved in mediating anesthetic-induced amnesia.[117-119]

Hippocampal θ rhythms (or θ oscillations) are the largest-amplitude synchronous EEG signals that can be recorded from mammalian brain. θ Oscillations have a characteristic frequency in the 5- to 12-Hz range in the behaving rat and dominate the EEG spectrum during NREM sleep (as discussed earlier), as well as during waking behavior essential for survival, such as exploration. Hippocampal θ oscillations are thought to facilitate mnemonic processes in vitro and in vivo. At the circuit level, anesthetics have recently been shown to alter hippocampal θ oscillations, a finding that may underlie anesthetic-induced amnesia.[120]

At the molecular level, propofol inhibits NMDA receptor–mediated activation of one subclass of the MAPK superfamily, extracellular signal–regulated protein kinase 1/2 (ERK1/2), in hippocampal neurons. This results in concurrent inhibition of transcriptional activity inasmuch as interference with MAPKs can uncouple synaptic events from nuclear responses. This finding might provide a molecular mechanism through which an anesthetic impairs transcription-dependent encoding of memory.[117,119] However, whether this mechanism represents a common action of anesthetic-induced amnesia awaits further elucidation.

The hippocampus is not the only limbic system structure thought to be involved in anesthetic-induced amnesia. It has now been established in animal models that the basolateral nucleus of the amygdala is critical for the amnestic effects of general anesthetics. Propofol, benzodiazepines, and sevoflurane lose their amnestic power if the basal nucleus of the amygdala is lesioned.[121,122] These data suggest that the amnestic doses of general anesthetics modulate output of the amygdala in such a way that memory formation is diminished. The role of the amygdala in anesthetic-mediated amnesia may be related to the hippocampus because the two structures are strongly interconnected. Furthermore, the inability of an anesthetic agent to suppress

memory has clinical implications for patients who are experiencing intraoperative awareness, a topic to which we turn in the next section.

Consciousness

Historical Background

It has been known since antiquity that inhalation of certain gases may alter consciousness. As Strabo (64 BC-AD 25) wrote of the Delphic oracles: "They say that the seat of the oracle is a cavern hollowed deep down in the earth, with a rather narrow mouth, from which rises a vapor that produces divine possession. A tripod is set above this cleft, mounting which, the Pythia inhales the vapor and prophesies." Only recently did evidence emerge that the general anesthetic ethylene may have been the vapor in the Temple of Apollo that induced these mystical states.[123]

In the modern era, renowned psychologist William James' experiments with nitrous oxide influenced one of his greatest works, *The Varieties of Religious Experience*, and yielded an 1898 article titled "Consciousness under Nitrous Oxide."[124] By the end of the 19th century, James and others regarded consciousness as a fundamental scientific question. In the 20th century, however, the dominating psychological paradigms of behaviorism and psychoanalysis disregarded or actively discouraged consciousness as a subject of serious inquiry. This antipathy toward the scientific study of consciousness persisted until the 1980s. Although Harvard anesthesiologist Henry Beecher promoted general anesthetics as a tool to study consciousness in the mid-20th century,[125] it was not until the 21st century that a true renaissance of interest in consciousness and anesthesia emerged. The current focus on consciousness within the field of anesthesiology is related primarily to anesthetic mechanisms or intraoperative awareness.

Neural Correlates of Consciousness

Whereas philosophers at the time of the Delphic oracles were concerned with the nature of being (ontology), the focus of 18th century thinkers such as Immanuel Kant was the nature and mechanism of knowing (epistemology). In his *Critique of Pure Reason*, Kant argued that our minds affect the ideas that we have about nature. Human experience of reality has two nonintersecting parts: (1) the part accessed by our senses (the phenomenal realm) and (2) the part outside cognition (the noumenal realm). The mind must possess, according to Kant, innate categories to be able to take the information in the phenomenal realm and make inferences about what lies in the noumenal one. Stated another way, he posited that the mind was modular, with discrete faculties that subserved specific cognitive functions. He recognized, however, that for these specific functions to be translated into a unified perceptual experience, there must be a process of integration that is essential.

Consistent with the philosophy of Kant, neuroscientist Giulio Tononi has proposed a 21st-century "information integration" theory of consciousness, as well as a theoretical model that expresses the capacity of neural systems to synthesize information.[126,127] Tononi suggests that consciousness reflects a higher capacity to integrate information processed in functionally specialized modules, which is why, for example, thalamocortical circuits seem to be more relevant to conscious processes than cerebellar circuits do.

In more concrete terms, the neural correlates of particular sensory modalities (e.g., the visual) must ultimately be combined with other sensory modalities (e.g., the tactile) to generate a unified perception. This is also true of the various submodalities of sensory perception (such as color, form, and motion in visual processing). For example, we do not perceive the sun as sequentially spherical, yellow, and warm, but instead experience all these distinct traits at one time. Thus, there is a unity to our conscious experience. Because, however, the brain processes these traits in a number of discrete neuronal subpopulations (e.g., visual and somatosensory cortices), there must be a higher-order process that synthesizes the information. This process is often referred to as "cognitive binding."[128,129]

Cognitive binding is thought to be necessary, though perhaps not sufficient, for consciousness itself. Several mechanisms for integration of neural information have been proposed, including convergence, assembly, and synchrony.[130,131] Binding by convergence is a hierarchic processing strategy characterized by transmission of information from primary to higher-order brain regions for integration.[132-134] Binding by assembly refers to information synthesized in a Hebbian cell assembly, that is, a group of interrelated neurons whose connections grow stronger with repeated firing together.[135] Finally, binding by synchrony introduces a temporal dimension to synthesis and is thought to be associated with neural events at the frequency of 40 Hz.[136-138]

Many of the neural regions or processes that are considered correlates of consciousness are linked to integration of information. Neural correlates may be identified through a number of methods, including clinicopathologic correlation, functional neuroimaging, and neurophysiologic recording. A number of candidates for the neural substrate of consciousness emerged in the 1980s and 1990s, including

- Extended reticular-thalamic activation system[139]
- Intralaminar nucleus in the thalamus[140]
- Reentrant loops in thalamocortical systems[141]
- 40-Hz rhythmic activity in thalamocortical systems[137]
- Neurons in the superior temporal sulcus[142]
- Neural activity in visual area V5/MT[143]
- Neurons in the extrastriate visual cortex projecting to prefrontal areas[144]
- Anterior cingulate system[145]
- Recurrent processing from higher to lower cortical areas[146]

Rees and colleagues discussed the evidence for many of these neural correlates of human consciousness.[147] As we discuss in the following sections, these correlates may serve as the anatomic or neurophysiologic substrates on which general anesthetics act to suppress consciousness.

Effects of Anesthetics on Neural Correlates

General anesthetics may generate unconsciousness by suppressing the activity of the neural correlates at various levels of neural organization, as well as by disrupting processes of information

integration. It has become clear that many of the proposed neural correlates of consciousness are modulated by general anesthetics.

Subcortical and Thalamocortical Effects

Functional neuroimaging by positron-emission tomography (PET) during isoflurane or halothane anesthesia demonstrated reduced cerebral glucose metabolism in subcortical structures associated with arousal, including the thalamus and midbrain reticular formation.[49] PET has also revealed suppression of thalamic activity in association with propofol-induced unconsciousness.[61] Other subcortical structures affected include the arousal-promoting TMN in the hypothalamus, which has been associated with anesthetic-induced hypnosis.[66]

Recent data acquired by electrophysiologic techniques in humans have brought into question the role of subcortical structures such as the thalamus. Because PET has poor temporal resolution,[148] Velly and associates compared cortical EEG tracings with recordings from subcortical deep brain electrodes in the human subthalamic nucleus. The authors were able to deduce that their field recordings were actually detecting thalamic rather than subthalamic activity. Loss of consciousness with propofol or sevoflurane was correlated with the cortical EEG, whereas minimal changes in the subcortical recording were identified. As discussed earlier, Alkire and colleagues demonstrated that nicotinic cholinergic agonism in the central medial thalamic nucleus could reverse sevoflurane-induced unconsciousness.[64] Although it would appear that these data contradict the findings of Velly and coworkers, administration of the nicotinic antagonist mecamylamine in the central medial nucleus did not induce anesthesia or even reduce anesthetic requirements. Alkire and associates concluded that the central medial nucleus may be an "on" switch for arousal but not an "off" switch for anesthesia.

The thalamocortical system is thought to be critical for consciousness. The resonance of thalamocortical circuits has been proposed as the "dynamic core" of consciousness[141] and is consistent with cognitive binding by 40-Hz oscillations.[137] Alkire and associates described a "unified theory of narcosis" based on the finding that thalamocortical circuits were disrupted under general anesthesia.[49] It has been demonstrated that isoflurane and halothane disrupt functional connectivity between the thalamus and cortex.[149] In this context, functional connectivity refers to the correlation of neurophysiologic activity in two spatially distinct brain regions.[150] Propofol has also been shown to induce a hyperpolarization block of thalamocortical neurons.[151]

Cortical and Corticocortical Effects

General anesthetics have been demonstrated to affect a number of cortical brain regions. Variable electromagnetic tomographic analysis has demonstrated that multiple general anesthetics induce reversible inhibition of the medial orbital and dorsolateral prefrontal and frontal cortex, anterior cingulate cortex, and paracentral gyrus.[152] The finding of frontal and cingulate cortex inhibition was consistent with previous PET findings of propofol-induced anesthesia.[61] As noted earlier, both the prefrontal and anterior cingulate cortices have been proposed as neural correlates of conscious processing.

It has been demonstrated that general anesthetics of distinct pharmacologic properties affect EEG coherence in a similar way during unconsciousness, an effect that is reversed on the return of consciousness.[152] In 176 cases of human surgical anesthesia using a variety of both inhaled and intravenous anesthetics, there were invariant changes in the electrical uncoupling of brain regions. Multivariate analysis of quantitative EEG recordings showed that γ oscillations (35 to 50 Hz) of the rostral and caudal regions of the brain became uncoupled from one another. These changes were associated with the onset of anesthesia, intensified with increasing depth of anesthesia, and reversed with the termination of anesthesia.

Rostrocaudal dissociation is of particular relevance given the proposed scans of 40-Hz oscillations that sweep from the frontal to the occipital cortex and back again.[137] In addition to this functional rostrocaudal disconnection, the hemispheres themselves became functionally disconnected. The effects of anesthesia on rostrocaudal processing have been studied in animal models as well. It has been demonstrated that processing of visual stimuli during anesthesia can be transmitted from the occipital to the frontal cortex, whereas recurrent processing from the frontal back to the occipital cortex is interrupted.[153] This finding is consistent with the proposed neural correlate of recurrent processing of neural information,[146] that is, transmission of signals from higher-order areas back to primary processing areas.

Other studies in humans have shown functional uncoupling of neural regions in association with general anesthesia. Peltier and colleagues demonstrated loss of functional connectivity in the cerebral cortex during sevoflurane anesthesia.[154] This provides further evidence that anesthetics uncouple the activity of cortical regions that might otherwise influence one another in the waking state.

Information Dissociation and Unconscious States

Based on the effect of anesthetic-mediated interruption of neural information synthesis, a "cognitive unbinding" paradigm of general anesthesia was postulated.[155,156] This framework explicitly stated that anesthetics may function by interrupting various cognitive binding processes from the cellular to the global brain level. This was based, in part, on findings by John and associates[152] that demonstrated functional uncoupling of the hemispheric and rostrocaudal axes of the brain (interruption of synchronous binding). The cognitive unbinding paradigm was also based on interruption of synthetic processes in cortical area MT under isoflurane (interruption of convergent binding).[157]

John and Prichep's "anesthetic cascade" supported the concept of cognitive unbinding while at the same time postulated a specific stepwise process by which anesthetics suppress consciousness.[158] The proposed "cascade" is as follows:

- Depression of the brainstem reduces the influence of the ascending reticular activating system on the thalamus and cortex.
- Depression of mesolimbic-dorsolateral prefrontal cortex interactions leads to blockade of memory storage.
- Further depression of the ascending reticular activating system leads to hyperpolarization of GABAergic neurons in the nucleus reticularis of the thalamus, which results in
- Blockade of thalamocortical reverberations and the associated γ oscillations underlying perception,

Functional uncoupling of parietal-frontal cortical activity, thereby interrupting cognition, and finally
Reduced awareness of and increase in frontal δ- and θ-band activity.

Recent data on the temporal relationship of subcortical anesthetic effects bring into question the first step of the cascade.[148] Furthermore, it is unclear how agents such as ketamine or nitrous oxide, which can lead to EEG activation rather than depression,[159,160] fit within the proposed anesthetic cascade. Nonetheless, the anesthetic cascade is one of the most specific and data-driven theories of anesthetic-induced unconsciousness.

Walling and Hicks supported both cognitive unbinding and the anesthetic cascade based on EEG phase-space analysis of emergence from sevoflurane anesthesia in humans.[161] Return of consciousness was characterized by a higher-dimensional phase space, reflecting a complexity of brain dynamics that could sustain consciousness. The fractal "strange attractors" that were identified on emergence were posited to be the coherence of γ-band frequencies associated with consciousness, in what the authors referred to as "cognitive rebinding."

These frameworks of anesthetic-induced unconsciousness as information dissociation are supported by recent studies of other unconscious states. Studies of brain-injured patients in vegetative states have revealed fragmented cerebral activity[162] and loss of effective cortical connectivity.[163] It has therefore been suggested that vegetative states are "disconnection" syndromes.[164] The neural regions affected in vegetative states include the frontal cortex, cingulate cortex, association cortices, and thalamus,[164] which are also targets for general anesthetics. Like anesthesia, recovery from vegetative states is associated with return of thalamocortical connectivity.[165]

As discussed earlier, sleep is a state with a number of traits similar to general anesthesia.[166] Using transcranial magnetic stimulation and EEG recordings of subjects either asleep or awake, Massimini and coworkers[167] demonstrated that NREM sleep is also characterized by loss of effective cortical connectivity. The loss of cortical connectivity associated with sleep suggests a common feature with anesthetic-induced unconsciousness and vegetative states.

Consciousness in the Operating Room

Although consciousness is emerging as an important scientific problem that is intimately linked to the mechanism of general anesthesia, it can also pose a clinical problem intraoperatively. Awareness during general anesthesia—which denotes both awareness and subsequent explicit recall of intraoperative events—is a complication receiving increased attention by both patients and clinicians. Dreaming is another subjective state that can occur during anesthesia, with an incidence of 22% in patients undergoing elective cases.[168] Although some cases represented "near-miss" experiences of awareness, others were thought to occur during recovery from anesthesia.

Despite recent attention by the medical community and the lay press, the incidence of intraoperative awareness—and hence the magnitude of the problem—remains uncertain. A multicenter study in the United States by Sebel and colleagues[169] estimated an incidence of awareness with explicit recall of approximately 0.13%, a rate consistent with large European studies demonstrating awareness in 1 to 2 per 1000 cases.[170] In contrast, a recent study of awareness in a regional medical system reported a much lower incidence of 1 episode of awareness per 14,560 cases, or 0.0069%.[171] The timing and content of postoperative interviews probably play a role in this discrepancy.

A proportion of patients experiencing awareness may subsequently exhibit serious psychological sequelae, including post-traumatic stress disorder.[172] Earlier studies reported a greater than 50% incidence of post-traumatic stress disorder, whereas more recent studies suggest a much lower rate of occurrence.[173] Because of the profound distress that it can induce in patients, a reliable and practical method of detecting intraoperative consciousness would be an important clinical advance.

Assessing Consciousness Intraoperatively

As early as 1937, Gibbs and coauthors reported that EEG measurements were sensitive to the effects of general anesthetics.[174] However, the use of unprocessed EEG data to assess anesthetic depth in the operating room is impractical for a number of reasons: (1) there is no unique electrical "signature" of an unprocessed EEG that is invariant, (2) the use of standard multiple-channel diagnostic EEG devices is cumbersome in the intraoperative setting, and (3) the use of such diagnostic devices—capable of localizing the source of abnormal signal patterns—generally requires a dedicated interpreter. Because of these limitations, EEG monitors with a minimal number of channels that use processing algorithms have been developed in an attempt to monitor anesthetic depth and detect intraoperative awareness (see Chapter 39).

Fourier transformation of raw EEG data enables the derivation of median power and spectral edge frequencies, and a number of devices available for intraoperative use are based on Fourier-transformed EEG data.[175] The bispectral index analyzes burst suppression, β-band power, and bispectral coherence.[176] The Narcotrend Monitor (MonitorTechnik, Bad Bramstedt, Germany) analyzes stages and substages of anesthesia and was based on a similar developmental process as the BIS (with a distinct algorithm).[177] The Patient State Index (PSI; Physiometrix, Inc., N. Billerica, MA) is derived from quantitative EEG techniques and is based on signal relationships between the frontal and occipital brain regions.[178] Entropy monitors (e.g., S/5, Instrumentarium Corp. [Datex-Ohmeda], Helsinki, Finland) are based on the concept of information entropy posited by Shannon[179] and analyze randomness in frequency and phase relationships with the use of both EEG and frontal EMG.[180] Entropy monitors measure state entropy (response over the range of 0.8 to 32 Hz, reflecting the EEG-dominant spectrum) and response entropy (response over the range of 0.8 to 47 Hz, reflecting both EEG and EMG spectra). Whereas the aforementioned monitors record spontaneous EEG, the stimulus-response technique of auditory evoked potentials has also been used to assess anesthetic depth and can be analyzed in conjunction with other EEG signaling parameters.[181,182] Because the BIS has been extensively studied and is the most frequently used monitor to assess depth of anesthesia, it will be the focus of the remaining sections.

Development and Validation of the BIS Monitor

The BIS monitor was developed empirically by analyzing a high-fidelity database of EEG recordings from approximately 2000 patients who received a variety of commonly used general

anesthetics, sedative-hypnotics, and opioids (see Chapter 39).[176] Segments of the EEG were compared with clinical findings of hypnosis; candidate spectral and bispectral features of these segments were computed and tested for their ability to distinguish the clinically described hypnotic states. The best of these features were then combined by multivariate statistical modeling to form a composite index (dimensionless number between 0 and 100, where 0 is isoelectric and 100 is awake), which underwent further prospective testing in a larger database.

In the mid-1990s, a number of studies demonstrated that changes in BIS values were associated with movement in response to noxious stimuli, as well as hemodynamic responses to interventions such as laryngoscopy. A multicentered study using movement as the measured outcome found that BIS values had better response with hypnotic drugs such as isoflurane and propofol than with opiates.[183] Whereas some studies focused on the relationship of BIS to movement in an attempt to validate the BIS in terms of MAC, other studies investigated the relationship of BIS to hypnosis, or MAC-awake. Flaishon and associates[184] used propofol or thiopental to induce anesthesia while continuously monitoring the BIS. BIS values above 60 were highly correlated with the ability of subjects to respond to verbal command. Another multicentered investigation focused on validation of the BIS monitor by comparing BIS values with anesthetic drug concentrations and level of sedation.[185] Other studies confirmed the value of the BIS in measuring hypnotic response to both inhaled and intravenous general anesthetics.[186,187] The BIS has also been validated for assessing the depth of anesthesia in children.[188,189]

One study in a high-risk population showed a significantly decreased incidence of confirmed awareness.[190] When combining both "possible" and "confirmed" awareness events, however, there was no difference between the BIS and control groups. Furthermore, the high number needed to treat (138) and the associated cost ($2200 U.S. dollars) in the high-risk group bring into question use of the BIS to prevent awareness in the general population.

Comparison of the BIS with Other EEG-Based Monitors

Because of validation of the BIS in a number of clinical studies, other emerging technologies have been compared with the BIS for validation. Chen and coworkers[191] demonstrated that the PSI correlated well with the BIS during anesthesia induction, maintenance, and emergence. The PSI and BIS were found to be comparable in a small study of intravenous and inhaled anesthetics, with the PSI reported to have less electrocautery artifact.[192]

The Narcotrend monitor has been shown to correlate well with predicted propofol concentrations in addition to the BIS.[177] The Narcotrend index correlated with the BIS during propofol and remifentanil anesthesia in a small number of patients (n = 26).[193] The BIS and Narcotrend indices were also shown to be comparable in monitoring the depth of isoflurane anesthesia.[177]

State entropy and response entropy show close correlation with the BIS in assessing sevoflurane anesthesia,[194] as well as propofol-remifentanil anesthesia.[195] In a small study evaluating loss of response to verbal command and loss of consciousness during propofol anesthesia, it was suggested that state entropy may be more useful than the BIS.[196] One study also demonstrated comparable performance of the BIS and entropy modules during both intravenous and inhaled anesthesia, with less electrocautery interference by the entropy monitor.[197]

Limitations of the BIS

There are numerous limitations associated with BIS monitoring.[198] One such limitation is that BIS values remain unchanged or even elevated during nitrous oxide anesthesia.[160,199] The intravenous anesthetic ketamine may also elevate BIS levels,[159,200] perhaps reflecting its ability to increase the beta power of the EEG spectrum.[201] It is of interest that both ketamine and nitrous oxide are thought to act primarily through NMDA glutamate receptors.[202] The anesthetic effect of xenon, which also acts on this receptor system, is similarly not reflected with BIS technology.[203] It is of further interest that although spectral entropy values are increased by ketamine in a similar manner to the BIS,[204] the addition of nitrous oxide has been shown to decrease state and response entropy values.[205] Conversely, BIS values are sensitive to nonanesthetic agents routinely administered in the operating room and have been shown to decrease in patients receiving neuromuscular blockers, while fully conscious[206] and while anesthetized.[207] BIS values derived from multiple sensors on the same patient have also been shown to be discordant, suggesting intrapatient variability and poor reproducibility of the index.[208] These and other limitations indicate the need for more sophisticated monitors of anesthetic depth that are linked to the neurophysiologic mechanisms of consciousness.

Conclusion

The oscillating states of sleep and wakefulness are fundamental features of our existence; as such, they have been pondered philosophically since antiquity and explored scientifically in modern times. The field of anesthesiology has much to gain from these investigations and, just as importantly, much to offer in return. Our further understanding of the neuroscientific mechanisms of general anesthesia may provide fundamental insight into the nature of consciousness, unconsciousness, and the memories that bind them together to form a stable sense of self.

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David B. Glick

12 The Autonomic Nervous System

Key Points

1. The autonomic nervous system works in concert with renin, cortisone, and other hormones to respond to internal and external stresses.
2. The hallmark of the sympathetic nervous system is amplification; the hallmark of the parasympathetic nervous system is targeted response.
3. Inhaled and intravenous anesthetics can alter hemodynamics by influencing autonomic function.
4. β-Adrenergic blockade has emerged as important prophylaxis for ischemia and as therapy for hypertension, myocardial infarction, and congestive heart failure.
5. The sympathetic nervous system demonstrates acute and chronic adaptation to stress presynaptically and postsynaptically (e.g., biosynthesis, receptor regulation).
6. Presynaptic α-receptors play an important role in regulating sympathetic release.
7. Many therapies for the treatment of hypertension are based on direct or indirect effects of sympathetic function.
8. The vagus nerve is the superhighway of parasympathetic function; it accommodates 75% of parasympathetic traffic.
9. Aging and many disease states (e.g., diabetes, spinal cord injury) are accompanied by important changes in autonomic function.

The autonomic nervous system (ANS) controls the body's involuntary (i.e., outside of consciousness) activities. It is, at once, the most primitive and among the most essential of the body's systems—primitive in that its characteristics are largely preserved across all mammalian species and essential in that it oversees the body's responses to immediate life-threatening challenges and the body's vital maintenance needs (including cardiovascular, gastrointestinal, and thermal homeostasis). The ANS is divided into two subsystems, the sympathetic nervous system and the parasympathetic nervous system. A third subsystem, the enteric nervous system, has been added to the original characterization of the ANS. Activation of the sympathetic nervous system elicits what is traditionally called the fight-or-flight response, including redistribution of blood flow from the viscera to skeletal muscle, increased cardiac function, sweating, and pupillary dilation. The parasympathetic system governs activities of the body more closely associated with maintenance of function, such as digestive and genitourinary function. A major goal of administration of anesthetics is maintaining optimum homeostasis in patients despite powerful challenges to a sometimes tenuous physiologic balance. Intelligent administration of anesthetic care to patients requires knowledge of ANS pharmacology to achieve desirable interactions of anesthetics with the involuntary control system and to avoid responses or interactions that produce deleterious effects. Disease states may impair ANS function to a significant extent and thereby alter the expected responses to surgery and anesthesia. In addition, possible harmful effects of the human stress response have long been appreciated, and considerable effort has been expended in examining the possibility that modification or ablation of the stress response may actually improve perioperative outcome.

History and Definitions

Initially, nerves were thought to be connected in a giant syncytium. Claude Bernard, a student of Magendie, postulated the theory of transmission via synapses through the release of chemical mediators. Later, Sherrington initiated a systematic study of reflexes and described some characteristics of reflex function. A chemist, J.J. Abel, first synthesized epinephrine in 1899, and his student Langley demonstrated that it caused effects similar to those produced by stimulating postganglionic sympathetic neurons. Furthermore, Langley found that when the nerve was cut and epinephrine was injected, a more profound effect was produced, thus demonstrating denervation supersensitivity. From these observations, the concept of chemical transmission in the ANS developed. Sir Henry Dale isolated choline and studied an ester, acetylcholine, in animals. He demonstrated

that it causes a marked decrease in blood pressure and vasodilation.

Nerves are traditionally classified by the chemical transmitters that they contain. Nerves containing acetylcholine are called *cholinergic*, whereas those containing norepinephrine are called *adrenergic*. In addition to classifying nerves, the term cholinergic refers to other structures or functions that relate in some way to acetylcholine. For instance, cholinergic receptors (i.e., cholinoceptors) are proteins in cell membranes that react with acetylcholine and cause the cell to respond in a characteristic way (e.g., muscles contract, glands secrete). Cholinergic agonists are drugs that act like acetylcholine on cholinoceptors to cause the cell to react in its characteristic way. They are sometimes referred to as cholinomimetic drugs. Cholinergic antagonists are drugs that react with cholinoceptors to block access by acetylcholine and thereby prevent its action. These drugs may also be referred to as cholinolytic, cholinergic-blocking, or anticholinergic drugs.

Because muscarine, a chemical isolated from a mushroom, causes effects similar to those produced by activation of the parasympathetic nervous system, it was thought to be the endogenous parasympathetic transmitter. Thus, drugs that mimic the effects of muscarine on parasympathetically innervated structures, including the heart, smooth muscles, and glands, have been called *muscarinic* drugs.

In the early 1900s, nicotine was found to act on ganglionic and skeletal muscle synapses and on nerve membranes and sensory endings. Accordingly, drugs that act on these parts of the cholinergic system are called *nicotinic* drugs. Nicotinic drugs that are more specific in their action have been discovered and are referred to by the name of the system that they affect, such as ganglionic drugs or neuromuscular drugs. Agonists and antagonists exist in each category, with little crossover of effect between drugs acting at the ganglia and those acting at the neuromuscular junction.

For the purposes of this chapter, cholinergic nerves include the following (Fig. 12-1):

1. All the motor nerves that innervate skeletal muscle
2. All postganglionic parasympathetic neurons
3. All preganglionic parasympathetic and sympathetic neurons
4. Some postganglionic sympathetic neurons, such as those that innervate the sweat glands and certain blood vessels
5. Preganglionic sympathetic neurons that arise from the greater splanchnic nerve and innervate the adrenal medulla
6. Central cholinergic neurons

Drugs mimicking the action of norepinephrine are referred to as *sympathomimetic*, whereas drugs inhibiting the effects of norepinephrine are called *sympatholytic*. Adrenergic nerves release norepinephrine at the neuroeffector junction, whereas epinephrine and norepinephrine are released by the adrenal medulla.

Adrenergic receptors have been identified and subdivided into α- and β-receptors and further subdivided into α_1, α_2, β_1, β_2, and other types. α_2-Adrenergic receptors are primarily located on the presynaptic membrane and modulate release of norepinephrine, whereas postsynaptic α_1-adrenergic receptors mediate smooth muscle vasoconstriction (Fig. 12-2). β_1-Adrenergic receptors are found primarily on cardiac tissue, and β_2-adrenergic receptors mediate smooth muscle relaxation in some organs. Adrenergic neurons can be defined as follows (see Fig. 12-1):

1. Postganglionic sympathetic neurons
2. Some interneurons
3. Certain central neurons

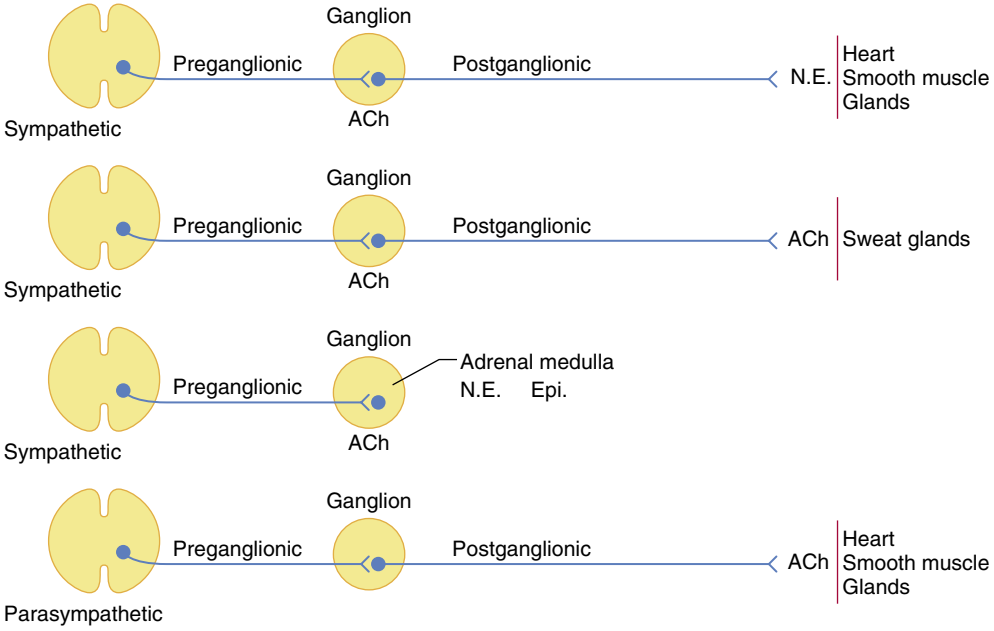

Figure 12-1 Autonomic nervous system neurotransmission. ACh, acetylcholine; Epi, epinephrine; NE, norepinephrine.

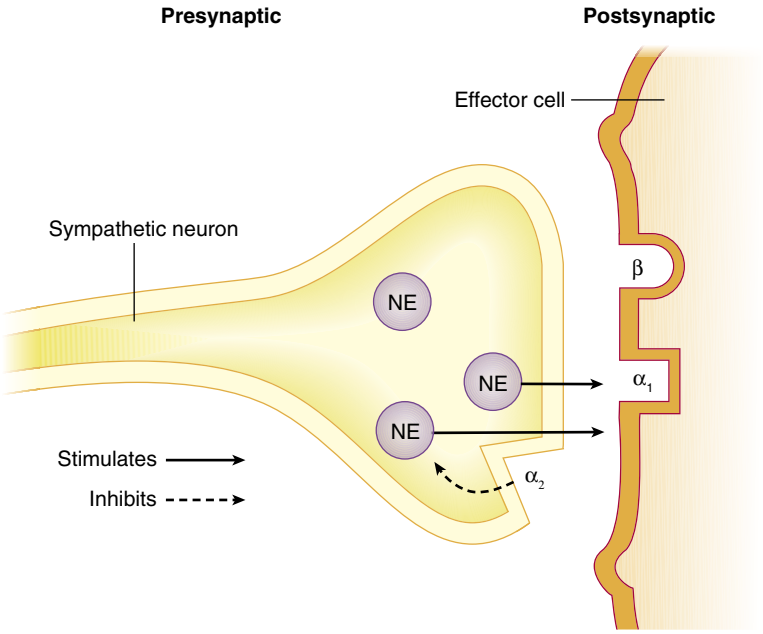

Figure 12-2 Preganglionic and postganglionic α-receptors of the sympathetic nervous system. The α_1-receptor is located postsynaptically on the membrane of the effector cell, whereas the α_2-receptor is located presynaptically on the cell membrane of the sympathetic nerve innervating the effector cell. NE, norepinephrine.

Functional Anatomy

Each branch of the ANS exhibits a different anatomic motif that is recapitulated on a cellular and molecular level. The underlying theme of the sympathetic nervous system is an amplification response, whereas that of the parasympathetic nervous system is a discrete and narrowly targeted response. The enteric nervous system is arranged nontopographically, as would be appropriate for the viscera, and relies on the mechanism of chemical coding to differentiate between nerves serving different functions.

Sympathetic Nervous System

The sympathetic nervous system originates from the spinal cord in the thoracolumbar region, from the first thoracic through the second or third lumbar segment. The preganglionic sympathetic neurons have cell bodies within the horns of the spinal gray matter (i.e., the intermediolateral columns). Nerve fibers from these cell bodies extend to three types of ganglia grouped as paired sympathetic chains, various unpaired distal plexuses, or terminal or collateral ganglia near the target organ.

The 22 paired ganglia lie along either side of the vertebral column. Nerve trunks connect these ganglia to each other, and gray rami communicantes connect the ganglia to the spinal nerves. The preganglionic fibers leave the cord in the anterior nerve roots, join the spinal nerve trunks, and enter the ganglion at their respective level through the white (myelinated) ramus. Leaving the ganglion, postsynaptic fibers reenter the spinal nerve through the gray (unmyelinated) ramus and then innervate the pilomotor and sudomotor (sweat gland) effectors and blood vessels of the skeletal muscle and skin (Fig. 12-3). Sympathetic postganglionic fibers innervate the trunk and limbs via the spinal nerves.

The sympathetic distribution to the head and neck, which enables and mediates vasomotor, pupillodilator, secretory, and pilomotor function, comes from the three ganglia of the cervical sympathetic chain. Preganglionic fibers of these cervical structures originate in the upper thoracic segments. In 80% of people, the stellate ganglion is formed by fusion of the inferior cervical ganglion with the first thoracic ganglion on each side.

The unpaired prevertebral ganglia reside in the abdomen and pelvis anterior to the vertebral column and are the celiac, superior mesenteric, aorticorenal, and inferior mesenteric ganglia. Postganglionic fibers arising from synaptic links of the upper thoracic sympathetic fibers in the vertebral ganglia form the terminal cardiac, esophageal, and pulmonary plexuses. The postganglionic fibers from the celiac, superior and inferior mesenteric plexuses innervate the viscera of the abdomen and pelvis (Fig. 12-4).

Ganglia of the third type, the terminal or collateral ganglia, are small, few in number, and near their target organs (e.g., the adrenal medulla). The adrenal medulla and other chromaffin tissue are homologous to the sympathetic ganglia, and all are derived embryonically from neural crest cells. Unlike sympathetic postganglionic fibers, however, the adrenal medulla releases epinephrine and norepinephrine.

Sympathetic preganglionic fibers are relatively short because sympathetic ganglia are generally close to the central nervous system (CNS), but they are distant from the effector organs; therefore, postganglionic fibers run a long course before innervating effector organs. The distribution is also diffuse and capable of amplification. Preganglionic sympathetic fibers may pass through multiple ganglia before synapsing, and their terminal fibers may contact large numbers of postganglionic neurons. The terminal fibers of preganglionic axons may synapse with more than 20 ganglia, and one cell may be supplied by several preganglionic fibers. Thus, preganglionic sympathetic fibers not only synapse at the ganglion of the level of their origin in the spinal cord but can also course up and down the paired ganglia. Sympathetic response, therefore, is not confined to the segment from which the stimulus originates, thereby allowing an amplified, diffuse discharge.

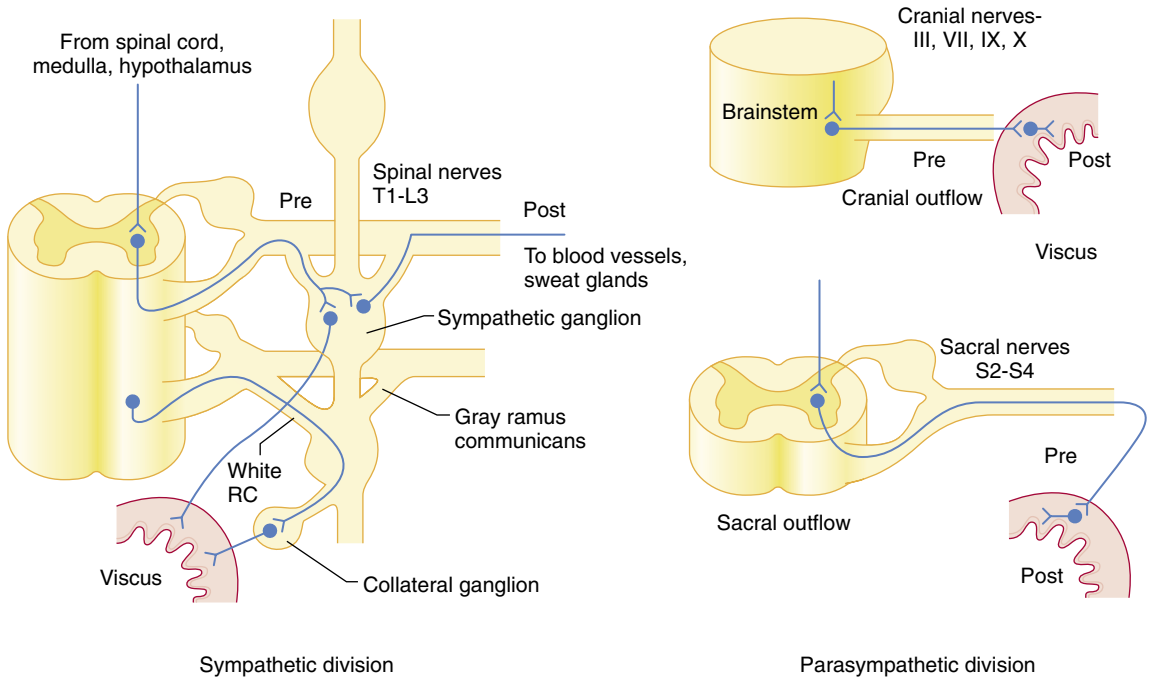

Figure 12-3 Autonomic nervous system. Pre, preganglionic neuron; Post, postganglionic neuron; RC, ramus communicans. *(From Ganong W: The autonomic nervous system.* In *Ganong W [ed]: Review of Medical Physiology, 15th ed. Norwalk, CT, Appleton & Lange, 1991, p 210.)*

Parasympathetic Nervous System

The parasympathetic nervous system arises from cranial nerves III, VII, IX, and X, as well as from sacral segments. Unlike the sympathetic nervous system, ganglia of the parasympathetic nervous system are in close proximity to or within the innervated organ. This location of ganglia makes the parasympathetic nervous system more targeted and less robust than the sympathetic nervous system.

Preganglionic fibers of the parasympathetic nervous system originate in three areas of the CNS: the midbrain, the medulla oblongata, and the sacral part of the spinal cord. Fibers arising in the Edinger-Westphal nucleus of the oculomotor nerve course in the midbrain to synapse in the ciliary ganglion. This pathway innervates the smooth muscle of the iris and the ciliary muscle. In the medulla oblongata lie parasympathetic components of the facial (lacrimatory nucleus), glossopharyngeal, and vagus (dorsal nucleus) nerves. The facial nerve gives off parasympathetic fibers to the chorda tympani, which subsequently synapses in ganglia of the submaxillary or sublingual glands, and to the greater superficial petrosal nerve, which synapses in the sphenopalatine ganglion. The glossopharyngeal nerve synapses in the otic ganglion. These postganglionic fibers innervate the mucous, salivary, and lacrimal glands; they also carry vasodilator fibers.

The vagus is the most important of the parasympathetic nerves and transmits fully three fourths of the traffic of the parasympathetic nervous system. It supplies the heart, tracheobronchial tree, liver, spleen, kidney, and entire gastrointestinal tract except for the distal part of the colon. The preganglionic fibers of the vagus are long, whereas the postganglionic fibers are short. Most vagal fibers do not synapse until they arrive at small ganglia on and about the thoracic and abdominal viscera. Although the parasympathetic nerves may synapse with a 1:1 ratio of nerve to effector cells, the vagal innervation of the Auerbach plexus may connect one nerve fiber to 8000 cells.

The second through fourth sacral segments contribute the nervi erigentes, or the pelvic splanchnic nerves. They synapse in terminal ganglia associated with the rectum and genitourinary organs.

Enteric Nervous System

Given the importance of clinical phenomena such as nausea, vomiting, and alterations in bowel and bladder function associated with anesthesia, it is surprising how little is understood about the third branch of the ANS. The enteric nervous system is the network of neurons and their supporting cells found within the walls of the gastrointestinal tract, including neurons within the pancreas and gallbladder. The enteric nervous system contains as many nerve cells as the spinal cord does. It is derived from neuroblasts of the neural crest that migrate to the gastrointestinal tract along the vagus nerve.

One major difference between the enteric nervous system and the sympathetic and parasympathetic branches of the ANS is its extraordinary degree of local autonomy. Digestion and peristalsis occur after spinal cord transection or during spinal anesthesia, although sphincter function may be impaired.

Although functionally discrete, the gut is influenced by sympathetic and parasympathetic activity. The sympathetic preganglionic fibers from T8 through L3 inhibit gut action via the celiac, superior, and inferior mesenteric ganglia; a spinal or epidural anesthetic covering the midthoracic levels removes this inhibition and yields a contracted, small intestine that may afford superior surgical conditions in combination with the profound

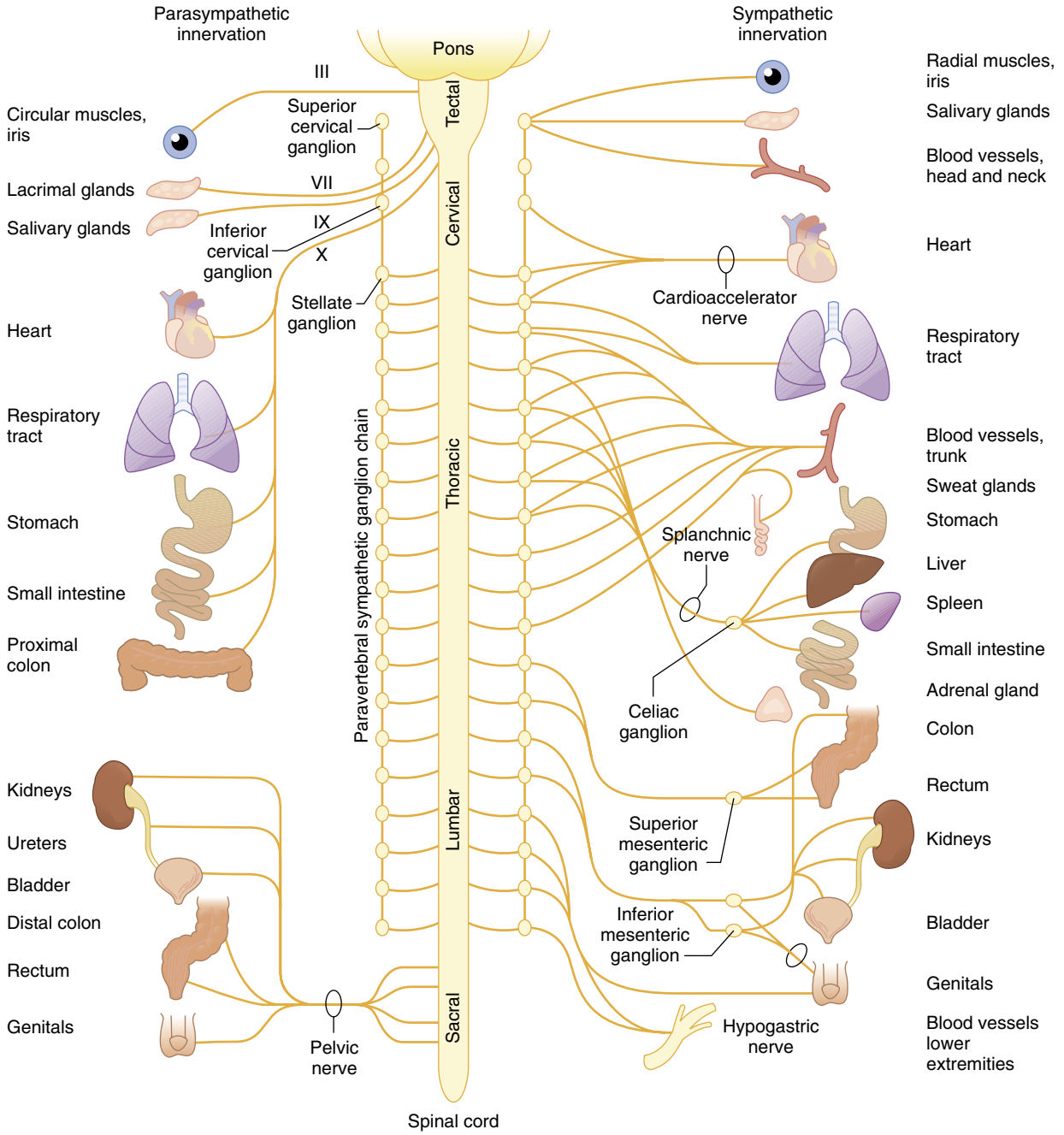

Figure 12-4 Schematic representation of the autonomic nervous system depicting the functional innervation of peripheral effector organs and the anatomic origin of peripheral autonomic nerves from the spinal cord. Although both paravertebral sympathetic ganglia chains are presented, the sympathetic innervation to the peripheral effector organs is shown only on the *right* part of the figure, whereas the parasympathetic innervation of peripheral effector organs is depicted on the *left*. The roman numerals on nerves originating in the tectal region of the brainstem refer to the cranial nerves that provide parasympathetic outflow to effector organs of the head, neck, and trunk. *(From Ruffolo R: Physiology and biochemistry of the peripheral autonomic nervous system.* In *Wingard L, Brody T, Larner J, et al [eds]: Human Pharmacology: Molecular to Clinical. St. Louis, Mosby–Year Book, 1991, p 77.)*

muscle relaxation of a spinal anesthetic. The sphincters are relaxed, and peristalsis is normally active.

Norepinephrine within the gut is the transmitter of postganglionic sympathetic neurons to the gut. For example, if the contents of the upper intestine become overly acidic or hypertonic, an adrenergically mediated enterogastric reflex reduces the rate of gastric emptying. The adrenergic neurons, which run to the myenteric ganglia of the gastrointestinal tract from the thoracic and lumbar spinal segments, are usually inactive in resting individuals. Reflex pathways within and external to the alimentary tract cause discharge of these neurons. When the viscera are handled during abdominal surgery, reflex firing of the adrenergic nerves inhibits motor activity of the intestine for an extended period. This adrenergic inhibition is thought to be the basis of the

common condition known as postoperative ileus. Loss of parasympathetic nervous control usually decreases bowel tone and peristalsis, but over time, the increased activity of the enteric plexus compensates for the loss. Spinal cord lesions may remove sacral parasympathetic input, but cranial parasympathetics may still be carried by branches of the vagus nerve down to the end-organ ganglia; colonic dilation and fecal impaction (which may precipitate hypertension in patients with autonomic dysreflexia) occur more often than small intestinal dysfunction.

Enteric neurons can be sensory and monitor tension in the wall of the intestine or its chemical contents, associative and act like interneurons, or motor and contract intestinal muscles, dilate vessels, or transport water and electrolytes. Motor neurons in the enteric nervous system may be excitatory or inhibitory.

Certain plexuses play important roles in the enteric nervous system. The myenteric plexus, also called the Auerbach plexus, is a network of nerve strands and small ganglia lying in the plane between the external longitudinal and circular muscle coats of the intestine. The submucous plexus (Meissner plexus) consists of nerve cell bodies, glial cells, and glial and neuronal processes, but it does not contain connective tissue or blood vessels. Within the ganglia, many neuronal processes contain vesicles that store neurotransmitters.

Unlike the sympathetic and parasympathetic nervous systems, in which geographic location can confer selective action, this is anatomically impossible in the gut, and an alternative pattern of chemical coding for function assumes an important organizational role. The combination of amines and peptides and their relative concentrations within the enteric neuron determine its function.

Acetylcholine, the principal excitatory trigger of the nonsphincteric portion of the enteric nervous system, causes muscle contraction. Cholinergic neurons have several roles in the enteric nervous system, including excitation of external muscle, activation of motor neurons augmenting secretion of water and electrolytes, and stimulation of gastric cells. Neural control of gastrointestinal motility is mediated through two types of motor neurons: excitatory and inhibitory. These neurons act in concert on the circular smooth muscle layer in sphincteric and nonsphincteric regions throughout the digestive tract and supply muscles of the biliary tree and the muscularis mucosae. Although excitatory motor neurons supply the external longitudinal muscle, the role of inhibitory motor neurons is not well established in this muscular layer. Enteric motor neurons to the circular muscle of the small and large intestine are activated by local reflex pathways contained within the wall of the intestine. Distention evokes polarized reflexes, including contraction proximally and relaxation distally, which in synchrony constitute peristalsis. Nicotinic antagonists abolish enteric reflexes, thus suggesting that the sensory neurons or interneurons in the pathway are cholinergic. In cases of cholinergic overload, such as insecticide poisoning or "over-reversal" of muscle relaxants, the gut (in which cholinesterase is inhibited) has a tendency to become hyperreactive.

There are many neuroactive compounds other than norepinephrine and acetylcholine that participate in the autonomic control of intestinal function. The predominant of these nonadrenergic noncholinergic (NANC) neurotransmitters appears to be nitric oxide (NO), a primary intrinsic inhibitor, but other NANC neurotransmitters such as substance P, a variety of opiate peptides, vasoactive intestinal polypeptide (VIP), and a growing population of peptide hormones are also present (Table 12-1) (see Chapter 31).

Table 12-1 Neuropeptides and Their Actions in the Gastrointestinal Tract

Peptide	Action(s)
Bombesin	Multiple stimulatory effects (including gastrin release)
Calcitonin gene–related peptide	Gastric acid secretion, muscle constriction
CCK8	Unknown
Dynorphin	Opiate effects
Endothelin-1	Vasoconstriction
Galanin	Muscle constriction
Leu-enkephalin	Opiate effects
Met-enkephalin	Opiate effects
Neuromedin U	Muscle constriction, vasoconstriction
Neuropeptide Y	Vasoconstriction
Pituitary adenylate cylase	Adenylate cyclase–activating peptide
Peptide histidine methionine	Muscle relaxation, secretion
Somatostatin	Multiple inhibitory effects (including gastrin inhibition)
Substance P	Vasodilation, muscle constriction
Vasoactive intestinal polypeptide	Vasodilation, muscle relaxation, secretion

Modified from Bishop A, Polak J: The gut and the autonomic nervous system. *In* Mathias C, Bannister R (eds): Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System, 4th ed. Oxford, Oxford University Press, 1999, p 120.

Function

Organization and Integration

The sympathetic system, in response to internal or external challenges, acts to increase the heart rate, arterial pressure, and cardiac output; dilate the bronchial tree; and shunt blood away from the intestines and other viscera to voluntary muscles. Parasympathetic nervous input acts primarily to conserve energy and maintain organ function and to support vegetative processes.

Most organs of the body exhibit dual innervation, with input from the sympathetic and parasympathetic systems frequently mediating opposing effects (Table 12-2).[1] Stimulation of one system may have an excitatory effect on the end organ, whereas stimulation of the other system may have an inhibitory effect. For example, sympathetic stimulation acts on the heart to increase the rate and vigor of contraction and enhance conduction through the atrioventricular (AV) node, whereas parasympathetic stimulation acts to decrease the heart rate, atrial

Table 12-2 Responses Elicited in Effector Organs by Stimulation of Sympathetic and Parasympathetic Nerves

Effector Organ	Adrenergic Response	Receptor Involved	Cholinergic Response	Dominant Response (A or C)
Heart				
Rate of contraction	Increase	β_1	Decrease	C
Force of contraction	Increase	β_1	Decrease	C
Blood vessels				
Arteries (most)	Vasoconstriction	α_1		A
Skeletal muscle	Vasodilation	β_2		A
Veins	Vasoconstriction	α_2		A
Bronchial tree	Bronchodilation	β_2	Bronchoconstriction	C
Splenic capsule	Contraction	α_1		A
Uterus	Contraction	α_1	Variable	A
Vas deferens	Contraction	α_1		A
Prostatic capsule	Contraction	α_1		A
Gastrointestinal tract	Relaxation	α_2	Contraction	C
Eye				
Radial muscle, iris	Contraction (mydriasis)	α_1		A
Circular muscle, iris			Contraction (miosis)	C
Ciliary muscle	Relaxation	β	Contraction (accommodation)	C
Kidney	Renin secretion	β_1		A
Urinary bladder				
Detrusor	Relaxation	β	Contraction	C
Trigone and sphincter	Contraction	α_1	Relaxation	A, C
Ureter	Contraction	α_1	Relaxation	A
Insulin release from pancreas	Decrease	α_2		A
Fat cells	Lipolysis	β_1		A
Liver glycogenolysis	Increase	α_1		A
Hair follicles, smooth muscle	Contraction (piloerection)	α_1		A
Nasal secretion			Increase	C
Salivary glands	Increase secretion	α_1	Increase secretion	C
Sweat glands	Increase secretion	α_1	Increase secretion	C

A, adrenergic; C, cholinergic.
From Ruffolo R: Physiology and biochemistry of the peripheral autonomic nervous system. *In* Wingard L, Brody T, Larner J, et al (eds): Human Pharmacology: Molecular to Clinical. St. Louis, Mosby–Year Book, 1991, p 77.

contractility, and conduction through the AV node. One of the two systems normally dominates the organ's function and thus provides its "resting tone" (Table 12-3). In a few organs, the sympathetic system alone provides innervation; most blood vessels, the spleen, and piloerector muscles are examples.

To predict the effects of drugs, the interaction of the sympathetic and parasympathetic system in different organs must be understood. Blockade of sympathetic function unmasks preexisting parasympathetic activity, and the converse relationship is also true. For example, administration of atropine blocks the resting muscarinic tone of the parasympathetically dominated heart, and the unopposed sympathetic tone then causes tachycardia. Clinically, cardiac autonomic denervation occurs with cardiac transplantation; it may occur with neuraxial anesthesia, diabetes, and MI; and it can be assessed by changes in the time interval between successive heartbeats (i.e., beat-to-beat or heart rate variability) as a measure of sympathovagal balance.[2]

Adrenergic Function

Overview of the Effects of Sympathetic Mediators

Adrenergic neurons influence and adjust body functions, their effects on circulation and respiration being among the most important (Table 12-4).

The endogenous catecholamines norepinephrine and epinephrine possess α- and β-receptor agonist activity. Norepinephrine has minimal β_2-receptor activity, whereas epine-

Table 12-3 Usual Sympathetic or Parasympathetic Dominance at Specific Effector Sites

Site	Predominant Tone
Ciliary muscle	Parasympathetic
Iris	Parasympathetic
Sinoatrial node	Parasympathetic
Arterioles	Sympathetic
Veins	Sympathetic
Gastrointestinal tract	Parasympathetic
Uterus	Parasympathetic
Urinary bladder	Parasympathetic
Salivary glands	Parasympathetic
Sweat glands	Sympathetic (cholinergic)

phrine stimulates β_1- and β_2-receptors (Table 12-5). α-Receptor–mediated activity is responsible for most of the sympathetically induced smooth muscle contraction throughout the body, including the ciliary muscle of the eye and vascular, bronchial, and ureteral smooth muscle. The gastrointestinal and genitourinary sphincter mechanisms are stimulated by α-adrenergic receptors. α-Receptor agonism also mediates sympathetic nervous system control of pancreatic insulin secretion, with stimulation of α_2-receptors leading to decreased release of insulin from pancreatic beta cells. In the peripheral vasculature, α_1- and α_2-receptors modulate vascular tone in response to humorally borne neurotransmitters and exogenously administered drugs.

β-Receptor agonism is primarily responsible for sympathetic stimulation of the heart, relaxation of vascular and bronchial smooth muscle, stimulation of renin secretion by the kidney,

Table 12-4 Effects of Activation of the Sympathetic Nervous System

Site of Action	Stimulation	Inhibition
Heart	Rate, conduction, contractility	
Blood vessels	Vasoconstriction (skin, gut, liver, heart, kidney)	Vasodilation (skeletal muscle, heart, brain)
Respiration	Respiratory center Bronchodilation	
Gastrointestinal tract	Sphincters	Smooth muscle
Genitourinary tract	Sphincters	Ureteral and uterine muscle
Metabolic and endocrine effects	Glycogenolysis (muscle, liver) Gluconeogenesis Insulin release (β_1) Renin release ADH release	Insulin release (α stimulation or β_1 antagonism) Lipolysis

ADH, antidiuretic hormone or arginine vasopressin.

Table 12-5 Adrenergic Receptor Differentiation

Receptor	Stimulation	Inhibition
Alpha		
Heart		
Blood vessels	Vasoconstriction (skin, gut, kidney, liver, heart)	
Gastrointestinal tract	Sphincters	
Genitourinary tract	Sphincters	
Metabolic and endocrine effects		Insulin release
Beta		
Heart	(1) Rate, conduction contractility	
Blood vessels		(2) Vasodilation (skeletal muscle, heart, brain)
Respiration	(?) Respiratory center (2) Bronchodilation	
Gastrointestinal tract		(2) Smooth muscle
Genitourinary tract		(2) Ureteral and uterine muscle
Metabolic and endocrine effects	(2) Glycogenolysis (muscle, liver) (1) Lipolysis (2) Gluconeogenesis (1) Insulin release (?) Renin release (?) Antidiuretic hormone release	

(1), Mediated by β_1-receptors; (2), mediated by β_2-receptors; (?), controversial.

and several metabolic consequences, including lipolysis and glycogenolysis. The β_1-receptor mechanism is thought to primarily be involved in cardiac effects[3] and release of fatty acids and renin, whereas β_2-receptors are primarily responsible for smooth muscle relaxation and hyperglycemia. In specialized circumstances, however, β_2-receptors may also mediate cardiac activity. Although acute changes in arterial pressure and heart rate can be caused by norepinephrine or epinephrine, chronic hypertension does not appear to be related to circulating levels of these hormones. Eighty-five percent of resting arterial pressure is determined by the level of renin activity (Fig. 12-5). An additional important effect of epinephrine is to increase gap junctions in bone, which causes an increase in circulating blood elements.[4]

Psychological and physical stimuli may evoke different sympathetic compensatory responses. Public speaking activates the adrenal gland with a disproportionate rise in serum epinephrine, whereas physical exercise elicits primarily a marked rise in serum norepinephrine.[5] Thus, the stress response should not be thought of as a uniform response; it can vary in mechanism, intensity, and manifestations.

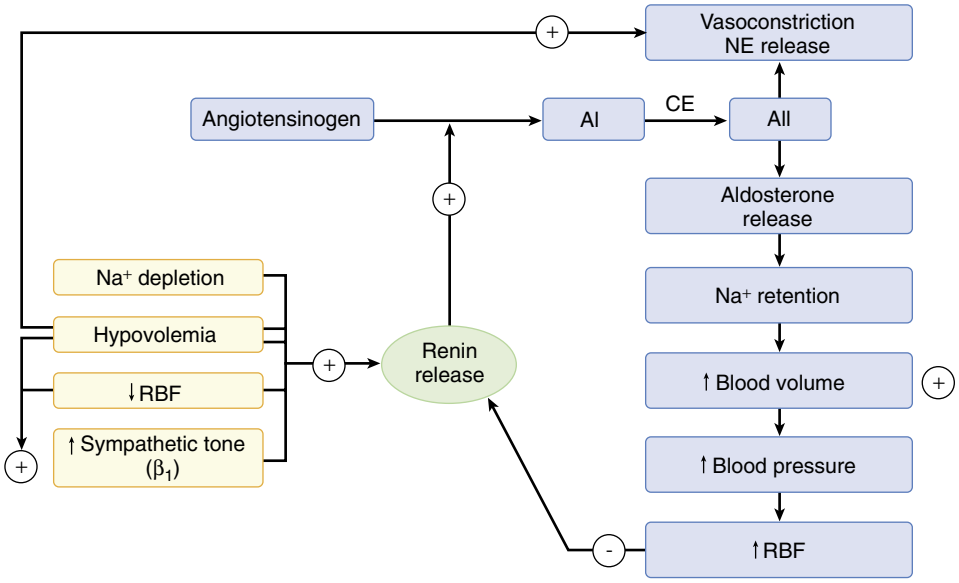

Figure 12-5 Interactions of the renin-angiotensin-aldosterone and sympathetic nervous systems in maintaining blood pressure and volume. AI, angiotensin I; AII, angiotensin II; CE, converting enzyme; NE, norepinephrine; RBF, renal blood flow; +, stimulating effects; –, inhibiting effects.

Blood Glucose

Sympathetic nervous stimulation of β-receptors increases glycogenolysis in liver and muscle and liberates free fatty acids from adipose tissue, thereby ultimately increasing blood glucose levels. In neonates, epinephrine plays an additional role in the exothermic breakdown of brown fat to maintain body temperature (i.e., nonshivering thermogenesis).

Also present in the pancreas are α_2 and β_2 receptors. α_2-Receptor activation suppresses insulin secretion by pancreatic islet cells; blockade of these receptors may increase release of insulin and thus could be associated with significant lowering of blood glucose levels. β_2-Receptor stimulation increases glucagon and insulin secretion and decreases peripheral sensitivity to insulin.[6]

Potassium Shift

Plasma epinephrine also takes part in regulation of the serum potassium concentration. β-Adrenergic activity can initiate transient hyperkalemia as potassium shifts out of hepatic cells with the glucose efflux produced by β_2-adrenergic stimulation. This effect is followed by a more prolonged hypokalemia as β_2-adrenergic stimulation drives potassium into red blood cells and muscle cells. Stimulation of the β_2-receptors of red blood cells by exogenously administered or endogenously released epinephrine activates adenylate cyclase and sodium-potassium adenosine triphosphatase (ATPase) and drives potassium into cells. This leads to a reduction in serum potassium concentration and may contribute to the cardiac arrhythmias accompanying MI and other stresses. β_2-Adrenergic blockade has the theoretical advantage of inhibiting this potassium shift. However, selective and nonselective β-blockers have been shown to be equivalent in protecting the postinfarction heart against arrhythmias.[7-11]

Cholinergic Function

Overview of the Effects of Acetylcholine

In contrast to the diffuse discharge of the sympathetic nervous system that constitutes the fight-or-flight response, the parasympathetic system is anatomically and functionally more localized in its effects. Parasympathetic activation conserves energy and maintains organ function. A massive parasympathetic response would prostrate the organism, leaving it helplessly salivating, weeping, wheezing, vomiting, urinating, defecating, and seizing. Although the sympathetic system is needed for the emergency response to stressful situations, it is not necessary for survival; the parasympathetic system is, however, essential for maintenance of life.

Release of acetylcholine is the hallmark of parasympathetic activation. The actions of acetylcholine are almost diametrically opposed to those of norepinephrine and epinephrine. In general, the muscarinic effects of acetylcholine are qualitatively the same as the effects of vagal stimulation.

Acetylcholine decreases the heart rate, the velocity of conduction in the sinoatrial and AV nodes, and atrial contractility (although this decrease is not as marked as the increase in contractility produced by sympathetic stimulation). In the sinoatrial node, acetylcholine causes membrane hyperpolarization, which delays attainment of the threshold potential and the ability to generate another action potential, thereby slowing the heart rate. In the AV node, acetylcholine decreases conduction velocity and increases the effective refractory period. This decrease in AV nodal conduction accounts for the complete heart block seen when large amounts of cholinergic agonists are given. In the ventricle, acetylcholine decreases automaticity in the Purkinje system, thereby increasing the fibrillation threshold. Cardiac presynaptic and postsynaptic muscarinic receptors are involved in these effects. Acetylcholine inhibits adrenergic stimulation of the heart presynaptically by inhibiting the release of norepinephrine from sympathetic nerve endings and postsynaptically by opposing the effects of catecholamines on the myocardium.

Parasympathetic activation has many effects outside the cardiovascular system. Cholinergic stimulation causes smooth muscle constriction, including that of the bronchial walls. In the gastrointestinal and genitourinary tracts, smooth muscle in the walls constricts, but the sphincter muscles relax, which results in incontinence. Topically administered acetylcholine constricts the smooth muscle of the iris and causes miosis.

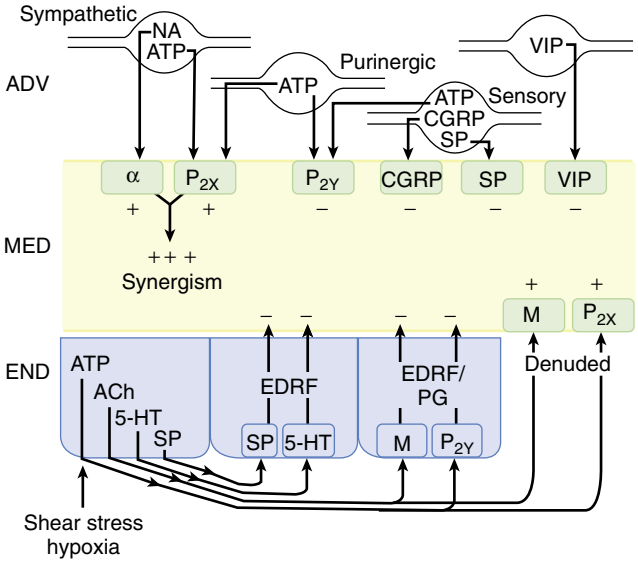

Figure 12-6 Schematic representation of potential modes of regulation of vascular tone by endothelial cell–related mechanisms. Norepinephrine (NA), adenosine triphosphate (ATP), calcitonin gene–related peptide (CGRP), substance P (SP), and vasoactive intestinal polypeptide (VIP) can be released from nerves in the adventitia (ADV) to act on their respective receptors in the media (MED) and cause vasoconstriction or vasodilation. ATP, acetylcholine (ACh), 5-hydroxytryptamine (5-HT), and SP released from endothelial cells (END) by shear stress or hypoxia act on their receptors on endothelial cells to cause release of endothelium-derived relaxing factors (EDRF) or prostaglandins (PG), which act on smooth muscle to cause relaxation. In areas denuded of endothelial cells, opposite effects may be produced by receptors on smooth muscle. α, noradrenaline receptor; M, muscarinic receptor; P_{2X}, P2X purinoceptor; P_{2Y}, P2Y purinoceptor. *(From Lincoln J, Burnstock G: Neural-endothelial interactions in control of local blood flow.* In *Warren J [ed]: The Endothelium: An Introduction to Current Research. New York, Wiley-Liss, 1990, p 21.)*

The signs and symptoms of cholinergic overload reflect all these effects, as well as nausea and vomiting, intestinal cramps, belching, urination, and urgent defecation. All glands innervated by the parasympathetic nervous system are stimulated to produce secretions, including the lacrimal, tracheobronchial, salivary, digestive, and exocrine glands.

Local Control of Vascular Tone

In addition to the pharmacologic effects of acetylcholine that are mediated by the parasympathetic nervous system, blood-borne acetylcholine has a significant effect on blood vessels in that it dilates virtually all vessels in vivo. Endothelial cells respond to acetylcholine stimulation by producing one or more endothelium-derived relaxing factors (EDRFs).[12] It now appears that endothelial cells have receptors for numerous agonists, including serotonin, adenosine, histamine, and catecholamines (Fig. 12-6). The radical NO was the first identified EDRF (see Chapter 31 for details). When the endothelium is damaged, as in atherosclerosis, production of EDRF diminishes and constriction increases. This change explains why patients with damaged or diseased vessels react differently.

An understanding of the biology of NO is fundamental to an appreciation of many vital body functions (see Chaper 31).[13] Endothelial cells play a role in control of the circulation in addition to the production of NO. Endothelial cells metabolize many vasoactive amines, convert angiotensin I to angiotensin II, and secrete prostacyclin and the vasoconstrictive peptide endothelin-1 (ET-1). NO, ET-1, and prostacyclin are local hormones released by endothelial cells to influence their immediate microenvironment. Prostacyclin and NO relax vascular smooth muscle, whereas in the lumen, they act separately or in concert to prevent platelets from clumping onto the endothelium. There is clear synergism between the antiaggregating effect of prostacyclin and subthreshold concentrations of NO. Substances that activate prostacyclin generally stimulate release of NO. Shear stress increases NO as an adaptive mechanism to dilate the circulation actively. NO works by the guanylate cyclase mechanism; prostacyclin works by activation of adenylate cyclase. Thus, although they work in concert, they activate different second messengers.

Whereas prostacyclin and NO are short-lived vasodilators, injection of the vasoconstrictor ET-1 causes a powerful and long-lasting pressor effect. ET-1, which is composed of 21 amino acids bound by two disulfide bonds, is generated enzymatically from the 39–amino acid ET-1 precursor known as big ET-1. The vasoconstrictor action of ET-1 results from activation of endothelin receptors on smooth muscle.[14]

NO, prostacyclin, and ET-1 appear to be operative in local control of the circulation. The prostacyclin system may be a redundant mechanism that reinforces the NO system in the presence of endothelial damage. Acting together, these two dilators are also a strong defense mechanism against intravascular thrombosis. ET-1 can be produced locally in response to trauma, such as wounds to the vessel wall, and it perhaps decreases blood loss. The long-term functions of these local hormones are of considerable interest in the pathophysiology of many disease states, including septic shock, pulmonary hypertension, and renal failure.[15,16] For more information on NO biology, see Chapter 31.

Pharmacology

Adrenergic Pharmacology

Synthesis of Norepinephrine

Norepinephrine is synthesized from tyrosine, which is actively transported into the varicosity of the postganglionic sympathetic nerve ending (Fig. 12-7). Tyrosine is synthesized from phenylalanine. In hypertensive rats, tyrosine may increase central adrenergic transmission, thereby decreasing peripheral sympathetic outflow.[17] In hypotensive (hemorrhaged) rats, tyrosine may increase peripheral synthesis and release of catecholamines. Precursors are taken up in greater amounts in shock and may have beneficial effects on the effort of the sympathetic nervous system to maintain perfusion pressure.

A series of steps results in conversion of tyrosine to norepinephrine and epinephrine (in the adrenal medulla). The first of these steps involves the rate-limiting cytoplasmic enzyme tyrosine hydroxylase (TH). High levels of norepinephrine inhibit TH, and low levels stimulate the enzyme. During stimulation of the sympathetic nervous system, an increased supply of tyrosine also increases the synthesis of norepinephrine. TH activity is modified by phosphorylation. TH depends on a pteridine cofactor and the presence of molecular oxygen. When the quantity of molecular oxygen is reduced, synthesis of norepinephrine may be decreased

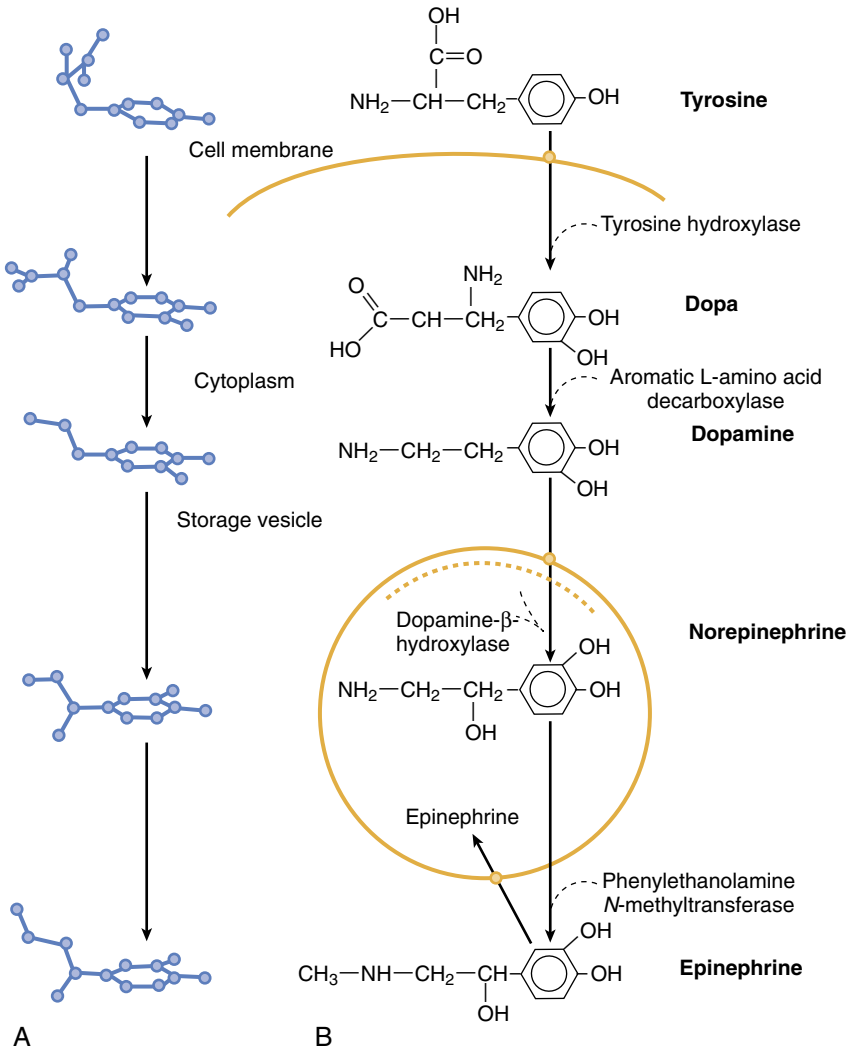

Figure 12-7 Biosynthesis of norepinephrine and epinephrine in sympathetic nerve terminal (and the adrenal medulla). **A,** Perspective view of molecules. **B,** Enzymatic processes. *(From Tollenaeré JP: Atlas of the Three-Dimensional Structure of Drugs. Amsterdam, Elsevier North-Holland, 1979; as modified by Vanhoutte PM: Adrenergic neuroeffector interaction in the blood vessel wall. Fed Proc 37:181, 1978.)*

significantly, which could account for changes in wakefulness. Whereas acute control of TH occurs by altering enzyme activity, chronic stress can elevate TH levels by stimulating the synthesis of new enzyme. Under the influence of TH, tyrosine is converted to dihydroxyphenylalanine (DOPA), which is decarboxylated to dopamine by aromatic amino acid decarboxylase (DOPA decarboxylase), a relatively promiscuous enzyme in its substrate specificity.

Dopamine can and does act as a neurotransmitter in some cells, but most of the dopamine produced is β-hydroxylated within the vesicles to norepinephrine by the enzyme dopamine β-hydroxylase (DβH). In the adrenal medulla and to a limited extent in discrete regions of the brain, another enzyme, phenylethanolamine *N*-methyltransferase (PNMT), methylates about 85% of the norepinephrine to epinephrine. Glucocorticoids from the adrenal cortex pass through the adrenal medulla and can activate the system, and stress-induced steroid release can increase the production of epinephrine. This local circulation amplifies the effects of glucocorticoid release.[18]

Storage of Norepinephrine

Norepinephrine is stored within large, dense-core vesicles. Electron microscopy suggests that the dense cores in these vesicles are filled not only with norepinephrine but also with binding proteins. In addition, the vesicles contain calcium, a variety of peptides, and adenosine 5′-triphosphate (ATP). Depending on the nature and frequency of physiologic stimuli, the ATP can be released selectively for an immediate postsynaptic effect through purinoreceptors. However, norepinephrine is the predominant neurotransmitter at sympathetic nerve endings.

Synaptic vesicles are heterogeneous and exist within functionally defined compartments. An actively recycling population of synaptic vesicles has been defined, together with a reserve population of vesicles that are mobilized only upon extensive stimulation. Functionally, norepinephrine is stored in compartments, 10% of which is readily releasable. In general, 1% of the stored norepinephrine is released with each depolarization, thus implying a significant functional reserve.

Release of Norepinephrine

There are several different processes by which the contents of the vesicle enter the synaptic cleft. The dominant physiologic mechanism of release is exocytosis, during which the vesicle responds to the entry of calcium by initiating vesicular docking, fusion, release of vesicular contents, and ultimately, endocytosis (the process by which the vesicular membrane and proteins are recap-

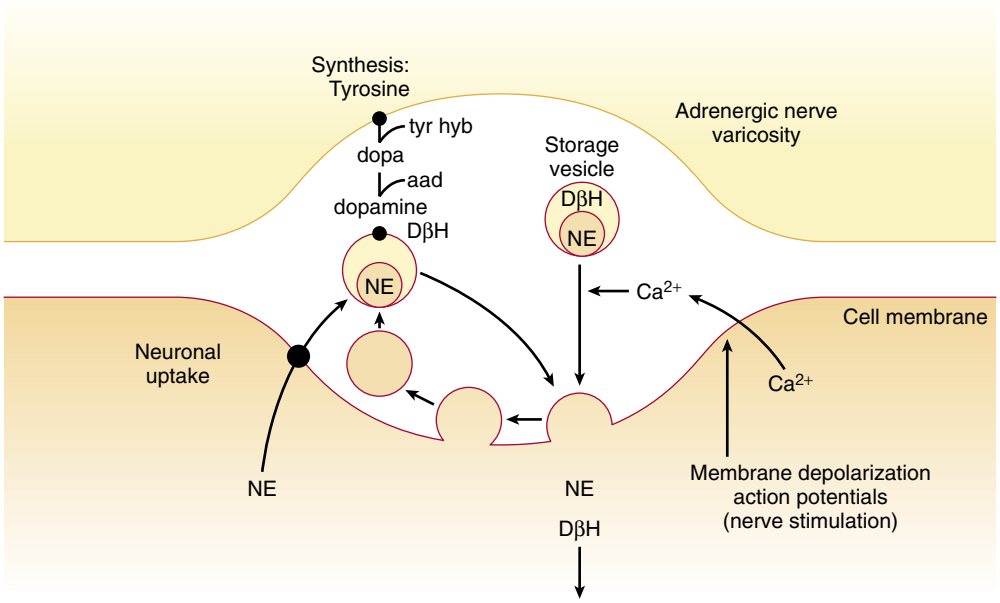

Figure 12-8 Release and reuptake of norepinephrine at sympathetic nerve terminals. aad, aromatic L-amino decarboxylase: DβH, dopamine β-hydroxylase; dopa, L-dihydroxyphenylalanine; NE, norepinephrine; tyr hyd, tyrosine hydroxylase; *solid circle*, active carrier. *(From Vanhoutte PM: Adrenergic neuroeffector interaction in the blood vessel wall. Fed Proc 37:181, 1978; as modified by Shepherd J, Vanhoutte P: Neurohumoral regulation.* In *Shepherd S, Vanhoutte P [eds]: The Human Cardiovascular System: Facts and Concepts. New York, Raven Press, 1979, p 107.)*

tured) (Fig. 12-8). The entire contents of the vesicle are liberated by stimulation of the nerve. The biology of vesicular release is not a random event, but a highly differentiated process. The fact that exocytosis is so highly conserved from species to species indicates its biologic importance. Angiotensin II, prostacyclin, and histamine potentiate release, whereas acetylcholine and prostaglandin E inhibit release.

Further details on neurotransmitter release are discussed in Chapter 23.

Although chromaffin cells in the adrenal medulla synthesize epinephrine and norepinephrine, the two compounds are stored in and secreted from distinct chromaffin cell subtypes. Pharmacologic differences between cells containing norepinephrine and epinephrine have been described, and data suggest that there may be preferential release from one or another form of chromaffin cell contingent on the nature of the stimulus. Nicotinic agonists or depolarizing agents cause the preferential release of norepinephrine, whereas histamine elicits predominantly epinephrine release.[19-21] Protein kinase C plays an important role in regulating secretion of catecholamine from norepinephrine-containing chromaffin cells.[22]

Inactivation

Most of the norepinephrine released is rapidly removed from the synaptic cleft by an amine mechanism (i.e., uptake-1 mechanism) or by non-neuronal tissue (i.e., uptake-2 mechanism). The uptake-1 mechanism represents the first and most important step in the inactivation of released norepinephrine. Most of the norepinephrine released is transported into storage vesicles for reuse. This uptake of neurotransmitter into synaptic vesicles is driven by an electrochemical proton gradient across the synaptic vesicle membrane. The vacuolar proton pump is a large hetero-oligomeric complex that contains eight to nine different subunits. After reuptake, the small amounts of norepinephrine not taken up into the vesicle are deaminated by cytoplasmic monoamine oxidase (MAO). There are several organ-specific forms of this enzyme.

Since its isolation and cloning in 1991, considerable information on the human norepinephrine transporter has accumulated.[23,24] The pharmacologic characteristics of this binding protein identify it as the cocaine binding site, although tricyclic antidepressants (i.e., desipramine and nortriptyline) are also potent antagonists.

Uptake of norepinephrine into the nerve varicosity and its return to the storage vesicle, albeit efficient, are not specific for the neurotransmitter. Some compounds structurally similar to norepinephrine may enter the nerve by the same mechanism and result in depletion of the neurotransmitter. These false transmitters can be of great clinical importance. Moreover, some drugs that block reuptake into the vesicle or into the synaptic ending itself may enhance the response to catecholamines; that is, more norepinephrine is available to receptors. Such drugs include cocaine and tricyclic antidepressants (Table 12-6).

Activity of the uptake-1 system varies greatly among different tissues. Because of anatomic barriers, peripheral blood vessels exhibit almost no reuptake of norepinephrine; consequently, rapid rates of norepinephrine synthesis are needed in peripheral blood vessels to modulate vascular tone. The highest rate of reuptake is found in the heart. Drugs or disease states that alter biosynthesis or storage (e.g., methyldopa decreases storage) have a more profound effect on blood pressure; those

Table 12-6 Comparison of Direct- and Indirect-acting Sympathomimetics

Pretreatment	Response of Effector Organ to: Direct Sympathomimetics (e.g., Epinephrine): Acts at the Receptor	Response of Effector Organ to: Indirect Sympathomimetics (e.g., Tyramine): Causes Release of NE after Its Uptake by Uptake 1
Denervation Loss of uptake-1 sites Receptor upregulation	Increased	Reduced
Reserpine Blocks vesicular uptake Depletes NE May cause upregulation	Slightly increased	Reduced
Cocaine Blocks uptake 1 Depletes NE	Increased	Reduced

NE, norepinephrine.
Adapted from Moore K: Drugs affecting the sympathetic nervous system. *In* Wingard L, Brody T, Larner J, et al (eds): Human Pharmacology: Molecular to Clinical. St. Louis, Mosby–Year Book, 1991, p 114.

that affect reuptake would be expected to affect cardiac rate and rhythm.

Typically, the lungs remove 25% of the norepinephrine that passes through the pulmonary circulation, whereas epinephrine and dopamine pass through unchanged. Pulmonary uptake of norepinephrine appears to be a sodium-dependent, facilitated transport process in the endothelial cells of precapillary and postcapillary vessels and pulmonary veins. There is no significant uptake by nerve endings. Primary or secondary pulmonary hypertension diminishes uptake of norepinephrine, presumably because of concomitant thickening of the pulmonary vasculature. Although the functional significance of the endothelial uptake mechanism of the pulmonary vascular wall is unknown, uptake of other powerful vasoactive compounds suggests that the pulmonary endothelium functions to protect the left heart.

Defects in the ANS are common in patients with congestive heart failure (CHF). The heart is depleted of catecholamines, and reuptake of norepinephrine is decreased.[25] Sustained sympathoexcitation results in increased neuronal release of norepinephrine.[26] Cardiac norepinephrine spillover rates differ widely, even among patients with end-stage heart failure awaiting cardiac transplantation, but some studies suggest that elevated plasma catecholamine levels portend a poorer prognosis than can be anticipated with traditional cardiovascular indices.[27,28] Because augmentation of catecholamine release is markedly impaired in patients with CHF, compensation for further decreases in systemic vascular resistance requires activation of the renin-angiotensin system. Together, these events result in increased adrenergic drive, desensitization of β-receptors, and depletion of norepinephrine stores, which contribute to insufficient inotropic function.[29,30]

Metabolism

During storage and reuptake, a small amount of norepinephrine escapes uptake into the nerve ending and enters the circulation, where it is metabolized by MAO, catechol *O*-methyltransferase (COMT), or both in the blood, liver, and kidney (Fig. 12-9).

Epinephrine, which is released by the adrenal medulla, is inactivated by the same enzymes. The final metabolic product of inactivation is vanillylmandelic acid (VMA). Because of its rapid clearance, the half-life of norepinephrine (and most biogenic amines) in plasma is short, less than 1 minute. This short half-life necessitates administration of these drugs by infusion. Another consequence of their short half-life is that a more ideal measure of catecholamine production may be metabolic products rather than the catecholamines themselves. For example, screening for a norepinephrine-producing pheochromocytoma is frequently done by measuring the level of urine metanephrine and VMA. Only a small percentage of norepinephrine appears in the urine for assay.

Inhibition of MAO has a large impact on the sympathetic function of a patient. MAO inhibitors (MAOIs) are generally well tolerated, but the stability of the patient belies the fact that amine handling is fundamentally changed. Clinically important, life-threatening drug interactions are discussed later in the section "Drugs and the Autonomic Nervous System."

Other compounds can be metabolized by catabolic enzymes to produce false transmitters. Though not used therapeutically, tyramine is the prototypical drug studied. Tyramine is present in many foods, particularly aged cheese and wine, and it can be synthesized from tyrosine. Tyramine enters the sympathetic nerve terminal through the uptake-1 mechanism and displaces norepinephrine from the vesicles into the cytoplasm. The released norepinephrine leaks out of the cytoplasm and is responsible for the hypertensive effect of tyramine. However, a secondary effect can occur. In the vesicle, tyramine is converted by DβH to octopamine, which is eventually released as a false transmitter in place of norepinephrine, but without the hypertensive effect because it has only 10% of the potency of norepinephrine.

Adrenergic Receptors

Initially, α-adrenergic receptors were distinguished from β-adrenergic receptors by their greater response to epinephrine and norepinephrine than to isoproterenol. The development of α- and β-antagonists further supported the existence of separate α-receptors. Traditionally, adrenergic receptors have been classified as α or β and more recently as α_1, α_2, β_1, or β_2 based on responses to specific drugs. With technologic advances in molecular biology, classification evolved to three major subtypes and nine subsubtypes (Fig. 12-10).[31] Table 12-7 describes the distribution, response, typical agonists, and antagonists of the α_1-, α_2-, β_1-, and β_2-receptors.

α-Adrenergic Receptors

Functional and binding assays and molecular biologic methods have unequivocally confirmed the classification of α-adrenoceptors into subtypes.[32] Within α_1-adrenergic receptors, $\alpha_{1a/d}$-, α_{1b}-, and α_{1c}-receptors have been characterized. Several α_2-isoreceptors (α_{2a}, α_{2b}, and α_{2c}) have also been described. α_2-Receptors are usually expressed presynaptically or even in nonneuronal tissue. α_2-Receptors are found in the peripheral nervous system, in the CNS, and in a variety of organs, including platelets, liver, pancreas, kidney, and eyes, where specific physiologic functions have been identified.[33] Later, the predominant α_2-receptor of the human spinal cord was identified as the α_{2a}-subtype.[31,34] It appears that mammalian genomes contain two sets of at least three unique genes encoding the α-adrenoceptors. Genes encoding α_2-receptors have been localized to chromosomes 2, 4, and

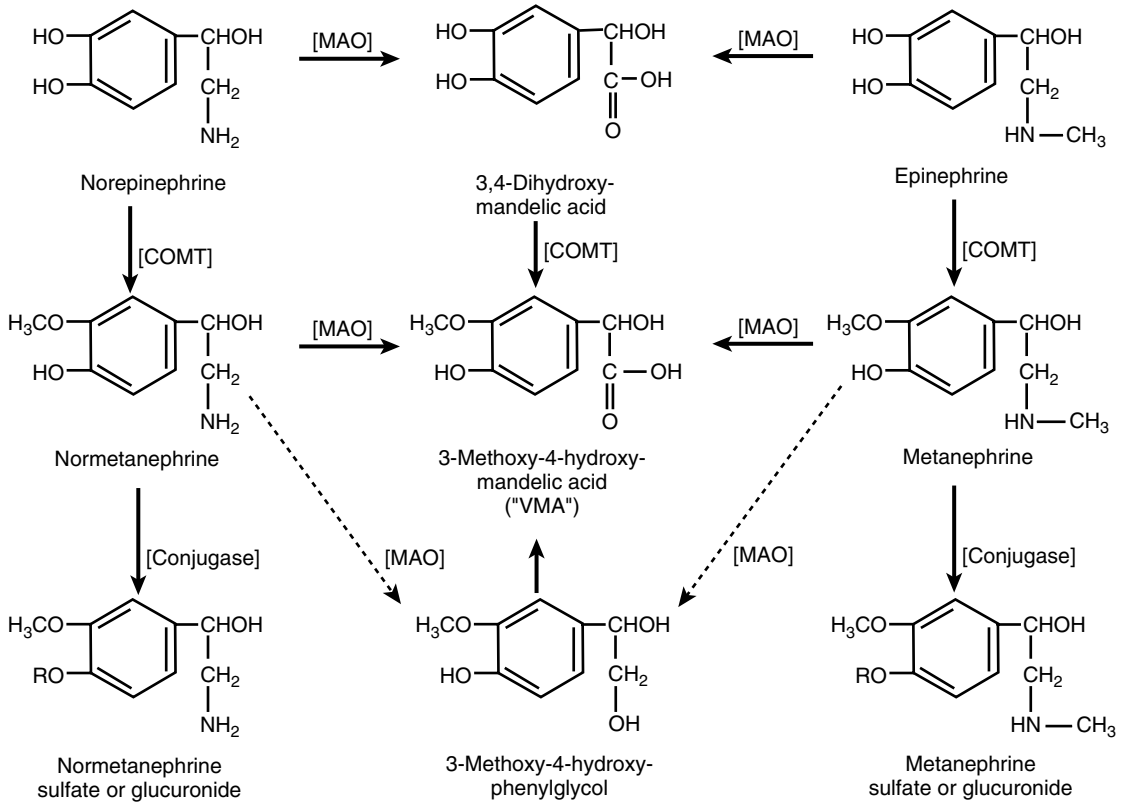

Figure 12-9 Metabolism of catecholamines. COMT, catechol *O*-methyltransferase; MAO, monoamine oxidase. *(From Lake CR, Chernow B, Feuerstein G, et al: The sympathetic nervous system in man, its evaluation and the measurement of plasma norepinephrine.* In *Zigler M, Lake C [eds]: Frontiers of Clinical Neuroscience, vol 2. Baltimore, Williams & Wilkins, 1984, p 1.)*

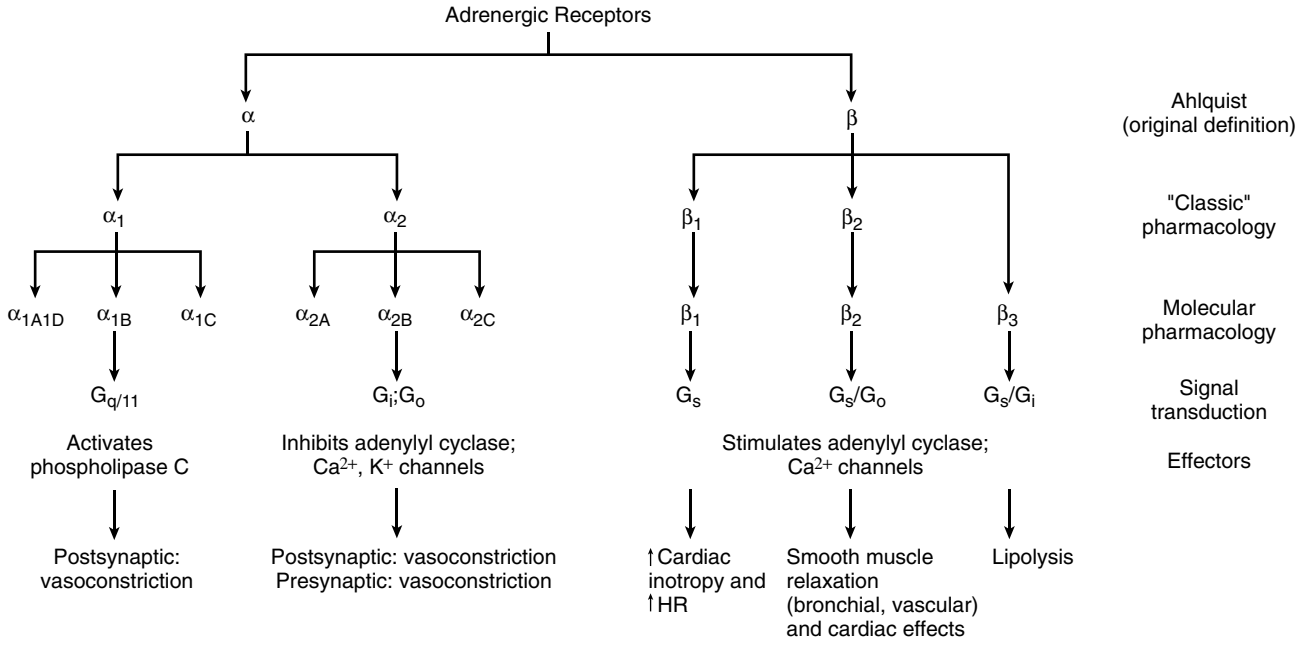

Figure 12-10 Classification of adrenergic receptors. HR, heart rate.

Table 12-7 Distribution of α- and β-Receptors

Receptor	Distribution	Response	Agonist	Antagonist
α_1	Smooth muscle	Constriction	Methoxamine Phenylephrine	Prazosin
α_2	Presynaptic	Inhibits norepinephrine release	Clonidine Dexmedetomidine	Yohimbine
β_1	Heart	Inotropy Chronotropy	Dobutamine	Metoprolol
β_2	Smooth muscle	Dilation Relaxation	Terbutaline	

10. There is more than theoretical relevance in the subclassification of receptors[35] in that mutations that decrease α_{2c} presynaptic function and enhance β_1-receptor linkage cause adrenergic hyperactivity and predispose to CHF.[36]

Amino acid sequence comparisons indicate that α-receptors are members of the seven–transmembrane segment gene superfamily, which uses G protein for signal transduction. A core of 175 amino acids constitutes the seven transmembrane regions and is highly conserved among different family members. The plethora of receptor subtypes remains incompletely explained, although the observation that different signal transduction mechanisms are used suggests finer control and physiologic significance. It may be important that there is considerable variability in α-adrenergic receptor subtypes among species.[37]

Receptors can be presynaptic as well as postsynaptic. Presynaptic receptors may act as heteroreceptors or autoreceptors. An *autoreceptor* is a presynaptic receptor that reacts with the neurotransmitter released from its own nerve terminal to provide feedback regulation. A *heteroreceptor* is a presynaptic receptor that responds to substances other than the neurotransmitter released from that specific nerve terminal. This regulatory scheme is present throughout the nervous system but is particularly important in the sympathetic nervous system.[38]

Although several presynaptic receptors have been identified, the α_2-receptor may have the greatest clinical import. Presynaptic α_2-receptors regulate the release of norepinephrine and ATP through a negative-feedback mechanism.[39] Activation of presynaptic α_2-receptors by norepinephrine inhibits subsequent release of norepinephrine in response to nerve stimulation. A similar inhibitory response is produced by attachment of acetylcholine to presynaptic cholinergic receptors. In the human brain, ligand studies reveal a high density of α_2-receptors, particularly in the cerebral cortex and medulla.[40] This latter distribution may account for the bradycardiac and hypotensive responses to α_2-agonist drugs.

β-Adrenergic Receptors

Like the α-receptor, the β-receptor is one of the superfamily of proteins that have seven helices woven through the cellular membrane. These transmembrane domains are labeled M_1 through M_7; antagonists have specific binding sites, whereas agonists are more diffusely attached to hydrophobic membrane-spanning domains (Fig. 12-11). The extracellular portion of the receptor ends in an amino group. A carboxyl group occupies the intracellular terminal, where phosphorylation occurs. At the cytoplasmic domains, there is interaction with G proteins and kinases, including β-adrenergic receptor kinase. The β-receptor has mechanistic and structural similarities with muscarinic but not nicotinic receptors, primarily in the transmembrane sections.

β-Receptors have been further divided into β_1-, β_2-, and β_3-subtypes, all of which increase cyclic adenosine monophosphate (cAMP) through adenylate cyclase and the mediation of G proteins.[41] Although β_1-receptors were traditionally thought to be isolated to cardiac tissue and β_2-receptors were believed to be restricted to vascular and bronchial smooth muscle, we now know that the β_2-receptor population in human cardiac tissue is substantial and accounts for 15% of β-receptors in the ventricles and 30% to 40% in the atria.[42] β_2-Receptors may help compensate for disease by maintaining response to catecholamine stimulation when β_1-receptors are downregulated during chronic catecholamine stimulation and in CHF.[43] The β_2-population is almost unaffected in end-stage congestive cardiomyopathy.[44] In addition to positive inotropic effects, β_2-receptors in the human atria participate in regulation of the heart rate. Generation of cAMP in the human heart appears to be mediated primarily by β_2-receptors, although this may be an artifact related to the lability of β_1-receptors.[44] Localization of β_3-receptors to fat cells suggests a new therapy for obesity. Polymorphism of this β-receptor subtype is associated with obesity and the potential for the development of diabetes.[45-47] Point mutations in genes encoding β_2-receptors are correlated with decreased downregulation of β-receptors and nocturnal asthma.[48,49]

Dopamine Receptors

Dopamine exists as an intermediate in the biosynthesis of norepinephrine, and in addition, exogenous dopamine exerts α- or β-adrenergic effects (depending on the dose administered). Furthermore, Goldberg and Rajfer[50] demonstrated physiologically distinct dopamine type 1 (DA_1) and dopamine type 2 (DA_2) receptors, and these remain the most important of the five dopamine receptors cloned (Fig. 12-12). DA_1 receptors are postsynaptic and act on renal, mesenteric, splenic, and coronary vascular smooth muscle to mediate vasodilation through stimulation of adenylate cyclase and increased production of cAMP. The vasodilatory effect tends to be strongest in the renal arteries. It is for this action, particularly the redistribution of blood flow to the kidneys, that dopamine is most frequently used. Additional renal DA_1 receptors located in the tubules modulate natriuresis through the sodium-potassium ATPase pump and the sodium-hydrogen exchanger.[50-53] DA_2 receptors are presynaptic; they may inhibit release of norepinephrine and perhaps acetylcholine. There are also central DA_2 receptors that may mediate nausea and vomiting,

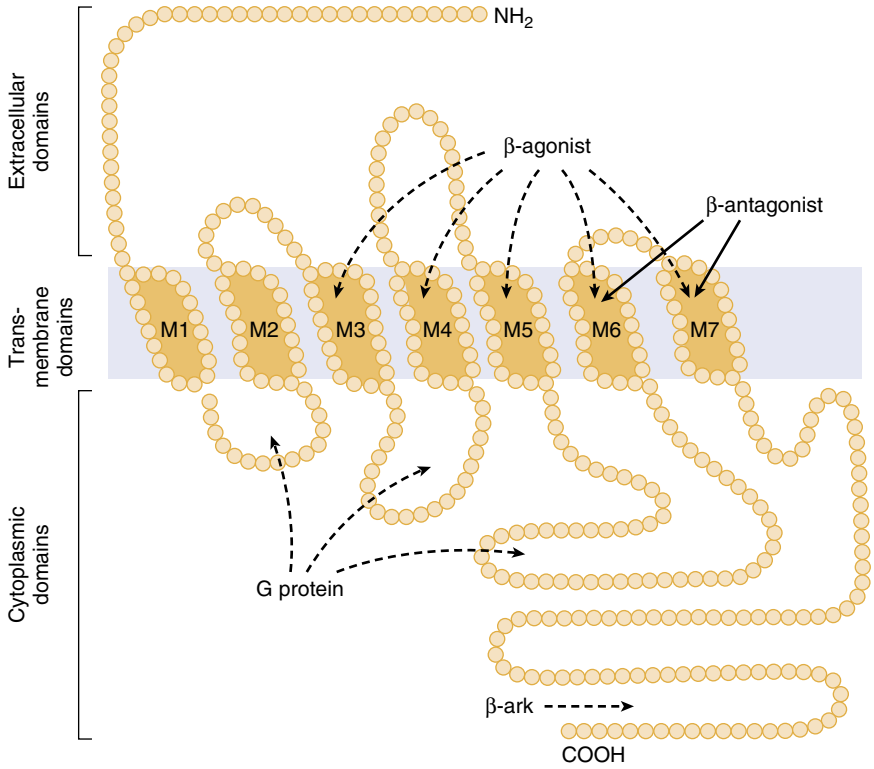

Figure 12-11 Molecular structure of the β-adrenergic receptor. Notice the three domains. The transmembrane domains act as a ligand-binding pocket. Cytoplasmic domains can interact with G proteins and kinases such as β-adrenergic receptor kinase (β-ARK). The latter can phosphorylate and desensitize the receptor. *(From Opie L: Receptors and signal transduction.* In *Opie LH [ed]: The Heart: Physiology and Metabolism. New York, Raven Press, 1991.)*

which may explain why the antiemetic activity of droperidol is thought to be related to its DA_2 activity.

GTP-Binding Regulatory Proteins (G Proteins)

After adrenergic receptor stimulation, the extracellular signal is transformed into an intracellular signal by a process known as signal transduction in which α_1- and β-receptors are coupled to G proteins. When activated, G proteins can modulate the synthesis or availability of intracellular second messengers (Fig. 12-13). The activated second messenger diffuses through the cytoplasm and stimulates an enzymatic cascade. The sequence of first messenger → receptor → G protein → effector → second messenger → enzymatic cascade is found in a wide variety of cells; the specific entities that fulfill the separate roles vary from cell to cell.[54] G proteins located on the inner surface of the cell membrane can also directly modify the activity of transmembrane ion channels.

G proteins are heterotrimeric compounds composed of three subunits labeled α, β, and γ. The β- and γ-subunits form a stable complex and the α-subunit associates with them in a reversible fashion. The β- and γ-subunits show little variation in their structure. In contrast, 20 different α-subunits have been

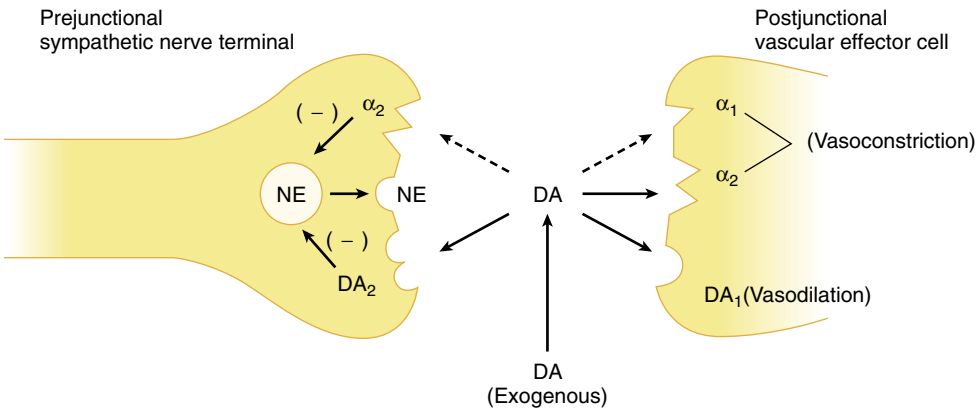

Figure 12-12 Location of dopamine type 1 (DA_1) receptors and α_1- and α_2-adrenoceptors on postganglionic vascular effector cells and DA_2 receptors and α_2-adrenoceptors on the prejunctional sympathetic nerve terminal. When dopamine is administered, activation of DA_1 receptors causes vasodilation, whereas activation of DA_2 receptors causes inhibition (–) of release of norepinephrine (NE) from storage granules. A larger dose of dopamine activates α_1- and α_2-adrenoceptors on the postjunctional effector cells to cause vasoconstriction and α_2-adrenoceptors on the prejunctional sympathetic terminal to inhibit release of NE. NE released from the prejunctional sympathetic terminal also acts on α_1- and α_2-adrenoceptors. *(From Goldberg LI, Rajfer SI: Dopamine receptors: Applications in clinical cardiology. Circulation 72:245, 1985.)*

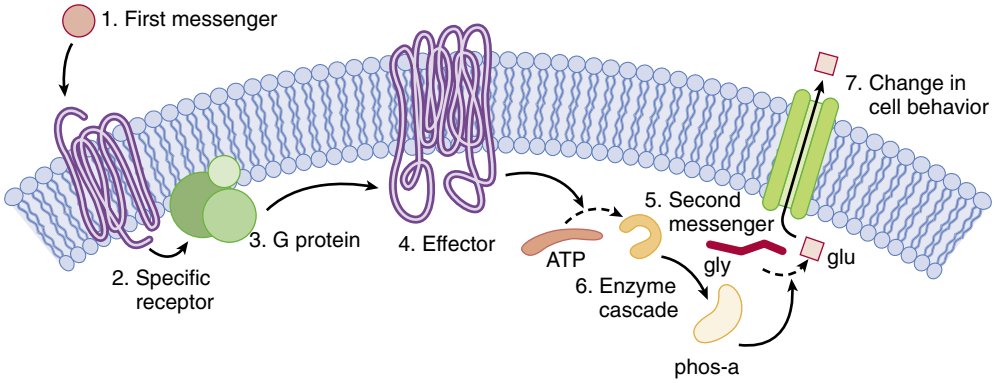

Figure 12-13 Epinephrine-stimulated glycogenolysis in a liver cell demonstrates the role of G proteins in cellular function. The first messenger (epinephrine) binds to its specific receptor and stimulates the G protein (in this case, G_s) to activate the effector adenylyl cyclase. This enzyme converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate, the second messenger, which then triggers a cascade of enzymatic reactions that stimulates the enzyme phosphorylase (phos-a) to convert glycogen into glucose, which the cell extrudes. *(From Linder ME, Gilman AG: G Proteins. Sci Am 267:56, 1992.)*

identified. The structure of the attached α-subunit defines the function of the G protein. Four classes of α-subunits have been defined: α_s, α_i, α_q, and α_{12}. The corresponding G protein complexes formed when these α-subunits bind to the βγ-structure are called G_s, G_i, G_q, and G_o.[55]

Each class of adrenergic receptor couples to a different major subfamily of G proteins, which are linked to different effectors. The major subtypes of α_1-, α_2-, and β-receptors are linked to G_q, G_i, and G_s, respectively, which are linked to activation of phospholipase C (α_1), inhibition of adenylyl cyclase (α_2), or stimulation of adenylyl cyclase (β) (see Fig. 12-10). In its resting state, the G protein is bound to guanosine diphosphate (GDP) and is not in contact with the receptor. When the receptor is activated by the first messenger, it stimulates the G protein to release GDP and bind guanosine triphosphate (GTP) to its α-subunit, thereby activating itself. The bound GTP signals the G protein to split into two parts consisting of the α-GTP structure and the βγ-subunit. The released α-subunit binds to the effector, activates it, and then converts its attached GTP to GDP, thereby returning itself to the resting state. The α-subunit joins with the βγ-unit, and the reconstructed G protein again waits at the inner membrane.

β-Receptor stimulation by G proteins enhances the activity of adenylate cyclase and the formation of cAMP. The briefest encounter of plasma membrane β-adrenergic receptors with epinephrine or norepinephrine results in profound increases (up to 400-fold higher than the basal level within minutes) in intracellular levels of cAMP. Increased cAMP synthesis activates protein kinases, which phosphorylate target proteins to elicit various cellular responses that complete the path between receptor and effect. Stimulation of α_2-receptors results in G_i inhibition of adenylate cyclase. The relative abundance of G proteins results in amplification of receptor agonism at the signal transduction step. The number of G protein molecules greatly exceeds the number of β-adrenergic receptors and adenylate cyclase molecules. It is the receptor concentration and ultimately adenylate cyclase activity that limit the response to catecholamines, which perhaps explains the efficacy of phosphodiesterase inhibitors.[56,57]

Myocardial cells respond to receptor stimulation differently, depending on the identity of the first messenger. Two opposing effects, inhibition and stimulation of contractility, are both produced by the sequence of receptor → G protein → effector → enzymatic cascade. However, the identity of the chemicals in the sequence differs.[58] Norepinephrine causes myocardial cells to contract with more vigor when the α-subunit of the stimulatory protein (G_s) activates adenylate cyclase. The α-subunits of this protein cause potassium channels to open and permit efflux of potassium ion. The force of contraction is diminished when acetylcholine acts as a first messenger and stimulates its receptor to activate the inhibitory protein G_i or G_o. Clinically important, second-to-second changes in heart rate can be explained by the simultaneous activation of G_s and G_o. The current caused by G_o is larger than that caused by G_s, which explains the clinical impression that vagal inhibition of heart rate predominates in the presence of sympathetic stimulation, such as may occur in unpremedicated patients.[58]

Upregulation and Downregulation

β-Adrenergic receptors are not fixed; they change significantly in dynamic response to the amount of norepinephrine present in the synaptic cleft or in plasma. For β-adrenergic receptors, this response is fast; within 30 minutes of denervation or adrenergic blockade, the number of receptors increases. Such upregulation may explain why sudden discontinuation of β-adrenergic receptor blocking drugs causes rebound tachycardia and increases the incidence of MI and ischemia. Many chronic phenomena, such as varicose veins[59] or aging, can decrease adrenergic receptor number or responsiveness systemically.

Clinically and at the cellular level, responses to many hormones and neurotransmitters wane rapidly despite continuous exposure to adrenergic agonists.[60] This phenomenon, called desensitization, has been particularly well studied for the stimulation of cAMP levels by plasma membrane β-adrenergic receptors. Mechanisms postulated for desensitization include uncoupling (e.g., phosphorylation), sequestration, and downregulation. The molecular mechanisms underlying rapid β-adrenergic receptor desensitization do not appear to require internalization of the receptors, but rather an alteration in the functioning of β-receptors themselves that uncouples the receptors from the stimulatory G_s protein. Agonist-induced desensitization involves phosphorylation of G protein–coupled receptors by two classes of serine-threonine kinases. One of these classes initiates receptor-specific or homologous desensitization. The other works through second messenger–dependent kinases and mediates a general cellular hyporesponsiveness called heterologous desensi-

tization. Ultimately, an inhibitory arrestin protein binds to the phosphorylated receptor and causes desensitization by blocking signal transduction. Because enzymatic phosphorylation occurs only in the activated state, transient β-blockade has been used in states of receptor desensitization such as CHF or cardiopulmonary bypass to achieve a "a receptor holiday."[61] Regeneration of a functional β-adrenergic receptor is contingent on sequestration of the receptor, with dephosphorylation and presumed recycling. There has been some evidence that the arrestins contribute to desensitization by uncoupling signal transduction and by contributing to the process of receptor internalization.[62,63] Receptor populations can change rapidly with such sequestration, which does not require protein synthesis.

Downregulation may be distinguished from these rapid mechanisms in that it occurs after hours of exposure to an agonist (as in chronic stress or CHF) and receptors are destroyed. New receptors must be synthesized before return to a baseline state is possible.

Chronic CHF is one of the most important and best-studied pathophysiologic situations in which tolerance or downregulation occurs. It was initially observed that the density of cardiac β-receptors decreases markedly in patients with terminal heart failure in response to the elevated plasma catecholamine levels. This finding explained why administration of exogenous β-agonists was relatively ineffectual in this syndrome. With the demonstration that β_1- and β_2-receptors coexist in human ventricles,[64] Bristow and coworkers, using radioligand techniques, documented that β_1-receptor density decreases without change in the density of β_2-receptors in human ventricles affected by CHF. Consequently, β_2-agonism accounted for 60% of the total inotropic response stimulated by isoproterenol in the failing heart as compared with 40% in a nonfailing heart.[65]

The activity of the thyroid gland influences receptor density, with hyperthyroidism increasing density and hypothyroidism decreasing density. Clinically, β-receptor blockade is important in the acute treatment of hyperthyroidism. There is some evidence that corticosteroids decrease receptor density. Consequently, the reaction of the body to well-characterized sympathetic agonists may be considerably different, depending on the pathologic and environmental circumstances. However, the structural similarity of thyroid hormone and tyrosine suggests that false transmitters may play a role (see Chapter 75).[66]

Cholinergic Pharmacology

Acetylcholine Synthesis

Many of our assumptions about cholinergic pharmacology are drawn from our understanding of cholinergic receptors at the neuromuscular junction. The chemistry of cholinergic synthesis and metabolism is covered in detail in Chapter 14.

Cholinergic Receptors

Traditionally, cholinergic receptors have been organized into two major subdivisions, nicotinic and muscarinic. Muscarinic receptors are present mostly in peripheral visceral organs; nicotinic receptors are found on parasympathetic and sympathetic ganglia (neuronal subtypes) and on the neuromuscular junctions of skeletal muscle (neuronal and muscle subtypes).

Although these two structurally and functionally distinct classes of receptors have significantly different responses to acetylcholine, the chemical itself exhibits no specificity. However, specific antagonists can exploit the difference between muscarinic and nicotinic receptors. As a result, structure-activity relationships have emerged. All cholinergic agonists appear to need a quaternary ammonium group, as well as an atom capable of forming a hydrogen bond through an unshared pair of electrons. The distance between the two sites may determine whether the agonism is nicotinic or muscarinic. With muscarinic agonists, the distance appears to be about 4.4 Å, whereas for nicotinic agonists, the distance is 5.9 Å.

The neuronal and muscle subtypes of nicotinic receptors on ganglia and motor end plates, respectively, differ. Nondepolarizing neuromuscular blocking agents block neuronal nicotinic acetylcholine receptors present in ganglia and at the neuromuscular junction (see Chapter 29),[67] whereas hexamethonium blocks the ganglionic receptors.

Some evidence indicates that ganglionic nicotinic receptors are far more sensitive to anesthetics than receptors in the neuromuscular junction are, but the clinical significance is unclear.[68]

The nicotinic receptors on ganglia and motor end plates are discussed in detail in Chapter 14. In brief, they are pentameric membrane proteins that form nonselective cation channels. There are two α-units (each 40 kd) and one each of the β-, ε-, and δ-units. These five subunits surround each ion channel through which sodium or calcium enters the cell or potassium exits. Each ion has its own separate channel. For the channel to open, acetylcholine must occupy a receptor site on each of the two α-subunits.

In contrast to the ion-gated nicotinic receptors, muscarinic receptors belong to the superfamily of G protein–coupled receptors. Muscarinic receptors therefore have greater homology to α- and β-adrenergic receptors than to nicotinic receptors. Like the other members of the family of receptors with seven helices (i.e., α_2, β_1, β_2, serotonin, rhodopsin, and opsin), muscarinic receptors use G proteins for signal transduction. Five muscarinic receptors (i.e., M_1 through M_5) exist, with the primary structural variability residing in a huge cytoplasmic loop between the fifth and sixth membrane-spanning domains. Although molecular studies have described five forms, four of which are defined pharmacologically (i.e., M_1, M_2, M_3, and M_4), selective muscarinic drugs are not available. The M_2 cholinergic postjunctional receptor predominates in visceral organs. M_2 and M_3 receptors have been identified in the airway smooth muscle of many species. In vitro studies reveal that the M_3 receptor mediates the contractile and secretory response. However, the excess of M_2 receptors could explain the relative ineffectiveness of β-adrenergic agonists in reversing cholinergic bronchoconstriction.[69]

The muscarinic receptors have diverse signal transduction mechanisms. The odd-numbered receptors (i.e., M_1, M_3, and M_5) work predominantly through hydrolysis of polyphosphoinositide, whereas the even-numbered receptors work primarily to regulate adenylate cyclase.[70]

When the M_3 muscarinic receptor is activated, G_q activates phospholipase C, which catalyzes the hydrolysis of phosphatidylinositol bisphosphate into diacylglycerol and inositol triphosphate. Receptors in the muscarinic series are coupled to second messenger systems, such as cyclic nucleotides or phosphoinositides. These are coupled to ion channels. In other cases, influx of a cation is the trigger for cellular response. In some cases, however, the influx of calcium ions acts as a messenger that reacts

with and opens other ion channels. In addition to affecting ion channels, the messenger calcium can stimulate various intracellular proteins to alter cell activity. In cardiac atria, activation of muscarinic receptors leads to the efflux of potassium and hyperpolarization of the cell membrane. This hyperpolarization slows conduction and slows or stops atrial pacemakers. In glands, an influx of calcium or sodium, or both, activates intracellular events and causes the cells to secrete. Similarly, influx of these ions into smooth muscle cells causes them to contract.

Muscarinic receptors are found on central and peripheral neurons; a single neuron may have muscarinic receptors with excitatory as well as inhibitory effects. Prejunctional autoreceptors are not as well studied in the parasympathetic nervous system as in the sympathetic nervous system. Presynaptic muscarinic receptors may inhibit the release of acetylcholine from postganglionic parasympathetic neurons; prejunctional nicotinic receptors may increase its release.

Because of the complex coupling, the response of the muscarinic system is sluggish; no response is seen for seconds to minutes after the application of acetylcholine. Similarly, the effect long outlives the presence of the agonist. Even though the transmitter is destroyed rapidly, the train of events that it initiates causes the cellular response to continue for many minutes. Muscarinic receptors are desensitized through agonist-dependent phosphorylation in a mechanism similar to that described earlier for β-adrenergic receptors.

Nonadrenergic, Noncholinergic Neurotransmission in the Autonomic Nervous System

NANC components such as monoamines, purines, amino acids, and polypeptides are part of the ANS. Other transmitter candidates demonstrated in perivascular nerves by histochemical and immunohistochemical techniques include ATP, adenosine, VIP, substance P, 5-hydroxytryptamine (5-HT), neuropeptide Y (NPY), and calcitonin gene–related peptide (CGRP). Immunocytochemical studies show that more than one transmitter or putative transmitter may be colocalized in the same nerve. The most common combinations of transmitters in perivascular nerves are norepinephrine, ATP, and NPY in sympathetic nerves (Fig. 12-14); acetylcholine and VIP in parasympathetic nerves (Fig. 12-15); and substance P, CGRP, and ATP in sensory-motor nerves. Many of these putative transmitters act through cotransmission, which is the synthesis, storage, and release of more than one transmitter by a nerve. Initially, the multiplicity of transmitters released in various combinations appeared random and bewildering, but a pattern is emerging that clarifies the situation. Autonomic nerves exhibit chemical coding—individual neurons serving a specific physiologic function contain distinct combinations of transmitter substances.[71]

The concepts of cotransmission and neuromodulation have become accepted mechanisms in autonomic nervous control. To establish that transmitters coexisting in the same nerves act as cotransmitters, it is necessary to demonstrate that on release, each substance acts postjunctionally on its own specific receptor to produce a response.

For many perivascular sympathetic nerves, there is evidence that norepinephrine and ATP act as cotransmitters and are released from the same nerves but act on α_1-adrenoceptors and P_2-purinoceptors, respectively, to produce vasoconstriction (see Fig. 12-14).[72,73] ATP, once thought to act only as an electrical buffer for the charged norepinephrine, is believed to mediate contraction through P_2 receptors by voltage-dependent calcium channels.[74] The fast component of contraction appears to be mediated by these purinoceptors, whereas norepinephrine sustains contraction of muscle by acting on the α_1-adrenoreceptor through receptor-operated calcium channels. ATP is stored in vesicles along nerve varicosities. It is released into the synaptic cleft via exocytosis and then binds to postsynaptic purinergic receptors. ATP is then broken down to adenosine by membrane-bound ATPases and 5′-nucleotidases. Adenosine is subsequently taken up into the presynaptic neuron, where ATP is resynthesized and incorporated into vesicles for later release.[75]

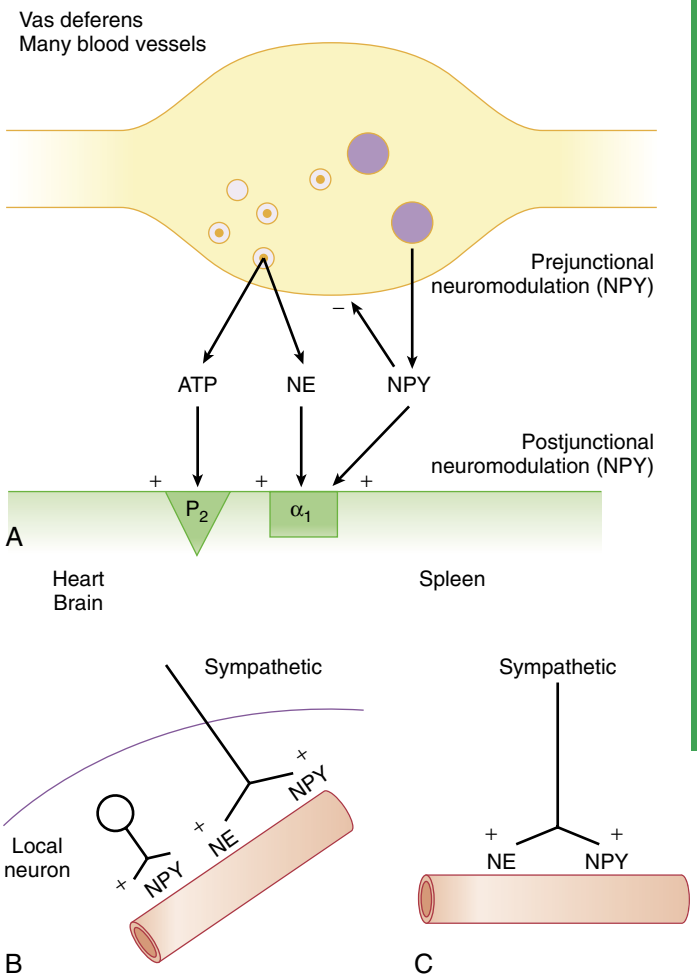

Figure 12-14 Schematic representation of different interactions that occur between neuropeptide Y (NPY) and adenosine triphosphate (ATP) and the norepinephrine (NE) released from single sympathetic nerve varicosities. **A,** Diagram showing what occurs in the vas deferens and many blood vessels, where NE and ATP, probably released from small granular vesicles, act synergistically to contract (+) the smooth muscle through α_1-adrenoceptors and P_2 purinoceptors, respectively. **B** and **C,** Sympathetic neurotransmission in the heart and brain (**B**) and the spleen (**C**). *(From Lincoln J, Burnstock G: Neural-endothelial interactions in control of local blood flow. In Warren J [ed]: The Endothelium: An Introduction to Current Research. New York, Wiley-Liss, 1990, p 21.)*

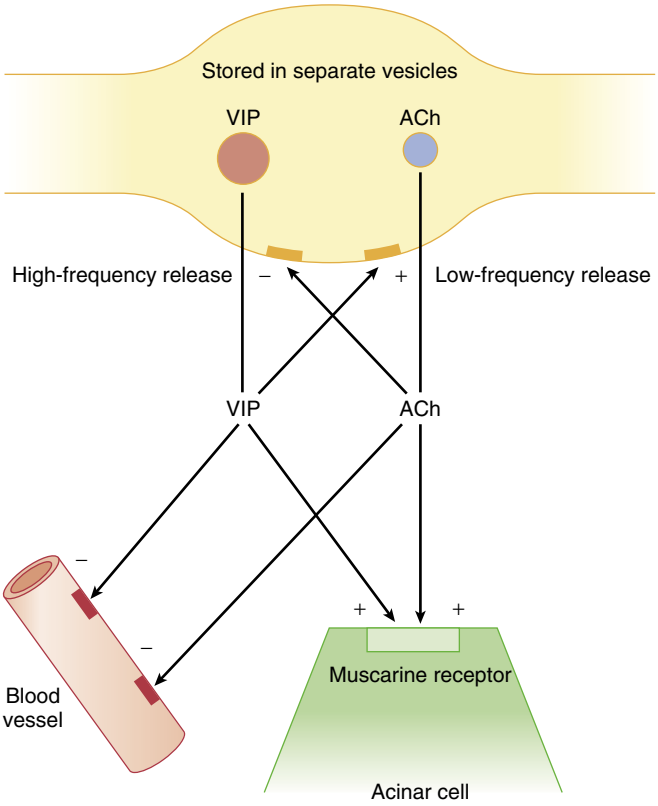

Figure 12-15 The classic transmitter acetylcholine (ACh) coexists with vasoactive intestinal polypeptide (VIP) in parasympathetic nerves supplying the cat salivary gland. ACh and VIP are stored in separate vesicles; they can be released differentially at different stimulation frequencies to act on acinar cells and glandular blood vessels. Cooperation is achieved by the selected release of ACh at low impulse frequencies and VIP at high frequencies. Prejunctional and postjunctional modulation is indicated. *(From Burnstock G: Local mechanisms of blood flow control by perivascular nerves and endothelium. J Hypertens Suppl 8:S95, 1990.)*

Purinergic receptors are categorized as P_1 or P_2 receptors. P_1 receptors bind adenosine, whereas P_2 receptors bind ATP. Four subtypes of P_1 receptors have been identified (A_1, A_{2A}, A_{2B}, and A_3). All the P_1 receptors are coupled to membrane-bound G proteins. There are two subclasses of P_2 receptors (P2X and P2Y). P2X receptors bind ATP and open ligand-gated ion channels. In contrast, P2Y receptors are coupled to G proteins and their associated secondary messenger systems. Seven P2X subtypes ($P2X_{1\text{-}7}$) and eight P2Y subtypes ($P2Y_{1,2,4,6,11,12,13,14}$) have been identified. Some P2Y receptors are preferentially activated by adenosine diphosphate rather than ATP, and some can be activated by pyrimidine nucleosides (uridine triphosphate), as well as purinergic agonists.

ATP released at nerve endings in the setting of hypertension leads to marked decreases in arterial pressure. ATP bound to $MgCl_2$ is a potent pulmonary vasodilator used to treat patients with pulmonary hypertension secondary to congenital heart disease. In addition, it is used to treat postischemic renal injury. Purinergic cotransmission is also seen in the gastrointestinal tract, where ATP (and NO) receptor stimulation inhibits peristalsis.

Neuromodulators modify the process of neurotransmission. They may be circulating neurohormones, local agents, or neurotransmitter substances released from the same nerves or from others nearby. Neuromodulation can occur prejunctionally by decreasing or increasing the amount of transmitter released during transmission or postjunctionally by altering the extent or time course of the neurotransmitter's effect. In all known examples in which prejunctional and postjunctional neuromodulation occurs, these substances act in concert to attenuate or augment effective transmission. The rationale for such effects may reflect the variable geometry of the autonomic neuroeffector junction.[76,77] Unlike the neuromuscular junction, the autonomic neuroeffector junction exists in a dynamic state and manifests only modest postjunctional specialization. Biogenic amines often must traverse wide distances. Given the short half-lives of these chemicals, neuromodulation provides a biologic mechanism for augmentation and prolongation of their action.[78]

NPY is also colocalized with norepinephrine and ATP. However, in some vessels, NPY has little or no direct action; instead, it acts as a neuromodulator prejunctionally to inhibit the release of norepinephrine from the nerve or postjunctionally to enhance the action of norepinephrine (see Fig. 12-14A).[79,80] In other vessels, notably those of the spleen, skeletal muscle, and cerebral and coronary vasculature, NPY has direct vasoconstrictor actions. In the heart and brain, local intrinsic (nonsympathetic) neurons use NPY as the principal transmitter (see Fig. 12-14B). In the spleen, NPY appears to act as a genuine cotransmitter with norepinephrine in perivascular sympathetic nerves (see Fig. 12-14C).[81] The frequency of stimulation determines which vesicles are mobilized to release their transmitters.

A classic transmitter such as acetylcholine coexists with VIP in the parasympathetic nerves of many organs, but in this instance, the two transmitters are stored in separate vesicles. They can be released differentially at different stimulation frequencies, depending on where they are located.[82,83] For example, in the salivary gland, they can act independently on acinar cells and glandular blood vessels (see Fig. 12-15).[73] Cooperation is achieved by the selective release of acetylcholine at low frequencies and VIP at high frequencies of stimulation. Elements of prejunctional and postjunctional modulation have also been described. It is becoming increasingly apparent that in many biologic states, including pregnancy,[84] hypertension, and aging, the relationships among cotransmitters may be an important determinant of a compensatory response to allow finer control of important physiologic function. Additionally, the large number of different receptors may provide targets for potential pharmacologic interventions.

Ganglionic Pharmacology

Ganglia serve far more complex functions than simply being a link between the nerve process of one cell and the cell body of its next connection. Integrative and processing functions contribute to the subtlety of response and organization of the ANS. The electrophysiology of ganglionic stimulation is complex, with at least four different types of responses to electrical stimulation (Table 12-8).[85]

The central event at the ganglion is the excitatory postsynaptic potential (EPSP) when acetylcholine interacts with a neuronal-type nicotinic receptor to depolarize the postsynaptic membrane. Depolarization results primarily from the influx of sodium ions through the nicotinic receptor channel, and it is sensitive to nondepolarizing nicotinic blocking drugs such as hexamethonium. The other changes in electrical potential are

Table 12-8 Fast and Slow Responses of Postganglionic Neurons in Sympathetic Ganglia

Potential	Duration	Mediator	Receptor
Fast EPSP	30 msec	Acetylcholine	Nicotinic cholinergic
Slow IPSP	2 sec	Dopamine	D_2
Slow EPSP	30 sec	Acetylcholine	M_1-cholinergic
Late slow EPSP	4 min	GnRH	GnRH

Adapted from Ganong W: The autonomic nervous system. *In* Ganong W (ed): Review of Medical Physiology, 15th ed. Norwalk, CT, Appleton & Lange, 1991, p 210.
D_2, dopamine receptor inhibiting adenylate cyclase through inhibitory G protein; EPSP, excitatory postsynaptic potential; GnRH, gonadotropin-releasing hormone; IPSP, inhibitory postsynaptic potential.

related to secondary or subsidiary pathways that augment or suppress; these pathways are insensitive to classic nicotinic antagonists.

Secondary pathways are indicated by the following changes in potential elicited by electrical stimulation of the ganglia: (1) slow EPSP, (2) late slow EPSP, and (3) inhibitory postsynaptic potential (IPSP).

Autonomic ganglia may be stimulated by two groups of drugs, nicotinic and muscarinic agonists. Nicotinic agonists cause a rapid onset of excitatory effects, mimic the initial EPSP, and are blocked by classic nondepolarizing ganglionic blocking drugs. Muscarinic agonists delay onset of the excitatory effects and are blocked by atropine.

Blockade of ganglionic transmission results primarily from action at the nicotinic receptor to stop or inhibit transmission. Two groups of drugs block ganglionic transmission. The first group is classically represented by nicotine and initially stimulates the receptor but then blocks it. This action is similar to the action of persistent depolarization. The second group does not cause initial stimulation or a change in ganglionic potentials. This group includes the drugs hexamethonium, trimethaphan, and mecamylamine. Trimethaphan acts by competing with acetylcholine at cholinergic receptor sites on the ganglia; hexamethonium blocks the channel when it is open. Either mechanism blocks the initial EPSP and ganglionic transmission.

Muscarinic antagonists or α-agonists are incapable of completely blocking transmission, but they may inhibit normal modulation of the nerve impulse. β-Adrenergic stimulation facilitates nicotinic and muscarinic transmission, whereas α-adrenergic stimulation inhibits it. 5-HT is mostly facilitative, but it can be inhibitory in certain areas. Dopamine may also be inhibitory through stimulation of the IPSP. The adrenal medulla is a specialized ganglionic synapse and is therefore under influences similar to those arising on the autonomic ganglia.

Drugs and the Autonomic Nervous System

The structure and function of the sympathetic and parasympathetic systems are discussed in the preceding sections. Pharmacologic manipulation of autonomic function is the basis of therapy for many acute and chronic illnesses. The complex physiology allows many points for intervention, including enhancement or inhibition of synthesis, storage, or receptor-mediated activity. In the following sections, specific autonomic drugs of interest to anesthesiologists and the mechanisms by which they work are discussed.

Drugs Affecting Adrenergic Transmission

Endogenous Catecholamines

The endogenous sympathetic transmitters norepinephrine, epinephrine, and dopamine are catecholamines, an important subclass of the sympathomimetic drugs (Fig. 12-16). The parent compound of this sympathomimetic group is β-phenylethylamine, the structure of which includes a benzene ring and an ethylamine side chain. Substitution of hydroxyl groups at the 3 and 4 positions of the benzene ring converts benzene to catechol, and these compounds are known as catecholamines. Although synthetic, isoproterenol and dobutamine are likewise catecholamines. Noncatecholamine drugs may also act as sympathomimetics and have a similar structure.

The catecholamines are primarily metabolized by COMT. The loss of either hydroxyl group enhances oral effectiveness and duration of action because the drug is no longer metabolized by COMT. Noncatecholamines are primarily metabolized by MAO. The noncatecholamines that have a substituted α-carbon have a

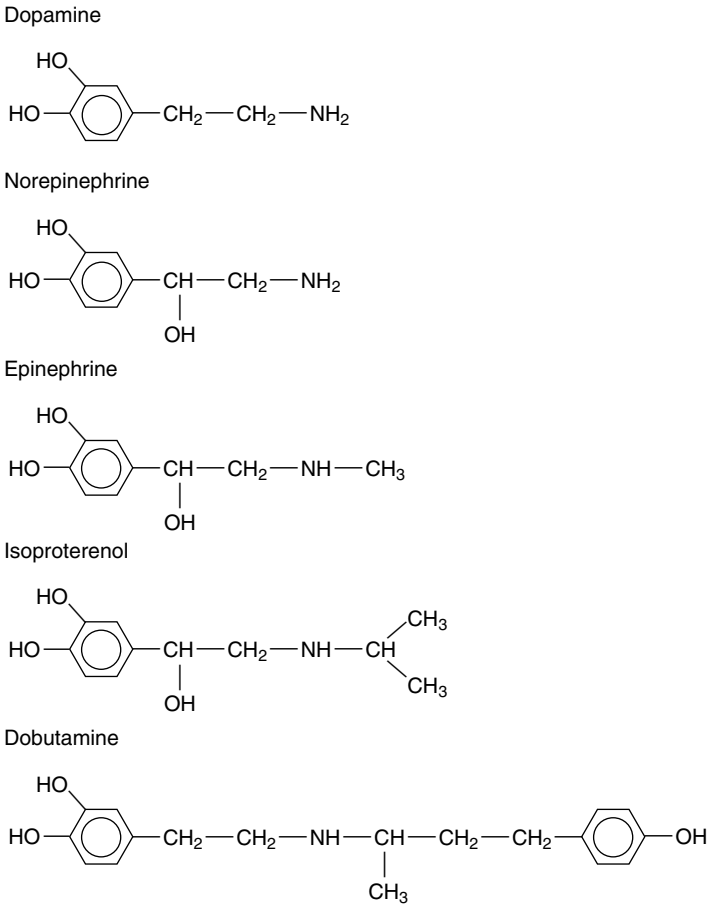

Figure 12-16 Catecholamine structures. A benzene ring with two adjacent hydroxyl groups forms the catechol nucleus.

longer duration of action because they are not metabolized by COMT or MAO.

Epinephrine

Epinephrine is used intravenously in life-threatening circumstances, including the treatment of cardiac arrest, circulatory collapse, and anaphylaxis, but it is also commonly used locally to limit the spread of local anesthetics or to reduce blood loss. The systemic effects of epinephrine are variable and are related to blood levels. The choice of dosing and the route of administration are determined by the indication for use and its urgency.

Epinephrine activates all adrenergic receptors: α_1, α_2, β_1, β_2, and β_3. Potential therapeutic effects of epinephrine include positive inotropy, chronotropy, and enhanced conduction in the heart (β_1); smooth muscle relaxation in the vasculature and bronchial tree (β_2); and vasoconstriction (α_1). With vasoconstriction, aortic diastolic pressure is increased, thereby promoting coronary flow during cardiac arrest, which may be the single most important determinant of survival.[86] Endocrine and metabolic effects of epinephrine include increased levels of glucose, lactate, and free fatty acids.

Epinephrine may be given intravenously as a bolus or by infusion. The usual bolus doses for pressure support begin at 2 to 8 µg given intravenously; 0.02 mg/kg or approximately 1.0 mg is given for cardiovascular collapse, asystole, ventricular fibrillation, electromechanical dissociation, or anaphylactic shock[87] (see also Chapter 97). The larger dose range is recommended in these critical situations to maintain myocardial and cerebral perfusion through peripheral vasoconstriction. High-dose epinephrine (0.1 to 0.2 mg/kg) has been studied in resuscitation from cardiac arrest, but it does not appear to improve rates of survival in adults. In pediatric patients, outcome after asystole and pulseless cardiac arrest is abysmal, and the current recommendation is an initial dose of 0.01 mg/kg repeated every 3 to 5 minutes throughout resuscitative attempts.[41,88] In unusual circumstances, higher doses may be given and doses as large as 0.2 mg/kg may be effective.[89] Patients vary tremendously in their response to epinephrine, and given rates of infusion cannot guarantee the expected serum levels in all patients; the "pressors" should therefore be carefully titrated, and measures to monitor renal, cerebral, and myocardial perfusion are more critical than adherence to a rigid dosing scheme (Table 12-9). A rate of 1 to 2 µg/min, though rarely used, should predominantly activate β_2-receptors, with resulting vascular and bronchial smooth muscle relaxation. A rate of 2 to 10 µg/min (25 to 120 ng/kg/min) increases heart rate, contractility, and conduction through the AV node and decreases the refractory period. Doses in excess of 10 µg/min (100 ng/kg/min) cause marked α-adrenergic stimulation with resultant generalized vasoconstriction. Epinephrine is a potent renal vasoconstrictor that acts directly by α-receptor stimulation and indirectly by stimulation of renin release. Although low-dose epinephrine increases the heart rate by direct β_1-adrenergic stimulation, reflex bradycardia is seen with higher doses because of the marked elevation in blood pressure resulting from peripheral vasoconstriction.

Racemic epinephrine (i.e., mixture of the levorotary and dextrorotary isomers) constricts edematous mucosa and is used for the treatment of severe croup[90] and postextubation and traumatic airway edema. A 2.25% solution (MicroNefrin or Vaponefrin) is diluted with water or saline in a 1:8 ratio and nebulized. Treatments may be given as frequently as every 2 hours, with effects lasting 30 to 60 minutes; the patient should remain under observation for at least 2 hours because initial improvement may be followed by rebound swelling up to 2 hours after administration. Although it is common clinical practice to use the racemic form of epinephrine for these clinical applications, data show that L-epinephrine is 15 to 30 times more potent than the mixture[91] and is equally effective and less expensive for treating these clinical complications.[92]

Bronchospasm may also be treated by subcutaneous administration of epinephrine in doses of 300 µg every 20 minutes with a maximum of three doses. In addition to its direct bronchodilatory effects, epinephrine may decrease antigen-induced release of endogenous bronchospastic substances from mast cells and is particularly useful in anaphylactic reactions.[93] Relative contraindications include advanced age, significant tachycardia, hypertension, and coronary occlusive disease. Absorption of subcutaneous epinephrine is extremely slow because of intense local vasoconstriction, and the effect of a very large subcutaneous dose of 0.5 to 1.5 mg is roughly equivalent to an intravenous infusion of 10 to 30 µg/min. Intravenous injection of epinephrine in a dose appropriate for subcutaneous administration can result in life-threatening ventricular arrhythmias, hypertension, and cerebral hemorrhage. Sus-Phrine, a sustained-release form of epinephrine, may be used in children by subcutaneous injection but should never be given intravenously.

Epinephrine is often applied locally to mucosal surfaces to decrease bleeding in the operative site. It is mixed with local anesthetics for infiltration into tissues or intrathecal injection. The α-mediated vasoconstriction decreases bleeding in the area and slows vascular uptake of local anesthetic, thereby prolonging the duration of effect and decreasing the peak serum level of the

Table 12-9 Dose-Dependent Actions of Inotropes and Chronotropes

Drug* (Proprietary Name)	Receptors	Usual Infusion Rate
Epinephrine (Adrenalin)	β_2 $\beta_1 + \beta_2$ α_1	1-2 µg/min 2-10 µg/min ≥10 µg/min† (bolus: 2-10 µg; 0.5-1.0 mg‡)
Norepinephrine (Levophed)	α_1, β_1, $\gg\beta_2$	4-12 µg/min†
Dopamine (Intropin)	Dopaminergic β α	0-3 µg/kg/min 3-10 µg/kg/min >10 µg/kg/min†
Dobutamine (Dobutrex)	$\beta_1 \gg \beta_2$, α	2.5-10 µg/kg/min†
Isoproterenol (Isuprel)	$\beta_1 > \beta_2$	0.5-10 µg/min
Amrinone (Inocor)	Increase cyclic adenosine monophosphate through inhibition of phosphodiesterase	0.75 mg/kg load over a period of 2-3 min 5- to 10-µg/kg/min infusion

*All agents have elimination half-lives of a few minutes except amrinone ($t_{1/2}$, 3.6 hours; 5.8 hours in congestive heart failure).
†Much higher doses have been used in clinical practice.
‡With anaphylaxis or cardiac arrest.
Data from Hoffman BB, Lefkowitz RJ: Catecholamines and sympathetic drugs. *In* Goodman A, Rall T, Nies A, et al (eds): Goodman and Gilman's the Pharmacological Basis of Therapeutics, 8th ed. New York, Pergamon Press, 1990, p 187.

local anesthetic. Although clinicians express concern about the possible systemic effects of such injections, the increases in plasma levels from vascular uptake are relatively modest and substantially less than levels seen during psychological stress.[94] This conclusion assumes the absence of overt intravenous injection.

Drug interactions with epinephrine are often predictable. Cocaine and other uptake inhibitors enhance the effect and duration of exogenous epinephrine. Preexisting α_1-blockade can cause the paradoxical phenomenon of epinephrine reversal (a hypotensive and tachycardic response) as the β_2-vasodilating effects are unmasked. Patients receiving nonselective β-blockers may demonstrate unopposed α-responses. Cardioselective (β_1) blockade does not have this effect.[95]

Halothane sensitizes the heart to catecholamines, and the potential for troublesome arrhythmias under light inhalational anesthesia has long been appreciated by clinicians. Epinephrine decreases the refractory period, which renders the heart more susceptible to arrhythmias. In adults, the epinephrine dose required to produce three premature ventricular contractions in 50% of patients (ED_{50}) at 1.25 minimum alveolar concentration (MAC) was 2.1 μg/kg for halothane, 6.7 μg/kg for isoflurane, and 10.9 μg/kg for enflurane.[96] Children appear to tolerate higher doses than adults do. It has been suggested that children undergoing halothane anesthesia can receive a maximum of 10 to 15 μg/kg of epinephrine subcutaneously every 10 minutes.[89] Hypocapnia potentiates this drug interaction.

Norepinephrine

Norepinephrine differs structurally from epinephrine only in its lack of a methyl group. Like epinephrine, norepinephrine acts at α- and β-receptors, but it is typically used for its potent α-agonism. It is frequently the pressor of last resort in supporting systemic vascular resistance. Because of its short half-life of 2.5 minutes, continuous infusion is preferred. Whereas less than 2 μg/min (30 ng/kg/min) may uncover the effects of β_1-adrenergic stimulation, the usual infusion rates of greater than 3 μg/min (50 ng/kg/min) elicit peripheral vasoconstriction from α-adrenergic stimulation.

Peripheral vasoconstriction increases blood pressure and may cause reflex bradycardia. Venous return is increased by the powerful venoconstriction. Cardiac output is frequently unchanged or decreased; oxygen consumption is markedly increased. Because pulmonary vascular resistance may be increased, norepinephrine should be used with caution in patients with pulmonary hypertension.[97]

Like epinephrine, norepinephrine is a potent constrictor of the renal and mesenteric vascular beds and can cause renal failure, mesenteric infarction, and peripheral hypoperfusion. The decrease in hepatic flow is of clinical relevance because plasma levels of hepatically metabolized drugs (e.g., lidocaine) are markedly increased. To ameliorate the renal effects, a low-dose dopamine infusion may be added to norepinephrine (see Chapters 92 and 96).[98] Extravasation of norepinephrine can cause tissue necrosis and may be treated by local infiltration of phentolamine. Prolonged infusion has caused gangrene of the digits. The potential for profound vasoconstriction makes careful patient selection and close monitoring mandatory.

Dopamine

Dopamine acts at α-adrenergic, β-adrenergic, and dopaminergic receptors; it also acts to release norepinephrine and therefore has mixed direct and indirect effects. Although dopamine is a precursor of norepinephrine, its most important ANS effect in the periphery may be to cause peripheral vasodilation. Improvement of blood flow through the renal and mesenteric beds in shocklike states is expected through its action at dopamine receptors on the postjunctional membrane. It is rapidly metabolized by MAO and COMT and has a half-life of about 1 minute. Like other endogenous catecholamines, it is given as a continuous intravenous infusion without a loading dose. At low doses (0.5 to 2.0 μg/kg/min), DA_1 receptors are stimulated, and renal and mesenteric vascular beds dilate.[99] In addition to an improvement in renal blood flow, the glomerular filtration rate and sodium excretion increase. With an infusion rate of 2 to 10 μg/kg/min, β_1-receptors are stimulated, and cardiac contractility and output are increased. Rates higher than 5 μg/kg/min stimulate the release of endogenous norepinephrine, which contributes to cardiac stimulation. In larger doses (10 to 20 μg/kg/min), α- and β_1-receptors are stimulated, the α-adrenergic vasoconstrictive effect predominates, and the benefit to renal perfusion may be lost.[100]

In the past, dopamine was frequently used for the treatment of shock (especially in vasodilated states such as sepsis). It was widely believed that infusions of dopamine, by increasing renal blood flow, could protect the kidney and aid in diuresis.[101] However, more recent studies have suggested that dopamine does not have a beneficial effect on renal function in shock states, and its routine use in these patients has therefore been called into question (see Chapters 92 and 96).[102,103]

Dopexamine hydrochloride (Dopacard), an inotropic vasodilator, is a synthetic parenteral dopamine analog (not available in the United States) that may be of use in CHF. Dopexamine is approximately 60 times more potent at β_2-adrenergic receptors than dopamine is, a third as potent at DA_1 receptors, and a seventh as potent at DA_2 receptors.[104,105] Unlike dopamine, it shows no α-adrenergic effects and negligible β_1-adrenergic effects and is consequently devoid of vasoconstrictive activity.[104,106] Dopexamine has a reported half-life of 3 to 7 minutes in healthy patients and approximately 11 minutes in patients with low cardiac output.[107] β_2-Agonism produces systemic vasodilation and indirect inotropic activity (through inhibition of neuronal uptake of norepinephrine).[104-106,108,109] Stimulation of dopaminergic receptors produces selective vasodilation of renal and splanchnic vessels and increases the glomerular filtration rate, diuresis, and natriuresis.[105,110-113]

The use of dopexamine is preferable when vascular resistance is high. Within the dose range of 1 to 6 μg/kg/min, the combined inotropic, vasodilative, diuretic, and natriuretic effects have shown benefit in the management of CHF,[114-117] but an indeterminate outcome in the treatment of septic shock.[116,118-122] Use of this agent has been limited by dose-dependent tachycardia, mainly at doses higher than 4 μg/kg/min.[123,124] The effects of dopexamine on intestinal mucosal and hepatic perfusion remain controversial.[125-130] In general, systemic vasodilation appears more pronounced with dopexamine, and positive inotropic effects appear more marked with dopamine[131] and dobutamine.[132]

Fenoldopam is a selective DA_1 agonist and potent vasodilator (i.e., six to nine times as potent as dopamine) that enhances natriuresis, diuresis, and renal blood flow.[133-137] Because of its poor bioavailability and varied results in clinical trials, fenoldopam is no longer being investigated as a candidate for the treatment of chronic hypertension or CHF. Instead, intravenous fenoldopam, given by infusion at rates of 0.1 to 0.8 μg/kg/min with incremen-

tal titration at 0.1 μg/kg/min, has been approved to treat severe hypertension. It is an alternative to sodium nitroprusside, with potentially fewer side effects (i.e., no thiocyanate toxicity, rebound effect, or coronary steal) and improved renal function. Its peak effects occur within 15 minutes.[138,139]

Noncatecholamine Sympathomimetic Amines

The β-agonist isoproterenol and the α-agonists phenylephrine and methoxamine act predominantly at only one type of receptor, but most noncatecholamine sympathomimetic amines act at α- and β-receptors because they have two mechanisms of action: directly at a receptor and indirectly by releasing endogenous norepinephrine.

Mephentermine (Wyamine), ephedrine, and metaraminol (Aramine) are mixed-acting drugs. Ephedrine increases blood pressure and has a positive inotropic effect. Because it does not have detrimental effects on uterine blood flow, ephedrine is widely used as a pressor in hypotensive parturient patients (see Chapter 69). As a result of its β_1-adrenergic–stimulating effects, ephedrine is helpful in treating moderate hypotension, particularly if accompanied by bradycardia. It also has some direct β_2-adrenergic–stimulating effects and has been used orally as a bronchodilator. The usual dose is 2.5 to 25 mg given intravenously or 25 to 50 mg administered intramuscularly. Mephentermine is similar to ephedrine in its effects, whereas metaraminol has relatively stronger direct α_1-adrenergic–stimulating effects and may be associated with reflex bradycardia.

Tachyphylaxis to the indirect effect may develop through depletion of norepinephrine stores. Although all sympathomimetic amines are capable of producing tolerance or tachyphylaxis, the mechanism has been studied best with metaraminol. Metaraminol is taken up into the sympathetic nerve ending, where it displaces norepinephrine and produces its sympathomimetic effect. However, after some time, the drug acts as a false transmitter, and subsequent sympathetic nerve stimulation results in much less effect. Consequently, the drug probably should not be used widely when other, more effective drugs are available. Its indirect action is attenuated in the presence of long-term reserpine or cocaine use, but these drugs may still be efficacious at higher doses. Although indirect-acting drugs are widely used as a first-line therapy for intraoperative hypotension, epidemiologic studies of adverse reactions under anesthesia suggest that dependence on these agents in life-threatening events may contribute to morbidity.[140]

α-Receptor Agonists

Phenylephrine and methoxamine are selective α_1-agonists. These drugs are commonly used when peripheral vasoconstriction is needed and cardiac output is adequate, as in the hypotension that may accompany spinal anesthesia, as well as in patients with coronary artery disease or aortic stenosis to increase coronary perfusion pressure without chronotropic side effects. Phenylephrine (Neo-Synephrine) has a rapid onset and relatively short duration of action (5 to 10 minutes) when given intravenously. It may be given in bolus doses of 40 to 100 μg or by infusion at a starting rate of 10 to 20 μg/min. Larger doses of up to 1 mg are used to slow supraventricular tachycardia through reflex action. Phenylephrine is also used as a mydriatic and nasal decongestant. In anesthetic practice, it is applied topically, alone or mixed with local anesthetic gel, to prepare the nostril for nasotracheal intubation. It is also added to local anesthetic to prolong subarachnoid blockade. In contrast, methoxamine (Vasoxyl) is a much longer-acting drug (30 to 60 minutes).[141] In larger doses, methoxamine possesses some membrane-stabilizing and β-blocking properties.

α_2-Agonists are assuming greater importance as anesthetic adjuvants and analgesics. Their primary effect is sympatholytic. They reduce peripheral norepinephrine release by stimulation of prejunctional inhibitory α_2-adrenoreceptors. They inhibit central neural transmission in the dorsal horn by presynaptic and postsynaptic mechanisms and also have direct sympatholytic effects on spinal preganglionic sympathetic neurons. Traditionally, they have been used as antihypertensive drugs, but applications based on their sedative, anxiolytic, and analgesic properties are being developed.

Clonidine, the prototypical drug of this class, is a selective partial agonist for α_2-adrenoreceptors, with a ratio of approximately 200:1 (α_2 to α_1). Its antihypertensive effects are caused by central and peripheral attenuation of sympathetic outflow and central activation of nonadrenergic imidazoline-preferring receptors.[142-144] The decrease in central sympathetic outflow reduces activity in peripheral sympathetic neurons without affecting baroreceptor reflexes.[145] Arterial blood pressure is thereby decreased without the accompanying orthostatic hypotension produced by many antihypertensive drugs.[146] Because clonidine is lipid soluble, it penetrates the blood-brain barrier to reach the hypothalamus and medulla, and unlike methyldopa, it does not require transformation into another substance.[147] Clonidine withdrawal may precipitate hypertensive crises, so it should be continued throughout the perioperative period (perhaps by patch) or at the least be replaced by close monitoring of blood pressure and ready ability to treat hypertension. The administration of nonselective β-blockers during clonidine withdrawal can worsen hypertension by leaving α_1-receptor–mediated vasoconstriction unopposed. Labetalol has been used to treat this withdrawal syndrome.

Although experience with α_2-agonists as sole anesthetics is limited,[148] these drugs reduce anesthetic requirement and provide a more stable cardiovascular course, presumably because of their sympatholytic effect and the need for lower doses of cardioactive anesthetics.[149,150] Data suggest that oral, intravenous, epidural, and intrathecal administration of clonidine potentiates the anesthetic action of other anesthetics, volatile or injectable, and reduces general and regional anesthetic requirements with correspondingly fewer side effects.[149,151-158] Additionally, a meta-analysis looking at the perioperative use of clonidine and the other α_2-agonists dexmedetomidine and mivazerol indicated a marked decrease in myocardial infarction and perioperative mortality in patients undergoing vascular surgery (see Chapter 62).[159]

Dexmedetomidine has a 1600:1 preference for α_2-receptors relative to α_1-receptors[160]; it was introduced into clinical practice as an adjunct to regional, local, and general anesthetics.[161] Dexmedetomidine has a half-life of 2.3 hours, although its distribution half-life is less than 5 minutes,[162] thus making its clinical effect quite short.

In healthy volunteers, dexmedetomidine increases sedation, analgesia, and amnesia and decreases heart rate, cardiac output, and circulating catecholamines in a dose-dependent fashion.[160] The purported MAC-reducing sedative and analgesic

effects demonstrated in preclinical and volunteer studies have largely been borne out in clinical practice. Although dexmedetomidine infusions attenuate the hemodynamic lability of induction, maintenance, and emergence, the dose of other anesthetics must be carefully reduced[163,164] because requirements for other anesthetics may decrease. Another use for this drug is to provide sedation for mechanically ventilated patients during weaning from the ventilator (see Chapter 92).[165]

In addition to their use in the operative setting, α_2-agonists provide effective analgesia for acute and chronic pain, particularly as adjuncts to local anesthetics and opioids. The addition of clonidine increases the duration of analgesia and reduces dose requirements for local and narcotic pain medications.[155,166-180] Epidural clonidine is indicated for the treatment of intractable pain, which is the basis for approval of parenteral clonidine in the United States as an orphan drug.[181] Patients with intractable pain that is unresponsive to maximum doses of oral or epidural opioids benefit from oral, patch, intramuscular, or neuraxial administration of clonidine,[182-185] as do patients with reflex sympathetic dystrophy[186] and neuropathic pain.[187] The intrinsic analgesic effects of α_2-agonists have been demonstrated with large doses of clonidine alone administered intrathecally (as much as 450 µg) or epidurally (1 to 2 µg/kg/hr) to control intraoperative and postoperative pain. Clonidine decreases postoperative oxygen consumption and the adrenergic stress response.[188,189] Although dose-dependent adverse effects such as hypotension and sedation and idiosyncratic adverse effects such as bradycardia do occur, clonidine does not induce profound respiratory depression and only mildly potentiates opiate-induced respiratory depression.[190,191] The relatively minor impact of α_2-induced sedation on respiratory function combined with the short duration of action of dexmedetomidine has led to several reports of the use of dexmedetomidine for awake fiberoptic intubation.[192,193] The authors emphasize the ability to maintain spontaneous ventilation in the context of adequate sedation for the procedure as the reason for selecting the short-acting α_2-agonist for sedation in patients with difficult or at-risk airways. Dexmedetomidine infusions have been used for the perioperative management of obese patients with obstructive sleep apnea to minimize their narcotic needs while providing adequate analgesia.[194]

Aside from its role as an anesthetic adjuvant and antihypertensive agent, clonidine has been used to treat panic disorder[195]; symptoms of opiate, benzodiazepine, and ethanol withdrawal[196]; cigarette craving after smoking cessation[197]; emesis in cancer chemotherapeutic regimens; and diabetic diarrhea. Clonidine may increase blood glucose concentrations by inhibiting release of insulin.[198] Unlike spinal opioids, clonidine does not cause urinary retention and may hasten the time to first micturition after spinal anesthesia.[199,200] Because it has come into wide clinical use only in recent years, the breadth of experience with dexmedetomidine is much less than with clonidine. Nevertheless, infusions of the short-acting intravenous α_2-agonist have been used for sedation during weaning from extubation in the intensive care unit,[201] during neurosurgical cases (to facilitate intraoperative wake-ups and to improve signal quality during neuromonitoring),[202] (see Chapters 46 and 63), and as part of a postoperative pain management regimen.[203] An important characteristic of dexmedetomidine that makes it an attractive choice in these settings is the "rousable" sedation that it creates. Specifically, patients will awaken from apparently deep states of sedation to verbal commands or light tactile stimulation.

β-Receptor Agonists

Nonselective β-Receptor Agonists

Dobutamine. Although at clinical doses it can act at β_2- and α_1-receptors, dobutamine, a synthetic analog of dopamine, has predominantly β_1-adrenergic effects. When compared with isoproterenol, it is reported to affect inotropy more than chronotropy, but it increases conduction velocity through nodal tissue to the same extent. It exerts less of a β_2-type effect than isoproterenol does and less of an α_1-type effect than norepinephrine does. Unlike dopamine, it does not directly release endogenous norepinephrine, nor does it act at dopaminergic receptors.

Dobutamine is particularly useful in CHF and MI complicated by a low-output state, although in cases of severe hypotension, it may not be effective because it lacks a significant α_1-pressor effect. It is relatively safe to use in patients with myocardial ischemia without increasing the size of the infarct or causing arrhythmias. Doses lower than 20 µg/kg/min do not produce tachycardia, but in especially severe CHF, significant tachycardia is the primary adverse effect. Because dobutamine directly stimulates β_1-receptors, it does not rely on norepinephrine stores and may still be effective in catecholamine-depleted states such as chronic CHF. However, in severe chronic CHF, the downregulation of β-adrenergic receptors may hamper its effectiveness.

The β_2-vasodilating effects of dobutamine are almost exactly offset by its α_1-constricting effects, which can be revealed experimentally by administering a nonselective β-blocking drug. Its modest ability to dilate the peripheral vasculature is probably more closely connected with its ability to relieve the high-adrenergic state of decompensated CHF than with specific β_2-mediated vasodilation.[204] Clinical situations that call for distinct afterload reduction may be better served by an agent such as nitroprusside.

Prolonged treatment with dobutamine causes downregulation of β-receptors; tolerance to its hemodynamic effects is significant after 3 days and may be temporarily offset by increasing the rate of infusion.[205] Intermittent infusions of dobutamine have been used in the long-term treatment of heart failure and have improved exercise tolerance[206] but not survival.[207]

Isoproterenol. Isoproterenol (Isuprel) provides relatively pure nonselective β-adrenergic stimulation with no significant effect at α-receptors. Its β_1-adrenergic stimulation is significantly stronger than its β_2 stimulation, but it still causes more β_2-adrenergic activity than dobutamine does. Since the development of other inotropes, its popularity has declined because of its adverse effects of tachycardia and arrhythmias. Isoproterenol was historically used for bradycardia or heart block resistant to atropine, but it is no longer included in the American Heart Association advanced cardiac life support protocol (see Chapter 97). Its primary use at this time is as a chronotropic agent in patients after heart transplantation. These patients are unable to generate an endogenous sympathetic response to challenges because the sympathetic fibers are divided when the native heart is removed. The availability of superior pharmacologic options for most clinical indications has led to removal of isoproterenol from many hospital formularies. Infusion rates start at 0.5 to 5 µg/min for adults. Because it is not taken up into adrenergic nerve endings,

its duration of action is slightly longer than that of the natural catecholamines.

Selective β_2-Receptor Agonists

In the past, isoproterenol was used in the treatment of bronchospasm for its β_2-adrenergic–stimulating properties, but unpleasant and dangerous β_1-mediated adverse effects have limited its use. The development of β_2-selective agents has made β-stimulants a cornerstone of the treatment of bronchospasm. However, this β_2-selectivity is only relative, and it may be lost at higher doses; in addition, β_2-receptors in the sinoatrial node may cause tachycardia when stimulated. The structures of these drugs have been modified to slow their metabolism, thereby prolonging their therapeutic benefit and enabling oral administration. In particular, the addition of bulky structures on the catecholamine amino group increases β_2-selectivity, decreases affinity for α-receptors, and protects against metabolism by COMT. These agents are aerosolized and given by inhaler for rapid onset and to minimize systemic drug levels and adverse effects.

An increase in the annual number of deaths from asthma has been well documented, and it has been suggested that this increase may be related to β_2-agonist use.[208-210] Susceptibility to arrhythmia by direct cardiac stimulation or by β_2-induced hypokalemia is a suggested mechanism of these agents. It has also been hypothesized that long-term use of these drugs may increase airway hyperreactivity. Nonetheless, their safe use in many thousands of patients is well documented.

Commonly used drugs include metaproterenol (Alupent, Metaprel), terbutaline (Brethine, Bricanyl), and albuterol (Proventil, Ventolin). Metaproterenol is probably less β_2-selective than albuterol or terbutaline. Terbutaline is the only β_2-selective agent that can be given subcutaneously and may therefore have particular use in status asthmaticus. The normal subcutaneous dose is 0.25 mg, which may be repeated after 15 to 30 minutes.

β_2-Agonists are also used to treat premature labor (see Chapter 69). Ritodrine (Yutopar) has been marketed for this purpose. β_1-Adrenergic adverse effects are common, particularly when the drugs are administered intravenously. The other β_2-selective drugs have also been used as tocolytics, and all have been associated with significant β_1-adrenergic adverse effects and the occasional development of pulmonary edema. As a consequence, their use for the purpose of tocolysis has been questioned.[211]

α-Receptor Antagonists

α_1-Antagonists have long been used clinically as antihypertensives, but they have become less popular over the years. α_1-Blockade vasodilates by blocking the arterial and venous constriction caused by endogenous catecholamines. The effects are potentiated when standing or in the presence of hypovolemia. Reflex tachycardia and fluid retention can ensue.

Phenoxybenzamine (Dibenzyline) is the prototypical α_1-antagonist, although it irreversibly binds to α_1- and α_2-receptors. New receptors must be synthesized before complete offset of its effects occurs. Its half-life after oral administration is unknown, but after an intravenous dose its half-life is about 24 hours. Phenoxybenzamine decreases peripheral resistance and increases cardiac output, and blood flow to the skin and viscera is increased. As expected, its primary adverse effect is orthostatic hypotension; nasal stuffiness may also occur. In addition to receptor blockade, phenoxybenzamine inhibits neuronal and extraneuronal uptake of catecholamines. Phenoxybenzamine is used for the treatment of pheochromocytoma; with extended use, it establishes a "chemical sympathectomy" preoperatively that aids in blood pressure control, permits correction of the contracted plasma volume, and protects against catecholamine-induced cardiac damage. Thus, phenoxybenzamine treatment allows a smoother perioperative course for patients undergoing removal of a pheochromocytoma. When exogenous sympathomimetics are administered after α_1-receptor blockade, their vasoconstrictive effects are inhibited. The effect of phenylephrine is completely blocked, whereas that of norepinephrine is limited to its β_1-adrenergic effect of cardiac stimulation. Epinephrine reversal caused by unopposed β_2-agonism when exogenous epinephrine is given is manifested as severe hypotension and tachycardia. Despite its irreversible binding to the receptor, the recommended treatment of phenoxybenzamine overdosage is norepinephrine infusion because some receptors remain free of the drug.[212]

Phentolamine (Regitine) is a shorter-acting drug that blocks α_1- and α_2-receptors. Historically used to treat pulmonary hypertension, it has largely been supplanted by nitroglycerin and nitroprusside. It is also used to treat the hypertension associated with clonidine withdrawal or with tyramine ingestion during MAOI therapy, but few data have been collected on its efficacy and safety for these indications. Phentolamine has also been infiltrated into affected tissues after extravasation of agents such as norepinephrine in an attempt to relax vasoconstriction; for this purpose, 5 to 10 mg is diluted in 10 mL of saline. Adverse effects of phentolamine include hypotension and gastrointestinal distress; reflex tachycardia and arrhythmias may result from action at α_2-receptors. Coronary artery disease and peptic ulcer disease are relative contraindications to its use. As in phenoxybenzamine overdosage, severe hypotension may require treatment with norepinephrine rather than epinephrine.

Prazosin (Minipress) is a potent selective α_1-adrenergic blocker often used as a prototypical antagonist in pharmacologic experiments. It antagonizes the vasoconstrictor effects of norepinephrine and epinephrine, thereby causing a decline in peripheral vascular resistance and venous return to the heart. Although the heart rate does not normally increase, orthostatic hypotension is a major problem. Unlike other antihypertensive drugs, prazosin improves lipid profiles by lowering low-density lipid levels while raising the level of high-density lipids. It is primarily used to treat hypertension. It has also been used in patients with CHF, but unlike the angiotensin-converting enzyme inhibitors (ACEIs), prazosin does not prolong life. It is metabolized by the liver. Supplied as 1-, 2-, and 5-mg tablets, its starting dose is usually 0.5 to 1 mg given at bedtime because of the orthostatic hypotension. Eventually, it can be taken twice daily.

α_2-Antagonists such as yohimbine increase sympathetic outflow by enhancing release of norepinephrine. These drugs have proved to be of little clinical utility in anesthesia, although they are used in urology.

β-Receptor Antagonists

Pharmacology

β-Adrenergic receptor antagonists (i.e., β-blockers) are among the most commonly prescribed drugs and are frequently taken by patients about to undergo surgery. Current indications for the use of β-blockade include ischemic heart disease, postinfarction management, arrhythmias, hypertrophic cardiomyopathy, hypertension, heart failure, and prophylaxis for migraine headache.

Concern that patients treated with β-blockers would be hemodynamically unstable under anesthesia has proved to be largely unjustified. These drugs are an important part of the armamentarium of the anesthesiologist in the ongoing attempt to limit stress responses perioperatively and to protect the cardiovascular system. A comprehensive analysis by the Agency for Healthcare Research and Quality found that the use of β-blockers perioperatively reduces morbidity and mortality in noncardiac surgery for patients at risk.[213] Several well-known clinical trials[214-218] and the widespread use and safety of these drugs in heart failure[219] have made β-blockade an evolving standard (see Chapter 34).

A wide spectrum of β-adrenergic blockers are available to the clinician. The most important properties to consider when choosing a β-blocker for long-term use are cardioselectivity, intrinsic sympathomimetic activity (ISA), and lipid solubility. In anesthetic practice, cardioselectivity, duration of action, and a formulation suitable for intravenous use are crucial factors (Table 12-10). β-Antagonists resemble isoproterenol in structure and bind competitively to the β-receptor, thereby blocking access by more potent β-agonists (Fig. 12-17). Competitive inhibition at the β-receptor can be overcome by increasing the available concentration of β-agonist. The potency of a β-blocker is often determined by its ability to inhibit induction of tachycardia by isoproterenol. Propranolol is assigned a potency of 1, and the other drugs are evaluated in relation to it.

Nonselective β-adrenergic blockers act at the β_1- and β_2-receptors and include propranolol, nadolol, pindolol, sotalol, oxprenolol, penbutolol, and timolol. Cardioselective β-blockers have stronger affinity for β_1-adrenergic receptors than for β_2-adrenergic receptors, and the predominant effects are therefore cardiac. With β_1-selective blockade, AV conduction velocity, heart rate, and cardiac contractility are decreased, as is release of renin by the juxtaglomerular apparatus and lipolysis at adipocytes. At larger doses, the relative selectivity for β_1-adrenergic receptors is lost and β_2-receptors are also blocked, with the potential for bronchoconstriction, peripheral vasoconstriction, and decreased glycogenolysis.

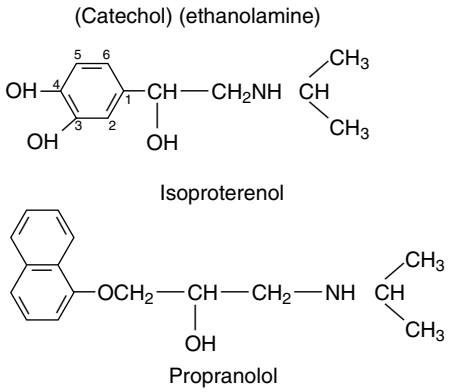

Figure 12-17 Structure of isoproterenol and propranolol. *(From Tollenaeré JP: Atlas of the Three-Dimensional Structure of Drugs. Amsterdam, Elsevier North-Holland, 1979.)*

Cardioselective drugs include atenolol, betaxolol, bevantolol, esmolol, and metoprolol. These drugs may be preferable for patients with obstructive pulmonary disease, peripheral vascular disease, Raynaud's phenomenon, and diabetes mellitus. Although previously a matter of controversy, a meta-analysis concluded that cardioselective β-blockers can be given safely to patients with chronic obstructive pulmonary disease.[220] Nevertheless, because the selectivity is only relative and may be lost at conventional clinical doses, extreme care should be taken when administering a β-blocker in the presence of pulmonary disease. Some β-antagonists also have vasodilatory effects, thus making them particularly useful in the treatment of hypertension and

Table 12-10 Pharmacokinetics and Pharmacology of Selected β-Adrenoceptor Blockers

Characteristic	Atenolol	Metoprolol	Propranolol HCl	Labetalol	Esmolol	Carvedilol
Proprietary name	Tenormin	Lopressor	Inderal Ipran	Trandate Normodyne	Brevibloc	Coreg
Relative β sensitivity	+	+	0	0	+	0
Intrinsic sympathetic activity	0	0	0	+	0	0
Membrane-stabilizing activity	0	0	++	0	0	—*
Lipophilicity†	Low	Moderate	High	Low	Low	High
Predominant route of elimination	RE (mostly unchanged)	HM	HM	HM	Hydrolysis by RBC esterase	HM
Drug accumulation in renal disease	Yes	No	No	No	No	No
Elimination half-life (hr)	6 to 9	3 to 4	3 to 4	≈6	9 min	2 to 8
Usual oral maintenance dose	50-100 mg qd	50-100 mg qid	60 mg qid	100-600 mg bid	N/A	25-50 mg bid
Usual intravenous dose (caution)		5 mg q5min × 3	0.1 mg/kg (maximum)	1-2 mg/kg	50 to 300 μg/kg/min infusion	15 mg

*Data not available.
†Determined by the distribution ratio between octanol and water.
HM, hepatic metabolism; N/A, not applicable; RBC, red blood cell; RE, renal excretion; 0, no effect; +, mild effect; ++ moderate effect.

CHF.[221,222] Labetalol vasodilates by blocking α_1-receptors and by direct β_2-receptor agonism.

β-Blockers exerting a partial agonist effect at the receptor while blocking access by more potent agonists possess ISA. Drugs with ISA include acebutolol, carteolol, celiprolol, dilevalol, oxprenolol, penbutolol, and pindolol. These drugs primarily decrease arterial blood pressure and, to a lesser extent, heart rate and left ventricular function. When sympathetic activity is high, such as during exercise, these drugs behave more like conventional β-blockers. The partial β_2-agonism of pindolol induces bronchodilation. ISA may therefore be useful if β-blockade is required in a patient with bradycardia, peripheral vascular disease, or very mild hyperreactive airway disease. Drugs with ISA may not be as effective in controlling symptoms in severe angina or in reducing mortality after MI.[223] ISA may protect against β-blocker withdrawal syndrome.[224]

Propranolol and acebutolol possess membrane-stabilizing activity (MSA), also referred to as the quinidine-like or local anesthetic effect. This effect reduces the rate of rise in cardiac action potential. The MSA of propranolol may explain the decrease in the oxygen affinity of hemoglobin when it is administered. However, MSA is seen only at concentrations 10 times those required for blockade of β-receptors and is probably of little clinical consequence. Overdose with drugs that exhibit MSA is associated with a higher incidence of fatality.[225]

Indications for Use

Perioperative β-Blockade. In the late 1990s, two important studies established the value of perioperative β-blockade in patients at risk for coronary ischemia who were undergoing noncardiac operations (see Chapters 34 and 35). Patients are labeled as "at risk" if they fit into one of two categories: they are undergoing high-risk vascular surgery and have no evidence of inducible coronary ischemia, or they are undergoing a nonvascular procedure but have traditional risk factors for coronary artery disease (elderly, high cholesterol, hypertension, cigarette smoking, family history of coronary disease, or diabetes).[226] The Multicenter Study of Perioperative Ischemia Research Group[215] enrolled 200 patients about to undergo surgery who had risk factors for coronary artery disease and randomized them to receive placebo or atenolol before and after surgery. Their results demonstrated that although there was no improvement in in-hospital outcomes (cardiac death or MI) in the atenolol-treated group, the treated group did have a lower incidence of cardiac events at the 6- to 8-month follow-up and a marked decrease in all-cause mortality that persisted at 2-year follow-up (survival rate at 2 years: 68% in the placebo group and 83% in the atenolol-treated group). The second study[216] enrolled patients with known ischemic disease demonstrated on preoperative stress echocardiography. The treatment group in this study was given bisoprolol and the dose was titrated to achieve a heart rate below the patients' ischemic threshold. The results of this study, whose participants were at much higher risk for ischemic events than those of the previous study, demonstrated a 10-fold decrease in perioperative cardiac death and MI (3.4% versus 34%). These powerful demonstrations that β-blockade could decrease perioperative cardiac risk and improve survival out to 2 years led to tremendous political and administrative pressure to increase the use of β-blockers perioperatively.[227] Unfortunately, more recent research has brought the value of routine perioperative β-blockade into question. The POBBLE study[228] results showed no reduction in 30-day cardiovascular morbidity in patients undergoing vascular surgery (one of the "at-risk" groups from previous studies). Similarly, the DIPOM study[229] showed no benefit of β-blockade in diabetics (another "at-risk" group) undergoing major noncardiac operations. Finally, a large retrospective study looking at in-hospital mortality in more than 780,000 patients demonstrated a neutral or even negative effect of perioperative β-blockade in patients without clear-cut coronary artery disease. β-Blockade was associated with a reduced mortality rate in only the 3% of patients who had three or more risk factors (based on the revised Cardiac Risk Index) for coronary ischemia.[230] Thus, until larger studies are completed, the only strong indication for initiating β-blockade preoperatively is for patients undergoing vascular surgery who are at high cardiac risk as a result of the finding of ischemia on preoperative testing.[227]

When perioperative β-blocker therapy is initiated, it should be titrated to a non–ischemia-inducing heart rate (usually 60 to 70 beats per minute) and not given as a standard fixed dose to all patients. β-blockers should be continued in patients who are already taking them as treatment of their angina, symptomatic arrhythmia, or hypertension.

The safety of continuing β-blockade perioperatively is well established, and initial concerns regarding interaction with general anesthesia have not been confirmed. Attempts to discontinue β-blockers increase the risk for rebound tachycardia (with or without atrial fibrillation) and myocardial ischemia in patients with coronary disease. These drugs should be given up to the time of surgery, and intravenous forms in appropriate dosages should be used whenever gastrointestinal absorption may be in question. If β-blockers have been omitted from the preoperative regimen, esmolol or labetalol may be used acutely to blunt tachycardia and hypertension. Cardioselective and nonselective β-blockers appear to be effective in blocking the chronotropic effects of endotracheal intubation and surgical stress.[231]

Myocardial Ischemia. Propranolol was initially introduced for the treatment of myocardial ischemia more than 3 decades ago, and β-blocking drugs remain an important part of drug therapy for myocardial ischemia (see Chapter 35). This class of drugs reduces oxygen demand by decreasing the heart rate and cardiac contractility. Cardioselective and nonselective β-blockers are effective. Atenolol, metoprolol, nadolol, and propranolol have been approved in the United States for the treatment of angina; metoprolol and atenolol are the only β-blockers approved for intravenous use in patients with acute MI. Although initially there was concern that β_2-receptor blockade could worsen ischemia through unopposed α-mediated vasoconstriction, this phenomenon is rarely seen, even in patients with variant angina. β-Antagonists are used to treat acute MI and on a long-term basis to reduce reinfarction and mortality in patients after infarction.[232-235] Early administration of intravenous β-blocking agents to patients receiving thrombolytic therapy appears to lower the incidence of ischemia and reinfarction[236] and may reduce the incidence of serious ventricular arrhythmias.[237] Long-term use of β-blockers (i.e., timolol, propranolol, metoprolol, and atenolol) has been shown to decrease mortality after MI. In usual clinical practice, the dose is increased until the heart rate is 60 to 80 beats/min at rest and there is no tachycardia with exercise.

Congestive Heart Failure. Over the past 5 to 10 years, β-blockers have become first-line agents for the treatment of CHF of ischemic and nonischemic origin. Clinicians had been disinclined to use β-blockers for heart failure patients because of the

drugs' negative inotropic effects. These effects have not turned out to be a significant concern in clinical practice. Early studies demonstrated a significant decrease in all-cause mortality for heart failure patients treated with metoprolol or bisoprolol. Several large studies[238,239] were stopped because the decrease in mortality in treated patients with moderate to severe heart failure was so pronounced. The benefits of β-blockers in patients with heart failure have been attributed to normalization and remodeling of the ventricle, which begin after 1 month of β-blockade[240]; to reduced norepinephrine-related cardiomyocyte apoptosis in the presence of β_1-blockade[241]; to decreased sudden cardiac death because of the β-blockers' antiarrhythmic activity; and most recently, to altered expression of genes in the myocardium that regulate contractility and pathologic hypertrophy.[242] To avoid worsening a patient's heart failure symptoms and to minimize negative inotropic effects, β-blockers are started at very low doses and are titrated to the target dose.[243] The only β-blockers approved for the treatment of CHF by the U.S. Food and Drug Administration are carvedilol and metoprolol, although their efficacy in patients with severe (i.e., New York Heart Association class IV) heart failure is still being studied. If decompensation occurs with the β-blocker, phosphodiesterase inhibitors are the inotropes of choice because their effects are not antagonized by β-blockade.[244]

Hypertension. The mechanisms by which β-antagonists treat hypertension are incompletely understood. Arterial blood pressure is specifically decreased in hypertensive patients because long-term treatment of normotensive individuals does not decrease blood pressure. Reduced cardiac output and renin release have been suggested as mechanisms. In hypertensive patients, β-antagonists without ISA may cause a 15% to 20% reduction in cardiac output and a 60% reduction in renin release. However, pindolol, which has ISA and minimal effect on renin, is also successful in treating hypertension.[245] Maximum renin suppression precedes significant changes in arterial blood pressure.[246] Initially, β-blockade increases peripheral vascular resistance and then over time lowers it.[247] The decrease in cardiac output and eventual lowering of peripheral resistance may account for much of the antihypertensive efficacy of these drugs. However, this too is an incomplete explanation because labetalol is an effective antihypertensive despite its lack of effect on cardiac output. A primary CNS effect is not likely to be a major mechanism because the antihypertensive efficacy of lipophilic and hydrophilic compounds is similar. Generally, β-blockade is ineffective as monotherapy in hypertensive African American patients older than 60 years.

Cardiac Arrhythmias. β-Blockers are widely used in the treatment of tachyarrhythmias as class II agents (see Chapters 35, 60, and 61). Two possible mechanisms of action are blockade of catecholamine effects and MSA, although the latter is most likely not clinically significant because antiarrhythmic effects are present in agents without MSA.[248] β-Antagonists slow the rate of depolarization of the sinus node and any ectopic pacemakers, slow conduction through atrial tissue and the AV node, and increase the refractory period of the AV node. These drugs can convert atrial arrhythmias to sinus rhythm,[249] but β-blockade is primarily used to slow the ventricular response. Reentrant tachyarrhythmias and those associated with Wolff-Parkinson-White syndrome, mitral valve prolapse, and a prolonged QT interval may also respond to these drugs. Care should be exercised if AV block is present, as in digitalis toxicity, although these drugs are useful in the treatment of digitalis-associated tachyarrhythmias. Sotalol, a β-blocker with added class III activity, is effective against ventricular tachyarrhythmias; however, in a trial comparing racemic sotalol with D-sotalol in post-MI patients, mortality increased with D-sotalol.[250] The trial was terminated when patients at lowest risk for arrhythmic events after MI had an increased mortality rate with this drug.[251]

Tachycardia. β-Antagonists are frequently used as adjuvants to moderate the reflex tachycardia associated with vasodilators (see Chapter 61). In addition to potentiating a reduction in blood pressure, β-blockade also reduces the velocity of left ventricular ejection (dp/dt) and attenuates the shearing force associated with the increased velocity of ventricular contraction when afterload is reduced with nitroprusside without concomitant β-blockade.[252] Labetalol has been particularly useful in this situation.[253]

Thyrotoxicosis. Cardiac complications are a primary cause of morbidity in thyrotoxicosis (see Chapter 75). β-Blockade can suppress the tachycardia and rhythm disturbances, although very large doses may be required. β-Antagonists also may be combined with digitalis for their synergistic effect on AV node conduction. Propranolol inhibits conversion of thyroxine to the active form triiodothyronine in the periphery.[254]

Miscellaneous Conditions. Timolol (Timoptic) and betaxolol (Betoptic) are β-blocking drugs used topically in the eye to treat glaucoma. They reduce the production of aqueous humor. Even topical use of these agents has been associated with significant systemic effects of β-blockade. β-Blockers are used in patients with idiopathic hypertrophic subaortic stenosis to reduce the dynamic obstruction to left ventricular outflow. The drugs are also effective in the prophylaxis but not the treatment of migraine headaches and in controlling acute panic symptoms and essential tremor.

Adverse Effects

The adverse effects of most concern are those involving cardiopulmonary function. Severe noncardiopulmonary reactions such as cutaneous reactions or anaphylaxis are rare. Life-threatening bradycardia, even asystole, may occur, and decreased contractility may precipitate CHF in vulnerable individuals. In patients with bronchospastic lung disease, β_2-blockade may be fatal. CNS effects, although an appropriate consideration with long-term therapy, are not a concern with the usual anesthetic use of these agents. Diabetes mellitus is a relative contraindication to the long-term use of β-antagonists because hypoglycemia in the face of sympathetic blockade is not accompanied by warning signs such as tachycardia and tremor and because compensatory glycogenolysis is blunted. However, most non–insulin-dependent diabetic patients can tolerate these drugs, although β-blockade may cause insulin resistance in rare cases. In addition to the potential worsening of peripheral perfusion by β_2-blockade in patients with peripheral vascular disease, Raynaud's phenomenon may be triggered in susceptible patients. Sudden withdrawal of β-blockers may cause myocardial ischemia and possibly infarction, but this is less of a problem with β-blockers that have ISA, such as pindolol.[255] Even though β-antagonists may reduce renal blood flow and the glomerular filtration rate, these agents can be used in renal failure. For such patients, the doses of lipid-insoluble drugs should be reduced. To avoid worsening of hypertension, use in pheochromocytoma should be avoided unless α-receptors have

previously been blocked. Nonselective agents may elicit hypertensive responses in cases of high sympathetic stimulation.[256]

Undesirable drug interactions are possible with β-blockers. The rate and contractility effects of verapamil are additive to those of β-blockers,[257,258] and care should be taken when combining these agents, especially the intravenous forms in acute situations such as supraventricular tachycardia. The combination of digoxin and β-blockers can have powerful effects on heart rate and conduction and should be used with special care. Pharmacokinetic interactions are predictable from the degree of lipid solubility of the drug. Cimetidine and hydralazine may reduce hepatic perfusion, thereby increasing plasma levels and half-lives of the lipid-soluble β-antagonists. Barbiturates, phenytoin, rifampin, and smoking may induce hepatic enzymes and enhance metabolism. Propranolol may reduce hepatic clearance of lidocaine and increase the risk for toxicity.

Overdose of β-blocking drugs may be treated with atropine, but isoproterenol, dobutamine, or glucagon infusions (or some combination) may be required along with cardiac pacing to ensure an adequate rate of contraction.

Specific Drugs

The drugs propranolol, metoprolol, labetalol, and esmolol are particularly useful in anesthetic practice because they are widely available in intravenous formulations and have well-characterized effects. If the drug that the patient has taken on a long-term basis is propranolol, metoprolol, or labetalol, it may be continued in intravenous form. In deciding which intravenous β-blocker to substitute in a patient taking a β-blocker on a long-term basis, the need for cardioselectivity is a primary consideration. Cardioselectivity is provided by metoprolol or esmolol. If the long-term agent has ISA, oxprenolol and acebutolol have intravenous forms, but they are not readily available. In many situations, esmolol may be substituted and titrated to effect, with the expectation that its effects will fade relatively rapidly if it is not well tolerated.

Propranolol. Propranolol (Inderal, Ipran), the prototypical β-blocker, is a nonselective β-blocking drug with MSA but no ISA. It readily penetrates the CNS. Because of its high lipid solubility, it is extensively metabolized in the liver, but metabolism varies greatly from patient to patient. Its effective dose is extremely variable: 10 mg to as much as 320 mg may be given orally each day. Clearance of the drug can be affected by liver disease or altered hepatic blood flow. Renal impairment does not require adjustment of dosing. Despite its half-life of 4 hours, its antihypertensive effect persists long enough to permit dosing once or twice daily. Propranolol is available in an intravenous form and was initially given as either a bolus or an infusion. Infusions of propranolol have largely been supplanted by esmolol. For bolus administration, doses of 0.1 mg/kg may be given, although most practitioners initiate therapy with much smaller doses, typically 0.25 to 0.5 mg, and titrate to effect. Propranolol shifts the oxyhemoglobin dissociation curve to the right, which perhaps accounts for its efficacy in vasospastic disorders.[259]

Metoprolol. Metoprolol (Lopressor) is approved for the treatment of angina pectoris and acute MI. It is cardioselective and lacks ISA and MSA. Because it is metabolized in the liver by the monooxygenase system, doses need not be adjusted in the presence of liver failure. The usual oral dose is 100 to 200 mg/day given once or twice daily for hypertension and twice daily for angina pectoris. It may be administered intravenously in doses of 2.5 to 5 mg every 2 to 5 minutes up to 15 mg, with titration to heart rate and blood pressure.

Labetalol. Labetalol (Trandate, Normodyne) is representative of a class of drugs that act as competitive antagonists at the α_1- and β-adrenergic receptors. Labetalol consists of four isomers that block the α_1-, β_1-, and β_2-receptors, inhibit neuronal uptake of norepinephrine (uptake 1), act as a partial agonist at β_2-receptors, and possibly have some direct dilating ability. The potency of the mixture for β-blockade is 5- to 10-fold that for α-blockade. The usual oral dose of labetalol is 200 to 400 mg twice daily, although much larger doses have been used. It is metabolized by the liver, and clearance is affected by hepatic perfusion. The dose need not be adjusted for renal dysfunction. Labetalol may be given intravenously every 5 minutes in 5- to 10-mg doses or up to a 2 mg/min infusion. It significantly blunts cardiovascular responses to tracheal intubation.[260] It can be effective in the treatment of aortic dissection,[252] hypertensive emergencies,[261,262] and postoperative cardiac surgical patients,[263] particularly because vasodilation is not accompanied by tachycardia. It may be used in pregnancy to treat hypertension on a long-term basis and in more urgent situations.[264] Uterine blood flow is not affected, even with a significant reduction in blood pressure (see Chapter 69).[265]

Carvedilol. Carvedilol, a mixed α- and β-antagonist, has been introduced as therapy for mild or moderate hypertension,[266-274] for the management of stable or unstable angina, and after acute MI.[275-279] Clinical trials of carvedilol for the treatment of controlled CHF (New York Heart Association class II to IV) suggest a significant reduction in mortality,[237,238,280,281] especially for patients with diabetes.[282]

Esmolol. Because of its hydrolysis by esterases, esmolol (Brevibloc) has a uniquely short half-life of 9 to 10 minutes, which makes it particularly useful in anesthetic practice. It is administered when β-blockade of short duration is desired or in critically ill patients for whom the adverse effects of bradycardia, heart failure, or hypotension may necessitate rapid withdrawal of the drug. The peak effects of a loading dose are seen within 5 to 10 minutes and diminish rapidly (within 20 to 30 minutes). It is cardioselective and may be given as a bolus of 0.5 mg/kg to blunt cardiovascular responses to tracheal intubation. If used as an infusion for the treatment of supraventricular tachycardia, 500 μg/kg is given over a 1-minute period, followed by an infusion of 50 μg/kg/min for 4 minutes. If the rate is not controlled, a repeat loading dose followed by a 4-minute infusion of 100 μg/kg/min is given, and this sequence is repeated with the infusion increased in 50-μg/kg/min increments up to 200 or 300 μg/kg/min if needed. The effect may persist for 20 to 30 minutes after discontinuation of the infusion. When compared with verapamil, esmolol is more likely to convert atrial fibrillation to sinus rhythm.[248] Esmolol is safe and effective for the treatment of intraoperative and postoperative hypertension and tachycardia.[283-285] If continuous use is required, it may reasonably be replaced by a longer-lasting cardioselective drug such as intravenous metoprolol. It has been used safely even in patients with compromised left ventricular function.[286,287]

Drugs that Inhibit Synthesis, Storage, or Release of Norepinephrine

Some early antihypertensive drugs acted by replacing norepinephrine in the nerve ending with a much less potent false transmitter. Methyldopa (Aldomet) is such a drug and was the most

popular nondiuretic antihypertensive used before the development of β-blockers.[213] Like DOPA, methyldopa enters the biosynthetic pathway for norepinephrine (see Fig. 12-7). It is then decarboxylated to α-methylnorepinephrine. Initially, this chemical was thought to act as a false transmitter, but it was found to be almost as potent as norepinephrine. In the CNS, methyldopa may be further metabolized to α-methylepinephrine, and it acts at α_2-receptors to decrease sympathetic outflow, which reduces blood pressure. Because of its sedating qualities, fluid retention, postural hypotension, and occasional reports of hepatic necrosis, methyldopa is now used much less often.

Methylparatyrosine (metyrosine, Demser) is a potent inhibitor of TH, which catalyzes the formation of DOPA from tyrosine (see Fig. 12-7). Because this is the rate-limiting step in the biosynthesis of norepinephrine, the drug significantly decreases levels of endogenous catecholamines and is useful in treating inoperable or malignant pheochromocytomas.

Reserpine affects the uptake of norepinephrine, not at the neuronal membrane but at the vesicular membrane, thereby inhibiting transport and storage of norepinephrine and dopamine. However, this drug is rarely used in modern medicine.

Guanethidine (Ismelin) acts initially by blocking the release of norepinephrine, and then it is taken up into adrenergic nerve endings by the uptake-1 mechanism and depletes norepinephrine stores. It is used to treat hypertension, usually after many other drugs have been tried. Its inability to cross the blood-brain barrier accounts for its lack of sedative effects. Guanadrel (Hylorel) is similar to guanethidine, but it has a faster onset and shorter duration of action.

Bretylium, a class III antiarrhythmic used parenterally to treat life-threatening ventricular tachyarrhythmias, is now largely of historical interest. Like guanethidine, it is taken up into adrenergic nerve terminals, but its mechanism of action is otherwise quite different. Bretylium initially causes release of norepinephrine and subsequently blocks that release by decreasing sympathetic nerve excitability. Unlike guanethidine, bretylium does not deplete norepinephrine stores. The initial catecholamine release may cause marked hypertension and worsen some arrhythmias, such as those associated with digitalis toxicity and myocardial ischemia.[234] As a consequence, bretylium, which had been part of the advanced cardiac life support protocols for treating ventricular arrhythmias, has been dropped from the algorithms.

MAO and COMT are enzymes important in degradation of the catecholamines. MAOIs bind irreversibly to the enzyme and increase the amine concentration within the presynaptic terminal. Chronic MAOI use is associated with antihypertensive, antidepressant, and antinarcoleptic effects. MAOIs are thought to exert their antihypertensive effect through a false transmitter mechanism. Tyramine is usually oxidatively deaminated in the gut by MAO. With administration of an MAOI, tyramine levels rise. When tyramine is taken up into the sympathetic nerve terminal by the uptake-1 mechanism, it enters the varicosities and is transformed by DβH into octopamine. On its subsequent release in place of norepinephrine, octopamine is only weakly reactive at sympathetic receptors, thereby resulting in lowering of blood pressure. The MAOIs are no longer used as antihypertensives because many other drugs with better risk-benefit profiles have been developed.

MAOIs are primarily used in psychiatric practice. The use of MAOIs as antidepressants is based on the theory that depression is caused by decreased amine in the synapses of the CNS. Inhibition of MAO makes more amine available for release. MAOIs available for the treatment of depression include isocarboxazid (Marplan), phenelzine sulfate (Nardil), and tranylcypromine sulfate (Parnate).

Based on substrate specificity, there are at least two forms of MAO. MAO-A acts on 5-HT, epinephrine, norepinephrine, tyramine, and dopamine, whereas MAO-B is specific for tyramine and dopamine. A specific MAO-B inhibitor, selegiline hydrochloride (deprenyl), has been developed for the treatment of Parkinson's disease in the hope that by blocking central dopamine breakdown, more dopamine will be preserved in the affected areas.[288]

Drug and food reactions have been of great concern in patients taking MAOIs. Tyramine-containing foods such as red wine and aged cheese must be avoided by patients taking these drugs. Consumption delivers a huge amount of tyramine to the adrenergic nerve terminal, with a subsequent massive release of norepinephrine. This release is manifested clinically as a hypertensive crisis with the potential for MI, cerebral hemorrhage, and death. Any intake of biogenic amine precursors can be expected to increase catecholamine levels greatly, as seen with the concurrent administration of levodopa with MAOIs. The effects of sympathomimetic amines, particularly the indirectly acting drugs, are enhanced. Narcotics, most notably meperidine, have been associated with hyperpyrexic coma and death in patients treated with MAOIs. The depressant effects of agents such as sedatives, alcohol, and general anesthetics are enhanced in these patients. Interactions between MAOI and tricyclic antidepressants can be disastrous. Anesthetic interactions with deprenyl have not been reported, but experience with this drug is limited. Great concern has been expressed that patients receiving long-term therapy with an MAOI risk life-threatening drug interactions during anesthesia. Emergency surgery in patients given an MAOI can be punctuated by marked hemodynamic instability. Severe reactions to narcotics and indirect-acting sympathomimetics, as well as altered metabolism of endogenous and exogenous catecholamines, make these patients potentially difficult to manage. Because of the possibly dangerous interactions of many drugs with MAOIs, controversy exists about the best way to anesthetize these patients.[289,290] It has been suggested that the level of concern expressed over the years may be excessive. Although prudence and custom dictate discontinuation of MAOIs at least 2 weeks in advance of elective procedures, there appear to be rational anesthetic choices based on pharmacology and risk-benefit considerations for patients when surgery cannot be delayed or no effective alternative psychiatric medications are available.

Drugs Affecting the Renin-Angiotensin System

The renin-angiotensin system maintains blood pressure and fluid balance. The major end product of the system, angiotensin II, is a potent vasoconstrictor that also stimulates release of aldosterone from the adrenal cortex. Aldosterone causes salt and water retention by the kidney. The mechanism by which angiotensin II

is produced is as follows. The juxtaglomerular cells of the renal cortex secrete the proteolytic enzyme renin, which cleaves angiotensinogen, a protein synthesized in the liver, and produces the decapeptide angiotensin I. Angiotensin I is converted almost immediately to angiotensin II by angiotensin-converting enzyme (ACE). This converting enzyme is located predominantly in the endothelial tissue of the lung. In addition to its direct vasoconstrictive activity, angiotensin II enhances the prejunctional release of norepinephrine from adrenergic nerve ending and increases efferent sympathetic nerve activity. Angiotensin II also affects sodium and water homeostasis by directly decreasing tubular reabsorption of sodium, increasing antidiuretic and adrenocorticotropic hormone secretion, and stimulating the secretion of aldosterone. ACE is also a kinase that degrades the vasodilator bradykinin. ACE inhibition blocks angiotensin II formation and delays the breakdown of bradykinin, along with effects on associated prostaglandins.[291]

Although only a small percentage of hypertensive patients have high circulating plasma renin levels, 70% of patients will respond to the antihypertensive effects of ACEIs. In patients who have elevated plasma renin levels (e.g., patients with CHF or salt depletion states), ACEI therapy must be initiated at lower doses because these patients are extremely sensitive to the effects of ACEIs and significant hypotension can follow the administration of a standard starting dose of these drugs.[213]

ACEIs have proved to be useful in the treatment of hypertension and CHF and have decreased mortality after MI.[292] Captopril (Capoten) was the first active oral agent available, followed by enalapril (Vasotec) and lisinopril (Prinivil, Zestril). ACEIs affect the renin-angiotensin-aldosterone system by inhibiting ACE activity.[293,294] Enalapril is the only ACEI available as an intravenous preparation at this time. Lisinopril offers once-daily dosing.

All the ACEIs are approved for the treatment of hypertension. Captopril, enalapril, ramipril, and trandolapril all decrease morbidity and mortality in patients with CHF. Captopril is associated with more frequent adverse effects than the other agents are, may have a few more drug interactions, and has a dosing regimen of two or three times daily, in contrast to the other ACEIs, which have a dosing regimen of once or twice daily.

Some adverse effects observed with ACEIs are common to the entire class, such as cough, angioedema, acute renal failure, and hyperkalemia. Angioedema, especially after the first dose, affects the face, extremities, lips, mucous membranes, tongue, glottis, or larynx.[295,296] Some occurrences may be fatal.[291,297] Rash and taste disturbances are more frequent with captopril than with the other ACEIs. Because impairment of renal function with an ACEI is usually reversible after withdrawal of the drug, renal function must be monitored, and because hyperkalemia may result from inhibition of aldosterone secretion, serum potassium levels should be monitored. ACEIs can cause fetal morbidity and mortality in humans. These agents should not be used at all during the second or third trimester of pregnancy.[293] The adverse effect profile of the ACEIs has led to the development of angiotensin II receptor blockers (ARBs). Losartan was the first of this new class of antihypertensive agents, which now includes six other ARBs. Initial trials have not demonstrated ARBs to be superior to ACEIs; however, the addition of these agents during chronic ACEI therapy reduced all-cause mortality and hospitalization in patients with heart failure.[298]

Cholinergic Drugs

Overview of Mechanisms of Action

Cholinergic drugs act by mimicking, amplifying, or inhibiting the effects of acetylcholine. Cholinergic drugs do not behave exactly like acetylcholine; their drug action is more specific, with fewer sites affected than with acetylcholine, and their duration of action is generally longer than that of acetylcholine.

Unlike adrenergic pharmacology, in which the clinician can select from a wide choice of drugs, there is a relative paucity of drugs that influence parasympathetic function. In general, drugs that affect the parasympathetic system act in one of four ways:

1. As an agonist by stimulating cholinergic receptors
2. As an antagonist by blocking or inhibiting the actions mediated by the cholinergic receptor
3. Blocking or stimulating receptors on autonomic ganglia
4. Inhibiting the metabolism of acetylcholine, thereby increasing and prolonging its effect

There are no effective clinically used drugs that act through mechanisms affecting the synthesis of acetylcholine (by inhibiting choline acetyltransferase) or by causing indirect release of acetylcholine. Hemicholinium, which interferes with choline uptake and could deplete acetylcholine stores, is not used clinically. Adenosine may inhibit the release of acetylcholine by decreasing the affinity of binding sites for calcium ions; aminoglycoside antibiotics compete with calcium for membrane calcium channels, as does magnesium. Exocytotic release of acetylcholine is inhibited by botulinum toxin. This toxin is sometimes given by local injection to treat strabismus and blepharospasm and has also been used for trigger point injections in pain clinics and to treat age lines. The popularity of off-label uses of this toxin increases the chance of botulism poisoning. In a full-blown botulism-poisoning syndrome, fatalities may result from muscle weakness and respiratory failure.

Cholinergic Agonists

Cholinergic agonists have limited therapeutic use because of their detrimental effects. As a result of its diffuse, nonselective actions and rapid hydrolysis by acetylcholinesterase and butyrylcholinesterase, acetylcholine has had almost no therapeutic use other than as an intraocular medication for transient constriction of the pupil during ophthalmic surgery.

Cholinergic agonists in clinical use have been derived from acetylcholine, but they resist hydrolysis by cholinesterase, which permits a useful duration of action. The different systemic effects of the cholinergic agonists are more quantitative than qualitative, but some limited organ selectivity is useful therapeutically, as seen with the synthetic choline esters bethanechol and carbachol. Methacholine and bethanechol are primarily muscarinic agonists; carbachol has significant nicotinic and muscarinic effects. Adding a methyl group to the β-position of the choline in acetylcholine produces methacholine, which is almost purely muscarinic and nearly totally resistant to hydrolysis by either of the cholinesterases. An intravenous infusion of methacholine causes hypotension and bradycardia; a small subcutaneous dose causes transient hypotension with a reflex increase in heart rate. The sole current

use of methacholine (Provocholine) is as a provocative agent in diagnosing hyperreactive airways, thereby making positive use of the deleterious bronchoconstrictive effect of muscarinic agonists. It is administered only by inhalation; serious adverse effects include gastrointestinal symptoms, chest pain, hypotension, loss of consciousness, and complete heart block when the drug is given orally or parenterally. An excessive bronchoconstrictive response should be treated by an inhaled β-agonist; coexisting β-blockade is considered a contraindication to the use of methacholine.

The carbamate derivative of methacholine, bethanecol (Urecholine), is occasionally used postoperatively to reinstitute peristaltic activity in the gut or to force the extrusion of urine from an atonic bladder. Bethanecol shows preferential activity at intestinal and urinary receptors relative to cardiac sites, so stimulation of the gastrointestinal tract and bladder is achieved with minimal cardiovascular effects. Bethanecol is usually given orally, but if there is inadequate gastrointestinal function to permit absorption of an oral dose, it can be given subcutaneously as well.

Carbachol is used topically or intraocularly to constrict the pupil for the long-term treatment of wide-angle glaucoma. When used topically, it is often better tolerated than the ophthalmic anticholinesterase agents, and it may be effective in patients resistant to pilocarpine and physostigmine. The rapid pupillary constriction is caused by the combination of ganglionic blockade and muscarinic effects. Another natural alkaloid, pilocarpine, was used to treat glaucoma until the advent of more modern drugs.

Muscarinic Antagonists

Muscarinic antagonists are the active ingredients in some common plants used since antiquity for medicinal and poisonous effects. Despite their age, muscarinic antagonists still represent important drugs in anesthesia and critical care.

Muscarinic antagonists compete with neurally released acetylcholine for access to muscarinic cholinoceptors and block its effects. They also antagonize the actions of muscarinic agonists at noninnervated, muscarinic cholinoceptors. Presynaptic muscarinic receptors on the adrenergic nerve terminal may inhibit release of norepinephrine, and muscarinic antagonists may enhance sympathetic activity. With the exception of quaternary ammonium compounds that do not readily cross the blood-brain barrier and have few CNS actions, there is no significant specificity of action among these drugs; they block all muscarinic effects with equal efficacy, although some quantitative differences in effect may be seen (Table 12-11). Research has revealed several subtypes of muscarinic receptors, and agonists and antagonists have been synthesized that bind preferentially to one or another of these subtypes. Pirenzepine preferentially blocks the M_1 receptor, tripitramine shows highest affinity for the M_2 receptor, and darifenacin binds preferentially to the M_3 receptor. The distinctive pharmacology of the various antimuscarinic agents has played a major role in the development of new treatments of overactive bladder disorders. Oxybutynin, tolterodine, darifenacin, solifenacin, and trospium have all been developed to optimize the relief of bladder symptoms while minimizing effects on muscarinic receptors outside the bladder.

Table 12-11 Muscarinic Anticholinergic Drugs

Drug	Duration	Central Nervous System*	Antisialagogue	Heart Rate
Atropine	Short	Stimulation	+	++
Glycopyrrolate	Long	0	++	+
Scopolamine	Short	Sedation	++	0/+

*The effects of atropine are limited with the usual clinical doses, but they can be significant in the elderly.
0, no effect; +, mild effect; ++, moderate effect.

Historically, muscarinic antagonists were used for peptic ulcer disease, various forms of spastic bowel syndrome, upper respiratory illness, and asthma. However, with the availability of specific histamine (H_2)-blocking drugs such as cimetidine for peptic ulcer disease, these uses have markedly decreased. Atropine, once used to treat bronchospasm, was displaced with the introduction of β_2-agonist drugs that did not dry secretions or diminish ciliary motility. Topical use of atropine analogs in ophthalmologic practice to dilate the pupil is still common.

The addition of a muscarinic anticholinergic drug to anesthetic premedication for decreasing secretions and preventing harmful vagal reflexes was mandatory in the era of ether anesthesia, but it is less important with modern inhaled agents. Routine preoperative use of these drugs as antisialagogues continues in some pediatric and otorhinolaryngologic cases or when fiberoptic intubation is planned.

Atropine has a tertiary structure that easily crosses the blood-brain barrier (Fig. 12-18). CNS effects have been seen with the relatively large doses (1 to 2 mg) given to block the adverse muscarinic effects of the anticholinesterase drugs that reverse neuromuscular blockade (see Chapter 29). In contrast, one of the synthetic antimuscarinic drugs, glycopyrrolate (Robinul), does not cross the blood-brain barrier because of its quaternary structure and has gained popularity for this use. Glycopyrrolate has a longer duration of action than atropine does.

Scopolamine, which resembles the others of this class in peripheral actions, has pronounced CNS effects. It is the active ingredient in most over-the-counter preparations sold as soporifics, and it is effective in preventing motion sickness. The patch preparation of scopolamine can be used prophylactically for motion sickness and for postoperative nausea and vomiting, but like the oral and parenteral forms, it may be associated with adverse eye, bladder, skin, and psychological effects.[299,300]

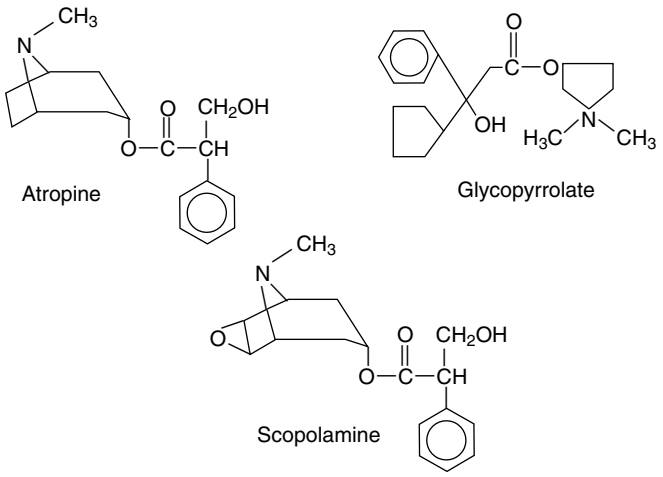

Figure 12-18 Structural formulas of clinically useful antimuscarinic drugs.

The development of ipratropium (Atrovent) reestablished antimuscarinic drugs for the treatment of asthma and bronchospastic disorders.[301] Although ipratropium is structurally similar to atropine and has essentially the same effects when administered parenterally, an important difference is that ipratropium is a quaternary ammonium compound. It is very poorly absorbed when inhaled and has few extrapulmonary effects, even in extremely large doses by this route. Ninety percent of the inhaled drug is swallowed, but only 1% of the total dose is absorbed systemically.

When administered to normal volunteers, ipratropium provides almost complete protection against bronchospasm induced by a variety of provocative agents. However, in asthmatic patients, results vary. The bronchospastic effects of some agents, such as methacholine or sulfur dioxide, are completely blocked, whereas there is little effect on leukotriene-induced bronchoconstriction. The onset of bronchodilation is slow, and the maximum effect is less than that seen with β-agonists. Unlike atropine, ipratropium has no negative effect on ciliary clearance. In general, the therapeutic effect of antimuscarinics, including ipratropium, is greater in patients with chronic obstructive pulmonary disease than in asthmatic patients.[298] Ipratropium is supplied as a metered-dose inhaler that dispenses 18 μg per puff. Two puffs are taken orally four times each day. Maximum bronchodilation occurs in 30 to 90 minutes and may last 4 hours.

The toxic effects of muscarinic antagonists come from the blockade of muscarinic cholinoceptors in the periphery and the CNS. The peripheral effects (e.g., dry mouth) may be irritating but are not life threatening in healthy adults. However, children depend more than adults on sweating for thermoregulation and can become dangerously hyperthermic when given these agents. Moreover, older individuals may not be able to tolerate the cardiac, ocular, or urinary effects of muscarinic blockade.

CNS effects are the usual cause of death or injury. Increasing doses of atropine or scopolamine cause greater distortions of mentation that progress from thought disorders to hallucinations, delusions, delirium, and severe psychoses. These effects are reversible, but the mental dysfunction can persist for weeks. Left alone, an intoxicated individual will die of starvation, dehydration, or trauma. People who have received more than 500 mg of atropine, which is more than 1000 times the usual dose, and have been disabled for weeks have recovered fully.

Small doses of atropine (0.05 mg) can evoke bradycardia, a finding that has led some clinicians to increase the dose in children. It was thought that a CNS effect of atropine could be responsible, but the time course and the fact that bradycardia occurred in vagotomized animals cast doubt on this explanation. Whether this paradoxical bradycardia is a central or peripheral effect, or both, and the role of muscarinic subtypes are still subjects of debate.[302]

Atropine and scopolamine toxicity has been treated for decades with the naturally occurring alkaloid physostigmine (Antilirium), which is an anticholinesterase that penetrates the blood-brain barrier. Use of this drug in doses of 1 to 2 mg given intravenously to treat the postoperative CNS effects of intravenous atropine or scopolamine has been successful. Physostigmine may also reverse the CNS effects of other compounds with anticholinergic activity, including the tricyclic antidepressants, several major tranquilizers, and antihistamine drugs. Physostigmine may also antagonize the sedative effects of the benzodiazepines, but a specific benzodiazepine antagonist, flumazenil (Romazicon), has supplanted physostigmine for this use.[303] Physostigmine must be administered with care because of its potentially lethal nicotinic effects, which are not prevented by the muscarinic antagonists, and because its half-life rarely matches that of the intoxicant.

Cholinesterase Inhibitors

Anticholinesterase drugs are a common means of producing sustained, systemic cholinergic agonism. These drugs are used to reverse neuromuscular blockade and to treat myasthenia gravis and certain tachyarrhythmias.

Three chemical classes of compounds are used as cholinesterase inhibitors: carbamates, organophosphates, and quaternary ammonium alcohols. Physostigmine, neostigmine, and pyridostigmine are carbamates, whereas edrophonium is a quaternary ammonium alcohol. The cholinesterase enzyme is inhibited as long as the esteratic site is bound to an acetate, carbamate, or phosphate. Carbamate and phosphate bonds are much more resistant to attack by hydroxyl groups than acetate bonds are. The acetylated form lasts for only microseconds, whereas the carbamylated form lasts for 15 to 20 minutes. Organophosphates include diisopropyl fluorophosphate, parathion, malathion, soman, sarin, VX, and a variety of other compounds used as insecticides. Although the toxicity of the organophosphate insecticides is primarily related to their anticholinesterase activity, the mechanism of this effect is different from the clinically used anticholinesterase drugs (see Chapter 74). The organophosphates produce irreversible enzyme inhibition and have CNS effects. Consequently, treatment of organophosphate insecticide poisoning relies on chemical compounds capable of displacing the insecticides from the enzyme to reactivate the cholinesterase activity. The best documented of these chemicals is pralidoxime (2-PAM). Physostigmine and most of the organophosphates are not quaternary ammonium compounds and have major effects on cholinergic functions in the CNS (see Chapter 74).

Because these compounds can increase the effect and duration of neurally released acetylcholine, they are useful in situations in which such release is deficient, such as myasthenia gravis. Anticholinesterase drugs are occasionally used to stimulate intestinal function and are applied topically in the eye as a miotic. An irreversible organophosphate anticholinesterase that is used clinically is echothiophate iodide (Phospholine), which is available as topical drops for the treatment of glaucoma. Its major advantage over other topical agents is its prolonged duration of action. Because this chemical also inactivates plasma cholinesterase, it may prolong the action of succinylcholine. Although prudence dictates discontinuation of echothiophate for 1 week before surgery, there are numerous case reports of successful anesthesia performed without discontinuation of echothiophate under emergency conditions.

Ganglionic Drugs

Ganglionic Agonists

Ganglionic agonists are essential for analyzing the mechanism of ganglionic function, but they have no therapeutic use. Nicotine is the classic ganglionic agonist, and its effects have been well described.

Parasympathetic drugs stimulate ganglia, but this action is usually masked by their other parasympathomimetic effects. Experimentally, relatively large doses of acetylcholine adminis-

tered intravenously after blockade of muscarinic receptors by atropine cause ganglionic stimulation and release of epinephrine by the adrenal medulla.

Ganglionic Antagonists

Ganglionic antagonists were the first effective therapy for the management of hypertension and were used extensively during the 1950s and 1960s. However, because of interference with transmission through sympathetic and parasympathetic ganglia, their antihypertensive action was accompanied by numerous undesirable effects. Hexamethonium, the prototypical drug of this class, has minimal neuromuscular and muscarinic activity. The systemic effects of ganglionic blockade are determined by the resting tone of a specific body system before the initiation of ganglionic blockade (see Table 12-3). With the disappearance of trimethaphan from clinical use, these drugs are largely of historical interest.

Autonomic Dysfunction

Assessment of Autonomic Function

The increased operative risk of patients with autonomic dysfunction that may occur with aging and diabetes[304] makes the diagnosis of autonomic neuropathy extremely important. A panel of five tests of cardiovascular function has been developed to evaluate autonomic function in diabetic patients (see Chapter 35).[305] The tests include heart rate responses to the Valsalva maneuver, standing up, and deep breathing and blood pressure responses to standing up and sustained handgrip. The tests involving changes in heart rate measure injury to the parasympathetic system, which precedes changes in the measures of blood pressure that reflect sympathetic injury. Early autonomic dysfunction is defined as a single abnormal or two borderline-abnormal results on the tests involving changes in heart rate. Definite involvement is dignosed when the results are abnormal on two of the tests of changes in heart rate. Severe dysfunction is defined as abnormalities in blood pressure assessments. Application of these standards requires that the investigator understand the proper techniques for performing the five tests and the expected results in patients without autonomic neuropathy (Table 12-12). If patients demonstrate an increase in heart rate of more than 20 beats/min with a vigorous handgrip, it can be assumed that they are incompletely β-blocked. The simplicity and effectiveness of this clinical assessment have led to its use in the evaluation of patients with nondiabetic causes of autonomic dysfunction as well.

Table 12-12 Noninvasive Tests for Assessing the Autonomic Nervous System

Clinical Examination	Technique	Normal Value
Parasympathetic		
HR response to a Valsalva maneuver	The seated subject blows into a mouthpiece (while maintaining a pressure of 40 mm Hg) for 15 seconds. The Valsalva ratio is the ratio of the longest R-R interval (which comes shortly after release) to the shortest R-R interval (which occurs during the maneuver)	Ratio of >1.21
HR response to standing	HR is measured as the subject moves from a resting supine position to standing. A normal tachycardic response is maximal around the 15th beat after rising. A relative bradycardia follows that is most marked around the 30th beat after standing. The response to standing is expressed as a 30:15 ratio and is the ratio of the longest R-R interval around the 30th beat to the shortest R-R interval around the 15th beat	Ratio of >1.04
HR response to deep breathing	The subject takes six deep breaths in 1 minute. The maximum and minimum heart rates during each cycle are measured, and the mean of the differences (maximum HR – minimum HR) during three successive breathing cycles is taken as the maximum-minimum HR	Mean difference >15 beats/min
Sympathetic		
BP response to standing	The subject moves from resting supine to standing, and standing SBP is subtracted from supine SBP	Difference <10 mm Hg
BP response to sustained handgrip	The subject maintains a handgrip of 30% of the maximum handgrip squeeze for up to 5 minutes. BP is measured every minute, and the initial DBP is subtracted from the DBP just before release	Difference >16 mm Hg

Plasma Catecholamines

Accurate and sensitive techniques for measuring plasma catecholamines have existed for 3 decades, but interpretation of the data that they yield has been controversial. Normal plasma epinephrine and norepinephrine levels are typically in the range of 100 to 400 pg/mL, and they can increase sixfold or more with stress.

Plasma concentrations of epinephrine, which reflect adrenal medullary activity if not overall sympathetic activity, are labile. Significant isolated adrenal medullary secretion results from certain stressful situations, such as public speaking.[5] Moreover, venous samples may reflect epinephrine kinetics in the organ being sampled rather than in the whole body, so arterial samples may be more reliable.

The significance of the norepinephrine concentration in plasma is even more controversial. Even though the adrenal medulla secretes some norepinephrine, levels in plasma generally reflect spillover from sympathetic stimulation that was not taken

up again by the nerve terminal. Although reuptake may be tissue specific and markedly influenced by alterations in physiology or diseases, spillover in humans is 10% to 20% of the synthesis rate of norepinephrine at baseline and may be greatly enhanced in periods of sympathetic activation.[306] The most compelling argument for the use of plasma norepinephrine as a marker of sympathetic activity comes from animal studies in which plasma norepinephrine levels directly mirrored nerve stimulation. Many important studies have correlated increases in plasma catecholamines with acute and chronic stress, which has led to the concept of stress-free anesthesia. A striking relationship between mortality rates for patients with CHF and elevated plasma norepinephrine levels resulted in the use of β-adrenergic antagonists to treat ventricular dysfunction.[307,308]

The development of experimental radiotracer techniques to assess the in vivo kinetics of catecholamines has provided additional information that is of clinical importance, particularly in relation to regional kinetics. For example, studies relying only on arterial and venous catecholamines suggested that the hepatomesenteric bed contributes significantly to total-body clearance of catecholamines but only minimally (<8%) to spillover. However, later studies of regional norepinephrine kinetics demonstrated that release of norepinephrine from the gut (≤25% of the total body) was largely obscured by efficient extraction (>80%) in the liver. Similarly, selective elevations in release of norepinephrine from the heart, which may be associated with ischemia, early onset of CHF, and tachyarrhythmias, may not be apparent in measured arterial or venous levels.[309] Observations involving regional spillover led to the realization that although stress may activate a generalized sympathetic response, there may be different patterns contingent on the stimulus. It is possible that the lack of consistency of plasma norepinephrine levels in the presence of clinically significant sympathetic activation may be a function of the measurement technique or the particular stressor.

It is my belief that given the effects of age, posture, and hydration, small changes in plasma catecholamine levels correlate poorly with hemodynamic changes and merit cautious interpretation whereas significant increases (>1000 pg/mL) in levels are good markers of activation of the sympathetic nervous system.

Clinical Syndromes

Surgical Stress Response

Surgical stress, particularly that associated with major operations, results in profound metabolic and endocrine responses. The combination of autonomic, hormonal, and catabolic changes that accompany surgery has been called the surgical stress response.[310] Despite widespread clinical intuition that attenuation of the stress response is beneficial, there has been long-standing debate about whether such a strategy affects outcome. Three separate lines of evidence suggest that attenuation of the surgical stress response can lead to improved outcomes. In a series of studies, interruption of the sympathetic response to surgery markedly reduced surgical stress intraoperatively and postoperatively. The use of continuous thoracic epidural infusions of local anesthetics minimized the rise in plasma catecholamines, cortisol, and glucagon and improved outcomes. Improved outcome was independent of the patient's level of pain because metabolic and endocrine responses to surgery were not similarly reduced in patients receiving other methods of pain relief, including nonsteroidal anti-inflammatory drugs and opioids.[311] Continuation of epidural infusions well into the postoperative period was regarded as essential to improving outcome. Inflammatory and immunologic responses, which are necessary for infection control and wound healing, appear to be unaffected. With the use of similar techniques and other stress-reducing maneuvers, faster and more complete recovery was achieved in elderly patients undergoing colon resection.[312]

A separate line of evidence supporting the hypothesis that long-term attenuation of the stress response alters outcome comes from the pediatric literature. When neonates with complex congenital heart disease underwent cardiac surgery, those who received high-dose sufentanil infusions intraoperatively and for the first 24 hours postoperatively to reduce the stress response had lower β-endorphin, norepinephrine, epinephrine, glucagon, aldosterone, and cortisol levels than controls did.[310] The mortality rate in the opiate group was significantly lower than in the study or historical controls, thus demonstrating that anesthetic techniques can have profound effects on the metabolic and endocrine responses to surgery and that effective management of these reflexes can alter outcomes.

A third line of evidence involves results from the multicenter study of the Perioperative Ischemia Research Group (see "Perioperative β-Blockade").[215] The ability to alter overall survival at 2 years with a perioperative regimen of β-blockade has provided compelling evidence of the benefit of attenuating the stress response[216,217,219] and has altered clinical practice in patients at risk for cardiac morbidity. Similar results have been achieved when perioperative α_2-agonists were given to "at-risk" patients as well.[313] Presumably, the decrease in sympathetic tone that accompanied administration of the β-blocker or the α_2-agonist suppressed the stress response and improved outcomes.

Diabetes Mellitus

Diabetic autonomic neuropathy is the most common form of autonomic neuropathy and the most extensively investigated (see Chapter 35). It occurs in 20% to 40% of all insulin-dependent diabetic patients. The symptoms associated with diabetic autonomic neuropathy confer an increased risk during anesthesia and surgery by direct and secondary mechanisms. Common manifestations of diabetic autonomic neuropathy include impotence, postural hypotension, gastroparesis, diarrhea, and sweating abnormalities. Early small-fiber damage is revealed by loss or impairment of vagally controlled normal heart rate variability, decreased peripheral sympathetic tone with a subsequent increase in blood flow, and diminished sweating. In a diabetic neuropathic foot, the senses of pain and temperature are lost before touch or vibration is affected. With sympathetic denervation, the sympathetic nerves normally found supplying small arterioles are entirely absent or are abnormally distant from their effector sites. When impotence or diarrhea is the sole manifestation, there is little effect on survival; however, with postural hypotension or gastroparesis, 5-year mortality rates are greater than 50%.

Most clinicians recognize that diabetic patients with autonomic neuropathy may be at additional risk during general anesthesia.[314] Gastroparesis is probably caused by vagal degeneration and is of clinical relevance because awake or rapid-sequence intubation may be required. Systemic injury to the vasa vasorum in patients with postural hypotension increases the risk for hemodynamic instability and cardiovascular collapse in the perioperative period. Mechanisms that maintain normal standing blood

pressure are altered, and normal precapillary vasoconstriction in the foot on standing may be diminished. Baroreceptors in the carotid sinus and aortic arch are compromised by diabetic neuropathy. Diabetic patients with orthostatic hypotension usually have lower norepinephrine levels.

Even in seemingly minor surgery, diabetic autonomic neuropathy can lead to significant complications.

Diabetics with autonomic neuropathy may have a significantly greater decline in blood pressure with induction and a greater need for vasopressors than diabetic patients without autonomic dysfunction.[314] Page and Watkins[315] reported five cases of unexpected cardiorespiratory arrest in young diabetic patients, all of whom had symptoms of autonomic neuropathy. In a large, prospective study of diabetic autonomic neuropathy involving use of the five evocative clinical tests discussed earlier, parasympathetic dysfunction preceded sympathetic failure in 96% of the patients.[316] This battery of autonomic tests identifies patients with autonomic neuropathy and is highly predictive of mortality and perioperative risk.[304]

Autonomic Changes with Aging

Aging is associated with alterations in vascular reactivity manifested clinically as exaggerated changes in blood pressure—hypertension and orthostatic hypotension (see Chapter 71). Orthostatic hypotension is quite common (about 20%) in the elderly and may result largely from diminished baroreceptor responsiveness. Heart rate responses to changes in blood pressure, the Valsalva maneuver, and the respiratory cycle are blunted with aging.[317]

Resting and exercise-induced norepinephrine levels increase with age in healthy subjects (by about 13% per decade), in part because of decreased clearance.[318] Previously a matter of controversy, it now appears that besides the well-documented reduction in vagal function associated with aging,[319] the primary autonomic defect in aging is an impairment in reuptake of norepinephrine, perhaps as a function of decreased nerve density. Although there is no apparent age-dependent decrement in nerve firing rates from sympathetic efferents in skeletal muscle,[320] kinetic studies reveal selective and dramatic increases in cardiac norepinephrine spillover attributable to the decreased reuptake in elderly patients subjected to mental stress or exercise.[306] This can precipitate clinical complications (i.e., arrhythmogenesis and sudden cardiac death) in patients with cardiac disease. However, end-organ responsiveness is blunted by compensatory downregulation of β_1-adrenoreceptors (i.e., decreased receptor density and affinity) and uncoupling of β_2-adrenoreceptors through decreased G_s activity.[321] Despite increased cardiac spillover, cardiac oxygen consumption is not altered.[322]

Attenuation of presynaptic α_2-adrenoreceptor–mediated inhibition of neuronal norepinephrine release[323-325] also accounts for the increased norepinephrine levels observed with age. Reduced postsynaptic α-adrenoreceptor activity decreases contractile responses and further attenuates vasoconstrictor tone. In a seemingly vicious cycle, the increase in circulating norepinephrine levels is associated with downregulation of platelet α_2-adrenoreceptor density and responsiveness. The loss of adrenergic control through the reduction of α_2- and β-receptor–mediated responses with age causes a decrease in the sympathetic nervous system's ability to maintain cardiovascular homeostasis, thus implying a relationship with or an explanation of the increased incidence of cardiovascular disorders such as CHF in the elderly.

Autonomic Changes in Spinal Cord Transection

The most drastic of all alterations in the ANS that an anesthesiologist may encounter is complete spinal cord transection (see Chapters 46, 63, and 72). Spinal cord transection affects motor and sensory function, and it may also result in profound changes in autonomic activity that can alter anesthetic care. As is obvious from sympathetic and parasympathetic outflow anatomy, spinal cord injuries or transection can cause various degrees of autonomic dysfunction, depending on the site, extent, and timing of the lesion. Many autonomic reflexes are inhibited by the supraspinal feedback that is lost after spinal cord transection. In paraplegic patients, small stimuli can evoke exaggerated sympathetic discharges.

In patients with cervical spinal cord transection, sympathetic and parasympathetic outflow is detached from central control mechanisms. In addition to the expected motor and sensory changes, there are profound abnormalities that alter the cardiovascular, thermoregulatory, gastrointestinal, and urinary systems. The autonomic consequences of transection are not always apparent because the distal portion of the spinal cord may retain some function and thereby result in unanticipated autonomic abnormalities.

There are fundamental differences between the acute and chronic effects of spinal cord transection. Initially, a transient state of decreased excitability occurs. This phenomenon, known as spinal shock, usually takes place immediately after the lesion and may last days to weeks. In these patients, the periphery is generally atonic and the peripheral blood vessels are dilated. In patients with high thoracic lesions who have sustained recent injury, basal supine blood pressure is usually low and accompanied by plasma catecholamine levels that are approximately 35% of normal.[326] Patients with recent low spinal injuries may exhibit compensatory tachycardia from intact parts of the ANS.

Patients with chronic high spinal lesions may fail to respond to hypovolemia with an increased heart rate and may exhibit bradycardia. The only intact efferent component of the baroreflex pathways in quadriplegic patients is the vagus. Bradycardia occurs with changes in position and with Valsalva maneuvers or increased intrathoracic pressure.[327]

One aspect of care that is frequently overlooked is the effect of tracheal suctioning on patients with high spinal transection. Given that many of these patients depend on artificial respiration because of their respiratory muscle paralysis, unopposed vagal stimuli may contribute to profound bradycardia. This vagal response is particularly accentuated during hypoxemia.

Because the sympathetic nervous system may be dysfunctional in these patients, the renin-angiotensin-aldosterone system compensates for the maintenance of blood pressure. Patients with spinal cord transection may be exquisitely sensitive to ACEIs, even with modest changes in intravascular volume or posture. The release of renin may be independent of sympathetic stimulation and may be caused by the renal baroreceptor stimulation that accompanies the decline in renal perfusion pressure.

Although pressure stimuli above the lesion do not usually change blood pressure, the phenomenon of autonomic dysreflexia can occur with stimulation below the lesion. Bladder or bowel distention can elicit the so-called mass reflex. This autonomic reflex includes a dramatic rise in blood pressure, a marked reduction in flow to the periphery, and flushing and sweating in areas above the lesion. In addition, there is often contraction of the bladder and rectum, skeletal muscle spasms, and penile erection.

The patient's heart rate may decline as a reflex. Surprisingly, evidence from microneurography studies indicates that there is only a modest rise in sympathetic nerve activity during activation of the mass reflex,[328] and plasma norepinephrine levels increase only modestly. Speculation has arisen that the exaggerated blood pressure response may be caused by supersensitivity of adrenoreceptors. As anticipated, quadriplegic patients exhibit an increase in sensitivity to exogenously administered pressors.[326] Blood pressure in quadriplegic patients may increase 5- to 10-fold in response to the exogenous administration of angiotensin and to catecholamines. Impairment of the descending inhibitory reflex pathways that are activated during hypertension may contribute to the supersensitivity. This hypothesis is supported by the finding that sensitivity is rarely increased when the lesion is below T5. There is apparently a normal level of adrenoreceptors in these patients with lower spinal lesions, even those with long-standing quadriplegia.

Management of autonomic dysreflexia is of clinical importance. Although the anesthesiologist may be tempted to opt for minimal anesthesia in a patient without sensory or motor function, significant visceral reflexes can be evoked. The anesthesiologist may use spinal anesthesia, general anesthesia, or a vasodilator such as nitroprusside or nitroglycerin to attenuate this reflex, even if pain is not appreciated. There has been some enthusiasm for using clonidine prophylactically to diminish this response.

An additional problem arising from the autonomic denervation of spinal cord transection is thermogenesis. In these patients, hypothermia may result from cutaneous vasodilation and the inability to shiver. Similarly, hyperthermia can occur because the normal sweating mechanism is impaired. It is therefore important to monitor temperature assiduously in these patients during the course of anesthesia.

New Concepts in Autonomic Activity

Genetic Contributors to Autonomic Function and Drug Responsiveness

In the past 5 years there has been an explosion in the knowledge of nonmendelian genetic contributors to human physiologic and pathophysiologic function. The Human Genome Project provided a starting point for the identification of genetic abnormalities. The next logical step is to define the implications of genetic variations on physiologic and pharmacologic responses. Genetic variations as small as a single-nucleotide polymorphism (SNP) to larger genetic insertions or deletions have been identified in the genes coding for essential components of the ANS. SNPs and, to a lesser extent, larger deletion and insertion sequences have been identified in the genes that code for nearly every adrenergic and dopaminergic receptor subtype (all save the α_{1d}-receptor). Genetic coding for the muscarinic receptor subtypes, on the other hand, is remarkably well conserved.[329] In addition to variants in coding for the autonomic receptors, genetic mutations in codes for the proteins responsible for catecholamine synthesis, reuptake, and breakdown have also been identified, as have variants for the receptor-coupled G proteins.[330] Although many potential genetic contributors to autonomic-related disease states (e.g., essential hypertension, lipid and glucose metabolism, and postural tachycardia syndrome[331]) have been identified, no single genetic mutation has completely explained any of the examined autonomic dysfunctions. It is almost certainly true that abnormalities in autonomic function are polygenic in origin and also involve significant environmental input. Thus, future investigations that attempt to explain autonomic diseases will require evaluation of larger genetic sequences (not SNPs or other short-segment variants) that contain multiple associated genetic variants. Once the collection of genetic variants responsible for the majority of the autonomic findings of a given disease are identified, the impact of the combined genetic contribution on responsiveness to a given drug or class of drugs will need to be assessed through directed clinical trials.

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Piyush M. Patel and John C. Drummond

13 Cerebral Physiology and the Effects of Anesthetic Drugs

Key Points

1. The brain has a high metabolic rate and receives approximately 15% of cardiac output. Under normal circumstances, cerebral blood flow (CBF) is approximately 50 mL/100 g/min. Gray matter receives 80% and white matter receives 20% of this blood flow.
2. Approximately 60% of the brain's energy consumption is used to support electrophysiologic function. The remainder of the energy consumed by the brain is involved in cellular homeostatic activities.
3. CBF is tightly coupled to local cerebral metabolism. When cerebral activity in a particular region of the brain increases, a corresponding increase in blood flow to that region takes place. Conversely, suppression of cerebral metabolism leads to a reduction in blood flow.
4. CBF is autoregulated and held constant over a mean arterial pressure range conservatively estimated at 65 to 150 mm Hg, given normal venous pressure. There is probably appreciable intersubject variability. CBF becomes pressure passive when mean arterial pressure is either below the lower limit or above the upper limit of autoregulation
5. CBF is also under chemical regulation. It varies directly with arterial carbon dioxide tension in the $Paco_2$ range of 25 to 70 mm Hg. With a reduction in Pao_2 to below 60 mm Hg, CBF increases dramatically. Changes in temperature affect CBF primarily by suppression of cerebral metabolism.
6. Systemic vasodilators (nitroglycerin, nitroprusside, hydralazine, calcium channel blockers) vasodilate the cerebral circulation and can, depending on mean arterial pressure, increase CBF. Vasopressors such as phenylephrine, norepinephrine, ephedrine, and dopamine do not have significant direct effects on the cerebral circulation. Their effect on CBF is dependent on their effect on systemic blood pressure. When mean arterial pressure is below the lower limit of autoregulation, vasopressors increase systemic pressure and thereby increase CBF. If systemic pressure is within the limits of autoregulation, vasopressor-induced increases in systemic pressure have little effect on CBF.
7. All modern volatile anesthetics suppress the cerebral metabolic rate (CMR) and, with the exception of halothane, can produce burst suppression of the electroencephalogram. At that level, CMR is reduced by about 60%. Volatile anesthetics have dose-dependent effects on CBF. In doses lower than the minimal alveolar concentration (MAC), CBF is not significantly altered. Beyond doses of 1 MAC, direct cerebral vasodilation results in an increase in CBF and cerebral blood volume.
8. Barbiturates, etomidate, and propofol decrease CMR and can produce burst suppression of the electroencephalogram. At that level, CMR is reduced by about 60%. Flow and metabolism coupling is preserved and therefore CBF is decreased. Opiates and benzodiazepines effect minor decreases in CBF and CMR, whereas ketamine can increase CMR (with a corresponding increase in blood flow) significantly.
9. Brain stores of oxygen and substrates are limited and the brain is exquisitely sensitive to reductions in CBF. Severe reductions in CBF (less than 10 mL/100 g/min) lead to rapid neuronal death. Ischemic injury is characterized by early excitotoxicity and delayed apoptosis.
10. Barbiturates, propofol, ketamine, volatile anesthetics, and xenon have neuroprotective efficacy and can reduce ischemic cerebral injury. Anesthetic neuroprotection is sustained only when the severity of the ischemic insult is mild; with moderate to severe injury, long-term neuroprotection is not achieved. Administration of etomidate is associated with regional reductions in blood flow, and this can exacerbate ischemic brain injury.

This chapter reviews the effects of anesthetic drugs and techniques on cerebral physiology, in particular, their effects on cerebral blood flow (CBF) and metabolism. The final section presents a brief discussion of pathophysiologic states, including cerebral ischemia, as well as discussion of cerebral protection. The chapter gives greatest emphasis to information that is of immediate relevance to the rationale for use of the anesthetic and intensive care management of patients with intracranial pathology. Chapter 63 presents the clinical management of these patients in detail. Neurologic monitoring, including the effects of anesthetics on the electroencephalogram (EEG) and evoked responses, is reviewed in Chapter 46.

Regulation of Cerebral Blood Flow

Anesthetic drugs cause dose-related and reversible alterations in many aspects of cerebral physiology, including CBF, cerebral metabolic rate (CMR), and electrophysiologic function (EEG, evoked responses). The effects of anesthetic drugs and techniques have the potential to adversely affect the diseased brain and conduct of the neurosurgical procedure and are thus of clinical importance in patients with neurosurgical disease. However, in certain instances, the effects of general anesthesia on CBF and CMR can be manipulated to improve both the operative course and the clinical outcome of patients with neurologic disorders.

The adult human brain weighs approximately 1350 g and therefore represents about 2% percent of total-body weight. However, it receives 12% to 15% of cardiac output. This high flow rate is a reflection of the brain's high metabolic rate. At rest, the brain consumes oxygen at an average rate of approximately 3.5 mL of oxygen per 100 g of brain tissue per minute. Whole-brain O_2 consumption (50 mL/min) represents about 20% of total-body oxygen utilization. Normal values for CBF, CMR, and other physiologic variables are provided in Table 13-1.

Approximately 60% of the brain's energy consumption is used to support electrophysiologic function. The depolarization-repolarization activity that occurs and is reflected in the EEG requires expenditure of energy for the maintenance and restoration of ionic gradients and for the synthesis, transport, and reuptake of neurotransmitters. The remainder of the energy consumed by the brain is involved in cellular homeostatic activities. Local CBF and CMR within the brain are very heterogeneous, and both are approximately four times greater in gray matter than in white matter. The cell population of the brain is also heterogeneous in its oxygen requirements. Glial cells make up about half the brain's volume and require less energy than neurons do. Besides providing a physically supportive latticework for the brain, glial cells are important in reuptake of neurotransmitters, in delivery and removal of metabolic substrates and wastes, and in blood-brain barrier (BBB) function.

The brain's substantial demand for substrate must be met by adequate delivery of oxygen and glucose. However, the space constraints imposed by the noncompliant cranium and meninges require that blood flow not be excessive. Not surprisingly, there are elaborate mechanisms for regulation of CBF. These mechanisms, which include chemical, myogenic, and neurogenic factors, are listed in Table 13-2.

Table 13-1 Normal Cerebral Physiologic Values

CBF	
Global	45-55 mL/100 g/min
Cortical (mostly gray matter)	75-80 mL/100 g/min
Subcortical (mostly white matter)	≈20 mL/100 g/min
$CMRO_2$	3-3.5 mL/100 g/min
CVR	1.5-2.1 mm Hg/100 g/min/mL
Cerebral venous Po_2	32-44 mm Hg
Cerebral venous So_2	55%-70%
ICP (supine)	8-12 mm Hg

CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen; CVR, cerebral vascular resistance; ICP, intracranial pressure.

Table 13-2 Factors Influencing Cerebral Blood Flow*

Factor	Comment
Chemical/Metabolic/Humoral	
CMR Anesthetics Temperature Arousal/seizures	CMR influence assumes intact flow-metabolism coupling, the mechanism of which is not fully understood
$Paco_2$	
Pao_2	
Vasoactive drugs Anesthetics Vasodilators Vasopressors	
Myogenic	
Autoregulation/MAP	The autoregulation mechanism is fragile, and in many pathologic states CBF is regionally pressure passive
Rheologic	
Blood viscosity	
Neurogenic	
Extracranial sympathetic and parasympathetic pathways	Contribution and clinical significance poorly defined
Intra-axial pathways	

*See text for discussion.
CBF, cerebral blood flow; CMR, cerebral metabolic rate; MAP, mean arterial pressure.

Chemical Regulation of Cerebral Blood Flow

Several factors, including changes in CMR, $Paco_2$, and Pao_2, cause alterations in the cerebral biochemical environment that result in adjustments in CBF.

Cerebral Metabolic Rate

Increased neuronal activity results in increased local brain metabolism, and this increase in CMR is associated with a well-matched,

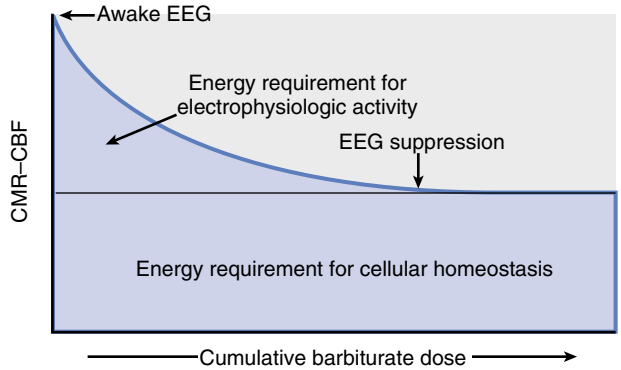

Figure 13-1 Interdependency of cerebral electrophysiologic function and cerebral metabolic rate (CMR). Administration of various anesthetics, including barbiturates, results in a dose-related reduction in the CMR of oxygen ($CMRO_2$) and cerebral blood flow (CBF). The maximum reduction occurs with the dose that results in electrophysiologic silence. At this point, the energy utilization associated with electrophysiologic activity has been reduced to zero, but the energy utilization for cellular homeostasis persists unchanged. Additional barbiturate causes no further decrease in CBF or $CMRO_2$.

proportional change in CBF and is referred to as flow-metabolism coupling. Although the precise mechanisms that mediate flow-metabolism coupling have not been defined, the data available implicate local by-products of metabolism (K^+, H^+, lactate, adenosine, and adenosine triphosphate [ATP]). Glutamate, released with increased neuronal activity, results in the synthesis and release of nitric oxide (NO), a potent cerebral vasodilator that plays an important role in coupling of flow and metabolism. More recent data have highlighted the role of glia in flow-metabolism coupling. Uptake of the glutamate released from neurons by glia triggers increased glial metabolism and lactate production. Glial processes make contact with neurons and capillaries, and hence glia may serve as a conduit for the coupling of increased neuronal activity with increased glucose consumption and regional blood flow. Nerves that innervate cerebral vessels release peptide neurotransmitters such as vasoactive intestinal peptide (VIP), substance P, cholecystokinin, somatostatin, and calcitonin gene–related peptide. These neurotransmitters may also potentially be involved in neurovascular coupling. Flow-metabolism coupling within the brain is a complex physiologic process that is regulated, not by a single mechanism, but by a combination of metabolic, glial, neural, and vascular factors.

CMR is influenced by several phenomena in the neurosurgical environment, including the functional state of the nervous system, anesthetic drugs, and temperature.

Functional State. CMR decreases during sleep and increases during sensory stimulation, mental tasks, or arousal of any cause. During epileptic activity, increases in CMR may be extreme, whereas regionally after brain injury and globally with coma, CMR may be substantially reduced.

Anesthetic Drugs. The effect of individual anesthetic drugs on CMR is presented in greater detail in the second section of this chapter. In general, anesthetic drugs suppress CMR, with ketamine and N_2O being notable exceptions. It appears that the component of CMR on which they act is that associated with electrophysiologic function. With several anesthetics, including barbiturates, isoflurane, sevoflurane, desflurane, propofol, and etomidate, increasing plasma concentrations cause progressive suppression of EEG activity and a concomitant reduction in CMR. However, increasing the plasma level beyond what is required to first achieve suppression of the EEG results in no further depression of CMR. The component of CMR required for maintenance of cellular integrity, the "housekeeping" component, is unaltered by intravenous anesthetic drugs (Fig. 13-1).

The cerebral metabolic rate of oxygen ($CMRO_2$) observed when complete suppression of the EEG is achieved with different anesthetic drugs is very similar. It should be noted, however, that anesthetic-induced EEG suppression is not a single physiologic state and is influenced by the agent that is used to produce suppression. When barbiturates are administered to the point of EEG suppression, a uniform depression in CBF and CMR occurs throughout the brain. When suppression occurs during administration of isoflurane, the relative reductions in CMR and CBF are greater in the neocortex than in other portions of the cerebrum. Electrophysiologic responsiveness also varies. Cortical somatosensory evoked responses to median nerve stimulation can readily be recorded at doses of thiopental far in excess of those required to cause complete suppression of the EEG but are difficult to elicit at concentrations of isoflurane associated with a burst-suppression pattern, such as 1.5 minimum alveolar concentration (MAC) (Fig. 13-2). In addition, the EEG characteristics of the burst-sup-

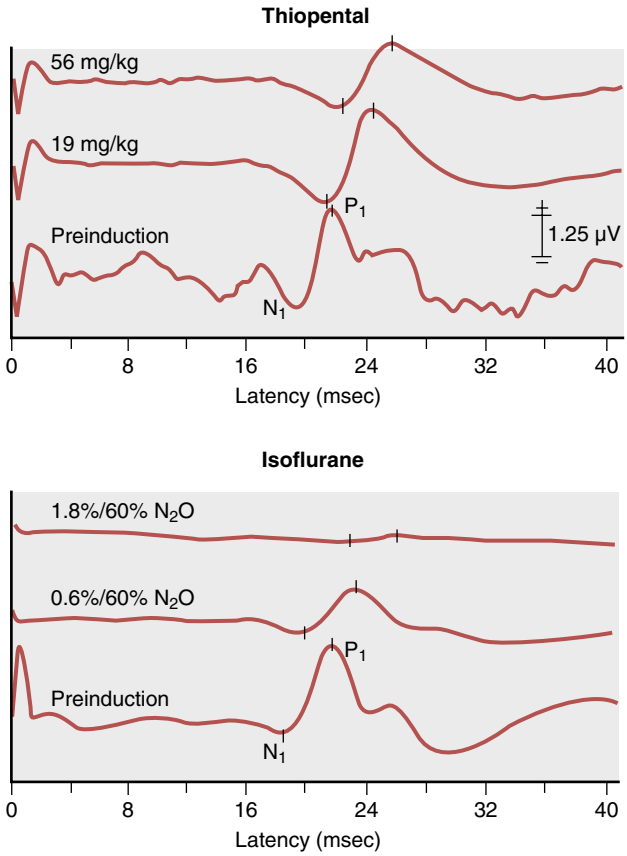

Figure 13-2 Cortical somatosensory evoked responses to median nerve stimulation in humans before induction and during anesthesia with thiopental and isoflurane/N_2O. Despite an equivalent or greater degree of reduction in the cerebral metabolic rate with thiopental, cortical evoked responses are better preserved[1] than during anesthesia with isoflurane.[2] This suggests that the electroencephalographic suppression achieved with different anesthetic drugs should not be assumed to be equivalent electrophysiologic states. The cumulative thiopental doses and expired concentrations of isoflurane and N_2O are indicated in the figure.

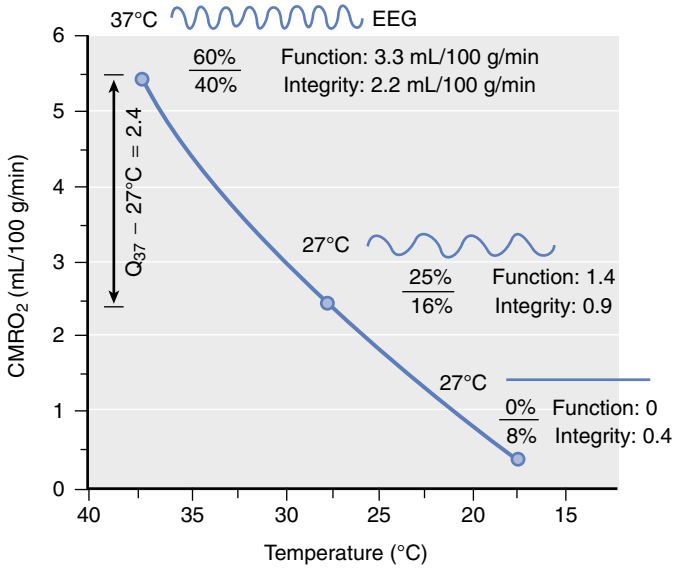

Figure 13-3 Effect of temperature reduction on the cerebral metabolic rate of oxygen ($CMRO_2$). Hypothermia reduces both of the components of cerebral metabolic activity identified in Figure 13-1: that associated with neuronal electrophysiologic activity ("Function") and that associated with maintenance of cellular homeostasis ("Integrity"). This is in contrast to anesthetics that alter only the functional component. The ratio of CMR at 37°C to that at 27°C, the Q_{10} ratio, is shown in the graph. *(Adapted from Michenfelder JD: Anesthesia and the Brain: Clinical, Functional, Metabolic, and Vascular Correlates. New York, Churchill Livingstone, 1988.)*

pression states that occur just before complete suppression differ among anesthetic drugs. These differences may be of some relevance to discussions of differences in the neuroprotective potential of drugs that can produce EEG suppression.

TEMPERATURE. The effects of hypothermia on the brain have been reviewed in detail.[3] CMR decreases by 6% to 7% per degree Celsius of temperature reduction. As is the case with some anesthetic drugs, hypothermia can also cause complete suppression of the EEG (at about 18°C to 20°C). However, in contrast with anesthetic drugs, temperature reduction beyond that at which EEG suppression first occurs *does* produce a further decrease in CMR (Fig. 13-3). This occurs because although anesthetic drugs reduce only the component of CMR associated with neuronal function, hypothermia decreases the rate of energy utilization associated with both electrophysiologic function and the basal component associated with maintenance of cellular integrity. These decreases were once assumed to be proportional. However, it has recently been demonstrated that mild hypothermia preferentially suppresses the basal component of CMR. $CMRO_2$ at 18°C is less than 10% of normothermic control values, and this probably accounts for or contributes to the brain's tolerance for moderate periods of circulatory arrest at these and lower temperatures.

Hyperthermia has an opposite influence on cerebral physiology. Between 37°C and 42°C, CBF and CMR increase. However, above 42°C, a dramatic reduction in cerebral oxygen consumption occurs, an indication of a threshold for a toxic effect of hyperthermia that may occur as a result of protein (enzyme) denaturation.

$Paco_2$. CBF varies directly with $Paco_2$ (Fig. 13-4). The effect is greatest within the range of physiologic $Paco_2$ variation. CBF changes 1 to 2 mL/100 g/min for each 1–mm Hg change in $Paco_2$ around normal $Paco_2$ values. This response is attenuated below a $Paco_2$ value of 25 mm Hg. Under normal circumstances, the sensitivity of CBF to changes in $Paco_2$ ($\Delta CBF/\Delta Paco_2$) appears to be positively correlated with resting levels of CBF. Accordingly, anesthetic drugs that alter resting CBF cause changes in the response of the cerebral circulation to CO_2. The magnitude of the reduction in CBF caused by hypocapnia is greater when resting CBF is high (as might occur during anesthesia with volatile agents). Conversely, when resting CBF is low, the magnitude of the hypocapnia-induced reduction in CBF is decreased. However, it should be noted that CO_2 responsiveness has been observed in normal brain during anesthesia with all of the numerous anesthetic drugs that have been studied.

The changes in CBF caused by $Paco_2$ are dependent on pH alterations in the extracellular fluid of the brain. NO, in particular NO of neuronal origin, is an important although not exclusive mediator of CO_2-induced vasodilation. The vasodilatory response to hypercapnia is also mediated in part by prostaglandins. The changes in extracellular pH and CBF occur rapidly after $Paco_2$ adjustments because CO_2 diffuses freely across the cerebrovascular endothelium. Note that in contrast with *respiratory* acidosis, acute systemic *metabolic* acidosis has little immediate effect on CBF because the BBB excludes hydrogen ion (H^+) from the perivascular space. The CBF changes in response to alterations in $Paco_2$ occur rapidly, but they are not sustained. Despite maintenance of an elevated arterial pH, CBF returns to normal over a period of 6 to 8 hours because the pH of cerebrospinal fluid (CSF) gradually normalizes as a result of extrusion of bicarbonate. Consequently, a patient who has had a sustained period of hyperventilation or hypoventilation deserves special consideration. Acute normalization of $Paco_2$ will result in a significant CSF acidosis (after hypocapnia) or alkalosis (after hypercapnia). The former results in increased CBF with a concomitant increase in intracranial pressure (ICP) that depends on the prevailing intracranial compliance. The latter conveys a theoretical risk for ischemia.

Pao_2. Changes in Pao_2 from 60 to greater than 300 mm Hg have little influence on CBF. Below a Pao_2 of

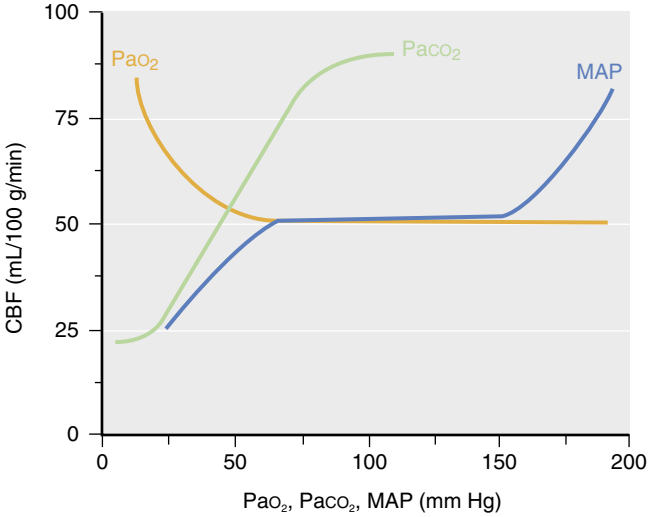

Figure 13-4 Changes in cerebral blood flow (CBF) caused by independent alterations in $Paco_2$, Pao_2, and mean arterial pressure (MAP).

60 mm Hg, CBF increases rapidly (see Fig. 13-4). The mechanisms mediating cerebral vasodilation during hypoxia are not fully understood but may include neurogenic effects initiated by peripheral and neuraxial chemoreceptors, as well as local humoral influences. At least part of the hyperemic response to hypoxia is mediated by NO of neuronal origin (see Chapter 31). Hypoxia-induced hyperpolarization of vascular smooth muscle by the opening of ATP-dependent K^+ channels also leads to vasodilation. Recent studies have indicated that the rostral ventrolateral medulla (RVM) serves as an oxygen sensor within the brain. Stimulation of the RVM by hypoxia results in an increase in CBF (but not CMR), and lesions of the RVM suppress the magnitude of the CBF response to hypoxia. The response to hypoxia is synergistic with the hyperemia produced by hypercapnia and acidosis. At high Pao_2 values, CBF decreases modestly. At 1 atm of oxygen, CBF is reduced by 12%.

Myogenic Regulation (Autoregulation) of Cerebral Blood Flow

Autoregulation refers to the capacity of the cerebral circulation to adjust its resistance to maintain CBF constant over a wide range of mean arterial pressure (MAP). In normal *human* subjects, the best available data—and they are limited—are consistent with the limits of autoregulation occurring at MAP values of approximately 70 and 150 mm Hg (see Fig. 13-4). The lower limit of autoregulation (LLA) has been widely quoted as an MAP of 50 mm Hg. Although this number may be correct for some animal species, the data available argue that the LLA is considerably higher in humans.[4] Note that the units used on the *x* axis of "autoregulation curves" will influence the correct inflection points of the curve. When the *x* axis is "mean arterial pressure", the normal average LLA is not less than 70 mm Hg (with considerable interindividual variation). Because ICP is not usually measured in normal subjects, cerebral perfusion pressure (CPP) (MAP – ICP) is rarely available. Assuming a normal ICP of 5 to 15 mm Hg in a supine subject, an LLA of 70 expressed as MAP corresponds to an LLA of 55 to 60 mm Hg expressed as CPP.

Above and below the autoregulatory plateau, CBF is pressure dependent (pressure passive) and varies linearly with CPP. Autoregulation is influenced by various pathologic processes, as well as the time course over which the changes in CPP occur. Even within the range over which autoregulation normally occurs, a rapid change in arterial pressure will result in a transient (3 to 4 minutes) alteration in CBF.

The "limits of autoregulation" are conceptual constructs for the purpose of analysis. They do not represent physiologic "all-or-none" responses. There is probably a continuum of vascular responsiveness in the knee of the both the lower and upper limits as the ability of the arteriolar bed to dilate or constrict is exhausted. Furthermore, the morphology of the autoregulation is strongly influenced by the background level of vasodilation or vasoconstriction (e.g., $Paco_2$ or anesthetic conditions).

The precise mechanism by which autoregulation is accomplished and its overlap with flow-metabolism coupling are not known. According to the myogenic hypothesis, changes in CPP lead to direct changes in the tone of vascular smooth muscle; this process appears to be passive. NO may participate in the vasodilation associated with hypotension. Autonomic innervation of cerebral blood vessels may also contribute to autoregulation of blood flow (discussed in the next section).

Neurogenic Regulation of Cerebral Blood Flow

The cerebral vasculature is extensively innervated.[5] The density of innervation declines with vessel size, and the greatest neurogenic influence appears to be exerted on larger cerebral arteries. This innervation includes cholinergic (parasympathetic and nonparasympathetic), adrenergic (sympathetic and nonsympathetic), serotonergic, and VIPergic systems of extra- and intra-axial origin. It is certain that in animals there is an extracranial sympathetic influence via the superior cervical ganglion, as well as parasympathetic innervation via the sphenopalatine ganglion. The intra-axial pathways are less well defined, although there is considerable evidence of innervation arising from several nuclei in animals, including the locus ceruleus, the fastigial nucleus, the dorsal raphe nucleus, and the basal magnocellular nucleus of Meynert. Evidence of the functional significance of neurogenic influences has been derived from studies of CBF autoregulation and ischemic injury. Hemorrhagic shock, a state of high sympathetic tone, results in a lower CBF at a given MAP than occurs when hypotension is produced with sympatholytic drugs, presumably because during shock, a sympathetically mediated vasoconstrictive effect shifts the lower end of the "autoregulatory" plateau (Fig. 13-5) to the right. It is not clear what the relative contributions of humoral and neural mechanisms are to this phe-

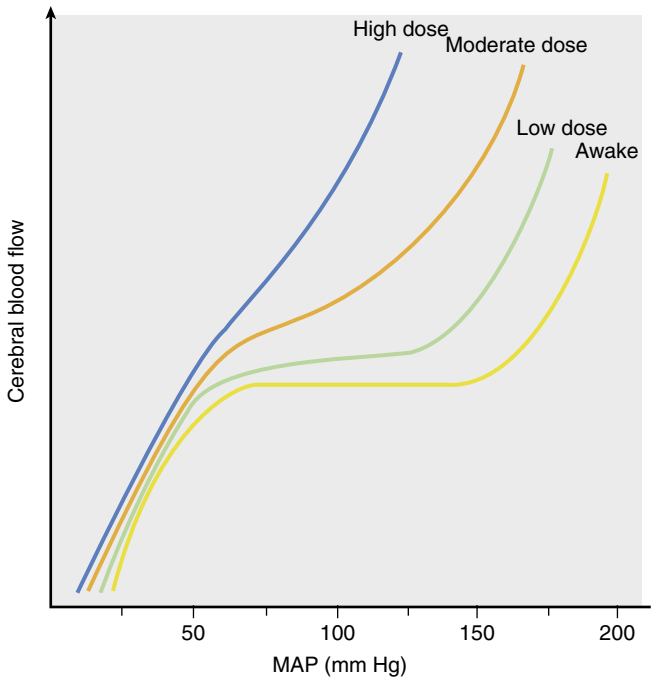

Figure 13-5 Schematic representation of the effect of increasing concentrations of a typical volatile anesthetic drug on autoregulation of cerebral blood flow. Dose-dependent cerebral vasodilation results in attenuation of autoregulatory capacity. Both the upper and lower thresholds are shifted to the left. MAP, mean arterial pressure.

nomenon; however, there is certainly a neurogenic component in some species because sympathetic denervation increases CBF during hemorrhagic shock. Moreover, sympathetic denervation produced by blockade of the stellate ganglion can increase CBF in humans.[6] Activation of cerebral sympathetic innervation also shifts the upper limit of autoregulation to the right and offers some protection against hypertensive breakthrough of the BBB. Experimental interventions that alter these neurogenic control pathways influence outcome after standardized ischemic insults, presumably by influences on vascular tone and therefore CBF. The nature and influence of such pathways in humans are not known, and their manipulation for purposes of clinical management remains to be investigated systematically.

Effects of Blood Viscosity on Cerebral Blood Flow

Blood viscosity can influence CBF. Hematocrit is the single most important determinant of blood viscosity.[7] In healthy subjects, variation of the hematocrit within the normal range (33% to 45%) probably results in only modest alterations in CBF. Beyond this range, changes are more substantial. In anemia, cerebral vascular resistance is reduced and CBF increases. However, this may result not only from a reduction in viscosity but also from reduced oxygen-carrying capacity of blood.[8] The effect of a reduction in viscosity on CBF is more obvious in the setting of focal cerebral ischemia, a condition in which vasodilation in response to impaired oxygen delivery is probably already maximal. In this situation, reducing viscosity by hemodilution results in increases in CBF in the ischemic territory. The best available information suggests that in patients with focal cerebral ischemia, a hematocrit of 30% to 34% will result in optimal delivery of oxygen. However, manipulation of viscosity in patients with acute ischemic stroke has not been shown to be of benefit in reducing the extent of cerebral injury.[9] Hence, viscosity is not a target of manipulation in patients at risk as a result of cerebral ischemia, with the possible exception of those with hematocrit values in excess of 55%.

Vasoactive Drugs

A large number of drugs with intrinsic vascular effects are used in contemporary anesthetic practice, including both anesthetic drugs and numerous vasoactive drugs used specifically for hemodynamic manipulation. This section deals with the latter. The actions of anesthetics are discussed in a later section.

Systemic Vasodilators

The majority of the drugs used to induce hypotension (including sodium nitroprusside, nitroglycerin, hydralazine, adenosine, and calcium channel blockers) also cause cerebral vasodilation. As a result, CBF either increases or is maintained at prehypotensive levels. In addition, when hypotension is induced with a cerebral vasodilator, CBF is maintained at lower MAP values than when induced by either hemorrhage or a noncerebral vasodilator. In contrast to direct vasodilators, the angiotensin-converting enzyme inhibitor enalapril does not have any significant impact on CBF.[10] Anesthetics that vasodilate the cerebral circulation simultaneously cause increases in CBV with the potential to increase ICP. The effects of these anesthetics on ICP are less dramatic when hypotension is induced slowly. This probably reflects the more effective interplay of compensatory mechanisms (shifts in CSF and venous blood) when changes occur more slowly.

Catecholamine Agonists/Antagonists

Numerous drugs with agonist and antagonist activity at catecholamine receptors (α_1, β_2, β, and dopamine) are in common use. The effects of these anesthetics on cerebral physiology are dependent on basal blood pressure, the magnitude of the systemic blood pressure changes that occur as a result of administration of the agent of interest, the status of the autoregulation mechanism, and the status of the BBB. A given agent may have direct effects on cerebral vascular smooth muscle or indirect effects mediated by the cerebral autoregulatory response to changes in systemic blood pressure (or both types of effects). When autoregulation is preserved, increases in systemic pressure would be expected to increase CBF if basal blood pressure is either below or above the lower and upper limits of autoregulation, respectively. When basal pressure is within the normal autoregulation range, an increase in systemic pressure does not affect CBF significantly because the normal autoregulatory response to a rising MAP entails cerebral vasoconstriction (an increase in cerebral vascular resistance) to maintain a constant CBF. When autoregulation is defective, CBF will vary in direct relation to systemic pressure. The information in the following paragraphs and in Table 13-3 emphasizes data obtained from investigations of pressor anesthetics in intact preparations and gives greatest weight to results obtained in humans and higher primates.

Table 13-3 Best Estimates of the Influence of Pure Catecholamine Receptor Agonists and Specific Pressor Substances on Cerebral Blood Flow and Cerebral Metabolic Rate*

Agonist	Cerebral Blood Flow	Cerebral Metabolic Rate
Pure		
α_1	0/–	0
α_2	–	0
β	+	+
β (BBB open)	+++	+++
Dopamine	++	0
Dopamine (high dose)	?–	?0
Fenoldopam	–	?0
Mixed		
Norepinephrine	0/–	0/+
Norepinephrine (BBB open)	+	+
Epinephrine	+	+
Epinephrine (BBB open)	+++	+++

*Where species differences occurred, data from primates were given preference. See text for complete discussion.
BBB, blood-brain barrier; +, increase; –, decrease; 0, no effect; the number of symbols indicates the magnitude of the effect.

α_1-Agonists. A frequently encountered clinical concern is that the administration of anesthetics with α_1-agonist effects (phenylephrine, norepinephrine) will lead to a reduction in CBF. Data derived from studies in both humans and nonhuman primates do not support this belief. Intracarotid infusion of norepinephrine in doses that significantly increase MAP result in no change in CBF. Administration of phenylephrine to patients maintained on cardiopulmonary bypass does not decrease CBF.[11] There are, however, some species differences with regard to the CBF response to α-agonists. α_1-Agonists also do not appear to cause cerebral vasoconstriction in rats but do produce modest decreases in CBF in dogs and goats; this reduction in CBF can be blocked by α_1-antagonists.

Increases in CBF have been attributed to norepinephrine. Such increases might occur if autoregulation were defective or its limit exceeded. In some instances the increases may be the result of abnormalities in the BBB. Some data suggest that β-mimetic drugs (norepinephrine has β_1 activity) cause activation of cerebral metabolism[12] with a coupled increase in CBF, and this effect is likely to be most apparent when these drugs can gain greater access to the brain parenchyma via a defective BBB (see the later section on epinephrine).

In summary, it seems likely that circulating α_1-agonists will have little direct influence on CBF in humans with the exception that norepinephrine may cause vasodilation when the BBB is defective.

β-Agonists. β-Receptor agonists, in low doses, have little direct effect on the cerebral vasculature. In larger doses and in association with physiologic stress, they can cause an increase in CMR with an accompanying increase in CBF.[13] The β_1-receptor is probably the mediator of these effects. In doses that do not result in substantial changes in MAP, intracarotid epinephrine does not change CBF in unanesthetized humans. However, with larger doses that lead to an increase in MAP, CBF and $CMRO_2$ can increase by about 20%.

There is evidence that a defect in the BBB enhances the effect of β-agonists.[14] Intracarotid norepinephrine, which does not normally affect CBF and CMR, increases CBF and CMR when BBB permeability is increased with hypertonic drugs. Artru and colleagues demonstrated that epinephrine causes an elevation in $CMRO_2$, but only when the BBB was made permeable.[14] These observations beg the interpretation that β-agonists will increase CBF and CMR *only* when the BBB is injured. However, in the human study of King and associates,[15] when epinephrine was given in doses that did not increase MAP significantly, increases in CBF/CMR occurred nonetheless. Accordingly, BBB injury may not be a necessary condition in humans for the occurrence of β-mediated increases in CBF and CMR, although it will probably exaggerate the phenomenon.

β-Blockers. β-Blockers have been variously reported to reduce or to have no effect on CBF and CMR. In two investigations in humans, propranolol, 5 mg intravenously,[16] and labetalol, 0.75 mg/kg intravenously,[17] had no effect on CBF and cerebral blood flow velocity (CBFV), respectively. Modest reductions in CBF occur after the administration of labetalol to craniotomy patients who become hypertensive during emergence from anesthesia. Esmolol has been reported to shorten seizures induced by electroconvulsive therapy (ECT), thus suggesting that it does cross the normal BBB. Catecholamine levels at the time of β-blocker administration or the status of the BBB (or both) may influence the effect of these drugs. The database with respect to these possibilities is incomplete. However, the data suggest that β-blockers are unlikely to have adverse effects on patients with intracranial pathology, other than effects secondary to changes in perfusion pressure.

Dopamine. Dopamine is widely used in the treatment of hemodynamic dysfunction. In addition, it is commonly used to augment the function of the normal cardiovascular system when an elevation in MAP is desired as an adjunct to the treatment of focal cerebral ischemia, especially in the setting of vasospasm. Nonetheless, its effects on CBF and CMR have not been defined with certainty. Taken together, the available data[18] suggest that the predominant effect of dopamine in the normal cerebral vasculature, when administered in low doses, is probably slight vasodilation with minimal change in CMR. Increased CMR in discrete regions of the brain, such as the choroid plexus and basal ganglia, has been reported. However, overall cortical blood flow is not influenced.[19] Vasoconstriction of the cerebral circulation is not observed even when dopamine is administered in doses of up to 100 μg/kg/min. In that same investigation, dobutamine was associated with 20% to 30% increases in CBF and CMR.[18] Fenoldopam is a dopamine agonist with activity at the DA_1 receptor and α_2-receptor. Administration of fenoldopam leads to systemic vasodilation and a reduction in systemic blood pressure. In humans, fenoldopam decreased systemic blood pressure to a level that was above the LLA; however, there was a modest (≈15%) reduction in CBF that did not increase to normal levels when systemic blood pressure was supported.[20] This reduction in CBF was attributed to the α_2 activity of fenoldopam. The impact of this reduction in CBF on the injured brain is not known.

α_2-Agonists. There is considerable current interest in α_2-agonists because of their analgesic and sedative effects. This class includes dexmedetomidine and clonidine, with the latter being a much less specific and less potent α_2-agonist. Two investigations in human volunteers have confirmed the ability of dexmedetomidine to decrease CBF. Dexmedetomidine dose-dependently decreased middle cerebral artery (MCA) flow velocity, with the maximum reduction being approximately 25%.[21] Dexmedetomidine (1-μg/kg loading dose and infusion at either 0.2 or 0.6 μg/kg/hr) decreased CBF by about 30%[22] in healthy human volunteers. In both these investigations, CMR was not measured and it is not clear whether the reduction in CBF was due to a direct vasoconstrictor activity of dexmedetomidine or to suppression of CMR with a corresponding reduction in CBF. In a more recent study of dexmedetomidine in which both MCA flow velocity and CMR were measured in healthy humans, dexmedetomidine decreased MCA flow velocity in parallel with a reduction in CMR.[23] These data indicate that the effects of dexmedetomidine on CBF are mediated primarily by its ability to suppress CMR. The well-know effect of dexmedetomidine to lower systemic blood pressure merits careful consideration if used in patients who are critically dependent on collateral perfusion pressure, especially in the recovery phase of an anesthetic.

Age

Aging from childhood to late adulthood is associated with a progressive reduction in CBF and $CMRO_2$.[24] This may reflect the progressive neuronal loss that occurs with age.

Effects of Anesthetics on Cerebral Blood Flow and Cerebral Metabolic Rate

This section deals with the effect of anesthetic drugs on CBF and CMR. It includes limited mention of influences on autoregulation, CO_2 responsiveness, and cerebral blood volume (CBV). Effects on CSF dynamics, the BBB, and epileptogenesis are discussed later.

In neuroanesthesia, considerable emphasis is placed on the manner in which anesthetic drugs and techniques influence CBF. The rationale is twofold. First, delivery of energy substrates is dependent on CBF, and in the setting of ischemia, modest alterations in CBF can substantially influence neuronal outcome. Second, control and manipulation of CBF are central to management of ICP because as CBF varies in response to vasoconstrictor-vasodilator influences, CBV varies with it.[25] With respect to ICP, it is CBV that is the more critical variable. In normal brain, CBV is approximately 5 mL/100 g of brain,[26] and over a $Paco_2$ range of approximately 25 to 70 mm Hg, CBV changes by about 0.049 mL/100 g for each 1–mm Hg change in $Paco_2$. In an adult brain weighing about 1400 g, this can amount to a 20-mL change in total CBV for a $Paco_2$ range of 25 to 55 mm Hg. Practically speaking, CBV is much more difficult to measure than CBF, so there is a relatively paucity of data, especially in human subjects.

Although CBV and CBF usually vary in parallel, the magnitude of change in CBV is less than the magnitude of change in CBF (Fig. 13-6); for a given increase in CBF, the increase in CBV is considerably less. In addition, CBV and CBF vary independently under some circumstances. During cerebral ischemia, for example, CBV increases whereas CBF is significantly reduced.[27] Autoregulation normally serves to prevent MAP-related increases in CBV. In fact, as the cerebral circulation constricts to maintain a constant CBF in the face of a rising MAP, CBV actually decreases.[28] When autoregulation is impaired or its upper limit (≈150 mm Hg) is exceeded, CBF and CBV then increase in parallel as arterial pressure rises (see Fig. 13-5). A declining MAP results in a progressive increase in CBV as the cerebral circulation dilates to maintain constant flow, and exaggerated increases in CBV occur as MAP falls below the LLA.[28] In normal subjects, the initial increases in CBV do not result in a significant elevation in ICP because there is latitude for compensatory adjustments by other intracranial compartments (e.g., translocation of venous blood and CSF to extracerebral vessels and the spinal CSF space, respectively). When intracranial compliance* is reduced, an increase in CBV can cause herniation or reduce CPP sufficiently to cause ischemia.

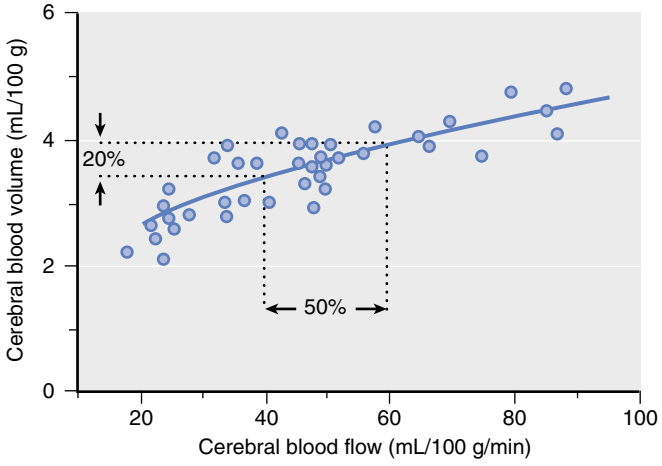

Figure 13-6 Relationship between cerebral blood flow (CBF) and cerebral blood volume (CBV). Note that although there is a linear relationship between CBF and CBV, the magnitude of the change in CBV for a given change in CBF is considerably less. In this figure, an increase in CBF of 50% results in a change in CBV of only 20%.

There have been several investigations of the effects of anesthetics on CBV in normal brain.[30,31] In general, the effects observed confirm a parallel relationship between CBF and CBV. However, the relationship is not consistently 1:1,[25,32] and CBF-independent influences on CBV may occur. It is also an unexplored possibility that anesthetic drugs may influence the venous side of the cerebral circulation. Although the intracranial veins are a largely passive compartment, there is evidence that in some species venous caliber is under active control by either neurogenic or humoral mechanisms. At present, there is no evidence that these direct effects have clinical significance. Nonetheless, the importance of blood volume on the venous side of the cerebral circulation should not be overlooked. Passive engorgement of these vessels as a result of the head-down posture, compression of the jugular venous system, or high intrathoracic pressure can have dramatic effects on ICP (see Fig. 63-5).

Intravenous Anesthetic Drugs

The general pattern of the effect of intravenous anesthetics is one of parallel alterations in CMR and CBF. The vast majority of intravenous anesthetics cause a reduction in both. Ketamine, which causes an increase in CMR and CBF, is the exception. The effects of selected intravenous anesthetic drugs on human CBF are compared in Figure 13-7.

It is probable that the changes in CBF induced by intravenous anesthetics are largely the result of effects on CMR with parallel (coupled) changes in CBF. If this were the entire explanation, the CBF/CMR ratio would be the same for all anesthetics. It is not. There are also direct effects on cerebral vascular smooth muscle (e.g., vasoconstriction, vasodilation, alteration of autoregulatory function) that make contributions to the net effect. For instance, although barbiturates are generally thought of as cerebral vasoconstrictors, some barbiturates actually cause relaxation of cerebral vascular smooth muscle in isolated vessel preparations.[45] However, a substantial reduction in CMR occurs in vivo, and the net effect at the point of EEG suppression is vasoconstriction and a substantial decrease in CBF.[46] It appears that in general,

*Note a well-entrenched misuse of terminology.[29] The "compliance" curve that is commonly drawn to describe the intracranial pressure-volume relationship (see Fig. 66-3) actually depicts the relationship $\Delta P/\Delta V$ (elastance) and not $\Delta V/\Delta P$ (compliance). What is here referred to as "reduced compliance" is more correctly described as "increased elastance." However, because the existing literature most commonly uses the "compliance" terminology, we have left the misuse uncorrected herein.

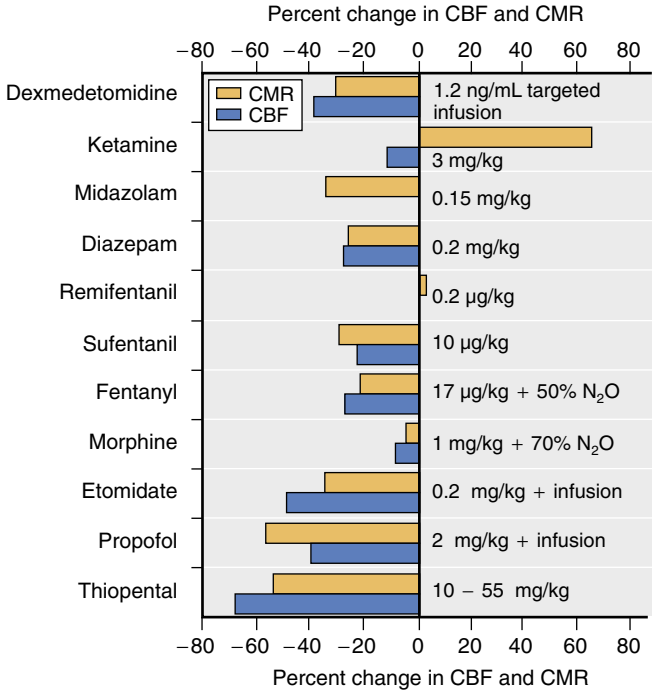

Figure 13-7 Changes in cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen ($CMRO_2$) caused by intravenous anesthetic drugs. The data are derived from human investigations and are presented as percent change from unanesthetized control values. Dexmedetomidine CMR values were determined on a background of 0.5% isoflurane anesthesia. See the text for details. No data for the $CMRO_2$ effects of midazolam in humans are available. *(Data from references 22 and 33-44.)*

autoregulation and CO_2 responsiveness are preserved during administration of intravenous anesthetic drugs.

Barbiturates

A dose-dependent reduction in CBF and CMR occurs with barbiturates. With the onset of anesthesia, CBF and $CMRO_2$ are reduced by about 30%.[47] When large doses of thiopental cause complete EEG suppression, CBF and CMR are reduced by about 50%.[46,48] Further increases in the dose of barbiturate have no additional effect on CMR.[46] These observations suggest that the major effect of nontoxic doses of depressant anesthetics is a reduction in the component of cerebral metabolism that is linked to electrical brain function (e.g., neurophysiologic activity), with only minimal effects on the second component, that related to cellular homeostasis (see Fig. 13-1).

Tolerance to the CBF/CMR effects of barbiturates may develop quickly.[49] In patients with severe head injury in whom "barbiturate coma" was maintained for 72 hours, the blood concentration of thiamylal required to maintain EEG burst suppression was observed to be increased by the end of the first 24 hours and continued to increase over the next 48 hours.[50] During deep pentobarbital anesthesia, autoregulation is maintained up to arterial pressures as low as 60 mm Hg. CO_2 responsiveness also persists.

Propofol

The effects of propofol (2,6-diisopropylphenol) on CBF and CMR appear to be quite similar to those of barbiturates. Investigations in humans have revealed substantial reductions in both CBF and CMR after the administration of propofol.[51] In healthy volunteers, surgical levels of propofol reduced regional CBF by 53% to 79% in comparison with the awake state.[52,53] Alkire and coworkers assessed cerebral glucose metabolism in volunteers by positron emission tomography (PET) before and during infusion of propofol to the point of unresponsiveness.[54] The whole-brain metabolic rate decreased by 48% to 58%, with limited regional heterogeneity observed. When compared with isoflurane-fentanyl or sevoflurane-fentanyl anesthesia, a combination of propofol and fentanyl decreased subdural pressure in patients with intracranial tumors and decreased the arteriovenous oxygen content difference ($AVDO_2$).[55] Collectively, these investigations in human subjects indicate that propofol effects reductions in CMR and secondarily decreases CBF, CBV, and ICP.

Both CO_2 responsiveness and autoregulation appear to be preserved in humans during the administration of propofol,[56,57] even when administered in doses that produce burst suppression of the EEG.[58] The magnitude of the reduction in CBF during hypocapnia is decreased during propofol administration. This effect is probably due to the cerebral vasoconstriction induced by suppression of CMR, which limits further hypocapnia-mediated vasoconstriction.

Etomidate

The effects of etomidate on CBF and CMR are also similar to those of barbiturates. Roughly parallel reductions in CBF and CMR occur in humans,[33,59] and in general they are accompanied by progressive suppression of the EEG. Induction of anesthesia with either thiopental or etomidate resulted in a similar reduction in MCA flow velocity of about 27%.[60] The CBF/CMR changes are substantial. Renou and colleagues[33] gave approximately 0.2 mg/kg of etomidate to adults and observed mean reductions in CBF and CMR of 34% and 45%, respectively. As is the case with barbiturates, no further reduction in CMR occurs when additional drug is administered beyond a dose sufficient to produce EEG suppression. This latter phenomenon has not been demonstrated in humans. However, Bingham and associates[61] observed that etomidate lowered ICP when administered to severely head-injured patients in whom EEG activity was well preserved but was ineffective when there was substantial antecedent EEG suppression. The global CMR suppression attainable with etomidate is slightly less profound than that achieved with isoflurane and barbiturates. This is consistent with the observation that unlike barbiturates, which cause CMR suppression throughout the brain, the CMR suppression caused by etomidate is regionally variable and occurs predominantly in forebrain structures.

Etomidate has been shown to be effective in reducing ICP without causing a reduction in CPP in patients with intracranial tumors[62] and head-injured patients.[63] However, administration of etomidate has been shown to result in an exacerbation of brain tissue hypoxia and acidosis in patients in whom the MCA was temporarily occluded during surgery.[64] Additional concerns regarding the occurrence of adrenocortical suppression and renal injury caused by the propylene glycol vehicle[65] will probably preclude more than episodic use.

Reactivity to CO_2 is preserved in humans during the administration of etomidate.[33,59] Autoregulation has not been evaluated. Myoclonus and epileptogenesis are discussed in a later section.

Narcotics

There are inconsistencies in the information available, but it is likely that narcotics have relatively little effect on CBF and CMR in the normal, unstimulated nervous system. When changes do occur, the general pattern is one of modest reductions in both CBF and CMR. The inconsistencies in the literature probably arise largely because in many studies, the "control" states entailed paralysis and nominal sedation, often with nitrous oxide alone. In these studies, in which substantial reductions in CBF and CMR were frequently observed, the effect of the narcotic was probably a combination of the inherent effect of the drug plus a substantial component attributable to reduction of arousal. Comparable effects related to reduction of arousal may occur and can be clinically important. However, they should be viewed as nonspecific effects of sedation or pain control, or both, rather than specific properties of narcotics. The following discussion emphasizes investigations in which control measurements were unlikely to have been markedly influenced by arousal phenomena.

Morphine. When morphine (~1 mg/kg) was administered as the sole drug to humans, Moyer and associates[66] observed no effect on global CBF and a 41% decrease in $CMRO_2$. The latter is a substantial reduction, and the absence of a simultaneous adjustment in CBF is surprising. There have been no other investigations of morphine alone in humans. Jobes and coworkers gave morphine (1 and 3 mg/kg) with 70% N_2O to patients and observed no significant change in CBF or CMR.[34] The N_2O that was used might be expected to have caused a tendency toward increases in CBF and CMR. The relative absence of *net* changes in these variables from awake control measurements suggests a small to moderate depressive effect of morphine on CBF and CMR at this large dose. It should be recalled, however, that morphine can cause substantial release of histamine in individual patients. Histamine is a cerebral vasodilator that will cause an increase in CBV and a CBF effect that will vary depending on the systemic blood pressure response.

Autoregulation was observed to be intact between MAP values of 60 and 120 mm Hg in human volunteers anesthetized with morphine, 2 mg/kg, and 70% N_2O.[67]

Fentanyl. Limited human data are available. Vernhiet and colleagues[35] measured CBF and $CMRO_2$ before and during anesthesia with 12 to 30 (mean, 16) µg/kg of fentanyl and 50% N_2O in patients about to undergo cerebral angiography. Atropine and pancuronium were the only other anesthetics administered. Neither CBF nor $CMRO_2$ changed significantly from awake control values in their group of six subjects. However, one of the patients (an epileptic with normal results on computed tomography [CT]) had dramatic and unexplained increases in both CBF and $CMRO_2$. For the remaining five, CBF and $CMRO_2$ decreased by 21% and 26%, respectively ($P < .05$). The data for fentanyl/N_2O presented in Figure 13-7 are derived from these five patients, who received an average of 17 µg/kg of fentanyl. Murkin and associates measured CBF before and after induction of anesthesia with high-dose fentanyl, 100 µg/kg, and diazepam, 0.4 mg/kg.[68] CBF fell by 25%, although part of this effect may well have been a result of the benzodiazepine (see later) rather than fentanyl. Firestone and coworkers, using PET, observed a heterogeneous CBF response to 1.5 µg/kg of fentanyl in healthy volunteers. Increases occurred in the frontal, temporal, and cerebellar areas simultaneous with decreases in discreet areas associated with pain-related processing.[69] CO_2 responsiveness and autoregulation are unaffected, and the hyperemic CBF response to hypoxia remains intact.

These data, taken together, suggest that fentanyl will cause a moderate global reduction in CBF and CMR in the normal quiescent brain and will, like morphine, cause larger reductions when administered during arousal.

Alfentanil. McPherson and associates[70] administered alfentanil, 320 µg/kg, to pentobarbital-anesthetized dogs. They observed no changes in CBF, CMR, CO_2 responsiveness, autoregulation, or the CBF response to hypoxia. There have been no studies of the effects of alfentanil on CMR in humans. Schregel and colleagues administered 25 to 50 µg/kg of alfentanil to patients receiving 60% N_2O after induction of anesthesia with thiopental.[71] CBFV decreased transiently. A Doppler measure of MCA diameter was simultaneously unchanged, thus suggesting that the reduction in CBFV was indicative of a decrease in CBF. Mayberg and coworkers also observed no change in CBFV in response to 25 to 50 µg/kg of alfentanil given to patients during maintenance of anesthesia with isoflurane-N_2O.[72]

Although there are fewer data, the general pattern is similar and the conclusions should be the same as for sufentanil (see the next paragraph).[73-77] Alfentanil was included with fentanyl and sufentanil in two of the investigations of conditions in the surgical field mentioned in connection with sufentanil.[78,79] No adverse effects were noted.

Sufentanil. The majority of investigations in both animals[80,81] and humans indicate that sufentanil causes, depending on the dose, either no change or a reduction in CBF and CMR. Stephan and colleagues[36] measured CBF and $CMRO_2$ in patients before and after induction of anesthesia with 10 µg/kg of sufentanil. They observed a 29% reduction in CBF and a 22% reduction in $CMRO_2$. Murkin and coworkers, in a study involving the same dose of sufentanil and a similar design, made essentially identical observations.[82] Mayer and associates gave 0.5 µg/kg of sufentanil to volunteers and observed no change in CBF.[83] Weinstabl and coworkers observed reductions in CBFV when 1.0 and 2.0 µg/kg of sufentanil were given to intensive care unit (ICU) patients with increased ICP.[84] Neither Weinstabl and colleagues[84] nor Mayer and associates,[83] who administered sufentanil to healthy volunteers, observed changes in CBFV after 0.5 µg/kg of sufentanil.

The data from the aforementioned studies led to anticipation of no change or a reduction in ICP as a result of administration of either sufentanil or alfentanil. With respect to sufentanil, the bulk of the data derived in humans[84-88] has revealed no change in ICP after its administration. However, in some investigations in humans, sufentanil was associated with modest increases in intracranial pressure.[73,89] Subsequent investigations appear to indicate that the increases in ICP associated with sufentanil are at least in large part the consequence of a normal autoregulatory response to the sudden reduction in MAP that can occur as a consequence of sufentanil administration.[90] Based on these data, sufentanil (and for that matter fentanyl as well[87]) are best administered in a manner that does not produce sudden reduction of MAP. MAP reduction will clearly reduce CPP and may increase ICP, each of which, in sufficient extreme, may be deleterious. However, it should be noted that the ICP increases attributed to sufentanil have been small. Furthermore, four investigations[78,79,91,92] that compared conditions in the surgical field, including pressure under brain retractors,[78] identified no adverse influences attribut-

able to sufentanil. Accordingly, sufentanil need not be viewed as in any way contraindicated, although it should be used with attention to its effect on MAP.

Remifentanil. Investigations of moderate doses of remifentanil in patients have revealed minimal effects that are very similar to those of the other synthetic narcotics (with the exception of its substantially shorter duration of action). In patients undergoing craniotomy for supratentorial space-occupying lesions, 1 μg/kg of remifentanil caused no change in ICP.[93] In a second investigation in craniotomy patients, approximately 0.35 μg/kg/min of remifentanil resulted in CBF values comparable to those observed with moderately deep anesthesia with either isoflurane/N_2O or fentanyl/N_2O,[94] and CO_2 responsiveness was preserved. Greater doses of remifentanil may have more substantial effects. CBFV in the MCA decreased 30% in response to 5 μg/kg followed by 3 μg/kg/min of remifentanil at a constant MAP in patients being anesthetized for bypass surgery.[37] A lower dose of 2 μg/kg followed by an infusion of 3 μg/kg/min, however, did not affect CBFV. Quantitatively similar observations were made after a large dose of sufentanil in patients undergoing cardiac anesthesia (see earlier).[36]

It should be noted that in the previously mentioned studies, remifentanil was administered with other drugs that might influence cerebral hemodynamics. More recent studies in human volunteers have demonstrated that the infusion of *low* (*sedative*) doses of remifentanil can increase CBF. A PET study in human subjects to whom remifentanil, 0.05 and 0.15 μg/kg/min, was administered revealed increases in CBF in the prefrontal, inferior parietal, and supplementary motor cortices; reductions in CBF were observed in the cerebellum, superior temporal lobe, and midbrain gray matter.[95] The relative increase in CBF was greater with administration of the higher dose of remifentanil. Similar data were obtained by Lorenz and colleagues, who used magnetic resonance imaging for determination of CBF.[96] In a PET investigation in human volunteers, Kofke and coworkers observed remifentanil-induced increases in regional CBF within the limbic system.[97] Although the underlying mechanisms of the increases in CBF are not clear, disinhibition produced by the low-dose remifentanil infusion, or perhaps the sensation of side effects (warmth, comfort, pruritus),[96] may have contributed. It should be noted that when combined with N_2O, CBF and CO_2 reactivity are similar in patients given remifentanil or fentanyl.[98] In aggregate, the available human data indicate that in low sedative doses, administration of remifentanil alone can effect minor increases in CBF. With higher doses or with the concomitant administration of anesthetic adjuvants, CBF is either unaltered or modestly reduced.

Benzodiazepines

Benzodiazepines cause parallel reductions in CBF and CMR in humans. CBF and $CMRO_2$ decreased by 25% when 15 mg of diazepam was given to head-injured patients.[38] The effects of midazolam on CBF (but not CMR) have also been studied in humans. Forster and associates observed a 30% to 34% reduction in CBF[39,99] after the administration of 0.15 mg/kg of midazolam to awake healthy human volunteers. Veselis and coworkers, using PET, observed a global 12% reduction in CBF after a similar dose and noted that the decreases occurred preferentially in the brain regions associated with arousal, attention, and memory.[100] CO_2 responsiveness was preserved.[101]

The foregoing studies indicate that benzodiazepines should cause a moderate reduction in CBF in humans and suggest that the effect may be metabolically coupled. The extent of the maximal CBF/CMR reduction produced by benzodiazepines is probably intermediate between the decreases caused by narcotics (modest) and barbiturates (substantial). It appears that benzodiazepines should be safe to administer to patients with intracranial hypertension, provided that respiratory depression and an associated increase in $Paco_2$ do not occur.

Flumazenil

Flumazenil is a highly specific, competitive benzodiazepine receptor antagonist. It had no effect on CBF when administered to unanesthetized human volunteers.[99,102] However, flumazenil reverses the CBF-, CMR-, and ICP-lowering effects of midazolam. Whereas Knudsen and colleagues[103] observed no change in either CBF or CMR when patients were aroused from midazolam anesthesia with flumazenil at the conclusion of craniotomy for brain tumor resection, Chiolero and coauthors[104] reported severe increases in ICP when flumazenil was given to midazolam-sedated head injury patients in whom ICP was poorly controlled before the administration of flumazenil. These latter observations are consistent with animal investigations in which flumazenil not only reversed the CBF and CMR effects of midazolam but also caused a substantial, though short-lived overshoot above premidazolam levels in both CBF (by 44% to 56%) and ICP (by 180% to 217%). CMR did not rise above control levels, thus indicating that the increase in CBF was not metabolically coupled. The CBF overshoot effect is unexplained, but it may be a neurogenically mediated arousal phenomenon. Flumazenil should be used very cautiously to reverse benzodiazepine sedation in patients with impaired intracranial compliance.

Droperidol

There have been no human investigations of the CBF/CMR effects of droperidol in isolation. However, the information available from animal investigations and combination drug administration in humans,[105,106] taken together, suggests that droperidol is not a cerebral vasodilator and probably has little effect on CBF and CMR in humans. The occasional increases in ICP that have been observed[105] probably reflect normal autoregulation-mediated vasodilation in response to an abrupt fall in MAP.

Ketamine

Among the intravenous anesthetics, ketamine is unique in its ability to cause increases in both CBF and CMR.[107] Animal studies indicate that the changes in CMR are regionally variable. In rats, substantial increases occur in limbic system structures with modest changes or small decreases in cortical structures.[108] PET studies in humans have demonstrated that subanesthetic doses of ketamine (0.2 to 0.3 mg/kg) can increase global CMR by about 25%.[109] The greatest increase in CMR occurred in the frontal and anterior cingulated cortex. A relative reduction in CMR in the cerebellum was also observed. Commercially available formulations of ketamine contain both the (*S*)- and (*R*)-ketamine enantiomers. The (*S*)-ketamine enantiomer increases CMR substantially, whereas the (*R*) enantiomer tends to decrease CMR, particularly in the temporomedial cortex and in the cerebellum.[110] These changes in CMR are accompanied by corresponding changes in CBF.[111] Increases in global (as well as regional) CBF in humans

that were not accompanied by similar increases in $CMRO_2$ after the administration of (*S*)-ketamine have been observed. However, the majority of investigations indicate that autoregulation is maintained during ketamine anesthesia[112]; the observed effects of ketamine on cerebral hemodynamics indicate that ketamine increases CMR and secondarily increases CBF. CO_2 responsiveness is preserved.

The anticipated ICP correlate of the increase in CBF has been confirmed to occur in humans. However, anesthetic drugs (diazepam, midazolam, isoflurane/N_2O, propofol) have been shown to blunt or eliminate the increases in ICP or CBF associated with ketamine.[113-115] In fact, decreases in ICP have been reported in response to relatively large doses of ketamine (1.5 to 5 mg/kg) administered to propofol-sedated head-injured patients.[116] Accordingly, although ketamine is probably best avoided as the sole anesthetic agent in patients with impaired intracranial compliance, it may be reasonable to use it cautiously in patients who are simultaneously receiving the other drugs mentioned earlier.

Lidocaine

Lidocaine produces a dose-related reduction in $CMRO_2$ in experimental animals.[117] In dogs, 3 mg/kg lowered $CMRO_2$ by 10% and 15 mg/kg reduced it by 27%. When very large doses (160 mg/kg) were given to dogs maintained on cardiopulmonary bypass, the reduction in $CMRO_2$ was apparently greater than that seen with high-dose barbiturates.[118] This may occur because the membrane-stabilizing effect of lidocaine also reduces the energy required for maintenance of membrane integrity. In unanesthetized human volunteers, Lam and colleagues observed reductions in CBF and CMR of 24% and 20%, respectively, after the administration of 5 mg/kg of lidocaine over a 30-minute period, followed by infusion of 45 µg/kg/min.[119]

Bedford and coworkers[120] compared the effectiveness of bolus doses of thiopental, 3 mg/kg, and lidocaine, 1.5 mg/kg, in controlling the acute increase in ICP that occurred after the application of a pin head holder or skin incision in craniotomy patients. The two regimens were equally effective in causing a reduction in ICP. However, the decrease in MAP was greater with thiopental. Accordingly, a bolus dose of lidocaine is a reasonable adjunct to the prevention or treatment of acute elevations in ICP and has been recommended for preventing increases in ICP associated with endotracheal suctioning. Note that large doses of lidocaine can produce seizures in humans and some experimental animals. Lidocaine-induced seizures have not been reported in anesthetized humans. Nonetheless, it seems appropriate to restrict lidocaine doses to amounts that achieve serum levels less than the seizure threshold (>5 to 10 µg/mL) in awake humans. After a 2-mg/kg bolus, peak serum concentrations of 6.6 to 8.5 µg/mL are below this seizure threshold. Bolus doses of 1.5 to 2.0 mg/kg therefore seem appropriate.

Inhaled Anesthetics

Volatile Anesthetics

The pattern of volatile anesthetic effects on cerebral physiology is a striking departure from that observed with the intravenous anesthetics, which generally cause parallel reductions in CMR and CBF. All volatile anesthetics, similar to intravenous sedative-hypnotic drugs, suppress cerebral metabolism in a dose-related manner.[121-125] Volatile anesthetics also possess intrinsic cerebral vasodilatory activity as a result of direct effects on vascular smooth muscle. The net effect of volatile anesthetics on CBF is therefore a balance between a reduction in CBF caused by CMR suppression and augmentation of CBF caused by the direct cerebral vasodilation. When administered at a dose of 0.5 MAC, CMR suppression–induced reduction in CBF predominates, and net CBF decreases in comparison to the awake state. At 1.0 MAC, CBF remains unchanged; at this dose, CMR suppression and vasodilatory effects are in balance. Beyond 1.0 MAC, the vasodilatory activity predominates, and CBF increases significantly even though CMR is substantially reduced.

The increase in CBF produced by volatile anesthetics at doses greater than 1.0 MAC has been interpreted as evidence of uncoupling of flow and metabolism. However, there is considerable evidence that coupling (CBF adjustments paralleling changes in CMR) persists during anesthesia with volatile agents.[126-129] Accordingly, it is probably more accurate to say that the CBF/CMR ratio is altered (increased) by volatile anesthetics. This alteration is dose related, and under steady-state conditions there is a positive correlation between MAC multiples and the CBF/$CMRO_2$ ratio[123,130]; that is, higher MAC levels cause greater "luxury" perfusion.

The important clinical consequences of administration of volatile anesthetics are derived from the increases in CBF and CBV—and consequently ICP—that can occur. Of the commonly used volatile anesthetics, the order of vasodilating potency is approximately halothane >> enflurane > desflurane ≈ isoflurane > sevoflurane.

Effects on Cerebral Blood Flow. Volatile anesthetics possess intrinsic vasodilatory activity, and they not only modify cerebral autoregulation but also produce dose-dependent reductions in systemic blood pressure. Hence, their effects on CBF and CMR are best evaluated when arterial pressure is supported to a common level. In addition, the cerebrovascular effects of volatile anesthetics are modulated by the simultaneous administration of other central nervous system (CNS)-active drugs. It is therefore important to understand the control state (awake, sedated, or anesthetized) against which the CBF and CMR effects of volatile anesthetics are compared. The best information about the cerebrovascular effects of volatile anesthetics is obtained in studies in which a nonanesthetized awake control state is used.

Data on the cerebrovascular effects of halothane and enflurane are limited. Initial studies in humans demonstrated that administration of 1 MAC halothane significantly increases CBF, even when systemic blood pressure is substantially reduced, in comparison to preanesthetic CBF.[131] The same investigators subsequently showed that in humans, when MAP is maintained at 80 mm Hg, 1.1 MAC levels of halothane increase CBF by as much as 191% and decrease CMR by about 10% (Fig. 13-8).[131,132] When compared with awake values, 1.2 MAC enflurane also increase CBF and decrease CMR by 45% and 15%, respectively.[136] The dramatic increases in CBF with a simultaneous modest reduction in CMR attest to the cerebral vasodilatory properties of halothane and enflurane. Isoflurane, by contrast, does not increase CBF as much as halothane or enflurane does. Human studies have shown that at doses of 1.1 MAC, isoflurane increases CBF by about 19% when systemic pressure is maintained within the normal range. CMR is reduced by about 45%.[129]

More recent investigations have shown that both sevoflurane and desflurane can significantly reduce CBF in humans

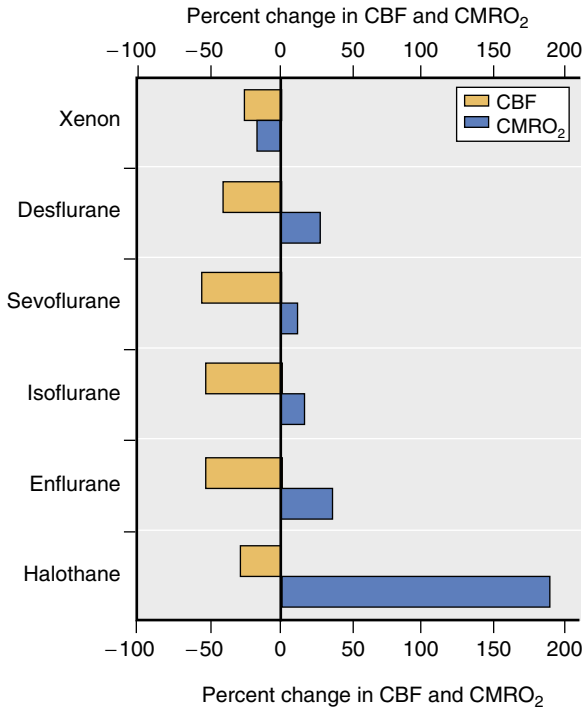

Figure 13-8 Estimated changes in cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen ($CMRO_2$) caused by volatile anesthetics. The CBF data for halothane, enflurane, and isoflurane were obtained during anesthesia (with blood pressure support) at 1.1 minimum alveolar concentration (MAC) in humans[132] and are expressed as percent change from awake control values. The $CMRO_2$ data for halothane, enflurane, and isoflurane were obtained in the cat[123,133] and are expressed as percent change from N_2O-sedated control values. The data for sevoflurane were obtained during 1.1 MAC anesthesia in the rabbit and are expressed as percent change from a morphine/N_2O-anesthetized control state.[125] CBF values were obtained in patients who received 1 MAC sevoflurane anesthesia.[134] Desflurane data were obtained in patients to whom 1 MAC desflurane was administered.[135]

when compared with CBF in awake, nonanesthetized patients. At 1.0 MAC concentrations, sevoflurane[134] and desflurane[136] decreased CBF by 38% and 22% and CMR by 39% and 35%, respectively. These results, which suggest that the cerebral vasodilation produced by isoflurane is greater than that produced by sevoflurane and desflurane, were obtained with CBF measured by the inert gas technique. This technique measures CBF primarily within the cortex and therefore may have substantially underestimated global CBF. PET studies in healthy humans have shown that sevoflurane dose-dependently suppresses $CMRO_2$ and CBF; at 1 MAC levels, the reduction in CBF and $CMRO_2$ is approximately 50% and 50% to 60%, respectively.[52,53] In addition, other investigations in humans, most using measurement of MCA flow velocity by transcranial Doppler, indicate that differences in the effects of isoflurane, desflurane (Fig. 13-9), and sevoflurane are, at best, modest.[137,138,151] It should be noted that a strictly quantitative comparison between these volatile anesthetics is not possible given the variations in blood pressure among study group patients. In addition, there is some discrepancy among studies in the literature regarding the magnitude of the effects of volatile anesthetics on CBF. Much of this may occur as a result of the interaction of regionally selective CBF methods with the heterogeneity within the cerebrum of the CBF effects of volatile anesthetics. See the later section "Distribution of Changes in Cerebral Blood Flow/Cerebral Metabolic Rate."

There is considerable interest in use of the inert gas xenon in the modern practice of anesthesia. The anesthetic properties of xenon were recognized several decades ago, but it is only now that the agent is being evaluated for possible use in patients. The MAC

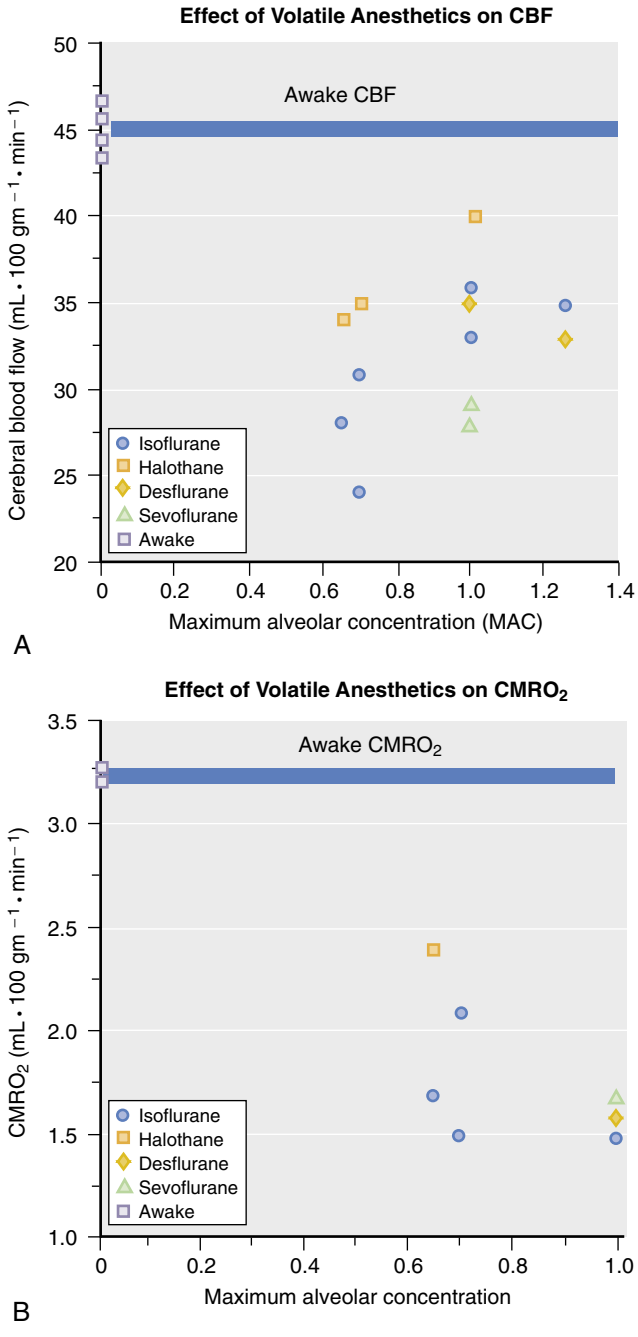

Figure 13-9 Effect of volatile anesthetics on cerebral blood flow (CBF) (**A**) and the cerebral metabolic rate of oxygen ($CMRO_2$) (**B**) in humans. The results are a composite of CBF and $CMRO_2$ values obtained from a number of separate investigations.[54,96,134,135,138-150] In these studies, $Paco_2$ was maintained in the normocapnic range (~35 to 40 mm Hg) and mean arterial pressure was supported. In most of the investigations, CBF was measured by the inert gas technique. This technique measures primarily cortical CBF and, as such, might underestimate global CBF.

of xenon has been estimated to be 63% to 71%, with females having significantly lower MAC values (51%).[152] Xenon is thought to exert its anesthetic effect primarily via noncompetitive antagonism of the *N*-methyl-D-aspartate (NMDA) receptor,[153] although activation of the TREK two-pore K^+ channel might also play a role.[154] In healthy humans, administration of 1 MAC xenon resulted in a reduction in CBF by approximately 15% in the cortex and by 35% in the cerebellum; interestingly, CBF in white matter increased by 22%.[155] This reduction in CBF is accompanied by a parallel reduction of 26% in the CMR of glucose (CMRg).[156] Cerebral autoregulation and CO_2 reactivity are preserved during xenon anesthesia in animals.[157] Under background pentobarbital anesthesia in an experimental model of increased ICP, administration of xenon did not increase ICP, and the response to both hypocapnia and hypercapnia was preserved.[158] Diffusion of xenon into air-containing spaces such as the bowel does occur, although the magnitude of air expansion is considerably less than that with N_2O.[159] Accordingly, caution will have to be exercised with the use of xenon in patients with intracranial air. Although the use of xenon in neurosurgical patients has not been evaluated, the data available suggest that it has a favorable profile for neuroanesthesia.

Effects on Cerebral Metabolic Rate. All of the volatile anesthetics cause reductions in CMR. The degree of reduction in $CMRO_2$ that occurs at a given MAC level is less with halothane than with the other four anesthetics (see Fig. 19-8). Sevoflurane's effect on $CMRO_2$ is very similar to that of isoflurane. The available information, derived in separate investigations, suggests that desflurane causes slightly less suppression of $CMRO_2$ than isoflurane does, especially at concentrations above 1.0 MAC.[124] Although a direct comparison of the $CMRO_2$ effects of all of the volatile anesthetics has not been performed in humans, collation of data from a number of investigations has shown that at doses of 1.0 MAC, isoflurane, sevoflurane, and desflurane reduce $CMRO_2$ ($AVDO_2$ in arterial and jugular bulb blood samples) by 25%,[139] 38%,[134] and 22%,[160] respectively. PET studies in humans have also shown that halothane (0.9 MAC) and isoflurane (0.5 MAC) can decrease CMRg by 40% and 46%, respectively.[54,140] The reduction in $CMRO_2$ is dose related. With isoflurane (and almost certainly desflurane and sevoflurane as well), the maximal reduction is attained simultaneously with the occurrence of EEG suppression.[124] This occurs at clinically relevant concentrations, such as 1.5 to 2.0 MAC in humans. In dogs, additional isoflurane up to 6.0% end-tidal volume results in no further reduction in CMR and no indication of metabolic toxicity. Halothane presents a contrast to this pattern. Halothane concentrations in excess of 4.0 MAC are required to achieve EEG isoelectricity in dogs, and additional halothane causes a further reduction in $CMRO_2$ in concert with alterations in energy charge. The latter changes, which are reversible, suggest interference with oxidative phosphorylation. These data indicate that unlike isoflurane, halothane can produce reversible toxicity when administered in very high concentrations.

There is some nonlinearity in the CBF and CMR dose-response relationships for volatile anesthetics. The initial appearance of an EEG pattern associated with the onset of anesthesia with halothane, enflurane, and isoflurane is accompanied by a precipitous decline in $CMRO_2$.[47] Thereafter, $CMRO_2$ declines in a slower dose-dependent manner. Such an effect has also been demonstrated for sevoflurane. In a dose escalation study in humans, the greatest reduction in entropy (a measure of anesthetic depth) was observed with 1 MAC sevoflurane anesthesia, with lesser reductions occurring at increasing concentrations.[161] Other studies during anesthetic induction with halothane found marked increases in CBF before any alteration in CMR. This suggests that the direct effect of a volatile agent on smooth muscle may develop more rapidly than influences related to depression of CMR.

Distribution of Changes in Cerebral Blood Flow/Cerebral Metabolic Rate. The regional distribution of anesthetic-induced changes in CBF and CMR differs markedly with halothane and isoflurane. Halothane produces relatively homogeneous changes throughout the brain. CBF is globally increased and CMR is globally depressed. The changes caused by isoflurane are more heterogeneous. Increases in CBF are greater in subcortical areas and hindbrain structures than in the neocortex.[128,162,163] For CMR the converse is true, with a greater reduction in the neocortex than in the subcortex.[164] In humans, 1.0 MAC sevoflurane (Fig. 13-10) results in a reduction in CBF within the cortex and an increase in CBF within the cerebellum.[141] These effects of sevoflurane are similar to those produced by isoflurane.[141,163] Desflurane has not been submitted to similar local CBF studies. However, given the similarity of its effects on the EEG (suggesting similar cortical CMR and CBF effects), the interim assumption of similar heterogeneity in CBF distribution seems reasonable. These distribution differences may explain certain apparent contradictions in reported CBF effects in the existing literature for isoflurane. Methods that assess global hemodynamic effects reveal greater changes than those that emphasize the cortical compartment. For instance, Eintrei and coworkers found no increase in CBF by surface Xe washout when isoflurane was administered to patients undergoing craniotomy,[165] yet others[166-168] have reported that administration of isoflurane to normocapnic subjects with intracranial pathology can result in increases in CSF pressure.

Cerebral Vasodilation by Volatile Anesthetics—Clinical Implications. Isoflurane, desflurane, and sevoflurane may have a modest cerebral vasodilating effect in the human cortex when administered at doses of 1 MAC or less. In fact, administration of volatile anesthetics can effect net decreases in CBF (see Fig. 13-9). These data, however, should be interpreted with considerable caution because the critical variable that is of interest in the clinical sphere is CBV. Although there is a direct correlation between CBF and CBV, as noted earlier, the relationship is not strictly 1:1. The magnitude of the changes in CBV is significantly less than the magnitude of the changes in CBF, and modest reduction in CBF may not necessarily be accompanied by reductions in CBV. This is exemplified by clinical investigations in which a significant increase in ICP (and by extension, CBV) was observed in patients to whom isoflurane was administered at doses that would be expected to effect a reduction in CBF.[166,168] Although induction of hypocapnia mitigated the increase in ICP in these studies, other investigations have revealed that hyperventilation may not be effective in blunting isoflurane-induced increases in ICP in patients with intracranial tumors.[167] In experimental investigations of cerebral injury, volatile anesthetics increased ICP significantly, and this rise in ICP was not ameliorated by hypocapnia.[169] Collectively, these data suggest that volatile anesthetics will have minimal effects on cerebral hemodynamics in patients with normal intracranial compliance. However, in patients with abnormal intracranial compliance, the potential for volatile agent–induced increases in CBV and ICP exists. Accordingly, there should be discretion in the use of volatile anesthetics in the setting of large or rapidly expanding mass lesions, unstable

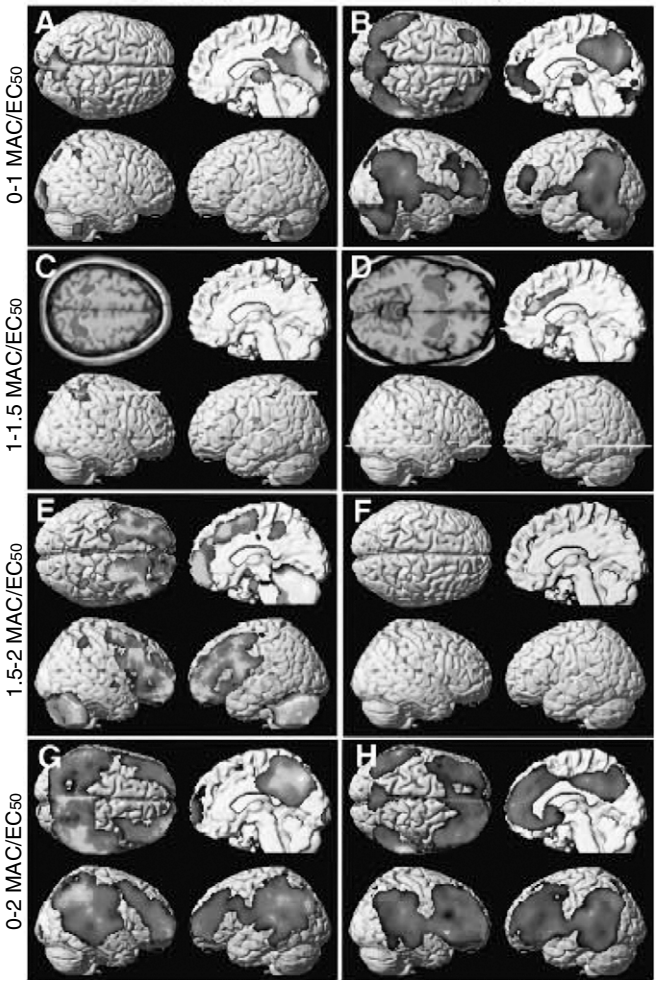

Figure 13-10 Dose-dependent redistribution of cerebral blood flow (CBF) in humans. **A** to **H**, Positron emission tomography (PET) scans demonstrate a dose-dependent reduction in CBF in both sevoflurane-anesthetized (*left*) and propofol-anesthetized (*right*) subjects. During sevoflurane anesthesia, an increase in concentration from 1.5 to 2.0 minimum alveolar concentration (MAC) leads to an increase in CBF within the subcortex, particularly in the cerebellum. There was a gradual reduction in mean arterial pressure (MAP) with increasing concentrations of sevoflurane, and MAP was not supported. The CBF values would be expected to be considerably greater had blood pressure been maintained within the normal range. Therefore, the CBF values represented in the figure probably *underestimate* true CBF during sevoflurane anesthesia. In propofol-anesthetized subjects, CBF was uniformly decreased and redistribution of CBF was not observed. *(Data from Kaisti K, Metsahonkala L, Teras M, et al: Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. Anesthesiology 96:1358-1370, 2002.)*

ICP, or other significant derangements of cerebral physiology in which CO_2 responsiveness and flow-metabolism coupling may be impaired. When they occur (a somnolent, vomiting patient with papilledema, a large mass, and compressed basal cisterns), the clinician may well be advised to use a predominantly intravenous technique until such time as the cranium and dura are open and the effect of the anesthetic technique can be assessed directly. Such circumstances will be relatively rare in elective neurosurgery.

Situations in which there has been substantial antecedent lowering of CMR by drug administration or disease processes should also justify caution in the use of volatile anesthetics. If a volatile agent has a substantial direct vasodilating effect on the cerebral vasculature that is normally offset by an opposing metabolically mediated vasoconstricting influence, it might be surmised that when near-maximal reduction of CMR has occurred, introduction of the volatile agent will have a predominantly vasodilating effect.[58,127] There are data to support this prediction. Maekawa and colleagues[164] measured CBF and local CMRg in rats both awake and during anesthesia with increasing concentrations of isoflurane. One MAC isoflurane resulted in an average decrease in CMRg of 54% of the awake control value in five cortical areas and no change in average CBF. An additional 1.0 MAC (i.e., a total of 2.0 MAC) caused a further reduction in CMRg of only 20% of the control value, and CBF simultaneously increased by 70% (Fig. 13-11). These data together suggest that isoflurane is a significant cerebral vasodilator when administered in concentrations at and above those associated with near-maximal CMR suppression or, perhaps, when administered in situations in which the component of CMR that is associated with electrophysiologic function is already suppressed by other drugs[58,127] or pathologic processes, such as traumatic brain injury.

The net vasodilating effect of equi-MAC concentrations of isoflurane, desflurane, and sevoflurane is less in humans than that of halothane, and the former are probably therefore preferable if a volatile agent is to be used in the setting of impaired intracranial compliance. That is not to say that halothane is contraindicated in these circumstances. It has been clearly demonstrated that when hypocapnia is established before the introduction of halothane, the increases in ICP that might otherwise occur in a nor-

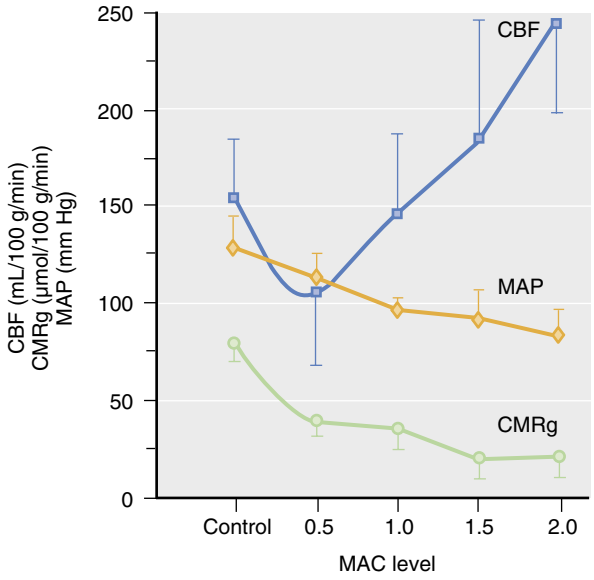

Figure 13-11 Relationship between changes in the cerebral metabolic rate of glucose (CMRg) and cerebral blood flow (CBF) in the motor-sensory cortex in rats during isoflurane anesthesia. The majority of the suppression in CMR caused by isoflurane has occurred by 1.0 minimum alveolar concentration (MAC), and in this concentration range CBF is not increased. Thereafter, additional isoflurane causes little further reduction in CMR, and cerebral vasodilation occurs. These data (±SD), from Maekawa and colleagues,[164] suggest the importance of metabolic coupling in determining the effects of isoflurane on CBF. MAP, mean arterial pressure.

mocapnic patient with poor intracranial compliance can be prevented or greatly attenuated. Nonetheless, most clinicians will prefer isoflurane, desflurane, or sevoflurane because the margin for error is probably wider than with halothane.

Time Dependence of Cerebral Blood Flow Effects. The effect of volatile anesthetic drugs on CBF has been shown to be time dependent in animal investigations. After an initial increase, CBF falls substantially and reaches a steady state near pre–volatile agent levels between 2½ and 5 hours after exposure.[162,170,171] The mechanism of this effect is not understood, and the phenomenon was not evident in humans studied during 3- or 6-hour exposure to halothane, isoflurane, desflurane, or sevoflurane.[151,172]

Cerebral Blood Volume. The extensive investigation of the influence of volatile anesthetics on CBF has been based primarily on the concern that the cerebral vasodilation produced by volatile anesthetics might increase ICP. It should be noted, however, that it is CBV and not CBF per se that influences ICP. The vast majority of intracranial blood is within the cerebral venous circulation, and although there is a reasonable correlation between vasodilation-induced increases in CBF and CBV, the magnitude of changes in CBF is considerably greater than that in CBV (see Fig. 13-6). Hence, changes in CBF do not reliably predict changes in CBV and, by extension, in ICP. Nonetheless, the available data do indicate that CBV is considerably greater during isoflurane anesthesia than during propofol or pentobarbital anesthesia.[25] In human volunteers, 1 MAC sevoflurane reduced regional CBF but not regional CBV; by contrast, propofol reduced both regional CBF and regional CBV (Fig. 13-12).[53] In addition, CBV responds to changes in $Paco_2$ by a reduction in CBV with hypocapnia and an increase in CBV with hypercapnia. The magnitude of the change in CBV is, however, less than the change in CBF. In aggregate, these data indicate clearly that although the effect of anesthetics and interventions on CBF may parallel the effect on CBV, there may well be substantial qualitative and quantitative differences.

CO_2 Responsiveness and Autoregulation. CO_2 responsiveness is well maintained during anesthesia with all of the volatile anesthetics.[142,173,174] As with all vasodilators, CBF is preserved up to lower MAP values during the administration of volatile anesthetics with no evidence of differences among the various anesthetics. Direct comparisons of CBF with isoflurane, desflurane, and sevoflurane anesthesia during hypotension are not available. By contrast, autoregulation of CBF in response to rising arterial pressure is impaired. This impairment appears to be most apparent with the anesthetics that cause the greatest cerebral vasodilation and is dose related (see Fig. 13-5). Sevoflurane may cause less impairment of autoregulation than other volatile anesthetics do. Recent studies surprisingly reported no change in CBFV in response to phenylephrine-induced increases in MAP during anesthesia with 1.2 to 1.5 MAC sevoflurane[175,176] or in CBF during hemorrhagic hypotension.[177] The autoregulatory response to rising pressure may be pertinent during acute episodes of hypertension, such as during laryngoscopy or mismatch of surgical stimulation to anesthetic depth. There may be some relevance to hyperemic states after carotid endarterectomy or resection of arteriovenous malformations (see Chapter 63).

Nitrous Oxide

The available data indicate that N_2O can cause increases in CBF, CMR, and ICP. At least a portion of the increases in CBF and CMR may be the result of a sympathoadrenal-stimulating effect of N_2O. The magnitude of the effect varies considerably according to the presence or absence of other anesthetic drugs (Fig. 13-13). When N_2O is administered alone, very substantial increases in CBF and ICP can occur. In sharp contrast, when N_2O is administered in combination with intravenous drugs, including barbiturates, benzodiazepines, narcotics, and propofol, its cerebral-vasodilating effect is attenuated or even completely inhibited. The addition of N_2O to anesthesia established with a volatile agent will result in moderate increases in CBF.

N_2O Administered Alone. The most dramatic reported increases in ICP or CBF in humans[181] and experimental animals[182] have occurred when N_2O was administered alone or with minimal background anesthesia. For instance, Henriksen and Jorgensen[181] recorded ICP before and during spontaneous breathing of 66% N_2O by patients with intracranial tumors. Mean ICP rose from

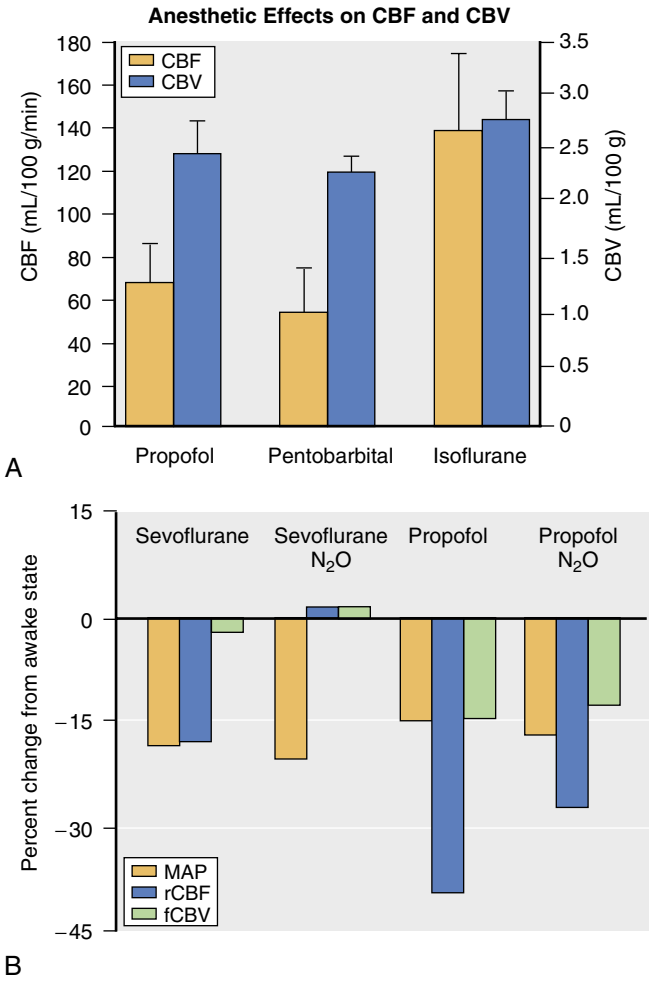

Figure 13-12 Effect of anesthetic drugs on cerebral blood flow (CBF) and cerebral blood volume (CBV). **A,** When compared with isoflurane, propofol and pentobarbital effected substantial reductions in CBF. However, reductions in CBV were more modest.[156] **B,** Although sevoflurane effected a significant reduction in regional CBF (rCBF), regional CBV (rCBV) was unchanged; had blood pressure been supported to normal levels, rCBV may have been greater than the awake state. By contrast, propofol effected a significant reduction in both rCBF and rCBV. These data indicate that the magnitude of the effect of anesthetics on rCBF is substantially greater than on rCBV. Hence, a reduction in rCBF may not lead to equivalent reductions in rCBV. MAP, mean arterial pressure.

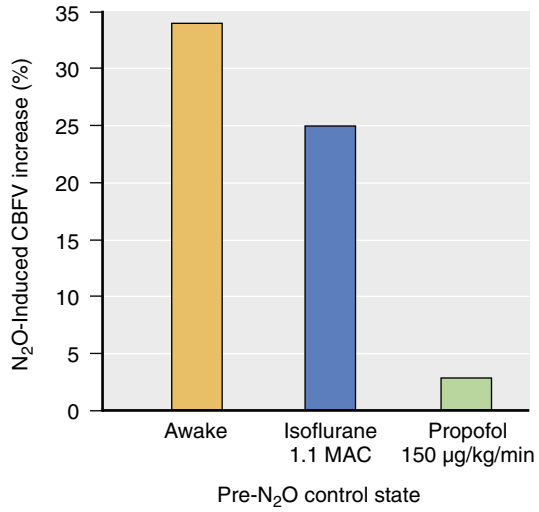

Figure 13-13 Mean percent increases in cerebral blood flow velocity (CBFV) in the middle cerebral artery of normocapnic subjects exposed to 60% N_2O after control recording in three conditions: awake[178]; 1.1 minimum alveolar concentration (MAC) of isoflurane[179]; and propofol, 150 µg/kg/min.[180]

13 to 40 mm Hg. The increases in CBF observed in humans are more modest than those observed in animals but are still substantial.[178] Whether these substantial increases represent the effects of N_2O per se or whether they reflect the nonspecific effects of a "second-stage" arousal phenomenon is not known.

N_2O Administered with Intravenous Anesthetics. When N_2O is administered in conjunction with certain intravenous anesthetics, its CBF effect may be considerably attenuated. Phirman and Shapiro[183] observed that a reproducible increase in ICP that had occurred in response to administration of 70% N_2O to a comatose patient was prevented by the previous administration of a combination of thiopental and diazepam despite no change in baseline ICP. In an investigation of patients with intracranial tumors and poor intracranial compliance (mean preinduction ICP, 27 mm Hg),[184] 50% N_2O introduced during barbiturate anesthesia and after the induction of hypocapnia had a negligible effect on ICP. Jung and associates compared lumbar CSF pressure in patients with brain tumors during administration of 0.7% isoflurane or 70% N_2O after induction of anesthesia with a barbiturate. Lumbar CSF pressure was modestly but significantly greater with N_2O.[185] That the increase was less dramatic than those cited earlier for N_2O alone may reflect the presence of residual barbiturate. Benzodiazepines administered alone have been shown to blunt the CBF response to N_2O in both animals and humans.[96] Narcotics appear to have a similar effect. Jobes and coauthors[34] reported that anesthesia with 1 mg/kg of morphine plus 70% N_2O resulted in no change in CBF from awake control values. Because of the very minor effect of morphine on CBF, these data suggest that N_2O did not cause substantial cerebral vasodilation. Although the addition of N_2O to propofol anesthesia in children increased MCA flow velocity,[186] such increases have not been demonstrated by other investigators.[180]

N_2O Administered with Volatile Anesthetics. In the majority of investigations, including several in humans, in which N_2O has been added to an anesthetic of 1.0 MAC or greater, substantial increases in CBF have been recorded.[179-187-190] Algotsson and associates[143] examined the effect of an approximately equi-MAC substitution of N_2O for isoflurane. They compared CBF in patients anesthetized with 1.5 MAC isoflurane and 0.75 MAC isoflurane with 65% N_2O. They observed 43% greater CBF with the latter, again consistent with a substantial vasodilating effect of N_2O in the presence of a volatile agent. Similar observations were made by Lam, Strebel, and their colleagues.[179,190] Several investigations have confirmed that CBF will be less with 1.0 MAC isoflurane than with a 1.0 MAC combination achieved with 50% to 65% N_2O and isoflurane.[143,144,191]

The result of an investigation in humans indicates that this vasodilating effect of N_2O may be positively correlated with the concentration of inhaled drug[190] and suggests that in general, the increase in CBF caused by N_2O is exaggerated at higher concentrations of both halothane and isoflurane. Of importance, however, is the observation of Reinstrup and coworkers, who demonstrated that administration of 50% N_2O to healthy volunteers did not significantly alter CBV.[192] In support of this observation, Kaisti and colleagues did not observe any effect of N_2O on CBV when added to a background of 1 MAC sevoflurane anesthesia.[53] These data indicate that although N_2O can increase CBF, its effect on CBV is modest at best.

Effects of N_2O on Cerebral Metabolic Rate. There is no uniform agreement about the effect of N_2O on CMR. Parallel changes in CBF and CMR,[182] increases in CBF without alteration of CMR,[193] and CMR alteration occurring without changes in CBF[194] have all been reported. This is doubtless the product of differences in species, methods, depth of background anesthesia, and interactions with simultaneously administered anesthetics. In a recent investigation in humans, administration of 70% N_2O on a background of either sevoflurane or propofol anesthesia resulted in modest increases in $CMRO_2$, thus indicating that N_2O does indeed increase cerebral metabolism.[53]

The CBF response to CO_2 is preserved during administration of N_2O.[195]

Clinical Implications. Despite the inconsistencies that are evident, data indicate that the vasodilatory action of N_2O can be clinically significant in neurosurgical patients with reduced intracranial compliance. However, it appears that N_2O-induced cerebral vasodilation can be considerably blunted by the simultaneous administration of intravenous anesthetics, although not all anesthetics have been evaluated and the dose-response relationships are not well defined. By contrast, addition of N_2O to a volatile drug–based anesthetic can increase cerebral metabolism and blood flow modestly. N_2O has been widely used in neurosurgery, and banishing it is inconsistent with the experience accumulated. Nonetheless, in circumstances wherein ICP is persistently elevated or the surgical field is persistently "tight," N_2O should be viewed as a potential contributing factor. Because N_2O rapidly enters a closed gas space, it should be avoided or omitted when a closed intracranial gas space may exist or intravascular air is a concern.

Muscle Relaxants

Nondepolarizing Relaxants

The only recognized effect of nondepolarizing relaxants on the cerebral vasculature occurs via the release of histamine (see Chapter 29). Histamine can result in a reduction in CPP because of the simultaneous increase in ICP (caused by cerebral vasodilation) and decrease in MAP.[196] It is not entirely clear, when the BBB

is intact, whether histamine directly causes cerebral vasodilation or whether it is a secondary (autoregulatory) response to a reduction in MAP. D-Tubocurarine is the most potent histamine releaser among available muscle relaxants. Metocurine, atracurium, and mivacurium also release histamine in lesser quantities. This effect is likely to be clinically inconsequential unless these anesthetics are administered in the large doses necessary to achieve intubating conditions rapidly. Of this group of drugs, cisatracurium has the least histamine-releasing effect. No evidence of histamine release was seen after the administration of 0.15 mg/kg (three times the ED_{95} for twitch depression) of cisatracurium to neurosurgical ICU patients.[197]

Vecuronium, in relatively large doses of 0.1 to 0.14 mg/kg, had no significant effect on cerebral physiology in patients with brain tumors.[198] Pipecuronium and rocuronium have not been studied but should similarly be without direct effect, and no adverse events have been reported.

The indirect actions of relaxants may also have effects on cerebral physiology. Pancuronium given as a large bolus dose can cause an abrupt increase in arterial pressure. This might elevate ICP in patients with impaired intracranial compliance and defective autoregulation; however, no significant clinical event has ever been reported. Muscle relaxation may reduce ICP because coughing and straining are prevented, and this results in lowering of central venous pressure with a concomitant reduction in cerebral venous outflow impedance.

A metabolite of atracurium, laudanosine, may be epileptogenic. However, although large doses of atracurium caused an EEG arousal pattern in dogs, CBF, CMR, and ICP were unaltered.[199] In rabbits, administration of laudanosine did not increase the severity of the epileptoid activity caused by direct application of a cephalosporin to the cortical surface.[200] It appears highly unlikely that epileptogenesis will occur in humans with atracurium.[201]

In summary, vecuronium, pipecuronium, rocuronium, atracurium, mivacurium, cisatracurium, metocurine, and pancuronium (if acute MAP increases are prevented with the latter) are all reasonable muscle relaxants for use in patients with or at risk for intracranial hypertension. Doses of metocurine, atracurium, and mivacurium should be limited to ranges not associated with hypotension.

Succinylcholine

Succinylcholine can produce modest increases (~5 mm Hg) in ICP in lightly anesthetized humans. This effect appears to be the result of cerebral activation (as evidenced by EEG changes and increases in CBF) caused by afferent activity from the muscle spindle apparatus.[202] Note, however, that there is poor correlation between the occurrence of visible muscle fasciculations and an increase in ICP. As might be expected with what appears to be an arousal phenomenon, deep anesthesia has been observed to prevent succinylcholine-induced increases in ICP in the dog. In humans, the increase in ICP is also blocked by paralysis with vecuronium and by "defasciculation" with metocurine, 0.03 mg/kg.[198] The efficacy of other defasciculating anesthetics has not been examined in humans.

Although succinylcholine *can* produce increases in ICP, it need not be viewed as contraindicated in circumstances in which its use for rapid attainment of paralysis is otherwise seen as appropriate. Kovarik and coauthors observed no change in ICP after the administration of succinylcholine, 1 mg/kg, to 10 nonparalyzed, ventilated neurosurgical ICU patients, 6 of whom had sustained a head injury.[203] Their observations are very relevant because it is in precisely this population of patients that the issue of the use of succinylcholine arises most frequently. Given that the ICP effects of succinylcholine may be an arousal phenomenon caused by increased afferent traffic from muscle spindles,[202] it is not unreasonable that disease processes that substantially blunt the level of consciousness might similarly blunt this response. As with many anesthetics, the concern should be not whether it is used but how it is used. If administered with proper attention to control of carbon dioxide tension, blood pressure, and depth of anesthesia and after defasciculation, little hazard should attend its use.

Other Effects of Anesthetics on Cerebral Physiology

Cerebrospinal Fluid Dynamics

There is approximately 150 mL of CSF in the adult human, half within the cranium and half in the spinal CSF space. CSF, which is formed in the choroid plexuses and to a lesser extent in the brain's interstitium with transependymal diffusion into the ventricular system, is replaced about three to four times per day. It functions both as a cushion for the CNS and as an excretory pathway. Anesthetics have been shown to influence both the rate of formation and the rate of reabsorption of CSF. Table 13-3 provides nonquantitative information about the direction of the influences of common anesthetic drugs. All the information has been derived from animals,[30,204-209] and these processes have not been examined in humans. Of the volatile anesthetics, halothane decreases secretion of CSF, isoflurane has no effect, and enflurane and desflurane increase secretion. Absorption of CSF is reduced by halothane and enflurane, unchanged by desflurane, and increased by isoflurane. Though probably of minimal relevance to clinical practice, a theoretical concern might be in the setting of a prolonged closed-cranium procedure in a patient with poor intracranial compliance. The most deleterious potential combination of effects in a patient with poor intracranial compliance is increased CSF production and decreased reabsorption. In the dog this pattern occurs with enflurane, which is perhaps another reason (in addition to the potential for epileptogenesis in the presence of cerebral injury and hypocapnia) for omission of enflurane in this circumstance.

Blood-Brain Barrier

In the majority of the body's capillary beds, there are fenestrations approximately 65 Å in diameter between endothelial cells. In the brain, with the exception of the choroid plexus, the pituitary, and the area postrema, tight junctions reduce this pore size to approximately 8 Å. As a result, large molecules and most ions are prevented from entering the brain's interstitium. There is little evidence that anesthetics alter the function of this "blood-brain

barrier" in most circumstances. However, acute hypertension can breach the barrier, and certain anesthetics facilitate this phenomenon.[210] Forster and colleagues[211] observed that extravasation of Evan blue into rabbit brain was greater when acute hypertension occurred during anesthesia with halothane than with thiopental. It is likely that the effect is a nonspecific result of cerebral vasodilation rather than a specific effect of halothane. These results were obtained in the setting of extreme, abrupt hypertension in animals with an initially normal BBB. To our knowledge, no peer-reviewed investigation has attempted a comparison of anesthetic effects on BBB function during anesthesia in normotensive humans.

Epileptogenesis

An extensive review of the convulsant and anticonvulsant effects of anesthetics and adjuvants is available.[212,213] Several commonly used anesthetics have some epileptogenic potential, particularly in predisposed individuals. A concern is that seizure activity may go unrecognized in an anesthetized and paralyzed patient and result in neuronal injury if substrate demand (CMR) exceeds supply for a prolonged period.[214] A second concern is that the epileptogenic effect will persist in the postanesthesia period when seizures may occur in less well controlled circumstances than exist in the operating room. In practice, it appears that spontaneous seizures during or after anesthesia have been extremely rare events. Nonetheless, in patients with processes that might predispose to seizures, it seems prudent to avoid the use of potentially epileptogenic drugs in situations in which there are reasonable alternatives.

Volatile Anesthetics

Enflurane is potentially epileptogenic in the clinical setting. Of particular relevance to neuroanesthesia is the observation that hypocapnia potentiates seizure-type discharges during enflurane anesthesia.[215] A 50% decrease in $CMRO_2$ was noted in human volunteers anesthetized with 3% enflurane, but with the onset of seizure activity, $CMRO_2$ returned to normal,[216] thus indicating preservation of flow-metabolism coupling. Note that there is no evidence that this type of EEG activity is deleterious when oxygen delivery is maintained during the event. However, because seizure activity can elevate brain metabolism by as much as 400%, the use of enflurane, especially at high doses and with hypocapnia, should probably be avoided in patients predisposed to seizures or with occlusive cerebrovascular disease.

The EEG-activating property of enflurane has been used intraoperatively to activate and identify seizure foci that are to be surgically resected, and in this situation spike activity not present preoperatively has been observed to persist after surgery.[217] There have also been two reports of seizures in the immediate postoperative period after enflurane anesthesia in both predisposed[218] and non-predisposed individuals.[219] No permanent sequelae appeared to occur as a result of these events, and in fact, this association is not a rigorously proven one. At worst, such occurrences are extremely uncommon.

Isoflurane can cause EEG spiking and myoclonus, but in the experimental setting it has not been associated with the frank epileptoid activity induced by enflurane. The clinical experience with isoflurane is very large, and unexplained "seizure-like activity" has been reported in only two patients. One occurrence was intraoperative[220] and the other immediately postoperative.[221] It therefore appears that epileptogenesis is not a clinical concern with isoflurane. In fact, isoflurane has been successfully used to control EEG seizure activity in refractory status epilepticus.[222]

Seizures occur during induction of anesthesia with high concentrations of sevoflurane in children, including those without a recognized seizure diathesis.[223] In two healthy human subjects, EEG burst suppression with 2 MAC sevoflurane was accompanied by epileptiform discharges that were observed during EEG monitoring.[224] These discharges were associated with a significant increase in CBF, thus demonstrating that flow-metabolism coupling was preserved. In patients with temporal lobe epilepsy, administration of 1.5 MAC sevoflurane elicited widespread paroxysmal interictal EEG activity. Of note was the observation that paroxysmal activity was not restricted to the ictal focus and that the administration of sevoflurane was not of any assistance in localization of the epileptogenic region of the brain.[225] The development of tonic-clonic movements indicative of seizure activity has also been reported in otherwise healthy patients on emergence from sevoflurane anesthesia.[226,227] In all of the reported cases of seizure activity attributable to sevoflurane anesthesia, untoward sequelae have not been documented. These reports highlight sevoflurane's ability, albeit small, to evoke epileptiform activity, and accordingly, the use of sevoflurane in patients with epilepsy should be undertaken with appropriate caution.

Methohexital

Myoclonic activity is sometimes observed with methohexital, and this agent has been used to activate seizure foci during cortical mapping.[224,228] In neurosurgical patients to whom larger doses of methohexital were administered to produce burst suppression of the EEG, refractory seizures have occurred.[229] Accordingly, it appears that patients with seizures of temporal lobe origin, typically of the psychomotor variety, or those to whom high doses are administered are at risk for seizure activation by methohexital. However, it should be noted that prolonged seizure activity after single-dose methohexital administration has not been reported in patients who undergo ECT.

Ketamine

Ketamine can elicit seizures in patients with an epileptic diathesis.[230] Depth electrode recordings in epileptic patients have revealed the occurrence of isolated subcortical seizure activity originating in the limbic and thalamic areas during ketamine anesthesia and demonstrated that this subcortical activation may not be reflected in surface EEG recordings.[231] Seizures have also been reported to occur after ketamine anesthesia in neurologically normal subjects on only two occasions,[232,233] and in one of these instances seizure thresholds may have been lowered by aminophylline.

Etomidate

Etomidate frequently produces myoclonus that is not associated with epileptiform activity on the EEG.[234] A single instance of severe, sustained myoclonus immediately after anesthesia with etomidate by infusion has been reported.[235] Etomidate has also been shown to precipitate generalized epileptic EEG activity in epileptic patients,[236] and its use in this population should probably be avoided. However, it has been used electively, in low doses, to activate seizure foci for the purposes of intraoperative EEG

localization.[237] In our experience (unpublished), selective activation of a quiescent focus can be achieved with 0.1 mg/kg. Larger doses are more likely to lead to generalized activation.

Etomidate is also associated with longer seizures in response to ECT than occur after methohexital or propofol. Remarkably, etomidate, in the dose range of 0.15 to 0.3 mg/kg, does not cause dose-related seizure inhibition during ECT as is readily demonstrated with the other two drugs.

The preceding information not withstanding, there are no convincing reports to indicate epileptogenesis in normal subjects, and use of etomidate need not be restricted on this basis. In fact, it has been used to control refractory status epilepticus.

Propofol

Seizures and opisthotonos have been reported to occur after propofol anesthesia. However, systematic studies in both humans[238] and animals,[239] though identifying the occurrence of occasional dystonic and choreiform movements, have failed to confirm the notion that propofol is proconvulsant. In fact, propofol appears to be anticonvulsant in mice.[239] Furthermore, ECT seizures were shorter after induction with propofol than after induction with methohexital,[240] which is more consistent with an *anticonvulsant* effect. In addition, propofol sedation has been widely used during "awake" resection of seizure foci and other intracranial lesions. Although pronounced high-amplitude β-frequency activity in the EEG has been observed,[241] there has not been an unexpected incidence of seizures.

Narcotics

Seizures or limbic system hypermetabolism (or both) can be readily elicited in some animal species with narcotics. Although an increase in CBF in deep brain structures associated with pain processing has been observed in human volunteers,[69] humans do not have a clinically apparent correlate of the hypermetabolism effect seen in animals. Several anecdotal accounts, unaccompanied by EEG recordings, have reported the occurrence of grand mal convulsions in patients who received both high and low doses of fentanyl. However, systematic investigations of EEG changes during the administration of relatively large doses of fentanyl, sufentanil, and alfentanil in humans have *not* documented neuroexcitatory activity,[242-244] and the "seizures" may have been an exaggerated rigidity phenomenon. There are exceptions. Tempelhoff and coauthors reported on induction of anesthesia with fentanyl for secondary craniotomy and anterior temporal lobectomy in patients with partial complex seizures. Eight of the nine patients displayed electrical seizure activity at a range of clinically relevant fentanyl doses (mean, 26 μg/kg).[245] Another study found that alfentanil, 50 μg/kg, augmented temporal lobe spike activity in patients with temporal lobe epilepsy.[246] Note that untreated rigidity may itself also have important CNS consequences. ICP elevation can occur during narcotic-induced rigidity, probably as a consequence of cerebral venous congestion.

Atracurium

See discussion regarding the atracurium metabolite laudanosine in the section on nondepolarizing muscle relaxants.

Neonatal Anesthetic Neurotoxicity

This subject is covered in detail in Chapter 82.

Cerebral Physiology in Pathologic States

Cerebral Ischemia—Pathophysiology

Critical Cerebral Blood Flow Thresholds

The brain has a high rate of energy utilization and very limited energy storage capacity. It is therefore extremely vulnerable in the event of interruption of substrate (oxygen, glucose) supply. Under normal circumstances, global CBF is maintained at approximately 50 mL/100 g/min. In the face of a declining CBF and therefore oxygen supply, neuronal function deteriorates progressively rather than in an all-or-none fashion (Fig. 13-14). There is a substantial reserve below normal CBF levels, and it is not until CBF has fallen to approximately 20 mL/100 g/min that EEG evidence of ischemia begins to appear. At a CBF level of approximately 15 mL/100 g/min, the cortical EEG is isoelectric. However, only when CBF is reduced to about 6 mL/100 g/min are indications of potentially irreversible membrane failure (elevated extracellular potassium[247] and loss of the direct cortical response) rapidly evident. As CBF decreases in the flow range between 15 and 10 mL/100 g/min, a progressive deterioration in energy supply occurs and eventually leads, with a time course that may last hours rather than minutes, to membrane failure and neuronal death. The brain regions falling within this CBF range (6 to 15 mL/100 g/min) encompass brain tissue in which neuronal dysfunction is temporarily reversible but within which neuronal death will occur if flow is not restored; such regions are referred to as the ischemic penumbra.[247,251] Studies defining progression to cerebral infarction within the penumbra have been performed principally in the cerebral cortex of primates, and the actual CBF levels at which the various decrements in function occur may vary with both anesthetic[250] and species. However, in humans anesthetized with halothane and

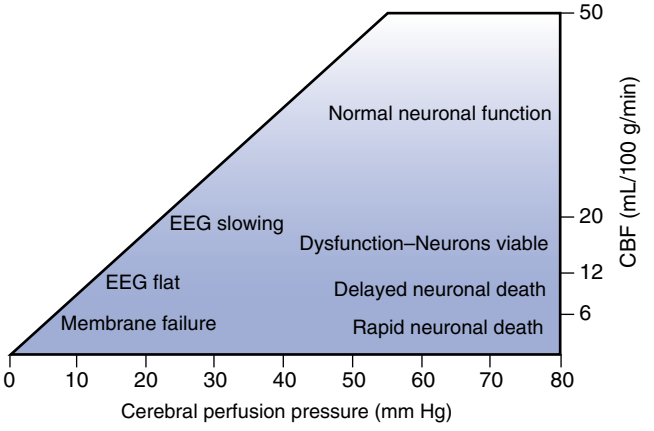

Figure 13-14 Relationships between cerebral perfusion, cerebral blood flow (CBF), the electroencephalogram (EEG), and the functional status/viability of neurons. Note that in the approximate CBF range of 6 to 12 mL/kg/min, the energy supply is insufficient to support electrophysiologic activity (i.e., EEG flat) but can prevent complete membrane failure and neuronal death for extended periods (see Fig. 13-15). These areas are referred to as the ischemic penumbra.[247] The data are derived from studies on the cerebral cortex of barbiturate-anesthetized baboons[247,248] and unanesthetized monkeys.[249] The CBF and mean arterial pressure thresholds may vary with anesthetic and species.[250]

N_2O, the CBF threshold for the initial EEG change[252] is similar to that observed in the animal investigations.

Models of Cerebral Ischemia

Much has been made of the difference between complete cerebral ischemia, as occurs during cardiac arrest, and incomplete cerebral ischemia, as may occur during occlusion of a major cerebral vessel or severe hypotension. However, from the clinician's vantage, the important difference is that the residual blood flow during incomplete ischemia may result in enough delivery of oxygen to allow some generation of ATP and thereby stave off the catastrophic irreversible membrane failure that occurs within minutes during normothermic complete cerebral ischemia. This difference in the rate of failure of the energy supply[253,254] (Fig. 13-15) can result in much greater apparent tolerance for focal or incomplete ischemia than for complete global ischemia (e.g., cardiac arrest).

Energy Failure and Excitotoxicity

Energy failure is the central event that occurs during cerebral ischemia.[255] ATP is required for maintenance of the normal membrane ionic gradient, and energy failure is rapidly attended by membrane depolarization and influx of sodium and calcium into the neuron. Voltage-dependent calcium channels are then activated and calcium gains entry into the cytosol. Depolarization of presynaptic terminals also results in the release of massive quantities of excitatory neurotransmitters, particularly glutamate, into the synaptic cleft. Activation of glutamatergic receptors, the NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazopropionic acid (AMPA) receptors, adds to the influx of Na^+ and Ca^{2+} (Fig. 13-16). Initiation of cellular signaling by activation of metabotropic receptors leads to the release of stored Ca^{2+} from the endoplasmic reticulum via inositol 1,4,5-triphosphate (IP_3) receptors. Ionic influx is accompanied by influx of water, and neuronal swelling occurs rapidly after membrane depolarization. The injury that is initiated by excessive glutamate receptor activity is referred to as excitotoxicity.

Calcium is a ubiquitous second messenger in cells, and it is a cofactor required for the activation of a number of enzyme systems. The rapid, uncontrolled increase in cytosolic Ca^{2+} levels initiates the activation of a number of cellular processes that contribute to injury. Cytoskeletal proteins such as actin are cleaved

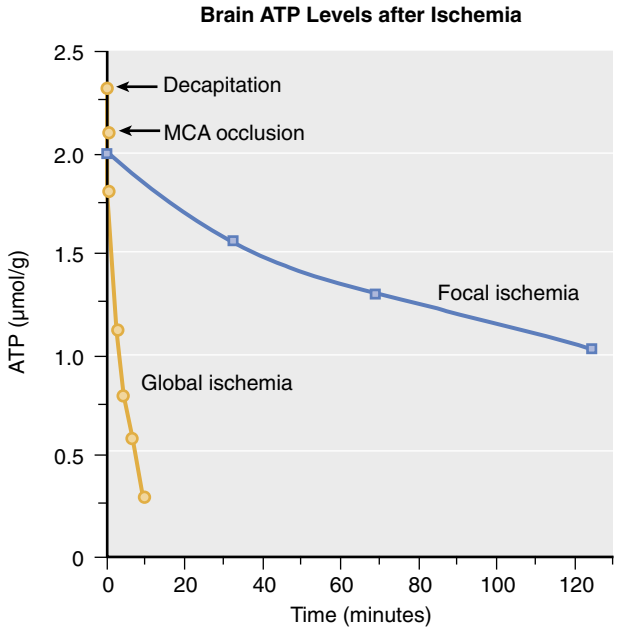

Figure 13-15 Comparison of rates of failure of energy supply (adenosine triphosphate) in complete global ischemia (produced by decapitation in dogs[254]) and in incomplete focal ischemia (middle cerebral artery [MCA] occlusion in monkeys[253]). In the presence of residual CBF, energy supply failure is substantially delayed.

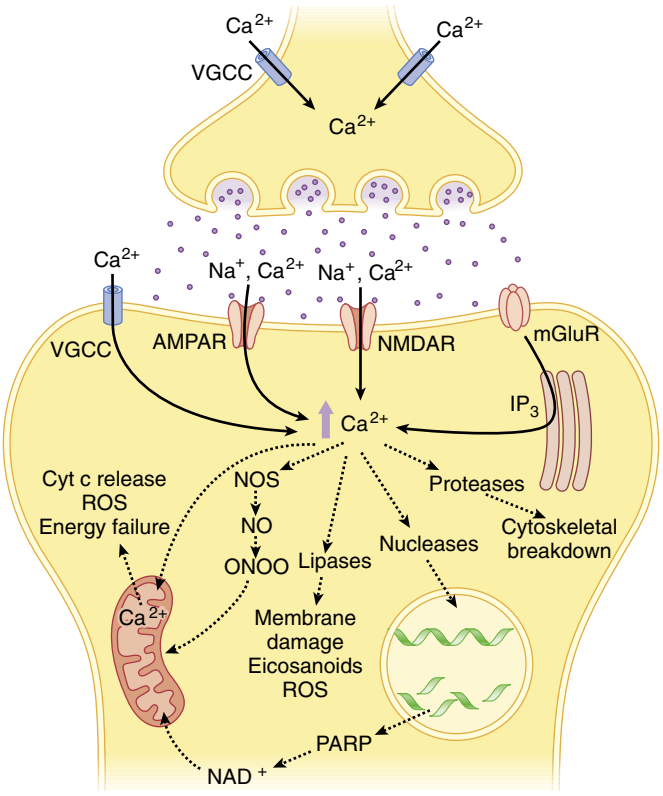

Figure 13-16 During ischemia, depletion of adenosine triphosphate leads to neuronal depolarization and the subsequent release of supranormal quantities of neurotransmitters, especially glutamate. Excessive stimulation of ligand-gated channels and the simultaneous opening of voltage-dependent Ca^{2+} channels permit rapid entry of Ca^{2+} into neurons. Stimulation of metabotropic glutamate receptors generates inositol 1,4,5-triphosphate (IP_3), which causes release of Ca^{2+} from the endoplasmic reticulum (ER)/mitochondria. Activation of the α-amino-3-hydroxy-5-methyl-4-isoxazopropionic acid receptor (AMPAR)-gated subset of glutamate receptors also permits excessive entry of sodium (Na^+). Excessive free Ca^{2+} results in activation of numerous enzymes: protease activation causes breakdown of the cytoskeleton of the neuron; lipases damage plasma membrane lipids and release arachidonic acid, which is metabolized by cyclooxygenases and lipooxygenases to yield free radicals and other mediators of cell injury; activation of nitric oxide synthase (NOS) leads to release of nitric oxide (NO) and, in turn, the generation of peroxynitrite (ONOO), a highly reactive free radical; and activated endonucleases damage DNA, thereby rendering the neuron susceptible to apoptosis. Injury to mitochondria leads to energy failure, generation of free radicals, and release of cytochrome *c* (Cyt c) from the mitochondria; the latter is one of the means by which neuronal apoptosis is initiated. mGluR, metabotropic glutamate receptor; NAD^+, oxidized form of nicotinamide adenine dinucleotide; NMDAR, *N*-methyl-D-aspartate receptor; PARP, poly-ADP-ribose polymerase; ROS, reactive oxygen species; VGCC, voltage-gated calcium channels.

by activated proteases. These enzymes also degrade a number of the protein constituents of the neuron. Lipases attack cellular lipids and produce membrane damage. An important lipase, phospholipase A_2, releases fatty acids such as arachidonic acid from membranes. Metabolism of arachidonic acid to prostaglandins and leukotrienes by cyclooxygenase and lipoxygenase is accompanied by the generation of superoxide free radicals. The latter, in combination with other free radicals generated in response to mitochondrial injury, can lead to lipid peroxidation and membrane injury. Prostaglandins and leukotrienes also evoke an inflammatory response and are powerful chemotactic drugs. Activation of platelets within cerebral microvessels, as well as influx of white blood cells into damaged areas, aggravates ischemic injury by occluding the vasculature.

DNA damage is also an important event during ischemic neuronal injury. Generation of free radicals from arachidonic acid metabolism, from injured mitochondria, and from the production of peroxynitrite from NO leads to oxidative injury to DNA. Activation of endonucleases also produces DNA strand breaks. Under normal circumstances, DNA injury results in the activation of poly-ADP-ribose polymerase (PARP), an enzyme that participates in DNA repair. With excessive DNA injury, PARP activity increases dramatically, and this can lead to the depletion of nicotinamide adenine dinucleotide (NAD), a substrate of PARP. NAD is also an important coenzyme in energy metabolism, and its depletion further exacerbates energy failure.

Lactate formation is an additional element of the pathophysiologic process. Lactic acid is formed as a result of the anaerobic glycolysis that takes place after failure of the supply of oxygen. The associated decline in pH contributes to deterioration of the intracellular environment. An increased preischemic serum glucose level may accelerate this process by providing additional substrate for anaerobic glycolysis.

NO, which has emerged as a probable mediator of CBF changes in many normal physiologic states (see the preceding sections), is also of relevance to the pathophysiology of ischemia. NO is, in fact, a weak free radical that in turn leads to the generation of a more reactive species (peroxynitrite), and it is a "killer substance" used by macrophages. In cerebral ischemia, NO is probably both friend and foe. It is likely that during a period of focal ischemia, the vasodilating effect of NO (probably constitutively elaborated NO of endothelial origin) serves to augment collateral CBF. However, in the postischemic phase, NO (probably derived from neurons or macrophages) contributes to neuronal injury.

Collectively, the simultaneous and unregulated activation of a number of cellular pathways overwhelms the reparative and restorative processes within the neuron and ultimately leads to neuronal death.

Nature of Neuronal Death

Neuronal death that occurs in response to these processes has been categorized as necrotic or apoptotic in nature (see Chapter 98). Necrotic death of neurons, mediated by excitotoxic injury, is characterized by rapid cellular swelling, condensation and pyknosis of the nucleus, and swelling of the mitochondria and endoplasmic reticulum. A characteristic of these necrotic neurons is the presence of acidophilic cytoplasm.[256] Necrotic neuronal death results in local infiltration of the brain by inflammatory cells. A consequence of this inflammation is a considerable amount of collateral damage.

Neuronal apoptosis, a form of cellular suicide, has also been demonstrated in a variety of models of cerebral ischemia. Apoptosis is characterized by chromatin condensation, involution of the cell membrane, swelling of mitochondria, and cellular shrinkage. In the later stages of apoptosis, neurons fragment into several apoptotic bodies, which are then cleared from the brain.[256] The lack of a substantial inflammatory response to apoptotic death limits injury to surrounding neurons that have survived the initial ischemic insult.

A number of biochemical pathways that lead to apoptosis have been described. Initiation of apoptosis by the release of cytochrome *c* from injured mitochondria has been studied the most (Fig. 13-17). Cytochrome *c* is restricted from the cytoplasm by the outer mitochondrial membrane.[257] When mitochondria are injured, pores within the outer membrane allow cytochrome *c* to be released into the cytoplasm, where it interacts with procaspase-9 and apoptosis-activating factor (APAF) to produce an apoptosome. Procaspase-9 undergoes activation by proteolytic cleavage. Activated caspase-9 then activates caspase-3. The latter serves as an executor of apoptosis by cleaving a number of protein substrates that are essential in DNA repair (such as PARP). Activation of caspase-3 can also occur by inflammatory signaling via tumor necrosis factor-α (TNF-α) and activation of caspase-8.[258] It should be noted that the neuronal injury that occurs in response to ischemia cannot easily be divided into necrosis or apoptosis. The

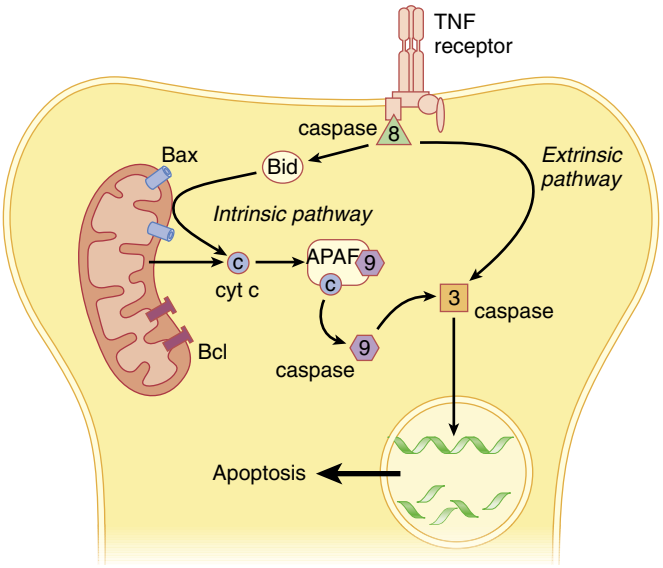

Figure 13-17 Cellular processes that lead to neuronal apoptosis. Cytochrome *c* (cyt c), which is normally restricted to the space between the inner and outer mitochondrial membranes, is released in response to mitochondrial injury. Cytochrome *c*, in combination with apoptosis-activating factor (APAF), activates caspase-9 by proteolytic cleavage. Activated caspase-9 then leads to activation of caspase-3. This enzyme cleaves a number of substrates, including those necessary for DNA repair. Within the mitochondria, Bax augments and Bcl prevents the release of cytochrome *c*. Release of cytochrome *c* can also be initiated by Bid, a substance that is activated by caspase-8 via tumor necrosis factor (TNF) signaling. In addition, caspase-8 can directly activate caspase-3. Excessive activation of poly-ADP-ribose polymerase (PARP), an enzyme integral to DNA repair, depletes cellular stores of oxidized nicotinamide adenine dinucleotide (NAD^+). Depletion of NAD^+ further exacerbates the energy failure because of its critical role in energy metabolism.

nature of neuronal death probably encompasses a spectrum in which some neurons undergo necrosis or apoptosis whereas others undergo cell death that has features of both necrosis and apoptosis.

Timing of Neuronal Death

The traditional concept of ischemic injury was that neuronal death was restricted to the time of ischemia and during the early reperfusion period. However, more recent data indicate that postischemic neuronal injury is a dynamic process in which neurons continue to die for a long period after the initiating ischemic insult (Fig. 13-18).[259] This delayed neuronal death, which was first demonstrated in models of global cerebral ischemia, has been demonstrated during focal ischemia as well. The extent of delayed neuronal death depends on the severity of the ischemic insult. With severe ischemia, most neurons undergo rapid death. With more moderate insults, neurons that survive the initial insult undergo delayed death. This ongoing neuronal loss contributes to the gradual expansion of cerebral infarction after focal ischemia. In experimental studies, evidence of cerebral inflammation, which can theoretically contribute to further injury, has been demonstrated even 6 to 8 months after the primary ischemia.

The occurrence of delayed neuronal death has important implications for the evaluation of studies in which neuroprotective strategies are being investigated. A wide variety of interventions have shown neuroprotective efficacy in studies in which the extent of injury is evaluated within 3 to 4 days after ischemia. However, this neuroprotective efficacy may not be sustained. Recent data indicate that cerebral infarction undergoes gradual expansion and that a reduction in injury attributed to a particular therapeutic intervention is no longer apparent when the injury is evaluated after a long postischemic recovery period.[259] Long-term (>1 month) evaluation of the efficacy of a particular intervention is therefore important.

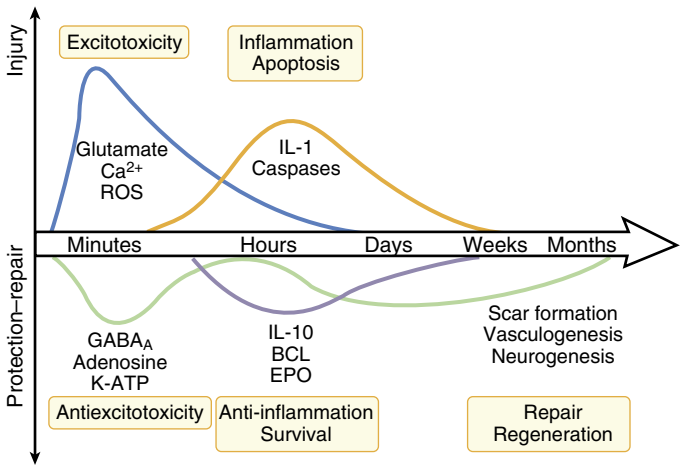

Figure 13-18 Time course of neuronal death. Excitotoxic (glutamate-mediated) injury results in neuronal death within the first few hours after the onset of ischemia. Brain tissue injury elicits an inflammatory response, an important process in removal of injured tissue and in healing, that leads to a substantial amount of collateral damage. Inflammation-mediated neuronal death can continue for several days. Neuronal apoptosis can occur in injured neurons that survived the initial insult. Apoptotic neuronal death has been demonstrated to occur for many days after the initiating ischemic insult. It is now apparent that ischemic neuronal death is a dynamic process in which neurons continue to die for a long period. *(Adapted from Dirnagl U, Iadecola C, Moskowitz M: Pathobiology of ischaemic stroke: An integrated view. Trends Neurosci 22:391-397, 1999.)*

Brain Protection

The literature on cerebral ischemia and brain protection is vast, and a detailed discourse on this topic is beyond the scope of the present discussion. A number of excellent recent reviews on the subject are available.[256,260-262]

Considerations Relevant to Complete Global Ischemia (Cardiac Arrest)

Maintenance of adequate perfusion pressure after cardiac arrest is of considerable importance. Hypotension developing after resuscitation from cardiac arrest may aggravate the microcirculatory and vasospastic processes occurring at this time and increase brain damage. A late phase of intracranial hypertension may occur and is due to the development of extensive cerebral edema, probably both vasogenic and cytotoxic in etiology, associated with brain necrosis. Attempts to control this type of intracranial hypertension with osmotherapy usually fail. ICP monitoring is not generally used because the patients in whom these delayed increases in ICP develop have sustained massive tissue damage.

Both barbiturates and calcium channel blockers have been administered after cardiac arrest. The former are ineffective.[263] In a small cohort (51 patients) of cardiac arrest victims, nimodipine was shown to improve CBF but not neurologic outcome.[264] In a second trial in approximately 150 cardiac arrest victims, no overall benefit in neurologic outcome was observed.[265] However, a subset of patients in whom initiation of advanced life support was delayed for more than 10 minutes demonstrated improved survival. This single study cannot serve as justification for the administration of nimodipine after cardiac arrest, especially in the face of the unequivocally negative results of the multicenter lidoflazine cardiac arrest study.[266] Once again, the important therapeutic objectives are maintenance of normocapnia and normotension, normalization of systemic pH, avoidance of hyperthermia, and prevention and treatment of seizures.

Induced mild hypothermia is effective in reducing mortality and morbidity in patients who sustain a cardiac arrest.[267] Induction of mild hypothermia in the range of 32°C to 34°C for a period of about 24 hours improved neurologic outcome and survival 6 months after cardiac arrest in comparison to a normothermic group. Mild hypothermia was induced without difficulty. Passive rewarming of patients was accomplished slowly over a period of 8 hours. The incidence of complications was similar to that in the control normothermic group. This important study is one of the first to demonstrate the feasibility and efficacy of induced hypothermia as a treatment to prevent injury from global ischemia. Undoubtedly, induced hypothermia will now be added to the armamentarium for the treatment of cerebral complications of cardiac arrest.

Considerations Relevant to Focal (Incomplete) Ischemia

Before discussing individual anesthetics, it should be noted that a general theme that can be extracted from the protection-by-anesthetics literature, in particular for anesthesia with volatile anesthetics, is that anesthesia per se is protective. It appears that for undefined reasons, reducing the level of systemic stress associated with a standardized experimental insult results in an

improved outcome.[268,269] In reviewing the protection-by-anesthetics literature, readers should be conscious of the possibility that the protective benefit ascribed to an intervention with an anesthetic drug may in fact be the product of exaggeration of the injury in a high-stress control state, such as N_2O "sedation."

Barbiturates. There have been numerous demonstrations of the protective efficacy of barbiturates in focal cerebral ischemia in animals[270-272] and a single demonstration of effectiveness in a human.[273] The effect has been attributed principally to suppression of CMR. However, the effects of CBF redistribution and free radical scavenging[274] have been suggested to contribute, and there is evidence that CMR suppression is not the sole mechanism.[275] Suppression of CMR might logically be expected to be of benefit to brain regions in which oxygen delivery is inadequate to meet normal demands but is sufficient to allow energy consumption by some on-going electrophysiologic activity (i.e., in which the EEG was abnormal but not flat). Such regions are likely to be limited in size in the setting of focal ischemia, yet several of the animal investigations suggest a very substantial protective effect.[270,271] Review of these experiments reveals that the methods used to monitor and maintain temperature, though accepted at the time, were below the standards that have evolved from more recent understanding of the effects of both deliberate[276,277] and inadvertent hypothermia. Unrecognized cerebral hypothermia may well have been a factor in some of the cited investigations, and it is therefore possible that the protective efficacy of barbiturates may have been overestimated. Although more recent publications involving suitable temperature control methods do in fact indicate a protective effect by barbiturates,[275,278,279] the magnitude of that effect was modest when compared with the results of earlier studies. Barbiturate-induced EEG suppression in an already anesthetized patient may still be logical therapy when it can be applied before or early in the course of a period of temporary focal ischemia (e.g., temporary occlusion during aneurysm surgery). However, the decision to institute such therapy should be made only after consideration of the risk of the occlusive event, the patient's cardiovascular status, and the physician's willingness to accept the possible prolongation of arousal, together with an objective view of the probable magnitude of the protective effect.

Numerous investigations in animals and humans have failed to demonstrate any protective effect of barbiturates in the setting of global cerebral ischemia (e.g., cardiac arrest).[263]

Because CMR suppression has been the presumed mechanism of effect, barbiturates have traditionally been administered to produce maximal reduction of CMR (which is nearly complete when EEG burst suppression has been achieved). However, data presented by Warner and colleagues[275] demonstrated that the same protective benefit (expressed as reduction of infarct volume) could be achieved with a third of the burst-suppression dose. This raises a clinically important issue. The various barbiturates (thiopental, thiamylal, methohexital, pentobarbital) have similar effects on CMR and have generally been assumed to have equal protective efficacy. However, if the mechanism of protection is a pharmacologic effect other than reduction in CMR, is it reasonable to assume equivalence among the barbiturates? Recent data suggest that the neuroprotective efficacy of barbiturates is not similar. In a direct comparison of three clinically used barbiturates, methohexital and thiopental, but not pentobarbital, reduced injury in an animal model of focal ischemia.[280] These data suggest that mechanisms other than or at least in addition to metabolic suppression may contribute to the protective effect of barbiturates.

Volatile Anesthetics. Isoflurane is also a potent suppressant of CMR in the cerebral cortex, and EEG evidence suggestive of a protective effect in humans has been reported.[250] In comparison to the awake or N_2O-fentanyl–anesthetized state, isoflurane is neuroprotective in models of hemispheric,[281] focal,[282] and nearly complete ischemia.[283,284] Of interest is the recent observation that isoflurane's neuroprotective efficacy is not sustained.[285] When injury is evaluated 2 days after ischemia, a robust reduction in injury is observed with isoflurane anesthesia. However, by 14 days this reduction in injury was not apparent. These data indicate that neuronal injury continues well into the postischemic recovery period and that the neuroprotection that is evident shortly after ischemia may not persist for the long term. More recent data have shown that long-term neuroprotection with isoflurane is achievable under conditions in which the severity of ischemia is limited and restoration of blood flow after ischemia is complete.[286] The neuroprotective effect of isoflurane is not substantially different from that of other volatile anesthetics. Sevoflurane reduces ischemic injury in animal models of focal[287] and hemispheric ischemia[288]; its efficacy is not different from that of halothane. Desflurane also reduces neuronal injury to the same extent that isoflurane does.[289] The available data therefore suggest that adequate anesthesia per se may have a protective effect[268,269] versus the awake state, but there does not appear to be any difference in neuroprotective efficacy among the volatile anesthetics.

Xenon. The inert gas xenon exerts its anesthetic action by noncompetitive blockade of NMDA receptors. As such, it is logical to suspect that it might provide neuroprotection against excitotoxic injury. The neuroprotective efficacy of xenon has been demonstrated against oxygen-glucose deprivation in vitro,[290] focal ischemia in vivo in mice,[291] and cardiopulmonary bypass–induced cognitive dysfunction in rats.[292] Of interest are observations that simultaneous administration of *subanesthetic* doses of xenon in combination with either hypothermia[293] or isoflurane[294] significantly reduces neuronal injury and improves neurologic function in a neonatal rodent model of hypoxia-ischemia; this protective effect was apparent as late as 30 days after injury. Moreover, administration of xenon has been shown to have a preconditioning effect on the brain[295]; previous exposure reduces the vulnerability of the brain to ischemic injury. Anesthetic drugs that have activity at NMDA receptors (ketamine) and γ-aminobutyric acid type A ($GABA_A$) receptors (volatile anesthetics, barbiturates, benzodiazepines, propofol) have been shown to cause neuronal injury in rodent neonatal pups during the critical period of synaptogenesis.[296] Although xenon has antagonist activity at NMDA receptors, the evidence to date suggests that it does not lead to apoptosis in the developing brain.[297] Note should be made, however, that long-term neuroprotection with xenon has not yet been demonstrated in adult experimental subjects. The specific use of xenon for the purpose of neuroprotection awaits results from outcome studies in humans.

Propofol. EEG suppression can also be achieved with clinically feasible doses of propofol. Anecdotal information suggests that it is being used to provide "protection" during both aneurysm surgery[298] and carotid endarterectomy. In experimental models of cerebral ischemia, the extent of neurologic injury in propofol-anesthetized animals was similar to that in halothane-anesthetized animals.[299] Given the previous demonstration that

halothane can reduce injury, these data provide indirect evidence of propofol's neuroprotective efficacy. In a more recent investigation, cerebral infarction was significantly reduced in propofol-anesthetized animals in comparison to awake animals.[300] Direct comparison of propofol to pentobarbital has also demonstrated that cerebral injury after focal ischemia is similar in animals anesthetized with the two drugs.[301] Similar to the situation with volatile anesthetics, initial investigations revealed that propofol protection is not sustained.[302] Durable protection with propofol is achievable if the severity of the ischemic insult is mild.[303] Collectively, these data are consistent with the premise that propofol can reduce ischemic cerebral injury.

Etomidate. Etomidate was proposed as a potential protective anesthetic in the setting of aneurysm surgery.[304] It too produces CMR suppression to an extent equivalent to barbiturates, and like the barbiturates, etomidate is an agonist at the (inhibitory) $GABA_A$ receptor. To the contrary, in an experimental model of focal ischemia, the volume of injury was not reduced by etomidate relative to a 1.2 MAC halothane-anesthetized control group. In fact, the volume of injury with etomidate was significantly larger than that in the control group. In patients subjected to temporary intracranial vessel occlusion, administration of etomidate results in greater tissue hypoxia and acidosis than equivalent desflurane anesthesia does. The aggravation of injury produced by etomidate (an imidazole) may be related to direct binding of NO as a consequence of etomidate-induced hemolysis[305] combined with direct inhibition of the NO synthase enzyme by etomidate. Therefore, there is no scientific support for the current use of etomidate for "cerebral protection."

Calcium Channel Blockers. It is now established clinical practice to administer nimodipine orally (the intravenous preparation is not approved for clinical use in North America) for 21 days beginning as soon as possible after subarachnoid hemorrhage.[306] However, it has not yet become standard practice to administer nimodipine or any other calcium channel blocker routinely after neurologic stroke occurring in the operating room or in any other environment. Despite favorable results in small trials, not all investigations in stroke victims have confirmed the benefits of nimodipine.[307]

Other Anesthetics. A remarkable number of anesthetics have shown neuroprotective efficacy in animal studies. However, to date, large-scale randomized trials of a variety of anesthetics in patients with stroke have not demonstrated neuroprotection for any drug. With the exception of tissue plasminogen activator (tPA) for thrombolysis and the calcium channel blockers nimodipine and nicardipine for the management of subarachnoid hemorrhage, pharmacologic neuroprotective anesthetics are not available for the treatment of patients with cerebral ischemia. Details about drugs that have undergone clinical trials and those that are currently being investigated in humans can be found at the Stroke Trials Registry (www.strokecenter.org/trials/TrialDetail.aspx?tid=338) of Washington University, St. Louis, MO.

Cerebral Ischemia: Influence of Physiologic Variables

Cerebral Perfusion Pressure. Measures designed to augment CBF (an important determinant of energy supply) are also important. In the "ischemic penumbra" (described earlier), small improvements in CBF have the potential to prolong neuronal survival substantially. Maintenance of high-normal CPP can augment collateral perfusion pressure and maintain CBF[308] and has been shown to result in improvement in various neurophysiologic parameters, including neurologic function.[309,310] By contrast, hypotension can reduce CBF and exacerbate injury. In trials of nimodipine in patients with acute stroke, a reduction in blood pressure of 10% to 20% increased the probability of an adverse outcome (either death or dependency) fourfold,[311] thus emphasizing the adverse impact of blood pressure reduction on an injured brain. Therefore, in patients with cerebral ischemia, hypotension should be treated promptly and normotension restored. Although it is quite obvious that the target MAP should be based on knowledge of a patient's preexisting blood pressure, there are insufficient data in humans to provide specific guidelines. In the majority of patients, maintenance of MAP in the 70– to 80–mm Hg range should be adequate. The available data provide support for reducing blood pressure to less than 180/105 mm Hg in patients with stroke who have been treated with tPA in the hope of reducing the incidence of hemorrhage into the ischemic brain.[312] In addition, blood pressure augmentation to a systolic pressure of 180 to 220 mm Hg in patients with subarachnoid hemorrhage–induced vasospasm and to a CPP of greater than 60 mm Hg in patients with traumatic brain injury is reasonable.[312] Note, however, that augmentation of CPP in the high-normal range carries the inadequately explored risks of increased edema and hemorrhagic infarction if used as support during more than brief periods of ischemia, particularly when several hours has elapsed since the onset of ischemia.

Carbon Dioxide Tension. Hypercapnia has the potential to cause intracerebral steal and may worsen intracellular pH. Despite some support for the occurrence of a favorable so-called Robin Hood or inverse steal,[313] hypocapnia has not generally proved effective in either laboratory or clinical settings.[314-316] Pending further information and in the absence of a means of verifying the perfusion response to manipulation of $Paco_2$, normocapnia remains standard practice.

Temperature. Hypothermia is firmly and justifiably established as the principal cerebral protective technique for circulatory arrest procedures (see Chapter 48). It unequivocally enhances cerebral tolerance for episodes of ischemia. For deep hypothermia, this effect has been presumed to be largely a function of the reduction in CMR. Although pharmacologic drugs such as barbiturates reduce only the component of CMR associated with electrophysiologic "work" (about 60% of $CMRO_2$ in the awake state), hypothermia causes a reduction in both electrophysiologic energy consumption and the energy utilization related to maintenance of cellular integrity, and mild hypothermia may preferentially suppress the latter.[317,318] Recently, there has been a surge of interest in *mild* hypothermia as a cerebral protective technique. A substantial number of laboratory studies have demonstrated that mild degrees of hypothermia (2°C to 4°C) during an episode of ischemia can confer substantial protection as measured histologically.[276,277] In addition, there is also evidence from animal studies that hypothermia initiated in the immediate postischemic period confers a protective benefit.[319,320]

In light of this dramatic protective effect of mild hypothermia, its use in the operating room setting has been advocated. Proponents of its use argue that hypothermia is readily achieved and not accompanied by significant myocardial depression or arrhythmias. In addition, the patient can easily be rewarmed in the operating room after the risk of ischemia has subsided. Results of a pilot study clearly demonstrated a trend toward improved

neurologic outcome in hypothermic patients undergoing intracranial aneurysm clipping.[321] Unfortunately, the subsequent definitive trial did not demonstrate any improvement in outcome that could be attributable to hypothermia.[322] However, it should be noted that the majority of the patients in that study had subarachnoid hemorrhage of grades I, II, and III. In addition, the number of patients who had temporary clips applied in excess of 20 minutes was quite small (five to six patients). Consequently, an argument has been made that mild hypothermia may well be of benefit in patients with high-grade aneurysms or in those in whom the complexity of the aneurysm clipping is such that prolonged temporary clipping may be required. Given that temperature reduction takes some time, the decision to induce hypothermia must be made in advance. Therefore, the therapeutic use of hypothermia may be considered in such "high-risk" patients.

The application of mild hypothermia after head injury reduced ICP[323] and improved neurologic outcome[324] in pilot trials. Of note is the finding that complications attributable to hypothermia were not observed. A subsequent multicenter trial of hypothermia in head-injured patients, however, failed to confirm the findings of the pilot studies.[325] Induction of mild hypothermia did not improve long-term neurologic outcome. Note should be made, however, of the post hoc finding that outcome in patients younger than 45 years who were initially hypothermic was worse if these patients were rewarmed; these data suggest that such patients should be rewarmed over a prolonged period.

A number of clinical trials of induced hypothermia in a limited number of stroke patients have been conducted. To date, these trials have demonstrated the feasibility of inducing hypothermia in the range of 33°C to 35°C, even in patients who are not subjected to endotracheal intubation and mechanical ventilation.[326] Hypothermia was associated with improved ICP and CPP. However, complications, particularly thrombocytopenia, bradycardia, ventricular ectopy, hypotension, and infection, are frequent. In addition, an intractable increase in ICP can occur during rewarming, even if the elevation in temperature is gradual and accomplished over a period of several hours. These side effects attest to the need to conduct proper randomized trials to properly evaluate the efficacy of mild hypothermia in stroke patients. Such trials are currently under way.

Data regarding the application of mild hypothermia in survivors of cardiac arrest are more positive. Two recent trials have demonstrated that induction of hypothermia (32°C to 34°C) after successful resuscitation from cardiac arrest resulted in a significantly better neurologic outcome 6 months after the arrest.[267,327] These studies demonstrate the clinical efficacy of hypothermia for purposes of reducing ischemic cerebral injury and provide support for the use of intraoperative hypothermia in patients who are considered to be at high risk.

By contrast, increases in brain temperature during and after ischemia aggravate injury.[328] An increase of as little as 1°C can dramatically increase injury. Ischemia that normally results in scattered neuronal necrosis produces cerebral infarction when body temperature is elevated. It therefore seems prudent to avoid hyperthermia in patients who have suffered an ischemic insult or in those who are risk for cerebral ischemia. In the operating room, hyperthermia is seldom a problem (witness our efforts to prevent hypothermia). One situation in which body temperature is often allowed to increase is during rewarming after hypothermic cardiopulmonary bypass. In that situation, hyperthermia (core body temperature in excess of 38°C) is not uncommon. The suggestion that increases in temperature in excess of 37°C to 38°C are detrimental has some merit given the recent information regarding the deleterious effect of hyperthermia.

Glucose. Withholding of glucose-containing solutions in situations in which cerebral ischemia may occur is now an established practice. The practice is based on numerous demonstrations in animal models of brain and spinal cord ischemia that elevation of plasma glucose before episodes of either complete or incomplete ischemia results in aggravation of neurologic injury. However, it should be noted that the majority of investigations have involved adult animals and that there is less certainty about the adverse effects of hyperglycemia in immature subjects, such as neonates.[329] Furthermore, it should be noted that only some[330,331] and not all[332] of the investigations in humans have provided confirmation of an independent effect of serum glucose on neurologic outcome. Nonetheless, in long-term outcome studies, hyperglycemia (diabetic and nondiabetic) has been shown to be an independent predictor of poor outcome.[331] In the National Institutes of Health–sponsored recombinant tPA stroke trial, hyperglycemia was associated with significantly lower odds for desirable clinical outcomes and a higher incidence of intracranial hemorrhage.[333] These data prompted a randomized clinical trial of the efficacy of insulin administration to patients with acute stroke. Although the trial was underpowered, the results showed that administration of insulin to control blood glucose levels in stroke patients did not improve outcome 3 months after stroke.[334] A recurrent theme in the discussion of these studies is that glucose elevation may be the *result* of the stress associated with a severe insult, either ischemic or traumatic, rather than its *cause.* In addition, the inevitable questions of whether and how quickly immediate prerisk treatment of an elevated plasma glucose level with insulin reduces risk to normoglycemic levels have not been examined thoroughly. It is our opinion that at this juncture, acute insulin administration (with its attendant risk of hypoglycemia) in patients with modest glucose elevation (~150 mg/dL) in the operating room setting is not yet justified.

By contrast, hypoglycemia is also associated with cerebral injury. With a gradual reduction in blood glucose values of about 40 mg/dL, a shift in EEG frequencies from α and β toward δ and θ occurs.[335] Below a blood glucose level of 20 mg/dL, suppression of the EEG (flat) is observed. Persistence of this level of hypoglycemia results in seizure activity and neuronal injury, particularly to the hippocampus.

Seizures, pH. Normalization of systemic pH, prevention and treatment of seizures, which dramatically increase CMR, and control of ICP and CPP are all, though mundane and lacking in appeal of the pharmacologic silver bullet, important elements of brain protection and resuscitation.

Volume/Hematocrit Manipulation. Although hemodilution has not proved effective in studies of human stroke, both laboratory and human data support the practice, and it is an established part of management of the ischemia associated with vasospasm. However, the data do not currently justify routine hemodilution (a hematocrit of 30% to 35% is the theoretical optimum) in patients in whom focal ischemia *might* occur in the operating room.[336] On the other hand, the potentially deleterious effects of hemoconcentration should help further suppress the out-of-date notion that neurosurgical patients should be "run dry." An elevated hematocrit, because of viscosity effects, reduces CBF.[7] It is our unsubstantiated opinion that in anticipation of a

procedure wherein incomplete ischemia might occur, such as carotid endarterectomy, a hematocrit in excess of 55% should be lowered by preoperative phlebotomy.

Summary of Anesthetics and Neuroprotection

In comparison to the awake or lightly sedated state, the vulnerability of the brain to ischemic injury is reduced under anesthesia. Volatile anesthetics, barbiturates, propofol, xenon, and ketamine have all been shown to reduce injury in experimental models, and there is support for the premise that administration of any of these anesthetics reduces injury in comparison to a pure nitrous oxide–narcotic anesthetic. However, direct comparison has not demonstrated the superiority of any one agent (or combination) over another. Therefore, based on the available data, use of a specific anesthetic or anesthetic regimen for the purpose of brain protection in the clinical setting cannot be advocated. A possible exception is barbiturate administration. In the setting of cardiac surgery under cardiopulmonary bypass, administration of barbiturates has been shown to reduce cerebral injury in humans.[273] The cardiovascular depression and hemodynamic instability attendant on the use of barbiturates have significantly restricted their use clinically. Of considerable importance is the observation that the neuroprotective efficacy of anesthetic drugs is achieved only by strict attention to maintenance of physiologic homeostasis; in fact, the potential for exacerbation of cerebral injury, either traumatic or ischemic, with physiologic mismanagement is significantly greater than the modest protection afforded by pharmacologic drugs. Accordingly, with respect to brain protection, efforts should be focused on maintenance of physiologic parameters (perfusion pressure, oxygenation, normocapnia, temperature management, control of hyperglycemia, and seizure prophylaxis) within the appropriate range and less on pharmacologic or anesthetic drugs to reduce cerebral injury.

Deferring Elective Procedures after Stroke

The risk of extension of cerebral infarction in the event of subsequent anesthesia and surgery has not been studied systematically. In patients who have suffered a stroke, CBF undergoes marked changes. Areas of both high and low CBF occur, and stabilization of regional CBF and CMR is apparent after about 2 weeks.[337] Loss of normal vasomotor responses (CO_2 responsiveness, autoregulation) in the early postinsult period is very common,[338-340] and these changes persist beyond 2 weeks in a small percentage of stroke victims.[339,340] BBB abnormalities, as reflected by accumulation of CT contrast material or brain scan isotopes, are still present 4 weeks after the insult,[341] and the histologic resolution of large infarcts is not complete for several months. The information available does not allow a definite statement regarding how long elective procedures should be deferred. A 6-week delay should give some assurance of the probable recovery of autoregulation, CO_2 responsiveness, and BBB integrity. However, the size and location of the infarction should be weighed. A small infarction in silent cortex may give wider latitudes than a large lesion that has resulted in a paresis that is still resolving. A small prospective study suggested that in patients with nondisabling stroke, early carotid endarterectomy can be safely performed within 2 weeks of the stroke.[342] However, in patients with larger strokes, pending other information, it seems reasonable to defer elective surgery for at least 4 weeks after a cerebral vascular accident and preferably for 6 weeks from the point at which a stable postinsult neurologic state has been achieved.

Chronic Arterial Hypertension

A recurrent concern is that of acceptable levels of blood pressure reduction in chronically hypertensive patients. Firm guidelines have not been established. However, from the vantage of cerebral well-being, limiting elective MAP reduction to 30% to 35% of resting mean levels seems appropriate for both hypertensive and normotensive patients. It is reasonable that the same guidelines might apply in both populations because in chronic hypertension, both the lower and upper limits of autoregulation are shifted to the right with apparently little distortion.[343]

The rationale for a limit of 30% to 35% is as follows. It has been demonstrated that MAP reductions of 50% in nonanesthetized patients, both normotensive and hypertensive, will commonly produce reversible symptoms of cerebral hypoperfusion.[343-345] Although even greater reductions will probably be tolerated provided that exposures are brief, the hematocrit is reasonable, and the cerebral vasculature is patent, we counsel against it. A reduction in MAP of this magnitude will significantly increase the probability of CPP being close to or below the LLA, thereby reducing cerebrovascular reserve. It has been demonstrated that a 25% reduction in MAP will bring both normotensive and hypertensive patients to the LLA.[343] As the reduction in MAP exceeds 25% of baseline, CBF values will be below normal, albeit in subjects free of occlusive vascular disease, but above the threshold for neurophysiologic dysfunction or injury (see Fig. 13-4). However, physiologic reserve is being encroached upon, thereby leaving little margin for error or for other causes of impaired cerebral oxygen delivery (low hematocrit, unrecognized cerebrovascular disease).

It has been demonstrated in animals that treatment of chronic hypertension can restore the LLA to normal.[346,347] A similar phenomenon has been observed in humans by Strandgaard, although restoration was incomplete and had failed to occur after as long as 12 months of treatment in some subjects.[343] It is an unexplored possibility that the extent of restoration of the LLA with antihypertensive therapy is agent dependent. Some may restore the LLA more effectively than others do. In particular, angiotensin-converting enzyme inhibitors have been shown to decrease the LLA acutely in both normotensive and hypertensive subjects.[348,349]

Intracranial Hypertension

Control of intracranial hypertension is discussed in detail in Chapter 63.

Brain Tumors

There are few data regarding the physiology of intracranial tumors. Arbit and colleagues[350] measured CBF in cerebral tumors with laser-Doppler technology. In general, they found that tumors had lower CBF than normal brain did. Autoregulation was occasionally apparent. Vascular responsiveness to changes in Pao_2[351] and $Paco_2$[352] are generally preserved in patients with gliomas. However, in some circumstances, hyperventilation can at times be associated with paradoxical increases in MCA flow velocity ipsilateral to the tumor.[353] Measurement of regional CBF in the area of the tumor might also be a useful predictor of the grade of intracranial gliomas; both regional CBF and regional CBV are

greater with higher-grade gliomas.[354] There is often considerable edema in association with intracranial tumors, and the radiologic extent of the edema (which presumably represents the extent of abnormal vessel leakiness) correlates with the severity of the elevation in ICP that occurs in association with intubation-related hypertension.[355] Edema formation in the peritumoral region can be characterized as either vasogenic with leakage of plasma proteins from the vascular space, hydrocephalic secondary to obstruction of CSF flow, or static as a result of venous obstruction by tumor.[356] Although the precise mechanisms by which edema formation occurs are not clear, loss of integrity of the tight junctions of components of the BBB, increased permeability induced by vascular endothelial growth factor expressed by tumors, and increased expression of leukotriene C_4 in peritumoral fluid probably play a role.[357] Osmotherapy with mannitol will effect a reduction in edema; however, with a permeable BBB, mannitol can diffuse into the peritumoral space and lead to rebound edema formation.[356] For acute reduction of ICP in the operating room, this is not a significant concern. Dexamethasone remains the mainstay of treatment of tumor edema; it causes a reduction in edema formation with little effect on edema reabsorption, a reduction in permeability of the BBB that can be seen as rapidly as 1 hour after administration,[358] and a modest reduction in tumor size. See Chapter 63 for a complete discussion.

Coma and Epilepsy

Regardless of its etiology, coma is associated with reductions in brain metabolism. In the case of lesions occurring in the reticular activating system, the reduction in CMR probably represents a normal physiologic adjustment to reduced functional activity. During generalized seizure activity, CMR and CBF may increase dramatically.[200] The intensive motor and brain activity associated with generalized seizures leads to the development of systemic and cerebral acidosis, often accompanied by a reduction in arterial oxygenation, an increase in $Paco_2$, and peripheral lactic acidosis. If generalized seizure activity continues unabated, arterial hypotension ensues. With muscular relaxation and measures ensuring adequate oxygenation and ventilation, the systemic acidosis and hypotension can be avoided and the severity of the cerebral acidosis diminished. During relatively brief episodes of continuous seizures, the brain seems able to meet the high metabolic demands.[214] However, even with effective ventilation and maintenance of perfusion pressure, when seizures continue for a prolonged period, they can lead to the development of irreversible neuronal damage.[359] Therapy aimed at interrupting the seizure and restoring a normal balance between cerebral metabolic demand and blood flow is indicated. Barbiturates, benzodiazepines, or other potent anticonvulsants are appropriate. Adequate ventilation, oxygenation, and maintenance of blood pressure are important adjunctive measures. Muscle relaxants must be viewed as purely symptomatic therapy because they do not alter the abnormal cerebral electrical activity.

The potentially injurious nature of seizures justifies attention to prevention. Practices vary. However, patients who have sustained a severe head injury or subarachnoid hemorrhage and any patient in whom a substantial cortical incision is planned are at risk, and prophylactic anticonvulsants should be considered.

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14 Neuromuscular Physiology and Pharmacology

Key Points

1. The neuromuscular junction provides a rich array of receptors and substrates for drug action. Several drugs used clinically have multiple sites of action, and muscle relaxants are not exceptions to the rule that most drugs have more than one site or mechanism of action. The major actions seem to occur by the mechanisms and at the sites described for decades: agonistic and antagonistic actions at postjunctional receptors for depolarizing and nondepolarizing relaxants. This description of neuromuscular drug action is a simplistic one. Neuromuscular transmission is impeded by nondepolarizers because they prevent access of acetylcholine to its recognition site on the postjunctional receptor.
2. If the concentration of nondepolarizer is increased, another, noncompetitive action—block of the ion channel—is superimposed. The paralysis is also potentiated by prejunctional actions of the relaxant, which prevents release of acetylcholine. The latter can be documented as fade that occurs with increased frequency of stimulation. A more accurate description of the effects of relaxants recognizes that the neuromuscular junction is a complex and dynamic system in which the phenomena produced by drugs are composites of actions that vary with drug, dose, activity in the junction and muscle, time after administration, presence of anesthetics or other drugs, and the age and condition of the patient.
3. Inhibition of postjunctional acetylcholinesterase by anticholinesterases increases the concentration of acetylcholine, which can compete with and displace the nondepolarizer and thus reverse the paralysis. These anticholinesterases also have other effects, including those on nerve terminals and on the receptor, by an allosteric mechanism. Cyclodextrins are a new class of compounds that reverse paralysis of only steroidal muscle relaxants by directly binding to them.
4. Depolarizing compounds initially react with the acetylcholine recognition site and, like the transmitter, open ion channels and depolarize the end-plate membrane. Unlike the transmitter, they are not subject to hydrolysis by acetylcholinesterase and therefore remain in the junction. Soon after administration of the drug, some receptors are desensitized and, although occupied by an agonist, they do not open to allow current to flow to depolarize the area.
5. If the depolarizing relaxant is applied in high concentration and allowed to remain at the junction for a long time, other effects occur, including entry of the drug into the channel to obstruct it or to pass through it into the cytoplasm. Depolarizing relaxants also have effects on prejunctional structures, and the combination of prejunctional and postjunctional effects plus secondary ones on muscle and nerve homeostasis results in the complicated phenomenon known as phase II blockade.
6. Intense research in the area of neuromuscular transmission continues at a rapid pace. Newer observations on receptors, ion channels, membranes, and prejunctional function reveal a much broader range of sites and mechanisms of action for agonists and antagonists.
7. Some of the other drugs used clinically (e.g., botulinum toxin) have effects on the nerve and therefore indirectly on muscle. Systemic infection with clostridial toxins (*Clostridium tetanus*, *Clostridium botulinum*) can lead to systemic paralysis as a result of decreased release of acetylcholine from the nerve terminal. Nondepolarizing muscle relaxants administered even for 12 hours or for prolonged periods can have effects on the postsynaptic receptor and simulate denervation (chemical denervation). In recognizing these sites and mechanisms, we begin to bring our theoretical knowledge closer to explaining the phenomena observed when these drugs are administered to living humans.
8. The most recent work seems to be focused on the postjunctional membrane and control of acetylcholine receptor expression in normal and diseased states. The presence or absence of mature and immature isoforms seems to complicate matters further. In certain pathologic states (e.g., stroke, sepsis, burns, immobilization, chronic use of relaxants), acetylcholine

receptors are upregulated, usually with expression of the immature isoform. More recently, another isoform of the acetylcholine receptor, previously described in neuronal tissues only, the α7 neuronal acetylcholine receptor, has been identified in muscle. These receptors have different functional and pharmacologic properties than conventional muscle postsynaptic receptors do. The altered functional and pharmacologic characteristics of the immature (γ-subunit) and neuronal (α7-subunit) receptors result in increased sensitivity to succinylcholine with hyperkalemia and resistance to nondepolarizers.

9. An area of increasing attention is control of the expression of mature versus the other two receptor isoforms. Re-expression of the immature γ and α7 receptors is probably related to aberrant growth factor signaling. Mutations in the acetylcholine receptor that result in prolonged open-channel time, similar to that seen with the immature receptor, can lead to a myasthenia-like state, even in the presence of normal receptor numbers. The weakness is usually related to the prolonged open-channel time. The role of the immature isoform of the receptor in the muscle weakness associated with critical illness such as burns is unknown.
10. Despite the fact that the neuromuscular junction is the most studied receptor, complete knowledge of its workings has not been achieved. This is an area of continuing interest for many researchers worldwide.

The physiology of neuromuscular transmission could be analyzed and understood at the most simple level by using the classic model of nerve signaling to muscle through the acetylcholine receptor (AChR). The mammalian neuromuscular junction is the prototypical and most extensively studied synapse. Research has provided more detailed information on processes that, within the classic scheme, can modify neurotransmission and response to drugs. One example is the role of qualitative or quantitative changes in AChRs that modify neurotransmission and response to drugs.[1-3] In myasthenia gravis, for example, the decrease in AChRs results in decreased efficiency of neurotransmission (and therefore muscle weakness)[4] and altered sensitivity to neuromuscular relaxants.[3] Another example is the importance of nerve-related (prejunctional) changes that alter neurotransmission and response to drugs.[3,5] At still another level is evidence that muscle relaxants act in ways that are not encompassed by the classic scheme of a unitary site of action. The observation that muscle relaxants can have prejunctional effects[6] or that some nondepolarizers can also have agonist-like stimulatory actions on the receptor[7] whereas others have effects not explainable by purely postsynaptic events[8] has provided new insight into some previously unexplained observations. Although muscle relaxants are known to have effects on the presynaptic and postsynaptic receptors of the neuromuscular junction, recent evidence indicates that they can react with nicotinic and muscarinic AChRs other than those in muscle, including receptors on the carotid sinus, on the vagus to the heart, and on bronchial smooth muscle.[9-11] Although this multifaceted action-response scheme makes the physiology and pharmacology of neurotransmission more complex, these added insights also bring experimentally derived knowledge much closer to clinical observations.

Crucial to the seminal concepts that have developed relative to the neurotransmitter acetylcholine and its receptor systems has been the introduction of powerful and contemporary techniques in molecular biology, immunology, and electrophysiology, as well as more elegant techniques for observation of the neuromuscular junction in vivo.[12] These techniques have augmented the more traditional pharmacologic, protein chemical, morphologic, and cytologic approaches.[13,14] Research has elucidated the manner in which the nerve ending regulates the synthesis and release of transmitter and the release of trophic factors, both of which control muscle function, and how these processes are influenced by exogenous and endogenous substances.[14-17] Research continues into how receptors are synthesized and anchored at the end plate, the role of the nerve terminal in the maturation process, and synthesis and control of acetylcholinesterase, the enzyme that breaks down acetylcholine. Several reviews that provide detailed insight into these areas are available.[15-19]

Neuromuscular Transmission

Neuromuscular transmission occurs by a fairly simple and straightforward mechanism. The nerve synthesizes acetylcholine and stores it in small, uniformly sized packages called vesicles. Stimulation of the nerve causes these vesicles to migrate to the surface of the nerve, rupture, and discharge acetylcholine into the cleft separating nerve from muscle. AChRs in the end plate of the muscle respond by opening their channels for influx of sodium ions into the muscle to depolarize the muscle. The end-plate potential created is continued along the muscle membrane by the opening of sodium channels present throughout the muscle membrane to initiate a contraction.[17] The acetylcholine immediately detaches from the receptor and is destroyed by the enzyme acetylcholinesterase, which is also present in the cleft. Drugs, notably depolarizing relaxants or nicotine and carbachol (a synthetic analog of acetylcholine not destroyed by acetylcholinesterase), can also act on these receptors to mimic the effect of acetylcholine and cause depolarization of the end plate. These drugs are therefore called agonists of the receptor because to a greater or lesser extent, they stimulate the receptor, at least initially. Nondepolarizing muscle relaxants (NDMRs) also act on the receptors, but they prevent acetylcholine from binding to the receptor and thus prevent depolarization by agonists. Because these nondepolarizers prevent the action of agonists (e.g., acetylcholine, carbachol, succinylcholine), they are referred to as antagonists of the AChR. Other compounds, frequently called reversal agents or antagonists of neuromuscular paralysis (e.g., neostigmine, prostigmine), inhibit acetylcholinesterase and therefore impair the hydrolysis of acetylcholine. The increased accumulation of undegraded acetylcholine can compete with NDMRs effectively and thereby displace the latter from the receptor (i.e., law of mass action) and antagonize the effects of NDMRs.

Morphology

The neuromuscular junction is specialized on the nerve side and on the muscle side to transmit and receive chemical messages.[12-17] Each motor neuron runs without interruption from the ventral horn of the spinal cord or medulla to the neuromuscular junction as a large, myelinated axon (Fig. 14-1A). As it approaches the muscle, it branches repeatedly to contact many muscle cells and gather them into a functional group known as a motor unit (see Fig. 14-1B). The architecture of the nerve terminal is quite different from that of the rest of the axon. As the terminal reaches the muscle fiber, it loses its myelin, forms a spray of terminal branches against the muscle surface, and is covered by Schwann cells. This arrangement conforms to the architecture on the synaptic area of the muscle membrane (see Fig. 14-1C). The nerve is separated from the surface of the muscle by a gap of approximately 20 nm, called the junctional or synaptic cleft. The nerve and muscle are held in tight alignment by protein filaments called basal lamina that span the cleft between the nerve and end plate. The muscle surface is heavily corrugated, with deep invaginations of the junctional cleft—the primary and secondary clefts—between the folds in the muscle membrane; thus, the end plate's total surface area is very large. The depths of the folds also vary between muscle types and species. Human neuromuscular junctions, relative to muscle size, are smaller than those of the mouse, although the junctions are located on muscle fibers that are much larger. Human junctions have longer junctional foldings and deeper gutters.[12] The functional significance of these folds is unclear. The shoulders of the folds are densely populated with AChRs, about 5 million of them in each junction. AChRs are sparse in the depths between the folds. Instead, these deep areas contain sodium channels (see Fig. 14-1D).

The trophic function of the nerve is vital for the development and maintenance of adequate neuromuscular function. Before birth, each muscle cell commonly has contacts with several nerves and has several neuromuscular junctions.[17,19] At birth, all but one of the nerves retract, and a single end plate remains. Once

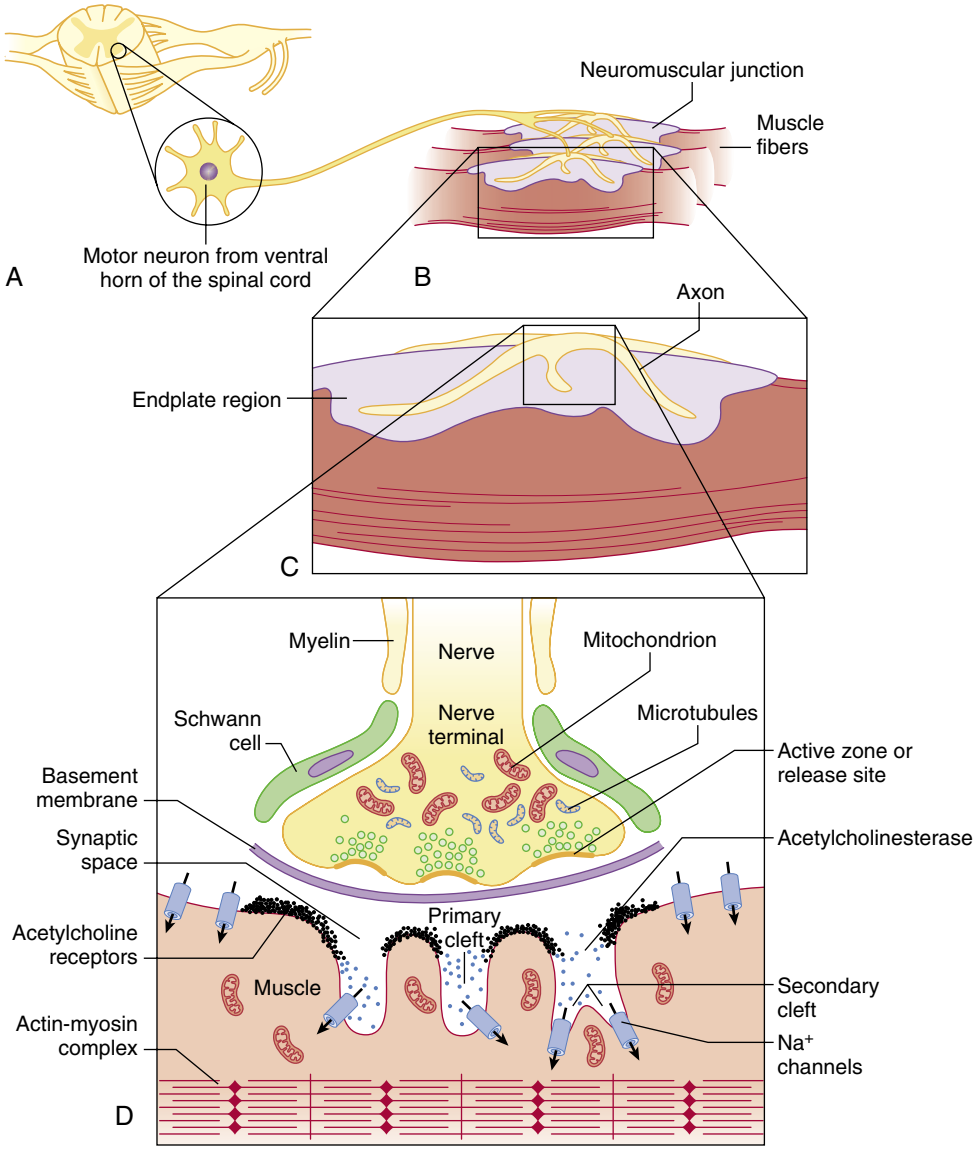

Figure 14-1 Structure of the adult neuromuscular junction showing the three cells that constitute the synapse: the motor neuron (i.e., nerve terminal), muscle fiber, and Schwann cell. **A,** The motor nerve originates in the ventral horn of the spinal cord or brainstem. **B,** As the nerve approaches its muscle fibers and before attaching itself to the surface of the muscle fiber, the nerve divides into branches that innervate many individual muscle fibers. **C,** Each muscle receives only one synapse. The motor nerve loses its myelin and further subdivides into many presynaptic boutons to terminate on the surface of the muscle fiber. **D,** The nerve terminal, covered by a Schwann cell, has vesicles clustered about the membrane thickenings, which are the active zones, toward its synaptic side and mitochondria and microtubules toward its other side. A synaptic gutter or cleft made up of a primary and many secondary clefts separates the nerve from the muscle. The muscle surface is corrugated, and dense areas on the shoulders of each fold contain acetylcholine receptors. Sodium channels are present at the bottom of the clefts and throughout the muscle membrane. The acetylcholinesterase and proteins and proteoglycans that stabilize the neuromuscular junction are present in the synaptic clefts.

formed, the nerve-muscle contact, especially the end plate, is durable. Even if the original nerve dies, the one replacing it innervates exactly the same region of the muscle. The nerve endings on fast muscles are larger and more complicated than those on slow muscles. The reason for this is unclear. These differences in the nerve endings on muscle surfaces may play a role in the difference in response of fast- and slow-twitch muscle fibers to muscle relaxants.

Because all the muscle cells in a unit are excited by a single neuron, stimulation of the nerve electrically or by an action potential originating from the ventral horn or by any agonist, including depolarizing relaxants (e.g., succinylcholine), causes all muscle cells in the motor unit to contract synchronously. Synchronous contraction of the cells in a motor unit is called *fasciculation* and often is vigorous enough to be observed through the skin. Although most adult human muscles have only one neuromuscular junction per cell, an important exception is some of the cells in extraocular muscles. The extraocular muscles are "tonic" muscles, and unlike other mammalian striated muscles, they are multiply innervated, with several neuromuscular junctions strung along the surface of each muscle cell.[20,21] Quite in contrast to other muscles, even the adult ocular muscle contains mature and immature fetal receptors (see "Postjunctional Acetylcholine Receptors") segregated into distinct synapses on different fibers.[20] The ocular muscles contract and relax slowly rather than quickly as other striated muscles do; they can maintain a steady contraction, or contracture, the strength of which is proportional to the stimulus received. Physiologically, this specialization apparently holds the eye steadily in position. These muscles are important to an anesthesiologist because depolarizing relaxants affect them differently than they do most skeletal muscles. Instead of causing a brief contraction followed by paralysis, the drugs cause a long-lasting contracture response that pulls the eye against the orbit and could contribute to an increase in intraocular fluid pressure.[22] The clinical significance of a succinylcholine-induced increase in intraocular pressure has been questioned. Although many textbooks invoke the reported extrusion of intraocular content with succinylcholine, the basis for this effect seems to be anecdotal.[23]

The perijunctional zone is the area of muscle immediately beyond the junctional area, and it is critical to function of the neuromuscular junction. The perijunctional zone contains a mixture of receptors, including a smaller density of AChRs and a high density of sodium channels (see Fig. 14-1D). The admixture enhances the capacity of the perijunctional zone to respond to the depolarization (i.e., end-plate potential) produced by AChRs and to transduce it into the wave of depolarization that travels along the muscle to initiate muscle contraction. The density of sodium channels in the perijunctional area is richer than in more distal parts of the muscle membrane.[17,24] The perijunctional zone is close enough to the nerve ending to be influenced by transmitter released from it. Moreover, special variants (i.e., isoforms) of receptors and sodium channels can appear in this area at different stages of life and in response to abnormal decreases in nerve activity (see "Biology of Prejunctional and Postjunctional Nicotinic Receptors"). Congenital abnormalities in the AChR[4,5] or in the sodium and calcium channels (i.e., mutations)[25,26] are also known. These variabilities seem to contribute to the differences in response to relaxants that are seen in patients with different pathologic conditions and ages.[1-3,27]

Quantal Theory

The contents of nerve ending are not homogeneous. As shown in Figures 14-1 and 14-2, vesicles are congregated in the portion toward the junctional surface, whereas microtubules, mitochondria, and other support structures are located toward the opposite side. The vesicles containing transmitter are ordered in repeating clusters alongside small, thickened, electron-dense patches of membrane referred to as active zones or release sites. This thickened area is a cross section of a band running across the width of the synaptic surface of the nerve ending that is believed to be the structure to which vesicles attach (active zones) before they rupture into the junctional cleft (see "Process of Exocytosis"). High-resolution scanning electron micrographs reveal small protein particles arranged alongside the active zone between vesicles. These particles are believed to be special channels—voltage-gated calcium channels—that allow calcium to enter the nerve and cause the release of vesicles.[28,29] The rapidity with which the neurotransmitter is released (200 μsec) suggests that voltage-gated calcium channels are close to the release sites. Proteomic studies suggest that at least 26 genes encode presynaptic proteins, and mutations in 12 of them cause defects in presynaptic structure that can lead to decreased acetylcholine release and muscle weakness.[30] These defects can be related to exocytosis, endocytosis, formation of active and periactive zones, vesicle transport, and neuropeptide modulation.[30]

When observing the electrophysiologic activity of a skeletal muscle, small, spontaneous depolarizing potentials at neuromuscular junctions can be seen. These potentials have only one hundredth the amplitude of the evoked end-plate potential produced when the motor nerve is stimulated. Except for amplitude, these potentials resemble the end-plate potential in the time course and manner in which they are affected by drugs. These small-amplitude potentials are called miniature end-plate potentials (MEPPs). Statistical analysis led to the conclusion that they are unitary responses; that is, there is a minimum size for the MEPP, and the sizes of all MEPPs are equal to or multiples of this minimum size. Because MEPPs are too big to be produced by a single molecule of acetylcholine, it was deduced that they are produced by uniformly sized packages, or quanta, of transmitter released from the nerve (in the absence of stimulation). The stimulus-evoked end-plate potential is the additive depolarization produced by the synchronous discharge of quanta from several hundred vesicles. The action potential that is propagated to the nerve ending allows entry of calcium into the nerve through voltage-gated calcium channels, and this causes vesicles to migrate to the active zone, fuse with the neural membrane, and discharge their acetylcholine into the junctional cleft.[28,29] Because the release sites are located immediately opposite the receptors on the postjunctional surface, little transmitter is wasted, and the response of the muscle is coupled directly with the signal from the nerve.[17,28]

Alignment of the presynaptic receptor site is achieved by adhesion molecules or specific cell-surface proteins located on both sides of the synapse that grip each other across the synaptic cleft and hold the prejunctional and postjunctional synaptic apparatuses together.[15,31-33] One such protein implicated in synapse adhesion is neurexin, which binds to neuroligins on the postsynaptic membrane. The amount of acetylcholine released by each nerve impulse is large, at least 200 quanta of about 5000 molecules each, and the number of AChRs activated by transmitter released

by a nerve impulse is also large, about 500,000 molecules. The ions (mostly Na^+ and some Ca^{2+}) that flow through the channels of activated AChRs cause maximum depolarization of the end plate, which results in an end-plate potential that is greater than the threshold for stimulation of the muscle. This system is very vigorous. The signal is carried by more molecules of transmitter than are needed, and they evoke a response that is greater than needed. At the same time, only a small fraction of the available vesicles and receptors or channels are used to send each signal. Consequently, transmission has a substantial margin of safety, and at the same time the system has substantial capacity in reserve.[34]

The Neuromuscular Junction

Formation of Neurotransmitter at Motor Nerve Endings

The axon of the motor nerve carries electrical signals from the spinal cord to muscles and has all of the biochemical apparatus needed to transform the electrical signal into a chemical one. All the ion channels, enzymes, other proteins, macromolecules, and membrane components needed by the nerve ending to synthesize, store, and release acetylcholine and other trophic factors are made in the cell body and transmitted to the nerve ending by axonal transport (Fig. 14-2).[19,31,33] The simple molecules choline and acetate are obtained from the environment of the nerve ending, the former by a special system that transports it from extracellular fluid to the cytoplasm and the latter in the form of acetyl coenzyme A from mitochondria. The enzyme choline acetyltransferase brings about the reaction of choline and acetate to form acetylcholine; the acetylcholine is stored in cytoplasm until it is transported into vesicles, which are in a better position for release.

Nerve Action Potential

During a nerve action potential, sodium from outside flows across the membrane, and the resulting depolarizing voltage opens calcium channels, which allows entry of calcium ions into the nerve and causes acetylcholine to be released. A nerve action potential is the normal activator that releases the transmitter acetylcholine. The number of quanta released by a stimulated nerve is greatly influenced by the concentration of ionized calcium in extracellular fluid. If calcium is not present, depolarization of the nerve, even by electrical stimulation, will not produce release of transmitter. Doubling the extracellular calcium results in a 16-fold increase in the quantal content of an end-plate potential.[35]

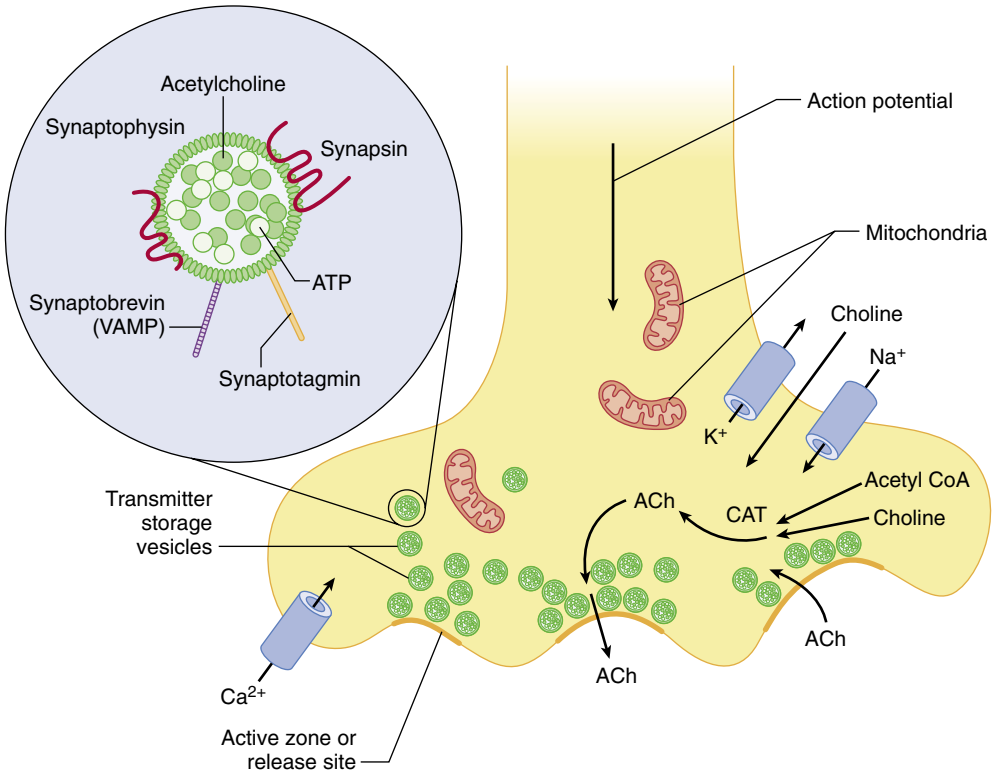

Figure 14-2 The working of a chemical synapse, the motor nerve ending, including some of the apparatus for synthesis of transmitter. The large intracellular structures are mitochondria. Acetylcholine (ACh), synthesized from choline and acetate by acetyl coenzyme A (acetyl CoA), is transported into coated vesicles, which are moved to release sites. A presynaptic action potential that triggers influx of calcium through specialized proteins (Ca^{2+} channels) causes the vesicles to fuse with the membrane and discharge transmitter. Membrane from the vesicle is retracted from the nerve membrane and recycled. Each vesicle can undergo various degrees of release of contents—from incomplete to complete. The transmitter is inactivated by diffusion, catabolism, or reuptake. The *inset* provides a magnified view of a synaptic vesicle. Quanta of ACh together with adenosine triphosphate (ATP) are stored in the vesicle and covered by vesicle membrane proteins. Synaptophysin is a glycoprotein component of the vesicle membrane. Synaptotagmin is the vesicle's calcium sensor. Phosphorylation of another membrane protein, synapsin, facilitates vesicular trafficking to the release site. Synaptobrevin (vesicle-associated membrane protein [VAMP]) is a SNARE protein involved in attaching the vesicle to the release site (see also Fig. 14-3). CAT, choline acetyltransferase.

The calcium current persists until the membrane potential is returned to normal by outward fluxes of potassium from inside the nerve cell. Along with calcium channels on the nerve terminal are potassium channels, including the voltage-gated and calcium-activated potassium channels, whose function is to limit entry of calcium into the nerve and therefore depolarization.[31,36] The calcium current can be prolonged by potassium channel blockers (e.g., 4-aminopyridine, tetraethylammonium), which slow or prevent the efflux of potassium out of the nerve. The increase in quantal content produced in this way can reach astounding proportions.[25,37] An effect of increasing calcium in the nerve ending is also seen clinically as the so-called post-tetanic potentiation, which occurs after a nerve of a patient paralyzed with an NDMR is stimulated at high, tetanic frequencies. Calcium enters the nerve with every stimulus, but because it cannot be excreted as quickly as the nerve is stimulated, it accumulates during the tetanic period. Because the nerve ending contains more than the normal amount of calcium for some time after the tetanus, a stimulus applied to the nerve during this time causes the release of more than the normal amount of acetylcholine. The abnormally large amount of acetylcholine antagonizes the relaxant and causes the characteristic increase in size of the twitch.

Calcium enters the nerve through specialized proteins called calcium channels.[15,25] Of the several types of calcium channels, two seem to be important for release of transmitter: P channels and the slower L channels. P channels, probably the type responsible for normal release of transmitter, are found only in nerve terminals.[13,38] In motor nerve endings, they are located immediately adjacent to the active zones (see Fig. 14-2). They are voltage dependent and opened and closed by changes in membrane voltage caused by the nerve action potential. In addition to calcium channels, several forms of potassium channels are present in the nerve terminal, including voltage-gated and calcium-activated potassium channels. Potassium channels limit the duration of nerve terminal depolarization and hence entry of calcium and release of transmitter.[25,31] Alterations in entry of calcium into the nerve ending can also alter release of transmitter. Eaton-Lambert myasthenic syndrome, which should not be confused with myasthenia gravis, is an acquired autoimmune disease in which antibodies are directed against voltage-gated calcium channels at nerve endings.[39] In this syndrome, decreased function of the calcium channel causes decreased release of transmitter, which results in inadequate depolarization and muscle weakness. Patients with myasthenic syndrome exhibit increased sensitivity to depolarizing and nondepolarizing relaxants.[3,4,31]

Higher than normal concentrations of bivalent inorganic cations (e.g., magnesium, cadmium, manganese) can also block entry of calcium through P channels and profoundly impair neuromuscular transmission. This is the mechanism for muscle weakness in the mother and fetus when magnesium sulfate is administered to treat preeclampsia. P channels, however, are not affected by calcium entry–blocking drugs such as verapamil, diltiazem, and nifedipine. These drugs have profound effects on the slower L channels present in the cardiovascular system. As a result, the L-type calcium channel blockers have no significant effect at therapeutic doses on the normal release of acetylcholine or on the strength of normal neuromuscular transmission. There have been a few reports, however, that calcium entry–blocking drugs may increase the block in neuromuscular transmission induced by NDMRs. The effect is small, and not all investigators have been able to observe it. The explanation may lie in the fact that nerve endings also contain L-type calcium channels.

Synaptic Vesicles and Recycling

There seem to be two pools of vesicles that release acetylcholine, a readily releasable pool and a reserve pool, sometimes called VP2 and VP1, respectively.[40,41] Vesicles in the former are a bit smaller and limited to an area very close to the nerve membrane, where they are bound to the active zones. These vesicles are the ones that ordinarily release transmitter. Electron microscopic studies have demonstrated that the majority of synaptic vesicles (VP1) are sequestered in the reserve pool and tethered to the cytoskeleton in a filamentous network composed mainly of actin, synapsin (an actin-binding protein), synaptotagmin, and spectrin.[40-42]

Release seems to occur when calcium ion enters the nerve through the P channels lined up on the sides of the active zones by SNARE proteins.[40-42] The SNARE (soluble *N*-ethylmaleimide–sensitive attachment protein receptors) proteins are involved in fusion, docking, and release of acetylcholine at the active zone. Calcium needs to move only a very short distance (i.e., a few atomic radii) to encounter a vesicle and activate the proteins in the vesicle wall involved in a process known as docking (see "Process of Exocytosis").[43] The reactivated proteins seem to react with the nerve membrane to form a pore through which the vesicle discharges its acetylcholine into the junctional cleft. Studies using fluorescent proteins have visualized how synaptic vesicles fuse with release sites and release their contents, which are then retrieved.[41] Some vesicles stay open briefly before retrieval and do not completely collapse into the surface membrane ("kiss and run"). Others stay open longer and probably do not collapse completely ("compensatory"). Still others collapse completely and are not retrieved until another stimulus is delivered ("stranded").[41]

The larger reserve (VP1) vesicles, from their position deeper from the nerve ending and firmly tethered to the cytoskeleton by many proteins, including actin, synapsin (an actin-binding protein), synaptotagamin, and spectrin,[40-42] may be moved to the readily releasable store to replace worn-out vesicles or to participate in transmission when the nerve is called on to work especially hard (e.g., when it is stimulated at very high frequencies or for a very long time). Under such strenuous circumstances, calcium may penetrate more deeply than normal into the nerve or may enter through L channels to activate calcium-dependent enzymes that break the synapsin links holding the vesicles to the cytoskeleton, thereby allowing the vesicles to be moved to the release sites. Repeated stimulation requires the nerve ending to replenish its store of vesicles filled with transmitter, a process known as *mobilization*. The term is commonly applied to the aggregate of all steps involved in maintaining the nerve ending's capacity to release transmitter—everything from the acquisition of choline and the synthesis of acetate to the movement of filled vesicles to release sites. Uptake of choline and the activity of choline acetyltransferase, the enzyme that synthesizes acetylcholine, are probably the rate-limiting steps.[13,29,38]

Process of Exocytosis

The readily releasable pool of synaptic vesicles constitutes the vesicles directly available for release. During an action potential

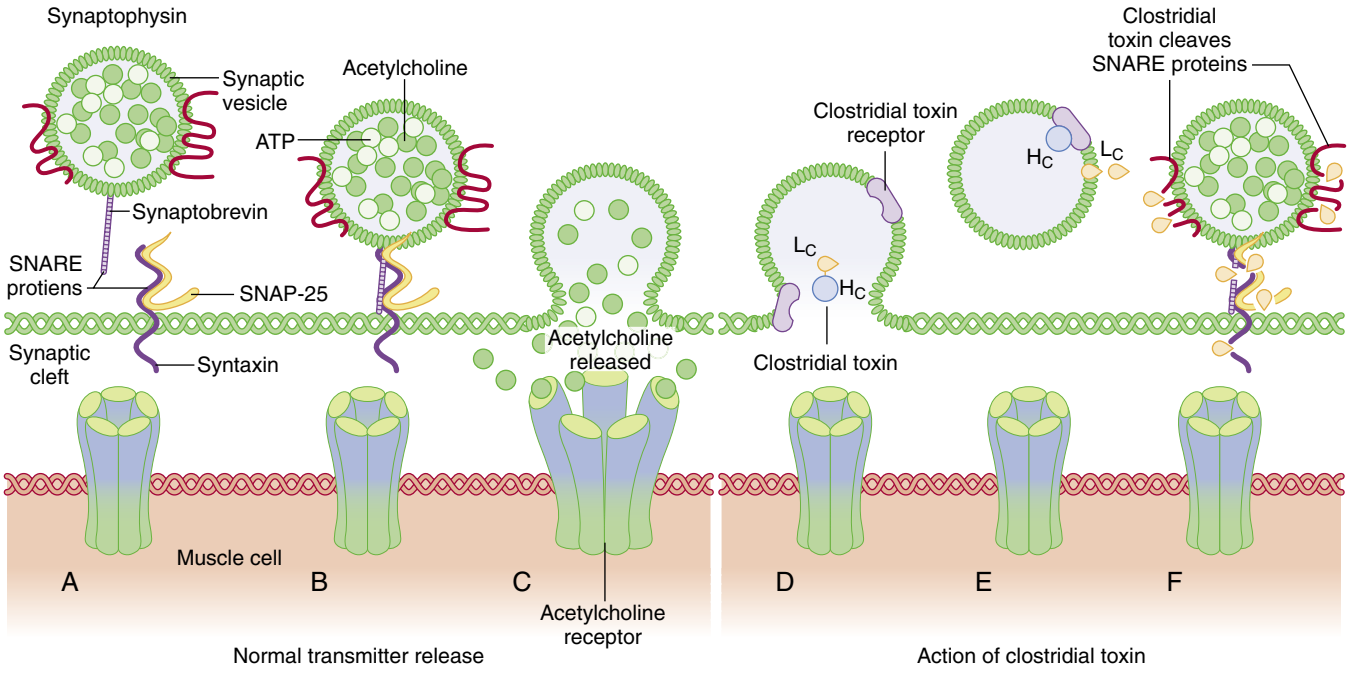

Figure 14-3 Model of protein-mediated membrane fusion and exocytosis. **A,** Release of acetylcholine from vesicles is mediated by a series of proteins collectively called SNARE proteins. Synaptotagmin is the neuronal calcium receptor that detects entry of calcium. Synaptobrevin (i.e., vesicle-associated membrane protein [VAMP]) is a filament-like protein on the vesicle. **B,** During depolarization and entry of calcium, synaptobrevin on the vesicle unfolds and forms a ternary complex with syntaxin/SNAP-25. This process is facilitated by phosphorylation of synapsin, also present on the vesicle membrane. **C,** Assembly of the ternary complex forces the vesicle in close apposition to the nerve membrane at the active zone with release of its contents, acetylcholine. The fusion is disassembled, and the vesicle is recycled. Clostridial toxins, including tetanus and botulinum, inhibit the release of acetylcholine and cause paralysis of muscles. The toxin consists of a light (L_c) and heavy (H_c) chain. **D,** The first stage in intoxication is interaction of the toxin with a thus far unidentified receptor. **E,** This is followed by internalization of the toxin within the vesicle and release of the light chain from the vesicle. The liberated L_c cleaves a variety of SNARE proteins, depending on the type of toxin released, thereby preventing assembly of the fusion complex and thus blocking release of acetylcholine.

and calcium influx, neurotransmitter is released. Studies have shed some light on the inner workings by which the vesicle releases its contents. The whole process is called *exocytosis*. The SNAREs include the synaptic-vesicle protein synaptobrevin and the plasmalemma-associated proteins syntaxin and synaptosome-associated protein of 25 kd (SNAP-25).[42] The current model of protein-mediated membrane fusion in exocytosis is as follows. Syntaxin and SNAP-25 are complexes attached to the plasma membrane. After initial contact, the synaptobrevin on the vesicle forms a ternary complex with syntaxin and SNAP-25. Synaptotagmin is the protein on the vesicular membrane that acts as a calcium sensor, localizes the synaptic vesicles to synaptic zones rich in calcium channels, and stabilizes the vesicles in the docked state.[44] Assembly of the ternary complex forces the vesicle close to the underlying nerve terminal membrane (i.e., the active zone), and the vesicle is then ready for release (Fig. 14-3). An action potential in the nerve terminal allows the entry of calcium. The close proximity of release sites, calcium channels, and synaptic vesicles and use of the calcium sensor lead to a burst of release of new transmitter synchronous with the stimulus.[42,44] The vesicle can release part or all of its contents, some of which can be recycled to form new vesicles as described previously (kiss and run, etc.).[40,41]

Botulinum toxin and tetanus neurotoxins, which selectively digest one or all of these SNARE proteins, block exocytosis of the vesicles.[45,46] The result is muscle weakness or paralysis. These toxins in effect produce a partial or complete chemical denervation. Botulinum toxin is used therapeutically to treat spasticity or spasm in several neurologic and surgical diseases and cosmetically to correct wrinkles.[47,48] Botulinum toxin consists of two protein segments known as heavy and light chains. The heavy chain interacts with lipid molecules called polysialogangliosides in the cell membrane and synaptotagmin on the vesicle to enter the vesicle. Once in the vesicle, the light chain inactivates neuromuscular transmission by breakdown and thereby inhibits the function of SNARE proteins (Fig. 14-4). Recent reports indicate an increased incidence of clostridial infections in both Canada and the United States, with *Clostridium botulinum* infection being particularly common after traumatic injuries, in drug abusers, and after musculoskeletal allografts.[49] Thus, systemic paralysis can occur after clostridial infection. Local injection for therapeutic purposes will usually result in localized paresis, although systemic effects have been reported.[50]

Acetylcholinesterase

The acetylcholine released from the nerve diffuses across the junctional cleft and reacts with specialized receptor proteins in the end plate to initiate muscle contraction. Transmitter molecules that do not react immediately with a receptor or those released after binding to the receptor are destroyed almost instantly by acetylcholinesterase in the junctional cleft. Acetyl-

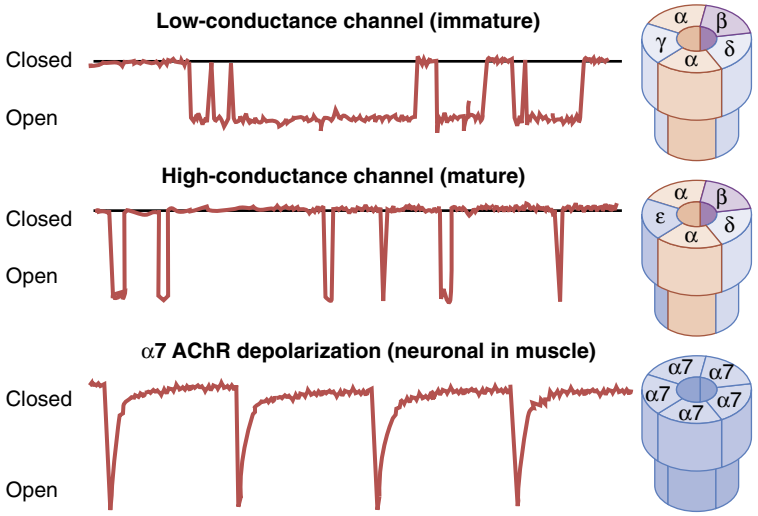

Figure 14-4 Sketch of acetylcholine receptor (AChR) channels (*right*) and tracings of cell-patch records of receptor channel openings (*left*). The mature, or junctional, receptor consists of two α-subunits and one each of β-, δ-, and ε-subunits. The immature, extrajunctional or fetal, form consists of two α- and one each of β, δ, and γ-subunits. The latter is thus called the γ-subunit receptor. Recently, a neuronal receptor consisting of five α7-subunits has been described in muscle. All the subunits are arranged around the central cation channel. The immature isoform containing the γ-subunit has long open times and low-amplitude channel currents. The mature isoform containing the ε-subunit has shorter open times and high-amplitude channel currents during depolarization. Substitution of the ε-subunit for the γ-subunit gives rise to the fast-gated, high-conductance channel type. As expected, application of acetylcholine to the α7 AchR also results in a fast, rapidly decaying inward current. All these depolarizing events are insensitive to treatment with atropine but sensitive to treatment with α-bungarotoxin or muscle relaxants, which block the flow of current.

cholinesterase at the junction is the asymmetric or A12-form protein made in the muscle, under the end plate. Acetylcholinesterase (enzyme classification 3.1.1.7) is a type B carboxylesterase enzyme. There is a smaller concentration of it in the extrajunctional area. The enzyme is secreted from the muscle but remains attached to it by thin stalks of collagen fastened to the basement membrane.[13,17] Most of the molecules of acetylcholine released from the nerve initially pass between the enzymes to reach the postjunctional receptors, but as they are released from the receptors, they invariably encounter acetylcholinesterase and are destroyed. Under normal circumstances, a molecule of acetylcholine reacts with only one receptor before it is hydrolyzed. Acetylcholine is a potent messenger, but its actions are very short lived because it is destroyed in less than 1 millisecond after it is released.

Some congenital and acquired diseases are caused by altered activity of acetylcholinesterase. Congenital absence of the secreted enzyme (in knock-out mice) leads to impaired maintenance of the motor neuronal system and organization of nerve terminal branches.[51] Many syndromes caused by congenital abnormalities in cholinesterase function have been described and result in neuromuscular disorders whose symptoms and signs usually resemble those of myasthenia gravis or myasthenic syndromes.[52,53] Denervation decreases acetylcholinesterase at the junctional and extrajunctional areas.[31] Other acquired diseases involving cholinesterases are related to chronic inhibition of acetylcholinesterase by organophosphate pesticides or nerve gas (e.g., sarin) or to chronic pyridostigmine therapy given as prophylaxis against nerve gas poisoning.[54,55] Symptoms ranging from chronic fatigue to muscle weakness have been attributed to chronic cholinesterase inhibition, thus underscoring the importance of acetylcholinesterase in normal and abnormal neuromuscular function.

Postjunctional Acetylcholine Receptors

The similarity of AChRs among many species and the abundance of AChRs from *Torpedo* electric fish have greatly facilitated research in this area. The availability of messenger RNA from humans and other species and DNA has allowed study of the receptor in artificial systems such as oocytes from frogs and in mammalian cells that do not express the receptor, such as COS or fibroblast cells. It is also possible to mutate receptors by molecular techniques so that they simulate pathologic states and then study receptor function in these artificial systems. By using these and related techniques, much has been learned about the synthesis, composition, and biologic function and the mechanisms that underlie physiologic and pharmacologic responses in AChRs.[56-59] Three isoforms of postjunctional nicotinic AChRs exist, a junctional or mature receptor, an extrajunctional or immature (fetal) receptor, and the most recently described neuronal α7 receptor (see "Biology of Prejunctional and Postjunctional Nicotinic Receptors").[1-3] The differences between receptor subtypes, however, can be neglected in a general discussion of the role of receptors in neuromuscular transmission.

AChRs are synthesized in muscle cells and are anchored to the end-plate membrane by a special 43-kd protein known as rapsyn. This cytoplasmic protein is associated with the AChR in a 1:1 ratio.[31] The receptors, formed of five subunit proteins, are arranged like the staves of a barrel into a cylindrical receptor with a central pore for ion channeling. The key features are sketched in Figure 14-4. The receptor protein has a molecular mass of about 250,000 daltons. Each receptor has five subunits. The mature receptor consists of α, β, δ, and ε and the fetal (immature, extrajunctional) receptor, α, β, δ, and γ; there are two subunits of α and one of each of the others. The neuronal α7 AChR consists of

five α7-subunits.[2] Each of all receptor subunits consists of approximately 400 to 500 amino acids. The receptor-protein complex passes entirely through the membrane and protrudes beyond the extracellular surface of the membrane and into the cytoplasm. The binding site for acetylcholine is on each of the α-subunits, and these are the sites of competition between receptor agonists and antagonists. Agonists and antagonists are attracted to the binding site, and either may occupy the site, which is located near cysteine residues (unique to the α-chain) at amino acid positions 192-193 of the α-subunit.[60] Radiolabeled α-bungarotoxin from the cobra, used to quantitate the receptor, binds to heptapeptide region 189-199 of the α-subunit.[61] Motor neuron–derived neuregulin-1β (NRβ-1), originally described as acetylcholine receptor–inducing activity (ARIA), induces AChR gene transcription in subsynaptic myonuclei by activating ErbB receptors.[62]

Synthesis and Stabilization of Postjunctional Receptors

Muscle tissue is formed from the mesoderm and initially appears as myoblasts. Myoblasts fuse to produce myotubes, which therefore have multiple nuclei. As the myotubes mature, the sarcomere, which is the contractile element of the muscle consisting of actin and myosin, develops.[63] The protein β-integrin seems to be essential for myoblast fusion and sarcomere assembly.[63] Shortly afterward, motor nerve axons grow into the developing muscle, and these axons bring in nerve-derived signals (i.e., growth factors), including agrin and neuregulins (NRβ-1 and NRβ-2), which are key to maturation of myotubes to muscle.[62] Agrin is a protein from the nerve that stimulates postsynaptic differentiation by activating muscle-specific kinase (MuSK), a tyrosine kinase expressed selectively in muscle. With signaling from agrin, the AChRs, which have been scattered throughout the muscle membrane, cluster at the area immediately beneath the nerve. Agrin together with other growth factors (neuregulins, etc.) also induce the clustering of other critical muscle-derived proteins, including MuSK, rapsyn, and ErbB proteins, all of which are necessary for maturation and stabilization of AChRs at the junction (Fig. 14-5). In addition to effects on postsynaptic differentiation, agrin and MuSK display effects on presynaptic differentiation as well. Agrin and MuSK induce retrograde signals that instruct axons to undergo neuron outgrowth and terminal differentiation.[19] Current understanding of presynaptic development of the neuromuscular junction, however, is much less advanced than understanding of postsynaptic development. Just before and shortly after birth, the immature, γ-subunit–containing AChRs are converted to the mature, ε-subunit–containing receptors. Although the mechanism of this change is unclear, a neuregulin, NRβ-1, also called ARIA, that binds to one of the ErbB receptors seems to play a role.[44,62-65]

Basic Electrophysiology of Neurotransmission

Progress in electrophysiologic techniques has moved at an equal pace with advances in molecular approaches for studying prejunctional and postjunctional receptors. Patch-clamping is a technique in which a glass micropipette is used to probe the membrane surface until a single functional receptor is encompassed. The tip of the pipette is pressed into the lipid of the membrane, and the electronic apparatus is arranged to keep the membrane potential clamped (i.e., fixed) and measure the current that flows through the channel of the receptor. The solution in the pipette can contain acetylcholine, muscle relaxant, another drug, or a mixture of drugs. By application of these drugs to the receptor through the micropipette, electrical changes can be monitored.

Figure 14-5 illustrates the results of the classic depolarizing action of acetylcholine on end-plate receptors. Normally, the pore of the channel is closed by approximation of the cylinders (i.e., subunits). When an agonist occupies both α-subunit sites, the protein molecule undergoes a conformational change in which a channel is formed in the center through which ions can flow along a concentration gradient. When the channel is open, sodium and calcium flow from the outside of the cell to the inside and

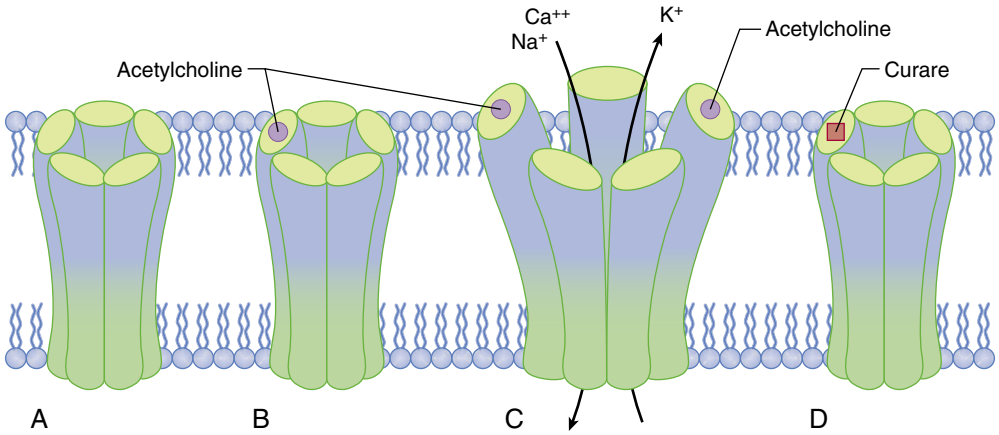

Figure 14-5 Actions of acetylcholine or curare on end-plate receptors. **A,** The ion channel is inactive and does not open in the absence of acetylcholine. **B,** Even binding of one acetylcholine molecule (*filled circle*) to one of two binding sites does not open the channel. **C,** When acetylcholine binds to the recognition sites of both α-subunits simultaneously (*filled circles*), a conformation change is triggered that opens the channel and allows ions to flow across the membrane. **D,** Action of antagonists such as curare (*filled square*). Acetylcholine is in competition with tubocurarine for the receptor's recognition site but may also react with acetylcholinesterase. Tubocurarine is a prototypical nondepolarizing muscle relaxant. Inhibiting the enzyme increases the lifetime of acetylcholine and the probability that it will react with a receptor. When one of the two binding (recognition) sites is occupied by curare, the receptor will not open, even if the other binding site is occupied by acetylcholine.

potassium flows from the inside to the outside. The channel in the tube is large enough to accommodate many cations and electrically neutral molecules, but it excludes anions (e.g., chloride). The current carried by the ions depolarizes the adjacent membrane. The net current is depolarizing and creates the end-plate potential that stimulates the muscle to contract. In this instance, downward-going (i.e., depolarizing) current can be recorded by the electrophysiologic technique described previously (see Fig. 14-4).

The pulse stops when the channel closes and one or both agonist molecules detach from the receptor. The current that passes through each open channel is minuscule, only a few picoamperes (about 10^4 ions/msec). However, each burst of acetylcholine from the nerve normally opens about 500,000 channels simultaneously, and the total current is more than adequate to produce depolarization of the end plate and contraction of muscle. Opening of a channel causes conversion of chemical signals from a nerve to flow of current to end-plate potentials, thereby leading to muscle contraction. We are used to thinking of the end-plate potential as a graded event that may be reduced in magnitude or extended in time by drugs, but in reality, the end-plate potential is the summation of many all-or-nothing events occurring simultaneously at myriad ion channels. It is these tiny events that are affected by drugs.

Receptors that do not have two molecules of agonist bound remain closed. Both α-subunits must be occupied simultaneously by agonist; if only one of them is occupied, the channel remains closed (see Fig. 14-5). This is the basis for prevention of depolarization by antagonists. NDMRs typified by tubocurarine act by binding to either or both α-subunits and thus preventing acetylcholine from binding and opening the channel. This interaction between agonists and antagonists is competitive, and the outcome—transmission or block—depends on the relative concentrations and binding characteristics of the drugs involved (see "Drug Effects on Postjunctional Receptors").

Individual channels are also capable of a wide variety of conformations.[66-68] They may open or stay closed and thereby affect total current flow across the membrane, but they can do more. They may open for a longer or shorter time than normal, open or close more gradually than usual, open briefly and repeatedly (i.e., chatter), or pass fewer or more ions per opening than they usually do. Their function is also influenced by drugs, changes in fluidity of the membrane, temperature, electrolyte balance in the milieu, and other physical and chemical factors.[68] Receptor channels are dynamic structures that are capable of a wide variety of interactions with drugs and of entering a wide variety of current-passing states. All these influences on channel activity are ultimately reflected in the strength or weakness of neuromuscular transmission and the contraction of a muscle.

Drug Effects on Postjunctional Receptors

Classic Actions of Nondepolarizing Muscle Relaxants

Neurotransmission occurs when acetylcholine released by the nerve action potential binds to AChRs. All NDMRs impair or block neurotransmission by competitively preventing the binding of acetylcholine to its receptor. The final outcome (i.e., block or transmission) depends on the relative concentrations of the chemicals and their comparative affinities for the receptor. Figure 14-5 shows a system exposed to acetylcholine and tubocurarine. One receptor has attracted two acetylcholine molecules and opened its channel, where current will flow to depolarize that segment of membrane. Another has attracted one tubocurarine molecule; its channel will not open, and no current will flow, even if one acetylcholine molecule binds to the other site. The third receptor has acetylcholine on one α-subunit and nothing on the other. What will happen depends on which of the molecules binds. If acetylcholine binds, the channel will open and the membrane will be depolarized; if tubocurarine binds, the channel will stay closed and the membrane will not be depolarized. At other times, one or two tubocurarine molecules may attach to the receptor, in which case the receptor is not available to agonists; no current flow is recorded. In the presence of moderate concentrations of tubocurarine, the amount of current flowing through the entire end plate at any instant is reduced from normal, which results in a smaller end-plate potential and, if carried far enough, a block in neurotransmission or production of neuromuscular paralysis.

Normally, acetylcholinesterase destroys acetylcholine and removes it from competition for a receptor, so tubocurarine has a better chance of inhibiting transmission. If, however, an inhibitor of acetylcholinesterase such as neostigmine is added, the cholinesterase cannot destroy acetylcholine. The concentration of agonist in the cleft remains high, and this high concentration shifts the competition between acetylcholine and tubocurarine in favor of the former, thereby improving the chance of two acetylcholine molecules binding to a receptor even though tubocurarine is still in the environment. Cholinesterase inhibitors overcome the neuromuscular paralysis produced by NDMRs by this mechanism. The channel opens only when acetylcholine attaches to both recognition sites. A single molecule of antagonist, however, is adequate to prevent depolarization of that receptor. This modifies the competition by biasing it strongly in favor of the antagonist. Mathematically, if the concentration of tubocurarine is doubled, the concentration of acetylcholine must be increased fourfold if acetylcholine is to remain competitive. Paralysis produced by high concentrations of antagonist is more difficult to reverse than that produced by low concentrations. After large doses of NDMRs, cholinesterase inhibitors may be ineffective until the concentration of relaxant in the perijunctional area decreases to a lower level by redistribution or elimination of the drug.

Classic Actions of Depolarizing Muscle Relaxants

Depolarizing relaxants, at least initially, simulate the effect of acetylcholine and can therefore be considered agonists despite the fact that they block neurotransmission after initial stimulation. Structurally, succinylcholine is two molecules of acetylcholine bound together. It is thus not surprising that it can mimic the effects of acetylcholine. Succinylcholine or decamethonium can bind to the receptor, open the channel, pass current, and depolarize the end plate. These agonists, similar to acetylcholine, attach only briefly; each opening of a channel is of very short duration, 1 millisecond or less. The response to acetylcholine, however, is over in milliseconds because of its rapid degradation by acetyl-

cholinesterase, and the end plate resets to its resting state long before another nerve impulse arrives. In contrast, the depolarizing relaxants characteristically have a biphasic action on muscle—an initial contraction, followed by relaxation lasting minutes to hours. Because they are not susceptible to hydrolysis by acetylcholinesterase, the depolarizing relaxants are not eliminated from the junctional cleft until after they are eliminated from plasma. The time required to clear the drug from the body is the principal determinant of how long the drug effect lasts. Whole-body clearance of the relaxant is very slow in comparison to acetylcholine, even when plasma cholinesterase is normal. Because relaxant molecules are not cleared from the cleft quickly, they react repeatedly with receptors, attaching to one almost immediately after separating from another, thereby repeatedly depolarizing the end plate and opening channels.

The quick shift from excitation of muscle contraction to blockade of transmission by depolarizing relaxants occurs because the end plate is continuously depolarized. This comes about as a result of juxtaposition of the edge of the end plate with the muscle membrane—a different kind of ion channel, the sodium channel, that does not respond to chemicals but opens when exposed to a transmembrane voltage change. The sodium channel is also a cylindrical transmembrane protein through which sodium ions can flow. Two parts of its structure act as gates that allow or stop the flow of sodium ions.[69] Both gates must be open if sodium is to flow through the channel; closing of either cuts off the flow. Because these two gates act sequentially, a sodium channel has three functional conformational states and can move progressively from one state to another (Fig. 14-6).

When the sodium channel is in its resting state, the lower gate (i.e., the time-dependent or inactivation gate) is open, but the upper gate (i.e., the voltage-dependent gate) is closed, and sodium ions cannot pass. When the molecule is subjected to a sudden change in voltage by depolarization of the adjacent membrane, the top gate opens, and because the bottom (time-dependent) gate is still open, sodium flows through the channel. The voltage-dependent gate stays open as long as the molecule is experiencing a depolarizing influence from the membrane around it; it will not close until the depolarization disappears. However, shortly after the voltage-dependent gate opens, the bottom gate closes and again cuts off the flow of ions. It cannot open again until the voltage-dependent gate closes. When depolarization of the end plate stops, the voltage-dependent gate closes, the time-dependent gate opens, and the sodium channel returns to its resting state. This whole process is short lived when depolarization occurs with acetylcholine. The initial response of a depolarizing muscle relaxant resembles that of acetylcholine, but because the relaxant is not hydrolyzed rapidly, depolarization of the end plate is not brief.

Depolarization of the end plate by the depolarizing relaxant initially causes the voltage gate in adjacent sodium channels to open, thereby producing a wave of depolarization that sweeps along the muscle and generates a muscle contraction. Shortly after the voltage-dependent gate opens, the time-dependent inactivation gate closes. Because the relaxant is not removed from the cleft, the end plate continues to be depolarized. Because the sodium channels immediately adjacent to the end plate are influenced by depolarization of the end plate, their voltage-dependent gates stay open and their inactivation gates stay closed. Since sodium cannot flow through a channel that has a closed inactivation gate, the perijunctional muscle membrane does not depolarize. When the flow of ions through sodium channels in the perijunctional zone stops because of closure of the inactivation gates, the channels downstream (beyond the perijunctional zone) are freed of depolarizing influence. In effect, the perijunctional zone becomes a buffer that shields the rest of the muscle from events at the end plate. Consequently, the muscle membrane is separated into three zones: the end plate, which is depolarized by succinylcholine; the perijunctional muscle membrane, in which the sodium channels are frozen in an inactivated state; and the rest of the muscle membrane, in which the sodium channels are in the resting state. Because a burst of acetylcholine from the nerve cannot overcome the inactivated sodium channels in the perijunctional zone, neuromuscular transmission is blocked. This phenomenon is also called *accommodation*. During accommodation, when the synapse is inexcitable through the nerve (transmitter), direct electrical stimulation of muscle causes muscle contraction because the sodium channels beyond the junctional area are in the resting excitable state.

The extraocular muscles contain tonic muscle, which is multiply innervated and chemically excitable along most of its surface.[20,21] Despite its innervation, the ocular muscles express both mature and fetal receptors.[20] Accommodation does not occur, and these muscles can undergo a sustained contracture in the presence of succinylcholine. The tension thus developed forces the eye against the orbit and accounts for part of the increase in intraocular pressure produced by depolarizing relaxants. There is also evidence that the extraocular muscles contain a special type of receptor that does not become desensitized (discussed later) during the continued presence of acetylcholine or other agonists.[21] Whether it is the immature γ-subunit AChR or the α7 AChR that plays a role in this resistance to desensitization in the ocular muscles is unknown.

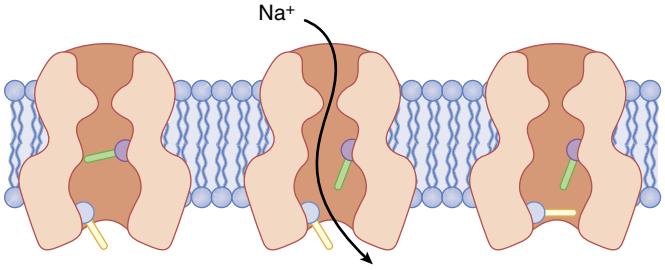

Figure 14-6 Sketch of a sodium channel. The *bars* represent parts of the molecule that act as gates. The *upper bar* is voltage dependent; the *lower bar* is time dependent. The left side of the drawing represents the resting state. Once activated by a change in voltage, the molecule and its gates progress as illustrated (left to right). See text for details.

Nonclassic and Noncompetitive Actions of Neuromuscular Drugs

Several drugs can interfere with the receptor, directly or through its lipid environment, and change transmission. These drugs react with the neuromuscular receptor to change its function and impair transmission but do not act through the acetylcholine binding site. These reactions cause drug-induced changes in the dynamics of the receptor, and instead of opening and closing sharply, the modified channels are sluggish. They open more slowly and stay open longer, or they close slowly and in several

steps, or both. These effects on channels cause corresponding changes in the flow of ions and distortions of the end-plate potential. The clinical effect depends on the molecular events. For example, procaine, ketamine, inhaled anesthetics, or other drugs that dissolve in the membrane lipid may change the opening or closing characteristics of the channel.[70,71] If the channel is prevented from opening, transmission is weakened. If, however, the channel is prevented from or slowed in closing, transmission may be enhanced. These drugs do not fit the classic model, and the impaired neuromuscular function is not antagonized by increasing perijunctional acetylcholine concentrations with cholinesterase inhibitors. Such drugs can be involved in two clinically important reactions: receptor desensitization and channel blockade. The former occurs in the receptor molecule, whereas the latter occurs in the ion channel.

Desensitization Block

The AChR, as a result of its flexibility and the fluidity of the lipid around it, is capable of existing in a number of conformational states.[68-73] Because the resting receptor is free of agonist, its channel is closed. The second state exists when two molecules of agonist are bound to the α-subunit of the receptor and the receptor has undergone the conformation change that opens the channel and allows ions to flow. These reactions are the bases of normal neuromuscular transmission. Some receptors that bind to agonists, however, do not undergo the conformational change to open the channel. Receptors in these states are called desensitized (i.e., they are not sensitive to the channel-opening actions of agonists). They bind agonists with exceptional avidity, but the binding does not result in opening of the channel. The mechanisms by which desensitization occurs are not known. The receptor macromolecule, 1000 times larger by weight than most drugs or gases, provides many places at which the smaller molecules may act. The interface between lipid and receptor protein provides additional potential sites of reaction. Several different conformations of the protein are known, and because acetylcholine cannot cause the ion channel to open in any of them, they all are included in the functional term *desensitization*. Some evidence suggests that desensitization is accompanied by phosphorylation of a tyrosine unit in the receptor protein.[74,75]

Although agonists (e.g., succinylcholine) induce desensitization, the receptors are in a constant state of transition between resting and desensitized states, regardless of whether agonists are present. Agonists do promote transition to a desensitized state or, because they bind very tightly to desensitized receptors, trap a receptor in a desensitized state. Antagonists also bind tightly to desensitized receptors and can trap molecules in these states. This action of antagonists is not competitive with that of acetylcholine; it may be augmented by acetylcholine if the latter promotes the change to a desensitized state. Desensitization can lead to significant misinterpretation of data. Superficially, the preparation seems to be normal, but its responsiveness to agonists or antagonists is altered. One variety occurs very rapidly, within a few milliseconds after application of an agonist. This may explain the increased sensitivity to nondepolarizers after prior administration of succinylcholine. There is also a phenomenon caused by prolonged administration of depolarizing relaxants that is known as *phase II block* (see "Phase II Block"). It is frequently referred to as a desensitization block but should not be because desensitization of receptors is only one of many phenomena that contribute to the process.

Many other drugs used by anesthetists also promote the shift of receptors from a normal state to a desensitized state.[70-73] These drugs, some of which are listed in Box 14-1, can weaken neuromuscular transmission by reducing the margin of safety that normally exists at the neuromuscular junction, or they can cause an apparent increase in the capacity of nondepolarizing agents to block transmission. These actions are independent of the classic effects based on competitive inhibition of acetylcholine. The presence of desensitized receptors means that fewer receptor channels than usual are available to carry transmembrane current. The production of desensitized receptors decreases the efficacy of neuromuscular transmission. If many receptors are desensitized, insufficient normal ones are left to depolarize the

Box 14-1 Drugs That Can Cause or Promote Desensitization of Nicotinic Cholinergic Receptors

- Volatile anesthetics
  - Halothane
  - Sevoflurane
  - Isoflurane
- Antibiotics
  - Polymyxin B
- Cocaine
- Alcohols
  - Ethanol
  - Butanol
  - Propanol
  - Octanol
- Barbiturates
  - Thiopental
  - Pentobarbital
- Agonists
  - Acetylcholine
  - Decamethonium
  - Carbachol
  - Succinylcholine
- Acetylcholinesterase inhibitors
  - Neostigmine
  - Pyridostigmine
  - Difluorophosphate
  - Edrophonium
- Local anesthetics
  - Dibucaine
  - Lidocaine
  - Prilocaine
  - Etidocaine
- Phenothiazines
  - Chlorpromazine
  - Trifluoperazine
  - Prochlorperazine
- Phencyclidine
- Calcium channel blockers
  - Verapamil

motor end plate, and neuromuscular transmission will not occur. Even if only some receptors are desensitized, neuromuscular transmission will be impaired, and the system will be more susceptible to block by conventional antagonists such as tubocurarine or pancuronium.

Channel Block

Local anesthetics and calcium entry blockers prevent the flow of sodium or calcium through their respective channels, thus explaining the term *channel-blocking drugs*. Similarly, block of the flow of ions can occur at the AChR with concentrations of drugs used clinically and may contribute to some of the phenomena and drug interactions seen at the receptor. Two major types, closed-channel and open-channel block, can occur.[76,77] In a closed-channel block, certain drugs can occupy the mouth of the channel and prevent ions from passing through the channel to depolarize the end plate. The process can take place even when the channel is not open. In an open-channel block, a drug molecule enters a channel that has been opened by reaction with acetylcholine but does not necessarily penetrate all the way through. Open-channel blockade is a use-dependent block, which means that molecules can enter the channel only when it is open. In open- and closed-channel blocks, the normal flow of ions through the receptor is impaired, thereby resulting in prevention of depolarization of the end plate and a weaker or blocked neuromuscular transmission. However, because the action is not at the acetylcholine recognition site, it is not a competitive antagonism of acetylcholine and is not relieved by anticholinesterases that increase concentrations of acetylcholine. Increasing the concentration of acetylcholine may cause the channels to open more often and consequently become more susceptible to blockade by use-dependent compounds. There is evidence that neostigmine and related cholinesterase inhibitors can act as channel-blocking drugs.[76]

Channel block is believed to play a role in some of the antibiotic, cocaine, quinidine, piperocaine, tricyclic antidepressant, naltrexone, naloxone, and histrionicotoxin-induced alterations in neuromuscular function. Muscle relaxants, in contrast, can bind to the acetylcholine recognition site of the receptor and occupy the channel. Pancuronium preferentially binds to the recognition site. Gallamine seems to act equally at the two sites. Tubocurarine is in between; at low doses, those that produce minimal blockage of transmission clinically, the drug is essentially a pure antagonist at the recognition site; at larger doses, it also enters and blocks channels. Decamethonium and succinylcholine, as agonists, can open channels and, as slender molecules, also enter and block them. Decamethonium and some other long, thin molecules can penetrate all the way through the open channel and enter the cytoplasm of muscle cells. Whether prolonged administration of NDMRs, as in the intensive care situation, can result in entry of the relaxant, occupation of the channel, and entry of drug into the cytosol is unknown. This effect may partially explain the muscle weakness associated with relaxant therapy in the intensive care unit.

Phase II Block

A phase II block is a complex phenomenon that occurs slowly at junctions continuously exposed to depolarizing agents. The junction is depolarized by the initial application of a depolarizing relaxant, but then the membrane potential gradually recovers toward normal, even though the junction is still exposed to drug. Neuromuscular transmission usually remains blocked throughout the exposure. Several factors are involved. The repeated opening of channels allows a continuous efflux of potassium and influx of sodium, and the resulting abnormal electrolyte balance distorts the function of the junctional membrane. Calcium entering the muscle through the opened channels can cause disruption of receptors and the sub–end-plate elements themselves. The activity of the sodium-potassium adenosine triphosphatase pump in the membrane increases with increasing intracellular sodium and, by pumping sodium out of the cell and potassium into it, works to restore the ionic balance and membrane potential toward normal. As long as the depolarizing drug is present, the receptor channels remain open and ion flux through them remains high.[78]

Factors influencing the development of a phase II block include the duration of exposure to the drug, the particular drug used and its concentration, and even the type of muscle (i.e., fast or slow twitch). Interactions with anesthetics and other agents also affect the process. All of these drugs may also have prejunctional effects on the rate and amount of transmitter released and mobilized. With so many variables involved in the interference with neuromuscular transmission, a phase II block is a complex and ever-changing phenomenon. The reversal response of a phase II block produced by a depolarizing muscle relaxant to administration of cholinesterase inhibitors is difficult to predict. It is therefore best that reversal by cholinesterase inhibitors not be attempted, although the response to tetanus or train-of-four stimulation resembles that produced by nondepolarizers.

Biology of Prejunctional and Postjunctional Nicotinic Acetylcholine Receptors

Postjunctional Conventional Acetylcholine Receptors in Muscle versus Neuronal Acetylcholine Receptors in Muscle

Currently, three variants of postjunctional AChRs have been identified. The AChR isoform present in the innervated, adult neuromuscular junction is referred to as the adult, mature, or junctional receptor. Another AChR isoform is expressed when there is decreased activity in muscle, as seen in the fetus before innervation or after chemically or physically induced immobilization; after lower or upper motor neuron injury, burns, or sepsis; or after other events that cause increased muscle protein catabolism, including sepsis or generalized inflammation.[1-3] To contrast with the mature or junctional receptors, the other isoform is referred to as the immature, extrajunctional, or fetal form of AChR. Some evidence suggests that the immature isoform is not seen in the muscle protein catabolism and wasting that occur with malnutrition.[79] Differences in the protein structure of the two isoforms cause significant qualitative variations in the responses of individual patients to relaxants and seem to be responsible for some of the anomalous results observed when administering relaxants to particular individuals. These qualita-

tive differences in isoforms can also cause variations in function of the muscle.[52,53]

In addition to their structural compositions, the two isoforms have other characteristics that are different.[1-3,31] At the molecular level, both types of receptors consists of five subunits (see Fig. 14-4). The mature junctional receptor is a pentamer of two α-subunits and one each of the β-, δ-, and ε-subunits. The immature receptor consists of two α-subunits and one each of the β-, δ-, and γ-subunits; that is, in the immature receptor the γ-subunit is present instead of the ε-subunit. The γ- and ε-subunits differ from each other very little in amino acid homology, but the differences are great enough to affect the physiology and pharmacology of the receptor and its ion channel. Although the names junctional and extrajunctional imply that each is located in the junctional and extrajunctional areas, this is not strictly correct. Junctional receptors are always confined to the end plate (perijunctional) region of the muscle membrane. The immature, or extrajunctional, receptor may be expressed anywhere in the muscle membrane. Despite the name extrajunctional, they are not excluded from the end plate. During development and in certain pathologic states, junctional and extrajunctional receptors can coexist in the perijunctional area of the muscle membrane (Fig. 14-7).

Quite in contrast to the conventional muscle AChRs consisting of α1, β1, δ, and ε/γ subunits described earlier, receptors formed of α7 AChR subunits have recently been found in skeletal muscle during development and denervation.[80,81] Preliminary evidence (Martyn JAJ, abstract ASA 2007) suggests increased protein expression (by Western blotting) of α7 AChRs in muscle after burn injury and immobilization. These α7 AChRs are homomeric (i.e., formed of the same subunits) channels arranged as pentameres (see Fig. 14-4). Ligand (drug) binding pockets are thought to be formed at negative and positive faces of the α7-subunit assembly interphases. As expected, the endogenous agonist acetylcholine binds to α7 AChRs, and each of the five subunits has the potential to bind acetylcholine or succinylcholine molecules.[82,83] Other agonists, including nicotine and choline, and antagonists, including muscle relaxants, pancuronium, cobra toxin, and α-bungarotoxin, also bind to the α7 AChR.[81-83]

The α7 AChRs in muscle display unusual functional and pharmacologic characteristics when compared with conventional muscle (α1, β1, δ, ε/γ) AChRs or neuronal α7 AChRs in the brain. Choline, a precursor and metabolite of acetylcholine (and succinylcholine), is an extremely weak agonist of conventional muscle AChRs but is a full agonist of muscle α7 AChRs; that is, concentrations of choline that do not open conventional AChR channels will open α7 AChR channels.[81] Furthermore, no desensitization of the α7 AChR occurs even during the continued presence of choline,[81] thus allowing a greater chance for potassium to efflux from within the cell (approximately 145 mEq/L in the cell) to the extracellular space, including plasma (approximately 4.5 mEq/L), down its concentration gradient. The chemical α-conotoxin GI specifically inhibits the conventional (mature and immature) AChRs in muscle but does not inhibit α7 AChRs. Muscle α7 AChRs are different from neuronal (autonomic ganglia and brain) α7 AChRs in that the former are not strongly inhibited by methyllycaconitine, a selective antagonist of neuronal α7 AChRs. The α7 AChRs expressed in neuronal tissue are also readily desensitized with choline,[83] a feature that contrasts with muscle α7 AChRs, which do not desensitize with choline.[81] The α7 AChR in muscle also has lower affinity for its antagonists, including pancuronium

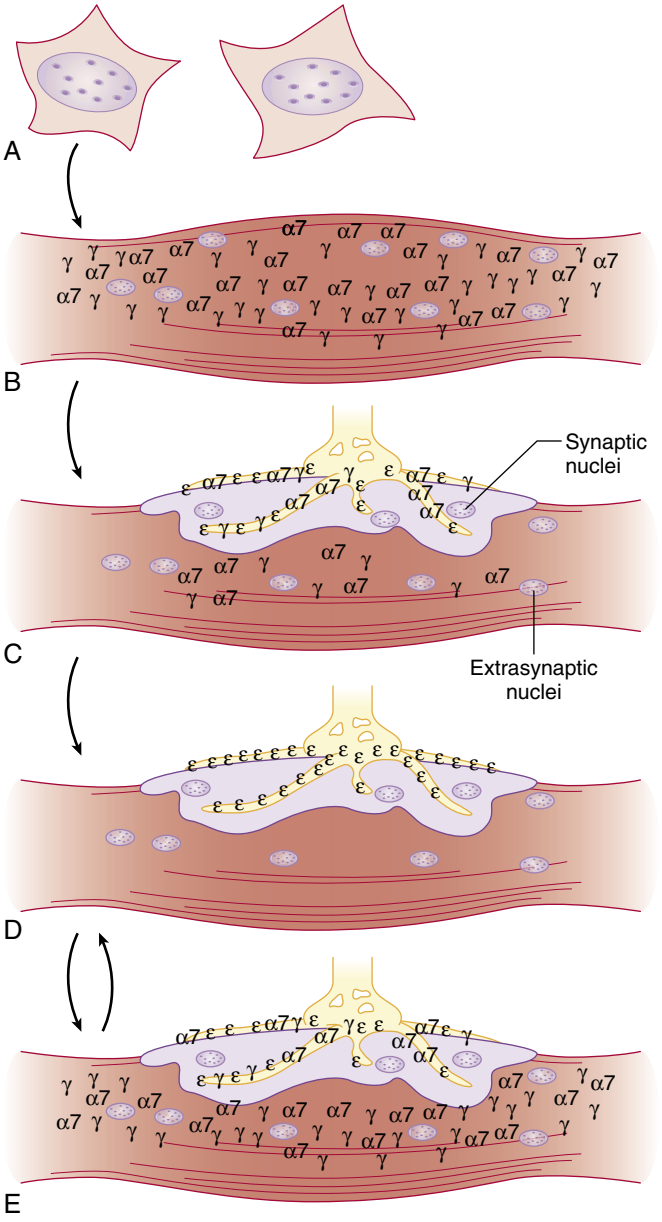

Figure 14-7 Distribution of acetylcholine receptors in developing adult, mature, denervated muscle or in immobilized or inflammation-induced catabolic muscle. **A** and **B,** In the early fetal stage, mononucleated myoblasts, derived from the mesoderm, fuse with each other to form multinucleated myotubes. The γ-subunit–containing immature acetylcholine receptors and the neuronal α7 acetylcholine receptors are scattered throughout the muscle membrane before innervation. **C,** As the nerve makes contact with muscle, clustering of the receptors occurs at the synapse and is associated with some loss of extrasynaptic receptors. **D,** Maturation of the junction is said to occur when ε-subunit–containing receptors replace the γ-subunit– and α7-containing acetylcholine receptors at the neuromuscular junction. Even mature muscle is multinucleated, but it is devoid of extrasynaptic acetylcholine receptors. **E,** Denervation and some other pathologic states, even without anatomic denervation (e.g., burns, immobilization, chronic muscle relaxant therapy, stroke, sepsis), lead to re-expression of the γ-subunit– and α7-containing acetylcholine receptors at the junctional and extrajunctional areas. The latter changes are potentially reversible if muscle immobilization/catabolism/inflammation is restored to normal.

and α-bungarotoxin; higher concentrations of these drugs are therefore required to block agonist-induced depolarization in α7 AChRs than in conventional muscle AChRs (α1, β1, δ, ε/γ).[81] In the conventional AChRs, binding of even one of the α1-subunits by an antagonist results in inactivation of that receptor because acetylcholine needs both α1-subunits of the AChR for its activation. In the α7 AChR, however, even when three subunits are bound by an antagonist (e.g., muscle relaxant), two other subunits are still available for binding to agonist and causing depolarization. This feature may account for the resistance of α7 AChRs, as opposed to conventional AChRs, to the blocking effects of drugs such as pancuronium.[2]

The clinical pharmacology of the muscle α7 AChR has not been studied yet, but its basic pharmacology provides some insight into succinylcholine-related hyperkalemia. Chemical or physical denervation of muscle results in not only upregulation and qualitative (ε-subunit → γ-subunit) changes in AChRs but also upregulation of α7 AChRs in muscle. Succinylcholine, a synthetic analog of acetylcholine that consists of two molecules of acetylcholine joined together, is capable of depolarizing not only conventional AChRs but also α7 AChRs in muscle.[83] In addition, the metabolite of succinylcholine, choline, can depolarize α7 AChRs with little desensitization. The depolarizing effects of succinylcholine and choline on the upregulated α7 AChRs can result in continued leakage of intracellular potassium and flooding of extracellular fluid, including plasma, thereby leading to hyperkalemia.

Maintenance of Mature Neuromuscular Junctions

Quite unlike other cells, muscle cells are unusual in that they have many, usually hundreds, of nuclei per cell. Each of these nuclei has the genes to make both types of receptors. Multiple factors, including electrical activity, growth factor signaling (e.g., insulin, agrin, neuregulins), and the presence or absence of innervation, control expression of the three types of receptor isoforms.[19,31] This is most clearly seen in the developing embryo as the neuromuscular junction is formed. Before they are innervated, the muscle cells of a fetus synthesize only immature and α7 AChRs—hence the term fetal isoform for the former receptor. Synthesis is directed by nearly all the nuclei in the cell, and the receptors are expressed throughout the membrane of the muscle cell (see Fig. 14-7). As the fetus develops and the muscles become innervated, muscle cells begin to synthesize the mature isoform of receptors, which are inserted exclusively into the developing (future) end-plate area. The nerve releases several growth factors that influence the synthetic apparatus of the nearby nuclei. First, nerve-supplied factors induce the subsynaptic nuclei to increase synthesis of AChRs. Next, the nerve-induced electrical activity results in repression of receptors in the extrajunctional area. Nerve-derived growth factors, including agrin and ARIA/neuregulin, cause the receptors to cluster in the subsynaptic area and prompt expression of the mature isoform (Fig. 14-8).[62-65] In conditions associated with insulin resistance, there seems to be a proliferation of AChRs beyond the junctional area. Conditions in which insulin resistance (i.e., decreased growth factor signaling) has been observed include immobilization, burns, and denervation.[84-86] In such conditions, there is associated upregulation of AChRs and

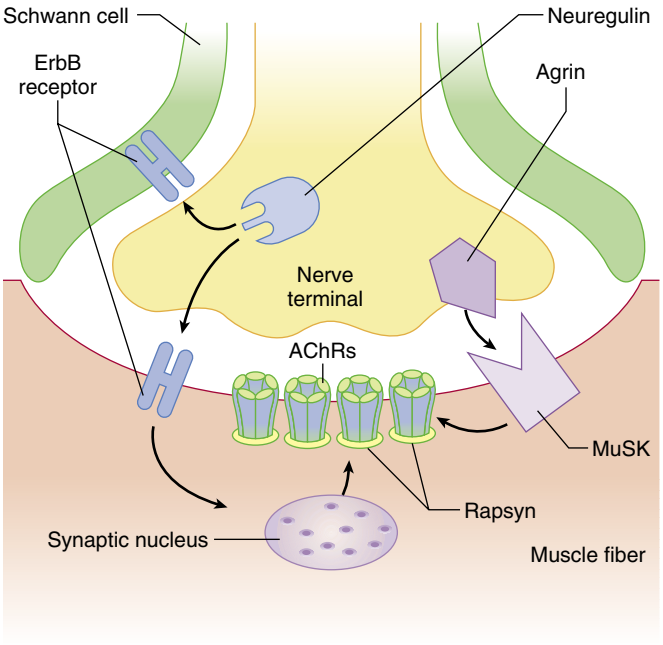

Figure 14-8 Diagram of agrin- and ARIA (acetylcholine receptor–inducing activity)/neuregulin-dependent events during maturation of the neuromuscular junction. After establishment of a nerve on the muscle, growth factors, including agrin and neuregulins, are released. Neuregulin signaling is essential for Schwann cell survival, and Schwann cells are essential for axonal maintenance. Agrin interacting with its receptor MuSK (muscle-specific kinase) enhances the clustering of synaptic proteins, including acetylcholine receptors (AChRs), rapsyn, and ErbB receptors. ARIA/neuregulin is the best candidate for involvement in the conversion of γ-subunit–containing immature receptor to ε-subunit–containing mature (innervated) receptor, which is synapse specific and therefore not inserted in the extrajunctional area.

expression of the immature and α7 AChR isoforms.[1-3] Therefore, agrin and neuregulin signaling may be important for suppression of α7 AChRs.

Before innervation, AChRs are present throughout the muscle membrane. After innervation, AChRs become more and more concentrated at the postsynaptic membrane and are virtually absent in the extrasynaptic area at birth. The innervation process progresses somewhat slowly during fetal life and matures during infancy and early childhood.[15,27,33] With time, the immature receptors diminish in concentration and disappear from the peripheral part of the muscle. In active, adult, normal innervated muscle, just the nuclei under and very near the end plate direct the synthesis of receptor; only the genes for expressing mature receptors are active. Nuclei beyond the junctional area are not active, and therefore no receptors are expressed anywhere in the muscle cells beyond the perijunctional area. Conversion of all of the γ-subunit– to ε-subunit–containing AChRs in the perijunctional area continues to take place after birth. In the rodent, it takes about 2 weeks.[15] In humans, this process takes longer. The timeframe for disappearance of α7 AChRs in the fetus or newborn is also unknown.

At birth, the postsynaptic membrane itself is also not as specialized; the newborn junction has simplified synaptic folds, a widened synaptic space, and reduced numbers of AChRs. Morphologically, the postsynaptic membrane of the newborn and that from a patient with myasthenia gravis are not too different. In

patients with myasthenia gravis, receptor numbers are usually decreased because of autoantibodies directed against the AChR.[4] It is not surprising, therefore, that neurotransmission is not as efficient in the newborn and patients with myasthenia gravis. A child is usually about 2 years old before nerve-muscle contacts are mature.[27]

Proteins implicated in linking of mature receptors to the cytoskeleton include utrophin, α- and β-dystroglycan, and rapsyn. Several lines of evidence indicate that clustering, expression, and stabilization of mature receptors are triggered by at least two growth factors: agrin, neuregulin/ARIA, and possibly calcitonin gene–related peptide.[62-65] Neuregulin and agrin are also released from muscle, but muscle-derived agrin does not seem to be as important in clustering and maturation of the receptor. ARIA is made in the nerve and seems to play a role in maturation of vesicular arrangement and conversion of the γ-to-ε switch.[65] All of these growth factors interact with distinct membrane and cytosolic receptor proteins to cause phosphorylation and activation of nuclear (gene) transcriptional systems. Agrin signals through MuSK and neuregulins through ErbB receptors (see Fig. 14-8). These receptors control qualitative and quantitative changes at the junction. Once begun, the process is very stable, and nuclei in the junctional area continue to express mature receptors.

Re-expression of Immature (Fetal) γ-Subunit and α7-Subunit AChRs in Adult Life

The extrajunctional immature receptors can reappear soon after upper and lower motor denervation and in certain pathologic states (e.g., burns, immobilization, chronic muscle relaxant therapy, loss of electrical activity). Stimulation of a denervated muscle with an external electrical stimulus can prevent the appearance of immature receptors. It has been suggested that the calcium that enters the muscle during activity is important in the suppression process.[16,17] In the pathologic states previously enumerated, if the process is severe and prolonged, extrajunctional receptors are inserted all over the surface of the muscle, including the perijunctional area (see Fig. 14-7). The junctional nuclei also continue to make mature receptors. The end plates consist of mature and immature receptors. The synthesis of immature receptors is initiated within hours of inactivity, but it takes several days for the whole muscle membrane to be fully covered with receptors. This upregulation of receptors has implications for the use of depolarizing and nondepolarizing relaxants. The changes in α7 AChRs seem to parallel the expression of immature receptors, although this has not been well studied.

The changes in subunit composition (γ versus ε) in the receptor confer certain changes in electrophysiologic (functional), pharmacologic, and metabolic characteristics.[1,33] Mature receptors are metabolically stable, with a half-life approximating 2 weeks, whereas immature receptors have a metabolic half-life of less than 24 hours. Immature receptors have a smaller single-channel conductance and a 2- to 10-fold longer mean channel open time than mature receptors do (see Fig. 14-4). The changes in subunit composition may also alter the sensitivity or affinity, or both, of the receptor for specific ligands. Depolarizing or agonist drugs such as succinylcholine and acetylcholine depolarize immature receptors more easily, thereby resulting in cation fluxes; doses one tenth to one hundredth of those needed for mature receptors can effect depolarization.[2] The potency of nondepolarizers is also reduced, as demonstrated by the resistance to nondepolarizers documented in patients with burns, denervation, and immobilization.[1,3] This resistance may be related to decreased affinity of the immature and α7 AChRs to NDMRs and to the upregulation of receptors in the perijunctional area. Data suggest that some NDMRs may also cause a partial agonist response in immature receptors, thus explaining the decreased potency.[7] The altered sensitivities for cholinergic ligands may also result from changes in composition of the lipid membrane surrounding the receptor that is known to occur in some pathologic states.[68]

The altered sensitivity to muscle relaxants may occur in just certain parts of the body or certain muscles if only some muscles are affected by the diminution in nerve activity (e.g., after a stroke). Sensitivity to relaxants can begin to change between 24 and 72 hours after an injury or hospitalization. The most serious side effect with the use of succinylcholine in the presence of upregulated AChRs in one or more muscles is hyperkalemia.[1-3] In these subjects, the receptors can be scattered over a large surface of the muscle. The AChR channels opened by the agonist (succinylcholine) allow potassium to escape from the muscle and enter the blood. If a large part of the muscle surface consists of upregulated (immature) receptor channels, each of which stays open for a longer time, the amount of potassium that moves from muscle to blood can be considerable. The resulting hyperkalemia can cause dangerous disturbances in cardiac rhythm, including ventricular fibrillation. Moreover, it is difficult to prevent the hyperkalemia by prior administration of NDMRs because the extrajunctional receptors are not very sensitive to blockade by NDMRs in the usual doses.[1] Larger than normal doses of NDMRs may attenuate the increase in blood potassium but cannot completely prevent it. However, hyperkalemia and cardiac arrest can occur after the administration of succinylcholine, even in the absence of denervation states. This is seen in certain congenital muscle dystrophies in which the muscle membrane is prone to damage by the potassium released into the circulation by succinylcholine.[87]

Prejunctional Acetylcholine Receptors

AChRs exist in a variety of forms apart from that seen in muscle.[6,88] These receptors are expressed in peripheral neurons, autonomic and sensory ganglia, and the central nervous system. There is also direct and indirect evidence of their existence in lymphocytes, fibroblasts, chondrocytes, macrophages, and granulocytes.[14] Diverse genes encode the heterogeneous AChRs, and the ion channel is formed of multiple subunits (multimers). Seventeen AChR genes have been cloned from vertebrates. They include various combinations of α-subunits (α1 through α10) and β-subunits (β1 through β4) and one each of γ-, δ-, and ε-subunits. The γ-, δ-, and ε-subunits are found only in muscle.

Prejunctional or nerve terminal–associated cholinergic receptors have been demonstrated pharmacologically and by molecular biologic techniques, but their form and functions are not as completely understood as those in the postjunctional area. Many drugs with an abundance of potential targets for drug action can affect the capacity of the nerve terminal to carry out its functions. The trophic function to maintain nerve-muscle contact involves release and replenishment of acetylcholine together with trophic factors that require signaling through many

receptors, of which the prejunctional nicotinic AChR is just one. Succinylcholine produces fasciculations that can be prevented by NDMRs. Because a fasciculation is, by definition, the simultaneous contraction of the multitude of muscle cells in a single motor unit and because only the nerve can synchronize all the muscles in its motor unit, it became apparent that succinylcholine must also act on nerve endings also. Because NDMRs prevent fasciculation, it was concluded that they acted on the same prejunctional receptor. Since then it has been shown many times that very small doses of cholinergic agonists (e.g., succinylcholine) and antagonists (e.g., NDMRs) affect nicotinic receptors on the nerve ending, the former by depolarizing the ending and sometimes inducing repetitive firing of the nerve and the latter by preventing the action of agonists.[6]

Another clue to differences between prejunctional and postjunctional AChRs was the finding that prejunctional AChRs can bind β-bungarotoxin only, whereas postjunctional receptors can also bind to α-bungarotoxin. Additional clues were found in the many demonstrations of quantitative differences in the reaction of prejunctional and postjunctional nicotinic receptors to cholinergic agonists and antagonists.[82,88] For instance, it was known that tubocurarine binds very poorly to the recognition sites of ganglionic nicotinic cholinoceptors and is not a competitive antagonist of acetylcholine at this site. Decamethonium is a selective inhibitor of the muscle receptor, and hexamethonium is a selective inhibitor of nicotinic receptors in the autonomic ganglia.[89,90] Instead, D-tubocurarine and hexamethonium can block the opened channels of these receptors and owe their ability to block ganglionic transmission to this property. The functional characteristics of prejunctional receptor channels may also be different. For example, the depolarization of motor nerve endings initiated by administration of acetylcholine can be prevented by tetrodotoxin, a specific blocker of sodium flux with no effect on the end plate.

Specific information on the molecular organization of neuronal nicotinic receptors on the motor neuron terminal is still lacking. Some of the subunit composition is similar, but other subunits do not resemble those of the postjunctional receptor. Of the 16 different nicotinic AChR gene products identified, only 12 (α2 to α10 and β2 to β4) are thought to contribute nicotinic receptors expressed on neurons. Most strikingly, nervous tissue does not contain genes for γ-, δ-, or ε-receptor subunits; it contains genes only for the α- and β-subunits. The α- and β-subunit genes in nerve and muscle are not exactly the same; they are variants. Muscle contains the genes for each of the α1 and α7 subunits. In contrast, nervous tissue does not contain α1 subunit gene but instead contains a number of related genes designated α2 through α10. To emphasize the distinction between neural and muscle nicotinic receptors, the former are sometimes designated Nn and the latter Nm. With so many different subunits available, there are many possible combinations, and it is not known which combinations are found in motor nerves. Their physiologic roles have also not been completely characterized. Expression of neuronal nicotinic AChRs in in vitro systems has confirmed that muscle relaxants and their metabolites can bind to some of these neuronal AChRs.[89,90]

The nicotinic receptor on the junctional surface of the nerve senses transmitter in the cleft and, by means of a positive-feedback system, causes the release of more transmitter. In other parts of the nervous system, this positive feedback is complemented by a negative-feedback system that senses when the concentration of transmitter in the synaptic cleft has increased appropriately and shuts down the release system. It is believed that tetanic fade and train-of-four fade during neuromuscular blockade with NDMRs arise from presynaptic cholinergic autoreceptors at the motor nerved ending.[58,59] The neuronal AChR subtype on the nerve terminal that causes fade has been identified as α3β2.[90-93] Quite in contrast, succinylcholine does not inhibit the presynaptic α3β2 autoreceptor at clinically relevant concentrations.[59,93] This may be reason for the typical lack of fade during succinylcholine-induced neuromuscular block. Succinylcholine, however, does not interact with α3β4 AChR found in autonomic ganglia.[59] It has also been shown that NDMRs reduce the hypoxic ventilatory response in partially paralyzed humans,[94] and the mechanism behind the depression might be related to inhibition of nicotine receptors on the carotid body.[9] The motor nerve terminal is also known to bear several other receptors, such as opioid, adrenergic, dopamine, purine, and adenosine receptors, as well as receptors for endogenous hormones, neuropeptides, and a variety of proteins. The physiologic roles of these receptors and the effects of anesthetics on them are unknown.

Antagonism of Neuromuscular Blockade

Mechanism of Antagonism

The NDMRs block neuromuscular transmission predominantly by competitive antagonism of acetylcholine at the postjunctional receptor. The most straightforward way to overcome their effects is to increase the competitive position of acetylcholine. Two factors are important, the first of which is the concentration of acetylcholine. Increasing the number of molecules of acetylcholine in the junctional cleft changes the agonist-to-antagonist ratio and increases the probability that agonist molecules will occupy recognition sites of the receptor. It also increases the probability that an unoccupied receptor will become occupied. Normally, only about 500,000 of the 5 million available receptors are activated by a single nerve impulse, and a large number of receptors are in "reserve" and could be occupied by an agonist. The second factor important to the competitive position of acetylcholine is the length of time that acetylcholine is in the cleft. Acetylcholine must wait for the antagonist to dissociate spontaneously before it can compete for the freed site. NDMRs bind to the receptor for slightly less than 1 millisecond, which is longer than the normal lifetime of acetylcholine. The destruction of acetylcholine normally takes place so quickly that most of it is destroyed before any significant number of antagonist molecules have dissociated from the receptor. Prolonging the time during which acetylcholine is in the junction allows time for the available acetylcholine to bind to receptor when the antagonist dissociates from the receptors.

Classes of Drugs Used

Three classes of drugs, potassium channel–blocking drugs, acetylcholinesterase inhibitors, and γ-cyclodextrin derivatives, can be used clinically to reverse nondepolarizer-induced

paralysis.[95,96] The best known of the potassium-blocking drugs is 4-aminopyridine. Its actions are predominantly prejunctional; it impedes efflux of potassium from the nerve ending. Because efflux of potassium is the event that normally ends the action potential of the nerve ending, this action prolongs depolarization of the nerve. Because the flux of calcium into the nerve continues for as long as the depolarization lasts, drugs of this class indirectly increase the flux of calcium into the nerve ending. The nerve releases more acetylcholine and for a longer time than usual, conditions that are effective in antagonizing NDMRs. Because they act prejunctionally, these drugs can antagonize a block produced by certain antibiotics that act on the nerve ending, notably the polymyxins. Although 4-aminopyridine and drugs like it can be used clinically, their use is severely restricted because they are not specific. They affect the release of transmitters by all nerve endings, including motor nerves, autonomic nerves, and central nervous system components. Their use is accompanied by a variety of undesirable effects, and in practice they are used only in special circumstances. A most serious side effect of potassium channel blockers is seizures.

The more commonly used antagonists of neuromuscular block (e.g., neostigmine, pyridostigmine, edrophonium) inhibit acetylcholinesterase by mechanisms that are similar but not identical.[95] Neostigmine and pyridostigmine are attracted by an electrostatic interaction between the positively charged nitrogen in the molecules and the negatively charged catalytic site of the enzyme. This produces a carbamylated enzyme that is not capable of further action (i.e., the catalytic site is blocked and the enzyme is inhibited). Edrophonium has neither an ester nor a carbamate group, but it is attracted and bound to the catalytic site of the enzyme by the electrostatic attraction between the positively charged nitrogen in the drug and the negatively charged acetylcholinesterase site of the enzyme. Edrophonium also seems to have prejunctional effects that enhance release of acetylcholine from the nerve terminal. This effect is therefore useful when deep neuromuscular block needs reversal. Of the three commonly used anticholinesterases, edrophonium shows far greater selectivity than acetylcholinesterase and butyrylcholinesterase, the serum esterase that hydrolyzes succinylcholine and mivacurium. It greatly favors the former enzyme and therefore seems to be the most desirable agent to reverse mivacurium. However, if the patient has normal serum esterase, pharmacokinetic factors are the principal determinants of the duration of block, and the activity of serum esterase or the lack of it plays only a minor role in recovery. There is little reason to prefer one or another reversal drug on these grounds. Anticholinesterases are administered for prolonged periods for the treatment of myasthenia gravis[4] and as prophylaxis in cases of nerve gas poisoning.[54,55] Ironically, prolonged administration of cholinesterase inhibitors can also lead to a myasthenia-like state with muscle weakness.[97]

Cholinesterase inhibitors act preferentially at the neuromuscular junction but also act at other synapses that use the same transmitter, including muscarinic receptors. An atropine-like drug should be administered with the cholinesterase inhibitor to counter the effects of the acetylcholine that accumulates in the muscarinic synapses of the gut, bronchi, and cardiovascular system. The three anticholinesterase inhibitors do not affect synapses in the central nervous system because all are quaternary ammonium ions that do not easily penetrate the blood-brain barrier. A quaternary ammonium derivative of atropine such as glycopyrrolate, which does not diffuse through the blood-brain barrier, is frequently used to limit the anticholinergic effects to the periphery. Other cholinesterase inhibitors, notably physostigmine and tacrine, are not quaternary ammonium compounds and they have profound effects on the central nervous system. They may be antagonized by atropine but not by its quaternary ammonium analog derivatives. Unlike the other cholinesterase inhibitors, physostigmine and tacrine are also potent inhibitors of the enzyme phosphodiesterase, which plays an important role in the regulation of transmitter release at many synapses in the central nervous system. This action may be related to the reported efficacy of these two drugs in the treatment of Alzheimer's dementia.

Cholinesterase inhibitors also have actions at the postjunctional membrane independent of their effects on the enzyme. Several of these compounds contain methyl groups on a positively charged nitrogen, and they can act as agonists on receptor channels by initiating flow of ions and enhancing neuromuscular transmission. Neostigmine, physostigmine, and certain organophosphates can increase the frequency of MEPPs and the quantal content of end-plate potentials, but the importance of the increased release of transmitter to reversal of neuromuscular blockade is not clear. Continuous exposure to carbamate- or organophosphate-containing inhibitors causes degeneration of prejunctional and postjunctional structures, apparently because these structures accumulate toxic amounts of calcium.[54,55] Calcium channel blockers such as verapamil prevent the neural actions of these drugs. All the drugs of this class also act in or on receptors to influence the kinetics of the open-close cycle and block the ion channel.[76,77] The clinical significance of the drugs on reversal of NDMRs is not known.

A new approach to reversing residual neuromuscular blockade is by direct binding of the relaxant by means of chemical interaction. Antidote drugs that work by binding other drugs include protamine, citrate anticoagulation, lead or copper chelators, and RNA molecules recombinantly engineered to bind drugs. Cyclodextrins (i.e., small, cyclic polysaccharides) are one such compound synthesized from starch by bacteria as early as 1891. The γ-cyclodextrin derivative ORG25969 (sugammadex) binds steroidal relaxants with very high affinity, which results in inactive muscle relaxants. The kidney then removes these complexes. Sugammadex has the potential to dramatically change clinical patterns of use of neuromuscular blocking drugs and their antagonists (i.e., neostigmine).[96]

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Göran Hedenstierna

15 Respiratory Physiology

Key Points

1. Removal of CO_2 is determined by alveolar ventilation, not by total, minute ventilation.
2. Dead space ventilation can be dramatically increased in patients with chronic obstructive pulmonary disease and pulmonary embolism to more than 80% to 90% of minute ventilation in the extreme case.
3. Breathing at low lung volume increases airway resistance and promotes closure of airways.
4. Hypoxemia can be caused by alveolar hypoventilation, diffusion impairment, ventilation-perfusion mismatch, and right-to-left shunt.
5. Almost all anesthetics reduce muscle tone, which in turn lowers functional residual capacity (FRC) to close to awake residual volume.
6. Lowered FRC during anesthesia together with ventilation with a high O_2 concentration causes atelectasis.
7. Preoxygenation before and during induction of anesthesia is a major cause of atelectasis.
8. General anesthesia causes ventilation-perfusion mismatch (airway closure) and shunt (atelectasis).
9. Hypoxic pulmonary vasoconstriction is blunted by most anesthetics, thereby enhancing any ventilation-perfusion mismatch.
10. Respiratory work is increased during anesthesia, a consequence of reduced respiratory compliance (reduced lung volume available for ventilation?) and increased airway resistance (lowered FRC and subsequent decrease in airway dimensions?).

Respiratory Function in Waking Subjects

The major task of the lung is to oxygenate the blood and eliminate carbon dioxide from it. This is accomplished by exchanging gas between alveoli and pulmonary capillary blood. Air is brought down to the alveoli by cyclic breathing, and oxygen in the inspired gas diffuses through the alveolar epithelial wall, the interstitial tissue, and the capillary endothelial wall, as well as through the plasma, and finally reaches the hemoglobin inside red blood cells. Carbon dioxide diffuses in the opposite direction, from the blood cells and plasma to the alveolar gas phase, and is expired. To establish gas exchange in the human lung, there must be ventilation of the alveoli, diffusion through the alveolar-capillary membranes, and circulation or perfusion of the pulmonary capillary bed.

The lung is regularly affected by anesthesia and mechanical ventilation. This occurs even in healthy volunteers or patients with no cardiopulmonary disease, and sometimes the dysfunction can be severe enough to cause life-threatening hypoxemia. In patients with preexisting lung disease, gas exchange will be further compromised in comparison to the awake state. Knowledge of the functional impairment that will ensue during anesthesia and mechanical ventilation will make possible ventilatory support that should, in the large majority of patients, prevent any disastrous impairment in gas exchange.

Ventilation

Dead Space and Alveolar Ventilation

Fresh air is brought into the lungs by cyclic breathing. A normal tidal breath at rest in an adult subject is approximately 0.5 to 0.6 L, and the respiratory frequency is around 16 breaths/min, with a range of 12 to 22 breaths/min. Metabolic demand and pulmonary function will determine the magnitude and rate, provided that the respiratory center in the brainstem is intact and functioning. This results in ventilation of approximately 7 to 8 L/min.[1]

All that is inspired does not reach the alveoli. Approximately 100 to 150 mL will be confined in the airways and does not participate in gas exchange. This "dead space" is approximately

30% of tidal volume; that is, the V_{DS}/V_T ratio is 0.3 (see Fig. 15-1 for different forms of dead space).[2] The remaining part of ventilation reaches the alveoli and respiratory bronchioles (with some alveoli tapered on the airway wall). Thus, "alveolar ventilation" is around 5 L/min, similar to cardiac output, which is also 5 L/min. The overall alveolar ventilation-perfusion ratio accordingly is 1.

There are several causes of increased minute ventilation, such as physical exercise, reduced inspired oxygen concentration (or rather, partial pressure of O_2), increased dead space ventilation, and metabolic acidosis.

Increased Dead Space Ventilation

If dead space is increased, ventilation must be raised to account for the "losses" and to maintain P_{ACO_2} at a normal level. Dead space is increased when ventilation is performed through a mouthpiece and a valve or through a facemask. This "apparatus dead space" is something between 25 and a few hundred mL, as compared with the 100 to 150 mL that the natural airways make up ("anatomic dead space").[3] Bronchiectasis increases anatomic dead space, but it adds only little to the total figure. A much larger increase can be caused by ventilation of alveoli that are not perfused, such as a pulmonary embolus stopping blood flow in a lung unit ("alveolar dead space") (Fig. 15-1). A worst case is plugging of the right or left main pulmonary artery, thereby leaving one lung essentially unperfused. In this case, the dead space fraction is doubled from the normal 0.3 to 0.6 or so.[4] Patients suffering from recurrent emboli, or pulmonary embolism, often have high V_{DS}/V_T ratios that can exceed 0.7 to 0.8, which means that to maintain an ordinary alveolar ventilation of 5 L/min, minute ventilation must be raised from 7 to 8 to 20 L/min. Patients with recurrent emboli also frequently complain of dyspnea, even in the absence of severe hypoxemia. The increased ventilatory demand may be the reason. Other patients who suffer from increased dead space are those with obstructive lung disease, including asthma, chronic bronchitis, and emphysema. Their major difficulty is that some regions are poorly ventilated because of airway obstruction, so these regions are underventilated in relation to their perfusion, commonly called a ventilation-perfusion mismatch ("$\dot{V}_A/\dot{Q}$" mismatch signified by low $\dot{V}_A/\dot{Q}$ ratios).[5] This forces inspired air to other regions, which may be ventilated in excess of their perfusion. Such opposite $\dot{V}_A/\dot{Q}$ mismatch (signified by high $\dot{V}_A/\dot{Q}$ ratios) has the same effect on gas exchange as an increase in dead space does and is also measured as dead space (see Fig. 15-1). Indeed, patients with advanced chronic bronchitis may have as high a $\dot{V}_A/\dot{Q}$ ratio as 0.8 to 0.9. Such patients would have to ventilate some 30 to 50 L/min to maintain normal P_{ACO_2}, a difficult task to perform even for a short period with healthy lungs. It should therefore come as no surprise that P_{ACO_2} is increasing as a result of alveolar "hypoventilation." This has led us to say, erroneously, that bronchitic patients are hypoventilating when in fact they are hyperventilating! Some help to these patients comes from the fact that CO_2 can be excreted by half the "normal" alveolar ventilation if P_{ACO_2} is doubled, as can be inferred from the alveolar gas equation (Box 15-1).

Because all subjects, even those with healthy lungs, do have some $\dot{V}_A/\dot{Q}$ mismatch, the sum of the anatomic and alveolar dead space, whether attributable to emboli or uneven ventilation and perfusion, is called "physiologic dead space."

Hyperventilation and Exercise

It is possible to voluntarily increase minute ventilation to a maximum that is almost 20-fold higher than resting ventilation, to above 100 L/min in women and above 150 L/min in men, but only for a brief period of half a minute or so.[1] In addition, hyperventilation without a simultaneous increase in metabolic demand

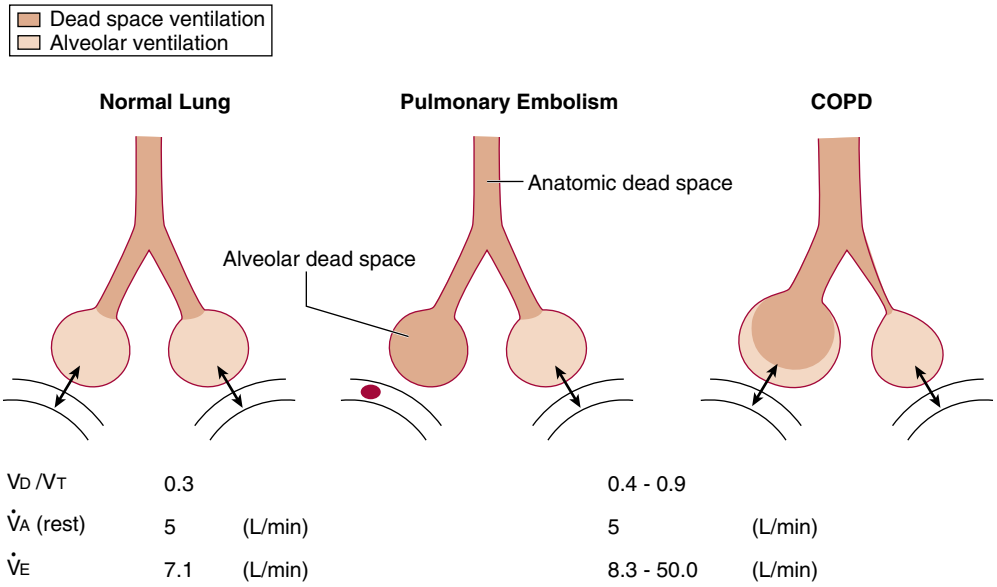


Figure 15-1 Dead space and alveolar ventilation in normal and diseased lungs. Note that both cessation of blood flow and excessive alveolar ventilation relative to perfusion cause an increase in dead space as measured by the conventional CO_2 elimination technique. See also the marked increase in minute ventilation that is required to maintain alveolar ventilation when dead space is increased. COPD, chronic obstructive pulmonary disease; $\dot{V}_A$, alveolar ventilation; V_D/V_T, dead space–to–tidal volume ratio; $\dot{V}_E$, minute ventilation (sum of dead space and alveolar ventilation). *(Courtesy of the editor of the BMJ series Respiratory Measurement.)*

Box 15-1 Alveolar Gas Equations

Alveolar Oxygen Tension (P_{AO_2})

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R} + \left[P_{ACO_2} \times F_{IO_2} \times \frac{1-R}{R} \right]$$

where P_{IO_2} is inspired oxygen tension, P_{ACO_2} is alveolar CO_2 tension (assumed to equal arterial P_{CO_2}), *R* is the respiratory exchange ratio (normally in the range of 0.8 to 1.0), and F_{IO_2} is the inspired oxygen fraction.

The term within brackets compensates for the larger O_2 uptake than CO_2 elimination over the alveolar capillary membranes.

A simplified equation can be written without the compensation term:

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R}.$$

Alveolar Ventilation

Alveolar ventilation ($\dot{V}_A$) can be expressed as

$$\dot{V}_A = f \times (V_T - V_{DS})$$

where f is breaths/min, V_T is tidal volume, and V_{DS} is physiologic dead space.

Alveolar ventilation can also be derived from

$$\dot{V}_{CO_2} = c \cdot \dot{V}_A \cdot F_{ACO_2}$$

where $\dot{V}_{CO_2}$ is CO_2 elimination, *c* is a conversion constant, and F_{ACO_2} is the alveolar CO_2 concentration.

If $\dot{V}_A$ is expressed in L/min, $\dot{V}_{CO_2}$ in mL/min, and F_{ACO_2} is replaced by P_{ACO_2} in mm Hg, $c = 0.863$. By rearranging,

$$\dot{V}_A = \frac{\dot{V}_{CO_2} \cdot 0.863}{P_{ACO_2}}.$$

will lower P_{aCO_2} and affect consciousness. In respiratory tests of ventilatory capacity it is therefore necessary to perform the test during rebreathing of expired gas or add CO_2 to the respiratory gas so that P_{aCO_2} is maintained at a normal or nearly normal level. The increase in ventilation is brought about by an increase in V_T to approximately two thirds of vital capacity (VC) (see later), or 2.5 to 4 L, and an increase in frequency to 40 breaths/min or greater. However, during maximum physical exercise, minute ventilation increases less, to around two thirds of maximum capacity, which means an increase to 65 to 100 L/min in normally fit women and men. In athletes, ventilation may exceed 150 L/min.

Lung Volumes

Functional Residual Capacity

There is a certain amount of air in the lungs after an ordinary expiration. This volume is called functional residual capacity (FRC) (Fig. 15-2). It amounts to approximately 3 to 4 L and is dependent on sex, age, height, and weight. FRC goes up with height and age and down with weight and is smaller in women than in men.[1,6] The balance of the inward force of the lung and the outward force of the chest wall determines the volume. The inward force of the lung, or "elastic recoil," consists of the elastic fibers of the lung tissue, as well as the contractile forces of airway smooth muscles and the surface tension of alveoli. The outward force of the chest wall is exerted by the ribs, joints, and muscles. It can be asked why any gas volume persists in the lung after expiration. There are two good reasons, at the least. One is that if alveoli collapse during expiration, much more effort would have to be spent to reopen them again than during a normal breath with no collapse because less resistance is encountered when expanding an alveolar wall in an open lung with a liquid-gas interphase unit than expanding a collapsed alveolus with a liquid-liquid interphase. The other reason is that the inspired air mixes with the remaining gas in the lung, thereby leveling off the variation in O_2 and CO_2 concentrations that occur during the respiratory cycle. With just little air in the lung, the gas variations in alveoli would be much greater, and they would cause a similarly varying P_{aO_2} and P_{aCO_2} in blood. This can indeed be observed in patients with reduced lung volumes (see later).

With increased ventilation, as during exercise, V_T is raised by increasing both inspiration and expiration so that FRC is lowered by approximately 0.5 L. However, in the presence of airway obstruction, as in asthma, for example, expiration is slowed down so that the end-expiratory level is elevated instead of being lowered.[7] This is called air trapping and is a means of reducing the resistance to gas flow in the narrowed airways (Fig. 15-2). However, it has to be paid for because the increased level of breathing increases the elastic work of breathing.

FRC increases with age because of loss of elastic lung tissue, which lessens the contractile force of the lung and moves the balancing point between the outward force of the chest wall and the inward force of the lung to higher lung volume. In patients with chronic obstructive pulmonary disease (COPD), FRC increases faster over the years than in normal subjects because of an effect of chronic air trapping and more severe loss of elastic tissue (in particular in emphysema).[1]

FRC is reduced in lung diseases characterized by fibrosis of the lung, such as idiopathic fibrosis, pneumoconiosis, and different forms of granulomatosis and vasculitis.[7] In extreme cases, the reduction can be down to 1.5 to 2 L (see Fig. 15-2). Obviously, pulmonectomy (e.g., for treatment of lung cancer) will also reduce FRC. However, the remaining lung will expand and fill in some of the space left after resection of lung tissue, sometimes called "compensatory emphysema."

Total Lung Capacity and Subdivisions

The gas volume in the lung after a maximum inspiration is called *total lung capacity* (TLC). It is typically 6 to 8 L.[1] TLC can be increased in patients with COPD either by overexpansion or "hyperinflation" of essentially normal alveoli or by destruction of the alveolar wall with loss of elastic tissue, as in emphysema (see Fig. 15-2).[7] In extreme cases, TLC can be increased by 50%, or up to 11 to 12 L. In restrictive disorders, TLC is reduced in proportion to the severity of the fibrotic process and may be as low as 3 to 4 L (see Fig. 15-2).[7]

Even after a maximum expiratory effort, some air is left in the lung and no region normally collapses. This persisting gas volume is called *residual volume* (RV) and amounts to 2 to 2.5 L.

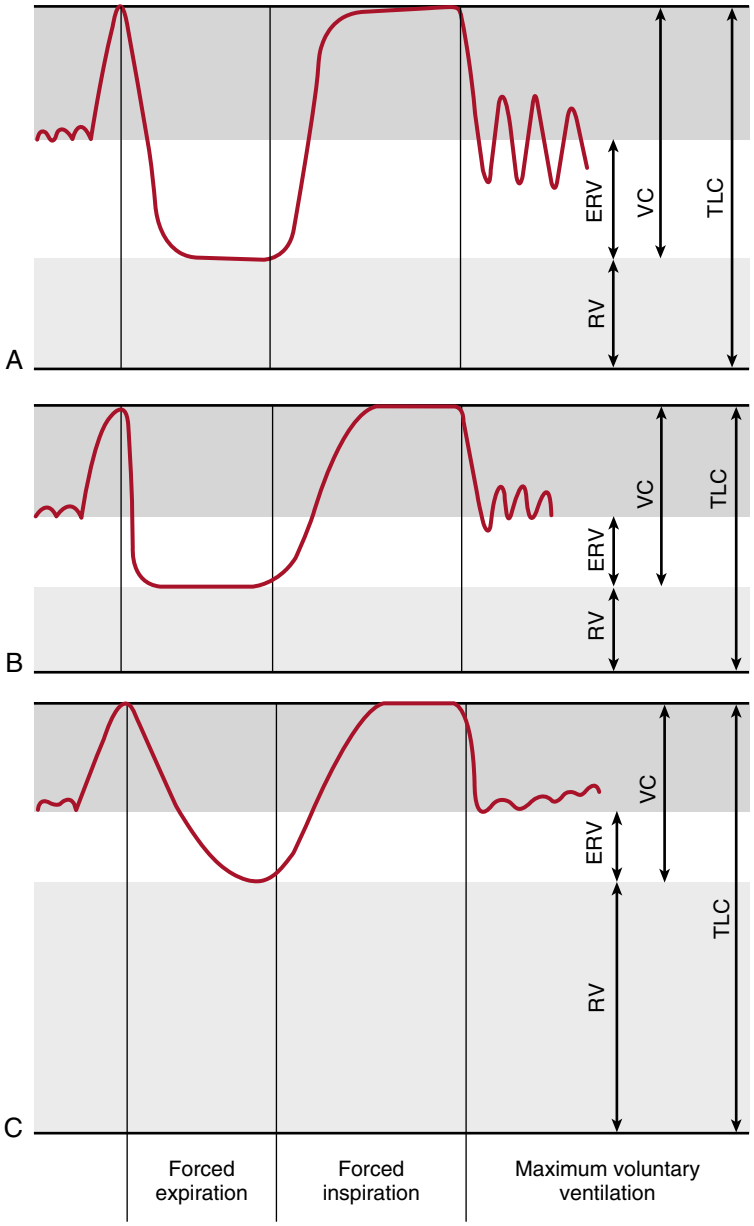


Figure 15-2 Ventilation and lung volumes in a healthy subject with normal lungs (**A**), a patient with restrictive lung disease (**B**), and a patient with chronic obstructive lung disease (**C**). Note the decrease in vital capacity (VC) and the increased expiratory flow (steeper than the normal slope of the forced expiratory curve) in the patient with lung fibrosis. Note also the increased residual volume (RV), reduction in VC, and the slow forced expiration in the obstructive, emphysematous patient. The latter patient demonstrates air trapping during hyperventilation. ERV, expiratory reserve volume; TLC, total lung capacity. *(Courtesy of the editor of the BMJ series: Respiratory Measurement.)*

The reason that expiration stops before all gas has been evacuated seems to be twofold. First, distal airways 2 mm or less in diameter close before alveoli collapse.[8] This trapping of gas will thus prevent the alveoli from being squeezed to emptiness. Second, the chest wall, rib cage, and diaphragm cannot be distorted to the point that all gas in the lung will be expelled. The advantage of not allowing lung tissue to collapse was presented earlier (see Fig. 15-2).

The maximum volume that can be inspired and expired is called *vital capacity*. VC is thus the difference between TLC and RV and is around 4 to 6 L. It is reduced in restrictive lung diseases, frequently before a decrease in RV. What may not be equally clear is that VC is also reduced in obstructive lung disease. This is an effect of the chronic "air trapping" that increases RV, mainly at the expense of VC.[7] However, as said earlier, TLC may also increase, but not in proportion to the rise in RV. The net effect can be a TLC of 12 L made up of an RV of 11 L and a VC as small as 1 L, in an extreme example of emphysema.

Respiratory Mechanics

Understanding the mechanics of the respiratory system serves at least two purposes. One, it gives a clue to what governs the distribution of inspired air, and second, recording of the mechanics can be used as a diagnostic and prognostic tool in lung disease. Here, we will begin with an analysis of the elastic and resistive forces that have to be overcome during breathing and how these forces are affected by pulmonary disorders. We will then continue to analyze the influence of respiratory mechanics on the distribution of inspired air.

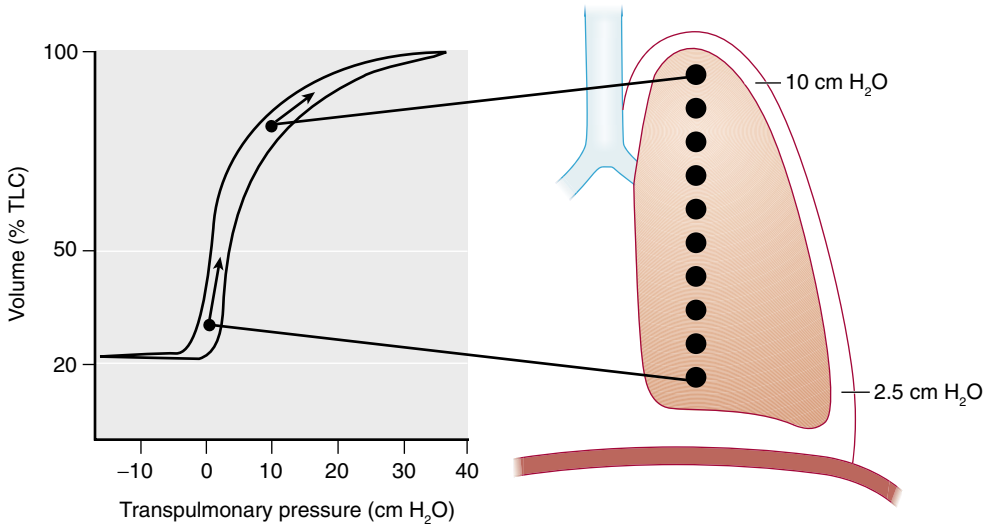


Figure 15-3 Pressure-volume relationships of the lung. Note the curved relationship, which is typical of an elastic structure. Note also the lower (more subatmospheric) pleural pressure in the upper regions. Regional transpulmonary pressure (mouth minus pleural pressure) is thus higher for apical lung units than for basal ones in an upright subject. This results in different positions of the upper and lower lung regions on the pressure-volume curve. The consequence will be that the lower lung regions expand more for a given increase in transpulmonary pressure than the upper units do. Thus, ventilation goes preferably to the lower lung regions.

Compliance of the Respiratory System

The lung recoils like an elastic rubber balloon. Thus, a certain pressure is required to keep it inflated. The pressure needed to keep the lung inflated at a certain volume is pleural minus alveolar pressure, or "transpulmonary pressure" (Ptp). It will be seen that more and more pressure is required for a given increment in volume the more the lung is inflated (Fig. 15-3).[9] Such a curved pressure-volume relationship is typical of elastic structures, and a similar curved force-length relationship will also be seen for a rubber band.

The elastic behavior of the lung is often analyzed in terms of compliance, which is the inverse of elastance. Thus, compliance is expressed as change in lung volume divided by the change in pressure required to cause the increment in volume (or the decrease in pressure that is accompanying a decrement in volume). Normal lung compliance is around 0.2 to 0.3 L/cm H_2O (2 to 3 L/kPa).[9] It varies with lung volume, as can be seen in Figure 15-3, and decreases with an increase in lung volume. Thus, compliance is critically dependent on the lung volume at which it is measured. This should be remembered if one does repeated recordings to monitor the progress of a disease. In addition, if a lung is resected or part of it, the measured compliance is reduced despite the fact that the remaining lung tissue is unaltered.

In fibrotic lung disease, compliance is reduced and the pressure-volume curve is flatter and shifted to the right, as shown in Figure 15-4 (obviously, the direction of a change in the pressure-volume curve depends on which axis is denoted pressure and which is volume; the figure shows the standard drawing).[9] Although the curve is sensitive to changes in the elastic properties of the lung, it is not good at discriminating between different diseases. Thus, idiopathic fibrosis, alveolar proteinosis, a granulomatosis-like sarcoidosis, and interstitial and alveolar edema will all reduce compliance and cause a flattening and right shift of the pressure-volume curve.

Loss of elastic lung tissue, as in emphysema, causes a steeper curve that is shifted to the left (see Fig. 15-4).[9] Similar changes are not seen in chronic bronchitis or asthma. Thus, recording of the pressure-volume curve can help in establishing the diagnosis of emphysema, which cannot easily be done with a conventional chest radiograph. The overaeration that can be seen on conventional chest radiographs does not enable a distinction between obstructive lung disease with and without loss of elastic tissue. High-resolution computed tomography (CT), however, enables visualization of the delicate lung structure and can be used for differential diagnosis.[10]

The chest wall itself also exerts an elastic impedance to breathing that goes undetected during spontaneous breathing

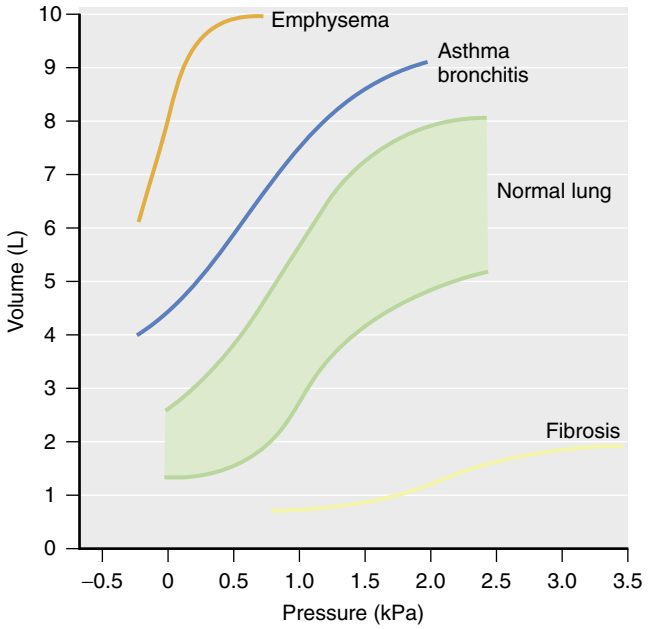


Figure 15-4 Examples of pressure-volume curves of the lung in health and lung disease. Note the much flatter slope of the curve in fibrotic lung disease, which reflects a considerable increase in pressure variation and respiratory work. Also, note the parallel shift in the pressure-volume curve of an asthmatic and bronchitic patient, which shows that compliance need not change in these diseases, although lung volume may have increased. Finally, note the steep slope of the curve of an emphysematous patient. This indicates loss of elastic tissue and might even suggest reduced respiratory work. However, such patients, as well as asthmatic and bronchitic patients, have increased airway resistance, which causes elevated respiratory work. *(Courtesy of the editor of the BMJ series: Respiratory Measurement.)*

because the chest wall is part of the pump itself. Chest wall mechanics can be measured in trained volunteers, but it requires tricky respiratory maneuvers with complete relaxation of the respiratory muscles.[11] During artificial ventilation and muscle relaxation, on the other hand, compliance of the chest wall can be measured because the respiratory muscles are allowed to rest and the rib cage and diaphragm exert elastic impedance only when the lungs are inflated and the chest wall is expanded. The change in lung volume divided by the change in pleural pressure will then give chest wall compliance. It can be seen that compliance of the chest wall is approximately the same magnitude as compliance of the lungs, around 0.2 L/cm H_2O. It may go down in obesity and in conditions associated with general edema, as well as in disorders affecting the joints, such as ankylosing spondylitis.[11]

Resistance of the Respiratory System

Pressure is required to overcome the resistance to gas flow through the airways during respiration. In addition, sliding of different components of lung tissue and the chest wall during inspiration and expiration exerts resistance.[12] This resistance is calculated as forcing pressure divided by gas flow. Flow can be measured at the airway opening, the mouth or nose, and is assumed to apply to the calculation of all three types of resistance (in airways, lung tissue, and the chest wall). The forcing pressure for airway resistance is mouth (or nose) pressure minus alveolar pressure, whereas the other driving pressures will be part of the changes in transpulmonary and pleural pressure.

Gas flow can be turbulent, with a disorderly pattern signified by vortices, or laminar, with a streamlined unidirectional flow pattern. Turbulent flow is proportional to the square of the pressure, and laminar flow, which is less pressure demanding, is linearly related to the pressure. Flow is turbulent in larger airways and at bifurcations and irregularities of the bronchi. It is laminar in the smaller airways. Thus, most of the energy, or pressure, involved in creating flow of gas is expended on overcoming resistance in the larger airways.[12] Only about 20% of the measured airway resistance, in a normal subject, is located in the small bronchi. A doubling of "peripheral" or "small" airway resistance may be difficult to detect by standard recording techniques. The difficulty in detecting changes in small airways, approximately 2 mm wide or less, has coined the expression "the lung's silent zone."

Airflow resistance is normally around 1 cm H_2O/L/sec. With obstructive lung disease it is increased to about 5 cm H_2O/L/sec in mild to moderate asthma and bronchitis and greater than 10 in more severe cases.[13] It is worth noticing that breathing through a size 8 endotracheal tube causes a resistance of 5 cm H_2O/L/sec at a flow of 1 L/sec and that a size 7 tube increases resistance to 8 cm H_2O/L/sec (i.e., comparable to moderate asthma).[14]

Airflow resistance can be higher during expiration than during inspiration, in particular during forced breathing and in patients with obstructive lung disease because the expiratory muscle effort will act not only on alveoli, to empty them, but also on airways, to make them smaller.[12] The inspiratory effort, on the other hand, helps dilate airways within the thorax by lowering pleural pressure, which acts on the outside of the airway wall. Finally, airways that are not in the thoracic cavity, specifically the pharynx, larynx, and trachea, are subject to lower pressure inside than outside their wall during inspiration because they are surrounded by atmospheric pressure, whereas luminal pressure is below atmospheric (otherwise no air would be sucked into that point of the airway tree).[12] These physiologic consequences can also be used to separate an increase in extrathoracic resistance from an increased resistance in other airways. If resistance is increased during inspiration, it is probably caused by narrowing of extrathoracic airways (e.g., sucking of a paralytic vocal chord into the lumen). Retraction of the upper airways and resultant strenuous breathing can also be seen in a neonate with respiratory distress (see Chapter 84).

Resistance of lung tissue and the chest wall has been studied to a lesser extent. Lung tissue resistance amounts to around 1 cm H_2O/L/sec in the normal case and can be increased threefold to fourfold in chronic lung disease.[15] Even less has been studied regarding chest wall resistance. However, it seems as though the sum of lung tissue and chest wall resistance is increased, and markedly so, in acute respiratory failure demanding mechanical ventilation.[16]

Respiratory resistance, in particular airway resistance, is dependent on lung volume. When it comes to airways, it can be understood that during inspiration, airways as well as alveoli are expanded and resistance in the airways will decrease. During expiration, the airways get narrower and resistance will accordingly increase. This is shown in Figure 15-5. Airway resistance may be around 1 cm H_2O/L/sec at the FRC level and is reduced further, although to a small extent, when breathing at higher lung volumes. In contrast, expiration down from FRC rapidly increases resistance, which may be 5 to 8 cm H_2O/L/sec when approaching RV. Indeed, a resistance-versus-lung volume plot as shown in Figure 15-5 approaches infinity at the end of a maximal expiration. This must be realized when taking airway resistance measurements at different lung volumes. One example is when resistance is compared between the waking state and during anesthesia. In the latter situation, FRC is reduced, as will be discussed later.

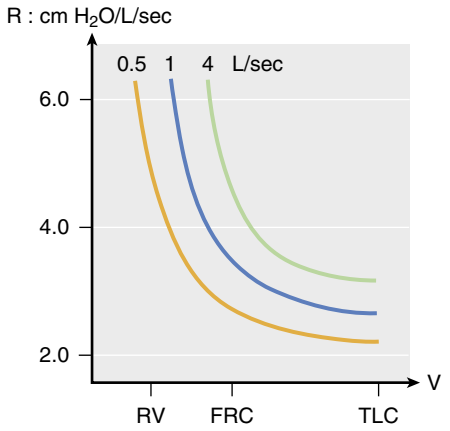


Figure 15-5 Schematic drawing of resistance against lung volume at different flow rates. Note that resistance increases with decreasing lung volume and more so below functional residual capacity (FRC) than at higher lung volume. Note also that resistance increases with an increase in flow rate. Note that at low lung volume, resistance is as high as can be seen in moderate to severe asthma (6 to 8 cm H_2O/L/sec). RV, residual volume; TLC, total lung capacity.

Inertia or Acceleration of Gas and Tissue

There is finally one additional component of the total impedance to breathing, and that is inertance, or the pressure required to accelerate air and tissue during inspiration and expiration. This component, however, is minor and can hardly be measured under normal breathing, regardless of whether the lungs are healthy. During very rapid breathing, such as during high-frequency oscillation in intensive care or the yogi exercise of rapid shallow breathing of around four breaths/sec, acceleration becomes more important and can contribute 5% to 10% of the total impedance to breathing.[17]

Gas Distribution

Distribution of Inspired Gas: Effect of Compliance, Resistance, and Airway Closure

The air that is inspired will not be evenly distributed in the lung. During quiet breathing, most gas goes to the lower, dependent regions—the basal, diaphragmatic areas in the upright or sitting position and the dorsal units in the supine position.[18] This also means that the lower part of the left lung will receive most of the air if the subject is in the left lateral position and that the right lung will be preferentially ventilated in the right position. The reason for this seemingly gravitational orientation of something as light as gas is the combined effect of the curved pressure-volume relationship of the lung tissue and the increasing pleural pressure down the lung. This topic will be discussed at some length in the next paragraph.

First, the curved pressure-volume curve, typical of an elastic tissue as stated earlier, means that with increasing lung volume, more and more pressure is required to inflate the lung with a given increment in volume (there may be a linear pressure-volume relationship for some distance). Second, the increasing pleural pressure, at constant alveolar pressure all over the lung, causes transpulmonary pressure to decrease from the top to the bottom of the lung. In the upright position, the apical lung regions are exposed to higher transpulmonary pressure than the dependent, basal ones are. Thus, the upper and lower lung regions are positioned at different levels of the pressure-volume curve (see Fig. 15-3). During inspiration, pleural pressure is lowered, which causes the lower lung regions to inflate more than the upper ones with a similar change in transpulmonary pressure (it is assumed that pleural pressure changes uniformly in the pleural space).[18] Thus, in a healthy subject, ventilation goes preferentially to the basal regions, as can be inferred from Figure 15-3 (the larger arrow in the lower, basal part of the lung indicates more ventilation than in the upper, apical regions with the subject in the upright position; Fig. 15-6). The pleural pressure gradient is oriented in a vertical, gravitational direction, which is why the distribution of ventilation changes with body position.

What causes the pleural pressure gradient? The major factor is the weight of the lung itself, with less lung tissue exerting pressure at a level higher up in the thoracic cavity than at a lower lung level. This pressure is exerted in all directions, including the pleural space. The specific density of an air-filled and perfused lung is on average approximately 0.3, and this causes the pleural pressure to increase by 0.3 cm H_2O/cm vertical distance. If the lung is heavier, as when it is suffering from edema, the pleural pressure gradient will increase, as does the vertical difference in alveolar size. If weight is reduced or eliminated, as in zero gravity or microgravity, there should be no vertical pleural pressure gradient, and lung expansion as well as gas distribution should be more even. During short parabolic flights causing very low gravity, inspiration and expiration of gases with different characteristics showed reduced inhomogeneity of the distribution of ventilation.[19] However, some inhomogeneity persisted, thus indicating that nongravitational factors also contribute to the distribution of ventilation. Such factors may be uneven convectional and diffusional flow in small lung units and may be related to differences in the anatomic structure of the airways (and parenchyma?).[20]

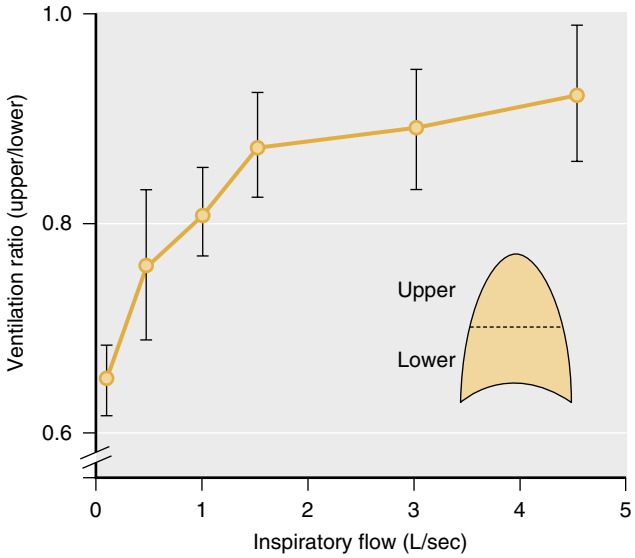


Figure 15-6 Ratio of ventilation to the upper and lower lung regions with a change in inspiratory flow. Note that the distribution of ventilation goes to the lower lung regions at a low flow rate. However, this is replaced by a more even distribution with increasing flow, as, for example, during exercise. This ensures more efficient use of lung tissue and the alveolar-capillary membranes for gas transfer (provided that pulmonary blood flow shows a similar distribution pattern). *(Redrawn from data in Bake B, Wood L, Murphy B, et al: Effect of inspiratory flow-rate on regional distribution of inspired gas. J Appl Physiol 37:8-17, 1974.)*

The vertical pleural pressure gradient may be smaller in the prone position than when supine.[21] This may be due to the weight of the heart, which is compressing the dependent parts of the lung in the supine position and permitting the nondependent regions to expand. In the prone position, the heart is resting on the sternum with less effect on the shape of the lung. The only force that can distort the lung is the weight of the lung itself. Moreover, as discussed earlier, differences in airway anatomy may contribute to differences in the distribution of ventilation when supine and prone. A more even distribution of inspired gas in the prone position has also been demonstrated by isotope technique.[22,23]

Thus far we have dealt with the distribution of inspired gas during, from a technical and purist point of view, static conditions (which, however, would not result in any gas flow). The distribution will be essentially the same during quiet breathing, up to a flow rate of 0.5 L/sec or so. However, with an increasing flow rate, regional differences in airway resistance (and in lung tissue and possibly to some extent chest wall resistance; they will be disregarded here) will play an increasing role in determining gas distribution. Because lung tissue, both alveoli and airways, is more expanded in the upper than in the lower regions, resistance to gas flow is less in the upper part of the lung. This results in a change

in the distribution pattern, with more gas going to the upper units.[24] At a flow of 0.3 L/sec, two thirds of ventilation went to the lower half of the lung as assessed by isotope technique, and when inspiratory flow was increased to 4 to 5 L/sec, distribution between the upper and lower half of the lung was even (see Fig. 15-6). This is advantageous for optimizing gas transfer in the lung, as for example during exercise, because the alveolar-capillary surface area will be more efficiently used. Perfusion distribution may be evenly distributed. Perfusion does adjust in the same way as ventilation, which will be discussed later in this section.

Airways become narrower during expiration, as can be inferred from the previous discussion. If the expiration is deep enough, airways in dependent regions will eventually close. The volume above RV at which airways begin to close during expiration is called *closing volume* (CV), and the sum of RV and CV is called *closing capacity* (CC).[25] Airway closure is a normal physiologic phenomenon and is the effect of increasing pleural pressure during expiration. When pleural pressure becomes "positive" (or rather, above atmospheric), it will exceed the pressure inside the airway, which is just or nearly atmospheric at a low flow rate. The higher pressure outside than inside will compress the airway and may close it. Because pleural pressure is higher in dependent regions than higher up, closure of airways begins in the bottom of the lung. The crucial point is thus the creation of "positive" pleural pressure (Fig. 15-7). In young subjects it may not occur until they have expired to RV. However, with increasing age, pleural pressure becomes "positive" at higher and higher lung volume, and at an age of 65 to 70 years, airway closure may occur above FRC.[26] This means that in elderly subjects, dependent lung regions are intermittently closed during the breath. These regions will reopen during inspiration, when lung volume exceeds CC. The impediment to ventilation that closure of airways causes seems to be the major explanation of why arterial oxygenation decreases with age (see Chapter 71).

Airway closure plays an even greater role in the supine position because FRC is reduced whereas CC is not affected by body position. Closure of airways may occur above FRC, even at an age of 45 to 50, and in a 70-year-old subject, the airways may be continuously closed if CC exceeds FRC plus VT. This is illustrated in Figure 15-8.

Airway closure occurs at higher lung volumes in patients with obstructive lung disease. Secretions, edema of the airway wall, and increased bronchial muscle tone all reduce the lumen of the airway and facilitate premature closure.[25] Because these changes are thought to begin in the small airways, recording of CV has been considered an ideal test for early detection of airway disease. However, use of CV is not as popular as it was earlier because its reproducibility is not as good as that of conventional spirometry. However, even if recording of airway closure as a diagnostic and quantitative measure of lung disease may not have been as successful as hoped for, it should not obscure the fact that airway closure is a most important phenomenon. Its detection has taught us a lot of the physiologic principles governing the distribution of ventilation.

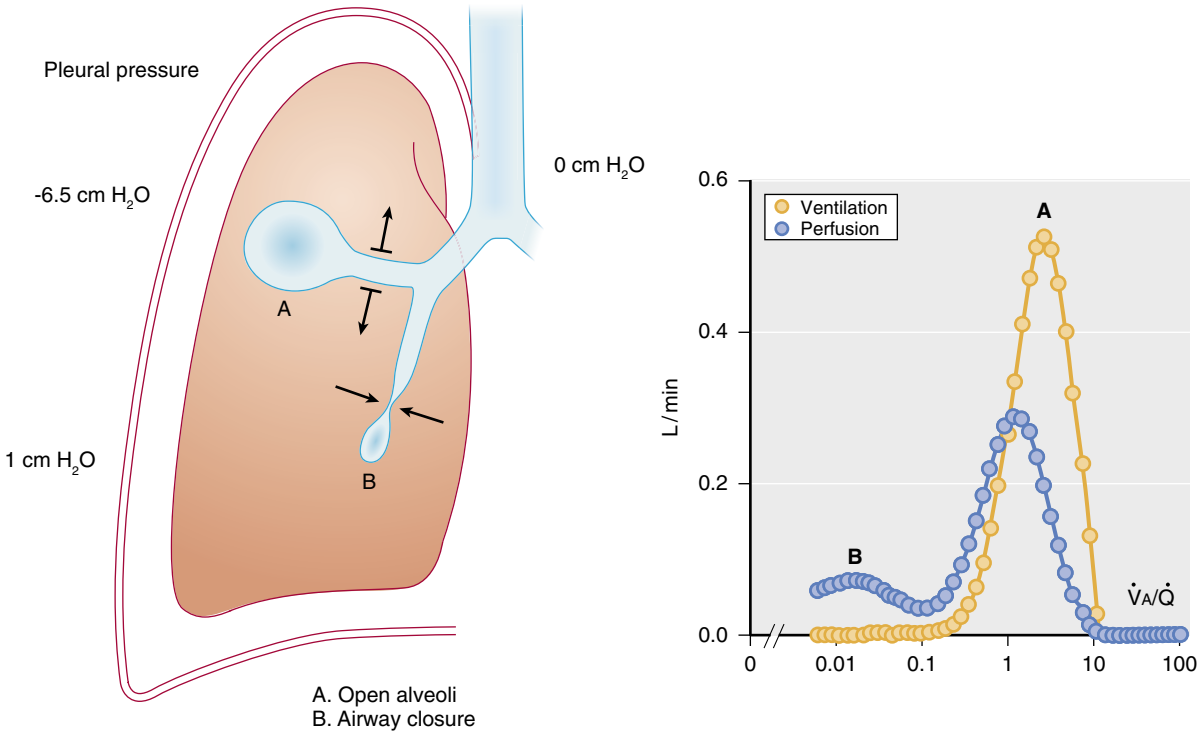


Figure 15-7 Schematic drawing of regional alveolar and airway volume at an upper (A) and a lower (B) lung level, *left panel*. There is a vertical pleural pressure gradient with a difference of approximately 7.5 cm H_2O between the uppermost and lowermost regions. This causes a transpulmonary pressure gradient with higher pressure inside the airway and alveolus in the upper part and higher pressure outside the alveolus and airway in the lower part. This results in closure of the airways with the potential for slow alveolar gas adsorption behind the occluded airway. The *right panel* shows a distribution of ventilation and perfusion ratios as obtained by the multiple inert gas elimination technique. A "normal" mode of ventilation and blood flow (A) can be seen corresponding to the open and ventilated alveoli in the upper parts of the lung. In addition, there is a mode of low $\dot{V}_A/\dot{Q}$ ratios with more perfusion than ventilation (B). This could apply to an elderly healthy subject with intermittent airway closure during breathing.

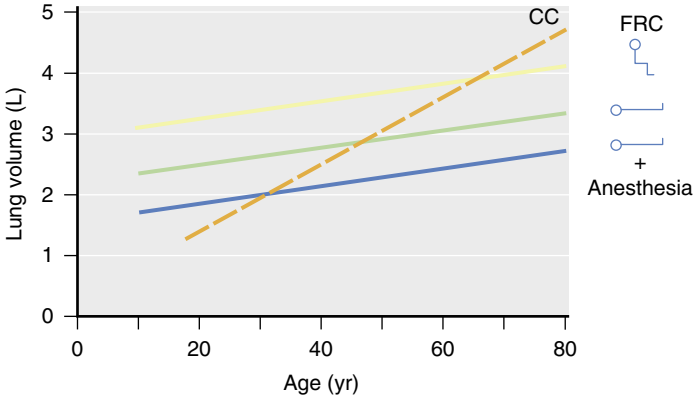


Figure 15-8 Resting lung volume (functional residual capacity [FRC]), upright and supine, and closing capacity (CC, unaffected by body position) at different ages in healthy subjects. Note the lower FRC, by approximately 0.7 to 0.8 L, in the supine position (an effect of cranial displacement of the diaphragm by the abdominal organs). As can be seen, there is also a slight increase in FRC with age at constant height and weight. This is an effect of the loss of elastic tissue with aging. Finally, observe the more rapid increase in CC with age. This results in airway closure above FRC in upright subjects at ages of 65 to 70 years or older. In the supine position, airways may close during breathing even at the age of 45 to 50 years! This relationship between CC and FRC is a likely explanation for the decreasing oxygenation of blood with age. The effect of anesthesia can also be seen with lowering of FRC so that airways may close already at 30-year-old subjects (see section on "Lung Volume and Respiratory Mechanics during Anesthesia"). The curves are based on pooled data from different studies.

As mentioned earlier, secretions, edema, and spasm reduce the airway lumen. This will affect gas distribution as well by decreasing or eliminating ventilation in regions that are affected by airway obstruction and by increasing it in other, less obstructed areas.

Expiring against resistance, such as against half-closed lips ("pursed-lips breathing"), is a technique sometimes taught to a patient with chronic obstructive disease. This may make breathing easier. Devices are also available to breathe out through that act as resistance. These devices build up higher pressure inside the airway, which prevents it from closing during expiration; this is the reason why breathing is more comfortable. Thus, the device "stabilizes" the airway and facilitates expiration.[27] Although the result may be the desired one, the explanation is wrong. The higher airway pressure can be generated only by increasing the expiratory effort, and this increases pleural pressure to the same extent as airway pressure. The decrease in pressure across the airway wall will be the same as without the expiratory resistance, and this will not make the airway more stable. What may explain a beneficial result is that the expiratory resistance increases lung volume and slows down expiration. The former (increase in lung volume) is the only way of increasing transpulmonary and transairway pressure, and this stabilizes the airway. Simultaneously, there is a general increase in airway caliber that further reduces resistance, as discussed earlier. The latter (slowed expiration) reduces the decrease in pressure from the alveoli toward the mouth because lower flow requires less driving pressure. By this means the point along the airway tree where pressure inside the airway has dropped to below that outside the airway (equal to pleural pressure) is moved toward the mouth (Fig. 15-9). Thus, slow expiratory flow may make it possible to move the "equal pressure point," where inside and outside airway pressure is equal, up to the larger airways or the mouth, which will prevent floppy airways from collapsing.[28]

Diffusion of Gas

Diffusion in Airways and Alveoli

Gas flow is convective in the larger and medium-sized airways, down to approximately the 14th generation. Airways at this level begin to be tapered with alveoli and participate in gas exchange with pulmonary blood. In the latter airway generations, from 15 to 23, the total cross-sectional area of the airway tree grows rapidly, from 2.5 cm^2 in the trachea, to 70 cm^2 in the 14th generation entering the acinus, to 0.8 m^2 in the 23rd generation.[29] The total alveolar surface is approximately 140 m^2. Gas flow velocity will decrease as the area increases. For an ordinary breath the average velocity of gas in the trachea will be around 0.7 m/sec, but at the alveolar surface it is no higher than 0.001 mm/sec. This is much slower than the diffusion rate of O_2 and CO_2 in the airway tree and the alveoli. Transport of O_2 and CO_2 is therefore accomplished by diffusion in the peripheral airways and in the alveoli, not by convective flow. CO_2 can be detected in the mouth after a few seconds of breath-holding. However, this is the result not only of diffusion but also of convection brought about by the beating heart, which acts as a mixing pump. Yet even in the absence of heartbeats, CO_2 appears within seconds at the airway opening. This rapid diffusion has an implication when measuring dead space by recording of the expiratory CO_2 curve—an inspiratory breath-hold reducing the measured dead space down to zero, if the breath is held for just a few seconds.

It has often been discussed whether gas mixing is complete in the alveoli of a normal lung during normal breathing or whether there are concentration gradients, often called "stratified inhomogeneity." Many consider alveolar concentrations to be homogeneous. However, if the alveolar dimensions grow, by expansion or confluence of several alveoli as in emphysema, the diffusion distance can be too great to allow complete mixing of inspired and alveolar gas during ordinary breathing. This will cause stratified inhomogeneity of respiratory gas concentrations within the alveolar unit and has an impeding effect on gas exchange, similar to uneven distribution of ventilation by other means.[30]

Diffusion Across Alveolar-Capillary Membranes

Oxygen diffuses passively from the alveolar gas phase into plasma and red cells, where it binds to hemoglobin. Carbon dioxide diffuses in the opposite direction, from plasma to the alveoli. The amount that can diffuse over the membranes for a given period is determined by (1) the surface area available for diffusion, (2) the thickness of the membranes, (3) the pressure difference of the gas across the barrier, (4) the molecular weight of the gas, and (5) the solubility of the gas in the tissues that it has to traverse.[31] These factors are discussed in the following paragraphs.

Surface Area. Lung volume will obviously be of importance. The smaller the lung, the less the overall diffusion. To this should be added that the lung surface can be used for diffusion only if there is circulating blood on the capillary side. Thus, pulmonary capillary blood volume is an important determinant of diffusion. The relative influence of membrane area and characteristics, as well as capillary blood volume, can be analyzed separately by performing a diffusion or transfer test at two different inspired oxygen concentrations. Carbon monoxide (CO) is normally used as the test gas. CO is inspired at a small concentration (0.3%) to TLC after a previous maximum expiration, and the

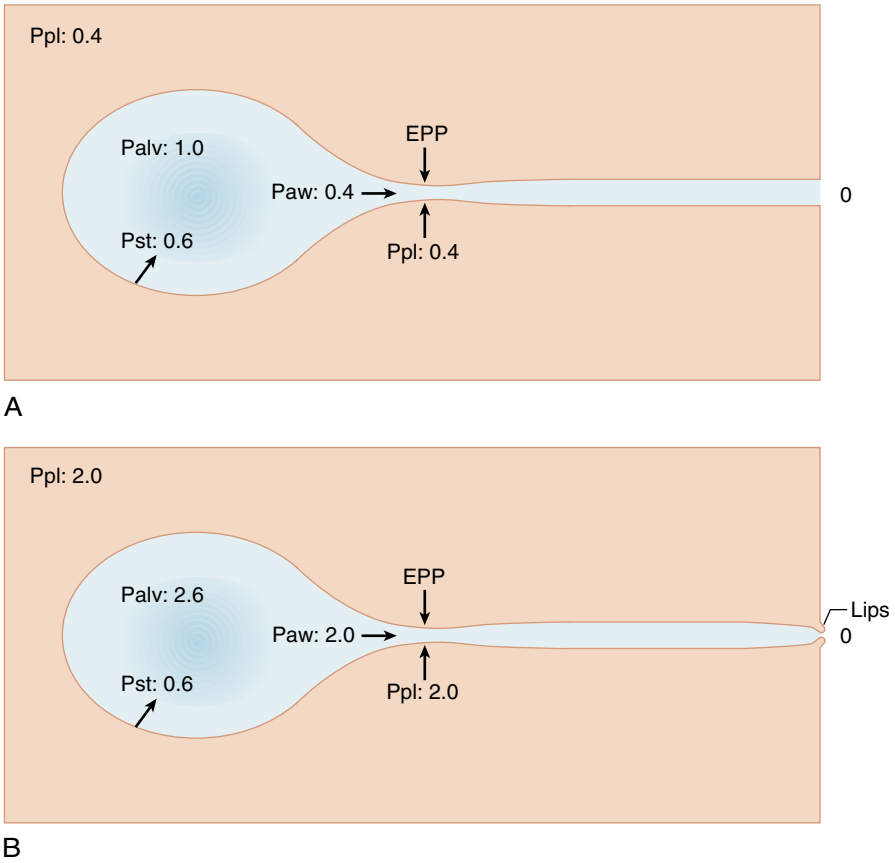


Figure 15-9 Schematic drawings of the "equal pressure point" (EPP) concept and dynamic compression of airways. **A,** Slightly forced expiration during otherwise normal conditions. With the application of some expiratory muscle effort, pleural pressure (Ppl) is positive, 4 cm H_2O (0.4 kPa). The elastic recoil pressure (Pst) of the alveoli (6 cm H_2O) and the pleural pressure add together to yield intra-alveolar pressure (Palv) (10 cm H_2O). This causes expiratory flow. At some point downstream toward the airway opening, airway pressure (Paw) has dropped by 6 cm H_2O, so intraluminal pressure and pleural, extraluminal pressure are the same. This is the EPP. From this point to the mouth, intraluminal airway pressure is lower than the surrounding, extraluminal pressure and the airway may be compressed. **B,** An attempt to stabilize the airway by so-called "pursed-lip" breathing. The increased resistance to expiratory flow requires increased expiratory effort to maintain gas flow. Thus, pleural pressure is increased in comparison to the normal conditions (Ppl = 20 cm H_2O). Alveolar elastic recoil pressure (Pst) is the same as in the earlier condition, provided that lung volume is the same. If expiratory flow is of the same magnitude as during normal breathing, pressure along the airway falls to the same extent as during normal breathing. Thus, the EPP will have the same location as during normal breathing, and no stabilization of the airway has been achieved. The two ways of moving the EPP toward the mouth and to less collapsible airways is by raising alveolar recoil pressure (Pst) by an increase in lung volume or by lowering the expiratory flow rate so that the pressure drop along the airway tree is slowed down.

breath is held for 10 seconds, followed by a deep expiration to RV. The amount of CO that has been taken up can be calculated from the difference between inspired and expired gas. Most of this CO has diffused to blood, where it binds easily to hemoglobin. However, a certain amount of the difference in concentration is due to dilution in the gas volume that was not expired (RV). This can be accounted for by inspiring another tracer gas that is poorly soluble or almost insoluble, such as helium. The dilution of helium (and CO) can be calculated, as can the diffusion or transfer factor of CO. Because oxygen and CO compete for binding to hemoglobin, measurement of diffusion at two different inspired oxygen concentrations as just described may enable distinction between capillary blood volume and the membrane in calculating the diffusion capacity or transfer factor. It is beyond the scope of this chapter to go into further details, but interested readers are referred to an article by Hughes and Bates.[32]

Membrane Thickness. The thicker the membrane, the longer the diffusion distance and the lower the diffusion capacity. In addition, solubility for O_2 (and CO_2) is lower in fibrotic tissue than in water. Thickening of the membranes may therefore impede diffusion even more than the increase in diffusion distance does.

Pressure Gradient. The larger the O_2 or CO_2 tension difference between the gas phase in the alveolus and plasma in the capillary, the greater the diffusion. The mixed venous blood entering the pulmonary capillary has a P_{O_2} of 40 mm Hg (5.3 kPa), and alveolar P_{O_2} is approximately 100 mm Hg (13.3 kPa), thus creating a driving pressure of 60 mm Hg (8 kPa). When blood flows through the capillary, it takes up oxygen (and delivers CO_2), but because oxygen pressure builds up in capillary blood, the diffusion rate slows down and becomes zero when pressure is equilibrated over the alveolar-capillary wall (Fig. 15-10). In a normal lung at low cardiac output, equilibrium has been reached within 25% to 30% of the capillary distance, and no or little gas transfer takes place in the remaining capillary. When cardiac output is increased, as during exercise, blood passes through the capillary faster, and a longer distance of the capillary is therefore required before equilibrium is reached, equilibration time being much the

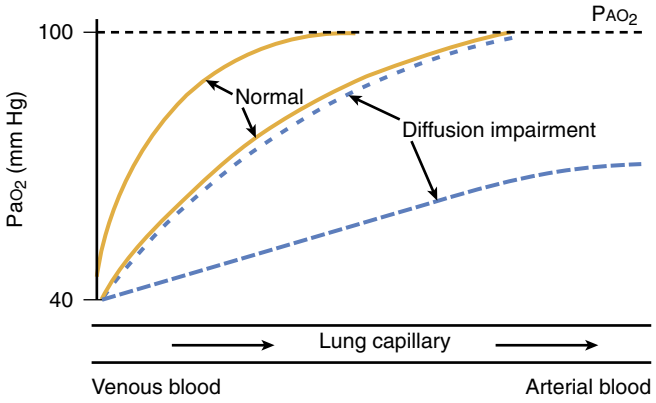


Figure 15-10 Oxygenation of pulmonary capillary blood at rest and during exercise in a normal subject and in a patient with fibrotic lung disease with impaired diffusion. In a normal subject, equilibration of oxygen tension in capillary blood with that in alveolar gas is rapid. This has been achieved within one third of the capillary distance. However, during exercise, most of the capillary distance must be used to reach equilibration between alveolar and pulmonary capillary oxygen tension. This is an effect of the shorter transit time of red blood cells caused by the increased cardiac output. Distention and recruitment of pulmonary capillaries may to some extent offset the effect of raised cardiac output on velocity of blood through the capillaries. With impaired diffusion, equilibration takes a longer time, but full equilibration may still be reached at rest. However, with increased blood velocity during exercise, equilibration of oxygen may be far from complete at the end of the pulmonary capillary, thereby causing desaturation of arterial blood, which may at times be severe.

same as during resting conditions (lower venous P_{O_2} speeds diffusion up in the beginning). Thickened alveolar-capillary membranes will prolong the equilibration process with the possible effect of causing hypoxemia.

It should also be mentioned that most of the oxygen that dissolves in plasma diffuses into the red cell and binds to hemoglobin. One gram of hemoglobin can bind 1.36 mL O_2 (numbers between 1.34 and 1.39 are used). This means that 1 L of blood with a hemoglobin content of 150 g/L can bind 204 mL of O_2 if fully saturated. With a saturation of 98%, which is normally achieved in arterial blood, the hemoglobin-bound oxygen amounts to 200 mL/L of blood. This should be compared with the mere 3 mL of O_2 that is physically dissolved in 1 L of blood at a P_{aO_2} of 100 mm Hg (13.3 kPa). The hemoglobin-bound oxygen creates no pressure in plasma, which is important because it allows much more oxygen to diffuse over the membranes before a pressure equilibration is reached. Anemia reduces and polycythemia increases diffusion capacity.

Molecular Weight. Diffusion is inversely related to the square root of the molecular weight of the gas. Thus, the larger the molecule, the more difficult it will be to pass through the membranes. O_2 is a relatively light gas with a molecular weight of 32. CO_2 is heavier with a molecular weight of 44 and should therefore be more limited in diffusion than O_2. However, taking the square root of the weights reduces the difference between the gases, and in practice, CO_2 is much more diffusible than O_2, as explained in the next paragraph.

Solubility. Diffusion is linearly related to solubility in tissue. It is usually set equal to that of water. CO_2 is almost 30 times more soluble in water than O_2 is and diffuses more than 20 times faster (the net effect of all previously mentioned factors).[31] In practice, this means that there is no lung disease compatible with life that causes measurable impairment in CO_2 diffusion.

Pulmonary Perfusion

Pressure-Flow Relationship

In contrast to the systemic circulation, the pulmonary circulation is a low-pressure system. The typical pulmonary artery pressure of 20 mm Hg systolic and 8 mm Hg diastolic is about 6 to 10 times lower than pressure in the systemic arteries. The lower pressure is achieved by the larger vascular diameter and shorter distance of the pulmonary vessels than the systemic ones. In particular, a large vascular lumen decreases the demand on driving pressure. According to Poiseuille's law, an increase in vascular radius reduces the pressure demand by an exponent of 4 to maintain a certain flow, if flow is linear. With turbulent flow, the dependence on vascular dimensions will be even higher. As a consequence of the lower resistance, pulmonary capillary blood flow is pulsatile, contrary to the steady flow in systemic capillaries.[33] Another, presumably more important consequence of the low pressure is that the capillary and alveolar walls can be made very thin without causing any leakage of plasma, and this facilitates diffusion of O_2 and CO_2. A sudden increase in pulmonary artery pressure to above a mean of 30 mm Hg causes effusion of plasma into the interstitial and alveolar spaces, thereby promoting lung edema. A slower increase in pressure, over a period of months or years, stimulates the growth of vascular smooth muscle ("vascular remodeling") with thickening of the vascular wall.[34] Edema is prevented better, despite even severe pulmonary hypertension, but diffusion capacity will be impaired.

Distribution of Lung Blood Flow

Blood flow through the lung is governed by driving pressure and vascular resistance. If these factors are unevenly distributed, perfusion may also be uneven. This seems to be the case. What the perfusion distribution looks like and the mechanisms behind it have become an interesting issue during recent years. Thus, the previously generally accepted explanation of a gravitational orientation of perfusion as demonstrated in the pioneering work by Permutt, West, Hughes and others (for a review, see Reference 35) has been challenged by others who propose a "fractal" distribution with gravity playing only a minor role.[36] Here we will first deal with the "gravitational" concept and then proceed to the "fractal" concept.

Gravitational Distribution of Blood Flow in the Lung

Pulmonary artery pressure increases down the lung, an effect of the hydrostatic pressure that builds up on the way from the top to the bottom of the lung. This pressure increases by 1 cm H_2O/cm distance down the lung (or 0.74 mm Hg/cm vertical distance; blood has a density close to 1, or 1.04). This causes a pressure difference in the pulmonary arterial vessels between the apex and the base of 11 to 15 mm Hg, depending on the height of the lung. There is thus less driving pressure to the top of the lung. Because mean pulmonary artery pressure is approximately 12 mm Hg at the level of the heart, it may approach zero in the apex of the lung in the upright position. Moreover, if alveolar pressure is increased, as during positive-pressure ventilation, it may exceed that in the pulmonary artery and compress the pulmonary capillaries. No blood will then flow through the vessels. That part of the lung is called zone I, according to the nomenclature introduced by West and associates (Fig. 15-11).[35] If arterial pressure and capillary pressure exceed alveolar pressure, as it will farther down the lung

$$\text{Pulmonary vascular resistance (PVR)} = \frac{\bar{P}_{PA} - P_{LA}}{\dot{Q}_T}$$

(true only if lung is in zone III)

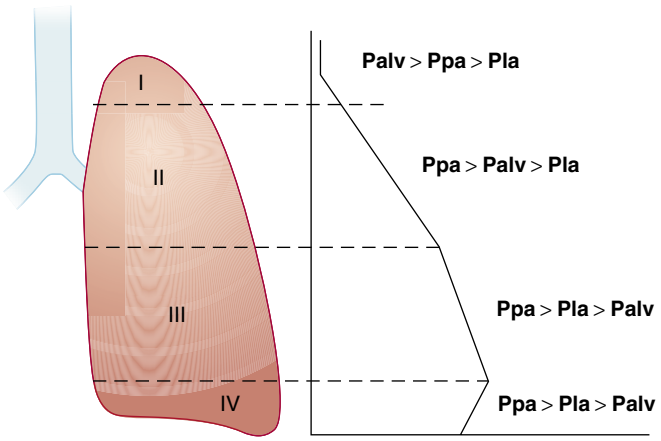


Figure 15-11 Vertical distribution of blood flow in the lung. The so-called zones I, II, III, and IV are indicated. As can be seen, zone I corresponds to a region in which alveolar pressure exceeds vascular pressure, which results in essentially no perfusion. Zone II is characterized by pulmonary artery pressure exceeding alveolar pressure, which in turn exceeds venous pressure. The driving pressure will then be arterial minus alveolar pressure. Farther down in zone III, both arterial pressure and venous pressure exceed alveolar pressure. The difference between arterial and venous pressure creates the driving force through this zone. In the bottom of the lung there is a decrease in blood flow that is explained by increasing interstitial pressure compressing extra-alveolar vessels. For further details see text. $\dot{Q}_T$, cardiac output; Palv, alveolar pressure; Pla, left atrial pressure; Ppa, pulmonary artery pressure.

because of the addition of hydrostatic pressure, blood flow will be established. Perfusion pressure will be arterial minus alveolar pressure, as long as the latter pressure exceeds that of the pulmonary veins. This is different from the systemic circulation, where perfusion pressure is arterial minus venous pressure. Moreover, the increasing pulmonary arterial pressure down the lung and the constant alveolar pressure increase the perfusion pressure down this part of the lung, called zone II. Blood flow therefore increases down this zone. Farther down the lung, both arterial pressure and venous pressure exceed that in the alveoli, so perfusion pressure is arterial minus venous pressure. This part of the lung is called zone III. Because both arterial pressure and venous pressure increase to the same extent down zone III, with hydrostatic pressure adding to both sides, perfusion pressure does not increase down the zone. Nonetheless, perfusion increases downward, albeit possibly less than the increase in zone II. The explanation proposed is that the increasing vascular pressure dilates the vessels down the lung and by this means reduces vascular resistance.[35]

A few years after these initial observations, it was noticed that blood flow decreases in the bottom of the lung, so a zone IV had to be added to the model of lung perfusion.[35] This called for a new explanation in which it was suggested that the increasing interstitial pressure down the lung presses on the extra-alveolar vessels and makes them narrower. The vertical distribution of blood flow could accordingly be explained by the influence of gravitation on vascular, alveolar, and interstitial pressure.

The homogeneity of blood flow distribution has also been tested during shuttle flights at zero gravity or microgravity. By using indirect techniques based on analysis of the variation in expired gas concentrations that are synchronous with heartbeats ("cardiogenic oscillations"), more uniform lung blood flow distribution has been recorded.[37]

Nongravitational Inhomogeneity of Blood Flow Distribution

In dog experiments, groups at the Mayo Clinic and subsequently in Seattle noticed that the vertical lung blood flow distribution was nearly even and did not change when position was altered between supine and prone.[36] This made the Seattle group conclude that gravity was of minor importance in determining the distribution of perfusion. The same group also showed that perfusion at a given vertical level is unevenly distributed on that horizontal plane, with an inhomogeneity far exceeding that in the vertical direction (Fig. 15-12). In carefully repeated experiments they could reproduce the same pattern of inhomogeneity.[38] This suggests that there are morphologic or functional differences (or both) between lung vessels that also—and perhaps more importantly than gravity—determine blood flow distribution. As an example, vascular resistance seems to be lower in the dorsal regions of horse lungs than in the anterior part.[39] Thus, in an animal that is standing or resting on its four legs most of the time, the vascular tree has adjusted to that position and, by increasing resistance in its anterior parts, has made blood flow more evenly distributed.

Other groups have also made observations that suggest an uneven distribution of blood flow that cannot be explained by gravity, with more blood going to the core of the lung and less to the periphery.[40] A longer distance to the peripheral bed was suggested as an explanation for the larger vascular resistance toward the periphery. However, others found less difference between central and peripheral lung regions. The application of positive end-expiratory pressure (PEEP) in anesthetized and mechanically ventilated dogs forced perfusion of the lung toward the periphery.[41] As always, the reliability of the techniques used is critical. It seems that the spatial distribution of blood flow as measured by single photon emission computed tomography (SPECT), a technique that has been used in some studies, suffers from reconstruction artifacts. Still others have used a microspheres technique and measured the distribution in excised lungs. Although it may suffer from other limitations, one may dare to conclude that enough evidence has accumulated to believe in a nongravitational inhomogeneity of lung perfusion.

Hypoxic Pulmonary Vasoconstriction

Hypoxic pulmonary vasoconstriction (HPV) seems to be a compensatory mechanism aimed at reducing blood flow in hypoxic

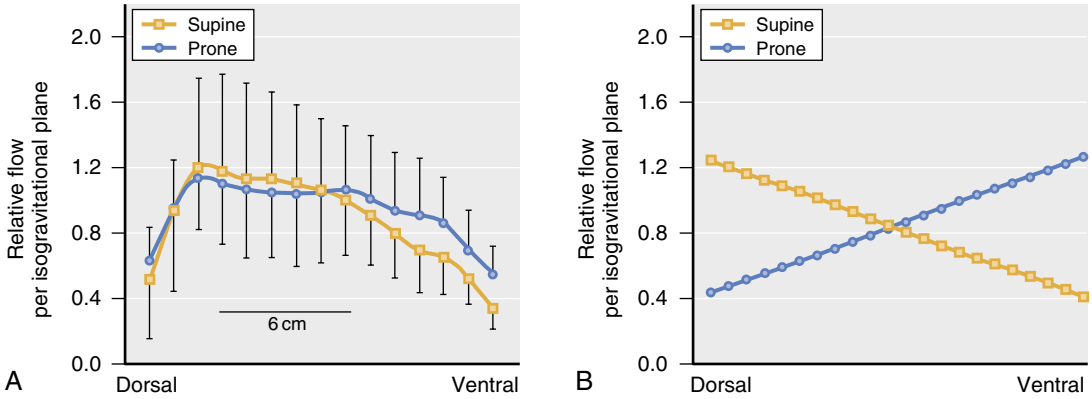


Figure 15-12 Distribution of blood flow from ventral to dorsal lung regions in a canine experiment with the animal supine and prone. Note the similar distributions from ventral to dorsal irrespective of posture. This may suggest that the distribution of perfusion in the vertical direction is determined by anatomic differences in the vasculature rather than by gravity. The *bars* show the spread of perfusion around the mean value. As can be seen, this nongravitational inhomogeneity is larger than that caused in the gravitational orientation. *(From Glenny RW, Lamm WJE, Albert RK, et al: Gravity is a minor determinant of pulmonary blood-flow distribution. J Appl Physiol 71:620-629, 1991.)*

lung regions. The major stimulus for HPV is low alveolar oxygen tension, whether caused by hypoventilation or by breathing gas with a low P_{O_2}. The stimulus of mixed venous P_{O_2} is much weaker.[42,43] The strength of the constriction is also dependent on the size of the lung segment exposed to the hypoxia, being stronger the smaller the region. Thus, in humans studied during intravenous anesthesia that was assumed to not affect the HPV, one-lung hypoxia with 8% and 4% O_2 during contralateral hyperoxia (F_{IO_2} of 1.0) caused blood flow to be diverted away from the hypoxic to the other, hyperoxic lung, from 52% to 40% and 30% of cardiac output.[44]

Pulmonary hypertension and pulmonary edema may develop in humans at high altitude because of more general pulmonary vasoconstriction.[45] Chronic lung disease with hypoxemia also causes HPV, but the slow progress of the disease allows time for remodeling of the pulmonary vascular wall, with thickening of the wall preventing edema formation.[32]

Causes of Hypoxemia and Hypercapnia

In the previous sections we discussed ventilation, gas distribution, and the respiratory mechanics that govern distribution, diffusion, and pulmonary perfusion. All these components of lung function can affect the oxygenation of blood, and all except diffusion can also measurably affect CO_2 elimination. The different mechanisms behind hypoxemia and CO_2 retention, or hypercapnia or hypercarbia, have been touched on in previous paragraphs but will be analyzed in more detail here.

Causes of hypoxemia can suitably be classified as hypoventilation, $\dot{V}_A/\dot{Q}$ mismatch, impaired diffusion, and right-to-left shunt. Hypercapnia can be caused by hypoventilation, $\dot{V}_A/\dot{Q}$ mismatch, and shunt, although in practice hypoventilation is the only cause of real importance (Tables 15-1 and 15-2).

Hypoventilation

If ventilation is low in proportion to metabolic demand, elimination of CO_2 will be inadequate and it will accumulate in the alveoli, blood, and other body tissues. Hypoventilation is often defined as ventilation that results in a P_{ACO_2} above 45 mm Hg (6 kPa). With this definition, hypoventilation can be present even when minute ventilation is high if the metabolic demand or dead space ventilation is increased more than minute ventilation.

The increased alveolar P_{CO_2} reduces the space available for oxygen in the alveoli. P_{AO_2} can be estimated by the alveolar gas equation, shown in Box 15-1. A simplified form is derived here. Thus, assuming a normal respiratory exchange ratio, P_{AO_2} can be calculated as

$$P_{AO_2} = P_{IO_2} - (1.25 \times P_{ACO_2})$$

The factor 1.25 is correct if the respiratory exchange ratio is 0.8, and this can reasonably be assumed under resting conditions. P_{ACO_2} can be assumed to equal P_{aCO_2}. Thus, with a P_{IO_2} of 149 mm Hg (19.9 kPa) and a P_{aCO_2} of 40 mm Hg (5.3 kPa), P_{AO_2} is 99 mm Hg (13.2 kPa), and during hypoventilation with a P_{aCO_2} of 60 mm Hg (8 kPa), P_{AO_2} is 74 mm Hg (9.9 kPa). That gives the highest possible P_{aO_2} that can exist at that level of alveolar ventilation. Thus, whether a low P_{aO_2} can be explained by hypoventilation can easily be tested with this simple formula. If there is a gap between the estimated P_{AO_2} and the measured P_{aO_2}, another or an additional cause of hypoxemia must be sought. It is also

Table 15-1 Causes of Hypoxemia

Disturbance	P_{aO_2} (breathing air) at Rest	P_{aO_2} (breathing oxygen) at Rest	P_{aO_2} (breathing air) with Exercise (Versus Rest)	P_{aCO_2}
Hypoventilation	Reduced	Normal	No change or further decrease	Increased
$\dot{V}_A/\dot{Q}$ mismatch	Reduced	Normal	No or minor increase or decrease	Normal
Shunt	Reduced	Reduced	No change or further decrease	Normal
Diffusion impairment	Reduced	Normal	Small to large decrease	Normal

Table 15-2 Mechanisms of Hypoxemia in Different Lung Disorders

Disorder	Hypoventilation	Diffusion Impairment	$\dot{V}_A/\dot{Q}$ Mismatch	Shunt
Chronic bronchitis	(+)	–	++	–
Emphysema	+	++	+++	–
Asthma	–	–	++	–
Fibrosis	–	++	+	+
Pneumonia	–	–	+	++
Atelectasis	–	–	–	++
Pulmonary edema	–	+	+	++
Pulmonary emboli	–	–	++	+
Acute respiratory distress syndrome	–	–	+	+++

obvious that the decrease in Pa_{O_2} that is caused by hypoventilation is easily overcome by increasing P_{IO_2} (which on the other hand, may decrease the stimulus to breath and cause further retention of CO_2).

Ventilation-Perfusion Mismatch

For optimum gas exchange, ventilation and perfusion must match each other in all lung regions. At rest, both ventilation and perfusion increase down the lung. Perfusion increases more than ventilation, the difference between the uppermost and lowermost 5-cm segments being 3 times for ventilation and 10 times for perfusion. This results in a mean $\dot{V}_A/\dot{Q}$ ratio of approximately 1 somewhere in the middle of the lung and a range of $\dot{V}_A/\dot{Q}$ ratios from 0.5 in the bottom of the lung to 5.0 in nondependent regions, as illustrated in Figure 15-13, upper panel (the perfusion distribution being a simplified drawing of what is shown in Fig. 15-11). Another way of showing the matching between ventilation and blood flow is by making a multicompartmental analysis of the ventilation distribution of blood flow against $\dot{V}_A/\dot{Q}$ ratios. This can be achieved by a multiple inert gas elimination technique (MIGET).[46] In short, MIGET is based on the constant infusion of a number (usually six) of inert gases with different solubilities in blood. When passing the lung, the different gases will be eliminated via alveoli and expired in proportion to their solubility. A poorly soluble gas will leave the bloodstream and be more or less completely eliminated (e.g., sulfur hexafluoride). A gas of medium solubility will be retained to some extent (e.g., halothane), and a gas with a very high solubility in blood will be retained to an almost full extent (e.g., acetone). This means that the concentration of the different gases in arterial blood will differ, with higher concentrations of gases with high solubility. Retention can be calculated as the ratio between arterial and mixed venous blood concentrations. Similarly, the ratio of expired gas concentration and mixed venous gas concentration can also be calculated and gives the excretion for each gas. With knowledge of the retention, excretion, and solubility of each gas, an essentially continuous distribution of blood flow against $\dot{V}_A/\dot{Q}$ ratios can be constructed. The lower panel in Figure 15-13 shows an example from a healthy subject. Note that ventilation and blood flow are well matched, being distributed to a limited number of compartments

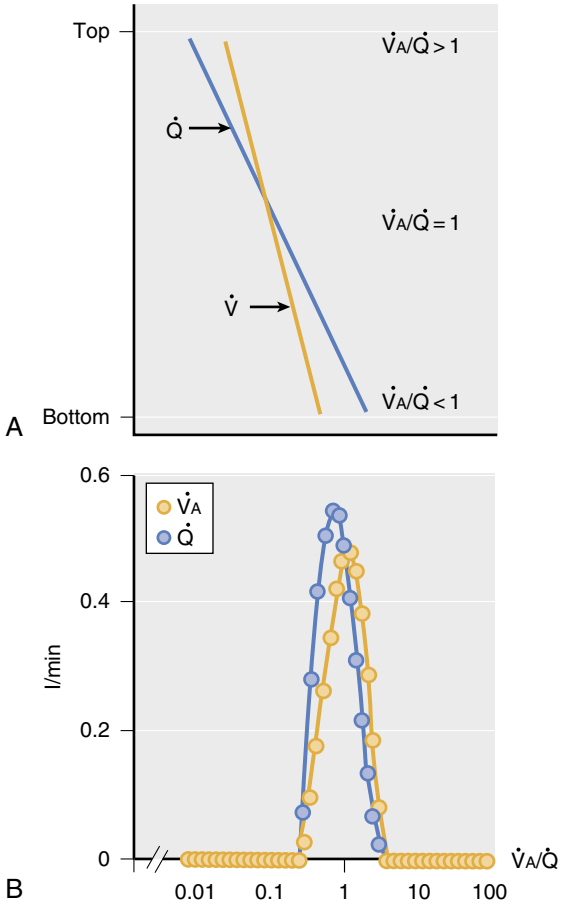


Figure 15-13 Schematic drawing of the vertical distributions of ventilation ($\dot{V}$) and blood flow through the lung ($\dot{Q}$) (**A**) and the resulting ventilation-perfusion distribution ($\dot{V}_A/\dot{Q}$) (**B**). Note the moderate increase in ventilation down the lung and the faster increase in perfusion. The $\dot{V}_A/\dot{Q}$ distribution is centered on a ratio of 1, which corresponds to the intersection of the ventilation and perfusion distribution curves. The slightly larger ventilation than perfusion in the upper lung regions contributes to the high $\dot{V}_A/\dot{Q}$ ratios above 1, whereas the larger perfusion than ventilation in the lower part of the lung is the cause of the lower $\dot{V}_A/\dot{Q}$ ratios, below 1.

centered on a $\dot{V}_A/\dot{Q}$ ratio of 1. MIGET has a high discriminatory capacity of detecting different ventilation/perfusion disturbances but does not have the potential of localizing where in the lung the impairment or variations are located. It is more like looking at a fingerprint of ventilation/perfusion match or mismatch. A number of variables that reflect the degree of mismatch can be calculated and are shown in Table 15-3. In the following paragraphs, examples of $\dot{V}_A/\dot{Q}$ mismatch are discussed.

If ventilation and perfusion are not matched, gas exchange will be affected. The most common cause of impaired oxygenation is indeed $\dot{V}_A/\dot{Q}$ mismatch. Low $\dot{V}_A/\dot{Q}$ will impede oxygenation because ventilation is too small to fully oxygenate the blood. The degree of impairment is dependent on the degree of mismatch, and even normally existing lung regions with a $\dot{V}_A/\dot{Q}$ ratio between 0.5 and 1 are unable to completely saturate the blood. Thus, Pa_{O_2} is seldom equal to alveolar P_{O_2}, but a difference ($P_{AO_2} - Pa_{O_2}$) of about 3 to 5 mm Hg (0.4 to 0.7 kPa) exists in the normal lung. With more $\dot{V}_A/\dot{Q}$ mismatch, the $P_{AO_2} - Pa_{O_2}$ difference is further increased. The $\dot{V}_A/\dot{Q}$ mismatch can account for all the hypoxemia seen in a severely obstructive patient.[47]

Table 15-3 Mean (SD) Ventilation-Perfusion Relationships with No Cardiopulmonary Disease (normal, $n = 45$), Awake and During General Anesthesia and Muscle Paralysis

	$\dot{Q}$mean	log SD$\dot{Q}$	$\dot{V}$mean	log SD$\dot{V}$	Shunt (% Q_T)	Dead Space (% V_T)	Pa_{O_2}/FI_{O_2}* (kPa)
Awake	0.76 (0-33)	0.68 (0.28)	1.11 (0.52)	0.52 (0.15)	0.5 (1.0)	34.8 (14.2)	59.5 (8.1)
Anesthetized	0.65 (0.34)	1.04 (0.36)	1.38 (0.76)	0.76 (0.31)	4.8 (4.1)	35.0 (9.9)	50.9 (15.2)

*FI_{O_2} (inspired oxygen fraction): awake, 0.21; anesthetized, 0.42.
log SD$\dot{Q}$, standard deviations of the logarithmic distribution of perfusion; log SD$\dot{V}$, standard deviations of the logarithmic distribution of ventilation; $\dot{Q}$mean, mean $\dot{V}_A/\dot{Q}$ of the perfusion distribution; $\dot{V}$mean, mean $\dot{V}_A/\dot{Q}$ of ventilation distribution.

Shunt, which is often claimed to exist in patients with COPD, is mostly absent when analyzed with more sophisticated technique such as MIGET. Indeed, shunt in an obstructive patient should be considered indicative of a complicating factor in the disease (Fig. 15-14, lower left panel).

In severe asthma it is common to see a distinct mode of low $\dot{V}_A/\dot{Q}$ ratios when using MIGET.[48] Thus, a bimodal distribution of $\dot{V}_A/\dot{Q}$ ratios can be seen (Fig. 15-14, upper right panel). The explanation is probably that alveoli behind completely obstructed airways (edema, mucous plug, spasm) can still be ventilated through alveolar pores and interbronchial communications, so-called collateral ventilation. This may also explain why shunting is not normally seen in patients with COPD. However, with standard techniques, such as calculation of shunt by the oxygen equation, low $\dot{V}_A/\dot{Q}$ cannot be separated from shunt. One should rather use the expression "venous admixture" in this case.

Airway obstruction is unevenly distributed over the lung, and a large variation in $\dot{V}_A/\dot{Q}$ ratios can be seen in a single patient. Indeed, ventilation is redistributed from regions with high airway resistance to other regions that may become overventilated in proportion to their perfusion. This causes high $\dot{V}_A/\dot{Q}$ ratios. There are normally regions in the upper part of the lung that have $\dot{V}_A/\dot{Q}$ ratios of up to 5, but in obstructive patients ratios of up to 100 or greater can be seen, thus making them practically indistinguishable from true dead space. This is what causes the increase in "physiologic" dead space in obstructive lung disease. The effect of high $\dot{V}_A/\dot{Q}$ is also the same as for airway dead space, that is, ventilation that seems to not participate in gas exchange ("wasted ventilation"). Consequently, at the same time an obstructive patient suffers from low $\dot{V}_A/\dot{Q}$, which causes hypoxemia, and high $\dot{V}_A/\dot{Q}$, which mimics dead space ventilation and impedes CO_2 elimination. However, the complexity of MIGET makes it essentially a research tool, and for clinical purposes and many scientific studies, calculation of dead space must rely on measurement of expired CO_2. Derivation of the CO_2 dead space is shown in Box 15-2.

$\dot{V}_A/\dot{Q}$ mismatch exists to varying degree in all patients with COPD and can, as said earlier, explain all hypoxemia in most of these patients. Hypoventilation may be a contributing factor, whereas impaired diffusion (to the extent that it causes hypoxemia) and shunt are less common (see later).

Pulmonary vessels can be affected by lung disease and cause $\dot{V}_A/\dot{Q}$ mismatch by impeding regional blood flow. Systemic diseases with vascular involvement such as periarteritis nodosa, disseminated lupus erythematosus, scleroderma, and rheumatoid diseases may cause severe pulmonary dysfunction with $\dot{V}_A/\dot{Q}$ mismatch, impaired diffusion, and shunt. $\dot{V}_A/\dot{Q}$ mismatch causes most of the hypoxemia that can be seen in pulmonary fibrosis at rest.[49] In addition, hypoxemia can be caused by impaired diffusion (in particular, during exercise, when it may dominate) and a varying degree of shunt (see later). Pulmonary emboli cause $\dot{V}_A/\dot{Q}$ mismatch because the occluded vascular bed forces blood flow to other, open regions, thus making these regions overperfused in relation to their ventilation. This, again, causes low $\dot{V}_A/\dot{Q}$. Shunt may be small unless pulmonary artery pressure is markedly increased.[50]

Pneumonia and various forms of acute respiratory failure are signified by shunt and to a varying extent by $\dot{V}_A/\dot{Q}$ mismatch (Fig. 15-14, lower right panel). This can easily be understood from the presence of atelectasis, fluid filling, and consolidation seen with these diseases.[51]

Is CO_2 removal less affected than oxygenation of blood by $\dot{V}_A/\dot{Q}$ mismatch? It is perhaps if the CO_2 content of blood is more linearly related to CO_2 tension than the O_2 content is related to P_{O_2}, according to the oxygen dissociation curve. However, this is not true. Elimination of CO_2 is even more limited by $\dot{V}_A/\dot{Q}$ mismatch than O_2 transfer is.[31] Still, it is rare to see hypercapnia caused by mismatch because any increase in CO_2 tension stimulates increased ventilation to bring Pa_{CO_2} back toward normal. If alveolar ventilation is already impaired and cannot be increased, the addition of $\dot{V}_A/\dot{Q}$ mismatch may make matters worse.

Impaired Diffusion

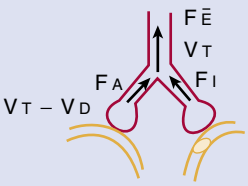
Impaired diffusion to the extent that it reduces Pa_{O_2} can occur if the alveolar-capillary membranes are thickened, as in fibrosis and systemic vascular diseases. Diffusion is slowed down and the whole capillary distance may be required before the capillary blood has been fully oxygenated, even in resting conditions. On

Box 15-2 Derivation of the Physiologic Dead Space Equation

$$F\bar{E} \times V_T = F_A(V_T - V_{DS}) + (F_I \times V_{DS})$$

By rearranging,

$$\frac{V_{DS}}{V_T} = \frac{F_A - F\bar{E}}{F_A - F_I}$$



If $F_I = 0$, F replaced by P, and P_A replaced by Pa, for CO_2,

$$\frac{V_{DS}}{V_T} = \frac{Pa_{CO_2} - P\bar{E}_{CO_2}}{Pa_{CO_2}}$$

where $F\bar{E}$, F_A, and F_I are mixed expired, alveolar, and inspired gas concentration, respectively, and V_T, V_{DS}, and V_A are tidal volume, dead space, and part of the tidal volume to perfused alveoli, respectively.

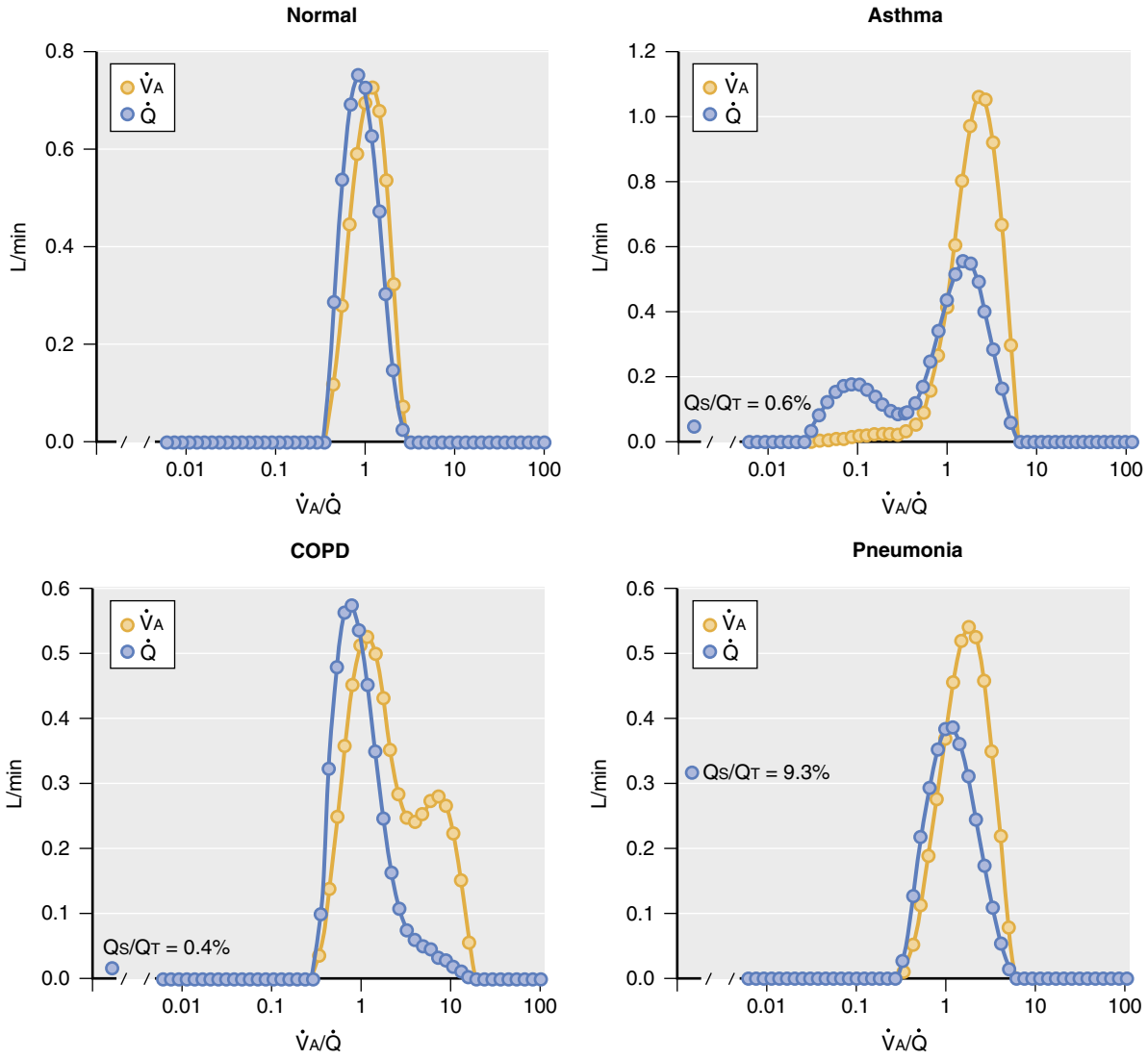


Figure 15-14 Ventilation-perfusion distributions in a normal subject (*upper left panel*), in a patient with asthma (*upper right panel*), in a patient with chronic obstructive pulmonary disease (COPD) (*lower left panel*), and in a patient with pneumonia (*lower right panel*). Note the good matching between ventilation and perfusion with a mode centered around a $\dot{V}_A/\dot{Q}$ ratio of 1 in the normal subject. This results in nearly optimal oxygenation of blood, as well as CO_2 removal. The asthmatic patient has broader distribution of $\dot{V}_A/\dot{Q}$ ratios, with some regions being ventilated well in excess of perfusion ($\dot{V}_A/\dot{Q}$ of 10 and higher), and there is another distinct mode of "low" $\dot{V}_A/\dot{Q}$ ratios centered around a $\dot{V}_A/\dot{Q}$ ratio of 0.1. This mode can reasonably be explained by collateral ventilation that maintains certain gas exchange behind otherwise occluded airways. Finally, no shunt can be seen. The chronic bronchitis patient may have a pattern that is not that different from the asthmatic patient, but there can also be a more clear "high"-$\dot{V}_A/\dot{Q}$ mode that adds to the dead space–like ventilation. A shunt cannot be seen, but if visible in the COPD patient, it indicates a complicating dysfunction (pneumonia, atelectasis, or something else?). The $\dot{V}_A/\dot{Q}$ pattern shown in the figure should not result in any considerable hypoxemia. The patient suffering from pneumonia shows minor widening of the $\dot{V}_A/\dot{Q}$ distribution, and the major finding is a pure shunt that is caused by consolidation of lung tissue that is still perfused but not ventilated. Q_S/Q_T, ratio of shunt blood flow to cardiac output.

the other hand, this means that a diffusion barrier may not cause hypoxemia as long as there is enough time and capillary distance to allow equilibration (see Fig. 15-10). However, when all reserve has been spent, Pao_2 begins to fall. This is particularly noticeable in patients with pulmonary fibrosis, who may have normal Pao_2 at rest but show dramatic decreases during exercise, down to 40 to 45 mm Hg (≈5 to 6 kPa).[31,49] There is almost no other condition that can cause such a decrease and, if found, should bring impaired diffusion into consideration. Obstructive lung disease does not cause such impairment of oxygenation; Pao_2 changes only a little and can even improve! The only condition that can lower Pao_2 to a similar extent is the appearance of or increase in right-to-left shunting in the heart, such as an atrial septal defect with a left-to-right shunt at rest that reverses during exercise because of increasing pulmonary hypertension.

Right-to-Left Shunt

If blood passes through the lung without coming into contact with ventilated alveoli, the blood will not be oxygenated or release CO_2. This is a shunt that lowers Pao_2 and increases, although less easy to observe, $Paco_2$. A small shunt of 2% to 3% of cardiac output can be seen in normal subjects and is caused by the thebesian veins that drain the heart and empty into the left atrium. In pathologic states, shunt may amount to anything between nearly normal to above 50% of cardiac output. Shunt may be considered an extreme of mismatch, with a $\dot{V}_A/\dot{Q}$ of zero. However, there

are clear differences between the concepts of mismatch and shunt. First, the anatomic basis differs. Regions with low $\dot{V}_A/\dot{Q}$ are caused by airway and vascular narrowing. This reduces ventilation and blood flow in some regions and increases them in others. Examples are obstructive lung disease and vascular disorders. Shunt is caused by the complete cessation of ventilation in a region, usually as a result of collapse (atelectasis) or consolidation (pneumonia, edema, obliterative processes). Contrary to what is normally said, asthma, bronchitis, and emphysema do not cause a shunt.[47] If a shunt is found, it indicates a complication. Second, the effect of "low $\dot{V}_A/\dot{Q}$" on oxygenation of blood can essentially be overcome by adding more oxygen to the inspired air. Even in a poorly ventilated lung unit, P_{AO_2} can be increased almost as much as in normal regions, the difference being caused by the higher P_{ACO_2} in the poorly ventilated units. The effect of a moderate shunt can be reduced, but not eliminated, by giving more oxygen because the nonventilated region cannot be reached by the inspired gas. Thus, shunt will always lower Pa_{O_2} at any P_{IO_2}, as compared with what would have been measured without shunt. When the shunt increases to 25%, the rise in Pa_{O_2} will be small, and with a shunt of 30% or greater, almost no effect of added O_2 can be seen.[51] This is the net effect of mixing blood with normal pulmonary end-capillary P_{O_2} and shunt blood with mixed venous P_{O_2}. If the latter is a large enough fraction of total lung blood flow, the additional O_2 that can be physically dissolved by the raised P_{IO_2} is so small that it is almost immeasurable. The shunt is said to be refractory.

Respiratory Function During Anesthesia

Anesthesia causes an impairment in pulmonary function, whether the patient is breathing spontaneously or is ventilated mechanically after muscle paralysis. Impaired oxygenation of blood occurs in most subjects who are anesthetized.[52] It has therefore become routine to add oxygen to the inspired gas so that the inspired oxygen fraction (F_{IO_2}) is maintained at around 0.3 to 0.4. Despite these measures, mild to moderate hypoxemia, defined as an arterial oxygen saturation of between 85% and 90%, may occur in approximately half of all patients undergoing elective surgery, and the hypoxemia can last from a few seconds to up to 30 minutes. About 20% of patients may suffer from severe hypoxemia, or oxygen saturation below 81% for up to 5 minutes.[53] Lung function remains impaired postoperatively, and clinically significant pulmonary complications can be seen in 1% to 2% after minor surgery in up to 20% after upper abdominal and thoracic surgery.[54]

In this section, the effect of anesthesia and mechanical ventilation on lung function will be described. The order of the different paragraphs will follow an order that relates to the sequence of events that affect the lung's ability to oxygenate the blood and to remove carbon dioxide. Thus, the first phenomenon that might be seen with anesthesia is loss of muscle tone with a subsequent change in the balance between outward forces (i.e., respiratory muscles) and inward forces (i.e., elastic tissue in the lung) leading to a fall in FRC. This causes or is paralleled by an increase in the elastic behavior of the lung (reduced compliance) and an increase in respiratory resistance. The decrease in FRC affects the patency of lung tissue with the formation of atelectasis (made worse with the use of high concentrations of inspired oxygen) and airway closure. This alters the distribution of ventilation and matching of ventilation and blood flow and impedes oxygenation of blood and removal of carbon dioxide.

Lung Volume and Respiratory Mechanics During Anesthesia

Lung Volume

Resting lung volume, or FRC, is reduced by 0.8 to 1.0 L by changing body position from upright to supine, and there is another 0.4- to 0.5-L decrease when anesthesia has been induced.[55] End-expiratory lung volume is thus reduced from approximately 3.5 to 2 L, the latter being close or equal to RV. The anesthesia per se causes a fall in FRC despite maintenance of spontaneous breathing,[56,57] and the decrease in FRC occurs regardless of whether the anesthetic is inhaled or given intravenously.[58] Muscle paralysis and mechanical ventilation cause no further decrease in FRC. The average reduction corresponds to around 20% of awake FRC and may contribute to an altered distribution of ventilation and impaired oxygenation of blood, as discussed later.

The decrease seems to be related to loss of respiratory muscle tone, which shifts the balance between the elastic recoil force of the lung and the outward force of the chest wall to a lower chest and lung volume. Maintenance of muscle tone, as during ketamine anesthesia, does not reduce FRC.[58] The influence of body position and anesthesia on FRC is shown in Figure 15-8. As can be seen in the figure, FRC increases with age if weight and height remain unaltered over the years.

The decrease in FRC is caused by a cranial shift of the diaphragm and a small decrease in the transverse thoracic area in a majority of studies as evidenced by repeated CT scanning.[58,59] However, somewhat conflicting results have been reported regarding the diaphragm, with only minor displacement of the diaphragm and the anterior part even being shifted caudally.[60] Such caudal displacement could in theory occur if the ribs are tilted downward during anesthesia.

Compliance and Resistance of the Respiratory System

Static compliance of the total respiratory system (lungs and chest wall) is reduced on average from 95 to 60 mL/cm H_2O during anesthesia.[61] Several studies on lung compliance have been carried out during anesthesia, and the vast majority of studies indicate a decrease in comparison to the awake state (e.g., static lung compliance fell from a mean of 187 mL/cm H_2O awake to 149 mL/cm H_2O during anesthesia when data from several studies were pooled).[61]

There are also studies on resistance of the total respiratory system and the lungs during anesthesia, most of them showing a considerable increase during both spontaneous breathing and mechanical ventilation.[61] However, the studies on resistance during anesthesia have been hampered by different experimental conditions during the awake and anesthetized situations. Thus, a study that enables comparison of resistance under both isovolume and isoflow conditions is still awaited. The possibility remains that the increased lung resistance merely reflects reduced FRC during anesthesia (Fig. 15-15).

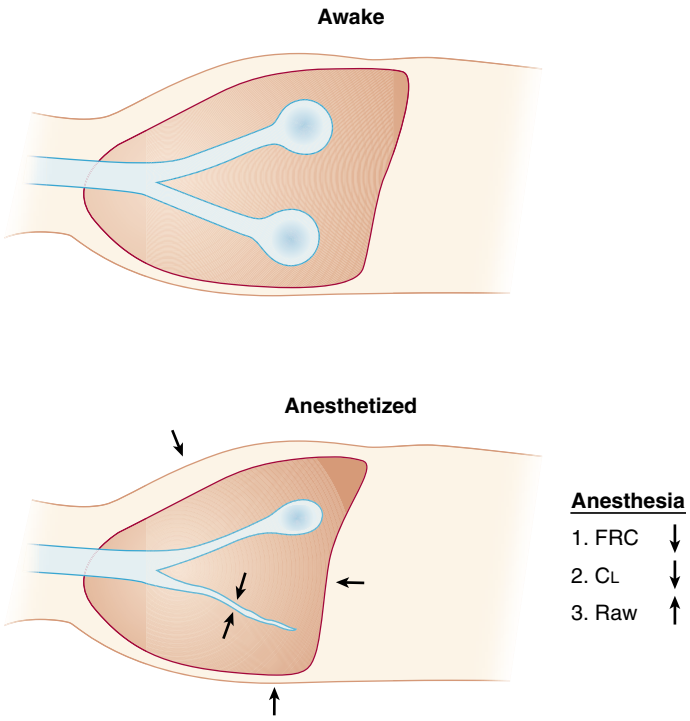


Figure 15-15 Cranial shift of the diaphragm and a decrease in transverse diameter of the thorax contribute to lowered functional residual capacity (FRC) during anesthesia. Decreased ventilated volume (atelectasis and airway closure) is a possible cause of reduced lung compliance (C_L). Decreased airway dimensions by the lowered FRC should contribute to increased airway resistance (Raw).

Atelectasis and Airway Closure During Anesthesia

Atelectasis

In their classic paper, Bendixen and coworkers proposed "a concept of atelectasis" as a cause of impaired oxygenation during anesthesia.[62] They had observed a successive decrease in compliance of the respiratory system and a similar successive decrease in arterial oxygenation in both anesthetized humans and experimental animals. This was interpreted as formation of atelectasis. However, other research groups who were unable to reproduce their findings noticed a more prompt fall in compliance and Pao_2 on induction of anesthesia. Moreover, atelectasis could not be shown on conventional chest radiography.

In the mid-eighties, new observations were made that may explain the altered function of the lung during anesthesia. On CT with transverse exposure of the chest, prompt development of densities in the dependent regions of both lungs could be shown during anesthesia. For a review with references from before 1990, see the ISPOCD1 study.[53] Morphologic studies of these densities in various animals supported the diagnosis of atelectasis. An example of atelectasis as seen on a CT scan is shown in Figure 15-16.

Atelectasis appears in approximately 90% of all patients who are anesthetized.[63] It is seen during spontaneous breathing and after muscle paralysis and whether intravenous or inhaled anesthetics are used.[58] The atelectatic area on a CT cut near the diaphragm is around 5% to 6% of the total lung area but can easily exceed 15% to 20%. It should also be remembered that the amount of tissue that is collapsed is even larger, the atelectatic area consisting of mainly lung tissue and the aerated lung consisting of only 20% to 40% tissue, the rest being air. Thus, 15% to 20% of the lung is regularly collapsed at the base of the lung during uneventful anesthesia, before any surgery has even been done! Abdominal surgery does not add much to the atelectasis, but it can remain for several days in the postoperative period.[64] It is likely that it is a focus of infection and can contribute to pulmonary complications.[65] It may also be mentioned that after thoracic surgery and cardiopulmonary bypass, more than 50% of the lung can be collapsed even several hours after surgery.[66] The amount of atelectasis decreases toward the apex, which is mostly spared (fully aerated) (Fig. 15-17).

There is a weak correlation between the size of the atelectasis and body weight or body mass index (BMI),[58,67] with obese patients showing larger atelectatic areas than lean ones do. Although this was expected, it came as a surprise that the atelectasis is independent of age, with children and young people showing as much atelectasis as elderly patients.[63] Another unexpected observation was that patients with COPD showed less or even no atelectasis during the 45 minutes of anesthesia that they were studied.[68] The mechanism that prevents the lung from collapse is not clear but may be airway closure occurring before alveolar collapse takes place, or it may be an altered balance between the chest wall and the lung that counters a decrease in lung dimensions.

There is good correlation between the amount of atelectasis and pulmonary shunt as measured by MIGET. A regression equation based on a total of 45 patients studied during anesthesia with inhaled anesthetics has been calculated as shunt = 0.8 × atelectasis + 1.7 ($r = .81$, $P < .01$), with atelectasis expressed as the percentage of lung area just above the diaphragm on CT scan and shunt expressed as the percentage of cardiac output. Interestingly, shunt did not increase with age.[63] By combining CT scanning and SPECT, the distribution of shunt and its location within the atelectatic area were confirmed (Fig. 15-18).[69]

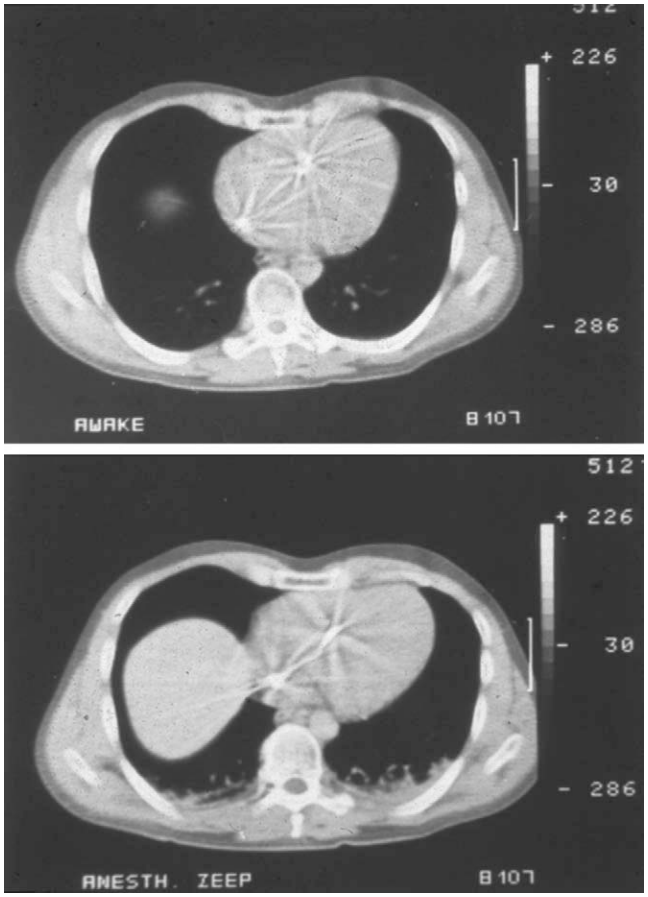


Figure 15-16 Computed tomography with transverse exposure of the chest when the subject is awake (*upper panel*) and then anesthetized (*lower panel*). Note the well-aerated lung in the awake condition. A few pulmonary vessels can be seen in the lower lung regions. The radiating beams in the heart are caused by a catheter that is positioned with its tip in the pulmonary artery. During anesthesia, atelectasis has developed in the most dependent regions of both lungs (seen as gray/white irregular areas). The large gray/white area in the middle of the right lung field is caused by a cranial shift of the diaphragm and the underlying liver. The exposure levels of the two scans are the same relative to the spine.

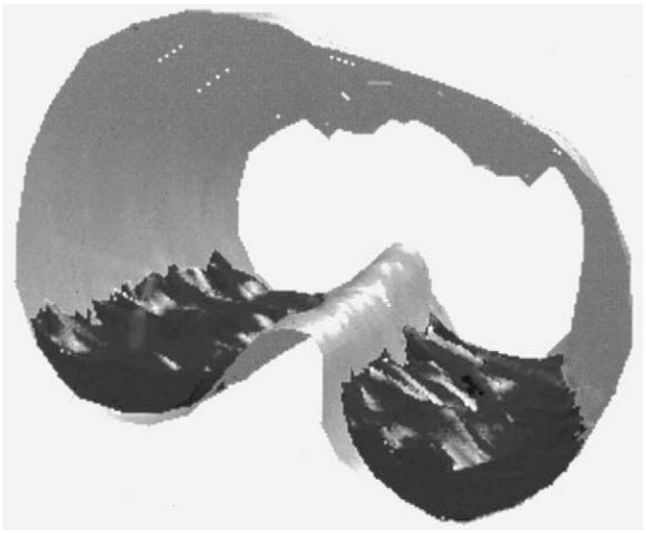


Figure 15-17 Three-dimensional reconstruction of the thorax of an anesthetized patient with atelectasis in the dependent regions of both lungs. Note the irregular shape of the atelectasis. There is a slight decrease in the amount of atelectasis toward the apex, which is at the distal end of the chest wall on the image. *(Redrawn from data in Reber A, Nylund U, Hedenstierna G: Position and shape of the diaphragm: Implications for atelectasis formation. Anaesthesia 53:1054-1061, 1998.)*

Prevention of Atelectasis During Anesthesia

Several interventions can help prevent atelectasis or even reopen collapsed tissue, as discussed in the following paragraphs.

Positive End-Expiratory Pressure. The application of 10–cm H_2O PEEP has been tested in several studies and will consistently reopen collapsed lung tissue. This is more likely an effect of increased inspiratory airway pressure than of PEEP per se.[58] However, some atelectasis persists in most patients. Whether a further increase in the PEEP will reopen this tissue was not analyzed in these studies. PEEP, however, does not appear to be the ideal procedure. First, shunt is not reduced proportionately, and arterial oxygenation may not improve significantly. Hewlett and coworkers warned even in 1974 of the "indiscriminate use of PEEP in routine anesthesia."[70] The persistence of shunt may be explained by a redistribution of blood flow toward more dependent parts of the lungs when intrathoracic pressure is increased by PEEP (Fig. 15-19). Under such circumstances, any persisting atelectasis in the bottom of the lung receives a larger share of the pulmonary blood flow than without PEEP.[71] Furthermore, increased intrathoracic pressure will impede venous return and decrease cardiac output. This results in a lower venous oxygen tension for a given oxygen uptake and reduces arterial oxygen tension. Second, the lung recollapses rapidly after discontinuation of PEEP. Within 1 minute after cessation of PEEP, the collapse is as large as it was before the application of PEEP.[58]

Maintenance of Muscle Tone. Use of an anesthetic that allows maintenance of respiratory muscle tone will prevent atelectasis from forming. Ketamine does not impair muscle tone and does not cause atelectasis. This is the only anesthetic thus far tested that does not cause collapse. However, if muscle relaxation is required, atelectasis will appear as with other anesthetics.[58]

Another technique used in an attempt to restore respiratory muscle tone is pacing of the diaphragm. This was tested by applying phrenic nerve stimulation, which did reduce the atelectatic area.[72] The effect was small, however, and this technique is certainly too complicated to be used routinely during anesthesia and surgery.

Recruitment Maneuvers. The use of a sigh maneuver, or a double V_T, has been advocated to reopen any collapsed lung tissue.[73] However, the atelectasis is not decreased by a double V_T or by a sigh up to an airway pressure of 20 cm H_2O.[67] Not until an airway pressure of 30 cm H_2O is reached does the atelectasis decrease to approximately half the initial size. For complete reopening of all collapsed lung tissue, an inflation pressure of 40 cm H_2O is required (Fig. 15-20). Such a large inflation corresponds to a maximum spontaneous inspiration, and it can thus be called a VC maneuver.

Because a VC maneuver may result in adverse cardiovascular events, the dynamics in resolving atelectasis during such a procedure was analyzed.[74] It was found that in adults with healthy lungs, inflation of the lungs to +40 cm H_2O maintained for no more than 7 to 8 seconds may re-expand all previously collapsed lung tissue.

Minimizing Gas Resorption. Ventilation of the lungs with pure oxygen after a VC maneuver that had reopened previ-

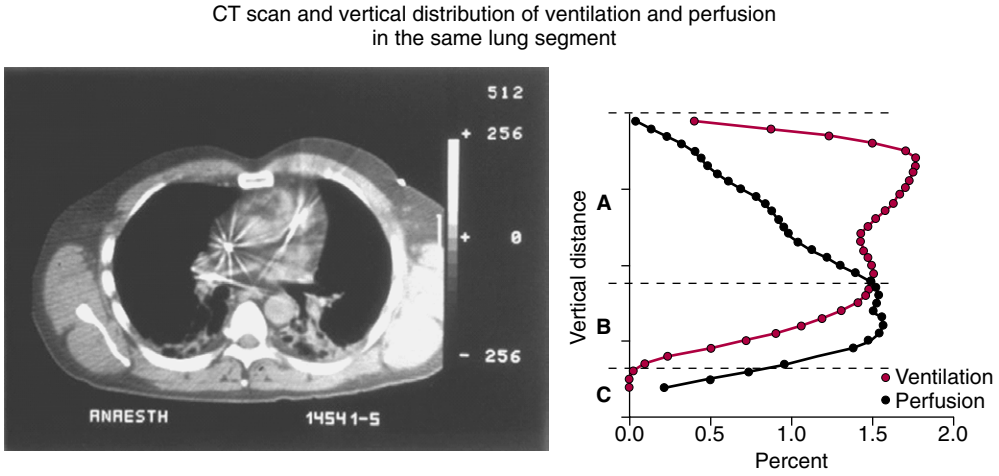


Figure 15-18 Transverse computed tomography (CT) scan with atelectasis visible in the dependent parts of both lungs (*left panel*) and corresponding vertical distributions of ventilation and lung blood flow (*right panel*) in an anesthetized subject. Note that ventilation is distributed preferentially to the upper lung regions, contrary to what is seen in an awake subject. Ventilation exceeds perfusion at that level, and this results in a dead space–like effect, or wasted ventilation (zone A in the *right panel*). Note also the decreasing ventilation in the lower half of the lung such that perfusion is larger at that level. This results in so-called low $\dot{V}_A/\dot{Q}$ and causes impaired oxygenation of blood. Intermittent airway closure is the probable mechanism behind the reduced ventilation (zone B). There is complete cessation of ventilation in the bottom, which corresponds to the atelectatic area. However, there is still perfusion producing a shunt (zone C). It can also be seen that perfusion increases down the lung, except for the bottom-most region, where a decrease can be seen. This so-called zone IV may be caused by increased interstitial lung pressure compressing extra-alveolar vessels and hypoxic pulmonary vasoconstriction. *(Redrawn from data in Tokics L, Hedenstierna G, Svensson L, et al: V/Q distribution and correlation to atelectasis in anesthetized paralyzed humans. J Appl Physiol 81:1822-1833, 1996.)*

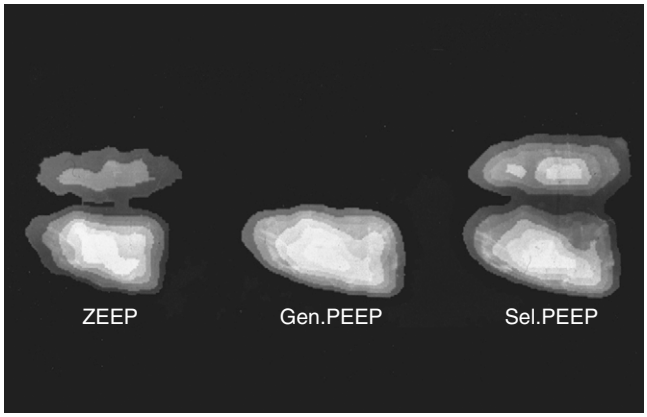


Figure 15-19 Gamma camera images of the distribution of lung blood flow in an anesthetized subject in the lateral position. During mechanical ventilation with zero end-expiratory pressure (ZEEP), perfusion goes mainly to the lower lung, but there is still perfusion of the upper lung, with the average distribution to the upper lung being 33% to 40% of total lung perfusion. With a general PEEP of 10 cm H_2O, perfusion is squeezed down to the lower lung, and in this particular example there is almost no perfusion at all in the upper lung. This causes a dramatic dead space–like effect. If, on the other hand, PEEP is applied selectively to the lower lung, in this example 10 cm H_2O, perfusion might be redistributed to the upper lung so that a more even distribution between the two lungs can be seen. It should be clear that the size of the upper and lower lungs, as shown on the image, does not reflect lung volume but perfused lung tissue. The upper lung should be expected to be larger than the lower lung in the lateral position. *(From Hedenstierna G, Baehrendtz S, Klingstedt C, et al: Ventilation and perfusion of each lung during differential ventilation with selective PEEP. Anesthesiology 61:369-376, 1984.)*

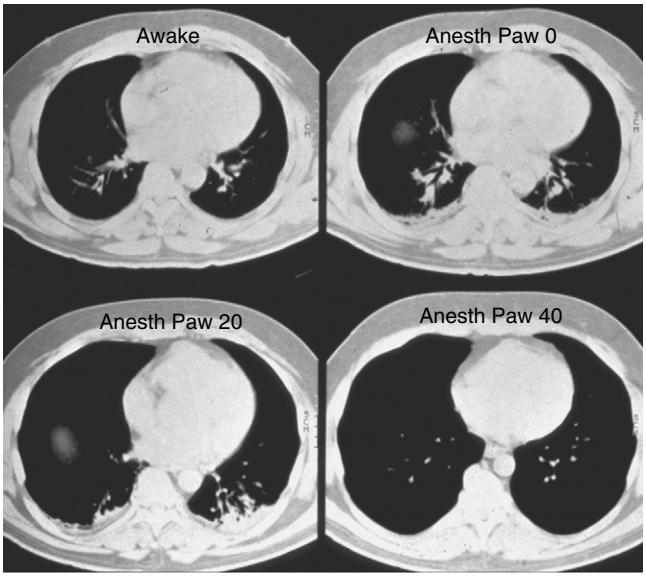


Figure 15-20 Computed tomography scans in a subject when awake (*upper left panel*); during anesthesia at zero end expiratory pressure (*upper right panel*); during anesthesia and an airway pressure of 20 cm H_2O, which corresponds to a double tidal volume (*lower left panel*); and during anesthesia at maximal inflation of the lungs to an airway pressure of 40 cm H_2O (*lower right panel*). Note that there is no atelectasis in the awake subject; only vessels can be seen in the lower part of the lung. During anesthesia with zero airway pressure, atelectasis can be seen in the dependent parts of both lungs. Inflation to 10 cm H_2O, corresponding to a regular tidal volume, does not open any tissue (not shown here). Inflation to 20 cm H_2O still did not open any lung tissue. Not until inflation to 30 cm H_2O (not shown here) did collapsed lung tissue start to open. A maximum inflation of 40 mm Hg airway pressure (Paw) was required to fully open the lung. Thus, a "vital" capacity maneuver was required to open the lung (the volume inflated corresponded to the maximum breath by the awake subject before anesthesia). *(From Rothen HU, Sporre B, Engberg G, et al: Reexpansion of atelectasis during general anaesthesia: A computed tomography study. Br J Anaesth 71:788-795, 1993.)*

ously collapsed lung tissue resulted in rapid reappearance of the atelectasis.[75] If, on the other hand, 40% O_2 in nitrogen is used for ventilation of the lungs, atelectasis reappears slowly, and 40 minutes after the VC maneuver only 20% of the initial atelectasis had reappeared. Thus, ventilation during anesthesia should be done with a moderate fraction of inspired oxygen (e.g., F_{IO_2} of 0.3 to 0.4) and should be increased only if arterial oxygenation is compromised.

The striking effects of oxygen during anesthesia raised the question of whether "preoxygenation" during induction of anesthesia has an effect on the formation of atelectasis. Breathing of 100% O_2, just for a few minutes before and during commencement of anesthesia, increases the safety margin in the event of difficult intubation of the airway with prolonged apnea. However, there turned out to be a price for it. Avoidance of the preoxygenation procedure (ventilation with 30% O_2) eliminated atelectasis formation during induction and subsequent anesthesia.[76] In a subsequent study, 12 patients were breathing 100% O_2 during induction of anesthesia, another 12 were breathing 80% O_2, and still another 12 breathed 60% O_2.[77] Atelectasis appeared in all patients receiving 100% O_2, was much smaller in the 80% O_2 group, and was almost absent in the 60% O_2 group (Fig. 15-21).

Preoxygenation can also be provided without producing atelectasis if undertaken with continuously increased airway pressure, as with continuous positive airway pressure (CPAP). By applying CPAP of 10 cm H_2O, Rusca and associates could induce anesthesia on 100% O_2 without any substantial atelectasis formation.[78] This technique might provide the greatest safety without atelectasis formation but it requires a tight system and might be complicated in clinical practice.

Postanesthetic Oxygenation. Preoxygenation promotes not only the formation of atelectasis but also the so-called postanesthetic oxygenation at the end of the surgery. This procedure is often combined with suctioning of the airway tree, and it is difficult to see how any other technique can be invented that is so likely to produce atelectasis as suctioning together with postanesthetic oxygenation! This will most likely deliver a patient to the postoperative ward with more atelectasis than at any other moment during anesthesia and surgery. Postanesthetic oxygenation (100% O_2) 10 minutes before termination of anesthesia together with a VC maneuver at the end of anesthesia did not protect against atelectasis at the end of anesthesia.[79] This is most likely the effect of first reopening collapsed tissue and then, under the influence of 100% O_2, derecruiting previously opened lung tissue. A VC maneuver followed by a lower O_2 concentration, 40%, kept the lung open after recruitment until the end of anesthesia. This is not unexpected in view of the findings earlier in the anesthesia procedure.

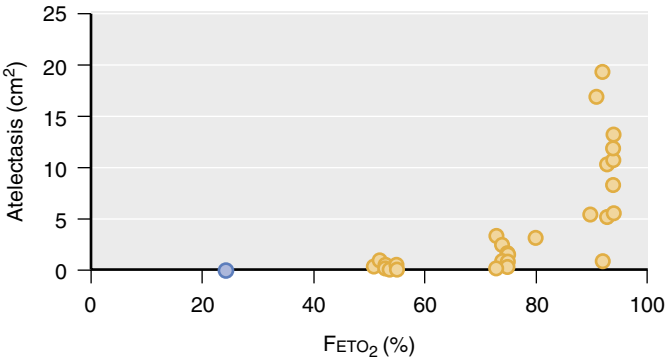


Figure 15-21 Formation of atelectasis in anesthetized subjects whose anesthesia has been induced with different inspired oxygen concentrations during the preoxygenation period. Twelve subjects were given 100% O_2, another 12 subjects 80%, and still another 12 subjects 60% O_2. The graph shows the expired oxygen concentration, which explains why the individual symbols are not at 60%, 80%, and 100%. Note the much larger atelectasis with preoxygenation of 100% (although there is large scatter) than at 80% and 60%, with almost no atelectasis at 60% preoxygenation. The *blue circle* at around an end-tidal oxygen concentration (F_{ETO_2}) of 25% corresponds to data obtained by Rothen and colleagues, who induced anesthesia in subjects given 30% O_2. *(From Rothen HU, Sporre B, Engberg G, et al: Prevention of atelectasis during general anesthesia. Lancet 345:1387-1391, 1995.)*

Airway Closure

In addition to atelectasis, intermittent closure of airways can be expected to reduce the ventilation of dependent lung regions. Such lung regions may then become "low-$\dot{V}_A/\dot{Q}$" units if perfusion is maintained or not reduced to the same extent as ventilation. Airway closure increases with age[25] (see also Fig. 15-7), as does perfusion to "low-$\dot{V}_A/\dot{Q}$" regions.[47] Because anesthesia causes a reduction in FRC of 0.4 to 0.5 L,[55] it may be anticipated that airway closure will become even more prominent in an anesthetized subject. There is accumulating evidence that such is the case.[80,81] The reduced ventilation in the lower half of the lung, just above the atelectasis, that can be seen in Figure 15-18 is reasonably explained by airway closure. It can also be seen that ventilation is smaller than perfusion, thereby causing "low-$\dot{V}_A/\dot{Q}$" regions. These regions contribute to impaired oxygenation during anesthesia.

As much as 74% of the impaired arterial oxygenation can be explained by atelectasis and airway closure taken together, according to the following equation[57]:

$$P_{aO_2}\,(\text{mm Hg}) = 218 - 22 \cdot \ln\ \text{atelectasis}\,(\text{cm}^2) - 0.06\,(\text{CV} - \text{ERV})\,(\text{mL})$$

($r = .86$, $P < .001$), where (CV − ERV) indicates the amount of airway closure occurring above FRC and ERV is expiratory reserve volume. A simple three-compartment lung model can be constructed to explain the impaired oxygenation during anesthesia. The model consists of one compartment with "normal" ventilation and perfusion, one compartment with airway closure that impedes ventilation, and a final compartment of collapsed lung with no ventilation at all. This is shown in Figure 15-22, left panel, together with the subsequent impact on $\dot{V}_A/\dot{Q}$ distribution.

Distribution of Ventilation and Blood Flow During Anesthesia

Distribution of Ventilation

Redistribution of inspired gas away from dependent to nondependent lung regions has been observed in anesthetized supine humans by isotope techniques. With the use of a radiolabeled aerosol and SPECT, ventilation was shown to be distributed mainly to the upper lung regions, and there was a successive decrease down the lower half of the lung.[69] Moreover, there was no ventilation at all in the bottom of the lung, a finding

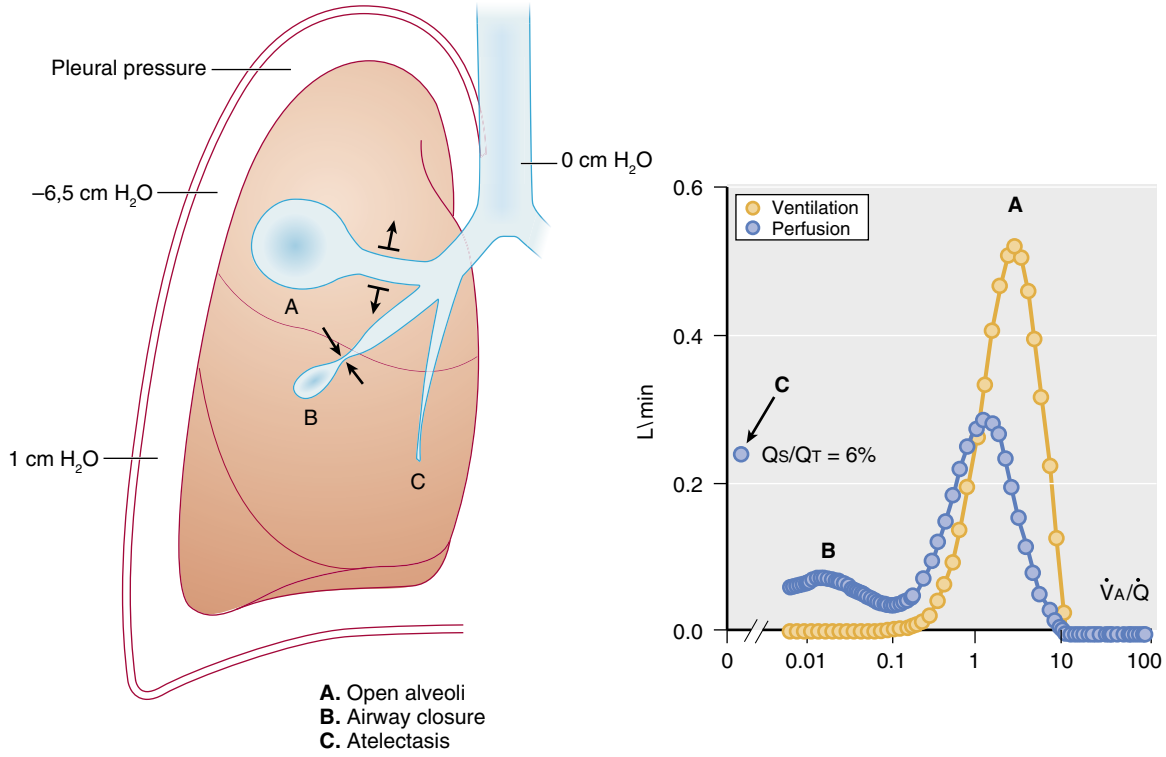


Figure 15-22 Three-compartment model of the lung in an anesthetized subject. In the upper part of the lung, the alveoli and airways are open (zone A). In the middle and lower parts of the lung, the airways are intermittently closed and impede ventilation (zone B), and in the bottom of the lung, the alveoli have collapsed (atelectasis, zone C). Compare with Figure 15-7. The corresponding ventilation-perfusion distribution as assessed by the multiple inert gas elimination technique can be seen in the *right panel*. Modes A and B correspond to a well-ventilated and perfused lung region and a region with intermittent airway closure, respectively, and are similar to what was shown in Figure 15-7. In addition, there is a shunt that is caused by perfusion of the atelectatic zone (C) in the bottom of the lung.

corresponding to the distribution of atelectasis that was simultaneously observed by CT (see Fig. 15-18).

PEEP increases dependent lung ventilation in anesthetized subjects in the lateral position, so the distribution of ventilation is more similar to that in the awake state.[82] Similar findings of more even distribution between the upper and lower lung regions have also been made in supine anesthetized humans after previous inflation of the lungs, similar to PEEP.[83] Thus, restoration of overall FRC toward or beyond the awake level returns gas distribution toward the awake pattern. It is reasonably an effect of the recruitment of collapsed, dependent lung regions (atelectasis), of reopening of closed airways in the lower lung regions, and possibly of increased expansion of the upper lung regions so that they become less compliant (and less ventilated).

Distribution of Lung Blood Flow

As discussed earlier, the distribution of lung blood flow has been studied by injection of radioactively labeled macroaggregated albumin and SPECT in anesthetized, mechanically ventilated patients.[69] A successive increase in perfusion down the lung, from the ventral to the dorsal aspect, was seen, with some reduction in the lowermost region. Thus, the lowermost portion of the lung, which was atelectatic as evidenced by simultaneous CT, was still perfused (see Fig. 15-18).

PEEP will impede venous return to the right heart and therefore reduce cardiac output. It may also affect pulmonary vascular resistance, although this may have less of an effect on cardiac output. In addition, PEEP causes a redistribution of blood flow toward dependent lung regions.[71,83] By this means, upper lung regions may be poorly perfused, thereby causing a dead space–like effect. Moreover, forcing blood volume downward to the dorsal side of the lungs may increase fractional blood flow through an atelectatic region.

Hypoxic Pulmonary Vasoconstriction

Several inhaled anesthetics have been found to inhibit HPV in isolated lung preparations. However, no such effect has been seen with intravenous anesthetics (barbiturates).[84] Results from human studies vary, reasonably explained by the complexity of the experiment, which causes several variables to change at the same time. The HPV response may thus be obscured by simultaneous changes in cardiac output, myocardial contractility, vascular tone, blood volume distribution, blood pH and CO_2 tension, and lung mechanics. In studies with no gross changes in cardiac output, isoflurane and halothane depress the HPV response by 50% at a minimum alveolar concentration (MAC) of 2 (Fig. 15-23).[85]

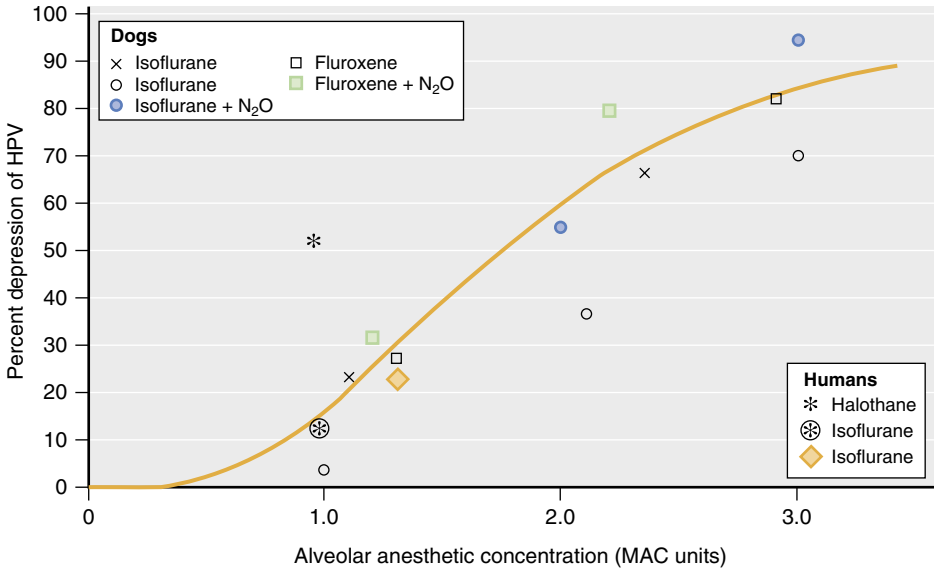


Figure 15-23 Attenuation of hypoxic pulmonary vasoconstriction (HPV) plotted against minimal alveolar anesthetic concentration (MAC units). Note that during anesthesia with different inhaled anesthetics at a MAC of 1, a depression of HPV of about 20% to 30% can be seen, and with higher anesthetic concentrations, HPV can be blunted much more. The consequence is that perfusion through a nonventilated region, as in atelectasis, will not be reduced at higher anesthetic concentrations. *(From Marshall BE. Hypoxic pulmonary Vasoconstriction. Acta Anaesthesiol Scand 94:37-41, 1990.)*

Ventilation-Perfusion Matching During Anesthesia

Dead Space, Shunt, and Ventilation-Perfusion Relationships

Both CO_2 elimination and oxygenation of blood are impaired in most patients during anesthesia. The impeded CO_2 elimination can be attributed to increased dead space ventilation. Single-breath washout recordings have demonstrated that "anatomic" dead space is unchanged, indicating that the "alveolar" or parallel dead space must have increased during anesthesia.[73] By MIGET, the increased CO_2 dead space during anesthesia is not really dead space but poorly perfused lung regions that are signified by so-called high $\dot{V}_A/\dot{Q}$ ratios (Fig. 15-24). Such "high $\dot{V}_A/\dot{Q}$" can be explained by the tiny perfusion of corner vessels in interalveolar septa in the upper lung regions (where alveolar pressure may exceed pulmonary vascular pressure [zone I]).[52] The impaired CO_2 elimination is most easily corrected by increasing the ventilation and is seldom a problem in routine anesthesia with mechanical ventilation.

The impairment in arterial oxygenation during anesthesia is generally considered to be more severe at higher ages, obesity worsens the oxygenation of blood, and smokers show more impairment in gas exchange than nonsmokers do.[86,87] Venous admixture, as calculated according to the standard oxygen "shunt" equation, is also increased during anesthesia to approximately 10% of cardiac output. However, the venous admixture includes not only perfusion of nonventilated lung tissue (true shunt) but also regions that are poorly ventilated or perfused in excess of their ventilation ("low-$\dot{V}_A/\dot{Q}$ regions"). The extent to which the venous admixture includes low-$\dot{V}_A/\dot{Q}$ regions depends on the inspired oxygen fraction (F_{IO_2}). The higher the inspired oxygen fraction, the less there are of the low-$\dot{V}_A/\dot{Q}$ regions. However, with high F_{IO_2}, regions with low $\dot{V}_A/\dot{Q}$ may collapse because of gas adsorption and be transformed to shunt regions.[88] A good correlation between venous admixture and the sum of "true" shunt and perfusion of "low-$\dot{V}_A/\dot{Q}$ regions" was seen in a study involving 45 anesthetized subjects (Fig. 15-25).[63] Derivation of the "oxygen shunt" or venous admixture is shown in Box 15-3.

In young healthy volunteers during anesthesia with thiopental and methoxyflurane, both ventilation and perfusion were distributed to wider ranges of $\dot{V}_A/\dot{Q}$ ratios, which can be expressed as an increase in the logarithmic standard deviation of the perfusion distribution (log SDQ). In a similar group of patients studied during halothane anesthesia and muscle paralysis, log SDQ was almost doubled, from 0.43 when awake to 0.80 during anesthesia. In addition, true shunt was increased to a mean of 8%. A similar increase in shunt from 1% awake to a mean of 9% during anesthesia was recorded in a study on middle-aged (37 to 64 years) surgical patients, and there was a widening of the $\dot{V}_A/\dot{Q}$ distribution (log SDQ of 0.47 when awake and 1.01 during anesthesia). In elderly patients with more severe impairment of lung function, halothane anesthesia with muscle paralysis, with or without nitrous oxide, caused considerable widening of the $\dot{V}_A/\dot{Q}$ distribution, with log SDQ increasing from 0.87 when awake to 1.73 during anesthesia. In addition, shunt increased to a mean of 15%, with large variation between patients (0% to 30%). Thus, the most consistent findings during anesthesia are an increased $\dot{V}_A/\dot{Q}$ mismatch, expressed as an increased log SDQ, and an increase in shunt. For review, see the article by Hedenstierna.[52]

Effects of Anesthetics on Respiratory Drive

Spontaneous ventilation is frequently reduced during anesthesia. Thus, inhaled anesthetics,[89] as well as barbiturates for intravenous use,[90] reduce sensitivity to CO_2. The response is dose dependent and entails decreasing ventilation with deepening anesthesia. Anesthesia also reduces the response to hypoxia. Attenuation of the hypoxic response may be attributed to an effect on the carotid body chemoreceptors.[91]

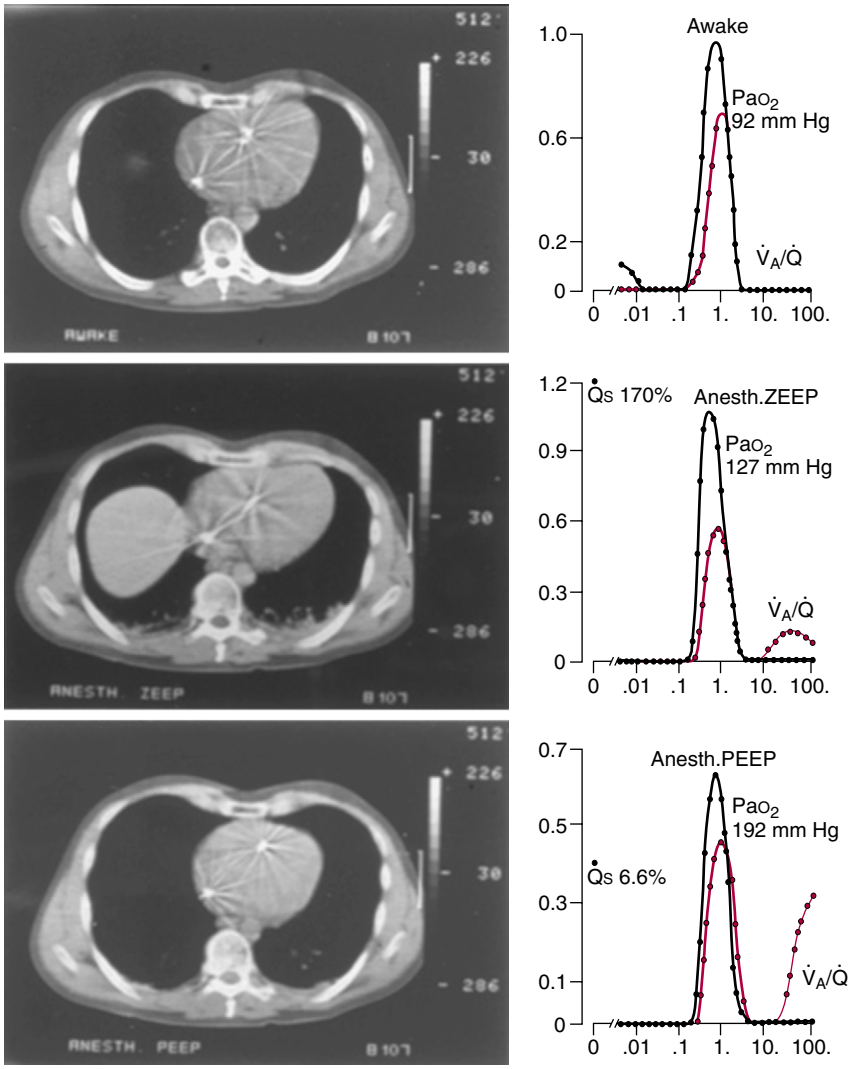


Figure 15-24 Computed tomography scans and $\dot{V}_A/\dot{Q}$ distributions in a lung-healthy subject when awake, during anesthesia with zero end-expiratory pressure (ZEEP), and during anesthesia with 10–cm H_2O positive end-expiratory pressure (PEEP). Note the absence of any atelectasis in the awake condition and the corresponding $\dot{V}_A/\dot{Q}$ distribution with a minor low-$\dot{V}_A/\dot{Q}$ mode that might be explained by intermittent airway closure. During anesthesia with ZEEP, atelectasis can be seen in the bottom of the lung, as well as the diaphragm in the middle of the right lung area (the diaphragm has been pushed cranially during anesthesia). A large shunt can be seen, whereas the "low" $\dot{V}_A/\dot{Q}$ has more or less disappeared, probably by conversion to atelectasis and shunt. Moreover, a small "high"-$\dot{V}_A/\dot{Q}$ mode can be seen that might reflect alveolar dead space in the upper lung regions. With PEEP, the collapsed lung tissue has been recruited and the shunt has been considerably reduced. Moreover, the "high"-$\dot{V}_A/\dot{Q}$ mode has increased in size and may reflect a further increase in nonperfused upper lung regions that has caused a dead space–like effect.

The effect of an anesthetic on respiratory muscles is nonuniform. Rib cage excursions diminish with deepening anesthesia.[92] The normal ventilatory response to CO_2 is produced by the intercostal muscles,[93,94] with no clear increase in rib cage motion with CO_2 rebreathing during halothane anesthesia. Thus, the reduced ventilatory response to CO_2 during anesthesia is due to impeded function of the intercostal muscles.

Factors That Influence Respiratory Function During Anesthesia

Spontaneous Breathing

Most studies on lung function have been performed on anesthetized, mechanically ventilated subjects or animals. Relatively few data have been obtained during spontaneous breathing. FRC is reduced to the same extent during anesthesia, regardless of whether a muscle relaxant is used,[56,58] and atelectasis occurs to almost the same extent in anesthetized spontaneously breathing subjects as during muscle paralysis.[95] Furthermore, the cranial shift of the diaphragm, as reported by Froese and Bryan in their classic paper,[96] was of the same magnitude both during general anesthesia with spontaneous breathing and with muscle paralysis, even though a difference in movement of the diaphragm from the resting position was noted. Thus, during spontaneous breathing, the lower, dependent portion of the diaphragm moved the most, whereas with muscle paralysis, the upper, nondependent part showed the largest displacement.

All these findings have raised the question of whether regional ventilation is different between spontaneous breathing and mechanical ventilation and whether mechanical ventilation worsens $\dot{V}_A/\dot{Q}$ as a consequence of poor ventilation of well-perfused, dependent lung regions. However, there is not much support for worsening of gas exchange by muscle paralysis in the literature, and there is also no support from the few studies on $\dot{V}_A/\dot{Q}$ distribution that have been performed. Dueck and coworkers[97] found the same increase in $\dot{V}_A/\dot{Q}$ mismatch in anesthetized sheep during anesthesia whether they were spontaneously breathing or mechanically ventilated. The log SDQ, indicating the degree of $\dot{V}_A/\dot{Q}$ mismatch, increased from 0.66 to 0.83 and 0.89 from awake to inhaled anesthesia with spontaneous breathing and mechanical ventilation, respectively. Shunt also increased with no significant difference between the two anesthesia conditions (from 1% awake to 11% and 14% during anesthesia with spontaneous breathing and mechanical ventilation). In a

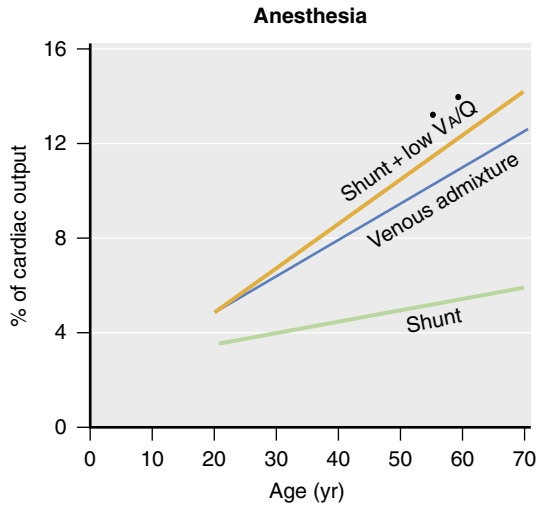


Figure 15-25 Influence of age on shunt, shunt + low $\dot{V}_A/\dot{Q}$, and venous admixture in anesthetized subjects. There is a slight and insignificant increase in shunt with age, whereas shunt + low $\dot{V}_A/\dot{Q}$ increases rapidly. Note also that venous admixture is more similar to shunt + perfusion of low $\dot{V}_A/\dot{Q}$ regions than to shunt alone. *(From Gunnarsson L, Tokics L, Gustavsson H, et al: Influence of age on atelectasis formation and gas-exchange impairment during general-anesthesia. Br J Anaesth 66:423-432, 1991.)*

study of anesthetized human subjects, shunt and log SDQ increased from 1% and 0.47 while awake to 6% and 1.03 during anesthesia with spontaneous breathing and 8% and 1.01 during mechanical ventilation.[52] Thus, most of the gas exchange effects of anesthesia can be seen even during spontaneous breathing, with little or no further derangement added by muscle paralysis and mechanical ventilation.

Increased Oxygen Fraction

In the studies cited thus far, an inspired oxygen fraction (F_{IO_2}) of around 0.4 was used. Anjou-Lindskog and associates[98] induced anesthesia on air (F_{IO_2} of 0.21) in middle-aged to elderly patients during intravenous anesthesia before elective lung surgery and found only small shunts of 1% to 2%, although log SDQ increased from 0.77 to 1.13. When F_{IO_2} was increased to 0.5, an increase in shunt of 3% to 4% was noticed. In another study on elderly patients during halothane anesthesia (see Hedenstierna[52]), an increase in F_{IO_2} from 0.53 to 0.85 caused an increase in shunt from 7% to 10% of cardiac output. Thus, a certain dependence on F_{IO_2} appears to exist, possibly explained by attenuation of the HPV response with increasing F_{IO_2}[85] or further development of atelectasis and shunt in lung units with low $\dot{V}_A/\dot{Q}$ ratios.[88]

Box 15-3 Derivation of the Venous Admixture ("Shunt") Equation

$$Ca \times \dot{Q}_T = (Cc' \times \dot{Q}c) + (C\bar{v} \times \dot{Q}s) \quad (1)$$

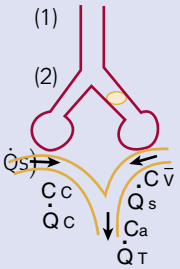
$$\dot{Q}c = \dot{Q}_T - \dot{Q}s \quad (2)$$

By inserting Equation 2 into Equation 1,

$$Ca \times \dot{Q}_T = (Cc \times [\dot{Q}_T - \dot{Q}s]) + (C\bar{v} \times \dot{Q}s)$$

Rearranging,

$$\frac{\dot{Q}s}{\dot{Q}_T} = \frac{Cc' - Ca}{Cc' - C\bar{v}}$$



where Cc', Ca, and $C\bar{v}$ are oxygen content in pulmonary end-capillary, arterial, and mixed venous blood, respectively; $\dot{Q}_T$ is cardiac output; $\dot{Q}c$ is capillary flow; and $\dot{Q}s$ is shunt.

Body Position

Because FRC is dramatically reduced by the combined effect of the supine position and anesthesia (see Chapter 36), it might be advantageous to choose a more upright position in an anesthetized subject to preserve FRC. This was tested by Heneghan and colleagues[99] in lung-healthy patients who underwent general anesthesia. However, no clear improvement in oxygenation was noticed when the patient was semirecumbent as opposed to the supine position. It is likely that pulmonary blood flow is impeded by the semirecumbent position because of a possible decrease in cardiac output and enhanced inhomogeneity of blood flow distribution. Fractional perfusion of the most dependent lung regions, which may still be poorly or not at all ventilated, may have been increased in the semirecumbent position. In the lateral position, differences in lung mechanics, resting lung volumes, and atelectasis formation between the dependent and nondependent portions of the lung have been demonstrated[100] and shown to result in further disturbance of the ventilation-perfusion match, with severe impairment in arterial oxygenation in some patients. However, there are large and unpredictable interindividual variations.[101] With the use of isotope techniques, an increase in $\dot{V}_A/\dot{Q}$ mismatch was also demonstrated in anesthetized, paralyzed patients in the lateral position,[102] and an improvement was noticed in the prone position.[103] There are findings suggesting that the vertical inhomogeneity of the distribution of perfusion is less obvious in the prone position.[104] This may indicate that there are regional differences in vascular configuration that promote perfusion of dorsal lung regions, regardless of whether they are in a dependent or nondependent position. It is also worthy of note that the ventilation distribution was more uniform in anesthetized subjects who were in the prone position.[105]

Age

It is well known that arterial oxygenation is further impeded with increasing age of the patient (see Chapters 71 and 82).[73] As mentioned earlier, formation of atelectasis does not increase with age in adults, and the sparse number of babies who have been studied in the CT scanner during anesthesia appear to have a larger percentage of atelectasis in the transthoracic area than patients of other ages do.[63] Similarly, shunt is independent of age in the tested range of 23 to 69 years. In contrast, there appears to be increasing $\dot{V}_A/\dot{Q}$ mismatch with age, with enhanced perfusion of low-$\dot{V}_A/\dot{Q}$ regions both in awake subjects and when they are subsequently anesthetized. Figure 15-25 shows the relationship between shunt, perfusion of low-$\dot{V}_A/\dot{Q}$ regions, and age of the patient. Thus, the major cause of impaired gas exchange during anesthesia at ages younger than 50 years is shunt, whereas at higher ages mismatch (increased log SDQ) becomes increasingly important. Because the correlation between log SDQ and age during anesthesia is almost parallel with that during the awake state, it can be said that anesthesia worsens the match of ventilation and blood flow by as much as 20 years of aging. Hopefully, log SDQ returns to the preanesthesia level after surgery!

Obesity

Obesity worsens the oxygenation of blood (see Chapter 64).[106,107] A major explanation appears to be a markedly reduced FRC, which promotes airway closure to a greater extent than in a normal subject.[108] The use of high inspired oxygen concentrations will promote rapid atelectasis formation behind closed airways.[57,77] Correlations between BMI and the size of atelectasis during anesthesia and postoperatvely[67,109] and between BMI and pulmonary shunt have been presented (Fig. 15-26).[108] Preventing a fall in FRC by CPAP during induction of anesthesia most likely prevents or reduces atelectasis formation and helps keep arterial oxygenation at a higher level.[87,110,111] The shorter time until desaturation during induction of anesthesia, as observed in morbidly obese patients, may also be prevented by PEEP or CPAP.[112] This can be explained by the increase in lung volume by PEEP or CPAP so that more oxygen is available for diffusion into the capillary blood.

The use of high inspired oxygen concentrations, regularly 100%, to keep an acceptable level of oxygenation during anesthesia and surgery may be the simplest but not necessarily the best method. It will promote further atelectasis formation,[75] and if the shunt is larger than 30%, which may well be the case in these patients, further oxygen will add little to arterial oxygenation.[51] The application of PEEP has been advocated as well. If high enough, PEEP may reduce the atelectasis[86,108,110] but will also have adverse effects such as reduced cardiac output and redistribution of blood flow toward dependent, still collapsed lung regions. Ventilation with near-VC inflations to reopen collapsed tissue, followed by PEEP ventilation, is another option. Body position may have a substantial effect on lung volume and should be considered to the extent that surgery allows.[113]

Preexisting Lung Disease

Smokers and patients with lung disease have more severe impairment of gas exchange in the awake state than healthy subjects do, and this difference also persists during anesthesia.[73] Interestingly, smokers with moderate airflow limitation may have less shunt as measured by MIGET than lung-healthy subjects do. Thus, in patients with mild to moderate bronchitis who were to undergo lung surgery or vascular reconstructive surgery in the leg, only a small shunt was noticed, but log SDQ was increased (for references, see the publication list in the article by Hedenstierna[52]). In patients with chronic bronchitis studied by MIGET and CT, no or very limited atelectasis developed during anesthesia and no or only minor shunt.[68] However, a considerable $\dot{V}_A/\dot{Q}$ mismatch was seen with a large perfusion fraction to low-$\dot{V}_A/\dot{Q}$ regions. Consequently, arterial oxygenation was more impaired than in lung-healthy subjects, but the cause was different from that in normal subjects. A possible reason for the absence of atelectasis and shunt in these patients may be chronic hyperinflation, which changes the mechanical behavior of the lungs and their interaction with the chest wall such that the tendency to collapse is reduced. It should be kept in mind that a patient with obstructive lung disease may have large regions with low $\dot{V}_A/\dot{Q}$ ratios that can be converted over time to resorption atelectasis. Thus, the "protection" against atelectasis formation during anesthesia by the obstructive lung disease need not last long. Regions with low $\dot{V}_A/\dot{Q}$ may be replaced by atelectasis as a result of slow resorption of gas behind occluded airways later during surgery and in the postoperative period.

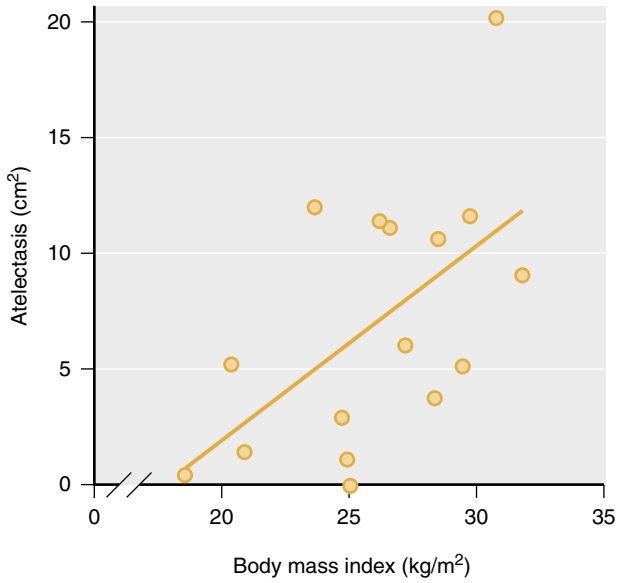


Figure 15-26 Plot of atelectasis during anesthesia versus body dimensions expressed as body mass index (BMI). Note that the larger the body mass index, the larger the atelectasis. *(From Rothen HU, Sporre B, Engberg G, et al: Reexpansion of atelectasis during general anaesthesia: A computed tomography study. Br J Anaesth 71:788-795, 1993.)*

Regional Anesthesia

The ventilatory effects of regional anesthesia depend on the type and extension of motor blockade (see Chapters 51 and 52). With extensive blocks that include all of the thoracic and lumbar segments, inspiratory capacity is reduced by 20% and expiratory reserve volume approaches zero.[114,115] Diaphragmatic function, however, is often spared, even in cases of inadvertent extension of subarachnoid or epidural sensory block up to the cervical segments.[114] Skillfully handled regional anesthesia affects pulmonary gas exchange only minimally. Arterial oxygenation and carbon dioxide elimination are well maintained during spinal and epidural anesthesia. This is in line with the findings of an unchanged relationship of CC and FRC[116] and unaltered distributions of ventilation-perfusion ratios assessed by MIGET during epidural anesthesia.[52]

Lung Function After Cardiac Surgery

Cardiac surgery produces the largest atelectasis in the postoperative period (see Chapter 60).[117] Cardiac surgery is generally undertaken with both lungs collapsed and the patient connected to an extracorporeal pump and oxygenator. If no precautions are taken in the immediate postoperative period, the lung will recruit slowly, and more than half the lung may be collapsed 1 to 2 days later with a shunt that is around 20% to 30% of cardiac output.[118,119] A recruitment maneuver consisting of inflating the lungs to an airway pressure of 30 cm H_2O for a 20-second period is sufficient to reopen the collapsed lung.[118] This lower airway pressure will do the same job as 40 cm H_2O in patients undergoing abdominal surgery because the maneuver is undertaken with an open chest before closure and return to mechanical ventilation. The clinical feasibility and effects on arterial oxygenation of doing such maneuvers were then tested in different clinical trials.[120-122] A few studies will be detailed. Dyhr and coworkers[123] studied 30 patients

after cardiac surgery, with (1) one group receiving a lung recruitment maneuver (LRM consisting of four 10-second insufflations to an airway pressure of 45 cm H_2O) and subsequent zero end-expiratory pressure (ZEEP) ventilation, (2) a 12–cm H_2O PEEP group, and (3) an LRM plus PEEP group. The patients were monitored for 75 minutes. Only transient improvement in Pao_2 and end-expiratory lung volume (EELV) was observed in the LRM group. In the PEEP group, no improvement in Pao_2 was seen, although EELV increased by more than 50%. Finally, in the LRM plus PEEP group, Pao_2 more than doubled, EELV increased by 75% to 80%, and both were maintained at these levels throughout the study period. The inspired oxygen fraction was 1.0. Application of 12–cm H_2O PEEP in the study by Dyhr and colleagues resulted in a considerable increase in EELV (+55%), but it was less than when both LRM and PEEP were applied (+80%). Respiratory compliance increased promptly with the recruitment maneuver but increased gradually over a 1-hour period in the PEEP group. These findings may suggest that the recruitment maneuver resulted in true opening of collapsed lung tissue whereas PEEP alone caused hyperinflation of already open alveoli but with slow recruitment over the following hour.

Pasquina and collaborators compared the effect of 30-minute periods four times a day of CPAP ventilation and noninvasive pressure support ventilation (NIPSV) after cardiac surgery.[124] They studied a large group of 150 patients equally distributed between the two treatment protocols. PEEP of 5 cm H_2O was used in both groups, and V_T was 8 to 10 mL/kg in the NIPSV group. Chest radiography showed a decrease in atelectasis in 60% of the patients on NIPSV versus 40% in the CPAP group. However, there was no difference in arterial oxygenation, any pulmonary function test, or length of stay between the groups. The authors concluded that there appears to be no clinical benefit with NIPSV. Nonetheless, it seems that the inspired oxygen fraction was adjusted according to the blood gas data, and with high FIO_2, a PEEP of 5 cm H_2O, as used in the present study, might be inappropriate to gain full effect on atelectasis formation. On the other hand, the patients might not have accepted a higher CPAP.

Miranda and colleagues focused on another potential effect of recruitment maneuvers after cardiac surgery—the possible increase in right ventricular afterload.[125] They used their open-lung concept technique with vigorous recruitment attempts at a peak airway pressure of 46 cm H_2O to achieve a Pao_2/FIO_2 of greater than 50 kPa. Moreover, to keep the lung open (i.e., without deterioration in Pao_2), PEEP of 17 cm H_2O was required. Despite this strong recruitment, neither pulmonary vascular resistance nor right ventricular ejection fraction changed significantly during the succeeding 3-hour observation period.

Another approach to cardiac surgery that is developing is off-pump coronary bypass grafting. Tschernko and coworkers[126] showed that patients who underwent surgery off-pump had a smaller increase in shunt. Moreover, the hospital stay was shorter in the off-pump group (7.5 versus 10.3 days in on-pump patients with a VC recruitment maneuver). Interestingly, a control group that did not receive any VC maneuver had an even longer hospital stay (12.6 days).

Respiratory Function During One-Lung Ventilation

In lung surgery, oxygenation may be a challenge even during anesthesia. One lung is nonventilated but still perfused, and in the postoperative period, restoration of lung integrity and ventilation/perfusion matching may take time (see Chapter 59).[127]

The technique of one-lung anesthesia and ventilation means that only one lung is ventilated and provides oxygenation of blood, as well as elimination of carbon dioxide from the blood. Persisting perfusion through the nonventilated lung causes a shunt and decreased Pao_2 (Fig. 15-27). Measures can be taken to reduce this blood flow by both mechanical and pharmacologic means, as summarized in a short review.[128] However, the dependent, ventilated lung will also contribute to the impeded oxygenation by formation of atelectasis in the dependent regions.[101] There are reasons to also consider a recruitment maneuver in one-lung ventilation (OLV). Tusman and colleagues[129] tested an "alveolar recruitment strategy" (ARS) in 10 patients who were undergoing open lobectomy first during two-lung ventilation and

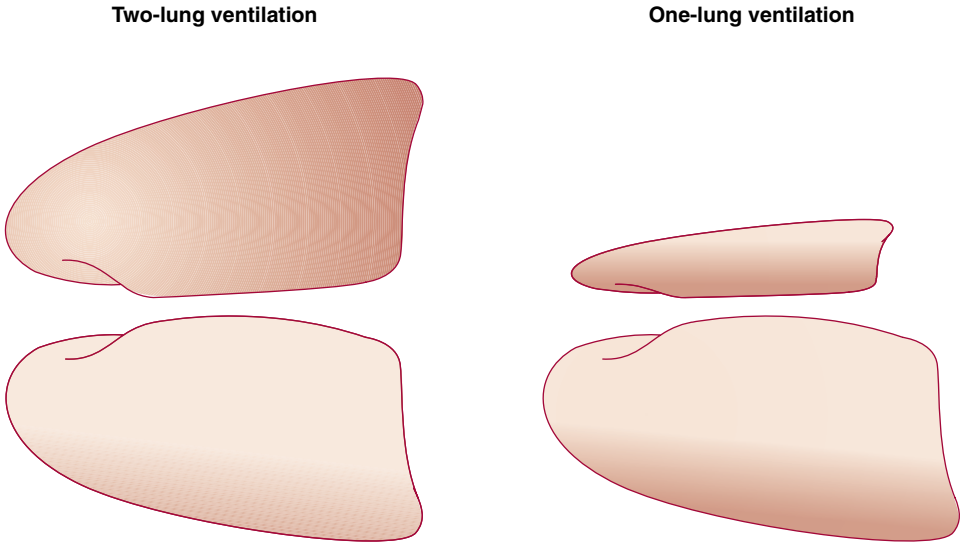


Figure 15-27 Schematic drawing of the distribution of shunt during anesthesia with two-lung ventilation and one-lung ventilation. The shunt region is indicated by the *dark area*, which can be seen in the lower lung during two-lung ventilation but in both the lower lung and in all of upper lung during one-lung ventilation. That the upper, nonventilated lung will act as a shunt region is well known, but one should not forget that the lower part of the dependent lung will also contribute to the shunting.

then during OLV before and then after ARS. The ARS maneuver was executed by increasing peak airway pressure minute by minute from 25 to 30, 35, and finally 40 cm H_2O and simultaneously increasing PEEP from 5 to 10, 15, and finally 20 cm H_2O. Airway pressure was then reduced to a peak of 25 and PEEP to 5 cm H_2O. This resulted in an increase in Pao_2 from 217 to 470 mm Hg after ARS. This substantial improvement in oxygenation suggests that more of the shunt is located in the dependent lung than is generally considered.

In another study by Tusman and associates, the effect of ARS on gas exchange and ventilation efficiency was studied, with a particular focus on dead space ventilation.[130] Again, ARS improved oxygenation. Moreover, dead space decreased and the slope of the CO_2 curve during a tidal expiration (phase III) was flatter, indicative of a more even distribution of inspired gas in relation to regional alveolar volume (or more synchronous alveolar emptying). The effect lasted for the total OLV period of 50 to 105 minutes. Thus, a secondary effect of recruiting collapsed lung tissue is more even distribution of ventilation and a decrease in the dead space fraction. If anything, this should facilitate the use of a smaller V_T.

Ishikawa and coworkers studied the effect of compressing the nondependent lung in patients who underwent esophagectomy.[131] By means of an intra-arterial sensor for continuous recording of arterial blood gas values, they noticed that by applying a retractor to expose the nonventilated right lung and subjecting it to compression, Pao_2 was increased, more so in some patients than in others. The mechanism has been proposed to be a shift of blood flow from the nondependent, nonventilated lung to the other lung. The clinical importance of the study is that it might indicate the value of deliberate compression of the nondependent lung during surgery to reduce shunting and improve oxygenation. However, whether manual compression of the nonventilated lung has any advantage over complete absorption atelectasis can be discussed.[132]

Patients who underwent OLV for thoracic surgery were receiving either ZEEP to the ventilated lung or PEEP adjusted to achieve the best respiratory compliance.[133] The PEEP that was applied was on average 4.3 cm H_2O during two-lung ventilation, 6.2 cm H_2O during closed-chest OLV, and 6.0 cm H_2O during open-chest OLV. This resulted in an average 10% higher compliance in the PEEP group, but Pao_2 was better in the ZEEP group (11.7 versus 10.5 kPa on an F_{IO_2} of 0.5). The opposing findings may not appear too surprising; PEEP should redistribute blood flow away from that lung to the other nonventilated lung with certain impairment of oxygenation. The rationale for identifying and using optimum PEEP has also been discussed by Slinger and associates.[134]

Other studies on oxygenation during OLV have focused on the sympatholytic effect of thoracic epidural anesthesia. Some studies report increased venous admixture and decreased Pao_2 with thoracic epidural anesthesia,[135] no effect,[136,137] or an improvement.[138] No clear conclusions can therefore be drawn.

Another method for control of deoxygenation during one-lung anesthesia is pharmacologic interference with pulmonary blood flow. In one study, the effects of 20 ppm inhaled nitric oxide (NO) alone or in combination with intravenous almitrine, a pulmonary vasoconstrictor, were studied. Almitrine has been shown to dose-dependently increase pulmonary artery pressure and to increase oxygenation in both patients with acute respiratory distress syndrome and those with sepsis. The effect has been attributed to enhancement of HPV, reduction of blood flow in nonventilated lung regions, and an improved ventilation-perfusion relationship. Little effect of NO alone was seen,[139] but oxygenation was significantly improved when NO was combined with almitrine.[140,141] The effect of almitrine alone during OLV has also been studied.[142] A significant improvement in oxygenation and a reduction in venous admixture in the almitrine group versus placebo were seen. Pulmonary artery pressure or cardiac output did not change at the dose of almitrine given.

Whether intravenous almitrine can be used to treat hypoxia has also been studied, and a moderate positive effect was observed.[143]

Careful analysis of the mechanical obstruction caused by kinking of pulmonary vessels and by HPV has shown that HPV is the important determinant of diversion of blood flow away from nonventilated lung (though not complete).[144] Moreover, positioning of the patient can affect the degree of shunting.[145]

The effects of selective vasodilation of the pulmonary circulation in OLV and in cardiac surgery have been reviewed in more detail in different publications, and two are referred to here.[146,147]

Pneumoperitoneum

Laparoscopic operations are becoming increasingly popular. They are usually performed by insufflation of CO_2 into the abdominal cavity (see Chapter 68). However, insufflation of CO_2 may interfere with cardiac and circulatory function, as well as respiratory function. CO_2 pneumoperitoneum may cause hypercapnia and acidosis.[148,149] The direct effects of carbon dioxide and acidosis lead to decreased cardiac contractility, sensitization of the myocardium to the arrhythmogenic effects of catecholamines, and systemic vasodilation.[150] There may even be long-lasting postoperative effects on breathing control. [151]

Pneumoperitoneum may also cause several respiratory changes, such as decreased FRC and VC,[152] formation of atelectasis,[153] reduced respiratory compliance,[154] and increased peak airway pressure.[155] Nonetheless, shunt is reduced and arterial oxygenation is mostly improved during CO_2 pneumoperitoneum.[156] This seeming paradox, more atelectasis and less shunt, suggests efficient redistribution of blood flow away from collapsed lung regions. CO_2 may enhance HPV, which may be the mechanism and explanation of the paradox.

Physiotherapy

Physiotherapy has often been debated after surgery, not the least after cardiac surgery (see Chapter 93). It has even been claimed in a recent review that physiotherapy may do more harm than good.[157] Westerdahl and colleagues showed with CT that breathing exercises consisting of maximum inspirations with the help of devices (flow bottle) or without (spontaneous VC maneuvers) did recruit collapsed lung tissue promptly after an exercise period.[158] Thus, as large an inspiration as possible and as early in the postoperative period as possible are presumably the two important factors in preventing postoperative lung complications. Whether the deep inspiration is done with or without a device for forced breathing is probably of little importance.

Normal Sleep

Ventilation is affected by sleep.[159] A significant reduction in V_T and inspiratory drive has been shown, and minute ventilation falls by approximately 5% to 16%, depending on the sleep stage, with the most marked fall occurring during rapid eye movement (REM) sleep. Lung volume is also reduced during sleep and manifested as a decrease in FRC.[160] The reduction in FRC occurs almost immediately after the onset of sleep, with the most marked fall taking place in REM sleep, during which time it amounts to approximately 0.3 L, or 10% of the awake value.[161]

The fall in FRC during sleep is accompanied by reduced aeration in the dependent lung regions, as shown in a CT study in healthy volunteers.[162] The loss of aeration was as marked as in anesthetized patients who were breathing gas with a moderate concentration of oxygen (F_{IO_2} of 0.3). When the anesthetized patients were switched to 100% O_2, atelectasis developed rapidly.[75] It is tempting to assume that normal sleep while breathing pure oxygen would also lead to the formation of atelectasis.

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Lena S. Sun and Johanna C. Schwarzenberger

16 Cardiac Physiology

Key Points

1. The cardiac cycle is the sequence of electrical and mechanical events during the course of a single heartbeat.
2. Cardiac output is determined by the heart rate, myocardial contractility, and preload and afterload.
3. The majority of cardiomyocytes consist of myofibrils, which are rodlike bundles that form the contractile elements within the cardiomyocyte.
4. The basic working unit of contraction is the sarcomere.
5. Gap junctions are responsible for electrical coupling of small molecules between cells.
6. Action potentials have four phases in the heart.
7. The key player in cardiac excitation-contraction coupling is the ubiquitous second messenger calcium.
8. β-Adrenoreceptors stimulate chronotropy, inotropy, lusitropy, and dromotropy.
9. Hormones with cardiac action can be synthesized and secreted by cardiomyocytes or produced by other tissues and delivered to the heart.
10. Cardiac reflexes are fast-acting reflex loops between the heart and central nervous system that contribute to regulation of cardiac function and maintenance of physiologic homeostasis.

The modern concept of circulation and that the heart is the generator for the circulation was initially advanced by Harvey in 1628. Since that time, the field of cardiac physiology has developed to now include the physiology of the heart as a pump, cellular and molecular biology of the cardiomyocyte, and regulation of cardiac function by neural and humoral factors. Moreover, we now appreciate that physiology of the heart is only a component of the interrelated and integrated cardiovascular and circulatory physiology. This chapter discusses only the physiology of the heart. It begins with the physiology of the intact heart. The second part of the chapter focuses on cellular cardiac physiology. Finally, we briefly discuss the various factors that regulate cardiac function.

The basic anatomy of the heart consists of two atria and two ventricles that provide two separate circulations in series. The pulmonary circulation, a low-resistance and high-capacitance vascular bed, receives output from the right side of the heart, and its chief function is bidirectional gas exchange. The left side of the heart provides output for the systemic circulation. It functions to deliver oxygen and nutrients and remove CO_2 and metabolites from various tissue beds.

Physiology of the Intact Heart

To understand the mechanical performance of the intact heart, it is important to have knowledge of the phases of the cardiac cycle and determinants of ventricular function.

Cardiac Cycle

The cardiac cycle is the sequence of electrical and mechanical events during the course of a single heartbeat. Figure 16-1 illustrates (1) the electrical events of a single cardiac cycle represented by the electrocardiogram (ECG) and (2) the mechanical events of a single cardiac cycle represented by left atrial and left ventricular pressure pulses correlated in time with aortic flow and ventricular volume.[1]

The cardiac cycle begins with initiation of the heartbeat. Intrinsic to the specialized cardiac pacemaker tissues is automaticity and rhythmicity. The sinoatrial (SA) node is usually the pacemaker; it can generate impulses at the greatest frequency and is the natural pacemaker.

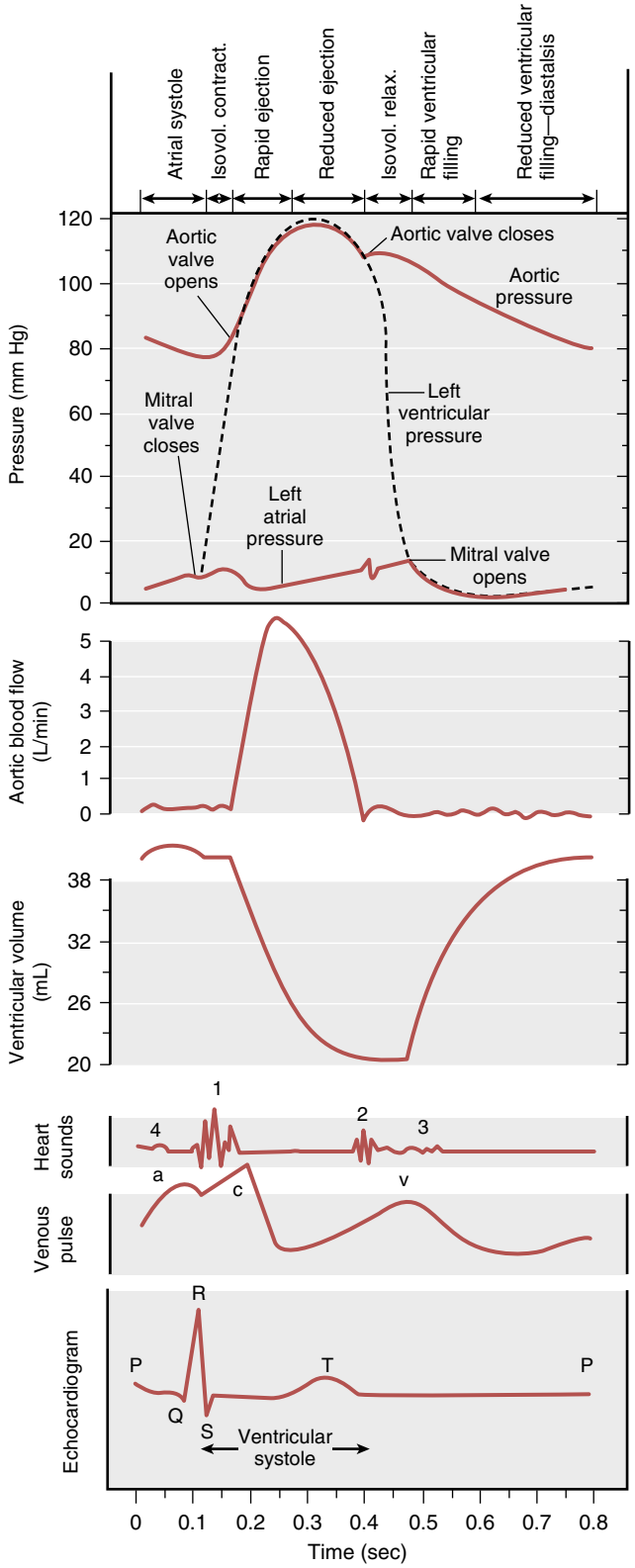

Figure 16-1 Electrical and mechanical events during a single cardiac cycle. Shown are the pressure curves of aortic blood flow, ventricular volume, venous pulse, and the electrocardiogram. *(From Berne RM, Levy MN: The cardiac pump.* In *Cardiovascular Physiology, 8th ed. St Louis, CV Mosby, 2001, pp 55-82.)*

Electrical Events and the Electrocardiogram

Electrical events of the pacemaker and the specialized conduction system are represented by the ECG at the body surface (also see Chapters 42 and 43). It is the result of differences in electrical potential generated by the heart at sites of the surface recording. The action potential initiated at the SA node is propagated to both atria by specialized conduction tissue, and it leads to atrial systole (contraction) and the P wave of the ECG. At the junction of the interatrial and interventricular septa, specialized atrial conduction tissue converges at the atrioventricular (AV) node, which is connected distally to the His bundle. The AV node is an area of relatively slow conduction, and a delay between atrial and ventricular contraction normally occurs at this locus. The PR interval can be used to measure the delay between atrial and ventricular contraction at the level of the AV node. From the distal His bundle, an electrical impulse is propagated through large left and right bundle branches and finally to the Purkinje system fibers, which are the smallest branches of the specialized conduction system. Finally, electrical signals are transmitted from the Purkinje system to individual ventricular cardiomyocytes. The spread of depolarization to the ventricular myocardium is manifested as the QRS complex on the ECG. Depolarization is followed by ventricular repolarization and appearance of the T wave on the ECG.[2]

Mechanical Events

The mechanical events of a cardiac cycle begin with return of blood to the right and left atria from the systemic and pulmonary circulation, respectively. As blood accumulates in the atria, atrial pressure increases until it exceeds the pressure within the ventricle, and the AV valve opens. Blood first flows passively into the ventricular chambers, and such flow accounts for approximately 75% of total ventricular filling.[3] The remainder of the blood flow is mediated by active atrial contraction or systole, known as the atrial "kick." The onset of atrial systole is coincident with depolarization of the sinus node and the P wave. While the ventricles fill, the AV valves are displaced upward and ventricular contraction (systole) begins with closure of the tricuspid and mitral valves, which corresponds to the end of the R wave on the ECG. The first part of ventricular systole is known as isovolumic or isometric contraction. The electrical impulse traverses the AV region and passes through the right and left bundle branches into the Purkinje fibers. This leads to contraction of ventricular myocardium and a progressive increase in intraventricular pressure. When intraventricular pressure exceeds pulmonary artery and aortic pressure, the pulmonic and aortic valves open and ventricular ejection occurs, which is the second part of ventricular systole.

Ventricular ejection can be further separated into the rapid ejection phase and the reduced ejection phase. During the rapid ejection phase, forward flow is maximal, and pulmonary artery and aortic pressure is maximally developed. In the reduced ejection phase, flow and great artery pressure taper with progression of systole. Pressure in both ventricular chambers falls as blood is ejected from the heart, and ventricular diastole begins with closure of the pulmonic and aortic valves. The initial period of ventricular diastole consists of the isovolumic/isometric relaxation phase. This phase is concomitant with repolarization of the ventricular myocardium and corresponds to the end of the T wave on the ECG. The final portion of ventricular diastole involves a rapid decrease in intraventricular pressure until it falls below

that of the right and left atria, at which point the AV valve reopens, ventricular filling occurs, and the cycle repeats itself.

Ventricular Structure and Function

Ventricular Structure

The specific architectural order of the cardiac muscles provides the basis for the heart to function as a pump. The ellipsoid shape of the left ventricle (LV) is a result of the laminar layering of spiraling bundles of cardiac muscles (Fig. 16-2). The orientation of the muscle bundle is longitudinal in the subepicardial myocardium and circumferential in the middle segment and again becomes longitudinal in the subendocardial myocardium. Because of the ellipsoid shape of the LV, there are regional differences in wall thickness that result in corresponding variations in the cross-sectional radius of the LV chamber. These regional differences may serve to accommodate the variable loading conditions of the LV.[4] In addition, such anatomy allows the LV to eject blood in a corkscrew-type motion beginning from the base and ending at the apex. The architecturally complex structure of the LV thus allows maximal shortening of myocytes, which results in increased wall thickness and generation of force during systole. Moreover, release of the twisted LV may provide a suction mechanism for filling of the LV during diastole. The LV free wall and the septum have similar muscle bundle architecture. As a result, the septum moves inward during systole in a normal heart. Regional wall thickness is a commonly used index of myocardial performance that can be assessed clinically, such as by perioperative echocardiography or magnetic resonance imaging.

Unlike the LV, which needs to pump against the higher-pressure systemic circulation, the right ventricle (RV) pumps against a much lower pressure circuit in the pulmonary circulation. Consequently, wall thickness is considerably less in the RV. In contrast to the ellipsoidal form of the LV, the RV is crescent shaped, as a result of which the mechanics of RV contraction are more complex. Inflow and outflow contraction is not simultaneous, and much of the contractile force seems to be recruited from interventricular forces of the LV-based septum.

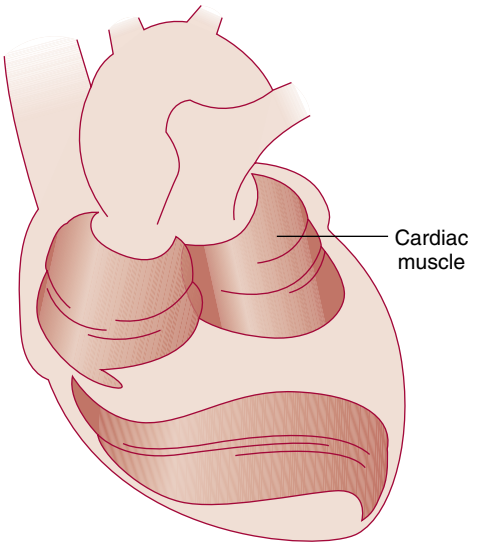

Figure 16-2 Muscle bundles. *(From Marieb EN: Human Anatomy & Physiology, 5th ed. San Francisco, Peason Benjamin Cummings, 2001, p 684.)*

An intricate matrix of collagen fibers form a scaffold of support for the heart and adjacent vessels. This matrix provides enough strength to resist tensile stretch. The collagen fibers are made up of mostly the thick collagen type I fiber, which cross-links with the thin collagen type III fiber, the other major type of collagen.[5] In close proximity to the collagen fibers are elastic fibers that contain elastin. They account for the elasticity of the myocardium.[6]

Systolic Function

The heart provides the driving force for delivering blood throughout the cardiovascular system to supply nutrients and remove metabolic waste. Because of the complexity of RV anatomy, the traditional description of systolic function is usually limited to the LV. Systolic performance of the heart is dependent on loading conditions and contractility. Preload and afterload are two interdependent factors extrinsic to the heart that govern cardiac performance.

Preload and Afterload

Preload is defined as the ventricular load at the end of diastole, before contraction has started. First described by Starling, a linear relationship exists between sarcomere length and myocardial force (Fig. 16-3). In clinical practice, surrogate representatives of LV volume such as pulmonary wedge pressure or central venous pressure are used to estimate preload.[3] With the development of transesophageal echocardiography, a more direct measure of ventricular volume is available.

Afterload is defined as systolic load on the LV after contraction has begun. Aortic compliance is an additional determinant of afterload.[1] Aortic compliance is the ability of the aorta to give way to systolic forces from the ventricle. Changes in the aortic wall (dilation or stiffness) can alter aortic compliance and thus afterload. Examples of pathologic conditions that alter afterload are aortic stenosis and chronic hypertension. Both impede ventricular ejection, thereby increasing afterload. Aortic impedance, or aortic pressure divided by aortic flow at that instant, is an accurate means of gauging afterload. However, clinical measurement of aortic impedance is invasive. Echocardiography can estimate aortic impedance noninvasively by determining aortic blood flow at the time of its maximal increase. In more general clinical practice, measurement of systolic blood pressure is adequate to approximate afterload, provided that aortic stenosis is not present.

Preload and afterload can be thought of as the wall stress that is present at the end of diastole and during LV ejection, respectively. Wall stress is a useful concept because it includes preload, afterload, and the energy required to generate contraction. Wall stress and heart rate are probably the two most relevant indices that account for changes in myocardial oxygen demand. The law of Laplace states that wall stress (σ) is the product of pressure (P) and radius (R) divided by wall thickness (h)[3]:

$$\sigma = P \times R/2h$$

The ellipsoid shape of the LV allows the least amount of wall stress such that as the ventricle changes its shape from ellipsoid to spherical, wall stress is increased. By using the ratio of the long axis to the short axis as a measure of the ellipsoid shape, a decrease in this ratio would signify a transition from ellipsoid to spherical.

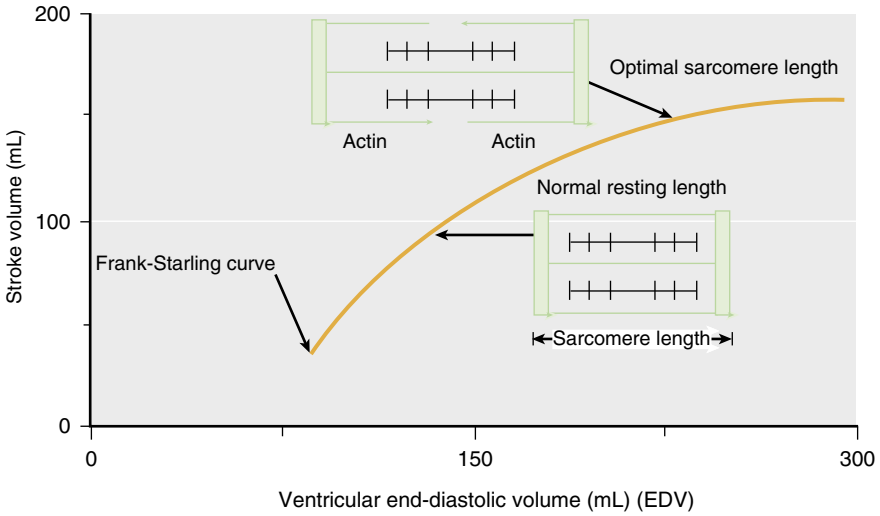

Figure 16-3 Frank-Starling relationship. The relationship between sarcomere length and tension developed in cardiac muscles is shown. In the heart, an increase in end-diastolic volume is the equivalent of an increase in myocardial stretch; therefore, according to Starling's law, increased stroke volume is generated.

Thickness of the LV muscle is an important modifier of wall stress. For example, in aortic stenosis, afterload is increased. The ventricle has to generate far higher pressure to overcome the increased load opposing systolic ejection of blood. To generate such high performance, the ventricle increases its wall thickness (LV hypertrophy). By applying Laplace's law, increased LV wall thickness will decrease wall stress despite the necessary increase in LV pressure to overcome the aortic stenosis (Fig. 16-4).[7] In a failing heart, the radius of the LV increases, thus increasing wall stress.

Frank-Starling Relationship

The Frank-Starling relationship is an intrinsic property of myocardium by which stretching of the myocardial sarcomere results in enhanced myocardial performance for subsequent contractions (see Fig. 16-3). Otto Frank first noted in 1895 that in skeletal muscle, the change in tension was directly related to its length and that in the heart, as pressure changed, a corresponding change in volume occurred.[8] E. H. Starling, using an isolated heart-lung preparation as a model, observed in 1914 that "the mechanical energy set free on passage from the resting to the contracted state is a function of the length of the muscle fiber."[9] If a strip of cardiac muscle is mounted in a muscle chamber under isometric conditions and stimulated at a fixed frequency, an increase in sarcomere length results in an increase in twitch force. Starling concluded that the increased twitch force was the result of a greater interaction of muscle bundles.

Electron microscopy has demonstrated that sarcomere length (2.0 to 2.2 μm) is positively related to the amount of actin and myosin cross-bridging and that there is an optimal sarcomere length at which the interaction is maximal. This concept is based on the assumption that the increase in cross-bridging is equivalent to an increase in muscle performance. Although this theory continues to hold true for skeletal muscle, the force-length relationship in cardiac muscle is more complex. When comparing force-strength relationships between skeletal and cardiac muscle, it is noteworthy that the reduction in force is only 10% even if cardiac muscle is at 80% sarcomere length.[8] The cellular basis of the Frank-Starling mechanism is still being investigated and will be discussed briefly later. A common clinical application of Starling's law is the relationship of left ventricular end-diastolic volume (LVEDV) and stroke volume. The Frank-Starling mechanism may remain intact even in a failing heart.[10] However, ventricular remodeling after injury or in heart failure may modify the Frank-Starling relationship.

Contractility

Each Frank-Starling curve specifies a level of contractility, or the inotropic state of the heart, which is defined as the work performed by cardiac muscle at any given end-diastolic fiber. Factors that modify contractility will create a family of Frank-Starling curves with different contractility (Fig. 16-5).[7] Among factors known to modify contractility are exercise, adrenergic

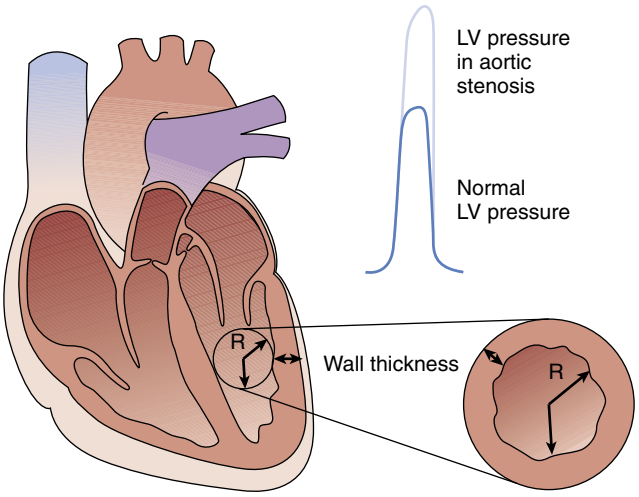

Figure 16-4 In response to aortic stenosis, left ventricular (LV) pressure increases. To maintain wall stress at control levels, compensatory LV hypertrophy develops. According to Laplace's law, wall stress = pressure × radius ÷ (2 × wall thickness). Therefore, the increase in wall thickness offsets the increased pressure, and wall stress is maintained at control levels. *(From Opie LH: Ventricular function.* In *The Heart. Physiology from Cell to Circulation, 4th ed. Philadelphia, Lippincott-Raven, 2004, pp 355-401.)*

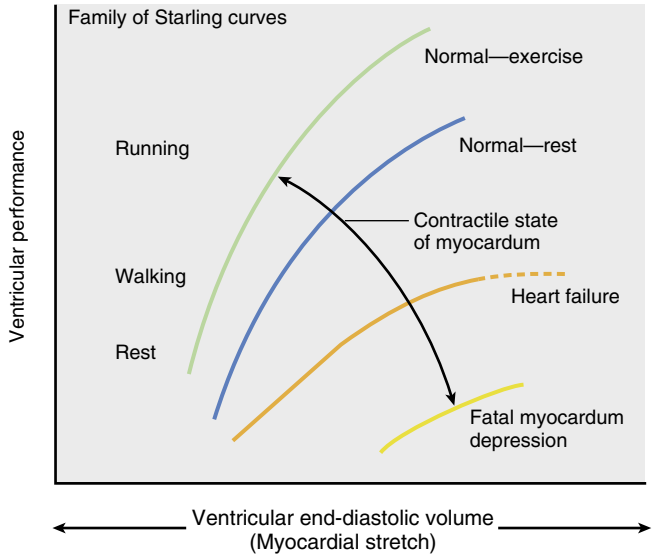

Figure 16-5 A family of Starling curves is shown. A leftward shift of the curve denotes enhancement of the inotropic state, whereas a rightward shift denotes decreased inotropy. *(From Opie LH: Ventricular function.* In *The Heart. Physiology from Cell to Circulation, 4th ed. Philadelphia, Lippincott-Raven, 2004, pp 355-401.)*

stimulation, changes in pH, temperature, and drugs such as digitalis. The ability of the LV to develop and generate pressure and sustain the pressure for ejection of blood is the intrinsic inotropic state of the heart.

In isolated muscle, the maximal velocity of contraction, or Vmax, is defined as the maximal velocity of ejection at zero load. Vmax is obtained by plotting the velocity of muscle shortening in isolated papillary muscle at varying degrees of force. Although this relationship can be replicated in isolated myocytes, Vmax cannot be measured in an intact heart because complete unloading is impossible. To measure the intrinsic contractile activity of an intact heart, several strategies have been attempted with varying success. Pressure-volume loops, albeit requiring catheterization of the left side of the heart, are currently the best way to determine contractility in an intact heart (Fig. 16-6).[7] The pressure-volume loop represents an indirect measure of the Starling relationship between force (pressure) and muscle length (volume). Clinically, the most commonly used noninvasive index of ventricular contractile function is the ejection fraction, which is assessed by echocardiography, angiography, or radionuclide ventriculography.

$$\text{Ejection fraction} = (\text{LVEDV} - \text{LVESV})/\text{LVEDV},$$

where LVESV is left ventricular end-systolic volume.

Cardiac Work

The work of the heart can be divided into external and internal work. External work is expended to eject blood under pressure, whereas internal work is expended within the ventricle to change the shape of the heart and prepare it for ejection. Internal work contributes to inefficiency in performance of the heart. Wall stress is directly proportional to the internal work of the heart.[11]

External work, or stroke work, is a product of the stroke volume (SV) and pressure (P) developed during ejection of the stroke volume.

$$\text{Stroke work} = \text{SV} \times \text{P or } (\text{LVEDV} - \text{LVESV}) \times \text{P}$$

The external work and internal work of the ventricle both consume O_2. The clinical significance of internal work is illustrated in the case of a poorly drained LV during cardiopulmonary bypass. Although external work is provided by the roller pump during bypass, myocardial ischemia can still occur because poor drainage of the LV creates tension on the LV wall and increases internal work.

The efficiency of cardiac contraction is estimated by the following formula[12]:

$$\text{Cardiac efficiency} = \text{External work}/\text{Engergy equivalent of oxygen consumption}$$

The corkscrew motion of the heart for the ejection of blood is the most favorable in terms of work efficiency based on the architecture in a normal LV (with the cardiac muscle bundles arranged so that a circumferentially oriented middle layer is sandwiched by longitudinally oriented outer layers). In heart failure, ventricular dilation reduces cardiac efficiency because it increases wall stress, which in turn increases oxygen consumption.[11]

Heart Rate and Force-Frequency Relationship

In isolated cardiac muscle, an increase in the frequency of stimulation induces an increase in the force of contraction. This relationship is termed the "treppe" (*Treppe* means staircase in German) phenomenon or the force-frequency relationship.[12,13] At between 150 and 180 stimuli per minute, maximal contractile force is reached in an isolated heart muscle at a fixed muscle length. Thus, an increased frequency incrementally increases inotropy, whereas stimulation at lower frequency decreases contractile force. However, when the stimulation becomes extremely rapid, the force of contraction decreases. In the clinical context, pacing-induced positive inotropic effects may be effective only up to a certain heart rate based on the force-frequency relationship. In a

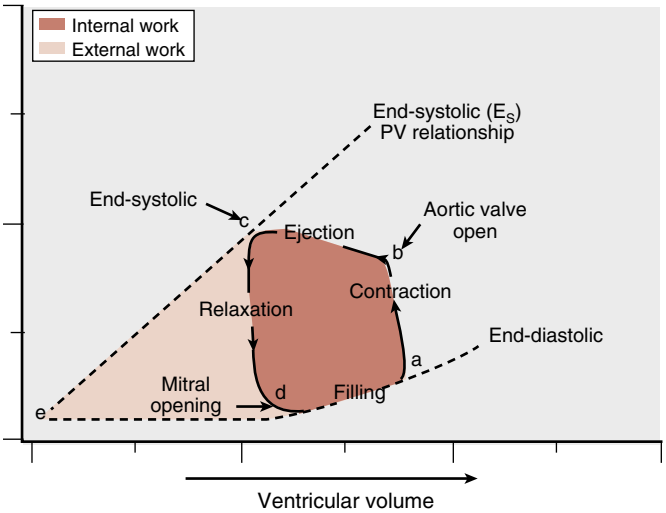

Figure 16-6 Pressure-volume loop. Point a depicts the start of isovolumic contraction. The aortic valve opens at point b, and ejection of blood follows (b→c). The mitral valve opens at d, and ventricular filling ensues. External work is defined by a, b, c, and d and internal work by e, d, and c. The pressure-volume area is the sum of external and internal work. *(From Opie LH: Ventricular function.* In *The Heart. Physiology from Cell to Circulation, 4th ed. Philadelphia, Lippincott-Raven, 2004, pp 355-401.)*

failing heart, the force-frequency relationship may be much less effective in producing a positive inotropic effect.[12]

Diastolic Function

Diastole is ventricular relaxation, and it occurs in four distinct phases: (1) isovolumic relaxation; (2) the rapid filling phase (i.e., the LV chamber filling at variable LV pressure); (3) slow filling, or diastasis; and (4) final filling during atrial systole. The isovolumic relaxation phase is energy dependent. During the auxotonic relaxation phases (phases 2 through 4), ventricular filling occurs against pressure. It encompasses a period during which the myocardium is unable to generate force and filling of the ventricular chambers takes place. The isovolumic relaxation phase does not contribute to ventricular filling. The greatest amount of ventricular filling occurs in the second phase, whereas the third phase adds only about 5% of total diastolic volume and the final phase provides 15% of ventricular volume from atrial systole.

To assess diastolic function, several indices have been developed. The most widely used index for examining the isovolumic relaxation phase of diastole is to calculate the peak instantaneous rate of decline in LV pressure ($-dP/dt$) or the time constant of isovolumic decline in LV pressure (τ). The aortic closing–mitral opening interval and the isovolumic relaxation time and peak rate of LV wall thinning as determined by echocardiography have both been used to estimate diastolic function during auxotonic relaxation. Ventricular compliance can be evaluated by pressure-volume relationships to determine function during the auxotonic phases of diastole.[12,14]

Many different factors influence diastolic function: systolic volume load, passive chamber stiffness, elastic recoil of the ventricle, the diastolic interaction between the two ventricular chambers, atrial properties, and catecholamines. Whereas systolic dysfunction is a reduced ability of the heart to eject, diastolic dysfunction is a decreased ability of the heart to fill. Abnormal diastolic function is now being recognized as the predominant cause of the pathophysiology of congestive heart failure.[15]

Ventricular interactions during systole and diastole are internal mechanisms that function as internal feedback to modulate stroke volume. Systolic ventricular interaction involves the effect of the interventricular septum on the function of both ventricles. Because the interventricular septum is anatomically linked to both ventricles, it will be part of the load against which each ventricle has to work. Therefore, any changes in one ventricle will also be present in the other. In diastolic ventricular interaction, dilatation of either the LV or RV will have an impact on effective filling of the contralateral ventricle and thereby modify function.

Cardiac Output

Cardiac output is the amount of blood pumped by the heart per unit of time $(\dot{Q})$ and is determined by four factors: two factors that are intrinsic to the heart—heart rate and myocardial contractility—and two factors that are extrinsic to the heart but functionally couple the heart and the vasculature—preload and afterload.

Heart rate is defined as the number of beats per minute and is influenced mainly by the autonomic nervous system. Increases in heart rate increase cardiac output as long as ventricular filling is adequate during diastole. Contractility can be defined as the intrinsic level of contractile performance that is independent of loading conditions. Contractility is difficult to define in an intact heart because it cannot be separated from loading conditions.[12,13] For example, the Frank-Starling relationship is defined as the change in intrinsic contractile performance based on changes in preload. Cardiac output in a living organism can be measured with the Fick principle, a schematic depiction of which is illustrated in Figure 16-7.[1]

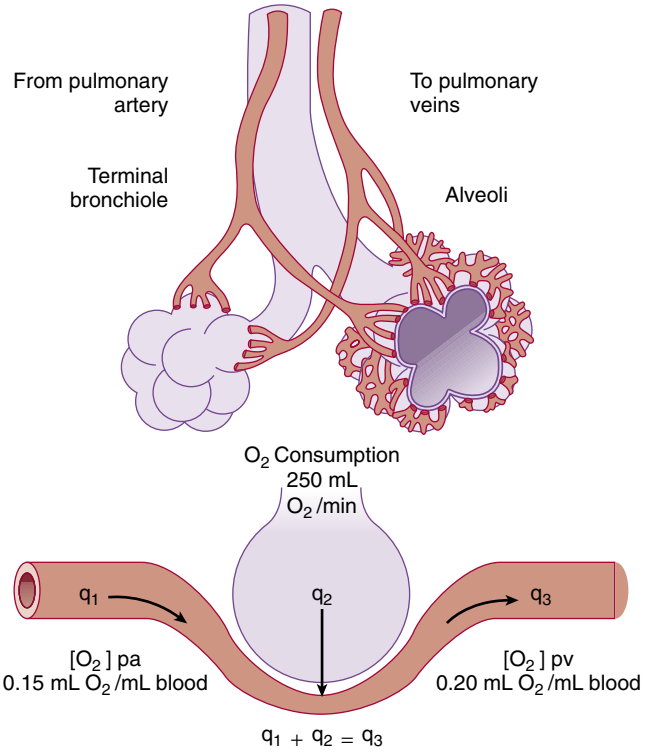

Figure 16-7 Illustration demonstrating the principle of determination of cardiac output according to the Fick equation. If the O_2 concentration of the pulmonary artery ($Cpao_2$), the O_2 concentration of the pulmonary vein ($Cpvo_2$), and O_2 consumption are known, cardiac output can be calculated. *(From Berne RM, Levy MN: The cardiac pump.* In *Cardiovascular Physiology, 8th ed. St Louis, CV Mosby, 2001, pp 55-82.)*

The Fick principle is based on the concept of conservation of mass such that the O_2 delivered from pulmonary venous blood (q_3) is equal to the total O_2 delivered to pulmonary capillaries through the pulmonary artery (q_1) and the alveoli (q_2).

The amount of O_2 delivered to the pulmonary capillaries by way of the pulmonary arteries (q_1) equals total pulmonary arterial blood flow $(\dot{Q})$ times the O_2 concentration in pulmonary arterial blood ($Cpao_2$):

$$q_1 = \dot{Q} \cdot Cpao_2$$

The amount of O_2 carried away from pulmonary venous blood (q_3) is equal to total pulmonary venous blood flow $(\dot{Q})$ times the O_2 concentration in pulmonary venous blood ($Cpvo_2$):

$$q_3 = \dot{Q} \cdot Cpvo_2$$

The pulmonary arterial O_2 concentration is the mixed systemic venous O_2, and the pulmonary venous O_2 concentration is the peripheral arterial O_2. O_2 consumption is the amount of O_2

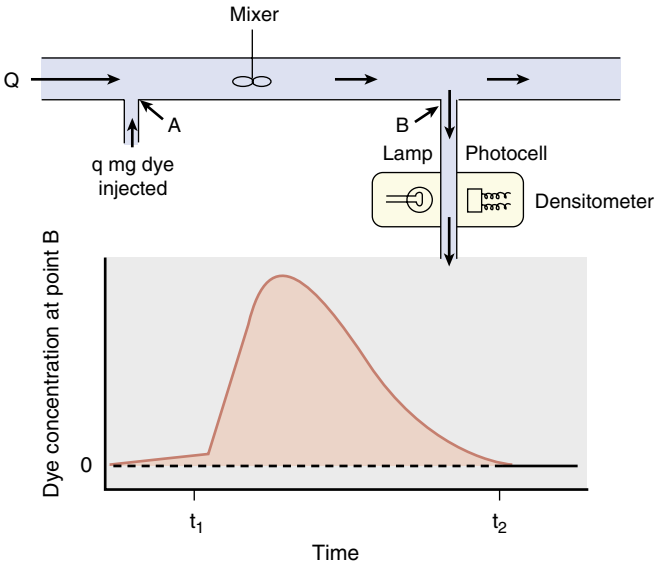

Figure 16-8 Illustration demonstrating the principle of determining cardiac output with the indicator dilution technique. This model assumes that there is no recirculation. A known amount of dye (q) is injected at point A into a stream flowing at $\dot{Q}$ (mL/min). A mixed sample of the fluid flowing past point B is withdrawn at a constant rate through a densitometer. The change in dye concentration over time is depicted in a curve. Flow may be measured by dividing the amount of indicator injected upstream by the area under the downstream concentration curve. *(From Berne RM, Levy MN: The cardiac pump. In Cardiovascular Physiology, 8th ed. St Louis, CV Mosby, 2001, pp 55-82.)*

delivered to the pulmonary capillaries from the alveoli (q_2). Because $q_1 + q_2 = q_3$,

$$\dot{Q}(Cpao_2) + q_2 = \dot{Q}(Cpvo_2)$$

$$q_2 = \dot{Q}(Cpvo_2) - \dot{Q}(Cpao_2)$$

$$q_2 = \dot{Q}(Cpvo_2) - Cpao_2$$

$$\dot{Q} = q_2 / (Cpvo_2 - Cpao_2)$$

Thus, if the O_2 concentration in the pulmonary artery ($Cpao_2$), the O_2 concentration in the pulmonary vein ($Cpvo_2$), and O_2 consumption (q_2) are known, cardiac output can be determined.

The indicator dilution technique is another method for determining cardiac output, and it is also based on the law of conservation of mass. The two most commonly used indicator dilution techniques are the dye dilution and the thermodilution methods. Figure 16-8 illustrates the principles of the dye dilution method.[1]

Cellular Cardiac Physiology

Cellular Anatomy

At the cellular level, the heart consists of three major components: cardiac muscle tissue (contracting cardiomyocytes), conduction tissue (conducting cells), and extracellular connective tissue. A group of cardiomyocytes with its connective tissue support network or extracellular matrix make up a myofiber (Fig. 16-9). Adjacent myofibers are connected by strands of collagen. The extracellular matrix is the synthetic product of fibroblasts and is made up of collagen, which is the main determinant of myocardial stiffness, and other major matrix proteins. One of the matrix proteins, elastin, is the chief constituent of elastic fibers. The elastic fibers account for, in part, the elastic properties of the myocardium.[6] Other matrix proteins include the glycoproteins or proteoglycans and matrix metalloproteins. Proteoglycans are proteins with short sugar chains, and they include heparan sulfate, chondroitin, fibronectin, and laminin. Matrix metalloproteins are enzymes that degrade collagen and other extracellular proteins. The balance between accumulation of extracellular matrix proteins by synthesis and their breakdown by matrix metalloproteins contributes to the mechanical properties and function of the heart.[6]

Cardiomyocyte Structure and Function

Individual contracting cardiomyocytes are large cells between 20 µm (atrial cardiomyocytes) and 140 µm (ventricular cardiomyocytes) in length. Approximately 50% of the cell volume in a contracting cardiomyocyte is made up of myofibrils, and the remainder consists of mitochondria, nucleus, sarcoplasmic reticulum (SR), and the cytosol. The myofibril is the rodlike bundle that forms the contractile elements within cardiomyocytes. Within each contractile element are contractile proteins, regulatory proteins, and structural proteins. Contractile proteins make up about 80% of the myofibrillar protein, with the remainder being regulatory and structural proteins.[16,17] The basic unit of contraction is the sarcomere, which will be described later.

The sarcolemma, or the outer plasma membrane, separates the intracellular and extracellular space. It surrounds the cardiomyocyte and invaginates into the myofibrils through an extensive tubular network known as transverse or T tubules, and it also forms specialized intercellular junctions between cells.[18,19]

Transverse or T tubules are in close proximity to an intramembrane system and the SR, which plays an important role in the calcium metabolism that is critical in excitation-contraction coupling (ECC) of the cardiomyocyte. The SR can be further divided into the longitudinal (or network) and the junctional SR. The longitudinal SR is involved in the uptake of calcium for initiation of relaxation. The junctional SR contains large calcium release channels (ryanodine receptors) that release SR calcium stores in

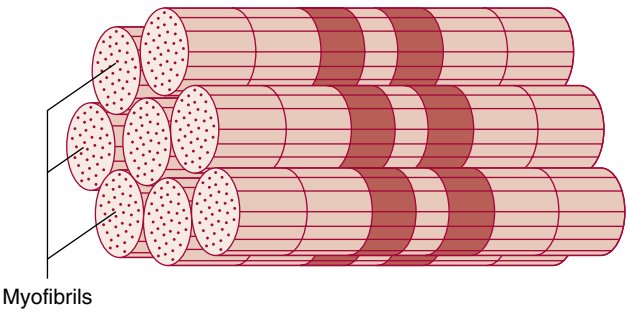

Figure 16-9 Organization of cardiomyocytes. Fifty percent of cardiomyocyte volume is made up of myofibrils; the remainder consists of mitochondria, nucleus, sarcoplasmic reticulum, and cytosol.

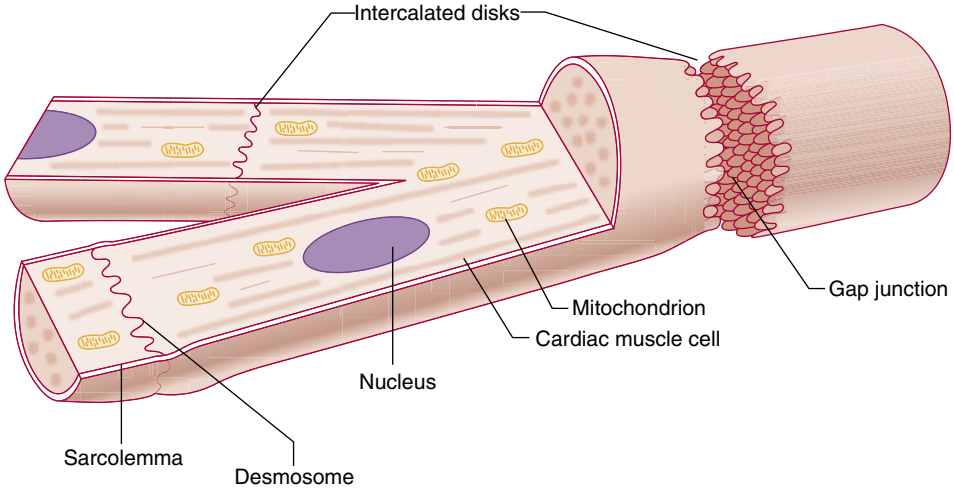

Figure 16-10 The sarcolemma that envelops cardiomyocytes becomes highly specialized to form the intercalated disks where ends of neighboring cells are in contact. The intercalated disks consist of gap junctions and "spot" and "sheet" desmosomes.

response to depolarization-stimulated calcium influx through the sarcolemmal calcium channels. The ryanodine receptors not only are calcium release channels but they also form the scaffolding proteins that anchor many of the key regulatory proteins.[20]

Mitochondria are found immediately beneath the sarcolemma, wedged between myofibrils within the cell. They contain enzymes that promote the generation of adenosine triphosphate (ATP), and they are the energy powerhouse for the cardiomyocyte. In addition, mitochondria can also function to accumulate calcium and thereby contribute to regulation of the cytosolic calcium concentration. Nearly all of the genetic information is found within the centrally located nucleus. The cytosol is the fluid-filled microenvironment within the sarcolemma, exclusive of the organelles and the contractile apparatus and proteins.

Cardiac muscle cells contain three different types of intercellular junctions: gap junctions, "spot" desmosomes, and "sheet" desmosomes (or fasciae adherens) (Fig. 16-10).[19,21] Gap junctions are responsible for electrical coupling and transfer of small molecules between cells, whereas desmosome-like junctions provide mechanical linkage. The adhesion sites formed by "spot" desmosomes anchor the intermediate filament cytoskeleton of the cell; those formed by the fasciae adherens anchor the contractile apparatus. Gap junctions consist of clusters of plasma membrane channels directly linking the cytoplasmic compartments of neighboring cells. Gap junction channels are constructed from connexins, a multigene family of conserved proteins. The principal connexin isoform of the mammalian heart is connexin 43; other connexins, notably connexins 40, 45, and 37, are also expressed, but in smaller quantities.[20,21]

The conducting cardiomyocytes, or Purkinje cells, are cells specialized for conducting propagated action potentials. These cells have a low content of myofibrils and a prominent nucleus and contain an abundance of gap junctions. Cardiomyocytes can be functionally separated into (1) the excitation system, (2) the ECC system, and (3) the contractile system.

Excitation System

The cellular action potential originating in the specialized conduction tissue is propagated to individual cells where it initiates the intracellular event that leads to contraction of the cell through the sarcolemmal excitation system.

Action Potential

Ion fluxes across plasma membranes result in depolarization (attaining a less negative membrane potential) and repolarization (attaining a more negative membrane potential). They are mediated by membrane proteins with ion-selective pores. Because these ion channel proteins open and close the pores in response to changes in membrane potential, the channels are voltage gated. In the heart, sodium, potassium, calcium, and chloride channels have been found to contribute to the action potential.

The types of action potential in the heart can be separated into two categories: fast-response action potentials, which are found in the His-Purkinje system and atrial or ventricular cardiomyocytes, and slow-response action potentials, which are found in the pacemaker cells in the SA and AV nodes. A typical tracing of an action potential in the His-Purkinje system is depicted in Figure 16-11.[12] The electrochemical gradient for potassium across the plasma membrane is the determinant for the resting membrane potential. Mostly as a result of the influx of Na^+, the membrane potential becomes depolarized, which leads to an extremely rapid upstroke (phase 0). As the membrane potential reaches a critical level, or threshold, during depolarization, the action potential is propagated. The rapid upstroke is followed by a transient repolarization (phase 1). Phase 1 is a period of brief and limited repolarization that is largely due to the activation of a transient outward potassium current, i_{to}. The plateau phase (phase 2) occurs with a net influx of Ca^{2+} through L-type calcium channels and efflux of K^+ through several potassium channels: the inwardly rectifying i_k, the delayed rectifier i_{k1}, and i_{to}. Repolarization (phase 3) is brought about when efflux of K^+ from the three outward potassium currents exceeds the influx of Ca^{2+}, thus returning the membrane to the resting potential. Very little ionic flux occurs during diastole (phase 4) in a fast-response action potential.

In contrast, during diastole (phase 4), pacemaker cells that show slow-response action potentials have the capability of spontaneous diastolic depolarization and generate the automatic

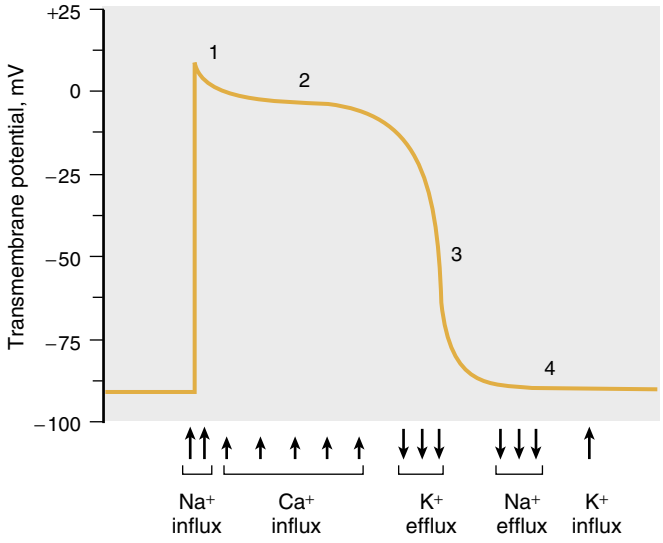

Figure 16-11 Phases of cellular action potentials and major associated currents in ventricular myocytes. The initial phase 0 spike and overshoot (1) are caused by a rapid inward Na^+ current, the plateau phase (2) by a slow Ca^{2+} current through L-type Ca channels, and repolarization (phase 3) by outward K^+ currents. Phase 4, the resting potential (Na^+ efflux, K^+ influx), is maintained by Na^+-K^+-ATPase. The Na^+-Ca^{2+} exchanger is mainly responsible for extrusion of Ca^{2+}. In specialized conduction system tissue, spontaneous depolarization takes place during phase 4 until the voltage resulting in opening of the Na channel is reached. *(From LeWinter MM, Osol G: Normal physiology of the cardiovascular system.* In *Fuster V [ed]: Hurst's The Heart, 10th ed. New York, McGraw-Hill, 2001, pp 63-94.)*

cardiac rhythm. Pacemaker currents during phase 4 are the result of an increase in the three inward currents and a decrease in the two outward currents. The three inward currents that contribute to spontaneous pacemaker activity include two carried by calcium, i_{CaL} and i_{CaT}, and one that is a mixed cation current, I_f. The two outward currents are the delayed rectifier potassium current i_k and the inward rectifying potassium current i_{k1}. When compared with the fast-response action potential, phase 0 is much less steep, phase 1 is absent, and phase 2 is indistinct from phase 3 in the slow-response action potential.[22]

During the cardiac action potential, movement of Ca^{2+} into the cell and Na^+ out of the cell creates an ionic imbalance. The Na^+-Ca^{2+} exchanger restores cellular ionic balance by actively transporting Ca^{2+} out of the cell against a concentration gradient while moving Na^+ into the cell in an energy-dependent manner.

Excitation-Contraction Coupling

Structures that participate in cardiac ECC include the sarcolemma, transverse tubules, SR, and myofilaments (Fig. 16-12A).[23] The process of ECC begins with depolarization of the plasma membrane and spread of electrical excitation along the sarcolemma of cardiomyocytes. Calcium enters through plasma membrane channels concentrated at the T tubules, and such entry triggers the release of calcium from the SR, which in turn stimulates myofibrillar contraction.[24]

The ubiquitous second messenger calcium is the key player in cardiac ECC (see Fig. 16-12B).[23] Cycling of calcium within the structures that participate in ECC initiates and terminates contraction. Activation of the contractile system depends on an increase in free cytosolic calcium and its subsequent binding to contractile proteins. Influx of calcium through the voltage-gated L-type calcium channels (dihydropyridine receptors) causes an initial small increase in intracellular calcium. The local increase in Ca^{2+} concentration as a result of entry of Ca^{2+} through the voltage-gated L-type calcium channels activates the calcium release channels (ryanodine receptors), induces further release of calcium from subsarcolemmal cisternae in the SR, and thus leads to a large increase in intracellular calcium. The increase in intracellular calcium, however, is transient inasmuch as calcium is removed by (1) active uptake by the SR calcium pump adenosine triphosphatase (ATPase), (2) extrusion of calcium from the cytosol by the Na^+-Ca^{2+} exchanger, and (3) binding of calcium to proteins.[25]

The SR provides the anatomic framework and is the major organelle for the cycling of calcium. It is the depot for intracellular calcium stores. The cyclic release plus reuptake of calcium by the SR regulates the cytosolic calcium concentration and couples excitation to contraction. The physical proximity between L-type calcium channels and ryanodine receptors at the SR membrane makes calcium-induced calcium release occur easily. The "foot" region of the ryanodine receptor is the part that extends from the SR membrane to the T tubules, where the L-type calcium channels are located.[16,25,26]

The SR is also concerned with the reuptake of calcium that initiates relaxation or terminates contraction. Sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) is the ATP-dependent pump that actively pumps the majority of the calcium back into the SR after its release. SERCA makes up close to 90% of all of the SR proteins, and it is inhibited by the phosphoprotein phospholamban at rest. Phospholamban is an SR membrane protein that is active in the dephosphorylated form. Phosphorylation by a variety of kinases as a result of β-adrenergic stimulation or other stimuli inactivates phospholamban and releases its inhibitory action on SERCA. Positive feedback ensues and leads to further phospholamban phosphorylation and greater SERCA activity. Active reuptake of calcium by SERCA then promotes relaxation.[16,25,26]

Once taken up into the SR, calcium is stored until it is released during the next cycle. Calsequestrin and calreticulin are two storage proteins in the SR. Calsequestrin is a highly charged protein located in the cisternal component of the SR near the T tubules. Because it lies close to the calcium release channels, the stored calcium can be quickly discharged for release once the calcium release channels are stimulated.

Cytosolic calcium can also be removed by extrusion through the sarcolemmal calcium pump and the activity of the sodium-calcium exchanger. An important "sensor" and regulator of intracellular calcium is the protein calmodulin.[18]

Contractile System

Contractile Elements

The basic working unit of contraction is the sarcomere. A sarcomere is defined as the distance between Z lines (Z is an abbreviation for the German *Zuckung*, or "contraction"), which join the sarcomeres in series. Each sarcomere consists of a central A band that is separated by half of an I band from the Z lines on each side because the Z line bisects the I band. A schematic representation is depicted in Figure 16-13.[12] Within each sarcomere are two principal contractile proteins (see the next section) and one noncontractile protein, titin.[25] The two contractile proteins are actin, the thin filament, and myosin, the thick filament. Actin filaments and titin are both tethered to the Z line, but myosin

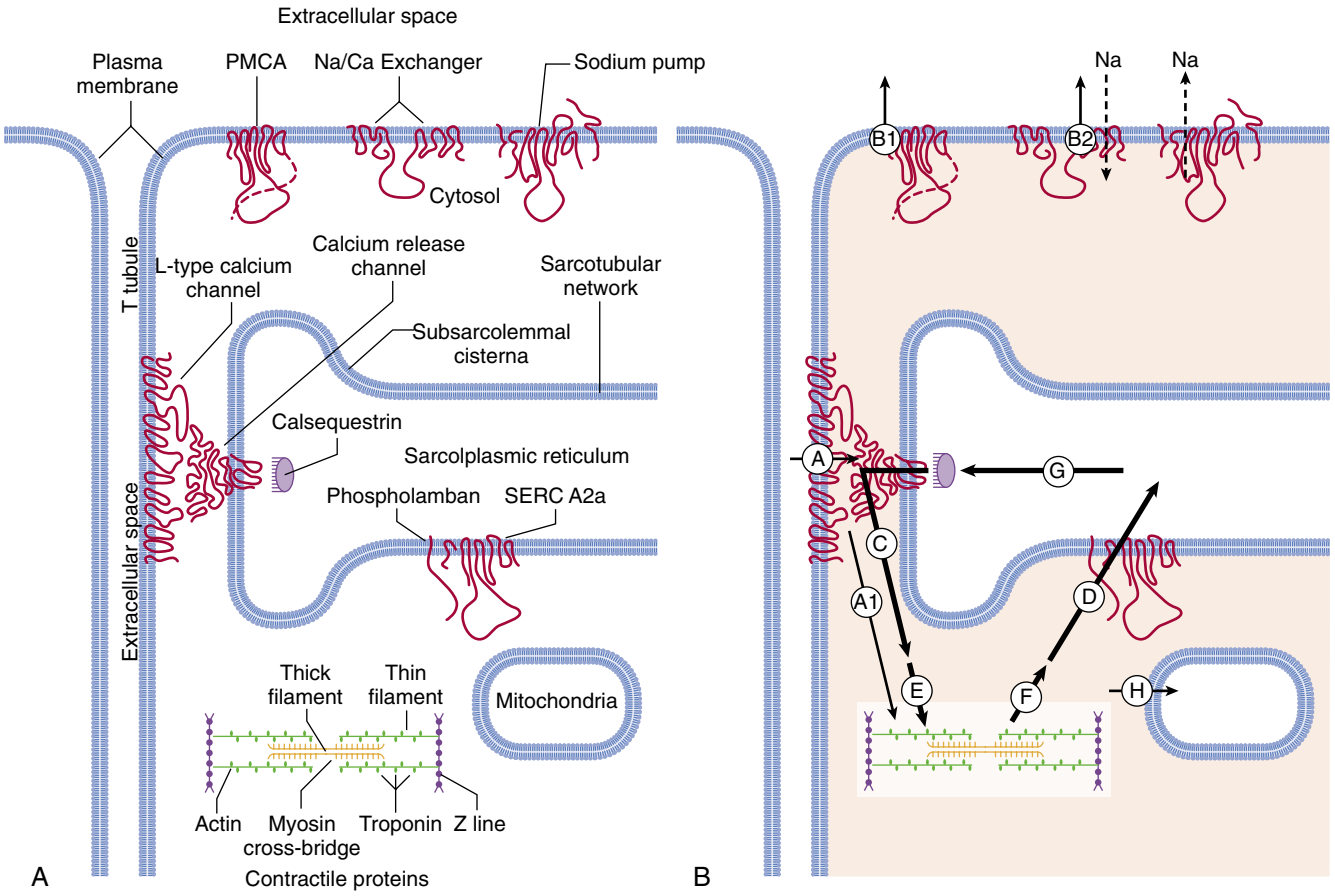

Figure 16-12 **A,** Diagram depicting the components of cardiac excitation-contraction coupling. Calcium pools are noted in **bold** letters. **B,** Extracellular (*arrows A*, *B1*, *B2*) and intracellular calcium flux (*arrows C*, *D*, *E*, *F*, *G*) is shown. The thickness of the *arrows* indicates the magnitude of the calcium flux, and the vertical orientations describe their energetics: *downward-pointing arrows* represent passive calcium flux, whereas *upward-pointing arrows* represent energy-dependent calcium transport. Calcium entering the cell from extracellular fluid through L-type calcium channels triggers release of calcium from the sarcoplasmic reticulum (SR). Only a small portion directly activates the contractile proteins (A1). *Arrow B1* depicts active transport of calcium into extracellular fluid by means of the plasma membrane pump ATPase and the Na^+-Ca^{2+} exchanger. Sodium that enters the cell in exchange for calcium (*dashed line*) is pumped out of the cytosol by the sodium pump. SR regulates calcium efflux from the subsarcolemmal cisternae (*arrow C*) and calcium uptake into the sarcotubular network (*arrow D*). *Arrow G* represents calcium that diffuses within the SR. Calcium binding to (*arrow E*) and dissociation from (*arrow F*) high-affinity calcium binding sites of troponin C activate and inhibit interactions of the contractile proteins. *Arrow H* depicts movement of calcium into and out of mitochondria to buffer the cytosolic calcium concentration. *(From Katz AM: Calcium fluxes.* In *Physiology of the Heart, 3rd ed. Philadelphia, Lippincott-Raven, 2001, pp 232-233.)*

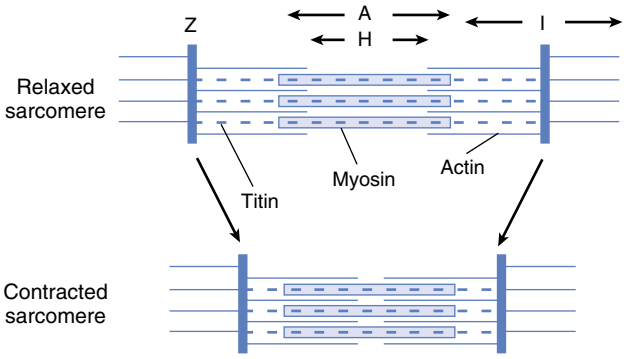

Figure 16-13 The basic unit of contraction is the sarcomere. A contracted and a relaxed sarcomere is depicted. Z lines are located at the ends of the sarcomere. The A band is the site of overlap between myosin and actin filaments. The I band is located on either side of the A band and contains only actin filament. The H zone is located in the center of the A band, and only myosin is present.

filaments do not actually reach the Z lines. Titin, the third filament protein, tethers the myosin thick filament to the Z line. The Z lines at the two ends of the sarcomere are brought closer together during contraction as the thick myosin filament heads interact with the thin actin filaments and slide over each other.[27,28]

Familial hypertrophic cardiomyopathy is an inherited autosomal dominant sarcomeric disease[29] that is the most common cause of sudden death in otherwise healthy individuals. Its clinical features are LV hypertrophy and myocyte/myofibrillar disarray. Mutations in at least eight different genes encoding sarcomere proteins have been identified to be the molecular basis for the disorder. These genes are β-cardiac myosin heavy chain, cardiac troponin T (TnT), α-tropomyosin, cardiac myosin binding protein C, essential or regulatory myosin light chain, cardiac troponin I (TnI), α-cardiac actin, and titin.[29]

Contractile Proteins

The contractile apparatus within the cardiomyocyte consists of contractile and regulatory proteins.[18,30,31] The thin-filament actin

and the thick-filament myosin are the two principal contractile proteins. Actin contains two helical chains. Tropomyosin, a double-stranded α-helical regulatory protein, winds around the actin array and forms the backbone for the actin thin filament. The myosin thick filament is made up of 300 myosin molecules. Each myosin molecule has two functional domains: the body or filament and the bilobar myosin head. The myosin head is composed of one heavy chain and two light chains. The heavy head chain has two domains: the larger one interacts with actin at the actin cleft and has an ATP binding pocket where myosin ATPase is located, and the other smaller one is flexible and attached to the two light chains. The regulatory troponin heterotrimer complex is found at regular intervals along tropomyosin. The heterotrimer troponins are made up of troponin C (TnC), the Ca^{2+} receptor; TnI, an inhibitor of actin-myosin interaction; and TnT, which links the troponin complex to tropomyosin. Tropomodulin is another regulatory protein. It is located at the end of the actin thin filament and caps the end to prevent any excessive elongation of the thin filament.[27,28]

Myocyte Contraction and Relaxation

At rest, cross-bridge cycling and generation of force do not occur because either the myosin heads are blocked from physically reacting with the thin filament or they are only weakly bound to actin (Fig. 16-14).[16] Cross-bridge cycling is initiated on binding of calcium to TnC, which increases TnC-TnI interaction and decreases the inhibitory TnI-actin interaction. These events that ensue from binding of Ca^{2+} to TnC lead to conformational changes in tropomyosin and permit attachment of the myosin head to actin. Cross-bridging involves detachment of the myosin head from actin and reattachment of myosin to another actin on hydrolysis of ATP by myosin ATPase. Binding of ATP to the

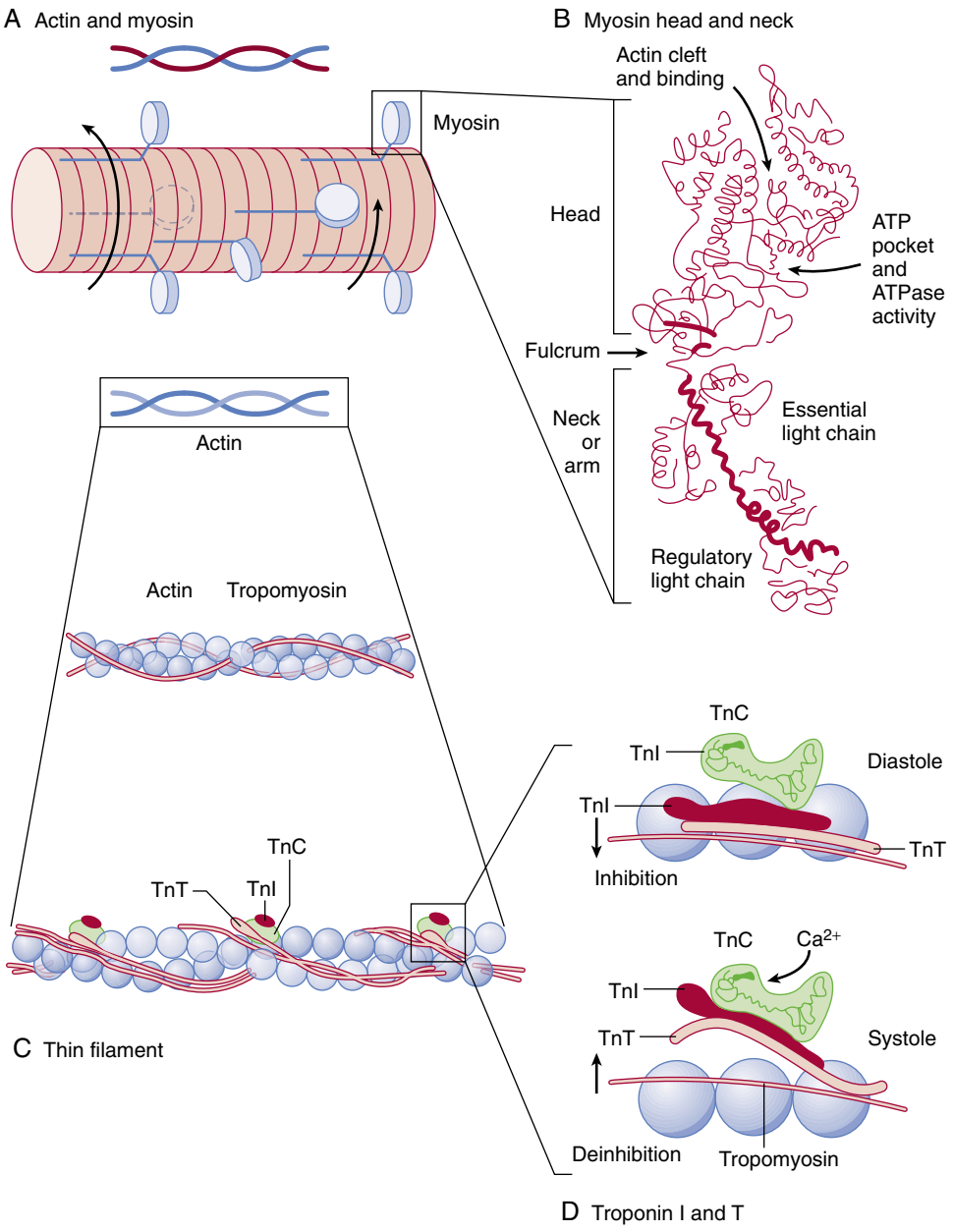

Figure 16-14 Molecules of the contractile system. TnC, TnI, TnT, troponin C, I, T. *(From Opie LH: Myocardial contraction and relaxation. In The Heart. Physiology from Cell to Circulation, 3rd ed. Philadelphia, Lippincott-Raven, 1998, pp 209-231.)*

nucleotide pocket of the myosin head leads to the activation of myosin ATPase,[26-28] ATP hydrolysis, and changes in configuration of the myosin head, all of which facilitate binding of the myosin head to actin and generation of the power stroke of the myosin head. Based on this model, it is apparent that the rate of cross-bridge cycling is dependent on the activity of myosin ATPase.[31] Turnoff of cross-bridge cycling is largely initiated by the fall in cytosolic calcium.

Myocyte relaxation is an energy-dependent process because restoration of cytosolic calcium to resting levels requires the expenditure of ATP. The fall in cytosolic calcium occurs through active reuptake of calcium into the SR by SERCA and extrusion of calcium by the Na^+-Ca^{2+} exchanger. This activity results in release of binding of Ca^{2+} to TnC and separation of the myosin-actin cross-bridge. Myocyte relaxation is dependent on the kinetics of cross-bridge cycling, the affinity of Ca^{2+} for TnC, and the activity of the calcium reuptake mechanisms. Relaxation is enhanced by the increased kinetics of cross-bridge cycling, decreased Ca^{2+} affinity for TnC, and increased activity of calcium reuptake mechanisms.[25]

Titin is a giant stringlike protein that acts as the third filament within the sarcomere. A single titin molecule spans half the sarcomere. Structurally, titin consists of an inextensible anchoring segment and an extensible elastic segment. Its two main functions involve muscle assembly and elasticity. Titin is the principal determinant of the passive properties of the myocardium at low ventricular volume.[32]

The Frank-Starling relationship states that an increase in end-diastolic volume results in enhanced systolic function.[33,34] At the cellular level, the key component for the Frank-Starling relationship is a length-dependent shift in Ca^{2+} sensitivity.[35-37] Several possible mechanisms for this change in Ca^{2+} sensitivity have been implicated, including (1) Ca^{2+} sensitivity as a function of myofilament lattice spacing, (2) Ca^{2+} sensitivity involving positive cooperativity in cross-bridge binding to actin, and (3) dependence of Ca^{2+} sensitivity on strain of the elastic protein titin.[31,36]

Cytoskeleton Proteins

The cytoskeleton is the protein framework within the cytoplasm that links, anchors, or tethers structural components inside the cell.[17,18] Microfilaments (actin filaments), microtubules, and intermediate filaments are three classes of cytoskeleton proteins found in the cytoplasm. Microfilament proteins are actin filaments, either sarcomeric or cortical, depending on their location. Sarcomeric actin filaments are the thin filaments in the contractile machinery that have already been described. Cortical actin filaments are found below the plasma membrane at the cell surface and are linked to several other microfilament proteins, including dystrophin, vinculin, and ankyrin. Microtubules assemble by polymerization of the α- and β-dimers of tubulin. They play a major role in intracellular transport and cell division.[38] Attachment of the ends of microtubules to cellular structures causes the microtubules to expand and contract, thereby pulling and pushing these structures around the cell. The intermediate filaments are relatively insoluble. They have been demonstrated to be important in normal mitochondrial function and behavior. The desmin intermediate filament in cardiomyocytes connects the nucleus to the plasma membrane and is important in transmission of the stress and strain of contractile force between cells.[39] The cytoskeleton provides the organization of microenvironments within the cell for enzyme/protein activity and interaction.

Whereas familial hypertrophic cardiomyopathy is a genetic sarcomeric disease, familial dilated cardiomyopathy (FDCM) is a disease of cytoskeleton proteins. The genetic basis of FDCM includes two genes for X-linked FDCM (dystrophin, G4.5) and four genes for the autosomal dominant form (actin, desmin, lamin A/C, δ-sarcoglycan).[17]

Control of Cardiac Function

Neural Regulation of Cardiac Function

The two limbs of the autonomic nervous system provide opposing input to regulate cardiac function.[40] The neurotransmitter of the sympathetic nervous system is norepinephrine, which provides positive chronotropic (heart rate), inotropic (contractility), and lusitropic (relaxation) effects. The parasympathetic nervous system has a more direct inhibitory effect in the atria and has a negative modulatory effect in the ventricles. The neurotransmitter of the parasympathetic nervous system is acetylcholine. Norepinephrine and acetylcholine both bind to seven-transmembrane–spanning G protein–coupled receptors to transduce their intracellular signals and effect their functional responses (Fig. 16-15).[41] At rest, the heart has a tonic level of parasympathetic cardiac nerve firing and little, if any, sympathetic activity. Therefore, the major influence on the heart at rest is parasympathetic. During exercise or stress, however, the sympathetic neural influence becomes more prominent.

Parasympathetic innervation of the heart is through the vagal nerve. Supraventricular tissue receives much greater vagal innervation than the ventricles do. The principal parasympathetic target neuroeffectors are the muscarinic receptors in the heart.[42,43] Activation of muscarinic receptors reduces pacemaker activity, slows AV conduction, decreases atrial contractile force directly, and exerts inhibitory modulation of ventricular contractile force. A total of five muscarinic receptors have been cloned.[44] M_2 receptors are the predominant subtype found in the mammalian heart. In the coronary circulation, M_3 receptors have been identified. Moreover, non-M_2 receptors have also been reported to exist in the heart. In general, for intracellular signaling, M_1, M_3, and M_5 receptors couple to $G_{q/11}$ protein and activate the phospholipase C–diacylglycerol–inositol phosphate system. On the other hand, the M_2 and M_4 receptors couple to the pertussis toxin–sensitive G protein $G_{i/o}$ to inhibit adenylyl cyclase. M_2 receptors can couple to certain K^+ channels and influence the activity of calcium channels, I_f current, phospholipase A_2, phospholipase D, and tyrosine kinases.

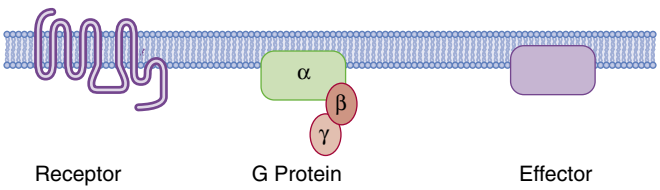

Figure 16-15 General scheme for a G protein–coupled receptor consisting of receptor, the heterotrimeric G protein, and the effector unit. *(Reprinted by permission from Bers DM: Cardiac excitation-contraction coupling. Nature 415:198-205, 2002. Copyright MacMillan Magazines Ltd.)*

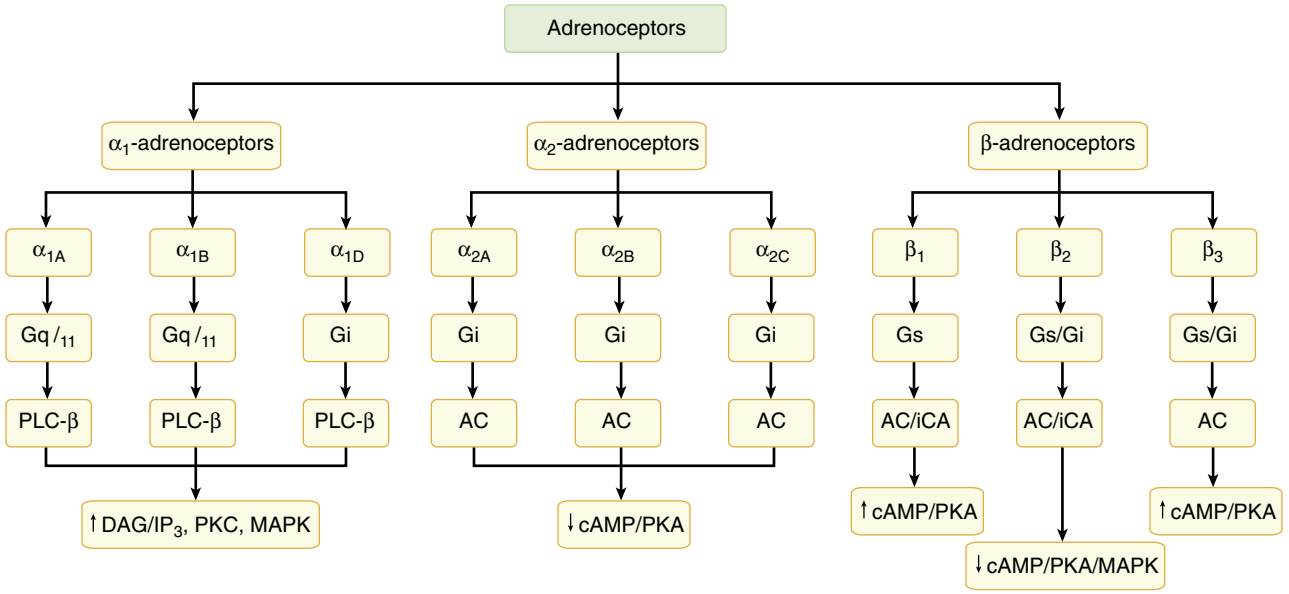

Figure 16-16 Adrenoceptor signaling cascades involving G proteins and effectors (AC, adenylyl cyclase; i_{CaL}, L-type calcium current; PLC-β, phospholipase β) in the heart. The intracellular signals are DAG (diacylglycerol), IP_3 (inositol 1,4,5-triphosphate), PKC (protein kinase C), cAMP (cyclic adenosine monophosphate), PKA (protein kinase A), and MAPK (mitogen-activated protein kinase).

In contrast to vagal innervation, sympathetic innervation of the heart is more predominant in the ventricle than in the atrium. Norepinephrine released from sympathetic nerve terminals stimulates adrenergic receptors (adrenoreceptors [ARs]) located in the heart. The two major classes of ARs are α and β, both of which are G protein–coupled receptors that transduce their intracellular signals by means of specific signaling cascades (Fig. 16-16).

βARs can be further divided into subpopulations of β_1, β_2, and β_3.[43,45] Although most mammalian hearts contain β_1ARs and β_2ARs, β_3ARs have also been demonstrated in many mammalian ventricular tissues. The relative contribution of each βAR subtype to modulation of cardiac function varies among species. In humans, β_1ARs are the predominant subtype in both the atria and ventricle, but a substantial proportion of β_2ARs are located in the atria and approximately 20% of β_2ARs are found in the LV. Much less is known about β_3ARs, but their existence has been documented in the human ventricle. Despite the fact that the β_1AR population is greater than the β_2AR population, the cardiostimulant effect is not proportional to the relative densities of these two subpopulations, which is largely attributable to the tighter coupling of β_2ARs than β_1ARs to the cyclic adenosine monophosphate (cAMP) signaling pathway. Both β_1ARs and β_2ARs activate a pathway that involves the stimulatory G protein (G_s), activation of adenylyl cyclase, accumulation of cAMP, stimulation of cAMP-dependent protein kinase A, and phosphorylation of key target proteins, including L-type calcium channels, phospholamban, and TnI.

Although traditional teaching is that both β_1ARs and β_2ARs are coupled to the G_s-cAMP pathway, more recent experimental evidence has indicated that β_2ARs also couple to the inhibitory G protein G_i to activate non–cAMP-dependent signaling pathways. Additionally, β_2ARs can couple to G protein–independent pathways to modulate cardiac function. βAR stimulation increases both contraction and relaxation, as summarized in Figure 16-17.

The two major subpopulations of αARs are α_1 and α_2. α_1ARs and α_2ARs can be further subdivided into different subtypes. α_1ARs are G protein–coupled receptors and include the α_{1A}, α_{1B}, and α_{1D} subtypes. The α_1AR subtypes are products of separate genes and differ in structure, G protein coupling, tissue distribution, signaling, regulation, and function. Both α_{1A}ARs and α_{1B}ARs mediate positive inotropic responses. However, the positive inotropic effect mediated by α_1ARs is believed to be of minor importance in the heart. α_1ARs are coupled to phospholipase C, phospholipase D, and phospholipase A_2; they increase intracellular Ca^{2+} and myofibrillar sensitivity to Ca^{2+}.

Cardiac hypertrophy is primarily mediated by α_{1A}ARs.[46,47] Cardiac hypertrophic responses to α_1AR agonists involve activation of protein kinase C and mitogen-activated protein kinase through G_q signaling mechanisms. Three subtypes of α_2ARs are recognized: α_{2A}, α_{2B}, and α_{2C}. In the mammalian heart, α_2ARs in the atrium play a role in the presynaptic inhibition of norepinephrine release. These prejunctional α_2ARs are believed to belong to the α_{2C} subtype.

Neural regulation of cardiac function involves a complex interaction between the different classes and subpopulations of adrenoceptors and their signaling pathways. Targeted therapeutics in cardiovascular medicine will involve the clinical application and manipulation of our basic understanding of adrenoceptor pharmacology.

Hormones Affecting Cardiac Function

Many hormones have direct and indirect actions on the heart (Table 16-1). Hormones with cardiac actions can be synthesized and secreted by cardiomyocytes or produced by other tissues and delivered to the heart. They act on specific receptors expressed in cardiomyocytes. The great majority of these hormone receptors are plasma membrane G protein–coupled receptors (GPCRs). Non-GPCRs include the natriuretic peptide receptors, which are

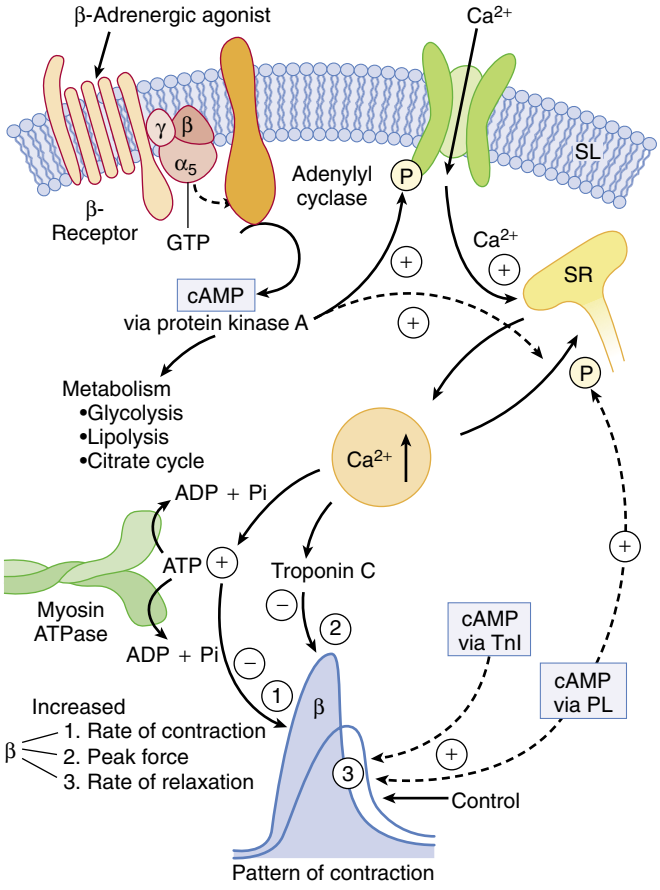

Figure 16-17 The β-adrenoceptor signaling system leads to an increased rate and force of contraction and increased relaxation. ADP, adenosine diphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; GTP, guanosine triphosphate; PL, phospholipase; SL, sarcolemma; SR, sarcoplasmic reticulum; TnI, troponin I. *(From Opie LH: Receptors and signal transduction.* In *The Heart. Physiology from Cell to Circulation, 3rd ed. Philadelphia, Lippincott-Raven, 1998, p 195.)*

guanylyl cyclase–coupled receptors, and the glucocorticoid/mineralocorticoid receptors, which bind androgens and aldosterone and are nuclear zinc finger transcription factors. Hormones can have activity in normal cardiac physiology or are active only in pathophysiologic conditions, or both situations can apply. Much of the understanding that has been gained over the past decade on the action of hormones in the heart has been derived from the endocrine changes associated with chronic heart failure.

Cardiac hormones are polypeptides secreted by cardiac tissues into the circulation in the normal heart. Natriuretic peptides,[51,52] aldosterone,[53] and adrenomedullin[54] are hormones secreted by cardiomyocytes. Angiotensin II, the effector hormone in the renin-angiotensin system, is also produced by cardiomyocytes.[55,56] The renin-angiotensin system is one of the most important regulators of cardiovascular physiology. It is a key modulator of cardiac growth and function. Angiotensin II stimulates two separate receptor subtypes, AT_1 and AT_2, both of which are present in the heart. AT_1 receptors are the predominant subtype expressed in the normal adult human heart. Stimulation of AT_1 receptors induces a positive chronotropic and inotropic effect. Angiotensin II also mediates cell growth and proliferation in cardiomyocytes and fibroblasts and induces release of the growth factors aldosterone and catecholamines through stimulation of AT_1 receptors. Activation of AT_1 receptors is directly involved in the development of cardiac hypertrophy and heart failure, as well as adverse remodeling of the myocardium. In contrast, AT_2 receptor activation is counter-regulatory and is generally antiproliferative. Expression of AT_2 receptors, however, is relatively scant in the adult heart because they are most abundant in the fetal heart and decline with development. In response to injury and ischemia, AT_2 receptors become upregulated. The precise role of AT_2 receptors in the heart remains to be defined.

The beneficial effects of blockade of the renin-angiotensin system with angiotensin-converting enzyme inhibitors in the treatment of heart failure have been attributed to inhibition of AT_1 receptor activity. In addition to the renin-angiotensin system,

Table 16-1 Actions of Hormones on Cardiac Function

Hormone	Receptor	Cardiac Action	Increase with CHF
Adrenomedullin	GPCR	+Inotropy/+chronotropy	+
Aldosterone	MR	?	+
Angiotensin	GPCR	+Inotropy/+chronotropy	+
Endothelin	GPCR	?	+
Natriuretic peptides	GCCR		
ANP (ANF)			+
BNP			+
Neuropeptide Y[48,49]	GPCR	–Inotropy	+
Vasopressin	GPCR	+Inotropy/+chronotropy	+
Vasoactive intestinal peptide[50]	GPCR	+Inotropy	No
Sex steroid hormones			
Estrogen	ERR-α/ERR-β	Indirect	No
Testosterone	AR	Indirect	No
Progesterone	PR	Indirect	No

ANF, atrial natriuretic factor; ANP, atrial natriuretic peptide; AR, androgen receptor; BNP, B-type natriuretic peptide; CHF, congestive heart failure; ERR, estrogen-related receptor; GCCR, guanylyl cyclase–coupled receptor; GPCR, G protein–coupled receptor; MR, cytosolic or nuclear mineralocorticoid receptor; PR, progesterone receptor.

other cardiac hormones that have been shown to play pathogenic roles in the promotion of cardiomyocyte growth and cardiac fibrosis, development of cardiac hypertrophy, and progression of congestive heart failure include aldosterone,[53] adrenomedullin,[57-59] natriuretic peptides,[51,52] angiotensin,[60,61] endothelin,[62] and vasopressin.[63,64]

Increased stretch of the myocardium stimulates the release of atrial natriuretic protein (ANP) and B-type natriuretic protein (BNP) from the atria and ventricles, respectively. Both ANP and BNP bind to natriuretic peptide receptors to generate the second messenger cyclic guanosine monophosphate and represent part of the cardiac endocrine response to hemodynamic changes caused by pressure or volume overload. They also participate in organogenesis of the embryo heart and cardiovascular system.[51,52] In patients with chronic heart failure, elevation of serum ANP and BNP levels has been documented to be a predictor of mortality.

Adrenomedullin is a recently discovered cardiac hormone that was originally isolated from pheochromocytoma tissue. It increases accumulation of cAMP and has direct positive chronotropic and inotropic effects.[54,57,58] Adrenomedullin, with interspecies and regional variations, has also been shown to increase nitric oxide production and it functions as a potent vasodilator.

Aldosterone is one of the cardiac-generated steroids, although its physiologic significance remains to be defined. It binds to mineralocorticoid receptors and can increase the expression or activity (or both) of cardiac proteins involved in ionic homeostasis or regulation of pH, such as cardiac Na^+/K^+-ATPase, the Na^+-K^+ cotransporter, Cl^--HCO_3^{2+}, and the Na^+-H^+ antiporter.[53] Aldosterone modifies cardiac structure by inducing cardiac fibrosis in both ventricular chambers and thereby leads to impairment of cardiac contractile function.

Sex Steroid Hormones and the Heart

Cardiac contractility is greater in premenopausal women than in age-matched men, and withdrawal of hormone replacement therapy in postmenopausal women leads to a reduction in cardiac contractile function. The gender dimorphism in heart function and its adaptive responses to injury and disease states are in part mediated by sex steroid hormones.

The most extensively studied sex steroid hormones are estradiol-17β (E2) and its bioactive metabolites. They bind and act on the two subtypes of estrogen receptors in the heart: ERα and ERβ. Progesterone and testosterone (two other sex steroid hormones) and the enzyme aromatase, which converts testosterone to estrogen, are much less well investigated. Progesterone and testosterone bind and act on their respective progesterone receptors and androgen receptors in the heart. Sex steroid hormones interact with their receptors to effect postsynaptic target cell responses and influence presynaptic sympathoadrenergic function. Cardiomyocytes are not only targets for the action of sex steroid hormones but are also the source of synthesis and site of metabolism of these hormones.[65]

E2 is derived from testosterone and is primarily metabolized in the liver to form hydroxyestradiols, catecholestradiol, and methoxyestradiols. Estradiol metabolism also takes place in vascular smooth muscle cells, cardiac fibroblasts, endothelial cells, and cardiomyocytes. Cardiomyocytes express nuclear steroid hormone receptors that modulate gene expression and nonnuclear receptors for the nongenomic effects of sex steroid hormones. They interact with many different coregulators to confer tissue and temporal specificity in their transcriptional actions. These cell-specific coactivator and corepressor proteins are known as estrogen-related receptors.[66] Sex steroid hormones can activate rapid signaling pathways without changing gene expression (Fig. 16-18). One such example is stimulation of vascular endothelial nitric oxide synthase to mediate vascular dilatation. Estrogen's vasodilatory effect might explain the lower systolic blood pressures of premenopausal women than age-matched men. In men, aromatase-mediated conversion of testosterone to estrogen maintains normal vascular tone. In addition to sex steroid hormone stimulation of nuclear or non-nuclear receptors, sex steroid hormone receptors could also induce rapid signaling of growth factor pathways in the absence of ligands.

There are gender differences in cardiac electrophysiologic function. The modulatory actions of estrogen on calcium channels might be responsible for sex-based differences in repolarization of the heart, such as the faster resting heart rate of women, as well as the higher propensity of women to have prolonged QT syndrome.[67] Estrogen, through the activation of ERβ receptors, confers protection after ischemia and reperfusion in murine models of myocardial infarction. In contrast, testosterone, in the same model, has the opposite effect. Aromatase also has protective effects, probably through its action to increase estrogen and decrease testosterone.

Gender differences in cardiac physiology should include consideration of the cellular physiology of sex steroid hormones in males and females; intrinsic differences in the physiology of cardiomyocytes, vascular smooth muscle cells, and endothelial cells between males and females; and gender-based differences in the autonomic modulation of cardiac physiology.

Cardiac Reflexes

Cardiac reflexes are fast-acting reflex loops between the heart and central nervous system (CNS) that contribute to regulation of cardiac function and maintenance of physiologic homeostasis. Specific cardiac receptors elicit their physiologic responses by various pathways. Cardiac receptors are linked to the CNS by myelinated or unmyelinated afferent fibers that travel along the vagus nerve. Cardiac receptors can be found in the atria, ventricles, pericardium, and coronary arteries. Extracardiac receptors are located in the great vessels and carotid artery. Sympathetic and parasympathetic nerve input is processed in the CNS. After central processing, efferent fibers to the heart or the systemic circulation will provoke a particular reaction. The response of the cardiovascular system to efferent stimulation varies with age and duration of the underlying condition that elicited the reflex in the first instance.

Baroreceptor Reflex (Carotid Sinus Reflex)

The baroreceptor reflex is responsible for maintenance of blood pressure. This reflex is capable of regulating arterial pressure around a preset value through a negative-feedback loop (Fig. 16-19).[68,69] In addition, the baroreceptor reflex is capable of establishing a prevailing set point for blood pressure when the preset value has been reset because of chronic hypertension. Changes in blood pressure are monitored by circumferential and longitudinal stretch receptors located in the carotid sinus and aortic arch. The nucleus solitarius, located in the cardiovascular center of the

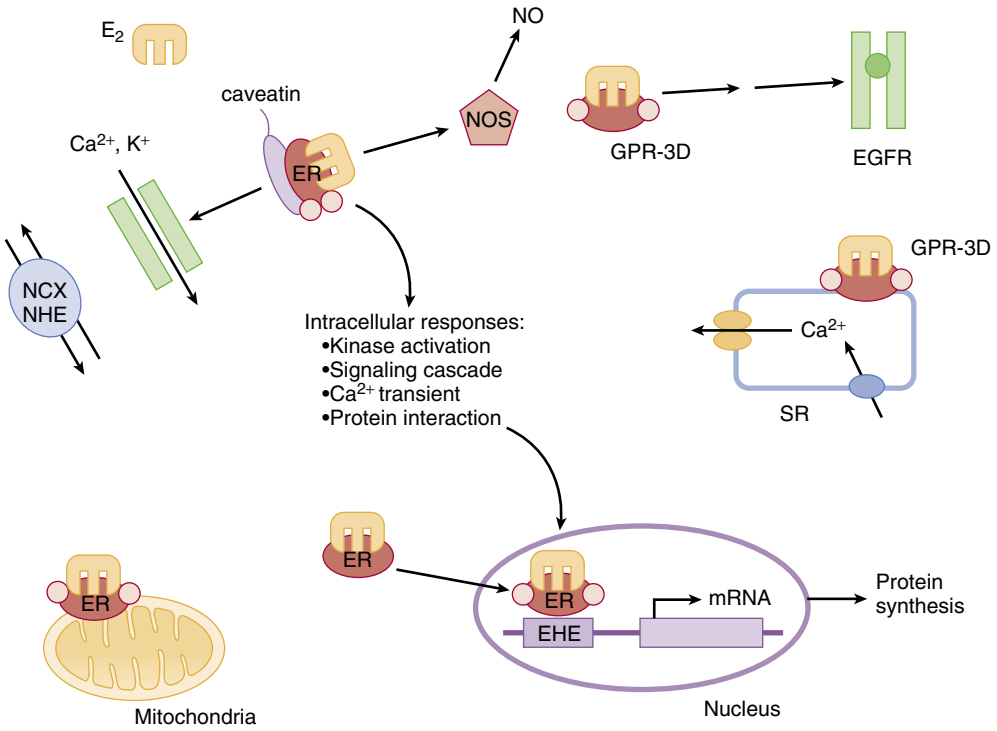

Figure 16-18 Signaling mechanism of nuclear and non-nuclear localized estrogen receptor (ER) and the estrogen binding receptor GPR-30. Nuclear ER influences the transcription of target genes by binding to an ER response element (ERE) within the promotor region of target genes. E2, estrogen; EGFR, epidermal growth factor receptor; NCX, Na^+-Ca^{2+} exchanger; NHE, Na^+-H^+ exchanger; NO, nitric oxide; NOS, nitric oxide synthase. *(From Du XJ, Fang L, Kiriazis H: Sex dimorphism in cardiac pathophysiology: Experimental findings, hormonal mechanisms, and molecular mechanisms. Pharmacol Ther 111:434-475, 2006.)*

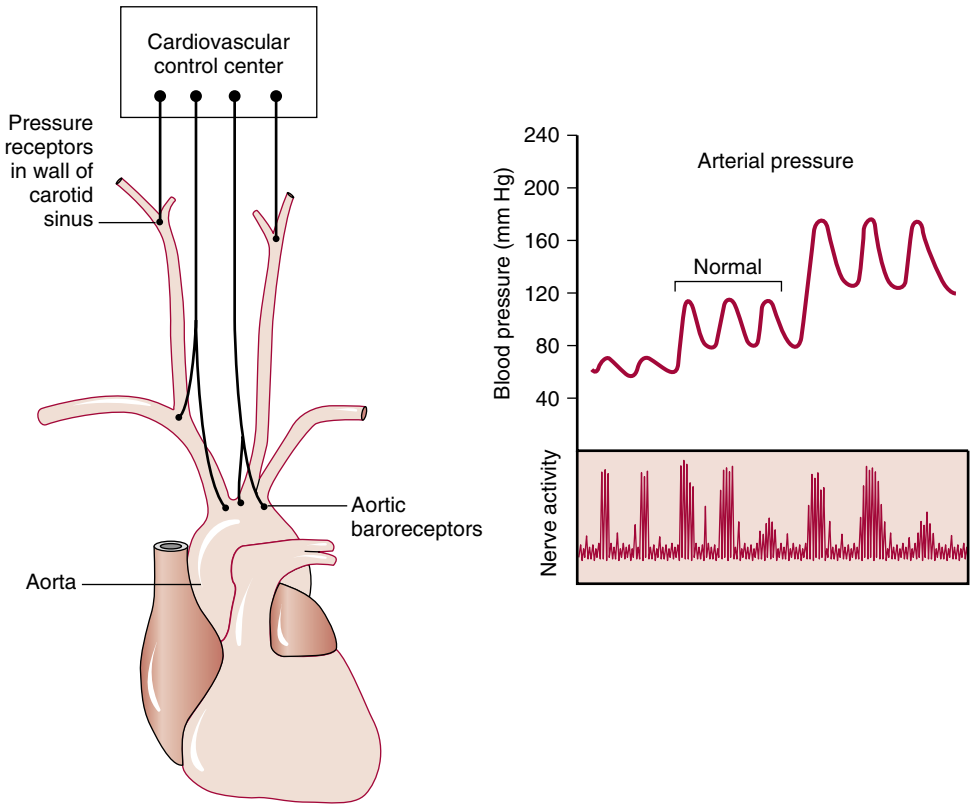

Figure 16-19 Anatomic configuration of the baroreceptor reflex. Pressure receptors in the wall of the carotid sinuses and aorta detect changes in arterial pressure in the circulation. These signals are conveyed to afferent receptive regions of the medulla through the Hering and vagus nerves. Output from effector portions of the medulla modulates peripheral tone and heart rate. The increase in blood pressure results in increased activation of the reflex (*right*), which effects a decrease in blood pressure. *(From Campagna JA, Carter C: Clinical relevance of the Bezold-Jarisch reflex. Anesthesiology 98:1250-1260, 2003.)*

medulla, receives impulses from these stretch receptors through afferents of the glossopharyngeal and vagus nerves. The cardiovascular center in the medulla consist of two functionally different areas: the area responsible for increasing blood pressure is located laterally and rostrally, whereas the area responsible for lowering arterial blood pressure is located centrally and caudally. The latter area also integrates impulses from the hypothalamus and the limbic system. Typically, stretch receptors are activated if systemic blood pressure is greater than 170 mm Hg. The response of the depressor system includes decreased sympathetic activity leading to a decrease in cardiac contractility, heart rate, and vascular tone. In addition, activation of the parasympathetic system further decreases the heart rate and myocardial contractility. Reverse effects are elicited with the onset of hypotension.

The baroreceptor reflex plays an important role during acute blood loss and shock. However, the reflex arch loses its functional capacity at a blood pressure lower than 50 mm Hg. Hormonal status and therefore sex differences have been implicated in altered baroreceptor responses.[70] Furthermore, volatile anesthetics (particularly halothane) inhibit the heart rate component of this reflex.[71] Concomitant use of calcium channel blockers, angiotensin-converting enzyme inhibitors, or phosphodiesterase inhibitors will lessen the cardiovascular response of raising blood pressure through the baroreceptor reflex. This lessened response is achieved by either their direct effects on the peripheral vasculature or, more importantly, their interference with CNS signaling pathways (calcium, angiotensin).[72] Patients with chronic hypertension often exhibit perioperative circulatory instability as a result of a decrease in their baroreceptor reflex response.

Chemoreceptor Reflex

Chemosensitive cells are located in the carotid bodies and the aortic body. These cells respond to changes in pH status and blood oxygen tension. At an arterial partial oxygen pressure (Pao_2) of less than 50 mm Hg or in conditions of acidosis, the chemoreceptors send their impulses along the sinus nerve of Hering (a branch of the glossopharyngeal nerve) and the 10th cranial nerve to the chemosensitive area of the medulla. This area responds by stimulating the respiratory centers and thereby increasing ventilatory drive. In addition, activation of the parasympathetic system ensues and leads to a reduction in heart rate and myocardial contractility. In the case of persistent hypoxia, the CNS will be directly stimulated, with a resultant increase in sympathetic activity.

Bainbridge Reflex

The Bainbridge reflex is elicited by stretch receptors located in the right atrial wall and the cavoatrial junction. An increase in right-sided filling pressure sends vagal afferent signals to the cardiovascular center in the medulla. These afferent signals inhibit parasympathetic activity, thereby increasing the heart rate. Acceleration of the heart rate also results from a direct effect on the SA node by stretching the atrium. The changes in heart rate are dependent on the underlying heart rate before stimulation.

Bezold-Jarisch Reflex

The Bezold-Jarisch reflex responds to noxious ventricular stimuli sensed by chemoreceptors and mechanoreceptors within the LV wall by inducing the triad of hypotension, bradycardia, and coronary artery dilatation.[69] The activated receptors communicate along unmyelinated vagal afferent type C fibers. These fibers reflexively increase parasympathetic tone. Because it invokes bradycardia, the Bezold-Jarisch reflex is thought of as a cardioprotective reflex. This reflex has been implicated in the physiologic response to a range of cardiovascular conditions such as myocardial ischemia or infarction, thrombolysis, or revascularization and syncope. Natriuretic peptide receptors stimulated by endogenous ANP or BNP may modulate the Bezold-Jarisch reflex. Thus, the Bezold-Jarisch reflex may be less pronounced in patients with cardiac hypertrophy or atrial fibrillation.[73]

Valsalva Maneuver

Forced expiration against a closed glottis produces increased intrathoracic pressure, increased central venous pressure, and decreased venous return. Cardiac output and blood pressure will be decreased after this (Valsalva) maneuver. This decrease will be sensed by baroreceptors and reflexively will result in an increase in heart rate and myocardial contractility through sympathetic stimulation. When the glottis opens, venous return increases and causes the heart to respond by vigorous contraction and an increase in blood pressure. This increase in blood pressure will in turn be sensed by baroreceptors, thereby stimulating the parasympathetic efferent pathways to the heart.

Cushing Reflex

The Cushing reflex is a result of cerebral ischemia caused by increased intracranial pressure. Cerebral ischemia at the medullary vasomotor center induces initial activation of the sympathetic nervous system. Such activation will lead to an increase in heart rate, blood pressure, and myocardial contractility in an effort to improve cerebral perfusion. As a result of the high vascular tone, reflex bradycardia mediated by baroreceptors will ensue.

Oculocardiac Reflex

The oculocardiac reflex is provoked by pressure applied to the globe of the eye or traction on the surrounding structures. Stretch receptors are located in the extraocular muscles. Once activated, stretch receptors will send afferent signals through the short and long ciliary nerves. The ciliary nerves will merge with the ophthalmic division of the trigeminal nerve at the ciliary ganglion. The trigeminal nerve will carry these impulses to the gasserian ganglion, thereby resulting in increased parasympathetic tone and subsequent bradycardia. The incidence of this reflex during ophthalmic surgery ranges from 30% to 90%. Administration of an antimuscarinic drug such as glycopyrrolate or atropine reduces the incidence of bradycardia during eye surgery (also see Chapter 75).

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17 Hepatic Physiology and Pathophysiology

Key Points

1. Roughly 25% of cardiac output flows through the liver via a dual blood supply. The portal vein conveys 75% of total hepatic blood flow; the hepatic artery provides the rest. Each vessel, however, delivers about 50% of the total hepatic oxygen supply.
2. Hepatic sinusoids are the capillaries of the liver. Blood reaches the sinusoids via terminal branches of the portal vein and hepatic artery; it exits the sinusoids via hepatic venules (i.e., central veins) and travels through a venous network before draining in the inferior vena cava. Postsinusoidal vessels are a major source of total hepatic vascular resistance.
3. The acinus is the functional microvascular unit of the liver. It has three circulatory zones, defined by hepatocellular proximity to the portal axis. Blood perfusing zone 1 hepatocytes (periportal) is rich in oxygen and nutrients. By contrast, zone 3 hepatocytes (centrilobular) are perfused with effluent blood from zones 1 and 2, which is relatively oxygen poor.
4. Hepatocytes of zone 3, which have the highest density of cytochrome P450 proteins, are the most susceptible to injury from drug metabolism, oxidative stress, severe hypotension, or hypoxia.
5. The hepatic arterial buffer response (HABR) is the main intrinsic regulator of liver blood flow. Since the liver lacks pressure-flow autoregulation (in the fasted state), low systemic arterial pressure leads to low portal venous flow. HABR induces a compensatory increase of hepatic arterial flow, thereby preserving hepatic oxygen delivery despite decreases of total hepatic blood flow. Pathologic disruptions of HABR increase the susceptibility of the liver to hypoxic injury.
6. The liver is integral to the splanchnic blood reservoir, which can transfer up to 1 L of whole blood to the systemic circulation within 30 seconds of sympathoadrenal activation in healthy, euvolemic adults. If this reservoir is dysfunctional, abrupt, yet mild losses of intravascular volume (10% to 15%) may cause severe hypotension.
7. The liver regulates the pathways of intermediary metabolism. When hepatic glycogen is depleted (e.g., due to prolonged fasting), the body depends on hepatic gluconeogenesis to supply blood glucose. Stress induces catabolic changes, including increased lipolysis, fatty acid oxidation, and hepatic ketone production. Ketosis develops. But ketosis triggers insulin release, thereby decreasing substrate (fatty acids) availability for ketogenesis. Thus, stress-induced ketosis tends to be self-limited, except in insulin-deficient states, when diabetic ketoacidosis may occur.
8. Hepatocytes play a central role in nitrogen metabolism. They remove nitrogen from various molecules, incorporate it into ammonia, and convert ammonia to urea. If liver failure occurs (without severe renal dysfunction), blood urea nitrogen levels typically remain low, while nitrogenous wastes accumulate in blood and other tissues.
9. Albumin is the most abundant hepatic protein. It is the main determinant of plasma oncotic pressure and an essential plasma transporter of exogenous substances and endogenous compounds, such as unconjugated bilirubin and free fatty acids.
10. Liver produces most of the molecular participants in coagulation pathways (besides factors III, IV, VIII). Hepatic proteins—such as factors II, VII, IX, X, proteins C and protein S—require vitamin K–dependent, posttranslational modifications, which enables their extrahepatic activation and subsequent involvement in the coagulation cascade.
11. Hepatocytes make, and regulate production of, bile salts. These natural ionic detergents have many physiologic roles, including enteric absorption, transport, and secretion of lipids. Disruption of biliary circulation predisposes to vitamin K deficiency; hepatocytes continue to synthesize procoagulants but cannot γ-carboxylate them. Parenteral vitamin K therapy should therefore correct the coagulopathy of cholestasis, unless liver failure has supervened.

12. The liver is the main site of xenobiotic biotransformation. Multifarious, complex chemical reactions of hepatic drug disposition fit in at least one of three broad metabolic categories (or phases): Phase 1 oxidizes drugs via cytochrome P450-mediated redox reactions; phase 2 produces conjugates of endogenous polar molecules and drugs (or their metabolites); phase 3 uses adenosine triphosphate transport proteins to facilitate biliary elimination of endogenous and exogenous substances.
13. The liver is the largest reticuloendothelial organ in the human body. Kupffer cells (macrophages) account for nearly 10% of the liver's mass. These macrophages filter the venous effluent of the gastrointestinal tract and in the process phagocytose microbes, destroy toxins, process antigens, modulate immunity, and regulate inflammatory responses. Kupffer cells, activated by such processes, release nitro-radicals, reactive oxygen species, proteases, chemokines, and cytokines, which recruit neutrophils to the liver and intensify the hepatic inflammation. If uncontrolled, these activated macrophages can damage normal hepatic parenchyma.
14. Portosystemic shunting (as occurs with cirrhosis-induced portal hypertension) circumvents the hepatic filtering mechanism and thereby allows drugs, nitrogenous waste, and toxins to enter the central circulation. Some of these substances are putative mediators of hepatic encephalopathy.
15. Standard liver function tests are used to screen for hepatobiliary diseases and identify categories of pathologic events within the hepatobiliary system, such as hepatocellular injury or biliary dysfunction.
16. The onset of portal hypertension signals depletion of the normal physiologic reserve of the liver. At this stage, severe pathophysiologic derangements develop and can give rise to life-threatening complications such as variceal hemorrhage, hepatic encephalopathy, and renal failure.
17. The cardiovascular hallmark of cirrhosis and portal hypertension is a hyperdynamic circulation in which cardiac output increases, total peripheral resistance decreases, and systemic blood pressure is slightly below normal. The hemodynamic profile is reminiscent of a large arteriovenous fistula because of extensive arteriovenous communications within the splanchnic vasculature and in organs throughout the body. Splanchnic vasculature may be engorged with blood even though effective plasma volume is perilously low. Cardiovascular responses to physiologic and pharmacologic vasoconstrictors are attenuated because of a plethora of endogenous vasodilators, dysfunction of the splanchnic reservoir, and occasionally, cardiac failure (e.g., cirrhotic cardiomyopathy).

Overview

The liver is the largest internal organ and largest gland in the human body. It accounts for about 2% of the total mass of healthy adults and 5% of neonates.[1] Its location within the thoracic portion of the abdominal cavity reflects its physiologic importance as an interface between the gastrointestinal tract and pulmonary/systemic circulation. It filters, excretes, or modifies an enormity of gut-derived substances—it destroys bacteria, inactivates antigens, and detoxifies chemicals that might otherwise injure the heart, lungs, or other vital organs. The liver is at the epicenter of intermediary metabolism, with versatile and massive biochemical pathways for molecular transformations. Such pathways work to maintain homeostatic blood levels of nutrients during feast and famine. As described in this chapter, the multiple and diverse functions of the liver have an impact on every tissue in the body. A fundamental knowledge of hepatic anatomy and physiology is therefore a prerequisite for understanding liver disease, its clinical manifestations, and its therapeutic challenges.

Hepatic Anatomy

Macroscopic Anatomy

The liver is a reddish brown boomerang-shaped gland that occupies the right hypochondrium, most of the epigastrium, and a variable portion of the left hypochondrium (Fig. 17-1). In the right midaxillary line, the liver spans from the 7th to the 11th ribs; the gallbladder lies beneath to the 9th costal cartilage. The liver is highly vascular, friable, and easily lacerated. Because of its sponginess, it conforms to the contours of less malleable, adjacent structures. Based on postmortem studies—using chemicals to harden the liver in situ—the organ is shaped like a right-angled triangular prism (wedge), with a rounded right angle. The three faces of this prism are the superior, inferior, and posterior surfaces of the liver; they provide frames of reference for gross anatomy (Figs. 17-2 and 17-3).

The hepatic ligaments are connective tissue bands that attach the liver to adjacent tissues. Most of these bands are overlapping folds of peritoneal membranes (i.e., membranous ligaments), but two are fibrous cords derived from obliterated fetal vessels, namely, the umbilical vein (ligamentum teres or round ligament) and the ductus venosus (ligamentum venosum). Although a couple of ligaments attach to nearby viscera (e.g., the hepatogastric and hepatoduodenal ligaments, which connect to the lesser curvature of the stomach and duodenum, respectively), most serve to tether the liver to the anterior abdominal wall or the underside of the diaphragm. Among the latter group are the coronary, left lateral, right lateral, falciform, and round ligaments.

Several factors maintain the liver in proper anatomic position. For example, the main posterior supports are (1) the diaphragm, via the coronary and triangular ligaments and the matrix of connective tissue on the bare area, and (2) the inferior vena cava, hepatic veins, and embedded connective tissue. The superior surface of the liver is form-fitted to the underside of the dia-

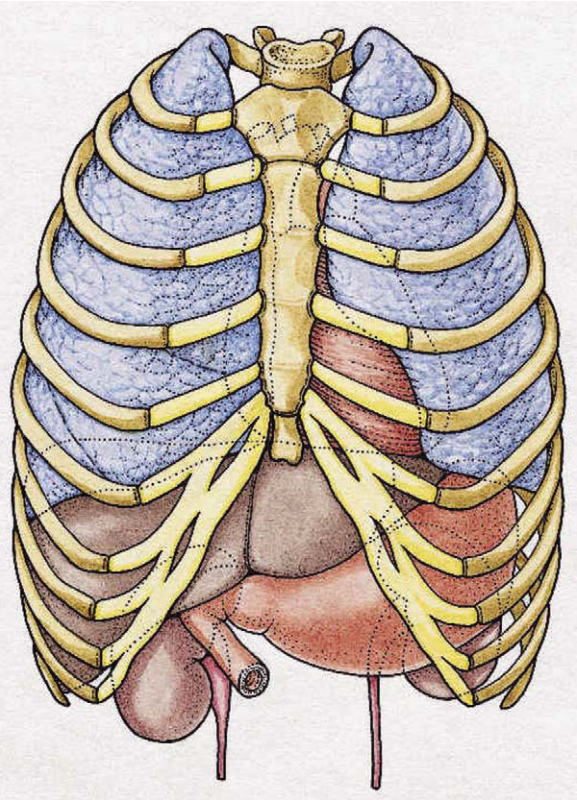

Figure 17-1 Anterior view of the liver and thoracic cage. The liver resides in the thoracic portion of the abdominal cavity; it occupies most of the right hypochondrium, much of the epigastrium, and a variable portion of the left hypochondrium. *(Reproduced © DK Images. Available from http://.dkimages.com/discover/previews/832/20113049.jpg/ Accessed October 23, 2008.)*

phragm, which could keep these structures in apposition at atmospheric pressure. Because abdominal viscera fill the abdominal cavity, the muscular walls of the abdomen remain in a state of tonic contraction. This tonic contraction generates positive intra-abdominal pressure, which pushes the liver against the underside of the diaphragm and keeps their surfaces together, even as the subatmospheric pressure of the thoracic cavity exerts upward pressure on the diaphragm. Because of its laxity, the falciform ligament does little to anchor the liver, although it may limit its lateral displacement.

Traditional Anatomy

Traditional or classic liver anatomy uses topologic landmarks to partition the liver into four lobes: the left, right, caudate, and quadrate.[2] On the superior hepatic surface, the falciform ligament separates the left and right lobes (see Fig. 17-2). Demarcations on posterior-inferior hepatic surfaces (Fig. 17-3) results from (1) the left sagittal fossa (ligamenta venosum and teres hepaticus), which separates left and right lobes; (2) the transverse fissure (porta hepatis), which is a shared border of quadrate and caudate lobes; (3) fossae for the umbilical vein and gallbladder, which border the quadrate lobe; (4) fossae for the ductus venosus (ligamentum venosum) and inferior vena cava fossa, which further delineate the caudate lobe.[3]

Internal Anatomy

After ascending to the porta hepatis (hilum), the portal vein and proper hepatic artery divide into their first-order branches—the left and right portal veins and the left and right hepatic arteries. These vessels enter the liver and travel in parallel as they ramify within the organ (Fig. 17-4). Their terminal branches drain into sinusoids of liver (i.e., the hepatic capillaries). Blood egresses from the sinusoids through intralobular (central) veins; it is conveyed via a series of larger conduits (i.e., the sublobular, interlobular, and lobular veins) to the right, middle, or left hepatic veins. The hepatic veins connect to the inferior vena cava (see Fig. 17-4).

The intrahepatic flow of bile occurs in a direction opposite the flow of afferent blood within the liver. Hepatic parenchymal cells produce bile; they secrete it into canaliculi that connect to bile ductules of the portal areas. Bile egresses from the portal canals and flows via a series of ducts to the left or right hepatic bile duct. These ducts unite to form the common hepatic bile duct, which descends from the porta hepatis and gives rise to the cystic duct and the common bile duct.

Physiologic Anatomy

Physiologic anatomy—also called functional, segmental, modern, or surgical anatomy—focuses on singular, independent segments of the liver (Fig. 17-5). Each independent segment has its own afferent blood supply and routes for venous and biliary drainage,

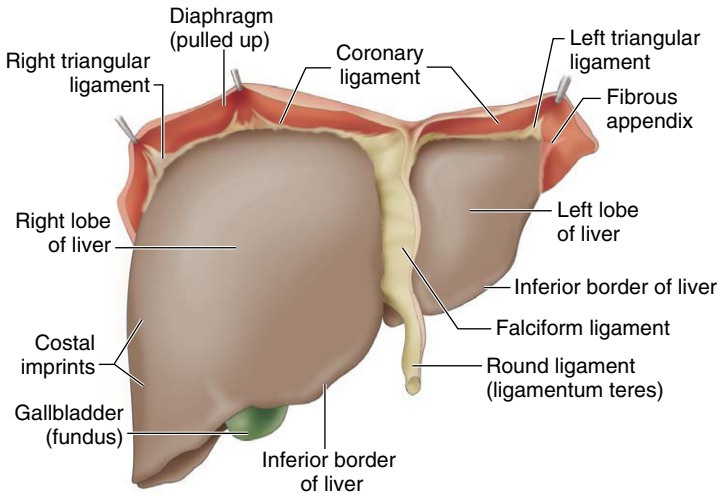

Figure 17-2 Superior hepatic surface: frontal view. The anterior hepatic edge (i.e., the inferior border of the liver) delineates the superior and inferior surfaces of the liver. A sickle-shaped peritoneal fold (falciform ligament) divides the liver into two parts of unequal size, the right lobe and the left lobe. Within the free margin or base of the falciform are paraumbilical veins and the round ligament (ligamentum teres), the latter being the remnant of the obliterated umbilical vein. *(From Strunk H, Stuckmann G, Textor J, et al: Limitations and pitfalls of Couinaud's segmentation of the liver in transaxial imaging. Eur Radiol 13:2472-2482, 2003.)*

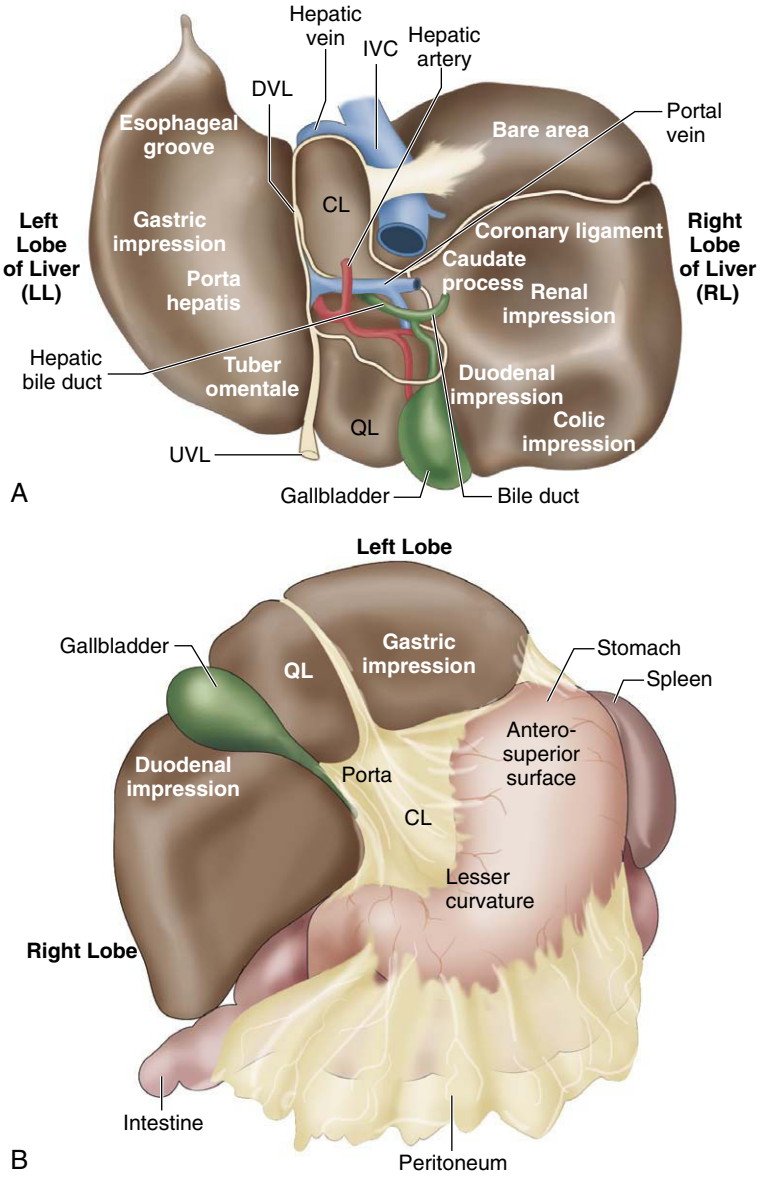

Figure 17-3 A, Posterior and inferior hepatic surfaces showing the relationship between four hepatic lobes: left lobe (LL), caudate lobe (CL), quadrate lobe (QL), right lobe (RL). They are delineated by five structures: the ductus venosus ligament (DVL), umbilical vein ligament (UVL), porta hepatis (PH), inferior vena cava (IVC), and gallbladder (GB). These structures can be envisaged as forming the letter H: • The two-part, left vertical bar (DVL in the back, UVL in the front) separates the LL from all the other lobes. • The three-part, right vertical bar (IVC in the back, caudate process in the middle, GB in the front) separates the RL from the others lobes. The caudate process, which connects the RL and CL, forms the upper boundary of the epiploic foramen (of the peritoneum). • The crossbar is the PH (or transverse fissure), which separates the CL in the back from the QL in the front. Notable anatomic features (left to right) are the narrow LL but broad and rounded RL. Protuberances and impressions (imp) on the hepatic surfaces result from contiguous viscera: the LL has an esophageal groove, gastric impression, and tuber omentale; the RL has duodenal, suprarenal, renal, and colic impressions. The vertebral column and crura of the diaphragm produce the deep concavity to the left of IVC. The omental bursa (upper part) lies between the papillary process (an elevation of the CL) and diaphragm. The surfaces of the liver are covered by peritoneum, with a few exceptions. Uncovered areas include (1) the GB attachment site; (2) the porta hepatis, with vessels and ducts splitting the two layers of the lesser omentum; (3) the right suprarenal impression; and (4) nonperitoneal surface (bare area of the liver) bounded by the coronary ligament (upper and lower lines of reflection), which is in direct contact with the diaphragm. **B,** Inferior (visceral) hepatic surface. The gastric impression on the liver molds to the convex, anterosuperior gastric surface. The tuber omentale (hepatic protuberance) fits in the concave, lesser curvature of stomach; it lies superficial to the anterior layer of lesser omentum and connects to the duodenum via the hepatogastric ligament. *(From Human Anatomy. http://theodora.com/anatomy/the_liver.html. Accessed February 11, 2009.)*

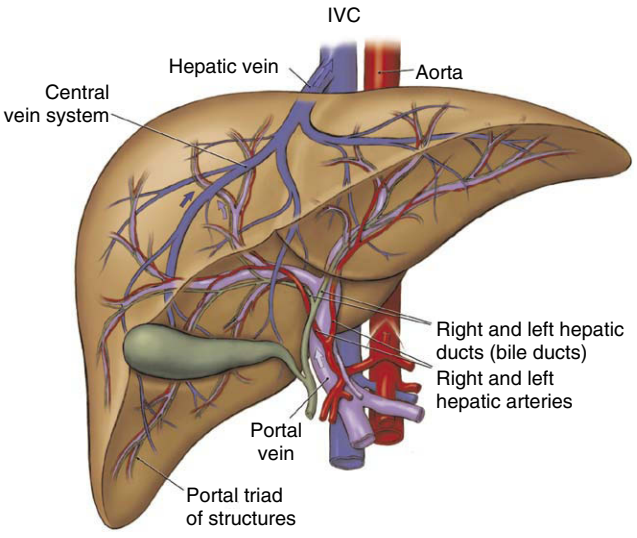

Figure 17-4 Internal anatomy of the liver. The portal vein (*lavender*) and proper hepatic artery (*red*) ascend to the porta hepatics (hilum), where they divide into their left and right main branches. These branches ramify within the liver before emptying into sinusoids. Blood exiting sinusoids is conveyed via central vein system to into hepatic veins (*blue*), which drain directly into the inferior vena cava (IVC; blue). Hepatocytes produce bile and secrete it into canaliculi; bile exits the liver flows though ductules of the portal triads, which drain into a series of intrahepatic ducts, and drains into the common hepatic bile duct (*gray*); the latter exits the liver at the porta hepatis and descends between peritoneal layers of the lesser omentum.
(© MediVisuals, Inc.)

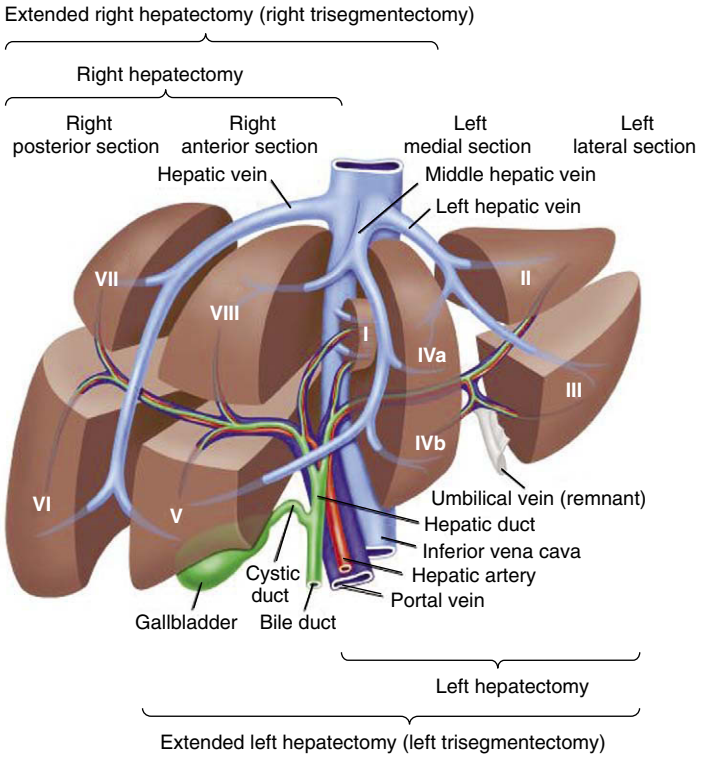

Figure 17-5 Schematic depiction of Couinaud segmental liver anatomy and the normal portal venous structures. Bracketed text shows hepatic segments resected during partial hepatectomies. *(Reproduced from Functional segments of the liver (Segmental_ anatomy_of_liver). Management of potentially resectable colorectal cancer liver metastases. Alan P Venook, MD. Steven A Curley, MD, FACS.©2007 UpToDate.)*

allowing it to remain functionally intact after surgical resection of neighboring segments. Owing to the manifold variations in branching patterns of the portal vein, hepatic artery, and hepatic bile duct, there is no universally accepted classification of segmental anatomy.[4] The most widely used classifications—such as those of Couinaud or Bismuth—are based on the anatomy of the portal and hepatic veins. The Couinaud system, for example, uses third-generation branches of the portal vein to partition the liver into eight physiologically independent segments (Fig. 17-5).[4] The geometry of dividing the liver into sectors and segments in accord with Bismuth's method is shown in Figure 17-6.[4]

Physiologic anatomy facilitates both planning and performance of hepatic surgery. For example, surgical incisions through the center of a segment would be likely to devitalize the

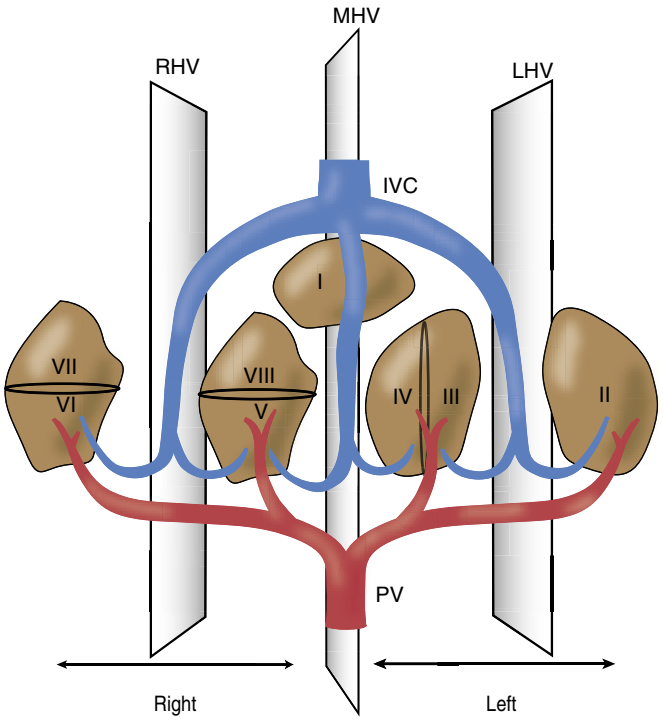

Figure 17-6 Physiologic liver anatomy: Bismuth classification. Three parallel planes host a single hepatic vein (right, RHV; middle, MHV; or left, LHV); each plane is split by a transverse plane (not shown) cutting through the right or left main portal veins (PV); this creates four sectors with portal pedicels (i.e., portal sectors). MHV divides the liver into a left and right hemiliver: LHV splits the former (into one lateral (II) and two medial (III, IV) segments) and RHV splits the latter (into two anterior (VI, VII) and two posterior (V, VIII) segments). In contrast to any other segment, segment I (the caudate lobe) gets its blood supply from both left and right main portal veins; and, its venous outflow—instead of entering a major hepatic vein—drains directly into the inferior vena cava (IVC). *(The authors are grateful to Jennifer Mushlin for designing and crafting this figure.)*

entire segment because therein lies the portal triads (portal vein, hepatic artery, bile duct). By contrast, incisions along the periphery of segments minimize unintentional injuries of major hepatic veins, which generally run in parallel to the segmental borders. If surgical disease affects any part of a segment, the goal is usually to remove the entire segment without disrupting its healthier neighbors. Clinical studies have shown lower rates of perioperative morbidity and mortality when liver surgery (resection of tumors, repair of traumatic injuries) is guided by the principles of physiologic anatomy.[5-7]

Real Anatomy

Because the human liver has so many anatomic variations, knowledge of an individual's real physiologic anatomy derives from advanced imaging techniques, such as contrast-enhanced helical computed tomography scans. These scans provide accurate information on the relationships of surface landmarks and internal hepatic anatomy. In fact, such scan data, when superimposed on normalized computer images of Couinaud segments, yield a data set with enough information to construct a three-dimensional model of a patient's liver. Accurate, see-through constructs can impart an instantaneous grasp of a patient's physiologic anatomy by detailing anatomic variants and precise locations of hepatic lesions. In addition, recent advances in ultrasonography have enabled real physiologic anatomy to be identified during surgical procedures.

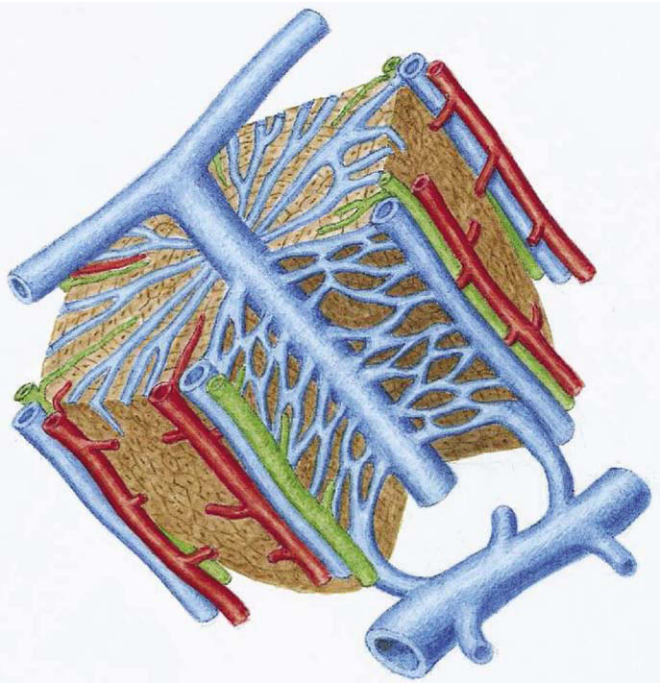

Figure 17-8 Idealized representation of a classic liver lobule. *(© DK Images.)*

Microanatomy

Classic Liver Lobule

The basic unit of the liver can be viewed as a classic lobule, a portal lobule, or a liver acinus; Figure 17-7 shows how these arbitrary units relate to one another. An idealized classic liver lobule is a hexagonal prism with a central vein at its center and six vertically aligned portal canals (Fig. 17-8). Each portal canal includes a connective tissue matrix, surrounding nerve fibers, lymphatic vessels, and a portal triad. The latter contains terminal branches of the portal vein and hepatic artery and a bile ductule.

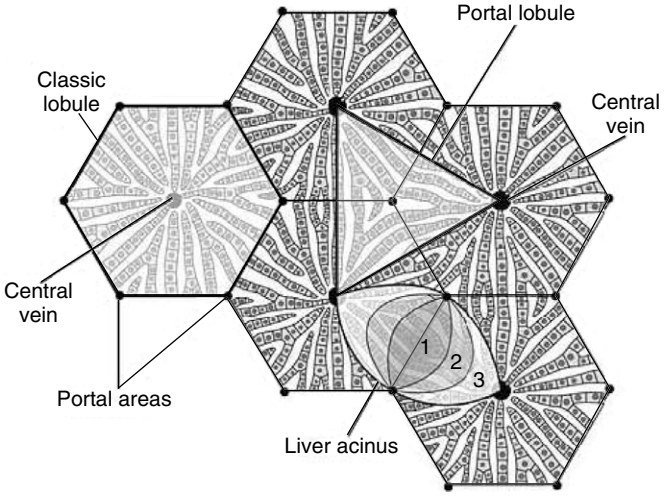

Figure 17-7 Schematic classifications of liver units: liver lobule, portal lobule, and liver acinus. Lobular units have well demarcated central structures (central vein or portal canal), whereas the liver acinus (zones 1, 2, 3; see Fig. 17-10) contains a central axis derived from two adjacent classic lobules. *(From Henrickson R, Kaye GI, Mazurkiewicz J: Liver and gallbladder. In Henrickson R, Kaye GI, Mazurkiewicz [eds]: NMS Histology, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 1997.)*

A transverse section of a liver lobule shows an array of anastomosing cords of cuboidal hepatocytes separated by vascular channels (lacunae) that radiate from the portal areas and converge on the central vein (see Fig. 17-8). The lacunar labyrinth permeates the entire lobule; it is confined, however, at the periphery of the lobule by a limiting plate of hepatocytes that form a nearly continuous wall. This wall separates the interior of the lobule from the portal canals. Only the tiniest branches of the hepatic artery, portal vein, and bile duct are able to penetrate fenestrae within the limiting plate.

Microscopic examination of the human liver, however, shows a lack of well-defined classic lobules because of a dearth of well-developed connective tissue between lobules. Indeed, the search for lobular boundaries led to the discovery of circumferential terminal hepatic arterioles, portal venules, and bile ductules (Fig. 17-9). This finding is fundamental to the acinar lobe concept, which posits that vessels encircling lobar peripheries, rather than those within portal canals, are the most immediate source of afferent blood to hepatocytes (Fig. 17-10; also see Fig. 17-7). In other words, blood flow to lobules originates along shared borders of classic lobules, which lie between two central veins (see Fig. 17-10).

The Liver Acinus

The acinus is the functional microvascular unit of the liver. It forms around a vertical axis (the portal canal) consisting of a portal venule, hepatic arteriole, bile ductule, lymph vessels, and nerves. Flow of blood within acini is directed radially toward the central veins and vertically to the portal canal.

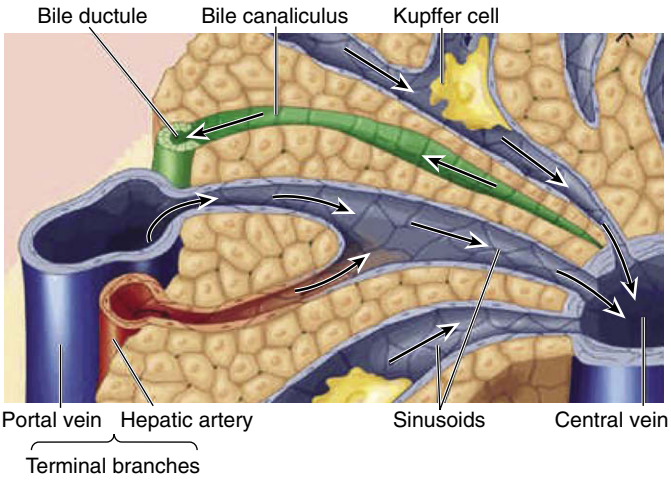

Figure 17-9 Diagram of a portal triad in cross section. Blood enters sinusoids (*blue*, *black arrows*) and egresses via a central vein (*blue*). Sinusoids contain Kupffer cells (*yellow*). Hepatocytes (*pinkish tan*) produce bile and secrete it into bile canaliculi (*green*, with *black arrows*), which drain into a bile ductule of the portal triad. *(From The Internet Encyclopedia of Science. http://daviddarling.info/encyclopedia/L/liver.html. Accessed February 11, 2009.)*

Microcirculation

The acinus has three heterogeneous circulatory zones[1] (see Fig. 17-10): zone 1 is periportal, zone 2 is the midzone, and zone 3 is pericentral. Blood supplied to zone 1, which is near the origin of the sinusoid, is rich in oxygen and nutrients. In contrast, zone 3, at the periphery of the acinus, receives blood that is oxygen poor because this blood has already perfused hepatocytes of zones 1 and 2 before it reaches zone 3.

The microvascular architecture of the acinus allows increases in the efficiency of substrate utilization and excretion of waste products.[8,9] Urea cycle enzymes are localized in zones 1 and 2. Hepatocytes within these zones convert amino acids to ketoacids and ammonia; the urea cycle (high capacity, low affinity) captures the ammonia and incorporates it into urea. Any ammonia that eludes the urea cycle is likely to encounter glutamine synthetase, which is expressed only in zone 3. This enzyme facilitates the capture of ammonia within the glutamine substrate. If glutamine substrate were present in zones 1 or 2, it would compete with urea cycle enzymes for ammonia and thereby decrease the liver's capacity to eliminate ammonia. By having glutamine synthetase localized in zone 3, pericentral hepatocytes more efficiently scavenge the ammonia that would otherwise reach the central circulation.[8]

Periportal hepatocytes have the highest density of mitochondria and are the major site of oxidative metabolism and glycogen synthesis. In contrast, pericentral hepatocytes—which have an abundance of smooth endoplasmic reticulum, reduced nicotinamide adenine dinucleotide phosphate (NADPH), and cytochrome P450 (CYP) proteins—are the major site of anaerobic metabolism and xenobiotic biotransformation. Not surprisingly, pericentral hepatocytes bear the brunt of injuries induced by reactive xenobiotic metabolites or hypoxic episodes. The clinical message is that ischemic injury or necrosis of the centrilobular region decreases the liver's capacity to excrete many drugs and other xenobiotics.

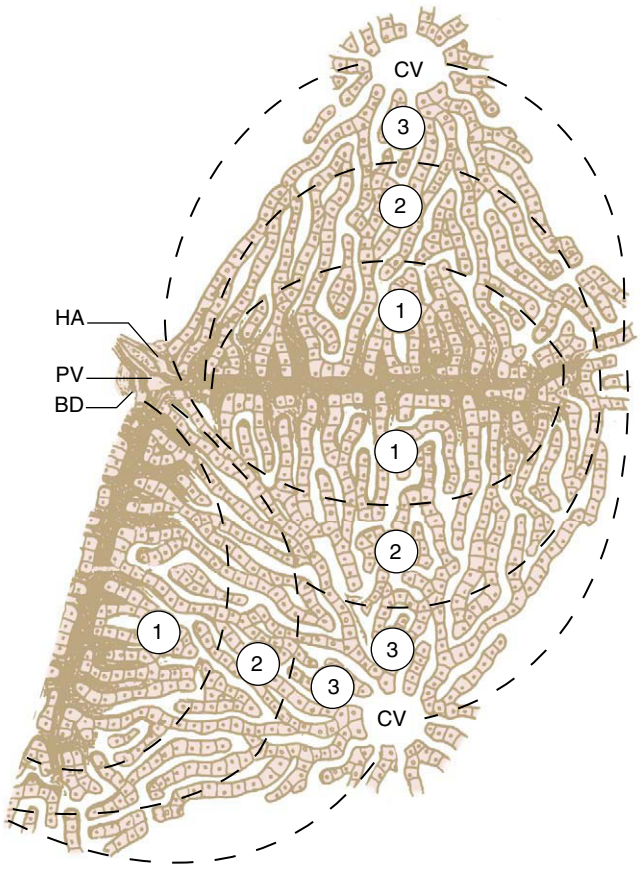

Figure 17-10 Blood supply of a liver acinus. Oxygen tensions and nutrient levels within sinusoids continuously decrease as blood flows from zone 1 through zone 3. The lower part of this figure shows zones 1, 2, and 3 of a neighboring acinus. BD, bile ductule; CV, central vein; HA, hepatic artery; PV, portal vein. *(Reprinted with permission from Jones AL: Anatomy of the normal liver.* In *Zakim D, Boyer T [eds]: Hepatology: A Textbook of Liver Disease, 3rd ed. Philadelphia, WB Saunders, 1996, p 3.)*

Splanchnic Circulation and Hepatic Blood Flow

Hepatic Blood Flow

The liver is at the hub of the splanchnic circulation. Hepatic blood flow is inextricably linked to and hence varies with the effects of intrinsic, extrinsic, and extrahepatic influences on the splanchnic vasculature. The liver receives roughly 25% of the total cardiac output (1 mL of blood per 1 g of liver) via a dual vascular supply. Arterial blood is supplied via the proper hepatic artery—a branch of the common hepatic artery that has its origin at the celiac trunk of the abdominal aorta (Fig. 17-11).[2,3] On the other hand, the portal vein has as its tributaries the superior mesenteric and splenic veins, which carry the entire venous drainage of the preportal splanchnic beds. The portal vein conveys about three fourths and the hepatic artery about one fourth of total hepatic blood flow. Each vessel, however, delivers about half of the total

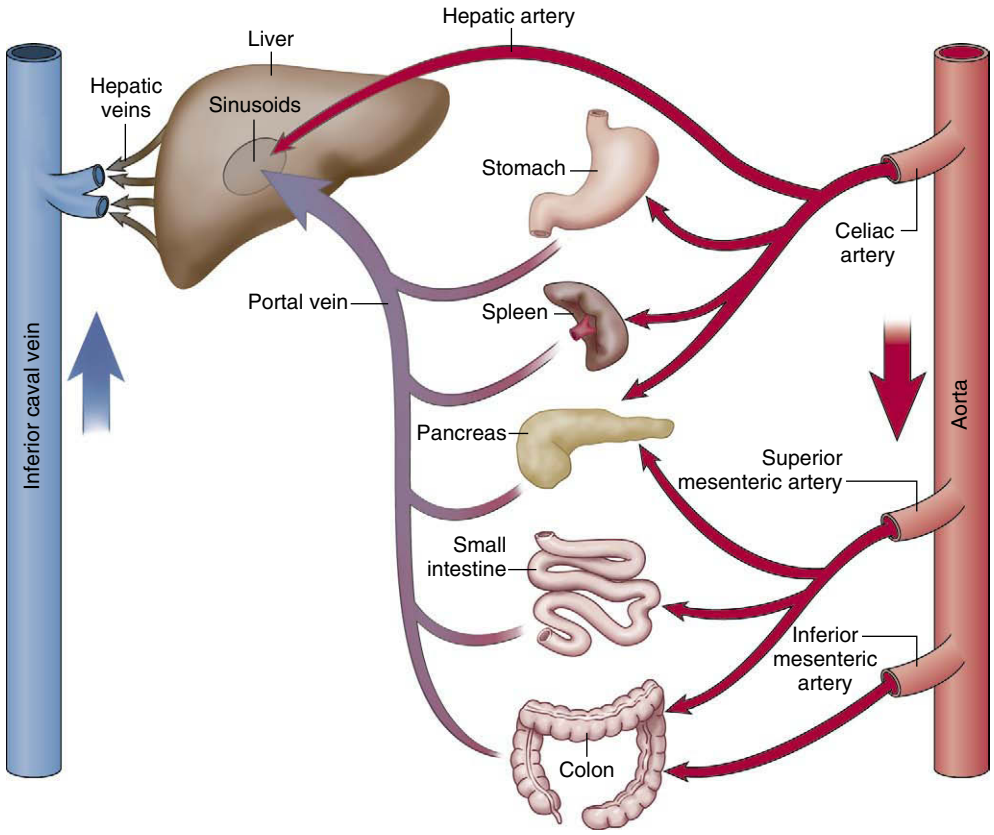

Figure 17-11 The splanchnic circulation. *(Redrawn with permission from Gelman S, Mushlin PS: Catecholamine induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology 100:434-439, 2004.)*

oxygen supply because arterial blood carries much more oxygen than portal venous blood does.[10]

Splanchnic Reservoir

The vasculature of the splanchnic organs can retain up to 15% of the total blood volume rendering it the largest physiologic reservoir of whole blood in the human body.[11] Generally, 20% of blood volume resides in arterial vessels, 10% in capillaries, and 70% in veins.[10] Therefore, the effects of neuroendocrine, pharmacologic, and pathophysiologic factors on venous capacitance and resistance vessels determine, to a large extent, the instantaneous volume within the splanchnic reservoir. For example, increases in resistance within the postsinusoidal veins of the liver can promote transudation of plasma into lymphatic vessels and the peritoneal cavity (through Glisson's capsule) and thereby result in edema, ascites, and hypovolemia. Indeed, minor changes in hepatic venous pressure can have major consequences on the effective circulatory volume.[3,12]

Regulation of Hepatic Blood Flow

Intrinsic and extrinsic mechanisms play important roles in the regulation of hepatic blood flow. Intrinsic mechanisms—such as the hepatic arterial buffer response (HABR), metabolic control, and pressure-flow autoregulation—work independently of neurohumoral factors.

Intrinsic Regulation

Hepatic Arterial Buffer Response The HABR is the most important intrinsic mechanism. With an intact HABR, changes in portal venous flow cause reciprocal changes in hepatic arterial flow.[13] That is, when portal venous flow decreases, the HABR compensates by increasing hepatic arterial flow, and vice versa. The HABR mechanism involves the synthesis and washout of adenosine (i.e., a vasodilator) from periportal regions.[14] When portal venous flow decreases, adenosine accumulates in the periportal regions, which lowers arteriolar resistance and thereby increases hepatic arterial flow. Conversely, when portal venous flow increases, adenosine is washed out of the periportal regions, which increases arteriolar resistance and decreases hepatic arterial flow. At a maximum, the HABR can double hepatic arterial flow. Therefore, it cannot fully restore hepatic blood flow when portal venous flow falls by more than 50%. Yet because hepatic arterial blood carries more oxygen than portal venous blood does, the HABR more effectively preserves hepatic oxygen supply than hepatic blood flow does. Various disorders (e.g., endotoxemia, splanchnic hypoperfusion) may decrease or even abolish the HABR and render the liver more vulnerable to hypoxic injury.[15,16]

Metabolic Control Many constituents of blood affect hepatic arterial and portal venous blood flow.[17] Decreases in oxygen tension or the pH of portal venous blood typically lead to increases in hepatic arterial flow. Postprandial hyperosmolarity increases hepatic arterial and portal venous flow.[17] The underlying metabolic and respiratory status (e.g., hypercapnia, alkalosis, arterial hypoxemia) also modulates the distribution of blood flow within the liver.

Pressure-Flow Autoregulation Pressure-flow autoregulation enables tissue-specific regulators to govern organ blood flow despite fluctuations in systemic arterial pressure. The mechanism involves myogenic responses of vascular smooth muscle to stretch. For example, a hypertensive episode increases transmural pressure, thereby stretching arterial smooth muscle. The resultant increase in myogenic tone (i.e., vasoconstriction) prevents the increases in organ blood flow that would otherwise occur. Conversely, transient hypotension lowers transmural pressure and myogenic tone (i.e., vasodilation), which helps sustain organ perfusion during systemic hypotension.

The hepatic artery exhibits pressure-flow autoregulation in metabolically active liver (postprandial) but not in the fasting state, which is the most prevalent status of surgical patients.[18] Pressure-flow autoregulation is nonexistent in the portal circulation. Thus, decreases in systemic blood pressure—as often occur during anesthesia—typically lead to proportional decreases in portal venous flow.[19,20] Bottom line, pressure-flow autoregulation has little if any role as an intraoperative regulator of hepatic blood flow, with the possible exception of emergency surgery on patients in the fed state.

Extrinsic Regulation

Neural Control Fibers of the vagus, phrenic, and splanchnic nerves (postganglionic sympathetic fibers from T6 through T11) enter the liver at the hilum; they course through the liver alongside the afferent hepatic blood vessels and bile ducts. The fibers form an intercommunicating plexus that innervates the terminal arterioles and venules. The sympathetic nervous system is an important regulator of the splanchnic vasculature. When sympathetic tone decreases, splanchnic reservoir volume increases. On the other hand, sympathoadrenal stimulation translocates blood volume from the splanchnic reservoir to the central circulation. Within seconds of splanchnic nerve stimulation, up to 80% of the hepatic blood volume (400 to 500 mL) could be transferred to the central circulation in dogs.[10,21] Vagal stimulation alters the tone of the presinusoidal sphincters[22]; the net effect is a redistribution of intrahepatic blood flow without changing total hepatic blood flow.

Humoral Control The hepatic arterial bed has α_1-, α_2-, and β_2-adrenergic receptors, whereas the portal vein has only α-receptors (Fig. 17-12).[3,23] Direct injection of epinephrine into the hepatic artery induces a biphasic response: vasoconstriction (α-receptor stimulation) followed by vasodilation (β-receptor stimulation). However, an injection of epinephrine into the portal vein causes only vasoconstriction (α-receptor response). The dopamine released during sympathoadrenal activation has weak vasoactive effects in the liver that are dwarfed by those of epinephrine and norepinephrine.[17,23]

Glucagon induces dose-dependent relaxation of hepatic arterial smooth muscle and blocks the effects of physiologic vasoconstrictors on the hepatic artery.[24] By contrast, angiotensin II constricts the hepatic arterial and portal venous beds.[25] Pharmacologic doses of angiotensin II can cause hepatic blood flow to plummet because of its ability to markedly decrease both mesenteric arterial and portal venous flow. Vasopressin, on the other hand, elevates splanchnic arterial resistance, but it lowers portal venous resistance. Because of its vascular profile, vasopressin may have efficacy in treating portal hypertension.[26]

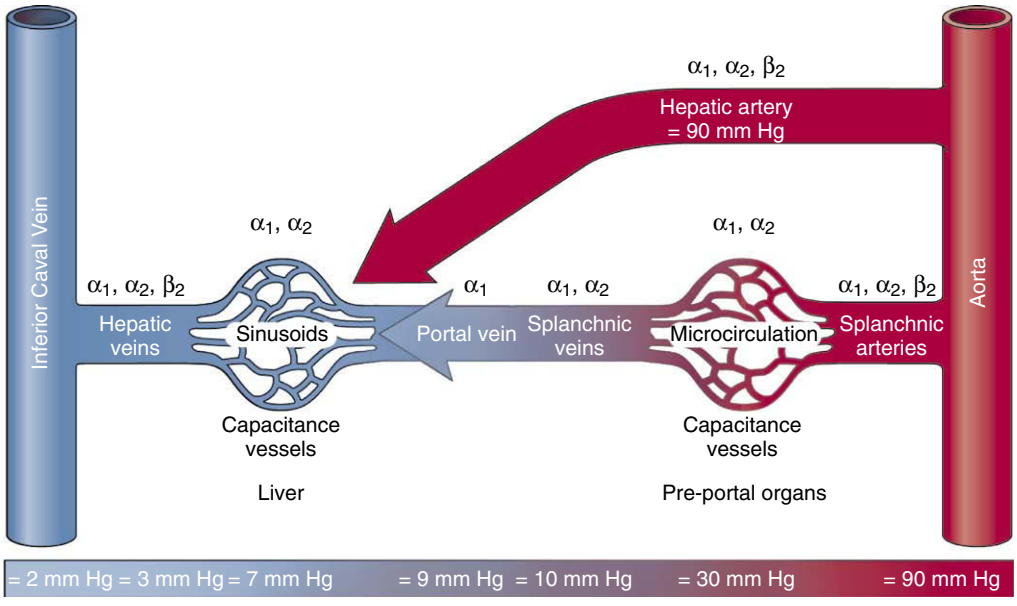

Figure 17-12 Adrenoceptor subtypes (α_1, α_2, β_2) and intravascular pressure within the splanchnic circulation. The splanchnic arteries represent the arterial supply to all preportal organs; the splanchnic veins represent the pooled venous blood from all these organs. *(Redrawn with permission from Gelman S, Mushlin PS: Catecholamine induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology 100:434-439, 2004.)*

Biochemical and Physiologic Functions of the Liver

Intermediary Metabolism

Protein Metabolism

The liver plays a central role in the production and breakdown of amino acids, peptides, and proteins. Hepatocytes metabolize amino acids to keto acids, glutamine, and ammonia via transamination and oxidative deamination reactions. The Krebs-Henseleit cycle is the major pathway for removing ammonia and other nitrogenous wastes from the body. This pathway captures nitrogen in the form of urea. Thus, with a failing liver (and normal renal function), blood urea nitrogen remains low whereas nitrogenous wastes such as ammonia accumulate in blood and other tissues.

Liver-derived proteins have an impact on every organ in the body. Such proteins include procoagulants, hormones, cytokines, chemokines, acute-phase reactants, and transport proteins. The most abundant of them is albumin, which accounts for roughly 15% of the liver's total protein production. Healthy adults produce 12 to 15 g of albumin every day; the total-body pool of albumin has a mass of about 500 g.[27] Factors that modulate the synthesis of albumin include plasma oncotic pressure,[28] dietary amino acids,[29] and hormones.[30] The main regulator of intravascular albumin is oncotic pressure. Albumin binds to and transports a wide variety of substances—free fatty acids, unconjugated bilirubin, hormones, xenobiotics, and metals. In this way, albumin affects the biologic activity and clearance of a multiplicity of substances.

α-Fetoprotein (AFP) resembles albumin both genetically and functionally. AFP comes mainly from the yolk sac, hepatocytes, and enterocytes.[31] During fetal and neonatal life, AFP has importance as a transport protein and is the major determinant of plasma oncotic pressure. By the postpartum age of 1 year, albumin has largely replaced AFP. Thus, an elevation in AFP in later life typically reflects hepatocellular proliferation as a result of hepatic injury, inflammation, or neoplasia. For example, elevations in AFP occur in nearly all patients with acute hepatitis.[32] However, large, progressive increases in plasma AFP—levels above 400 ng/mL that continue to rise with time—are a hallmark feature of hepatocellular carcinoma (HCC).

Carbohydrate Metabolism

The liver is the epicenter of carbohydrate metabolism. It is an important homeostatic regulator of blood glucose.[33-35] Whether the liver is a net producer or consumer of glucose is dependent on many factors, including the neuroendocrine milieu (i.e., insulin, catecholamines, glucagon)[36-41] and glucose concentration in sinusoidal blood.[9,42-44] The severity of hyperglycemia or hypoglycemia also influences the rate of glucose uptake or release by hepatocytes. Hepatic production of glucose is inversely related to glycogen production by the liver. In the fed state, hepatocytes polymerize glucose and store it as glycogen; in the unfed state, hepatocytes depolymerize glycogen to glucose and release it into the bloodstream. Regulation of glycogen metabolism involves two rate-limiting enzymes: (1) glycogen synthase, which catalyzes the synthesis of glycogen from monomers of uridine diphosphate (UDP) glucose, and (2) glycogen phosphorylase, which catalyzes the sequential cleavage of glycogen to monomers of glucose 1-phosphate.

When liver glycogen stores are depleted—as is likely after prolonged exercise or a 24-hour fast—the body depends on hepatic gluconeogenesis to replenish blood glucose. Substrates for gluconeogenesis include (1) lactate; (2) glycerol from the hydrolysis of triglycerides; and (3) glucogenic amino acids such as alanine and glutamine, which are derived from protein catabolism in skeletal muscle.[9,45] Endocrine modulators of gluconeogenesis include glucagon, catecholamines, and insulin. Both glucagon and catecholamines stimulate gluconeogenesis. Glucagon works via cyclic adenosine monophosphate (cAMP)-dependent protein kinase, and catecholamines use both cAMP-dependent and cAMP-independent mechanisms.[46,47] By contrast, insulin inhibits gluconeogenesis, and it blocks the stimulatory effects of catecholamines and glucagon on this pathway.

Lipid Metabolism

The liver produces, takes up, retains, releases, and oxidizes fatty acids in accord with nutritional and endocrine influences.[48-52] Dietary fatty acids absorbed in the small intestines reach the liver via blood and the lymphatics, mainly in the form of chylomicrons. When replete with glycogen, hepatocytes convert glucose to fatty acids—and may store them as triglycerides (fat). Thus, the major sources of intrahepatic fatty acids include (1) free fatty acids extracted from blood, (2) de novo lipogenesis, (3) hydrolysis of cytoplasmic triglycerides, and (4) hepatocellular uptake and metabolism of blood-borne lipoproteins.[48]

Esterification and β-oxidation pathways have pivotal roles in the hepatic disposition of fatty acids. Esterification of glycerol and fatty acids produces triglycerides—the main storage form of free fatty acids. The liver may either retain triglycerides or package them into lipoproteins, primarily very-low-density lipoproteins (VLDLs), for transport to other tissues. Free fatty acids regulate VLDL production, but endocrine and nutritional factors govern VLDL secretion.[48,53] β-Oxidation is the pathway of fatty acid catabolism. Glucagon activates this pathway, whereas insulin inhibits it. β-Oxidation sequentially cleaves fatty acids to yield monomers of acetyl coenzyme A (acetyl CoA).

Acetyl CoA is at the epicenter of intermediary metabolism. It is a building block for lipids (triglycerides, phospholipids, cholesterol) and a product of the oxidative breakdown of fatty acids and carbohydrates. Mitochondria oxidize acetyl groups to yield carbon dioxide, water, and adenosine triphosphate (ATP). If more acetyl CoA is produced than the tricarboxylic acid cycle can handle, the surplus is metabolized to ketone bodies—namely, acetoacetate, β-hydroxybutyrate, and acetone.[9] Hepatocytes cannot extract energy from ketones, however, because they lack ketoacyl CoA transferase (acetoacetate:succinyl-CoA transferase). This enzyme exists in all organs except the liver.[8] Thus, ketones are an important extrahepatic energy source during catabolic states, most notably starvation. Insulin modulates ketogenesis by inhibiting lipolysis in adipocytes.[54] Stress-induced ketosis is typically a self-limited process because ketones stimulate the release of insulin, thereby limiting availability of substrate (fatty acid) for hepatic ketogenesis.[45] Without insulin, this feedback loop is nonexistent and diabetic ketoacidosis may ensue.[9]

Bile Metabolism and the Enterohepatic Circulation

Daily production of bile ranges from 600 to 800 mL. Although bile contains many different substances (e.g., electrolytes, organic

anions, lipids), bile salts (also called bile acids) account for about 85% of biliary solids.[55] Bile salts are natural ionic detergents with important roles in absorption, transport, and secretion of lipids.[56,57] They activate lipases (bile acid dependent), promote micelle formation, and enable the intestinal uptake of fat-soluble vitamins, cholesterol, and other lipids. Bile salts also facilitate the excretion of numerous lipophilic substances, including exogenous compounds such as xenobiotics and endogenous molecules such as bilirubin, cholesterol, and amphipathic steroid hormonal derivatives.

Bile salts are end products of cholesterol synthesis and regulators of lipid metabolism. Bile salts produce their regulatory effects by binding to and activating farnesoid X receptor (FXR). When activated, hormone nuclear receptors (such as FXR) are transferred from cytoplasm to the nucleus; they bind to hormone response elements on DNA to induce either expression or transrepression of specific gene products. An important effect of FXR activation is to decrease the transcription of cholesterol 7α-hydroxylase (CYP7A1), which catalyzes the rate-limiting step in the conversion of cholesterol to bile salts. Bile salts modulate plasma lipid levels by regulating the expression of lipoprotein receptors that enable hepatocytes to remove lipoprotein cholesterol from the bloodstream.[56,58]

The body avidly conserves bile salts by recycling them around 20 to 30 times daily in the enterohepatic circulation. Hepatocellular transport proteins (transporters) regulate both the uptake (from sinusoids) and secretion (into canalicular spaces) of bile salts. Activated transporters on canalicular surfaces overcome large osmotic gradients to pump bile salts into the intrahepatic bile ducts. As bile flows through the ductular collecting system, it is diluted and alkalinized.[55] After reaching the common hepatic bile duct, bile either enters the cystic duct (for storage in the gallbladder) or passes through the common bile duct into the small intestine. The terminal ileum (using sodium-dependent bile salt transporters) reclaims 95% of the bile salts, which it returns to the liver in the portal circulation. These bile salts are taken up by transporters on the sinusoidal surfaces of hepatocellular plasma membranes. Sometime later, the same bile salts are again pumped into the canalicular space, thereby completing one cycle of the enterohepatic circulation. Of note, opioid analgesics (μ-agonists) can disrupt bile flow by inducing intense, painful spasms of the bile ducts and sphincter of Oddi.[59] Fortunately, this opioid effect is usually rapidly reversed by medications, including glucagon, opioid antagonists (naloxone), smooth muscle relaxants (nitroglycerin), antimuscarinic drugs (atropine), and volatile anesthetics.

Coagulation

Coagulants and Procoagulants

Hepatocytes make most of the procoagulants, with notable exceptions such as factors III (tissue thromboplastin), IV (calcium), and VIII (von Willebrand factor). The liver also makes protein regulators of coagulation and the fibrinolytic pathways. Such regulators include protein S, protein C, protein Z, plasminogen activator inhibitor (PAI), and antithrombin III. To further elaborate, protein Z facilitates the degradation of factor Xa, and protein S is a cofactor of activated protein C that inactivates factor VIIIa-Va complexes; a deficiency of protein S increases the risk for venous thrombosis. PAI-1 is an indirect inhibitor of fibrinolysis. This serine protease inhibitor blocks the effects of plasminogen activators, such as urokinase or tissue plasminogen activator, to convert plasminogen to plasmin; a deficiency of PAI increases the risk for uncontrolled fibrinolysis. To summarize, hepatocytes make most of the procoagulants and many proteins that modulate the consumption of clotting factor.[60]

Vitamin K Cofactor and γ-Carboxylation

The vitamin K–dependent proteins include factors II, VII, IX, and X and proteins C and S. These proteins undergo a vitamin K–dependent, post-translational modification; the process involves carboxylation of the γ-position of glutamate residues at the amino terminus and produces the amino acid carboxyglutamate.[45,61] This modification (called γ-carboxylation) enables procoagulants to form complexes with calcium or other divalent cations.[62] Thus, γ-carboxylated procoagulants are primed for activation to serine proteases (e.g., via extrahepatic phospholipids) and for participation in the clotting cascade.[45,63]

The γ-carboxylation pathway holds the key to understanding how warfarin exerts its anticoagulant effect. γ-Carboxylation occurs in two stages.[63] The first involves γ-carboxylation of precursor proteins via vitamin K–dependent γ-carboxylase and the oxidation of vitamin K cofactor (naphthol hydroquinone) to 2,3-epoxide vitamin K. The second stage regenerates the vitamin K cofactor via reactions catalyzed by vitamin K 2,3-epoxide reductase.[64-67] Warfarin targets the second stage. It inhibits vitamin K epoxide reductase and thereby traps vitamin K in the epoxide form. This eventually depletes vitamin K cofactor and shuts down the γ-carboxylation pathway. Warfarin inhibits γ-carboxylation almost immediately after its absorption from the gut, but its anticoagulant effect takes longer than 1 day to develop. This disparity reflects low clearance of the prothrombin complex from the circulation (i.e., half-life of about 14 hours) and the insensitivity of the prothrombin time (PT) to falling blood levels of procoagulants. As a rule, the PT stays in the normal range until the prothrombin complex in blood is at least 70% below the lower limit of normal.

Therapeutic use of vitamin K may help uncover the cause of an unexplained prolongation in PT. For example, PT abnormalities caused by malnutrition or warfarin are correctable with enteral or parenteral vitamin K therapy. When PT abnormalities result from malabsorption syndromes, parenteral vitamin K is superior to oral therapy. However, if PT abnormalities result from liver dysfunction (acute hepatitis, cirrhosis), vitamin K will be ineffective because the problem is not a deficiency of vitamin K but rather a deficiency of hepatic procoagulants.

Erythropoiesis and Erythrocytosis

Heme Metabolism

The liver is the main site of erythrocyte production during fetal life through early infancy. As the bone marrow matures, hematopoietic cells begin to disappear from the liver; occasionally, however, they persist or reappear as a result of disorders such as congenital hemolytic anemias, bone marrow failure, or myeloproliferative diseases. Most of the protein in erythrocytes exists as globulin chains of hemoglobin; the heme portion of hemoglobin contains protoporphyrin IX and ferrous iron. In healthy adults, 20% of the total heme production is from liver; the rest comes

from bone marrow. The biochemical pathways that make heme are similar in the two organs.[64,68,69]

Heme synthesis begins with the condensation of glycine and succinyl CoA to produce 5-aminolevulinic acid (ALA). This reaction, catalyzed by ALA synthase, is the rate-limiting step in the heme pathway. Heme inhibits ALA synthase and thereby regulates its own synthesis. ALA is made in mitochondria; it diffuses into the cytoplasm and encounters ALA dehydratase. This enzyme joins two ALA molecules together to form porphobilinogen (PBG). PBG molecules are positioned in a linear arrangement by PBG deaminase to form hydroxymethylbilane (HMB). HMB is transformed to uroporphyrinogen III, which is the precursor of coproporphyrinogen III. The latter is taken up by mitochondria and converted—via coproporphyrinogen oxidase and protoporphyrin oxidase—to protoporphyrin IX. In the final step of the pathway, ferrochelatase catalyzes the formation of a complex of ferrous iron and protoporphyrin IX to produce heme.

Porphyrias Porphyrinogens exposed to O_2 are readily oxidized to the corresponding porphyrins. Accumulation of porphyrins in tissues leads to porphyrias. Porphyrias are rare, genetic diseases characterized by aberrations in heme production. Patients with these disorders are typically asymptomatic until some stressor (exogenous or endogenous) induces a porphyric crisis.[70] The clinical syndrome includes recurrent, dramatic, and occasionally fatal neurologic reactions, accompanied by abdominal pain (90%) and dark urine (80%).

Acute intermittent porphyria (AIP) is the most common porphyria. Its prevalence in the general population is about 1 in 10,000, but it may reach 1 in 500 in psychiatric patients. AIP has a fivefold higher frequency in women than in men.

Substances known to trigger porphyric crises include sex hormones, glucocorticoids, cigarette smoke, and various medications, most notably barbiturates and other CYP inducers.[57,71] Recall that induction of CYP entails the production of CYP hemoproteins. When heme is inserted into these newly minted CYP proteins, intracellular levels of heme decline.[71-74] The result is less feedback inhibition of ALA synthetase and therefore more ALA production.[75] Defects in the heme pathway cause the precursors of heme—made proximal to the site of the block—to accumulate. Consider, for example, patients with a genetic deficiency of PBG deaminase; when ALA synthetase activity increases, so too do tissue levels of ALA and PBG. These heme precursors, which have chemical structures similar to the inhibitory neurotransmitter γ-aminobutyric acid (GABA), are likely contributors to the neurotoxic effects of porphyrias.

Bilirubin Metabolism

The main source of serum bilirubin is heme metabolism. Healthy adults make about 300 mg of bilirubin daily, 80% of which is derived from phagocytosis of senescent erythrocytes by macrophages in the spleen, liver, and bone marrow. These reticuloendothelial cells extract protein from hemoglobin and convert heme to bilirubin.[57] The first step is rate limiting. Heme oxygenase (HO), with O_2 as a substrate, oxidatively cleaves the porphyrin macrocycle of heme to yield biliverdin-IXα, carbon monoxide (CO), and free divalent iron in equimolar amounts.

Most of the endogenous CO production is derived from HO reactions. Thus, the biologic importance of HO may extend beyond the breakdown of heme. To clarify, CO has many physiologic roles, including regulation of vascular tone (vasodilator), platelet aggregation, vascular myocyte proliferation, and neurotransmitter release.[76] Furthermore, CO exerts cytoprotective, antiapoptotic, and antioxidant effects in organs throughout the body.[77,78] Biliverdin also confers protection from oxidative stress[77]; it is rapidly converted to bilirubin by cytoplasmic reductases.[79]

After release from reticuloendothelial cells, bilirubin becomes tightly bound to plasma albumin. Hepatocytes avidly extract this bilirubin from albumin. They produce conjugates of bilirubin (through the action of glucuronic acid and bilirubin UDP-glucuronosyltransferase) and secrete these conjugates into canalicular bile. Although the gut excretes most of this bilirubin, a small amount returns to the liver in the enterohepatic circulation. Thus, the bloodstream normally has a modicum of bilirubin conjugates, which arrive directly via the enterohepatic circulation or indirectly from the bile ducts and lymphatics.

Endocrine Physiology

The liver is the largest gland in human beings and it plays important roles in the metabolism of hormones and hormone-binding proteins.[60] Hepatocytes produce a wide variety of endocrine substances, including angiotensinogen, thrombopoietin, and insulin-like growth factor I (IGF-I).[80] They take up thyroxine (T_4), the major product of the thyroid gland, and may activate it to triiodothyronine (T_3) or inactivate it. The liver inactivates many other hormones, including aldosterone, antidiuretic hormone, estrogens, androgens, and insulin. Nearly half of the insulin released by the pancreas may not reach the systemic circulation because of hepatic degradation.[81]

Immune and Inflammatory Responses

The liver is the largest reticuloendothelial organ in the human body. Hepatic macrophages (Kupffer cells) account for nearly 10% of the total liver mass. Kupffer cells protect and defend the body against foreign intrusions. Before splanchnic venous blood enters the central circulation, it is filtered by Kupffer cells, which degrade toxins, process antigens, and phagocytose bacteria.[82] In addition, Kupffer cells are important modulators of inflammation[83]: they attenuate inflammatory responses by removing inciting substances from the bloodstream; but they can also induce and intensify inflammation by producing and releasing proinflammatory mediators and recruiting neutrophils to the liver.[83] Among these mediators are various cytokines, chemokines, leukotrienes, proteases, nitro-radicals, and reduced oxygen species. If not properly controlled, these same mediators can induce or aggravate injuries to parenchymal and other liver cells.[83-87] For example, endothelial cells of the sinusoids and terminal hepatic veins—because of their low glutathione content—are highly vulnerable to oxidative stress and drug-induced vascular injury.[88] Stellate cells reside mainly in the perisinusoidal spaces and are the liver's major source of matrix deposition. When activated by oxidative stress or toxic chemicals, stellate cells may be transformed to collagen-synthesizing myofibroblasts, which can cause extensive fibrosis of the liver (e.g., methotrexate-induced hepatic fibrosis).

Xenobiotic (Drug) Metabolism and Excretion

Although xenobiotics may be in tissues through the body (lung, liver, kidney, intestines, skin); the liver is the epicenter for biotransformation reactions. Most oral medications contain lipophilic regions that increase their gastrointestinal absorption, membrane penetrability, and biologic activity. Lipid solubility also lowers drug excretion rates and increases drug retention by the body. Whereas the kidney readily excretes most small polar molecules, it cannot efficiently eliminate most lipophilic substances. Lipophilic molecules often bind tightly to plasma proteins, thereby evading glomerular filtration. Even when the glomerulus filters such molecules, the renal tubules usually reabsorb them. The liver, on the other hand, chemically transforms drugs in ways that increase their water solubility. Generally, hepatic biotransformations not only increase drug excretion but also inactivate or attenuate the biologic activity of drugs. However, xenobiotic metabolism produces reactive chemicals that cause severe liver damage (either directly or indirectly by immune sensitization, as is probably involved in the pathogenesis of halothane hepatitis).[89-91]

Pathways of Drug Metabolism

The myriad chemical reactions that hepatocytes use to eliminate drugs fit into three broad categories (or phases). Phase 1 metabolism uses CYP and mixed-function oxidases to increase the polarity of drugs. Phase 2 metabolism increases the polarity of drugs (or their metabolites) by conjugating them with endogenous water-soluble substrates. Phase 3 elimination uses energy-dependent transporters to excrete drugs into canalicular bile. The hepatic clearance of drugs involves at least one of these phases.[90,92,93]

Phase 1 Metabolism Phase 1 reactions (e.g., oxidations, reductions, hydrolysis) convert drugs to more polar compounds by inserting polar groups (e.g., OH, NH_2, SH) or removing nonpolar groups. Generally, the products of phase 1 metabolism are more readily excreted in bile or urine than their precursors are. Such products may also be substrates for phase 2 conjugations.

Microsomal Oxidases and Cytochrome P450. More than 90% of drug biotransformations involve microsomal oxidases and hemoproteins of the CYP gene superfamily. The human liver has more than 20 different CYP isozymes[90-94] that mediate redox reactions in diverse pathways, including steroid, lipid, and bile salt metabolism. Zone 3 (centrilobular) has the highest total CYP content. In fact, the acinar location of specific isozymes of CYP may clarify relationships between drug metabolism and liver injury.[90] For example, centrilobular necrosis is the classic acetaminophen-induced injury; the probable explanation is that CYP2E—the CYP isoform involved in acetaminophen metabolism—is localized in zone 3.

CYP reactions generate metabolites that are highly reactive and potentially toxic. In brief, the CYP reaction cycle begins with oxygen binding to heme iron; this oxygen becomes activated after receiving an electron from a flavoprotein reductase—NADPH: hemoprotein oxidoreductase (CYP).[91-94] Insertion of activated oxygen into lipophilic molecules (e.g., xenobiotics) produces substrates for mixed-function oxidase reactions. These oxidases transfer a singlet oxygen atom from O_2 to the target molecule; another substrate (e.g., NADPH) simultaneously delivers electrons that reduce the residual oxygen singlet, thereby enabling its incorporation into water. To summarize, oxidases promote the formation of highly active chemicals, including reduced oxygen species and free radical intermediates, which can cause or aggravate liver injury.[95]

A plethora of substances—drugs, nutritional supplements, contaminants, insecticides—alter hepatic microsomal drug metabolism.[91] Some chemicals, such as phenobarbital and phenytoin, induce many different CYP isoforms. Other chemicals are much more selective.[91-94] For example, alcohol selectively induces CYP2E1 and CYP3A4[90,96]; smoke from cigarettes or cannabis increases CYP1A2[97]; isoniazid increases CYP2E1; and rifampicin and hypericum (active ingredient of St. John's wort) selectively induce CYP3A4.[98] With long-term use, CYP inducers often increase their own metabolism while stimulating alkaline phosphatase (AP) and γ-glutamyl transpeptidase (GGTP) production. The latter effect which occurs via activation of transcriptional regulators of nuclear orphan receptors as part of the "hepatic adaptation" to chronic drug administration.[90]

Molecular Genetic Basis of CYP Induction. Studies of CYP3A4—the predominant CYP isoform in human liver—have clarified the molecular genetics of CYP induction.[99] For example, rifampin, a potent inducer of CYP3A4, activates the pregnane X receptor (PXR), which is a transcriptional regulator of the orphan nuclear receptor family. PXR works in concert with another xenobiotic nuclear receptor, constitutive androstane receptor (CAR), to coordinate protective hepatic responses to potentially toxic stimuli.[100] Activated PXR and the analogous CAR bind to cognate nucleotide sequences upstream of the CYP3A4 structural gene within a "xenobiotic responsive enhancer module" (XREM).[99,101] Such binding activates the CYP3A4 promoter (downstream) and thereby induces the synthesis of mRNA for CYP3A4 protein. Similar mechanisms are involved in regulating other CYP pathways.[99,101]

Phase 2 Metabolism Phase 2 reactions conjugate xenobiotics (or their metabolites) with endogenous hydrophilic molecules such as glucuronic acid, acetate, sulfates, amino acids, and glutathione.[90,102] Many conjugations involve glucuronic acid and UDP-glucuronosyltransferase. Other conjugations are catalyzed by sulfatases, glutathione-*S*-transferases, acetyl-*N*-transferases, or amino acid *N*-transferases. When compared with their precursors, conjugated xenobiotics are usually less efficacious, less toxic, more hydrophilic, and more readily excreted in bile or urine.

Phase 3 Elimination Phase 3 reactions involve specific molecular transporters—known as ATP-binding cassette (ABC) transport proteins—that facilitate the excretion of xenobiotics and endogenous compounds. These proteins use ATP hydrolysis to drive molecular transport. Major ABC transport proteins include cystic fibrosis transmembrane conductance regulator (CFTR), canalicular copper transporters, and multidrug resistance protein (MDR). MDR-1 (formerly called P-glycoprotein) resides on the canalicular surfaces of hepatocytes and enables biliary excretion of cationic compounds, including anticancer drugs.[103,104]

Another family of ABC proteins—multidrug resistance–related protein (MRP)—excretes conjugated molecules. MRP-1, located on the lateral surfaces of hepatocytes, can transport drug conjugates into the sinusoids. MRP-2 (formerly, canalicular mul-

tispecific organic anion transporter [cMOAT]), on the canalicular surfaces of hepatocytes, secretes conjugates of drugs and endogenous wastes (e.g., bilirubin diglucuronide, glutathionyl-leukotriene conjugates) into canalicular bile. Thus, dysfunction of ABC transport proteins can disrupt the flow of bile, impair excretion of xenobiotics and endogenous compounds, and induce cholestatic liver injury.[105,106]

Determinants of Drug Metabolism

Dose-related responses to drugs often vary considerably within individuals and populations. Much of this variability is due to the heterogeneity of drug disposition and metabolism, which is mainly influenced by genetic and environmental factors. Genetics control the expression of CYP isozymes. Environmental factors (e.g., drugs, other chemicals) modify genetic expression and thereby alter drug biotransformation.[90,92,93] Numerous conditions and disorders are capable of altering the production of CYP proteins.[107] For example, obesity, fasting, and diabetes mellitus may lead to upregulation of CYP2E1.[90,92,93] On the other hand, conditions that may result in downregulation of CYP include systemic inflammatory disorders,[108] fever,[109] nitrogen-free solutions,[110] nitrogen-rich solutions,[111] and hepatic cirrhosis.[92,93] Hypothyroidism and hypopituitarism may selectively downregulate CYP1A and CYP3A4, respectively.[92,93]

Pharmacokinetics

Perfusion models of drug elimination generally focus on three major parameters: intrinsic hepatic clearance, hepatic blood flow, and protein binding. The intrinsic hepatic clearance of a drug divided by hepatic blood flow is the drug's extraction ratio (ER); ER provides a measure of the relative efficiency with which the liver extracts or eliminates a given drug.[112-116] Box 17-1 shows a compilation of drugs with high and low ERs.[116] Such information enables general rules to be made about pharmacologic categories and intrinsic clearances. For example, hepatocytes are efficient extractors of calcium channel blockers, β-adrenoceptor blockers (except atenolol), opioid analgesics, tricyclic antidepressants, and organic nitrates. On the other hand, the liver poorly extracts warfarin, aspirin, alcohol, and many anticonvulsants. For low-ER drugs, hepatic elimination rates are capacity limited. Such rates often change when protein binding or intrinsic hepatic clearance changes, but they are insensitive to fluctuations in hepatic blood flow. For high-ER drugs, hepatic elimination rates are flow dependent. These elimination rates are highly dependent on and directly related to liver blood flow; they are unaffected by changes in either protein binding or the activity of drug-metabolizing enzymes (Table 17-1).

Box 17-1 Drugs that are Efficiently Versus Poorly Extracted from Blood Flowing through the Liver

Efficiently Extracted Drugs	Poorly Extracted Drugs
Amitriptyline	Acetaminophen
Desipramine	Amobarbital
Imipramine	Antipyrine
Labetalol	Aspirin
Lidocaine	Clindamycin
Meperidine	Diazepam
Metoprolol	Digitoxin
Morphine	Ethanol
Nortriptyline	Hexobarbital
Pentazocine	Phenobarbital
Propoxyphene	Phenytoin
Propranolol	Tolbutamide
Ranitidine	Valproic acid
Verapamil	Warfarin
Zidovudine	

Evaluation of the Liver

Clinical Assessment

The only clues to liver disease may be mild, nonspecific symptoms, such as loss of appetite, easy fatigability, malaise, altered sleep patterns, or subtle changes in personality. The history addresses major risk factors for liver disease: (1) alcoholism; (2) illicit drug use; (3) sexual promiscuity; (4) blood transfusions; (5) occupational exposure to hepatotoxins; (6) prior bouts of jaundice, particularly after anesthesia; and (7) genetic diseases such as hemochromatosis, α_1-antitrypsin (α_1-AT) deficiency, and Wilson's disease. Clinical findings consistent with liver disease include nonspecific symptoms (as just mentioned), pruritus, abdominal pain, indigestion, and changes in urine or stool color. The physical examination focuses on stigmata of advanced liver disease, such as icterus, jaundice, ascites, spider angiomas, xanthelasma, encephalopathy, palmar erythema, and fetor hepaticus.

Table 17-1 Flow-Dependent Versus Capacity-Limited Elimination of Drugs by the Liver

Type of Hepatic Elimination	Extraction Ratio (ER)	Rate of Hepatic Drug Metabolism
Flow-dependent elimination	*High ER*: At clinically relevant concentrations, most of the drug in the afferent hepatic blood is eliminated on first pass through the liver	*Rapid*: Because drugs with a high ER are metabolized so rapidly, their hepatic clearances roughly equal their rates of transport to the liver (i.e., hepatic blood flow)
Capacity-limited elimination (also referred to as dose-dependent, nonlinear, saturable, or zero-order elimination)	*Low ER*: Hepatic elimination of these drugs is determined by their plasma concentration	*Slow*: When the capacity of the liver to eliminate a drug is less than the dosing rate, a steady state is unachievable; plasma levels of drug will continue to rise unless the dosing rate is decreased. Drug clearance has no real meaning in such settings

Standard Laboratory Tests

Standard test panels used to evaluate hepatobiliary status are often called "liver function tests" (Table 17-2).[27,117] To be precise, this terminology is a misnomer because none of the tests measure any specific liver function. Instead, they point to broad categories of hepatobiliary pathology: hepatitis, hepatobiliary dysfunction, or insufficient protein synthesis. These categories include large subsets of diseases—for example, all possible causes of hepatitis.

Detection of Hepatocellular Injury

Aminotransferases Hepatocellular injury is the usual cause of elevated serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), formerly named serum glutamic-pyruvic transaminase (SGPT) and serum glutamic-oxaloacetic transaminase (SGOT), respectively. Both enzymes are involved in gluconeogenesis. They catalyze the transfer of an amine group to α-ketoglutarate to yield glutamate and either pyruvate (via ALT) or oxaloacetate (via AST). ALT is mainly a cytoplasmic liver enzyme. In contrast, cytoplasmic and mitochondrial isozymes of AST are found in most extrahepatic tissues, including the heart, skeletal muscle, brain, kidney, pancreas, adipose tissue, and blood. It is rare to encounter concomitant elevations in AST and ALT when the liver is normal and disease free. In those rare instances, the elevations in AST and ALT levels would most likely result from muscle injury.[117]

Elevated ALT and AST levels are sometimes described in qualitative terms: mild (100 to 249 IU/L), moderate (250 to 999 IU/L), large (1000 to 1999 IU/L), and extreme (>2000 IU/L). Mild elevations in AST and ALT may arise from any disorder that injures hepatocytes. Common causes include steatosis, medications, alcohol consumption, hemochromatosis, cholestasis, chronic viral hepatitis, neoplasms, and cirrhosis. Moderate ALT and AST elevations are characteristic of acute viral hepatitis, drug-induced liver injury, and flare-ups of chronic liver disease (e.g., viral hepatitis, steatohepatitis). Large elevations often reflect acute hepatitis superimposed on chronic active liver disease. Extreme elevations signify massive hepatic necrosis. Typical causes are fulminant viral hepatitis, severe drug-induced liver injury (e.g., from acetaminophen), shock liver or hypoxic hepatitis, and in rare instances, autoimmune hepatitis or acute biliary obstruction.[117]

Ratios of aminotransferases may hold keys to the diagnosis of hepatic disorders. For example, when both AST and ALT are elevated, an AST-to-ALT ratio higher than 4 is characteristic of Wilson's disease, ratios between 2 and 4 are typical of alcoholic liver disease, and a ratio below 1 suggests nonalcoholic steatohepatitis (without cirrhosis). When elevations of AST and ALT are mild, ratios above 2 are consistent with alcoholic liver disease or cirrhosis of any etiology.[117] If the ratio is elevated and ALT is normal, the elevation in AST is most likely from an extrahepatic source of AST.

Although concomitant elevations in AST and ALT are a reliable indicator of hepatocellular injury, aminotransferase levels by themselves seldom reveal the extent of liver damage. For instance, patients with florid liver failure can have normal enzyme levels—when the liver damage is so extensive that too few viable hepatocytes remain to bring about increases in ALT or AST. In addition, chronic, smoldering liver diseases such as hepatitis C can destroy the liver, slowly and silently, without overt increases in ALT or AST.

Lactate Dehydrogenase Elevated serum lactate dehydrogenase (LDH) levels may reflect hepatocellular injury, extrahepatic disorders, or both. Extreme increases signify massive liver damage, which may result from fulminant viral hepatitis, drug-induced liver failure, or hypoxic hepatitis. Prolonged, concurrent elevations in LDH and AP suggest malignant infiltration of the liver. Notable extrahepatic disorders that cause moderate elevations in LDH include hemolysis, rhabdomyolysis, tumor necrosis, renal

Table 17-2 Liver Blood Tests and the Differential Diagnosis of Hepatobiliary Disorders

	Predominant Abnormality		
Blood Test	**Bilirubin Overload (Hemolysis)**	**Hepatocellular Injury**	**Cholestasis**
Aminotransferases	Normal	Increased—may be normal or decreased in advanced stages	Normal—may be increased in advanced stages
Serum albumin	Normal	Decreased—may be normal in acute fulminant hepatic failure	Normal—may be decreased in advanced stages
Prothrombin time*	Normal	Prolonged	Normal—may be prolonged in advanced stages
Bilirubin (main form present)	Unconjugated (also mild increase in conjugates)	Conjugated	Conjugated
Alkaline phosphatase	Normal	Normal—may be increased by hepatic infiltrative disease	Increased
γ-Glutamyl transpeptidase 5′-nucleotidase	Normal	Normal	Increased
Blood urea nitrogen	Normal—may be increased by renal dysfunction	Normal—may be decreased by severe liver disease and normal kidney function	Normal
BSP/ICG (dye)	Normal	Retention of dye	Normal or retention of dye

*Used interchangeably with the international normalized ratio.
BSP/ICG, bromsulphalein/indocyanine green.

infarction, acute cerebrovascular accident, and myocardial infarction. Such disorders cause more pronounced LDH elevations in patients with acute liver injury (e.g., severe preeclampsia). An elevation in LDH that is solely due to hepatocellular injury is typically accompanied by elevations in AST and ALT. Thus, LDH rarely yields information about liver injury beyond that already provided by AST and ALT.[27,117]

Glutathione-S-Transferase Glutathione-*S*-transferase (GST) is a sensitive and specific test for some patterns of drug-induced liver injury.[118] The enzyme has a brief plasma half-life (90 minutes) and is released rapidly into the circulation after hepatocellular injury. Thus, serial GST measurements can reveal the time course of hepatic injury, from its onset to its resolution. In contrast to AST and ALT, which reside in acinar zone 1, GST localizes in acinar zone 3 (centrilobular region).[119] The zone contains the hepatocyte population with the highest susceptibility to injury from hypoxia or reactive drug metabolites. Accordingly, GST would be more sensitive than AST or ALT as a marker of centrilobular necrosis in its incipient stages.

Assessment of Hepatic Protein Synthesis

Serum Albumin Serum albumin yields information about hepatocellular function (i.e., protein synthesis) and is used to evaluate chronic liver disease—with notable caveats. First, hypoalbuminemia has many causes besides low rates of albumin synthesis; examples include renal losses of albumin, increased albumin catabolism, expansion of plasma volume, and maldistribution of total body albumin. In fact, the total body mass of albumin (in the exchangeable pool) is often normal in patients with liver cirrhosis, ascites, and hypoalbuminemia.[120] Second, there is no clear relationship between serum albumin and the instantaneous rate of albumin synthesis because plasma albumin has a half-life of nearly 3 weeks. Thus, if hepatic protein synthesis came to an abrupt and permanent halt, this change would not be reflected as a decrease in the serum albumin level for at least a few days.

Prothrombin Time When compared with albumin, liver-derived procoagulants have short half-lives, which range from 4 hours for factor VII to 4 days for fibrinogen. Plasma levels of such procoagulants start to descend shortly after the liver begins to fail. PT (or the international normalized ratio [INR]) is widely used to evaluate and monitor patients with acute liver dysfunction. A prolonged PT secondary to liver failure generally reflects a low blood level of factor VIIa, which has the shortest plasma half-life of hepatic coagulant factors.[117] Besides diagnostic utility, PT is used as a prognostic indicator. It is a common parameter of models or algorithms designed to facilitate timely, yet correct decisions about the need for liver transplantation. In this regard, PT is of value for patients with drug-induced liver failure[121] or those with active liver disease and a surgical condition that needs immediate attention.[122]

Detection of Cholestatic Disorders

Alkaline Phosphatase Serum AP is used to screen for disorders of the liver or biliary tree, including hepatitis, malignancies, and cholestatic diseases. Because AP isoenzymes exist in plasma membranes throughout the body, AP lacks specificity for hepatobiliary disease.[117] Mild, transient increases in AP may occur in up to a third of those subjected to routine laboratory testing. Major sources of AP include bone, intestine, kidney, leukocytes, placenta (third trimester of gestation), and neoplasms. Increased metabolic activity in one or more of these tissues may lead to elevations in AP. Increased serum AP usually reflects increased production or release of AP rather than decreased clearance of AP. For example, fatty meals increase serum AP by inducing the release of AP isozymes from the plasma membranes of enterocytes in the small bowel.

The AP elevations in cholestatic disorders may reflect the action of bile salt on the plasma membranes of hepatocytes. Serum AP may remain normal for a couple of days after the onset of biliary obstruction—not increasing until hepatocytes produce (and release) more AP. Because it has a half-life of nearly a week, serum AP may remain elevated for days after bile flow is restored.[117] Extreme increases in AP suggest (1) a major block in biliary flow as a result of disorders such as primary biliary cirrhosis and choledocholithiasis or (2) a hepatic malignancy (primary or metastatic) that is compressing small intrahepatic bile ducts. Multifocal blocks of intrahepatic ducts can increase serum AP without increasing serum bilirubin. On the other hand, AP may be normal despite extensive hepatic metastasis or large duct obstruction. The bottom line is that serum AP does not reliably distinguish between bile duct obstruction (intrahepatic or extrahepatic) and malignant infiltration of the liver.[117]

Identifying the Source of Increased Alkaline Phosphatase. Finding the origin of an elevated AP level seldom requires more than a history, physical examination, and imaging studies. The history helps sort through the usual extrahepatic sources of increased AP, including (1) normal bone, especially during puberty and growth spurts; (2) placenta, mainly in the third trimester of pregnancy; (3) bone disorders such as Paget's disease, rickets, and osteomalacia; and (4) intestines (see Table 17-2).

5′-Nucleotidase and γ-Glutamyl Transpeptidase Laboratory tests used to distinguish between hepatic and extrahepatic sources of AP include 5′-nucleotidase (5′-NT) or leucine aminopeptidase (LAP) and GGTP. With regard to 5′-NT, it is as sensitive as AP in detecting hepatobiliary disorders, and it is a much more specific test for such disorders. Although 5′-NT exists in many tissues—placenta, bone, brain, intestine, heart, blood vessels, endocrine pancreas—most of the serum 5′-NT is derived from the hepatobiliary tree. One explanation is that release of 5′-NT from the plasma membranes of hepatocytes requires the detergent action of bile salts. Changes in AP that are secondary to hepatobiliary disease are usually followed by commensurate changes in 5′-NT.[117]

However, increases in AP and 5′-NT have differing time courses—most notably during onset and resolution of biliary disease. For example, shortly after bile flow becomes disrupted, serum AP and GGTP begin to increase in tandem, whereas 5′-NT may not change for days.[117] In this regard, GGTP is preferable to 5′-NT because it more closely tracks AP. However, GGTP also has disadvantages. First, it is an inducible microsomal enzyme (e.g., by alcohol, anticonvulsants, warfarin), which may confound interpretation of elevations in serum GGTP. Second, GGTP is less specific than 5′-NT for hepatobiliary disease. Serum GGTP may come from many extrahepatic sites, including the kidney, spleen, pancreas, heart, lung, and brain. Bone, however, contains very little GGTP. Thus, serum GGTP may be used to distinguish between osseous and hepatobiliary sources of AP.[117]

Serum Bilirubin Serum bilirubin is the most widely used test for hepatic excretory dysfunction. Total bilirubin is normally below 1 mg/dL, but up to 10% of healthy adults have higher levels, mainly in the form of unconjugated bilirubin. This is usually a benign condition (Gilbert's syndrome) that reflects genetically low levels of bilirubin UDP-glucuronosyltransferase. Serum bilirubin levels above 4 mg/dL are discernible on physical examination as jaundice—a yellowish discoloration of body tissues. With natural light, scleral icterus is detectable at bilirubin levels of or below 3 mg/dL.[117,123]

Conjugated hyperbilirubinemia generally results from one or two fundamental problems: (1) flow of bile is blocked within the hepatobiliary tree, or (2) hepatocytes produce more bilirubin conjugates than they can efficiently transport into the canalicular space. Massive hemolysis causes unconjugated and conjugated hyperbilirubinemia. Increases in unconjugated bilirubin occur because hepatocytes are presented with more bilirubin than they can conjugate. Increases in conjugated bilirubin result because hepatocytes conjugate bilirubin faster than hepatocellular transporters can secrete them into canalicular bile. Bilirubinuria usually reflects conjugated hyperbilirubinemia. The kidneys readily excrete bilirubin conjugates, whereas unconjugated bilirubin, which binds tightly to plasma albumin, is neither filtered nor excreted by normal kidneys.[117,123]

Testing for Specific Diseases

Targeted testing is used to identify specific hepatic or biliary diseases. Examples include (1) serologic testing to identify viral, microbial, and autoimmune causes[124,125]; (2) genetic testing to diagnose heritable metabolic disorders; and (3) tumor marker assays to detect hepatic malignancies.

Identifying viral markers—antibodies, antigens, and genetic material—is the key for diagnosis of hepatitis from hepatotropic viruses (A, B, C, E) and herpesviruses such as cytomegalovirus and Epstein-Barr virus.[32] Patients infected with hepatitis B or C virus often have markers of immune pathology, including anti–smooth muscle antibodies, antinuclear antibodies, and mixed cryoglobulins.[32,126] Autoimmune hepatitis and hepatitis A virus infection are commonly associated with anti–asialoglycoprotein receptor antibodies. Autoimmune cholangitides have distinctive serologic profiles.[127] For example, antimitochondrial antibodies usually develop with primary biliary cirrhosis[125,128-130] but are typically absent with primary sclerosing cholangitis. Characteristic findings of primary sclerosing cholangitis include anti–smooth muscle and antinuclear antibodies.[125,131,132]

Special tests are needed to confirm diagnoses of inborn errors of metabolism. Tests for α_1-AT deficiency include serum α_1-AT and phenotype analysis. Hallmarks of Wilson's disease (an autosomal recessive disorder of copper overload) include low serum ceruloplasmin and high urinary copper levels, particularly after the administration of penicillamine.

Markers for hepatic malignancy include AFP and des-γ-carboxylated prothrombin.[60,133-136] As a test for HCC, plasma AFP is 90% specific; its sensitivity ranges from 50% to 90%, depending on population subgroups.[60] Another test for HCC is the plasma γ-carboxylated prothrombin level. HCC cells usually make procoagulants without γ-carboxylating them.[133,136] High levels of des-γ-carboxylated, vitamin K–dependent proteins occur in up to 91% of patients with HCC. In at least two thirds of these patients, levels are above 300 ng/mL, which far exceeds the typical value in patients with liver cirrhosis or acute hepatitis. After surgical removal of HCC, levels of des-γ-carboxylated factors begin to decrease. Subsequent increases suggest tumor recurrence.[137]

Quantitative Liver Tests

Total hepatocellular mass can be estimated by measuring the clearance of a substance that is avidly extracted by the liver, such as bromsulphalein, indocyanine green (ICG), and rose Bengal.[138] However, these are rough estimations because clearance is subject to many influences and unknowns. For example, hepatic clearance of highly extracted substances (1) changes in direct proportion to variations in liver blood flow, (2) is altered by extrahepatic retention or clearance of the substance, and (3) may be affected by anomalous hepatobiliary function.

Drug-metabolizing capacity of the liver can be measured by several methods, such as caffeine clearance, galactose elimination capacity, aminopyrine breath test, antipyrine clearance, and monoethylglycinexylidide (MEGX).[117,139-142] Techniques are available for measuring caffeine clearance noninvasively.[140] For example, subjects take an oral dose of caffeine (150 to 300 mg), and caffeine metabolites in saliva are measured for up to 24 hours. MEGX is an invasive method that has recently gained popularity for measuring liver blood flow in critically ill patients. Fifteen minutes after an intravenous injection of lidocaine (1 mg/kg), a blood sample is obtained and assayed for MEGX, the major metabolite of lidocaine. Currently, quantitative tests are in the domain of research tools; when compared with standard liver chemistry tests, they are expensive and time consuming, with no compelling evidence of being superior, either diagnostically or prognostically.

Measurement of Liver Blood Flow

Methods used to measure hepatic blood flow fall into three broad categories: clearance techniques, indicator dilution techniques, and direct measurements.

Clearance Techniques

Extraction methods using the indirect Fick principle closely approximate hepatic blood flow and are valid for substances with high intrinsic hepatic clearance and total body clearance. Such substances include ICG dye, propranolol, lidocaine, and colloidal particles. Constant infusion of ICG is among the most reliable extraction methods. Hepatocytes take up nearly all of the ICG infused and excrete it unchanged in bile. Clearance methods may also be based on the ability of Kupffer cells to avidly phagocytose radiolabeled colloidal particles such as gold 198. After injecting such particles, one can compute the area under the initial curve (of radioactivity versus time) to obtain a valid measurement of hepatic blood flow—assuming that the reticuloendothelial system is functioning normally.[143] The bottom line is that severe liver disease renders clearance techniques unreliable because of indeterminable disease-related effects on liver blood flow and hepatic capacity to eliminate substances. The latter decreases in direct proportion to the loss of hepatocellular mass.[144]

Indicator Dilution Techniques

Unlike clearance methods, measurements of liver blood flow by indicator dilution techniques are unaffected by liver disease. After

a radiolabeled indicator (e.g., iodinated albumin) is injected into the spleen, hepatic flow is computed from indicator dilution curves. These curves are obtained by continuous sampling from one of the hepatic veins or by external γ-scintillation counting. For this technique to be valid, the indicator must be uniformly mixed upon injection and resistant to hepatic clearance.[145]

Direct Measurements

Electromagnetic flow probes provide direct measurements of blood flow through the hepatic artery or portal vein.[146] However, the surgical procedures used to implant the probes can themselves alter hepatic blood flow. Thus, the probes are often left in place after the implantation procedure, and blood flow is subsequently measured via telemetry.

Radiologic and Endoscopic Methods

Radiologic and endoscopic techniques offer therapeutic alternatives to surgery. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTHC) are used to evaluate hepatobiliary disorders. ERCP provides intraductal access to the biliary tree and pancreatic duct. Its main use is to diagnose and treat extrahepatic biliary disorders such as gallstones, tumors, inflammatory strictures, or postsurgical anastomotic leaks. Successful endoscopic papillotomy can obviate surgical removal of stones in the common bile duct.[147] ERCP is less invasive than surgery, but it too can lead to major complications, most notably pancreatitis. Radionuclide and ultrasonic scanning detect space-occupying lesions of the hepatobiliary tree.[147,148] PTHC provides a means of evaluating the intrahepatic bile ducts of patients with unexplained intrahepatic cholestasis or jaundice. Dilated intrahepatic bile ducts on PTHC indicate mechanical blockage of intrahepatic ducts. When no such blockage exists, the most likely cause of intrahepatic cholestasis is hepatic parenchymal disease.

Esophagogastroscopy is an important technique for evaluating and treating submucosal varices in patients with cirrhosis and portal hypertension. Splenoportography provides information about the status of the splenic and portal veins. Portal venography, via three-dimensional computed tomography with a multidetector row technique, can render vascular maps that are superior to those obtained by classic angiography.[149] Such vascular maps show the extent and location of portosystemic collateral communications, which may include abnormalities in gastric, paraumbilical, and abdominal wall veins; esophageal varices; and splenorenal and gastrorenal shunts.

Hepatic Pathophysiology

Mechanisms of Cell Death

Necrosis

Hepatocellular death often results from hypoxia or anoxia. Hypoxia decreases intracellular ATP. This stimulates breakdown of glycogen and anaerobic glycolysis, which raises lactic acid levels and lowers intracellular pH. Sudden, precipitous decreases in ATP initiate a series of events that may culminate in hepatocellular necrosis. Such events include abrupt failure of the energy-dependent ion pumps that regulate intracellular fluid and electrolyte homeostasis. Plasma membranes become dysfunctional, and hepatocytes swell rapidly and then rupture and extrude their contents. This cellular debris, which contains hepatic enzymes and reactive chemicals such as aldehydes, lipid peroxides, and eicosanoids, incites an inflammatory response. The release of cytokines and chemoattractants recruits circulating neutrophils to the liver and augments the hepatic inflammation.

Apoptosis

In contrast to necrosis, apoptosis is an energy-dependent process. Most agents of liver disease (toxins, viruses, oxidants) can activate proapoptotic intracellular signaling pathways or proapoptotic cell-surface receptors such as Fas, tumor necrosis factor receptor (TNFR), and other members of the TNFR superfamily.

Apoptosis has several ultrastructural hallmarks, including (1) a shrunken cell and nucleus; (2) condensed, marginated nuclear chromatin; (3) blebs on the plasma membrane; and (4) apoptotic bodies, which consist of membrane-bound cellular fragments and intact organelles. Epithelial and mesenchymal cells engulf the apoptotic bodies, and their lysosomes digest and recycle the contents of apoptotic bodies, such as intact mitochondria and nucleic acids. Apoptosis and necrosis may be related events at opposite ends of a spectrum of overlapping morphologic and mechanistic cell death processes.[85,150]

Oxidative Stress and the Glutathione System

Hepatocytes continuously produce reactive oxygen species. During aerobic metabolism, mitochondria work nonstop transferring electrons from reduced substrates to molecular oxygen (O_2). This process involves the tetravalent reduction of O_2; the reduced oxygen atoms are incorporated into water. However, small amounts of O_2 undergo univalent or divalent reductions that give rise to superoxide and hydrogen peroxide.[151] Nonparenchymal cells in the liver—Kupffer cells, endothelial cells, polymorphonuclear leukocytes, macrophages—can also generate large amounts of reduced oxygen species and nitro-radicals.[86,152-154]

In health, hepatocytes have many ways to keep oxidant concentrations within a safe range (<1 μM).[90,155] Their defenses against oxidative injury include (1) micronutrients, such as vitamins C and E; (2) metal-sequestering proteins, such as ferritin; (3) enzymes that dispose of reactive oxygen species, such as catalase and superoxide dismutase; (4) enzymes that detoxify lipid peroxides, such as glutathione peroxidase; and (5) thiol-rich peptides, most notably glutathione (γ-glutamyl-cysteine-glycine). Glutathione is the single most important intracellular antioxidant.[150,156-160]

The liver is the main site of glutathione synthesis. Accordingly, hepatocytes have high cytoplasmic concentrations of glutathione, ranging from 5 to 10 mmol/L.[90] Glutathione serves as a cofactor for major enzymes involved in the elimination of oxidants—notably glutathione peroxidase and thiol/disulfide exchangers. Glutathione peroxidase plays a key role as a detoxifier of organic peroxides and free radicals. Another enzyme, GST, helps eliminate toxic electrophiles by attaching them to the free thiol of reduced glutathione (GSH). GSH also participates in

nonenzymatic detoxification reactions, which yield oxidized glutathione (GSSG) and mixed disulfides of glutathione and protein.

GSH is the predominant form of glutathione under normal conditions; it is the main determinant of the redox capacity of hepatocytes. Oxidative stress decreases GSH levels by converting GSH to GSSG. The enzyme glutathione reductase helps regenerate GSH and restore the normal redox state. NADPH is the cofactor for glutathione reductase, and its synthesis requires ATP. High-energy phosphates are also needed to actively transport GSH into mitochondria. Disruption of this transport process leads to mitochondrial damage.[150] Thus, conditions that decrease ATP render hepatocytes more susceptible to oxidative injury.[156] Adverse conditions, such as malnutrition, hepatitis, and chemically induced liver injury, can quickly exhaust hepatic GSH. In such instances, therapy with thiol-rich agents such as cysteamine (mercaptoethylamine) or *N*-acetylcysteine may be lifesaving. The beneficial effects of thiol-rich agents relate to their ability to increase glutathione synthesis, replenish the intracellular GSH pool, and restore the capacity of the liver to combat oxidative stress.[156]

Ischemia-Reperfusion Injury

Ischemia-reperfusion (I/R) injury results from both hypoxia during an ischemic episode and cytotoxic events during reperfusion.[153,161-163] Reperfusion induces the production of highly reactive chemicals that can cause necrosis or apoptosis, such as superoxide, hydrogen peroxide, and hydroxyl radicals. After relatively brief ischemic intervals, most of the injury is due to reperfusion. With more prolonged ischemia, hypoxia accounts for a larger fraction of the overall injury from I/R.

Role of Xanthine Dehydrogenase/Xanthine Oxidase

The liver and intestines contain large amounts of xanthine dehydrogenase/xanthine oxidase (XDH/XO).[164] XDH catalyzes the rate-limiting step in nucleic acid degradation by using nicotinamide adenine dinucleotide (NAD) rather than O_2 as the electron acceptor. Thus, no oxygen radicals are produced in healthy tissue. However, ischemic conditions transform XDH to XO. Because XO reactions involve O_2, they produce free radicals. During reperfusion, XO-derived oxidants increase the production and release of leukotriene B_4 and platelet-activating factor, which promote neutrophil adherence and migration. When activated, neutrophils can wreak havoc on the microvascular circulation as they release proteases and physically disrupt the endothelial barrier. Liver injury, independent of the cause, imperils extrahepatic tissue because damaged hepatocytes spew out XO and other inflammatory mediators.[151,155,165-170] XO enters the bloodstream and binds to vascular endothelial cells in many organs.[164,171-173] Endothelial cells produce superoxide, which reacts with nitric oxide (NO·) to form peroxynitrite ($OONO^-$).[152,174] Peroxynitrite is intensely reactive and can increase the severity of injuries to local and remote tissues.

Therapeutic agents that may confer protection from I/R-induced injury include (1) antioxidants, (2) oxygen radical scavengers such as superoxide dismutase and dimethyl sulfoxide, (3) inhibitors of leukocyte adherence and migration,[175-177] and (4) inhibitors of XO. For example, laboratory studies show that allopurinol (inhibits XO) treatment before induction of I/R prevents the usual I/R-related increases in microvascular permeability and epithelial cell necrosis.[175,178]

Hepatic Injury from Liver Transplantation

Preservation Injury. The University of Wisconsin solution protects the donor liver for about 1 day. However, use of this solution for more than 24 hours may lead to microcirculatory disturbances (e.g., leukocyte and platelet adhesion) after liver transplantation. The adverse effects result from (1) depletion of hepatocellular antioxidants over time and (2) biochemical changes that lead to a profusion of reactive oxidants during reperfusion of the transplanted liver.[178] Hypothermic preservation solutions also induce apoptotic changes in endothelial cells, which may engineer their destruction after graft implantation.

The pathogenesis of I/R injury is complex.[179-182] Characteristic events include (1) Kupffer cell activation[183,184]; (2) XO formation[170,185]; (3) profusion of oxidants—superoxide, nitric oxide, peroxynitrite, and hydroxyl radicals; (4) release of proinflammatory cytokines into the bloodstream[186]; and (5) destruction of endothelial cells.[187-190] Flushing grafts (after storage in preservation solution) with various rinse solutions can decrease Kupffer cell activation, reduce endothelial cell damage, and improve graft survival.[191] Contents of the Carolina rinse solution include antioxidants, adenosine, a calcium channel blocker, energy substrates, and glycine, at pH 6.5. Another way to improve graft survival might be through downregulation of Kupffer cells with agents such as pentoxifylline, gadolinium, or calcium channel blockers.

Bacterial, Viral, and Immune Injury

Endotoxins are lipopolysaccharide complexes of the outer membranes of gram-negative bacteria. All endotoxins have a common lipid component (lipid A), a core R antigen, and two variable polysaccharide regions—bacterial strain-specific O-antigen. Lipid A binds to high-density lipoproteins in blood and other tissues, and it mediates the biologic actions common to endotoxins. Endotoxins bind more extensively to Kupffer cells than to hepatic parenchyma. They can induce hepatocellular or cholestatic injury directly or indirectly via activation of Kupffer cells and release of proinflammatory mediators (e.g., cytokines, eicosanoids).[192]

Like endotoxins, viruses may cause direct and indirect hepatocellular injury. Hepatotropic viruses and some herpesviruses can induce cytokine production leading to lymphocyte- or macrophage-dependent cytotoxicity. Antigens on hepatocellular membranes may be primary targets of cell-mediated injury. Antibodies to such antigens are often increased selectively in patients with autoimmune hepatitis and primary biliary cirrhosis. Other potential antigenic focuses for cell-mediated cytotoxicity include liver-specific lipoproteins and hepatic lectins, which may be targets in hepatitis B and other liver diseases.

Drug-Induced Liver Injury

Adverse reactions to drugs fall into two general categories: dose-related toxicity and idiosyncratic drug-induced injury. The former is predictable and develops in all individuals with escalation of the drug dose. The latter is a rare event, inducible with subclinical doses of the drug; it is most likely an immune-mediated injury that occurs in just a tiny fraction of those receiving the drug.

Although obvious differences exist between the two categories of drug reactions, there are also remarkable similarities. For example, both categories involve covalent binding of drugs (or their metabolites) to endogenous macromolecules. Such binding can lead to inactivation of important enzymes, depletion of intracellular antioxidants, and peroxidation of membrane lipids. The body's response to such molecular perturbations determines whether a drug-induced injury is categorized as dose related or idiosyncratic. When drug-induced subcellular damage induces immune sensitization, re-exposure to even a very low dose of the sensitizing drug can cause severe liver injury (e.g., halothane hepatitis).

The hepatotoxic effects of drugs and environmental substances usually involve CYP-mediated production of oxidants such as reduced oxygen species, carbon-based radicals, and nitro-radicals. Examples include (1) carbon tetrachloride metabolism via CYP, which yields trichloromethyl radical—a highly toxic intermediate that induces centrilobular necrosis; and (2) metabolism of nitrofurantoin or other aromatic compounds, which generates free radical intermediates that induce hepatic injury. Similar to CYP of the smooth endoplasmic reticulum, mitochondrial electron transporters transform xenobiotics to reactive metabolites. For example, the nitro-radicals that form during cocaine or nitrofurantoin metabolism[90,150] reduce O_2 via flavoprotein reductases to yield superoxide and other oxidizing species. Redox cycling, as occurs with anthracycline chemotherapeutics and imidazole antimicrobials, is yet another source of toxic oxidizing species.

Oxidant formation during drug metabolism contributes to or causes liver injury by weakening the antioxidant defenses of hepatocytes. For example, acetaminophen and bromobenzene cause dose-related decreases in hepatocellular GSH, rendering the liver increasingly susceptible to necrosis.[193,194] This increases the likelihood of oxidants damaging (1) proteins and enzymes, (2) phospholipids in membranes, and (3) nucleotides via activation of proteases, phospholipases, and endonucleases. Oxidative stress can also induce pathologic increases in cytosolic Ca^{2+} by increasing Ca^{2+} uptake by hepatocytes while inducing release of Ca^{2+} from the endoplasmic reticulum or mitochondria. These events can lead to apoptosis, necrosis, or both.

Occasionally, conjugation reactions generate hepatotoxic by-products.[95,195-197] For example, phase 2 metabolism of carboxylate drugs yields acyl glucuronides. These molecules can induce hepatic injury as they covalently bind to and inactivate nucleophiles, thiol-rich proteins, and nucleic acids. Intermediates of phase 2 metabolism can also deplete hepatocellular antioxidants and promote the formation of neoantigens and autoantigens, which trigger immune-mediated liver injury after re-exposure to the inciting agent.

Drug-Induced Apoptosis

Apoptotic pathways can be activated by drug-induced mitochondrial injury.[150,156,198] The sequence of events may be as follows: (1) drug metabolism produces oxidants and depletes GSH; (2) oxidants induce mitochondrial injury, with release of cytochrome *c* and initiation of the mitochondrial membrane permeability transition; and (3) caspase is activated and triggers apoptosis.[198-201] The hepatic pathology of Reye's syndrome may involve mitochondrial injury from drugs such as tetracycline, aspirin, valproic acid, and nucleoside analogs (e.g., zidovudine).[201] Mitochondrial enzymes are likely to be pathogenic targets of *N*-acetyl-*p*-benzoquinone imine (NAPQI), the acetaminophen metabolite associated with hepatocellular necrosis. Whether mitochondrial injury will lead to apoptosis or necrosis depends on the intracellular energy state and the severity of the injury.[150]

Immunopathology

Immunopathology often underlies idiosyncratic adverse drug reactions, such as halothane hepatitis. The clinical syndrome often includes fever, rash, lymphadenopathy, eosinophilia, and inflammatory infiltrates in the liver. Characteristically, the syndrome has a delayed onset after the first-ever dose of the drug, but with subsequent exposures, the onset is more rapid and the syndrome is more severe. Immunopathologic events may include (1) production of antibodies that lyse hepatocytes via molecular mimicry with host enzymes[202]; (2) antibody-dependent cell-mediated immunity, as with diclofenac[203]; (3) dysregulation of the immune system; and (4) drug-induced autoimmunity.[204,205]

According to the altered-antigen concept, drugs (or their metabolites) chemically react with and thereby modify certain intracellular proteins, which gives rise to neoantigens or antigenic drug-protein adducts. The pathogenesis of halothane hepatitis, for example, seems to involve trifluoroacylated (TFA) adducts that form during exposure to halogenated anesthetics.[206] Patients recovering from halothane-induced liver injury typically have circulating antibodies directed against TFA protein adducts. Yet the specificity and pathogenicity of these antibodies remain unclear[206] because such antibodies develop in most individuals after halothane anesthesia without liver injury developing.

Dysregulation of the immune system contributes to the formation of autoantibodies. Some lack tissue specificity (e.g., antinuclear and smooth muscle antibodies). Others are organ specific, such as the liver-kidney microsomal (LKM) antibodies that target microsomal enzymes; halothane hepatitis is associated with LKM antibodies directed against CYP2E1.

Alcohol-Induced Disease

Alcoholism (five or more drinks per day) induces several patterns of liver injury—notably steatosis (fatty liver), alcoholic hepatitis, and cirrhosis. Steatosis develops in nearly everyone who drinks excessively, but cirrhosis develops in only 10% to 20% of these individuals.[207] When compared with the general population, people with alcoholic liver disease have a higher prevalence of health-related disorders—malnutrition, immune incompetence, fluid and electrolyte imbalance. Such individuals are at increased risk for postoperative morbidity secondary to hemorrhage, sepsis, or cardiopulmonary decompensation (from alcoholic or cirrhotic cardiomyopathy).[208]

Characteristic pathologic findings of alcoholic liver disease include (1) acetaldehyde-induced subcellular injury, (2) abnormalities in metabolism, (3) microvascular hypoxia, (4) increased oxygen and nitrogen radical formation, and (5) depletion of antioxidant defenses. Alcohol metabolism is integral to the pathology of alcoholic liver disease.[209-213] The rate-limiting step in ethanol metabolism is catalyzed by alcohol dehydrogenase (ADH). This polymorphic zinc metalloenzyme has more than 20 different isozymes.[207,214] Although it exists in many tissues, hepatocytes metabolize more than 95% of the alcohol consumed. Genetic polymorphisms of ADH explain much of the variability in the relationship between ethanol consumption (dose) and liver

disease (response).[214-216] For example, the risk of alcoholic cirrhosis developing relates directly to polymorphisms at the *ADH2* gene locus (i.e., high frequency of the B allele).[217]

Cytoplasmic ADH is the main enzyme involved in oxidizing ethanol to acetaldehyde. Liver disease can decrease ADH activity and cause a higher proportion of ethanol oxidation to occur in peroxisomes via catalase and in endoplasmic reticulum via ethanol-induced CYP2E1.[218] Liver disease can also depress the mitochondrial enzyme aldehyde dehydrogenase (ALDH), which catalyzes the conversion (detoxification) of acetaldehyde to acetate.[215,218,219] Deficiency of ALDH leads to increased acetaldehyde levels in blood and other tissues, which amplifies the intrahepatic and extrahepatic toxicity of alcohol.[220] Acetaldehyde may induce tissue injury by (1) forming adducts with intracellular proteins,[221] (2) binding to GSH, (3) depleting intracellular antioxidant levels,[222] (4) altering plasma membranes to increase superoxide formation,[223] (5) promoting collagen production and fibroplasia,[224] and (6) stimulating the release of chemotactic agents that recruit neutrophils to the liver.[224,225]

Similarities in Hepatic Injuries from Hypoxia and Ethanol

Hepatic injuries from hypoxic episodes and ingestion of ethanol are similar in many respects. Hypoxic injuries promote the release of proinflammatory cytokines, tumor necrosis factor-α, and interleukin-1 and interleukin-6. These signaling molecules lead to increased expression of adhesion molecules, decreased velocity and increased margination of neutrophils, increased platelet adherence, and decreased hepatic blood flow.[226] Hepatoenteric ischemia releases cytokines and XO and leads to activation of complement. This intensifies the local inflammation and can induce systemic inflammatory responses, with subsequent pulmonary and cardiac injury.[151,155,227,228]

Similarly, alcoholic-related liver injury promotes the release of proinflammatory mediators.[229] Alcohol ingestion can markedly increase hepatic oxygen consumption, which would predispose to hypoxic injury.[207,230] The earliest manifestations of ethanol-induced injury occur in acinar zone 3 (the centrilobular region), which has the highest ADH content and the lowest oxygen supply.[90,218,231,232] Prolonged ethanol use leads to increased expression of NO· synthase, increased NO· production, and vasodilation. Such effects of alcohol on the nitric oxide pathway may represent a microcirculatory adaptive response to ethanol-induced vasoconstriction.[233,234]

The notion that ethanol imposes a significant oxidant stress on hepatocytes is strongly supported by indirect (lipid peroxidation)[235] and direct (electron spin resonance data) evidence.[236] Alcohol stimulates the formation of oxidants, and it disrupts antioxidant defenses. It increases consumption of antioxidants while decreasing their production.[213,235] Alcohol use can decrease the genetic expression of antioxidant enzymes because of its intrinsic hepatotoxicity or because of alcohol-related disorders such as malnutrition.[237] The major source of oxidant formation after alcohol intake is alcohol metabolism rather than alcohol itself. Metabolism of alcohol via microsomal and cytosolic oxidases yields superoxide and other reactive compounds. Such chemicals activate inflammatory cells (including Kupffer cells),[238] which stimulates nitric oxide synthetase (iNOS) and peroxynitrite formation[174] in hepatic parenchymal cells, macrophages, endothelial cells, and vascular myocytes.[239] Peroxynitrite—the product of NO· and $O_2{\cdot}^-$ reactions—is an unstable anion that oxidizes and nitrosylates lipids and proteins.[240-244] When intracellular antioxidants such as GSH and α-tocopherol are depleted, alcohol metabolism becomes a more potent inducer of liver injury.[235,245]

Cirrhosis and Portal Hypertension

Liver cirrhosis is a chronic disease in which normal hepatic tissue is replaced by fibrotic scar tissue or regenerative nodules. With advancing hepatic fibrosis, there is progressive loss of liver function, and portal hypertension develops. The usual causes of cirrhosis include alcoholism, viral hepatitis, and metabolic disorders, although many other causes exist.[246] Although the etiologic agents of cirrhosis are disparate, the patterns of injury that they produce are remarkably similar and thus suggest similar or overlapping subsets of molecular mechanisms. Alcoholic- and nonalcoholic steatohepatitis–related cirrhosis involves similar patterns of fibrosis despite its overtly disparate etiologic categories.

Characteristic precirrhotic changes include cellular hypertrophy, fatty metamorphosis, mitochondrial and lysosomal dysfunction, disrupted transport and storage processes, and increased fibroplasia. When hepatocytes throughout the liver are encircled by fibrous tissue, cirrhosis exists.[247]

Cirrhosis can develop and progress in an insidious, indolent manner. Indeed, this is prerequisite for cryptogenic cirrhosis and is characteristic of hepatitis C–induced cirrhosis, which often remains clinically silent while destroying up to 70% of the liver. What enables this to happen is the substantial physiologic reserve of the liver, which compensates well for the progressive loss of viable hepatocytes. The development of portal hypertension signals depletion of this reserve. Signs and symptoms include anorexia, nausea, vomiting, abdominal discomfort, weakness, jaundice, spider nevi, ascites, splenomegaly, a firm liver, esophageal varices, and portosystemic encephalopathy. The pathophysiology of this condition can lead to sudden, devastating complications, including massive hemorrhage, sepsis, renal failure, coma, and death.[248]

Pulmonary Dysfunction

Advanced liver disease often leads to pulmonary dysfunction. Hypoxemia may develop for several reasons.[249,250] First, extensive intrapulmonary arteriovenous communications are common. Second, impairment of hypoxic pulmonary vasoconstriction develops secondary to disease-related increases in endogenous vasodilators such as NO·, glucagon, adenosine, and prostacyclin. Third, erythrocyte 2,3-diphosphoglycerate levels often increase and shift the oxyhemoglobin dissociation curve rightward. Fourth, ventilation-perfusion mismatching occurs because of atelectasis or restrictive pulmonary pathophysiology—secondary to ascites or pleural effusions. In fact, hepatic hydrothorax (pleural effusions without coexisting cardiopulmonary disease) develops in up to 10% of patients with cirrhosis.[251]

Renal Dysfunction

Renal dysfunction typically develops in patients with cirrhosis and portal hypertension. The glomerular filtration rate (GFR) steadily decreases, and the renal tubules avidly retain sodium, with no overt glomerular or tubular injury. Urinalysis is unremarkable except for a low urine sodium level.

The main causes of acute renal failure (ARF) in this patient population are prerenal failure and acute tubular necrosis (ATN).

Prerenal failure usually results from hypovolemia, sepsis, or type 1 hepatorenal syndrome (HRS).[252-255] End-stage liver disease puts patients at high risk for systemic hypovolemia as a result of (1) the formation of profuse ascites, (2) aggressive diuretic therapy, (3) gastrointestinal hemorrhage, and (4) sequestration of blood in the splanchnic vasculature. Therapy for prerenal ARF is straightforward; all that is generally required is to restore renal blood flow.

The most common cause of ATN is prerenal ARF—when it is protracted and severe enough to cause ischemic renal tubular injury. Other causes of ATN include nephrotoxic substances such as radiocontrast agents and nonsteroidal anti-inflammatory drugs. Unlike prerenal ARF, there is no specific therapy for ATN; treatment is mainly supportive.[256]

Prerenal failure secondary to type I HRS has a poor prognosis. In many instances, the only effective therapy is liver transplantation. Interventions that may transiently improve renal performance in such patients include (1) intravenous vasoconstrictors, notably terlipressin, norepinephrine, and midodrine, in combination with octreotide, and (2) devices or procedures that support the liver, such as a molecular adsorbent recirculation system (MARS) or transjugular intrahepatic portosystemic shunt (TIPS).[256-258]

Hematologic Dysfunction

Coagulopathies and other hematologic abnormalities are common with end-stage liver disease.[60] Anemia often develops for many reasons, including gastrointestinal bleeding, hemolysis, hypersplenism, malnutrition, vitamin deficiencies, bone marrow depression, and plasma volume expansion. As the liver begins to fail, it cannot make enough vitamin K–dependent procoagulants. When factor VII drops by 70% of the normal level, the PT becomes prolonged. Thrombocytopenia and thrombopathy develop as a result of (1) splenic sequestration syndrome, (2) bone marrow suppression secondary to alcoholism or medications such as interferon, or (3) platelet destruction from immune-mediated, platelet-associated IgG. Dysfibrinogenemia—the activation of fibrinolysis—may develop. Laboratory results typically include increased D-dimer levels, increased fibrin degradation products, and normal or nearly normal fibrinogen levels. However, before attributing any fibrinolytic disorder to liver failure, it is essential to conduct a thorough search for all possible reversible causes of disseminated intravascular coagulation.

Gastrointestinal Complications

Gastrointestinal hemorrhage is always a concern; nearly a third of cirrhosis-related deaths are due to ruptured esophagogastric varices. Portal hypertensive gastropathy, esophageal varices, or gastric varices develop in most patients with cirrhosis and portal hypertension.[259] Hemorrhage from esophageal varices occurs more often than hemorrhage from gastric varices, but the latter is generally more severe than the former. Variceal size is a good predictor of when varices will rupture, and rates of variceal enlargement parallel the severity of liver disease. Less than 2 years after cirrhosis and portal hypertension are diagnosed, 20% to 30% of patients suffer a variceal hemorrhage.[259] The first hemorrhage is acutely lethal in about 7% of cases, with a 6-week mortality rate of around 30%. Untreated survivors of variceal hemorrhage have a 60% chance of rebleeding within 2 years; if this should occur, the death rate would be 40% to 50%.

Endocrinopathies

Because the liver produces, processes, and metabolizes many endocrine substances, advanced liver disease leads to endocrine abnormalities. For example, plasma levels of glucagon and growth hormone increase with liver disease and contribute to insulin resistance. IGF-I decreases in children with liver disease and adversely affects their growth and development.[80] Gonadal dysfunction develops in men and women because of disruptions in the metabolism of sex hormones. Men undergo feminization, with the development of gynecomastia, testicular atrophy, infertility, and impotence. In women, oligomenorrhea, amenorrhea, and infertility are common.

Central Nervous System Dysfunction

Hepatic encephalopathy is a complex neuropsychiatric syndrome that develops in 50% to 70% of patients with cirrhosis.[252] Pathophysiologic phenomena that contribute to the syndrome include (1) hepatobiliary dysfunction, (2) decreased hepatic blood flow, and (3) extrahepatic diversion of portal venous flow through collateral vessels (i.e., portacaval blood flow). Various gut-derived chemicals, including mercaptans, phenols, ammonia, short-chain fatty acids, and manganese, may play a role in the pathogenesis of hepatic encephalopathy. Central nervous system depression may result from false neurotransmitters (e.g., octopamine) or endogenous ligands that increase central inhibitory outflow, such as activators of GABA benzodiazepine receptors. Other possible contributors to encephalopathy are disruptions of the blood-brain barrier and defective cerebral energy metabolism. The pathogenesis and management of hepatic encephalopathy are described in detail elsewhere.[60,252]

Cardiovascular Dysfunction

A hyperdynamic circulation, with high cardiac output and low total peripheral resistance, is a hallmark of cirrhosis and portal hypertension.[260] Generally, systemic arterial pressure is slightly below normal, the heart rate is mildly increased, and central filling pressure is normal. Mixed venous O_2 saturation is elevated, and the arteriovenous O_2 content gap is low. Overall, the hemodynamic profile resembles a peripheral arteriovenous (AV) fistula. Indeed, advanced liver disease causes extensive, widespread AV communications (collateral vessels) within the splanchnic organs, lungs, muscle, and skin. High blood flow through these collateral vessels may result from cirrhosis-induced increases in endogenous vasodilators, such as glucagon, NO·, vasoactive intestinal polypeptide (VIP), and ferritin.[261-265]

Endogenous vasodilators may also explain why severe liver disease diminishes cardiovascular responses to physiologic and pharmacologic vasoconstrictors.[266] Laboratory studies show that NO·, by itself, can induce quintessential cardiovascular and renal hallmarks of cirrhosis and portal hypertension.[267,268] Experimental models of chronic portal hypertension—via partial portal vein ligation or CCl_4-induced cirrhosis—show that NO· induces elevations in cyclic guanosine monophosphate (cGMP), which correlate directly with peripheral arterial dilation.[268,269] Inhibitors of NO· synthase can (1) prevent the characteristic increases in cardiac output and decreases in vascular resistance, (2) restore plasma aldosterone and arginine vasopressin levels, and (3) correct the derangements in sodium and water excretion. In addition, clinical studies comparing healthy subjects and patients with liver cirrhosis show a positive correlation between exhaled NO· and the cardiac index.[270]

Pathogenesis of Portal Hypertension

Characteristic features of cirrhosis-induced portal hypertension include (1) high resistance to intrahepatic blood flow, (2) high preportal blood flow, and (3) high blood flow through portacaval collateral vessels. The pathogenesis of cirrhosis-induced portal hypertension is complex. Putative mechanisms include the "backward" and "forward" concepts, which are not mutually exclusive. According to the backward concept, proliferating intrahepatic fibrosis leads to increased resistance to the flow of blood through the portal vein; this elevates portal venous pressure (i.e., at constant rates of portal venous flow). Experimental narrowing of the portal vein induces portal hypertension characterized by (1) increased mesenteric vascular resistance, (2) decreased mesenteric blood flow, (3) decreased splanchnic venous oxygen saturation, and (4) an increased AV oxygen content gap of mesenteric blood. However, such changes are exactly opposite those that occur when portal hypertension develops in patients with cirrhosis. The forward concept regarding vasodilation may explain this[271]; portal hypertension develops because of cirrhosis-induced changes in the systemic and splanchnic arterial circulations. The hypothesis is supported by observations in cirrhotic patients, including (1) increased blood levels of endogenous vasodilators, (2) widespread AV shunt formation, and (3) high cardiac output with low total peripheral resistance. Putative mediators of the hyperdynamic circulation include NO·, glucagon, prostacyclin, adenosine, CO, and hydrogen sulfide.[272] These substances not only induce direct vasodilation but may also support the formation and patency of extensive AV shunts (AV fistulas) in the intestines, spleen, and other organs. Activation of K_{ATP} channels in arterial smooth muscle cells may mediate increased blood flow in the systemic and splanchnic arterial circulations.[272]

Control of Circulatory Volume

Avid renal retention of sodium is integral to the pathophysiology of cirrhosis and portal hypertension. Volume receptors that detect low effective plasma volume stimulate the sympathetic nervous system and lead to release of renin from the kidney.[273] This increases the production of angiotensin II and aldosterone, which enhances renal tubular uptake of sodium. Norepinephrine levels in blood correlate inversely with renal blood flow. Both norepinephrine and angiotensin II redistribute intrarenal blood flow in a manner that increases retention of sodium by the kidney. Additional factors that may augment sodium retention include the kallikrein-kinin system and some extremely potent renal vasoconstrictors, such as $F_{2\alpha}$-isprostanes[274] and endothelin. Renal vasoconstrictors are likely inducers of the renal dysfunction that accompanies cirrhosis and ascites. In such settings, endogenous vasodilators (e.g., prostaglandins) become increasingly important to counteract the intense vasoconstriction and protect renal blood flow. Accordingly, inhibitors of prostaglandin synthesis can significantly decrease renal plasma flow and GFR and thereby increase the risk for acute renal injury.

Pathogenesis of Ascites

Cirrhosis-induced portal hypertension leads to massive increases in total body water, edema, and ascites formation.[275] The problem can be traced to excessive sodium retention by the kidney (Fig. 17-13).[2,276] However, the principal driver of the sodium retention is unclear. One explanation—the overflow model—is that hepatic cirrhosis gives rise to chemicals that stimulate the kidney to retain sodium. A second explanation—the underfill model—is that renal retention of sodium is a normal physiologic response to a low effective blood volume.[273]

The essence of the overflow model is that excessive renal retention of sodium causes intravascular volume to expand, with two major and direct consequences: (1) plasma oncotic pressure decreases, with the liver unable to produce sufficient albumin to correct the hypoalbuminemia, and (2) portal hydrostatic pressure increases (i.e., portal hypertension). The combination of low oncotic pressure and portal hypertension accelerates the formation of edema and ascites. A pivotal assumption of the overflow model is that a cirrhosis-induced mediator causes normal kidneys to retain sodium and water despite an overfilled intravascular compartment. At present, no such mediator (or process) has been identified.

The underfill model recognizes that homeostatic reflexes work in concert with the kidney to tightly regulate intravascular volume. This model posits that cirrhosis causes the effective plasma volume to decrease, which activates homeostatic mechanisms to retain sodium and water. As Schrier and Abraham point out,[273] "the integrity of the arterial circulation, as determined by cardiac output and peripheral arterial resistance, is the primary determinant of renal sodium and water excretion." That is, with decreases in arterial volume, whether from arterial dilation or low cardiac output, the kidney is instructed to retain sodium and water. Cirrhosis-induced decreases in effective plasma (or arterial) volume can result from arterial dilation or intravascular volume depletion, or both. Although the latter has many possible causes, edema and ascites formation from unbalanced Starling forces are sufficient to significantly decrease intravascular volume. The overflow and underfill models are not mutually exclusive; a primary defect in sodium excretion could be the major factor in earlier stages of cirrhosis, whereas a low effective plasma volume could be the more important factor in progression to end-stage liver disease.[275]

Cholestatic Disease

Cholestasis refers to impaired biliary flow and has a complex pathogenesis[106,277-295] (Box 17-2). The usual cause of intrahepatic cholestasis, whether inherited or acquired, is dysfunction of the bile transporter.[295,296] In contrast, extrahepatic cholestasis most often results from mechanical blockage of the biliary tree. With cholestasis, there are high blood levels of biliary constituents, including hepatocellular enzymes (AP, GGTP, 5′-NT, LAP),

Box 17-2 Etiology of Intrinsic Cholestatic Disorders

- Drugs[106,279,280]
- Alcoholism[281]
- Pregnancy[282,283]
- Inflammation[284]
- Sepsis[285-287]
- Parenteral nutrition[288,289]
- Primary biliary cirrhosis[290]
- Primary sclerosing cholangitis[291]
- Genetic cholestatic liver diseases[292-295]

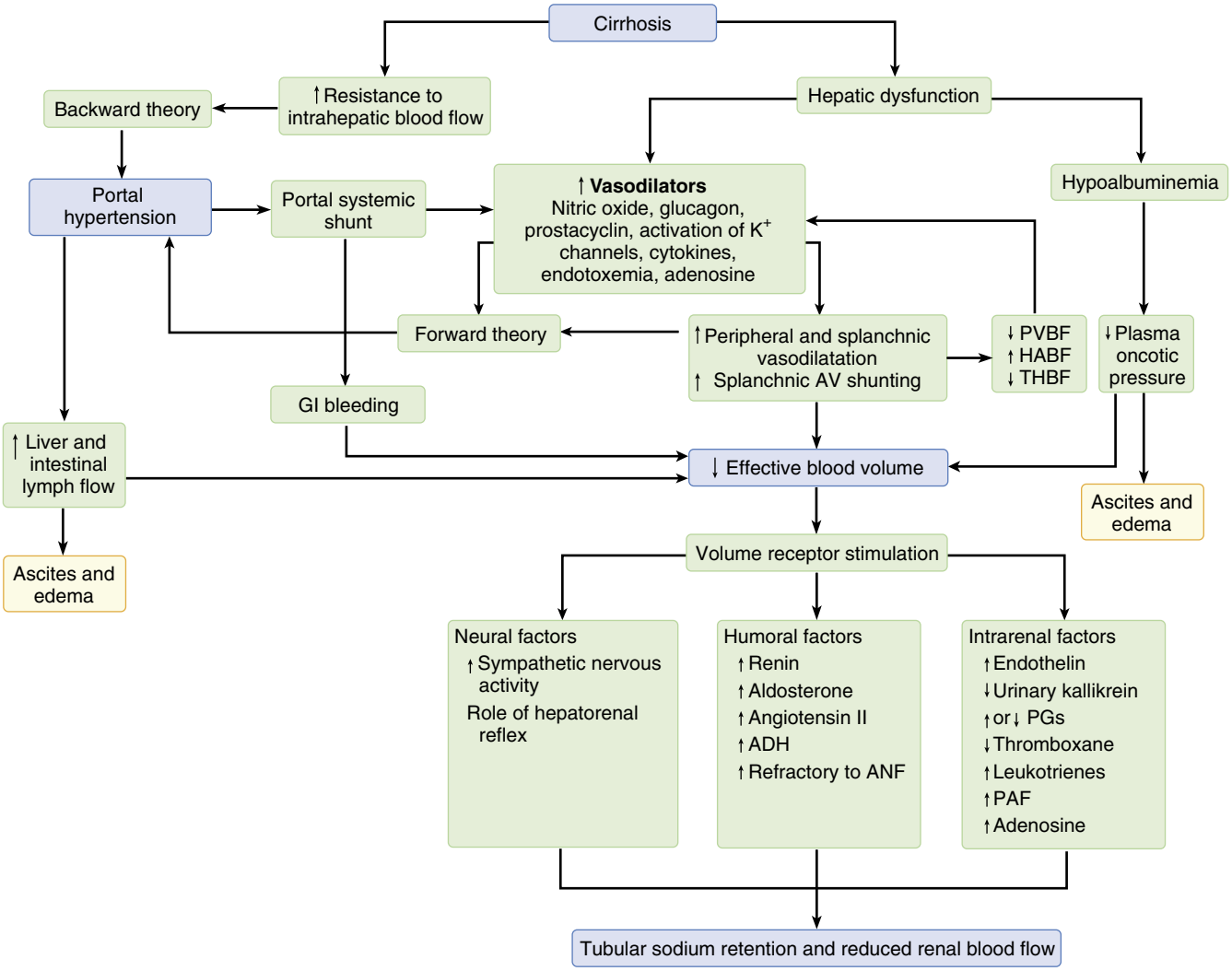

Figure 17-13 Schematic of pathways for cirrhosis-induced portal hypertension: the forward and backward theories. Cirrhosis and portal hypertension induce circulatory changes that decrease effective blood volume. This activates volume receptors and stimulates neurohumoral and intrarenal reflexes, which decreases renal blood flow and increases renal retention of sodium. ADH, antidiuretic hormone; ANF, atrial natriuretic factor; AV, arteriovenous; HABF, hepatic arterial blood flow; PAF, platelet-activating factor; PGs, prostaglandins; PVBF, portal venous blood flow; THBF, total hepatic blood flow. *(Reprinted with permission from Mushlin PS, Gelman S: Anesthesia and the liver.* In *Barash PG, Cullen BF, Stoelting RK* [eds]*: Clinical Anesthesia, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, p 1088.)*

immunoglobulin A, cholesterol, and various forms of bile salts and bilirubin. The most toxic of these is unconjugated bilirubin; high concentrations of unconjugated bilirubin cause membrane dysfunction and disrupt major metabolic pathways such as the tricarboxylic acid cycle and oxidative phosphorylation. Patients with cholestatic syndromes typically have marked increases in serum bile salts, but normal or slightly elevated serum bilirubin.

The clinical findings in cholestatic syndromes are dependent on the severity of the cholestatic disorder and its pathogenesis.[297-301] Pruritus is a hallmark feature and results mainly from retained bile salts.[277,284,302,303] As cholestatic disorders increase in severity, jaundice develops.[304] The stool becomes lighter in color and the urine darkens as bile pigments are diverted from the gut to the kidney for excretion.

Coagulation Disorders

Enteric absorption of lipids such as vitamin K requires bile salts and an intact enterohepatic circulation. With cholestasis-induced coagulopathies, the liver continues to make procoagulants. However, without vitamin K, hepatocytes cannot add the γ-carboxyl glutamate residues that these procoagulants need for subsequent activation. Parenteral vitamin K should correct this coagulopathy, but if it does not, there must be another cause of the problem. Prolonged cholestasis can induce liver dysfunction and a coagulopathy that would not be cured by vitamin K therapy.

Renal Dysfunction

Cholestatic disorders can cause dysfunction of the splanchnic reservoir. Because the reservoir cannot effectively transfer blood volume to the central circulation, severe hypotension and renal hypoperfusion can result from even mild losses of plasma volume. This predisposes to prerenal ARF and ATN from the prerenal ARF. If liver dysfunction supervenes, ATN may result from unconjugated bilirubin, which can directly cause renal tubular injury.

Cardiovascular Dysfunction

Cholestatic syndromes induce hemodynamic changes that are similar, but less severe than the changes associated with cirrhosis and portal hypertension. Cardiac output increases and peripheral vascular resistance decreases. Portal venous blood flow may decrease as portal venous resistance increases. Yet the mechanisms by which cholestasis alters cardiovascular parameters are incompletely understood and challenging to study for several reasons. First, bile is a heterogeneous fluid with variable compositions and many different forms of bile salts and bilirubin. Second, individual constituents of bile exert dissimilar cardiovascular effects. Third, differing causes of cholestatic syndromes lead to disparate pathophysiologic conditions, which can confound the direct and indirect cardiovascular actions of specific constituents of bile.

The direct cardiac effects of bile salts (primary, conjugated, and secondary) have been studied in isolated heart preparations to obviate concern about the indirect cardiovascular effects of biliary constituents. In isolated ventricular muscle, bile salts, at concentrations similar to those in patients with cholestatic jaundice, exert negative inotropic effects. They decrease (1) peak tension, (2) the maximum rate of tension development, (3) the duration of contraction, and (4) the action potential duration. Electrophysiologic actions of sodium taurocholate, ascertained from voltage clamping of ventricular myocytes, include decreases in the slow inward current and slight increases in the outward potassium current. Taken collectively, these data suggest that bile salts directly induce negative inotropic effects, which could result from altered membrane currents.[305]

Experiments in animals show that high blood levels of bile salts (cholemia) can block the cardiovascular effects of agents such as norepinephrine, angiotensin II, and isoproterenol. It is possible that cholemia exerts such effects by disrupting receptor complexes in plasma membranes.[305-307] On the other hand, acute cholestasis can decrease cardiac contractility without affecting cardiac β-adrenoceptors, as shown in animal studies in which acute cholestasis was induced by bile duct ligation.[306] After experiencing 3 days of extrahepatic cholestasis, myocardial contractility was impaired globally, but β-adrenoceptors were intact.

Studies in animals show that cholestasis can alter homeostatic circulatory reflex responses.[307] For example, removal of 10% of the blood volume of healthy rats had little effect on their arterial blood pressure, whereas removing this same volume of blood from rats with cholestasis caused a 50% decrease in blood pressure. Healthy animals compensated for the blood loss by mobilizing 15% of the blood volume of the pulmonary and splanchnic vasculature; however, animals with cholestasis mobilized only 7% of their pulmonary blood volume, with no contribution from the splanchnic reservoir.[307] These data show that cholestasis induces dysfunction of physiologic blood reservoirs. Whether such laboratory findings are relevant for patients with cholestasis is unclear. A final note of caution about patients with cholestatic disorders is warranted: decompression of the biliary tract, by itself, may lead to significant cardiovascular depression.[308]

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Robert N. Sladen

18 Renal Physiology

Key Points

1. To cross the filtration barrier between plasma and tubular fluid, a molecule must pass in succession through the endothelial fenestrations, the glomerular basement membrane, and the epithelial slit diaphragm. The capillary endothelium restricts the passage of cells, but the basement membrane filters plasma proteins. All three layers contain negatively charged glycoproteins, which retard the passage of other negatively charged proteins. Thus, the filtration barrier is size selective and charge selective.[1]
2. A primary determinant of glomerular filtration rate (GFR) is the glomerular filtration pressure, which depends not only on the renal artery perfusion pressure but also on the balance between afferent and efferent arteriolar tone. In the presence of decreased afferent arteriolar pressure or blood flow, low levels of catecholamines, angiotensin, and arginine vasopressin (AVP) induce preferential efferent arteriolar constriction, which maintains glomerular filtration pressure. This is reflected by an increase in calculated filtration fraction (FF), which is the GFR expressed as a fraction of the renal plasma flow (RPF), that is, FF = GFR/RPF. High levels of catecholamines and angiotensin (but not AVP) increase afferent arteriolar tone and decrease glomerular filtration pressure (and GFR) out of proportion to RPF, and FF decreases (see Fig. 18-4).
3. Tubuloglomerular feedback may be a primary mechanism in renal autoregulation.[3] When GFR is increased, distal tubular NaCl delivery is enhanced. The increase in chloride is sensed by the macula densa, which triggers the release of renin from the adjacent afferent arteriole. Angiotensin is elaborated and arteriolar constriction ensues, which decreases GFR. When the thick ascending loop becomes ischemic, reabsorption of NaCl ceases, the ability of the tubule to concentrate urine is lost, and, theoretically, intractable polyuria should result. Thurau and Boylan[5] suggested that the increased delivery of NaCl to the macula densa triggers angiotensin-mediated arteriolar constriction, which decreases GFR, induces oliguria, conserves intravascular volume, and protects the organism from dehydration—so-called acute renal success.
4. Autoregulation enables the kidney to maintain solute and water regulation independently of wide fluctuations of arterial blood pressure. It is noteworthy that urinary flow rate is not subject to autoregulation. Tubular water reabsorption determines urinary flow rate and is closely related to the hydrostatic pressure in the peritubular capillaries. Hypotension, whether induced or inadvertent, results in decreased urinary flow rate that may be correctable only when the arterial blood pressure is restored toward normal.
5. The tubule has an enormous capacity for reabsorption of water and NaCl. Each day, 180 L of protein-free glomerular ultrafiltrate is formed, of which almost 99% of the water and 99% of the sodium is reabsorbed. Many other filtered substances are completely reabsorbed, but some, such as glucose, have a maximum rate of tubular reabsorption (tubular maximum). Tubular reabsorption of glucose increases at a rate equal to that of the filtered load.
6. The ability of the kidney to concentrate urine is dependent on the interaction of at least three processes: (1) the generation of a hypertonic medullary interstitium by the countercurrent mechanism and urea recycling, (2) concentration and then dilution of tubular fluid in the loop of Henle, and (3) the action of antidiuretic hormone (now known as arginine vasopressin [AVP]) in increasing water permeability in the last part of the distal tubule and collecting ducts.
7. Serum creatinine reflects the balance between creatinine production by muscle and creatinine excretion by the kidney, which is dependent on the GFR. Creatinine generation rate varies with muscle mass, physical activity, protein intake, and catabolism. However, when these processes are in equilibrium and renal function is stable, serum creatinine is a useful marker of GFR. The relationship between serum creatinine and GFR is inverse and exponential. A doubling of the serum creatinine implies a halving of the GFR. An increase in serum creatinine from 0.8 to 1.6 mg/dL may not generate much attention, but it indicates a 50% decrease in GFR. A much larger increase from 4 to 8 mg/dL also

represents a 50% decrease in GFR, but by this time renal insufficiency is well established (see Fig. 18-11). After a transient renal insult (e.g., suprarenal aortic cross-clamping), serum creatinine may increase for a few days while GFR is actually recovering.

8. The juxtaglomerular apparatus consists of three groups of specialized tissues. In the afferent arteriole, modified fenestrated endothelial cells produce renin; in the juxtaposed distal tubule, cells of the macula densa act as chemoreceptors; and in the glomerulus, mesangial cells have contractile properties (see Fig. 18-3). Together these provide an important regulating system for blood pressure, salt, and water homeostasis.[46]

9. Hypothalamic osmoreceptors are sensitive to increases in serum osmolality of as little as 1% above normal. As illustrated in Figure 18-21A, the threshold for AVP secretion (and the sensation of thirst) is between 280 and 290 mOsm/kg. When this is exceeded, the secretion rate has a very steep gain.[52] Even mild dehydration results in a rapid antidiuresis, and urine osmolality can increase from 300 to 1200 mOs/kg as plasma AVP levels rise from 0 to 5 pg/mL (see Fig. 18-21B). Decreases in intravascular volume also stimulate AVP secretion, mediated by stretch receptors with vagal afferents in the left atrium and pulmonary veins. Hypovolemia-induced secretion of AVP overrides osmolar responses and contributes to the perioperative syndrome of inappropriate antidiuretic hormone secretion (SIADH): fluid retention, hypo-osmolality, and hyponatremia. The situation is exacerbated by administration of large volumes of hypotonic solutions that decrease serum osmolality. Psychic stress, via cortical input, also induces AVP release and can override osmotic and volume sensors.

10. All anesthetic techniques and drugs tend to decrease GFR and intraoperative urine flow. Some drugs also decrease renal blood flow (RBF), but filtration fraction is usually increased, which implies that angiotensin-induced efferent arteriolar constriction limits the decrease in GFR. However, these effects are much less significant than those caused by surgical stress or aortic cross-clamping and after emergence from anesthesia usually resolve promptly. Any anesthetic technique that induces hypotension will result in decreased urine flow because of altered peritubular capillary hydrostatic gradients, even if renal autoregulation is preserved (as it usually is during anesthesia). Permanent injury seldom results, unless the kidneys are abnormal to begin with or the hypovolemic insult is prolonged and exacerbated by nephrotoxic injury.

11. Clinically significant renal injury with the use of low-flow sevoflurane anesthesia has not been reported in patients, even with moderate preexisting renal dysfunction. The relationship between compound A formation, biochemical injury, and clinically relevant renal dysfunction remains unclear and unproven. Nonetheless it appears prudent to follow current FDA guidelines, which recommend a fresh gas flow of at least 2 L/min to inhibit compound A formation and its rebreathing and to enhance its washout.

12. Regardless of the position of the aortic cross-clamp, RBF is decreased to 50% of normal during surgical preparation of the aorta, presumably due to direct compression or reflex spasm of the renal arteries. After release of the suprarenal cross-clamp, RBF increases above normal (reflex hyperemia), but GFR remains depressed to one third of control for up to 2 hours. After 24 hours, GFR is still only two thirds of control. Tubular functions (concentrating ability, sodium, and water conservation) are markedly impaired, but urine flow is maintained. Myers and Moran[106] observed that these changes resemble an attenuated form of acute tubular necrosis. In the above study all patients received mannitol pretreatment, which probably limited the tubular insult because oliguria was uncommon and recovery was relatively rapid. Cross-clamp times longer than 50 minutes are associated with prolonged depression of GFR and transient azotemia.[107]

13. In contrast to dopamine, there does appear to be increasing evidence to support a renoprotective effect for infusion of low-dose fenoldopam infusion (0.1-0.3 μg/kg/min) during cardiac surgery. A meta-analysis of 13 randomized and case-matched studies on 1059 patients found that fenoldopam infusion is associated with a significant decrease in dialysis requirement, intensive care unit length of stay, and in-hospital mortality.[136] Most studies have been relatively small and identified improved serum creatinine and creatinine clearance rather than renal outcome.[137,138] The most convincing evidence thus far comes from a randomized, double-blinded study in 193 high-risk patients by Cogliati and associates.[139] Risk factors included elevated preoperative serum creatinine (>1.5 mg/dL), age older than 70 years, diabetes, and previous cardiac surgery. Patients who received fenoldopam had a decreased incidence of acute kidney injury (12.6 versus 27.6%, $P = .02$) and requirement for dialysis (0 versus 8.2%, $P = .004$).

14. The beneficial effect of AVP on renal function in sepsis may in part be due to its ability to increase low renal perfusion pressure back into the autoregulatory range. Another important factor is that, unlike norepinephrine, even at high local concentrations AVP preferentially constricts the efferent arteriole, thereby improving filtration fraction and GFR.[53] However, in a large, prospective, randomized, blinded trial in 778 patients with severe septic shock, low-dose AVP (0.01-0.03 unit/min) did not provide a mortality benefit or decrease the requirement for dialysis when compared with an infusion of norepinephrine (5-15 μg/min).[194]

The kidneys contain approximately 2 million nephrons, each of which consists of a glomerulus and a tubule, which empties into a collecting duct. Together they regulate intravascular volume, osmolality, and acid-base and electrolyte balance and excrete end products of metabolism and drugs. Urine is formed by the combination of glomerular ultrafiltration and tubular reabsorption and secretion. The nephron also elaborates hormones that contribute to fluid homeostasis (renin, prostaglandins, kinins), bone metabolism (1,25-dihydroxycholecalciferol), and hematopoiesis (erythropoietin). The function of the nephron is closely integrated with the vascular supply of the kidney (Fig. 18-1).

Anatomy and Physiology

The Glomerulus (Renal Corpuscle)

The glomerulus consists of five distinct components: capillary endothelium, glomerular basement membrane, visceral epithelium (which together make up the filtration barrier), parietal epithelium (Bowman's capsule), and mesangium (interstitial cells).[1,2] The glomerular tuft, a highly convoluted series of capillary loops, is fed by the afferent arteriole and drains into the efferent arteriole (Fig. 18-2).

The capillary endothelium synthesizes nitric oxide and endothelin-1, which, by governing vasodilation and vasoconstriction, control renal blood flow. The endothelium has fenestrations about 70 to 100 nm in diameter and lies atop the glomerular basement membrane, which has a total cross section of about 350 nm. The visceral epithelium, which is applied to the underside of the basement membrane, consists of podocytes with filamentous, interdigitating foot processes that contain contractile actin filaments. Filtration slits form 25- to 60-nm gaps between the foot processes and are bridged by a protein membrane slit diaphragm, whose size and permeability are altered by contraction of the foot processes.

The blind parietal epithelial sac of the renal tubule is invaginated around the capillary tuft as Bowman's capsule and meets the visceral epithelium at the vascular pole of the glomerulus. Bowman's space, between the visceral and parietal layers of the capsule, becomes the lumen of the proximal tubule at the urinary pole of the glomerulus, and the parietal endothelium merges with the cuboidal cells of the proximal tubule.

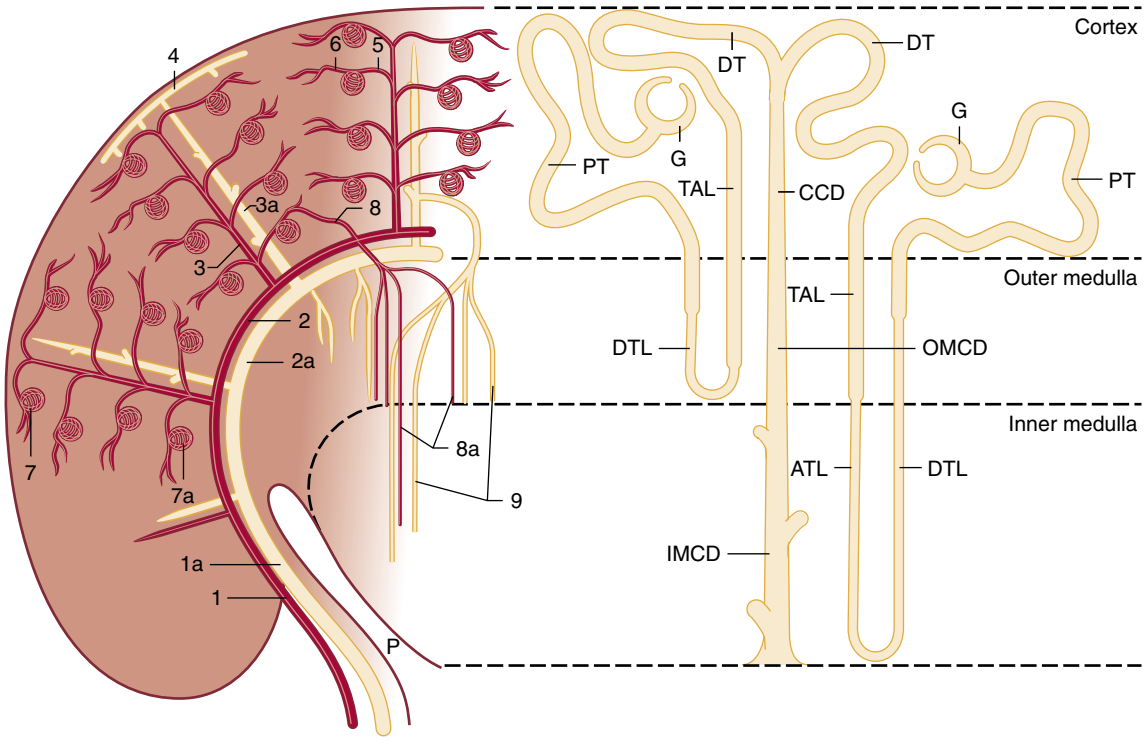


Figure 18-1 Anatomic relationships of the nephron and the renal vasculature. The left side of the diagram represents the renal vasculature as distributed through the inner medulla, outer medulla, and cortex. Arteries are drawn as *solid lines,* veins as *hollow tubes.* The renal artery divides serially into interlobar arteries (1), arcuate arteries (2), and interlobular arteries (3). The afferent arterioles (5) branch off laterally and provide the capillary tufts of the renal glomeruli in the outer cortex (7), whose efferent arterioles (6) supply the cortical capillary network (not shown). In the juxtamedullary zone (7a), the efferent arterioles become the vasa recta, which are closely applied to the long loops of Henle (8, 8a, 9). The venous drainage consists of stellate veins (4), interlobular veins (3a), arcuate veins (2a), and interlobar veins (1a). The right side of the diagram represents two nephrons. On the left is the more numerous superficial cortical nephron with a short loop of Henle. On the right is the juxtamedullary nephron with a long loop of Henle, which dives deep into the inner medulla to generate the hyperosmotic interstitium required for tubular urine concentration. ATL, ascending thin loop of Henle; CCD, cortical collecting duct; DT, distal tubule; DTL, descending thin loop of Henle; G, glomerulus; IMCD, inner medullary collecting duct; OMCD, outer medullary collecting duct; PT, proximal tubule; TAL, thick ascending loop. *(From Kriz W: A standard nomenclature for structures of the kidney. Kidney Int 33:1-7, 1988.)*

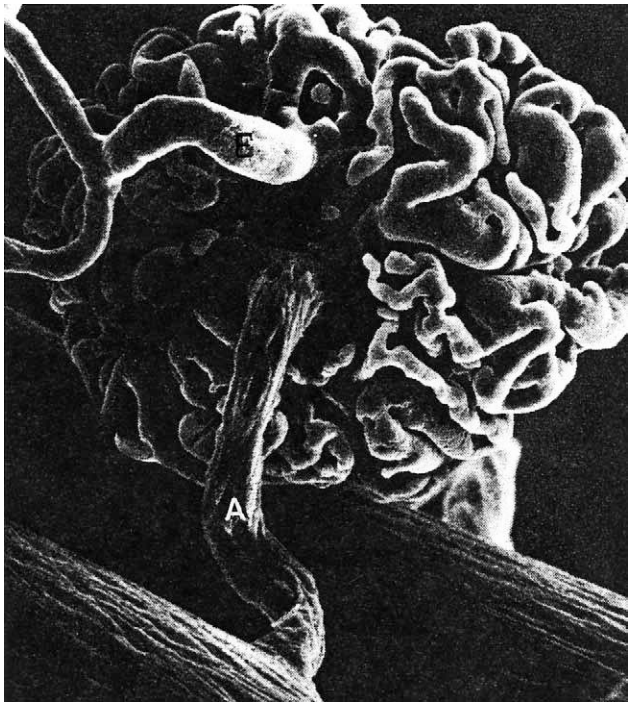


Figure 18-2 Photomicrograph of a cast of a glomerulus without Bowman's capsule. At lower left the afferent arteriole (A) originates from an interlobular artery and enters the glomerulus with its many capillary loops. At upper left the efferent arteriole (E) leaves the glomerulus and branches to form the peritubular capillary plexus (×300). (*From Tisher CC, Madsen KM: Anatomy of the kidney.* In *Brenner BM [ed]: Brenner & Rector's The Kidney, 6th ed. Philadelphia, WB Saunders, 2000, pp 3-67.*)

The central or interstitial mesangial cells are specialized pericytes with numerous functions, including structural support, matrix elaboration, and phagocytosis. They contain myofilament-like threads of actin and myosin. Mesangial contraction in response to vasoactive substances such as angiotensin II restricts blood flow to fewer capillary loops. The mesangial cells thereby regulate the effective glomerular surface area for filtration and, as a consequence, glomerular permeability.[3]

Formation of the Glomerular Ultrafiltrate

To cross the filtration barrier between plasma and tubular fluid, a molecule must pass in succession through the endothelial fenestrations, the glomerular basement membrane, and the epithelial slit diaphragm. The capillary endothelium restricts the passage of cells, but the basement membrane filters plasma proteins. All three layers contain negatively charged glycoproteins, which retard the passage of other negatively charged proteins. Thus, the filtration barrier is both size selective and charge selective.[1] Molecules with an effective radius of less than 1.8 nm (e.g., water, sodium, urea, glucose, inulin) are freely filtered. Molecules larger than 3.6 nm (e.g., hemoglobin, albumin) are not filtered. Filtration of molecules between 1.8 and 3.6 nm depends on their electrical charge. Cations are filtered, whereas anions are not. In glomerulonephritis, the negatively charged glycoproteins are destroyed, polyanionic proteins are filtered, and proteinuria ensues.

Glomerular ultrafiltration is governed by the balance of Starling forces regulating fluid flux across the filtration barrier.[4] Glomerular filtration rate (GFR) depends on the permeability of the filtration barrier and the net difference between the hydrostatic forces pushing fluid into Bowman's space and the osmotic forces keeping fluid in the plasma:

$$GFR = K_{uf}\left[\left(P_{gc} - P_{bs}\right) - \left(\pi_{gc} - \pi_{bs}\right)\right]$$

where uf = ultrafiltration, gc = glomerular capillary, and bs = Bowman's space.

The ultrafiltration coefficient, K_{uf}, reflects capillary permeability and glomerular surface area. Renal arterial pressure determines the hydrostatic pressure in the glomerular capillary, P_{gc}. Afferent arteriolar plasma flow determines the plasma oncotic pressure (π_{gc}): rapid blood flow washes out osmotically effective molecules and lowers π_{gc}, and vice versa.

The Juxtaglomerular Apparatus

The juxtaglomerular apparatus provides a remarkable integration of tubular and glomerular structure and function (Fig. 18-3). A modified portion of the thick ascending limb, the macula densa, is applied to the glomerulus at the vascular pole between the afferent and efferent arterioles.[1] The cells of the macula densa are chemoreceptors and sense the tubular concentration of sodium chloride (NaCl). The juxtaposed segments of the afferent and efferent arterioles contain modified smooth muscle cells (granular cells), which produce renin. The arterioles are innervated by sympathetic nerve fibers and contain baroreceptors that respond

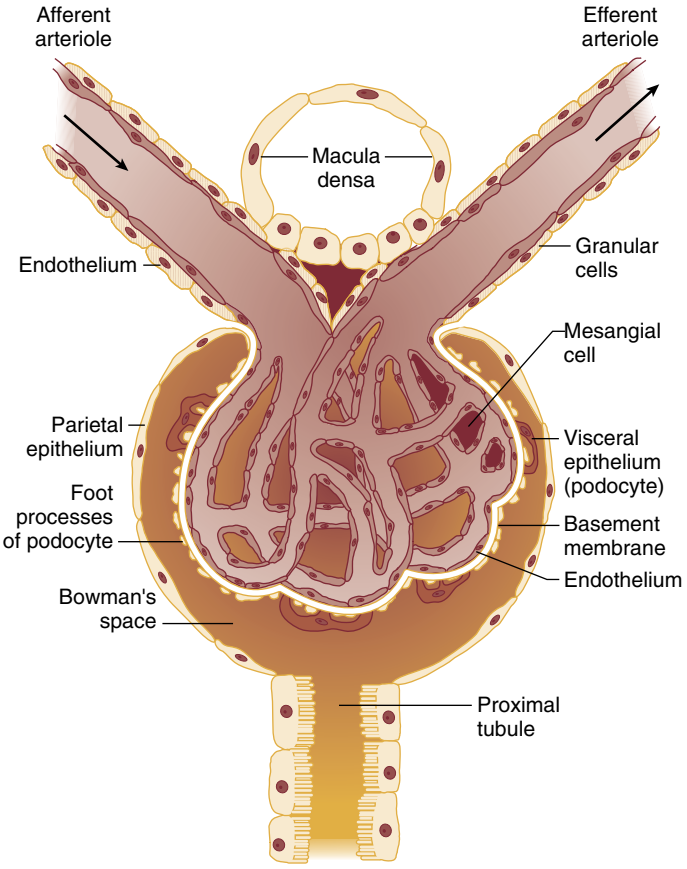


Figure 18-3 The juxtaglomerular apparatus. (*From Stanton BA, Koeppen BM: Elements of renal function.* In *Berne RM, Levy MN [eds]: Physiology, 4th ed. St. Louis, Mosby, 1998, pp 677-698.*)

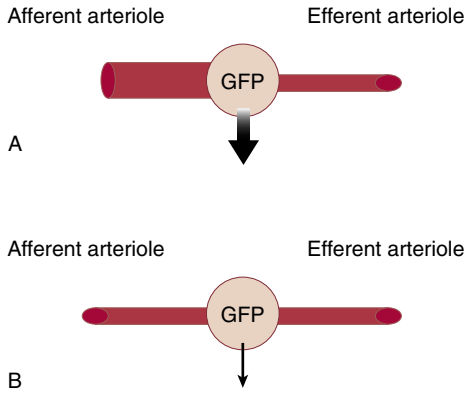


Figure 18-4 Afferent and efferent arteriolar control mechanisms. (*From Sladen RN, Landry D: Renal blood flow regulation, autoregulation, and vasomotor nephropathy. Anesthesiol Clin North Am 18:791-807, ix, 2000.*)

to changes in intraluminal blood pressure. Renin catalyzes the formation of angiotensin, which modulates efferent and afferent arteriolar tone and GFR (see later).

Afferent and Efferent Arteriolar Control Mechanisms

A primary determinant of GFR is the glomerular filtration pressure, which depends not only on the renal artery perfusion pressure but also on the balance between afferent and efferent arteriolar tone. In the presence of decreased afferent arteriolar pressure or blood flow, low levels of catecholamines, angiotensin, and arginine vasopressin (AVP) induce preferential efferent arteriolar constriction, which maintains glomerular filtration pressure (Fig. 18-4A). This is reflected by an increase in calculated filtration fraction (FF), which is the GFR expressed as a fraction of the renal plasma flow (RPF), that is, FF = GFR/RPF. High levels of catecholamines and angiotensin (but not AVP) increase afferent arteriolar tone and decrease glomerular filtration pressure (and GFR) out of proportion to RPF, and FF decreases (Fig. 18-4B).

Tubuloglomerular Feedback

Tubuloglomerular feedback may be a primary mechanism in renal autoregulation.[3] When GFR is increased, distal tubular NaCl delivery is enhanced. The increase in chloride (Cl^-) is sensed by the macula densa, which triggers the release of renin from the adjacent afferent arteriole. Angiotensin is elaborated and arteriolar constriction ensues, which decreases GFR.

When the thick ascending loop becomes ischemic, reabsorption of NaCl ceases, the ability of the tubule to concentrate urine is lost and, theoretically, intractable polyuria should result. Thurau and Boylan[5] suggested that the increased delivery of NaCl to the macula densa triggers angiotensin-mediated arteriolar constriction, which decreases GFR, induces oliguria, conserves intravascular volume, and protects the organism from dehydration—so-called acute renal success.

Renal Autoregulation

Autoregulation enables the kidney to maintain solute and water regulation independently of wide fluctuations of arterial blood pressure. In 1951, the classic dog studies of Shipley and Study[6] demonstrated that the kidney maintains a constant renal blood flow and GFR through an arterial pressure range of 80 to 180 mm Hg (Fig. 18-5). Urinary flow rate is not subject to autoregulation. Tubular water reabsorption determines urinary flow rate and is closely related to the hydrostatic pressure in the peritubular capillaries. Hypotension, whether induced or inadvertent, results in decreased urinary flow rate that may be correctable only when the arterial blood pressure is restored toward normal.

There is considerable evidence to support two major mechanisms for renal autoregulation.[3] As mean arterial pressure decreases, renal vascular resistance decreases and renal blood flow (RBF) is maintained. The most plausible explanation is a myogenic response, that is, the arterioles constrict in response to increased arterial pressure and vice versa. Tubuloglomerular feedback via the juxtaglomerular apparatus also plays a role.[3,4,7] When arterial pressure increases through the autoregulatory range, delivery of sodium chloride is enhanced to the chemosensors of the macula densa, which generate adenosine triphosphate (ATP) and adenosine that stimulate the adenosine A_1 receptor and induce afferent arteriolar constriction (Fig. 18-6). This, in turn, decreases RBF and GFR back to the previous levels. The opposite effect occurs when arterial pressure declines. Local release of nitric oxide attenuates tubuloglomerular feedback, whereas release of angiotensin II enhances it.[4]

Autoregulation is impaired by calcium channel blockade, implying that a calcium-dependent mechanism is involved but not by most anesthetic agents. It is reset in chronic hypertension and may be lost in the diabetic kidney. There is experimental evidence that autoregulation is lost in acute renal failure[8]; in part this may be due to endothelial dysfunction through excessive nitric oxide because inducible nitric oxide synthase is activated by renal ischemia-reperfusion injury.[9] Pressure-dependence of RBF is observed during cardiopulmonary bypass (CPB)[10] and in severe sepsis,[11] but this may simply be due to hypotension below the autoregulatory range, rather than abnormal autoregulation

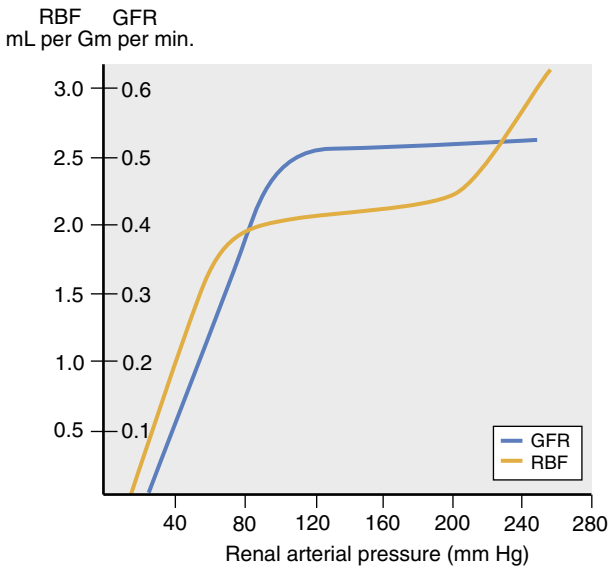
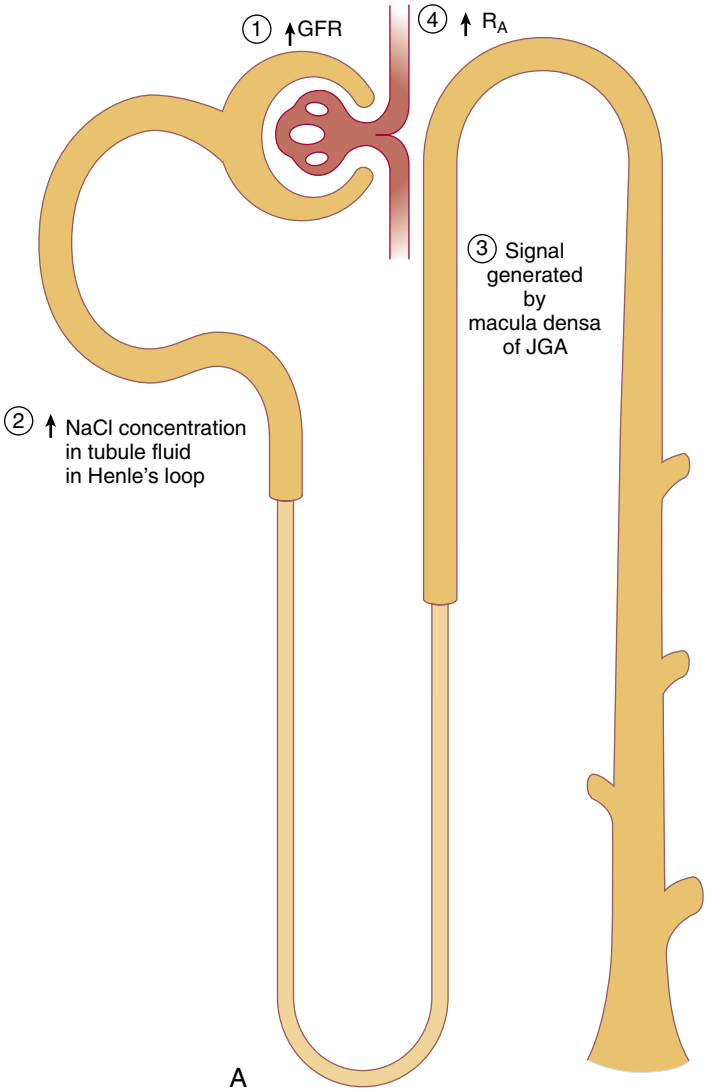


Figure 18-5 Autoregulation of glomerular filtration rate (GFR) and renal blood flow (RBF). GFR and RBF remain constant between renal arterial pressures of 80 and 180 mm Hg. (*Based on the original work of Shipley and Study.*[5] *From Pitts RF: Physiology of the Kidney and Body Fluids. Chicago, Year Book Medical Publishers, 1974.*)



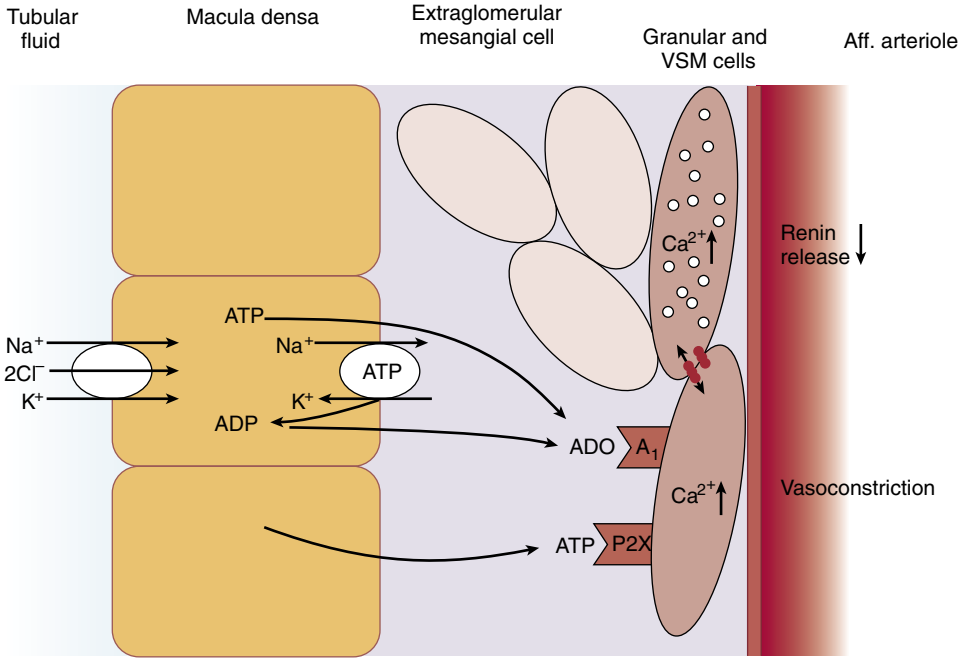


Figure 18-6 **A** and **B,** Tubuloglomerular feedback. An increase in glomerular filtration rate (GFR) (1) increases sodium chloride (NaCl) concentration in the tubular fluid in the loop of Henle. This is sensed by chemosensors in the modified distal tubular cells of the macula densa in the juxtaglomerular apparatus (JGA) (3). The cells of the macula densa generate adenosine triphosphate (ATP) and adenosine (ADO) that induces afferent arteriolar constriction and increases its resistance (R_A) (4). This returns the GFR to its former level. A decline in the GFR has the opposite effect. (*From Koeppen BM, Stanton BA: Glomerular filtration and renal blood flow.* In *Koeppen BM, Stanton BA [eds]: Renal Physiology, 4th ed. Philadelphia, Mosby Elsevier, 2007, pp 31-46.*)

per se. Normalization of renal perfusion pressure improves RBF, even if this is achieved by vasoconstrictor therapy.

The Tubule

The tubule has four distinct segments: the proximal tubule, the loop of Henle, the distal tubule, and the connecting segment. The loop of Henle itself is divided into the pars recta (the straight portion of the proximal tubule), the descending and ascending thin limb segments, and the thick ascending limb. Each distal tubule drains into a collecting duct, which courses through the cortex, outer medulla, and inner medulla before entering the renal pelvis at the papilla (see Fig. 18-1).

There are two populations of nephrons. The cortical nephrons populate the outer and middle renal cortex, are far more numerous, receive about 85% of the renal blood flow, and have short loops of Henle. The juxtamedullary nephrons populate the inner renal cortex, receive about 10% of the RBF, and have larger glomeruli and long loops of Henle, which dive deeply into the inner medulla.[2] Their efferent arterioles drain into elongated vascular conduits, the vasa recta, which are closely applied to the loops of Henle. Although the vasa recta receive less than 1% of the RBF, they play an important role in generating the countercurrent mechanism for medullary hypertonicity and renal concentrating ability (see later).

Tubular Reabsorption and Secretion

The tubule has an enormous capacity for reabsorption of water and NaCl. Each day, 180 L of protein-free glomerular ultrafiltrate is formed, of which almost 99% of the water and 99% of the sodium is reabsorbed.

Many other filtered substances are completely reabsorbed, but some, such as glucose, have a maximum rate of tubular reabsorption (tubular maximum). Tubular reabsorption of glucose increases at a rate equal to that of the filtered load. If the GFR is constant, the rate is directly proportional to the plasma glucose. Once plasma glucose exceeds the tubular maximum (375 mg/dL), no further glucose is reabsorbed and glycosuria results. Thereafter, the amount of glucose excreted in the urine increases in direct proportion to the filtered load.

Many important endogenous and exogenous solutes are secreted into the tubular lumen from the capillary blood. Some also have a tubular maximum for secretion, such as *p*-aminohippurate (PAH), which is used to calculate RPF. There is a striking relationship between the structure and function of the different segments of the tubule (Fig. 18-7). The most metabolically active components of the tubule are the proximal tubule, the thick ascending loop of Henle, and the first part of the distal tubule.

Figure 18-8 illustrates a tubular cell in the thick ascending loop of Henle, which encompasses all the major mechanisms of reabsorption and secretion. From each apical cell membrane pro-

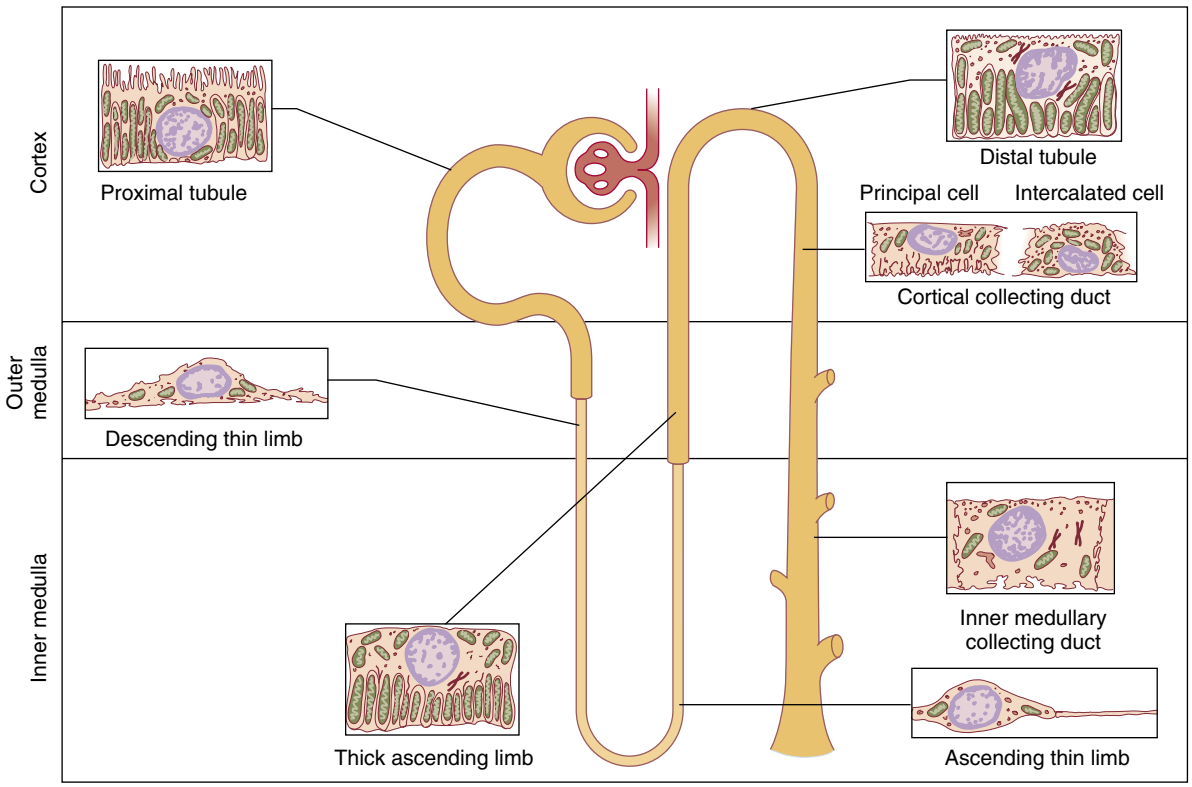


Figure 18-7 Structure-function relationships in the renal tubule. The most metabolically active components of the tubule are the proximal tubule, the thick ascending loop of Henle, and the first part of the distal tubule. Their cells are large, and on the capillary surface (basolateral membrane) there are many invaginations rich in mitochondria. The cells of the proximal tubule have a brush-border on the luminal surface (apical cell membrane), whereas the cells of the descending and thin ascending loops of Henle are flattened with few mitochondria. The second part of the distal tubule and collecting duct are intermediate in nature. The intercalated cells of the distal tubule have many mitochondria; the principal cells are few. (*From Stanton BA, Koeppen BM: Elements of renal function. In Berne RM, Levy MN [eds]: Physiology, 4th ed. St. Louis, Mosby, 1998, pp 677-698.*)

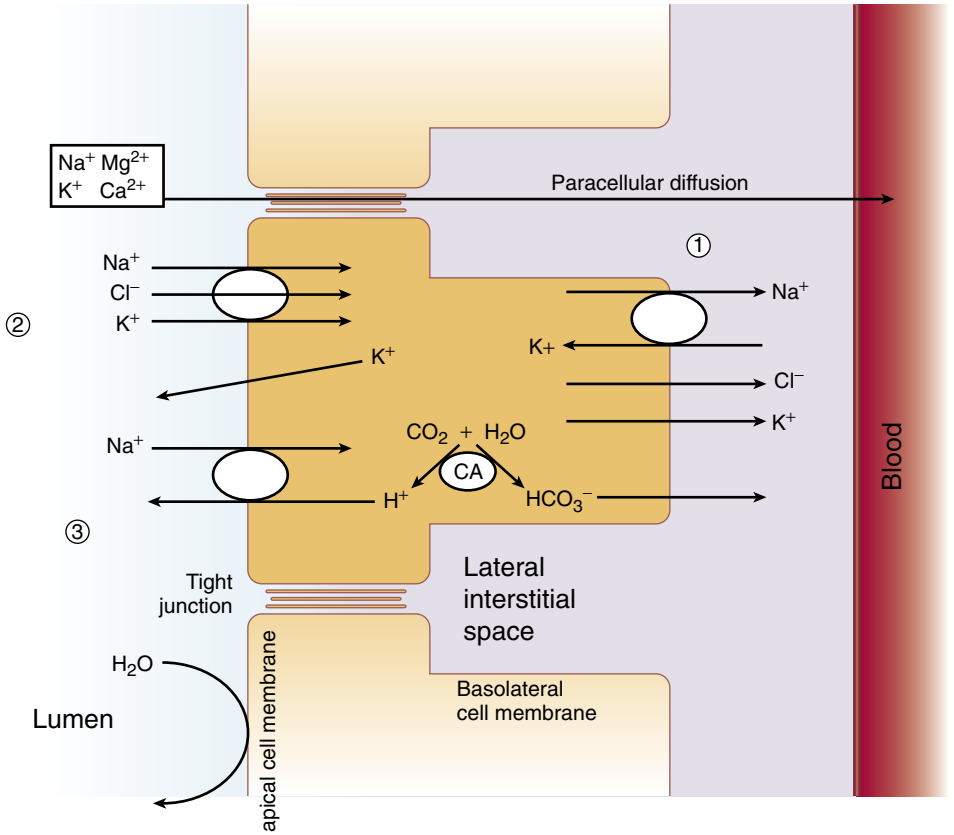


Figure 18-8 Mechanisms of tubular secretion and reabsorption. This tubular cell in the thick ascending loop of Henle encompasses the major mechanisms of secretion and reabsorption, one or more of which is used by various segments of the tubule. The most ubiquitous and important transport mechanism is the energy-requiring Na^+-K^+-ATPase pump in the basolateral cell membrane (1), which pumps sodium out into the interstitium against its concentration gradient and maintains a low intracellular concentration. This favors inward movement of sodium from the tubular lumen, facilitated by a sodium chloride symporter system on the apical cell membrane (2), which creates enough potential energy to draw in potassium against its concentration gradient and which is the primary inhibitory site of action of loop diuretics. An Na^+-H^+ antiporter system on the apical cell membrane (3) aids sodium reabsorption and extrudes H^+, thereby promoting reaction of water with carbon dioxide to form H^+ and HCO_3^- under the influence of carbonic anhydrase (CA). HCO_3^- diffuses out into the capillary. Sodium reabsorption is thereby coupled to H^+ loss and HCO_3^- reabsorption. The transport proteins create a positive charge in the lumen, which drives ions such as sodium, calcium, potassium, and magnesium passively through the tight junctions by paracellular diffusion. The thick ascending loop of Henle is uniquely highly water impermeable so that luminal osmolality progressively falls to less than 150 mOsm/kg (the "diluting segment"). *(Modified from Stanton BA, Koeppen BM: Elements of renal function.* In *Berne RM, Levy MN [eds]: Physiology, 4th ed. St. Louis, Mosby, 1998, pp 677-698.*)

trudes a primary cilium equipped with a flow-sensitive mechanosensor and a chemosensor, both linked to calcium-dependent signaling pathways that control kidney cell function and apoptosis.[1]

There are a number of protein-based active transport systems. Of these, the most important is the sodium-potassium adenosine triphosphatase (Na^+-K^+-ATPase) system, situated in the basolateral membrane. It pumps sodium out of the tubular cell into the interstitial fluid (and capillary blood) against a concentration and an electrical gradient, in exchange for potassium from inside the tubular cell. The consequent decrease in intracellular sodium concentration facilitates passive reabsorption of sodium from the tubular lumen into the cell. The transport of virtually all solutes is coupled to that of sodium.

Active transport systems that move solutes in the same direction into or out of the cell are called symporter systems, whereas those that move solutes in opposite directions are called antiporter systems. Solutes are transported by active and passive mechanisms, but water always diffuses passively along an osmotic gradient.

Proximal Tubule

The first part of the proximal tubule reabsorbs about 100% of the filtered glucose, lactate, and amino acids as well as some phosphate by coupling with sodium-symporter systems.[12] Hydrogen ions are extruded into the tubule by an Na^+/H^+ antiporter system in exchange for bicarbonate. The absorption of organic anions and bicarbonate in the first part of the proximal tubule results in a relatively high chloride concentration downstream, promoting passive ingress of chloride. This leaves the tubular fluid positively charged relative to blood, further promoting the movement of sodium from the tubular fluid into the cell.

Most NaCl is absorbed transcellularly by an Na^+/H^+ and chloride-based antiporter system in the apical cell membrane. The Na^+/K^+-ATPase system pumps sodium into the interstitial space, and a K^+/Cl^- symporter system pumps chloride. The resulting increase in osmolality draws water across as well. In all, about two thirds of the filtered water, chloride, and potassium are reabsorbed by the proximal tubule, coupled with, and strongly influenced by, sodium absorption.[12]

The proximal tubule is also an important site of secretion of many endogenous anions (bile salts, urate), cations (creatinine,

dopamine), and drugs (diuretics, penicillin, probenecid, cimetidine). Organic ions compete with each other for protein transport systems. Thus, administration of probenecid impairs tubular secretion of penicillin and prolongs its action. In chronic renal insufficiency there is an accumulation of organic acids that competes with drugs such as furosemide for secretor proteins, thereby conferring an apparent "resistance" to loop diuretics.

Thick Ascending Loop of Henle

The metabolically active component of the loop of Henle is the thick ascending loop, which reabsorbs about 20% of the filtered sodium, chloride, potassium, and bicarbonate. Only the descending loop is permeable to water. In the water-impermeable thick ascending loop, sodium is actively reabsorbed, but water remains. In this so-called diluting segment of the kidney, tubular fluid osmolality decreases to less than 150 mOsm/kg H_2O.

As in the proximal tubule, the Na+/K+-ATPase pump in the basolateral membrane is the engine that drives the resorptive capacity of the thick ascending loop.[12] Sodium moves from the tubular lumen by passive diffusion along its concentration gradient. An Na^+/H^+ antiporter system in the apical cell membrane mediates the net secretion of H^+ and reabsorption of bicarbonate.

An important symporter protein system couples the reabsorption of sodium, chloride, and potassium (the latter against its concentration gradient) across the apical membrane. Blockade of this system is the major site of action of loop diuretics in inhibiting NaCl reabsorption in the thick ascending loop of Henle.

Oxygen Balance in the Medullary Thick Ascending Loop

The kidneys receive 20% of the total cardiac output but extract relatively little oxygen. The renal arteriovenous oxygen difference $[(a\text{-}v)O_2]$ is only 1.5 mL/dL. However, there is a marked discrepancy between the renal cortex and medulla with regard to blood flow, oxygen delivery, and oxygen consumption (Fig. 18-9 and Table 18-1). The medulla receives only 6% of the RBF and has an average oxygen tension (Po_2) of 8 mm Hg. Thus, it is possible that severe hypoxia could develop in the medulla despite a relatively adequate total RBF, and the metabolically active medullary thick ascending loop of Henle is particularly vulnerable.[13]

Table 18-1 Distribution of Renal Blood Flow Between Cortex and Medulla

	Cortex	Medulla
Percent of renal blood flow	94	6
Blood flow (mL/min/g)	5.0	0.03
Po_2 (mm Hg)	50	8
O_2 extraction ratio (Vo_2/Do_2)	0.18	0.79

The renal medulla receives only a small fraction of the total renal blood flow, and flow rates are extremely slow. As a result, the tissue oxygen tension is extremely low and the medulla extracts almost 80% of the oxygen delivered to it. A very mild reduction in total and cortical renal blood flow may therefore induce ischemia and hypoxia in the renal medulla.
Do_2, oxygen delivery; O_2, oxygen; Vo_2, oxygen consumption; Po_2, oxygen tension.
Data from Brezis M, et al: The pathophysiological implications of medullary hypoxia. Am J Kidney Dis 13:253-258, 1989.

The medullary thick ascending loop is also a potential site for nephrotoxic injury. Intrarenal blood flow is regulated by endogenous vasoactive compounds. In the outer cortex, at variance to its vasodilator actions elsewhere, adenosine induces vasoconstriction by stimulation of the adenosine A_1 receptor. In the deep juxtamedullary zone, endogenous prostaglandins and nitric oxide promote vasodilation. The net effect is to direct as much available blood flow to the medulla as possible. Drugs that inhibit prostaglandin synthesis, such as nonsteroidal anti-inflammatory agents (NSAIDs), can upset this compensatory mechanism and result in medullary ischemia.

Stress (pain, trauma, hemorrhage, hypoperfusion, sepsis, congestive heart failure) activates the sympathoadrenal system and results in renal cortical constriction and potential tubular ischemia. The kidney is relatively devoid of β_2-receptors so epinephrine release induces predominant vasoconstriction through α-receptor or angiotensin activation.

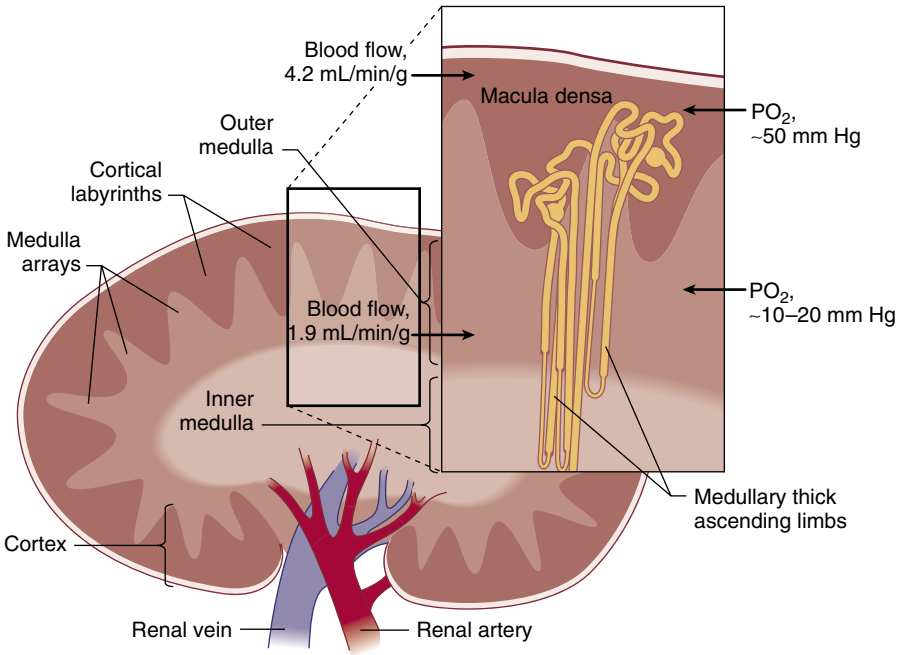


Figure 18-9 Medullary oligemia. To generate and maintain the countercurrent exchange that provides urinary concentrating ability, medullary blood flow must be slow. The juxtamedullary and medullary regions are zones of low blood flow and relative tissue hypoxia. Components of the nephron that have high oxygen consumption such as the medullary thick ascending limb (mTAL) are at high risk of oxygen supply-demand imbalance and ischemic injury. (*From Brezis M, Rosen S: Hypoxia of the renal medulla—its implications for disease. N Engl J Med 332:647-655, 1995.*)

In hemodynamically mediated renal injury, the initial response to renal hypoperfusion is increased active NaCl absorption in the thick ascending limb. This increases oxygen consumption in the presence of decreased oxygen delivery. Subsequent sympathoadrenal responses and renal cortical vasoconstriction may be a compensatory attempt to redistribute blood flow to the medulla. Ultimately, ATP stores become depleted and active NaCl reabsorption winds down. This increases the NaCl concentration in tubular fluid reaching the macula densa in the distal tubule, resulting in angiotensin release and afferent arteriolar constriction (i.e., tubuloglomerular feedback). Teleologically, the resultant decrease in GFR benefits renal oxygen balance by decreasing solute reabsorption and oxygen consumption in the medullary thick ascending loop of Henle.[13]

This hypothesis implies that ischemic or nephrotoxic insults to the renal tubules could be alleviated by the administration of loop diuretics or dopaminergic agents. These drugs inhibit active sodium reabsorption in the thick ascending limb, thereby decreasing oxygen consumption and enhancing tubular oxygen balance.

Distal Tubule and Collecting Duct

Sodium reabsorption is mediated by an apical cell membrane NaCl symporter system, which is the site of action of thiazide diuretics.[12] The last part of the distal tubule is composed of two types of cells. Principal cells reabsorb sodium and water and secrete potassium via the Na^+/K^+-ATPase pump, and intercalated cells secrete H^+ and reabsorb bicarbonate by an H^+-ATPase pump in the apical cell membrane.

Regulatory Mechanisms in Salt and Water Reabsorption

Osmotic Equilibrium

The ability of the kidney to concentrate urine is dependent on the interaction of at least three processes: (1) the generation of a hypertonic medullary interstitium by the countercurrent mechanism and urea recycling, (2) concentration and then dilution of tubular fluid in the loop of Henle, and (3) the action of antidiuretic hormone (now known as arginine vasopressin [AVP]) in increasing water permeability in the last part of the distal tubule and collecting ducts.

The medullary interstitium is rendered hypertonic by the countercurrent multiplier effect of the loop of Henle. The primary mechanism is the separation of solute from water (the single effect) by the combination of NaCl reabsorption and water impermeability in the ascending limb. This results in increased NaCl concentration and osmolality in the medullary interstitium. The descending limb is freely permeable to water, which diffuses into the interstitium along the osmotic gradient; and the tubular fluid becomes progressively hyperosmotic at the bend of the loop.

The vasa recta, which are closely applied to the long loops of Henle of juxtamedullary nephrons, maintain this condition by removing water and adding solute as they pass through the medullary interstitium. A standing osmotic gradient is thereby set up between the cortex (300 mOsm/kg), juxtamedullary zone (600 mOsm/kg), and deep medulla (1200 mOsm/kg). This process is enhanced by the passive recycling of urea, which diffuses out of the inner medullary collecting duct into the interstitium and thence into the distal loop of Henle. These processes are summarized in Figure 18-10.

Tubular Concentration and Dilution

Hypovolemia

Contraction of the extracellular volume (hypovolemia) activates a series of vasoconstrictor, salt-retaining neurohormonal systems: the sympathoadrenal system, the renin-angiotensin-aldosterone axis, and AVP. Initially, the GFR and filtered load of sodium decrease. Sodium reabsorption in the proximal tubule is increased from about 66% to 80% by sympathetic activity and angiotensin II as well as by the decline in peritubular capillary pressure induced by renal vasoconstriction. Sodium delivery to the thick ascending loop of Henle, distal tubule, and collecting duct is decreased, but aldosterone promotes reabsorption of sodium at these sites. Under the influence of AVP, water is also avidly reabsorbed in the collecting duct so that the urine becomes highly concentrated (osmolality, 600 mOsm/kg) but with virtually no sodium (10 mEq/L).

Diuretics abolish the kidney's ability to concentrate urine by washing out the hypertonic medulla. They do this either by an osmotic effect that prevents water reabsorption (e.g., mannitol) or by inhibition of active NaCl transport in the thick ascending loop (e.g., furosemide) or the first part of the distal tubule (e.g., hydrochlorothiazide). An early and important manifestation of acute tubular necrosis is the loss of urinary concentrating ability caused by the breakdown of the energy-requiring Na^+/K^+-ATPase pump in the thick ascending loop of Henle.

Hypervolemia

Expansion of the extracellular volume or hypervolemia is controlled by a series of vasodilator, salt-excreting neuropeptides, of which atrial, or A-type, natriuretic peptide (ANP) is predominant. The GFR and filtered sodium load increase because of a combination of reflex decreases in sympathetic and angiotensin II activity and the release of ANP. Together with the increase in peritubular capillary hydrostatic pressure, these responses cause sodium reabsorption in the proximal tubule to decrease from 67% to 50%. The decline in plasma aldosterone decreases sodium absorption from the thick ascending loop of Henle to the collecting duct. The presence of ANP and absence of AVP impairs water absorption at the collecting duct so that dilute urine (osmolality, 300 mOsm/kg) with abundant sodium (80 mEq/L) is produced.

Loop diuretics, which depress tubular resorptive capacity, and acute tubular necrosis, which abolishes it completely, may generate an identical urinary profile (low osmolality, high urinary sodium) even in the presence of hypovolemia.

Evaluation of Renal Function

Clinical Markers of Renal Function

Urine Output

Perioperative oliguria is common, is almost always prerenal, and rarely implies acute renal failure. On the other hand, the absence of oliguria does not exclude it. Perioperative oliguria is defined as a urine flow rate less than 0.5 mL/kg/hr and is often interpreted as a sign of renal dysfunction. However, in the perioperative

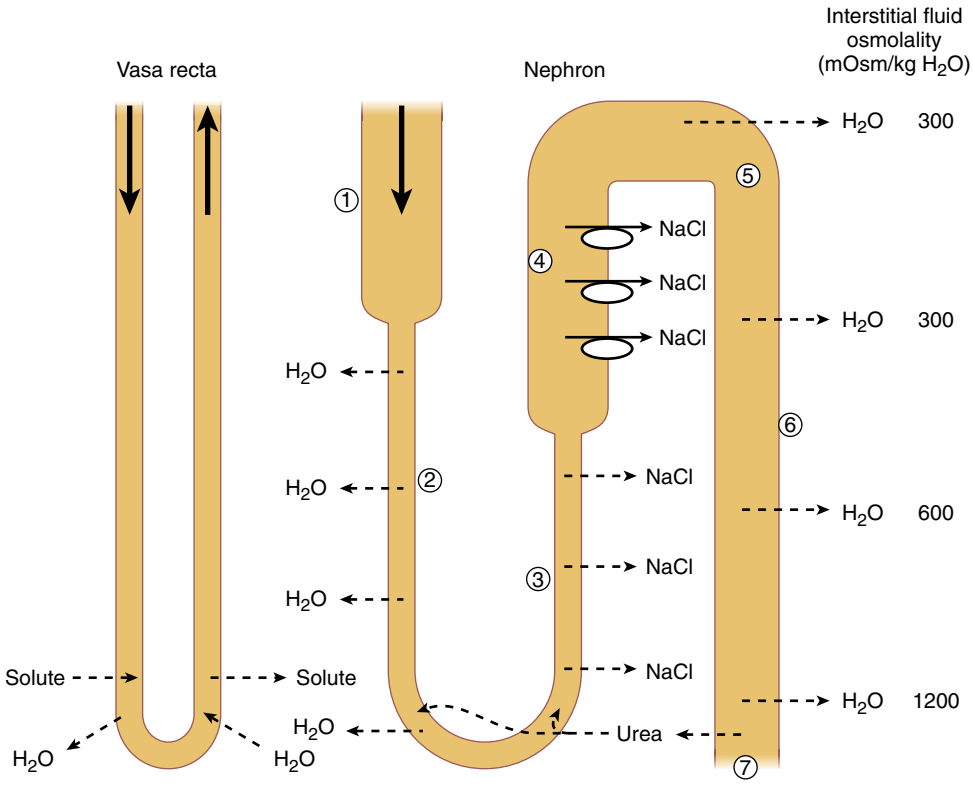


Figure 18-10 Tubular concentration of urine. The juxtamedullary nephrons have long loops of Henle associated with the vasa recta. *Dashed arrows* represent passive movement of fluid or solutes along concentration or osmolar gradients; *solid arrows* represent active transport. (1) Tubular fluid enters the distal proximal tubule iso-osmotic with plasma (300 mOsm/kg). In the descending limb of Henle (2), water rapidly diffuses out into the increasingly hypertonic medulla and is removed by the vasa recta so that the tubular fluid becomes hypertonic, owing largely to concentration of sodium chloride (NaCl). Urea diffuses in from the hypertonic interstitium, further increasing tubular fluid osmolality (1200 mOsm/kg). In the thin ascending loop of Henle (3), NaCl passively diffuses into the interstitium along its concentration gradient but water is trapped in the water-impermeable tubule, which progressively decreases tubular fluid osmolality. Urea passively diffuses into the tubular fluid (urea recycling). Tubular dilution is accelerated by active reabsorption of NaCl in the thick ascending loop (the diluting segment) and proximal distal tubule (4). The fluid entering the distal tubule is quite hypo-osmotic (100 mOsm/kg). In the collecting segment (5), the osmolality of the tubular fluid returns to that of plasma (300 mOsm/kg) but, unlike the contents of the proximal tubule, the solute component consists largely of urea, creatinine, and other excreted compounds. Increased plasma antidiuretic hormone renders the cortical and medullary collecting ducts (6) permeable to water, which passively diffuses into the hypertonic medullary interstitium. Even though some urea diffuses out into the medulla, the maximal osmolality of concentrated urine (7) approaches that of the hypertonic medullary interstitium, about 1200 mOsm/kg. In the absence of antidiuretic hormone, the collecting ducts remain impermeable to water and the urine is diluted. (*From Stanton BA, Koeppen BM: Control of body fluid osmolality and volume.* In *Berne RM, Levin HR [eds]: Physiology, 4th ed. St. Louis, Mosby, 1998, pp 715-743.*)

period, oliguria is almost inevitable. It is induced by hypotension, occurs as an (appropriate) prerenal response to intravascular hypovolemia, or is a manifestation of the physiologic response to surgical stress[14] (see "Neurohormonal Regulation of Renal Function").

Complete, often abrupt cessation of urine flow suggests a postrenal obstruction, which could occur at the level of the renal pelvis, ureters, bladder, urethra, or urinary catheter. However, subtotal obstruction may also develop into acute renal failure even though urine flow persists, albeit at a decreased rate.

Urine flow rate is an unreliable marker of acute renal failure and may vary from anuric (zero flow), to oliguric (urinary flow rate <15 mL/hr), to nonoliguric (15-80 mL/hr), to polyuric (>80 mL/hr). An attempt has been made to unify the definition of acute kidney injury by the RIFLE criteria, based on changes in serum creatinine and urine flow.[15] The first three categories (Risk, Injury, Failure) are defined in part by oliguria (<0.5 mL/kg/hr) for 6, 12, and 24 hours, respectively. However, this does not take into consideration that nonoliguric renal failure is the most common manifestation of perioperative acute kidney injury.

Blood Urea Nitrogen

Urea is continuously formed by the metabolism of ammonia in the liver. Hepatic deamination implies the splitting off of amide ($-NH_2$) groups from amino acids, and their conversion to ammonia, which enters the arginine cycle and is converted to urea. Urea nitrogen is a small, uncharged molecule, not protein bound, that is rapidly cleared from the blood by glomerular filtration. It subsequently undergoes reabsorption by the tubules so the blood urea nitrogen (BUN) does not correlate directly with GFR.

The normal range of BUN is 5 to 10 mg/dL; given the normal range of serum creatinine (0.5-1.0 mg/dL), the normal ratio of BUN to serum creatinine is about 10:1. An increase in BUN to serum creatinine ratio of greater than 20:1 implies the existence of a prerenal syndrome (prerenal azotemia). However, elevation of BUN out of proportion to decreases in GFR occurs whenever there is increased protein catabolism and formation of urea nitrogen. This scenario occurs with absorption of blood from the gastrointestinal tract, corticosteroid therapy, major trauma, and sepsis. In contrast, the BUN may be misleadingly low

when its production is impaired by severe malnutrition (protein depletion) or severe liver disease (inability to convert ammonia to urea).

Serum Creatinine

Serum creatinine reflects the balance between creatinine production by muscle and creatinine excretion by the kidney, which is dependent on the GFR. Creatinine generation rate varies with muscle mass, physical activity, protein intake, and catabolism. However, when these processes are in equilibrium and renal function is stable, serum creatinine is a useful marker of GFR.

The relationship between serum creatinine and GFR is inverse and exponential. A doubling of the serum creatinine concentration implies a halving of the GFR. An increase in the serum creatinine value from 0.8 to 1.6 mg/dL may not generate much attention, but it indicates a 50% decrease in GFR. A much larger increase from 4 to 8 mg/dL also represents a 50% decrease in GFR, but by this time renal insufficiency is well established (Fig. 18-11). After a transient renal insult (e.g., suprarenal aortic cross-clamping), the serum creatinine level may increase for a few days while GFR is actually recovering. In oliguric acute renal failure, the serum creatinine value is directly proportional to the creatinine generation rate. Creatinine clearance is reliably low but is associated with a wide variability of serum creatinine concentration.

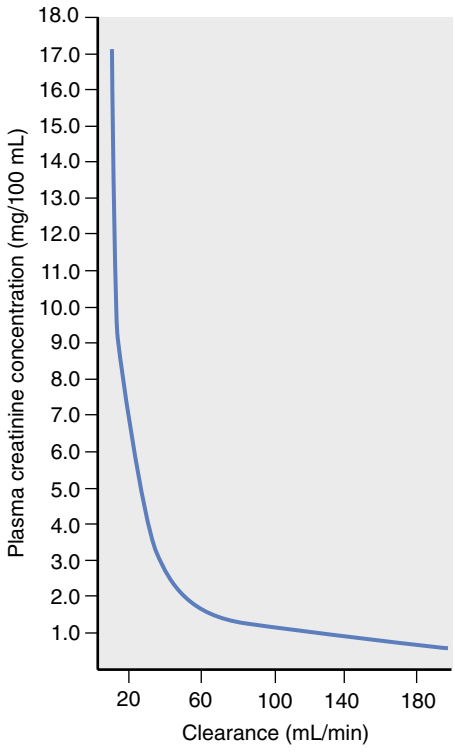


Figure 18-11 Relationship between serum creatinine and GFR. The relationship between serum creatinine and GFR as measured by creatinine clearance is reciprocal and exponential. Doubling of the serum creatinine corresponds to halving of the GFR. Relatively large declines in GFR from normal are associated with small increases in serum creatinine until GFR decreases below 60 mL/min; further decrements are associated with large increases in serum creatinine. (*From Alfrey AC, Chan L: Chronic renal failure: Manifestations and pathogenesis.* In *Schrier RW [ed]: Renal and Electrolyte Disorders, 4th ed. Boston, Little, Brown, 1992, p 541.*)

Limitations to Serum Creatinine as a Reflection of GFR

Serum creatinine is usually measured by the Jaffé reaction, a chromogenic assay based on the red color of the creatinine complex with alkaline picrate. It also picks up other normally occurring chromogens, such as glucose, protein, ketones, and ascorbic acid, which represent about 14% of total creatinine when renal function is normal, although substantially less when the serum creatinine level is elevated. Ketoacidosis, barbiturates, and cephalosporin antibiotics may artifactually increase the serum creatinine level by as much as 100%, and cimetidine and trimethoprim block its secretion by the tubule. *N*-acetylcysteine, an antioxidant advocated as a renoprotective agent in contrast nephropathy,[16] decreases serum creatinine levels, which may in part account for its apparently beneficial effect on renal function.[17]

The serum creatinine concentration does not increase above the normal range until the GFR declines below 50 mL/min, and large declines in GFR may occur above this level without a concomitant increase in the serum creatinine value. The creatinine generation rate is relatively consistent in a given individual, but it varies with muscle mass, rate of catabolism, physical activity, and protein intake.[18] In a cachectic patient with very low muscle mass, creatinine generation may be so feeble that the serum creatinine level remains "normal" (<0.9 mg/dL) even in the presence of a GFR less than 25 mL/min. The GFR declines progressively and predictably with age, from about 125 mL/min in a healthy 20-year old to about 60 mL/min in an 80-year old (or a 60-year old with atherosclerosis). Because these changes occur at a GFR greater than 50 mL/min, the impairment induced by aging is not reflected by the serum creatinine concentration.

Creatinine is soluble, freely distributes through the total body water, and is diluted by the 10% to 15% increases in total body water that occur with fluid administration and retention during major surgery. It is not uncommon for the serum creatinine concentration to be decreased from baseline on the first postoperative day (e.g., 1.5 to 1.2 mg/dL). Subsequently, when total body water is decreased by fluid mobilization and diuresis, the serum creatinine value increases (e.g., from 1.2 to 1.5 mg/dL). This does not necessarily imply acute kidney injury and a decline in GFR but may simply represent hemoconcentration and a re-equilibration to baseline.

Serum creatinine is a useful marker of stable renal function, but it is unreliable when GFR is rapidly changing.[18] If there are no changes in its volume of distribution (see earlier), the serum creatinine concentration represents an equilibrium between the creatinine generation rate, dependent on muscle mass and catabolic activity, and the creatinine excretion rate, dependent on (and reflective of) the GFR. An intervention such as suprarenal aortic cross-clamping causes instantaneous cessation of renal blood flow, GFR, and urinary creatinine excretion. However, measured serum creatinine would still be at baseline and would not detectably increase for several hours. Because it may take up to 48 hours for GFR to return to baseline, in the postoperative period the serum creatinine value may still increase for a few days while GFR is actually recovering.

Cystatin C

There is great interest in defining endogenous plasma markers that provide a more reliable, early indicator of changing GFR, especially in acute kidney injury.[19] One that has received prominence is cystatin C, a cysteine-protease inhibitor that is released into the circulation by all nucleated cells. It is completely filtered

by the glomerulus and not secreted by the tubular epithelium so that its serum levels bear a close relationship to serum creatinine, and thereby GFR.[20] Unlike creatinine, however, serum cystatin C is not affected by muscle mass, age, or gender and in certain clinical situations appears to be a more accurate predictor of low GFR than serum creatinine does.[21,22] However, there is also evidence that factors such as cigarette smoking, inflammation (elevated C-reactive protein), and immunosuppressive therapy affect cystatin C levels independently of GFR.[23] At this stage, cystatin C remains an investigational marker and has not supplemented serum creatinine in clinical practice.

Assessment of Glomerular Filtration Rate

Serum Creatinine–Based Nomograms

In clinical investigation, nomograms based on population studies are commonly used to estimate GFR while avoiding the necessity of a timed urine collection. One example is that formulated by Cockroft and Gault utilizing age, weight, serum creatinine concentration, and gender:

$$\mathrm{GFR}\left(\text{in mL/min}\right)=\left(140-\text{age}\right)\times\text{weight in kg}/\text{serum creatinine}\times 72$$

For females, the result is multiplied by 0.85 to obtain the derived GFR.

In this formula, the body weight that is used may substantially alter the derived GFR. In obese or edematous patients, the total body weight is much greater than the lean body mass from which creatinine is derived, and GFR is overestimated. In cachectic patients with depleted lean body mass, creatinine production is so low that serum creatinine is frequently less than 1.0 mg/dL and overestimates the true GFR. Robert and associates[24] adjusted the Cockroft-Gault equation to incorporate ideal body weight from a nomogram and serum creatinine concentration corrected to 1.0 mg/dL (if < 1.0 mg/dL). Using this modification they found that single measurements in hemodynamically stable patients correlate more closely with inulin clearance than either a 30-minute or a 24-hour creatinine clearance.

A more complex nomogram, based on a study called Modification of Diet in Renal Disease (MDRD),[25] is independent of body weight:

$$\mathrm{GFR}\left(\text{in mL/min}\right)=170\times\text{serum creatinine}^{-0.999}\times\text{age}^{-0.176}\times\text{BUN}^{-0.170}\ \text{albumin}^{0.318}$$

For females, the derived GFR is multiplied by 0.762; and for black patients, by 1.18.

When renal function is rapidly changing, serum creatinine–based nomograms are subject to the same limitations as serum creatinine itself. In fact, serum creatinine levels do not begin to increase above normal until the GFR declines below 50 mL/min/1.73 m^2, and occasionally they will remain normal even when the GFR dips as low as 20 to 40 mL/min/1.73 m^2.

Renal Clearance Techniques

Clearance is the most commonly used technique to estimate GFR, using compounds that are predominantly filtered by the glomerulus and neither secreted nor reabsorbed by the renal tubules.[26]

Based on the Fick principle, the amount of substance *x* excreted by the kidney equals the amount delivered in the arterial supply minus the amount in the venous return:

$$\text{Excretion}_x=\text{delivery}_x-\text{return}_x$$

Therefore,

$$\text{Delivery}_x=\text{return}_x+\text{excretion}_x$$

The amount of substance *x* delivered to the kidney is the product of the arterial plasma concentration (Pa_x) and RBF. The amount returning from the kidney is the product of the venous plasma concentration (Pv_x) and RBF. The urinary excretion rate of substance *x* is the product of its urinary concentration (U_x) and the urine flow rate in milliliters per minute (V).

Therefore,

$$\left(\mathrm{Pa}_x\cdot\ \mathrm{RBF}\right)=\left(\mathrm{Pv}_x\cdot\ \mathrm{RBF}\right)+\left(\mathrm{U}_x\cdot\ \mathrm{V}\right)$$

However, in practice, RBF and venous return are not measured. Instead, the removal of substance *x* from the plasma by the kidney is expressed in the concept of clearance. Clearance (C) is defined as the virtual volume of plasma cleared of substance *x* per unit time, in milliliters per minute. This allows the urinary excretion rate of *x* to be equated to its renal arterial plasma concentration:

$$\mathrm{Pa}_x\cdot\ \mathrm{C}=\mathrm{U}_x\cdot\ \mathrm{V}$$

If the assumption is made that the concentration of *x* in renal arterial and venous plasma is identical, the clearance of substance *x* may be calculated using a urine sample, arm venous sample, and measured urinary flow rate:

$$\mathrm{C}_x\cdot\ =\mathrm{U}_x\cdot\ \mathrm{Pa}_x/\mathrm{V}$$

Inulin Clearance

Inulin is an inert polyfructose sugar that is completely filtered by the glomerulus and is neither secreted nor reabsorbed by the renal tubules. The volume in milliliters of plasma cleared of inulin per minute represents the GFR (in mL/min). After an intravenous loading dose of 30 to 50 mg/kg, a continuous infusion of inulin is given to establish a steady-state plasma concentration of 15 to 20 mg/dL. The bladder is usually flushed with air to eliminate any pooled urine. After a carefully timed urine collection (which can be as short as 30 minutes), urine and plasma inulin concentration (U_{IN}, P_{IN}) are measured and inulin clearance (C_{IN}) is calculated:

$$\mathrm{GFR}=\mathrm{C}_{\mathrm{IN}}=\mathrm{U}_{\mathrm{IN}}\cdot\ \mathrm{V}/\mathrm{P}_{\mathrm{IN}}$$

Normal values for inulin clearance are 110 to 140 mL/min/1.73 m^2 (males) and 95 to 125 mL/min/1.37 m^2 (females).

Although inulin clearance is the "gold standard" for measurement of GFR, it is seldom used clinically because its accurate measurement is laborious and requires meticulous attention to detail. Large changes in blood glucose during the test may interfere with its measurement. The predicted variability of inulin clearance is 20% when measurements are compared at two different times in the same individual and 40% when measurements are compared between two individuals.[26]

Sodium iothalamate, a radiocontrast dye, has been substituted for inulin and facilitates accurate assessment of rapid changes in GFR in acute kidney injury.[27]

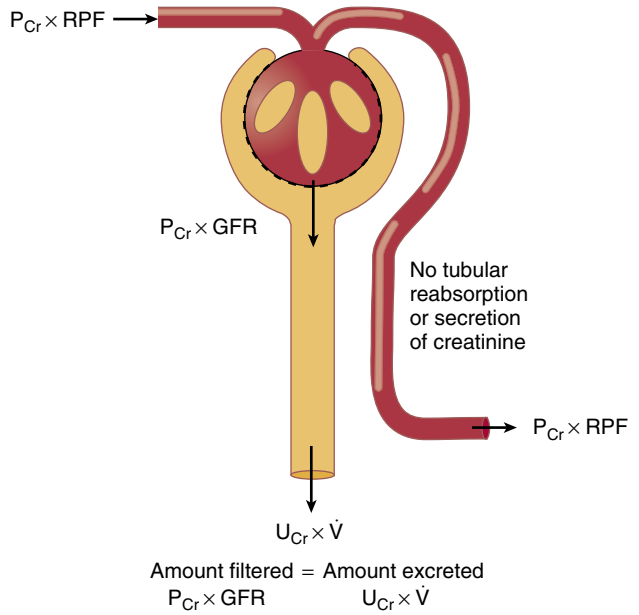


Figure 18-12 Renal handling of creatinine. Creatinine is freely filtered by the glomerulus and there is normally an inconsequential amount secreted or reabsorbed by the tubules. Thus, the amount of creatinine filtered is equivalent to the amount excreted in the urine. For a more detailed explanation, see text. P_{Cr}, plasma creatinine concentration; RPF, renal plasma flow; U_{Cr}, urinary concentration of creatinine; V, urine flow rate. (*From Koeppen BM, Stanton BA: Glomerular filtration and renal blood flow In Koeppen BM, Stanton BA [eds]: Renal Physiology, 4th ed. Philadelphia, Mosby Elsevier, 2007, pp 31-46.*)

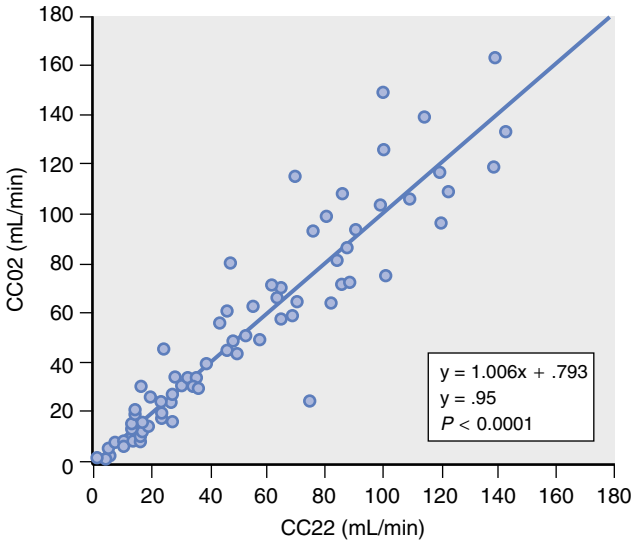


Figure 18-13 Creatinine clearance: 2-hour versus 22-hour values. There is a close and significant correlation in creatinine clearance estimation from a 2-hour and a 22-hour urine collection. CC02, 2-hour urine collection; CC22, 22-hour urine collection. (*From Sladen RN, Endo E, Harrison T: Two-hour versus 22-hour creatinine clearance in critically ill patients. Anesthesiology 67:1013-1016, 1987.*)

Creatinine Clearance

Creatinine, the endogenous end product of creatine phosphate metabolism, is normally generated from muscle at a very uniform rate and is handled by the kidney in a manner similar to that of inulin (Fig. 18-12). Thus, creatinine clearance (C_{CR}) provides a simple, inexpensive bedside estimate of GFR. A single blood sample is drawn at the midpoint of a carefully timed urine collection, and urine and plasma creatinine (U_{CR}, P_{CR}) and urinary flow rate in mL/min (V) are used to calculate GFR:

$$GFR = C_{CR} = U_{CR} \cdot V/P_{CR}$$

The creatinine clearance is far more accurate in tracking rapid alterations in GFR than the serum creatinine alone, because changes in GFR immediately alter the *creatinine excretion rate,* which is incorporated into the equation above as $U_{CR} \times V$.

The precise timing, not the duration, of the urine collection is the critical issue. If a brisk urine flow is induced by diuresis, and care is taken to empty the bladder, the variability of creatinine clearance is no greater with a 1-hour urine collection than with a 24-hour collection. In catheterized patients with urine flow rates of more than 15 mL/hr, creatinine clearance obtained with a 2-hour urine collection gives values equivalent to those obtained with a 22-hour collection.[28] In the previous example, a 2-hour creatinine clearance obtained at the beginning and end of the 24-hour period would truly reflect the halving of GFR represented by a doubling of the serum creatinine value from 1 to 2 mg/dL. In critically ill patients, a changing GFR can be closely tracked by serial estimations of using a short, carefully timed urine collection (Figs. 18-13 to 18-15). In trauma patients, a 1-hour creatinine clearance of less than 25 mL/min determined within 6 hours of surgery reliably predicted postoperative acute renal failure, despite the absence of oliguria.[29]

There is considerable variation in the normal range of creatinine clearance. Tobias and associates reported a variation in creatinine clearance between 88 and 148 mL/min and in serum creatinine concentration between 0.9 and 1.5 mg/dL in a single healthy individual over 5 years. There is also a diurnal variation, with higher values in the afternoon and a variance of up to 25% around mean values. It is prudent to obtain short-collection creatinine clearance estimations at the same time each day to minimize diurnal variability. "Normal" creatinine clearance is related to body surface area and weight, so values may fluctuate widely in patients with cachexia or edema.

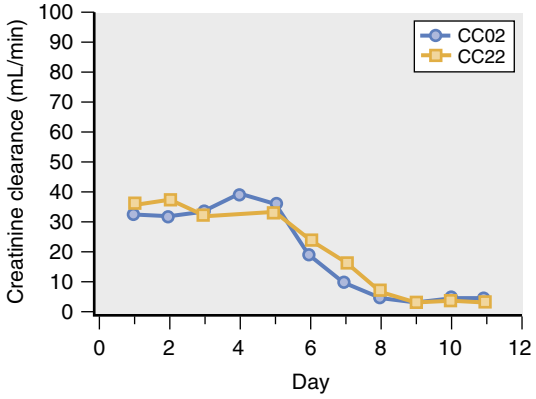


Figure 18-14 New-onset acute renal failure. In a patient developing acute renal failure in the intensive care unit, the exponential decline in creatinine clearance is tracked equally well whether a 2-hour (CC02) or a 22-hour (CC22) urine collection is used. However, data from the 2-hour collection are available well before those from the 22-hour collection.

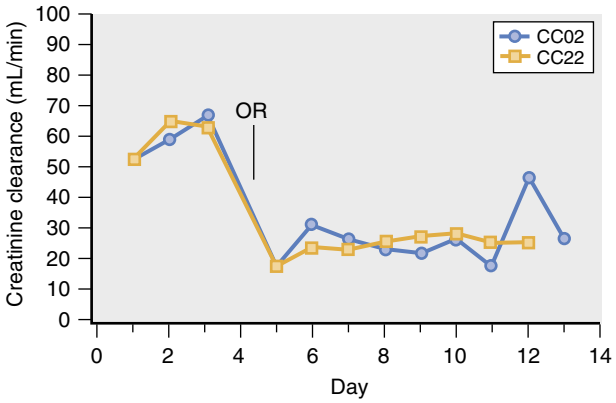


Figure 18-15 Renal revascularization. A patient with renovascular hypertension and renal insufficiency was admitted to the intensive care unit for preoperative monitoring and stabilization. Bilateral renal revascularization was performed, and after return from the operating room there was a substantial decline in renal function. These changes were tracked equally well by creatinine clearance derived from a 2-hour (CC02) and a 22-hour (CC22) collection.

Creatinine clearance has a number of inherent limitations even if collection error is carefully avoided. First, it is subject to many of the limitations imposed by the measurement of creatinine itself (see earlier). Unlike inulin, about 20% of creatinine is secreted by the proximal tubule, so that creatinine clearance overestimates GFR, and the ratio between the clearance of creatinine and inulin is 1.2:1. As the GFR declines, tubular secretion of creatinine increases. When GFR is less than 40 mL/min/1.73 m^2, a creatinine:inulin clearance ratio as high as 1.81 to 2.51 may be achieved. In patients with normal renal function, the underestimate of GFR induced by the Jaffé reaction is balanced by the overestimate of GFR induced by tubular creatinine secretion, and creatinine clearance provides a reasonable representation of GFR. However, widely used drugs such as trimethoprim, H_2-antagonists, and salicylates block tubular secretion of creatinine and may elevate serum creatinine and decrease creatinine clearance. When serum levels of creatinine are very high, it is excreted into the gut and undergoes extrarenal metabolism by intestinal organisms.

Given these constraints, an isolated creatinine clearance estimation may not reveal early renal dysfunction. Nonetheless, serial estimations of creatinine clearance provide a useful clinical guide to alterations in renal function and prognosis. Postoperatively, daily measurement of creatinine clearance is useful in guiding the dosing of renally excreted, potentially nephrotoxic aminoglycoside antibiotics (gentamicin, tobramycin, amikacin) or calcineurin antagonists (cyclosporine, tacrolimus). Because the GFR may decline to less than 50% of normal before serum creatinine increases above the normal range, an observed decrease in creatinine clearance may allow down-adjustment of drug dosing before nephrotoxicity becomes established and the drug accumulates even further.

The variability of creatinine clearance diminishes as GFR declines; in fact, loss of variability is a clue to deteriorating renal function. Directional changes between creatinine clearance and inulin clearance show good agreement. At low levels of GFR, a creatinine:inulin clearance ratio as high as 2:1 (e.g., 12 versus 6 mL/min) would induce little actual difference in clinical management.

Plasma Clearance

Measurement of the rate of disappearance (plasma clearance) of a substance that is completely eliminated by glomerular filtration is an alternate method for measuring GFR without the need for a simultaneous urine collection. It involves an intravenous bolus dose and/or infusion of the marker, followed by measurement of multiple plasma levels to calculate its disappearance rate. The methodology does depend on the achievement of a steady-state plasma concentration of the marker, which is difficult to achieve with rapid changes in GFR.[27]

Numerous markers are used, including nonradioactive inulin and iothalamate, as well as radioisotopes such as ^{51}Cr-ethylenediaminetetraacetic acid (EDTA), ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA), and ^{125}I-iothalamate. The latter two markers, which utilize measurement of decay in radiation, have shown promise in the rapid assessment of GFR.

Tubular Function Tests

Tests of renal tubular function measure urinary concentrating ability and sodium and urea handling. As such, they can distinguish oliguria due to dehydration (prerenal syndrome) from that due to tubular injury (acute tubular necrosis).

In prerenal oliguria, tubular function is preserved; in fact, it is "switched on" to retain salt and water, resulting in concentrated urine that is low in sodium. With the exception of refractory prerenal states such as severe sepsis and end-stage liver failure (see later), normalization of hemodynamic status reverses oliguria and tubular activation. The administration of potent diuretics may override tubular conservation, resulting in dilute urine that is high in sodium (natriuresis), indistinguishable from acute tubular necrosis (see later). However, if intravascular hypovolemia is severe enough, tubular sodium retention and low urinary sodium may persist despite the administration of diuretics such as low-dose dopamine.[30]

In established acute tubular necrosis, concentrating ability and sodium conservation are lost, resulting in dilute urine with high sodium that is not reversed by restoration of normal RBF. However, in nonoliguric renal failure, which accounts for as much as 75% of cases of acute tubular necrosis encountered clinically,[31] the changes in tubular function are less distinct from those of the prerenal syndrome.

Urinary Concentrating Ability

Concentrating ability is a very sensitive barometer of tubular function. In prerenal states, urinary osmolar concentration is markedly increased. In acute tubular necrosis, the ability to concentrate urine may be lost 24 to 48 hours before serum creatinine or BUN starts to increase.

Urine-to-Plasma Osmolar Ratio

The normal tubular response to dehydration or hypovolemia is to concentrate the urine and increase urine osmolality above 450 mOs/kg, compared with a normal serum or plasma osmolality of 280 to 300 mOs/kg. Thus, a prerenal syndrome is indicated by a urine-to-plasma osmolar ratio ($U:P_{OSM}$) of greater than 1.5. Loss of concentrating ability, or isosthenuria ($U:P_{OSM} = 1.0$), in the presence of oliguria implies tubular damage and established acute renal failure. However, isosthenuria can be induced in a prerenal state when diuretics are administered (see earlier).

Free Water Clearance

Free water clearance (C_{H_2O}) is a measure of renal water regulation by tubular dilution or concentration of urine. In essence, free water is cleared by the tubules in response to hypervolemia ("positive free water clearance") or retained in response to hypovolemia ("negative free water clearance"). The kidney's capacity for water regulation is enormous, and C_{H_2O} can vary from +18 L to −8 L/day.[32] C_{H_2O} is calculated by distinguishing the renal clearance of solute from that of free water.

The solute or osmolar clearance (C_{OSM}) is calculated by standard methods, using urine osmolality in mOs/kg (U_{osm}), plasma osmolality in mOs/kg (P_{OSM}), and urine flow in mL/min (V):

$$C_{OSM} = \left(U_{OSM} \cdot V\right) / P_{OSM} \left(\text{in mL/min}\right)$$

Then, the osmolar clearance is subtracted from the urine flow rate to give free water clearance:

$$C_{H_2O} = V - C_{OSM} \left(\text{in mL/min}\right)$$

This implies that when urine is diluted and flow is greater than osmolar clearance, C_{H_2O} is positive, and when urine is concentrated and flow is less than osmolar clearance, C_{H_2O} is negative. Negative free water clearance (i.e., free water retention) is also known as tubular conservation of water (TC_{H_2O}) and represents the volume of fluid that would have to be added to the urine to make its osmolality equivalent to that of plasma.[32]

With the onset of acute tubular necrosis and loss of concentrating ability, the urine becomes isosmotic, and C_{H_2O} approaches zero (± 0.25 mL/min). However, in distinguishing between prerenal and intrarenal oliguria, C_{H_2O} does not really provide any more information about concentrating ability than $U:P_{OSM}$, and, in addition, it requires a timed urine collection.

Water Conservation

Urine-to-Plasma Creatinine Ratio

The urine-to-plasma creatinine ratio ($U:P_{CR}$) represents the proportion of water filtered by the glomerulus that is abstracted by the entire tubule. Normally, about 98% of water is abstracted and urine creatinine is much greater than plasma creatinine. The ratio can increase 100-fold in severe prerenal states. When tubular function is lost, the ratio declines to less than 20:1.

For example, two patients have oliguria with a serum creatinine elevated to 2.0 mg/dL. In patient A, the urine creatinine is 100 mg/dL, and in patient B, it is 20 mg/dL. Patient A likely has a prerenal state because tubular water abstraction is high (U:P creatinine = 50:1), whereas patient B likely has acute tubular necrosis because tubular water abstraction is impaired (U:P creatinine = 10:1).

Sodium and Urea Conservation

Urine Sodium

Dehydration or hypovolemia markedly stimulates tubular sodium reabsorption at the medullary thick ascending limb and distal tubule. In the prerenal syndrome, oliguria is characterized by a very low urine sodium (U_{Na}) value, less than 20 mEq/L. Typically, this response is reversed by restoration of intravascular volume. However, in two situations, severe sepsis and the hepatorenal syndrome of liver failure, refractory oliguria with low urine sodium persists despite aggressive fluid resuscitation. The pathogenesis is multifactorial, but common to both syndromes is endotoxemia, which induces renal vasoconstriction and avid tubular sodium reabsorption.

In established acute renal failure, the tubular ability to conserve sodium and protect the intravascular volume is lost and urine sodium exceeds 60 to 80 mEq/L. Note that after recent diuretic therapy a high urine sodium value cannot be interpreted as tubular injury but a persistently low urine sodium value implies the existence of an intense prerenal state (see earlier).[30]

Fractional Excretion of Sodium

Fractional excretion of sodium (FE_{Na}) is an additional means of evaluating tubular responses to hypovolemia and hypervolemia. FE_{Na} expresses sodium clearance as a percentage of creatinine clearance. The implication is that in hypovolemia, sodium clearance (and thus FE_{Na}) declines to reflect tubular sodium conservation; in hypervolemia, the opposite occurs.

FE_{Na} is calculated as follows:

$$FE_{Na} = \left(\text{sodium clearance/creatinine clearance}\right) \cdot 100\%$$

Based on the relationship expressed earlier:

$$FE_{Na} = \left(U_{Na} \cdot V / P_{Na}\right) / \left(U_{Cr} \cdot V / P_{Cr}\right) \times 100\%$$

Urine flow rate (V) is identical in the numerator and denominator and it cancels out:

$$FE_{Na} = \left(U_{Na} / P_{Na}\right) / \left(U_{Cr} / P_{Cr}\right) \cdot 100\%$$

Thus, FE_{Na} may be calculated from a spot sample of blood and urine without requiring a timed urine collection.

During dehydration or hypovolemia, sodium clearance and FE_{Na} are decreased to less than 1% of creatinine clearance. When tubular ability to conserve sodium is lost in acute renal failure, FE_{Na} increases to more than 3%. However, FE_{Na} increases with normal tubular function after diuretic therapy and during postoperative sodium mobilization. Sequential increases in FE_{Na} associated with a declining creatinine clearance provide a more reliable indicator of deteriorating renal function than an isolated high FE_{Na}.

Fractional Excretion of Urea Nitrogen

Unlike sodium, handling of urea in the ascending loop of Henle and distal tubule is subject to passive forces and is little influenced by loop diuretic therapy. Fractional excretion of urinary nitrogen (FE_{UN}) is related to water reabsorption in the proximal tubules, which increases to compensate for impaired renal perfusion in a prerenal state. Urea is also reabsorbed, leading to an increased BUN:SCr ratio and decreased FE_{UN}. It has been suggested that the FE_{UN} is more sensitive and specific than the FE_{Na} in differentiating oliguria due to acute tubular necrosis from a prerenal syndrome, especially in the presence of loop diuretic therapy.[33] The FE_{UN} is calculated identically to FE_{Na}:

$$FE_{UN} = \left(U_{UN} / BUN\right) / \left(U_{Cr} / P_{Cr}\right) \cdot 100\%$$

where U_{UN} is the urinary urea nitrogen, U_{Cr} is urine creatinine, and P_{Cr} is plasma creatinine.

In oliguric patients, an FE_{UN} of less than 35% indicates a prerenal syndrome, whereas an FE_{UN} of 50% to 65% suggests established acute renal failure, even in the presence of loop diuretic therapy.[33]

The major limitation to the FE_{UN} is the concomitant administration of proximal tubule diuretics such as acetazolamide and

of osmotic diuretics such as mannitol. These agents impair water reabsorption in the proximal tubule and ameliorate a decrease in FE_{UN} in a prerenal state. Excessive urea production in highly catabolic states may itself induce an osmotic diuresis and render the FE_{UN} inaccurate.

Indices of Tubular Injury

β_2-Microglobulin

β_2-Microglobulin is a small protein component of the major histocompatibility complex that is present on the surface of almost all cells. It is normally filtered by the glomerulus and then undergoes partial tubular reabsorption. The ratio of β_2-microglobulin between serum and urine may help distinguish glomerular from tubular injury, although the relationship between increased urinary β_2-microglobulin and subsequent acute tubular necrosis has not been characterized.

In glomerular injury, serum β_2-microglobulin levels increase and urine levels decrease. This assessment has been utilized as an early sign of rejection in renal transplantation.[34]

In primary tubular injury, reabsorption of β_2-microglobulin is impaired, so urinary levels increase and serum levels decline. In a study in which CPB with pulsatile flow was used, there was a significant decrease in plasma renin activity but urinary β_2-microglobulin increased on CPB with pulsatile or nonpulsatile flow.[35] The implication is that although pulsatile flow maintains better renal perfusion it does not prevent a subclinical renal tubular injury.

Urinary N-Acetyl-β-D-glucosaminidase

The assay of increased urinary concentrations of the tubular enzyme *N*-acetyl-β-D-glucosaminidase (NAG) is a well-established method of identifying subclinical tubular injury. Urinary NAG levels, or the ratio of its isoenzymes, have been used in the early detection of rejection in transplant patients or to follow the course of chronic renal disease (e.g., lupus nephritis).[36] However, there are few data on the relationship between tubular enzymuria and clinical indices of perioperative renal outcome, such as the need for renal replacement therapy.

Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25-kDA polypeptide expressed in proximal tubular cells whose mRNA undergoes dramatic upregulation after ischemic tubular injury.[37] Upregulation can be detected within minutes of ischemia-reperfusion injury and increases threefold to fourfold within 2 to 3 hours and up to 10,000-fold by 24 hours. NGAL is protease resistant and is readily detected in tiny (micromilliliter) amounts of urine almost immediately after renal injury, preceding the appearance of NAG and β_2-microglobulin.

Urinary NGAL has been demonstrated to increase significantly within 2 hours of CPB in pediatric or adult patients who subsequently went on to develop a 50% increase in postoperative serum creatinine, whose peak was delayed until 1 to 3 days after surgery.[38,39] Aprotinin is an antifibrinolytic kallikrein inhibitor that is associated with acute kidney injury.[40] In a study on 369 patients undergoing cardiac surgery, urinary NGAL levels were 18 times higher 3 hours after CPB in the 205 patients given aprotinin compared with those who had received ε-aminocaproic acid.[41] These data suggest that urinary NGAL may represent an early, sensitive, noninvasive urinary biomarker for ischemic and nephrotoxic renal injury.

Renal Hemodynamics

Renal Plasma Flow and Renal Blood Flow

p-Aminohippurate Clearance

p-Aminohippurate (PAH) is an organic anion filtered by the glomerulus and secreted by the tubule that is almost completely cleared from the plasma in a single pass through the kidney. Thus, clearance of PAH (C_{PAH}) represents RPF.

Like inulin clearance, the test is laborious and requires intravenous and urinary catheters. A PAH infusion is set up to maintain a steady-state PAH concentration of about 2 mg/dL, together with a carefully timed catheter urine collection.[26] Because 10% of the RPF bypasses the peritubular capillaries, C_{PAH} underestimates the true RPF and is referred to as *effective* RPF.

$$\text{Effective RPF} = C_{PAH} = U_{PAH} \cdot V/P_{PAH}$$

In young healthy adults, effective RPF is 660 mL/min/1.73 m^2.

Effective renal blood flow (RBF) may be derived if the hematocrit level (Hct) is known and expressed as a decimal (i.e., 35% = 0.35):

$$\text{Effective RBF} = \text{Effective RPF}/1 - \text{Hct}$$

As an example, if effective RPF is 600 mL/min and Hct is 30% (0.3), effective RBF is 600/0.7, i.e., 860 mL/min.

Unfortunately, C_{PAH} is an unreliable indicator of RPF during surgical stress because hypovolemia and oliguria induce sequestration of PAH in the kidney. Ironically, the most important limitation of C_{PAH} is renal injury, because about 80% of PAH is cleared by tubular secretion. In the presence of proximal tubular injury, PAH secretion declines and C_{PAH} underestimates RPF.[42]

These errors can be overcome if renal vein sampling is accessible (e.g., during major abdominal vascular surgery). Measurement of the difference between arterial and renal vein PAH allows calculation of the renal extraction of PAH (E_{PAH}), an index of proximal tubular function:

$$E_{PAH} = \text{arterial PAH} - \text{renal vein PAH}/\text{arterial PAH}$$

When renal function is normal, renal vein PAH is close to zero and E_{PAH} approaches 100% (1.0). With worsening proximal tubular function, renal vein PAH concentration progressively increases and E_{PAH} progressively declines.

True RPF is calculated by dividing PAH clearance by PAH extraction:

$$\text{RPF} = C_{PAH}/E_{PAH}$$

Filtration Fraction

The fraction of the RPF that is filtered by the glomerulus is called the filtration fraction (FF) and can be measured indirectly via the C_{PAH} and C_{IN}:

$$\text{FF} = \text{GFR}/\text{RPF} = C_{IN}/C_{PAH}$$

Normally, GFR is about 125 mL/min and RPF is about 660 mL/min, so that the filtration fraction approximates 125/660, or about 0.2. Changes in filtration fraction are considered to represent changes in periglomerular arteriolar tone (see "Afferent and Efferent Arteriolar Control Mechanisms," earlier). An increase in filtration fraction indicates that GFR is increased relative to RPF. This could be achieved by efferent arteriolar constriction or

afferent arteriolar dilation and maintains glomerular filtration pressure in the presence of decreased RPF. Conversely, a decrease in filtration fraction implies that GFR is decreased relative to RPF by afferent arteriolar constriction or efferent arteriolar dilation.

Total Renal Blood Flow

Flow Probes

Flow measurement by electromagnetic flow probes is based on the creation of a magnetic field around the circumference of the vessel. The field is disrupted by blood flow, and a voltage output proportional to blood velocity is generated. Ultrasonic flow probes use the Doppler technique, in which high-frequency sound is transmitted across the lumen of the vessel. A shift in sound frequency is created by the movement of blood and is proportional to blood velocity.

$$\text{Flow}\,(\text{in mL/min}) = \text{blood velocity}\,(\text{in cm/min}) \cdot \text{area of vessel}\,(\text{in cm}^2)$$

Flow-probe placement is invasive and requires direct surgical exposure of the renal arteries. Probes must be calibrated in vitro before and after measurements. However, they are generally accurate.

Thermodilution Estimation of Renal Vein Effluent

Schaer and associates[43] used a double-lumen pigtail catheter with a thermistor placed in the renal vein of dogs under direct vision or with fluoroscopy. RBF was calculated by thermodilution with cold saline, which allowed repeated measurements in conscious animals. The effect of the presence of the probe itself on RBF is unknown. A similar technique was used by Haywood and associates[44] to measure RBF for the assessment of renal oxygen delivery and consumption during septic shock in pigs.

Contrast Ultrasonography

Aronson and coworkers[45] attempted to measure RBF in vivo using contrast ultrasonography. They injected sonicated albumin microspheres into the aorta of anesthetized dogs and then recorded simultaneous ultrasonograpic images of the kidney and aorta and calculated RBF using a mathematical model. RBF was altered by means of a renal artery occluder or vasoactive drugs (dopamine or fenoldopam), and the results were compared with direct measurements by electromagnetic flow probe. Although the correlation between ultrasonography and flow probe measurements of RBF was reasonable (0.84), there was a large bias (in many cases greater than 200 mL/min) and variance. Ultrasonography tended to overestimate RBF, especially when cardiac output was changing. The authors concluded that this method allows estimation of trends in RBF and may be helpful in the qualitative assessment of regional distribution of blood flow between the renal cortex and medulla.

Neurohormonal Regulation of Renal Function

Two mutually dependent but opposing neurohormonal systems maintain blood pressure, intravascular volume, and salt and water homeostasis (Fig. 18-16). The sympathoadrenal axis, the renin-angiotensin-aldosterone system, and AVP defend against hypotension and hypovolemia by promoting vasoconstriction and salt and water retention. The prostaglandins and natriuretic peptides defend against hypertension and hypervolemia by promoting vasodilation and salt and water excretion (Fig. 18-17).

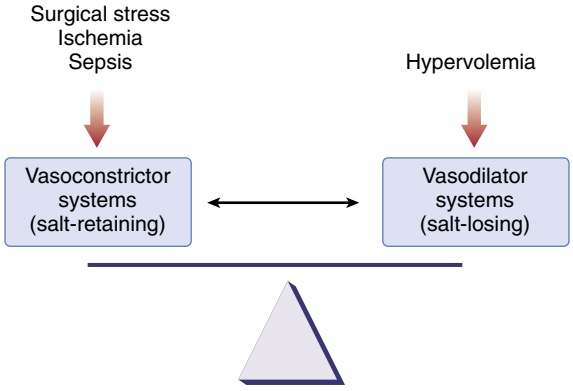


Figure 18-16 Neurohormonal regulation of renal function. Normally, there is a balance between those systems promoting renal vasoconstriction and sodium retention versus those systems promoting renal vasodilation and sodium excretion. Surgical stress, ischemia, and sepsis tip the balance in favor of vasoconstriction and sodium retention. On the other hand, hypervolemia (or the induction of atrial stretch) tips the balance in favor of vasodilation and sodium excretion.

Anesthesia does not perturb these systems to any substantial degree. In the intact organism, anesthetics appear to affect renal function through extrarenal circulatory changes rather than by their direct actions on the kidney. Surgical or traumatic injury, on the other hand, induces profound vasoconstriction and salt and water retention, which may persist for several days. The clinical sequel is postoperative oliguria and edema. Renal vasoconstriction also predisposes the kidney to further perioperative ischemic and nephrotoxic insults. Release of endogenous natriuretic peptides by atrial and ventricular stretch reinforces the notion that renal vasoconstriction can be prevented or modified by maintenance of normal or increased intravascular volume.

Vasoconstrictor Systems	Vasodilator Systems
Sympathoadrenal system Renin-angiotensin system Aldosterone Antidiuretic hormone (ADH)	Prostaglandins Kinins Atrial natriuretic peptide (ANP)
↓ RBF ↓ GFR ↓ Urine flow ↓ Na excretion	↑ RBF ↑ GFR ↑ Urine flow ↑ Na excretion

Figure 18-17 Neurohormonal renal regulatory systems. GFR, glomerular filtration rate; Na, sodium; RBF, renal blood flow; ↓, decreased; ↑, increased. (*Modified from Sladen RN: Effect of anesthesia and surgery on renal function. Crit Care Clin 3:380, 1987.*)

Systems Promoting Vasoconstriction and Salt Retention

The Sympathoadrenal Axis

Sympathetic effects on the kidney are mediated by circulating epinephrine and neuronal release of norepinephrine. The renal cortex has a dense plexus of autonomic nerve fibers derived from the T12 to L4 spinal segments via the celiac plexus. The primary stimulus to the sympathetic response is a decrease in arterial blood pressure sensed by baroreceptors in the aortic arch, carotid sinus, and afferent arteriole. Afferent fibers travel via the vagus nerve and decrease impulse transmission rate to the mediating centers in the hypothalamus, which results in increased adrenergic nerve activity. The kidney does not have any parasympathetic innervation.

A G protein–coupled phospholipase-C receptor populates vascular smooth muscle and the mesangium and responds to α-adrenergic stimulation by epinephrine and norepinephrine. It also mediates vasoconstriction induced by a variety of other hormones and peptides, including angiotensin II, vasopressin, endothelin, platelet-activating factor, and leukotrienes.[3] The receptor subunit in the cell membrane is coupled through G_q protein to phospholipase C, which hydrolyzes phosphatidylinositol biphosphate (PIP_2) to inositol triphosphate (IP_3) and diacylglycerol (DAG). In turn, DAG activates protein kinase, opening up a calcium channel in the membrane, and IP_3 triggers the release of calcium from the sarcoplasmic or endoplasmic reticulum. Both mechanisms result in a rapid increase in intracellular calcium, which binds with calmodulin and thereby activates myosin light-chain kinase, resulting in smooth muscle contraction. The calcium-calmodulin complex simultaneously activates phospholipase A_2, resulting in the production of vasodilator prostaglandins (see later).

Mild α-adrenergic stimulation appears to cause preferential efferent arteriolar constriction, which preserves the filtration fraction. Severe α-adrenergic stimulation causes predominant afferent arteriolar constriction and decreases filtration fraction. Thus, the adrenergic response to a moderate decrease in renal perfusion (e.g., general anesthesia) favors the preservation of the GFR. In contrast, the adrenergic response to shock exacerbates the decrease in GFR already induced by renal hypoperfusion (see Fig. 18-4).

Adrenergic nerves also supply the proximal tubule, thick ascending limb of the loop of Henle, and collecting duct, and their stimulation enhances NaCl reabsorption at these sites. Gas tracer studies suggested that sympathetic activation caused sodium retention by intrarenal redistribution of RBF from the outer cortex to salt-retaining juxtamedullary nephrons, but this was not confirmed by microsphere studies.

There is a close relationship between sympathetic stimulation and activation of the renin-angiotensin system. Adrenergic stimulation releases renin from the juxtaglomerular apparatus, and adrenergically induced vasoconstriction can be blocked by angiotensin-converting enzyme (ACE) inhibitor drugs such as captopril.

The effects of the administration of exogenous adrenergic drugs depend on their agonist activity. Drugs with predominantly α-adrenergic effects, such as norepinephrine, epinephrine, phenylephrine, and high-dose dopamine (>10 μg/kg/min) exacerbate the endogenous sympathetic responses to hypotension. Drugs with predominantly β_1- and β_2-adrenergic activity, such as dobutamine or isoproterenol, cause marked increases in cardiac output and thus RBF, but it is difficult to ascertain their intrarenal effects. Dopaminergic agonists (Table 18-2) selectively increase RBF and may oppose α-adrenergic renal vasoconstriction.[43]

Table 18-2 Dopamine and its Analogs

Receptor	DA_1	DA_2	β_1	β_2	α_1
Dopamine	+++	++	++	±	+++
Dobutamine	0	0	+++	++	±
Dopexamine	++	+	±	+++	0
Fenoldopam	++++	0	0	0	0

Dobutamine, dopexamine, and fenoldopam are all pharmacologic analogs of dopamine. However, dobutamine is devoid of dopaminergic activity; dopexamine has about one third of the dopaminergic activity of dopamine; and fenoldopam is a pure, selective $dopamine_1$-receptor agonist. α_1, $alpha_1$-receptor; β_1, $beta_1$-receptor; β_2, $beta_2$-receptor; DA_1, $dopamine_1$-receptor; DA_2, $dopamine_2$-receptor.

The Renin-Angiotensin-Aldosterone System

Renin and Angiotensin

The juxtaglomerular apparatus consists of three groups of specialized tissues. In the afferent arteriole, modified fenestrated endothelial cells produce renin; in the juxtaposed distal tubule, cells of the macula densa act as chemoreceptors; and in the glomerulus, mesangial cells have contractile properties (see Fig. 18-3). Together these provide an important regulating system for blood pressure, salt, and water homeostasis.[46]

Renin secretion is stimulated by hypovolemia that may be overt (hemorrhage, diuresis, sodium loss or restriction) or covert (positive-pressure ventilation, congestive heart failure, sepsis, or cirrhosis with ascites). A decrease in renal artery perfusion pressure triggers baroreceptors in the afferent arterioles. Sympathetic nerve stimulation and circulating catecholamines act on β-adrenergic receptors in the afferent arterioles. An increase in chloride concentration in the distal tubular fluid activates the cells of the macula densa, which trigger renin release from the afferent arteriole. This tubuloglomerular feedback appears to play a role in modulating GFR during normal and abnormal renal function through a continuous feedback loop.[4,5]

Renin acts on angiotensinogen, a large circulating glycoprotein released from the liver, and cleaves off a decapeptide, angiotensin I. In the kidney and in the lung angiotensin I is further cleaved by endothelial-based ACE to form an octapeptide, angiotensin II, a potent vasoconstrictor (Fig. 18-18). Renin is the rate-limiting enzyme in the production of angiotensin II.[47]

Activation of modest amounts of angiotensin II causes renal cortical vasoconstriction predominantly at the level of the efferent arterioles (see Fig. 18-4). This acts to maintain glomerular filtration fraction in the presence of mild to moderate decreases in RBF or perfusion pressure. The importance of this protective mechanism is emphasized by the deterioration in GFR that occurs when angiotensin-converting enzyme inhibitors are administered to patients with hypotension, renal insufficiency, or unilateral renal artery stenosis.[48,49] Severe stress induces the release of high levels of angiotensin II, which constricts the glomerular mesangial cells and decreases the glomerular filtration fraction. Angiotensin II promotes systemic vasoconstriction at about one tenth of its renal effect. The effect of angiotensin II in causing salt and

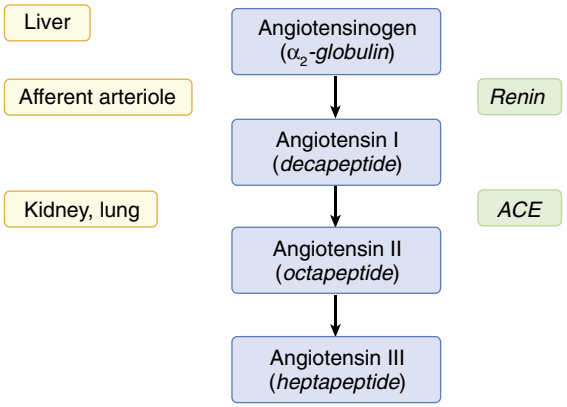


Figure 18-18 Renin-angiotensin system. For explanation, see text. ACE, angiotensin-converting enzyme.

water retention is enhanced by its actions in stimulating aldosterone secretion by the adrenal cortex, AVP secretion by the posterior pituitary, and NaCl reabsorption by the proximal tubule.[46]

Angiotensin II triggers a number of responses that modulate or oppose its own actions. It inhibits renin secretion by a negative feedback mechanism. Blockade of angiotensin formation by ACE inhibitors causes vasodilation but increases plasma renin levels. Angiotensin II activates phospholipase A_2, which triggers the synthesis of intrarenal prostaglandins. Vasodilator prostaglandins modulate the action of angiotensin II and may be responsible for its preferential activity on the efferent arteriole at low plasma levels.[47] Angiotensin-induced vasoconstriction increases atrial pressure and releases ANP, which opposes the renin-angiotensin-aldosterone system.

The consequences of ACE inhibition on renal function depend on the patient's volume status, systemic hemodynamics, and baseline renal perfusion. In the long-term treatment of hypertension and congestive heart failure, especially in diabetics, the administration of ACE inhibitors decreases renal vascular resistance and appears to benefit renal function. Short-term pretreatment with captopril may prevent a decrease in RBF and GFR and preserve sodium excretion during CPB.[50] However, deterioration in renal function and hyperkalemia have been reported with the use of ACE inhibitors in patients with hypotension, renal insufficiency, or unilateral renal artery stenosis, probably related to the blockade of compensatory angiotensin-mediated efferent arteriolar constriction.[49] It may be prudent to avoid their use when hemodynamics are unstable in the immediate perioperative period.

Aldosterone

Aldosterone is a steroid hormone secreted by the zona glomerulosa of the adrenal cortex in response to hyperkalemia or hyponatremia. Angiotensin II and adrenocorticotropic hormone (ACTH) also trigger its release. It acts at the thick ascending limb of the loop of Henle, the principal cells of the distal tubule, and the collecting duct to increase active absorption of sodium and passive absorption of water, culminating in an expanded blood volume. Sodium retention in vessel walls appears to enhance their response to vasoconstrictor agents.

In contrast to the immediate sympathetic angiotensin II response to hypovolemia, there is a delay of 1 to 2 hours from the secretion of aldosterone to its action on sodium reabsorption. As illustrated in Figure 18-19, aldosterone forms a complex with a receptor at the cell membrane in the principal cells of the distal tubule. The aldosterone-receptor complex travels to the cell nucleus, where it induces cytoplasmic transcription of messenger ribonucleic acid (mRNA). This fosters synthesis of proteins that form sodium channels in the apical cell membrane and enhance the Na+/K+-ATPase pump in the basolateral cell membrane.[51] Sodium is transported from the tubular fluid into the peritubular capillary in exchange for potassium. Long-standing stimulation of aldosterone secretion, characteristically induced by the intravascular volume depletion of chronic ascites, culminates in potassium depletion and hypokalemic alkalosis.

Arginine Vasopressin

Arginine vasopressin (AVP), previously known as antidiuretic hormone (ADH), regulates urinary volume and osmolality and controls diuresis and antidiuresis. It is a 9-amino-acid peptide, 8-arginine vasopressin, that is synthesized in the supraoptic and paraventricular nuclei of the anterior hypothalamus.[51] These nuclei are essentially the cell bodies of neurons whose axons extend down into nerve terminals in the posterior pituitary, together comprising the neurohypophysis (Fig. 18-20). When

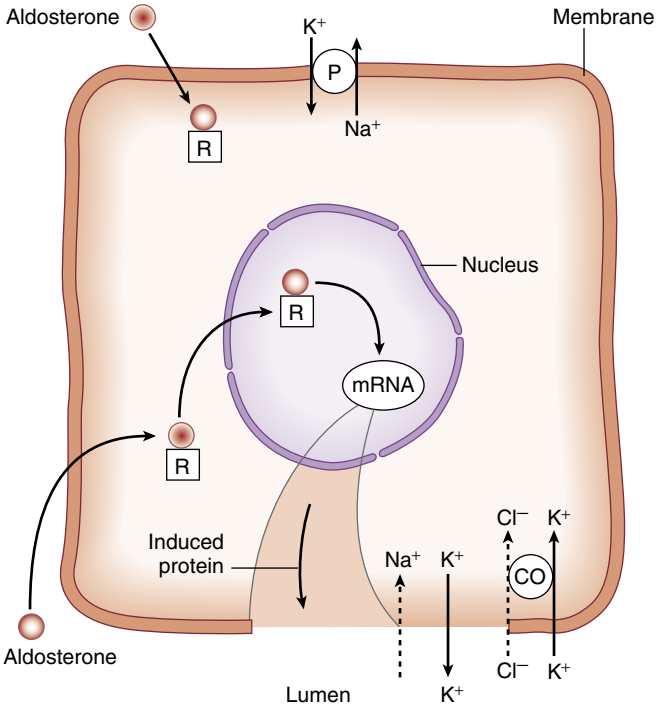


Figure 18-19 Action of aldosterone. Aldosterone enters the distal tubular cytoplasm and attaches to a receptor, then migrates to the nucleus where it induces the formation of a messenger RNA (mRNA). The mRNA in turn induces the synthesis of a protein that enhances the permeability of the apical (luminal) membrane to sodium and potassium. The reabsorption of sodium stimulates the basolateral membrane Na-K-ATPase pump, the intracellular concentration of potassium rises, and it follows its concentration gradient out into the lumen. The net effect of aldosterone's action is sodium reabsorption and potassium loss. Cl^-, chloride; CO, cotransporter (= symporter); K^+, potassium; mRNA, messenger ribonucleic acid; Na^+, sodium; P, sodium-potassium ATPase pump; R, receptor. (*From Wingard LB, Brody TM, Larner J, Schwartz A: Diuretics: Drugs that increase excretion of water and electrolytes.* In *Wingard LB, Brody TM, Larner J, Schwartz A [eds]: Human Pharmacology: Molecular-to-Clinical. London, Wolfe Publishing, 1991, p 249.*)

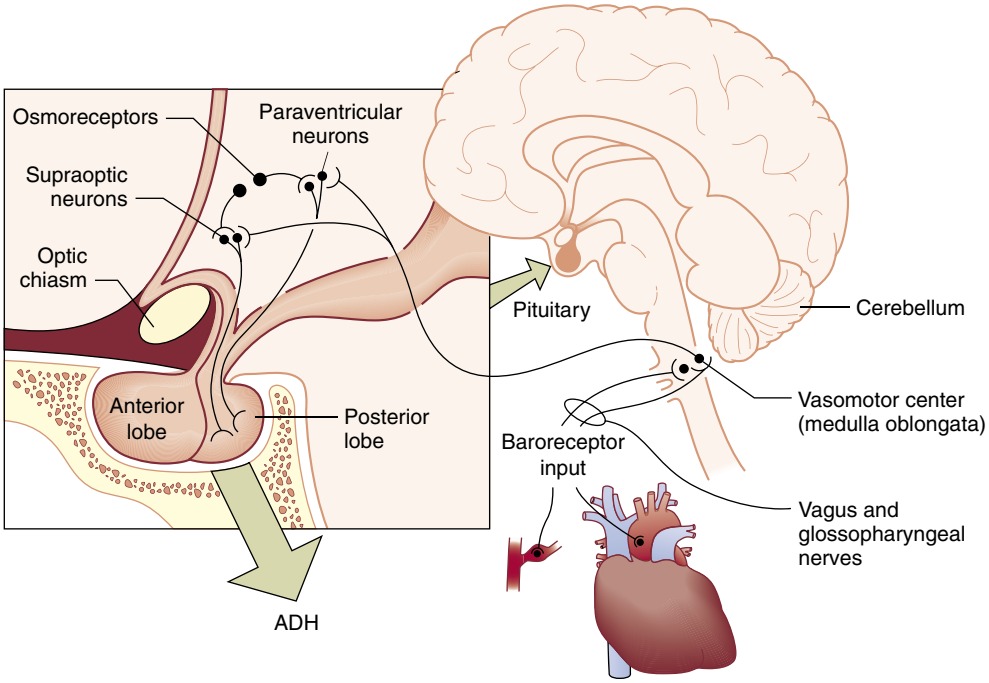


Figure 18-20 Elaboration and control of arginine vasopressin (AVP). *Osmotic control.* An increase in serum osmolality is detected by osmoreceptors in the supraoptic and paraventricular neurons of the hypothalamus. Granules of AVP are elaborated and axonally transported to the posterior lobe of the pituitary gland. From there they are released into the circulation to reach the V_2 receptors in the distal tubule, where they retain water and restore the serum osmolality. *Hemodynamic control.* Decreases in venous volume are sensed by stretch receptors in the atria and great veins, and decreases in arterial pressure are sensed by baroreceptors in the aortic arch and carotid sinus. The afferent arc is via the vagal and glossopharyngeal nerves to the solitary nucleus in the medulla oblongata (vasomotor center). The efferent arc, from the vasomotor center to the hypothalamic nuclei, induces AVP release. At low levels (< 5 pg/mL), AVP stimulation of V_2 receptors may cause inappropriate water retention. At high levels (> 20 pg/mL), AVP stimulation of V_{1a} receptors causes vasoconstriction and participates in the baroreceptor reflex. (*From Koeppen BM, Stanton BA: Regulation of body fluid osmolality: regulation of water balance.* In *Koeppen BM, Stanton BA [eds]: Renal Physiology, 4th ed. Philadelphia, Mosby Elsevier, 2007, pp 71-90.*)

AVP is synthesized it undergoes neuroaxonal transport to the posterior pituitary gland, where it is stored in granules. Neural stimulation of the cell bodies triggers exocytosis of AVP from the terminal vesicles into the circulation.

AVP acts on specific V_2-receptors in the collecting ducts to induce water reabsorption and a decreased flow of concentrated urine. It also increases NaCl reabsorption from the thick ascending loop of Henle into the medullary interstitium, which maintains its hypertonicity and facilitates movement of water out of the collecting duct along the osmotic gradient. This results in tubular conservation of water and free water retention (i.e., negative free water clearance). The net effect is that AVP increases urine osmolality and decreases plasma osmolality, without significant alteration in solute excretion.

The V_2-receptor on the basolateral cell membrane of the collecting duct responds to AVP via a receptor mechanism analogous to the β-adrenergic receptor.[51] Through activation of G protein–coupled adenylyl cyclase, ATP is converted to cyclic adenosine monophosphate (cAMP). This, in turn, activates a protein kinase that causes preformed vesicles containing aquaporin-2 water channels to migrate and fuse with the apical cell membrane. This results in a dramatic increase in membrane permeability to water, which is reabsorbed into the cell and thence into the peritubular capillary. AVP has a short plasma half-life of between 5 and 15 minutes, and this process rapidly reverses as plasma AVP levels decline.

Regulation of AVP Secretion

Hypothalamic osmoreceptors are sensitive to increases in serum osmolality of as little as 1% above normal. As illustrated in Figure 18-21A, the threshold for AVP secretion (and the sensation of thirst) is between 280 and 290 mOsm/kg. Once this is exceeded, the secretion rate has a very steep gain.[52] Even mild dehydration results in a rapid antidiuresis, and urine osmolality can increase from 300 to 1200 mOs/kg as plasma AVP levels rise from 0 to 5 pg/mL (see Fig. 18-21B).

Decreases in intravascular volume also stimulate AVP secretion, mediated by stretch receptors with vagal afferents in the left atrium and pulmonary veins. Hypovolemia-induced secretion of AVP overrides osmolar responses and contributes to the perioperative syndrome of inappropriate antidiuretic hormone secretion (SIADH): fluid retention, hypo-osmolality, and hyponatremia. The situation is exacerbated by administration of large volumes of hypotonic solutions that decrease serum osmolality. Psychic stress, via cortical input, also induces AVP release and can override osmotic and volume sensors.

By far, the most potent trigger for AVP release is systemic arterial hypotension, mediated by aortic and carotid baroreceptors. It overrides all other triggers, and plasma AVP may reach levels 10- to 1000-fold greater than normal (see Fig. 18-21C). At these concentrations AVP acts as a vasoconstrictor, especially in the outer renal cortex. It does so by stimulating the V_{1a} receptor, which exists on vascular smooth muscle, glomerular mesangial

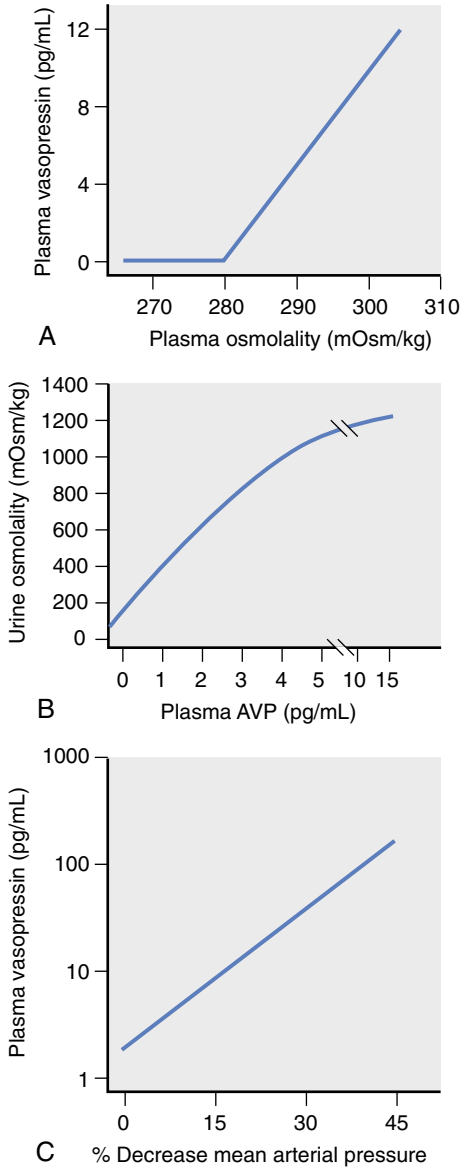


Figure 18-21 **A** to **C,** Physiologic regulation of arginine vasopressin (AVP). For explanation, see text. (*From Landry DW: Vasopressin deficiency and hypersensitivity in vasodilatory shock: Discovery of a new clinical syndrome. P & S Med Rev 3:3-7, 1996.*)

cells, and the vasa recta and promotes vasoconstriction via the phosphatidylinositol pathway.[52] AVP maintains effective glomerular filtration pressure because it is an extremely potent constrictor of the efferent arteriole and, unlike catecholamines and angiotensin, it has little effect on the afferent arteriole even at high plasma levels.[53]

Anesthetic agents have little direct effect on AVP secretion, except via the changes that they induce in arterial blood pressure, venous volume, and serum osmolality. Surgical stimulation is a major stimulus to AVP secretion. This stress response, whether mediated by pain or by volume changes, is profound and lasts at least 2 to 3 days after the surgical procedure.

Systems Promoting Vasodilation and Salt Excretion

Prostaglandins and Kinins

Prostaglandins

Intrarenal prostaglandins play an important role in endogenous renal protection, largely by vasodilating juxtamedullary blood vessels and maintaining inner cortical blood flow.[54] Prostaglandins are called autocoids because unlike true hormones they are produced in minute amounts and have a local, evanescent action. Because their structure is based on a 20-carbon fatty acid they are also referred to as eicosanoids, after *eicosa*, the Greek word meaning "twenty." The synthesis of intrarenal prostaglandins is summarized in Figure 18-22.

Phospholipase A_2, which resides in the inner lipid layer of the cell membrane, controls prostaglandin production through its formation of the prime precursor arachidonic acid. It is stimulated by ischemia and hypotension and also by norepinephrine, angiotensin II, and AVP. Thus, the factors that induce and mediate the stress response simultaneously activate prostaglandins, which defend the kidney against their actions. Cyclooxygenase-1 acts on arachidonic acid to form prostaglandin G_2, the precursor of the family of vasodilator prostaglandins that includes prostaglandins D_2, E_2, and I_2 (prostacyclin). They induce vasodilation through activation of cyclic adenosine monophosphate (AMP), which blocks distal tubule sodium reabsorption, and they oppose the actions of norepinephrine, angiotensin II, and AVP. Prostaglandins may be particularly important in decreasing the vasoconstrictor activity of angiotensin II on the afferent arteriole and glomerular mesangial cells.[47] Production of prostaglandins promotes renal vasodilation, maintains intrarenal hemodynamics, and enhances sodium and water excretion. The renal vasodilator response to mannitol during hypoperfusion appears to be mediated through prostaglandin activation.[55] At the same time, prostaglandins also stimulate renin secretion so that there is a constant "yin and yang" between the two systems.[56]

Cyclooxygenase-2 forms derivatives of arachidonic acid that induce inflammation and renal vasoconstriction and are important in pathologic states. Thromboxane (TXA_2) is derived from cyclic endoperoxides by the action of thromboxane synthetase. It induces vasoconstriction and platelet aggregation, and in the kidney it causes mesangial cell contraction. This decreases GFR by diminishing the effective glomerular surface area and filtration constant (K_f). Renal levels of thromboxane are increased in experimental acute renal failure and sepsis. In animal experiments, the administration of a specific thromboxane synthetase inhibitor prevents the deterioration in renal function induced by the injection of endotoxin.[57] Another vasoconstrictor prostaglandin, PGF_2, which acts on the thromboxane receptor, is formed when arachidonic acid is oxidized by free radicals liberated by leukostasis during acute inflammation. The leukotrienes, which are arachidonic acid derivatives formed by lipooxygenase, are also released from endotoxin-activated leukocytes. Like thromboxane, leukotrienes C_4 and D_4 induce mesangial cell contraction and decrease GFR.

Kinins

Kinins act as vasodilators that interact with and enhance the actions of prostaglandins while modulating the renin-angiotensin system.[58,59] For example, kinins stimulate phospholipase A_2 and

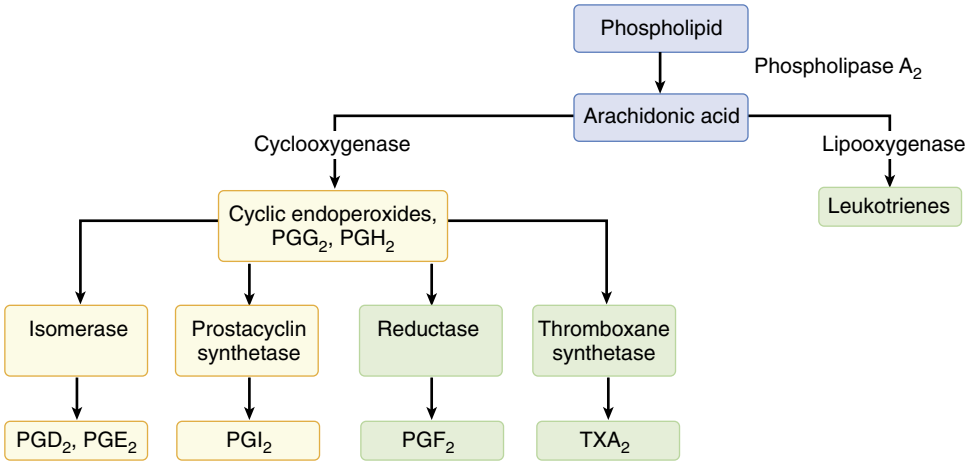


Figure 18-22 Synthesis of renal prostaglandins. Phospholipase A_2 is stimulated by ischemia, norepinephrine, and angiotensin II and cleaves arachidonic acid from its bond with membrane phospholipid. Cyclooxygenase acts on arachidonic acid to form evanescent cyclic endoperoxides (prostaglandins G_2 and H_2). Action of isomerase and prostacyclin synthetase culminates in the formation of vasodilator prostaglandins D_2, E_2, and I_2 (prostacyclin), which oppose the actions of the renin-angiotensin system on the kidney and protect against ischemic stress. Inhibition of cyclooxygenase by nonsteroidal anti-inflammatory drugs predisposes the kidney to damage. Under hypoxic or ischemic conditions, cyclic endoperoxides undergo reduction to the vasoconstrictor PGF_2, which acts on thromboxane receptors. Endotoxin increases the activity of leukocyte lipooxygenase and thromboxane synthetase. Leukotrienes (especially C_4 and D_4) and thromboxane (TXA_2) induce renal vasoconstriction and contribute to the vasomotor nephropathy of sepsis.

prostacyclin formation as well as endothelial nitric oxide formation. Kininase, which controls intrarenal kinin concentration, is blocked by angiotensin-converting enzyme inhibitors, resulting in increased bradykinin levels. This may be beneficial in diseases such as diabetes and hypertension, because two important intrarenal kinins, bradykinin and kallidin, decrease renal vasoconstriction and sodium retention induced by adrenergic hormones and angiotensin II.

Natriuretic Peptides

In 1972, Gorfinkel and colleagues[59a] demonstrated a profound difference in the canine renal response to shock depending on concomitant atrial pressure. Hypovolemic shock resulted in rapid diminution of RBF to 10% of control, whereas in cardiogenic shock RBF was preserved at 75% of control. The primary difference was that in cardiogenic shock atrial pressures were elevated, suggesting that atrial distention caused the release of a renal protective hormone. In 1981, de Bold and associates[60] confirmed the existence of ANP by demonstrating that an extract of atrial tissues caused natriuresis in rats, and the important actions of ANP on renal hemodynamics and sodium excretion were characterized.[61,62]

Subsequently, an entire series of peptides with a similar precursor was identified, with a common 25 to 32 amino acid core. These include ANP (atrial or A-type natriuretic peptide), released from electron-dense granules in atrial myocytes in response to local wall stretch and increased atrial volume, BNP (brain or B-type natriuretic peptide), released from the ventricles when they are distended, CNP (C-type natriuretic peptide) released from the endothelium of major vessels, and urodilatin, a natriuretic peptide produced in the lower urinary tract.[63] Human recombinant analogs have been developed for exogenous administration, including anaritide, derived from ANP, and nesiritide, derived from BNP. All these compounds induce arterial and venous dilation, increase RBF and GFR, and suppress the actions of norepinephrine, angiotensin, and endothelin.[64]

Natriuretic peptides dilate vascular smooth muscle through activation of guanylate cyclase and formation of cyclic guanosine monophosphate (GMP). At the phospholipase C-linked receptor, natriuretic peptides competitively block norepinephrine and noncompetitively block angiotensin II, thus reversing vascular smooth muscle constriction. They cause a prompt, sustained increase in GFR and glomerular filtration fraction, even when RBF is not increased or when arterial pressure is decreased. This suggests that natriuretic peptides promote afferent arteriolar dilation with or without efferent arteriolar constriction. The increased GFR increases the filtered load of sodium, but natriuresis may be due to increased medullary blood flow, which washes out the concentration gradient.

Natriuretic peptides appear to have a mutually antagonistic interaction with endothelin, the endogenous vasoconstrictor peptide produced by vascular endothelium.[47] They oppose the renin-angiotensin-aldosterone system on several fronts (Fig. 18-23). Natriuretic peptides inhibit renin secretion and decrease angiotensin-stimulated aldosterone release. They also inhibit aldosterone release directly at the zona glomerulosa of the adrenal cortex and block the salt-retaining action of aldosterone at the distal tubule and collecting duct. Through cyclic GMP activation, they inhibit NaCl reabsorption at the medullary portion of the collecting duct.[12] Natriuretic peptides also promote diuresis by inhibiting AVP secretion from the posterior pituitary and antagonizing its effect on the antidiuretic V_2-receptor in the collecting duct.

The renal protective role of endogenous ANP was elucidated by Shannon and colleagues,[65] who noticed that patients undergoing mitral valve replacement had lower urine output after cardiac surgery than those undergoing aortic valve replacement or coronary revascularization. They discovered that patients whose postoperative mean left atrial pressure declined by more than 7 mm Hg from preoperative values (which commonly occurs with correction of mitral valve disease) had significantly decreased postoperative urine sodium excretion and flow rate. Furthermore,

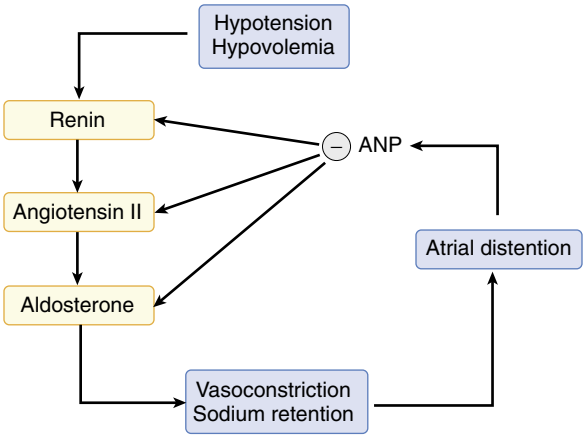


Figure 18-23 Interactions between ANP and the renin-angiotensin-aldosterone system. Hypotension or hypovolemia triggers release of renin from the afferent arteriole, causing the formation of angiotensin II, which stimulates release of aldosterone from the adrenal cortex. Angiotensin II and aldosterone cause vasoconstriction and sodium retention, ultimately resulting in reexpansion of the intravascular volume; this causes atrial distention, which triggers release of ANP. ANP inhibits release of renin, renin's action on angiotensinogen to form angiotensin II, angiotensin- induced vasoconstriction, stimulation of aldosterone secretion by angiotensin II, and the actions of aldosterone on the collecting duct. Thus, the actions of ANP promote vasodilation and sodium excretion. Therapeutic administration of fluids to distend the atrium and release ANP is an important intervention to curtail renal vasoconstriction and sodium retention. ANP, atrial natriuretic pressure.

there was a direct correlation between the quantitative decrease in left atrial pressure and a postoperative decline in circulating ANP levels (Fig. 18-24). In other words, patients with mitral valve disease and high left atrial pressure have a constant stimulus to ANP release. Valve replacement or repair results in decreased left atrial pressure, decreased ANP, and therefore decreased sodium excretion and urinary flow rate.

The Dopaminergic System

There are two subtypes of dopaminergic (DA) receptors (see Chapter 12).[66] At the end organ, DA_1-receptors occur not only on the renal and splanchnic vasculature but also on the proximal tubule itself.[67] Stimulation of the DA_1-receptor activates cyclic AMP and induces renal vasodilation, increased RBF and GFR, natriuresis, and diuresis. However, natriuresis can occur independently of increases in RBF and GFR and is abolished by specific DA_1 receptor antagonists.[68] In the proximal tubule, dopamine inhibits the Na^+/H^+ antiporter system at the brush-border membrane. In the medullary thick ascending limb, it also inhibits the Na^+/K^+-ATPase pump at the basolateral membrane.[68]

Neuronal DA_2-receptors exist on the presynaptic terminal of postganglionic sympathetic nerves. Stimulation inhibits the release of norepinephrine from presynaptic vesicles, a mechanism analogous to stimulation of the presynaptic α_2-receptor. Through inhibition of norepinephrine, DA_2-receptor activation facilitates vasodilation.

The dopaminergic system plays an integral role in the endogenous vasodilator-natriuresis system and the maintenance of normal blood pressure. Endogenous dopamine appears to constitutively activate the DA_2-receptor, which synergistically enhances the activation of the DA_1-receptor.[69] It acts as an autocrine and paracrine natriuretic factor by inhibiting tubular Na^+/K^+-ATPase activity, especially when sodium intake is increased.[70] It also opposes the anti-natriuretic effects of norepinephrine, angiotensin II and aldosterone. There is some evidence that endogenous ANP acts via the renal dopamine system by recruiting "silent" DA_1-receptors from the interior of the cell toward the plasma membrane[70] and also enhances dopamine accumulation.[71]

Urinary dopamine excretion is increased with salt loading; decreased dopaminergic activity may contribute to the pathogenesis of idiopathic edema, which manifests as retention of salt and water in the upright position. There is evidence that the endogenous dopamine system is activated in compensated cirrhosis and helps to maintain renal sodium excretion.[72]

Nitric Oxide

Endogenous formation of nitric oxide (see Chapter 31) is controlled by the enzyme nitric oxide synthase (NOS), which catalyzes the hydroxylation of the nonessential amino acid L-arginine to L-citrulline.[73] Most actions of nitric oxide are mediated through its activation of soluble guanylate cyclase, which catalyzes the

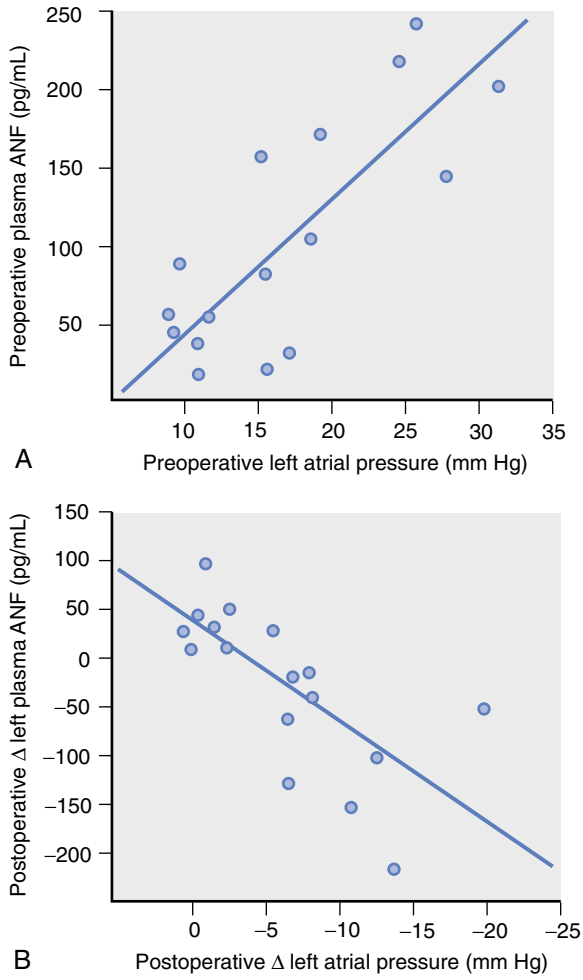


Figure 18-24 Correlation between left atrial pressure and plasma ANP in a group of patients undergoing cardiac surgery. **A,** There is significant correlation ($r = 0.8$, $P < .001$) between absolute preoperative left atrial pressure and plasma ANP. **B,** There is a significant correlation ($r = 0.72$, $P < .002$) between the postoperative decrease in left atrial pressure and postoperative decrease in plasma ANP. ANF, atrial natriuretic factor, synonymous with ANP; ANP, atrial natriuretic pressure; Δ, change. (*From Shannon RP, Libby E, Elahi D, et al: Impact of acute reduction in chronically elevated left atrial pressure on sodium and water excretion. Ann Thorac Surg 46:430-437, 1988.*)

conversion of guanidine triphosphate (GTP) to cyclic GMP. Cyclic GMP has two major actions: relaxation of vascular smooth muscle and suppression of the inflammatory response. It inhibits leukocyte adhesion, platelet activation and aggregation, and cellular proliferation. Cyclic GMP is converted to GMP by phosphodiesterase I and V. Thus, the local action of nitric oxide can be enhanced by the administration of a selective phosphodiesterase V inhibitor, such as sildenafil. Nitric oxide itself is rapidly inactivated by binding to intracellular heme and heme proteins (oxyhemoglobin, oxymyoglobin, guanylate cyclase, cyclooxygenase, cytochrome P_{450}).

Nitric Oxide Synthase (NOS)

There are several distinct subtypes of NOS that determine the site and function of nitric oxide synthesis. Constitutive NOS is calcium and calmodulin dependent and releases small amounts of nitric oxide for short periods of time ("tonic" release). Constitutive NOS has two subtypes: neuronal NOS, which acts as a peripheral neurotransmitter and induces cerebral vasodilation, and endothelial NOS, which exists in the vascular endothelium and mediates the activity previously ascribed to endothelium derived relaxing factor (EDRF). The latter is an important modulator of systemic and pulmonary vascular resistance. In the kidney, endogenous nitric oxide preserves blood flow to the oligemic juxtamedullary cortex and medulla and may also provide endogenous protection against ischemic and nephrotoxic medullary injury.[74-76]

Inducible NOS is calcium and calmodulin independent and is induced by cytokines predominantly in inflammatory cells (macrophages, granulocytes) but also in vascular smooth muscle. At low levels of activation, inducible NOS enhances the response to infection and promotes inflammation and wound healing. In severe sepsis, inducible NOS produces huge amounts of nitric oxide for protracted periods of time ("phasic" release) and is largely responsible for the characteristically profound systemic vasodilation that is refractory to norepinephrine.[77] High levels of nitric oxide, and its reactive products nitrogen dioxide and peroxynitrite, induce lipid peroxidation and denaturation of proteins that drive the systemic inflammatory response syndrome (SIRS) and its attendant acute renal injury.

Duality of Nitric Oxide in Renal Function and Injury

Goligorsky and coworkers[78] have framed the hypothesis that an imbalance between the expression and activity of constitutive and inducible NOS plays an important role in the pathophysiology of acute renal failure. In experimental models of sepsis, nonselective inhibitors of both constitutive and inducible NOS improve blood pressure but worsen overall perfusion, including renal perfusion. Selective inhibitors of inducible NOS show promise in suppressing severe inflammation and vasodilation while maintaining tonic perfusion to vital organs, including the kidneys.[79]

The Renal Adenosine System

Adenosine Receptors

Adenosine, the endogenous degradation product of ATP, is produced by every mammalian cell type and is normally thought of as a potent vasodilator. However, in the kidney, it plays an essential role in regulating intrarenal blood flow by inducing outer cortical vasoconstriction and preserving juxtamedullary perfusion. This variance in function is explained by the identification of at least four subtypes of adenosine receptor: A_1, A_{2a}, A_{2b}, and A_3 (Table 18-3). Activation of the A_1 adenosine receptor induces outer cortical vasoconstriction; it also decreases renin release and inhibits diuresis and natriuresis. In contrast, A_{2a} adenosine receptors increase medullary renal blood flow and enhance renin release, diuresis, and natriuresis.

Table 18-3 Adenosine Receptor Subtypes and Functions

Receptor	Agonist Function	Ischemic Injury
A_1	Outer cortical vasoconstriction	Highly protective
	Decreased renin release	
	Inhibition of diuresis and natriuresis	
A_{2a}	Juxtamedullary vasodilation	Highly protective
	Increased renin release	
	Promotion of diuresis and natriuresis	
A_{2b}	Unknown	
A_3	Unknown	Potentiates injury

From Fozard JR, Hannon JP: Adenosine receptor ligands: potential as therapeutic agents in asthma and COPD. Pulm Pharmacol Ther 12:111-114, 1999.

Perioperative Ischemic and Nephrotoxic Injury

This section will review perioperative agents and events that may disrupt normal renal physiology. If the disruption is severe enough or occurs in susceptible individuals, it may induce ischemic or nephrotoxic acute tubular necrosis, the most common form of perioperative acute kidney injury.

Pathogenesis

Ischemia-Reperfusion Injury

In many clinical situations (e.g., hypovolemic shock, suprarenal aortic-cross clamping) the kidney is subject to a classic ischemia-reperfusion injury that involves several distinct phases.[80] Acute injury to the tubular epithelium and vascular endothelium initiates a rapid decline in GFR. The injury is extended by epithelial and endothelial cell apoptosis and necrosis. The injury becomes stabilized during the maintenance phase, with the beginning of cellular reorganization that culminates in the recovery phase. The initiation phase is often transient, so the extension phase is the most important "window of opportunity" for therapeutic intervention that might reverse acute kidney injury. This emphasizes the importance of early, sensitive detection of rapid declines in GFR.[27]

Nephrotoxic Injury

The putative mechanisms of nephrotoxic tubular injury have been previously discussed (see "Oxygen Balance in the Medullary Thick Ascending Loop"). The risk of nephrotoxic acute kidney injury is exponentially related to the number of nephrotoxic insults.[13] An isolated nephrotoxin (e.g., radiocontrast dye) is unlikely to cause acute kidney injury when the kidney is well perfused. In animal models of nephrotoxic acute tubular necrosis,

injection of radiocontrast dye predictably injures more than 50% of the renal medullary thick ascending limb only when the kidney is previously "primed" by a sequence of three other insults: dehydration, LMMA (a nitric oxide synthase inhibitor), and indomethacin (a prostaglandin synthesis inhibitor).[81]

Anesthetic Drugs

The choice of an anesthetic technique to preserve renal function during and after surgery is predicated on the preservation of RBF and perfusion pressure, the suppression of vasoconstrictor, salt-retaining stress responses to surgical stimulation and postoperative pain, and the avoidance or curtailment of nephrotoxic insults. No single anesthetic drug alone meets these criteria.

Regional Anesthesia

Spinal or epidural anesthesia that achieves sympathetic blockade of the fourth through tenth thoracic segments (see Chapters 51 and 52) is extremely effective in suppressing the sympathoadrenal stress response and release of catecholamines, renin, and AVP. During major surgery, RBF and GFR are preserved as long as adequate renal perfusion pressure is maintained.[82] This implies careful titration of the block, especially in elderly patients with cardiovascular disease, and may necessitate a 25% to 50% increase in intraoperative fluid administration. However, Gamulin and coworkers[83] found that renal sympathetic blockade obtained by epidural anesthesia did not block increases in renal vascular resistance induced by infrarenal aortic cross-clamping, nor did it prevent postoperative decreases in creatinine clearance. Combined spinal-epidural anesthesia for nephrectomy in living related donors appeared to promote graft renal blood flow more than general anesthesia, but there was no difference in renal function or outcome in recipients.[84]

General Anesthesia

The overall effect on renal function of anesthetic drugs in common use has been well reported.[85,86] All anesthetic techniques and agents tend to decrease GFR and intraoperative urine flow. Some drugs also decrease RBF, but filtration fraction is usually increased, which implies that angiotensin-induced efferent arteriolar constriction limits the decrease in GFR. However, these effects are much less significant than those caused by surgical stress or aortic cross-clamping and after emergence from anesthesia usually resolve promptly. Any anesthetic technique that induces hypotension will result in decreased urine flow because of altered peritubular capillary hydrostatic gradients, even if renal autoregulation is preserved (as it usually is during anesthesia). Permanent injury seldom results, unless the kidneys are abnormal to begin with or the hypovolemic insult is prolonged and exacerbated by nephrotoxic injury (see Chapter 24).

Halothane, enflurane, or isoflurane with nitrous oxide induce mild to moderate reductions in RBF and GFR, primarily due to their effects on the central circulation (myocardial depression, peripheral pooling).[85] These effects can be attenuated by prior hydration. High-dose opioid techniques using fentanyl or sufentanil do not depress myocardial contractility and have minimal effect on RBF and GFR. They are also considerably more effective in suppressing the release of catecholamines, angiotensin II, aldosterone, and AVP during surgery than are volatile agents. However, during CPB both AVP and catecholamine levels rise markedly despite high-dose opioid anesthesia. Intravenous agents such as thiopental and diazepam cause minor changes in renal function, about 10% to 15% deviation from control. Ketamine increases RBF but decreases urine flow rate, possibly through sympathetic activation; it preserves RBF during hemorrhagic hypovolemia.[86]

Nephrotoxicity of Volatile Anesthetics

The potential nephrotoxicity of volatile anesthetics (see Chapter 24) is due to their metabolic breakdown to free fluoride ions, which cause a tubular lesion that results in loss of concentrating ability and polyuric acute renal failure. Toxicity is exacerbated by aminoglycosides or prior renal dysfunction. Peak fluoride levels less than 50 μm/L seldom induce injury, whereas levels greater than 150 μm/L are associated with a high incidence of polyuric acute renal failure.[87] Administration of methoxyflurane at more than one minimum alveolar concentration (MAC) for more than 2 hours is capable of generating a peak fluoride level greater than 100 μm/L and for this reason this anesthetic is no longer used. Enflurane is metabolized more rapidly, and most studies indicated that peak fluoride levels seldom rose above 25 μm/L. The antituberculotic agent isoniazid enhances fluoride production, but only isolated reports of fluoride-induced nephrotoxicity due to enflurane ever appeared. Isoflurane produces peak fluoride levels less than 4 μm/L, and halothane is not metabolized to fluoride at all.[88]

The potential nephrotoxicity of sevoflurane remains controversial. Although its metabolism generates more fluoride than enflurane does, clinically significant fluoride-induced nephrotoxicity has not been detected. Compound A, a vinyl ether formed by degradation of sevoflurane at low flow through carbon dioxide absorbents, is capable of inducing renal injury in rats. Although acute renal failure has not been reported in humans, Eger and associates reported evidence of transient renal injury (albuminuria, tubular enzymuria) in volunteers subjected to 8 hours of 1.25 MAC sevoflurane at 2 L/min gas flow.[89] There were no changes in urinary concentrating ability, serum creatinine, or BUN. Subsequently, Eger and associates[90] described a dose-response relationship between biochemical markers of glomerular and tubular injury (urinary albumin, α-glutathione-*S*-transferase) and compound A exposure expressed as parts per million-hours (ppm/h). They suggested that the threshold of renal injury is 80 to 168 ppm/h based on their observation of altered biochemical markers with 1.25 MAC sevoflurane at 2 L/min for 4 hours, which was not seen after 2 hours, and not seen at all with desflurane.

Other laboratories have disputed Eger's findings. Bito and coworkers compared 6-hour patient exposure to low- and high-flow sevoflurane with exposure to low-flow isoflurane and found no differences in BUN, creatinine, or tubular enzymes for 3 days postoperatively.[91] Kharasch and coworkers[92] had similar results with the use of sevoflurane or isoflurane at 1 L/min in 73 patients undergoing procedures lasting longer than 2 hours, and they concluded that moderate duration of low-flow sevoflurane anesthesia, even with the formation of compound A, is as safe as low-flow isoflurane anesthesia. Ebert and associates[93] attempted to duplicate the original 8-hour Eger sevoflurane study in volunteers at two sites with blinded laboratory analyses. Biochemical derangements were minimal and transient, and there were no significant changes in BUN, creatinine, or creatinine clearance. Despite the similarity in experimental design, the mean level of compound A was about 25% lower, and the mean arterial pressure was about

10% higher than the Eger study and may have accounted for the difference in results.

In summary, clinically significant renal injury with the use of low-flow sevoflurane anesthesia has not been reported in patients, even with moderate preexisting renal dysfunction. The relationship between compound A formation, biochemical injury, and clinically relevant renal dysfunction remains unclear and unproven. Nonetheless it appears prudent to follow current U.S. Food and Drug Administration (FDA) guidelines, which recommend a fresh gas flow of at least 2 L/min to inhibit compound A formation and its rebreathing and to enhance its washout.

Volatile Anesthetics and Ischemia-Reperfusion Injury

There is experimental evidence that volatile anesthetics can ameliorate ischemia-reperfusion injury in the kidney. In a murine model, Lee and Emala demonstrated that anesthesia with desflurane, sevoflurane, isoflurane, and halothane significantly attenuated the rise in serum creatinine compared with pentobarbital or ketamine.[94] The mechanism appears to be independent of K^+-ATP channels but related to suppression of the proinflammatory cytokine and chemokine activation in response to ischemia-reperfusion.

Mechanical Ventilation

Mechanical ventilation (see Chapter 93) and positive end-expiratory pressure (PEEP) may cause decreased RBF, GFR, sodium excretion, and urine flow rate or even acute renal injury.[95] Transmission of increased airway and intrapleural pressures to the intravascular space leads to decreases in venous return, transmural (i.e., effective) cardiac filling pressures, and cardiac output. Transmission may actually be attenuated in acute lung injury because of poor lung compliance. High levels of mean airway pressure may compress the pulmonary arterial circulation, increase right ventricular afterload, and induce the intraventricular septum to shift into the left ventricle and decrease its filling and cardiac output.[96] Positive-pressure ventilation increases inferior vena caval pressure and renal venous pressure and may increase tubular sodium reabsorption by increases in peritubular capillary pressure.

The decrease in cardiac output and systemic arterial pressure results in a carotid and aortic baroreceptor-mediated increase in sympathetic nerve tone to the kidney, with renal vasoconstriction, antidiuresis, and anti-natriuresis. Volume receptors in the atria respond to decreased filling by decreased ANP secretion, resulting in increased sympathetic tone, renin activation, and AVP activity.

Salt and water retention during airway pressure therapy was originally thought to be due to an AVP effect,[97] but it is now considered that sympathetic responses are more important and that sodium retention is largely the result of decreased sodium delivery to the tubules. The renin-angiotensin-aldosterone system undoubtedly augments the renal responses to positive-pressure ventilation. Annat and coworkers[98] found that 15 cm H_2O PEEP depressed cardiac output, RBF, GFR, and urine volume by 20% to 30% and was associated with increases in renin and aldosterone but not AVP. The impairment in renal function induced by airway pressure therapy can be prevented or reversed by preserving normal circulatory status, either by hydration[99] or by use of dopamine.[100]

Although theoretically the extent of depression of renal function depends on the mean airway pressure, there appears to be no difference in creatinine clearance and FE_{Na} whether volume-control ventilation or pressure-support ventilation is used.[101] Therapeutic maneuvers used in severe acute lung injury such as permissive hypercapnia or permissive hypoxemia may promote renal vasoconstriction.[95]

Finally, in experimental lung injury there is evidence that an injurious ventilatory mode induces acute inflammation associated with renal epithelial cell apoptosis and dysfunction.[102] These findings appear to be in keeping with the clinical observation of multiorgan dysfunction in patients with acute respiratory distress syndrome and with its amelioration when a lung protective strategy of mechanical ventilation is used.[95]

Induced Hypotension

During anesthesia with induced hypotension, substantial reduction of GFR and urine flow rate is common. However, when the duration of hypotension is less than 2 hours, no permanent impairment of renal function occurs, even in elderly patients.[103] Vasodilator agents used to induce hypotension differ in their effect on RBF. Administration of sodium nitroprusside decreases renal vascular resistance but tends to shunt blood flow away from the kidney. Moreover, its administration is associated with marked renin-angiotensin activation and catecholamine release, which results in rebound hypertension if the infusion is suddenly discontinued. Nitroglycerin decreases RBF less than sodium nitroprusside.[104] The selective DA_1-dopaminergic agonist fenoldopam is capable of providing induced hypotension without any significant decrease in RBF.[105]

Aortic Cross-Clamping

The relative effects of suprarenal and infrarenal aortic cross-clamping (see Chapter 62) on renal function in patients undergoing major vascular surgery have been studied. Regardless of the position of the aortic cross-clamp, RBF is decreased to 50% of normal during surgical preparation of the aorta, presumably owing to direct compression or reflex spasm of the renal arteries. After release of the suprarenal cross-clamp, RBF increases above normal (reflex hyperemia) but GFR remains depressed to one third of control for up to 2 hours. After 24 hours, GFR is still only two thirds of control. Tubular functions (concentrating ability, sodium, and water conservation) are markedly impaired, but urine flow is maintained. Myers and Moran[106] observed that these changes resemble an attenuated form of acute tubular necrosis. In this study all patients received mannitol pretreatment, which probably limited the tubular insult because oliguria was uncommon and recovery was relatively rapid. Cross-clamp times longer than 50 minutes are associated with prolonged depression of GFR and transient azotemia.[107]

In animal models, suprarenal aortic cross-clamping induces a decrease in renal endothelial nitric oxide; nitric oxide synthesis and cortical blood flow are enhanced by the administration of its substrate arginine.[108] Whether this intervention might attenuate the renal consequences of cross-clamping awaits further investigation.

Infrarenal aortic cross-clamping may also impair RBF and GFR by inducing decreases in cardiac output in response to increased systemic vascular resistance.[109] Atheromatous embolism of the renal arteries may be induced by cross-clamping or manipulation in areas of dense aortic plaque. Partial or complete cortical necrosis may occur, which is usually irreversible.

Renal Protection During Aortic Cross-Clamping

Mannitol has been used for more than 40 years to provide renal protection during aortic cross-clamping (see Chapter 62). Its protective effects have been clearly demonstrated in animal models of ischemic acute tubular necrosis,[110] but few prospective controlled human studies exist. Low-dose dopamine has commonly been used during major vascular surgery. In a canine study of thoracic aortic cross-clamping, RBF, GFR, and urine flow remained impaired for a considerable time after cross-clamp release. This delay was not prevented by prophylactic administration of dopamine.[111] In a human study of infrarenal cross-clamping, Paul and colleagues[112] compared diuretic therapy with a combination of mannitol and dopamine versus fluid loading with saline to a pulmonary artery occlusion pressure (PAOP) of 12 to 15 mm Hg. Although mannitol and dopamine substantially increased urine flow and sodium excretion during cross-clamping, they were no better than saline in attenuating residual GFR depression after cross-clamp release.

Fenoldopam, a synthetic phenolated dopamine analog that is a selective agonist of the DA1-receptor, increases renal blood flow in a dose-dependent manner.[113] Infusion of fenoldopam has demonstrated a renoprotective effect in experimental suprarenal aortic cross-clamping.[114] In a controlled, randomized, blinded study in 28 patients undergoing infrarenal aortic cross-clamping, fenoldopam, 0.1 μg/kg/min, or placebo was infused intravenously before surgical skin incision and continued until release of the aortic cross-clamp.[115] Fenoldopam significantly attenuated the decrease in creatinine clearance and increase in serum creatinine observed in patients who received placebo. Larger studies with this agent appear warranted.

Cardiopulmonary Bypass

The incidence of acute renal failure is very low (< 2%) after uncomplicated cardiac surgery in patients with previously normal renal function. It increases with the complexity of surgery (e.g., combined procedures versus simple revascularization). In a prospective review of more than 4000 cases at the Cleveland Clinic, Higgins and associates observed that the risk of renal morbidity and mortality increases exponentially when the preoperative serum creatinine value is greater than 1.9 mg/dL.[116] When it does occur after cardiac surgery, acute renal failure has a devastating effect on mortality, increasing it 15-fold with acute kidney injury (peak postoperative SCr > 1 mg/dL) and 30-fold when renal replacement therapy is required.[117] During CPB (see Chapter 60), hypotension with nonpulsatile flow promotes renal vasoconstriction and decreases RBF. Norepinephrine levels increase progressively during bypass, and the renin-angiotensin system is activated. Acute renal failure has been associated with persistent elevation of plasma renin levels.[106] Thromboxane, released from activated platelets, and vascular elaboration of endothelin could add to renal vasoconstriction during extracorporeal circulation. Tubular enzymuria and microalbuminuria, an index of subclinical injury to the nephron, is consistently observed during CPB.[118]

Renal Protection during Cardiopulmonary Bypass

Pulsatile Perfusion During CPB

In animal and human studies, pulsatile perfusion during CPB enhances renal cortical blood flow and decreases circulating catecholamines, endothelin, and cytokine activation (see Chapter 60).[119,120] However, these physiologic advantages have not translated into clinical benefit. Although plasma renin activity is suppressed by pulsatile perfusion, evidence of glomerular injury (in this case, microalbuminuria) persists.[35] In a randomized prospective study on 215 pediatric patients undergoing repair of congenital heart disease, the use of pulsatile flow during CPB was associated with decreased inotropic requirement, shorter intensive care unit and hospital length of stay, and greater urine output, but there was no difference in serum creatinine value.[121] Intra-aortic balloon counterpulsation was used to provide pulsatile flow during CPB in a randomized, prospective study on 100 adult patients undergoing cardiac surgery.[122] Pulsatile flow attenuated the decline in GFR, but there was no difference in urine flow or renal outcome. In a large nonrandomized observational study, pulsatile flow was provided during CPB in 915 of 1820 patients but did not appear to provide increased protection against perioperative renal injury.[123]

Avoidance of CPB

The benefit to renal function of off-pump coronary artery bypass (OPCAB, also known as beating heart surgery) also remains equivocal. In low-risk patients, there appears to be little difference in the incidence of acute kidney injury whether or not CPB is used.[124] Most published studies to date have been small (<60 patients), and although they demonstrate that OPCAB is associated with less evidence of acute kidney injury, as manifested by lower levels of serum creatinine, cystatin C, microalbuminuria, and NAG, this has not translated into a benefit to renal outcome, morbidity, or mortality.[125,126] In a larger study on 201 patients, the use of CPB resulted in a significant increase in acute kidney injury, defined as a greater than 50% increase in postoperative serum creatinine concentration (27.7 versus 14.0%, $P < .03$).[127] Although the OPCAB technique was identified as the only independent factor associated with a lower incidence of acute kidney injury, the study was not randomized and all procedures were performed by the same experienced surgeon.

Perfusion Pressure During CPB

It has been observed in animal studies of CPB that RBF is dependent on renal perfusion pressure and that infusion of dopamine does not increase RBF during low-pressure states.[10] This suggests that autoregulation may be impaired during CPB. However, Hilberman and colleagues[128] found no relationship between low flow (<50 mL/kg/min) and low mean arterial pressure (<50 mm Hg) and postoperative acute renal failure. Instead, the severity of postoperative renal dysfunction and its outcome correlated with the severity of cardiac dysfunction after CPB.[129]

Dopaminergic and Diuretic Drugs

In a study comparing equi-inotropic doses of dopamine and dobutamine after cardiac surgery, the two agents had similar effects on GFR, RBF, renal vascular resistance, and filtration fraction but dopamine caused greater urine flow rate, natriuresis, FE_{Na}, and potassium excretion, indicating a diuretic effect independent of

changes in RBF and GFR.[130] However, there is no evidence that the "prophylactic" administration of low doses of dopamine has a protective role during CPB in patients with previously normal[131,132] or impaired renal function.[124,133]

In part, the lack of benefit may be due to the variable pharmacokinetic effect of dopamine. In a study on normal volunteers, McGregor and coworkers found a 30-fold intersubject variability in plasma dopamine levels.[134] Some subjects given an infusion of "low dose" dopamine had plasma levels consistent with those associated with doses in the high, α-adrenergic range. Even at low doses it can cause unwanted tachycardia, and its postoperative infusion is associated with a higher incidence of supraventricular and ventricular arrhythmias.[135]

In contrast to dopamine, there does appear to be increasing evidence to support a renoprotective effect for infusion of low-dose fenoldopam infusion (0.1-0.3 μg/kg/min) during cardiac surgery. A meta-analysis of 13 randomized and case-matched studies on 1059 patients found that fenoldopam infusion is associated with a significant decrease in dialysis requirement, intensive care unit length of stay, and in-hospital mortality.[136] Most studies have been relatively small and identified improved serum creatinine and creatinine clearance rather than renal outcome.[137,138] The most convincing evidence thus far comes from a randomized, double-blinded study in 193 high-risk patients by Cogliati and colleagues.[139] Risk factors included elevated preoperative serum creatinine (>1.5 mg/dL), age older than 70 years, diabetes, and previous cardiac surgery. Patients who received fenoldopam had a decreased incidence of acute kidney injury (12.6 versus 27.6%, $P = .02$) and requirement for dialysis (0 versus 8.2%, $P = .004$).

Prophylactic administration of diuretics during CPB may actually be harmful: in a study on 126 patients undergoing elective cardiac surgery, perioperative infusion of furosemide (0.5 μg/kg/min) worsened serum creatinine level compared with low-dose dopamine and placebo.[131]

Natriuretic Peptides

Exogenous administration of anaritide (human recombinant ANP) decreases systemic blood pressure through arterial and venous dilation. There has been considerable interest in the ability of infused anaritide to reverse established acute renal failure ("renal rescue"). Animal studies of ischemic and nephrotoxic acute tubular necrosis,[140] as well as preliminary clinical studies,[141] offered promise. A large prospective study demonstrated significantly greater dialysis-free survival with anaritide infusion in oliguric acute renal failure, but in nonoliguric acute renal failure survival actually worsened.[31] Subsequently, a randomized, double-blind, placebo-controlled trial on 222 patients with oliguric acute renal failure found no differences in dialysis requirement, dialysis-free survival, or 60-day mortality between anaritide and placebo.[142] However, patients receiving anaritide had significantly more hypotension during infusion of the study drug.

Infusion of anaritide has been studied during CPB.[143] Compared with controls, patients who received anaritide had significantly lower plasma levels of renin, angiotensin II, and aldosterone and higher GFR and urine output.

Nesiritide (human recombinant BNP) is approved by the FDA for the parenteral treatment of advanced decompensated congestive heart failure. It decreases elevated cardiac preload and afterload, enhances cardiac function, and promotes diuresis and relieves symptoms related to pulmonary congestion and edema.[144] The major adverse effect is dose-related hypotension, which if excessive, can impair renal function.[145] A meta-analysis of studies of nesiritide infusion in patients with advanced decompensated heart failure suggested that its use is associated with worsening serum creatinine.[146] However, there is evidence that perioperative infusion of low doses (0.01 μg/kg/min) of nesiritide in high-risk patients undergoing cardiac surgery may have a renoprotective effect.[147] In a prospective, randomized, blinded study of 279 patients with left ventricular dysfunction (ejection fraction < 40%) undergoing coronary revascularization or mitral valve surgery, patients who received nesiritide had increased urine output, an attenuated postoperative increase in serum creatinine concentration, and improved survival 6 months after surgery. Further studies of nesiritide appear warranted.

N-Acetylcysteine

N-Acetylcysteine is an antioxidant that directly scavenges reactive oxygen species, and there is considerable evidence to support its use to prevent radiocontrast nephropathy (see later). However, a similar benefit has not been demonstrated by its perioperative administration in cardiac surgery. In two prospective, blinded randomized studies, neither intermittent injection[148] nor continuous infusion[149] of *N*-acetylcysteine had any impact on renal function or outcome after cardiac surgery. A large study on 254 patients with chronic renal insufficiency (GFR < 60 mL/min) was similarly unable to demonstrate any significant benefit from intermittent injection of *N*-acetylcysteine.[150]

Nephrotoxic Insults

Drug-Induced Nephrotoxicity

Nephrotoxic injury by drugs or contrast dyes seldom occurs without the presence of coexisting risk factors,[13] including shock, hypovolemia, congestive heart failure or advanced age, diabetes, or chronic renal insufficiency. The risk of nephrotoxicity increases exponentially with the number of risk factors and nephrotoxic combinations.

Nephrotoxic acute renal failure is usually nonoliguric, with loss of concentrating ability and slowly progressive azotemia. As GFR declines, accumulation of renally excreted drugs exacerbates nephrotoxicity, unless drug levels are carefully monitored and dosage is repeatedly adjusted. However, the prognosis for recovery is good if these agents are discontinued in time and when no coexistent organ failure exists.[151]

Aminoglycosides

Aminoglycosides (gentamicin, tobramycin, amikacin) are polycationic compounds that are filtered into the proximal tubule, where they bind to anionic brush-border membrane phospholipids. Their nephrotoxicity is directly related to their polycationic status, so that neomycin (six cationic sites) is more destructive than gentamicin (five sites) or streptomycin (three sites).[152] They are absorbed into intracellular lysosomes by endocytosis and thence released into the cytosol. Within the cell they induce the formation of reactive oxygen metabolites that injure lysosomes, plasma membranes, and mitochondria and, in particular, inhibit oxidative phosphorylation and the synthesis of high-energy phosphate compounds such as ATP. Aminoglycoside-induced nephrotoxicity is directly related to sustained high trough serum levels, especially when associated with advanced age, preexisting renal disease, renal vasoconstrictive states (sepsis, hypovolemia, liver

disease, congestive heart failure), adjuvant drug therapy (loop diuretics, vancomycin, cephalosporins, NSAIDs, cyclosporine, amphotericin B), and electrolyte disorders (hypokalemia, hypomagnesemia, hypercalcemia, and metabolic acidosis).[153]

Prevention of aminoglycoside nephrotoxicity depends on maintenance of adequate hydration, avoidance or removal of the risk factors just listed, and careful monitoring of serum aminoglycoside levels. A daily 2-hour creatinine clearance can also be helpful in the early detection of aminoglycoside-induced nephrotoxicity and appropriate dose adjustment for GFR. Once-daily administration of aminoglycosides to achieve a high therapeutic level with an adequate trough period for renal recovery may limit the occurrence of nephrotoxicity.[154]

Nonsteroidal Anti-inflammatory Drugs

Cyclooxygenase-1 is inhibited by NSAIDs (see Chapter 26) such as indomethacin, meclofenamate, and ketorolac for about 8 to 24 hours. A single dose of aspirin causes its irreversible acetylation. In platelets, the impact lasts for the lifetime of these cells (7 to 10 days), but the kidney resynthesizes cyclooxygenase within 24 to 48 hours. The renal protective function of prostaglandins is "switched on" by injury, illustrated by the fact that NSAIDs cause nephrotoxicity in ischemic but not in normal kidneys. During conditions of stress, impaired prostaglandin activity results in decreased RBF and GFR, increased renal vascular resistance, attenuated diuretic responsiveness, and hyperkalemia.

Adverse effects of NSAIDs and aspirin occur in animal models of hemorrhage, endotoxemia, increased venous pressure, and low cardiac output and in humans with mild underlying renal dysfunction who also have congestive heart failure, ascites, or systemic lupus erythematosus.[155] Postoperative analgesia with a single analgesic such as ketorolac is extremely unlikely to cause injury in a relatively young, healthy, well-hydrated patient. The risk of nephrotoxic injury increases exponentially with the addition of concomitant nephrotoxins (e.g., contrast dye, aminoglycosides) in the presence of acute or chronic cardiovascular instability.

NSAIDs selective for cyclooxygenase-2 (celecoxib, rofecoxib, valdecoxib) appear to be less likely to cause gastric irritation and erosion. However, there is no evidence that they decrease the risk of nephrotoxic injury compared with nonselective cyclooxygenase inhibitors.[156] Their use has been severely curtailed after reports of increased adverse cardiovascular events in clinical trials.

Calcineurin Antagonists (Cyclosporine, Tacrolimus)

Cyclosporine is a remarkably potent immunosuppressive agent and, together with corticosteroids and azathioprine, is routinely used to prevent rejection after organ transplantation. Indeed, heart, lung, and liver transplantation increased exponentially after its release in 1981. It causes renal injury, in part because it induces sympathetic hyperreactivity, hypertension, and renal vasoconstriction. Preexisting renal dysfunction, hypovolemia, and other nephrotoxic insults exacerbate its nephrotoxic effects. Many transplant patients must tolerate a moderately elevated serum creatinine (1.5-2 mg/dL) to sustain adequate immunosuppression. A related calcineurin immunosuppressive agent, tacrolimus (FK506), is somewhat less nephrotoxic than cyclosporine and has largely replaced it in liver transplantation.

In patients undergoing cadaveric renal transplantation, the calcium channel blocker diltiazem was added to the graft preservative solution, infused into the donor for 48 hours, and then given orally.[157] The incidence of transplant acute tubular necrosis decreased from 41% to 10%, and when acute renal failure did occur, hemodialysis requirement was significantly less. Diltiazem impairs cyclosporine metabolism so that plasma cyclosporine levels are higher, with fewer episodes of early acute rejection, but it protects against cyclosporine nephrotoxicity.[158] Cyclosporine dosage may be reduced by 30% to achieve the same drug levels, representing a substantial savings to patients.

An alternative approach that is gaining some traction is to replace cyclosporine or tacrolimus with the non-calcineurin agent sirolimus, which appears to have similar immunosuppressive effects with considerably less potential to induce renal injury.[159]

Radiocontrast Nephropathy

The nephrotoxicity of contrast dyes (see Chapter 79) probably involves microvascular obstruction by crenated red cells as well as direct tubular toxicity by release of free oxygen radicals. The risk is markedly increased in diabetic renal insufficiency, hypovolemia, congestive heart failure, and myeloma.[160] Radiocontrast dyes are hypertonic and cause an osmotic diuresis, which induces a false sense of security but exacerbates hypovolemia and renal damage. Azotemia commences 24 to 48 hours after exposure and peaks at 3 to 5 days. Surgery performed during this period greatly increases the risk of perioperative acute renal failure.

Prevention of radiocontrast nephropathy depends on adequate hydration (e.g., 1 mL/kg normal saline initiated at least 4 hours before and continued for 12 hours after radiocontrast administration).[161] Elective surgical procedures should be deferred until the effects of the dye have been evaluated and treated.[162] Nonionic, low-, or iso-osmolar radiocontrast media are less nephrotoxic but are expensive and offer optimal cost-benefit ratio when used in high-risk situations only (e.g., diabetic nephropathy).[154]

A number of pharmacologic agents have possible roles in preventing or attenuating contrast nephropathy but none replaces hydration as first-line protection. Intravenous mannitol has been used for many years but may exacerbate injury if it induces dehydration though excessive osmotic diuresis.

N-Acetylcysteine

Tepel and associates reported that prophylactic administration of the antioxidant *N*-acetylcysteine (600 mg orally twice daily) attenuated renal injury in a study on 83 patients with chronic renal insufficiency (mean serum creatinine, 2.4 mg/dL) undergoing contrast radiography.[163] Only 2% of patients receiving *N*-acetylcysteine had an increase in serum creatinine of more than 0.5 mg/dL, compared with 21% of patients receiving saline placebo, and mean serum creatinine concentrations actually decreased. Subsequent studies either did not confirm these results[164] or found that *N*-acetylcysteine provided better protection than saline alone only when a low dose of contrast dye was used.[165] Moreover, there is evidence that *N*-acetylcysteine itself decreases serum creatinine levels.[17] However, in a study on 354 patients undergoing primary angioplasty, *N*-acetylcysteine significantly decreased the incidence of radiocontrast nephropathy, dialysis requirement, and hospital mortality in a dose-dependent manner.[166]

Fenoldopam

Preliminary evidence demonstrated that fenoldopam infusion prevented the decrease in RPF induced by radiocontrast media.[167] However, a large, multicenter randomized clinical trial on 315 patients with preexisting renal insufficiency (creatinine clearance < 60 mL/min) showed that it had no benefit on renal function compared with placebo.[168]

Pigment Nephropathy

Pigment nephropathy implies acute renal injury due to the nephrotoxic effect of the heme pigments myoglobin, hemoglobin, and bilirubin.

Rhabdomyolysis and Myoglobinemia

Muscle necrosis (rhabdomyolysis) occurs most commonly with direct trauma involving major crush or thermal injury (see Chapter 72). However, it also occurs with acute muscle ischemia induced by vascular disease or injury or by prolonged immobilization. Compartment syndromes exacerbate rhabdomyolysis. They are particularly likely to occur with major hemorrhage in an extremity or when vascular insufficiency coexists with tissue edema (e.g., femoral placement of an intra-aortic balloon after vein harvesting). Dramatic increases in metabolic rate (severe exercise, prolonged fever, status epilepticus, or myoclonus), severe hypophosphatemia, or direct proteolysis (acute pancreatitis) can all precipitate rhabdomyolysis.[169]

Myoglobin, the oxygen-carrying heme pigment of muscle, is released into the bloodstream (myoglobinemia) and rapidly excreted by the glomerulus at a plasma threshold of 0.03 mg/dL. Delivery of myoglobin to the proximal tubule is greater in a well-muscled individual with normal GFR than in a cachectic patient with low GFR. At a urine pH less than 5.6, myoglobin is transformed into ferrihematin, which precipitates in the proximal tubule.[170] Renal damage is facilitated by hypovolemia (i.e., low tubular flow) and acidic urine. Because of the associated hypercatabolic state, oliguria is associated with acute hyperkalemia, hypocalcemia, anion-gap metabolic acidosis, and rapid azotemia. Serum creatinine and BUN increase very rapidly (1.0-1.5 mg/dL/day and 20-30 mg/dL/day, respectively).

The most important aid to the diagnosis of rhabdomyolysis is a high index of suspicion. The affected muscle may be obviously ischemic or swollen, painful, and edematous. Urine myoglobin often tests positive without reddish urine. The serum is clear because of the low renal threshold for myoglobin excretion, whereas hemoglobinemia is associated with pink serum. Serial total creatinine phosphokinase (CPK) is a helpful guide to the severity of rhabdomyolysis (i.e., CPK-MM release).[171] Renal damage is much more likely when total CPK exceeds 10,000 units/L.

Prevention of acute nephrotoxic tubular necrosis is dependent on the maintenance of high RBF and tubular flow. Urine flow should be kept between 100 to 150 mL/hr by osmotic diuresis with intravenous mannitol, 6.25 to 12.5 g every 6 hours, with or without intravenous furosemide, 10 to 20 mg as required.[172] Urine pH should be kept above pH 5.6 with intravenous sodium bicarbonate, 50 mEq intravenously, as required, and/or acetazolamide, 250 mg every 6 hours. However, because there are no prospective data that confirm the beneficial effect of urinary alkalinization, urine pH should not be increased at the expense of causing significant acid-base imbalance. Calcium should be given to treat hyperkalemia only.

Hemolysis and Hemoglobinemia

Acute intravascular hemolysis (see Chapter 52) due to mismatched blood transfusion (ABO incompatibility) represents a direct and devastating renal insult. Renal damage is thought to be predominantly due to red blood cell stroma rather than to free hemoglobin. Management is essentially the same as for rhabdomyolysis.

Jaundice and Bilirubinemia

There is a direct correlation between the degree of preoperative obstructive jaundice and postoperative renal dysfunction.[173] When cholestasis causes the conjugated bilirubin to increase above 8 mg/dL, bile salt excretion effectively ceases, resulting in portal septicemia and renal damage. This situation is analogous to hepatorenal syndrome and sepsis, in which circulating endotoxins induce renal vasoconstriction and damage (vasomotor nephropathy).

Administration of preoperative oral bile salts (e.g., sodium taurocholate) or intravenous mannitol may provide perioperative renal protection in patients with severe obstructive jaundice. In a prospective, randomized study in patients with obstructive jaundice undergoing surgery, Plusa and Clark[174] found no difference in renal outcome between these two regimens. However, mannitol provokes a brisk osmotic diuresis and it is important to replace urinary losses appropriately. Diuresis-induced hypovolemia negates the protective effect of mannitol.[175]

Sepsis

Sepsis is the most common cause of new-onset acute renal failure in the postoperative period (see Chapters 91 and 92). Renal function may deteriorate progressively without defined episodes of hypotension. In addition, sepsis predisposes the kidney to further ischemic and nephrotoxic insults (e.g., from concomitant aminoglycoside usage).[176] Acute renal failure itself and hemodialysis perpetuate sepsis by activating leukocytes. There is a reasonable amount of evidence to suggest that renal autoregulation may be impaired in sepsis and that RBF and GFR decline pari passu with systemic vascular resistance and mean arterial pressure. Hypotension sets off a cascade of neurohormonal responses (sympathoadrenal activity; renin-angiotensin, vasopressin, and thromboxane activation) that result in decreased RBF, GFR, sodium excretion, and urine flow. The severity of renal dysfunction is directly related to the severity of sepsis and the degree of plasma renin activation.[177]

Renal dysfunction in sepsis is characterized as a vasomotor nephropathy, which implies renal vasoconstriction in the presence of increased total cardiac index. Renal vasoconstriction, mesangial cell contraction, decreased ultrafiltration coefficient, and decreased GFR are induced by endotoxin and by compounds activated in sepsis.[178] These include endothelin and eicosanoids, such as thromboxane, prostaglandin F_2, and the leukotrienes C4 and D4. Prostaglandin F_2, which mimics the action of thromboxane, is formed during leukostasis when arachidonic acid is oxidized by free oxygen radicals.

It has been estimated that 10% to 26% of septic patients receiving aminoglycoside antibiotics will develop nephrotoxic renal insufficiency.[153] Aminoglycoside nephrotoxicity is enhanced by the interaction of fever, renal vasoconstriction, hypovolemia, and endotoxin. In the presence of these and other risk factors (see earlier), alternative non-nephrotoxic antibiotics should be con-

sidered to treat gram-negative infections, including penicillins (ticarcillin), cephalosporins (ceftazidime), carbapenems (imipenem), or monobactams (aztreonam).

Renal Protection in Septic Shock

Anti-inflammatory Agents

Cumming and coworkers[179] demonstrated a marked renal protective effect of a selective thromboxane synthetase inhibitor (U63557A) in laparotomy on a volume-loaded sheep peritonitis model. Administration of the selective inhibitor either before or 30 minutes after surgery prevented deterioration in creatinine clearance, urinary sodium excretion, and urine flow rate. Beneficial effects have also been observed with aprotinin, perhaps through its anti-inflammatory action.[57] In contrast, nonselective cyclooxygenase inhibition by NSAIDs worsens renal function in sepsis by decreasing the synthesis of the renal vasodilator prostacyclin.[180]

The use of pharmacologic doses of methylprednisolone in septic shock was discredited by two large multicenter studies showing no beneficial effect on outcome.[181,182] Moreover, patients who received corticosteroids had significant increases in BUN but not in serum creatinine concentration, suggesting a prerenal state induced by increased protein catabolism.[183] Other potentially adverse effects of high-dose corticosteroids include impaired mitochondrial function, impaired leukocyte function, and inhibition of phospholipase A_2, resulting in decreased synthesis of intrarenal vasodilator prostaglandins.

Supranormal Oxygen Delivery

Over the past decade there has been considerable controversy in the concept of supranormal oxygen delivery to the tissues to overcome the defect that exists in oxygen utilization by septic tissues.[184] This approach utilizes inotropic support and blood transfusion to drive global oxygen delivery (Do_2) to one of three end points: a Do_2 level consistently found in survivors (600 mL/min/m^2), or when global oxygen consumption (Vo_2) no longer increases with increasing Do_2 (consumption independence), or when blood lactate levels start to decline. The benefits on outcome of supranormal oxygen delivery have been disputed, and high-dose inotropic and vasopressor support may themselves have adverse consequences. Moreover, renal Do_2 and Vo_2 differ markedly from systemic indices. Renal Vo_2 is largely determined by tubular metabolic function, which is regulated by fluid and electrolyte changes. In a volume-loaded septic porcine model, inotropic support with dobutamine increased systemic Do_2 and Vo_2 but did not increase renal indices.[44] Furthermore, decreased global renal Do_2 does not appear to cause tubular damage, possibly because tubular work and Vo_2 are decreased when GFR declines.[185]

Dopaminergic Agents

Low-dose dopamine (1-3 μg/kg/min) is frequently administered to septic patients in the belief that it confers renal protection through renal vasodilation or perhaps by inhibition of the Na^+/K^+-ATPase pump and decreases in renal tubular Vo_2.

In patients with sepsis syndrome (signs of sepsis without hypotension), low-dose dopamine infusion doubled urine flow rate and increased creatinine clearance by 60% without any change in systemic hemodynamics.[186] However, the renal response to dopamine decreased significantly after 48 hours of dopamine infusion, possibly owing to downregulation of the renal dopaminergic receptors or diuresis-induced contraction of the intravascular volume. In patients with established septic shock who required catecholamines for blood pressure support, low-dose dopamine did not alter systemic hemodynamics or renal function.

The prophylactic administration of low-dose dopamine in sepsis appears to have been laid to rest by a large prospective controlled study conducted by the Australian and New Zealand Intensive Care Society (ANZICS). They randomized 328 patients with signs of the systemic inflammatory response syndrome (SIRS) and early renal dysfunction (oliguria or increasing serum creatinine) to dopamine, 2 μg/kg/min, or placebo. They found no differences in serum creatinine, dialysis requirement, intensive care unit or hospital length of stay or overall mortality.[187]

The potential role of dopexamine in septic shock remains speculative. Most studies have examined its role in splanchnic and hepatic perfusion rather than in renal protection. In animal models of sepsis, dopexamine has improved splanchnic and hepatic Do_2, but its β_2-adrenergic activity in causing tachycardia and hypotension may limit its application in clinical sepsis. Smithies and colleagues[188] administered dopexamine to patients with sepsis syndrome, acute respiratory failure, and at least one other organ system failure. Cardiac index increased and gastric intramucosal pH (an index of splanchnic perfusion) improved significantly.

Norepinephrine

In patients with septic shock, profound hypotension, and oliguria, vasopressor therapy with norepinephrine may actually improve renal function by enhancing renal perfusion pressure. Desjars and coworkers[11] evaluated a group of septic patients who remained oliguric despite volume resuscitation and the use of dopamine up to doses of 15 μg/kg/min. The addition of norepinephrine and reduction of dopamine to a low-dose level resulted in an improvement in mean arterial pressure from 50 to 70 mm Hg, a tripling of urine flow, and a doubling of creatinine clearance. Norepinephrine increased the systemic vascular resistance (SVR) with little change in cardiac index or Do_2. Subsequent studies have confirmed that the use of norepinephrine to keep mean arterial pressure greater than 60 mm Hg results in improved cardiac function (increase in stroke volume and decrease in heart rate) and GFR without deleterious effects on cardiac index, Vo_2, or oxygen extraction.[189] Large doses of norepinephrine may be required to achieve these goals, because in septic shock, the peripheral vasculature is notoriously refractory to norepinephrine-induced vasoconstriction. This occurs because of massive inducible nitric oxide release as well as vasopressin deficiency (see later). Nonetheless, these findings strongly support the concept that renal autoregulation is impaired in sepsis and that maintenance of adequate renal perfusion pressure is an important component of renal protection.

Arginine Vasopressin

Patients in vasodilatory shock have inappropriately low plasma levels of AVP and marked vascular sensitivity to its exogenous administration at low doses.[190] Vasodilatory shock is defined as hypotension, increased cardiac index, and low systemic vascular resistance refractory to pressors such as norepinephrine. Septic shock is its most common manifestation, but it is also characteristic of the contact activation syndrome induced by CPB or ventricular assist devices.[191]

Landry and coworkers[192] observed unusual sensitivity to the vasoconstrictor effects of infused AVP in patients with septic shock with profound hypotension despite catecholamine infusion. Infusion of AVP at doses of 2.4 units/hr, less than one tenth of those used in the treatment of bleeding esophageal varices, resulted in a dramatic increase in systolic blood pressure from 92 ± 4 to 146 ± 4 mm Hg (mean ± SEM, $P < .001$), and catecholamine infusions were able to be discontinued. In an associated report,[193] the authors observed that urine flow increased concomitantly in three of five patients, from an average of 30 mL/hr to 110 mL/hr.

Plasma AVP levels were remarkably low (3.1 ± 1.0 pg/mL) and significantly lower than in a cohort of patients in cardiogenic shock also receiving catecholamines (22.7 ± 2.2 pg/mL, $P < .001$).[192] It has been postulated that this "AVP deficiency" may be the result of excessive baroreceptor-mediated AVP release from sustained hypotension. This is strongly supported by a canine study demonstrating almost complete depletion of radiolabeled AVP in the posterior pituitary after 1 hour of hemorrhagic shock.[190]

A second mechanism for sensitivity to AVP in septic patients is explained by its effect on the potassium-ATP (K_{ATP}) channel.[190] Intracellular acidosis, lactic acid accumulation, and ATP depletion close K_{ATP} channels in the sarcolemma of vascular smooth muscle. This traps potassium outside the cell and hyperpolarizes the membrane, which in turn closes calcium channels essential for norepinephrine-induced vasoconstriction. AVP binds at the K_{ATP} channel and opens it, reversing membrane hyperpolarization and restoring sensitivity to norepinephrine.

The beneficial effect of AVP on renal function in sepsis may in part be due to its ability to increase low renal perfusion pressure back into the autoregulatory range. Another important factor is that, unlike norepinephrine, even at high local concentrations, AVP preferentially constricts the efferent arteriole, thereby improving filtration fraction and GFR.[53] However, in a large, prospective, randomized, blinded trial in 778 patients with severe septic shock, low-dose AVP (0.01-0.03 unit/min) did not provide a mortality benefit or decrease the requirement for dialysis when compared with an infusion of norepinephrine (5-15 µg/min).[194]

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19 Basic Principles of Pharmacology

Key Points

1. The fundamental pharmacokinetic processes are dilution into volumes of distribution and clearance. These processes are governed by the physical properties of the drug and the metabolic capacity of the patient. Anesthetic drugs tend to be highly bound to protein in plasma and highly bound to lipid in peripheral tissues. Most anesthetic drugs are metabolized in the liver.
2. The pharmacokinetics of anesthetic drugs are typically described by mathematical models with a central compartment and one or two peripheral compartments. These compartments do not directly correspond to any anatomic or physiologic structures. Computer simulations can be used to predict the time course of plasma concentration and drug effect after any dose.
3. Drugs exert their effects through binding to receptors. The fraction bound is determined by the law of mass action, which yields a sigmoidal relationship between fractional occupancy and drug concentration.
4. Drugs can be agonists, partial agonists, neutral antagonists, or inverse agonists. Receptors can exist in many states, but for simplicity, one can think of them as having just two states: activated and inactivated. The intrinsic efficacy of a drug is determined by the extent to which it stabilizes the active form of the receptor (agonists) or the inactive form (inverse agonists) or simply displaces agonists from the binding site without favoring either form (neutral antagonists).
5. A fraction of receptors are in the activated state when drug is present. Thus, a "baseline effect" in the absence of drug does not represent the true baseline if all receptors are inactivated. This can be observed only by giving an inverse agonist that forces nearly all receptors into the inactivated state.
6. Four main receptor types of relevance in anesthesia are G protein–coupled receptors (opioids, catecholamines), ligand-gated ion channels (hypnotics, benzodiazepines, muscle relaxants, ketamine), voltage-gated ion channels (local anesthetics), and enzymes (neostigmine, amrinone, caffeine). The first three are located in cell membranes. Enzymes can be located anywhere.
7. Many drugs act through second messengers, which amplify drug action. Common second messengers are G proteins, which can release stimulating or inhibitory subunits in response to drug binding at the receptor; cyclic adenosine monophosphate, which is frequently a target of G protein stimulation or inhibition; inositol 1,4,5-triphosphate and diacylglycerol, also targets of G-protein regulation; and intracellular ions, especially calcium.
8. Advances in molecular pharmacology are helping identify the specific function of individual receptors, the role of individual amino acids in mediating receptor action, and the specific sites of action of many anesthetic drugs. Tools to explore the mechanism of drug action include site-directed mutagenesis to create "designer" receptors and knock-out/knock-down (underexpressed) or transgenic (overexpressed) murine models to understand the physiologic action of individual receptors.
9. The fundamental properties of the concentration-versus-response relationship are potency and efficacy. Potency is the concentration associated with a 50% drug effect. Efficacy is the maximal possible drug effect.
10. Drugs can interact both pharmacokinetically, through enzymatic induction or inhibition, or pharmacodynamically, through synergy or antagonism. Anesthetic techniques typically take advantage of the synergy between hypnotics and opioids to produce the anesthetic state at far lower doses of each drug than would be required if they were used alone.
11. Pharmacogenetics is gradually explaining some of the variability in response to drugs. Genetic variability in pharmacokinetics can be attributed to variability in hepatic cytochromes (e.g., CYP2D6, CYP2C19), circulating enzymes (e.g., pseudocholinesterase), or transporters. Genetic variability in pharmacodynamics can be attributed to alterations in receptors, as has been demonstrated for multiple adrenergic receptor variants. Malignant hyperthermia has been clearly linked to variability in the ryanodine receptor.

12. Variability in response to drugs can also be attributed to nongenetic causes, such as aging, disease, exposure to environmental toxins, and the pharmacokinetic or pharmacodynamic influence of other drugs. Variability is also introduced through continuous exposure to a single drug, which can trigger desensitization (tolerance) or, if the drug is an antagonist, increased receptor sensitivity to the agonist.

Anesthesiologists administer drugs to produce hypnosis, amnesia, analgesia, and muscle relaxation, and to support physiologic homeostasis while minimizing side effects and toxicity. Anesthesiologists select appropriate doses through a combination of scientifically guided administration and empirical titration. Both approaches are enhanced by a thorough understanding of the basic principles of pharmacology.

This chapter is divided into three major sections: pharmacokinetic principles, pharmacodynamic principles, and the principles that underlie variability in drug response. Pharmacokinetics is the relationship between drug administration and drug concentration at the site of action. The fundamental concepts include volumes of distribution, drug clearance, transfer of drugs between plasma and tissues, and binding of drugs to circulating plasma proteins. The section on pharmacokinetics introduces both the physiologic processes that determine pharmacokinetics and the mathematical models used to relate dose to concentration. Pharmacodynamics is the relationship between drug concentration and pharmacologic effect. The broad areas of transduction of biologic signals, fundamental receptor theory and structure, the role of new developments in molecular biology, and clinical evaluation of drug effects are all presented. The last section explores processes that contribute to variability in drug response, including pharmacogenetics, the influence of patient physiology on pharmacokinetics and pharmacodynamics, and drug interactions.

Pharmacokinetics

Pharmacokinetics is the relationship between drug dose and drug concentration in plasma or at the site of drug effect. The processes of absorption, distribution, and clearance govern this relationship. Absorption is not relevant to intravenously administered drugs but is relevant to all other routes of drug delivery. The time course of intravenously administered drugs is a function of volumes of distribution and clearance. We will first discuss the physiologic basis of pharmacokinetics and then review pharmacokinetic models that relate dose to plasma or tissue concentration.

Fundamental Pharmacokinetic Concepts

Volume of Distribution

The distribution of a drug throughout plasma and tissues can be viewed as a process of dilution from the highly concentrated solution in the syringe to the dilute concentration in plasma. This dilution follows the mixing of drug into blood and transfer into tissues. The pharmacokinetic concept of volume is simply the apparent size of the tank required to explain the observed drug concentration. Figure 19-1 shows the dilution of administered drug into a tank of fluid. By definition, the concentration in the tank is the amount of drug administered divided by the volume of the tank. If we do not know the volume beforehand but can measure the concentration, we can rearrange the definition of concentration to calculate the volume of the tank:

$$\text{Volume} = \frac{\text{Amount (or dose)}}{\text{Concentration}} \quad (1)$$

As soon as the volume of the tank is known, the concentration after any bolus of drug can be calculated as the dose per volume. Just as the tank has a volume regardless of whether there is drug in it, the volume of distribution of a drug is an intrinsic property of the drug and individual regardless of whether any drug has been given.

Central Volume of Distribution

If we assume that the drug is injected into an arm vein and that the initial concentration is measured in an artery, the central volume of distribution reflects the volume of the heart, great vessels, and the venous volume of the upper part of the arm. It also reflects drug uptake by the lungs. For example, alfentanil is less lipophilic than fentanyl or sufentanil, which results in less pulmonary uptake and a smaller central volume for alfentanil than fentanyl or sufentanil. The central volume also reflects any metabolism that occurs between the venous injection site and the arterial sample.

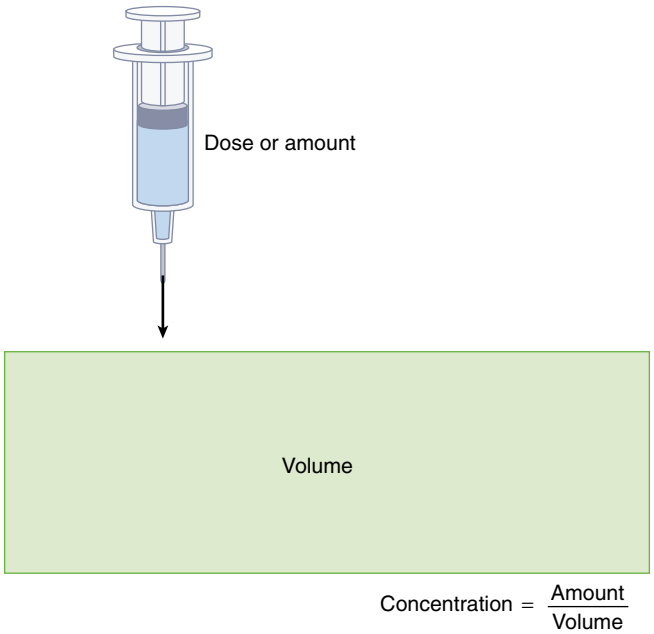

Figure 19-1 Volume represents the dilution of drug from the more concentrated form in the syringe to the dilute form in blood.

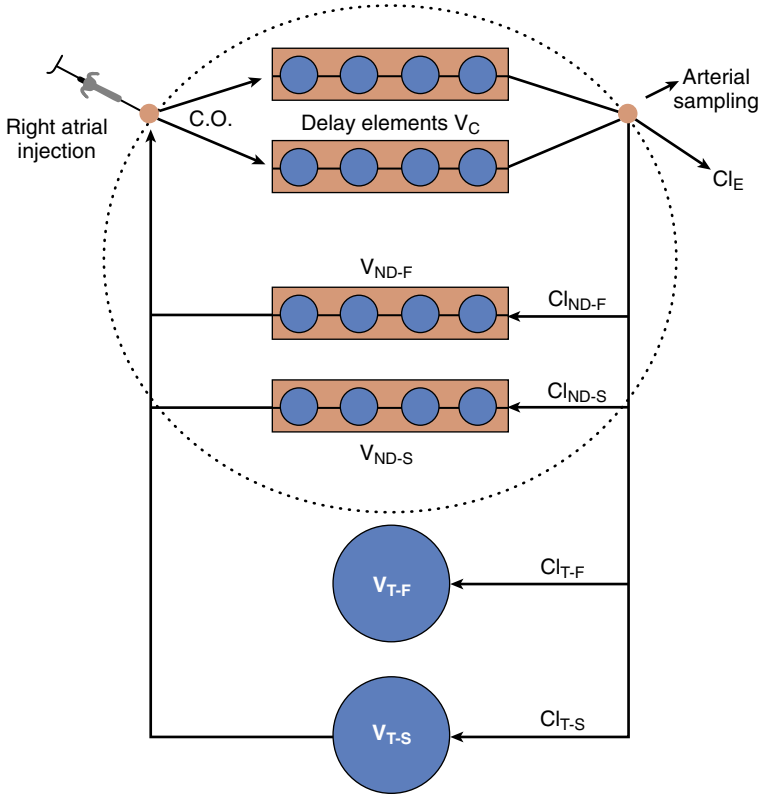

Figure 19-2 A recirculatory model accounting for cardiac output (C.O.), transit delays and pulmonary uptake (Delay Elements V_C), and nondistributive mixing pathways (V_{ND} and Cl_{ND}).[1] All the components within the *dashed circle* are required to accurately model the central volume of distribution. In most situations, this complexity is not required, and the simpler approach of assuming instantaneous mixing within the central volume is an adequate approximation. Cl_{ND-F} and Cl_{ND-S}, fast and slow nondistributive clearance; Cl_{T-F} and Cl_{T-S}, fast and slow tissue clearance; V_{ND-F} and V_{ND-S}, fast and slow nondistributive volume; V_{T-F} and V_{T-S}, fast and slow tissue volume. (*From Krejcie TC, Avram MJ, Gentry WB, et al: A recirculatory model of the pulmonary uptake and pharmacokinetics of lidocaine based on analysis of arterial and mixed venous data from dogs. J Pharmacokinet Biopharm 25:169-190, 1997.*)

The central volume of distribution is the most problematic pharmacokinetic concept. The central volume assumes that an intravenous bolus instantly mixes in this volume, with the peak concentration occurring at the moment of injection. Obviously, mixing is not instantaneous, and drug appears in the arterial circulation 30 to 40 seconds after injection. This 30- to 40-second delay is of no consequence outside anesthesia, but within the field of anesthesia the pharmacokinetic determinants of anesthetic induction are clinically important. The mathematics of the true time course, including the time delay and recirculatory peaks, have been worked out in detail by Henthorn, Avram, and Krejcie, as shown in Figure 19-2.[1]

Despite the assumption of instantaneous mixing, the concept of central volume of distribution is useful. The central volume represents the backward (and upward) extrapolation of the concentration-versus-time curve from its peak at about 30 seconds to the *y* axis. It can be thought of as the initial concentration, had circulation been infinitely fast. Because of this backward extrapolation, estimates of central volume are highly influenced by study design. A study with arterial samples will have higher initial concentrations and thus estimate a smaller central volume than a study with venous samples will. The timing of blood samples also influences estimation of the central volume of distribution. Over the first few minutes after bolus injection, the concentration of anesthetic drugs falls very rapidly, possibly by an order of magnitude. If the first sample is drawn at 30 seconds, backward extrapolation of the concentration-versus-time curve to the *y* axis predicts a high concentration at time 0 and thus a small central volume. If the first sample is drawn at 5 minutes, backward extrapolation of the concentration-versus-curve to the *y* axis predicts a much lower concentration and thus a larger central volume.

Peripheral Volumes of Distribution

Anesthetic drugs distribute extensively into peripheral tissues. This distribution into the periphery is represented pharmacokinetically as additional volumes of distribution that are attached to the central volume. Peripheral volumes are linked to the central compartment (plasma) by blood flow, a process called "intercompartmental clearance." The linkage of peripheral volumes to a central volume is called a "mammillary" model. This name refers to the structure of the plumbing: peripheral piglets suckling off a central (mother) pig. At least that is how the term was explained to us.

The size of the peripheral volumes of distribution reflects the drug's solubility in tissue relative to blood or plasma. The more soluble a drug is in peripheral tissue relative to blood or plasma, the larger the peripheral volumes of distribution. Because tissue solubility depends on simple physiochemical constants, it would seem likely that variability in peripheral volumes of distribution reflects differences in body habitus.

Peripheral volumes of distribution explain the apparent dilution of the drug into all body tissues. However, we usually do not know the actual solubility of drugs in peripheral tissues, nor do we care. The convention in pharmacokinetics is to assume that the solubility of the drug in tissue is the same as the solubility in plasma. This assumption does not compromise the role of peripheral compartments in characterizing the dilution of drugs into tissues, but it does lead to very large volumes of distribution for highly soluble drugs (e.g., 5000 L for propofol).

The volume of distribution at steady state (Vd_{ss}) is the volume that relates the plasma drug concentration at steady state (i.e., during a very long infusion) to the total amount of drug in the body. Vd_{ss} is the total amount of drug in the body at steady state divided by the plasma drug concentration. Hence, Vd_{ss} equals the central volume plus the peripheral volumes.

Clearance

Clearance removes drug from a volume. Systemic clearance permanently removes drug from the body, either by eliminating the parent molecule or by transforming it into metabolites. Intercompartmental clearance moves drug between plasma and peripheral tissues. Clearance is defined in units of flow, that is, the volume completely cleared of drug per unit of time (e.g., liters/minute). Clearance is most easily envisioned as flow to a clearing organ, as shown in Figure 19-3.[2] Clearance describes the body's capacity to remove drug, regardless of whether there is any drug in the body. The actual rate of drug removal is clearance times the concentration of the drug. If clearance is 1 L/min, the actual rate of drug elimination is 0 if the concentration is 0, 1 mg/min if the concentration is 1 mg/L, 10 mg/min if the concentration is 10 mg/L, and so on.

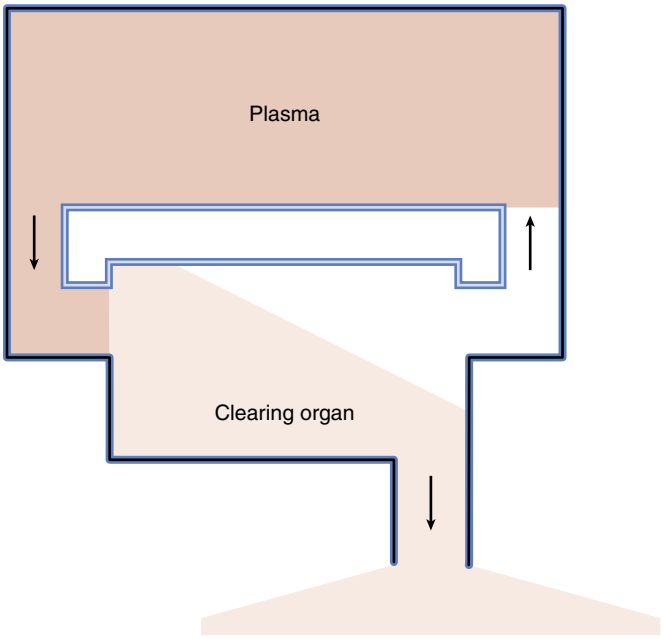

Figure 19-3 Clearance represents the flow of blood or plasma that is completely cleared of drug. If all of the drug is extracted by the clearing organ (i.e., extraction ratio ≈ 1), clearance is simply the flow to the organ, as illustrated here. *(Modified from Shafer S: Principles of pharmacokinetics and pharmacodynamics.* In *Longnecker DE, Tinker JH, Morgan GE [eds]: Principles and Practice of Anesthesiology, 2nd ed. St. Louis, Mosby–Year Book, 1997.)*

Hepatic Clearance

Most anesthetic drugs are cleared by hepatic biotransformation. The synthetic pathways for biotransformation are covered in detail in many biochemistry texts. Briefly, the liver metabolizes drugs through oxidation, reduction, hydrolysis, or conjugation. Oxidation and reduction occur in the cytochrome P450 system. These enzymes can be induced by exposure to certain drugs and increase the liver's intrinsic metabolic capacity. On the other hand, drugs or hepatic disease can inhibit these enzymes. Routes of oxidative metabolism include hydroxylation, dealkylation, deamination, desulfuration, epoxidation, and dehalogenation. Conjugation and hydrolysis often occur outside the P450 system, although glucuronidation involves the P450 system as well. The effect of conjugation is to transform hydrophobic molecules into water-soluble molecules through the addition of polar groups and thus render the metabolites easier to excrete via the kidneys. The metabolites generated by the liver are generally inactive, although some drugs (e.g., morphine, midazolam) have metabolites that are as potent as the parent drug. Genetic polymorphism can occur in all of these pathways, and this accounts for part of the variability in clearance in the population, as discussed in detail in the last section of this chapter.

Although most anesthetic drugs are cleared by hepatic metabolism, remifentanil, succinylcholine, and esmolol are cleared in the plasma and tissues by ester hydrolysis, and pancuronium is cleared via the kidney. The relationship between metabolism and clearance is complex. The following exploration of this relationship will assume hepatic metabolism, although the principles apply to the metabolism of drug in any tissue.

The rate of metabolism for most anesthetic drugs is proportional to the concentration of drug distributed via circulation to the liver. As will be shown later, this means that metabolic clearance is usually constant and independent of dose. This is such a common and fundamental assumption for anesthetic pharmacokinetics that we will explore the conditions that must be satisfied for it to be valid.

It cannot be true that metabolism is always proportional to concentration because the metabolic capacity of the liver is not infinite. At some rate of drug flow into the liver the metabolic capacity becomes saturated, and the rate of metabolism is no longer proportional to concentration. To understand the rate of metabolism quantitatively, we will start with a simple observation of mass balance: the rate at which drug flows *out* of the liver must be the rate at which drug flows *into* the liver minus the rate of metabolism. The rate at which drug flows into the liver is liver blood flow, $\dot{Q}$, times the concentration of drug flowing in, C_{inflow}. The rate at which drug flows out of the liver is liver blood flow, $\dot{Q}$, times the concentration of drug flowing out, $C_{outflow}$. Putting this together, the rate of hepatic metabolism by the liver, R, is the difference between the drug concentration flowing into the liver and the drug concentration flowing out of the liver, times the rate of liver blood flow:

$$\text{Rate of drug metabolism} = R = \dot{Q}\left(C_{inflow} - C_{outflow}\right) \qquad (2)$$

This relationship is illustrated in Figure 19-4. Because hepatic metabolism does not have infinite capacity, the relationship between the rate of hepatic metabolism, R, and concentration must be saturable. The saturation equation shows up repeatedly in pharmacokinetics and pharmacodynamics, so we will inspect it carefully:

$$\text{Response} = \frac{C}{C_{50} + C} \qquad (3)$$

"Response" in this equation varies from 0 to 1, depending on the value of C. When C is 0, the response is 0. If C is greater than 0 but much less than C_{50}, the response is nearly proportional to C: $\text{Response} \approx \frac{C}{C_{50}}$. If C equals C_{50}, the

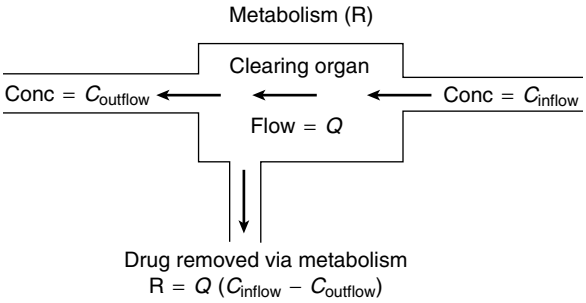

Figure 19-4 The rate of metabolism can be computed as the rate of liver blood flow times the difference between the inflowing and outflowing drug concentrations. This is a common approach to analyzing metabolism or tissue uptake across an organ in mass-balance pharmacokinetic studies.

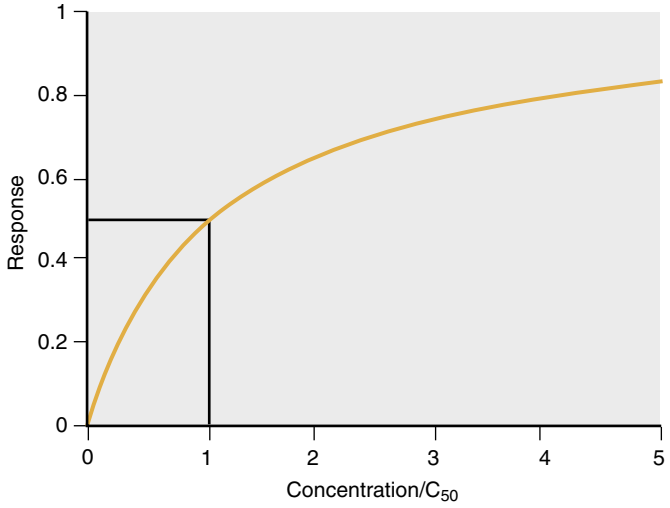

Figure 19-5 The saturation equation, response = C/(C_{50} + C), shows the decreasing incremental response as the system approaches saturation. Variations of this equation show up repeatedly in pharmacokinetics and pharmacodynamics.

response is $\frac{C_{50}}{C_{50}+C_{50}}$, which is simply 0.5. This is where the term "C_{50}" comes from; that is, it is the concentration associated with a 50% response. As C becomes much greater than C_{50}, the equation approaches $\frac{C}{C}$, which is 1.0. The shape of this relationship is shown in Figure 19-5. It is linear at low concentrations, but at high concentrations the response saturates at 1.

We can model the relationship between hepatic metabolism and drug concentration by using the saturation equation, but what concentration determines the rate of metabolism: the concentration flowing into the liver, the average concentration within the liver, or the concentration flowing out of the liver? All three have been used, but the most widely used model of metabolism views the rate of metabolism as a function of the concentration flowing *out* of the liver, $C_{outflow}$. This is discussed extensively by Wagner.[3]

We can expand our equation of metabolism to include the observation that the rate of metabolism, R, approaches saturation at the maximum metabolic rate, V_m, as a function of $C_{outflow}$:

$$\text{Rate of drug metabolism} = R = \dot{Q}\left(C_{inflow} - C_{outflow}\right) = V_m \frac{C_{outflow}}{K_m + C_{outflow}} \quad (4)$$

V_m is the maximum possible metabolic rate. The saturation part of this equation, $\frac{C_{outflow}}{K_m + C_{outflow}}$, determines the fraction of the maximum metabolic rate. K_m, also called the Michaelis constant, is the outflow concentration at which the metabolic rate is 50% of the maximum rate (V_m). This relationship is shown graphically in Figure 19-6. The *x* axis is the outflow concentration, $C_{outflow}$, as a fraction of K_m, the concentration that yields 50% of the maximum metabolic rate. The *y* axis is the rate of drug metabolism as a fraction of V_m, the maximum rate of drug metabolism. By normalizing $C_{outflow}$ to K_m and the metabolic rate to V_m, the relationship in Figure 19-6 is true for all values of V_m and K_m. Figure 19-6 shows that as long as the outflow concentration is less than half of K_m, there is a nearly proportional change in metabolic rate with a proportional change in outflow concentration. For most anesthetic drugs, the clinical concentrations do not exceed half of K_m, and thus metabolism of anesthetic drugs is nearly proportional to concentration. We can also interpret Figure 19-6 in terms of the metabolic rate (*y* axis). As long as the metabolic rate is less than a third of the maximum metabolic capacity, the rate of metabolism increases proportionally with concentration. The clinical message is that metabolism will be proportional to concentration and therefore the pharmacokinetics will remain

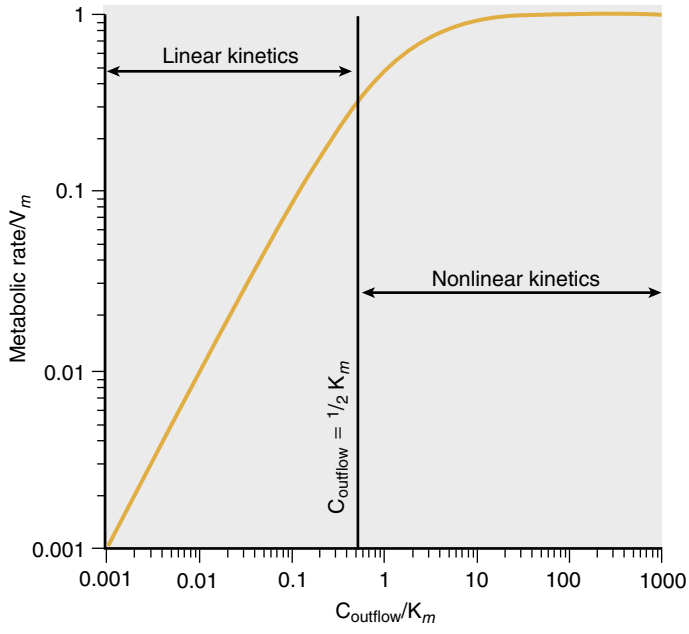

Figure 19-6 Relationship between concentration as a fraction of K_m (Michaelis constant) and drug metabolism as a fraction of V_m (maximum rate). As long as the outflow concentration is less than half K_m, a change in concentration is matched by a proportional change in metabolic rate. This is true of nearly all anesthetic drugs. *(From Shafer S: Principles of pharmacokinetics and pharmacodynamics.* In *Longnecker DE, Tinker JH, Morgan GE [eds]: Principles and Practice of Anesthesiology, 2nd ed. St. Louis, Mosby–Year Book, 1997.)*

linear, provided that the rate of intravenous administration at steady state does not exceed a third of the maximum metabolic capacity.

If the liver could completely extract the drug from the afferent flow, clearance would equal liver blood flow, $\dot{Q}$. However, the liver cannot remove every last drug molecule. There is always some drug in the effluent plasma. The fraction of inflowing drug extracted by the liver is $\frac{C_{inflow} - C_{outflow}}{C_{inflow}}$. This is called the extraction ratio. Clearance is the amount of blood completely cleared of drug per unit time. We can calculate clearance as liver blood flow times the extraction ratio:

$$\text{Clearance} = \dot{Q} \times ER = \dot{Q}\left(\frac{C_{inflow} - C_{outflow}}{C_{inflow}}\right) \quad (5)$$

With this basic understanding of clearance, let us divide each part of Equation 4 by C_{inflow}:

$$\begin{aligned}\frac{\text{Rate of drug metabolism}}{C_{inflow}} &= \frac{R}{C_{inflow}} \\ &= \dot{Q}\left(\frac{C_{inflow} - C_{outflow}}{C_{inflow}}\right) \\ &= \frac{C_{outflow}}{C_{inflow}}\left(\frac{V_m}{K_m + C_{outflow}}\right)\end{aligned} \quad (6)$$

The third term is clearance as defined in Equation 5: $\dot{Q}$ times the extraction ratio. Thus, each term must be clearance. Consider the first term, $\text{Clearance} = \frac{\text{Rate of drug metabolism}}{C_{inflow}}$. This indicates that clearance is a proportionality constant that relates inflowing (e.g., arterial) concentration to the rate of metabolism. If we want to maintain a given steady-state arterial drug concentration, we must infuse drug at the same rate that it is being metabolized. Thus, the infusion rate to maintain a given concentration is clearance times the desired concentration.

What should we make of the third and fourth terms, $\text{Clearance} = \dot{Q}\left(\frac{C_{inflow} - C_{outflow}}{C_{inflow}}\right)$ and $\text{Clearance} = \frac{C_{outflow}}{C_{inflow}}\left(\frac{V_m}{K_m + C_{outflow}}\right)$? Taken together, these equations relate clearance to liver blood flow and the extraction ratio, as shown in Figure 19-7.[4] For drugs with an extraction ratio of nearly 1 (e.g., propofol), a change in liver blood flow produces a nearly proportional change in clearance. For drugs with a low extraction ratio (e.g., alfentanil), clearance is nearly independent of the rate of liver blood flow. This makes intuitive sense. If nearly 100% of the drug is extracted by the liver, this implies that the liver has tremendous metabolic capacity for the drug. In this case, the rate-limiting step in metabolism is flow of drug to the liver, and such drugs are said to be "flow limited." Any reduction in liver blood flow, such as usually accompanies anesthesia, can be expected to reduce clearance. However, moderate changes in hepatic metabolic function per se will have little impact on clearance because hepatic metabolic capacity is overwhelmingly in excess of demand.

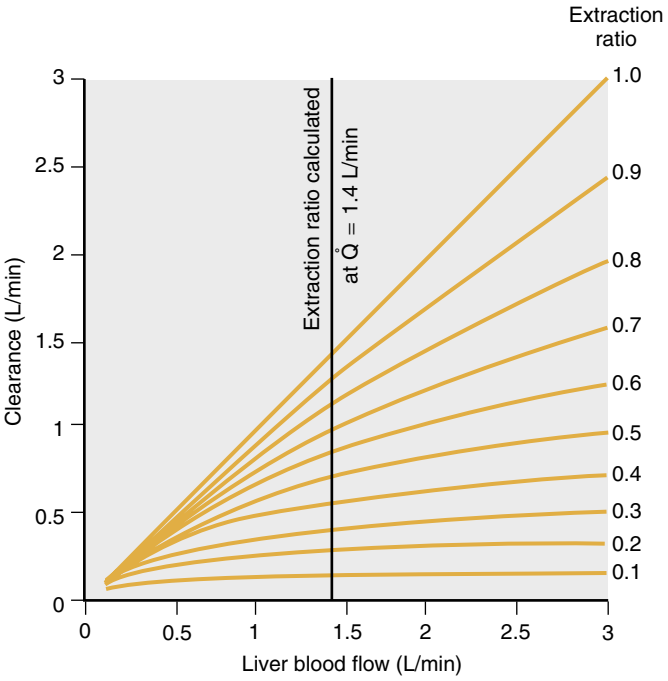

Figure 19-7 Relationship between liver blood flow ($\dot{Q}$), clearance, and extraction ratio. For drugs with a high extraction ratio, clearance is nearly identical to liver blood flow. For drugs with a low extraction ratio, changes in liver blood flow have almost no effect on clearance. *(Adapted from Wilkinson GR, Shand DG: Commentary: A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 18:377-390, 1975.)*

For many drugs (e.g., alfentanil), the extraction ratio is considerably less than 1. For these drugs, clearance is limited by the capacity of the liver to take up and metabolize the drug. These drugs are said to be "capacity limited." Clearance will change in response to any change in the capacity of the liver to metabolize such drugs, as might be caused by liver disease or enzymatic induction. However, changes in liver blood flow, as might be caused by the anesthetic state itself, usually have little influence on clearance because the liver handles only a fraction of the drug that it sees anyway.

The last two components of Equation 6 can also be used to show how the extraction ratio governs the response of clearance to changes in metabolic capacity (V_m). Figure 19-8 shows the clearance of drugs with an extraction ratio ranging from 0.1 to 1, based on a liver blood flow of 1.4 L/min. The extraction ratios were calculated for a V_m of 1. Changes in V_m, as might be caused by liver disease (reduced V_m) or enzymatic induction (increased V_m), have little effect on drugs with a high extraction ratio. However, drugs with a low extraction ratio have a nearly linear change in clearance with a change in intrinsic metabolic capacity (V_m).

Inasmuch as V_m and K_m are often not known, it is occasionally useful to condense them into a single term that summarizes hepatic metabolic capacity: "intrinsic clearance." Because $\text{clearance} = \frac{C_{outflow}}{C_{inflow}}\left(\frac{V_m}{K_m + C_{outflow}}\right)$, consider what happens if hepatic blood flow increases to infinity with no change in hepatic

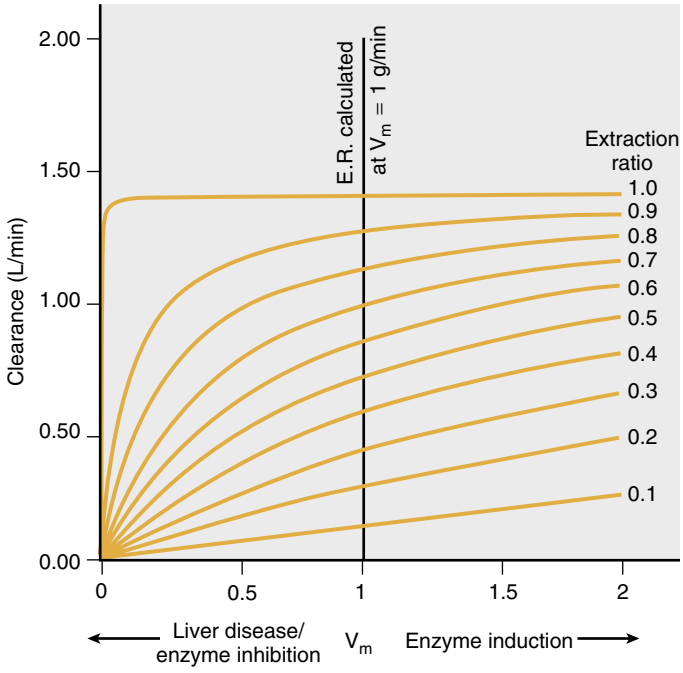

Figure 19-8 Corollary to Figure 19-7 showing the relationship between metabolic capacity, clearance, and extraction ratio (E.R.). Changes in maximum metabolic velocity (V_m) have little effect on drugs with a high extraction ratio, but they cause a nearly proportional decrease in clearance of drugs with a low extraction ratio.

metabolic capacity. $C_{outflow}$ becomes indistinguishable from C_{inflow} because the finite hepatic capacity metabolizes only an infinitesimal fraction of the drug flowing through the liver. As a result, clearance becomes $\frac{V_m}{K_m + C_{inflow}}$. We can solve for this in the "linear range" by finding clearance when $C_{inflow} = 0 : \frac{V_m}{K_m}$. This is the intrinsic clearance, Cl_{int}. In brief, it can be readily demonstrated (although we will spare you the details) from the definition of Cl_{int} that in the linear range, Cl_{int} is directly related to the extraction ratio:

$$\text{Extraction ratio} = \frac{Cl_{int}}{\dot{Q} + Cl_{int}} \tag{7}$$

Combining this with Equation 6 yields the relationship between hepatic clearance and Cl_{int}:

$$\text{Hepatic clearance} = \frac{\dot{Q}\, Cl_{int}}{\dot{Q} + Cl_{int}} \tag{8}$$

The relationship between intrinsic clearance and extraction ratio is shown in Figure 19-9 and was calculated at a hepatic blood flow of 1400 mL/min. In general, true hepatic clearance and extraction ratio are more useful concepts for anesthetic drugs than intrinsic clearance is. However, intrinsic clearance is introduced here because it is occasionally used in pharmacokinetic analysis of anesthetic drugs.

Thus far we have focused on linear pharmacokinetics, that is, the pharmacokinetics of drugs whose metabolic rate at clinical doses is less than $V_m/3$. Clearance of such drugs is generally expressed as a constant (e.g., propofol clearance = 1.6 L/min). Some drugs, such as phenytoin, exhibit saturable pharmacokinetics (i.e., have such low V_m that typical doses exceed the linear portion of Fig. 19-6). Clearance of drugs with saturable metabolism is a function of drug concentration rather than a constant.

Renal Clearance

The kidneys clear drug from plasma by filtration at the glomerulus and direct transport into the tubules. Renal blood flow is inversely correlated with age, as is creatinine clearance, which can be predicted from age and weight according to the equation of Cockroft and Gault[5]:
Men:

$$\text{Creatinine clearance } (\text{mL/min}) = \frac{(140 - \text{Age [yr]} \times \text{Weight [kg]})}{72 \times \text{Serum creatinine (mg\%)}} \tag{9}$$

Women:
85% of the above.

Equation 9 shows that age is an independent predictor of creatinine clearance. Thus, elderly patients have decreased creatinine clearance, even in the presence of normal serum creatinine levels. Inhaled anesthetics also decrease renal blood flow. Decreased renal clearance will delay the offset of effect for renally excreted drugs or their metabolites.

Tissue Clearance

Some anesthetic drugs are cleared in other tissues, such as blood, muscle, and the lungs. For example, remifentanil is cleared by nonspecific esterases located primarily in muscle and intestines, with the lungs, liver, kidneys, and blood each contributing minimally to clearance of remifentanil. Succinylcholine, mivacurium, and 2-chloroprocaine are all metabolized by plasma butyrylcho-

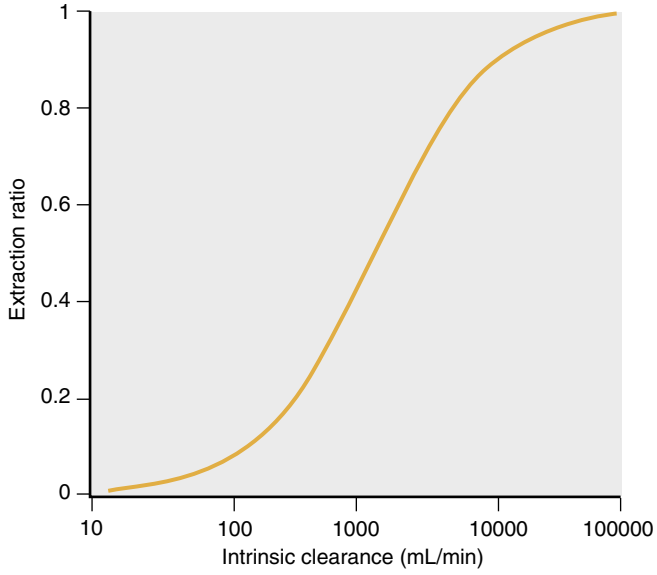

Figure 19-9 Relationship between intrinsic clearance and extraction ratio, calculated for a liver blood flow of 1400 mL/min.

linesterases (formerly called pseudocholinesterase). The half-life of succinylcholine, mivacurium, and 2-chloroprocaine in plasma is about 3 minutes, 5 minutes, and 25 seconds, respectively. About half of atracurium's metabolism is hepatic, and the balance occurs in blood via nonspecific cholinesterases (but not by butyrylcholinesterases). Hofmann degradation is a spontaneous process in plasma at normal pH and temperature and does not depend on any circulating esterases. Hofmann degradation is a minor route of metabolism of atracurium but is the major route of metabolism of cisatracurium, an isomer of atracurium. This is an important distinction: unlike atracurium and mivacurium, metabolism of cisatracurium is unaffected by disease or genetic variants of cholinesterase metabolism.

Clearance by tissues other than blood can be analyzed by using models similar to those for hepatic clearance. Tissue clearance can be flow limited, capacity limited, or both. Clearance within the blood itself cannot be flow limited and thus is entirely dependent on the intrinsic metabolic capacity of the blood.

Distribution Clearance

Distribution clearance is the transfer of drug between blood or plasma and peripheral tissues. Unlike metabolic clearance, distribution clearance does not permanently remove drug from the body. Distribution clearance is a function of cardiac output, tissue blood flow, and permeability of the capillary walls to the drug. For a drug that readily crosses into peripheral tissues, such as propofol, the sum of metabolic clearance and distribution clearance approaches cardiac output. For drugs that are metabolized directly in plasma or in many peripheral tissues, such as succinylcholine and remifentanil, the sum of metabolic clearance and distribution clearance can exceed cardiac output.

Protein Binding

Many drugs are bound to plasma proteins, particularly to albumin and α_1-acid glycoprotein. The relationship between drugs and their binding proteins can be described as

$$[\text{Free drug}] + [\text{Unbound protein binding sites}] \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} [\text{Bound drug}]$$

where [Free drug] is the free drug concentration, [Unbound protein binding sites] is the concentration of the available unbound protein binding sites, [Bound drug] is the concentration of drug bound to plasma proteins, k_{on} is the rate constant for binding of drug to plasma protein, and k_{off} is the rate constant for dissociation of bound drug from plasma protein. It can be inferred from this relationship that the rate of formation of bound drug is

$$\frac{d[\text{Bound drug}]}{dt} = [\text{Free drug}][\text{Unbound protein binding sites}]k_{on} - [\text{Bound drug}]k_{off} \quad (10)$$

At equilibrium (which is nearly instantaneous), d[Bound drug]/dt = 0, which permits us to solve for k, the ratio of k_{on}/k_{off}, as

$$k = \frac{k_{on}}{k_{off}} = \frac{[\text{Bound drug}]}{[\text{Free drug}][\text{Unbound protein binding sites}]} \quad (11)$$

Plasma proteins may have more than one binding site. Therefore, the total number of binding sites is the protein concentration, [Protein], times n, the average number of binding sites per protein molecule. For drugs used in anesthesia, the number of binding sites actually bound is only a trivial fraction of the total available binding sites, and thus we can reasonably approximate [Unbound protein binding sites] by n [Protein]. Because n, the number of binding sites per molecule, is constant, we can fold it into our rate constant k by defining the association constant K_a as

$$K_a = n\frac{k_{on}}{k_{off}} = \frac{[\text{Bound drug}]}{[\text{Free drug}][\text{Protein}]} \quad (12)$$

Let us define f_u as the free fraction of drug:

$$f_u = \frac{[\text{Free drug}]}{[\text{Bound drug}] + [\text{Free drug}]} \quad (13)$$

By combining Equations 12 and 13, we can solve for f_u in terms of the unbound drug concentration:

$$f_u = \frac{1}{1 + K_a[\text{Protein}]} \quad (14)$$

Two observations can be drawn from Equation 14. First, the fraction bound to plasma protein solely depends on the protein concentration, not on the drug concentration, provided that [Bound drug] << n[Protein]. This approximation is always true for anesthetic drugs because of their high potency. Even for thiopental, possibly the least potent drug used in contemporary anesthetic practice, [Bound drug] << n[Protein], and protein binding is independent of the concentration of thiopental. Second, if we solve Equation 14 for $f_u = 0.5$, we find that

$$K_a = \frac{1}{[\text{Protein}]_{50}} \quad (15)$$

where $[\text{Protein}]_{50}$ is the concentration of protein at which 50% of the drug is bound. Thus, another way of thinking about the association constant is that it is the inverse of the protein concentration associated with 50% binding. If we substitute $\frac{1}{[\text{Protein}]_{50}}$ for K_a in Equation 14, we get the relationship

$$f_u = \frac{[\text{Protein}]_{50}}{[\text{Protein}]_{50} + [\text{Protein}]} \quad (16)$$

This relationship is shown graphically in Figure 19-10. On the left side of Figure 19-10, [Protein] is much smaller than $[\text{Protein}]_{50}$. In this situation the drug has little affinity for protein binding, so there is far less protein around than required to bind 50% of the drug. The drug is mostly free, and f_u is nearly 1. On the right side of Figure 19-10, [Protein] is much greater than $[\text{Protein}]_{50}$. This means that there is far more protein present than would be required to bind 50% of the drug. The result is that drug will be mostly bound to plasma proteins, and f_u will be nearly 0.

The association constant K_a and its inverse $[\text{Protein}]_{50}$ reflect the affinity of the drug for plasma protein. They should not change in the presence of disease. However, [Protein] can change with disease, age, or concurrent drugs. Figure 19-11 shows the relationship between changes in protein concentration and

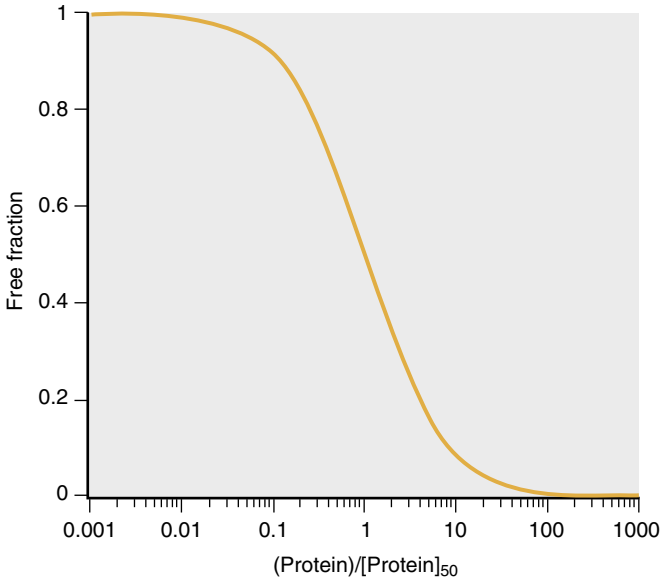

Figure 19-10 Relationship between plasma protein concentration as a fraction of the concentration associated with 50% binding and the fraction of drug that is unbound. This is another example of the saturation equation shown in Figure 19-5.

changes in the free fraction of drug for drugs with different degrees of protein binding in normal clinical use. The lines on the graph correspond to different drugs whose free fraction in normal plasma ranges from 1.0 (horizontal line) to approximately 0.0 (straight diagonal line).

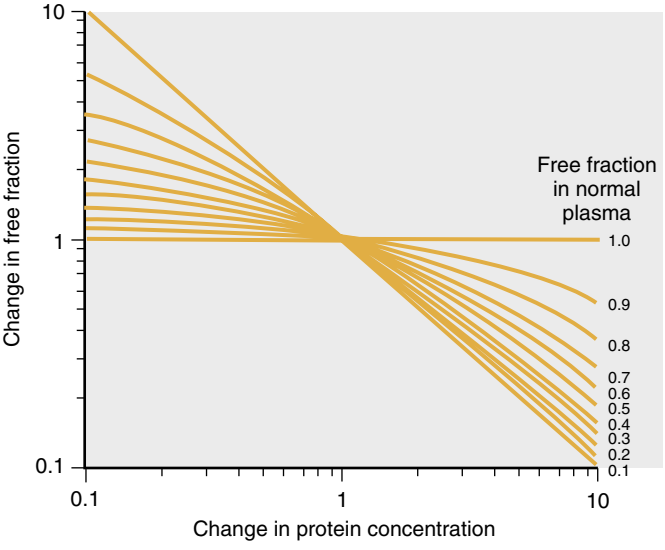

Figure 19-11 Relationship between changes in protein concentration and changes in free fraction. The relationship depends on the free fraction in normal plasma at typical clinical doses. For a drug that is not bound (free fraction ≈ 1), there is no change in free fraction with a change in protein concentration. For a highly bound drug with a free fraction that is nearly 0, any change in protein causes a nearly inversely proportional change in free fraction. *(From Shafer S: Principles of pharmacokinetics and pharmacodynamics.* In *Longnecker DE, Tinker JH, Morgan GE [eds]: Principles and Practice of Anesthesiology, 2nd ed. St. Louis, Mosby–Year Book, 1997.)*

For drugs that are not bound (free fraction = 1.0), there is no relationship between free fraction and protein concentration, as indicated by the flat horizontal line. For drugs whose free fraction is typically 90%, there will be a small change in free drug concentration with changes in protein concentration. For drugs that are highly protein bound, the free drug concentration changes nearly inversely with the change in protein concentration. As the proportion of binding approaches 100% (free drug → 0.0), the relationship between change in protein concentration and change in free fraction becomes inversely proportional. Note that there is never a greater than proportional change in free drug concentration with a change in plasma concentration. For example, the most that a 10% change in protein concentration would produce is a 10% change in free drug concentration, and that would be the case only if the drug were nearly 100% bound to plasma protein.

The in vitro observation that changing protein concentration results in changing free drug concentration, as shown in Figure 19-11, does not necessarily apply to the in vivo situation. It is the free (e.g., unbound) drug that equilibrates between plasma and tissues. If plasma protein binding is decreased, the free drug concentration gradient between plasma and peripheral tissues will increase. As a result, when protein binding decreases, equilibrium is achieved between plasma and the tissue free drug concentration at a lower total plasma drug concentration. This lower concentration gives the appearance that the drug has distributed into a larger total space. Thus, decreased protein binding causes an increase in the apparent volume of distribution when referenced to total, rather than free, drug concentration.

The increased volume of distribution at steady state, Vd_{ss}, seen with decreased plasma protein binding is mostly an illusion. Were only the unbound drug concentration measured, there would be almost no change in the apparent volume of distribution for lipophilic drugs (such as most of those in anesthesia practice) because it is partitioning of drug within peripheral tissues that primarily governs the free concentration of lipophilic drugs.

Changes in protein binding may affect the clearance of drugs. If a drug has a high extraction ratio, the liver is going to remove nearly all the drug flowing to it, regardless of the extent of protein binding. However, if the drug has a low hepatic extraction ratio, an increase in the free fraction of drug will result in an increase in the driving gradient along with an associated increase in clearance. Protein binding also affects the apparent potency of a drug when referenced to the total plasma drug concentration. An increase in free fraction increases the driving pressure to the site of drug effect. Thus, a change in free fraction will increase the concentration at the effect site. Because of this change in apparent potency, decreased protein binding may decrease the dose required to produce a given drug effect, even in the absence of other pharmacokinetic changes.

Stereochemistry

Typical pharmacokinetic analyses describe fictitious drugs. For example, the pharmacokinetics and pharmacodynamics of thiopental, ketamine, and bupivacaine describe drugs that do not exist. The reason is that many anesthetic drugs are chiral and supplied as racemic mixtures. The body is a chiral environment, and drugs interact stereospecifically with enzymes, proteins, and receptors. The pharmacokinetics and pharmacodynamics of the enantiomers may differ. The enantiomers of bupivacaine and

ketamine have been particularly well studied, and the levo-isomer of bupivacaine is available commercially as levobupivacaine. Although the importance of studying the pharmacokinetics and pharmacodynamics of individual stereoisomers is widely appreciated, the difficulty of performing such studies has precluded widespread use.

Pharmacokinetic Models

Zero- and First-Order Processes

The body's consumption of oxygen and production of carbon dioxide are processes continuing at a constant rate. These are called zero-order processes. The rate of change (dx/dt) for a zero-order process is

$$\frac{dx}{dt} = k \tag{17}$$

Equation 17 states that the rate of change is constant. If x represents an amount of drug and t represents time, the unit of k is amount/time. If we want to know the value of x at time t, x(t), we can compute it as the integral of Equation 17 from time 0 to time t:

$$x(t) = x_0 + k \cdot t \tag{18}$$

where x_0 is the value of x at time 0. This is the equation of a straight line with a slope of k and an intercept of x_0.

Many processes occur at a rate proportional to the amount. For example, the interest payment on a loan is proportional to the outstanding balance, and the rate at which water drains from a bathtub is proportional to amount (height) of water in the tub. These are examples of first-order processes. The rate of change in a first-order process is only slightly more complex than that for a zero-order process:

$$\frac{dx}{dt} = k \cdot x \tag{19}$$

Here, the unit of k is 1/time because the x on the right-hand side already includes the unit for amount. If we want to know the value of x at time t, x(t), it can be computed as the integral from time 0 to time t:

$$x(t) = x_0 \cdot e^{kt} \tag{20}$$

where x_0 is the value of x at time 0. If k is greater than 0, x(t) increases exponentially. If k is less than 0, x(t) decreases exponentially. In pharmacokinetics, k is negative because concentrations decrease over time. For clarity, the minus sign is usually explicit, so k is expressed as a positive number. Thus, the identical equation for pharmacokinetics, with the minus sign explicitly written, is

$$x(t) = x_0 \times e^{-kt} \tag{21}$$

Figure 19-12 shows the relationship between x and time, as described by Equation 21. In Figure 19-12, x continuously decreases over time. However, the slope of the curve continuously increases (i.e., becomes less negative). Taking the natural logarithm of both sides of Equation 21 gives

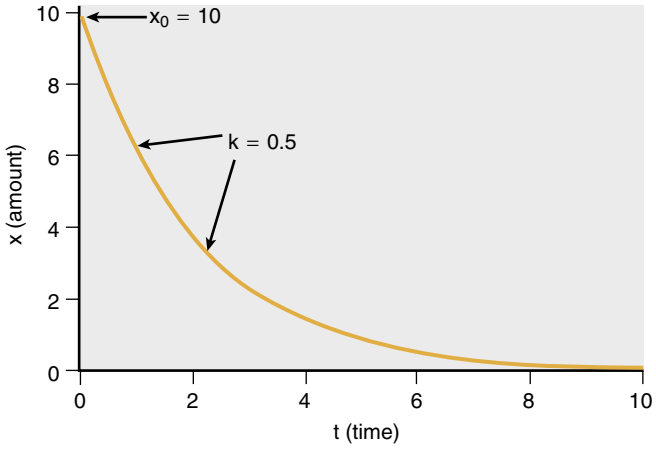

Figure 19-12 Exponential decay curve, as given by $x(t) = x_0 e^{-kt}$, plotted on standard axes, with $x_0 = 10$ and $k = 0.5$.

$$\begin{aligned} \ln(x[t]) &= \ln\left(x_0 \times e^{-kt}\right) \\ &= \ln(x_0) + \ln(e^{-kt}) \\ &= \ln(x_0) - (k \times t) \end{aligned} \tag{22}$$

This is the equation of a straight line, as shown in Figure 19-13, where the vertical axis is ln(x[t]), the horizontal axis is *t*, the intercept is $\ln(x_0)$, and the slope of the line is $-k$.

How long will it take for x to go from a certain value, x_1 to half that value, $(x_1/2)$? Because k is the slope of a straight line relating ln(x) to time,

$$k = \frac{\Delta \ln(x)}{\Delta t} = \frac{\ln(x_1) - \ln\left(\frac{x_1}{2}\right)}{t_{1/2}} \tag{23}$$

where $t_{1/2}$ is the "half-life", or the time required for a 50% decrease in *x*. We can simplify the numerator to

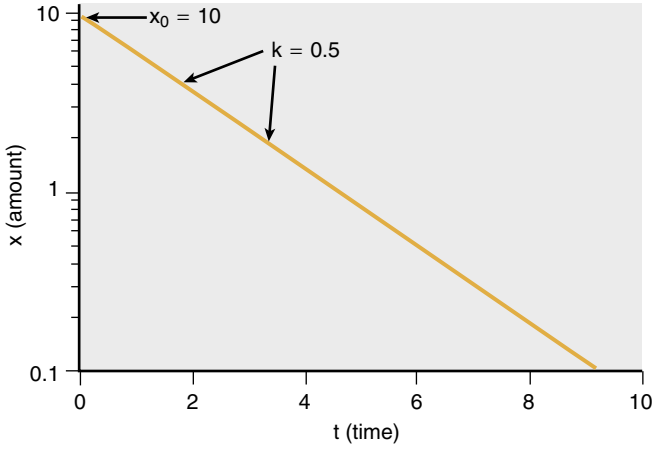

Figure 19-13 The same exponential decay curve, $x(t) = x_0 e^{-kt}$, as in Figure 19-12, but now plotted on a log *y* axis.

$$\ln(x_1) - \ln\left(\frac{x_1}{2}\right) = \ln\left(\frac{x_1}{\frac{x_1}{2}}\right) = \ln(2) \approx 0.693 \quad (24)$$

This succinctly relates slope (or "rate constant"), k, to half-life, $t_{½}$:

$$k = \frac{0.693}{t_{½}} \quad (25)$$

Thus, if we measure the time that it takes for x to fall by 50%, $t_{½}$, we know the rate constant k. If we know k, we can easily calculate from Equation 25 the time that it will take for x to fall by 50%:

$$t_{½} = \frac{0.693}{k} \quad (26)$$

Physiologic Pharmacokinetic Models

It is possible to analyze volumes and clearances for each organ in the body and construct models of pharmacokinetics by assembling the organ models into physiologically and anatomically accurate models of the entire animal. Figure 19-14 shows such a model for thiopental in rats.[6] Subsequent studies have shown that individual tissue volumes and blood flow can be scaled up from rats to humans to result in accurate models of human pharmacokinetics.[7] This illustrates the potential utility of physiologically based pharmacokinetic models in developing human pharmacokinetic models from animal models.

Models that work with individual tissues are mathematically cumbersome and do not offer a better prediction of plasma drug concentration than models that lump the tissues into a few compartments. If the goal is to determine how to give drugs to obtain therapeutic plasma drug concentrations, all that is needed is to mathematically relate dose to plasma concentration. For this purpose, conventional "compartmental" models are usually adequate.

Compartmental Pharmacokinetic Models

Compartmental models are built on the same basic concepts as physiologic models, but with gross simplifications. The "one-compartment model" seen in Figure 19-15 contains a single volume and a single clearance, as though we were built like buckets. For anesthetic drugs, we resemble several buckets connected by pipes. These are usually modeled by two- or three-compartment models, also shown in Figure 19-15. The volume to the right in the two-compartment model—and in the center of the three-compartment model—is the central volume. The other volumes are peripheral volumes. The sum of the all volumes is the volume of distribution at steady state, Vd_{ss}. Clearance in which the central compartment is left for the outside is the "central" or "metabolic" clearance. Clearances between the central compartment and the peripheral compartments are the "intercompartmental" clearances.

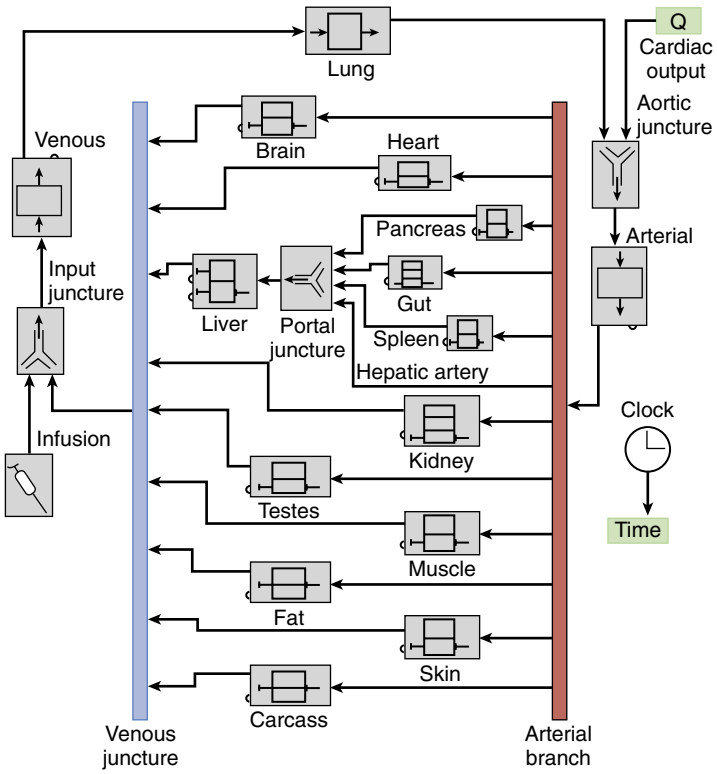

Figure 19-14 Physiologic model for thiopental in rats. The pharmacokinetics of distribution into each organ has been determined individually. The components of the model are linked by zero-order (flow) and first-order (diffusion) processes. *(From Ebling WF, Wada DR, Stanski DR: From piecewise to full physiologic pharmacokinetic modeling: Applied to thiopental disposition in the rat. J Pharmacokinet Biopharm 22:259-292, 1994.)*

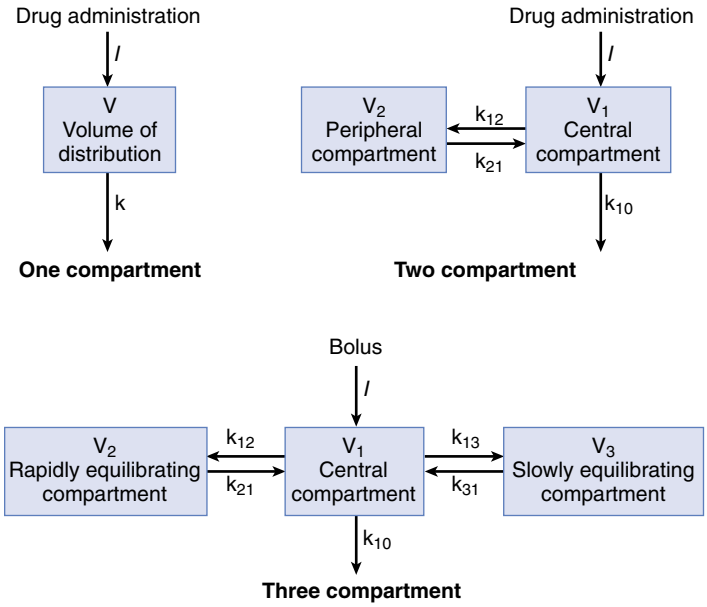

Figure 19-15 One-, two-, and three-compartment mammillary models.

One-Compartment Model

Bolus Pharmacokinetics. Think of the body as a bucket into which we pour drug. Let us call the amount of drug that we pour into the bucket x_0 (x at time 0). The initial concentration is x_0/V, where V is the volume of fluid within the bucket. Returning to Equation 1, if we know the concentration that we want to achieve, C_T (target concentration), and V, the volume in the bucket, we can calculate the dose to achieve C_T by rearranging the definition of concentration: Dose = $C_T \times V$.

Let us assume that the fluid is being circulated through a clearing organ at a constant rate, which we call clearance, Cl. What is the rate, dx/dt, by which the drug leaves the bucket? Because concentration is x/V and Cl is the rate that the fluid in the bucket is flowing out through the clearing organ, the rate at which the drug is leaving must be $x/V \times Cl$. This rate is a first-order process if—and only if—it equals a constant, *k*, times the amount of drug in the bucket. Does it?

$$\begin{aligned}\frac{dx}{dt} &= \frac{x}{V}Cl \\ &= \frac{Cl}{V}x \\ &= kx?\end{aligned} \tag{27}$$

We stated earlier that flow through the clearing organ, Cl, was constant. The volume, V, is constant because the clearing organ returns the flow to the bucket. Because Cl and V are both constants, $\frac{Cl}{V}$ is also a constant. Referring back to Equation 27, k, a constant by definition of first-order processes, equals $\frac{Cl}{V}$, a constant by definition of clearance and volume. This can be rearranged to yield the fundamental identity of linear pharmacokinetics:

$$\begin{aligned}Cl\ (\text{clearance}) &= k\ (\text{rate constant}) \\ &\cdot\ V\ (\text{volume of distribution})\end{aligned} \tag{28}$$

What does this identity tell us about the relationship between half-life, volume, and clearance? Rearranging the above as $k = \frac{Cl}{V}$ and remembering that $t_{1/2} = \frac{0.693}{k}$, we can conclude that half-life is proportional to volume and inversely proportional to clearance:

$$\begin{aligned}t_{1/2} &= 0.693\frac{V}{Cl} \\ t_{1/2} &\propto \frac{V}{Cl}\end{aligned} \tag{29}$$

Figure 19-16 shows a one-compartment model with an identical clearance but a bigger volume than is seen in Figure 19-3. It takes longer to clear drug from this bigger volume, so the half-life will increase, as predicted by Equation 29. Figure 19-17 shows a one-compartment model with an identical volume but faster clearance than is seen in Figure 19-3. The concentrations will fall more quickly (shorter half-life) with the larger clearance, as predicted by Equation 29.

Because this is a first-order process, $\frac{dx}{dt} = k\,x$, and the integral of this process gives us the amount of drug at time t in terms of the amount at time 0, $x(t) = x_0\ e^{-kt}$. If we divide both sides by V and remember that x/V is the definition of concentration, we get the equation that relates concentration after an intravenous bolus to time and initial concentration:

$$C(t) = C_0 e^{-kt} \tag{30}$$

This equation defines the "concentration-over-time" curve for a one-compartment model and has the log-linear shape seen in

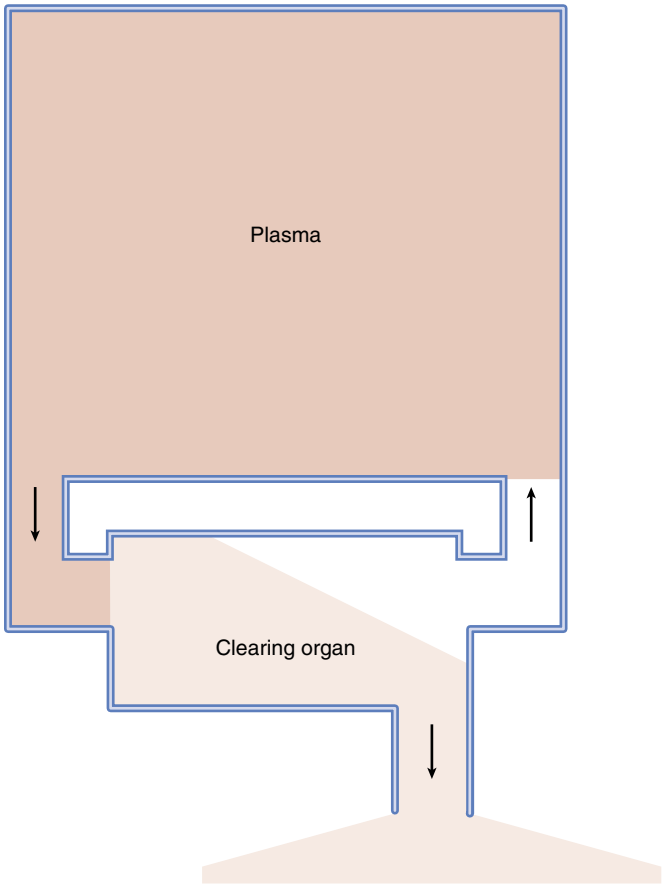

Figure 19-16 A one-compartment model similar to Figure 19-3, but with an increased volume of distribution. After drug administration, concentrations will fall more slowly in this model than in the model shown in Figure 19-3.

Figure 19-13. We can calculate the clearance, Cl, in one of two ways. First, we can calculate V by rearranging the definition of concentration, V = dose/initial concentration = dose/C_0. Referring back to Equation 28, if we measure the slope, –k, we can calculate clearance as k × V. A more general solution is to consider the integral of the concentration-over-time curve, Equation 30, known in pharmacokinetics as the area under the curve (AUC):

$$\begin{aligned} AUC &= \int_0^\infty C_0 e^{-kt} dt \\ &= \int_0^\infty \frac{x_0}{V}\left(e^{-\frac{Cl}{V}t}\right) dt \,(\text{substituting for } C_0 \text{ and } k) \\ &= \frac{x_0}{V} \times \frac{V}{Cl} (\text{evaluating the above integral}) \\ &= \frac{x_0}{Cl} \end{aligned} \tag{31}$$

We can rearrange Equation 31 to solve for clearance, Cl:

$$Cl = \frac{x_0}{AUC} \tag{32}$$

Because x_0 is the dose of drug, clearance equals the dose divided by AUC. This fundamental property of *linear* pharmacokinetic models applies to one-compartment models, multicompartment models, and any type of intravenous drug dosing (provided that the *total* dose administered systemically is used as the numerator). It directly follows that AUC is proportional to dose for linear models (i.e., models in which Cl is constant).

Infusion Pharmacokinetics. If we give an infusion at a rate of I (for input), the plasma concentration will rise as long as the rate of drug going in the body, I, exceeds the rate at which drug leaves the body, C × Cl, where C is the drug concentration. When I = C × Cl, drug is going in and coming out at the same rate, and the body is at steady state. We can calculate the concentration at steady state by observing that the rate of drug going in must equal the rate of drug coming out. From Equation 6 we know that rate of drug metabolism at steady state is

$$\text{Metabolic rate} = C_{ss} \cdot Cl \tag{33}$$

where C_{ss} is the arterial concentration at steady state. Because by definition at steady state the infusion rate must equal the metabolic rate, the infusion rate, I, at steady state must be $I = C_{ss} \times Cl$. Solving this for the concentration at steady state, C_{ss}, gives $\frac{I}{Cl}$. Thus, the steady state concentration during an infusion is the rate of drug input divided by clearance. It follows that if we want to calculate the infusion rate that will achieve a given target concentration, C_T, at steady state, the infusion rate must be $C_T \times Cl$.

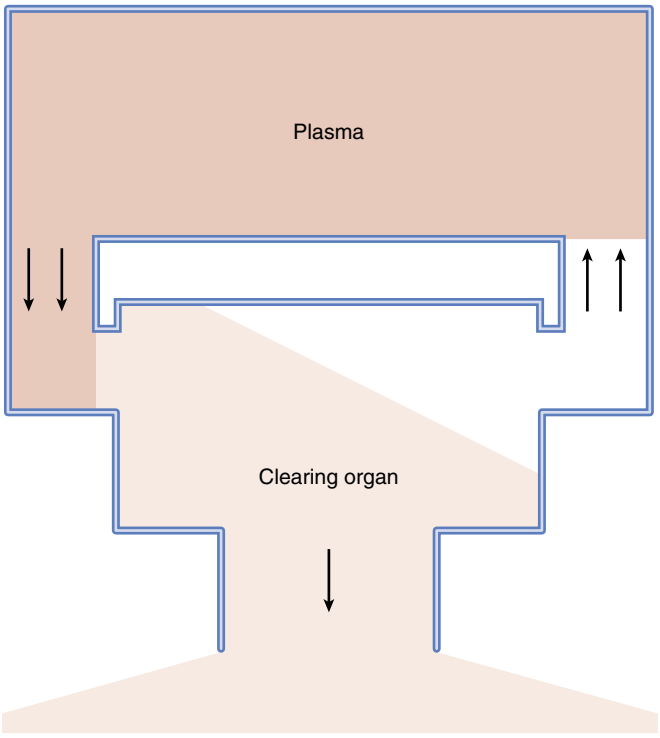

Figure 19-17 A one-compartment model similar to Figure 19-3, but with increased clearance. After drug administration, concentrations will fall faster in this model than in the model shown in Figure 19-3.

$C_\infty = \frac{I}{Cl}$ is similar in form to the equation describing the concentration after a bolus injection: $C_0 = \frac{x_0}{V}$. Thus, volume is a scalar relating bolus to initial concentration, and clearance is a scalar relating infusion rate to steady-state concentration. It follows that the initial concentration after a bolus is independent of clearance and that the steady-state concentration during a continuous infusion is independent of volume.

During an infusion, the rate of change in the amount of drug, x, is rate of inflow, I, minus the rate of outflow, $k \times x$.

$$\frac{dx}{dt} = I - k\,x \tag{34}$$

We can calculate x at any time t as the integral from time 0 to time *t*. Assuming that $x_0 = 0$ (i.e., we are starting with no drug in the body), the result is

$$x(t) = \frac{I}{k}\left(1 - e^{-kt}\right) \tag{35}$$

As $t \to \infty$, $e^{-kt} \to 0$, and Equation 35 reduces to

$$x_{ss} = \frac{I}{k} \tag{36}$$

How long does it take to reach 50% of the final steady-state concentration (i.e., to reach a concentration of $\frac{x_{ss}}{2}$) during an infusion? From Equation 36 we know that $\frac{x_{ss}}{2} = \frac{I}{2k}$. Substituting $\frac{I}{2k}$ for x(t) in Equation 35, we get

$$\frac{I}{2k} = \frac{I}{k}\left(1 - e^{-kt}\right) \tag{37}$$

Solving Equation 37 for t, we get $\frac{\ln(2)}{k}$. In Equation 26 we found that the half-life, $t_{1/2}$, after a bolus injection was $\frac{\ln(2)}{k}$. Here, we again have a parallel between boluses and infusions. During an infusion it takes one half-life to reach 50% of the steady-state concentration. Similarly, it takes two half-lives to reach 75%, three half-lives to reach 87.5%, and five half lives to reach 97% of the steady-state concentration. By four to five half-lives we typically consider the patient to be at steady state, although the concentrations only asymptotically approach the steady-state value.

Absorption Pharmacokinetics. When drugs are given intravenously, all of the drug reaches the systemic circulation. When drugs are given by a different route, such as orally, transdermally, epidurally, or intramuscularly, the drug must first reach the systemic circulation. Oral drugs may be only fractionally absorbed, and what is absorbed may be subjected to first-past hepatic metabolism before reaching the systemic circulation. Transdermally applied drugs may be sloughed off with the stratum corneum without being absorbed. We cannot assume that the dose given to the patient is the same as the dose that reaches the systemic circulation when using alternative routes of drug delivery. The dose that reaches the systemic circulation is the administered dose times f, the fraction "bioavailable."

Alternative routes of drug delivery are often modeled by assuming that the drug is absorbed from a reservoir or depot, which is usually modeled as an additional compartment with a monoexponential rate of transfer to the systemic circulation:

$$A(t) = f \times D_{oral} \times k_a \times e^{-k_a t} \tag{38}$$

where A(t) is the absorption rate at time t, f is the fraction bioavailable, D_{oral} is the dose taken orally (or intramuscularly, applied to the skin, etc.), and k_a is the absorption rate constant. Because the integral of $k_a \times e^{-k_a t}$ is 1, the total amount of drug absorbed is $f \times D_{oral}$. To compute the concentrations over time, we first reduce the problem to differential equations, (e.g., Equations 19 and 34) and integrate. The differential equation for the amount, x, with oral absorption into a one-compartment disposition model is

$$\begin{aligned} \frac{dx}{dt} &= \text{inflow} - \text{outflow} \\ &= A(t) - k \times x \\ &= D_{oral} \times f \times k_a \times e^{-k_a t} - k \times x \end{aligned} \tag{39}$$

This is simply the rate of absorption at time t, A(t), minus the rate of exit, $k \times x$. To solve for the amount of drug, x, in the compartment at time t, we integrate this from 0 to time t, knowing that $x(0) = 0$:

$$x(t) = \frac{D_{oral} \times f \times k_a}{k - k_a}\left(e^{-k_a t} - e^{-kt}\right) \tag{40}$$

Equation 40 describes the amount of drug in the systemic circulation after first-order absorption from a depot, such as the stomach, an intramuscular injection, the skin, or even an epidural dose. To describe concentrations rather than amounts of drug, it is necessary to divide both sides of Equation 40 by V, the volume of distribution.

This covers the standard pharmacokinetic equations for one-compartment models. The one-compartment model introduces the concepts of rate constants and half-lives and relates them to the physiologic concepts of volume and clearance. Unfortunately, none of the drugs used in anesthesia can be accurately characterized by one-compartment models. The distribution of anesthetic drugs into and out of peripheral tissues plays a crucial role in the time course of anesthetic drug effect. To describe intravenous anesthetics, we must extend the one-compartment model to account for distribution into tissues.

Multicompartment Models

Plasma concentrations over time after an intravenous bolus resemble the curve in Figure 19-18. In contrast to Figure 19-13, Figure 19-18 is not a straight line, even though it is plotted on a log *y* axis. This curve has the characteristics common to most drugs when given by intravenous bolus. First, the concentrations continuously decrease over time. Second, the rate of decline is initially steep but continuously becomes less steep, until we get to a portion that is "log-linear."

For many drugs, three distinct phases can be distinguished, as suggested by Figure 19-18. There is a "rapid-distribution" phase (solid line in Fig. 19-18) that begins immediately after injection

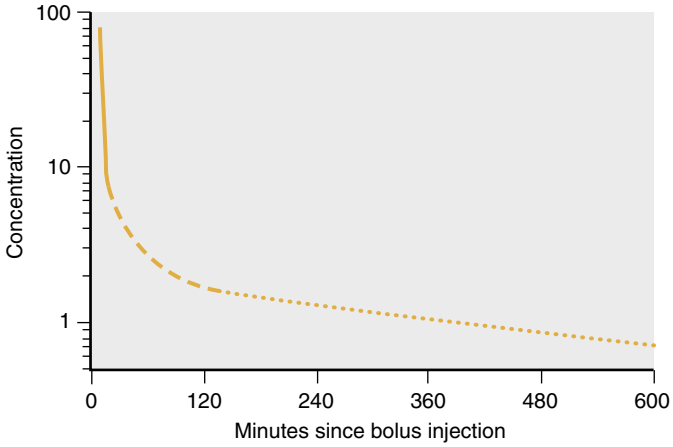

Figure 19-18 Concentration-versus-time relationship showing a very rapid initial decline after injection of a bolus. The terminal log-linear portion is seen only after most of the drug has left the plasma. This is characteristic of most anesthetic drugs. Different line types highlight the rapid, intermediate, and slow (log-linear) portions of the curve.

of the bolus. Very rapid movement of the drug from plasma to the rapidly equilibrating tissues characterizes this phase. Frequently there is a second "slow-distribution" phase (dashed line in Fig. 19-18) that is characterized by movement of drug into more slowly equilibrating tissues and return of drug to plasma from the most rapidly equilibrating tissues. The terminal phase (dotted line in Fig. 19-18) is a straight line when plotted on a semilogarithmic graph. The terminal phase is often called the "elimination phase" because the primary mechanism for decreasing drug concentration during the terminal phase is elimination of drug from the body. The distinguishing characteristic of the terminal elimination phase is that the plasma concentration is lower than tissue concentrations and the relative proportion of drug in plasma and peripheral volumes of distribution remains constant. During this "terminal-phase" drug returns from the rapid- and slow-distribution volumes to plasma and is permanently removed from plasma by metabolism or excretion.

The presence of three distinct phases after bolus injection is a defining characteristic of a mammillary model with three compartments. It is possible to develop hydraulic models, as shown in Figure 19-19, for intravenous drugs.[8] In this model, there are three tanks corresponding (from left to right) to the slowly equilibrating peripheral compartment, the central compartment (the plasma, into which drug is injected), and the rapidly equilibrating peripheral compartment. The horizontal pipes represent intercompartmental clearance or (for the pipe draining onto the page) metabolic clearance. The volumes of each tank correspond to the volumes of the compartments for fentanyl. The cross-sectional areas of the pipes correlate with fentanyl systemic and intercompartmental clearance. The height of water in each tank corresponds to drug concentration.

By using this hydraulic model we can follow the processes that decrease drug concentration over time after bolus injection. Initially, drug flows from the central compartment to both peripheral compartments via intercompartmental clearance and completely out of the model via metabolic clearance. Because there are three places for drug to go, the concentration in the central compartment decreases very rapidly. At the transition between the solid line and the dashed line, there is a change in the role of the most rapidly equilibrating compartment. At this transition, the concentration in the central compartment falls below the concentration in the rapidly equilibrating compartment, and the direction of flow between them is reversed. After this transition (dashed line), drug in plasma has only two places to go: into the slowly equilibrating compartment or out the drain pipe. These processes are partly offset by the return of drug to plasma from the rapidly equilibrating compartment. The net effect is that once the rapidly equilibrating compartment has come to equilibration, the concentration in the central compartment falls far more slowly than before.

Once the concentration in the central compartment falls below both the rapidly and slowly equilibrating compartments (dotted line), the only method of decreasing the plasma concentration is metabolic clearance, the drain pipe. Return of drug from both peripheral compartments to the central compartment greatly slows the rate of decrease in plasma drug concentration.

Curves that continuously decrease over time, with a continuously increasing slope (i.e., curves that look like Figs. 19-18 and 19-19), can be described by a sum of negative exponentials. In pharmacokinetics, one way of denoting this sum of exponentials is to say that the plasma concentration over time is

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} \qquad (41)$$

where t is the time since the bolus, C(t) is the drug concentration after a bolus dose, and A, α, B, β, C, and γ are parameters of a pharmacokinetic model. A, B, and C are called coefficients, whereas α, β, and γ are called exponents. After a bolus injection, all six of the parameters in Equation 41 will be greater than 0.

The main reason that polyexponential equations are used is that they describe the plasma concentrations observed after

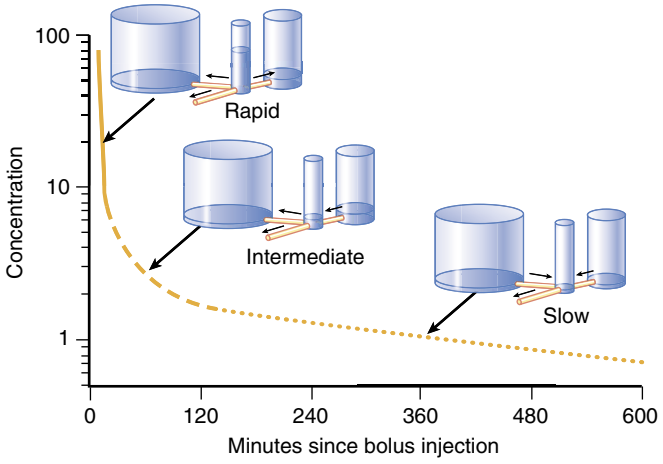

Figure 19-19 Hydraulic model of fentanyl pharmacokinetics. Drug is administered into the central tank, from which it can distribute into two peripheral tanks, or it may be eliminated. The volume of the tanks is proportional to the volumes of distribution. The cross-sectional area of the pipes is proportional to clearance. *(Modified from Youngs EJ, Shafer SL: Basic pharmacokinetic and pharmacodynamic principles.* In *White PF [ed]: Textbook of Intravenous Anesthesia. Baltimore, Williams & Wilkins, 1997, p 10.)*

bolus injection, except for the mis-specification in the first few minutes mentioned previously. Compartmental pharmacokinetics is strictly empirical: the models describe the data, not the processes by which the observations came to be. Fortunately, polyexponential equations permit us to use the one-compartment ideas just developed, with some generalization of the concepts. This involves translating Equation 41 into a model of volumes and clearances that has an appealing, though inaccurate physiologic flavor.

Equation 41 says that concentrations over time are the algebraic sum of three separate functions, $Ae^{-\alpha t}$, $Be^{-\beta t}$, and $Ce^{-\gamma t}$. Typically $\alpha > \beta > \gamma$ by about 1 order of magnitude. We can describe each of these functions separately as graphs, as well as their sum, as shown in Figure 19-19. At time 0 (t = 0), Equation 41 reduces to

$$C_0 = A + B + C \tag{42}$$

The sum of the coefficients A, B, and C, equals the concentration immediately after a bolus. It follows that A + B + C = bolus amount V_1.

Special significance is often ascribed to the smallest exponent. This exponent determines the slope of the final log-linear portion of the curve. When the medical literature refers to the half-life of a drug, unless otherwise stated, the half-life will be the terminal half-life (i.e., 0.693/smallest exponent). However, the terminal half-life for drugs with more than one exponential term is nearly uninterpretable. The terminal half-life sets an upper limit on the time required for the concentrations to decrease by 50% after drug administration. Usually, the time needed for a 50% decrease will be much faster than that upper limit. This is discussed further in Chapter 28.

Constructing pharmacokinetic models represents a trade-off between accurately describing the data, having confidence in the results, and mathematical tractability. Adding exponents to the model generally provides a better description of the observed concentrations. However, adding more exponent terms usually decreases our confidence in how well we know each coefficient and exponential and greatly increases the mathematical burden of the models. This is why most pharmacokinetic models are limited to two or three exponents.

Part of the continuing popularity of polyexponential models of pharmacokinetics is that they can be mathematically transformed from the admittedly unintuitive exponential form in Equation 41 to a more easily intuited compartmental form, as shown in Figure 19-15. Micro rate constants, expressed as k_{ij}, define the rate of drug transfer from compartment i to compartment j. Compartment 0 is the compartment outside the model, so k_{10} is the micro rate constant for processes acting through metabolism or elimination that irreversibly remove drug from the central compartment (analogous to k for a one-compartment model). The intercompartmental micro rate constants (k_{12}, k_{21}, etc.) describe movement of drug between the central and peripheral compartments. Each peripheral compartment has at least two micro rate constants, one for drug entry and one for drug exit. The micro rate constants for the two- and three-compartment models can be seen in Figure 19-15. The differential equations describing the rate of change for the amount of drugs in compartments 1, 2, and 3 follow directly from the micro rate constants. For the two-compartment model, the differential equations for each compartment are

$$\begin{aligned} \frac{dx_1}{dt} &= I + x_2 k_{21} - x_1 k_{10} - x_1 k_{12} \\ \frac{dx_2}{dt} &= x_1 k_{12} - x_2 k_{21} \end{aligned} \tag{43}$$

where I is the rate of drug input. For the three-compartmental model, the differential equations for each compartment are

$$\begin{aligned} \frac{dx_1}{dt} &= I + x_2 k_{21} + x_3 k_{31} - x_1 k_{10} - x_1 k_{12} - x_1 k_{13} \\ \frac{dx_2}{dt} &= x_1 k_{12} - x_2 k_{21} \\ \frac{dx_3}{dt} &= x_1 k_{13} - x_3 k_{31} \end{aligned} \tag{44}$$

An easy way to model pharmacokinetics is to convert these differential equations to difference equations so that dx becomes Δx and dt becomes Δt. With a Δt of 1 second, the error from linearizing the differential equations is less than 1%. In this way, desktop computers can easily simulate pharmacokinetics by using a spreadsheet.

For the one-compartment model, k was both the rate constant and the exponent. For multicompartment models, the relationships are more complex. The interconversion between micro rate constants and exponents becomes exceedingly complex as more exponents are added because every exponent is a function of every micro rate constant and vice versa. Individuals interested in such interconversions can find them in the Excel spreadsheet convert.xls, which can be downloaded from http://www.opentci.org/doku.php?id=code:code.

The Time Course of Drug Effect

The plasma is not the site of drug effect for anesthetic drugs. There is a time lag between plasma drug concentration and effect-site drug concentration. For example, one significant difference between fentanyl and alfentanil is the more rapid onset of alfentanil's drug effect. The orange bar in the top graph of Figure 19-20 shows the duration of a fentanyl infusion.[9] Rapid arterial samples document the rise in fentanyl concentration. The time course of the electroencephalographic effect (spectral edge) lags 2 to 3 minutes behind the rapid rise in arterial concentration. This lag is called hysteresis. The plasma concentration peaks at the moment that the infusion is turned off. After the peak plasma concentration (and the "Mickey Mouse" silhouette that appears at the peak plasma concentration), the fentanyl concentration decreases rapidly. However, the offset of fentanyl drug effect again lags well behind the decrease in concentration. The lower graph in Figure 19-20 shows the same study design in a patient receiving alfentanil. Because of alfentanil's rapid blood-brain equilibration, there is less hysteresis with alfentanil than with fentanyl.

Typically, the relationship between plasma and the site of drug effect is modeled with an "effect-site" model, as shown in Figure 19-21. The site of drug effect is connected to plasma by a first-order process. The equation that relates effect-site concentration to plasma concentration is

$$\frac{dCe}{dt} = k_{e0} \times Cp - k_{e0} \times Ce \tag{45}$$

where Ce is the effect-site concentration, Cp is the plasma drug concentration, and k_{e0} is the rate constant for elimination of drug

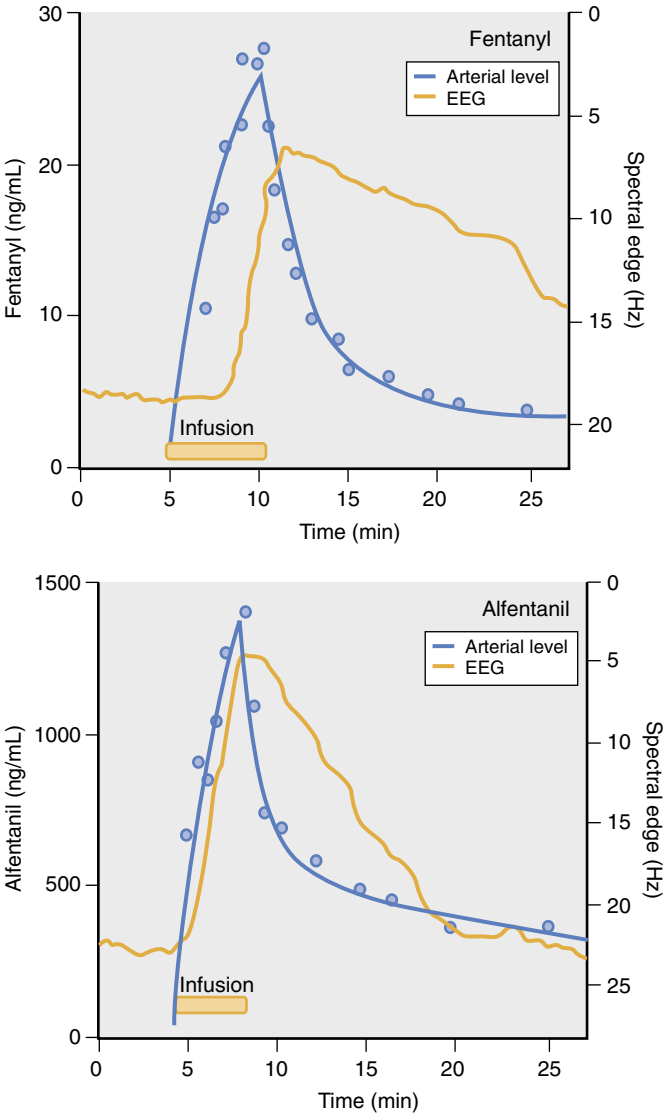

Figure 19-20 Fentanyl and alfentanil arterial concentrations (*circles*) and electroencephalographic (EEG) response (*irregular line*) to an intravenous infusion. With each drug there is a time lag between the rise and fall in arterial concentration and the EEG response, but the time lag is much greater for fentanyl than for alfentanil. *(Modified from Scott JC, Ponganis KV, Stanski DR: EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 62:234-241, 1985.)*

from the effect site. It is most easily understood in terms of its reciprocal, $0.693/k_{e0}$, the half-time for equilibration between plasma and the site of drug effect.

The constant k_{e0} has a large influence on the rate of rise in drug effect, the rate of offset of drug effect, and the dose that is required to produce the desired drug effect. The mathematical basis of these relationships is explored in Chapter 28.

Summary

Pharmacokinetics involves fundamental physiologic processes, including metabolism, protein binding, tissue distribution, and drug transport to the site of drug effect. Pharmacokinetic models are mathematical relationships between dose and concentration, either in plasma or at the site of drug effect. Such models can be used to determine how best to give drugs to achieve a therapeutic objective, but only when the relationship between drug concentration and drug effect is understood. This is the subject of the next section.

Pharmacodynamics

Pharmacodynamics describes the relationship between plasma drug concentration and pharmacologic effect. Simply stated, pharmacokinetics describes what the body does to the drug, whereas pharmacodynamics describes what the drug does to the body. Although the study of clinically important drug effects is multifaceted, we will divide pharmacodynamics into three general areas: transduction of biologic signals (receptor theory and structure), developments in molecular pharmacology, and clinical evaluation of drug effects.

Transduction of Biologic Signals

Receptor Theory

Definition

In the broadest sense, a receptor is a component of a cell that interacts selectively with an extracellular compound to initiate a cascade of biochemical events that culminate in the pharmacologic effects of the compound. Binding of a drug to a receptor

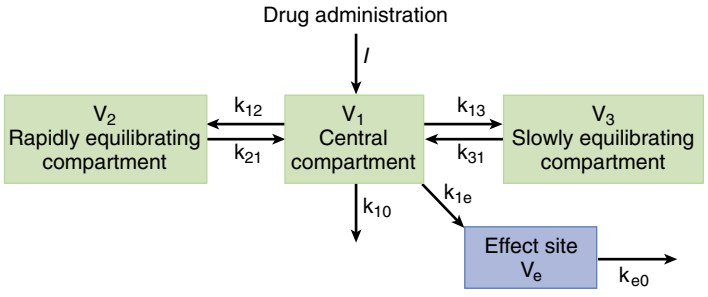

Figure 19-21 A three-compartment model with an added effect site to account for the delay in equilibration between the rise and fall in arterial drug concentrations and the onset and offset of drug effect. The effect site is assumed to have a negligible volume.

determines (1) the quantitative relationship between a given dose of a drug and the resulting effect, (2) the selectivity of a given drug's activity and effect, and (3) the pharmacologic activity of receptor agonists, antagonists, and inverse agonists. Receptors therefore serve to mediate and amplify the effect of a drug on the biologic system.

Historical Perspective

Although the overall concept of receptors is generally attributed to Paul Erhlich (1854-1915), earlier work performed by Claude Bernard (1813-1878) paved the way for receptor theory. This earlier work is of particular interest to anesthesiologists because it centered on elucidation of the mechanism of action of curare in poisoned arrows. In his experiments, Claude Bernard ligated vessels leading to one hind limb of a frog while leaving nerve input intact. He then administered intravenous curare. Pinching the paralyzed hind limb produced reflex movements in the opposite unparalyzed vessel-ligated hind limb. These experiments and others demonstrated for the first time the separation between the sensory and motor nervous systems and also revealed that circulating "substances" produce selective effects on organ systems, a concept important in the development of receptor theory.

The concept of selectivity of effect eventually led Paul Erhlich to his conclusion that "agents cannot act unless they are bound," a cornerstone of receptor theory. Erhlich's contemporary, J. N. Langley (1852-1926), coined the phrase "receptive substance." Langley showed that nicotine and curare have mutually antagonistic effects on the same receptive substance and that the substance was neither nerve nor muscle. Today, we recognize this "receptive substance" as the nicotinic acetylcholine receptor in the neuromuscular junction. Several decades of research has refined receptor theory to the point that receptors are now recognized as discrete excitable proteins.

Classic Receptor Theory

Binding of a ligand, L, to its receptor, R, follows the laws of mass action and can be summarized by the relationship

$$[L]+[R]\underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}}[LR] \qquad (46)$$

where k_{on} is the rate constant for binding of the ligand to the receptor, k_{off} is the rate constant for the dissociation of the ligand from the receptor, [L] is the concentration of the ligand, [R] is the concentration of the unbound receptor, and [LR] is the concentration of the bound receptor. Note that the units for k_{on} are time^{-1} · units of [L]$^{-1}$. The units of L are typically nanomoles per liter. The units for k_{off} are time^{-1}. The rate of formation of [LR] is $\frac{d[LR]}{dt} = [L][R]k_{on} - [LR]k_{off}$. At steady state, which is nearly instantaneous, the net rate of formation is 0, and thus [L] [R] k_{on} = [LR] k_{off}. The term K_d, or dissociation constant, defines the characteristics of ligand/receptor interactions at equilibrium. Mathematically,

$$K_d = \frac{[L][R]}{[LR]} = \frac{k_{off}}{k_{on}} \qquad (47)$$

The units of K_d are the units of [L], that is, units of concentration. When enough drug is administered to occupy exactly 50% of the receptors (i.e., [R] = [LR]), the measured K_d is equal to the drug concentration. A low K_d indicates that less drug is required to occupy 50% of the receptors, implying that each molecule of drug is tightly associated with the receptor. A high K_d indicates that more drug is required to occupy 50% of receptors, implying weak binding to the receptor. The reciprocal of K_d is K_a, the association constant, which is exactly analogous to the K_a defined for protein binding. K_a is a measure of the affinity of the drug for the receptor. Hence, a drug with a low K_d has a high K_a and therefore high affinity for the receptor.

In practice, it is difficult to measure precise drug-receptor occupancy. It is often assumed that the drug-receptor complex represents an intermediate step in the production of a specific effect. Therefore, many investigators apply pharmacodynamic theory to compare a given dose of a drug with a resulting effect. An effect can be any biochemical or physiologic variable that is measurable. A measured effect can be an alteration in a biochemical compound or an enzyme level, a physiologic variable such as heart rate or blood pressure, or a response to any graded input into the biologic system. For example, in evaluating the pharmacodynamics of muscle relaxants, the measured effect is not a direct measurement of drug-receptor complexes, but rather a response to a neuromuscular stimulus as delivered by a nerve stimulator.

The amount of drug at the receptor is a function of dose, time, and pharmacokinetic properties of the drug. If the receptor is located within the central compartment, there may be nearly instantaneous equilibration after an intravenous injection, and hence the peak effect may occur immediately. If drug must cross from the central compartment into a tissue to reach the site of drug effect, there will be a delay in onset. The onset of drug effect can also be delayed by the time required for the body to respond to the drug. This delay may occur anywhere on the path between drug-receptor binding and clinical manifestation of drug effect. Examples of post-transduction time delays are drug-receptor complex–induced changes in secondary messengers, increased enzyme synthesis, and the time required for physiologic change (e.g., reduced fluid content).

Receptor Agonists and Antagonists. Drugs that are agonists mimic endogenous hormones or neurotransmitters when bound to a receptor. This effect may be excitatory or inhibitory. As described earlier, the term *affinity* as related to a given agonist is a measure of the attraction between the given drug and receptor. A drug with low affinity for a given receptor tends not to bind to the receptor and hence produces little or no effect. An agonist that binds avidly (or with high affinity) to a given receptor produces the receptor-determined effect at a lower given dose.

Full agonists completely activate a receptor, whereas partial agonists only partially activate a receptor, even at very high concentrations (Fig. 19-22). The difference between full and partial agonists results from differing intrinsic efficacy for each drug. Efficacy should not be confused with affinity. Two drugs can have identical affinity for a receptor (and therefore bind to the same extent at a given drug concentration), yet they may produce different levels of activation of the receptor. Both are agonists, but the drug that produces maximal receptor activation is called a full agonist and has high efficacy, whereas the drug that produces less than maximal receptor activation is called a partial agonist with less intrinsic efficacy. The mechanisms underlying whether a drug is a full versus a partial agonist are unclear, but they may be related to the ability of the drug to stabilize the high-activity state

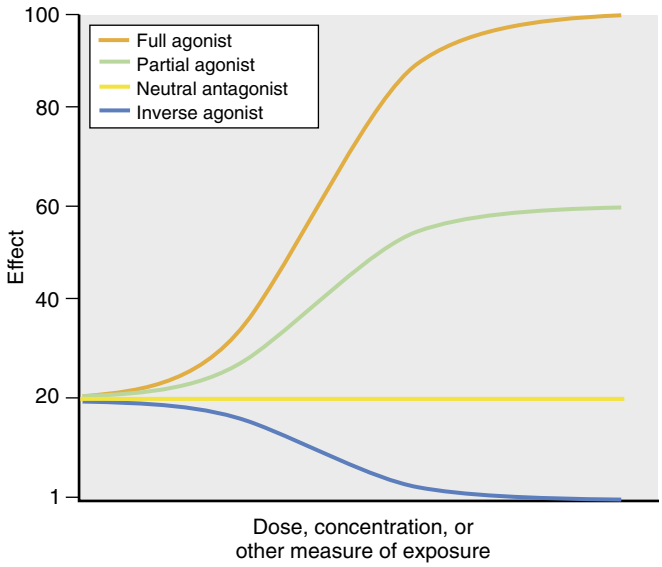

Figure 19-22 Effect of various types of ligands on receptor responses. A full agonist produces complete (100%) activation of a receptor at high concentrations, whereas partial agonist binding results in less than 100% activation, even at very high concentrations. A neutral antagonist has no activity of its own. However, note that in the absence of drug there is still a 20% effect because some receptors are in the activated state in the absence of drug. Inverse agonists can be thought of as "super antagonists" inasmuch as binding of these ligands produces a response below the baseline response measured in the absence of drug because nearly all of the receptors are forced into the unactivated state by the inverse agonist. If the physiologic effect of the baseline levels of activated receptor is small, antagonists and inverse agonists may not be clinically distinguishable.

of the receptor (described under the next heading, "Receptor States").

Drugs that are competitive antagonists inhibit or prevent receptor-mediated agonist effects by competing for the binding site at the receptor. A competitive antagonist can generally be displaced from the receptor complex by the administration of a large enough concentration of receptor agonist, thus permitting the agonist to produce the expected effect despite the presence of antagonist. A noncompetitive antagonist usually binds irreversibly to the receptor complex and produces loss of the expected effect that cannot be compensated by administration of high concentrations of receptor agonist. For example, vecuronium is a competitive antagonist of acetylcholine. Acetylcholine mediates muscle contraction via the postsynaptic nicotinic acetylcholine receptor at the neuromuscular junction. When vecuronium occupies the postsynaptic acetylcholine receptor, acetylcholine agonism is blocked, and neuromuscular transmission is inhibited. The result is flaccid paralysis. Neuromuscular transmission may be reinstated by administering an acetylcholine esterase inhibitor. Acetylcholine esterase inhibitors prevent the breakdown of acetylcholine, thereby effectively raising the concentration of the agonist, acetylcholine, at the receptor, which then displaces vecuronium from the receptor complex. When enough vecuronium is displaced, muscle contraction is reinstated. Most antagonist drugs used in clinical medicine are competitive antagonists.

Inverse agonists can be thought of as "superantagonists" because they decrease receptor responses to less than the "baseline" (see Fig. 19-22) response seen in the absence of drug. Figure 19-23 shows the electroencephalographic response to four different benzodiazepines.[10] Midazolam is a full agonist, whereas RO

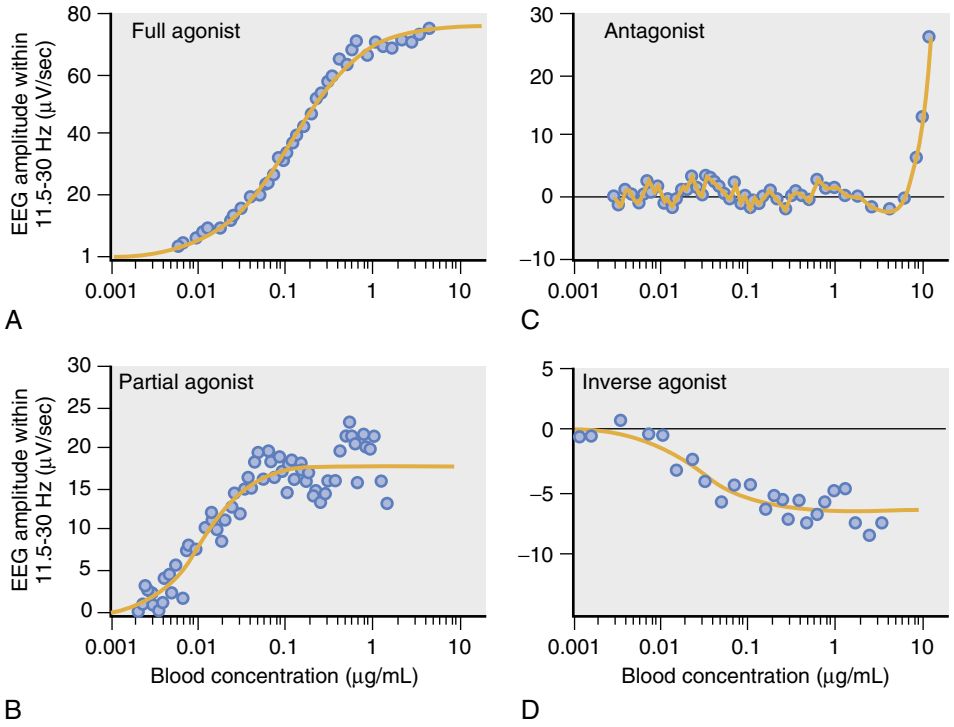

Figure 19-23 The concentration-electroencephalographic (EEG) response relationship for four benzodiazepines: midazolam (full agonist) (**A**), bretazenil (partial agonist) (**B**), flumazenil (antagonist) (**C**), and RO 19-4063 (an inverse agonist) (**D**). The maximum effect seen on the electroencephalogram correlates with clinical action (full agonist > partial agonist > antagonist > inverse agonist). *(From Shafer S: Principles of pharmacokinetics and pharmacodynamics.* In *Longnecker DE, Tinker JH, Morgan GE [eds]: Principles and Practice of Anesthesiology, 2nd ed. St Louis, Mosby–Year Book, 1997; based on Mandema JW, Kuck MT, Danhof M: Differences in intrinsic efficacy of benzodiazepines are reflected in their concentration-EEG effect relationship. Br J Pharmacol 105:164-170, 1992.)*

19-4063 is an inverse agonist. Note that in Figure 19-22, the "baseline" effect in the absence of drug is 20% effect because some receptors are in the activated state. Only in the presence of the inverse agonist are nearly all of the receptors forced into the unactivated state, thereby revealing the physiologic response in the complete absence of receptor activation.

Receptor States. Classic receptor theory describes the interaction between ligand and receptor according to the laws of mass action. At a molecular level, this interaction has been interpreted over the years to suggest that binding of agonist to receptor initiates a change in receptor conformation that converts the receptor from an inactive (R) to an activated (R*) state (Fig. 19-24). In this model the change in receptor conformation facilitates coupling of activated receptor to intermediary proteins (e.g., guanine nucleotide [G] proteins) or second messengers (effectors, E), which then initiate a rapid cascade of cellular responses.

Transgenic animal experiments have shed light on ligand and receptor interactions. In an elegant set of experiments, β_2-adrenergic receptors (β_2ARs) were massively overexpressed in mouse myocardium.[11] Second messenger responses were increased in the absence of ligand when compared with normal mouse myocardium. In fact, adenylyl cyclase activity (the second messenger most commonly studied for β_2ARs) was the same at baseline in transgenic animals (in the absence of drug) as in normal mice stimulated with isoproterenol (a β_2AR agonist). Furthermore, stimulation of transgenic animals with isoproterenol failed to further increase adenylyl cyclase activity higher than this elevated baseline. This finding suggests that a subpopulation of receptors was already fully activated in the transgenic animals.

These findings imply that a small percentage of receptors spontaneously exist in the activated (R*) state. Because a fraction of the receptors are normally activated, the activity of these R* receptors is part of the baseline effect measured in the absence of drug. However, after massive overexpression of β_2ARs in a transgenic animal, this fraction of total receptors becomes a very large number of activated receptors. This mimics the effect of a maximal dose of agonist, which would produce similar numbers of receptors in the R* state.

These findings have broad implications for understanding receptor states and drug-receptor interactions. Instead of ligand binding causing a change from R to R* (as suggested by Fig. 19-24), these data suggest spontaneous conversion from the R to the R* state (Fig. 19-25). The effect of the ligand is to stabilize the R* state, which increases the fraction of activated receptors. In most tissues, the concentration of R* represents a small fraction of the total overall receptor population (hence the large arrow pointing toward R in Fig. 19-25). This finding explains the action of inverse agonists as drugs that stabilize R, thereby reducing the number of receptors in the activated state and decreasing the physiologic response to less than the "clinical baseline." It also suggests that there is a "true baseline," which is the clinical state in the complete absence of activated receptors. The biggest differences between "clinical baseline" and "true baseline" would probably occur in tissues with the highest concentrations of spontaneous R*. Inverse agonists would therefore be most efficacious in such tissues.

Figure 19-23D illustrates a tissue, the central nervous system (CNS), with enough activated type A γ-aminobutyric acid ($GABA_A$) ligand-gated ion channels (R*) to see electroencephalographic changes with an inverse agonist. Finally, it is important to note that the discussion thus far assumes only two receptor states, R (completely inactive) and R* (fully activated). There may be many transition states between R and R* (hence the use of curved lines in addition to straight lines in Fig. 19-25). However, in the interest of simplicity, this chapter discusses only R and R*.

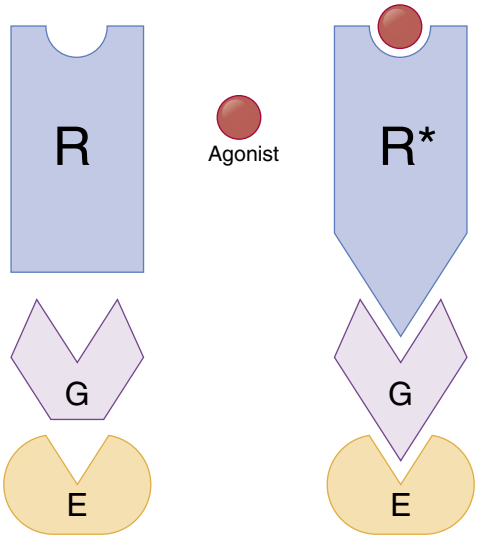

Figure 19-24 Schematic of classic receptor activation. For years, binding of ligand was thought to cause receptors to change from an inactive state (R) to an activated state (R*). The activated receptor then interacts with intermediary guanine nucleotide (G) proteins or directly with second messenger cascades (effectors, E), or with both. More recent information suggests a more complicated equilibrium between R and R*, as shown in Figures 19-25 to 19-27.

As shown in Figure 19-26, agonists stabilize (or energetically favor) the R* state, thereby removing the receptor from instantaneous equilibration with R and driving (by mass action) more receptors toward R* (Fig. 19-27). Hence the probability of being in the R* state increases in the presence of agonist. Inverse agonists drive the equation to the left, thereby stabilizing the R configuration. Neutral antagonists bind equally to R and R*, thereby preventing agonist binding without altering the equilib-

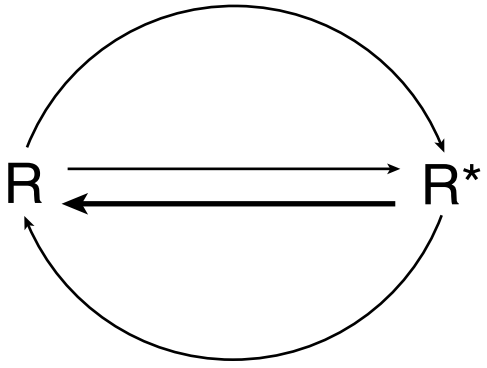

Figure 19-25 Spontaneous conversion of receptors from an inactive (R) to an active (R*) state. In most tissues, R* represents a small fraction of the total receptor population.

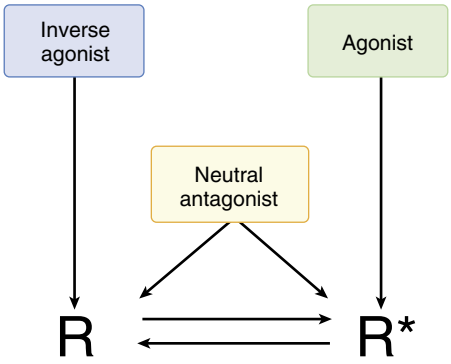

Figure 19-26 Ligand stabilization of receptor states. Agonists stabilize active receptors (R*), inverse agonists stabilize inactive receptors (R), and neutral antagonists bind equally to R and R* without affecting the equilibrium between the two receptor states.

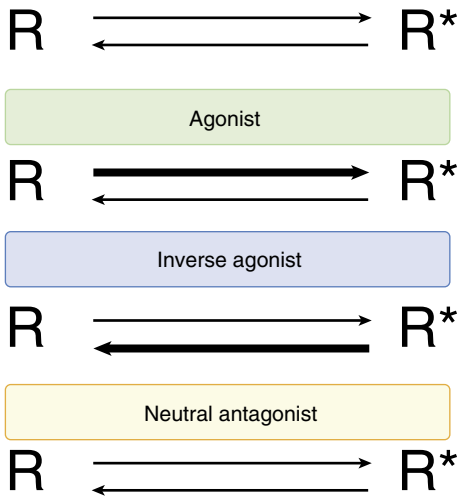

Figure 19-27 Equilibrium between inactive receptors (R) and active receptors (R*) is tissue specific and depends on the type of ligand administered. By stabilizing R*, agonists drive the equilibrium to the right. In contrast, inverse agonists stabilize R, which drives the equilibrium to the left. Because neutral antagonists bind equally to R and R*, they do not affect tissue-specific equilibrium between R and R*.

rium between R and R*. Hence, neutral antagonists do not change the observed baseline response (see Fig. 19-22).

Many classic "antagonists" have been found to be inverse agonists rather than neutral antagonists. For example, the common used β_2AR antagonists, metoprolol and bisoprolol, show significant inverse agonist activity. Carvedilol has weaker inverse agonist properties at β_2ARs and displays neutral antagonist activity at β_1ARs. Alprenolol has even weaker (20%) inverse agonist activity at β_2ARs. Xamoterol displays partial agonist activity at β_1ARs.[12,13] Because inverse agonists may have theoretical advantages in treating certain diseases (e.g., seizures, congestive heart failure), clinicians should critically evaluate recent pharmacologic data before using an antagonist to distinguish whether the drug is a neutral antagonist or an inverse agonist.

Receptor Structure

Receptors are ubiquitous in the cell, being present in cell membranes, cytoplasm, intracellular organelle membranes, and the nucleus. The overall physical structure of a receptor depends on the type of receptor and its location. Cytoplasmic and nuclear receptors bind ligands that readily traverse cell membranes. These ligands must therefore contain significant hydrophobic (lipophilic) components. Examples of cytoplasmic and nuclear receptors include steroid and thyroid hormone receptors. In contrast, the receptors of most interest to anesthesiologists are located on the cell membrane and include membrane receptors, ligand-gated ion channels, and voltage-gated ion channels (Fig. 19-28). Receptors on the cell membrane bind water-soluble ligands that are typically unable to cross lipid bilayers and mediate a cellular response via intermediary proteins (e.g., G protein–coupled receptors) or by causing changes in ion flux (e.g., ligand-gated ion channels). Each of these types of membrane receptor has a role in mediating the action of various drugs important in anesthesiology. It is beyond the scope of this chapter to list all currently identified receptor proteins. However, prototypical examples are used to illustrate important pharmacodynamic principles.

Structure-activity relationships between drug and the three-dimensional configuration of the receptor binding site are critically important in determining binding properties. Though perhaps obvious, the chemical structure of a drug must match the three-dimensional configuration of the binding area of a receptor. Hence, subtle changes in drug structure may dramatically alter the ability of a drug to bind to a specific receptor population. In addition, two drugs with seemingly unrelated two-dimensional chemical structures may bind to the same receptor if their three-dimensional structures and charged areas are similar. The three-dimensional components of a ligand that interact with

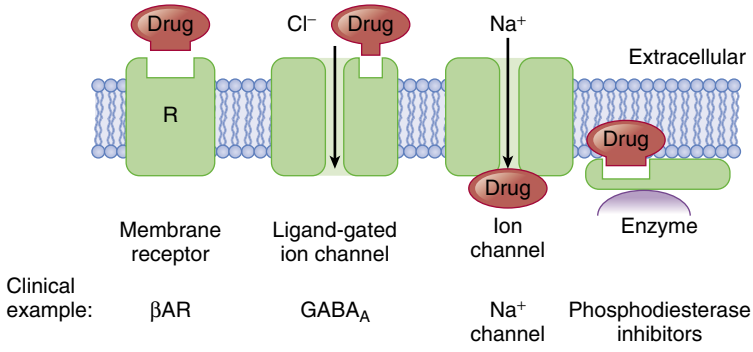

Figure 19-28 Schematic of four types of membrane-associated drug targets in anesthesia: membrane (G protein–coupled) receptor, ligand-gated ion channel, voltage-sensitive ion channel, and an enzyme. Potential sites of drug action are shown. βAR, β-adrenergic receptor; GABA$_A$, γ-aminobutyric acid.

ligand recognition portions of a receptor are called the "pharmacophore."

Guanine Nucleotide (G) Protein–Coupled Receptors

One of the most common methods by which membrane receptors translate agonist occupancy into intracellular "action" is via intermediary G proteins. G protein–coupled receptors are the most abundant type of receptor known. The overall structure of G protein–coupled receptors is shown schematically in Figure 19-29. Two-dimensional representation reveals an extracellular amino terminus containing glycosylation sites, an intracellular carboxyl terminus, fatty acid attachment (usually via palmitoylation or myristoylation of a carboxyl-terminal cysteine residue), three extracellular loops, and four intracellular loops. Major sites of G protein interaction with the receptor occur in the third and fourth (and to a lesser extent the second) intracellular loops, whereas major sites of phosphorylation (often correlated with desensitization [or dampening of receptor responses]) generally occur in the third intracellular loop and carboxyl terminus.

Even though a two-dimensional schematic is shown in Figure 19-29, it is important to remember that G protein–coupled receptors are three-dimensional structures with transmembrane segments coalescing around a central binding pocket (Fig. 19-30).[14] Although transmembrane amino acids must be hydrophobic overall (to be energetically favored in the lipid membrane), side chains on individual amino acids may be charged to act as counter ions for anchoring charged (water-soluble) hormone or drug to the receptor.

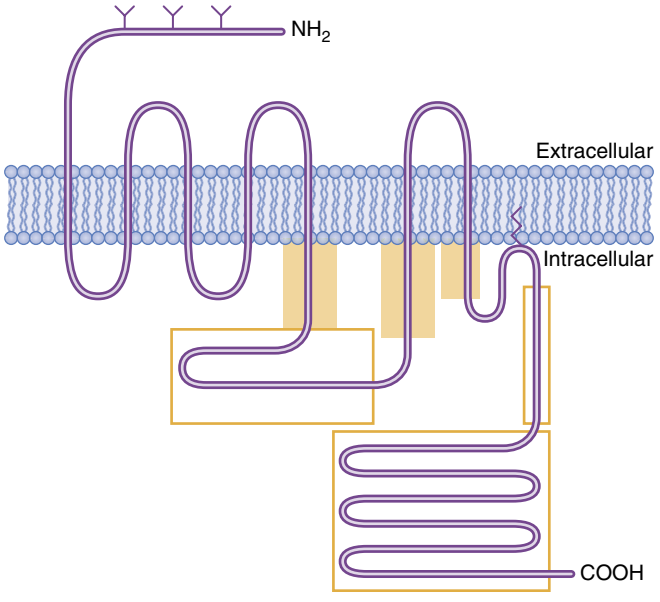

Figure 19-29 Schematic of G protein–coupled receptors. A two-dimensional version of receptor structure is shown with seven transmembrane domains, an extracellular amino (NH_2) terminus (with associated glycosylation sites [Y]), an intracellular carboxyl (COOH) terminus, palmitoylated cysteine residue (denoted by the *crooked line* extending into the membrane), three extracellular loops, and four intracellular loops. Major sites of G protein interactions with the receptor are *speckled*; potential sites of phosphorylation in the third intracellular loop and carboxyl terminus are enclosed in *boxes*.

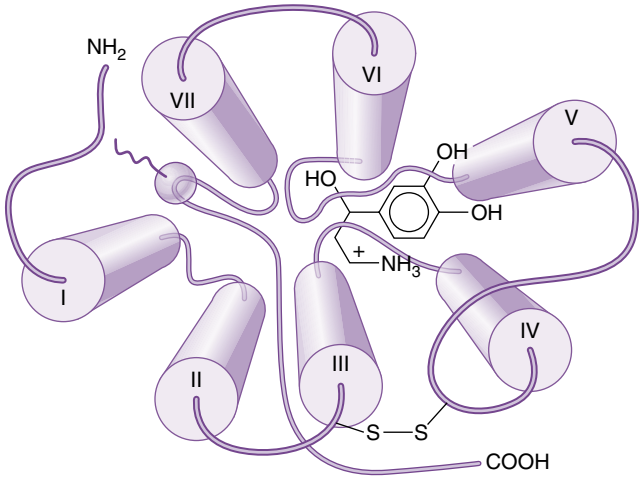

Figure 19-30 Schematic of the three-dimensional structure of the β_2-adrenergic receptor (a prototypical G protein–coupled receptor), looking from the outside of the cell inward. Transmembrane domains (denoted by *cylinders* and numbered with *Roman numerals*) coalesce to form a binding pocket. The correct orientation of the agonist norepinephrine is shown. Note that agonist affinity is determined by specific amino acids located in transmembranes III, IV, and VII. These critical sites in transmembrane domains have been determined experimentally via chimeric receptor and mutagenesis approaches combined with sophisticated computer modeling techniques. Ultimate confirmation of these structures will require crystallographic data. This is currently being attempted by several laboratories. *(From Stapelfeldt WH: The autonomic nervous system.* In *Schwinn DA [ed]: Scientific Principles of Anesthesia, vol 2. Philadelphia, Current Medicine, 1998.)*

Ion Channels

Some anesthetic drugs target voltage-gated ion channels. These receptors mediate neural signaling by modulating ion permeability in electrically excitable membranes in response to changes in membrane potential. Voltage-gated ion channels such as the sodium channel have charged regions that span the cell membrane. The formation of ion pairs between many positive and negative charges helps stabilize the ion-conducting pore. Voltage-dependent gating of the sodium channel is made possible by the presence of a voltage sensor, a collection of charges that move under the influence of the cell-membrane electrical field, hence the name voltage-gated ion channel. During depolarization, positively charged sodium ions move intracellularly. The change in membrane potential causes a conformational change in the central pore consisting of rearrangement of ion pairs that favors sodium permeability. Local anesthetics work by blocking voltage-gated sodium channels, as discussed in detail in Chapter 30.

The ligand-gated ion channel is a combination of a classic receptor protein and an ion channel. Ligand-gated ion channels permit certain drugs to directly alter membrane potentials. Many anesthetic drugs act on ligand-gated ion channels, such as the nicotinic acetylcholine receptor and the $GABA_A$ receptor. The structure of the $GABA_A$ receptor is shown in Figure 19-31.[15,16] Ligand-gated ion channels have both hydrophobic and charged transmembrane regions. The hydrophobic regions stabilize the structure in the membrane, whereas the centrally charged region serves as the pore for ion flux. Binding of drugs to ligand-gated ion channels usually enhances or dampens an already existing neurotransmitter-induced ion flux. For example, the neurotransmitter GABA binds to its receptor within the $GABA_A$ ligand-

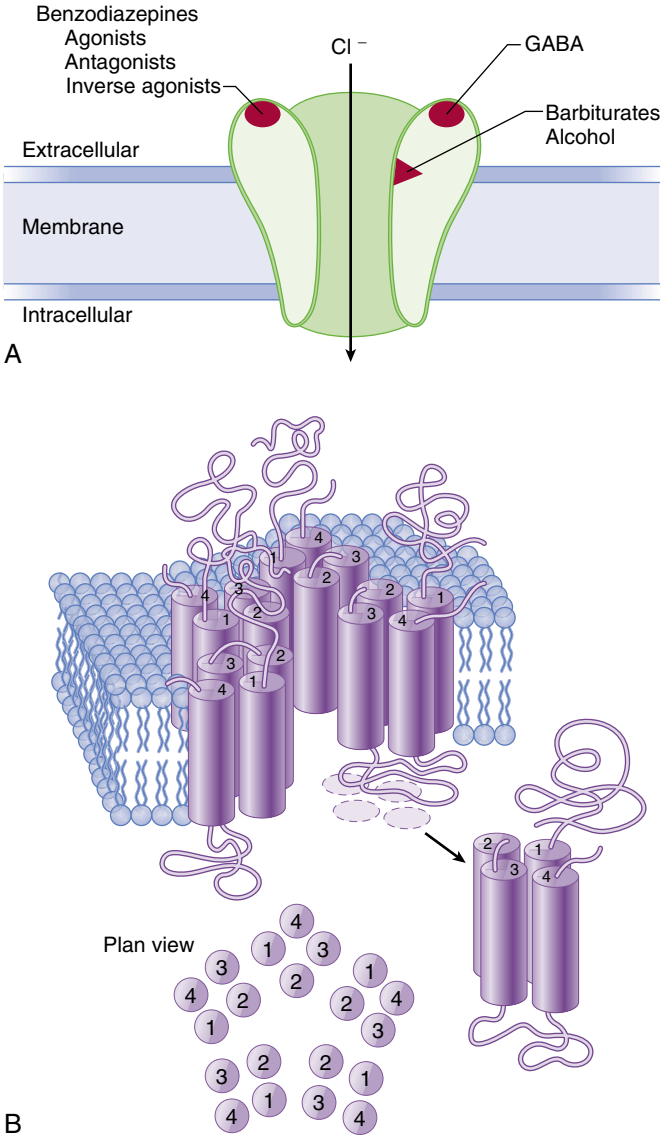

Figure 19-31 Cross section of a schematized γ-aminobutyric acid (GABA)-benzodiazepine receptor complex (a prototypical ligand-gated ion channel complex). Binding of benzodiazepine agonists to the $GABA_A$ ligand-gated ion channel facilitates the action of endogenous GABA. This results in increased inhibitory chloride ion flux in the central nervous system. **A,** Schematic of the $GABA_A$ ligand-gated ion channel complex showing receptor sites for benzodiazepines and GABA, as well as distinct receptor sites for barbiturates and alcohol. **B,** Model of the $GABA_A$ receptor–chloride ion channel protein complex composed of a hetero-oligomer of five subunits, including α, β, and γ, as well as δ or ρ polypeptides. Each subunit has four putative membrane-spanning domains (numbered 1 to 4, represented by *cylinders*). (***A,*** *From Berkowitz DE: Cellular signal transduction.* In *Schwinn DA [ed]: Scientific Principles of Anesthesia, vol 2. Philadelphia, Current Medicine, 1998;* ***B,*** *from Firestone L, Quinlan J, Gyulai F: Mechanisms of anesthetic action.* In *Schwinn DA [ed]: Scientific Principles of Anesthesia, vol 2. Philadelphia, Current Medicine, 1998.)*

gated ion channel complex and causes the intracellular flux of chloride ions. This action results in hyperpolarization of the membrane potential, a hallmark of inhibitory neurotransmission. Drugs binding to other sites on the $GABA_A$ receptor facilitate the action of the endogenous ligand GABA (see Fig. 19-31). Most hypnotics (benzodiazepines, barbiturates, propofol, etomidate, and possibly the hypnotic action of inhaled anesthetics) act through potentiation of endogenous GABA at the $GABA_A$ ligand-gated ion channel.

Ion Pumps

Another type of excitable membrane protein is the ion pump. The sodium-potassium–adenosine triphosphatase (ATPase) pump is perhaps the most familiar ion pump to the anesthesiologist because it is inhibited by digitalis. Extracellular fluid is high in sodium and low in potassium, whereas intracellular fluid is high in potassium and low in sodium. Because the nerve at rest is selectively permeable to potassium but not to sodium, potassium moves extracellularly and creates a net positive extracellular charge and a net negative intracellular charge. Action potentials activate sodium channels, thereby allowing sodium to flux intracellularly along a combined chemical and electrical gradient. The sodium-potassium-ATPase pump then rapidly pumps sodium out of the cell in exchange for potassium, thereby returning the cell to its original cation composition and electrical gradient. Drugs that act on ion pumps alter intracellular/extracellular cation ratios, which results in altered membrane resting potential.

Digitalis acts by inhibiting the sodium-potassium-ATPase pump. This is of special importance in the myocardial cell, where sodium-potassium-ATPase exchange is replaced by slower sodium-calcium exchange, thereby increasing intracellular calcium concentrations. Because calcium increases myocardial contractility, improved myocardial pump function results.

Second Messengers

Binding of a ligand to a receptor does not instantly produce its clinical effects. Instead, a series of rapid biochemical events couples receptor binding to ultimate clinical effects. These biochemical events are called second messengers. Because alterations in second messenger coupling can change the effectiveness of a drug, it is important that the anesthesiologist understand the general principles of second messenger action.

Many membrane receptors couple to their second messenger through G proteins, which are intermediate regulatory molecules. Coupling of G proteins to receptor-hormone complexes requires energy in the form of guanosine triphosphate (GTP). The hydrolysis of G protein–associated GTP to guanosine diphosphate (GDP) is regulated by yet another set of proteins called *RGS proteins*. Once the receptor interacts with the G protein, the biochemical reaction in the effector cascade is triggered. There are stimulating (e.g., G_s, G_q) and inhibitory (e.g., G_i, G_o) G proteins. The physiologic effect is determined by the specific G protein and subsequent cellular response. G proteins are heterotrimeric, composed of three subunits—α, β, and γ. Receptor–G protein interactions result in dissociation of the G protein subunits into α and βγ. The α-subunit of most G proteins confers specificity between receptor and effectors. Although βγ-subunits were originally thought to simply anchor G proteins to the cell membrane, it is now clear that dissociated βγ-subunits are capable of directly stimulating second messengers. In addition, βγ-subunits play a role in anchoring regulatory kinases to the cell membrane, which leads to enhanced phosphorylation of membrane receptors.

One of the best-understood second messenger systems is the adenylyl cyclase system. In this system, stimulatory G protein–

receptor-hormone complexes increase activity of the enzyme adenylyl cyclase, which results in increased levels of cyclic adenosine 3′,5′-monophosphate (cAMP) in the cell (Fig. 19-32). Inhibitory G protein–receptor-hormone complexes decrease the activity of adenylyl cyclase, thereby resulting in decreased levels of cellular cAMP. In general, intracellular cAMP activates protein kinases that phosphorylate various proteins, ion channels, and second messenger enzymes.

Another example of a second messenger system is the phosphatidylinositol system. Here, hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) in the cell membrane, catalyzed by activation of phospholipase C by G_q, generates two main second messenger molecules, inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG). IP_3 then mobilizes intracellular calcium from nonmitochondrial intracellular stores by interacting with distinct IP_3 receptors on the surface of these organelles. The resulting increase in intracellular calcium levels produces biologic effects such as smooth muscle contraction. α_1-Adrenergic agonists, endothelin, and muscarinic (M_1, M_3, M_5) agonists all mediate hydrolysis of phosphatidylinositol.

Stimulation of receptors and second messengers ultimately leads to physiologic effects in a given tissue. The physiologic effects produced depend on the presence of specific receptor subtypes, G proteins, and second messengers within that tissue. An example of the wide-ranging cardiovascular effects produced by the predominant sympathetic neurotransmitter norepinephrine can be seen in Figure 19-33.

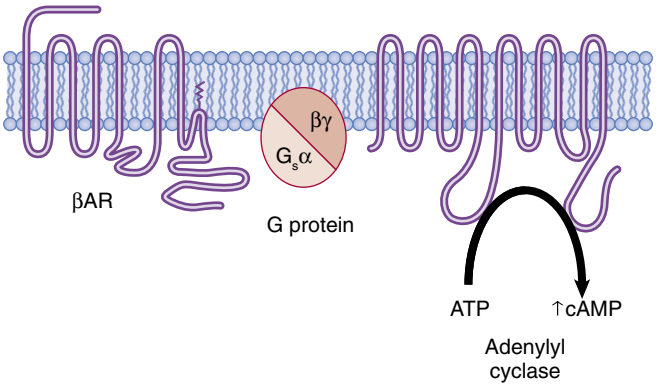

Figure 19-32 Schematic of the β-adrenergic receptor signal transduction cascade. βAR, β-adrenergic receptor; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; $G_s\alpha$, α subunit of the stimulatory G protein (G_s); βγ, stimulatory G protein, βγ-subunit.

Developments in Molecular Pharmacology

The field of molecular pharmacology has advanced our understanding of excitable membrane proteins and their mechanisms of action. Novel molecular techniques provide unique opportunities to learn more about receptors, including their structure and function down to the DNA level. Hitherto unknown receptors and receptor subtypes continue to be discovered, paving the way for future development of receptor-specific pharmacologic agents. We will briefly review the general field of molecular pharmacology because future drugs for perioperative use will probably target receptor and receptor subtypes discovered by such molecular approaches.

Molecular pharmacology takes advantage of the finding that all proteins, including excitable membrane proteins, are encoded in the human genome as nucleic acids. Every amino acid present in a protein is encoded by a specific combination of three nucleotides in DNA. Therefore, if the DNA sequence that encodes a receptor protein can be determined, the putative primary structure (amino acid sequence) of the receptor can be deduced. In addition, encoding DNA sequences (i.e., genes) can be inserted into special cells that will express (manufacture, assemble, and deliver to the appropriate location in the cell) the receptor protein in high quantity. This approach has several advantages.

First, studies on the receptor itself can be performed. By changing (mutating) nucleotide sequences, an abnormal (synthetic or "designer") receptor can be created. This abnormal receptor can then be compared with the original receptor to see whether the changes made affect binding of drug to the receptor or coupling of it to second messengers. In this manner, the function of each portion of the receptor can be studied. This type of

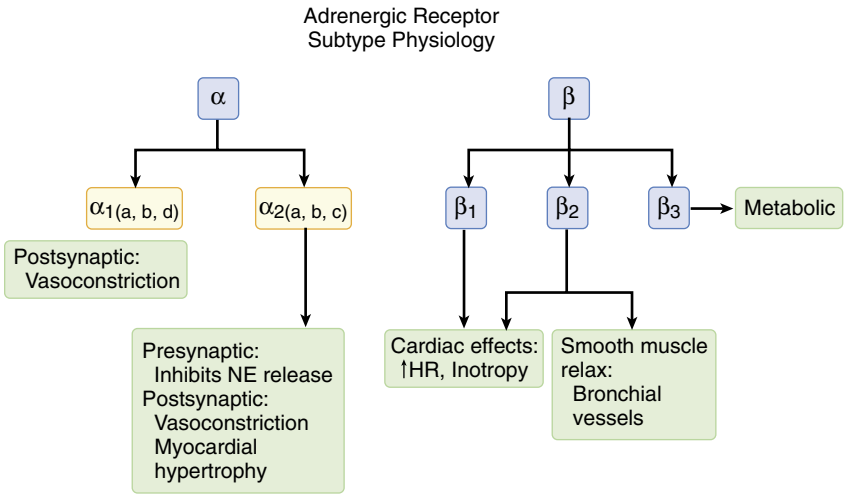

Figure 19-33 Adrenergic receptor subtype physiology. HR, heart rate; NE, norepinephrine.

information is often called structure-activity relationships. G proteins and second messengers can be investigated in a similar manner. More recently, naturally occurring human receptor variants have been investigated and tested for alterations in pharmacologic properties (see the later section "Pharmacogenetics").

The second advantage of using molecular techniques in pharmacology is that new receptors and receptor subtypes can be discovered by searching the genome for DNA sequences similar to those of known receptors. Once these new receptors are discovered, they can easily be characterized because high expression in cells enables them to be screened by various pharmacologic agents. The recent availability of DNA sequences for the full human genome has accelerated the discovery of new receptors through DNA homology searching.

Finally and perhaps the most immediately clinically relevant, new investigational drugs can be rapidly screened for effects on a spectrum of native and variant receptors. In this way, the pharmacologic effects of individual receptors can be studied in a controlled manner, isolated from other receptors and receptor subtypes. Such studies have the potential to lead to the development of new drugs for use in the perioperative period, as well as understanding of the effects of these drugs in patients with receptor variants.

Although there are many advantages to using molecular approaches for understanding the physiologic pathways of individual receptors and for drug discovery, there are also some disadvantages. Cell lines are not integrated organisms, so the function of the receptor protein in a network of physiologic systems cannot be assessed. An approach to understanding the function of previously identified and new gene products that is now classic is to develop mouse (murine) models in which the gene of interest has been eliminated (knock-out mice) or overexpressed (transgenic mice). The physiologic consequence of such altered protein expression is then examined. Although details of these technologies are beyond the scope of this chapter, they have become standardized and are widely available. The transgenic and knock-out mouse models are robust and useful, but they also have important limitations. First, the genetic background of the animals created must be examined carefully. If not carefully controlled, altered phenotypes may result from differences in animal "strain" (or genetic background) rather than from an overexpressed or knocked-out gene product. Second, elimination of specific receptors may be compensated by alterations in other gene products. In this case, the final phenotype represents not only the effect of the absent gene but also the compensatory expression of other genes. Compensation is of particular concern when elimination of a gene is lethal because surviving progeny by definition have compensated in a way that enhances survival and therefore may not be representative of the results of the single gene that was knocked-out. Finally, some receptors and proteins have different tissue localization in humans versus other animal species. Therefore, results from transgenic and knock-out animal studies should be extrapolated cautiously to humans.

Despite these potential limitations, transgenic and knock-out animal models have proved very important in elucidating novel functions of receptors and proteins. Many unexpected physiologic roles for gene products have been discovered, and important physiologic questions have been answered and confirmed with these approaches. Table 19-1 lists conclusions drawn from transgenic and knock-out mice based on alterations in adrenergic receptors and their signal transduction cascade. Novel functions for specific adrenergic receptor subtypes (e.g., the role of α_{2A}ARs in sedation and CNS-mediated hypotension, α_{2B}ARs in mediating vasoconstriction, and α_{2C}ARs in temperature control) have been discovered. Table 19-1 illustrates that alterations in adrenergic receptor signal transduction pathways and modulating kinases have physiologic consequences in the whole animal.

As a result of these advances, we now know the precise location of action of many anesthetic drugs (Table 19-2).[17] This includes identifying the receptor, characterizing the binding site, and studying the downstream consequences of receptor binding responsible for the drug effect. For example, Jurd and colleagues have demonstrated that etomidate and propofol both bind to the same pocket of the β_3-subunit of the $GABA_A$ receptor and have created a genetically altered mouse that is relatively resistant to the hypnotic effects of both drugs.[18] Although most hypnotics and sedatives act by potentiating the action of GABA (the most important inhibitory neurotransmitter in the CNS), the search for the site of action continues for inhaled anesthetics.

Clinical Evaluation of Drug Effects

General Principles

Once pharmacologic agents have exerted their actions on a molecular level, stimulated their targets, and produced a physiologic effect, it is important to evaluate the effect on the whole organism. This section focuses on methods of evaluating clinical drug effects such as dose-response curves, efficacy, potency, the median effective dose (ED_{50}), the median lethal dose (LD_{50}), and the therapeutic index.

Concentration-Versus-Response Relationships

The standard comparison of a drug with its clinical effect is the concentration-versus-response curve, shown in Figure 19-34. The relationship illustrated is the time-independent relationship between dose, concentration, or some other measure of exposure to the drug (*x* axis) and the measured effect (*y* axis). The measured effect can be an absolute response (e.g., twitch height), a normalized response (e.g., percentage of twitch height depression), or a population response (e.g., fraction of subjects moving upon incision). The standard equation for this relationship is the "Hill" equation, sometimes called the "sigmoid-E_{max} relationship":

$$\text{Effect} = E_0 + (E_{max} - E_0)\frac{C^\gamma}{C_{50}{}^\gamma + C^\gamma} \qquad (48)$$

This is another example of the saturation equation shown in Figure 19-5. In this equation, E_0 is the baseline effect in the absence of drug and E_{max} is the maximum possible drug effect. C is typically concentration or dose, although other measures of drug exposure (e.g., peak concentration, area under the concentration-versus-time curve) can be used. C_{50} is the concentration associated with 50% of peak drug effect and is a measure of drug potency. The exponent γ, also called the "Hill coefficient," relates to the sigmoidicity and steepness of the curve. If γ is less than 1 and the curve is plotted on a standard *x* axis, the curve appears hyperbolic (see Figure 19-5). If γ is greater than 1, the curve appears sigmoidal, as in Figure 19-34. If the *x* axis is plotted on

Table 19-1 Summary of Results from Knock-Out and Transgenic Mice in Which Various Portions of Adrenergic Receptor Signaling Pathways were Targeted (Emphasis on Cardiovascular Effects)

Model	Target	Result
Transgenic	↑β_2AR	↑Basal AC, ↑LV fn, ↑atrial contractility, ↑supraventricular premature beats, ↓HR variability
Knock-out	↓β_2AR	No observable effects (except mild exercise effects)
Transgenic	↑β_1AR	Dilated cardiomyopathy and early death, fibrosis
Knock-out	↓β_1AR	70% prenatal death rate, survivors: nl AC, ↓ISO-stim
Transgenic	↑AC-V	↑HR, ↑fractional shortening, no ISO-stim effects
Transgenic	↑GRK2	↓AC activity, ↓fn βARs, ↓ISO-stim (rescued with βARK-ct peptide, which inhibits GRK2)
Transgenic	↑GRK5	Enhanced βAR desensitization, but not angiotensin II desensitization
Transgenic	↑GRK2 inhibitor	Enhanced cardiac contractility with ISO (functional ↓GRK2)
Knock-out	↓GRK2	Lethal phenotype, gestational hyperplasia of LV, LVEF ↓70% in embryos
Transgenic	↑$G_s\alpha$	No Δ baseline EF, ↑ ISO-stim, myocardial fibrosis
Knock-out	↓Phospholamban	↓βAR-mediated contractile responses
Transgenic	↑α_{1A}AR	Hypertension, ↑inotropy
Transgenic	↑α_{1B}AR	Myocardial hypertrophy, hypertension, nociception, memory (constitutively active)
Transgenic	↑α_{1B}AR	No myocardial hypertrophy, hypertension (wild type)
Transgenic	↑α_{1D}AR	Nociception, memory
Transgenic	↑G_q	Myocardial hypertrophy ≈4-fold overexpression, higher expression give heart failure
Transgenic	↑G_q inhibitor	Prevention of myocardial hypertrophy (functional ↓G_q)
Knock-out	↓α_{2A}AR	Presynaptic α_2AR, mediates sedation/hypnosis, ↓BP (central hypotension), analgesia, regulation of DA/5-HT, antiepileptogenic effects of NE
Knock-out	↓α_{2B}AR	Mediates ↑BP (peripheral vasoconstriction)
Knock-out	↓α_{2C}AR	Mediates hypothermia, DA synthesis/metabolism, presynaptic α_2AR also (low-frequency stimulation)

AC, adenylyl cyclase; AR, adrenergic receptor; βARK-ct, c terminal fragment of the, β-adrenergic receptor kinase; BP, blood pressure; DA, dopamine; EF, ejection fraction; fn, function; HR, heart rate; 5-HT, 5-hydroxytryptamine; ISO, isoproterenol; LV, left ventricle; GRK, G protein–coupled receptor kinase; LVEF, left ventricular ejection fraction; NE, norepinephrine.

a log scale, the curve will always appear sigmoidal regardless of the value of γ.

Potency and Efficacy

Considerable confusion exists around the definition of potency because of competing definitions of the term. One use of potency is to describe the effect of a given dose of the drug. Consider two different oral preparations of an identical drug: one that dissolves quickly in the stomach and is rapidly absorbed and one that never completely dissolves and is poorly absorbed. A given dose of the rapidly absorbed formulation would produce a more profound drug effect and thus be considered more potent than an identical dose of the slowly absorbed formulation. Consequently, from a therapeutic perspective, potency is often defined in terms of the dose-versus-response relationship.

However, from a pharmacologic perspective, potency is best described in terms of the concentration-versus-response relationship. As shown in Figure 19-34, a drug with a left-shifted concentration-versus-response curve (i.e., lower C_{50}) is considered more potent, whereas a right-shifted dose-versus-response curve renders it less potent. To be precise, potency should be defined in terms of a specific drug effect (e.g., 50% of maximal effect). This is particularly important if the two drugs have different Hill coefficients or efficacies (E_{max}).

Efficacy is a measure of the intrinsic ability of a drug to produce a given physiologic or clinical effect (Fig. 19-35). For example, in G protein–coupled receptors, efficacy is influenced by coupling of receptor to G proteins, activation of second messengers, and the ability to generate maximal physiologic responses. The scale used to describe intrinsic efficacy at a given receptor ranges from 0 to 1. Efficacy is 1.0 for full agonists, 0 for neutral antagonists, and between 0 and 1.0 for partial agonists. In contrast, the term *potency* refers to the quantity of drug that must be administered to produce a specific effect. Two drugs may have the same efficacy, but if one drug produces the maximum effect at 1 mg whereas the second drug produces the maximum effect only at 100 mg, the second drug is less potent. The difference between a full agonist and a partial agonist (see Figs. 19-22 and 19-23) represents a difference in efficacy.

Effective Dose and Lethal Dose

The ED_{50} is the dose of a drug required to produce a specific effect in 50% of individuals to whom it is administered. The LD_{50} is the dose of a drug required to produce death in 50% of patients (or,

Table 19-2 Site of Action of Sedatives and Hypnotics

Anesthetic	$GABA_A$	Glycine	Neuronal nAChR	$5\text{-}HT_3$	AMPA (GluR1-4)	NMDA
Barbiturates	+++	+/0	–––	–/0	–––	0
Chloroform	+++	+++	–––	Unknown	–––	0
Diethyl ether	+++	+++	–––	+++	–––	–––
Enflurane	+++	+++	–––	+++	–––	–/0
Etomidate	+++	+/0	–/0	0	Unknown	Unknown
Halothane	+++	+++	–––	+++	–––	–/0
Isoflurane	+++	+++	–––	+++	–––	–/0
Ketamine	+/0	0	–––	+/0	0	–––
Methoxyflurane	+++	+++	–––	+++	Unknown	Unknown
Nitrous oxide	+++	+/0	Unknown	Unknown	–/0	–––
Propofol	+++	+++	–/0	0	–/0	–/0
Sevoflurane	+++	+++	–––	Unknown	Unknown	Unknown
Steroidal anesthetics	+++	0	–/0	–/0	0	0
Xenon	0	Unknown	Unknown	Unknown	0	–––

AMPA, α-amino-3-hyudroxy-5-methyl-4-isoxazoleproprionate; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine; nAChR, nicotinic acetylcholine receptor; NMDA, ***N***-methyl-D-aspartate; +++, potentiation of the agonist; –––, inhibition of the agonist; +/0 and –/0, little potentiation or inhibition, except at concentrations well in excess of the clinical range; 0, no effect at any concentration.
From Krasowski MD, Harrison NL: General anaesthetic actions on ligand-gated ion channels. Cell Mol Life Sci 55:1278-1303, 1999.

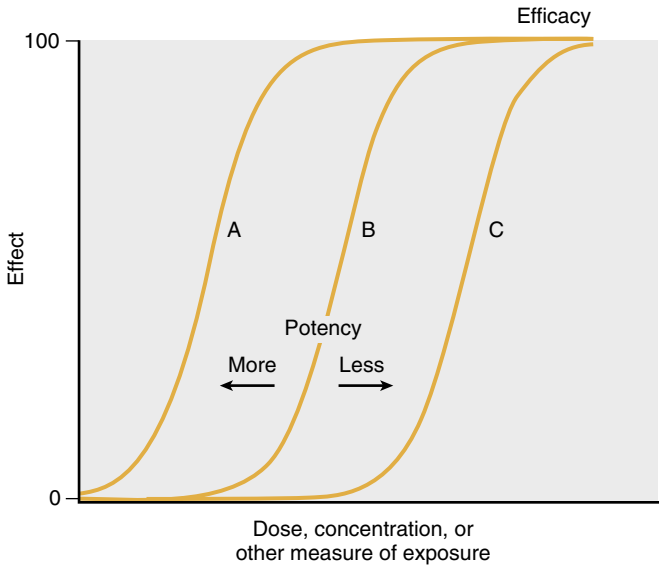

Figure 19-34 Dose- or concentration-versus-response relationships. A sigmoidal concentration-response curve is generated when the log drug concentration is plotted against the clinical response or effect. The concentration-response curve is shifted to the right (B→C) in the presence of a competitive antagonist after desensitization. Curve C might also represent an agonist with lower receptor affinity (K_a) or potency than curve B (or both). Curve A represents an agonist with higher receptor affinity or potency than curve B.

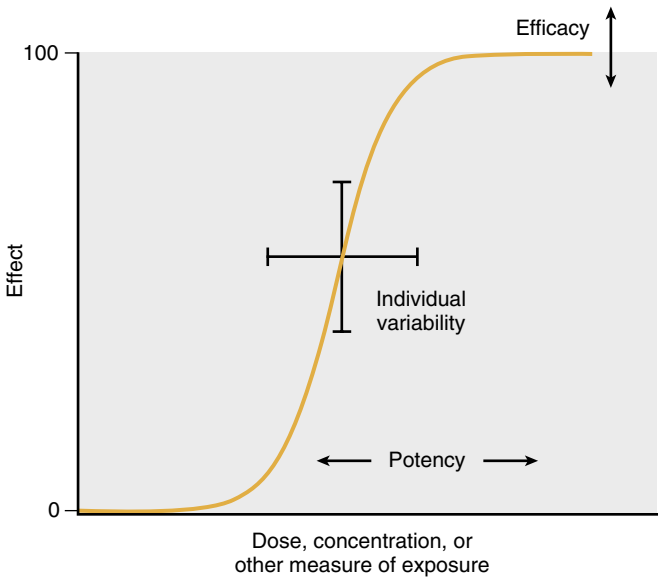

Figure 19-35 Relationship among efficacy, potency, and individual variability as they relate to a typical sigmoidal dose- or concentration-versus-response curve.

more often, animals) to whom it is administered. The therapeutic index of a drug is the ratio between the LD_{50} and the ED_{50} (LD_{50}/ED_{50}). The larger the therapeutic index of a drug, the safer the drug for clinical administration. The relationship among ED_{50}, LD_{50}, and therapeutic index is shown in Figure 19-36.

Drug Interactions

Actions at the Same Receptor

Agonists and antagonists modify dose-response relationships for concurrently administered drugs. If two agonists have identical affinity (K_a) for a given receptor and identical effectiveness in coupling to second messengers, their resultant dose-response curves should be superimposable. However, if two agonists have different receptor affinities despite identical effectiveness in coupling to second messengers, their dose-response curves will be parallel (with the rightward-shifted curve corresponding to the drug with lower receptor affinity; see Fig. 19-34, curves B and C). When two agonists are administered simultaneously, the clinical effect depends on the total amount of drug-receptor complexes generated.

As stated earlier, full agonists produce maximal responses, whereas partial agonists produce less than maximal response at the same receptor occupancy. The precise molecular mechanism that explains this blunting of the maximal response by partial agonists is not known, but it may relate to the ability of full agonists to stabilize the activated state, R*, most effectively. Partial agonists shift the dose-response curve of the agonist to the right (B → C in Fig. 19-34).

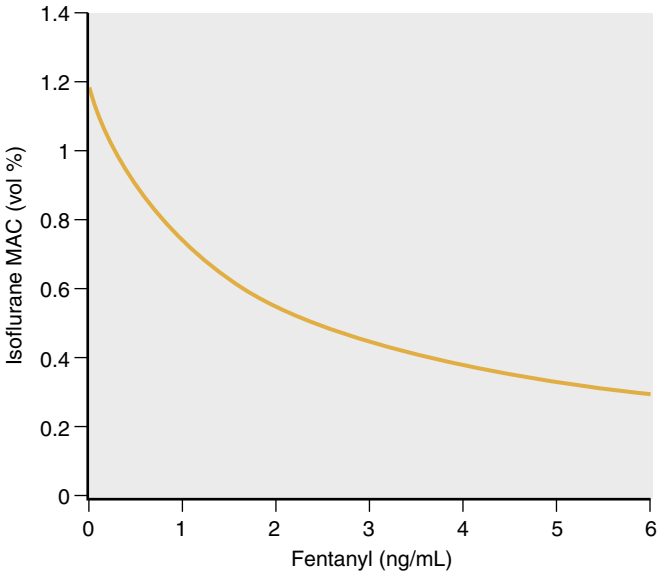

Figure 19-37 Influence of fentanyl on the minimum alveolar concentration (MAC) of isoflurane associated with a 50% probability of movement on incision. Modest amounts of fentanyl greatly reduce the MAC of isoflurane, but a ceiling in MAC reduction is quickly reached. Even with large opioid doses, some isoflurane is required to ablate the movement response. *(Adapted from McEwan AI, Smith C, Dyar O, et al: Isoflurane minimum alveolar concentration reduction by fentanyl. Anesthesiology 78:864-869, 1993.)*

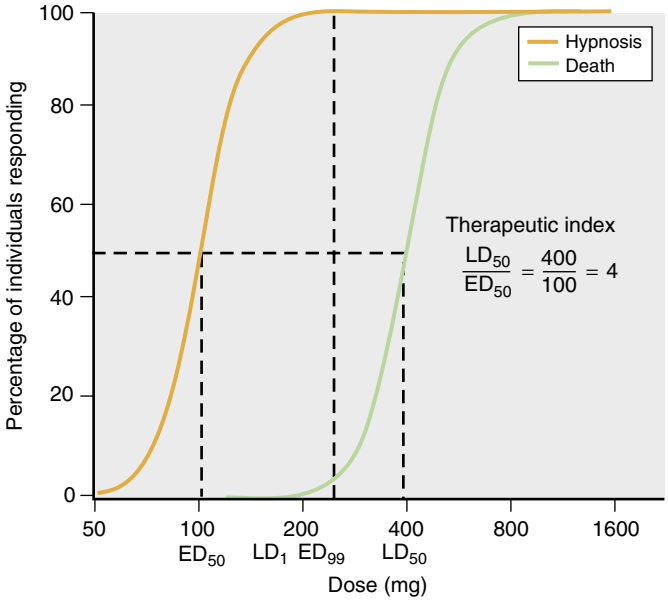

Figure 19-36 Relationship between median effective dose (ED_{50}), median lethal dose (LD_{50}), and therapeutic index. These curves were generated from data in which animals were injected with varying doses of a sedative-hypnotic and clinical responses were determined. ED_{50} is the dose of drug required to produce a specific effect (hypnosis) in 50% of animals to which it is administered (*left curve*). LD_{50} is the dose of drug required to produce death in 50% of animals to which the drug is administered (*right curve*). The therapeutic index of the drug is the ratio between LD_{50} and ED_{50} (LD_{50}/ED_{50}). LD_1 is the lethal dose in 1% of the population. ED_{99} is the effective dose in 99% of the population. As drawn, LD_1 is less than ED_{99}, which would not be clinically acceptable.

The addition of a competitive antagonist also shifts the dose-response curve to the right (B → C in Fig. 19-34). By contrast, the addition of a noncompetitive agonist shifts the dose response curve to the right and reduces the efficacy of the agonist because maximal response cannot be achieved at any agonist dose since blockade of effect (noncompetitive antagonism) cannot be reversed.

Actions at Different Receptors

Anesthesia is the practice of applied drug interactions. As discussed in Chapter 39, general anesthesia is, at a minimum, a combination of hypnosis, immobility, and antinociception. As such, there has been extensive work looking at the interaction of hypnotic drugs, which include inhaled anesthetics and GABA agonists (propofol, barbiturates, etomidate, and benzodiazepines), muscle relaxants, and analgesic drugs.

A prototypical study of the relationship between inhaled anesthetics and opioids is the study of McEwan and colleagues, who characterized the interaction between isoflurane and fentanyl.[19] The isoflurane concentration associated with a 50% chance of moving on incision (minimum alveolar concentration [MAC]) versus the plasma fentanyl concentration is shown in Figure 19-37. Initially, the interaction is profound, with a 50% reduction in isoflurane MAC at a plasma fentanyl concentration of 1.7 ng/mL and a 63% reduction in isoflurane MAC associated with a plasma fentanyl concentration of 3 ng/mL. Beyond 3 ng/mL, there is very little benefit from additional fentanyl. The first clinical implication of this interaction is that a modest amount of opioid dramatically reduces the concentration of inhaled anesthetic required to prevent movement. The second clinical implication is that even with huge doses of opioids, some hypnotic

component must be added to the anesthetic to prevent movement.

Similar work has been done for propofol. In a series of elegant studies, Vuyk and colleagues characterized the interaction of propofol with alfentanil.[20] As shown in Figure 19-38, the interaction is markedly synergistic, with modest amounts of alfentanil greatly decreasing the amount of propofol associated with a 50% chance of response to intubation or surgical incision. Vuyk and colleagues also documented the interaction of propofol and alfentanil on return of consciousness, likewise shown in Figure 19-38. As discussed in Chapter 28, studies such as these provide the basis for rational selection of opioids and design of optimal opioid infusion regimens.

Hendrickx and colleagues have recently surveyed the interaction of anesthetic drugs that affect nociception, analgesia, and hypnosis.[21] They examined two end points: "hypnosis," defined as loss of consciousness in humans and loss of the righting reflex in animals, and immobility, defined as loss of the movement response to noxious stimulation in a nonparalyzed subject.[21] As shown in Figure 19-39, the interaction between pairs of intravenous drugs and between intravenous drugs and inhaled anesthetics is typically synergistic. The exception is the *N*-methyl-D-aspartate (NMDA) antagonists, ketamine and nitrous oxide, which demonstrate synergy, additivity, or infra-additivity in different models. By contrast, the inhaled anesthetics are strictly additive in their interactions with other inhaled anesthetics, suggesting a common mechanism of action.

Classic interaction studies such as those just described examine the concentrations associated with a particular response (such as a 50% chance of moving) for two drugs evaluated separately and in combination. However, a more general view is that any combination of two drugs is associated with a response. This is best viewed as a "response surface" in which the *x* and *y* axes of the surface are concentrations (or doses) of drugs A and B and the *z* axis is the response to the particular combination. Minto and colleagues have proposed a mathematical framework for response surfaces for a variety of interaction surfaces of interest to anesthesiologists.[22] Figure 19-40 shows six examples of possible response surfaces, depending on the nature of the interaction.

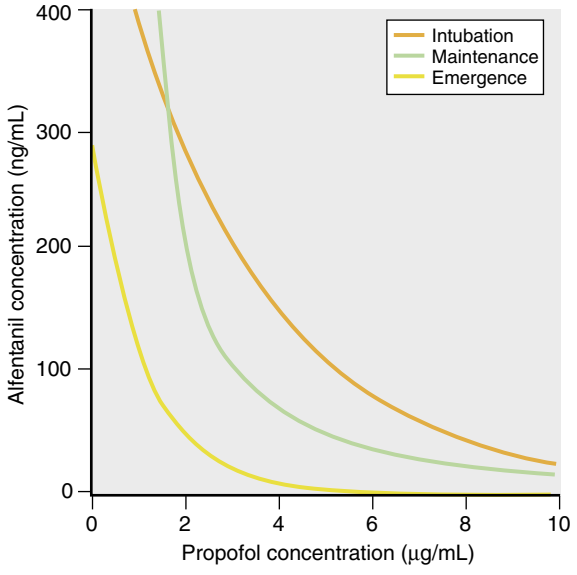

Figure 19-38 Influence of alfentanil on the concentration of propofol associated with a 50% probability of response to intubation and incision, as well as a 50% probability of awakening at the end of surgery. Moderate doses of alfentanil greatly reduce the dose of propofol required to ablate the response to noxious stimulation. However, below propofol concentrations of approximately 2 μg/mL, even large doses of alfentanil cannot reliably ablate the response to noxious stimulation. *(Adapted from Vuyk J, Lim T, Engbers FH, et al: The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. Anesthesiology 83:8-22, 1995.)*

Variability in Drug Response

Anesthesiologists observe individual variation in clinical response to administered drugs every day. This variability can occur as a result of differences in pharmacokinetic processes such as absorption, distribution, metabolism, and excretion of a drug. Individual variation can also be due to differences in pharmacodynamics, such as intrinsic differences in receptor sensitivity, upregulation and downregulation, and alterations in other targets that affect drug action. The relationship between patient variability and a typical dose-response curve is shown in Figure 19-35. Sources of pharmacokinetic and pharmacodynamic variability include genetics, patient physiology, and drug interactions.

Pharmacogenetics

The field of pharmacology that describes effects of genetic variation on drug action is called *pharmacogenetics*. Pharmacogenetics refers to genetic diversity in the body's absorption, metabolism, and distribution of drugs (inborn pharmacokinetic variability) or in the body's response to the drug, as might be caused by differences in receptor structure or patient physiology (inborn pharmacodynamic variability). To understand the effect of genetic variation on pharmacokinetics and pharmacodynamics, it is important to first define genetic variants, or polymorphisms.

Genetic polymorphism refers to any type of variation in a gene. More precise language is used to describe each specific type of genetic variant. When one nucleotide is exchanged for another, this variant is called a *single-nucleotide polymorphism* (SNP). The rare substituted nucleotide is defined as the minor allele, whereas the more common "wild-type" nucleotide is defined as the major allele. Most SNPs are biallelic, with only two nucleotides possible, either the minor or the major allele. In rare cases, SNPs can be triallelic, with two possible minor alleles and three total possible nucleotides present. With four total nucleotides available in DNA, it is theoretically possible to have each of the four nucleotides represented, but this almost never happens. We will confine our discussion to biallelic SNPs because they are the most common.

Allele frequency refers to the frequency of the minor allele, notated $f(-)$. The frequency of the major allele is therefore $1-f(-)$. Because this is the minor allele, by definition $f(-)$ is less than 0.5. Individuals have two copies of each allele, so there are three possible combinations of biallelic SNPs: AA, Aa, aa, in which A is a major allele and a is a minor allele. The Hardy-Weinberg equation provides the frequency of each of these combinations based on the generally correct assumption that paring of alleles is random:

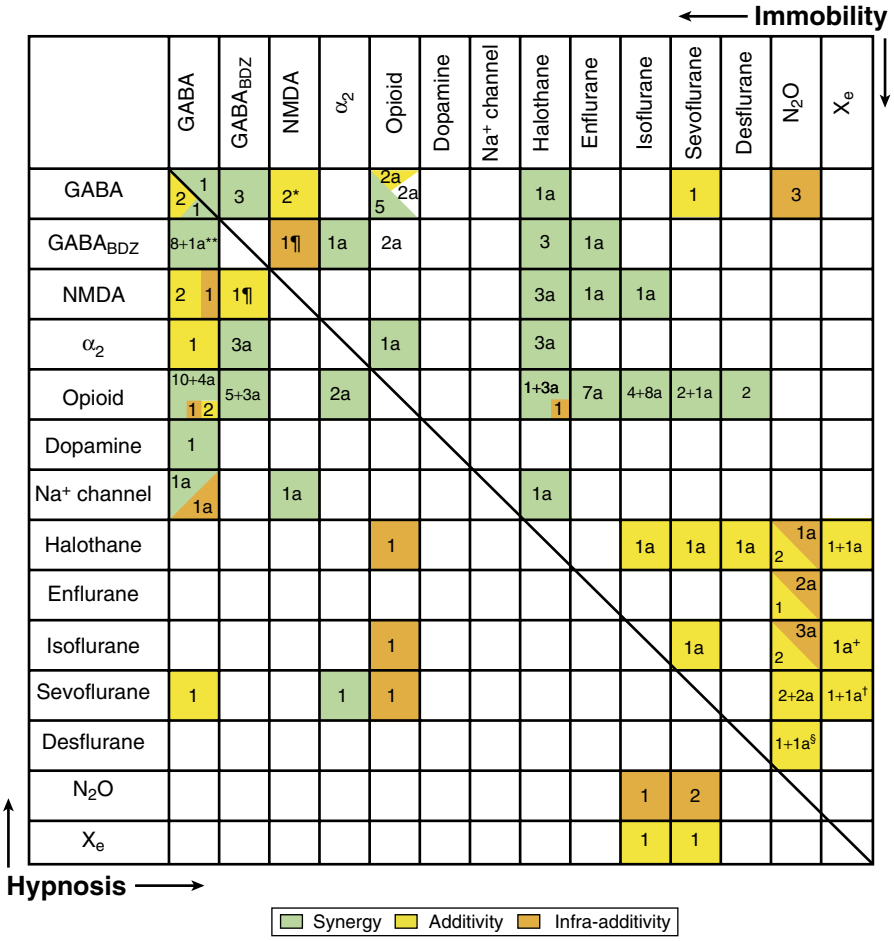

Figure 19-39 Summary of drug interactions in humans and animals for hypnosis (loss of consciousness in humans, loss of righting reflex in animals) and immobility (loss of movement response to noxious stimulation). The numbers in each cell refer to the number of papers supporting the finding. γ-Aminobutyric acid (GABA) = propofol, thiopental, methohexital, etomidate; GABA$_{BDZ}$ = midazolam, diazepam; *N*-methyl-D-aspartate (NMDA) = ketamine; α_2 = dexmedetomidine, clonidine; opioid = morphine, alfentanil, fentanyl, sufentanil, remifentanil; dopamine = droperidol, metoclopramide; Na$^+$ channel = lidocaine, bupivacaine. *(From Hendrickx JFA, Eger EI, Sonner JM, Shafer SL: Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. Anesth Analg 107:494-506, 2008.)*

aa (homozygous minor allele): $f(-)^2$
AA (homozygous major allele): $(1-f[-])^2$
Aa (heterozygous): $2\,f(-)\,(1-f[-])$

The sum of these frequencies is 1.

In addition to SNPs, other types of genetic variants include insertions/deletions, in which stretches of genomic DNA are missing or added, and microsatellite repeats, in which several nucleotides repeat (e.g., the dinucleotide repeat GCGCGCGC [*n* = 4 GC repeats] or the trinucleotide repeat TACTACTACTAC-TACTAC [*n* = 6 TAC repeats]). The number of repeats in a microsatellite correlates with some diseases and can be used in genome-wide scans to identify chromosome regions associated with disease.

Catastrophic DNA changes often include DNA deletions or insertions that are not multiples of three in the coding region. Such changes result in a frameshift in the triplet nucleotide sequence used to encode amino acids in proteins, with the probable result being a nonsense protein. SNPs that change an encoded amino acid to a stop codon may also be catastrophic because they could result in a truncated protein.

Not all genetic variants have biologic consequences. Just as differences in eye color or fingerprint pattern do not have medical consequences, many genetic variants provide "background" variation without overt biologic consequences. In fact, genetic variants with biologic/medical effects represent the minority of all genetic variants known to exist. The sum total of genetic variation (with and without biologic implications) does provide a unique genetic fingerprint, a fact used in forensic science to identify suspects or relatives (or both).

Determining the association between genetic variants and disease, drug therapy, or patient outcome is not straightforward and ideally should involve the help of a statistical geneticist. Clinical covariants and even genetic population structure (loosely defined as genetic variation caused by global population movement) must be carefully taken into account in pharmacogenetic studies. Depending on the number of genes to be examined, statistical testing for association ranges from straightforward simple analyses (using the chi-square approach to test whether a variant or haplotype [a group of SNPs] is enriched in the target population) to very complicated analyses (complex modeling, permutation testing, prospective sequential testing, etc.). In clinical association studies it is important to ensure that clinical end point data are reproducible and ideally include intermediate end points such as protein levels or enzyme activity. As more clinically relevant human genetic variants become known, our knowledge of the role of genetics in drug response and patient outcome should be significantly enhanced.

Genetic Variability in Pharmacokinetics

Naturally occurring genetic variants can affect the activity of enzymes responsible for drug metabolism, most often by altering

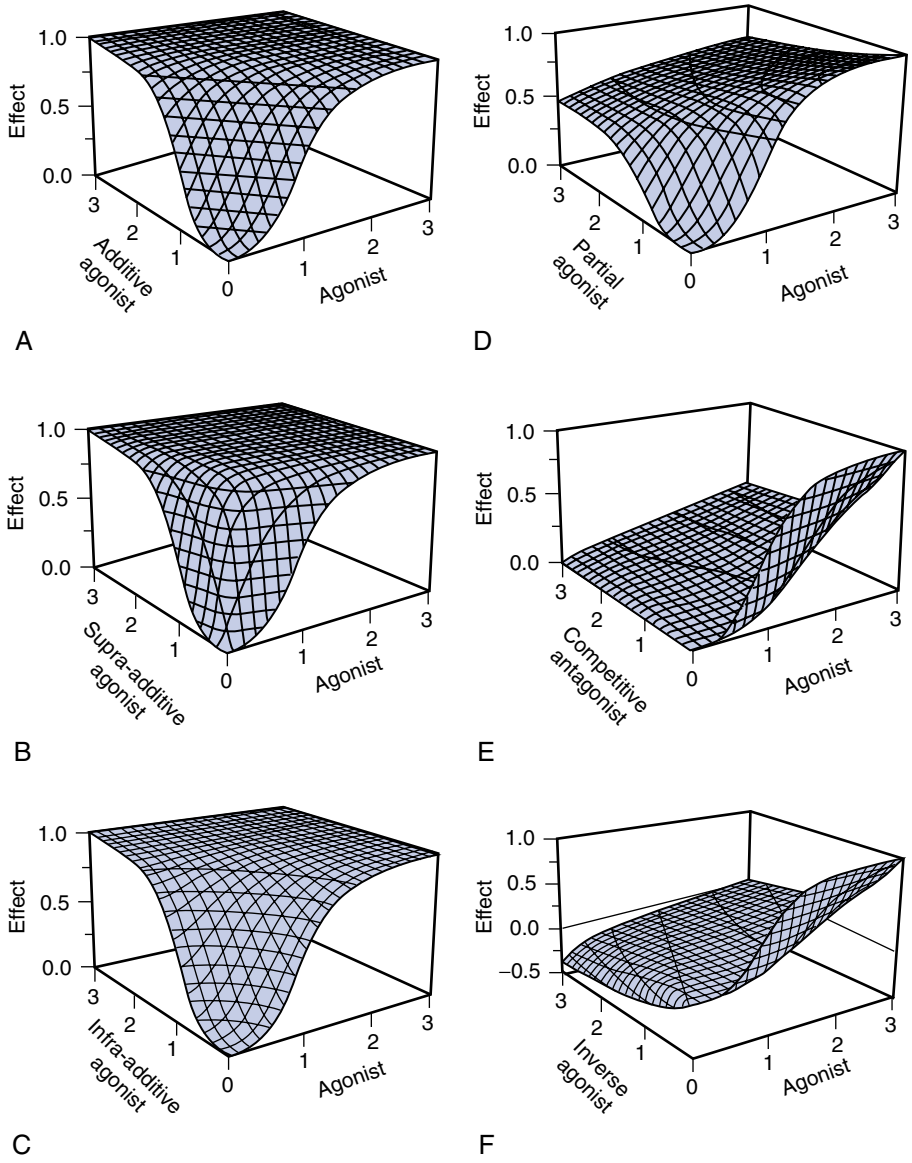

Figure 19-40 Response surfaces for potential pharmacodynamic interactions of anesthetic drugs. **A,** Additive interaction between two agonists that have the same mechanism of action (e.g., interaction of fentanyl and alfentanil). **B,** Supra-additive interaction between two agonists (e.g., isoflurane and fentanyl). **C,** Infra-additive interaction between two agonists (reported for cyclopropane and nitrous oxide). **D,** Partial agonist and full agonist (e.g., hypothetical interaction of nalbuphine and fentanyl). **E,** Competitive antagonist and full agonist (e.g., naloxone and fentanyl). **F,** Inverse agonist and full agonist (e.g., RO 19-4063 and midazolam).

a key amino acid in or near the site of enzymatic action. In practical terms, this enzymatic diversity is rarely evident in the absence of drug therapy. In the presence of drug therapy, pharmacogenetic variation in metabolism is evident as unexpected toxicity, duration of action, or lack of efficacy of administered drugs.

Of particular interest to anesthesiologists is the activity of cytochrome P450 (CYP) 3A4. This is the most abundant cytochrome in the liver and intestines and is responsible for the metabolism of almost half of all drugs, including many important drugs in anesthesia: opioids (fentanyl, alfentanil, sufentanil, methadone), benzodiazepines (diazepam, midazolam, alprazolam, triazolam), local anesthetics (cocaine, lidocaine, ropivacaine), steroids, calcium channel blockers, haloperidol, and halothane. Of the many described genetic mutants of the CYP3A4 enzyme, however, only two alter enzyme activity, with CYP3A4*18 decreasing and CYP3A4*19 increasing drug turnover.[23,24] It is important to note that most of these CYP3A4 studies have examined only heterozygous (Aa genotype) individuals thus far. This enzyme is readily inducible and inhibited by multiple substances. CYP3A4 induction and inhibition significantly overshadow the effects of currently described genetic variants.

In contrast to the lack of genetically important CYP3A4 variants, a different story exists for CYP2C19, the enzyme system responsible for metabolizing mephenytoin, omeprazole, diazepam, proguanil, propranolol, and certain antidepressants. Newly described SNPs in this gene, expressed most commonly in African Americans, appear to decrease the metabolism of these drugs in vitro.[25] Effects on drug plasma concentrations, clinical efficacy, and toxicity need further testing in prospective human clinical trials.

One of the best-studied pharmacogenetic variants is CYP2D6, also called "debrisoquine hydroxylase" or "sparteine oxygenase." About 7% to 10% of white individuals are homozygous for an inactive variant of CYP2D6. This alters metabolism for at least 40 drugs. For example, codeine is a prodrug with no intrinsic analgesic efficacy. Codeine, oxycodone, and hydrocodone all undergo *O*-demethylation to morphine, oxymorphone, and hydromorphone, their more pharmacologically active metabo-

lites, via CYP2D6. Individuals who are homozygous for inactive CYP2D6 have little to no analgesic efficacy from codeine.[26] Such individuals are likely to receive very little anesthesia from oral codeine and need to be rescued by another analgesic agent. CYP2D6 polymorphisms have also been shown to impair dextromethorphan and metoprolol metabolism. In contrast, other CYP2D6 polymorphisms result in a rapid metabolizer phenotype that is associated with high morphine levels after codeine administration that can lead to toxicity. When patients can be assayed for CYP2D6 activity, this will become a useful screen before initiating pain therapy with opioids.

Anesthesiologists are familiar with the role of genetics in determining butyrylcholinesterase (pseudocholinesterase) activity. Subjects with abnormal butyrylcholinesterase are at risk for prolonged paralysis from succinylcholine and exaggerated systemic effects from ester-based local anesthetics. Not surprisingly, there are ethnic differences in cholinesterase activity. For example, individuals of Middle Eastern descent are likely to have less butyrylcholinesterase activity than those of European descent. Molecular approaches have permitted extensive characterization of plasma cholinesterase variants. Most of these variants are not "all or none" but rather reflect a spectrum of enzymatic activity.

There may be an evolutionary explanation for pharmacogenetic variability in metabolism. It is probable that variability in drug metabolism is a natural adaptive response to an environment that can present a huge variety of toxins. Enzymatic diversity is probably maintained through natural selection to ensure survival when we are confronted with novel environmental toxins.

Genetic Variability in Pharmacodynamics

In addition to variants that affect drug pharmacokinetics, it is now well recognized that genetic variants can alter drug activity by pharmacodynamic mechanisms. Biologically active genetic polymorphisms have been found in numerous receptors, second messenger systems, and ion channels. One of the most intensively studied receptors in this regard is β_2AR. Several β_2AR SNPs have particular relevance to this discussion.[27] One variant, located at –47(T/C) in the 5′-untranslated sequence (referred to as the 5′-leader cistron), increases levels of normal (nonvariant) β_2AR mRNA and protein by 72%. This increase in airway wild-type β_2AR expression is protective against methacholine challenge. Another β_2AR SNP present in the amino terminus is Arg16Gly. Expression of Gly at position 16 increases sensitivity to agonists[28] and enhances agonist-promoted downregulation.[29] Because β_2AR stimulation in vessels is important in mediating vasodilation, an SNP such as Gly16 that enhances desensitization (and therefore dampens receptor responsiveness) is not surprisingly associated with a higher incidence of higher blood pressure, hypertension, and cardiomyopathy. In contrast, patients who are homozygous for Arg at position 16 are poorly responsive to β-agonist therapy for asthma.[30] Interestingly Arg16Gly usually travels together with yet another β_2AR, Gln27Glu, such that Gly16 usually occurs with Glu27. The Glu27 variant is also associated with enhanced responsiveness to β_2AR agonists.[29] This region of the β_2AR is said to be in linkage disequilibrium, with the three SNPs defining a haplotype (regions of DNA that travel together). Gly16, Arg19 (another SNP variant), and Glu27 or Arg16, Cys19, and Gln27 are the two possible haplotypes. This has practical implications because only one of the SNPs in the haplotype needs to be genotyped to infer the entire haplotype. This greatly enhances power and decreases cost in genetic association studies. Finally, another β_2AR SNP (Thr164Ile), located in the fourth membrane-spanning domain, has altered catecholamine binding (lower affinity for isoproterenol, epinephrine, and norepinephrine), along with markedly depressed basal and agonist-stimulated adenylyl cyclase activity in comparison to wild-type Thr164. This poorer coupling appears to result in depressed myocardial function and congestive heart failure, with the variant particularly enriched in heart transplant candidates.

It is likely that many forms of genetically based variability in response to drugs reflect the interaction of many polymorphisms that subtly affect receptor structure, cellular function, and physiologic response. Understanding the interaction of multiple genes on the variability of drug response presents daunting technical challenges in pharmacogenetic research.

Patient Physiology

Age

Total body water is decreased in the elderly. One pharmacokinetic result is a reduced initial mixing volume. This smaller central volume of distribution leads to higher peak concentrations after a bolus or during the early part of an infusion in elderly patients. A decreased central volume of distribution partly accounts for the increased sensitivity of elderly patients to many anesthetic drugs (also see Chapter 71).

Aging is also associated with decreased lean body mass and increased body fat. Because the lipid content of elderly patients is higher than that of young patients, elderly patients have more potential for lipophilic drugs to accumulate in peripheral volumes of distribution, which may be one factor behind the increased duration of effect for many anesthetic drugs seen in the elderly.

Liver volume, liver blood flow, and hepatic metabolic capacity decrease with advanced age. These changes in hepatic physiology account for the decreased clearance of opioids, hypnotics, benzodiazepines, and muscle relaxants and contribute to the increased sensitivity of elderly subjects to anesthetic drugs.

Age per se only modestly reduces cardiac output in the absence of hypertension, coronary artery disease, valvular heart disease, or other cardiovascular pathology. Advancing age can thus be expected to modestly reduce intercompartmental clearance of anesthetic drugs. The effect of decreased intercompartmental clearance is to increase initial plasma concentrations during drug administration. After termination of drug administration, the role of decreased intercompartmental clearance is complex. In general, plasma concentrations will decrease more rapidly after long infusions when intercompartmental clearance is decreased.

Albumin and α_1-acid glycoprotein are the primary sites of protein binding. The albumin concentration decreases with advancing age, hepatic disease, and malnutrition. In contrast, the α_1-acid glycoprotein concentration increases with advancing age and acute disease. Thus, the effects of age and disease on protein binding depend on which protein binds the drug. For example, because diazepam binds primarily to albumin, the free fraction of diazepam increases in elderly patients. This may partly explain the increased sensitivity in elderly subjects. In contrast, lidocaine binds primarily to α_1-acid glycoprotein. In elderly patients,

increased α_1-acid glycoprotein reduces the free fraction of lidocaine, which may contribute to reduced lidocaine clearance.

Although important age-related pharmacokinetic differences have been investigated in detail, there is a paucity of data addressing pharmacodynamic differences between age groups. Overall, the presence or absence of age-related pharmacodynamic differences appears to depend on the drug. For example, both antiepileptic agents and digoxin have been examined in adults and children, and the effective plasma concentration is the same. This finding suggests that for these two types of drugs, no age-related differences in pharmacodynamic responses occur. However many drugs with CNS effects (e.g., thiopental,[31] midazolam,[32] opioids,[33,34] propofol[35]) appear to be intrinsically more potent in the elderly, and this change in potency has been quantitated in pharmacodynamic models. Understanding the biologic basis of increased sensitivity in the elderly to anesthetic and perioperative drugs is an area of active investigation by many researchers.

Disease States

Various diseases contribute to variation in drug response. Although diseases frequently result in pharmacokinetic variations (e.g., decreased liver perfusion in heart failure or decreased elimination in renal failure), pharmacodynamic variation is also observed. Conditions such as diabetes, thyroid disease, adrenal disease, myasthenia gravis, and hypertension alter receptor function and therefore represent pharmacodynamic effects. Some diseases directly affect drug receptors. For example, in patients with myasthenia gravis, antibodies to the postsynaptic nicotinic acetylcholine receptor effectively decrease the number of receptors present. Muscle weakness characterizes the disease. As a result, these patients have less reserve at the neuromuscular junction and are exquisitely sensitive to muscle relaxants that act on the nicotinic acetylcholine receptor.

Drug Interactions

Pharmacokinetic Interactions

Historically, certain foods and drugs were known to inhibit drug metabolism. The inhibition of CYP3A4 by grapefruit juice is among the more dramatic of such interactions. As previously mentioned, CYP3A4 is responsible for nearly half of all drug metabolism. Ingestion of grapefruit juice has been shown to increase the plasma concentration of drugs metabolized by CYP3A4.[36] Many drugs also inhibit CYP3A4, including the antifungal drugs ketoconazole and itraconazole; the protease inhibitors ritonavir, indinavir, and saquinavir; the antibiotics troleandomycin, clarithromycin, erythromycin; and the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and sertraline. Propofol also inhibits CYP3A4, although it is unclear whether there is any clinical consequence. Conversely, several drugs induce CYP3A4, thereby increasing the metabolism of 3A4 substrates. Such drugs include rifampin, rifabutin, tamoxifen, glucocorticoids, carbamazepine, and barbiturates and the herb Saint John's wort.

CYP2D6, responsible for the conversion of codeine to morphine, is also subject to inhibition. In particular, quinidine and the SSRIs fluoxetine and paroxetine produce significant inhibition at standard clinical doses. Thus, codeine, oxycodone, or hydrocodone would be relatively poor analgesic choices for patients taking SSRIs.

Anesthetics also interact pharmacokinetically with many drugs by reducing cardiac output and hepatic blood flow. The reduction in cardiac output probably decreases intercompartmental clearance of most drugs, whereas the reduction in hepatic blood flow would be expected to decrease the metabolic clearance of drugs with high hepatic extraction ratios.

Pharmacodynamic Drug Interactions

Drug-Time Interaction: Desensitization

Desensitization is broadly defined as waning of physiologic responsiveness to a drug over time. For example, acute desensitization ("tachyphylaxis") typically occurs to sodium nitroprusside. Therefore, it is often necessary to increase the nitroprusside infusion rate over time to maintain the desired amount of vasodilation.

In general, stimulation of receptor pathways results in the activation of kinases (e.g., protein kinase A, G protein–coupled receptor kinases, protein kinase C) that phosphorylate specific regions of the receptor and thereby prevent further interaction of the receptor with G proteins or second messengers, or with both. Thus, continuous stimulation of a receptor provides a negative-feedback mechanism for receptor stimulation that results in desensitization. Although desensitization was initially thought to occur only at the receptor level, it is now well recognized that alterations in G proteins and second messengers also occur in response to agonist stimulation. Effectively, desensitization shifts the dose-response curve to the right (e.g., Fig. 19-34, curve B → C) or decreases the maximal drug effect (or both). Thus, both efficacy and potency can be diminished by desensitization.

Desensitization of receptor responses is a feature of many diseases present in the aging population and is therefore relevant to consider during the perioperative period. Common diseases in which desensitization is important include congestive heart failure, hypertension, and diabetes. A hallmark of each of these diseases is elevation of hormone (agonist) concentrations. In the case of congestive heart failure, poor cardiac output induces compensatory sympathetic nervous system stimulation, which often results in a doubling of circulating catecholamine concentrations (in particular, the sympathetic neurotransmitter norepinephrine). On a long-term basis, this results in desensitization of the myocardial βAR signal transduction pathway; specifically, β_1AR density and function decrease (75%) with relative sparing of β_2ARs (25%). G_i levels also increase without a change in G_s. Furthermore, G protein–coupled receptor kinase concentrations increase and modulation of adenylyl cyclase isoforms occurs. The physiologic effects of changes important in desensitization of myocardial βARs have been examined with the use of transgenic and knock-out mice (see Table 19-1 and the earlier discussion of molecular pharmacology). To break the cycle of elevated agonist exposure and resultant desensitization, cardiologists now cautiously use long-term, low-dose βAR antagonists (approximately a 10th the usual dose for hypertension or myocardial ischemia) in patients with congestive heart failure. This therapy has been shown to improve functional classification and longevity.

Drug-Time Interaction: Increased Receptor Sensitivity

The opposite of desensitization is increased receptor sensitivity. Long-term exposure to a drug often results in compensatory

responses by the receptor system. For example, when a receptor antagonist is administered on a long-term basis, receptor number (density) often increases. If the receptor antagonist is suddenly discontinued, exaggerated responsiveness to agonist may occur. This is the rationale for continuing long-term βAR antagonists during the perioperative period. Abrupt discontinuation of these drugs leaves the myocardium vulnerable to an exaggerated heart rate and inotropic responses to routine procedures such as tracheal intubation, thereby potentially leading to myocardial ischemia and infarction. Finally, a much-feared anesthetic example of increased receptor sensitivity is the upregulation of nicotinic receptors at the neuromuscular junction in patients with spinal cord injuries, burns, or prolonged immobilization. The potential for such patients to have a life-threatening hyperkalemic response to succinylcholine is described in detail in Chapter 29.

Drug-Drug Interactions

There are a huge variety of mechanisms by which drugs can interact pharmacodynamically. The nature of pharmacodynamic drug-drug interactions is so diverse that an anesthesiologist can safely assume that there will be some interaction between anesthetic drugs and virtually all drugs that have action on either the CNS or the cardiovascular system.

Some of these drug interactions, such as those between opioids and hypnotics, are fundamental to the practice of anesthesia and were discussed earlier. An example of interactions between anesthetics and nonanesthetics is the influence of nonanesthetic drugs on the MAC of inhaled anesthetics. Drugs that increase central catecholamines in general increase MAC. This has been clearly demonstrated for amphetamines (acute exposure), ephedrine, and monoamine oxidase inhibitors. Conversely, drugs that decrease central catecholamines decrease MAC. This has been shown for methyldopa, reserpine, and α_2-adrenergic agonists. It has also been demonstrated for chronic amphetamine use.

Summary

This chapter reviews general pharmacology by examining the basic principles of pharmacokinetics, pharmacodynamics, and sources of pharmacologic variability. Careful consideration of these principles should permit the anesthesiologist to understand drug movement from the site of administration through various body compartments to the site of action and the mechanisms by which drugs act on receptors to bring about the desired clinical effect. Many factors may alter the pharmacokinetic and pharmacodynamic processes by which drugs exert their effects, including genetics, age, disease, and concurrent drug therapy. Understanding basic pharmacologic processes and how they may differ between individuals should facilitate drug titration for each patient. There is a biologic basis for finding just the right drug in just the right dose to provide safe and effective care of perioperative patients. Our knowledge of the biologic basis for finding the right dose of the right drug for each individual is currently in its infancy but is rapidly growing with new discoveries.

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20 Inhaled Anesthetics: Mechanisms of Action

Key Points

1. Anesthesia consists of separable and independent components or substates, each of which involves distinct, but possibly overlapping, mechanisms at different sites in the central nervous system.
2. The potency of general anesthetics correlates with their solubility in oil, indicating the importance of their interaction with hydrophobic targets.
3. General anesthetics act by binding directly to amphiphilic cavities in proteins. Binding sites are being identified by a combination of site-directed mutagenesis and high-resolution structural analysis of anesthetic binding.
4. The effects of inhaled anesthetics cannot be explained by a single molecular mechanism. Rather, multiple targets contribute to the effects of each agent.
5. The immobilizing effect of inhaled anesthetics involves a site of action in the spinal cord, whereas sedation/hypnosis and amnesia involve supraspinal mechanisms.
6. Volatile inhaled anesthetics enhance inhibitory synaptic transmission postsynaptically by potentiating ligand-gated ion channels activated by γ-aminobutyric acid (GABA) and glycine, extrasynaptically by enhancing GABA receptors and leak currents, and presynaptically by enhancing basal GABA release.
7. Inhaled anesthetics suppress excitatory synaptic transmission presynaptically by reducing glutamate release (volatile agents) and postsynaptically by inhibiting excitatory ionotropic receptors activated by glutamate (gaseous agents).
8. No comprehensive theory of anesthesia describes the sequence of events leading from the interaction between an anesthetic molecule and its targets to the behavioral effects.

Despite widespread clinical use, current understanding of the molecular and cellular mechanisms of general anesthetic action is incomplete. This critical gap in the pharmacology of one of medicine's most important drug classes not only impedes rational use of available anesthetics but also hinders the development of newer agents to selectively achieve the desirable end points of anesthesia with fewer adverse cardiovascular, respiratory, and neuropsychological side effects. Although major progress has been made in understanding the pharmacology of the intravenous anesthetics by molecular genetic approaches (see Chapter 26), the actions of the inhaled anesthetics at the molecular and cellular levels are more enigmatic. It is still not possible to trace precisely the sequence of events that leads from inhaled anesthetic-target interactions, through ascending levels of biologic complexity, to the various behavioral effects that characterize the composite state of clinical anesthesia in humans. Nevertheless, investigations continue to reveal fundamental principles of action and have led to a framework for understanding anesthetic effects at different organizational levels. The focus of this chapter is on the mechanisms involved in the principal therapeutic effects (anesthesia) and on the side effects of the inhaled anesthetics (Fig. 20-1), a chemically and pharmacologically diverse group that includes the potent halogenated ether (isoflurane, sevoflurane, desflurane, enflurane) and alkane (halothane) volatile anesthetics and the gaseous anesthetics (nitrous oxide and xenon). This critical summary of the current state of knowledge begins with an historical overview and a review of the behavioral end points of anesthesia. We then trace, where possible, inhaled anesthetic effects through ascending levels of organization from molecules, cells, circuits, networks, and organs to mammalian behavior; an overview is provided in Table 20-1. A large body of work on anesthetic effects in model organisms, for which the correct anesthetic end points are unclear, is touched on briefly.[1]

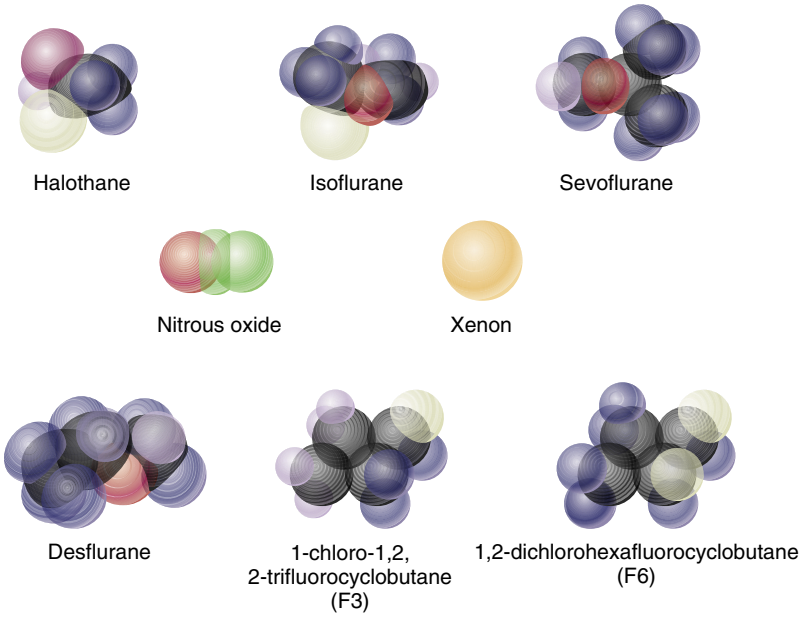

Figure 20-1 Structure of representative general anesthetics and a nonimmobilizer shown as space-filling models.

History

Unitary, Lipid-Based Theories

Inhaled general anesthetics were first used clinically more than 160 years ago, and interest in the mechanisms responsible for their remarkable effects was immediately kindled. The affinity of anesthetic drugs for lipids was soon recognized, which led to early lipid-based hypotheses of anesthetic action. The formulation of the Meyer-Overton correlation at the end of the 19th century was a watershed event, introducing a rigorous scientific approach into anesthesia research. Meyer concluded in 1899 that "All chemically indifferent substances that are soluble in fat are anesthetics … their relative potency as anesthetics will depend on their affinity to fat on the one hand and water on the other hand, that is, on the fat/water partition coefficient,"[2] a conclusion that was reached

Table 20-1 Overview of Proposed Sites of Anesthetic Action

	Site	Effect	Target(s)
Proteins	Amphiphilic binding sites	Conformational flexibility, ligand binding	Ion channels, receptors, signaling proteins
Action Potential	Nervous system	Small reduction in amplitude	Na^+ channels
	Cardiovascular system	Reduced amplitude, duration	Ca^{2+} channels, K^+ channels
Synaptic Transmission			
Inhibitory	Presynaptic terminal	Enhanced transmitter release	?
	Postsynaptic receptors	Enhanced transmitter effects	Glycine, $GABA_A$ receptors
Excitatory	Presynaptic terminal	Reduced transmitter release	Na^+ channels, K_{2P} channels
	Postsynaptic receptors	Reduced transmitter effects	NMDA receptors, nicotinic acetylcholine receptors
Neuronal Networks	Neuronal circuit	Altered LTP/LTD	Synaptic plasticity
	Neuronal integration	Altered rhythmicity, coherence	HCN channels, K_{2P} channels, extrasynaptic $GABA_A$ receptors, etc.
Central Nervous System	Neocortex, hippocampus, amygdala	Sedation, amnesia	θ-rhythms, γ-rhythms, synchrony
	Diencephalon (thalamus), brainstem (reticular formation)	Unconsciousness	γ-band transfer entropy?
	Spinal cord	Immobility	Thalamic deafferentation?
			Nocifensive reflex
Cardiovascular System			
	Myocardium	Negative inotropy	Excitation-contraction coupling
	Conduction system	Dysrhythmias	Action potential
	Vasculature	Vasodilation	Direct and indirect vasoregulation

independently by Overton.[3] The striking simplicity of the Meyer-Overton correlation (Fig. 20-2A) of anesthetic potency with solubility in olive oil led to the conclusion that lipids must be the anesthetic target. This focused attention on anesthetic effects on the bulk physical properties of cell membranes, which were known at that time to consist primarily of lipid molecules. Such nonspecific or "unitary" anesthetic mechanisms dominated the field for the ensuing decades.

Minimum Alveolar Concentration: A Bridge Between Past and Present

The introduction of the minimum alveolar concentration (MAC) concept as a universal measure for inhaled anesthetic potency in the 1960s had far-reaching implications for both clinical anesthesia and anesthesia research. The potencies of inhaled anesthetics for immobilization were established in the classic studies of Eger and colleagues,[4,5] who defined the "minimum alveolar concentration" of an inhaled anesthetic at atmospheric pressure required to prevent movement in response to a noxious stimulus in 50% of subjects. Because inhaled anesthetic concentrations reflect concentrations in other organs after equilibration, which is most rapidly achieved for well-perfused organs such as the brain and heart, MAC is analogous to the plasma EC_{50} (concentration for 50% effect) for intravenous anesthetics. In clinical applications, MAC is usually expressed as volume percent, which varies considerably with temperature due to changes in aqueous solubility, whereas the equivalent liquid-phase molar concentration is temperature-independent.[6] The MAC concept provided researchers and clinicians with a universal standard to measure a defined anesthetic end point (immobility), making meaningful comparisons of experimental results possible and accelerating laboratory and clinical research into anesthetic mechanisms. Today, a more nuanced understanding of MAC takes into account the structural and functional diversity of the biologic substrates of the different components of the anesthetic state.

Evolution from Lipid- to Protein-Centered Mechanisms

The formulation of the MAC concept was followed by evidence that proteins are plausible alternatives to lipids as anesthetic targets. Noncompetitive inhibition of the soluble firefly enzyme luciferase[7] demonstrated direct interference by anesthetics with the function of a lipid-free protein. Accurate measurements of anesthetic potency also revealed contradictions in lipid-based theories of anesthetic action such as the cutoff in anesthetic potency in homologous series of long-chain anesthetic alcohols and the identification of drugs that do not obey the Meyer-Overton correlation.[8,9] A focus on protein targets gained momentum in the 1980s owing largely to the work of Franks and Lieb,[10] who convincingly demonstrated that protein targets are also compatible with the Meyer-Overton correlation (see Fig. 20-2B) and proposed that anesthetics competitively antagonize protein function.[11] The enantiomeric selectivity of several anesthetics further strengthened the case for specific binding sites on proteins, such as ion channels, as the principal molecular targets of inhaled

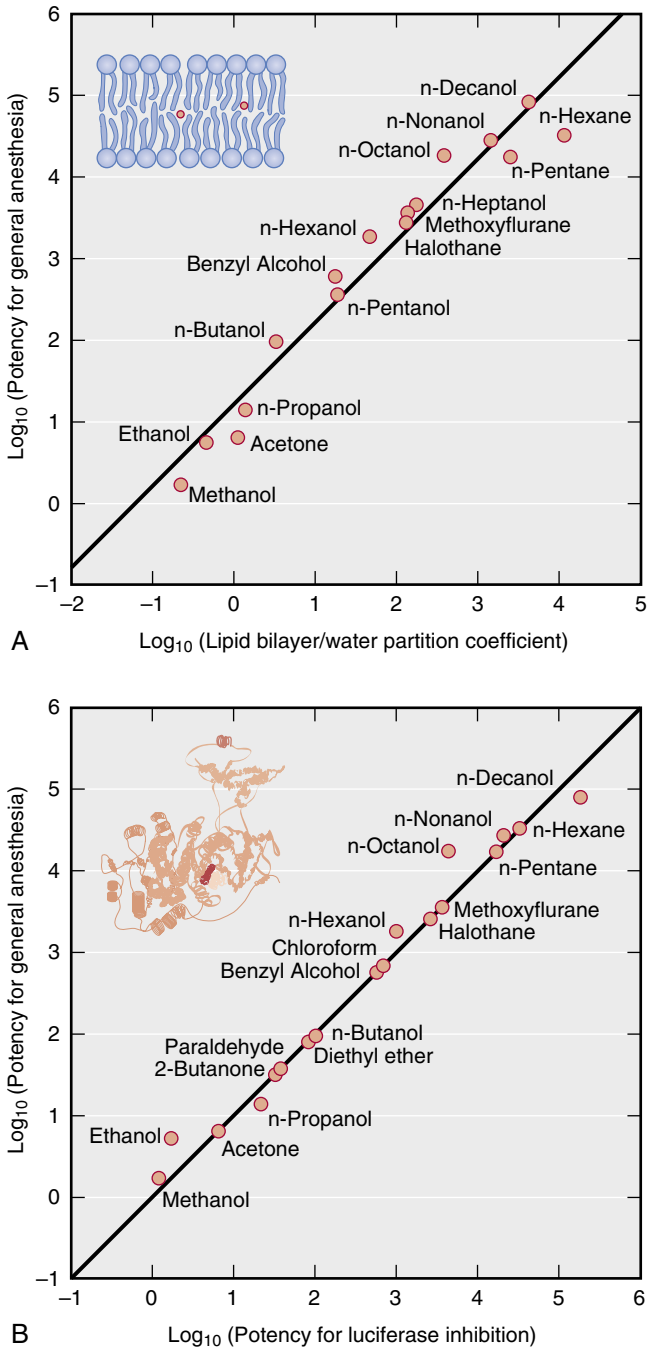

Figure 20-2 General anesthetics act by binding directly to proteins. **A,** The iconic Meyer-Overton correlation (c. 1900) was initially interpreted as evidence that lipids of nerve membranes were the principal anesthetic target sites based on the correlation between anesthetic potency and lipid-water partition coefficient. **B,** Progress in the 20th century showed that general anesthetic potencies correlate equally well with their ability to inhibit activity of the soluble firefly enzyme luciferase. The crystal structure of luciferase is shown in the *inset* with bound anesthetic in *red.* (*Reprinted with permission from Franks NP, Lieb WR: Molecular and cellular mechanisms of general anesthesia. Nature 367:607-614, 1994.*)

anesthetics.[12] Today, there is widespread (but not universal) acceptance of the notion that critical signaling proteins (e.g., ion channels and receptors) are the relevant molecular targets of anesthetic action even though the mechanisms of their modulation by anesthetics are debated, and much of the current work in

the field seeks to determine which proteins contribute to which anesthetic end points.

A Confusing Diversity of Anesthetic Targets

At high concentrations in vitro, most inhaled anesthetics affect multiple proteins, many of which can be plausibly connected to the anesthetic state. However, when considering a specific end point, anesthetics are effective in vivo over a quite narrow concentration range. This makes the concentration at which an effect is observed a critical consideration.[13] The mechanistic relevance of subtle effects observed in vitro at relevant concentrations is less clear, that is, what effect is too small to be considered relevant to anesthesia.[13-15] Whether anesthesia results from the sum of minor perturbations at multiple sites that are amplified in cascades across multiple levels of integration to produce the macroscopic effect or from strong effects on a small number of targets should be resolved as results of reductionist molecular studies are integrated into more complex molecular and cellular networks and as genetic studies are extended to encompass inhaled anesthetics. The emerging realization of the complexity of anesthesia is consistent with the modern concept that multiple cellular and molecular targets in distinct brain regions are involved in their desired and their adverse effects.

Anesthesia: A Complex Composite State

Along with progress in identifying the molecular mechanisms of anesthesia, our understanding of the nature of the anesthetic state has evolved. Whereas a coma-like state of general anesthesia can be induced by inhaled anesthetics administered at appropriate concentrations (approximately 1.3 times MAC, equivalent to the EC_{95} of a volatile anesthetic), the use of such high concentrations is fraught with short- and possibly long-term side effects. It is now clear that anesthesia consists of separable and at least partially independent components or substates, each of which involves distinct, but possibly overlapping, mechanisms at different sites in the central nervous system (CNS) and with variations in relative potencies between specific agents.[16] Immobilization, the core measure of MAC, is mediated largely at the level of the spinal cord by inhaled anesthetics[17,18] but not by barbiturates.[19] On the other hand, the spinal cord is unlikely to be the major site of anesthetic actions, producing such phenomena as amnesia, sedation, and unconsciousness, which are associated with cerebral cortical function (Fig. 20-3). A functional separation between amnesia and sedation has been demonstrated for intravenous anesthetics[20] and is likely for inhaled anesthetics as well. These and similar findings have led to the concept that general anesthesia consists of multiple independent components that are experimentally and clinically identifiable. Theoretically, each component can be preferentially induced in a concentration and agent-specific manner employing individual cellular/molecular pathways in various regions of the CNS. For example, injections of pentobarbital into discrete sites in the mesopontine tegmentum induce an anesthetic state,[21] whereas sedation induced by systemic administration of propofol can be reversed by microinjections of $GABA_A$ receptor antagonists into the tuberomammillary nucleus, a sleep-regulating nucleus in the hypothalamus.[22] Thus, general anesthetics produce separate identifiable anesthetic substates via agent-specific actions at discrete anatomic sites in the CNS by different molecular targets. An important consequence of this complexity is that MAC, which is based exclusively on the motor response, might not proportionately reflect other components of anesthesia. Although this heterogeneity of anesthetic action complicates a mechanistic understanding, it does open the possibility of developing substate-specific drugs.

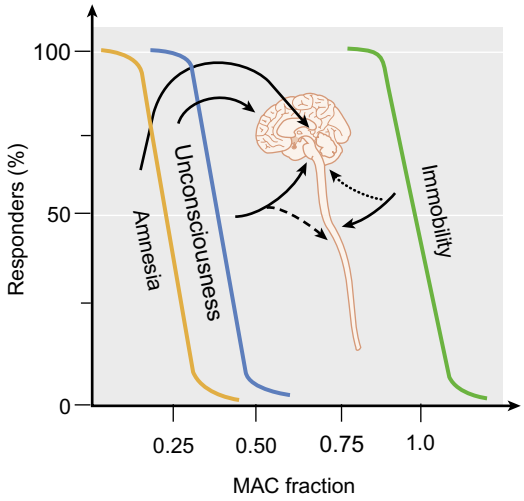

Figure 20-3 Multiple behavioral end points and sites of action underlie inhaled anesthetic action. Amnesia, the most sensitive anesthetic end point, probably involves the hippocampus, amygdala, mediotemporal lobe, and possibly other cortical structures. Unconsciousness likely involves the cerebral cortex, thalamus, and reticular formation. Sedation and hypnosis are part of the consciousness-unconsciousness continuum and are not shown. Immobility occurs by anesthetic action in the spinal cord, although supraspinal effects (*dotted arrow*) are likely important for some anesthetics. Anesthetic action in the spinal cord blunts ascending impulses arising from noxious stimulation and might indirectly contribute to anesthetic-induced unconsciousness and amnesia (*dashed arrow*). Cardiovascular responses occur at even greater MAC fractions (not shown). (*Courtesy of Joseph Antognini, University of California, Davis.*)

Integrated Effects on Central Nervous System Function

Immobility

Failure to find a correlation between quantitative measures of electroencephalographic activity and immobility in response to noxious stimulation spawned the somewhat radical (at the time) hypothesis that immobility was not a "cerebral" phenomenon.[23] Experimental demonstration that volatile anesthetics act on the spinal cord to suppress movement[17,18] supported this hypothesis and was a major factor leading to the contemporary separation of anesthetic substates, of which immobility requires the highest anesthetic concentrations (see Fig. 20-3). Taking advantage of the unusual blood supply to the goat CNS that allows separate perfusion of brain and spinal cord, Antognini and coworkers showed that immobility requires anesthetic delivery to the spinal cord because selective delivery of isoflurane or halothane only to the brain required 2.5- to 4-fold higher concentrations.[17,24] Surgical separation of the forebrain from the spinal cord in rats confirmed

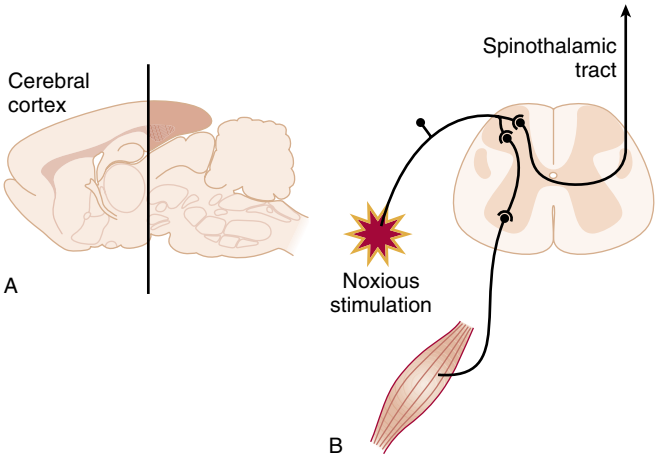

Figure 20-4 Inhaled anesthetics produce immobility at the spinal level. **A,** Decerebration by removal of the forebrain rostral to the *heavy black line* does not alter the MAC of isoflurane in rats, indicating that volatile anesthetic immobilization does not depend on the cerebral cortex. **B,** Anesthetics suppress the nocifensive withdrawal reflex response to noxious stimulation transmitted to the dorsal horn by sensory nerves at the spinal level. Current efforts are focused on identifying the molecular, cellular, and anatomic substrates for this effect. (***A** modified from Rampil IJ, Mason P, Singh H: Anesthetic potency [MAC] is independent of forebrain structures in the rat. Anesthesiology 78:707-712, 1993.*)

that immobilization involves primarily suppression of the nocifensive withdrawal reflex arc at the level of the spinal cord (Fig. 20-4).[18]

Recent studies have focused on the mechanisms by which inhaled anesthetics produce immobility. A pharmacologic approach to identify receptor-level contributions to MAC involves intrathecal administration of selective antagonists of neurotransmitter receptors in vivo. This strategy revealed that actions at spinal *N*-methyl-D-aspartate (NMDA)–type glutamate receptors[25] and glycine receptors[26] contribute to isoflurane-induced immobilization, whereas actions at $GABA_A$ receptors appear to be unimportant.[27] Glycine and $GABA_A$ receptors also appear to play little role in immobilization by cyclopropane,[26] which derives at least in part from antagonism of NMDA receptors.[28] Complementary research strategies have excluded other possible targets. Sensitivity to nonimmobilizer compounds excluded a role for inhibition of nicotinic acetylcholine receptors in immobilization,[29] and anesthetic-resistant transgenic mice confirmed that $GABA_A$ receptors containing α_1- or α_3-subunits do not contribute to the immobilizing action of isoflurane.[30,31] In contrast, mutant mice lacking the TASK-1, TASK-3, and TREK-1 K_{2P} channels have higher MAC values for volatile anesthetics but not intravenous anesthetics,[32-34] indicating a role for these channels, possibly by a presynaptic mechanism.[35] Even though the gross anatomic site for immobility has been identified and specific molecular targets have been implicated, an integrated hypothesis of the mechanism of inhaled anesthetic-induced immobility is still lacking (see reference 36 for review).

Unconsciousness

Consciousness, as a quality of the mind, is easy to recognize but difficult to define (see Chapter 39). As a neurobiologic process realized in the brain, it is within the reach of objective science but is currently poorly understood. Loss of consciousness (or hypnosis) is a hallmark of the onset of anesthesia, which raises the exciting possibility that anesthetic drugs will be useful as tools for understanding consciousness by defining the "neural correlates of consciousness" (NCC).[37] Although there is no universally accepted scientific definition, consciousness consists of inner, qualitative, subjective states of "sentience or awareness"[38] or "explicit awareness."[39]

Understanding how anesthetics ablate consciousness is entwined with theories of how consciousness is generated, many of which lack either experimental support or testable predictions. In contrast, neuroscientific approaches to consciousness are experimentally tractable. The "thalamic theory" of anesthesia proposes a somatosensory deafferentation by anesthetic action in the thalamus as a mechanism of unconsciousness.[40] In support of this hypothesis, isoflurane hyperpolarizes and shunts thalamic neurons,[41] an action consistent with impaired thalamic transfer of information observed in vivo.[42] Functional human brain imaging shows preferential suppression of thalamic activity by some, but not all, anesthetics, and this has led to the "thalamic switch" hypothesis.[43] However, loss of consciousness occurs within a very narrow range of anesthetic concentrations,[44,45] typically at less than 0.5 MAC,[46,47] whereas quantifiable effects in the thalamus occur above this concentration range and are typically incremental (dimmer-like) rather than sudden (switch-like). A comprehensive theory of anesthetic-induced unconsciousness must be more inclusive than a simple block of information transfer through the thalamus to be compatible with existing evidence[48] and must also explain the suppression of endogenous cortical activity that is generated without external stimulation.

Contemporary neuroscience has replaced the cartesian view of an anatomically discrete brain structure as the center of consciousness with the concept that consciousness requires integration of information between multiple brain regions across large-scale cerebral networks.[49,50] Anesthetic interference with the operational synchronicity and coherence of these networks with consequent disruption of cortical functional connectivity, as observed during natural sleep[51] and vegetative states, could result in "cognitive unbinding"[52] with loss of consciousness.[38] Unconsciousness[53] would be characterized not by the absence but by the disintegration of cortical processing.[39] Although the mechanism of "binding" (i.e., creating the unity of perception) is uncertain, synchronicity of neuronal activity in the 40- to 90-Hz range across functionally connected cortical areas (commonly referred to as 40 Hz- or γ-rhythm) is a viable candidate. Animal[54-56] and human[44] data implicate activity in the γ-band throughout the cortex as a network-level target of general anesthetics. Anesthetic actions on cortical information processing probably consist not merely of suppression of responses but of reduced complexity and variability reflected counterintuitively in increased reliability and precision of evoked responses.[57]

Learning and Memory

Anterograde amnesia, one of the core desirable anesthetic effects, is achieved at lower anesthetic concentrations (~0.25 MAC) than those required for unconsciousness (~0.5 MAC). Perhaps the closest analog in rodents to explicit memory in humans is hippocampus-dependent spatial learning. This can be tested by a variety of experimental paradigms, including fear conditioning to

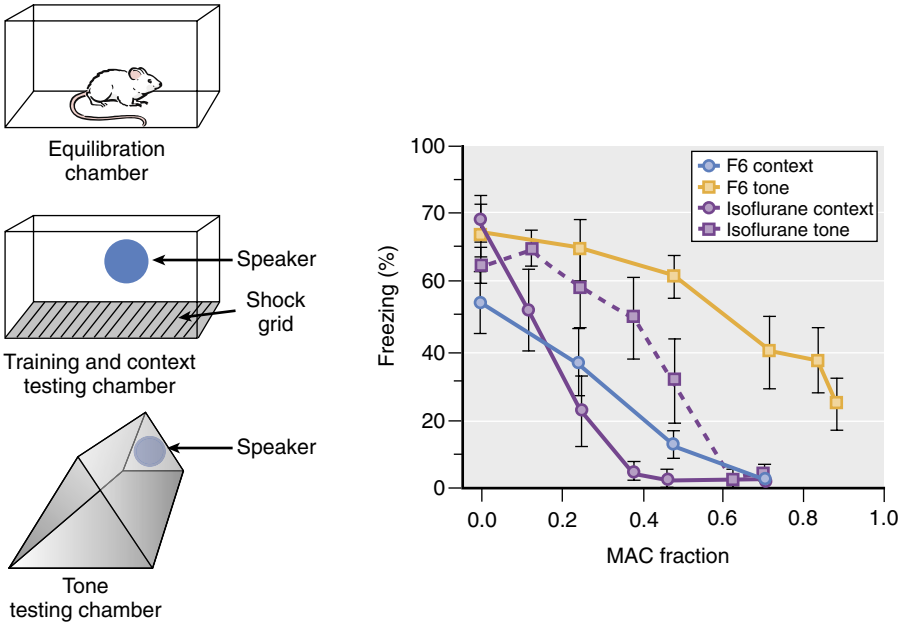

Figure 20-5 Differential sensitivity of different types of learning to anesthetics and nonimmobilizers. Freezing in anticipation of a noxious stimulus is a measure of learning in rats; less freezing indicates less learning. **Left,** The learning protocol involves pre-equilibration of rats in the equilibration chamber to isoflurane or the nonimmobilizer F6 at the desired concentration before placement into the training chamber. For testing of memory to context, training and test chamber are identical. For testing of memory to tone, training and testing take place in different chambers. **Right,** Hippocampus-dependent learning (fear conditioning to context, *closed symbols*) is inhibited by isoflurane (*purple circles*) at lower concentrations than hippocampus-independent learning (fear conditioning to tone, *purple squares*). This differential sensitivity is mirrored by the non-immobilizer F6 (*blue circles* and *yellow squares* for context and tone, respectively). (***Left panel*** *adapted with permission from Eger EI 2nd, et al: Isoflurane antagonizes the capacity of flurothyl or 1,2-dichlorohexafluorocyclobutane to impair fear conditioning to context and tone. Anesth Analg 96: 1010-1018, 2003;* ***Right panel*** *data points reconstructed from Dutton RC, et al: Short-term memory resists the depressant effect of the nonimmobilizer 1-2-dichlorohexafluorocyclobutane (2N) more than long-term memory. Anesth Analg 94:631-639, 2002, and Dutton RC, et al: The concentration of isoflurane required to suppress learning depends on the type of learning.*

context (Fig. 20-5). Other learning paradigms, such as fear conditioning to tone, are, by contrast, independent of the hippocampus. Isoflurane and the nonimmobilizer F6 both inhibit hippocampus-dependent learning at about half the concentration necessary for hippocampus-independent learning.[58] Because anesthetic concentrations that inhibit explicit memory in humans are similarly lower than concentrations that impair implicit memory,[47] anesthetic effects on hippocampal function are implicated in explicit memory suppression. Effects on other structures, such as the amygdala, may be crucial to anesthetic impairment of implicit or other types of memory.[59]

Comparison of the amnesic potency of five inhaled anesthetics using the inhibitory avoidance paradigm revealed that nitrous oxide was the most potent and halothane the least potent amnestic (expressed in MAC fractions), with the halogenated ethers of intermediate potency.[60] Because inhaled anesthetics affect multiple cellular targets at amnesic concentrations, it is difficult to attribute amnesia to specific cellular mechanisms. It is also unclear whether inhibition of learning and memory by drugs known to have different receptor affinities shares common mechanisms at some level of integration. Comparison with more selective drugs provides some insight. Abundant evidence indicates that θ-rhythms (4-12 Hz) are important for hippocampus-dependent learning and memory.[61] Benzodiazepines[62] and cannabinoids[63] slow and suppress hippocampal θ-rhythms in proportion to their ability to impair hippocampus-dependent learning. Isoflurane and the nonimmobilizer F6 have comparable effects on θ-rhythms at amnesic concentrations while having different receptor-level profiles and opposite effects on sedation.[56] Thus, alterations in neuronal synchrony provide a common network-level substrate for memory impairment. The synchronization between amygdalar and hippocampal θ-rhythms that occurs during fear memory retrieval indicates that this principle might also apply to other forms of memory and their impairment by anesthetics.[64] As with other components of the anesthetic state, the precise mechanisms of memory impairment by anesthetics, and of memory itself, remain to be fully elucidated.

Sedation

Sedation (defined as a decrease in activity, alertness, arousal, and/or vigilance) and its behavioral continuum hypnosis are achieved at low anesthetic concentrations (<0.5 MAC), near those that produce amnesia. There is no clear mechanistic or clinical separation between sedation and hypnosis. By contrast, even though sedation can be difficult to separate from amnesia, evidence obtained for intravenous anesthetics supports separate but overlapping substrates for these two end points.[20,65] The mechanisms involved in these behavioral effects probably resemble those of less promiscuous drugs, for which genetic approaches have been informative. An amino acid knock-in mutation (H101R) in mice that renders the α_1 $GABA_A$ receptor subunit insensitive to modulation by benzodiazepines produces resistance to the sedative and amnesic effects of benzodiazepines while maintaining other behavioral effects, among them anxiolysis.[66] The α_1 subunit is abundantly expressed in the CNS, mainly in cortical areas and thalamus. Volatile anesthetics have qualitatively similar effects on α_1-containing $GABA_A$ receptors (but also those containing other subunits) at low concentrations. The observation that the nonim-

mobilizer F6, which is devoid of sedative properties,[56] is amnesic[67] but does not modulate benzodiazepine-sensitive α_1-containing $GABA_A$ receptors[68,69] is compatible with a role for α_1-containing receptors in volatile anesthetic-induced sedation, because few other targets are affected at purely sedative concentrations. Possible targets for the sedative effects of the gaseous anesthetics nitrous oxide and xenon, which do not affect $GABA_A$ receptors, include NMDA receptor antagonism[70,71] and K_{2P} channel activation.[72] Consistent with this distinct pharmacologic profile, nitrous oxide has strikingly different effects from benzodiazepines in behavioral tests aimed at evaluating sedation in mice.[73]

Recognizing that there may be more than a superficial similarity between natural sleep and anesthetic-induced sedation and hypnosis, some anesthetics apparently "hijack" natural sleep mechanisms by directly activating discrete sleep-promoting nuclei in the hypothalamus.[22,74] The observations that electroencephalographic patterns during natural slow-wave sleep and anesthesia show some similarities[75] and that recovery from sleep deprivation can occur during propofol anesthesia[76] support this concept. Anesthetic effects on other cortical[77] and subcortical structures[21] also contribute to anesthetic-induced sedation and hypnosis.

Anesthetic Neurotoxicity and Neuroprotection

Recent animal experiments indicate that general anesthetics can cause persistent neurologic effects beyond their classic reversible production of anesthesia (see Chapter 46). The clinical significance of these changes is largely unknown, but attention has been drawn to the potential for adverse effects.[78] Possible anesthetic damage to the developing rodent CNS has attracted particular scrutiny recently, although clinical evidence in humans is lacking. Postnatal exposure of the developing rodent brain to high doses of commonly used anesthetic drugs, in isolation or in combination, for a period of several hours, can induce apoptotic cell death with potentially long-term functional consequences.[79] However, this appears not to occur with postnatal exposure in precocial species.[80] It is also unclear whether anesthetics contribute to the clinical syndrome of postoperative cognitive dysfunction in the aged brain, primarily owing to difficulty in establishing a robust animal model. More evidence supports a deleterious effect of nitrous oxide than of volatile anesthetics in aged animals.[81] Recent evidence also points to immune-mediated changes triggered by surgical trauma as a potential mechanism of postoperative cognitive dysfunction (see also Chapter 89).[82]

Pharmacologic neuroprotection from cerebral ischemia is a rapidly evolving area of research that is characterized by great potential but comparable disappointments as promising animal studies have failed to translate into clinical benefits. Despite considerable research, clinical evidence for ischemic brain protection by inhaled anesthetics remains controversial.[83] Ischemic neuronal injury results from early excitotoxic cell death mediated by excessive release of excitatory amino acid transmitters such as glutamate together with delayed cell death due to apoptosis.[84,85] Volatile anesthetics (e.g., isoflurane) and xenon exhibit early neuroprotection in animal models that is sustained only for mild insults. This is consistent with a beneficial effect on excitotoxicity but minimal effects on delayed cell death due to apoptosis. A therapeutic strategy to extend this early neuroprotection is suggested by the finding that isoflurane combined with caspase inhibitors to prevent apoptosis results in more sustained neuroprotection.[86] In contrast, xenon appears to have an intrinsic antiapoptotic action that contributes to its neuroprotective properties consistent with its distinct molecular mechanisms.[87] In addition, volatile anesthetics probably protect by suppression of brain energy requirements due to inhibition of excitatory transmission and potentiation of inhibitory receptors and ion channels.[84] The potential for beneficial effects from anesthetic-induced cardiac preconditioning has also received considerable recent attention (see the following section).

Integrated Effects on the Cardiovascular and Respiratory Systems

The cardiovascular effects of the volatile anesthetics are classically recognized as deleterious and undesired side effects that limit their use in the critically ill, but recent studies indicate direct cardioprotective effects of inhaled anesthetics.[88] All volatile anesthetics produce agent- and dose-dependent reductions in myocardial contractility, systemic vascular resistance, and cardiac preload with consequent reduction in mean arterial pressure, but significant differences exist in the relative potencies of these effects among agents (see Chapter 23).[89] Volatile anesthetics depress contractility by reducing Ca^{2+} availability and/or Ca^{2+} sensitivity of the contractile apparatus.[90] The major targets responsible for the negative inotropic effects of volatile anesthetics are cardiac Ca^{2+} channels, sarcoplasmic Ca^{2+} handling, and the contractile apparatus. Inhibition of depolarization-induced increases in myoplasmic Ca^{2+} concentration occur primarily via inhibition of cardiac L-type voltage-gated Ca^{2+} currents and shortening of action potential duration.[91] Volatile anesthetics also inhibit the sarco-endoplasmic Ca^{2+} ATPase (SERCA), while halothane, but not isoflurane or sevoflurane, opens sarcoplasmic reticulum (SR) Ca^{2+} release channels (ryanodine receptors), depleting SR Ca^{2+} content and reducing excitation-evoked SR Ca^{2+} release.[90] The resulting negative inotropic effect of this reduced Ca^{2+} availability is enhanced by reductions in the Ca^{2+} sensitivity of myofibrils. In contrast, xenon has no effects on ventricular contractility, conduction, or major cation currents,[91,92] consistent with its lack of significant cardiovascular effects. Nitrous oxide causes mild reductions in ventricular function[92] by poorly characterized effects on Ca^{2+} availability. This is usually accompanied by sympathetic nervous system stimulation that increases vascular resistance and counteracts the myocardial depression.[93,94]

Volatile anesthetics can produce vasodilation at clinical concentrations.[95] The vascular effects of volatile anesthetics are multifactorial and tissue specific, and the precise cellular mechanisms are poorly understood.[96,97] Peripheral vasodilation is mediated both by direct endothelium-independent vasodilating effects on vascular smooth muscle cells and indirect effects involving the sympathetic nervous system and the vascular endothelium. The mechanisms of these effects involve agent-specific effects on presynaptic norepinephrine release, inhibition of smooth muscle Ca^{2+} influx via L-type Ca^{2+} channels, activation of hyperpolarizing K_{ATP} and K_{Ca} channels, and endothelium-dependent factors, including nitric oxide.[98]

As with the CNS, cardiovascular function depends on the integrated function of multiple ion channels, many of which are expressed in both of these excitable tissues. Volatile anesthetics have agent-specific effects on heart rate and induction of arrhythmias due to actions on cardiac ion channels. Because multiple cardiac ion channels are sensitive to volatile anesthetics at clinical concentrations, and because most manipulations of cardiac ion channel function are potentially proarrhythmic, it is difficult to link anesthetic arrhythmogenicity to actions on specific channels.[99] Electrophysiologic studies indicate that cardiac L-type Ca^{2+} channels, which are critical to the plateau phase of the cardiac action potential and electromechanical coupling, are inhibited by volatile anesthetics, leading to shortening of the refractory period. Multiple voltage-gated K^+ channels are also inhibited and might predispose to arrhythmias by delaying repolarization. On the other hand, inhaled anesthetics can protect the heart against ischemia and reperfusion injury, possibly involving antioxidant, anti-inflammatory, and/or preconditioning mechanisms.[100,101] Volatile anesthetics[102] and xenon[103] can mimic the strong cardioprotective effects produced by ischemic preconditioning (termed *anesthetic preconditioning* by analogy) through activation of various cytoprotective G-protein–coupled receptors and protein kinases, including protein kinase C (PKC), mitogen-activated protein kinases (MAP kinases), extracellular signal-regulated kinases (ERK), Akt (protein kinase B), and tyrosine kinases.[88,104] Although not entirely clarified, sarcolemmal and putative mitochondrial adenosine triphosphate (ATP)-sensitive K^+ (K_{ATP}) channel activation, involving PKC activation and increased formation of free radicals and nitric oxide, are the likely end effectors of anesthetic preconditioning in the heart.

Inhaled anesthetics also have important effects on the respiratory system. All volatile anesthetics cause significant respiratory depression at concentrations necessary for surgical anesthesia. The peripheral chemoreflexes and upper airway patency are particularly sensitive to subanesthetic concentrations of volatile anesthetics.[105] The mechanisms involved in these potentially serious effects involve depression of central respiratory networks mediated by depression of excitatory and facilitation of inhibitory transmission. The precise molecular targets responsible for the exquisite sensitivity of these networks to low concentrations of volatile anesthetics remain to be elucidated (see Chapter 22).

Identification of Molecular Sites of Anesthetic Action

Criteria for Identifying Sites Relevant to Anesthesia

Specific criteria have been proposed to evaluate the relevance of the many potential molecular targets of anesthetics.[106] These criteria include:

1. Reversible alteration of target function at clinically relevant concentrations. This criterion requires comparable in vivo and in vitro sensitivity and depends on the anesthetic end point under consideration. For example, targets involved in immobility must be sensitive to anesthetics near MAC, whereas targets mediating memory impairment must be affected at a fraction of MAC. Recent evidence for persistent effects of inhaled anesthetics demonstrable in the absence of continued anesthetic exposure is challenging the notion of reversibility for certain effects.
2. Expression of the target in appropriate anatomic locations to mediate the specific anesthetic end point. For example, immobilization by inhaled agents appears to involve primarily depression of reflex pathways in the spinal cord independent of drug actions in the brain.
3. Concordant stereoselectivity of anesthetic effects in vivo and on the target in vitro. In the absence of a specific pharmacologic antagonist of anesthesia, correlation between the stereoselective actions of general anesthetics in vivo and in vitro is a useful test of pharmacologic relevance of putative molecular targets. Stereoselectivity data correlating in vivo potency and in vitro receptor actions implicate $GABA_A$ receptors as a target for the anesthetic actions of etomidate, pentobarbital, neurosteroid anesthetics, and possibly isoflurane and the NMDA receptor for the actions of ketamine.
4. Appropriate sensitivity or insensitivity to model anesthetic and nonanesthetic compounds. Anesthetic halogenated cyclobutanes together with structural analogs that do not produce anesthesia at concentrations predicted to be anesthetic by the Meyer-Overton correlation (nonimmobilizers) can be used to discriminate relevant volatile anesthetic targets in vitro. For example, the anesthetic F3 (1-chloro-1,2,2-trifluorocyclobutane), but not the structurally similar nonanesthetic F6 (1,2-dichlorohexafluorocyclobutane), affect $GABA_A$, glycine, AMPA, kainate, and $5\text{-}HT_3$ receptors, and Na^+ channels, consistent with a role in immobility, whereas both F3 and F6 affect neuronal nicotinic, M1 muscarinic, $5\text{-}HT_{2C}$, and mGluR5 receptors, indicating that these targets are not involved in immobility. F6 is interesting in that it lacks sedative and immobilizing effects but does possess amnesic effects, hence the more accurate term "nonimmobilizer", thus making it a useful pharmacologic tool for discriminating targets for these actions.

Physicochemical Properties of Anesthetic Binding Sites

A convergence of x-ray crystallography, molecular modeling, and structure-function data indicate that inhaled anesthetics bind in hydrophobic cavities formed within proteins.[107] The lipophilic (or hydrophobic) nature of these binding sites explains their adherence to the Meyer-Overton correlation. An element of amphiphilicity (possessing both polar and nonpolar characteristics) is also required for effective interaction with these cavities, as indicated by improvements in the Meyer-Overton correlation with more polar solvents.

From Model Proteins to Receptors

Identifying inhaled anesthetic binding sites on plausible target proteins is difficult due to their low-affinity interactions and the paucity of atomic resolution structures of pharmacologically rel-

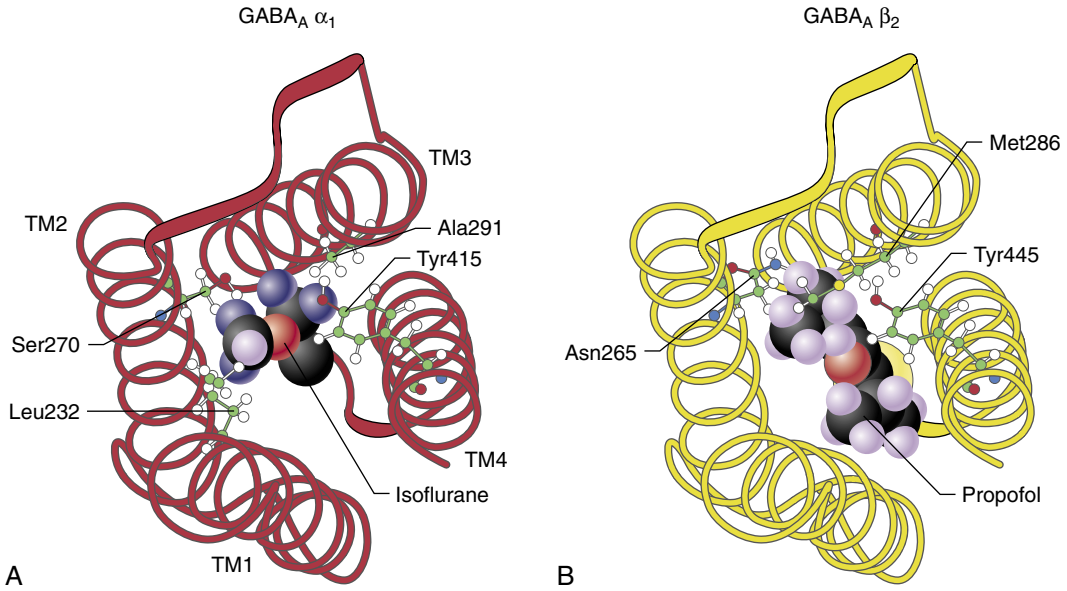

Figure 20-6 Putative anesthetic binding sites on GABA$_A$ receptors. **A,** Model of rat GABA$_A$ α_1-subunit with Leu232, Ser270, Ala291, and Tyr415 rendered in ball-and-stick. A molecule of isoflurane built at the same scale is positioned in the putative binding site. The transmembrane (TM) α-helices are numbered 1-4. **B,** Corresponding model of GABA$_A$ β_2-subunit with Asn265, Met286, and Tyr445 rendered in ball-and-stick. A model of propofol built at the same scale is positioned in the putative binding site. (*From Hemmings HC Jr, Akabas MH, Goldstein PA, et al: Emerging molecular mechanisms of general anesthetic action. Trends Pharmacol Sci 26:503-510, 2005.*)

evant target proteins. Consequently, most anesthetic binding sites have been identified in well-characterized model proteins for which three-dimensional atomic resolution structures are available, such as luciferase and albumin.[107] These studies indicate that anesthetics bind in pockets with both nonpolar and polar noncovalent chemical interactions. Binding involves weak hydrogen bond interactions with polar amino acid residues and water molecules, nonpolar van der Waals interactions, and a polarizing effect of the amphiphilic binding cavity on the relatively hydrophobic anesthetic molecules. Internal cavities are important for the conformational flexibility involved in ion channel gating and ligand-induced signal transduction of receptor proteins. Occupation of a critical volume within these cavities by anesthetics provides a plausible mechanism for alteration of receptor and ion channel function by selective stabilization of a particular confirmation (e.g., an open or inactivated state of an ion channel). Anesthetics also obtain binding energy from the entropy generated by displacing bound water from these relatively promiscuous binding sites. Studies of glycine, GABA$_A$, and NMDA receptors provide convincing evidence for the existence of anesthetic binding sites in critical neuronal signaling proteins.[108] Amino acid residues critical for volatile anesthetic actions and, by inference, binding have been identified in the α-subunit of the GABA$_A$ receptor.[108-110]

Molecular modeling based on structurally homologous proteins has also been used to identify putative anesthetic binding sites in the transmembrane domains of GABA$_A$ and glycine receptors (Fig. 20-6).[111] This model suggests that different drugs might either bind in different orientations within a single amphiphilic cavity or occupy different cavities within the protein, causing similar functional effects. Refinement of these molecular models will continue to provide new insights in the molecular basis for general anesthetic action that can be experimentally tested. Potential sites of interaction of xenon and isoflurane with the NMDA receptor have also been identified using this approach. One site, which can contain up to three xenon atoms or one molecule of isoflurane, overlaps the known binding site for the co-agonist glycine in the NR1 subunit (Fig. 20-7).[112] This suggests

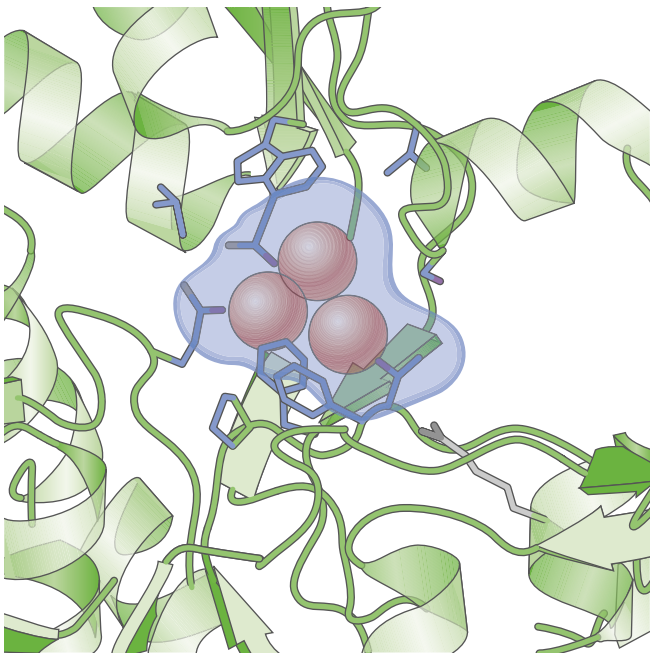

Figure 20-7 Crystal structure of the ligand binding domain of the *NMDA receptor* showing xenon binding sites predicted by molecular modeling. The *red spheres* represent xenon atoms at the center of the density clusters that comprise the binding sites. The predicted xenon binding sites occupy the site normally occupied by glycine. The same site is also large enough to accommodate isoflurane. (*Modified from Dickinson R, Peterson BK, Banks P, et al: Competitive inhibition at the glycine site of the N-methyl-D-aspartate receptor by the anesthetics xenon and isoflurane. Anesthesiology 107:756-767, 2007.*)

that two chemically dissimilar inhaled anesthetics inhibit NMDA receptors by direct competitive inhibition of agonist binding.

Molecular Targets of Inhaled Anesthetics

Ion channels have emerged as the most promising molecular targets for inhaled anesthetics. Neurotransmitter-gated ion channels, in particular $GABA_A$, glycine, and NMDA-type glutamate receptors, are leading candidates owing to their appropriate CNS distributions, essential physiologic roles in inhibitory and excitatory synaptic transmission, and sensitivities to clinically relevant concentrations of anesthetics.[16,113,114] Other ion channels that are sensitive to inhaled anesthetics include the HCN (hyperpolarization-activated cyclic nucleotide-gated) family of channels that give rise to pacemaker currents[115] and regulate dendritic excitability, two-pore domain (K_{2P}) "leak" K^+ channels that maintain resting membrane potential in many cells,[116] and voltage-gated Na^+ and Ca^{2+} channels.[117]

Inhaled anesthetics can be divided into two classes based on their distinct pharmacologic properties. The first class is the potent inhaled (volatile) anesthetics, which exhibit positive modulation of $GABA_A$ receptors, also produce significant, anesthesia-compatible effects on a number of other receptors/channels, including enhancement of inhibitory glycine receptors, inhibition of excitatory NMDA and neuronal nicotinic acetylcholine receptors, activation of K_{2P} channels, and inhibition of presynaptic Na^+ channels. Intravenous anesthetics such as propofol and etomidate represent more potent and specific positive modulators of $GABA_A$ receptors. The second class is the gaseous inhaled anesthetics, which include cyclopropane, nitrous oxide, and xenon. These anesthetics are inactive at $GABA_A$ receptors, but block NMDA receptors and activate certain K_{2P} channels at clinical concentrations. The intravenous anesthetic ketamine is a more potent and specific blocker of NMDA receptors.

Ligand-Gated Ion Channels

Potentiation of Inhibitory $GABA_A$ and Glycine Receptors

The ether anesthetics (including isoflurane, sevoflurane, and desflurane), the alkane anesthetic halothane, most intravenous anesthetics (including propofol, etomidate, barbiturates), and the neurosteroid anesthetics enhance $GABA_A$ and glycine receptor (GlyR) function. $GABA_A$ and GlyRs are members of the same Cys-loop ligand-gated ion channel superfamily that also includes the cation-permeable nicotinic acetylcholine and $5HT_3$ receptors. $GABA_A$ receptors are the principal transmitter-gated Cl^- channels in the neocortex and allocortex, whereas GlyRs fulfill this function in the spinal cord, with some overlap in the diencephalon and brainstem. Activated receptors conduct chloride ions, driving the membrane potential toward the Cl^- equilibrium potential. Both receptors are considered to be inhibitory because the Cl^- equilibrium potential is usually more negative than the normal resting potential. Channel opening also reduces membrane resistance and "shunts" excitatory responses. Most functional $GABA_A$ and GlyRs are heteropentamers, typically consisting of three different $GABA_A$ subunits (e.g., two α, two β, and one γ or δ) or two different GlyR subunits (three α and two β).[118] The subunit composition of $GABA_A$ receptors determines their physiologic and pharmacologic properties and varies between and within brain areas as well as between different compartments of individual neurons. Examples are the preferential expression of the α_5-subunit in the dendritic field of the hippocampal CA1 area (a region important for memory formation), of the α_4-subunit in the thalamus, and of the α_6-subunit in the cerebellum. Presence of a γ-subunit is required for benzodiazepine modulation of $GABA_A$ receptors and can also influence modulation by inhaled anesthetics. While the molecular mechanisms of receptor modulation by inhaled anesthetics are not definitively settled, these receptors have been key to our understanding of anesthetic-receptor interactions. Using chimeric receptor constructs between anesthetic-sensitive $GABA_A$ and insensitive GlyR subunits, specific amino acid residues in the transmembrane domains 2 and 3 critical to the action of inhaled anesthetics have been identified.[119] This laid the groundwork for the construction of anesthetic-resistant $GABA_A$ receptors and the generation of transgenic mice with altered anesthetic sensitivity (see later).

The related cation-permeable 5-hydroxytryptamine (serotonin)-3 ($5HT_3$) receptors are similarly potentiated by volatile anesthetics.[120-122] $5HT_3$ receptors are involved with autonomic reflexes and probably contribute to the emetogenic properties of volatile anesthetics (see Chapter 86).

Inhibition of Excitatory Acetylcholine and Glutamate Receptors

Neuronal nicotinic acetylcholine receptors (nnAChRs), like the other members of the Cys-loop family, are heteropentameric. They are composed of α- and β-subunits, but functional homomeric receptors can be formed by certain α-subunits. In the CNS, nnAChRs are localized primarily presynaptically.[123] Homomeric α_7-receptors have high permeability to Ca^{2+} that can exceed that of NMDA receptors.[123] In contrast to $GABA_A$ and GlyRs, nnAChRs pass cations when activated and therefore depolarize the membrane potential. Receptors containing $\alpha_4\beta_2$ subunits are very sensitive to block by isoflurane and propofol.[124,125] Relevance of nnAChR block to immobilization, sedation, and unconsciousness by inhaled anesthetics is unlikely because nnAChRs are also blocked by nonimmobilizers, although it is possible that they do contribute to amnesia.[9]

NMDA (*N*-methyl-D-aspartate) receptors are a major postsynaptic receptor subtype of ionotropic receptors for glutamate, the principal excitatory neurotransmitter in the mammalian CNS.[126] Typical NMDA receptors, defined pharmacologically by their selective activation by the exogenous agonist NMDA, are heteromers consisting of an obligatory NR1 subunit and modulatory NR2 subunits. Channel opening requires glutamate (or another agonist such as NMDA) binding to the NR2 subunit while the co-agonist glycine binds to the NR1 subunit. NMDA receptors also require membrane depolarization to relieve the voltage-dependent block by Mg^{2+}. The depolarization is typically provided by binding of glutamate to non-NMDA glutamate receptors (see later). Because of this "dual" requirement (transmitter release and postsynaptic depolarization), synaptic NMDA receptors function as coincidence detectors, and this characteristic is thought to be central to their role in learning and memory. NMDA receptors are also involved in the development of chronic pain, perhaps due to similar mechanisms underlying synaptic

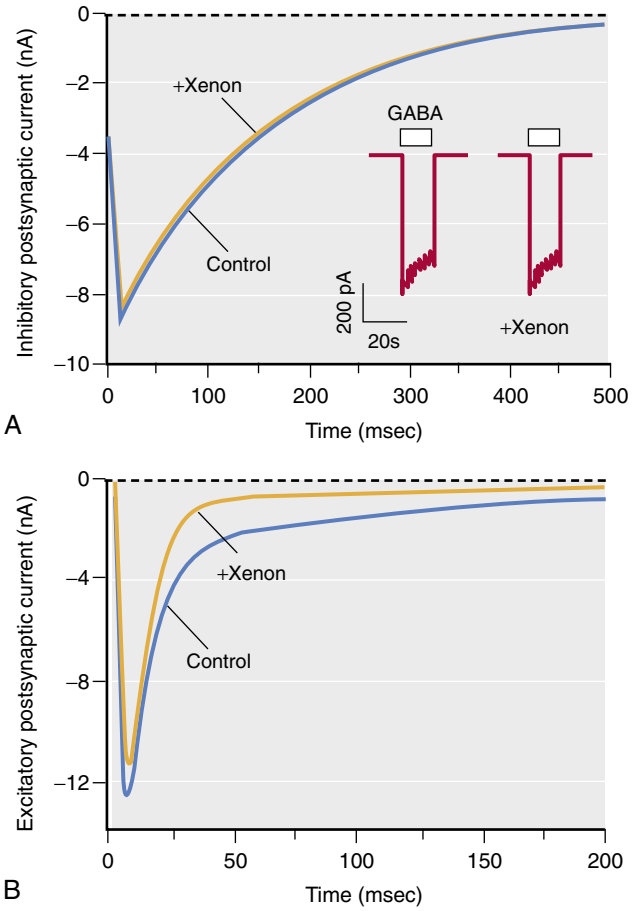

Figure 20-8 The actions of xenon on inhibitory GABAergic and excitatory glutamatergic synapses in cultured rat hippocampal neurons. Xenon (3.4 mM, ~1 MAC) has no significant effect on the inhibitory postsynaptic current (**A**) but greatly depresses the excitatory glutamatergic synaptic current, almost exclusively the slow NMDA receptor-mediated component of the current (**B**). In contrast, the principal effects of ~1 MAC isoflurane are a prolongation in the inhibitory current decay and a reduction in excitatory current peak height with little change in time course (not shown, see Fig. 20-10). (*Reprinted in modified form by permission from de Sousa SLM, et al: Contrasting synaptic activity of the inhalational general anesthetics isoflurane and xenon. Anesthesiology 92:1055-1066, 2000.*)

plasticity, and in ischemia-induced excitotoxicity by virtue of their capacity to allow entry of the ubiquitous intracellular signal Ca^{2+} on activation. The nonhalogenated inhaled anesthetics xenon, nitrous oxide, and cyclopropane, as well as the intravenous anesthetic ketamine, have minimal effects on $GABA_A$ receptors but depress excitatory glutamatergic synaptic transmission postsynaptically via NMDA glutamate receptor blockade (Figs. 20-7 and 20-8).[70,71,127] Volatile anesthetics can also inhibit isolated NMDA receptors at higher concentrations.[128] Along with presynaptic inhibition of glutamate release, this might contribute to their depression of NMDA receptor–mediated excitatory transmission.

A second class of ionotropic glutamate receptors includes the non-NMDA receptors, which are subdivided into AMPA and kainate receptors based again on their sensitivities to selective exogenous agonists.[126] Inhaled anesthetics only weakly inhibit AMPA receptors, so this action is unlikely to be important in their actions.[129] Interestingly, kainate receptors are enhanced by inhaled anesthetics, but this is unlikely to be involved in immobility because MAC is not altered in mice deficient in the GluR6 receptor subunit.[130] Most evidence suggests that the principal mechanism for depression of glutamatergic transmission by volatile anesthetics is presynaptic, with minor contributions from postsynaptic receptor blockade[117,131-133] (see "Cellular Mechanisms").

Voltage-Gated and Other Ion Channels

Na^+ Channels

Voltage-gated Na^+ channels are critical to axonal conduction, synaptic integration, and neuronal excitability. In contrast to findings in invertebrate giant axons,[134] axonal conduction in small (0.1-0.2 μm) unmyelinated hippocampal axons is depressed by volatile anesthetics[135,136] and small reductions in preterminal action potential amplitude significantly depress transmitter release and hence postsynaptic responses at a mammalian synapse.[137]

Heterologously expressed mammalian voltage-gated Na^+ channels are sensitive to clinically relevant concentrations of volatile anesthetics. The Na^+ channel family consists of nine homologous pore-forming α-subunits with distinct cellular and subcellular distributions.[138] Isoflurane and other volatile anesthetics inhibit the major mammalian Na^+ channel isoforms, including neuronal ($Na_v1.2$), skeletal muscle ($Na_v1.4$), and cardiac ($Na_v1.5$) channels, but the peripheral isoform $Na_v1.8$ is apparently resistant.[139] Volatile anesthetics, but not nonimmobilizers, also inhibit native neuronal and nerve terminal Na^+ channels,[140-143] lending support to the notion that Na^+ channel blockade contributes to the depression of synaptic neurotransmitter release.[143] In contrast, xenon has no detectable effect on Na^+, Ca^{2+}, or K^+ channels in isolated cardiomyocytes.[92] The recent demonstration that NaChBac, a prokaryotic homolog of voltage-gated Na^+ channels, is also inhibited by volatile anesthetics opens the way for structure-function studies of these channels.[141]

Ca^{2+} Channels

Multiple cellular functions depend on the tightly controlled concentration of intracellular free Ca^{2+} ($[Ca^{2+}]_i$), which is determined by the integrated activity of voltage-gated Ca^{2+} channels, capacitative Ca^{2+} channels, plasma membrane and sarco/endo-plasmic reticulum Ca^{2+}-ATPases (pumps), Na^+/Ca^{2+} exchangers, and mitochondrial Ca^{2+} sequestration. Alteration of any of these mechanisms by anesthetics could affect the many cellular processes regulated by the second messenger actions of Ca^{2+}, including synaptic transmission, gene expression, cytotoxicity, and muscle excitation-contraction coupling. Excitable cells translate their electrical activity into action by Ca^{2+} fluxes mediated primarily by voltage-gated Ca^{2+} channels in the plasma membrane. Distinct Ca^{2+} subtypes are expressed in various cells and tissues and are classified pharmacologically and functionally by the degree of depolarization required to gate the channel, such as low voltage–activated (LVA; T-type) and high voltage–activated (HVA; L-, N-, R-, and P/Q-type) channels. More recently, the molecular identity of their pore-forming α-subunits has been used for classification.[144] There is convincing evidence that volatile anesthetics inhibit certain Ca^{2+} channel isoforms but not others (for review see reference 145).

Inhibition of the presynaptic voltage-gated Ca^{2+} channels coupled to transmitter release has been proposed as a mechanism by which volatile anesthetics reduce excitatory transmission.[146]

Indeed, N-type ($Ca_v2.2$) and P-type ($Ca_v2.1$) channels, which mediate Ca^{2+} entry coupled to neurotransmitter release, are modestly sensitive to volatile anesthetics[147,148] but not in all neuron types,[149] suggesting the importance of auxiliary subunits, post-translation modification, or other potential modulators of anesthetic sensitivity. A modest contribution of R-type Ca^{2+} channels ($Ca_v2.3$) to anesthesia is suggested by its sensitivity to volatile anesthetics and a small increase in MAC produced by its genetic deletion in mice.[150] T-type Ca^{2+} channels are particularly sensitive to volatile anesthetics[151] and nitrous oxide.[152] However, mutant mice lacking a major neuronal T-type Ca^{2+} channel isoform ($Ca_v3.1$) have normal volatile anesthetic sensitivity, although the onset of anesthesia is delayed.[153] Thus, the role that inhibition of these or other Ca^{2+} channels plays in the CNS effects of inhaled anesthetics is unclear.

By contrast, a role for Ca^{2+} channel inhibition in the negative inotropic effects of volatile anesthetics, prominent at higher doses, is well established. The force of myocardial contraction is determined by the magnitude of cytosolic Ca^{2+} increase after electrical excitation, the responsiveness of the contractile proteins to Ca^{2+}, and sarcomere length. Negative inotropic effects of volatile anesthetics are mediated by reductions in Ca^{2+} availability, Ca^{2+} sensitivity of the contractile proteins, and the rate of cytosolic Ca^{2+} clearance. Volatile anesthetics reduce the Ca^{2+} transient and shorten action potential duration in cardiomyocytes primarily by inhibiting L-type ($Ca_v1.2$) Ca^{2+} currents, resulting in a negative inotropic effect and arrhythmogenicity.[90,99,154] In contrast, xenon does not depress myocardial function or inhibit L-type Ca^{2+}, Na^+, or K^+ currents in isolated cardiomyocytes.[91,92] Inhibition of transsarcolemmal Ca^{2+} influx through cardiac L-type Ca^{2+} channels plays a major role in the negative inotropic effects of volatile anesthetics, greatest for halothane, along with contributions from effects on myofilament Ca^{2+} sensitivity and sarcolemmal Ca^{2+} release.[99,155]

In contrast to voltage-gated Ca^{2+} channels that regulate the influx of extracellular Ca^{2+}, intracellular Ca^{2+} channels regulate Ca^{2+} release from intracellular stores, particularly the endoplasmic reticulum (ER) and sarcoplasmic reticulum (SR). These include 1,4,5-trisphosphate receptors (IP_3Rs), regulated by the second messenger IP_3, and ryanodine receptors (RyRs), which mediate the rapid release of intracellular Ca^{2+} critical to excitation-contraction coupling in muscle. Volatile anesthetic-induced Ca^{2+} leak occurs via both IP_3R and RyR channels, which leads to depletion of intracellular Ca^{2+} stores from the SR and ER. This blunts changes in intracellular Ca^{2+} in response to stimulation and also contributes to the smooth muscle–relaxing properties of volatile anesthetics that underlie bronchodilation and vasodilation.[156] Malignant hyperthermia susceptibility is a pharmacogenetic disorder that manifests as a potentially fatal hypermetabolic crisis triggered by volatile anesthetics, particularly halothane. It is often associated with mutations in RyR1 and the physically associated L-type Ca^{2+} channel ($Ca_v1.1$) that functions as the voltage sensor.[157] Volatile anesthetics activate the abnormal RyRs, resulting in uncontrolled intracellular Ca^{2+} release, muscle contraction, and metabolic activity[158] (see also Chapter 37.)

K^+ Channels and HCN Channels

Potassium (K^+) channels are an extremely diverse ion channel family noted for their varied modes of activation. They regulate electrical excitability, muscle contractility, and neurotransmitter release and are important in determining the input resistance and in driving repolarization and thus determine excitability and action potential duration. Given the large diversity in K^+ channel structure, function, and anesthetic sensitivity, it is not surprising that there is considerable diversity in their sensitivity and response to inhaled anesthetics[159]: from relatively insensitive (voltage-gated K^+ channels $K_v1.1$, K_v3)[160] to sensitive (some members of the two-pore domain K^+ channels [K_{2P}] family), resulting in either inhibition, activation, or no effect on K^+ currents.

Volatile anesthetic activation of certain "leak" K^+ channels was first observed in the snail *Lymnaea,*[161] although the molecular identity of the affected ion channels was unknown. Activation of K_{2P} channels by volatile and gaseous anesthetics, including xenon, nitrous oxide, and cyclopropane, was subsequently observed in mammals.[162] Increased K^+ conductance can hyperpolarize neurons, reducing responsiveness to excitatory synaptic input and altering network synchrony. Targeted deletion of the TASK-1, TASK-3, and TREK-1 K_{2P} channels in mice reduces sensitivity to immobilization by volatile anesthetics, implicating these channels as anesthetic targets in vivo.[32-34] Other members of this large family of K^+ channels are also sensitive to xenon and volatile anesthetics.[163]

The recognition that inherited channelopathies are arrhythmogenic and constitute an important contributor to sudden cardiac death,[164] particularly in young children,[165] highlights the importance of analyzing anesthetic modulation of cardiac ion channels. Recombinant HERG (human ether-a-go-go related) channels are moderately inhibited by halothane, and their depression likely contributes to arrhythmogenic effects of volatile anesthetics.[99,166] HERG channels are also involved in acquired (drug-induced) and inherited long QT syndrome. Cardiac inward-rectifying (K_{IR}), voltage-gated (K_v), and Ca^{2+}-activated K^+ channels are generally relatively insensitive to clinical concentrations of volatile anesthetics and xenon.[91,99,167] In contrast, there is considerable evidence that volatile anesthetics and xenon activate cardiac mitochondrial and sarcolemmal K_{ATP} channels,[100] an effect that plays a critical role in anesthetic preconditioning. Direct electrophysiologic effects of anesthetics with preconditioning properties have been demonstrated on both mitochondrial and sarcolemmal K_{ATP} channels, although the precise mechanisms remain to be clarified.

Volatile anesthetics also inhibit HCN "pacemaker" channels, reducing the rate of rise of pacemaker potentials and the bursting frequency of certain neurons showing autorhythmicity. They decrease I_h conductance in neurons[168] and modulate recombinant HCN1 and HCN2 channel isoforms at clinically relevant concentrations.[169] Because HCN channels contribute to resting membrane potential, control action potential firing, dendritic integration, neuronal automaticity, and temporal summation, and determine periodicity and synchronization of oscillations in many neuronal networks,[170] the anesthetic modulation of these channels could play an important role in anesthetic effects on neuronal integrative functions.

Intracellular Signaling Mechanisms

Cell signaling mechanisms are critical to all phases of organ function and have been attractive targets for the broad effects of general anesthetics. Anesthetics have poorly understood actions on intracellular cell signaling pathways, which include processes downstream from cell surface receptors and ion channels, such

as effects of second messengers, protein phosphorylation pathways, and other regulatory mechanisms.[171]

G Protein–Coupled Receptors

A variety of signals, including hormones, neurotransmitters, cytokines, pheromones, odorants, and photons, produce their intracellular actions by interactions with metabotropic receptors that activate heterotrimeric guanine nucleotide (GTP)-binding proteins (G proteins). In contrast to the ionotropic receptors that directly couple to ion-selective channels, G proteins act as indirect molecular switches to relay information from activated plasma membrane receptors to appropriate intracellular targets. Heterotrimeric G proteins consist of a large α-subunit and a smaller β/γ-subunit dimer, each expressed as multiple isoforms with distinct properties and downstream targets. G proteins regulate a plethora of downstream effectors to control the levels of cytosolic second messengers such as Ca^{2+}, cyclic adenosine monophosphate (cAMP), and inositol triphosphate (IP_3). These, in turn, regulate effector proteins such as ion channels and enzymes, either directly or via second messenger–regulated protein phosphorylation pathways. Drugs that act through G protein-coupled receptors (GPCRs), such as agonists for μ opioid and α_2-adrenergic receptors, can affect anesthetic sensitivity (reduce MAC). Inhaled anesthetics can also directly affect signaling via GPCRs.[172] For example, volatile anesthetics activate multiple rat olfactory GPCRs in vivo in a receptor- and agent-selective manner.[173] Analogous effects on related GPCRs more relevant to critical anesthetic end points are possible but remain to be demonstrated. The observation that both volatile anesthetics and nonimmobilizers inhibit mGluR5 glutamate receptors, $5\text{-}HT_{2A}$ serotonin receptors, and muscarinic acetylcholine receptors suggest that these GPCR effects do not contribute to anesthetic immobilization.[174-176]

Protein Phosphorylation

Phosphorylation of proteins on specific serine, threonine, or tyrosine hydroxyl groups, a post-translational modification involved in the regulation of many anesthetic-sensitive receptors and ion channels, is pivotal to synaptic plasticity (e.g., LTP). Phosphorylation is controlled by the balance of activity between protein kinases and phosphatases, several of which are plausible anesthetic targets. The protein kinase C (PKC) family of multifunctional protein kinases is activated by the lipid signaling molecule diacylglycerol and is involved in the regulation of many ion channels and receptors. Halothane[177] and sevoflurane[178] enhance the activity of some PKC isoforms and stimulate phosphorylation of specific PKC substrates. Structural studies have identified a potential binding site in the diacylglycerol binding domain of PKCδ, consistent with the ability of certain anesthetics to mimic this natural regulator by binding to the activating site.[179] A specific role for a direct pharmacologically relevant effect mediated by anesthetic activation of PKC or of any other kinase has yet to be demonstrated. Intrathecal injection of isoform-specific inhibitors of PKC does not affect sensitivity to halothane in vivo.[180] Knockout mice lacking the PKCγ isoform show normal sensitivity to halothane and desflurane while isoflurane MAC was increased,[181] suggesting that PKC is not critical to volatile anesthetic immobilization.

An important role for effects of volatile anesthetics and xenon on cell signaling mechanisms has been discovered for anesthetic-induced preconditioning of heart (see Chapter 23) and brain against ischemic damage.[83,87,102] Anesthetic-induced and ischemic cardiac preconditioning share critical signaling mechanisms, including activation of multiple GPCRs (e.g., adenosine, opioid, adrenergic) and protein kinases (e.g., src kinase, PKCδ, PKCε, Akt, mitogen-activated protein kinases [MAPKs]) and their downstream targets, particularly sarcolemmal and/or mitochondrial K_{ATP} channels, possibly initiated by changes in reactive oxygen species as the critical second messenger.[88] Volatile anesthetics and xenon share cardioprotective and neuroprotective effects involving these signaling pathways.[102]

The effects of anesthetics on the phosphorylation of individual residues in specific substrates can be studied using phosphorylation state-specific antibodies that are able to detect the phosphorylated form of kinase substrates. A comparison of the effects of three mechanistically diverse anesthetics (isoflurane, propofol, and ketamine) on critical intracellular protein phosphorylation signaling pathways that are known to integrate multiple second messenger systems reveals both shared and agent-specific actions in vivo.[182] All three anesthetics reduce phosphorylation of activating sites on NMDA (S897) and AMPA (S831) glutamate receptors and of the downstream extracellular signal-regulated kinase ERK2, which are involved in synaptic plasticity, consistent with depression of normal glutamatergic synaptic transmission in the anesthetized mouse cerebral cortex. This effect is somewhat selective in that several other PKA substrates examined are not affected, indicating a substrate-specific effect rather than a general inhibition of PKA activity.[183] Additional studies will be required to determine which anesthetic effects on kinase pathways represent direct effects, as occurs with PKC, and which are indirect due to anesthetic-induced alterations in signaling molecules known to regulate protein kinase and phosphatase activity such as Ca^{2+} and other second messengers.

Gene Expression

The ability of general anesthetics to alter gene expression in the brain was first observed for the highly reactive acute early genes c-*fos* and c-*jun*.[184] Anesthetic effects on gene expression have since been observed for multiple anesthetics and organs.[185] In the hippocampus of aged rats, changes in gene expression persisted for up to 2 days in rats exposed to isoflurane and nitrous oxide,[186] and changes in protein expression have been observed 3 days after exposure to desflurane.[187] The significance of these changes in gene and protein expression persisting after recovery from the classic signs of anesthesia remains to be established (see reference 78 for review).

Cellular Mechanisms

Neuronal Excitability

Neuronal excitability is determined by resting membrane potential, threshold for action potential initiation, and input resistance (an indication of overall channel activity), which can differ between compartments within an individual neuron owing to subcellular specializations (e.g., soma versus dendrite). High concentrations of volatile anesthetics hyperpolarize hippocampal pyramidal cells in slice preparations by less than 5 mV at more than five times MAC.[188,189] At relevant concentrations, neither resting membrane potential nor input resistance is significantly affected in hippocampal[190] or spinal cord neurons.[191] Anesthetic

effects on the firing properties of hippocampal neurons are complex: increased or decreased thresholds (for enflurane) have been reported.[190,192] By contrast, thalamic neurons hyperpolarize in the presence of isoflurane and are less likely to fire action potentials due to a decrease in input resistance (increased shunting), attributed to increased K^+ conductance.[193] Similar effects are observed in hypoglossal motor neurons and neurons from the locus coeruleus, where a TASK-type K_{2P} channel has been causally implicated.[115]

A role for $GABA_A$ receptors located at extrasynaptic sites has been suggested recently for volatile anesthetic effects (Fig. 20-9). Extrasynaptic $GABA_A$ receptors, which differ from synaptic receptors in their subunit composition, mediate tonic inhibition (as opposed to phasic inhibition mediated by synaptic $GABA_A$ receptors) and are remarkably sensitive to many general anesthetics. Extrasynaptic $GABA_A$ receptors have a high affinity for GABA, desensitize slowly, and are tonically exposed to low ambient GABA concentrations,[194] at which the potentiating effect of anesthetics is most significant. The effects of anesthetics on tonic inhibition have been characterized in the hippocampus, which is critically involved in learning and memory. Hippocampal neurons generate a robust tonic current via activation of α_5-subunit–containing $GABA_A$ receptors[195-199] that is highly sensitive to etomidate, propofol, midazolam, and isoflurane. $GABA_A$ receptors containing the α_5-subunit are highly sensitive to low concentrations of propofol and isoflurane that produce amnesia but not unconsciousness. Thus, these receptors provide a potential substrate for the amnesic properties of anesthetics.

Presynaptic versus Postsynaptic Effects on Synaptic Transmission

General anesthetics have potent and specific effects on synaptic transmission, including presynaptic actions (by altering transmitter release) and postsynaptic actions (by altering the responses of neurons to specific transmitters). The relative contributions of presynaptic versus postsynaptic anesthetic effects on synaptic transmission have been difficult to resolve, probably because the effects are transmitter- and synapse-specific.[117] The net effect of anesthetics on synaptic transmission is determined by the relative magnitude and direction of both their presynaptic and postsynaptic effects.

Synaptic excitation is decreased by volatile anesthetics (Fig. 20-10). Experiments in various slice preparations indicate that reduced excitation is primarily due to presynaptic mechanisms (Fig. 20-11).[131,191,200-202] A postsynaptic mechanism is also involved because neuronal excitation to directly applied glutamate is reduced to some degree.[202-204] Volatile anesthetics have inconsistent effects on cloned AMPA or NMDA glutamate receptors but potentiate kainate receptors,[112,205-207] which is consistent with a predominantly presynaptic mechanism for inhibition of glutamatergic synapses, whereas the effects of the nonhalogenated inhaled anesthetics (xenon, nitrous oxide, cyclopropane) are mediated primarily by inhibition of postsynaptic NMDA receptors (see earlier). In contrast, augmentation of GABAergic inhibition by most general anesthetics is mediated both by presynaptic and postsynaptic mechanisms. Enhancement of postsynaptic and extrasynaptic $GABA_A$ receptors is well recognized.[113] Remarkably, however, volatile anesthetics also increase spontaneous GABA release and inhibitory postsynaptic current (IPSC) frequency,[208-212] that is, their presynaptic effects at GABAergic terminals are distinct from those at glutamatergic synapses.

The mechanisms for the presynaptic effects of inhaled anesthetics, like those for their postsynaptic effects, are complex and involve multiple targets. Although a synapse-specific contribution of presynaptic Ca^{2+} channels is likely, presynaptic Na^+ channels are more sensitive than the Ca^{2+} channels coupled to glutamate release. This is consistent with observations that the predominant Ca^{2+} channel coupled to neurotransmitter release at hippocampal glutamatergic synapses (P/Q-type) is insensitive to isoflurane.[149] Other presynaptic mechanisms have been proposed, including actions on the vesicle fusion process as demonstrated in the model organism *Caenorhabditis elegans.*[213,214] However, isoflurane effects on exocytosis in rat hippocampal neurons occur primarily upstream of vesicle fusion[137,245] (see reference 117 for review).

The general effects of inhaled anesthetics are to increase inhibitory synaptic transmission and to inhibit excitatory synaptic transmission (Fig. 20-12). The relative importance of anesthetic effects on excitatory versus inhibitory synaptic transmission, and the mechanisms of these effects, are likely to differ for different anesthetics and for specific synapses and networks.[105,215] This concept extends to other putative targets and mechanisms and is incorporated in "agent-specific multiple-site" hypotheses of anesthesia.[215,216]

Simple Circuits and Complex Networks

Simple Circuit Phenomena

To reach a mechanistic understanding of phenomena involving multiple elements of a complex circuit, anatomically reduced (in vitro) or physiologically simplified (in vivo) preparations have been complemented by models with simulations (in silico). These approaches will be essential for integrating reductionist observations of the multiple molecular effects of anesthetics into functional models relevant to behavioral end points. Anatomically, simplified preparations containing native circuitry typically consist of isolated tissue slices. Anesthetic effects have been studied in acute brain slice preparations from various regions of the CNS (hippocampus, amygdala, cortex, thalamus, brainstem, spinal cord). Acute slices preserve native connections but usually lack natural inputs and outputs. Slices from developing mammalian brain can be cultured in vitro. These "organotypic slice cultures" preserve a high degree of synaptic connectivity and display spontaneous network activity, typically absent from acute slices. Physiologically, simplified preparations involve phenomena (typically evoked responses) with *relatively* well understood circuitry. Examples include paired-pulse depression (PPD), synaptic plasticity (long-term potentiation [LTP] and long-term depression [LTD]), and certain sensory-evoked responses. Computer models and simulations can assist in generating hypotheses for experimental testing and test hypotheses based on experimental data.

Synaptic Plasticity

Paired-pulse depression (PPD) and paired-pulse facilitation (PPF) are examples of short-term plasticity in response to exter-

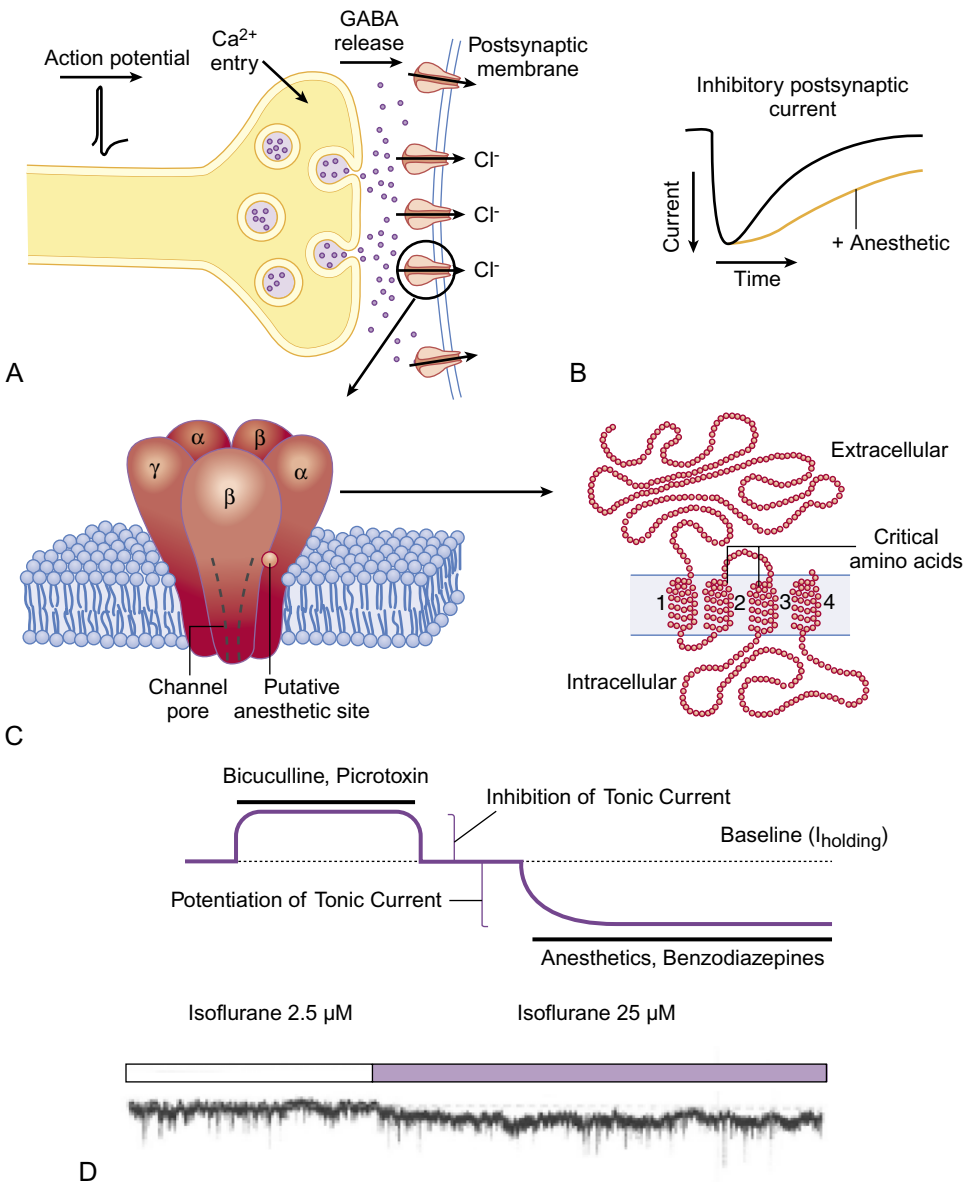

Figure 20-9 Synaptic and extrasynaptic $GABA_A$ receptors are targets for inhaled anesthetics. **A,** On binding of GABA (γ-aminobutyric acid) to the $GABA_A$ receptor, its chloride-permeable channel opens, leading to hyperpolarization. Volatile anesthetics have a relatively low potency but high efficacy at synaptic $GABA_A$ receptors and a high potency and low efficacy at extrasynaptic $GABA_A$ receptors. **B,** General anesthetics prolong channel opening and increase postsynaptic inhibition. The cartoon illustrates the prolongation of miniature inhibitory synaptic currents (mIPSCs) by the slowing of current decay. **C,** A pentameric $GABA_A$ receptor complex in the lipid bilayer membrane (*left*), with a blow-up of a single subunit showing the location of residues critical to anesthetic efficacy in the second and third transmembrane dornains (*right*). **D,** A tonic inhibitory conductance is revealed by the application of a $GABA_A$ receptor antagonist (bicuculline or picrotoxin), as shown by the upward shift in the baseline current. Anesthetics and benzodiazepines increase the tonic conductance as indicated by the inward shift in the current. (*Modified from Hemmings HC Jr, Akabas MH, Goldstein PA, et al: Emerging molecular mechanisms of general anesthetic action. Trends Pharmacol Sci 26:503-510, 2005.*)

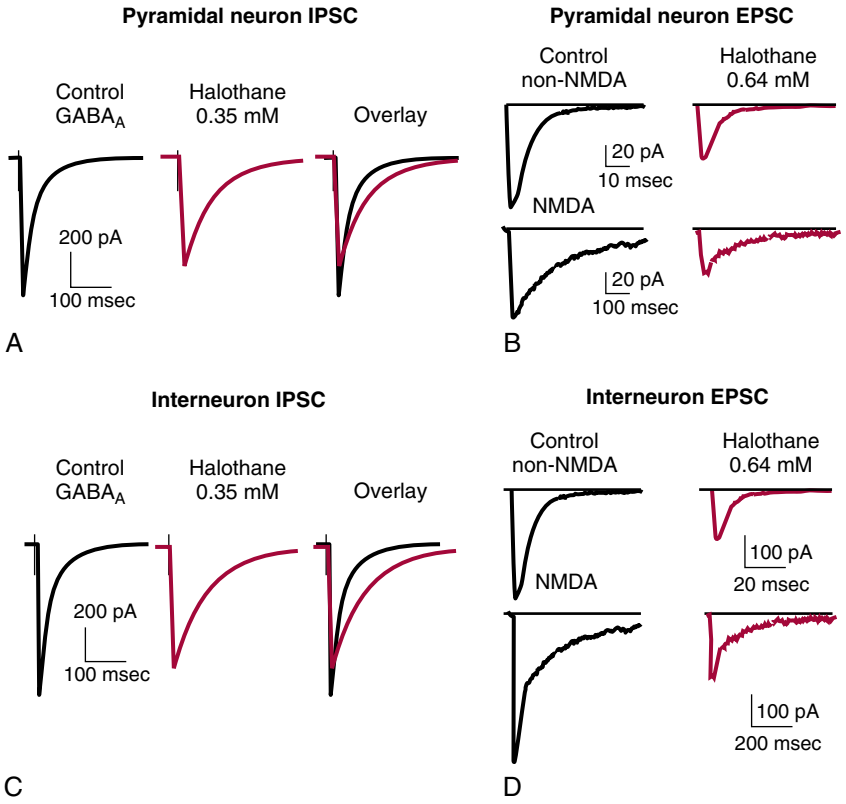

Figure 20-10 Halogenated anesthetics enhance inhibitory and depress excitatory synaptic transmission. Halothane slows the decay of $GABA_A$ receptor–mediated postsynaptic inhibitory currents (IPSCs, **A**) and depresses the amplitude of glutamatergic excitatory postsynaptic currents without affecting the decay (EPSC, **B**, **D**) in hippocampal pyramidal neurons (**A**, **B**) and interneurons (**C**, **D**). *(Panels A and C redrawn with permission from Nishikawa K, MacIver MB: Membrane and synaptic actions of halothane on rat hippocampal pyramidal neurons and inhibitory interneurons. J Neurosci 20:5915-5923, 2000. Panels B and D redrawn with permission from Perouansky M, et al: Effects of halothane on glutamate receptor-mediated excitatory postsynaptic currents: A patch-clamp study in adult mouse hippocampal slices. Anesthesiology 83:109-119, 1995.)*

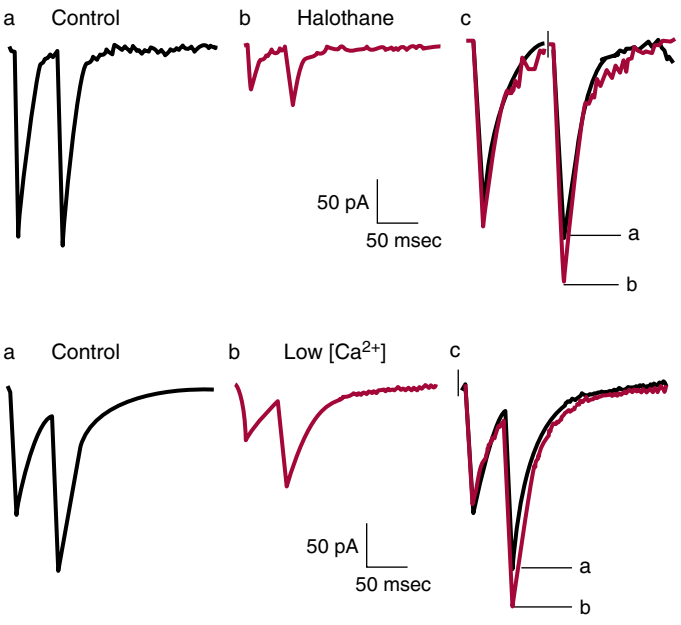

Figure 20-11 Excitatory synaptic transmission is depressed by a presynaptic action. In the paired-pulse facilitation paradigm, halothane (0.64 mM; ~2 MAC) increases the amplitude of the second paired response, an effect similar to that produced by reducing extracellular Ca^{2+} (low Ca^{2+}), indicating a presynaptic site of action. Responses to exogenous, iontophoretically applied AMPA or NMDA are much less sensitive than the presynaptic reduction in transmitter release (not shown). *(Redrawn with permission from Kirson ED, et al: Presynaptic and postsynaptic actions of halothane at glutamatergic synapses in the mouse hippocampus. Br J Pharmacol 124:1607-1614, 1998.)*

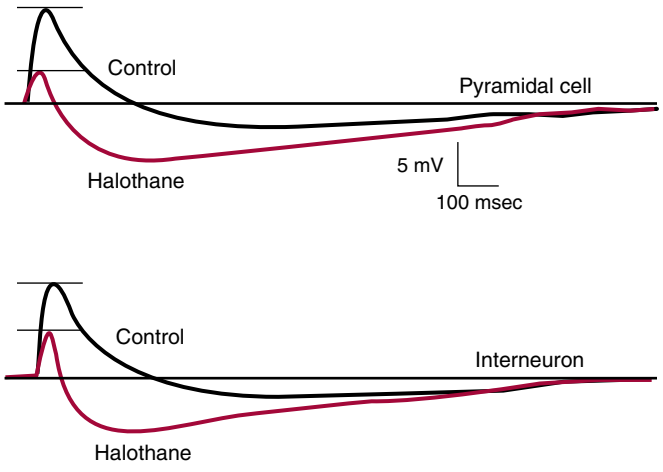

Figure 20-12 Anesthetics affect excitation and inhibition simultaneously. Halothane depresses the excitatory depolarization and augments the inhibitory hyperpolarization in both hippocampal pyramidal cells and interneurons. The net result will depend on the underlying circuitry and its function. *(Redrawn with permission form Nishikawa K, MacIver MB: Membrane and synaptic actions of halothane on rat hippocampal pyramidal neurons and inhibitory interneurons. J Neurosci 20:5915-5923, 2000.)*

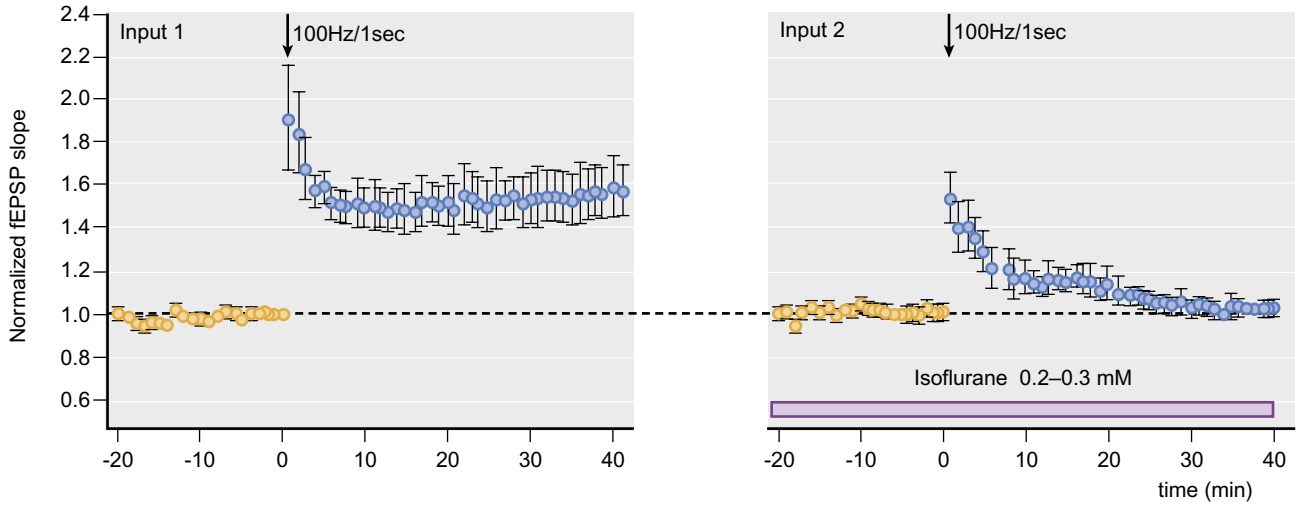

Figure 20-13 Isoflurane blocks the induction of synaptic plasticity (an in-vitro model of learning and memory). Long-term potentiation (an increase in synaptic strength) in hippocampal slices evoked by tetanic stimulation of excitatory synapses is blocked by 200-300 μM of isoflurane. (*Redrawn with permission from Simon W, et al: Isoflurane blocks synaptic plasticity in the mouse hippocampus. Anesthesiology 94:1058-1065, 2001.*)

nal stimulation. Synaptic inhibition is prolonged by volatile anesthetics in vivo[217] and in vitro[218], in general agreement with the notion that anesthetics enhance functional inhibition in the CNS. Enhancement of PPF has been attributed to the presynaptic depressant effect of volatile agents (see Fig. 20-11).[131,201]

LTP (a cellular model of learning and memory) consists of use-dependent strengthening of excitatory synaptic connections mediated by glutamate receptors (see Chapter 11).[219] The few experiments investigating volatile anesthetic effects on LTP have yielded somewhat inconsistent results: halothane, enflurane, and isoflurane do not block LTP induction in vivo, whereas ketamine does.[217] By contrast, isoflurane blocks LTP in the hippocampal slice by enhancing $GABA_A$ receptor–mediated inhibition (Fig. 20-13).[220] LTD, a use-dependent weakening of excitatory connections that is effectively a homeostatic counterpart of LTP, is also blocked by isoflurane.[220] The discrepancy between these findings in vivo and in vitro could reflect differences in the balance between excitatory and inhibitory circuitry activated by the electrical stimuli employed. Etomidate, at amnesic concentrations, blocks LTP by enhancing specific subtypes of $GABA_A$ receptors,[199] whereas ketamine blocks LTP in urethane-anesthetized animals by blocking NMDA receptors.[221,222]

Spontaneously Active Circuits

Spontaneous neuronal activity is decreased by a range of volatile anesthetics both in vivo and in cortical brain slices. This effect is largely $GABA_A$ receptor dependent and marked even at low "sedative" concentrations.[77] Because the cultured slice lacks subcortical input, these results suggest that volatile anesthetics can cause some effects (e.g., sedation) via direct cortical action. However, changes in raw neuronal firing rates might not be a precise quantitative measure of higher cognitive function. Anesthetic effects have also been tested on the circuitry underlying locomotion, a well-studied central pattern generator. Results with isoflurane in the in vitro lamprey spinal cord preparation support the spinal cord as the primary target for volatile anesthetic-induced immobility.[223]

Rhythms and Simulations

Brains perpetually generate complex electrical rhythms that range in frequency from fractions to hundreds of Hertz. Although their physiologic roles are not clear, the prevailing notion is that they reflect, subserve, or constitute fundamental higher-order processing in mammalian brains. Their modulation by anesthetics therefore deserves scrutiny. Two rhythms that have been investigated both in vitro and in vivo in the context of anesthetic mechanisms are γ-rhythms and θ-rhythms.

γ–Rhythms

Isoflurane slows the frequency of evoked γ-oscillations (30-90 Hz, also known as "40 Hz" rhythms) in humans.[224] Studies of γ-oscillations in vitro suggest that their frequency depends on the time constant of decay of $GABA_A$ receptor–mediated synaptic currents in inhibitory networks.[225] Isoflurane slows γ-rhythms in hippocampal[226] and neocortical brain slices[227] to a comparable degree as in humans,[224] providing a tentative link between receptor and circuit-level effects. However, the interaction between anesthetics and behaviorally relevant network effects is unlikely to be unitary, because flash-evoked γ-oscillations in the primary visual cortex are not affected by inhaled agents[54] whereas feedback information transfer at γ frequencies between the visual and frontal cortices is disrupted.[228]

θ-Rhythms

θ-rhythms, present in various cortical structures, are most prominent in the hippocampus where they signal its "online state." They are associated with sensorimotor and mnemonic functions in awake, behaving animals.[229] One component of the θ-rhythm (type I or atropine-resistant) can be affected by amnesic concentrations of isoflurane as well as by the amnestic nonimmobilizer F6,[56] indicating a potential network-level signature effect for anesthetic-induced amnesia. Type II θ-rhythm (atropine-sensitive) can be evoked under anesthesia and is slowed and potentiated by halothane.[230] The γ- and θ-rhythms are interlinked in complex

ways, but the nature of their modulation by anesthetics as well as its relevance are far from clear.

Models and Simulations

On the atomic scale, modeling the interaction of anesthetic molecules with target-like proteins has defined "binding motifs" that characterize the amphiphilic binding cavities for anesthetic molecules (see earlier, "Identification of Molecular Sites of Anesthetic Action").[107] Modeling anesthetic interaction with firefly luciferase using gaussian and anisotropic network modeling suggests that anesthetics act by disrupting the modes of motion essential for protein function.[231]

On the macroscopic scale, computer simulations can provide an integrated picture of the modulation of dynamic neuronal and network activity. Simulations based on two different strategies have been published in anesthesia research. A "bottom-up," neuron-by-neuron approach is based on computational models of individual neurons, known anesthetic effects on intrinsic and synaptic membrane conductances, and simple network models. Computer simulations of anesthetic effects on integrated outputs can be generated (e.g., the firing of pacemaker neurons).[232] These models obviously rely on the accuracy of the derived characteristics of real neurons and networks, and the scale of simulations is limited by the complexity of its elements. An alternative is a "top-down" approach such as mean-field modeling in which individual accuracy is sacrificed in favor of global dynamics. Global cortical phenomena, such as anesthetic-induced seizures,[233] are modeled as phase transitions based on mean interactions between populations of averaged neurons (analogous to the EEG signal that also averages the signals of neuronal populations). This approach can be extended to other global cortical phenomena such as consciousness.[234] Neuronal modeling and computer simulations will likely gain importance in the future as bridges between theoretical and experimental studies of anesthesia.

Research Strategies for the Future

The search for anesthetic mechanisms is driven by advances in the basic sciences. Some strategies that should facilitate understanding of anesthetic mechanisms include use of agonists/antagonists in vivo, nonanesthetics/nonimmobilizers, transgenic animals, and high-resolution imaging of the functioning brain.

Pharmacologic

Agonists/Antagonists and Experimental Anesthetics

Use of receptor-specific agonists and antagonists provides a pharmacologic approach to bridging in-vitro with in-vivo studies. A receptor implicated in a specific end point (e.g., immobility) is selected according to the criteria presented earlier, for example the strychnine-sensitive glycine receptor (GlyR). A contribution of spinal GlyRs to isoflurane-induced immobility is indicated if a selective GlyR antagonist applied to the spinal cord in vivo affects immobilization by isoflurane more than immobilization by an anesthetic that is inactive at GlyRs in vitro. This approach did not yield conclusive results for the roles of $GABA_A$ and GlyR for immobilization,[27,235,236] probably owing to the intricacies of drug-receptor interactions on different levels of integration in complex networks like the spinal cord. The same pharmacologic strategy did exclude an important role for NMDA receptor block in the immobilizing action of volatile anesthetics.[28] A complementary pharmacologic approach that employs experimental anesthetics, which are structurally diverse compounds that inhibit NMDA receptors in vitro with different potencies, supports the conclusion that NMDA receptor blockade does not contribute significantly to immobility by conventional volatile anesthetics.[28] A refinement of this strategy involves the anatomically discrete application of drugs to nuclei with known function. Thus, the tuberomammillary nucleus (part of the sleep pathway) has been suggested to mediate the sedative component of anesthesia for some intravenous anesthetics (e.g., propofol).[22] A discrete "general anesthesia site" for GABAergic drugs in the mesopontine tegmentum has also been proposed based on this strategy.[21,234]

Nonimmobilizers

Nonimmobilizers are compounds with physicochemical characteristics similar to those of conventional inhaled anesthetics but predicted anesthetizing concentrations (based on their lipid solubility and the Meyer-Overton correlation: MAC_{pred}) of these drugs do not induce immobility (Fig. 20-14).[8] Initially termed *nonanesthetics,* the terminology was revised when it was discovered that they cause amnesia at similar MAC_{pred} fractions as classic volatile anesthetics.[67] If a molecular or cellular process is affected in

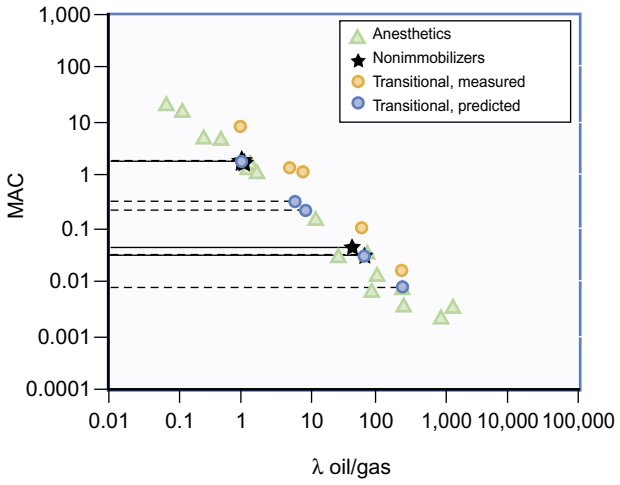

Figure 20-14 Nonimmobilizers disobey the Meyer-Overton correlation. Lipid solubility correlates well with MAC for conventional inhaled anesthetics (*green triangles*), but underestimates experimentally determined MAC for transitional compounds (*orange circles*). *Blue circles* and *dashed drop lines* show MAC values predicted based on lipid solubility for transitional compounds, and *black stars* with *solid drop lines* show predicted MAC values based on lipid solubility for nonimmobilizers. Note that predicted MAC is lower than experimentally determined MAC for transitional compounds, while it can only be calculated for nonimmobilizers, because these drugs do not immobilize at experimentally testable concentrations. MAC values (in volume %) determined in rodents. *(Data for transitional compounds and nonimmobilizers from Koblin DD, et al: Polyhalogenated and perfluorinated compounds that disobey the Meyer-Overton hypothesis. Anesth Analg 79:1043-1048, 1994.)*

similar ways by an anesthetic and a nonimmobilizer, that process is not relevant for the anesthetic state, with the notable exception of amnesia. Despite this elegant rationale, only a limited number of receptors have been excluded because, compared with volatile anesthetics, nonimmobilizers are relatively target-selective. These compounds have the potential to provide insights beyond the initially envisaged receptor-level studies by allowing the separation of sedation from amnesia for the study of underlying network activity in vivo.[56]

Genetic

Genetic strategies take two forms known as "forward" and "reverse" genetics.[238] Reverse genetics approaches focus on a particular gene, chosen because there are reasons to believe that its product might be important to anesthesia. Examples of this strategy are targeted mutations that alter the sensitivity of specific neurotransmitter receptors to anesthetics.[119] Initially, these mutations were used to identify anesthetic binding sites. Subsequently, transgenic animals rendered resistant to anesthetics, either by deletion of a putative target protein from the genome or by expressing a target receptor engineered to be insensitive to an anesthetic, were used to test behavioral relevance of the altered gene product for the anesthetic phenotype. Forward genetics, by contrast, involves the study of randomly generated mutations (either experimentally induced or naturally occurring polymorphisms) in a population that affect the phenotype of interest.

Knock-out and Knock-in Approaches

In the knock-out approach, expression of the gene encoding a protein of interest is disrupted by a specific deletion or insertion. A well-recognized problem with the global knock-out approach is that sometimes extensive compensatory changes can be induced in the proteome of the animal, from anomalies that are lethal in utero to insidious but experimentally confounding differences from wild-type. A complementary strategy is the conditional knock-out, in which the genetic deletion takes place in a restricted fashion—either anatomically (limited to certain brain regions) or temporally (that is, a gene is deleted at a known point in time). These strategies can minimize developmental anomalies and reduce the likelihood of compensatory changes. In the knock-in approach, a mutation, usually of a single amino acid residue, is targeted to produce a protein with altered sensitivity to a drug of interest. Ideally, this mutation remains completely silent in the absence of the drug, that is, it does not perturb the normal expression and function of the protein of interest or alter the expression of other genes.

$GABA_A$ Receptors

Results from transgenic animals illustrate both the utility and the difficulties of the genetic approach with respect to inhaled agents. The conditional forebrain-restricted $GABA_A$ receptor α_1-subunit knock-out mouse is less sensitive to isoflurane-induced amnesia than the wild-type, leading to the conclusion that action at these receptors contributes to its amnesic effects.[239] By contrast, a mouse harboring a mutation of the $GABA_A$ receptor α_1-subunit that renders the receptor insensitive to isoflurane in vitro did not show reduced sensitivity to either the amnesic or the immobilizing effects of isoflurane, leading to the conclusion that this subunit does not mediate the impairment of learning and memory by isoflurane.[31] Similar experiments indicate that action at the $GABA_A$ receptor β_3-subunit does not mediate immobility or amnesia by isoflurane.[30] This "bottom-up" genetic approach is a work-intensive but powerful tool that has yielded clear results with the receptor-specific intravenous anesthetics[16] but has proved more challenging to apply to the more promiscuous inhaled agents.

Two-Pore Domain K^+ Channels

Use of mice harboring knock-out mutations of several two-pore domain K^+ channel (K_{2P}) family members (TASK-1, TASK-3, TREK-1) has demonstrated a role for these channels in volatile anesthesia.[32-34] For example, TREK-1 knock-out mice are partially resistant to all volatile anesthetics tested with respect to both loss of righting reflex (a measure of consciousness) and immobility, but anesthesia can still be induced, albeit at higher anesthetic concentrations. Interestingly, responses to pentobarbital are unaffected, indicating that the mutation does not cause a generalized resistance to anesthesia.

Forward and Population Genetics

The nematode *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster,* with 300 and 100,000 neurons, respectively, have also been used as model organisms in anesthesia research. The genomes of both organisms have been sequenced and homologous genes in higher organisms can be identified for many genes. Mutations in a number of *C. elegans* genes affect sensitivity to volatile anesthetics, such as *unc64,*[214] *stomatin,*[240] and *gas1.* Mutations in the latter gene confer hypersensitivity to enflurane. Cloning of this gene revealed that it encodes the worm homolog of a subunit of NADH hydrogenase expressed in neurons.[241] Yeasts have also been used as model organisms, with even more obvious limitations with respect to identification of appropriate anesthetic end points.

Sensitivity to anesthetics is a quantitative trait (varying continuously in a population). Quantitative genetics is the study of the heritability of continuous traits. These traits are controlled by genes represented in quantitative trait loci (QTLs). A top-down population-based approach has been used to localize QTLs that govern susceptibility of individuals to anesthetics, in higher as well as lower organisms. Starting from the observation that inbred mouse strains vary in their sensitivity to isoflurane, microsatellite-based linkage analysis on one hand and single nucleotide polymorphism-based analysis of genetic variation on the other hand localized a QTL for isoflurane immobilization to the proximal part of mouse chromosome 7.[242] This type of analysis promises to assist in defining the genetic basis for variability in the susceptibility to both primary anesthetic end points and to side effects.

Imaging

Identification of the anatomic substrates for anesthetic effects on consciousness, memory, and immobility is now approachable with improved functional imaging techniques. Imaging is based on mapping of either hemodynamic or metabolic changes as surrogate measures of neuronal activity, as in positron emission tomography (PET) and functional MRI (fMRI), or on mapping the

electrical activity with high-density EEG and low-resolution brain electromagnetic tomography (LORETA). Properties of receptors can also be probed with radioactive ligands (PET). These techniques have the capacity to identify neuroanatomic substrates of drug action, with method-specific limitations. Results from functional PET imaging suggest that propofol suppresses episodic memory by targeting prefrontal and posterior parietal cortex as opposed to the medial temporal lobe[243] and that suppression of consciousness is due to anesthetic action in the thalamus, parts of the medial and posterior parietal cortex, and/or the posterior cingulate and medial parietal cortex (see reference 244 for review). Although observations of regionally specific and global suppressive effects of anesthetics on metabolic activity are unlikely to provide a definitive mechanistic understanding, such information can facilitate hypotheses and experimentally testable predictions.

Summary

The nut of "inhaled anesthetic mechanisms" has proved more difficult to crack than envisaged a generation ago, when the paradigm shifted from lipids to amphiphilic cavities in proteins as anesthetic targets. Despite a remarkable accumulation of factual knowledge, a comprehensive *theory of general anesthetic action* has not yet been formulated. Why has progress toward this goal been so difficult? Important pharmacologic characteristics of inhaled anesthetics that have impeded identification of their relevant molecular targets are their low potency (millimolar), their promiscuous activity at multiple targets, and the lack of specific antagonists. The situation is different for intravenous anesthetics that exhibit more conventional receptor pharmacology. Moreover, accumulating evidence indicates that no universal target exists to explain the actions of every general anesthetic, or even of a single anesthetic agent. It is now clear that the composite state of anesthesia and its core components (i.e., amnesia, sedation/unconsciousness, immobility) are separable behavioral states in vivo that have limited reproducibility in vitro. Resolution of these phenomena at the molecular and cellular levels represents the cutting edge of contemporary neuroscience. Of the multiple molecular and cellular anesthetic effects identified, it is unclear which are critical for the desired behavioral end points, which are harmless or beneficial side effects (e.g., preconditioning), and which, if any, could have long-lasting or delayed undesirable consequences (e.g., cell death, cognitive dysfunction). Progress in identifying the molecular targets of general anesthetics provides a foundation for identification of the network and systems level effects relevant to their behavioral and peripheral end points. As the biologic foundations of behaviors once thought to be exclusively the realm of psychology are unraveled, for which anesthetics provide a valuable investigative tool, a comprehensive theory of anesthesia will also develop.

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Edmond I Eger II

21 Inhaled Anesthetics: Uptake and Distribution

Key Points

1. During induction and maintenance of anesthesia, ventilation, the first of five factors that govern the pulmonary inhaled anesthetic concentration, delivers anesthetic to the lung and thereby increases the alveolar concentration.
2. Uptake of anesthetic by blood passing through the lung opposes the effect of ventilation by drawing anesthetic from the lung.
3. An increased inspired concentration of anesthetic decreases the effect of uptake (the concentration effect), and at 100% inspired concentration, uptake no longer opposes the effect of ventilation.
4. Metabolism of anesthetics can increase uptake.
5. Anesthetic uptake may be enhanced by movement of anesthetic between tissues (intertissue diffusion), especially from highly perfused tissues (e.g., intestine) to poorly perfused tissues with a great capacity for anesthetic (e.g., mesenteric fat).
6. Three factors determine uptake by blood: solubility (the blood-gas partition coefficient), pulmonary blood flow (cardiac output), and the difference in anesthetic partial pressure between the lungs and venous blood returning to the lungs.
7. Solubility differentiates one anesthetic from another in that lower solubility translates to faster recovery from anesthesia.
8. Changes in ventilation and the distribution of ventilation, cardiac output (and its distribution), and inflow rate each influence anesthetic concentration in predictable ways.

The modern anesthetist expeditiously develops and then sustains anesthetic concentrations in the central nervous system that are sufficient for surgery, doing so with agents and techniques that usually permit rapid recovery from anesthesia. Producing a sufficient concentration requires delivery of anesthetic that is adequate but does not impose excessive depression. Knowledge of the factors that govern the relationship between the delivered anesthetic and brain (or heart or muscle) concentrations enhances the optimum conduct of anesthesia.

The Inspired-to-Alveolar Anesthetic Relationship

Of the steps between delivered and brain anesthetic partial pressure, none is more pivotal than that between the inspired and alveolar gases. Alveolar partial pressure governs the partial pressure of anesthetic in all body tissues: all must approach and ultimately equal alveolar partial pressure. With use of high inflow rates (and hence conversion to a non-rebreathing system), the anesthetist can precisely control the partial pressure of anesthetic that is inspired.

The Effect of Ventilation

Two factors determine how quickly the alveolar concentration of an anesthetic (F_A) rises toward the concentration being inspired (F_I): the inspired concentration itself (see "The Concentration Effect") and alveolar ventilation. Ventilation exerts a powerful effect. On induction, the unopposed effect of ventilation rapidly increases the alveolar concentration (i.e., F_A/F_I quickly approaches 1). This occurs with oxygen during the course of preoxygenation. Normally, 95% or greater washin of oxygen occurs in 2 minutes or less when a non-rebreathing (or high inflow rate) system is used (Fig. 21-1).

However, the F_A/F_I ratio for inhaled anesthetics does not mimic the F_A/F_I ratio for oxygen. In contrast to oxygen, appreci-

Table 21-1 Partition Coefficients at 37°C

Anesthetic	Blood-Gas	Brain-Blood	Liver-Blood	Kidney-Blood	Muscle-Blood	Fat-Blood
Desflurane	0.45	1.3	1.4	1.0	2.0	27
Nitrous oxide	0.47	1.1	0.8	—	1.2	2.3
Sevoflurane	0.65	1.7	1.8	1.2	3.1	48
Isoflurane	1.4	1.6	1.8	1.2	2.9	45
Enflurane	1.8	1.4	2.1	—	1.7	36
Halothane	2.5	1.9	2.1	1.2	3.4	51
Diethyl ether	12	2.0	1.9	0.9	1.3	5
Methoxyflurane	15	1.4	2.0	0.9	1.6	38

Data from references 1 through 8.

able quantities of anesthetics are taken up because the solubilities of anesthetics far exceed the solubility of oxygen (or nitrogen). At low inspired concentrations, the balance between delivery of anesthetic by ventilation and removal of anesthetic by uptake determines the FA/FI ratio. The relationship is a simple one. For example, if uptake removes a third of the inspired anesthetic molecules, FA/FI equals two thirds; if uptake removes two thirds of the inspired molecules, FA/FI equals a third.

Anesthetic Uptake Factors

Three factors determine anesthetic uptake: solubility (λ), cardiac output (Q), and alveolar-to-venous partial pressure difference ($P_A - P_v$).[1] Uptake equals the product of these factors: $\lambda \times Q \times (P_A - P_v)$ divided by barometric pressure.

Because uptake is the product of these factors rather than a sum, if any factor approaches zero, uptake must approach zero, and ventilation rapidly drives the FA/FI ratio to 1.0. Thus, if solubility is low (as in the case of oxygen), if cardiac output approaches zero (as in profound myocardial depression or death), or if the alveolar-to-venous difference becomes inconsequential (as might occur after an extraordinarily long course of anesthesia), uptake would be minimal, and FA/FI would equal 1.

Solubility

A partition coefficient describes the relative affinity of an anesthetic for two phases and hence how that anesthetic partitions itself between the two phases when equilibrium has been achieved. The blood-gas partition coefficient (λ, or "blood solubility") describes the partitioning of an anesthetic between blood and gas. For example, isoflurane has a blood-gas partition coefficient of 1.4, which means that at equilibrium, the concentration of isoflurane in blood is 1.4 times its concentration in the gas (alveolar) phase. "Equilibrium" means that no difference in partial pressure exists (i.e., a blood-gas partition coefficient of 1.4 does not indicate that the partial pressure in blood is 1.4 times that in the gas phase). The partition coefficient may be thought of in another way—it indicates the relative capacity of the two phases. Thus, a value of 1.4 means that each milliliter of blood holds 1.4 times as much isoflurane as a milliliter of alveolar gas does.

A larger blood-gas partition coefficient produces greater uptake and hence a lower FA/FI ratio. Because the partial pressure of an anesthetic in the alveoli is transmitted to arterial blood and thence to all tissues (especially the central nervous system), development of an adequate central nervous system anesthetic partial pressure may be delayed in the case of highly blood-soluble agents such as ether and methoxyflurane (Table 21-1).[1-8] Indeed, the delay in development of an anesthetizing cerebral partial pressure has contributed to the elimination of such highly blood-soluble agents from anesthetic practice. Even the moderate solubility of isoflurane could slow induction of anesthesia were it not for the use of anesthetic overpressure—that is, we compensate for the uptake of anesthetic by delivering a higher concentration than we hope to achieve in the alveoli, perhaps 2% isoflurane to produce an alveolar concentration of 1%.

Cardiac Output

The effect of altering cardiac output is intuitively obvious. If more blood passes through the lungs, more blood is available to remove anesthetic and thereby lower the FA/FI ratio. To the student of

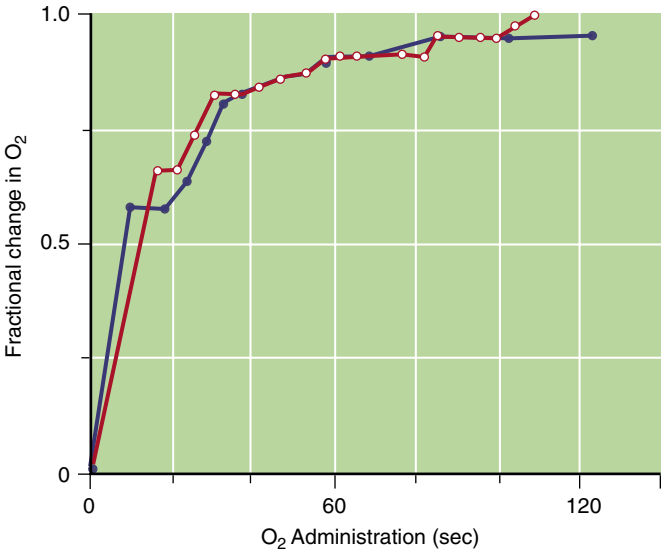

Figure 21-1 Washin of oxygen was determined in two patients breathing from a mask. A 63% change was obtained in about 30 seconds, an 86% change in about 1 minute, and a 95% to 98% change in 2 minutes. *(From Eger EI II [unpublished data].)*

uptake and distribution, this may appear to produce a conflict. It would seem that if more agent were taken up and delivered more rapidly to tissues, the tissue anesthetic partial pressure would rise more rapidly. In one sense this is true: an increase in cardiac output does hasten the equilibration of tissue anesthetic partial pressures with the partial pressure in arterial blood.[9] This reasoning, however, ignores the lower F_A/F_I ratio found with normal cardiac output. The partial pressure in the central nervous system cannot exceed that in blood, and thus a lower F_A/F_I ratio produces a lower anesthetic partial pressure in the brain—although that lower partial pressure might be achieved more rapidly.

The effect of a change in cardiac output is analogous to the effect of a change in solubility. As already noted, doubling solubility doubles the capacity of the same volume of blood to hold anesthetic. Doubling cardiac output would also double capacity, but in this case by doubling the volume of blood exposed to anesthetic.

The Alveolar-to-Venous Anesthetic Gradient

The alveolar-to-venous anesthetic partial pressure gradient, or the difference between partial pressure in the alveoli and that in venous blood, results from tissue uptake of anesthetic. Were there no tissue uptake, the venous blood returning to the lungs would contain as much anesthetic as it had when it left the lungs as arterial blood. That is, the alveolar (which equals arterial)-to-venous partial pressure difference would be zero. The presumption that alveolar and arterial anesthetic partial pressures are equal is reasonable in normal patients who have no barrier to diffusion of anesthetic from the alveoli to pulmonary capillary blood and who do not have ventilation-perfusion abnormalities. Later, we shall consider the effect of ventilation-perfusion abnormalities on anesthetic uptake.

Factors that determine the fraction of anesthetic removed from the blood traversing a given tissue parallel the factors that govern uptake at the lungs: tissue solubility, tissue blood flow, and arterial-to-tissue anesthetic partial pressure difference. Again, uptake is the product of these three factors. If any single factor approaches zero, so does uptake. The succeeding paragraphs discuss the characteristics of each of these factors and then how uptake by individual tissues can be summed to give the venous component of the alveolar-to-venous anesthetic partial pressure difference.

Blood-gas partition coefficients span values ranging from 0.45 for desflurane to 15 for methoxyflurane (see Table 21-1), a 33-fold difference. In contrast, tissue-blood partition coefficients (i.e., tissue solubility) lie between 1 and 2 for all lean tissue except muscle, for which the values for potent anesthetics lie between 2 and 3.4 (see Table 21-1)—that is, different lean tissues have similar capacity per milliliter of tissue. Put another way, a given anesthetic has roughly the same affinity for lean tissue and blood. As with blood-gas partition coefficients, tissue-blood partition coefficients define the concentration ratio of anesthetic at equilibrium between the two phases. For example, an isoflurane brain-blood partition coefficient of 1.6 means that 1 cm^3 of brain can hold 1.6 times as much isoflurane as 1 cm^3 of blood can with the same isoflurane partial pressure.

Lean tissues differ in the volume of tissue relative to the volume of blood passing that tissue. A larger volume of tissue relative to flow (as with muscle) has two implications. First, the large tissue capacity increases the transfer of anesthetic (more is lost) from blood to tissue. Second, it takes longer to fill up a tissue with a large capacity (i.e., the tissue takes longer to equilibrate with the anesthetic partial pressure being delivered in arterial blood). Thus, a large tissue volume relative to blood flow sustains the arterial-to-tissue anesthetic partial pressure difference (and hence uptake) for a longer time. In contrast, with its high perfusion per cubic centimeter of tissue, brain equilibrates rapidly with the anesthetic partial pressure. Per cubic centimeter of tissue, muscle has about a 20th the perfusion of brain, and this factor alone means that muscle takes 20 times longer than brain to equilibrate. The muscle-blood partition coefficient relative to the brain-blood partition coefficient causes a further delay. For example, the 3.1 muscle-blood partition coefficient for sevoflurane means that each 100 cm^3 of muscle has the capacity of 310 mL of blood, whereas the brain-blood partition coefficient is 1.7. Thus, equilibration is not simply 20 times longer, it is $20 \times 3.1/1.7$, or 36 times longer than with brain.

The tissue-blood coefficient for fat greatly exceeds 1 for more potent anesthetics (see Table 21-1). Fat-blood coefficients range from 2.3 (nitrous oxide) to 48 (sevoflurane). That is, each cubic centimeter of fat tissue contains 2.3 times more nitrous oxide or 48 times more sevoflurane than does a milliliter of blood with the same nitrous oxide or sevoflurane partial pressure. This enormous capacity of fat for potent inhaled anesthetics means that most of the anesthetic contained in the blood perfusing fat is transferred to the fat. Although most of the anesthetic moves from blood to fat, the anesthetic partial pressure in fat rises slowly because fat has a large capacity and low perfusion per cubic centimeter of fat.

Tissue Groups

The algebraic sum of uptake by individual tissues determines the alveolar-to-venous partial pressure difference and hence uptake at the lungs. However, we do not need to analyze the effect of individual tissues to arrive at the algebraic sum; instead, we can group tissues in terms of their perfusion and solubility characteristics (i.e., in terms of features that define the duration of a substantial arterial-to-tissue anesthetic partial pressure difference). Four tissue groups result from such an analysis (Table 21-2).[1]

The brain, heart, splanchnic bed (including the liver), kidney, and endocrine glands make up the vessel-rich group (VRG). These organs account for less than 10% of body weight but receive 75% of cardiac output. This high perfusion confers several features. The large blood flow permits the VRG to receive and remove a relatively large volume of anesthetic in the earliest moments of induction. However, the small volume of tissue relative to perfusion produces rapid equilibration of this tissue group with the anesthetic delivered in arterial blood. The time to half-equilibration (i.e., the time at which the VRG anesthetic partial pressure equals half that in arterial blood) varies from about 1 minute for nitrous oxide to 2 minutes for sevoflurane. The longer time to equilibration with sevoflurane results from its higher tissue-blood partition coefficients (see Table 21-1). Equilibration of the VRG with the anesthetic partial pressure in arterial blood is more than 90% complete in 4 to 8 minutes. Thus, after 8 minutes, uptake by the VRG is too small (i.e., the arterial-to-VRG anesthetic partial pressure difference is too small) to significantly influence the alveolar concentration. For a substantial period after 8 minutes, the muscle group (MG) determines most of uptake.

Muscle and skin, which make up the MG, have similar blood flow and solubility (lean tissue) characteristics. The lower perfusion (about 3 mL of blood per 100 cm^3 of tissue per minute)

Table 21-2 Tissue Group Characteristics

	Group			
	Vessel Rich	**Muscle**	**Fat**	**Vessel Poor**
Percentage of body mass	10	50	20	20
Perfusion as a percentage of cardiac output	75	19	6	0

Adapted from Eger EI II: Uptake of inhaled anesthetics: The alveolar to inspired anesthetic difference. *In* Eger EI II: Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974, pp 77-96.

distinguishes the MG from the VRG (70 mL per 100 cm^3 per minute). Although the MG represents about half of the body's bulk, it receives only 1 L/min blood flow at rest. That is, the amount of anesthetic delivered to the MG is a quarter of that delivered to the VRG, and initially the MG takes up only a quarter as much anesthetic. The large bulk relative to perfusion means two things: (1) during induction, most of the anesthetic delivered to the MG is removed from the MG blood flow, and (2) the MG continues to remove anesthetic from its blood supply for a long time. The time to half-equilibration ranges from 20 to 25 minutes (nitrous oxide) to 70 to 80 minutes (sevoflurane or isoflurane). Thus, long after equilibration of the VRG has taken place, the MG continues to take up substantial quantities of anesthetic and requires 2 to 4 hours to approach equilibration.

Once MG equilibration is complete, only fat (i.e., the fat group [FG]) serves as an effective depot for uptake. In a normal lean patient, the FG occupies a fifth of the body's bulk and receives a blood flow of about 400 mL/min (i.e., the perfusion per 100 cm^3 of fat nearly equals the perfusion per 100 cm^3 of resting muscle). Thus, during the initial delivery of anesthetic to tissues, the FG receives only 40% as much anesthetic as delivered to the MG (i.e., blood flow to the FG is 40% of that to the MG). The FG has far greater affinity than the MG for anesthetic, a property that greatly lengthens the time over which it absorbs anesthetic. The half-time to equilibration of fat ranges from 70 to 80 minutes for nitrous oxide to 30 hours for sevoflurane and isoflurane. Equilibration with fat does not occur in the course of anesthesia with any potent inhaled anesthetic.

One tissue group, the vessel-poor group (VPG), remains to be defined. The VPG consists of ligaments, tendons, bone, and cartilage (i.e., lean tissues that have little or no perfusion). The absence of significant blood flow means that the VPG does not participate in the uptake process despite the fact that it represents a fifth of the body's mass.

Synthesis of Factors Governing the Rise in FA/FI Ratio

Now consider the combined impact of ventilation, tissue volume, solubility, and blood flow distribution on the rate of rise in FA/FI. The initial rate is rapid for all agents, regardless of their solubility (Fig. 21-2).[10,11] At the start of anesthesia, this rapidity results from the absence of an alveolar-to-venous anesthetic partial pressure difference (there is no anesthetic present in the lung to create a gradient) and hence absence of uptake. Without uptake, the effect of ventilation to generate a sudden rise in FA/FI is unopposed, and the rise initially parallels that noted for oxygen (see Fig 21-1). As ventilation delivers anesthetic to the alveoli, a progressively greater alveolar-to-venous partial pressure difference develops. The resulting rise in uptake increasingly opposes the effect of ventilation to drive the alveolar concentration upward. Ultimately, a rough balance is struck between anesthetic input by ventilation and its removal by uptake. The height of the FA/FI ratio at which the balance is struck depends on the solubility factor in the uptake equation (see the earlier equation for anesthetic uptake). Greater solubility increases uptake for a given alveolar-to-venous partial pressure difference. Hence, the initial rapid rise in FA/FI is halted at a lower level with a more soluble agent. This results in the first "knee" in the curve—higher for desflurane than for sevoflurane, higher for sevoflurane than for isoflurane, and higher for isoflurane than for methoxyflurane. The position of nitrous oxide is discussed later (see "The Concentration Effect"). At 1 minute of anesthetic administration, the FA/FI ratio is approximately 0.6 for desflurane, which indicates that the FA/FI ratio still has 40% to rise (i.e., uptake is removing 40% of the desflurane delivered by ventilation). In contrast, the FA/FI ratio for methoxyflurane has risen only 6.5%, thus indicating that 93.5% of the methoxyflurane delivered by ventilation is taken up.

The balance struck between ventilation and uptake does not remain constant. FA/FI continues to rise, albeit at a slower rate than seen in the first minute. This rise results from the progressive decrease in uptake by the VRG, a decrease to an inconsequential amount after 8 minutes. Thus, by about 8 minutes, three quarters of the cardiac output returning to the lungs (i.e., the blood from the VRG) contains nearly as much anesthetic as it did when it left the lungs. The consequent rise in venous anesthetic partial pressure decreases the alveolar-to-venous partial pressure difference and hence uptake, thereby allowing ventilation to drive the alveolar concentration upward to a second knee at roughly 8 minutes.

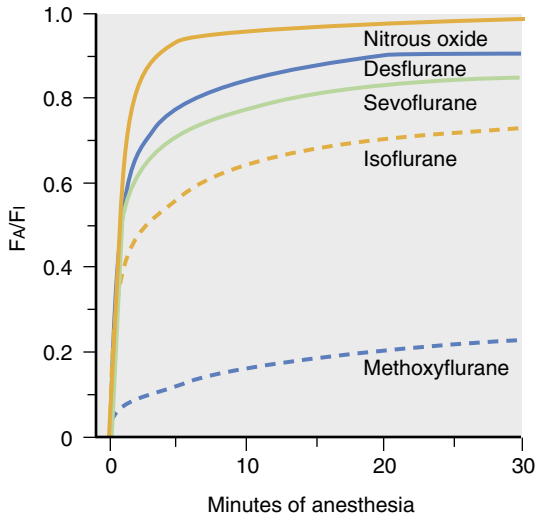

Figure 21-2 The rise in alveolar (FA) anesthetic concentration toward the inspired (FI) concentration is most rapid with the least soluble anesthetic, nitrous oxide, and slowest with the most soluble anesthetic, methoxyflurane. All data are from human studies. *(Data from Yasuda N, Lockhart SH, Eger EI II, et al: Kinetics of desflurane, isoflurane, and halothane in humans. Anesthesiology 74:489-498, 1991; and Yasuda N, Lockhart SH, Eger EI II, et al: Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg 72:316-324, 1991.)*

With the termination of effective uptake by the VRG, the MG and FG become the principal determinants of tissue uptake. The slow rate of change in the anesthetic partial pressure difference between arterial blood and MG or FG produces the gradual ascent of the terminal portion of the FA/FI ratio as the MG and, slower still, the FG progressively equilibrate with the arterial anesthetic partial pressure. If the graphs were extended for several hours, a third knee would be found that indicates equilibration of the MG. After that time, uptake would principally depend on the partial pressure gradient between arterial blood and fat.

The Concentration Effect

The previous analysis ignores the impact of the concentration effect on FA/FI. The inspired anesthetic concentration influences both the rate of rise and the height of the FA/FI ratio.[12] Increasing the inspired concentration accelerates the rate of rise. At an inspired concentration of 100%, the rate of rise is dictated solely by the rate at which ventilation washes gas into the lung; that is, at 100% inspired concentration, uptake no longer opposes the level to which FA/FI may rise. The cause of this extreme effect is readily perceived. At 100% inspired concentration, uptake of anesthetic creates a void that draws sufficient gas down the trachea to replace the gas taken up. Because the replacement gas concentration is 100%, uptake cannot modify the alveolar concentration. This explains why the rise in nitrous oxide shown in Figure 21-2 is more rapid than the rise in desflurane despite their nearly equal blood-gas partition coefficients: the nitrous oxide was given at an inspired concentration of 70%, whereas that of desflurane was 2%.

The concentration effect results from two factors, a concentrating effect and augmentation of inspired ventilation (Fig. 21-3).[13] The first rectangle (see Fig. 21-3A) represents a lung containing 80% (volumes per 100 volumes) nitrous oxide. If half this gas is taken up, the remaining 40 volumes exist in a total of 60 volumes, for a concentration of 67% (see Fig. 21-3B). That is, uptake of half the nitrous oxide does not halve the concentration because the remaining gases are "concentrated" in a smaller volume. If the void created by the uptake of 40 volumes is filled by drawing an equal volume of gas into the lungs (an augmentation of inspired ventilation), the final concentration equals 72% (see Fig. 21-3C).

This explanation has been criticized as being overly simplistic and ignoring the realities of some aspects of ventilation.[14] For example, if ventilation is controlled with a volume-limited respirator, an augmentation in inspired ventilation is limited to the period of the expiratory pause. Spontaneous ventilation minimizes this limitation. In any event, the reader needs to be aware that although Figure 21-3 describes the basic factors governing the concentration (and second gas effects—see the next section), the actual situation is more complex.

The impact of the concentration effect on FA/FI may be thought of as being identical to the impact of a change in solubility[15]: as the inspired concentration increases, the effective solubility decreases. Thus, at 50% inspired nitrous oxide, FA/FI rises as rapidly as the FA/FI of an anesthetic that has half the solubility of nitrous oxide and is given at a 1% inspired concentration, and 75% inspired nitrous oxide acts as an anesthetic given at 1% that has a quarter the solubility of nitrous oxide.

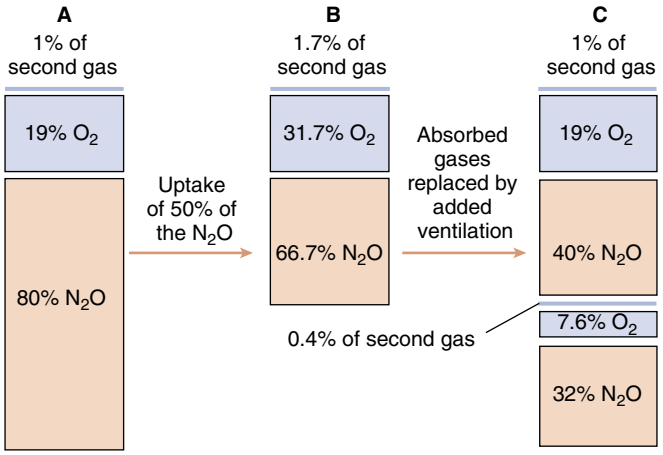

Figure 21-3 The rectangle to the left (**A**) represents a lung filled with 80% nitrous oxide plus 1% of a second gas. Uptake of 50% of the nitrous oxide does not halve the concentration of nitrous oxide (**B**) because the reduction in volume thereby increases its concentration, as well as the concentrations of all "second" gases (the oxygen and the second gas). Restoration of lung volume by the addition of gas with the same concentration as that introduced into the rectangle in **A** will increase the nitrous oxide concentration and add to the amount of second gas present in the lung (**C**). *(Modified from Stoelting RK, Eger EI II: An additional explanation for the second gas effect: A concentrating effect. Anesthesiology 30:273-277, 1969.)*

The Second Gas Effect

The factors that govern the concentration effect also influence the concentration of any potent anesthetic given concurrently.[13] The loss of volume associated with the uptake of nitrous oxide concentrates the potent anesthetic (see Fig. 21-3B). Replacement of the gas taken up by an increase in inspired ventilation augments the amount of potent anesthetic present in the lung (see Fig. 21-3C).

Experiments in dogs[16] and humans[17] demonstrate both the concentration and second gas effects. Humans given 4% desflurane with 5% or 65% nitrous oxide have a more rapid increase in FA/FI for both nitrous oxide and desflurane when 65% nitrous oxide is given (Fig. 21-4).[17]

Hendrickx and colleagues[18] confirmed the presence of the second gas effect but found, further, that the effect persists long after the majority of the uptake of nitrous oxide has ceased. They did not provide an explanation for this finding. An explanation would follow from an assumption of ventilation-perfusion abnormalities. Imagine that half the lung is poorly ventilated and the other half is well ventilated with both sides equally perfused. In the poorly ventilated half, uptake of oxygen will increase the concentration of nitrous oxide, possibly even above the inspired concentration. The increased concentration of nitrous oxide will augment its uptake and thus produce both factors that underlie the concentration and second gas effects (see Fig. 21-3). Furthermore, the half of the lung that is poorly ventilated is usually hypoventilated because of increased airway resistance. The increased airway resistance causes the poorly ventilated lung to empty last, which produces the characteristic upward sloping curve for expired carbon dioxide in patients with chronic obstructive pulmonary disease. Thus, the poorly ventilated lung would provide the increased recorded (literally the end-tidal) values for both nitrous oxide and the second gas.

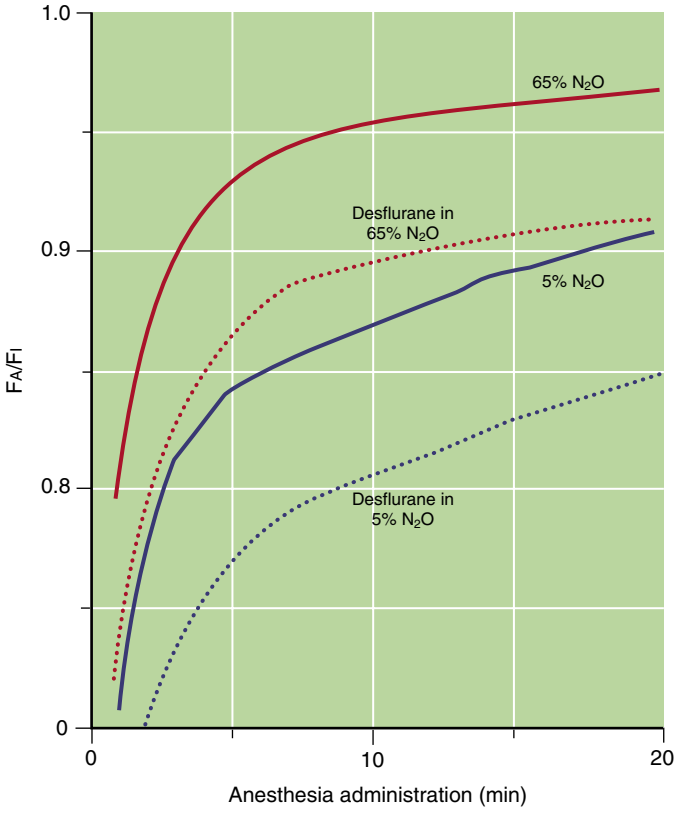

Figure 21-4 In humans, administration of 65% nitrous oxide produces a more rapid rise in the FA/FI ratio of nitrous oxide than does the administration of 5% (concentration effect, *continuous two curves*). The FA/FI ratio for 4% desflurane rises more rapidly when given with 65% nitrous oxide than when given with 5% (second gas effect, *dashed two curves*). *(Modified from Taheri S, Eger EI II: A demonstration of the concentration and second gas effects in humans anesthetized with nitrous oxide and desflurane. Anesth Analg 89:774-780, 1999.)*

Percutaneous and Visceral Anesthetic Loss

Anesthetics may be lost via three routes other than the lungs: (1) transcutaneous movement, (2) transvisceral movement, and (3) metabolism. Although transcutaneous movement does occur, such movement is small.[19-21] The greatest loss per alveolar anesthetic percent occurs with nitrous oxide. Loss of nitrous oxide might equal 5 to 10 mL/min with an alveolar concentration of 70%. Movement of anesthetic across visceral or pleural surfaces during abdominal or pulmonary surgery is greater than movement across skin, but such visceral losses are usually small relative to total uptake.[22]

Metabolism of Anesthetics

Although percutaneous loss of anesthetic may not appreciably affect anesthetic uptake, loss of anesthetic by biodegradation can significantly change uptake, particularly with agents that undergo extensive biodegradation. Carpenter and coworkers[23] found that as much as half of the halothane and three quarters of the methoxyflurane that are taken up undergo biodegradation. They speculated that such biodegradation could explain the finding that the alveolar concentration of halothane decays more rapidly on recovery from anesthesia than does the alveolar concentration of isoflurane, an anesthetic that is significantly less soluble in blood.[24,25] Two reasons suggest that agents such as isoflurane and desflurane are less likely to be affected: first, they are not metabolized as readily as halothane or methoxyflurane,[24,25] and second, anesthetizing concentrations appear to saturate the enzymes responsible for metabolism of the anesthetic.[26] Saturation of enzymes in particular may limit the impact of metabolism during the washin as opposed to the washout of anesthetic. The combined effect of these factors remains to be determined, but it appears that metabolism is not a significant determinant of FA/FI during anesthesia with isoflurane or desflurane.[10,11] A small influence on the kinetics of sevoflurane may exist and thus explain why there is a more substantial difference between the FA/FI for desflurane versus sevoflurane during induction and maintenance of anesthesia than for the parallel washout curves (F_A/F_{A_0}) during recovery.[11]

Intertissue Diffusion

Carpenter and associates[24] examined the washin and washout of isoflurane, enflurane, halothane, and methoxyflurane given simultaneously for fixed times to healthy young patients. Washout was examined for several days after discontinuation of administration of the anesthetics. Analysis suggested that a model with five compartments best explained the resulting data for all the anesthetics (i.e., the model was independent of solubility and metabolism of the anesthetics). Four of these compartments had half-times consistent with the model described earlier in this chapter: compartments related to washin and washout of the lungs, the VRG, the MG, and the FG.

The additional, fifth, compartment was more difficult to explain. This compartment had a half-time of roughly 300 minutes, which is between that for muscle and fat. This additional compartment was important because it accounted for almost a third of the anesthetic taken up. Part of the compartment could be explained by uptake by highly perfused fat, such as that found in bone marrow. However, perfusion of marrow fat alone could not account for the amount of uptake by this compartment. Carpenter and coauthors[24] speculated that this uptake resulted from diffusion of anesthetic from lean tissues to adjacent thin layers of fat tissue. Such diffusion could be from the heart to pericardial fat, from the kidney to perirenal fat, from the intestine to mesenteric and omental fat, and from the dermis to subcutaneous fat. Yasuda and coworkers[10,11] confirmed these findings and extended them to desflurane and sevoflurane.

Factors Modifying the Rate of Rise in FA/FI

Alteration of the factors that govern the rate of delivery of anesthetic to or removal from the lungs changes the alveolar concentration of anesthetic. We have seen the importance of differences in solubility (see Fig. 21-2). The succeeding sections examine the impact of differences in ventilation and circulation and the interaction of these differences with factors such as solubility.

The Effect of Ventilatory Changes

By augmenting delivery of anesthetic to the lungs, increased ventilation accelerates the rate of rise in FA/FI (Fig. 21-5).[1,27] A change in ventilation produces a greater relative change in FA/FI with a more soluble anesthetic. In Figure 21-5, a doubling of ventilation increases the methoxyflurane concentration at 10 minutes of anesthetic administration by 75%, increases the isoflurane concentration by 18%, and increases the desflurane concentration by only 6%.

The impact of solubility may be explained as follows. With a poorly soluble agent such as desflurane, FA/FI increases rapidly, even with hypoventilation. Because FA normally cannot exceed FI, there is little room for augmentation of ventilation to further increase FA/FI. With a highly soluble agent such as methoxyflurane, most of the anesthetic delivered to the lungs is taken up, so if uptake at 4-L/min ventilation equaled x, uptake at 8 L/min would approach 2x. Thus, if cardiac output is held constant, ventilation at 8 L/min produces an arterial methoxyflurane concentration that is nearly twice the concentration produced by ventilation at 4 L/min. Because arterial and alveolar concentrations are in equilibrium, our example suggests that doubling ventilation must nearly double the concentration of a highly soluble anesthetic in the alveoli or blood.

These observations imply that imposed alterations in ventilation (e.g., an increase produced by conversion from spontaneous to controlled ventilation) produce greater changes in anesthetic concentration (and thus effect) with more soluble agents. Because such effects include both anesthetic depth and depression of circulation, greater caution must be exercised when ventilation is augmented during anesthesia produced with a highly soluble agent.

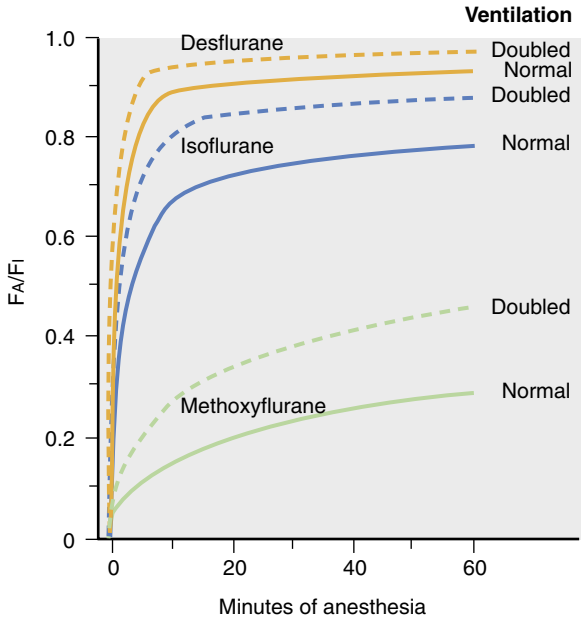

Figure 21-5 The FA/FI ratio rises more rapidly if ventilation is increased, in this case doubled. Solubility modifies this impact of ventilation: the effect on the anesthetizing partial pressure is greatest with the most soluble anesthetic (methoxyflurane) and least with the least soluble anesthetic (desflurane). *(Derived from simulations using GAS MAN from Philip JH: GAS MAN Computer Program. Chestnut Hill, MA, Med Man Simulations, Inc., 2002.)*

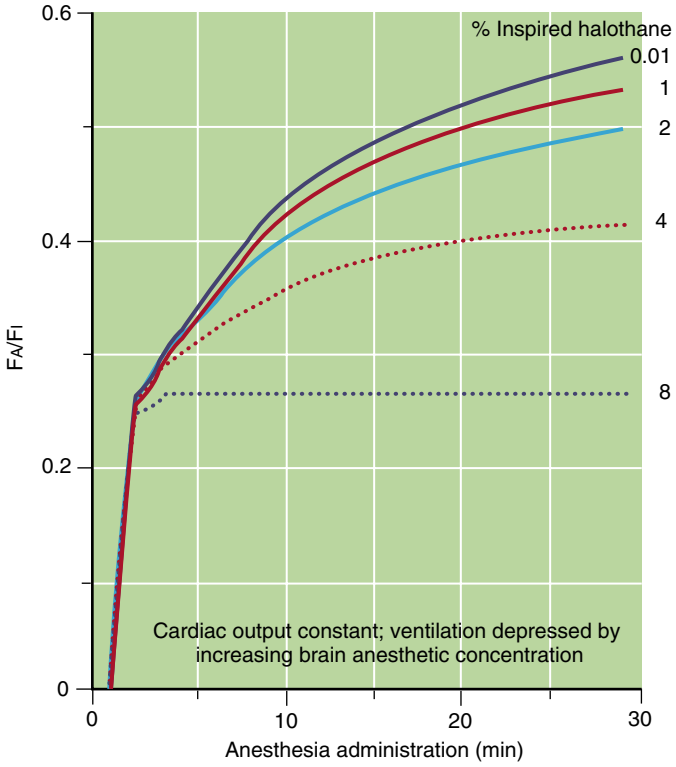

Figure 21-6 An increase in the inspired halothane concentration does not produce a proportional increase in the alveolar concentration because of the progressively greater depression of ventilation that occurs as alveolar halothane is increased. The initial "overshoot" seen with 10% to 20% inspired halothane results from the delay in transfer of alveolar halothane partial pressure to the brain (i.e., time must pass before the brain receives and is depressed by the very great concentrations attained in the lungs). *(From Munson ES, Eger EI II, Bowers DL: Effects of anesthetic-depressed ventilation and cardiac output on anesthetic uptake. Anesthesiology 38:251-259, 1973.)*

Anesthetics themselves may alter ventilation and thereby alter their own uptake.[9,28] Modern potent agents (desflurane, halothane, isoflurane, sevoflurane) are profound respiratory depressants whose capacity to depress ventilation is directly related to anesthetic dose.[29-32] At some concentration, all inhaled anesthetics probably produce apnea, a feature that must limit the maximum alveolar concentration (MAC) that can be obtained with spontaneous ventilation.

Thus, administration of an anesthetic concentration that produces significant respiratory depression decreases delivery of anesthetic to the alveoli.[9,33] As a result, doubling the inspired concentration does not double the alveolar concentration attained at a given point in time. At high inspired concentrations, further increases in inspired concentration produce little absolute change in alveolar concentration (Fig. 21-6). Anesthetics can thereby exert a negative-feedback effect on their own alveolar concentration, an effect that increases the safety of spontaneous ventilation by limiting the maximum concentration that is attained in the alveoli.

The Effect of Changes in Cardiac Output

The previous section assumed constant cardiac output and examined the effect of changes in ventilation; in this section we assume constant ventilation and examine the effect of changes in cardiac

output. An increase in cardiac output augments uptake and thereby hinders the rise in FA/FI.[1,33] As with a change in ventilation, a change in cardiac output affects the alveolar concentration of a poorly soluble agent less than it does the alveolar concentration of a highly soluble agent (Fig. 21-7). The reason for the impact of a change in solubility is similar to the reason explaining the effect of a change in ventilation. A decrease in cardiac output can do little to increase the FA/FI ratio of a poorly soluble agent because the rate of rise is rapid at any cardiac output. In contrast, nearly all of a highly soluble agent is taken up, and a halving of blood flow through the lungs must concentrate the arterial (equals alveolar) anesthetic, nearly doubling its partial pressure in the case of an extremely soluble agent.

This effect of solubility suggests that conditions that lower cardiac output (e.g., shock) will increase alveolar anesthetic concentrations more with anesthetics that have greater solubility. The higher FA/FI ratio should be anticipated and the inspired anesthetic concentration should be lowered accordingly to avoid further circulatory depression. Because shock tends to increase ventilation and decrease cardiac output, it presents a two-pronged problem: an increase in ventilation and a decrease in cardiac output accelerate the rise in FA/FI. Perhaps this is an argument for the use of nitrous oxide in patients in shock. In contrast to more soluble anesthetics (e.g., isoflurane), the alveolar concentration of nitrous oxide would be little influenced by the associated cardiorespiratory changes.

Anesthetics also affect the circulation. They can depress cardiac output.[34] In contrast to the negative feedback that results from respiratory depression, circulatory depression produces a positive feedback: depression decreases uptake, and this increases the alveolar concentration, which in turn further decreases uptake.

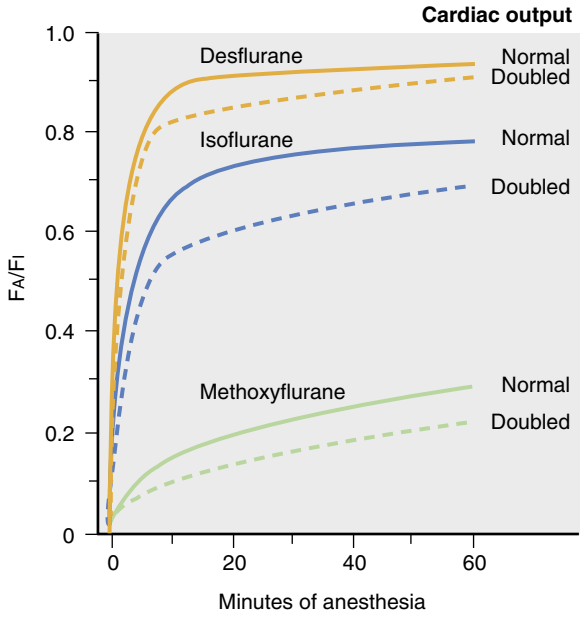

Figure 21-7 If unopposed by a concomitant increase in ventilation, an increase in cardiac output will decrease alveolar anesthetic concentration by augmenting uptake. The resulting alveolar anesthetic change is proportionately greatest (i.e., as a fraction of the "normal" curve; the "doubled" curve is least) with the most soluble anesthetic. *(Derived from simulations using GAS MAN from Philip JH: GAS MAN Computer Program. Chestnut Hill, MA, Med Man Simulations, Inc., 2002.)*

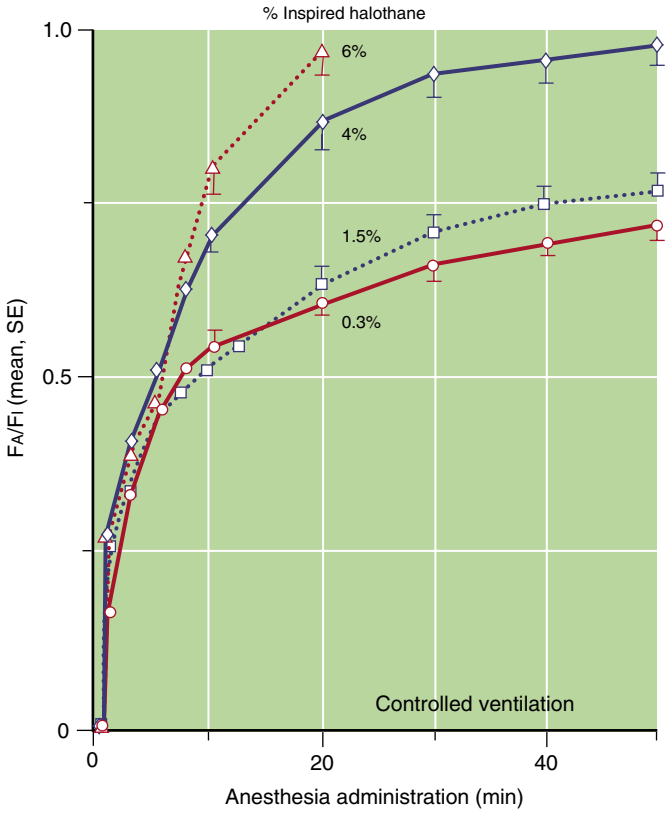

Figure 21-8 Dogs given constant ventilation demonstrate different rates of rise in FA/FI. The rates of rise depend on the inspired halothane concentration. The two greatest concentrations accelerate the rate of rise by depressing cardiac output and thereby decreasing uptake. *(Modified from Gibbons RT, Steffey EP, Eger EI II: The effect of spontaneous versus controlled ventilation on the rate of rise of alveolar halothane concentration in dogs. Anesth Analg 56:32-34, 1977.)*

A potentially lethal acceleration of the rise in FA/FI results from the depression of cardiac output (Fig. 21-8).[9,28,35] The impact of this acceleration increases in importance with increasing anesthetic solubility.

The Effect of Concomitant Changes in Ventilation and Perfusion

The preceding considerations of the effects of ventilatory and circulatory alterations presume that one variable changed while the other remained constant. In fact, both may change concomitantly. If both ventilation and cardiac output increase proportionately, an intuitive expectation might be that FA/FI would not be altered. After all, uptake equals the product of solubility, cardiac output, and the alveolar-to-venous anesthetic partial pressure difference (see the anesthetic uptake equation earlier). In the absence of other changes, doubling cardiac output doubles uptake, and this should exactly balance the influence of doubling of ventilation on FA/FI. That is, a doubling of both delivery of anesthetic to the lungs and removal of anesthetic from the lungs should produce no net change in alveolar concentration.

This reasoning ignores one other factor in the equation that defines uptake. An increase in cardiac output increases tissue blood flow and thereby accelerates the rate at which tissue equi-

libration occurs. Thus, an increase in cardiac output accelerates the narrowing of the alveolar-to-venous partial pressure difference[36] and consequently reduces the impact of the increase in cardiac output on uptake. The net result is that a proportional increase in ventilation and cardiac output increases the rate of rise in FA/FI.

The magnitude of acceleration of the rise in FA/FI depends in part on the distribution of the increase in cardiac output. If the increase is distributed proportionately to all tissues (e.g., if a doubling of output doubles flow to all tissues), the increase is fairly small (Fig. 21-9).[36,37] Thus, conditions such as hyperthermia and thyrotoxicosis only slightly influence the development of an anesthetizing anesthetic concentration through their influence on FA/FI. However, if the increase in cardiac output is diverted to the VRG, a greater effect is seen. Perfusion of the VRG is normally high and the VRG normally equilibrates rapidly. Further increases in perfusion can hasten the rate of equilibration, but the process is rapid for both normal and accelerated equilibration. Because blood returning from the VRG soon has the same partial pressure that it had leaving the lungs, it cannot remove more anesthetic from the lungs. Thus, after a few minutes, the increase in ventilation is not matched, even in part, by an increase in uptake. The result is a considerable acceleration in the rise in FA/FI. This effect may be seen in a comparison of the FA/FI curves for children and adults (Fig. 21-10). Children (especially infants) have relatively greater perfusion of the VRG and consequently show a significantly faster rise in FA/FI.[6,38,39] A clinical result of this accelerated rise is more rapid development of anesthesia in young patients. The higher perfusion of the brain further accelerates the development of anesthesia.

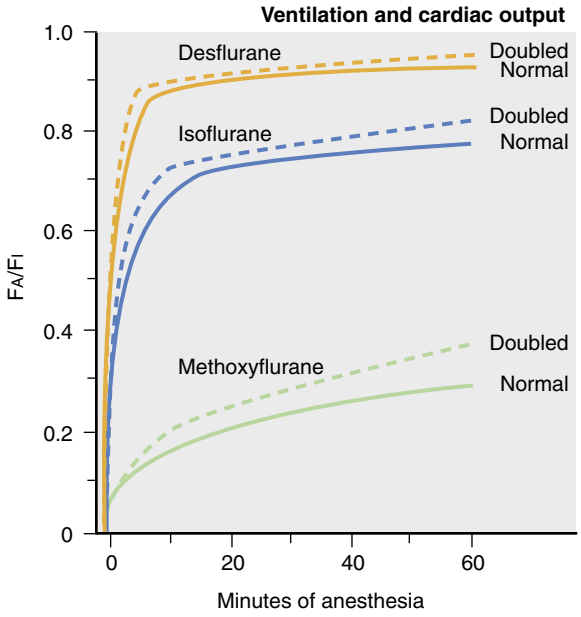

Figure 21-9 Proportional increases in alveolar ventilation (VA) and cardiac output (Q) will increase the rate at which FA/FI rises.[37] As indicated in the illustration, the effect is relatively small if the increase in cardiac output is distributed proportionately to all tissues (i.e., if cardiac output is doubled, all tissue blood flows are doubled). The greatest effect occurs with the most soluble anesthetic. *(Derived from simulations using GAS MAN from Philip JH: GAS MAN Computer Program. Chestnut Hill, MA, Med Man Simulations, Inc., 2002.)*

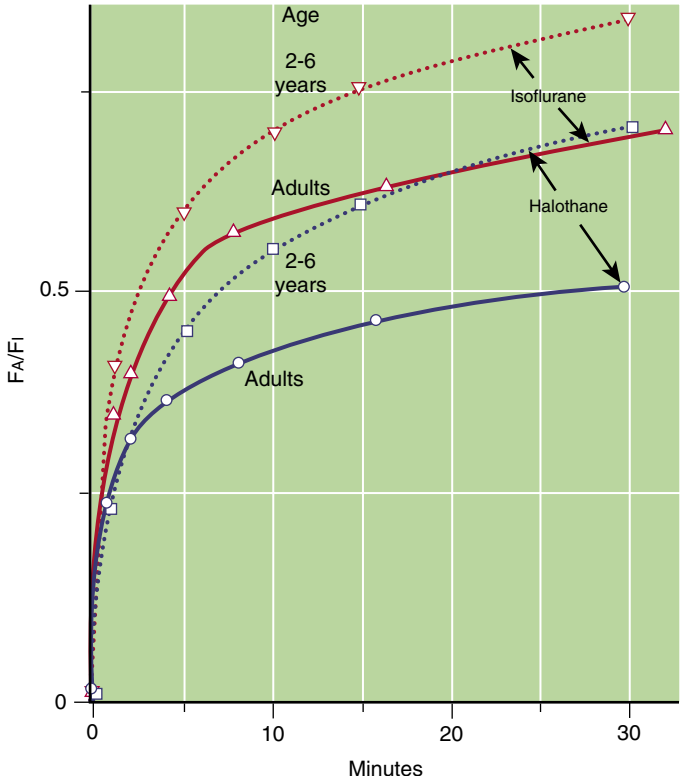

Figure 21-10 The alveolar rate of rise in halothane is more rapid in children (*upper curve*) than in adults (*lower curve*). The difference probably results from the greater ventilation and perfusion per kilogram of tissue in children and the fact that a disproportionate amount of the increased perfusion is devoted to the vessel-rich group. *(Modified from data from several sources.[6,38,39])*

Ventilation-Perfusion Abnormalities

Up to this point I have assumed that alveolar and arterial anesthetic partial pressures are equal (i.e., that the alveolar gases completely equilibrate with the blood passing through the lungs). For normal patients, this assumption is approximately correct, but diseases such as emphysema and atelectasis, as well as congenital cardiac defects, produce substantial deviations in equilibration. The associated abnormality in the ventilation-perfusion ratio does two things: (1) it increases the alveolar (end-tidal) anesthetic partial pressure and (2) it decreases the arterial anesthetic partial pressure (i.e., a partial pressure difference appears between alveolar gas and arterial blood). The relative change depends on the solubility of the anesthetic. With a poorly soluble agent, the end-tidal concentration is slightly increased, but the arterial partial pressure is significantly reduced. The opposite occurs with a highly soluble anesthetic.[40]

The considerable decrease in arterial anesthetic partial pressure that occurs with poorly soluble agents may be explained as follows. Abnormalities in the ventilation-perfusion ratio increase ventilation relative to perfusion of some alveoli, whereas in other alveoli, the reverse occurs. With a poorly soluble anesthetic, an increase in ventilation relative to perfusion does not appreciably increase the alveolar or arterial anesthetic partial pressure issuing from those alveoli (see effect for desflurane in

Fig. 21-5). However, when ventilation decreases relative to perfusion, a significant effect can occur, particularly when ventilation is absent, as in a segment of atelectatic lung. Blood emerges from that segment with no additional anesthetic. Such anesthetic-deficient blood then mixes with blood from the ventilated segments containing a normal complement of anesthetic. The mixture produces an arterial anesthetic partial pressure that is considerably below normal.

With highly soluble agents, a different situation results from similar abnormalities in the ventilation-perfusion ratio. In alveoli receiving more ventilation relative to perfusion, the anesthetic partial pressure rises to a higher level than usual (see Fig. 21-5 for effect with methoxyflurane). That is, blood issuing from these alveoli has an increased anesthetic content, the increase being nearly proportional to the increased ventilation. Assuming that overall (total) ventilation remains normal, this increase in the anesthetic contained by blood from the relatively hyperventilated alveoli compensates for the lack of uptake of anesthetic in unventilated alveoli.

These effects are illustrated in Figure 21-11 for a condition that may be iatrogenically produced, endobronchial intubation.

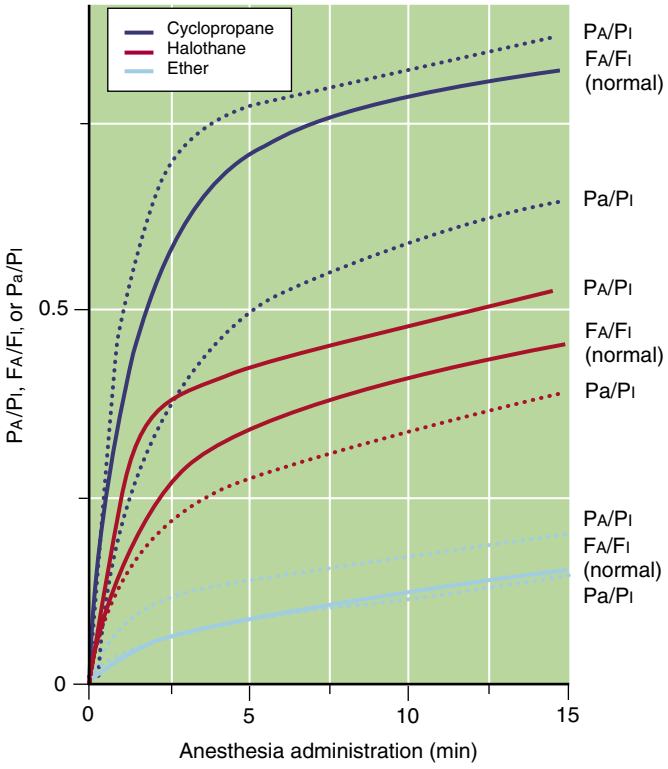

Figure 21-11 When no ventilation-perfusion abnormalities exist, the alveolar (P_A or P_{ET}) and arterial (Pa) anesthetic partial pressures rise together (*continuous lines*) toward the inspired partial pressure (P_I). Shunting of 50% of cardiac output through the lungs accelerates the rate of rise in end-tidal partial pressure (*dashed lines*) and retards the rate of rise in arterial partial pressure (*dot-dashed lines*). The greatest retardation of the rise in P_a/P_I is found with the least soluble anesthetic, cyclopropane, and the least with the very soluble anesthetic ether. *(From Eger EI II, Severinghaus JW: Effect of uneven pulmonary distribution of blood and gas on induction with inhalation anesthetics. Anesthesiology 25:620-626, 1964.)*

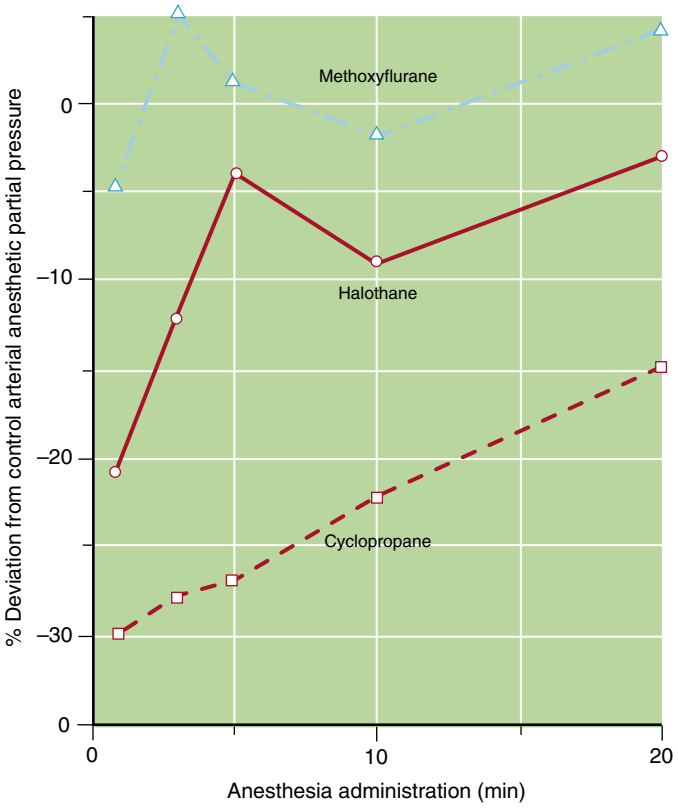

Figure 21-12 In dogs, when only the right lung was ventilated, the increase in the very soluble anesthetic methoxyflurane in arterial blood was normal (i.e., did not deviate from control), whereas the increase in the poorly soluble anesthetic cyclopropane (a blood-gas partition coefficient similar to that of sevoflurane) was significantly slowed. *(From Stoelting RK, Longnecker DE: Effect of right-to-left shunt on rate of increase in arterial anesthetic concentration. Anesthesiology 36:352-356, 1972.)*

Because all ventilation is now directed to the intubated lung, this lung is hyperventilated relative to perfusion. F_A/F_I for this lung is slightly increased (above that obtained in the absence of endobronchial intubation) with the poorly soluble cyclopropane (solubility similar to that of sevoflurane) and greatly increased with the highly soluble ether. As indicated earlier, the increase with ether compensates for the absence of uptake from the unventilated lung, a compensatory mechanism that is not available with cyclopropane. The result is that the arterial partial pressure of cyclopropane is well below normal, whereas the arterial partial pressure of ether is scarcely changed.

These concepts have been confirmed experimentally by comparing the rate of rise in arterial anesthetic with and without endobronchial intubation in dogs.[41] Endobronchial intubation significantly slowed the arterial rate of rise in cyclopropane but did not influence the rise with methoxyflurane. An intermediate result was obtained with halothane (Fig. 21-12). These data suggest that in the presence of ventilation-perfusion ratio abnormalities, the anesthetic effect of agents such as nitrous oxide, desflurane, and sevoflurane may be delayed more than the anesthetic effect of isoflurane.

The Effect of Nitrous Oxide on Closed Gas Spaces

Volume Changes in Highly Compliant Spaces

During the course of anesthetic administration, appreciable volumes of nitrous oxide can move into closed gas spaces. Although such transfer does not influence FA/FI, it may have important functional consequences. There are two types of closed gas spaces in the body, those enclosed by compliant walls and those enclosed by noncompliant walls. The former (bowel gas, pneumothorax, pneumoperitoneum, or air emboli) are subject to changes in volume secondary to transfer of nitrous oxide into these spaces.[42] These spaces normally contain nitrogen (from air), a gas whose low solubility (blood-gas partition coefficient of 0.015) limits its removal by blood. The far greater solubility of nitrous oxide in blood (blood-gas partition coefficient of 0.47) enables blood to carry more nitrous oxide to the enclosed space than it can carry away nitrogen, and the result is an increase in volume. The theoretical limit to the increase in volume is a function of the alveolar nitrous oxide concentration because this is the concentration ultimately achieved in the closed gas space. That is, at equilibrium, the concentration of nitrous oxide in the closed gas space must equal its concentration in the alveoli. An alveolar concentration of 50% might double the gas space volume, and a 75% concentration might produce a fourfold increase.

These theoretical limits may be approached if equilibrium is achieved rapidly, as with pneumothorax or gas emboli. Administration of 75% nitrous oxide in the presence of pneumothorax may double the volume of the pneumothorax by 10 minutes and may triple it by 30 minutes (Fig. 21-13).[42] Because this increase in volume may seriously impair cardiorespiratory function,[43] the use of nitrous oxide is contraindicated in the presence of a significant pneumothorax.

A still more rapid expansion of volume occurs if air inadvertently enters the bloodstream in a patient anesthetized with nitrous oxide. Expansion may be complete in seconds rather than minutes. The volume of an air embolus that is lethal decreases in animals breathing nitrous oxide as opposed to air,[44] doing so by an amount that would be predicted from the maximum theoretical expansion (Fig. 21-14). These results suggest caution in the use of nitrous oxide for procedures in which air embolization is a risk (e.g., posterior fossa craniotomies, laparoscopy). They also suggest that if air embolization is suspected, administration of nitrous oxide should be discontinued immediately. Conversely, a nitrous oxide "challenge" may be used to test whether air embolization has occurred.[45]

An endotracheal tube cuff filled with air is also susceptible to expansion by nitrous oxide[46]; 75% nitrous oxide surrounding such a cuff can double or triple the volume of the cuff. The result may be an unwanted increase in pressure exerted on the tracheal mucosa. Similarly, nitrous oxide may expand the cuffs of balloon-tipped (e.g., Swan-Ganz) catheters[47] when the balloons are inflated with air. The expansion is rapid, and a doubling of volume may occur within 10 minutes, a concern if the cuff lies within the pulmonary artery. Finally, entry of nitrous oxide into the air-filled cuff of a laryngeal mask airway can increase the volume and pressure of gas within the cuff.[48]

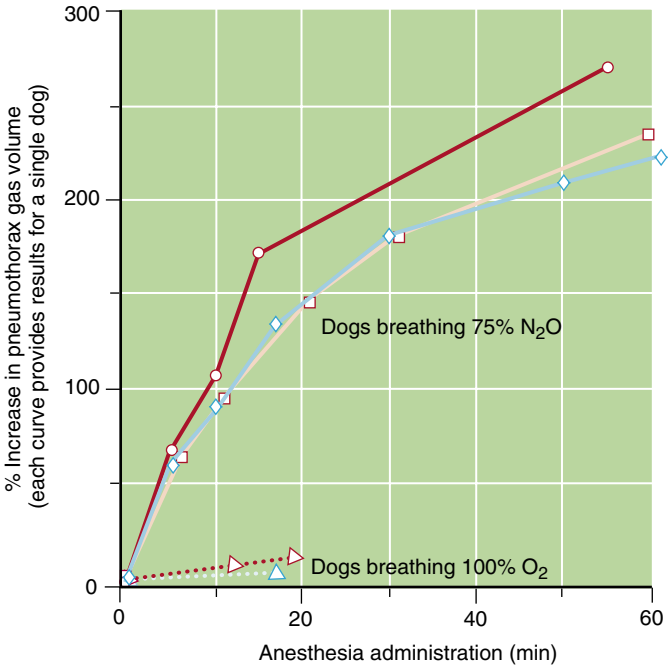

Figure 21-13 The volume of a pneumothorax created by air injection is little affected when oxygen is subsequently breathed (*filled triangle* and *circles*). However, if 75% nitrous oxide is breathed, the volume doubles in 10 minutes and triples in a half-hour (*open circles*, *squares*, and *triangles*). *(From Eger EI II, Saidman LJ: Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax. Anesthesiology 26:61-66, 1965.)*

Pressure Changes in Poorly Compliant Spaces

Entrance of nitrous oxide into gas cavities surrounded by poorly compliant walls can increase intracavity pressure. Administration of nitrous oxide may impose untoward increases in intraocular pressure after intravitreal injection of sulfur hexafluoride.[49] Other examples include the gas space created by pneumoencephalography (now rare as a deliberate procedure) and the natural gas space in the middle ear. Pressure in the head or middle ear may rise by 20 to 50 mm Hg because of the ingress of nitrous oxide.[50,51] Recognition of this problem has decreased the use of nitrous oxide for tympanoplasty because the increased pressure may displace the graft. An increase in middle ear pressure may cause adverse postoperative effects on hearing.[52] The capacity of nitrous oxide to expand the gas in the middle ear has also been used to elevate an adherent atelectatic tympanic membrane off the promontory and ossicles.[53]

Anesthetic Circuitry

The previous discussions generally considered that the alveolar anesthetic concentration (FA) was moving toward a constant inspired anesthetic concentration (FI). In practice, the inspired concentration is not usually constant because a non-rebreathing system is not used. The rebreathing that results from the use of an anesthetic circuit causes the inspired concentration to be less than that in the gas delivered from the anesthetic machine. The

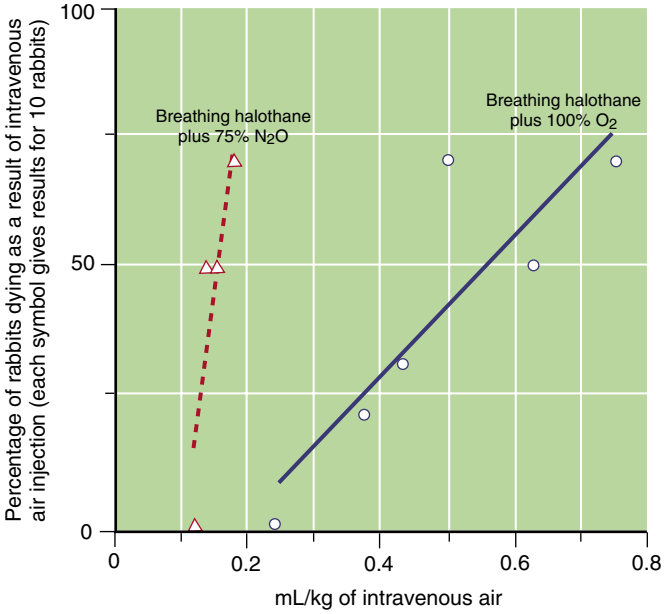

Figure 21-14 An intravenous air embolus equaling 0.55 mL/kg administered to rabbits killed half the rabbits when they breathed oxygen. If they breathed 75% nitrous oxide, only 0.16 mL/kg was required to kill half the animals. *(Modified from Munson ES, Merrick HC: Effect of nitrous oxide on venous air embolism. Anesthesiology 27:783-787, 1966.)*

inspired concentration is thus influenced by the delivered concentration, by the need to "wash in" the circuit, and by the depletion of anesthetic in rebreathed gases produced by uptake of anesthetic.

Washin of the Circuit

To begin anesthesia, anesthetic must be washed into the volume of the circuit. At inflow rates of 1 to 5 L/min and a circuit volume of 7 L (3-L bag, 1-L carbon dioxide absorber, 1 L of various fittings, and 2 L of corrugated hoses), washin of the circuit is 75% to 100% complete in 10 minutes (Fig. 21-15). Higher inflow rates accelerate the rise in inspired concentration, which suggests that induction can be accelerated and made more predictable with the use of high inflow rates.

Loss of Anesthetic to Plastic and Soda Lime

Uptake of anesthetic by several circuit components can also constitute a hindrance to the development of an adequate inspired anesthetic concentration. The rubber or plastic components of the circuit could remove significant amounts of some older anesthetics. However, uptake of nitrous oxide, desflurane, or sevoflurane by circuit components is too insignificant to materially hinder development of the inspired anesthetic concentration.[54,55]

Older normal (moist) carbon dioxide absorbents (e.g., soda lime) containing 13% to 15% water can degrade sevoflurane and thereby slightly increase requirements for sevoflurane.[56] Degradation removes hydrogen fluoride and produces an unsaturated compound (compound A). Nitrous oxide, desflurane, and isoflurane are not materially degraded. Degradation of sevoflurane has been a concern because compound A is nephrotoxic.[57] However, toxicity results only from prolonged sevoflurane administration at high concentrations and appears to require degradation by the obsolete absorbent Baralyme.[58] Some new absorbents, those lacking monovalent bases (e.g., NaOH), do not degrade sevoflurane.[59]

In contrast to normal (moist) carbon dioxide absorbents, older desiccated absorbents materially degrade all potent inhaled anesthetics.[60] Desiccated older absorbents degrade all anesthetics containing the CHF_2-O- moiety (i.e., desflurane and isoflurane) to carbon monoxide.[60] Degradation by soda lime is minimal at hydrations approximately 10% or greater than those found in normal soda lime.[60] Some new absorbents (again, those lacking monovalent bases) do not produce clinically important concentrations of carbon monoxide, even when completely dry.[61]

The Effect of Rebreathing

Inspired gas contains two gases: that delivered from the anesthetic machine and that previously exhaled by the patient and subsequently rebreathed. Because the patient removes (takes up) anesthetic from the rebreathed gas, the amount taken up and the amount rebreathed influence the inspired anesthetic concentration. An increase in uptake or rebreathing lowers the inspired concentration of a highly soluble gas more than the inspired concentration of a poorly soluble gas. This effect of uptake can be diminished by increasing the inflow rate to decrease rebreathing. An inflow rate that equals or exceeds minute ventilation eliminates rebreathing.[62]

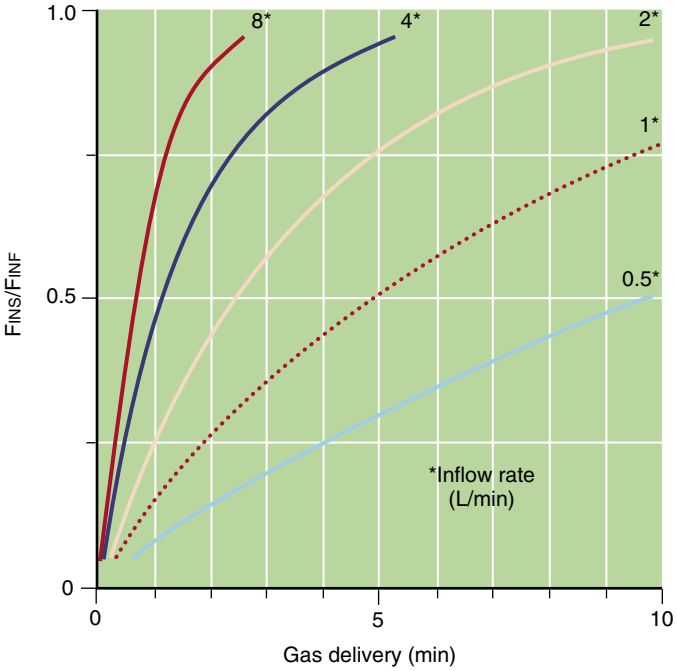

Figure 21-15 The inflow rate and circuit volume determine the rate at which the inspired anesthetic concentration (FINS) rises toward the inflowing concentration (FINF). In the case illustrated here, the circuit volume is 7 L. *(From Eger EI II: Effect of anesthetic circuit on alveolar rate of rise.* In *Eger EI [ed]: Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974, pp 192-205.)*

High inflow rates (i.e., ≥5 L/min) have the advantage of increasing the predictability of the inspired anesthetic concentration but the disadvantages of being wasteful and increasing atmospheric pollution. High inflow rates may be unacceptably costly because they increase consumption of expensive volatile anesthetics. High inflow rates may also dry inspired gas and make it difficult to estimate ventilation from excursions of the rebreathing bag. These several disadvantages prompt the use of low inflow rates.

Low-Flow or Closed-Circuit Delivery of Anesthesia

Much of the previous discussion assumed the use of a nonrebreathing system and a fixed inspired concentration of anesthetic. Although this approach does not invalidate the principles described earlier, it also does not reflect the variety of approaches applied in practice. Practice often deviates in two ways: (1) most anesthetists use lower inflow (fresh gas flow) rates to provide more economical delivery of anesthesia (Fig. 21-16), and (2) most anesthetists apply a constant alveolar rather than a constant inspired concentration because a constant alveolar concentration more closely reflects a constant level of anesthesia.

A low inflow rate provides several advantages and a few disadvantages, the latter particularly applying to kinetics. The advantages of low-inflow administration (defined as fresh gas flow of less than half the minute volume, usually less than 3 L/min) or closed-circuit anesthesia (defined as delivery of gases in amounts sufficient to replace only the gases—oxygen and anesthetic—removed by the patient) include lower cost, increased humidification, reduced heat loss, decreased release of anesthetic to the environment, and better capacity to assess physiologic variables such as ventilation. On the debit side, one must be more concerned about oxygen levels (especially if nitrous oxide is used because the patient also contributes nitrogen from stores in the body, and such nitrogen can slightly decrease the inspired concentration of oxygen). However, the debit of most immediate concern is the lack of control that low flow and especially closed circuits offer.

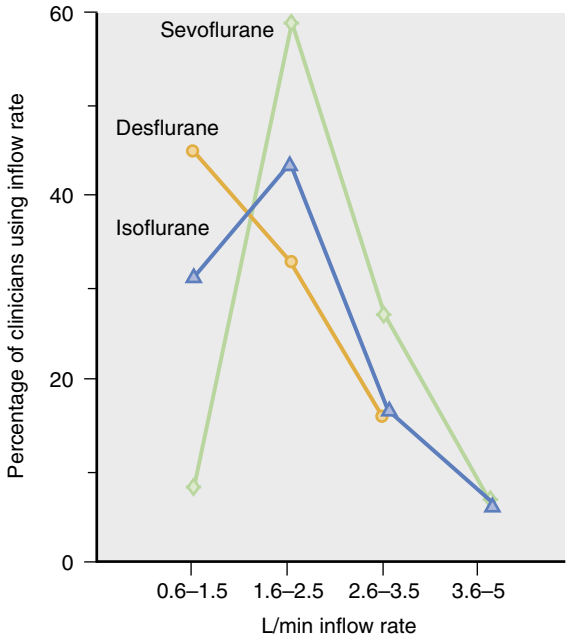

Figure 21-16 In 2005, anesthetists were surveyed regarding the inflow rates that they commonly used for maintenance of anesthesia. The responses varied broadly, but the majority used low-flow systems in which inflow rates of 2 L/min or less were applied. *(Unpublished data from Inform Research Flow Rate Tracking Study, May 2005, supplied as a personal communication by Baxter Healthcare Corp. to E. I. Eger II.)*

Closed-Circuit Anesthesia

Use of a closed circuit represents an extreme of anesthetic administration, one infrequently used because few systems completely eliminate leakage of gas from the circuit. Indeed, anesthetists often draw off approximately 200 mL/min for analysis of oxygen, carbon dioxide, and anesthetic levels.

Usually, closed-circuit anesthesia requires replacement of three gases: (1) oxygen, (2) nitrous oxide, and (3) a potent volatile anesthetic. Each replacement implies somewhat different considerations. Oxygen replacement remains constant unless metabolism changes as a result of a sympathetic response to stimulation, alteration in body temperature, or shivering. Replacement of nitrous oxide follows a fairly predictable course, in part because the concentration applied does not usually vary. Furthermore, nitrous oxide is the least soluble of anesthetics, especially in fat, and is the most prone to percutaneous loss (a constant value). Of most interest and potential variability is uptake of the potent inhaled anesthetics.

Uptake of potent anesthetics may be estimated from the values (constants) obtained by Yasuda and colleagues[10,11] in human volunteers. These values may be applied to achieve uptake at a constant alveolar concentration. To provide an appropriate level for comparison, I have assumed an alveolar concentration equal to MAC. The resulting figure (Fig. 21-17) reveals parallel shapes for each anesthetic, shapes dictated by the perfusion and solvent characteristics of the three major tissue compartments (plus intertissue diffusion). Thus, the large initial uptake rapidly decreases to a much lower level in 5 to 10 minutes as a result of the high initial uptake in the VRG (high because of its large perfusion) and the rapid decrease in uptake imposed by a short time constant (the time constant is obtained by taking the ratio of the capacity of a system to the flow through the system; it is useful in that it indicates the time for a 63% change to take place in the system). The subsequent slower decrease primarily results from the longer time constant of the MG, which dominates this period until its uptake declines below that provided by fourth compartment and the FG.

Although the curves for each anesthetic do not differ in shape, they differ in position. The height of each curve (i.e., uptake) is directly proportional to two factors: solubility and MAC. This relationship tends to minimize differences among anesthetics because solubility and MAC tend to move inversely. For example, although the MAC for desflurane is five times that for isoflurane, its uptake is less than twice that of isoflurane because of its lower solubility in blood and tissues.

Uptake may be estimated from the "square-root-of-time rule," first proposed by Severinghaus[63] and expanded greatly by

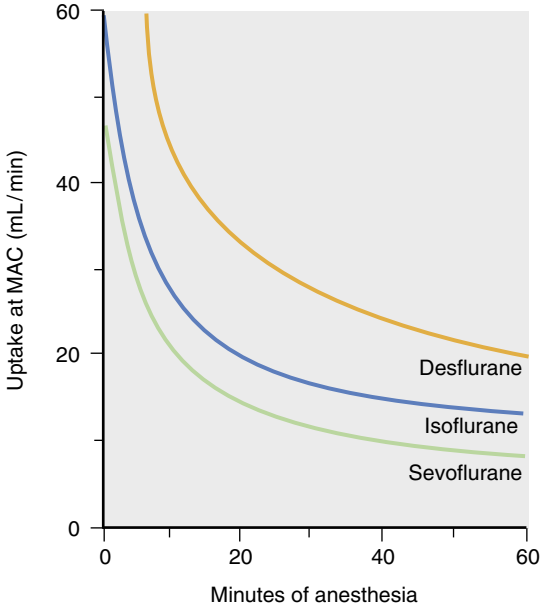

Figure 21-17 The uptake (in milliliters per minute), as illustrated in this graph, resulted from the application of constants calculated by Yasuda and coworkers[10,11] from their measurements in human volunteers. The application also assumed that alveolar concentration equals the minimum alveolar concentration (MAC) required to produce immobility in 50% of patients subjected to a surgical incision. Uptake is a function of both MAC and solubility of the anesthetic in blood and tissues. Thus, the fivefold higher MAC for desflurane than isoflurane is offset by a threefold lower solubility, which produces less than a twofold difference in uptake at any point in time. Uptake for all anesthetics initially declines rapidly as a function of the rate at which the vessel-rich group equilibrates. The further decline after 5 to 10 minutes is a function of the approach to equilibration of the muscle group. *(Data from Yasuda N, Lockhart SH, Eger EI II, et al: Kinetics of desflurane, isoflurane, and halothane in humans. Anesthesiology 74:489-498, 1991; and Yasuda N, Lockhart SH, Eger EI II, et al: Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg 72:316-324, 1991.)*

Lowe and Ernst[64] in their classic description of closed-circuit anesthesia. This rule states that uptake at any point in time may be estimated as uptake during the first minute of anesthesia divided by the square root of time in minutes. Making certain assumptions permits an estimate of uptake during the first minute. In general, uptake equals the product of blood solubility, cardiac output, and alveolar-to-venous anesthetic partial pressure difference. Several sources supply standard values for solubility and cardiac output, and the alveolar-to-venous anesthetic partial pressure difference may be estimated if we determine what alveolar partial pressure we wish and assume that the venous anesthetic partial pressure is inconsequential. At the start of anesthesia, an inconsequential venous partial pressure is reasonable because no anesthetic can appear in venous blood before recirculation (about 30 seconds), and even the anesthetic that appears is small in amount because tissue uptake is maximal during the first minute. Thus, we might estimate isoflurane uptake in a normal adult as $1.4 \times 5400 \times 0.0115$, or 87 mL, where 1.4 is the blood-gas partition coefficient, 5400 is cardiac output, and 0.0115 is MAC as a fraction of 1 atm. By 4 minutes, uptake would equal 87 mL/2; by 9 minutes, 87 mL/3; and by 64 minutes, 87 mL/8.

Hendrickx and associates[65] questioned the accuracy of the square-root-of-time rule and suggested that the rule overestimates the decrease in uptake with the passage of time. This author[66] considered whether the evidence provided by Hendrickx and colleagues overturned the square-root-of-time rule, and the matter continues to be debated.

Replacement of the anesthetic taken up may be accomplished by infusion of liquid anesthetic directly into the anesthetic circuit, either continuously or as boluses. Bolus injection from a syringe has an elegant simplicity but two disadvantages: (1) the circuit concentration modestly oscillates, and (2) the anesthetist is required to remember when and how much to inject. An alternative solution applies a variable bypass (Tec-type) vaporizer, one capable of accurate delivery of a range of concentrations at low inflow rates (e.g., 200 mL/min). This solution may not be applicable in the initial delivery of anesthesia because the demand for vapor may exceed the capability of presently available vaporizers. For example, the maximum output of a conventional isoflurane vaporizer is 5%, and at a 200-mL/min flow of oxygen, only approximately 10 mL of isoflurane vapor can be produced per minute, far less than the 87 mL estimated earlier. Even after 1 hour of anesthesia, an isoflurane vaporizer is barely capable of meeting the demand for anesthetic (Fig. 21-18A). This difficulty may be overcome in several ways. If a concentration less than MAC is acceptable, less delivery of vapor is required. Thus, the concurrent use of nitrous oxide decreases demand on the vaporizer. In addition, the use of nitrous oxide also increases the total fresh gas flow to compensate for the considerable uptake of nitrous oxide. If fresh gas flow increases to 1500 mL/min, 79 mL of isoflurane vapor can be produced. Another solution is to select an anesthetic with a vaporizer capability closer to demand. Such a solution tends to be available for less soluble anesthetics. For example, we calculate the uptake of desflurane in the first minute of anesthesia to be $0.45 \times 5400 \times 0.06$, or 146 mL. At a 200-mL/min flow of oxygen, the 18% maximum output of a desflurane vaporizer permits delivery of 44 mL. Although it is still inadequate to meet demand in the first minute, this figure is 2.6 times closer to meeting that demand than the isoflurane vaporizer, and within 10 minutes, the desflurane vaporizer can supply the required volume (see Fig. 21-18A).

Figure 21-18A suggests one of the major difficulties associated with the closed-circuit approach, namely, control. Clearly, there is an enormous difference between delivered (i.e., vaporizer dial) and alveolar concentrations. The differences decrease with less soluble anesthetics, but even with an anesthetic such as desflurane and even after the initial high-uptake period is passed, the dialed concentration markedly exceeds the alveolar concentration that it sustains. This means that changes in uptake (e.g., secondary to the increase in cardiac output that may result from surgical stimulation) can considerably alter alveolar anesthetic concentration unless the delivered concentration is changed. The alveolar concentration changes for two reasons: (1) assuming constant ventilation, the difference between alveolar and inspired concentrations varies directly with uptake (e.g., greater uptake increases the difference), and (2) because of rebreathing, the inspired concentration varies inversely with uptake (e.g., increased uptake lowers the inspired concentration). Thus, the sum of these effects either decreases or increases the alveolar concentration. A closed circuit has an inherent element of instability not present in an open circuit.

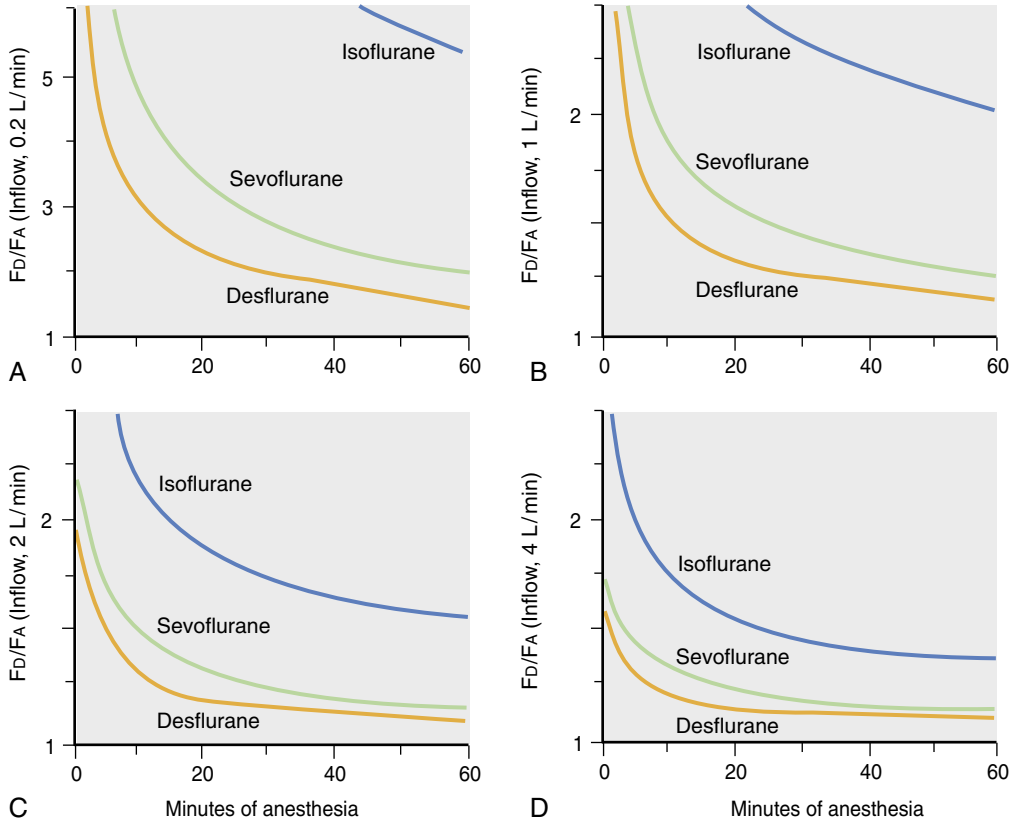

Figure 21-18 **A** to **D,** The ratio of delivered to alveolar concentrations (FD/FA) required to sustain the alveolar concentration constant at, for example, the minimum alveolar concentration (MAC) is a function of several factors. First, it is determined by uptake (see Fig. 21-17) and thus is greatest with the most soluble anesthetic, isoflurane. Second, it is determined by rebreathing and thus decreases with increasing inflow rates. Although these graphs have the same shape, the concentrations at any point in time progressively decrease as the inflow rate increases. The lowest values for any anesthetic result from a non-rebreathing system (i.e., when the inflow rate equals or exceeds minute ventilation).

Low-Flow Anesthetic Delivery

The instability of the closed circuit may be greatly mitigated by the use of low-flow (less than half minute ventilation) anesthetic delivery. Low-flow delivery may provide most of the advantages of closed systems while retaining considerable advantages over open systems in economy, maintenance of humidification and temperature, and limitation of atmospheric pollution. Low-flow delivery also diminishes the disadvantages of the closed circuit in the areas of constancy of oxygen and anesthetic levels and elimination of carbon monoxide and toxic anesthetic breakdown products.

In a low-flow delivery system, two factors control the relationship between the concentration delivered from a vaporizer (FD) and that in the alveoli (FA), a relationship that may best be described as the ratio of the two variables (FD/FA). First, we have already seen that uptake governs this ratio in a closed system (see Fig. 21-18A). Thus, FD/FA is higher for more soluble anesthetics, and regardless of solubility, the ratio is highest early in anesthetic administration and decreases rapidly in the first 5 to 10 minutes of anesthesia (as uptake by the VRG of tissues decreases to the point of near-equilibration) and more slowly thereafter (as uptake by tissue groups with longer time constants, such as muscle, the fourth compartment, and fat, decreases).

Second, the inflow rate also governs FD/FA. The relationship is inverse: the higher the inflow rate, the lower the ratio (compare Fig. 21-18B to D with Fig. 21-16A). An increase in inflow rate decreases FD/FA by decreasing rebreathing. Rebreathing is important because uptake of anesthetic depletes the concentration of anesthetic in rebreathed gases, and hence the concentration in delivered gases (FD) must be sufficient to compensate for this depletion. The higher the inflow rate, the less the compensation required because rebreathing is less.

However, increases in the inflow rate do not produce proportional decreases in FD/FA. The greatest reduction in FD/FA is achieved with modest increases in the inflow rate. Thus, a large decrease occurs when the inflow rate is changed from that needed for a closed circuit (Fig. 21-18A) to a 1-L/min inflow rate (Fig. 21-18B), whereas only a small decrease occurs when the inflow rate is increased from 2 to 4 L/min (Fig. 21-18C and D). Once the inflow rate exceeds minute ventilation (i.e., a non-rebreathing system exists), further increases in inflow rate have no effect on FD/FA, and FD/FA is the same as the ratio of inspired concentration (FI) to alveolar concentration (i.e., FD/FA = FI/FA).

I have used the term *anesthetic tether* as a metaphor for the FD/FA ratio.[67] A large ratio equates to a long tether, one permitting considerable variability in the alveolar concentration. With a long tether, changes in uptake secondary to changes in physiologic variables (e.g., an increase in cardiac output consequent to surgi-

cal stimulation) can appreciably alter the alveolar concentration and thus the level of anesthesia. In the example just cited, there is positive feedback because by increasing uptake, surgical stimulation decreases the alveolar concentration and thereby increases the perception of that stimulation. Most anesthetists prefer a short anesthetic tether because it provides tighter control over the level of anesthesia. A shorter tether is produced by the use of less soluble anesthetics or higher inflow rates, or both.

Another benefit of a short tether accrues to the rare anesthetist who does not have access to an agent-specific analyzer. In the absence of such an analyzer, some anesthetists may rely on the dial setting of the vaporizer to indicate the concentration of anesthetic in the patient's lungs (i.e., would assume that F_D equals F_A). Although the vaporizer setting may correlate with the concentration in the lungs, the correlation may be a distant one. The correlation is poor (1) early in anesthesia for all agents, (2) later in anesthesia with closed circuits or very low inflow rates, and (3) later in anesthesia for more soluble agents, such as isoflurane, even at higher inflow rates. Note that with poorly soluble anesthetics, such as sevoflurane and desflurane, by 30 to 60 minutes after the inception of anesthetic administration, the concentration delivered by the vaporizer may be less than 20% greater than that in the alveoli (i.e., the F_D/F_A ratio is 1.2), even at inflow rates of 1 to 2 L/min (Fig. 21-18B and C).

Economic concerns increasingly dictate the practice of anesthesia. The reader may wish to appreciate the differences in anesthetic consumption as a function of the choice of inflow rate, the duration of anesthesia, and the choice of anesthetic. The reports by Yasuda and coauthors[10,11] provide constants that may be used to estimate the uptake of commonly available potent inhaled anesthetics. By using the gas laws and published values for specific gravities, values for uptake of vapor may be converted to milliliters of liquid taken up. Combining this information with knowledge of the function of circuit rebreathing systems[68] allows an estimate of the amount of liquid in milliliters that must be delivered at various inflow rates to provide a constant alveolar concentration equal to MAC (Table 21-3).[68] The relative costs of anesthesia may be estimated by applying the price of the anesthetic of interest to the number of milliliters needed to sustain anesthesia.

Table 21-3 Milliliters of Liquid Anesthetic at Various Inflow Rates Needed to Sustain an Alveolar Concentration Equal to Minimum Alveolar Concentration

Anesthetic	Anesthetic Duration (min)	Inflow Rate (L/min, Not Including Anesthetic)				
		0.2	1.0	2.0	4.0	6.0
Halothane	30	3.0	4.1	5.4	8.0	10.5
	60	4.6	6.5	9.0	13.9	18.8
Isoflurane	30	4.0	5.8	8.0	12.3	16.7
	60	6.3	9.6	13.9	22.3	30.7
Sevoflurane	30	3.3	6.3	10.1	17.6	25.2
	60	4.9	10.9	18.2	33.0	47.8
Desflurane	30	6.7	14.8	25.0	45.2	65.4
	60	10.1	26.1	46.0	85.8	126

Modified from Weiskopf RB, Eger EI II: Comparing the costs of inhaled anesthetics. Anesthesiology 79:1413-1418, 1993.

If both economy and a low F_D/F_A ratio are desirable, the aforementioned considerations suggest that a good compromise is the use of a low-flow delivery system after an initial period of higher flow. Higher flow (4 to 6 L/min) might be applied early in anesthesia (i.e., at the time of highest uptake) and then be decreased progressively as uptake decreases. Flow rates of 2 to 4 L/min might be given for the period from 5 to 15 minutes after induction of anesthesia, and flow rates of 1 to 2 L/min may be given thereafter. If the average inflow rate were 2 L/min, 1 hour of anesthesia with the four potent anesthetics listed in Table 21-3 would require the administration of 9.0 to 46.0 mL of liquid. This fivefold range of values is smaller than the eightfold range of potency (MAC) values because the amount of anesthetic delivered must account for more than potency. The amount delivered must also compensate for uptake and loss of anesthetic through the overflow valve. The relatively smaller uptake and loss of the less soluble desflurane and sevoflurane are what accounts for the reduction from eightfold to fivefold. An even smaller range is found at lower inflow rates, with approximately twofold decreases for a closed circuit. However, such flows should not be used with sevoflurane because of the greater concentrations of compound A that result.

Recovery from Anesthesia

Nearly all the factors that govern the rate at which the alveolar anesthetic concentration rises on induction apply to recovery. Thus, the immediate decline is extremely rapid because the washout of functional residual capacity by ventilation is as rapid as the washin. Only 2 minutes is required to eliminate 95% to 98% of nitrogen from the lungs when pure oxygen is breathed.

Nitrogen, however, is a poorly soluble gas relative to the inhaled anesthetics. As ventilation sweeps anesthetic from the alveoli, an anesthetic partial pressure gradient develops between the partial pressure in the returning venous blood and the partial pressure in the alveoli. This gradient drives anesthetic into the alveoli, thereby opposing the tendency of ventilation to lower the alveolar concentration. The effectiveness of the venous-to-alveolar gradient in opposing the tendency of ventilation to decrease the alveolar anesthetic partial pressure is in part determined by the solubility of the anesthetic such that an agent with greater solubility, such as isoflurane, opposes the elimination produced by ventilation more than an agent with lesser solubility does, such as desflurane and sevoflurane, because a greater reserve exists in blood for the more soluble anesthetics. Thus, the fall in the alveolar partial pressure of isoflurane is slower than the fall with desflurane and sevoflurane. The rapidity of recovery largely depends on the solubility of the anesthetic.[69]

Differences Between Induction and Recovery

Recovery differs from induction in two crucial ways. First, on induction, the effect of solubility to hinder the rise in alveolar anesthetic concentration could be overcome by increasing the inspired anesthetic concentration (i.e., by applying overpressure). No such luxury is available during recovery; the inspired concen-

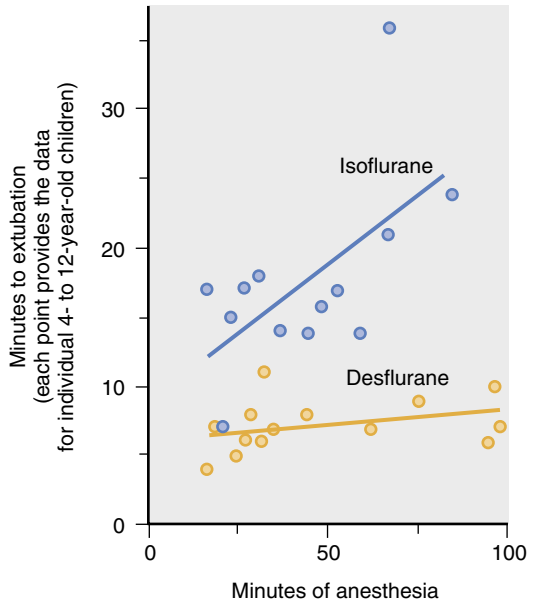

Figure 21-19 Solubility and duration of anesthesia affect the decrease in alveolar concentration on recovery and hence the time needed to recover from anesthesia. The time to tracheal extubation after anesthesia with anesthetics that have different solubilities illustrates these two aspects of recovery.[72] The time to extubation is longer after anesthesia in children anesthetized with isoflurane (the more soluble anesthetic) than in those anesthetized with desflurane. In addition, the duration of anesthesia has less impact on the time to extubation after anesthesia with the less soluble desflurane because most of the desflurane is cleared at the lung (does not recirculate to delay recovery.) *(Data from Nordmann GR, Read JA, Sale SM, et al: Emergence and recovery in children after desflurane and isoflurane anaesthesia: Effect of anaesthetic duration. Br J Anaesth 96:779-785, 2006.)*

tration cannot be reduced below zero. Second, on induction, all the tissues initially have the same anesthetic partial pressure—zero. On recovery, the tissue partial pressures are variable. The VRG has a pressure that usually equals that required for anesthesia; that is, the VRG has come to equilibrium with the alveolar anesthetic partial pressure. The MG may or may not have the same partial pressure as that found in the alveoli. A longer anesthetic course (2 to 4 hours) might permit equilibrium to be approached, but a shorter one would not. The high capacity of fat for all anesthetics except nitrous oxide precludes equilibration of the FG with the alveolar anesthetic partial pressure until hours or even days after anesthesia.

The failure of muscle and fat to equilibrate with the alveolar anesthetic partial pressure means that these tissues cannot initially contribute to the transfer of anesthetic back to the lungs. In fact, as long as an anesthetic partial pressure gradient exists between arterial blood and tissue blood, that tissue will continue to take up anesthetic. Thus, for the first several hours of recovery from anesthesia, fat continues to take up anesthetic and by so doing accelerates the rate of recovery. Only after the alveolar (equals arterial) anesthetic partial pressure falls below that in a tissue can the tissue contribute anesthetic to the alveoli.

The failure of several tissues to reach equilibration with the alveolar anesthetic partial pressure means that the rate of decrease in alveolar anesthetic on recovery is more rapid than its rate of increase on induction and that recovery depends in part on the duration of anesthesia.[70,71] A longer duration of anesthesia puts more anesthetic into the slowly filling muscle and fat depots. Obviously, these reservoirs can supply more anesthetic to the blood returning to the lungs when they are filled than when they are empty and can thereby prolong the time to recovery.[69]

Solubility influences the effect of duration of anesthesia on the rate at which the alveolar anesthetic partial pressure declines.[71] The decline in partial pressure of a poorly soluble agent is rapid in any case, and thus the acceleration imparted by a less than complete tissue equilibration cannot significantly alter the rate of recovery. The approach to equilibration becomes important with increasing solubility. With a more soluble anesthetic, recovery may be rapid after a short duration of anesthesia but may be slow after a prolonged duration. Recovery from anesthesia with desflurane and sevoflurane is more rapid and less influenced by the duration of anesthesia than with isoflurane.[69] For example, in children the time to extubation is longer after anesthesia with isoflurane than after anesthesia with desflurane (Fig. 21-19).[72] In addition, the duration of anesthesia minimally affects the time to extubation after desflurane anesthesia but has a substantial effect after isoflurane anesthesia (see Fig. 21-19).[72] Similarly, in volunteers anesthetized with 1.25 MAC desflurane versus sevoflurane, response to command and orientation occur sooner after desflurane, and duration has less of an impact on the time to respond and be oriented (Fig. 21-20).[73]

The importance of solubility and duration of anesthesia on the rate of recovery may be appreciated with the use of context-dependent times, or times to reach particular levels of washout of the alveoli or the VRG after the administration of anesthetics of specific duration.[74,75] Regardless of the duration of anesthesia, the alveolar concentrations of poorly soluble anesthetics (nitrous oxide, desflurane, sevoflurane) and a moderately soluble anesthetic (isoflurane) decrease by 60% in roughly the same period

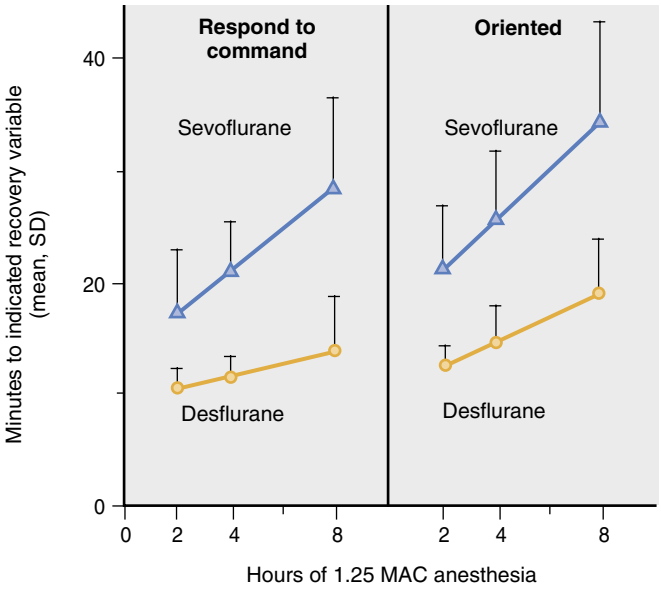

Figure 21-20 A differential time to awakening and a differential effect of anesthetic duration is shown after 2, 4, or 8 hours of anesthesia at 1.25 minimum alveolar concentration (MAC) for desflurane versus sevoflurane. Awakening to respond to a command or to orientation is more rapid after anesthesia with the less soluble desflurane, and the duration of anesthesia has less of an impact. *(From Eger EI II, Gong D, Koblin DD, et al: Effect of anesthetic duration on kinetic and recovery characteristics of desflurane vs. sevoflurane [plus compound A] in volunteers. Anesth Analg 86:414-421, 1998.)*

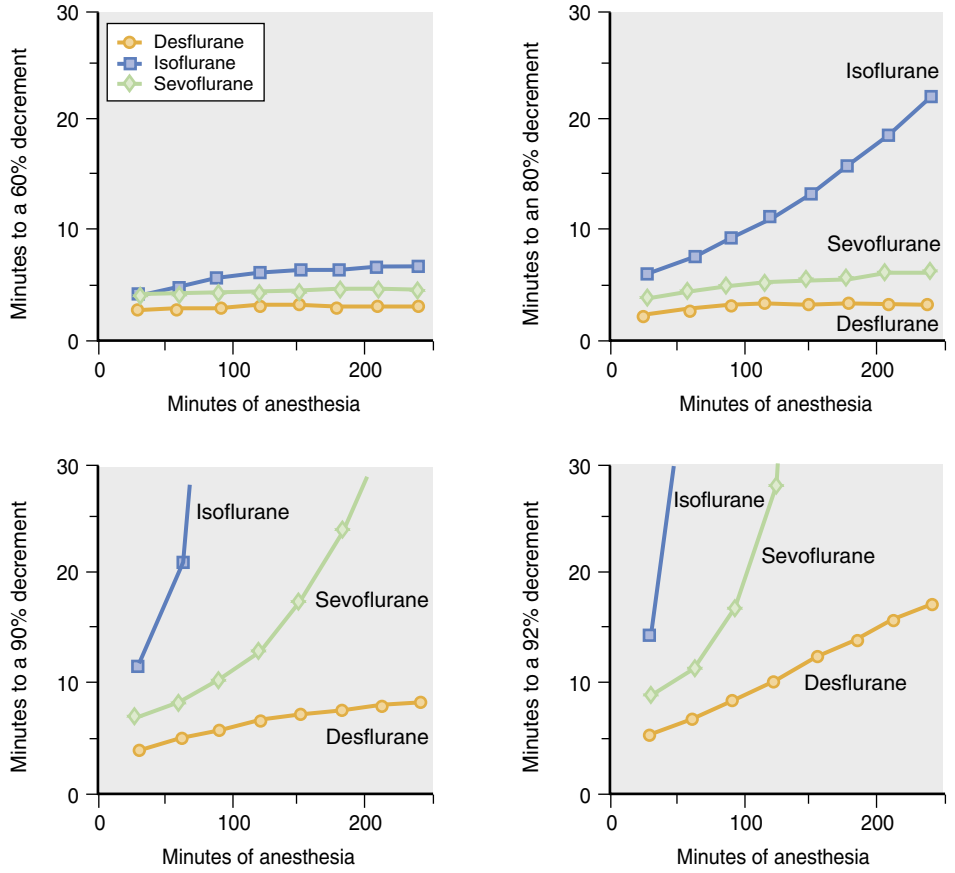

Figure 21-21 The time to decrease partial pressure in the alveoli or vessel-rich group by a certain fraction directly depends on several factors, primary among which are the solubility of the anesthetic and the duration of anesthesia. If a decrement of 60% is needed, little difference in time to recovery will be found for a comparison of isoflurane, sevoflurane, and desflurane. If an 80% decrement is needed to permit awakening, awakening from isoflurane will be delayed for progressively longer times as the duration of anesthesia is increased, but awakening from desflurane or sevoflurane will be minimally affected. If 90% of the anesthetic must be eliminated, awakening from both sevoflurane and isoflurane will be delayed more and more as the duration of anesthesia increases (isoflurane more than sevoflurane), but awakening from desflurane will be minimally affected. At a 92% decrement, the duration of anesthesia will also affect recovery from desflurane. *(Modified from Eger EI II, Shafer SL: Tutorial: Context-sensitive decrement times for inhaled anesthetics. Anesth Analg 101:688-696, 2005.)*

(Fig. 21-21).[75] If the desired recovery were attained at a 60% decrease, the choice of anesthetic would matter little on the time to recovery from anesthesia, even after prolonged anesthesia. If an 80% decrement is required, an increasing duration of anesthesia markedly affects recovery from isoflurane but minimally affects recovery from sevoflurane and desflurane (see Fig. 21-21). At a 90% decrement, the duration of anesthesia considerably affects recovery from both isoflurane and sevoflurane, and at a 92% decrement, recovery from desflurane begins to be affected (see Fig. 21-21).

More than 90% elimination of anesthetic may be required to restore pharyngeal reflexes to normal. Significant pharyngeal dysfunction may be found at 25% of MAC-awake (i.e., 5% to 8% of MAC).[76] At such small MAC values, context-sensitive decrement times become of increasing importance to recovery. McKay and associates[77] found that the capacity to drink 20 mL of water without coughing or drooling occurred sooner after desflurane than after sevoflurane (Fig. 21-22).

Pharmacodynamics adds to the determination of recovery. If immobility is accomplished with an inhaled anesthetic, the concentration exceeds MAC. Recovery sets a different goal, namely, awakening—that is, reaching MAC-awake, the concentration of anesthetic allowing appropriate response to command in 50% of subjects. MAC-awake differs among anesthetics. As a fraction of MAC, the MAC-awake of nitrous oxide (65% of MAC) exceeds that of desflurane isoflurane, and sevoflurane (approximately 33% of MAC).[78-80] The MAC-awake of propofol is still less (20%).[81] A lower MAC-awake value correlates with a greater capacity to provide amnesia: propofol is most potent and nitrous oxide least potent. However, a high MAC-awake means that awakening will occur at a higher anesthetic concentration relative to that required for anesthesia. All other factors being equal, awakening from nitrous oxide anesthesia is more rapid than awakening from anesthesia with desflurane, isoflurane, or sevoflurane.

Can I Have My Cake and Eat It Too?

The less soluble new inhaled anesthetics desflurane and sevoflurane offer more rapid recovery from anesthesia than with more soluble older anesthetics, such as isoflurane. However, this rapid recovery comes at a price: the new anesthetics are more expensive. Might it be possible to have the best of both worlds by using isoflurane for the major portion of anesthesia and reserve desflurane

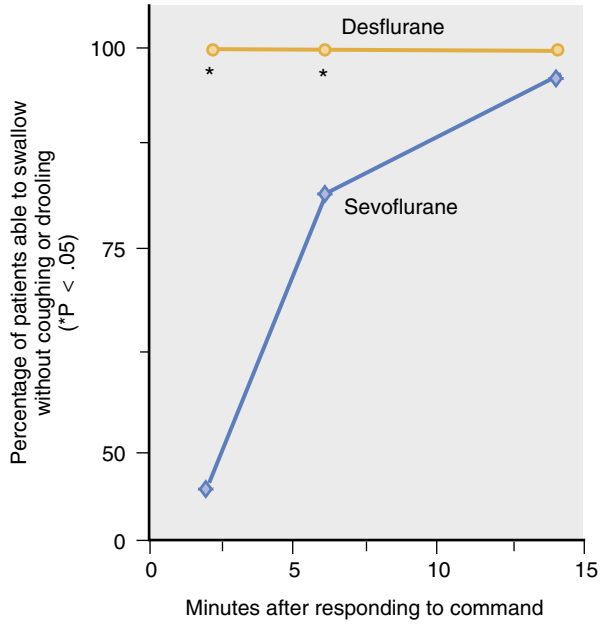

Figure 21-22 Recovery of function of pharyngeal muscles may require a decrement of 92% to 95% in anesthetic concentration.[76] At such substantial amounts of elimination, context-sensitive decrement times would suggest the possibility of more rapid recovery of airway reflexes with the less soluble desflurane, even though both anesthetics are poorly soluble. McKay and colleagues[77] measured the time from responding to command to the time that patients could swallow 20 mL of water without coughing or drooling. All patients anesthetized with desflurane could swallow 20 mL of water without coughing or drooling 2 minutes after responding to command, but fewer than 50% of patients anesthetized with sevoflurane could do so. At 6 minutes after responding to command, a significant percentage of patients given sevoflurane still could not swallow the water without coughing or drooling.

(or sevoflurane) for the final minutes? The premise would be that such an approach would provide the economy of isoflurane and the rapid recovery of desflurane. Neumann and colleagues[82] tested this premise. Volunteers were anesthetized for 2 hours on three occasions: once with 1.25 MAC isoflurane, once with 1.25 MAC desflurane, and once with 1.5 hours of 1.25 MAC isoflurane followed by 0.5 hours of a combination of desflurane and isoflurane ("crossover"). The combination provided a total of 1.25 MAC (i.e., desflurane was added as the isoflurane was eliminated, the addition being sufficient to sustain a total of 1.25 MAC). To ensure economy, all anesthetics were delivered at an inflow rate of 2 L/min. The premise was not realized. Recovery after crossover was no faster than recovery after isoflurane alone (Fig. 21-23). Recovery after desflurane alone was considerably faster than recovery after either isoflurane or the crossover from isoflurane to desflurane.

Impact of Metabolism

Saturation of the enzymes responsible for the metabolism of anesthetics may limit the ability of metabolism to significantly alter the rate at which the alveolar anesthetic partial pressure rises. This limitation does not exist on recovery, and metabolism may be an important determinant of the rate at which the alveolar anesthetic partial pressure declines. However, such metabolism applies significantly only to obsolete anesthetics such as halothane and methoxyflurane.[23] Sevoflurane is only slightly metabolized and desflurane and isoflurane undergo so little metabolism that such degradation cannot affect their kinetics.[10,11]

Diffusion Hypoxia

Uptake of large volumes of nitrous oxide on induction of anesthesia gives rise to the concentration and second gas effects. On recovery from anesthesia, the outpouring of large volumes of nitrous oxide can produce what Fink[83] called diffusion anoxia. These volumes may cause hypoxia (Fig. 21-24) in two ways. First, they may directly affect oxygenation by displacing oxygen.[83] Second, by diluting alveolar carbon dioxide, they may decrease respiratory drive and hence ventilation.[83,84] Both these effects require that large volumes of nitrous oxide be released into the alveoli. Because large volumes of nitrous oxide are released only during the first 5 to 10 minutes of recovery, this is the period of greatest concern. This concern is enhanced by the fact that the first 5 to 10 minutes of recovery may also be the time of greatest respiratory depression. For these reasons, many anesthetists administer 100% oxygen for the first 5 to 10 minutes of recovery. This procedure may be particularly indicated in patients with preexisting lung disease or in those in whom postoperative respiratory depression is anticipated (e.g., after nitrous oxide–narcotic anesthesia).

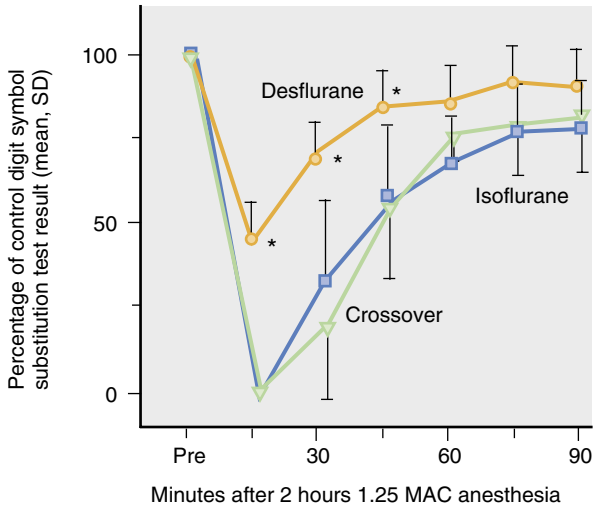

Figure 21-23 Volunteers were anesthetized for 2 hours on three occasions: once with 1.25 minimum alveolar concentration (MAC) isoflurane; once with 1.25 MAC desflurane; and once with 1.5 hours of 1.25 MAC isoflurane, followed by 0.5 hour of a combination of desflurane and isoflurane ("crossover"). The combination provided a total of 1.25 MAC (i.e., desflurane was added as the isoflurane was eliminated, the addition being sufficient to sustain a total of 1.25 MAC). All anesthetics were delivered at a 2-L/min inflow rate. At the end of 2 hours, anesthetic administration was discontinued and a non-rebreathing system was applied. The digit symbol substitution test (DSST) was applied at 15-minute intervals and the results were displayed as a percentage of the control (preanesthesia) results. Recovery of judgment and cognition as defined by the DSST was more rapid at 15, 30, and 45 minutes with desflurane given alone (*asterisks* indicate significant differences from isoflurane or crossover results), and recovery was less affected by the duration of anesthesia with desflurane. *(Data from Neumann MA, Weiskopf RB, Gong DH, et al: Changing from isoflurane to desflurane towards the end of anesthesia does not accelerate recovery in humans. Anesthesiology 88:914-921, 1998.)*

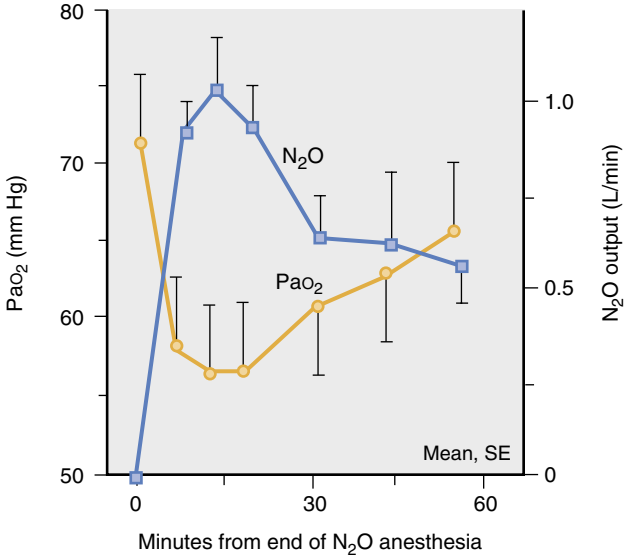

Figure 21-24 At time zero, the inspired gas was changed from 21% oxygen/79% nitrous oxide to 21% oxygen/79% nitrogen. Arterial oxygen subsequently fell in association with the outpouring of nitrous oxide. *(Modified from Sheffer L, Steffenson JL, Birch AA: Nitrous-oxide–induced diffusion hypoxia in patients breathing spontaneously. Anesthesiology 37:436-439, 1972.)*

Impact of the Anesthetic Circuit

The anesthetic circuit may limit the rate of recovery just as it limits induction. If not disconnected from the circuit on cessation of anesthetic delivery, the patient may continue to inspire anesthetic. To reduce the inspired level to zero or nearly zero, two factors must be taken into account: the anesthetic within the circuit must be washed out, and the patient's exhaled air, which contains anesthetic, must not be rebreathed. The effect of each of these factors on raising the inspired anesthetic concentration can be overcome with the use of high inflow rates of oxygen (i.e., 5 L/min or greater).

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22 Pulmonary Pharmacology

Key Points

1. Inhaled anesthetics affect every facet of pulmonary physiology, from the variety of forces controlling ventilation and pulmonary blood flow to surface tension, secretion of mucus, airway smooth muscle tone, and lung inflammatory responses.
2. The bronchodilatory actions of volatile anesthetics occur through several complex mechanisms that involve both a decrease in intracellular calcium concentration and a reduction in calcium sensitivity. Volatile anesthetics increase baseline pulmonary dynamic compliance, but these agents are more effective at attenuating increases in pulmonary airway resistance caused by chemical or mechanical stimuli. Inhaled anesthetics preferentially dilate the distal airways rather than the proximal airways.
3. Inhaled anesthetics diminish the rate of mucus clearance by decreasing ciliary beat frequency, disrupting metachronism, or altering the characteristics of mucus.
4. Pulmonary surfactant decreases the work of breathing by reducing alveolar surface tension. Volatile anesthetics cause progressive, yet reversible reductions in phosphatidylcholine, the main lipid component of surfactant. The roles of depressed mucociliary function and alterations in type II alveolar cell function in postoperative pulmonary complications after the administration of a volatile agent are unknown.
5. The multiple sites of actions of inhaled anesthetics on the pulmonary parenchyma and vasculature complicate direct assessment of anesthetic-induced alterations in pulmonary vascular resistance. Volatile anesthetics cause a biphasic contraction-relaxation response in pulmonary vascular smooth muscle that is mediated at multiple sites through a Ca^{2+}-mediated signaling pathway. Overall, the net effect of inhaled anesthetic–induced changes in pulmonary vascular resistance is relatively small.
6. Hypoxic pulmonary vasoconstriction (HPV) is an important mechanism by which pulmonary blood is preferentially redistributed away from poorly ventilated lung regions to those with adequate alveolar ventilation. Most inhaled anesthetics attenuate HPV in vitro and exert relatively modest inhibitory effects on HPV, shunting, or oxygenation in vivo.
7. Inhaled anesthetics (with the exception of xenon) reduce tidal volume and minute ventilation and cause tachypnea in a dose-related fashion. The relative effect of inhaled anesthetics in increasing arterial carbon dioxide tension (as an index of respiratory depression) is enflurane > desflurane = isoflurane > sevoflurane = halothane > nitrous oxide.
8. Inhaled anesthetics affect the inspiratory and expiratory respiratory muscles to varying degrees, possibly as a result of the differential sensitivity of bulbospinal inspiratory and expiratory neurons.
9. All inhaled anesthetics depress the ventilatory responses to hypercapnia and hypoxia by altering central and peripheral chemoreceptor function in a dose-dependent fashion. The effects of subanesthetic concentrations of inhaled agents on hypercapnic responses are controversial. Inhibition of hypoxic responses by subanesthetic concentrations of volatile agents depends on the agent used and perhaps the baseline state of central nervous system arousal. These findings may have important clinical implications during the perioperative period.
10. Volatile anesthetics may exhibit proinflammatory actions and worsen acute lung injury. Alternatively, volatile anesthetics have been shown to reduce inflammation and improve both chemical and physiologic pulmonary function in acute lung injury.

This chapter describes the pulmonary pharmacology of inhaled anesthetics. The lungs are unique in their exposure to a wide variety a physical forces, including ventilation, blood flow, and surface tension, and inhaled anesthetics selectively modulate each of these properties. Specific sections of this chapter focus on airway tone, pulmonary vascular resistance (PVR), mucociliary function, surfactant production, ventilatory control, and acute lung injury. The actions of volatile anesthetics on each of these systems are discussed.

Bronchomotor Tone

Transient increases in airway resistance may be caused, at least in part, by an increase in bronchiolar smooth muscle tone. Patients without recent symptoms of asthma have a very low frequency of perioperative respiratory complications, yet perioperative bronchospasm develops in approximately 6% of patients with asthma. Prospective studies have demonstrated that 1.7% of patients with asthma experience a poor respiratory outcome[1] and that 25% wheeze after the induction of anesthesia.[2] Of the 40 cases of bronchospasm resulting in settled malpractice claims reported by the American Society of Anesthesiologists Closed Claims Project,[3] 88% involved brain damage or death, and only half of these patients had a history of asthma or chronic obstructive pulmonary disease (COPD). Because significant bronchospasm may occur in normal subjects without underlying lung disease, understanding of the physiologic effects of inhaled agents on bronchial smooth muscle is very important.

Pharmacology of Bronchial Smooth Muscle

Pinto-Pereira and colleagues[4] summarized the mechanisms by which increases in airway resistance might occur. Airway smooth muscle extends as far distally as the terminal bronchioles and is affected by autonomic nervous system activity and nonadrenergic, noncholinergic mechanisms. Parasympathetic nerves originating in vagal centers within the central nervous system mediate baseline airway tone and reflex bronchoconstriction. Changes in intracellular calcium (ICa^{2+}) levels and Ca^{2+} influx may be caused by alterations in cyclic nucleotides within bronchial smooth muscle. Agonist-induced contraction is mediated by an increase in myosin light chain kinase activity, phosphorylation of the 20-kd regulatory myosin light chain, and an increase in Ca^{2+} sensitivity.[5] Exogenous administration of acetylcholine or stimulation of the vagus nerve increases the level of cyclic guanosine monophosphate (cGMP) relative to cyclic adenosine monophosphate (cAMP) and results in bronchial smooth muscle contraction. Activation of bronchial smooth muscle cells by agonist also involves the second messenger cyclic adenosine diphosphate ribose, which indirectly releases Ca^{2+} from the sarcoplasmic reticulum (SR) by activating ryanodine channels.[6] Agonist-induced stimulation of particulate guanylyl cyclase relaxes bronchial smooth muscle by decreasing Ca^{2+} current. In contrast, stimulation of soluble guanylyl cyclase by substances such as nitric oxide (NO) reduces ICa^{2+} concentration and Ca^{2+} sensitivity.[7]

Release of histamine in the airway or various forms of mechanical or chemical stimulation may increase afferent vagal activity and produce reflex bronchoconstriction. This increase in bronchomotor tone is attenuated by the cholinergic antagonist atropine. M_2 and M_3 muscarinic receptors on airway smooth muscle mediate bronchoconstriction by increasing Ca^{2+} sensitivity.[8] Presynaptic M_2 muscarinic receptors have also been identified that inhibit release of acetylcholine, and thus drugs that preferentially inhibit M_2 receptors (e.g., ipratropium bromide) may paradoxically produce bronchoconstriction,[9] although this effect is not commonly observed in patients.

Adrenergic receptors in bronchial smooth muscle are classified into α and β_2 types. α-Receptors have been characterized in the human bronchial tree, but their activity may be clinically insignificant. In contrast, the β_2-receptor subtypes play an important role in bronchiolar smooth muscle responsiveness. Stimulation of β_2-adrenoreceptors causes cAMP-mediated relaxation via activation of protein kinase A and subsequent efflux of Ca^{2+} out of the cell and into the SR. Notably, asthma, as well as allergy- and methacholine-induced bronchospasm, does not appear to be genetically linked to a dominant β_2-adrenoceptor gene.[10]

Respiratory epithelium releases substances that modulate bronchial smooth muscle tone. Epithelial removal enhances contractile responses to acetylcholine, histamine, and serotonin in large airways and decreases relaxation responses to isoproterenol in small airways. These actions are analogous to the effect of endothelial damage on vascular smooth muscle tone. However, porcine bronchiolar epithelium–mediated bronchomotor activity is not significantly affected by cardiopulmonary bypass, in contrast with the vascular endothelium–mediated smooth muscle dysfunction seen in this situation.[11] Although endogenous epithelial factors have been identified, NO may play an important vasodilatory role in respiratory epithelium, similar to that of vascular endothelium. Endothelin-1 is also a potent endogenous bronchoconstrictor, as well as vasoconstrictor, that functions by activation of the inositol triphosphate (IP_3) pathway.[12]

Volatile Anesthetics

Volatile anesthetics are all bronchodilators, but some controversy remains about which volatile anesthetic exerts the most potent bronchodilation. In many studies using animal models, it appears that halothane has the most pronounced effect of relaxing airway smooth muscle. It is important to eliminate the indirect effects of arterial carbon dioxide tension when examining the actions of volatile agents on bronchial tone, especially during spontaneous ventilation, because hypercapnia-induced bronchodilation and hypocapnia-induced bronchoconstriction are both attenuated by isoflurane.[13] What may be interpreted as a dose-dependent effect of deepening the level of anesthesia with volatile anesthetics may actually be due to an indirect action mediated by a progressive increase in carbon dioxide tension. Isoflurane and halothane (1.5 minimum alveolar concentration [MAC]) produce similar reductions in airway resistance in a canine model of bronchospasm induced by aerosolized *Ascaris* antigen. Similar results were obtained with volatile agents during methacholine-induced airway constriction. Taken together, these data suggest that isoflurane and halothane produce direct bronchodilation and depress airway reflexes. Isoflurane appears to share significant bronchodilating properties with halothane and enflurane, but halothane increases dynamic compliance (a measure of small airway resistance) to a greater extent than isoflurane does. This finding may be particularly important in view of the fact that isoflurane

preferentially relaxes bronchioles rather than bronchi in vitro.[14] The structure of the respiratory epithelium changes from pseudostratified columnar cells of the large airways to thinner, cuboidal cells of the bronchioles, and thus a relatively large amount of histologic heterogeneity exists between these regions. Although all volatile anesthetics bronchodilate, their specific effects on bronchioles depend on the location in and structure of the respiratory tree. Park and colleagues[15] demonstrated that isoflurane and halothane dilate fourth-order bronchi at equivalent MAC values. Halothane, isoflurane, sevoflurane, and desflurane, at concentrations of up to 1 MAC, similarly attenuated methacholine-induced bronchoconstriction in open-chest, pentobarbital-anesthetized rats.[16]

Using computed tomography (CT), Brown and coworkers[17,18] showed that halothane causes greater bronchodilation than isoflurane does at low concentrations (Fig. 22-1). Halothane also had a more pronounced relaxing effect than isoflurane did at a similar MAC in intact airway smooth muscle as measured by high-resolution CT.[19] All volatile agents, including sevoflurane[20,21] and desflurane,[22,23] relax airway smooth muscle. Sevoflurane (1 MAC) reduced respiratory system resistance (determined via an isovolume technique) by 15% in patients undergoing elective surgery. In contrast, desflurane did not significantly alter resistance.[24] Halothane, desflurane, and isoflurane appear to relax the distal airways (i.e., bronchioles) to a greater extent than the proximal airways (i.e., bronchi).[22] Similarly, isoflurane and sevoflurane had greater inhibitory effects on bronchial than on tracheal smooth muscle contraction.[25] These differential effects appear to be related to the type of voltage-dependent Ca^{2+} channels (VDCs) present in these regions. Administration of volatile anesthetics to children undergoing elective imaging studies resulted in progressive reductions in the cross-sectional area of the upper airway musculature and subsequent pharyngeal airway collapse.[26] As observed with isoflurane and halothane in animal models, the effects of sevoflurane in children were not uniformly distributed along the upper airway (also see Chapter 82).

Inhalation of 1 or 2 MAC halothane, enflurane, sevoflurane, or isoflurane does not alter baseline pulmonary resistance and dynamic pulmonary compliance. However, these anesthetics significantly attenuated increases in pulmonary resistance and decreases in dynamic pulmonary compliance in response to intravenous histamine. Halothane was most effective in altering indices of bronchodilation, whereas responses to isoflurane, enflurane, and sevoflurane were nearly identical.[21] In contrast, desflurane produced bronchodilation at 1 MAC but increased airway resistance at 2 MAC.[27] Halothane, enflurane, and sevoflurane were found to be equivalent in dilating third- or fourth-generation bronchi as measured directly with a fiberoptic bronchoscope in vivo.[28]

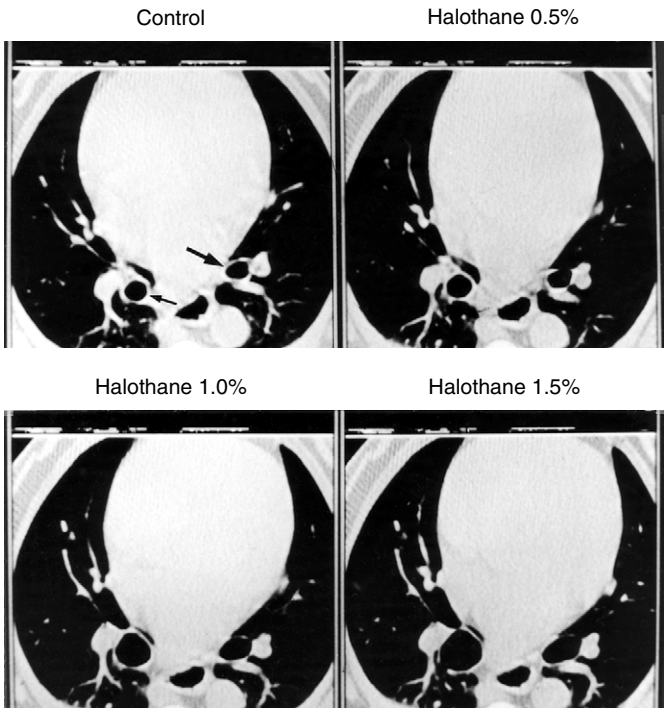


Figure 22-1 High-resolution computed tomography scan from one dog. **Upper left,** control; **upper right,** during 0.5% halothane; **lower left,** during 1.0% halothane; **lower right,** during 1.5% halothane. Note the progressive dilation of the airways as indicated by the *arrows*. *(Reproduced from Brown RH, Mitzner W, Zerhouni E, et al: Direct in vivo visualization of bronchodilation induced by inhalational anesthesia using high-resolution computed tomography. Anesthesiology 78:295, 1993, with permission.)*

Mechanisms of Action

Volatile anesthetics relax airway smooth muscle by directly depressing smooth muscle contractility. This action appears to result from direct effects on bronchial epithelium and airway smooth muscle cells and indirect inhibition of reflex neural pathways. The mechanisms responsible for the direct relaxation effects involve decreases in ICa^{2+}, an important regulator of smooth muscle reactivity. Several intracellular mediators responsible for mobilization of Ca^{2+} are potential sites for the action of volatile anesthetics, but the predominant mechanism appears to be inhibition of cell-membrane–associated VDCs, an action that reduces entry of Ca^{2+} into the cytosol.[29] Volatile anesthetic–induced increases in cAMP concentration cause decreases in free ICa^{2+} by stimulating efflux of Ca^{2+} and increasing uptake of Ca^{2+} into the SR. This action contributes to airway smooth muscle relaxation.[30] In addition to the decrease in ICa^{2+} levels, volatile anesthetic–induced decrease in calcium sensitivity as a result of inhibition of protein kinase C activity[31] and inhibition of G protein function are also reported mechanisms.[32] It has been suggested that volatile anesthetics differentially modify pulmonary resistance by altering the density of the gas mixture (Fig. 22-2).[31] In a laboratory lung model with fixed resistance, high concentrations of volatile agents increased the density of the gas mixture and the calculated resistance, with desflurane having the greatest increase at all MAC values studied.

The effects of volatile anesthetics on proximal versus distal airways may be related to differential effects on VDCs and the relative distribution of these channels. Long-lasting (L-type) VDCs appear to be the predominant mechanism for entry of Ca^{2+} into tracheal smooth muscle, whereas both transient (T-type) and L-type VDCs are present in bronchial smooth muscle cells.[25,33] Yamakage and associates[25] demonstrated that isoflurane and sevoflurane inhibit both types of VDCs in a dose-dependent fashion but that their effects on T-type VDCs in bronchial smooth muscle were much greater (Fig. 22-3). The differential effects of volatile anesthetics on tracheal as opposed to bronchial smooth muscle may also be related to effects on Ca^{2+}-activated chloride

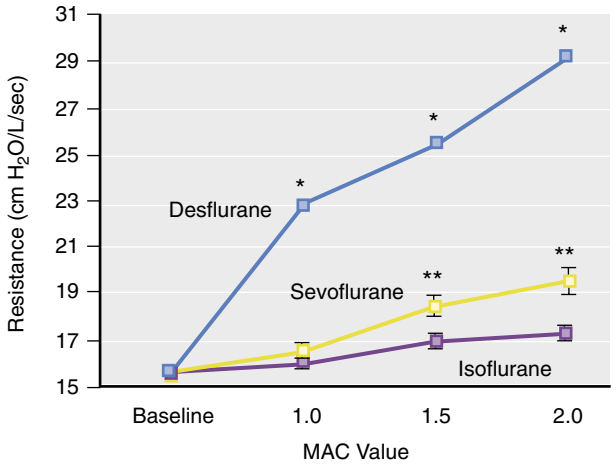


Figure 22-2 Comparison of the effect of different volatile anesthetics at equivalent concentrations on total pulmonary resistance. At 1 minimum alveolar concentration (MAC), only desflurane significantly increased pulmonary resistance when compared with isoflurane and sevoflurane. At 1.5 and 2 MAC, sevoflurane significantly increased total pulmonary resistance when compared with isoflurane, whereas desflurane caused a more pronounced increase than the other two agents did. *Increased pulmonary resistance in comparison to sevoflurane and isoflurane; **increased pulmonary resistance in comparison to isoflurane. *(Reproduced from Nyktari VG, Papaioannou AA, Prinianakis G, et al: Effect of the physical properties of isoflurane, sevoflurane and desflurane on pulmonary resistance in a laboratory lung model. Anesthesiology 104:1202, 2006, with permission.)*

channel activity[34,35] or differential sensitivity of K^+ channel subtypes.[34] Early studies proposed that volatile anesthetics relax airway smooth muscle by opening adenosine triphosphate (ATP)-sensitive potassium channels (K_{ATP}). However, halothane was found to exert minimal effects on tracheal smooth muscle K_{ATP} channels.[36]

The proposed signaling pathways underlying volatile anesthetic–induced bronchodilation are depicted in Figure 22-4. In addition to effects on VDCs, halothane reduces ICa^{2+} by depleting SR Ca^{2+}.[37,38] Halothane-induced reductions in SR Ca^{2+} appear to occur through enhancement of IP_3 and ryanodine receptor channels,[38] but whether halothane exerts direct effects on IP_3 concentrations remains controversial. Warner and coworkers[39] also demonstrated that halothane attenuates acetylcholine-induced Ca^{2+} sensitization in canine tracheal smooth muscle to a greater extent than isoflurane or sevoflurane does. These findings are analogous to the differential effects of volatile anesthetics on relaxing airway smooth muscle. Halothane may reduce free Ca^{2+} in the cytoplasm or limit influx of Ca^{2+} across the cell membrane. Alterations in Ca^{2+} sensitivity are an important mechanism by which volatile anesthetics cause smooth muscle relaxation. This effect appears to be mediated, at least in part, by an increase in smooth muscle protein phosphatase[40] and modulation of G proteins that exert actions on cGMP, specifically G_q and G_i.[32,41] Volatile anesthetics affect the function of G proteins in a variety of tissues, but halothane-induced relaxation of airway smooth muscle occurs independent of pertussis toxin–sensitive inhibitory G proteins, which are sensitive to the relaxation effects of β-adrenoceptor agonists.[42] Volatile anesthetics interact with the muscarinic receptor–heterotrimeric G protein complex to prevent agonist-promoted nucleotide exchange at the Gα subunit of the G protein.[43] It is perhaps through this mechanism that volatile anesthetics inhibit signaling proteins such as phospholipase C, protein kinase C, and ion channels. In addition to the role of volatile anesthetics as inhibitors of muscarinic agonist–induced guanine nucleotide exchange, they also appear to exert direct effects on the G protein–receptor complex.[42] The final pathway in airway smooth muscle contraction is the generation of force and shortening of smooth muscles regulated by myosin cross-bridge number and kinetics. Isoflurane modulated both cross-bridge number and the cycling rates of isolated rat airway smooth muscle.[44]

The bronchoconstricting effects of low inhaled concentrations of carbon dioxide were attenuated by inhaled but not by intravenous halothane, thus suggesting a direct action on airway musculature or local neural reflex arcs rather than centrally controlled reflex pathways. Halothane-, isoflurane-, sevoflurane-, and desflurane-induced dilatation of distal bronchial segments partially depends on the presence of bronchial epithelium.[15,45] A prostanoid (e.g., prostaglandin E_2 or I_2) or NO may mediate the bronchodilatory effects of these volatile anesthetics. For example, isoflurane-mediated bronchodilation appears to more dependent on NO than on prostanoids, but the converse is true for halothane. Focal epithelial damage or inflammation may occur in the small airways of patients with asthma or after exposure to allergen, and as a consequence, the bronchodilatory response to volatile anesthetics may be reduced.[46] The greatest bronchodilatory action of volatile agents in patients with chronic reactive airway disease occurs primarily in the proximal rather than the distal airways.

Stimulation of intrinsic airway nerves in vitro produces a cholinergic contractile response that is inhibited by atropine. In addition to the direct effects just described, volatile anesthetic–induced bronchodilation also occurs via modulation of airway cholinergic neural transmission mediated through prejunctional and postjunctional mechanisms.[47,48] The combination of atropine and halothane did not increase airway caliber over that attained with either drug alone. These findings suggest that halothane dilates airways by blocking vagal tone during unstimulated conditions.[17] Release of histamine and the nonadrenergic, noncholinergic bronchodilatory neural reflex, believed to be mediated by NO,[49] do not appear to play a significant role in low-dose halothane-induced bronchodilation. Potent tracheal constriction occurs in response to the endogenously produced polypeptide endothelin-1. Administration of isoflurane at a clinically relevant dose (2%) depressed endothelin-1–induced airway smooth muscle contraction in rat tracheal rings, thus suggesting another potential mechanism for airway smooth muscle relaxation.[50]

Effects of Inhaled Anesthetics on Bronchomotor Tone in Humans

Volatile anesthetics may be an effective method of treating status asthmaticus when other more conventional treatments have failed.[51] One percent halothane administered to 12 patients in status asthmaticus rapidly improved bronchospasm, reduced the incidence of barotrauma, and enhanced arterial blood gas ten-

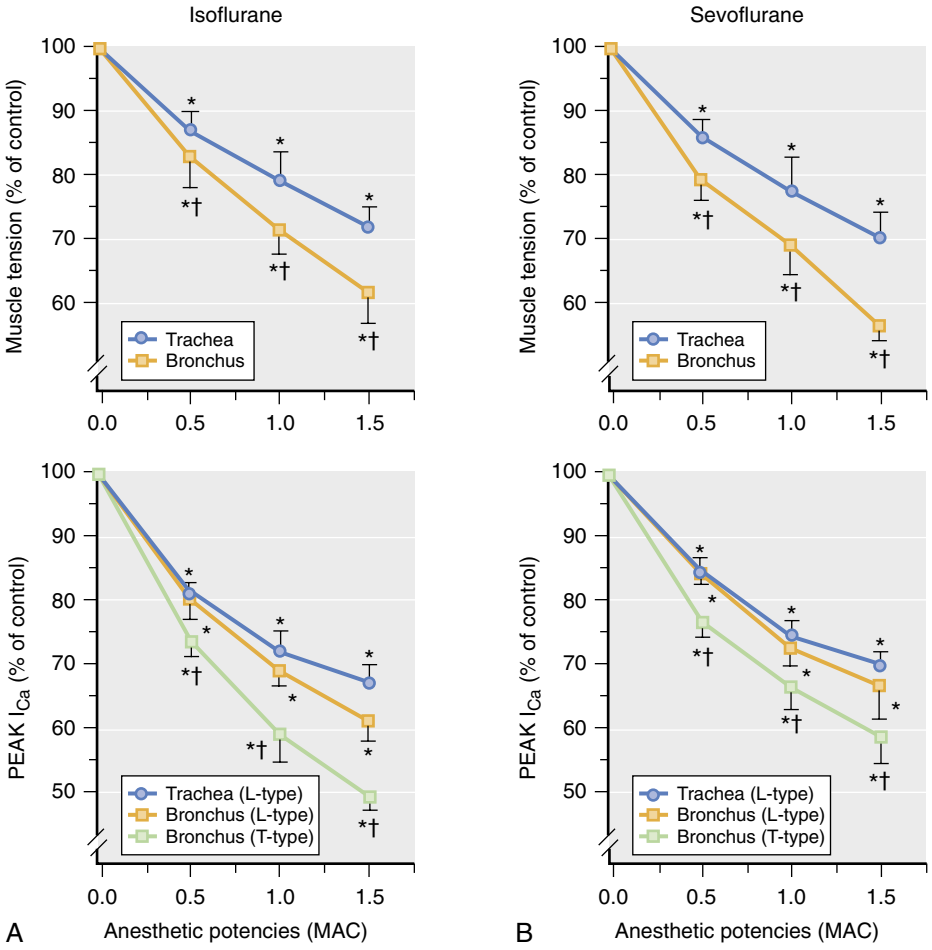


Figure 22-3 Effect of isoflurane and sevoflurane on porcine tracheal versus bronchial smooth muscle tension or inward Ca^{2+} current (I_{Ca}) through T- and L-type voltage-dependent Ca^{2+} channels (VDCs). There were no differences in the inhibition of L-type VDCs. Both anesthetics had greater inhibitory effects on T-type VDCs in bronchial smooth muscle. Symbols represent means ± SD. *$P < .05$ versus 0 MAC. †$P < .05$ versus tracheal smooth muscle in **A** and †$P < .05$ versus L-type VDCs in **B**. *(Reproduced from Yamakage M, Chen X, Tsuijiguchi N, et al: Different inhibitory effects of volatile anesthetics on T- and L-type voltage-dependent Ca^{2+} channels in porcine tracheal and bronchial smooth muscles. Anesthesiology 94:683, 2001, with permission.)*

sions in the absence of adverse hemodynamic effects.[52] However, the possibility of cardiac arrhythmias, depression of myocardial contractility, and lack of availability in the United States suggest that other agents may be preferred in the treatment of status asthmaticus.

Rooke and associates[53] compared the bronchodilating effects of halothane, isoflurane, sevoflurane, and thiopental/nitrous oxide in 66 healthy patients undergoing induction of anesthesia and tracheal intubation (Fig. 22-5). In contrast to thiopental or nitrous oxide, all volatile anesthetics significantly reduced respiratory system resistance. At equivalent MAC, sevoflurane and halothane decreased resistance to a similar degree, whereas isoflurane produced substantially less bronchodilation in vivo. Previously described animal studies demonstrating equal potency of sevoflurane and isoflurane and relatively greater potency of halothane for bronchodilation must be extrapolated with caution because *Ascaris*- or histamine-mediated experimental bronchospasm may not precisely mimic tracheal intubation–induced bronchospasm in humans. In contrast to these findings in experimental animals, Arakawa and colleagues[51] showed that similar inspired concentrations of halothane, isoflurane, and sevoflurane produce nearly identical reductions in airway resistance in patients with status asthmaticus.

Although the use of β-adrenoceptor agonists may be beneficial for the treatment of bronchospasm in patients anesthetized with halothane,[42,54] this may not be the case with other inhaled agents. The β_2-adrenergic agonist fenoterol lowered respiratory system resistance after endotracheal intubation but did not reduce resistance further when administered in the presence of 1.3% isoflurane.[55] These data should be interpreted with caution because the technique used to determine respiratory system resistance may be partially responsible for these results inasmuch as this index incorporates alterations in lung and chest wall resistance, as well as tissue viscosity.

The actions of volatile anesthetics on bronchomotor tone are dependent on the agent eliciting contraction in vitro.[19] Relaxation of tracheal smooth muscle by halothane and isoflurane is greater in the presence of the endogenous mediator serotonin (potentially representing anaphylactoid or immunologic reactions) than in the presence of acetylcholine (representing the

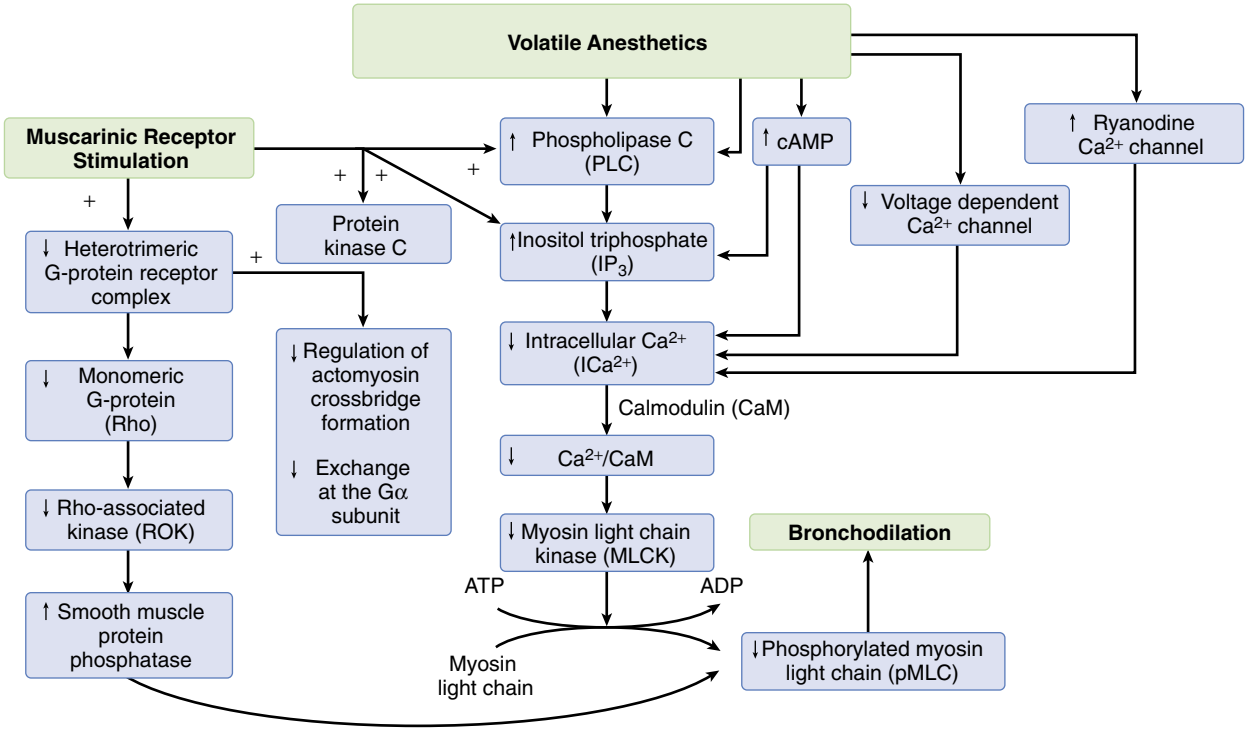


Figure 22-4 Proposed signaling pathways underlying volatile anesthetic (specifically, halothane)-induced bronchodilation or inhibition (or both) of muscarinic agonist–induced contraction of airway smooth muscle. +, excitatory action of muscarinic receptor agonist; ↑, activation or increase attributable to the volatile anesthetic; ↓, inhibition or decrease attributable to the volatile anesthetic. Signal transduction along pathway A is supported by work from Warner and coworkers on a role of halothane in decreasing Ca^{2+} sensitivity rather than a change in ICa^{2+} content. *(Adapted from Pabelick CM, Prakash YS, Kannan MS, et al: Effects of halothane on sarcoplasmic reticulum calcium release channels in porcine airway smooth muscle cells. Anesthesiology 95:207, 2001; and Hanazaki M, Jones KA, Perkins WJ, et al: Halothane increases smooth muscle protein phosphatase in airway smooth muscle. Anesthesiology 94:129, 2001, with permission.)*

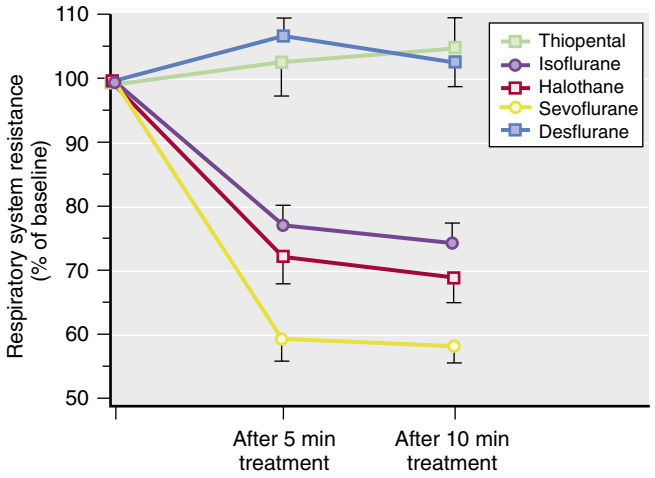


Figure 22-5 Percent change in respiratory system resistance in patients after 5 and 10 minutes of maintenance anesthesia with either 0.25 mg/kg/min thiopental plus 50% nitrous oxide or 1.1 minimum alveolar concentration (MAC) sevoflurane, halothane, or isoflurane or approximately 1 MAC desflurane. All volatile anesthetics except desflurane decreased resistance. Sevoflurane decreased resistance more than isoflurane did. *(Modified from Rooke GA, Choi J-H, Bishop MJ: The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after tracheal intubation. Anesthesiology 86:1294, 1997; and Goff MJ, Arain SR, Ficke DJ, et al: Absence of bronchodilation during desflurane anesthesia: A comparison to sevoflurane and thiopental. Anesthesiology 93:404, 2000, with permission.)*

neurally derived mediator of reflex bronchospasm). Inhaled anesthetics may remain effective bronchodilators even with severe serotonin- or histamine-induced bronchospasm that is refractory to β_2-adrenoceptor therapy.

Volatile anesthetic–induced decreases in bronchomotor tone and neurally mediated airway reflexes may be partially opposed by a simultaneous reduction in functional residual capacity (FRC) in anesthetized patients. This decrease in FRC increases airway resistance. An increased risk for morbidity and mortality during the perioperative period has been well established in patients with asthma and may be partially attributed to these FRC-mediated increases in airway resistance. Exposure of airway smooth muscle to low temperatures may abolish the inhibitory effects of volatile anesthetics on carbachol-induced contraction.[56] These findings suggest that intraoperative hypothermia also may attenuate volatile anesthetic–induced bronchodilation.

Bronchospasm may occur with respiratory diseases other than asthma. For example, healthy patients undergoing surgical stimulation of the pulmonary parenchyma or airways (including tracheal stimulation by an endotracheal tube) are at risk for bronchospasm. The choice of preoperative medication, induction agent, muscle relaxant, and type of inhaled agent are important factors in determining the development of bronchospasm in patients with known reactive airway disease. Recently, Iwasaki and coworkers[29] demonstrated that sevoflurane-induced relaxation of airway smooth muscle and VDCs was dependent on

the type of hyperreactive airway model. Sevoflurane had smaller effects in a chronic cigarette-smoking model (enlarged alveolar ducts and lesser muscarinic hyperreactivity) than in an acute ovalbumin-sensitized (antigen–acute asthmatic) model. Morphologic changes in the peripheral airways may be responsible to some degree for the decrease in bronchodilator efficacy of volatile anesthetics in cigarette smokers, but sevoflurane and isoflurane decrease respiratory system resistance in patients with COPD.[57] In contrast with an acute asthmatic model characterized by eosinophilic inflammation and airway wall changes, the inflammation in chronic asthma involves many other cell types, including mast cells, macrophages, epithelial cells, and bronchial smooth muscle cells. In addition, chronic inflammation is associated with remodeling of bronchial epithelium to produce smooth muscle hypertrophy, gland hyperplasia, and neovascularization. In a murine model of chronic asthma, administration of sevoflurane acted at the airway level and lung periphery to reduce resistive and viscoelastic pressure, as well as lung static resistance, when compared with animals anesthetized with pentobarbital.[58]

Although halothane may be a more potent bronchodilator than other inhaled anesthetics, the often-profound respiratory irritation produced in the upper airways (even though better tolerated than isoflurane and desflurane) may have outweighed the benefit of a direct bronchodilatory action. Thus, subtle differences in the bronchodilating effects of volatile anesthetics certainly exist, but avoiding or minimizing airway irritation and maintaining adequate depth of anesthesia are probably of greater clinical importance.

Advances in manufacturing technology and scavenging systems have made the use of xenon more economically feasible[59] (also see Chapter 21). Clinical use of xenon remains limited in the United States. Xenon may have important neuroprotective and cardiovascular advantages over volatile anesthetics.[60] The effects of xenon on airway resistance differ markedly from those of volatile agents because this anesthetic gas has higher density and viscosity than air.[61-63] In pentobarbital-anesthetized pigs, baseline airway resistance was significantly greater during 70% xenon-oxygen than during 70% nitrous oxide–oxygen anesthesia, although measured peak and mean airway pressure was unaffected. In contrast, airway pressure and resistance were moderately increased during xenon anesthesia and methacholine-induced bronchoconstriction.[62] In addition, pulmonary resistance during inhalation of 50% xenon was similar to that observed during inhalation of 50% nitrous oxide or 70% nitrogen in methacholine-treated dogs.[64] A randomized, double-blind comparison of xenon and nitrous oxide showed that although both agents similarly increased expiratory lung resistance, fewer patients receiving xenon experienced decreases in oxygen saturation.[65] Administration of 33% xenon to long-term mechanically ventilated patients may transiently, but significantly elevate peak airway pressure.[61] This increase in airway pressure may be attenuated by reducing the inspiratory flow rate. The higher density and viscosity of xenon lead to increases in the Reynolds number and probably cause the zone of transition from turbulent to laminar gas flow to move more distally to smaller airways. Theoretically, this action may result in exacerbation of bronchospasticity in patients with preexisting small airway disease or a decrease in arterial oxygen tension. Other studies have shown that arterial oxygen and carbon dioxide tension is unaffected during administration of xenon and nitrous oxide mixtures,[66] but caution has nevertheless been suggested when using xenon in patients with bronchospastic or obstructive pulmonary disease.

Mucociliary Function and Surfactant

Normal Mucociliary Function

Foreign particulate matter, microorganisms, and dead cells are removed by the upward clearance of mucus from the tracheobronchial tree as a primary pulmonary defense mechanism. Ciliated respiratory epithelium extends throughout the respiratory tract as far as the terminal bronchioles and decreases in density from trachea to alveoli. Ciliary motion consists of a rapid stroke in a cephalad direction, followed by a slower recovery stroke in the opposite direction. Movements of cilia are closely coordinated in a proximal-to-distal direction to move matter toward the trachea efficiently. This resulting wave of motion is known as *metachronism*. The bending of individual cilia results from ATP-dependent sliding of two parallel fibers within the ciliary filament.

Mucus is a mixture of water, electrolytes, and macromolecules (e.g., lipids, mucins, enzymes) secreted by goblet cells and mucosal glands. Thicker layers of mucus slow the removal of surface particles from the airway, whereas low-viscosity mucus promotes more rapid ciliary transport. The amount and physical properties of the mucus layer may also promote the coordination of ciliary beats.[67] Mucociliary function may be assessed by high-speed videomicroscopy to examine the ciliary beat frequency. In vivo techniques in experimental animals have used a tracheal window model. The velocity of mucus movement has been measured with radioactive markers or fiberoptic bronchoscopy in humans.

Impaired mucociliary function in the upper airways correlates with low levels of nasal NO, but the clinical significance of this finding remains to be defined.[68] Maintenance of bronchial perfusion is also critically important to preservation of normal mucociliary function.[69] Although nervous control of ciliary coordination has not been demonstrated in vertebrates, mucociliary clearance is closely related to autonomic nervous system activity, most likely related to changes in the physical characteristics of respiratory secretions.[67]

Postoperative hypoxemia and atelectasis are common causes of perioperative morbidity. Many factors can affect mucociliary function in mechanically ventilated patients and potentially contribute to these complications. Poorly humidified inspired gases are known to reduce ciliary movement and desiccate mucus. The flow rate of mucus was maintained within the normal range during a 40-minute exposure to an inspired air temperature higher than 32°C in dogs. However, 3 hours of inhalation of dry air resulted in complete cessation of the flow of tracheal mucus, which was restored by the subsequent use of inspired gases with 100% relative humidity at 38°C. Several anesthesia-related factors also reduce the rate of mucus movement, including administration of a high inspired oxygen concentration, adjuvant medications (cortisone, atropine, β-receptor blockers), the presence of a cuffed endotracheal tube, and positive-pressure ventilation.[70]

Effects of Inhaled Anesthetics on Mucociliary Function

Volatile anesthetics and nitrous oxide may diminish rates of mucus clearance by decreasing ciliary beat frequency, disrupting metachronism, or altering the physical characteristics or quantity of mucus. Halothane, enflurane, isoflurane, and sevoflurane, in contrast to many intravenous anesthetics,[71,72] reduced ciliary movement and beat frequency in vitro.[73-75] Among the volatile anesthetics, sevoflurane exhibited the weakest cilia-inhibitory effects in rat cultured tracheal epithelial cells in vitro (Fig. 22-6).[75]

Gamsu and colleagues[76] compared the rate of tantalum clearance from the lungs of postoperative patients who had undergone general anesthesia for either intra-abdominal or lower extremity operations. Tantalum is a powder that adheres to airway mucus and can be used to study mucociliary transport. Retention of tantalum was demonstrated for as long as 6 days after intra-abdominal surgery, with an average retention time three times greater than that observed in the control group. Tantalum retention was closely correlated with retention of mucus (Fig. 22-7). Teflon disks placed on the tracheal mucosa and observed with fiberoptic bronchoscopy were used to study tracheal mucus velocity in young women undergoing gynecologic surgery.[77] Administration of halothane (1% to 2%) and nitrous oxide (60%) rapidly decreased the rate of mucus movement. Little or no mucus motion was observed after 90 minutes' exposure to halothane-N_2O. The inspired gases were humidified, but high-inspired concentrations of oxygen, a cuffed endotracheal tube, and positive-pressure ventilation were confounding factors in this study. Bronchial mucosal transport velocity was also determined with the use of radiolabeled albumin microspheres deposited distally in the mainstem bronchi via fiberoptic bronchoscopy in healthy patients.[78] In contrast to the findings of the study with halothane, mucus velocity was unchanged during the administration of isoflurane (1.5 MAC). Whether this relative lack of effect of isoflurane on mucus transport was specifically related to the type of volatile agent was unclear. However, mucus pooling has been observed during and after anesthesia, and impaired bronchial mucus transport velocity is associated with increased pulmonary complications.

Konrad and colleagues[79] have shown that smokers have significantly slower bronchial mucus transport velocity and more frequent pulmonary complications than do nonsmokers undergoing abdominal or thoracic surgery. The specific effects of volatile anesthetics on mucus movement in smokers has not been well studied, but one may presume that there would be a further decrement in mucus transport. Impairment of mucociliary function also occurs after lung transplantation. The mechanism for this dysfunction may be related to alterations in the surface properties of mucus and marked impairment of mucociliary transport distal to the bronchial transection and reanastomosis.[80] The effects of volatile anesthetics on mucus transport in pulmonary transplant patients have not been described; however, the baseline reductions in mucociliary movement would predispose patients to postoperative respiratory complications.

The effects of sevoflurane and remifentanil on bronchial mucus transport were compared with those of total intravenous anesthesia (consisting of propofol and remifentanil) in patients undergoing general surgery.[81] In contrast to the in vitro results,[75] bronchial mucus transport velocity was significantly reduced 30 minutes after endotracheal intubation in patients receiving sevoflurane. The data indicate that pulmonary therapy directed at enhancing clearance of secretions from the airways may be beneficial in the immediate postoperative period regardless of the type of inhaled anesthetic chosen.

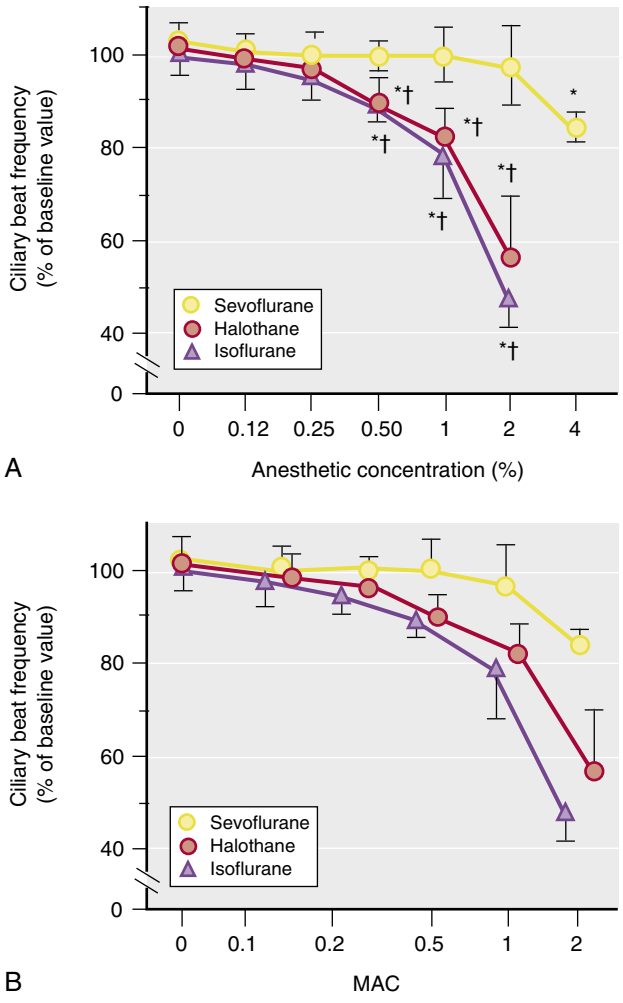


Figure 22-6 Effects of sevoflurane, halothane, and isoflurane on ciliary beat frequency (CBF) in cultured rat tracheal epithelial cells. CBF was measured at baseline and 30 minutes after exposure to various anesthetic concentrations. Values represent means ± SD. **A,** Plot of percent baseline CBF versus anesthetic concentration. *$P < .05$ versus 0% vehicle and †$P < .05$ versus sevoflurane at the same concentration. **B,** Percent baseline CBF versus minimum alveolar concentration (MAC). *(Modified from Matsuura S, Shirakami G, Iada H, et al: The effect of sevoflurane on ciliary motility in rat cultured tracheal epithelial cells: A comparison with isoflurane and halothane. Anesth Analg 102:1703, 2006, with permission.)*

Effects of Inhaled Anesthetics on Surfactant

Pulmonary surfactant decreases the work of breathing by reducing surface tension at the fluid-gas interface. Surfactant is a mixture of proteins and phospholipids synthesized by alveolar type II cells. Similar to mucus, surfactant plays a role in removing foreign particles from airways while also enhancing the bactericidal actions of alveolar macrophages. Both halothane[82] and iso-

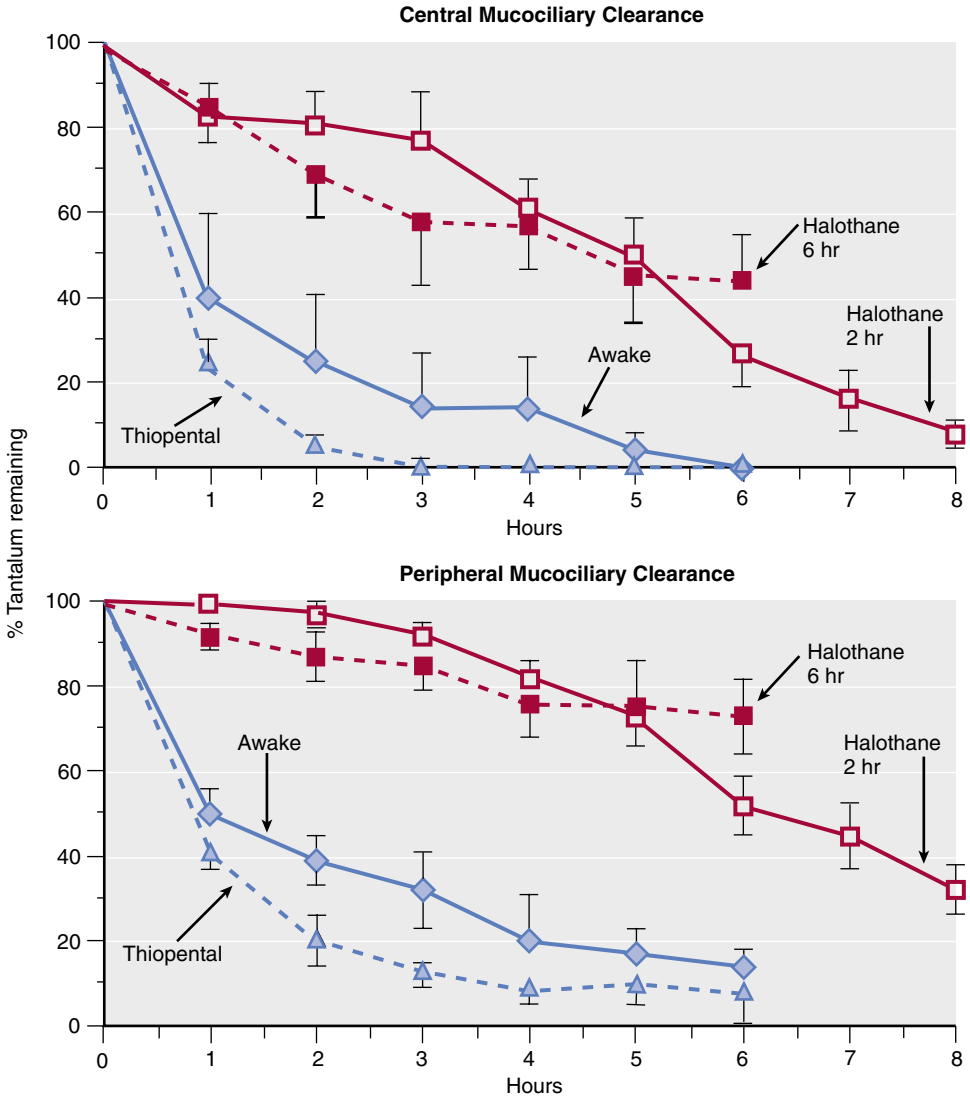


Figure 22-7 Mucociliary clearance measured as tantalum clearance in patients undergoing surgery under either general or local anesthesia (awake). Note the decrease in mucociliary clearance in both the peripheral and central airways during halothane anesthesia. *(Modified from Forbes AR, Gamsu G: Mucociliary clearance in the canine lung during and after general anesthesia. Anesthesiology 50:26, 1979, with permission.)*

flurane[83] transiently reduced phosphatidylcholine synthesis by alveolar cells in a dose-dependent manner during a 4-hour exposure. High concentrations of halothane also disrupted the energy metabolism of cultured alveolar cells as indicated by reduced ATP content and enhanced glycolytic metabolism. Halothane and isoflurane potentiated the hydrogen peroxide–mediated reduction of phosphatidylcholine in alveolar type II cells,[83,84] possibly via halothane-specific effects on cell energetics. Halothane decreased Na^+/K^+-adenosine triphosphatase (ATPase) and Na^+ channel activity in alveolar type II cells, an effect that was probably related to alterations in ICa^{2+} concentrations or ATP depletion.[85] A similar decrease in type II alveolar cell Na^+/K^+-ATPase has been shown after treatment with isoflurane.[86] Transepithelial Na^+ transport helps regulate alveolar fluid balance, and thus significant impairment in such transport may promote alveolar edema. This observation is particularly important because halothane and isoflurane decrease alveolar epithelial fluid clearance.[87] The phospholipid makeup of surfactant is critical to its functional integrity. However, the hydrophobic surfactant-associated protein C, which is synthesized exclusively by alveolar type II cells, confers the properties of rapid surface adsorption and reduction of surface tension to phospholipids, facilitates the adsorption and spreading of phospholipids to form the surfactant monolayer, and enhances lipid uptake in alveolar type II cells. In addition, exogenous surfactant that contains surfactant-associated protein C is effective in decreasing rates of barotrauma and mortality in vivo. Clinically relevant concentrations of halothane increased surfactant-associated protein C mRNA in vitro but exerted the converse effect in mechanically ventilated rats.[88] In contrast, thiopental administration increased the content of surfactant-associated protein C mRNA in both in vitro and in vivo (mechanically ventilated) models (Fig. 22-8).[88] Extrapolation of these findings to patients undergoing anesthesia should be done with caution, but these results suggest a potentially additive and deleterious role of halothane and mechanical ventilation on surfactant production and homeostasis of the alveolar space, particularly in the presence

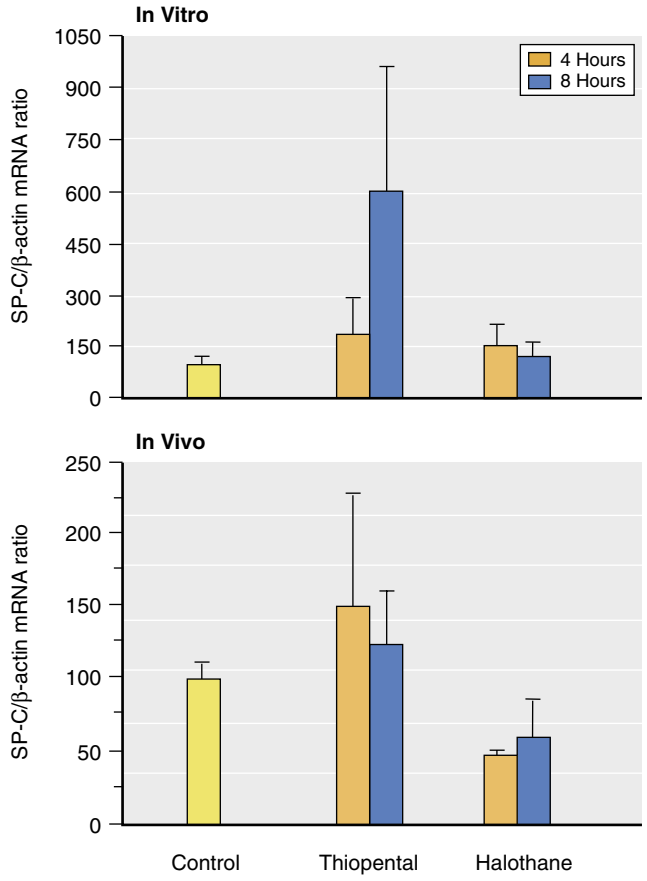


Figure 22-8 Halothane increases surfactant-associated protein C (SP-C) mRNA in vitro but exerts the opposite effects in mechanically ventilated rats. Thiopental administration increased the content of surfactant-associated protein C mRNA in both in vitro and in vivo models. *(Modified from Paugam-Burtz C, Molliex S, Lardeux B, et al: Differential effects of halothane and thiopental on surfactant protein C messenger RNA in vivo and in vitro in rats. Anesthesiology 93:805, 2000, with permission.)*

of acute lung injury. The actions of desflurane and sevoflurane on pulmonary surfactant metabolism have yet to be evaluated.

The specific roles of depressed mucociliary function and alterations in type II alveolar cells on pulmonary complications remain unclear, but impairment of ciliary motility, bronchial mucus transport, and surfactant production may play a significant role in perioperative morbidity. As discussed later, inhaled anesthetics may also play an important immunomodulatory role on type II alveolar cells during lung injury.

Prolonged administration of inhaled anesthetics may lead to mucus pooling and adversely alter alveolar cell surfactant metabolism. These actions may result in deleterious effects on pulmonary function, including atelectasis and infection. Patients at greatest risk appear to include those with excessive or abnormal mucus or surfactant production and those with acute lung injury (e.g., chronic bronchitis, asthma, cystic fibrosis, and chronic mechanical ventilation). Nevertheless, controlled studies of the effects of inhaled anesthetics on mucociliary function, surfactant metabolism, and immunomodulation in patients with or animal models of compromised pulmonary performance have yet to be performed.

Pulmonary Vascular Resistance

Determinants of Pulmonary Vascular Tone

PVR is lowest at a lung volume equivalent to FRC. Pulmonary blood vessels are compressed at high lung volumes, whereas vessels become shorter, narrower, and more tortuous because of loss of the supportive tethering of surrounding lung parenchyma at low lung volumes. Changes in pulmonary arterial pressure and PVR have significant effects on gas and fluid exchange in the lung. An increase in PVR causes a corresponding increase in pulmonary arterial pressure that promotes interstitial fluid transudation. PVR is also increased by positive end-expiratory pressure, alveolar hypoxia and hypercapnia, and critical closing pressure. Inhaled anesthetics tend to reduce lung volume and may therefore have indirect effects on PVR through this mechanism as well.

Direct changes in pulmonary vascular tone alter PVR by changing the slope of the pressure-flow relationship. Such direct changes may be produced by a rapid rise in ICa^{2+} or by alterations in sympathetic nervous system tone, arterial oxygen and carbon dioxide tension, acid-base balance, or circulating concentrations of catecholamines. Hypercapnia at constant pH (i.e., isohydria) does not alter isolated pulmonary arterial tone, but normocapnic acidosis relaxes isolated pulmonary arteries by an endothelium-independent mechanism.[89] Nevertheless, pulmonary arterial endothelial dysfunction has also been reported to potentiate hypercapnic vasoconstriction.[90]

Vasoactive substances can affect vascular tone as well. Inducible, endothelial, and neuronal NO synthases are widely distributed in the lung, are extensively involved in vascular homeostasis, and are intimately linked to the pulmonary oxygen environment (also see Chapter 31). NO synthase appears to play little role in the regulation of PVR in a healthy, normoxic lung,[91,92] but this enzyme and its metabolite NO are critical mediators of PVR during hypoxia.[93] In addition to producing vasodilation in ventilated, normoxic pulmonary regions during one-lung hypoxia, NO may also release an endogenous inhibitor of NO synthase that vasoconstricts nonventilated, hypoxic regions.[94] NO may be beneficial in the treatment of high-altitude pulmonary edema[95] and neonatal pulmonary hypertension resulting from a variety of congenital heart diseases, hypoplastic lung, and meconium aspiration. NO is also beneficial in the treatment of adult pulmonary hypertension as long as the resistance is not "fixed," such as in acute severe mitral regurgitation, congestive heart failure, and heart or lung transplantation. However, inhalation of NO during acute bronchospasm may paradoxically worsen the hypoxemia.[96] Whether this adverse action is mediated by direct bronchodilatory actions on less constricted peripheral airways or by worsening intrapulmonary shunt is unclear. The pulmonary endothelial dysfunction associated with cardiopulmonary bypass impairs endothelium-dependent vasodilation.[97] Nonetheless, use of NO in pediatric and adult cardiac surgical patients has become a common means of reducing PVR in this setting. Similar to NO, carbon monoxide (CO) stimulates guanylyl cyclase and increases cGMP levels in pulmonary arterial vascular smooth muscle cells to regulate vascular tone. Inhaled CO also attenuates the hypoxemia-induced increases in PVR through this mechanism.[98] Prostacyclin is another endogenous vasodilatory substance released from endothelium that elicits smooth muscle relaxation through stimulation of adenylyl cyclase and production of cAMP.

More recently, a role for endothelium-derived hyperpolarizing factor (EDHF) was identified as a third pathway for endothelium-mediated vasorelaxation.[99] EDHF produces relaxation by hyperpolarizing vascular smooth muscle in a process involving activation of potassium channels. Production of EDHF may be elicited by endothelial agonists or alterations in wall shear stress.[99] Although EDHF appears to be an important regulator of pulmonary blood flow, its role in modulating PVR has not been well defined.

Mechanism of Hypoxic Pulmonary Vasoconstriction

Regional alterations in PVR affect the regional distribution of blood flow within the lung, produce changes in ventilation-perfusion matching, and simultaneously affect gas exchange (also see Chapter 15). The distribution of pulmonary blood flow and ventilation in the lung, which was once thought to primarily be a gravity-mediated phenomenon, now appears to also be due to regional heterogeneity caused by asymmetric branching of the airways and blood vessels.[100] An increase in PVR occurring within an area of atelectasis causes localized tissue hypoxia but optimizes overall gas exchange (e.g., decreases the alveolar-arterial oxygen tension gradient [$P_{AO_2} - P_{aO_2}$]) by shifting blood flow away from the atelectatic segment to well-ventilated regions of the lung. This phenomenon, termed hypoxic pulmonary vasoconstriction (HPV), is unique to the pulmonary circulation in that other vascular beds (e.g., coronary, cerebral) dilate in response to hypoxia. Thus, HPV maintains oxygenation, and drugs (including anesthetics) that interfere with HPV may adversely affect gas exchange.

HPV is a locally mediated phenomenon that occurs when alveolar oxygen tension falls below 100 mm Hg and is maximal when oxygen tension is approximately 30 mm Hg. The specific mechanisms underlying HPV and the precise location of oxygen sensors remain unclear.[101,102] Mixed venous oxygen tension may influence HPV in the atelectatic lung because alveolar oxygen tension approaches venous oxygen tension under these conditions. Hypercapnia-induced acidosis increases PVR in intact animals and isolated, perfused lungs. Acidosis-induced increases in PVR are relatively minor at normal alveolar oxygen tensions but are dramatically enhanced during alveolar hypoxia. Local acidosis and increases in alveolar carbon dioxide tension may augment HPV and further improve arterial oxygenation in healthy lungs. High carbon dioxide concentrations reduce NO levels,[103] but whether this action is responsible for hypercapnia-induced improvements in the ratio of ventilation to perfusion is unknown.[104]

Inhaled Anesthetics and Hypoxic Pulmonary Vasoconstriction

All volatile anesthetics vasodilate the pulmonary vascular bed. Akata[105] presented a thorough review of the mechanisms by which inhaled anesthetics produce this vasodilation, including a reduction in free cytosolic calcium and inhibition of myofilament calcium sensitivity. Although nitrous oxide increases PVR, the pulmonary vasodilator effect of volatile agents is relatively small in normal lungs. The limited decreases in PVR produced by volatile anesthetics are frequently offset by a concomitant reduction in cardiac output in vivo. The net effect of these actions results in little if any change in pulmonary artery pressure and a small decrease in total pulmonary blood flow. In contrast with their direct vasodilatory actions, halothane, isoflurane, enflurane, and desflurane attenuate K_{ATP} channel– and endothelin-mediated pulmonary vasodilation in chronically instrumented dogs.[106-108] Inhibition of pulmonary vasodilation is not a uniform observation during administration of volatile anesthetics under all conditions. For example, isoflurane and halothane, but not enflurane, enhance isoproterenol-mediated vasodilation.[109,110] Unlike the findings with other volatile agents, K_{ATP} channel–mediated pulmonary vasodilation in response to lemakalim is preserved during sevoflurane anesthesia.[108] Indeed, there is evidence that halothane, enflurane, and isoflurane but not sevoflurane differentially modulate pulmonary vascular tension through calcium-activated or voltage-sensitive K^+ channels, at least in isolated rabbit lungs.[111] In isolated lungs, halothane- and enflurane-induced constriction of pulmonary vessels was potentiated by Kv channel inhibition. Vasoconstriction during halothane administration was also attenuated by K_{Ca} channel blockade. Isoflurane did not affect pulmonary vessels when Kv channels were inhibited. In contrast to the findings with halothane and enflurane, sevoflurane dilated pulmonary vessels and the dilation was not influenced by K^+ channel subtype inhibitors (Fig. 22-9). Isoflurane also attenuated hypotension-induced pulmonary vasoconstriction.[112]

Rather than causing pure vasodilation, volatile anesthetics produced a paradoxical initial dose-dependent increase in force in isolated pulmonary arterial strips because of release of Ca^{2+} from intracellular stores. Subsequently, a decrease in force (associated with activation of Ca^{2+}-calmodulin–dependent protein kinase II) occurs (Fig. 22-10).[113,114] Extrapolation of these results to humans in vivo must be approached with caution, but these studies suggest that vasodilatory responses may be more profound in patients with reduced SR Ca^{2+} stores (e.g., neonates) or those with depressed protein kinase activity (e.g., primary pulmonary hypertension).

Several mechanisms contribute to the diminished FRC, reduced oxygenation, and increased alveolar-arterial oxygen gradient during anesthesia. Volatile anesthetics contribute to this process by affecting HPV. The effects of volatile agents on HPV are multifactorial and involve direct actions on the pulmonary vasculature combined with indirect effects mediated by systemic hemodynamics, the autonomic nervous system, and humoral actions. In general, in vitro studies have demonstrated that all known inhaled anesthetics attenuate HPV to some degree in isolated perfused lungs or in in situ preparations with constant perfusion (Fig. 22-11), whereas most intravenous anesthetics do not. Addition of the Ca^{2+} channel blocker verapamil to a volatile anesthetic further reduces HPV by an additional 35% to 40%, thus suggesting that volatile anesthetics and Ca^{2+} channel antagonists may inhibit HPV through different sites of action. The mechanism of the direct inhibitory action of volatile anesthetics on HPV is unclear but may be related to enhancement of arachidonic acid metabolism[115] or other endothelial-derived vasodilating factors.[116] Conversely, other evidence suggests that anesthetic-induced inhibition of HPV may occur independent of the presence of pulmonary vascular endothelium, NO, or guanylate cyclase.[117-119]

Volatile anesthetics also disrupt Ca^{2+} homeostasis in vascular smooth muscle and thereby interfere with pulmonary vasoconstriction. Halothane and isoflurane attenuated

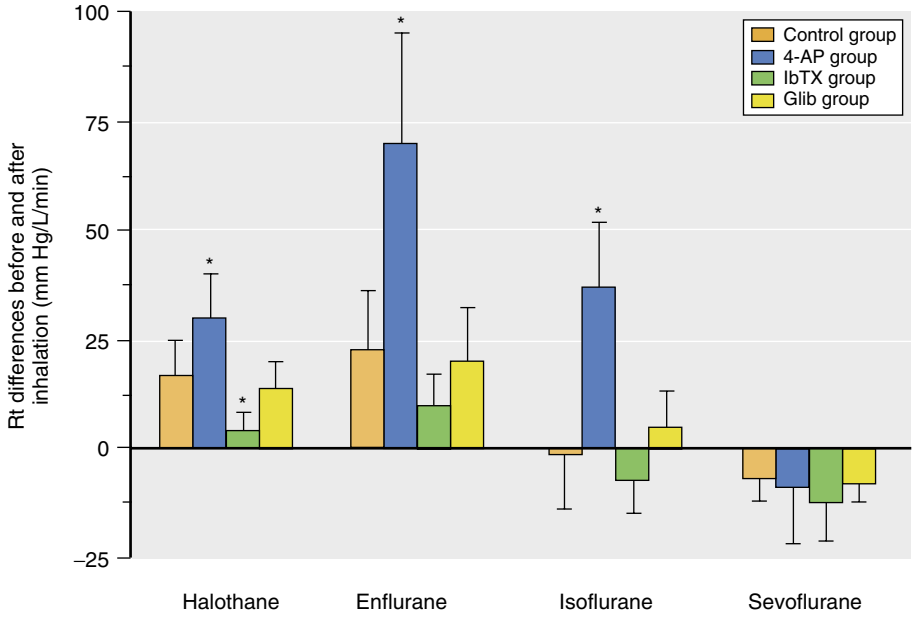
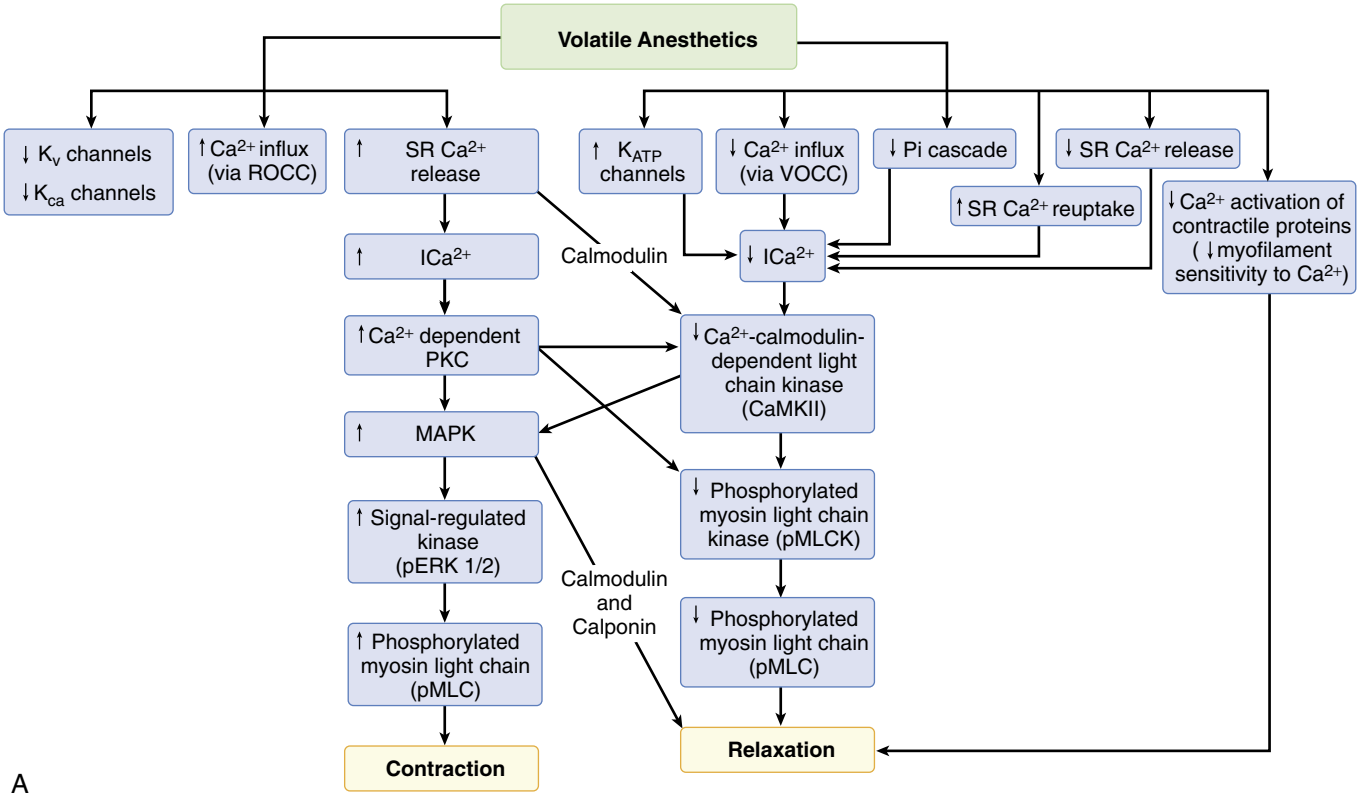


Figure 22-9 Total pulmonary vascular resistance (Rt) before and after anesthetic inhalation. Data are means ± SD. *$P < .01$ versus control group. 4AP, voltage-sensitive K^+ channel inhibitor; Glib, glibenclamide, an adenosine triphosphate–sensitive K^+ channel inhibitor; IbTX, calcium-activated K^+ channel inhibitor; Rt difference, resistance after administration of anesthetic minus resistance before administration of anesthetic. *(Modified from Liu R, Ishibe Y, Okazaki N, et al: Volatile anesthetics regulate pulmonary vascular tension through different potassium channel subtypes in isolated rabbit lungs. Can J Anaesth 50:301, 2003, with permission.)*

endothelium-dependent vasodilation by inhibiting accumulation of cGMP[119] and K_{ATP} channel–mediated interaction between NO and prostacyclin in isolated canine pulmonary artery rings.[120] In contrast, isoflurane modulated the HPV response, at least in part, through Ca^{2+}-activated and voltage-sensitive K^+ but not K_{ATP} channels in isolated rabbit lungs. Attenuation of HPV by sevoflurane occurred independent of K^+ channel function.[121] Rats with liver cirrhosis exhibited a blunted HPV response and arterial hypoxemia. These cirrhotic rats demonstrated increased NO and reduced endothelin concentrations, but the blunted HPV response observed in these animals did not involve these systems and was mediated instead by activation of Ca^{2+}-activated K^+ channels.[122]

The action of volatile anesthetics on HPV in vivo have been poorly delineated, in part because of several factors that are known to impair HPV, including temperature, pH, carbon dioxide tension, relative degree of hypoxia, size of the hypoxic area, surgical trauma, and concomitant medications. During one-lung ventilation, the direct inhibitory effects of volatile anesthetics on HPV may increase perfusion in the nonventilated lung. This enhanced perfusion potentially leads to an increase in shunt fraction and a reduction in arterial oxygenation. However, volatile anesthetics may also affect HPV, lung perfusion, and oxygenation by indirect actions on cardiac output and mixed venous oxygen saturation.[123] The direct effects of anesthetics on HPV, as opposed to indirect actions mediated through alterations in pulmonary perfusion, must be appreciated. The efficacy of HPV varies inversely with pulmonary arterial blood flow, and a direct inhibition of HPV by anesthetics may be opposed by a simultaneous reduction in cardiac output such that HPV may appear to be unaffected. Thus, the net HPV response to volatile anesthetics remains unchanged when cardiac output is reduced, but it may be fully intact or only minimally attenuated when pulmonary blood flow is preserved. A reduction in cardiac output also decreases mixed venous oxygenation, which leads to pulmonary vasoconstriction. These data emphasize the flow dependence of HPV during administration of a volatile anesthetic. Baseline pulmonary blood flow and pressure also modulate the effects of HPV. Elevated pulmonary artery pressure may cause passive distention of constricted vascular beds and thus reverse the HPV. Alternatively, reflex pulmonary and systemic vasoconstriction in response to hypotension may increase PVR in healthy lung segments, thereby leading to a shift of pulmonary blood flow to hypoxic areas of lung.

Early studies suggested that nitrous oxide attenuates HPV in animal models in vivo. In contrast, clinically relevant concentrations of halothane, isoflurane, enflurane, sevoflurane, and desflurane appear to have minimal effects on HPV in vivo (Fig. 22-12).[124,125] As opposed to the findings with isoflurane,[115] inhibition of HPV was not observed during sevoflurane or desflurane anesthesia[124] in chronically instrumented dogs subjected to gradual occlusion of the right main pulmonary artery. Nitrous oxide,[126] desflurane, and isoflurane,[127] but not xenon,[126] reduced mixed venous oxygen saturation, cardiac output, and arterial oxygenation during one-lung ventilation in pigs. However, nitrous oxide,[126] xenon,[126] desflurane,[127,128] and isoflurane[127,129] did not alter perfusion of the nonventilated lung or reduce the shunt fraction during one-lung ventilation. In animals with a preexisting gas exchange defect as a result of pneumoperitoneum, sevoflurane but not isoflurane caused more pronounced abnormalities in gas exchange than did propofol.[130] Thus, although reductions in HPV by inhaled anesthetics, as predicted by in vitro studies, have been relatively small in vivo, coexisting pulmonary disease may worsen anesthetic-induced gas exchange abnormalities.



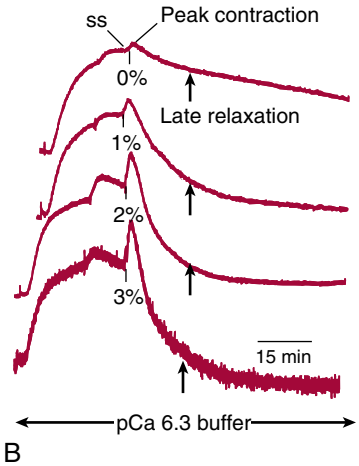


Figure 22-10 A, Proposed signaling pathways underlying volatile anesthetic–induced contraction and relaxation in pulmonary artery smooth muscle. Intracellular calcium (ICa^{2+}) may be increased by release from the sarcoplasmic reticulum (SR), by inhibition of voltage-sensitive (K_v) or calcium-activated (K_{Ca}) potassium channels, or by receptor-operated Ca^{2+} channels. Increased ICa^{2+} results in an initial dose-dependent increase in force (associated with activation of protein kinase C and increased mitogen-activated protein kinase [MAPK]). Volatile anesthetics also decrease ICa^{2+} by activating K_{ATP} channels, thereby inhibiting Ca^{2+} influx via voltage-operated Ca^{2+} channels (VOCC), decreasing SR-induced release of Ca^{2+}, inhibiting the phosphatidylinositol (Pi) cascade, and enhancing SR-mediated reuptake of Ca^{2+}. The resultant decrease in force is associated with activation of Ca^{2+}-calmodulin–dependent protein kinase II. It is important to note that there are many agent-specific effects of volatile anesthetics on each component of these pathways. **B,** Example of a biphasic (contraction/relaxation) effect of halothane on pulmonary arterial smooth muscle. 0%, 1%, 2%, and 3%, halothane concentrations; ss, control force at steady state before halothane. Halothane dose-dependently enhanced Ca^{2+}-activated peak force, as well as late relaxation. *(Modified from Akata[105], Su and Vo[113], and Zhong and Su,[114] with permission.)*

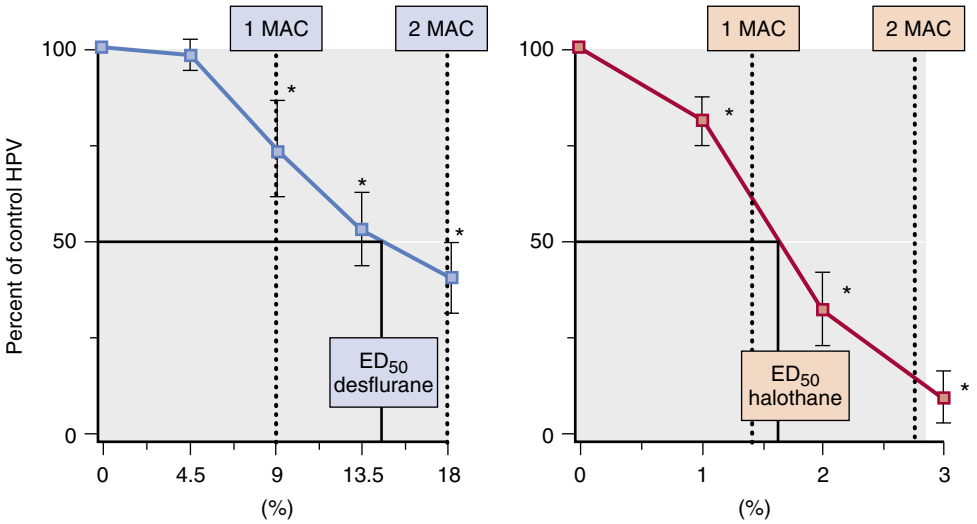


Figure 22-11 Concentration-dependent inhibition of hypoxic pulmonary vasoconstriction (HPV) in isolated rabbit lungs by desflurane (*blue squares*) and halothane (*red squares*), Values are means ± SEM and expressed as a percentage of control. **P* < .05 versus control HPV. The half-maximum inhibiting effect (ED_{50}) values were within the range of 1 and 2 minimum alveolar concentration (MAC) (for rabbits) for both agents. *(Reproduced from Loer SA, Scheeren T, Tarnow J: Desflurane inhibits hypoxic pulmonary vasoconstriction in isolated rabbit lungs. Anesthesiology 83:552, 1995, with permission.)*

Effects of Inhaled Anesthetics on the Pulmonary Vasculature in Humans

Isoflurane does not alter pulmonary shunt function in healthy patients, even at concentrations that produce systemic hypotension.[131] Most clinical thoracic surgery is usually undertaken with the patient in the lateral position with an open chest, which dramatically alters the relative distribution of ventilation and perfusion. Under these circumstances, a diseased nondependent lung may substantially affect pulmonary vascular responsiveness to hypoxia, as may surgical manipulation of the lung itself. Most observations in experimental animals or patients undergoing single-lung ventilation fail to demonstrate clinically significant attenuation of HPV during administration of a volatile anesthetic. There do not appear to be significant differences in shunt fraction, PVR, or oxygenation between isoflurane and sevoflurane anesthesia in patients with lung cancer undergoing one-lung ventilation for lobectomy.[132] Two studies demonstrated that the shunt fraction is similar in patients receiving propofol or either isoflurane[133] or sevoflurane[134] during single-lung ventilation. No significant differences in shunt fraction or arterial oxygen tension were observed when pulmonary gas exchange was compared during intravenous infusion of ketamine (which does not inhibit HPV) and administration of enflurane. In contrast, isoflurane[135,136] and sevoflurane[136] impaired oxygenation and decreased shunt fraction more than intravenous infusion of propofol did during single-lung ventilation in humans. However, the differences in oxygenation observed in these studies were small and of little clinical relevance. Interpretation of the differences in findings between these intravenous and volatile anesthetics observed in studies may be complicated by the depth of anesthesia. In contrast, the doses of propofol and sevoflurane selected were based on similar depth of anesthesia (determined with a bispectral index [BIS] monitor), and comparable reductions in arterial oxygenation were observed in patients undergoing one-lung ventilation.[137] Similar and rather modest changes in shunt fraction and oxygenation were shown to occur with halothane,[138] isoflurane,[132,138,139] desflurane,[139] and sevoflurane[132] in patients undergoing thoracotomy and single-lung ventilation (Fig. 22-13).

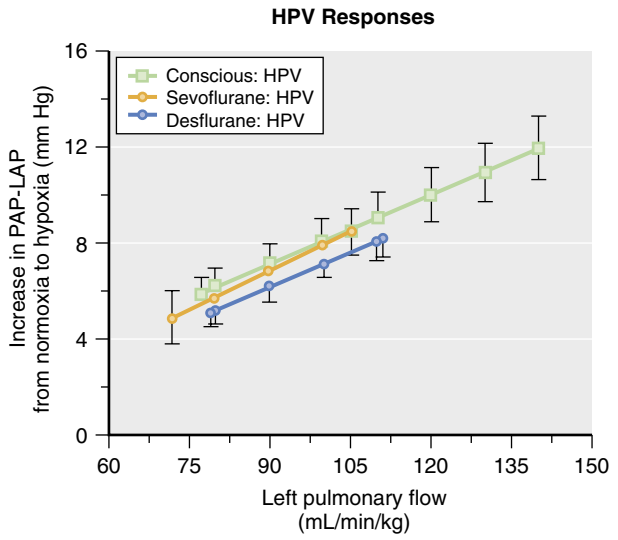


Figure 22-12 Composite hypoxic pulmonary vasoconstriction (HPV) responses (increase in pulmonary artery pressure [PAP] minus left atrial pressure [LAP]) as a function of left pulmonary flow in the same seven chronically instrumented dogs in the conscious state and during sevoflurane and desflurane anesthesia. Neither anesthetic affected the magnitude of HPV when compared with the response in the conscious state. *(From Lesitsky MA, Davis S, Murray PA: Preservation of hypoxic pulmonary vasoconstriction during sevoflurane and desflurane anesthesia compared to the conscious state in chronically instrumented dogs. Anesthesiology 89:1501, 1998, with permission.)*

There is convincing evidence that all volatile anesthetics may be used safely in patients undergoing thoracotomy and single-lung ventilation (also see Chapter 59). The increase in shunt and decrease in oxygenation caused by halothane or isoflurane[138] was consistent with an approximately 20% inhibition of

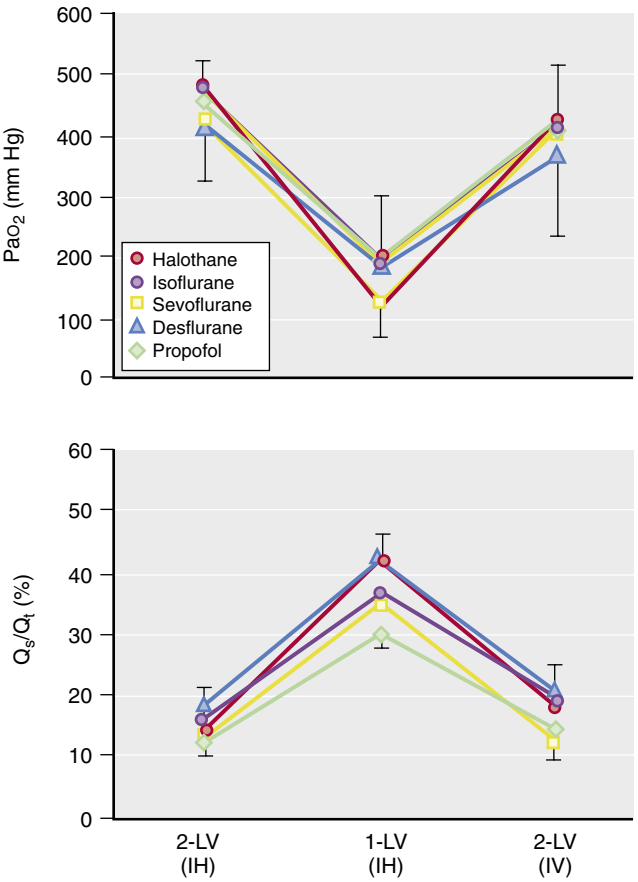


Figure 22-13 Arterial oxygenation (Pao_2) and intrapulmonary shunt (Q_s/Q_t) in patients with both lungs ventilated (2-LV) or with one lung ventilated (1-LV). Patients received an inhaled agent (IH)—halothane, isoflurane, sevoflurane, or desflurane—or the intravenous anesthetic propofol. Note the minimal effect on Pao_2 and shunt that occurs when changing from a volatile anesthetic to an intravenous agent. *(Adapted from Abe et al.,[132,136] Benumof et al.,[138] and Pagel et al.,[139] with permission.)*

HPV at 1 MAC. Instead of a 50% reduction in pulmonary blood flow in a hypoxic lung in the absence of a volatile agent, blood flow decreases by 40% during hypoxia in the presence of 1 MAC isoflurane. This change in flow corresponds to an increase in pulmonary shunt by about 4% of cardiac output. Carlsson and colleagues[140] applied multiple inert gas elimination techniques to measure the true shunt fraction in humans anesthetized with volatile agents and demonstrated a 2% to 3% increase in shunt fraction corresponding to approximately 20% HPV inhibition with 1.5% isoflurane. There were also no significant effects on arterial oxygenation with clinically relevant concentrations of isoflurane or enflurane. Indeed, the use of total intravenous anesthesia with propofol and alfentanil as opposed to a volatile anesthetic did not decrease the risk for hypoxemia during single-lung ventilation.[133] Not only does isoflurane appear to be safe to use during single-lung ventilation, but administration of isoflurane before pulmonary ischemia also protects against ischemia-reperfusion injury. Isoflurane attenuated increases in PVR and reductions in the coefficient of filtration and the wet-to-dry ratio in isolated rabbit lungs subjected to ischemia and reperfusion.[141]

Marked increases in shunting have been demonstrated by the administration of pulmonary vasodilators (e.g., sodium nitroprusside, nitroglycerin) in dogs with oleic acid–induced pulmonary edema. Theoretically, volatile anesthetics may produce a similar response in patients with adult respiratory distress syndrome or with other types of pulmonary pathology associated with large right-to-left intrapulmonary shunts, but this hypothesis has yet to be comprehensively examined. Isoflurane did not attenuate the enhanced pulmonary vasoconstrictor response to sympathetic α-adrenoreceptor activation or influence pulmonary vascular tone in the presence of increased PVR secondary to endothelin-mediated receptor activation[142] after single-lung transplantation.[143] These findings may have important implications for the intraoperative anesthetic management of patients with similar abnormalities in pulmonary vasoregulation because volatile anesthetics may produce smaller reductions in PVR than might be expected.

The precise effects of inhaled anesthetics on HPV and pulmonary shunt in patients with preexisting pulmonary disease remain to be defined, but the action of these agents on the pulmonary vasculature itself must be considered when evaluating causes of hypoxemia during anesthesia. Clinical observations suggest that volatile anesthetics exert only mild, if any inhibitory effects on HPV and oxygenation. This relatively minor inhibition of HPV by volatile anesthetics should not significantly influence clinical decision-making, especially given the efficacy of continuous positive airway pressure in improving oxygenation of the nondependent lung. Thus, the net effect of volatile anesthetics on HPV is multifactorial and not only depends on the direct effects of these agents on pulmonary vasomotor tone but is also determined by indirect actions that commonly occur during anesthesia and surgery.

Control of Ventilation

Many different stimuli interact in a complex manner to control ventilation in humans. The traditional approach to studying the effects of drugs on ventilation has been to measure ventilatory responsiveness (e.g., expired minute volume, respiratory frequency, arterial carbon dioxide tension) before and after drug administration. A complete description of ventilatory control is beyond the scope of this chapter, and several excellent reviews of this subject already exist.[144-150] However, an understanding of normal ventilatory responses and control mechanisms is necessary to appreciate the actions of anesthetics and the methods by which these effects are measured.

Control of Breathing—Central Controllers, Sensors, Effectors

A control system that modulates ventilation is required to maintain the stability of arterial blood gas tension and acid-base status, as well as to integrate the respiratory rate and tidal volume to minimize the work of breathing in response to variations in total ventilatory requirements (Fig. 22-14). The system responsible for receiving and integrating input signals and ultimately producing movement of air in and out of the lungs is composed of the following:

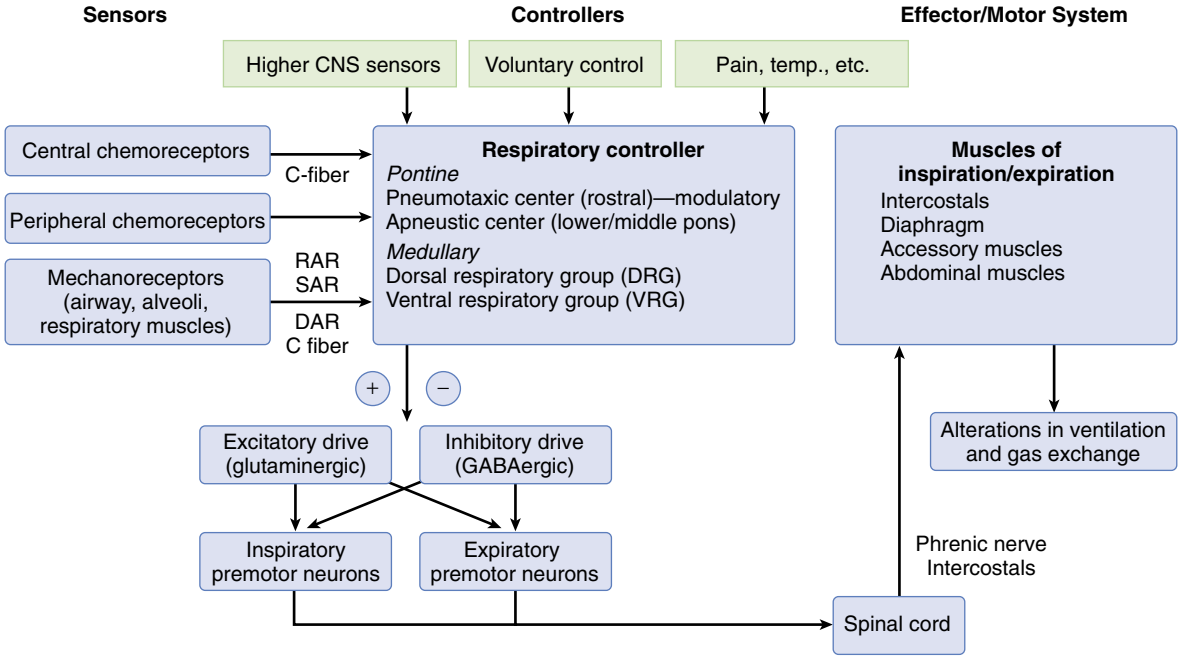


Figure 22-14 Some aspects of the reflex control of ventilation. Sensors include central and peripheral chemoreceptors, as well as a variety of mechanoreceptors. Input from these many sources interacts to alter ventilatory controller output from pontomedullary sites to muscles of respiration, thus altering ventilation and ultimately gas exchange. Central and peripheral chemoreceptors transmit information via nonmyelinated C fibers. Mechanoreceptors, such as rapidly (RAR) and slowly (SAR) adapting stretch receptors and deflation-activated receptors (DAR) are found in airway smooth muscle, alveoli, and respiratory muscle. C fibers may also transmit information from mechanoreceptors. Inspiratory bulbospinal neurons in the medulla are premotor neurons that drive phrenic and intercostal motoneurons and ultimately the diaphragm and muscles of inspiration. Excitatory drive to these motoneurons is mediated by glutaminergic neurotransmission. The neurons of timing and pattern generation, as well as premotor neurons, are also subject to tonic γ-aminobutyric acid (GABA)-mediated inhibition.

The *sensory system* may be chemical (i.e., peripheral and central chemoreceptors) or mechanical (i.e., distortion receptors located in airways, alveoli, and respiratory muscles).

The *respiratory control system* integrates the signal input from receptor sites, centers of consciousness, and other influences (e.g., pain) and subsequently produces nerve traffic to the muscles of respiration.

The *motor system* is composed of the chest wall, intercostal, diaphragmatic, and abdominal muscles, all of which respond to signals from the control center through phrenic and spinal nerves.

The respiratory rhythm generator resides within the brainstem and consists of two primary types of respiratory neurons: the dorsal respiratory group (DRG), chiefly associated with inspiration, and the ventral respiratory group (VRG), which contains inspiratory and expiratory neurons. The cortex is able to override these brainstem centers if voluntary control is desired. Other parts of the brain, such as the hypothalamus and limbic system, may modulate ventilation during certain emotional states. The precise mechanism of rhythm generation remains unknown, but regions in the ventrolateral medulla (including the rostral VRG) contain rhythm-generating, self-oscillating neurons. Central terminations of afferent airway sensory fibers are found in the caudal portion of the nucleus tractus solitarius. Second-order neurons then innervate neurons located in respiratory-related regions of the pons, medulla, and spinal cord. Medullary regions involved in the generation and modulation of respiratory and sympathetic nervous system vasomotor output, such as the retrotrapezoid nucleus, may also contain neurons functioning as central oxygen detectors.[151] The rostral pons contains the pneumotaxic center, which has inspiratory and expiratory neurons and plays a critical modulating role by fine-tuning respiratory rhythm and integrating vagal and chemoreceptive input. The apneustic center, located in the lower portion of the pons, appears to have an excitatory effect on the inspiratory area of the medulla. Whether this center plays an important role in normal respiration is unclear. Central respiratory control mechanisms regulate tidal volume and inspiratory and expiratory times to achieve adequate ventilation and gas exchange. Excitatory drive to bulbospinal inspiratory neurons of the caudal VRG is mediated by tonic input (acting through *N*-methyl-D-aspartate [NMDA] receptors) and phasic input (primarily consisting of non-NMDA glutamate receptors).[152,153] Neurotransmission in bulbospinal expiratory neurons is mediated via NMDA-type glutamate receptor input and modulated by γ-aminobutyric acid type A ($GABA_A$) receptors.[152]

Input signals originate from chemoreceptors and mechanoreceptors in the upper airways, lungs, and chest wall and are transmitted by the vagus and spinal nerves. Extensive discussion of these receptors and their physiologic consequences is beyond the scope of the current chapter. However, because volatile anesthetics may differentially affect pulmonary sensory receptors, a basic understanding of the types, function, and location of these receptors is important. Traditionally, lung sensory receptors were divided into three groups: slowly and rapidly adapting stretch receptors (SARs and RARs, respectively) and bronchopulmonary C fibers. SARs lie within airway smooth muscle, discharge regularly during sustained inflation, and demonstrate little adaptation. Stimulation of these receptors by lung inflation results in slowing

of the respiratory rate because of an increase in expiratory time. The opposite effect is observed during lung deflation, which initiates inspiratory activity. This phenomenon, known as the Hering-Breuer reflex, is largely inactive in adult humans but appears to be active and potentially important in neonates. Activation of SARs by persistent elevations in end-expiratory lung volume produced an inhibitory effect on central drive (i.e., an increase in the apneic threshold) and an attenuated ventilatory response to progressive hypercapnia.[154] RARs, also known as irritant receptors, lie between airway epithelial cells and are stimulated by dust, cold air, and other noxious airway irritants. These receptors initially discharge vigorously and cause bronchoconstriction and hyperpnea, but their responses are extinguished rapidly.[147] RARs in the bronchi are more chemosensitive than those located in the more proximal airway but will also cause coughing, mucus secretion, bronchoconstriction, and laryngospasm. In addition, RARs in the bronchi stimulate hyperventilation.[155] C fiber receptors are nonmyelinated chemosensors but may also respond to lung inflation at high thresholds. Activation of these receptors results in tachypnea, bronchoconstriction, and secretion of mucus. Several other receptor types have been described, including Aδ-nociceptors, "cough" receptors, J receptors, deflation-activated receptors (DARs), and a variety of mechanically driven receptors in the upper airways, intercostal muscles, and diaphragm.[146,148]

Changes in chest wall position produce alterations in efferent impulses from stretch receptors in intercostal muscle spindles that act to maintain relatively constant tidal volume during variations in inspiratory resistance. Increases in spindle discharge enhance motor activity to muscle fibers until muscle shortening relieves tension in the spindles. With increased inspiratory resistance, the muscle spindles detect a failure of shortening by the appropriate amount and increase afferent signals to the motor neuron pool. Accessory muscles of inspiration may also be recruited. This reflex increase in inspiratory effort sustains tidal volume and minute ventilation despite a greater inspiratory resistive load. These and other forces maintain normal ventilation with changes in body position, inspiratory resistance, and compliance. Extrapolation of these data obtained from experimental animals to humans should be approached with caution. For example, tension receptors in the diaphragm, not the muscle spindles, induce reflex inhibition of inspiratory intercostal activity associated with a decrease in inspiratory duration in dogs, but not humans. This effect appears to be mediated at the supraspinal level.[156]

Central and peripheral chemoreceptors respond to changes in the chemical composition of blood or the surrounding fluid. A complete discussion of chemical control of ventilation may be found in several excellent reviews.[157-160] Briefly, central and peripheral chemoreceptors are critical to chemical control of respiration. Central chemoreceptors are located near the ventrolateral medulla and other brainstem sites and respond to changes in the hydrogen ion (H^+) concentration in cerebrospinal fluid and not to arterial carbon dioxide tension or pH. Unlike H^+, carbon dioxide diffuses rapidly through the blood-brain barrier. Central chemoreceptors are more profoundly affected by respiratory than by metabolic alterations in arterial carbon dioxide tension. In contrast, peripheral chemoreceptors, located in the carotid bodies, are sensitive to changes in arterial carbon dioxide tension, pH, and most importantly, arterial oxygen tension. The mechanisms by which peripheral chemoreceptive cells respond to hypoxia and hypercapnia appear to be separate and synergistic because hypoxemia potentiates the chemical drive to a carbon dioxide challenge. Peripheral chemoreceptors appear to contribute about a third to total resting minute ventilation at normocapnia and normoxia as determined by respiratory functional testing. This contribution falls to 15% during hyperoxic normocapnia, thus suggesting that central chemoreceptors control 85% of the carbon dioxide drive during hyperoxia. Both stimuli cause membrane depolarization and activation of afferent nerve transmission.

Changes in ventilation secondary to alterations in arterial carbon dioxide tension are mediated principally at the level of the medulla. Patients whose peripheral chemoreceptors have been denervated by bilateral carotid endarterectomy demonstrate a modestly attenuated increase in ventilation in response to inhaled carbon dioxide. Inspiration of carbon dioxide in normal subjects increases minute ventilation by approximately 3 L/min/mm Hg of arterial carbon dioxide tension. This observation demonstrates high gain from central chemoreceptors in response to variations in arterial carbon dioxide tension. The slope of the relationship between minute ventilation and arterial carbon dioxide tension is an index of ventilatory drive, provided that hypoxic conditions are avoided to minimize peripheral chemoreceptor stimulation. NO is increased in the carotid bodies during hypoxia,[161] plays an inhibitory role in both the peripheral and central chemoreflex pathways during hypoxia,[162] and may act as a respiratory stimulant under normoxic conditions.[163] Experiments to determine the relationship between minute ventilation and arterial carbon dioxide tension require interpretation with these potential confounding variables in mind.

A biphasic response to hypoxia exists in humans. Adults and neonates display a similar initial hypoxia-induced increase in ventilation, but neonates exhibit a more pronounced ventilatory decline in response to hypoxic oxygen concentrations than adults do. This reaction may represent a balance between active inhibition of brainstem neuronal activities and augmentation of peripheral chemoreceptor function. Acute hypoxemia stimulates oxygen-sensitive (type I—glomus) cells in the carotid bodies to initiate a cascade of responses, including closure of K^+ channels and resultant membrane depolarization. Reactive oxygen species generated by reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitochondria, or heme oxygenase have been proposed as mediators of this response.[158] Release of ATP subsequently activates chemoafferent fibers of the carotid sinus nerve to relay the information to the brainstem respiratory control centers.[160] Similarly, release of ATP by central chemoreceptors on the ventral surface of the medulla after hypercapnic stimulation immediately precedes an increase in respiratory drive.[160]

General Ventilatory Effects of Anesthetics

In general, all volatile anesthetics decrease tidal volume in a dose-dependent manner. A concomitant increase in respiratory rate only partially offsets the depression of minute ventilation. As a result, an increase in resting arterial carbon dioxide tension takes place (Fig. 22-15). Early studies demonstrated that isoflurane produces more profound respiratory depression than halothane does, but in contrast to halothane, isoflurane did not progressively increase the respiratory rate.[164] Like halothane, enflurane reduces tidal volume and minute ventilation concomitant with compensatory tachypnea in a dose-related manner.[165] Prolonged administration (3 to 7 hours) of halothane or enflurane decreases the

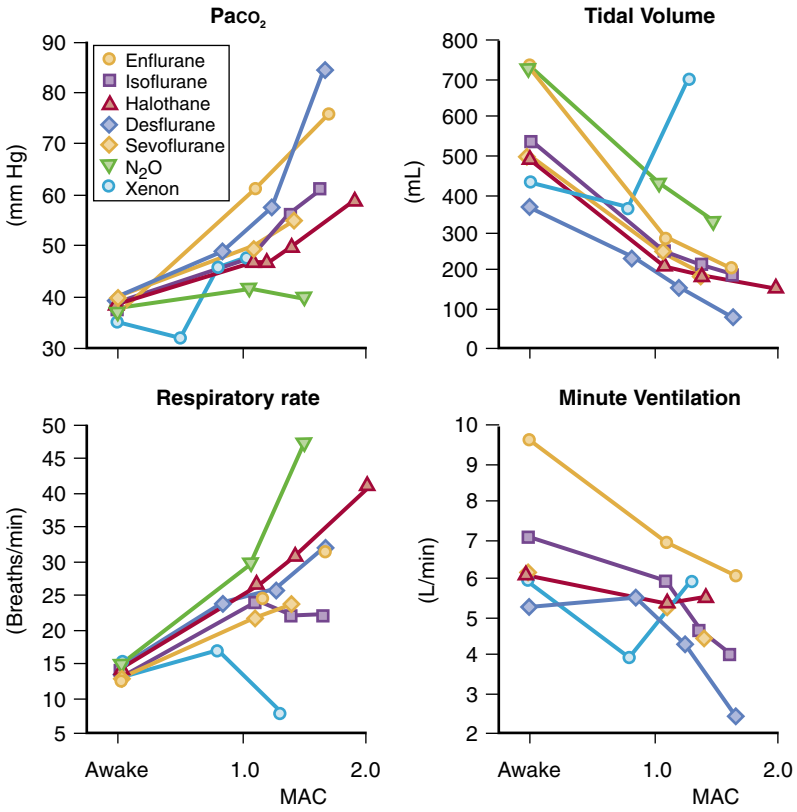


Figure 22-15 Comparison of mean changes in resting $Paco_2$, tidal volume, respiratory rate, and minute ventilation in patients anesthetized with either halothane, isoflurane, enflurane, sevoflurane, desflurane, nitrous oxide, or xenon. Anesthetic-induced tachypnea compensates in part for the ventilatory depression caused by all volatile anesthetics (decrease in minute ventilation and tidal volume and concomitant increase in $Paco_2$). Desflurane results in the greatest increase in $Paco_2$ with corresponding reductions in tidal volume and minute ventilation. Isoflurane, like all other inhaled agents, increases the respiratory rate; however, isoflurane does not result in dose-dependent tachypnea. MAC, minimum alveolar concentration. *(Data from references 164-169. Note that the data for xenon have been extrapolated from several sources[63,170,171] because there have been no well-controlled studies measuring all variables.)*

degree of respiratory depression as indicated by resting arterial carbon dioxide tension.[165,172]

Desflurane and sevoflurane also exhibit dose-related ventilatory depression, primarily by reducing tidal volume.[166,167,173] Unlike isoflurane, sevoflurane and desflurane cause dose-related increases in the respiratory rate. Thus, desflurane does not significantly reduce minute ventilation at concentrations less than 1.6 MAC. The reduction in respiratory rate produced by desflurane at higher concentrations was less than that caused by halothane. The relative effect of inhaled anesthetics (<1.24 MAC) in increasing arterial carbon dioxide tension (as an index of respiratory depression) is enflurane > desflurane = isoflurane > sevoflurane = halothane > nitrous oxide. Halothane and sevoflurane also cause similar respiratory changes in spontaneously breathing children. Nevertheless, potentially important differences between these two agents have been identified and include reduced minute ventilation and respiratory rate, a delay in the timing of peak inspiratory flow, and an earlier occurrence of peak expiratory flow during sevoflurane than during halothane anesthesia.[174] The ventilatory depression produced by higher concentrations of desflurane and sevoflurane is similar to that caused by enflurane and isoflurane, respectively. Isoflurane-induced respiratory depression is reduced by surgical stimulation (Fig. 22-16).[175] The respiratory depression observed during desflurane or sevoflurane anesthesia is reduced in the presence of nitrous oxide at equivalent MAC values.[176] This phenomenon is principally related to the reduction in volatile anesthetic required when nitrous oxide is added to the inspired gas mixture. The alteration in ventilatory pattern caused by anesthetics has been attributed to relative sensitization of pulmonary stretch receptors that subsequently produce tachypnea and low tidal volumes. The presence of a volatile anesthetic increased vagal afferent discharge at varying lung volumes in decerebrate cats (i.e., sensitization of pulmonary stretch receptors),[177] but little evidence exists of such a mechanism in humans. Halothane-induced tachypnea is primarily a suprapontine effect that may occur in cats, but the mechanism of

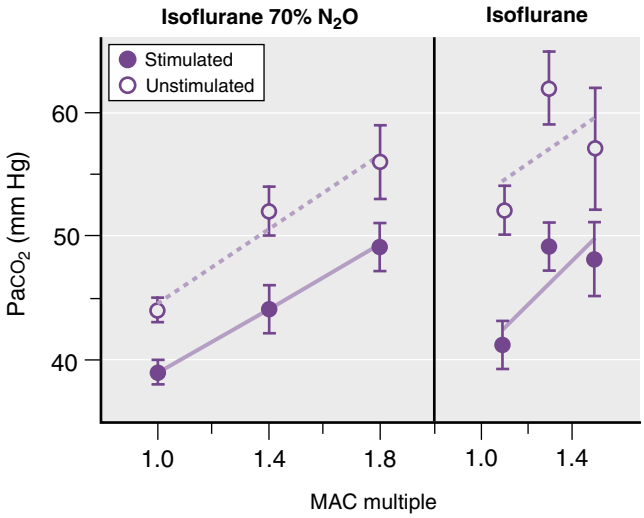


Figure 22-16 Effect of surgical stimulation on the ventilatory depression of inhaled anesthesia with isoflurane in the presence and absence of nitrous oxide. Surgical stimulation increased alveolar ventilation and decreased $Paco_2$ at all depths of anesthesia examined. MAC, minimum alveolar concentration. *(Modified from Eger EI, Dolan WM, Stevens WC, et al: Surgical stimulation antagonizes the respiratory depression produced by Forane. Anesthesiology 36:544, 1972, with permission.)*

production of tachypnea with decreased tidal volume in anesthetized humans remains unclear.

The respiratory depressant effects of xenon were first described more than 50 years ago. Xenon (1 MAC) causes a reduction in minute ventilation and a rise in arterial carbon dioxide tension. However, unlike other inhaled anesthetics, the decrease in minute ventilation is due to decreases in the respiratory rate, which are partially compensated by increases in tidal volume.[170] At lower concentrations of xenon (33% or approximately 0.5 MAC), the decrease in respiratory rate may be entirely offset by an increase in tidal volume. Depression of the pontine pneuomotaxic center may be the mechanism for this "xenon effect." Minute ventilation may actually increase and arterial carbon dioxide tension remain the same or decrease in healthy humans.[171]

Lung and Airway Receptors

The receptors responsible for eliciting protective airway reflexes are nonuniformly distributed. Sensitivity to airway irritation appears to be greater at the larynx and trachea than at the more peripheral airways in spontaneously breathing anesthetized patients in the presence of a laryngeal mask airway (LMA). Increasing concentrations of sevoflurane had little effect in altering these responses. The direct effects of halothane, isoflurane, and enflurane on pulmonary and laryngeal irritant receptors and tracheobronchial SARs have been investigated in spontaneously breathing and vagotomized, paralyzed dogs.[178,179] Volatile anesthetics increase the activity of laryngeal irritant receptors[178] and inhibit pulmonary irritant receptors.[179] Volatile anesthetics also elevate the excitation threshold and increase the sensitivity of low-threshold stretch receptors. Halothane and, to a lesser extent, sevoflurane attenuate the end-expiratory discharge frequency of SARs.[179,180] These agents may not affect or may even augment inspiratory activity. The clinical implications of these findings have yet to be precisely determined, but these anesthetic-induced changes in SAR function may play a role in the reduction of bronchomotor tone observed with volatile anesthetics. The severity of airway hyperreactivity was determined in 123 children breathing spontaneously through LMAs and undergoing either isoflurane or sevoflurane anesthesia.[181] Isoflurane was associated with greater airway hyperreactivity and more adverse airway events during LMA removal. An ongoing debate lingers in the anesthesiology literature regarding comparisons of upper airway reactivity between sevoflurane and desflurane. Sevoflurane (1 MAC) may provide greater suppression of responses to tracheal[182] and LMA[183] stimulation than desflurane does in elective surgical patients (Fig. 22-17). Higher concentrations (1.8 MAC) of these agents produce similar attenuation of coughing, tachycardia, and hypertension associated with tracheal stimulation, yet desflurane may irritate the respiratory tract at concentrations exceeding 1 MAC. Nevertheless, there were no differences in airway irritation with the use of an LMA in elective surgical patients receiving low concentrations of either desflurane or sevoflurane.[184] However, a significant increase in airway irritation was observed in smokers independent of the type of volatile agent.[185] The concomitant use of propofol and fentanyl in these patients and the relatively lower concentrations of desflurane than sevoflurane may have limited the ability to detect differences between these two anesthetic

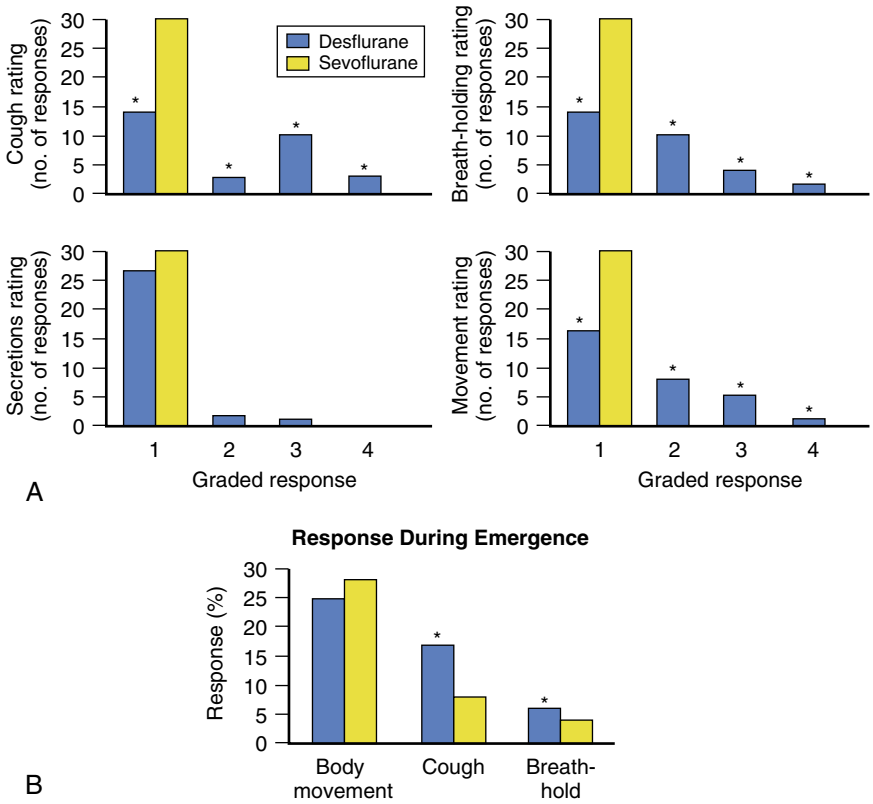


Figure 22-17 **A,** Graded responses to body movement, coughing, breath-holding, and secretions during transition to 2 minimum alveolar concentration (MAC) desflurane and sevoflurane anesthesia. **B,** Percentage of patients experiencing body movement, coughing, and breath-holding during emergence associated with sevoflurane and desflurane. *Desflurane caused more events than sevoflurane did in elective surgical patients. *(Modified from Arain S, Shankar H, Ebert TJ: Desflurane enhances reactivity during the use of the laryngeal mask airway. Anesthesiology 103:495, 2005, with permission.)*

agents in this study. The profound cardiovascular stimulation induced by rapid increases in the concentration of desflurane is due to activation of tracheopulmonary RARs.[186]

Volatile anesthetics produce a greater magnitude of depression of upper airway electromyographic[187] or nerve activity[188] than diaphragmatic activity in anesthetized, spontaneously breathing (Fig. 22-18) or paralyzed, ventilated, vagotomized cats. The extent to which this depression of upper airway motor neuron activity occurs as a result of anesthetic-induced inhibition of the reticular activating system is unknown. Upper airway caliber represents a balance between dilating and constricting forces. Outward-dilating forces are produced by neurogenic activity in the genioglossus, posterior cricoarytenoid, and hyoid muscles, whereas during inspiration, subatmospheric intraluminal pressure causes an inward collapsing force. It has been suggested that volatile anesthetics may cause relaxation of the genioglossus muscle with resultant posterior tongue displacement, a reduction in airway caliber, and consequent upper airway obstruction. Halothane, isoflurane and sevoflurane have all been shown to relax the upper airway musculature. Inhibition of upper airway muscle activity by isoflurane was independent of dose, and even subanesthetic concentrations totally abolished genioglossus activity.[189] In contrast, sevoflurane-induced changes in upper airway caliber was dose-dependent in children[26] (Fig. 22-19) and primarily occurred in an anterior-posterior dimension. In addition to these direct effects of sevoflurane on airway musculature, sevoflurane may also increase upper airway resistance by reducing lung volumes (which causes rostral tracheal displacement) or by increasing pharyngeal constrictor muscle activity.[26] Interestingly, whereas propofol predominantly caused narrowing in the hypopharynx at the level of the epiglottis,[190] sevoflurane more profoundly reduced airway caliber at the level of the soft palate. Respiratory premotor neurons are inhibited by the effects of volatile anesthetics through enhancement of GABAergic inhibitory activity and simultaneous depression of excitatory glutaminergic mechanisms.[153,191] However, hypoglossal motor neurons (which innervate all tongue muscles and are intimately involved in maintaining airway patency during inspiration) are extremely sensitive to subanesthetic concentrations of volatile anesthetics.[192] This inhibition of inspiratory hypoglossal motor neurons by volatile anesthetics is not related to actions at a K^+ leak channel but may be due to an enhancement of a tonic modulatory inhibition (Fig. 22-20).

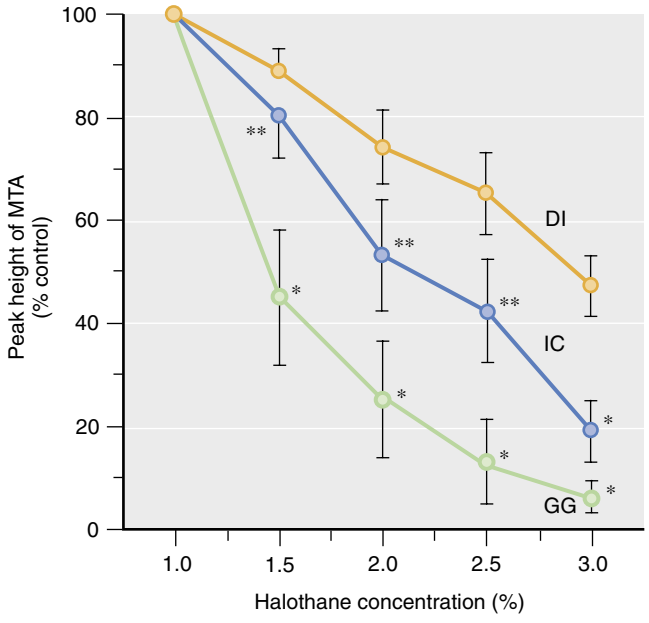


Figure 22-18 Decrease in phasic inspiratory muscle activity expressed as peak height of the moving time average (MTA), in percent change from control (1% halothane), during halothane anesthesia in adult cats. Values are means ± SEM. IC, intercostal muscle. *P < .05 versus the diaphragm (DI); **P < .05 versus the genioglossus muscle (GG). Note the differential sensitivities of these respiratory muscles. *(From Ochiai R, Guthrie RD, Motoyama EK: Effects of varying concentrations of halothane on the activity of the genioglossus, intercostals, and diaphragm in cats: An electromyographic study. Anesthesiology 70:812, 1989, with permission.)*

Ventilatory Mechanics and Mechanoreceptors in the Chest Wall

Induction of general anesthesia reduces FRC. Loss of tonic parasternal intercostal muscle activity,[193,194] development of phasic expiratory activity of respiratory muscles (Fig. 22-21),[194] alteration in diaphragm position,[193] and changes in thoracic blood volume have been proposed as mechanisms responsible for anesthetic-induced decreases in FRC. In contrast to intercostal muscle function, diaphragmatic activity is relatively spared during halothane anesthesia.[194] A change in diaphragmatic shape occurs during anesthesia, with dependent regions shifting cephalad and nondependent regions shifting caudad (Fig. 22-22).[195] Anesthesia-enhanced expiratory muscle activity results in inward displacement of the rib cage, an action that contributes to the reduction in FRC. In contrast, inspiratory rib cage expansion may remain relatively well preserved because of phasic inspiratory activity of the scalene muscles despite the attenuation of parasternal intercostal muscle activity.[193] Areas of atelectasis in dependent lung regions frequently occur in anesthetized, spontaneously ventilating humans and may be related to alterations in respiratory muscle tone but not specifically to any single chest wall structure.[195] There is no direct correlation between changes in FRC and anesthesia-induced atelectasis.[196] As a result of the reduction in lung volume secondary to decreases in FRC, airway resistance increases. This action may partially counteract the direct bronchodilatory effects of volatile anesthetics.

Reasons for the differential effects of inhaled anesthetics on inspiratory and expiratory respiratory muscles are unknown but may be related to direct actions on brainstem control mechanisms or differential sensitivity of premotor and motor neurons. Stuth and coworkers[197-199] showed that bulbospinal respiratory neurons are more resistant than phrenic nerve activity to the depressant effects of volatile anesthetics in vagotomized, decerebrate dogs. The inhibition of expiratory premotor neurons by volatile agents is mediated by presynaptic reduction of glutaminergic excitation and enhancement of $GABA_A$ergic inhibitory receptor function (Fig. 22-23).[152,153,191] Sevoflurane also depressed phrenic nerve activity and enhanced the overall inhibition of inspiratory motor neurons to a greater extent than halothane did. Increases in carbon dioxide drive only partially compensated for these anesthetic-induced depressant actions. There appears to be less halothane-induced depression of expiratory than inspiratory bulbospinal premotor neurons. These findings suggest that the effects

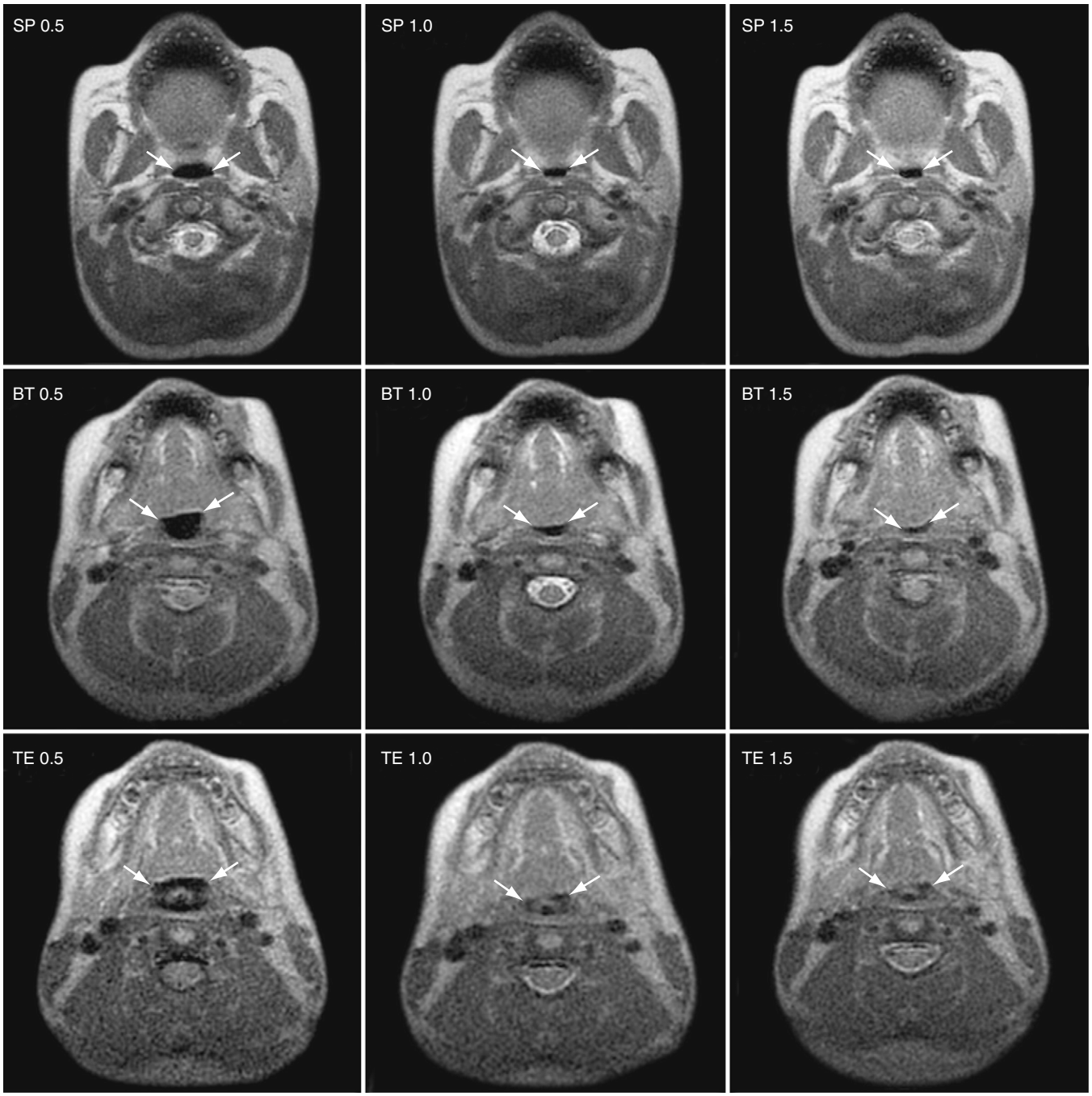


Figure 22-19 Magnetic resonance images at the level of the soft palate (SP), base of the tongue (BT), and tip of the epiglottis (TE) of a child in early expiration demonstrating a progressive reduction in cross-sectional area with increasing concentration of sevoflurane (0.5, 1, 1.5 minimum alveolar concentration). *Arrows* show the site of the collapsible pharyngeal airway. *(From Crawford MW, Arrica M, Macgowan CK, Yoo S-J: Extent and localization of changes in upper airway caliber with varying concentrations of sevoflurane in children. Anesthesiology 105:1147, 2006, with permission.)*

of volatile agents on respiratory muscle function may be due to a relatively greater influence on motor efferent pathways (including spinal respiratory motor neurons) than on brainstem-mediated mechanisms (Fig. 22-24).[198]

Volatile anesthetics differentially depress neuromuscular transmission and skeletal muscle contractility. Halothane impairs excitation-contraction coupling and neuromuscular transmission to equivalent degrees, whereas isoflurane, sevoflurane, and enflurane depress diaphragmatic contraction primarily through alterations in neuromuscular transmission.[200,201] Isoflurane, enflurane, and sevoflurane depress diaphragmatic tension in response to phrenic nerve stimulation. These results may partially explain clinical observations in humans, but a wide range of species variations also exist that make extrapolation of results obtained from experimental animals to humans difficult. Similar to volatile agents, nitrous oxide affects chest wall function and breathing by

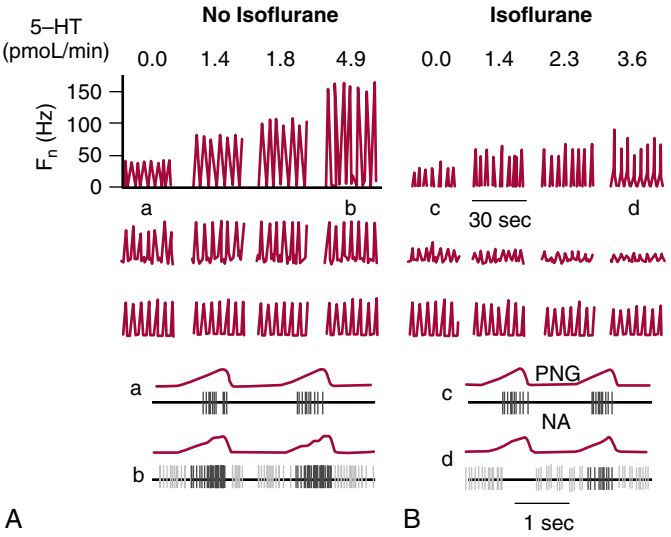


Figure 22-20 Inhibition of inspiratory hypoglossal motoneurons (XII) by a subanesthetic concentration (0.3 minimum alveolar concentration) of isoflurane in the absence and presence of graded doses of serotonin (5-HT). This inhibition in the presence of 5-HT rules out a major contribution of K^+ leak channels. Note the significant decline in hypoglossal nerve activity (≈60%) with isoflurane as opposed to phrenic nerve activity (PNG) (<10%). F_n represents the neurons' spontaneous peak discharge frequency. The letters a to d indicate the records for which time-enlarged views are shown. NA, neuronal activity. *(From Brandes IF, Zuperku EJ, Stucke AG, et al: Isoflurane depresses the response of inspiratory hypoglossal motoneurons to serotonin in vivo. Anesthesiology 106:736, 2007, with permission.)*

changing the distribution and timing of the neural drive to the respiratory muscles.[202] Nitrous oxide decreases tidal volume as a result of a reduction in rib cage motion and increased phasic expiratory activity in humans. In contrast, xenon does not affect transdiaphragmatic pressure or diaphragmatic electromyography

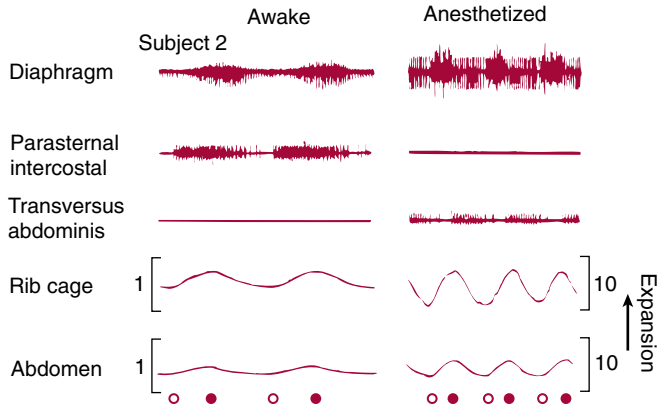


Figure 22-21 Representative record from one subject while awake and during halothane anesthesia. The *upper* three tracings are electromyograms. The *lower* tracings represent rib cage and abdominal dimensions measured by respiratory impedance plethysmography. *Open circles* and *closed circles* denote the beginning and end of inspiration, respectively. Note that the amplitude of rib cage and abdominal excursions diminishes during halothane anesthesia but the relationship between their amplitudes is preserved. *(From Warner DO, Warner MA, Ritman EL: Human chest wall function while awake and during halothane anesthesia. I. Quiet breathing. Anesthesiology 82:6, 1995, with permission.)*

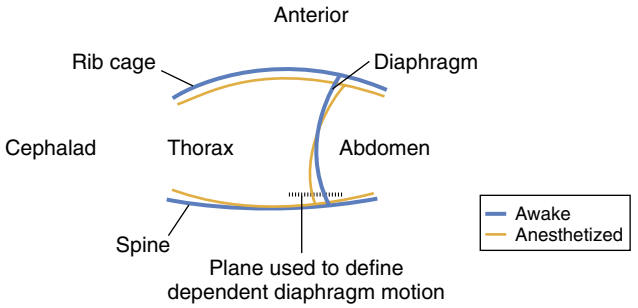


Figure 22-22 Diagram of a midsagittal section of the thorax while awake (*blue lines*) and while anesthetized (*yellow lines*) with a 1.2 minimum alveolar concentration of halothane. The chest wall configuration was determined by using images of the thorax obtained by three-dimensional fast computed tomography. *(Adapted from Warner DO, Warner MA, Ritman EL: Atelectasis and chest wall shape during halothane anesthesia. Anesthesiology 85:49, 1996, with permission.)*

because this anesthetic noble gas preserves neuromuscular transmission.[63]

The work of breathing expressed in joules is defined as pressure or force multiplied by the tidal volume during inspiration. The respiratory work of the lung is further broken down into elastic work (required to overcome recoil of the lung) and resistive work (required to overcome airway flow resistance and the viscoelastic resistance of pulmonary tissue in the absence or presence of an airway apparatus). The work of breathing is usually derived from transpulmonary pressure–tidal volume curves. Volatile anesthetics increase the work of breathing in adults and children. Sevoflurane anesthesia increased viscoelastic and elastic pressure in the lung, findings indicative of a reduction in pulmonary compliance mediated at the lung periphery rather than at the airway level in normal rats.[203] This finding was supported histologically by the observation of increased areas of alveolar collapse alternating with hyperinflation. In contrast, most studies in humans demonstrate that low concentrations of volatile anesthetics significantly reduce upper and lower respiratory system resistance (Fig. 22-25).[204] In a murine model of chronic asthma, sevoflurane anesthesia significantly decreased resistance in the central and distal airways in addition to lowering resistance in the lung periphery.[58] These data suggest that sevoflurane exerts a beneficial action in the presence of chronic airway obstruction and implies that volatile agents reduce the work of breathing (Fig. 22-26).

Expiration is passively affected by the recoil characteristics of the lung during normal breathing. In anesthetized patients, the ventilatory response to expiratory resistance is reduced to a greater extent than the response to inspiratory resistance. Conscious and anesthetized humans exhibit decreases in the respiratory rate during expiratory resistive loads, but the rib cage–abdominal wall motion asynchrony that causes less effective ventilation and increases in carbon dioxide is seen only in anesthetized subjects.[205] This concept may be particularly important in spontaneously breathing, anesthetized patients who demonstrate expiratory obstruction, such as may occur with partial occlusion of a breathing circuit, asthma, emphysema, or airway secretions. Interestingly, the ventilation-perfusion inhomogeneity caused by volatile anesthetics has been proposed as a new mechanism by which nitrous oxide produces a second gas effect in the presence of sevoflurane.[206]

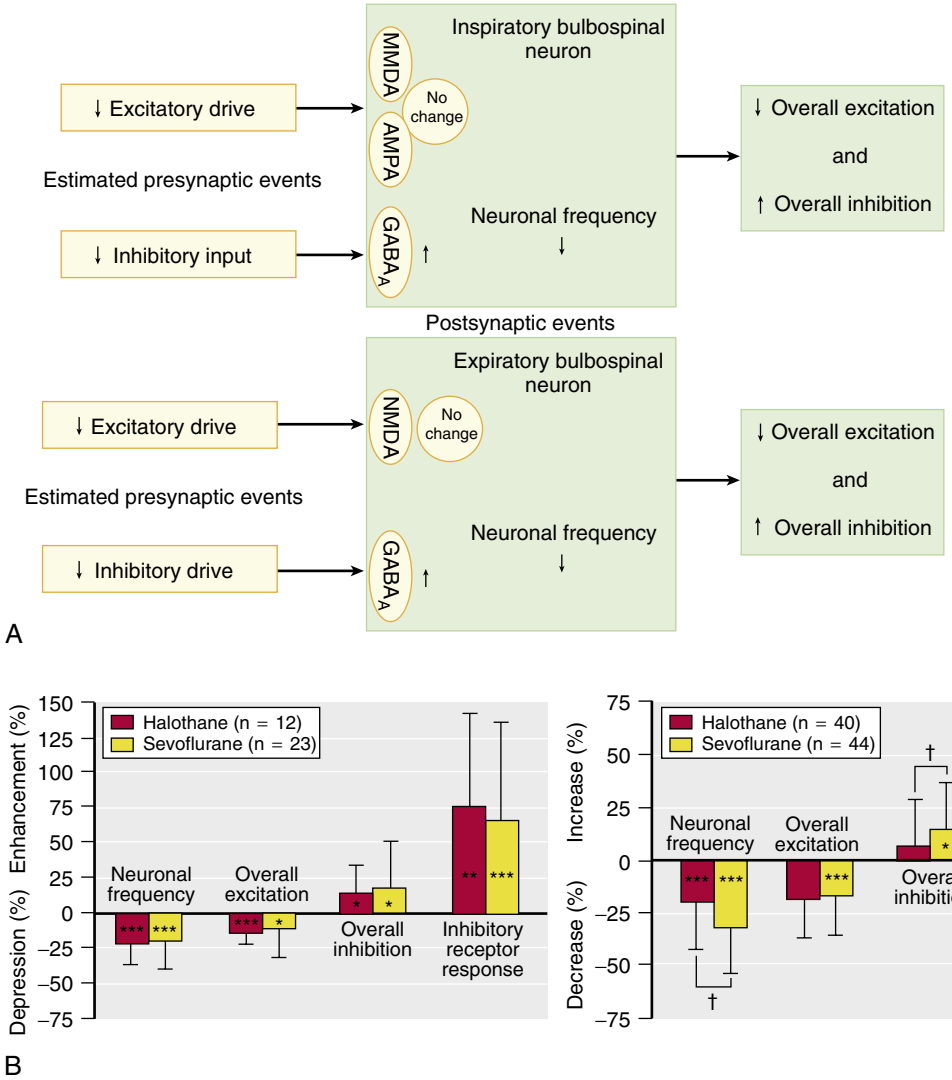


Figure 22-23 A, Schematic diagram of the effects of volatile anesthetics on synaptic transmission to expiratory and inspiratory premotor neurons in the caudal ventral respiratory group. In expiratory neurons, the overall glutaminergic excitatory drive is reduced without affecting *N*-methyl-D-aspartate (NMDA) receptor function, and overall inhibition is increased because of an increase in type A γ-aminobutyric acid ($GABA_A$) receptor function. The presynaptic inhibitory drive is also reduced and leads to a decrease in the control discharge frequency of the premotor neuron. In inspiratory neurons, there is a reduction in overall glutaminergic excitation with an increase in overall inhibitory input. Postsynaptic α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) and NMDA receptor responses were not changed, thus suggesting that the presynaptic excitatory drive is diminished. **B,** Effects of halothane and sevoflurane on excitatory and inhibitory neurotransmission to canine medullary expiratory (left graph) and inspiratory (right graph) neurons. Values are mean changes ± SD for neuronal control frequency, overall excitation, overall inhibition, and inhibitory receptor response by a 1 minimum alveolar concentration of halothane and sevoflurane. There were no differences in anesthetic-induced changes between halothane and sevoflurane in expiratory neurons. †$P < 0.05$ sevoflurane enhanced overall inhibition and depressed neuronal frequency more than halothane did in inspiratory neurons. *$P < .05$, **$P < .01$, ***$P < .001$ versus no change. *(Adapted from Stucke and colleagues[152,153,189] with permission.)*

Effects of Anesthetics on Ventilatory Response to Chemical Stimuli

The effects of inhaled anesthetics on respiratory drive are typically characterized by the ventilatory response to alterations in arterial carbon dioxide tension or hypoxia. Arterial carbon dioxide tension is the most important stimulus for ventilation. The apneic threshold, defined as the highest arterial carbon dioxide tension at which a subject remains apneic, is approximately 4 or 5 mm Hg below resting arterial carbon dioxide tension. There are no significant agent-specific or depth-related effects of ether, halothane, or isoflurane on the relationship between apneic thresholds and resting arterial carbon dioxide tension in humans. Volatile anesthetic–induced ventilatory depression increases resting carbon dioxide tension and the apneic threshold to similar degrees. Thus, *assisted* ventilation, which lowers arterial carbon dioxide tension below the apneic threshold during anesthesia, ultimately becomes *controlled* ventilation. Return of spontaneous ventilation in a mechanically hyperventilated patient is dependent on return of carbon dioxide tension toward the apneic threshold after cessation of positive-pressure ventilation. The duration of apnea required before a patient will begin to breathe spontaneously is dependent on anesthetic depth. Continuation of positive-pressure ventilation (or intentional hyperventilation) to eliminate volatile agents and maintenance of relative hypercapnia during

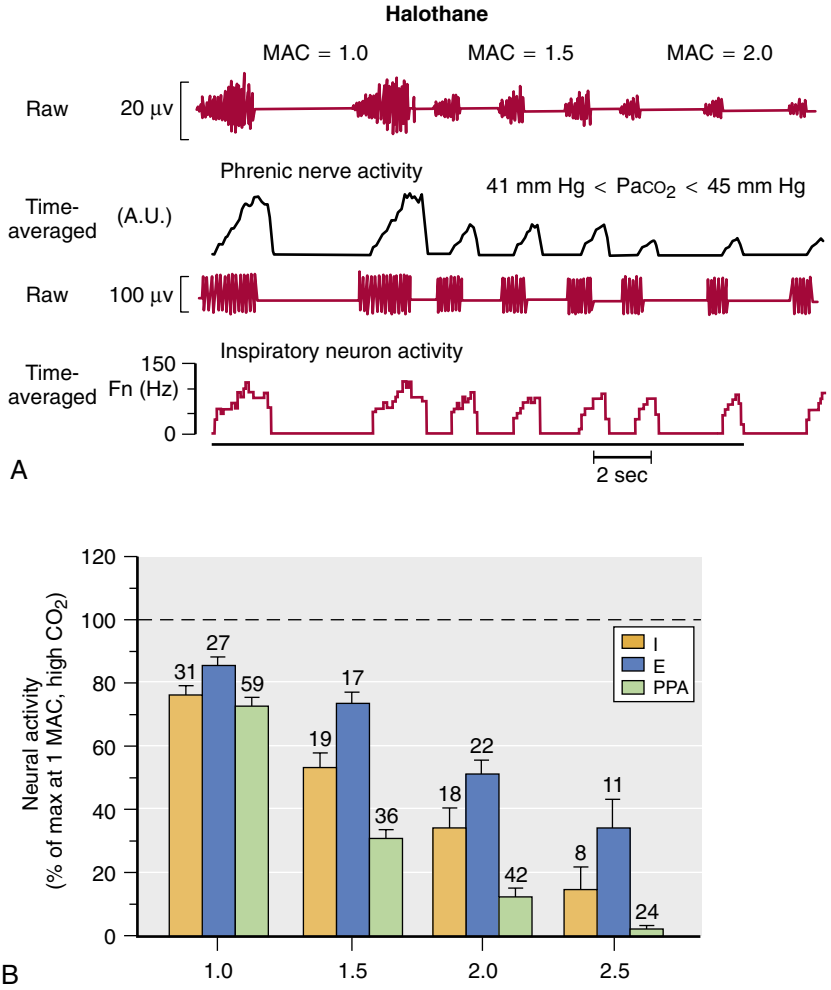


Figure 22-24 Effect of increasing halothane on phrenic nerve and neuron activity. With increasing anesthetic depth, both peak phrenic nerve (PPA) and peak neuron activities are depressed. PPA shows the greatest sensitivity to halothane. **A,** Phrenic nerve activity and the discharge frequency of an inspiratory bulbospinal neuron. Inspiratory (phrenic burst) duration decreases with increasing anesthetic depth. **B,** Peak expiratory neuron (E) activity, peak inspiratory neuron (I) activity, and PPA. Expiratory neuronal activity was most resistant to the effects of halothane. *Bars* show normalized means ± SEM, and the numbers above the *bars* indicate the numbers of neurons studied for each condition. Raw, airway resistance. *(Adapted from Stuth EAE, Tonkovic-Capin M, Kampine JP, et al: Dose-dependent effects of halothane on expiratory and inspiratory bulbospinal neurons and the phrenic nerve activities in dogs. Anesthesiology 81:1470, 1994, with permission.)*

mechanical ventilation are two commonly used clinical strategies to shorten the emergence time. Such maneuvers decrease the apneic threshold or increase resting arterial carbon dioxide tension and reduce emergence time during isoflurane, desflurane, or sevoflurane anesthesia (Fig. 22-27).[207,208] Rebreathing of carbon dioxide[209] or gradual increases in the concentration of sevoflurane[210] may reduce the incidence of apnea during induction with inhaled anesthetics. The activity of expiratory brainstem neurons may be temporarily "switched off" during rapid increases in anesthetic concentration and thereby contribute to apnea under these conditions.[210]

Carbon Dioxide Response Curves

Volatile anesthetics depress the ventilatory response to hypercapnia in a dose-dependent fashion. Moderate concentrations (<1 MAC) of volatile agents markedly attenuate or entirely eliminate hypercapnia-induced increases in ventilatory drive. Even low concentrations of nitrous oxide may substantially affect responses to hypercapnia. The slope of the minute ventilation–arterial carbon dioxide tension relationship returns toward normal after 6 hours of halothane anesthesia, but ventilatory responsiveness to carbon dioxide nevertheless remains profoundly depressed. The addition of nitrous oxide to halothane depresses ventilation less than equivalent-MAC halothane alone does, but the carbon dioxide–ventilatory response slope was unaltered when either a nitrous oxide–desflurane combination or desflurane alone was used.[166] Interestingly, the response to hypercapnia was more profoundly depressed during desflurane than during isoflurane or sevoflurane anesthesia at 0.5 MAC in C3 mice (C3 mice have a blunted response to hypercapnia and hypoxia at baseline).[211]

Subanesthetic concentrations (<0.2 MAC) of volatile anesthetics may depress the peripheral chemoreflex loop and inhibit the ventilatory response to hypercapnia.[212,213] At higher concentrations, central chemoreceptors may also be affected. In contrast, Pandit and colleagues[214] showed that subanesthetic concentrations of sevoflurane did not affect the response to acute or sustained hypercapnia. The apparent discrepancies between these results may be related to the sustained nature of the hypercapnic responses or differences in the state of central nervous system arousal under baseline conditions. A review of all published studies investigating the effect of low concentrations of volatile anesthetics on hypercapnic drive suggests a relative lack of any substantial inhibitory effect.[166]

Depression of ventilatory responsiveness to inhaled carbon dioxide is clinically important. Accumulation of carbon dioxide and concomitant acidemia may cause dysfunction in several organ systems, including the heart (e.g., arrhythmias), lungs (e.g., pulmonary hypertension), and brain (e.g., increased intracranial

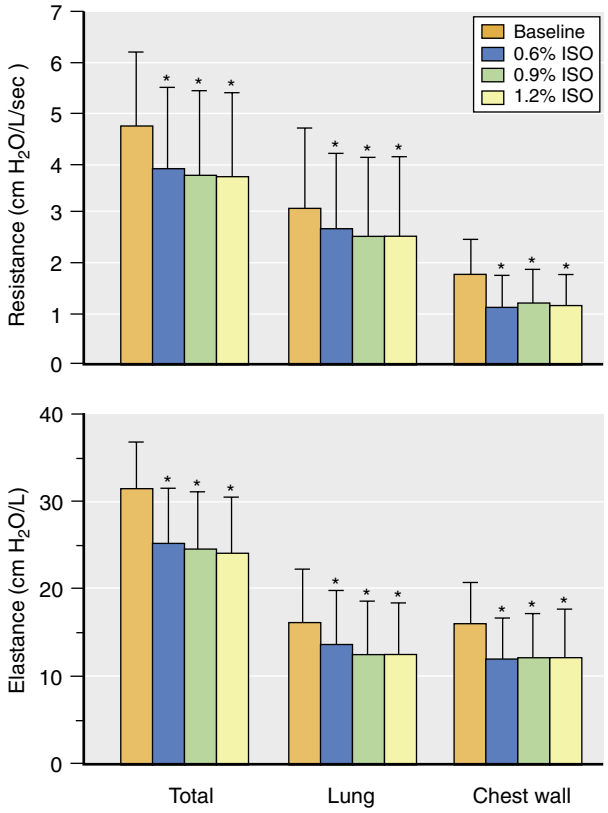


Figure 22-25 Isoflurane at 0.6% reduced respiratory system elastance (E in cm H_2O/L) and resistance (R in cm H_2O/L/sec). "Total" represents the total respiratory system (lung + chest wall). Values are means ± SD. *P < .05 versus baseline. There were no further reductions with increasing concentrations of isoflurane. *(Adapted from Ruiz P, Chartrand D: The effect of isoflurane 0.6% on respiratory mechanics in anesthetized-paralyzed humans is not increased at concentrations of 0.9% and 1.2%. Can J Anaesth 50:67, 2003, with permission.)*

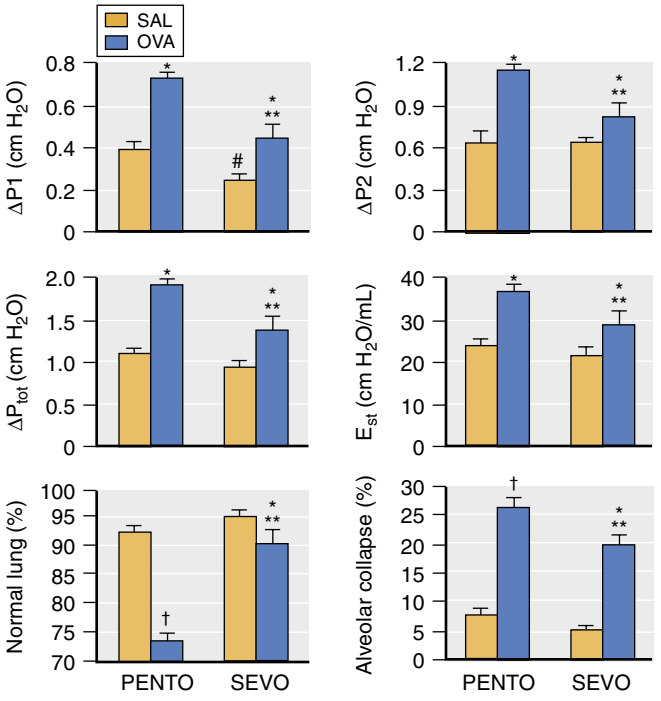


Figure 22-26 Mean ± SEM for ΔP1 (pressure to overcome airway resistance), ΔP2 (viscoelastic lung properties), ΔP_{tot} (total of ΔP1 and ΔP2), and E_{st}, static lung elastance. Also shown are percent normal area and percent alveolar collapse in mice repeatedly challenged with intratracheal instillation of saline (SAL) or ovalbumin (OVA). Animals were anesthetized with pentobarbital sodium (PENTO) or sevoflurane (SEVO), 1 minimum alveolar concentration. *P < .05 versus the corresponding SAL group. **P < .001 versus the OVA-PENTO group. #P < .05 versus the SAL-PENTO group. †P < .001 versus the SAL-PENTO group. *(Adapted from Burburan SM, Xisto D, Ferreira HC, et al: Lung mechanics and histology during sevoflurane anesthesia in a model of chronic allergic asthma. Anesth Analg 104:631, 2007, with permission.)*

pressure) in patients with or without coexisting disease. Inadequate respiratory system compensation for elevations in arterial carbon dioxide tension may occur in response to rebreathing of carbon dioxide from malfunctioning anesthetic circuits, from abdominal carbon dioxide insufflation during laparoscopic surgery, or as a result of increased metabolic production of the gas during anesthesia. The reduction in ventilatory drive induced by hypercapnia may also occur in the immediate postoperative period and can contribute to significant morbidity, especially in patients with chronic lung disease.

Experimental studies have shown that rebreathing carbon dioxide recruits expiratory respiratory muscles, including the internal intercostals, but is incapable of reversing the profound depression of parasternal intercostal muscle activity produced by halothane.[215] The peripheral chemoreceptor transduction (i.e., phrenic nerve response) to acute, severe carbon dioxide stimulation was also depressed by halothane in paralyzed, vagotomized dogs in a dose-related manner.[216] Carbon dioxide sensitivity was diminished, but not abolished, by concentrations of halothane usually required for surgical anesthesia. Furthermore, halothane depressed peripheral and central carbon dioxide sensitivity to similar degrees, but the peripheral chemoreceptors contributed only approximately 15% of the total carbon dioxide sensitivity.

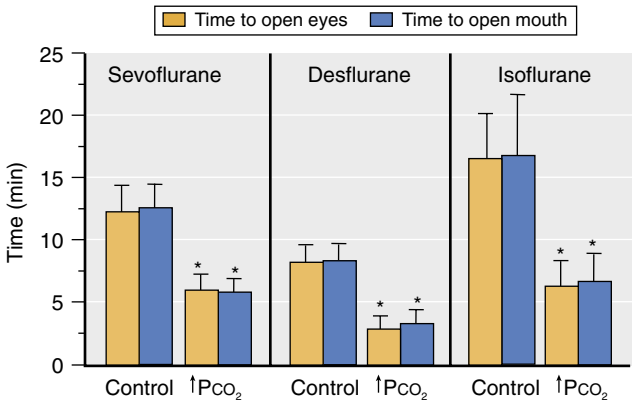


Figure 22-27 Average time between turning off the vaporizer and patients opening their eyes or mouth during the control condition (mild hypocapnia) and during hypercapnia (↑P_{CO_2}). Patients were anesthetized with either isoflurane, sevoflurane, or desflurane. Data are means ± SD. *P < .05 versus control—hypocapnia). *(Adapted from Sakata DJ, Golapakrishnan NA, Orr JA, et al: Rapid recovery from sevoflurane and desflurane with hypercapnia and hyperventilation. Anesth Analg 105:79, 2007; and Sakata DJ, Golapakrishnan NA, Orr JA, et al: Hypercapnic hyperventilation shortens emergence time from isoflurane anesthesia. Anesth Analg 104:587, 2007, with permission.)*

These data suggest that the response of peripheral chemoreceptors to carbon dioxide may appear to be of minimal clinical significance. However, if the response of peripheral chemoreceptors to hypoxia is abolished by low concentrations of volatile anesthetics, marked respiratory impairment during episodes of hypercapnia and hypoxia (such as those encountered in the perioperative period) may occur.

Ventilatory Responses to Hypoxemia

Volatile anesthetics and nitrous oxide attenuate the ventilatory response to hypoxia in experimental animals and humans in a dose-dependent manner.[217,218] Peripheral chemoreceptors appear to be the major site of this inhibitory action. Rapid inhibition (30 seconds) of the hypoxic response and reductions in carotid sinus nerve discharge were observed when peripheral chemoreceptors were stimulated during the administration of halothane (0.5% to 1.0%) to decerebrate cats.[219] Alternatively, Stuth and coworkers[220] demonstrated that the phrenic nerve response to hypoxia is attenuated, but not abolished, by halothane in vagotomized dogs. The cause of these differences may be attributed to the more pronounced degree of hypoxia (arterial oxygen tension < 40 mm Hg) achieved in experimental animals than in humans (Pao_2 ~50 mm Hg). Volatile anesthetics attenuated the usual synergistic effect of hypoxia and hypercapnia on ventilation, but the ventilatory response to hypoxia depends on the degree to which arterial carbon dioxide tension exceeds the peripheral chemoreflex threshold rather than its elevation above resting partial pressure.[221] The response is also influenced by the presence of NO (and presumably fully functional pulmonary arterial endothelium).[222] This latter role of NO may be more complex because in addition to local release, NO is also released in the ventrolateral medulla after activation of peripheral chemoreceptors during hypoxia in response to sympathoexcitation.[223]

Halothane also produced a biphasic ventilatory response (similar to that observed in newborns) in kittens that have previously attained an adult-like hyperventilatory hypoxic response.[224] Whether the cause of this altered response during halothane anesthesia is mediated by peripheral chemoreceptors is unknown, but it is unlikely that activity at the level of the brainstem is solely responsible for this phenomenon.[225]

The ventilatory response to hypoxia is substantially more sensitive to the effects of volatile anesthetics than is the response to hypercapnia.[217,226] Attenuation of peripheral chemoreceptor responses occurs at concentrations of volatile anesthetics as low as 0.1 MAC. As with the hypercapnic ventilatory drive, controversy exists about the influence of subanesthetic concentrations of volatile agents on the hypoxic ventilatory drive. Administration of 0.1 MAC sevoflurane[227] or isoflurane has little to no effect on the hypoxic drive in humans.[228] Other investigators[229] have demonstrated that anesthetic-induced blunting of the ventilatory response to acute hypoxemia occurs with all volatile anesthetics except desflurane.[230] In analyzing studies on the effect of low concentrations of volatile anesthetics on hypoxic ventilatory responses (including negative studies), Pandit[231] proposed the following order of sensitivity: halothane (most depressant, 42%) > enflurane (52%) > isoflurane (71%) > sevoflurane (72%) > desflurane (96%) (Fig. 22-28). Notably, subanesthetic concentrations of desflurane decrease hypoxic sensitivity during hypercapnia, thus suggesting that this agent exerts an effect at the peripheral chemoreceptors.[230] The reasons for inconsistencies between many of these studies may be related to differences in the state of patient arousal during administration of the subanesthetic concentrations of volatile agent, the specific agent administered, the rate of application of the hypoxic stimulus, and the presence or absence of simultaneous hypercapnia. Attenuation of the acute hypoxic ventilatory response appears to be agent specific inasmuch as the effects of isoflurane, but not halothane or sevoflurane, were blunted in the presence of audiovisual stimulation.[217] The mechanisms by which low concentrations of volatile anesthetics attenuate the hypoxic ventilatory drive is unknown despite extensive study. Interestingly, administration of antioxidants to healthy volunteers reversed the attenuation of the hypoxic ventilatory response to halothane and isoflurane.[218] These results suggest that volatile anesthetics may depress the hypoxic response by influencing the oxidation-reduction state of oxygen-sensing elements in the carotid bodies (Fig. 22-29). How antioxidants mediate this response is unclear but may be related to actions on the mitochondrial electron transport chain, volatile anesthetic binding sites, or potassium channel function.

The profound depression of hypoxic responsiveness produced by volatile anesthetics (with the exception of desflurane as noted earlier) suggests that patients may manifest a diminished ventilatory response to hypoxemia in the recovery room for some time after use of the agent has been discontinued. Audiovisual stimulation may attenuate the effects of low residual concentra-

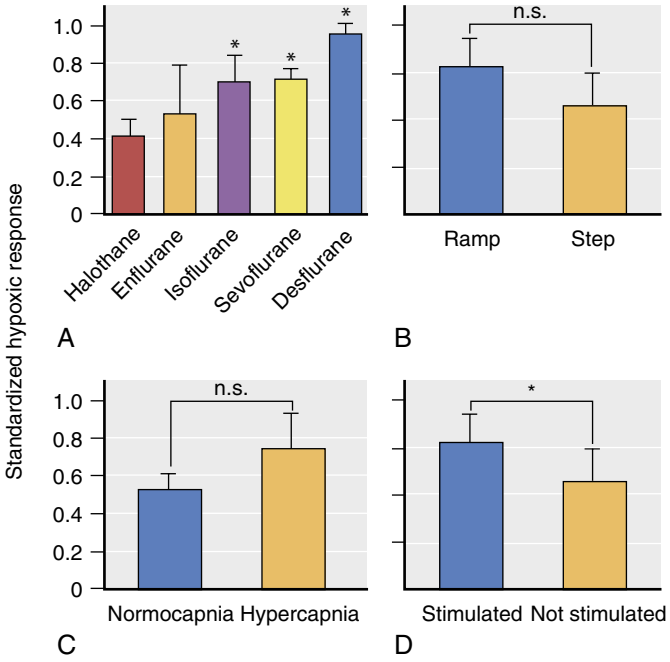


Figure 22-28 Analysis of data groups from 37 separate studies investigating the effect of low-dose volatile anesthetics on the acute ventilatory response to hypoxia in humans. **A,** Anesthetics depress the hypoxic ventilatory response in the order halothane > enflurane > isoflurane > sevoflurane > desflurane. *P < 0.05 versus halothane. **B,** Data grouped according to the speed of the hypoxic stimulus. **C,** Data grouped according to background carbon dioxide. **D,** Data grouped according to whether the hypoxic challenge occurred in the presence or absence of subject stimulation. *P < .05. *Error bars* represent 95% confidence intervals. *(Adapted from Pandit JJ: The variable effect of low-dose volatile anaesthetics on the acute ventilatory response to hypoxia in humans: A quantitative review. Anaesthesia 57:632, 2002, with permission.)*

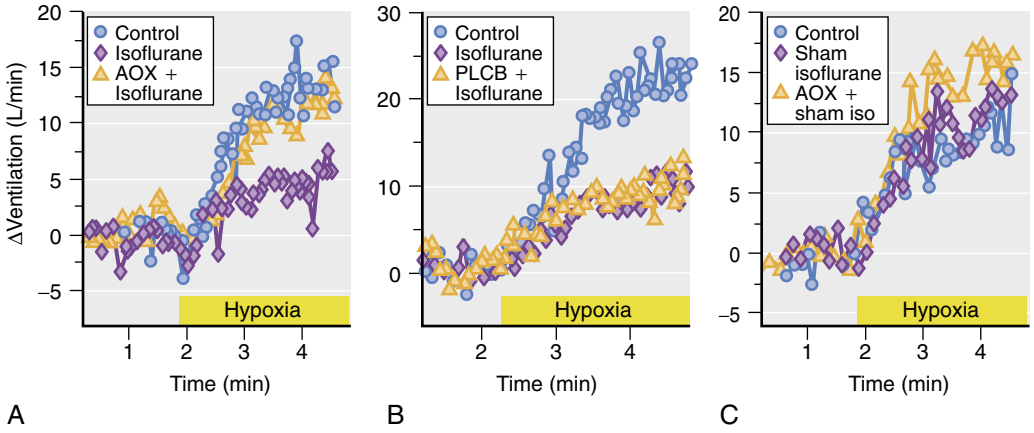


Figure 22-29 Effect of (sham) isoflurane, antioxidants (AOXs), and placebo on the acute hypoxic response in one individual. **A,** Depression of the hypoxic response by isoflurane and its reversal by antioxidants. **B,** Isoflurane reduces the hypoxic response, but placebo (PLCB) does not reverse it. **C,** Sham isoflurane or antioxidants do not significantly alter the hypoxic response. *(From Teppema LJ, Romber RR, Dahan A: Antioxidants reverse reduction of the human hypoxic ventilatory response by subanesthetic isoflurane. Anesthesiology 102:747, 2005, with permission.)*

tions of anesthetics in postoperative patients. In contrast, pain appears to be a poor stimulus to blunt the hypoxic ventilatory response to volatile agents. This phenomenon may be especially important in patients who depend to some degree on a hypoxic drive to establish their level of ventilation (e.g., those with chronic respiratory failure). In these circumstances, the ability of these patients to maintain adequate spontaneous ventilation in the presence of a volatile anesthetic may be severely impaired. Although there appear to be few clinically relevant differences between volatile anesthetics in hypoxia-induced depression of the ventilatory response in normal subjects, the effects in patients with pulmonary disease have not been studied extensively.

Hypoxia may occur postoperatively for several reasons. Diffusion hypoxia is well known and may occur during recovery from nitrous oxide anesthesia. Rapid elimination of nitrous oxide from blood to the alveoli combined with slower nitrogen diffusion reduces the alveolar oxygen concentration. In contrast, diffusion hypoxia may not occur during xenon anesthesia because the blood-gas partition coefficient of the noble gas (0.12) is similar to that of nitrogen and thus diffusion into alveoli may be slower.[66] The specific actions of xenon on the hypoxic ventilatory drive have not been clearly defined.

Acute Lung Injury

Mechanisms of Acute Lung Injury

Acute lung injury and acute respiratory distress syndrome are inflammatory disorders characterized by excessive infiltration of neutrophils, release of inflammatory mediators, and destruction of the alveolar-capillary membrane (also see Chapters 91 and 93). This series of events results in compromised gas exchange and pulmonary edema. There are a variety of causes of acute lung injury, including sepsis and positive-pressure ventilation. Endotoxin-induced lung injury is typified by hypoxemia resulting from a ventilation-perfusion mismatch with shunting through collapsed alveoli. This clinical condition associated with sepsis may be modeled in the laboratory by injection or inhalation of lipopolysaccharide, a component of the outer membrane of gram-negative bacteria. Lipopolysaccharides bind to Toll-like receptor 4 to activate nuclear factor κB, upregulate adhesion molecules, and stimulate cytokine-induced neutrophil migration into the pulmonary parenchyma. The alveolar epithelium, which may be injured by endotoxin, plays a critical role in maintaining alveolar homeostasis by the production of specific proteins, including surfactant and a variety of cytokines, and by clearing excess alveolar liquid. Notably, failure of the alveolar epithelium is even associated with increased mortality.[232]

Acute ventilator-induced lung injury is manifested as severe distention of and damage to bronchoalveolar structures, lung overinflation, and bronchiectasis.[233] Caveolae are flask-shaped invaginations of the plasma membrane that are involved in endocytosis, signal transduction, and transendothelial albumin transport. Caveolin-1, an integral membrane protein and component of endothelial caveolae, regulates the endothelial uptake and transport of albumin.[234] Inflammatory cytokines, including tumor necrosis factor-α, interleukin-1β, and macrophage inflammatory protein 2, may be released from alveolar epithelial cells, neutrophils, and macrophages. Cytokines are important mediators of leukocyte recruitment and activation. In general, attenuation of the cytokine response is considered beneficial in terms of reducing potential lung injury. Alternatively, in certain clinical situations such as immunocompromised patients, blunting of the release of inflammatory mediators and failure of neutrophil migration into the inflamed lung may predispose to a greater risk for pulmonary infections. Unfortunately, release of cytokines is highly variable and depends on experimental conditions. For example, altering the ventilation strategy alone may modify lung cytokine responses to lipopolysaccharide,[231] and positive-pressure ventilation in the absence of anesthesia may exacerbate the inflammatory responses.[235] The molecular mechanisms mediating acute lung injury have not been well defined. Nitric oxide, derived from inducible nitric oxide synthase (iNOS) in response to inflammation and endotoxin, appears to play an important role in acute lung injury inasmuch as inhibition of iNOS substantially reduced pulmonary lymph filtration and improved oxygenation during endotoxemia in conscious sheep.[236]

The presence of preexisting pulmonary disease, such as chronic bronchitis, pneumonia, or COPD, or smoking may exacerbate the pulmonary damage that occurs in response to an acute lung injury.[185] As with acute lung injury, smoking induces an inflammatory state. In contrast to acute lung injury, tobacco abuse increases the number but decreases the response of macrophages and neutrophils. Thus, these cells are less capable of releasing cytokines during infection. In addition, goblet cell hyperplasia, decreased mucociliary clearance, and increased airway reactivity occur and also contribute to potential infection, bronchospasm, and acute lung injury.[237]

Effects of Inhaled Anesthetics on Acute Lung Injury

Previous studies suggested that volatile anesthetics may augment the inflammatory response during mechanical ventilation,[238-240] but results of another investigation indicated that short-term positive-pressure ventilation with high tidal volumes does not affect systemic proinflammatory or anti-inflammatory cytokines in the lungs of healthy, isoflurane-anesthetized patients.[241] Volatile anesthetics have been shown to promote macrophage aggregation, enhance gene expression of proinflammatory cytokines,[238,242] (Fig. 22-30) exacerbate the extent of lung injury, and increase mortality after experimental aspiration.[240] Halothane also caused DNA and cell damage, nuclear fragmentation, and apoptotic-like changes in isolated pulmonary epithelial cells.[243] One mechanism by which volatile anesthetics may worsen acute lung injury is through an increase in alveolar membrane permeability. Halothane and isoflurane were found to transiently increase pulmonary vascular endothelial damage on radionuclide scanning.[244] Isoflurane also enhanced alveolar epithelial permeability in patients undergoing surgery.[245] Desflurane increased lipid peroxidation as measured in bronchoalveolar lavage samples from healthy surgical patients.[246] These data suggest that desflurane may promote pulmonary alveolar membrane injury. In contrast, sevoflurane caused less pronounced effects in this model, thus suggesting that this agent may exert a protective effect. Furthermore, isoflurane but not sevoflurane increased albumin permeability and transport in isolated rat lungs.[234] This deleterious action appeared to be related to enhancement of caveolin-1–mediated albumin uptake. Similarly, pretreatment with isoflurane but not sevoflurane enhanced neurogenic pulmonary edema in rats.[247] The proinflammatory response and enhanced cytokine levels in patients were also more pronounced after desflurane than after sevoflurane anesthesia.[242] In contrast to the transient effects of halothane and isoflurane, there were no significant effects on alveolar integrity or ultrastructure after high concentrations of sevoflurane were administered to pigs.[248] However, administration of sevoflurane to pigs[238] and healthy surgical patients[242] moderately enhanced inflammatory mediators such as leukotriene C_4, nitrate, nitrite, tumor necrosis factor-α, interleukin-1β, and interleukin-6. Inhalation of volatile anesthetics, including sevoflurane, was associated with an increase in proinflammatory cytokine protein from and gene expression in macrophages obtained from mechanically ventilated rats.[239] As with previous studies, sevoflurane appeared to produce relatively less pronounced effects than other volatile agents did. Oleic acid–induced lung injury was associated with impaired pulmonary gas exchange because of a ventilation-perfusion mismatch and shunting in mechanically ventilated dogs. Low concentrations of isoflurane exacerbated this impairment and worsened oxygen delivery.[249]

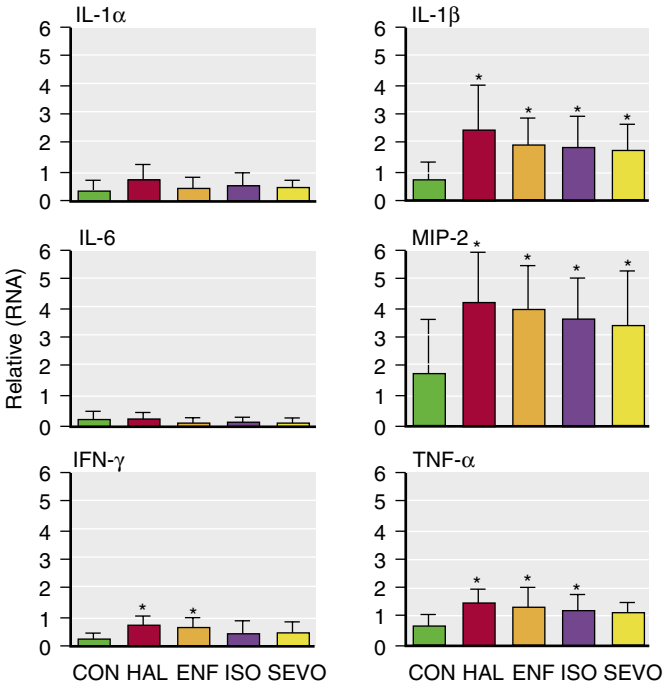


Figure 22-30 Changes in expression of proinflammatory cytokines from macrophages during mechanical ventilation without (CON, control) and with volatile anesthetics (HAL, halothane, ENF, enflurane, ISO, isoflurane, SEVO, sevoflurane). Values are the ratio of cytokine mRNA to β-actin mRNA and are presented as means ± SD. *$P < .05$ versus the control group (mechanical ventilation without volatile anesthetics). Gene expression for interleukin-1β (IL-1β), macrophage inflammatory protein 2 (MIP-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) all increased significantly in comparison to mechanical ventilation alone. *(Adapted from Kotani N, Takahashi S, Sessler DI, et al: Volatile anesthetics augment expression of proinflammatory cytokines in rat alveolar macrophages by mechanical ventilation. Anesthesiology 91:187, 1999, with permission.)*

The actions of volatile anesthetics on lung inflammatory reactions are not clear. Under certain conditions, volatile anesthetics appear to play an anti-inflammatory and protective role in lung injury. One determinant of whether volatile anesthetics reduce or exacerbate pulmonary cytokine formation appears to be the cell types studied and the conditions under which the cytokine expression is measured. Volatile anesthetics increase the secretion and gene expression of some cytokines in alveolar macrophages but decrease the formation of proinflammatory cytokines in alveolar type II cells.[235,250,251] When compared with thiopental anesthesia, pigs anesthetized with sevoflurane exhibited reduced expression of tumor necrosis factor and interleukin-1β in lung tissue.[252] Pretreatment with 1.1% sevoflurane also significantly reduced the inflammatory response by alveolar type II cells exposed to lipopolysaccharide and attenuated the endotoxin-induced chemotaxis of neutrophils.[253] The latter data suggested another potential role of volatile agents in mediating inflammatory responses.

Under controlled conditions, volatile anesthetics tend to increase cytokine formation and appear to enhance inflammatory responses. In contrast, in models of lung acutely injured by stimulation with lipopolysaccharide, *Escherichia coli* endotoxin, or

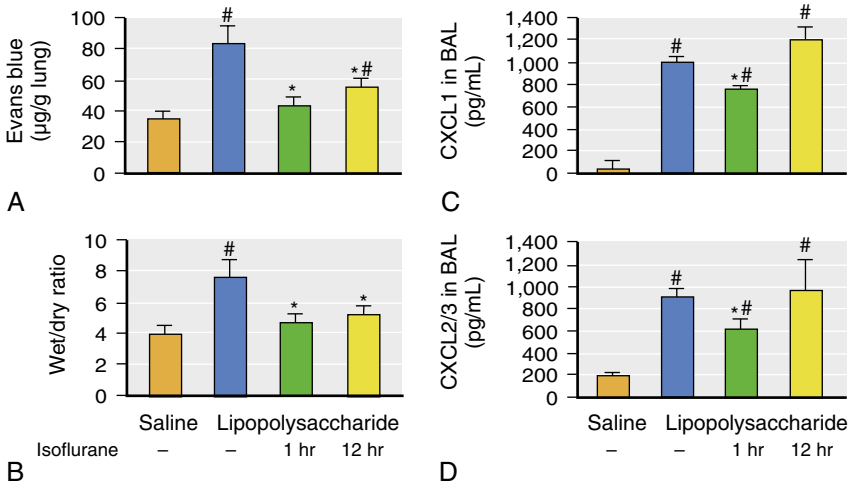


Figure 22-31 Capillary protein leakage measured by extravasation of Evans blue dye (**A**) and formation of lung edema measured by the ratio of wet to dry lung weight (**B**) in mice receiving saline, lipopolysaccharide, or isoflurane 1 or 12 hours before lipopolysaccharide. Endotoxin aerosol induced a significant increase in both capillary protein leakage and edema formation, which was reduced by pretreatment with isoflurane. **C** and **D,** Alveolar release of the two most important neutrophil-attracting chemokines CXCL1 and CXCL2/3 measured with an enzyme-linked immunosorbent assay 2 hours after receipt of lipopolysaccharide. Early, but not late (12 hour) isoflurane pretreatment reduced chemokine secretion significantly. Data are means ± SD. #Significant change between control and endotoxin-treated mice. *Significant difference between animals with and without isoflurane treatment. *(Adapted from Reutershan J, Chang D, Hayes JK, Ley K: Protective effects of isoflurane pretreatment in endotoxin-induced lung injury. Anesthesiology 104:511, 2006, with permission.)*

interleukin-1β, volatile anesthetics appear to exert anti-inflammatory effects, including inhibition of cytokine formation, reduction of neutrophil migration into the lung interstitium and alveolar space, and attenuation of protein leakage and pulmonary edema (Fig. 22-31).[235,250,251] Peri-ischemic inhalation of low concentrations of sevoflurane appears to provide endothelial protection in humans subjected to forearm ischemia-reperfusion injury.[254] Inhibition of leukocyte adhesion has been postulated as a mechanism for this protection. Isoflurane, given after the initiation of ischemia, also protects against warm ischemia-reperfusion injury in an isolated, perfused rat lung model.[255] This protective effect may be related to modulation of potassium channels and prevention of excessive intracellular calcium overload. Hypoxia induces a series of responses, including erythropoiesis, angiogenesis, and glycolysis, to maintain homeostasis. Under hypoxic conditions, hypoxia inducible factor is responsible for the activation of hypoxia-responsive genes, such as iNOS, heme oxygenase, and vascular endothelial growth factor, in the lung. Exposure of isolated cells to isoflurane resulted in significant increases in hypoxia inducible factor 1α, and enhanced gene expression for hypoxia-responsive genes.[256] Whether these actions are involved in the protective effects of volatile anesthetics in acute lung injury remains unknown. The specific effects of nitrous oxide or xenon on pulmonary inflammatory reactions or acute lung injury remain to be examined.

Summary

Inhaled anesthetics have potent and clinically significant effects on respiratory function. Volatile anesthetics reduce bronchial smooth muscle tone, adversely affect mucociliary function, and dilate the pulmonary vasculature. Volatile anesthetics also alter the activity of respiratory sensors, the central nervous system, and muscles of respiration. These actions are mediated by direct effects on pulmonary parenchyma and indirect actions on afferent, central, and efferent neural pathways. The depressant effects of these volatile anesthetics are further enhanced in patients with pulmonary disorders. The inhaled anesthetics nitrous oxide and xenon also affect the respiratory system. Although many actions of xenon have not been as well described, this agent is unusual in that it increases tidal breathing and decreases the respiratory rate, an action opposite that of other anesthetics. The effects of volatile anesthetics on acute lung injury have been described as both proinflammatory and anti-inflammatory. Further investigations are needed to determine the precise role of these agents as friend or foe. An understanding of the multifactorial actions of inhaled anesthetics on the respiratory system is critical to the safe delivery of anesthesia.

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23 Cardiovascular Pharmacology

Key Points

1. In a normal heart, volatile anesthetics produce dose-related depression in left ventricular, right ventricular, and left atrial myocardial contractility; left ventricular diastolic function; and left ventricular–arterial coupling.
2. The negative inotropic effects of volatile anesthetics are related to alterations in intracellular Ca^{2+} homeostasis within the cardiac myocyte.
3. Volatile anesthetics affect the determinants of left ventricular afterload to varying degrees in the presence of normal and dysfunctional myocardium.
4. The systemic hemodynamic effects of volatile anesthetics are complex and determined by the interaction of myocardial effects, direct actions on the arterial and venous vasculature, and alterations in autonomic nervous system activity.
5. Volatile anesthetics sensitize myocardium to the arrhythmogenic effects of epinephrine to varying degrees and may prevent or facilitate the development of atrial or ventricular arrhythmias during myocardial ischemia or infarction, depending on the concentration of the agent, the extent of the injury, and the location affected within the conduction pathway.
6. Volatile anesthetics are relatively weak coronary vasodilators that are not capable of producing coronary steal at typically used clinical concentrations, even in patients with steal-prone coronary artery anatomy.
7. Volatile anesthetics exert important cardioprotective effects against reversible and irreversible myocardial ischemia in experimental animals and humans when administered before, during, or immediately after the onset of coronary artery occlusion and reperfusion.
8. Volatile anesthetics depress baroreceptor reflex control of arterial pressure to varying degrees.
9. Nitrous oxide causes direct negative inotropic effects, does not substantially affect left ventricular diastolic function, and produces modest increases in pulmonary and systemic arterial pressure via a sympathomimetic effect. These actions are dependent to some degree on the baseline anesthetic.
10. Xenon is essentially devoid of cardiovascular effects but has been shown to protect myocardium against infarction in experimental animals.

This chapter comprehensively describes the cardiovascular pharmacology of modern volatile anesthetics (including isoflurane, desflurane, and sevoflurane), nitrous oxide, and xenon. Comparison to older volatile anesthetics (halothane and enflurane) will be made only when necessary because these drugs are no longer clinically available. The actions of inhaled anesthetics on cardiovascular function, cardiac electrophysiology, the coronary circulation, and autonomic nervous system control of the circulation will be examined in detail.

Volatile Anesthetics and Cardiovascular Function

Myocardial Contractility

Isoflurane, desflurane, and sevoflurane depress myocardial contractility in vitro and in vivo. Investigations conducted in the

1960s demonstrated that the older volatile anesthetics halothane and enflurane produce dose-related depression of force-velocity relationships and Frank-Starling curves in isolated cardiac muscle preparations and intact, closed-chest dogs, respectively. These findings supported clinical observations of circulatory depression during halothane and enflurane anesthesia in humans. Isoflurane produces direct negative inotropic effects as indicated by decreases in the maximal velocity of shortening, peak developed force, and maximal rate of force development during isotonic contraction in isolated feline papillary muscles. These reductions in myocardial contractility by isoflurane also contribute to the cardiovascular depression observed with this anesthetic in humans. Similarly, desflurane and sevoflurane depress the intrinsic inotropic state in isolated myocardium, and these actions play an important role in determining the hemodynamic effects of these volatile anesthetics in humans with or without heart disease.

The relative degree of myocardial depression produced by volatile anesthetics in vivo has been more difficult to establish because simultaneous alterations in systemic and pulmonary hemodynamics and autonomic nervous system activity complicate assessment of left ventricular (LV) systolic function. Isovolumic and ejection-phase measures of myocardial contractility demonstrated that halothane and enflurane cause very similar negative inotropic effects in experimental animals and humans. These findings were subsequently confirmed by using the slope (E_{es}) of the LV end-systolic pressure–midaxis diameter relationship as a relatively heart rate– and load-independent index of the inotropic state in chronically instrumented dogs. In contrast, isoflurane produces less myocardial depression in vivo than the older anesthetics do. For example, isoflurane caused smaller reductions in the maximum rate of LV pressure development (dP/dt) than halothane did when identical minimum alveolar concentrations (MACs) were directly compared in the presence and absence of autonomic nervous system function, which suggested that the differences in myocardial depression caused by these anesthetics occur independent of autonomic nervous system activity. Differences in the negative inotropic effects of halothane and isoflurane have been quantified by using the slope (M_w) of the regional preload recruitable stroke work relationship derived from differentially loaded LV pressure–segment length diagrams. In these studies, conducted in chronically instrumented dogs, isoflurane maintained contractility an average of 20% higher than halothane did at identical MAC. Differences in the relative degree of myocardial depression produced by isoflurane and the older volatile anesthetics halothane and enflurane were also inferred in humans by using isovolumic and ejection-phase measures of the contractile state. The negative inotropic actions of all volatile anesthetics are exacerbated by hypocalcemia, calcium (Ca^{2+}) channel blockers, and β_1-adrenoceptor antagonists and may be reversed by the administration of exogenous Ca^{2+}, cardiac phosphodiesterase fraction III inhibitors, β_1-adrenoceptor agonists, Ca^{2+} channel agonists, and myofilament Ca^{2+} sensitizers. The differential effects of isoflurane and the older volatile anesthetics halothane and enflurane on myocardial contractility are maintained during the depression or augmentation of the inotropic state produced by these vasoactive drugs.

Desflurane causes systemic and coronary hemodynamic effects that are remarkably similar to those produced by isoflurane. Desflurane and isoflurane have been shown by isovolumic and ejection-phase measures of contractility to depress myocardial function to equivalent degrees in experimental animals and humans. These observations have been verified by using both end-systolic pressure-volume relationships and preload recruitable stroke work (Fig. 23-1) in the presence and absence of autonomic nervous system activity.[1] However, the unique cardiovascular stimulation associated with rapid increases in inspired desflurane concentration in humans may lead to transient increases in myocardial contractility as a result of augmentation of sympathetic nervous system tone. The effects of sevoflurane on myocardial contractility have also been shown to be virtually indistinguishable from those produced by isoflurane in dogs. Sevoflurane caused less myocardial depression than an equivalent halothane MAC in pigs did and produced less myocardial depression than enflurane did in humans as evaluated by echocardiography. Sevoflurane decreased contractile function to approximately 40% to 45% of control values at 1.75 MAC in the presence and absence of autonomic nervous system tone as determined by regional preload recruitable stroke work in dogs. This magnitude of myocardial depression agreed with previous data for isoflurane and desflurane in an identical experimental model. Thus, the vast

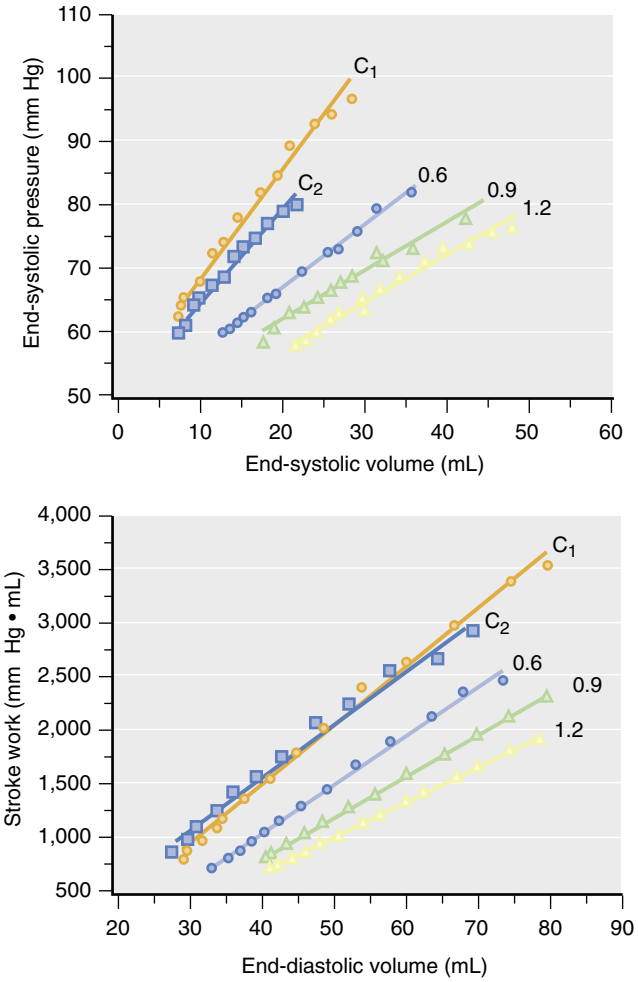

Figure 23-1 End-systolic pressure-volume (*top panel*) and stroke work–end-diastolic volume relationships (*bottom panel*) before (control 1; C_1), during 0.6, 0.9, and 1.2 minimum alveolar concentration, and after isoflurane (control 2; C_2) in an experiment in an open-chest dog. *(Adapted from Hettrick DA, Pagel PS, Warltier DC: Desflurane, sevoflurane, and isoflurane impair canine left ventricular–arterial coupling and mechanical efficiency. Anesthesiology 85:403-413, 1996.)*

majority of evidence collected to date indicates that isoflurane, desflurane, and sevoflurane depress the contractile state to similar degrees in normal ventricular myocardium.

The effects of volatile anesthetics on myocardial contractility in animal models or patients with LV dysfunction have been less extensively studied. An early in vitro study demonstrated that isoflurane causes greater reductions in maximum shortening velocity and the peak rate of force development in feline papillary muscles from failing hearts subjected to chronic pressure overload than in muscles from normal hearts. The older volatile anesthetic halothane also produced more pronounced myocardial depression in ischemic than in normal myocardium. Isoflurane and halothane were shown to cause relatively greater negative inotropic effects in ventricular myocardium obtained from cardiomyopathic hamsters than from normal hamsters (Fig. 23-2).[2] Isoflurane and sevoflurane also produced greater depression of contractility in right ventricular (RV) papillary muscles obtained from ferrets with experimental pressure-overload hypertrophy than from ferrets with normal myocardium.[3] These findings suggested that the myocardial depression caused by volatile anesthetics in failing or hypertrophied myocardium was accentuated and provided indirect evidence that patients with underlying contractile dysfunction may be more sensitive to the negative inotropic effects of volatile anesthetics. This hypothesis has not been comprehensively examined in vivo, however. In contrast, isoflurane, sevoflurane, and desflurane caused similar declines in contractility in ventricular myocytes obtained from rats with and without chemically induced chronic hyperglycemia.[4] These data suggested that volatile anesthetics do not cause a more exaggerated negative inotropic effect in myocardium obtained from this model of diabetes mellitus.

Volatile anesthetic–induced declines in contractile function were well tolerated and did not precipitate frank systolic dysfunction in experimental models of myocardial ischemia or infarction. In fact, volatile anesthetics have been shown to exert important beneficial effects on mechanical function during myocardial ischemia and reperfusion injury. Volatile anesthetics reduced experimental myocardial infarct size,[5] preserved metabolic and structural integrity during regional ischemia and reperfusion, enhanced the functional recovery of stunned myocardium, and improved indices of LV diastolic performance during brief coronary artery occlusion. Isoflurane was also shown to produce beneficial decreases in LV preload and afterload in patients with ischemic heart disease. These improvements in loading conditions in patients with compromised LV function may serve to offset the direct negative inotropic effects of anesthetics and contribute to relative maintenance of cardiac performance by optimizing the Starling operating range of the heart or by improving LV diastolic function. Isoflurane produced dose-related depression of myocardial contractility in a canine model of moderate LV dysfunction induced by chronic rapid LV pacing, but isoflurane anesthesia was well tolerated and did not precipitate frank LV failure in this model.[6] These findings with isoflurane were attributed to simultaneous improvements in LV loading conditions and filling dynamics that contributed to relative maintenance of cardiac output in the setting of moderate LV dysfunction despite concomitant reductions in contractility.

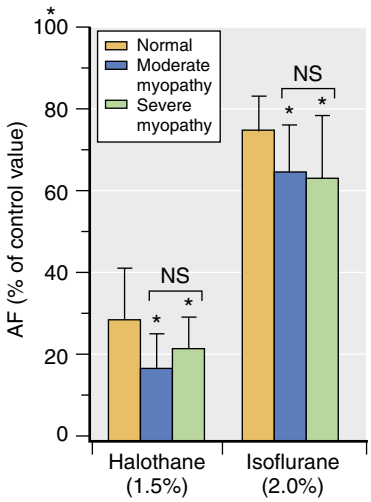

Figure 23-2 Comparison of the effects of halothane (*left*) and isoflurane (right) on isometric active force (AF) of papillary muscles from healthy hamsters (*yellow bars*) and those with cardiomyopathy (*blue and green bars*). Probability values refer to between-group differences. *Significantly ($P < .05$) different from control values. *(Adapted from Vivien B, Hanouz J-L, Gueugniaud P-Y, et al: Myocardial effects of halothane and isoflurane in hamsters with hypertrophic cardiomyopathy. Anesthesiology 87:1406-1416, 1997.)*

Cellular Mechanisms of Myocardial Depression

Volatile anesthetics depress myocardial contractility via alterations in intracellular Ca^{2+} homeostasis at several subcellular targets in the normal cardiac myocyte. Volatile anesthetics caused dose-related inhibition of the transsarcolemmal Ca^{2+} transient by affecting both L- and T-type Ca^{2+} channels. Isoflurane produced less pronounced reductions in the intracellular Ca^{2+} transient than the older volatile anesthetics did. The structural conformation and functional integrity of voltage-dependent Ca^{2+} channels were directly altered by volatile anesthetics as indicated by the attenuated binding of Ca^{2+} channel blockers. The partial inhibition of Ca^{2+} influx via sarcolemmal Ca^{2+} channels has several important consequences, including declines in the availability of Ca^{2+} for contractile activation, depression of Ca^{2+}-dependent release of Ca^{2+} from the sarcoplasmic reticulum (SR), and reduction of the amount of Ca^{2+} that can subsequently be stored in the SR. In contrast to the older volatile anesthetics halothane and enflurane, isoflurane did not stimulate release of Ca^{2+} from the SR nor directly activate ryanodine-sensitive SR Ca^{2+} release channels, thereby reducing SR Ca^{2+} storage. Unlike halothane, isoflurane also did not appear to provoke nonspecific leakage of Ca^{2+} from the SR, an action that contributes to further decreases in accumulation of the Ca^{2+} available for release during contraction in the presence of the older volatile agent. When combined with decreases in transsarcolemmal Ca^{2+} flux, these alterations in SR function represent important mechanisms by which older volatile anesthetics depress the intracellular Ca^{2+} transient and reduce myocardial contractility to a greater extent than with identical MAC concentrations of isoflurane, desflurane, or sevoflurane. In addition, isoflurane and sevoflurane have been shown to inhibit Ca^{2+} transport from the cell through sarcolemmal Ca^{2+}-adenosine triphosphatase (ATPase), an action that partially offsets reductions in SR Ca^{2+} stores. The partial preservation of the myocardial

positive frequency staircase effect observed with newer volatile anesthetics at physiologic excitation rates in vitro may also be attributed to this relative maintenance of SR function, in contrast to the findings with halothane or enflurane.

Volatile anesthetics also depress contractile function by inhibiting Na^+-Ca^{2+} exchange and reducing the intracellular Ca^{2+} concentration independent of the voltage-dependent Ca^{2+} channel in vitro. This effect may be particularly important in neonatal myocardium because it is more sensitive to the negative inotropic actions of volatile anesthetics than adult myocardium is. The relative contribution of inhibition of the Na^+-Ca^{2+} exchanger to anesthetic-induced depression of myocardial contractility in the intact heart remains controversial, but a role for inhibition of Na^+-Ca^{2+} exchange in anesthetic preconditioning was demonstrated recently.[7] Volatile anesthetics may also exert direct effects on the contractile apparatus and reduce myofilament Ca^{2+} sensitivity. Volatile anesthetics decreased tension development in skinned cardiac myofibrils and reduced myofibrillar ATPase activity. These actions may contribute to declines in actin-myosin cross-bridge kinetics during contraction, but not through a direct interaction with cardiac cross-bridge mechanics.[8] In addition, volatile anesthetics may modestly reduce myofilament Ca^{2+} sensitivity, but this mechanism probably plays a relatively minor role in the negative inotropic effects of these anesthetics at clinically relevant concentrations in vivo.

The cellular mechanisms responsible for volatile anesthetic–induced depression of myocardial contractility in failing myocardium have not been studied in detail. The most comprehensive investigation published to date examined the effects of isoflurane and sevoflurane on intracellular Ca^{2+} homeostasis in a ferret model of RV pressure-overload hypertrophy.[3] Isoflurane and sevoflurane produced more pronounced reductions in peak intracellular Ca^{2+} concentration and exaggerated decreases in myofilament Ca^{2+} sensitivity in ventricular myocytes obtained from hypertrophied hearts than in normal myocytes.[3] Whether similar alterations in intracellular Ca^{2+} regulation are produced by volatile anesthetics in other forms of heart failure remains to be determined. Profound abnormalities in Ca^{2+} homeostasis are characteristic features of failing myocardium, and it appears highly likely that volatile anesthetics will cause further reductions in contractile function by producing additive or synergistic effects on Ca^{2+} metabolism under these conditions.

Diastolic Function

Definitions of heart failure based solely on contractile dysfunction are inadequate because LV function during diastole significantly influences overall cardiac performance. The heart serves dual roles: it propels blood into the high-pressure arterial vasculature during systole and collects blood from the low-pressure venous circulation during diastole. Thus, heart failure may occur not only as a result of impaired contractility but also as a result of altered LV diastolic function. The timing, rate, and extent of LV filling are determined by several major factors, including the rate and degree of myocardial relaxation, the intrinsic mechanical properties of the left ventricle itself and those imposed by external constraints, and the structure and function of the left atrium, the pulmonary venous circulation, and the mitral valve. Although abnormalities in LV diastolic function may be linked to decreases in myocardial contractility, heart failure may result from primary diastolic dysfunction in the absence of or before the appearance of alterations in LV systolic function in a variety of pathologic conditions, including ischemic heart disease, pressure- or volume-overload hypertrophy, hypertrophic obstructive cardiomyopathy, and restrictive disease processes.

Volatile anesthetics produce dose-related prolongation of LV isovolumic relaxation in vivo. This delay in isovolumic relaxation is associated with declines in early LV filling but is not of sufficient magnitude to affect LV chamber stiffness. Coronary blood flow is highest during isovolumic relaxation, and the delays in relaxation produced by volatile anesthetics contribute to impairment of coronary flow during early diastole. Prolongation of LV relaxation probably occurs as a result of simultaneous depression of myocardial contractility and not because of a direct negative lusitropic effect. In fact, volatile anesthetics modestly enhanced relaxation of isolated ferret myocardium in vitro. Volatile anesthetics cause concentration-related decreases in the rate and extent of early LV filling concomitant with negative inotropic effects. They also reduce LV filling associated with atrial systole.[9] Isoflurane, desflurane, and sevoflurane did not alter invasively derived indices of regional myocardial or chamber stiffness, thus indicating that LV distensibility was unaffected by these volatile anesthetics. The older volatile anesthetic halothane also did not directly alter the intrinsic viscoelastic properties of myocardium despite producing relatively greater negative inotropic effects.

The effects of isoflurane and halothane on LV diastolic function in a canine model of dilated cardiomyopathy were described.[6] In contrast to the findings in dogs with normal LV function, isoflurane improved several indices of LV relaxation and filling in cardiomyopathic dogs despite producing simultaneous negative inotropic effects. In addition, halothane did not exacerbate the preexisting diastolic dysfunction inherent in this experimental model. The findings with isoflurane and halothane were most likely related to favorable reductions in LV preload produced by these volatile anesthetics and were not due to direct positive lusitropic effects. These data further suggested that isoflurane-induced improvements in LV isovolumic relaxation and filling dynamics may contribute to relative maintenance of cardiac output in the presence of LV dysfunction despite simultaneous reductions in contractility. The findings in cardiomyopathic dogs supported earlier clinical observations that patients with severe ischemic heart disease or congestive heart failure tolerate isoflurane or halothane anesthesia without acute hemodynamic decompensation.

The dependence of LV relaxation on afterload is markedly enhanced in failing myocardium. Thus, a reduction in afterload may increase not only LV systolic performance by decreasing impedance to LV ejection but also the rate of LV relaxation and contribute to improvements in LV diastolic filling and compliance. The effects of isoflurane and halothane on the dependence of LV relaxation on afterload were explored in dogs before and after the development of rapid LV pacing–induced cardiomyopathy.[10] The dependence of LV relaxation on afterload was unaffected by isoflurane and halothane anesthesia in dogs with dilated cardiomyopathy (Fig. 23-3), thus further suggesting that these volatile anesthetics do not exert direct actions on LV isovolumic relaxation in failing myocardium independent of negative inotropic effects.

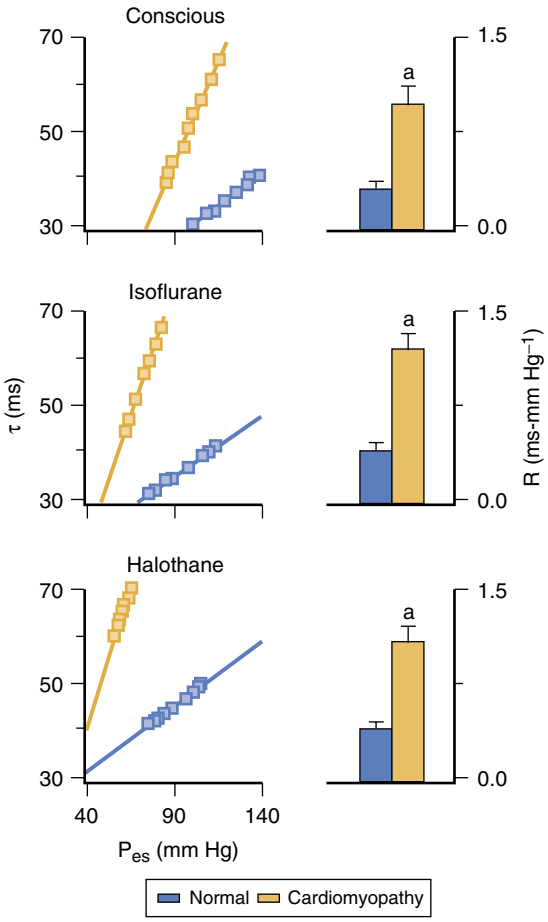

Figure 23-3 Linear relationship between the time constant of isovolumic relaxation (τ) and left ventricular end-systolic pressure (P_{es}) during inferior vena cava occlusion (*left panels*) in a typical dog before (*yellow squares*) and after (*blue squares*) the development of pacing-induced cardiomyopathy in the conscious state and during isoflurane and halothane anesthesia. The histograms on the *right* illustrate the slope (R) of the τ-versus-P_{es} relationship in the conscious state (*top right panel*) and during isoflurane (*middle right panel*) and halothane (*bottom right panel*) anesthesia before (*yellow bars*) and after (*blue bars*) pacing. a, Significantly ($P < .05$) different from normal myocardium. *(Adapted from Pagel PS, Hettrick DA, Kersten JR, et al: Isoflurane and halothane do not alter the enhanced afterload sensitivity of left ventricular relaxation in dogs with pacing-induced cardiomyopathy. Anesthesiology 87:952-962, 1997.)*

Left Ventricular–Arterial Coupling and Mechanical Efficiency

Optimum transfer of stroke volume from the left ventricle to the arterial circulation requires appropriate matching of these mechanical systems. LV-arterial coupling has most often been described by using a series elastic chamber model of the cardiovascular system. The elastances of the contracting left ventricle (E_{es}) and the arterial vasculature (E_a) are determined from LV end-systolic pressure-volume and end-systolic arterial pressure–stroke volume relationships, respectively. The ratio of E_{es} to E_a defines coupling between the left ventricle and the arterial circulation and provides a useful technique for assessment of the actions of drugs, including volatile anesthetics, on LV-arterial matching in vivo. Analysis of the pressure-volume relationship also creates a framework for the study of LV mechanical efficiency as defined by the ratio of stroke work to pressure-volume area. LV-arterial coupling may theoretically be maintained during anesthesia because declines in LV afterload may balance simultaneous reductions in myocardial contractility. Low concentrations of isoflurane (1 MAC), but not halothane, maintained E_{es}/E_a in barbiturate-anesthetized, acutely instrumented dogs, consistent with preservation of mechanical coupling between the left ventricle and the arterial circulation. However, isoflurane decreased E_{es}/E_a at 2 MAC, thus suggesting that the vasodilating effects of this anesthetic were unable to compensate for the relatively greater declines in contractility. Desflurane, sevoflurane, and isoflurane maintained optimum LV-arterial coupling and mechanical efficiency as evaluated by E_{es}/E_a and stroke work–pressure-volume area ratios at low anesthetic concentrations (<0.9 MAC) by producing simultaneous declines in myocardial contractility and LV afterload.[1] However, mechanical matching between the left ventricle and the arterial vasculature and the efficiency of total LV energy transfer to external stroke work degenerate at higher anesthetic concentrations, thus indicating that anesthetic-induced reductions in contractility are not appropriately balanced by declines in afterload. Halothane (<1.0 MAC) but not isoflurane also reduced the ratio of oscillatory to mean hydraulic power in vivo, which indicates that this anesthetic decreases LV mechanical efficiency as well. The detrimental alterations in LV-arterial coupling produced by volatile anesthetics contribute to the reductions in overall cardiac performance observed with higher concentrations of these anesthetics in vivo.

Left Ventricular Afterload

A definition of LV afterload that describes the mechanical properties of the arterial vasculature opposing LV ejection is clear, but quantitative evaluation of afterload in vivo remains a difficult problem whose solution often confuses this clinically intuitive concept. Systemic vascular resistance, calculated as the ratio of mean arterial pressure to cardiac output, is the most commonly used estimate of LV afterload. However, systemic vascular resistance inadequately describes LV afterload because this index ignores the mechanical characteristics of the blood and arterial walls, fails to account for the frequency-dependent, phasic nature of arterial blood pressure and blood flow, and does not consider the potential effects of arterial wave reflection. As a result, systemic vascular resistance cannot be used reliably to quantify changes in LV afterload produced by drugs, including volatile anesthetics, or cardiovascular disease. Aortic input impedance ($Z_{in}[\omega]$) obtained from power spectral or Fourier series analysis of aortic pressure and blood flow waveforms provides a comprehensive description of LV afterload because $Z_{in}(\omega)$ incorporates arterial viscoelasticity, frequency dependence, and wave reflection. However, analysis of $Z_{in}(\omega)$ is conducted in the frequency domain and not as a function of time, and as a result, $Z_{in}(\omega)$ is very difficult to apply in a clinical setting. $Z_{in}(\omega)$ is most often interpreted by using an electrical three-element Windkessel model of the arterial circulation that describes characteristic aortic impedance (Z_c), total arterial compliance (C), and total arterial resistance (R). Z_c represents aortic resistance to LV ejection, C is determined primarily by the compliance of the aorta

and represents the energy storage component of the arterial circulation, and R equals the combined resistance of the remaining arterial vasculature. The three-element Windkessel model has been shown to closely approximate $Z_{in}(\omega)$ in a variety of physiologic conditions.

Volatile anesthetics alter $Z_{in}(\omega)$ by affecting the mechanical properties of the arterial vascular tree. In contrast to the results obtained with the older agent halothane, isoflurane produced dose-related decreases in R in a canine model, consistent with the known effects of this drug on systemic vascular resistance. Isoflurane and halothane also caused similar increases in C and Z_c concomitant with reductions in mean arterial pressure. Thus, the major difference between the effects of isoflurane and halothane on LV afterload derived from the Windkessel model of $Z_{in}(\omega)$ was related to R, a property of arteriolar resistance vessels, and not to C or Z_c, the mechanical characteristics of the aorta. In contrast to the findings with sevoflurane, desflurane also reduced R in dogs, thus suggesting that this agent is a more potent peripheral vasodilator. Importantly, the inverse relationship between C and mean arterial pressure remains unchanged by volatile anesthetics, unlike the findings with the arterial vasodilator sodium nitroprusside or the intravenous anesthetic propofol. These data emphasize that volatile anesthetics do not fundamentally affect aortic mechanical characteristics.

Isoflurane and halothane produced alterations in $Z_{in}(\omega)$ in an experimental model of heart failure that are somewhat different from those observed in the normal cardiovascular system. These volatile anesthetics decreased arterial pressure but did not affect C and Z_c in the presence of LV dysfunction. Isoflurane also did not reduce R in the presence of dilated cardiomyopathy, in contrast to the actions of this volatile anesthetic in the presence of normal LV performance. Thus, neither isoflurane nor the older agent halothane reduced arterial hydraulic resistance or favorably improved the rectifying properties of the aorta in the presence of pacing-induced cardiomyopathy. The findings suggest that volatile anesthetics do not exert beneficial actions on LV afterload in the presence of heart failure.

Right Ventricular Function

The crescent-shaped right ventricle is composed of embryologically distinct inflow and outflow tracts that differ in their structure and response to autonomic nervous system activity. Sequential contraction of the RV inflow and outflow tracts establishes regional pressure gradients within the right ventricle during systole and accounts for the peristaltic mechanical action of this pump. True isovolumic relaxation does not occur in the right ventricle. Instead, ejection of blood from the outflow tract into the pulmonary artery continues after the inflow tract has begun to relax. The effects of volatile anesthetics on the function and contraction sequence of the RV inflow and outflow tracts have been incompletely studied. Halothane produced similar depression of contractile function in the RV inflow and outflow tracts when a uniform definition of end-systole and end-diastole was used for both regions of the RV. Halothane also caused dose-related decreases in RV contractility as evaluated by using regional preload recruitable stroke work derived from RV pressure–segment length diagrams in the RV inflow and outflow tracts in the presence and absence of autonomic nervous system reflexes.[11] Importantly, halothane also abolished the normal RV sequential contraction pattern without exerting differential negative inotropic effects on different regions of the right ventricle, thus suggesting that volatile anesthetics may alter RV contraction dynamics by adversely affecting cardiac autonomic nervous system activity. Isoflurane also exerted qualitatively different effects on RV and LV afterload and hydraulic power generation that were also partially mediated by the autonomic nervous system.[12] Hence, isoflurane probably produces fundamentally different actions on RV and LV contraction dynamics in vivo.

Left Atrial Function

The left atrium serves three major roles that exert a profound effect on LV filling and overall cardiovascular performance. The left atrium is a contractile chamber that actively empties immediately before the onset of LV systole and establishes the final LV end-diastolic volume. The left atrium is a reservoir that stores pulmonary venous return during LV contraction and isovolumic relaxation after closure and before opening of the mitral valve. The left atrium is also a conduit that empties its contents into the left ventricle down a pressure gradient after the mitral valve opens and continues to passively transfer pulmonary venous blood flow during LV diastasis. These contraction, reservoir, and conduit functions of the left atrium mechanically facilitate the transition between the almost continuous flow through the pulmonary venous circulation and the intermittent filling of the left ventricle. Advances in the understanding and clinical significance of left atrial (LA) mechanical function were recently reviewed.[9]

The negative inotropic effects of the older volatile anesthetics halothane and methoxyflurane were initially described in rat atrial myocardium in vitro. Volatile anesthetics also depressed the contractile function of atrial human myocardium.[13] These actions have been attributed to reductions in transsarcolemmal Ca^{2+} influx through voltage-dependent Ca^{2+} channels and decreases in Ca^{2+} availability from the SR, mechanisms that are very similar to those responsible for anesthetic-induced depression of LV myocardium. The negative inotropic effects of volatile anesthetics in the intact left atrium were quantified by pressure-volume analysis (Fig. 23-4).[14] Desflurane, sevoflurane, and isoflurane reduced LA contractility (i.e., E_{es}) by approximately 50% at an end-tidal concentration of 1.2 MAC. The magnitude of this effect on LA myocardium was similar to the degree of LV contractile depression produced by these anesthetics as quantified by LV end-systolic pressure-volume relationships.[1] Desflurane, sevoflurane, and isoflurane also impaired LA and LV relaxation to similar degrees. These data indicate that volatile anesthetics produce equivalent alterations in contractility and relaxation in LA and LV myocardium.[14] The magnitude of reductions in the LA inotropic and lusitropic state produced by volatile anesthetics was also similar in the intact left atrium, thus supporting the results obtained in isolated human atrial myocardium.[13]

Desflurane, sevoflurane, and isoflurane altered the passive mechanical behavior of the left atrium.[14] LA reservoir function (V loop area and reservoir volume) was maintained during the administration of anesthetic at concentrations of less than 1.0 MAC. Such preservation of reservoir function contributed to the relative maintenance of LV stroke volume[1] by compensating for decreases in LV filling associated with a reduced contribution of LA contraction. The volatile anesthetics also reduced dynamic LA chamber stiffness, an action that most likely contributed to

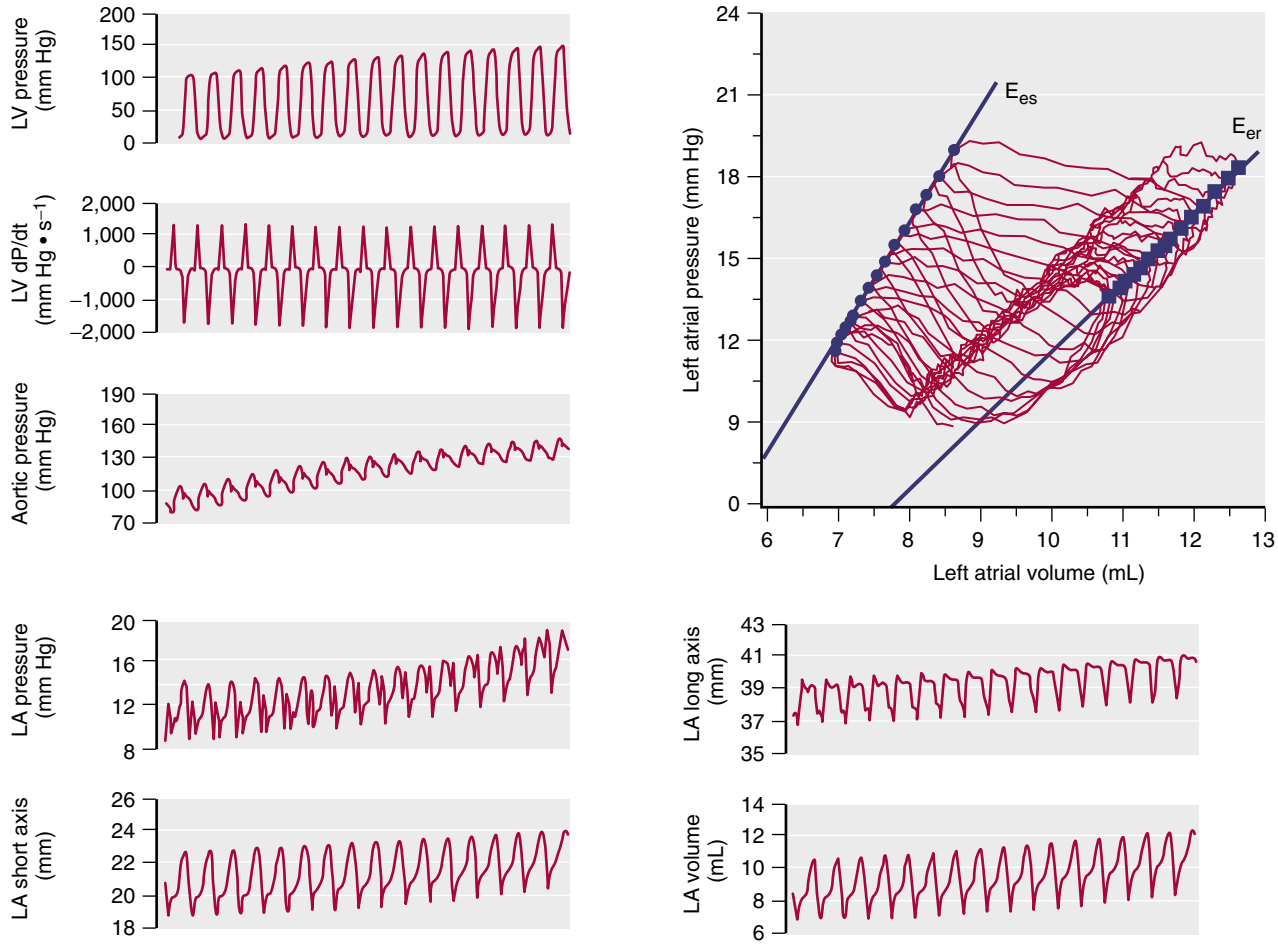

Figure 23-4 Continuous left ventricular (LV) pressure, LV dP/dt, aortic pressure, left atrial (LA) pressure, LA short- and long-axis dimensions, and LA volume waveforms (*left*) and corresponding LA pressure-volume diagrams (*right*) resulting from the intravenous administration of phenylephrine (200 µg) observed in a typical experiment. The maximum LA elastance (*solid dots*) and end-reservoir pressure and volume (*solid squares*) for each pressure-volume diagram were used to obtain the slopes (E_{es} and E_{er}) and extrapolated volume intercepts of the LA end-systolic and end-reservoir pressure-volume relationships to quantify myocardial contractility and dynamic chamber stiffness, respectively. *(Adapted from Gare M, Schwabe DA, Hettrick DA, et al: Desflurane, sevoflurane, and isoflurane affect left atrial active and passive mechanical properties and impair left atrial–left ventricular coupling in vivo. Analysis using pressure-volume relations. Anesthesiology 95:689-698, 2001.)*

the preservation of reservoir function because the delays in LA relaxation and declines in LV systolic function that also occurred would be expected to decrease reservoir function.[15] However, LA reservoir function was reduced during the administration of higher concentrations of volatile anesthetics because further impairment of LA relaxation and LV contractility occurred. Decreases in the ratio of LA stroke work to total pressure-volume diagram area and increases in the ratio of LA conduit to total reservoir volume were also produced by desflurane, sevoflurane, and isoflurane. These data indicate that the LA contribution to LV filling becomes less active and more passive during the administration of volatile anesthetics.

Desflurane, sevoflurane, and isoflurane decreased the ratio of LA to LV elastance (E_{es}/E_{LV}), consistent with impaired mechanical matching between these chambers. As described earlier, volatile anesthetics have been shown to produce LV diastolic dysfunction by delaying LV isovolumic relaxation and impairing early LV filling in association with direct negative inotropic effects. Thus, the attenuation of transfer of kinetic energy from the left atrium to the left ventricle probably resulted from the combination of LA contractile depression and LV systolic and diastolic dysfunction. Volatile anesthetic–induced abnormalities in LA-LV matching were greater than the analogous impairment in LV-arterial coupling evaluated via a similar series elastic chamber model in a previous investigation[1] because these anesthetics produced beneficial alterations in the determinants of LV afterload that partially compensate for simultaneous depression of LV myocardial contractility.

The influence of isoflurane on LA function in the presence of preexisting LV dysfunction has also been examined.[16] Isoflurane depressed LA contractility, impaired LA-LV coupling, and reduced the active LA contribution to LV filling in dogs with pacing-induced cardiomyopathy, findings that were similar in magnitude to those observed in healthy canine hearts.[14] In contrast to the findings in normal dogs,[14] LA reservoir function was reduced in dogs with LV dysfunction at lower isoflurane concentrations (0.6 and 0.9 MAC).[16] These findings indicate that the ability of the left atrium to act as a reservoir for pulmonary venous return is attenuated during isoflurane anesthesia. Such an isoflurane-induced reduction in LA storage ability suggested that the quantity of blood transferred from the left atrium to the left ventricle when the mitral valve opens may be reduced, thereby

providing another potential mechanism by which volatile anesthetics can reduce early LV filling in the presence of preexisting LV dysfunction.

Systemic Hemodynamics

Volatile anesthetics cause direct negative chronotropic actions in vitro by depressing sinoatrial node activity, but alterations in heart rate in vivo are primarily determined by the interaction of volatile anesthetics and baroreceptor reflex activity. Halothane does not appreciably change the heart rate in humans because this anesthetic attenuates baroreceptor reflex responses. In contrast, isoflurane increases the heart rate in response to simultaneous decreases in arterial pressure. These findings occur with this volatile agent because baroreceptor reflexes are relatively preserved when compared with older anesthetics. Desflurane also causes dose-related increases in heart rate in humans. Desflurane- and isoflurane-induced tachycardia may be more pronounced in pediatric patients or in the presence of vagolytic drugs and, conversely, may be attenuated in neonates and geriatric patients or by the concomitant administration of opioids (see Chapters 71 and 82). Rapid increases in the inspired desflurane concentration above 1 MAC may be associated with further transient increases in heart rate and arterial pressure as a result of activation of the sympathetic nervous system. Interestingly, similar increases in heart rate also occur when the inspired isoflurane concentration is increased rapidly. The cardiovascular stimulation induced by rapid increases in desflurane or isoflurane concentration in humans resulted from activation of tracheopulmonary and systemic receptors and was attenuated by pretreatment with β_1-adrenoceptor antagonists, α_2-adrenoceptor agonists, or opioids. In contrast to the findings with isoflurane and desflurane, sevoflurane did not alter heart rate or cause cardiovascular stimulation during rapid increases in anesthetic concentration in humans.

All modern volatile anesthetics cause concentration-related decreases in arterial pressure. The mechanism by which these anesthetics reduce arterial pressure differs between anesthetics. The decreases in arterial pressure produced by halothane and enflurane were attributed to reductions in myocardial contractility and cardiac output, whereas isoflurane, desflurane, and sevoflurane decrease arterial blood pressure primarily as a result of reductions in LV afterload. Thus, isoflurane, desflurane, and sevoflurane maintain cardiac output because these anesthetics produce less pronounced reductions in myocardial contractility and greater decreases in systemic vascular resistance in humans than halothane or enflurane does. Isoflurane and desflurane may also preserve autonomic nervous system regulation of the circulation to a greater degree than other volatile anesthetics do. The baroreceptor reflex–mediated tachycardia that occurs during isoflurane and desflurane anesthesia serves to maintain cardiac output despite modest declines in contractility and stroke volume. The declines in arterial pressure produced by volatile anesthetics may be attenuated by surgical stimulation or concomitant administration of nitrous oxide. Volatile anesthetics also cause modest, dose-related increases in right atrial pressure in humans. These effects probably occur as a result of direct negative inotropic actions. The cardiovascular effects of volatile anesthetics are altered by the duration of anesthesia. Increases in myocardial contractility and cardiac output and decreases in LV preload and afterload occur after several hours of constant MAC anesthesia. Recovery from circulatory depression is greatest during halothane anesthesia but is somewhat less pronounced during prolonged administration of isoflurane and desflurane.

The systemic hemodynamic effects of volatile anesthetics in the presence of LV dysfunction are similar but not identical to those observed in the normal heart. Volatile anesthetics, including isoflurane, modestly increase or do not affect the heart rate in experimental animals with pacing- or doxorubicin-induced dilated cardiomyopathy and patients with coronary artery disease and LV dysfunction. These findings may be attributed to altered baroreceptor reflex activity, β_1-adrenoceptor downregulation, increases in central sympathetic nervous system activity, and withdrawal of parasympathetic nervous system tone associated with heart failure. Isoflurane and halothane caused pronounced reductions in LV end-diastolic pressure and chamber dimension in cardiomyopathic dogs concomitant with decreases in mean arterial pressure.[6] These findings supported previously observed declines in pulmonary artery pressure during isoflurane anesthesia in patients with coronary artery disease and heart failure and suggested that venodilation represents a major hemodynamic consequence of this volatile agent in experimental and clinical heart failure. In contrast to the findings in normal dogs, isoflurane did not beneficially influence, and the older agent halothane detrimentally affected, the determinants of LV afterload in cardiomyopathic dogs. As a result of these actions and the simultaneous declines in LV preload and myocardial contractility, cardiac output may be more profoundly reduced during isoflurane or halothane anesthesia in the presence of preexisting LV dysfunction.

Volatile Anesthetics and Cardiac Electrophysiology

Cardiac Conduction

Volatile anesthetics slow the rate of sinoatrial node discharge by direct and indirect effects on sinoatrial node automaticity. These actions may be altered in vivo by vasoactive drugs or autonomic nervous system activity. Older volatile anesthetics and, to a lesser extent, isoflurane shorten the cardiac action potential and the effective duration of the refractory period in normal Purkinje fibers, but volatile anesthetics also prolong His-Purkinje and ventricular conduction times. Halothane, enflurane, and isoflurane also prolong atrioventricular conduction time and refractoriness. When combined with the direct actions of volatile anesthetics on sinoatrial node discharge, these data suggest that volatile anesthetics have the potential to produce bradycardia and atrioventricular conduction abnormalities. However, primary disturbances in atrioventricular conduction leading to second- or third-degree atrioventricular block in humans probably do not occur with volatile anesthetics in the absence of conduction disease or drugs that directly prolong the atrioventricular conduction time.

Volatile anesthetics may have proarrhythmogenic or antiarrhythmogenic actions against the abnormal cardiac electrophysiologic mechanisms produced by myocardial ischemia or infarction. Halothane, enflurane, and isoflurane have been shown to be cardioprotective against ventricular fibrillation produced by coronary artery occlusion and reperfusion. Protective effects against ouabain-induced arrhythmias have also been demonstrated with the older volatile agent halothane. Volatile anesthetics

may exert antiarrhythmic effects by opposing subsidiary pacemaker activity in infarcted myocardium. Conversely, halothane and, to a lesser extent, isoflurane may be arrhythmogenic in Purkinje fibers in experimental myocardial infarction by facilitating reentrant activity or increasing temporal dispersion of refractory period recovery. These actions may be related to inhibition of the slow Na^+ current in false tendon fibers and induction of reentry of premature impulses into more refractory Purkinje fibers in the border zone of an ischemic area. Halothane, enflurane, and isoflurane prolong the QT_c interval in humans. These data suggest that patients with idiopathic or acquired long QT syndrome may be at greater risk for the development of torsades de pointes ventricular tachycardia during anesthesia with these agents.

Epinephrine-Induced Arrhythmias

Halothane and, to a lesser extent, other volatile anesthetics sensitize myocardium to the arrhythmogenic effects of epinephrine. Sensitization is the interaction between volatile anesthetics and catecholamines that leads to reductions in the threshold for both atrial and ventricular arrhythmias. Sequentially escalating doses of epinephrine produce premature ventricular contractions and sustained ventricular tachyarrhythmias during halothane anesthesia. Halothane-epinephrine–induced arrhythmias are attenuated by pretreatment with sodium thiopental, presumably via effects on the atrioventricular node or the upper His bundle. A synergistic interaction between α_1- and β-adrenoceptors has been strongly implicated in the pathogenesis of halothane-epinephrine–induced ventricular arrhythmias. Stimulation of the α_{1A}-adrenoceptor in the His-Purkinje system by epinephrine during halothane anesthesia transiently slows Purkinje fiber conduction. This proarrhythmogenic effect is mediated by phospholipase C and the intracellular second messenger inositol triphosphate. Enhanced conduction in the Purkinje–ventricular muscle junction accompanied by simultaneous α_1-adrenoceptor–mediated depression of Purkinje conduction also plays an important role in halothane-epinephrine–induced arrhythmias. The doses of epinephrine required to produce ventricular arrhythmias during desflurane or sevoflurane anesthesia are similar to but significantly less than those observed during administration of isoflurane and halothane. Halothane-catecholamine sensitization also promotes abnormal automaticity of the dominant and latent atrial pacemakers. These effects may produce premature ventricular contractions and arrhythmias originating from the His bundle. Intact sinoatrial node function reduces the incidence of epinephrine-induced ventricular escape during halothane anesthesia and is protective against His bundle arrhythmias.

Volatile Anesthetics and the Coronary Circulation

Coronary Vascular Effects in Vitro

Volatile anesthetics cause direct coronary artery vasodilation in vitro; however, the simultaneous reductions in determinants of myocardial oxygen consumption (MVo_2), including heart rate, preload, afterload, and inotropic state, produced by these anesthetics cause coronary vasoconstriction in vivo via metabolic autoregulation. Volatile anesthetic–induced alterations in coronary blood flow are also affected by the reductions in coronary perfusion pressure produced by these anesthetics. Thus, the combination of direct and indirect actions determines the net effect of volatile anesthetics on coronary vascular tone. Isoflurane and halothane caused vasodilation of isolated coronary arteries. Halothane produced more profound coronary artery dilation than isoflurane did at similar MAC in isolated coronary arteries larger than 2000 μm. In contrast, isoflurane caused vasodilation of predominantly small (<900 μm) canine epicardial coronary arteries. Halothane may produce greater vasodilatory effects in large coronary arteries than isoflurane does because halothane causes more pronounced suppression of the voltage-dependent Ca^{2+} current.

The direct negative inotropic effects of volatile anesthetics caused a reduction in coronary blood flow in isolated, contracting hearts during precise control of ventricular loading conditions via flow-metabolism coupling. Thus, a decrease in myocardial O_2 demand was accompanied by an increase in coronary vascular resistance, findings that may be incorrectly interpreted as suggesting that volatile anesthetics produce coronary vasoconstriction. However, examination of the actions of volatile anesthetics on myocardial O_2 extraction and the ratio of myocardial O_2 delivery to MVo_2 revealed that these drugs are coronary vasodilators. Halothane and isoflurane decreased myocardial O_2 extraction and increased the ratio of O_2 delivery to consumption in isolated, beating hearts.[17] These findings indicate that volatile anesthetics produce direct coronary vasodilation in isolated hearts because myocardial O_2 delivery exceeds MVo_2 and coronary sinus O_2 tension increases. Halothane, isoflurane, and sevoflurane also caused similar reductions in adenosine-induced coronary flow reserve in tetrodotoxin-arrested, isolated hearts. Because mechanical work was not performed in this preparation, these findings supported the hypothesis that volatile anesthetics cause direct coronary vasodilation of similar magnitude.

Coronary Vascular Effects in Vivo

Halothane has variable effects on coronary blood flow and coronary vascular resistance in vivo that occur concomitant with changes in MVo_2. Decreases in MVo_2 caused declines in coronary blood flow with relative maintenance of or modest increases in coronary vascular resistance during halothane anesthesia. Despite the decreases in coronary blood flow, halothane increased coronary sinus O_2 tension and decreased O_2 extraction, thus indicating that halothane is a relatively weak coronary vasodilator. Like halothane, isoflurane variably altered coronary blood flow in vivo.[18,19] Isoflurane reduced MVo_2 and simultaneously decreased O_2 extraction, findings indicative of direct coronary vasodilation.[18] Isoflurane produced mild, transient increases in blood flow independent of changes in MVo_2 and autonomic nervous system activity during induction of anesthesia with inhaled anesthetics. Perfusion of the left anterior descending coronary artery with blood previously equilibrated with isoflurane dramatically increased coronary blood flow,[20] but only mild coronary vasodilation occurred after a period of anesthetic equilibration in a similar experimental model.[19] Isoflurane-induced increases in coronary blood flow were not accompanied by epicardial coronary artery dilation, thus verifying that isoflurane dilates predominantly

small coronary arteries. However, adenosine, a potent coronary vasodilator, caused considerably greater vasodilation in coronary microvessels than isoflurane did. The more profound decreases in myocardial O_2 extraction produced by isoflurane than by enflurane indicate that isoflurane is a more potent coronary vasodilator than its structural isomer is.

The influence of desflurane and sevoflurane on coronary blood flow in the intact cardiovascular system has been incompletely examined. Desflurane and isoflurane caused similar increases in the ratio of O_2 delivery to consumption and decreased O_2 extraction, consistent with coronary vasodilation. However, the increases in coronary blood flow produced by desflurane, but not by isoflurane, were attenuated by pharmacologic blockade of the autonomic nervous system, which suggests that isoflurane causes relatively greater direct coronary vasodilation in vivo than desflurane does. Sevoflurane did not produce any significant degree of coronary vasodilation, in contrast to the findings with other volatile anesthetics.

Coronary Vasodilator Reserve and Autoregulation

Volatile anesthetics alter coronary vasodilator reserve, defined as the ratio of peak coronary blood flow after brief coronary artery occlusion (reactive hyperemia) to baseline flow. Coronary vasodilator reserve was greater during isoflurane than during halothane anesthesia. This observation suggested that the older agent halothane may be a more potent coronary vasodilator than isoflurane because greater baseline coronary vasodilation should be accompanied by a reduced ability to further increase coronary blood flow in response to a brief ischemic episode. However, halothane also reduced the determinants of MVo_2 to a greater degree in vivo than isoflurane did. Peak coronary blood flow during reactive hyperemia and percent flow debt repayment are directly related to the intensity of the ischemic stimulus and the magnitude of the O_2 debt accumulated during coronary artery occlusion. Thus, the differences in coronary vasodilator reserve produced by isoflurane and halothane may reflect differences in the intensity of ischemia during coronary occlusion and not the relative vasodilator efficacy of these volatile anesthetics.

Dilation of coronary arteriolar resistance vessels by volatile anesthetics altered pressure autoregulation in the coronary vasculature.[21] The changes in autoregulation produced by vasoactive drugs, including volatile anesthetics, are typically determined by the slope of the pressure-flow curve generated by progressive constriction of a coronary artery. Changes in these pressure-flow curves demonstrated that autoregulation is disrupted during anesthesia as opposed to the conscious state (Fig. 23-5). Isoflurane produced more profound alterations in autoregulation than the older volatile anesthetics did, as indicated by greater increases in the slope of the pressure-flow relationship. Coronary perfusion pressure also played a more important role in the determination of coronary blood flow during anesthesia. Volatile anesthetics impaired coronary autoregulation to some degree, but these anesthetics did not produce the profound degree of coronary vasodilation and inhibition of autoregulation seen with adenosine or dipyridamole.[21] In contrast to volatile anesthetics, these drugs cause maximal coronary vasodilation and inhibit pressure autoregulation to such a degree that coronary blood flow becomes directly dependent on coronary perfusion pressure. Thus, volatile anesthetics are weak coronary vasodilators.

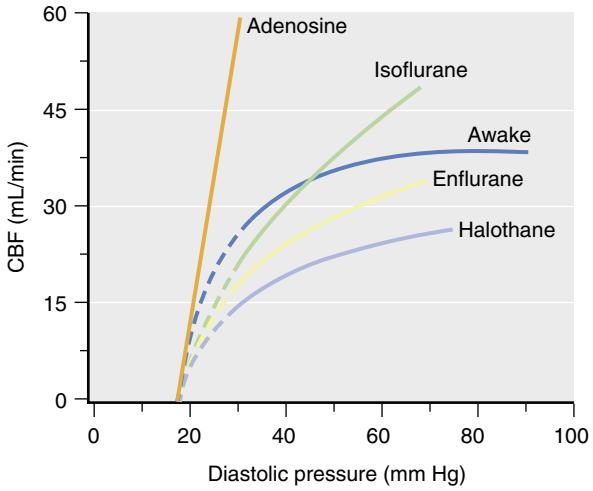

Figure 23-5 Qualitative description of the effects of volatile anesthetics on the coronary blood flow (CBF)–diastolic pressure relationship as compared with the effect of adenosine-induced maximal coronary vasodilation in awake and anesthetized dogs. *Solid lines* are drawn from mean slopes determined by linear regression analysis. *Dashed lines* represent the nonlinear portion of the curve and are estimates. When compared with the findings obtained in awake dogs, the anesthetics affect absolute CBF variably but do not increase the slope of the CBF-pressure plots. *(Adapted from Hickey RF, Sybert PE, Verrier ED, Cason BA: Effects of halothane, enflurane, and isoflurane on coronary blood flow autoregulation and coronary vascular reserve in the canine heart. Anesthesiology 68:21-30, 1988.)*

Mechanisms of Volatile Anesthetic–Induced Coronary Vasodilation

Volatile anesthetics produce direct coronary artery relaxation by affecting intracellular Ca^{2+} regulation at several locations in the vascular smooth muscle cell. Volatile anesthetics inhibited influx of Ca^{2+} through voltage- and receptor-operated Ca^{2+} channels in coronary vascular smooth muscle. Volatile anesthetics also reduced accumulation of Ca^{2+} in and release by the coronary vascular smooth muscle SR, inhibited G proteins linked to phospholipase C, and decreased formation of the second messenger inositol triphosphate. The coronary vasodilating actions of volatile anesthetics are probably not related to the production or release of nitric oxide (NO). Investigations conducted in isolated coronary and aortic vascular preparations and in the intact canine coronary circulation[20] demonstrated that volatile anesthetic–induced coronary vasodilation occurs independent of NO. Some experimental evidence suggested that the direct coronary vasodilator effects of isoflurane may be mediated by the vascular endothelium, but other data indicated that volatile anesthetics, including isoflurane, may adversely affect the release or action of NO.[22] The results of one investigation demonstrated that NO-induced formation of cyclic guanylate monophosphate is partially attenuated by the older agent halothane,[23] whereas other studies have indicated that volatile anesthetics do not affect vasodilation produced by the NO donors sodium nitroprusside or nitroglycerin.[24] Volatile anesthetics may also reduce the stability of NO

by generating oxygen-derived free radicals[24] while leaving NO release and its action on vascular smooth muscle unaffected.[22] Whether the results of these later studies conducted in isolated aortic preparations are applicable to the coronary circulation requires further evaluation, but these investigations have provided important information about the potential interactions between NO metabolism and volatile anesthetics in the coronary circulation.

Isoflurane and halothane cause coronary vasodilation by activation of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels.[25,26] Increases in coronary blood flow in response to halothane and isoflurane were attenuated by the nonselective K_{ATP} channel antagonist glyburide in isolated rat hearts and anesthetized pigs, respectively.[25,26] Glyburide also partially blocked increases in coronary blood flow during intracoronary administration of volatile anesthetic–equilibrated blood in canine hearts in situ.[27] Isoflurane-induced reductions in coronary vascular resistance were attenuated by the selective adenosine$_1$ (A_1) receptor antagonist 8-cyclopentyl-1,3,dipropylxanthine (DPCPX).[28] These data suggest that the coronary vasodilation produced by isoflurane may occur partially as a result of stimulation of A_1 receptors coupled to K_{ATP} channels.[28]

Volatile Anesthetics and Ischemic Myocardium

Isoflurane and halothane decreased subendocardial blood flow and myocardial lactate extraction, produced contractile dysfunction, and caused electrocardiographic changes in the presence of coronary stenosis concomitant with declines in coronary perfusion pressure. Regional ischemia during isoflurane- or halothane-induced reductions in perfusion pressure was functionally indicated by the appearance of paradoxical systolic lengthening and postsystolic shortening.[29] Contractile dysfunction in the region distal to a critical coronary stenosis was more severe during isoflurane than during halothane anesthesia coincident with higher flow in the normal zone and lower flow in the ischemic zone. These findings suggest that the coronary vasodilation produced by isoflurane may cause a detrimental redistribution of coronary blood flow away from ischemic myocardium if hypotension is allowed to occur ("coronary steal"). However, these potentially adverse effects of volatile anesthetics on ischemic myocardium were avoided if coronary perfusion pressure was restored. Subendocardial blood flow in the perfusion bed distal to a critical coronary stenosis was reduced during isoflurane-induced declines in arterial pressure, but treatment of hypotension with phenylephrine restored subendocardial blood flow to values observed before the administration of isoflurane. The transmural distribution of coronary blood flow between the subendocardium and subepicardium (endo/epi ratio) decreased during isoflurane anesthesia despite control of arterial pressure. Administration of phenylephrine to maintain arterial pressure constant increased subepicardial blood flow more than subendocardial flow. This increase in subepicardial perfusion accounted for the decline in the endo/epi ratio in the absence of an absolute reduction in subendocardial flow. Restoration of coronary perfusion pressure to baseline levels during isoflurane anesthesia also increased coronary collateral blood flow and normalized myocardial oxygen tension in the ischemic zone.[21]

Investigations in dogs with steal-prone anatomy (complete occlusion of a coronary artery with collateral flow from an adjacent vessel with a critical stenosis) have repeatedly demonstrated that isoflurane and halothane do not alter collateral-dependent or ischemic-zone myocardial blood flow, endocardial-to-epicardial coronary blood flow distribution, or electrocardiographic findings when diastolic arterial pressure is held constant. Coronary collateral perfusion was unchanged during isoflurane or halothane anesthesia in dogs at a mean arterial pressure of 50 mm Hg. Coronary steal did not occur in a chronically instrumented canine model of coronary artery disease with the administration of isoflurane,[30] halothane,[31] desflurane,[32] or sevoflurane[33] independent of severe coronary stenosis or the development of coronary collaterals. These findings refuted earlier evidence in dogs with amaroid constrictor–induced augmentation of the coronary collateral circulation in which it was suggested that isoflurane reduces collateral blood flow and causes coronary steal in vivo. These effects of volatile anesthetics were in stark contrast to those obtained with adenosine, a potent coronary vasodilator that produces coronary steal when arterial pressure is maintained at control levels in models of multivessel coronary artery disease (Fig. 23-6).

Volatile Anesthetic–Induced Myocardial Protection

Acute Preconditioning by Volatile Anesthetics

The controversy about volatile anesthetic–induced coronary vasodilation and coronary steal has detracted from substantial experimental evidence indicating that volatile anesthetics exert important protective effects during myocardial ischemia and reperfusion injury. The older anesthetic halothane attenuated ST-segment changes caused by brief coronary artery occlusion and decreased ST-segment elevation to a greater extent than propranolol and sodium nitroprusside did despite producing similar hemodynamic effects. Isoflurane and desflurane produced beneficial actions on LV diastolic mechanics during acute regional myocardial ischemia.[29] Isoflurane and sevoflurane decreased myocardial reperfusion injury and improved functional recovery after global ischemia in isolated hearts.[34,35] Volatile anesthetics also enhanced systolic functional recovery of postischemic-reperfused ("stunned") myocardium when these anesthetics were administered before brief periods of myocardial ischemia in vivo. These salutary effects were accompanied by preservation of high-energy phosphate levels.[36] Volatile anesthetics have been shown to attenuate the effect of oxygen-derived free radicals on development of LV pressure in isolated hearts. Halothane also preserved contractile function and ultrastructural integrity during reperfusion after normothermic cardioplegic arrest.[37] In 1997, three research groups independently reported that administration of halothane or isoflurane before prolonged coronary artery occlusion and reperfusion reduces myocardial infarct size in vivo (Fig. 23-7).[5,38,39] Termed "anesthetic preconditioning," this beneficial effect was found to persist despite discontinuation of the volatile anesthetic before coronary artery occlusion.[5] This short-term memory phase was similar to that observed during ischemic preconditioning.

Anesthetic preconditioning has been shown to be dose related in experimental animals[40,41] independent of alterations in

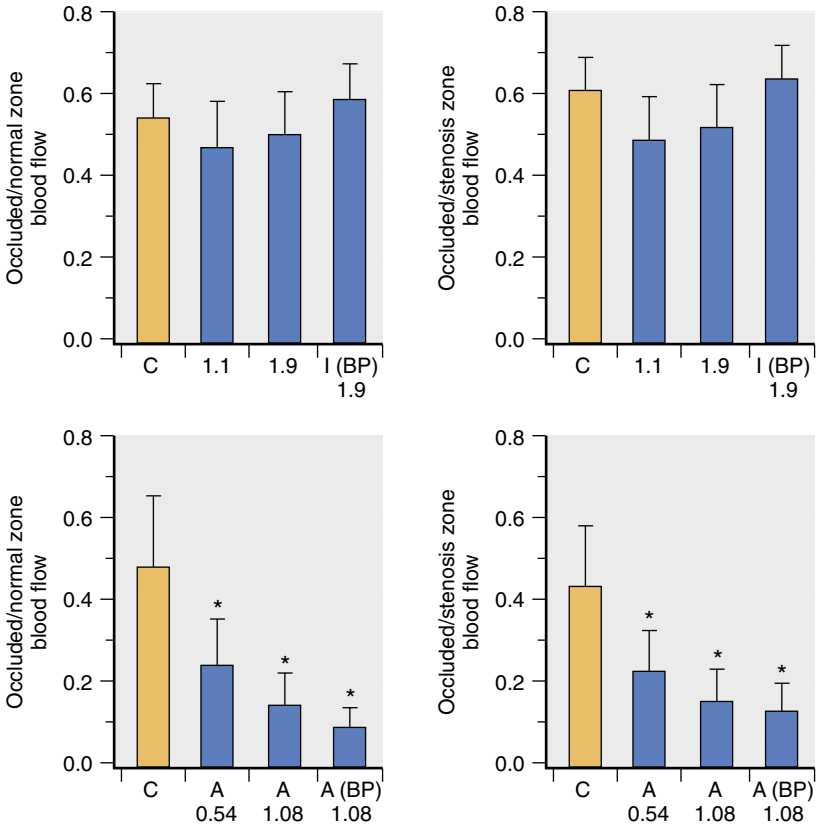

Figure 23-6 Comparison of occluded to normal and occluded to stenotic-zone myocardial blood flow in dogs with steal-prone coronary artery anatomy in the conscious state (C), during administration of isoflurane at 1.1 and 1.9 minimum alveolar concentration (I), during adenosine (A) infusions (0.54 and 1.08 mg/min), and during maintenance of heart rate and arterial pressure at conscious values during the highest doses (BP). Isoflurane does not cause coronary steal, in contrast to the significant (*$P < .05$) reductions in blood flow to collateral-dependent myocardium produced by adenosine. *(Adapted from Hartman JC, Kampine JP, Schmeling WT, Warltier DC: Actions of isoflurane on myocardial perfusion in chronically instrumented dogs with poor, moderate, or well-developed coronary collaterals. J Cardiothorac Anesth 4:715-725, 1990.)*

systemic hemodynamics or coronary collateral blood flow. Isoflurane and sevoflurane also produced dose-dependent preservation of isolated ventricular myocyte viability during ischemia in vitro.[42] Isoflurane elicited cardioprotection when the volatile agent was discontinued 15 or 30 minutes before prolonged coronary artery occlusion and reperfusion in rabbits[43] and dogs,[5] respectively. In contrast, sevoflurane failed to reduce the extent of myocardial infarction if the anesthetic was discontinued 30 minutes before the onset of prolonged ischemia.[44] These data suggest that the memory period of anesthetic preconditioning may differ between volatile anesthetics on the basis of species and pharmacokinetics. Dual as opposed to single exposure to sevoflurane improved anesthetic preconditioning in guinea pig hearts, thus indicating that repetitive administration of a volatile agent appears to confer an additional benefit.[45] The cardioprotection resulting from anesthetic preconditioning was shown to be restricted to a range of ischemia durations between 25 and 40 minutes in Langendorff perfused isolated guinea pig hearts.[46] Accordingly, anesthetic preconditioning may be especially beneficial in patients with ongoing myocardial ischemia of intermediate duration. Interestingly, the mechanism of sevoflurane-induced cardioprotection was independent of the type of ischemic stimulus (hypoxia versus metabolic inhibition) in isolated rat ventricular trabeculae.[47] These results indirectly suggested that anesthetic

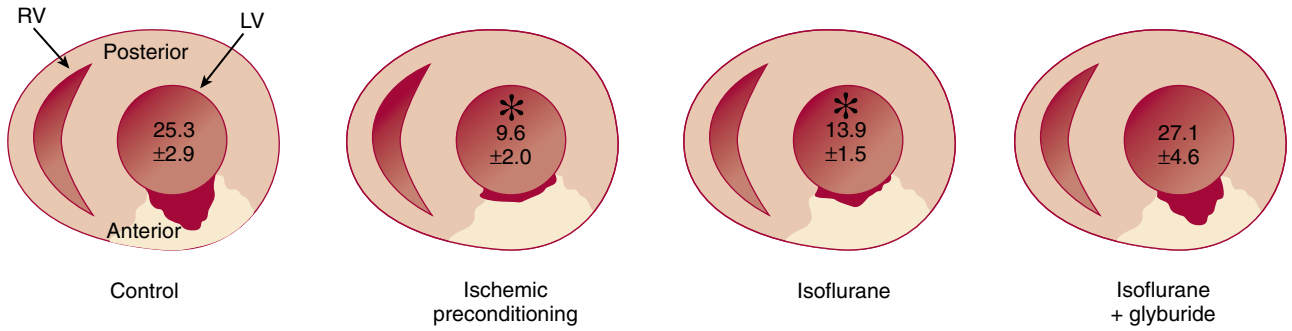

Figure 23-7 Schematic illustration of canine myocardium subjected to 60-minute coronary artery occlusion and reperfusion and then stained to identify the region of myocardial infarction (*dark red area*) within the area of myocardium at risk for infarction (*light yellow area*). Isoflurane decreased the extent of myocardial infarction. The protective effect of isoflurane was equivalent to that produced by ischemic preconditioning and was abolished by pretreatment with glyburide. *Significantly ($P < .05$) different from control. *(Adapted from Kersten JR, Schmeling TJ, Pagel PS, et al: Isoflurane mimics ischemic preconditioning via activation of K_{ATP} channels. Reduction of myocardial infarct size with acute memory phase. Anesthesiology 87:361-370, 1997.)*

preconditioning may be equally effective at preserving myocardial integrity during supply or demand myocardial ischemia in patients with coronary artery disease, but this intriguing hypothesis remains to be formally tested. Advanced age and increased heart size attenuated the efficacy of sevoflurane preconditioning in rats[48] and guinea pigs.[49] These experimental observations may also have important clinical ramifications in elderly patients at risk for the development of myocardial ischemia. In contrast, sevoflurane was capable of exerting cardioprotective effects in ischemic newborn rabbit myocardium.[50]

Volatile anesthetics may also produce beneficial effects on blood flow to and neutrophil interaction with ischemic myocardium. Volatile anesthetics produce coronary vasodilation by activating K_{ATP} channels or by favorably affecting intracellular Ca^{2+} homeostasis in vascular smooth muscle. Decreases in collateral blood flow after coronary artery occlusion have been shown to be less pronounced than declines in flow to normal myocardium in the presence of the older agent halothane. The ratio of myocardial O_2 delivery to MVo_2 was also increased in collateral-dependent myocardium during halothane anesthesia. Halothane inhibited platelet thrombi formation via increases in platelet cyclic adenosine monophosphate concentration and thereby decreased cyclic variations in coronary blood flow associated with a critical coronary artery stenosis. Sevoflurane increased blood flow to collateral-dependent myocardium when arterial pressure was maintained at conscious values mediated by Ca^{2+}-activated potassium (BK_{Ca}) channels.[51] Sevoflurane also improved recovery of coronary vascular reactivity and enhanced endothelial NO release in isolated hearts subjected to global ischemia and reperfusion. Volatile anesthetics attenuated adhesion of neutrophils and platelets in the coronary vasculature after ischemia and reperfusion. Isoflurane pretreatment also inhibited cytokine-induced cell death after ischemia-reperfusion injury in vitro.[52] Furthermore, isoflurane and sevoflurane preconditioned against neutrophil-induced contractile dysfunction in isolated rat hearts through activation of adenosine receptors.[53] Taken together, the results of these investigations suggest that the salutary actions of volatile anesthetics on coronary perfusion and neutrophil function may, to some degree, be responsible for the protection against ischemia-reperfusion injury afforded by these drugs.

The mechanisms responsible for volatile anesthetic–induced protection during myocardial ischemia and reperfusion have been intensively investigated in recent years and are the subject of several major reviews.[54-57] The beneficial effects of volatile anesthetics may be attributed to a favorable reduction in the myocardial oxygen demand required for active contraction along with concomitant preservation of energy-dependent vital cellular processes because these anesthetics cause direct negative inotropic, lusitropic, and chronotropic effects and decrease LV afterload. However, the older agent halothane exerted protective effects during complete functional arrest induced by cardioplegia.[37] Isoflurane, desflurane, and sevoflurane also produced cardioprotection when administered solely during reperfusion.[58] These data indicate that preferential alterations in myocardial oxygen supply-demand relationships are not solely responsible for the anti-ischemic actions of volatile anesthetics. Isoflurane and halothane may significantly lower excessive intracellular Ca^{2+} during reperfusion via a direct decline in the net transsarcolemmal Ca^{2+} transient resulting from partially inhibited Ca^{2+} channel activity or an indirect reduction of oxygen-derived free radical formation. In contrast to this rather nonspecific intracellular Ca^{2+} reduction hypothesis, a large body of very compelling evidence has convincingly demonstrated that cardioprotection by volatile anesthetics occurs as a consequence of the activation of endogenous signal transduction pathways. To date, K_{ATP} channels,[5] G protein–coupled receptor ligands (e.g., adenosine, opioid),[39,59] isoforms of protein kinase C (PKC),[60] protein tyrosine kinase (PTK),[60] reactive oxygen and nitrogen species, nuclear factor κB (NF-κB),[61] and several components of the prosurvival reperfusion injury salvage kinase cascade[62] have all been shown to mediate acute preconditioning by volatile anesthetics. These elements will now be discussed in detail.

Mitochondrial and Sarcolemmal K_{ATP} Channels

The K_{ATP} channel plays a central role in ischemic and anesthetic preconditioning. The K_{ATP} channel is a heteromultimeric complex consisting of an inwardly rectifying K^+ channel (K_{ir}) and a sulfonylurea receptor (SUR).[63] Pharmacologically distinct K_{ATP} channels have been identified in cardiac sarcolemmal and mitochondrial membranes. It was originally proposed that opening of sarcolemmal K_{ATP} channels protects ischemic myocardium by shortening the duration of the action potential and preventing intracellular Ca^{2+} overload. However, subsequent studies performed after discovery of the mitochondrial K_{ATP} channel indicated that the beneficial actions of K_{ATP} channel opening occur independent of the action potential duration. Nevertheless, ischemic preconditioning was not observed in the absence of the sarcolemmal K_{ir} channel in transgenic mice.[64] These data suggest that protection against ischemic injury requires contribution of the sarcolemmal K_{ATP} channel. In contrast, mitochondrial K_{ATP} channels appear to be the primary mediators of ischemic preconditioning.[65] Preservation of mitochondrial bioenergetic function appears to be vital for cellular protection against myocardial ischemia.[66] Mitochondrial K_{ATP} channel openers maintained intracellular Ca^{2+} homeostasis and inhibited mitochondrial Ca^{2+} overload.[67] These actions enhanced myocyte survival by preventing tissue necrosis or apoptosis (programmed cell death).[68] In contrast to the well-known generalized cellular destruction and profound inflammatory response that typify necrosis, the highly regulated, ATP-dependent phenomenon of apoptosis is characterized by selective DNA lysis associated with the formation of apoptotic bodies, appearance of condensed chromatin, absence of inflammation, and preservation of cell membrane structure.[69] Activation of mitochondrial K_{ATP} channels inhibited apoptosis in rat ventricular myocytes by attenuating oxidant stress during reperfusion.[70] Alteration of the mitochondrial oxidation-reduction state by activation of K_{ATP} channels may also promote cellular protection.[71] Experiments conducted in isolated cardiac mitochondria indicated that membrane depolarization, matrix swelling, and uncoupling of ATP synthesis occur as a result of increased oxygen consumption, are associated with opening of mitochondrial K_{ATP} channels, and may mediate cellular viability during ischemic preconditioning.[71] Opening of mitochondrial K_{ATP} channels depolarized the inner mitochondrial membrane and caused transient swelling of the mitochondrial matrix[72] because of a shift in ionic balance.[73] Mitochondrial K_{ATP} channel opening initially reduced ATP production as a result of membrane depolarization[74] but subsequently stimulated a compensatory increase in respiration that optimized the efficiency of oxidative phosphorylation, in part by regulating energy-dependent matrix volume. Influx of potassium into mitochondria occurred as a consequence of the balance between K^+ influx through the mitochondrial K_{ATP}

channel and K^+ efflux produced by the mitochondrial K^+-H^+ antiporter. The mitochondrial K_{ATP} channel agonist diazoxide promoted K^+ influx and caused matrix alkalinization in isolated rat ventricular myocardium.[75] These actions were abolished by 5-hydroxydecanoate (5-HD) and ATP. Thus, a moderate disturbance in mitochondrial homeostasis caused by opening of mitochondrial K_{ATP} channels may promote myocardial tolerance to ischemic stress by altering energetic systems to reduce Ca^{2+} overload, prevent the activation of necrotic or apoptotic pathways, or attenuate oxidant stress.

The endogenous mechanisms involved in anesthetic preconditioning are strikingly similar to those implicated in ischemic preconditioning, although differences between these phenomena have been suggested by microarray gene chip analysis.[76] It is hypothesized that a "trigger" (e.g., a brief ischemic episode, exposure to a volatile anesthetic) initiates a cascade of signaling events leading to activation of an "end-effector" that is responsible for resistance to injury. K_{ATP} channel activation has been implicated as the end-effector in this protective scheme during anesthetic preconditioning. Administration of isoflurane and sevoflurane preserved myocyte viability in a cellular model of ischemia, in contrast to cells that were not exposed to a volatile agent.[42] The selective mitochondrial K_{ATP} channel antagonist 5-HD but not the selective sarcolemmal K_{ATP} channel antagonist HMR-1098 abolished this protective effect.[42] The nonselective K_{ATP} channel blocker glyburide (also known as glibenclamide) attenuated the recovery of contractile function produced by isoflurane in stunned myocardium (Fig. 23-8). Isoflurane-induced reductions in canine myocardial infarct size[5] and the ATP-sparing effects of this agent were also abolished by glyburide. 5-HD inhibited preconditioning by isoflurane in rats,[40] rabbits,[77] and isolated human myocardium.[78] Both HMR-1098 and 5-HD abolished the protective effects of desflurane in dogs,[79] thus supporting a role for both sarcolemmal and mitochondrial K_{ATP} channels in anesthetic acute preconditioning. However, HMR-1098 did not affect desflurane preconditioning of isolated human right atrial myocardium.[80] Thus, controversy continues to exist about the relative importance of sarcolemmal versus mitochondrial K_{ATP} channels in anesthetic preconditioning.

Results from in vitro experiments also strongly suggest that volatile anesthetics produce profound effects on sarcolemmal K_{ATP} channel function. Isoflurane stimulated outward K^+ current through sarcolemmal K_{ATP} channels in isolated ventricular myocytes during patch-clamping.[81] Volatile anesthetics also reduced sarcolemmal K_{ATP} channel sensitivity to inhibition by ATP, thereby increasing the probability of being in the open state.[82] However, other patch-clamp experiments failed to confirm these results and suggested that volatile anesthetics do not open sarcolemmal K_{ATP} channels. For example, isoflurane did not alter sarcolemmal K_{ATP} channel current in human atrial cells[78] and, furthermore, inhibited sarcolemmal K_{ATP} channel activity in rabbit ventricular myocytes.[82] Nevertheless, volatile anesthetics have been shown to enhance sarcolemmal K_{ATP} channel current by facilitating channel opening after initial activation. The ε-isoform of PKC (PKC-ε) was shown to prime the sarcolemmal K_{ATP} channel to open in the presence of isoflurane.[83] Facilitation of sarcolemmal K_{ATP} channel current by isoflurane during reduced intracellular ATP concentrations was also dependent on PKC-dependent signaling.[84] In addition, reactive oxygen species (ROS) contributed to isoflurane-induced sensitization of the sarcolemmal K_{ATP} channel to the opener pinacidil.[85] Isoflurane also directly

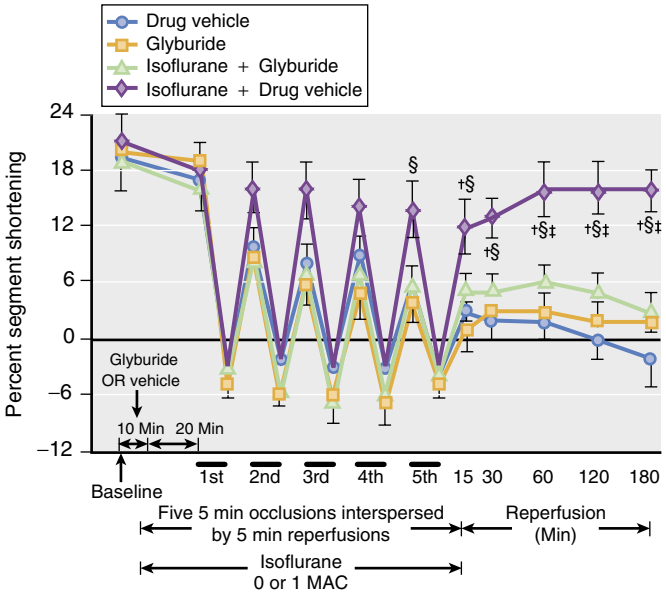

Figure 23-8 Percent segment shortening (%SS) in the intermittently ischemic and reperfused left anterior descending coronary artery (LAD) region. %SS decreases significantly ($P < .05$) from baseline during each 5-minute LAD occlusion and reperfusion in all groups. Significant decreases in %SS during each 5-minute reperfusion and throughout 180 minutes of final reperfusion are observed in dogs pretreated with glyburide, a nonselective K_{ATP} channel antagonist, in the presence or absence of isoflurane. %SS recovers to baseline values after reperfusion in dogs receiving isoflurane alone. †Significantly ($P < .05$) different from dogs pretreated with drug vehicle. ‡Significantly ($P < .05$) different from dogs receiving glyburide and isoflurane. §Significantly ($P < .05$) different from dogs pretreated with glyburide. *(From Kersten JR, Schmeling TJ, Hettrick DA, et al: Mechanism of cardioprotection by isoflurane: Role of adenosine triphosphate–regulated potassium [K_{ATP}] channels. Anesthesiology 85:794-807, 1996.)*

opened sarcolemmal K_{ATP} channels during intracellular acidosis of a magnitude similar to that observed during ischemia.[86] The sarcolemmal K_{ATP} channel acted as an effector during isoflurane preconditioning against oxidative stress in adult ventricular myocytes.[87] The effects of volatile anesthetics on sarcolemmal K_{ATP} channel function may persist beyond the duration of administration,[84] suggesting a cellular basis for the early "memory" phase of anesthetic preconditioning in vivo. Isoflurane preconditioning produced prolonged sensitization of the sarcolemmal K_{ATP} channel to opening by a PKC δ-isoform (PKC-δ)-mediated mechanism[88] or by enhancing induction of sarcolemmal K_{ATP} channel current via a diacylglycerol PKC activator.[84] Isoflurane preconditioning caused persistent reductions in the sensitivity of the sarcolemmal K_{ATP} channel to inhibition by ATP and adenosine 5′-diphosphate.[89] The nucleotide binding domains of the regulatory sulfonylurea receptor SUR2A were shown to play important roles in isoflurane-induced facilitation of sarcolemmal K_{ATP} channel activity during moderate intracellular acidosis, similar to that encountered during early ischemia.[90] These data support the contention that isoflurane directly interacts with subunits of the cardiac sarcolemmal K_{ATP} channel.[90]

It is also clear, based on several experimental studies, that volatile anesthetics directly or indirectly open mitochondrial K_{ATP} channels in vitro. Isoflurane and sevoflurane increased mitochondrial flavoprotein oxidation, an index of mitochondrial K_{ATP} channel activity, in guinea pig cardiac myocytes, and this increase in fluorescence was inhibited by the selective mitochondrial K_{ATP} channel inhibitor 5-HD.[91] Isoflurane also directly activated the

mitochondrial K_{ATP} channels reconstituted in lipid bilayers.[92] Isoflurane-induced increases in mitochondrial flavoprotein fluorescence were not inhibited by pretreatment with adenosine, PKC, PTK, or p38 mitogen-activated protein kinase (MAPK) inhibitors, suggesting that isoflurane may directly activate mitochondrial K_{ATP} channels.[93] In contrast, isoflurane and sevoflurane failed to directly enhance flavoprotein fluorescence in rat ventricular myocytes, but these anesthetics did enhance fluorescence induced by the mitochondrial K_{ATP} channel agonist diazoxide.[42] These data suggest that volatile anesthetics may not directly open but, instead, indirectly prime mitochondrial K_{ATP} channels by acting on other intracellular signaling elements that modulate the activity of the channel. Sarcolemmal K_{ATP} channels may also be linked to the function of the inner mitochondrial membrane. The ROS generated by mitochondria may act to open sarcolemmal K_{ATP} channels. An uncoupler of mitochondrial oxidative phosphorylation (2,4-dinitrophenol) reversibly activated sarcolemmal K_{ATP} channel current concomitant with nicotinamide adenine dinucleotide oxidation. These and other data led to the contention that crosstalk may occur between sarcolemmal and mitochondrial K_{ATP} channels during preconditioning phenomena.[94] However, such crosstalk has yet to be specifically demonstrated during anesthetic preconditioning. To summarize, the experimental results collected to date provide somewhat conflicting results about a possible direct action of volatile anesthetics on sarcolemmal and mitochondrial K_{ATP} channel activity. Nevertheless, volatile anesthetics clearly prime the activation of these channels in both sarcolemmal and mitochondrial membranes.

K_{ATP} channels in vascular smooth muscle cells are essential regulators of coronary vascular tone when ATP production is reduced. Volatile anesthetic–induced coronary vasodilation[95] was attenuated by glyburide, thus indicating an important role for K_{ATP} channels in this process. The beneficial actions of anesthetic preconditioning may therefore be partially attributed to increases in myocardial oxygen supply mediated by K_{ATP} channel–dependent coronary vasodilation. However, the fact that sevoflurane caused an increase in coronary collateral blood flow in vivo in the presence of glyburide indicates that this volatile anesthetic may enhance coronary collateral blood flow independent of activation of K_{ATP} channels. Sevoflurane-induced increases in collateral perfusion occur as a result of Ca^{2+}-regulated potassium (BK_{Ca}) and not K_{ATP} channel activation.[51] Thus, the cardioprotection provided by volatile anesthetics is unlikely to be solely related to favorable alterations in coronary vascular tone mediated by K_{ATP} channels.

G Proteins and Their Coupled Receptor Ligands

The sequential activation of several intracellular elements in a transduction pathway may facilitate amplification of the initial signal between other redundant systems. This concept was clearly illustrated by the observation that the direct K_{ATP} channel opener nicorandil enhances the cardioprotective effects of isoflurane.[96] G protein–coupled receptor ligands and their downstream signaling elements have been shown to converge on the K_{ATP} channel during anesthetic preconditioning. Pertussis toxin abolished the reductions in infarct size produced by isoflurane, thus indicating that inhibitory guanine (G_i) nucleotide–binding proteins are linked to the signal transduction pathways that mediate anesthetic preconditioning.[97] In contrast, pertussis toxin did not prevent the beneficial effects of direct K_{ATP} channel opening produced by nicorandil. These data strongly support the contention that volatile anesthetics modulate K_{ATP} channel activity through a second messenger. Halothane-induced protection against infarction was completely abolished by blockade of the adenosine A_1 receptor,[39] and the selective A_1 receptor antagonist DPCPX also partially attenuated the beneficial effects of isoflurane on stunned myocardium.[98] Isoflurane eliminated increases in interstitial adenosine during repetitive periods of coronary artery occlusion and reperfusion as demonstrated via a myocardial microdialysis technique.[98] These findings suggest that ATP preservation and a subsequent reduction in adenosine released into the interstitium occur during isoflurane anesthesia. The results were also very similar to those obtained during ischemic preconditioning and pharmacologic preconditioning with bimakalim. Thus, volatile anesthetics may either directly activate A_1 receptors or indirectly enhance A_1 receptor sensitivity to diminished endogenous adenosine concentrations.[98] The preservation of cardiac myocyte viability during ischemia produced by volatile anesthetics was also sensitive to adenosine receptor– and G_i protein–mediated signaling blockade.[42] Adenosine also enhanced isoflurane preconditioning through both mitochondrial K_{ATP} channel–dependent and channel-independent mechanisms in isolated, buffer-perfused rat hearts.[99]

The nonselective opioid antagonist naloxone also abolished isoflurane-induced preconditioning in the rat.[40] These data indicate an important link between volatile anesthetics and another family of G_i protein–coupled receptors. Volatile anesthetics competitively inhibited the ligand binding site of G_i protein–coupled receptors.[100] Thus, anesthetic preconditioning appears to be associated with the activation of at least two separate receptor-mediated pathways (A_1 and opioid) that are linked to G_i proteins. Interestingly, the combination of isoflurane and a selective δ_1-opioid receptor agonist amplified the preconditioning response in the rat.[59] This effect was synergistic and sensitive to inhibition by glyburide.[59] The combined administration of isoflurane and morphine also markedly reduced infarct size in vivo, and this protective effect was abolished by 5-HD.[40] Hence, combined administration of a volatile anesthetic and an opioid capable of agonist action at the δ_1-opioid receptor may stimulate similar or cooperative signaling cascades that amplify K_{ATP} channel activation to profoundly augment myocardial protection beyond that produced by either drug alone. A G_s protein–coupled receptor ligand system, the β_1-adrenoceptor and its downstream target protein kinase A, was also recently shown to mediate desflurane and sevoflurane but not ischemic preconditioning in rabbits.[101] These data suggest that both G_i and G_s may play important roles in anesthetic preconditioning in vivo.

Protein Kinases

Ischemic preconditioning has been shown to produce translocation and phosphorylation of several protein kinases, most importantly PKC, involved in cardioprotective signal transduction. PKC is an essential component of the signaling pathway involved in protecting myocardium against cell death during ischemia and reperfusion.[102] The diverse PKC isoform family is a large group of serine-threonine protein kinases that are distinguished by variable regulatory domains and cofactors and also display diverse tissue and species distributions. G protein–coupled receptor ligands, including A_1, δ_1-opioid, and bradykinin, have been shown to activate PKC during ischemic preconditioning. Volatile anesthetics stimulated PKC translocation and activity, possibly by interacting with regulatory domain of the enzyme. Inhibition of

PKC partially attenuated isoflurane-induced augmentation of the functional recovery of stunned myocardium in dogs.[103] The beneficial actions of the older agent halothane were entirely blocked by selective inhibition of PKC in rabbits.[39] Colchicine, a drug that depolymerizes microtubule assemblies, prevented isoflurane-induced reductions in myocardial infarct size in rabbits. This interesting result suggests that an intact cytoskeleton is essential for translocation of the PKC to occur. In fact, volatile anesthetic–induced PKC translocation and activation appear to be required to open K_{ATP} channels and produce cardioprotection. For example, the nonselective PKC antagonist chelerythrine abolished sevoflurane-induced increases in mitochondrial K_{ATP} channel activity in rat ventricular myocyte and prevented protection from ischemic damage.[42] Patch-clamp experiments demonstrated that isoflurane does not facilitate K_{ATP} channel opening in excised membranes but enhances K_{ATP} channel current in a whole-cell configuration concomitant with PKC stimulation.[104] These observations were supported by findings that both adenosine and PKC enhance K_{ATP} channel activity during ischemic preconditioning. Specific PKC consensus sites were demonstrated on K_{ATP} channels, thereby suggesting a molecular basis for phosphorylation and activation of the channel by this critical enzyme.[105] Translocation of PKC-δ but not PKC-ε plays an important role in isoflurane preconditioning in isolated perfused rat hearts.[106] Phosphorylation of the serine 643 residue of PKC-δ appeared to mediate transfer of the preconditioning stimulus (exposure to 1.5 MAC isoflurane) to mitochondrial K_{ATP} channels.[106] Both PKC-δ and PKC-ε translocation was implicated in isoflurane (1.0 MAC) preconditioning in rats in vivo, and opening of mitochondrial K_{ATP} channels and generation of ROS were shown to be upstream events that accompanied PKC activation in this model (Fig. 23-9).[60] Another study implicated PKC-ε alone during sevoflurane preconditioning in isolated perfused guinea pig hearts.[107] A role for PKC-ε was also demonstrated in isoflurane preconditioning in rats by another research group,[108] but only at lower concentrations (<0.5 MAC) of the volatile agent. Desflurane preconditioning produced time-dependent translocation of PKC-ε through activation of extracellular signal–regulated kinases 1 and 2 (ERK1/2).[109] In contrast, PKC-δ mediated sevoflurane preconditioning through ROS production independent of mitochondrial K_{ATP} channels in isolated rat trabeculae.[110] Taken as a whole, these experimental data strongly suggest that at least two different isoforms of PKC (ε and δ) appear to be important mediators of anesthetic preconditioning.

PKC has been shown to stimulate PTK[111] and several MAPK moieties[112] during ischemic preconditioning, and some evidence also indicates a role for these proteins in anesthetic-induced cardioprotection independent of receptor activation. The PTK inhibitor lavendustin A and the Src-selective inhibitor PP1 abolished isoflurane preconditioning in rats.[60] In contrast, lavendustin A and another nonselective PTK inhibitor (genistein) did not alter desflurane preconditioning in rabbits.[113] These data suggest that the role of PTK in anesthetic preconditioning may be dependent on the species. The MAPK family of proteins plays important roles in signal transduction from the cell surface to the nucleus and in the initiation and progression of apoptosis. ERK1 and ERK2 are MAPKs that mediate cell division, proliferation, and survival.[62] They were previously implicated in ischemia and opioid-induced preconditioning in rats. The reductions in infarct size and ERK1/2 phosphorylation produced by administration of desflurane before ischemia and reperfusion were abolished by a selective ERK1/2 inhibitor,[109] thereby providing the first evidence suggesting that ERK1/2 mediates anesthetic preconditioning. ERK1/2 was also shown to trigger isoflurane preconditioning in rabbits.[114] In addition, ERK1/2-related signaling proteins control the expression of several genes concerned with cell survival, including hypoxia-inducible factor-1α (HIF-1α), an important DNA-binding complex whose activity is influenced by intracellular oxygen tension. Myocardial hypoxia is a potent inducer of HIF-1α protein expression, and the combination of reduced oxygen tension and activation of ERK1/2 signaling is known to potentiate HIF-1α expression and activity.[115] Furthermore, HIF-1α upregulates transcription of vascular endothelial growth factor (VEGF).[116] This important angiogenic protein plays a central role in coronary collateral development in response to chronic myocardial ischemia,[117] and enhanced expression of both HIF-1α and VEGF occurs during myocardial ischemia in rats.[118] ERK1/2-dependent upregulation of HIF-1α and VEGF has also been shown during ischemic and hypoxic preconditioning.[119] Administration of isoflurane likewise produced temporal upregulation of HIF-1α and VEGF expression by activating ERK1/2 in rabbit myocardium (Figs. 23-10 and 23-11).[114] Another MAPK (p38) strongly implicated in ischemic preconditioning also appeared to mediate anesthetic preconditioning in isolated rat hearts.[120] p38 MAPK has been shown to interact with the actin cytoskeleton through MAPK-activated protein kinase 2 (MAPKAPK-2) and heat shock protein 27 (HSP-27). Isoflurane and xenon preconditioning were recently demonstrated to activate both MAPKAPK-2 and HSP-27 downstream of PKC and p38 MAPK.[121] These exciting data provide another potential link between anesthetic preconditioning and the cytoskeleton, thereby suggesting another mechanism by which signaling elements involved in cardioprotection may be transported to appropriate locations within the cell. Activated protein kinase G (PKG) has been shown to open mitochondrial K_{ATP} channels during ischemic and pharmacologic preconditioning. PKG was recently demonstrated to transmit G_i protein-receptor ligand coupled from the cytosol to the inner mitochondrial membrane by a pathway that includes PKC-ε to produce cardioprotection.[122] Whether PKG also mediates anesthetic preconditioning has yet to be determined.

The prosurvival protein phosphatidylinositol-3′-kinase (PI3K) has been shown to be responsible for the phosphorylation of a variety of subcellular targets implicated in cell survival, protein synthesis, and metabolism. Activation of this kinase pathway not only reduces cell necrosis but also contributes to the preservation of viable myocardium by inhibiting apoptosis and maintaining mitochondrial integrity.[62] PI3K converts phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-triphosphate (PIP_3),[123] and PIP_3-stimulated phosphorylation of the serine-threonine kinase Akt by phosphoinositide-dependent kinase 1 (PDK1) subsequently inhibits the formation of several proapoptotic proteins (e.g., Bad, Bax, caspases). PDK1 is a also potent activator of other protein kinases,[123] including PKC and PTK, implicated in anesthetic preconditioning.[56] A role for PI3K signaling in isoflurane preconditioning was recently demonstrated. A selective inhibitor of PI3K (wortmannin) abolished reductions in infarct size and also blocked phosphorylation of the downstream enzyme target Akt that were produced by administration of isoflurane before prolonged coronary artery occlusion in rabbits.[124] Isoflurane preconditioning increased Akt phosphorylation and expression of the antiapoptotic B-cell lymphoma-2 (Bcl-2) protein and reduced expression of the apoptotic protein

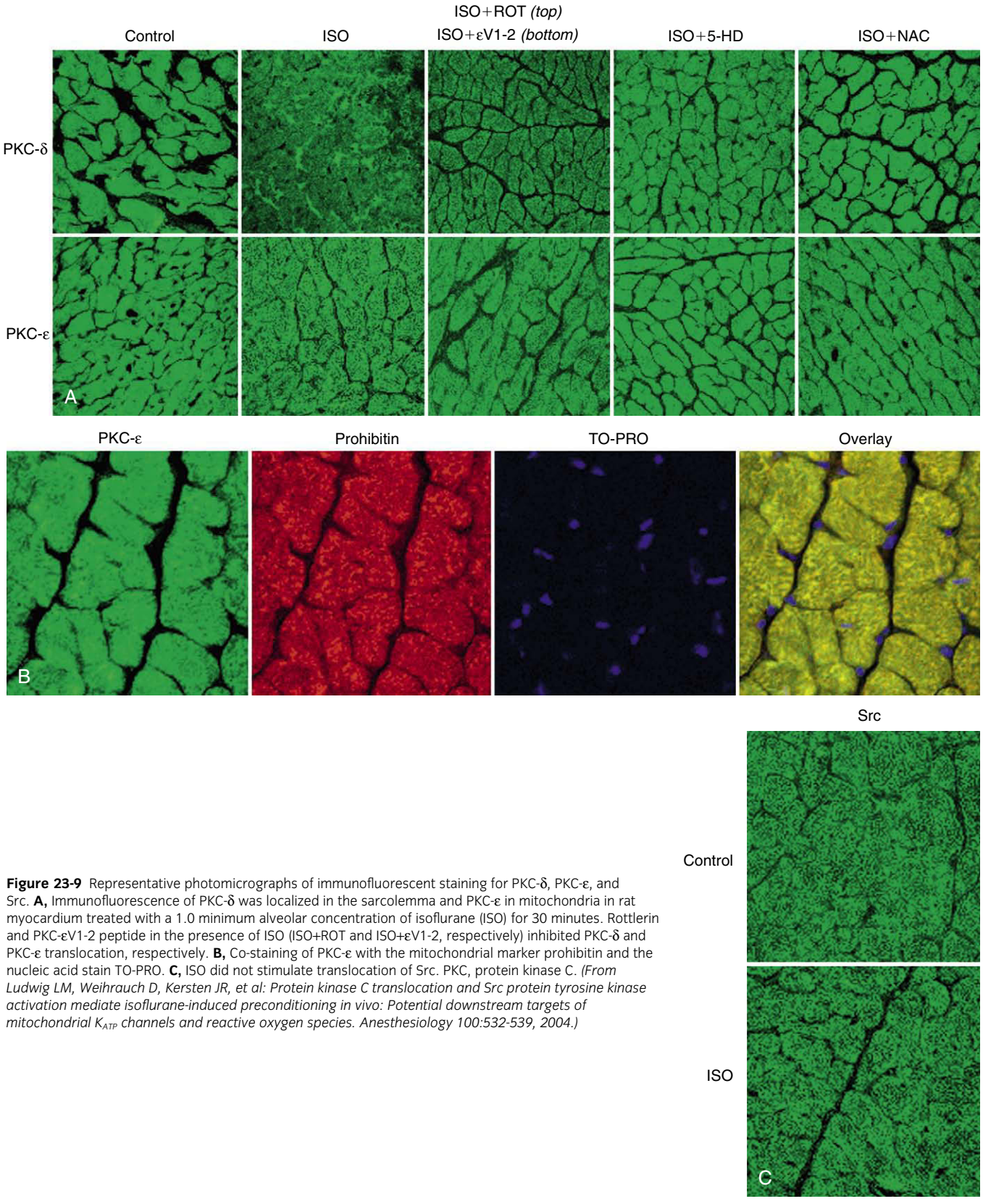

Figure 23-9 Representative photomicrographs of immunofluorescent staining for PKC-δ, PKC-ε, and Src. **A,** Immunofluorescence of PKC-δ was localized in the sarcolemma and PKC-ε in mitochondria in rat myocardium treated with a 1.0 minimum alveolar concentration of isoflurane (ISO) for 30 minutes. Rottlerin and PKC-εV1-2 peptide in the presence of ISO (ISO+ROT and ISO+εV1-2, respectively) inhibited PKC-δ and PKC-ε translocation, respectively. **B,** Co-staining of PKC-ε with the mitochondrial marker prohibitin and the nucleic acid stain TO-PRO. **C,** ISO did not stimulate translocation of Src. PKC, protein kinase C. *(From Ludwig LM, Weihrauch D, Kersten JR, et al: Protein kinase C translocation and Src protein tyrosine kinase activation mediate isoflurane-induced preconditioning in vivo: Potential downstream targets of mitochondrial K_{ATP} channels and reactive oxygen species. Anesthesiology 100:532-539, 2004.)*

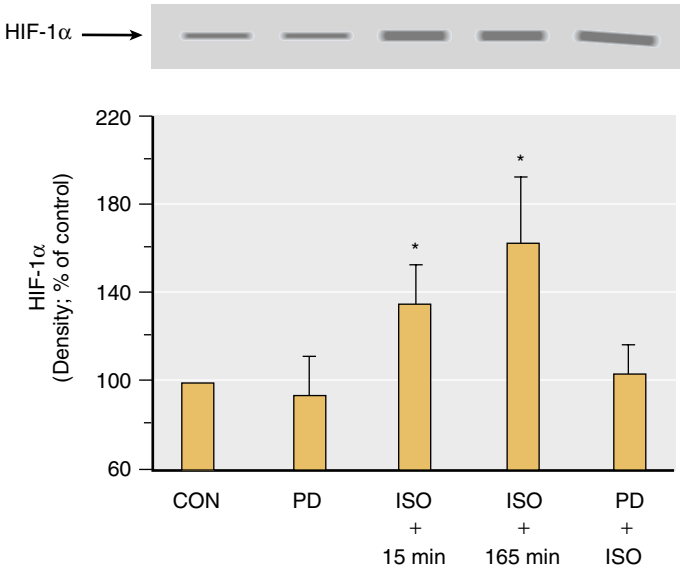

Figure 23-10 Representative immunoblots (*top panel*) of hypoxia-inducible factor-1α (HIF-1α) in rats receiving 0.9% saline (CON), PD 098059 (PD, 1.0 mg/kg), 1.0 minimum alveolar concentration of isoflurane (ISO) administered for 30 minutes, and PD 098059 (1.0 mg/kg) administered before ISO. Left ventricular tissue samples were obtained 15 or 165 minutes after administration of ISO or at a corresponding time point in rats that did not receive the volatile anesthetic. Histograms illustrating HIF-1α expression in each experimental group are depicted in the *lower panel*. All data are means ± SD. *Significantly ($P < .05$) different from CON. *(From Wang C, Weihrauch D, Schwabe DA, et al: Extracellular signal–regulated kinases trigger isoflurane preconditioning concomitant with upregulation of hypoxia-inducible factor-1α and vascular endothelial growth factor in rats. Anesth Analg 103:281-288, 2006.)*

Bax in rabbits concomitant with decreases in infarct size and the number of apoptotic myocytes.[125] Wortmannin and another selective PI3K antagonist (LY294002) abolished these actions, thus indicating that PI3K-induced modulation of proapoptotic and antiapoptotic protein balance plays a role in isoflurane cardioprotection.[125] Activation of Akt by isoflurane was also shown to protect rat atrial and ventricular myocytes against apoptosis in vitro produced by exposure to hypoxia, hydrogen peroxide, or activated neutrophils concomitant with increased expression of Bcl-2.[126] Collectively, these data suggest that prosurvival PI3K signaling plays a central role in anesthetic preconditioning.

A transition in mitochondrial permeability caused by opening of the mitochondrial permeability transition pore (mPTP) may be a critical end-effector in the myocardial necrosis and apoptosis resulting from ischemia-reperfusion injury. This event has been shown to be modulated by PI3K-mediated signaling pathways.[127] The mPTP is located on the inner mitochondrial membrane, and opening of the pore abolishes the mitochondrial membrane potential ($\Delta\Psi_m$), inhibits oxidative phosphorylation, and facilitates the release or activation of several proapoptotic proteins, including cytochrome *c*. These actions rapidly produce cell death. Opening of the mPTP appears to occur specifically at the onset of reperfusion,[128] in part as a consequence of intracellular Ca^{2+} overload and the presence of large quantities of cytotoxic oxygen-derived free radicals. The protective effects of classic[127] and delayed[129] ischemic preconditioning were mediated by inhibition of mitochondrial permeability transition. A role for mPTP inhibition was also suggested in the preconditioning produced by the selective mitochondrial K_{ATP} channel agonist diazoxide.[127] Similar to the findings with ischemic preconditioning, desflurane preconditioning improved mPTP resistance to Ca^{2+}-induced opening in isolated mitochondria obtained from pretreated rabbits.[130] The selective mitochondrial K_{ATP} channel antagonist 5-HD abolished this effect.[130] Isoflurane preconditioning also elicited partial mitochondrial uncoupling and reduced mitochondrial Ca^{2+} uptake in intact ventricular myocytes,[131] presumably mediated through mPTP or mitochondrial K_{ATP} channels.

Reactive Oxygen Species

Reperfusion of ischemic myocardium is associated with the release of large quantities of ROS that disrupt intracellular Ca^{2+} homeostasis, cause lipid peroxidation, damage cell membranes, depress contractility, and produce reversible and irreversible tissue injury.[132] Isoflurane and the older volatile anesthetics have been shown to attenuate the toxic effects of oxygen-derived free radicals on LV pressure development in isolated hearts. Isoflurane decreased hydroxyl radical generation in the ischemic rat heart, and halothane had a similar effect in dogs.[133] The protective effects of sevoflurane were associated with reduced dityrosine formation, an indirect marker of reactive oxygen and nitrogen species.[134] These results supported the contention that volatile anesthetics may reduce the release of deleterious quantities of ROS immediately after coronary artery occlusion and reperfusion.

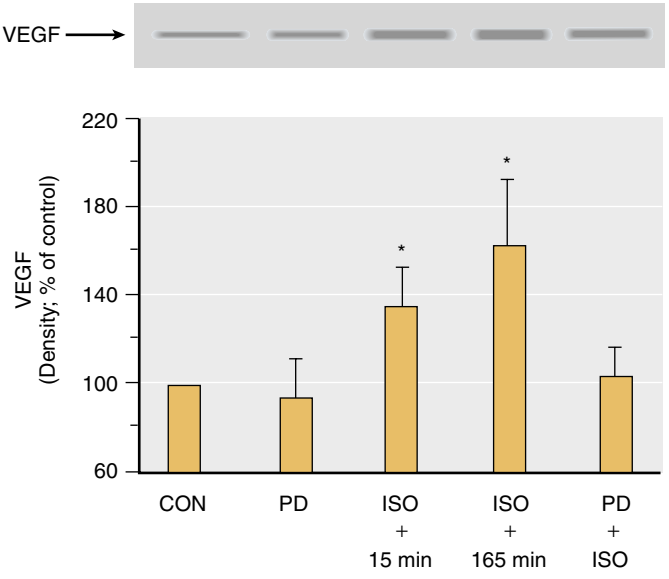

Figure 23-11 Representative immunoblots (*top panel*) of vascular endothelial growth factor (VEGF) in rats receiving 0.9% saline (CON), PD 098059 (PD, 1.0 mg/kg), 1.0 minimum alveolar concentration of isoflurane (ISO) administered for 30 minutes, and PD 098059 (1.0 mg/kg) administered before ISO. Left ventricular tissue samples were obtained 15 or 165 minutes after the administration of ISO or at a corresponding time point in rats that did not receive the volatile anesthetic. Histograms illustrating VEGF expression in each experimental group are depicted in the *lower panel*. All data are means ± SD. *Significantly ($P < .05$) different from CON. *(From Wang C, Weihrauch D, Schwabe DA, et al: Extracellular signal–regulated kinases trigger isoflurane preconditioning concomitant with upregulation of hypoxia-inducible factor-1α and vascular endothelial growth factor in rats. Anesth Analg 103:281-288, 2006.)*

In contrast to these data implicating a pathologic role of large amounts of ROS, a variety of preconditioning stimuli, including brief ischemia, mitochondrial K_{ATP} channel openers, opioids, and volatile anesthetics, stimulate a small burst of ROS that paradoxically appears to initiate downstream signaling events and produce protection from subsequent ischemic injury. Pretreatment with low concentrations of ROS mimicked the beneficial effects of ischemic preconditioning,[135] and free radical scavengers administered before or during ischemia attenuated this cardioprotection.[136] These findings suggest that ischemic preconditioning is mediated by small quantities of ROS released during the preconditioning stimulus. Scavengers of superoxide anion and inhibition of nitric oxide synthase (NOS) abolished the beneficial actions of sevoflurane against ischemic damage.[134] Similarly, desflurane preconditioning was mediated by NO.[137] These results indicate that that superoxide anion may act to trigger anesthetic preconditioning and also suggest that NO may scavenge superoxide anion upon reperfusion to reduce injury. Scavengers of ROS attenuated isoflurane-induced reductions in myocardial infarct size in rabbits[138] (Fig. 23-12) and also inhibited the salutary actions of opening of mitochondrial K_{ATP} channels.[139] Isoflurane was shown with the fluorescent probe dihydroethidium and laser confocal microscopy to directly increase superoxide anion formation in vivo independent of ischemia and reperfusion.[43] Thus, volatile anesthetics may be capable of producing small amounts of superoxide anion that exert protective effects during subsequent ischemia. These data provide compelling evidence that small quantities of ROS play a critical role in anesthetic preconditioning.

ROS act as critical regulatory mediators in many signaling processes that protect the cardiac myocyte from oxidative stress. Activation of PKC[135] and MAPKs[140] by ROS was implicated in ischemic and pharmacologic preconditioning. Hydrogen peroxide activated several MAPK subtypes in neonatal rat ventricular myocytes, but stimulation of p38 MAPK and subsequent phosphorylation of HSP-25/27 appeared to be particularly important in producing cardioprotection. ROS also activated G proteins ($G_i\alpha$ and $G_o\alpha$) that may likewise play a role in preconditioning.[141] Furthermore, there is indirect evidence linking ROS production by volatile anesthetics to activation of protein kinases implicated in the signaling pathways responsible for anesthetic preconditioning. For example, ROS scavengers inhibited isoflurane-induced PKC translocation.[60]

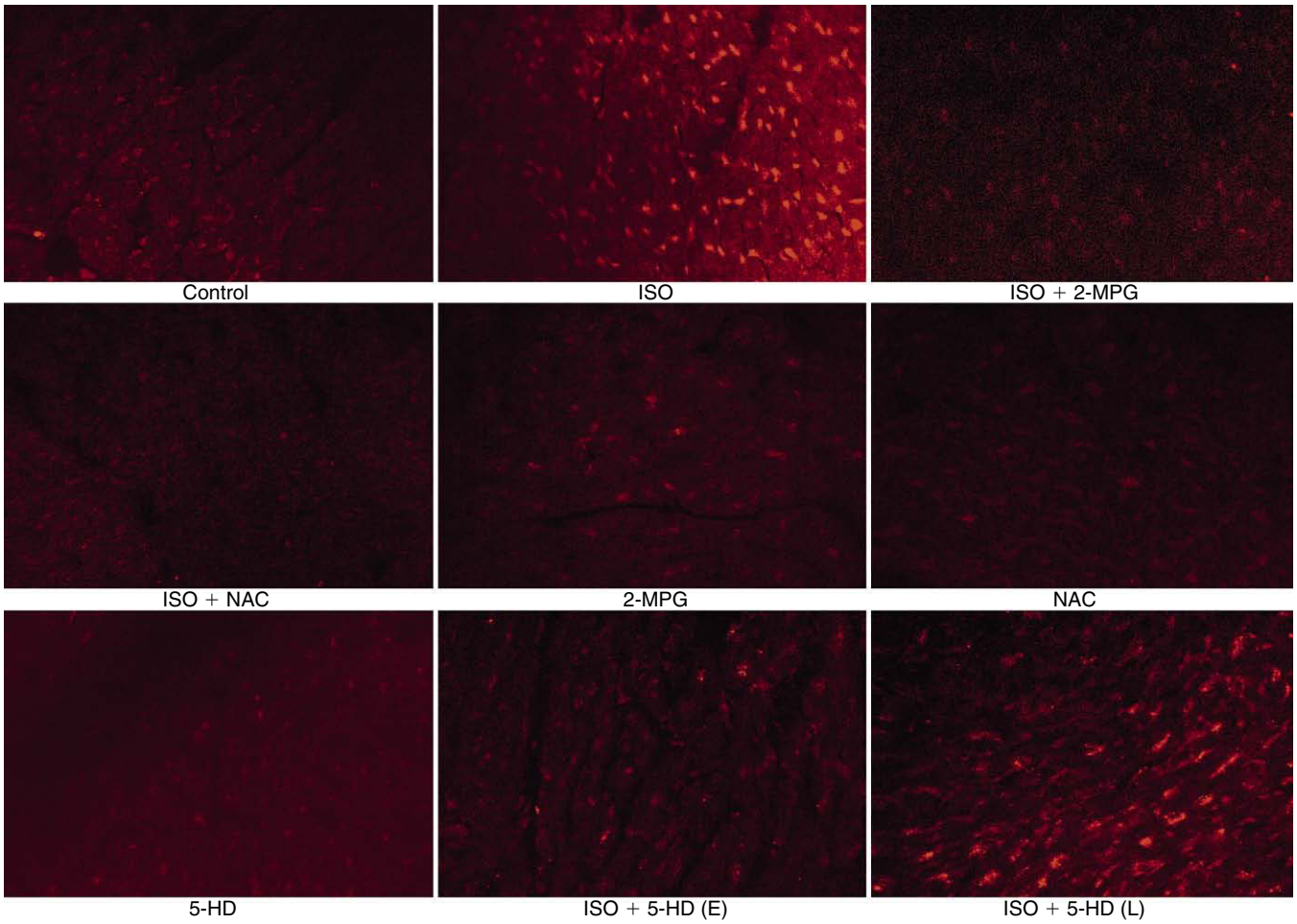

Figure 23-12 Superoxide anion production measured by dihydroethidium fluorescence in control rabbits (CON) and rabbits receiving *N*-acetylcysteine (NAC), *N*-2-mercaptopropionyl glycine (2-MPG), or 5-hydroxydecanoate (5-HD) in the presence and absence of a 1.0 minimum alveolar concentration of isoflurane (ISO). *Significantly ($P < .05$) different from isoflurane. *(From Tanaka K, Weihrauch D, Ludwig LM, et al: Mitochondrial adenosine triphosphate–regulated potassium channel opening acts as a trigger for isoflurane-induced preconditioning by generating reactive oxygen species. Anesthesiology 98:935-943, 2003.)*

The temporal relationship between mitochondrial K_{ATP} channel opening and ROS production during ischemic or pharmacologic preconditioning remains somewhat controversial. Mitochondrial K_{ATP} channels triggered preconditioning by generating ROS.[139] Opening of mitochondrial K_{ATP} channels by selective agonists generated ROS that appeared to be essential for activation of MAPK and the subsequent beneficial effects against ischemic injury. For example, the selective mitochondrial K_{ATP} channel agonist diazoxide enhanced cell viability after hypoxia and reoxygenation in vitro concomitant with the generation of oxygen-derived free radicals.[142] These beneficial actions were attenuated in cells pretreated with 5-HD or ROS scavengers, thus suggesting that the cardioprotection produced by mitochondrial K_{ATP} channel agonists occurs as a result of triggering by ROS. Morphine increased the fluorescence intensity of the hydrogen peroxide–sensitive probe 2′,7′-dichlorofluorescein, an action that was blocked by 5-HD.[143] These data also demonstrated a link between activation of mitochondrial K_{ATP} channels by opioids and ROS production. Diazoxide and another mitochondrial K_{ATP} channel opener (cromakalim) directly caused release of superoxide anion from complex I of the electron transport chain in isolated rat heart mitochondria concomitant with matrix alkalinization.[144] In contrast, other investigations suggested that ROS modulated activity of the mitochondrial K_{ATP} channels. For example, xanthine oxidase–derived superoxide anion–activated mitochondrial K_{ATP} channels from bovine ventricular myocardium reconstituted in lipid bilayers.[145] In addition, ROS triggered opening of mitochondrial K_{ATP} channels, and this event subsequently generated additional quantities of both ROS and NO.[146] Thus, whether mitochondrial K_{ATP} channel opening acts as a trigger or end-effector of ischemic or pharmacologic preconditioning remains unclear.[147] However, a complementary interaction between ROS and mitochondrial K_{ATP} channels appears to exist that may create a positive-feedback interaction between these elements and thereby contribute to cardioprotection.

Whether opening of mitochondrial K_{ATP} channels by volatile anesthetics precedes or follows ROS production during anesthetic preconditioning also remains unclear. Pretreatment with 5-HD or a ROS scavenger (e.g., *N*-acetylcysteine, *N*-2-mercaptoproprionyl glycine) before exposure to isoflurane abolished ROS production in rabbits.[77] However, 5-HD administered after discontinuation of isoflurane but before prolonged coronary artery occlusion only partially attenuated this effect, thus suggesting that mitochondrial K_{ATP} channel opening acted as a trigger for anesthetic preconditioning by producing ROS (Fig. 23-13). In contrast, sevoflurane-induced ROS production was not inhibited by 5-HD pretreatment in isolated guinea pig hearts.[148] Despite the rather equivocal nature of these two studies,[77,148] it is quite evident that ROS play a major role in anesthetic preconditioning in conjunction with mitochondrial K_{ATP} channels. Interestingly, a quantity of ROS that exceeds a critical threshold produced opening of the mPTP and a subsequent burst of ROS[149] that stimulated further release of additional ROS from other mitochondria.[150] This "ROS-induced ROS release" contributed to mPTP-dependent cell death in adult rat myocytes after ischemia-reperfusion.[151] Thus, volatile anesthetics or other mitochondrial K_{ATP} channel openers may prevent opening of the mPTP in an oxidant-sensitive fashion to produce cardioprotection. Desflurane preconditioning increased resistance of Ca^{2+}-induced mPTP opening,[130] but the dependence of this process on ROS has not been examined. Further investigation will be required

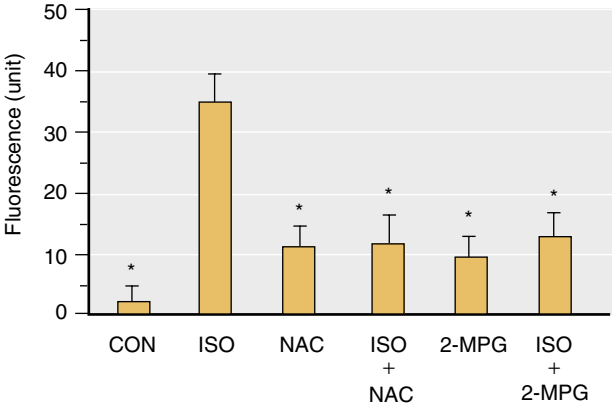

Figure 23-13 Superoxide anion production measured using dihydroethidium fluorescence in rabbits receiving (CON), *N*-acetylcysteine (NAC), or *N*-2-mercaptopropionyl glycine (2-MPG) in the presence and absence of 1.0 minimum alveolar concentration isoflurane (ISO). *Significantly ($P < 0.05$) different from isoflurane. *(From Tanaka K, Weihrauch D, Kehl F, et al: Mechanism of preconditioning by isoflurane in rabbits: a direct role for reactive oxygen species. Anesthesiology 97:1485-1490, 2002.)*

to more clearly define the precise relationship between ROS, mitochondrial K_{ATP} channels, and mPTP during anesthetic preconditioning.

NF-κB is an important transcription factor activated during ischemia-reperfusion injury that is involved in the inflammatory response to oxidative stress. The regulatory protein IκB-α maintains NF-κB in its inactive form under normal conditions, but activation of IκB-α kinase by ROS or inflammatory cytokines during ischemia removes this passive inhibition of NF-κB. Dissociated NF-κB translocates to the nucleus, binds to promoter gene regions, and initiates transcription. Ischemic preconditioning reduces NF-κB activation and blunts the production of inflammatory cytokines, chemokines, and adhesion molecules, thereby contributing to a reduction in myocardial necrosis. Sevoflurane preconditioning also attenuated activation of NF-κB and reduced NF-κB–dependent inflammatory gene expression in isolated rat hearts.[61] These data suggest that inhibition of NF-κB also mediates anesthetic preconditioning. The role of ROS in this process is currently unknown.

ROS derived from mitochondrial oxidative phosphorylation have been shown to mediate ischemic[152] and pharmacologic preconditioning.[143] The complex III inhibitor myxothiazol inhibited hypoxia-[152] and acetylcholine-induced[153] ROS production and abolished preconditioning in vitro. Volatile anesthetics inhibited electron transport chain complexes I and II in isolated cardiac mitochondria.[154,155] Sevoflurane-induced complex I inhibition was attenuated by a superoxide dismutase mimetic[155] and an NOS inhibitor,[156] thus suggesting that ROS, NO, or their reaction products may inhibit mitochondrial respiration through a positive-feedback mechanism to amplify free radical signals for triggering anesthetic preconditioning. Conversely, because myxothiazol, but not a complex I inhibitor, abolished isoflurane cardioprotection and ROS generation,[157] it was thought that complex III may be the source of ROS during anesthetic preconditioning. These data suggested the possibility that volatile anesthetics may modulate multiple sites of the electron transport chain either directly or indirectly through a ROS-mediated feedback mechanism. An

inhibitor of cyclooxygenase-2 (COX-2) (celecoxib) but not COX-1 (aspirin) or COX-3 (acetaminophen) blocked isoflurane-induced cardioprotection in rabbits,[158] so selective modulation of arachidonic acid metabolism by volatile anesthetics may represent another potential source of ROS during anesthetic preconditioning. Hence, at least three sources of oxygen- or nitrogen-derived free radicals (mitochondrial electron transport, NOS, and COX-2) have been identified to date, but whether other enzymes (e.g., nicotinamide adenine dinucleotide oxidase, lipoxygenase, xanthine oxidase, cytochrome P450) known to generate such reactive intermediates are involved in anesthetic preconditioning remains unknown.

The precise identity of the ROS involved in anesthetic preconditioning has also not been defined. Superoxide anion directly opened mitochondrial K_{ATP} channels in vitro,[145] thus implicating this reactive intermediate in ischemic preconditioning. Isoflurane directly enhanced ethidium fluorescence in rabbit myocardium independent of subsequent ischemia and reperfusion.[43,77] Dihydroethidium is oxidized by intracellular superoxide anion to produce ethidium, which subsequently binds to DNA, thereby further amplifying its fluorescence. These data strongly suggest that superoxide anion mediates anesthetic preconditioning. Sevoflurane also generated superoxide anion before ischemia and reperfusion in isolated hearts.[148] In contrast to these findings with superoxide anion, another ROS (hydrogen peroxide) stimulated PTK-dependent activation of phospholipase C in mouse embryonic fibroblasts and rendered these cells resistant to stress. Hydrogen peroxide activates G_i and G_o proteins,[141] as well as protein kinases involved in reducing cellular injury.[159] Hydrogen peroxide may also be converted to more reactive species that subsequently modify cysteine residues specific to G proteins and selectively activate these proteins.[160] Thus, hydrogen peroxide or its immediate free radical metabolites represent another group of ROS known to affect many of the signaling molecules implicated in anesthetic preconditioning. Dismutation of superoxide anion leads to the production of hydrogen peroxide, hydroxyl radical, and peroxynitrite, and these radicals may differentially alter channel or protein kinase activity. For example, superoxide anion and hydrogen peroxide enhanced, but peroxynitrite reduced Ca^{2+}-regulated K^+ channel function.[161] Whether anesthetic preconditioning also produces other ROS that activate mitochondrial K_{ATP} channels or inhibit the formation of intermediates that adversely affect these channels, such as peroxynitrite, remains to be elucidated.

Delayed Preconditioning by Volatile Anesthetics

Ischemic preconditioning is characterized by an early phase (limited to 1 to 3 hours after the brief ischemic stimulus) and a late, "delayed," or "second-window" phase of preconditioning that occurs after 24 hours and persists for as long as 72 hours after the ischemic episode.[162] Several protein kinases,[163,164] COX-2,[165] NOS,[166] and NF-κB[167] have been implicated in the signaling responsible for delayed preconditioning. NO donors, G protein–coupled receptor ligands (e.g., δ-opioid, adenosine), and mitochondrial K_{ATP} channel openers mimic the protective effects of delayed preconditioning. Experimental evidence indicates that volatile anesthetics may also be capable of producing late pharmacologic preconditioning. Tonkovic-Capin and colleagues first described delayed preconditioning by isoflurane in isolated perfused neonatal rabbit hearts subjected to a 2-hour exposure to 1% of the volatile agent 24 hours before the onset of ischemia.[168] Remote administration of isoflurane reduced myocardial infarct size and enhanced the recovery of LV pressure development in pretreated rabbit hearts as compared with those that had not previously been exposed to the volatile agent.[168] The magnitude of the delayed cardioprotective effect was similar to that observed during isoflurane preconditioning. The second window of cardioprotection produced by isoflurane was abolished by the mitochondrial K_{ATP} channel antagonist 5-HD and was also partially attenuated by the selective sarcolemmal K_{ATP} channel antagonist HMR-1098.[168] Sevoflurane-delayed preconditioning was also inhibited by pretreatment with 5-HD.[169] These findings established a central role for K_{ATP} channels in anesthetic late preconditioning. Remote exposure to 2.5% sevoflurane for 1 hour decreased infarct size, reduced release of creatine kinase, improved LV function, maintained intracellular ATP concentrations, and preserved intracellular Na^+ and Ca^{2+} homeostasis in isolated rat hearts but not in those not receiving sevoflurane pretreatment.[170] The salutary actions of sevoflurane were more pronounced at 48 than at 24 hours after exposure to the volatile agent.[170] Acute preconditioning with sevoflurane also conferred additional cardioprotection after ischemic late preconditioning in rabbits through activation of mitochondrial K_{ATP} channels.[171]

In contrast to the findings in rabbits and rats, exposure to 1.0 MAC isoflurane for 6 hours did not produce late preconditioning against myocardial infarction in dogs when the volatile agent was administered 24 hours before prolonged coronary artery occlusion and reperfusion in vivo.[172] The results occurred independent of alterations in systemic hemodynamics or coronary collateral perfusion and suggested that delayed cardioprotection by volatile anesthetics may be species specific.[172] Intravenous emulsified sevoflurane produced delayed preconditioning against myocardial infarction in rabbits.[173] The blood concentration of sevoflurane required for this beneficial effect was equivalent to a MAC value of approximately 0.17, suggesting that only a small amount of the volatile agent is required to produce cardioprotection. Similarly, inhalation of subanesthetic (0.5% or 1.0%) concentrations of sevoflurane by healthy volunteers produced time-dependent alterations in gene expression in white blood cells, including several transcripts that have been strongly implicated in late ischemic preconditioning.[174] Sevoflurane also reduced expression of the proinflammatory L-selectin (CD62L) in granulocytes concomitant with increased resistance to inflammatory activation 24 and 48 hours after exposure to the volatile agent.[174] These exciting data provided the first evidence that volatile anesthetics have the potential to produce a second window of cardioprotection in humans.

Several investigations have begun to explore the mechanisms responsible for delayed anesthetic preconditioning in experimental animals. COX-2 mediated late ischemic and δ-opioid–induced pharmacologic preconditioning in rabbits. Delayed ischemic and δ-opioid–induced pharmacologic preconditioning was also shown to increase COX-2 transcription and translation and enhance myocardial concentrations of prostaglandin E_2 (PGE_2) and 6-keto-$PGF_2\alpha$ 24 hours after the initial ischemic stimulus.[165] A role for COX-2 has been demonstrated in the second window of isoflurane preconditioning. Administration of the selective COX-2 antagonist celecoxib after but not before remote isoflurane exposure abolished reductions in myocardial infarct size associated with the volatile agent.[175] These data indicate that COX-2 functions as a mediator but not as a trigger of delayed isoflurane cardioprotection.[175] In contrast to the

findings with late ischemic and δ-opioid–induced preconditioning,[165] COX-2 protein expression was unaffected by remote isoflurane administration, suggesting that an increase in COX-2 activity may instead mediate the cardioprotective effect of volatile anesthetics in this setting.[175] Inducible NOS (iNOS) regulates COX-2 activity during the late phase of ischemic preconditioning.[176] NO functions as a trigger and mediator of this second window of ischemic preconditioning.[177] Neuronal NOS (nNOS) may also mediate the late phase of ischemic preconditioning in concert with COX-2.[178] A central role for NO metabolism was described during isoflurane-induced delayed preconditioning in rabbits.[179] Administration of the nonselective NOS antagonist L-arginine methyl ester (L-NAME), but not selective iNOS or nNOS inhibitors, before remote isoflurane exposure or coronary artery occlusion and reperfusion abolished reductions in infarct size produced by the volatile agent.[179] Increases in endothelial NOS (eNOS) but not iNOS transcription and translation were also observed during the second window of isoflurane preconditioning.[179] These data demonstrated that the NO produced by eNOS triggers and mediates late isoflurane preconditioning in rabbits. Administration of isoflurane 24 to 72 hours before global ischemia and reperfusion also reduced infarct size and preserved LV function in isolated rat hearts.[180] In contrast to the findings in rabbits, upregulation and activation of iNOS mediated isoflurane delayed preconditioning in rats.[180] Interestingly, a second window of isoflurane preconditioning did not occur in female rabbits.[181] This gender specificity may be related to an estrogen-related upregulation of eNOS in female rabbits that confers substantial protection against infarction independent of subsequent remote administration of a volatile anesthetic.[181]

A role for reactive oxygen and nitrogen species in isoflurane delayed preconditioning has also been demonstrated in rats.[182] Reductions in infarct size occurred after remote 2-hour inhalation of isoflurane concentrations as low as 0.8%, which confirmed that subanesthetic concentrations of a volatile anesthetic are capable of providing a second window of cardioprotection.[173,174] Pretreatment with a superoxide anion scavenger or a nonselective NOS antagonist abolished the protection produced by remote isoflurane exposure. As observed in isoflurane acute preconditioning,[77] remote administration of the volatile agent increased ethidium fluorescence consistent with the generation of superoxide anion, and pretreatment with an inhibitor of the mitochondrial electron transport chain inhibited this response.[182] Delayed cardioprotection mediated by 12-lipoxygenase expression and activity has been linked to opioid receptor activation.[183] 12-Lipoxygenase was also demonstrated to mediate isoflurane delayed preconditioning in mice.[184] A selective inhibitor of 12-lipoxygenase abolished reductions in infarct size produced by the administration of isoflurane 24 hours before prolonged coronary occlusion and reperfusion. These cardioprotective effects were accompanied by enhanced expression of 12-lipoxygenase localized to the intercalated disk regions adjoining adjacent ventricular myocytes.[184]

Postconditioning by Volatile Anesthetics

The first minutes of reperfusion are critical for salvaging ischemic myocardium, but reperfusion also paradoxically exacerbates the initial damage caused by the ischemic insult.[185] Modulation of conditions during reperfusion favorably affects the extent of ischemic injury. Studies of controlled reperfusion after ischemia have indicated that gradual reperfusion at low intracoronary pressure reduces myocardial damage.[186,187] Such control over coronary hemodynamics during early reperfusion reduced myocardial infarct size, preserved postischemic contractile function, limited endothelial injury, and attenuated myocardial edema. Despite these data, most of the experimental and clinical research examining the adverse consequences of ischemia-reperfusion injury and how they may be minimized has instead focused on interventions performed before the onset of ischemia. Clearly, coronary artery occlusion cannot be temporally predicted in most patients with acute myocardial infarction with any degree of certainty, and as a result, application of preconditioning strategies may be primarily limited to clinical situations in which the precise onset of ischemia is well defined (e.g., inflation of an angioplasty balloon, application of an aortic cross-clamp during cardiopulmonary bypass).

In 2003, Zhao and Vinten-Johansen reported that brief episodes of coronary artery occlusion conducted during early reperfusion after prolonged ischemia reduced myocardial infarct size, attenuated neutrophil accumulation, partially inhibited the generation of cytotoxic reactive oxygen species, decreased endothelial dysfunction, and diminished apoptosis.[187-189] This phenomenon was initially termed "ischemic postconditioning" and later shortened to simply "postconditioning." The reductions in myocardial infarct size caused by postconditioning were shown to be remarkably similar to those produced by ischemic preconditioning.[189] Activation of ERK1/2 and formation of NO were initially shown to mediate this form of cardioprotection.[189,190] Subsequently, the prosurvival PI3K-Akt signaling cascade, including the downstream enzymes eNOS and target of rapamycin (TOR)/70-kd ribosomal protein s6 kinase (p70s6K), was shown to play a central role in postconditioning.[191] These signaling elements are critical mediators of cellular necrosis and apoptosis via their actions on the balance of proapoptotic and antiapoptotic proteins, the activity of the regulatory enzyme glycogen synthase kinase-3β (GSK-3β), and the transition state of the mPTP (Fig. 23-14).[192,193] Postconditioning has also been shown to occur in the human heart.[194] Administration of a diverse variety of drugs (e.g., G protein–coupled receptor ligands [adenosine, bradykinin, opioids], insulin, statins, urocortin, growth factors [basic fibroblast growth factor, insulin-like growth factor I]) immediately before or during early reperfusion mimics the beneficial actions of postconditioning. Many elements of prosurvival signaling mediate this "pharmacologic postconditioning."[195]

Although anesthetic preconditioning has been studied extensively and many of the mechanisms responsible for this phenomenon have been characterized in detail, substantially less attention has been directed toward exploration of the possible beneficial effects of volatile anesthetics when administered immediately before or during reperfusion (termed "anesthetic postconditioning"). Nevertheless, some experimental evidence indicates that volatile anesthetics are capable of exerting cardioprotective effects under these conditions. The older volatile agent halothane prevented reoxygenation-induced hypercontracture of cardiac myocytes in vitro, a potential cause of myocyte necrosis during early reperfusion.[196] Halothane also reduced reperfusion injury after regional ischemia in rabbit hearts.[197] Desflurane and sevoflurane reduced infarction size when administered during the first 15 minutes of reperfusion in rabbits.[198] Isoflurane enhanced the functional recovery of isolated rat hearts when administered solely during reperfusion.[58] The salutary actions of sevoflurane during reperfusion were shown to be dose dependent in rats.[199]

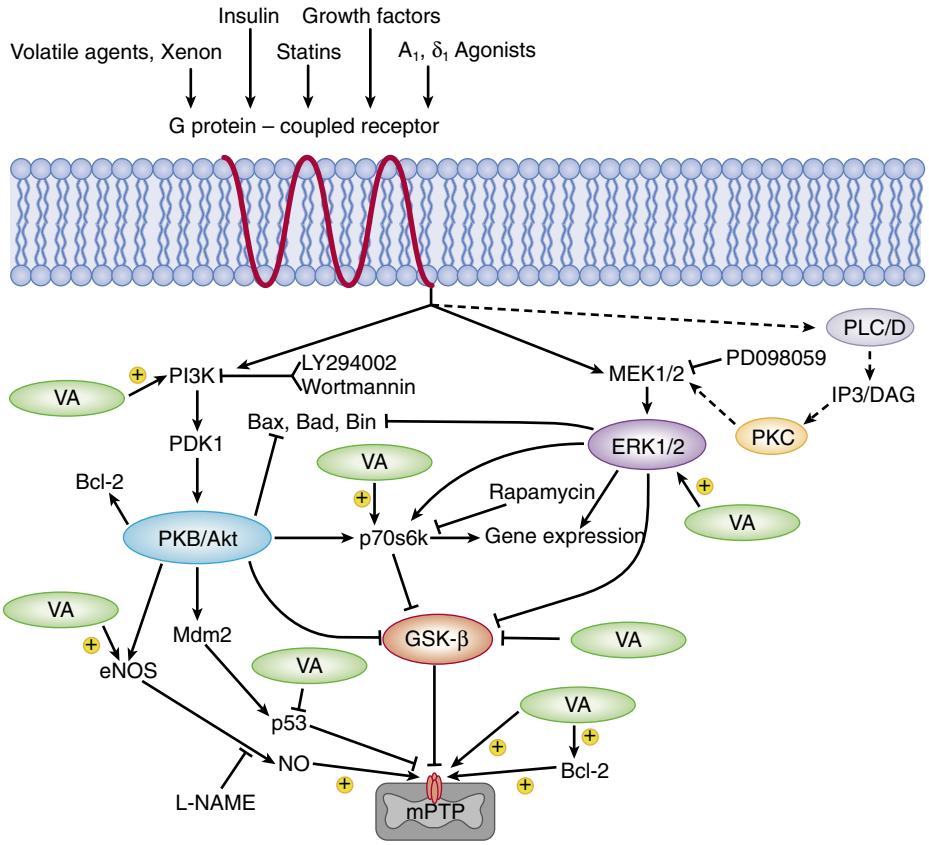

Figure 23-14 Schematic illustration depicting the potential sites of action of volatile anesthetics (VA) on cardioprotective signaling during early reperfusion. G protein–coupled receptor ligands (e.g., adenosine A_1, opioid δ_1), VA, insulin, statins, and growth factors activate parallel phosphoinositol 3-kinase (PI3K) or extracellular signal–regulated kinase (ERK1/2) cascades to produce protection. G protein–coupled activation of protein kinase C (PKC) by phospholipases (PLC/D) through the second messengers diacylglycerol (DAG) and inositol triphosphate (IP3) also contributes to activation of PI3K and ERK1/2. PI3K phosphorylates phosphoinositide-dependent kinase (PDK1), which activates Akt (also known as protein kinase B [PKB]). This moiety stimulates the activity of antiapoptotic proteins (e.g., B-cell lymphoma-2 [Bcl-2]) and simultaneously inhibits the activity of proapoptotic proteins (e.g., Bax, Bad, Bim, caspases). Akt/PKB also inhibits the β-isoform of glycogen synthase kinase (GSK-β) and activates endothelial nitric oxide synthase (eNOS), 70-kd ribosomal protein s6 kinase (p70s6K), and murine double-minute-2 (Mdm2) protein. p70s6K also inhibits GSK-β activity. Nitric oxide (NO) produced by eNOS inhibits whereas Mdm2-induced phosphorylation of the proapoptotic protein p53 opens the mitochondrial permeability transition pore (mPTP). Inhibition of GSK-β and activation of mitochondrial K_{ATP} channels also act to close the mPTP. The transition state of the mitochondrial pore is critical for preservation of mitochondrial integrity and cell viability during ischemia and reperfusion. Activation of ERK1/2 also inhibits GSK-β and blocks the formation of proapoptotic proteins. LY294002 and wortmannin, rapamycin, PD 098059, and L-arginine methyl ester (L-NAME) block the activity of PI3K, p70s6K, ERK1/2, and eNOS, respectively. Volatile anesthetics have been proposed to enhance the activity of PI3K-Akt, p70s6k, ERK1/2, and eNOS. Volatile anesthetics have also been suggested to directly inhibit GSK-β and mPTP concomitant with enhanced expression of Bcl-2 and inhibition of p53. Volatile anesthetic–induced activation of mitochondrial K_{ATP} channels also inhibits mPTP. These actions of volatile anesthetics may contribute to the cardioprotective effects during early reperfusion.

Administration of sevoflurane after ischemia also improved contractile and metabolic function concomitant with reduced myoplasmic Ca^{2+} loading in isolated guinea pig hearts.[200]

The mechanisms by which volatile anesthetics produce cardioprotection during reperfusion have yet to be firmly established. Halothane abolished reoxygenation-induced attenuation of SR-dependent oscillations of intramyoplasmic Ca^{2+} concentration in isolated cardiac myocytes.[196] These[196] and other findings[200] suggested that volatile anesthetics may prevent intracellular Ca^{2+} overload during early reperfusion. Isoflurane and sevoflurane also reduced postischemic adhesion of polymorphonuclear leukocytes.[201] However, the precise mechanisms by which volatile anesthetics act to reduce intracellular Ca^{2+} overload or attenuate the adverse consequences of large quantities of reactive oxygen intermediates during early reperfusion were not elucidated by these previous studies. Although it is certainly tempting to propose that similar signaling pathways mediate anesthetic preconditioning and postconditioning, substantial differences between the genomic responses associated with these phenomena have been demonstrated.[202] These findings suggest that the mechanisms responsible for anesthetic preconditioning and postconditioning may not be identical.

Chiari and coworkers demonstrated that brief exposure to 1.0 MAC isoflurane administered during the final 3 minutes of coronary artery occlusion and the first 2 minutes of reperfusion reduces myocardial infarct size in rabbits.[203] The degree of myocardial preservation observed with isoflurane postconditioning was similar in magnitude to the cardioprotection afforded by isoflurane preconditioning in an identical experimental preparation.[77] Postconditioning with 0.5 MAC isoflurane (a concentration that did not produce cardioprotection alone) also reduced the time threshold required for ischemic postconditioning. The beneficial actions of isoflurane before and during early reperfusion with or without subthreshold ischemic postconditioning

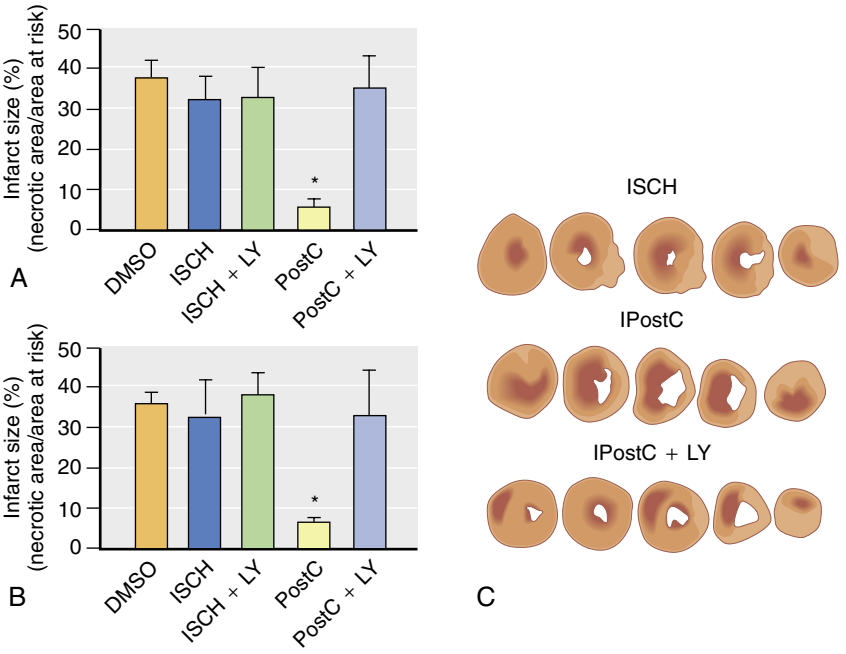

Figure 23-15 Infarct size was determined by 1% triphenyltetrazolium chloride staining. Areas infarcted in vivo by coronary artery ligation were excluded from determination of infarct size (**A**). The scarred chronic infarct resulting from coronary ligation was distinguished from fresh infarcts (*salmon pink*). Release of lactate dehydrogenase during reperfusion (**B**) served as an independent method to estimate infarct size. **C,** Transverse sections of representative experiments. DMSO, dimethyl sulfoxide (<0.1%; used to dissolve the phosphatidylinositol-3′-kinase antagonist LY294002); PostC, ischemic postconditioning; ISCH, unprotected remodeled hearts exposed to ischemia-reperfusion alone; LY, LY294002 (15 μM); PostC, anesthetic postconditioning. Data are given as means ± SD ($n = 5$ in each group). *$P < 0.05$ versus ISCH. *(From Feng J, Fischer G, Lucchinetti E, et al: Infarct-remodeled myocardium is receptive to protection by isoflurane postconditioning. Role of protein kinase B/Akt signaling. Anesthesiology 104:1004-1014, 2006.)*

were blocked by pretreatment with the selective PI3K antagonist wortmannin. Isoflurane also increased phosphorylation of the PI3K downstream target protein Akt, and this effect was also inhibited by wortmannin pretreatment. These data demonstrated for the first time that activation of the PI3K signaling pathway directly mediates the protective effects of isoflurane postconditioning in vivo.[203] A central role for PI3K-Akt signaling in isoflurane postconditioning was subsequently demonstrated in infarct-remodeled myocardium as well (Fig. 23-15), thus suggesting that postconditioning by volatile anesthetics may also be maintained in diseased myocardium.[204]

Reperfusion after a prolonged ischemic insult initiates or hastens apoptosis.[205] Isoflurane postconditioning reduced cytochrome *c* translocation from mitochondria (an important early marker of apoptosis mediated by PI3K-Akt) and decreased the number of terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL; another indicator of apoptosis)-positive ventricular myocytes in situ.[206] These data provided the first direct evidence indicating that isoflurane postconditioning preserves myocardial integrity, in part by attenuating apoptotic cell death. Volatile anesthetics were previously shown to abolish norepinephrine-induced apoptosis in rat ventricular myocytes as indicated by reductions in TUNEL-positive cell staining, attenuation of increases in annexin V staining (an index of DNA laddering), and inhibition of elevated caspase-9 activity.[207]

When administered in a dose that did not alter infarct size alone, morphine enhanced isoflurane postconditioning against myocardial infarction.[206] The protective effects of the combination of subthreshold doses of morphine and isoflurane during early reperfusion were abolished by pretreatment with wortmannin, thus indicating that the cardioprotection observed was mediated by activation of PI3K. The nonselective opioid antagonist naloxone also inhibited the protective effects of morphine, isoflurane, and their combination during early reperfusion, thus suggesting that opioid receptor activation also mediates isoflurane postconditioning and its augmentation by morphine. Cardioprotection by opioids during reperfusion occurs as a result of activation of δ_1-opioid receptors,[208] and postconditioning against infarction by isoflurane and its potentiation by the clinically relevant opioid morphine may also be mediated by the δ_1-opioid receptor. This hypothesis remains to be tested, but a role for the δ_1-opioid receptor in anesthetic preconditioning was described previously.[59]

Activation of ERK1/2 is a redundant mechanism by which downstream elements of the PI3K cascade may be stimulated to favorably modulate reperfusion injury.[62] ERK1/2 mediates ischemic[209] and pharmacologic[210] postconditioning and also plays an important role in the preconditioning produced by volatile anesthetics.[109,114] Selective inhibition of ERK1/2 abolished the reductions in infarct size produced by isoflurane postconditioning.[211] Both PI3K-Akt and ERK1/2 phosphorylate TOR/p70s6K, an important regulator of protein translation.[62] A selective inhibitor of this enzyme (rapamycin) abolished cardioprotection during ischemic[191] and pharmacologic[208] postconditioning. Isoflurane postconditioning was also inhibited by rapamycin in normal and infarct-remodeled myocardium, thus implicating a role for p70s6K in this phenomenon as well.[211,212]

PI3K-Akt activates eNOS and increases the formation of NO,[191] and a central role for NO has been demonstrated in postconditioning by ischemia[191] or G protein–coupled receptor ligands.[210] A nonselective NOS inhibitor, but not selective iNOS or nNOS inhibitors, abolished reductions in infarct size produced by the administration of isoflurane before and during early reperfusion in rabbits, a finding suggesting that eNOS mediates isoflurane postconditioning.[211] Furthermore, isoflurane inhaled at the onset of reperfusion enhanced the cardioprotective effect of ischemic postconditioning through a NO-dependent mechanism in rabbits.[213] Isoflurane postconditioning also enhanced expression of eNOS in infarct-remodeled rat myocardium, and a selective PI3K antagonist inhibited this isoflurane-induced phosphorylation of eNOS.[204] These data suggest that NO derived from

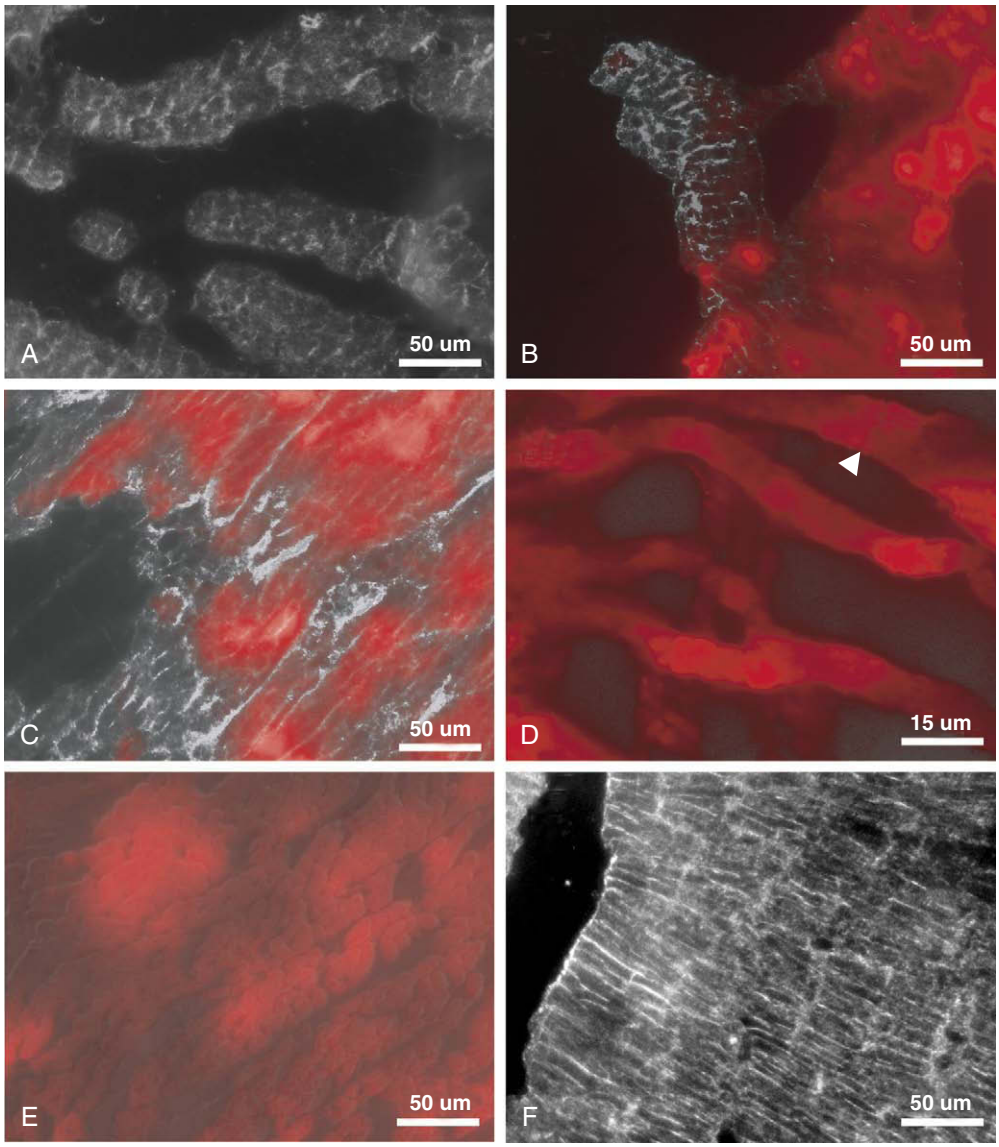

Figure 23-16 Postischemic uptake of MitoTracker Red 580 in the mitochondria of isolated perfused rat hearts. Unprotected hearts show no staining (**A**) except for superficial epicardial layers of the myocardium (**B**). In contrast, postconditioned protected hearts exhibit marked accumulation of MitoTracker Red 580 in tissue (**C** and **D**), similar to control hearts not subjected to ischemia-reperfusion (time-matched perfusion) (**E**). Atractyloside, a direct opener of the mitochondrial permeability transition pore, completely abolished the isoflurane effects (**F**). **A** through **F** are epifluorescence micrographs (*red channel*) merged with phase-contrast images. **D** shows at higher magnification the syncytial net of postconditioned myocytes containing brightly staining mitochondria (*red channel*). The *arrow* indicates intercalated disks. *(From Feng J, Lucchinetti E, Ahuja P, et al: Isoflurane postconditioning prevents opening of the mitochondrial permeability transition pore through inhibition of glycogen synthase kinase 3β. Anesthesiology 103:987-995, 2005.)*

eNOS plays an important role in anesthetic postconditioning in healthy and infarct-remodeled myocardium.

Inhibition of mPTP has been shown to mediate ischemic postconditioning.[214] Isoflurane postconditioning was abolished by the mPTP opener atractyloside and enhanced by the mPTP inhibitor cyclosporine in rabbits.[215] Similarly, atractyloside and a selective PI3K antagonist (LY294002) abolished isoflurane postconditioning in rats.[212] LY294002 also inhibited phosphorylation of the regulatory enzyme GSK-3β and opened the mPTP as determined by nicotinamide adenine dinucleotide measurements (Fig. 23-16).[212] Taken together, these data[212,215] indicate that administration of isoflurane during early reperfusion protects against reperfusion injury by preventing mPTP opening via a PI3K-dependent mechanism through inhibition of GSK-3β.

Experimental evidence has strongly suggested that mitochondrial K_{ATP} channel activation is an end-effector during anesthetic preconditioning.[56] Opening of mitochondrial K_{ATP} channels during ischemic or pharmacologic preconditioning may produce small alterations in intramitochondrial homeostasis that promote protection against subsequent ischemic damage through energy-dependent regulation of mitochondrial matrix volume. Opening of mitochondrial K^+ influx pathways favorably regulated matrix volume and improved function during simulated ischemia and reperfusion.[216] A selective mitochondrial K_{ATP} channel antagonist (5-HD) inhibited isoflurane postconditioning,[215] suggesting that mitochondrial K_{ATP} channel opening by brief administration of isoflurane during early reperfusion may be responsible for cardioprotection in rabbits. Mitochondrial K_{ATP} channels mediate

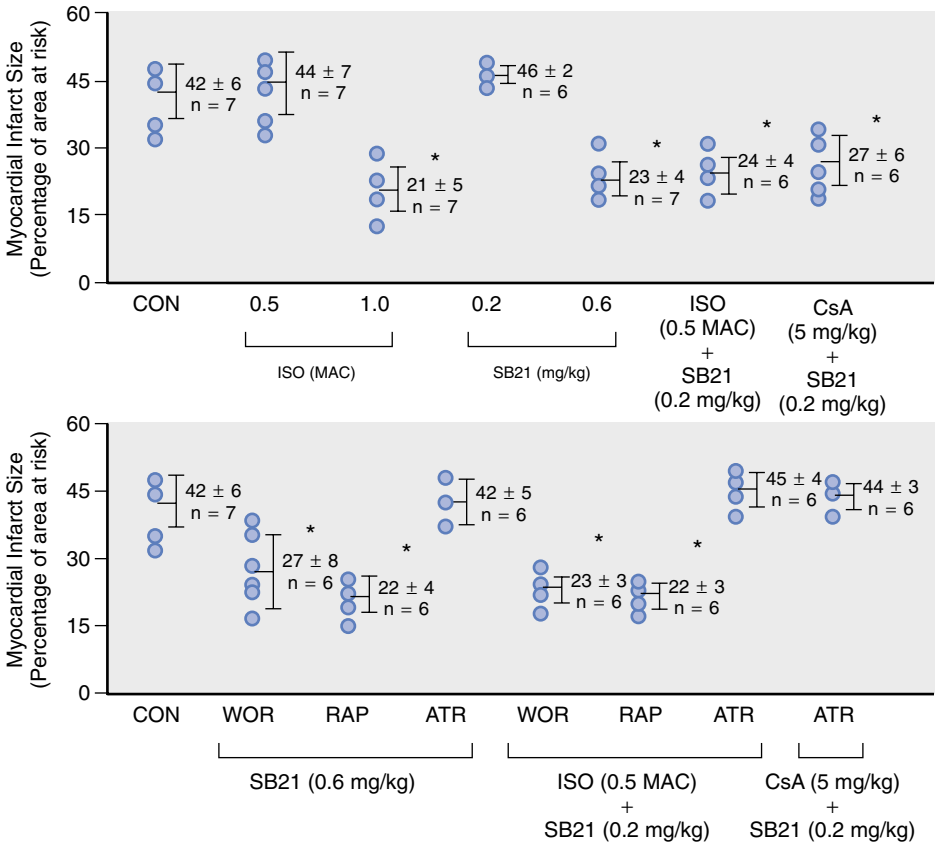

Figure 23-17 Myocardial infarct size depicted as a percentage of the left ventricular area at risk in rabbits receiving 0.9% saline (control, CON), isoflurane (ISO, 0.5 or 1.0 minimum alveolar concentration [MAC]), SB 216763 (SB21, 0.2 or 0.6 mg/kg), 0.5 MAC ISO plus 0.2 mg/kg SB21, or cyclosporine (CsA, 5 mg/kg) plus 0.2 mg/kg SB21 (*top panel*). Infarct sizes in rabbits receiving 0.6 mg/kg SB21 or 0.5 MAC ISO plus 0.2 mg/kg SB21 in the presence of wortmannin (WOR, 0.6 mg/kg), rapamycin (RAP, 0.25 mg/kg), or atractyloside (ATR, 5 mg/kg) are depicted in the *bottom panel*. Infarct sizes in rabbits receiving A (CsA, 5 mg/kg) plus 0.2 mg/kg SB21 in the presence of atractyloside pretreatment are also illustrated in the *bottom panel*. Each point represents a single experiment. All data are means ± SD. *Significantly ($P < .05$) different from CON. *(From Pagel PS, Krolikowski JG, Neff DA, et al: Inhibition of glycogen synthase kinase potentiates isoflurane-induced protection against myocardial infarction during early reperfusion in vivo. Anesth Analg 102:1348-1354, 2006.)*

sevoflurane postconditioning in rats.[217] However, a close interaction between mitochondrial K_{ATP} channels and mPTP was previously identified during diazoxide and desflurane preconditioning.[127,130] Hence, isoflurane postconditioning may not be solely attributable to the actions of the volatile agent on mitochondrial K_{ATP} channels alone but, instead, may be dependent on the interaction between mitochondrial K_{ATP} channel opening and mPTP inhibition.

GSK-3β is an important mediator of cellular function whose activation has been implicated in the pathogenesis of diabetes mellitus and Alzheimer's disease. Inhibition of GSK-3β may play a critical role in protection against myocardial ischemia-reperfusion injury inasmuch as selective blockade of the enzyme mimics the beneficial actions of ischemic preconditioning[218] and opioid postconditioning.[208] GSK-3β was shown to be a central regulator of several prosurvival signaling enzymes (e.g., PI3K, p70s6K, PKC, protein kinase A) during cardioprotection against hypoxia-reoxygenation injury in isolated ventricular myocytes.[192] Selective inhibition of GSK-3β also limited mPTP opening.[192] Thus, many endogenous signaling pathways appear to converge on and regulate the activity of GSK-3β, thereby favorably modulating mitochondrial permeability transition and producing protection against ischemia-reperfusion injury. Administration of isoflurane during early reperfusion phosphorylated and inactivated GSK-3β in a PI3K- and mPTP-dependent fashion concomitant with cardioprotection in isolated perfused rats.[212] A selective inhibitor of GSK-3β (SB 216763) was also shown to lower the threshold of isoflurane postconditioning against infarction in rabbits.[219] The salutary actions of the effects of GSK-3β inhibition were abolished by the mPTP opener atractyloside but not the PI3K or p70s6K antagonists wortmannin or rapamycin.[219] These data suggest that isoflurane postconditioning is mediated by the combined actions of SB 216763 and volatile anesthetic on the mPTP and provide pharmacologic evidence suggesting that isoflurane produces a direct inhibitory effect on GSK-3β independent of its actions on PI3K and p70s6K activity (Fig. 23-17).

Mitochondria are the putative target of several apoptotic proteins that either directly damage mitochondrial membranes or indirectly open the mPTP and lead to release of cytochrome *c*. Phosphorylation of Bad by PI3K results in its sequestration from mitochondria and inhibits apoptosis.[220] Similarly, activation of PI3K prevents Bax-induced apoptosis by inhibiting the critical conformational change required for its translocation to mitochondrial membranes.[221] Activation of PI3K has also been shown to phosphorylate and inactivate procaspase-9 and thereby inhibit this important mediator of apoptotic cell death.[222] The mechanisms by which inhibition of GSK-3β favorably affects the mPTP to cause protection against ischemia-reperfusion injury have not been clearly elucidated. Activated GSK-3β binds to and promotes the actions of p53,[223] a tumor suppressor protein known to interact with and stimulate the disruption of mitochondria during apoptosis.[224] p53 translocates to mitochondria, increases mitochondrial membrane permeability by directly interacting with Bax, abolishes $\Delta\Psi_m$, and causes the release of cytochrome *c*.[225]

A central role for inhibition of p53 in myocardial and neuronal protection against cellular injury has been characterized. Activation of p53 by hypoxia or ROS[226] produces immediate or delayed programmed cell death by stimulating mitochondrial apoptotic pathways and enhancing the transcription of other proapoptotic proteins (e.g., Bax, apoptosis-inducing factor

[AIF]).[227] Enhanced p53 expression was observed after ischemia and reperfusion in isolated rat ventricular myocytes, and ischemic preconditioning substantially reduced this effect.[228] Ischemic preconditioning also attenuated p53 transcription and translation in hippocampal pyramidal neurons in a rat model of global forebrain ischemia and reperfusion.[229] Inhibition of p53 with the selective antagonist pifithrin-α or stimulated degradation of the protein by PI3K-mediated phosphorylation of murine double-minute-2 protein (Mdm2), an oncogenic factor known to facilitate p53 degradation, has previously been shown to protect against ischemic injury in isolated rat hearts.[230] Phosphorylated Mdm2 associates with p53 and inactivates the latter protein by blocking its active site and promoting subsequent degradation of it through ubiquitin complex formation.[231] Thus, ischemic preconditioning may have abrogated the deleterious actions of p53 by PI3K-mediated phosphorylation of the downstream moiety Mdm2.[230] Direct inhibition of p53 with pifithrin-α protected against neuronal cell death produced by ischemia, excitotoxins, or amyloid β-peptide.[232] Targeted deletion of p53 prevented cardiac rupture after infarction in transgenic mice, presumably by simulating the protective actions of ischemic preconditioning via inhibition of apoptotic cell death, thereby preserving myocardial integrity.[233] Inhibition of p53 by pifithrin-α was recently demonstrated to lower the threshold of isoflurane postconditioning in vivo.[234] Blockade of this action by atractyloside indicated that the cardioprotection observed was mediated by actions of the selective p53 inhibitor and the volatile anesthetic on the mPTP. Thus, experimental evidence suggests that administration of isoflurane during early reperfusion may affect the interaction between GSK-3β and p53 to modulate the transition state of the mPTP.

Bcl-2 protein has been identified in the outer mitochondrial membrane, regulates the mPTP, and inhibits apoptosis.[235] Overexpression of Bcl-2 attenuated apoptosis and protected against ischemia-reperfusion injury in transgenic mice.[236] A key interaction between Bcl-2 and mPTP inhibition was previously implicated during delayed ischemic preconditioning.[129] A selective inhibitor (HA14-1) of Bcl-2 abolished isoflurane-induced Bcl-2 expression and attenuated reductions in apoptosis (e.g., cytochrome *c* release, TUNEL staining) in isolated atrial and ventricular myocytes subjected to hypoxia-reoxygenation injury, hydrogen peroxide, or activated neutrophils.[126] HA14-1 also inhibited isoflurane and ischemic postconditioning in vivo but did not affect cardioprotection produced by the direct mPTP inhibitor cyclosporine.[237] Thus, the salutary actions of isoflurane on transient, repetitive ischemia during early reperfusion may also occur as a result of indirect modulation of the mPTP mediated "upstream" by Bcl-2.[237] In fact, PI3K has been shown to phosphorylate and activate Bcl-2 concomitant with inactivation of proapoptotic proteins, including Bad, Bax, and p53.[238] As a result, activation of PI3K signaling by isoflurane postconditioning appears to produce cardioprotection by several redundant mechanisms that affect apoptotic protein homeostasis.

Coronary Vascular Effects of Volatile Anesthetics in Humans

Evaluation of the actions of volatile anesthetics on the human coronary circulation is difficult not only because the methods used to determine coronary blood flow in humans are limited but also because interpretation of clinical findings during anesthesia is complicated by changes in hemodynamics, the impact of surgery, and the use of adjuvant anesthetics or vasoactive drugs. Halothane decreases MVo_2 and variably alters coronary blood flow in patients with coronary artery disease, but metabolic or electrocardiographic evidence of ischemia has not been observed during halothane anesthesia. A report published in 1983[239] described the occurrence of myocardial ischemia, as indicated by new electrocardiographic changes and abnormal myocardial lactate extraction, in 10 of 21 patients anesthetized with isoflurane who were undergoing major vascular surgery. Five patients were treated with phenylephrine and pacing to return arterial pressure and heart rate to control values, and after these interventions, the electrocardiographic and metabolic derangements resolved in two of the five patients. Despite the apparent dependence of these new episodes of myocardial ischemia on alterations in systemic hemodynamics, the author[239] proposed that isoflurane had caused coronary steal in these patients, even though no specific evidence of redistribution of blood flow between normal and collateral-dependent zones was presented. The data have not been uniformly supported by subsequent studies. Coronary blood flow remained unchanged during isoflurane anesthesia in patients undergoing coronary artery bypass graft (CABG) surgery, but coronary sinus O_2 content increased consistent with modest coronary vasodilation. Isoflurane alone did not produce electrocardiographic or metabolic evidence of ischemia. Instead, myocardial ischemia occurring during isoflurane anesthesia was most often associated with tachycardia or hypotension. In addition, isoflurane actually increases the tolerance to pacing-induced ischemia in patients with coronary artery disease. Comparison of studies examining the effects of isoflurane on the incidence of intraoperative myocardial ischemia was also complicated by differences in patient age, surgical procedure, operative time, and preoperative LV ejection fraction. Importantly, compelling evidence demonstrating redistribution of coronary blood flow away from ischemic to normal myocardium in humans anesthetized with isoflurane has yet to be reported.

The incidence of intraoperative myocardial ischemia in susceptible patients has been difficult to define. Less than 50% of intraoperative ischemic episodes have been linked to alterations in systemic hemodynamics.[240] The strongest predictor of intraoperative ischemia remains preexisting ischemia on arrival at the operating room and not anesthetic technique.[241] The only hemodynamic event definitively related to intraoperative ischemia in patients undergoing CABG surgery is tachycardia.[241] Perioperative use of β_1-adrenoceptor antagonists to prevent myocardial ischemia strongly supports this contention.[242] Sternotomy caused greater increases in calculated indices of MVo_2, myocardial lactate production, and the incidence of hypertension requiring treatment with vasoactive drugs during morphine than during halothane anesthesia. In contrast, induction of anesthesia with desflurane in patients undergoing CABG surgery may be associated with tachycardia, hypertension, and a greater incidence of ischemia than during induction with sufentanil.[243] Steal-prone anatomy was identified in 23% of patients with coronary artery disease enrolled in the Coronary Artery Surgery Study.[244] However, patients with steal-prone coronary anatomy did not have a greater incidence of ischemia during desflurane anesthesia than did patients with other forms of coronary artery disease.[243] The incidence of myocardial ischemia and adverse cardiac outcomes in cardiac patients undergoing noncardiac surgery has been shown

to be similar during sevoflurane and isoflurane anesthesia. New electrocardiographic changes, the incidence of postoperative myocardial infarction, and mortality were similar in patients undergoing CABG surgery independent of anesthetic technique or the presence of steal-prone anatomy.[245] In summary, despite the findings that volatile anesthetics are mild coronary vasodilators, these anesthetics did not cause abnormal redistribution of myocardial perfusion resulting in ischemia when tachycardia and hypotension were avoided in patients with coronary artery disease.

Cardioprotection by Volatile Anesthetics in Humans

Anesthetic preconditioning most likely occurs in human myocardium, but evaluation of this process in patients at risk for myocardial ischemia is complicated by simultaneous alterations in systemic and coronary hemodynamics; the use of other anesthetics, analgesics, or vasoactive drugs; preexisting disease states; and the influence of surgery on cardiovascular homeostasis. Isoflurane[78] and desflurane[80] enhanced the recovery of contractile function in human atrial trabeculae by stimulation of adenosine receptors and activation of K_{ATP} channels. A role for adenosine receptors, MAPKs, and ROS has previously been demonstrated in other forms of preconditioning in human atrial myocytes concomitant with mitochondrial K_{ATP} channel opening. Isoflurane decreased postoperative release of troponin I and the myocardial form of creatine kinase in patients undergoing CABG surgery, thus suggesting a reduction in the severity of myocardial necrosis.[246] Administration of the older agent enflurane before cardioplegic arrest also enhanced postischemic recovery of contractile function in patients undergoing CABG surgery.[247] Sevoflurane, but not the intravenous anesthetic propofol, was shown to preserve myocardial function in patients undergoing CABG surgery or aortic valve replacement concomitant with a reduction in the release of troponin I (Fig. 23-18).[248,249] Desflurane or sevoflurane, but not propofol, maintained contractile function and caused less pronounced release of troponin I after cardiopulmonary bypass in elderly patients with three-vessel coronary artery disease and preexisting LV dysfunction who were undergoing CABG surgery.[250] The beneficial effects of sevoflurane were most apparent when the volatile anesthetic was administered throughout CABG surgery versus before the initiation of cardiopulmonary bypass or after construction of the coronary anastomoses alone.[251] The incidence of atrial fibrillation early after CABG surgery may also be reduced by the intraoperative administration of sevoflurane instead of intravenous anesthetics.[252]

In a double-blind, placebo-controlled study of 72 patients undergoing CABG surgery with cardiopulmonary bypass, sevoflurane preconditioning (inhalation of 4% sevoflurane during the first 10 minutes of cardiopulmonary bypass), but not placebo, reduced postoperative release of brain natriuretic peptide (BNP), a biochemical marker of LV dysfunction, and cystatin C, an indicator of renal dysfunction, concomitant with translocation of PKC-δ and PKC-ε (Fig. 23-19).[253] Postoperative biochemical markers of hepatic injury were also lower with a sevoflurane-based anesthetic technique than with intravenous propofol anesthesia in patients undergoing CABG surgery with cardio-

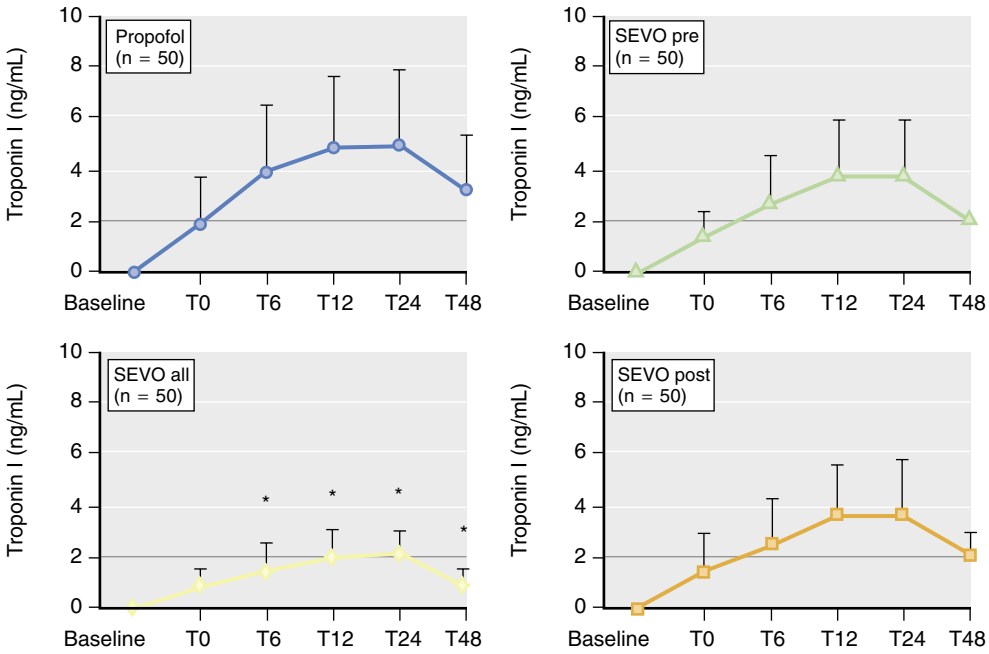

Figure 23-18 Cardiac troponin I concentrations in the four groups before surgery (baseline), at arrival in the intensive care unit (T0), and after 6 (T6), 12 (T12), 24 (T24), and 48 (T48) hours. Data are presented as means ± SD. *Statistically significant difference with the propofol group ($P < .05$). In all groups, a transient increase in troponin I concentrations was observed. Only in the SEVO all group was this increase significantly less than in the propofol group. For the sake of clarity, the SD bars are represented in only one direction. SEVO, sevoflurane. *(From De Hert SG, ten Broecke PW, Mertens E, et al: Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. Anesthesiology 97:42-49, 2002.)*

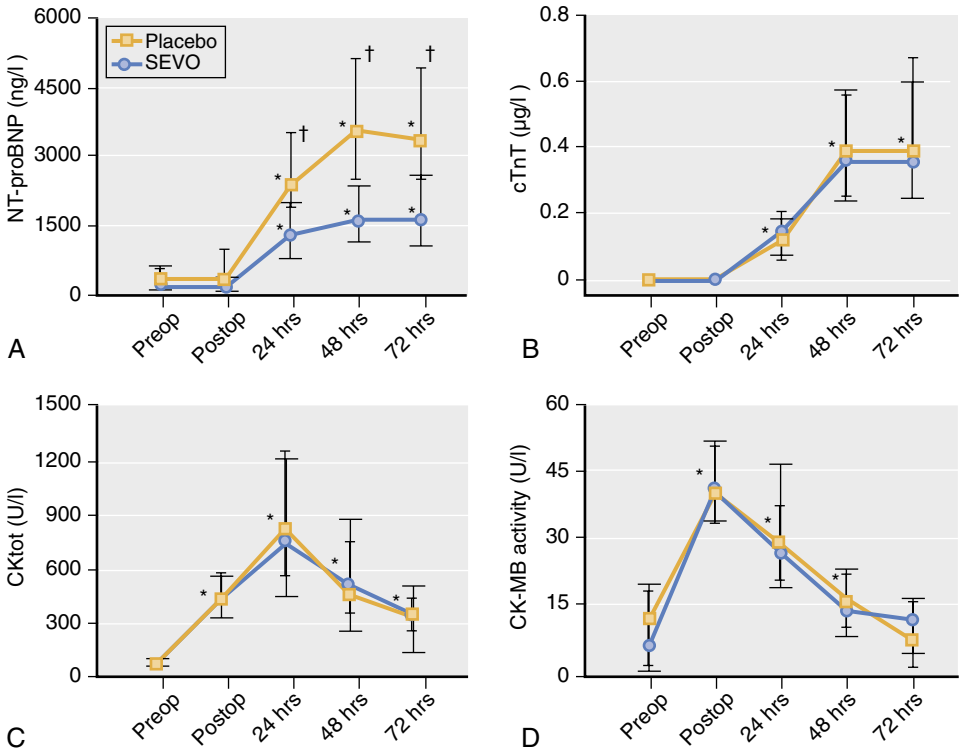

Figure 23-19 Biomarkers of myocardial injury at various time points for the placebo (PLACEBO)- and sevoflurane (SEVO)-treated groups: N-terminal pro–brain natriuretic peptide (NT-proBNP) (**A**), cardiac troponin T (cTnT) (**B**), total creatine kinase (CKtot) (**C**), and creatine kinase-MB (CK-MB) isoenzyme activity (**D**). Two-factor repeated-measures analysis of variance indicated that the groups differed significantly in plasma NT-proBNP concentrations (time effect, $P < .001$; group effect, $P < .001$; group-time interaction, $P = .003$). There was no difference in cTnT, CKtot, and CK-MB concentrations. Multiple *t*-tests with the Bonferroni correction for multiple comparisons were used to compare plasma concentrations of the different biomarkers at each time point with the respective preoperative baseline value within groups and to compare plasma concentrations at each time point between groups. *Significantly increased in comparison to baseline values ($P < 0.05$). †Significant difference between groups ($P < 0.05$). PLACEBO, group with a narrow cap; SEVO, group with a wide cap. The plot shows medians and lower and upper quartiles. *(From Julier K, da Silva R, Garcia C, et al: Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: A double-blinded, placebo-controlled multicenter study. Anesthesiology 98:1315-1327, 2003.)*

pulmonary bypass.[254] When compared with placebo, brief (10-minute) administration of 4% sevoflurane reduced platelet–endothelial cell adhesion molecule-1 (PECAM-1/CD31) and increased catalase expression in atrial biopsy specimens concomitant with a reduction in the indices of myocardial injury (e.g., cardiac troponin T, N-terminal pro-BNP) in patients undergoing CABG surgery and cardiopulmonary bypass.[255] The membrane protein PECAM-1 has been shown to play important roles in atherosclerotic plaque instability and migration of leukocytes through the vascular endothelium. Notably, an improvement in 1-year cardiovascular outcome was also observed in sevoflurane-preconditioned patients in this study.[255] These compelling data suggest that volatile anesthetics may exert long-term beneficial effects against ischemic injury in patients with coronary artery disease, in part by favorably modulating transcription of protective and antiprotective proteins.

More recently, low end-tidal concentrations (0.5% to 1.0%) of sevoflurane were shown to protect against endothelial damage in human volunteers undergoing 15-minute forearm ischemia followed by reperfusion.[256] A marked reduction in reactive hyperemic response (an indicator of ischemic injury and endothelial function) and attenuation of leukocyte activation (as measured by CD11a expression) were observed in volunteers pretreated with sevoflurane but not in those who were not.[256] Sevoflurane-induced alterations in genetic regulatory control of myocardial energy metabolism were also recently suggested to predict postoperative cardiac function in patients undergoing off-pump CABG surgery.[257] These data confirmed and extended previous findings indicating that desflurane decreases troponin I release, reduces inotropic drug use, and decreases the number of patients requiring prolonged hospitalization when compared with a propofol-opioid–based intravenous anesthetic technique in patients undergoing off-pump CABG surgery.[258] A meta-analysis of 22 previous studies incorporating more than 2800 patients undergoing CABG surgery suggested that sevoflurane and desflurane anesthesia was associated with reductions in postoperative troponin I release, but whether this decrease in a major index of myocardial necrosis translated into improved long-term outcome was unclear.[259] Thus, clinical investigations conducted to date provide tantalizing evidence suggesting that volatile anesthetics may represent an important therapeutic modality to reduce the risk for perioperative myocardial ischemia and infarction, but this contention will require a large-scale, randomized clinical trial for confirmation.

Volatile Anesthetics and Neural Control of the Circulation

Volatile anesthetics have been shown to depress baroreceptor reflex control of arterial pressure in experimental animals to varying degrees. This inhibition of baroreceptor reflex activity occurs as a result of depression of central nervous system integration of afferent baroreceptor input, attenuation of efferent autonomic nervous system activity, and reductions in ganglionic transmission and end-organ response. Volatile anesthetics increase resting afferent nerve traffic and enhance the sensitivity of arterial baroreceptors by a Ca^{2+}-dependent mechanism. These anesthetic-induced increases in baroreceptor sensitivity and discharge frequency tonically reduce overall sympathetic nervous system activity and attenuate sympathetic responses to declines in arterial pressure.[260] Isoflurane and the older volatile anesthetics halothane and enflurane inhibited preganglionic sympathetic efferent activity at clinically relevant concentrations in vivo. Volatile anesthetics reduced postganglionic sympathetic nerve activity, suggesting that attenuation of ganglionic transmission represents a major mechanism by which volatile anesthetics depress sympathetic nerve traffic. Depression of the sympathetic outflow caused by volatile anesthetics has also been suggested by examination of endogenous plasma norepinephrine kinetics. Isoflurane and halothane decreased plasma concentrations of norepinephrine to varying degrees by causing more pronounced reductions in norepinephrine spillover than clearance. Volatile anesthetics may also attenuate parasympathetic nervous system function. The older agent halothane was shown to depress vagal nerve efferent activity by direct measurement of parasympathetic nerve activity. These findings were supported by the results of several other studies demonstrating that volatile anesthetics inhibit reflex bradycardia in response to increases in arterial pressure. Parasympathetic and sympathetic nervous system outflow appears to be depressed to an equivalent degree during halothane or isoflurane anesthesia.

The effects of volatile anesthetics on neural control of the cardiovascular system have been incompletely examined in healthy humans and have not been described in patients with autonomic nervous system dysfunction. Halothane and enflurane produced greater attenuation of baroreceptor reflex regulation of the heart rate than equivalent MAC concentrations of isoflurane did. Depression of baroreceptor function by these volatile anesthetics may be more profound than with fentanyl, diazepam, and nitrous oxide anesthesia. Baroreceptor-mediated control of peripheral arteriolar tone was also attenuated in young volunteers during halothane anesthesia. Steady-state anesthetic concentrations of sevoflurane were shown to cause greater depression of sympathetic nerve activity measured directly by microneurography than desflurane did at equivalent levels of hypotension.[261] These findings paralleled results demonstrating pronounced sympathetic hyperactivity during rapid increases in inspired desflurane concentration in humans.[262] Importantly, the actions of volatile anesthetics on baroreceptor reflex control of the circulation may be profoundly altered during autonomic dysfunction in elderly patients or in those with essential hypertension, diabetes mellitus, or heart failure.

Nitrous Oxide and Cardiovascular Function

Myocardial Contractility and Left Ventricular Diastolic Function

Experiments in papillary muscle and isolated heart preparations have consistently demonstrated that nitrous oxide produces a direct negative inotropic effect. Conflicting results about the influence of nitrous oxide on contractility have been observed in experimental animals and healthy volunteers. Several problems have contributed to the apparently contradictory results in vivo. The changes in contractile function observed may be influenced by the actions of nitrous oxide on the systemic circulation or by autonomic nervous system reflex effects because nitrous oxide may increase sympathetic nervous system tone.[263] Studies using nitrous oxide alone are difficult to perform and interpret because this gas does not produce total anesthesia at partial pressures of less than 1 atm. The effects of nitrous oxide on contractile function may be influenced by different baseline anesthetics. Finally, lack of use of load-insensitive measures of myocardial contractility has allowed only qualitative assessment of the effects of nitrous oxide on the intrinsic inotropic state in the intact heart.

The regional preload recruitable stroke work relationship demonstrated that nitrous oxide depresses myocardial contractility in dogs anesthetized with isoflurane or sufentanil in the absence of autonomic nervous system activity.[264] Seventy percent nitrous oxide decreased M_w by 28% and 41% during sufentanil and isoflurane anesthesia, respectively. These results indicated that 70% nitrous oxide decreases contractility to approximately the same extent as 1 MAC isoflurane does. Similar findings were reported with the use of LV end-systolic pressure-dimension relationships in acutely instrumented dogs. These nitrous oxide–induced myocardial depressant effects may be offset by concomitant increases in sympathetic nervous system tone. The negative inotropic actions of nitrous oxide may be more pronounced in the presence of preexisting LV dysfunction.[265] In addition, nitrous oxide–induced depression of contractile function appeared to overcome the mild sympathomimetic effect of this anesthetic gas in patients with coronary artery or valvular heart disease and LV dysfunction because increases in baseline sympathetic nervous system activity were not further augmented by nitrous oxide in these clinical conditions.

The actions of nitrous oxide on LV diastolic function have been incompletely studied. Modest increases in maximal lengthening velocity and maximal rate of decline in force were observed in ferret papillary muscle concomitant with decreases in the contractile state.[266] No changes in the rate of isometric or isotonic relaxation were observed, indicating that nitrous oxide does not substantially modify myocardial relaxation. Nitrous oxide modestly increased segmental indices of LV chamber stiffness and reduced early LV filling in acutely instrumented dogs. These findings were supported by evidence indicating that nitrous oxide may produce LV diastolic dysfunction after cardiopulmonary bypass in patients undergoing CABG surgery.[267] Nitrous oxide caused dose-related reductions in the intracellular Ca^{2+} transient in vitro.[268] This finding indicated that nitrous oxide–induced depression of myocardial contractility was related to

decreases in the availability of Ca^{2+} for contractile activation. Nitrous oxide did not affect myofibrillar sensitivity to Ca^{2+} or Ca^{2+} uptake and release from the SR. In addition, the diastolic Ca^{2+} transient was unaffected by nitrous oxide, suggesting that this anesthetic gas does not alter myocardial relaxation kinetics.[266,268]

Hemodynamics

Assessment of the hemodynamic effects of nitrous oxide in humans is often complicated by concomitant administration of volatile anesthetics, opioids, or other anesthetic adjuvants in the presence or absence of cardiovascular disease. Typical clinical concentrations of nitrous oxide (e.g., 40% to 70%) caused modest increases in heart rate in healthy volunteers. Small increases in heart rate also occurred when hyperbaric concentrations of nitrous oxide were administered or when this anesthetic gas was added to volatile anesthetics. Declines in heart rate were observed with nitrous oxide in patients with coronary artery disease who were anesthetized with isoflurane. Modest reductions in heart rate have also been reported in patients anesthetized with morphine or fentanyl who were undergoing cardiac surgery. Sixty percent nitrous oxide caused small increases in arterial pressure in humans. Increases in arterial pressure also occurred under hyperbaric conditions or during volatile anesthesia in volunteers, consistent with a mild sympathomimetic effect. Other studies have also indicated that partial substitution of nitrous oxide for a volatile anesthetic either did not affect or modestly increased arterial pressure during isoflurane or desflurane anesthesia in experiments conducted at constant MAC. In contrast, reductions in arterial pressure have been observed in patients with coronary artery disease who received nitrous oxide in the presence and absence of opioids.

Small increases in cardiac output and stroke volume have been observed during the administration of 60% nitrous oxide in oxygen to volunteers, but cardiac output remained unchanged in the presence of hyperbaric nitrous oxide. Cardiac output has been shown to be greater in volunteers anesthetized with nitrous oxide and the older agent halothane than in those receiving halothane alone concomitant with increases in sympathetic nervous system tone. The addition of nitrous oxide to isoflurane or desflurane anesthesia also modestly increased cardiac output. In contrast, nitrous oxide reduced cardiac output and stroke volume in healthy volunteers and patients with cardiac disease receiving opioids. Hyperbaric nitrous oxide (1.5 MAC) caused a modest reduction in systemic vascular resistance. In contrast, systemic vascular resistance was higher during volatile anesthesia in the presence of nitrous oxide than in its absence. Pretreatment with the ganglionic blocker hexamethonium attenuated the relative increase in systemic vascular resistance observed during the administration of halothane and nitrous oxide, findings that may be consistent with a reduction in sympathetic nervous system tone. Nitrous oxide–induced increases in systemic vascular resistance have also been reported in volunteers and patients with cardiac disease who were anesthetized with opioids.

Nitrous oxide increases venous tone and decreases venous capacitance in conscious volunteers. This anesthetic gas has also been shown to modestly increase pulmonary artery pressure and pulmonary vascular resistance in patients with coronary artery disease who are anesthetized with morphine and diazepam or a volatile anesthetic. Thus, the combined effects of enhanced venous return, elevated pulmonary vascular resistance, and depressed contractile function probably contributed to the increases in central venous pressure observed with nitrous oxide in humans. Hyperbaric nitrous oxide also enhanced central venous pressure in association with increases in pulmonary vascular resistance. Nitrous oxide inhibited uptake of norepinephrine by the lung, and subsequent increases in plasma norepinephrine levels detected in the pulmonary vasculature may be partially responsible for the characteristic increases in pulmonary vascular resistance observed during administration of this agent. Nitrous oxide–induced increases in pulmonary vascular resistance may be more pronounced in adults with pulmonary hypertension and children with increased pulmonary blood flow. Increases in pulmonary artery pressure and vascular resistance have also been described during the administration of nitrous oxide to neonatal lambs. Such increases in pulmonary vascular resistance may potentially enhance right-to-left atrial or ventricular shunts and thereby compromise arterial oxygenation in patients with congenital heart disease.

Nitrous Oxide and Cardiac Electrophysiology

Reversible atrioventricular dissociation occurs in humans anesthetized with nitrous oxide and volatile or opioid-based anesthetics. The addition of nitrous oxide to halothane anesthesia lowered the threshold at which arrhythmias occur. This observation may result from a combination of stimulation of the sympathetic nervous system by nitrous oxide and myocardial sensitization by halothane. The incidence of arrhythmias was lower during combined nitrous oxide–opioid anesthesia than during halothane anesthesia alone.

Nitrous Oxide and the Coronary Circulation

Nitrous oxide did not produce direct effects on the coronary vasculature in vitro.[269] This anesthetic gas altered coronary blood flow concomitant with changes in MVo_2 in dogs. Nitrous oxide decreased myocardial segment shortening,[270] increased postsystolic shortening, and redistributed transmural coronary blood flow preferentially to the subepicardium (decreased endo/epi ratio) in experimental models of coronary artery disease. Nitrous oxide decreased the recovery of contractile function of canine stunned myocardium[271] and, in contrast to the findings with isoflurane, did not reduce myocardial infarct size in rats.[272] These data suggested that administration of nitrous oxide before or during transient or prolonged coronary artery occlusion and reperfusion is not associated with a cardioprotective effect. Nitrous oxide–induced sympathetic nervous system activation and imbalances in myocardial O_2 supply and MVo_2 are potential mechanisms for the absence of any beneficial effect during reversible or irreversible ischemic injury. In the presence of a volatile

anesthetic, nitrous oxide decreased MVo_2 and myocardial O_2 extraction and may exacerbate myocardial ischemia during concomitant reductions in arterial pressure in patients with coronary artery disease. However, the addition of nitrous oxide to volatile or opioid anesthetics did not increase the incidence of new regional wall motion abnormalities as assessed by transesophageal echocardiography in this patient population.

Nitrous Oxide and Neural Control of the Circulation

Nitrous oxide caused pupillary dilation, diaphoresis, and increases in systemic vascular resistance, central blood volume, and forearm vascular resistance in volunteers during volatile anesthesia, suggesting that nitrous oxide activates the sympathetic nervous system. A subsequent study demonstrated that nitrous oxide increases sympathetic nerve traffic measured via sympathetic microneurography in human volunteers, especially during the first 15 to 30 minutes of exposure to this anesthetic gas. Baroreceptor reflex–mediated control of heart rate was impaired during the administration of nitrous oxide, but regulation of sympathetic outflow to peripheral blood vessels was preserved.[263] This finding suggested that nitrous oxide does not alter sympathetic vasoconstrictor–induced maintenance of arterial pressure, which may be partially responsible for the relative stability of hemodynamics during nitrous oxide anesthesia.

Xenon

The anesthetic properties of the noble gas xenon were first described more than 50 years ago. Xenon has a blood-gas partition coefficient less than that of nitrous oxide, does not undergo biotransformation, provides rapid induction and emergence from anesthesia,[273] and exerts analgesic effects[274] independent of α_2-adrenergic and opioid receptors.[275] Despite these advantageous properties, xenon has not been routinely used for clinical anesthesia in the United States because it is more expensive than nitrous oxide and volatile anesthetics. In recent years, more efficient manufacturing techniques and the development of low-flow administration and recycling systems have reduced the cost of xenon and rekindled interest in its clinical use. Many of these issues are succinctly summarized in two excellent reviews.[276,277]

Xenon causes minimal systemic and pulmonary hemodynamic effects in vivo,[278] preserves or very modestly reduces myocardial contractility,[279,280] and attenuates alterations in hemodynamics and increases in plasma epinephrine and cortisol concentrations associated with surgical stimulation.[281,282] Xenon did not alter cardiac function or major ion currents in isolated guinea pig hearts and ventricular myocytes.[283] Similar findings were observed in isolated human atrial myocytes.[284] Several studies have recently identified the cardiac and neural protective effects of Xe.[277] The cellular mechanisms responsible for these salutary actions were initially unclear based on data indicating that xenon does not affect the amplitudes of Na^+, L-type Ca^{2+}, and inwardly rectifying K^+ channels in whole-cell patch-clamped myocytes.[283] Xe was initially shown to produce cardioprotection when the anesthetic noble gas was administered early during reperfusion in rabbits.[285] Subsequently, pretreatment with 70% Xe before ischemia was demonstrated to reduce infarct size in rats (from 51% to 28% of the LV area at risk) by activating PKC-ε and its downstream targets p38 MAPK,[286] MAPKAPK-2,[121] and HSP-27.[121] Roles for mitochondrial K_{ATP} channels, PDK1, and ERK1/2 were also implicated in Xe preconditioning,[287,288] suggesting that prosurvival signaling may play an important role in cardioprotection by Xe. Whether Xe preserves myocardial integrity by favorably modulating proteins responsible for the regulation of apoptosis through the mPTP remains unclear. Because Xe and volatile anesthetics exert similar actions on endogenous cardioprotective signal transduction, the reductions in infarct size produced by this noble gas have been assumed to be related to its anesthetic actions.[277] However, other noble gases without anesthetic properties (e.g., helium, neon) also produce cardioprotection by activating prosurvival signaling and inhibiting the mPTP.[289]

The effects of xenon in experimental models of or patients with congestive heart failure have not been studied extensively. Systemic hemodynamics, LV systolic and diastolic function, and the determinants of LV afterload were examined in chronically instrumented dogs before and after the development of rapid LV pacing–induced cardiomyopathy.[279] Xenon was remarkably devoid of hemodynamic effects in normal and cardiomyopathic dogs anesthetized with isoflurane. Xenon did not alter isoflurane-induced reductions in the preload recruitable stroke work slope (M_w) in the presence and absence of pacing-induced LV dysfunction. Xenon caused greater increases in the time constant of isovolumic relaxation in isoflurane-anesthetized, cardiomyopathic dogs than in normal dogs, but indices of early LV filling and chamber compliance remained unchanged, which suggested that xenon does not appreciably influence LV diastolic function during isoflurane anesthesia. Xenon also produced relatively minor alterations in the determinants of LV afterload in dogs before and after pacing. Taken together, these data indicate that xenon produces very subtle cardiovascular effects during isoflurane anesthesia in dogs with and without experimental dilated cardiomyopathy.[1] Finally, 56% xenon (end-tidal concentration) depressed sympathetic and parasympathetic nervous system transmission to a greater extent than did 0.8 MAC isoflurane in healthy patients undergoing elective surgery.

Summary

Volatile anesthetics exert profound effects on the cardiovascular system by altering the inotropic, chronotropic, dromotropic, and lusitropic state of the heart. These anesthetics also have significant actions on both the preload and afterload systems. These pharmacologic effects cause dramatic changes in hemodynamics that may be accentuated in patients with underlying cardiovascular disease. Less profound but equally important effects are observed with nitrous oxide and xenon. Volatile anesthetics and xenon but not nitrous oxide are cardioprotective and directly reduce the sequelae of ischemia and reperfusion injury. The use of inhaled anesthetics requires a clear understanding of their complex cardiovascular pharmacology.

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Jackie L. Martin

24 Inhaled Anesthetics: Metabolism and Toxicity

Key Points

1. The liver is the major site of endogenous and exogenous drug metabolism. The primary result of drug metabolism is the production of more water-soluble and therefore more easily excreted drug metabolites. Drugs are sometimes biotransformed into more reactive metabolites that may lead to toxicity.
2. Most drug metabolism is catalyzed by phase 1 or phase 2 enzymes. The predominant phase 1 enzymes are the cytochrome P450 (CYP) monooxygenases. Approximately 50 of the more than 1000 CYP isoforms are functionally active in humans. The predominant isoform catalyzing the metabolism of inhaled anesthetics is CYP2E1. The major phase 2 enzyme is uridine diphosphate glucuronosyltransferase.
3. Many factors affect drug metabolism. Perhaps the most important are pharmacogenetic factors. Genetics ultimately determines absorption, distribution, metabolism, and excretion. Other important determinants are environmental factors, age, gender, disease states, and other drugs or medications. Induction and inhibition of CYP enzymes because of concurrent medications can have an important impact on therapeutic drug levels and pharmacologic effects.
4. Pharmacogenomics, or the influence of DNA sequence variation on the effect of a drug, provides a basis for understanding the interindividual variation observed in drug responses.
5. Nitrous oxide and xenon are both nonhalogenated anesthetics. Xenon is not currently approved for clinical use; however, aside from the expense associated with its use, it may be the most ideal and environmentally friendly anesthetic agent.
6. The combination of drug-related antibodies, the apparent need for prior sensitization, and the association of fever and eosinophilia all support an immune basis for anesthetic-induced hepatitis.
7. Halothane, enflurane, isoflurane, and desflurane are all metabolized to trifluoroacylated hepatic protein adducts that have been reported to induce liver injury in susceptible patients. The propensity to produce liver injury appears to parallel metabolism of the parent drug; thus, halothane (20%) ⋙ enflurane (2.5%) ≫ isoflurane (0.2%) > desflurane (0.02%). The incidence of halothane hepatitis in the adult population is roughly 1 in 10,000. Sevoflurane does not produce acylated protein adducts.
8. Halothane hepatitis has been reported in the pediatric population. The incidence appears to be approximately 1 in 200,000.
9. Toxicity and liver injury have been reported after repeat exposure on subsequent occasions to different fluorinated anesthetics. This phenomenon of cross-sensitization has also been reported with hydrochlorofluorocarbons, the chlorofluorocarbon replacement agents.
10. Sevoflurane is metabolized to hexafluoroisopropanol, formaldehyde, inorganic fluoride, and carbon dioxide. Although very high fluoride levels have been reported after sevoflurane anesthesia, fluoride-associated renal injury has not been reported.
11. The major base-catalyzed breakdown product of sevoflurane is compound A. Compound A is a nephrotoxic vinyl ether that induces both dose- and time-dependent renal injury. The threshold for renal injury in rats and humans appears to be approximately 150 ppm-hours of exposure to compound A (i.e., 50 ppm for 3 hours). The toxic threshold appears to be reached only under clinical conditions of prolonged sevoflurane anesthesia, and changes in glucosuria and enzymuria are observed. Blood urea nitrogen and creatinine levels remain unchanged. To date, no significant clinical renal toxicity has been associated with the use of sevoflurane.
12. Desiccated carbon dioxide absorbent and inhaled anesthetic interactions can lead to the production of carbon monoxide in the anesthesia circuit (desflurane ⋙ enflurane > isoflurane). Negligible amounts of carbon monoxide are formed from halothane and sevoflurane.
13. New calcium hydroxide–based CO_2 absorbents, such as Amsorb and DragerSorb Free, contain neither NaOH or KOH and thus are chemically inert and do not degrade inhaled anesthetics to carbon monoxide or degrade sevoflurane to compound A.

14. The interaction of inhaled anesthetics with CO_2 absorbents is an exothermic reaction resulting in the production of heat. The temperature of CO_2 canisters during routine clinical use averages 25°C to 45°C but increases inversely with decreased fresh gas flow, and sevoflurane is associated with the greatest production of heat. Hydrogen is an important by-product of this reaction. The high yield of hydrogen, ease of ignition, and low tissue solubility make hydrogen the most likely fuel in anesthesia machine fires because of its reactions with desiccated CO_2 absorbents and sevoflurane. This reaction can be significant and result in fire, toxic gas, and patient injury.
15. There appears to be no risk associated with brief periods of low-level occupational exposure to waste anesthetic gases (operating room, postanesthesia care unit, intensive care unit). Occupational exposure to high concentrations (10^3 ppm) may be correlated with an increased incidence of abortions and decreased fertility. Individuals with vitamin B_{12} deficiency may be at risk for neurologic injury from nitrous oxide.
16. Fluorinated inhaled anesthetics containing bromine and chlorine deplete ozone (halothane ⋙ enflurane > isoflurane) and contribute to the greenhouse gas effect and global warming. N_2O does not deplete ozone, but it does contribute to the greenhouse gas effect and global warming.

Once a drug is administered, it undergoes the processes of absorption, distribution, target interaction, metabolism, and excretion. Unlike most drugs, the inhaled anesthetics are administered in great excess of the amount metabolized, and thus biotransformation has little effect on the pharmacologic activity of anesthetics but may have a significant effect on anesthetic toxicities. It was once thought that the inhaled anesthetics were chemically inert. We now know that many of these anesthetic agents undergo significant metabolism and in many cases biotransform and chemically breakdown to reactive and potentially toxic intermediates. The metabolic processes are affected by many factors, including age, disease, drug-drug interactions, and perhaps most important, genetics. This chapter focuses on the current understanding of mechanisms of anesthetic-associated toxicities, particularly liver injury and the role of drug metabolism in many of these processes. The mechanisms and risks resulting from the interaction of carbon dioxide absorbents with inhaled anesthetics, as well as other side effects of inhaled anesthetics, are also reviewed.

Drug Metabolism and Biotransformation

The Liver and Drug Metabolism

The lipophilic characteristics of drugs that promote their passage through biologic membranes hinder their excretion from the body. Drug metabolism is therefore essential for elimination and termination of the biologic activity of lipophilic drugs because it usually results in the formation of more hydrophilic products that are less pharmacologically active and more readily excreted from the body (Fig. 24-1). Drug metabolism sometimes results in the formation of intermediates whose pharmacologic or toxicologic activity is equal to, greater than, or different from that of the parent drug.[1] Unlike most drugs, the inhaled anesthetics are administered in great excess of the amount metabolized and are excreted mainly by exhalation. Thus, biotransformation has little effect on the pharmacologic activity of anesthetics, but it may have a significant effect on the toxicity of these agents.[2] The inhaled anesthetics are absorbed through the epithelium and mucous membranes of the respiratory tract. Because of the large pulmonary surface area, access to the circulation is rapid, with

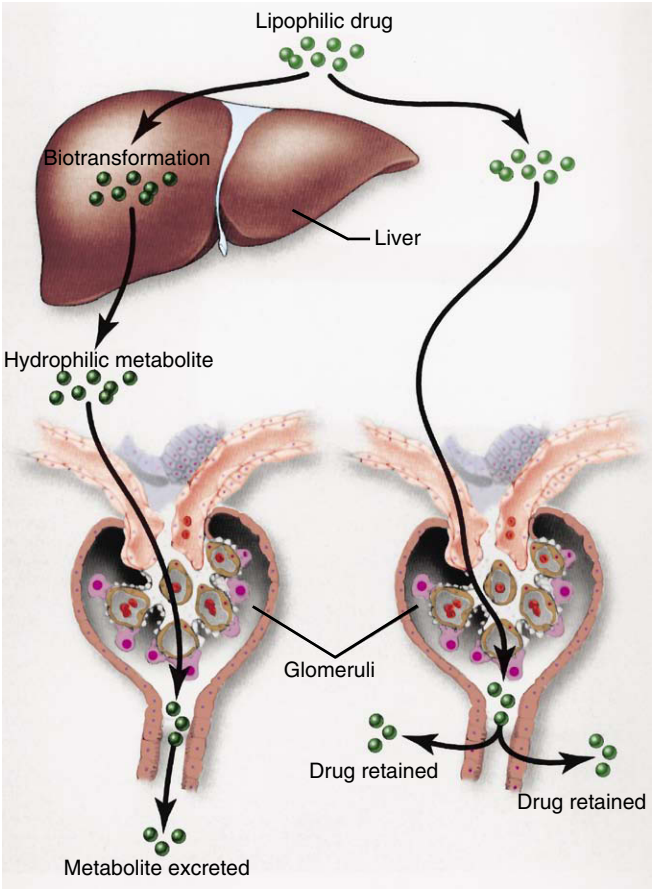


Figure 24-1 Effect of drug metabolism on excretion. Lipophilic (fat-soluble) drugs are metabolized to form relatively more hydrophilic (water-soluble) metabolites than the parent drug, and these metabolites are thus more easily excreted. *(From Weinshilboum R: Inheritance and drug response. N Engl J Med 348:529-557, 2003.)*

almost instantaneous absorption of these agents into blood and avoidance of hepatic first-pass metabolism. Thus, the pharmacologic effects of inhaled anesthetics are quite rapid and less dependent on factors governing the activities of other drugs, such as the amount of drug administered, the extent and rate of absorption, protein binding, excretion, secretion, and metabolism.[3]

The liver is the primary organ of drug metabolism because of its large size, rich concentration of drug-metabolizing enzymes, and unique double blood supply consisting of 70% of flow from the portal vein and 30% from the hepatic artery. Blood in the portal vein comes from the alimentary tract, pancreas, and spleen. Toxic materials absorbed from the alimentary tract are processed by the liver before they enter the systemic circulation. Blood flows through the hepatic sinusoids from the periphery of the hepatic lobule, fed by portal veins and hepatic arteries, to the centrally located hepatic venule or central vein. Hepatocytes, which are bathed by the sinusoidal blood supply, are the major drug-metabolizing cells in the liver and body. Several drug-metabolizing enzyme systems are located within the smooth endoplasmic reticulum of hepatocytes, whereas others are found in the cytosol of these cells. Organs with significant drug-metabolizing activity in addition to the liver are the gastrointestinal tract, kidneys, and lungs.[4,5]

The major enzymatic reactions biotransforming drugs into metabolites are oxidation, hydrolysis, and conjugation. It is very common for a drug to be metabolized into several metabolites. The ratios of various metabolites of a drug depend on enzymatic reaction rates, drug concentration near the enzymes, physicochemical reactions between metabolites and enzymes, competition of multiple drugs or endogenous substrates for the same enzyme, and many other factors.[5] Drug biotransformation reactions are broadly classified into phase 1 functionalization reactions or phase 2 biosynthetic conjugation reactions. Phase 1 reactions are catalyzed by enzymes that introduce or expose a polar functional group such as a hydroxyl or amino moiety in a drug by oxidation and hydrolytic reactions, respectively, whereas phase 2 reactions often lead to enzymatic conjugation of these polar functional groups to very polar molecules. The net effect of these reactions is the formation of molecules that are more easily excreted into urine through the kidneys or into the gastrointestinal tract by biliary excretion. *N*-Acetylation is the exception because it leads to the formation of less water-soluble metabolites.

The phase 1 enzymes most relevant to the metabolism of inhaled anesthetics are the cytochrome P450 (CYP) isoforms. These enzymes are capable of catalyzing several different types of oxidation reactions, including dehalogenation, *N*- and *O*-dealkylation, *N*- and S-oxidation, and deamination reactions. All these reactions require CYP, O_2, and reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent cytochrome P450 reductase for activity and occur in the endoplasmic reticulum of cells, particularly hepatocytes. Under conditions of low oxygen tension, these enzymes may catalyze reductive reactions. Approximately 50 of the more than 1000 CYP isoforms are functionally active in humans and are categorized into 17 families and subfamilies. Sequences that are greater than 40% homologous belong to the same family and are identified by an Arabic number. The sequences of subfamily members are at least 55% identical and are distinguished by a capital letter. An Arabic number is used to distinguish individual isoforms within a subfamily. CYP2E1, for example, is a member of the CYP2 family, a large group of isozymes that metabolize many diverse drugs and endogenous compounds.[6] Approximately 10 isoforms in the CYP1, CYP2, and CYP3 families are responsible for the majority of drug metabolism in humans (Fig. 24-2). Most CYP isoforms metabolize multiple drugs, and some overlap in substrate specificity can be seen between the various isoforms. Thus, two or more CYP isoforms may be involved in the overall metabolism of a drug. In human liver, the CYP3A4 and CYP3A5 subfamilies account for as much as 60% of the total CYP present. CYP2E1 is particularly important in the oxidative metabolism of halogenated inhaled anesthetics, and like many CYP isozymes, it is concentrated in perivenular hepatocytes.

In phase 2 reactions, a polar molecule such as glucuronic acid, sulfate, or glycine is conjugated to a drug or its metabolites to produce highly hydrophilic products that are readily excreted into urine or in some cases into bile and the gastrointestinal tract. Glucuronidation is perhaps the most important conjugation reaction, and uridine 5′-diphosphate glucuronosyltransferase (UGT) catalyzes the transfer of glucuronic acid to aromatic and aliphatic alcohols, carboxylic acids, amines, and free sulfhydryl groups to form *O*-, *N*-, and *S*-glucuronides, respectively. UGTs, like CYPs, exist as multiple isoforms with differing substrate specificities and are localized in the endoplasmic reticulum, whereas most other phase 2 enzymes are concentrated in the cytosol. Glucuronidation is also important in the elimination of endogenous steroids, bilirubin, bile acids, and fat-soluble vitamins. Cytosolic sulfation is another important conjugation reaction that involves the catalytic transfer, by various sulfotransferase members, of inorganic sulfate from activated 3′-phosphoadenosine-5′ phosphosulfate to the hydroxyl group of phenols and aliphatic alcohols. Thus, drugs and primary metabolites with a hydroxyl group often form both glucuronide and sulfate conjugates. Two *N*-acetyltransferases, NAT1 and NAT2, are involved in the acylation of amines, hydrazines, and sulfonamides (see Fig. 24-2).

Factors Affecting Drug Metabolism

Various factors may affect drug metabolism, including environmental determinants, disease, age, gender, and genetics. The activity of many drug-metabolizing enzymes may be increased (*induced*) or decreased (*inhibited*) by concomitantly administered substances or drugs. Enzyme induction is due to enhanced gene transcription after prolonged exposure to an induction agent or, in some instances, is due to a decreased rate of enzyme degradation. Induction of CYP isozymes by numerous drugs and environmental agents has been studied extensively.[7] Enzyme inducers are often highly lipophilic drugs and environmental chemicals that are metabolized by the CYP isozymes that they induce. The inducing properties of a drug are unrelated to the nature of its pharmacologic or toxicologic activity and may differ markedly from those of other drugs in the same class. Induction by drugs such as phenobarbital results in proliferation of the smooth endoplasmic reticulum and an increase in liver weight. With this type of inducer, NADPH–cytochrome P450 reductase and specific CYP isozymes are preferentially increased. Although other inducers increase the synthesis of specific CYP isozymes, they do not affect cytochrome P450 reductase or liver weight. The mechanism by which CYP3A4 is induced is shown in Figure 24-3A, and the effect on plasma felodipine concentrations in healthy subjects is shown in Figure 24-3B.[8] Importantly, CYP3A4 induction is the result of de novo protein synthesis, and thus several weeks is needed before steady-state levels are reached. Likewise, once use

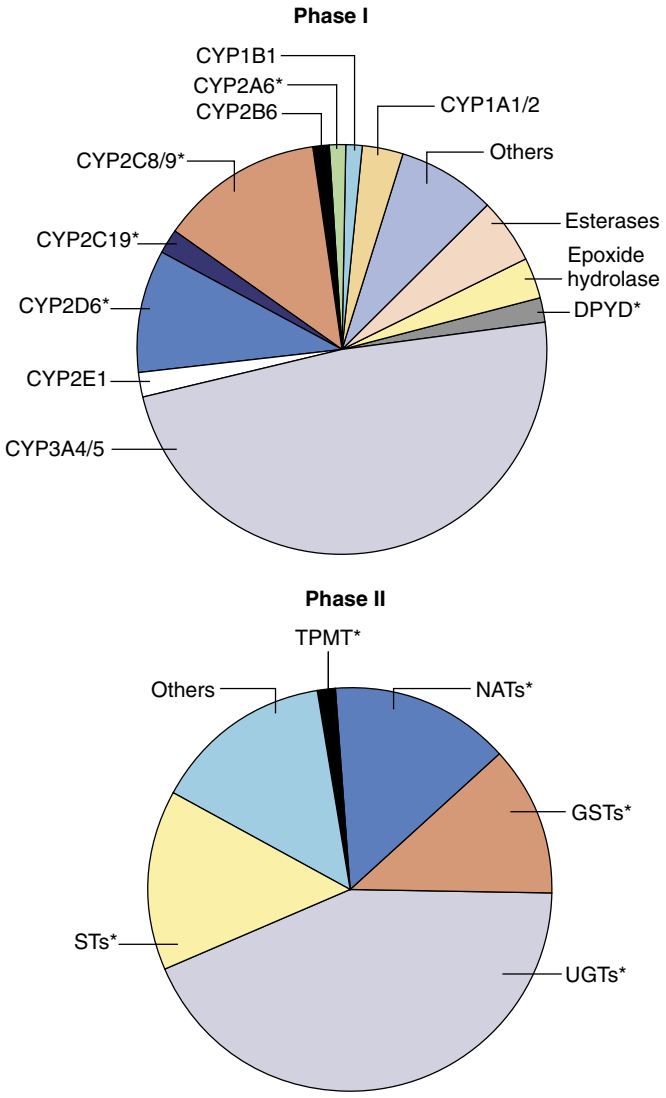


Figure 24-2 Proportion of drugs metabolized by major phase 1 or phase 2 enzymes. The relative size of each pie section indicates the estimated percentage of phase 1 (*top panel*) or phase 2 (*bottom panel*) metabolism that each enzyme contributes to the metabolism of drugs based on literature reports. Enzymes that have functional allelic variants are indicated by an *asterisk*. In many cases, more than one enzyme is involved in a particular drug's metabolism. CYP, cytochrome P450; DPYD, dihydropyridine dehydrogenase; GST, glutathione-*S*-transferase; NAT, *N*-acetyltransferase; STs, sulfotransferases; TPMT, thiopurine methyltransferase; UGT, uridine diphosphate glucuronosyltransferases. *(Adapted from Wilkinson G: Pharmacokinetics: The dynamics of drug absorption, distribution and elimination.* In *Hardman JG, Limbird LE, Goodman GA [eds]: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th ed. New York, McGraw-Hill, 2001.)*

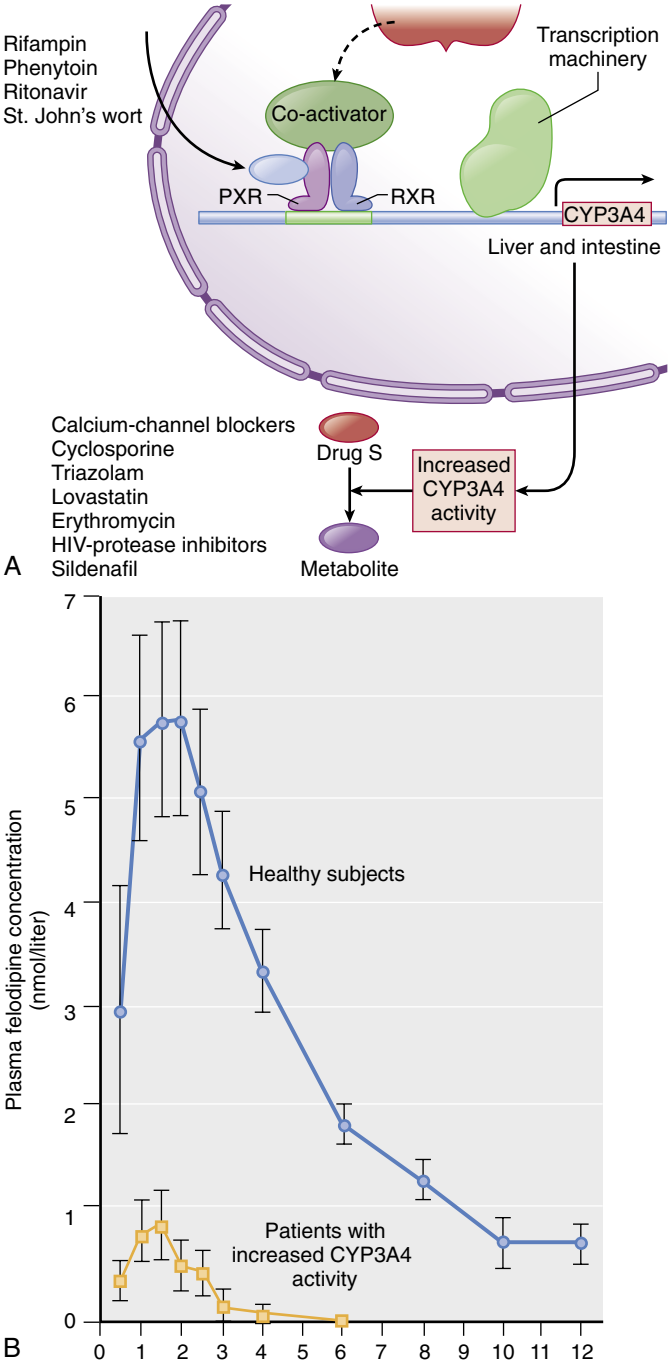


Figure 24-3 Mechanism of induction of CYP3A4-mediated metabolism of drug substrates (**A**) and the resulting reduced plasma drug concentration (**B**). In **A**, an inducing agent (Drug) interacts with the nuclear pregnane X receptor (PXR) to form a heterodimer with the retinoid X receptor (RXR); in turn, the heterodimer binds to cognate recognition sites in the 5′ regulatory region of the CYP3A4 gene. As a result, transcription of DNA is upregulated, which leads to increased synthesis of CYP3A4 enzyme and enhanced oxidative metabolism of its substrates (Drug S). This causes a reduction in the plasma drug concentration as exemplified by felodipine (**B**) and, subsequently, decreased drug effects. The same molecular mechanism is also responsible for the induction of other metabolizing enzymes and membrane transporters important in drug disposition. Comparison of the plasma felodipine concentration-time profiles in **B** with those in **A** indicates the wide range of CYP3A activity that is possible. *I bars* denote standard errors. *(From Wilkinson GR: Drug metabolism and variability among patients in drug response. N Engl J Med 352:2211-2221, 2005.)*

of the inducing drug is discontinued, it may be several weeks before baseline levels of CYP3A4 are established. Many classes of drugs and environmental chemicals, including anesthetics, anticonvulsants, insecticides, sedatives, steroids, tranquilizers, and the anti–human immunodeficiency virus (HIV) agents efavirenz and nevirapine contain one or more compounds thought to be enzyme inducers.[7] St. John's wort is also a known inducer of CYP3A. If the parent compound is toxic, enhanced metabolism may decrease its toxicity. In contrast, when metabolites are more toxic than the parent compound, metabolism increases toxicity. In many cases

involving induction, the dosage of an affected drug must be increased to maintain the therapeutic effect. Enzyme-inducing agents have the potential to modify acute and chronic toxicities of anesthetics. In view of the current practice of polypharmacy, enzyme induction may be more common in patients who are undergoing surgery than previously appreciated.

Enzyme inhibition can have as great an effect on therapeutic activity and toxicity as enzyme induction. Enzyme inhibition can lead to an increase in the plasma concentration of the parent drug and a reduction in drug metabolites, as well as exaggerated and prolonged pharmacologic effects and increased potential for toxicity. Many compounds inhibit the activity of drug-metabolizing enzymes and thereby alter the duration and intensity of pharmacologic action and the severity of toxic effects. There are several mechanisms of inhibition. Inhibitors of protein synthesis such as cycloheximide decrease enzyme synthesis and thereby reduce enzyme concentrations. Other agents are reversible inhibitors that compete for the active site of the same enzyme responsible for metabolism of the drug of interest. Still others are irreversible inhibitors that degrade the heme in cytochrome P450. Inhibition of CYP3A is common and important because of the high expression of CYP3A in intestinal epithelium and the fact that oral ingestion is the most common route of entry for drugs. After oral ingestion, bioavailability is potentially increased because of a reduction in first-pass metabolism. Inhibition of CYP3A4, for example, is noted with the ingestion of grapefruit juice. Regular consumption of 250 mL of grapefruit juice will inhibit intestinal CYP3A4 activity. A patient taking oral felodipine with grapefruit juice will experience side effects associated with an overdose of this calcium channel antagonist, such as hypotension and tachycardia, as a result of decreased levels of CYP3A4 (Fig. 24-4).[8] Potent CYP3A inhibitors include ritonavir, diltiazem, nicardipine, verapamil, and several anti-HIV agents (delavirdine, indinavir, ritonavir, and saquinavir). More general CYP inhibitors include amiodarone, cimetidine, and the macrolide antibiotics erythromycin, clarithromycin, and troleandomycin.

Some sex-related differences in drug-metabolizing activity have been observed, particularly for CYP3A, but such differences are minor relative to previously described factors. An exception is the treatment of seizure patients with phenytoin during pregnancy. Because the liver is the major site of drug metabolism, intrinsic liver disease leading to hepatic dysfunction can result in impaired drug metabolism. Diseases such as hepatitis, primary biliary cirrhosis, alcoholic liver disease, cirrhosis, and hepatocarcinoma can lead to a 50% impairment of enzymatic activity. Severe cardiac failure with decreased hepatic perfusion and impaired metabolism can also occur, as evidenced by the twofold difference in loading and maintenance doses of lidocaine for treatment of dysrhythmia in heart failure patients. Moreover, viral infections can lead to the inhibition of CYP-mediated reactions.

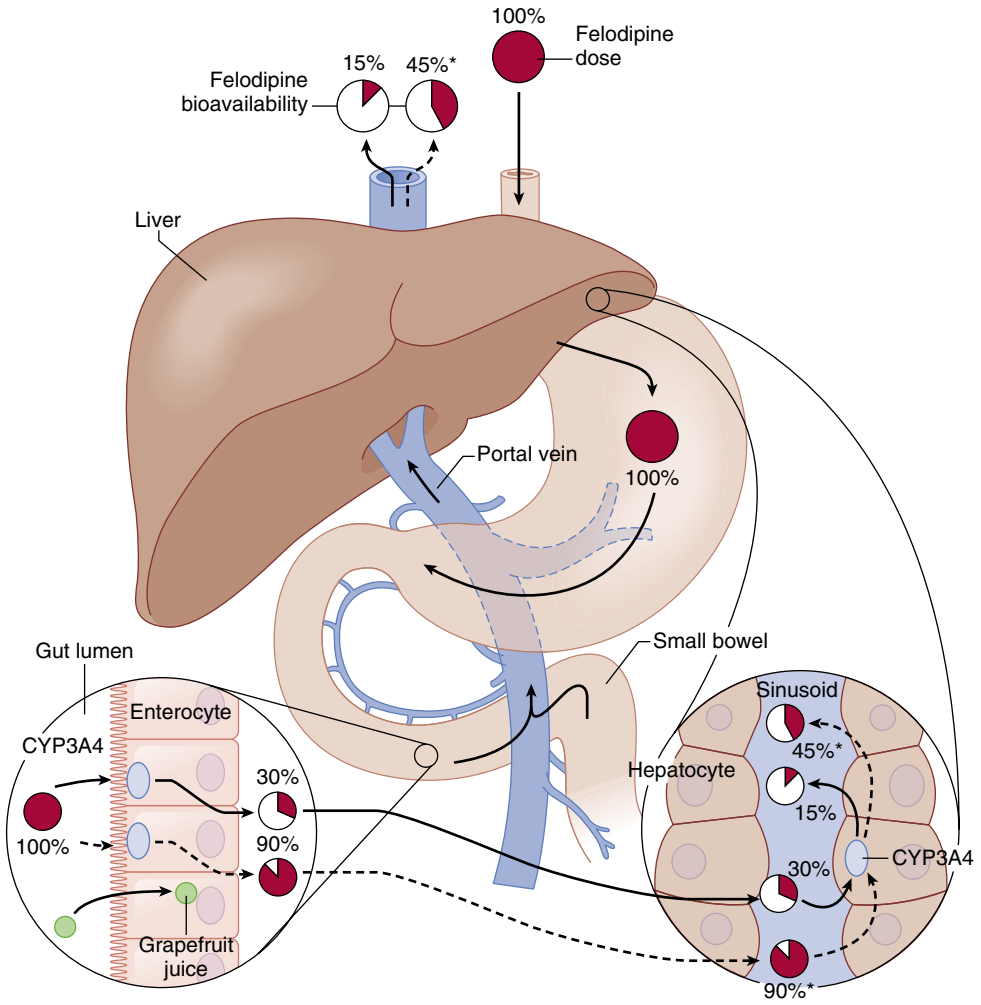


Figure 24-4 First-pass metabolism after the oral administration of a drug, as exemplified by felodipine and its interaction with grapefruit juice. The CYP3A enzymes (e.g., CYP3A4) present in enterocytes of the intestinal epithelium extensively metabolize felodipine during its absorption, and on average only 30% of the dose administered enters the portal vein (*solid line*). Subsequently, CYP3A enzymes in the liver further metabolize the drug so that only 15% of the dose is bioavailable and finally reaches the systemic circulation, where it is able to exert its effects. Grapefruit juice selectively inhibits CYP3A in the enterocyte, with the net result being an increase in the oral bioavailability of felodipine by a factor of 3, denoted by the *asterisks* and the *dashed lines*. *(From Wilkinson GR: Drug metabolism and variability among patients in drug response. N Engl J Med 352:2211-2221, 2005.)*

Developmental Differences in Infants and Children

Both phase 1 and phase 2 enzymes begin to mature during the postnatal period (also see Chapter 82), but the levels may be low enough in some cases to result in toxicity if drug therapy is not carefully monitored. For example, impairment of bilirubin glucuronidation at birth can lead to hyperbilirubinemia of the newborn and the "gray baby" syndrome as a result of high levels of the antibiotic chloramphenicol.[9,10] As children age, phase 1 enzymes appear to be affected to a greater degree than phase 2 enzymes. The predominant isoform expressed in fetal liver is CYP3A7, which peaks shortly after birth and then declines rapidly to levels that are undetectable in most adults.[11] Within hours of birth, CYP2E1 activity increases, followed by CYP2D6, CYP3A4, CYP2C9, and CYP2C19. CYP1A2 is the last isoform to appear at about 2 months of age. CYP2C9 and CYP2C19 are responsible for the biotransformation of phenytoin. The apparent half-life of phenytoin is prolonged to about 75 hours in preterm neonates but decreases to about 20 hours in term neonates during the first week of life and to 8 hours by the second week.[12]

Pharmacogenetics of Drug Metabolism

Advances in the field of genetics have had a major impact on drug metabolism and have provided the experimental tools to probe the genetic basis of intersubject variability in human drug pharmacokinetics, metabolism, and toxicity.[13] Although CYPs are most often thought of as being responsible for the deactivation of toxic compounds, they are in fact also responsible for the metabolic activation of drugs and chemicals to toxic forms. Any factor that can influence metabolism has the potential to affect toxicity. As previously discussed, drug biotransformation may be affected by many factors, including route of administration, frequency of administration, exposure to other chemicals, sex, age, diet, and genetics. The concept of pharmacogenetics originated from the clinical observation that there were patients with very low or very high plasma or urinary drug levels, followed by the realization that the biochemical traits leading to this variation were inherited. Soon thereafter, drug-metabolizing enzymes were identified, followed by discovery of the genes encoding the proteins and the DNA sequences within the genes. Most of the early pharmacogenetic traits were monogenic, involving a single gene, and most were due to genetic polymorphism.

The early discovery that impairment in the phase 1 hydrolysis of succinylcholine by butyrylcholinesterase was inherited served as an early stimulus to the development of pharmacogenetics. About 1 in 3500 white individuals is homozygous for a gene encoding an atypical form of butyrylcholinesterase. These individuals have less ability to hydrolyze succinylcholine, and thus the neuromuscular blocking effects of this drug are prolonged.[14,15] More recent studies have demonstrated that CYP2D6 represents one of the best understood examples of pharmacogenetic variation in drug metabolism. Substrates for CYP2D6 include codeine, metoprolol, nortriptyline, dextromethorphan, debrisoquin, and sparteine.[16] Approximately 5% to 10% of white subjects were found to be deficient in the ability to metabolize the antihypertensive drug debrisoquin[16] and the antiarrhythmic drug sparteine,[17] which resulted in low levels of urinary metabolites and high plasma concentrations of the parent compounds. These deficiencies were found to be inherited as an autosomal recessive trait.[17,18] The cDNA for the gene encoding CYP2D6 has been cloned, and a number of genetic variants responsible for the deficient activity of CYP2D6 have been identified. Other subjects have multiple copies of active forms of CYP2D6 that result in rapid elimination of drugs leading to subtherapeutic levels. Such is the case with the antidepressant nortriptyline (Fig. 24-5). Many other examples of poor metabolizers of drugs who have genetic variants of other CYP isoforms have been described. For example, CYP2C9 variants can lead to poor metabolism of warfarin and phenytoin and subsequent toxic levels of these compounds. Similarly, polymorphisms in the phase 2 metabolizing enzyme NAT can lead to bimodal differences in *N*-acetylation and inactivation of the antituberculosis drug isoniazid (Fig. 24-6). More recent molecular cloning studies have shown that there are two NAT genes in humans, *NAT1* and *NAT2*, and that the common genotypic polymorphism responsible for the pharmacogenetic variation in isoniazid metabolism involves the *NAT2* gene.[19] The frequency of each acetylation phenotype is dependent on race but not on sex or age. Fast acetylation is found in the Inuit and Japanese, whereas slow acetylation predominates among Scandinavians and North African white individuals.[20] Another example of the role of genetics in phase 2 metabolism concerns the antineoplastic drug azathioprine, a prodrug that is converted to the active drug 6-mercaptopurine. Thiopurines such as 6-mercaptopurine are metabolized by thiopurine-*S*-methyltransferase (TPMT).[21] This enzymatic activity is inherited in an autosomal codominant fashion. Individuals homozygous for alleles encoding inactive TPMT and receiving standard doses of azathioprine are at risk for the development of severe pancytopenia.

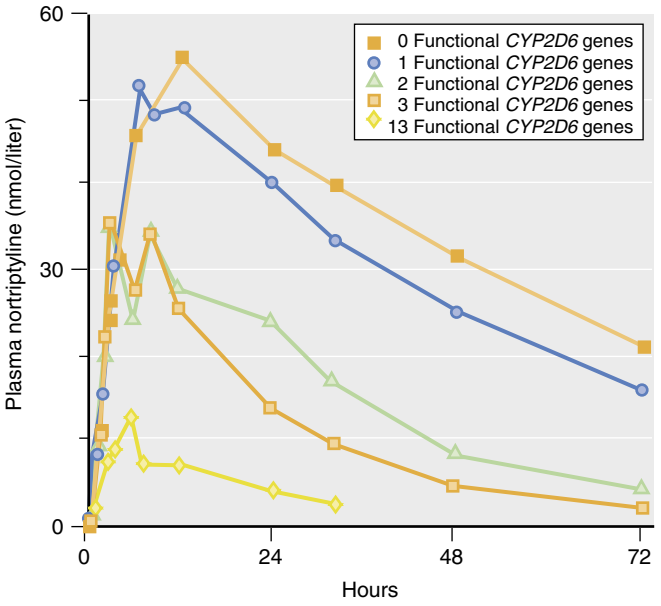


Figure 24-5 Pharmacogenetics of nortriptyline. Mean plasma concentrations of nortriptyline after a single 25-mg oral dose are shown in subjects with 0, 1, 2, 3, or 13 functional CYP2D6 genes. *(Adapted from Weinshilboum R: Inheritance and drug response. N Engl J Med 348:529-537, 2003.)*

Pharmacogenomics of Drug Metabolism

The convergence of pharmacogenetics and human genomics has resulted in the field of *pharmacogenomics*, a term used to describe

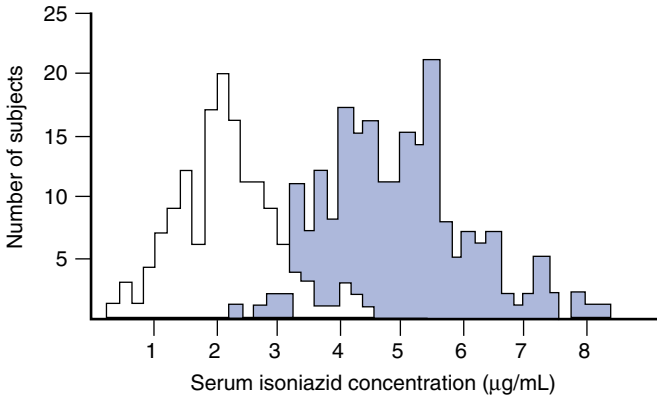


Figure 24-6 Bimodal distribution of serum isoniazid concentrations in a large group of Finnish patients. More than 300 patients were given intravenous injections of 5 mg/kg of isoniazid. Serum drug concentrations were assayed at multiple times after injection. The distribution of serum concentrations of isoniazid is shown 180 minutes after injection. The *blue* histogram represents rapid inactivators and the *black* histogram, slow inactivators. *(From Petri WA Jr: Antimicrobial Mycobacterium complex disease and leprosy. In Hardman JG, Limbird LE, Goodman GA [eds]: Goodman and Gillman's The Pharmacological Basis of Therapeutics, 10th ed. New York, McGraw-Hill, 2001.)*

the influence of variations in DNA sequence on drug responses. Pharmacogenomics holds the promise of personalized medicine: offering patients a precisely targeted drug at a precisely calibrated dose to address a specific condition. The field of pharmacogenomics began with a focus on drug metabolism but has been extended to include the full spectrum of drug disposition, including absorption, transporters, excretion, drug targets, and signal transduction. With completion of the Human Genome Project, the time is rapidly approaching when the sequences of virtually all genes encoding enzymes that catalyze both phase 1 and phase 2 reactions will be known. More than 1.4 million single-nucleotide polymorphisms were identified in the initial screening of the human genome, with over 60,000 in the coding region for genes. Some of these single-nucleotide polymorphisms have already been associated with substantial changes in the metabolism or effects of medications, and some are currently being used to predict clinical response. The potential exists for pharmacogenomics to yield a powerful set of molecular diagnostic tools with which clinicians will select medications and drug doses for individual patients. For example, a growing understanding of pharmacogenomics has led to the implementation of clinical genotyping of certain narrow–therapeutic index drugs such as the thiopurine derivatives azathioprine and 6-mercaptopurine for acute lymphoblastic lymphoma[22] and the colorectal agent irinotecan.[23] The anticoagulant warfarin, which has a narrow therapeutic range and large variations in individual patient dosage requirements, has been studied, and it has been found that mean maintenance doses depend on the CYP2C9 genotype.[24] In reports investigating the genes encoding CYP2C9 and vitamin K epoxide reductase (VKORC1), researchers demonstrated that patients with CYP2C9*2 and CYP2C9*3 allelic variants and the VKORC1 haplotype A/A require lower dosages of warfarin to achieve adequate levels of warfarin with minimal risk of bleeding.[25,26] A more recent report showed that the initial variability in the international normalized ratio (INR) response to warfarin was more strongly associated with genetic variability related to VKORC1 than to CYP2C9.[27] Both the CYP2C9 genotype and the VKORC1 haplotype had a significant influence on the warfarin dose required after the first 2 weeks of therapy. In effect, the maintenance dose of warfarin in persons heterozygous for CYP2C9*2/*3 is lower than the dose in patients who are homozygous for the normal enzyme or in compound heterozygotes. For the homozygous CYP3C9*3 genotype, even smaller doses are required to achieve the desired INR levels for anticoagulation. In the summer of 2007, the Food and Drug Administration found the accumulated evidence related to warfarin dosing compelling enough to warrant a change in the package labeling of warfarin "to highlight the potential relevance of genetic information to prescribing decisions." Predictably, drugs that inhibit CYP2C9, such as amiodarone and fluconazole, when taken with warfarin will result in an enhanced anticoagulant effect and increased risk of bleeding. In contrast, drugs that impair the metabolism of warfarin, such as cimetidine and omeprazole, have only slight potentiating effects on anticoagulation.

Metabolism of Inhaled Anesthetics

Nonhalogenated Inhaled Anesthetics

Nitrous Oxide

Nitrous oxide (N_2O) is the only nonhalogenated anesthetic that currently remains in routine clinical use. This agent is not metabolized in human tissue. However, by means of a physicochemical reaction of N_2O with vitamin B_{12}, N_2O is reductively metabolized by rat and human intestinal bacteria to molecular nitrogen (N_2). Reduction of N_2O in bacteria may occur via a single electron transfer process that results in the formation of nitrogen gas (N_2) and free radicals. N_2O can oxidize vitamin B_{12} and inhibit its coenzyme function. For example, this could affect the activity of methionine synthase, which catalyzes the transmethylation from methyltetrahydrofolate and homocysteine to produce tetrahydrofolate and methionine. Inhibition of methionine synthase has the potential to lead to decreased levels of tetrahydrofolate and methionine and subsequent impairment of DNA synthesis and "carbon 1" metabolic reactions, including methylation. However, such an effect on the activity of vitamin B_{12} would probably be inconsequential with the short courses of exposure to N_2O during anesthesia.

Xenon

The inert noble gases helium, neon, argon, krypton, xenon, and radon have found diverse and expanding applications in clinical medicine.[28] Xenon, krypton, and argon are all chemically inert in most circumstances, and all have anesthetic properties. Xenon is of particular interest because it is the only inert gas that is an anesthetic under normobaric conditions. Xenon was first identified as an anesthetic agent in 1951.[29] Although not approved for clinical use, xenon has been submitted for regulatory medical approval in Europe. Xenon is a normal constituent in atmospheric air at a concentration no greater than 0.086 ppm and thus, unlike all other inhaled anesthetics, it is not an environmental pollutant. The gas cannot be manufactured but is

Table 24-1 Anesthetic Properties of Xenon versus Other Anesthetics

	Xenon	Nitrous Oxide	Isoflurane	Desflurane	Sevoflurane
Oil-gas partition coefficient	1.9	1.4	90	18.7	53.4
Blood-gas partition coefficient	0.14	0.47	1.4	0.42	0.6
Minimum alveolar concentration (%)	71	≈105	1.15	6.0	1.71

recovered in the process of fractional distillation of liquefied air, and after several separation steps, a purity of greater than 99.99% can be obtained. The cost of xenon is presently about $10.00 (U.S.) per liter (100 times more expensive than nitrous oxide), and it may be unlikely to enjoy widespread use because of the expense associated with its extraction from air. If this problem could be overcome, xenon would be the most ideal inhaled anesthetic agent because xenon (minimum alveolar concentration [MAC] of 71%) is more potent than nitrous oxide, can provide surgical anesthesia in 30% oxygen, is very insoluble (blood-gas partition coefficient of 0.14), and has positive medical and environmental effects (Table 24-1). Xenon exhibits minimal cardiovascular and hemodynamic side effects, is not known to be metabolized in the liver or kidney, is not teratogenic, and does not trigger malignant hyperthermia in susceptible swine.[30] Recent evidence suggests both a neuroprotective[31] and a cardioprotective effect after exposure to xenon.[32] Environmental positives are that xenon does not deplete stratospheric ozone or contribute to global warming and the greenhouse effect. The unique combination of analgesia, hypnosis, and lack of cardiovascular depression in this one agent makes xenon a very attractive choice for patients with limited cardiovascular reserve. Xenon has a density of 5.887 g/L, with nitrous oxide and air having densities of 1.53 and 1.00 g/L, respectively. Because of its greater density, xenon does lead to an increase in pulmonary resistance, which results in an increase in the work of breathing.[33] Thus, xenon should be used with caution in patients with moderate to severe chronic obstructive pulmonary disease, the morbidly obese, premature infants, and any other patient in whom an increase in the work of breathing might have adverse effects.

Xenon was first used successfully for general anesthesia in human volunteers and patients in the 1950s,[29,34] was largely forgotten for 40 years, and then was rediscovered in 1990.[35] Over the past 20 years, xenon has been studied intensively in Europe and Japan in a number of clinical trials with very promising results.[36-38] Lachmann and colleagues showed that patients anesthetized with 70% xenon and 30% oxygen required 80% less supplemental fentanyl than did a similar group anesthetized with 70% nitrous oxide and 30% oxygen.[35] In a comparison of 30 American Society of Anesthesiologists (ASA) class I and II patients undergoing total abdominal hysterectomy and receiving either 60% xenon, 60% nitrous oxide with 0.5% isoflurane, or 60% nitrous oxide with 0.7% sevoflurane (all patients had epidurals and received mepivacaine to control the heart rate and blood pressure to within 20% of baseline), Goto and associates found that emergence from xenon anesthesia was two to three times faster than either comparison group.[39] In a randomized controlled multicenter trial, a total of 224 patients from six centers received either 60% xenon in 40% oxygen or 60% nitrous oxide in 0.5% isoflurane, with 1 µg sufentanil administered if indicated by defined criteria.[40] This study demonstrated significantly faster recovery from xenon anesthesia than from isoflurane–nitrous oxide anesthesia. Goto and coworkers showed that hemodynamic stability was better with xenon than with nitrous oxide with respect to maintenance of left ventricular systolic function.[41] More recently, a randomized multicenter trial was undertaken to compare left ventricular function in patients without cardiac disease who were undergoing elective surgery under either xenon or isoflurane anesthesia.[42] Xenon did not reduce contractility, whereas isoflurane decreased the contractile index, suggesting that xenon provides favorable cardiovascular stability in patients without cardiovascular disease. Although it is clear that emergence from xenon anesthesia is more rapid than emergence from desflurane or propofol anesthesia, studies have not found any significant differences in postoperative cognitive measures in patients exposed to these two agents.[43] In a recent study involving ASA III patients undergoing aortic surgery and receiving xenon ($n = 20$) or remifentanil ($n = 19$), no advantage of total intravenous anesthesia over xenon was demonstrated.[44] A recent study that included 40 ASA III and IV patients with known coronary artery disease randomized to either xenon ($n = 20$) or propofol ($n = 20$) anesthesia, both supplemented with remifentanil, showed higher arterial pressure and better left ventricular function, as assessed by echocardiograph indices, with xenon than with propofol.[45] It is certainly too early to know whether xenon anesthesia improves clinical outcomes, particularly in high-risk patients, and thus justifies the additional cost associated with its use in clinical anesthesia.

During xenon anesthesia, nitrogen released from the patient's body accumulates in the anesthesia circuit. Consequently, it is necessary to perform prolonged denitrogenation before starting xenon administration to reduce the risk for hypoxia. Another technical challenge lies in the transition from denitrogenation to closed-circuit xenon anesthesia. One could simply increase fresh gas flow (too expensive) or add xenon to the circuit as oxygen is consumed by the patient. This second method is too slow because patients typically consume only 200 to 250 mL of oxygen per minute. Several investigators use a second anesthesia machine already primed with 4 L of xenon. Thus, xenon must be given with a rebreathing system, low fresh gas flow, or a closed-circuit system. A closed-circuit system is the most economical technique for the clinical use of xenon. In the 2-hour study from Japan by Goto and colleagues, the estimated cost of providing anesthesia per patient was $170.00 for xenon ($17.00/L), $57.00 for isoflurane, and $60.00 for sevoflurane.[39] These differences in cost would be different in the United States, where xenon is $10.00/L, and would become progressively smaller with a longer duration of anesthesia because the rate of xenon consumption declines exponentially as body tissues become saturated in a closed rebreathing system. The total yearly production of xenon is approximately 6 million L, or enough for about 400,000 anesthetic procedures. If delivery systems become available that allow recycling of anesthetic gases, xenon anesthesia may become more economical and accessible to selected patients who might benefit from its lack of adverse systemic effects.

Halogenated Inhaled Anesthetics

Halothane

Approximately 25% of the halothane ($CF_3CHBrCl$) administered is metabolized to trifluoroacetic acid, chloride (Cl^-), and bromide (Br^-) (Fig. 24-7). The major metabolite in humans is trifluoroacetic acid (CF_3COOH), formed from oxidative metabolism primarily by CYP2E1 and to a lesser extent by CYP2A6.[46] The rate-limiting step in oxidative metabolism is breakage of the carbon-hydrogen bond. The first intermediate formed is probably 1,1,1-trifluoro-2-chloro-2-bromoethanol, which would be expected to rapidly decompose and produce hydrogen bromide and the reactive metabolite trifluoroacetyl chloride (TFA-Cl). This latter metabolite reacts with water to produce HCl and trifluoroacetic acid and with phosphatidylethanolamine, a membrane phospholipid, to form *N*-trifluoroacetyl-2-aminoethanol, which has been identified in urine. The TFA-Cl metabolite of halothane also reacts with tissue proteins to form trifluoroacetylated (TFA)-protein adducts, which will be discussed in the section on hepatotoxicity. Although trifluoroethanol has been identified in the urine of experimental animals, this metabolite and its glucuronide conjugate have not been found in human urine. Likewise, trifluoroacetaldehyde, another possible metabolite, has not been isolated from human urine.

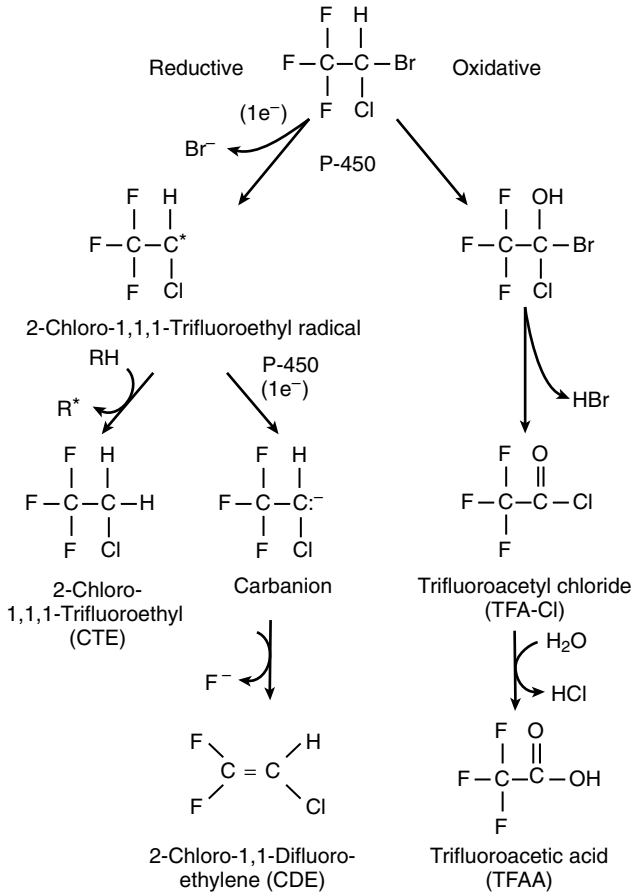


Figure 24-7 Major by-products of oxidative and reductive CYP4502E1-catalyzed halothane metabolism.

An alternative and minor route of halothane metabolism (i.e., <1% of the halothane absorbed) is via a reductive pathway that requires low oxygen tension and can be catalyzed by CYP2A6 and CYP3A4 (see Fig. 24-7).[46] Inorganic Br^- and F^- are end products of this pathway. Two volatile metabolites (2-chloro-1,1-difluoro-ethylene [CDE] and 2-chloro-1,1,1-trifluorethane [CTE]) and a volatile decomposition product of halothane (2-bromo-2-chloro-1,1-difluoroethylene [DBE]) were first identified in the exhaled gases of patients anesthetized with halothane. The formation of CDE and release of F^- probably result from a CYP-mediated two-electron reduction of halothane, whereas the formation of CTE and production of tissue free radicals result from a CYP-mediated one-electron reduction. The suicidal inactivation of CYP observed under hypoxic conditions (<40 torr O_2) is presumably the result of covalent binding of a reactive intermediate of CTE to CYP formed during the metabolism of CTE by CYP. A major pathway of formation of DBE is via the base-catalyzed dehydrofluorination of halothane as a result of its interaction with soda lime. CYP2E1 is inducible by both ethanol and isoniazid and is inhibited by disulfiram.[47] Prolonged exposure to subanesthetic concentrations of halothane results in increased drug metabolism in humans.

Enflurane

Enflurane (CHF_2-O-CF_2-CHClF) is essentially no longer used in the United States, but examination of its metabolism serves to illustrate how relatively minor changes in chemical structure can dramatically affect the extent of metabolism. Approximately 2.5% of the enflurane absorbed is metabolized (Fig. 24-8). Initial oxidation and breaking of the carbon-hydrogen bond may occur at either the chlorofluoromethyl carbon or the difluoromethyl carbon. Studies of the metabolism of enflurane with human hepatic microsomes[48] and isolation of difluoromethoxydifluoroacetic acid from rat liver, human urine, human hepatic microsomes, and cDNA-expressed CYP2E1[48] suggest that primary metabolism occurs at the chlorofluoromethyl carbon. Detection of insignificant amounts of chlorofluoroacetic acid further suggests that there is very little metabolism at the difluorormethyl carbon. The reactive intermediate formed from oxidation at the chlorofluoromethyl carbon can either hydrolyze to produce difluoromethoxydifluoroacetic acid or acetylate tissue protein to produce an adduct with immunogenic potential.[49] In either case, inorganic F^- is a product of these chemical reactions.

Surgical patients treated on a long-term basis with phenobarbital, phenytoin, or diazepam or who consumed ethanol before anesthesia with enflurane did not have elevated serum F^- concentrations when compared with untreated patients. In contrast, about 50% of surgical patients maintained on chronic isoniazid therapy demonstrated significantly elevated serum F^- concentrations.[50] Studies with purified CYP2E1 from humans[51] demonstrate that this CYP isoform is predominantly, if not exclusively, responsible for the defluorination of enflurane in human liver. Isoniazid treatment seems to significantly enhance enflurane metabolism in humans.[51]

Isoflurane

Isoflurane (CHF_2-O-CHCl-CF_3), an isomer of enflurane, is metabolized even more slowly than halothane or enflurane is (≈0.2%) (see Fig. 24-8). The metabolism of isoflurane results from oxidation of the α-carbon by hepatic CYP2E1.[52,53] The initial hydroxylated intermediate can decompose to produce a reactive

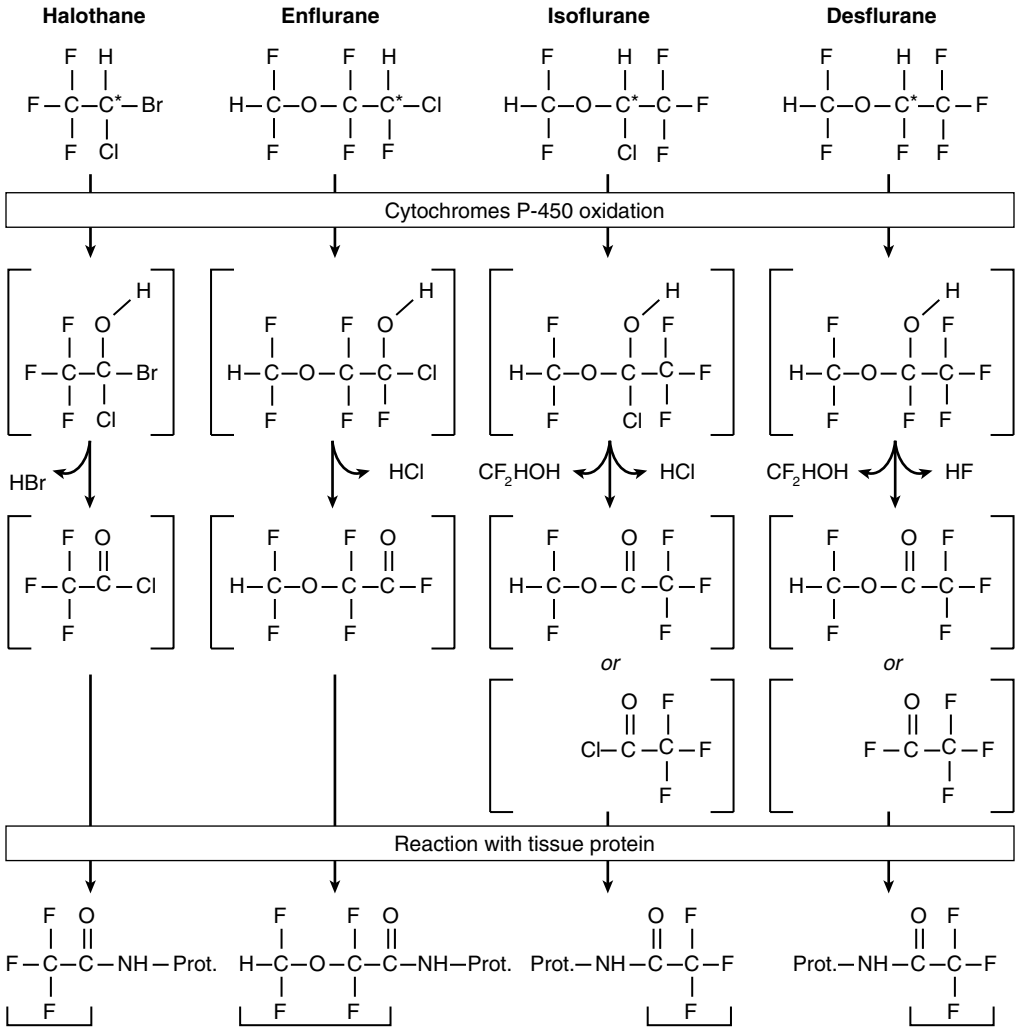


Figure 24-8 Proposed pathways for the CYP4502E1-catalyzed metabolism of halothane, enflurane, isoflurane, and desflurane to acylated hepatic proteins. For halothane, isoflurane, and desflurane, the trifluoracetylated protein adducts are identical in structure, whereas for enflurane the adduct is immunologically similar.

TFA-Cl metabolite identical to halothane or a reactive trifluoroacetyl ester intermediate. Both these products would be expected to react with water to form trifluoroacetic acid or with protein to produce TFA-protein adducts. Very small amounts of inorganic fluoride would be expected to be formed during this metabolism.

Desflurane

Desflurane (CHF_2-O-CHF-CF_3) is thought to be metabolized in a manner similar to isoflurane because these two molecules differ by only one atom at the α-carbon position, with desflurane having a fluorine atom and isoflurane having a chlorine atom (see Fig. 24-8). However, the fluorine atom substitution decreases metabolism at the α-carbon position significantly so that the F^- and nonvolatile organic fluorine compounds formed from the metabolism of desflurane are considerably less than with isoflurane. Peak serum F^- concentrations are seen immediately after exposure to desflurane.[54]

Sevoflurane

The rate of sevoflurane (CH_2F-O-CH-$[CF_3]_2$) defluorination in vitro is approximately the same as that of methoxyflurane. However, serum F^- concentrations after sevoflurane administration are significantly less than those after methoxyflurane,[55-57] presumably the result of large differences in the blood-gas partition coefficients of the two agents (0.69 for sevoflurane versus 10.2 for methoxyflurane). Approximately 5% of the sevoflurane absorbed is biotransformed.[57,58] The fluoromethoxy C-H bond is the site of oxidative metabolism of sevoflurane, which leads to the formation of hexafluoroisopropanol (HFIP) and inorganic F^- (Fig. 24-9).[59,60] Experiments using CYP2E1 purified from humans have confirmed the results of in vitro studies with liver microsomes that this isozyme is the predominant, if not the only CYP participating in sevoflurane oxidation and F^- formation.

In a study of human volunteers, HFIP accounted for 80% of the nonvolatile organic fluorine-containing compounds detected in the blood and urine of volunteers anesthetized with sevoflurane. HFIP is not subject to further degradation, but it is conjugated to form a glucuronide conjugate.[58,61] Studies in patients and volunteers have shown that much of the metabolism of sevoflurane to F^- occurs during anesthetic exposure, presumably because of the low tissue solubility of sevoflurane and the stability of its metabolites.[62,63] Peak serum F^- concentrations are reached within a few hours of the end of anesthesia.

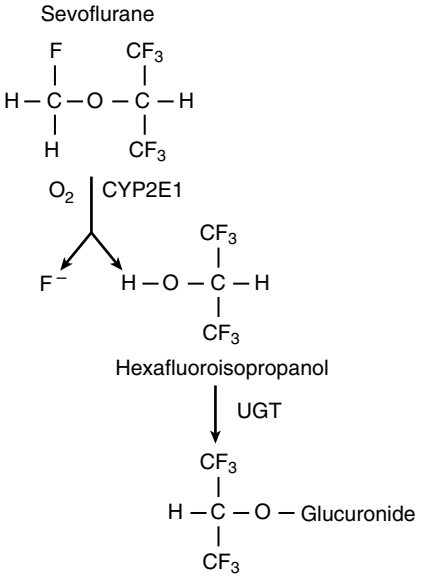


Figure 24-9 In vivo metabolism of sevoflurane to inorganic fluoride and hexafluoroisopropanol. UGT, uridine 5′-diphosphate glucuronosyltransferase

Stereoselective Metabolism of Inhaled Anesthetics

Until recently, drug stereochemistry has been an area of relative neglect with regard to the preparation of therapeutic agents. Many drugs, including the fluorinated anesthetics, are commercially prepared and used therapeutically as racemic mixtures. A racemic mixture contains an equal amount of the two enantiomers. Enantiomers are simply nonsuperimposable mirror images, such as your left and right hands. Clinical experience has made it increasingly clear that enantiomeric forms of drugs may differ in their potency, toxicity, and pharmacologic, pharmacokinetic, and pharmacodynamic properties and actions.[64-67] Such nonsuperimposable objects are said to be chiral. The most common chiral origin is the presence of an asymmetric center, a carbon atom attached to four different substitute groups. Enantiomers are optically active; that is, a single enantiomeric form rotates the plane of polarized light passing through an aqueous solution of the enantiomer in a clockwise or counterclockwise direction. The preferred method of the International Union of Pure and Applied Chemistry (IUPAC) for the classification of enantiomers is the Cahn-Perlog-Ingold convention or (*R*/*S*) classification. In this system the four substitutions around the chiral center are assigned priorities that depend on atomic number and atomic mass. When looking down the carbon bond to the substituent with the lowest priority, if the other substituents are ordered from higher to lower in a clockwise direction, the assignment is the (*R*)-configuration; if counterclockwise, the (*S*)-configuration is designated.

The reduced cost of production of purified enantiomeric solutions has made these compounds increasingly available for clinical use. Whether the clinical use of a single stereoisomer provides significant advantages depends on both the pharmacokinetic and the pharmacodynamic properties of the respective enantiomers. For example, (*S*)-penicillamine is used to treat Wilson's disease, cystinuria, and rheumatoid arthritis because of toxicities associated with the racemic drug.[68] The calcium channel blocker (*S*)-verapamil is 10 to 20 times more potent than (*R*)-verapamil and thus appears to be a better antiarrhythmic, antianginal, and antihypertensive agent.[69] The cardiovascular drug (*S*)-propranolol is clinically useful as an antihypertensive and antianginal agent, whereas (*R*)-propranolol, which lacks cardiovascular effects, is useful in the treatment of hypothyroidism.[70,71] Ketamine is provided for clinical use as a racemic mixture, although (*S*)-ketamine has superior efficacy, faster elimination and recovery characteristics, and fewer side effects ranging from restlessness and agitation to emergence reactions than racemic ketamine does.[72] (*S*)-Ketamine is also three times more potent than (*R*)-ketamine as an anesthetic and analgesic agent, and enantiomeric stereoselectivity of the hepatic metabolism of ketamine by microsomal enzymes has been demonstrated.[73] Ropivacaine, the (*S*)-enantiomer of a bupivacaine homolog, and levobupivacaine ([*S*]-bupivacaine) were developed as alternatives to racemic bupivacaine because of its known central nervous system and cardiovascular toxicity. Ropivacaine is less potent than (*S*)-bupivacaine or racemic bupivacaine in blocking sodium channels, although the anesthetic and analgesic effects of the two drugs are similar.[74] Even though both bupivacaine and ropivacaine demonstrate similar plasma protein binding, ropivacaine has lower lipid solubility, higher plasma clearance, and a shorter elimination half-life $\left(t_{1/2\beta}\right)$ than racemic bupivacaine does.[75] Like ropivacaine, levobupivacaine has been shown to have a reduced incidence of toxicity in comparison to its (*R*)-isomer.[76] (*R*)-Cisatracurium offers clinical advantages over racemic atracurium because of its lack of histamine-releasing properties and its higher neuromuscular blocking potency. Ethanol is widely used as a pharmaceutical solvent and has recently been shown to decrease the unbound fraction of (*S*)-warfarin while increasing the unbound portion of (*R*)-warfarin. Perhaps the most infamous example of enantiomeric differences between optical isomers was observed with the drug thalidomide. The (*R*)- and (*S*)-isomers of thalidomide, as well as the racemic mixture, are equally active hypnotics; however, (*S*)-thalidomide is transformed into metabolites that proved to be embryogenic and teratogenic.[77]

Commercial halothane is a racemic mixture of (*R*)- and (*S*)-enantiomers (Fig. 24-10). As discussed previously, metabolic studies have shown that racemic halothane undergoes oxidative metabolism catalyzed by CYP2E1 to TFA-Cl, which covalently binds to several hepatic proteins that are believed to be involved in the immune response leading to halothane hepatotoxicity. To investigate whether CYP2E1 catalyzes the metabolism of halothane in a stereoselective fashion, the enantiomers of halothane were prepared and tested in vivo for their ability to form covalently bound TFA-protein adducts in the liver of mice. It was found that halothane does undergo stereoselective metabolism, with the (*R*)-isomer producing significantly greater amounts of TFA-protein adducts in liver than the (*S*)-isomer does (Fig. 24-11).[78] Because the anesthetic potency of the isomers appears to be equal,[79] these findings suggest that the (*S*)-isomer of halothane might be a safer inhaled anesthetic agent than the (*R*)-isomer or the racemic mixture. This idea is supported by the observation that the hepatotoxicity caused by halothane, enflurane, isoflurane, and desflurane is related to their relative degree

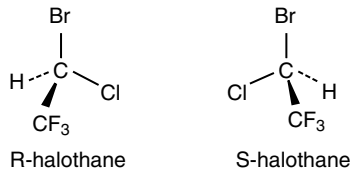


Figure 24-10 (*R*)- and (*S*)-enantiomers of halothane

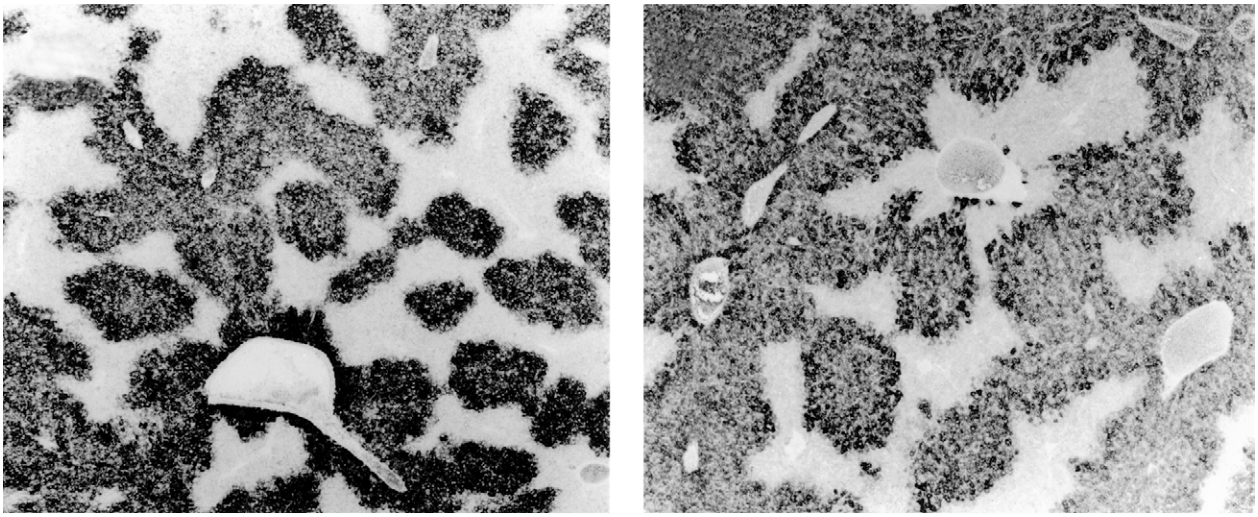


Figure 24-11 Immunochemical detection of trifluoracylated proteins in the livers of mice 24 hours after treatment with (*R*)- or (*S*)-halothane. **A**, From a mouse treated with (*R*)-halothane. **B**, From a mouse treated with (*S*)-halothane (original magnification ×50). *(From Njoku D, Laster MJ, Gong DH, et al: Biotransformation of halothane, enflurane, isoflurane and desflurane to trifluoroacetylated liver proteins: Association between protein acylation and liver injury. Anesth Analg 84:173-178, 1997.)*

of oxidative metabolism in vivo to reactive acyl halide metabolites (see Fig. 24-8). Because enflurane, isoflurane, and desflurane also contain an asymmetric carbon atom, the potential for stereoselective metabolism also exists with these agents. Indeed, other researchers have found that the ratio of (*R*)-enflurane metabolism to (*S*)-enflurane metabolism in human liver microsomes was 1.9:1.[48] It has also been demonstrated that optical isomers of isoflurane exhibit a significant difference in anesthetic potency,[80] differentially increase sleep time in mice,[81] and exhibit modest but significant stereoselectivity at the type A γ-aminobutyric acid ($GABA_A$) receptor.[82-84] Investigations with stereoisomers of anesthetic agents such as etomidate[85] also help provide a better understanding of the mechanisms of action of anesthetic agents. The clinical use of chiral anesthetic drugs as equal mixtures of their enantiomers has been accepted practice in medicine and anesthesia. With increased knowledge and awareness regarding drug toxicities, future anesthetic drugs may be developed and marketed as single, more potent and potentially less toxic optically active isomers.

Toxicity of Inhaled Anesthetics

Hepatitis

Volatile halogenated inhaled anesthetics have been associated with hepatotoxicity since the introduction of chloroform in 1847. Chloroform, as well as carbon tetrachloride and trichloroethylene, were all abandoned as anesthetic agents because of the often observed hepatotoxicity associated with their use. With the introduction of halothane into clinical practice in 1956, this compound quickly gained widespread acceptance and use. Halothane was the first of the fluorinated alkane anesthetics and represented a major advance in general anesthetics because it was safe, nonflammable, nonexplosive, and well tolerated by patients. However within 2 years of its introduction, numerous reports of hepatotoxicity and massive and often fatal hepatic necrosis associated with its use appeared in the medical literature. As a result of continuing reports, a large retrospective analysis was undertaken, "The National Halothane Study," under the auspices of the Committee on Anesthesia of the National Academy of Sciences National Research Council.[86] The purpose of this study was to compare the mortality and incidence of postoperative hepatic necrosis associated with halothane with that of other general anesthetics (ether, cyclopropane, and balanced anesthesia). The study reviewed 865,515 general anesthetics from 1959 to 1962 at 34 medical institutions and identified 82 cases of fatal hepatic necrosis. Drug-induced hepatic injury was suggested in nine of these cases, and seven of the nine patients had received halothane. Furthermore, four of the seven patients had received halothane on more than one occasion during the preceding 6 weeks. The study concluded that the mortality associated with the use of halothane compared favorably with that of other general anesthetics in use at the time and estimated the incidence of fatal hepatic necrosis associated with halothane to be 1 in 10,000 halothane anesthetics. It was further concluded that "unexplained fever and jaundice in a specific patient following the use of halothane should serve as a warning sign to avoid its subsequent use in that patient."[86] These findings provided the impetus for much of the work done over the past 50 years on the etiology of inhaled anesthetic hepatotoxicity, which is now accepted as a distinct clinical entity. Indeed, several hundred cases of hepatotoxicity have been attributed to halothane and approximately 50 cases to enflurane, but the incidence appears to be even lower with isoflurane and desflurane.[87]

Drug-induced liver injury may be caused by intrinsic or idiosyncratic mechanisms. Liver injury that is intrinsic to a particular pharmacologic agent is predictable and largely independent of host influences. Acetaminophen and chloroform are examples of pharmacologic agents that cause an intrinsic form of

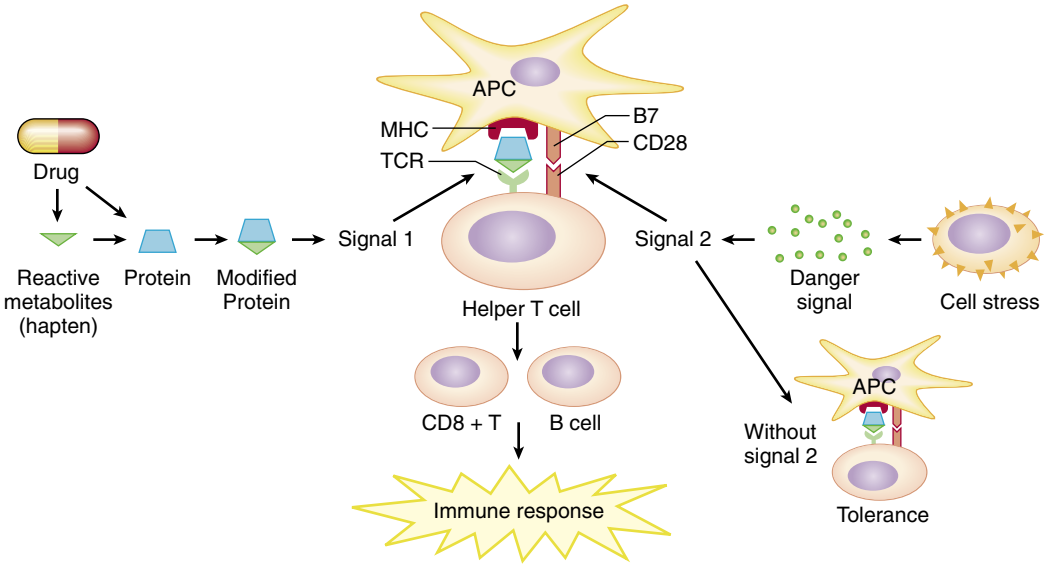


Figure 24-12 Hapten and danger hypotheses. The hapten hypothesis involves a chemically reactive drug or reactive metabolite acting as a hapten by binding to protein, which is then taken up by an antigen-presenting cell (APC) and processed. The processed antigen is presented in the context of the major histocompatibility complex (MHC) to a helper T cell; this represents signal 1. The danger hypothesis involves cell damage or stress (possibly caused by the drug or reactive metabolite) leading to the release of danger signals that result in upregulation of costimulatory factors; this is signal 2. Without signal 2, the result is immune tolerance. *(Redrawn from Uetrecht J: Idiosyncratic drug reactions: Past, present, and future. Chem Res Toxicol 21:84-92, 2008.)*

liver injury. The dose threshold for intrinsic toxicity may be achieved as a result of increased production, altered tissue sequestration, or decreased elimination of toxic metabolites. Moreover, other pharmacologic agents or chemicals, altered physiologic states, or pathologic states may affect the dose threshold for these toxicities. Nonetheless, when the dose threshold is surpassed, tissue injury may be caused by direct actions of the metabolite, which may result in inhibition or modification of the enzymatic and structural systems necessary for maintaining cellular integrity. In contrast to the intrinsic mechanisms of toxicity, many pharmacologic agents produce adverse reactions through an idiosyncratic pathway. These reactions are generally host dependent, relatively rare, and difficult to produce in animals in which the mechanisms can be systematically studied. Many idiosyncratic reactions, including liver injury caused by inhaled anesthetics, may have an immune basis. The injury is not due to the prodrug itself because small molecules are not immunogenic. Instead, reactive metabolites bind irreversibly to tissue proteins and produce a drug-protein adduct (or hapten-carrier conjugate) that can induce an immune response. The hapten hypothesis involves a chemically reactive drug or reactive metabolite acting as a hapten by binding to protein, which is then taken up by an antigen-presenting cell and processed. The processed antigen is presented in the context of the major histocompatibility complex to a helper T cell (signal 1). The danger hypothesis involves cell damage or stress (possibly caused by the drug or reactive metabolite) leading to the release of danger signals that result in the upregulation of costimulatory factors (signal 2). Without signal 2, the result is immune tolerance (Fig. 24-12).[88] In addition to the inhaled anesthetics halothane, enflurane, isoflurane, and desflurane, other examples of well-studied immune-mediated idiosyncratic drug reactions include penicillin and acetaminophen.[89]

Immune-Mediated Halothane Hepatotoxicity

Two distinct types of hepatic injury have been associated with the clinical use of halothane (Table 24-2). Mild injury occurs in 20% of adults who receive halothane, and laboratory tests show mild elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The second type of injury is the fulminant form, commonly known as halothane hepatitis, which is characterized by elevated ALT, AST, bilirubin, and alkaline phosphatase levels; massive hepatic necrosis; and a fatality rate ranging from 50% to 75%. Because of the potential for halothane-induced hepatitis, halothane is not generally recommended for use in adults. In several medical malpractice cases, injury or death as a result of the use of halothane has been successfully litigated against anesthesia health care providers. Although there are some indications for the use of halothane in adults, they must be clearly evaluated and written in the medical record before each such use.

Table 24-2 Clinical Features of Halothane Hepatitis

Mild Form	Fulminant Form
Incidence, 1 : 5	Incidence, 1 : 10,000
Repeat exposure not necessary	Multiple exposures
Mild elevation of ALT, AST	Marked elevation of ALT, AST, bilirubin, alkaline phosphatase
Focal necrosis	Massive hepatic necrosis
Self-limited	Mortality rate, 50%
	Antibodies to halothane-altered protein antigens

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 24-3 Halothane Antigens

Molecular Mass (kd)	Protein
100	Endoplasmin
82	GRP-78
80	ERP-72
63	Calreticulin
59	Carboxylesterase
58	Protein disulfide isomerase (isoform)
57	Protein disulfide isomerase
54	Cytochrome P450

Halothane hepatotoxicity appears to link reactive metabolite formation and the hapten hypothesis. Halothane is oxidized by CYP2E1 to the reactive TFA-Cl metabolite (see Fig. 24-12). Although the incidence of liver failure is low, most patients in whom halothane hepatitis develops have antibodies against TFA-modified proteins. This implies that modification of protein by the reactive metabolite has led to an immune response. In addition, many patients have antibodies against native proteins. Patients often have a clinical history of multiple anesthetic exposure to halothane and one or more symptoms suggestive of ongoing immune processes, including fever, rash, arthralgia, and eosinophilia.[90-98] There is no evidence that the antibodies observed in halothane hepatitis actually mediate liver damage; it is entirely possible that they are just markers of an immune response. It appears that the TFA-protein adducts (Table 24-3) produced by the oxidative metabolism of halothane induce a cytotoxic T-cell response in sensitized individuals that on subsequent exposure leads to halothane hepatitis (Fig. 24-13).[99,100]

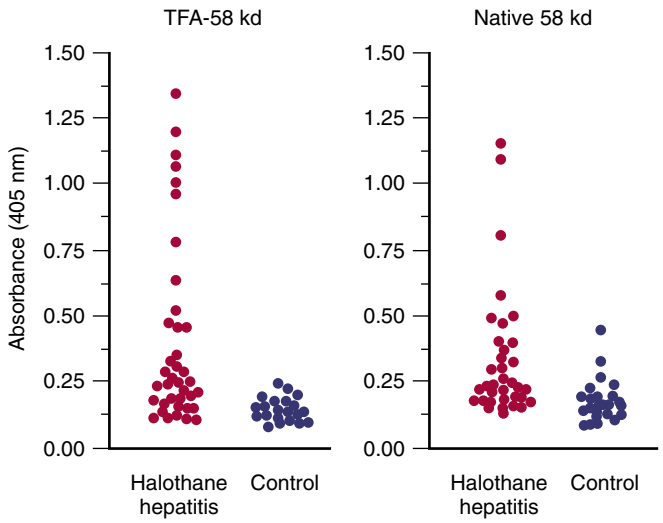


Figure 24-13 Enzyme-linked immunosorbent assay for the sera screening of patients with halothane hepatitis for antibodies that react with trifluoroacetylated 58-kd and native 58-kd proteins. All sera from 40 halothane hepatitis patients and 32 control patients were assayed at a 1 : 100 dilution. *(Adapted from Martin JL, Reed GF, Pohl LR: Association of anti-58 kDa endoplasmic reticulum antibodies with halothane hepatitis. Biochem Pharmacol 46:1247-1250, 1993.)*

Halothane Hepatitis in the Pediatric Population

The first case of halothane hepatitis in a child was reported in 1959.[101] Since that time there have been numerous reports of hepatotoxicity and massive hepatic necrosis after halothane anesthesia in children (also see Chapter 82). Two retrospective studies have examined the incidence of halothane-associated hepatotoxicity in children. The first explored 165,400 halothane anesthetics in a children's hospital in the United Kingdom over the 23-year period from 1957 to 1979 and determined the incidence of halothane hepatitis in children to be 1 in 82,000.[102] The second study examined 200,311 cases from 1958 to 1983 in a children's hospital in the United States. Only one patient in this study was concluded to have halothane hepatitis.[103] In 1987, data were reported describing halothane hepatitis in seven children aged 11 months to 15 years, all of whom had received multiple halothane anesthetics.[104] The diagnosis in this study was confirmed in all but one child by the presence of serum antibodies that reacted with halothane-altered hepatocyte antigens. There was one fatality in this group, and other causes of liver disease were excluded by the investigators. These findings indicate that the clinical syndrome of halothane hepatitis does exist in prepubertal children, although it is much rarer than in adults. The reason for the difference in incidence of halothane hepatitis observed between adults and children is not clear at present because halothane has been found to be metabolized to a similar degree in both adults and children and immune competence is known to exist from birth.

Enflurane, Isoflurane, Desflurane, and Sevoflurane

The incidence of liver injury caused by the fluorinated inhaled anesthetics follows the order of halothane > enflurane > isoflurane > desflurane and correlates with the extent of their oxidative metabolism (see Fig. 24-8), which is halothane (≈20%), enflurane (≈2.5%), isoflurane (≈0.2%), and desflurane (≈0.01%).[105] Because all of these inhaled anesthetics appear to form protein adducts that are identical or related in structure to those of halothane, it seems possible that they may cause liver injury by a mechanism similar to that of halothane, though at an appreciably lower incidence (Fig. 24-14). This lower incidence would be due to the lower levels of potentially immunogenic protein adducts formed from these drugs than from halothane when they are oxidatively metabolized by CYP2E1 (Fig. 24-15).

Enflurane was first used in North America in 1966. Although it is used much less commonly today, during the period of its highest use there were relatively few case reports of liver damage associated with it. In 1986, Eger and coauthors reviewed 10 published reports and several unpublished reports of liver damage after enflurane. Many of the cases were missing critical information on the duration of anesthetic exposure, histologic confirmation of hepatic lesions, and previous exposure to hepatic disease and hepatotoxic agents. In addition, several patients had been hypotensive or severely ill or demonstrated signs of shock and underwent operations with known potential for hepatic dysfunction. Obviously, these investigators had no choice but to conclude that the evidence did not support the existence of enflurane-associated hepatic dysfunction similar to that seen with halothane. Nevertheless, several case reports suggest that enflurane anesthesia given to patients previously anesthetized with or sensitized to halothane can result in hepatotoxicity. For example, it was found that protein adducts of halothane and enflurane, formed in the liver of rats treated separately with these drugs,

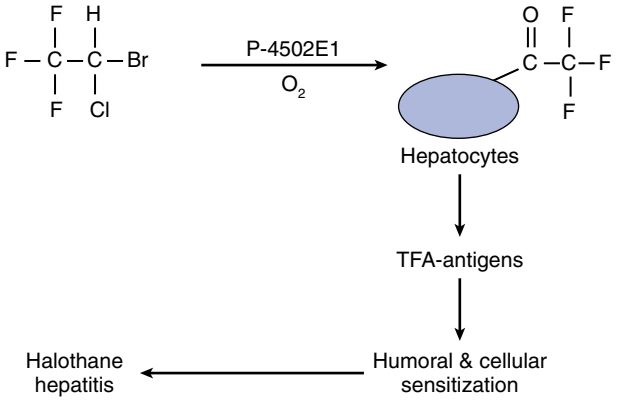


Figure 24-14 Pathway for generation of the immune response after exposure to anesthetic by susceptible patients. Halothane is metabolized to a trifluoroacetylated (TFA) adduct that binds to liver proteins. The altered protein is seen as nonself and generates an immune response, which on subsequent exposure leads to toxicity and cell death. A similar process may occur after exposure to other fluorinated drugs that generate a TFA or similar adduct. *(Adapted from Njoku D, Laster MJ, Gong DH, et al: Biotransformation of halothane, enflurane, isoflurane and desflurane to trifluoroacetylated liver proteins: Association between protein acylation and liver injury. Anesth Analg 84:173-178, 1997.)*

reacted with serum antibodies from patients in whom halothane hepatitis was diagnosed.[106] This apparent cross-reactivity could be explained by the similarity in structure of the protein adducts of halothane and enflurane (see Fig. 24-8).

Isoflurane, the structural isomer of enflurane, became available clinically in 1981. The combination of its minimal oxidative metabolism and low blood-gas solubility contributed to the popularity of this anesthetic agent. Moreover, for several years after its introduction there were no published reports of hepatic injury after the administration of this anesthetic. In 1991, a case report of fulminant hepatic failure after repeated isoflurane exposure was published.[107] In the same patient, the second isoflurane anesthetic for pyloroplasty was administered for a 2-hour period, and the third anesthetic for gastrojejunostomy was isoflurane for 30 minutes, followed by enflurane for 150 minutes. This patient had a far greater serum transaminase and alkaline phosphatase concentration after the second anesthetic than after the third exposure to anesthesia. In 2000, a case of fatal hepatotoxicity after re-exposure to isoflurane was reported in which histologic evidence of centrilobular injury and microvesicular fatty changes were found.[108] Similar histopathologic changes were observed in another case of isoflurane liver injury.[109] In addition, TFA-protein

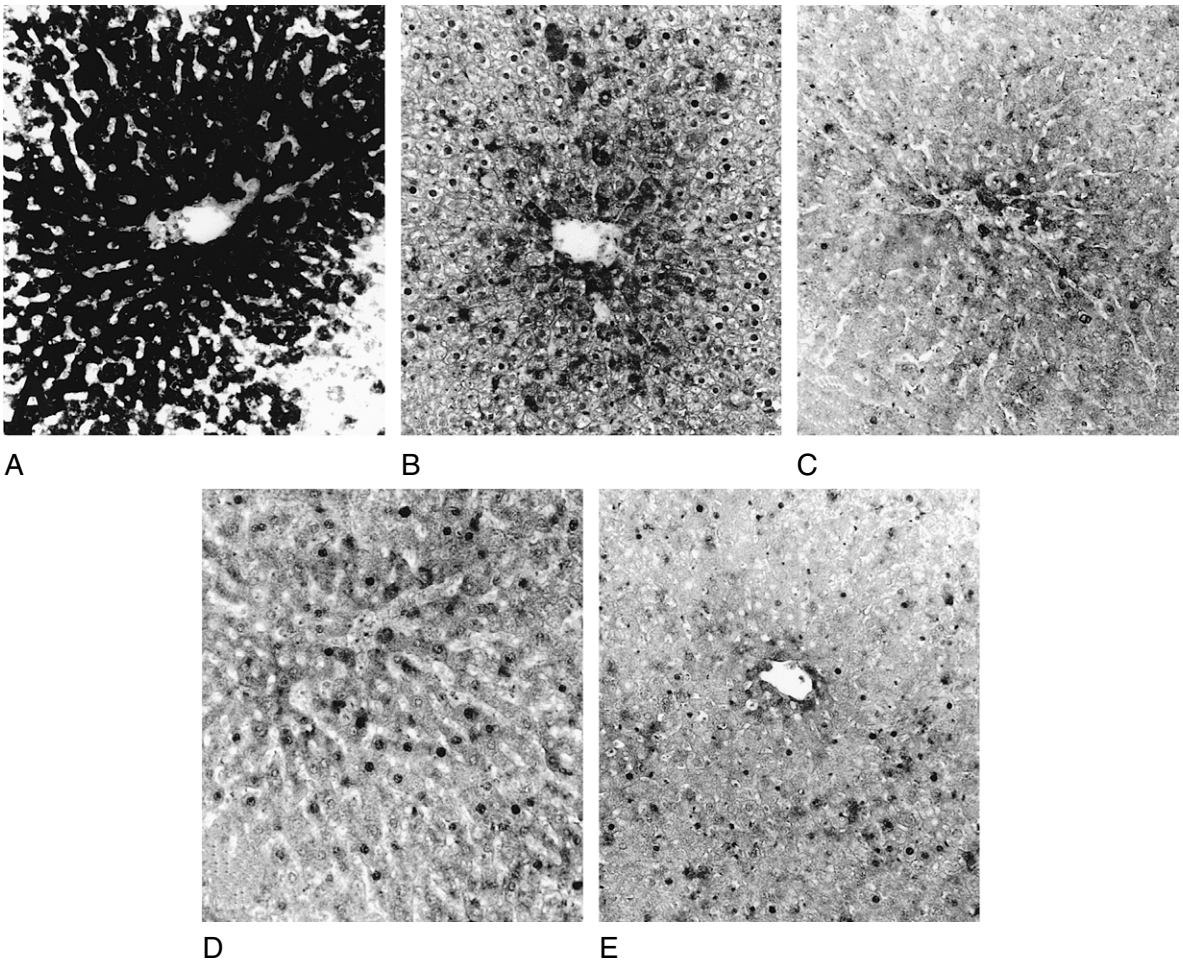


Figure 24-15 Livers from rats exposed to either halothane (**A**), enflurane (**B**), isoflurane (**C**), desflurane (**D**), or oxygen (**E**) were incubated with antitrifluoroacetylated rabbit serum to detect the presence of trifluoroacetylated liver proteins after exposure to anesthetic. Evidence of an immune response to trifluoroacetylated liver proteins can be seen in **A**, **B**, and **C**. No immunoreactivity is evident in **D** or **E**.

adducts were detected in the damaged mitochondria by electron microscopy. This finding suggests that the TFA-protein adducts may have contributed to the mitochondrial injury by a mechanism that was unrelated to an immunopathologic reaction induced by the TFA-protein adducts.

Although earlier studies of patients and volunteers did not suggest that desflurane is associated with hepatotoxicity in humans,[110,111] there are a handful of reports describing postoperative hepatotoxicity after exposure to desflurane. The first was a patient in whom fulminate hepatitis developed 12 days after receiving a desflurane anesthetic.[87] Because this patient had been exposed to halothane 10 and 18 years previously for periods of less than 1 hour, it is possible that the patient may have been sensitized to halothane. After exposure to desflurane, a cross-sensitization reaction may have occurred because both halothane and desflurane can form TFA-protein adducts. A second case has been reported in which a weak association between desflurane exposure and hepatotoxicity was described.[112] More recently, two additional cases were reported; the first was in an adult patient,[113] and the other is the first report of desflurane toxicity in a pediatric patient.[114]

There are several early case reports in the Japanese literature of sevoflurane being associated with postoperative hepatic dysfunction in patients ranging in age from 11 months to 63 years.[115,116] However, in all these reports, the association between sevoflurane exposure and liver injury as manifested by elevations in liver transaminases is extremely weak. In a single recent report from this country, postoperative liver injury was seen after sevoflurane anesthesia for appendectomy. However, this 3-year-old girl was suffering from iatrogenic acetaminophen intoxication, and it may be more likely that her injury was the result of acetaminophen rather than sevoflurane.[117] There has been a single case of fulminant hepatic failure and death attributed to sevoflurane anesthesia.[118] This patient died of multiple organ failure triggered by acute hepatic failure 2 days after open heart surgery with sevoflurane, sufentanil, and propofol anesthesia. Other possible causes of liver failure were excluded. It is worth noting again that sevoflurane is not metabolized to antigenic TFA-adducts, so the mechanism of injury in this case remains unexplained. However, it does reinforce the point that any patient sensitized to any of the fluorinated inhaled anesthetics should not be exposed to any of these agents. Several clinical considerations for the safe and reasonable use of fluorinated anesthetic agents are outlined in Box 24-1.

Box 24-1 Clinical Considerations

Halothane should not be used in adult patients without a specific, well-documented indication.

In patients experiencing postoperative hepatotoxicity after fluorinated inhaled anesthetics, these anesthetics should be avoided in the future.

Despite reports of halothane hepatitis in children, halothane remains an acceptable anesthetic choice for use in children.

Enflurane, isoflurane, and desflurane remain safer inhaled anesthetics.

Anesthetic-induced hepatitis remains a diagnosis of exclusion.

Hydrochlorofluorocarbons

Until the year 2000, the chlorofluorocarbons (CFCs) were widely used as industrial refrigerants, foam-blowing agents in the manufacture of plastics, aerosol propellants, food preservatives, and cleaning and sterilizing agents. The major source of CFC environmental contamination was the venting of automobile and truck air conditioning units into the atmosphere. CFCs are extremely stable, nontoxic, and nonflammable and were first identified as the compounds responsible for stratospheric ozone depletion in 1985. CFC molecules emitted into the lower atmosphere may take up to 7 years to diffuse upward into the stratosphere, where intense ultraviolet radiation liberates chlorine atoms, which catalyze reactions that destroy ozone molecules. The ozone-depleting potential of all halogenated hydrocarbons is a function of their molecular stability, stratospheric lifetime, and breakdown products (bromide being the most destructive and fluoride the least). Once in place, these compounds may exist for 100 or more years. Depletion of stratospheric ozone may have adverse health effects worldwide, such as increases in the incidence of skin cancer and cataract formation. As a result, recommendations put forth by The Montreal Protocol on Substances That Deplete the Ozone Layer were adopted by the Environmental Protection Agency in the United States and by several other countries. These recommendations called for total elimination of CFCs by the year 2000.

The addition of hydrogen atoms to CFC molecules to form hydrochlorofluorocarbon (HCFC) molecules (Fig. 24-16) allows degradation of these compounds in the lower atmosphere with little effect on stratospheric ozone. HCFC-123 and HCFC-124 are currently used as a CFC replacement. Because of the striking structural similarity between HCFCs and halothane, it seemed possible that the HCFCs would also form TFA-protein adducts similar to halothane (Fig. 25-17) and possibly cause liver injury. In studies in rats, the relative concentrations of TFA-protein adducts formed in the liver after the administration of these compounds were similar between halothane and HCFC-123, much lower for HCFC-124, and nearly undetectable for HCFC-125.[119] Acute exposure to HCFC-123 has been shown to produce severe hepatotoxicity in guinea pigs, which was enhanced by prior glutathione depletion.[120] In subchronic studies performed in rats and dogs, increased liver weight, slight focal liver necrosis, induction of peroxisomal activity, and hepatocellular and testicular adenomas have been found.[121,122]

Human liver microsomes in vitro show a much higher capacity than rat liver microsomes to bioactivate HCFC-123 to reactive metabolites, suggesting that HCFCs might be hepatotoxic to humans. In this regard, HCFC-123 and HCFC-124 have been implicated in liver injury in humans.[123] In this report, nine workers were accidentally exposed to a mixture of HCFC-123 and HCFC-124 repeatedly. All nine exposed workers were affected to varying degrees. For one severely affected worker, liver biopsy and immu-

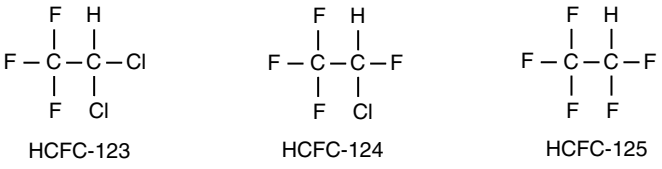


Figure 24-16 Chemical structures of the hydrochlorofluorocarbon analogs of halothane, HCFC-123, HCFC-124, and HCFC-125.

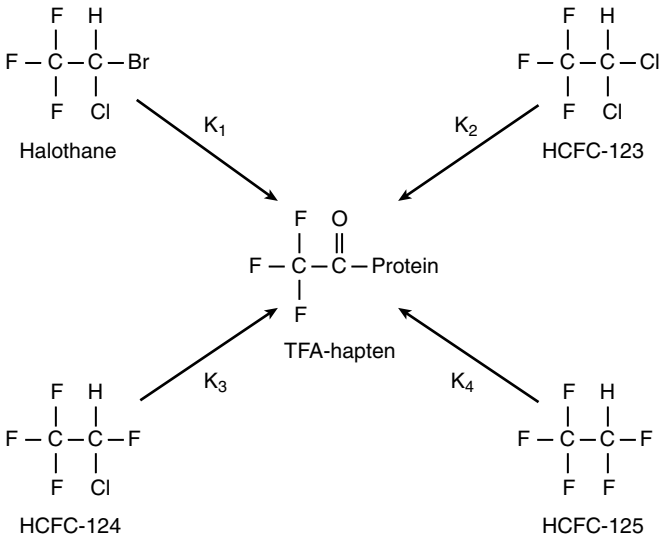


Figure 24-17 Metabolism of halothane and the hydrochlorofluorocarbon replacements HCFC-123, HCFC-124, and HCFC-125 to an identical trifluoroacetyl (TFA) metabolite.

nohistochemical staining for the presence of TFA-protein adducts were performed. The liver biopsy sample showed hepatocellular necrosis that was prominent in perivenular zone 3 and extended focally from portal tracts to portal tracts. TFA-adducted proteins were detected in the surviving hepatocytes. Autoantibodies against CYP2E1 or P58 were found in the sera of five of the nine affected workers. This report demonstrates that repeated exposure of human beings to HCFC-123 and HCFC-124 can result in serious liver injury in a high proportion of the exposed population. By contrast, halothane hepatitis occurs in only a small fraction of individuals repeatedly anesthetized with this compound. A possible explanation for this difference is that halothane is administered acutely to patients, whereas the injured workers were subchronically exposed to the HCFCs. It is possible that protracted formation of TFA-adducted proteins may result in direct toxicity. Alternatively, on the basis of in vitro metabolic studies with human liver CYP2E1, exposure of human beings to HCFC-123 might result in higher concentrations of TFA-adducted liver proteins than produced by halothane.[119] The presence of P58 and CYP2E1 autoantibodies in the serum of the exposed workers indicates that an immune component may have a role in the pathogenesis of HCFC-induced hepatotoxicity.

Presently, HFC-134a is used in virtually all automobile air conditioning units. In 2006, the European Union (EU) agreed to ban any fluorinated gas with global-warming potential (GWP) 150 times greater than an equivalent amount of CO_2 (the GWP of CO_2 is 1). Effectively, HFC-134a will be eliminated in EU countries by 2011. The best replacement candidate to date is a hydrofluoroolefin with a GWP of 4, HFO-1234yf, although unlike HFC-134a, this compound is mildly flammable. Interestingly, beginning in 2011, the German Association for Automotive Industry, which includes Audi, BMW, Daimler, Porsche, and Volkswagen, will begin replacing HFC-134a with CO_2 known in the industry as R-744. The atmospheric burden of CFCs is decreasing as a result of implementation of the Montreal Protocol. The importance of volatile anesthetics on the environment, particularly bromine-containing halothane, continues to be of some concern.

Methoxyflurane

No discussion of immune-mediated hepatotoxicity after inhaled halogenated anesthetics is complete without a brief discussion of methoxyflurane. From a historical perspective, methoxyflurane was introduced into clinical practice in the United States in 1960. There have been a number of reports of hepatic dysfunction and death from hepatic coma after exposure to methoxyflurane. A review of 24 cases of methoxyflurane-associated hepatitis revealed that a syndrome similar to halothane hepatitis may occur.[124] The authors suggested that a rare and indirect immunologic hepatic injury may occur that may have a direct effect on the liver by interfering with the splanchnic circulation. Fortunately, in humans the adverse minor changes in liver function appear to be reversible and may be related to dose, and it is still unclear whether hepatic dysfunction, as measured by bromsulphalein retention and serum hepatic enzyme elevation, was the result of the depth and duration of the anesthetic exposure, the type of operation, the extent of preexisting hepatic disease, or methoxyflurane itself.

Risk Factors for Anesthetic-Induced Hepatitis

The physiologic effects of inhaled halogenated anesthetics on the liver may affect the susceptibility to hepatic dysfunction after their administration. It is well known that inhaled anesthetics can reduce hepatic blood flow to some degree and may in this way contribute to postoperative hepatic dysfunction. However, studies of healthy volunteers found no evidence of hypoxia or anaerobic metabolism in the liver, but hypoxia or abnormalities in hepatic synthetic function may be present in patients with preexisting liver damage or other illnesses. In general, surgical manipulation or disturbance of the surgical site appears to be a more important factor in decreasing hepatic blood flow than the anesthetic agent or technique. In addition, preexisting conditions such as chronic liver disease secondary to alcoholism, viral infection (e.g., viral hepatitis and cytomegalovirus), septicemia, severe burns, nutritional deficiency, and previous or concomitant drug treatment may predispose patients to postoperative hepatic dysfunction. Unfortunately, a patient demonstrating clinical evidence of hepatic dysfunction after exposure to inhaled halogenated anesthetics presents a challenge to the anesthesia care provider because clinical tests to assess hepatic function can be nonspecific and reflect only severe hepatic dysfunction. Even so, traditional measures of hepatic function, such as serum enzymes, aminotransferases, proteins, bilirubin, and alkaline phosphatase, are still used to assess liver damage.

The mortality associated with halothane hepatitis has been reported to range from 40% to 75%. A variety of risk factors have been identified that are commonly associated with this clinical syndrome[125] (Box 24-2). Numerous studies have demonstrated that the risk for halothane hepatitis is greatly increased with use of an increasing number of anesthetics over a short period. Although the basis of this observation is not known, it is possible that increased exposure to TFA-protein adducts as a result of multiple treatments with halothane promotes the chance of a hypersensitivity reaction.

Halothane hepatitis may have a hereditary basis. The low incidence of the disease and the decreasing use of halothane make study of the genetic effects difficult and emphasize the

Box 24-2 Risk Factors for Anesthetic-Induced Hepatitis

- Gender
- Age
- Obesity
- Enzyme induction
- Prior anesthetic exposure
- Genetics

importance of developing an animal model of this disease. Several other associations exist for development of this disease. There is a clear sex difference observed in patients with halothane hepatitis. The disease develops in approximately twice as many females as males, the reason for which is unclear at present. In addition, the vast majority of cases of halothane hepatitis have occurred in middle-aged adults, with relatively few cases reported in prepubertal children,[102,103] and the disease is more common in obese than in nonobese patients. There is currently no evidence to suggest that the incidence of halothane hepatitis is increased in patients with liver disease unrelated to previous halothane exposure. However, because halothane can cause direct hepatotoxicity and other alternatives exist for the provision of general anesthesia, it is prudent to avoid halothane, as well as the other related fluorocarbon inhaled anesthetics, in patients with preexisting hepatic dysfunction.

Assays to Detect Patients Sensitized to Fluorinated Anesthetics

The diagnosis of halothane hepatitis has always been one of exclusion, whereas other potential causes of liver injury, such as hepatitis A, hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus, hepatotoxic drugs, hypotension, and hypoxia, are systematically ruled out as precipitating causes. One of the important goals of halothane hepatitis research is the development of an assay capable of detecting sensitized patients who may be at risk for the development of a hypersensitivity response on re-exposure to halothane or other fluorinated anesthetics, as well as detecting patients with the disease (Box 24-3). The assays that have been developed measure serum antibodies in halothane hepatitis patients. Two general types of immunochemical assays have been reported for detection of these antibodies. The first is immunoblotting. In this procedure, test antigens are microsomal proteins from halothane-treated rats or rabbits that have been separated into constituent polypeptides by sodium dodecyl sulfate–polyacrylamide gel electrophoresis and transferred electrophoretically to the surface of nitrocellulose membranes. With this technique, 42 of 68 (62%) patients with a clinical diagnosis of halothane hepatitis have been found to test positive for the halothane-induced antibodies.[92] Although this approach provides important information about the apparent molecular mass of the neoantigens reacting with the patients' antibodies, it is laborious and time consuming. It also has the potential disadvantage of being inherently less sensitive than other methods because it involves the protein-denaturing conditions of sodium dodecyl sulfate–polyacrylamide gel electrophoresis. This could lead to a decreased level of response if a patient's antibodies were directed against, at least in part, conformational epitopes of the TFA neoantigens.

The second immunochemical assay that has been used for detection of antibodies in the sera of patients with a clinical diagnosis of halothane hepatitis is based on the more rapid, facile, and potentially more sensitive enzyme-linked immunosorbent assay methodology, in which test antigen is applied directly to the wells of a microtiter plate. One reported enzyme-linked immunosorbent assay procedure uses microsomes from halothane-treated rabbits as test antigen. With this approach, investigators have demonstrated the presence of the antibodies in the sera of 16 of 24 (67%)[126] and 28 of 39 (72%)[126] patients with a clinical diagnosis of halothane hepatitis. In another enzyme-linked immunosorbent assay that uses the TFA hapten as test antigen in the form of TFA–rabbit serum, albumin-positive responses in patients with a clinical diagnosis of halothane hepatitis were found in two of six (33%) patients[127] and five of six patients (83%).[128] More recently, purified proteins from rat liver have been used as test antigens in the enzyme-linked immunosorbent assay. In a study using three of the purified TFA-protein neoantigens (100, 80, and 57 kd), 79% of a group of 24 halothane hepatitis patients tested positive with this assay.[129]

Box 24-3 Investigation of Postoperative Liver Dysfunction

- History and physical examination
- Medications
- Previous anesthetic exposure
- Intraoperative course
- Postoperative course
- Clinical tests
- Antibody screening

Fluoride-Associated Nephrotoxicity

Evidence suggests that inhaled anesthetics may induce differential effects on renal physiology. For example, halothane and enflurane decrease the glomerular filtration rate and renal blood flow, whereas isoflurane may also decrease the glomerular filtration rate but has minimal effects on renal blood flow. Conversely, the newest inhaled halogenated anesthetics have minimal effects on renal physiology. Nevertheless, despite these physiologic effects, renal autoregulation protects the kidney from decreases in blood flow that may be caused by the inhaled anesthetic. Moreover, it has been suggested that decreases in the glomerular filtration rate caused by decreases in arterial pressure will return to baseline when arterial pressure normalizes. The metabolism of certain inhaled halogenated anesthetics can produce inorganic fluoride, which may be directly nephrotoxic. The potential for fluoride-associated nephrotoxicity after the administration of inhaled halogenated anesthetics is reviewed subsequently.

Methoxyflurane

Methoxyflurane is no longer used in clinical practice; however, nephrotoxicity from inorganic fluoride released after the metabolism of methoxyflurane is discussed as a basis for understanding the nephrotoxic potential of all current and future fluorinated anesthetics. Studies investigating methoxyflurane demonstrated an association with polyuric renal failure as a result of high levels of inorganic fluoride. Patients with inorganic fluoride levels of less

than 50 µmol/L had no evidence of renal injury. Levels of 50 to 80 µmol/L were associated with moderate injury and 80 to 120 µmol/L with severe injury. Several patients who had inorganic fluoride levels higher than 120 µmol/L died.

Various mechanisms have been proposed to explain the renal injury from inorganic fluoride after the administration of methoxyflurane. One mechanism involves an inorganic fluoride–induced reduction in adenyl cyclase activity and subsequent effect on antidiuretic hormone.[130] Another mechanism involves effects on the renal countercurrent concentrating system by fluoride-induced increases in renal medullary blood flow. Nonetheless, the mechanism involving intrarenal metabolism of methoxyflurane and subsequent intrarenal production of fluoride ion is believed to be a significant cause of the renal toxicity of methoxyflurane.[131]

Despite the overall correlation between nephrotoxicity and peak serum fluoride concentrations, there is individual variability in the level of nephrotoxicity after methoxyflurane. Genetic heterogeneity, drug interactions, preexisting renal disease, and a host of other factors could account for the differences observed among patients.

Enflurane

In contrast to the renal effects of methoxyflurane, enflurane has been associated with only transient decreases in renal concentrating ability. When compared with methoxyflurane, serum fluoride concentrations after enflurane anesthesia peak earlier and fall more rapidly, thus emphasizing the important role of lipid solubility in determining total fluoride exposure (Fig. 24-18). Some clinicians have speculated that enflurane administered to patients with significant preexisting renal disease could produce additional renal dysfunction. Such fears have not been borne out, however.

Isoflurane

Isoflurane, an isomer of enflurane, is defluorinated much less than enflurane is. Because of the resistance to defluorination and the decreased likelihood of other toxicities, prolonged isoflurane administration has been investigated for use outside the operating room. Isoflurane was investigated for its effectiveness in long-term sedation of patients maintained on mechanical ventilation.[132,133] In the first study, the highest serum fluoride concentration was measured in a 2-year-old child who received 73 MAC-hours of isoflurane and had a serum fluoride level of 37.4 µmol/L.[134] In the second study, pediatric patients undergoing mechanical ventilation received isoflurane for 13 to 497 MAC-hours. The highest serum F^- concentration was 26.1 µmol/L, with no alterations in serum creatinine or osmolality.[133] From these studies we can safely conclude that isoflurane can be administered for very long periods without producing clinically significant serum fluoride concentrations; however, influences on metabolism and renal and hepatic function should be carefully considered.

Sevoflurane

Sevoflurane is defluorinated through oxidative metabolism (see Fig. 24-9) to approximately the same extent as enflurane.[135] Clinical studies show that serum fluoride concentrations often peak above 50 µmol/L even when sevoflurane is administered during surgery of average duration.[134] Because of sevoflurane's low blood-gas solubility and its rapid elimination, fluoride concentrations

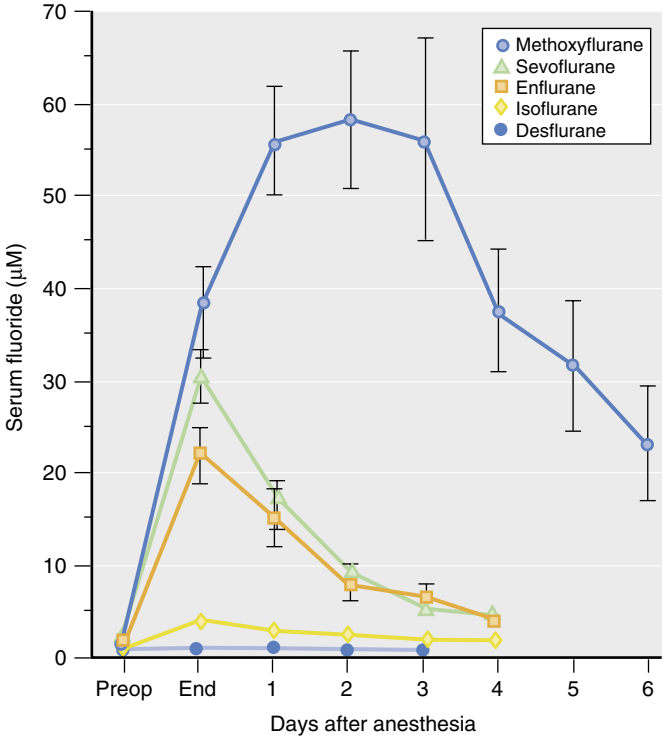


Figure 24-18 Serum inorganic fluoride (F^-) concentration before and after the administration of methoxyflurane, sevoflurane, enflurane, isoflurane, and desflurane anesthesia. After 2 to 3 minimum alveolar concentration (MAC)-hours of methoxyflurane, the mean peak F^- concentration was 61 ± 8 mol/L, which slowly declined. Sevoflurane anesthesia of 3.7 MAC-hours resulted in a mean peak F^- concentration of 30.6 ± 2 mol/L, which declined more rapidly than methoxyflurane but remained elevated for several days. After 2.7 MAC-hours of enflurane, mean peak F^- concentrations were 22.2 ± 2.8 mol/L, which also declined over a period of several days. There was no increase and almost no increase in F^- concentrations after desflurane and isoflurane administration, respectively.

fall very quickly after surgery, and renal toxicity is not expected from sevoflurane administration. In vivo studies have shown that although peak fluoride levels are comparable to those with enflurane, sevoflurane has less nephrotoxic potential, as measured by maximum urine-concentrating ability and the production of *N*-acetyl-β-glucosaminidase (NAG), an indicator of renal tubular damage.[136-138]

In a 1994 study, inorganic fluoride levels were also compared after sevoflurane and isoflurane anesthesia.[138] The elimination half-life of fluoride was 8 hours. Mean fluoride levels after sevoflurane were 30 µmol/L, although five of the patients had levels higher than 50 µmol/L. The mean for isoflurane was significantly lower at 3.9 µmol/L. However, despite the high levels in five patients, there was no evidence of renal injury as detected by blood urea nitrogen (BUN) or creatinine in this study. A similar study comparing isoflurane and sevoflurane with longer MAC-hour exposure (13.5 hours) resulted in a longer fluoride elimination half-life of about 58 hours in the sevoflurane patients and dramatically higher mean levels of inorganic fluoride (42.5 µmol/L).[134] Half of all sevoflurane-exposed patients had fluoride levels higher than 50 µmol/L, but again no renal injury was apparent as evidenced by BUN and creatinine measurements. Higuchi and coworkers measured renal concentrating ability after 10.6 MAC-hour sevoflurane or 8.5 MAC-hour isoflurane in surgical patients. Mean peak fluoride levels were 41.9 ± 2.5 µM in the sevoflurane

and 5.8 ± 0.4 μM in the isoflurane group.[139] There was no difference in the response to vasopressin between the groups. In a large multinational open-label comparative study, patients received either low-flow (1 L/min) sevoflurane ($n = 98$) or isoflurane ($n = 90$) anesthesia for at least 2 hours. BUN, creatinine, urine glucose, protein pH, and specific gravity were used to assess renal function up to 3 days after exposure. Peak fluoride levels were higher with sevoflurane (40 ±16 μM) than with isoflurane (3 ± 2 μM). BUN and creatinine decreased in both groups, and no clinically significant differences were found with respect to any measured parameter.[140]

To accurately assess the potential for injury from inorganic fluoride with sevoflurane, more sensitive measures may have to be used, including creatinine clearance (CCr), maximal urinary osmolality, urinary excretion of NAG, β_2-microglobulin, and alanine aminopeptidase. One study used several of these parameters and found evidence of transient subclinical nephrotoxicity with sevoflurane anesthesia.[141] In this study, patients underwent peripheral orthopedic procedures lasting longer than 5 hours and were exposed to either isoflurane or sevoflurane. Results were reported for two groups of sevoflurane patients, those with inorganic fluoride levels lower than 50 μM/L ($sevo_{low}$) and those with levels higher than 50 μM/L ($sevo_{high}$). This categorization was based on levels of inorganic fluoride determined 1 hour postoperatively: 4.8 μM/L for isoflurane, 36.8 μM/L for the $sevo_{low}$ group, and 55.8 μM/L for the $sevo_{high}$ group. BUN, creatinine, and CCr were normal in all groups throughout the study. Maximal urine osmolality showed a tendency toward the development of injury in the $sevo_{high}$ group. NAG levels were twice as high as isoflurane levels in the $sevo_{low}$ group and three times higher in the $sevo_{high}$ group, the latter showing evidence of subclinical renal injury. Clinically, transient loss of renal concentrating ability occurred in half the patients in the $sevo_{high}$ group. The dysfunction resolved within 6 days. An accompanying editorial suggested that this study raises the possibility of renal injury with sevoflurane in patients with impaired renal function and cautioned against its use in this patient group.[142] A second report of fluoride-induced renal injury in patients after sevoflurane anesthesia has recently been published.[143] However, a number of clinical reports have demonstrated very high levels of inorganic fluoride in some patients after sevoflurane anesthesia without obvious adverse effects. A report in 1996 described two such patients with refractory status asthmaticus, both treated with prolonged sevoflurane exposure under non-rebreathing conditions.[144] Despite very high inorganic fluoride levels, no obvious injury followed. It appears that the potential for significant renal impairment or injury after sevoflurane anesthesia in healthy patients solely as a result of inorganic fluoride is not an important clinical problem.

However, whether sevoflurane further affects renal tubular function in patients with impaired renal function is a question investigated by several groups. Cozen and associates compared sevoflurane ($n = 21$) with enflurane ($n = 20$) at 4-L/min fresh gas flow rates in patients with chronically impaired renal function (creatinine >1.5 mg/dL). Although peak fluoride levels were significantly higher in the sevoflurane group (25 ± 2.2 μM) than in the enflurane group (13.3 ± 1.1 μM), no difference was found in postoperative renal impairment.[145] Tsukamoto and colleagues compared sevoflurane ($n = 7$) with isoflurane ($n = 7$) in patients with moderately impaired renal function (CCr between 10 and 55 mM/min). Fluoride, urine NAG, γ-glutamyl transpeptidase (γ-GTP), and β_2-microglobulin were measured up to 2 weeks after surgery. With the exception of fluoride levels (sevoflurane group ⋙ isoflurane group), no differences in renal parameters were noted between the groups.[146] In a more recent study, Morita and colleagues[147] evaluated the effect of sevoflurane ($n = 15$) and propofol ($n = 15$) anesthesia on urine concentration and aquaporin-2 (AQP2) levels. AQP2 is an arginine vasopressin (AVP)-regulated water channel protein localized in the apical region of renal collecting duct cells. In both groups, plasma and urinary concentrations of AVP increased, although plasma osmolality remained unchanged. Urinary AQP2 excretion increased in the propofol group along with changes in urinary and plasma AVP. Urinary AQP2 was significantly lower at 90 minutes in the sevoflurane group, and urine osmolality showed a transient but significant decrease in parallel with AQP2 suppression, thus suggesting that sevoflurane may have produced a transient impairment of the APQ2 response to an increase in intrinsic AVP. However, because other inhaled anesthetics were not tested, it is not clear whether this observation applies to sevoflurane alone or is also a characteristic effect of other fluorinated inhaled anesthetic agents.

Desflurane

Clinical studies performed with desflurane thus far show no evidence of nephrotoxicity. Desflurane is extremely resistant to defluorination, and serum fluoride concentrations in surgical patients after exposure to desflurane are not increased above background concentrations.[148] From these findings, desflurane does not appear to be nephrotoxic.

Halothane

Halothane is not significantly defluorinated under normal clinical conditions and is not nephrotoxic. In patients who received about 19 MAC-hours of halothane, peak plasma fluoride levels were much higher in the isoflurane group than in the halothane group.[136]

In summary, fluoride-induced nephrotoxicity is a well-known entity historically associated with methoxyflurane administration and prolonged exposure to enflurane. During the administration of sevoflurane, serum inorganic fluoride levels can exceed 50 μmol/L, the level known to produce nephrotoxicity; however, no correlation with sevoflurane and polyuric renal failure has been documented. Two factors may help explain the differences seen with methoxyflurane and sevoflurane. First, it is not the peak serum fluoride concentration that determines injury but rather the duration of the systemic increase in fluoride (the area under the curve for serum fluoride). In addition, sevoflurane is an order of magnitude less soluble than methoxyflurane and thus is eliminated much more rapidly from the body. Second, the liver is the primary organ of sevoflurane metabolism, whereas both the liver and kidney metabolize methoxyflurane, and it is thought that the high intrarenal fluoride production from methoxyflurane contributes to its nephrotoxicity.

Anesthetic Degradation by Carbon Dioxide Absorbents

Sevoflurane and Compound A

Several decomposition products are formed during the interaction of sevoflurane with carbon dioxide absorbents, and

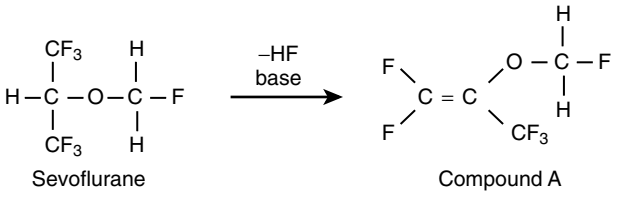


Figure 24-19 Sevoflurane degradation in the presence of base.

fluoromethyl-2-2-difluoro-1-(trifluoromethyl) vinyl ether (compound A) is the major degradation product detected (Fig. 24-19).[149-151] The dehydrofluorination of sevoflurane to form compound A is initiated by soda lime abstraction of a proton from the isopropyl group of sevoflurane in a manner that is similar to the base-catalyzed deprotonation of halothane by soda lime to yield bromochlorodifluoroethane (BCDFE, F_2C = CBrCl).

Compound A has been the subject of intense research and debate since the introduction of sevoflurane into clinical practice in the United States in 1995. Morio and coworkers found that high concentrations of compound A could cause renal injury and death in rats.[142] Other investigators have confirmed the findings of Morio and coworkers and have shown further that kidney injury occurs when levels of compound A reach 25 to 50 ppm or greater.[152] Necrosis is found primarily in the proximal tubular cells within the outer strip of the medulla, and the percentage of injured cells was lower 4 days after exposure than 1 day after exposure, consistent with repair after renal injury.[153] These and other studies suggest a threshold for renal injury of 150 to 300 ppm-hours of exposure to compound A, (e.g., 50 ppm of compound A administered for 3 hours).[153,154] Keller and coauthors reported that inspired concentrations of compound A greater than 114 ppm were associated with concentration-dependent increases in BUN, creatinine, and the urinary NAG/creatinine ratio.[153] Moderately severe histopathologic changes were noted at 202 ppm, and all chemical and histopathologic changes reversed within 14 days of exposure. This renal toxicity is both dose and time dependent: the higher the exposures over time, the greater the observed injury. During sevoflurane anesthesia in a closed or semiclosed system at low fresh gas inflow, patients are routinely exposed to compound A.

Several studies in surgical patients and human volunteers have been undertaken to investigate the possible association between sevoflurane anesthesia and renal injury as a result of exposure to compound A during sevoflurane anesthesia. In an early study, Bito and Ikeda exposed 10 patients to sevoflurane for longer than 5 hours under closed-circuit conditions with soda lime used as the absorbent.[149] Peak compound A concentrations were 19.5 ± 5.4 ppm, and serum BUN, creatinine, and electrolytes were essentially unchanged. In a follow-up study by the same investigators, 10 patients were exposed to sevoflurane at 1-L/min fresh gas flow for 10 hours. Mean compound A levels were 24.3 ± 2.4 ppm, and routine tests of renal function showed no change from preoperative values.[155] Frink and associates measured compound A levels in 16 surgical patients during low-flow sevoflurane anesthesia of 3 hours' duration with either soda lime ($n = 8$) or Baralyme ($n = 8$) used as the absorbent.[156] Maximum compound A concentrations averaged 8.16 ± 2.67 ppm with soda lime and 20.28 ± 8.6 ppm with Baralyme. A compound A concentration of 60.8 ppm was found in the breathing circuit of one of eight subjects to whom sevoflurane was administered with Baralyme absorption. In the same study, no compound A level exceeding 50 ppm was found in the eight volunteers in whom soda lime was used to scrub the carbon dioxide.

In a more comprehensive investigation, Bito and Ikeda studied 100 surgical patients undergoing resection of head and neck tumors in which surgery was expected to last longer than 10 hours. Patients received either sevoflurane ($n = 50$) or isoflurane ($n = 50$) anesthesia at low fresh gas inflow (1 L/min).[157] Mean peak compound A concentrations in the sevoflurane group were 24.6 ± 7.2 ppm. Although bilirubin, AST, and ALT levels increased postoperatively in both the sevoflurane and isoflurane groups, there were no significant differences in these parameters between the groups. Preoperative and postoperative BUN and creatinine levels remained unchanged. A number of other reports have used BUN and serum creatinine as markers of renal damage to evaluate renal function after closed-circuit or low-flow sevoflurane anesthesia,[158] and none of these studies demonstrated any change in either of these markers preoperatively and postoperatively.[157-159]

It has been argued that BUN and creatinine are not sensitive enough tests for detecting renal damage after exposure to compound A.[157-160] In an early attempt to address this issue, Kumano and colleagues measured urinary excretion of several renal tubular enzymes as measures of renal injury. Renal excretion of alanine aminopeptidase and NAG (enzymatic markers of renal integrity) increased 7 days after exposure to 7.6 MAC-hours of enflurane, but no increase was observed in patients receiving 9.6 MAC-hours of sevoflurane. Renal excretion of γ-GTP, β_2-microglobulin, BUN, and creatinine was unchanged.[161] Bito and associates studied 48 patients undergoing gastrectomy under both low-flow (1 L/min) ($n = 16$) and high-flow (6 to 10 L/min) ($n = 16$) sevoflurane anesthesia and low-flow isoflurane (1 L/min) ($n = 16$) anesthesia and looked not only at BUN and creatinine but also at CCr, NAG, and alanine aminopeptidase.[162] The average inspired compound A levels were 20 ppm in the $sevo_{low}$ group, and the average duration of exposure to this concentration was 6.11 hours. The only difference noted between the $sevo_{low}$ and the $sevo_{high}$ groups was the degree of compound A formation. Postanesthesia laboratory data showed no significant effects of compound A during sevoflurane anesthesia on any markers of renal function. Postanesthesia BUN and creatinine levels decreased, CCr increased, and urinary excretion of NAG and alanine aminopeptidase increased in all groups in comparison to preanesthesia values, but there was no significant differences observed between any of the groups. Kharasch and colleagues[163] completed a similar study in which 73 surgical patients received either sevoflurane or isoflurane anesthesia at a 1-L/min fresh gas flow. The duration of anesthesia was 3.7 or 3.9 hours, and the maximum inspired concentration of compound A was 27 ppm (range, 10 to 67 ppm). Areas under the inspired and expired compound A concentration-versus-time curves were 79 ppm-hours (range, 10 to 223 ppm-hours) and 53 ppm-hours (range, 6 to 159 ppm-hours), respectively. There were no significant differences between anesthetic groups in postoperative BUN, creatinine or urinary excretion of protein, or glucose (markers of proximal tubular resorptive function) or in NAG, proximal tubular α-glutathione-*S*-transferase (α-GST), or distal tubular π-GST (markers of tubular cell necrosis). The authors concluded that a moderate duration of low-flow sevoflurane anesthesia during which compound A formation occurs was as safe as low-flow isoflurane

Table 24-4 Percentage of Volunteers with Abnormal Renal Test Results after 8 Hours of 1.25 MAC Sevoflurane Anesthesia

	Eger Study[165]			Ebert Study[166]		
Determination	**Day 1 (%)**	**Day 2 (%)**	**Day 3 (%)**	**Day 1 (%)**	**Day 2 (%)**	**Day 3 (%)**
Glucose	75	50	80	15		
Albumin	88	60	90	31	31	31
α-GST	43	70	70	54	54	
π-GST	25	38	38	*		
MAC-hr exposure	328 ppm/hr			240 ppm/hr		

*The group mean was significantly increased above baseline. No individual data were reported. Blood urea nitrogen and creatinine levels were normal in all patients at all time points.
GST, glutathione-*S*-transferase; MAC, minimum alveolar concentration.

anesthesia. Nishiyama and associates studied the effect of repeat sevoflurane exposure within 30 to 90 days in neurosurgical patients.[164] Ten patients received sevoflurane at 6-L/min fresh gas flow rates on two occasions. Serum inorganic fluoride was measured 1 day after surgery, and BUN, creatinine, serum and urine β_2-microglobulin, urine NAG, and serum AST, ALT, and total bilirubin were measured 7 days postoperatively. Urine β_2-microglobulin, AST, and ALT all increased to abnormal levels after both anesthetics, with no differences observed between the anesthetics. Thus, the second sevoflurane exposure did not change the hepatic or renal metabolism of sevoflurane. These changes were indicative of mild hepatic and renal injury. The duration of anesthesia for the first and second anesthetics was 4.3 ± 0.6 hours and 4.0 ± 0.6 hours, respectively.

More recent studies in humans that have reported renal changes after the administration of sevoflurane have all occurred under conditions of prolonged sevoflurane exposure. Both Eger and colleagues[165] and Ebert and colleagues[166] exposed human volunteers to 8 hours of 1.25 MAC sevoflurane or desflurane anesthesia at a 2-L/min fresh gas flow rate and investigated pre-exposure and postexposure BUN, creatinine, and enzymatic markers of urinary function for up to 3 days or 5 to 7 days after exposure (Table 24-4). Both investigators found no difference in pre-exposure and postexposure BUN or creatinine levels in either group, but they found significant differences in enzymatic markers of renal integrity (α-GST and π-GST), albuminuria, and glucosuria in the sevoflurane-exposed group. All renal changes were transient, with normal return of renal function by 4 days after exposure in all but one volunteer, whose renal function was normal 2 weeks after exposure. In Eger's volunteers, rebreathing of sevoflurane produced an average inspired compound A concentration of 41 ppm and total exposure to compound A of 328 ppm-hours. In the Ebert study, volunteers were exposed to an average inspired compound A concentration of 27 ppm and a total exposure of 216 ppm-hours. With the exception or BUN and creatinine, both studies showed significant changes in urinary markers, the Ebert volunteers being lower on the compound A toxicity threshold curve and exhibiting less drastic changes in all markers of injury. When Goldberg and coworkers replicated Eger and colleagues' study, they obtained lower average compound A levels (253 ppm-hours) and found similar qualitative renal results.[167] Higuchi and associates[168] found increased excretion of urinary enzymes after average compound A concentrations of 215 ppm-hours. In another study, Higuchi and associates also found proteinuria in patients who were given low-flow (1 L/min) ($n = 14$) sevoflurane anesthesia and were undergoing orthopedic or dental surgeries, but not in those given high-flow (6 L/min) ($n = 14$) sevoflurane or low-flow isoflurane ($n = 14$).[169] Increased urinary NAG excretion was seen in the low-flow and high-flow sevoflurane groups, whereas BUN, creatinine, and CCr were unchanged in all groups. In human volunteers exposed to 1.25 MAC sevoflurane or desflurane for 4 hours ($n = 9$) or 2 hours ($n = 7$) at 2-L/min fresh gas flow, Eger and colleagues found average inspired compound A levels of 40 ppm. Relative to desflurane, sevoflurane given for 4 hours resulted in slightly increased urinary albumin and serum creatinine and increased urinary α-GST.[170] In a later study, Ebert and coworkers found that 5 MAC-hours of sevoflurane exposure at 1-L/min fresh gas flow, in which mean peak compound A levels were 39 ppm and total exposure to compound A was 152 ppm-hours, produced no changes in BUN, creatinine, or enzymatic markers of renal or hepatic (AST, ALT, and alkaline phosphatase) injury.[171]

Several studies have examined the use of sevoflurane in the pediatric population (also see Chapter 82). In a recent report, sevoflurane was compared with halothane anesthesia in children with a mean age of 6 years.[172] With comparable exposure, the sevoflurane group had significantly higher inorganic fluoride levels. There were no significant differences in BUN and creatinine levels, and there have been no reports of fluoride-associated renal toxicity in pediatric patients after sevoflurane anesthesia. Other tests of renal integrity were not performed. In another study, ASA class I and II children ranging in age from 3 months to 7 years received 1 MAC sevoflurane exposure at a fresh gas flow rate of 2 L/min.[173] The mean anesthetic exposure was 240 minutes, and fresh carbon dioxide absorbent was used for each patient. The soda lime temperature varied from 23°C to almost 41°C, and the inspired and expired compound A concentrations were 5.4 and 3.7 ppm, respectively. There were no differences in clinical chemical parameters, as reflected by AST, ALT, alkaline phosphatase, bilirubin, BUN, and creatinine. The maximum soda lime temperature correlated with both maximum compound A concentrations and the body surface area of the child. Therefore, to date, there have been no reports of markedly abnormal renal chemical findings in pediatric patients after exposure to sevoflurane.

There is some potential concern in pediatric patients related to HFIP, the major metabolite of sevoflurane, because levels of this metabolite may become relatively high as a result of a deficiency in UGTs that conjugate glucuronic acid to HFIP (see Fig. 24-9). For example, in one study neonatal rats were found to have

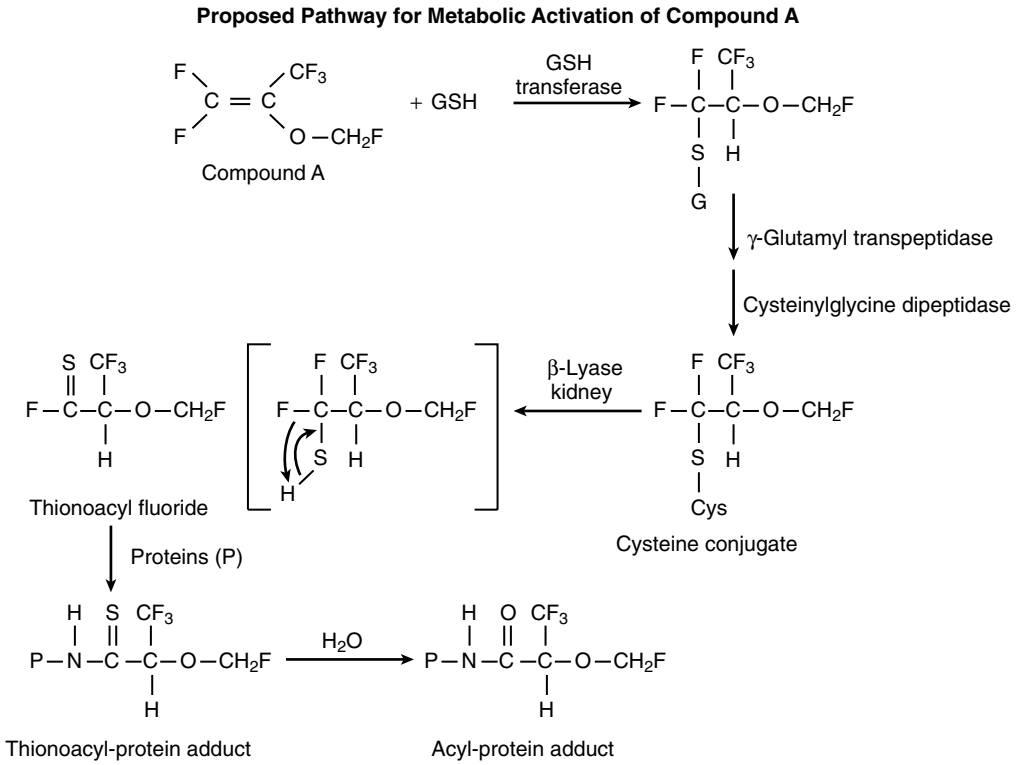


Figure 24-20 Proposed pathway for the metabolic activation of compound A showing the formation of an intrahepatic glutathione (GSH) conjugate of compound A that is translocated to the kidney, where γ-glutamyl transpeptidase, cysteinyl glycine dipeptidase, and the renal cysteine conjugate β-lyase catalyze the formation of a nephrotoxic thiol that can acylate kidney proteins. *(Adapted from Martin JL, Kandel L, Laster, MJ, et al: Studies of the mechanism of nephrotoxicity of compound A in rats. J Anesth 11:32-37, 1997.)*

high levels of free HFIP for as long as 21 postnatal days after sevoflurane exposure.[174]

It has been hypothesized that the reason that compound A causes serious injury to kidneys in rats but not humans is because of differences in levels of renal cysteine conjugate β-lyase enzymes,[175] which have been hypothesized to catalyze the conversion of compound A to a reactive thionoacyl fluoride metabolite that can acylate kidney proteins and cause toxicity (Fig. 24-20). Indeed, renal cytosolic and mitochondrial β-lyase enzyme levels in rats are approximately 20 to 30 times higher than those found in humans.[176-178] There is evidence to support the β-lyase theory of compound A–induced nephrotoxicity. Renal β-lyase appears to mediate the renal toxicity produced by several fluorinated alkenes that are structurally similar to compound A,[179-181] and metabolic intermediates of the β-lyase pathway have been identified in the bile and urine of rats and human tissues exposed to compound A.[158,163,177,178,182] Moreover, the glutathione-*S*-conjugate of compound A is nephrotoxic,[183] and the administration of aminooxyacetic acid (AOAA), an inhibitor of β-lyase (Fig. 24-21), protects against the nephrotoxicity of compound A in rats.[184] However, there is some controversy surrounding the relevance of the β-lyase pathway in compound A–induced renal injury.[182,185,186] More recently, Altuntas and coauthors reported an additional pathway of compound A metabolism, sulfoxidation.[187] The investigators showed that compound A cysteine and mercapturic acid conjugates are metabolized both enzymatically and nonenzymatically to sulfoxide metabolites. The enzymatic process was catalyzed by CYP3A1/2 and CYP3A4/5, and there exists a species difference in rat and human liver and kidney microsomes (rat > human and liver > kidney). Sulfoxide conjugates have recently been shown to be more toxic than the corresponding parent cysteine or mercapturic acid compound A conjugate. However, the toxicologic significance of *S*-conjugate sulfoxidation of compound A remains unknown. It represents an alternative route of metabolism to the deacetylation or the β-lyase pathways. Whether sulfoxidation occurs in vivo is uncertain, as is its toxicologic significance.

Investigators have reported that pretreatment of rats with AOAA and acivicin (AT-125), inhibitors of the β-lyase pathway (see Fig. 24-19),[185] did not attenuate the nephrotoxicity produced by compound A but rather was associated with nearly a threefold increase in renal injury, from 19% to 53%. These findings suggest that the β-lyase pathway may actually be a detoxification pathway. In this regard, a report by Kharasch and coworkers[186] showed that pretreatment of rats with AOAA partially protected against compound A–induced diuresis and proteinuria but failed to protect against glucosuria. In another report, AOAA again failed to decrease histologic renal injury, and pretreatment with acivicin significantly increased renal injury.[185] Moreover, using an immunochemical approach, other investigators were unable to detect protein adducts of a thionoacyl fluoride metabolite of compound A in the kidneys of rats after compound A treatment, suggesting that the β-lyase pathway of compound A metabolism in rats either does not occur or is a minor pathway of metabolism. Therefore, these findings suggest that another pathway of metabolism of compound A may be responsible for the nephrotoxicity of compound A.

Higuchi and colleagues studied the effect of low-flow sevoflurane or isoflurane anesthesia (1 L/min) on 17 patients with

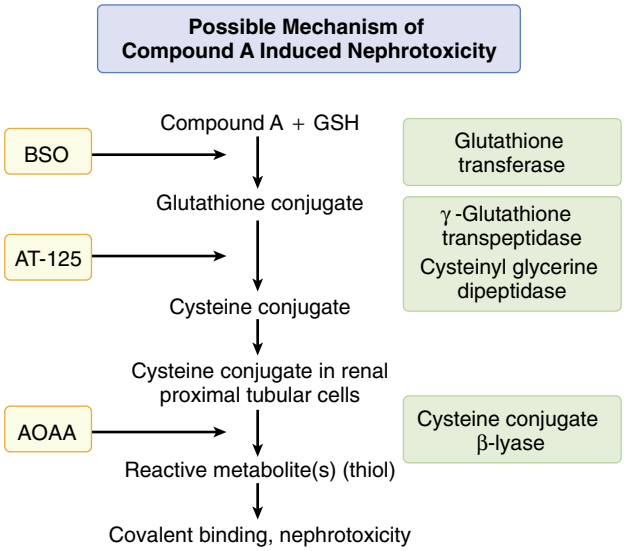


Figure 24-21 Crucial steps in the β-lyase pathway: first, conjugation of compound A with glutathione in the liver mediated by glutathione-*S*-transferase; this conjugate is then transported to the kidney. Second, the glutathione-*S*-conjugate is converted to a cysteine-*S*-conjugate, a process mediated by γ-glutamyl transpeptidase. Finally, the cysteine-*S*-conjugate of compound A is then converted to a reactive thiol, mediated by the renal cysteine conjugate β-lyase; DL-buthionine-(*S*,*R*)-sulfoximine (BSO) depletes endogenous stores of glutathione in the body, acivicin (AT-125) inhibits the activity of γ-glutamyl transpeptidase, and aminooxyacetic acid (AOAA) inhibits the activity of β-lyase. Compound A, its conjugates, and the reactive thiol have all been postulated to cause the renal necrosis that can occur in rats after the administration of compound A and the glucosuria and enzymuria that can result in rats and humans from the administration of compound A.

stable moderate renal failure (serum creatinine >1.5 mg/dL). They found no difference in BUN or creatinine up to 14 days after exposure or in CCr at 7 days after exposure in either group for patient exposures less than 130 ppm-hours of compound A.[188] In a recent multicenter randomized controlled trial, Conzen and coworkers studied 116 patients with stable renal insufficiency (CCr >1.5 mg/dL) who were administered either low-flow (1 L/min) sevoflurane (n = 59) or isoflurane (n = 57) anesthesia.[189] Total exposure to sevoflurane was 201.3 ± 98 minutes, with an average total compound A exposure of 18.9 ± 7.6 ppm. Isoflurane exposure averaged 213.6 ± 83.4 minutes, and Baralyme was used as the carbon dioxide absorbent. No significant changes above baseline values for serum creatinine, BUN, CCr, urine protein, or glucose were found at 24 or 72 hours after exposure to either anesthetic.

So what does this all mean and how does it translate into clinical care of patients? In a rebreathing system with a carbon dioxide absorber in lime (soda lime or Baralyme), patients exposed to sevoflurane will breathe compound A. The typical levels seen in clinical conditions will vary and are dependent on several factors, the most important being the inspired fresh gas flow rate. The key factor in determining potential toxicity from sevoflurane is total exposure rather than the absolute concentration, with exposure being expressed as the product of concentration and time. It appears from the many studies published to date that the lower threshold for renal changes associated with sevoflurane exposure and compound A is approximately 150 ppm-hours. At a fresh gas inflow of 2 L/min, these levels would be expected to be seen only in conditions of prolonged sevoflurane exposure and are not of concern to the vast majority of patients undergoing anesthesia and surgery. With prolonged sevoflurane exposure, when renal changes have been observed, they have been transient. It appears that compound A is of theoretical concern and academic interest, but to date no significant clinical renal toxicity has been associated with the use of sevoflurane. It is recommended that patients with preexisting renal disease not be exposed to sevoflurane and that sevoflurane be administered according to approved package labeling guidelines.

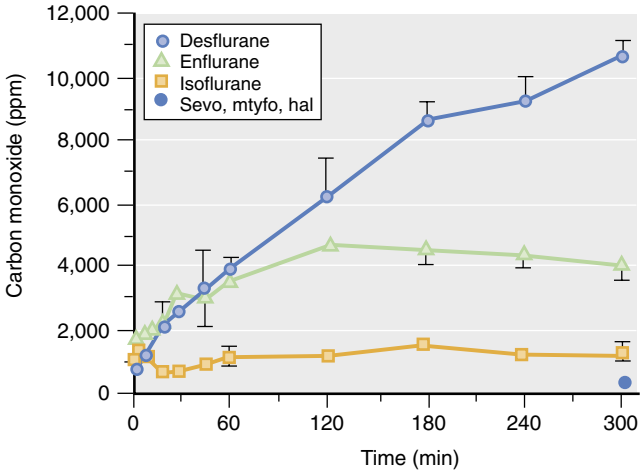
Halothane and Bromochlorodifluoroethane

Carbon dioxide absorbents also degrade halothane by a dehydrofluorination reaction to form BCDFE (F_2C = CBrCl). The potential nephrotoxicity of BCDFE was compared with that of compound A in a study by Eger and coworkers,[190] who found that (1) BCDFE was 80% less reactive than compound A; (2) halothane degraded to BCDFE 20- to 40-fold less than sevoflurane did to compound A in a standard circle system; (3) BCDFE was 75% less nephrotoxic to rats than compound A was; and (4) compounds that blocked the renal β-lyase pathway either did not change or decreased renal injury from BCDFE, whereas the same blockers either did not change or increased renal injury from compound A (see Fig. 24-21), suggesting that BCDFE and compound A may cause kidney injury by different mechanisms. These studies clearly indicate that the chance of BCDFE causing nephrotoxicity when halothane is being used as an anesthetic is negligible.

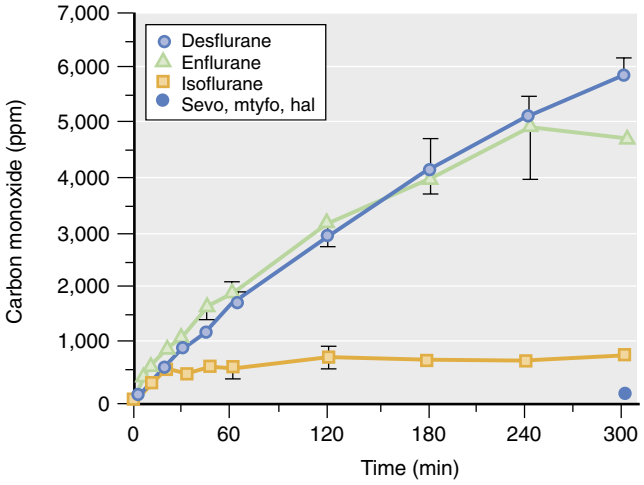
Carbon Monoxide and Heat

Carbon monoxide (CO) is an odorless, colorless, gas that is poisonous because it displaces oxygen from hemoglobin in blood and thereby leads to the formation of carboxyhemoglobin. Its affinity for binding hemoglobin is 250 times greater than that of oxygen. All humans have some CO bound to hemoglobin in their blood, on average 1% for nonsmokers and as much as 10% for those who smoke. High levels of CO can produce neuropsychiatric problems in patients, and when levels of carboxyhemoglobin reach 50%, death can occur. The problem of CO poisoning has been reported during clinical anesthesia.[191-196] The difficulty in monitoring CO levels clinically arises from the fact that pulse oximeters have not distinguished between carboxyhemoglobin and oxyhemoglobin. Masimo has just developed such a pulse oximeter that should correct this problem.

All inhaled anesthetics produce some CO as a result of their interaction with the strong bases in relatively dry carbon dioxide (CO_2) absorbents (water content <5%).[197] Several factors influence the level of CO production, including the choice of anesthetic agent, the inspired anesthetic concentration, and the type, temperature, and most important, the degree of dryness of the CO_2 absorbent.[198] Of the inhaled anesthetics, desflurane produces the most CO, followed by enflurane, isoflurane, and negligible amounts from sevoflurane and halothane (Fig. 24-22).[198,199] Intraoperative formation of CO has been reported with desflurane, enflurane, and isoflurane, with CO levels exceeding those established as safe by the U.S. Environmental Protection Agency. Desflurane, enflurane, and isoflurane are all difluoromethyl-ethyl ethers, whereas sevoflurane is a monofluoromethyl ether and halothane is an alkane. The specific mechanism appears to be abstraction of a base-catalyzed difluoromethoxy proton from the anesthetic agent (Fig. 24-23).[199] Furthermore, it has been shown



A



B

Figure 24-22 Anesthetic degradation to carbon monoxide at equivalent minimum alveolar concentrations (1.5 MAC) by barium hydroxide lime (**A**) and soda lime (**B**). Each data point is the mean ± SD ($n = 3$). The single data point at 300 minutes reflects undetectable carbon monoxide from sevoflurane (sevo), methoxyflurane (mtyfo), or halothane (hal). *(Adapted from Baxter PJ, Garton K, Kharasch ED: Mechanistic aspects of carbon monoxide formation from volatile anesthetics. Anesthesiology 89:929-941, 1998.)*

that abstraction of a proton from the difluoromethoxy group is greater with potassium (KOH) than with sodium hydroxide (NaOH).[199,200] Barium hydroxide ($Ba[OH]_2$) contains 4.6% KOH, whereas soda lime contains only 2.5% KOH and 1.5% NaOH. Unlike KOH and NaOH, $Ba(OH)_2$ does not abstract a proton from the difluoromethoxy moiety and catalyze the formation of CO from inhaled anesthetics. Because the divalent $Ca(OH)_2$ and $Ba(OH)_2$ bases are the major active components of the absorbents, the capacity to produce CO is rapidly exhausted, whereas the absorbents retain their capacity to remove CO_2.

New calcium hydroxide–based CO_2 absorbents such as Amsorb and DragerSorb Free contain neither NaOH or KOH and are chemically inert and do not degrade inhaled anesthetics to CO or degrade sevoflurane to compound A.[201] Fully hydrated or rehydrated absorbents do not degrade inhaled anesthetics to CO. Soda lime contains 15% water by weight, and only after this level of hydration has been decreased to about 1.4% will appreciable amounts of CO be formed. In contrast, Baralyme contains 13% water by weight and the threshold of hydration before CO is formed is 4.8%. However, even at these threshold levels, very little CO is actually produced. Production of large amounts of CO requires complete or nearly complete desiccation of the absorbent, a process that requires high flow of dry gas (10 L) for prolonged periods (1 to 2 days). Certain patients had high levels of CO, particularly prevalent in the first case on Mondays.[191] This appeared to be related to the practice of flushing the anesthesia machine with high fresh gas flow over the weekend, which dries out the CO_2 absorbent. Higher temperatures are also associated with increased CO production.

In general, CO toxicity has little clinical significance, regardless of the anesthetic used, as long as simple guidelines to minimize or eliminate CO are observed, including the use of fresh absorbent, the use of soda lime instead of Baralyme, or perhaps better yet, the use of a calcium hydroxide–based CO_2 absorbent. Avoidance of techniques that dehydrate the CO_2 absorbent in the anesthetic circuit is also helpful, such as low fresh gas flow, which is more economical and limits desiccation of the absorbent. Finally, as a last resort the absorbent can be rehydrated simply by adding approximately one cup of water (230 mL) per 1.2 kg of absorbent (standard canister).

The interaction of inhaled anesthetics with CO_2 absorbents is an exothermic reaction that results in the production of heat. The temperature of CO_2 canisters during routine clinical use averages 25°C to 45°C but increases inversely with decreased fresh gas flow; sevoflurane is associated with the greatest production of heat. By-products of this reaction also include HFIP, formaldehyde, methanol, sodium formate, and importantly, hydrogen. The high yield of hydrogen, up to 3 mol of hydrogen per mole of sevoflurane, ease of ignition, and low tissue solubility make it the most likely fuel in anesthesia machine fires because of reactions with desiccated CO_2 absorbents and sevoflurane.[202] These reactions can be significant and result in fires, toxic gases, and patient injury.[203,204] In laboratory settings, prolonged exposure of 1 MAC

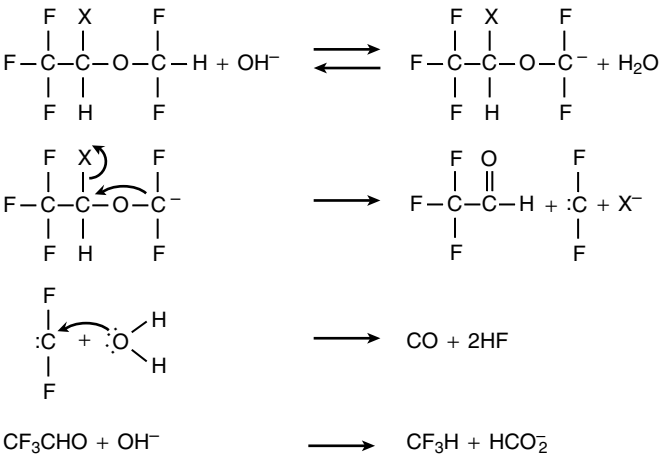


Figure 24-23 Proposed mechanism of carbon monoxide formation from difluoromethyl-ethyl ether anesthetics. Shown is the backbone structure for isoflurane (X = Cl) and desflurane (X = F). Also shown is a putative mechanism for the concomitant formation of trifluoromethane. Water in line 3 may also react as OH^-. *(Adapted from Baxter PJ, Garton K, Kharasch ED: Mechanistic aspects of carbon monoxide formation from volatile anesthetics. Anesthesiology 89:929-941, 1998.)*

sevoflurane to desiccated CO_2 absorbents resulted in canister temperatures in excess of 300°C.[205] At these high temperatures, patient injuries as a result of explosions, fires, and smoldering and melting of the plastic components of anesthesia equipment are all real possibilities. Two recent studies have documented lower concentrations of toxic sevoflurane breakdown products with use of the new-generation CO_2 absorbents.[206,207] Perhaps at some time in the near future the sodium hydroxide– and barium hydroxide –based CO_2 absorbents will be replaced by the nondestructive newer, less reactive calcium hydroxide–based CO_2 absorbents.

Other Toxicities

Nitrous Oxide and Inhaled Anesthetics

Nitrous oxide has been used and abused since its introduction into clinical practice in 1845. It is unique in its ability to oxidize vitamin B_{12} and inactivate methionine synthase and is the only anesthetic known to produce hematologic toxicity and neurotoxicity with long-term administration. Both these toxicities are the result of disruption of several pathways involved in one-carbon chemistry. After several hours of routine anesthesia with N_2O, methionine synthase activity is very low. Methionine synthase catalyzes the conversion of methyltetrahydrofolate and homocysteine to tetrahydrofolate and methionine. Failure to produce these products has a number of biochemical consequences, including reduced synthesis of thymidine, which is an essential DNA base. The reduction in thymidine synthesis takes somewhat longer to develop but lasts several days. The clinical syndrome associated with oxidation of vitamin B_{12} is essentially the same as that seen in pernicious anemia: megaloblastic hematopoiesis and subacute combined degeneration of the spinal cord. The time required to produce megaloblastic hematopoiesis with exposure to N_2O varies among patients. In healthy patients undergoing routine surgery, mild megaloblastic bone marrow changes are not seen after 6 hours, but they are seen after about 12 hours of exposure to 50% N_2O; after 24 hours of exposure, the changes are marked. Complete bone marrow failure can be expected after several days of continuous exposure. Limited evidence suggests that N_2O produces bone marrow changes earlier in seriously ill patients, and evidence also suggests that the bone marrow changes are preventable by pretreating patients with large doses of folinic acid. This drug is converted to the 5,10-methylene tetrahydrofolate needed for the synthesis of thymidine (Fig. 24-24). The neurologic disease, subacute combined degeneration of the spinal cord, develops only after several months of daily exposure to N_2O. Symptoms and signs include numbness and paresthesia in the extremities, loss of balance and unsteady gait, impairment of touch, and muscle weakness. Earlier, the disease was recognized to be similar to vitamin B_{12} deficiency, but treatment with vitamin B_{12} did not alleviate the symptoms or enhance recovery; thus, it occurs in those who abuse N_2O on a long-term basis.[208,209] Sporadic reports of postoperative neurologic disorders in patients exposed to N_2O continue to appear.[210-212] For all of the reasons just described and other environmental concerns that will be discussed later, there are serious discussions in the European Union and Japan regarding the possible elimination of nitrous oxide from modern clinical anesthesia.

Effects on Reproduction and Development

Thousands of pregnant women undergo anesthesia and surgery during gestation for indications unrelated to pregnancy. The incidence of unexpected abortion or premature labor is clearly higher after anesthesia. What is not immediately obvious is whether the patient's disease, surgery, anesthesia, or a combination of these factors is the precipitating cause. Perhaps an even greater concern is that anesthesia during pregnancy may lead to an increased incidence of congenital abnormalities in the offspring of the

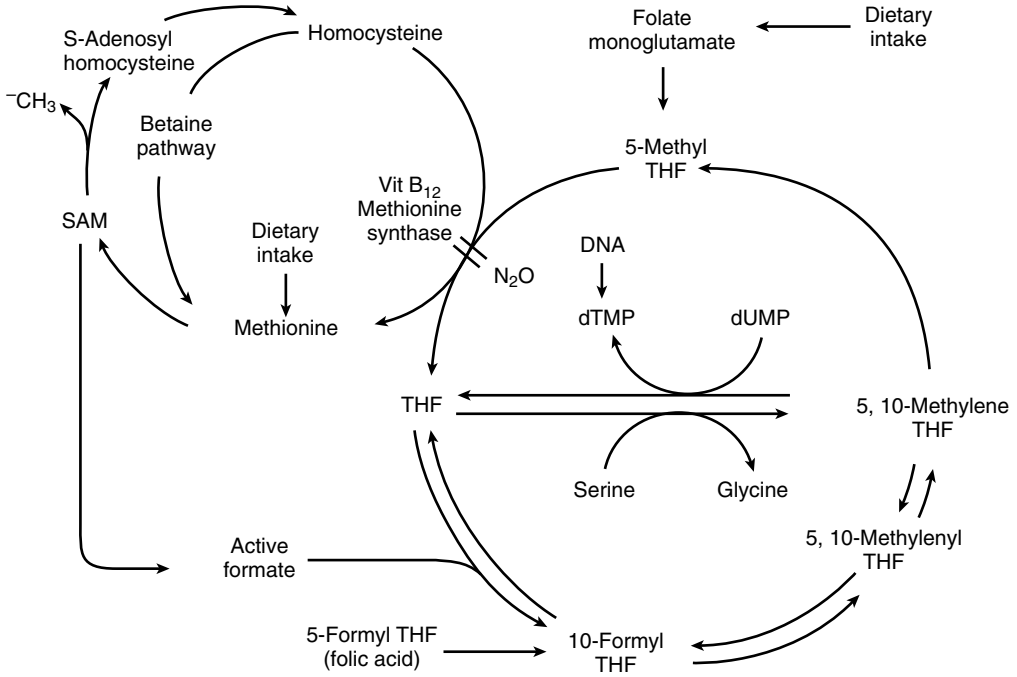


Figure 24-24 Conversion of methyltetrahydrofolate (5-Methyl THF) and homocysteine to tetrahydrofolate and methionine. dTMP, d-thymidine monophosphate; dUMP, d-uridine monophosphate; SAM, s-adenosyl methionine.

patient. A number of studies have been undertaken over the past 40 years to assess the incidence of various anesthesia- and surgery-related hazards occurring during pregnancy. In short, these studies have found that women who underwent surgery did not have an increased incidence of stillbirths or congenital anomalies among offspring. In contrast, the incidence of postnatal death within 7 days of delivery was increased when an operation occurred during the second or third trimester but not during the first trimester. The incidence of low birth weight and premature delivery was increased regardless of the trimester in which an operation occurred. The cause of these hazards was not determined, although the finding that no particular type of operation or anesthesia was associated with a higher incidence of adverse outcomes suggests that the patient's disease played the major role in determining the outcome.

In recent years, the increasing popularity of in vitro fertilization has afforded some opportunity to study the effects of anesthetics on ova. Various anesthetic regimens have been examined for their effects on rates of fertilization and cleavage of oocytes, pregnancy, and carriage to term. The results with general anesthetics have been variable, although there is some consensus that regimens that include inhaled anesthetics produce adverse effects.[213,214] In a well-controlled study of in vitro fertilization, no difference in fertilization or pregnancy rates was found in patients undergoing isoflurane anesthesia with or without N_2O, a finding implying that short exposure to N_2O is not harmful.[215] A publication on transvaginal oocyte retrieval and reproductive outcome[216] reported that general anesthesia with N_2O in combination with opiates, barbiturates, and halothane resulted in significantly lower clinical pregnancy rates (14.5%) than in patients receiving local anesthesia (23.7%) or an epidural block (25.8%). There were no adverse effects reported for oocyte collection, embryo yield, or embryo transfer. Several reports of epidemiologic surveys have been published in which the reproductive performance of operating room and dental personnel exposed to waste gases was examined. Interested readers are referred to a review of these studies.[217] One of the acknowledged shortcomings of many of the earlier published studies was the lack of a quantitative measure of anesthetic exposure, which was addressed in two more recent retrospective analyses[217,218] that attempted to quantitate N_2O exposure in female dental assistants. These investigators reported that in unscavenged dental suites, exposure to more than 5 and 3 hours of N_2O per day, respectively, was associated with reduced fertility and increased spontaneous abortion rates.

In general, N_2O is the only inhaled anesthetic that has been convincingly shown to be directly teratogenic in experimental animals, but only under experimental conditions that are considered extreme. High concentrations (50% to 75%) delivered to rats for 24-hour periods during organogenesis and low concentrations (0.1%) delivered to rats continuously throughout pregnancy result in an increased incidence of fetal resorption and visceral and skeletal abnormalities. A particularly interesting abnormality produced by high N_2O exposure is situs inversus, in which there is a disturbance in the left/right body axis so that organs such as the heart are on the wrong side of the body.[219] Although effects in rodents are seen only after extended periods of continuous exposure, it is not known whether humans are more sensitive than rodents and would show effects after shorter periods of exposure. It appears that lack of methionine rather than lack of thymidine plays the critical role in all the adverse reproductive effects other than situs inversus.[220] With situs inversus, stimulation of α_1-adrenergic receptors by N_2O appears to be the mechanism.[221] The effect is mediated by activation of calmodulin kinase 11.[222] N_2O teratogenesis is actively being investigated, not only because of its relevance to patient and occupational safety but also because N_2O can be used to determine the importance of vitamin B_{12}, folates, one-carbon chemistry, and the adrenergic system in developmental processes. The consensus is that the teratogenic effects observed in animals exposed to inhaled anesthetics are caused by physiologic changes associated with anesthesia rather than by inherent teratologic properties of the anesthetics themselves. Nonetheless, all findings emphasize the potential for anesthetics to interfere with developmental processes regardless of the mechanism.

Human studies have generally focused on the long-term behavioral effects of maternal obstetric medication, including epidural anesthesia. Claims have been made that the medication given at delivery to the mother produces depressed motor skills and impaired language ability in the infant and child for several years. Such claims, however, are controversial. Behavioral abnormalities in offspring whose mothers received inhaled anesthetics at any time during delivery have not been well studied. Furthermore, studies have not been done to assess the neurobehavioral function of children of operating room personnel who have been exposed to waste anesthetic gases. Firm conclusions about the risk for behavioral teratogenesis in the offspring of exposed personnel or in exposed patients therefore await further investigation. Finally, there is no evidence that the modern fluorinated inhaled anesthetics are mutagenic or carcinogenic.

General Anesthetics and Neurotoxicity

The issue of general anesthetics and neurotoxicity is an area of growing concern in the anesthesia community.[223] An increasing body of experimental evidence from animal studies suggests that general anesthetics can be neurotoxic in the developing and senescent brain through a process of accelerated apoptotic neurodegeneration.[224] The present nonclinical data implicate both *N*-methyl-D-aspartate receptor antagonists and drugs that potentiate GABA signal transduction as being potentially damaging to the developing brain.[225] The potential exists for combinations of anesthetic agents that have activity at both receptors to induce greater toxicity. Importantly, recent data suggest that even low nonapoptotic concentrations of anesthetics can perturb neuronal dendritic development and thereby lead to impairment of developing neuronal networks.[226] Moreover, in the rodent, this neurodegeneration is associated with cognitive impairment characterized by learning and memory deficits manifested in adulthood.[227] Several human cohort studies have shown an association between surgery in the neonatal period and poor neurodevelopmental outcomes[228,229] (also see Chapter 82). A large cohort study found a clear association between poor sensineural outcomes and surgery in preterm infants,[230] and more recently, neonates undergoing repair of patent ductus arteriosus were reported to have poorer outcomes.[231] These studies are interesting but are not conclusive evidence of a positive association. Epidemiologic observations suggest that the onset of Alzheimer's disease is related to cumulative anesthetic exposure before the age of 50 years,[232] and both halothane and isoflurane have been shown to increase the generation and toxicity of β-amyloid, a protein strongly implicated in the pathogenesis of Alzheimer's disease. Studies have further confirmed that inhaled anesthetics enhance the production, aggregation, and neurotoxicity of β-amyloid peptides,[233] the

appearance of brain plaques, and deficits characteristic of Alzheimer's disease.[234]

The central nervous system seems to be susceptible to anesthetic neurotoxicity at the extremes of ages, and general anesthetics produce neurotoxicity and enduring cognitive impairment in young animals. Extrapolating neurodevelopmental data from animals to humans to examine their clinical applicability is a challenge, and the implications of these findings to clinicians remain unclear. Current evidence is insufficient to recommend substantial changes in current clinical practice. Future animal studies are needed at comparable neurodevelopmental stages and with clinically relevant anesthetic doses and durations in animals exposed to a surgical stimulus and followed with appropriate physiologic monitoring. Further human clinical study is required, and comparison of outcomes in a large cohort study of neonates undergoing surgery under either general or regional anesthesia seems indicated. A study of this type would prove useful in helping to answer this important question, provide data to help guide clinical decisions, and further develop strategies for assessing the safety of anesthetics in neonates and children.

Exposure to Waste Anesthetic Gases

Inhaled anesthetics present a potential for adverse effects in patients administered inhaled anesthetics and in health care personnel exposed to waste anesthetic gases both in and out of the operating room environment. Recognition of postoperative exposure to exhaled waste anesthetic gases in postanesthesia care units (PACUs), intensive care units, and other patient care areas represents a new challenge. The recommended thresholds for trace inhaled anesthetic concentrations are less than 2 ppm for a volatile anesthetic when used alone and less than 0.5 ppm when used with N_2O. The recommended time-weighted average for N_2O is less than 25 ppm, which is much lower than the level of N_2O (1000 ppm) known to produce detectable inactivation of methionine synthase. To control occupational exposure to waste anesthetic gases, it is not sufficient to merely adopt scavenging systems in operating rooms; appropriate work practices, engineering controls, and occupational management protocols are also required throughout the perioperative process in all patient care areas. Many factors affect waste anesthetic gas concentrations, including the efficiency of air handling, room type and size, number of patients in a room or ward, and time spent in a particular patient care area.

Several studies have documented excessive levels of waste anesthetic gases in poorly ventilated PACU areas.[235-239] However, to date, none of these studies have documented any significant long-term adverse health effects.[235,236] An increased incidence of sister chromatid exchange has been found in operating room personnel in three of four recent studies, but the long-term implications of this finding are unknown at present.[240-243] In the only long-term prospective study with or without scavenging of waste anesthetic gases, Spence[244] found no causal relationship between exposure to waste anesthetic gases and adverse health effects.

Environmental Toxicities

The Greenhouse Effect. Solar radiation loads heat energy on the Earth, and to maintain a stable temperature, the Earth returns this load to space via infrared radiation. The primary constituents of the atmosphere, nitrogen and oxygen, are transparent to these rays. In the absence of other gases, the Earth's temperature would be −20°C. Naturally occurring gases such as methane, carbon dioxide, and N_2O absorb the infrared radiation. To overcome this absorption, the Earth has increased its temperature to approximately 15°C—the greenhouse effect. The contribution of major gases to the greenhouse effect is estimated to be 60% for carbon dioxide, 20% for methane, 14% for chlorofluorocarbons, and 6% for N_2O.[245] It is estimated that since the industrial revolution, the number of molecules of CO_2 per million molecules of air has increased from 280 to 385 ppm. *Global warming* is the increase in the average temperature of the Earth's near surface air and oceans since the mid-20th century and its projected continuation. The global air temperature rose 0.74°C during the 100 years ending in 2005. The Intergovernmental Panel on Climate Change (IPCC) concluded that "most of the observed increases in globally averaged temperatures since the mid-twentieth century is very likely due to the observed increase in anthrogenic greenhouse gas concentrations" via the greenhouse effect. The IPCC has predicted an average global rise in temperature of 1.4°C to 5.8°C between 1990 and 2100. Increasing global temperatures will decrease polar ice and thereby cause sea levels to rise and are expected to change precipitation patterns and increase the intensity of severe weather events. As a result, the Kyoto Protocol was negotiated and ratified by 175 countries and came into force on February 16, 2005. The United States is the only major industrialized country that is not a party to this agree-

Table 24-5 Summary of Atmospheric Lifetimes, Relative Input into the Stratosphere, Ozone-Depleting Potential (ODP), and Global-Warming Potential (GWP) Values for CFC-11, CFC-12, and Halogenated Volatile Anesthetics

Compound	M (g/mol)	$T_{½}$ (yr)	Input into Stratosphere (%)	ODP	S (cm^2/atm)	GWP
CFC-11	137.5	50	100	1.00	2500	0.033
CFC-12	121.0	102	100	1.55	3300	1.00
Halothane	197.4	6.6	13.2	1.56	1400	0.02
Enflurane	184.5	8.2	16.2	0.04	4800	0.08
Isoflurane	184.5	5.9	14.6	0.03	3900	0.05
Desflurane	168.0	21.4	21.4	0.00	3000	0.14
Sevoflurane	200.0	4.0	12.6	0.00	2550	0.02

CFC, chlorofluorocarbon; S, integrated infrared absorption cross section.
From Langbein T, Sonntag H, Trapp D, et al: Volatile anaesthetics and the atmosphere: Atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane. Br J Anaesth 82:66-73, 1999.

Table 24-6 Global-Warming (GWP) and Ozone-Depleting Potential (PDP) of Anesthetics

Chemical	Formula	Lifetime (yr)	GWP (100-yr integral) in CO_2 Mass Equivalents	ODP (10-yr integral) in CFC-11 Mass Equivalents
Isoflurane	$CHF_2OCHICH$	2.6	350	≈0.02
Sevoflurane	$CH_2FOCH(CF_3)_2$	≈3.7	420	0
Nitrous oxide	N_2O	114	298	<0.01

CFC, chlorofluorocarbon; GWP, global-warming potential; ODP, ozone-depleting potential.
From McGain F: Why anaesthetists should no longer use nitrous oxide. Anaesth Intensive Care 35:808-809, 2007.

ment. The United States is a signatory but has not ratified or withdrawn from the protocol. Essentially, this is an agreement under which industrialized countries will reduce their collective emissions of greenhouse gases by 5.2% relative to the year 1990 via a "cap and trade" system (effectively a 29% decrease over expected emission levels without the cuts). The goal is to lower overall emission of six greenhouse gases: carbon dioxide, methane, nitrous oxide, sulfur hexafluoride, hydrofluorocarbons, and perfluorocarbons, averaged over the period 2008 to 2112. National limitations range from reduction of 8% for the European Union, 7% for the United States, and 6% for Japan. The global-warming and ozone-depleting potential of several halocarbons, including the common fluorinated anesthetics and N_2O, is summarized in Tables 24-5[246] and 24-6.[247] N_2O is extremely stable with an atmospheric lifetime of 100 to 150 years. Its only sink is degradation by ultraviolet radiation outside the ozone layer. N_2O contributes about 5% of the greenhouse gas effect, and medical use of N_2O contributes approximately 0.35% to 2% of this total.[248,249] Like N_2O, in addition to contributing to the greenhouse effect, chlorine-containing compounds such as halothane, enflurane, isoflurane, and desflurane also deplete stratospheric ozone.[246] Present protocols call for elimination of these compounds by 2030. In addition, there is an ongoing movement in Japan[250] and the European Union to reduce and eventually eliminate N_2O from anesthesia. The contribution of anesthetic-released N_2O and chlorinated volatile agents to global warming, the greenhouse effect, and ozone depletion is minor in comparison to that generated by the combustion of fossil fuels and nitrogen-containing fertilizers. N_2O contributes 1% to ozone depletion and 0.05% to the greenhouse effect, whereas the anesthetics contribute 0.01% to ozone depletion and 0.1% to the greenhouse effect. We have reduced the toxicity of anesthetics to patients and health care workers since the inception of modern anesthesia; however, environmental toxicities may prove to be the Achilles heel of these valuable agents. Until such time as these agents are eliminated from practice or better, more stable substitutes become available, we as anesthesia providers can reduce the adverse environmental consequences of these agents by using low-flow anesthesia systems whenever possible and thus can have a small but important positive impact on the environment.

Summary

Volatile anesthetic agents, like most drugs, undergo metabolism in the body and are sometimes associated with toxic reactions. Scientific investigations and industry research have led to the development of more stable anesthetics with more desirable clinical properties. Inhaled agents that are more heavily metabolized are associated with the greatest numbers of reported toxicities. As with most drugs, these toxicities occur when the anesthetics are given as "standard-dose medications"; that is, the appropriate medication and dose are given at the proper time, in the correct manner, to the right patient. Thus, these associated toxicities under most circumstances meet the definition of adverse drug reactions (ADRs). More than 2 million ADRs are reported each year in the United States and result in more than 100,000 deaths. It should be noted that 51% of approved drugs have serious ADRs not detected before approval and that ADRs are responsible for 6% of all hospital admissions, occur in 10% to 20% of hospitalized patients, and are the cause of death in 0.1% of medical and 0.01% of surgical patients. They are the fourth leading cause of death in hospitalized patients (0.32% of hospitalized patients). When compared with most therapeutic agents, the safety of fluorinated inhaled anesthetics is remarkable. Future developments in the field of personalized medicine, in which both the selection of a specific therapeutic agent and its associated dosing are tailored to an individual patient on the basis of individual genetic profiles, will have ramifications for increased efficacy and patient safety. Idiosyncratic toxicities that involve the human immune system continue to present some of the greatest challenges to anesthesia and medicine, but new insight into the structure-toxicity relationships of drugs at the molecular level may provide the necessary tools to solve this puzzle.

The use of any anesthetic agent must be based on specific knowledge of its benefits and risks, how it may produce toxicity, and in which patients it may be most safely administered. Clearly, the perfect anesthetic agent does not exist yet, and individual patient circumstances will continue to dictate the choice and use of inhaled anesthetics in clinical practice. As ongoing research attempts to uncover emerging toxicities, the clinician is challenged to balance new information with current clinical practices and choose the safest, most effective agents for each patient.

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25 Inhaled Anesthetic Delivery Systems

Key Points

1. The low-pressure circuit (LPC) is the "vulnerable area" of anesthesia machines because it is most subject to breakage and leaks. The LPC is located downstream from all safety features of anesthesia machines except the oxygen analyzer, and it is the portion of the machine that is missed if an inappropriate LPC leak test is performed.
2. It is mandatory that the LPC be checked for leaks before administering an anesthetic because leaks in the LPC can cause delivery of a hypoxic mixture or patient awareness during anesthesia (or both).
3. Because many GE/Datex-Ohmeda anesthesia machines have a one-way check valve in the LPC, a negative-pressure leak test is required to detect leaks in the LPC. A positive-pressure leak test will not detect leaks in the LPC of most GE/Datex-Ohmeda products.
4. Internal vaporizer leaks can be detected only with the vaporizer turned on.
5. Before administering an anesthetic, the circle system must be checked for leaks and for flow. To test for leaks, the circle system is pressurized to 30 cm H_2O, and the circle system airway pressure gauge is observed (static test). To check for appropriate flow to rule out obstruction and faulty valves, the ventilator and a test lung (breathing bag) are used (dynamic test).
6. Some new anesthesia workstation self-tests do not detect internal vaporizer leaks unless each vaporizer is individually turned on during the self-test.
7. In the event of pipeline crossover, two actions must be taken. The backup oxygen cylinder must be turned "on," and the wall supply sources must be disconnected.
8. Fail-safe valves and proportioning systems help minimize delivery of a hypoxic mixture, but they are not foolproof. Delivery of a hypoxic mixture can result from (1) the wrong supply gas, (2) a defective or broken safety device, (3) leaks downstream from the safety devices, (4) administration of an inert gas, and (5) dilution of the inspired oxygen concentration by high concentrations of inhaled anesthetics.
9. Because of desflurane's low boiling point and high vapor pressure, controlled vaporization of desflurane requires special sophisticated vaporizers such as the Datex-Ohmeda Tec 6 and the Aladin cassette vaporizer.
10. Misfilling a conventional variable-bypass vaporizer with desflurane could theoretically be catastrophic and result in delivery of a hypoxic mixture and a massive overdose of inhaled desflurane anesthetic.
11. Inhaled anesthetics can interact with carbon dioxide absorbents and produce toxic compounds. During sevoflurane anesthesia, compound A can be formed, particularly at low fresh gas flow rates, and during desflurane anesthesia, carbon monoxide can be produced, particularly with desiccated absorbents.
12. Desiccated strong-base absorbents (particularly Baralyme) can react with sevoflurane and produce extremely high absorber temperatures and combustible decomposition products. In combination with the oxygen- or nitrous oxide–enriched environment of the circle system, these effects can produce fires within the breathing system.
13. Anesthesia ventilators with ascending bellows (bellows that ascend during the expiratory phase) are safer than descending bellows because disconnections will be readily manifested by failure ascending bellows to refill.
14. With ascending bellows anesthesia ventilators, fresh gas flow and oxygen flushing during the inspiratory phase contribute to the patient's tidal volume because the ventilator relief valve is closed. Oxygen flushing during the inspiratory phase can cause volutrama and/or barotrauma, (particularly in pediatric patients). Therefore, the oxygen flush should never be activated during the inspiratory phase of mechanical ventilation.

15. New ventilators that use fresh gas decoupling technology virtually eliminate the possibility of barotrauma from oxygen flushing during the inspiratory phase because fresh gas flow and oxygen flush flow are diverted to the reservoir breathing bag. However, if the breathing bag has a leak or is absent, patient awareness under anesthesia and delivery of a lower than expected oxygen concentration could occur because of entrainment of room air.

16. With newer GE/Datex-Ohmeda anesthetic ventilators such as the 7100 and 7900 SmartVent, scavenging of both the patient gas and the drive gas results in substantially increased volumes of scavenged gas. Thus, the scavenging systems must be set appropriately to accommodate the increased volume or pollution of the operating room environment could result.

Over the years, the anesthesia delivery system has evolved from a simple pneumatic device to a complex multisystem workstation, and new technologies continue to advance its development at a rapid pace (Figs. 25-1 and 25-2). These continuing changes to one of the most important pieces of equipment used by anesthesia care providers can make maintaining a current knowledge base (sufficient for their safe use) difficult for many to achieve. To prevent mishaps, providers must be aware of the functional anatomy of the anesthesia workstation. Furthermore, this knowledge base must even include the newer systems as they become available, to the extent that they are represented in an individual's practice. Fortunately, the most basic workstation components are generally fairly consistent from one platform to another. These basic component systems include what was formerly referred to as the anesthesia machine proper (i.e., the pressure-regulating and gas-mixing components), the vaporizers, the anesthesia breathing circuit, the ventilator, the scavenging system, and respiratory and physiologic monitoring systems.

For anesthesia care providers to safely use the many features of today's anesthesia workstation, a thorough understanding of its operation is essential. Because of large-scale education efforts, in addition to improvements in engineering and design of the anesthesia workstation, malpractice claims associated with gas delivery equipment are becoming less frequent. On the other hand, because of the continual development of new volatile anesthetics, aftermarket add-on devices, and even new anesthesia workstation features, equipment-related mishaps are not likely to disappear completely. In fact, in a review of the anesthesia closed-claims literature, Caplan and coworkers found that although claims related to the medical gas delivery system were rare, when they did occur, they were usually severe and death or permanent brain injury frequently resulted.[1]

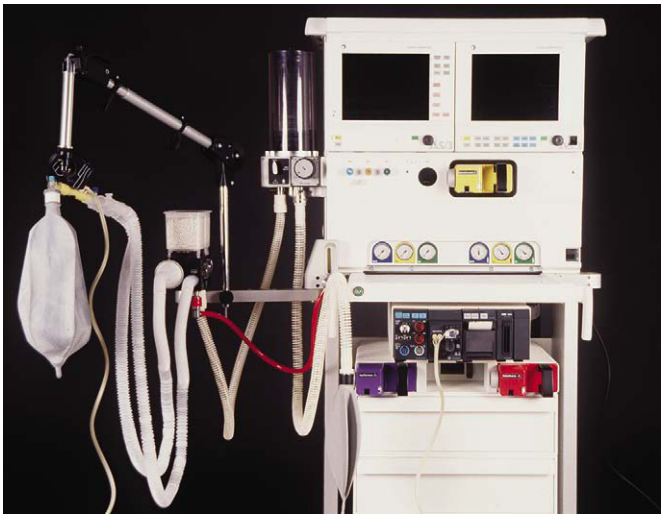

Figure 25-1 GE/Datex-Ohmeda S/5 Anesthesia Delivery Unit (ADU) workstation. *(Courtesy of GE Medical.)*



Figure 25-2 Dräger Narkomed 6000 anesthesia workstation.

In this chapter we examine the anesthesia workstation piece by piece. We will describe the normal operation, function, and integration of major anesthesia workstation subsystems. More important, we illustrate potential problems and hazards associated with the various components of the anesthesia delivery system and the appropriate preoperative checks that may help detect and prevent such problems.

Anesthesia Workstation Standards and Pre-use Procedures

A few years ago, fundamental knowledge of basic anesthesia machine pneumatics would suffice for most anesthesia care pro-

viders. Today, a detailed understanding of pneumatics, electronics, and even computer science is helpful to fully understand the capabilities and complexities of the anesthesia workstation. Along with changes in the composition of the anesthesia workstation, including more complex ventilation systems and integrated monitoring, recently there has also been increasing divergence between anesthesia workstation designs from different manufacturers. In 1993, a joint effort between the American Society of Anesthesiologists (ASA) and the U.S. Food and Drug Administration (FDA) produced the 1993 FDA Anesthesia Apparatus Checkout Recommendations (Appendix 1). This pre-use checklist was versatile in that it could be applied to most commonly available anesthesia machines equally well, and it did not require users to vary the pre-use procedure significantly from machine to machine.

Today, because of increasing fundamental anesthesia workstation design variations, the 1993 FDA pre-use checklist may no longer be applicable to certain anesthesia workstations. In such cases, anesthesia care providers must be aware of this and follow the original equipment manufacturer's recommended pre-use checklist. Some of the latest workstations even have computer-assisted self-tests that automatically perform all or a part of the pre-use machine checkout procedure. The availability of such automated checkout features further adds to the complexity of constructing a standardized pre-use anesthesia machine checklist such as the one that the anesthesia community has enjoyed in the recent past. Ultimately, the responsibility for performing adequate pre-use testing of the anesthesia workstation falls to the anesthesia care provider. It will be the anesthesia care provider of record who must be aware of which anesthesia workstation components are tested by these automated self-tests and which ones are not. Because of the number of machines available and the variability among their self-testing procedures, we will limit their discussion to general topics related to these systems.

Standards for Anesthesia Machines and Workstations

Standards for anesthesia machines and workstations provide guidelines for manufacturers regarding their minimum performance, design characteristics, and safety requirements. During the past 2 decades, the progression of anesthesia machine standards has been as follows:

1979: American National Standards Institute (ANSI) Z79.8-1979[2]
1988: American Society for Testing and Materials (ASTM) F1161-88[3]
1994: ASTM F1161-94[4] (reapproved in 1994 and discontinued in 2000)
2000: ASTM F1850-00[5]

To comply with the 2000 ASTM F1850-00 standard, newly manufactured workstations must have monitors that measure the following parameters: continuous breathing system pressure, exhaled tidal volume, ventilatory carbon dioxide concentration, anesthetic vapor concentration, inspired oxygen concentration, oxygen supply pressure, arterial oxygen saturation of hemoglobin, arterial blood pressure, and continuous electrocardiogram. The anesthesia workstation must have a prioritized alarm system that groups the alarms into three categories: high, medium, and low priority. These monitors and alarms may be automatically enabled and made to function by turning on the anesthesia workstation, or the monitors and alarms can be manually enabled and made functional by following a pre-use checklist.[5]

Checking Your Anesthesia Workstation

A complete anesthesia apparatus checkout procedure must be performed each day before the anesthesia workstation is first used. An abbreviated version should be performed before each subsequent case. Several checkout procedures exist, but the 1993 FDA Anesthesia Apparatus Checkout Recommendations reproduced in Appendix 1 are the most popular and remain applicable to the majority of anesthesia machines in use worldwide.[6-10] Anesthesia care providers should also be aware that many machines have been modified in the field. The addition of aftermarket products may mandate modification of the pre-use checklist. The user must always refer to the original equipment manufacturer's operator's manual for special procedures or precautions related to particular workstations.

Because of the divergent nature of many contemporary anesthesia workstation designs, the philosophy of "one pre-use machine checkout procedure fits all machines" has had to be changed to a philosophy of "not all workstations are created equally." As a result, in 2005 the ASA's Committee on Equipment and Facilities began to develop a revised pre-use checklist that was designed to be more workstation specific and, indeed, was intended to eventually replace the 1993 FDA Anesthesia Apparatus Checkout Recommendations. Instead of the 1993 checklist, which elaborated specific checks and how they should be performed, the new pre-use guideline elaborates only specific systems and subsystems that must be evaluated. It is ultimately up to the user, in conjunction with workstation manufacturers, and local policy to determine the actual mechanisms/specific tests that will be used to accomplish these subsystem evaluations. Appendix 2 contains the most current version of these recommendations. Although the new recommendations also now address who (personnel-wise) may be responsible for performing such machine pre-use evaluations, every anesthesia care provider must be aware that the ultimate responsibility for proper machine pre-use safety checks rests on the provider using the machine to deliver anesthetic care. The current guidelines for developing institution-specific checkout procedures before anesthesia delivery can also be found on the ASA website at www.asahq.org/clinical/fda.htm. Also located at the same website are sample workstation-specific pre-use checklists developed by other institutions that can be adapted/modified for use in other practice settings.

Testing Specific Components of the Anesthesia Delivery System

The three most important preoperative checks are (1) calibration of the oxygen analyzer, (2) the low-pressure circuit leak test, and (3) the circle system tests. Each is discussed in the following paragraphs. Additional details regarding these systems will be presented in subsequent sections describing the anatomy of the anesthesia workstation. For a simplified diagram of a two-gas

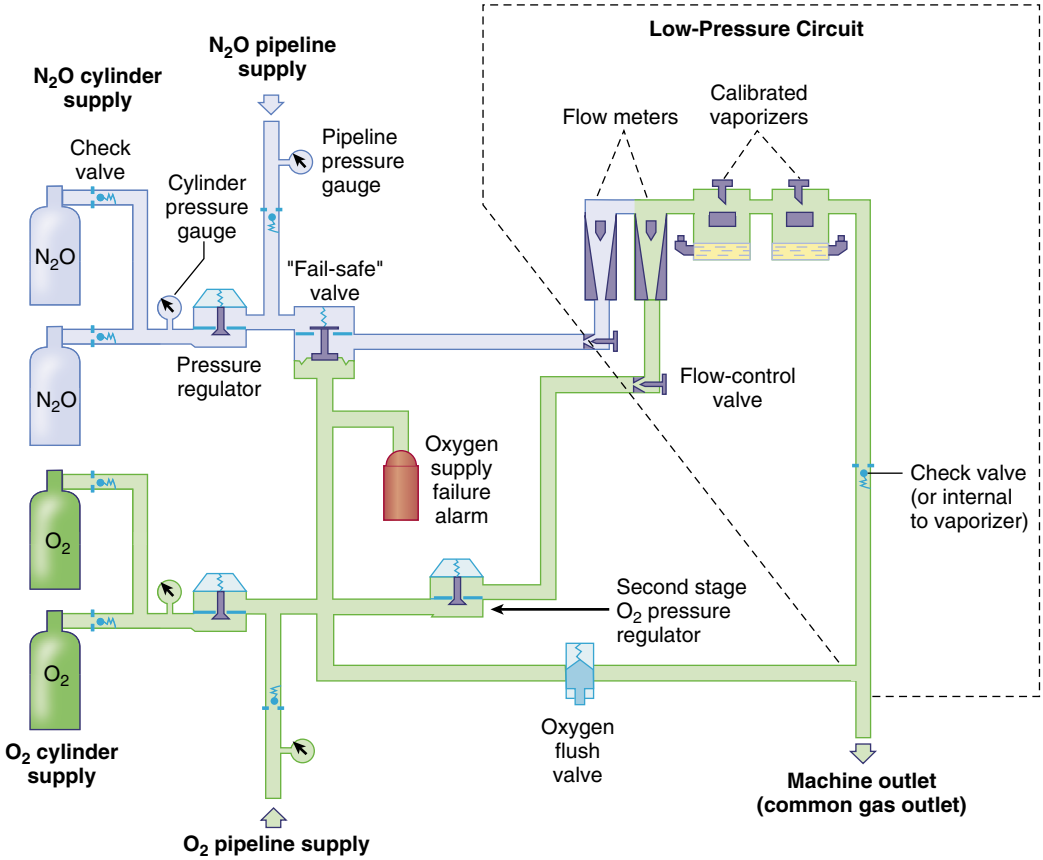

Figure 25-3 Diagram of a generic two-gas anesthesia machine. *(Modified with permission from Check-Out, a Guide for Preoperative Inspection of an Anesthesia Machine. Park Ridge, IL, American Society of Anesthesiologists, 1987.)*

anesthesia machine and the components described in the following discussion, please refer to Figure 25-3. A comprehensive discussion of Figure 25-3 can also be found in the section "Anesthesia Workstation Pneumatics."

Calibration of the Oxygen Analyzer

The oxygen analyzer is one of the most important monitors on the anesthesia workstation. It is the only machine safety device that evaluates the integrity of the low-pressure circuit in an ongoing fashion. Other machine safety devices, such as the fail-safe valve, the oxygen supply failure alarm, and the proportioning system, are all upstream from the flow control valves. The only machine monitor that detects problems downstream from the flow control valves is the oxygen analyzer. Calibration of this monitor is described in Appendix 1 (Anesthesia Apparatus Checkout Recommendations, 1993, No. 9). The actual procedure for calibrating the oxygen analyzer has remained reasonably similar over the recent generations of anesthesia workstations. Generally, the oxygen concentration–sensing element must be exposed to room air for calibration to 21%. This may require manually setting a dial on older machines, but on newer ones, it usually involves only temporary removal of the sensor, selecting and then confirming that the oxygen calibration is to be performed from a set of menus on the workstation's display screen, and finally reinstalling the sensor.

Low-Pressure Circuit Leak Test

The low-pressure leak test checks the integrity of the anesthesia machine from the flow control valves to the common gas outlet. It evaluates the portion of the machine that is downstream from all safety devices except the oxygen analyzer. The components located within this area are *precisely* the ones most subject to breakage and leaks. Leaks in the low-pressure circuit can cause hypoxia and/or patient awareness.[11,12] Flow tubes, the most delicate pneumatic component of the machine, can crack or break. A typical three-gas anesthesia machine has 16 O-rings in the low-pressure circuit. Leaks can occur at the interface between the glass flow tubes and the manifold and at the O-ring junctions between the vaporizer and its manifold. Loose filler caps on vaporizers are a common source of leaks, and these leaks can cause patient awareness under anesthesia.[11,13]

Several different methods have been used to check the low-pressure circuit for leaks, including the oxygen flush test, the common gas outlet occlusion test, the traditional positive-pressure leak test, the North American Dräger positive-pressure leak test, the Ohmeda 8000 internal positive-pressure leak test, the Ohmeda negative-pressure leak test, the 1993 FDA universal negative-pressure leak test, and others. One reason for the large number of methods is that the internal design of various machines differs considerably. The most notable example is that most GE Healthcare/Datex-Ohmeda (hereafter referred to as Datex-

Table 25-1 Check Valves and Manufacturer-Recommended Leak Test

Anesthesia Machine	Machine Outlet Check Valve	Vaporizer Outlet Check Valve	Leak Test Recommended by Manufacturer	
			Positive Pressure	Negative Pressure (Suction Bulb)
Dräger Narkomed 2A, 2B, 2C, 3, 4, GS	No	No	X	
Fabius GS	No	No	Self-test	
Narkomed 6000	No	No	Self-test	
Ohmeda Unitrol	Yes	Variable		X
Ohmeda 30/70	Yes	Variable		X
Ohmeda Modulus I	Yes	Variable		X
Ohmeda Modulus II	Yes	No		X
Ohmeda Excel series	Yes	No		X
Ohmeda Modulus II Plus	No	No		X
Ohmeda CD	No	No		X
Datex-Ohmeda Aestiva	Yes	No		X
Datex-Ohmeda S5/ADU	No	No	Self-test	

Data from Ohio Medical Products, Ohmeda, Datex-Ohmeda, North American Dräger, Dräger Medical.

Ohmeda) workstations have a check valve near the common gas outlet whereas Dräger Medical workstations do not. The presence or absence of the check valve profoundly influences which preoperative check is indicated.

Several mishaps have resulted from application of the wrong leak test to the wrong machine.[14-17] It is therefore mandatory that the appropriate low-pressure leak test be performed each day. To do so, it is essential that the exact location and operating principles of the Datex-Ohmeda check valve be understood. Many Datex-Ohmeda anesthesia workstations have a machine outlet check valve located in the low-pressure circuit (see Table 25-1). The check valve is located downstream from the vaporizers and upstream from the oxygen flush valve (Fig. 25-3). It is open (Fig. 25-4, left) in the absence of backpressure. Gas flow from the manifold moves the rubber flapper valve off its seat and allows gas to proceed freely to the common outlet. The valve closes (Fig. 25-4, right) when backpressure is exerted on it.[8] Backpressure sufficient to close the check valve may occur with the following conditions: oxygen flushing, peak breathing circuit pressures generated during positive-pressure ventilation, or use of a positive-pressure leak test.

Generally speaking, the low-pressure circuit of anesthesia workstations without an outlet check valve can be tested with a positive-pressure leak test, and machines with check valves must

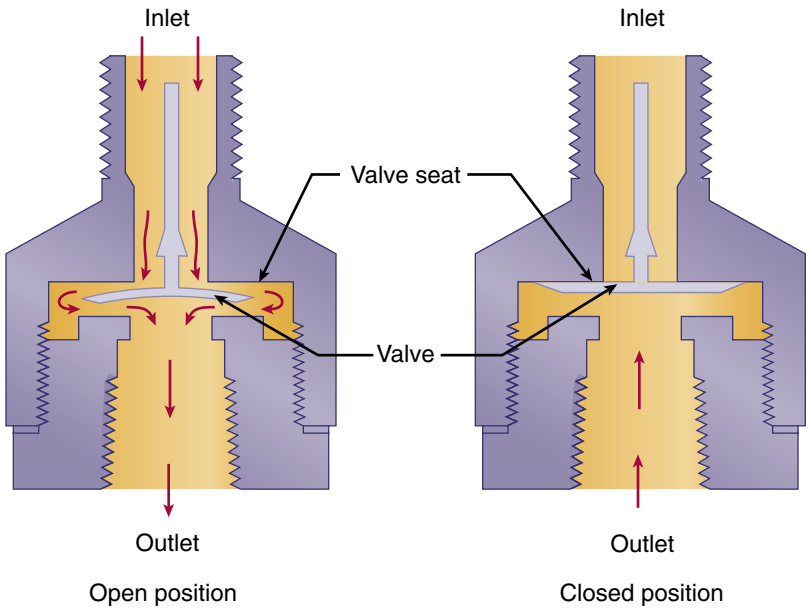

Figure 25-4 Machine outlet check valve. See text for details. *(Reproduced with permission from Bowie E, Huffman LM: The Anesthesia Machine: Essentials for Understanding. Madison, WI, Ohmeda, a Division of BOC Health Care, Inc., 1985.)*

be tested with a negative-pressure leak test. When performing a positive-pressure leak test, the operator generates positive pressure in the low-pressure circuit by using flow from the anesthesia machine or from a positive-pressure bulb to detect a leak. When performing a negative-pressure leak test, the operator creates negative pressure in the low-pressure circuit by using a suction bulb to detect leaks. Two different low-pressure circuit leak tests are described in the following paragraphs.

Oxygen Flush Positive-Pressure Leak Test Historically, older anesthesia machines did not have check valves in the low-pressure circuit. Therefore, it was common practice to pressurize the breathing circuit and the low-pressure circuit with the oxygen flush valve to test for internal anesthesia machine leaks. Because many modern Datex-Ohmeda machines now have check valves in the low-pressure circuit, however, application of a positive-pressure leak test to these machines can be misleading or even dangerous (Fig. 25-5). Inappropriate use of the oxygen flush valve or the presence of a leaking flush valve may lead to inadequate evaluation of the low-pressure circuit for leaks. In turn, this can lull the anesthesia care provider into a false sense of security despite the presence of large leaks.[15-19] Positive pressure from the breathing circuit results in closure of the outlet check valve, and the value on the airway pressure gauge will fail to decline. The system appears to be tight, but in actuality, only the circuitry downstream from the check valve is leak free.[20] Thus, a vulnerable area exists from the check valve back to the flow control valves because this area is not tested by a positive-pressure leak test.

1993 FDA Negative-Pressure Leak Test The 1993 FDA universal negative-pressure leak test[10] (Appendix 1, No. 5) was named "universal" because at that time it could be used to check all contemporary anesthesia machines, regardless of the presence or absence of check valves in the low-pressure circuit. It remains effective for many anesthesia workstations and can be applied to many Datex-Ohmeda machines, Dräger Medical machines, and others. Unfortunately, some newer machines are no longer compatible with this test. The ASA's Committee on Equipment and Facilities in conjunction with the FDA is expected to update the 1993 Anesthesia Apparatus Checkout Recommendations as this chapter comes to press. Until the new recommendations become available, the 1993 guidelines should continue to be followed as closely as possible because they remain applicable to the vast majority of anesthesia workstations in use worldwide.

The 1993 FDA checklist is based upon the Datex-Ohmeda negative-pressure leak test (Fig. 25-6). It is performed with a negative-pressure leak-testing device, which is a simple suction bulb. The machine's master switch, flow control valves, and vaporizers are turned off. The suction bulb is attached to the common fresh gas outlet and squeezed repeatedly until it is fully collapsed. This action creates a vacuum in the low-pressure circuitry. The machine is free of leaks if the hand bulb remains collapsed for at least 10 seconds. A leak is present if the bulb reinflates during this period. The test is repeated with each vaporizer individually turned to the "on" position because internal vaporizer leaks can be detected only with the vaporizer turned on.

The FDA "universal" negative-pressure low-pressure circuit leak test has several advantages.[21] It is quick and simple to perform,

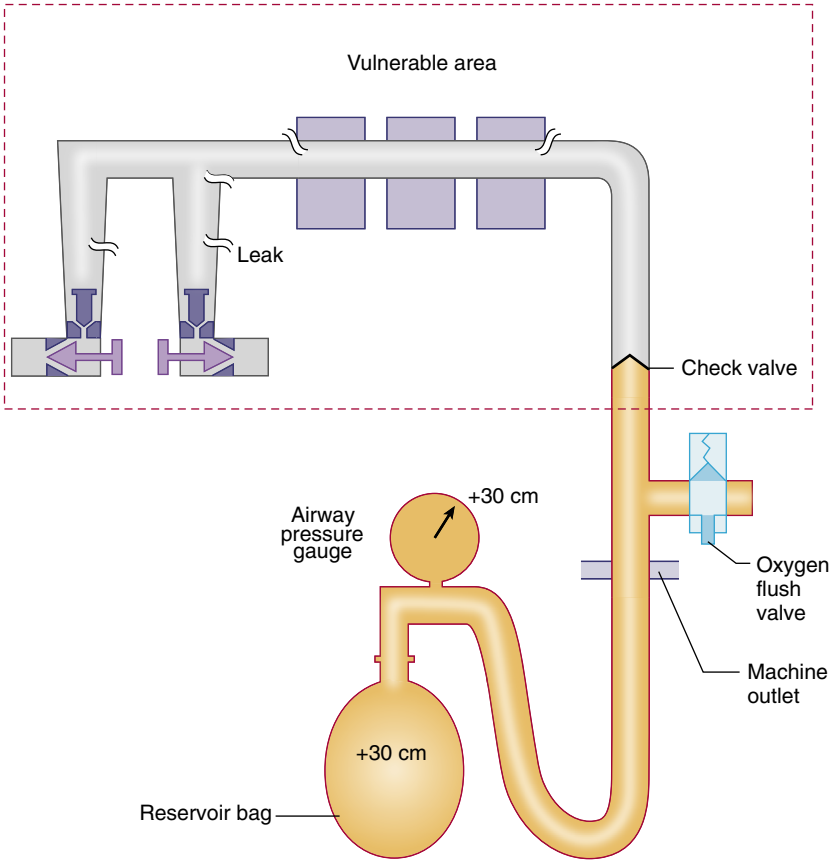

Figure 25-5 Inappropriate use of the oxygen flush valve to check the low-pressure circuit of an Ohmeda machine equipped with a check valve. The area within the *rectangle* is not checked by inappropriate use of the oxygen flush valve. The components located within this area are *precisely* the ones most subject to breakage and leaks. Positive pressure within the patient circuit closes the check valve, and the value on the airway pressure gauge does not decline despite leaks in the low-pressure circuit.

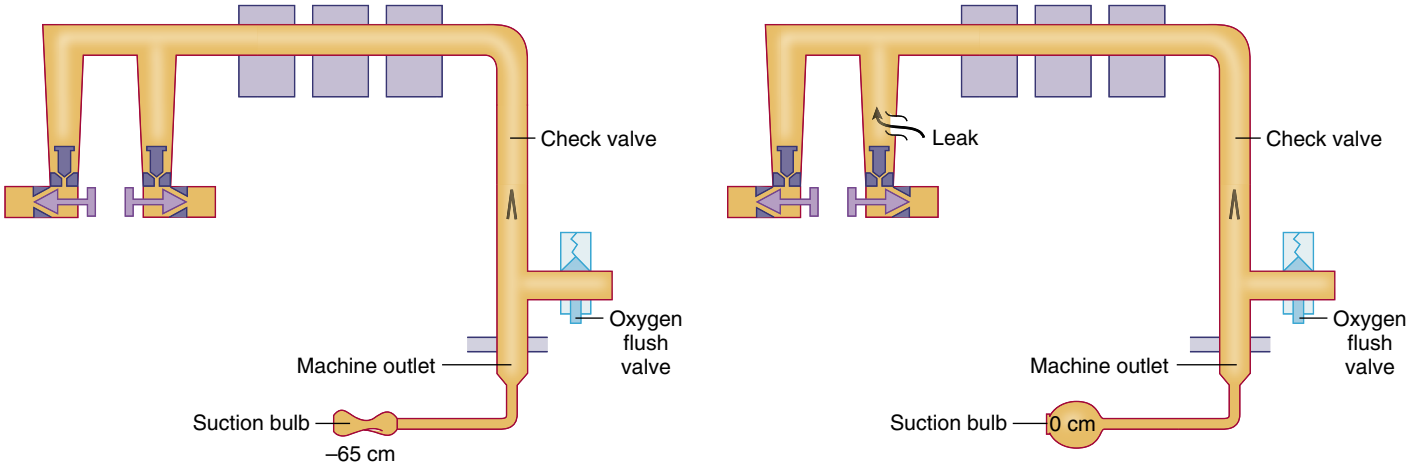

Figure 25-6 Food and Drug Administration negative-pressure leak test. **Left,** A negative-pressure leak-testing device is attached directly to the machine outlet. Squeezing the bulb creates a vacuum in the low-pressure circuit and opens the check valve. **Right,** When a leak is present in the low-pressure circuit, room air is entrained through the leak and the suction bulb inflates. *(Reprinted with permission from Andrews JJ: Understanding anesthesia machines.* In *1988 Review Course Lectures. Cleveland, OH, International Anesthesia Research Society, 1988, p 78.)*

has an obvious end point, and may help isolate the problem. For example, if the bulb reinflates in less than 10 seconds, a leak is present somewhere in the low-pressure circuit. Therefore, it differentiates between breathing circuit leaks and leaks in the low-pressure circuit. The "universal" negative-pressure leak test is the most sensitive of all contemporary leak tests because it is not dependent on volume. That is, it does not involve the use of a breathing bag or corrugated hoses whose compliance could mask a significant leak. It can detect leaks as small as 30 mL/min. Finally, the operator does not need detailed or in-depth knowledge of proprietary design differences. If the operator performs the universal test correctly, the leak will be detected.

Circle System Tests

The circle system tests (Appendix 1, Nos. 11 and 12) evaluate the integrity of the circle breathing system, which spans from the common gas outlet to the Y-piece (Fig. 25-7). It has two parts—the *leak test* and the *flow test*. To thoroughly check the circle system for leaks, valve integrity, and obstruction, both tests must be performed preoperatively. The *leak test* is performed by closing the pop-off valve, occluding the Y-piece, and pressurizing the circuit to 30 cm H_2O with the oxygen flush valve. The value on the pressure gauge will not decline if the circle system is leak free, but this does not ensure valve integrity. The value on the gauge will read 30 cm H_2O even if the unidirectional valves are stuck shut or the valves are incompetent.

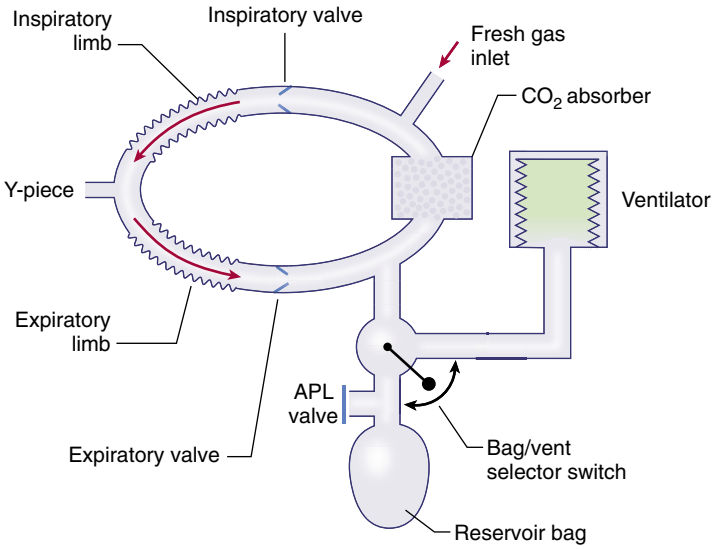

Figure 25-7 Components of the circle system. APL, adjustable pressure-limiting; B, reservoir bag; V, ventilator. *(Reproduced with permission from Brockwell RC: Delivery systems for inhaled anesthesia.* In *Barash PG [ed]: Clinical Anesthesia, 5th ed. Philadelphia, Lippincott Williams & Wilkins, 2006, p 562.)*

The *flow test* checks the integrity of the unidirectional valves, and it detects obstruction in the circle system. It can be performed by removing the Y-piece from the circle system and breathing through the two corrugated hoses individually. The valves should be present, and they should move appropriately. The operator should be able to inhale but not exhale through the inspiratory limb and able to exhale but not inhale through the expiratory limb. The flow test can also be performed by using the ventilator and a breathing bag attached to the "Y"-piece as described in the 1993 FDA Anesthesia Apparatus Checkout Recommendations (Appendix 1, No. 12).[10]

Workstation Self-Tests

As mentioned previously, many new anesthesia workstations now incorporate technology that allows the machine to either automatically or manually walk the user through a series of self-tests to check for functionality of the electronic, mechanical, and pneumatic components. Tested components commonly include the gas supply system, flow control valves, circle system, ventilator, and, in the case of the Datex-Ohmeda Anesthesia Delivery Unit (ADU), even the Aladin cassette vaporizer. The comprehensiveness of these self-diagnostic tests varies from one model and manufacturer to another. If these tests are to be used, all manufacturer recommendations must be read and strictly followed. Although a thorough understanding of what the particular workstation's self-tests include is very helpful, this information is often difficult to obtain and may vary greatly between devices.

One particularly important point of caution with self-tests should be noted on systems with manifold-mounted vaporizers such as the Dräger Medical Fabius GS and the Narkomed 6000 series. A manifold-mounted vaporizer does not become part of an anesthesia workstation's gas flow stream until its concentration control dial is turned to the "on" position. Therefore, to detect internal vaporizer leaks on this type of system, the "leak test" portion of the self-diagnostic must be repeated separately with each individual vaporizer turned to the "on" position. If this precaution is not taken, large leaks that could potentially result in patient awareness, such as from a loose filler cap or cracked fill indicator, could go undetected.

Anesthesia Workstation Pneumatics

Anatomy of an Anesthesia Workstation

A simplified diagram of a generic two-gas anesthesia machine is presented in Figure 25-3. The pressures within the anesthesia workstation can be divided into three circuits: a high-pressure, an intermediate-pressure, and a low-pressure circuit (see Fig. 25-3). The *high-pressure circuit* is confined to the cylinders and the cylinder primary pressure regulators. For oxygen, the pressure range of the high-pressure circuit extends from a high of 2200 pounds per square inch gauge (psig) to 45 psig, which is the regulated cylinder pressure. For nitrous oxide in the high-pressure circuit, pressures ranges from a high of 750 psig in the cylinder to a low of 45 psig. The *intermediate-pressure circuit* begins at the regulated cylinder supply sources at 45 psig, includes the pipeline sources at 50 to 55 psig, and extends to the flow control valves. Depending on the manufacturer and specific machine design, second-stage pressure regulators may be used to decrease pipeline supply pressure to the flow control valves to an even lower pressure such as 14 or 26 psig within the intermediate-pressure circuit.[22,23] Finally, the *low-pressure circuit* extends from the flow control valves to the common gas outlet. Therefore, the low-pressure circuit includes the flow tubes, vaporizer manifold, vaporizers, and the one-way check valve on most Datex-Ohmeda machines.[22]

Both oxygen and nitrous oxide have two supply sources: a pipeline supply source and a cylinder supply source. The pipeline supply source is the primary gas source for the anesthesia machine. The hospital pipeline supply system provides gas to the machine at approximately 50 psig, which is the normal working pressure of most machines. The cylinder supply source serves as a backup if the pipeline supply fails or as the primary supply if the anesthesia workstation is being used in a location without the availability of pipeline-supplied gases. As previously described, the oxygen cylinder source is regulated from 2200 to approximately 45 psig, and the nitrous oxide cylinder source is regulated from 745 to approximately 45 psig.[22-24]

A safety device traditionally referred to as the *fail-safe* valve is located downstream from the nitrous oxide supply source. It serves as an interface between the oxygen and nitrous oxide supply sources. This valve shuts off or proportionally decreases the supply of nitrous oxide (and other gases) if the oxygen supply pressure declines. To meet ASTM standards, contemporary machines have an alarm device to monitor the oxygen supply pressure. A high-priority alarm is actuated as the declining oxygen supply pressure reaches a predetermined threshold such as 30 psig.[22-24]

Many Datex-Ohmeda machines have a second-stage oxygen regulator located downstream from the oxygen supply source in the intermediate-pressure circuit. It is adjusted to a precise pressure level, such as 14 psig.[23] This regulator supplies a constant pressure to the oxygen flow control valve regardless of fluctuating oxygen pipeline pressures. For example, flow from the oxygen flow control valve will be constant if the oxygen supply pressure is greater than 14 psig.

The flow control valves represent an important anatomic landmark within the anesthesia workstation because they separate the intermediate-pressure circuit from the low-pressure circuit. The low-pressure circuit is the part of the machine that lies downstream from the flow control valves. The operator regulates flow entering the low-pressure circuit by adjusting the flow control valves. The oxygen and nitrous oxide flow control valves are linked mechanically or pneumatically by a proportioning system to help prevent inadvertent delivery of a hypoxic mixture. After leaving the flow tubes, the mixture of gases travels through a common manifold and may be directed to a calibrated vaporizer. Precise amounts of inhaled anesthetic can be added, depending on the vaporizer control dial setting. The total fresh gas flow plus the anesthetic vapor then travel toward the common gas outlet.[22,23]

Many Datex-Ohmeda anesthesia machines have a one-way check valve located between the vaporizer and the common gas outlet in the mixed-gas pipeline. Its purpose is to prevent backflow into the vaporizer during positive-pressure ventilation, thereby minimizing the effects of intermittent fluctuations in downstream pressure on the concentration of inhaled anesthetic (see "Intermittent Backpressure" in the section "Vaporizers"). The

presence or absence of this check valve *profoundly* influences which preoperative leak test is indicated (see "Checking Your Anesthesia Workstation"). The oxygen flush connection joins the mixed-gas pipeline between the one-way check valve (when present) and the machine outlet. Thus, when the oxygen flush valve is activated, the pipeline oxygen pressure has a "straight shot" to the common gas outlet.[22,23]

Pipeline Supply Source

Under normal conditions, the pipeline supply serves as the primary gas source for the anesthesia machine. Most hospitals today have a central piping system to deliver medical gases such as oxygen, nitrous oxide, and air to the operating room. The central piping system must supply the correct gases at the appropriate pressure for the anesthesia workstation to function properly. Unfortunately, this does not always occur. Proven as recently as 2002, even large medical centers with huge cryogenic bulk oxygen storage systems are not immune to component failures that may contribute to critical oxygen pipeline supply failures.[25] In this case, rupture of a faulty joint at the bottom of the primary cryogenic oxygen storage tank released 8000 gallons of liquid oxygen to flood the streets in the surrounding area. This mishap suddenly compromised oxygen delivery in a major medical center.

In a survey of approximately 200 hospitals in 1976, 31% reported difficulties with pipeline systems.[26] The most common problem was inadequate oxygen pressure, followed by excessive pipeline pressure. The most devastating reported hazard, however, was accidental crossing of oxygen and nitrous oxide pipelines, which has led to many deaths. This problem caused 23 deaths in a newly constructed wing of a general hospital in Sudbury, Ontario, during a 5-month period.[26,27] More recently, in 2002 two additional hypoxic deaths were reported in New Haven, Connecticut. These deaths resulted from a medical gas system failure in which an altered oxygen flow meter was inadvertently connected to a wall supply source for nitrous oxide.[28]

In the event that a pipeline crossover is ever suspected, the anesthesia care provider must immediately make *two* corrective actions. First, the backup oxygen cylinder should be turned on. Then the pipeline supply must be disconnected. This second step is mandatory because the machine will preferentially use the inappropriate 50-psig pipeline supply source instead of the lower pressure (45 psig) oxygen cylinder source if the wall supply is not disconnected.

Gas enters the anesthesia machine through the pipeline inlet connections (arrows in Fig. 25-3). The pipeline inlet fittings are gas-specific Diameter Index Safety System (DISS) threaded body fittings. The DISS provides threaded noninterchangeable connections for medical gas lines to minimize the risk of misconnection. A check valve located downstream from the inlet prevents reverse flow of gases from the machine to the pipeline or the atmosphere.

Cylinder Supply Source

Anesthesia workstations have E-cylinders for use when a pipeline supply source is not available or the pipeline system fails. As has been shown again in the recent literature, anesthesia care providers can easily become complacent in assuming that backup gas cylinders are in fact present on the back of the anesthesia workstation and, furthermore, if present, that they contain an adequate supply of compressed gas. Any pre-use checklist should contain steps that confirm both.[29]

Medical gases supplied in E-cylinders are attached to the anesthesia machine via the hanger yoke assembly. The hanger yoke assembly orients and supports the cylinder, provides a gas-tight seal, and ensures unidirectional flow of gases into the machine.[22] Each hanger yoke is equipped with the Pin Index Safety System (PISS). The PISS is a safeguard introduced to eliminate cylinder interchanging and the possibility of accidentally placing the incorrect gas on a yoke designed to accommodate another gas. Two metal pins on the yoke assembly are arranged so that that they project into corresponding holes on the cylinder valve. Each gas or combination of gases has a specific pin arrangement.[30]

Once the cylinders are turned on, compressed gases may pass from their respective high-pressure cylinder sources into the anesthesia machine (see Fig. 25-3). A check valve is located downstream from each cylinder if a double-yoke assembly is used. This check valve serves several functions. First, it minimizes transfer of gas from a cylinder at high pressure to one with lower pressure. Second, it allows an empty cylinder to be exchanged for a full one while gas flow continues from the other cylinder into the machine with minimal loss of gas or supply pressure. Third, it minimizes leakage from an open cylinder to the atmosphere if one cylinder is absent.[22,23] A cylinder supply pressure gauge is located downstream from the check valves. The gauge will indicate the pressure in the cylinder with the higher pressure when two reserve cylinders of the same gas are opened at the same time.

Each cylinder supply source has a pressure-reducing valve known as the cylinder pressure regulator. It reduces the high and variable storage pressure present in a cylinder to a lower, more constant pressure suitable for use in the anesthesia machine. The oxygen cylinder pressure regulator reduces the oxygen cylinder pressure from a high of 2200 psig to approximately 45 psig. The nitrous oxide cylinder pressure regulator receives pressure of up to 745 psig and reduces it to approximately 45 psig.[22,23]

The gas supply cylinder valves should be turned off when not in use, except during the preoperative machine checkout period. If the cylinder supply valves are left on, the reserve cylinder supply can be silently depleted whenever the pressure inside the machine decreases to a value lower than the regulated cylinder pressure. For example, oxygen pressure within the machine can decrease below 45 psig with oxygen flushing or possibly even during use of a pneumatically driven ventilator, particularly at high inspiratory flow rates. Additionally, the pipeline supply pressures of all gases can fall to less than 45 psig if problems exist in the central piping system. If the cylinders are left on when this occurs, they will eventually become depleted and no reserve supply may be available if a pipeline failure occurs.[20,23]

The amount of time that an anesthesia machine can operate from E-cylinder supplies is commonly of concern. This is becoming particularly important to anesthesia care providers now that anesthesia machines are being used more frequently in the setting of office-based and remote (outside the operating room) anesthesia care within hospitals. For oxygen, the volume of gas remaining in the cylinder is proportional to cylinder pressure. One author has proposed the following equation to help estimate the time remaining[31]:

$$\text{Approximate remaining time (hr)} \approx \frac{\text{Oxygen cylinder pressure (psig)}}{200 \times \text{Oxygen flow rate (L/min)}}$$

It should be noted that this calculation will provide a gross estimate of the time remaining and may not be exact. Furthermore, users should be cautioned that use of a pneumatically driven mechanical ventilator will dramatically increase oxygen utilization rates, thus decreasing the time remaining until depletion of the cylinder. Hand ventilation at low fresh gas flow rates may consume less than 5% of the amount of oxygen consumed by intermediate flow meter settings coupled with the use of pneumatically powered mechanical ventilation.[25] Because piston-type anesthesia ventilators such as found in the Dräger Medical Fabius GS and Narkomed 6000 series do not affect oxygen consumption rates, they may be preferable to conventional gas-driven ventilators in practice settings that are dependent on the use of compressed gas cylinders as the primary gas source.

Oxygen Supply Pressure Failure Safety Devices

Oxygen and nitrous oxide supply sources existed as independent entities in older models of anesthesia machines, and they were not pneumatically or mechanically interfaced. Therefore, abrupt or insidious oxygen pressure failure had the potential to lead to the delivery of a hypoxic mixture. The 2000 ASTM F1850-00 standard states that "The anesthesia gas supply device shall be designed so that whenever oxygen supply pressure is reduced to below the manufacturer specified minimum, the delivered oxygen concentration shall not decrease below 19% at the common gas outlet."[5] Contemporary anesthesia machines have a number of safety devices that act together in a cascade manner to minimize the risk of delivery of a hypoxic gas mixture as oxygen pressure decreases. Several of these devices are described in the following sections.

Pneumatic and Electronic Alarm Devices

Many older anesthesia machines have a pneumatic alarm device that sounds a warning when the oxygen supply pressure decreases to a predetermined threshold value, such as 30 psig. The 2000 ASTM F1850-00 standard mandates that a medium-priority alarm be activated within 5 seconds when oxygen pressure decreases below a manufacturer-specific pressure threshold.[5] Electronic alarm devices are now used to meet this guideline.

Fail-Safe Valves

A fail-safe valve is present in the gas line supplying each of the flow meters except oxygen. Controlled by oxygen supply pressure, the valve shuts off or proportionally decreases the supply pressure of all other gases (nitrous oxide, air, carbon dioxide, helium, nitrogen) as the oxygen supply pressure decreases. Unfortunately, the misnomer "fail safe" has led to the misconception that the valve prevents administration of a hypoxic mixture. Such is not the case. Machines that either are not equipped with a flow proportioning system (see "Proportioning Systems") or whose system may be disabled by the user can deliver a hypoxic mixture under normal working conditions. On such a system, the oxygen flow control valve can be closed intentionally or accidentally. Normal oxygen pressure will keep the other gas lines open so that a hypoxic mixture can result.[22,23]

Many Datex-Ohmeda machines are equipped with a fail-safe valve known as the pressure sensor shut-off valve (Fig. 25-8). This valve operates in a threshold manner and is either open or closed. Oxygen supply pressure opens the valve, and the valve return spring closes the valve. Figure 25-8 shows a nitrous oxide pressure sensor shut-off valve with a threshold pressure of 20 psig. In Figure 25-8A, an oxygen supply pressure greater than 20 psig is exerted on the mobile diaphragm. This pressure moves the piston and pin upward and the valve opens. Nitrous oxide flows freely to the nitrous oxide flow control valve. In Figure 25-8B, the oxygen supply pressure is less than 20 psig, and the force of the valve return spring completely closes the valve.[23] Nitrous oxide flow stops at the closed fail-safe valve, and it does not advance to the nitrous oxide flow control valve.

North American Dräger uses a different fail-safe valve known as the oxygen failure protection device (OFPD) to interface the oxygen pressure with that of other gases, such as nitrous oxide or other inert gases. In contrast to Datex-Ohmeda's oxygen pressure sensor shut-off valve, the OFPD is based on a proportioning principle rather than a threshold principle. The pressure of all gases controlled by the OFPD will decrease proportionally with the oxygen pressure. The OFPD consists of a seat nozzle

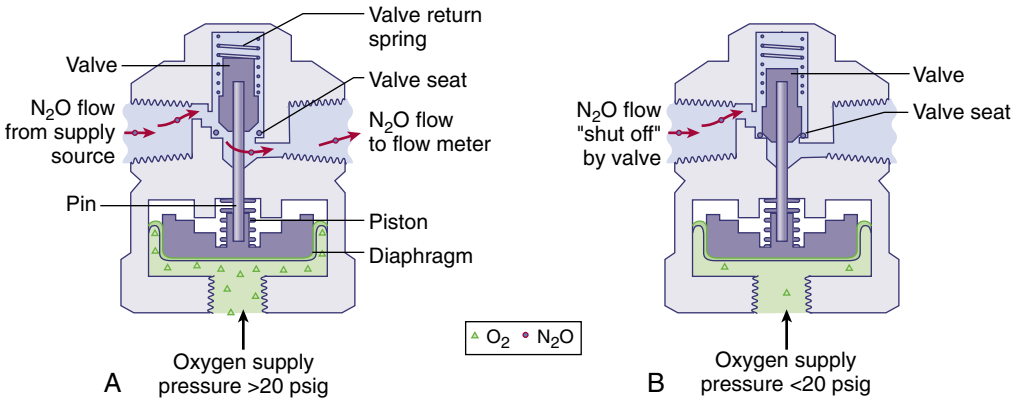

Figure 25-8 Pressure sensor shut-off valve. The valve is open in **A** because the oxygen supply pressure is greater than the threshold value of 20 psig. The valve is closed in **B** because of inadequate oxygen pressure. *(Redrawn with permission from Bowie E, Huffman LM: The Anesthesia Machine: Essentials for Understanding. Madison, WI, Ohmeda, A Division of BOC Health Care, Inc., 1985.)*

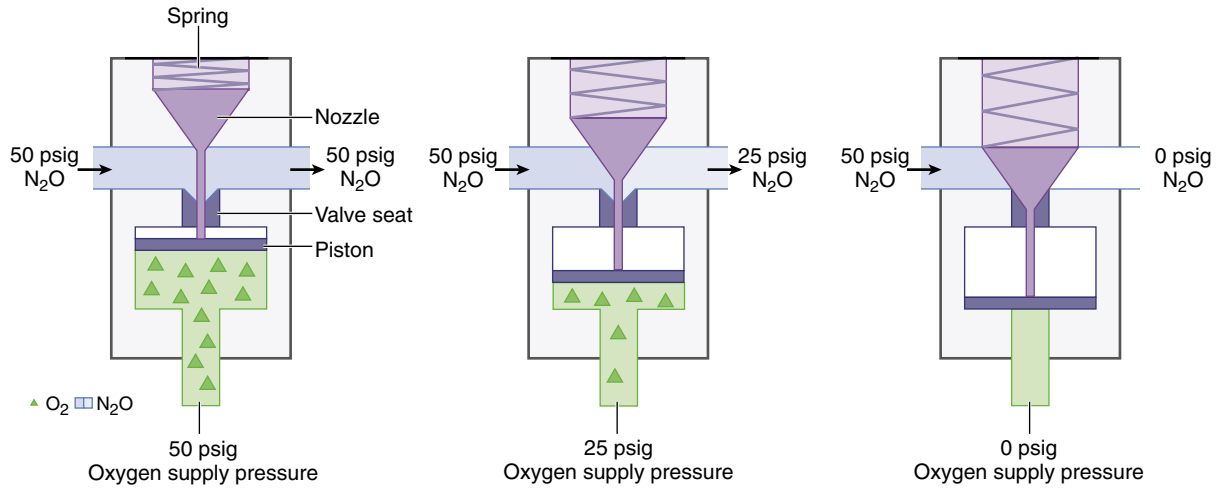

Figure 25-9 An oxygen failure protection device that responds proportionally to changes in oxygen supply pressure. See text for details. *(Redrawn with permission from Narkomed 2A Anesthesia System. Technical Service Manual, 6th ed. Telford, PA, North American Dräger, June 1985.)*

assembly connected to a spring-loaded piston (Fig. 25-9). The oxygen supply pressure in the left panel of Figure 25-9 is 50 psig. This pressure pushes the piston upward, which forces the nozzle away from the valve seat. Nitrous oxide alone or combined with other gases advances toward the flow control valve at 50 psig. The oxygen pressure in the right panel is 0 psig. The spring is expanded and forces the nozzle against the seat, thereby preventing flow through the device. Finally, the center panel shows an intermediate oxygen pressure of 25 psig. The force of the spring partially closes the valve. The nitrous oxide pressure delivered to the flow control valve is 25 psig. There is a continuum of intermediate configurations between the extremes (0 to 50 psig) of oxygen supply pressure. These intermediate valve configurations are responsible for the proportional nature of the OFPD. An important concept to be understood with these particular fail-safe devices is that the Datex-Ohmeda pressure sensor shut-off valve is threshold in nature (all or nothing) whereas the Dräger OFPD is a variable-flow type proportioning system.

Second-Stage Oxygen Pressure Regulator

Most contemporary Datex-Ohmeda workstations have a second-stage oxygen pressure regulator set at a specific value ranging from 12 to 19 psig. Output from the oxygen flow meter is constant when the oxygen supply pressure exceeds the threshold (minimal) value. The pressure sensor shut-off valve of Datex-Ohmeda is set at a higher threshold value (20 to 30 psig) to ensure that oxygen is the last gas flowing if oxygen pressure failure occurs.

Flow Meter Assemblies

The flow meter assembly (Fig. 25-10) precisely controls and measures gas flow to the common gas outlet. With traditional glass flow meter assemblies, the flow control valve regulates the amount of flow that enters a tapered, transparent flow tube known as a Thorpe tube. A mobile indicator float inside the flow tube indicates the amount of flow passing through the associated flow control valve. The quantity of flow is indicated on a scale associated with the flow tube.[22,23] Some newer anesthesia workstations

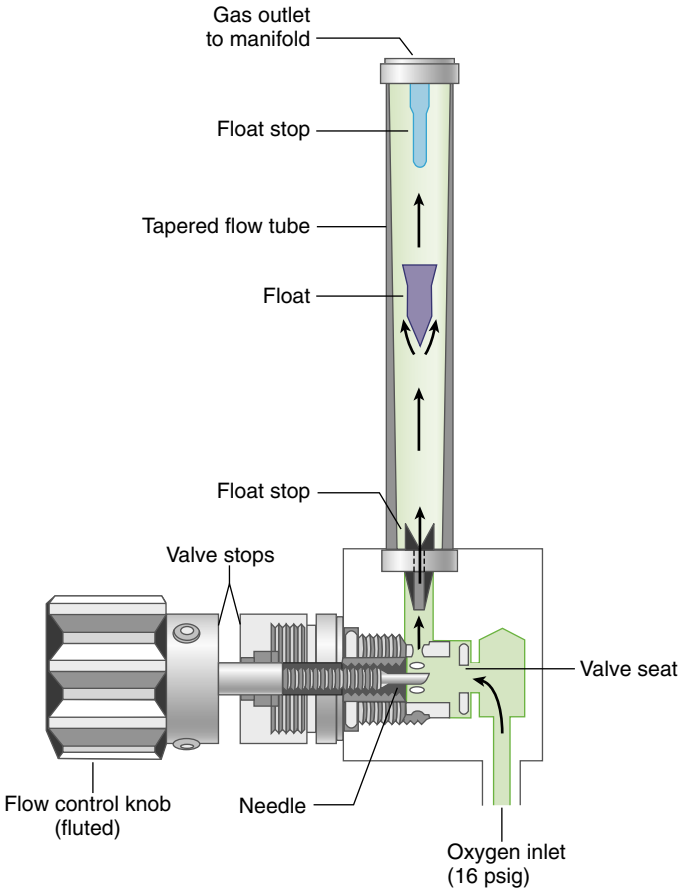

Figure 25-10 Oxygen flow meter assembly. The oxygen flow meter assembly is composed of the flow control valve assembly plus the flow meter subassembly. *(Reproduced with permission from Bowie E, Huffman LM: The Anesthesia Machine: Essentials for Understanding. Madison, WI, Ohmeda, A Division of BOC Health Care, Inc., 1985.)*

have now replaced the conventional glass flow tubes with electronic flow sensors that measure the flow of the individual gases. These flow rate data are then presented to the anesthesia care provider in either numerical format, graphic format, or a combination of the two. Integration of these "electronic flow meters" is an essential step in the evolution of the anesthesia workstation if it is to become fully integrated with anesthesia data-capturing systems such as computerized anesthesia record-keeping systems.

Operating Principles of Conventional Flow Meters

Opening the flow control valve allows gas to travel through the space between the float and the flow tube. This space is known as the annular space (Fig. 25-11). The indicator float hovers freely in an equilibrium position where the upward force resulting from gas flow equals the downward force on the float resulting from gravity at a given flow rate. The float moves to a new equilibrium position in the tube when flow is changed. These flow meters are commonly referred to as *constant-pressure* flow meters because the decrease in pressure across the float remains constant for all positions in the tube.[22,30,32]

Flow tubes are tapered, with the smallest diameter at the bottom of the tube and the largest diameter at the top. The term *variable orifice* designates this type of unit because the annular space between the float and the inner wall of the flow tube varies with the position of the float. Flow through the constriction created by the float can be laminar or turbulent, depending on the flow rate (Fig. 25-12). The characteristics of a gas that influence its flow rate through a given constriction are viscosity (laminar flow) and density (turbulent flow). Because the annular space is tubular at low flow rates, laminar flow is present and *viscosity* determines the gas flow rate. The annular space simulates an orifice at high flow rates, and turbulent gas flow then depends predominantly on the *density* of the gas.[22,32]

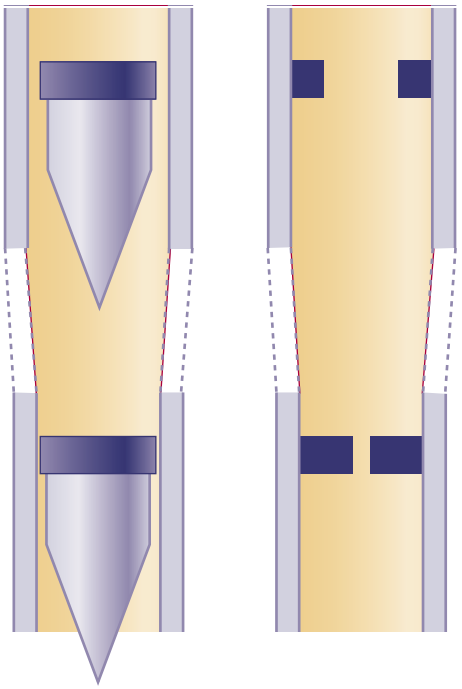

Figure 25-12 Flow tube constriction. The *lower* pair of illustrations represents the lower portion of a flow tube. The clearance between the head of the float and the flow tube is narrow. The equivalent channel is tubular because its diameter is less than its length. Viscosity is dominant in determining the gas flow rate through this tubular constriction. The *upper* pair of illustrations represents the upper portion of a flow tube. The equivalent channel is orificial because its length is less than its width. Density is dominant in determining the gas flow rate through this orificial constriction. *(Redrawn with permission from Macintosh R, Mushin WW, Epstein HG: Physics for the Anaesthetist, 3rd ed. Oxford, Blackwell Scientific, 1963.)*

Components of the Flow Meter Assembly

Flow Control Valve Assembly The flow control valve (see Fig. 25-10) assembly is composed of a flow control knob, a needle valve, a valve seat, and a pair of valve stops.[22] The assembly can receive its pneumatic input either directly from the pipeline source (50 psig) or from a second-stage pressure regulator. The location of the needle valve in the valve seat changes to establish different orifices when the flow control valve is adjusted. Gas flow increases when the flow control valve is turned counterclockwise, and it decreases when the valve is turned clockwise. Extreme clockwise rotation may result in damage to the needle valve and valve seat. Therefore, flow control valves are equipped with valve "stops" to prevent such occurrence.[23]

Safety Features. Contemporary flow control valve assemblies have numerous safety features. The oxygen flow control knob is physically distinguishable from other gas knobs. It is distinctively fluted, projects beyond the control knobs of the other gases, and is larger in diameter than the flow control knobs of other gases. All knobs are color-coded for the appropriate gas, and the chemical formula or name of the gas is permanently marked on each. Flow control knobs are recessed or protected with a shield or barrier to minimize inadvertent change from a preset position. If a single gas has two flow tubes, the tubes are arranged in series and controlled by a single flow control valve.[5]

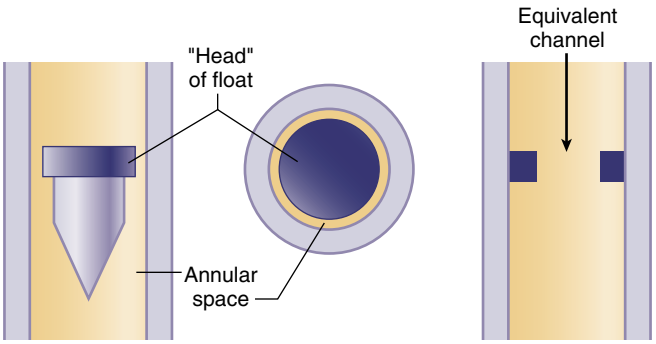

Figure 25-11 The annular space. The clearance between the head of the float and the flow tube is known as the annular space. It can be considered an equivalent to a circular channel of the same cross-sectional area. *(Redrawn with permission from Macintosh R, Mushin WW, Epstein HG: Physics for the Anaesthetist, 3rd ed. Oxford, Blackwell Scientific, 1963.)*

Flow Meter Subassembly The flow meter subassembly (see Fig. 25-10) consists of the flow tube, the indicator float with float stops, and the indicator scale.[22]

Flow Tubes. Contemporary flow tubes are made of glass. Most have a single taper in which the inner diameter of the flow tube increases uniformly from bottom to top. Manufacturers

provide double flow tubes for oxygen and nitrous oxide to provide better visual discrimination at low flow rates. A fine flow tube indicates flow from approximately 200 to 1 L/min, and a coarse flow tube indicates flow from approximately 1 to 10 to 12 L/min. The two tubes are connected in series and supplied by a single flow control valve. The total gas flow is that shown on the higher flow meter.

Indicator Floats and Float Stops. Contemporary anesthesia machines use several different types of bobbins or floats, including plumb-bob floats, rotating skirted floats, and ball floats. Flow is read at the top of plumb-bob and skirted floats and at the center of the ball on ball-type floats.[22] Flow tubes are equipped with float stops at the top and bottom of the tube. The upper stop prevents the float from ascending to the top of the tube and plugging the outlet. It also ensures that the float will be visible at maximum flows instead of being hidden in the manifold. The bottom float stop provides a central foundation for the indicator when the flow control valve is turned off.[22,23]

Scale. The flow meter scale can be marked directly on the flow tube or to the right of the tube.[5] Gradations corresponding to equal increments in flow rate are closer together at the top of the scale because the annular space increases more rapidly than the internal diameter from bottom to top of the tube. Rib guides are used in some flow tubes with ball-type indicators to minimize this compression effect. They are tapered glass ridges that run the length of the tube. There are usually three rib guides spaced equally around the inner circumference of the tube. In the presence of rib guides, the annular space from the bottom to the top of the tube increases almost proportionally with the internal diameter. This results in a nearly linear scale.[22] Rib guides are used on many Dräger Medical flow tubes.

Safety Features. The flow meter subassemblies for each gas on the Datex-Ohmeda Modulus I, Modulus II, Modulus II Plus, CD, and Aestiva are housed in independent, color-coded, pin-specific modules. The flow tubes are adjacent to a gas-specific, color-coded backing. The flow scale and the chemical formula (or name of the gas) are permanently etched on the backing to the right of the flow tube. Flow meter scales are individually hand-calibrated to the specific float to provide a high degree of accuracy. The tube, float, and scale make an inseparable unit. The entire set must be replaced if any component is damaged.

Dräger Medical does not use a modular system for its flow meter subassembly. The flow scale, the chemical symbol, and the gas-specific color codes are etched directly onto the flow tube. The scale in use is obvious when two flow tubes for the same gas are used.

Problems with Flow Meters

Leaks Flow meter leaks are a substantial hazard because the flow meters are located downstream from all machine safety devices except the oxygen analyzer.[33] Leaks can occur at the O-ring junctions between the glass flow tubes and the metal manifold or in cracked or broken glass flow tubes, the most fragile pneumatic component of the anesthesia machine. Even though gross damage to conventional glass flow tubes is usually apparent, subtle cracks and chips may be overlooked and result in errors in delivered flow.[34] The use of electronic flow meters and removal of conventional glass flow tubes from some newer anesthesia workstations (Datex-Ohmeda S/5 ADU and the Dräger Fabius) may help eliminate this potential source of leaks (see "Electronic Flow Meters").

Eger and colleagues in 1963[35] demonstrated that in the presence of a flow meter leak, a hypoxic mixture is less likely to occur if the oxygen flow meter is located downstream from all other flow meters.[32] Figure 25-13 is a more contemporary version of the figure in Eger's original publication. The unused airflow tube has a large leak. Nitrous oxide and oxygen flow rates are set at a ratio of 3:1. A potentially dangerous arrangement is shown in Figure 25-13A and B because the nitrous oxide flow meter is located in the downstream position. A hypoxic mixture can result because a substantial portion of the oxygen flow passes through the leak and all nitrous oxide is directed to the common gas outlet. A safer configuration is shown in Figure 25-13C and D. The oxygen flow meter is located in the downstream position. A portion of the nitrous oxide flow escapes through the leak, and the remainder goes toward the common gas outlet. A hypoxic mixture is less likely because all the oxygen flow is advanced by the nitrous oxide.[35] North American Dräger flow meters are arranged as in Figure 25-13C, and Datex-Ohmeda flow meters are arranged as in Figure 25-13D.

A leak in the oxygen flow tube may result in creation of a hypoxic mixture even when oxygen is located in the downstream position (Fig. 25-14).[33,34] Oxygen escapes through the leak and nitrous oxide continues to flow toward the common outlet, particularly at high ratios of nitrous oxide to oxygen flow.

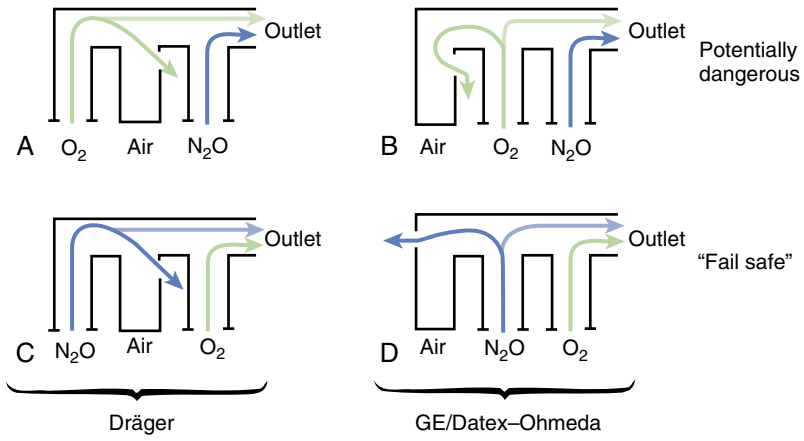

Figure 25-13 The flow meter sequence is a potential cause of hypoxia. In the event of a flow meter leak, a potentially dangerous arrangement exists when nitrous oxide is located in the downstream position (**A** and **B**). The safest configuration exists when oxygen is located in the downstream position (**C** and **D**). See text for details. *(Modified with permission from Eger EI II, Hylton RR, Irwin RH, et al: Anesthetic flow meter sequence—a cause for hypoxia. Anesthesiology 24:396, 1963.)*

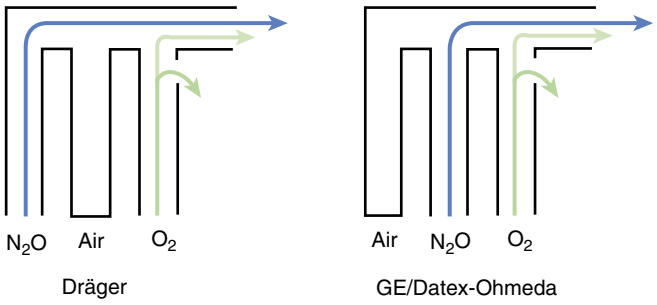

Figure 25-14 An oxygen leak from the flow tube can produce a hypoxic mixture regardless of the arrangement of the flow tubes.

Inaccuracy Flow measurement error can occur even when flow meters are assembled properly with appropriate components. Dirt or static electricity can cause a float to stick, and the actual flow may be higher or lower than that indicated. Sticking of the indicator float is more common in the low flow ranges because the annular space is smaller. A damaged float can cause inaccurate readings because the precise relationship between the float and the flow tube is altered. Backpressure from the breathing circuit can cause a float to drop so that it reads less than the actual flow. Finally, if flow meters are not aligned properly in the vertical position (plumb), readings can be inaccurate because tilting distorts the annular space.[17,22,34]

Ambiguous Scale Before the standardization of flow meter scales and the widespread use of oxygen analyzers, at least two deaths resulted from confusion created by ambiguous scales.[17,34,36] The operator read the float position beside an adjacent, but erroneous scale in both cases. Today, this error is less likely to occur because contemporary flow meter scales are marked either directly on the flow tube or immediately to the right of it.[5] The possibility of confusion is minimized when the scale is etched directly onto the tube.

Electronic Flow Meters

As mentioned earlier, some newer anesthesia workstations such as the Datex-Ohmeda S/5 ADU and the North American Dräger Fabius GS, among others, have conventional control knobs and flow control valves but have electronic flow sensors and digital displays rather than glass flow tubes. The output from the flow control valve is represented graphically, numerically, or by both means in liters per minute on the workstation's integrated user interface. These systems are dependent on electrical power to provide a precise display of gas flow. However, even when electrical power is totally interrupted, because the flow control valves themselves are nonelectronic, oxygen should continue to flow. Because these machines do not have individual flow tubes that physically quantitate the flow of each gas, electronic flow sensors and often a small conventional pneumatic "fresh gas" or "total flow" indicator are provided to give the user an estimate of the total quantity of fresh gas flowing from all flow control valves. This miniature flow tube indicator serves to inform the user of the approximate quantity of gas that is leaving the anesthesia workstation's common gas outlet, and it is functional even in the event of total power failure.

Proportioning Systems

Manufacturers equip anesthesia workstations with proportioning systems in an attempt to prevent the creation and delivery of a hypoxic mixture. Nitrous oxide and oxygen are interfaced mechanically or pneumatically (or both ways) so that the minimum oxygen concentration at the common gas outlet is between 23% and 25%, depending on the manufacturer.

Datex-Ohmeda Link-25 Proportion-Limiting Control System

Conventional Datex-Ohmeda machines use the Link-25 system. The heart of the system is mechanical integration of the nitrous oxide and oxygen flow control valves. It allows independent adjustment of either valve, yet automatically intercedes to maintain a minimum 25% oxygen concentration with a maximum nitrous oxide–oxygen flow ratio of 3:1. The Link-25 automatically increases oxygen flow to prevent delivery of a hypoxic mixture.

Figure 25-15 illustrates the Datex-Ohmeda Link-25 system. The nitrous oxide and oxygen flow control valves are identical. A 14-tooth sprocket is attached to the nitrous oxide flow control valve and a 28-tooth sprocket to the oxygen flow control valve. A chain physically links the sprockets. When the nitrous oxide flow control valve is turned through two revolutions, or 28 teeth, the oxygen flow control valve will revolve once because of the 2:1 gear ratio. The final 3:1 flow ratio results because the nitrous oxide flow control valve is supplied by approximately 26 psig whereas the oxygen flow control valve is supplied by 14 psig. Thus, the combination of the mechanical and pneumatic aspects of the system yields the final oxygen concentration. The Datex-Ohmeda Link-25 proportioning system can be thought of as a system that *increases oxygen flow* when necessary to prevent delivery of a fresh gas mixture with an oxygen concentration of less than 25%.

Recently, a few reports related to failures of the Datex-Ohmeda Link-25 system have been published. The authors of these reports describe failures that either resulted in an inability to administer oxygen without nitrous oxide or allowed creation of a hypoxic mixture. These reported failures of the Link-25 on the Datex-Ohmeda Excel series anesthesia machines should cer-

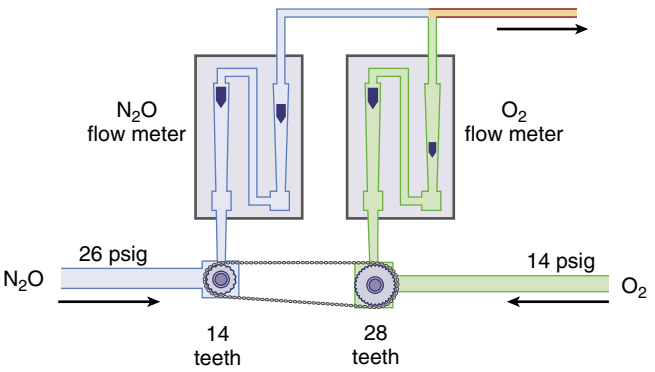

Figure 25-15 Ohmeda Link-25 Proportion-Limiting Control system. See text for details.

tainly raise the awareness of clinicians to the possibility of failure of this type of proportioning system.[36-40]

North American Dräger Oxygen Ratio Monitor Controller/Sensitive Oxygen Ratio Controller System

North American Dräger's proportioning system, the Oxygen Ratio Monitor Controller (ORMC), is used on the North American Dräger Narkomed 2A, 2B, 3, and 4 series. An equivalent system known as the Sensitive Oxygen Ratio Controller (S-ORC) is used on some newer Dräger anesthesia workstations such as the Dräger Fabius GS and Narkomed 6000 series. The ORMC and the S-ORC are pneumatic oxygen–nitrous oxide interlock systems designed to maintain a fresh gas oxygen concentration of at least 25% ± 3%. They maintain the fresh gas oxygen concentration at levels substantially higher than 25% at oxygen flow rates of less than 1 L/min. The ORMC and S-ORC limit nitrous oxide flow to prevent delivery of a hypoxic mixture. This is unlike the Datex-Ohmeda Link-25, which actively increases oxygen flow.

A schematic of the ORMC is shown in Figure 25-16. It is composed of an oxygen chamber, a nitrous oxide chamber, and a nitrous oxide slave control valve. All are interconnected by a mobile horizontal shaft. Pneumatic input into the device is from the oxygen and nitrous oxide flow meters. These flow meters are unique in that they have specific resistors located downstream from the flow control valves. These resistors create backpressure directed to the oxygen and nitrous oxide chambers. The value of the oxygen flow tube resistor is three to four times that of the nitrous oxide flow tube resistor, and the relative value of these resistors determines the value of the controlled fresh gas oxygen concentration. Backpressure in the oxygen and nitrous oxide chambers pushes against rubber diaphragms attached to the mobile horizontal shaft. Movement of the shaft regulates the nitrous oxide slave control valve, which feeds the nitrous oxide flow control valve.

If the oxygen pressure is proportionally higher than the nitrous oxide pressure, the nitrous oxide slave control valve opens wider to allow more nitrous oxide to flow. As the nitrous oxide flow is increased manually, the nitrous oxide pressure forces the shaft toward the oxygen chamber. The valve opening becomes more restrictive and limits flow of nitrous oxide to the flow meter.

Figure 25-16 illustrates the action of a single ORMC/S-ORC under different sets of circumstances. The backpressure exerted on the oxygen diaphragm, in the upper configuration, is greater than that exerted on the nitrous oxide diaphragm. This causes the horizontal shaft to move to the left, thereby opening the nitrous oxide slave control valve. Nitrous oxide is then able to proceed to its flow control valve and out through the flow meter. In the bottom configuration, the nitrous oxide slave control valve is closed because of inadequate oxygen backpressure.[24]

To summarize, in contrast to the Datex-Ohmeda Link-25 system, which actively increases oxygen flow to maintain a fresh gas oxygen concentration greater than 25%, the Dräger ORMC and S-ORC are systems that limit nitrous oxide flow to prevent delivery of a fresh gas mixture with an oxygen concentration of less than 25%.

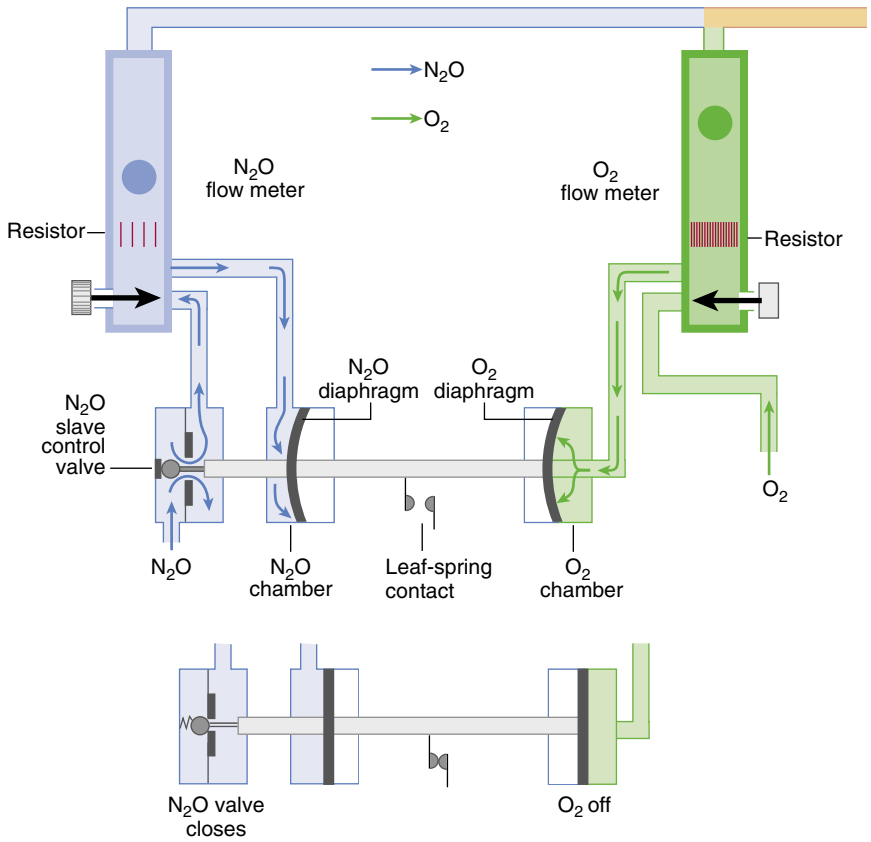

Figure 25-16 North American Dräger Oxygen Ratio Monitor Controller. See text for details. *(Redrawn with permission from Schreiber P: Safety Guidelines for Anesthesia Systems. Telford, PA, North American Dräger, 1984.)*

Limitations

Proportioning systems are not foolproof. Workstations equipped with proportioning systems can still deliver a hypoxic mixture under certain conditions. In the following sections we briefly present some situations in which this can occur.

Wrong Supply Gas Both the Datex-Ohmeda Link-25 and the Dräger ORMC/S-ORC will be fooled if a gas other than oxygen is present in the oxygen pipeline. In the Link-25 system, the nitrous oxide and oxygen flow control valves will continue to be mechanically linked. Nevertheless, a hypoxic mixture can proceed to the common gas outlet. In the case of the Drager ORMC or S-ORC, the rubber diaphragm for oxygen will reflect adequate supply pressure on the oxygen side even though the incorrect gas is present, and flow of both the wrong gas plus nitrous oxide will result. The oxygen analyzer is the only workstation monitor besides an integrated multigas analyzer that would detect this condition in either system.

Defective Pneumatics or Mechanics Normal operation of the Datex-Ohmeda Link-25 and the North American Dräger ORMC/S-ORC is contingent on pneumatic and mechanical integrity.[41] Pneumatic integrity in the Datex-Ohmeda system requires properly functioning second-stage regulators. A nitrous oxide–oxygen ratio other than 3:1 will result if the regulators are not precise. The chain connecting the two sprockets must be intact. A 97% nitrous oxide concentration can occur if the chain is cut or broken.[42] In the North American Dräger system, a functional OFPD is necessary to supply appropriate pressure to the ORMC. The mechanical aspects of the ORMC/S-ORC, such as the rubber diaphragms, the flow tube resistors, and the nitrous oxide slave control valve, must likewise be intact.

Leaks Downstream The ORMC/S-ORC and the Link-25 function at the level of the flow control valves. A leak downstream from these devices, such as a broken oxygen flow tube (see Fig. 25-14), can result in delivery of a hypoxic mixture to the common gas outlet. In this situation, oxygen escapes through the leak, and the predominant gas delivered is nitrous oxide. The oxygen monitor and the integrated multigas analyzer are the only machine safety devices that can detect this problem.[33] For the majority of its products, Dräger Medical recommends a preoperative positive-pressure leak test to detect such a leak. However, in addition to this test, for many North American Dräger products, application of the negative-pressure leak test as well may provide a more sensitive way to detect such a leak. Datex-Ohmeda almost universally recommends a preoperative negative-pressure leak test for its workstations because of the frequently present check valve located at the common gas outlet (see "Checking Your Anesthesia Workstation").

Inert Gas Administration Administration of a third inert gas, such as helium, nitrogen, or carbon dioxide, can cause a hypoxic mixture because contemporary proportioning systems link only nitrous oxide and oxygen.[43] Use of an oxygen analyzer is mandatory (or preferentially a multigas analyzer when available) if the operator uses a third inert gas.

Dilution of Inspired Oxygen Concentration by Volatile Inhaled Anesthetics Volatile inhaled anesthetics are added to the mixed gases downstream from both the flow meters and the proportioning system. Concentrations of less potent inhaled anesthetics such as desflurane may account for a larger percentage of the total fresh gas composition than is the case with more potent agents. This can be seen when the maximum vaporizer dial settings of the various volatile agents are examined (e.g., a desflurane maximum dial setting of 18% versus an isoflurane maximum dial setting of 5%). Because significant percentages of these inhaled anesthetics may be added downstream of the proportioning system, the resulting gas-vapor mixture may contain an inspired oxygen concentration less than 21% despite a functional proportioning system. The anesthesia care provider must be aware of this possibility, particularly when high concentrations of less potent volatile inhaled anesthetics are used.

Oxygen Flush Valve

The oxygen flush valve allows direct communication between the oxygen high-pressure circuit and the low-pressure circuit (see Fig. 25-3). Flow from the oxygen flush valve enters the low-pressure circuit downstream from the vaporizers and most importantly downstream from the Datex-Ohmeda machine outlet check valve. The spring-loaded oxygen flush valve stays closed until the operator opens it by depressing the oxygen flush button. Actuation of the valve delivers 100% oxygen at 35 to 75 L/min to the breathing circuit.[23]

The oxygen flush valve can provide a high-pressure oxygen source suitable for jet ventilation under the following circumstances: (1) the anesthesia machine is equipped with a one-way check valve positioned between the vaporizers and the oxygen flush valve, and (2) when a positive-pressure relief valve exists downstream of the vaporizers, this pressure relief valve must be upstream of the outlet check valve. Because the Ohmeda Modulus II has such a one-way check valve and its positive-pressure relief valve is upstream from the check valve, the entire oxygen flow of 35 to 75 L/min is delivered to the common gas outlet at a high pressure of 50 psig. On the other hand, the Ohmeda Modulus II Plus and some Ohmeda Excel machines are not capable of functioning as an appropriate oxygen source for jet ventilation. The Ohmeda Modulus II Plus, which does not have the check valve, provides only 7 psig at the common gas outlet because some oxygen flow travels retrogradely through an internal relief valve located upstream from the oxygen flush valve. The Ohmeda Excel 210, which does have a one-way check valve, also has a positive-pressure relief valve downstream from the check valve and therefore is unsuitable for jet ventilation. Older North American Dräger machines such as the Narkomed 2A (which also does not have an outlet check valve) provide an intermediate pressure of 18 psig to the common gas outlet because some pressure is vented retrogradely through a pressure relief valve located in the vaporizers.[44]

Several hazards have been reported with the oxygen flush valve. A defective or damaged valve can stick in the fully open position and result in barotrauma.[45] A valve sticking in a partially open position can result in patient awareness because oxygen flow from the incompetent valve dilutes the inhaled anesthetic.[19,46] Improper use of normally functioning oxygen flush valves also can result in problems. Overzealous intraoperative oxygen flushing can dilute inhaled anesthetics. Oxygen flushing during the inspiratory phase of positive-pressure ventilation can produce barotrauma if the anesthesia machine does not incorporate fresh

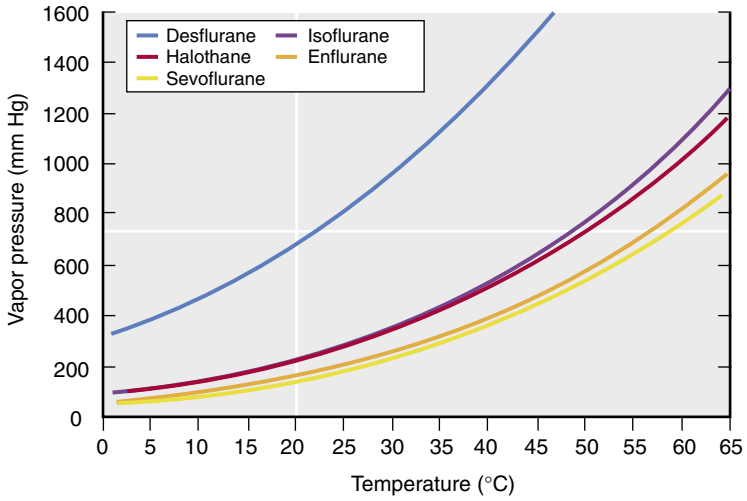

Figure 25-17 Vapor pressure–versus-temperature curves for desflurane, isoflurane, halothane, enflurane, and sevoflurane. The vapor pressure curve for desflurane is both steeper and shifted to higher vapor pressures than the curves for other contemporary inhaled anesthetics are. *(From inhaled anesthetic package insert equations and Susay SR, Smith MA, Lockwood GG: The saturated vapor pressure of desflurane at various temperatures. Anesth Analg 83:864-866, 1996.)*

gas decoupling or an appropriately adjusted inspiratory pressure limiter. Anesthesia systems (Dräger Narkomed 6000 series, Julian, Fabius GS, and Datascope Anestar) with fresh gas decoupling are inherently safer from the standpoint of minimizing the chance of producing barotrauma as a result of inappropriate oxygen flush valve use. These systems physically divorce the fresh gas inflow from either the flow meters or the oxygen flush valve from the delivered tidal volume presented to the patient's lungs (see "Fresh Gas Decoupling"). With traditional anesthesia breathing circuits, excess volume cannot be vented during the inspiratory phase of mechanical ventilation because the ventilator relief valve is closed and the APL valve is either out of circuit or closed.[47] An alternative way to manage this problem can be seen with the Datex-Ohmeda S/5 ADU and Aestiva. These circle systems use an integrated adjustable pressure limiter. If this device is properly adjusted, it functions like the APL valve to limit the maximum airway pressure to a safe level, thereby reducing the possibility of barotrauma.

Some very old anesthesia systems made use of a freestanding vaporizer downstream from the common gas outlet, and with these systems oxygen flushing could rapidly deliver large quantities of inhaled anesthetic to the patient. Finally, inappropriate preoperative use of the oxygen flush to evaluate the low-pressure circuit for leaks can be misleading, particularly on Datex-Ohmeda machines with a one-way check valve at the common outlet.[18] Because backpressure from the breathing circuit closes the one-way check valve air-tight, major low-pressure circuit leaks can go undetected with this leak test (see "Checking Your Anesthesia Workstation").

Vaporizers

As dramatic as the evolution of the anesthesia workstation has been over recent years, vaporizers have also changed from rudimentary ether inhalers and copper kettles to the present temperature-compensated, computer-controlled, and flow-sensing devices that we use today. In 1993, with the introduction of desflurane to the clinical setting, an even more sophisticated vaporizer was introduced to handle the unique physical properties of this agent. Now, a new generation of anesthesia vaporizers blending both "old" copper kettle–like technology and "new" computerized control technology has emerged in the Datex-Ohmeda Aladin cassette vaporizer system. Before discussion of variable-bypass vaporizers, the Datex-Ohmeda Tec 6 desflurane vaporizer and the Datex-Ohmeda Aladin cassette vaporizer, certain physical principles will be reviewed briefly to facilitate understanding of the operating principles, construction, and design of contemporary volatile anesthetic vaporizers.

Physics

Vapor Pressure

Contemporary inhaled volatile anesthetics exist in the liquid state at temperatures below 20°C. When a volatile liquid is in a closed container, molecules escape from the liquid phase to the vapor phase until the number of molecules in the vapor phase is constant. These molecules in the vapor phase bombard the wall of the container and create a pressure known as the *saturated vapor pressure*. As the temperature increases, more molecules enter the vapor phase, and the vapor pressure increases (Fig. 25-17). Vapor pressure is independent of atmospheric pressure and is contingent only on the temperature and physical characteristics of the liquid. The *boiling point* of a liquid is defined as the temperature at which vapor pressure equals atmospheric pressure.[48-50] At 760 mm Hg, the boiling points for desflurane, isoflurane, halothane, enflurane, and sevoflurane are approximately 22.8°C, 48.5°C, 50.2°C, 56.5°C, and 58.5°C, respectively. Unlike other contemporary inhaled anesthetics, desflurane boils at temperatures that may be encountered in clinical settings such as operating rooms for pediatric and burn patients. This unique physical characteristic alone mandates a special vaporizer design to control the delivery of desflurane. If agent-specific vaporizers are inadvertently misfilled with incorrect liquid anesthetic agents, the resulting mixtures of volatile agents may demonstrate properties uniquely different from those of the individual component agents. The altered vapor pressure and other physical properties of the resulting azeotropic mixtures caused by the mixing of various agents may change the output of the anesthetic vaporizer (see "Misfilling" in the section "Variable-Bypass Vaporizers").[51]

Latent Heat of Vaporization

When a molecule is converted from a liquid to the gaseous phase, energy is consumed because the molecules of a liquid tend to cohere. The amount of energy that is consumed for a given liquid to be converted to a vapor is referred to as the *latent heat of vaporization*. It is more precisely defined as the number of calories required to change 1 g of liquid into vapor without a change in temperature. The energy for vaporization must come from either the liquid itself or an outside source. The temperature of the liquid itself will decrease during vaporization in the absence of an outside energy source. This energy loss can lead to significant decreases in temperature of the remaining liquid and greatly diminish subsequent vaporization.[48,50,52]

Specific Heat

The *specific heat* of a substance is the number of calories required to increase the temperature of 1 g of a substance by 1°C.[21,48,50] The substance can be a solid, liquid, or gas. The concept of specific heat is important to the design, operation, and construction of vaporizers because it is applicable in two ways. First, the specific heat for an inhaled anesthetic is important because it indicates how much heat must be supplied to the liquid to maintain a constant temperature when heat is being lost during vaporization. Second, manufacturers select vaporizer component materials that have high specific heat to minimize the temperature changes associated with vaporization.

Thermal Conductivity

Thermal conductivity is a measure of the speed at which heat flows through a substance. The higher the thermal conductivity, the better the substance conducts heat.[48] Vaporizers are constructed of metals that have relatively high thermal conductivity, which helps maintain a uniform internal temperature.

Variable-Bypass Vaporizers

The Datex-Ohmeda Tec 4, Tec 5, and Tec 7, as well as the North American Dräger Vapor 19.n and 20.n vaporizers, are classified as variable-bypass, flow-over, temperature-compensated, agent-specific, out-of-breathing-circuit vaporizers.[48] *Variable bypass* refers to the method of regulating the concentration of anesthetic agent output from the vaporizer. The concentration control dial setting determines the ratio of flow that goes through the bypass chamber and the vaporizing chamber as fresh gas from the flow meters enters the vaporizer inlet. The gas channeled through the vaporizing chamber flows over a wick system saturated with the liquid anesthetic and subsequently also becomes saturated with vapor. Thus, *flow-over* refers to the method of vaporization and is in contrast to the bubble-through system that may be seen in some copper kettle–type vaporizers of old. The Tec 4, Tec 5, Tec 7, and Dräger Vapor 19.n and 20.n are further classified as *temperature compensated*. Each of these vaporizers is equipped with an automatic temperature-compensating device that helps maintain constant vaporizer output over a wide range of operating temperatures. These vaporizers are *agent specific* and *out of circuit* because each is designed to accommodate a single anesthetic agent and to be physically located outside the breathing circuit. Variable-bypass vaporizers are used to deliver halothane, enflurane, isoflurane, and sevoflurane, but not desflurane.

Basic Operating Principles

A diagram of a generic, variable-bypass vaporizer is shown in Figure 25-18. Vaporizer components include the concentration control dial, the bypass chamber, the vaporizing chamber, the filler port, and the filler cap. The operator fills the vaporizing chamber with liquid anesthetic through the filler port. The

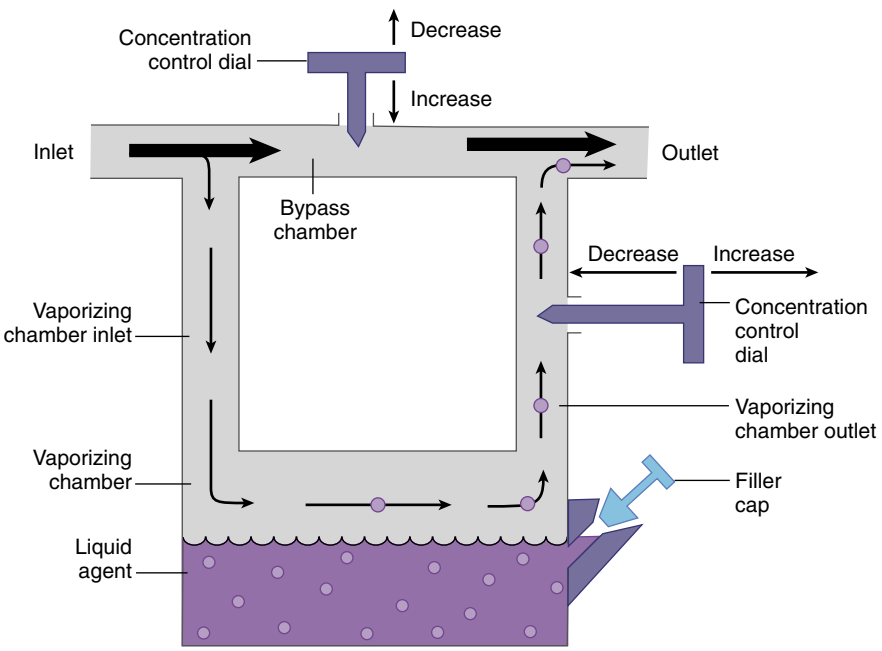

Figure 25-18 Generic variable-bypass vaporizer. See text for details.

maximum safe fill level is predetermined by the position of the filler port, which is situated to minimize the chance of overfilling. If a vaporizer is overfilled or tilted, liquid anesthetic can spill into the bypass chamber. If this were to happen, both the vaporizing chamber flow and the bypass chamber flow could potentially be carrying saturated anesthetic vapor, and an overdose would result. The concentration control dial is a variable restrictor, and it can be located either in the bypass chamber or in the outlet of the vaporizing chamber. The function of the concentration control dial is to regulate the relative flow rates through the bypass and vaporizing chambers.

Flow from the flow meters enters the inlet of the vaporizer. More than 80% of the flow passes straight through the bypass chamber to the vaporizer outlet, and this accounts for the name "bypass chamber." Less than 20% of the flow from the flow meters is diverted through the vaporizing chamber. Depending on the temperature and vapor pressure of the particular inhaled anesthetic, the fresh gases entering the vaporizing chamber entrain a specific flow of the inhaled anesthetic agent. The mixture that exits the vaporizer is the combination of flow through the bypass chamber, flow through the vaporizing chamber, and flow of entrained anesthetic vapor. The final concentration of inhaled anesthetic is the ratio of the flow of the inhaled anesthetic to the total gas flow.[48,53]

The vapor pressure of an inhaled anesthetic depends on the ambient temperature (see Fig. 25-17). For example, at 20°C the vapor pressure of isoflurane is 238 mm Hg, whereas at 35°C the vapor pressure almost doubles (450 mm Hg). Variable-bypass vaporizers have an internal mechanism to compensate for variations in ambient temperature. The temperature-compensating valve of the Datex-Ohmeda Tec 4 is shown in Figure 25-19. At relatively high ambient temperatures, such as those commonly seen in operating rooms designated for the care of pediatric or burn patients, the vapor pressure inside the vaporizing chamber is high. To compensate for this increased vapor pressure, the bimetallic strip of the temperature-compensating valve leans to the right, thereby decreasing resistance to flow through the bypass chamber and allowing more flow to pass through the bypass chamber and less flow to pass through the vaporizing chamber. In contrast, in a cold operating room environment, the vapor pressure inside the vaporizing chamber is reduced. To compensate for this decrease in vapor pressure, the bimetallic strip leans to the left, which increases resistance to flow through the bypass chamber and causes more flow to pass through the vaporizing chamber and less to pass through the bypass chamber. The net effect in both situations is maintenance of relatively constant vaporizer output.

Factors That Influence Vaporizer Output

If an ideal vaporizer existed, with a fixed dial setting its output would be constant regardless of varied flow rates, temperature, backpressure, and carrier gases. Designing such a vaporizer is difficult because as ambient conditions change, the physical properties of gases and vaporizers themselves can change.[53] Contemporary vaporizers approach ideal but still have some limitations. Even though some of the most sophisticated vaporizer systems now available use computer-controlled components and multiple sensors, they have yet to become significantly more accurate than conventional vaporizers. Several factors that affect vaporizer performance in general are described in the following paragraphs.

Flow Rate With a fixed dial setting, vaporizer output can vary with the rate of gas flowing through the vaporizer. This variation is particularly notable at the extremes of flow rates. The output of all variable-bypass vaporizers is less than the dial setting at low flow rates (<250 mL/min) because of the relatively high density of volatile inhaled anesthetics. Insufficient turbulence is generated in the vaporizing chamber at low flow rates to upwardly advance the vapor molecules. At extremely high flow rates, such as 15 L/min, the output of most variable-bypass vaporizers is less than the dial setting. This discrepancy is attributed to incomplete mixing and failure to saturate the carrier gas in the vaporizing chamber.

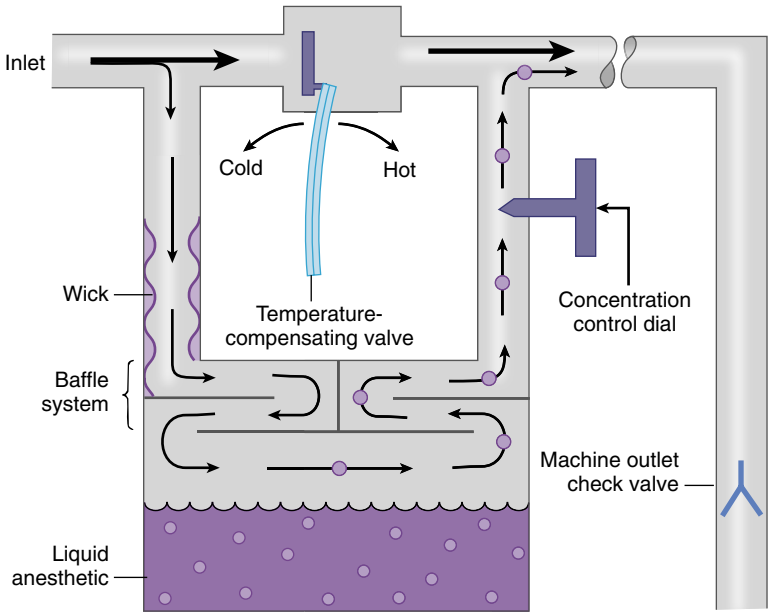

Figure 25-19 Simplified schematic of the Ohmeda Tec–type vaporizer. See text for details

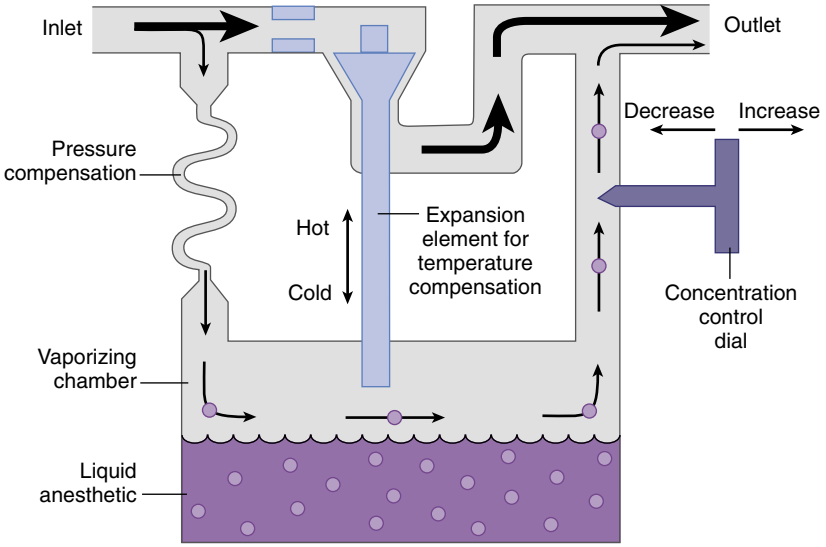

Figure 25-20 Simplified schematic of the North American Dräger Vapor 19.n and 20.n vaporizers. See text for details.

In addition, the resistance characteristics of the bypass chamber and the vaporizing chamber can vary as flow increases. These variations can result in decreased vapor output concentration.[53]

Temperature Because of improvements in design, the output of contemporary temperature-compensated vaporizers is almost linear over a wide range of temperatures. Automatic temperature-compensating mechanisms in the bypass chamber maintain constant vaporizer output with varying temperatures.[23] As previously described, a bimetallic strip (Fig. 25-19) or an expansion element (Fig. 25-20) directs a greater proportion of gas flow through the bypass chamber as temperatures increase.[53] Additionally, the wick systems are placed in direct contact with the metal wall of the vaporizer to help replace energy (heat) consumed during vaporization. The materials that vaporizers are constructed of are chosen because they have a relatively high specific heat and high thermal conductivity. These factors help minimize the effect of cooling during vaporization.

Intermittent Backpressure The intermittent backpressure that results from either positive-pressure ventilation or use of the oxygen flush valve may lead to higher than expected vaporizer output. This phenomenon, known as the *pumping effect*, is more pronounced at low flow rates, low dial settings, and low levels of liquid anesthetic in the vaporizing chamber.[48,53-56] Additionally, the pumping effect is increased by rapid respiratory rates, high peak inspired pressures, and rapid drops in pressure during expiration.[46-50] Newer variable-bypass vaporizers such as the Datex-Ohmeda Tec 4, Tec 5, and Tec 7 and the North American Dräger Vapor 19.n and 20.n are relatively immune from the pumping effect. One proposed mechanism for the pumping effect is dependent on retrograde transmission of pressure from the patient circuit to the vaporizer during the inspiratory phase of positive-pressure ventilation. Gas molecules are compressed in both the bypass and vaporizing chambers. When the backpressure is suddenly released during the expiratory phase of positive-pressure ventilation, vapor exits the vaporizing chamber both through the vaporizing chamber outlet and retrogradely through the vaporizing chamber inlet because the output resistance of the bypass chamber is lower than that of the vaporizing chamber, particularly at low dial settings. The enhanced output concentration results from the increment of vapor that travels in the retrograde direction to the bypass chamber.[53-56]

To decrease the pumping effect, the vaporizing chambers of newer systems are smaller than those of early variable-bypass vaporizers such as the Fluotec Mark II (750 mL).[55] Therefore, no substantial volumes of vapor can be discharged from the vaporizing chamber into the bypass chamber during the expiratory phase. The North American Dräger Vapor 19.n and 20.n vaporizers (see Fig. 25-20) have a long spiral tube that serves as the inlet to the vaporizing chamber.[55] When the pressure in the vaporizing chamber is released, some of the vapor enters this tube but does not enter the bypass chamber because of tube length.[49] The Tec 4 (see Fig. 25-19) has an extensive baffle system in the vaporizing chamber, and a one-way check valve has been inserted at the common gas outlet to minimize the pumping effect. This check valve attenuates but does not eliminate the increase in pressure because gas still flows from the flow meters to the vaporizer during the inspiratory phase of positive-pressure ventilation.[48,57]

Carrier Gas Composition Vaporizer output is influenced by the composition of the carrier gas that flows through the vaporizer.[58-65] During experimental conditions, when the carrier gas is changed rapidly from 100% oxygen to 100% nitrous oxide, a sudden transient decrease in vaporizer output occurs, followed by a slow increase to a new steady-state value (B in Fig. 25-21).[63,64] Because nitrous oxide is more soluble than oxygen in the halogenated liquid within the vaporizer sump, when this switch occurs, the output from the vaporizing chamber is transiently reduced.[63] Once the anesthetic liquid is totally saturated with nitrous oxide, vaporizing chamber output increases somewhat, and a new steady state is established.

The explanation for the new steady-state output value is less well understood.[65] With contemporary vaporizers such as the North American Dräger Vapor 19.n and 20.n and the Ohmeda Tec–type conventional vaporizers, the steady-state output value is less when nitrous oxide is the carrier gas instead of oxygen (see B in Fig. 25-21). Conversely, the output of some older vaporizers is enhanced when nitrous oxide is the carrier gas instead of oxygen.[58,60] The steady-state plateau is achieved more rapidly with

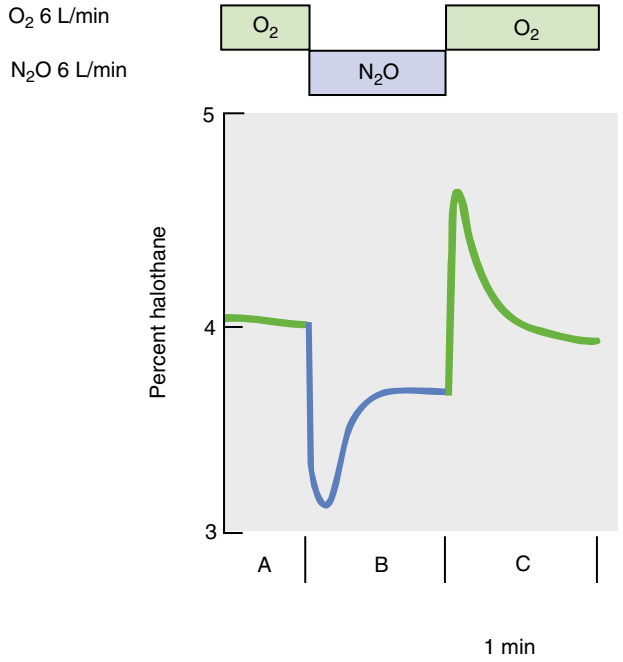

Figure 25-21 Halothane output of a North American Dräger Vapor 19.n vaporizer with different carrier gases. The initial output concentration is approximately 4% halothane when oxygen is the carrier gas at flows of 6 L/min (A). When the carrier gas is quickly switched to 100% nitrous oxide (B), the halothane concentration decreases to 3% within 8 to 10 seconds. A new steady-state concentration of approximately 3.5% is then attained within 1 minute. See text for details. *(Modified with permission from Gould DB, Lampert BA, MacKrell TN: Effect of nitrous oxide solubility on vaporizer aberrance. Anesth Analg 61:939, 1982.)*

increased flow rates, regardless of the ultimate output value.[64] Factors that contribute to the characteristic steady-state response resulting when various carrier gases are used include the viscosity and density of the carrier gas, the relative solubility of the carrier gas in the anesthetic liquid, the flow-splitting characteristics of the specific vaporizer, and the concentration control dial setting.[60,63-65]

Safety Features

Newer generations of anesthesia vaporizers, including the North American Dräger 19.n and 20.n and the Datex-Ohmeda Tec 4, Tec 5, and Tec 7, now have built-in safety features that have minimized or eliminated many hazards once associated with variable-bypass vaporizers. Agent-specific, keyed filling devices help prevent filling a vaporizer with the wrong agent. Overfilling of these vaporizers is minimized because the filler port is located at the maximum safe liquid level. Finally, today's vaporizers are firmly secured to a vaporizer manifold on the anesthesia workstation. Thus, problems associated with vaporizer tipping have become much less frequent. Contemporary interlock systems prevent the administration of more than one inhaled anesthetic.

Hazards

Despite many safety features, some hazards are still associated with contemporary variable-bypass vaporizers.

Misfilling Vaporizers not equipped with keyed fillers have occasionally been misfilled with the wrong anesthetic liquid.[66] A potential for misfilling exists even on contemporary vaporizers equipped with keyed fillers.[67-69] When vaporizer misfilling occurs, either an anesthetic overdose or underdose will result if the anesthesia care provider is depending on the concentration control dial markings to determine the anesthetic dose. The use of supplemental monitoring such as a multigas analyzer may alert the user to such a problem.

Contamination Contamination of anesthetic vaporizer contents has occurred as a result of filling an isoflurane vaporizer with a contaminated bottle of isoflurane. A potentially serious incident was avoided because the operator did not use the contaminated vaporizer after detecting an abnormal acrid odor.[70]

Tipping Tipping of a vaporizer can occur when it is incorrectly "switched out" or moved. However, short of the entire machine being turned over, tipping is unlikely when a vaporizer is attached to the anesthesia workstation manifold. Excessive tipping can allow the liquid agent to enter the bypass chamber and cause an output with an extremely high concentration of agent.[71] The Tec 4 is slightly more immune to tipping than the North American Dräger Vapor 19.n because of its extensive baffle system. However, if either vaporizer is tipped, it should not be used until it has been flushed for 20 to 30 minutes at high fresh gas flow rates. During this procedure, having the vaporizer concentration control dial set at a low concentration maximizes bypass chamber flow and will aid in removal of any residual liquid anesthetic in that area.[48] After this procedure, use of a multigas analyzer is strongly recommended. The Dräger Vapor 20.n series vaporizers now have a transport ("T") dial setting that helps prevent tipping-related problems. When the dial is placed in this position, the vaporizer sump is isolated from the bypass chamber, thereby reducing the likelihood of tipping and resulting in an accidental overdose. Therefore, any time that one of these vaporizers is moved separate from the anesthesia workstation, the control dial should be placed in the "T" position.

The design of the Tec 6 and the Aladin cassette vaporizer systems, both from Datex-Ohmeda, has practically eliminated the possibility of tipping with these products. Because the Aladin cassette vaporizer's bypass chamber is physically separated from the "cassette" and permanently resides in the anesthesia workstation, the possibility of tipping is virtually eliminated, sparing overturning the entire anesthesia workstation. Tipping of the Aladin cassettes themselves when they are not installed in the vaporizer is not problematic.

Overfilling Improper filling procedures combined with failure of the vaporizer sight glass can cause overfilling and patient overdose. Liquid anesthetic enters the bypass chamber, and up to 10 times the intended vapor concentration can be delivered to the common gas outlet.[72] Most modern vaporizers are now relatively immune to overfilling because of side-fill rather than top-fill designs. Side-fill systems largely prevent overfilling.

Underfilling Just as with overfilling, underfilling of anesthetic vaporizers may be problematic. When a Tec 5 sevoflurane vaporizer is in a low fill state and used under conditions of high fresh gas flow rates (>7.5 L/min) and high dial settings (such as seen during inhalational induction), output from the vaporizer may abruptly decrease to less than 2%. The cause of this problem is most likely multifactorial. However, the combination of a low

vaporizer fill state (<25% full) and a high vaporizing chamber flow rate can result in a clinically significant and reproducible fall in vaporizer output.[73] Because sevoflurane has become a particularly popular agent for use during inhalational induction, all anesthesia care providers should be aware of this particular hazard.

Simultaneous Administration of Inhaled Anesthetics On some older anesthesia machines from Datex-Ohmeda (equipped with the Select-a-Tec three-vaporizer manifold) that did not use a vapor interlock system, two inhaled anesthetics could be administered simultaneously when the center vaporizer was removed. On such machines, the left or right vaporizer needed to be moved to the central position if the central vaporizer was removed (as indicated by the manifold warning label). Once this was done, the vaporizer's interlock system would operate properly and allow only one agent to be administered at a time. More contemporary Select-a-Tec–type vaporizer manifolds from GE and Dräger Medical have a built-in vapor interlock or vapor exclusion devices that prevent this problem. On these newer two- or three-vaporizer systems, the vaporizers do not necessarily have to be in adjacent positions on the manifold for the vapor exclusion systems to work properly. In one basic type of system used on early GE workstations, a U-shaped plastic device linked the vaporizer extension rods even when the vaporizers were not adjacent to one another on the manifold to prevent simultaneously turning on two vaporizers. On such a system, the manifold and the vaporizers themselves comprise the vapor interlock or vapor exclusion system. This type of system reduced the chance of accidental simultaneous administration of two volatile anesthetic agents.

Leaks Vaporizer leaks occur frequently and can result in patient awareness during anesthesia.[11,15,54,74] A loose filler cap is the most common source of vaporizer leaks. With some key-filled Penlon and Dräger vaporizers, a loose filler screw clamp allows saturated anesthetic vapor to escape.[11] Leaks can occur at the O-ring junctions between the vaporizer and its manifold. To detect a leak within a vaporizer, the concentration control dial must be in the "on" position. Even though vaporizer leaks in Dräger systems can potentially be detected with a conventional positive-pressure leak test (because of the absence of an outlet check valve), a negative-pressure leak test is more sensitive and allows the user to detect even small leaks. Datex-Ohmeda recommends a negative-pressure leak-testing device (suction bulb) to detect vaporizer leaks in the Modulus I, Modulus II, Excel, and Aestiva workstations because of the check valve located just upstream of each machine's fresh gas outlet (see "Checking Your Anesthesia Workstation").

Many newer anesthesia workstations are capable of performing self-testing procedures, which in some cases may eliminate the need for the conventional negative-pressure leak testing. However, it is of vital importance that anesthesia care providers understand that these self-tests may not detect internal vaporizer leaks on systems with add-on vaporizers. For the self-tests to determine whether an internal vaporizer leak is present, the leak test must be repeated with each vaporizer sequentially while its concentration control dial is turned to the "on" position. Recall that when a vaporizer's concentration control dial is set in the "off" position, it may not be possible to detect even major internal leaks such as an absent or loose filler cap.

Anesthesia Vaporizers and Environmental Considerations Today more than ever, anesthesia care providers are being asked to provide anesthesia to patients outside the operating room. One such location that has sometimes proved difficult to work in is the magnetic resonance imaging (MRI) suite. The presence of a powerful magnet field, significant noise pollution, and limited access to the patient during the procedure all complicate care in this setting. Essential to the anesthesia care provider is an understanding of the extremely powerful magnetic fields used in these devices. It is imperative that only nonferrous (MRI-compatible) equipment be used in these settings. Some anesthesia vaporizers, although they may appear nonferrous by testing with a horseshoe magnet, may indeed contain substantial internal ferrous components. Inappropriate use of such devices in an MRI suite may potentially turn them into a dangerous missile if left unsecured.[75]

The Datex-Ohmeda Tec 6 Vaporizer for Desflurane

Because of its unique physical characteristics, controlled vaporization of desflurane required a novel approach to vaporizer design. Datex-Ohmeda developed the Tec 6 vaporizer, the first such system, and released it into clinical use in the early 1990s. The Tec 6 vaporizer is an electrically heated, pressurized device specifically designed to deliver desflurane.[76,77] The vapor pressure of desflurane is three to four times that of other contemporary inhaled anesthetics, and it boils at 22.8°C,[78] which is near room temperature (see Fig. 25-17). Desflurane has minimum alveolar anesthetic concentration (MAC) values of 6% to 7%.[78] Desflurane is valuable because it has a low blood-gas solubility coefficient of 0.45 at 37°C, and recovery from anesthesia is more rapid than with many other potent inhaled anesthetics.[78] In 2004, Dräger Medical received FDA approval for its own version of the Tec 6 desflurane vaporizer. The operating principles described in the following discussion are applicable to either system, even though we refer to the Tec 6 specifically.

Unsuitability of Contemporary Variable-Bypass Vaporizers for Controlled Vaporization of Desflurane

Desflurane's high volatility and moderate potency preclude its use with contemporary variable-bypass vaporizers such as Datex-Ohmeda Tec 4, Tec 5, and Tec 7 or the North American Dräger Vapor 19.n or 20.n for two primary reasons[76]:

1. At 20°C the vapor pressure of desflurane is near 1 atm. The vapor pressures of enflurane, isoflurane, halothane, and desflurane at 20°C are 172, 240, 244, and 669 mm Hg, respectively (see Fig. 25-17).[78] Equal amounts of flow through a traditional vaporizer would vaporize many more volumes of desflurane than any other of these agents. For example, at 1 atm and 20°C, 100 mL/min passing through the vaporizing chamber would entrain 735 mL/min of desflurane versus 29, 46, and 47 mL/min of enflurane, isoflurane, and halothane, respectively.[76] Under these same conditions, to produce a 1% desflurane output, the amount of bypass flow necessary to achieve sufficient dilution of the large volume of desflurane-saturated anesthetic vapor would be approximately 73 L/min versus 5 L/min or less

for the other three anesthetics. Additionally, above 22.8°C at 1 atm, desflurane will boil. The amount of vapor produced would be limited only by the heat energy available from the vaporizer because of its specific heat.[76]

2. Contemporary vaporizers lack an external heat source. The latent heat of vaporization for desflurane is approximately equal to that of enflurane, isoflurane, and halothane; however its MAC is four to nine times higher than those of the other three inhaled anesthetics. Thus, the absolute amount of desflurane vaporized over a given period is considerably greater than that of the other anesthetic drugs. Supplying desflurane via a conventional vaporizer in higher (equivalent MAC) concentrations would lead to excessive cooling of the vaporizer and significantly reduce its output. In the absence of an external heat source, temperature compensation with the traditional mechanical devices would be almost impossible. Because of the broad range of temperatures seen in the clinical setting and because of desflurane's steep vapor pressure–versus-temperature curve (see Fig. 25-17), delivery of desflurane in a conventional anesthetic vaporizer would be at best unpredictable.[767]

Operating Principles of the Tec 6 and Tec 6 Plus

To achieve controlled vaporization of desflurane, Datex-Ohmeda introduced the Tec 6 vaporizer to widespread clinical practice in 1993. This was the first clinically available vaporizer ever to be electrically heated and pressurized. The physical appearance and operation of the Tec 6 and contemporary vaporizers are similar, but some aspects of the internal design and operating principles are radically different. The Tec 6 Plus represents a later version of the original Tec 6. The Tec 6 Plus has the same basic Tec 6 design, but it also incorporates an enhanced audible alarm system not previously available on the Tec 6.

Functionally, operation of the Tec 6 is more accurately described as a dual-gas blender than as a vaporizer. A simplified schematic of the Tec 6 is shown in Figure 25-22. The vaporizer has two independent gas circuits arranged in parallel. The fresh gas circuit is shown in orange, and the vapor circuit is shown in blue. Fresh gas from the flow meters enters at the fresh gas inlet, passes through a fixed restrictor (R1), and exits at the vaporizer gas outlet. The vapor circuit originates at the desflurane sump, which is electrically heated and thermostatically controlled to 39°C, a temperature well above desflurane's boiling point. The heated sump assembly serves as a reservoir of desflurane *vapor*. At 39°C, the vapor pressure in the sump is approximately 1300 mm Hg absolute,[79] or approximately 2 atm absolute (see Fig. 25-17). Just downstream from the sump is the shut-off valve. After the vaporizer warms up, the shut-off valve fully opens when the concentration control valve is turned to the "on" position. A pressure-regulating valve located downstream from the shut-off valve downregulates the pressure to approximately 1.1 atm absolute (74 mm Hg gauge) at a fresh gas flow rate of 10 L/min. The operator controls the output of desflurane by adjusting the concentration control valve (R2), which is a variable restrictor.[76]

The vapor flow through R2 joins the fresh gas flow through R1 at a point downstream from the restrictors. Until this

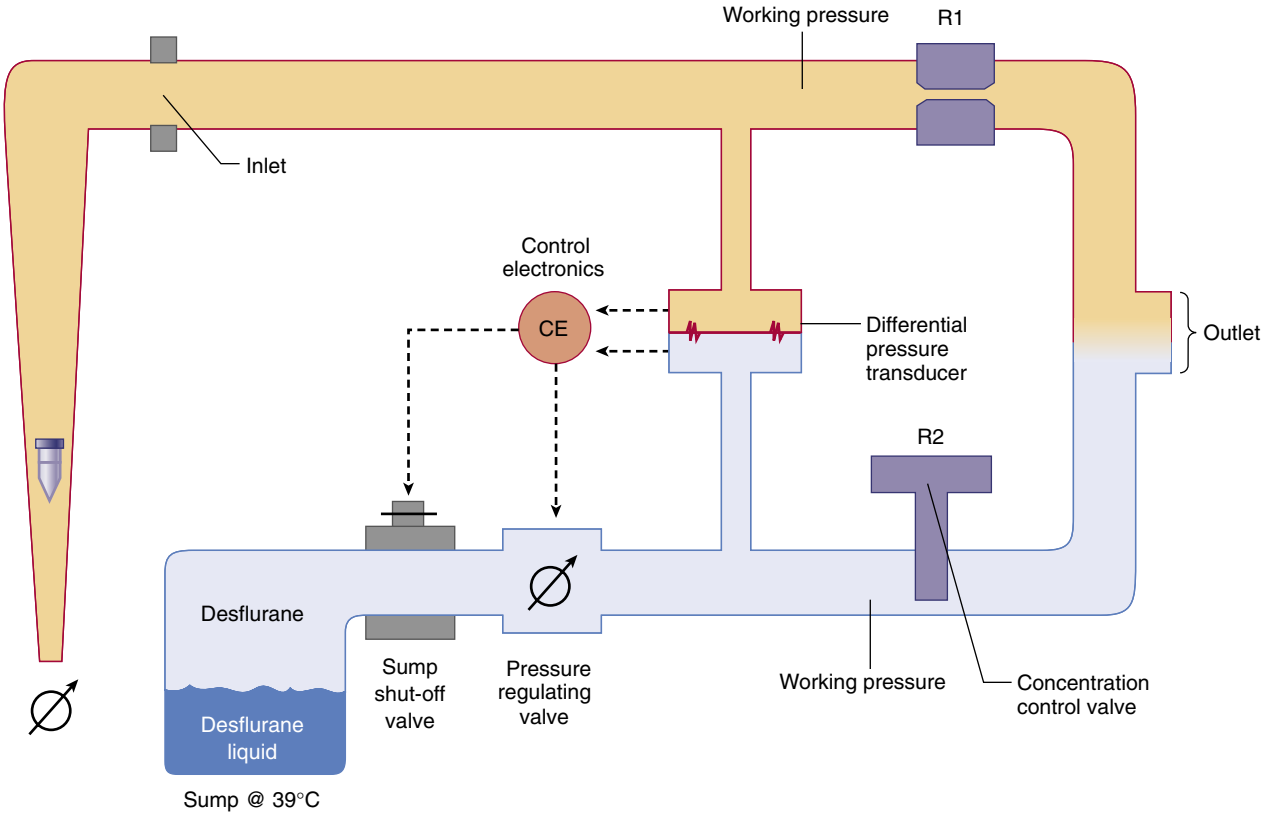

Figure 25-22 Simplified schematic of the Tec 6 desflurane vaporizer. *(From Andrews JJ: Operating Principles of the Ohmeda Tec 6 Desflurane Vaporizer: A Collection of Twelve Color Illustrations. Washington, DC, Library of Congress, 1996, with permission.)*

point, the two circuits are physically divorced. They are interfaced pneumatically and electronically, however, through differential pressure transducers, a control electronics system, and a pressure-regulating valve. When a constant fresh gas flow rate encounters the fixed restrictor R1, a specific backpressure proportional to the fresh gas flow rate pushes against the diaphragm of the control differential pressure transducer. The differential pressure transducer conveys the pressure difference between the fresh gas circuit and the vapor circuit to the control electronics system. The control electronics system regulates the pressure-regulating valve so that the pressure in the vapor circuit equals the pressure in the fresh gas circuit. This equalized pressure supplying R1 and R2 is the working pressure, and the working pressure is constant at a fixed fresh gas flow rate. If the operator increases the fresh gas flow rate, more backpressure is exerted on the diaphragm of the control pressure transducer, and the working pressure of the vaporizer increases.[76]

Table 25-2 shows the approximate correlation between the fresh gas flow rate and working pressure for a typical vaporizer. At a fresh gas flow rate of 1 L/min, the working pressure is 10 millibars, or 7.4 mm Hg gauge. At a fresh gas flow rate of 10 L/min, the working pressure is 100 millibars, or 74 mm Hg gauge. Therefore, there is a linear relationship between the fresh gas flow rate and working pressure. When the fresh gas flow rate is increased 10-fold, the working pressure increases 10-fold.[76]

Listed below are two specific examples to demonstrate the operating principles of the Tec 6.[76]

Example A: *Constant fresh gas flow rate of 1 L/min with an increase in the dial setting.* With a fresh gas flow rate of 1 L/min, the working pressure of the vaporizer is 7.4 mm Hg. That is, the pressure supplying R1 and R2 is 7.4 mm Hg. As the operator increases the dial setting, the opening at R2 becomes larger, thereby allowing more vapor to pass through R2. Specific vapor flow values at different dial settings are shown in Table 25-3.

Example B: *Constant dial setting with an increase in fresh gas flow from 1 to 10 L/min.* At a fresh gas flow rate of 1 L/min, the working pressure is 7.4 mm Hg, and at a dial setting of 6%, the vapor flow rate through R2 is 64 mL/min (see Tables 25-2 and 25-3). With a 10-fold increase in the fresh gas flow rate, there is a concomitant 10-fold increase in the working pressure to 74 mm Hg. The ratio of R2 to R1 resistance is constant at a fixed dial setting of 6%. Because R2 is supplied by 10 times more pressure, the vapor flow rate through R2 increases 10-fold to 640 mL/min. Vaporizer output is constant because both fresh gas flow and vapor flow increase proportionally.

Table 25-2 Fresh Gas Flow Rate Versus Working Pressure

Fresh Gas Flow Rate (L/min)	Working Pressure at R1 and R2 (Gauge) (Gas Inlet Pressure)		
	Millibar	cm H_2O	mm Hg
1	10	10.2	7.4
5	50	51.0	37.0
10	100	102.0	74.0

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Table 25-3 Dial Setting Versus Flow through Restrictor R2

Dial Setting (vol%)*	Fresh Gas Flow Rate (L/min)	Approximate Vapor Flow Rate through R2 (mL/min)
1	1	10
6	1	64
12	1	136
18	1	220

* Volume percent $= \frac{\text{Vapor flow rate}}{\text{Fresh gas flow rate} + \text{Vapor flow rate}} \cdot 100\%$

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Factors That Influence Vaporizer Output

Varied altitude and carrier gas composition influence Tec 6 output. Each is discussed in the following paragraphs.

Varied Altitudes Although ambient pressure changes affect conventional vaporizer output significantly in terms of volume percent (%vol/vol; i.e., concentration), their effect on anesthetic potency (partial pressure) is minimal. This effect is illustrated with the example of isoflurane in Table 25-4. With a constant dial setting of 0.89%, at 1 atm, if perfectly calibrated, the %vol/vol delivered would be 0.89%, and the partial pressure of isoflurane would be 6.8 mm Hg. Maintaining the same dial setting and lowering the atmospheric pressure to 0.66 atm or 502 mm Hg (roughly equivalent to an elevation of 10,000 ft) would result in an increase in the concentration output to 1.75% (almost double), but the partial pressure increases to only 8.77 mm Hg (just a 29% increase) because of the proportional decline in ambient pressure.

In general, it is thought that the partial pressure of the volatile anesthetic agent in the central nervous system, not its concentration, is responsible for the anesthetic effect. Therefore, to maintain a constant depth of anesthesia when a gross change in barometric pressure occurs, %vol/vol must be changed in inverse proportion to atmospheric pressure. For the most part, traditional variable-bypass vaporizers automatically compensate for this change, and for practical purposes the effect of barometric pressure can generally be ignored.

This should be considered in stark contrast to the response of the Tec 6 desflurane vaporizer at varied altitudes (Table 25-4). One must remember this device is more accurately described as a dual-gas blender than a vaporizer. Regardless of ambient pressure, the Tec 6 will maintain a constant concentration of vapor output (%vol/vol), not a constant partial pressure. This means that at high altitudes, the partial pressure of desflurane will decrease in proportion to the reduction in atmospheric pressure divided by the calibration pressure (normally 760 mm Hg) per the following formula:

$$\text{Required dial setting} = \text{Normal dial setting (vol\%)} \cdot \frac{760 \text{ mm Hg}}{\text{Ambient pressure (mm Hg)}}$$

For example, at an altitude of 2000 m or 6564 feet, where the ambient pressure is 608 mm Hg, the operator must advance the concentration control dial from 10% to 12.5% to maintain the required anesthetic partial pressure. In hyperbaric settings, the

Table 25-4 Performance of "Tec"-Type Vaporizers Versus the Tec 6 Desflurane Vaporizer at Varying Ambient Pressure

		Isoflurane Vaporizer with a Dial Setting of 0.89%			Tec 6 Desflurane Vaporizer with a Dial Setting of 6%
Atmospheres	Ambient Pressure (mm Hg)	mL Isoflurane Vapor Entrained by 100 mL O_2	Output Concentration (%)	Partial Pressure Output (mm Hg)	Partial Pressure Output of Desflurane (mm Hg)
0.66 (2/3)	500 (10,000 ft)	91	1.753	8.77	30
0.74	560	74	1.429	8.0	33.6
0.80	608 (6564 ft)	64.32	1.25	7.6	36.5
1.0	760	46	0.89	6.8	45.6
1.5	1140	26.4	0.515	5.87	68.4
2	1520	19	0.36	5.5	91.2
3	2280	11.65	0.228	5.198	136

Adapted from Ehrenwerth J, Eisenkraft J: Anesthesia vaporizers. *In* Ehrenwerth J, Eisenkraft J (eds): Anesthesia Equipment—Principles and Applications. St Louis, CV Mosby, 1993, pp 69-71.

operator must decrease the dial setting to prevent delivery of an overdose.

Carrier Gas Composition Vaporizer output approximates the dial setting when oxygen is the carrier gas because the Tec 6 vaporizer is calibrated with 100% oxygen. At low flow rates when a carrier gas other than 100% oxygen is used, however, a clear trend toward reduction in vaporizer output emerges. This reduction parallels the proportional decrease in viscosity of the carrier gas. Nitrous oxide has lower viscosity than oxygen does, so the backpressure generated by resistor R1 (see Fig. 25-22) is less when nitrous oxide is the carrier gas, and the working pressure is reduced. At low flow rates and with nitrous oxide used as the carrier gas, vaporizer output is approximately 20% less than the dial setting. This suggests that at clinically useful fresh gas flow rates, gas flow across resistor R1 is laminar, and the working pressure is proportional to both the fresh gas flow rate and the viscosity of the carrier gas.[80]

Safety Features

Because desflurane's vapor pressure is near 1 atm, misfilling contemporary vaporizers with desflurane could theoretically result in both desflurane overdose and creation of a hypoxic gas mixture.[81] Datex-Ohmeda has introduced a unique, anesthetic-specific filling system to minimize occurrence of this potential hazard. The agent-specific filler of the desflurane bottle, known as the "Saf-T-Fill" adapter, is intended to prevent its use with traditional vaporizers. The filling system also minimizes spillage of liquid or vapor anesthetic by maintaining a "closed system" during the filling process. Each desflurane bottle has a spring-loaded filler cap with an O-ring on the tip. The spring seals the bottle until it is engaged in the filler port of the vaporizer. Thus, this anesthetic-specific filling system interlocks the vaporizer and the dispensing bottle and thereby prevents loss of anesthetic to the atmosphere. One recent case report described misfilling of a Tec 6 desflurane vaporizer with sevoflurane. This error was possible because of similarities between a new type of keyed filler for sevoflurane and the desflurane Saf-T-fill adapter. In this case, the desflurane vaporizer detected this error and automatically shut itself off.[69]

Major vaporizer faults cause the shut-off valve located just downstream from the desflurane sump (see Fig. 25-22) to close and produce a no-output situation. The valve is closed and a "no-output" alarm is activated immediately if any of the following conditions occur: (1) the anesthetic level decreases to below 20 mL, (2) the vaporizer is tilted, (3) a power failure occurs, or (4) there is a disparity between the pressure in the vapor circuit and the pressure in the fresh gas circuit that exceeds a specified tolerance.

Summary

The Tec 6 vaporizer is an electrically heated, thermostatically controlled, constant-temperature, pressurized, electromechanically coupled dual-circuit, gas-vapor blender. The pressure in the vapor circuit is electronically regulated to equal the pressure in the fresh gas circuit. At a constant fresh gas flow rate, the operator regulates vapor flow with a conventional concentration control dial. When the fresh gas flow rate increases, the working pressure increases proportionally. For a given concentration setting even when varying the fresh gas flow rate, the vaporizer output is constant because the amount of flow through each circuit remains proportional.[76]

The Datex-Ohmeda Aladin Cassette Vaporizer

The vaporizer system used in the Datex-Ohmeda S/5 ADU is unique in that the single electronically controlled vaporizer is designed to deliver five different inhaled anesthetics, including halothane, isoflurane, enflurane, sevoflurane, and desflurane. The vaporizer consists of a permanent internal control unit housed within the ADU and an interchangeable Aladin agent cassette that contains anesthetic liquid. The Aladin agent cassettes are color-coded for each anesthetic agent, and they are also magnetically coded so that the Datex-Ohmeda ADU can identify which anesthetic cassette has been inserted. The cassettes are filled using agent-specific fillers.[48,82]

Though very different in external appearance, the functional anatomy of the S/5 ADU cassette vaporizer (Fig. 25-23) is very similar to that of the Dräger Vapor 19.n and 20.n and the Datex-Ohmeda Tec 4, Tec 5, and Tec 7 vaporizers. The Aladin

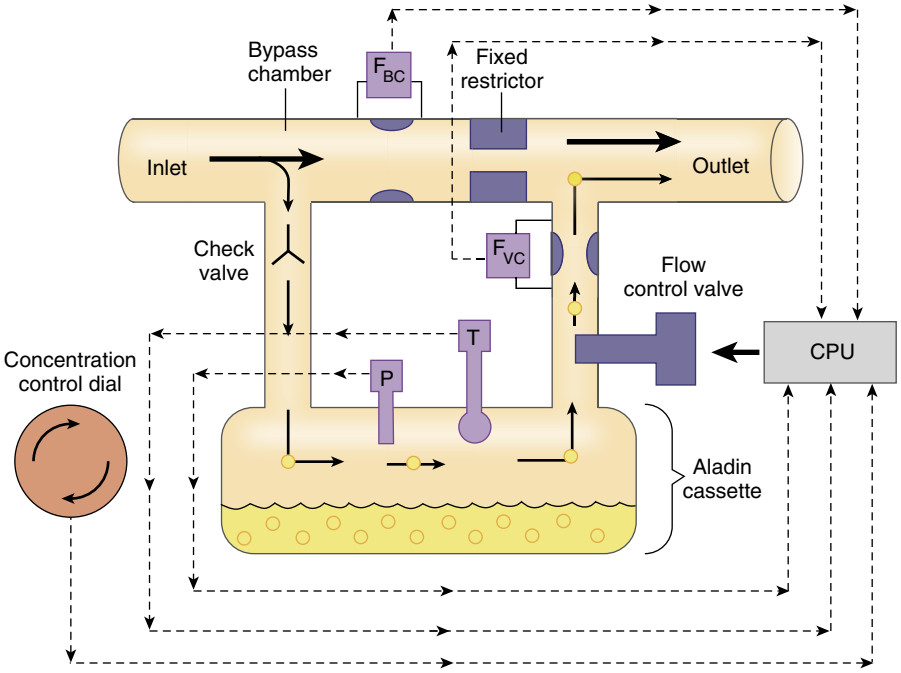


Figure 25-23 Simplified schematic of Datex-Ohmeda Aladin Cassette Vaporizer. The *black arrows* inside the vaporizer represent flow from the flow meters, and the *yellow circles* represent anesthetic vapor. The heart of the vaporizer is the electronically controlled flow control valve located in the outlet of the vaporizing chamber. CPU, central processing unit; F_{BC}, flow measurement unit that measures flow through the bypass chamber; F_{VC}, flow measurement unit that measures flow through the vaporizing chamber; P, pressure sensor; T, temperature sensor. *(Modified from Andrews JJ: Operating Principles of the Datex-Ohmeda Aladin Cassette Vaporizer: A Collection of Color Illustrations. Washington, DC, Library of Congress, 2000.)*

system is functionally similar to these conventional vaporizers because it is also made up of a bypass chamber and vaporizing chamber. A fixed restrictor is located in the bypass chamber, and flow measurement sensors are located both in the bypass chamber and in the outlet of the vaporizing chamber. The heart of the S/5 ADU cassette vaporizer is the electronically regulated flow control valve located in the vaporizing chamber outlet. This valve is controlled by a central processing unit (CPU). The CPU receives input from multiple sources, including the concentration control dial, a pressure sensor located inside the vaporizing chamber, a temperature sensor located inside the vaporizing chamber, a flow measurement unit located in the bypass chamber, and a flow measurement unit located in the outlet of the vaporizing chamber. The CPU also receives input from the flow meters regarding the composition of the carrier gas. By using data from these multiple sources, the CPU is able to precisely regulate the flow control valve to obtain the desired vapor concentration output. Appropriate electronic control of the flow control valve is essential to proper functioning of this vaporizer.[48,83]

A fixed restrictor is located in the bypass chamber, and it causes flow from the vaporizer inlet to split into two flow streams (see Fig. 25-23). One stream passes through the bypass chamber, and the other portion enters the inlet of the vaporizing chamber and passes through a one-way check valve. The presence of this check valve is unique to the Aladin system. This one-way valve prevents retrograde flow of the anesthetic vapor back into the bypass chamber, and its presence is crucial when delivering desflurane if room temperature is higher than the boiling point of desflurane (22.8°C).[48] A precise amount of vapor-saturated carrier gas passes through the flow control valve, which is regulated by the CPU. This flow then joins the bypass flow and is directed to the outlet of the vaporizer.[48]

As mentioned during discussion of the Tec 6, controlled vaporization of desflurane presents a unique challenge, particularly when room temperature is greater than the boiling point of desflurane (22.8°C). At higher temperatures, the pressure inside the vaporizer sump increases, and the sump becomes pressurized. When sump pressure exceeds pressure in the bypass chamber, the one-way check valve located in the vaporizing chamber inlet closes to prevent carrier gas from entering the vaporizing chamber. At this point the carrier gas passes straight through the bypass chamber and its flow sensor. Under these conditions, the electronically regulated flow control valve simply meters in the appropriate flow of pure desflurane vapor needed to achieve the desired final concentration selected by the user. At least one case report has described failure of the vaporizing chamber inlet check valve to function as designed. In this case, an anesthetic overdose occurred as a result of regurgitation of desflurane from the vaporizing chamber in a retrograde fashion back into the bypass chamber. Because of this report, ADU users should be cautious of this potential problem, especially when desflurane is used.[83]

During operating conditions in which high fresh gas flow rates or high dial settings (or both) are used, large quantities of anesthetic liquid are vaporized rapidly. As a result, the temperature of the remaining liquid anesthetic and the vaporizer itself decreases because of energy consumption, or the latent heat of vaporization. To offset this cooling effect, the S/5 ADU is equipped with a fan that forces warmed air from an "agent heating resistor" across the cassette (vaporizer sump) to raise its temperature when necessary. The fan is activated during two common clinical scenarios: (1) desflurane induction and maintenance and (2) sevoflurane induction.

Anesthetic Breathing Circuits

As the prescribed mixture of gases from the flow meters and vaporizer exits the anesthesia workstation at the common gas outlet, it then enters an anesthetic breathing circuit. The function of the anesthesia breathing circuit is not only to deliver oxygen and anesthetic gases to the patient but also to eliminate carbon

dioxide. Carbon dioxide can be removed either by washout with adequate fresh gas inflow or by the use of carbon dioxide absorbent media (e.g., soda lime absorption). The following discussion focuses on semiclosed rebreathing circuits and the circle system.

Mapleson Systems

In 1954 Mapleson described and analyzed five different semiclosed anesthetic systems, and they are now classically referred to as the Mapleson systems and are designated with letters A through E (Fig. 25-24).[84] Subsequently, in 1975 Willis and coauthors described the F system that was added to the original five.[85] The Mapleson systems consist of several common components, including a facemask, a spring-loaded pop-off valve, reservoir tubing, fresh gas inflow tubing, and a reservoir bag. Within the Mapleson systems, three distinct functional groups can be seen: A, BC, and DEF groups. The Mapleson A, also known as the Magill circuit, has a spring-loaded pop-off valve located near the facemask, and fresh gas flow enters the opposite end of the circuit near the reservoir bag. In the B and C systems, the spring-loaded pop-off valve is located near the facemask, but the fresh gas inlet tubing is located near the patient. The reservoir tubing and breathing bag serve as a blind limb where fresh gas, dead space gas, and alveolar gas can collect. Finally, in the Mapleson D, E, and F or "T-piece" group, fresh gas enters near the patient, and excess gas is popped off at the opposite end of the circuit.

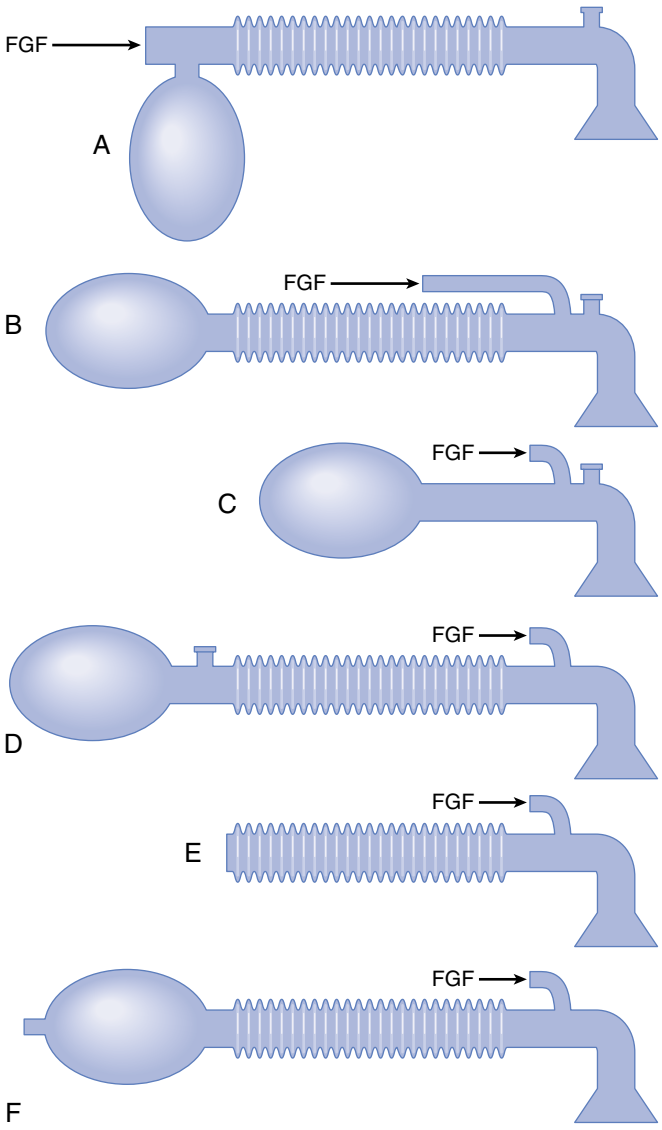


Figure 25-24 Mapleson breathing systems A-F. *(Redrawn with permission from Willis BA, Pender JW, Mapleson WW: Rebreathing in a T-piece: Volunteer and theoretical studies of the Jackson-Rees Modification of Ayer's T-piece during spontaneous respiration. Br J Anesth 47:1239, 1975.)*

Even though the components and their arrangement are simple, functional analysis of the Mapleson systems can be complex.[86,87] The amount of carbon dioxide rebreathing associated with each system is multifactorial, and variables that dictate the ultimate carbon dioxide concentration include the following: (1) the fresh gas inflow rate, (2) minute ventilation, (3) the mode of ventilation (spontaneous or controlled), (4) tidal volume, (5) the respiratory rate, (6) the inspiratory-to-expiratory ratio, (7) the duration of the expiratory pause, (8) the peak inspiratory flow rate, (9) the volume of the reservoir tube, (10) the volume of the breathing bag, (11) ventilation by mask, (12) ventilation through an endotracheal tube, and (13) the CO_2 sampling site.

The performance of the Mapleson systems is best understood by studying the expiratory phase of the respiratory cycle.[88] Illustrations of the various arrangements of Mapleson system component may be found in Figure 25-24. During spontaneous ventilation, the Mapleson A has the best efficiency of the six systems in that it requires a fresh gas inflow rate of only 1 times minute ventilation to prevent rebreathing of carbon dioxide.[89] However, it has the worst efficiency during controlled ventilation because a minute ventilation as high as 20 L/min is needed to prevent rebreathing. Systems DEF are slightly more efficient than systems BC. To prevent rebreathing CO_2, the DEF systems require a fresh gas inflow rate of approximately 2.5 times minute ventilation, whereas the fresh gas inflow rates required for BC systems are somewhat higher.[87]

The following summarizes the relative efficiency of different Mapleson systems with respect to prevention of rebreathing during spontaneous ventilation: A > DFE > CB. During controlled ventilation, DFE > BC > A.[84,87] The Mapleson A, B, and C systems are rarely used today, but the D, E, and F systems are commonly used. In the United States, the most popular representative from the DEF group is the Bain circuit.

Bain Circuit

The Bain circuit is a coaxial circuit and a modification of the Mapleson D system. Fresh gas flows through a narrow inner tube within the outer corrugated tubing.[90] The central fresh gas tubing enters the outer corrugated hose near the reservoir bag, but the fresh gas actually empties into the circuit at the patient end (Fig. 25-25). Exhaled gases enter the corrugated tubing and are vented through the expiratory valve near the reservoir bag. The Bain circuit may be used for both spontaneous and controlled ventilation. The fresh gas inflow rate necessary to prevent rebreathing is 2.5 times minute ventilation.

The Bain circuit has many advantages over other systems. It is lightweight, convenient, easily sterilized, and potentially reusable. Scavenging of gases from the expiratory valve is facilitated because the valve is located away from the patient. Exhaled gases in the outer reservoir tubing add warmth to the inspired fresh

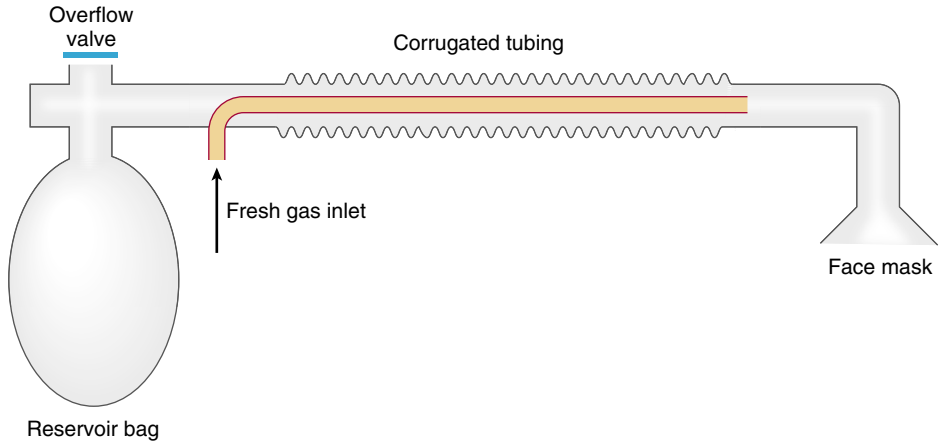


Figure 25-25 The Bain circuit. *(Redrawn with permission from Bain JA, Spoerel WE: A streamlined anaesthetic system. Can Anaesth Soc J 19:426, 1972.)*

gases by countercurrent heat exchange. The main hazards related to use of the Bain circuit are either an unrecognized disconnection or kinking of the inner fresh gas hose. These problems can cause hypercapnia as a result of inadequate gas flow or increased respiratory resistance. As with other circuits, an obstructed antimicrobial filter positioned between the Bain circuit and the endotracheal tube can result in increased resistance in the circuit. This may produce hypoventilation and hypoxemia and may even mimic the signs and symptoms of severe bronchospasm.[91]

The outer corrugated tube should be transparent to allow ongoing inspection of the inner tube. The integrity of the inner tube can be assessed as described by Pethick.[92] With his technique, high-flow oxygen is fed into the circuit while the patient end is occluded until the reservoir bag is filled. The patient end is opened, and oxygen is flushed into the circuit. If the inner tube is intact, the venturi effect occurs at the patient end. This causes a decrease in pressure within the circuit, and as a result, the reservoir bag deflates. Conversely, a leak in the inner tube allows fresh gas to escape into the expiratory limb, and the reservoir bag will remain inflated. This test is recommended as part of the preanesthesia check if a Bain circuit is used.

Circle Breathing Systems

For many years, the overall design of the circle breathing system has changed very little from one anesthesia workstation manufacturer to the next. Both the individual components and the order in which they appeared in the circle system were consistent across major platforms. In recent years, however, with the increasing technologic complexity of the anesthesia workstation, the circle system has undergone some major changes as well. These changes have resulted in part from an effort to improve patient safety (as in the integration of fresh gas decoupling and inspiratory pressure limiters) but have also allowed the deployment of new technologic advances. Two such major new technologies used in some new workstations have been (1) a return to the application of single-circuit piston-type ventilators and (2) the use of new spirometry devices that are located at the Y-connector instead of at the traditional location on the expiratory circuit limb. The following discussion focuses first on the traditional circle breathing system and is then followed by a brief discussion of some variations in the design of newer circle systems.

The Traditional Circle Breathing System

The circle system remains the most popular breathing system in the United States. It is so named because its components are arranged in a circular manner (see Fig. 25-7). One version of the traditional circle system, referred to as either a "universal F" or a "single-limb circuit," has increased in popularity in recent years. Although these systems appear very different externally, they have the same overall functional layout as the traditional circle system, and the following discussion is applicable to both the traditional circle system and the "universal F" system.

The circle system prevents rebreathing of carbon dioxide by use of carbon dioxide absorbents but allows partial rebreathing of other exhaled gases. The extent of rebreathing of the other exhaled gases depends on the arrangement of the breathing circuit components and the fresh gas flow rate. A circle system can be semiopen, semiclosed, or closed, depending on the amount of fresh gas inflow.[93] A semiopen system has no rebreathing and requires a very high flow of fresh gas. A semiclosed system is associated with some rebreathing of exhaled gases and is the most commonly used application in the United States. A closed system is one in which the inflow gas exactly matches that being taken up, or consumed, by the patient. In a closed system there is complete rebreathing of exhaled gases after absorption of carbon dioxide, and the overflow (pop-off or APL) valve or ventilator relief valve remains closed.

The circle system (see Fig. 25-7) consists of seven primary components, including (1) a fresh gas inflow source, (2) inspiratory and expiratory unidirectional valves, (3) inspiratory and expiratory corrugated tubes, (4) a Y-piece connector, (5) an overflow or pop-off valve referred to as the APL valve, (6) a reservoir bag, and (7) a canister containing a carbon dioxide absorbent. The inspiratory and expiratory valves are placed in the system to ensure that gas flow through the corrugated hoses remains unidirectional. The fresh gas inflow enters the circle by a connection from the common gas outlet of the anesthesia machine.

Numerous variations of the circle arrangement are possible, depending on the relative positions of the unidirectional valves, the pop-off valve, the reservoir bag, the carbon dioxide

absorber, and the site of fresh gas entry. However, to prevent rebreathing of carbon dioxide *in a traditional circle system*, three rules must be followed: (1) a unidirectional valve must be located between the patient and the reservoir bag on both the inspiratory and expiratory limbs of the circuit, (2) the fresh gas inflow cannot enter the circuit between the expiratory valve and the patient, and (3) the overflow (pop-off) valve cannot be located between the patient and the inspiratory valve. If these rules are followed, any arrangement of the other components will prevent rebreathing of carbon dioxide.[89] Some newer anesthesia workstations now use less traditional circle breathing systems. Two of these systems are discussed in detail later (see "Anesthesia Workstation Variations").

The most efficient circle system arrangement with the highest conservation of fresh gases is one in which the unidirectional valves are near the patient and the pop-off valve is located just downstream from the expiratory valve. This arrangement minimizes dead space gas and preferentially eliminates exhaled alveolar gases. A more practical arrangement, the one used on most conventional anesthesia machines (see Fig. 25-7), is somewhat less efficient because it allows alveolar and dead space gases to mix before they are vented.[94,95]

The main advantages of the circle system over other breathing systems include (1) maintenance of relatively stable inspired gas concentrations, (2) conservation of respiratory moisture and heat, and (3) prevention of operating room pollution. Additionally, the circle system can be used for closed-system anesthesia or semiclosed with very low fresh gas flows. The major disadvantage of the circle system stems from its complex design. Commonly, the circle system may have 10 or more different connections. These multiple connection sites set the stage for misconnections, disconnections, obstructions, and leaks. In a recent closed-claim analysis of adverse anesthetic outcomes arising from gas delivery equipment, more than a third (25/72) of malpractice claims resulted from breathing circuit misconnections or disconnections.[1] Malfunction of the circle system's unidirectional valves can result in life-threatening problems. Rebreathing can occur if the valves stick in the open position, and total occlusion of the circuit can occur if they are stuck shut. If the expiratory valve is stuck in the closed position, breath stacking and barotrauma or volutrauma can result. Obstructed filters located in the expiratory limb of the circle breathing system have caused increased airway pressure, hemodynamic collapse, and bilateral tension pneumothorax. Causes of circle system obstruction and failure include manufacturing defects, debris, patient secretions, and particulate obstruction from other odd sources such as albuterol nebulization.[96-99] Some systems, such as the Datex-Ohmeda 7900 SmartVent, use flow transducers located on both the inspiratory and expiratory limbs of the circle system. In one report, cracks in the flow transducer tubing used by this system produced a leak in the circle system that was difficult to detect.[100]

Carbon Dioxide Absorbents

Much has appeared in the literature lately regarding the issue of adverse chemical reactions between carbon dioxide absorbent materials and anesthetic agents. Some of these undesirable interactions are quite dramatic, such as sevoflurane interacting with desiccated Baralyme and resulting in fires within the breathing system and severe patient injury.[101,102] Although other sources of ignition and fire in the breathing system continue to be described,[103] the Baralyme-sevoflurane problem is somewhat unique in that nothing "unusual" is added to or removed from the breathing system for this to occur. Other reactions such as desflurane or sevoflurane with desiccated strong-base absorbents can produce more insidious patient morbidity and even death from the release of by-products such as carbon monoxide (CO) or compound A.[104] Although absorbent materials may be problematic, they still represent an important component of the circle breathing system. Different anesthesia breathing systems eliminate carbon dioxide with varying degrees of efficiency. The closed and semiclosed circle systems both *require* that carbon dioxide be absorbed from the exhaled gases to avoid hypercapnia. If one could design an ideal carbon dioxide absorbent, its characteristics would include lack of reactivity with common anesthetics, absence of toxicity, low resistance to airflow, low cost, ease of handling, and efficiency in carbon dioxide absorption.

The Absorber Canister

On modern anesthesia machines, the absorber canister (see Fig. 25-7) is composed of one or two clear plastic canisters alone or arranged in series. The canisters can be filled either with loose bulk absorbent or with absorbent supplied by the factory in prefilled plastic disposable cartridges called *prepacks*. Free granules from bulk absorbent can create a clinically significant leak if they lodge between the clear plastic canister and the O-ring gasket of the absorber. Leaks have also been caused by defective prepacks that were larger than factory specifications.[105] Prepacks can also cause total obstruction of the circle system if the clear plastic shipping wrapper is not removed before use.[106]

Chemistry of Absorbents

Two formulations of carbon dioxide absorbents are commonly available today: soda lime and calcium hydroxide lime (Amsorb). Of these agents, the most commonly used is soda lime. All serve to eliminate carbon dioxide from the breathing circuit with varying degrees of efficiency. Formerly, a product known as Baralyme, or barium hydroxide lime, was frequently used. This compound had significant interaction with contemporary volatile anesthetic drugs and was voluntarily removed from the market after several mishaps were reported in the literature (see later).

By weight, the approximate composition of "high-moisture" soda lime is 80% calcium hydroxide, 15% water, 4% sodium hydroxide, and 1% potassium hydroxide (an activator). Small amounts of silica are added to produce calcium and sodium silicate. This addition produces a harder, more stable pellet and thereby reduces dust formation. The efficiency of soda lime absorption varies inversely with its hardness; therefore, little silicate is used in contemporary soda lime. Sodium hydroxide is the catalyst for the carbon dioxide absorptive properties of soda lime.[107,108] Baralyme is a mixture of approximately 20% barium hydroxide and 80% calcium hydroxide. It may also contain some potassium hydroxide. Baralyme is the primary carbon dioxide

absorbent implicated as an agent that may produce fires in the breathing system when used with sevoflurane. Calcium hydroxide lime is one of the newest clinically available carbon dioxide absorbents. It consists primarily of calcium hydroxide and calcium chloride and contains two setting agents: calcium sulfate and polyvinylpyrrolidine. The latter two agents serve to enhance the hardness and porosity of the agent.[109] The most significant advantage of calcium hydroxide lime over other agents is its lack of the strong bases sodium and potassium hydroxide. Absence of these chemicals eliminates the undesirable production of CO and the nephrotoxic substance known as compound A, and it may reduce or eliminate the possibility of a fire in the breathing circuit.[110] The most significant disadvantages of calcium hydroxide lime are (1) less absorptive capacity—about 50% less than absorbents containing strong bases—and (2) generally higher cost per unit than other absorbents.[111,112]

The size of the actual absorptive granules has been determined over time by trial and error. The current particle sizes represent a compromise between resistance to airflow and absorptive efficiency.[113] The smaller the granule size, the greater the surface area that is available for absorption. However, as particle size decreases, airflow resistance increases. The granular size of soda lime and Baralyme used in clinical practice is between 4 and 8 mesh, a size at which absorptive surface area and resistance to flow are optimized. Mesh size refers to the number of openings per linear inch in a sieve through which the granular particles can pass. A 4-mesh screen means that there are four quarter-inch openings per linear inch. Likewise, an 8-mesh screen has eight per linear inch.[107]

Absorption of carbon dioxide by absorbents such as soda lime occurs via a series of chemical reactions; it is not a physical process like water soaking into a sponge. Carbon dioxide combines with water to form carbonic acid. Carbonic acid reacts with the hydroxides to form sodium (or potassium) carbonate and water. Calcium hydroxide accepts the carbonate to form calcium carbonate and sodium (or potassium) hydroxide. The equations are as follows:

1. $CO_2 + H_2O \rightleftharpoons H_2CO_3$
2. $H_2CO_3 + 2NaOH\ (KOH) \rightleftharpoons Na_2CO_3\ (K_2CO_3) + 2H_2O +$ Heat
3. $Na_2CO_3\ (K_2CO_3) + Ca(OH)_2 \rightleftharpoons CaCO_3 + 2NaOH\ (KOH)$

Some carbon dioxide may react directly with $Ca(OH)_2$, but this reaction is much slower.

Absorptive Capacity

The maximum amount of carbon dioxide that can be absorbed by soda lime is 26 L of CO_2 per 100 g of absorbent. The absorptive capacity of calcium hydroxide lime is significantly less and has been reported to be 10.2 L per 100 g of absorbent.[109,112] However, as mentioned previously, absorptive capacity is the product of both available chemical reactivity and physical (granule) availability. As the absorbent granules stack up in the absorber canisters, small passageways inevitably form. These small passages channel gases preferentially through low-resistance areas. Because of this phenomenon, the functional absorptive capacity of either soda lime or calcium hydroxide lime may be substantially decreased. In practice, as a result of channeling, the efficiency of soda lime may be reduced such that only 10 to 20 L or less of carbon dioxide can actually be absorbed per 100 g of absorbent.[114]

Indicators

Ethyl violet is the pH indicator added to both soda lime and calcium hydroxide lime to help assess the functional integrity of the absorbent. This compound is a substituted triphenylmethane dye with a critical pH of 10.3.[108] Ethyl violet changes from colorless to violet when the pH of the absorbent decreases as a result of carbon dioxide absorption. When the absorbent is fresh, the pH exceeds the critical pH of the indicator dye, and it exists in its colorless form (Fig. 25-26A). However, as absorbent becomes exhausted, the pH decreases below 10.3, and ethyl violet changes to its violet form (Fig. 25-26B) because of alcohol dehydration. This change in color indicates that the absorptive capacity of the material has been consumed. Unfortunately, in some circumstances ethyl violet may not always be a reliable indicator of the functional status of absorbent. For example, prolonged exposure of ethyl violet to fluorescent light can produce photodeactivation of this dye. When this occurs, the absorbent appears white even though it may have a reduced pH and its absorptive capacity has been exhausted.[115]

Some newer absorbent materials may also include indicators that reveal whether the material has become desiccated. Users should refer to the product manufacturers' literature to determine whether their absorbent material uses this type of indicator.

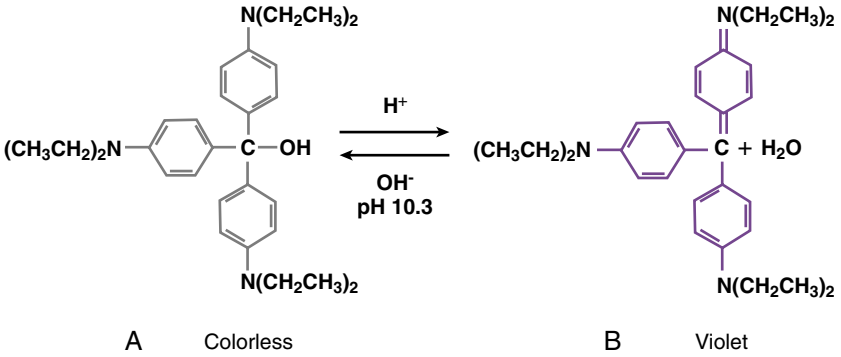


Figure 25-26 **A** and **B**, Ethyl violet. See text for details. *(Reprinted with permission from Andrews JJ, Johnston RV Jr, Bee DE, Arens JF: Photodeactivation of ethyl violet: A potential hazard of Sodasorb. Anesthesiology 72:59, 1990.)*

Interactions of Inhaled Anesthetics with Absorbents

It is important and desirable to have carbon dioxide absorbents that neither release toxic particles or fumes nor produce toxic compounds when exposed to common anesthetics. Soda lime and Baralyme generally fit this description, but inhaled anesthetics do interact with absorbents to some extent. Historically speaking, an uncommon anesthetic, trichloroethylene, reacts with soda lime to produce toxic compounds. In the presence of alkali and heat, trichloroethylene degrades into the cerebral neurotoxin dichloroacetylene, which can cause cranial nerve lesions and encephalitis. Phosgene, a potent pulmonary irritant, is also produced and can cause adult respiratory distress syndrome.[116]

Sevoflurane has been shown to produce degradation products upon interaction with carbon dioxide absorbents.[104,117,118] The major degradation product produced is an olefin compound known as fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether, or compound A. During sevoflurane anesthesia, factors apparently leading to an increase in the concentration of compound A include (1) low-flow or closed-circuit anesthetic techniques, (2) use of Baralyme rather than soda lime, (3) higher concentrations of sevoflurane in the anesthetic circuit, (4) higher absorbent temperatures, and (5) fresh absorbent.[117-120] Interestingly, dehydration of Baralyme increases the concentration of compound A, but dehydration of soda lime decreases the concentration of compound A.[121,122] Apparently, the degradation products released during clinical conditions do not commonly result in adverse effects in humans, even during low-flow anesthesia,[119] but further studies are needed to verify this observation.[123-125]

Desiccated strong-base absorbents can also degrade contemporary inhaled anesthetics to clinically significant concentrations of CO, as well as trifluoromethane, which can interfere with monitoring of anesthetic gases.[104] Under certain conditions, this process can produce very high carboxyhemoglobin concentrations that reach 35% or greater.[126] Higher levels of CO are more likely after prolonged contact between absorbent and anesthetics, as well as after disuse of an absorber for at least 2 days, especially over a weekend. Thus, case reports describing CO poisoning have been most common in patients anesthetized on Monday morning, presumably because continuous flow from the anesthesia machine dehydrated the absorbents over the weekend.[127,128] Fresh gas flow rates of 5 L/min or greater through the breathing system and absorbent (without a patient connected) are sufficient to cause critical drying of the absorbent material. The situation is even worse when the breathing bag is left off the breathing circuit. Absence of the reservoir bag facilitates retrograde flow through the circle system (see Fig. 25-7).[126] Because the inspiratory valve leaflet produces some resistance to flow, fresh gas flow takes the retrograde path of least resistance through the absorbent and out the 22-mm breathing bag mount.

Several factors appear to increase the production of CO and resultant elevated carboxyhemoglobin levels, including (1) the inhaled anesthetic used (for a given MAC multiple, the magnitude of CO production from greatest to least is desflurane ≥ enflurane > isoflurane >> halothane = sevoflurane), (2) dryness of the absorbent (completely dry absorbent produces more CO than hydrated absorbent does), (3) the type of absorbent (at a given water content, Baralyme produces more CO than soda lime does), (4) the temperature (increased temperature increases CO production), (5) the anesthetic concentration (more CO is produced with higher anesthetic concentrations),[129] (6) low fresh gas flow rates, and (7) reduced experimental animal (patient) size per 100 g of absorbent.[104,130]

Several interventions have been suggested to reduce the incidence of CO exposure in humans undergoing general anesthesia.[128] Such interventions include (1) educating anesthesia personnel regarding the cause of CO production; (2) turning off the anesthesia machine at the conclusion of the last case of the day to eliminate fresh gas flow, which dries the absorbent; (3) changing the CO absorbent if fresh gas is found to be flowing during the morning machine check; (4) rehydrating desiccated absorbent by adding water to the absorbent[112]; (5) changing the chemical composition of soda lime to reduce or eliminate potassium hydroxide (such products now available include Dragersorb 800 Plus, Sofnolime, and Spherasorb), and (6) using absorbent material that is free of both sodium and potassium hydroxide, such as calcium hydroxide lime. Elimination of sodium and potassium hydroxide from desiccated soda lime diminishes or eliminates degradation of desflurane to CO and sevoflurane to compound A, but it does not compromise carbon dioxide absorption.[110,131]

One extremely rare, but potentially life-threatening complication related to the carbon dioxide absorbent used is the development of fires within the breathing system. Specifically, this can occur as a result of interactions between the strong-base absorbents (particularly Baralyme) and the inhaled anesthetic sevoflurane. In August 2003, Abbott Laboratories changed the package insert for sevoflurane to describe this rare phenomenon and the conditions under which it could occur. Almost 1 year later, in autumn 2004, several case reports describing patient injuries related to this problem were published (all involving Baralyme). It seems that when desiccated strong-base absorbents are exposed to sevoflurane, absorber temperatures of several hundred degrees may result from their interaction.[102] The buildup of very high temperatures, the formation of combustible degradation byproducts (formaldehyde, methanol, and formic acid), and the oxygen- or nitrous oxide–enriched environment provide all the substrates necessary for a fire to occur.[104] Avoidance of use of the combination of sevoflurane with strong-base absorbents, particularly Baralyme and especially if it has become desiccated, is the best way to prevent this unusual, potentially life-threatening complication.

Anesthesia Ventilators

The ventilator on the modern anesthesia workstation serves as a mechanized substitute for the hand of the anesthesia care provider in manipulating the reservoir bag of the circle system, the Bain circuit, or another breathing system. As recently as the late 1980s, anesthesia ventilators were mere adjuncts to the anesthesia machine. Today, they have attained a prominent central role in newer anesthesia workstations. In addition to the nearly ubiquitous role of the anesthesia ventilator in today's anesthesia workstation, many advanced intensive care unit (ICU)-style ventilation features have also been integrated into anesthesia ventilators (Fig. 25-27). Anesthesia care providers should be aware that even though more similarities exist between today's anesthesia ventilator and the ICU ventilator than ever before, some fundamental differences in ventilation parameters and control systems still

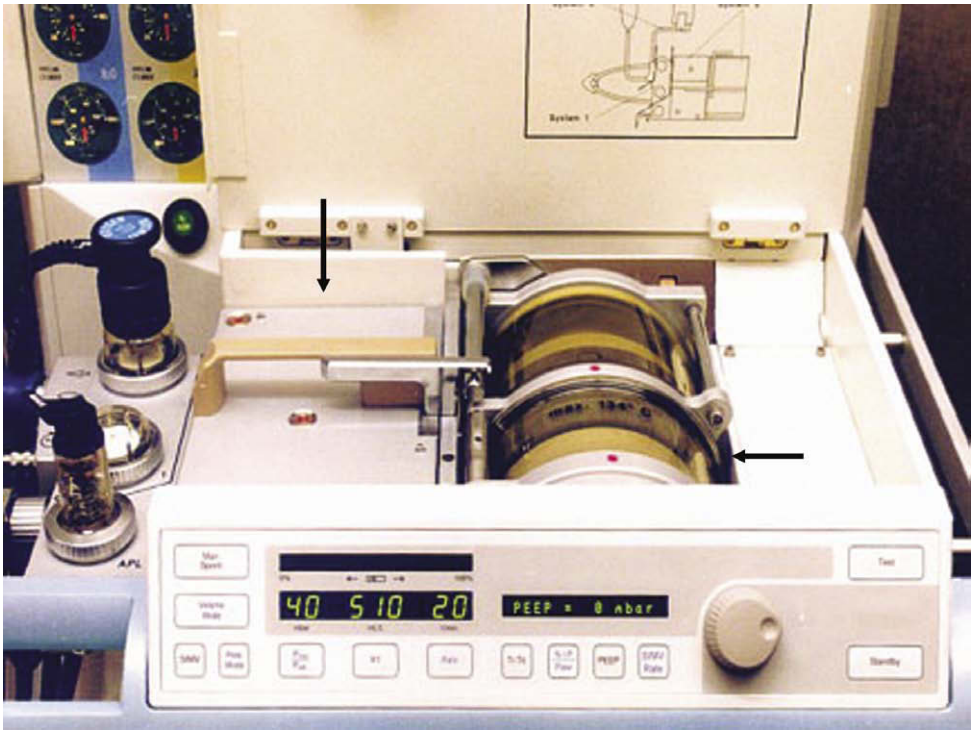


Figure 25-27 The Dräger Medical Narkomed 6000 with its single-circuit ventilator. The *horizontal arrow* indicates the piston cylinder unit of the Divan ventilator. The *vertical arrow* indicates the rectangular valve manifold for fresh gas decoupling.

remain. This discussion focuses on the classification, operating principles, and hazards associated with contemporary anesthesia ventilators.

Classification

Ventilators can be classified according to their power source, drive mechanism, cycling mechanism, and type of bellows.[132,133] The following sections review ventilator classification and terminology before the discussion of specific anesthesia workstation ventilators.

Power Source

The power source required to operate a mechanical ventilator is provided by compressed gas, electricity, or both. Older pneumatic ventilators required only a pneumatic power source to function properly. Contemporary electronic ventilators from Dräger Medical, Datex-Ohmeda, and others require either an electrical-only or both an electrical and a pneumatic power source.

Drive Mechanism and Circuit Designation

Double-circuit ventilators are most commonly used on modern anesthesia workstations. Generally, these conventional ventilators are pneumatically driven. In a double-circuit ventilator, a driving force such as pressurized gas compresses a component analogous to the reservoir bag known as the ventilator bellows. The bellows then in turn delivers ventilation to the patient. The driving gas in the Datex-Ohmeda 7000, 7810, 7100, and 7900 is 100% oxygen. In the North American Dräger AV-E and AV-2+, a venturi device mixes oxygen and air. Some newer pneumatic anesthesia workstations enable the user to select whether compressed air or oxygen is used as the driving gas.

In recent years, with the introduction of circle breathing systems that integrate fresh gas decoupling, a resurgence in the use of mechanically driven anesthesia ventilators has occurred. These "piston"-type ventilators use a computer-controlled stepper motor instead of compressed drive gas to actuate gas movement in the breathing system. In these systems, rather than having dual circuits with patient gas in one and drive gas in another, a single patient gas circuit is present. Thus, they are classified as piston-driven single-circuit ventilators. The piston operates much like the plunger of a syringe to deliver the desired tidal volume or airway pressure to the patient. Sophisticated computerized controls are able to provide advanced types of ventilatory support such as synchronized intermittent mandatory ventilation (SIMV), pressure-controlled ventilation (PCV), and pressure-support assisted ventilation, in addition to the conventional control-mode

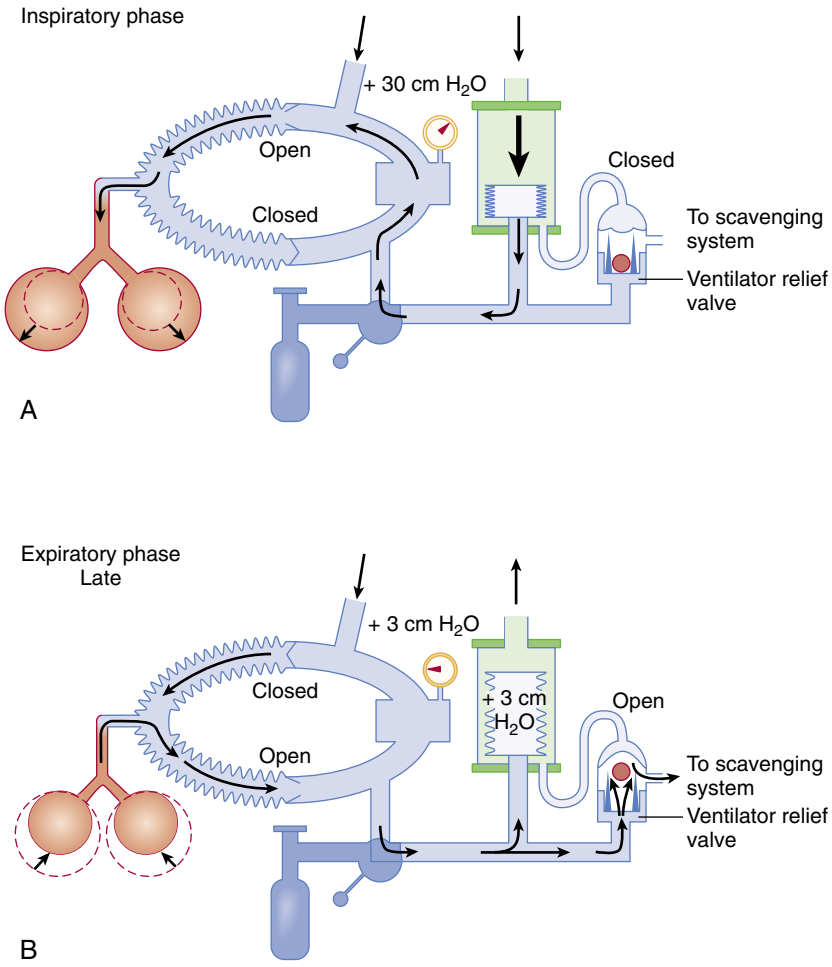
ventilation. Because the patient's mechanical breath is delivered without the use of compressed gas to actuate a bellows, these systems consume dramatically less compressed gas during ventilator operation than traditional pneumatic ventilators do. This improvement in efficiency may have clinical significance when the anesthesia workstation is used in a setting where no pipeline gas supply is available (e.g., remote locations or office-based anesthesia practices).

Cycling Mechanism

Most anesthesia machine ventilators are time cycled and provide ventilator support in the control mode. The inspiratory phase is initiated by a timing device. Older pneumatic ventilators use a fluidic timing device. Contemporary electronic ventilators use a solid-state electronic timing device and are thus classified as time cycled and electronically controlled. More advanced ventilation modes such as SIMV, PCV, and modes that use a pressure-support option may have an adjustable threshold pressure trigger as well. In these modes, pressure sensors provide feedback to the ventilator control system to allow it to determine when to initiate or terminate the respiratory cycle.

Bellows Classification

The direction of bellows movement during the *expiratory phase* determines the bellows classification. Ascending (standing) bellows ascend during the expiratory phase (Fig. 25-28B), whereas descending (hanging) bellows descend during the expiratory phase. Older pneumatic ventilators and some new anesthesia workstations use weighted descending bellows, but most contemporary electronic ventilators have an ascending bellows design. Of the two configurations, the ascending bellows is generally safer. An ascending bellows will not fill if a total disconnection occurs. However, the bellows of a descending bellows ventilator will continue its upward and downward movement despite patient disconnection. The driving gas pushes the bellows upward during the inspiratory phase. During the expiratory phase, room air is entrained into the breathing system at the site of the disconnection because gravity acts on the weighted bellows. The disconnection pressure monitor and the volume monitor may be fooled even if a disconnection is complete (see "Breathing Circuit Problems").[33] Some contemporary anesthesia workstation designs have returned to the descending bellows to integrate fresh gas decoupling (Dräger Medical Julian and Datascope Anestar). An



Figures 25-28 Inspiratory (**A**) and expiratory (**B**) phases of gas flow in a traditional circle system with an ascending bellows ventilator. The bellows physically separates the driving gas circuit from the patient gas circuit. The driving gas circuit is located outside the bellows, and the patient gas circuit is inside the bellows. During the inspiratory phase (**A**), the driving gas enters the bellows chamber, which causes the pressure within it to increase. This causes the ventilator relief valve to close, thereby preventing anesthetic gas from escaping into the scavenging system, and the bellows to compress, thereby delivering anesthetic gas within the bellows to the patient's lungs. During the expiratory phase (**B**), pressure within the bellows chamber and the pilot line decreases to zero, which causes the mushroom portion of the ventilator relief valve to open. Gas exhaled by the patient refills the bellows before any scavenging occurs because a weighted ball is incorporated into the base of the ventilator relief valve. Scavenging occurs only during the expiratory phase because the ventilator relief valve is open just during expiration. *(Reprinted with permission from Andrews JJ: The Circle System. A Collection of 30 Color Illustrations. Washington, DC, Library of Congress, 1998.)*

essential safety feature on any anesthesia workstation that uses a descending bellows is an integrated CO_2 apnea alarm that cannot be disabled while the ventilator is in use.

Operating Principles of Ascending Bellows Ventilators

Contemporary examples of ascending bellows, double-circuit, electronic ventilators include the Dräger Medical AV-E and AV-2+ and the Datex-Ohmeda 7000, 7800, and 7900 series. A generic ascending bellows ventilator is illustrated in Figure 25-28. It may be viewed as a breathing bag (bellows) located within a clear plastic box. The bellows physically separates the driving gas circuit from the patient gas circuit. The driving gas circuit is located outside the bellows, and the patient gas circuit is inside the bellows. During the inspiratory phase (see Fig. 25-28A), the driving gas enters the bellows chamber, which causes the pressure within it to increase. This increase in pressure is responsible for two events. First, the ventilator relief valve closes, thereby preventing anesthetic gas from escaping into the scavenging system. Second, the bellows is compressed, and the anesthetic gas within the bellows is delivered to the patient's lungs. This compression action is analogous to the hand of the anesthesiologist squeezing the breathing bag.[48]

During the expiratory phase (see Fig. 25-28B), the driving gas exits the bellows housing. This produces a drop to atmospheric pressure within both the bellows housing and the pilot line to the ventilator relief valve. The decrease in pressure to the ventilator relief valve causes the "mushroom valve" portion of the assembly to open. Exhaled patient gases refill the bellows before any scavenging can begin. The bellows refills first because a weighted ball (like those used in ball-type positive end-expiratory pressure [PEEP] valves) or similar device is incorporated into the base of the ventilator relief valve. Because this ball produces 2 to 3 cm H_2O of backpressure, scavenging occurs only after the bellows fills completely and the pressure inside the bellows exceeds the pressure threshold of the "ball valve." This design causes all ascending bellows ventilators to produce 2 to 3 cm H_2O of PEEP within the breathing circuit when the ventilator is in use. Scavenging occurs just during the expiratory phase because the ventilator relief valve is open only during expiration.[47]

It is important for anesthesia care providers to understand that on most anesthesia workstations, gas flow from the anesthesia machine into the breathing circuit is continuous and independent of ventilator activity. During the inspiratory phase of mechanical ventilation, the ventilator relief valve is closed (see Fig. 25-28A), and the breathing system's APL valve (pop-off valve) is most commonly out of circuit. Therefore, the patient's lungs receive the volume from the bellows plus that from the flow meters during the inspiratory phase. Factors that influence the correlation between set tidal volume and exhaled tidal volume include the flow meter settings, inspiratory time, compliance of the breathing circuit, external leakage, and the location of the tidal volume sensor. Usually, the volume gained from the flow meters during inspiration is counteracted by the volume lost to compliance of the breathing circuit, and the set tidal volume generally approximates the exhaled tidal volume. However, certain conditions such as inappropriate activation of the oxygen flush valve during the inspiratory phase can result in barotrauma or volutrauma (or both) because excess pressure and volume may not be able to be vented from the circle system.[47]

Problems and Hazards

Numerous hazards are associated with anesthesia ventilators, including problems with the breathing circuit, the bellows assembly, and the control assembly.

Traditional Circle System Problems

Breathing circuit misconnections and disconnection are a leading cause of critical incidents in anesthesia.[1,134] The most common disconnection site is at the Y-piece. Disconnections can be complete or partial (leaks). In the past, a common source of leaks with older absorbers was failure to close the APL valve (or pop-off valve) on initiation of mechanical ventilation. On today's anesthesia workstations, the bag/ventilator selector switch has virtually eliminated this problem because the APL valve is usually out of circuit when the ventilator mode is selected. Preexisting undetected leaks can exist in compressed, corrugated, disposable anesthetic circuits. To detect such a leak preoperatively, the circuit must be fully expanded before being checked for leaks.[135] As mentioned previously, disconnections and leaks are manifested more readily with the ascending bellows ventilator systems because they result in a situation in which the bellows will not refill.[33]

Several disconnection monitors exist. The most important monitor is a vigilant anesthesia care provider monitoring breath sounds and chest wall excursion in addition to both the mechanical (spirometers and pressure sensors) and physiologic monitors.

Pneumatic and electronic pressure monitors are helpful in diagnosing disconnections. Factors that influence monitor effectiveness include the disconnection site, the location of the pressure sensor, the threshold pressure alarm limit, the inspiratory flow rate, and the resistance of the disconnected breathing circuit.[136,137] Various anesthesia workstations and ventilators have different locations for the airway pressure sensor and different values for the threshold pressure alarm limit. The threshold pressure alarm limit may be preset at the factory or may be adjustable. An audible or visual alarm is actuated if the peak inspiratory pressure of the breathing circuit does not exceed the threshold pressure alarm limit. When an adjustable threshold pressure alarm limit is available, such as on many workstations from Dräger Medical, the operator should set the pressure alarm limit to within 5 cm H_2O of the peak inspiratory pressure. On systems that have an "autoset" feature, when activated, the threshold limit is automatically set at 3 to 5 cm H_2O pressure below the current peak inspiratory pressure. On such systems, failure to reset the threshold pressure alarm limit may result in either an "apnea pressure" or "threshold low" alert. Figure 25-29 illustrates how a partial disconnection (leak) may be unrecognized by the low-pressure monitor if the threshold pressure alarm limit is set too low or the factory preset value is relatively low.

Respiratory volume monitors are useful in detecting disconnections. Volume monitors may sense exhaled tidal volume, inhaled tidal volume, minute volume, or all three. The user should bracket the high and low threshold volumes slightly above and below the exhaled volumes. For example, if the exhaled minute volume of a patient is 10 L/min, reasonable alarm limits would

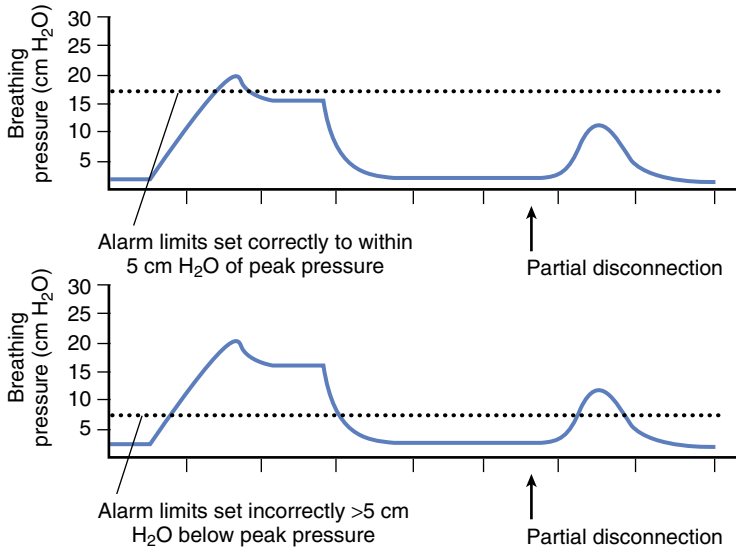


Figure 25-29 Threshold pressure alarm limit. **Top,** The threshold pressure alarm limit (*dotted line*) has been set appropriately. An alarm is actuated when a partial disconnection occurs (*arrow*) because the threshold pressure alarm limit is not exceeded by the breathing circuit pressure. **Bottom,** A partial disconnection is unrecognized by the pressure monitor because the threshold pressure alarm limit has been set too low. *(Redrawn with permission from Baromed Breathing Pressure Monitor. Operator's Instruction Manual. Telford, PA, North American Dräger, August 1986.)*

be 8 to 12 L/min. Many Datex-Ohmeda ventilators are equipped with volume monitor sensors that use infrared light/turbine technology. These volume sensors are usually located in the expiratory limb of the breathing circuit and thus measure exhaled tidal volume. In the case of the Datex-Ohmeda S/5 ADU, a special attachment known as the D-Lite spirometry connector is placed in the breathing circuit. This device is actually placed at or near the level of the patient connection and permits measurement of both inhaled and exhaled volume and pressure (see "Anesthesia Workstation Variations"). With the older infrared-type sensors, exposure to a direct beam of light from the overhead surgical lighting could cause erroneous volume readings if the surgical beam interferes with the infrared sensor.[138] Other types of expiratory volume sensors can be seen in systems such as the Datex-Ohmeda Aestiva, Aespire, and other workstations that incorporate the 7100 ventilator or 7900 SmartVent. These systems generally use differential pressure transduction technology to determine inhaled and exhaled volume, as well as to measure airway pressure. The Dräger Medical Narkomed 6000 series, 2B, and GS workstations commonly use an ultrasonic flow sensor located on the expiratory limb. Still other systems from Dräger measure exhaled volume with "hot-wire" sensor technology. With this type of sensor, a tiny array of two platinum wires is electrically heated to a high temperature. As gas flows past the heated wires, they tend to be cooled. The amount of energy required to maintain the temperature of the wire is proportional to the volume of gas flowing past it. This system has been associated in at least one report with accidental development of a fire in the breathing circuit.[103]

Carbon dioxide monitors are probably the best devices for revealing patient disconnections. The carbon dioxide concentration is measured near the Y-piece either directly (mainstream) or by aspiration of a gas sample to the instrument (sidestream). Either a sudden change in the difference between inspiratory and end-tidal carbon dioxide concentration or the acute absence of measured carbon dioxide indicates a disconnection, a nonventilated patient, or other problems.[33]

Misconnections of the breathing system are unfortunately not uncommon. Despite the efforts of standards committees to eliminate this problem by assigning different diameters to various hoses and hose terminals, they continue to occur. Anesthesia workstations, breathing systems, ventilators, and scavenging systems incorporate many of these diameter-specific connections. The ingenuity of anesthesia care providers in outwitting these "foolproof" systems has led to various hoses being cleverly adapted or forcefully fitted to inappropriate terminals and even to various other solid cylindrically shaped protrusions of the anesthesia machine.[33]

Occlusion (obstruction) of the breathing circuit may occur. Tracheal tubes can become kinked. Hoses throughout the breathing circuit are subject to occlusion by internal obstruction or external mechanical forces that can impinge on flow and have severe consequences. For example, blockage of a bacterial filter in the expiratory limb of the circle system has resulted in bilateral tension pneumothorax.[97] Incorrect insertion of flow direction–sensitive components can result in a no-flow state.[33] Examples of these components include some PEEP valves and cascade humidifiers. Depending on the location of the occlusion relative to the pressure sensor, a high-pressure alarm may alert the anesthesiologist to the problem.

Excess inflow to the breathing circuit from the anesthesia machine during the inspiratory phase can cause barotrauma. The best example of this phenomenon is oxygen flushing. Excess volume cannot be vented from the system during inspiration because the ventilator relief valve is closed and the APL valve is out of circuit.[47] A high-pressure alarm, if present, may be activated when the pressure becomes excessive. With many Dräger Medical systems, both audible and visual alarms are actuated when the high-pressure threshold is exceeded. In the Modulus II Plus System, the Datex-Ohmeda 7810 ventilator automatically switches from the inspiratory to the expiratory phase when the adjustable peak pressure threshold is exceeded.

On workstations equipped with adjustable inspiratory pressure limiters (e.g., the Datex-Ohmeda S/5 ADU and Aestiva and the Dräger Medical Narkomed 6000 series, 2B, 2C, GS, and Fabius GS), maximal inspiratory pressure may be set by the user to a desired peak airway pressure. An adjustable pressure relief valve will open when the predetermined user-selected pressure is reached. This theoretically prevents the generation of excessive airway pressure. Unfortunately, this feature is dependent on the

user having preset the appropriate "pop-off" pressure. If the setting is too low, insufficient pressure for ventilation may be generated and result in inadequate minute ventilation; if set too high, the excessive airway pressure may still occur and result in barotrauma. The piston-driven Fabius GS, as well as others, may also include a factory-preset inspiratory pressure safety valve that opens at a preset airway pressure, such as 75 cm H_2O, to minimize the risk of barotrauma. These strategies may reduce the risk of barotrauma and volutrauma; however, they are no substitute for vigilance of the anesthesia care provider.

Bellows Assembly Problems

Leaks can occur in the bellows assembly. Improper seating of the plastic bellows housing can result in inadequate ventilation because a portion of the driving gas is vented to the atmosphere. A hole in the bellows can lead to alveolar hyperinflation and possibly barotrauma in some ventilators because high-pressure driving gas can enter the patient circuit. The oxygen concentration of the patient gas may increase when the driving gas is 100% oxygen, or it may decrease if the driving gas is composed of an air-oxygen mixture.[139]

The ventilator relief valve can cause problems. Hypoventilation occurs if the valve is incompetent because anesthetic gas is delivered to the scavenging system during the inspiratory phase instead of to the patient. Gas molecules preferentially exit into the scavenging system because it represents the path of least resistance, and the pressure within the scavenging system can be subatmospheric. Ventilator relief valve incompetency can result from a disconnected pilot line, a ruptured valve, or a damaged flapper valve.[140,141] A ventilator relief valve stuck in the closed or partially closed position can produce either barotrauma or undesired PEEP.[142] Excessive suction from the scavenging system can draw the ventilator relief valve to its seat and close the valve during both the inspiratory and expiratory phases.[33] In this case, breathing circuit pressure escalates because the excess anesthetic gas cannot be vented. It is worthwhile to note that during the expiratory phase, some newer machines from Datex-Ohmeda (S/5 ADU, 7100 and 7900 SmartVent) scavenge both excess patient gas and the exhausted ventilator drive gas. That is, when the ventilator relief valve opens and waste anesthetic gases are vented from the breathing circuit, the drive gas from the bellows housing joins with it to enter the scavenging system. Under certain conditions, the large volume of exhaust gases could overwhelm the scavenging system and result in pollution of the operating room with waste anesthetic gases (see "Scavenging Systems"). Other mechanical problems that can occur include leaks within the system, faulty pressure regulators, and faulty valves. Unlikely problems such as an occluded muffler on the Dräger AV-E ventilator can result in barotrauma. In this case, obstruction of driving gas outflow closes the ventilator relief valve, and excess patient gas cannot be vented.[143]

Control Assembly and Power Supply Problems

The control assembly can be the source of both electrical and mechanical problems. Electrical failure can be total or partial; the former is the more obvious. As anesthesia workstations are becoming more dependent on integrated computer-controlled systems, power interruptions become more significant. Battery backup systems are designed to continue operation of essential electronics during brief outages (up to several hours). However, even with these systems, in the event of a failure some time may be required for "rebooting" after an electrical outage has occurred. During this time the availability of certain workstation features such as manual or mechanical ventilation can be variable. One cluster of electrical failures that could have potentially resulted in operating room fires was reported early after release of the Dräger Medical Narkomed 6000. Problems with the workstation's power supply printed circuit boards prompted a corrective recall action in November 2002.[144]

Anesthesia Workstation Variations

With the introduction of new technology often comes the need for adaptation of current technology to successfully allow its integration into existing systems. Otherwise, a more comprehensive redesign of an entire anesthesia system from the ground up could be necessary. One such example of adaptation in the anesthesia workstation can be seen with two new design variations of the circle breathing system. The first of these is found on the Datex-Ohmeda S/5 ADU (see Fig. 25-1), and the second is incorporated into the Dräger Narkomed 6000 series (see Fig. 25-2) and Fabius GS workstations. Because use of the circle system is fundamental to day-to-day practice for most anesthesiologists, a comprehensive understanding of these new systems is crucial for their safe use.

The Datex-Ohmeda S/5 ADU

The Datex-Ohmeda S/5 ADU (see Fig. 25-1) debuted as the AS/3 ADU in 1998. Along with its more comprehensive safety features and integrated design that eliminated glass flow tubes and conventional anesthesia vaporizers in exchange for a computer screen with digital fresh gas flow scales and the built-in Aladin Cassette vaporizer system, the machine had a radically different appearance in general. It is not until closer inspection that the other unique properties of the ADU begin to stand out. The principal difference in the ADU's circle system lies in incorporation of the specialized "D-lite" flow and pressure transducer fitting into the circle at the level of the Y-connector. On most traditional circle systems, exhaled tidal volume is measured by a spirometry sensor located in proximity to the expiratory valve. Placement of the D-lite fitting at the Y-connector provides a better location for measuring exhaled volume, allows monitoring of airway gas composition and pressure to be done with a single adapter instead of with multiple fittings added to the breathing circuit, and provides the ability to assess both inspiratory and expiratory gas flow and therefore the generation of complete flow-volume spirometry. Relocation of the spirometer sensor to the Y-connector also makes it possible to move the location of the fresh gas inlet to the "patient" side of the inspiratory valve without adversely affecting the accuracy of exhaled tidal volume measurement.

This atypical circle system arrangement with the fresh gas entering on the patient side of the inspiratory valve is advantageous for several reasons. It is likely to be more efficient in delivering fresh gas to the patient while preferentially eliminating exhaled gases. Importantly, it is also less likely to cause desiccation of the carbon dioxide absorbent (see "Interactions of Inhaled

Anesthetics with Absorbents"). Other notable changes on the S/5 ADU circle system include a compact proprietary carbon dioxide absorbent canister design that can be changed during ventilation without loss of circle system integrity, as well as relocation of the inspiratory and expiratory unidirectional valves from a horizontal position to a vertical position on the "compact block" assembly just below the absorbent canister. Reorientation of the unidirectional valves reduces the breathing circuit resistance encountered by a spontaneously ventilated patient. The vertically oriented unidirectional valves only have to be tipped away from the vertical position to be opened, unlike conventional horizontal valve disks, which have to be physically lifted off the valve seat against gravity to be opened.

The Dräger Medical Narkomed 6000 Series and Fabius GS

Several important differences exist between the traditional circle breathing systems of the newest Dräger products. At first glance, the most notable difference lies in the appearance and design of the ventilators used with these systems. From the inconspicuous horizontally mounted Divan piston ventilator of the Narkomed 6000 series (see Fig. 25-2) to the vertically mounted and visible piston ventilator of the Fabius GS with its absent flow tubes and glowing electronic fresh gas flow indicators, these systems appear drastically different from traditional anesthesia systems. The piston ventilator of the Dräger Narkomed 6000 and Fabius GS anesthesia systems may be classified as electrically powered, piston driven, single circuit, electronically controlled with fresh gas decoupling.

The circle breathing systems used by these Dräger workstations incorporate a feature known as *fresh gas decoupling* (FGD). Incorporation of this patient safety–enhancing technology has required a significant redesign of the traditional circle system. A functional schematic of a circle system similar to the one used by the Dräger Narkomed 6000 series during both the inspiratory and expiratory phases of mechanical ventilation can be seen in Figure 25-30A and B. To understand the operating principles of FGD, it is important to have a good understanding of gas flow in a traditional circle system during both the inspiratory and expiratory phases of mechanical ventilation. A complete discussion of this subject was presented earlier in the section "Operating Principals of Ascending Bellows Ventilators."

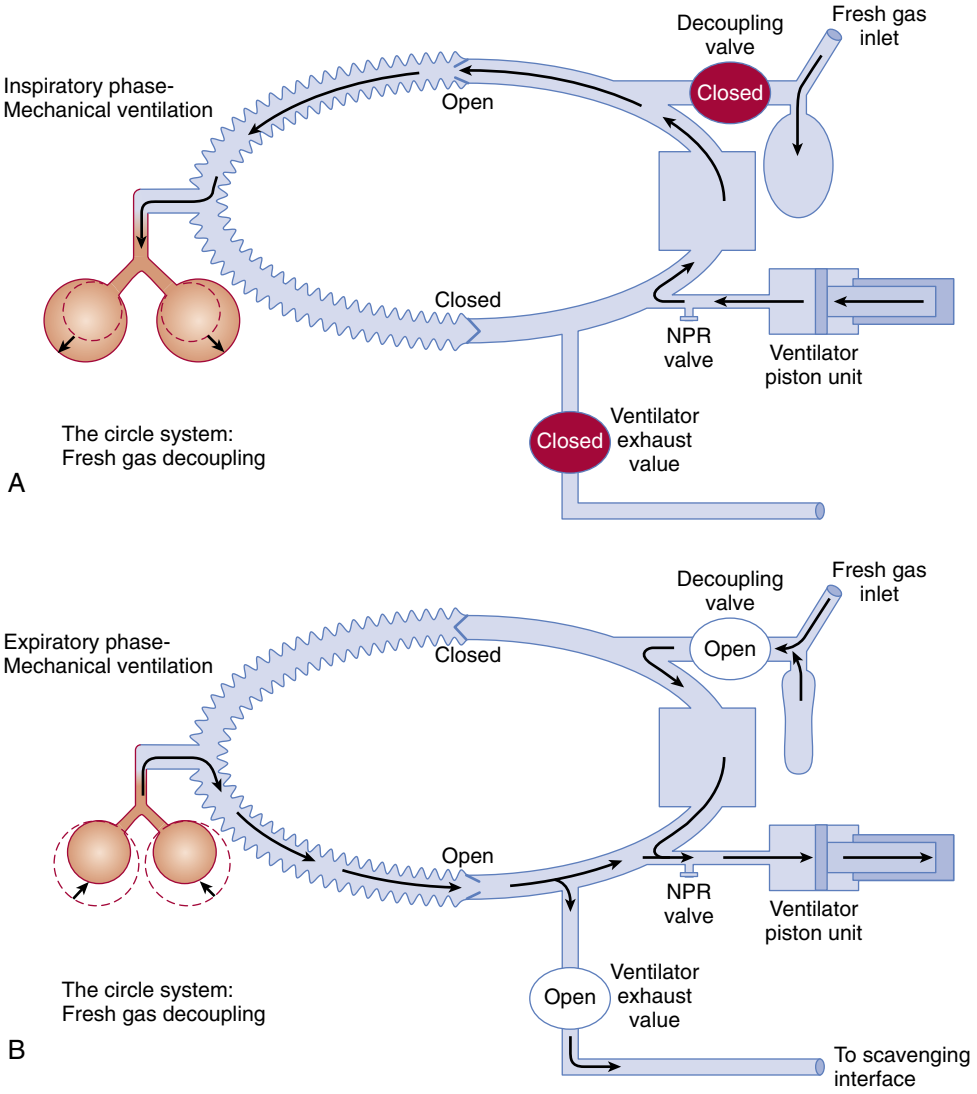
The key concept of the FGD breathing system can be illustrated during the inspiratory phase of mechanical ventilation. With the traditional circle system, several events are occurring (see Fig. 25-28A): (1) continuous fresh gas flow from the flow meters or the oxygen flush valve, or from both, is entering the circle system at the fresh gas inlet; (2) the ventilator is delivering the prescribed tidal volume to the patient's lungs; and (3) the ventilator relief valve (ventilator exhaust valve) is closed, so no gas is escaping the circle system except into the patient's lungs.[145] In a traditional circle system, when these events coincide and fresh gas inflow is coupled directly into the circle system, the total volume delivered to the patient's lungs is the sum of the volume from the ventilator plus the volume of gas that enters the circle via the fresh gas inlet. In contrast, when FGD is used, during the inspiratory phase (see Fig. 25-30A) the fresh gas coming from the anesthesia workstation via the fresh gas inlet is diverted into the reservoir bag by a decoupling valve located between the fresh gas source and the ventilator circuit. The reservoir (breathing) bag serves as an accumulator for fresh gas until the expiratory phase begins. During the expiratory phase (see Fig. 25-30B), the decoupling valve opens to allow the accumulated fresh gas in the reservoir bag to be drawn into the circle system to refill the piston ventilator chamber or descending bellows. Because the ventilator exhaust valve also opens during the expiratory phase, excess fresh gas and exhaled patient gas are allowed to escape to the scavenging system.

Current FGD systems are designed with either piston-type or descending bellows–type ventilators. Because the bellows in either of these types of systems refills under slight negative pressure, the accumulated fresh gas from the reservoir bag can be drawn into the ventilator for delivery to the patient during the next ventilator cycle. As a result of this design requirement, it is unlikely that FGD, as described here, can be used with conventional ascending bellows ventilators, which refill under slight positive pressure.

The most significant advantage of circle systems using FGD is a decreased risk for barotrauma and volutrauma. With a traditional circle system, increases in fresh gas flow from the flow meters or from inappropriate use of the oxygen flush valve may contribute directly to tidal volume, which if excessive, may result in pneumothorax or other injury. Because systems with FGD isolate fresh gas coming into the system from the patient while the ventilator exhaust valve is closed, the risk of barotrauma is greatly reduced.

Possibly the greatest disadvantage of the new anesthesia circle systems that use FGD is the possibility of entraining room air into the patient gas circuit. As discussed previously, in an FGD system the bellows or piston refills under slight negative pressure. If the volume of gas contained in the reservoir bag volume plus the returning volume of gas exhaled from the patient's lungs is inadequate to refill the bellows or piston, negative patient airway pressure could develop. To prevent this problem, a negative pressure relief valve is placed in the breathing system (see Fig. 25-30A and B). If breathing system pressure falls below a preset value, such as −2 cm H_2O, the relief valve opens and ambient air is entrained into the patient gas circuit. If this goes undetected, the entrained atmospheric gases could lead to dilution of either or both the inhaled anesthetic agents and the enriched oxygen mixture (lowering the enriched oxygen concentration toward 21%). If unchecked, this could lead to either intraoperative awareness or hypoxia. High-priority alarms with both audible and visual alerts should notify the user that fresh gas flow is inadequate and room air is being entrained.

Another potential problem with an FGD system such as seen on the Narkomed 6000 series lies in its reliance on the reservoir bag to accumulate the incoming fresh gas. If the reservoir bag is removed during mechanical ventilation or if it has a significant leak from poor fit on the bag mount or a perforation, room air may enter the breathing circuit as the ventilator piston unit refills during the expiratory phase. This may also result in dilution of either or both the inhaled anesthetic agents and the enriched oxygen mixture and potentially result in awareness during anesthesia or hypoxia. Furthermore, this type of a disruption could lead to significant pollution of the operating room with anesthetic gases because fresh gases would be allowed to escape into the atmosphere. Other FGD designs, such as those seen in the Dräger Medical Fabius GS and the soon to be released Apollo



Figures 25-30 **A** and **B,** Inspiratory- and expiratory-phase gas flows of a Dräger Narkomed 6000 circle system with a piston ventilator and fresh gas decoupling. NPR valve, negative-pressure relief valve. See text for details. *(Reprinted with permission from Andrews JJ: The Circle System. A Collection of 30 Color Illustrations. Washington, DC, Library of Congress, 1998.)*

anesthesia systems, do not use the breathing bag as the fresh gas reservoir but instead have an alternative location for accumulation of fresh gas during the inspiratory phase.

Scavenging Systems

Scavenging is the collection and subsequent removal of waste anesthetic gases from the operating room.[146] In most cases, the amount of gas used to anesthetize a patient for a given anesthetic far exceeds the minimal amount needed. Therefore, scavenging minimizes operating room pollution by removing this excess of gases. In 1977, the National Institute for Occupational Safety and Health (NIOSH) prepared a document titled "Criteria for a Recommended Standard: Occupational Exposure to Waste Anesthetic Gases and Vapors."[147] Although it was maintained that a minimal safe level of exposure could not be defined, the NIOSH proceeded to issue the recommendations shown in Table 25-5.[147] In 1991, ASTM released the ASTM F1343-91 standard titled "Standard Specification for Anesthetic Equipment—Scavenging Systems for Anesthetic Gases."[148] The document provided guidelines for devices that safely and effectively scavenge waste anesthetic gases to reduce contamination in anesthetizing areas.[148] In 1999 the ASA Task Force on Trace Anesthetic Gases developed a booklet titled "Waste Anesthetic Gases: Information for Management in Anesthetizing Areas and the Postanesthesia Care Unit." This publication addresses analysis of the literature, the role of regulatory agencies, scavenging and monitoring equipment, and recommendations.[149]

The two major causes of waste gas contamination in the operating room are the anesthetic technique used and equipment issues.[149,150] Regarding the anesthetic technique, the following factors cause operating room contamination: (1) failure to turn off the gas flow control valves at the end of an anesthetic procedure, (2) poorly fitting masks, (3) flushing the circuit, (4) filling

Table 25-5 NIOSH Recommendations for Trace Gas Levels

Anesthetic Gas	Maximum TWA Concentration (ppm)
Halogenated agent alone	2
Nitrous oxide	25
Combination of halogenated agent plus nitrous oxide	
Halogenated agent	0.5
Nitrous oxide	25
Dental facilities (nitrous oxide alone)	50

Time-weighted average (TWA) sampling, also known as time-integrated sampling, is a sampling method that evaluates the average concentration of anesthetic gas over a prolonged period, such as 1 to 8 hours.
NIOSH, National Institute for Occupational Safety and Health.
Reprinted with permission from US Department of Health, Education, and Welfare: Criteria for a Recommended Standard: Occupational Exposure to Waste Anesthetic Gases and Vapors. Washington DC, US Department of Health, Education, and Welfare, March 1977.

anesthetic vaporizers, (5) use of uncuffed endotracheal tubes, and (6) use of breathing circuits that are difficult to scavenge, such as the Jackson-Rees. Equipment failure or lack of understanding of proper equipment use can also contribute to operating room contamination. Leaks can occur in the high-pressure hoses, the nitrous oxide tank mounting, the high- and low-pressure circuits of the anesthesia machine, or the circle system, particularly at the carbon dioxide absorber assembly. The anesthesia care provider must be certain that the scavenging system is operational and adjusted properly to ensure adequate scavenging. If sidestream carbon dioxide or multigas analyzers are used, the analyzed gas (50 to 250 mL/min) must be directed to the scavenging system or returned to the breathing system to prevent pollution of the operating room.[149,150]

Components

Scavenging systems generally have five components (Fig. 25-31): (1) the gas-collecting assembly, (2) the transfer means, (3) the scavenging interface, (4) the gas disposal assembly tubing, and (5) an active or passive gas disposal assembly.[148] An "active system" uses a central evacuation system to eliminate waste gases. The "weight" or pressure of the waste gas itself produces flow through a "passive system."

Gas-Collecting Assembly

The gas-collecting assembly captures excess anesthetic gas and delivers it to the transfer tubing.[133] Waste anesthetic gases are vented from the anesthesia system either through the adjustable pressure-limiting (APL) valve or through the ventilator relief valve. All excess patient gas is either vented into the room (e.g., from a poor facemask fit or endotracheal tube leak) or exits the breathing system through one of these valves. Gas passing through these valves accumulates in the gas-collecting assembly and is directed to the transfer means. In some newer Datex-Ohmeda systems such as the S/5 ADU and others that incorporate either the 7100 or 7900 ventilators, the ventilator drive gas is also exhausted into the scavenging system. This is significant because under conditions of high fresh gas flow and high minute ventilation, the gases flowing into the scavenging interface may overwhelm the evacuation system. If this occurs, waste anesthetic gases may overflow the system via the positive-pressure relief valve (closed systems) or through the atmospheric vents (open systems) and pollute the operating room. In contrast, most other pneumatic ventilators from both Datex-Ohmeda and Dräger exhaust their drive gas (100% oxygen or oxygen/air mixture) into the operating room through a small vent on the back of the ventilator control housing.

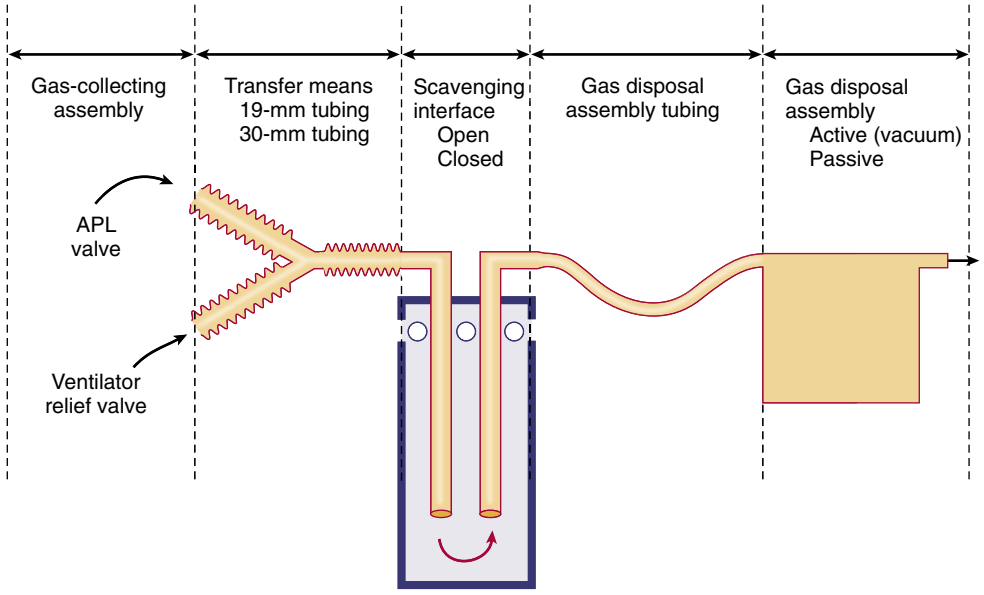


Figure 25-31 Components of a scavenging system. APL valve, adjustable pressure-limiting valve. *(Reproduced with permission from Brockwell RC: Delivery systems for inhaled anesthesia.* In *Barash PG [ed]: Clinical Anesthesia, 5th ed. Philadelphia, Lippincott Williams & Wilkins, 2006, p 589.)*

Transfer Means

The transfer means carries excess gas from the gas-collecting assembly to the scavenging interface. The tubing must be either 19 or 30 mm, as specified by the ASTM F1343-91 standard.[148] The tubing should be sufficiently rigid to prevent kinking and as short as possible to minimize the chance of occlusion. Some manufacturers color-code the transfer tubing with yellow bands to distinguish it from 22-mm breathing system tubing. Many machines have separate transfer tubes for the APL valve and for the ventilator relief valve. The two tubes frequently merge into a single hose before they enter the scavenging interface. Occlusion of the transfer means can be particularly problematic because it is upstream from the pressure-buffering features of the scavenging interface. If the transfer means is occluded, baseline breathing circuit pressure will increase and barotrauma can occur.

Scavenging Interface

The scavenging interface is the most important component of the system because it protects the breathing circuit or ventilator from excessive positive or negative pressure.[146] The interface should limit the pressure immediately downstream from the gas-collecting assembly to between −0.5 and +10 cm H_2O under normal working conditions.[148] Positive-pressure relief is mandatory, irrespective of the type of disposal system used, to vent excess gas in case of occlusion downstream from the interface. If the disposal system is an "active" system, negative-pressure relief is necessary to protect the breathing circuit or ventilator from excessive subatmospheric pressure. A reservoir is highly desirable with active systems because it stores waste gases until the evacuation system can remove them. Interfaces can be open or closed, depending on the method used to provide positive- and negative-pressure relief.[146]

Open Interfaces An open interface contains no valves and is open to the atmosphere, thereby allowing both positive- and negative-pressure relief. Open interfaces should be used only with active disposal systems that have a central evacuation system. Open interfaces require a reservoir because waste gases are intermittently discharged in surges whereas flow from the evacuation system is continuous.[146]

Many contemporary anesthesia machines are equipped with open interfaces such as those in Figure 25-32A and B.[151] An open canister provides reservoir capacity. The volume of the canister should be large enough to accommodate a variety of waste gas flow rates. Gas enters the system at the top of the canister and travels through a narrow inner tube to the canister base. Gases are stored in the reservoir between breaths. Positive- and negative-pressure relief is provided by holes in the top of the canister. The open interface shown in Figure 25-32A differs somewhat from the one shown in Figure 25-32B. The operator can regulate the vacuum by adjusting the vacuum control valve shown in Figure 25-32B.[151]

The efficiency of an open interface depends on several factors. The vacuum flow rate per minute must equal or exceed the minute volume of excess gases to prevent spillage. The volume of the reservoir and the flow characteristics within the interface are important. Spillage will occur if the volume of a single exhaled breath exceeds the capacity of the reservoir. The flow character-

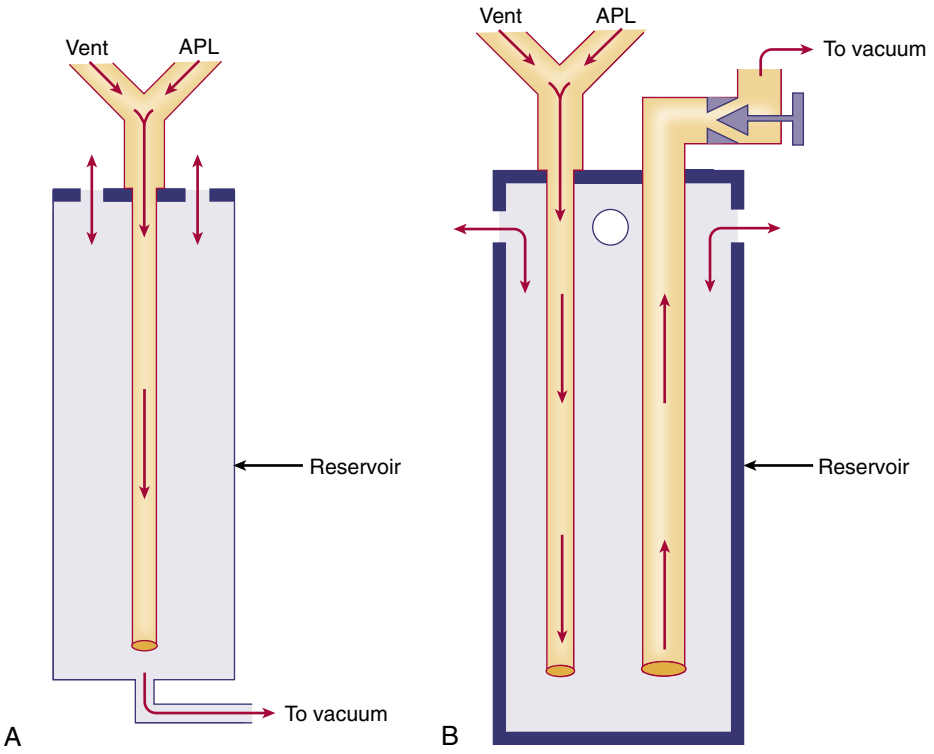


Figure 25-32 **A** and **B,** Two open scavenging interfaces. Each requires an active disposal system. APL, adjustable pressure-limiting valve; Vent, ventilator relief valve. See text for details. *(Modified with permission from Dorsch JA, Dorsch SE: Controlling trace gas levels.* In *Dorsch JA, Dorsch SE* [*eds*]*: Understanding Anesthesia Equipment, 4th ed. Baltimore, Williams & Wilkins, 1999, p 355.)*

istics of the system are important because gas leakage can occur long before the volume of waste gas equals the reservoir volume if significant turbulence occurs within the interface.[152]

Closed Interfaces A closed interface communicates with the atmosphere through valves. All closed interfaces must have a positive-pressure relief valve to vent excess system pressure if obstruction occurs downstream from the interface. A negative-pressure relief valve is mandatory to protect the breathing system from subatmospheric pressure if an active disposal system is used.[146] Two types of closed interfaces are commercially available. One has positive-pressure relief only; the other has both positive- and negative-pressure relief. Each type is discussed in the following paragraphs.

Positive-Pressure Relief Only. This interface (Fig. 25-33, left) has a single positive-pressure relief valve and is designed to be used only with passive disposal systems. Waste gas enters the interface at the waste gas inlets. Transfer of the waste gas from the interface to the disposal system relies on the "weight" or pressure of the waste gas itself because a negative-pressure evacuation system is not used. The positive-pressure relief valve opens at a preset value such as 5 cm H_2O if an obstruction between the interface and the disposal system occurs.[153] On this type of system, a reservoir bag is not required.

Positive- and Negative-Pressure Relief. This interface has a positive-pressure relief valve and at least one negative-pressure relief valve, in addition to a reservoir bag. It is used with active disposal systems. Figure 25-33 (right) is a schematic of Dräger Medical's closed interface for suction systems. A variable volume of waste gas intermittently enters the interface through the waste gas inlets. The reservoir intermittently accumulates excess gas until the evacuation system eliminates it. The operator should adjust the vacuum control valve so that the reservoir bag is properly inflated (A), not overdistended (B) or completely deflated (C). Gas is vented to the atmosphere through the positive-pressure relief valve if the system pressure exceeds +5 cm H_2O. Room air is entrained through the negative-pressure relief valve if the system pressure is more negative than −0.5 cm H_2O. On some systems, a backup negative-pressure relief valve opens at −1.8 cm H_2O if the primary negative-pressure relief valve becomes occluded.

The effectiveness of a closed system in preventing spillage depends on the rate of waste gas inflow, the evacuation flow rate, and the size of the reservoir. Leakage of waste gases into the atmosphere occurs only when the reservoir bag becomes fully inflated and the pressure increases sufficiently to open the positive-pressure relief valve. In contrast, the effectiveness of an open system in preventing spillage depends not only on the volume of the reservoir but also on the flow characteristics within the interface.[152]

Gas Disposal Assembly Conduit The gas disposal assembly conduit (see Fig. 25-31) conducts waste gas from the scavenging interface to the gas disposal assembly. It should be collapse proof and should run overhead, if possible, to minimize the chance of accidental occlusion.[148]

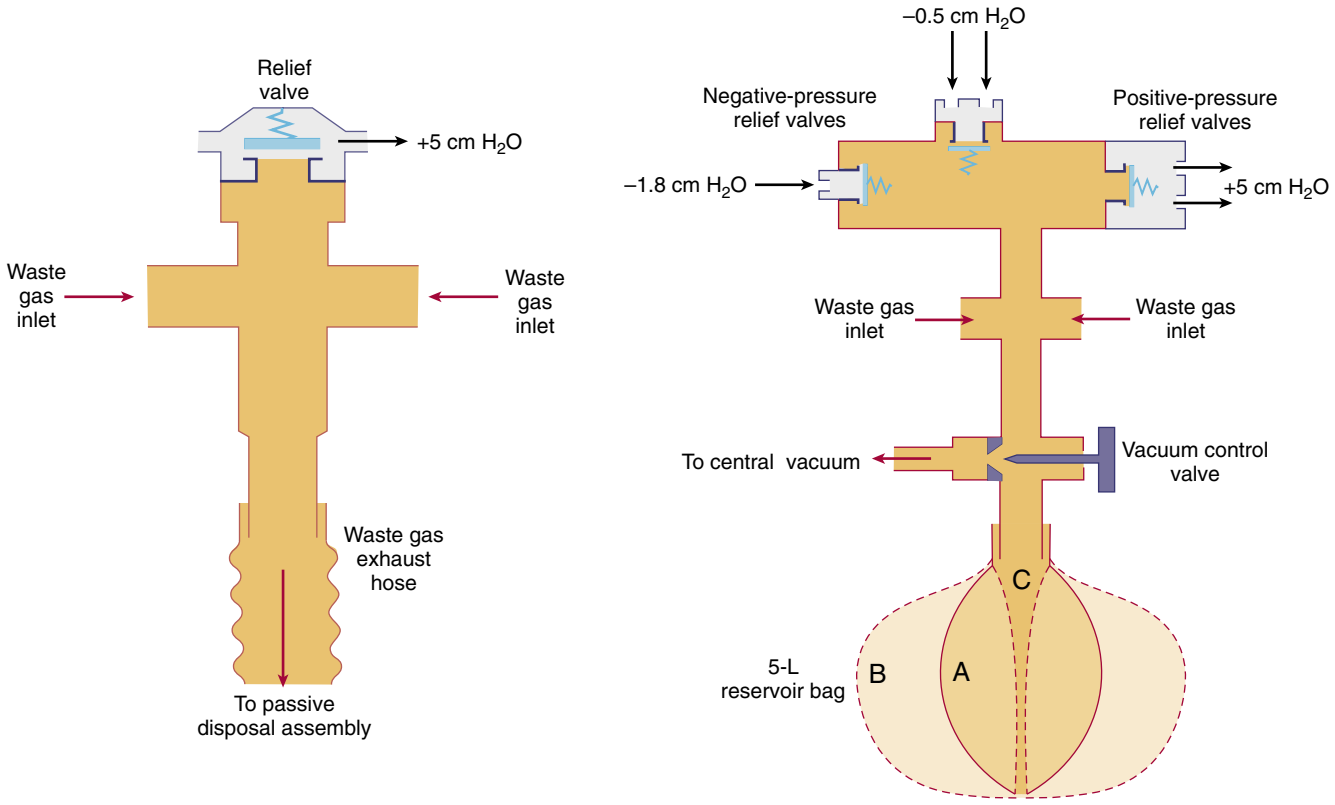


Figure 25-33 Closed scavenging interfaces. **Left,** Interface used with a passive disposal system. **Right,** Interface used with an active system. See text for details. (***Left,*** *Modified with permission from Scavenger Interface for Air Conditioning. Instruction Manual. Telford, PA, North American Dräger, October 1984;* ***right,*** *from Narkomed 2A Anesthesia System. Technical Service Manual. Telford, PA, North American Dräger, 1985.)*

Gas Disposal Assembly The gas disposal assembly ultimately eliminates excess waste gas (see Fig. 25-31). There are two types of disposal systems: active and passive. The most common method of gas disposal is the active assembly, which uses a central evacuation system. A vacuum pump serves as the mechanical flow-inducing device that removes the waste gases, usually to the outside of the building. An interface with a negative-pressure relief valve is mandatory because the pressure within the system is negative. A reservoir is very desirable, and the larger the reservoir, the lower the suction flow rate needed.[146,152]

A passive disposal system does not use a mechanical flow-inducing device. Instead, the "weight" or pressure from the heavier-than-air anesthetic gases produces flow through the system. Positive-pressure relief is mandatory, but negative-pressure relief and a reservoir are unnecessary. Excess waste gases can be eliminated from the operating room suite in a number of ways. Some include venting through the wall, ceiling, or floor or to the room exhaust grill of a non-recirculating air-conditioning system.[146,152]

Hazards

Scavenging systems minimize operating room pollution, yet they add complexity to the anesthesia system. A scavenging system functionally extends the anesthesia circuit all the way from the anesthesia machine to the ultimate disposal site. This extension increases the potential for problems. Obstruction of scavenging pathways can cause excessive positive pressure in the breathing circuit, and barotrauma can occur. Excessive vacuum applied to a scavenging system can result in undesirable negative pressures within the breathing system. Finally, in 2004 another unusual problem that resulted from waste gas scavenging was reported in the *ASA Newsletter* by Lees and coworkers. They reported fires in engineering equipment rooms that house the vacuum pumps used for evacuation of waste anesthetic gases. It seems that in some hospitals, waste gases are not directly vented outside but may be vented into machine rooms that have vents opening to the outside. Because some new anesthesia machines such as the Datex-Ohmeda S/5 ADU and Aestiva, among others, now also scavenge ventilator drive gas (which is 100% oxygen in most cases) in addition to gas from the breathing system, the environments in these machine rooms may become highly enriched with oxygen gas. The result has been the production of fires in these spaces outside the operating room. These sites may contain equipment or materials such as petroleum distillates (pumps/oil/grease) that in the presence of an oxygen-enriched atmosphere could be excessively combustible and a severe fire hazard.[154]

Summary

Rapid advances in technology within the anesthesia workstation industry have made it increasingly difficult for the anesthesia care provider to keep up with latest anesthesia workstation technologies. Nevertheless, a thorough understanding of the anesthesia workstation is mandatory for the safe practice of our specialty. Machines are equipped with dozens of safety features, yet none of them is foolproof. Anesthesia care providers must still check their workstations appropriately before surgery with the correct pre-use checkout procedures to ensure safe delivery of anesthesia for every patient.

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Appendix 1

Anesthesia Apparatus Checkout Recommendations, 1993

This checkout, or a reasonable equivalent, should be conducted before administration of anesthesia. These recommendations are valid only for an anesthesia system that conforms to current and relevant standards and includes an ascending bellows ventilator and at least the following monitors: capnograph, pulse oximeter, oxygen analyzer, respiratory volume monitor (spirometer), and breathing system pressure monitor with high- and low-pressure alarms. This is a guideline that users are encouraged to modify to accommodate differences in equipment design and variations in local clinical practice. Such local modifications should undergo appropriate peer review. Users should refer to the operator's manual for the manufacturer's specific procedures and precautions, especially the manufacturer's low-pressure leak test (step 5).

Emergency Ventilation Equipment

*1. **Verify That Backup Ventilation Equipment Is Available and Functioning.**

High-Pressure System

*2. **Check Oxygen Cylinder Supply.**
   a. Open the O_2 cylinder and verify that it is at least half full (≈1000 psi).
   b. Close the cylinder.

*3. **Check Central Pipeline Supplies.**
   a. Check that hoses are connected and pipeline gauges read about 50 psi.

Low-Pressure System

*4. **Check Initial Status of Low-Pressure System.**
   a. Close the flow control valves and turn the vaporizers off.
   b. Check the fill level and tighten the vaporizers' filler caps.

*5. **Perform Leak Check of Machine Low-Pressure System.**
   a. Verify that the machine master switch and flow control valves are OFF.
   b. Attach a "suction bulb" to the common (fresh) gas outlet.
   c. Squeeze the bulb repeatedly until it is fully collapsed.
   d. Verify that the bulb stays *fully* collapsed for at least 10 seconds.
   e. Open one vaporizer at a time and repeat steps c and d as above.
   f. Remove the suction bulb and reconnect the fresh gas hose.

*6. **Turn on Machine Master Switch and All Other Necessary Electrical Equipment.**

*7. **Test Flow Meters.**
   a. Adjust the flow of all gases through their full range while checking for smooth operation of the floats and undamaged flow tubes.
   b. Attempt to create a hypoxic O_2/N_2O mixture and verify correct changes in flow and/or alarm.

Scavenging System

*8. **Adjust and Check Scavenging System.**
   a. Ensure proper connections between the scavenging system and both the APL (pop-off) valve and ventilator relief valve.
   b. Adjust the waste gas vacuum (if possible).
   c. Fully open the APL valve and occlude the Y-piece.
   d. With minimum O_2 flow, allow the scavenger reservoir bag to collapse completely and verify that the absorber pressure gauge reads about zero.
   e. With the O_2 flush activated, allow the scavenger reservoir bag to distend fully and then verify that absorber pressure gauge reads less than 10 cm H_2O.

Breathing System

*9. **Calibrate O_2 Monitor.**
   a. Ensure that the monitor reads 21% in room air.
   b. Verify that the low-O_2 alarm is enabled and functioning.
   c. Reinstall the sensor in the circuit and flush the breathing system with O_2.
   d. Verify that the monitor now reads greater than 90%.

10. **Check Initial Status of Breathing System.**
   a. Set the selector switch to "Bag" mode.
   b. Check that the breathing circuit is complete, undamaged, and unobstructed.
   c. Verify that CO_2 absorbent is adequate.
   d. Install the breathing circuit accessory equipment (e.g., humidifier, positive end-expiratory pressure [PEEP] valve) to be used during the procedure.

11. **Perform Leak Check of Breathing System.**
   a. Set all gas flows to zero (or minimum).
   b. Close the APL (pop-off) valve and occlude the Y-piece.
   c. Pressurize the breathing system to about 30 cm H_2O with an O_2 flush.
   d. Ensure that the pressure remains fixed for at least 10 seconds.
   e. Open the APL (pop-off) valve and ensure that the pressure decreases.

*If an anesthesia provider uses the same machine for successive procedures, these steps need not be repeated or may be abbreviated after the initial checkout.

Manual and Automatic Ventilation Systems

12. **Test Ventilation Systems and Unidirectional Valves.**
    a. Place a second breathing bag on the Y-piece.
    b. Set the appropriate ventilator parameters for the next patient.
    c. Switch to automatic ventilation (Ventilator) mode.
    d. Turn the ventilator ON and fill the bellows and breathing bag with an O_2 flush.
    e. Set O_2 flow to minimum and other gas flows to zero.
    f. Verify that during inspiration the bellows delivers appropriate tidal volume and that during expiration the bellows fills completely.
    g. Set the fresh gas flow to about 5 L/min.
    h. Verify that the ventilator bellows and simulated lungs fill *and empty* appropriately without sustained pressure at end expiration.
    i. Check for proper action of the unidirectional valves.
    j. Check the breathing circuit accessories to ensure proper function.
    k. Turn the ventilator OFF and switch to manual ventilation (Bag/APL) mode.
    l. Ventilate manually and ensure inflation and deflation of the artificial lungs and appropriate feel of system resistance and compliance.
    m. Remove the second breathing bag from the Y-piece.

Monitors

13. **Check, Calibrate, and/or Set Alarm Limits of All Monitors.**
    a. Capnometer
    b. Oxygen analyzer
    c. Pressure monitor with high– and low–airway pressure alarms
    d. Pulse oximeter
    e. Respiratory volume monitor (spirometer)

Final Position

14. **Check Final Status of Machine.**
    a. Vaporizers off
    b. APL valve open
    c. Selector switch to "Bag"
    d. All flowmeters to zero (or minimum)
    e. Patient suction level adequate
    f. Breathing system ready to use

Appendix 2

2007 Guidelines for Preanesthesia Checkout Procedures

Background

Improperly checking anesthesia equipment before use can lead to patient injury and has also been associated with an increased risk for severe postoperative morbidity and mortality.[1,2] In 1993, a preanesthesia checkout (PAC) was developed and widely accepted to be an important step in the process of preparing to deliver anesthesia care.[3] Despite the accepted importance of the PAC, the evidence available suggests that the current version is neither well understood nor reliably used by anesthesia providers.[4-6] Furthermore, anesthesia delivery systems have evolved to the point that one checkout procedure is not applicable to all anesthesia delivery systems currently on the market. For these reasons, a new approach to the PAC has been developed. The goal was to provide guidelines applicable to all anesthesia delivery systems so that individual departments can develop a PAC that can be performed consistently and expeditiously.

General Considerations

The following document is intended to serve not as a PAC itself but rather as a template for developing checkout procedures that are appropriate for each individual anesthesia machine design and practice setting. When using this template to develop a checkout procedure for systems that incorporate automated checkout features, items that are not evaluated by the automated checkout need to be identified and supplemental manual checkout procedures included as needed.

Simply because an automated checkout procedure exists does not mean that it can completely replace a manual checkout procedure or that it can be performed safely without adequate training and thorough understanding of what the automated checkout accomplishes. An automated checkout procedure can be incomplete or misleading, or both. For example, the leak test performed by some current automated checkouts does not test for leaks at the vaporizers. As a result, a loose vaporizer filler cap or a leak at the vaporizer mount could easily be missed.

Ideally, an automated checkout procedure should clearly reveal to the user the functions that are being checked, any deficient function that is found, and recommendations to correct the problem. Documentation of the automated checkout process should preferably be accomplished in a manner that can be recorded on the anesthesia record.

The operator manuals that accompany anesthesia delivery systems include extensive recommendations for checking the equipment out. Although these recommendations are quite extensive and typically not used by anesthesia providers, they are nevertheless important references for developing machine-specific and institution-specific checkout procedures.

Personnel Performing the Preanesthesia Checkout

The previously accepted Anesthesia Apparatus Checkout Recommendation placed all the responsibility for pre-use checkout on the anesthesia provider. This guideline identifies aspects of the PAC that could be completed by a qualified anesthesia or biomedical technician. Using technicians to perform some aspects of the PAC may improve compliance with the PAC. Steps completed by a technician may be part of the morning pre-use check or part of a procedure performed at the end of each day. Critical checkout steps (e.g., availability of backup ventilation equipment) will benefit from intentional redundancy (i.e., having more than one individual responsible for checking the equipment). *Regardless of the level of training and support by technicians, the anesthesia care provider is ultimately responsible for proper function of all equipment used to provide anesthesia care.*

Adaptation of the PAC to local needs, assignment of responsibility for the checkout procedures, and training are the responsibilities of the individual anesthesia department. Training procedures should be documented. Proper documentation should include records of completed coursework (e.g., a manufacturer course) or, for in-house training, a listing of the competency items taught and records of successful completion by trainees.

Objectives for a New Preanesthesia Checkout

- Outline the essential items that need to be available and functioning properly before delivering every anesthetic.
- Identify the frequency with which each of the items needs to be checked.
- Suggest which items may be checked by a qualified anesthesia technician, biomedical technician, or manufacturer-certified service technician.

Basic Principles

- The anesthesia care provider is ultimately responsible for ensuring that the anesthesia equipment is safe and ready for use. This responsibility includes adequate familiarity with the equipment, following relevant local policies for performing and documenting the PAC, and being knowledgeable about these procedures.
- Depending on the staffing resources in a particular institution, anesthesia technicians or biomedical technicians (or both) can participate in the PAC. Biomedical technicians are often trained and certified by manufacturers to perform on-site maintenance of anesthesia delivery systems and can therefore be a useful resource for completing regular checkout procedures. Anesthesia technicians are not commonly trained to perform checkout procedures. Involvement of anesthesia technicians is intended to enhance compliance with the PAC. Each department should decide whether the available technicians can or should be trained to assist with checkout procedures. Formal certification of anesthesia technicians by the American Society of Anesthesia Technicians and Technologists (ASATT) is encouraged but does not necessarily guarantee familiarity with checkout procedures.
- Critical items will benefit from redundant checks to avoid errors and omissions.
- When more than one person is responsible for checking an item, all parties should perform the check if intentional redundancy is deemed important, or either party may be acceptable, depending on the resources available.
- Whoever conducts the PAC should provide documentation of successful performance. The anesthesia provider should include this documentation on the patient chart.
- Whenever an anesthesia machine is moved to a new location, a complete beginning-of-the-day checkout should be performed.
- Automated checks should clearly distinguish the components of the delivery system that are checked automatically from those that require manual checkout.
- Ideally, the date, time, and outcome of the most recent check or checks should be recorded and the information made accessible to the user.
- Specific procedures for pre-use checkout cannot be prescribed in this document because they vary with the delivery systems. Clinicians must learn how to effectively perform the necessary pre-use check for each piece of equipment that they use.
- Each department or health care facility should work with the manufacturer or manufacturers of their equipment to develop pre-use checkout procedures that satisfy both the following guidelines and the needs of the local department.
- Default settings for ventilators, monitors, and alarms should be checked to determine whether they are appropriate.
- These checkout recommendations are intended to replace the preexisting Food and Drug Administration (FDA)-approved Anesthesia Apparatus Checkout Recommendations. They are not intended to be a replacement for required preventive maintenance.
- The PAC is essential for safe care but should not delay initiation of care if patient needs are so urgent that the time taken to complete the PAC could worsen the patient's outcome.

Guidelines for Developing Institution-Specific Checkout Procedures before Anesthesia Delivery

These guidelines describe a basic approach to checkout procedures and rationale to ensure that these priorities are satisfied. They should be used to develop institution-specific checkout procedures designed for the equipment and resources available. (Examples of institution-specific procedures for current anesthesia delivery systems are published at www.ASAHQ.org/clinical/FDA.htm.)

Requirements for Safe Delivery of Anesthesia Care

- Reliable delivery of oxygen at any appropriate concentration up to 100%

- Reliable means of positive-pressure ventilation
- Backup ventilation equipment available and functioning
- Controlled release of positive pressure from the breathing circuit
- Anesthesia vapor delivery (if intended as part of the anesthetic plan)
- Adequate suction
- Means to conform to standards for patient monitoring[7,8]

Specific Items

The following items need to be checked as part of a complete PAC. The intent is to identify what to check, the recommended frequency of checking, and the individual or individuals who could be responsible for the item. For these guidelines, the responsible party would fall into one of four categories: Provider, Technician, Technician or Provider, or Technician and Provider. The designation "Technician and Provider" means that the provider must perform the check regardless of whether it has been completed by a technician. It is not intended to make the use of technician checks mandatory. The intent is not to specify how an item needs to be checked because the specific checkout procedure will depend on the equipment being used.

Item 1: Verify that the auxiliary oxygen cylinder and self-inflating manual ventilation device are available and functioning.
Frequency: Daily.
Responsible Parties: Provider and technician.
Rationale: Failure to be able to ventilate is a major cause of morbidity and mortality related to anesthesia care. Because equipment failure with resulting inability to ventilate the patient can occur at any time, a self-inflating manual ventilation device (e.g., Ambu bag) should be present at every anesthetizing location for every procedure and should be checked for proper function. In addition, a source of oxygen separate from the anesthesia machine and pipeline supply, specifically, an oxygen cylinder with a regulator and a means to open the cylinder valve, should be immediately available and checked. After checking the cylinder pressure, it is recommended that the main cylinder valve be closed to avoid inadvertent emptying of the cylinder through a leaky or open regulator.

Item 2: Verify that patient suction is adequate to clear the airway.
Frequency: Before each use.
Responsible Parties: Provider and technician.
Rationale: Safe anesthetic care requires the immediate availability of suction to clear the airway if needed.

Item 3: Turn on the anesthesia delivery system and confirm that AC power is available.
Frequency: Daily.
Responsible Parties: Provider or technician.
Rationale: Anesthesia delivery systems typically function with backup battery power if AC power fails. Unless the presence of AC power is confirmed, the first obvious sign of power failure can be a complete system shutdown when the batteries can no longer power the system. Many anesthesia delivery systems have visual indicators of the power source showing the presence of both AC and battery power. These indicators should be checked and connection of the power cord to a functional AC power source confirmed.

Desflurane vaporizers require electrical power, and recommendations for checking power to these vaporizers should also be followed.

Item 4: Verify the availability of required monitors and check alarms.
Frequency: Before each use.
Responsible Parties: Provider or technician.
Rationale: Standards for patient monitoring during anesthesia are clearly defined.[7,8] The ability to conform to these standards should be confirmed for every anesthetic. The first step is to visually verify that the appropriate monitoring supplies (blood pressure cuffs, oximetry probes, etc.) are available. All monitors should be turned on and proper completion of power-up self-tests confirmed. Given the importance of pulse oximetry and capnography to patient safety, verifying proper function of these devices before anesthetizing the patient is essential. Capnometer function can be verified by exhaling through the breathing circuit or gas sensor to generate a capnogram or by verifying that the patient's breathing efforts generate a capnogram before the patient is anesthetized. Visual and audible alarm signals should be generated when this is discontinued. Pulse oximeter function, including an audible alarm, can be verified by placing the sensor on a finger and observing for a proper recording. The pulse oximeter alarm can be tested by introducing a motion artifact or removing the sensor.

Audible alarms have also been reconfirmed as essential to patient safety by the American Society of Anesthesiologists (ASA), American Association of Nurse Anesthetists (AANA), Anesthesia Patient Safety Foundation (APSF), and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Proper monitor functioning includes visual and audible alarm signals that function as designed.

Item 5: Verify that pressure is adequate in the spare oxygen cylinder mounted on the anesthesia machine.
Frequency: Daily.
Responsible Parties: Provider and technician.
Rationale: Anesthesia delivery systems rely on a supply of oxygen for various machine functions. At a minimum, the oxygen supply is used to provide oxygen to the patient. Pneumatically powered ventilators also rely on a gas supply. The oxygen cylinder or cylinders should be mounted on the anesthesia delivery system and determined to have acceptable minimum pressure. Acceptable pressure depends on the intended use, the design of the anesthesia delivery system, and the availability of piped oxygen.

- Typically, an oxygen cylinder will be used if the central oxygen supply fails.
- If the cylinder is intended to be the primary source of oxygen (e.g., remote-site anesthesia), a cylinder supply sufficient to last for the entire procedure is required. If a pneumatically powered ventilator that uses oxygen as its driving gas will be used, a full "E" oxygen cylinder may provide only 30 minutes of oxygen. In that case, the maximum duration of oxygen supply can be obtained from an oxygen cylinder if it is used to provide only fresh gas to the patient in conjunction with manual or spontaneous ventilation. Mechanical ventilators will consume the oxygen supply if pneumatically powered ventilators

that require oxygen to power the ventilator are used. Electrically powered ventilators do not consume oxygen, so the duration of a cylinder supply will depend only on total fresh gas flow.

- The oxygen cylinder valve should be closed after it has been verified that adequate pressure is present, unless the cylinder is to be the primary source of oxygen (i.e., piped oxygen is not available). If the valve remains open and the pipeline supply should fail, the oxygen cylinder can become depleted while the anesthesia provider is unaware of the oxygen supply problem.
- Other gas supply cylinders (e.g., heliox, CO_2, air, N_2O) need to be checked only if that gas is required to provide anesthetic care.

Item 6: Verify that piped gas pressures are 50 psig or greater.
Frequency: Daily.
Responsible Parties: Provider and technician.
Rationale: A minimum gas supply pressure is required for proper function of the anesthesia delivery system. Gas supplied from a central source can fail for a variety of reasons. Therefore, the pressure in the piped gas supply should be checked at least once daily.

Item 7: Verify that the vaporizers are adequately filled and, if applicable, the filler ports are tightly closed.
Frequency: Before each use.
Responsible Parties: Provider. Technician if redundancy is desired.
Rationale: If delivery of anesthetic vapor is planned, an adequate supply is essential to reduce the risk of light anesthesia or recall, especially if an anesthetic agent monitor with a low-agent alarm is not being used. Partially open filler ports are a common cause of leaks that may not be detected if the vaporizer control dial is not open when a leak test is performed. This source of leakage can be minimized by tightly closing the filler ports. Newer vaporizer designs have filling systems that automatically close the filler port when filling is completed.

High– and low–anesthetic agent alarms are useful to help prevent overdosage or underdosage of anesthetic vapor. Use of these alarms is encouraged, and they should be set to the appropriate limits and enabled.

Item 8: Verify that there are no leaks in the gas supply lines between the flow meters and the common gas outlet.
Frequency: Daily and whenever a vaporizer is changed.
Responsible Parties: Provider or technician.
Rationale: The gas supply in this part of the anesthesia delivery system passes through the anesthetic vaporizer or vaporizers on most anesthesia delivery systems. To perform a thorough leak test, each vaporizer must be turned on individually to check for leaks at the vaporizer mount or inside the vaporizer. Furthermore, some machines have a check valve between the flow meters and the common gas outlet that requires a negative-pressure test to adequately check for leaks. Automated checkout procedures typically include a leak test but may not evaluate leaks at the vaporizer, especially if the vaporizer is not turned on during the leak test. When relying on automated testing to evaluate the system for leaks, the automated leak test would need to be repeated for each vaporizer in place. This test should also be completed whenever a vaporizer is changed. The risk of a leak at the vaporizer depends on the vaporizer design. Vaporizer designs in which the filler port closes automatically after filling can reduce the risk of leaks occurring.

Technicians can provide useful assistance with this aspect of the machine checkout because it can be time consuming.

Item 9: Test for adequate functioning of the scavenging system.
Frequency: Daily.
Responsible Parties: Provider or technician.
Rationale: A properly functioning scavenging system prevents room contamination by anesthetic gases. Proper function depends on correct connections between the scavenging system and the anesthesia delivery system. These connections should be checked daily by a provider or technician. Depending on design of the scavenging system, proper function may also require that the vacuum level be adequate, which should also be confirmed daily. Some scavenging systems have mechanical positive- and negative-pressure relief valves. Positive- and negative-pressure relief is important to protect the patient circuit from pressure fluctuations related to the scavenging system. Proper checkout of the scavenging system should ensure that positive- and negative-pressure relief is functioning properly. Because of the complexity of checking for effective positive- and negative-pressure relief and the variations in scavenging system design, a properly trained technician can facilitate this aspect of the checkout process.

Item 10: Calibrate or verify calibration of the oxygen monitor and check the low-oxygen alarm.
Frequency: Daily.
Responsible Parties: Provider or technician.
Rationale: Continuous monitoring of the inspired oxygen concentration is the last line of defense against delivering hypoxic gas concentrations to the patient. The oxygen monitor is essential for detecting adulteration of the oxygen supply. Most oxygen monitors require calibration once daily, although some are self-calibrating. For self-calibrating oxygen monitors, they should be verified to read 21% when sampling room air. This is a step that is easily completed by a trained technician. When more than one oxygen monitor is present, the primary sensor that will be relied on for oxygen monitoring should be checked.

The low-oxygen concentration alarm should also be checked at this time by setting the alarm above the measured oxygen concentration and confirming that an audible alarm signal is generated.

Item 11: Verify that the carbon dioxide absorbent is not exhausted.
Frequency: Before each use.
Responsible Parties: Provider or technician.
Rationale: Proper function of a circle anesthesia system relies on the absorbent to remove carbon dioxide from rebreathed gas. Exhausted absorbent, as indicated by the characteristic change in color, should be replaced. It is possible for absorbent material to lose the ability to absorb CO_2, yet the characteristic color change may be absent or difficult to see. Some newer absorbents do change color when desiccated. Capnography should be used for every anesthetic, and with use of a circle anesthesia system, rebreathing carbon dioxide as indicated by an inspired CO_2 concentration greater than 0 can also indicate exhausted absorbent (see Note 2).

Item 12: Test for breathing system pressure and leaks.
Frequency: Before each use.
Responsible Parties: Provider and technician.
Rationale: The breathing system pressure and leak test should be performed with the circuit configuration to be used during anesthetic delivery. If any components of the circuit are changed after this test is completed, the test should be performed again. Although the anesthesia provider should perform this test before each use, anesthesia technicians who replace and assemble circuits can also perform this check and add redundancy to this important checkout procedure.

Proper testing will demonstrate that pressure can be developed in the breathing system during both manual and mechanical ventilation and that pressure can be relieved during manual ventilation by opening the adjustable pressure-limiting (APL) valve.

Automated testing is often implemented in the newer anesthesia delivery systems to evaluate the system for leaks and also to determine the compliance of the breathing system. The compliance value determined during this testing will be used to automatically adjust the volume delivered by the ventilator to maintain constant delivery of volume to the patient. It is important that the circuit configuration that is to be used be in place during the test.

Item 13: Verify that gas flows properly through the breathing circuit during both inspiration and exhalation.
Frequency: Before each use.
Responsible Parties: Provider and technician.
Rationale: Pressure and leak testing does not identify all obstructions in the breathing circuit or confirm proper function of the inspiratory and expiratory unidirectional valves. A test lung or second reservoir bag can be used to confirm that flow through the circuit is unimpeded. Complete testing includes both manual and mechanical ventilation. The presence of unidirectional valves can be assessed visually during the PAC; however, proper function of these valves cannot be visually assessed because subtle valve incompetence may not be detected. Checkout procedures to identify valve incompetence that may not be visually obvious can be implemented but are typically too complex for daily testing. A trained technician can perform regular valve competence tests (see Note 4). Capnography should be used during every anesthetic, and the presence of carbon dioxide in the inspired gases can help detect an incompetent valve.

Item 14: Document completion of checkout procedures.
Frequency: Before each use.
Responsible Parties: Provider and technician.
Rationale: Each individual responsible for checkout procedures should document completion of these procedures. Documentation gives credit for completing the job and can be helpful if an adverse event should occur. Some automated checkout systems maintain an audit trail of completed checkout procedures that are dated and timed.

Item 15: Confirm ventilator settings and evaluate readiness to deliver anesthesia care (ANESTHESIA TIME-OUT).
Frequency: Immediately before initiating the anesthetic.
Responsible Parties: Provider.
Rationale: This step is intended to avoid errors resulting from production pressure or other sources of haste. The goal is to confirm that appropriate checks have been completed and that essential equipment is indeed available. The concept is analogous to the "time-out" used to confirm patient identity and the surgical site before incision. Improper ventilator settings can be harmful, especially if a small patient is following a much larger patient or vice versa. Pressure limit settings (when available) should be used to prevent excessive delivery of volume from improper ventilator settings.
Items to check:

- Monitors functional?
- Capnogram present?
- Oxygen saturation by pulse oximetry measured?
- Flow meter and ventilator settings proper?
- Manual/ventilator switch set to manual?
- Vaporizer(s) adequately filled?

Summary of Checkout Recommendations by Frequency and Responsible Party

To Be Completed Daily	Responsible Party
Item 1: Verify that the auxiliary oxygen cylinder and self-inflating manual ventilation device are available and functioning	Provider and tech
Item 2: Verify that patient suction is adequate to clear the airway	Provider and tech
Item 3: Turn on the anesthesia delivery system and confirm that AC power is available	Provider or tech
Item 4: Verify the availability of required monitors, including alarms	Provider or tech
Item 5: Verify that pressure is adequate on the spare oxygen cylinder mounted on the anesthesia machine	Provider and tech
Item 6: Verify that piped gas pressures are ≥50 psig	Provider and tech
Item 7: Verify that vaporizers are adequately filled and, if applicable, that filler ports are tightly closed	Provider or tech
Item 8: Verify that there are no leaks in the gas supply lines between the flow meters and the common gas outlet	Provider or tech
Item 9: Test scavenging system function	Provider or tech
Item 10: Calibrate or verify calibration of the oxygen monitor and check the low-oxygen alarm	Provider or tech
Item 11: Verify that the carbon dioxide absorbent is not exhausted	Provider or tech
Item 12: Check for proper breathing system pressure and leaks	Provider and tech
Item 13: Verify that gas flows properly through the breathing circuit during both inspiration and exhalation	Provider and tech

Item 14: Document completion of checkout procedures	Provider and tech
Item 15: Confirm ventilator settings and evaluate readiness to deliver anesthesia care (ANESTHESIA TIME-OUT)	Provider
To Be Completed before Each Procedure	
Item To Be Completed	**Responsible Party**
Item 2: Verify that patient suction is adequate to clear the airway	Provider and tech
Item 4: Verify the availability of required monitors, including alarms	Provider or tech
Item 7: Verify that vaporizers are adequately filled and, if applicable, that filler ports are tightly closed	Provider
Item 11: Verify that the carbon dioxide absorbent is not exhausted	Provider or tech
Item 12: Check for proper breathing system pressure and leaks	Provider and tech
Item 13: Verify that gas flows properly through the breathing circuit during both inspiration and exhalation	Provider and tech
Item 14: Document completion of checkout procedures	Provider and tech
Item 15: Confirm ventilator settings and evaluate readiness to deliver anesthesia care (ANESTHESIA TIME-OUT)	Provider

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Supplement: Additional Notes on Preanesthesia Checkout

Note 1. *Testing the flow meters*: This step is present in the 1993 checkout recommendation and is intended to check the oxygen/nitrous oxide proportioning system. It has been eliminated from the PAC in these guidelines because proper function is verified during preventive maintenance and failures of this system in a properly maintained delivery system are rare.

Note 2. *Desiccated carbon dioxide absorbent*: It has been well established that carbon dioxide absorbents that contain sodium, potassium, or barium hydroxide may become dangerous when desiccated and produce carbon monoxide or excessive heat leading to fires (or both). Unfortunately, it is not possible to reliably identify when the absorbent material has been desiccated. Some departments elect to change all absorbent material on Monday morning to eliminate the possibility of using absorbent exposed to continuous fresh gas flow throughout the weekend. Other departments elect to use absorbent materials that do not pose a risk when desiccated. It is important to have a strategy to prevent hazards related to using absorbents containing the problematic hydroxides that have desiccated. There are no steps that could be included in the checkout recommendation that can reliably identify desiccated absorbent. If a department uses absorbent that may be hazardous when desiccated, it may be prudent to change the absorbent material whenever the duration of exposure to high fresh gas flow cannot be determined and is likely to have been prolonged.

A protocol for preventing absorbent hazards should be part of every department's risk management strategy.

Note 3. *Anesthesia information systems and automated record keepers*: These systems are being adopted by an increasing number of anesthesia departments and are the mainstay of the record-keeping process in these departments. The presence of reliably functioning systems is therefore important to the conduct of anesthesia, though not essential to patient safety in the same fashion as the anesthesia delivery system and patient monitors. For departments that rely on these systems, it would be prudent to have a protocol for checking connections and the proper functioning of associated computers, displays, and network function.

Note 4. *Testing circle system valve competence*: As part of test Item 13 (verify that gas flows properly through the breath-

ing circuit during both inspiration and exhalation), the inspiratory and expiratory valves are visually observed for proper cycling (opening and closing fully). Visual inspection will also detect a missing valve leaflet. Ascertainment of full closure of the valve is subjective. Incompetence of the valve may also be detected during Item 13 by spirometry at the expiratory limb. For malfunction of the expiratory valve, a spirometer with reverse flow detection will signal an alarm when gas flows retrogradely in the expiratory limb. For malfunction of the inspiratory valve, the measured exhaled tidal volume will be less than the expected value. Capnography may also help detect incompetence of the unidirectional valves. Intraoperatively, malfunction of an inspiratory valve may not be indicated by elevation of the inspired CO_2 baseline. If the delivered tidal volume exceeds the volume of gas in the inspiratory limb containing CO_2, rebreathing will appear on the capnogram as a gradual instead of a sharp downstroke. Malfunction of an expiratory valve is indicated by an elevated CO_2 baseline because there is typically a large volume of exhaled gas containing CO_2 that can return to the patient.

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26 Intravenous Anesthetics

Key Points

1. The introduction of thiopental into clinical practice in 1934 marked the advent of modern intravenous (IV) anesthesia. Today, IV anesthetics are used for induction of anesthesia, maintenance of anesthesia, and provision of conscious sedation.
2. The most commonly used IV anesthetic is propofol, an alkylphenol presently formulated in a lipid emulsion. Propofol provides rapid onset and offset with context-sensitive decrement times of approximately 10 minutes when infused for less than 3 hours and less than 40 minutes when infused for up to 8 hours. Its mechanism of action is thought to be potentiation of γ-aminobutyric acid (GABA)–induced chloride currents. At therapeutic doses, propofol produces a moderate depressant effect on ventilation. It causes a dose-dependent decrease in blood pressure primarily through a decrease in cardiac output and systemic vascular resistance. A unique action of propofol is its antiemetic effect, which remains present at concentrations less than those producing sedation. The induction dose is 1 to 2 mg/kg for loss of consciousness with a maintenance infusion of 100 to 200 μg/kg/min. For conscious sedation, rates of 25 to 75 μg/kg/min are usually adequate.
3. Until more recently, the most commonly used IV induction agents were the barbiturates. Thiopental provides rapid onset and offset when used as a single dose, but it accumulates rapidly with prolonged administration and leads to slow recovery. Methohexital has a rapid onset and offset similar to propofol for procedures lasting less than 2 hours. The barbiturates are administered as sodium salts diluted in a water base at an alkaline pH. Similar to propofol, the barbiturates are thought to provide their hypnotic effects largely through action on the $GABA_A$ receptor. Barbiturates provide cerebral protection and are output from induction of anesthesia used primarily for this purpose. They cause a moderate dose-dependent decrease in blood pressure (primarily as a result of peripheral vasodilation) and respiratory drive. The barbiturates are contraindicated in patients with porphyria. The induction dose of thiopental is 4 mg/kg, and the induction dose for methohexital is 2 mg/kg. Methohexital can be used for maintenance of anesthesia at 100 to 200 μg/kg/min or for conscious sedation at 25 to 75 μg/kg/min.
4. The benzodiazepines are used primarily for anxiolysis and amnesia or for conscious sedation. The water-soluble benzodiazepine midazolam is the most frequently used intravenously because of its rapid onset and offset and lack of active metabolites compared with other benzodiazepines (e.g., diazepam). The onset of midazolam is slower than that of propofol and barbiturates, and its offset, especially when used at higher doses or in a prolonged infusion, is considerably longer than that of propofol or methohexital. The benzodiazepines act through the GABA receptor. Flumazenil is a specific benzodiazepine antagonist. It can be used to reverse the effects of benzodiazepines. The benzodiazepines generally produce only a mild decrease in blood pressure and mild-to-moderate respiratory depression. The dose of midazolam for anxiolysis and mild sedation is 0.015 to 0.03 mg/kg intravenously and is generally repeated in 30 to 60 minutes as needed.
5. Ketamine is a phencyclidine derivative that is uniquely different from the above-mentioned hypnotics. It produces a dissociative state of hypnosis and analgesia. It has been used for induction and maintenance of anesthesia. Ketamine acts primarily, but not entirely, through the *N*-methyl-D-aspartate (NMDA) receptor. Ketamine is associated with significant adverse psychological effects at higher doses and several other side effects. It is used now primarily for its analgesic properties. It has rapid onset and relatively rapid offset, even after an infusion of several hours. It has sympathomimetic action that preserves cardiac function. Ketamine has minimal effect on respiration and tends to preserve autonomic reflexes. The induction dose is 2 to 4 mg intravenously. An infusion of ketamine provides analgesia and can be given with propofol in a total IV anesthesia technique. A dose of 10 to 20 mg preoperatively has been shown to provide preemptive analgesia.
6. Etomidate is an imidazole derivative used primarily for induction of anesthesia, especially in elderly patients and

patients who have cardiovascular compromise. It has a rapid onset of effect and a rapid offset even after a continuous infusion. Prolonged infusion results in inhibition of adrenocortical synthesis and potential mortality in intensive care unit (ICU) patients. The major advantage of etomidate is its minimal effect on the cardiovascular and respiratory systems. It is associated with a high incidence of burning on injection, thrombophlebitis, and postoperative nausea and vomiting (PONV), limiting its popularity. The induction dose is 0.2 to 0.3 mg/kg.

7. Dexmedetomidine is the most recently released IV anesthetic. It is a highly selective α_2-adrenergic agonist that produces sedation, hypnosis, and analgesia. Dexmedetomidine is presently approved only for brief (<24 hours) postoperative sedation, although it is finding increasing use in the perioperative period as an adjunct sedative. Its primary action is as an agonist on α_2 receptors in the locus caeruleus. It has minimal effect on respiration. Dexmedetomidine produces a biphasic effect on blood pressure; at low concentrations, mean blood pressure is decreased, and at higher concentrations, blood pressure is increased. Heart rate and cardiac output show a concentration-dependent decrease. Dosing for sedation is a loading dose of 0.25 to 1 mg/kg over a 10-minute period, followed by an infusion of 0.1 to 1 μg/kg/hr.
8. Droperidol, a butyrophenone and major tranquilizer, was initially used to produce a state of neuroleptanesthesia. More recent concern regarding its effect on prolonging the QT interval has resulted in its withdrawal in several countries and its limitation to the treatment of postoperative nausea and vomiting (PONV) with a black box warning in the United States. Because the use of low-dose droperidol (<1.25 mg) for PONV has not been approved by the U.S. Food and Drug Administration (FDA), the black box warning does not relate to this use. Clinically significant prolongation of the QT interval by doses used for PONV (0.625 to 1.25 mg) has been challenged by several editorials, and this effect has not been substantiated by review of the cases reported or any literature. Low-dose droperidol remains an effective antiemetic therapy.

The introduction of thiopental into clinical practice in 1934 marked the advent of modern intravenous (IV) anesthesia. Thiopental and other barbiturates are not ideal IV anesthetics, however, primarily because they provide only hypnosis. The ideal IV anesthetic drug would provide hypnosis, amnesia, analgesia, and muscle relaxation without undesirable cardiac and respiratory depression. Because no single drug is ideal, many newer IV anesthetics, often used together, have been introduced that offer some or all of the desired effects. These drugs were introduced steadily into clinical practice with varying degrees of acceptance. With an increasing number of compounds and superior methods of IV anesthetic drug delivery available (see Chapter 28), the use of IV anesthetics continues to grow.

The future of anesthetic management involves the simultaneous use of several drugs, including inhaled anesthetics. A 1988 survey of mortality in 100,000 cases of anesthesia reveals that the practice of combined anesthetic drug use may be safer than the use of only one or two drugs[1]; the relative odds of dying within 7 days was 2.9 times greater when one or two anesthetic drugs were used than when three or more were used. Although it is exceedingly difficult to interpret these data, the use of several drugs may be beneficial to anesthetic care. The skillful use of multiple IV anesthetics is not only possible, but also preferable. This chapter provides information on the major nonopioid IV anesthetic drugs available for clinical use today.

Propofol

History

Propofol is the most frequently used IV anesthetic today. Work in the early 1970s on substituted derivatives of phenol with hypnotic properties resulted in the development of 2,6-diisopropofol. The first clinical trial, by Kay and Rolly and reported in 1977, confirmed the potential of propofol as an anesthetic to induce anesthesia.[1a] Propofol is insoluble in water and was initially prepared with Cremophor EL (BASF A.G.). Because of anaphylactoid reactions associated with Cremophor EL in this early formulation of propofol, the drug was reformulated in an emulsion. Propofol is used for induction and maintenance of anesthesia and for sedation in and outside the operating room.

Physicochemical Characteristics

Propofol (Fig. 26-1) is one of a group of alkylphenols that have hypnotic properties in animals.[2] The alkylphenols are oils at room temperature and are insoluble in aqueous solution, but they are highly lipid soluble. Numerous formulations are marketed today. The formulation that followed the removal of Cremophor consists of 1% (wt/vol) propofol, 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide. Following concerns regarding microbial growth in the emulsion, disodium edetate (0.005%) was added as a retardant of bacterial growth. This formulation has a pH of 7 and appears as a slightly viscous, milky white substance. In Europe, a 2% formulation and a formulation in which the emulsion contains a mixture of medium-chain and long-chain triglycerides also are available.

All formulations available commercially are stable at room temperature and are not light sensitive. If a dilute solution of propofol is required, it is compatible with 5% dextrose in water. Changes in the diluent theoretically may result in slight changes in pharmacokinetics, cracking of the emulsion, spontaneous degradation of propofol, and possibly changes in pharmacologic effect. Commercially available formulations of propofol do not have major differences in their clinical utility.

Probably the most interesting formulation likely to be approved soon by the U.S. Food and Drug Administration (FDA) is fospropofol (Aquavan), a phosphorylated prodrug of propofol,

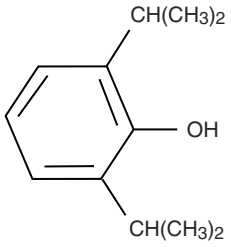


Figure 26-1 Structure of propofol, an alkylphenol derivative.

which produces a unique and distinct pharmacokinetic and pharmacodynamic profile. Compared with propofol emulsion, fospropofol is associated with a slightly longer time to peak effect and a more prolonged pharmacodynamic effect.[3]

Metabolism

Propofol is rapidly metabolized in the liver by conjugation to glucuronide and sulfate[4] to produce water-soluble compounds, which are excreted by the kidneys.[4] Less than 1% propofol is excreted unchanged in urine, and only 2% is excreted in feces.[4] The metabolites of propofol are thought to be inactive. Because clearance of propofol exceeds hepatic blood flow, extrahepatic metabolism or extrarenal elimination has been suggested. Extrahepatic metabolism has been confirmed during the anhepatic phase of patients receiving a transplanted liver.[5] In two more recent studies, the role of the kidneys in propofol metabolism was established, accounting for 30% of total body clearance.[6,7] In in vitro studies with human kidney and small intestine, microsomes in these tissues showed an ability to form propofol glucuronide.[8]

The lungs also may play an important role in this extrahepatic metabolism. The lungs are responsible for approximately 30% of the uptake and first-pass elimination after a bolus dose.[9] During a continuous infusion of propofol, there is a 20% to 30% decrease in propofol concentration measured across the lung in humans and a higher concentration of the metabolite 2,6-diisopropyl 1,4-quinol on the arterial side of the circulation.[10] Other sites of propofol metabolism also are possible. Propofol itself results in a concentration-dependent inhibition of cytochrome P-450 and may alter the metabolism of drugs dependent on this enzyme system (e.g., opiates).[11]

Fospropofol is a prodrug of propofol and is chemically described as phosphono-*O*-methyl-2,6-diisopropylphenol, disodium salt ($C_{13}H_{19}O_5PNa_2$). Phosphono-*O*-methyl prodrugs undergo hydrolysis most notably by endothelial cell surface alkaline phosphatases liberating propofol (the active metabolite), phosphate, and formaldehyde. From the molecular weights of 332.24 D for fospropofol and 178.27 D for propofol, one would expect that 1 mg of fospropofol would liberate 0.54 mg of propofol. When released, propofol undergoes the same metabolic pathway as previously described.[12]

Pharmacokinetics

The pharmacokinetics of propofol has been described by two-compartment and three-compartment models (Table 26-1). After a single bolus injection, whole-blood propofol levels decrease rapidly as a result of redistribution and elimination (Fig. 26-2). The initial distribution half-life of propofol is 2 to 8 minutes.[4,13] Studies in which the disposition of propofol is described by a three-compartment model give initial and slow distribution half-lives of 1 to 8 minutes and 30 to 70 minutes and an elimination half-life of 4 to 23.5 hours.[14,15] This longer elimination half-life indicates a deep compartment with limited perfusion, which results in a slow return of propofol back to the central compartment. Because of the rapid clearance of propofol from the central compartment, the slow return of propofol from this deep compartment contributes little to the initial rapid decrease in propofol concentrations. The context-sensitive half-time for propofol (Fig. 26-3) for infusions of up to 8 hours is less than 40 minutes.[16]

Because the required decrease in concentration for awakening after anesthesia or sedation with propofol is generally less

Table 26-1 Pharmacokinetic Variables for Commonly Used Intravenous Anesthetics

Elimination	Elimination Half-Life (hr)	Clearance (mL/kg/min)	Vd_{ss} (L/kg)
Dexmedetomidine	2-3	10-30	2-3
Diazepam	20-50	0.2-0.5	0.7-1.7
Droperidol	1.7-2.2	14	2
Etomidate	2.9-5.3	18-25	2.5-4.5
Flumazenil	0.7-1.3	5-20	0.6-1.6
Ketamine	2.5-2.8	12-17	3.1
Lorazepam	11-22	0.8-1.8	0.8-1.3
Methohexital	2-6	10-15	1.5-3
Midazolam	1.7-2.6	6.4-11	1.1-1.7
Propofol	4-7	20-30	2-10
Thiopental	7-17	3-4	1.5-3

Vd_{ss}, apparent volume of distribution at steady state.

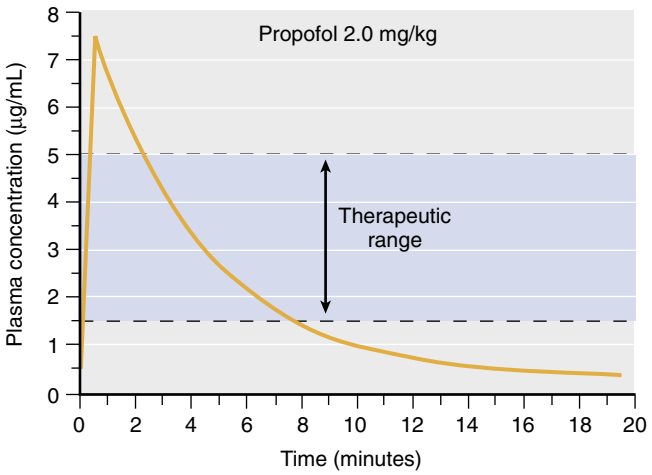


Figure 26-2 Simulated time course of whole blood levels of propofol after an induction dose of 2 mg/kg. Blood levels required for anesthesia during surgery are 2 to 5 µg/mL, with awakening usually occurring at a blood level less than 1.5 µg/mL.

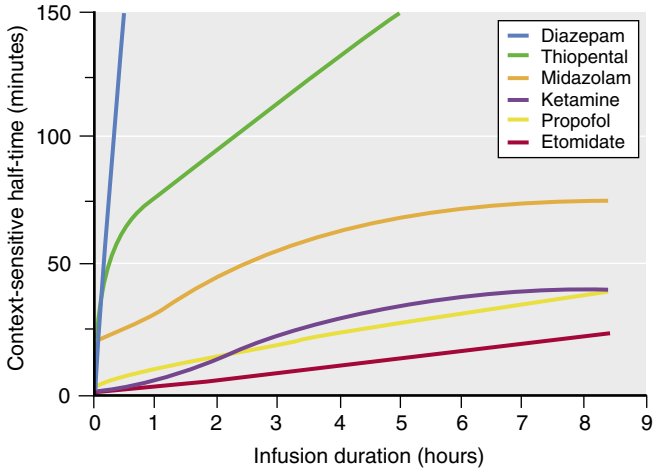


Figure 26-3 The context-sensitive half-times for commonly used IV anesthetic drugs. The context-sensitive half-time is the time for the plasma level of the drug to decrease 50% after cessation of infusion. The duration of infusion is plotted on the horizontal axis. The rapidity with which the drug level decreases is directly related to the time of infusion (i.e., the longer the drug is infused, the longer the half-time). Etomidate, propofol, and ketamine have significantly shorter half-times than thiopental and diazepam, which makes them more suitable for prolonged infusion.

than 50%, recovery from propofol remains rapid even after prolonged infusions. The volume of distribution of the central compartment has been calculated as 20 to 40 L, and the volume of distribution at steady state has been calculated as 150 to 700 L. The clearance of propofol is extremely high—1.5 to 2.2 L/min. As discussed earlier, this exceeds hepatic blood flow, and extrahepatic metabolism has been shown.[5,17]

The equilibrium constant for propofol based on suppression of the electroencephalogram (EEG) (which is strongly correlated with loss of consciousness) is about 0.3 min^{-1}, and the half-life of equilibrium between plasma concentration and EEG effect is 2.5 minutes. The time to peak effect is 90 to 100 seconds.[18] The onset of EEG effect with propofol seems to be independent of age. The onset of decreasing arterial blood pressure is much slower (double the time) and increases with age.[19] For EEG and blood pressure changes, elderly patients show a concentration-dependent increasing sensitivity (see Chapter 71).[19,20]

The pharmacokinetics of propofol may be altered by various factors (e.g., gender, weight, preexisting disease, age, and concomitant medication).[13,21-23] Propofol may impair its own clearance by decreasing hepatic blood flow.[24] Of clinical significance is that propofol may alter its own intercompartmental clearances because of its effects on cardiac output. Changes in cardiac output alter propofol concentrations after a bolus dose and during a constant infusion. Increasing cardiac output leads to a decrease in propofol plasma concentrations and vice versa.[25,26] In a hemorrhagic shock model propofol, concentrations increase 20% until uncompensated shock occurs, when there is a rapid and marked increase in propofol concentrations.[27]

In term and preterm neonates, variability of propofol clearance was accounted for largely by postmenstrual and postnatal age with very fast maturation of clearance in neonatal life. Dosing in these neonates needs to be calculated with extreme care.[28] Women have a larger volume of distribution and higher clearance rates, but the elimination half-life is similar for males and females.[13,22] Elderly individuals have decreased clearance rates, but a smaller central compartment volume.[21,22] During cardiopulmonary bypass, the central volume and initial clearance increase, necessitating higher initial infusion rates to maintain the same propofol plasma concentration.[29] Children have a larger central compartment volume (50%) and a more rapid clearance (25%).[30] In children older than 3 years, volumes and clearances should be weight adjusted.[31] Children younger than 3 years also show weight-proportional pharmacokinetic parameters, but with larger central compartment and systemic clearance values than in adults or older children.[31] This finding explains the larger dosing requirements in this age group (see Chapter 82).[32] Hepatic disease seems to result in a larger steady state and central compartment volumes; clearance is unchanged, but the elimination half-life is slightly prolonged, as is time to recovery.[33]

The effect of fentanyl administration on propofol pharmacokinetic parameters is controversial. Some studies suggest that fentanyl may reduce intercompartmental and total body clearance rates and volumes of distribution.[34] When propofol was administered with alfentanil at similar infusion rates, the measured propofol concentrations were 22% larger than when propofol was administered alone.[35] A separate study found that fentanyl did not alter propofol pharmacokinetics after a single dose of both drugs.[36] Some of these differences in propofol pharmacokinetics when given with an opioid may be explained by studies in cats that showed that pulmonary uptake of propofol is reduced by 30% when propofol is administered immediately after fentanyl, but not if it is administered 3 minutes later.[37] In addition, in vitro studies on human hepatocytes showed that propofol inhibited in a dose-dependent manner the enzymatic degradation of sufentanil and alfentanil.[38] Propofol kinetics is unaltered by renal disease.[23]

The disposition of fospropofol (the parent compound) is best described by a three-compartment model with a relatively small volume of distribution, a fast distribution, and a short terminal half-life of approximately 40 minutes. Fospropofol-delivered propofol has a different pharmacokinetic and pharmacodynamic profile than propofol emulsion, however. Decline of plasma concentrations is slower for fospropofol propofol, and area under the curve values are larger than for a propofol emulsion. Apparent clearance and volume of distribution are much higher in fospropofol propofol than those measured from a propofol emulsion. The peak propofol concentrations from calculated equipotent doses of fospropofol also are higher. Lipid-free formulations of propofol also result in higher peak concentration than equal doses of a lipid emulsion.

Fospropofol also showed a nonlinear relationship between its dose and propofol disposition. Even the propofol maximum concentration was nonlinearly related to dose. Time to maximum concentration of fospropofol was approximately 7 minutes, although at 2 minutes 70% of time to maximum concentration had been reached. Bolus administration of fospropofol achieves loss of response to a verbal command at a similar time and bispectral index (BIS) value as an equipotent amount of propofol emulsion, but shows a longer time to produce a decrease in BIS (almost double) and a more prolonged recovery profile (almost double). Differences in maximum concentration and nonlinearity make simple conversion of dosing from lipid emulsions of propofol to fospropofol difficult.[12,39,40]

Pharmacology

Effects on the Central Nervous System

The hypnotic action of propofol is mostly mediated by enhancing γ-aminobutyric acid (GABA)–induced chloride current through its binding to the β-subunit of $GABA_A$ receptor. Sites on the β_1-subunit (M 286), β_2-subunit (M 286), and β_3-subunit (N265) of the transmembrane domains are crucial for the hypnotic action of propofol.[41,42] The α-subunit and γ_2-subunit subtypes also seem to contribute to modulating the effects of propofol on the GABA receptor.[43] Propofol through its action on $GABA_A$ receptors in the hippocampus inhibits acetylcholine release in the hippocampus and prefrontal cortex.[44] The α_2-adrenoreceptor system also seems to play an indirect role in the sedative effects of propofol.[45] Propofol results in widespread inhibition of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor through modulation of sodium channel gating,[46] an action that also may contribute to the drug's central nervous system (CNS) effects. Studies have shown that propofol has a direct depressant effect on neurons of the spinal cord.[47] In acutely dissociated spinal dorsal horn neurons, propofol acts on $GABA_A$ and glycine receptors.[48] The hypnotic action of propofol is pressure reversible, and it adheres to the correlation exhibited by other general anesthetics between anesthetic potency and octanol/water distribution coefficient.[49] In contrast to barbiturates, propofol is not antianalgesic.

Two notable side effects of propofol are its antiemetic effect and a sense of well-being in patients. Propofol increases dopamine concentrations in the nucleus accumbens (a phenomenon noted with drugs of abuse and pleasure-seeking behavior).[50] Propofol's antiemetic action may be explained by the decrease in serotonin levels it produces in the area postrema, probably through its action on GABA receptors.[51]

The onset of hypnosis after a dose of 2.5 mg/kg is rapid (one arm–brain circulation), with a peak effect seen at 90 to 100 seconds. The median effective dose (ED_{50}) of propofol for loss of consciousness is 1 to 1.5 mg/kg after a bolus. The duration of hypnosis is dose-dependent, being 5 to 10 minutes after 2 to 2.5 mg/kg.[52] Age markedly affects the induction dose, being largest at ages younger than 2 years (ED_{95} 2.88 mg/kg) and decreasing with increasing age.[53] Increasing age decreases the propofol concentration required for loss of consciousness.[54] At subhypnotic doses, propofol provides sedation and amnesia.[55-57] Propofol infusions of at least 2 mg/kg/hr were necessary to provide amnesia in unstimulated volunteers.[58] Awareness during surgery at higher infusion rates has been reported.[59] During surgical procedures, extremely high infusion rates may be necessary to prevent awareness if propofol is used as the sole anesthetic.[54] Propofol also tends to produce a general state of well-being.[60] Hallucinations,[61] sexual fantasies, and opisthotonos[62] have been reported after propofol administration.

The effect of propofol on the EEG as assessed after 2.5 mg/kg followed by an infusion shows an initial increase in alpha rhythm followed by a shift to gamma and theta frequency. High infusion rates produce burst suppression.[63] EEG power analysis indicates that amplitude increases after induction, but is thereafter unaltered at propofol blood concentrations of 3 to 8 μg/mL.[64] At propofol concentrations greater than 8 μg/mL, amplitude markedly decreases, with periods of burst suppression.[64] Propofol causes a concentration-dependent decrease in the BIS, with 50% and 95% of patients unable to respond to a verbal command at a BIS of 63 and 51. The propofol concentration at which 50% of volunteers failed to respond to verbal command was 2.35 μg/mL. Lack of recall was observed in 95% of patients at a BIS value of 77.[65] Propofol produces a decrease in amplitude of the early components of somatosensory evoked potentials,[66] and a small nonsignificant increase in latency of the P_{40} and N_{50} components.[66]

Similar to other IV anesthetics, propofol does not alter brainstem auditory evoked potentials.[67] There are, however, a dose-dependent prolongation of latency and a decrease in amplitude of cortical middle latency auditory potentials, which are concentration-dependent.[67] Propofol effect site concentrations provide similar correlation with decreases in the spectral entropy variable derived from the EEG as it does with BIS, and a similar ability to titrate propofol anesthetic effect.[68] The effect of propofol on epileptogenic EEG activity is controversial. Seizures after propofol administration have been reported, mainly on induction or emergence from anesthesia, rarely during maintenance, and occasionally postoperatively. In various models, a direct anticonvulsant effect of propofol has been shown, which is dose-dependent.[69,70] In a few reports, propofol has been used to treat epileptic seizures.[71] Propofol also results in a shorter duration of motor and EEG seizure activity after electroconvulsive therapy compared with methohexital.[72] Propofol has been associated with grand mal seizures, however, and has been used for cortical mapping of epileptogenic foci.[73,74] There have been a few reports of convulsions after propofol administration that have occurred 6 days after anesthesia. Most of these patients had a history of previous convulsions. The incidence of this adverse effect is rare (1 in 50,000 administrations).

Tolerance to the effects of propofol remains controversial. Repeated dosing to children presenting for radiation therapy showed lack of tolerance for each treatment session,[75] whereas increasingly larger doses were required for repeated electroconvulsive therapy.[76] Of more importance are reports[77] of addiction to propofol. Propofol has been used to treat chronic refractory headache with doses of 20 to 30 mg every 3 to 4 minutes (400 mg maximum).[78]

Propofol decreases intracranial pressure (ICP) in patients with either normal or increased ICP.[79] The decrease in ICP (30% to 50%) is associated with significant decreases in cerebral perfusion pressure (CPP), however. The use of propofol in head-injured patients should be restricted to doses providing mild-to-moderate sedation (i.e., blood concentration of 2 μg/mL, infusion of 25-75 μg/kg/min) (see Chapters 47 and 63).[80] The lesser vasodilatory effects of propofol on the cerebral vasculature compared with volatile anesthetics may provide advantages in certain surgical procedures. Propofol acutely reduces intraocular pressure by 30% to 40%. Compared with thiopental, propofol produces a larger decrease in intraocular pressure and is more effective in preventing an increase in intraocular pressure secondary to succinylcholine and endotracheal intubation (see Chapter 29).[81] Normal cerebral reactivity to carbon dioxide and autoregulation are maintained during a propofol infusion.[82]

The neuroprotective effects of propofol remain controversial. Propofol administered to burst suppression results in significantly better neurologic outcome and less brain tissue injury in an incomplete ischemia model in rats compared with fentanyl.[83] Propofol administered at sedative concentrations started either

immediately after or at 1 hour after an ischemic insult significantly reduced infarct size compared with awake controls infused with intralipid.[84] Pretreatment with propofol fails to protect against focal ischemic insult.[85] In a spinal cord injury model, propofol reduced lipid peroxidation without improving ultrastructure at 1 hour after injury compared with thiopental, which reduced both.[86] The neuronal protective effect of propofol may be due to the attenuation of changes in adenosine triphosphate, calcium, sodium, and potassium caused by hypoxic injury[87] and its antioxidant action by inhibiting lipid peroxidation.[88] Current evidence indicates that propofol can protect neurons against ischemic injury caused by excitotoxicity, but neuroprotection may be sustained only if the ischemic insult is relatively mild and is not sustained after a prolonged recovery period.[89] Prolonged propofol sedation in children is associated with adverse neurologic sequelae (see Chapter 82).[90]

Many anesthetic-related drugs decrease the required dose or blood concentrations of propofol's pharmacologic action. The propofol Cp_{50} (blood concentration needed for 50% of subjects to not respond to a defined stimulus) for loss of response to verbal command in the absence of any other drug is 2.3 to 3.5 μg/mL.[54,91,92] The propofol Cp_{50} to prevent movement on skin incision is 16 μg/mL; this is markedly reduced by increasing concentrations of fentanyl or alfentanil.[54,91,92] The propofol Cp_{50} for skin incision when combined with benzodiazepine premedication (lorazepam, 1 to 2 mg) and 66% nitrous oxide is 2.5 μg/mL (venous).[22,92] This concentration is reduced to 1.7 μg/mL when morphine (0.15 mg/kg) rather than lorazepam is used for premedication.[93] The concentration of propofol (when combined with 66% nitrous oxide) required during minor surgery is 1.5 to 4.5 μg/mL,[15,22] and the concentration for major surgery is 2.5 to 6 μg/mL.[54] Awakening usually occurs at concentrations less than 1.6 μg/mL,[15,22,52] and orientation occurs at concentrations less than 1.2 μg/mL[15,22] when the propofol concentration is decreasing. When equilibration between blood and effect site is allowed, however, awakening concentrations (2.2 μg/mL) are much closer to concentrations associated with loss of verbal command.[94]

Effects on the Respiratory System

Apnea occurs after an induction dose of propofol; the incidence and duration of apnea depend on dose, speed of injection, and concomitant premedication. An induction dose of propofol results in a 25% to 30% incidence of apnea.[96] The duration of apnea occurring with propofol may be prolonged to more than 30 seconds, however. The incidence of prolonged apnea (>30 seconds) is increased further by addition of an opiate, either as premedication or just before induction of anesthesia.[96,97] The incidence of apnea with propofol is more frequent than with other commonly used IV induction anesthetics.[96,98] The onset of apnea usually is preceded by marked tidal volume reduction and tachypnea.[97] In volunteers, dose-dependent apnea was more pronounced with propofol emulsion than with fospropofol.[40]

In nearly every clinical setting propofol is used, it is a profound respiratory depressant. A maintenance infusion of propofol (100 μg/kg/min) results in a 40% decrease in tidal volume and a 20% increase in respiratory frequency, with an unpredictable change in minute ventilation.[97] Doubling the infusion rate from 100 to 200 μg/kg/min causes a further moderate decrease in tidal volume (455 to 380 mL), but no change in respiratory frequency.[97] The ventilatory response to carbon dioxide also is decreased during a maintenance infusion of propofol.[97] At 100 μg/kg/min, there is a 58% reduction in the slope of the carbon dioxide–response curve.[97] This is similar to the depression after a brief infusion of 3 mg/kg/min of thiopental. Doubling the infusion rate (and presumably the blood level) of propofol results in only a minimal further decrease in carbon dioxide responsiveness.[97] Propofol, 1.5 to 2.5 mg/kg, results in an acute (13% to 22%) increase in $Paco_2$ and a decrease in pH. Pao_2 does not change significantly. These changes are similar to the changes seen after an induction dose of thiopental. During a maintenance infusion of propofol (54 μg/kg/min), $Paco_2$ is moderately increased from 39 to 52 mm Hg. Doubling this infusion rate does not result in a further increase in $Paco_2$.

Propofol (50 to 120 μg/kg/min) also depresses the ventilatory response to hypoxia, presumably by a direct action on carotid body chemoreceptors.[99] Propofol induces bronchodilation in patients with chronic obstructive pulmonary disease.[100] Propofol attenuates vagal (at low concentrations) and methacholine-induced (at high concentrations) bronchoconstriction,[101] and seems to have a direct action on muscarinic receptors. Propofol inhibits the receptor coupled signal transduction pathway through inositol phosphate generation and inhibition of Ca^{2+} mobilization.[102] The preservative used with propofol seems to be important in its bronchodilator activity. Propofol with metabisulfite (compared with propofol without metabisulfite) does not inhibit vagal or methacholine-induced bronchoconstriction.[103]

Propofol also may have an impact on the pulmonary pathophysiology of adult respiratory distress syndrome. In an animal model of septic endotoxemia, propofol (10 mg/kg/hr) significantly reduced free radical mediated and cyclooxygenase catalyzed lipid peroxidation. In addition, Pao_2 and hemodynamics were maintained closer to baseline.[104] These benefits of propofol have not yet been confirmed in humans. Propofol at therapeutic concentrations also protects mouse macrophages from nitric oxide–induced apoptosis and cell death.[105]

Propofol also attenuates the magnitude of hypoxic pulmonary vasoconstriction.[106] The effect of propofol on pulmonary vasomotor tone inhibits acetylcholine-induced pulmonary vasodilation through nitric oxide and a cytochrome P-450 metabolite (likely endothelium-derived hyperpolarizing factor).[107]

Effects on the Cardiovascular System

The cardiovascular effects of propofol have been evaluated after its use for induction and for maintenance of anesthesia (Table 26-2).[108] The most prominent effect of propofol is a decrease in arterial blood pressure during induction of anesthesia. Independent of the presence of cardiovascular disease, an induction dose of 2 to 2.5 mg/kg produces a 25% to 40% reduction of systolic blood pressure.[108,112,113] Similar changes are seen in mean and diastolic blood pressure. The decrease in arterial pressure is associated with a decrease in cardiac output/cardiac index (±15%),[112,113] stroke volume index (±20%),[113] and systemic vascular resistance (15% to 25%).[112] Left ventricular stroke work index also is decreased (±30%). When looking specifically at right ventricular function, propofol produces a marked reduction in the slope of the right ventricular end-systolic pressure-volume relationship.[114]

In patients with valvular heart disease, pulmonary artery and pulmonary capillary wedge pressure also are reduced, a finding that implies the resultant decrease in pressure is due to a decrease in preload and afterload. Although the decrease in systemic pressure after an induction dose of propofol is due to

Table 26-2 Hemodynamic Changes after Induction of Anesthesia with Nonbarbiturate Hypnotics

	Diazepam	Droperidol	Etomidate*	Ketamine	Lorazepam	Midazolam	Propofol
HR	–9 ± 13%	Unchanged	–5 ± 10%	0-59%	Unchanged	–14 ± 12%	–10 ± 10%
MBP	0-19%	0-10%	0-17%	0 ± 40%	–7-20%	–12-26%	–10-40%
SVR	–22 ± 13%	–5-15%	–10 ± 14%	0 ± 33%	–10-35%	0-20%	–15-25%
PAP	0-10%	Unchanged	–9 ± 8%	+44 ± 47%	—	Unchanged	0-10%
PVR	0-19%	Unchanged	–18 ± 6%	0 ± 33%	Unchanged	Unchanged	0-10%
PAO	Unchanged	+25 ± 50%	Unchanged	Unchanged	—	0-25%	Unchanged
RAP	Unchanged	Unchanged	Unchanged	+15 ± 33%	Unchanged	Unchanged	0-10%
CI	Unchanged	Unchanged	–20 ± 14%	0 ± 42%	0 ± 16%	0-25%	–10-30%
SV	0-–8%	0-10%	0-20%	0-21%	Unchanged	0-18%	–10-25%
LVSWI	0-36%	Unchanged	0-33%	0 ± 27%	—	–28-42%	–10-20%
dP/dt	Unchanged	—	0-18%	Unchanged	—	0-12%	Decreased

*The larger deviations are in patients with valvular disease.
CI, cardiac index; dP/dt, first derivative of pressure measured over time; HR, heart rate; LVSWI, left ventricular stroke work index; MBP, mean blood pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; PAO, pulmonary artery occluded pressures; RAP, right atrial pressure; SV, stroke volume; SVR, systemic vascular resistance.

vasodilation, the direct myocardial depressant effects of propofol are more controversial. The decrease in cardiac output after propofol administration may be via its action on sympathetic drive to the heart. Propofol at high concentrations (10 μg/mL) abolishes the inotropic effect of α but not β adrenoreceptor stimulation, and enhances the lusitropic (relaxation) effect of β stimulation.[115] Clinically, the myocardial depressant effect and the vasodilation seem to be dose-dependent and plasma concentration–dependent.[116] The vasodilatory effect of propofol seems to be due to a reduction in sympathetic activity,[117] a direct effect on intracellular smooth muscle calcium mobilization,[118] inhibition of prostacyclin synthesis in endothelial cells,[119] reduction in angiotensin II–elicited calcium entry,[120] activation of K^+ adenosine triphosphate channels, and stimulation of nitric oxide. The stimulation of nitric oxide may be modulated by intralipid rather than propofol.[121]

Heart rate does not change significantly after an induction dose of propofol. Propofol either may reset or may inhibit the baroreflex, reducing the tachycardic response to hypotension.[122] Propofol also decreases cardiac parasympathetic tone in a dose-dependent manner.[123] Propofol has a minimal direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction.[124] Propofol attenuates the heart rate response to atropine in a dose-dependent manner. During an infusion of 10 mg/kg/hr of propofol, a cumulative dose of atropine of 30 μg/kg increased heart rate greater than 20 beats/min in only 20% of subjects compared with 100% in the absence of propofol.[125] Propofol suppresses atrial (supraventricular) tachycardias and probably should be avoided during electrophysiologic studies.[126]

In retrospective review of 2406 patients, Reich and colleagues[127] showed that 9% of patients experienced severe hypotension 0 to 10 minutes after induction of general anesthesia. Statistically significant multivariate predictors of hypotension 0 to 10 minutes after anesthetic induction included American Society of Anesthesiologists (ASA) class III through V, baseline mean arterial pressure (MAP) less than 70 mm Hg, age 50 years or older, use of propofol for induction of anesthesia, and increasing induction dosage of fentanyl. The combination of propofol with fentanyl was a particularly potent stimulus for hypotension. A prolonged postoperative stay or death was more common in patients with versus patients without postinduction hypotension; however, the use of propofol per se was not associated with increased morbidity.[127] Limited data indicate that 0.5 mg/kg of ketamine is able to better prevent decreases in hemodynamics after a propofol induction alone or in combination with fentanyl (1 μg/kg).[128]

During maintenance of anesthesia with a propofol infusion, arterial systolic blood pressure also is decreased to 20% to 30% less than preinduction of anesthesia levels. In patients allowed to breathe room air during a maintenance infusion of 100 μg/kg/min of propofol, there is a significant decrease in systemic vascular resistance (30%), but cardiac index and stroke index are unaltered. In contrast, in patients receiving a narcotic premedication and nitrous oxide with an infusion of propofol (54 μg/kg/min and 108 μg/kg/min) for maintenance during surgery, systemic vascular resistance is not significantly decreased from baseline, but cardiac output and stroke volume are decreased. This situation is probably explained by the observation that propofol infusions produce a dose-dependent decrease of sympathetic nerve activity, attenuating the reflex responses to hypotension. In the presence of hypercarbia, the reflex sympathetic responses are better maintained.[129]

Increasing the infusion rate of propofol from 54 to 108 μg/kg/min (blood concentration 2.1 to 4.2 μg/mL) produces only a slightly greater decrease in arterial blood pressure (–10%). The peak plasma concentrations obtained after a bolus dose are substantially higher than the concentrations seen with a continuous infusion. Because the vasodilatory and myocardial depressant effects are concentration-dependent, the decrease in arterial blood pressure from propofol during the infusion phase (maintenance of anesthesia) is much less than that seen after an induction of anesthesia bolus. When propofol was compared with midazolam for sedation after coronary revascularization, propo-

fol resulted in a 17% less frequent incidence of tachycardia, a 28% less frequent incidence of hypertension, and a 17% more frequent incidence in hypotension. These differences in hemodynamic variables resulted in no difference in the number or severity of ischemic events between the two groups. An infusion of propofol results in a significant reduction in myocardial blood flow and myocardial oxygen consumption,[108,111] a finding that suggests that the global myocardial oxygen supply-to-demand ratio is preserved.

The cardioprotective effect of propofol versus volatile anesthetics in patients having cardiac surgery on or off cardiopulmonary bypass is less debatable. In two large studies comparing propofol with sevoflurane in patients undergoing cardiac surgery, postoperative troponin were lower and hemodynamic function better in patients receiving sevoflurane.[130,131] A study comparing desflurane with propofol in patients undergoing off-pump coronary artery bypass showed similar results.[132] In contrast, a small study that administered high-dose propofol (120 µg/kg/min), low-dose propofol (60 µg/kg/min) while on pump, or titrated isoflurane throughout surgery showed improved troponin levels and better hemodynamic function in the large-dose propofol group compared to the isoflurane or low-dose propofol group.[133] This study may indicate that cardioprotection with propofol is dose dependent, but needs confirmation.

Heart rate may increase,[111] decrease,[110] or remain unchanged[109] when anesthesia is maintained with propofol. The extent of hypotension, the ability for the patient to compensate, and the use of any other concomitant drugs are likely the most important factors in determining what happens to the heart rate after propofol administration.

Other Effects

Propofol, similar to thiopental, does not enhance neuromuscular blockade produced by neuromuscular blocking drugs. Propofol produces no effect on the evoked electromyogram or twitch tension; however, good intubating conditions after propofol alone have been reported.[134] Propofol does not trigger malignant hyperthermia and is an appropriate choice in patients with this condition.[135]

Propofol after a single dose or a prolonged infusion does not affect corticosteroid synthesis or alter the normal response to adrenocorticotropic hormone (ACTH) stimulation.[136] Propofol in the emulsion formulation does not alter hepatic, hematologic, or fibrinolytic function. Lipid emulsion per se reduces in vitro platelet aggregation, however.[137] Anaphylactoid reactions to the present formulation of propofol have been reported. In at least some patients, the immune response was entirely due to propofol and not to the lipid emulsion. A high percentage of the patients developing the anaphylactoid response to propofol had a previous history of allergic responses. In patients with multiple drug allergies, propofol should be used with caution.[138] Propofol alone in intralipid does not trigger histamine release.[139] Fospropofol is metabolized to propofol and formate. Formate concentrations do not increase after fospropofol administration.[40]

Propofol also possesses significant antiemetic activity at low (subhypnotic) doses. It has been used successfully to treat postoperative nausea in a bolus dose of 10 mg.[140] The median concentration of propofol that was associated with an antiemetic effect was 343 ng/mL.[141] This concentration can be achieved by a propofol infusion of 10 to 20 mg loading dose followed by 10 µg/kg/min. Propofol used as a maintenance anesthetic during breast surgery was more effective than 4 mg of ondansetron given as prophylaxis in preventing postoperative nausea and vomiting (PONV). In the same study, the maintenance propofol infusion also was superior to adding propofol only at the end of the procedure (sandwich technique).[142] Propofol as an infusion of 1 mg/kg/hr (17 µg/kg/min) also has provided excellent antiemetic action after anticancer chemotherapy. At subhypnotic doses, propofol relieves cholestatic pruritus and is as effective as naloxone in treating pruritus induced by spinal opiates,[143] although not all studies have confirmed this effect of propofol.

Propofol decreases polymorphonuclear leukocyte chemotaxis, but not adherence phagocytosis and killing. This action contrasts with the effect of thiopental, which inhibits all these chemotactic responses.[144] Propofol inhibits phagocytosis and killing of *Staphylococcus aureus* and *Escherichia coli,* however.[145] These findings are particularly pertinent in view of the observation of increased life-threatening systemic infections associated with the use of propofol.[146] In hospitals where these infections occurred, opened vials and syringes of propofol had positive cultures for the offending organisms. The intralipid that acts as the solvent for propofol is an excellent culture medium. Disodium edetate or metabisulfite has been added to the formulation of propofol in an attempt to retard such bacterial growth. Strict aseptic technique still must be observed.

The administration of propofol also has been associated with the development of pancreatitis.[147] The development of pancreatitis seems to be related to hypertriglyceridemia. Patients who developed hypertriglyceridemia tended to be older, had a longer intensive care unit (ICU) stay, and received propofol for a longer duration. It seems prudent, if propofol is being used for prolonged sedation or at higher infusion rates (especially in elderly patients), that serum triglyceride concentrations should be routinely monitored.[148]

Uses

Induction and Maintenance of Anesthesia

Propofol is suitable for the induction and maintenance of anesthesia (Table 26-3). The induction dose is 1 to 2.5 mg/kg. Physiologic characteristics that best determine the induction dose are age, lean body mass, and central blood volume.[149] Premedication with an opiate or a benzodiazepine, or both, markedly reduces the induction dose.[150,151] A dose of 1 mg/kg (with premedication) to 1.75 mg/kg (without premedication) is recommended for inducing anesthesia in patients older than 60 years (see Chapter 71).[152] As noted earlier, older and sicker (ASA class III to IV) patients develop more profound hypotension, especially when propofol is

Table 26-3 Uses and Doses of Intravenous Propofol

Induction of general anesthesia	1-2.5 mg/kg IV dose reduced with increasing age
Maintenance of general anesthesia	50-150 µg/kg/min IV combined with N_2O or an opiate
Sedation	25-75 µg/kg/min IV
Antiemetic	10-20 mg IV, can repeat every 5-10 min or start infusion of 10 µg/kg/min

N_2O, nitrous oxide.

combined with an opiate.[127] To prevent hypotension in sicker patients or in patients presenting for cardiac surgery, a fluid load should be administered as tolerated, and the propofol can be administered in small incremental doses (10 to 30 mg or as an infusion) until the patients lose consciousness. To limit the dose and retain the fastest onset time, an infusion of 80 mg/kg/hr is optimal. Diluting propofol to 0.5 mg/mL further reduces the impact of this induction dose on hemodynamics.[153] For induction in children, the ED_{95} (2 to 3 mg/kg) is increased, primarily because of pharmacokinetic differences (see Chapter 82).[154]

Propofol, when used for induction of anesthesia in briefer procedures, results in a significantly quicker recovery and an earlier return of psychomotor function compared with thiopental or methohexital, regardless of the anesthetic used for maintenance of anesthesia. The incidence of nausea and vomiting when propofol is used for induction also is markedly less than after the use of other IV anesthetics, probably because of the antiemetic properties of propofol.[155]

Because of its pharmacokinetics, propofol provides a rapid recovery and is superior to barbiturates for maintenance of anesthesia, and it seems to be equal to enflurane, isoflurane and sevoflurane.[156] Recovery from desflurane is slightly more rapid than recovery from propofol.[157] Propofol can be given as intermittent boluses or as a continuous infusion for maintenance. After a satisfactory induction dose, a bolus of 10 to 40 mg is needed every few minutes to maintain anesthesia. Because these doses need to be given frequently, it is more suitable to administer propofol as a continuous infusion.

Several infusion schemes have been used to achieve adequate plasma concentrations of propofol.[158] After an induction dose, an infusion of 100 to 200 μg/kg/min is usually needed. The infusion rate is titrated to individual requirements and the surgical stimulus. When combined with propofol, the required infusion rate and concentration of opiates, midazolam, clonidine, or ketamine is reduced. Because opioids alter the concentration of propofol required for adequate anesthesia, the relative dose of either opioid or propofol markedly affects the time from termination of drug to awakening and recovery. The infusion rate required to achieve the combination with the shortest recovery is propofol, 1 to 1.5 mg/kg followed by 140 μg/kg/min for 10 minutes followed by 100 μg/kg/min, and alfentanil, 30 μg/kg followed by an infusion of 0.25 μg/kg/min, or fentanyl, 3 μg/kg followed by 0.02 μg/kg/min. Propofol also has been used as a single mixture with alfentanil, containing 1 mg of alfentanil (2 mL) to 400 mg of propofol (40 mL). When this mixture was administered at infusion rates commonly used for propofol (i.e., 166 μg/kg/min for 10 minutes, 133 μg/kg/min for 10 minutes, and 100 μg/kg/min thereafter), it provided an outcome equal to that obtained by using the two drugs as separate infusions.[159]

Increasing age is associated with a decrease in propofol infusion requirements (see Chapter 71), whereas these requirements are higher in children and infants (see Chapter 82).[30] The blood levels of propofol alone for loss of consciousness are 2.5 to 4.5 μg/mL, and the blood concentrations (when combined with nitrous oxide) required for surgery are 2.5 to 8 μg/mL.[15,22,52,93,160,161] Similar concentrations are necessary when propofol is combined with an opioid for a total IV technique. The knowledge of these levels and of the pharmacokinetics of propofol has enabled the use of pharmacokinetic model–driven infusion systems to deliver propofol as a continuous infusion for the maintenance of anesthesia. A meta-analysis of recovery data after either propofol for maintenance or the newer volatile anesthetics indicated only minor differences in times to reach recovery goals; however, the incidence of nausea and vomiting remained significantly lower in the patients administered propofol for maintenance.[162]

Several studies have investigated the utility of propofol as a maintenance infusion regimen for cardiac surgery. Using reduced and titrated doses of propofol for induction and titrated infusion rates of 50 to 200 μg/kg/min combined with an opioid for maintenance, propofol provided intraoperative hemodynamic control and ischemic episodes similar to those with either enflurane/opioid or a primary opioid technique.[163,164]

Sedation

Propofol has been evaluated for sedation during surgical procedures[55,56,165] and for patients receiving mechanical ventilation in the ICU (see Chapter 92).[166] Propofol by continuous infusion provides the ability to titrate to a desired level of sedation and provide a rapid recovery after infusion is terminated, regardless of the duration of the infusion.[56,168] In a study of patients sedated in the ICU for 4 days with propofol, recovery to consciousness was rapid (±10 minutes). The rate of recovery and the decrease in plasma concentration were similar at 24 hours and at 96 hours, when the infusion was discontinued. In addition, the plasma concentrations required for sedation and for awakening were similar at 24 hours and 96 hours, a finding that implies that tolerance to propofol did not occur.[168] As noted earlier, there have been more recent reports of tolerance with propofol.

Infusion rates required for sedation to supplement regional anesthesia in healthy patients are half or less than the rates required for general anesthesia (i.e., 30 to 60 μg/kg/min).[55] In elderly patients (>65 years old) and in sicker patients, the infusion rates that are necessary are markedly reduced.[55,166,167] It is important to titrate the infusion individually to the desired effect. A 1992 report[169] linked propofol with several deaths in children requiring sedation for mechanical ventilation secondary to upper respiratory tract infections. This rare syndrome (propofol infusion syndrome) also may occur in adults (see later). A potential advantage of propofol for sedation of ICU patients is that it seems to possess antioxidant properties.[170]

Although the pharmacokinetic profile and to a large extent the pharmacology of propofol make it an excellent choice for long-term (days) sedation, this always must be weighed against the hemodynamic effects, the often concomitant need for an analgesic, tolerance, and rare occurrences of hypertriglyceridemia (and potential pancreatitis) or propofol infusion syndrome. Maintaining the lowest possible dose required for the desired level of sedation with potential "sedation holidays" should considered as part of a long-term propofol sedation regimen. In addition, the FDA has specifically recommended against the use of propofol for the prolonged sedation of pediatric patients. The sedation guidelines of the American College of Critical Care Medicine also recommend "that patients receiving propofol for long term sedation should be monitored for unexplained metabolic acidosis or arrhythmias. Alternative sedative agents should be considered for patients with escalating vasopressor or inotrope requirements or cardiac failure during high-dose propofol infusions."[171] The recommended maximal dose of propofol infusion rate is 80 μg/kg/min (<5 mg/kg/hr).[171]

Generally, at propofol infusion rates greater than 30 μg/kg/min, patients are amnesic.[167] Compared with midazolam when used to maintain sedation, propofol provides equal or better

control and more rapid recovery.[56,167] In mechanically ventilated patients, more rapid recovery translates to more rapid extubation when sedation is terminated.[167] Propofol also has been used successfully in patient-controlled sedation. Propofol was rated better than midazolam when used by this technique, probably owing to its much more rapid onset and offset.[172] Patient-controlled sedation has been compared with anesthesia provider sedation. Generally, patients use less propofol and recover more quickly, and there are limited differences in patient satisfaction.[173,174]

Side Effects and Contraindications

Induction of anesthesia with propofol is associated with several side effects, including pain on injection, myoclonus, apnea, hypotension, and, rarely, thrombophlebitis of the vein into which propofol is injected. Pain on injection is less than or equal to that with etomidate, equal to that with methohexital, and greater than that after thiopental.[175,154] Pain on injection is reduced by using a large vein, avoiding veins in the dorsum of the hand, and adding lidocaine to the propofol solution or changing the propofol formulation. Multiple other drugs and distraction techniques have been investigated to reduce the pain on injection of propofol. Pretreatment with a small dose of propofol, opiates, nonsteroidal anti-inflammatory drugs, ketamine, esmolol/metoprolol, magnesium, a flash of light, clonidine/ephedrine combination, dexamethasone, and metoclopramide all have been tested with variable efficacy.

Fospropofol causes less pain on injection, but an equal incidence of tingling/discomfort in the genital areas.[40] Myoclonus occurs more frequently after propofol than after thiopental, but less frequently than after etomidate or methohexital.[154] Apnea after induction with propofol is common. The incidence of apnea may be similar to that after thiopental or methohexital; however, propofol produces a greater incidence of apnea lasting longer than 30 seconds.[98,160] The addition of an opiate increases the incidence of apnea, especially prolonged apnea.[95,160]

The most common side effect during induction of anesthesia is hypotension, which is augmented by the concomitant administration of opioids.[113] Conversely, with laryngoscopy and endotracheal intubation, the changes in MAP, heart rate, and systemic vascular resistance are less significant after propofol compared with thiopental.[110,113]

Propofol infusion syndrome is a rare but lethal syndrome associated with infusion of propofol at 4 mg/kg/hr or more for 48 hours or longer. It was first described in children, but subsequently has been observed in critically ill adults. The clinical features of propofol infusion syndrome are acute refractory bradycardia leading to asystole, in the presence of one or more of the following: metabolic acidosis (base deficit >10 mmol/L^{-1}), rhabdomyolysis, hyperlipidemia, and enlarged or fatty liver.[176] Other features include cardiomyopathy with acute cardiac failure, skeletal myopathy, hyperkalemia, hepatomegaly, and lipemia.[151,177] Theories about its causality include mitochondrial toxicity, mitochondrial defects, impaired tissue oxygenation, and carbohydrate deficiency. The major risk factors for its development seem to be poor oxygen delivery, sepsis, serious cerebral injury, and high propofol dosage. In some reports, an increasing lipemia has been noted and was likely to be due to a failure of hepatic lipid regulation, possibly related to poor oxygenation or a lack of glucose or both. In some cases, an increasing lipemia was the first indication of impending propofol infusion syndrome onset, so it should not be viewed as a benign sign.[178]

Barbiturates

History

Thiopental was introduced clinically by Waters and Lundy (Fig. 26-4), and became preferred clinically because of its rapid onset of action and short duration, without the excitatory effects of hexobarbital.[179] Although criticized after many casualties during the attack on Pearl Harbor as "the ideal form of euthanasia in war surgery," the barbiturates continued to be widely used in clinical practice.[180] Although many other barbiturate derivatives have been synthesized throughout the past several decades, none have enjoyed the clinical success and popularity of thiopental.

Physicochemical Characteristics

Chemistry and Formulation

Barbiturates are hypnotically active drugs that are derivatives of barbituric acid (2,4,6-trioxohexahydropyrimidine), a hypnotically inactive pyrimidine nucleus that is formed by the condensation of malonic acid and urea (Fig. 26-5). The two major divisions of barbiturates are those with an oxygen at position 2 and those with a sulfur in position 2—the classes of oxybarbiturates and thiobarbiturates, respectively. Through keto-enol tautomerization, the oxygen or sulfur in position 2 becomes a reactive species in the enol form, allowing for the formation of water-soluble barbiturate salts in alkaline solutions. This solubility permits the IV use of barbiturates. Although tautomerization to the enol form allows for the creation of salts, it is substitution of the hydrogen attached to the carbon atom in position 5 with aryl or alkyl groups that gives the barbiturates their hypnotic activity. Only thiopental and thiamylal, thiobarbiturates, and methohexital, an oxybarbiturate, have been commonly used for induction of anesthesia (Fig. 26-6).

The formulation of barbiturates involves preparing them as sodium salts (mixed with 6% by weight anhydrous sodium carbonate) and then reconstituting with either water or normal saline to produce a 2.5% solution of thiopental, a 2% solution of thiamylal, or a 1% solution of methohexital. The thiobarbiturates are stable for 1 week if refrigerated after reconstitution, and methohexital remains available for use for 6 weeks after reconstitution. A decrease in the alkalinity of the solution can result in precipitation of the barbiturates as free acids, which is why they cannot be reconstituted with lactated Ringer's solution or mixed with other acidic solutions. Examples of drugs that are not to be coadministered or mixed in solution with the barbiturates are pancuronium, vecuronium, atracurium, alfentanil, sufentanil, and midazolam. Studies have shown that in rapid-sequence induction, the mixing of thiopental with vecuronium or pancuronium results in the formation of precipitate that may occlude the IV line.[181]

Structure-Activity Relationships

As noted earlier, substitutions at the 5, 2, and 1 positions confer different pharmacologic activities to the barbiturate nucleus. Sub-

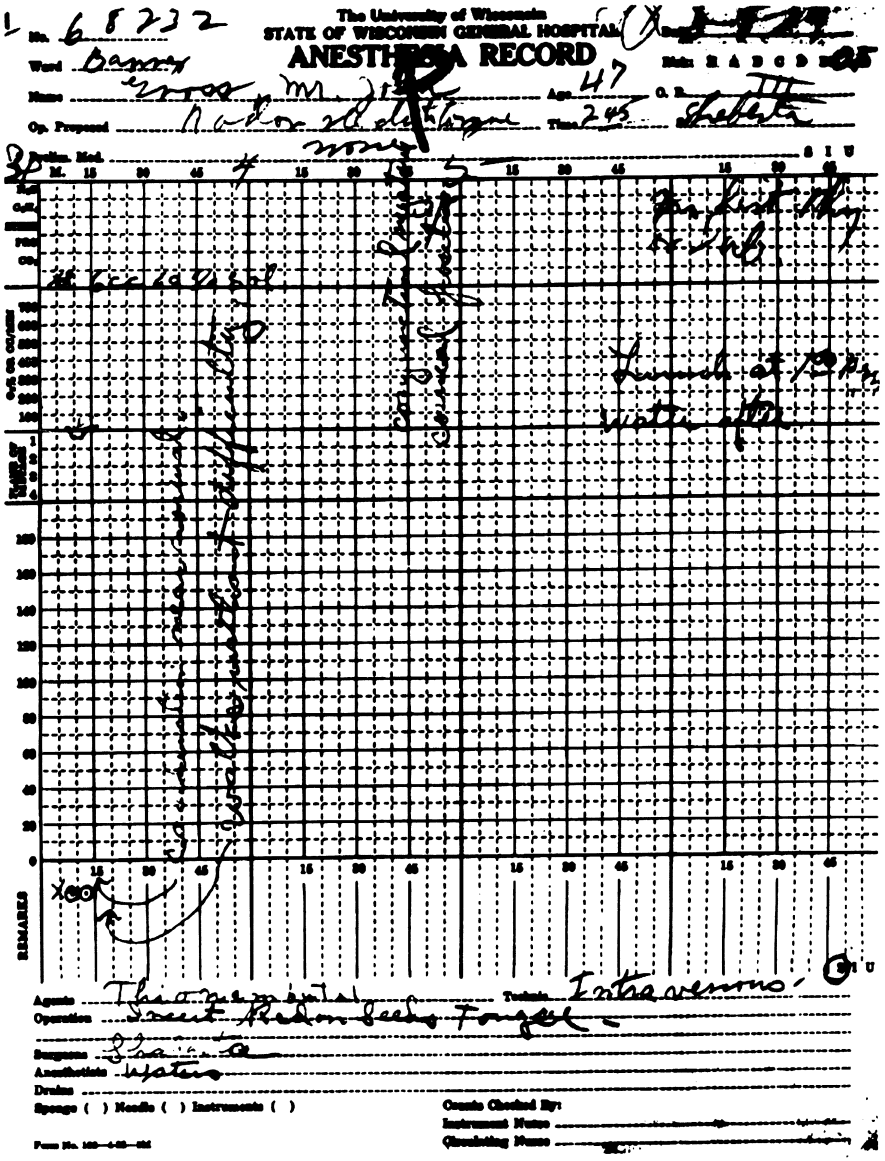


Figure 26-4 Reproduction of the first administration of thiopental by Waters on March 8, 1934. *(From Dundee JW, Wyant GM: Intravenous Anaesthesia. Edinburgh, Churchill Livingstone, 1974.)*

stitutions at position 5 with either aryl or alkyl groups produce hypnotic and sedative effects. A phenyl group substitution at C5 produces anticonvulsant activity. An increase in length of one or both side chains of an alkyl group at C5 increases hypnotic potency. Barbiturates used in clinical practice have either an oxygen or sulfur at C2. Substitution of a sulfur at position 2 produces a more rapid onset of action, as with thiopental. The addition of a methyl or ethyl group at position 1 also may produce a more rapid onset of action, but excitatory side effects, including tremor, hypertonus, and involuntary movement, may occur with administration, as with methohexital.

Metabolism

The barbiturates (with the exception of phenobarbital) are hepatically metabolized. The metabolites that are formed are almost all inactive, water-soluble, and excreted in the urine. Barbiturates are biotransformed by four processes: (1) oxidation of the aryl, alkyl, or phenyl moiety at C5; (2) *N*-dealkylation; (3) desulfuration of the thiobarbiturates at C2; and (4) destruction of the barbituric acid ring.[182] Oxidation is the most important pathway, producing polar (charged) alcohols, ketones, phenols, or carboxylic acids. These metabolites are readily excreted in the urine or as glucuronic acid conjugates in the bile. The barbituric acid ring is so stable in vivo that hydrolytic cleavage of the ring is a minimal contribution to the total metabolism of barbiturates. Drugs that induce the oxidative microsomes enhance the metabolism of barbiturates. Long-term administration of barbiturates also induces the enzymes.[182] The hepatic enzyme induction of barbiturates is responsible for the recommendation that they not be administered to patients with acute intermittent porphyria because barbiturates may precipitate an attack by stimulating γ-aminolevulinic acid synthetase, the enzyme responsible for the production of porphyrins.[183]

As mentioned earlier, hepatic metabolism accounts for the elimination of all of the barbiturates with the exception of phenobarbital. Renal excretion is important in the elimination of

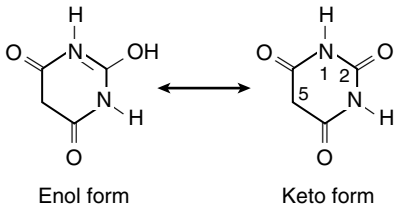


Figure 26-5 The keto and enol tautomeric forms of barbituric acid with the sites of substitution in the hypnotically active barbiturates identified as 1, 2, and 5.

phenobarbital, accounting for 60% to 90% of drug excretion in an unchanged form. Only trivial amounts of other barbiturates are excreted unchanged by the kidney. The alkalinization of urine with bicarbonate enhances the renal excretion of phenobarbital.

Methohexital is metabolized in the liver by oxidation to an alcohol and *N*-dealkylation. Compared with thiopental, methohexital exhibits similar distribution half-lives, volumes of distribution, and protein bindings. A marked difference exists, however, in plasma disappearance and elimination half-lives (4 hours for methohexital and 12 hours for thiopental). This difference is due to the threefold more rapid rate of hepatic clearance of methohexital (mean 7.8 to 12.5 mL/kg/min).[184] The hepatic extraction ratio of methohexital (clearance to hepatic blood flow) is approximately 0.5, indicating that the liver extracts 50% of the drug presented to it. This ratio contrasts to the lower hepatic extraction ratio of thiopental (0.15).

Pharmacokinetics

Barbiturate pharmacokinetics has been described in physiologic and compartmental models, with the latter gaining more support in recent years.[185] Physiologic models of barbiturates describe a rapid mixing of the drug with the central blood volume followed by a quick distribution of the drug to highly perfused, low-volume tissues (i.e., brain) with a slower redistribution of the drug to lean tissue (muscle), which terminates the effect of the induction dose. In these models, adipose tissue uptake and metabolic clearance (elimination) play only a minor role in the termination of the effects of the induction dose because of the minimal perfusion ratio compared with other tissues and the slow rate of removal. Compartmental model values for thiopental and methohexital, the most commonly used induction barbiturates, are given in Table 26-1.

Both of these pharmacokinetic models describe rapid redistribution as the primary mechanism that terminates the action of a single induction dose. The compartmental model explains the delay of recovery when a continuous infusion of a barbiturate is used. This model describes the phenomena whereby the termination of effect becomes increasingly dependent on the slower process of uptake into adipose tissue and elimination clearance through hepatic metabolism. After prolonged infusions, the pharmacokinetics of barbiturate metabolism is best approximated by nonlinear Michaelis-Menten metabolism.

In usual doses (4 to 5 mg/kg), thiopental exhibits first-order kinetics (i.e., a constant *fraction* of drug is cleared from the body per unit time); however, at very high doses of thiopental (300 to 600 mg/kg) with receptor saturation, zero-order kinetics occur (i.e., a constant *amount* of drug is cleared per unit time). The volume of distribution is slightly larger in female patients, causing longer elimination half-lives.[186] Pregnancy also increases the volume of distribution of thiopental, prolonging the elimination half-life.[187] As noted previously, the clearance rate of thiopental is not altered in patients with cirrhosis because the amount of protein available for the drug to bind to is still adequate even at fairly advanced stages of the disease process.[188]

Because of its affinity for fat, relatively large volume of distribution, and low rate of hepatic clearance, thiopental can accumulate in tissues, especially if given in large doses over a prolonged period. The plasma drug level increases when repeat doses of drug are given.[189] Appropriately designed infusion schemes ensure constant blood levels, maintaining the hypnotic effect, although this is not used in routine clinical practice.

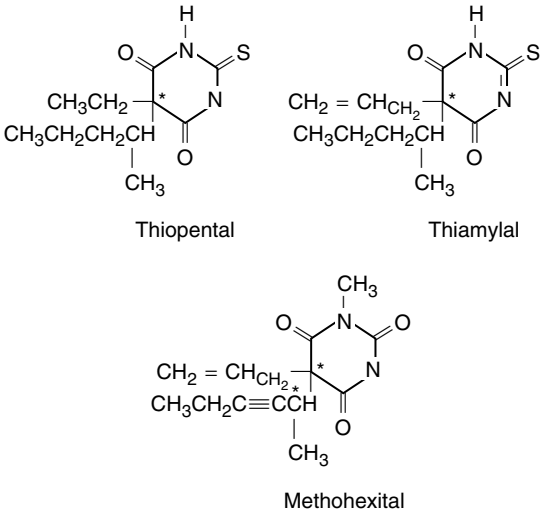


Figure 26-6 Hypnotically active barbiturates commonly used for induction, with their asymmetric centers indicated by an asterisk.

Pharmacology

Mechanism of Action

Much research has been conducted to delineate the mechanisms of action of barbiturates on the CNS, but until more recently, with the exception of their action on $GABA_A$ receptor, these have remained largely unknown.[190,191] Numerous more recent studies have begun to elucidate the role of NMDA receptors in the actions of barbiturates.[192-195] The selectivity of actions of barbiturates on CNS neurophysiologic systems has been grouped into two general categories: (1) enhancement of the synaptic actions of *inhibitory* neurotransmitters, and (2) blockade of the synaptic actions of *excitatory* neurotransmitters.[196]

GABA is the principal inhibitory neurotransmitter in the mammalian CNS, and the $GABA_A$ receptor is the only site that has been proved to be involved in barbiturate-induced anesthesia.[191] The $GABA_A$ receptor is a chloride ion channel that is composed of at least five subunits with specific sites of action for GABA, barbiturates, benzodiazepines, and other molecules.[179] Barbiturate binding to the $GABA_A$ receptor enhances and mimics the action of GABA by increasing chloride conductance through

the ion channel, causing hyperpolarization of the cell membrane and increasing the threshold of excitability of the postsynaptic neuron.[197] At low concentrations, barbiturates enhance the effects of GABA, decreasing the rate of dissociation of GABA from its receptor and increasing the duration of GABA-activated chloride ion channel openings. This enhancement of the action of GABA is considered to be responsible for the sedative-hypnotic effects of the barbiturates. At higher concentrations, the barbiturates directly activate the chloride channels without the binding of GABA, acting as the agonist itself. The GABA-mimetic effect at slightly higher concentrations may be responsible for what is termed *barbiturate anesthesia*.[191]

The barbiturates also inhibit synaptic transmission of excitatory neurotransmitters, such as glutamate and acetylcholine.[191] The actions of the barbiturates to block excitatory CNS transmission are specific for synaptic ion channels. Thiopental may exert GABA-independent effects, however, on the glutaminergic-NMDA system.[194] In two studies of rat prefrontal cortex, thiopental was shown to decrease extracellular glutamate levels in the CNS and decrease NMDA-gated currents in a concentration-dependent manner.[192,193] In a similar study in mice, thiopental has GABA-independent actions that inhibit the excitatory activities through inhibition of NMDA receptors.[194]

Effects on Cerebral Metabolism

Barbiturates, similar to other CNS depressants, have potent effects on cerebral metabolism (see Chapters 13 and 63). A dose-related depression of cerebral metabolic oxygen consumption rate ($CMRO_2$), produces a progressive slowing of the EEG, a reduction in the rate of adenosine triphosphate consumption, and protection from incomplete cerebral ischemia.[198] The relationship of depressed metabolism to drug dosage was shown in dogs in which circulation at high thiopental doses was preserved by an extracorporeal circulation pump.[199] When the results of the EEG became isoelectric, a point at which cerebral metabolic activity is roughly 50% of baseline,[200] no further decrements in $CMRO_2$ occurred. These findings support the hypothesis that metabolism and function are coupled. It is the portion of metabolic activity concerned with neuronal signaling and impulse traffic that is reduced by barbiturates, however, not the portion corresponding to basal metabolic function. The only way to suppress baseline metabolic activity concerned with cellular activity is through hypothermia.[200] The effect of barbiturates on cerebral metabolism is maximized at a 50% depression of cerebral function, in which less oxygen is required as $CMRO_2$ is diminished, leaving all metabolic energy to be used for the maintenance of cellular integrity.

With the reduction in $CMRO_2$, there is a parallel reduction in cerebral perfusion, which is seen in decreased cerebral blood flow and ICP. With reduced $CMRO_2$, cerebral vascular resistance increases, and CBF decreases.[201] The ratio of CBF to $CMRO_2$ is unchanged. The reduction in CBF after the administration of barbiturates causes a concurrent decrease in ICP. Even though the MAP decreases, barbiturates do not compromise the overall CPP because the CPP = MAP − ICP. In this relationship, ICP decreases more relative to the decrease in MAP after barbiturate use, preserving CPP.

Pharmacodynamics

Barbiturates produce the clinical effects of sedation and sleep. Sufficient doses produce a CNS depression that is termed *general anesthesia* and is attended by loss of consciousness, amnesia, and respiratory and cardiovascular depression. The response to pain and other noxious stimulation during general anesthesia seems to be obtunded. The results of pain studies reveal that barbiturates may decrease the pain threshold, however.[202] This antanalgesic effect occurs only at low blood levels of barbiturates, such as with small induction doses of thiopental or after emergence from thiopental when the blood levels are low. The amnesic effect of barbiturates has not been well studied, but it is less pronounced than that produced by benzodiazepines.

Onset of Central Nervous System Effects

Drugs with high lipid solubility and low degree of ionization cross the blood-brain barrier rapidly, producing a fast onset of action.[191] Most barbiturates exist in a nonionized form. The degree of lipid solubility of the nonionized form of the drug works in conjunction with the amount of drug that exists in the nonionized form (reflection of pK_a) to determine the rapidity with which a drug crosses the blood-brain barrier. Thiopental and methohexital are more lipid soluble than pentobarbital, which clinically corresponds to the more rapid onset of action of thiopental and methohexital compared with pentobarbital.[203,204]

Only the nonionized form of a drug can directly traverse the cellular membranes. Thiopental has a pK_a of 7.6. Approximately 50% of thiopental is nonionized at physiologic pH, which accounts partly for the rapid accumulation of thiopental in the cerebrospinal fluid (CSF) after IV administration.[205] Methohexital is 75% nonionized at pH 7.4, a fact that may explain the slightly more rapid effect of this drug compared with the effect of thiopental. As pH decreases, with poor perfusion, barbiturates have a larger proportion of nonionized drug available to cross the blood-brain barrier.[204,205]

Protein binding affects the onset of action in the CNS. Barbiturates are highly bound to albumin and other plasma proteins. Because only unbound drug (free drug) can cross the blood-brain barrier, an inverse relationship exists between the degree of plasma protein binding and the rapidity of drug passage across the blood-brain barrier.[206] Drugs have different degrees of protein binding, and generally the thiobarbiturates are more highly bound than are the oxybarbiturates.[207] The degree of protein binding of a drug is influenced by the physiologic pH and disease states, which alter the absolute amount of protein. Most barbiturates tend to experience peak protein binding at or around pH 7.5.

The final factor governing the rapidity of drug penetration of the blood-brain barrier is the plasma drug concentration. Simply as a result of concentration gradient, higher levels of drug concentrations in the plasma produce greater amounts of drug that diffuses into the CSF and brain. The two primary determinants of the plasma concentration are the *dose* administered and the *rate* (speed) of administration. As the dose of thiopental over the same time is increased, an increased percentage of patients are anesthetized.[208] Concerning absolute dose, 2 mg/kg produced anesthesia in 20% of patients, whereas a dose of 2.4 mg/kg produced anesthesia in 80% of patients. Similarly, the speed of injection influences the effect of thiopental.[209] When a fixed initial dose of thiopental of approximately 2.75 mg/kg was used, a significantly ($P < .001$) smaller amount of drug was required to produce anesthesia when the dose rate of the administration was over 5 seconds as opposed to over 15 seconds. The dose *and* rate of IV administration can profoundly affect the onset of barbiturate CNS effect.

Termination of Effect

Because there exists an equilibrium between brain concentration and plasma concentration, factors that determine the rate of onset of barbiturate effects also affect their termination. Lipid solubility, degree of ionization, and CSF drug concentration affect the movement of drugs from the CSF to plasma. As plasma levels decrease, drug levels in the brain and CSF decrease. The most important factors in the termination of drug effect are those that govern plasma disappearance of the drug. These are generally divided into a rapid redistribution phase and a slow metabolic and second redistribution phase.

In a classic pharmacologic study, Brodie and coworkers[210] conclusively showed that awakening from thiopental occurred because the plasma level rapidly declined. They further showed that the cause of the rapid plasma decay of thiopental was *not metabolism* of the drug, but rather was a *redistribution* of the drug to other tissues throughout the body (lean tissue). The role of slow phase distribution to adipose tissue and elimination clearance via metabolism from the plasma was elucidated later.[207] The relationship of the plasma drug level to the onset and termination of effect as it relates to drug redistribution is illustrated in Figure 26-7. Clinically, patients awake from a single dose of thiopental 5 to 10 minutes after administration because the drug level in the brain has decreased (along with the decline in blood level). Drug is redistributed from highly perfused CNS tissues to well-perfused lean tissues. In the case of constant infusion or repeated dosing with saturation of all tissue sites, patients awake at a much delayed rate as first-order hepatic metabolism begins to play a larger role in decreasing plasma levels of the barbiturates. The termination of effect after multiple drug administrations or constant infusion depends on the elimination of the drug from the blood, which becomes more and more dependent on metabolism than redistribution and is a function of its context-sensitive decrement time (see Fig. 26-3).

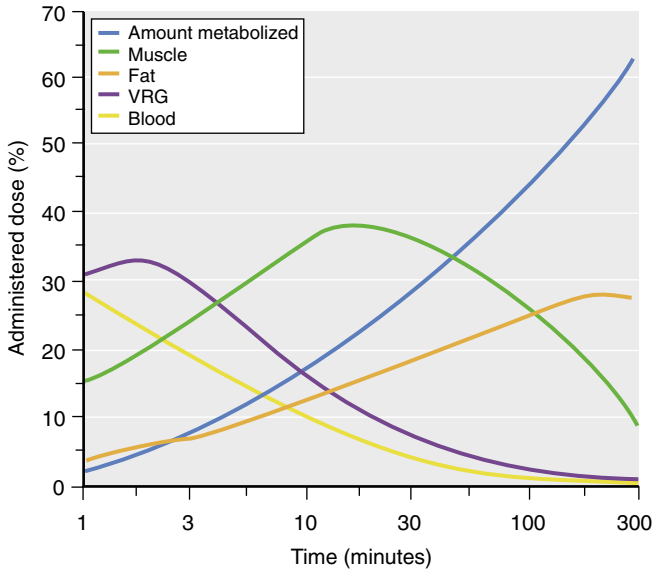


Figure 26-7 After delivery of an IV bolus, the percentage of thiopental remaining in blood rapidly decreases as drug moves from blood to body tissues. The time to attainment of peak tissue levels is a direct function of tissue capacity for barbiturate relative to blood flow. A larger capacity or smaller blood flow is related to a longer time to a peak tissue level. Initially, most thiopental is taken up by the vessel-rich group (VRG) of tissues because of their high blood flow. Subsequently, drug is redistributed to muscle and to a lesser extent to fat. Throughout this period, small but substantial amounts of thiopental are removed and metabolized by the liver. In contrast to removal by tissues, this removal is cumulative. The rate of metabolism equals the early rate of removal by fat. The sum of this early removal by fat and metabolism is the same as the removal by muscle. *(Redrawn from Saidman LJ: Uptake, distribution and elimination of barbiturates.* In *Eger EI [ed]: Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974.)*

Awakening may be delayed in older patients because of increased CNS sensitivity, alterations in metabolism, or decreased central volume of distribution relative to younger adults (see Chapter 71).[211] The initial volume of distribution is less in elderly patients compared with that in young patients, which explains a lower dose requirement for the onset of EEG and hypnotic effects.[211] Pediatric patients (<13 years old) seem to have a more rapid rate of total clearance and a shorter rate of plasma thiopental clearance than do adults, which theoretically might result in earlier awakening, especially after multiple doses of the drug (see Chapter 82).[212]

There is little difference in thiopental and methohexital with regard to distribution, which may explain the similar wake-up time of methohexital and thiopental. There is, however, a difference in the rate of total body clearance, with methohexital being higher. This disparity explains the difference found in the psychomotor skills of patients and the earlier full recovery after methohexital. Sensitive tests of psychomotor skills tend to show better early performance after methohexital than after thiopental use. A driving test reveals, however, abnormal skills for 8 hours after anesthesia, suggesting that despite plasma clearance there is residual CNS impairment for about 1 day.[213] Despite these residual effects, methohexital is cleared more rapidly than thiopental, which explains why methohexital is preferred for use by some clinicians when rapid awakening is desirable, such as in outpatient anesthesia. This prolongation of early and late recovery by the barbiturates is why they have been largely replaced by propofol.

Uses

Barbiturates are used clinically in the practice of anesthesia for induction and maintenance of anesthesia and premedication. Less frequently, barbiturates are used to provide cerebral protection to patients at risk of developing incomplete ischemia. The three barbiturates that are used most commonly in the United States for IV anesthesia and maintenance of anesthesia are thiopental, thiamylal, and methohexital.

Thiopental is an excellent drug to use for induction of anesthesia. The prompt onset (15 to 30 seconds) of action and smooth induction noted with its use make thiopental superior to most other available drugs. The rapid emergence, particularly after single use for induction, also was a reason for the widespread use of thiopental in this setting. Thiopental does not possess analgesic properties, and it must be supplemented with analgesic drugs to obtund reflex responses to noxious stimuli during anesthesia and surgical procedures. Thiopental can be used to maintain general anesthesia because repeated doses reliably sustain unconsciousness and contribute to amnesia. Thiopental is not a perfect choice, however, to use as the hypnotic component of a balanced anesthetic.

Table 26-4 Recommended Doses of Barbiturates for Anesthesia Induction and Maintenance

Drug	Induction Dose (mg/kg)*†	Onset (sec)	Intravenous Maintenance Infusion
Thiopental	3-4	10-30	50-100 mg every 10-12 min
Methohexital	1-1.5	10-30	20-40 mg every 4-7 min

*Adult and pediatric IV doses are roughly the same in milligrams per kilogram.
†Methohexital can be given rectally in pediatric patients as 20-25 mg/kg/dose.

Methohexital is the only IV barbiturate used for induction that offers a serious challenge to thiopental. With a dose of 1 to 2 mg/kg, induction is swift, and so is emergence. Methohexital also may be used as the hypnotic component to maintain anesthesia. Similar to thiopental, it is not an analgesic. Additional opioids or volatile anesthetics are required to provide a balanced technique satisfactory for general anesthesia during surgery. Because methohexital is cleared more rapidly than thiopental, it is superior to thiopental for the maintenance of anesthesia, as accumulation and saturation of peripheral sites takes longer. For brief infusion (<60 minutes), recovery from a methohexital infusion titrated to maintain hypnosis (50 to 150 µg/kg/min) is similar to that provided by propofol. There are probably upper limits of safe infusion doses yet to be defined, but seizures have occurred in neurosurgical patients after large doses of methohexital (24 mg/kg).[214] Finally, some clinicians advocate the use of methohexital in pediatric patients as a rectal premedication drug (see Chapter 82). Methohexital may be given rectally and is absorbed rapidly. Mean peak plasma levels occur within 14 minutes after rectal administration and are associated with a rapid hypnotic effect. The dose recommended for this use is 25 mg/kg rectal instillation (10% solution through a 14F catheter, 7 cm into rectum).[215] With this method of administration, sleep onset is rapid.

Dosing

Dosing for the three most commonly used barbiturates is listed in Table 26-4. The usual doses of thiopental (3 to 4 mg/kg) and thiamylal (3 to 4 mg/kg) are about twice the dose of methohexital (1 to 2 mg/kg). In dose-response studies, the ED_{50} for thiopental ranged from 2.2 to 2.7 mg/kg, and the ED_{50} for methohexital was 1.1 mg/kg.[208] Because the ED_{50} induces anesthesia in only 50% of a given group of patients, higher doses are needed to induce anesthesia reliably in all patients. The usual dose of thiopental is 3 to 4 mg/kg given intravenously over 5 to 15 seconds. There is less interpatient variability in the dose response to barbiturates than to benzodiazepines when used for anesthesia induction, but there still is significant variability in the doses of thiopental required to induce anesthesia.[208]

Interpatient dose variability is related to the presence of hemorrhagic shock, cardiac output, lean body mass, obesity, sex, and age. Hemorrhagic shock, lean body mass, age, and obesity explain variability of patient response owing to a decrease in the central volume of distribution. Less blood volume (patients with shock, patients with dehydration) or less lean body mass (obese patients, elderly patients, female patients) decreases the volume in which the drug is diluted (less blood volume), or decreases the volume into which it is quickly redistributed (less lean body mass). Finally, patients who have severe anemia, burns, malnutrition, widespread malignant disease, uremia, ulcerative colitis, or intestinal obstruction also require lower induction doses of barbiturate.

Side Effects

The effects of barbiturates on various organ systems have been studied extensively. Some side effects occur in unpredictable, varying proportions of patients, whereas cardiovascular and pulmonary side effects are dose related. There are no important differences between the barbiturates with regard to their effects on the various organ systems (respiratory, cardiovascular, gastrointestinal, hepatic, and renal), but there are differences in other complications with these drugs. The complications of injecting barbiturates include a garlic or onion taste (40% of patients), allergic reactions, local tissue irritation, and rarely tissue necrosis. An urticarial rash may develop on the head, neck, and trunk that lasts a few minutes. More severe reactions, such as facial edema, hives, bronchospasm, and anaphylaxis, can occur. Treatment of anaphylaxis is symptomatic.

Thiopental and thiamylal produce fewer excitatory symptoms with induction than methohexital, which produces cough, hiccough, tremors, and twitching approximately five times more often. Tissue irritation and local complications may occur more frequently with the use of thiopental and thiamylal than with methohexital. In comparative studies, pain on injection was shown to be greater with methohexital (12%) than with thiopental (9%). Results also show phlebitis occurs more frequently with methohexital use (8%) than with thiopental use (1%).[216] Tissue and venous irritation are more common if a 5% solution is used, rather than the standard 2% solution.

Rarely, intra-arterial injection can occur. The consequences of accidental arterial injection may be severe. The degree of injury is related to the concentration of the drug. Treatment consists of (1) dilution of the drug by the administration of saline into the artery, (2) heparinization to prevent thrombosis, and (3) brachial plexus block. Overall, the proper administration of thiopental intravenously is remarkably free of local toxicity.

Cardiovascular System

Cardiovascular depression from barbiturates is a result of central and peripheral (direct vascular and cardiac) effects. The hemodynamic changes produced by barbiturates have been studied in healthy subjects and in patients with heart disease.[217,218] The primary cardiovascular effect of barbiturate induction is peripheral vasodilation that results in a pooling of blood in the venous system.[219] A decrease in contractility is another effect, which is related to reduce availability of calcium to the myofibrils. There also is an increase in heart rate.[218] Mechanisms for the decrease in cardiac output include (1) direct negative inotropic action, (2) decreased ventricular filling owing to increased capacitance, and (3) transiently decreased sympathetic outflow from the CNS.[214,220]

The increase in heart rate (10% to 36%) that accompanies thiopental administration probably results from the baroreceptor-mediated sympathetic reflex stimulation of the heart in response to the decrease in output and pressure. Thiopental produces dose-related negative inotropic effects, which seem to result

from a decrease in calcium influx into the cells with a resultant diminished amount of calcium at sarcolemma sites. The cardiac index is unchanged or is reduced, and MAP is maintained or is slightly reduced. Thiopental infusions and lower doses tend to be accompanied by smaller hemodynamic changes than the changes noted with rapid bolus injections. In the dose ranges studied, no relationship between plasma thiopental level and hemodynamic effect has been found. A sympathetic discharge in response to intubation increases heart rate and blood pressure and can be attenuated by the administration of fentanyl (1 to 3 μg/kg).

There is little difference in the responses after thiopental and methohexital administration in patients with heart disease. The increase in heart rate (11% to 36%) encountered in patients with coronary artery disease anesthetized with thiopental (1 to 4 mg/kg) is potentially deleterious because of the obligatory increase in myocardial oxygen consumption that accompanies the increased heart rate. In a more recent study in dogs, thiopental prolonged the QT interval, flattened T waves, and increased QT dispersion during and after induction.[221] It is *possible* that thiopental may not be the most appropriate choice for patients with a susceptibility to ventricular dysrhythmias or a prolonged QT interval, such as acidotic patients or patients with conditions that prolong the QT interval, such as long-term dialysis or advanced cirrhosis; however, this remains to be shown in humans. Patients who have normal coronary arteries have no difficulty in maintaining adequate coronary blood flow to meet the increased myocardial oxygen consumption.[222] Thiopental should be avoided in hypovolemic patients because there is a significant reduction in cardiac output (69%) and a significant decrease in blood pressure.[223] Patients without adequate compensatory mechanisms may have serious hemodynamic depression with thiopental induction.

Respiratory System

Barbiturates produce dose-related central respiratory depression. There also is a significant incidence of transient apnea after administration of barbiturates for induction of anesthesia. The evidence for central depression is a correlation between EEG suppression and minute ventilation. With increased anesthetic effect, there is diminished minute ventilation. The time course of respiratory depression has not been fully studied, but it seems that peak respiratory depression (as measured by the slope of carbon dioxide concentration in the blood) and minute ventilation after delivery of thiopental (3.5 mg/kg) occurs 1 to 1.5 minutes after administration. These variables return to predrug levels rapidly, and within 15 minutes the drug effects are barely detectable.[224]

Patients with chronic lung disease are slightly more susceptible to the respiratory depression of thiopental. Apnea occurs during anesthesia induction with thiopental in at least 20% of cases, but the duration of apnea is short, approximately 25 seconds.[225] The usual ventilatory pattern with thiopental induction has been described as "double apnea." The initial apnea that occurs during drug administration lasts a few seconds and is succeeded by a few breaths of reasonably adequate tidal volume, which is followed by a lengthier apneic period. During the induction of anesthesia with thiopental, ventilation must be assisted or controlled to provide adequate respiratory exchange.

Similar to other barbiturates, methohexital is a central respiratory system depressant. Induction doses (1.5 mg/kg) significantly decrease the slope of the ventilatory response to carbon dioxide.[226] Maximal reduction in ventilatory response to carbon dioxide occurred 30 seconds after drug administration and began to approach normal levels within 15 minutes. The peak decrease in tidal volume occurred 60 seconds after methohexital delivery and returned to baseline within 15 minutes. In contrast to the effects on ventilation, patients were awake within about 5 minutes after the administration of methohexital (1.5 mg/kg). There is no difference in the duration of ventilatory depression after methohexital use and after thiopental delivery when the drugs are studied in a similar manner.[224]

Contraindications

Wood has listed the contraindications to IV barbiturate use.[227] (1) When there is respiratory obstruction or an inadequate airway, thiopental may worsen respiratory depression. (2) Severe cardiovascular instability or shock may preclude its use. (3) Status asthmaticus is a condition in which airway control and ventilation may be worsened further by thiopental. (4) Porphyria may be precipitated or acute attacks may be accentuated by the administration of thiopental. (5) Without proper equipment (IV instrumentation) and airway equipment (means of artificial ventilation), thiopental should not be administered.

Benzodiazepines

History

Diazepam (Valium) was synthesized by Sternbach in 1959 in a search for a new and better compound. It was first described for use as an IV anesthetic induction in 1965.[228] Oxazepam (Serax), a metabolite of diazepam, was synthesized in 1961 by Bell. Lorazepam (Ativan), a 2′ chloro-substitution product of oxazepam, was synthesized in 1971 in an attempt to produce a more potent benzodiazepine. The next major achievement was Fryer and Walser's 1976 synthesis of midazolam (Versed), the first clinically used water-soluble benzodiazepine.[229] Midazolam was the first benzodiazepine that was produced primarily for use in anesthesia.[230]

The benzodiazepines have many of the characteristics sought by anesthesiologists. Specific benzodiazepine receptors were described when ligands were found to interact with a central receptor.[231] The discovery and understanding of the mechanism of the benzodiazepine receptor have enabled chemists to develop many agonist compounds and to produce a specific antagonist for clinical use.

Physicochemical Characteristics

Three benzodiazepine receptor agonists are commonly used in anesthesia in the United States: midazolam, diazepam, and lorazepam (Fig. 26-8 and Table 26-5). All these molecules are relatively small and are lipid soluble at physiologic pH. Each milliliter of diazepam solution (5 mg) contains propylene glycol 0.4 mL, alcohol 0.1 mL, benzyl alcohol 0.015 mL, and sodium benzoate/benzoic acid in water for injection (pH 6.2 to 6.9). Lorazepam solution (2 or 4 mg/mL) contains 0.18 mL polyethyl-

Table 26-5 Physicochemical Characterization of Three Benzodiazepines

	Diazepam	Lorazepam	Midazolam
Molecular weight (D)	284.7*	321.2*	362*
pK_a	3.3 (20°)	11.5 (20°)	6.2 (20°)*
Water soluble	No*	Almost insoluble	Yes†
Lipid soluble	Yes*	Yes (less so, however)	Yes†
	Highly lipophilic	Relatively less lipophilic	Highly lipophilic

*Data from Moffet.[581]
†pH dependent: pH >4, lipid soluble; pH <4, water soluble.

ene glycol, with 2% benzyl alcohol as a preservative. Midazolam solution (1 or 5 mg/mL) contains 0.8% sodium chloride and 0.01% disodium edetate, with 1% benzyl alcohol as a preservative. The pH is adjusted to 3 with hydrochloric acid and sodium hydroxide. Midazolam is the most lipid soluble of the three drugs in vivo,[232] but because of its pH-dependent solubility, it is water soluble as formulated in a buffered acidic medium (pH 3.5). The imidazole ring of midazolam accounts for its stability in solution and rapid metabolism. The high lipophilicity of all three accounts for the rapid CNS effect and relatively large volumes of distribution.[233]

Metabolism

Biotransformation of the benzodiazepines occurs in the liver. The two principal pathways involve either hepatic microsomal oxidation (*N*-dealkylation or aliphatic hydroxylation) or glucuronide conjugation. The difference in the two pathways is significant because oxidation is susceptible to outside influences and can be impaired by certain population characteristics (e.g., old age), disease states (e.g., hepatic cirrhosis), or the coadministration of other drugs that can impair oxidizing capacity (e.g., cimetidine). Conjugation is less susceptible to these factors. Midazolam and diazepam undergo oxidation reduction or phase I reactions in the liver. The fused imidazole ring of midazolam is oxidized rapidly by the liver, much more rapidly than the methylene group of the diazepine ring of other benzodiazepines. This fast oxidation accounts for the greater hepatic clearance of midazolam compared with diazepam. Lorazepam is less affected by enzyme induction and some of the other factors known to alter the cytochrome P-450 and other phase I enzymes.

Cimetidine inhibition of oxidative enzyme function impairs the clearance of diazepam,[234] but it has no effect on lorazepam. Age decreases and smoking increases the clearance of diazepam,[235] but neither has a significant effect on midazolam biotransformation. Habitual alcohol consumption increases the clearance of midazolam.[236] Race, because of differences in isoenzymes responsible for hydroxylations, produces genetic differences in drug metabolism.[237] The high frequency of mutated alleles in Asians in the genes coding for CYP2C19 may explain the reduced hepatic biotransformation of diazepam.

The metabolites of the benzodiazepines can be important. Diazepam forms two active metabolites, oxazepam and desmethyldiazepam, which add to and prolong the drug's effects. Midazolam is biotransformed to hydroxymidazolams, which have activity, and when given over a longer time can accumulate.[238] These metabolites are rapidly conjugated and excreted in the urine, however. The α-hydroxymidazolam has an estimated clinical potency 20% to 30% of midazolam.[239] It is excreted largely by the kidneys and can cause profound sedation in patients with renal impairment.[240] The primary hydroxymetabolite is cleared more rapidly[90] than midazolam in healthy patients (Table 26-6). The metabolites are less potent and normally cleared more rapidly than midazolam, making them of little concern in patients with normal hepatic and renal function. Lorazepam has five metabolites, but the principal one is conjugated to glucuronide. This

Table 26-6 Pharmacokinetic and Pharmacodynamic Comparison of Midazolam and Its Active Metabolite*

	EC_{50}^{EEG}	EC_{50}^{SVT}	Clearance	V_{ss}	Clearance Half-Life
Midazolam	1.8 ng/mL	0.9 mg/mL	523 mL/min	60 L	98 min
α-Hydroxymidazolam	10.2 ng/mL	5.3 ng/mL	680 mL/min	69 L	69 min

*All values are significantly ($P < .05$) different between midazolam and α-hydroxymidazolam.
EC_{50}, median effective concentration; EEG, peak electroencephalogram change; SVT, saccadic velocity (eye movement); V_{ss}, volume at steady state.
From Mandema JW, Tuk B, van Steveninck AL, et al: Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteers. Clin Pharmacol Ther 51:715-728, 1992.

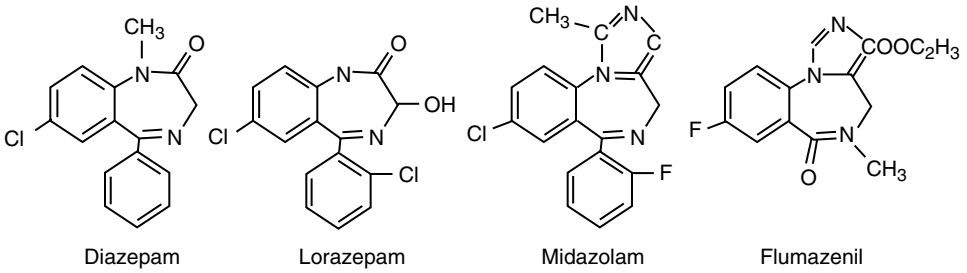


Figure 26-8 The structures of four benzodiazepines used in clinical anesthesia practice.

metabolite is inactive, water soluble, and rapidly excreted via the kidney.

Pharmacokinetics

The three benzodiazepines used in anesthesia are classified as short-lasting (midazolam), intermediate-lasting (lorazepam), and long-lasting (diazepam), according to their metabolism and plasma clearance (see Table 26-1). The plasma disappearance curves of all the benzodiazepines can be fitted to a two-compartment or three-compartment model. Protein binding and volumes of distribution are not much different among these three benzodiazepines, but the clearance is significantly different. The clearance rate of midazolam ranges from 6 to 11 mL/kg/min, whereas the clearance of lorazepam is 0.8 to 1.8 mL/kg/min, and the clearance of diazepam is 0.2 to 0.5 mL/kg/min. Because of these differences in clearance, the drugs have predictably different plasma disappearance curves (Fig. 26-9). They also have different context-sensitive half-times (see Fig. 26-3). Although the termination of action of these drugs is primarily a result of redistribution of the drug from the CNS to other tissues after use in anesthesia, after daily (long-term) repeated administration, or after prolonged continuous infusion, midazolam blood levels decrease more rapidly than blood levels of the other drugs because of greater hepatic clearance. Patients given continuous infusions of midazolam or repeated boluses over days should awaken faster than patients given diazepam or lorazepam.

Factors that may influence the pharmacokinetics of benzodiazepines are age, gender, race, enzyme induction, and hepatic and renal disease. Diazepam is sensitive to some of these factors, particularly age. Increasing age tends to reduce the clearance of diazepam[241] significantly and the clearance of midazolam to a lesser degree.[242] Lorazepam is resistant to the effects of age, gender, and renal disease on pharmacokinetics. These drugs all are affected by obesity. The volume of distribution is increased as drug goes from the plasma into the adipose tissue. Although clearance is not altered, elimination half-lives are prolonged, owing to the delayed return of the drug to the plasma in obese patients.[242] Generally, sensitivity to benzodiazepines in some groups, such as elderly patients, is greater despite relatively modest pharmacokinetic effects; factors other than pharmacokinetics must be considered when these drugs are used.

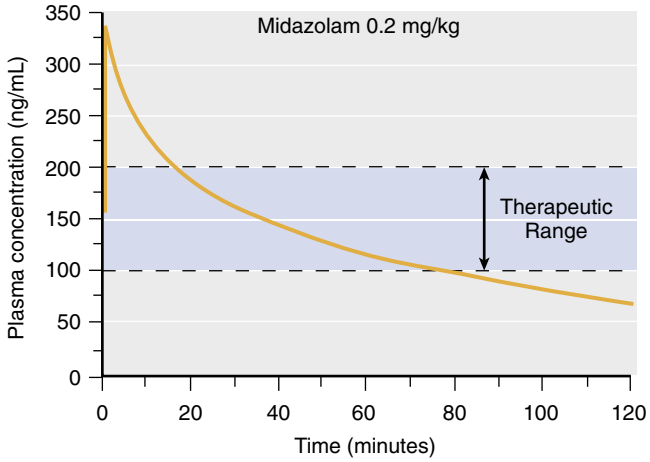


Figure 26-9 Simulated time course of plasma levels of midazolam after an induction dose of 0.2 mg/kg. Plasma levels required for hypnosis and amnesia during surgery are 100 to 200 ng/mL, with awakening usually occurring at levels less than 50 ng/mL.

Pharmacology

All benzodiazepines have hypnotic, sedative, anxiolytic, amnesic, anticonvulsant, and centrally produced muscle-relaxing properties. The drugs differ in their potency and efficacy with regard to each of the pharmacodynamic actions. The chemical structure of each drug dictates its particular physicochemical properties and pharmacokinetics and its receptor binding characteristics. The binding of benzodiazepines to their respective receptors is of high affinity and is stereospecific and saturable; the order of receptor affinity (potency) of the three agonists is lorazepam > midazolam > diazepam. Midazolam is approximately 3 to 6 times,[243] and lorazepam 5 to 10 times, as potent as diazepam.

The mechanism of action of benzodiazepines is reasonably well understood.[244-246] The interaction of ligands with the benzodiazepine receptor is one of the few examples in which the complex systems of biochemistry, molecular pharmacology, genetic mutations, and clinical behavioral patterns can be explained. More is understood about the mechanism of action of benzodiazepines than about the mechanism of action of many other general anesthetics. More recent genetic studies have found the $GABA_A$ subtypes mediate the different effects (amnesic, anticonvulsant, anxiolytic, and sleep).[246] Sedation, anterograde amnesia, and anticonvulsant properties are mediated via *α1* receptors,[246] and anxiolysis and muscle relaxation are mediated by the *a2* $GABA_A$ receptor.[246] Drug effect is a function of blood level. By using plasma concentration data and pharmacokinetic simulations, it has been estimated that a benzodiazepine receptor occupancy of less than 20% may be sufficient to produce the anxiolytic effect, sedation is observed with 30% to 50% receptor occupancy, and unconsciousness requires 60% or greater occupation of benzodiazepine agonist receptors.[247]

The benzodiazepine receptors are found in highest densities in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra, and inferior colliculus, but lower densities are found in the striatum, lower brainstem, and spinal cord. Spinal cord benzodiazepine receptors can play an important role in analgesia, however, further elucidating the mechanism of action of this drug class.[248,249] Intrathecal midazolam reduces excitatory GABA-mediated neurotransmission in interneurons, leading to a decrease in the excitability of spinal dorsal horn neurons.[248] Intrathecal midazolam added to a bupivacaine spinal increases analgesia and shortens the time to return of motor function.[249]

A fascinating and therapeutically significant discovery regarding the benzodiazepine receptor is that the pharmacologic spectrum of ligands includes three different types or classes,[244] which have been termed *agonists, antagonists,* and *inverse agonists* (Fig. 26-10), names that connote their actions. Agonists (e.g., midazolam) alter the conformation of the $GABA_A$ receptor complex so that binding affinity for GABA is increased, with a resultant opening of the chloride channel. Agonist and antagonist bind to a common (or at least overlapping) area of the receptor by forming differing reversible bonds with the receptor. The well-known effects of an agonist then occur (anxiolysis, hypnosis, and anticonvulsant action). Antagonists (e.g., flumazenil) occupy the

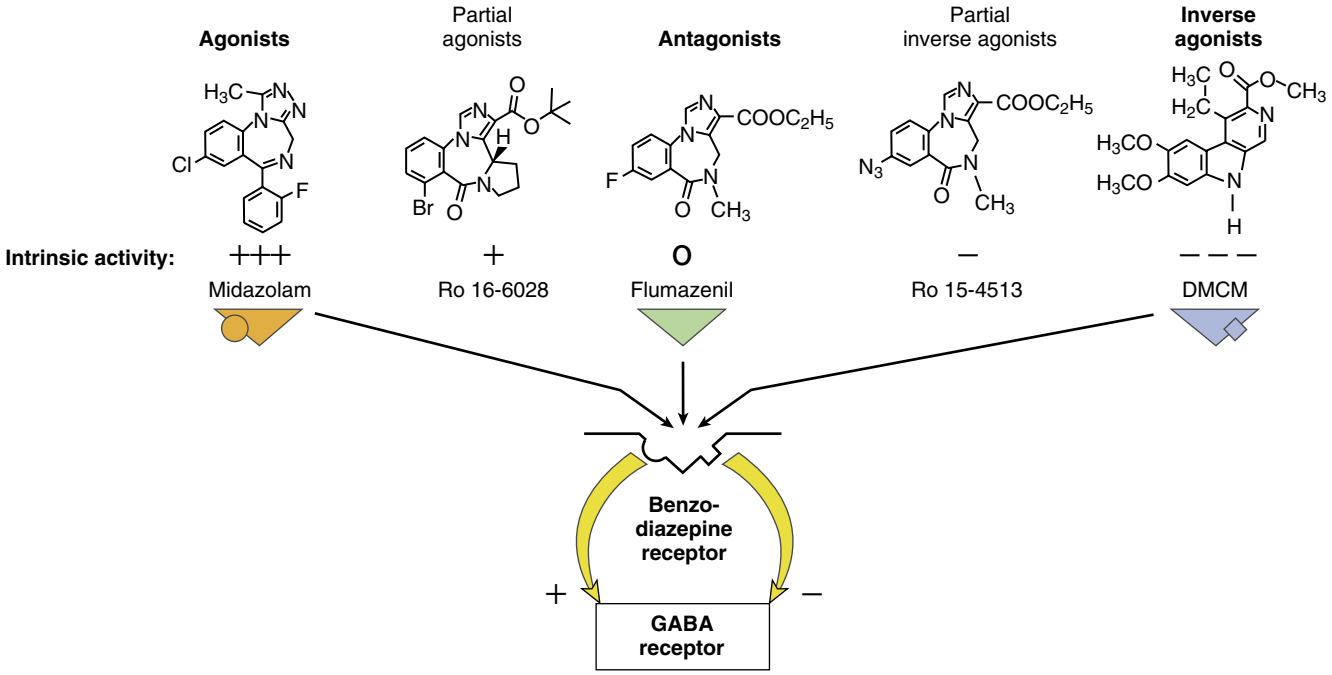


Figure 26-10 Spectrum of the intrinsic activities of benzodiazepine receptor ligands, which range from agonists to inverse agonists. Structures of agonist, partial agonist, antagonist, partial inverse agonist, and inverse agonist compounds are shown. Intrinsic activity is greatest among agonists and is least among inverse agonists. Intrinsic activities are schematically indicated as positive by a plus sign and as negative by a minus sign, with 0 indicating a lack of intrinsic activity. GABA, γ-aminobutyric acid. *(Redrawn with modification from Mohler H, Richards JG: The benzodiazepine receptor: A pharmacological control element of brain function. Eur J Anaesthesiol Suppl 2:15-24, 1988.)*

benzodiazepine receptor, but they produce no activity and block the actions of the agonists and inverse agonists. Inverse agonists reduce the efficiency of GABA-adrenergic synaptic transmission, and because GABA is inhibitory, the result of decreased GABA is CNS stimulation. The potency of the ligand is dictated by its affinity for the benzodiazepine receptor and the duration of effect by the rate of clearance of the drug from the receptor.

Long-term administration of benzodiazepines produces tolerance, which is defined as the decrease of efficacy of the drug over time.[250] Although the mechanism of chronic tolerance is not fully understood, it seems that long-term exposure to benzodiazepines causes decreased receptor binding and function (i.e., downregulation of the benzodiazepine–$GABA_A$ receptor complex). This would explain the increased dose requirements of benzodiazepines for anesthesia in patients who take them on a long-term basis. It seems that after the cessation of long-term use of benzodiazepines, there is upregulation of the receptor complex,[250] which could mean an increased susceptibility to benzodiazepines during a period after recent use.

The onset and duration of action of a bolus IV administration of a benzodiazepine depend on the lipid solubility of the drug, a finding that probably explains the differences in onset and duration of action of midazolam, diazepam, and lorazepam. Midazolam and diazepam have a more rapid onset (usually within 30 to 60 seconds) of action than lorazepam (60 to 120 seconds). The half-life of equilibrium between plasma concentration and EEG effect of midazolam is approximately 2 to 3 minutes and is not affected by age.[251] This is about two times longer[252] than that of diazepam, but compared with diazepam midazolam has a sixfold greater intrinsic potency.[243] Similar data for other benzodiazepines are unavailable. Similar to onset, the duration of effect also is related to lipid solubility and blood level. The more rapid redistribution of midazolam and diazepam compared with lorazepam (presumably because of the lower lipid solubility of lorazepam)[232] accounts for the shorter duration of their actions.

Effects on the Central Nervous System

The benzodiazepines, in a dose-related manner, reduce the $CMRO_2$ and CBF (see Chapters 13, 46, and 63). Midazolam and diazepam maintain a relatively normal ratio of CBF to $CMRO_2$. In healthy human volunteers, midazolam, 0.15 mg/kg, induces sleep and reduces CBF by 34%, despite a slight increase in $Paco_2$ from 34 to 39 mm Hg.[253] Brown and coworkers[254] studied EEG tracings after administration of 10 mg of IV midazolam and showed the appearance of rhythmic beta activity at 22 Hz within 15 to 30 seconds of administration in healthy volunteers. Within 60 seconds, there was a second beta rhythm at 15 Hz. Alpha rhythm started to reappear at 30 minutes; however, after 60 minutes, there was resistant rhythmic beta activity at 15- to 20-μV amplitude. The EEG changes were similar to EEG effects with diazepam and were not typical of light sleep, although the patients were clinically asleep.

Midazolam, diazepam, and lorazepam all increase the seizure initiation threshold to local anesthetics and decrease the mortality rate in mice exposed to lethal doses of local anesthetics.[255] Midazolam and diazepam cause a dose-related protective effect against cerebral hypoxia, shown by extending mouse survival time when mice were placed in 5% oxygen. The protection afforded by midazolam is superior to that of diazepam, but less than that of pentobarbital.[255] Antiemetic effects are not a prominent action of the benzodiazepines.

Effects on the Respiratory System

Benzodiazepines, similar to most IV anesthetics, produce dose-related central respiratory system depression. Lorazepam (2.5 mg) produces a similar but shorter lasting decrease in tidal volume and minute ventilation than diazepam (10 mg) in patients with lung disease.[256] Peak decrease in minute ventilation after midazolam (0.15 mg/kg) is almost identical to that produced in healthy patients given diazepam (0.3 mg/kg), as determined by carbon dioxide response data.[257] The slopes of the ventilatory response curves to carbon dioxide are flatter than normal (control), but not shifted to the right, as with opioids. Judging from the plasma level and steepness of the dose-response effect on $Paco_2$ curves,[258] midazolam is about five to nine times as potent as diazepam.

The peak onset of ventilatory depression with midazolam (0.13 to 0.2 mg/kg) is rapid (about 3 minutes), and significant depression remains for about 60 to 120 minutes.[224] The rate of midazolam administration affects the onset time of peak ventilatory depression; the faster the drug is given, the more quickly this peak depression occurs. The respiratory depression of midazolam is more pronounced and of longer duration in patients with chronic obstructive pulmonary disease, and the duration of ventilatory depression is longer with midazolam (0.19 mg/kg) than with thiopental (3.3 mg/kg).[224,259] Lorazepam (0.05 mg/kg) alone does not depress the carbon dioxide response, but when lorazepam is combined with meperidine, there is predictable respiratory depression.[259] Benzodiazepines and opioids produce additive or supra-additive (synergistic) respiratory depression, even though they act at different receptors.

Apnea occurs with benzodiazepines in a dose-dependent manner. The incidence of apnea after thiopental or midazolam when these drugs are given for induction of anesthesia is similar. Apnea occurred in 20% of 1130 patients given midazolam for induction and 27% of 580 patients given thiopental in clinical trials with midazolam.[230] Apnea is more likely to occur in the presence of opioids. Old age, debilitating disease, and other respiratory depressant drugs probably also increase the incidence and degree of respiratory depression and apnea with benzodiazepines.

Effects on the Cardiovascular System

The benzodiazepines used alone have modest hemodynamic effects. The hemodynamic changes reported with anesthetic induction doses of diazepam, midazolam, and lorazepam are shown in Table 26-2. These values represent the peak hemodynamic effect in the first 10 minutes after administration and are derived from studies of healthy subjects and patients with ischemic and valvular heart diseases.[260-264] The predominant hemodynamic change is a slight reduction in arterial blood pressure, resulting from a decrease in systemic vascular resistance. The mechanism by which benzodiazepines maintain relatively stable hemodynamics involves the preservation of homeostatic reflex mechanisms,[230] but there is evidence that the baroreflex is impaired by midazolam and diazepam.[265] Midazolam causes a slightly larger decrease in arterial blood pressure than the other benzodiazepines, but the hypotensive effect is minimal and about the same as seen with thiopental.[266] Despite the hypotension, midazolam, even in doses of 0.2 mg/kg, is safe and effective for induction of anesthesia even in patients with severe aortic stenosis (see Chapter 60).

The hemodynamic effects of midazolam and diazepam are dose related: the higher the plasma level, the greater the decrease in systemic blood pressure[258]; however, there is a plateau plasma drug effect above which little change in arterial blood pressure occurs. The plateau plasma level for midazolam is 100 ng/mL, and that for diazepam is about 900 ng/mL.[258] Heart rate, ventricular filling pressures, and cardiac output are maintained after induction of anesthesia with benzodiazepines. In patients with elevated left ventricular filling pressures, diazepam and midazolam produce a "nitroglycerin-like" effect by decreasing the filling pressure and increasing cardiac output.

The stresses of endotracheal intubation and surgery are not blocked by midazolam.[260] Adjuvant anesthetics, usually opioids, are often combined with benzodiazepines. The combination of benzodiazepines with opioids and nitrous oxide has been investigated in patients with ischemic and valvular heart diseases.[264,267] The addition of nitrous oxide to midazolam (0.2 mg/kg) and diazepam (0.5 mg/kg) has trivial hemodynamic consequences, whereas the combination of benzodiazepines with opioids does have a supra-additive effect. The combinations of benzodiazepines with opiates produce greater decreases in systemic blood pressure than does each drug alone. The mechanism for this synergistic hemodynamic effect is not completely understood, but it is probably related to a reduction in sympathetic tone when the drugs are given together.[268] There is evidence that diazepam and midazolam decrease catecholamines,[269] a finding consistent with this hypothesis.

Uses

Intravenous Sedation

Benzodiazepines are used for sedation as preoperative premedication, intraoperatively during regional or local anesthesia, and postoperatively. The anxiolysis, amnesia, and elevation of the local anesthetic seizure threshold are desirable benzodiazepine actions. The drugs should be given by titration for this use; end points of titration are adequate sedation or dysarthria (Table 26-7). The onset of action is more rapid with midazolam, usually with peak effect reached within 2 to 3 minutes of administration; time to peak effect is slightly longer with diazepam and is longer still with lorazepam. The duration of action of these drugs depends primarily on the dose used. Although the onset is more rapid with midazolam than with diazepam after bolus administration, the recovery is similar,[270] probably because both drugs have similar early plasma decay (redistribution) patterns (see Fig. 26-9). With lorazepam, sedation and particularly amnesia are slower in onset and are longer lasting than with the other two benzodiazepines.[238,271]

There is often a disparity in the level of sedation compared with the presence of amnesia (patients seem conscious and reasonably coherent, yet they are amnesic for events and instructions) with all three benzodiazepines. Lorazepam is particularly unpredictable with regard to duration of amnesia, and this is undesirable in patients who wish or need to have recall in the immediate postoperative period. The degree of sedation and the reliable amnesia and preservation of respiratory and hemodynamic function are better overall with benzodiazepines than with other sedative-hypnotic drugs used for conscious sedation. When midazolam is compared with propofol for sedation, the two are generally similar except that emergence or wake-up is more rapid with propofol. Propofol requires closer medical supervision because of its respiratory depression,[272] and respiratory function

Table 26-7 Uses and Doses of Intravenous Benzodiazepines

	Midazolam	Diazepam	Lorazepam
Induction	0.05-0.15 mg/kg	0.3-0.5 mg/kg	0.1 mg/kg
Maintenance	0.05 mg/kg prn 1 µg/kg/min	0.1 mg/kg prn	0.02 mg/kg prn
Sedation*	0.5-1 mg repeated 0.07 mg/kg IM	2 mg repeated	0.25 mg repeated

*Incremental doses given until desired degree of sedation is obtained.
prn, as required to keep patient hypnotic and amnestic.

must be monitored when these drugs are used for sedation to prevent undesirable degrees of respiratory depression. There may be a slight synergistic action between midazolam and spinal anesthesia with respect to ventilation.[273] The use of midazolam for sedation during regional and epidural anesthesia requires vigilance with regard to respiratory function, similar to when these drugs are given with opioids.

Sedation for longer periods, such as in the ICU, also is accomplished with benzodiazepines. Prolonged infusion results in accumulation of drug and, in the case of midazolam, significant concentration of the active metabolite. Reviews have pointed out concerns and advantages of benzodiazepine sedation.[238,274,275] The chief advantages are the amnesia and hemodynamic stability, and the disadvantage compared with propofol is the sometimes longer dissipation of effects when infusions are terminated. The superiority of one drug over the other has not been established; both drugs should always be titrated downward to maintain sedation as required. Dosing should not be fixed, but it should be reduced over time to avoid accumulation of parent or metabolites during prolonged infusion.

Finally, two more recent studies have challenged the idea that maternal sedation with midazolam may be unsafe for neonates and infants of breastfeeding mothers (see Chapter 69). Frolich and colleagues[276] showed that a single IV dose of midazolam (0.02 mg/kg) combined with a single IV dose of fentanyl (1 µg/kg) before cesarean section was a safe practice, showing no detriment in Apgar scores, neurobehavioral scores, continuous oxygen saturation, or the ability of the mother to recall the birth events.[276] Nitsun and associates[277] found that 0.005% of the maternal dose of midazolam is transferred into the breast milk during a 24-hour milk collection. Although verification of these findings is needed, they highlight an important clinical use of midazolam that may be safe for mother and infant.

Oral Sedation

For many years, diazepam was given orally for preoperative sedation. It is still used in 5- to 15-mg doses in adults for this purpose. More recently, an oral formulation of midazolam has been used primarily for oral premedication in pediatric patients (see Chapter 82). The dose is 0.5 mg/kg, and one preparation is from the Roche parenteral formulation of 0.5 mg/mL (Roche Laboratories, Inc, Nutley, NJ) mixed in with 10 mg/kg of oral acetaminophen (McNeil-PPC, Inc, Fort Washington, PA).[278] Other preparations have been developed, including strawberry-flavored glucose (pH 4.5) prepared by the pharmacy, which is stable for 8 weeks.[279] The 0.5-mg/kg oral dose is rapid-acting, providing reliable amnesia within 10 minutes and rendering children effectively sedated for anesthesia induction.[278]

Induction and Maintenance of Anesthesia

Midazolam is the benzodiazepine of choice to induce anesthesia. When midazolam is used in appropriate doses (see Table 26-7), induction occurs less rapidly than with thiopental,[230] but the amnesia is more reliable. Numerous factors influence the rapidity of action of midazolam and the other benzodiazepines when used for induction of general anesthesia, including dose, speed of injection, degree of premedication, age, ASA physical status, and concurrent anesthetic drugs.[230,280] In a well-premedicated, healthy patient, midazolam (0.2 mg/kg given in 5 to 15 seconds) induces anesthesia in 28 seconds, whereas induction occurs in 39 seconds with diazepam (0.5 mg/kg given in 5 to 15 seconds).[260] Elderly patients require smaller doses of midazolam than younger patients (Fig. 26-11).[281,282] Patients older than 55 years and patients with ASA physical status greater than III require a 20% or greater reduction in the induction dose of midazolam.[230] The usual induction dose of midazolam in premedicated patients is 0.05 to 0.15 mg/kg. When midazolam is used with other anesthetic drugs (coinduction), there is a synergistic interaction,[254,283] and the induction dose is less than 0.1 mg/kg (Fig. 26-12). The synergy is seen when midazolam is used with opioids or other hypnotics, such as thiopental and propofol.

Awakening after benzodiazepine anesthesia (defined as orientation to time and place) of young, healthy volunteers who received 10 mg of IV midazolam occurred in about 15 minutes,[254] and awakening occurred in about 17 minutes after an induction dose of 0.15 mg/kg.[284] Emergence time is related to the dose of midazolam and to the dose of adjuvant anesthetic drugs.[230] Emergence from midazolam (0.32 mg/kg)/fentanyl anesthesia is about 10 minutes longer than emergence from thiopental (4.75 mg/kg)/fentanyl anesthesia,[262] and is more prolonged than with propofol.[285] This difference accounts for some anesthesiologists' preference for propofol induction for short operations.

Benzodiazepines lack analgesic properties and must be used with other anesthetic drugs to provide sufficient analgesia; however, as maintenance anesthetic drugs during general anesthesia, benzodiazepines provide hypnosis and amnesia. Double-blind studies comparing midazolam and thiopental as the hypnotic component for balanced anesthesia[262,286] have shown that mida-

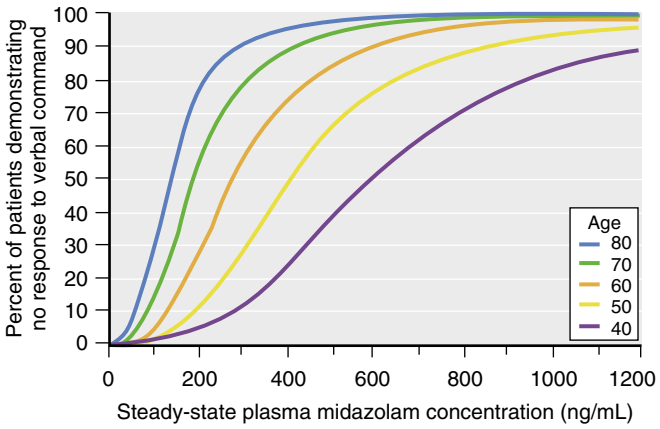


Figure 26-11 Simulated quantal concentration-response curves generated by the parameterized pharmacodynamic model for midazolam. *(Redrawn from Jacobs JR, Reves JG, Marty J, et al: Aging increases pharmacodynamic sensitivity to the hypnotic effects of midazolam. Anesth Analg 80:143-148, 1995.)*

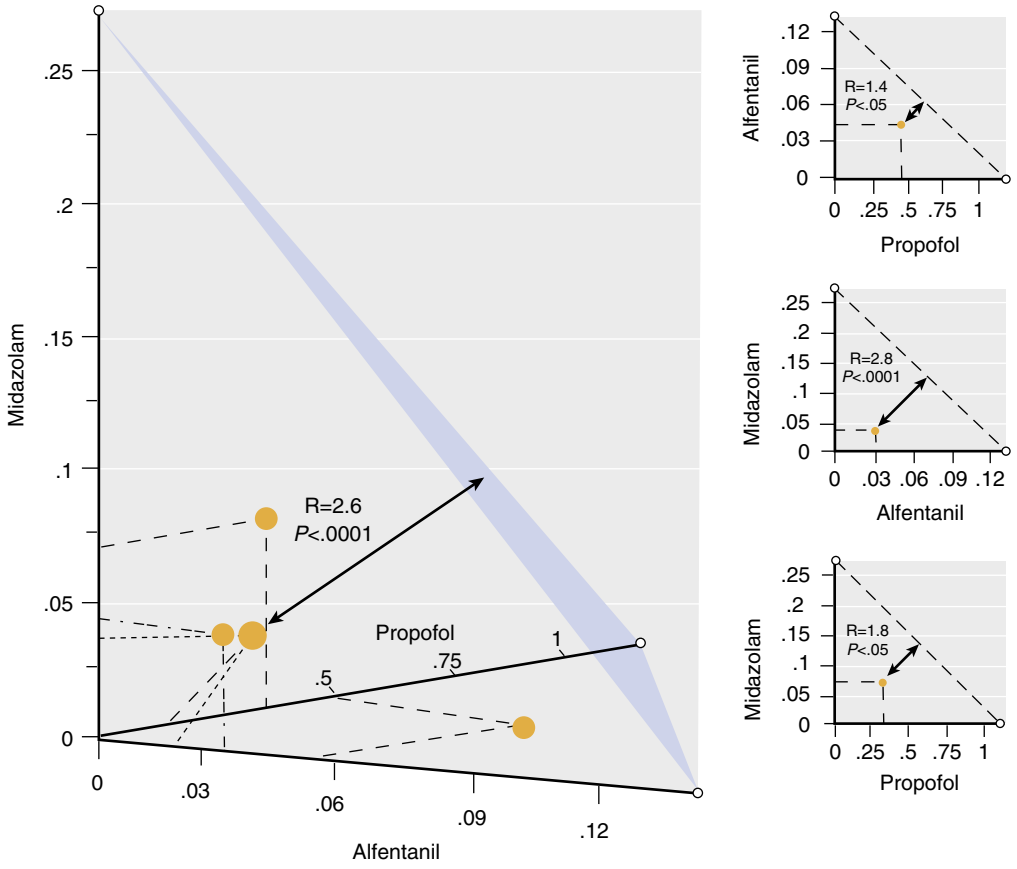


Figure 26-12 Vertical axes all represent drug dose in milligrams per kilogram. On the right, median effective dose (ED_{50}) isobolograms for the hypnotic interactions among midazolam, alfentanil, and propofol are shown. The *dotted lines* are additive effect lines; all combinations fall within the line representing synergism or supra-additive effect. On the left, a triple interaction is depicted. The *shaded area* represents an additive plane passing through three single-drug ED_{50} points (*small open circles*). The largest *closed circle* (with *arrows*) is the ED_{50} point for the triple combination. The smaller *closed circles* are ED_{50} points for the binary combinations. R ratios on all graphs represent the interaction (1.0 indicates an additive effect) of the various drug combinations. The combination of midazolam and alfentanil produces the greatest synergism, but the combination of all three also is synergistic. *P* values denote the significance of the additive effects. *(Redrawn with modification from Vinik HR, Bradley EL Jr, Kissin I: Triple anesthetic combination: Propofol-midazolam-alfentanil. Anesth Analg 76:S450, 1993.)*

zolam is superior for this use because of better amnesia and a smoother hemodynamic course. Opioid requirements are less with midazolam. Midazolam (0.6 mg/kg) decreases the minimum alveolar concentration of inhaled anesthetics.[287] The amnesic period after an anesthetic dose is about 1 to 2 hours. Infusions of midazolam have been used to ensure a constant and appropriate depth of anesthesia.[287] Experience indicates that a plasma level of more than 50 ng/mL when used with adjuvant opioids (e.g., fentanyl) or inhalation anesthetics (e.g., nitrous oxide, volatile anesthetics) is achieved with a bolus loading dose of 0.05 to 0.15 mg/kg and a continuous infusion of 0.25 to 1 µg/kg/min.[283] This plasma level is sufficient to keep the patient asleep and amnesic but arousable at the end of surgery. Smaller infusion doses may be required in some patients and with certain opioids.

Midazolam, diazepam, and lorazepam accumulate in the blood with repeated bolus administrations or with continuous infusion, just as most IV anesthetics do on repeated injection. If the benzodiazepines do accumulate with repeated administrations, prolonged arousal time can be anticipated. This is less of a problem with midazolam than with diazepam and lorazepam because of the shorter context-sensitive half-time and greater clearance of midazolam.

Nausea and Vomiting Prophylaxis

Numerous studies in the past several years have highlighted the role that benzodiazepines, specifically midazolam, may play in the prevention of PONV (see Chapter 86). Jung and colleagues[288] found that in women undergoing middle ear surgery, IV midazolam, 0.075 mg/kg after induction, reduced the incidence of PONV and the need for rescue antiemetics with no difference from placebo in pain intensity or drowsiness. Similarly, Lee and associates[289] found no difference in the incidence of PONV after minor gynecologic or urologic surgery when comparing IV ondansetron, 4 mg, and IV midazolam, 2 mg. Finally, Riad and colleagues[289a] effectively illustrated that IV midazolam, 0.05 mg/kg, reduces PONV after pediatric (4 to 12 years old) strabismus surgery compared with placebo or IV dexamethasone, 0.5 mg/kg. No child vomited with midazolam alone or with the midazolam-dexamethasone combination.

Side Effects and Contraindications

Benzodiazepines have limited allergenic effects and do not suppress the adrenal gland.[290] The most significant problem with

midazolam is respiratory depression. The major side effects of lorazepam and diazepam in addition to respiratory depression are venous irritation and thrombophlebitis, problems related to aqueous insolubility and requisite solvents.[230] When used as sedatives or for induction and maintenance of anesthesia, benzodiazepines can produce an undesirable degree or prolonged interval of postoperative amnesia, sedation, and, rarely, respiratory depression. These residual effects can be reversed with flumazenil.

Flumazenil

Flumazenil (Anexate, Romazicon) is the first benzodiazepine antagonist approved for clinical use.[291] Preclinical pharmacologic studies with flumazenil revealed it to be a benzodiazepine receptor ligand with high affinity, great specificity, and by definition minimal intrinsic effect. Flumazenil, similar to the agonists it replaces at the benzodiazepine receptor, interacts with the receptor in a concentration-dependent manner. Because it is a competitive antagonist at the benzodiazepine receptor, its antagonism is reversible and surmountable. Flumazenil has minimal intrinsic activity,[292] which means that its benzodiazepine receptor agonist effects are very weak, significantly less than those of clinical agonists. Flumazenil, similar to all competitive antagonists at receptors, does not displace the agonist, but rather occupies the receptor when an agonist dissociates from the receptor. The half-time (or half-life) of a receptor-ligand bond is a few milliseconds to a few seconds, and new ligand receptor bonds are immediately formed. This dynamic situation accounts for the ability of either an agonist or an antagonist to occupy the receptor readily.

The ratio of agonist to total receptors produces the effects of the agonist drug, but the antagonist can alter this ratio, depending on its concentration and dissociation constant. Flumazenil, which is an avid (high-affinity) ligand, replaces a relatively weak agonist, such as diazepam, as long as it is given in sufficient dose. Flumazenil is cleared rapidly, however, and the proportion of receptors occupied by agonist increases, and the potential for resedation exists (Fig. 26-13). This situation is less likely to occur when flumazenil is used to reverse midazolam, which has a more rapid clearance than other benzodiazepine agonists. Another important finding is that in the presence of extremely high doses of agonist (e.g., when a mistake in dosing has occurred, or suicide is attempted), flumazenil in a low dose attenuates the deep CNS depression (loss of consciousness, respiratory depression) by reducing the fractional receptor occupancy by the agonist without decreasing the agonist effects that occur at low fractional receptor occupancy (drowsiness, amnesia).

Conversely, large doses of flumazenil in the presence of small doses of agonist completely reverse virtually all the agonist effects. Flumazenil can precipitate withdrawal symptoms in animals or in humans physically dependent on a benzodiazepine receptor agonist.[293,294] This is not a problem when flumazenil is used to reverse benzodiazepine receptor agonists in anesthesia.

Physicochemical Characteristics

Flumazenil, synthesized in 1979, is similar to midazolam and other classic benzodiazepines except for the absence of the phenyl group, which is replaced by a carbonyl group (see Fig. 26-8).[295] It forms a colorless, crystalline powder; has a dissociation constant of 1.7; and has weak but sufficient water solubility to permit its preparation in aqueous solution. Its octanol/aqueous buffer partition coefficient is 14, showing moderate lipid solubility at pH 7.4.[295]

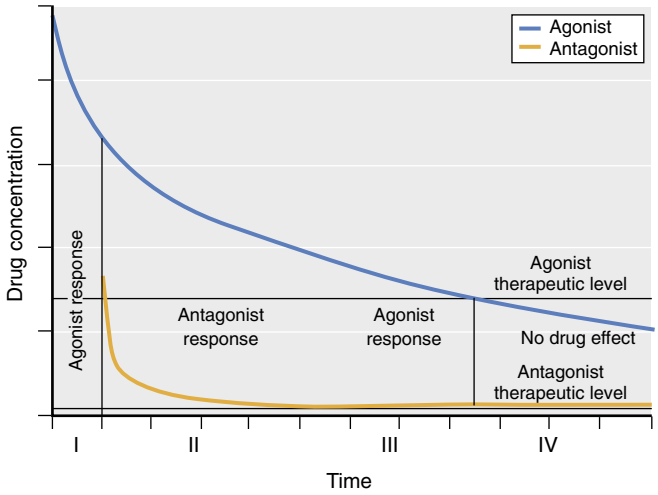


Figure 26-13 Schematic representation of the interaction of a short-acting antagonist with a longer acting agonist resulting in resedation. The *upper curve* shows disappearance of agonist from blood, and the *lower curve* shows disappearance of antagonist from plasma. Four conditions are represented: I, agonist response; II, antagonist response (the antagonist reverses the agonist effect); III, agonist response (resedation or resumption of agonist response with disappearance of short-lasting antagonist); and IV, no drug effect, with disappearance of agonist and antagonist (both drugs are below the therapeutic level).

Metabolism

Flumazenil, similar to the other benzodiazepines, is metabolized in the liver; is rapidly cleared from the plasma; and has three known metabolites, *N*-desmethylflumazenil, *N*-desmethylflumazenil acid, and flumazenil acid.[296] The activities of these metabolites and their corresponding glucuronides are unknown at present. The glucuronides probably are excreted in the urine.

Pharmacokinetics

Flumazenil is a short-lived compound. Table 26-1 includes a summary of its pharmacokinetics, which are described in various clinical settings.[251,296] Compared with benzodiazepine receptor agonists, flumazenil has the most rapid clearance and shortest elimination half-life. The plasma half-life of flumazenil is about 1 hour—it is the shortest lived of all benzodiazepines used in anesthetic practice. The potential exists for the antagonist to be cleared, leaving sufficient concentrations of agonist at the receptor site to cause resedation.[293] To maintain a constant therapeutic blood level over a prolonged time, either repeated administration or a continuous infusion is required. An infusion rate of 30 to 60 µg/min (0.5 to 1 µg/kg/min) has been used for this purpose.[297] The rapid blood clearance of flumazenil approaches hepatic blood flow, a finding that indicates that liver clearance partially depends

on hepatic blood flow. Compared with other benzodiazepines, flumazenil has a high proportion of unbound drug; its protein binding is low, with the free fraction ranging from 54% to 64%. This property of flumazenil could contribute to its rapid onset and greater clearance, but this hypothesis is unproved.

Pharmacology

When given in the absence of a benzodiazepine receptor agonist, flumazenil has little discernible CNS effect. Although intrinsic (agonist and inverse agonist) effects have been ascribed to flumazenil,[292] they are clinically unimportant. It has been postulated that in small doses a stimulating effect can be seen, and in high doses a central depressant effect becomes more likely.[298] When given to volunteers and patients in clinically relevant doses, flumazenil has no effect on the EEG or cerebral metabolism.[251,299] In animals, flumazenil has no anticonvulsant properties, and reverses the anticonvulsant properties of benzodiazepines in local anesthetic–induced seizures.[300]

When administered to patients who have benzodiazepine-induced CNS depression, flumazenil produces rapid and dependable reversal of unconsciousness, respiratory depression, sedation, amnesia, and psychomotor dysfunction.[247] Flumazenil can be given before, during, or after the agonist to block or reverse the CNS effects of the agonist. The usual clinical need is to reverse the effects of agonists given before flumazenil. Flumazenil has successfully reversed the effects of midazolam, diazepam, lorazepam, and flunitrazepam. The onset is rapid, with peak effect occurring in 1 to 3 minutes,[247] which coincides with the detection of C-flumazenil in human brain.[301] Flumazenil reverses the agonist by replacing it at the benzodiazepine receptor, and its onset and duration are governed by the law of mass action. A predicted therapeutic plasma level for flumazenil is 20 ng/mL because the relative binding characteristics of agonist and antagonist in part dictate benzodiazepine receptor occupation by the residual agonist, and different doses and plasma levels of flumazenil are required to reverse the effects of particular agonists.

Flumazenil is devoid of the respiratory and cardiovascular depressant effects of benzodiazepine receptor agonists. A large dose of flumazenil (0.1 mg/kg) given to volunteers did not produce significant respiratory depression.[302] When flumazenil is given in the presence of agonists, however, there are significant respiratory effects because it reverses respiratory depression caused by the agonists (e.g., when given to volunteers made apneic with midazolam).[303] The reversal of midazolam-induced (0.13 mg/kg) respiratory depression with flumazenil (1 mg) lasts 3 to 30 minutes. Other agonists and other doses would have different durations of antagonism of respiratory depression. If respiratory depression is related to opioid administration, flumazenil would not reverse it.[304]

Incremental doses, up to 3 mg intravenously, in patients with ischemic heart disease had no significant effect on cardiovascular variables.[303] Administration of flumazenil to patients given agonists is remarkably free of cardiovascular effects,[247,305] in contrast to the experience of opioid reversal with naloxone. Of particular interest is the effect on plasma catecholamines of benzodiazepine receptor agonist reversal with flumazenil because this effect on catecholamines is the suspected mechanism of hyperdynamic response in opioid reversal. Although flumazenil does reverse sedation, it is not associated with significantly higher catecholamines than are found in patients receiving saline,[305] but the increase in catecholamines that accompanies arousal is more rapid after flumazenil.[306]

Table 26-8 Uses and Doses of Flumazenil

Reversal of benzodiazepines*	0.2 mg repeated† up to 3 mg
Diagnosis in coma	0.5 mg repeated up to 1 mg

*The dose required to reverse each benzodiazepine (BZD) depends on residual BZD and the particular BZD (i.e., higher doses are required for more potent BZDs) (see text).
†The degree of reversal should be titrated by repeating 0.2-mg increments every 1-2 min until desired level of reversal is achieved.

Uses and Doses

Uses for a benzodiazepine antagonist (Table 26-8) include the diagnostic and therapeutic reversal of the effects of benzodiazepine receptor agonists. For diagnostic use in suspected benzodiazepine overdose, flumazenil may be given in incremental IV doses of 0.2 to 0.5 mg up to 3 mg. If there is no change in CNS sedation, it is unlikely that CNS depression is based solely on benzodiazepine overdose. More commonly in anesthesia, flumazenil is used to reverse the residual sedation of a patient after administration of a benzodiazepine for conscious sedation or for general anesthesia.

Flumazenil reliably reverses the sedation, respiratory depression, and amnesia of benzodiazepines. There is now evidence, however, of differential reversal effects on the different agonist actions. Flumazenil tends to reverse the hypnotic and respiratory effects more than the amnesic effects of the agonist benzodiazepine.[304,307] Dosage guidelines are given in Table 26-8, but large-scale dosing studies have not been performed yet. The dose varies with the particular benzodiazepine being reversed, and the duration of reversal depends on the kinetics of the agonist and of flumazenil. Surveillance is recommended if a long-lasting benzodiazepine is reversed with a single administration of flumazenil because of the relatively short-lived effect. Flumazenil may be administered by continuous infusion to prevent resedation with longer lasting benzodiazepine receptor agonists.

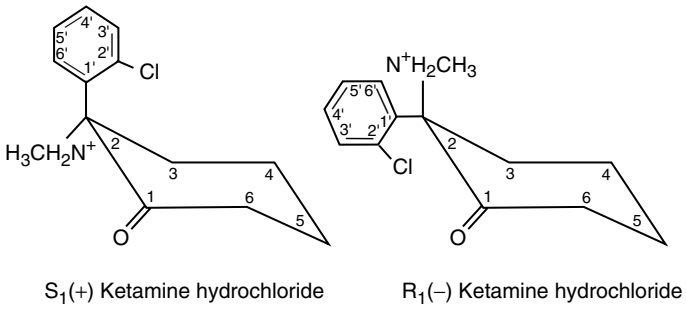
Side Effects and Contraindications

Flumazenil has been given in large oral and IV doses with remarkably few toxic reactions.[247] It is free of local or tissue irritant properties, and there are no known organotoxicities. Similar to all benzodiazepines, it apparently has a high safety margin, probably higher than the safety margins of agonists, because it does not produce prominent CNS depression. An important caution is that resedation could occur because of the relatively short half-life of the drug.

Phencyclidines (Ketamine)

History

Phencyclidine was the first drug of its class to be used for anesthesia, but had unacceptable side effects. Ketamine (Ketalar) was



S_1(+) Ketamine hydrochloride R_1(–) Ketamine hydrochloride

Figure 26-14 Stereoisomers of ketamine as it is formulated.

synthesized in 1962 by Stevens and was first used in humans in 1965 by Corssen and Domino. Ketamine was released for clinical use in 1970 and is still used in various clinical settings. Ketamine differs from most other drugs used to induce anesthesia because it has a significant analgesic effect. It usually does not depress the cardiovascular and respiratory systems,[308] but it does possess some of the adverse psychological effects found with the other phencyclidines. Ketamine consists of two stereoisomers, S(+) and R(–). The S(+) is more potent and is associated with fewer side effects. Interest in ketamine has increased more recently because of its effects on hyperalgesia and opiate tolerance, use in chronic pain states, potential neuroprotective effects, increasing popularity of total IV anesthesia, and the availability (in some countries) of S(+) ketamine.

Physicochemical Characteristics

Ketamine (Fig. 26-14) has a molecular weight of 238 kD, is partially water soluble, and forms a white crystalline salt with a pK_a of 7.5.[308] It has a lipid solubility 5 to 10 times that of thiopental.[309]

Metabolism

Ketamine is metabolized by hepatic microsomal enzymes. The major pathway involves *N*-demethylation to form norketamine (metabolite I), which is then hydroxylated to hydroxynorketamine. These products are conjugated to water-soluble glucuronide derivatives and are excreted in the urine.[308] The activity of the principal metabolites of ketamine has not been well studied, but norketamine (metabolite I) has significantly less (20% to 30%) activity than the parent compound. More recent modeling of norketamine suggests that it does contribute in prolonging the analgesia provided by either a bolus or infusion of ketamine.[310]

Pharmacokinetics

Ketamine pharmacokinetics have been examined after bolus administration of anesthetizing doses (2 to 2.5 mg/kg),[311] after a subanesthetic dose (0.25 mg/kg),[311,312] and after continuous infusion (steady-state plasma level 2000 ng/mL). Regardless of the dose, ketamine plasma disappearance can be described by a two-compartment model.[311] Table 26-1 contains the pharmacokinetic values from bolus administration studies. Of note is the rapid distribution reflected in the relatively brief distribution half-life of 11 to 16 minutes (Fig. 26-15). The high lipid solubility of ketamine is reflected in its large volume of distribution, nearly 3 L/kg. Clearance also is high, 890 to 1227 mL/min, which accounts for the short elimination half-life of 2 to 3 hours. The mean total body clearance (1.4 L/min) is approximately equal to liver blood flow, which means that changes in liver blood flow affect clearance. Low-dose alfentanil increases the volume of distribution and clearance of ketamine. In addition, alfentanil increases the distribution of ketamine into the brain.[313] The pharmacokinetic model of Clements[311] provided the best accuracy when used to administer low-dose ketamine to volunteers using a target-controlled infusion device.[314]

The pharmacokinetics of the two isomers is different. S(+) ketamine has a larger elimination clearance and larger volume of distribution than R(–) ketamine.[315] When the pharmacokinetics of S(+) ketamine was tested in a target-controlled infusion device for procedures of 1 hour and in combination with propofol, the authors found that the accuracy of the pharmacokinetic parameters was improved with a much smaller Vc (167 mL/kg). They also noted that ketamine clearance was not normally distributed, and this was not related to age.[316] The S(+) enantiomer also seems to be more potent in suppressing the EEG than either R(–) or the racemic mixture.[317]

Ketamine is increasingly being given by alternative routes, especially orally and via an intranasal spray. Administration by either of these routes is subject to significant first-pass metabolism. The bioavailability via oral administration is 20% to 30%, and via the intranasal route is approximately 40% to 50%.[318]

Pharmacology

Effects on the Central Nervous System

Ketamine produces dose-related unconsciousness and analgesia. The anesthetized state has been termed *dissociative anesthesia* because patients who receive ketamine alone appear to be in a cataleptic state, in contrast with other states of anesthesia that resemble normal sleep. Patients anesthetized with ketamine have

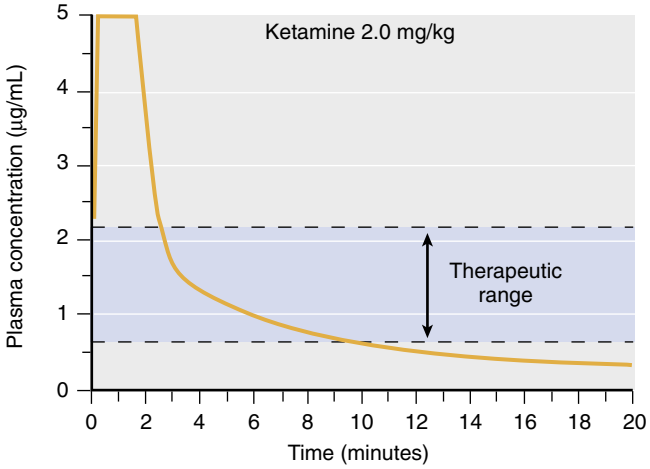


Figure 26-15 Simulated time course of plasma levels of ketamine after an induction dose of 2 mg/kg. Plasma levels required for hypnosis and amnesia during surgery are 0.7 to 2.2 µg/mL, with awakening usually occurring at levels less than 0.5 µg/mL.

profound analgesia, but keep their eyes open and maintain many reflexes. Corneal, cough, and swallow reflexes all may be present, but should not be assumed to be protective. There is no recall of surgery or anesthesia, but amnesia is not as prominent with ketamine as with the benzodiazepines. Because ketamine has a low molecular weight, a pK_a near the physiologic pH, and relatively high lipid solubility, it crosses the blood-brain barrier rapidly and has an onset of action within 30 to 60 seconds of administration. The maximal effect occurs in about 1 minute.

After ketamine administration, pupils dilate moderately, and nystagmus occurs. Lacrimation and salivation are common, as is increased skeletal muscle tone, often with coordinated but seemingly purposeless movements of the arms, legs, trunk, and head. Although there is great interindividual variability, plasma levels of 0.6 to 2 μg/mL are considered the minimum concentrations for general anesthesia; children may require slightly higher plasma levels (0.8 to 4 μg/mL).[319] The duration of ketamine anesthesia after a single IV administration of a general anesthetic dose (2 mg/kg) is 10 to 15 minutes (see Fig. 26-15), and full orientation to person, place, and time occurs within 15 to 30 minutes.

The S(+) enantiomer enables quicker recovery (by a couple of minutes) than the racemic mixture.[320,321] This is thought to be due to the lower dose necessary to produce an equianesthetic effect and to the 10% faster hepatic biotransformation.[321]

The duration of ketamine anesthesia is determined by the dose; larger doses produce more prolonged anesthesia, and the concurrent use of other anesthetics prolongs the time of emergence. Because there is a good correlation between blood level of ketamine and CNS effect, it seems that the relatively short duration of action of ketamine is due to its redistribution from the brain and blood to the other tissues in the body. The termination of effect after a single bolus administration of ketamine is caused by drug redistribution from the well-perfused to the less well-perfused tissues. Concomitant administration of benzodiazepines, a common practice, may prolong the effect of ketamine.[322] When used in combination with a benzodiazepine, the S(+) enantiomer was no different in terms of awareness at 30 minutes, but it was significantly better at 120 minutes than the racemic mixture.[323] Analgesia occurs at considerably lower blood levels than loss of consciousness.

Ketamine provides important postoperative analgesia. The plasma level at which pain thresholds are elevated is 0.1 μg/mL or greater. This means there is a considerable period of postoperative analgesia after ketamine general anesthesia, and subanesthetic doses can be used to produce analgesia. Ketamine has been shown to inhibit nociceptive central hypersensitization.[324] Ketamine also attenuates acute tolerance after opiate administration.[325]

The primary site of CNS action of ketamine seems to be the thalamoneocortical projection system. The drug selectively depresses neuronal function in parts of the cortex (especially association areas) and thalamus, while stimulating parts of the limbic system, including the hippocampus. This process creates what is termed a *functional disorganization* of nonspecific pathways in midbrain and thalamic areas.[326,327] There also is evidence that ketamine depresses transmission of impulses in the medial medullary reticular formation, which is important for transmission of the affective-emotional components of nociception from the spinal cord to higher brain centers.[328] In volunteers experiencing heat pain, functional magnetic resonance imaging (MRI) studies showed ketamine produced a dose-dependent effect on pain processing by decreasing activation of the secondary somatosensory cortex (S2), insula, and anterior cingulate cortex.[329] Blockade of CNS sodium channels has been shown not to be the mechanism of action by which ketamine produces anesthesia.[330] There is some evidence that ketamine occupies opiate receptors in the brain and spinal cord, and this property could account for some of the analgesic effects.[179,308,331] The S(+) enantiomer has been shown to have some opioid μ-receptor activity, accounting for part of its analgesic effect.[332] NMDA receptor interaction may mediate the general anesthetic effects and some analgesic actions of ketamine.[333,334] The spinal cord analgesic effect of ketamine is postulated to be due to inhibition of dorsal horn wide dynamic range neuronal activity.[335] Although some drugs have been used to antagonize ketamine, no specific receptor antagonist is yet known that reverses all the CNS effects of ketamine.

Ketamine increases cerebral metabolism, CBF, and ICP (see Chapter 63). Because of its excitatory CNS effects, which can be detected by generalized EEG development of theta wave activity and by petit mal seizure–like activity in the hippocampus,[336] ketamine increases $CMRO_2$. Although theta wave activity signals the analgesic activity of ketamine, alpha waves indicate its absence. There is an increase in CBF, which appears higher than the increase in $CMRO_2$ would mandate. With the increase in CBF and the generalized increase in sympathetic nervous system response, there is an increase in ICP after ketamine.[337,338] The increase in $CMRO_2$ and CBF can be blocked by the use of thiopental[339] or diazepam.[337,338] Cerebrovascular responsiveness to carbon dioxide seems to be preserved with ketamine; reducing $Paco_2$ attenuates the increase in ICP after ketamine.[337]

In animal models of incomplete cerebral ischemia and reperfusion, ketamine reduces necrosis and improves neurologic outcome.[340] Decreased sympathetic tone and inhibition of NMDA receptor–mediated ion currents were believed to mediate the reduction of necrotic cell death. More recently, S (+) ketamine was found to influence the expression of apoptosis-regulating proteins in rat brains 4 hours after cerebral ischemia/reperfusion.[341] The neuroprotection observed with ketamine may involve antiapoptotic mechanisms in addition to reducing necrotic cell death.

In contrast, ketamine or other NMDA receptor antagonists accentuate apoptosis in the newborn brain of animals.[342] This has been shown with other anesthetics either at high relative doses or with prolonged exposure. This finding has sparked controversy over the use of ketamine in neonates. An editorial in the journal *Anesthesiology* and the Anesthetic and Life Support Drugs Advisory Committee of the U.S. FDA cautioned changing clinical practice based on present available data.[343]

Ketamine, similar to other phencyclidines, produces undesirable psychological reactions, which occur during awakening from ketamine anesthesia and are termed *emergence reactions*. The common manifestations of these reactions, which vary in severity and classification, are vivid dreaming, extracorporeal experiences (sense of floating out of body), and illusions (misinterpretation of a real, external sensory experience).[344] These incidents of dreaming and illusion are often associated with excitement, confusion, euphoria, and fear.[345] They occur in the first hour of emergence and usually abate within 1 to several hours. It has been postulated that the psychic emergence reactions occur secondary to ketamine-induced depression of auditory and visual relay nuclei, leading to misperception or misinterpretation

of auditory and visual stimuli.[308] The incidence ranges from 3%[179,308] to 100%.[344] A clinically relevant range is probably 10% to 30% of adult patients who receive ketamine as a sole or major part of the anesthetic technique.

Factors that affect the incidence of emergence reactions are age,[346] dose,[179] gender, psychological susceptibility,[347] and concurrent drugs. Pediatric patients do not report as high an incidence of unpleasant emergence reactions as do adult patients; men also report a lower incidence compared with women. Larger doses and rapid administration of large doses seem to predispose patients to a higher incidence of adverse effects.[348,349] Finally, certain personality types seem prone to the development of emergence reactions. Patients who score high in psychotism on the Eysenck Personality Inventory are prone to develop emergence reactions,[347] and individuals who commonly dream at home are more likely to have postoperative dreams in the hospital after ketamine.[348] Numerous drugs have been used to reduce the incidence and severity of postoperative reactions to ketamine[179,308]; the benzodiazepines seem to be the most effective group of drugs to attenuate or to treat ketamine emergence reactions. Midazolam,[308] lorazepam,[350] and diazepam[351] are useful in reducing reactions to ketamine. Midazolam reduces the psychotomimetic effect of the S (+) enantiomer.[352]

Effects on the Respiratory System

Ketamine has minimal effects on the central respiratory drive as reflected by an unaltered response to carbon dioxide.[353] There can be a transient (1 to 3 minutes) decrease in minute ventilation after the bolus administration of an induction dose of ketamine (2 mg/kg intravenously). Unusually large doses can produce apnea,[354] but this is seldom seen. Arterial blood gases generally are preserved when ketamine is used alone for anesthesia or analgesia. With the use of adjuvant sedatives or anesthetic drugs, however, respiratory depression can occur. Ketamine has been shown to affect ventilatory control in children and should be considered a possible respiratory depressant when the drug is given to them in bolus doses.[355]

Ketamine is a bronchial smooth muscle relaxant. When it is given to patients with reactive airway disease and bronchospasm, pulmonary compliance is improved.[356] Ketamine is as effective as halothane or enflurane in preventing experimentally induced bronchospasm.[357] The mechanism for this effect is probably a result of the sympathomimetic response to ketamine, but there are isolated bronchial smooth muscle studies showing that ketamine can directly antagonize the spasmogenic effects of carbachol and histamine.[358] Owing to its bronchodilating effect, ketamine has been used to treat status asthmaticus unresponsive to conventional therapy.[359]

A potential respiratory problem, especially in children (see Chapter 82), is the increased salivation that follows ketamine administration. This increased salivation can produce upper airway obstruction, which can be complicated further by laryngospasm. The increased secretions also may contribute to or may complicate further laryngospasm. In addition, although swallow, cough, sneeze, and gag reflexes are relatively intact after ketamine administration, there is evidence that silent aspiration can occur during ketamine anesthesia.

Effects on the Cardiovascular System

Ketamine also has unique cardiovascular effects; it stimulates the cardiovascular system and is usually associated with increases in blood pressure, heart rate, and cardiac output (see Table 26-2). Other anesthetic induction drugs either cause no change in hemodynamic variables or produce vasodilation with cardiac depression. The S(+) enantiomer, despite hope that reducing the dose by half (equianesthetic potency) would attenuate side effects, is equivalent to the racemic mixture regarding hemodynamic response.[352] The increase in hemodynamic variables is associated with increased work and myocardial oxygen consumption. The healthy heart is able to increase oxygen supply by increased cardiac output and decreased coronary vascular resistance, so that coronary blood flow is appropriate for the increased oxygen consumption.[360] The hemodynamic changes are not related to the dose of ketamine (e.g., there is no hemodynamic difference between IV administration of 0.5 mg/kg and 1.5 mg/kg).[361] A second dose of ketamine produces hemodynamic effects less than or even opposite to the effects of the first dose.[362]

The hemodynamic changes after anesthesia induction with ketamine tend to be the same in healthy patients and in patients with various acquired or congenital heart diseases.[361] In patients with congenital heart disease, there are no significant changes in shunt directions or fraction[363] or systemic oxygenation after ketamine induction of anesthesia.[364] In patients who have elevated pulmonary artery pressure (as with mitral valvular and some congenital lesions), ketamine seems to cause a more pronounced increase in pulmonary than systemic vascular resistance.[363]

The mechanism by which ketamine stimulates the circulatory system remains enigmatic. It seems not to be a peripheral mechanism such as baroreflex inhibition, but rather to be central. There is some evidence that ketamine attenuates baroreceptor function via an effect on NMDA receptors in the nucleus tractus solitarius.[365] Ketamine injected directly into the CNS produces an immediate sympathetic nervous system hemodynamic response.[366] Ketamine also causes the sympathoneuronal release of norepinephrine, which can be detected in venous blood. Blockade of this effect is possible with barbiturates, benzodiazepines, and droperidol.[367] Ketamine in vitro probably has negative inotropic effects. Myocardial depression has been shown in chronically instrumented dogs,[368] and isolated canine heart preparations.[369] In isolated guinea pig hearts, ketamine was the least depressant of all the major induction drugs, however.[370] The finding that ketamine may exert its myocardial effects by acting on myocardial ionic currents (which may exert different effects from species to species or among tissue types) may explain the tissue and animal model variances in direct myocardial action.[371]

The centrally mediated sympathetic responses to ketamine usually override the direct depressant effects of ketamine. Some peripheral nervous system actions of ketamine play an undetermined role in the hemodynamic effects of the drug. Ketamine inhibits intraneuronal uptake of catecholamines in a cocaine-like effect,[160,161] and inhibits extraneuronal norepinephrine uptake.[372]

Stimulation of the cardiovascular system is not always desirable, and certain pharmacologic methods have been used to block the ketamine-induced tachycardia and systemic hypertension. Successful methods include use of adrenergic antagonists (α and β), various vasodilators,[373] and clonidine.[374] Probably the most fruitful approach has been prior administration of benzodiazepines. Modest doses of diazepam, flunitrazepam, and midazolam all attenuate the hemodynamic effects of ketamine. It also is possible to decrease the tachycardia and hypertension caused by ketamine by using a continuous infusion technique with or

without a benzodiazepine.[375] Inhalation anesthetics[376] and propofol blunt the hemodynamic effect of ketamine. Ketamine can produce hemodynamic depression in the setting of deep anesthesia, when sympathetic responses do not accompany its administration.

Uses

The many unique features of ketamine pharmacology, especially its propensity to produce unwanted emergence reactions, have limited its use for routine anesthesia. Nevertheless, ketamine has an important niche in the practice of anesthesiology when its unique sympathomimetic activity and bronchodilating capabilities are indicated during induction of anesthesia. It is used for premedication, sedation, induction, and maintenance of general anesthesia (Table 26-9). There has been increased interest in the routine use of ketamine in small doses (20 to 60 mg) for preventive analgesia and for the treatment or prevention of opiate tolerance and hyperalgesia.

Induction and Maintenance of Anesthesia

Most candidates for ketamine induction are poor-risk patients (ASA class IV) with respiratory and cardiovascular system disorders (excluding ischemic heart disease), in particular, patients with reactive airway disease or patients with hemodynamic compromise based on either hypovolemia or cardiomyopathy (not coronary artery disease). Ketamine bronchodilation and profound analgesia allowing the use of high oxygen concentrations make ketamine an excellent choice for induction in patients with reactive airway disease. Otherwise healthy trauma victims whose blood loss is extensive also are candidates for rapid-sequence anesthesia induction with ketamine.[377] Patients with septic shock also may benefit from ketamine.[378] The intrinsic myocardial depressant effect of ketamine may manifest in this situation, however, if trauma or sepsis has caused depletion of catecholamine stores before the patient's arrival in the operating room. Use of ketamine in these patients does not obviate the need for appropriate preoperative preparation, including restoration of blood volume.

Other cardiac diseases that can be well managed with ketamine anesthesia are cardiac tamponade and restrictive pericarditis.[379] The finding that ketamine preserves heart rate and right atrial pressure through its sympathetic stimulating effects makes ketamine an excellent anesthetic induction and maintenance drug in this setting. Ketamine also is often used in patients with congenital heart disease, especially patients in whom the propensity for right-to-left shunting exists. Use of ketamine has been reported in a patient susceptible to malignant hyperthermia.[380]

Ketamine combined with propofol or midazolam can be given by continuous infusion to produce satisfactory cardiac anesthesia for patients with valvular and ischemic heart disease. The combination of a benzodiazepine[375] or of a benzodiazepine plus sufentanil[381] with ketamine attenuates or eliminates the unwanted tachycardia and hypertension and postoperative psychological derangements. With this technique, there are minimal hemodynamic perturbations, profound analgesia, dependable amnesia, and an uneventful convalescence. The use of propofol plus low-dose ketamine also has gained increasing popularity as a total IV anesthesia technique for patients undergoing noncardiac surgery. The advantages of this combination are maintenance of stable hemodynamics and minimal ventilatory depression when allowing spontaneous ventilation.

Table 26-9 Uses and Doses of Ketamine

Induction of general anesthesia*	0.5-2 mg/kg IV 4-6 mg/kg IM
Maintenance of general anesthesia	0.5-1 mg/kg IV with N_2O 50% in O_2 15-45 µg/kg/min IV with N_2O 50-70% in O_2 30-90 µg/kg/min IV without N_2O
Sedation and analgesia	0.2-0.8 mg/kg IV over 2-3 min 2-4 mg/kg IM
Preemptive/preventive analgesia	0.15-0.25 mg/kg IV

*Lower doses are used if adjuvant drugs such as midazolam or thiopental also are given.
N_2O, nitrous oxide.

Pain Management

Ketamine administered in small doses decreases postoperative analgesic consumption (see Chapter 87). Several meta-analyses of the use of low-dose ketamine (20 to 60 mg) perioperatively have been done. These meta-analyses showed an overall decrease in opiate use or improved analgesia and a decrease in opiate-induced side effects, especially PONV. Side effects, especially psychotomimetic effects, were minimal, especially if a benzodiazepine also was administered.[382] Ketamine in a 1:1 combination with morphine using an 8-minute lockout interval provided optimal postoperative analgesia for this combination.[383] Alternatively, an initial bolus of 0.5 mg/kg of ketamine followed by a continuous infusion of 3 µg/kg/min during surgery and 1.5 µg/kg/min for 48 hours after surgery has been used successfully in total knee arthroplasty.[384]

The action of ketamine on opiate tolerance and hyperalgesia combined with its direct analgesic activity has prompted increasing use of ketamine in chronic pain states. Ketamine may be effective in the treatment of cancer pain, chronic peripheral and central neuropathic pain, phantom and ischemic limb pain, fibromyalgia, complex regional pain syndrome, visceral pain, and migraine. These indications are based largely on a few short-term trials with limited clinical application or limited nonrandomized trials and case studies.[385] There also have been a limited number of reports that indicate the value of multimodal pain therapy including ketamine in preventing postoperative chronic pain.[386,387]

The epidural/caudal administration of ketamine (0.5 to 1 mg/kg) has been increasingly reported. Although the efficacy of these doses of ketamine seems to be established, the safety of this technique has not yet received regulatory approval. The preservative of racemic mixture is potentially neurotoxic, whereas studies to date indicate preservative-free S(+) ketamine may be safe.[388]

Sedation

Ketamine is particularly suitable for sedation of pediatric patients undergoing procedures outside of the operating room (see Chapter 82). Pediatric patients have fewer adverse emergence reactions[346] than adults, and this feature makes the use of keta-

mine in pediatric patients more versatile. Ketamine is used for sedation or general anesthesia for the following pediatric procedures: cardiac catheterization, radiation therapy, radiologic studies, dressing changes,[389] and dental work.[322]

Usually, a subanesthetic dose (≤1.0 mg/kg intravenously) is used for dressing changes; this dose provides adequate operating conditions, but a rapid return to normal function, including the resumption of eating, which is important in maintaining proper nutrition in burn patients.[308,179] Often, ketamine is combined with premedication of a barbiturate or benzodiazepine and an antisialagogue (e.g., glycopyrrolate) to facilitate management. The premedications reduce the dose requirement for ketamine, and the antisialagogue reduces the sometimes troublesome salivation.

In adults and children, ketamine can be used as a supplement or an adjunct to regional anesthesia, extending the usefulness of the primary (local anesthetic) form of anesthesia (see Chapter 52). In this setting, ketamine can be used before the application of painful blocks,[390] but more commonly it is used for sedation or supplemental anesthesia during long or uncomfortable procedures. When used for supplementation of regional anesthesia, IV ketamine (0.5 mg/kg) can be combined with IV diazepam (0.15 mg/kg).[391] In outpatients, premedication with midazolam (1 to 2 mg), concurrent low-dose propofol infusion, and intermittent ketamine (for analgesia) in doses less than 3 mg/kg[392] or as an infusion of 0.15 to 0.3 μg/kg/min provides excellent sedation, analgesia, and recovery (see Chapter 78). Ketamine also may be considered for sedation of patients in a critical care unit because of its combined sedative and analgesic properties and favorable effects on hemodynamics. Although controversial, a more recent review on the use of ketamine for patients with brain injury concluded, "Ketamine can be used safely in neurologically impaired patients under conditions of controlled ventilation, coadministration of a GABA receptor agonist, and avoidance of nitrous oxide."[393]

Doses and Routes of Administration

Ketamine has been administered intravenously, intramuscularly, transcutaneously, orally, nasally, and rectally, and as a preservative-free solution epidurally or intrathecally.[394] Most clinical use involves the IV and intramuscular (IM) routes, by which the drug rapidly achieves therapeutic levels. The dose depends on the desired therapeutic effect and on the route of administration. Table 26-9 contains general recommended doses for the IV and IM administration of ketamine for various therapeutic goals.[308] Intranasal administration has an onset closer to IV administration; an oral dose of 3 to 10 mg/kg generates a sedative effect in 20 to 45 minutes.

For sedation, ketamine may be given in an IM dose of 2 to 4 mg/kg. It also has been administered orally in doses of 3 to 10 mg/kg, with 6 mg/kg providing optimal conditions in 20 to 25 minutes in one study and 10 mg/kg providing sedation in 87% of children within 45 minutes in another study.[395,396]

Side Effects and Contraindications

The common psychological emergence reactions were discussed earlier. Contraindications to ketamine relate to specific pharmacologic actions and patient diseases. Patients with increased ICP and with intracranial mass lesions breathing spontaneously should not receive ketamine because it can increase ICP and has been reported to cause apnea.[397] The S (+) enantiomer also increases CBF and is probably similarly contraindicated.[283] In ventilated patients, because ketamine retains the response of CBF to carbon dioxide, its use for sedation in head-injured patients may be valuable owing to its potential neuroprotective effect.[393]

Ketamine may be contraindicated in patients with an open eye injury or other ophthalmologic disorder, in which a ketamine-induced increase in intraocular pressure would be detrimental (see Chapter 75). Because ketamine has a propensity to cause hypertension and tachycardia, with a commensurate increase in myocardial oxygen consumption, it is contraindicated as the sole anesthetic in patients with ischemic heart disease.[398] Likewise, it is unwise to give ketamine to patients with vascular aneurysms because of the possible sudden change in arterial pressure. Psychiatric disease, such as schizophrenia, and a history of adverse reaction to ketamine or one of its congeners also are contraindications.[179] One also should consider carefully using ketamine when there is a possibility of postoperative delirium from other causes (e.g., delirium tremens, possibility of head trauma), and a ketamine-induced psychomimetic effect would confuse the differential diagnosis.

As mentioned earlier, ketamine or other NMDA receptor antagonists accentuate apoptosis in the newborn brain of animals, and the clinical implications of this are unknown. Finally, because ketamine's preservative, chlorobutanol, has been shown to be neurotoxic, this formulation of ketamine for subarachnoid or epidural administration is contraindicated.[399] S(+) ketamine is available in a preservative-free solution. The FDA has not approved the use of intrathecal or epidural ketamine.

Etomidate

History

The properties of etomidate (Amidate, Hypnomidate) include hemodynamic stability, minimal respiratory depression, cerebral protection, and pharmacokinetics enabling rapid recovery after either a single dose or a continuous infusion. In animals, etomidate also provides a wider margin of safety (ED_{50}/LD_{50}) than thiopental (26.4 versus 4.6).[400] These beneficial properties led to widespread use of etomidate for induction, for maintenance of anesthesia, and for prolonged sedation in critically ill patients. Anesthesiologists' enthusiasm for etomidate was tempered, however, by reports that the drug can cause temporary inhibition of steroid synthesis after single doses and infusions.[401,402] This effect, combined with other minor disadvantages (e.g., pain on injection, superficial thrombophlebitis, myoclonus, and a high incidence of nausea and vomiting), led to several editorials[403,404] questioning the role of etomidate in modern anesthetic practice. Use of the drug waned significantly after those editorials, but it has expanded as a result of a rediscovery of etomidate's beneficial physiologic profile combined with a lack of any new reports describing clinically significant adrenocortical suppression after an induction dose or brief infusions.

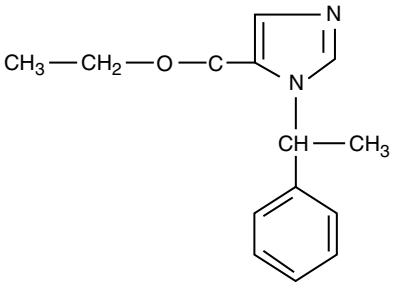


Figure 26-16 Structure of etomidate, an imidazole derivative.

Physicochemical Characteristics

Etomidate is an imidazole derivative (R-(+)-pentylethyl-1H-imidazole-5 carboxylate sulfate). Its chemical structure is illustrated in Figure 26-16. With a molecular weight of 342.36 kD,[179] etomidate exists as two isomers, the (+) isomer being the one active as a hypnotic.[179] Etomidate is water insoluble and is unstable in a neutral solution. It has been formulated with several solvents. In the United States, it is supplied as a 2-mg/mL propylene glycol (35% by volume) solution with a pH of 6.9 and an osmolality of 4640 mOsm/L. In Europe, lipid emulsion has been introduced in an attempt to reduce some of the side effects of etomidate.[405] In contrast to sodium thiopental, when etomidate is mixed with other commonly used anesthetics, such as neuromuscular blockers, vasoactive drugs, or lidocaine, it does not cause precipitation.[406]

Metabolism, Induction, and Maintenance of Anesthesia

Etomidate is metabolized in the liver primarily by ester hydrolysis to the corresponding carboxylic acid of etomidate (major metabolite) or by *N*-dealkylation.[179] The main metabolite is inactive.[406] Only 2% of the drug is excreted unchanged, the rest being excreted as metabolites by the kidney (85%) and bile (13%).[406]

Etomidate has been used for induction and maintenance of anesthesia (Table 26-10). The induction dose of etomidate is 0.2 to 0.6 mg/kg,[407] and it is reduced by premedication with an opiate, a benzodiazepine, or a barbiturate. Onset of anesthesia after a routine induction dose of 0.3 mg/kg of etomidate is rapid (one arm–brain circulation) and is equivalent to anesthesia obtained with an induction dose of thiopental or methohexital.[407] The duration of anesthesia after a single induction dose is linearly related to the dose—each 0.1 mg/kg administered provides about 100 seconds of loss of consciousness.[408] Repeat doses of etomidate by bolus or infusion prolong the duration of hypnosis. Recovery after multiple doses or an infusion of etomidate is still usually rapid.[409-411] The addition of small doses of fentanyl with etomidate for short surgical procedures reduces the required dose of etomidate and allows earlier awakening. In children, induction by rectal administration of etomidate has been obtained with 6.5 mg/kg. Hypnosis occurs in 4 minutes. At this dose, hemodynamics are unaltered, and recovery is still rapid.[412]

Various infusion schemes have been devised to use etomidate as a maintenance anesthetic for the hypnotic component of anesthesia. Most regimens aim to achieve a plasma level of 300 to 500 ng/mL, which is the concentration necessary for hypnosis.[413] Two-stage and three-stage infusions have been used successfully. These consist of an initial rapid infusion of 100 µg/kg/min for 10 minutes followed by 10 µg/kg/min thereafter,[414] or of 100 µg/kg/min for 3 minutes, 20 µg/kg/min for 27 minutes, and 10 µg/kg/min thereafter.[415] Loss of consciousness with these techniques occurs after 100 to 120 seconds.[415] The infusion is usually terminated 10 minutes before desired awakening.[415]

Table 26-10 Uses and Doses of Etomidate

Induction of general anesthesia	0.2-0.6 mg/kg IV
Maintenance of general anesthesia	10 µg/kg/min IV with N_2O and an opiate
Sedation and analgesia	Limited to periods of brief sedation because of inhibition of corticosteroid synthesis

N_2O, nitrous oxide.

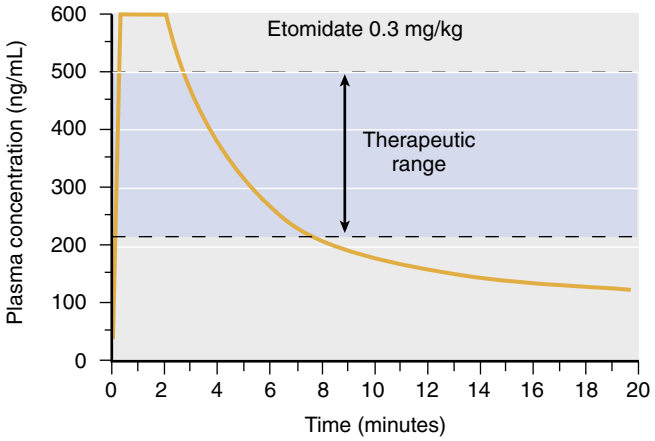


Figure 26-17 Simulated time course of plasma levels of etomidate after an induction dose of 0.3 mg/kg. Plasma levels required for hypnosis during surgery are 300 to 500 ng/mL, with awakening usually occurring at levels less than 225 ng/mL.

Pharmacokinetics

The pharmacokinetics of etomidate has been calculated after single bolus doses and after continuous infusion (see Table 26-1).[416] The time course of plasma disappearance after a 0.3-mg/kg bolus is shown in Figure 26-17. The kinetics of etomidate is best described by an open three-compartment model. The drug has an initial distribution half-life of 2.7 minutes, a redistribution half-life of 29 minutes, and an elimination half-life of 2.9 to 5.3 hours.[416] Clearance of etomidate by the liver is high (18 to 25 mL/kg/min), with a hepatic extraction ratio of 0.5 ± 0.9 [407,413] Drugs affecting hepatic blood flow alter the elimination half-life. Because redistribution is the mechanism whereby the effect of a bolus of etomidate is dissipated, hepatic dysfunction should not appreciably alter recovery from an induction dose. Etomidate is 75% protein bound.[417] Pathologic conditions altering serum proteins (e.g., hepatic or renal disease) vary the amount of the free (unbound) fraction and may cause a given dose to have an exaggerated pharmacodynamic effect.[417] A hemorrhagic shock model

in pigs bled to a mean pressure of 50 mm Hg did not alter etomidate pharmacokinetics or pharmacodynamics.[418] This finding contrasts with the marked changes seen in this same model with other IV anesthetics.

In patients with cirrhosis, the volume of distribution is doubled, whereas clearance is normal; the result is an elimination half-life that is twice normal.[419] The initial distribution half-life and clinical effect are likely unchanged. Increasing age is associated with a smaller initial volume of distribution and a decreased clearance of etomidate.[420] The short elimination half-life and the rapid clearance of etomidate make it suitable for administration in a single dose, in multiple doses, or in a continuous infusion.

Pharmacology

Effects on the Central Nervous System

The primary action of etomidate on the CNS is hypnosis, which is achieved in one arm–brain circulation after a normal induction dose (0.3 mg/kg).[407] Etomidate has no analgesic activity. Plasma levels required for the maintenance of anesthesia are approximately 300 to 500 ng/mL, for sedation are 150 to 300 ng/mL, and for awakening are 150 to 250 ng/mL (see Fig. 26-17).[413,414,416] The mechanism by which etomidate produces hypnosis is not fully elucidated; however, it seems largely (but not solely) related to GABA. Its action may be antagonized by GABA antagonists.[421] Generally, the mechanism of action of etomidate seems to be similar to that established so far for propofol (see earlier).[422] For etomidate, it seems that the β2 and β3 subunits are more important for its hypnotic action than the α1 $GABA_A$ subunit.[42,423]

At a dose of 0.2 to 0.3 mg/kg, etomidate reduces CBF (by 34%) and $CMRO_2$ (by 45%) without altering MAP.[424] CPP is maintained or increased, and there is a beneficial net increase in the cerebral oxygen supply-to-demand ratio.[424] Etomidate given in doses sufficient to produce EEG burst suppression acutely decreases ICP by 50% in patients with already increased ICP, returning increased ICP to almost normal values.[425,426] The decrease in ICP is maintained in the period immediately after intubation.[426] To maintain the effects of etomidate on ICP, high infusion rates (60 μg/kg/min) are necessary.[427] In contrast to the situation with other neuroprotective drugs such as thiopental, reduction of ICP and maintenance of burst suppression are not associated with a decrease in MAP.[426] Because cerebrovascular reactivity is still maintained after etomidate administration,[427] hyperventilation theoretically may reduce ICP further when used in conjunction with etomidate. In animals, etomidate reduced neuronal death after acute cortical ischemic insult.[428,429] Other investigators disagree on the neuroprotective qualities of etomidate.[430] Deeper structures, such as the brainstem, may not be afforded ischemic protection by etomidate.[431]

Etomidate produces changes in the EEG similar to those produced by the barbiturates.[432] There is an initial increase in alpha amplitude with sharp beta bursts followed by mixed delta-theta waves, with delta wave activity predominating before the onset of periodic burst suppression.[432] The absence of beta waves in the initial phase of induction with etomidate is the major difference in EEG changes compared with thiopental.[432] Etomidate has been associated with grand mal seizures[433,434] and produces increased EEG activity in epileptogenic foci. This feature has proved useful for intraoperative mapping of seizure foci before surgical ablation.[434] Etomidate also is associated with a frequent incidence of myoclonic movement.[409,410] Myoclonus is not thought to be associated with seizure-like EEG activity.[432] The myoclonic movement is believed to result from activity either in the brainstem or in deep cerebral structures.

The effect of etomidate on auditory evoked potentials is similar to that produced by the inhaled anesthetics. There is a dose-dependent increase in latency and a decreasing amplitude of the early cortical components (Pa and Nb).[435]

Effects on the Respiratory System

Etomidate has less effect on ventilation than other anesthetics used to induce anesthesia. It does not induce histamine release either in healthy patients or in patients with reactive airway disease.[436] Ventilatory response to carbon dioxide is depressed by etomidate, but the ventilatory drive at any given carbon dioxide tension is greater than that following an equipotent dose of methohexital.[226] Induction with etomidate produces a brief period of hyperventilation, sometimes followed by a similarly brief period of apnea,[437] which results in a slight (±15%) increase in $Paco_2$, but no change in the partial pressure of arterial oxygen (Pao_2).[438] The incidence of apnea is altered by premedication.[439] Hiccups or coughing may accompany etomidate induction, with an incidence similar to that after methohexital induction.[407]

In laboratory models, etomidate seems to be as effective as propofol in relaxing precontracted tracheal rings, but less effective than propofol in preventing tracheal ring contraction by muscarinic agonists.[440] Etomidate's action on pulmonary vascular tone are similar to the actions observed with ketamine and propofol.[441]

Effects on the Cardiovascular System

The minimal effect of etomidate on cardiovascular function sets it apart from other rapid-onset anesthetics (see Table 26-2).[442,443] An induction dose of 0.3 mg/kg of etomidate given to cardiac patients for noncardiac surgery results in almost no change in heart rate, MAP, mean pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, stroke volume, cardiac index, and pulmonary and systemic vascular resistance.[442] A large dose of etomidate, 0.45 mg/kg (which is 50% larger than a normal induction dose),[444] also produces minimal changes in cardiovascular variables. In patients with ischemic heart disease or valvular disease, etomidate (0.3 mg/kg) produces similar minimal alterations in cardiovascular variables.[442] In patients with mitral or aortic valve disease, etomidate may produce greater changes in MAP (an approximate 20% decrease)[438] than in patients without cardiac valvular disease. After induction (18 mg) and infusion (2.4 mg/min), etomidate produces a 50% decrease in myocardial blood flow and oxygen consumption, and a 20% to 30% increase in coronary sinus blood oxygen saturation.[108] The myocardial oxygen supply-to-demand ratio is well maintained. There is minimal effect on the QT interval.[445]

The hemodynamic stability seen with etomidate may be due partly to its unique lack of effect on the sympathetic nervous system and on baroreceptor function.[122] Etomidate lacks analgesic efficacy, however, and needs to be combined with an opiate to prevent hemodynamic perturbations during laryngoscopy and intubation.

Endocrine Effects

Ledingham and Watt[401] in 1983 first raised concerns regarding long-term etomidate infusion in critically ill patients. They pos-

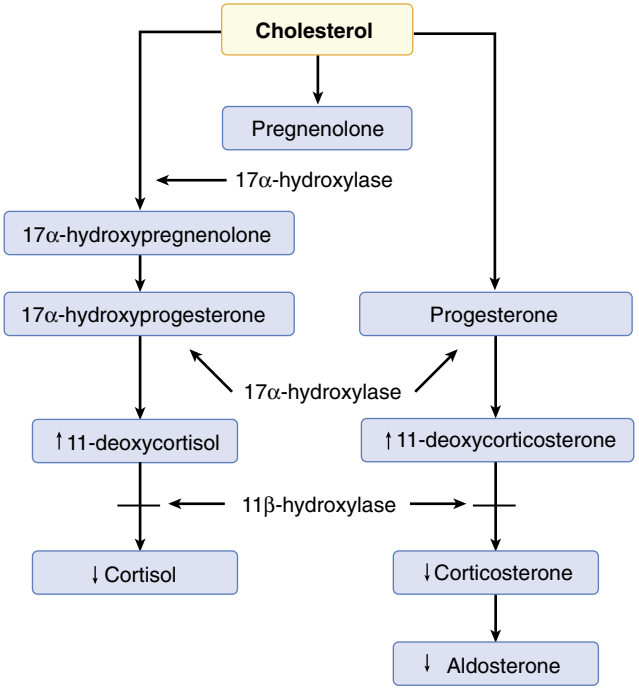


Figure 26-18 Pathway for the biosynthesis of cortisol and aldosterone. The sites at which etomidate affects cortisol-aldosterone synthesis by its action on 11β-hydroxylase (major site) and 17α-hydroxylase (minor site) are illustrated.

tulated that adrenocortical suppression secondary to long-term etomidate infusion was the cause of the increased mortality.[401]

The specific endocrine effects manifested by etomidate are a dose-dependent reversible inhibition of the enzyme 11β-hydroxylase, which converts 11-deoxycortisol to cortisol, and a relatively minor effect on 17α-hydroxylase (Fig. 26-18).[446,447] This activity results in an increase in the cortisol precursors 11-deoxycortisol and 17-hydroxyprogesterone and an increase in ACTH. The blockade of 11β-hydroxylase and, to a lesser extent, 17α-hydroxylase[446] seems to be related to the free imidazole radical of etomidate-binding cytochrome P-450.[447,448] This results in inhibition of ascorbic acid resynthesis, which is required for steroid production in humans.[448] The blockade of the cytochrome P-450–dependent enzyme 11β-hydroxylase also results in decreased mineralocorticoid production and an increase in intermediaries (11-deoxycorticosterone).[402,404] Vitamin C supplementation restores cortisol levels to normal after the use of etomidate.[448] Because minor adrenocortical suppressive effects were shown to follow even single bolus doses,[446] concerns about the use of etomidate for anesthetic induction arose.[403] No large prospective studies have been done, but several smaller studies have provided some insight into the exact nature of adrenocortical suppression after an induction dose.

Duthie and colleagues[449] showed that in otherwise healthy patients undergoing minor peripheral surgery, plasma cortisol levels were slightly depressed from the preinduction levels for 1 hour postoperatively. The nadir of mean cortisol levels did not fall out of the normal range. 11-Deoxycorticosterone, substrate for the etomidate-inhibited 11β-hydroxylase, peaked at very high levels compared with the thiopental control group.[449] In another study, patients undergoing orthopedic surgery were given an etomidate induction followed by an infusion of etomidate (average total dose 68 mg). Temporary adrenocortical suppression, as measured by a reduced response to ACTH stimulation, was documented for 6 hours postoperatively and returned to normal by 20 hours postoperatively. Postoperative cortisol levels in the etomidate study patients were not significantly different from the levels in patients who received a midazolam induction. As in the study by Duthie and colleagues,[449] mean cortisol levels in the etomidate group remained in the normal range at all times postoperatively.[450] Other studies have shown similar results when evaluating etomidate induction doses; none reported adverse outcomes secondary to short-term adrenocortical suppression.[402,446]

In each of the prospective etomidate studies documenting adrenocortical suppression without associated clinical sequelae, a conclusion of safety was not forthcoming. The reason was that these studies did not address high-stress procedures, in which the benefit of a high cortisol level in response to a major stress could be desirable, and etomidate's blockade of the response to ACTH could be detrimental. In 1994, the cortisol levels during and after coronary artery bypass surgery were compared in patients receiving total IV anesthesia with etomidate/fentanyl (mean etomidate dose of 87 ± 3 mg) versus midazolam/fentanyl. Except for the first hour after induction, cortisol levels were the same or higher in the etomidate group compared with the midazolam group, a finding implying that the body's ability to respond to a high surgical stress was still intact despite high doses of etomidate. This finding suggests that etomidate is probably safe for use in major surgery.[451]

Three facts suggest that the issue of temporary adrenocortical suppression after perioperative induction doses of etomidate is not clinically significant: (1) Although there is one questionable case report suggesting acute symptomatic postoperative adrenocortical suppression in a 74-year-old ICU patient,[452] there are no other known reports of any negative clinical outcome associated with an etomidate induction despite millions of uses. (2) After etomidate induction, the nadir of cortisol levels usually remains in the low-normal range, and the adrenocortical suppression is a short-lived phenomenon. (3) High-stress surgery can overcome the temporary adrenocortical suppression caused by etomidate.

Other Effects

Although etomidate provides stable hemodynamics and minimal respiratory depression, it is associated with several adverse effects when used for induction, including nausea and vomiting, pain on injection, myoclonic movement, and hiccups. Etomidate has been associated with a frequent (30% to 40%) incidence of nausea and vomiting.[409-411,439] More recently, etomidate in a lipid emulsion was associated with an equal incidence of postoperative nausea compared with propofol.[453]

Superficial thrombophlebitis of the vein used may occur 48 to 72 hours after etomidate injection.[454] The incidence may be 20% when etomidate is given alone through a small (21-gauge) IV needle. Intra-arterial injection of etomidate is not associated with local or vascular disease. Pain on injection, similar in incidence to pain with propofol,[175] can be essentially eliminated by injecting lidocaine immediately before injection of etomidate; 20 to 40 mg may be enough.[455] Pain on injection is reduced further by using a large vein. The incidence of pain on injection is 0 to 50%. The lipid formulation of etomidate also is associated with a much lower incidence of pain on injection, thrombophlebitis, and histamine release on injection.[456]

The incidence of muscle movement (myoclonus) and of hiccups also is highly variable (0 to 70%), but myoclonus is reduced by premedication with either a narcotic or 0.015 mg/kg of midazolam 90 seconds before induction.[457] Etomidate enhances the neuromuscular blockade of nondepolarizing neuromuscular blockers.[458] In vitro, etomidate inhibits aminolevulinic acid synthetase, but it has been administered to patients with porphyria without inducing an acute attack of porphyria.[459]

The carrier for etomidate, propylene glycol, also has been reported to have some negative effects. Some reports suggest that propylene glycol can be associated with a small degree of hemolysis.[405] Additionally, high-dose prolonged infusion has been reported to result in propylene glycol toxicity (a hyperosmolar state).[460]

Uses

Etomidate is most appropriate in patients with cardiovascular disease, reactive airway disease, intracranial hypertension, or any combination of disorders indicating the need for an induction agent with limited or beneficial physiologic side effects. The hemodynamic stability of etomidate is unique among the rapid-onset anesthetics used to induce anesthesia.

Etomidate has been used primarily in sick patients. In multiple studies, etomidate has been used for induction in patients with a compromised cardiovascular system who are undergoing coronary artery bypass surgery or valve surgery, and in patients requiring induction of general anesthesia for percutaneous transluminal coronary angioplasty, aortic aneurysm repair, and thoracic surgery. When etomidate is used in combination with fentanyl, titrating etomidate up to 0.6 mg/kg maintains blood pressure and heart rate in a narrow range, preserving coronary perfusion pressure in these patients with probable coronary artery disease, while blunting the response to intubation and avoiding unnecessary stress. For cardioversion, the rapid onset, quick recovery, and maintenance of blood pressure in these sometimes hemodynamically tenuous patients, combined with continued spontaneous respiration, make etomidate an acceptable choice,[175] although there is one report of myoclonus interfering with electrocardiographic evaluation.[461]

Although definitive proof of the neuroprotective effect of etomidate in humans is lacking, the combination of animal data and anecdotal reports of successful use of etomidate in neurosurgical procedures such as giant aneurysm clippings makes etomidate a reasonable choice during neurosurgical induction.[414,426,428] In addition, etomidate should be considered as an anesthetic to reduce increased ICP when maintenance of cerebral or coronary perfusion pressure also is important. Trauma patients with questionable volume status may be well served by an etomidate induction. Although the indirect sympathomimetic effect seen with ketamine induction is absent, there is no direct myocardial depression and no confusion in the differential diagnosis of postoperative delirium. This is especially important in patients whose trauma may be related to drug or alcohol use. When using the drug in trauma patients, loss of consciousness by itself can be associated with decreased adrenergic output, and postinduction controlled ventilation by itself can exacerbate a decreased preload (see Chapter 72). Both of these factors may cause a significant decrease in blood pressure at induction despite etomidate having no direct cardiovascular drug effect.

During an infusion, hemodynamic status is well maintained, and adequate spontaneous ventilation is present.[294] The incidence of pain on injection and of myoclonus and thrombophlebitis tends to be less with an infusion technique.[413,462]

Short-term sedation with etomidate is useful in hemodynamically unstable patients, such as patients requiring cardioversion[175] or patients requiring sedation after an acute myocardial infarction or with unstable angina for a minor operative procedure.[463] Etomidate also is useful for intubation in the emergency department and in the ICU. When used during electroconvulsive therapy, etomidate can produce longer seizures compared with other hypnotics.[464] Prolonged sedation for patients in the ICU, although initially popular after the release of etomidate, is now contraindicated owing to inhibition of corticosteroid and mineralocorticoid production, with subsequent increase in morbidity.[401,403,465]

α-Adrenergic Agonists: Dexmedetomidine

History

The α_2-adrenergic agonists provide sedation, anxiolysis, hypnosis, analgesia, and sympatholysis. The initial impetus for the use of α_2 agonists in anesthesia resulted from observations made in patients during anesthesia who were receiving clonidine therapy.[466,467] This was soon followed by a description of the minimum alveolar concentration (MAC) reduction of halothane by clonidine.[468] Dexmedetomidine is a more selective α_2 agonist with a 1600 greater selectivity for the α_2 receptor compared with the α_1 receptor. It was introduced in clinical practice in the United States in 1999 and approved by the FDA only as a short-term (<24 hours) sedative for mechanically ventilated adult ICU patients. Dexmedetomidine is now being used off-label outside of the ICU in various settings, including sedation and adjunct analgesia in the operating room, sedation in diagnostic and procedure units, and for other applications such as withdrawal/detoxification amelioration in adult and pediatric patients.[469,470]

Physicochemical Characteristics

Dexmedetomidine is the d-enantiomer of medetomidine, a substance that has been used for sedation and analgesia in veterinary medicine for many years.[471] It shows a high ratio of specificity for the α_2 receptor (α_2/α_1 1600:1) compared with clonidine (α_2/α_1 200:1), making it a complete α_2 agonist.[472] Dexmedetomidine belongs to the imidazole subclass of α_2 receptor agonists, similar to clonidine, and its structure is illustrated in Figure 26-19. It is freely soluble in water.

Metabolism and Pharmacokinetics

Dexmedetomidine is rapidly distributed and extensively metabolized in the liver and excreted in urine and feces. It undergoes conjugation (41%), n-methylation (21%), or hydroxylation fol-

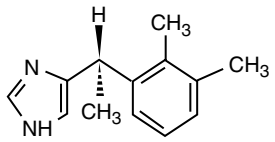


Figure 26-19 Chemical structure of dexmedetomidine.

lowed by conjugation. Dexmedetomidine is 94% protein bound, and its concentration ratio between whole blood and plasma is 0.66. Dexmedetomidine has profound effects on cardiovascular variables and may alter its own pharmacokinetics. With large doses, there is marked vasoconstriction, which probably reduces the drug's volumes of distribution. In essence, dexmedetomidine displays nonlinear pharmacokinetics.[473] Dyck and coworkers[474] found that its pharmacokinetics in volunteers is best described by a three-compartment model (see Table 26-1). These pharmacokinetic parameters apparently are unaltered by age or weight or renal failure, but clearance is a function of height.[473,475] The elimination half-life of dexmedetomidine is 2 to 3 hours, with a context-sensitive half-time ranging from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion. Postoperative patients sedated with dexmedetomidine display similar pharmacokinetics to the pharmacokinetics seen in volunteers.[476]

Pharmacology

Dexmedetomidine is a nonselective α_2 agonist. Alpha$_2$ adrenoreceptors are membrane-spanning G proteins. Intracellular pathways include inhibition of adenylate cyclase and modulation of ion channels Three subtypes of α_2 adrenoreceptors have been described in humans: α_{2A}, α_{2B}, and α_{2C} (Fig. 26-20).[477] The α_{2A} adrenoreceptors are primarily distributed in the periphery, whereas α_{2B} and α_{2C} are in the brain and spinal cord. Postsynaptic located α_2 adrenoreceptors in peripheral blood vessels produce vasoconstriction, whereas presynaptic α_2 adrenoreceptors inhibit the release of norepinephrine, potentially attenuating the vasoconstriction. The overall response to α_2 adrenoreceptors agonists is related to the stimulation of α_2 adrenoreceptors located in the CNS and spinal cord. These receptors are involved in the sympatholysis, sedation, and antinociception effects of α_2 adrenoreceptors.[478]

Effects on the Central Nervous System

Sedation

The α_2 agonists produce their sedative-hypnotic effect by an action on α_2 receptors in the locus caeruleus and an analgesic action at α_2 receptors within the locus caeruleus and within the spinal cord.[479] The quality of sedation produced by dexmedetomidine seems different compared with that produced by other sedatives acting through the GABA systems. Patients receiving dexmedetomidine infusions as part of their sedation regimen in the postoperative ICU setting have been described as being very easy to wake up and having the ability to follow commands and cooperate while being tracheally intubated. Undisturbed, patients were noted to fall asleep right away.[480] Despite sound levels of sedation with dexmedetomidine, there is limited respiratory depression, providing wide safety margins.[481] This characteristic allows for "daily wake up" tests to be done in a safe fashion. This

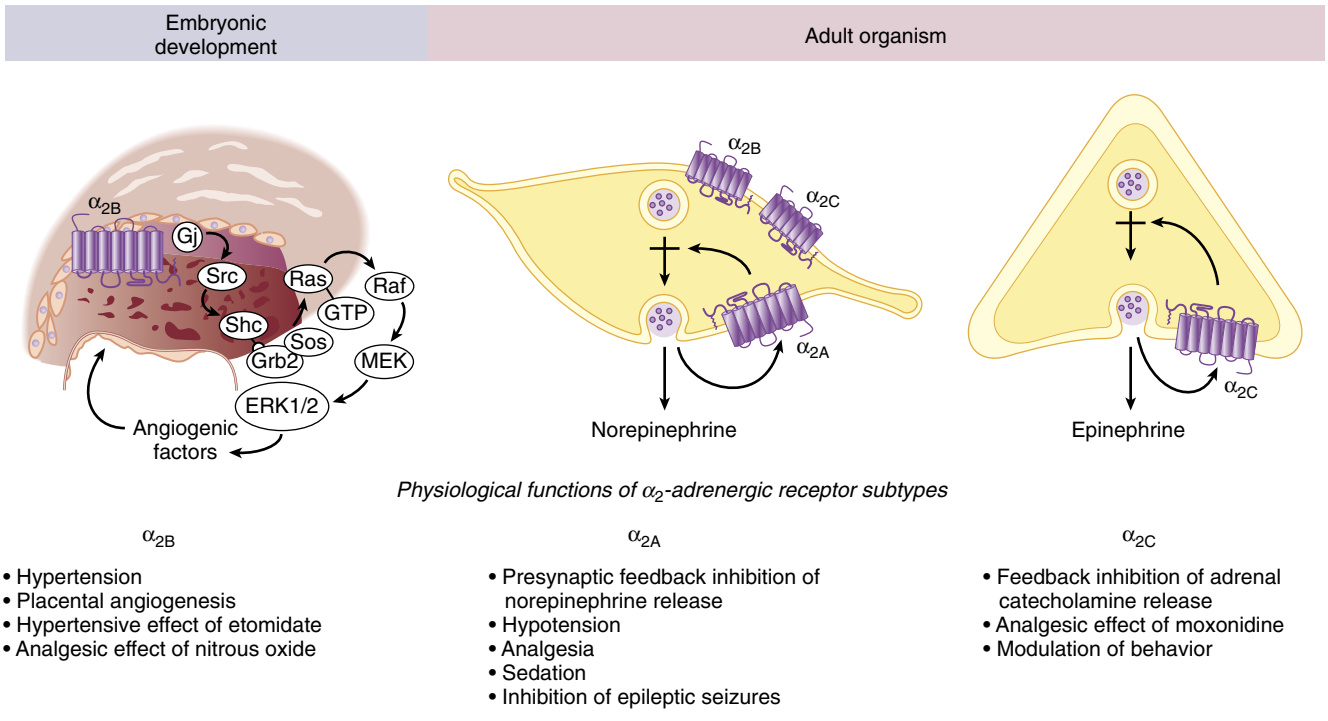


Figure 26-20 The different physiologic functions of α_2 adrenoreceptors. The *top panel* depicts the three α_2 receptor subtypes acting as presynaptic inhibitory feedback receptors to control the release of norepinephrine and epinephrine from peripheral or central adult neurons. Also, a negative feedback loop has been seen in the adrenal gland. Alpha$_{2B}$ receptors have been involved in the development of the placental vascular system during prenatal development. The *lower panel* lists a series of physiologic effects with its associated α_2 adrenoreceptors. *(From Paris A, Tonner PH: Dexmedetomidine in anaesthesia. Curr Opin Anaesthesiol 18:412-418, 2005.)*

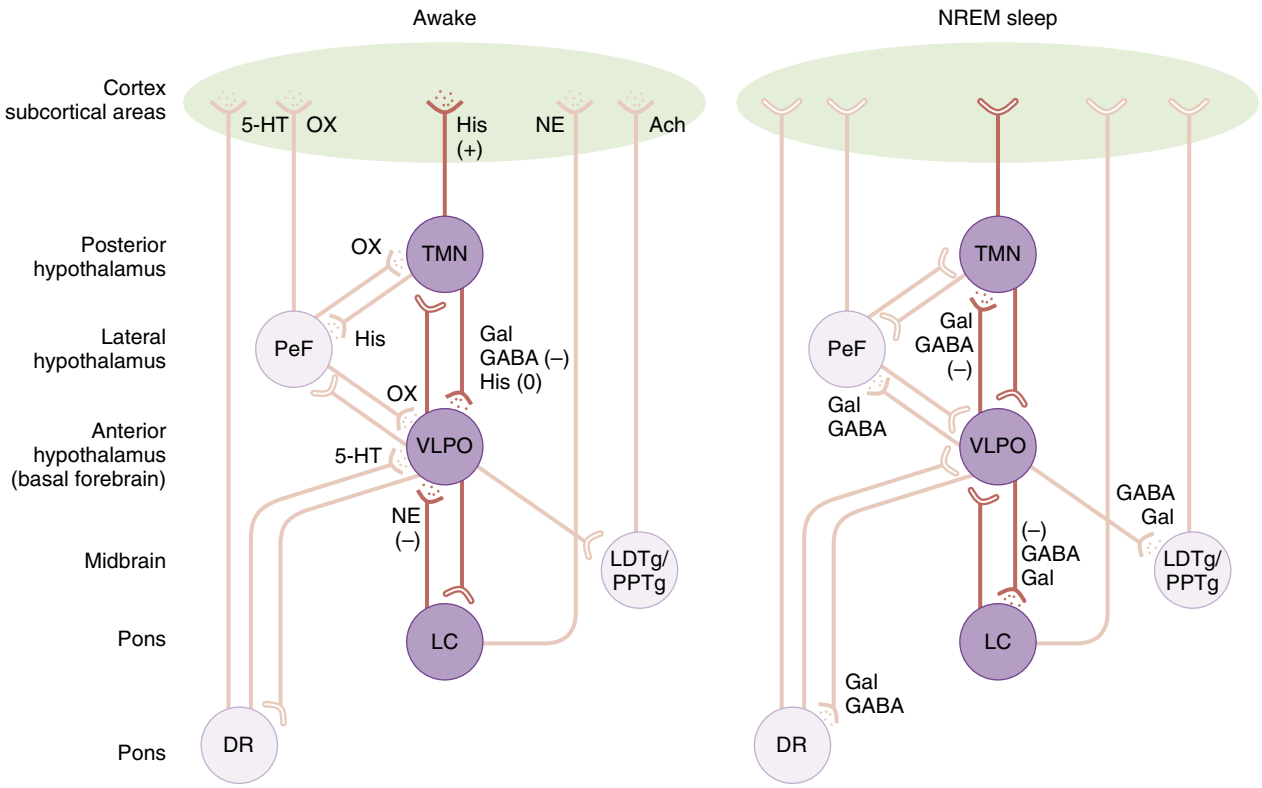


Figure 26-21 Dexmedetomidine has been shown to induce a non–rapid eye movement sleeping pattern (NREM). The stimulation of the locus caeruleus (LC) by dexmedetomidine (*right diagram*) releases the inhibition the LC has over the ventrolateral preoptic nucleus (VLPO). The VLPO subsequently releases γ-aminobutyric acid (GABA) onto the tuberomammillary nucleus (TMN). This inhibits the release of the arousal-promoting histamine on the cortex and forebrain, inducing the loss of consciousness. *(From Ebert T, Maze M: Dexmedetomidine: Another arrow for the clinician's quiver. Anesthesiology 101:569-570, 2004.)*

critical test—when ventilated ICU patients are taken off all sedatives to assess their mental status and titrate sedation—shortens their ventilated and ICU length of stay.[482]

The α_2 agonists act through the endogenous sleep-promoting pathways to exert their sedative effect (Fig. 26-21). Dexmedetomidine produces a decrease in activity of the projections of the locus caeruleus to the ventrolateral preoptic nucleus. This increases GABAergic and galanin release in the tuberomammillary nucleus, producing a decrease in histamine release in cortical and subcortical projections.[483] The α_2 agonists seem to inhibit ion conductance through L-type or P-type calcium channels and facilitate conductance through voltage-gated calcium-activated potassium channels.[484] The similarity between natural sleep (non–rapid eye movement) and dexmedetomidine-induced hypnosis has been speculated to maintain cognitive and immunologic function in the sleep-deprived states (as in the ICU).[485] Dexmedetomidine can produce profound sedation, and it has been used as a total IV anesthetic when given at 10 times the normal sedation concentration range.[486]

The α_2 agonists have the advantage that their effects are readily reversible by α_2-adrenergic antagonists (e.g., atipamezole).[487] Atipamezole is not currently approved for human use. Similar to other adrenergic receptors, the α_2 agonists also show tolerance after prolonged administration.[488] Because dexmedetomidine is approved by the FDA only for short-term sedation (24 hours), tolerance, dependence, or addiction does not seem to be a problem. Dexmedetomidine can be employed for addiction treatment; dexmedetomidine has been described for use in rapid opioid detoxification, cocaine withdrawal, and iatrogenic induced benzodiazepine and opioid tolerance after prolonged sedation.[489] In animals, dexmedetomidine, in contrast to opioids, does not result in hyperalgesia or allodynia after its withdrawal.[490] Rats rendered tolerant to morphine also show a decrease in efficacy of hypnotic and analgesic effects of dexmedetomidine. As tolerance to opioids recovers, there is a more rapid recovery of the hypnotic effect of dexmedetomidine than its analgesic efficacy.[491] These data would tend to indicate a possible cross-tolerance between receptors.

Analgesia

The analgesic effects of dexmedetomidine are complex. Alpha$_2$ agonists do have an analgesic effect when injected via the intrathecal or epidural route.[492] Clonidine injected in the neural axis helps with short-term pain, cancer pain, and neuropathic pain.[493,494] Intrathecally injected dexmedetomidine in sheep reduces blood pressure in 1 minute. When dexmedetomidine is injected into the epidural space, it rapidly diffuses into the CSF (in one study,[495] 22% of the injected dose was identified in the CSF). The effects on blood pressure are slower in onset with an epidural injection than with an intrathecal administration. Epidural effects are seen in 5 to 20 minutes. The primary site of analgesic action is thought to be the spinal cord.[495] Systemic use of dexmedetomidine shows narcotic sparing. In the postoperative ICU setting, narcotic requirements were reduced by 50% when patients were receiving a dexmedetomidine drip compared with placebo.[480]

Some of the systemic analgesic effects have been attributed to the confounding sedative effects.[496] In human pain studies, the

results of systemically administered dexmedetomidine are inconsistent. Modest reductions in pain were observed in cold pressor tests when patients were receiving dexmedetomidine.[497] More recently, in a model of heat and electrical pain in human volunteers, dexmedetomidine was not capable of attenuating the pain response in the clinical dose range when subjects were conscious.[485] The analgesic effect of dexmedetomidine has been compared with remifentanil. In a noxious heat versus pain intensity plot obtained in a group of volunteers, dexmedetomidine was less effective in reducing pain (less of a right shift of the curve) than remifentanil. Also, the slope was different, suggesting a different mechanism of action and an effect from sedation.[498] In the clinical setting, when pain is likely to occur, if dexmedetomidine is to be used, the addition of a narcotic seems warranted.

Central Nervous System Protection and Other Central Nervous System Effects

The CNS protective effects are not well defined. Dexmedetomidine in animal models of incomplete cerebral ischemia and reperfusion reduces cerebral necrosis and improves neurologic outcome. In a model of focal ischemia in rabbits, dexmedetomidine, administered at doses that reduced the MAC of halothane by 50%, resulted in less cortical neuronal damage than when halothane was administered alone at equieffective MAC concentrations.[499] In a rat model of unilateral carotid ligation accompanied by systemic hypotension, the administration of dexmedetomidine provided for lower plasma catecholamines with less neurologic and histopathologic damage.[500] The prevalent idea was that dexmedetomidine reduced the intracerebral catecholamine outflow during injury and resulted in less neural tissue damage with better neurologic outcome.[501] Others have found no reduction in cerebral catecholamines after receiving dexmedetomidine during injury.[502] The neuroprotection may be attributed to modulation of proapoptotic and antiapoptotic proteins.[341] Also, the reduction of the excitatory neurotransmitter glutamate during injury may explain some of the protective effects.[503]

The neuroprotective properties of dexmedetomidine in humans have not been investigated. Little is known of the effects of dexmedetomidine alone on ICP and CBF. In patients after pituitary surgery, a target concentration of 600 ng/mL of dexmedetomidine resulted in no increase in lumbar CSF pressure.[504] In dogs, in the presence of volatile anesthetics and dexmedetomidine, CBF was decreased, and oxygen consumption was maintained.[505,506] CBF velocity, as measured by transcranial Doppler, decreased with increasing concentrations of dexmedetomidine in parallel with decreasing MAP and increasing $Paco_2$.[507] These decreases in CBF are not accompanied by a reduction in $CRMO_2$. Despite the significant reduction in CBF with dexmedetomidine, there was no evidence of cerebral ischemia in a dog model.[551] In a preliminary study in patients undergoing cerebrovascular surgery using dexmedetomidine, there was no evidence of a detrimental effect on local brain tissue oxygenation.[508] More recently, in a study in six normal volunteers, the administration of dexmedetomidine to achieve serum levels of 0.6 ng/mL and 1.2 ng/mL (with and without hyperventilation) produced the predicted reduction of CBF with a concomitant reduction in $CRMO_2$.[509] This finding suggests the maintenance of the cerebral oxygen supply-to-demand relationship; however, further work in injured brains needs to be done.

In a rat seizure model, dexmedetomidine showed significant proconvulsant action, which is consistent with previous findings that inhibition of central noradrenergic transmission facilitates seizure expression.[510] This finding is in contrast to an anticonvulsant effect shown in rats after kainic acid–induced seizures.[511] As yet, there have been no reports of seizures in humans. Dexmedetomidine has been used in neurosurgical procedures involving neurophysiologic monitoring. Cortical evoked potentials amplitudes and latencies were minimally affected when using dexmedetomidine intraoperatively when patients underwent craniotomies.[508] Dexmedetomidine also is able to reduce muscle rigidity after high-dose opioid administration.[512] In resting volunteers, dexmedetomidine increased growth hormone secretion in a dose-dependent manner, but it had no effect on other pituitary hormones.[513,514] Dexmedetomidine ablates memory in a dose-dependent manner. In concentrations used for clinical sedation (i.e., 0.7 ng/mL), recall of picture cards is preserved. Increasing the concentration of dexmedetomidine to 2 ng/mL largely ablates recall and recognition of a picture card.[515]

Effects on the Respiratory System

In volunteers, dexmedetomidine at concentrations producing significant sedation reduces minute ventilation, but retains the slope of the ventilatory response to increasing carbon dioxide.[516] The changes in ventilation appeared similar to those observed during natural sleep. Ebert and colleagues,[515] infusing dexmedetomidine to concentrations of 15 ng/mL in spontaneously breathing volunteers, showed no change in arterial oxygenation or pH. At the highest concentrations, $Paco_2$ increased by 20%. Respiratory rate increased with increasing concentration from 14 breaths/min to 25 breaths/min.[515] When dexmedetomidine and propofol were titrated to equal sedative end points (BIS of 85), both resulted in no change in respiratory rate.[517] In a study comparing the effects of remifentanil and dexmedetomidine on respiratory parameters in normal volunteers,[518] the hypercapnic ventilatory response was unaffected even at doses that produced unresponsiveness to vigorous stimulation. $Paco_2$ increased mildly with dexmedetomidine, but it reached a plateau after the first increment. Dexmedetomidine also exhibited a hypercarbic arousal phenomenon, which has been described during normal sleep and is a safety feature. IV or inhaled dexmedetomidine has been implicated in blocking histamine-induced bronchoconstriction in dogs.[519]

Effects on the Cardiovascular System

The basic effects of α_2 agonists on the cardiovascular system are decreased heart rate; decreased systemic vascular resistance; and indirectly decreased myocardial contractility, cardiac output, and systemic blood pressure. By developing highly selective α agonists, it has been hoped to decrease some of these adverse cardiovascular effects and to maximize the desirable hypnotic-analgesic properties. The hemodynamic effects of a bolus of dexmedetomidine in humans have shown a biphasic response. An acute IV injection of 2 μg/kg resulted in an initial increase in blood pressure (22%) and decrease in heart rate (27%) from baseline that occurred at 5 minutes after injection. This initial increase in blood pressure is probably due to the vasoconstrictive effects of dexmedetomidine when stimulating peripheral α_2 receptors. Heart rate returned to baseline by 15 minutes, and blood pressure gradually declined to approximately 15% below baseline by 1 hour. After an IM injection of the same dose, the initial increase in blood pressure was not seen, and heart rate and blood pressure remained within 10% of baseline.[473]

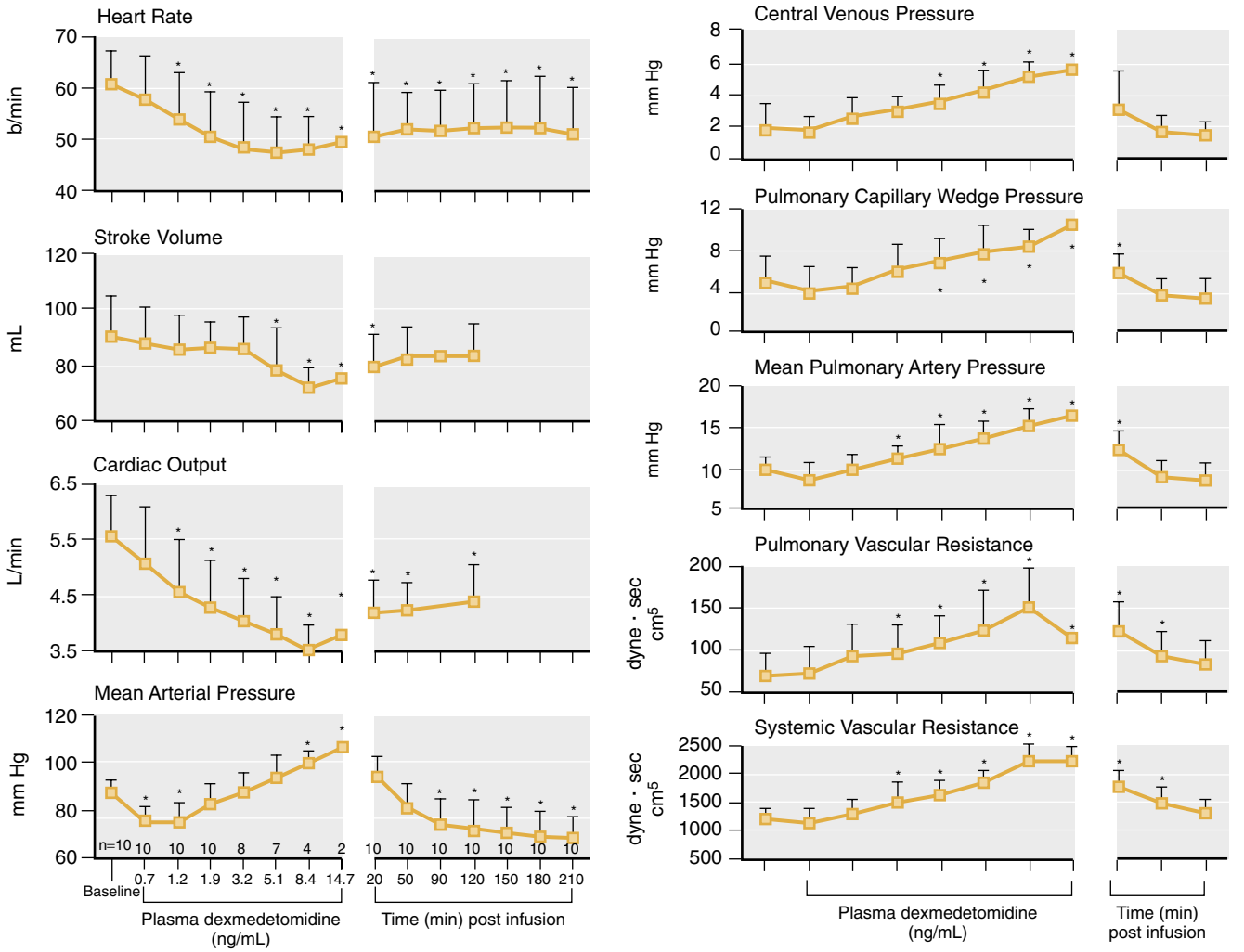


Figure 26-22 Effects of increasing plasma concentrations of dexmedetomidine.

Ebert and colleagues[515] performed an elegant study in volunteers using a target-controlled infusion system to provide increasing concentrations (0.7 to 15 ng/mL) of dexmedetomidine (Fig. 26-22). The lowest two concentrations produced a decrease in MAP (13%) followed by progressive increase (12%). Increasing concentrations of dexmedetomidine also produce progressive decreases in heart rate (maximum 29%) and cardiac output (35%).[515] Infusion of dexmedetomidine in volunteers also has been shown to result in a compensated reduction in systemic sympathetic tone without changes in baroreflex sensitivity. It also blunts the heart rate and systemic sympathetic activation owing to sweating, but is less effective in blunting cardiac sympathetic response to shivering.[520]

The incidence of hypotension and bradycardia may be related to the administration of a loading dose. Omitting the loading dose or not giving more than 0.4 μg/kg reduces the incidence of hypotension, or makes it less pronounced. Giving the loading dose over 20 minutes also minimizes the transient hypertension.[521] In several studies after IM and IV administration, dexmedetomidine caused, in a small percentage of patients, profound bradycardia (<40 beats/min) and occasionally sinus arrest/pause. Generally, these episodes resolved spontaneously or were readily treated without adverse outcome by anticholinergics. It would be expected from its profile that dexmedetomidine would be beneficial to the ischemic myocardium. In animal models, dexmedetomidine showed some beneficial effects on the ischemic heart through decreased oxygen consumption and redistribution of coronary flow from nonischemic zones to ischemic zones after acute brief occlusion.[522] Dexmedetomidine also decreases serum lactate in a dog model of coronary ischemia with an associated decrease in heart rate and measured catecholamines. It also produced an increase in the endocardial/epicardial blood flow ratio by 35%.[523]

The perioperative use of α_2 agonists reduces the incidence of perioperative myocardial ischemia.[524] More recently, Wallace and associates[525] showed that the administration of clonidine in the preoperative period reduces the incidence of perioperative cardiac ischemia from 31% to 14%, and reduces the mortality for 2 years from 29% to 15% compared with placebo. The only data on potential benefits in perioperative ischemia prevention with dexmedetomidine are provided in an underpowered study in vascular surgery patients who received the drug in the perioperative period. Blood pressure and heart rate were lower in the dexmedetomidine group, but these patients also needed the use of more

drugs intraoperatively to sustain blood pressure and heart rate. No reductions of ischemic events were noted.[189] No rebound effects have been found when discontinuing dexmedetomidine drips, even when it is given for more than 24 hours.[526]

A frequently reported side effect of dexmedetomidine has been a dry mouth. Dry mouth is due to a decrease in saliva production.[527]

Uses

Dexmedetomidine has been approved as a short-term sedative for adult intubated patients in the ICU. Given its well-documented beneficial effects of anxiolysis, sedation, analgesia, and sympatholysis with minimal respiratory depression, it also has been used in various other clinical scenarios.

Intensive Care Unit

Dexmedetomidine has advantages over propofol for sedation in mechanically ventilated postoperative patients. When both drugs were titrated to equal sedation as assessed by the BIS (approximately 50) and Ramsay sedation score (5), dexmedetomidine patients required significantly less narcotics (alfentanil 2.5 mg/hr versus 0.8 mg/hr). Heart rate was slower in the dexmedetomidine group, whereas MAP was similar. The Pao_2/Fio_2 ratio was significantly higher in the dexmedetomidine group. Time to extubation after discontinuation of the infusion was similar at 28 minutes. Patients receiving dexmedetomidine seemed to have greater recall of their stay in the ICU, but all described this as pleasant overall.[528]

Several other studies have confirmed the decreased requirement for opioids (>50%) when dexmedetomidine is used for sedation compared with propofol or benzodiazepines. Most studies also describe more stable hemodynamics during weaning when dexmedetomidine is used for sedation.[529] This is of obvious benefit in patients with high risk for myocardial ischemia. For sedation in the ICU, loading doses of 0.5 to 1 μg/kg have been used. Omitting the bolus or giving the lower dose has been associated with fewer episodes of severe bradycardia and other hemodynamic perturbations. Infusion rates of 0.1 to 1 μg/kg/hr are generally needed to maintain adequate sedation. Delirium in the ICU is a risk factor for increased length of stay and increased mortality.[530] In a double-blind, randomized controlled trial of sedation in ventilated patients with dexmedetomidine versus lorazepam, it was found that using dexmedetomidine infusions provided more days alive without delirium or coma and a greater amount of time spent at the appropriate sedation level compared with lorazepam.[531]

α_2-adrenoreceptor agonists have been used in the treatment of alcohol and drug withdrawal. In a comparison between clonidine and chlordiazepoxide in the treatment of patients with alcohol withdrawal, clonidine proved to give better anxiolysis with better hemodynamics.[532] Dexmedetomidine has been successfully used in the treatment of withdrawal of narcotics, benzodiazepines, alcohol, and recreational drugs. Maccioli[489] reported the successful use of dexmedetomidine in two adult patients, one with cocaine and alcohol withdrawal symptoms, and another with withdrawal from prolonged use of benzodiazepines and narcotics in the ICU. Dexmedetomidine controlled withdrawal behavior and allowed for successful detoxification of young cardiothoracic patients (spanning the ages of days to 17 years) who developed drug withdrawal from prolonged use of benzodiazepines and narcotics in the ICU.[533]

The unique characteristics of dexmedetomidine—providing adequate sedation with minimal respiratory depression—can be used when weaning patients from the ventilator. Siobal and colleagues[534] reported the successful weaning of five ventilated patients who had failed weaning secondary to agitation. Infusions of dexmedetomidine of 0.5 to 0.7 μg/kg/hr were used (no loading) and permitted the discontinuation of propofol in four of five patients. All patients were extubated while still on the dexmedetomidine infusion. One patient required reintubation for upper airway obstruction. The use of dexmedetomidine to facilitate daily "wake up" tests in mechanically ventilated patients seems attractive, but few data have been published.[535]

The FDA approved the use of dexmedetomidine infusions for 24 hours or less. Multiple studies have shown the safety of using this drug for longer periods, however. In data collected from prescribing patterns in 10 institutions, it was shown that dexmedetomidine was used longer than 24 hours in 33.8% of cases. It also was noted that 33% of patients received a loading dose, 27% of patients received a dose higher than the recommended maximum, and 60% of patients remained on the infusion after extubation.[536]

Anesthesia

As a premedicant, dexmedetomidine, at IV doses of 0.33 to 0.67 μg/kg given 15 minutes before surgery, seems efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia.[537] Within this dosage range, dexmedetomidine reduces thiopental requirements (by ±30%) for short procedures,[537] reduces the requirements of volatile anesthetics (by ±25%), and more effectively attenuates the hemodynamic response to endotracheal intubation compared with 2 μg/kg of fentanyl.[538] Dexmedetomidine also has been evaluated as an IM injection (2.5 μg/kg) with or without fentanyl administered 45 to 90 minutes before surgery. This regimen was compared with IM midazolam plus fentanyl and was found to provide equal anxiolysis, reduced response to intubation, smaller volatile anesthetic requirements, and a decreased incidence of postoperative shivering but a higher incidence of bradycardia. Atipamezole, a selective α_2 antagonist, at 50 μg/kg was effective in reversing the sedation of dexmedetomidine (2 μg/kg intramuscularly), when used to provide sedation for brief operative procedures.[487] This reversal of effects resulted in a more rapid recovery than occurred after equisedative doses of midazolam.

Dexmedetomidine has been used for sedation for monitored anesthesia care. In a study comparing the efficacy of dexmedetomidine or propofol as a sedative agent in a group of 40 patients receiving local anesthesia or regional blocks, dexmedetomidine (1 μg/kg given over 10 minutes) when used for intraoperative sedation resulted in a slower onset than propofol (75 μg/kg/min for 10 minutes), but similar cardiorespiratory effects when titrated to equal sedation. The average infusion rate of dexmedetomidine intraoperatively to maintain a BIS value of 70 to 80 was 0.7 μg/kg/min. Sedation was more prolonged after termination of the infusion, as was recovery of blood pressure. Smaller doses of opioid were needed in the first hour, however.[517]

Dexmedetomidine sedation has been done successfully in pediatric patients. Two studies, comprising 140 children 1 to 7 years old, reported successful sedation for MRI scans compared with midazolam or propofol.[539,540]

When dexmedetomidine is used as a premedication 10 minutes before general surgery for cataract removal, intraocular pressure is decreased (33%), catecholamine secretion is reduced, perioperative analgesic requirements are less, and recovery is more rapid.[541,542]

For maintenance of anesthesia, dexmedetomidine has been used in patients undergoing multiple types of surgery. In patients given an infusion regimen to achieve a plasma concentration of slightly less than 1 ng/mL, combined with 70% nitrous oxide, dexmedetomidine reduced isoflurane requirements by 90% compared with a control group.[543] One retrospective study and two prospective, randomized controlled trials in bariatric surgical patients have found that a balanced anesthetic with desflurane or propofol plus dexmedetomidine (0.5 to 0.8 µg/kg bolus plus 0.4 µg/kg/hr infusion) reduces postoperative pain scores and morphine consumption, and improves hemodynamics compared with desflurane-fentanyl or propofol-fentanyl anesthetics.[544-546]

In patients presenting for vascular surgery, three infusion rates of dexmedetomidine were compared with a placebo infusion starting 1 hour before surgery and administered until 48 hours after surgery. In the groups receiving dexmedetomidine, more vasoactive agents were required to maintain hemodynamics intraoperatively, but less tachycardia was noted postoperatively. No other significant differences were noted between the groups.[547]

Grant and colleagues[548] described the use of dexmedetomidine when securing the airway with a fiberoptic intubation in three patients undergoing cervical spine surgery. The procedure was well tolerated with no hemodynamic compromise or respiratory depression. Because this drug provides good sedation with minimal respiratory depression, it has been used in patients undergoing awake craniotomies with functional testing and electrocorticography[549] or awake carotid endarterectomies with fewer fluctuations from the desired sedation level and more stable hemodynamics.[550]

Another use of dexmedetomidine has been as an anesthetic adjunct or sedative agent for patients who are susceptible to narcotic-induced respiratory depression or sleep apnea. In a morbidly obese patient, the narcotic-sparing effects of dexmedetomidine were evident intraoperatively and postoperatively after bariatric surgery.[551] The addition of dexmedetomidine infusions to assist on transesophageal echocardiography examination has been described, with better hemodynamic profile and improved patient satisfaction than with benzodiazepine and narcotics alone, with no added respiratory depression.

The use of dexmedetomidine has dramatically increased. This highly selective α_2 agonist has a set of unique effects that include titratable sedation, sympatholysis, and analgesia without significant respiratory depression. Originally approved as a sedative in the ICU, it has found many off-label applications in the ICU, the operating room, and perioperative environment. The off-label use of dexmedetomidine in infants and children is rapidly increasing. More than 800 reports have been published regarding its use in this population.[470]

Droperidol

History

Janssen[552] synthesized haloperidol, the first member of the butyrophenones, which became the primary neuroleptic component in neuroleptanesthesia. In 1959, DeCastro and Mundeleer[553] combined haloperidol with phenoperidine (a meperidine derivative also synthesized by Janssen) in the forerunner to the practice of neuroleptanesthesia. Droperidol, a derivative of haloperidol, and fentanyl (a phenoperidine congener), both synthesized by Janssen, were used by DeCastro and Mundeleer[553] in a combination they reported to be superior to haloperidol and phenoperidine. This neuroleptanesthesia combination produced more rapid onset of analgesia, less respiratory depression, and fewer extrapyramidal side effects. The fixed combination of droperidol and fentanyl, marketed as Innovar in the United States, was the drug primarily used for neuroleptanesthesia.

The use of neuroleptanesthesia has largely disappeared in modern anesthetic practice. The primary use of droperidol in anesthesia has been as an antiemetic and to a lesser extent as a sedative and antipruritic. The present package insert for droperidol in the United States carries a black box warning regarding the potential for fatal arrhythmias and recommendations that it be administered only during continuous electrocardiogram monitoring. With the withdrawal of droperidol in certain countries and more stringent labeling regarding potentially lethal dysrhythmias in others, the use of droperidol has decreased tremendously. The validity of the risk of low-dose droperidol in causing QT prolongation, dysrhythmias, and death has been challenged by numerous editorials, articles, and letters reviewing the cases that prompted this action.[554-559]

Droperidol is a butyrophenone, a fluorinated derivative of phenothiazines (Fig. 26-23).[345] Butyrophenones produce CNS depression, characterized by marked apparent tranquility and cataleptic immobility. They are potent antiemetics. Droperidol is a potent butyrophenone, and, similar to the others, it produces its action centrally at sites where dopamine, norepinephrine, and serotonin act. It has been postulated that butyrophenones may occupy GABA receptors on the postsynaptic membrane, reducing synaptic transmission and resulting in a buildup of dopamine in the intersynaptic cleft.[345,552] In particular, droperidol results in a submaximal inhibition of the $GABA_A$ α_1, β_1, and γ_2 acetylcholine receptors and full inhibition of α_2 acetylcholine receptors. This submaximal inhibition of GABA receptors by droperidol may explain the anxiety, dysphoria, and restlessness that may occur with its administration.[560] An imbalance in dopamine and acetylcholine is thought to occur, which results in alteration in normal transmission of signals in the CNS. The chemoreceptor trigger

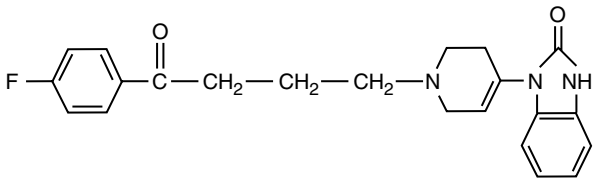


Figure 26-23 Structure of droperidol, a butyrophenone derivative.

zone is the emetic center, and "red" astrocytes transport neurolept molecules from the capillary to dopaminergic synapses in the chemoreceptor trigger zone, where they occupy GABA receptors. This is thought to be the mechanism by which droperidol exerts its antiemetic effect.[561]

Metabolism and Pharmacokinetics

Droperidol is biotransformed in the liver into two primary metabolites.[562] Its plasma decay can be described by a two-compartment model. The pharmacokinetics is shown in Table 26-1.[563]

Pharmacology

Effects on the Central Nervous System

The effects of neuroleptanesthetics on human CBF and $CMRO_2$ have not been studied. In dogs, droperidol causes potent cerebral vasoconstriction, producing a 40% reduction in CBF (see Chapter 13). No significant change in $CMRO_2$ occurs during droperidol administration.[564] The EEG in conscious patients shows some reduction in frequency, with occasional slowing.[565] Low-dose droperidol also has been shown to cause balance disturbances at the time of discharge after doses used for antiemetic prophylaxis.[566] Droperidol may produce extrapyramidal signs and worsens symptoms of Parkinson's disease. It also rarely may precipitate malignant neuroleptic syndrome.

Effects on the Respiratory System

When used alone, droperidol has little effect on the respiratory system.[567] Droperidol (0.044 mg/kg) given to surgical patients produced a slight reduction in respiratory rate,[568] and IV droperidol (3 mg) had no significant effect on tidal volume in volunteers.[569] More detailed respiratory studies are unavailable.

Effects on the Cardiovascular System

Similar to most antipsychotics, droperidol may prolong the QT interval by delaying myocardial repolarization and precipitating torsades de pointes. This seems to be dose dependent and may be of clinical significance when other causes of QT prolongation also are present.[570] Droperidol also may possess some antiarrhythmic effects that are similar to those of quinidine.[571] Droperidol produces vasodilation with a decrease in blood pressure (see Table 26-2). This effect is considered to be a result of moderate α-adrenergic blockade.[562] The dopamine-induced increase in renal blood flow (renal artery flowmeter methodology) is not significantly impaired by administration of droperidol.[572] Droperidol has little effect on myocardial contractility.[571]

Uses

Use of droperidol today in the perioperative period is largely restricted to its antiemetic and sedative effects. It is an effective antiemetic[573]; the dose for this use ranges from 10 to 20 μg/kg (0.6 to 1.25 mg for a 70-kg individual).[574] These doses of droperidol, given at the start of anesthesia for operations lasting 1 hour, reduce the incidence of nausea and vomiting by about 30%. These doses given at induction have little effect on wake-up time, but should they be given at the end of surgery, there could be some residual hypnotic effect. Overall, antiemetic efficacy of droperidol alone is equal to that of ondansetron and results in an equal number of side effects, but droperidol is more cost-effective.[575] The efficacy of droperidol as an antiemetic is enhanced when used in combination with serotonin antagonists or dexamethasone or both.

Droperidol also has been shown to be effective in the treatment and prevention of pruritus secondary to opioid administration. It has been given intravenously and into the epidural space for this purpose.[576,577] When used in this fashion, droperidol also effectively reduces nausea, but it increases sedation. The safety of droperidol administration into the epidural space has not been fully evaluated, however, and it is not approved for administration via this route.

Summary

Many different IV drugs are available for use in the care of patients requiring general anesthesia. The selection of a particular drug must be based on the individual patient's need for hypnosis, amnesia, and analgesia. Drug selection must match the physiology or the pathophysiology or both of the individual patient with the pharmacology of the particular drug. A patient in shock who requires anesthesia induction should receive the drug that would produce rapid onset of effect without causing further hemodynamic compromise. The knowledge of the clinical pharmacology of each of the IV anesthetic drugs enables the clinician to induce and maintain sedation or general anesthesia safely and effectively. There is no single perfect drug for any particular patient, but rather the informed practitioner wisely employs the appropriate drug or drugs in the practice of good anesthesia care.

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27 Opioids

Key Points

1. An increased understanding of the molecular pharmacology of opioid receptors and opioid-induced cellular responses allows the use of innovative techniques for analgesia.
2. Opioids suppress pain by their action in the brain, spinal cord, and peripheral nervous system.
3. Opioids affect many organ systems, including the respiratory and cardiovascular systems, and can cause a variety of adverse effects. Proper dosing and monitoring allow the adverse effects to be minimized.
4. New pharmacokinetic principles have allowed more intelligent use of opioids along with more predictable durations of action.
5. The pharmacokinetic and pharmacodynamic properties of opioids are affected by a variety of factors, such as age, body weight, organ failure, and shock. To appropriately use opioids, these factors should be taken into consideration.
6. During total intravenous anesthesia, the use of opioids is a vital part of providing the analgesic component of anesthesia. Short-acting drugs, such as remifentanil, allow dissipation of total intravenous anesthesia even more rapidly than with inhaled anesthetics.
7. New opioid delivery systems, such as transdermal fentanyl patches, are continually being developed. Such systems allow more flexibility in providing analgesia, both inside and outside the operating room.
8. Opioids can pharmacokinetically or pharmacodynamically interact with drugs used perioperatively. Drug interaction should be understood for proper patient management.

The term *opioid* refers broadly to all compounds related to opium. The word "opium" is derived from *opos*, the Greek word for juice, inasmuch as the drug is derived from the juice of the opium poppy *Papaver somniferum*. Opiates are drugs derived from opium and include the natural products morphine, codeine, and thebaine, as well as many semisynthetic congeners derived from them.

The first undisputed reference to opium is found in the writings of Theophrastus in the third century BC. During the Middle Ages, many of the uses of opium were appreciated. Opium contains more than 20 distinct alkaloids. In 1806, Sertürner reported the isolation of a pure substance in opium that he named morphine after Morpheus, the Greek god of dreams. By the middle of the 19th century, the use of pure alkaloids rather than crude opium preparations began to spread throughout the medical world.

In addition to the remarkable beneficial effects of opioids, the toxic side effects and addictive potential of these drugs have also been known for centuries. Synthetic opioid analgesics without side effects were explored, but many of the synthetic opioids share the side effects of natural opioids. The search for new opioid agonists led to the synthesis of opioid antagonists and compounds with mixed agonist/antagonist properties, which expanded therapeutic options and provided important tools for exploring the mechanisms of opioid actions. Furthermore, new methods of opioid administration, including patient-controlled analgesia (PCA) and computer-based infusion techniques, have been developed.

Pharmacology of Opioids

Classification of Opioid Compounds

Opioids can be classified as naturally occurring, semisynthetic, and synthetic (Box 27-1). The naturally occurring opioids can be divided into two chemical classes, phenanthrenes (morphine and codeine) and benzylisoquinolines (papaverine). The semisynthetic opioids are morphine derivatives in which one of several changes have been made. Synthetic opioids are classified into four groups, the morphinan derivatives (levorphanol), the diphenyl or methadone derivatives (methadone, *d*-propoxyphene), the benzomorphans (phenazocine, pentazocine), and the phenylpiperidine derivatives (meperidine, fentanyl, alfentanil, sufentanil, and remifentanil). Structures of opioid compounds are shown in Figure 27-1[1] and Table 27-1.[1]

Box 27-1 Classification of Opioid Compounds

Naturally Occurring

Morphine

Codeine

Papaverine

Thebaine

Semisynthetic

Heroin

Dihydromorphone/morphinone

Thebaine derivatives (e.g., etorphine, buprenorphine)

Synthetic

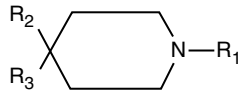
Morphinan series (e.g., levorphanol, butorphanol)

Diphenylpropylamine series (e.g., methadone)

Benzomorphan series (e.g., pentazocine)

Phenylpiperidine series (e.g., meperidine, fentanyl, sufentanil, alfentanil, remifentanil)

From Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. *In* Miller RD (ed): Anesthesia, 5th ed. New York, Churchill Livingstone, 2000, p 276.



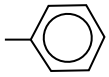
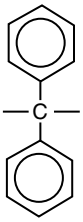
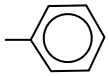
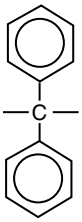
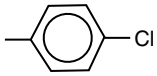
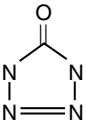
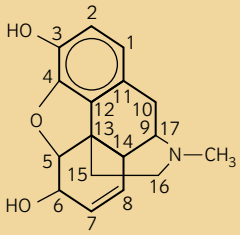
Compound	R_1	R_2	R_3
Meperidine	$-CH_3$		$-COCH_2CH_3$ (=O)
Diphenoxylate	$-CH_2CH_2-C(CN)$ 		$-COCH_2CH_3$ (=O)
Loperamide	$-CH_2CH_2-C(-C(=O)-N(CH_3)_2)$ 	 Cl	$-OH$
Fentanyl	$-CH_2CH_2-$ 	$-H$	$-N-CCH_2CH_3$ (=O)
Sufentanil	$-CH_2CH_2-$ 	$-CH_2OCH_3$	$-N-CCH_2CH_3$ (=O)
Alfentanil	$-CH_2CH_2-N(-C(=O)-N(-CH_2CH_3)-N=N)$ 	$-CH_2OCH_3$	$-N-CCH_2CH_3$ (=O)
Remifentanil	$-CH_2CH_2C(=O)-O-CH_3$	$-C(=O)-O-CH_3$	$-N-CCH_2CH_3$ (=O)

Figure 27-1 Chemical structures of piperidine and phenylpiperidine analgesics. *(From Gutstein HB, Akil H: Opioid analgesics.* In *Hardman JG, Limbird LE [eds]: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th ed. New York, McGraw-Hill, 2001, pp 569-619.)*

Table 27-1 Structures of Opioids and Opioid Antagonists Chemically Related to Morphine



MORPHINE

	Chemical Radicals and Position*			
Nonproprietary Name	**3**	**6**	**17**	**Other Changes†**
Morphine	—OH	—OH	—CH_3	—
Heroin	—$OCOCH_3$	—$OCOCH_3$	—CH_3	—
Hydromorphone	—OH	=O	—CH_3	(1)
Oxymorphone	—OH	=O	—CH_3	(1), (2)
Levorphanol	—OH	—H	—CH_3	(1), (3)
Levallorphan	—OH	—H	—$CH_2CH{=}CH_2$	(1), (3)
Codeine	—OCH_3	—OH	—CH_3	—
Hydrocodone	—OCH_3	=O	—CH_3	(1)
Oxycodone	—OCH_3	=O	—CH_3	(1), (2)
Nalmefene	—OH	=CH_2	—CH_2—	(1), (2)
Nalorphine	—OH	—OH	—$CH_2CH{=}CH_2$	—
Naloxone	—OH	=O	—$CH_2CH{=}CH_2$	(1), (2)
Naltrexone	—OH	=O	—CH_2—	(1), (2)
Buprenorphine	—OH	—OCH_3	—CH_2—	(1), (4)
Butorphanol	—OH	—H	—CH_2—	(1), (2), (3)
Nalbuphine	—OH	—OH	—CH_2—	(1), (2)

*The numbers 3, 6, and 17 refer to positions in the morphine molecule, as shown in the line drawing.
†Other changes in the morphine molecule are as follows:
(1) Single instead of double bond between C7 and C8
(2) OH added to C14
(3) No oxygen between C4 and C5
(4) Endoetheno bridge between C6 and C14; 1-hydroxy-1,2,2-trimethylpropyl substitution on C7
From Gutstein HB, Akil H: Opioid analgesics. *In* Hardman JG, Limbird LE (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th ed. New York, McGraw-Hill, 2001, pp 569-619.

Opioids can be classified as agonists, partial agonists, mixed agonist-antagonists, and antagonists on the basis of their interaction with opioid receptors.

Opioid Receptors

In 1973, based on radioligand binding assays, three types of opioid receptors were postulated. They were named μ for the morphine type, κ for the ketocyclazocine type, and σ for the SKF10047 (*N*-allylnormetazocine) type. In addition, a high-affinity receptor for enkephalins was found in the mouse vas deferens and designated the δ-receptor. Furthermore, an ε-receptor was proposed as the binding site for β-endorphin in the rat vas deferens. The pharmacologic actions of opioids and the involved receptors have been analyzed (Table 27-2).

Biochemical studies were performed to purify the opioid receptor protein but have not been successful. Since the early 1990s, molecular biologic studies have elucidated the molecular structures and signal transduction mechanisms of the opioid

Table 27-2 Pharmacologic Actions of Opioids and Opioid Receptors in Animal Models

	Actions of		
	Receptor	**Agonists**	**Antagonists**
Analgesia			
Supraspinal	μ, δ, κ	Analgesic	No effect
Spinal	μ, δ, κ	Analgesic	No effect
Respiratory function	μ	Decrease	No effect
Gastrointestinal tract	μ, κ	Decrease transit	No effect
Psychotomimesis	κ	Increase	No effect
Feeding	μ, δ, κ	Increase feeding	Decrease feeding
Sedation	μ, κ	Increase	No effect
Diuresis	κ	Increase	
Hormone secretion			
Prolactin	μ	Increase release	Decrease release
Growth hormone	μ and/or δ	Increase release	Decrease release
Neurotransmitter release			
Acetylcholine	μ	Inhibit	
Dopamine	δ	Inhibit	

receptors. Four different cDNAs have been isolated as members of the opioid receptor family.[2] Three of them correspond to the pharmcacologically defined μ-, δ-, and κ-opioid receptors. The fourth receptor did not bind with opioid ligands with high affinity. Later, a novel peptide named nociceptin/orphanin FQ was identified as an endogenous agonist of the fourth member of the opioid receptor family.[3,4] The characteristics of three opioid receptors and the nociceptin/orphanin FQ receptor are listed in Table 27-3.

The μ-receptors are located in both the brain and spinal cord[5] and mediate a variety of pharmacologic effects of opioids. Further pharmacologic classification of the μ-receptor as μ_1, μ_2, and μ_3 has been proposed. Perhaps post-translational modification of the μ-receptor is the molecular basis of the μ-receptor subtypes. However, the molecular identity of these receptors still remains to be clarified.

Hydropathy analysis of the primary structures of the opioid receptors indicates that the opioid receptors possess seven transmembrane domains (Fig. 27-2), a characteristic structural feature of the G protein–coupled receptor. The μ-, δ-, and κ-opioid receptors and the nociceptin receptor share approximately 50% amino acid sequence homology with each other.

Several single-nucleotide polymorphisms have been identified in the human μ-opioid receptor gene.[6] The A118G mutation, an A-to-G substitution in exon 1 that results in exchange of asparagine at position 40 for aspartate (N40D), is the most common mutation leading to a change in the gene product in the human μ-opioid receptors. It was suggested that cancer patients who were homozygous for the A118G variant required higher doses of oral morphine for long-term treatment of their pain.[7] A118G mutation of the human μ-opioid receptor gene reduces analgesic responses to morphine-6-glucuronide (M6G) but does not significantly affect the respiratory depression induced by M6G.[8] Furthermore, morphine consumption via intravenous PCA after total abdominal hysterectomy was significantly greater in women homozygous for the A118G variant than in other patients.[9]

Endogenous Opioid Peptides

Enkephalin, β-endorphin, and dynorphin were identified as endogenous agonists for the δ-, μ-, and κ-opioid receptors, respectively. After purification of these peptides from mammalian tissues, cDNAs for the precursors of these peptides were cloned. cDNA cloning and amino acid determination of proopiomelanocortin demonstrated that cleavage of this precursor protein produces not only β-endorphin but also several other neuro-

Table 27-3 Characteristics of Opioid Receptors

	μ	**δ**	**κ**	**Nociceptin**
Tissue bioassay	Guinea pig ileum	Mouse vas deferens	Rabbit vas deferens	
Endogenous ligand	β-Endorphin	Leu-enkephalin	Dynorphin	Nociceptin
	Endomorphin	Met-enkephalin		
Agonist	Morphine	DPDPE	Buprenorphin	
	Fentanyl	Deltorphin	Pentazocine	
	DAMGO		U50,488	
Antagonist	Naloxone	Naloxone	Naloxone	
	Naltrexone	Naltrindole	NorBNI	
Coupled G-protein	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Adenylate cyclase	Inhibition	Inhibition	Inhibition	Inhibition
Voltage-gated Ca^{2+} channels	Inhibition	Inhibition	Inhibition	Inhibition
Inwardly rectifying K^+ channels	Activation	Activation	Activation	Activation

DPDPE, [D-penicillamine^2, D-penicillamine^5]enkephalin; DAMGO, [D-Ala^2, MePhe^4, Gly-ol^8]enkephaline; NorBNI, norbinaltorphimine.

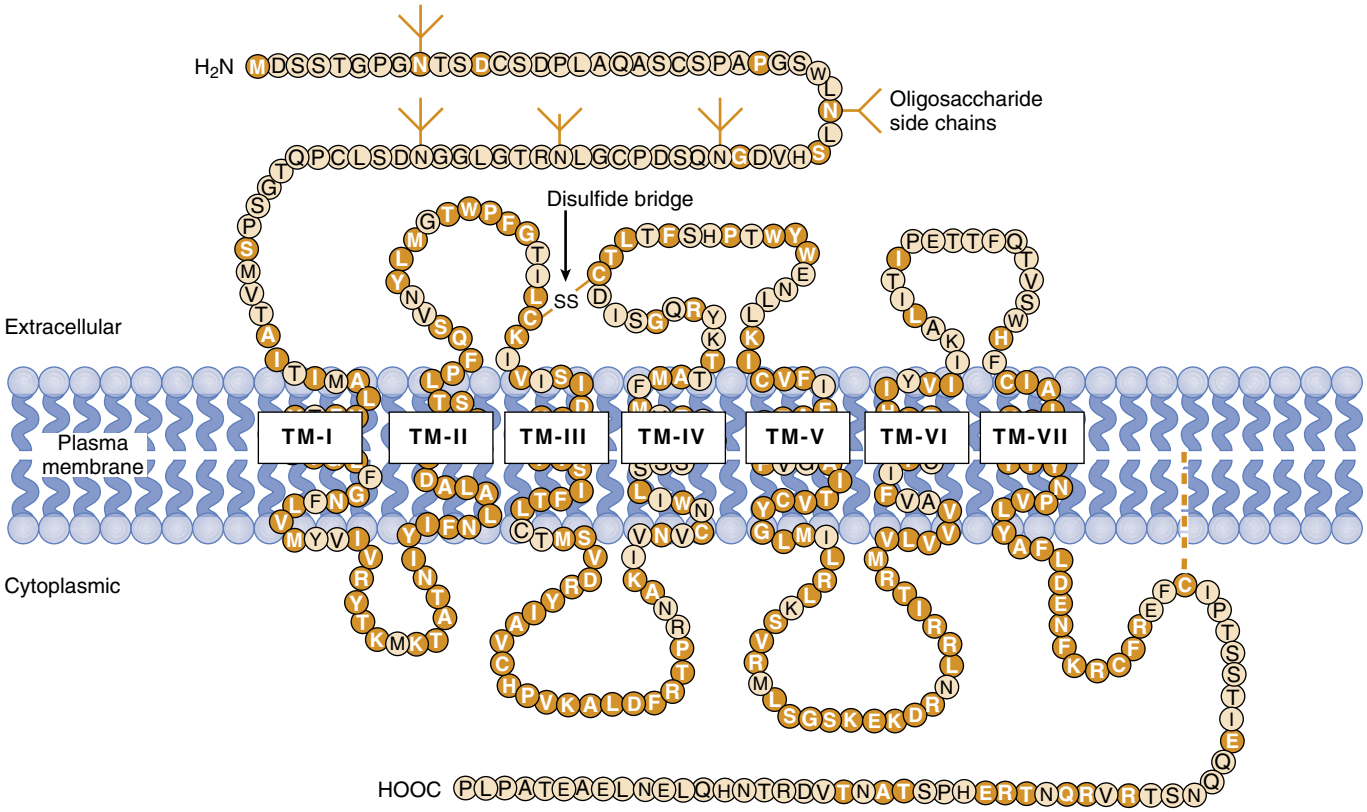


Figure 27-2 Proposed structure of the μ-opioid receptor. *Filled circles* indicate amino acid residues identical in the μ- and δ-opioid receptors. TM-I to TM-VII show putative transmembrane segments composed of hydrophobic amino acid residues.

peptides, including methionine enkephalin, adrenocorticotropic hormone, and α-melanocyte–stimulating hormone. Amino acid sequencing of preproenkephalin indicates that four methionine enkephalins and one leucine enkephalin are cleaved from this precursor. Furthermore, the primary structure of preprodynorphin, the precursor of dynorphin, was determined by cDNA cloning.

A novel endogenous opioid peptide with significant sequence homology to dynorphin was isolated in 1995.[3,4] This peptide was called orphanin FQ or nociceptin because it lowered the pain threshold under certain conditions, in contrast to the other endogenous opioid peptides. Pharmacologic and physiologic studies have demonstrated that orphanin FQ/nociceptin has behavioral and pain modulatory properties distinct from those of the three classic opioid peptides.[10] Studies of the effect of orphanin FQ/nociceptin on pain sensitivity have produced conflicting results, which may suggest that the effects of orphanin FQ/nociceptin on pain sensitivity depend on the underlying behavioral state of the subject. Prepronociceptin, the precursor of orphanin FQ/nociceptin, was cloned, and its amino acid sequence suggested the existence of prepronociceptin-derived neuropeptides other than orphanin FQ/nociceptin.[11]

The search for an endogenous ligand that binds to the μ-receptor with high affinity and high selectivity led to the discovery of a class of novel endogenous opioids termed endomorphin-1 and endomorphin-2.[12] These peptides are tetrapeptides with the sequence Tyr-Pro-Trp-Phe and Tyr-Pro-Phe-Phe, respectively. An endomorphin gene has yet to be cloned, and much remains to be learned about the anatomic distribution, mode of interaction with opioid receptors, function in vivo, and potential existence of other related peptides that are highly selective for each of the opioid receptors.

Intracellular Signal Transduction Mechanism

The opioid receptors belong to the G protein–coupled receptor family. Activation of the opioid receptors leads to activation of the pertussis toxin–sensitive G proteins (G_i and/or G_o). Expression of the cloned opioid receptors in cultured cells by transfection of the cloned cDNA has facilitated analysis of the intracellular signal transduction mechanisms activated by the opioid receptors (Fig. 27-3).[2] Adenylate cyclase is inhibited by activation of the opioid receptor, thereby resulting in a reduction in cellular cyclic adenosine monophosphate (AMP) content. Electrophysiologically, the voltage-gated Ca^{2+} channel is inhibited and the inwardly rectifying K^+ channels are activated by the opioid receptors. As a result, neuronal excitability is reduced by activation of the opioid receptors. In contrast, it was reported that opioids also stimulate the influx of Ca^{2+} into neuronal cultured cells.[13] Recently, it was shown that extracellular signal–related kinase, a class of mitogen-activated protein kinases, is activated by the opioid receptors.[14]

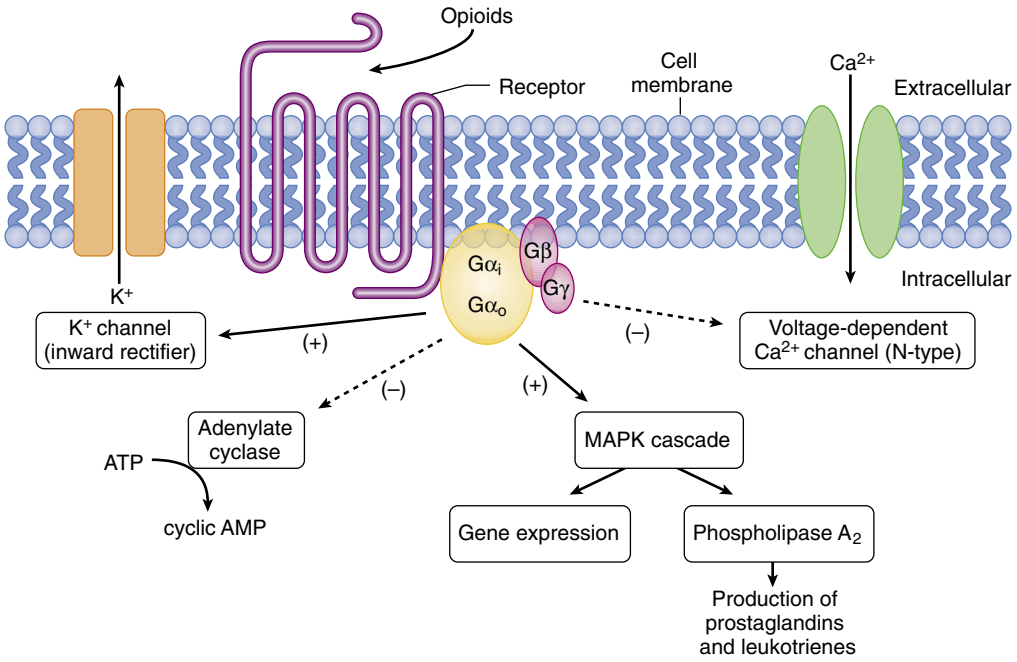


Figure 27-3 Intracellular signal transduction mechanisms linked with the opioid receptors. Binding of opioid agonists with the opioid receptors leads to activation of the G protein. The activity of adenylate cyclase and the voltage-dependent Ca^{2+} channels is suppressed. On the other hand, the inwardly rectifying K^+ channels and mitogen-activated protein kinase (MAPK) cascade are activated. AMP, adenosine monophosphate; ATP, adenosine triphosphate.

Opioid-induced activation of extracellular signal–related kinase can lead to an increase in release of arachidonate[14] and expression of the immediate early genes c-fos and junB.[15]

Chronic exposure of the opioid receptors to agonists induces cellular adaptation mechanisms that may be involved in opioid tolerance, dependence, and withdrawal symptoms. Short-term desensitization probably involves phosphorylation of the opioid receptors via protein kinase C.[16] A number of other kinases have also been implicated, including protein kinase A and β-adrenergic receptor kinase (βARK).[17] BARKs selectively phosphorylate agonist-bound receptors, thereby promoting interactions with β-arrestins, which interfere with G protein coupling and promote receptor internalization. Acute morphine-induced analgesia was enhanced in mice lacking β-arrestin 2, suggesting that this protein contributes to regulation of responsivity to opioids in vivo.[18]

Like other G protein–coupled receptors, the opioid receptors can undergo rapid agonist-mediated internalization via a classic endocytic pathway.[19,20] These processes may be induced differentially as a function of the class of the ligand. For example, certain agonists, such as etorphine and enkephalins, cause rapid internalization of the μ-receptor, whereas morphine, although it decreases adenylyl cyclase activity equally well, does not cause internalization of the μ-receptor.[21] These findings may suggest that different ligands induce different conformational changes in the receptor that lead to divergent intracellular events. Furthermore, they may provide an explanation for differences in the efficacy and abuse potential of various opioids.[22]

Long-term tolerance to opioids has been thought to be associated with superactivation of adenylyl cyclase activity—a counter-regulatory response to the decrease in cyclic AMP levels seen after acute opioid administration.[23] This effect is prevented by pretreatment of cells with pertussis toxin, thus demonstrating the involvement of G proteins (G_i and/or G_o).

Mechanism of Analgesia

Pain control by opioids needs to be considered in the context of brain circuits modulating analgesia and the functions of the various types of receptors in these circuits.[24] The analgesic effects of opioids arise from their ability to directly inhibit ascending transmission of nociceptive information from the spinal cord dorsal horn and to activate pain control circuits that descend from the midbrain, via the rostral ventromedial medulla (RVM), to the spinal cord dorsal horn. Petrovic and colleagues used an experimental pain model and positron emission tomography (PET) to study the mechanisms of action of the short-acting μ-opioid agonist remifentanil and found drug-induced activation of the rostral anterior cingulate cortex, insula, orbitofrontal cortex, and brainstem areas.[25] The latter overlapped with brain areas that have been implicated in pain modulation, such as the periaqueductal gray matter (PAG). Interestingly, placebo analgesia acts similarly on the activity of these brain areas, presumably via endogenous opioid release.[26]

Immunohistochemical studies and in situ hybridization analysis have demonstrated that opioid receptors are expressed in various areas in the central nervous system (CNS),[5] including the amygdala, mesencephalic reticular formation, PAG, and RVM. However, the role of opioid receptors in all these areas has not been completely clarified.

Microinjection of morphine into the PAG or direct electrical stimulation of this area produces analgesia that can be blocked by naloxone. Opioid actions at the PAG influence the RVM, which in turn modulates nociceptive transmission in the dorsal horn of the spinal cord through the action of the descending inhibition pathway. Thus, opioids produce analgesia not only by direct actions on the spinal cord but also by neurally mediated action in regions separate from the site of opioid administration.

The distribution of opioid receptors in descending pain control circuits indicates substantial overlap between μ- and κ-receptors. Interactions between the κ-receptor and the μ-receptor may be important for modulating nociceptive transmission from higher nociceptive centers, as well as in the spinal cord dorsal horn. The μ-receptor produces analgesia within descending pain control circuits, at least in part by the removal of GABAergic (transmitting or secreting γ-aminobutyric acid) inhibition of RVM-projecting neurons in the PAG and spinally projecting neurons in the RVM.[24] The actions of μ-receptor agonists are invariably analgesic, whereas those of κ-receptor agonists can be either analgesic or antianalgesic. The pain-modulating effects of κ-receptor agonists in the brainstem appear to oppose those of μ-receptor agonists.[27]

Local spinal mechanisms, in addition to descending inhibition, underlie the analgesic action of opioids. In the spinal cord, opioids act at synapses either presynaptically or postsynaptically. Opioid receptors are abundantly expressed in the substantia gelatinosa, where release of substance P from the primary sensory neuron is inhibited by opioids.

There is significant opioid receptor-ligand binding and little detectable receptor mRNA expression in the spinal cord dorsal horn but high levels of opioid receptor mRNA in the dorsal root ganglia. This distribution might suggest that the actions of opioid receptor agonists relevant to analgesia at the spinal level are predominantly presynaptic. It is well known that opioids decrease the pain-evoked release of tachykinins from primary afferent nociceptors. However, at least 80% of tachykinin signaling in response to noxious stimulation remains intact after the intrathecal administration of large doses of opioids.[28] These results suggest that although opioid administration may reduce release of tachykinin from primary afferent nociceptors, this reduction has little functional impact on the actions of tachykinin on postsynaptic pain-transmitting neurons.

The actions of opioids in the bulbospinal pathways are critical to their analgesic efficacy. Opioid actions in the forebrain clearly contribute to analgesia because decerebration prevents analgesia when rats are tested for pain sensitivity with the formalin test[29] and microinjection of opioids into several forebrain regions is analgesic in this test.[30] The analgesia induced by systemic administration of morphine in both the tail flick and formalin tests was disrupted either by lesioning or by reversibly inactivating the central nucleus of the amygdala, thus demonstrating that opioid actions in the forebrain contribute to analgesia after tissue damage, as well as after acute phasic nociception.[31,32]

Opioids may also produce analgesia through a peripheral mechanism.[33] Immune cells infiltrating an inflammatory site may release endogenous opioid-like substances that act on opioid receptors located on the primary sensory neuron.[33] However, others do not support this conclusion.[34,35]

Mood Alterations and Rewarding Properties

The mechanisms by which opioids produce euphoria, tranquility, and other alterations in mood (including rewarding properties) are not entirely clear. Behavioral and pharmacologic evidence points to the role of dopaminergic pathways, particularly those involving the nucleus accumbens, in drug-induced reward. Functional magnetic resonance imaging studies have demonstrated that a small intravenous dose (4 mg) of morphine induces positive signal changes in reward structures, including the nucleus accumbens, sublenticular extended amygdala, orbitofrontal cortex, and hippocampus, and decreases signal in cortical areas similar to the action of sedative-hypnotics such as propofol and midazolam.[36] These observations are consistent with results from pharmacologic studies.

The shell of the nucleus accumbens is the site that may be involved directly in the emotional and motivational aspects of drug-induced reward. All three opioid receptor types are present on the nucleus accumbens and are thought to mediate, at least in part, the motivational effects of opiate drugs.[5] Selective μ- and δ-receptor agonists are rewarding when defined by place preference and intracranial self-administration paradigms. Conversely, selective κ-receptor agonists produce aversive effects. The positive motivational effects of opioids are partially mediated by release of dopamine at the level of the nucleus accumbens.

The locus ceruleus contains both noradrenergic neurons and high concentrations of opioid receptors and is postulated to play a critical role in feelings of alarm, panic, fear, and anxiety. Neural activity in the locus ceruleus is inhibited by both exogenous opioids and endogenous opioid peptides.

Analysis of Knock-out Mice

The physiologic roles of the opioid receptors and endogenous opioid peptides have been investigated mainly by pharmacologic and physiologic methods. However, it has been difficult to analyze the functional roles of these proteins. Recently, knock-out mice, in which a specific gene is inactivated by molecular biologic methods, have been produced. By analysis of knock-out mice the physiologic significance of the respective opioid receptors and endogenous opioid peptide precursors can be deteremined.[37]

In μ-receptor knock-out mice, analgesia, the reward effect, and the withdrawal effect of morphine are lost.[38,39] Morphine-induced respiratory depression was not observed in the μ-receptor knock-out mice.[40] Therefore, the μ-receptor is a mandatory component of the opioid system for morphine action. In μ-receptor knock-out mice, ketamine-induced respiratory depression and antinociception are diminished,[41] suggesting that ketamine interacts with the μ-receptor to lead to these phenomena. Furthermore, the significantly higher minimum alveolar concentration (MAC) of sevoflurane in the μ-receptor knock-out mice than in wild-type mice suggest that the μ-receptor is involved in the anesthetic potency of sevoflurane.[40] δ-Receptor knock-out mice display a markedly reduced analgesic effect of opioids selective for δ-receptors at the spinal cord level.[42] However, at the supraspinal level, analgesia can be induced by δ-receptor agonists in δ-receptor knock-out mice, suggesting the existence of a second

δ-like analgesic system. Because disruption of the κ-receptor abolishes the analgesic, hypolocomotive, and aversive actions of the κ-receptor agonists and induces hyperreactivity in the abdominal constriction test, the κ-receptor is thought to be involved in the perception of visceral chemical pain.[43]

In mice lacking β-endorphin, morphine induces normal analgesia, but naloxone-reversible stress-induced analgesia cannot be observed.[44] Preproenkephalin knock-out mice are more anxious than wild-type mice, and males display increased offensive aggressiveness.[45] The mutant mice show a marked difference from controls in supraspinal but not in spinal responses to painful stimuli.

Thus, the functional roles of individual components of the opioid system have been elucidated by analysis of knock-out mice. However, many points remain to be clarified.

Actions of Opioids on Targets Other Than Opioid Receptors

Recent progress in molecular pharmacologic analysis has shown that opioids can interact with molecules other than the opioid receptors. In cardiac myocytes, it was shown that morphine can inhibit voltage-dependent Na^+ current in a naloxone-insensitive manner, thus suggesting the existence of a signal transduction mechanism that is not dependent on the opioid receptors.[46] Meperidine is an agonist of both μ- and κ-receptors. In addition, it was demonstrated that meperidine can block voltage-dependent Na^+ channels in amphibian peripheral nerves,[47] as well as in a *Xenopus* oocyte expression system (Fig. 27-4).[48] Furthermore, meperidine exerts agonist activity at the α_{2B}-adrenoreceptor.[49] Yamakura and coworkers have shown that high concentrations of opioids, including meperidine, morphine, fentanyl, codeine, and naloxone, directly inhibit the *N*-methyl-D-aspartate (NMDA) receptor expressed in *Xenopus* oocytes.[50] Methadone is used clinically as a racemic mixture of the *l* and *d* isomers. The opioid-like activity of the racemate seems to be almost entirely due to *l*-methadone, whereas *d*-methadone acts as an NMDA antagonist.[51] The commercially available remifentanil solution Ultiva, which contains glycine, directly activates the NMDA receptor expressed in *Xenopus* oocytes.[52] Furthermore, an electrophysiologic study involving the rat spinal cord showed that remifentanil hydrochloride does not directly activate NMDA receptors, the NMDA current recorded after the application of Ultiva is related to the

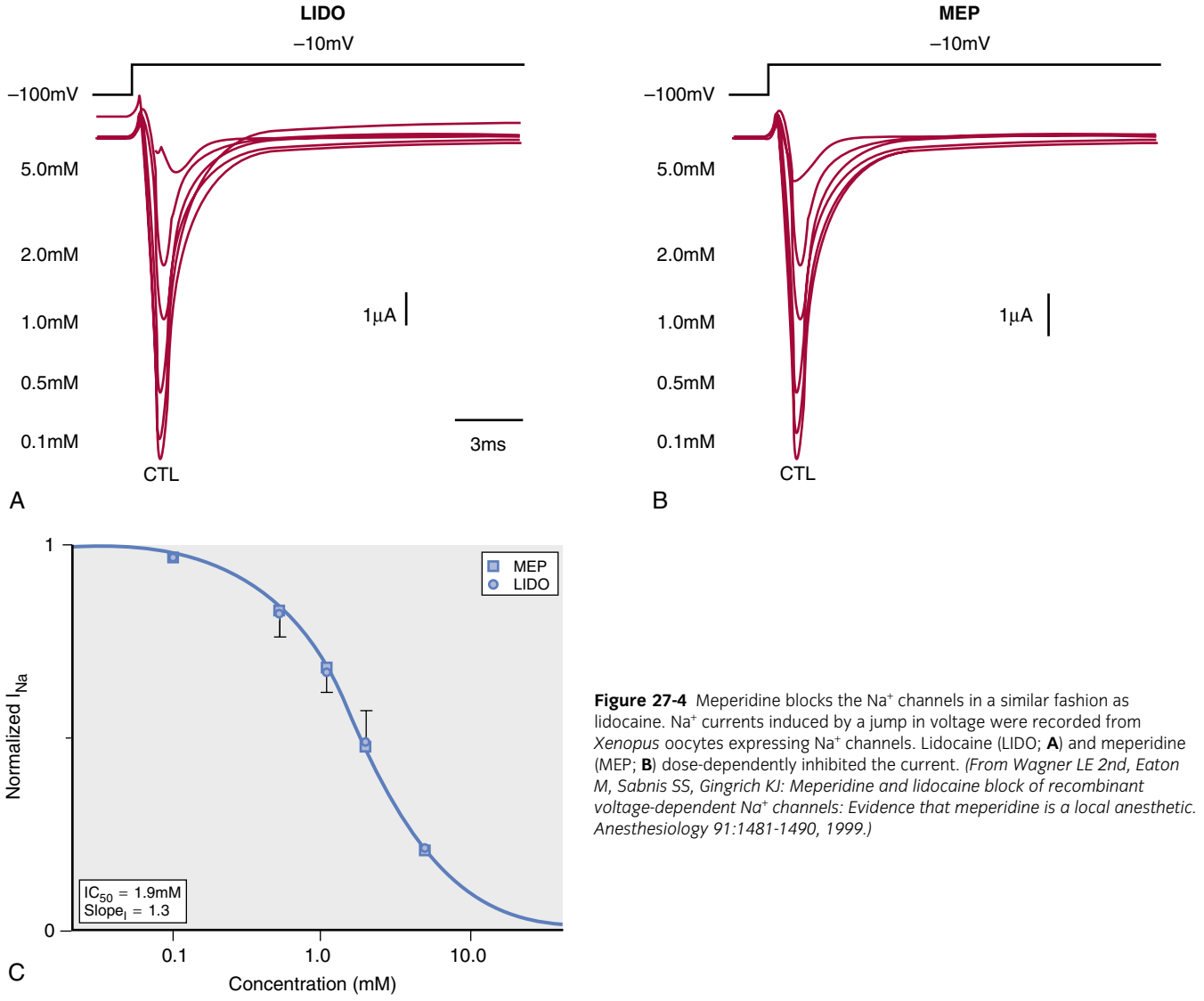


Figure 27-4 Meperidine blocks the Na^+ channels in a similar fashion as lidocaine. Na^+ currents induced by a jump in voltage were recorded from *Xenopus* oocytes expressing Na^+ channels. Lidocaine (LIDO; **A**) and meperidine (MEP; **B**) dose-dependently inhibited the current. *(From Wagner LE 2nd, Eaton M, Sabnis SS, Gingrich KJ: Meperidine and lidocaine block of recombinant voltage-dependent Na^+ channels: Evidence that meperidine is a local anesthetic. Anesthesiology 91:1481-1490, 1999.)*

presence of glycine, and the glycine-induced NMDA current is potentiated by the application of remifentanil hydrochloride through a pathway involving the μ-opioid receptor.[53] The serotonin 5-HT_{3A} receptor, which is directly and indirectly linked to gastrointestinal motility, visceral pain, nausea, and vomiting, was shown to be competitively inhibited by morphine, as well as by naloxone.[54]

Whether these actions of opioids on targets other than the opioid receptor have physiologic or clinical implications is not known.

The Role of Nociceptin/Orphanin FQ in Pain Modulation

Nociceptin/orphanin FQ is a 17–amino acid peptide, the sequence of which resembles that of opioid peptides. Nociceptin/orphanin FQ precursor mRNA and peptide are present throughout the descending pain control circuits. In the spinal cord, there is stronger nociceptin/orphanin FQ receptor mRNA expression in the ventral horn than in the dorsal horn, but higher levels of ligand binding in the dorsal horn. Targeted disruption of the nociceptin/orphanin FQ receptor in mice had little effect on basal pain sensitivity in several measures, whereas targeted disruption of the nociceptin/orphanin FQ precursor consistently elevated basal responses in the tail flick test, suggesting an important role for nociceptin/orphanin FQ in regulating basal pain sensitivity.[55,56] Intrathecal injections of nociceptin/orphanin FQ have been shown to be analgesic[57]; however, supraspinal administration has produced either hyperalgesia, antiopioid effects, or a biphasic hyperalgesic/analgesic response.[58] Nociceptin/orphanin FQ inhibits both pain-facilitating and analgesia-facilitating neurons in the RVM.[59] The effects of nociceptin/orphanin FQ on pain responses appear to depend on the preexisting state of pain in the animal. Yamamoto and Sakashita reported that intrathecal injection of nociceptin/orphanin FQ significantly attenuated the level of mechanical hyperalgesia induced by skin incision, which suggests involvement of the nociceptin/orphanin FQ receptor in maintaining postoperative pain.[57] The physiologic implications of nociceptin/orphanin FQ remain to be elucidated.

Neurophysiologic Effects of Opioids

Analgesic Action of Opioids

In human beings, morphine-like drugs produce analgesia, drowsiness, changes in mood, and mental clouding. A significant feature of opioid analgesia is that it is not associated with loss of consciousness. When morphine in the same dose is given to a normal, pain-free individual, the experience may be unpleasant. Relief of pain by morphine-like opioids is relatively selective in that other sensory modalities are not affected. Patients frequently report that the pain is still present but that they feel more comfortable. It is also important to distinguish between pain caused by stimulation of nociceptive receptors and transmitted over intact neural pathways (nociceptive pain) and pain caused by damage to neural structures, often involving neural supersensitivity (neuropathic pain). Although nociceptive pain is usually responsive to opioid analgesics, neuropathic pain typically responds poorly to opioid analgesics and may require higher doses of drug.[60] Not only is the sensation of pain altered by opioid analgesics, but the affective response is changed as well. However, alteration of the emotional reaction to painful stimuli is not the sole mechanism of analgesia.

The level of antinociception produced by an opioid is determined by the intensity of the nociceptive stimulus and the intrinsic efficacy of the opioid. When opioids are given in combination, the effects can be predicted only on the basis of the nociception experienced when the drugs are administered alone.[61] The antinociceptive effects of opioids are enhanced in animal models of inflammation. The sensitization to opioids is related to a central rather than a peripheral site of action.[62]

Animal and human studies indicate the existence of sex-related differences in opioid-mediated behavior.[63] Sarton and associates examined the influence of morphine on experimentally induced pain in healthy volunteers and demonstrated sex differences in morphine analgesia, with greater morphine potency but slower speed of onset and offset in women.[64] The mechanism of the sex difference remains to be clarified.

The analgesia produced by the peripheral actions of opioids is still a source of controversy. Recent reviews have concluded from meta-analysis that intra-articularly administered morphine has a definite, but mild analgesic effect.[65] It may be dose dependent, and a systemic effect cannot be completely excluded. The addition of opioids to brachial plexus blocks has been reported to improve the success rate and postoperative analgesia.[66,67] In contrast, the addition of sufentanil did not prolong the duration of brachial plexus blockade.[68] Because of its local anesthetic effect on peripheral nerves, meperidine was tested for intravenous regional anesthesia. However, doses of meperidine large enough to produce effective postoperative analgesia cause a significant incidence of side effects.[69]

Opioids As Anesthetics

Cortical acetylcholine originates in the basal forebrain and is essential for maintaining normal cognition and arousal. Injection of morphine into the substantia innominata or intravenous administration of morphine significantly decreased release of acetylcholine within the prefrontal cortex in the rat, which might be the neurochemical basis of opioid-induced change in consciousness.[70] Whether opioids alone are capable of producing anesthesia was a subject of debate in the past.[71] Reports of patient awareness during high-dose fentanyl anesthesia highlighted the potential for this problem (see Chapter 39). The anesthetic potential of opioids was tested by measurement of MAC.[72] Studies in rats demonstrated that opioids reduce the MAC of volatile anesthetics to a greater degree than in other animals. Interspecies differences in opioid actions are significant.[73] Fentanyl can reduce the MAC of isoflurane at skin incision in patients by at least 80%.[74] The relationship between the plasma fentanyl concentration and reduction in MAC is not linear, and there is a sub-MAC ceiling effect of fentanyl on reduction of the MAC of isoflurane. The MAC of sevoflurane was also dose-dependently reduced by fentanyl, with 3 ng/mL resulting in a 61% reduction in MAC (Fig. 27-5).[75] A ceiling effect was observed for MAC, with 6 ng/

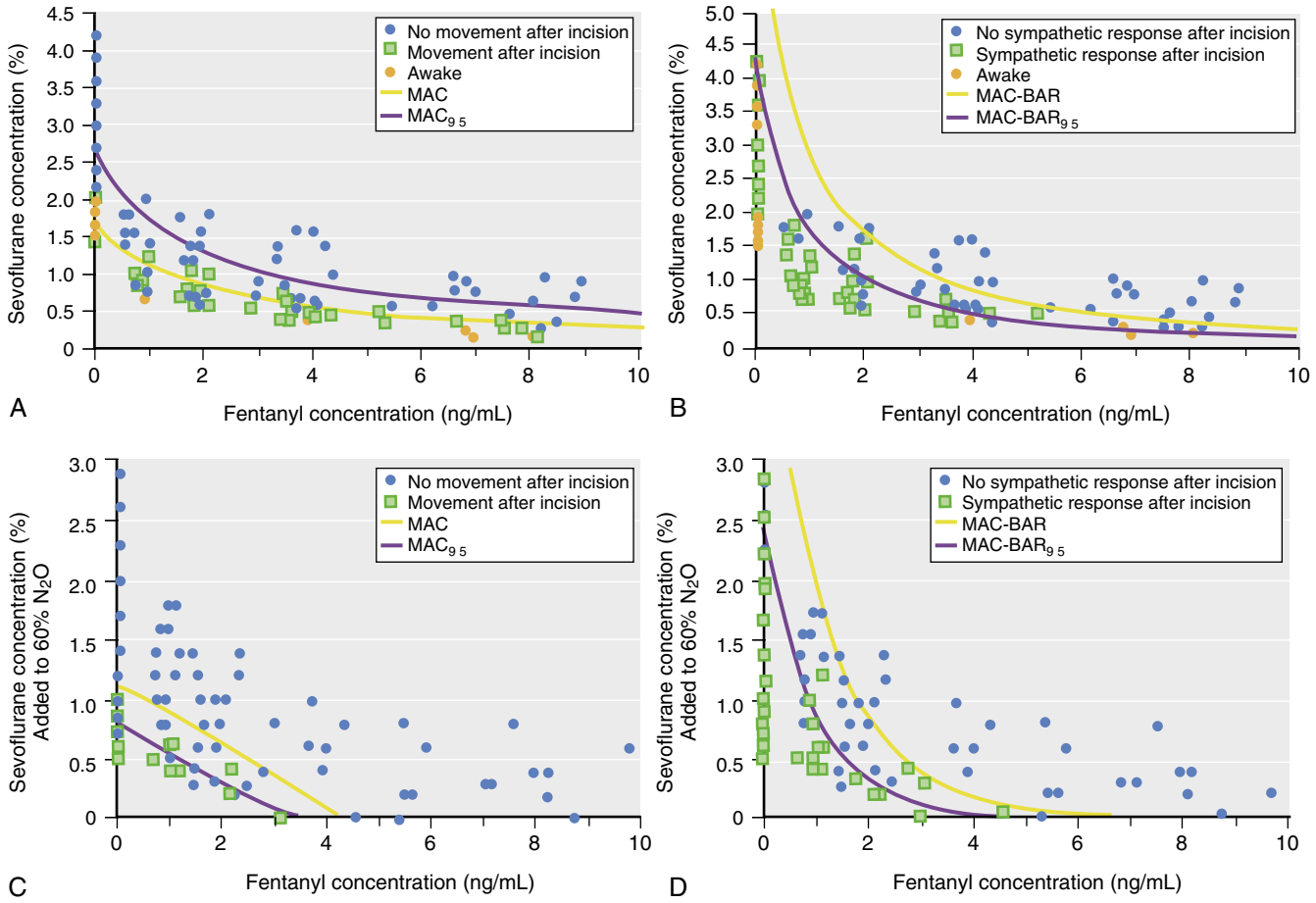


Figure 27-5 Effects of increasing concentration of fentanyl on the minimum alveolar concentration (MAC) and MAC-BAR (MAC that prevents sympathetic responses to surgical incision in 50% of patients) of sevoflurane. **A** and **C,** Reduction of the concentration of sevoflurane by increasing concentrations of fentanyl at which 50% or 95% of patients did not move at skin incision (MAC or MAC_{95}, respectively). **B** and **D,** Reduction of the concentration of sevoflurane by increasing concentrations of fentanyl at which 50% or 95% of patients did not show sympathetic responses (an increase in heart rate or mean arterial pressure >15%) at skin incision (MAC-BAR or $MAC\text{-}BAR_{95}$, respectively). Analysis was performed in the absence or presence of 60% nitrous oxide in **A** and **B** and in **C** and **D,** respectively. *(From Katoh T, Kobayashi S, Suzuki A, et al: The effect of fentanyl on sevoflurane requirements for somatic and sympathetic responses to surgical incision. Anesthesiology 90:398-405, 1999.)*

mL fentanyl providing only an additional 13% reduction in the MAC of sevoflurane. The potency ratios for fentanyl, sufentanil, alfentanil, and remifentanil, based on MAC reduction studies in humans, are approximately 1:12:0.0625:1.2.[76] Esmolol, a short-acting β_1-receptor antagonist, significantly decreased the MAC of isoflurane in the presence of alfentanil, although it did not significantly affect it in the absence of alfentanil.[77] The mechanism of the interaction is unknown. It was demonstrated that epidural fentanyl infusion reduces the awakening concentration of isoflurane more than intravenous fentanyl infusion does despite the lower plasma concentration, possibly by modulating afferent nociceptive input in the spinal cord.[78] The hypnotic effect of midazolam is also significantly enhanced by alfentanil.[79]

The MAC that prevents movement in response to laryngoscopy and tracheal intubation in 50% of patients (MAC-TI) is higher than the MAC that prevents movement in response to surgical incision (MAC). The MAC-TI of sevoflurane was 3.55% and was markedly reduced to 2.07%, 1.45%, and 1.37% by the addition of fentanyl, 1, 2, and 4 μg/kg, with no significant difference in the reduction between 2 and 4 μg/kg, thus showing a ceiling effect.[80] The MAC that prevents sympathetic responses to surgical incision in 50% of patients (MAC-BAR) decreased with increasing concentrations of fentanyl in plasma, and the initial steep reduction was followed by a ceiling effect (see Fig. 27-5).[75] In the presence of nitrous oxide, MAC and MAC-BAR decreased similarly but did not exhibit a ceiling effect.

The bispectral index (BIS) has been proposed as a measure of the effects of anesthetics on the brain (see Chapter 39). In the presence of fentanyl, alfentanil, remifentanil, or sufentanil, loss of consciousness occurred at a lower effect-site concentration of propofol and at a higher BIS value than with propofol alone.[81] This finding suggests that the hypnotic effect of propofol is enhanced by analgesic concentrations of opioids without changes in the BIS value. On the other hand, infusion of remifentanil (effect-site target concentrations of 0.25, 2.5, and 10 ng/mL), combined with propofol infusion adjusted to a BIS of approximately 60, dose-dependently decreased the BIS, thus suggesting a sedative or hypnotic effect of remifentanil.[82] Response surface analysis showed considerable synergy between opioids and hypnotics for sedation and suppression of responses to various noxious stimuli (Fig. 27-6).[83]

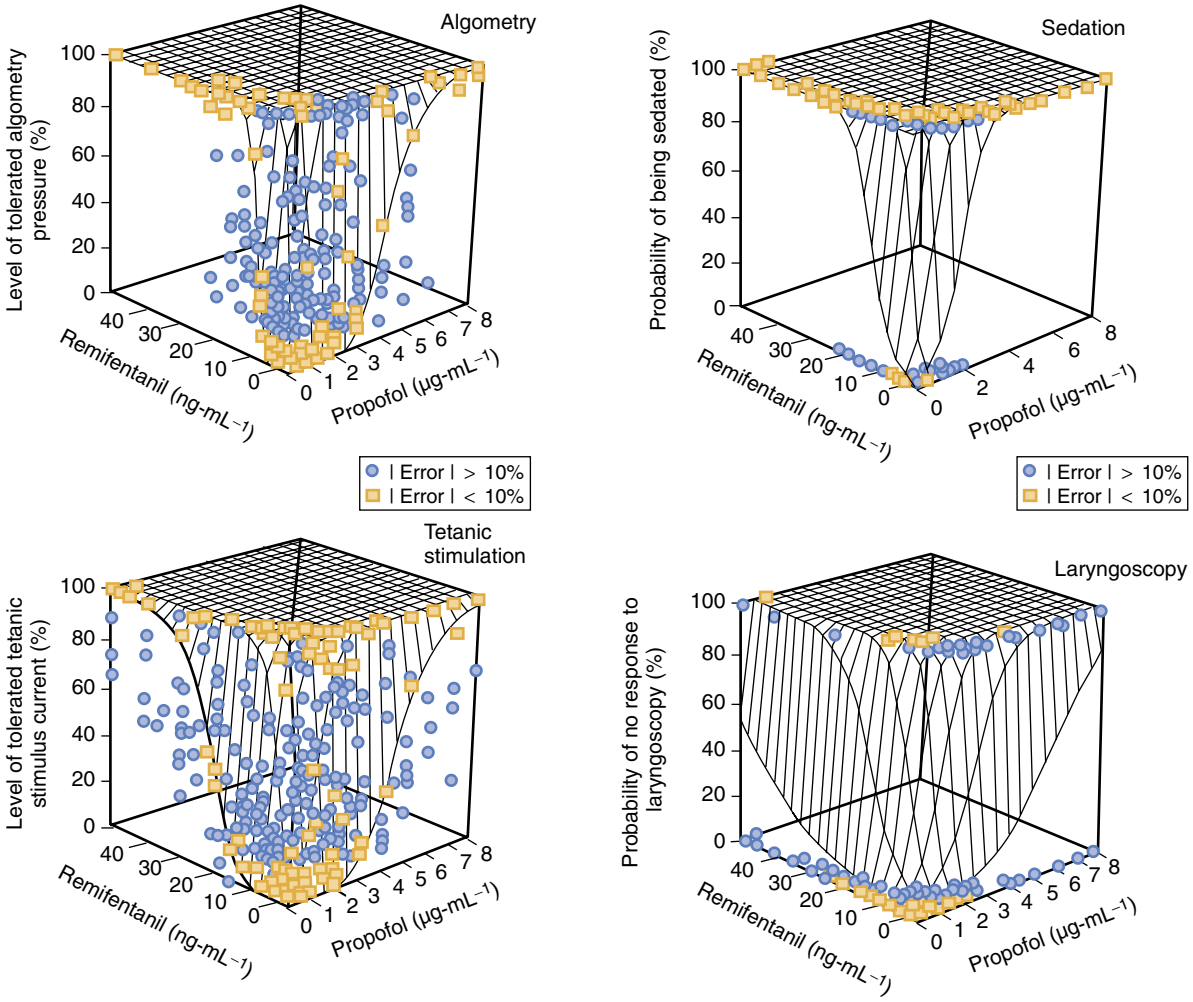


Figure 27-6 Prediction of sedation and blunting of the response to noxious stimuli, including tibial pressure algometry, electrical tetany, and laryngoscopy, by a response surface model. Sedation is indicated by an alertness/sedation score of 0 to 3 as assessed by an observer. Response to the noxious stimuli was based on whether the subjects exhibited withdrawal movement, painful verbalization, or a 20% increase in heart rate over the prestimulus level. The symbols show actual measured responses from the study subjects. *(From Kern SE, Xie G, White JL, Egan TD: A response surface analysis of propofol-remifentanil pharmacodynamic interaction in volunteers. Anesthesiology 100:1373-1381, 2004.)*

Although unconsciousness in humans can be produced with large doses of opioids alone, opioid anesthesia can be unpredictable and inconsistent.[84] Therefore, opioids are not suitable as the sole drug for intravenous induction of anesthesia.[85]

Electroencephalography

Increasing concentrations of inhaled anesthetics produce a continuum of changes on the electroencephalogram (EEG) and eventually result in burst suppression and a flat EEG. In contrast, a ceiling effect is reached with opioids. Increasing opioid dosage, when this ceiling has been attained does not further affect the EEG.[86] Problems with lead placement and signal processing need to be resolved before analysis of the EEG can be used as a routine monitor of the depth of opioid anesthesia.

Although the potency and rate of equilibrium between plasma and brain are different among opioids, the effects of fentanyl, alfentanil, sufentanil, and remifentanil are consistent (Fig. 27-7).[87] Small doses of fentanyl (200 μg) produce minimal changes on the EEG, whereas higher doses (30 to 70 μg/kg) result in high-voltage slow (δ) waves that are suggestive of a state consistent with anesthesia. Although transient isolated (usually frontotemporal) sharp wave activity can be observed after large doses of fentanyl and other opioids, it is not generalized.

As an effect-site measure, the EEG can be used to assess the onset of drug action and drug potency ratios. The spectral edge and serum concentration are closely parallel for remifentanil,[88] whereas significant time lag is found for recovery of the spectral edge for fentanyl and sufentanil (Fig. 27-8).[89] The serum concentration ratio of fentanyl and sufentanil was 12:1 at half-maximal slowing of the EEG.[89] Similar studies suggest that fentanyl and remifentanil are 75 and 16 times as potent as alfentanil, respectively.[88] Potency ratios based on the EEG are similar to those obtained from studies determining the plasma drug levels of each opioid necessary to reduce the MAC of isoflurane by 50%. Potency ratios of sufentanil:fentanyl:remifentanil: alfentanil for reducing the MAC of isoflurane are nearly 1:1/10:1/10:1/100.[74,90-92]

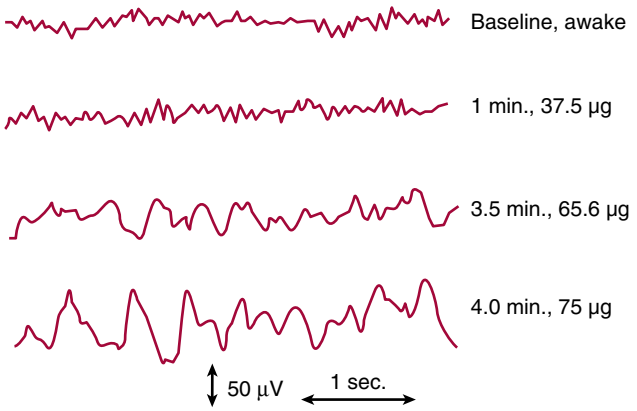


Figure 27-7 Representative 4-second tracings on the electroencephalogram (EEG) during infusion of sufentanil (total dose shown in the *right column*). The awake baseline EEG consists of mixed β and α activity. At 1 minute, the EEG showed loss of β activity and the presence of primarily α waves (8 to 13 Hz). At 3.5 minutes, the EEG consisted of mixed θ (4 to 7 Hz) and δ (<4 Hz) waves, and at 4.0 minutes, it consisted of δ waves of high amplitude. *(From Scott JC, Cooke JE, Stanski DR: Electroencephalographic quantitation of opioid effect: Comparative pharmacodynamics of fentanyl and sufentanil. Anesthesiology 74:34-42, 1991.)*

Evoked Responses

Because opioids do not appreciably alter sensory evoked potentials (SEPs) elicited at the posterior tibial or median nerve, SEPs can be used to monitor spinal cord function during anesthesia with opioids.[93] Remifentanil produced a dose-dependent reduction in auditory evoked potentials.[94] Remifentanil infusion (target plasma concentrations of 1, 2, and 3 ng/mL) did not affect evoked potential amplitudes and latencies.[95]

In healthy human volunteers receiving 3 µg/kg fentanyl, the amplitude and latency of motor evoked responses to transcranial stimulation were not significantly affected.[96] Kawaguchi and coauthors reported that intraoperative monitoring of myogenic motor evoked potentials is feasible during isoflurane or sevoflurane anesthesia with fentanyl.[97]

The middle latency auditory evoked response has been shown to change after the administration of opioids. However, it remains unclear whether these changes are due to a direct depressant effect of opioids on the middle latency auditory evoked response itself or an indirect effect because of their action in attenuating CNS arousal associated with noxious stimuli. Wright and colleagues examined the effect of remifentanil (1 or 3 µg/kg/min) on the middle latency auditory evoked response in intubated and nonintubated patients and showed that remifentanil has an effect on the middle latency auditory evoked response in attenuating the arousal associated with intubation of the trachea but has no effect in the absence of a stimulus.[98]

Cerebral Blood Flow and Cerebral Metabolic Rate

Opioids generally produce modest decreases in the cerebral metabolic rate (CMR) and intracranial pressure, although such changes are influenced by the concomitant administration of other agents and anesthetics, as well as by patient conditions (see Chapter 63). When vasodilation is produced by coadministered anesthetics, opioids are more likely to cause cerebral vasoconstriction. Opioids also decrease cerebral blood flow (CBF) when combined with N_2O. When opioids are administered alone or when the coadministered anesthetics cause cerebral vasoconstriction, opioids usually have no influence or result in a small increase in CBF.

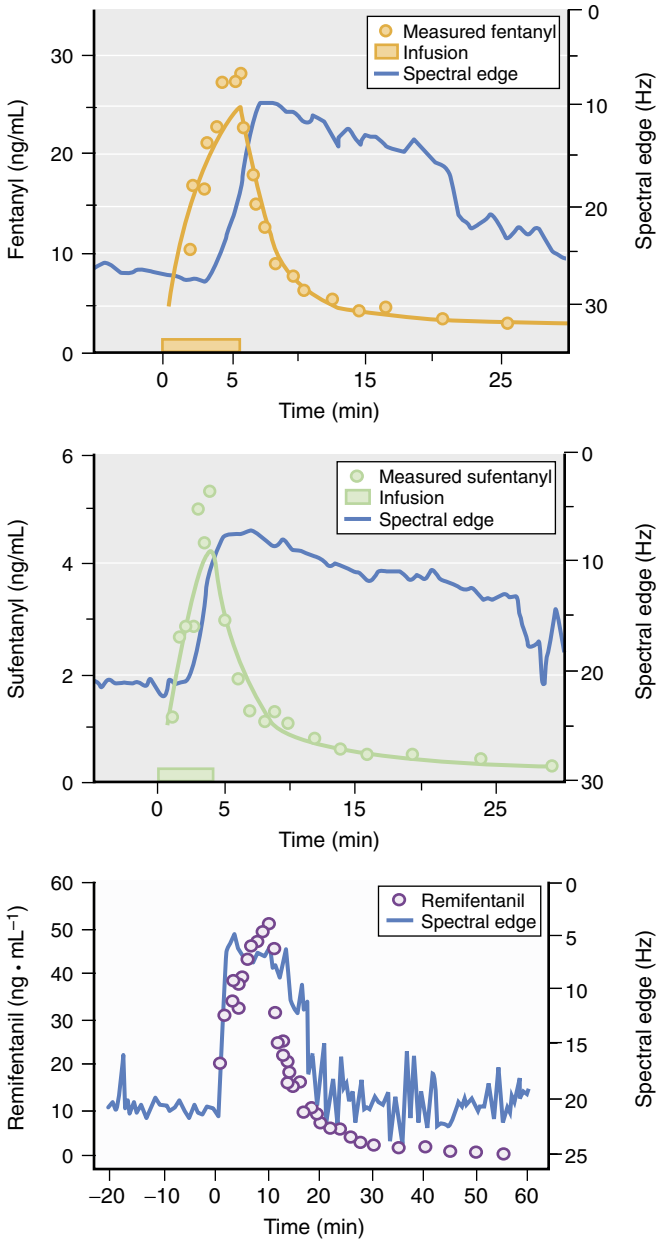


Figure 27-8 Time course of the spectral edge and serum opioid concentration. Fentanyl (*upper panel*) and sufentanil (*middle panel*) were infused at 150 and 18.75 µg/min, respectively. Remifentanil (*lower panel*) was administered at 3 µg/kg/min for 10 minutes. The spectral edge changes lag behind the changes in serum concentration in the case of fentanyl and sufentanil, whereas the spectral edge and serum concentration are closely parallel in the case of remifentanil. *(From Scott JC, Ponganis KV, Stanski DR: EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 62:234-241, 1985; and Egan TD, Minto CF, Hermann DJ, et al: Remifentanil versus alfentanil: Comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. Anesthesiology 84:821-833, 1996.)*

Endogenous opioid activity is present in the cerebral arteries, although exogenously administered opioids were found to exert little effect on pial artery diameter in several animal models.[99] Fentanyl (100 µg/kg) causes dose-related reductions in CBF and $CMRO_2$ in rats receiving N_2O. In the piglet, fentanyl, alfentanil, and sufentanil decrease arteriolar diameter in a dose-dependent, naloxone-reversible manner.[100] In human volunteers, PET demonstrated that the CBF changes induced by fentanyl are regionally heterogeneous.[101]

The effect of sufentanil on CBF in the dog may be dose and time dependent. It was reported that sufentanil (20 µg/kg intravenously [IV]) produces 30% to 40% decreases in CBF 5 to 10 minutes after opioid administration.[102] Another report showed that sufentanil (10 to 200 µg/kg) produces transient increases in CBF that peak 2 minutes after drug administration in the dog.[103] In humans, both fentanyl and sufentanil can increase middle cerebral artery blood flow velocity by about 25%.[104] In healthy volunteers, sufentanil (0.5 µg/kg IV) produces no significant effect on CBF.[104] Alfentanil (25 to 50 µg/kg IV), when administered to patients receiving isoflurane (0.4% to 0.6%)-N_2O anesthesia, produces minimal reductions in middle cerebral artery flow velocity.[105]

In the dog, alfentanil and remifentanil decrease regional blood flow by 40% to 50% in the cortex, hippocampus, and caudate.[106] A PET study in human volunteers showed that remifentanil induces dose-dependent changes in relative regional CBF in areas involved in pain processing, such as the lateral prefrontal cortex, inferior parietal cortex, and supplementary motor area.[107] In patients scheduled to undergo supratentorial tumor surgery and receiving N_2O, remifentanil (1 µg/kg/min), similar to fentanyl (2 µg/kg/min), reduced CBF and did not significantly affect cerebrovascular carbon dioxide reactivity.[108]

Opioids usually produce mild to moderate decreases in CMR that remain coupled to CBF. However, opioid-induced neuroexcitation and focal seizure activity can cause regional increases in brain metabolism. Regional increases in glucose utilization induced by high doses of alfentanil in the rat are associated not only with epileptiform activity but also with neuropathic lesions.[109] In humans, PET evaluation demonstrated that a 1- to 3-µg/kg/min infusion of remifentanil induces a significant increase in the CMR of glucose.[110]

Neuroprotection

Although certain early studies suggested potentially adverse effects of µ-opioid agonists on ischemic brain, other studies have documented that at least certain opioid agents, such as the κ-agonists, can be neuroprotective, at least in animal models of focal ischemia.[111,112] It was also shown that activation of δ-opioid receptors increases the survival time of mice during lethal hypoxia.[113,114] An in vitro study involving rat cerebellar brain slices demonstrated that pretreatment with morphine at clinically relevant concentrations induces acute neuroprotection mediated by activation of δ_1-opioid receptors, activation of adenosine triphosphate (ATP)-sensitive K^+ channels, and production of free radicals in mitochondria.[115] In contrast, Charchaflieh and coworkers demonstrated in the rat hippocampal slice model that fentanyl is neither neurotoxic nor protective against anoxic injury to neurons when used in concentrations comparable to those applied in clinical practice.[116] In the rat focal ischemia model, in contrast to isoflurane, fentanyl neither increased nor decreased brain injury when compared with awake unanesthetized rats.[117]

Table 27-4 Potential Problems Associated with Opioid-Induced Rigidity

System	Problem
Hemodynamic	↑CVP, ↑ PAP, ↑ PVR
Respiratory	↓ Compliance, ↓ FRC, ↓ ventilation
	Hypercapnia
	Hypoxemia
Miscellaneous	↑ Oxygen consumption
	↑ Intracranial pressure
	↑ Fentanyl plasma levels

CVP, central venous pressure; FRC, functional residual capacity; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance.
Modified from Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. *In* Miller RD (ed): Anesthesia, 5th ed. New York, Churchill Livingstone, 2000, p 291.

Muscle Rigidity

Opioids can increase muscle tone and may cause muscle rigidity. The incidence of rigidity noted with opioid anesthetic techniques varies greatly because of differences in the dose and speed of opioid administration, concomitant use of N_2O, presence or absence of muscle relaxants, and patient age. Opioid-induced rigidity is characterized by increased muscle tone that sometimes progresses to severe stiffness with the potential for serious problems (Table 27-4). Clinically significant opioid-induced rigidity usually begins just as or after a patient loses consciousness. Mild manifestations of rigidity, such as hoarseness, can occur in conscious patients. It has been demonstrated that vocal cord closure is primarily responsible for the difficult ventilation with bag and mask that follows the administration of opioids. Delayed or postoperative rigidity is probably related to the second peaks that can occur in plasma opioid concentrations, similar to the recurrence of respiratory depression.

The precise mechanism by which opioids cause muscle rigidity is not clearly understood. Muscle rigidity is not due to direct action on muscle fibers because it can be decreased or prevented by pretreatment with muscle relaxants. Mechanisms of opioid-induced muscle rigidity involving the CNS have been postulated. Pharmacologic studies using selective agonists and antagonists have suggested that systemic opioid-induced muscle rigidity is primarily due to the activation of central µ-receptors, whereas supraspinal δ_1- and κ_1-receptors may attenuate this effect.[118] Some aspects of opioid-induced catatonia and rigidity (increased incidence with age, muscle movements resembling extrapyramidal side effects) are similar to Parkinson's disease and suggest similarities in neurochemical mechanisms. Parkinsonian patients, particularly if inadequately treated, may experience reactions such as dystonia after opioid administration.[119]

Pretreatment with or concomitant use of nondepolarizing muscle relaxants can decrease the incidence and severity of rigidity. Induction doses of thiopental and subanesthetic doses of diazepam and midazolam prevent, attenuate, or successfully treat rigidity. Persisting in an attempt to mask-ventilate a patient with opioid-induced rigidity will probably result in gastric insufflation

and inadequate ventilation or oxygenation until a muscle relaxant is administered. To minimize the occurrence of muscle rigidity and facilitate ventilation and airway management, anesthesiologists should anticipate the need for rapid neuromuscular blockade when doses of opioids are administered that produce rigidity.

Neuroexcitatory Phenomena

Fentanyl causes seizure activity on the EEG in animals, but evidence of seizure activity after fentanyl, alfentanil, and sufentanil is generally lacking in humans. Remifentanil induces generalized tonic-clonic seizure–like activity in otherwise healthy adults.[120] Morphine produces tonic-clonic activity after epidural and intrathecal administration.[121] Focal neuroexcitation on the EEG (e.g., sharp and spike wave activity) occasionally occurs in humans after large doses of fentanyl, sufentanil, or alfentanil.

The mechanisms underlying opioid-induced neuroexcitatory phenomena are not completely clear. Excitatory opioid actions may be related to their coupling to mitogen-activated protein kinase cascades.[122] Local increases in CBF and metabolism are also of theoretical concern because prolonged seizure activity, even if focal, could lead to neuronal injury or cellular death. In large doses in rats, fentanyl, alfentanil, and sufentanil also induce hypermetabolism and histopathologic alterations in the limbic system.[123] Midazolam, naloxone, and phenytoin prevent seizure activity on the EEG and histologically evident brain damage induced by high-dose fentanyl in rats.[124]

Measurement of CBF via magnetic resonance imaging in human volunteers has indicated that the cingulate cortex is the most susceptible to activation by remifentanil (0.05 to 0.2 μg/kg/min) and that susceptibility is affected by the apolipoprotein E genotype.[125] These findings support the notion that neuroactivation of limbic areas via the perioperative use of opioids might have a role in the genesis of postoperative cognitive dysfunction.

Pupil Size

Morphine and most μ- and κ-agonists cause constriction of the pupil by an excitatory action on the parasympathetic nerve innervating the pupil. Opioids abolish cortical inhibition of the Edinger-Westphal nucleus, thereby resulting in papillary constriction. After the intravenous administration of morphine (0.125 mg/kg), there was a 26% decrease in pupil diameter at 1 hour, and longer than 6 hours was necessary for complete recovery of pupil diameter.[126] Alfentanil in a dose-dependent manner attenuates the reflex papillary dilatation that normally follows noxious stimulation in anesthetized individuals.[127] The changes in pupil size associated with opioid action may be too slight to be of clinical utility in assessing the degree of opioid effect.

Thermoregulation and Shivering

Opioid-based anesthesia probably reduces thermoregulatory thresholds to an extent similar to that of the potent inhaled agents (see Chapter 48).[128] However, meperidine is unique among opioids in its ability to effectively terminate or attenuate shivering. The antishivering effect of meperidine is primarily related to a reduction in the shivering threshold[129] and seems to be mediated by meperidine's activity on the κ-receptor.[130] However, the relatively specific κ-receptor agonist nalbuphine did not show significant antishivering activity.[131] Meperidine exerts agonist activity at the α_{2B}-adrenoreceptor subtype, suggesting possible involvement of this novel action in the antishivering action of meperidine.[49] Alfetanil, morphine, and fentanyl are not as effective as meperidine in the treatment of postoperative shivering. Tramadol (0.5 mg/kg) suppressed post–epidural anesthetic shivering in parturients as effectively as meperidine did (0.5 mg/kg),[132] but the incidence of somnolence was lower with tramadol than with meperidine.

Pruritus

Intrathecal morphine–induced itching in monkeys was suggested to be mediated by the μ-receptor.[133] Naloxone reverses opioid-induced itching, and this finding supports a receptor-mediated central mechanism for pruritus. However, opioid antagonists are not ideal therapeutic agents against pruritus because opioid analgesia is also reversed by these agents. Perhaps some mixed opioids with low to medium efficacy at both the μ- and κ-receptors, such as nalbuphine and butorphanol, are useful antipruritics because they may partially antagonize μ actions with intact κ actions to maintain analgesic function.[134,135] Recently, ondansetron has been proposed for the treatment of spinal or epidural morphine–induced pruritus.[136] Tenoxicam, a nonsteroidal anti-inflammatory drug, was reported to be effective for pruritus induced by epidural fentanyl.[137] Intravenous administration of droperidol (1.25 mg), propofol (20 mg), or alizapride (100 mg) reduced the incidence of pruritus induced by the use of morphine, 0.2 mg intrathecally, in patients undergoing cesarean section under spinal anesthesia.[138] Histamine release, once thought to underlie this phenomenon, is not causative because non–histamine-releasing opioids also produce pruritus.

Facial itching may not necessarily be a manifestation of direct opioid action at the level of the trigeminal nucleus; instead, it may be a reflection of opioid-triggered neural transmission at a distant site. It is not known why the face is prone to pruritus even after spinal opioids. Interestingly, pruritus secondary to cholestasis is ameliorated by opioid antagonists.[139]

Respiratory Effects of Opioids

The respiratory depressant actions of opioids are their most serious adverse effect. Although significant adverse events related to opioid-induced respiratory depression are presumably preventable, they persist with a perioperative incidence of approximately 0.1% to 1%, no matter what the route of administration.[140] Even though some early studies indicated both μ- and δ-opioid receptor involvement, a recent report demonstrated that activation of the μ-opioid receptor in the caudal medullary raphe region, which is important for pain regulation and respiratory modulation, inhibits the ventilatory response to hypercapnia in anesthetized rats.[141] Furthermore, administration of morphine or M6G did not produce significant respiratory depression in μ-

opioid receptor knock-out mice.[142] Polymorphism of the μ-opioid receptor at nucleotide position 118, which is known to affect M6G-induced analgesia, does not significantly change susceptibility to the respiratory depressive effect of M6G.[8] This result may suggest that analgesia and respiratory depression are mediated by different signal transduction mechanisms activated by the μ-opioid receptor. In dogs, naltrindole, a highly selective antagonist of the δ-opioid receptor, can reverse the sufentanil-induced respiratory depression without significant effect on the analgesic action of sufentanil.[143]

Several studies have reported a depressant effect of morphine on respiratory mucus transport, which is one of the most important defenses against respiratory tract infections. However, morphine had no effect on the beating frequency of nasal cilia in vitro.[144]

Therapeutic Effects

Opioids, by decreasing pain and central ventilatory drive, are effective agents in preventing hyperventilation induced by pain or anxiety.[145,146] The lack of adequate pain relief can also cause postoperative respiratory dysfunction. Opioids can be used as postoperative analgesics to prevent respiratory dysfunction. The antitussive actions of opioids are well known and central in origin. However, fentanyl, sufentanil, and alfentanil curiously elicit a brief cough in up to 50% of patients when injected by intravenous bolus.[147] Fentanyl, administered via a peripheral intravenous cannula, provoked cough when injected rapidly, but the incidence was decreased significantly as the injection time was increased[148] or by the administration of 1.5 mg/kg lidocaine 1 minute before fentanyl administration.[149] In addition, current smokers had a lower incidence of cough than nonsmokers did, whereas heavy smokers did not.

Opioids are also excellent agents for depressing upper airway, tracheal, and lower respiratory tract reflexes, but the mechanism is not clear. Although opioids can affect the contractile responses of airway smooth muscles, the clinical significance and relevance of opioid-induced effects on airway resistance remain controversial.[150] Opioids blunt or eliminate somatic and autonomic responses to tracheal intubation. They allow patients to tolerate endotracheal tubes without coughing or "bucking." Opioids can also help avoid increases in bronchomotor tone in asthma. In addition, fentanyl has antimuscarinic, antihistaminergic, and antiserotoninergic actions and may be more effective than morphine in patients with asthma or other bronchospastic diseases.

Nontherapeutic Effects

Opioids activating the μ-receptor cause dose-dependent depression of respiration, primarily through a direct action on brainstem respiratory centers. How the various respiratory centers involved in the ventilatory drive, respiratory rhythm generation, chemoreception, and neural integration are affected by opioids is unclear.

The stimulatory effect of CO_2 on ventilation is significantly reduced by opioids. The hypercapneic response can be separated into central and peripheral components. Morphine-induced changes in the central component were equal in men and women, whereas changes in the peripheral component were larger in women.[151] In addition, the apneic threshold and resting end-tidal P_{ETCO_2} are increased by opioids (Fig. 27-9). Opioids also decrease the hypoxic ventilatory drive.

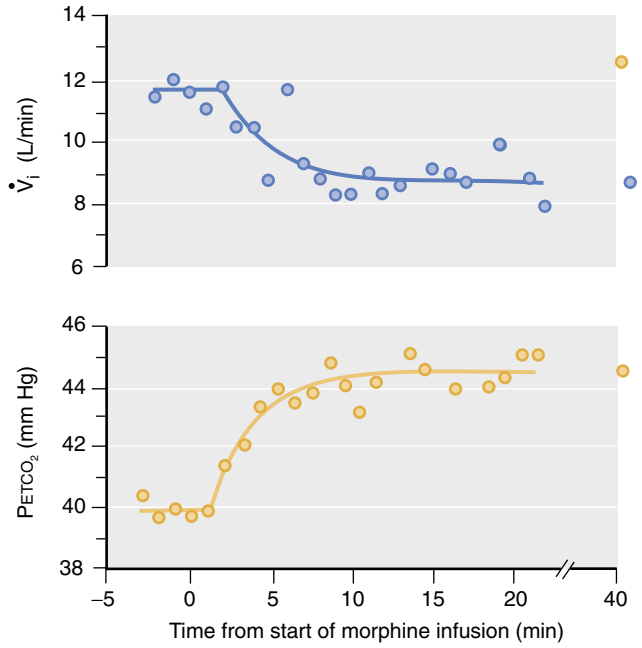


Figure 27-9 Influence of morphine administration (bolus dose of 100 μg/kg given at time t = 0 minutes, followed by a continuous infusion of 30 μg/kg/hr) on resting inspired minute ventilation and resting pressure of end-tidal CO_2 in a single subject. A one-component exponential was fitted to the data. The estimated time constant is 3.0 minutes for the V_I data and 2.6 minutes for the P_{ETCO_2} data. The time delays are between 1 and 2 minutes. *(From Sarton E, Teppema L, Dahan A: Sex differences in morphine-induced ventilatory depression reside within the peripheral chemoreflex loop. Anesthesiology 90:1329-1338, 1999.)*

The respiratory rate is usually drastically slowed in opioid overdose, although a hypoxic CNS insult can counter this effect. The prolonged expiratory time in the respiratory cycle induced by opioids frequently results in greater reductions in respiratory rate than in tidal volume. Monitoring of breath intervals can sensitively detect fentanyl-induced respiratory depression and can be used as a measure of dynamic opioid effect.[152] High doses of opioids usually eliminate spontaneous respirations without necessarily producing unconsciousness. Patients receiving high doses of opioids may still be responsive to verbal command and often breathe when directed to do so.

The peak onset of respiratory depression after an analgesic dose of morphine is slower than after comparable doses of fentanyl: 30 ± 15 minutes versus 5 to 10 minutes. The respiratory depression induced by small doses of morphine usually lasts longer than after equipotent doses of fentanyl. Sufentanil (0.1 to 0.4 μg/kg) produces shorter-lasting respiratory depression and longer-lasting analgesia than fentanyl does (1.0 to 4.0 μg/kg).[153] Plasma fentanyl concentrations of 1.5 to 3.0 ng/mL are generally associated with significant decreases in CO_2 responsiveness. With higher doses of fentanyl (50 to 100 μg/kg), respiratory depression can persist for many hours. When moderately large (20 to 50 μg/kg or greater) doses of fentanyl are used, the potential need for

Box 27-2 Factors Increasing the Magnitude or Duration of Opioid-Induced Respiratory Depression

- High dose
- Sleep
- Old age
- Central nervous system depressant
  - Inhaled anesthetics, alcohol, barbiturates, benzodiazepines
- Renal insufficiency
- Hyperventilation, hypocapnia
- Respiratory acidosis
- Decreased clearance
  - Reduction of hepatic blood flow
- Secondary peaks in plasma opioid levels
  - Reuptake of opioids from muscle, lung, fat, and intestine
- Pain

postoperative mechanical ventilation should be anticipated. The effects of remifentanil, no matter what the dose, are attenuated rapidly and completely within 5 to 15 minutes after termination of its administration. In healthy humans, the median effective concentration (EC_{50}) causing depression of minute ventilation with remifentanil and alfentanil was 1.17 and 49.4 ng/mL, respectively.[154]

Although the mechanism by which pain modulates ventilatory control is unknown, daily clinical practice provides indirect evidence that pain stimulates ventilation, especially during emergence from anesthesia. Combes and colleagues demonstrated that pain relief via a nerve block in knee surgery patients who had previously been treated with morphine PCA increases the incidence of abnormal respiratory events associated with oxygen desaturation.[155]

Naloxone is standard therapy for opioid-induced respiratory depression. However, there have been reports of naloxone-resistant respiratory depression after intrathecal morphine.[156]

Factors Affecting Opioid-Induced Respiratory Depression

Many factors affect the magnitude and duration of opioid-induced respiratory depression (Box 27-2).

Older patients are more sensitive to the anesthetic and respiratory depressant effects of opioids. They experience higher plasma concentrations of opioids when administered on a weight basis. Morphine can produce greater respiratory depression on a weight basis in neonates than in adults because it easily penetrates the brain in neonates and infants with incomplete blood-brain barriers.

The respiratory depressant effects of opioids are increased or prolonged (or both) when administered with other CNS depressants, including the potent inhaled anesthetics, alcohol, barbiturates, benzodiazepines, and most of the intravenous sedatives and hypnotics.[153] Exceptions are droperidol, scopolamine, and clonidine, which do not enhance the respiratory depressant effects of fentanyl or other opioids.[157]

Although opioid action is usually dissipated by redistribution and hepatic metabolism rather than by urinary excretion, the adequacy of renal function may influence the duration of opioid activity. In renal insufficiency, the respiratory depressant properties of the morphine metabolite M6G would become evident as it accumulated. One study indicated that M6G is a somewhat weaker respiratory depressant than morphine is.[158]

Hypocapnic hyperventilation enhances and prolongs postoperative respiratory depression after fentanyl (10 and 25 μg/kg). Intraoperative hypercapnia produces the opposite effects. Possible explanations for these findings include increased brain opioid penetration (increased un-ionized fentanyl with hypocapnia) and removal (decreased CBF with hypocapnia). In patients who hyperventilate because of anxiety or pain, even small intravenous doses of opioids can result in transient apnea because of acute shifts in apneic thresholds.

Delayed or recurring respiratory depression has been reported with most opioids. Mechanisms for this phenomenon may include augmented release of fentanyl or other opioids from skeletal muscle into the systemic circulation on rewarming, shivering, motion, or any other condition that enhances muscle perfusion.

Cardiovascular Effects of Opioids

Large doses of opioids, administered as the sole or primary anesthetic, result in hemodynamic stability throughout the operative period. The choice of opioid can affect the perioperative hemodynamic profile. For example, alfentanil is less reliable than fentanyl and sufentanil in blocking increases in heart rate and blood pressure during induction of anesthesia, sternotomy, sternal spread, and aortotomy in patients with ischemic heart disease who undergo coronary artery surgery.[159]

Neurologic Mechanisms

Key areas of the brainstem that integrate cardiovascular responses and maintain cardiovascular homeostasis are the nucleus solitarius, the dorsal vagal nucleus, the nucleus ambiguus, and the parabrachial nucleus. The nucleus solitarius and parabrachial nucleus play an important role in the hemodynamic control of vasopressin secretion. Enkephalin-containing neurons and opioid receptors are distributed in these regions. Direct administration of μ-agonists into the CNS of animals most commonly, but not always, produces hypotension and bradycardia.[160] In addition, the ventrolateral PAG region, a key central site mediating opioid analgesia, affects hemodynamic control.[161] Opioids can also modulate the stress response through receptor-mediated actions on the hypothalamic-pituitary-adrenal axis. Most opioids reduce sympathetic and enhance vagal and parasympathetic tone. Patients who are intravascularly volume depleted or individuals depending on high sympathetic tone or exogenous catecholamines to maintain cardiovascular function are predisposed to hypotension after the administration of opioids.

The predominant and usual effect of opioids on the heart rate is to produce bradycardia from stimulation of the central

vagal nucleus. Blockade of sympathetic actions may also play a role in opioid-induced bradycardia. Meperidine, in contrast to other opioids, rarely results in bradycardia but can cause tachycardia. Tachycardia after meperidine may be related to its structural similarity to atropine, to normeperidine, its principal metabolite, or to early manifestations of its toxic CNS effects.

Cardiac Mechanisms

The direct cardiac actions of opioids, in particular, the effects on myocardial contractile mechanisms, are significantly less than those of many other intravenous and inhaled anesthetics. However, opioid receptors have been demonstrated in the cardiac myocytes of several species.

Contractility

Some investigators suggest that opioids produce direct positive inotropic effects on the heart.[162] However, others report negative inotropic actions with some agents (meperidine) and no direct effects with others (morphine).[163] Some investigators suggest that local anesthetic–like effects and not receptor-related opioid actions mediate some of the negative inotropic effects of opioids, especially with high drug concentrations.

Morphine decreases Ca^{2+} transients but not cardiac contraction and enhances myofilament Ca^{2+} sensitivity through action on the δ_1-opioid receptor expressed in the heart.[164] In rabbit ventricular myocytes, morphine prolongs the action potential duration by increasing the L-type Ca^{2+} current, an effect mediated by δ- and κ-opioid receptors, and hyperpolarizes cardiac resting membrane potential by increasing the inwardly rectifying K^+ current, which is not mediated by opioid receptors.[165] On the other hand, it was demonstrated that morphine decreases the isometric force of contraction in atrial muscles from nonfailing and failing human hearts through a naloxone-insensitive mechanism.[166] Fentanyl produces little or no change in myocardial contractility.[167] Usually, most hemodynamic variables remain unchanged after large doses of fentanyl. However, fentanyl has positive inotropic effects. Possible mechanisms of the dose-dependent positive inotropic effects of fentanyl, as well as sufentanil, include release of catecholamines or direct myocardial adrenergic activation. Alfentanil, at concentrations achieved in clinical practice, increases contraction in ventricular cells by a mechanism involving an increase in the sensitivity of the contractile apparatus to Ca^{2+}.[168] The negative inotropic effect of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) on ventricular myocytes caused by disruption of sarcoplasmic reticulum Ca^{2+} handling and the Ca^{2+} transient was ameliorated by alfentanil, but this response may not be mediated by opioid receptors.[169] Studies in dogs have demonstrated little change in hemodynamics with moderate doses (160 μg/kg) of alfentanil and transient cardiac stimulation (increases in left ventricular contractility, aortic blood flow velocity, and acceleration) with very large doses (5 mg/kg). In dogs, remifentanil produces hemodynamic effects that include decreases in contractility and cardiac output, as well as reductions in heart rate and blood pressure.[170]

Heart Rate and Rhythm

Opioid-induced bradycardia is primarily mediated by the CNS. Opioids have direct effects on cardiac pacemaker cells. Alfentanil significantly decreased the frequency of contractions of the right atrial–sinoatrial node in a dose-related manner in isolated cardiac tissue from young adult rabbits.[162] Premedication with or concomitant administration of β-adrenergic or Ca^{2+} channel entry blockers can exacerbate the bradycardia and may result in asystole after the administration of opioids. Periods of asystole, 10 to 12 seconds in duration, may resolve on their own, but they usually respond to atropine (0.4 to 0.8 mg IV).

Cardiac Conduction

Fentanyl may depress cardiac conduction by a mechanism mediated by direct membrane actions as opposed to opioid receptor interactions.[171] During induction of anesthesia in patients undergoing coronary artery bypass graft surgery, the QT interval increased significantly after the injection of fentanyl.[172] In contrast, both sufentanil and alfentanil have been demonstrated to be devoid of electrophysiologic effects on the normal or accessory pathways in patients with Wolff-Parkinson-White syndrome.[173,174] Clinically, cardiac conduction disturbances attributable to opioids are rare, but they may be more likely to occur in the presence of Ca^{2+} channel entry or β-adrenergic blockers.

The overall effect of opioid anesthesia is antiarrhythmogenic.[175] It was reported that naloxone, morphine, and levorphanol protected against arrhythmia induced by coronary artery occlusion in rats.[176] A direct effect on ionic currents in cardiac muscle was suggested as the mechanism of the antiarrhythmogenic activity of opioids. It was also reported that opioid antagonists are more antiarrhythmogenic than agonists in rats.[177] Some of the electrophysiologic actions of opioids resemble those of class III antiarrhythmogenic drugs.

Ischemia

Determining the effects and consequences of opioid action on myocardial ischemia is complex because the results can depend on such factors as the species studied and experimental design. Opioids can mimic ischemic preconditioning. Stimulation of the opioid receptor results in a reduction in infarct size similar to that produced by ischemic preconditioning (Fig. 27-10).[178] Although the preconditioning effect of opioids is mediated mainly by cardiac κ- and δ-opioid receptors,[179] part of the protective effect of remifentanil may be produced by μ-agonist activity outside the heart.[180] Late preconditioning, in which cardioprotective effects can be observed 24 hours after drug administration, can also be produced by morphine-induced activation of the opioid receptor in rat hearts.[181] Remote preconditioning by brief ischemia in other distant organs, such as the intestine, kidney and limb, likewise provides cardioprotection that is as effective as classic ischemic preconditioning. The myocardial κ-opioid receptors were demonstrated to mediate cardioprotection by remote preconditioning.[182] Volatile anesthetics may also be capable of protecting against ischemic injury when administered solely on reperfusion. This anesthetic-induced postconditioning can be enhanced by morphine through the activation of phosphatidyl-3-kinase and opioid receptors.[183]

Stimulation of the δ_1-opioid receptor generates oxygen radicals via mitochondrial ATP-sensitive K^+ channels and thereby results in attenuation of oxidant stress and cell death in cardiomyocytes.[184] Involvement of the adenosine A_1 receptor and protein kinase C in the cardioprotective effect of opioids was also suggested.[185,186] Whether the experimental results showing protective effects of opioid against myocardial ischemia will translate into reductions in morbidity and mortality in patients with coronary

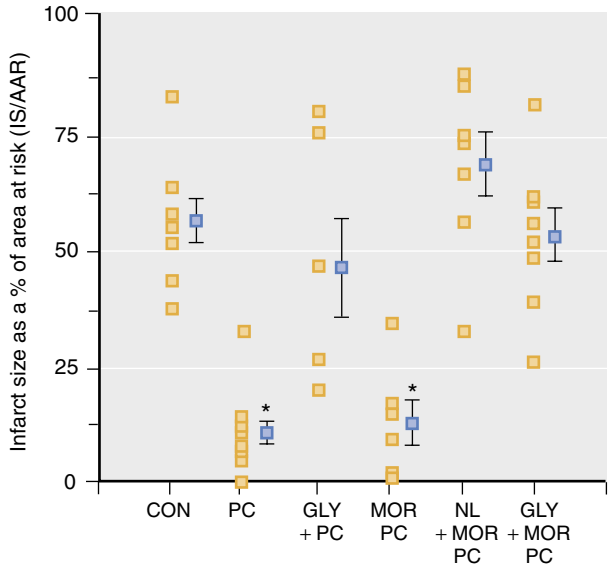


Figure 27-10 Infarct sizes in rat hearts subjected to control conditions (CON), ischemic preconditioning (PC), glibenclamide (0.3 mg/kg intravenously) given 30 minutes before ischemic PC (GLY + PC), morphine-induced PC (3 × 100 μg/kg, 5-minute intravenous infusion) (MOR PC), naloxone (3 mg/kg intravenously) given 10 minutes before morphine-induced PC (NL + MOR PC), and glibenclamide (0.3 mg/kg intravenously) given 30 minutes before morphine-induced PC (GLY + MOR PC). *(From Schultz JE, Hsu AK, Gross GJ: Morphine mimics the cardioprotective effect of ischemic preconditioning via a glibenclamide-sensitive mechanism in the rat heart. Circ Res 78:1100-1104, 1996.)*

artery disease has yet to be established in clinical trials.[187] Clinically, high doses of opioids can maintain myocardial perfusion and the O_2 supply-demand ratio as well as or better than inhalation-based techniques can.[188,189]

Coronary Circulation

Opioids appear to have no significant effect on coronary vasomotion or myocardial metabolism, do not produce steal phenomena, and do not diminish the ability of large coronary arterioles to respond to vasoactive agents.[190] Coronary conductance is regulated by arterial baroreflex control, and a vasodilator response is induced by a rise in aortic pressure. This baroreflex control is enhanced by low plasma concentrations of fentanyl (1 to 2 ng/mL) but appears to be depressed with increasing plasma concentrations of fentanyl.[191] In a study of the effects of opioids and neuroendocrine modulators on porcine coronary arteries, fentanyl, but not sufentanil or morphine, antagonized acetylcholine-induced contractions.[192] The effect of fentanyl was not reversible by naloxone and thus was thought to represent a direct smooth muscle effect.

Circulatory Reflexes

In an experiment examining baroreceptor reflex responses induced by perfusion of the carotid sinus at predetermined levels, baroreceptor reflexes were well preserved with moderate doses of fentanyl, whereas high doses of fentanyl depressed the baroreceptor reflexes.[193] The oculocardiac reflex, which is caused by traction on the extraocular muscles during strabismus surgery, was significantly augmented by fentanyl, sufentanil, and remifentanil.[194] In pediatric patients undergoing strabismus surgery and anesthetized with propofol (12 mg/kg/hr) and alfentanil (0.04 mg/kg/hr), an oculocardiac reflex developed in virtually all patients, and atrioventricular rhythm disorders were frequent.[195]

Histamine Release

Morphine causes release of histamine and sympathoadrenal activation. Codeine and meperidine induce mast cell activation with the release of histamine, probably by a mechanism other than the μ-opioid receptors.[196]

Increases in plasma histamine after morphine cause dilatation of terminal arterioles and direct positive cardiac chronotropic and inotropic actions. The cardiovascular changes after morphine are similar when patients are pretreated with diphenhydramine (histamine H_1-antagonist) or cimetidine (histamine H_2-antagonist). However, in patients pretreated with both H_1- and H_2-antagonists, cardiovascular responses were significantly attenuated despite comparable increases in plasma histamine concentration. Meperidine also causes histamine release more frequently than most other opioids do. Unlike morphine or meperidine, fentanyl, alfentanil, and remifentanil do not produce increases in plasma histamine, and hypotension is less frequent with these opioids.

Vascular Mechanisms

A new pharmacologically defined opioid receptor subtype, designated μ_3, is opiate alkaloid sensitive and opioid peptide insensitive, including peptides previously shown to have affinity for μ-opioid receptors. This receptor is expressed in human endothelial cells and is coupled to vasodilation via production of nitric oxide. Morphine-induced vasodilation may be caused in part by activation of the μ_3-receptor.[197] Pharmacologic studies evaluating alfentanil, fentanyl, and sufentanil in the dog have demonstrated direct peripheral vessel smooth muscle relaxation.[198] Measurement of forearm blood flow after infusion of sufentanil into the brachial artery indicated that sufentanil has a direct vasodilatory effect on human vascular tissue that is probably independent of a neurogenic or systemic mechanism.[199] A supraclinical dose of alfentanil attenuates the phenylephrine-induced contraction via an inhibitory effect on calcium influx by blocking the L-type calcium channels in the rat aortic vascular smooth muscle.[200] Remifentanil can cause transient instability in hemodynamic variables. However, this change may not solely be the result of autonomic or CNS inhibition or centrally mediated vagal stimulation. A pharmacologic study using rat thoracic aortic rings indicated that remifentanil vasodilates by an endothelium-dependent mechanism involving release of prostacyclin and nitric oxide from the endothelium, as well as by an endothelium-independent mechanism probably mediated by suppression of voltage-sensitive Ca^{2+} channels.[201]

Opioids may affect the pulmonary vasculature, as well as the systemic circulation. It was recently shown that phenylephrine-induced contraction of the canine pulmonary artery is mediated primarily by activation of the α_{1B}-adrenergic receptor and is attenuated by fentanyl binding to and directly inhibiting the α_{1B}-adrenergic receptor.[202] Pharmacologic studies in cats have demonstrated that sufentanil and remifentanil have potent vasodepressor activity in the pulmonary vascular bed and that these responses may be mediated by the histamine and opioid receptor–sensitive pathway.[203,204]

Activation of the muscarinic acetylcholine receptors expressed on endothelial cells results in the activation of nitric oxide synthase and release of nitric oxide, which relaxes vascular smooth muscle by activation of 3,5-cyclic guanosine monophosphate. It was shown that fentanyl attenuates acetylcholine-induced relaxation of rat aorta precontracted with phenylephrine via an inhibitory effect at a level proximal to activation of nitric oxide synthase on the pathway involving endothelial M_3 muscarinic receptor activation.[205]

Endocrinologic Effects of Opioids

The main components of the neuroendocrine stress response are the corticotropin-releasing hormone brain centers (e.g., the paraventricular hypothalamic nucleus) and the locus ceruleus–norepinephrine/autonomic nervous system.[206] Increased levels of stress hormones are considered undesirable because they promote hemodynamic instability and intraoperative and postoperative metabolic catabolism. In some circumstances, the hormonal and metabolic responses to surgery are extreme and thought to contribute to operative mortality.[207]

Opioids are capable of reducing the stress response by modulating nociception at several different levels of the neuraxis, as well as by influencing centrally mediated neuroendocrine responses. Opioids are potent inhibitors of the pituitary-adrenal axis.[208] Endogenous opioid peptides may serve as stress hormones themselves and not just as modulators of the secretion of other hormones. This activity is suggested by the finding that β-endorphin and adrenocorticotropic hormone (ACTH) are derived from the same precursor proopiomelanocortin and cosecreted during stress.

Morphine modifies hormonal responses to surgical trauma in a dose-related fashion. Morphine can prevent the release of ACTH, suppress surgically induced increases in plasma cortisol, and attenuate the pituitary-adrenal response to surgical stress. Morphine can increase some stress-responding hormones by increasing plasma histamine release, adrenal medullary release mechanisms, and release of catecholamine from sympathetic nerve endings.

Fentanyl and its congeners are more effective than morphine in modifying hormonal responses to surgery. The efficacy of fentanyl in controlling the hormonal manifestations of the stress response can be dose dependent. Fentanyl doses of 50 μg/kg or greater can help reduce the hyperglycemic response to cardiac surgery in pediatric patients to less than 200 mg/dL throughout surgery.[209] In contrast, neither fentanyl nor sufentanil alone can completely block the sympathetic and hormonal stress responses, and perhaps no dose-response relationship exists for opioid-associated control of the stress response.[71] The stress response to cardiopulmonary bypass (CPB) is difficult to suppress with sufentanil or fentanyl. Alfentanil can suppress increases in plasma cortisol and catecholamines before but not during CPB and may prevent increases in antidiuretic hormone (ADH) and growth hormone throughout coronary artery bypass surgery. A randomized controlled trial showed that remifentanil (0.85 μg/kg/min), when compared with fentanyl (total doses of 15 and 28 μg/kg), blunts the hypertensive responses and cortisol excretion associated with cardiac surgery but is associated with more hypotension.[210]

Stress Reduction and Outcome

Anesthetic techniques or drugs that minimize the stress response may reduce morbidity and mortality in a variety of circumstances. Sufentanil appears to be the most likely opioid to modify stress responses and outcome successfully.[211,212] Anand and Hickey[211] evaluated the impact of sufentanil versus morphine-halothane anesthesia on hormonal and metabolic responses and morbidity and mortality in neonates undergoing cardiac surgery. Most strikingly, a statistically significant difference in postoperative mortality was observed (0 of 30 given sufentanil versus 4 of 15 given halothane plus morphine). Mangano and coauthors[212] also reported that after myocardial revascularization, patients receiving intense postoperative analgesia with sufentanil (1 μg/kg/hr) experience a lower incidence and severity of electrocardiographically documented ischemia than do patients receiving intermittent intravenous morphine (2.2 ± 2.1 mg/hr) for postoperative analgesia. It was also shown that high-dose opioids (remifentanil, 0.85 μg/kg/min, or fentanyl, 28 μg/kg) are associated with a decreased rate of myocardial infarction after cardiac surgery.[210]

Many different hormonal changes induced by surgery have been described. However, the concomitant neural, cellular, immune, and biochemical changes have been less well defined, and little is understood or proven with regard to how modifying hormonal responses alters outcome.[213] Additional studies are necessary for complete elucidation of the relationship between control of surgically induced hormonal responses and outcome.

Opiate Tolerance and Addiction

The mechanisms of dependence and tolerance involve genetic, molecular, cellular, physiologic, and functional factors. In the locus ceruleus, the major noradrenergic nucleus in the brain, long-term opioid exposure results in inhibition of adenylyl cyclase, reduced activity of protein kinase A, and upregulation of the cyclic AMP pathway.[214] The changes in μ-receptor density that occur before or during the development of tolerance do not appear to be essential for the development of opioid tolerance.[215] Possible mechanisms involve protein kinase signal transduction cascades that link extracellular signals to cellular changes by regulating target gene expression. Central glucocorticoid receptors (GRs) have been implicated in the cellular mechanism of neuronal plasticity, which has many cellular steps in common with the mechanism of opioid tolerance. It was shown that the development of tolerance to the antinociceptive effect of morphine was substantially attenuated when a GR antagonist was coadministered with morphine but that the GR agonist dexamethasone facilitated the development of morphine tolerance, suggesting an important role of spinal GRs in the cellular mechanisms of morphine tolerance in rats.[216] Morphine tolerance occurs more rapidly in younger rats than in older rats and is unlikely to be the result of differences in drug metabolism or clearance, an observation suggesting that aging may have an impact on the molecular processes involved in the development of tolerance.[217]

Acute administration of opioids results in analgesia and side effects, whereas tolerance and dependence were thought to occur only after chronic administration. However, tolerance can also develop rapidly after acute opioid exposure in animals and humans.[218-220] Intraoperative remifentanil infusion (0.3 μg/kg/

min) in patients undergoing major abdominal surgery under desflurane anesthesia increased postoperative pain and morphine requirements when compared with low-dose remifentanil (0.1 μg/kg/min), suggesting the development of acute remifentanil tolerance.[221] In contrast, there is a report that target-controlled infusion of alfentanil and remifentanil for postoperative analgesia does not lead to opioid tolerance.[222] In human volunteers, continuous infusion of remifentanil (0.08 μg/kg/min) for 3 hours did not decrease the pain threshold.[223] Thus, the development of acute opioid tolerance in humans remains controversial. Opioids can elicit hyperalgesia in experimental models after repeated opioid administration or continuous delivery.[224] This phenomenon seems to be related to opioid tolerance.[225] In rats, thermal hyperalgesia and mechanical allodynia were observed for several days after cessation of morphine administration (40 mg/kg/day for 6 days).[226] The opioid-induced hyperalgesia is due to spinal sensitization to glutamate and substance P.[227] Furthermore, cholecystokinin and the NMDA–nitric oxide system are responsible for the development of acute tolerance to opioids,[228] which is also affected by spinal serotonin activity.[229] Opioid-induced hyperalgesia and subsequent acute opioid tolerance can be prevented by ketamine, suggesting involvement of the NMDA receptor.[230,231] Methadone is unique in possessing both μ-opioid and NMDA antagonist properties. Opioid-induced hyperalgesia resulted from the presence of *l*-methadone (μ-opioid agonist) in the racemate and was antagonized by the presence of *d*-methadone (NMDA antagonist).[232] Spinal cyclooxygenase-2 (COX-2) is upregulated and release of prostaglandin E_2 in the spinal cord is increased after morphine withdrawal in rats.[233] In humans, hyperalgesia after a 30-minute intravenous infusion of remifentanil (0.1 μg/kg/min) could be prevented by the administration of parecoxib, a COX-2 inhibitor, before the infusion of remifentanil,[234] findings suggesting involvement of COX-2 in opioid-induced hyperalgesia. Genetic analysis in mice suggested that genetic variants of the β_2-adrenergic receptor gene seem to explain some of the differences between various strains of mice in the development of opioid-induced hyperalgesia, and the selective β_2-adrenergic receptor antagonist butoxamine was shown to dose-dependently reverse opioid-induced hyperalgesia.[235] Human data generally support the existence of opioid-induced hyperalgesia in a few specific settings. The conditions under which opioid-induced hyperalgesia is expressed should be clarified and its clinical significance elucidated.[236]

The peripheral effects of morphine have been suggested to be less prone to tolerance.[237] Thus, the method and schedule of drug administration may also affect the development of tolerance.[238] However, modifying an opioid administration schedule to modulate the development of tolerance may not always be useful or effective.[239] Certain patients may appear to be tolerant to opioids but instead suffer from pathophysiologic conditions that are poorly responsive to opioids, such as neuropathies.[240]

Management of Opioid-Dependent Patients

A variety of problems should be taken into consideration in the anesthetic management of opioid-dependent patients.[241] Complications in opioid-addicted patients include cardiopulmonary problems, renal problems, and anemia. Long-term morphine administration causes adrenal hypertrophy and impairs corticosteroid secretion. Viral and nonviral hepatitis, acquired immunodeficiency syndrome, osteomyelitis, muscle weakness, and neurologic complications may be found in addicted patients. Anesthetic management of an opiate-dependent or opiate-addicted patient should include adequate premedication with opioids, administration of supplemental intraoperative and postoperative opioids, and provision of nonopioid analgesics and neural blockade. There is no ideal anesthetic approach for a chronic addict or a patient with an acute opiate overdose. Support of the circulatory system with fluids and monitoring of arterial blood gases and pulmonary function are also important.

Recently, rapid detoxification with a high dose of naloxone or naltrexone has been reported for the treatment of opioid addiction. For such treatment, general anesthesia is induced before the start of opioid antagonism and maintained for several hours to prevent the perception of withdrawal symptoms by the patient.[242,243] Blockade of μ-opioid receptors by naloxone (total dose of 12.4 mg) in opioid-addicted patients induces sympathetic neural activation, including an increase in plasma catecholamine concentration and cardiovascular stimulation, which is abolished by α_2-agonists.[244]

Renal and Urodynamic Effects of Opioids

μ-Receptor activation causes antidiuresis and decreases electrolyte excretion. κ-Receptor stimulation predominantly produces diuresis with little change in electrolyte excretion. The stable dynorphin analog E-2078 causes κ-mediated diuretic effects in the isolated perfused rat kidney.[245] Indirect actions may involve inhibiting or altering the secretion of ADH and atrial natriuretic peptide.[246] The absence of increases in plasma ADH, renin, and aldosterone indicates that fentanyl, sufentanil, alfentanil, and probably remifentanil most likely preserve or minimally alter renal function in humans. If renal function does change during opioid anesthesia and surgery, it is probably due to secondary changes in systemic and renal hemodynamics.

The mechanism by which opioids cause urinary retention is incompletely understood. Effects of opioids on the lower urinary tract include disturbances in micturition characterized by urinary retention, especially after intrathecal opioid administration. Intrathecal administration of morphine and sufentanil caused dose-dependent suppression of detrusor contractility and decreased sensation of urge.[247] Mean times to recovery of normal lower urinary tract function were 5 and 8 hours after 10 and 30 μg sufentanil and 14 and 20 hours after 0.1 and 0.3 mg morphine, respectively. Not all opioid agonists behave similarly, and morphine appears to be particularly potent with regard to producing urodynamic problems. Malinovsky and associates compared the urodynamic effects of intravenously administered morphine (10 mg), buprenorphine (0.3 mg), fentanyl (0.35 mg), and nalbuphine (20 mg).[248] All of the opioids altered bladder sensation, but detrusor contraction decreased only after the administration of fentanyl and buprenorphine. Urinary retention induced by intravenous infusion of remifentanil, 0.15 μg/kg/min, could be reversed by a single intravenous dose of methylnaltrexone, 0.3 mg/kg, or naloxone, 0.01 mg/kg.[249] Reversal of urinary retention by methylnaltrexone indicates that peripheral mechanisms may play a role in opioid-induced bladder dysfunction.

Gastrointestinal Effects of Opioids

Opioids decrease gastrointestinal motility,[250] and this action underlies their use as antidiarrheal agents. Patients receiving parenteral opioid therapy preoperatively are more likely to have "full stomachs" regardless of their "NPO" status.

Several opioid receptor types can be demonstrated on myenteric neurons, and both κ- and μ-receptor agonists regulate cholinergic transmission in the myenteric plexus. κ-Agonists appear to modulate release of acetylcholine more potently than μ-agonists do by inhibition of N-type voltage-sensitive Ca^{2+} channels via a pertussis toxin–sensitive G protein in guinea pig ileum.[251]

The effect of morphine on esophageal motility has not been explored very extensively. Morphine (80 μg/kg) increased the velocity but did not alter the amplitude or duration of primary peristalsis of the esophagus, and it decreased the duration and magnitude of swallow-induced relaxation of the lower esophageal sphincter.[252] Gastric emptying is delayed by opioids via supraspinal (vagus nerve–mediated) and spinal as well as peripheral mechanisms. Intrathecal morphine (0.4 mg) significantly decreased gastroduodenal propagation velocity and acetaminophen absorption, and intramuscular morphine (4 mg) resulted in additional effects.[253] Tramadol (1.25 mg/kg IV) has a measurable but smaller inhibitory effect on gastric emptying than codeine (1 mg/kg IV) and morphine (0.125 mg/kg IV) do.[254] Opioids administered epidurally as well as intrathecally reduce gastrointestinal motility.[255,256] It was reported that translocation of enteric microorganisms from the intestinal tract to extraintestinal sites is promoted by reduction of gut propulsion after morphine treatment in rats.[257] Propofol (0.3- mg/kg bolus and 1.0 mg/kg/hr) abolished the decrease in gastric tone induced by morphine (0.1 mg/kg IV) but did not abolish morphine-induced delay of gastric emptying.[258]

Naloxone reverses opioid-induced delays in gastric emptying. Methylnaltrexone, a quaternary naloxone derivative that does not cross the blood-brain barrier, can attenuate morphine-induced delays in gastric emptying, thus suggesting that a peripheral mechanism is involved in the opioid effect on the gastrointestinal tract.[250] Naloxone (0.7 mg/kg) significantly inhibited gastric emptying of saline and milk in rats.[259] This observation might suggest that opioids can affect the gastrointestinal tract by a mechanism independent of the opioid receptors. Intravenous, but not intramuscular metoclopramide (10 mg) can also reverse morphine-induced delays in gastric emptying.[260]

Opioid effects on the intestine are complex. Transit time from the mouth to the ileum may not be significantly altered by morphine because morphine enhances ileal propulsion before decreasing motility. Opioids increase tone and decrease propulsive activity in most of the intestine. In rats, pretreatment with epidural or intraperitoneal morphine can attenuate ischemia-induced inhibition of bowel motility.[261]

Biliary and Hepatic Effects

Opioid agonists increase biliary duct pressure and sphincter of Oddi (choledochoduodenal sphincter) tone in a dose- and drug-dependent manner through opioid receptor–mediated mechanisms. However, the clinical consequences of opioid-induced biliary tract actions are usually minimal. Although traditional teaching dictates that morphine induces "spasm" in the sphincter of Oddi and should not be used in patients with acute pancreatitis, no studies or evidence exists to indicate that morphine is contraindicated for use in acute pancreatitis.[262] Increases in biliary pressure caused by opioids are, with the exception of meperidine, reversible with naloxone. Oddi sphincter manometry via choledochoscopy demonstrated that the regular dose of morphine could increase common bile duct pressure, whereas pethidine had no effect and tramadol inhibited motility of the sphincter of Oddi.[263] Fragen and colleagues studied the effect of remifentanil (0.1 μg/kg/min) on the flow of dye from the gallbladder into the duodenum and showed that remifentanil delays the drainage of dye from the gallbladder into the duodenum but the delay is shorter than that reported after morphine or meperidine.[264] Opioids produce minimal effects on liver function during anesthesia and surgery.

Nausea and Vomiting

Postoperative nausea/vomiting is a serious problem that often embarrasses patients and anesthesiologists (also see Chapter 86).[265,266] The cause, treatment, and prevention of postoperative nausea and vomiting have been investigated extensively (Fig. 27-11).[267] Intraoperative use of opioids is a well-known risk factor for postoperative nausea and vomiting. Opioids stimulate the chemoreceptor trigger zone in the area postrema of the medulla, possibly through δ-receptors, and thereby lead to nausea and vomiting. When compared with approximately equipotent doses of fentanyl and sufentanil, alfentanil is associated with a lower incidence of postoperative nausea and vomiting.[268]

The use of propofol in balanced or total intravenous anesthesia (TIVA) significantly reduces the incidence of opioid-induced nausea and vomiting.[269] The incidence of postoperative nausea and vomiting can be as low as 5% to 20% after propofol-alfentanil anesthesia.

When opioids are administered, antiemetic prophylaxis should be considered, including drugs with anticholinergic activity, butyrophenones, dopamine antagonists, serotonin antagonists, and acupressure. Ondansetron, a serotonin type 3 receptor antagonist, was found to be effective for postoperative opioid-induced nausea and vomiting.[270] Nausea and vomiting after epidural morphine (3 mg) for post–cesarean section analgesia could be prevented by dexamethasone (8 mg IV) as efficiently as droperidol (1.25 mg IV).[271] Cannabinoid receptor agonists have been demonstrated to be effective antiemetics in some clinical settings. Animal experiments have shown that the cannabinoid agonist suppresses opioid-induced retching and vomiting by activation of the cannabinoid CB1 receptor.[272]

Other Opioid Effects

Obstetrics

Alfentanil and pethidine have been used safely as analgesics during the harvesting of human oocytes for subsequent in vitro

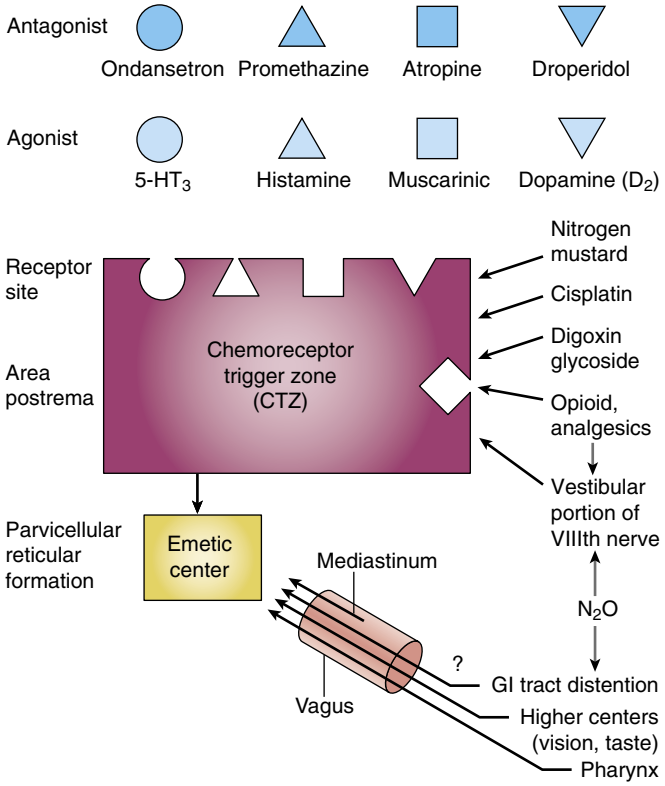


Figure 27-11 The chemoreceptor trigger zone and the emetic center with the agonist and antagonist sites of action of various anesthetic-related agents and stimuli. GI, gastrointestinal. *(From Watcha MF, White PF: Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 77:162-184, 1992.)*

fertilization.[273,274] The teratogenic actions of opioids, including fentanyl, sufentanil, and alfentanil, appear to be minimal, at least in animal models.

Parenteral administration of opioids before delivery remains a commonly used method of analgesia (also see Chapter 69). Nociception as a result of uterine cervical distention could be suppressed by μ- and κ-agonists in rats,[275] but the analgesic effect of μ-agonist but not κ-agonist was reduced by estrogen.[276] Aortocaval compression and associated hypotension may be exacerbated by parenteral opioids, especially after the use of morphine or meperidine. Fatal manifestations of maternal opioid administration include decreases in heart rate variability. Adverse neonatal effects can occur after the administration of either morphine or meperidine to mothers. Fetal acidosis increases transfer of opioid from the mother. Attempts to minimize the neonatal effects of opioids include restricting opioid administration to the first stage of labor. The short-acting opioid alfentanil administered before cesarean delivery attenuated the maternal stress response but led to a slightly reduced Apgar score.[277]

In sheep, neither intravenous nor epidural injection of sufentanil (50 μg) affected maternal mean arterial pressure, uterine blood flow, maternal heart rate, fetal mean arterial pressure, fetal heart rate, or blood gases and acid-base status in the mother and fetus.[278] Because the fetus is capable of pain perception after the 26th week of gestation, adequate postoperative fetal pain management is essential after fetal surgery. It was shown that the sheep fetus absorbs sufentanil after intra-amniotic instillation and that significantly greater plasma concentrations were achieved in the fetal lamb than in the ewe.[279]

Morphine and meperidine have been found in the breast milk of mothers receiving intravenous opioid analgesia.[280,281] Although both fentanyl and morphine are concentrated in breast milk in milk-to-plasma ratios of 2:1 to 3:1, newborn exposure is reported to be insignificant. Newborns of addicted mothers can exhibit opioid withdrawal and require observation and appropriate treatment.[282]

Anaphylactoid Reactions

True allergic reactions and systemic anaphylactoid reactions to opioids are rare. More commonly, local reactions caused by preservatives or histamine may occur. In 32% of heroin addicts dying suddenly after injection, the concentration of tryptase was elevated (>10 μg/L), but no correlation was found between IgE levels and tryptase, thus supporting the hypothesis that mast cell degranulation was not mediated by allergic reaction.[283] This report suggests that many heroin fatalities are caused by an anaphylactoid reaction.

Ocular Effects

The use of fentanyl, sufentanil, and alfentanil during induction of anesthesia can help prevent increases in intraocular pressure (see Chapter 75). Fentanyl, alfentanil, and sufentanil doses as low as 2.5, 10, and 0.1 μg/kg, respectively, may be sufficient as long as appropriate anesthetic depth is achieved before tracheal intubation. Remifentanil (1 μg/kg) combined with propofol (2 mg/kg) or thiopental (5 mg/kg) is effective for prevention of changes in intraocular pressure after succinylcholine and tracheal intubation.[284,285]

Immune Effects

It is now firmly established that opioids influence immune regulation. Direct effects of opioid agonists include modulation of immune cellular activity, as well as modulation of specific enzymatic degradation and regulation processes.[286] Several immune cell populations, including T cells, macrophages, and natural killer (NK) cells, serve as targets for the effects of opioids. It was shown that maximal suppression of NK cell activity, proliferation of splenic T and B cells, and interferon-γ production are observed 0.5 to 1 hour after the injection of 15 mg/kg morphine into rats.[287] The time course was nearly concordant with the antinociceptive effect of morphine. Postoperative administration of morphine (10 mg intramuscularly [IM]) did not significantly affect NK cell activity, whereas tramadol (100 mg IM) did enhance NK cell activity.[288] It was reported that intravenously administered fentanyl causes a rapid increase in NK cell cytotoxicity, which was coincident with an increase in the percentage of $CD16^+$ and $CD8^+$ cells in peripheral blood.[289] When compared with fentanyl (1000 μg), administration of morphine (40 mg) as part of a balanced anesthetic technique suppressed several components of the inflammatory response (IL-6, CD11b, CD18, postoperative hyperthermia) to cardiac surgery and CPB.[290]

Table 27-5 Physicochemical and Pharmacokinetic Data for Commonly Used Opioid Agonists

	Morphine	Meperidine	Fentanyl	Sufentanil	Alfentanil	Remifentanil
pK_a	8.0	8.5	8.4	8.0	6.5	7.1
% Un-ionized at pH 7.4	23	<10	<10	20	90	67?
Octanol-H_2O partition coefficient	1.4	39	813	1778	145	17.9
% Bound to plasma protein	20-40	39	84	93	92	80?
Diffusible fraction (%)	16.8	2.2	1.5	1.6	8.0	13.3?
$t_{½\alpha}$ (min)	1-2.5	—	1-2	1-2	1-3	0.5-1.5
$t_{½\beta}$ (min)	10-20	5-15	10-30	15-20	4-17	5-8
$t_{½\gamma}$ (hr)	2-4	3-5	2-4	2-3	1-2	0.7-1.2
Vd_c (L/kg)	0.1-0.4	1-2	0.4-1.0	0.2	0.1-0.3	0.06-0.08
Vd_{ss} (L/kg)	3-5	3-5	3-5	2.5-3.0	0.4-1.0	0.2-0.3
Clearance (mL/min/kg)	15-30	8.18	10-20	10-15	4-9	30-40
Hepatic extraction ratio	0.6-0.8	0.5-0.7	0.8-1.0	0.7-0.9	0.3-0.5	NA

$t_{½}$ α, β, γ are the half-lives of a three-compartment model; Vd_c, volume of distribution of the central compartment; Vd_{ss}, volume of distribution at steady state.
From Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. *In* Miller RD (ed): Anesthesia, 5th ed. New York, Churchill Livingstone, 2000, p 312.

As a potential mechanism of the immunosuppressive effects of morphine, it was demonstrated that activation of the nuclear factor NF-κB by an inflammatory stimulus was inhibited by morphine-induced activation of μ_3-opioid receptors in a nitric oxide–dependent manner.[291] Several investigators have independently reported direct effects of morphine on apoptosis in cultured human peripheral blood lymphocytes, which may result in compromised immune function.[292,293] However, there is also a report that morphine has no effect on apoptosis-related molecules and does not promote apoptosis of human peripheral blood lymphocytes.[294]

Pharmacokinetics and Pharmacodynamics of Opioids

With the advent of modern drug assay technology and the widespread availability of computers, it is now possible to analyze pharmacologic data with combined pharmacokinetic-pharmacodynamic models to separate drug response into its pharmacokinetic and pharmacodynamic components. Pharmacokinetic parameters govern the relationship between opioid dose and opioid concentrations in blood (or other body fluid). Pharmacodynamic parameters describe the relationship between the opioid concentration in blood (or other fluid) and opioid effect.

Physicochemical Properties

Opioids are weak bases. When dissolved in solution, they are dissociated into protonated and free-base fractions, with the relative proportions depending on the pH and pK_a. The free-base fraction is more lipid soluble than the protonated fraction. High lipid solubility facilitates transport of opioid into the biophase or site of action. Therefore, highly lipid-soluble opioids have a more rapid onset of action. However, because the opioid receptor "recognizes" an opioid molecule in the protonated form, the intensity of opioid effects is closely related to the ionized concentration of drug in the biophase.

All opioids are to some extent bound to plasma proteins, including albumin and α_1-acid glycoprotein. It is only the un-ionized, unbound fraction that constitutes the diffusible fraction and provides the concentration gradient that promotes diffusion of opioid from blood to the tissue of interest. Thus, the speed of onset of opioid effect is affected by both lipid solubility and protein binding.

Common Pharmacokinetic Features of Opioids

Representative pharmacokinetic parameters for the opioids commonly used in anesthesia are displayed in Table 27-5.

After intravenous injection, arterial plasma concentrations of opioids rise to a peak within one circulation time. Thereafter, they exhibit a rapid redistribution phase and a slower elimination phase typical of drugs whose pharmacokinetics is described by compartmental models. After administration into a central compartment, opioids are either eliminated from the central compartment (by excretion or biotransformation) or distributed to peripheral compartments. In general, opioids are cleared from plasma by biotransformation in the liver. However, extrahepatic metabolism is important for some opioids.

As a rule, because of their high lipid solubility, opioids are widely distributed in body tissues. In pharmacokinetic terms, this means that opioids typically have a high apparent volume of distribution at steady state. Because opioids are distributed so widely and so rapidly to various body tissues, redistribution has a prominent impact on the decline in opioid concentration, particularly

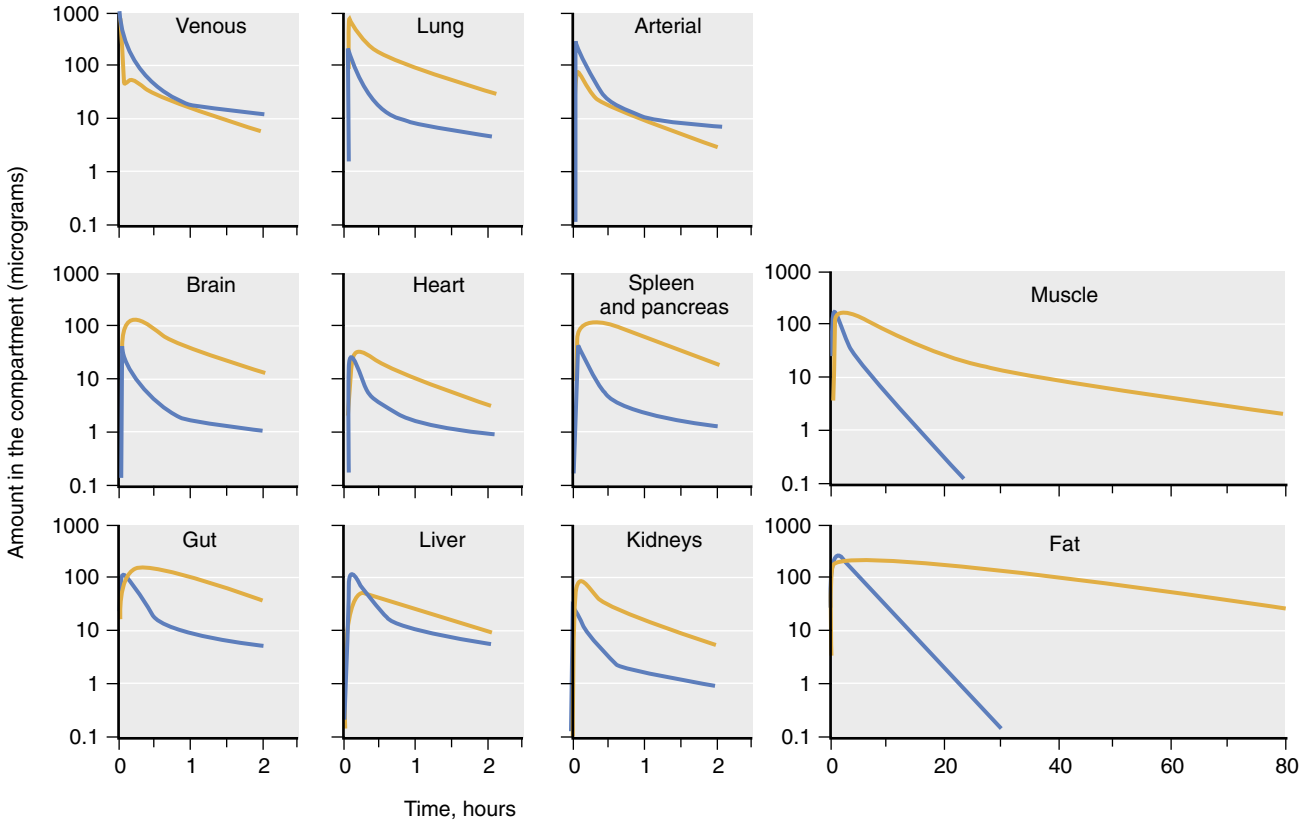


Figure 27-12 Computer simulations of the amounts of fentanyl (*yellow lines*) or alfentanil (*blue lines*) in various organs and tissues in a 70-kg human after a bolus intravenous injection of 1 mg of each drug. *(From Bjorkman S, Stanski DR, Verotta D, Harashima H: Comparative tissue concentration profiles of fentanyl and alfentanil in humans predicted from tissue/blood partition data obtained in rats. Anesthesiology 72:865-873, 1990.)*

in the early period after injection. Figure 27-12 shows a computer simulation of opioids in various organs. The difference in physicochemical properties between fentanyl and alfentanil causes the marked overall difference in disposition. Distribution to muscle and fat is extensive and declines slowly because of limited blood flow.

Opioid uptake by the lung has a significant implication in opioid pharmacokinetics. The time necessary to reach the peak concentration of an opioid is influenced by the degree of pulmonary uptake. Pulmonary uptake of fentanyl is more extensive than the pulmonary uptake of alfentanil, which may be explained by the difference in sequestration into pulmonary endothelial cells. Pulmonary uptake of opioids can affect the pharmacokinetics of other drugs. It was shown that pulmonary uptake of propofol is significantly reduced by the administration of fentanyl 30 seconds before the injection of propofol in cats.

Pharmacokinetic Features of Individual Drugs

Morphine

Morphine pharmacokinetics is notably different from that of the fentanyl congeners. This difference is due in large part to morphine's comparatively low lipid solubility. There is relatively little transient first-pass uptake of morphine by the lung.

The pK_a of morphine (8.0) is greater than physiologic pH, and thus after intravenous injection only a small fraction (10% to 20%) of morphine is un-ionized. Penetration of morphine into and out of the brain is presumably slower than that of other opioids. Approximately 20% to 40% of morphine is bound to plasma proteins, mostly albumin.

Morphine is principally metabolized by conjugation in the liver, but the kidney plays a key role in the extrahepatic metabolism of morphine. Morphine-3-glucuronide (M3G) is the major matabolite of morphine, but it does not bind to opioid receptors and possesses little or no analgesic activity. M3G may actually antagonize morphine, and this effect may contribute to both variability in response and resistance to morphine analgesic therapy. M6G accounts for nearly 10% of the morphine metabolite; it is a more potent μ-receptor agonist than morphine is and has a similar duration of action. It was reported that M6G contributes substantially to morphine's analgesic effects, even in patients with normal renal function. Especially in patients with renal dysfunction, accumulation of M6G can lead to an increased incidence of adverse effects, including respiratory depression. A recent report suggested that a single-nucleotide polymorphism at the μ-opioid receptor affects the susceptibility to M6G-related opioid toxicity. Because the hepatic extraction ratio of morphine is high, the bioavailability of orally administered morphine is significantly lower (20% to 30%) than after intramuscular or subcutaneous injection. It appears that M6G is in fact the primary active compound when morphine is administered orally (Fig. 27-13). In contrast to

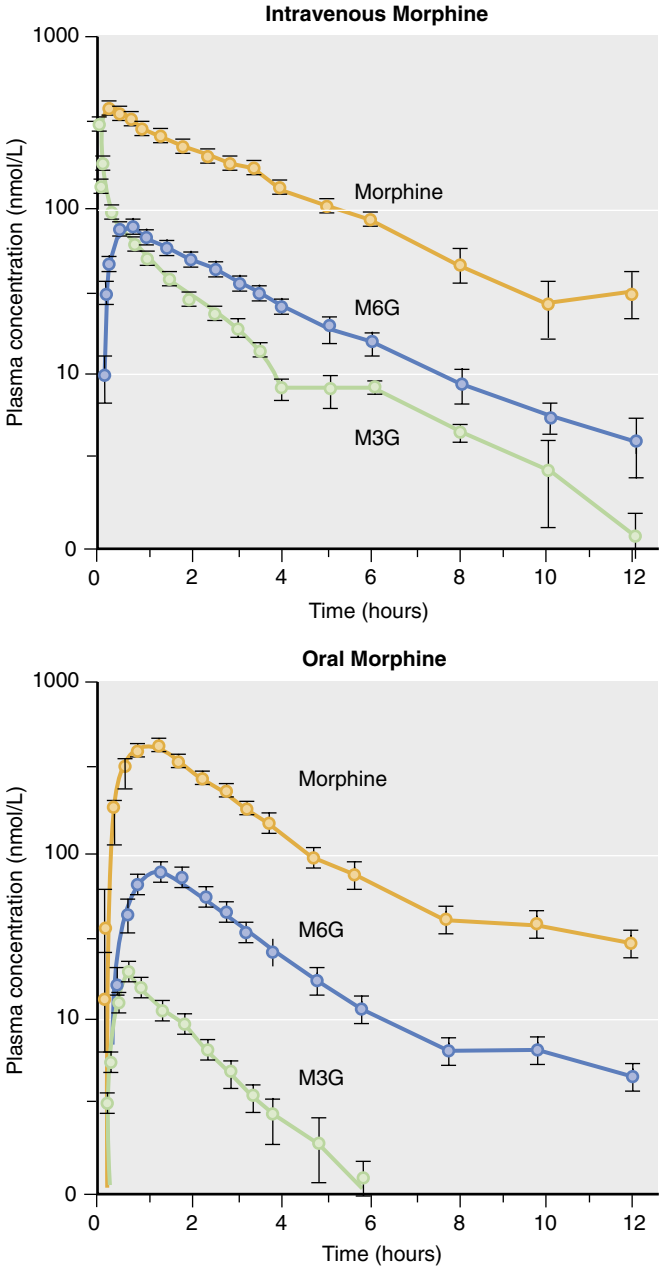


Figure 27-13 Mean plasma concentrations (± SEM) of morphine, morphine-6-glucuronide (M6G), and morphine-3-glucuronide (M3G) after intravenous and oral administration of morphine. *(From Osborne R, Joel S, Trew D, Slevin M: Morphine and metabolite behavior after different routes of morphine administration: Demonstration of the importance of the active metabolite morphine-6-glucuronide. Clin Pharmacol Ther 47:12-19, 1990.)*

reports suggesting a high potency of M6G, others have shown that short-term intravenous administration of M6G does not provide effective analgesia.

Meperidine

Unlike morphine, after intravenous injection, first-pass uptake of meperidine by the lungs is approximately 65%. Meperidine is more highly bound to plasma proteins than morphine is, principally (70%) to α_1-acid glycoprotein. As with morphine, a relatively high hepatic extraction ratio results in biotransformation that is dependent on hepatic blood flow. Normeperidine, the major metabolite, has analgesic activity and is roughly twice as potent as meperidine in producing seizures in animals. The elimination half-life of normeperidine is considerably greater than that of meperidine, and thus repeated doses can easily cause this toxic metabolite to accumulate in patients with renal disease and potentially produce seizures.

Fentanyl

A three-compartment model is typically used to describe decay of plasma fentanyl concentrations. The lungs exert a significant first-pass effect and transiently take up approximately 75% of an injected dose of fentanyl. Approximately 80% of fentanyl is bound to plasma proteins, and significant amounts (40%) are taken up by red blood cells. Fentanyl is relatively long acting, in large part because of this widespread distribution in body tissues.

Fentanyl is primarily metabolized in the liver by *N*-dealkylation and hydroxylation. Metabolites begin to appear in plasma as early as 1.5 minutes after injection. Norfentanyl, the primary metabolite, is detectable in urine for up to 48 hours after intravenous fentanyl in humans.

Alfentanil

After intravenous injection, plasma concentrations of alfentanil are described by either a two-compartment or a three-compartment model. Alfentanil is bound to plasma proteins (mostly glycoproteins) in higher proportions (90%) than fentanyl is. At physiologic pH, it is mostly (90%) un-ionized because of its relatively low pK_a (6.5). Thus, despite more intense protein binding, alfentanil's diffusible fraction is higher than that of fentanyl. This explains, in part, its short latency to peak effect after intravenous injection.

The main metabolic pathways of alfentanil are similar to those of sufentanil and include oxidative *N*-dealkylation and *O*-demethylation, aromatic hydroxylation, and ether glucuronide formation. The degradation products of alfentanil have little, if any, opioid activity. Human alfentanil metabolism may be accomplished predominantly, if not exclusively, by cytochrome P450 3A3/4 (CYP3A3/4). This enzyme is known to display at least an eightfold difference in activity in humans. Alfentanil is also metabolized by human liver microsomal CYP3A5, which shows more than 20-fold pharmacogenetic variability in expression and thus results in significant differences in human liver alfentanil metabolism. An in vitro study demonstrated that propofol in clinically relevant concentrations interferes with oxidative metabolic degradation of alfentanil and sufentanil in the microsomal fraction of pig and human liver.

Sufentanil

The pharmacokinetic property of sufentanil is adequately described by a three-compartment model. After intravenous injection, first-pass pulmonary extraction, retention, and release are similar to those of fentanyl. The pK_a of sufentanil at physiologic pH is the same as that of morphine (8.0), and therefore only a small amount (20%) exists in the un-ionized form. Sufentanil is twice as lipid soluble as fentanyl and is highly bound (93%) to plasma proteins, including α_1-acid glycoprotein.

The major metabolic pathways of sufentanil include *N*-dealkylation, oxidative *O*-demethylation, and aromatic hydroxylation. Major metabolites include *N*-phenylpropanamide.

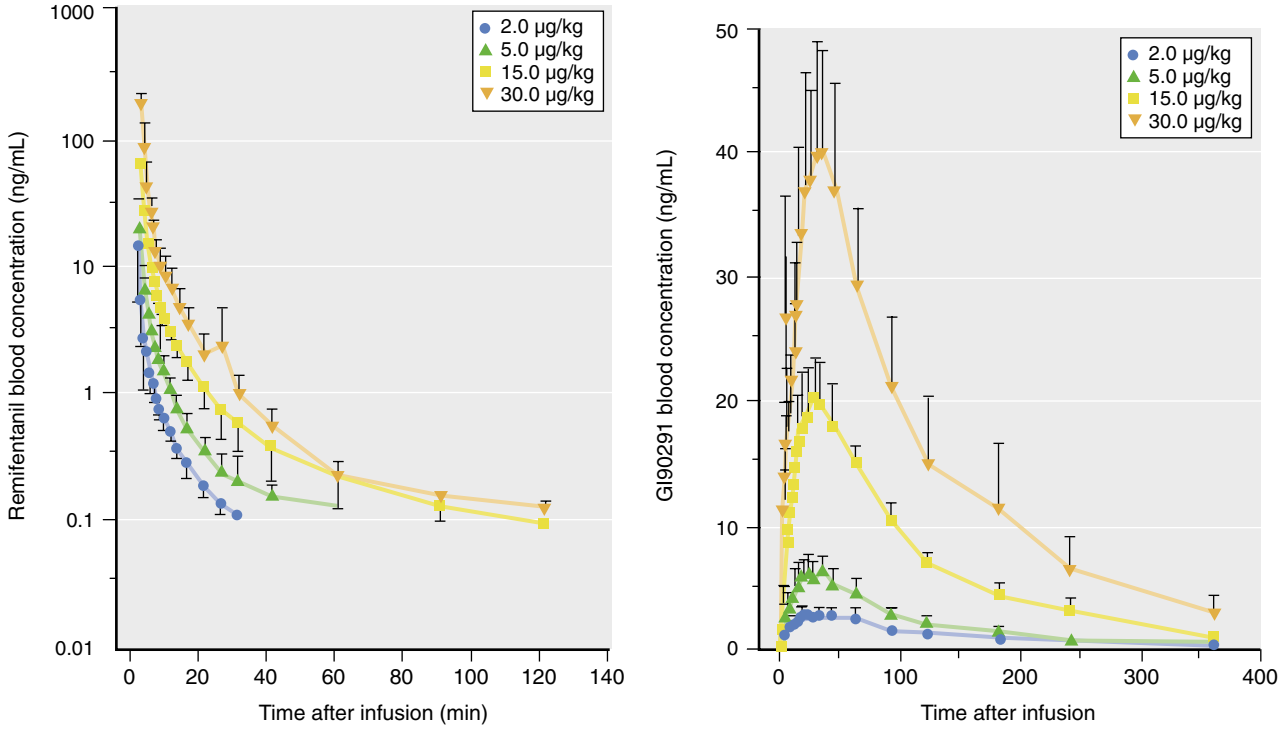


Figure 27-14 Mean (± SD) blood concentration-time curves of remifentanil and its metabolite GI90291 after a 1-minute transfusion of remifentanil of 2, 5, 15, and 30 µg/kg; $n = 6$ for each dose. *(From Westmoreland CL, Hoke JF, Sebel PS, et al: Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. Anesthesiology 79:893-903, 1993.)*

Remifentanil

Although chemically related to the fentanyl congeners, remifentanil is structurally unique because of its ester linkages. Remifentanil's ester structure renders it susceptible to hydrolysis by blood- and tissue-nonspecific esterases, which results in rapid metabolism and rapid reduction of blood concentrations after cessation of infusion (Fig. 27-14). Remifentanil thus constitutes the first "ultrashort"-acting opioid for use as a supplement to general anesthesia.

The pharmacokinetic properties of remifentanil are best described by a three-compartment model.[88] Its clearance is several times more rapid than normal hepatic blood flow, consistent with widespread extrahepatic metabolism. However, remifentanil is not significantly metabolized or sequestered in the lungs. It is a weak base with a pK_a of 7.07. It is highly lipid soluble with an octanol-water partition coefficient of 19.9 at pH 7.4. Remifentanil is highly bound (70%) to plasma proteins (mostly α_1-acid glycoprotein). The remifentanil free base is formulated with glycine. Because glycine has been shown to act as an inhibitory neurotransmitter that causes a reversible motor weakness when injected intrathecally into rodents, remifentanil is not approved for spinal or epidural use.

The primary metabolic pathway of remifentanil is de-esterification to form a carboxylic acid metabolite, GI90291 (Fig. 27-15), which is 0.003 to 0.001 times as potent as remifentanil. The low in vivo potency of GI90291 can be explained by low affinity to the µ-receptor in combination with poor brain penetration. Excretion of GI90291 is dependent on renal clearance mechanisms. Evidence from dogs suggests that the remifentanil metabolites are, for practical purposes, completely inactive, even in patients with renal failure. Its pharmacokinetics is not appreciably influenced by renal or hepatic failure. In blood, remifentanil is metabolized primarily by enzymes within erythrocytes. Remifentanil is not a good substrate for pseudocholinesterase and therefore is not influenced by pseudocholinesterase deficiency.

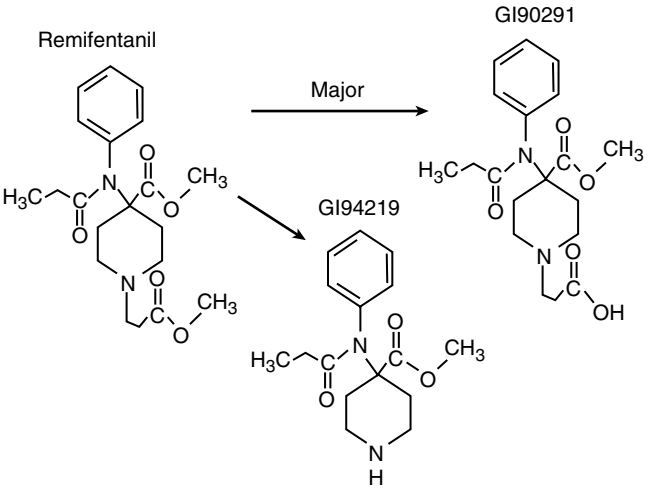


Figure 27-15 Metabolic pathway of remifentanil. De-esterification by nonspecific plasma and tissue esterases to form a carboxylic acid metabolite (GI90291) that has only 1/300 to 1/1000 the potency of the parent compound is the primary metabolic pathway. *N*-Dealkylation of remifentanil to GI94219 is a minor metabolic pathway. *(From Egan TD, Lemmens HJ, Fiset P, et al: The pharmacokinetics of the new short-acting opioid remifentanil [GI87084B] in healthy adult male volunteers. Anesthesiology 79:881-892, 1993.)*

Computerized Delivery Methods in Clinical Practice

Advances in pharmacokinetic modeling and infusion pump technology have made it possible to administer opioids (and other drugs) via a computer-controlled infusion pump (CCIP).[295] The physician operating a CCIP designates a target concentration to achieve rather than specifying an infusion rate. The CCIP then calculates the necessary infusion rates to achieve the targeted concentration.

Delivery of an opioid via a CCIP requires a different approach by clinicians. Rather than setting an infusion rate based on clinical experience and literature recommendations, the anesthesiologist using a CCIP designates a target concentration, and the CCIP calculates the infusion rates necessary to achieve the concentration over time. It has been reported that target-controlled infusion of alfentanil and remifentanil was useful for intraoperative and postoperative analgesia.[296,297] Successful use of a CCIP thus requires knowledge of the therapeutic concentrations appropriate for the clinical setting.

Surrogate Measures of Opioid Potency

Because a high-resolution measure of analgesia is not available, opioid potencies are usually estimated by some surrogate measures. Reduction of the MAC required to produce lack of movement to skin incision has been a frequently used surrogate measure for estimation of opioid potency (Fig. 27-16).[90,92] However, the MAC is not useful as a surrogate measure of opioid potency outside the operating room.

The EEG has been another widely used surrogate measure in estimating opioid potency.[89] The EEG is advantageous because it is noninvasive and can be used as an effect measure when an experimental subject is unconscious or apneic. When processed by Fourier spectral analysis, the raw changes on the EEG translate into a significant decrease in the value of the spectral edge, a parameter that quantitates the frequency below which a given percentage (usually 95%) of the power in the signal of the EEG is found. Although the clinical meaning of the changes on the EEG produced by opioids is unclear, the opioid potencies estimated by using the EEG as a surrogate measure appear to be clinically reliable because they relate to clinically determined potencies in a proportional, reproducible fashion.

For opioids, because the surrogate measures do not always assess the drug effect of clinical interest (analgesia), estimations of potency based on surrogate measures must be interpreted with some caution.

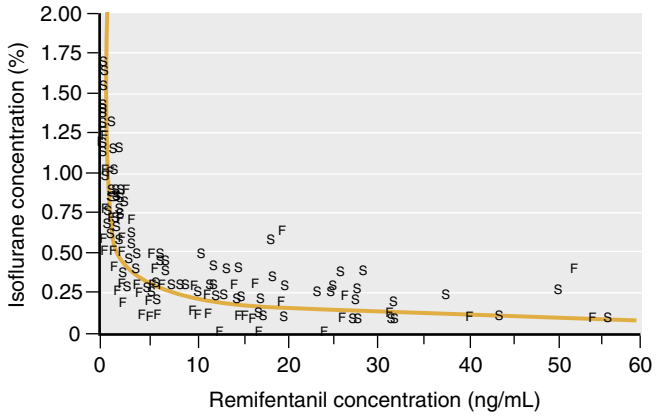


Figure 27-16 The reduction in isoflurane concentration to prevent movement at skin incision in 50% of patients by increasing measured remifentanil whole-blood concentrations. F represents a patient who moved and S a patient who did not move. The *solid line* is the logistic regression solution for a patient 40 years of age. *(From Lang E, Kapila A, Shlugman D, et al: Reduction of isoflurane minimal alveolar concentration by remifentanil. Anesthesiology 85:721-728, 1996.)*

Factors Affecting the Pharmacokinetics and Pharmacodynamics of Opioids

Age

The pharmacokinetics and pharmacodynamics of opioids can be influenced by age (see Chapter 71). It is clear that neonates exhibit a reduced rate of elimination of essentially all opioids,[298] presumably because of immature metabolic mechanisms, including the cytochrome P450 system. The prolonged elimination of opioids observed in the neonatal period quickly normalizes toward adult values within the first year of life.[298]

With advanced age, although pharmacokinetic changes may play a minor role, pharmacodynamic differences are primarily responsible for the decreased dose requirement in the elderly. Age was inversely correlated with the central volume of distribution, clearance, and potency of remifentanil (Fig. 27-17).[299] These combined pharmacokinetic and pharmacodynamic changes mandate a reduction in remifentanil dosage by at least 50% or more in the elderly.

Body Weight

Many opioid pharmacokinetic parameters, especially clearance, appear to be more closely related to lean body mass, which means that opioid dosage regimens may best be based on lean body mass and not total body weight. Total body weight–based dosing in an obese patient results in much higher remifentanil effect-site concentrations than lean body mass–based dosing does.[300] In contrast, for lean patients, the concentrations that result from total body weight–based dosing are not much greater than those based on body mass (Fig. 27-18). Clinically, context-sensitive half-times are not significantly different between obese and lean subjects (Fig. 27-19). Mounting evidence suggests that lean body mass is a better predictor of metabolic capacity than total body weight is. Ideal body weight, a parameter closely related to lean body mass and one that is perhaps more easily estimated by the clinician, is probably an acceptable alternative.

Renal Failure

Renal failure has implications of major clinical importance with respect to morphine and meperidine.[301] For the fentanyl congeners, the clinical importance of renal failure is less marked.

Morphine is an opioid with active metabolites that are dependent on renal clearance mechanisms for elimination. Morphine is principally metabolized by conjugation in the liver, and the water-soluble glucuronides (M3G and M6G) are excreted via the kidney. The kidney also plays a role in the conjugation of morphine and accounts for nearly 40% of its metabolism. Very

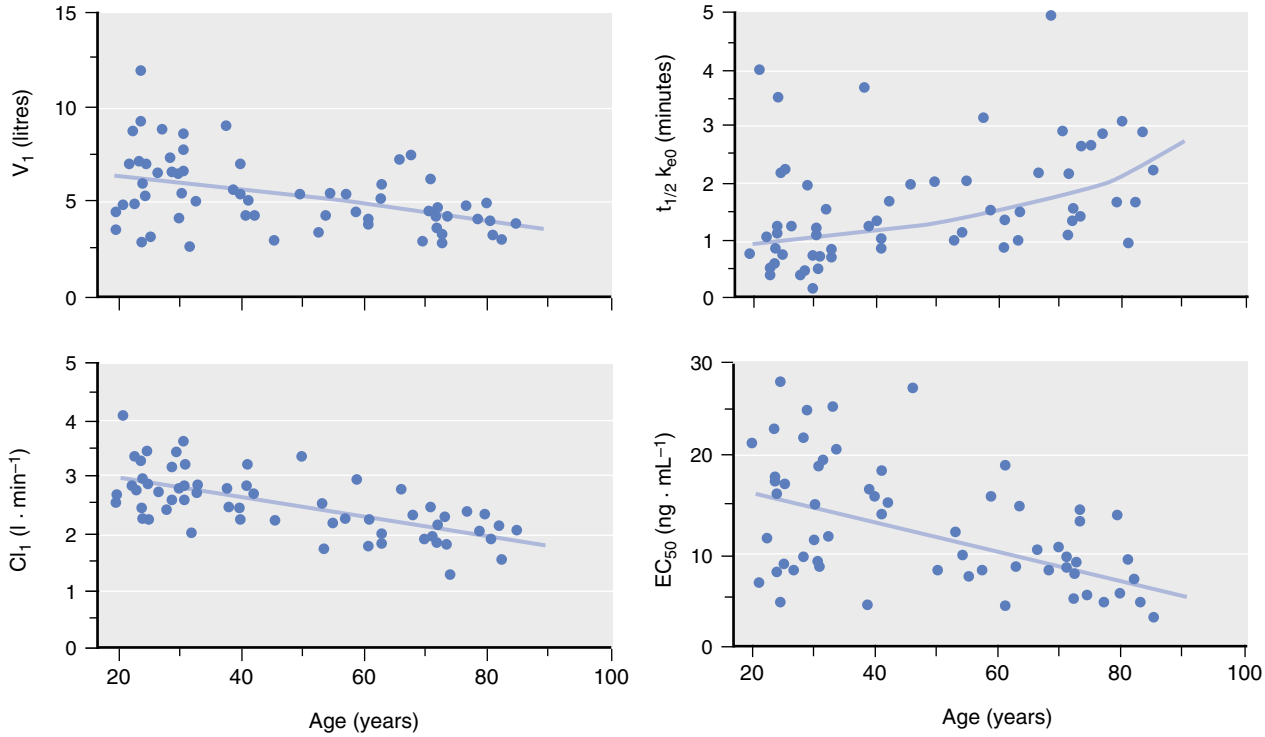


Figure 27-17 Relationship between pharmacokinetic and pharmacodynamic parameters and age for remifentanil. V_1 and Cl_1 are estimated from a three-compartment model. $t_{½}k_{e0}$ is a half-life corresponding to k_{e0}, a first-order rate constant for elimination of drug from the effect compartment. *(From Minto CF, Schnider TW, Shafer SL: Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology 86:24-33, 1997.)*

high levels of M6G and life-threatening respiratory depression can develop in patients with renal failure (Fig. 27-20).[302] In view of these changes induced by renal failure, morphine may not be a good choice in patients with severely altered renal clearance mechanisms.

The clinical pharmacology of meperidine is also significantly altered by renal failure. Normeperidine, the main metabolite, has analgesic and excitatory CNS effects. Because the active metabolites are subject to renal excretion, this potential CNS toxicity secondary to accumulation of normeperidine is especially a concern in patients with renal failure.

The clinical pharmacology of the fentanyl congeners is not grossly altered by renal failure, although a decrease in plasma protein binding may potentially alter the free fraction of the fentanyl class of opioids.[301] In the presence of renal impairment, fentanyl, alfentanil, sufentanil, and remifentanil do not deliver a

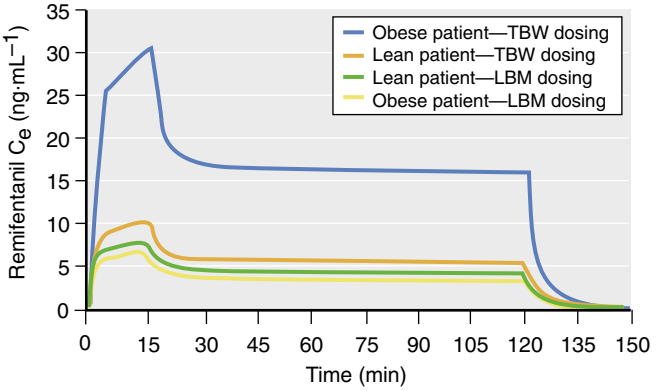


Figure 27-18 Computer simulation of the time course of change in remifentanil concentration when the dosage regimen is calculated according to lean body mass (LBM) or total body weight (TBW) for both obese and lean patients. Note that TBW-based dosing in an obese patient results in dramatically higher concentrations. *(From Egan TD, Huizinga B, Gupta SK, et al: Remifentanil pharmacokinetics in obese versus lean patients. Anesthesiology 89:562-573, 1998.)*

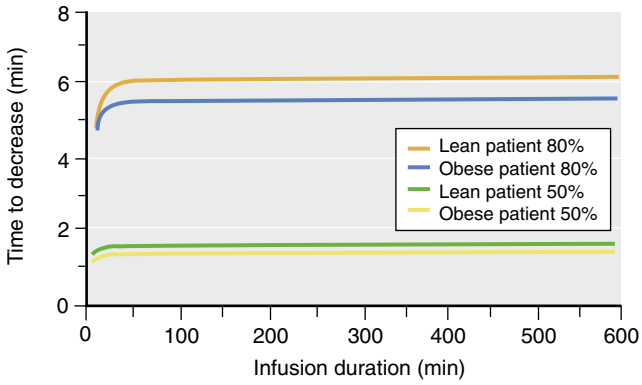


Figure 27-19 Computer simulation of the context-sensitive half-times (50% decrement times) and 80% decrement times of remifentanil in obese versus lean subjects. Note that in clinical terms the curves are not grossly different in obese versus lean subjects. *(From Egan TD, Huizinga B, Gupta SK, et al: Remifentanil pharmacokinetics in obese versus lean patients. Anesthesiology 89:562-573, 1998.)*

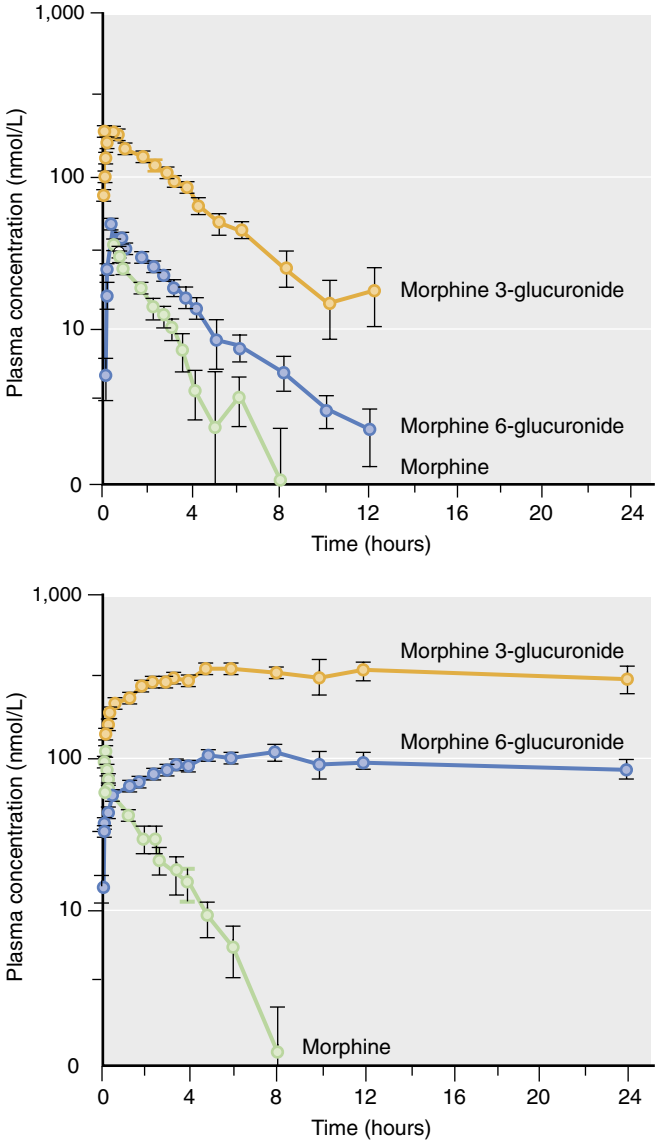


Figure 27-20 Effect of renal failure on the pharmacokinetics of morphine. The graphs show the time-dependent change in serum concentration of morphine and its metabolite in patients with normal renal function (*top*) and those with renal failure (*bottom*) who received 0.1 mg/kg of morphine intravenously. *(From Osborne R, Joel S, Grebenik K, et al: The pharmacokinetics of morphine and morphine glucuronides in kidney failure. Clin Pharmacol Ther 54:158-167, 1993.)*

high active metabolite load or suffer from significantly prolonged clearance.[303] Neither the pharmacokinetics nor the pharmacodynamics of remifentanil is altered by impaired renal function. The levels of GI90291 that develop during remifentanil infusion in patients with renal failure are not likely to produce any clinically significant effects.

Hepatic Failure

Even though the liver is the metabolic organ primarily responsible for opioid biotransformation, the degree of liver failure typically observed in perioperative patients, with the exception of patients undergoing liver transplantation, does not have a major impact on the pharmacokinetics of most opioids. In addition to reduced metabolic capacity (i.e., cytochrome P450 system and conjugation), liver disease may also lead to reductions in hepatic blood flow, hepatocellular mass, and plasma protein binding. The increase in total body water and the edema of advanced liver disease may alter the distribution characteristics of a drug. Enzyme induction, such as that observed in early alcoholism, can actually increase the metabolic capacity of the liver.

The pharmacokinetics of morphine is relatively unchanged by developing liver disease, such as liver cirrhosis and hepatic carcinoma, because of the substantial compensatory extrahepatic metabolism of morphine. A reduction in hepatic blood flow would be expected to slow the decline in morphine plasma concentrations. After liver resection, M6G/morphine and M3G/morphine ratios were significantly reduced and the circulating morphine concentration was increased, mainly as a result of lower morphine clearance.[304] In patients with cirrhosis the metabolism of meperidine is decreased, which leads to accumulation of the parent drug and possible CNS depressive effects similar to hepatic encephalopathy. Although elimination of normeperidine is decreased as well in these patients, the ratio of normeperidine to meperidine is generally low, and the narcotic effects of meperidine usually predominate.[305] The disposition of fentanyl and sufentanil appears to be unaffected by liver disease.[306] The reductions in liver blood flow that result from either liver disease or some other disorder (e.g., shock) can affect the pharmacokinetic parameters of alfentanil, fentanyl, and sufentanil.[307] A significant decrease in clearance of alfentanil was demonstrated in patients with mild to moderate cirrhosis when compared with volunteers from the historical control group.[308] Greater elimination half-lives (3.7 ± 2.6 hours) have also been observed for alfentanil in patients undergoing abdominal aortic surgery.[309] Remifentanil is an opioid whose phamacokinetics is completely unchanged by liver disease (Fig. 27-21). Its kinetics does not change during the anhepatic phase of orthotopic liver transplantation.[310]

Cardiopulmonary Bypass

CPB produces significant alterations in the pharmacokinetics of most opioids (see Chapter 60).[311] These alterations are a result of CPB-induced modifications in distribution volumes (secondary to priming) and changes in acid-base balance, organ blood flow, plasma protein concentrations, and body temperature. Binding of drugs to components of the bypass circuit can also alter opioid pharmacokinetics.

When morphine is given as a premedicant before cardiac anesthesia, its concentrations decline significantly on initiation of CPB.[312] Miller and colleagues examined the effect of CPB on plasma fentanyl concentrations and showed that the total concentration of fentanyl in plasma was significantly decreased and the unbound fraction of fentanyl rose on initiation of CPB.[313] The total fentanyl concentration remained relatively stable during bypass until near the end of CPB, at which time the mean total concentration increased, coincident with rewarming. Population pharmacokinetic modeling applied to concentration-versus-time data from patients undergoing coronary artery bypass grafting with CPB demonstrated that the effect of CPB on fentanyl pharmacokinetics is clinically insignificant and that a simple three-compartment model accurately predicts fentanyl concentrations throughout surgery involving the use of CPB.[314] Elimination of alfentanil is prolonged by CPB primarily because of increased distribution.[315] The volume of distribution in steady state (Vd_{ss}) and the volume of the central compartment for alfentanil were

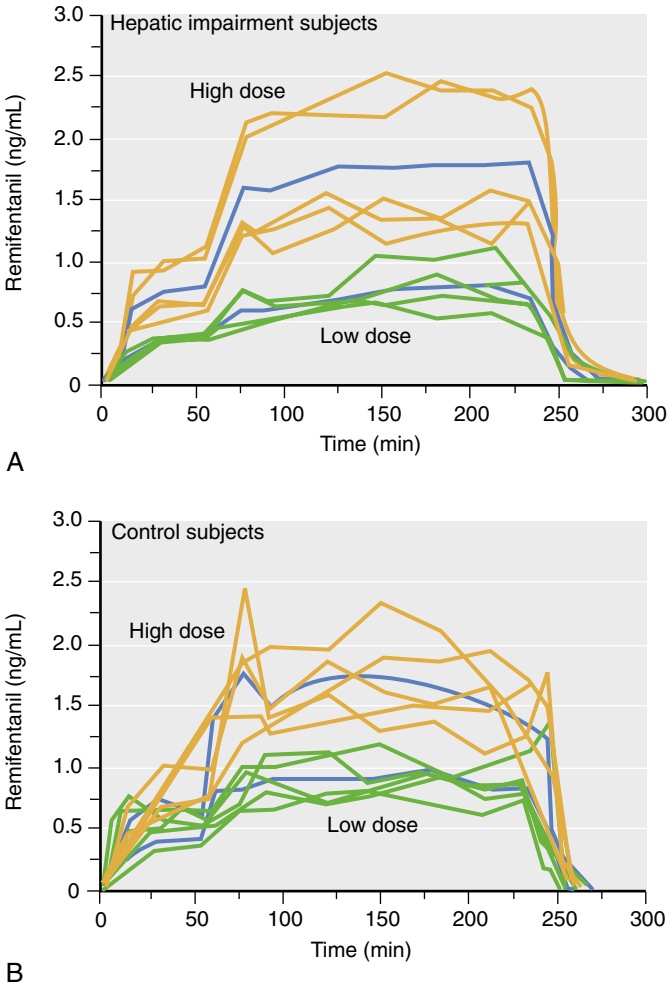


Figure 27-21 Time-dependent changes in the blood concentration of remifentanil in patients with liver disease (*top*) and control subjects (*bottom*). In the low-dose group, remifentanil was infused at 0.0125 µg/kg/min for 1 hour and then at 0.025 µg/kg/min for 3 hours. In high-dose group, the infusion rate of remifentanil was 0.025 µg/kg/min for 1 hour and then 0.05 µg/kg/min for 3 hours. *(From Dershwitz M, Hoke JF, Rosow CE, et al: Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with severe liver disease. Anesthesiology 84:812-820, 1996.)*

significantly greater in the CPB groups than in the nonbypass group.[316] However, the elimination half-life $(T_{½\beta})$ of alfentanil did not differ significantly between the normothermic CPB, hypothermic CPB, and nonbypass groups. No significant differences in Vd_{ss}, clearance, or $T_{½\beta}$ were found between the normothermic and hypothermic CPB groups. The free fraction of alfentanil during CPB remains constant despite complex changes in binding protein concentrations.[317] In adult patients undergoing elective myocardial revascularization with hypothermic CPB who received continuous infusions of remifentanil, 1.0 to 2.0 µg/kg/min, no evidence of accumulation or sequestration was found. Russell and coauthors reported that normothermic CPB did not significantly affect the clearance of remifentanil but that hypothermic CPB reduced it by an average of 20%, which was attributed to the effect of temperature on blood and tissue esterase activity (Fig. 27-22).[318] In pediatric patients undergoing CPB for repair of atrial septal defects, there was no change in Vd_{ss}, volume of the central compartment, $T_{½\alpha}$ and $T_{½\beta}$, but clearance values increased 20% in the postbypass period.[319] In patients undergoing coronary artery bypass graft surgery with hypothermic CPB and receiving a continuous infusion of remifentanil, the volume of distribution increased by 86% with the institution of CPB and remained increased after CPB, and elimination clearance decreased by 6.37% for each degree lower than 37°C.[320] Thus, although clearance of remifentanil is reduced during CPB, remifentanil remains a very short-acting drug, even during CPB.

Acid-Base Changes

Changes in pH influence the protein binding of fentanyl, sufentanil, and alfentanil such that protein binding increases with alkalosis and decreases with acidosis.[307] These effects are greater for fentanyl than for sufentanil and for sufentanil than for alfentanil. Relative changes in the free drug fraction with variation in pH from 7.4 to 7.0 were much higher for fentanyl (52%) than for sufentanil (29%) and alfentanil (6%). The dependence of plasma protein binding of the opioids on pH significantly correlates with their partition between an organic and aqueous phase, thus suggesting the hydrophobic character of the interaction between plasma proteins and opioids. Increased ionization decreases the amount of fentanyl available for hepatic metabolism or renal excretion. Intraoperative hyperventilation during surgical procedures can significantly influence the pharmacokinetics of sufentanil and result in an increased distribution volume and prolonged elimination half-time. Thus, both intraoperative respiratory alkalosis and respiratory acidosis, especially in the immediate postoperative period, can prolong and exacerbate opioid-induced respiratory depression.

Hemorrhagic Shock

It is common practice to administer reduced doses of opioids to patients suffering from hemorrhagic shock to minimize any adverse hemodynamic consequences and prevent prolonged opioid effect. This is at least partially attributable to a pharmacokinetic mechanism. Analysis of pigs receiving fentanyl suggested that central clearance and central and second compartment distribution volumes were significantly reduced in hemorrhagic shock, with higher fentanyl concentrations for any given dosage and a prolonged context-sensitive half-time (Fig. 27-23).[321] Hemorrhagic shock also altered the pharmacokinetics of remifentanil, suggesting that less remifentanil would be required to maintain a target plasma concentration (Fig. 27-24).[322] However, because of its rapid metabolism, changes in context-sensitive half-time are small.

Anesthetic Techniques Using Opioids

Analgesia

Opioids are frequently used to relieve pain during monitored anesthesia care and regional anesthesia.

A single bolus of opioids can provide significant pain relief. Morphine is slow in onset and does not allow rapid titration to effect. Meperidine (50 to 100 mg IV) produces variable degrees of pain relief and is not always effective in patients with severe

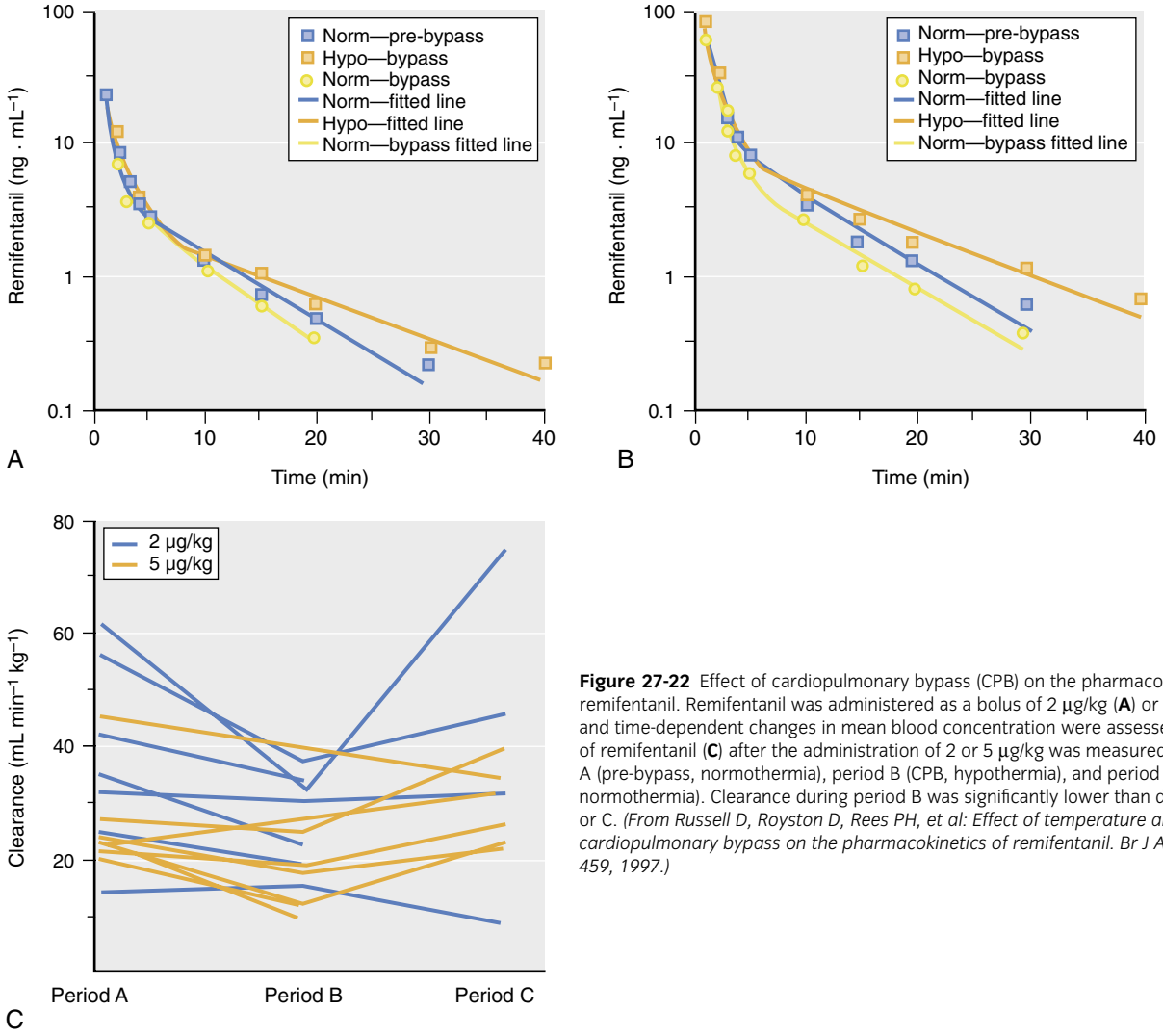


Figure 27-22 Effect of cardiopulmonary bypass (CPB) on the pharmacokinetics of remifentanil. Remifentanil was administered as a bolus of 2 μg/kg (**A**) or 5 μg/kg (**B**), and time-dependent changes in mean blood concentration were assessed. Clearance of remifentanil (**C**) after the administration of 2 or 5 μg/kg was measured during period A (pre-bypass, normothermia), period B (CPB, hypothermia), and period C (CPB, normothermia). Clearance during period B was significantly lower than during period A or C. *(From Russell D, Royston D, Rees PH, et al: Effect of temperature and cardiopulmonary bypass on the pharmacokinetics of remifentanil. Br J Anaesth 79:456-459, 1997.)*

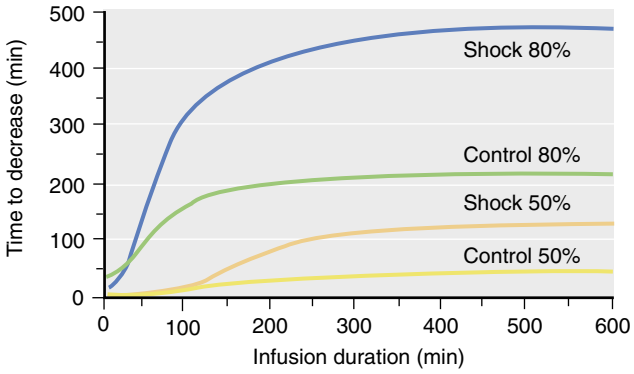


Figure 27-23 Computer simulation of the context-sensitive half-times (50% decrement times) and 80% decrement times of fentanyl in shock versus control animals. *(From Egan TD, Kuramkote S, Gong G, et al: Fentanyl pharmacokinetics in hemorrhagic shock: A porcine model. Anesthesiology 91:156-166, 1999.)*

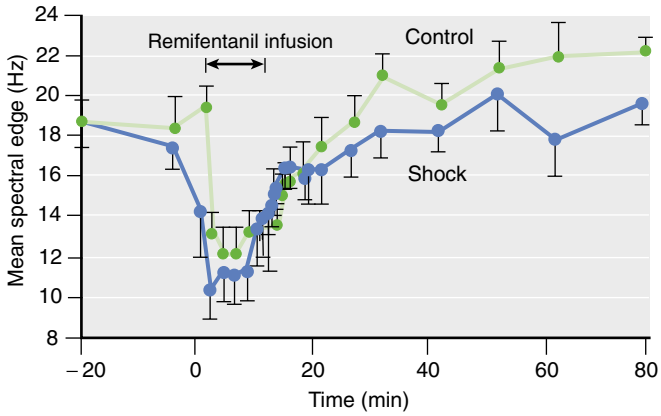


Figure 27-24 Mean spectral edge changes versus time during remifentanil infusion. The *green* and *blue* indicate spectral edge measurements for the control animals and animals with hemorrhagic shock, respectively. *(From Johnson KB, Kern SE, Hamber EA, et al: Influence of hemorrhagic shock on remifentanil: A pharmacokinetic and pharmacodynamic analysis. Anesthesiology 94:322-332, 2001.)*

Table 27-6 Range of Approximate Plasma (or Whole Blood for Remifentanil) Opioid Concentrations (ng/mL)

	Fentanyl	Sufentanil	Alfentanil	Remifentanil
Predominant agent	15-30	5-10	400-800	—
Major surgery	4-10	1-3	200-400	2-4
Minor surgery	3-6	0.25-1	50-200	1-3
Spontaneous ventilation	1-3	<0.4	<200	0.3-0.6
Analgesia	1-2	0.2-0.4	50-150	0.2-0.4

From Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. *In* Miller RD (ed): Anesthesia, 5th ed. New York, Churchill Livingstone, 2000, p 330.

pain. Intravenous boluses of fentanyl (1 to 3 µg/kg), alfentanil (10 to 20 µg/kg), or sufentanil (0.1 to 0.3 µg/kg) can produce potent and short-lasting analgesia. Infusion rates range from 0.01 to 0.05 µg/kg/min for fentanyl, 0.0015 to 0.01 µg/kg/min for sufentanil, 0.25 to 0.75 µg/kg/min for alfentanil, and 0.05 to 0.25 µg/kg/min for remifentanil. The plasma concentrations of opioids needed for various purposes are listed in Table 27-6.

Changes in the excitability of central neurons play an important role in the establishment of pain. Low doses of fentanyl block the synaptic form of central sensitization in the rat spinal cord in vivo, suggesting the possibility of preemptive analgesia by fentanyl, but larger doses do not have this effect.[323] Reductions in postoperative pain and improved recovery have been attributed to preemptive analgesia with either epidural fentanyl or bupivacaine after radical prostatectomy.[324] In contrast, in patients undergoing transperitoneal tumor nephrectomy, preoperative intravenous administration of a combination of morphine, ketamine, and clonidine failed to exert a clinically relevant effect on postoperative pain.[325] Aida and coauthors reported that the effectiveness of preemptive analgesia varies according to the type of surgery and that preemptive analgesia with epidural morphine was reliably effective in limb and breast surgery but ineffective in abdominal surgery.[326] A meta-analysis demonstrated that the results of preemptive analgesia with systemic administration of opioids are equivocal.[327] Thus, whether preemptive analgesia can be effectively achieved clinically by the early administration of opioids remains uncertain.

PCA with opioids is now a cornerstone of postoperative analgesia (see Chapter 87). PCA with opioids may improve outcome.[328] Nevertheless, pharmacokinetic optimization of opioid treatment in acute pain is a complex matter.[329] Without considering effect-site drug concentrations over time, the choice of opioid and the amount, method, and frequency of its administration cannot be optimized.[329] Morphine remains a popular and rational choice for PCA therapy[330] (see also Chapter 87).

Sedation

Critically ill subjects in the intensive care unit (ICU) often experience anxiety and agitation while being exposed to numerous stressful or noxious stimuli. ICU patients generally require a combination of analgesia and sedation to relieve their state of anxiety, improve adaptation to the endotracheal tube, and aid compliance with mechanical ventilation. Morphine is the most frequently used intravenous analgesic agent in the ICU.[331] A randomized double-blind study indicated that remifentanil (0.15 µg/kg/min) and morphine (0.75 µg/kg/min) could provide comparable levels of sedation and that the remifentanil-based regimen allowed more rapid emergence from sedation and facilitated earlier extubation.[332]

Balanced Anesthesia

The term "balanced anesthesia" was introduced by Lundy in 1926. Lundy suggested that a balance of agents and techniques be used to produce the different components of anesthesia (i.e., analgesia, amnesia, muscle relaxation, and abolition of autonomic reflexes with maintenance of homeostasis). Anesthesia with a single agent can require doses that produce excessive hemodynamic depression.[333] The inclusion of an opioid as a component of balanced anesthesia can reduce preoperative pain and anxiety, decrease somatic and autonomic responses to airway manipulation, improve hemodynamic stability, lower requirements for inhaled anesthetics, and provide immediate postoperative analgesia. Opioids interact synergistically and markedly reduce the dose of propofol and other sedative-hypnotics required for loss of consciousness and during noxious stimulation such as skin incision (Fig. 27-25).[334] Although the intent of combining opioids with sedative-hypnotics or volatile anesthetics (or with both) is to produce anesthetic conditions with stable hemodynamics before as well as after noxious stimulation, this ideal is not always achieved.[335,336]

The timing, rate of administration, and dose of supplemental opioid should also be tailored to the specific condition of the patient and the expected duration of the operation to avoid problems. Giving a large dose of any opioid shortly before the end of surgery is very likely to result in postoperative respiratory depression. However, analgesic concentrations of opioids have little effect on the MAC-awake of inhaled anesthetics.[337]

Choice of Opioid

The ideal opioid would permit rapid titration, successfully prevent unwanted responses to noxious stimuli, require little supplementation, not depress cardiovascular function, permit the return of adequate spontaneous ventilation in a timely manner, and produce residual, if not complete, postoperative analgesia with minimal side effects. Alfentanil and remifentanil provide the greatest ability to titrate opioids rapidly because of their extremely rapid time to onset (1 to 2 minutes) of peak effect. Sufentanil, alfentanil, and remifentanil are arguably superior to fentanyl in most respects. Antagonism of opioid action with naloxone for troublesome respiratory depression is required less frequently after alfentanil and sufentanil than after fentanyl. Pharmacologic antagonism is rarely required after administration of remifentanil.

Fentanyl

Anesthetic induction is usually achieved by combining a loading dose of fentanyl (2 to 6 µg/kg) with a sedative-hypnotic, most commonly thiopental or propofol, and a muscle relaxant. Maintenance of anesthesia can be achieved with N_2O (60% to 70%) in O_2, low concentrations of potent inhaled anesthetics, and additional fentanyl (intermittent boluses of 25 to 50 µg every 15 to 30 minutes or a constant infusion of 0.5 to 5.0 µg/kg/hr).

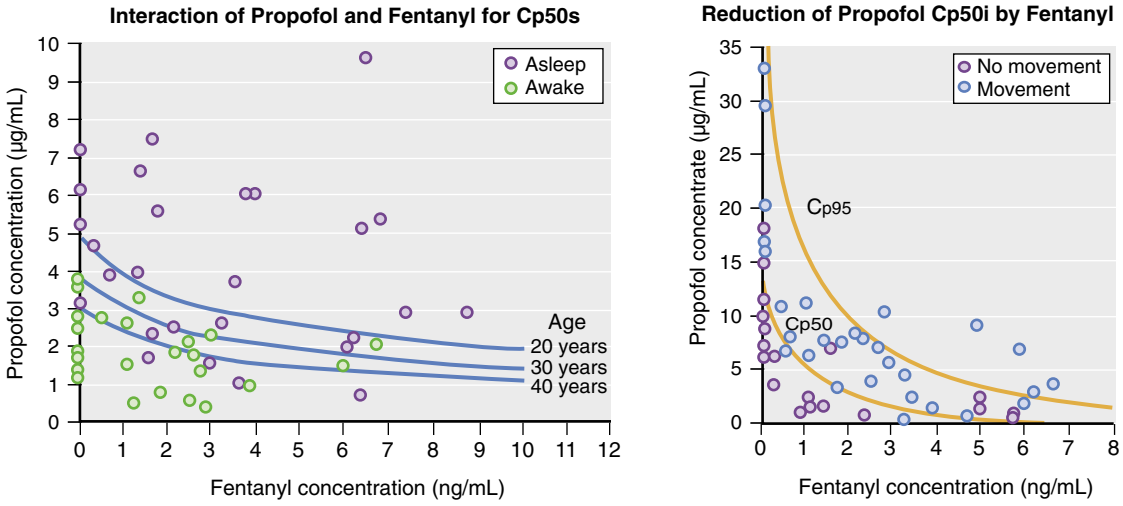


Figure 27-25 Left, Measured arterial propofol and fentanyl concentrations at which patients did and did not respond to a verbal command at 10 minutes after initiation of infusion of these drugs. *Solid lines* represent the modeled concentration of propofol according to decade of age when combined with measured fentanyl concentrations at which 50% of patients did not respond to verbal command (Cp_{50}). **Right,** Reduction of the propofol concentration at which 50% or 95% of patients did not move at skin incision by increasing the concentration of fentanyl (Cp_{50} and Cp_{95}, respectively). *Sold lines* represent logistic regression solutions. *(From Smith C, McEwan AI, Jhaveri R, et al: The interaction of fentanyl on the Cp_{50} of propofol for loss of consciousness and skin incision. Anesthesiology 81:820-828, 1994.)*

The plasma concentration of fentanyl required for postoperative analgesia was approximately 1.5 ng/mL,[338] but levels of at least 2 to 3 ng/mL are usually required during surgery if the only inhaled agent is N_2O. In unpremedicated patients anesthetized with a fentanyl infusion and N_2O in O_2, the Cp_{50} (minimal steady-state plasma concentration of an intravenous analgesic/anesthetic required to prevent a somatic response in 50% of patients after skin incision) and Cp_{50}-BAR (minimal plasma concentration of an intravenous analgesic/anesthetic required to prevent either a somatic, hemodynamic, or autonomic response in 50% of patients after skin incision) for fentanyl at skin incision are 3.26 and 4.17 ng/mL, respectively.[339] The MAC of isoflurane at skin incision can be reduced by 50% and 63% with plasma fentanyl concentrations of 1.67 and 3.0 ng/mL, respectively.[74] Increasing plasma fentanyl concentrations from 3.0 to 10 ng/mL only further reduced the MAC of isoflurane from 63% to 82%. The intraoperative requirement for propofol is also reduced by fentanyl. In patients undergoing spine fusion, to keep mean arterial pressure within 15% of the control value when fentanyl was infused to keep the plasma concentration at 0, 1.5, 3.0, and 4.5 ng/mL, average propofol infusion rates were 10.1 ± 2.5 (mean ± SD), 7.5 ± 1.2, 5.7 ± 1.1, and 4.9 ± 1.2 mg/kg/hr, respectively.[340]

Opioid pharmacokinetics and pharmacodynamics vary considerably among patients. It was reported that basing the fentanyl dose on total body weight may cause overdosing in obese patients.[338] Nevertheless, a balanced technique with fentanyl, titrated in anticipation of various stimuli and patient responses with pharmacokinetic guidelines in mind, will often result in a stable hemodynamic course and rapid awakening in a pain-free patient. Repeated doses or continuous infusions of fentanyl are most likely to result in significant depression of spontaneous ventilation.

Alfentanil

Because alfentanil penetrates the brain so rapidly, equilibration of alfentanil between plasma and the CNS can be achieved while plasma alfentanil levels are quite high relative to those of sufentanil and fentanyl. This property explains how low doses (10 to 30 µg/kg) of alfentanil, administered just before or simultaneously with a sedative-hypnotic, are effective.

Alfentanil (25 to 50 µg/kg IV), followed by small titrated sleep doses of any sedative-hypnotic (e.g., 50 to 100 mg sodium thiopental), is usually successful in preventing significant hemodynamic stimulation from laryngoscopy and intubation. Further opioid supplementation can be achieved with an alfentanil infusion (0.5 to 2.0 µg/kg/min) or intermittent boluses of alfentanil (5 to 10 µg/kg) for shorter procedures. In balanced anesthetic techniques in which potent inhaled anesthetics are also administered, relatively low plasma alfentanil concentrations (e.g., 29 ng/mL) can reduce the MAC of isoflurane by approximately 50%.[90] The EC_{50} of alfentanil during propofol anesthesia, in which the plasma concentration of propofol was kept at target concentrations of 3 µg/mL, was 92 ng/mL for intubation, 55 ng/mL for skin incision, 84 ng/mL for opening of the peritoneum, and 66 ± 38 ng/mL for the intra-abdominal portion of the surgery.[341] It was reported that the hemodynamic changes induced by propofol might have an important influence on the pharmacokinetics of alfentanil. Propofol (target concentration, 1.5 µg/mL) decreased the elimination clearance of alfentanil by 15%, rapid distribution clearance by 68%, slow distribution clearance by 51%, and lag time by 62%.[342] Alfentanil infusions or repeated doses should be minimized 15 to 30 minutes before the end of surgery to avoid problematic residual respiratory depression.

Sufentanil

The mean plasma sufentanil concentration reported to be the Cp_{50} for prevention of hemodynamic responses to laryngoscopy and tracheal intubation was 1.08 ng/mL with a range of 0.73 to 2.55. Maintenance of anesthesia can be achieved with N_2O (60% to 70%) in O_2 and additional sufentanil (intermittent boluses of 0.1 to 0.25 µg/kg or a constant infusion of 0.5 to 1.5 µg/kg/hr). The Cp_{50} for sufentanil during skin incision (2.08 ± 0.62 ng/mL)

is twice as great as that for intubation in unpremedicated patients.[343] Cp_{50} ratios at skin incision for sufentanil, fentanyl, and alfentanil in N_2O-O_2 anesthesia are approximately 1:2:150 and represent different and probably more accurate potency ratios than those traditionally published on the basis of drug dose. In patients undergoing coronary artery bypass grafting, sufentanil doses greater than 1.25 ± 0.21 ng/mL reduced isoflurane requirements to less than 0.5% throughout the operation.[344]

Remifentanil

The very short duration of action of remifentanil mandates that an infusion (0.1 to 1.0 µg/kg/min) be started before or soon after the bolus dose to ensure a sustained opioid effect. Maintenance infusion rates of remifentanil range from 0.1 to 1.0 µg/kg/min for balanced anesthesia. Remifentanil can reliably suppress autonomic, hemodynamic, and somatic responses to noxious stimulation and allows predictable and rapid emergence from anesthesia.[345]

The use of remifentanil permits rapid (5 to 15 minutes) emergence without postoperative respiratory depression.[346] Infusion rates of 0.1 ± 0.05 µg/kg/min should allow the return of spontaneous ventilation and responsiveness with maintenance of analgesia. A randomized, double-blind, placebo-controlled study demonstrated that the combination of 0.05 to 0.1 µg/kg/min remifentanil and 2 mg midazolam provided effective sedation and analgesia during outpatient surgical procedures performed under local anesthesia.[347] Administration of remifentanil, 1 µg/kg followed by 0.5 µg/kg/min, with propofol and 66% N_2O provided sufficient anesthesia for craniotomy with stable hemodynamics and rapid tracheal extubation.[348]

During emergence from remifentanil anesthesia, the need for alternative analgesic therapies should be anticipated and administered in timely fashion. It was reported that perioperative administration of morphine (0.15 or 0.25 mg/kg IV) or fentanyl (0.15 mg) did not provide entirely adequate immediate postoperative pain control after remifentanil-based anesthesia for major abdominal surgery.[349,350] Administration of ketamine (0.15 mg/kg followed by 2 µg/kg/min) decreased intraoperative remifentanil use during abdominal surgery and postoperative morphine consumption without increasing the incidence of side effects.[351] In children undergoing strabismus surgery, the combination of sevoflurane (2.5%) and remifentanil (1 µg/kg followed by 0.1 to 0.2 µg/kg/min) produced less frequent postoperative vomiting but higher postoperative pain scores than fentanyl did (2 µg/kg followed by 1 µg/kg every 45 minutes).[352]

Postoperative pain relief with low-dose remifentanil infusion was also reported. After general anesthesia with propofol (75 µg/kg/min) and remifentanil (0.5 to 1.0 µg/kg/min) for abdominal or thoracic surgery, continuous infusion of remifentanil (0.05 or 0.1 µg/kg/min) provided adequate analgesia.[353]

Neuroleptanalgesia-Neuroleptanesthesia

In 1949, Laborit and Huygenard introduced the concept of an anesthetic technique that blocked not only cerebrocortical responses but also some cellular, endocrine, and autonomic mechanisms usually activated by surgical stimulation. This state was called "ganglioplegia" or "neuroplegia" (artificial hibernation) and was achieved with the use of a lytic cocktail consisting of chlorpromazine, promethazine, and meperidine. From this idea, in 1959 De Castro and Mundeleer derived the concept of neuroleptanalgesia, which involved the combination of a major tranquilizer (usually the butyrophenone droperidol) and a potent opioid analgesic (fentanyl) to produce a detached, pain-free state of immobilization and insensitivity to pain. Neuroleptanalgesia is characterized by analgesia, absence of clinically apparent motor activity, suppression of autonomic reflexes, maintenance of cardiovascular stability, and amnesia in most patients. The addition of an inhaled agent, usually N_2O, improves amnesia and has been called neuroleptanesthesia.

"Neuroleptic" drugs traditionally include the phenothiazines (e.g., chlorpromazine) and the butyrophenones (e.g., haloperidol and droperidol). Butyrophenones cause sedation, tranquility, immobility, antiemesis, an extrapyramidal syndrome with face and neck dyskinesia, oculogyric crises, torticollis, agitation, and hallucinations. Administering droperidol alone, without analgesics or other sedatives, often produces feelings of discomfort or dysphoria in patients. The cardiovascular effects of droperidol are most often limited to mild hypotension, which is thought to be mediated through α-adrenergic blockade. There is little respiratory depression induced by droperidol, although significant variability exists and respiratory depression may be noted occasionally. Droperidol and other butyrophenones may enhance hypoxic-induced increases in ventilation in humans because of their antidopaminergic effects at the carotid body. Droperidol can be used as a premedicant (0.025 to 0.075 mg/kg IM), an antiemetic (0.01 to 0.02 mg/kg IV), an adjunct for awake intubation (0.025 to 0.1 mg/kg IV), and therapy for agitated, belligerent, or psychotic patients (0.05 to 0.2 mg/kg IV or IM).

Neuroleptanalgesia or neuroleptanesthesia is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs), in those who abuse drugs or alchohol, or in patients with Parkinson's disease.

Total Intravenous Anesthesia

Many different intravenous compounds can be used in a number of combinations to provide TIVA. Most commonly, an opioid is combined with another drug more likely to provide hypnosis and amnesia. For example, the combination of alfentanil and propofol produces excellent TIVA. Alfentanil provides analgesia and hemodynamic stability while blunting responses to noxious stimuli. On the other hand, propofol provides hypnosis and amnesia and is antiemetic. Profound synergism also exists when more than two agents, such as propofol-alfentanil-midazolam, are combined.[354,355] Induction of anesthesia with alfentanil (25 to 50 µg/kg) and propofol (0.5 to 1.5 mg/kg), followed by infusions of alfentanil at 0.5 to 1.5 µg/kg/min and propofol at 80 to 120 µg/kg/min, will produce anesthesia in patients ventilated with air and O_2 with or without N_2O for a variety of procedures. It is proposed that alfentanil concentrations as low as 85 ng/mL, when combined with a blood propofol concentration of 3.5 µg/mL, can produce both optimal anesthetic conditions and speed of recovery.[355] Stanski and Shafer suggested that bolus doses and initial infusion rates would be 30 µg/kg and 0.35 µg/kg/min for alfentanil and 0.7 mg/kg and 180 µg/kg/min for propofol.[356] Recognizing that these calculations were based on EC_{50} data in patients undergoing only moderately painful procedures, anesthesiologists should adjust these doses accordingly. Premedication before alfentanil-propofol anesthesia can prolong postoperative recov-

ery and should be avoided if appropriate.[357] In patients undergoing ear-nose-throat surgery, TIVA with remifentanil and propofol provided more rapid respiratory recovery after brief surgical procedures than TIVA with alfentanil and propofol did.[358]

The optimal propofol-opioid concentrations that ensure adequate anesthesia and rapid emergence were determined by computer modeling. The optimal propofol concentration decreases in the order of fentanyl > alfentanil > sufentanil ≫ remifentanil. A shorter context-sensitive half-time allows the administration of greater amounts of opioid (and less propofol) during anesthesia without creating prolonged opioid effects.

Maintenance infusions vary according to patient condition and surgical stimuli. Propofol (75 to 125 μg/kg/min) and alfentanil (1.0 to 2.0 μg/kg/min) are initially recommended. Drug infusions should be terminated 10 to 20 minutes before the end of anesthesia if N_2O is used. Otherwise, propofol infusions should be terminated 5 to 10 minutes before anticipated patient awakening. Alfentanil infusion rates do not need to be less than 0.25 to 0.5 μg/kg/min until surgery is terminated. A multicenter evaluation demonstrated that in patients undergoing elective inpatient surgery, remifentanil, 1 μg/kg intravenously, followed by 1.0 μg/kg/min, when combined with propofol, 75 μg/kg/min, effectively controlled responses to tracheal intubation.[346] Reduction of the remifentanil infusion rate to 0.25 to 0.40 μg/kg/min after tracheal intubation was also recommended.

Midazolam-opioid combinations can also provide complete anesthesia. However, midazolam-alfentanil TIVA has not been found to compare favorably with propofol-alfentanil TIVA, even with flumazenil reversal of benzodiazepine action.[359]

TIVA techniques are especially useful when delivery of inhaled agents is compromised. By keeping the goals of balanced anesthesia in mind, combining modern opioids and other drugs, using infusion pumps, and having an increased understanding of pharmacokinetics, clinicians can successfully perform a variety of TIVA techniques. Approximate opioid doses and infusion rates for TIVA are listed in Table 27-7.

Opioid-Based (High-Dose Opioid) Anesthesia for Cardiac Surgery

Opioids can be administered as the primary or sole anesthetic in opioid-based anesthetic techniques. High-dose opioid anesthesia was introduced as a stress-free anesthetic method for cardiac surgery (also see Chapter 60). However, several factors have diminished the popularity of high-dose opioid anesthesia, even in cardiac anesthesia, including the lack of evidence substantiating any significant outcome benefit associated with the use of large doses of opioids, the added drug costs, and the trend toward "fast-track" approaches to cardiac patients that can be impeded by large doses of opioids, especially fentanyl.[212,360] Nonetheless, opioids, particularly when administered by continuous infusion, are still among the most effective anesthetics for patients undergoing cardiac or other extensive operations. High-dose opioid anesthesia was first performed with morphine. However, fentanyl and sufentanil were recommended later.

In an attempt to decrease the cost of cardiac surgery, fast-track programs have become popular. Engoren and associates reported that the more expensive but shorter-acting opioids sufentanil and remifentanil produce equally rapid extubation, similar stays, and similar costs to fentanyl, indicating that any of these opioids can be recommended for fast-track cardiac surgery.[361]

Table 27-7 Approximate Opioid Loading (Bolus) Doses, Maintenance Infusion Rates, and Additional Maintenance Doses for Total Intravenous Anesthesia

	Loading Dose (μg/kg)	Maintenance Infusion Rate	Additional Boluses
Alfentanil	25-100	0.5-2 μg/kg/min	5-10 μg/kg
Sufentanil	0.25-2	0.5-1.5 μg/kg/hr	2.5-10 μg
Fentanyl	4-20	2-10 μg/kg/hr	25-100 μg
Remifentanil	1-2	0.1-1.0 μg/kg/min	0.1-1.0 μg/kg

From Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. *In* Miller RD (ed): Anesthesia, 5th ed. New York, Churchill Livingstone, 2000, p 335.

Fentanyl

Many different techniques have been used to achieve anesthesia with fentanyl.[360,362] Rapid or slow bolus injections of fentanyl range from 5 to 75 μg/kg. These doses will establish plasma fentanyl concentrations (10 to 30 ng/mL) that are often sufficient to provide stable hemodynamics throughout the induction/intubation sequence. Continuous infusions of fentanyl for cardiac surgery range from 0.1 to 1.0 μg/kg/min up to or continuing through CPB. High-dose fentanyl anesthesia has also proved effective and safe for pediatric heart surgery. It was indicated that fentanyl, 25 to 50 μg/kg, combined with isoflurane, 0.2% to 0.4%, was sufficient to obtund hemodynamic and stress responses in the pre-CPB phase of open heart surgery in infants and young children (Fig. 27-26).[363] On the other hand, high-dose fentanyl, 75 to 100 μg/kg, was shown to cause prolonged suppression of NK cell function.[364] It was reported that 57 of 59 eligible patients were successfully extubated at 34 ± 14 minutes after termination of fentanyl (total dose, 127 ± 64 μg/kg) with naloxone (total bolus, 3.4 ± 2.6 μg/kg) and recovered fully without ventilatory support under the naloxone infusion, which was terminated at 11 ± 7 hours.[365] These results suggest that naloxone infusion with individual dose titration facilitates the use of high-dose opioid anesthesia while maintaining the advantage of this anesthesia. It was recently shown that high-dose fentanyl (50 μg/kg) is not associated with a difference in the incidence of postoperative cognitive dysfunction at 3 or 12 months after coronary artery bypass surgery in the elderly, whereas low-dose fentanyl (10 μg/kg) leads to shorter postoperative ventilation times and may be associated with a greater incidence of postoperative cognitive dysfunction 1 week after surgery.[366]

Alfentanil

Induction of anesthesia with large doses of alfentanil has been applied to cardiac surgery.[367] Large doses of alfentanil (150 μg/kg) may be used with or without thiopental to induce anesthesia. Other investigators claim that anesthesia cannot be reliably induced with alfentanil alone, at least in young and healthy adults.[85] Continuous infusions of alfentanil (2 to 12 μg/kg/min) have been used to maintain moderate to very high plasma alfentanil concentrations (<3000 ng/mL) during cardiac surgery. Enthusiasm for high-dose alfentanil anesthesia techniques is limited by the amount (and cost) of drug required and sugges-

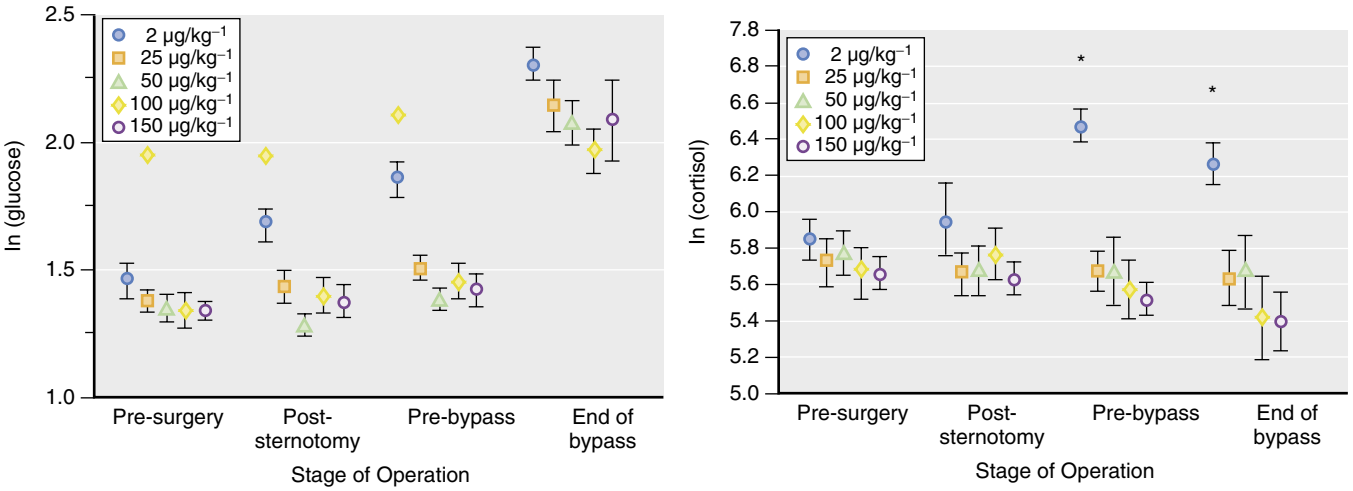


Figure 27-26 Suppression of stress responses in the pre-bypass phase of open heart surgery in infants and young children by fentanyl combined with a low concentration (0.2% to 0.4%) of isoflurane: mean (± SE) ln (glucose) (*left*) or ln (cortisol) (*right*) versus stage of surgery for each dose of fentanyl. The values for the 2-μg/kg group indicated by *asterisks* were significantly higher ($P < .01$) than in the other groups. ln, natural logarithm. *(From Benthuysen JL, Foltz BD, Smith NT, et al: Prebypass hemodynamic stability of sufentanil-O_2, fentanyl-O_2, and morphine-O_2 anesthesia during cardiac surgery: A comparison of cardiovascular profiles. J Cardiothorac Anesth 12:749-757, 1988.)*

tions that alfentanil anesthesia for cardiac surgery is inadequate and associated with more cardiovascular adverse effects than is the case with fentanyl and sufentanil. More modest doses of alfentanil have been successfully administered in combination with sedative-hypnotics such as propofol for cardiac anesthesia.[368]

Sufentanil

Advantages of high-dose sufentanil include more rapid induction, better blunting or elimination of hypertensive episodes, greater reduction in left ventricular stroke work, and higher cardiac output and more stable hemodynamics intraoperatively and postoperatively.[369] Induction doses of sufentanil range from 2 to 20 μg/kg administered as a bolus or infused over a period of 2 to 10 minutes. Total doses of sufentanil used in high-dose techniques usually range from 15 to 30 μg/kg, but no additional benefit could be demonstrated in terms of hemodynamic control or EEG signs by increasing the dose of sufentanil from 3 to 15 μg/kg for induction of anesthesia in patients premedicated with lorazepam.[370] It has been thought that muscle rigidity during induction of anesthesia with high-dose opioid causes difficult ventilation with a mask. However, it was shown that the difficult ventilation during induction of anesthesia with sufentanil, 3 μg/kg, is due to upper airway closure at the level of the glottis or above.[371]

The amount of sufentanil required can be markedly influenced by the supplements administered concomitantly. For patients undergoing coronary artery surgery, induction (0.4 ± 0.2 μg/kg) and total maintenance (2.4 ± 0.8 μg/kg) doses of sufentanil were used in combination with propofol (1.5 ± 1 mg/kg for induction and 32 ± 12 mg/kg total). Interestingly, sufentanil requirements tripled when midazolam was used instead of propofol.[372] Etomidate, combined with an opioid, can provide excellent anesthetic conditions with minimal hemodynamic perturbations. Inducing anesthesia with sufentanil (0.5 to 1.0 μg/kg) and etomidate (0.1 to 0.2 mg/kg) frequently confers hemodynamic stability. Maintenance of anesthesia with an infusion of sufentanil (1.0 to 2.0 μg/kg/hr) in a balanced anesthetic technique achieves the advantages of opioid-based anesthesia and avoids prolonged opioid action into the postoperative period.

Remifentanil

Remifentanil has been used in cardiac anesthesia.[318] It was shown that induction with remifentanil, 2 μg/kg, and propofol and maintenance with remifentanil at 0.25 or 0.5 μg/kg/min provided appropriate anesthesia for minimally invasive coronary artery bypass surgery with rapid awakening and tracheal extubation (Fig. 27-27).[373] Kazmaier and coworkers compared high-dose remifentanil (2.0 μg/kg/min) and remifentanil (0.5 μg/kg/min) combined with propofol (target-controlled infusion aiming at a plasma concentration of 2.0 μg/mL) in patients undergoing elective coronary artery bypass grafting.[374] It was demonstrated that high-dose remifentanil reduces the stroke volume index, heart rate, mean arterial pressure, myocardial blood flow, and myocardial oxygen uptake and that its effects do not differ from those of remifentanil/propofol anesthesia. Geisler and colleagues examined the efficacy and safety of high-dose remifentanil anesthesia in patients undergoing coronary artery bypass graft surgery.[375] It was demonstrated that continuous infusions of remifentanil at 1.0 to 2.0 μg/kg/min in combination with propofol, 3 mg/kg/hr, provided profound suppression of responses to surgical stimuli in the majority of patients, but there was a high incidence of muscle rigidity when remifentanil was used to induce anesthesia. They concluded that there was no apparent advantage in starting the remifentanil infusion rate above 1.0 μg/kg/min and that remifentanil is not suitable for use as a sole induction agent.

Other Applications of Opioids

Transdermal Therapeutic System

Transdermal drug delivery generally requires high solubility in both water and oil, low molecular weight, high potency, and little or no skin irritation. Fentanyl is available in a transdermal therapeutic system (TTS). Potential advantages of delivering fentanyl

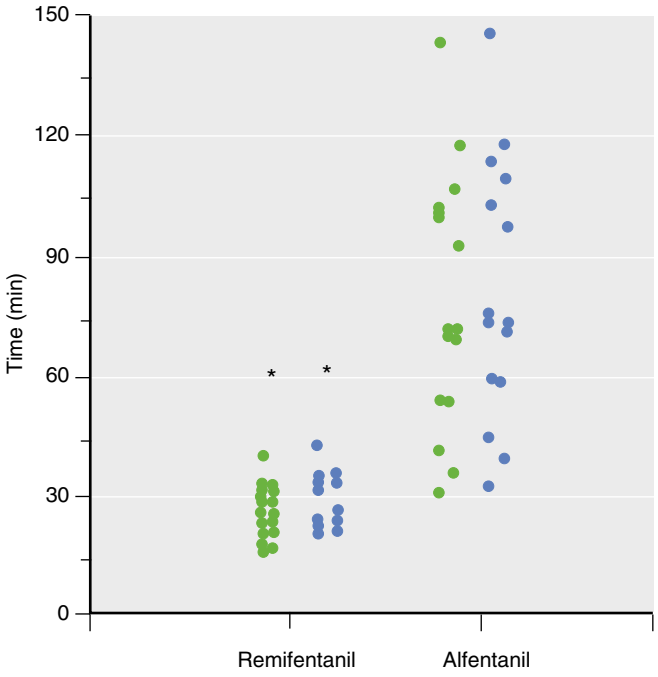


Figure 27-27 Times to awakening (*green circles*) and tracheal extubation (*blue circles*) in patients who underwent minimally invasive direct coronary artery bypass surgery after intravenous anesthesia with remifentanil-propofol or alfentanil-propofol. *(From Ahonen J, Olkkola KT, Verkkala K, et al: A comparison of remifentanil and alfentanil for use with propofol in patients undergoing minimally invasive coronary artery bypass surgery. Anesth Analg 90:1269-1274, 2000.)*

transdermally include no first-pass drug metabolism by the liver; improved patient compliance, convenience, and comfort; and consistent analgesia. Doses of TTS fentanyl include 20, 50, 75, and 100 µg/hr, and blood levels ranging from less than 1.0 to 2.0 ng/mL are achieved, although significant variability exists.[376] The pharmacokinetics of transdermally delivered fentanyl (50 µg/hr) was compared in 10 young adult (25- to 38-year-old) and 8 elderly (64- to 82-year-old) patients.[377] It was shown that the mean half-time (time for plasma concentrations to double after patch application) was 4.2 and 11.1 hours and the mean maximum plasma concentration was 1.9 and 1.5 ng/mL in the younger and elderly groups, respectively. There were no differences in the time at which maximum plasma concentrations occurred or the elimination half-life after patch removal. Elevated body temperature accelerates either release of fentanyl from the patch or distribution from the subcutaneous fat depot. Portenoy and coworkers demonstrated that a steady-state serum concentration was achieved by repeated application of TTS fentanyl and that the apparent half-life following system removal after repeated application was relatively long, presumably because of ongoing absorption from a subcutaneous depot (Fig. 27-28).[378]

The results of clinical trials using the transdermal fentanyl system for postoperative analgesia have demonstrated a high incidence of significant respiratory depression, and this application is not recommended.[376] In cancer pain, TTS fentanyl offers an alternative to oral morphine, and its effectiveness and tolerability for this indication have been demonstrated in a number of trials.[379] Its usefulness in chronic pain of nonmalignant origin remains to be confirmed in controlled trials. In general, TTS fentanyl produces the same adverse effects as other opioids, mainly sedation, nausea, vomiting, and constipation. In comparison to oral morphine, TTS fentanyl causes fewer gastrointestinal adverse events. The risk of hypoventilation is comparatively low in cancer patients. Sufentanil and buprenorphine may also be suitable for transdermal delivery, but clinical results are not yet available. Transdermal morphine is useful only if applied to de-epithelialized skin.

Iontophoresis

Iontophoresis is a technique by which drug passage through the skin is augumented with an external electric current. Clinically significant doses of morphine and fentanyl can be delivered iontophoretically.[380] The fentanyl HCl iontophoretic transdermal system (fentanyl ITS) is a novel PCA system that has been approved in the United States and Europe for the management of acute, moderate to severe postoperative pain.[381] This system allows patients to self-administer preprogrammed doses of fentanyl noninvasively through the use of iontophoretic technology. To assess the efficacy and safety of patient-controlled fentanyl ITS (40-µg infusion over a 10-minute period) versus standard intravenous morphine PCA (1-mg bolus every 5 minutes; maximum of 10 mg/hr), a prospective, randomized, controlled, parallel-group trial was performed.[382] The results indicated that the fentanyl ITS can provide pain control equivalent to that of standard morphine PCA, with a similar incidence of opioid-related adverse events. Fentanyl ITS may offer a number of clinical advantages over existing PCA modalities.[381] Its method of drug delivery avoids the risk of complications from needle-related injuries and infection, and its preprogrammed electronics eliminate the potential for manual programming errors and excessive dosing. In addition, the compact size of the system could enable greater patient mobility after surgery. Patient-controlled fentanyl ITS has the potential to become a valuable option in the management of acute postoperative pain.

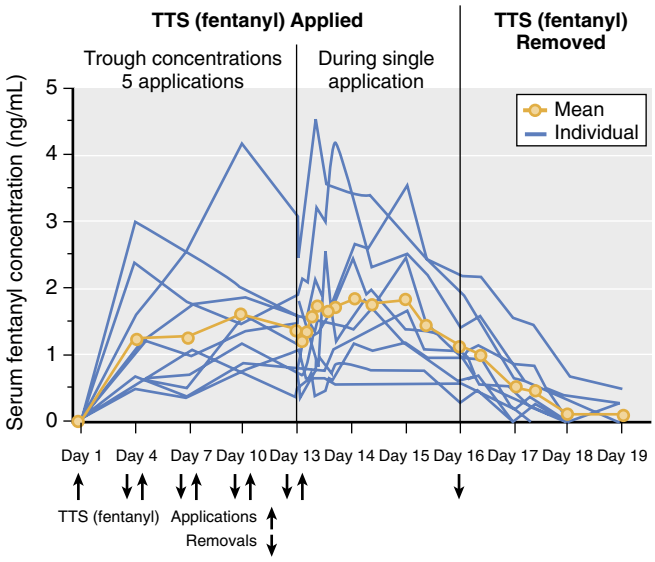


Figure 27-28 Individual and mean (SE) serum fentanyl concentration-time profiles measured in 10 patients during five consecutive applications of the transdermal fentanyl system. *(From Portenoy RK, Southam MA, Gupta SK, et al: Transdermal fentanyl for cancer pain. Repeated dose pharmacokinetics. Anesthesiology 78:36-43, 1993.)*

Transmucosal Drug Delivery

Similar to transdermal drug delivery, transmucosal delivery through the oropharynx and nasopharynx eliminates hepatic first-pass metabolism (drugs are absorbed directly into the systemic circulation) and improves patient comfort, convenience, and compliance.

Buprenorphine, a potent synthetic morphine analog with mixed opioid agonist-antagonist properties and a long half-time, is readily absorbed from sublingual mucosal tissues. The portion of the drug that is swallowed is almost completely metabolized by the liver, and only a small fraction can reach the systemic circulation when swallowed. Systemic bioavailability after sublingual buprenorphine is approximately 50% of that after intravenous administration. In several studies, sublingual buprenorphine (0.4 mg) was compared with conventional intramuscular morphine or meperidine and found to provide comparable and satisfactory analgesia.[383]

The initial experience with buccal morphine for postoperative analgesia had been promising. However, in female patients undergoing lower abdominal surgical procedures, buccal morphine did not significantly reduce postoperative pethidine consumption when compared with placebo, and all patients receiving buccal morphine reported a taste that reduced its acceptability.[384] The low lipid solubility of morphine makes it an unlikely candidate for effective transmucosal absorption. Opioids with high lipid solubility, such as buprenorphine, fentanyl, and methadone, are more effectively absorbed sublingually than those with low lipid solubility, such as morphine.

Oral transmucosal fentanyl citrate (OTFC) is a solid dosage form of fentanyl that consists of fentanyl incorporated into a sweetened lozenge on a stick. A portion of the fentanyl is absorbed through the oral mucosa, and the rest is swallowed and absorbed through the gastrointestinal tract. The swallowed fentanyl has low bioavailability because of hepatic first-pass metabolism. Recommended doses range from 5 to 20 µg/kg.[385,386] OTFC should be administered approximately 30 minutes before surgery (or a painful procedure) to obtain peak effect. Plasma concentrations after administration of OTFC peak at 2.0 ± 0.5 ng/mL 15 to 30 minutes after administration and then decline to less than 1 ng/mL an hour later.[387] Unlike transdermal fentanyl, OTFC leaves no significant depot in mucosal tissues after it is removed. The systemic bioavailability of OTFC is 50%, and this figure reflects both buccal and gastrointestinal absorption. OTFC bioavailability is similar to that of buprenorphine (55%), but much greater than the bioavailability of buccal morphine and other opioids with low lipid solubility. Egan and associates demonstrated that the pharmacokinetics of OTFC did not change with repeated dosing and that the decline in plasma concentration was as rapid as when administered intravenously (Fig. 27-29).[388] Preoperative OTFC was reported to be effective for postoperative analgesia in pediatric tonsillectomy patients.[389] However, OTFC can induce perioperative emesis and respiratory depression. It is also being evaluated for the treatment of breakthrough cancer pain.[390] OTFC may be ideally suited to treat breakthrough cancer pain because fentanyl is rapidly absorbed from OTFC and patients can easily self-administer OTFC.

Delivery of opioids through the nasal mucosa has also been investigated. Pharmacokinetic studies in volunteers have been reported for fentanyl, alfentanil, sufentanil, butorphanol, oxycodone, and buprenorphine.[391] Mean times to achieve maximum serum concentrations vary from 5 to 50 minutes, whereas bioavailability varies from 46% to 71%. Fentanyl, pethidine, and butorphanol have been studied for postoperative pain. Mean onset times vary from 12 to 22 minutes and times to peak effect from 24 to 60 minutes. Transnasal butorphanol provides superior and more prolonged analgesia than do similar doses given intravenously for postoperative pain after cesarean section.[392] PCA with intranasal fentanyl was demonstrated to be effective for postoperative pain management.[393] Side effects of intranasal sufentanil in children include reduced ventilatory compliance (chest wall rigidity), hypoxemia, impaired manual ventilation, and nausea and vomiting.[394,395] It appears that further exploration of the transnasal approach to drug delivery for pain management is merited. Improvements in nasal sprayer devices and opioid formulations may improve the clinical outcome.

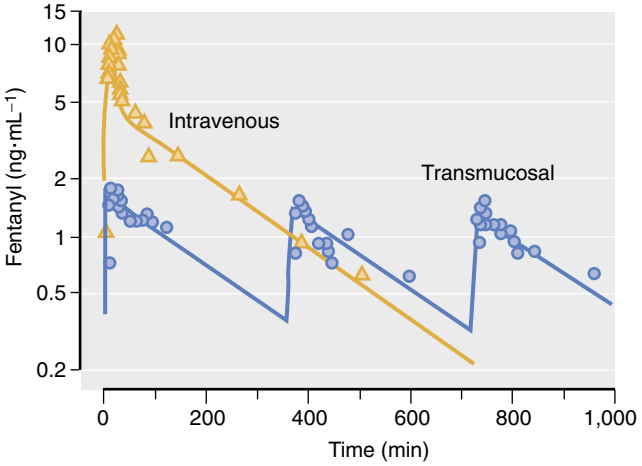


Figure 27-29 Typical result of the time-dependent change in plasma concentration of fentanyl after the application of oral transmucosal fentanyl citrate OTFC) and intravenous administration. Three 800-µg doses of OTFC were administered at 6-hour intervals, and fentanyl was infused at a constant rate of 50 µg/min to a total of 15 µg/kg. *(From Egan TD, Sharma A, Ashburn MA, et al: Multiple dose pharmacokinetics of oral transmucosal fentanyl citrate in healthy volunteers. Anesthesiology 92:665-673, 2000.)*

Inhalation of fentanyl (300 µg) produces a low plasma drug level (0.1 ng/mL) after 15 minutes and analgesia that may be disproportionately greater than expected.[396] Inhaled liposome-encapsulated fentanyl was also demonstrated to be a noninvasive route of administration that provides a rapid increase in and prolonged maintenance of the plasma fentanyl concentration.[397] Inhaled nebulized fentanyl citrate significantly improved patient perception of breathing, the respiratory rate, and oxygen saturation in terminally ill cancer patients.[398] This inexpensive and readily available treatment may offer substantial relief of end-of-life dyspnea. The advent of specialized and efficient pulmonary drug delivery systems has facilitated the evaluation of inhaled opioids, such as morphine and fentanyl, for the management of severe pain associated with surgery or malignant disease.[399]

The rectal mucosa is another site for transmucosal drug delivery. The bioavailability of a 30-mg morphine sulfate controlled-release suppository formulation was significantly greater than that of 30-mg oral controlled-release morphine sulfate tablets, which may be the result of partial avoidance of hepatic biotransformation with rectal administration.[400] The hydrogel formulation of rectal morphine may also be useful for premedication and analgesia in pediatric patients.[401]

Oral Controlled-Release Medications

Despite the high first-pass metabolism of opioid analgesics, morphine has been formulated into an oral, sustained-release tablet (MST) and evaluated for premedication, for postoperative analgesia, and as an analgesic for chronic cancer pain. MST provides unreliable preoperative anxiolysis and postoperative pain relief, possibly because of delayed time to the onset of peak effects (3 to 5 hours), which can be increased by impaired gastric emptying and absorption from the small intestine. As an analgesic for chronic cancer pain, MST was shown to be an excellent choice.[402]

A controlled-release formulation of oxycodone administered every 12 hours for a maximum of 7 days was shown to provide adequate pain control in patients undergoing abdominal, orthopedic, or gynecologic surgery.[403] The relative analgesic potency of single doses of oral controlled-release oxycodone (20 or 40 mg) and oral controlled-release morphine (45 or 90 mg) was compared in a randomized, double-blind trial in women with moderate to severe pain after abdominal hysterectomy.[404] Controlled-release oxycodone at doses of 20 or 40 mg was comparable to controlled-release morphine at doses of 45 or 90 mg, respectively, in total and peak analgesic effects, thus indicating that oral controlled-release oxycodone was twice as potent as oral controlled-release morphine. A randomized, double-blind, crossover trial indicated that controlled-release oxycodone is as safe and effective as controlled-release morphine in the treatment of cancer pain.[405]

Other Opioid Agonists

Codeine (methylmorphine) is half as potent as morphine and has a high oral-parenteral potency ratio (2:3) and a plasma half-life of 2 to 3 hours. Codeine has mild to moderate analgesic but strong cough-suppressant properties after oral administration. CYP2D6 is the enzyme responsible for *O*-demethylation of codeine to morphine.[406] Intravenous codeine produces profound hypotension and is neither approved nor recommended.[407]

Hydromorphone is structurally related to morphine but is approximately 5 to 10 times as potent. Analgesia after hydromorphone lasts 4 to 5 hours.[408] The effects of hydromorphone are essentially indistinguishable from those of heroin.[409] Hydromorphone has been used for both acute and chronic pain conditions in adults and children.[410] It was reported that hydromorphone PCA provided adequate postoperative analgesia with improved mood and that it can be an alternative to morphine PCA.[411]

Levorphanol is an opioid agonist of the morphinan series with a long (12- to 19-hour) half-life. It is five times as potent as morphine with an intramuscular-oral potency ratio of 1:2. Levorphanol may have particular utility in patients who have chronic pain and demonstrate morphine tolerance, perhaps because of differences in opioid receptor activity. The analgesia produced by levorphanol is mediated via its interactions with μ-, δ-, and κ-opioid receptors. Levorphanol is also an NMDA receptor antagonist. The long half-life of the drug increases the potential for drug accumulation.[412]

Methadone has equivalent potency but a longer duration of action than morphine does. The plasma half-life of methadone is very long and variable (13 to 100 hours). Despite this property, many patients require dosing every 4 to 8 hours to maintain analgesic effects. Its major clinical applications are for the prevention of opioid withdrawal symptoms and the treatment of chronic pain. It was shown that the same intravenous dose of methadone (20 mg) that is effective for postoperative pain is also suitable for induction of anesthesia in combination with etomidate and that methadone may have the potential to produce histamine release.[413]

Oxymorphone is a semisynthetic opioid agonist that is specific for the μ-opioid receptor and approved to treat both acute and chronic pain. Because of extensive liver metabolism, oral oxymorphone is contraindicated in patients with moderate to severe hepatic impairment.[414] Oxymorphone, structurally related to morphine, is almost 10 times as potent as morphine but has a similar duration of action. It was shown that in patients with acute moderate to severe postsurgical pain, oral immediate-release oxymorphone, 10, 20, or 30 mg, provided significant dose-related pain relief in comparison to placebo and that this relief was maintained for a period of several days with a safety profile comparable to that of immediate-release oxycodone.[415]

Piritramide, a synthetic opioid structurally related to meperidine, is devoid of emetic activity and is used for postoperative analgesia in several European countries.[416] Pharmacokinetic analysis has shown that piritramide is distributed extensively and eliminated slowly, and intermittent bolus administration is recommended.[417]

Tramadol is a synthetic 4-phenyl-piperidine analog of codeine with a dual mechanism of action. Tramadol stimulates the μ-receptor and, to a lesser extent, the δ- and κ-opioid receptors, and like tricyclic antidepressants, it also activates spinal inhibition of pain by decreasing the reuptake of norepinephrine and serotonin.[418] It is suggested that tramadol may have a direct serotonin-releasing action.[419] Tramadol is one fifth to one tenth as potent as morphine. In rats, tramadol could reduce the MAC of isoflurane in a naloxone-sensitive manner.[420] It was shown that intravenously administered tramadol was effective for post-thoracotomy pain relief.[421] Analgesic doses of tramadol may produce less respiratory depression, in part because of its non–opioid receptor–mediated actions,[422] and have minimal effects on gastrointestinal motor function.[423] Seizures have been reported in patients taking the drug. Caution should be exercised when combining tramadol with MAOIs, neuroleptic agents, and other drugs that lower the seizure threshold. It was suggested that tramadol has local anesthetic properties on peripheral nerves when used alone.[424] Tramadol added to lidocaine for intravenous regional anesthesia provided a shorter time to onset of sensory blockade.[425]

Sameridine possesses both local anesthetic and opioid properties. In patients undergoing arthroscopic knee joint surgery, sameridine was administered intrathecally and provided clinically adequate anesthesia.[426] A large intravenous dose of sameridine depressed resting ventilation and the hypercapnic ventilatory response, whereas a smaller clinical dose did not.[427,428]

M6G is a potent metabolite of morphine. In contrast to morphine, M6G is not metabolized but excreted via the kidneys and exhibits enterohepatic cycling inasmuch as it is a substrate for multidrug resistance transporter proteins in the liver and intestines.[429] M6G exhibits a delay in its analgesic effect (blood effect-site equilibration half-life of 4 to 8 hours), which is partly related to slow passage through the blood-brain barrier and distribution within the brain compartment. In humans, the potency

of M6G is just half of that of morphine. Trials to use M6G as an analgesic have been reported. Osborne and colleagues reported that 0.5 to 4 mg of M6G intravenously was effective for cancer pain for 2 to 24 hours without nausea and vomiting.[430] M6G, 100 µg and 125 µg given intrathecally, provided excellent analgesia after total hip replacement, as did intrathecal morphine sulfate, 500 µg.[431]

Agonist-Antagonist Opioid Compounds

Nalorphine, the first agonist-antagonist opioid, was successfully synthesized by Weijland and Erickson in 1942 and found to be strongly antagonistic to almost all the properties of morphine. Although nalorphine was found to possess strong analgesic actions, it was unsuitable for clinical use because of its psychotomimetic effects. Nalorphine was used in lower doses as an opioid antagonist.

Agonist-antagonist opioids are usually produced by alkylation of the piperidine nitrogen and addition of a three-carbon side chain such as a propyl, allyl, or methyl allyl to morphine. Buprenorphine is a partial agonist at the µ-receptor. The other compounds are µ-antagonists and full or partial agonists at the κ-receptor. Agonist-antagonist opioids are less prone (but not immune) to abuse because they cause less euphoria and are associated with less drug-seeking behavior and physical dependence.

Dosing data of these compounds are shown in Table 27-8. Agonist-antagonist compounds depress respiration in a similar manner as morphine, but ceiling effects exist (Table 27-9). Effects on the cardiovascular system differ among these compounds (Table 27-10).

Pentazocine

The analgesia produced by pentazocine is primarily related to stimulation of the κ-receptor. Pentazocine is one half to one fourth as potent as morphine. Ceilings in both analgesia and respiratory depression occur after 30 to 70 mg of pentazocine. Although the potential for abuse is less than with morphine, prolonged use of pentazocine can lead to physical dependence.

Table 27-8 Dosing Data for Agonist-Antagonist Opioids and Morphine

	Equianalgesic Intramuscular Dose (mg)	Duration of Analgesia (hr)	Oral-Intramuscular Efficacy Ratio
Morphine	10	4-5	1 : 6
Buprenorphine	0.3-0.4	>6	1 : 2*
Butorphanol	2	3-4	—
Nalbuphine	10	3-6	1 : 4-5
Pentazocine	40	3	1 : 3

*Sublingual-intramuscular ratio.

Table 27-9 Respiratory Depressant Effects of Agonist-Antagonists Compared with Morphine*

Drug	Correlation of Respiratory Depression with Dose
Morphine	Increases proportionally with dose
Buprenorphine	Ceiling effect at 0.15-1.2 mg in adults
Butorphanol	Ceiling effect at 30-60 µg/kg
Nalbuphine	Ceiling effect at 30 mg in adults
Pentazocine	Ceiling effect suggested, but difficult to study because of psychotomimetic effects

*Low or moderate naloxone doses readily reverse the respiratory effects produced by therapeutic doses of all the drugs listed except buprenorphine.
From Zola EM, McLeod DC: Comparative effects of analgesic efficacy of the agonist-antagonist opioids. Drug Intell Clin Pharm 17:411, 1983.

Nalorphine-like dysphoric side effects are common, especially after high doses (>60 mg) of pentazocine in the elderly. The dysphoric effects of pentazocine can be reversed with naloxone. Pentazocine depresses myocardial contractility and increases arterial blood pressure, heart rate, systemic vascular resistance, pulmonary artery pressure, and left ventricular work index. Pentazocine also increases blood catecholamine levels.

Pentazocine inhibited gastric emptying and gastrointestinal transit in rats, whereas U50488H, a pure κ-agonist, did not significantly inhibit either.[432] Therefore, it might be speculated that pentazocine affects gastrointestinal function through a mechanism other than the opioid receptors.

Pentazocine has limited application because it is associated with a high incidence of postoperative nausea and vomiting, provides limited analgesia, partially antagonizes other opioids, and can produce undesirable cardiovascular and psychotomimetic effects.

Butorphanol

Butorphanol is an agonist at κ-receptors. Its activity at µ-receptors is either antagonistic or partially agonistic. It is five to eight times as potent as morphine and is available only in parenteral form. After intramuscular injection, the onset of effect is rapid,

Table 27-10 Hemodynamic Effects of Agonist-Antagonist Compounds Compared with Morphine

Drug	Cardiac Workload	Blood Pressure	Heart Rate	Pulmonary Artery Pressure
Morphine	↓	↓	=↓	=↓
Buprenorphine	↓	↓	↓	?
Butorphanol	↑	=↑	=	↑
Nalbuphine	↓	=	=↓	=
Pentazocine	↑	↑	↑	↑

From Zola EM, McLeod DC: Comparative effects of analgesic efficacy of the agonist-antagonist opioids. Drug Intell Clin Pharm 17:411, 1983.

and peak analgesia occurs within 1 hour. Whereas the duration of action of butorphanol is similar to that of morphine, its plasma half-life is only 2 to 3 hours. Although butorphanol (10 mg IM) causes as much respiratory depression as the same dose of morphine, higher doses reach a ceiling. Side effects after butorphanol include drowsiness, sweating, nausea, and CNS stimulation. In healthy volunteers, butorphanol (0.03 or 0.06 mg/kg IV) produces no or minimal cardiovascular changes. However, in patients with cardiac disease, butorphanol causes significant increases in cardiac index, left ventricular end-diastolic pressure, and pulmonary artery pressure.

Because butorphanol decreases the MAC for enflurane by only a small fraction, it cannot serve as an anesthetic agent like the fentanyl congeners. Butorphanol is subject to less abuse and has less addictive potential than morphine or fentanyl does. Acute biliary spasm can occur after butorphanol, but increases in biliary pressure are less than after equipotent doses of fentanyl or morphine. Transnasal butorphanol is effective in relieving migraine and postoperative pain.[433]

Buprenorphine

Buprenorphine is a thebaine derivative, μ-receptor partial agonist and similar in structure to morphine but approximately 33 times more potent. Whereas fentanyl dissociates rapidly from μ-receptors (half-life of 6.8 minutes), buprenorphine has higher affinity and takes much longer (half-life of 166 minutes). The onset of action of buprenorphine is slow, its peak effect may not occur until 3 hours, and its duration of effect is prolonged (<10 hours). The volume of distribution of buprenophine is 2.8 L/kg and its clearance is 20 mL/kg/min. The metabolites of buprenorphine, buprenorphine-3-glucuronide and norbuprenorphine, are significantly less potent and have lower affinity for the μ-receptor.

The subjective effects (e.g., euphoria) of buprenorphine are similar to those of morphine. Buprenorphine produces depression of minute ventilation, which leveled off at doses higher than 3.0 μg/kg to about 50% of baseline, in contrast to fentanyl, in which dose-dependent respiratory depression results in apnea at doses higher than 2.9 μg/kg (Fig. 27-30).[434] Buprenorphine has been used successfully for premedication (0.3 mg IM), as the analgesic component in balanced anesthesia (4.5 to 12 μg/kg), and for postoperative pain control (0.3 mg IM). Buprenorphine, like the other agonist-antagonist compounds, is not acceptable as a sole anesthetic, and its receptor kinetic profile restricts its usefulness if other μ-agonists are used. Opioid withdrawal symptoms develop slowly (5 to 10 days) when buprenorphine is discontinued after long-term use.

Nalbuphine

Nalbuphine is an agonist-antagonist opioid that is structurally related to oxymorphone and naloxone and binds to μ-receptors, as well as to κ- and δ-receptors. Nalbuphine acts as an antagonist at the μ-receptor and as an agonist at the κ-receptor. Activation of supraspinal and spinal κ-receptors results in limited analgesia, respiratory depression, and sedation. Nalbuphine, like other agonist-antagonist compounds, interferes with the analgesia produced by pure μ-agonists. In rats, coadministration of nalbuphine with morphine dose-dependently blocked the development of morphine tolerance and dependence, without attenuation of the antinociceptive effect of morphine.[435] Nalbuphine is available only for parenteral use. The onset of effect is rapid (5 to 10 minutes), and its duration is long (3 to 6 hours) because of an extended plasma elimination half-life (5 hours).

Premedication with nalbuphine (0.1 mg/kg) in patients scheduled for cardiac surgery results in sedation, relief of anxiety, and respiratory depression similar to morphine (0.1 mg/kg), but

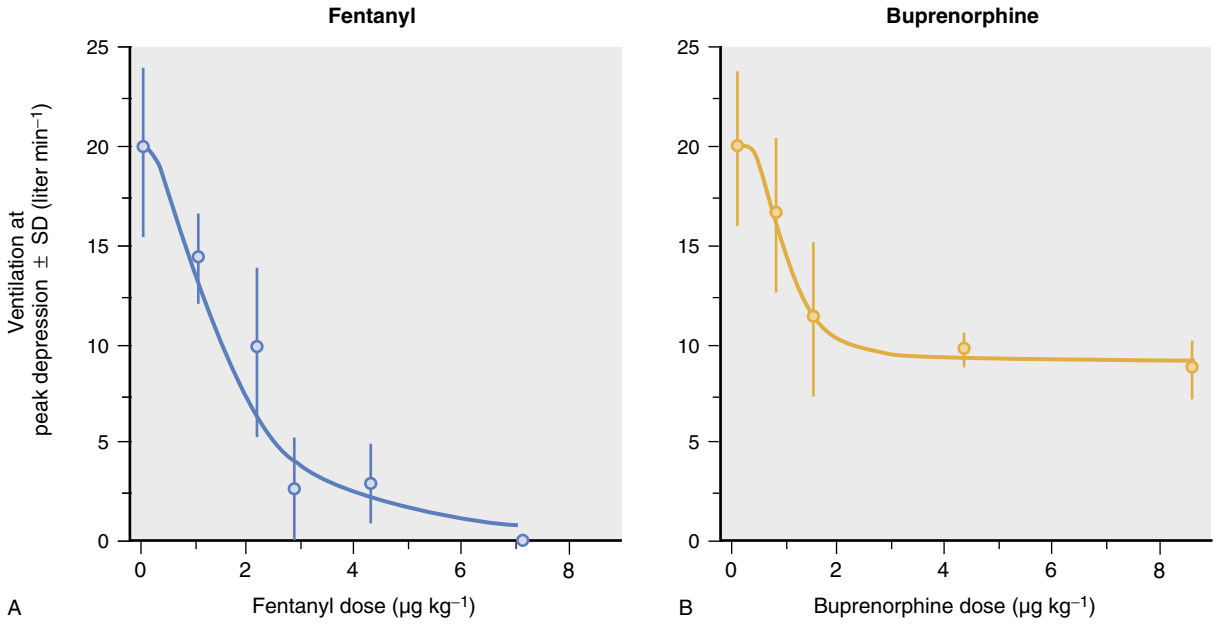


Figure 27-30 Dose-response relationships for reduction of minute ventilation induced by fentanyl (**A**) and buprenorphine (**B**). The response is the peak ventilatory depression at each dose. The line through the data is the fit to the Hill equation; 0 μg/kg is placebo. Data are means ± SD. *(From Dahan A, Yassen A, Bijl H, et al: Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. Br J Anaesth 94:825-834, 2005.)*

it causes no significant hemodynamic changes. Nalbuphine (10 mg) caused no significant changes in systemic, pulmonary arterial, and pulmonary capillary wedge pressure in patients experiencing myocardial infarction.

Nalbuphine has been administered as an analgesic supplement for conscious sedation or balanced anesthesia and as an analgesic for postoperative and chronic pain problems. For postoperative patient-controlled epidural analgesia, the combination of hydromorphone, 0.075 mg/mL, and nalbuphine, 0.04 mg/mL, resulted in a lower incidence of nausea and decreased need for bladder catheterization when compared with hydromorphone alone.[436] In patients undergoing myocardial revascularization, continuous infusion of nalbuphine (0.05 to 0.1 mg/kg/min) and fentanyl (0.15 to 0.3 μg/kg/min) was compared.[437] It was shown that nalbuphine lacks the ability to attenuate cardiovascular and hormonal responses to tracheal intubation and surgical procedures, and it was concluded that continuous infusion of nalbuphine cannot be recommended for anesthesia in patients undergoing myocardial revascularization.

A prospective randomized double-blind study demonstrated that nalbuphine (4 mg IV) was as effective as ondansetron (4 to 8 mg IV) for the prevention of intrathecal morphine–induced pruritus after cesarean delivery.[438] Some reports showed that nalbuphine provides a rapid and potent antishivering effect, similar to meperidine.[439] However, a quantitative systematic review of randomized controlled trials did not support this conclusion.[440]

Other Compounds

Dezocine

Dezocine is slightly more potent and acts faster than morphine; it has a similar duration of action and is a partial agonist at μ- and probably δ-receptors. Its side effects are similar to those of morphine. Although shown to be an effective alternative to fentanyl when administered during outpatient laparoscopy with propofol and nitrous oxide, dezocine was associated with a high incidence of postoperative nausea and a delayed discharge time.[441] In adult patients who underwent arthroscopic surgery with general anesthesia, dezocine (5 mg IV) and morphine (5 mg IV) were similarly effective for postoperative analgesia and showed comparable side effects.[442]

Meptazinol

Meptazinol has been reported to cause minimal respiratory depression because of its selectivity for μ_1 (high-affinity) receptors. In patients receiving meptazinol (2.5 mg/kg) with a barbiturate, no cardiovascular changes were observed at tracheal intubation, whereas blood pressure and heart rate were significantly increased in patients receiving fentanyl (5 μg/kg).[443] Side effects (nausea and vomiting) limit its use to relief of severe pain.

Opioid Antagonists

Naloxone

Clinically, opioid antagonists are used to restore spontaneous ventilation in patients who breathe inadequately after opioid overdose or opioid anesthesia. In addition, opioid antagonists can reduce or reverse opioid-induced nausea and vomiting, pruritus, urinary retention, rigidity, and biliary spasm associated with numerous therapies using opioids, such as neuraxial analgesic techniques. It was reported that the naloxone-nalbuphine potency ratio for antagonism of the pruritic effects of epidural morphine was approximately 40 : 1.[444]

Morphine requirements were significantly less in patients receiving naloxone, thus suggesting that naloxone enhances analgesia.[445] Possible mechanisms proposed for this apparent paradoxical effect of naloxone include enhanced release of endogenous opioids and opioid receptor upregulation.

Although naloxone is generally considered to be a pure opioid receptor antagonist, it delays gastric emptying of saline or milk, as does morphine in the rat.[259] Furthermore, high-dose naloxone possesses partial agonistic activity on μ- and κ-opioid receptors in cultured cells.[446]

Reversal of Respiratory Depression by Naloxone

In the early 1950s, nalorphine and levallorphan were evaluated as opioid antagonists. They were often found unacceptable because of a high incidence of side effects, as well as incomplete reversal. Naloxone was introduced into clinical practice in the late 1960s. There have been reports of side effects (increases in heart rate and blood pressure) and more serious complications (e.g., pulmonary edema). Initial naloxone dose recommendations ranged from 0.4 to 0.8 mg. The onset of action of intravenous naloxone is rapid (1 to 2 minutes), and its half-life and duration of effect are short, approximately 30 to 60 minutes. If intravenous access is not available, naloxone, in doses similar to those given intravenously, is effectively absorbed after intratracheal administration.[447] Reversal with naloxone is limited by high affinity for and slow dissociation from the μ-opioid receptor of buprenorphine and depends on the buprenorphine dose and the correct naloxone dose window (Fig. 27-31).[448] Because respiratory depression from buprenorphine may outlast the effects of naloxone boluses or short infusions, continuous infusion of naloxone may be required to maintain reversal of respiratory depression.[448]

Several mechanisms produce increases in arterial blood pressure and heart rate, as well as other significant hemodynamic alterations, after naloxone reversal of opioids. These mechanisms include pain, rapid awakening, and sympathetic activation not necessarily caused by pain. When patients receiving naloxone for opioid agonist reversal are hypothermic because of intraoperative heat loss, O_2 consumption and minute ventilation can increase twofold to threefold.[449] Such metabolic demands also stress the cardiovascular system by increasing cardiac output. In addition, greater degrees of hypercapnia at the time of opioid antagonism will result in greater degrees of cardiovascular stimulation because of associated sympathetic stimulation. Opioid reversal may be particularly hazardous in patients with pheochromocytoma or chromaffin tissue tumors.[450] However, it was also reported that intravenous administration of 10-mg naloxone did not significantly change the plasma catecholamine concentration and blood pressure.[451]

Recurrence of respiratory depression after naloxone is due to the short half-life of naloxone. "Renarcotization" occurs more frequently after the use of naloxone to reverse longer-acting opioids such as morphine. Short-acting opioids such as alfentanil rarely pose a danger of renarcotization because of a rapid plasma decay curve and weaker opioid receptor binding than with fentanyl and sufentanil.

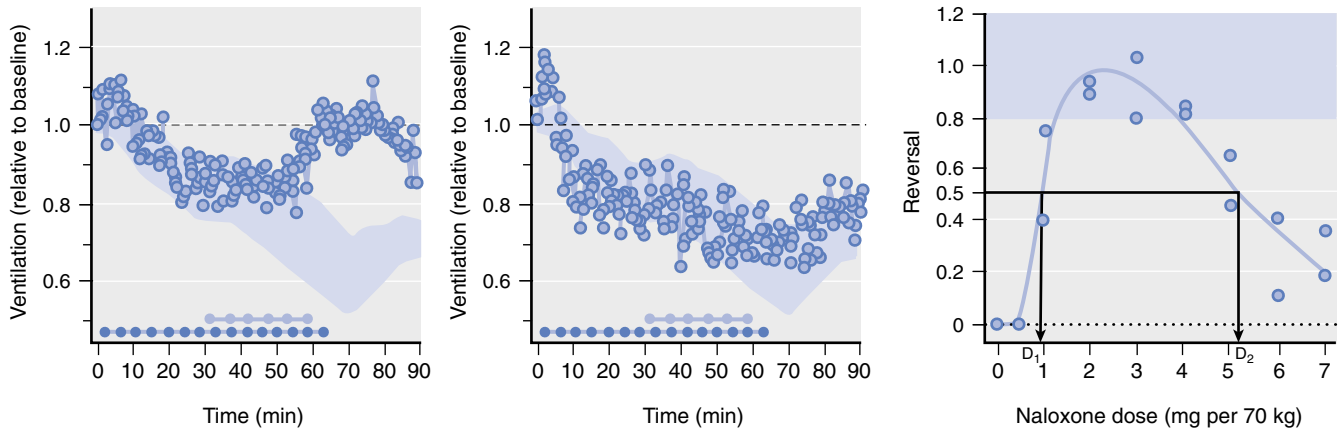


Figure 27-31 Reversal of buprenorphine-induced respiratory depression with naloxone depends on the correct naloxone dose window. Respiratory depression induced by 0.2 mg buprenorphine was reversed by naloxone, 2 mg (**left**) and 6 mg (**middle**), given over a 30-minute period in one subject. The *light blue field* in the background is the result of the placebo group, in which saline was infused instead of naloxone. *Dark blue dots* and *light blue dots* represent buprenorphine and naloxone infusion, respectively. **Right,** Influence of 0 (placebo) and 0.5 to 7 mg naloxone on respiratory depression induced by 0.2 mg intravenous buprenorphine. Reversal was calculated from the naloxone-induced change in ventilation and ranged from 0 (effect not different from placebo) to 1 (reversal to predrug baseline level). *(From van Dorp E, Yassen A, Sarton E, et al: Naloxone reversal of buprenorphine-induced respiratory depression. Anesthesiology 105:51-57, 2006.)*

Naloxone, though active at μ-, δ-, and κ-receptors, has greatest affinity for μ-receptors, which mediate most potent opioid effects, including respiratory depression and analgesia. Careful titration of naloxone can often restore adequate spontaneous ventilation without reversal of adequate analgesia.

Other Applications of Naloxone

Reversal of the effects of alcohol, barbiturates, and benzodiazepines by naloxone has been reported. However, it was also reported that naloxone potentiates the anxiolytic-like action of benzodiazepines and barbiturates in the rat.[452] It is not advisable to try to reverse the effects of overdose of benzodiazepines and barbiturates with naloxone. Although it was suggested that the μ-opioid receptor is involved in the antinociceptive action of ketamine in mice,[41] naloxone did not affect the action of ketamine on secondarty hyperalgesia induced by burn injury in humans.[453]

Evidence indicates that endogenous opioid peptides participate in the control of cardiovascular regulation during hemorrhagic shock. Intracerebroventricular administration of 10 mg of naloxone resulted in a significant increase in the bleeding volume required to lower arterial pressure from 60 to 40 mm Hg in rats.[454] In patients with documented septic shock and resistance to a 1-L fluid challenge, administration of naloxone by an initial bolus of 0.03 mg/kg followed by infusion at a rate of 0.2 mg/kg/hr significantly increased mean arterial pressure but did not affect survival.[455] This effect may be due to centrally mediated increases in sympathetic tone and decreases in parasympathetic output or antagonism of endogenous opioids. However, the clinical usefulness of naloxone in treating shock remains to be determined, and additional randomized clinical trials are needed to assess its usefulness.[456]

It has been reported that naloxone may ameliorate the neurologic deficit after an ischemic or traumatic neurologic insult in animals.[457] In humans, a randomized controlled trial demonstrated that naloxone (a bolus of 5.4 mg/kg, followed by infusion at 4.0 mg/kg/hr for 23 hours) does not improve neurologic recovery after acute spinal cord injury.[458] However, it was reported that combined use of cerebrospinal fluid drainage and naloxone reduces the risk of paraplegia in patients undergoing thoracoabdominal aneurysm repair.[459] Naloxone may also have a therapeutic role in heat stroke disorders[460] and cholestasis-induced pruritus.[461] Although intravenous naloxone has been claimed to produce pain relief in opioid-resistant central poststroke pain, a double-blind trial concluded that intravenous naloxone was of no value in alleviating central poststroke pain.[462]

Other Opioid Antagonists

Naltrexone

Naltrexone is a μ-, δ-, and κ-opioid receptor antagonist. It is longer acting than naloxone (plasma half-life of 8 to 12 versus 0.5 to 1.5 hours), and it is active when taken orally. A double-blind, placebo-controlled study of patients undergoing cesarean section indicated that naltrexone (6 mg) was an effective oral prophylactic against the pruritus and vomiting associated with intrathecal morphine but was associated with a shorter duration of analgesia.[463]

Nalmefene

Nalmefene has a greater preference for μ-receptors than for δ- or κ-receptors. It is equipotent to naloxone.[464] Nalmefene is long acting after oral (0.5 to 3.0 mg/kg) and parenteral (0.2 to 2.0 mg/kg) administration. Bioavailability after oral administration is 40% to 50%, and peak plasma concentrations are reached in 1 to 2 hours. The mean terminal elimination half-life of nalmefene is 8.5 hours as compared with 1 hour for naloxone. Prophylactic administration of nalmefene significantly decreased the need for antiemetics and antipruritic medications in patients receiving intravenous PCA with morphine.[465]

Methylnaltrexone

Methylnaltrexone is the first quarternary ammonium opioid receptor antagonist that does not cross the blood-brain barrier. It

can reverse the adverse effects of opioid medications mediated by peripheral opioid receptors, whereas the opioid effects mediated by opioid receptors in the CNS, such as analgesia, are not affected. The delayed gastric emptying induced by 0.09 mg/kg morphine could be attenuated by 0.3 mg/kg methylnaltrexone in healthy volunteers.[250] It was also reported that methylnaltrexone was effective in reversing the constipation from chronic methadone use.[466] Because methylnaltrexone does not cross the dura, it might have potential to reverse the peripherally mediated side effects of epidural opioids.[467]

Drug Interactions with Opioids

Opioids are frequently combined with other anesthetic agents to produce optimal anesthetic conditions. In anesthesia, most concomitantly administered drugs interact. Although some of these interactions are intentionally sought, others are unwanted and adverse. There are three general types of mechanisms of drug interactions: pharmaceutical, pharmacokinetic, and pharmacodynamic.[468]

Pharmaceutical interactions are chemical in nature, as illustrated when an alkaline solution of thiopental and an acidic solution of succinylcholine precipitate when simultaneously administered intravenously.

Pharmacokinetic interactions occur when the administration of one agent alters the pharmacokinetics or disposition of another. The hemodynamic changes induced by one agent can affect the pharmacokinetic behavior of the other agent. Sufentanil, which has a greater hepatic extraction ratio than alfentanil does, is more likely to be affected by decreases in hepatic blood flow. Opioid plasma levels also increase in the presence of propofol.[469] Decreased opioid metabolism by the CYP3A4 isoform of the cytochrome P450 enzyme responsible for the oxidative metabolism of more than 50 drugs may also underlie the pharmacokinetic interactions. A wide range of chemical compounds, including many drugs, can interact with the cytochrome P450 system and cause either increased activity (enzyme induction) or enzyme inhibition (Box 27-3).[468]

Pharmacodynamic interactions between opioids and inhaled anesthetics were assessed by evaluating classic MAC reduction in animals and humans. Although marked synergism between opioids and inhaled anesthetics occurs with analgesic doses of opioids, there is a ceiling effect to MAC reduction by opioids. The pharmacodynamic synergism between opioids and sedative-hypnotics such as propofol is profound. Choosing an opioid with a short context-sensitive half-life allows greater doses of that opioid to be administered, along with reduced doses of propofol, without compromising the time needed for recovery from anesthesia. Thus, the optimal plasma level of propofol is estimated to be approximately 30% less when it is combined with remifentanil instead of alfentanil.[469]

Drug dosing regimens and a plasma concentration of opioid and sedative-hypnotics that provide optimal hemodynamic control during a range of noxious stimuli are necessary. However, complicating our understanding of drug interactions is the observation that the same degree of interaction does not apply across different types of stimuli.

Box 27-3 Drugs That Inhibit or Induce Cytochrome P450 Enzymes

Inhibitors

- Antibiotics
  - Maclorides
    - Troleandromycin
    - Erythromycin
  - Fluoroquinolones
  - Isoniazid
- Azole antifungal drugs
  - Ketoconazole
  - Itraconazole
- Calcium entry blockers
  - Diltiazem
  - Verapamil
- Omeprazole
- Cimetidine
- Propofol
- Grapefruit juice

Inducers

- Barbiturates
- Antiepileptics
  - Carbamazepine
  - Phenytoin
  - Primidone
- Rifampicin
- Dichloralphenazone
- Ethanol
- Tobacco smoke

From Bovill JG: Adverse drug interactions in anesthesia. J Clin Anesth 9:3S, 1997.

Sedative-Hypnotics

Alfentanil was found to reduce the median effective dose (ED_{50}) of midazolam for induction of anesthesia in a dose-dependent fashion. The smallest dose of alfentanil (3 μg/kg) that causes a marked shift in the midazolam dose-response curve to the left along the dose axis (from an ED_{50} of 270 μg/kg to an ED_{50} of 142 μg/kg) represents approximately 2% of the alfentanil ED_{50} for induction of unconsciousness (130 μg/kg).[463] On the contrary, with regard to the antinociceptive effect, interaction between these two types of drugs may be less than additive.[470,471] Midazolam enhances opioid-induced antinociception at the spinal level but inhibits it at the supraspinal level.[472] Many studies reveal that benzodiazepine-opioid interactions for many properties other than analgesia are synergistic (supra-additive). Both the cardiovascular and respiratory actions of opioids can be significantly altered by the concomitant administration of benzodiazepines.[473] In anesthetized rabbits, fentanyl and midazolam synergistically caused depression of phrenic nerve activity.[474] Combinations of benzodiazepines and opioids, though occasionally preserving ventricular function, can result in significant and occasionally profound decreases in blood pressure, cardiac index, heart rate, and systemic vascular resistance. Fluid loading may

attenuate the circulatory depression that occurs when benzodiazepines and opioids are combined.

Barbituraes can potentiate or produce hypotension if a large dose is administered with opioids. Hypotension after a barbiturate-opioid combination is due to venodilatation, decreased cardiac filling, myocardial depression, and decreased sympathetic nervous system activity. Reducing induction doses of barbiturates administered concomitantly with opioids is recommended.

The administration of propofol-opioid combinations provides unconsciousness and blocks responses to noxious stimuli. However, when given as an intravenous bolus for induction of anesthesia, propofol can create moderate to severe preintubation hypotension. The addition of 2 to 4 μg/kg fentanyl significantly potentiated the decrease in mean blood pressure induced by 2.0 to 3.5 mg/kg propofol.[475] Propofol-fentanyl and propofol-sufentanil anesthesia for coronary artery bypass surgery may provide acceptable conditions, but mean arterial pressure can decrease to levels that may jeopardize coronary perfusion, especially during induction of anesthesia.[476] In healthy volunteers, the addition of alfentanil (effect-site concentration of 50 or 100 ng/mL) did not affect the changes in BIS induced by propofol but blocked the increase in BIS induced by painful stimuli.[477] In patients undergoing spine fusion, infusion of fentanyl (blood levels of 1.5 to 4.5 ng/mL) reduced the infusion rate of propofol necessary to maintain mean arterial pressure but delayed spontaneous eye opening and recovery of orientation.[340] In patients undergoing ambulatory gynecologic laparoscopy, administration of fentanyl (25 to 50 μg IV) at the time of induction of anesthesia reduced the maintenance propofol requirement but failed to provide effective postoperative analgesia and increased the need for postoperative use of antiemetics.[478] Pharmacokinetic interaction, as well as pharmacodynamic interaction, between propofol and opioids has been reported. Target-controlled infusion of alfentanil (target concentration, 80 ng/mL) was shown to increase the blood propofol concentration by 17% and decrease the elimination clearance, distribution clearance, and peripheral volume of distribution of propofol.[479]

Other anesthetic induction agents such as etomidate and ketamine can be combined in low doses with opioids with little loss of cardiovascular stability. In patients scheduled for coronary artery bypass grafting, etomidate (0.25 mg/kg) plus fentanyl (6 μg/kg) resulted in less hypotension after induction and intubation than propofol (1 mg/kg) plus fentanyl (6 μg/kg) did.[480] As described in the previous section, opioid-induced hyperalgesia and subsequent acute opioid tolerance can be prevented by ketamine in rats, suggesting the usefulness of the combination of ketamine and opioids for postoperative analgesia. However, it was reported that the combination of ketamine (2.5 or 10 mg IV) and alfentanil (0.25 or 1 mg IV) provides no advantage over a larger dose of either drug alone in relieving pain caused by intradermal capsaicin injection in healthy volunteers.[481] Furthermore, the combination of ketamine, 1 mg/mL, and morphine, 1 mg/mL, for PCA did not provide benefit to patients undergoing major abdominal surgery.[482] In contrast, Lauretti and coauthors reported that oral ketamine and transdermal nitroglycerin effectively reduced the daily consumption of oral morphine in patients with cancer pain.[483]

Gabapentin, a structural analog of GABA, is a novel anticonvulsant drug that has analgesic effects in patients with neuropathic pain. It was suggested that pharmacodynamic and pharmacokinetic interaction between morphine and gabapentin leads to increased analgesic effects.[484] Furthermore, intrathecal administration of gabapentin was shown to prevent the development of opioid tolerance induced by repeated intrathecal injection of morphine.[485] $GABA_A$ receptors contribute to inhibitory control at the spinal cord level. Intrathecal administration of muscimol or baclofen, $GABA_A$ and $GABA_B$ receptor agonists, respectively, increased the analgesic action of morphine in intensity and duration.[486]

Inhaled Anesthetics

N_2O produces analgesia that is in part mediated by release of the proenkephalin-derived family of endogenous opioid peptides.[487] This may imply that interaction between opioids and N_2O is neither synergistic nor additive. Combining N_2O with an opioid in a balanced technique may not best take advantage of drug interaction synergism. Although amnesia and intraoperative conditions may be improved somewhat, N_2O does not produce any effects that are not already produced by either an opioid or a sedative-hypnotic. The advent of short-acting intravenous anesthetics and volatile anesthetics with a blood-gas partition coefficient comparable to that of N_2O has decreased the popularity of N_2O in balanced anesthesia.

Volatile anesthetics are frequently combined with opioids to ensure amnesia and promote immobility and hemodynamic stability. Clinical trials of opioids supplemented with newer volatile anesthetics for cardiac surgery demonstrate well-preserved cardiac output and minimal decreases in mean arterial blood pressure.[488,489] Myocardial ischemia may not, however, always be ameliorated by approaches that combine opioids with potent inhaled agents despite apparent "good" hemodynamic control. Some of the potent inhaled anesthetics can increase sympathetic nervous system activity and may increase the risk for myocardial ischemia in cardiac patients.[490,491] Prior administration of fentanyl, in doses as low as 1.5 μg/kg, can markedly attenuate such responses.[490] Alfentanil (10 μg/kg) is also effective in attenuating these effects.

Muscle Relaxants

Pancuronium bromide has been used frequently for muscle relaxation during high-dose opioid anesthesia. It was reported that the vagolytic action of pancuronium can attenuate opioid-induced bradycardia and support blood pressure,[492] but other reports have cautioned against the use of pancuronium with high-dose opioids.[493] In patients undergoing coronary artery bypass grafting and administered sufentanil (3 to 8 μg/kg), pancuronium (120 μg/kg) caused a significant increase in mean arterial pressure, heart rate, and cardiac output but did not induce myocardial ischemia.[494] Pancuronium-induced tachycardia was easily and rapidly treated and caused no differences in ischemia or perioperative myocardial infarction. Many factors alter the impact of pancuronium and other muscle relaxants on hemodynamics when combined with opioids, including the dose, timing, and rate of administration of each relaxant, as well as the premedication, intravascular volume, left ventricular function, and presence of other drugs with autonomic nervous system actions.[492]

Combinations of vecuronium and high doses of opioids produce negative chronotropic and inotropic effects that result in

decreases in heart rate, cardiac output, and blood pressure and increases in the need for vasopressor support.[495] In patients scheduled for coronary artery surgery and administered 40 μg/kg sufentanil in combination with vecuronium (0.1 mg/kg), heart rate, mean arterial pressure, and systemic vascular resistance decreased from baseline values after tracheal intubation with neither a significant change in cardiac output nor evidence of new myocardial ischemia.[492]

In patients anesthetized with fentanyl, 50 μg/kg, and scheduled to undergo elective coronary artery bypass grafting, rocuronium, 0.6 mg/kg (approximately equivalent to 2 × ED_{95} doses), was associated with changes of only small magnitude in hemodynamic variables, including increases in stroke volume index (+15%) and cardiac index (+11%) and a decrease in pulmonary capillary wedge pressure (−25%).[496] In patients undergoing coronary artery bypass surgery under fentanyl anesthesia, mivacurium, 0.15 or 0.2 mg/kg, produced decreases in mean arterial pressure and systemic vascular resistance, possibly mediated by histamine release, whereas atracurium (0.5 mg/kg) produced no significant hemodynamic changes.[497] Pipecuronium (150 μg/kg) has been found to be devoid of circulatory actions in patients undergoing coronary artery bypass grafting surgery with midazolam-sufentanil (3 to 8 μg/kg) anesthesia.[494] In patients administered 50 μg/kg fentanyl, doxacurium caused a small decrease in mean arterial pressure.[498]

Miscellaneous

MAOIs can underlie the most serious and potentially fatal interactions of opioid and other drugs. It was reported that the combination of meperidine and an MAOI can induce the serotonin syndrome, which is caused by excess availability of serotonin in the CNS at the 5-HT_{1A} receptor and characterized by confusion, fever, shivering, diaphoresis, ataxia, hyperreflexia, myoclonus, and diarrhea.[499] The phenylpiperidine series opioids, including meperidine, tramadol, and methadone, appear to be weak serotonin reuptake inhibitors and have all been involved in serotonin toxicity reactions with MAOIs, whereas morphine, codeine, oxycodone, and buprenorphine are known to not be serotonin reuptake inhibitors and do not precipitate serotonin toxicity with MAOIs.[500] Alfentanil and remifentanil could be used with MAOIs without complications.[501,502]

Because opioids can inhibit voltage-dependent Ca^{2+} channel activity through the activation of G proteins, it may be possible that opioid action is potentiated by Ca^{2+} channel blockers. Numerous animal studies and few clinical studies have documented that opioid-induced analgesia is potentiated by L-type Ca^{2+} channel blockers. Systemically administered nifedipine was shown to potentiate morphine analgesia in both rats and humans.[503] Furthermore, intrathecal administration of verapamil, diltiazem, and nicardipine enhanced the antinociceptive effect of low-dose morphine in rats.[504] However, there is also a report that L-type Ca^{2+} channel blockers do not potentiate morphine analgesia at clinically relevant doses.[505] N-type Ca^{2+} channels are involved in the release of neurotransmitters from sensory neurons in the spinal cord. It was reported that intrathecal administration of a blocker of this channel, ω-conotoxin GVIA, produces antinociception and interacts synergistically with opioids at the spinal cord level.[506]

Erythromycin can inhibit the metabolism of several compounds. It supposedly reduces the oxidizing activity of cytochrome P450. Alfentanil, but not sufentanil, may have its action prolonged as a result of impaired metabolism in patients receiving erythromycin.[507,508] Cimetidine can prolong opioid effects by decreasing hepatic blood flow or diminishing hepatic metabolism (or by both means). Other drugs that inhibit certain cytochrome systems can increase endogenous morphine production from codeine.[406]

Magnesium has been shown to have antinociceptive effects, probably because of its antagonistic action on the NMDA receptor. Intravenous administration of magnesium sulfate, 50 mg/kg preoperatively and 8 mg/kg/hr intraoperatively, significantly reduced the intraoperative and postoperative fentanyl requirement.[509] However, passage of magnesium across the blood-brain barrier is limited. Intrathecal administration of fentanyl, 25 μg, plus magnesium sulfate, 50 mg, provided significantly prolonged analgesia when compared with fentanyl alone in patients requesting analgesia for labor.[510] It is likely that magnesium can potentiate opioid analgesia by both central and peripheral mechanisms.[511]

Nonsteroidal anti-inflammatory drugs such as ibuprofen, diclofenac, and ketorolac have been administered perioperatively to reduce the opioid requirement. Preoperative administration of ibuprofen (2 × 800 mg) to patients scheduled for lower abdominal gynecologic surgery was shown to reduce postoperative morphine consumption without an increase in side effects.[512] It was also reported that perioperative administration of diclofenac (75 mg twice daily) reduces morphine consumption and the incidence of adverse effects such as sedation and nausea after total abdominal hysterectomy.[513] In healthy volunteers, ketoprofen (1.5 mg/kg IV) reduced the respiratory depression induced by morphine (0.1 mg/kg).[514]

The tricyclic antidepressants are widely used to treat various chronic inflammatory and neuropathic pain conditions. Results in clinical studies were not consistent with respect to interactions between opioids and tricyclic antidepressants. An isobolographic analysis demonstrated that systemic administration of amitriptyline and morphine synergistically inhibits cutaneous orofacial inflammatory pain in rats.[515]

Diphenhydramine, a histamine H_1-receptor antagonist, is used as a sedative, an antipruritic, and an antiemetic drug. When administered alone, it modestly stimulates ventilation by augmenting the interaction of hypoxic and hypercapnic ventilatory drives. Diphenhydramine counteracts the alfentanil-induced decrease in the slope of the ventilatory response to carbon dioxide.[516]

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Peter S. A. Glass, Steven L. Shafer, and J. G. Reves

28 Intravenous Drug Delivery Systems

Key Points

1. Anesthetic drugs are described by multicompartmental models. Accurate intravenous drug delivery requires adjusting the dose for accumulation of drug in peripheral tissues.
2. The biophase is the site of action of anesthetic drugs. Initiation, maintenance, and titration of intravenous anesthetics must account for the delay in equilibration between plasma and the site of drug effect.
3. Some drug effects directly reflect the concentration of drug in the biophase (direct-effect models). Other drug effects reflect the alteration of feedback systems by anesthetics (indirect-effect models). The influence of opioids on ventilation reflects the dynamic influence of opioids on the feedback between ventilation and carbon dioxide and is thus an example of an indirect drug effect.
4. The target concentration in the effect site is the same as the target concentration in plasma at steady state. The target concentration is influenced by patient physiology, surgical stimulation, and concurrent drug administration. Typically, one must set a target concentration for the hypnotic (volatile anesthetic or propofol) and the analgesic (opioid) that properly accounts for the synergy between them.
5. To achieve an effective target concentration, the conventional teaching of administering a loading dose calculated as target concentration times volume of distribution, followed by a maintenance rate calculated as target concentration times clearance, is inaccurate. The initial loading dose may be calculated as the target concentration times the volume of distribution at peak effect. Maintenance rates must initially account for distribution of drug in peripheral tissues and are turned down to the target concentration times clearance only after equilibration with peripheral tissues.
6. The terminal half-life does not reflect the clinical time course of drug concentration. The context-sensitive decrement time is the time for a given decrement in drug concentration as a function of the duration of infusion for an infusion that maintains a steady plasma concentration. Context-sensitive decrement times properly incorporate the multicompartmental behavior of intravenous anesthetics. The context-sensitive half-time is the time for a 50% decrement in concentration.
7. Alfentanil, fentanyl, sufentanil, remifentanil, propofol, thiopental, methohexital, etomidate, ketamine, and midazolam can all be given by intravenous infusion. Specific caveats, infusion rates, and titration guidelines are presented in the text.
8. Target-controlled infusions use pharmacokinetic models to titrate intravenous anesthetics to specified plasma or effect-site drug concentrations. The Diprifusor is a propofol target-controlled infusion system that is available worldwide except in North America.
9. Closed-loop drug delivery systems have used the median electroencephalographic frequency, bispectral index, and auditory evoked potentials to control intravenous anesthetic delivery. These systems have generally performed well clinically but remain investigational.

Anesthetic drugs must reach their site of action to be effective. In 1628, William Harvey proved in *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* that venous blood was transported to the arterial circulation and thus to the organs of the body by the heart. It was recognized almost immediately that drugs injected into veins could be rapidly carried to the entire body. In 1657 Christopher Wren injected opium intravenously by means of a quill and bladder (Fig. 28-1A) into dogs and humans and rendered them unconscious. Eight years later, Sigismund Elsholtz gave an opioid solution for the purpose of rendering subjects insensitive, but it was not until 1874 that Pierre-Cyprien Ore administered chloral hydrate intravenously for a surgical procedure. This landmark event followed unsuccessful attempts by the Russian surgeon Pirogoff to administer ether intravenously in

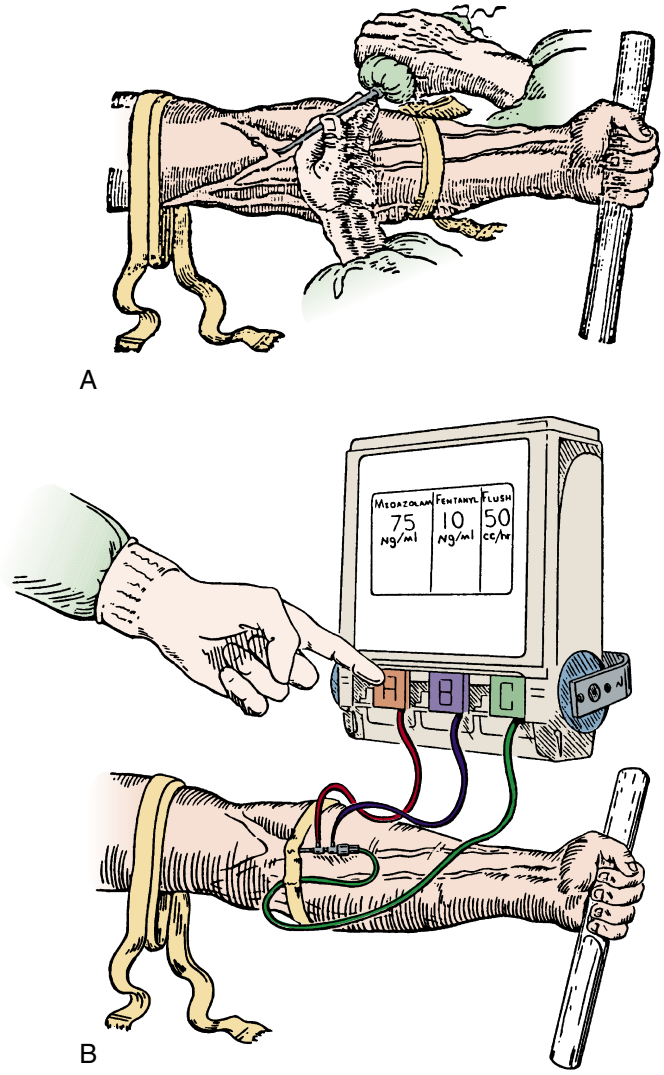

Figure 28-1 Intravenous drug delivery, past and future. **A,** A depiction of the first intravenous injection of opium with a quill and bladder. **B,** The future of intravenous drug delivery. Drugs are delivered with the aid of a small, sophisticated infusion pump, which permits dosing in terms of plasma drug concentration rather than amount.

1846, shortly after Crawford Long and William Morton had independently demonstrated the efficacy of ether inhalation for surgery.[1]

Intravenous methods of anesthetic drug delivery have depended on steady improvement in technology. The quill and bladder used by Wren were not significantly improved until Alexander Wood used a needle and syringe to administer intravenous medications in 1853. The hollow hypodermic needle and a functional syringe were developed by Frances Rynd and Charles Pravaz, respectively.[1] Contemporary needles, catheters, and syringes are descendants of these early devices. A more recent technologic development in intravenous anesthesia was the introduction of computerized pharmacokinetic model–driven continuous-infusion devices (see Fig. 28-1B), first reported by Helmut Schwilden[2] in 1981. Schwilden demonstrated the ability to attain desired plasma levels of an intravenous anesthetic drug by using a computer-controlled infusion pump operated in accordance with the published pharmacokinetics of the drug. These efforts resulted in release of the first commercial target-controlled infusion (TCI) device in Europe, developed by Zeneca specifically for the administration of propofol. The March 1998 issue of the journal *Anaesthesia* was devoted entirely to a review of TCI and the role of TCI devices in clinical practice. Since that time, nearly the rest of the world, with the notable exception of the United States, has approved TCI devices for the delivery of anesthetic drugs.

The ultimate development in anesthetic delivery systems will be devices for closed-loop administration of intravenous drugs during anesthesia. Systems have been developed for closed-loop administration of sodium nitroprusside and muscle relaxants based on defined and measurable end points. The lack of an unequivocal measure of "anesthetic depth" has hindered the development of closed-loop anesthetic delivery systems. Most such systems have been developed with the electroencephalogram (EEG) used as the measure of anesthetic drug effect. Schwilden developed closed-loop systems for infusion of methohexital[3,4] and propofol[5] on the basis of the median EEG frequency. Other investigators have developed closed-loop systems based on other derivatives of the EEG (e.g., auditory evoked potentials[6] or the bispectral index [BIS][7]).

The development of new techniques has coincided with the development of new drugs. Rapid intravenous induction became popular with the introduction of sodium thiopental in 1934. The pharmacokinetics of thiopental, however, prevented its becoming popular for maintenance of anesthesia. During the past 50 years, numerous intravenous hypnotics (methohexital, 1957; propanidid, 1957; althesin, 1971; etomidate, 1973; propofol, 1977), anxiolytics (diazepam, 1966; midazolam, 1978), and analgesics (fentanyl, 1959; ketamine, 1966; sufentanil, 1979; alfentanil, 1980; remifentanil, 1996; dexmedetomidine, 1999) have been introduced. The general trend in the introduction of these newer agents has been to provide drugs with further shortening of the time needed for recovery from drug effect. In this context, the newer intravenous drugs propofol and remifentanil provide a rapid onset of anesthesia, a stable maintenance phase, and rapid recovery.

Before reviewing delivery techniques and devices for intravenous anesthesia, this chapter presents pharmacokinetic and pharmacodynamic principles as background for understanding how to administer intravenous drugs to their best advantage. Specifically, intravenous anesthesia delivery systems can be used to rationally determine the dose of intravenous drugs used in clinical practice. Further discussion of the principles of pharmacokinetics and pharmacodynamics can be found in Chapter 19.

Pharmacokinetic Considerations

The goal of administering anesthetics is to produce the clinically desired time course of anesthetic effect. Usually, such a course includes a rapid onset, smooth maintenance, and rapid recovery after termination of the anesthetic. Conventional pharmacokinetic models assume that a bolus of drug is instantaneously mixed into plasma and produces an immediate peak in its plasma concentration. The concentration then declines continuously until the next bolus. Except for a transient perioperative stimulus (endotracheal intubation, surgical incision, bowel traction), the

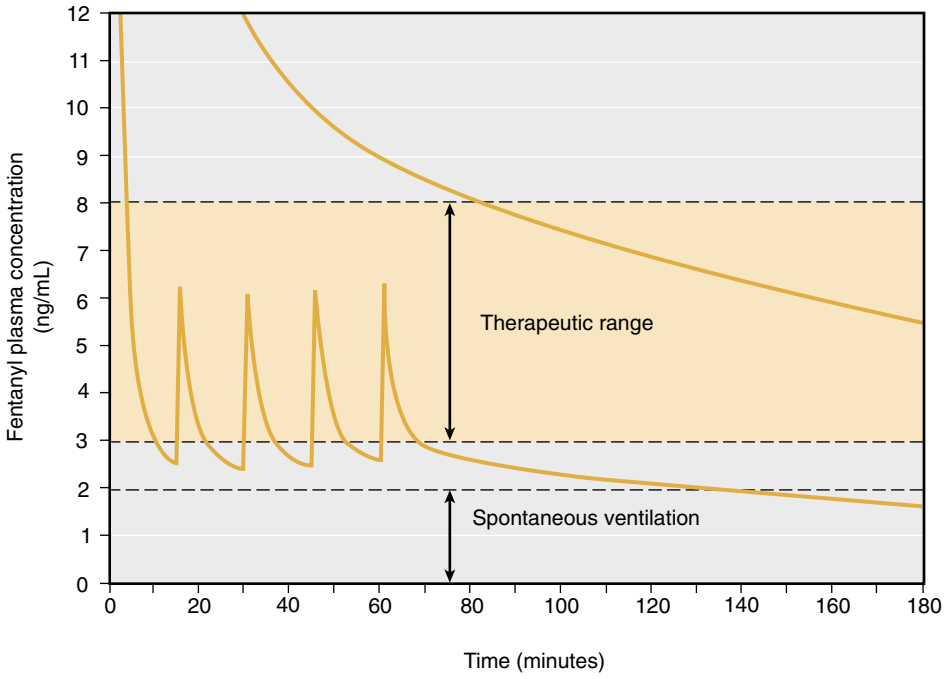

Figure 28-2 Pharmacokinetic simulation of a single large bolus of fentanyl (*upper curve*; 50 μg/kg) and a smaller fentanyl bolus (*lower curve*; 8 μg/kg) followed by intermittent boluses (1.5 μg/kg) every 15 minutes. The single large bolus results in plasma drug concentrations far in excess of those required, whereas the intermittent bolus scheme results in plasma concentrations that periodically fall below the therapeutic range. Ideally, the plasma drug concentration should be continuously within the therapeutic range, which can best be accomplished with a continuous infusion.

patient's anesthetic requirements will probably not follow the saltatory time course of anesthetic effect seen with repeated bolus injections. Thus, the technique of intermittent boluses results in excessive drug effect at the time of the bolus, inadequate drug effect before the next bolus, or both (Fig. 28-2). The technique of giving the entire anesthetic as an initial bolus produces a needlessly huge initial peak and, depending on the dose, grossly excessive or possibly subtherapeutic levels later in the procedure. This technique is well tolerated for opioids in paralyzed patients whose lungs are mechanically ventilated. However, this approach would produce considerable hypotension if attempted with propofol.

To produce a time course of drug effect that follows the time course of anesthetic requirement, a continuous infusion titrated to the perceived anesthetic requirement should be used. Ideally, just enough drug is given to achieve the therapeutic blood or plasma drug concentration, and it is then continuously titrated throughout surgery (Fig. 28-3). This method of drug delivery avoids the peaks and valleys in drug concentration seen with intermittent drug boluses. Theoretical advantages of continuous infusions over intermittent bolus injections include fewer periods of poor anesthetic control, a reduction in the total amount of drug used, and more rapid recovery from anesthesia.[8,9]

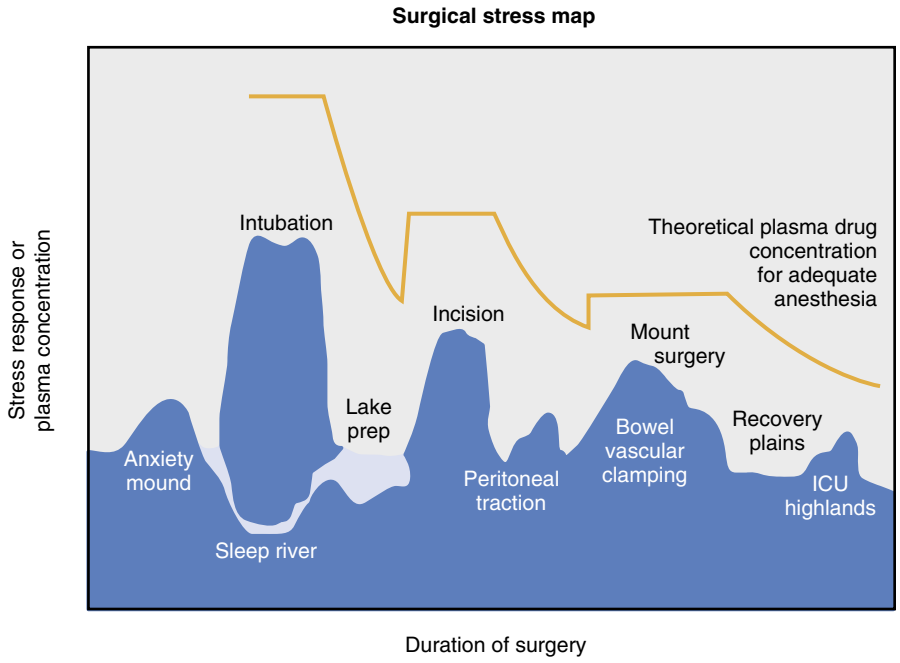

Figure 28-3 Landscape of surgical anesthesia. The stimuli of surgery are not constant; therefore, the plasma concentration of the anesthetic drug should be titrated to match the needs of the patient.

The dose of anesthetic needed to produce the desired time course of plasma concentration can be calculated from pharmacokinetic models. Pharmacokinetic models exist for every intravenous anesthetic drug, but they are of limited use without computer simulation. In this chapter we will describe how pharmacokinetic models can be used to develop rational dosing guidelines for use with intravenous infusion delivery systems. We first review some basic pharmacokinetic concepts and define the relevant terminology.

Pharmacokinetic models are mathematical descriptions of how the body "disposes" of drugs. The parameters describing this process are estimated by administering a known dose of the drug and measuring the resulting plasma concentrations. A mathematical model then relates the input over time, I(t), with the concentrations over time, C(t). These models can take many forms. Figure 28-4 shows concentrations in plasma over time after a single intravenous bolus of drug at time 0. Drug concentrations continuously decrease after the bolus, and the rate of decrease is approximately proportional to the amount of drug in plasma. Typically, it is convenient to describe this behavior with the use of exponential models. The curve might have a single exponent, in which case the plasma concentrations over time might be described by the function $C(t) = Ae^{-kt}$, where A is the concentration at time 0 and k is a constant that describes the rate of decrease

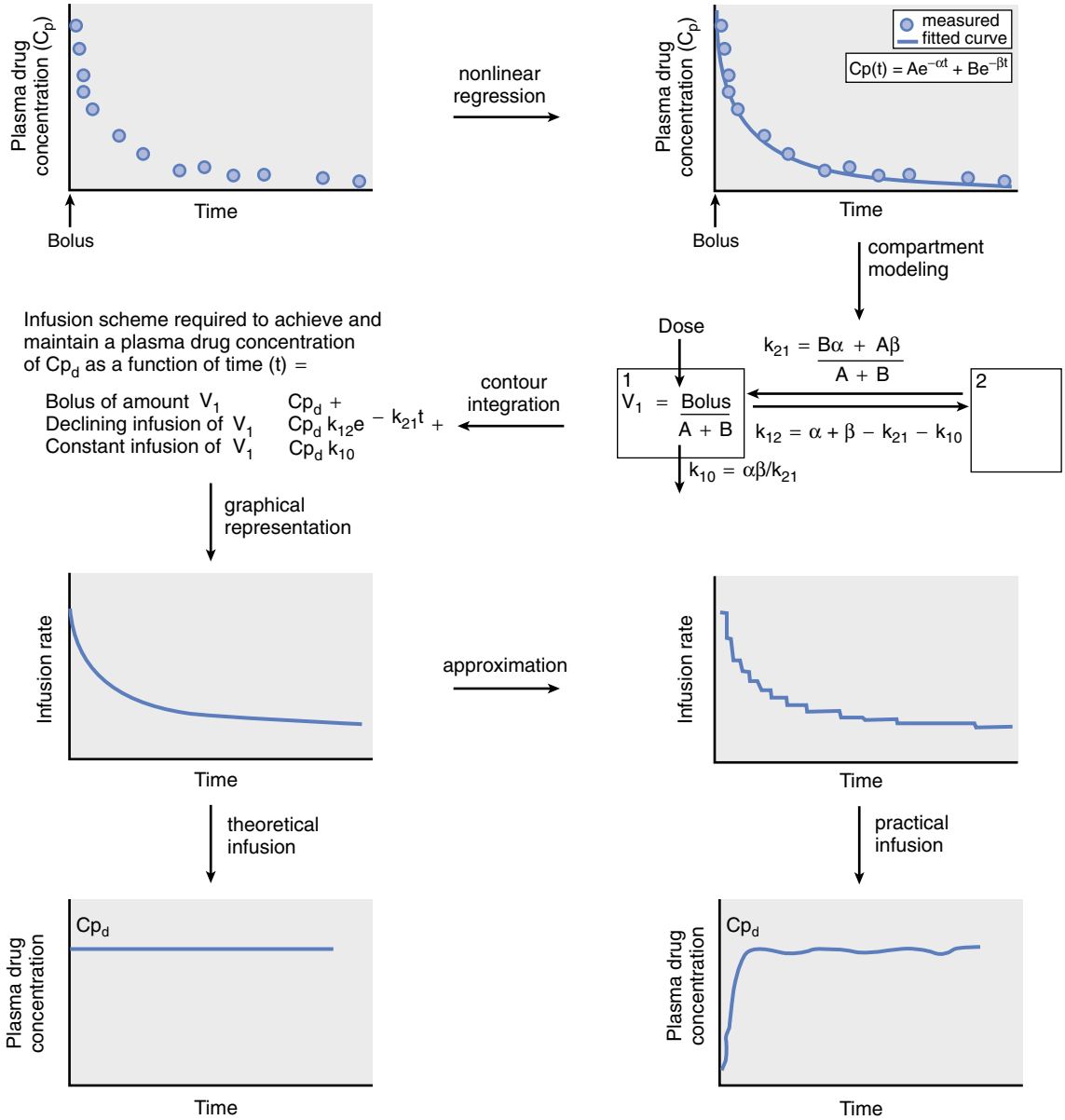

Figure 28-4 Steps involved in pharmacokinetic model–driven infusion. Typically, pharmacokinetic models are derived from experiments in which plasma drug concentrations are measured at intervals after bolus administration of the drug. Nonlinear regression is used to fit a monoexponential, biexponential, or triexponential curve to the resulting concentration-versus-time data. There is an algebraic relationship between the exponential decay curves and a one-, two-, or three-compartment pharmacokinetic model. The "BET" infusion scheme is developed and consists of a bolus, a continuous infusion to replace drug eliminated from the body, and an exponentially declining infusion to replace drug transferred out of plasma to other body compartments. BET infusion results in maintenance of a constant specified plasma drug concentration. Practical implementation of the BET scheme with real infusion pumps and infusion rates that change only at discrete intervals of time results in a plasma drug concentration profile that approximates that resulting from a BET infusion.

in concentration. The relationship appears to be a straight line when graphed as the log of concentration versus time. The pharmacokinetics of intravenous anesthetic drugs is more complex because after the bolus, a period of rapid decline is observed before the terminal "log-linear" portion (e.g., the part that is a straight line when described as log concentration versus time). It is possible to model this process by taking several monoexponential (i.e., one exponent) curves and adding them together. The result is a polyexponential curve. For example, the concentrations after an intravenous bolus might be described by an equation with two exponents, $C(t) = Ae^{-\alpha t} + Be^{-\beta t}$, or an equation with three exponents, $C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$.

There are ways of administering intravenous anesthetic drugs besides single boluses. A more general way to think of pharmacokinetics is to decompose the input into a series of small bits (boluses) and consider each bit of drug separately. The general pharmacokinetic model of drug disposition commonly used in anesthesia considers each bit of drug independently and analyzes its contribution by means of polyexponential decay over time. The formal mathematical description of each bit of drug in terms of polyexponential decay over time is the relationship

$$C(t) = I(t) * \sum_{i=1}^{n} A_i e^{-\lambda_i t} \quad (1)$$

where C(t) is the plasma concentration at time t and I(t) is drug input (i.e., a bolus or infusion). The summation after the asterisk (described later) is the function describing how each bit of drug is disposed of (hence its name the "disposition" function). Note that this is again a sum of *n* exponentials, as described in the previous paragraph.

Pharmacokinetic modeling is the process of estimating the parameters within this function. The integer *n* is the number of exponentials (i.e., compartments) and is usually two or three. Each exponential term is associated with a coefficient A_i and an exponent λ_i. The λ values are inversely proportional to the half-lives (half-life = $0.693/\lambda$), with the smallest λ representing the longest (terminal) half-life. The A values are the relative contribution of each half-life to overall drug disposition. If a drug has a very long terminal half-life but a coefficient that is much smaller than the other coefficients, the long half-life is likely to be clinically meaningless. Conversely, if a drug has a very long half-life with a relatively large coefficient, the drug will be long lasting even after brief administration. The * operator is the mathematical process called "convolution," which is simply the process of breaking the infusion into "bits" of drug and then adding up the results to see the overall concentrations.

The pharmacokinetic model shown has some useful characteristics that account for its enduring popularity in pharmacokinetic analysis. Most important, the model describes observations from studies reasonably well, the sine qua non for models. Second, these models have the useful characteristic of "linearity." Simply stated, if you double the dose, I, (e.g., give a bolus twice as large or an infusion twice as fast), you double the concentrations.

More generally, linearity implies that the system (i.e., the body acting to produce a plasma drug concentration output from a drug dosage input) behaves in accordance with the principle of superposition. The superposition principle states that the response of a linear system with multiple inputs can be computed by determining the response to each individual input and then summing the individual responses. In other words, when the body treats each bit of drug by polyexponential decay over time, the "disposing" of each bit of drug does not influence the disposing of other bits of drug.

The third reason for the continuing popularity of these models is that they can be mathematically transformed from the admittedly unintuitive exponential form shown earlier to a more easily intuitive compartmental form, as shown in Figure 28-5. The fundamental parameters of the compartment model are the volumes of distribution (central, rapidly equilibrating, and slowly equilibrating peripheral volumes) and clearances (systemic, rapid, and slow intercompartmental). The central compartment (V_1) represents a distribution volume and includes the rapidly mixing portion of the blood and first-pass pulmonary uptake. The peripheral compartments are composed of tissues and organs that show a time course and extent of drug accumulation (or dissipation) different from that of the central compartment. In the three-compartment model, the two peripheral compartments may correspond roughly to splanchnic and muscle tissues (rapidly equilibrating) and fat stores (slowly equilibrating). The sum of the compartment volumes is the apparent volume of distribution at steady state (Vd_{ss}) and is the proportionality constant relating the plasma drug concentration at steady state to the total amount of drug in the body. The intercompartmental rate constants (k_{12}, k_{21}, and so on) describe the movement of drug between the central and peripheral compartments. The elimination rate constant (k_{10}) encompasses processes acting through biotransformation or elimination that irreversibly remove drug from the central compartment.

Despite their physiologic flavor, compartmental models are simply mathematical transformations of the polyexponential disposition functions computed from observed plasma concentrations. Thus, physiologic interpretation of volumes and clearances (with the possible exception of systemic clearance and Vd_{ss} [the algebraic sum of the volumes]) is entirely speculative.

The last reason that these models have been popular is that they can be used to design infusion regimens, the point of introducing them in this chapter. If we abbreviate the disposition function

$$\sum_{i=1}^{n} A_i e^{-\lambda_i t} \quad (2)$$

as simply D(t), we can rewrite the relationship among concentration, dose, and the pharmacokinetic model D(t) as

$$C(t) = I(t) * D(t) \quad (3)$$

where * is the convolution operator, as noted earlier. In the usual pharmacokinetic study we know I(t), the dose that we gave the patient, and we measure C(t), the concentrations over time. Our goal is to find D(t), the pharmacokinetic disposition function. Pharmacokinetic analysis can be thought of as a simple rearrangement of Equation 3 to solve for D(t):

$$D(t) = \frac{C(t)}{I(t)} \quad (4)$$

where the symbol $\frac{}{\times}$ means deconvolution, the inverse operation of convolution. Deconvolution is like division, but of functions rather than simple numbers. When we design dosing regimens from known pharmacokinetic models and a desired course for the plasma concentration over time, the known values

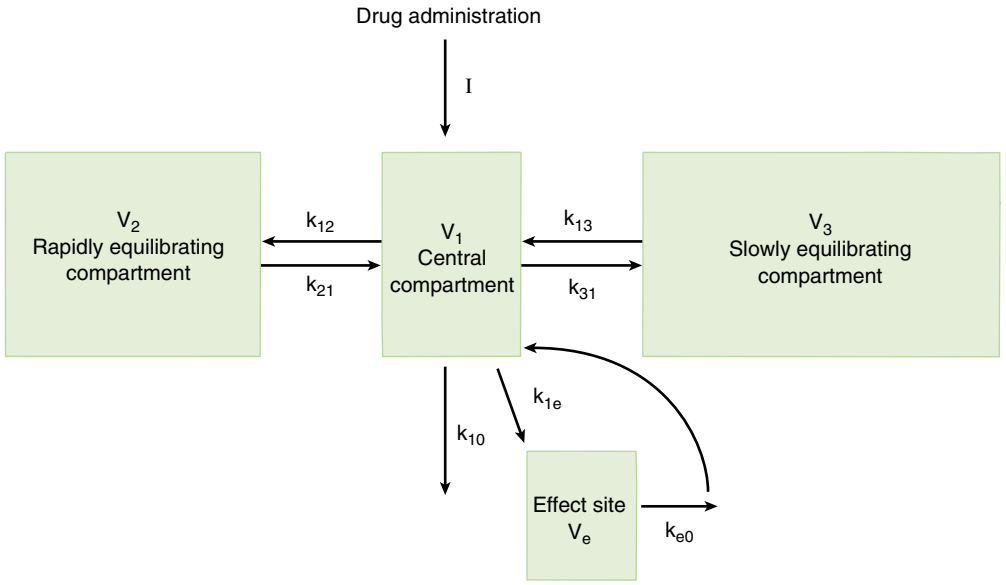

Figure 28-5 Three-compartment model (including the biophase) schematizing the basic pharmacokinetic processes that occur after intravenous drug administration. I, dosing scheme as a function of time; k_{10}, rate constant reflecting all processes acting to irreversibly remove drug from the central compartment; k_{ij}, intercompartmental rate constants; V_1, central compartment volume, usually expressed in liters or liters per kilogram.

are D(t) (the pharmacokinetics) and $C_T(t)$ (the desired target concentrations), and the drug dosing scheme is:

$$I(t) = C_T(t) \otimes D(t) \quad (5)$$

Thus, one can calculate the necessary infusion rates, I(t), given desired target concentrations, $C_T(t)$, and the pharmacokinetics, D(t), by applying the same tools used to calculate the original pharmacokinetics. Unfortunately, such a solution might require some negative infusion rates, which are obviously impossible. Because we cannot suck drug out of the body (i.e., give negative infusions), we must restrict ourselves to plasma concentrations over time that can be achieved with non-negative infusion rates.

The standard pharmacokinetic model has one glaring shortcoming. It assumes that after a bolus injection there is complete mixing within the central compartment such that the peak concentration occurs precisely at time 0. It actually takes about 30 to 45 seconds for the drug to make its transit from the venous injection site to the arterial circulation. This model misspecification over the first minute or so may not seem significant, but it can cause problems in attempts to relate the drug effect after a bolus to drug concentrations in the body.[10] Researchers are modifying the standard polyexponential pharmacokinetic models to provide more accurate models of plasma drug concentration in the first minute after bolus injection.[11]

Pharmacodynamic Considerations

The Biophase

Although the plasma concentration after an intravenous bolus peaks nearly instantaneously, no anesthesiologist would push an intravenous bolus of hypnotic and immediately intubate the patient's trachea. The reason, of course, is that although the plasma concentration peaks almost instantly, additional time is required for the drug concentration in the brain to rise sufficiently to induce unconsciousness. This delay between peak plasma concentration and peak concentration at the effect site is called *hysteresis*. Hysteresis is the clinical manifestation of the fact that plasma is not the site of anesthetic action, only the mechanism of transport. Drugs exert their pharmacologic effect in the *biophase*, which is also called the "effect site." Physically, the biophase is the immediate milieu in which the drug acts on the body, including membranes, receptors, and enzymes.

The concentration of drug in the biophase cannot be measured for two reasons. First, it is usually inaccessible, at least in human subjects. Second, even if we could take tissue samples, the drug concentration in the microscopic environment of the receptive molecules would not be the same as the concentration measured in, for example, homogenated brain. Although it is not possible to actually measure drug concentration in the biophase, we can characterize the time course of drug effect by using rapid measures of drug effect. Knowing the time course of drug effect, we can characterize the rate of drug flow in and out of the biophase (or "effect site") with the use of mathematical models,[12,13] as well as the apparent drug concentration in the biophase in terms of the steady-state plasma concentration that would produce the same effect.

Measures of effect used to characterize the time course of drug between plasma and the biophase will vary with the drug being evaluated. For neuromuscular blockers, the twitch response is an ideal measure of effect. For opioids and hypnotics, the measure of effect is more challenging. The desired effect for opioids is analgesia, which is a subjective measure that is difficult to monitor and quantify moment by moment. Similarly for hypnotics, until recently there has been no validated monitor of drug effect. For these reasons investigators have turned to the EEG as an objective measure of opioid and hypnotic drug effect. Even if the EEG did not measure the clinically desired effect of opioids

and hypnotics, it was assumed that changes in the EEG would at least reflect the time course of clinical effects. Thus, the time course for opioids and hypnotics to equilibrate between plasma and the biophase has largely been defined from the EEG. The validity of this approach has been confirmed by several studies. Glass and colleagues measured the blood concentration of remifentanil and its analgesic response in volunteers.[14] The time course for equilibration between plasma and the biophase calculated in this study was essentially identical to the time course determined by using the spectral edge of the EEG as the measure of effect.[15] Ludbrook and associates measured propofol concentrations in the carotid artery and jugular bulb to establish movement of propofol into and equilibration with the brain.[16] They measured the BIS simultaneously and found close correlation between brain concentration (calculated by mass balance) and changes in the BIS.

Direct-Effect Models

Just as shown for plasma pharmacokinetics earlier, the biophase concentration is the convolution of an input function (in this case, the plasma drug concentration over time) and the disposition function of the biophase. This relationship can be expressed as

$$C_{biophase}(t) = C_{plasma}(t) * D_{biophase}(t) \quad (6)$$

The disposition function of the biophase is typically modeled as a single exponential decay:

$$D_{biophase}(t) = k_{e0} e^{-k_{e0}t} \quad (7)$$

The monoexponential disposition function implies that the effect site is simply an additional compartment in the standard compartmental model that is connected to the plasma compartment (see Fig. 28-5). The effect site is the hypothetical compartment that relates the time course of plasma drug concentration to the time course of drug effect, and k_{e0} is the rate constant of elimination of drug from the effect site. By definition, the effect compartment receives such small amounts of drug from the central compartment that it has no influence on plasma pharmacokinetics.

We cannot directly measure either $C_{biophase}(t)$ or $D_{biophase}(t)$, but we can measure drug effect. Knowing that the observed drug effect is a function of the drug concentration in the biophase, we can predict the drug effect as

$$\text{Effect} = f_{PD}\left[C_{plasma}(t) * D_{biophase}(t), P_{PD}, k_{e0}\right] \quad (8)$$

where f_{PD} is a pharmacodynamic model (typically sigmoidal in shape), P_{PD} represents the parameters of the pharmacodynamic model, and k_{e0} is the rate constant for equilibration between plasma and the biophase. Nonlinear regression programs are used to find values of P_{PD} and k_{e0} that best predict the time course of drug effect. Knowledge of these parameters can then be incorporated into dosing regimens that produce the desired time course of drug effect.[17,18]

If a constant plasma concentration is maintained, the time required for the biophase concentration to reach 50% of the plasma concentration ($t_{½}\ k_{e0}$) can be calculated as $0.693/k_{e0}$. After a bolus dose, the time to peak biophase concentration is a function of both plasma pharmacokinetics and k_{e0}. For drugs with a very rapid decline in plasma concentration after a bolus (e.g., adenosine, which has a half-life of several seconds), the effect-site concentration peaks within several seconds of the bolus, regardless of k_{e0}. For drugs with a rapid k_{e0} and a slow decrease in concentration after a bolus injection (e.g., pancuronium), the peak effect-site concentration is determined more by k_{e0} than by plasma pharmacokinetics. The time to peak effect and the $t_{½}\ k_{e0}$ for several intravenous anesthetics are listed in Table 28-1.

Table 28-1 Time to Peak Effect and $t_{½}\ k_{e0}$ after a Bolus Dose

Drug	Time to Peak Drug Effect (min)	$t_{½}\ k_{e0}$ (min)
Fentanyl	3.6	4.7
Alfentanil	1.4	0.9
Sufentanil	5.6	3.0
Remifentanil	1.6	1.3
Propofol	2.2	2.4
Thiopental	1.6	1.5
Midazolam	2.8	4.0
Etomidate	2.0	1.5

$t_{½}\ k_{e0} = 0.693/k_{e0}$, the rate constant for transfer of drug from the site of drug effect to the environment.

Indirect-Effect Models

Thus far, effects that are an instantaneous function of drug concentration at the site of drug effect have been discussed, as implied by Equation 8. For example, once hypnotics reach the brain or muscle relaxants reach the muscles, drug action is seen almost instantaneously. On the other hand, some effects are much more complex. For example, consider the effect of opioids on ventilation. Initially, opioids depress ventilation, and as a result of this ventilatory depression, CO_2 starts to accumulate. Accumulation of CO_2 acts to stimulate ventilation, thereby partly counteracting the ventilatory depressant effects of opioids. Ventilatory depression is an example in which there is a direct and indirect drug effect. The direct effect of the opioid is to depress ventilation, and the indirect effect is to increase CO_2. Modeling the time course of opioid-induced ventilatory depression requires consideration of both components. Bouillon and colleagues have developed a model of ventilatory depression that incorporates both direct and indirect effects.[19,20] As is generally the case with indirect-effect models, characterizing drug-induced ventilatory depression requires considering the entire time course of drug therapy, which is embodied by the following differential equation:

$$\frac{d}{dt}Pa_{CO_2} = k_{el} \cdot Pa_{CO_2}(0) - k_{el} \cdot \left[1 - \frac{Cp(t)\gamma}{C_{50}\gamma + Cp(t)\gamma}\right] \cdot \left[\frac{P_{biophase}CO_2(t)}{P_{biophase}CO_2(0)}\right]^F \cdot Pa_{CO_2}(t) \quad (9)$$

where Pa_{CO_2} is arterial CO_2, $P_{biophase}CO_2$ is CO_2 in the biophase (i.e., ventilation control centers), k_{el} is the rate constant for elimination of CO_2, C_{50} is the effect-site opioid concentration associated with a 50% reduction in ventilatory drive, and F is the steepness or "gain" of the effect of CO_2 on ventilatory drive.

Dose Implications of the Biophase

The delay in onset has important clinical implications. After a bolus, the plasma concentration peaks nearly instantly and then declines steadily. The effect-site concentration starts at zero and increases over time until it equals the descending plasma concentration. The plasma concentration continues to decline, and after the moment of identical concentrations, the gradient between plasma and the effect site favors removal of drug from the effect site, and the effect-site concentration decreases. The rate at which the effect site rises toward the peak after a bolus dictates how much drug must be injected into plasma to produce a given effect. For alfentanil, its rapid plasma effect-site equilibration (large k_{e0}) causes the effect-site concentration to rise rapidly, with a peak produced in about 90 seconds. At the time of the peak, about 60% of the alfentanil bolus has been distributed into peripheral tissues or eliminated from the body. For fentanyl, the effect site concentration rises much more slowly and peaks 3 to 4 minutes after the bolus.[21] At the time of the peak, more than 80% of the initial bolus of fentanyl has been distributed into tissues or eliminated. As a result of slower equilibration with the effect site, relatively more fentanyl than alfentanil must be injected into plasma, which makes the rate of offset of drug effect after a fentanyl bolus slower than after an alfentanil bolus.

This difference in pharmacokinetics suggests that k_{e0} must be incorporated into dosing strategies. For rapid onset of effect, a drug with a large k_{e0} (short $t_{1/2}$ k_{e0}) should be chosen. For example, for rapid-sequence induction, alfentanil or remifentanil may be the opioid of choice because the peak opioid effect-site concentration coincides with endotracheal intubation. However, for a slower induction in which a nondepolarizing neuromuscular blocking drug is used, it may be appropriate to choose an opioid with a slower onset of drug effect to coincide with the peak effect of the muscle relaxant. In this case, a bolus of fentanyl or sufentanil at the time of induction may be more appropriate. The time to peak effect for the commonly used opioids is shown in Figure 28-6. Knowing k_{e0} (or time to peak effect) also improves titration of the drug by identifying the time at which the clinician should make an assessment of drug effect. For example, midazolam has a slow time to peak effect, and repeat bolus doses should be spaced at least 3 to 5 minutes apart to avoid inadvertent overdosing.

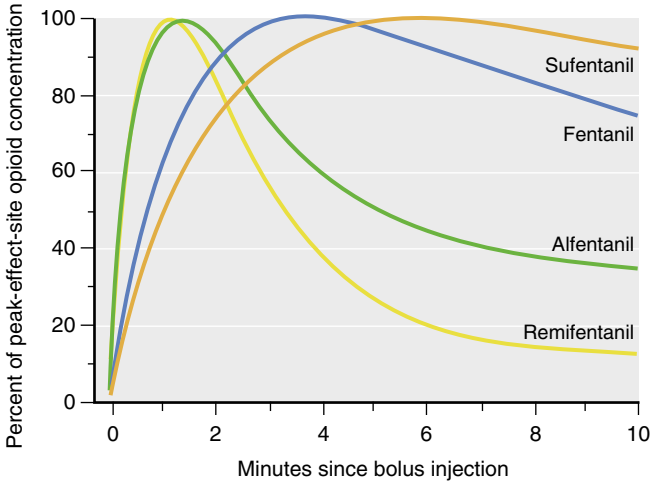

Figure 28-6 Simulated onset and time to peak effect of commonly used opioids based on their k_{e0} and pharmacokinetic parameters. k_{e0}, rate constant for transfer of drug from the site of drug effect to the environment.

Drug Potency

Having established that we can produce almost any desired concentration time course at the effect site, what concentration should we choose? The pharmacokinetics and pharmacodynamics of inhaled anesthetics are greatly simplified by the equilibrium established at the alveolar gas-blood interface, which permits measurement of the minimum alveolar concentration (MAC) associated with a 50% likelihood of movement in response to noxious stimulation.[22] Considerable effort has gone into developing a concept equivalent to MAC for intravenous anesthetic drugs.

The pharmacodynamics of intravenous anesthetics is reported in terms of C_{50}, the concentration that produces 50% of the maximum possible drug effect. There are many ways of thinking about C_{50}. It might be the drug concentration that prevents response (e.g., movement, hypertension, release of catecholamines) to a particular stimulus (e.g., incision, intubation, sternal spreading) in 50% of patients. In this case, each combination of stimulus and response may have a unique C_{50}. For example, Ausems and colleagues defined the C_{50} for alfentanil in the presence of 66% nitrous oxide for several noxious stimuli.[23] When C_{50} is defined as the drug concentration that produces a given response in 50% of patients, it is also the concentration associated with a 50% probability of response in a given patient. Note that defining C_{50} as the concentration that produces a given effect in 50% of individuals implicitly assumes that the effect can be achieved in all individuals. Some drugs exhibit a ceiling effect. For example, there appears to be a ceiling on the ability of opioids to suppress response to noxious stimulation. When a ceiling in drug effect exists, some patients may not exhibit the drug effect even at infinitely high doses. In this case, C_{50} is not the concentration that causes the drug effect in 50% of patients but is the concentration associated with the drug effect in half of whatever fraction of patients are able to respond.

Several studies have been performed to establish appropriate concentrations of intravenous anesthetics. C_{50} values for alfentanil, fentanyl, and remifentanil in the presence of 70% nitrous oxide have been defined for skin incision (Table 28-2). C_{50} values for loss of consciousness and skin incision have also been defined for the hypnotics thiopental,[24,25] propofol,[26-28] and midazolam (see Table 28-2).[29] Defining the C_{50}, like MAC, provides a measure of relative potency between intravenous anesthetics.

Another interpretation of C_{50} is the concentration that produces 50% of the maximum possible physiologic response. For example, the C_{50} for an EEG response is the drug concentration that provides 50% of the maximal EEG effect. The C_{50} for EEG response has been measured for the opioids alfentanil,[30] fentanyl,[30] sufentanil,[31] and remifentanil.[32-34] It has also been determined for thiopental,[24,35,36] etomidate,[37] propofol,[38] and benzodiazepines (see Table 28-2).[39]

Although C_{50} values for all combinations of stimuli and measures have not been determined experimentally for each opioid, they can be estimated accurately by scaling the values of C_{50} determined experimentally for other opioids according to their relative potency.[40] For example, the C_{50} of alfentanil for

Table 28-2 Steady-State Concentrations for Predefined Effects*

Drug	C_{50} for EEG Depression†	C_{50} for Incision or Painful Stimulus‡	C_{50} for Loss of Consciousness§	C_{50} for Spontaneous Ventilation¶	C_{50} for Isoflurane MAC Reduction	MEAC
Propofol (μg/mL)	3-4	4-8	2-3	1.33	Not studied	—
Thiopental (μg/mL)	15-20	35-40	8-16	—	—	—
Midazolam (ng/mL)	250-350	—	125-250	—	—	—
Alfentanil (ng/mL)	500-600	200-300	—	170-230	50	10-30
Fentanyl (ng/mL)	6-10	4-6	—	2-3	1.7	0.5-1
Sufentanil (ng/mL)	0.5-0.75	(0.3-0.4)	—	(0.15-0.2)	0.15	0.025-0.05
Remifentanil (ng/mL)	10-15	4-6	—	2-3	1.2	0.5-1

*Values in parentheses are estimated by scaling to the alfentanil C_{50} (see text for details).
†The C_{50} for depression of the electroencephalogram (EEG) is the steady-state serum concentration that causes a 50% slowing of the maximal EEG, except for midazolam, where the C_{50} is associated with 50% activation of the EEG.
‡The C_{50} for skin incision is the steady-state plasma concentration that prevents a somatic or autonomic response in 50% of patients.
§The C_{50} for loss of consciousness is the steady-state plasma concentration for absence of a response to a verbal command in 50% of patients.
¶The C_{50} for spontaneous ventilation is the steady-state plasma concentration associated with adequate spontaneous ventilation in 50% of patients.
MEAC, minimum effective plasma concentration providing postoperative analgesia.

spontaneous ventilation is about 40% of the C_{50} for EEG response (see Table 28-2). Knowing this, we can estimate the C_{50} of sufentanil for spontaneous ventilation (which has not yet been determined experimentally) as 0.2 to 0.3 ng/mL, that is, 40% of the C_{50} for EEG response (0.7 ng/mL).

To be entirely independent of dosing history, C_{50} must be determined at steady state, which is rarely possible because most anesthetic drugs do not reach steady state during a continuous infusion until many hours have passed. However, if the drug exhibits rapid equilibration between plasma and the effect site and the investigator waits long enough after starting the infusion, this choice can be reasonably satisfactory. For example, in their experiments Ausems and colleagues[23,41] used a continuous infusion of alfentanil, which equilibrated quickly. They also took their measurements after the effect-site concentration had equilibrated with plasma.

A second alternative to performing a true steady-state experiment is to use mathematical modeling to calculate the effect-site concentrations of drug at the time of measurement, as proposed by Hull and colleagues[12] and Sheiner and colleagues.[13] The relationship between effect-site and plasma concentrations is represented graphically in Figure 28-5 and mathematically in Equation 6. Calculating effect-site concentrations is the same as attempting to determine the steady-state plasma concentrations that would produce the observed drug effect. When the C_{50} reflects effect-site concentrations, it is represented as Ce_{50} to distinguish it from values of C_{50} that are based on plasma concentrations, which are then termed Cp_{50}. However, the distinction is artificial. In both cases, C_{50} is intended to represent the steady-state plasma drug concentration associated with a given drug effect.

A third alternative to performing a steady-state experiment is to establish a pseudo–steady state with the use of computer-controlled drug delivery. This has become the state-of-the-art method for determining the C_{50} for anesthetic drugs, and many of the C_{50} values referenced earlier were determined at pseudo–steady state with the use of computer-controlled drug delivery. Typically, maintaining a constant plasma steady-state concentration for four to five plasma effect-site equilibration half-lives (e.g., 10 to 15 minutes for fentanyl) is required. Such a long delay is not necessarily needed when computer-controlled drug delivery is used. For example, computer-controlled infusions can be used to target initially higher plasma target concentrations to provide more rapid achievement of the desired effect-site concentration.[42] This can be automated by having the computer actually target the concentration at the effect-site rather than plasma and thereby rapidly establish plasma–effect site equilibration.[17,18]

Thus, there are several ways to establish C_{50} in terms of steady-state concentrations. C_{50} can be estimated through mathematical effect-site modeling or can be measured experimentally with the use of computer-controlled drug delivery to quickly establish a pseudo–steady state. Either way, when performing studies to define the concentration-effect relationship, equilibrium must exist or be modeled for between the biophase (the site of effect) and plasma or blood (where the concentration is actually measured).

When C_{50} is defined in terms of the concentration associated with a response in half of a population, that same C_{50} is the concentration associated with a 50% probability of response in a typical individual. However, individual patients are not typical individuals but instead will have their own value for C_{50}. Expressed in clinical terms, different patients have different anesthetic requirements for the same stimulus. For example, the minimal effective analgesic concentration of fentanyl is 0.6 ng/mL, but it varies among patients from 0.2 to 2.0 ng/mL.[43] The minimal effective analgesic concentrations of alfentanil[44,45] and sufentanil[46] similarly vary among patients by a factor of 5 to 10. This range encompasses both variability in the intensity of the stimulus and variability of the individual patient. However, this wide range reflects the clinical reality that must be accounted for when dosing regimens are designed. Because of this variability, intravenous anesthetics should be titrated to each patient's unique anesthetic requirement for the given stimulus.

Pharmacodynamic Drug Interactions

Drug interactions cause the C_{50} of one drug to shift in response to administration of a second drug. We have already referred to

the ability of opioids to reduce MAC, a clinically useful drug interaction with a long history. In 1901, George Crile suggested that opioids be administered with supplemental drugs for intravenous anesthesia. In 1959, DeCastro and Mundeleer introduced the term "neurolept anesthesia," which consists of a tranquilizer, opioid, and nitrous oxide. Today, the term coined by John Lundy, "balanced anesthesia," is used to describe the concurrent administration of several anesthetic drugs so that no single drug is given in a dosage sufficient to produce toxicity during or after surgery. The interaction of hypnotics and opioids in producing the anesthetic state is complex but predictable.

The MAC of volatile anesthetics appears to be additive when several inhaled anesthetics are administered concurrently.[47,48] The additivity of MAC suggests a uniform mechanism of action for the inhaled anesthetics, although the "unitary theory" of inhalational anesthesia has fallen into disfavor.[49,50] The intravenous anesthetics encompass categories of drugs (hypnotics, opioids, psychotomimetics, anxiolytics, neuroleptics, local anesthetics, and so on) with different receptors and mechanisms of action. In the absence of a uniform mechanism of action, there is no reason to anticipate simple additivity, for example, that maintaining 30% C_{50} of drug A plus 40% C_{50} of drug B will produce the same effect as 70% C_{50} of either drug A or drug B.

The assumption of balanced anesthesia is that drug combinations will be synergistic in anesthetic effect (however defined) but not in toxicity. Such synergism has been demonstrated for a variety of drug combinations but not for others.[51,52] For example, Smith and coworkers[28] found minimal synergy between propofol and fentanyl for the end point loss of consciousness, but profound synergy between propofol and fentanyl for the end point loss of response to skin incision (Fig. 28-7). More profound synergy for such end points related to analgesia and hypnosis has also been demonstrated for the interaction between propofol and alfentanil[27] and for that between sevoflurane and fentanyl.[53] Thus, when anesthetic regimens are designed that rely on synergy to produce the anesthetic state, it is important to distinguish the desired end point—loss of consciousness or ablation of response to noxious stimulation. Different combinations of drugs may be required to achieve each end point.

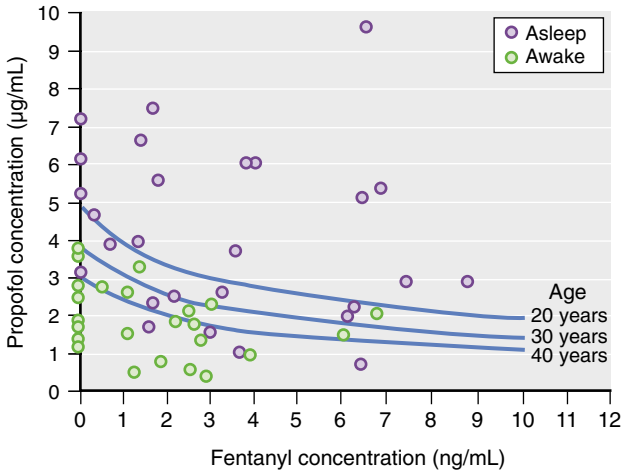

Figure 28-7 Interaction of propofol and fentanyl in preventing a somatic response at skin incision. The *solid line* represents the concentrations of propofol and fentanyl when administered together that are required to prevent purposeful movement in 50% of patients at skin incision. The *dashed line* represents the concentration of propofol and fentanyl when administered together that is required to prevent purposeful movement in 95% of patients at skin incision. *(From Smith C, McEwan AI, Jhaveri R, et al: Reduction of propofol Cp_{50} by fentanyl. Anesthesiology 77:A340, 1992.)*

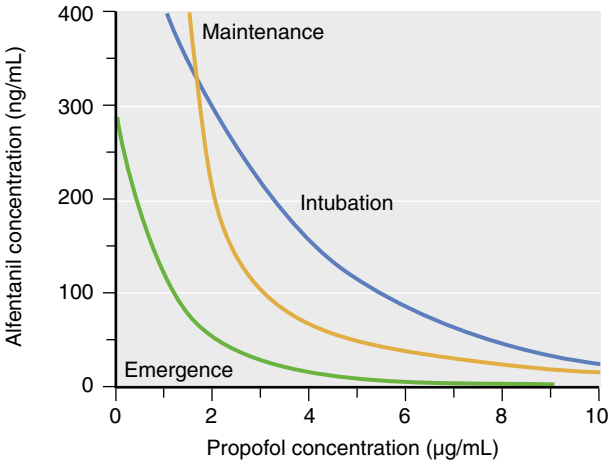

Figure 28-8 Interaction between alfentanil and propofol on three different end points: response to intubation (*blue line*), maintenance of anesthesia (*orange line*), and concentrations associated with emergence from anesthesia (*green line*). The curve shows the concentrations associated with a 50% probability of the respective end point. *(Adapted from Vuyk J, Lim T, Engbers FH, et al: The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. Anesthesiology 83:8-22, 1995.)*

Vuyk and colleagues characterized the interaction between propofol and alfentanil for several end points: loss of response to intubation, loss of response to intraoperative stimulation, and emergence from anesthesia (Fig. 28-8).[27] The most profound stimulation was tracheal intubation, and abolition of that stimulus required a propofol concentration of at least 2 µg/mL.

MAC is defined as the steady-state alveolar concentration of anesthetic gas that inhibits movement upon incision in 50% of patients. It is a well-established measure of potency. MAC is also a useful guideline for clinical dosage, provided that the clinician remembers that it is the concentration in 50% of patients that inhibits a movement response and that it is defined in terms of an analgesic end point—loss of movement in response to noxious stimulation. To establish the interaction between volatile anesthetics and opioids, the reduction in MAC can be used. When such studies are performed, it is important that both the volatile anesthetic and the opioid be maintained at stable concentrations and have equilibrated with their effect site. For the volatile anesthetic, this is readily achieved with use of a calibrated vaporizer. For the opioid, target-controlled delivery devices described in this chapter are used to maintain constant opioid concentrations within the effect compartment.

Reduction of the MAC of isoflurane by fentanyl,[54] sufentanil,[55] alfentanil,[56] and remifentanil[57] (see also Chapter 27) has been defined for all. The concentrations of these opioids that provide a 50% reduction in MAC are listed in Table 28-2. McEwan and associates[54] demonstrated that the MAC of isoflurane is reduced by 50% at a fentanyl concentration of 1.7 ng/mL (Fig. 28-9). This corresponds with a fentanyl loading dose of 4 µg/kg followed by a 1.75-µg/kg/hr infusion. The minimum effective analgesic concentration of fentanyl is 0.6 ng/mL,[43] and clinically significant respiratory depression may occur with plasma fentanyl concentrations above 2 ng/mL.[58] The steepest reduction in MAC

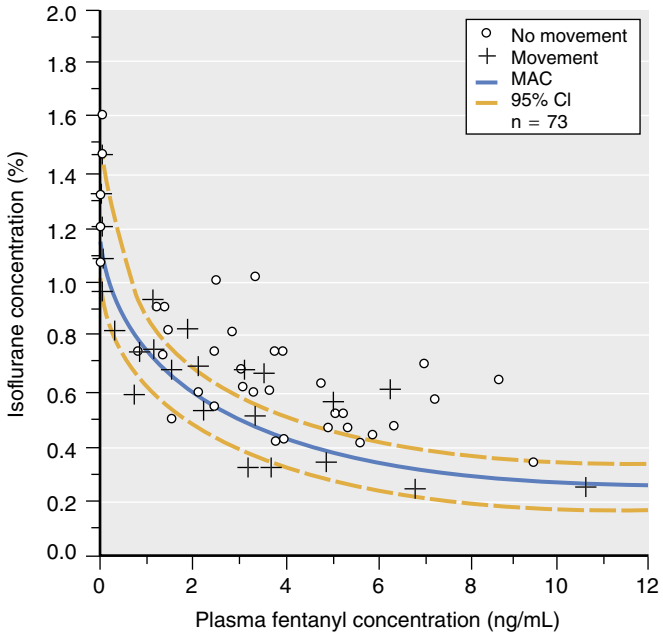

Figure 28-9 Interaction of isoflurane and fentanyl in preventing a somatic response at skin incision (i.e., minimum alveolar concentration [MAC] reduction of isoflurane). The *blue line* represents the concentrations of isoflurane and fentanyl when administered together that are required to prevent purposeful movement in 50% of patients at skin incision. The *yellow lines* represent the 95% confidence interval of the MAC at each combination of fentanyl and isoflurane. *(From McEwan AI, Smith C, Dyar O, et al: Isoflurane MAC reduction by fentanyl. Anesthesiology 78:864-869, 1993.)*

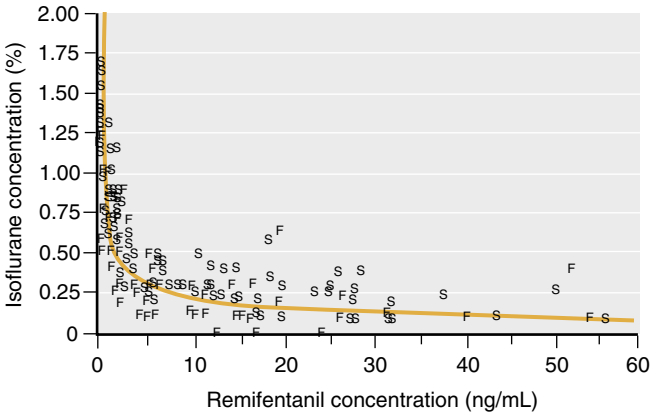

Figure 28-10 Interaction of isoflurane and remifentanil in preventing a somatic response at skin incision (i.e., minimum alveolar concentration [MAC] reduction of isoflurane). The *solid line* represents the concentrations of isoflurane and remifentanil when administered together that are required to prevent purposeful movement in 50% of patients at skin incision. *(From Lang E, Kapila A, Shlugman D, et al: Reduction of isoflurane minimal alveolar concentration by remifentanil. Anesthesiology 85:721-728, 1996.)*

thus occurs within the useful analgesic range for fentanyl (i.e., 0.6 to 2 ng/mL). In other words, by maintaining fentanyl within an analgesic range, the MAC of isoflurane can be reduced by 50%. The study by McEwan and colleagues also demonstrated that beyond a fentanyl plasma concentration of 5 ng/mL, a plateau is seen with a maximum MAC reduction of approximately 80%. The maximum reduction in isoflurane was to a concentration of ±0.3%, that is, a value close to the MAC-awake value for isoflurane.[59]

Alfentanil,[56] sufentanil,[55] and remifentanil[57] produce similar reductions in isoflurane MAC, with an initial steep reduction at lower concentrations and a ceiling effect at higher concentrations. Because remifentanil is metabolized rapidly,[15] it is possible to give huge doses during MAC studies and still awaken patients after surgery. The reduction in isoflurane MAC by remifentanil is shown in Figure 28-10.[57] Even with very high plasma concentrations (>30 ng/mL), a ceiling of opioid effect is observed, and the MAC of isoflurane is not reduced below 0.2% to 0.3%. Similar results have been demonstrated with the other volatile anesthetics and opioids. Thus, there is little clinical benefit in administering opioid at concentrations exceeding those that produce a ceiling in MAC reduction. This occurs at a concentration of 3 to 5 ng/mL for fentanyl and remifentanil, 200 to 400 ng/mL for alfentanil, and 0.25 to 0.5 ng/mL for sufentanil. Keeping the opioid dose within an analgesic range prevents the very slow recovery that is associated with high opioid concentrations.

The relationship between opioids and hypnotics on the C_{50}, the concentration of drug associated with 50% of maximum effect, has been examined. The interaction between two drugs describes a surface in which each drug has its own axis and the third axis is the effect from any combination of the two drugs. Figure 28-11 shows the relationship between the three-dimensional response surfaces and the more commonly shown relationship in two dimensions between the C_{50} of two drugs. Minto and colleagues published "response surfaces" for combinations of midazolam-alfentanil, propofol-alfentanil, and midazolam-propofol associ-

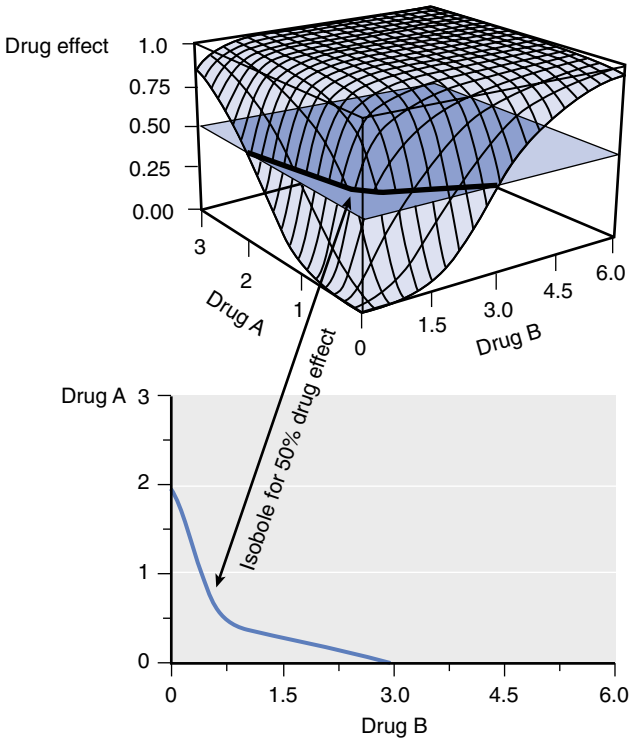

Figure 28-11 Relationship between a response surface and a standard isobologram. Conventional "isobolographic" analysis, whether for doses or concentrations, describes only the concentration of both drugs that yields a 50% drug effect and thus fails to capture the entire response surface. *(From Minto CF, Schnider TW, Short TG, et al: Response surface model for anesthetic drug interactions. Anesthesiology 92:1603-1616, 2000.)*

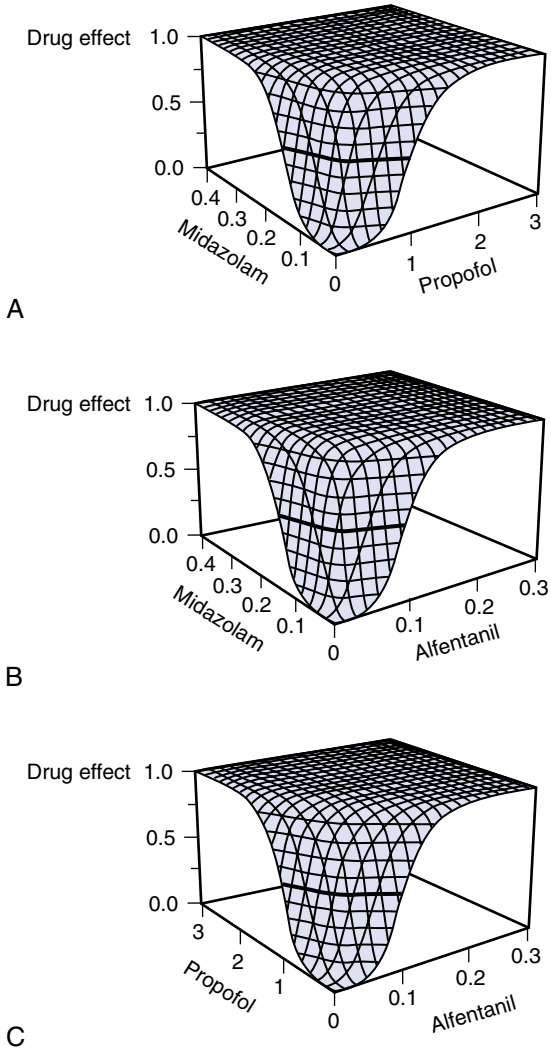

Figure 28-12 Response surface for each of the paired interactions between propofol and midazolam (**A**), alfentanil and midazolam (**B**), and alfentanil and propofol (**C**) on the probability of opening eyes to verbal command. The isoboles for a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90% response are shown. *(From Minto CF, Schnider TW, Short TG, et al: Response surface model for anesthetic drug interactions. Anesthesiology 92:1603-1616, 2000.)*

ated with loss of response to verbal command, as shown in Figure 28-12.[60] They also extended response surface methodology to describe the simultaneous interaction of three drugs. Rendering the full interaction surface for three drugs would require drawing the graph in four dimensions. If the graph is limited to the interaction at 50% drug effect, it can be rendered in three dimensions, as shown in Figure 28-13.

Sensitivity varies from patient to patient, as well as in the level of stimulation associated with different surgical procedures. Thus, each patient is a challenge, with the clinician learning the individual patient's C_{50} for the combination of drugs used during the administration of each anesthetic. Despite this variability, dosing guidelines play an important role in the practice of anesthesia. The concentration ranges of intravenous anesthetics for anesthesia, sedation, and analgesia are given in Table 28-3. These ranges provide starting estimates on which subsequent titration can be based. They also provide a means of estimating whether the patient is having a typical or an atypical response. If the patient's dosing requirements deviate greatly from established guidelines, it is reasonable to determine whether something else might be affecting either the patient or the drug delivery system.

Designing Dosing Regimens

Bolus Dose Calculations

The definition of concentration is amount divided by volume. We can rearrange the definition of concentration to find the amount of drug required to produce any desired concentration for a known volume:

$$\text{Amount} = C_T \cdot \text{Volume} \tag{10}$$

where C_T is the desired or "target" concentration. Many introductory pharmacokinetic texts suggest using this formula to calculate the loading bolus required to achieve a given concentration. The problem with applying this concept to anesthetic drugs is that there are several volumes: V_1 (central compartment), V_2 and V_3 (the peripheral compartments), and Vd_{ss}, the sum of the individual volumes. V_1 is usually much smaller than Vd_{ss}, and thus it is tempting to say that the loading dose should be something between $C_T \times V_1$ and $C_T \times Vd_{ss}$.

Consider the dose of fentanyl required to attenuate the hemodynamic response to intubation when combined with thiopental. The C_{50} for fentanyl, combined with thiopental for intubation, is approximately 3 ng/mL. The V_1 and Vd_{ss} for fentanyl are 13 and 360 L, respectively. The aforementioned equations can thus be interpreted as suggesting that an appropriate dose of fentanyl to attenuate the hemodynamic response is between 39 µg (3 ng/mL × 13 L) and 1080 µg (3 ng/mL × 360 L). A fentanyl bolus of 39 µg achieves the desired concentration in plasma for an initial instant, but plasma levels almost instantly decrease

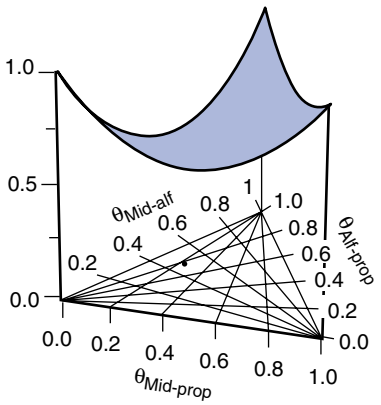

Figure 28-13 Interaction at 50% drug effect between propofol, midazolam, and alfentanil. Downward deflection of the surface represents synergy, in units of fractional reduction in C_{50}. The three edges represent relative amounts of propofol to midazolam ($\theta_{Mid\text{-}prop}$), alfentanil to midazolam ($\theta_{Mid\text{-}alf}$), and alfentanil to propofol ($\theta_{Alf\text{-}prop}$). The surface between the edges represents the relative synergy of all three drugs taken together. *(From Minto CF, Schnider TW, Short TG, et al: Response surface model for anesthetic drug interactions. Anesthesiology 92:1603-1616, 2000.)*

Table 28-3 Plasma Drug Concentration Ranges

Drug*	Stimulus			Spontaneous Ventilation	Awakening	Analgesia or Sedation
	Skin Incision	Major Surgery	Minor Surgery			
Alfentanil (ng/mL)	200-300	250-450	100-300	<200-250	—	50-100
Fentanyl (ng/mL)	3-6	4-8	2-5	<1-2	—	1-2
Sufentanil (ng/mL)	1-3	2-5	1-3	<0.2	—	0.02-0.2
Remifentanil (ng/mL)	4-8	4-8	2-4	<1-3	—	1-2
Propofol (µg/mL)	2-6	2.5-7.5	2-6	—	0.8-1.8	1.0-3.0
Methohexital (µg/mL)	5-10	5-15	5-10	—	1-3	2-5
Thiopental (µg/mL)	7.5-12.5 (with N_2O) 35-45 (without N_2O)	10-20	10-20	—	4-8	7.5-15.0
Etomidate (ng/mL)	400-600	500-1000	300-600	—	200-350	100-300
Midazolam (ng/mL)	—	50-250 (combined with an opioid)	50-250 (combined with an opioid)	—	15-200 (reduced to 20-70 in the presence of an opioid)	40-100
Ketamine (µg/mL)	—	—	1-2	—	—	0.1-1
Dexmedetomidine† (ng/mL)						0.1-0.6

*Drug levels when combined with 65% to 70% nitrous oxide (N_2O) unless otherwise stated. Effective plasma concentrations may differ markedly, depending on premedication and intraoperative drug combinations.
†Dexmedetomidine provides sedation and mild analgesia at the concentrations listed. It may be combined with other sedatives or analgesics to reduce their C_{50} for the end points listed.

below the desired target. Levels at the effect site will never be close to the desired target concentration of 3 ng/mL. A fentanyl bolus of 1080 µg, not surprisingly, produces a marked overshoot in plasma levels that persists for hours (Fig. 28-14). Additionally, it is absurd to use equations to calculate the fentanyl dose if the resulting recommendation is "pick a dose between 39 and 1080 µg."

The usual dosing guidelines for a bolus dose, presented earlier, are designed to produce a specific plasma concentration. Because plasma is not the site of drug effect, it is illogical to base calculation of the initial bolus on a desired plasma concentration. As pointed out previously, by knowing the k_{e0} of an intravenous anesthetic, we can design a dosing regimen that yields the desired concentration at the site of drug effect. If we do not want to overdose the patient, we should select a bolus that produces the desired peak concentration at the effect site.

The decline in plasma concentration between the initial concentration after the bolus (amount/V_1) and the concentration at the time of peak effect can be thought of as dilution of the bolus into a larger volume than the volume of the central compartment. This introduces the concept of Vd_{pe}, the apparent volume of distribution at the time of peak effect,[17,61] or pseudo-equilibration between plasma and the site of drug effect.[62] The size of this volume can readily be calculated from the observation that the plasma and effect-site concentrations are the same at the time of peak effect:

$$Vd_{pe} = \frac{\text{Bolus amount}}{C_{pe}} \qquad (11)$$

where C_{pe} is the plasma concentration at the time of peak effect.

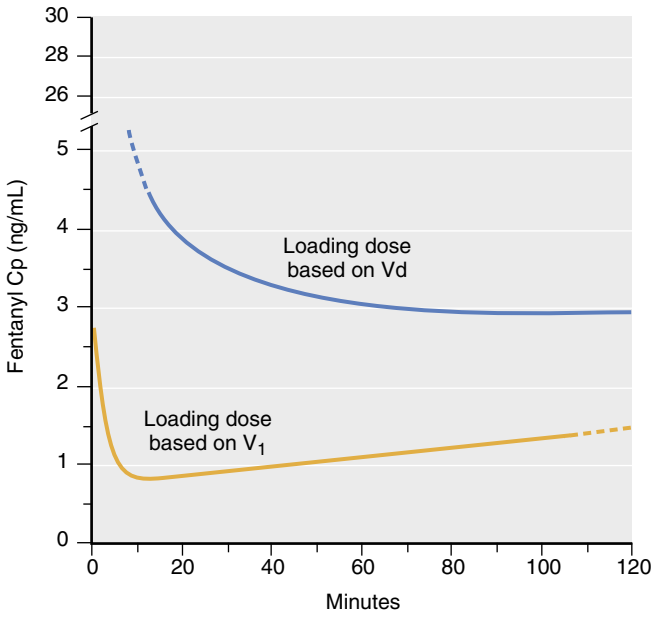

Figure 28-14 Pharmacokinetic simulation demonstrating the limitations of infusion regimens based on simple pharmacokinetic parameters, with fentanyl used as an example. These infusion schemes were designed to achieve a plasma fentanyl concentration of 3 ng/mL. The *upper blue curve* shows that a regimen using a loading dose based on the volume of distribution followed by a constant infusion based on clearance results in a transient period of very high plasma concentrations. If the same maintenance infusion is given but the loading dose is based on the volume of the central compartment, distribution of drug to the peripheral compartments causes the plasma concentration to fall below the desired level until the compartments reach steady-state concentrations, as shown in the *lower yellow curve*. Cp, plasma drug concentration.

Table 28-4 Volume of Distribution at the Time of Peak Effect

Drug	V_1 (L)	Vd_{pe} (L)
Fentanyl	12.7	75
Alfentanil	2.19	5.9
Sufentanil	17.8	89
Remifentanil	5.0	17
Propofol	6.7	37
Thiopental	5.6	14.6
Midazolam	3.4	31

V_1, volume of the central compartment; Vd_{pe}, apparent volume of distribution at the time of peak effect.

Let us assume that our clinical goal is to select the dose required to achieve a certain drug effect without producing an overdose. We can rearrange Equation 11 by substituting C_T, the target concentration (which is the same in plasma and the effect site at the moment of peak effect), for C_{pe} to calculate the size of the initial bolus:

$$\text{Loading dose} = C_T \cdot Vd_{pe} \quad (12)$$

The Vd_{pe} for fentanyl is 75 L. To achieve a peak fentanyl effect-site concentration of 3.0 ng/mL requires 225 µg, which produces a peak effect in 3.6 minutes. This is a much more reasonable dosing guideline than the previous recommendation of a dose between 39 and 1080 µg. Table 28-4 lists V_1 and Vd_{pe} for fentanyl, alfentanil, sufentanil, remifentanil, propofol, thiopental, and midazolam. Table 28-1 lists the time to peak effect and the $t_{½}$ k_{e0} of the commonly used intravenous anesthetics.

Maintenance Infusion Rate

By definition, the rate at which drug exits the body is systemic clearance, Cl_S, times the plasma concentration. To maintain a given target concentration, C_T, drug must be delivered at the same rate that it is exiting the body. Thus,

$$\text{Maintenance infusion rate} = C_T \cdot Cl_S \quad (13)$$

For drugs with multicompartmental pharmacokinetics, which includes all of the intravenous drugs used in anesthetic practice, drug is distributed into the peripheral tissues as well as cleared from the body. The rate of distribution into tissues changes over time as the tissues equilibrate with plasma. Equation 13 is correct only after the peripheral tissues have fully equilibrated with plasma, which requires many hours. At all other times, this maintenance infusion rate underestimates the infusion rate to maintain a target concentration.

In some situations this simple maintenance rate calculation may be acceptable. For example, if an infusion at this rate is used along with a bolus dose based on Vd_{pe} and the drug has a long delay between the bolus and peak effect, much of the distribution of drug into tissues may have occurred by the time that the effect-site concentration reaches the target concentration. In this case, the maintenance infusion rate calculated as clearance times target concentration may be accurate because Vd_{pe} is sufficiently higher than V_1 to account for the distribution of drug into peripheral tissues. Unfortunately, most drugs used in anesthesia achieve sufficiently rapid equilibration between plasma and the effect site that Vd_{pe} does not adequately encompass the distribution process, thus making this approach unsuitable.

Another example of calculating infusion rates for drugs with multicompartmental pharmacokinetics is the two-step approach proposed by Wagner.[63] In this method, two infusions, Q_1 and Q_2, are administered in sequence. The loading infusion, Q_1, is selected on the basis of convenience and the degree of overshoot in plasma concentration that will be clinically acceptable. The second infusion, Q_2, is calculated as $C_T \times Cl_S$, exactly as noted earlier. The Wagner two-step approach does not consider the time course of drug effect and thus is probably not appropriate for most anesthetic drugs.

Having considered two approaches that do not work very well, we now turn to approaches that are mathematically and clinically sound. Because the net flow of drug into peripheral tissues decreases over time, the infusion rate required to maintain any desired concentration must also decrease over time. If the initial bolus has been based on Vd_{pe}, no infusion need be administered until the effect-site concentrations peak. After the peak in effect-site concentration, the (nearly) correct equation to maintain the desired concentration is

$$\text{Maintenance infusion rate} = C_T \times V_1 \times \left(k_{10} + k_{12}e^{-k_{21}t} + k_{13}e^{-k_{31}t}\right) \quad (14)$$

This equation indicates that a high infusion rate is initially required to maintain C_T. Over time, the infusion rate gradually decreases (see Fig. 28-4). At equilibrium ($t = \infty$), the infusion rate decreases to $C_T \times V_1 \times k_{10}$, which is the same as $C_T \times Cl_S$. Few anesthesiologists would choose to mentally solve such an equation during administration of an anesthetic. Fortunately, there are simple techniques that can be used in place of solving such a complex expression.

Figure 28-15 is a nomogram in which Equation 14 has been solved; the infusion rates at different times necessary to maintain any desired concentration of fentanyl, alfentanil, sufentanil, and propofol are shown. This nomogram is complex, so we will review it in detail. The *y* axis represents the target concentration C_T. The *x* axis is the time since the beginning of the anesthetic (i.e., since the initial bolus). The suggested initial target concentrations (shown in red) are based on the work of Vuyk and colleagues[27] with propofol and alfentanil (see Fig. 28-8) and are scaled to fentanyl and sufentanil according to their relative potencies.[61] The intersections of the target concentration line and the diagonal lines indicate the infusion rate appropriate at each point in time. For example, to maintain a fentanyl concentration of 1.5 ng/mL, the appropriate rates are 4.5 µg/kg/hr at 15 minutes, 3.6 µg/kg/hr at 30 minutes, 2.7 µg/kg/hr at 60 minutes, 2.1 µg/kg/hr at 120 minutes, and 1.5 µg/kg/hr at 180 minutes. Of course, it is possible to select target concentrations and different times of rate adjustment, depending on clinical circumstances and your assessment of how accurately the intravenous drug needs to be titrated.

Another recent approach to manually determine infusion rates for maintenance of anesthesia to a desired target concentration is through the application of concepts involving the use of a slide rule.[64] Figure 28-16 illustrates such a slide rule for propofol. As described by Bruhn and colleagues, "The bolus dose required to reach a given target plasma concentration is the product of the (weight-related) distribution volume and required concentration.

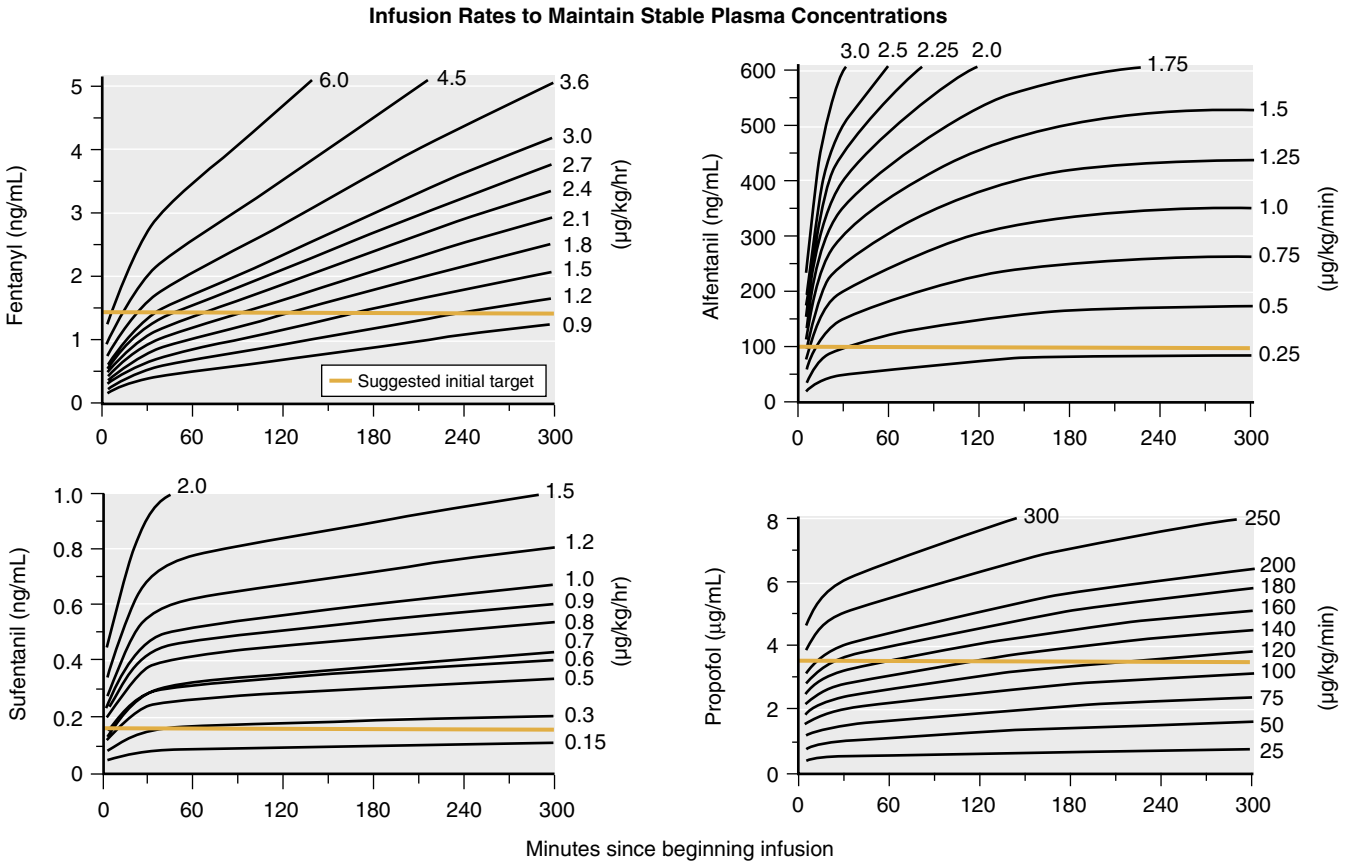

Figure 28-15 Nomogram for calculating maintenance infusion rates to maintain a stable concentration of fentanyl, alfentanil, sufentanil, or propofol. The *y* axis is the desired concentration. The *x* axis is the time relative to the initial bolus. The *diagonal lines* show the infusion rates at different times required to maintain the desired concentration selected on the *y* axis.

Similarly, the infusion rate at a particular time point is the product of target concentration, body weight, and a correction factor that depends on the time elapsed from the start of the initial infusion. This factor can be determined for each time point using a PK simulation program."[64] When compared with computer simulation programs, this manual device performed within an acceptable degree of accuracy (within 7% of the simulated target concentration) for a single target concentration and decreased in accuracy (within 20%) when applied to changing target concentrations.

Recovery from Anesthesia

Recovery from anesthesia is determined by the pharmacokinetic principles that govern the rate of decrease in drug from the effect compartment once drug administration is terminated, as well as by the pharmacodynamics of the drug. Although the terminal elimination half-life is often interpreted as a measure of how short or long lasting a drug is, the rate at which drug decreases is dependent on both elimination and redistribution of the drug from the central compartment. The contribution of both

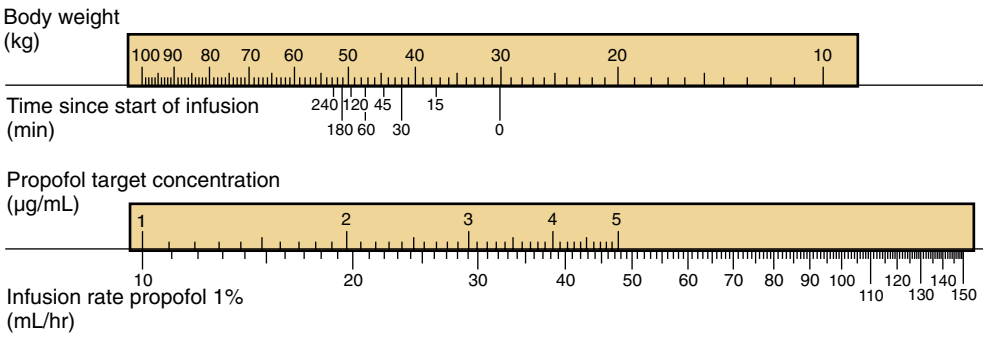

Figure 28-16 Slide rule for calculating the maintenance propofol infusion rate from the patient's weight, the desired target concentration, and the elapsed time. *(Adapted from Bruhn J, Bouillon TW, Ropcke H, Hoeft A: A manual slide rule for target-controlled infusion of propofol: Development and evaluation. Anesth Analg 96:142-147, 2003.)*

redistribution and elimination toward the rate of decrease in drug concentration varies according to the duration for which the drug has been administered.[61,65]

In 1985, Schwilden[66] developed a mathematical model to relate the time course of offset of action of inhaled anesthetics to the duration of anesthetic drug delivery. Similarly, Fisher and Rosen[67] demonstrated how accumulation of muscle relaxants in peripheral volumes of distribution results in slowed recovery with increasing duration of administration. They introduced two measures of the time course of recovery, the time for twitch tension to recover from 5% to 25% and the time for twitch tension to recover from 25% to 75%.

Since then, the time for the plasma concentration to decrease by 50% from an infusion that maintains a constant concentration (e.g., the infusion given by Equation 14) has been termed the "context-sensitive half-time" (Fig. 28-17),[65] with the context being the duration of the infusion. The 50% decrease was chosen both for tradition (e.g., half-lives are the time for a 50% decrease with a one-compartment model) and because, very roughly, a 50% reduction in drug concentration appears to be necessary for recovery after the administration of most intravenous hypnotics at the termination of surgery. Depending on circumstances, decreases other than 50% may be clinically relevant. Additionally, sometimes it is the plasma concentration that is of interest, and sometimes it is the effect-site concentration that is of interest. A more general term is the context-sensitive "decrement time,"[68] in which the decrement in concentration is specifically noted, as is the compartment where the decrease is modeled (plasma or effect site). For example, the relationship between

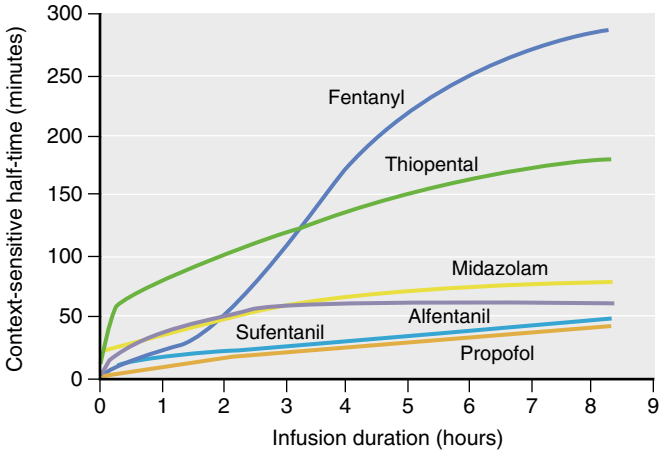

Figure 28-17 Context-sensitive half-times as a function of infusion duration (the "context") derived from pharmacokinetic models of fentanyl, sufentanil, alfentanil, propofol, midazolam, and thiopental. *(From Hughes MA, Glass PSA, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 76:334-341, 1992.)*

infusion duration and time required for a 70% decrease in fentanyl effect-site concentration is the "context-sensitive 70% effect-site decrement time."

Context-sensitive effect-site decrement times for varying percent decreases in alfentanil, fentanyl, and remifentanil concentration are illustrated in Figure 28-18. To determine when an infusion should be terminated (to enable awakening of the patient

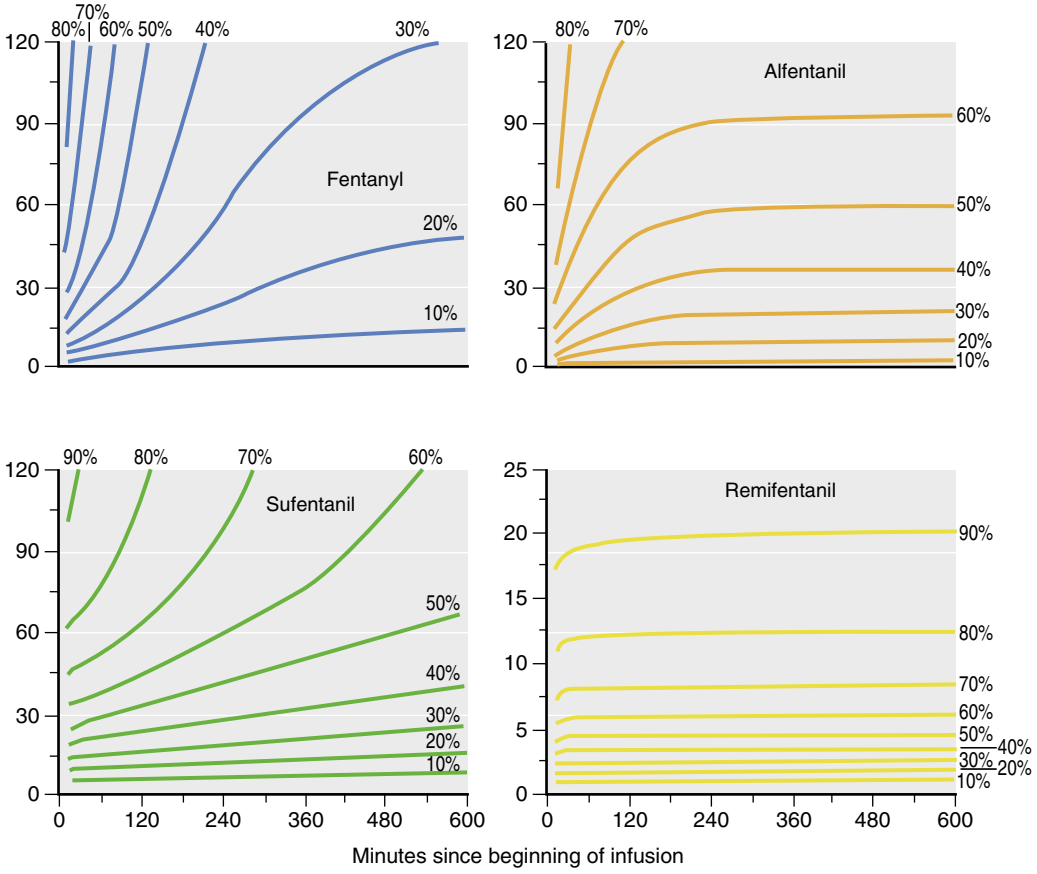

Figure 28-18 Context-sensitive effect-site decrement times for alfentanil, fentanyl, sufentanil, and remifentanil showing the time required for decreases of a given percentage (labeled for each curve) from the maintained effect-site concentration after termination of the infusion.

at the end of surgery), the clinician needs to bear in mind the decrease in concentration necessary for recovery, the duration of the infusion (the context), and the context-sensitive effect-site decrement time required for the necessary decrease.

Context-sensitive decrement times are fundamentally different from the elimination half-life. With monoexponential decay, each 50% decrease in concentration requires the same amount of time, and this time is independent of how the drug is given. This is not true for the context-sensitive half-time. First, as the name is intended to imply, the time needed for a 50% decrease is absolutely dependent on how the drug was given, with infusion duration being the context to which the name refers. In addition, small changes in percent decrement can result in surprisingly large increases in the time required. As can be seen from Figure 28-18, in some situations the time required for a 60% decrease in drug concentration can be more than twice the time required for a 50% decrease.

Context-sensitive decrement times are based on the assumption that plasma or the effect site is maintained at a constant concentration. Such is rarely the case clinically, but maintenance of constant concentrations is a necessary assumption to provide a unique mathematical solution to the time required for a given percent decrement in plasma or effect-site concentration. Because plasma and effect-site concentrations are rarely kept constant, it is important that context-sensitive decrement times be used as general guidelines for interpreting the pharmacokinetics of intravenous drugs and not as absolute predictions for any given case or infusion regimen. Automated drug delivery systems can provide more precise predictions of the time required for the plasma or effect-site concentration to decrease to any desired concentration based on the actual drug dosing in the individual patient. This provides the clinician with guidance for the most appropriate time to terminate the infusion.

Context-sensitive decrement times focus on the role of pharmacokinetics in recovery from anesthesia. Pharmacodynamics plays an important role in recovery as well. Bailey[69] used integrated pharmacokinetic/pharmacodynamic models to define the "mean effect time" as the average time to responsiveness after maintenance of anesthesia at the 90% probability of unresponsiveness. The mean effect time demonstrates that when drugs have a very shallow concentration-versus-response relationship, concentrations must decrease by a significant fraction to provide adequate emergence. This delays recovery from anesthesia. In contrast, recovery is hastened by a steep concentration-versus-response relationship, in which emergence from anesthesia occurs after a relatively small fractional decrease in concentration. Most intravenous hypnotics have a fairly steep concentration-versus-response relationship.

Pharmacodynamic drug interactions also play a role in recovery from anesthesia. Interaction relationships predict that the same anesthetic state can be achieved by different ratios of two drugs. One way of selecting the best ratio might be the combination that offers the most rapid recovery. For example, when an opioid is combined with a hypnotic, recovery from anesthesia depends on the opioid and hypnotic concentrations, the rate of decrease in both drugs, and the relative synergy between them for loss of response to noxious stimulation (i.e., the state maintained during anesthesia) versus the relative synergy for loss of consciousness. Although the time course of decreases in opioid and hypnotic concentrations can be approximately described by their respective context-sensitive decrement times for both drugs

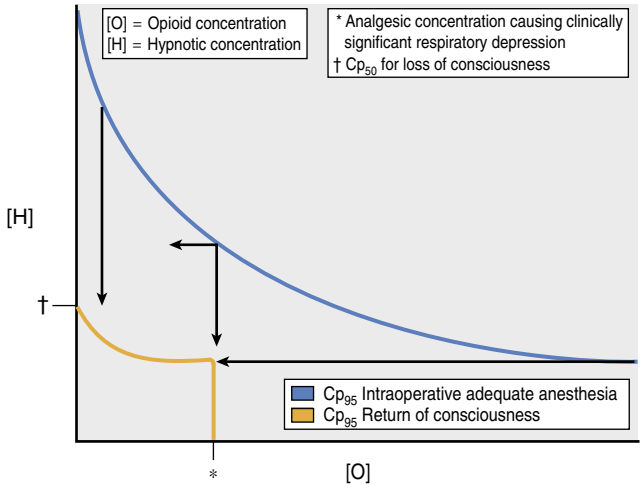

Figure 28-19 Interaction between hypnotics and opioids for prevention of movement after a noxious stimulus and for awakening and adequate spontaneous ventilation at the end of a surgical procedure. From this it can be seen that the time to recover at the end of a procedure is dependent on the concentration of both drugs used during surgery and the time for both to decrease below that required for consciousness and adequate spontaneous ventilation (i.e., their context-sensitive decrement times).

(Fig. 28-19; for propofol/alfentanil, see Fig. 28-8), the influence of relative synergy for different end points must be captured by separate models of the interaction of the drugs for adequate anesthesia and emergence from anesthesia.

Vuyk and coworkers[70] modeled the predicted time to awakening when propofol is combined with fentanyl, sufentanil, alfentanil, or remifentanil on the basis of the interaction between propofol and these opioids to provide adequate anesthesia and the interaction between propofol and opioids on emergence from anesthesia, as seen in Figures 28-20 and 28-21. Recovery times vary with the choice of opioid and the relative balance of opioid and propofol during maintenance of anesthesia. For example, in the upper left of Figure 28-20 is a simulation of emergence from a propofol/fentanyl anesthetic of 10 minutes' duration. The simulations assume a steady concentration of fentanyl and propofol throughout the anesthesia, similar to the underlying assumption of context-sensitive decrement times. The red curve in the lower plane is the interaction curve between fentanyl and propofol; it ranges from no fentanyl and 12 µg/mL of propofol on the left to 6 ng/mL of fentanyl and 1.8 µg/mL of propofol on the right. In theory, any point along this curve would provide equivalent maintenance of anesthesia. When the infusion is turned off after 10 minutes of anesthesia, the concentrations of both drugs decrease. The decreasing concentrations of propofol and fentanyl when the infusion is turned off can be found by the upward lines drawn from different points on the interaction curve, with the distance away from the lower plane representing time. Taken together, these upward lines represent a "recovery surface." The red line drawn on the recovery surface shows the points at which the fentanyl-propofol interaction model predicts emergence.

Figure 28-20 shows that after 10 minutes of maintaining 1.8 µg/mL of propofol and 6 ng/mL of fentanyl (right edge of the interaction curve), approximately 12 minutes is needed for the concentrations of both drugs to decrease enough to permit emergence. However, if one maintains concentrations of 3.5 µg/mL of propofol and 1.5 ng/mL of fentanyl (toward the middle of the

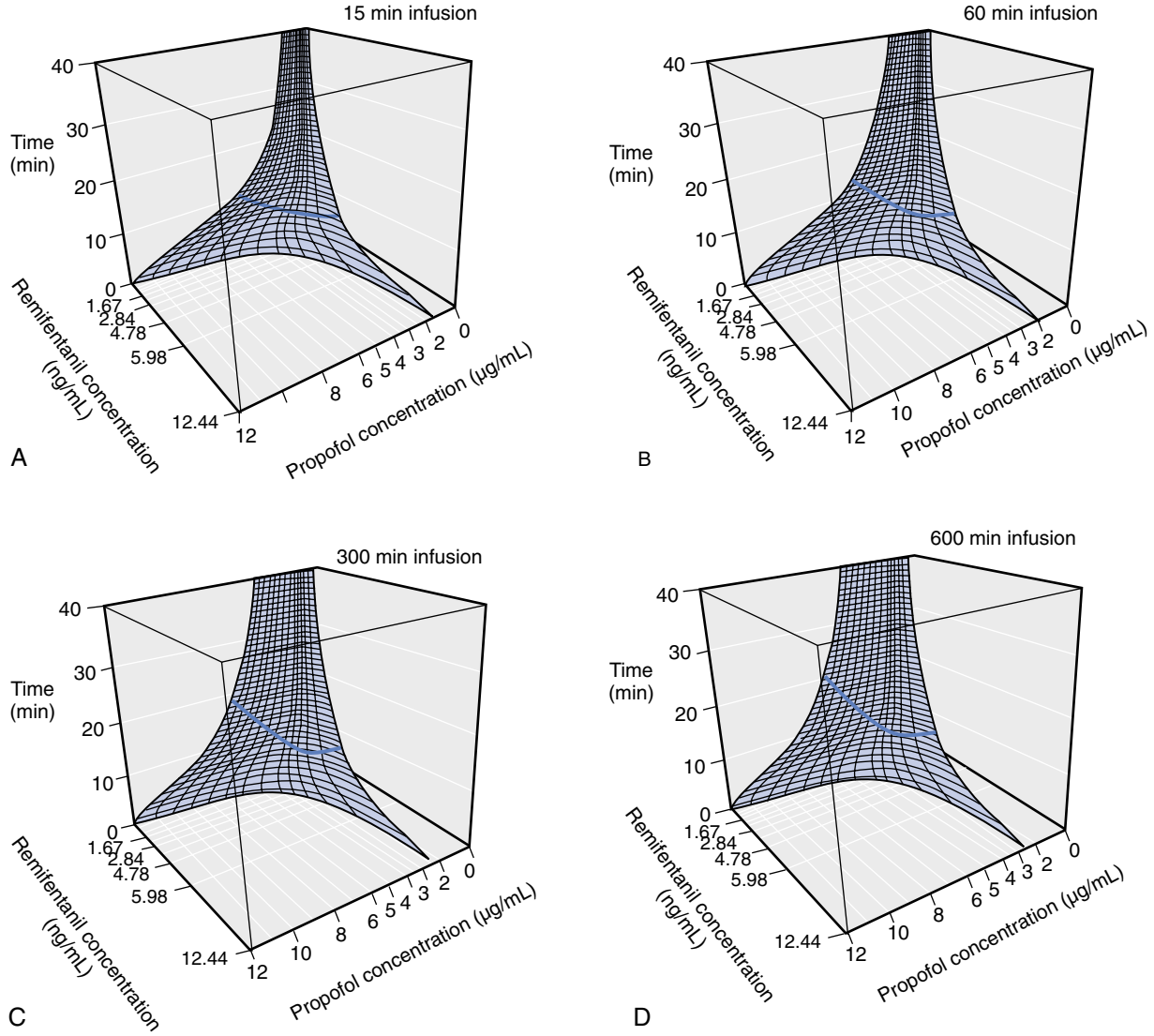

Figure 28-20 Simulation of the interaction of propofol and fentanyl in preventing a somatic response at skin incision and time to recovery. On the *x* axis is the fentanyl concentration, and on the *y* axis, the propofol concentration. The *blue curve* in the lower plane shows the propofol-fentanyl interaction required to provide adequate anesthesia. When the infusion is turned off, the concentrations of each drug decrease, as shown on the *z* axis. The *blue curve* drawn on the recovery surface shows the time to emergence from anesthesia for combinations of fentanyl and propofol after an anesthetic of 15 minutes' (**A**), 60 minutes' (**B**), 180 minutes' (**C**), or 600 minutes' (**D**) duration. Note that the optimal combination for the most rapid recovery is a propofol concentration of 3.0 to 3.5 µg/mL combined with 1.5 ng/mL fentanyl. As the concentration of propofol or fentanyl increases, the time for recovery increases. In addition, the longer the duration of drug infusion, the longer recovery takes, especially if the optimal combination is not used. *(Adapted from Vuyk J, Mertens MJ, Olofsen E, et al: Propofol anesthesia and rational opioid selection: Determination of optimal EC_{50}-EC_{95} propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. Anesthesiology 87:1549-1562, 1997.)*

interaction curve), emergence can be expected just 8 minutes after the infusions are turned off. Examination of the curves for 60, 300, and 600 minutes of propofol/fentanyl anesthesia suggests that the fentanyl target concentration that provides the most rapid emergence is approximately 1.0 to 1.5 ng/mL, which requires a propofol concentration of approximately 3.0 to 3.5 µg/mL to maintain adequate anesthesia. This is consistent with the earlier observation that most of the MAC reduction benefit of fentanyl occurs within the analgesic range and that exceeding this range is of little benefit during anesthesia. In similar simulations, Vuyk and colleagues demonstrated that maintaining alfentanil and sufentanil concentrations in excess of the analgesic range (i.e., approximately 80 ng/mL for alfentanil and 0.15 ng/mL for sufentanil) is of little clinical benefit but can be expected to delay recovery from anesthesia. A second conclusion from these simulations is that if the patient demonstrates inadequate anesthesia, to prevent prolongation of recovery, it is preferable to increase the hypnotic concentration than to increase the opioid concentration beyond the analgesic range.

The situation is different for remifentanil because of its unusual pharmacokinetic properties (Fig. 28-21). When a remifentanil infusion is terminated, the extraordinary clearance of remifentanil results in very rapid offset of opioid drug effect. In Figure 28-21, the lower plane again shows equivalent anes-

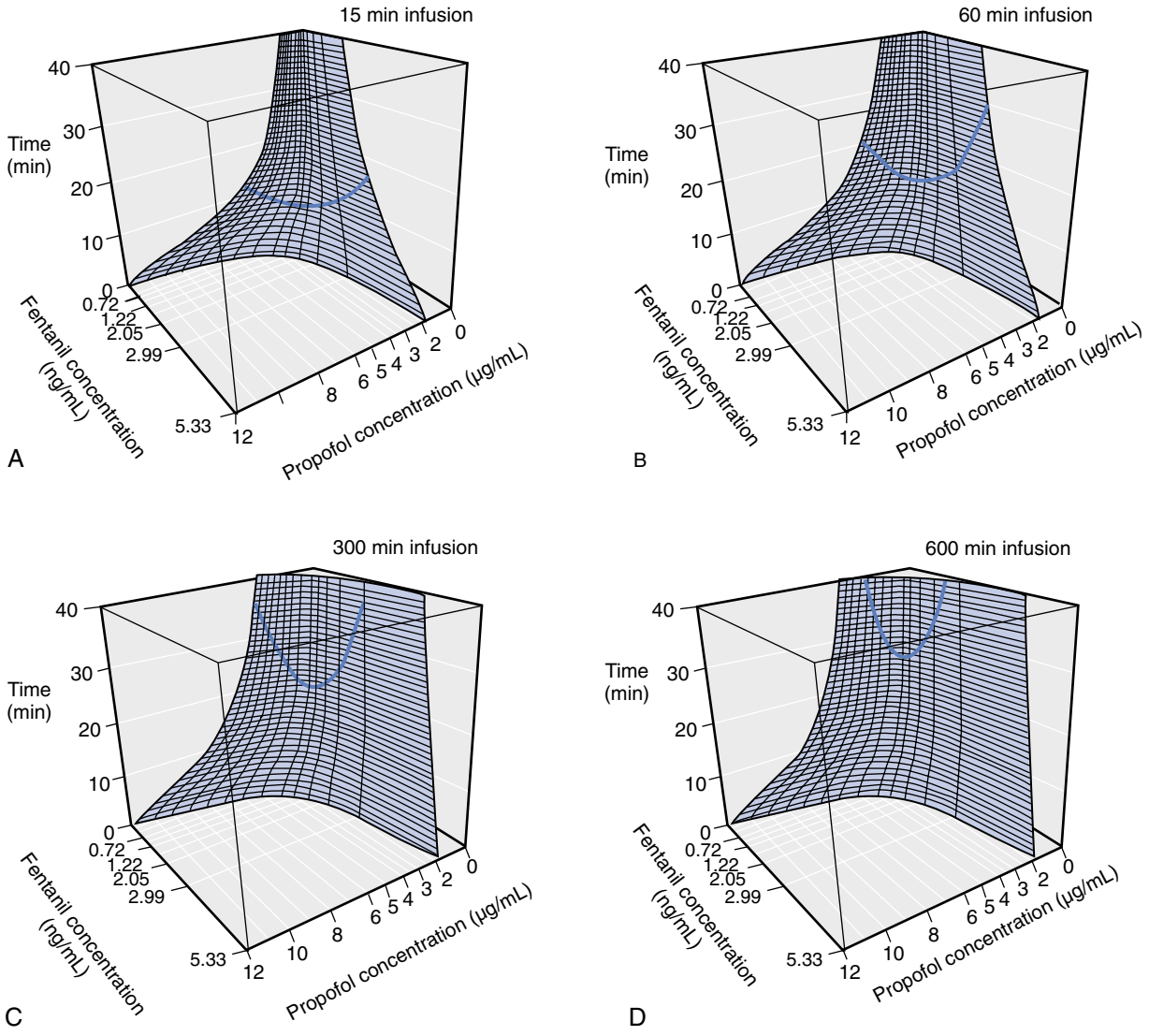

Figure 28-21 Simulation of the interaction of propofol and remifentanil in preventing a somatic response at skin incision and time to recovery. Note that with remifentanil, the optimal combination is a propofol concentration of 2.5 µg/mL and, with remifentanil, 5 to 7 ng/mL; also note that increasing the duration of the infusion has minimal impact on recovery time if the optimal dose of remifentanil is not used. However, if the propofol dose is increased, recovery is prolonged. *(Adapted from Vuyk J, Mertens MJ, Olofsen E, et al: Propofol anesthesia and rational opioid selection: Determination of optimal EC_{50}-EC_{95} propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. Anesthesiology 87:1549-1562, 1997.)*

thetic states during maintenance with an opioid, remifentanil, and propofol. High doses of remifentanil permit a modest reduction in the dose of propofol needed for adequate anesthesia. However, the recovery surfaces show that high doses of remifentanil, with a modest reduction in the propofol dose, permit considerably faster emergence from anesthesia. For example, it takes approximately 12 minutes to awaken from 600 minutes of anesthesia maintained with 3 µg/mL of propofol and 2.5 ng/mL of remifentanil (Fig. 28-20, lower left graph). If the remifentanil concentration is increased to 5 ng/mL, the propofol concentration can be reduced to 2 to 2.5 µg/mL, and emergence can be anticipated within 6 minutes of discontinuation of the infusions. One might be concerned that such a technique places patients at increased risk for awareness because a propofol concentration of 2 µg/mL is below the C_{50} value for wakefulness.[26,28] Therefore, it is probably reasonable to combine such a technique with intraoperative EEG monitoring to assess anesthetic adequacy.

The offset of isoflurane and sevoflurane is similar to that of propofol. The offset of desflurane is slightly quicker than that of propofol. We can draw some logical extrapolations from these propofol/opioid simulations to anesthesia consisting of volatile anesthetics combined with opioids. When fentanyl, alfentanil, or sufentanil is combined with a volatile anesthetic, the most rapid recovery occurs when the opioid concentration is maintained at an analgesic concentration equivalent to 1 to 1.5 ng/mL of fentanyl (Table 28-5). Concurrently, the volatile anesthetic should be administered at the lowest concentration required to provide adequate anesthesia but no less than an end-tidal concentration of 0.3 MAC, the MAC value for return of consciousness. If the patient demonstrates signs of inadequate anesthesia, it is preferable to increase the volatile anesthetic because this has less of an effect on prolonging the wake-up time than increasing the opioid does (with the exception of remifentanil) and is more likely to ensure that awareness does not occur.

Table 28-5 Infusion Rates for Opioids to Achieve Preset Concentrations

Drug	Target Plasma Concentration (ng/mL)	Bolus (μg/kg)	Infusion Rate (μg/kg/min)
Fentanyl (low)	1	3	0.02
Fentanyl (high)	4	10	0.07
Alfentanil (low)	40	20	0.25
Alfentanil (high)	160	80*	1
Sufentanil (low)	0.15	0.15	0.003
Sufentanil (high)	0.5	0.5	0.01
Remifentanil (low)	2	0.5-1*	0.06-0.1
Remifentanil (high)	10	1-2*	0.3-0.5

*Give as a rapid infusion over a 1- to 2-minute period.

Infusion Devices

Manual Delivery

When an infusion of an intravenous anesthetic is administered, the infusion regimen can be controlled by a variety of mechanisms varying from the simple Cair clamp or Dial-a-Flo (Abbott Laboratories) to complex computer-controlled infusion pumps. Simplicity of mechanical design, however, is not necessarily correlated with ease of use. This has prompted ongoing advances in infusion device technology.

Infusion devices can be classified as either controllers or positive displacement pumps. Explicit in their title, controllers contain mechanisms that control the rate of flow produced by gravity, whereas positive displacement pumps contain active pumping mechanisms.

The most commonly used pumps for administration of intravenous anesthetics are positive displacement syringe pumps that use a variety of mechanisms. These pumps are highly accurate and have several features that make them particularly suitable for anesthetic delivery. An important advance has been the introduction of a calculator feature within the pump so that the clinician can set the weight of the patient, the drug concentration, and the infusion rate in dose/unit weight/unit time and the pump will then calculate the infusion in volume/unit time. These pumps also permit simple application of a staged infusion scheme (e.g., the two-stage approach of Wagner[63]) by allowing a loading dose and a maintenance infusion rate to be programmed into the pump. Numerous syringe pumps also now include automated recognition of syringe size. Further enhancements are drug libraries by class of drug, suggested dosing schemes, and maximal dosing alerts. These modest advances in pump technology and design enable intravenous anesthetics to be delivered conveniently.

Table 28-6 offers recommendations for delivering intravenous anesthetics via conventional infusion pumps based on integrated pharmacokinetic-pharmacodynamic models. However, it is the patient's response, demonstrating adequate or inadequate anesthesia, that ultimately determines the rate of drug administration. Individuals vary markedly in their response to a given drug dose or concentration, and it is therefore essential to titrate to an adequate drug level for each individual patient. Drug concentrations required to provide adequate anesthesia also vary according to the type of surgery (e.g., surface surgery versus upper abdominal surgery). The end of surgery requires lower drug levels, and hence titration often involves judicious lowering of the infusion rate toward the end of surgery to facilitate rapid recovery.

If the infusion rate proves to be insufficient to maintain adequate anesthesia, both an additional loading (bolus) dose and an increase in infusion are required to rapidly raise the plasma (biophase) drug concentration. Various interventions also require greater drug concentrations, usually for brief periods (e.g., laryngoscopy, endotracheal intubation, skin incision) (see Fig. 28-3). Therefore, the infusion scheme should be tailored to provide peak concentrations during these brief periods of intense stimulation. An adequate drug level for endotracheal intubation is often achieved with the initial loading dose, but for procedures such as skin incision, a further bolus dose may be necessary.

Infusion schemes such as those shown in Table 28-6 do not approach the convenience and precision of use associated with the delivery of an inhaled anesthetic via a calibrated vaporizer. This level of precision can be achieved by using TCI devices (such as the commercially available Diprifusor). Such devices go beyond simple calculator pumps to the creation of pumps with automated drug delivery.

Automated Delivery

Automated drug delivery implies that electronic or mechanical instrumentation performs adjustments in dose rate independent of human intervention (in contrast with the manual devices described in the previous section). The desired target (e.g., drug concentration and clinical response) is still chosen by the clinician. Preprogrammed dosing (either bolus or infusion) is the simplest form of automated drug delivery. It consists of a preprogrammed infusion (usually calculated to provide a single target blood or effect concentration) that is automatically implemented by the microprocessor in the pump.[71] Preprogrammed devices are limited in their application for intravenous anesthetic drugs because of their inability to allow the user to vary the target concentration.[72] There are two different methods of automated target-based anesthetic drug delivery: model-based (a form of open-loop control) and closed-loop systems.

Terms and Definitions

Open- and closed-loop systems require a set point (Fig. 28-22).[73] The set point is a quantifiable entity (e.g., plasma concentration, percent T1 of the electromyogram, or BIS value) related to the clinical objective (e.g., level of anesthesia, neuromuscular blockade). Accordingly, the set point is the value (i.e., target) that the automated system is attempting to maintain. The feedback signal is the measured (e.g., percent T1 of the electromyogram) or predicted (e.g., predicted effect-site concentration from pharmacokinetic simulation) value that has resulted from the automated delivery process.

Open-loop model-based drug delivery is most useful when the feedback signal cannot be readily measured and clinical judgment is required to assess drug effect. The model is the mathematical (e.g., pharmacokinetic) relationship between dose and predicted concentration in plasma and at the site of drug effect.

Table 28-6 Manual Infusion Schemes*

	Anesthesia		Sedation or Analgesia	
Drug	**Loading Dose (μg/kg)**	**Maintenance Infusion (μg/kg/min)**	**Loading Dose (μg/kg)**	**Maintenance Infusion (μg/kg/min)**
Alfentanil	50-150	0.5-3	10-25	0.25-1
Fentanyl	5-15	0.03-0.1	1-3	0.01-0.03
Sufentanil	0.5-5	0.01-0.05	0.1-0.5	0.005-0.01
Remifentanil	0.5-1.0	0.1-0.4	†	0.025-0.1
Ketamine	1500-2500	25-75	500-1000	10-20
Propofol	1000-2000	50-150	250-1000	10-50
Midazolam	50-150	0.25-1.5	25-100	0.25-1
Methohexital	1500-2500	50-150	250-1000	10-50
Dexmedetomidine‡			0.5-1 over 10 min	0.2-0.7

*After the loading dose, an initially high infusion rate to account for redistribution should be used and then titrated to the lowest infusion rate that will maintain adequate anesthesia or sedation. When using opiates as part of a nitrous-narcotic technique or for cardiac anesthesia, the dosing scheme listed under anesthesia is used. When the opiate is combined as part of balanced anesthesia, dosing listed for analgesia is needed.
†For analgesia or during sedation, an initial loading dose of remifentanil should not be given because its very rapid onset may result in apnea or muscle rigidity.

Consequently, the accuracy of any model-based control system depends on how well the model represents the process under control. In an open-loop system, it is the clinician who learns about the patient and adapts drug administration to the needs of the individual patient.

In a closed-loop "adaptive" controller, the device itself makes a measurement of drug effect and adjusts the internal model to better represent the individual patient. Closed-loop signals require precisely measured end points. For example, a closed-loop system to control blood pressure with sodium nitroprusside will have an expected dosing regimen that is likely to be quite conservative to avoid profound hypotension. As the system learns about individual patient sensitivity, it will adjust the dosing of sodium nitroprusside to the sensitivity of the individual patient by adapting the internal pharmacokinetic/pharmacodynamic model to better reach the clinical target. In anesthesia, closed-loop systems have typically used some signal derived from the EEG as the basis of adaptive closed-loop control.

Target Control Infusion Systems

Devices

In 1968, Kruger-Thiemer[74] described the infusion regimen theoretically required to quickly achieve and maintain a constant plasma concentration of an intravenously administered drug whose kinetics is described by a two-compartment model. This regimen has become known as the "BET scheme" (see Fig. 28-4) and consists of an initial bolus of $C_T V_1$, infusion at a rate of $C_T Cl_S$ to replace drug eliminated from the body, and an exponentially decreasing infusion at a rate given by Equation 14 to replace drug transferred to the peripheral tissues. The earlier section on designing dosage regimens demonstrates that the bolus portion, calculated as $C_T V_1$, will probably be inadequate for reaching the desired effect-site concentration. Mathematically, the "ET" portion of the BET scheme is identical to the exponentially declining maintenance infusion rate shown in the section "Designing Dosing Regimens." Precise implementation of this complex dosage regimen requires infusion rates that change continuously as a function of time until steady state is achieved.

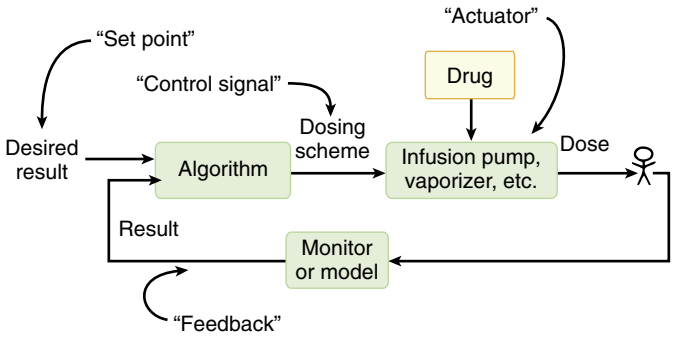

Figure 28-22 Components of a typical automated drug delivery system.

More than a decade after publication of Kruger-Thiemer's classic paper, Schwilden and colleagues[2,75,76] interfaced a microcomputer to an infusion pump and demonstrated clinical application of the BET infusion scheme. Many other groups have since implemented either the BET algorithm or modifications of this algorithm on microcomputers connected to infusion pumps. These algorithms are based on the same polyexponential equations or compartment models described previously and calculate the infusion rates theoretically required to obtain the desired plasma or effect-site drug concentration. In implementing these algorithms it is necessary to consider the physical limitations of the system. For example, infusion rates must be positive or zero. Additionally, some pumps have limitations on precision and accuracy that can reduce the accuracy of the infusion.

Although there are minor differences in the approaches taken by different investigators using pharmacokinetic model–driven infusion systems, all are conceptually similar. Each consists of a microcomputer interfaced to an infusion pump, as seen in Figure 28-23. The microcomputer executes a program that incorporates the pharmacokinetic model. In using the device, the anesthesiologist enters a target plasma or effect-site drug concentration (Fig. 28-24). This target concentration is based on knowledge of the pharmacokinetic-pharmacodynamic relationship of



Figure 28-23 The CACI system used at Duke University Medical Center. The CACI consists of a laptop computer electronically linked to an infusion pump. The desired drug plasma or effect-site concentration is entered via the keyboard.

the drug and the desired effect, as well as on the individual responses of the patient. At frequent intervals (e.g., every 9 to 15 seconds), the program compares the target concentration with the current prediction of the plasma or effect-site drug concentration, which is computed by real-time simulation of a pharmacokinetic model of the drug being infused. The computer calculates the infusion rate required to achieve the desired target concentration and transmits this rate to the pump after adjusting the rate to reflect the physical capabilities of the pump. The pump then delivers drug to the patient at the desired rate.

At each step the computer makes sure that the pump has delivered the drug that it was instructed to give and checks for errors reported by the infusion pump (e.g., air in the line, out of drug). The computer then calculates what the pump delivered during the previous interval and updates the internal pharmacokinetic model on the basis of the reported drug delivered. The cycle is completed when the computer calculates the infusion rate required over the next interval to reach the desired target concentration and transmits this rate to the infusion pump. Concurrently, the computer supplies the anesthesiologist with information about the state of the model, the state of the pump, any problems reported by the pump, the anticipated time course for elimination of drug from the patient, the total amount of drug delivered, the current infusion rate, and other information that may be of assistance in providing clinical care.

As a result of the increasing popularity of intravenous anesthesia and continuous-infusion techniques, the inherent reasonableness of pharmacokinetically based drug delivery, and the promising results achieved with automated administration of a variety of drugs by research groups around the world, pharmacokinetic model–driven infusion of propofol has become widely available worldwide except in the United States.[77] This system consists of a commercial pump and software that provides the control algorithm.

Several device companies are now providing TCI pumps that permit users to select from a variety of drugs and patient groups. Pharmacokinetic parameters for various drugs are already programmed into the device, and the devices have the ability to target the plasma concentration or the concentration at the site of drug effect. Such devices are well adapted to the need for rapid titration in anesthesia. The user selects the drug to be infused, enters information about the patient (e.g., weight, age, and gender), and ensures that the infusion setup is primed with drug at a specified concentration. The user titrates the target concentration during anesthesia in the same manner as for adjustment of the inspired concentration of an inhaled anesthetic.

Pharmacokinetic models are being incorporated into the next generation of anesthesia workstations. These workstations could then control many different brands of infusion pumps and provide a common platform for implementing precise titration of intravenous anesthetics in the concentration domain.

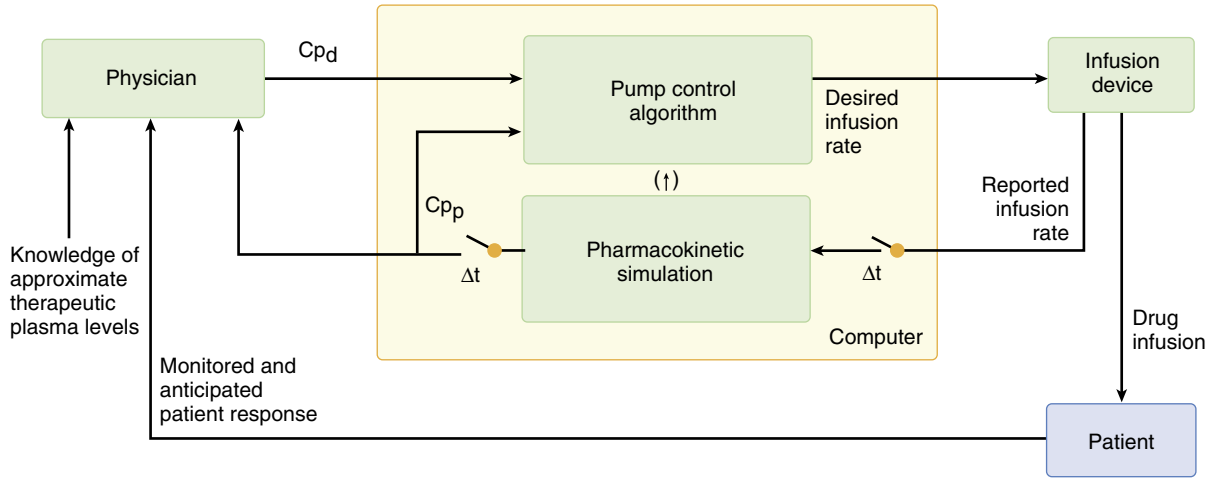

Figure 28-24 Schematic illustration of pharmacokinetic model–driven drug delivery. The physician enters the target plasma or biophase drug concentration (Cp_d). An infusion device control algorithm uses a pharmacokinetic model for the drug being infused to determine what the infusion rate should be for the next infusion interval (e.g., 9 to 15 seconds). The infusion device delivers drug to the patient, and the infusion rate is fed into a simulation of the pharmacokinetic model to compute the current predicted plasma drug concentration (Cp_p). The variables computed in the simulation are available to the infusion algorithm, which then calculates the infusion rate necessary for the next 9 to 15 seconds to achieve the target concentration. On the basis of monitored and anticipated patient responses, knowledge of approximate therapeutic plasma drug concentrations (e.g., Cp_{50}), and Cp_p, the physician can titrate Cp_d as necessary.

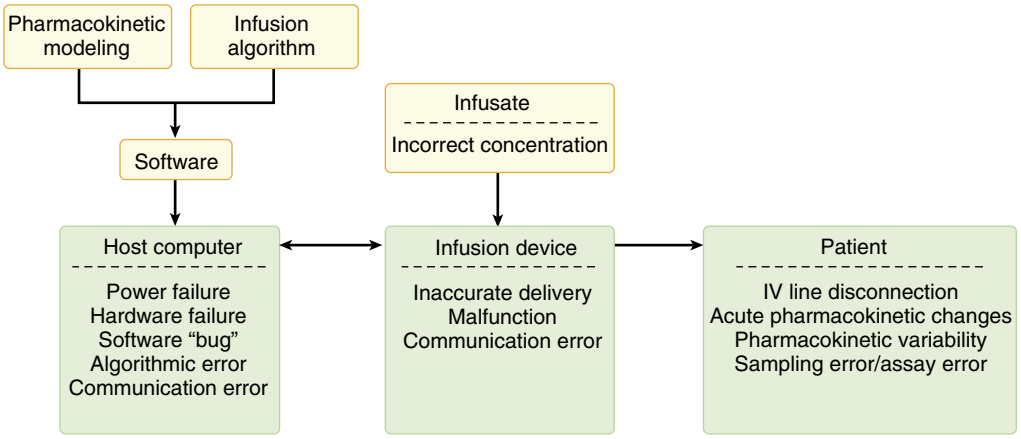

Figure 28-25 Major sources of potential error in pharmacokinetic model–driven drug delivery. In a commercial device, the computer functions would be incorporated into the infusion device itself.

Evaluation of Target-Controlled Drug Delivery

Acceptance of target-controlled drug delivery of intravenous anesthetics requires evaluation of both accuracy, defined as the difference between predicted and measured concentrations, and outcome of patients in whom automated drug delivery has been used. Sources of inaccuracy with pharmacokinetic model–driven devices include the software, the hardware, and pharmacokinetic variability (Fig. 28-25).

Inaccuracy in the software results from incorrect mathematical implementation of the pharmacokinetic model. Computer simulations can be used to test the infusion rates calculated by a software program, and thus software errors are fairly simple to identify and correct.[78] Inaccurate drug delivery from the infusion pump occurs infrequently with present syringe-pump technology and thus contributes little to the overall inaccuracy of these devices. The major cause of inaccuracy is biologic variability, of which there are two sources: (1) the pharmacokinetic model is always wrong, and (2) the pharmacokinetics of the patient is never that programmed into the model. The pharmacokinetic model is always wrong because individuals are far more complex than implied by simple compartmental models, and thus no such model can precisely predict the concentrations, even if the pharmacokinetic parameters in the individual were known with absolute precision. However, even if the pharmacokinetic model truly reflected the underlying biology, the parameters of the model would be average parameters for the population and not the parameters in the individual patient. Even if the parameters are modified to reflect the influence of demographic factors such as age, gender, hypovolemia, and coadministration of other drugs, they will still deviate from the true pharmacokinetic parameters in the individual. Thus, biologic variability fundamentally precludes the possibility of precisely achieving the desired target concentration when automated drug delivery devices are used. It is important to realize that biologic variability always exists, no matter how drugs are given, and that this same biologic variability affects all methods of drug delivery. Indeed, the variability with TCI devices will always be less than the variability observed after a single bolus injection.[79]

Optimization of Target-Controlled Drug Delivery

The performance of computer-controlled drug administration must be interpreted in terms of the therapeutic expectations of the clinician. Possible goals include accurately producing a desired concentration in plasma, precisely titrating the plasma drug concentration, achieving the desired drug effect, and producing the desired time course of drug effect. Over the past decade, investigators have addressed each of these goals and have refined the performance of automated drug delivery devices accordingly.

The ability of an automated drug delivery system to rapidly achieve and then maintain a selected target concentration is a logical measure of the performance of such a device. There are several ways of expressing the difference between the measured and target concentrations. The most simple means is either to diagram a plot of the target and measured concentration of each sample in each individual patient (Fig. 28-26) or to diagram an *xy* plot of the measured to target concentration and observe how much the plots vary from the line of identity (Fig. 28-27).[58] The primary concern is how far the measured concentration is from the predicted one, and this is now most frequently described in terms of performance error, which is the difference between the measured and target concentrations as a percentage of the desired target (i.e., [measured − target]/target × 100%).[80] The median value of the performance error for a patient or a population is referred to as the median performance error (MDPE) and represents the average overshoot or undershoot of the system. The median absolute performance error (MDAPE) is the median of the absolute values of all performance errors. The MDAPE is commonly used as a measure of the inaccuracy of an automated drug delivery device. An MDAPE of zero is perfect performance, and an MDAPE of 20% means that half the plasma concentrations will be within 20% of the target and half will be outside that range. A further assessment of accuracy is whether the system maintains a stable target concentration. This is best measured by the wobble of the system. Varvel and colleagues[80] asked a group of clinicians to evaluate the performance of automated drug delivery devices and demonstrated that the MDAPE best predicted the adequacy of performance of the automated delivery device, as judged by experienced clinicians.

As observed earlier, it is not reasonable to expect all performance errors to be zero. However, it would be desirable if positive and negative errors offset each other so that the MDPE of an automated drug delivery device were 0%. The MDPE does not indicate the range of performance errors (because positive and negative performance errors offset each other), but it does indicate whether the plasma concentrations achieved with the

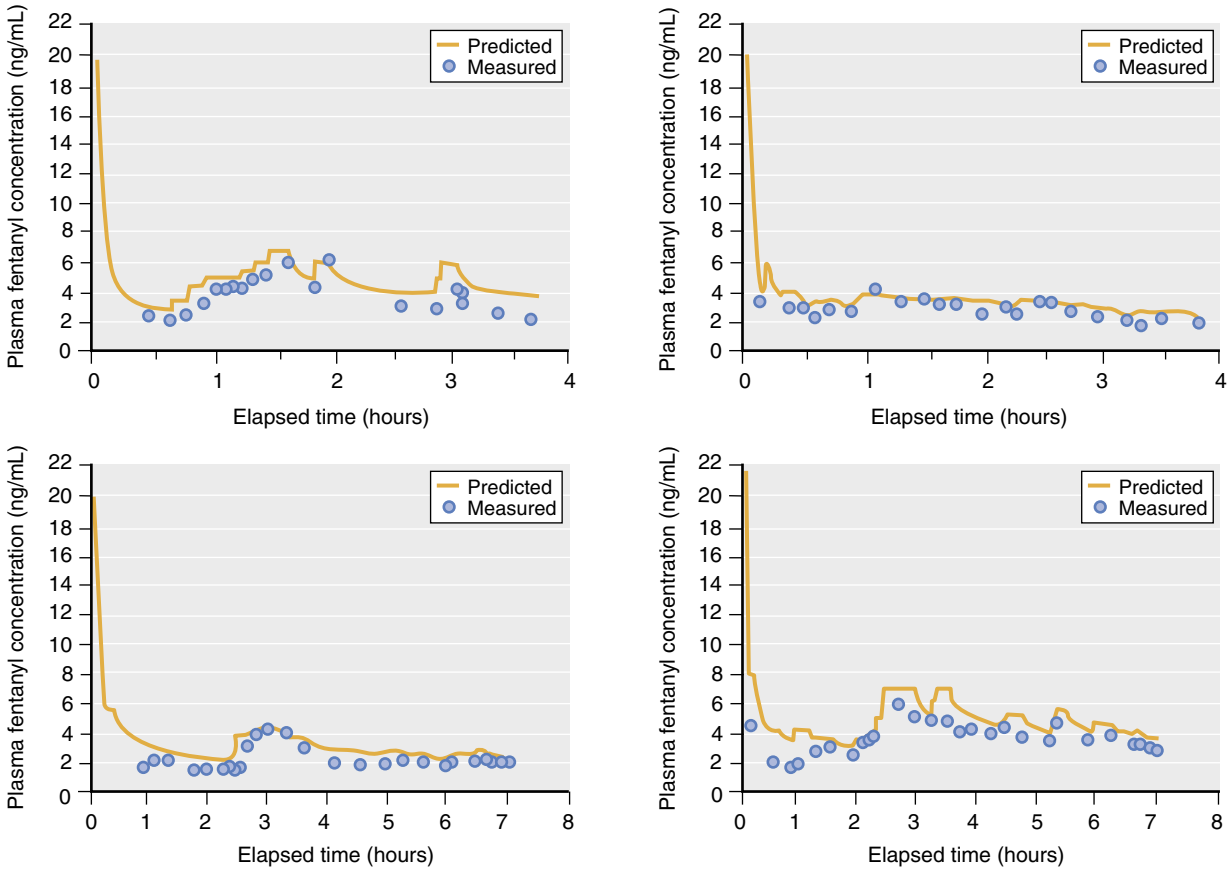

Figure 28-26 Individual plots of the target plasma fentanyl concentration (*solid line*) and measured concentration (*dots*) in four separate patients.

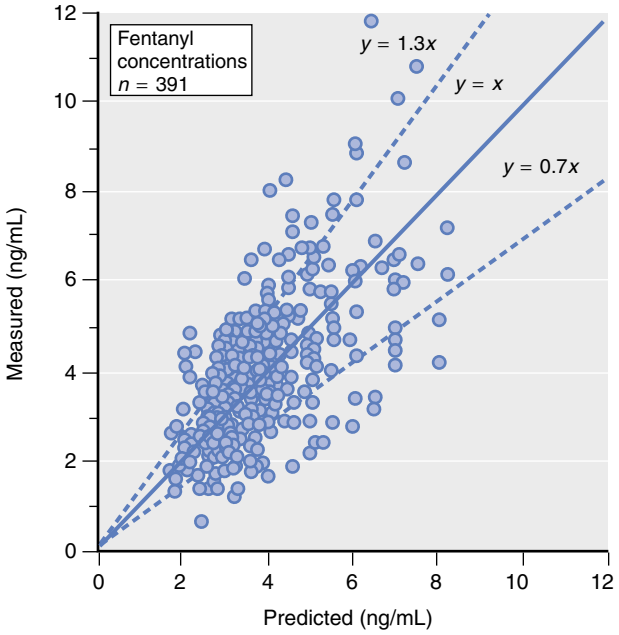

Figure 28-27 Plot of the measured to predicted concentration of fentanyl administered via CACI in 24 patients. The *solid line* represents the line of identity; that is, the target concentration is equal to the measured concentration. The *dashed lines* represent a bias of ±30%.

device tend to overshoot (+MDPE) or undershoot (–MDPE) the desired target.

Many groups have evaluated the accuracy of many different pharmacokinetic sets for virtually all the intravenous analgesics and hypnotics.[23,58,71,81-88] Based on many of these studies the expected performance of such devices, at best, tends to be around 20% to 30% MDAPE. The pharmacokinetics of propofol has been the most frequently tested. Coetzee and coworkers[87] tested the accuracy of three parameter sets and found those of Marsh[88] Tackley[89] and their colleagues to provide the best accuracy in adult patients (Fig. 28-28). To demonstrate the effect of the three different pharmacokinetic parameters on propofol dosing, the infusion rates required to produce a set of target concentrations are plotted in Figure 28-29. The pharmacokinetic parameter set of Marsh and colleagues is the one included in the Diprifusor software. Better accuracy has been obtained in children[81] because they may have less pharmacokinetic variability as a result of their general lack of chronic disease and more narrow distribution of weight at any given age than found in adults.

There are numerous published pharmacokinetic parameter sets for each of the drugs used in anesthesia. The pharmacokinetic parameters within each set may vary considerably depending on a variety of factors, such as the mode of drug administration (e.g., bolus versus infusion), duration of sampling, site of drug sampling (arterial versus venous), sensitivity of the assay, and evalu-

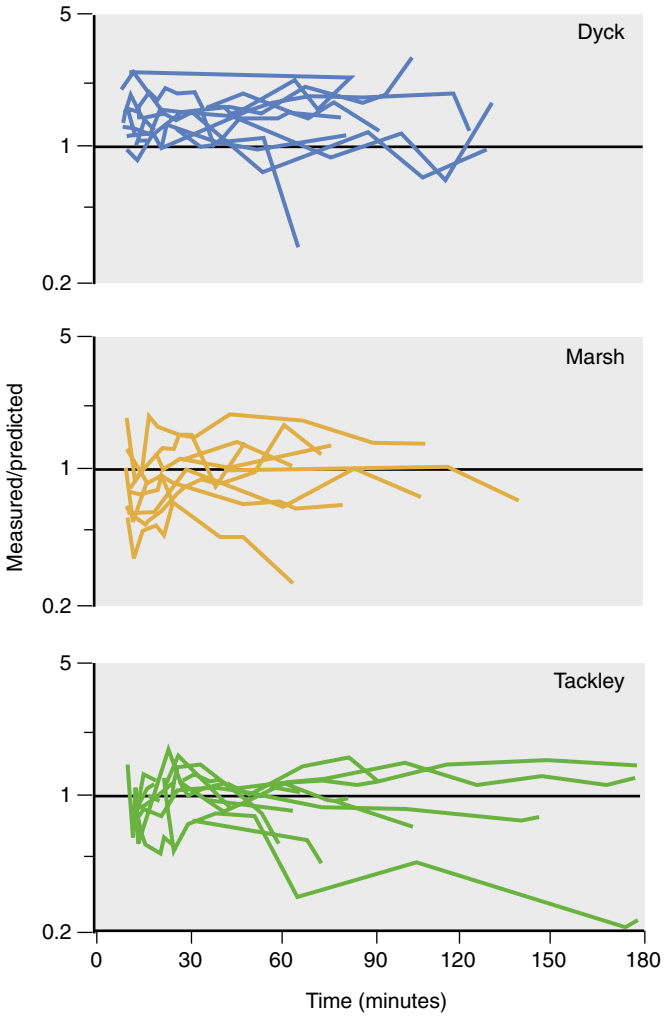

Figure 28-28 Evaluation of three pharmacokinetic parameter sets for propofol. Plotted is the measured-to-predicted ratio for samples obtained during administration of propofol via a target-controlled infusion device programmed with pharmacokinetics derived by Dyck, Marsh, or Tackley (*n* = 10 per group). A ratio of 1 means that measured equals predicted. Note that the pharmacokinetic parameters of Dyck provide a consistently positive bias.

ation of population covariates in determining the model parameters. The implications of such differences are not always obvious and it is therefore important to test the parameter set to determine whether the parameters provide adequate accuracy for clinical use. For example, as shown in Figure 28-30A-C,[85] the accuracy of fentanyl delivered according to the pharmacokinetics reported by Scott and Stanski[30] is much better than the accuracy of fentanyl delivered on the basis of the pharmacokinetics reported by McClain and Hug.[90] Glass and coworkers[58] examined the performance of a pharmacokinetic model–driven infusion device by using the same fentanyl pharmacokinetics described by McClain and Hug.[90] They demonstrated an MDAPE of 21% and an MDPE of +4% (i.e., an almost completely unbiased performance), much better performance than demonstrated by Shafer and associates[85] for the same pharmacokinetic set. This is explained by differences in study methodology, such as arterial versus venous samples, rapid sampling after changes in target concentration versus sampling only when a pseudo–steady state was achieved, and a different set of patients—cardiac versus noncardiac.

With the goal of improving pharmacokinetic model–driven infusion device performance, Shafer and coworkers[85] recalculated the optimal pharmacokinetic parameters of fentanyl directly from the observed concentrations that were obtained when fentanyl was administered via a pharmacokinetic model–driven infusion device by use of the initial pharmacokinetics of McLean and Hug.[90] Figure 28-30C shows the performance errors over time for the optimal fentanyl pharmacokinetics estimated for that population of patients (versus those of McLean and Hug[90] and Scott and associates[30] in the same group of patients). The optimal pharmacokinetic parameter set still had a median residual error of 21% when retrospectively tested against the same group of patients. This represents the limit imposed by pharmacokinetic variability on the possible performance of any fentanyl parameter set for dosing to a similar adult population. In other words, it is unlikely that any fentanyl pharmacokinetic parameter set would produce less than a 21% MDAPE.

Marsh and colleagues[88] took the same approach to optimizing the performance of a pharmacokinetic model–driven infusion device for administration of propofol to children. They initially used a pharmacokinetic parameter set derived from adult subjects in their device and obtained an MDAPE of 25% and an MDPE of −18.5%. They subsequently derived new propofol pharmacokinetics for children and prospectively demonstrated that they had decreased the MDAPE to 16%, with a bias of less than 3%. This is highly accurate performance for a model-based device. Ginsberg and coworkers[91] similarly derived a pharmacokinetic set for fentanyl in children, as did Fiset and associates[92] for alfentanil. Several other studies have also demonstrated that pharmacokinetic parameters vary with certain subsets of patients. For example, the pharmacokinetic parameters of propofol for patients about to undergo open heart surgery are different from the previously verified pharmacokinetic parameters for the general population. These new pharmacokinetic parameters for propofol also vary both during bypass and after bypass.[93] Similarly for patients undergoing liver transplantation, the Marsh pharmacokinetics performs poorly.[94]

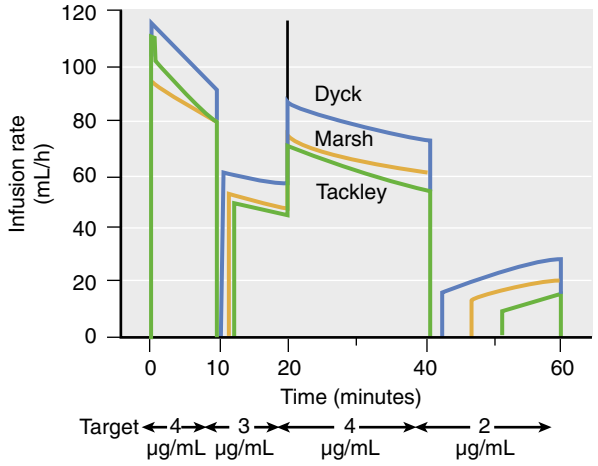

Figure 28-29 Infusion rates (mL/hr) calculated to achieve propofol target concentrations of 4 (10 minutes), 3 (10 minutes), 4 (20 minutes), and 2 μg/mL (20 minutes) based on the three pharmacokinetic parameter sets of Dyck, Marsh, and Tackley.

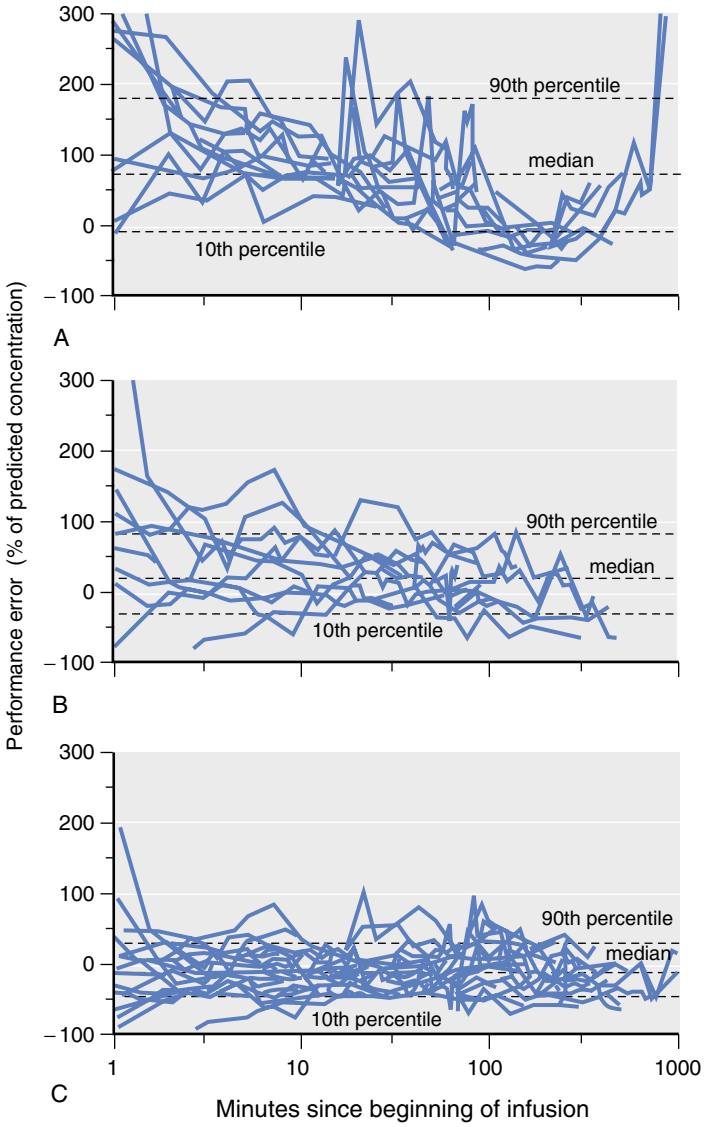

Figure 28-30 Performance errors over time for fentanyl derived from the pharmacokinetics reported by McClain and Hug (**A**) and Scott and Stanski (**B**) and a parameter set derived from these observations (**C**). *(From Shafer SL, Varvel SL, Aziz N, et al: The pharmacokinetics of fentanyl administered by computer controlled infusion pump. Anesthesiology 73:1091-1102, 1990.)*

Interest has recently focused on what other factors may be responsible for alterations in pharmacokinetic with the objective of reducing variability and increasing the accuracy of TCI systems. Such factors include, among others, the influence of age, gender, hemorrhagic shock, and administration of a second drug. Numerous studies have investigated the effect of age (both young and old) on pharmacokinetic parameters. For propofol and fentanyl, it has been shown that an adult pharmacokinetic set performs poorly in children and that age-specific parameters improve accuracy.[88,91] Although it is well known that pharmacokinetic parameters are altered in the elderly, it has not been well established whether these changes are sufficiently different to impact the accuracy of the adult parameter sets that are used in a TCI device. The effect of gender on pharmacokinetics has been variable. For propofol, Vuyk and colleagues have recently demonstrated an effect of gender on propofol pharmacokinetic parameters in the elderly.[95] In a pharmacokinetic analysis of several pooled databases of propofol, Schuttler and Ihmsen found that gender was not a significant covariate.[96] Similarly, there is no clear indication that gender has a significant effect on opioids pharmacokinetic parameters. Several authors have looked at the effect of hemorrhagic shock on pharmacokinetic parameters. In a pseudo–steady-state model of propofol, compensated hemorrhage increased propofol concentrations by only 20%; however, when uncompensated shock was induced, propofol concentrations increased by 375%.[97] Using a non–steady-state model, Egan and associates found that hemorrhagic shock reduced central clearance and central volumes of fentanyl[98] and remifentanil,[99] thereby resulting in higher fentanyl concentrations in animals in shock. Investigators have also focused on the impact of simultaneous administration of a second drug, especially another anesthetic. Propofol, midazolam, and etomidate have been shown in in vitro studies to reduce the clearance of opioids because of an interaction on the cytochrome P450 system. In turn, several studies have shown that alfentanil may alter the pharmacokinetic parameters of propofol.[100-102] The exact mechanism of this interaction is unclear. It is unlikely to be related to any interaction with cytochrome P450 systems because the pharmacokinetics of propofol are limited by liver blood flow and thus are not likely to be affected by modest alterations in hepatic metabolic capacity. The differences may

result from alterations in cardiac output or reductions in hepatic blood flow. In contrast with alfentanil, remifentanil at concentrations of 0 to 4 ng/mL did not alter the pharmacokinetics of propofol.[103] However, propofol decreased the central volume of distribution and distributional clearance of remifentanil by 41% and elimination clearance by 15%. Of interest in a study of propofol administered to critically ill patients, two covariates established in the model that best described the pharmacokinetics of these patients were temperature and serum triglyceride concentration for terminal clearance.[104] Not all of the factors that have been shown to alter pharmacokinetic parameters have been associated with a change in outcomes or in the utility of TCI devices. However, some have, and thus in principle, pharmacokinetic sets adapted to the appropriate clinical milieu should be determined for each of the commonly used drugs to enhance the accuracy of TCI drug administration. It is incumbent on users to be aware of which pharmacokinetic set is being used in their TCI system and the reasonableness of this set in providing sufficient accuracy for clinical application in the particular patient in which it is being used.

Not only is there interindividual variability, but there may also be significant intraindividual variability. Hill and colleagues[105] studied volunteers to learn the individual's own pharmacokinetics for morphine and alfentanil. These investigators then used that volunteer's unique pharmacokinetic values to subsequently control a pharmacokinetic model–driven infusion device. With this technique of personalized pharmacokinetics, they reduced the average error to just less than 20%. It appears that studies in which the pharmacokinetics of an individual is used to infuse the same drug to the same individual later result in bias and an MDAPE similar to those seen when an optimal pharmacokinetic set derived from the general population is used. The implication of these data is that although highly specific pharmacokinetic sets are desirable, they may not necessarily improve overall accuracy. They also demonstrate that biologic variability precludes obtaining better than approximately 20% accuracy with TCI devices.

It is unlikely that we will have the opportunity to conduct a full pharmacokinetic study on patients *during a single anesthetic*. However, bayesian forecasting is a statistical technique by which a few measured plasma concentrations from an individual can be incorporated into pharmacokinetic parameters to improve the performance of a pharmacokinetic model–driven infusion device. Maitre and Stanski[106] demonstrated the theoretical improvement in such devices when using bayesian forecasting for alfentanil. In this study, Maitre and Stanski demonstrated that measurement of a single plasma alfentanil concentration could potentially reduce the inaccuracy by half, to a 14% average performance error. Unfortunately, a rapid assay does not exist for any of the intravenous drugs used in anesthetic practice. However, there are rapid assays for lidocaine, and at least one pharmacokinetic model–driven infusion device (STANPUMP, developed by Shafer and Maitre at Stanford and available at http://anesthesia.stanford.edu/pkpd) performs real-time bayesian forecasting from measured lidocaine levels for use in coronary care units.

In the absence of rapid assays for anesthetic drugs, the obvious method to decrease variability is to observe the drug effect and adjust the target to the concentration that produces the desired level of drug effect.[17,18] As discussed earlier under "Pharmacodynamic Considerations," by knowing the rate constant k_{e0}, it is possible to model the concentration at the site of drug effect. Figure 28-31 shows the plasma fentanyl concentrations that could theoretically be obtained over the course of a brief operation. Figure 28-31B shows the fentanyl concentrations at the effect site for the same anesthetic shown in Figure 28-31A. Even if the pump produced precisely the concentrations shown in Figure 28-31A (i.e., had perfect performance), the lag between concentrations in plasma and the site of drug effect would, at best, produce a very slurred response because of the delay in equilibration between plasma and the effect site. Several pharmacokinetic model–driven infusion devices now simultaneously display both plasma and effect-site concentrations. Such devices permit the clinician to target the concentration in the effect site rather than plasma to provide more precise control of drug effect.

By targeting the effect site there is an overshoot in the plasma concentration of the drug. The k_{e0} used to model the effect site for intravenous anesthetics has been derived from surrogate measures of effect (i.e., derivatives of the EEG). Thus, for TCI devices that target the effect site, it is important to establish that the k_{e0} value used actually results in the desired effect. Glass[107] and Struys[108] and their colleagues conducted similar studies in which they targeted either plasma or an effect-site concentration of propofol and then observed the time and plasma versus effect-site concentration at loss of consciousness. In both studies, regardless of whether the effect-site or plasma concentration was targeted,

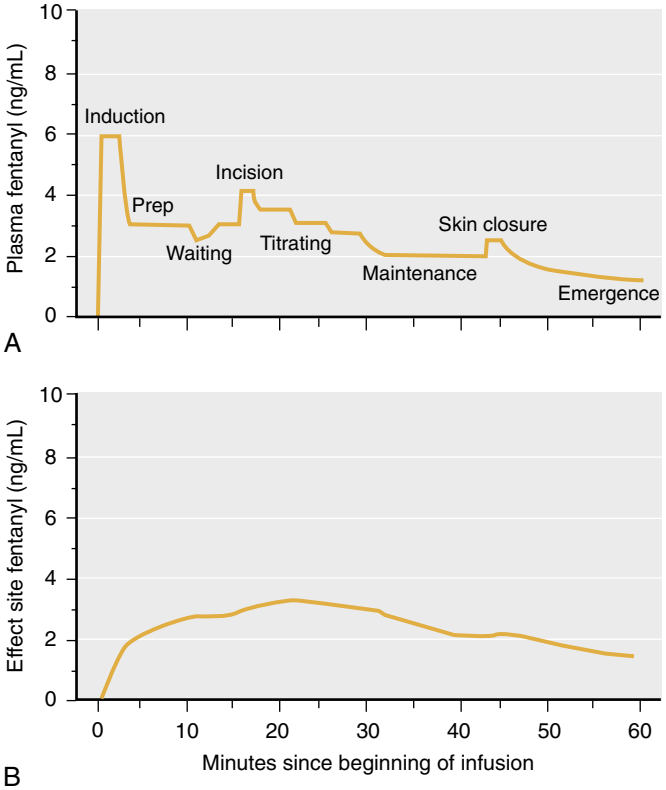

Figure 28-31 **A,** Simulated plasma fentanyl concentrations over time for a brief anesthetic showing the rapid rise and fall and impression of precise titration that can be created by a target-controlled drug delivery device. **B,** Effect-site concentrations for the same anesthetic course demonstrating that precise control of the plasma concentration does not necessarily translate into precise control at the site of drug effect. *(Adapted from Shafer SL, Gregg K: Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer controlled infusion pump. J Pharmacokinet Biopharm 20:147-169, 1992.)*

loss of consciousness occurred when the appropriate *effect-site* concentration for loss of consciousness was achieved, thus validating the concept. Two other important observations were made during these studies. First, hemodynamics was not different whether plasma or the effect site was targeted, even though higher plasma concentrations were achieved in the effect-site group. This implies, at least for propofol, that the time course for its hemodynamic effects is similar (or longer)[109] to that for its anesthetic effects. Second, k_{e0} is dependent on the pharmacokinetic set from which it is derived.[110] One cannot take a k_{e0} value from one pharmacokinetic set and use it with another pharmacokinetic set. Just as various demographics may alter the pharmacokinetics, they may also alter k_{e0}. Hence, it is desirable to use the k_{e0} best adapted for the clinical milieu. An ideal test of whether targeting plasma or the effect site is better is to compare their use in a closed-loop system where a measure of effect (e.g., the BIS) is used as the target of control. In a small study of 10 patients per group, Absalom and Kenny showed that maintenance of the targeted BIS (as measured by MDPE, MDAPE, and wobble) was somewhat improved and induction times were significantly shorter when the pharmacokinetic model was for the effect site rather than plasma.[111]

In summary, automated drug delivery devices appear to be able to achieve and maintain desired plasma concentrations with a median expected error of about 20% to 30% of the target. Although pharmacokinetic analysis after automated drug delivery results in a reduction in the median error to closer to 20% in adults and possibly lower in children, biologic variability sets a limit on the expected accuracy of these devices. More accurate performance could be obtained with bayesian feedback and the use of rapid intraoperative assays, but this is unavailable for the intravenous drugs used in anesthetic practice. However, the delay in equilibration between plasma and the effect site is such that excessive focus on plasma concentrations may be unwarranted. Instead, learning about the pharmacokinetic/pharmacodynamic characteristics of the specific patient by titrating to a readily measured drug effect appears to be the most promising method for optimizing the performance of automated drug delivery devices to the clinical needs of the individual patient.

Outcome

Evaluation of outcome with TCI devices is more difficult than evaluation of accuracy because of the difficulty of precisely measuring patient outcome. Because contemporary anesthetic practice produces very little morbidity, outcome measures are usually based on readily measured variables, such as blood pressure, heart rate, and duration of recovery room stay, rather than on substantive measures of patient morbidity. Evaluation of outcome with automated drug delivery devices requires a comparison of manual methods of administration of the same drug with automated drug delivery of intravenous anesthetics and volatile anesthetics. Several studies have evaluated administration of intravenous anesthetics by automated drug delivery devices for both brief and complex surgery, in children and in adults, in short-term sedation, in prolonged sedation (days), and in chronic pain management.

Two decades ago, Ausems and coworkers[9] compared pharmacokinetic model–driven administration with intermittent bolus administration of alfentanil. Automated drug delivery produced fewer episodes of muscular rigidity, hypotension, and bradycardia on induction. Automated drug delivery during maintenance resulted in a significantly lower incidence of hemodynamic response, which resulted in a greater percentage of anesthesia time within 15% of the desired blood pressure and heart rate. Recovery after TCI was associated with significantly less use of naloxone for adequate ventilation.

Pharmacokinetic model–driven infusion of fentanyl during cardiac surgery resulted in better hemodynamic control with fewer additional drug interventions and significantly fewer episodes of either hypotension or hypertension than occurred with bolus dose administration.[86] A small study comparing manual alfentanil administration with pharmacokinetic model–driven infusion of alfentanil showed no statistical differences during maintenance or recovery.[112] Theil and colleagues[113] compared double-blind manual administration of fentanyl/midazolam with pharmacokinetic model–driven infusion of these two anesthetics in a small group of patients undergoing cardiac surgery. Both systems were titrated simultaneously (one containing placebo), with the aim of maintaining hemodynamics within 20% of baseline values. Both systems were equally effective in providing hemodynamic control as dictated by the protocol. The most significant difference between the two modes of delivery was the greater variability in drug plasma concentrations in the manual group. This suggested that pharmacokinetic model–driven infusion maintained patients within a narrower therapeutic range.

Several comparative studies have been performed with the commercial TCI device for propofol. Struys and colleagues[114] ($N = 90$), Russel and colleagues[115] ($N = 160$), and Servin,[116] in a large multicenter study ($N = 562$), found when they compared manual infusion of propofol with TCI administration that there were small differences between the two means of propofol administration. Of interest in the TCI groups, the maintenance infusion rate tended to be higher, which was associated with a lower incidence of patient movement. Both Servin and Russel and their coworkers noted that there was a marked preference of clinicians for the TCI system, even though this was their first use of the device. In contrast, when TCI propofol or manual propofol was titrated to a target BIS, no differences were observed between the two groups.[117] Remifentanil delivered manually and by TCI has also been evaluated in patients undergoing carotid surgery.[118] TCI remifentanil provided improved hemodynamic control both intraoperatively and postoperatively with less remifentanil and similar propofol infusion rates. As discussed, targeting the plasma concentration does not provide optimal control of effect. When manual propofol administration has been compared with target effect-site administration, there was a lower incidence of movement, improved hemodynamic stability, and more rapid recovery with the latter.[119]

Pharmacokinetic model–driven infusion of propofol compares favorably with thiopental/isoflurane anesthesia for general surgery lasting several hours.[120] Induction, maintenance, and recovery were similar between the two groups. Godet and colleagues compared sevoflurane, propofol followed by isoflurane, and TCI propofol in patients undergoing carotid surgery. They found minor differences in hemodynamics that tended to favor TCI propofol and no differences in recovery parameters.[121] Sneyd and coworkers compared TCI propofol with sevoflurane in patients undergoing neurosurgical procedures and similarly found little difference between the two techniques.[122] This implies that given the appropriate means for administration, intravenous anesthetics can be equal to inhaled anesthetics in providing the objectives of anesthesia, that is, rapid induction and recovery with stable maintenance. Suttner and associates examined the cost and

recovery characteristics of target-controlled propofol infusion regimens and standard methodologies.[123] They found that "target-controlled infusion/total IV anesthesia was associated with the largest intraoperative costs but allowed the most rapid recovery from anesthesia, was associated with fewest postoperative side effects, and permitted earlier discharge from the postanesthesia care unit."

In noncomparative studies, pharmacokinetic model–driven infusion has been used to administer most of the potent opioids, as well as the hypnotics. Different anesthetic techniques have also been tested with pharmacokinetic model–driven infusion devices, including nitrous-opioid anesthesia, supplementation of volatile anesthetics, total intravenous anesthesia, sedation for monitored anesthesia care, and intensive care unit sedation. In all these studies, outcome, as measured by hemodynamics and recovery, has been within the expectations of normal clinical care. Etomidate, methohexital, midazolam, propofol, thiopental, dexmedetomidine, alfentanil, fentanyl, remifentanil, and sufentanil have all been used with TCI. When these drugs were used with target-controlled drug delivery systems for total intravenous anesthesia or to supplement nitrous oxide or volatile anesthetics, hemodynamics was well maintained during induction and intubation, as well as during maintenance. Recovery milestones were reached at times comparable to those achieved with similar drug combinations used in manual infusion schemes. In none of these studies have authors commented on adverse outcomes resulting from target-controlled drug delivery.

TCI devices have also been used to provide patient-controlled analgesia. Hill and colleagues studied patient-controlled analgesia devices using morphine, fentanyl, or alfentanil[105,124] and demonstrated the clinical utility of such devices.[125-128] Van den Nieuwenhuyzen and colleagues[44] demonstrated advantages of such a system with alfentanil over routine morphine patient-controlled anesthesia.

From the body of literature presently available, it appears that automated drug delivery of intravenous anesthetics is at least equal to manual delivery of these drugs. Intravenous drug administration via target-controlled drug delivery is analogous to inhaled vapor delivery via a calibrated vaporizer. Like the vaporizer, pharmacokinetic model–driven infusion facilitates drug delivery based on plasma or biophase concentration rather than on drug dosage. There is variability with the use of a calibrated vaporizer, including variability in the accuracy of drug delivery with vaporizers, slow equilibration between the fresh gas flow and the circuit at low flow rates, and variable uptake by the patient. This variability does not particularly complicate the titration of inhaled anesthetics. The variability with target-controlled drug delivery is of a similar magnitude and can be demonstrated to be less than the variability associated with vaporizers, and likewise, it does not particularly complicate titration of intravenous anesthetics. Indeed, the time-varying stresses of surgery and the variability in patient response require that the anesthesiologist titrate the administration of potent inhaled anesthetics by using the calibrated vaporizer as a tool. These same factors require that the anesthesiologist vigilantly titrate the infusion of intravenous anesthetic drugs when using automated drug delivery as a tool.

Target-controlled drug delivery has advantages beyond a delivery system to simplify the clinical administration of intravenous anesthetics. Another significant contribution of these delivery devices is their use in research. The pseudo–steady state that can be almost instantly achieved with these devices permits the plasma and effect site to rapidly come into equilibrium. This is critically important in studies examining concentration-response relationships (i.e., C_{50} values) for anesthetic drugs.[9,24,42] In addition, these systems enable interactions involving intravenous drugs to be clearly defined.[54-56] Closed-loop target delivery will eventually enable unbiased and more precise comparisons between drugs. Finally, as noted earlier, target-controlled delivery has provided us with the ability to prospectively test pharmacokinetic parameter sets and modeling approaches and may ultimately provide the most suitable pharmacokinetic parameters for any intravenous drug delivery.[85,88,92,129]

Closed-Loop Drug Delivery Systems

The next step in automated drug delivery is to feed the measured drug effect directly back into the automated drug delivery device so that the model can be updated from observed measures of drug effect, thus providing a closed-loop system.[3-7,130-137] In this instance the set point is the measured effect rather than a particular drug concentration. It has been proposed that closed-loop control of anesthesia may provide several advantages: increased stability of the control variable because of more frequent sampling of the effect with more frequent adjustment of drug delivery; more customized dose delivery to account for interindividual pharmacokinetic and pharmacodynamic differences; and as a result of the first two advantages, improvement in hemodynamic stability, inadvertent awareness, and recovery.[137]

Closed-loop systems fall into two general categories. All controllers are based on measuring the error between the target effect and the observed effect. Conventional "proportional/integral/derivative" (PID) controllers adjust the infusion rates in a manner that is proportional to the magnitude of the error, the integral of the error over time, and the derivative of the error over time. A "model-based" controller has an internal model of the system, typically set up as an integrated pharmacokinetic/pharmacodynamic model relating dose to concentration (pharmacokinetics) and concentration to drug effect (pharmacodynamics). The model is updated to explain the difference between the measured and predicted drug effect.

An example of the model-based approach is the system described by Struys and colleagues in which the response to a loading propofol bolus was used to estimate the sigmoidal concentration-versus-effect relationship for the individual patient.[134] As shown in Figure 28-32, the device starts with a population estimate that a particular concentration, C_1, will produce the desired effect. It then monitors the drug effect in response to the initial bolus of propofol. As shown by point X, the patient did not reach the desired effect at an effect-site concentration of C_1. The device recalculates the shape of the concentration-versus-response relationship and determines that C_2 is the proper target effect-site concentration. The device then raises the target concentration to C_2 to produce the desired effect.

Bayesian optimization is used in pharmacokinetic-dynamic modeling to individualize a drug dosing regimen by combining individual information with the knowledge of an a priori probability density function containing the statistical properties of the parameter to be estimated. These values are adjusted to reflect the patient's own parameters over time based on the observed response of the individual patient under varying circumstances. In a simulation study, De Smet and colleagues compared a PID

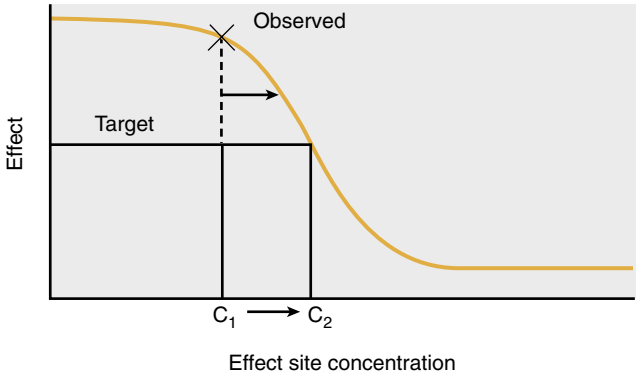

Figure 28-32 Real-time model–based adjustment of the "Hill equation" describing the relationship between propofol concentration and hypnotic effect. The system sets a target concentration and starts out with an assumed value of the effect-site concentration, C_1, needed to reach the effect. After administering an adequate dose, the system discovers that the desired effect has not been reached. It then re-estimates the concentration-versus-effect relationship based on the observed data point (X) and now has a more precise estimation of the concentration, C_2, required to reach the desired effect. *(Adapted from Struys MM, De Smet T, Versichelen LF, et al: Comparison of closed-loop controlled administration of propofol using bispectral index as the controlled variable versus "standard practice" controlled administration. Anesthesiology 95:6-17, 2001.)*

controller with a bayesian model–based controller, both targeting a BIS of 30, 50, and 70.[138] They demonstrated robust performance under a variety of challenging scenarios.

As mentioned earlier, the ability to measure adequacy of anesthesia is limited. Anesthesia is a composite of several effects: hypnosis or loss of consciousness, amnesia, analgesia, lack of movement, and hemodynamic stability. There are now several derivatives of the EEG that show a strong correlation with hypnosis/loss of consciousness. Fortunately, amnesia is also reflected by the EEG signal and appears to precede the derived EEG values associated with drug-induced loss of consciousness. The major component of anesthesia for which we do not have a monitor of effect is analgesia. This continues to constitute an impediment to the general application of closed-loop anesthesia. Noxious stimuli during surgery are extremely variable. Intravenous hypnotics (with the exception of ketamine and dexmedetomidine) have limited or no analgesic activity. Thus, a closed-loop system based solely on a derivative of the EEG may provide perfect hypnosis in the absence of a stimulus, but awakening and movement are likely to occur as soon as a noxious stimulus is administered. To overcome this hurdle, investigators have taken several approaches to test closed-loop systems for anesthesia in patients. They have been used in combination with a regional anesthetic, thereby preventing any painful stimulus from reaching the brain. Most have used a low-dose constant opioid concentration for superficial surgery or a high-dose opioid concentration for more extensive surgery. Another interesting approach is a combination of an analgesic concentration of opioid and application of a noxious stimulus (e.g., tetany) at regular short intervals to minimize oscillations as a result of surgical stimuli.

It is unclear whether closed-loop systems offer any benefits over open-loop TCI systems. Morley and coworkers compared closed-loop administration of isoflurane or a propofol/alfentanil mixture and manual control of these agents to provide a BIS of 50.[139] The closed-loop system used a PID control algorithm. The authors were unable to demonstrate any advantage of their closed-loop system over manual control when intraoperative control of the BIS, hemodynamic stability, intraoperative drug use, or recovery parameters were used as measures of outcome. More recently, Locher and coworkers demonstrated that their closed-loop system for controlling the BIS with isoflurane provided significantly better performance than manual isoflurane administration did in terms of periods of inadequate control (BIS >65 for longer than 3 minutes) or time beyond a BIS of less than 40 or a BIS greater than 60.[140]

Struys and associates also performed a study to determine whether there are any advantages of a closed-loop system over manual administration of propofol for lower abdominal surgery.[134] The closed-loop control group achieved statistically significant better control of both its control variable (BIS, 89% ± 10%) and systolic pressure (51% ± 27%) than the manual group did (systolic pressure, 34% ± 31%; BIS, 49% ± 29%). In addition, recovery was also improved in the closed-loop group (Fig. 28-33). This study does not definitively answer whether closed-loop delivery of anesthesia is better than any manual system, nor does it define what an optimal closed-loop control system is; however, its results are encouraging and should further stimulate work on developing closed-loop anesthetic drug delivery for day-to-day anesthesia.[141]

In a multicenter study of 164 patients randomized to either closed-loop control of propofol or manual TCI propofol with a target BIS of 40 to 60, Lin and colleagues found that the closed-loop system performed significantly better in nearly all performance metrics: lower overall drug dose, BIS closer to the target level throughout anesthesia, and faster recovery.[142] During maintenance the control system made more frequent and smaller adjustments in the propofol dose and enabled more rapid recovery to endotracheal extubation. The performance parameters MDPE, MDAPE, and wobble, as well as the percentage of time that the BIS was maintained between 40 and 60, was significantly better in the closed-loop group. This study demonstrated the feasibility of using a closed-loop system in daily anesthesia practice with a large variation in age and patient comorbid conditions.

Closed-loop control is also a valuable investigative tool. It can be used to determine the unbiased interaction between two drugs. It has been used with neuromuscular blockers to determine their interaction with various anesthetics.[143,144] Similarly, closed-loop control can be used to determine the interaction between opioids and intravenous anesthetics.[145,146] Closed-loop systems may also have the potential to diagnose different pathologic states based on drug dosing. Albrecht and coworkers observed that when using closed-loop sedation with propofol, trauma patients required lower EEG set points and needed more propofol to achieve the same level of sedation.[147] As the number of investigators who have access to closed-loop systems for anesthesia increases, the utility of such devices for research is likely to increase substantially.

Summary

When compared with intermittent bolus administration, continuous infusion of intravenous anesthetic drugs provides greater control of anesthetic depth, thus ensuring (1) better hemodynamic control with fewer episodes of hemodynamic instability, (2) smaller total drug doses, and (3) more rapid return to the awake state. Improved drug administration techniques combined with several new intravenous anesthetic agents have provided greater impetus for the use of intravenous anesthesia in clinical practice. Devices for the administration of intravenous

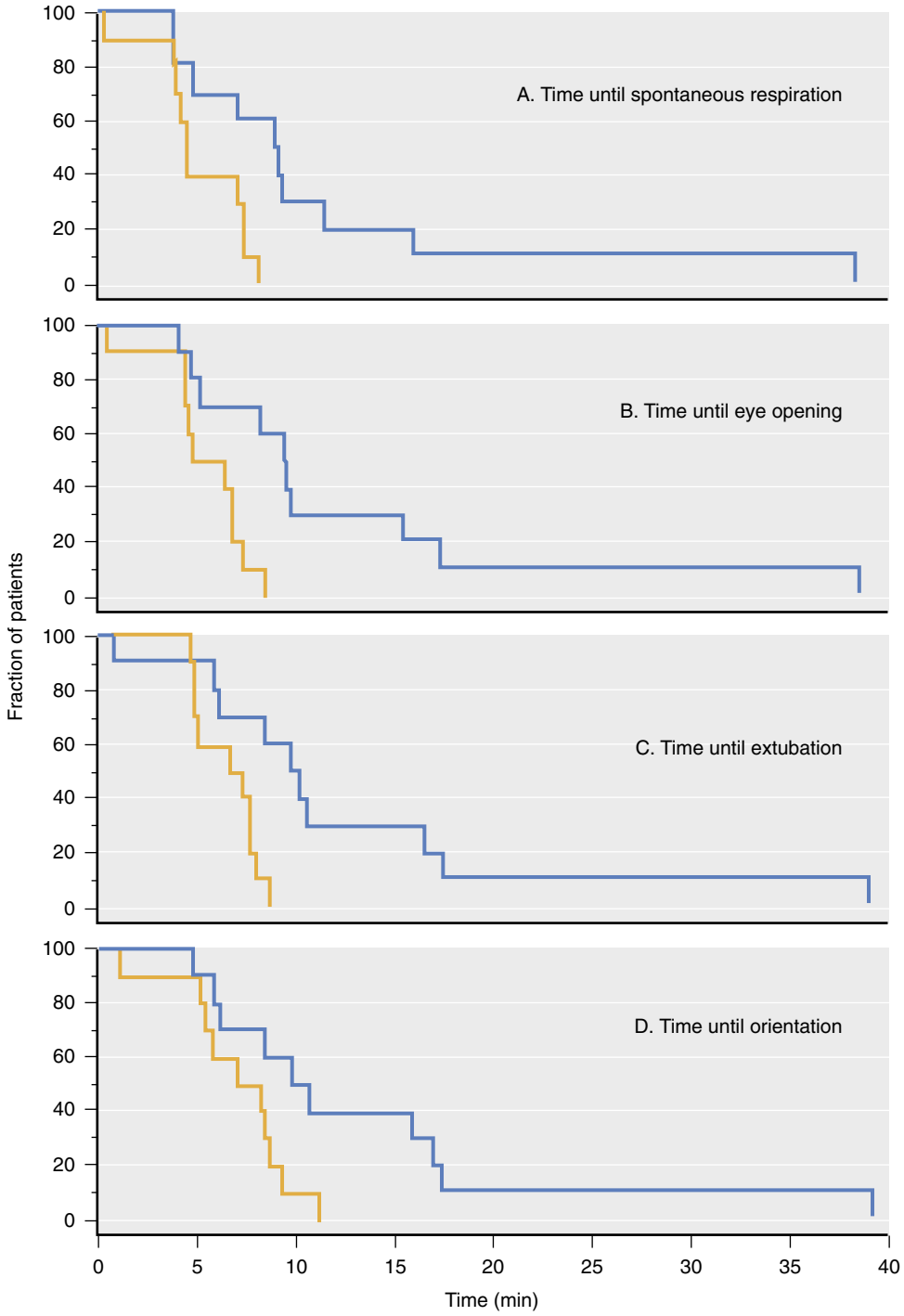

Figure 28-33 Comparison of manual and closed-loop anesthetic control on the time course of return of spontaneous ventilation (**A**), eye opening (**B**), extubation (**C**), and orientation (**D**). In each case, the more rapid curve is the closed-loop control, and the slower curve is the manual control. *(Adapted from Struys MM, De Smet T, Versichelen LF, et al: Comparison of closed-loop controlled administration of propofol using bispectral index as the controlled variable versus "standard practice" controlled administration. Anesthesiology 95:6-17, 2001.)*

anesthetics are continuing to evolve. The introduction of pumps designed specifically for continuous intravenous delivery of anesthetic drugs has enhanced intravenous anesthesia. Automated drug delivery is becoming routine in many countries. There are several theoretical advantages of pharmacokinetic model–driven infusion over manual infusion systems, such as further improvements in hemodynamic control and more predictable rapid awakening. Studies comparing outcomes with automated drug delivery of intravenous anesthetics versus manual methods or inhaled anesthetics have either demonstrated improved outcome or been equivocal. No studies have identified clinical or safety problems with automated anesthetic drug delivery. It thus appears that pharmacokinetic model–driven infusion systems, though limited by the same biologic variability that affects manual drug delivery, are safe and effective in clinical use.

With the advent of monitors of hypnosis and increased understanding of the components of anesthesia, closed-loop drug delivery for anesthesia is showing promise to provide further advantages. Many hurdles still need to be overcome before such devices will come into routine use. However, present knowledge and the results of recent studies are sufficiently encouraging to pursue this goal.

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Mohamed Naguib and Cynthia A. Lien

29 Pharmacology of Muscle Relaxants and Their Antagonists

Key Points

1. Two different populations of nicotinic acetylcholine receptors exist at the mammalian neuromuscular junction. In adults, the nicotinic acetylcholine receptor at the postsynaptic (muscular) membrane is composed of $\alpha_2\beta\delta\varepsilon$-subunits. Each of the two α-subunits has an acetylcholine binding site. The presynaptic (neuronal) nicotinic receptor is also a pentameric complex composed of $\alpha_3\beta_2$-subunits.
2. Nondepolarizing muscle relaxants produce neuromuscular blockade by competing with acetylcholine for postsynaptic α-subunits. In contrast, succinylcholine produces prolonged depolarization that results in decreased sensitivity of the postsynaptic nicotinic acetylcholine receptor and inactivation of sodium channels so that propagation of the action potential across the muscle membrane is inhibited.
3. Different forms of neuromuscular stimulation test for neuromuscular blockade at different areas of the motor end plate. Depression of the response to single-twitch stimulation is probably due to blockade of postsynaptic nicotinic acetylcholine receptors, whereas fade in the response to tetanic and train-of-four stimuli results from blockade of presynaptic nicotinic receptors.
4. Succinylcholine is the only available depolarizing neuromuscular blocker. It is characterized by rapid onset of effect and ultrashort duration of action because of its rapid hydrolysis by butyrylcholinesterase.
5. The nondepolarizing neuromuscular blockers available can be classified according to chemical class (steroidal, benzylisoquinolinium, or other compounds) or, alternatively, according to onset or duration of action (long-, intermediate-, and short-acting drugs) of equipotent doses.
6. The speed of onset is inversely proportional to the potency of nondepolarizing neuromuscular blocking agents. With the exception of atracurium, molar potency is highly predictive of a drug's rate of onset of effect. Rocuronium has a molar potency ($ED_{95} \approx 0.54$ μM/kg) that is about 13% that of vecuronium and 9% that of cisatracurium. Its onset of effect is more rapid than that of either of these agents.
7. Neuromuscular blockade develops faster, lasts a shorter time, and is recovered from more quickly in the more centrally located neuromuscular units (e.g., laryngeal adductors, diaphragm, and masseter muscle) than in the more peripherally located adductor pollicis.
8. The long-acting neuromuscular blockers undergo minimal or no metabolism, and they are eliminated, largely unchanged, primarily by renal excretion. Neuromuscular blockers with an intermediate duration of action have more rapid clearance than the long-acting agents do because of multiple pathways of degradation, metabolism, and elimination. Mivacurium, a short-acting neuromuscular blocker, is cleared rapidly and almost exclusively via metabolism by butyrylcholinesterase.
9. After the administration of nondepolarizing neuromuscular blocking agents, it is essential to ensure adequate return of normal neuromuscular function. Residual paralysis decreases upper esophageal tone, coordination of the esophageal musculature during swallowing, and the hypoxic ventilatory drive.

History and Clinical Use

In 1942, Griffith and Johnson[1] suggested that *d*-tubocurarine (dTc) is a safe drug to use during surgery to provide skeletal muscle relaxation. One year later, Cullen[2] described its use in 131 patients who had received general anesthesia for their surgery. In 1954, Beecher and Todd[3] reported a sixfold increase in mortality in patients receiving dTc in comparison with those who had not received a relaxant. The increased mortality was due to a general lack of understanding of the pharmacology of neuromuscular blockers and their antagonism. The effect of residual neuromuscular blockade postoperatively was not appreciated, guidelines for monitoring muscle strength had not been established, and the importance of pharmacologically antagonizing any residual blockade was not understood.

Succinylcholine, introduced by Thesleff[4] and Foldes and colleagues[5] in 1952, changed anesthetic practice drastically. Its rapid onset of effect and ultrashort duration of action permitted rapid endotracheal intubation.

In 1967, Baird and Reid[6] first reported on clinical administration of the synthetic aminosteroid pancuronium.

Development of the intermediate-acting neuromuscular blockers built on the compounds' metabolism and resulted in the introduction of vecuronium,[7] an aminosteroid, and atracurium,[8] a benzylisoquinolinium, into clinical practice in the 1980s.

Mivacurium, the first short-acting nondepolarizing neuromuscular blocker, was introduced into clinical practice in the 1990s,[9] as was rocuronium,[10] an intermediate-acting nondepolarizing blocker with rapid onset of effect.

Other neuromuscular blockers have been introduced into clinical practice since the use of dTc was first advocated. Such blockers include pipecuronium, doxacurium, cisatracurium, and rapacuronium. Although all do not remain in use, each represented an advance or improvement in at least one aspect over its predecessors. Still other neuromuscular blockers, such as gantacurium,[11] are undergoing investigation.

Neuromuscular blockers should be administered only to anesthetized individuals to provide relaxation of skeletal muscles. They should not be administered to stop patient movement because they have no analgesic or amnestic properties. Awareness during surgery[12] and in the intensive care unit (ICU)[13] has been described in multiple publications. Neuromuscular blockers are valuable adjuncts to general anesthetics and should be used as such. As stated by Cullen and Larson, "muscle relaxants given inappropriately may provide the surgeon with optimal [operating] conditions in … a patient [who] is paralyzed but not anesthetized—a state that [is] wholly unacceptable for the patient." Additionally, "muscle relaxants used to cover up deficiencies in total anesthetic management … represent an … inappropriate use of the valuable adjuncts to anesthesia." To administer relaxants for maintenance of neuromuscular blockade intraoperatively, the patient's depth of neuromuscular blockade must be monitored and the depth of anesthesia continuously assessed.

That said, the use of neuromuscular blockers in the operating room is quite common and has been important in the growth and development of anesthesia and surgery. As stated by Foldes and colleagues,[5] "… [the] first use of … muscle relaxants … not only revolutionized the practice of anesthesia but also started the modern era of surgery and made possible the explosive development of cardiothoracic, neurologic, and organ transplant surgery." Certainly, neuromuscular blockers are now used routinely to facilitate endotracheal intubation and mechanical ventilation and are commonly used to maintain neuromuscular blockade through any number of different surgical procedures. This chapter reviews the pharmacology and clinical use of neuromuscular blocking agents and anticholinesterases in the anesthesia and intensive care settings. Finally, the economics of providing neuromuscular blockade is considered.

Principles of Action of Neuromuscular Blockers at the Neuromuscular Junction

For a comprehensive overview of neuromuscular blocker effects, see Chapter 14. This section provides a brief introduction to the principles of action of these agents. In the following, a brief introduction is made for the purpose of this chapter.

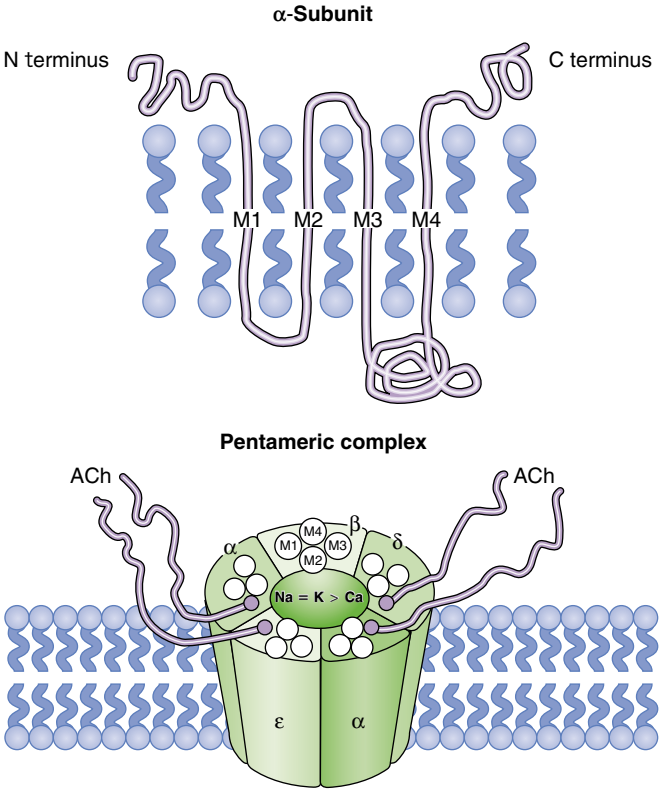


Figure 29-1 Subunit composition of the nicotinic acetylcholine (ACh) receptor (nAChR) in the end-plate surface of adult mammalian muscle. The adult AChR is an intrinsic membrane protein with five distinct subunits ($\alpha_2\beta\delta\varepsilon$). Each subunit contains four helical domains, labeled M1 to M4. The M2 domain forms the channel pore. The *upper panel* shows a single α-subunit with its N and C termini on the extracellular surface of the membrane lipid bilayer. Between the N and C termini, the α-subunit forms four helices (M1, M2, M3, and M4) that span the membrane bilayer. The *lower panel* shows the pentameric structure of the nAChR of adult mammalian muscle. The N termini of two subunits cooperate to form two distinct binding pockets for ACh. These pockets occur at the ε-α– and the δ-α–subunit interface. The M2 membrane-spanning domain of each subunit lines the ion channel. The doubly liganded ion channel has equal permeability to Na^+ and to K^+; Ca^{2+} contributes approximately 2.5% to the total permeability. *(From Naguib M, Flood P, McArdle JJ, Brenner HR: Advances in neurobiology of the neuromuscular junction: Implications for the anesthesiologist. Anesthesiology 96:202-231, 2002, with permission from Anesthesiology.)*

Postjunctional Effects

In adult mammalian skeletal muscle, the nicotinic acetylcholine receptor (nAChR) is a pentameric complex of two α-subunits in association with single β-, δ-, and ε-subunits (Fig. 29-1). These subunits are organized to form a transmembrane pore (i.e., a channel), as well as extracellular binding pockets, for acetylcholine and other agonists or antagonists.[14] Each of the two α-subunits has an acetylcholine binding site. These sites are proteins located in pockets approximately 3.0 nm above the surface membrane at the interfaces of the α_H-ε- and α_L-δ-subunits.[15] α_H and α_L indicate the high- and low-affinity binding sites, respectively, for dTc and probably result from the contribution of the different neighboring subunits.[16] For instance, the binding affinity of dTc for the α_H-ε site is approximately 100 to 500 times higher than that for the α_L-δ site.[16] The fetal nAChR contains a γ-subunit instead of an adult ε-subunit. The mature nAChR has a shorter

burst duration and higher conductance for Na^+, K^+, and Ca^{2+} than the fetal nAChR does.[14]

Functionally, the ion channel of the acetylcholine receptor is closed in the resting state. Simultaneous binding of two acetylcholine molecules to the α-subunits initiates conformational changes that open the channel. On the other hand, it is enough for one molecule of a nondepolarizing neuromuscular blocker (i.e., a competitive antagonist) to bind to one subunit to produce blockade. Paul and coworkers[17] found a correlation between the ED_{50} (the dose that produces a 50% depression in twitch tension) and the potency of nondepolarizing blockers at the adult nAChR.

Depolarizing neuromuscular blockers such as succinylcholine produce prolonged depolarization of the end-plate region, which results in (1) desensitization of the nAChR, (2) inactivation of voltage-gated sodium channels at the neuromuscular junction, and (3) increases in potassium permeability in the surrounding membrane. The end result is failure of action potential generation, and blockade ensues. It should be noted that although acetylcholine produces depolarization, it results in muscle contraction under physiologic conditions because it has a very short duration of action (a few milliseconds). Acetylcholine is rapidly hydrolyzed by acetylcholinesterase to acetic acid and choline. Administration of large doses of acetylcholine to experimental animals, however, produces neuromuscular blockade.

The fetal nAChR is a low-conductance channel, in contrast to the high-conductance channel of the adult nAChR. Thus, release of acetylcholine causes brief activation and a reduced probability of opening of the channel.[14] The upregulation of nAChRs found in states of functional or surgical denervation is characterized by the spreading of predominantly fetal-type nAChRs. These receptors are resistant to nondepolarizing neuromuscular blockers and more sensitive to succinylcholine.[18] When depolarized, the immature isoform has a prolonged open channel time that exaggerates the efflux of K^+.[19]

Prejunctional Effects

Prejunctional receptors are involved in modulating the release of acetylcholine in the neuromuscular junction. The existence of both nicotinic and muscarinic receptors on motor nerve endings has been described. Bowman[20] suggested that the prejunctional nicotinic receptors are activated by acetylcholine and function in a positive-feedback control system that serves to maintain the availability of acetylcholine when demand for it is high (e.g., during tetany).[20] Blockade of these receptors by nondepolarizing neuromuscular blockers would explain the "fade" phenomenon seen with tetanic and train-of-four (TOF) stimulation (four stimuli delivered over a period of 2 seconds).[20,21] The G protein–coupled muscarinic receptors are also involved in feedback modulation of acetylcholine release.[22] The prejunctional muscarinic M_1 and M_2 receptors are involved in facilitation and inhibition of acetylcholine release, respectively, via modulation of Ca^{2+} influx.[22] The prejunctional nicotinic receptors are involved in mobilization of acetylcholine but not directly in the release process.[23] Hence, blockade of the prejunctional nicotinic receptors by nondepolarizing neuromuscular blockers prevents acetylcholine from being made available fast enough to support tetanic or TOF stimulation. In contrast, the prejunctional muscarinic receptors are involved in upregulation or downmodulation of the release mechanism.

Monitoring Neuromuscular Function

Details of monitoring neuromuscular function are discussed in Chapter 47. In this chapter, only the general concepts of monitoring as they relate to the clinical use of neuromuscular blockers are presented.

Monitoring of neuromuscular function after the administration of neuromuscular blocking agents is extremely important for appropriate dosing of these agents and for better guaranteeing patient safety. In the operating room or ICU, the depth of neuromuscular blockade is typically monitored by observing the response to stimulation of any superficially located neuromuscular unit. Most commonly, contraction of the adductor pollicis muscle associated with stimulation of the ulnar nerve, either at the wrist or at the elbow, is monitored. In certain circumstances, depending on patient positioning, when access to the patients' arms may be limited or because of the nature of the patient's injury, the peroneal nerve or the facial nerve may be monitored.

The pattern of response to TOF stimulation or a tetanic stimulus varies with the type of neuromuscular blocker administered because of the different mechanisms of action of the two relaxant types, depolarizing and nondepolarizing. With complete blockade, no response to either mode of stimulation should occur. However, during partial neuromuscular blockade, different responses to these modes of stimulation are seen, depending on the agent administered. Nondepolarizing neuromuscular blocking agents are competitive inhibitors of the acetylcholine receptor and compete with acetylcholine for the active, or binding, sites on the α-subunits of the receptor. Because of a decrease in the amount of acetylcholine released from the prejunctional nerve terminal with repetitive or intense stimulation, the response to stimulation fades over time. The fourth response to a TOF stimulus is decreased relative to the first response (Fig. 29-2) because the lesser amount of acetylcholine released into the synaptic cleft with the fourth stimulus cannot overcome the competitive blockade as readily. Similarly, fading is seen in response to tetanic

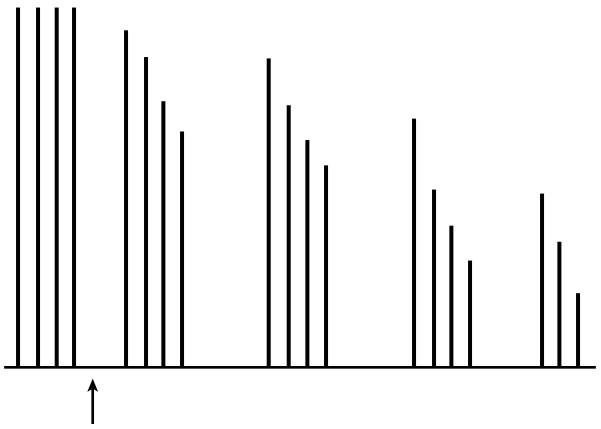


Figure 29-2 Schematic representation of the onset of neuromuscular blockade after the administration of a nondepolarizing neuromuscular blocking agent at the *arrow*. Neuromuscular function is monitored with repetitive train-of-four stimuli (four stimuli 0.5 msec in duration administered over a 2-second period).

stimuli when partial nondepolarizing neuromuscular blockade is present. During neuromuscular blockade with nondepolarizing agents, if one administers a TOF stimulus shortly after a tetanic stimulus, the response to stimulation is augmented and neuromuscular function appears stronger than it did just a couple of minutes earlier. This presumably occurs because with the tetanic stimuli, acetylcholine is mobilized toward the presynaptic portion of the nerve terminal and then, with subsequent stimulation (TOF), an increased amount of acetylcholine is released into the synaptic cleft and the blockade imposed by the nondepolarizing agent is more readily overcome. It may take 1 to 10 minutes for recovery to return to pretetanic or baseline values.[24] In the case of administration of a depolarizing neuromuscular blocking agent such as succinylcholine, the response that has classically been described is quite different. With repetitive TOF stimuli after the administration of doses of succinylcholine that cause 100% paralysis, four equal responses are seen with each stimulus, but there is a weakening of response with each successive TOF stimulus (Fig. 29-3). Similarly, there is no fading or weakening of the response to a tetanic stimulus; however, the entire response will be weaker than it was at baseline. The onset of blockade after the administration of small doses of succinylcholine, 0.05 to 0.3 mg/kg, is accompanied by fading of the TOF response, as has been described for nondepolarizing agents. Interestingly, although one would not necessarily anticipate that there would be posttetanic potentiation after the administration of succinylcholine, it has been described.[25] The reason for this observation has yet to be elucidated.

The neuromuscular blockade develops faster in centrally located muscles, such as the larynx, jaw, and diaphragm, than in more peripherally located muscles, such as the adductor pollicis.[26] In addition to developing more quickly, neuromuscular blockade in these regions, at a given dose, is less profound and recovers more quickly (Fig. 29-4) (for details, see the later section "Neuromuscular Blockers and Tracheal Intubation").[26] Consequently, the choice of monitoring site is important.

To determine the depth of blockade during maintenance and recovery of neuromuscular function, the response of the adductor pollicis to stimulation of the ulnar nerve should be monitored. If recovery in this neuromuscular unit is complete,

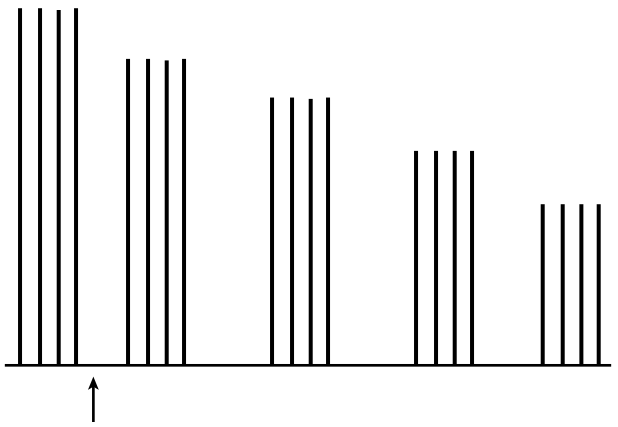


Figure 29-3 Schematic representation of the onset of neuromuscular blockade after the administration of a depolarizing neuromuscular blocking agent at the *arrow*. Neuromuscular function is monitored by repetitive train-of-four stimuli (four stimuli 0.5 msec in duration administered over a 2-second period).

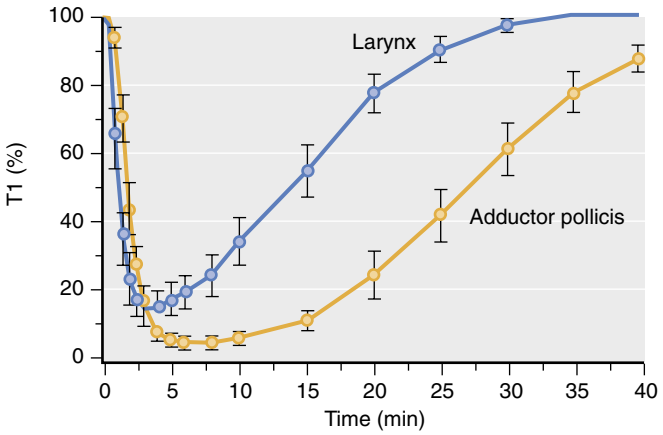


Figure 29-4 Evolution of neuromuscular blockade in the larynx and thumb (adductor pollicis) after a 0.07-mg/kg dose of vecuronium. Onset and recovery from blockade occur more rapidly in the larynx. (*From Donati F, Meistelman C, Plaud B: Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis. Anesthesiology 74:833-837, 1991.*)

recovery in the musculature of the airway should also be complete.[26] It is recommended that objective monitoring (e.g., the TOF ratio displayed digitally in real time) be used clinically. Subjective (visual or tactile) evaluation of the evoked muscular response to TOF stimulation is extremely inaccurate.

Pharmacology of Succinylcholine

Structure-Activity Relationships

All neuromuscular blockers, being quaternary ammonium compounds, are structurally related to acetylcholine. Positive charges at these sites in the molecules mimic the quaternary nitrogen atom of the transmitter acetylcholine and are the principal reason for the attraction of these drugs to muscle- and neuronal-type nAChRs at the neuromuscular junction. These receptors are also located at other physiologic sites of acetylcholine in the body, such as the neuronal-type nicotinic receptors in autonomic ganglia and as many as five different muscarinic receptors on both the parasympathetic and sympathetic sides of the autonomic nervous system. In addition, populations of neuronal nicotinic and muscarinic receptors are located prejunctionally at the neuromuscular junction.

The depolarizing neuromuscular blocker succinylcholine is composed of two molecules of acetylcholine linked back to back through the acetate methyl groups (Fig. 29-5). As described by Bovet,[27] succinylcholine is a long, thin, flexible molecule. Like acetylcholine, succinylcholine stimulates cholinergic receptors at the neuromuscular junction and at nicotinic (ganglionic) and muscarinic autonomic sites, thereby opening the ionic channel in the acetylcholine receptor.

Pharmacokinetics and Pharmacodynamics

Succinylcholine is the only available neuromuscular blocker with a rapid onset of effect and an ultrashort duration of action. The

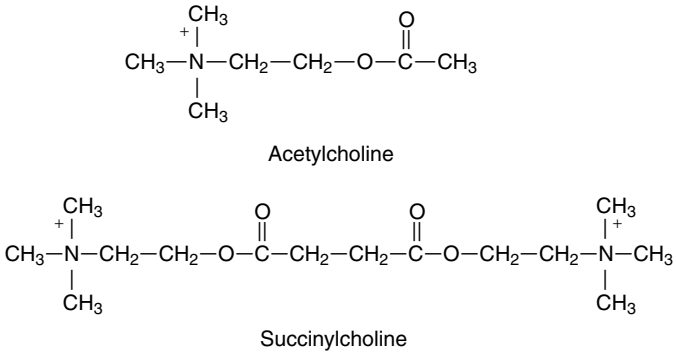


Figure 29-5 Structural relationship of succinylcholine, a depolarizing neuromuscular blocking agent, and acetylcholine. Succinylcholine consists of two acetylcholine molecules linked through the acetate methyl groups. Like acetylcholine, succinylcholine stimulates nicotinic receptors at the neuromuscular junction.

ED_{95} of succinylcholine (the dose causing on average 95% suppression of neuromuscular response) is 0.51 to 0.63 mg/kg.[28] Using cumulative dose-response techniques, Kopman and coworkers[29] estimated that its potency is far greater, with an ED_{95} of less than 0.3 mg/kg.

Administration of 1 mg/kg of succinylcholine results in complete suppression of response to neuromuscular stimulation in approximately 60 seconds.[30] In patients with genotypically normal butyrylcholinesterase (also known as plasma cholinesterase or pseudocholinesterase) activity, recovery to 90% muscle strength after the administration of 1 mg/kg succinylcholine requires 9 to 13 minutes.[31]

The short duration of action of succinylcholine is due to its rapid hydrolysis by butyrylcholinesterase to succinylmonocholine and choline. Butyrylcholinesterase has an enormous capacity to hydrolyze succinylcholine, and only 10% of the administered drug reaches the neuromuscular junction.[32] The initial metabolite, succinylmonocholine, is a much weaker neuromuscular blocking agent than succinylcholine and is metabolized much more slowly to succinic acid and choline. The elimination half-life of succinylcholine is estimated to be 47 seconds.[33]

Because there is little or no butyrylcholinesterase at the neuromuscular junction, the neuromuscular blockade of succinylcholine is terminated by its diffusion away from the neuromuscular junction back into the circulation. Butyrylcholinesterase, therefore, influences the onset and duration of action of succinylcholine by controlling the rate at which the drug is hydrolyzed before it reaches and after it leaves the neuromuscular junction.

Dibucaine Number and Butyrylcholinesterase Activity

Butyrylcholinesterase is synthesized by the liver and found in plasma. The neuromuscular blockade induced by succinylcholine is prolonged by a decreased concentration or activity of the enzyme. The activity of the enzyme refers to the number of substrate molecules (μmol) hydrolyzed per unit of time, often expressed in international units (IU). The normal range of butyrylcholinesterase activity is quite large[31]; significant decreases in butyrylcholinesterase activity result in modest increases in the time required to return to 100% twitch recovery (Fig. 29-6).

Factors that have been described as lowering butyrylcholinesterase activity are liver disease,[34] advanced age,[35] malnutrition, pregnancy, burns, oral contraceptives, monoamine oxidase inhibitors, echothiophate, cytotoxic drugs, neoplastic disease, anticholinesterase drugs,[36] tetrahydroaminacrine,[37] hexafluorenium, and metoclopramide.[38] The histamine type 2 receptor antagonists have no effect on butyrylcholinesterase activity or the duration of succinylcholine's effect.[39] Bambuterol, a prodrug of terbutaline, produces marked inhibition of butyrylcholinesterase activity and causes prolongation of succinylcholine-induced blockade.[40] The β-blocker esmolol inhibits butyrylcholinesterase but causes only minor prolongation of succinylcholine blockade.[41]

Despite all the publications and efforts to identify situations in which normal butyrylcholinesterase enzyme activity may be low, this has not been a major concern in clinical practice because even large decreases in butyrylcholinesterase activity result in only moderate increases in the duration of action of succinylcholine. When butyrylcholinesterase activity is reduced to 20% of normal by severe liver disease, the duration of apnea after the administration of succinylcholine increases from a normal duration of 3 minutes to just 9 minutes. Even when treatment of glaucoma with echothiophate decreased butyrylcholinesterase activity from 49% of control to no activity, the increase in duration of neuromuscular blockade varied from 2 to 14 minutes. In no patient did the total duration of neuromuscular blockade exceed 23 minutes.[42]

Dibucaine Number and Atypical Butyrylcholinesterase Activity

Succinylcholine-induced neuromuscular blockade can be significantly prolonged if the patient has an abnormal genetic variant

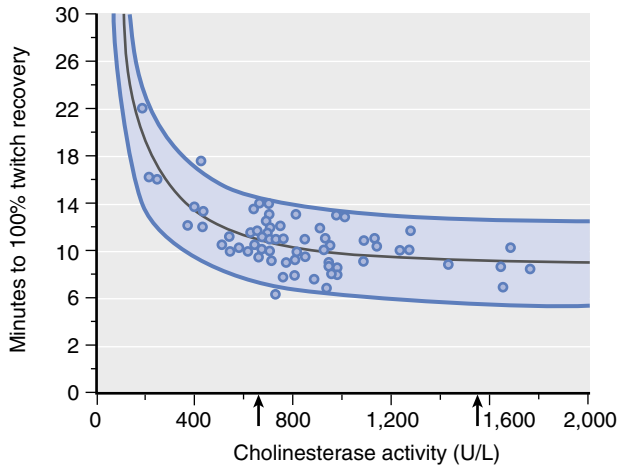


Figure 29-6 Correlation between the duration of succinylcholine neuromuscular blockade and butyrylcholinesterase activity. The normal range of activity lies between the *arrows*. *(From Viby-Mogensen J: Correlation of succinylcholine duration of action with plasma cholinesterase activity in subjects with the genotypically normal enzyme. Anesthesiology 53:517-520, 1980.)*

Table 29-1 Relationship between Dibucaine Number and Duration of Succinylcholine or Mivacurium Neuromuscular Blockade

Type of Butyrylcholinesterase	Genotype	Incidence	Dibucaine Number*	Response to Succinylcholine or Mivacurium
Homozygous typical	$E_1^uE_1^u$	Normal	70-80	Normal
Heterozygous atypical	$E_1^uE_1^a$	1/480	50-60	Lengthened by 50%-100%
Homozygous atypical	$E_1^aE_1^a$	1/3200	20-30	Prolonged to 4-8 hr

*The dibucaine number indicates the percentage of enzyme inhibited.

of butyrylcholinesterase. The variant was found by Kalow and Genest[43] to respond to dibucaine differently than normal butyrylcholinesterase does. Dibucaine inhibits normal butyrylcholinesterase to a far greater extent than it inhibits the abnormal enzyme. This observation led to development of the test for dibucaine number. Under standardized test conditions, dibucaine inhibits expression of the normal enzyme by about 80% and the abnormal enzyme by about 20% (Table 29-1). Subsequently, many other genetic variants of butyrylcholinesterase have been identified, although the dibucaine-resistant variants are the most important. The review by Jensen and Viby-Mogensen[44] can be consulted for more detailed information on this topic.

Although the dibucaine number indicates the genetic makeup of an individual with respect to butyrylcholinesterase, it does not measure the concentration of the enzyme in plasma, nor does it indicate the efficiency of the enzyme in hydrolyzing a substrate such as succinylcholine or mivacurium. Both of the latter factors are determined by measuring butyrylcholinesterase activity, which may be influenced by genotype.

The molecular biology of butyrylcholinesterase is well understood. The amino acid sequence of the enzyme is known, and the coding errors responsible for most genetic variations have been identified.[44] Most variants are due to a single amino acid substitution error or sequencing error at or near the active site of the enzyme. For example, in the case of the "atypical" dibucaine-resistant (A) gene, a mutation occurs at nucleotide 209, where guanine is substituted for adenine. The resultant change in this codon causes substitution of glycine for aspartic acid at position 70 in the enzyme. In the case of the fluoride-resistant (F) gene, two amino acid substitutions are possible, namely, methionine for threonine at position 243 and valine for glycine at position 390. Table 29-1 summarizes three of the known genetic variants of butyrylcholinesterase: the amino acid substitution at position 70 is written as Asp Ø Gly. New variants of butyrylcholinesterase genotypes continue to be discovered.[45]

Side Effects

Cardiovascular Effects

Succinylcholine-induced cardiac dysrhythmias are many and varied. The drug stimulates all cholinergic autonomic receptors: nicotinic receptors on both sympathetic and parasympathetic ganglia[46] and muscarinic receptors in the sinus node of the heart. At low doses, both negative inotropic and chronotropic responses may occur. These responses can be attenuated by prior administration of atropine. With large doses of succinylcholine, these effects may become positive[47] and result in tachycardia. A prominent clinical manifestation of generalized autonomic stimulation is the development of cardiac dysrhythmias, principally manifested as sinus bradycardia, junctional rhythms, and ventricular dysrhythmias. Clinical studies have described these dysrhythmias under various conditions in the presence of the intense autonomic stimulus of tracheal intubation. It is not entirely clear whether the cardiac irregularities are due to the action of succinylcholine alone or to the added presence of extraneous autonomic stimulation. An in vitro study using the ganglionic acetylcholine receptor subtype $\alpha_3\beta_4$ expressed in *Xenopus laevis* oocytes suggested that at clinically relevant concentrations, succinylcholine had no effect on the expressed receptors.[48] Only at high doses of succinylcholine was inhibition of ganglionic acetylcholine receptors noted.[48] The significance of these findings is difficult to extrapolate into clinical practice because the method used (*Xenopus laevis* oocyte expression model) does not match clinical reality.

Sinus Bradycardia. The autonomic mechanism involved in sinus bradycardia is stimulation of cardiac muscarinic receptors in the sinus node. This is particularly problematic in individuals with predominantly vagal tone, such as children who have not received atropine. Sinus bradycardia has also been noted in adults and appears more commonly after a second dose of the drug is given approximately 5 minutes after the first.[49] The bradycardia may be prevented by the administration of thiopental, atropine, ganglion-blocking drugs, and nondepolarizing neuromuscular blockers.[50] The implication of this information is that direct myocardial effects, increased muscarinic stimulation, and ganglionic stimulation may all be involved in the bradycardia response. The higher incidence of bradycardia after a second dose of succinylcholine suggests that the hydrolysis products of succinylcholine (succinylmonocholine and choline) may sensitize the heart to a subsequent dose.

Nodal (Junctional) Rhythms. Nodal rhythms commonly occur after the administration of succinylcholine. The mechanism probably involves relatively greater stimulation of muscarinic receptors in the sinus node, which suppresses the sinus mechanism and allows emergence of the atrioventricular node as the pacemaker. The incidence of junctional rhythm is greater after a second dose of succinylcholine but is prevented by prior administration of dTc.[50]

Ventricular Dysrhythmias. Under stable anesthetic conditions, succinylcholine lowers the threshold of the ventricle to catecholamine-induced dysrhythmias in the monkey and dog. Circulating catecholamine concentrations increase fourfold and potassium concentrations increase by a third after administration of succinylcholine to dogs.[51] Similar increases in catecholamine levels after administration of succinylcholine to humans are also observed.[52] Other autonomic stimuli, such as endotracheal intubation, hypoxia, hypercapnia, and surgery, may be additive to the

effect of succinylcholine. The possible influence of drugs such as digitalis, tricyclic antidepressants, monoamine oxidase inhibitors, exogenous catecholamines, and anesthetic drugs such as halothane and cyclopropane, all of which may lower the ventricular threshold for ectopic activity or increase the arrhythmogenic effect of catecholamines, must also be considered. Ventricular escape beats may also occur as a result of severe sinus and atrioventricular nodal slowing secondary to succinylcholine administration. The development of ventricular dysrhythmias is further encouraged by the release of potassium from skeletal muscle as a consequence of the depolarizing action of the drug.

Hyperkalemia

Administration of succinylcholine to an otherwise well individual for an elective surgical procedure increases plasma potassium levels by approximately 0.5 mEq/dL. This increase in potassium is due to the depolarizing action of the relaxant. With activation of the acetylcholine channels, movement of sodium into the cells is accompanied by movement of potassium out of the cells. This slight increase in potassium is well tolerated by most individuals and generally does not cause dysrhythmias.

Several early reports suggested that patients in renal failure may be susceptible to a hyperkalemic response to succinylcholine.[53] Nevertheless, more controlled studies have shown that such patients are no more susceptible to an exaggerated response to succinylcholine than those with normal renal function are.[54] One might postulate that patients who have uremic neuropathy may be susceptible to succinylcholine-induced hyperkalemia, although the evidence supporting this view is scarce.[53,54]

However, severe hyperkalemia may follow the administration of succinylcholine to patients with severe metabolic acidosis and hypovolemia.[55] In rabbits, the combination of metabolic acidosis and hypovolemia results in a high resting potassium level and an exaggerated hyperkalemic response to succinylcholine.[56] In this situation, the potassium originates from the gastrointestinal tract, not from muscle as in the classic hyperkalemic response.[57] In patients with metabolic acidosis and hypovolemia, correction of the acidosis by hyperventilation and administration of sodium bicarbonate should be attempted before administration of succinylcholine. Should severe hyperkalemia occur, it can be treated with immediate hyperventilation, 1.0 to 2.0 mg of calcium chloride intravenously, 1 mEq/kg of sodium bicarbonate, and 10 units of regular insulin in 50 mL of 50% glucose for adults or, for children, 0.15 units of regular insulin per kilogram in 1.0 mL/kg of 50% glucose.

Kohlschütter and associates[58] found that four of nine patients with severe abdominal infections had an increase in serum potassium levels of as much as 3.1 mEq/L after the administration of succinylcholine. These investigators found that in patients with intra-abdominal infections persisting for longer than 1 week, the possibility of a hyperkalemic response to succinylcholine should be considered.

Stevenson and Birch[59] described a single, well-documented case of a marked hyperkalemic response to succinylcholine in a patient with a closed head injury but no peripheral paralysis.

In studying soldiers who had undergone trauma during the Vietnam War, Birch and colleagues[60] found that a significant increase in serum potassium did not occur in 59 patients until about 1 week after the injury, at which time a progressive increase in the serum potassium level was noted after the infusion of succinylcholine. Three weeks after injury, three of these patients with especially severe trauma showed marked hyperkalemia with an increase in serum potassium of greater than 3.6 mEq/L, sufficient to cause cardiac arrest. Birch and coworkers[60] found that prior administration of 6 mg of dTc prevented the hyperkalemic response to succinylcholine. In the absence of infection or persistent degeneration of tissue, a patient is susceptible to the hyperkalemic response for probably at least 60 days after massive trauma or until adequate healing of damaged muscle has occurred.

In addition, patients with any number of conditions that result in the proliferation of extrajunctional acetylcholine receptors, such as neuromuscular disease, are likely to have an exaggerated hyperkalemic response after the administration of succinylcholine. The response of these patients to neuromuscular blocking agents is reviewed in detail later in this chapter. These disease states include cerebrovascular accident with resultant hemiplegia or paraplegia, muscular dystrophies, and Guillain-Barré syndrome (see also Chapter 37). The hyperkalemia occurring after the administration of succinylcholine may be of such an extent that cardiac arrest ensues. For a recent review on succinylcholine-induced hyperkalemia in patients with acquired pathologic states, see Martyn and Richtsfeld.[61]

Increased Intraocular Pressure

Succinylcholine usually causes an increase in intraocular pressure (IOP). The increased IOP is manifested within 1 minute after injection, peaks at 2 to 4 minutes, and subsides by 6 minutes.[62] The mechanism by which succinylcholine increases IOP has not been clearly defined, but it is known to involve contraction of tonic myofibrils or transient dilatation of choroidal blood vessels (or both). Sublingual administration of nifedipine has been reported to attenuate the increase in IOP from succinylcholine, thus suggesting a circulatory mechanism.[63] Despite this increase in IOP, the use of succinylcholine for eye operations is not contraindicated unless the anterior chamber is open. Although Meyers and associates[64] were unable to confirm the efficacy of precurarization in attenuating increases in IOP after the administration of succinylcholine, numerous other investigators have found that prior administration of a small dose of nondepolarizing neuromuscular blocker (such as 3 mg of dTc or 1 mg of pancuronium) will prevent a succinylcholine-induced increase in IOP.[65] Furthermore, Libonati and coauthors[66] described the anesthetic management of 73 patients with penetrating eye injuries who received succinylcholine; no loss of global contents resulted. Thus, despite the potential concerns of Meyers and coworkers,[64] Libonati and colleagues[66] found that the use of succinylcholine in patients with penetrating eye injuries, after pretreatment with a nondepolarizing neuromuscular blocker and with carefully controlled, rapid-sequence induction of anesthesia, is an acceptable technique. Succinylcholine is only one of many factors, such as endotracheal intubation and "bucking" on the tube, that may elevate IOP.[64] Of prime importance is ensuring that the patient is well anesthetized and not straining or coughing. Because nondepolarizing neuromuscular blockers with shorter times to onset of effect are now available, providing an anesthetic that allows the trachea to be intubated rapidly without administering succinylcholine is now an option. Finally, should a patient's anesthesia become too light over the course of intraocular surgery, succinylcholine should not be given to immobilize the patient. Rather, the surgeon should be asked to pause while the anesthesia is deepened. If necessary, the depth of neuromuscular blockade can also be increased with nondepolarizing relaxants.

Increased Intragastric Pressure

Unlike the rather consistent increase in IOP, the increase in intragastric pressure (IGP) caused by succinylcholine is quite variable. The increase in IGP from succinylcholine is presumed to be due to fasciculations of abdominal skeletal muscle. This is not surprising because more coordinated abdominal skeletal muscle activity (e.g., straight-leg raising) may increase IGP to values as high as 120 cm H_2O. In addition to skeletal muscle fasciculations, the acetylcholine-like effect of succinylcholine may be partly responsible for the observed increases in IGP. Greenan[67] noted consistent increases in IGP of 4 to 7 cm H_2O with direct vagal stimulation.

Miller and Way[68] found that 11 of 30 patients had essentially no increase in IGP after the administration of succinylcholine, yet 5 of the 30 had an increase in IGP of greater than 30 cm H_2O. The increase in IGP from succinylcholine appeared to be related to the intensity of the abdominal skeletal muscle fasciculations. Accordingly, when fasciculations were prevented by prior administration of a nondepolarizing neuromuscular blocker, no increase in IGP was observed.

Are the increases in IGP after succinylcholine administration enough to cause incompetence of the gastroesophageal junction? Generally, an IGP of greater than 28 cm H_2O is required to overcome the competence of the gastroesophageal junction. However, when the normal oblique angle of entry of the esophagus into the stomach is altered, as may occur with pregnancy, an abdomen distended by ascites, bowel obstruction, or a hiatal hernia, the IGP required to cause incompetence of the gastroesophageal junction is frequently less than 15 cm H_2O.[68] In these circumstances, regurgitation of stomach contents after the administration of succinylcholine is a distinct possibility, and precautionary measures should be taken to prevent fasciculation. Endotracheal intubation may be facilitated by administration of either a nondepolarizing neuromuscular blocker or a defasciculating dose of a nondepolarizing relaxant before the succinylcholine.

Apparently, succinylcholine does not increase IGP appreciably in infants and children, which may be related to the minimal or absent fasciculations from succinylcholine in these age groups.[69]

Increased Intracranial Pressure

Succinylcholine has the potential to increase intracranial pressure.[70] The mechanisms and clinical significance of this transient increase are unknown, but the rise in intracranial pressure does not occur after pretreatment with nondepolarizing neuromuscular blockers.[70]

Myalgias

The incidence of muscle pain after the administration of succinylcholine varies from 0.2% to 89%.[71] It occurs more frequently after minor surgery, especially in women and in ambulatory rather than bedridden patients.[72] Waters and Mapleson[72] postulated that the pain is secondary to damage produced in muscle by the unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis. That damage to muscle may occur has been substantiated by finding myoglobinemia and increases in serum creatine kinase after succinylcholine administration.[73] Prior administration of a small dose of a nondepolarizing neuromuscular blocker clearly prevents succinylcholine-related fasciculations.[73] However, the efficacy of this approach in preventing muscle pain is questionable. Although some investigators claim that pretreatment with a defasciculating dose of a nondepolarizing neuromuscular blocker has no effect,[71] many believe that the pain from succinylcholine is at least attenuated.[73] Pretreatment with a prostaglandin inhibitor (e.g., lysine acetyl salicylate) has been shown to be effective in decreasing the incidence of muscle pain after succinylcholine.[74] This suggests a possible role for prostaglandins and cyclooxygenases in succinylcholine-induced myalgias. Other investigators have found that myalgias after outpatient surgery occur even in the absence of succinylcholine.[75]

Masseter Spasm

An increase in tone of the masseter muscle is a frequent response to succinylcholine in adults[76] and children.[77] Meakin and coworkers[77] suggested that the high incidence of spasm in children may be due to an inadequate dosage of succinylcholine. In all likelihood, this increase in tone is an exaggerated contractile response at the neuromuscular junction and cannot be used to establish a diagnosis of malignant hyperthermia. Although an increase in tone of the masseter muscle may be an early indicator of malignant hyperthermia, it is not consistently associated with that syndrome.[78] There is currently no indication to change to a "nontriggering" anesthetic in instances of isolated masseter spasm.[79]

Clinical Uses

Despite its many adverse effects, succinylcholine remains in common use. Its popularity is probably due to its rapid onset of effect, the profound depth of neuromuscular blockade that it produces, and its short duration of action. Although it may be less commonly used than in the past for routine endotracheal intubation, it is the neuromuscular blocker of choice for rapid-sequence induction of anesthesia. In a study comparing intubating conditions after the administration of 1 mg/kg of succinylcholine with those after the administration of 0.1 mg/kg of vecuronium or 0.1 mg/kg of pancuronium 30 seconds after administration of the relaxant and at 30-second intervals after that up for 120 seconds, intubation could be accomplished in all patients receiving succinylcholine at 30 seconds, in contrast with the other neuromuscular blockers studied.[80] Furthermore, at all time points studied up to 90 seconds, intubating conditions were better after the administration of succinylcholine than after either of the other neuromuscular blockers. Although 1.0 mg/kg of succinylcholine has long been recommended to facilitate endotracheal intubation at 60 seconds, a recent study indicated that 0.5 to 0.6 mg/kg of succinylcholine should allow adequate intubating conditions 60 seconds after administration.[81] Reduction of the succinylcholine dose from 1.0 mg/kg to 0.6 mg/kg decreased the incidence of hemoglobin saturation from 85% to 65% but did not shorten the time to spontaneous diaphragmatic movement.[82] However, a significant fraction of patients would be at risk if there were failure to intubate and ventilate regardless of whether succinylcholine is administered or the dose of succinylcholine administered.[82]

A small dose of nondepolarizing neuromuscular blocker is commonly given 2 minutes before the intubating dose of succinylcholine. This defasciculating dose of nondepolarizing neuromuscular blocker will attenuate any increases in IGP and intracranial pressure and minimize the incidence of fasciculations in response to succinylcholine. Prior administration of a

Table 29-2 Clinical Characteristics of Phase 1 and Phase 2 Neuromuscular Blockade during Succinylcholine Infusion

Characteristic	Phase 1	Transition	Phase 2
Tetanic stimulation	No fade	Slight fade	Fade
Post-tetanic facilitation	None	Slight	Yes
Train-of-four fade	No	Moderate fade	Marked fade
Train-of-four ratio	>0.7	0.4-0.7	<0.4
Edrophonium	Augments	Little effect	Antagonizes
Recovery	Rapid	Rapid to slow	Increasingly prolonged
Dose requirements (mg/kg)*	2-3	4-5	>6
Tachyphylaxis	No	Yes	Yes

*Cumulative dosage of succinylcholine by infusion under nitrous oxide anesthesia supplemented with intravenous agents. The dosage required to cause a phase 2 block is less in the presence of potent anesthetic vapors, such as isoflurane.
Adapted from Lee C, Katz RL: Neuromuscular pharmacology. A clinical update and commentary. Br J Anaesth 52:173-188, 1980.

nondepolarizing agent will render the muscle relatively resistant to succinylcholine, however, so the succinylcholine dose should be increased by 50%.[83] The use of a defasciculating dose of a nondepolarizing neuromuscular blocker may also slow the onset of succinylcholine and produce less favorable conditions for tracheal intubation.[73]

Typically after administration of succinylcholine for intubation, a nondepolarizing neuromuscular blocker is given to maintain neuromuscular blockade. Succinylcholine given first may enhance the depth of blockade induced by a subsequent dose of nondepolarizing neuromuscular blocker.[84-86] However, the effect on duration of action is variable. Succinylcholine has no effect on the duration of action of pancuronium, pipecuronium, or mivacurium[86,87] but increases that of atracurium and rocuronium.[84,85] The reasons for these differences are not clear.

The changing characteristics of succinylcholine neuromuscular blockade over the course of prolonged administration have been reviewed by Lee and Katz[88] and are summarized in Table 29-2. TOF stimulation is a very safe and useful guide for detecting the transition from a phase 1 to a phase 2 block. A phase 1 block has all the characteristics of a depolarizing block as described previously in the monitoring section. A phase 2 block has the characteristics of a nondepolarizing block. With the administration of large doses of succinylcholine, the nature of the block, as determined by a neuromuscular blockade monitor, changes from that of a depolarizing agent to that of a nondepolarizing agent. Clearly, both the dose and the duration of administration of succinylcholine are important variables, although the relative contribution of each has not been established. In practical terms, if administration of the drug is terminated shortly after TOF fading is clearly evident, rapid return of normal neuromuscular function should ensue. In addition, the decision whether to attempt antagonism of a phase 2 block has always been controversial. However, if the TOF ratio is less than 0.4, administration of edrophonium or neostigmine should result in prompt antagonism. Ramsey and associates[89] recommended that antagonism of a succinylcholine-induced phase 2 block with edrophonium or neostigmine be attempted after spontaneous recovery of the twitch has been observed for 20 to 30 minutes and has reached a plateau phase with further recovery proceeding slowly. These researchers stated that in this situation, edrophonium and neostigmine invariably produce "dramatic" acceleration of the return of the TOF ratio toward normal.[89] In any event, monitoring neuromuscular function via TOF stimuli will help avoid succinylcholine overdose, detect the development of phase 2 blockade, observe its rate of recovery, and assess the effect of edrophonium or neostigmine on recovery.

A recent study showed that post-tetanic potentiation and fade in response to TOF and tetanic stimuli are characteristics of neuromuscular blockade after bolus administration of different doses of succinylcholine.[25] It seems that some characteristics of phase 2 blockade are evident after an initial dose of succinylcholine (i.e., as small as 0.3 mg/kg).[25]

Interactions with Anticholinesterases

Another interaction with succinylcholine involves neostigmine or pyridostigmine. For example, after dTc has been used for intra-abdominal surgery of long duration and the neuromuscular blockade has been reversed by neostigmine, the surgeon announces that another 15 minutes is needed to retrieve a missing sponge. Succinylcholine should not be administered to reestablish neuromuscular blockade because it produces relaxation that will last up to 60 minutes when given soon after the administration of neostigmine. Sunew and Hicks[36] found that the effect of succinylcholine (1 mg/kg) was prolonged from 11 to 35 minutes when given 5 minutes after the administration of neostigmine (5 mg). This can be partly explained by the inhibition of butyrylcholinesterase by neostigmine and, to a lesser extent, by pyridostigmine. Ninety minutes after the administration of neostigmine, butyrylcholinesterase activity will have returned to less than 50% of its baseline value.

Nondepolarizing Neuromuscular Blockers

The use of neuromuscular blocking drugs in anesthesia has its origin in the South American Indians' arrow poisons or curare. Several nondepolarizing neuromuscular blockers are still purified from naturally occurring sources. For example, although dTc can be synthesized, it is still less expensive to isolate from the Amazonian vine *Chondodendron tomentosum*. Similarly, intermediates for the production of metocurine and alcuronium, which are semisynthetic, are obtained from *Chondodendron* and *Strychnos toxifera*. Malouetine, the first steroidal neuromuscular blocking drug, was originally isolated from *Malouetia bequaertiana*, which grows in the jungles of the Democratic Republic of Congo in central Africa. The agents pancuronium, vecuronium, pipecuronium, rocuronium, rapacuronium, atracurium, doxacurium, mivacurium, cisatracurium, gantacurium, and gallamine are entirely synthetic.

The available nondepolarizing neuromuscular blockers can be classified according to chemical class (steroidal, benzylisoquinolinium, or other compounds) or, alternatively, according to

Table 29-3 Classification of Nondepolarizing Neuromuscular Blockers According to Duration of Action (Time to T1 = 25% of Control) after Twice the ED_{95}

Class of Blocker	Clinical Duration			
	Long-Acting (>50 min)	**Intermediate-Acting (20-50 min)**	**Short-Acting (15-20 min)**	**Ultrashort-acting (<10-12 min)**
Steroidal compounds	Pancuronium Pipecuronium	Vecuronium Rocuronium		
Benzylisoquinolinium compounds	*d*-Tubocurarine Metocurine Doxacurium	Atracurium Cisatracurium	Mivacurium	
Others				
Asymmetrical mixed-onium chlorofumarates				Gantacurium
Phenolic ether	Gallamine			
Diallyl derivative of toxiferine	Alcuronium			

A majority of nondepolarizing neuromuscular blockers are bisquaternary ammonium compounds. *d*-Tubocurarine, vecuronium, rocuronium, and rapacuronium are monoquaternary compounds, and gallamine is a trisquaternary ammonium compound.

onset or duration of action (long-, intermediate-, and short-acting drugs) of equipotent doses (Table 29-3).

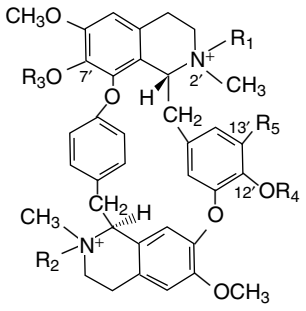
Structure-Activity Relationships

Nondepolarizing neuromuscular blocking drugs were originally classified by Bovet[27] as pachycurares, or bulky molecules having the amine functions incorporated into rigid ring structures. Two extensively studied chemical series of synthetic nondepolarizing neuromuscular blockers are the aminosteroids (steroidal), in which the interonium distance is maintained by an androstane skeleton, and the benzylisoquinolinium series, in which the distance is maintained by linear diester-containing chains or, in the case of curare, by benzyl ethers. For a detailed account of structure-activity relationships, see Lee.[90]

Benzylisoquinolinium Compounds

dTc is a neuromuscular blocker in which the amines are present in the form of two benzyl-substituted tetrahydroisoquinoline structures (Fig. 29-7). The quaternary or tertiary nature of the two amines was initially questioned; however, with the use of nuclear magnetic resonance spectroscopy and methylation-demethylation studies, Everett and coworkers[91] demonstrated that dTc contains only three *N*-methyl groups. One amine is quaternary (i.e., permanently charged with four nitrogen substituents) and the other is tertiary (i.e., pH-dependent charge with three nitrogen substituents). At physiologic pH, the tertiary nitrogen is protonated to render it positively charged. The structure-activity relationships of the bis-benzylisoquinolines (see Fig. 29-7) have been described by Waser[92] and by Hill and associates[93] as follows:

1. The nitrogen atoms are incorporated into isoquinoline ring systems. This bulky molecule favors nondepolarizing rather than depolarizing activity.
2. The interonium distance (distance between charged amines) is approximately 1.4 nm.
3. Both the ganglion-blocking and the histamine-releasing properties of dTc are probably due to the presence of the tertiary amine function.
4. When dTc is methylated at the tertiary amine and at the hydroxyl groups, the result is metocurine, a compound with greater potency (by a factor of 2 in humans) but much weaker ganglion-blocking and histamine-releasing properties than dTc has (see Fig. 29-7). Metocurine contains three additional methyl groups, one of which quaternizes the tertiary nitrogen of dTc; the other two form methyl ethers at the phenolic hydroxyl groups.
5. Bisquaternary compounds are more potent than their monoquaternary analogs. The bisquaternary derivative of dTc, chondocurine, has more than double the potency of dTc (Fig. 29-7).
6. Substitution of the methyl groups on the quaternary nitrogen with bulkier groups causes a reduction in both potency and duration of action.



Cyclic benzylisoquinoline

Cyclic benzylisoquinoline derivatives

Name	R_1	R_2	R_3	R_4	R_5	1	1'
d-Tubocurarine	CH_3	H	H	H	H	*S*	*R*
Metocurine	CH_3	CH_3	CH_3	CH_3	H	*S*	*R*
Chondocurine	CH_3	CH_3	H	H	H	*S*	*R*

R and S represent the stereochemical configuration about the designated carbon

Figure 29-7 Chemical structures of *d*-tubocurarine, metocurine, and chondocurine.

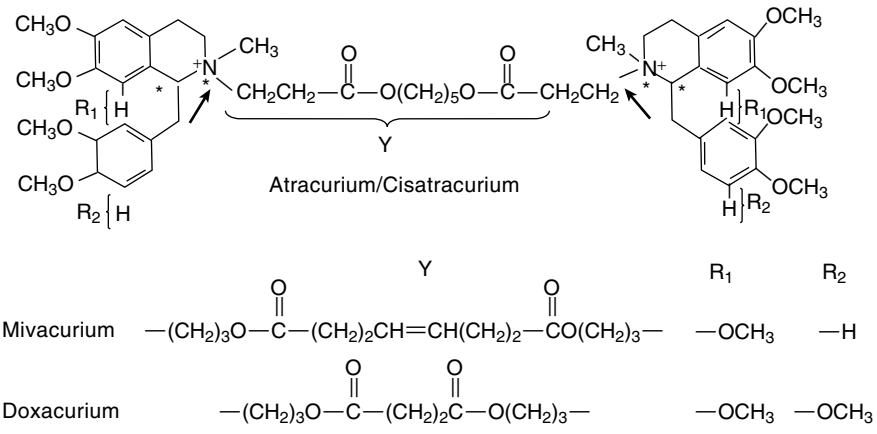


Figure 29-8 Chemical structures of atracurium, cisatracurium, mivacurium, and doxacurium. The *asterisks* indicate chiral centers; *arrows* show cleavage sites for Hofmann elimination.

Atracurium is a bis-benzyltetrahydroisoquinolinium with isoquinolinium nitrogens connected by a diester-containing hydrocarbon chain (Fig. 29-8). The presence (in duplicate) of two-carbon separations between quaternary nitrogen and ester carbonyl provides the basis for a Hofmann elimination reaction.[94] Furthermore, it can undergo ester hydrolysis. In a Hofmann elimination reaction, a quaternary ammonium group is converted to a tertiary amine by cleavage of a carbon-nitrogen bond. This is a pH- and temperature-dependent reaction in which higher pH and temperature favor elimination. The actual structure of the quaternary centers is the laudanosinium moiety, as in metocurine. Atracurium has four chiral centers at each of the adjacent chiral carbons of the two amines. The marketed product has 10 isomers.[94] These isomers have been separated into three geometric isomer groups that are designated *cis-cis*, *cis-trans*, and *trans-trans* according to their configuration about the tetrahydroisoquinoline ring system.[94] The ratio of the *cis-cis*, *cis-trans*, and *trans-trans* isomers is approximately 10:6:1, which corresponds to 50% to 55% *cis-cis*, 35% to 38% *cis-trans*, and 6% to 7% *trans-trans* isomers.

Cisatracurium is the 1R *cis*–1′R *cis* isomer of atracurium and represents about 15% of the marketed atracurium mixture by weight but more than 50% in terms of potency or neuromuscular blocking activity (see Fig. 29-8). R designates the absolute stereochemistry of the benzyl tetrahydroisoquinoline rings and *cis* represents the relative geometry of the bulky dimethoxy and 2-alkyester groups at C(1) and N(1), respectively.[95,96] Cisatracurium is metabolized by Hofmann elimination. It is approximately four times as potent as atracurium, but unlike atracurium, it does not cause release of histamine in the clinical dose range.[95,97] This indicates that the phenomenon of histamine release may be stereospecific.[95,98] Cisatracurium is the second benzylisoquinolinium (after doxacurium) to be largely free of this side effect.

Mivacurium differs from atracurium by the presence of an additional methylated phenolic group (see Fig. 29-8). When compared with other isoquinolinium neuromuscular blockers, the interonium chain of mivacurium is longer (16 atoms).[93] Mivacurium consists of a mixture of three stereoisomers.[99] The two most active are the *trans-trans* and *cis-trans* isomers (57% and 37% wt/wt, respectively), which are equipotent; the *cis-cis* isomer (6% wt/wt) has only a 10th the activity of the others in cats and monkeys.[99] Mivacurium is metabolized by butyrylcholinesterase at 70% to 88% the rate of succinylcholine to a monoester, a dicarboxylic acid.[9]

Doxacurium is a bisquaternary benzylisoquinolinium diester of succinic acid (see Fig. 29-8). The interonium chain is shorter than that of either atracurium or mivacurium. Lee[90] pointed out that the number of methoxy groups on benzylisoquinolinium heads is increased from four (atracurium) and five (mivacurium) to six (doxacurium).[93] This increase was associated with both an increase in potency and a reduction in the propensity to release histamine.[90,93]

Steroidal Neuromuscular Blockers

In the steroidal compounds, it is probably essential that one of two nitrogen atoms in the molecule be quaternized. The presence of acetyl ester (acetylcholine-like moiety) is thought to facilitate its interaction with nAChRs at the postsynaptic muscle membrane.

Pancuronium is characterized by the presence of two acetyl ester groups on the A and D rings of the steroidal molecule. Pancuronium is a potent neuromuscular blocking drug with both vagolytic and butyrylcholinesterase-inhibiting properties (Fig. 29-9).[100] Deacetylation of the 3-OH or 17-OH groups decreases its potency.[101]

Vecuronium is the *N*-demethylated derivative of pancuronium in which the 2-piperidine substituent is not methylated (i.e., vecuronium lacks the *N*-methyl group at position 2) (see Fig. 29-9).[7] At physiologic pH, the tertiary amine is largely protonated, as it is in dTc. The minor molecular modification relative to pancuronium results in (1) a slight change in potency; (2) a marked reduction in vagolytic properties; (3) molecular instability in solution, which explains in part the shorter duration of action of vecuronium than pancuronium; and (4) increased lipid solubility, which results in greater biliary elimination of vecuronium than pancuronium.[93]

Pancuronium and vecuronium are very similar in structure, yet vecuronium is prepared as a lyophilized powder. Vecuronium is degraded by the hydrolysis of acetyl esters at either or both the C3 and C17 positions. Hydrolysis at the C3 position is the primary degradation product. The acetate at position 3 is more susceptible to hydrolysis in aqueous solutions. Vecuronium is less stable in solution because of the group effect of the adjacent basic piperidine at position 2, which facilitates hydrolysis of the 3-acetate. Therefore, vecuronium cannot be prepared as a ready-to-use solution with a sufficient shelf life, even as a buffered solution. In pancuronium, the 2-piperidine is quaternized and no

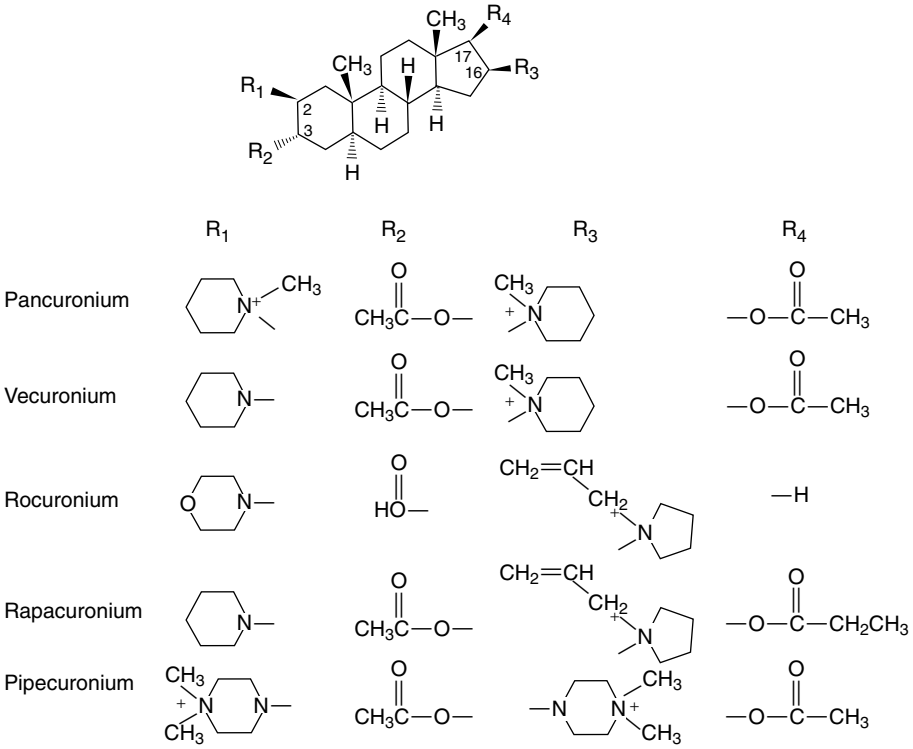


Figure 29-9 Chemical structures of different steroidal neuromuscular blockers.

longer alkaline. Thus, it does not participate in catalysis of the 3-acetate hydrolysis.

Pipecuronium, like pancuronium, is a bisquaternary compound. Pipecuronium has piperazine rings attached to the A and D rings of the steroid nucleus, whereas pancuronium has piperidine rings (see Fig. 29-9).[93] Pipecuronium is a nonvagolytic substitute for pancuronium. Changes in the quaternary groups in which the quaternary nitrogen atoms are placed at the distal (4-position) aspect of the 2,16-β-substitutions lessen the vagolytic effects.[93] As a result, pipecuronium is about 10 times less vagolytic than pancuronium.

Rocuronium lacks the acetyl ester that is found in the steroid nucleus of pancuronium and vecuronium in the A ring (see Fig. 29-9). The introduction of cyclic substituents other than piperidine at the 2- and 16-positions results in a fast-onset compound.[102] The methyl group attached to the quaternary nitrogen of vecuronium and pancuronium is replaced by an allyl group in rocuronium. As a result, rocuronium is about 6 and 10 times less potent than vecuronium and pancuronium, respectively.[102-104] Replacement of the acetyl ester attached to the A ring by a hydroxy group has made it possible to present rocuronium as a stable solution. At room temperature, rocuronium is stable for only 60 days, whereas pancuronium is stable for 6 months. The reason for this difference in shelf life is related to the fact that rocuronium is terminally sterilized in manufacturing and pancuronium is not. Terminal sterilization causes some degree of degradation.

Asymmetric Mixed-Onium Chlorofumarates

Gantacurium (Fig. 29-10) represents a new class of nondepolarizing neuromuscular blockers called asymmetric mixed-onium chlorofumarates. The presence of three methyl groups between the quaternary nitrogen and oxygen atom at each end of the carbon chain suggests that similar to mivacurium, this compound will not undergo Hofmann elimination.[105] Gantacurium has an ultrashort duration of action in human volunteers and in different animal species. A study in anesthetized human volunteers using an earlier formulation of gantacurium estimated the ED_{95} to be 0.19 mg/kg.[106] The pattern of blockade resembled that of succinylcholine. The time to onset of 90% blockade ranged from 1.3 to 2.1 minutes, depending on the dose. Clinical durations ranged from 4.7 to 10.1 minutes and increased with increasing dose. Spontaneous recovery to a TOF of 0.9 develops in the thumb within about 12 to 15 minutes after the administration of doses as large as 0.54 mg/kg (or three times the ED_{95}). Recovery is accelerated by edrophonium. Transient cardiovascular side effects were observed at doses beginning at three times the ED_{95} and were suggestive of histamine release.[106]

Phenolic Ether Derivative

Gallamine is a trisquaternary compound (Fig. 29-11). Its potent vagolytic activity is due to the presence of three positively charged nitrogen atoms. Gallamine was originally synthesized by Bovet[27] as part of an extensive structure-activity study that helped evolve the concepts of "pachycurares" and "leptocurares." Succinylcholine also evolved from this work, for which Bovet received the Nobel Prize.

Diallyl Derivative of Toxiferine

Introduced in 1964, alcuronium is a long-acting agent that is the semisynthetic diallyl derivative of toxiferine (Fig. 29-12). The latter is purified from *Strychnos toxifera*. The advantage of alcuronium at the time of its introduction was a relative lack of side effects. It is mildly vagolytic and is excreted unchanged by the kidney with a minor secondary biliary pathway.

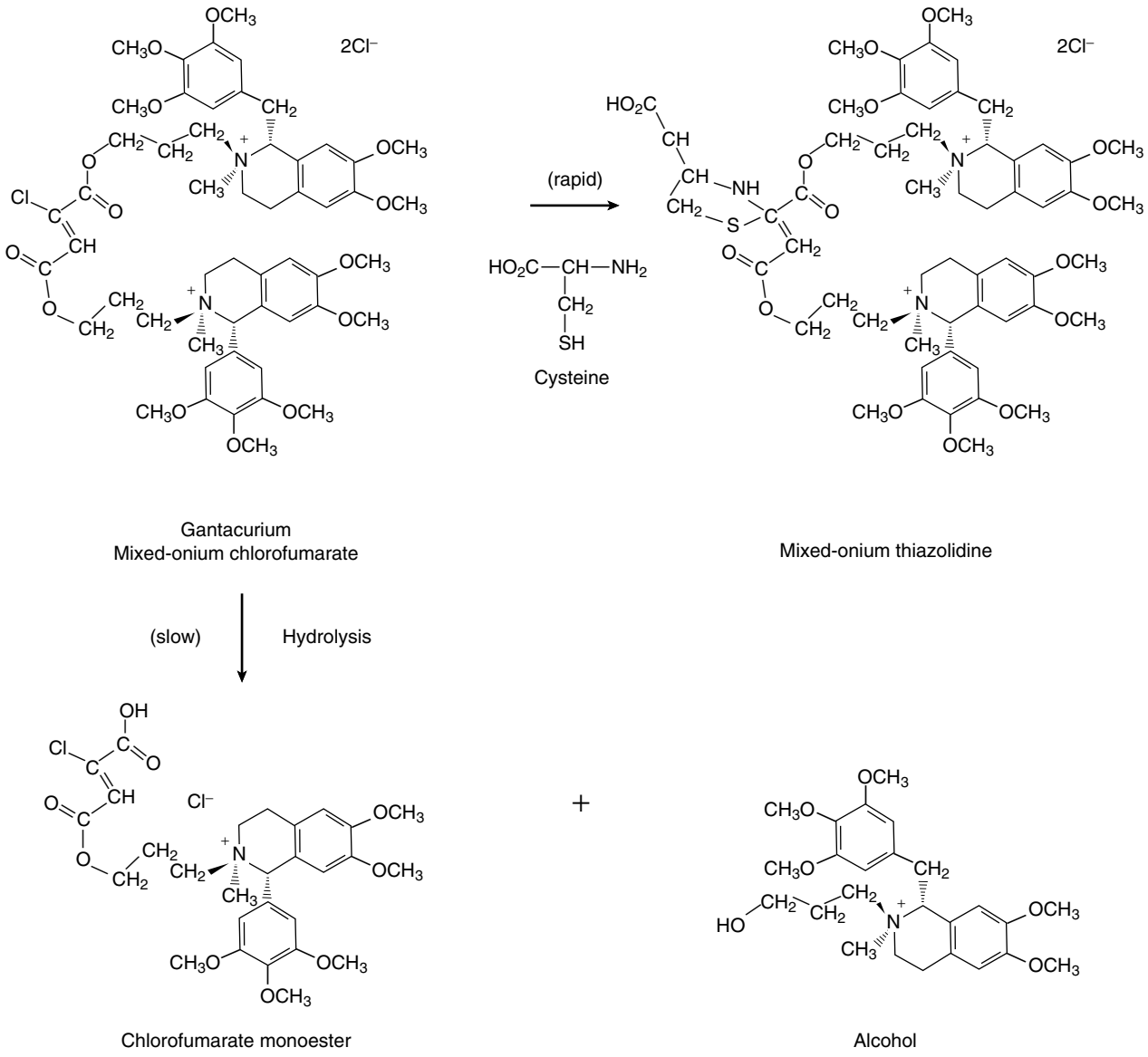


Figure 29-10 Chemical structure of gantacurium (a mixed-onium chlorofumarate). In whole human blood, two pathways of deactivation occur, neither of which is enzymatic: (1) rapid formation of an apparently inactive cysteine adduction product, with cysteine replacing chlorine, and (2) slower hydrolysis of the ester bond adjacent to the chlorine substitution to chlorofumarate monoester and alcohol. *(From Boros EE, Samano V, Ray JA, et al: Neuromuscular blocking activity and therapeutic potential of mixed-tetrahydroisoquinolinium halofumarates and halosuccinates in rhesus monkeys. J Med Chem 46:2502-2515, 2003.)*

Potency of Nondepolarizing Neuromuscular Blockers

Drug potency is commonly expressed by the dose-response relationship. The dose of a neuromuscular blocking drug required to produce an effect (e.g., 50%, 90%, or 95% depression of twitch height, commonly expressed as ED_{50}, ED_{90}, and ED_{95}, respectively) is taken as a measure of its potency.[9,11,103,107-117] The neuromuscular blocking drugs have different potencies, as illustrated in Table 29-4 and Figure 29-13. For factors affecting the potency of neuromuscular blockers, see the section on drug interactions later in this chapter. The dose-response relationship for nondepolarizing neuromuscular blockers is sigmoidal in shape (see Fig. 29-13) and has been derived in various ways. The simplest method is to perform linear regression over the approximately linear portion of a semilogarithmic plot between 25% and 75% neuromuscular blockade. Alternatively, the curve can be subjected to probit or logit transformation to linearize it over its whole length or can be subjected to nonlinear regression using the sigmoid E_{max} model of the form

$$\text{Effect}(e) = .\backslash F\left(\text{dose}_e{}^{\gamma}, \text{dose}_e{}^{\gamma} + \text{dose}_{e50}{}^{\gamma}\right)$$

This can be applied to the raw data.[119] More complex models relating the concentration of neuromuscular blockers at the neuromuscular junction to their pharmacologic effect have been developed, as discussed later.[120,121]

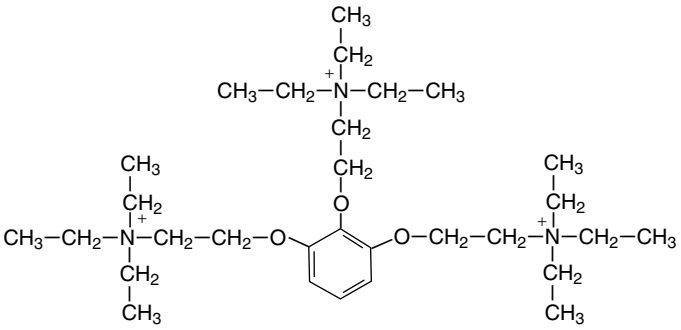


Figure 29-11 Chemical structure of gallamine, a trisquaternary ether of gallic acid. Gallamine is the only trisquaternary compound available. Its strong vagolytic property is probably due to its trisquaternary structure.

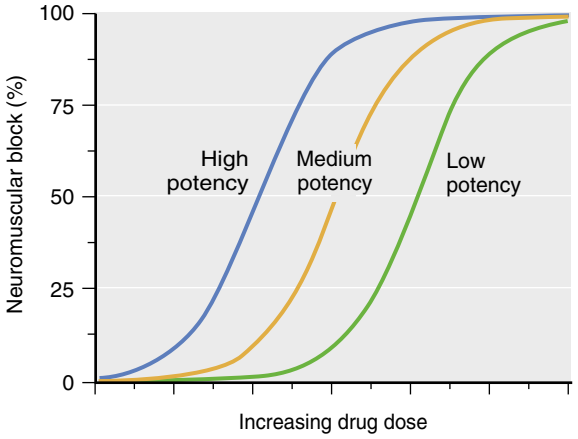


Figure 29-13 Schematic representation of a semilogarithmic plot of a muscle relaxant dose versus neuromuscular blockade. A drug of high potency is doxacurium; one of medium potency, atracurium; and one of low potency, gallamine. The graph illustrates that the relative potencies of muscle relaxants span a range of approximately 2 orders of magnitude.

Pharmacokinetics and Pharmacodynamics

As defined by Wright,[122] pharmacokinetics and pharmacodynamics are "empirical mathematical model[s] … that [describe] drug effect time course after administration." In pharmacokinetic modeling, the concept of "compartments" represents different organs or tissues (or both) grouped together on the basis of their degree of blood perfusion (high or low). After a neuromuscular blocker is injected into the circulation, its concentration in plasma decreases rapidly at first and then more slowly (Fig. 29-14). The shape of this curve is determined by the processes of distribution and elimination. Classically, this curve is divided into an initial (distribution) phase and a terminal (elimination) phase. This curve can be represented mathematically by biexponential or triexponential equations in the form

$$\text{Concentration (at time t)} = Ae^{-\alpha t} + Be^{-\beta t}\left(+Pe^{-\pi t}\right)$$

These multiexponential equations express the concept of drug distribution between two or three theoretical compartments.

Figure 29-15 illustrates the classic model, in which the drug is administered intravenously into a central compartment with volume V_1 and is distributed and eliminated from this compartment only. The drug is distributed very rapidly throughout this

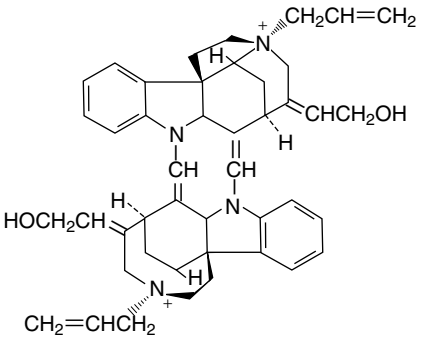


Figure 29-12 Chemical structure of alcuronium, the semisynthetic diallyl derivative of toxiferine. The quaternizing allyl groups actually reduce its potency by a factor of 3 to 5.

Table 29-4 Dose-Response Relationships of Nondepolarizing Neuromuscular Blocking Drugs in Human Subjects

	ED_{50} (mg/kg)	ED_{90} (mg/kg)	ED_{95} (mg/kg)	Reference(s)
Long-Acting				
Pancuronium	0.036 (0.022-0.042)	0.056 (0.044-0.070)	0.067 (0.059-0.080)	103, 107
d-Tubocurarine	0.23 (0.16-0.26)	0.41 (0.27-0.45)	0.48 (0.34-0.56)	107
Intermediate-Acting				
Rocuronium	0.147 (0.069-0.220)	0.268 (0.200-0.419)	0.305 (0.257-0.521)	103, 108-110
Vecuronium	0.027 (0.015-0.031)	0.042 (0.023-0.055)	0.043 (0.037-0.059)	107
Atracurium	0.12 (0.08-0.15)	0.18 (0.19-0.24)	0.21 (0.13-0.28)	107
Cisatracurium	0.026 (0.015-0.031)	—	0.04 (0.032-0.05)	11, 111, 112, 118
Short-Acting				
Mivacurium	0.039 (0.027-0.052)	—	0.067 (0.045-0.081)	9, 113-115
Ultrashort-Acting				
Gantacurium	0.09	—	0.19	106

Data are medians and ranges of reported values. ED_{50}, ED_{90}, and ED_{95} are the doses of each drug that produce, respectively, a 50%, 90%, and 95% decrease in the force of contraction or amplitude of the electromyogram of the adductor pollicis muscle after ulnar nerve stimulation.

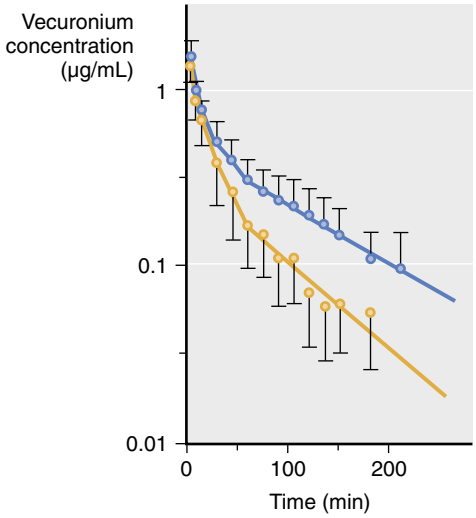


Figure 29-14 Disappearance of vecuronium from plasma after a single bolus dose of 0.2 mg/kg as shown in a semilogarithmic plot of mean concentration versus time for patients with normal hepatic function (*yellow circles*) and cirrhotic patients (*blue circles*). *Error bars* are the standard deviation for that value. *(From Lebrault C, Berger JL, D'Hollander AA, et al: Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) in patients with cirrhosis. Anesthesiology 62:601-605, 1985.)*

central compartment, which includes the plasma volume and the organs of elimination; in the case of neuromuscular blockers, the organs of elimination are the kidneys and liver. The "k" terms are the rate constants for movement of drug between compartments in the direction of the arrows. The peripheral compartments (usually one or two, here represented by V_2 and V_3) can be thought of as the "tissues." The "effect" compartment, which will be discussed later, is the neuromuscular junction. For computational purposes, it has infinitesimal volume and therefore does not influence overall drug distribution. Drug administration and elimination are unidirectional; distribution is bidirectional.

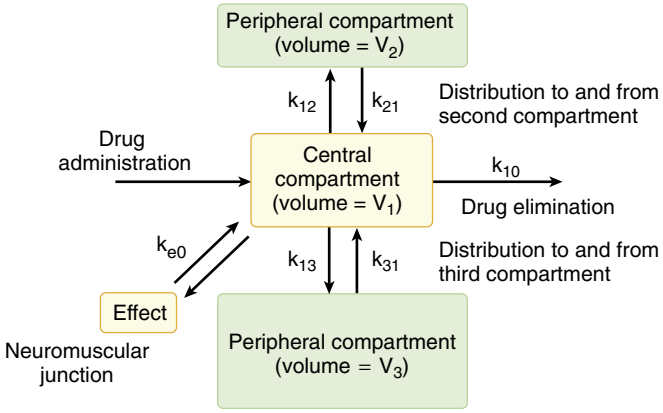


Figure 29-15 Schematic representation of drug disposition into different compartments. These compartments are mathematical concepts only and do not represent real physiologic spaces. The effect compartment in this case would be the neuromuscular junction; for computational purposes, it has infinitesimal volume. The terms k_{nm} are the rate constants for drug movement, in the direction of the *arrow*, between these theoretical compartments. See text for further discussion.

Initially, the drug concentration in the central compartment (i.e., the plasma concentration) will exceed that in the peripheral compartment (i.e., the tissue concentration), and the drug will move from plasma to tissues. Later, as the plasma concentration decreases, it becomes less than the tissue concentration, and the net direction of drug movement is now from tissues to plasma. In general, this conceptual model is appropriate for all the neuromuscular blockers, with the exception of atracurium and cisatracurium, which also undergo elimination (by degradation) from tissues.[123] For simplicity, the following discussion assumes the presence of only one peripheral compartment.

The volume of distribution is the volume to which the drug has distributed when the processes of distribution and elimination are in equilibrium. Elimination is represented by the variable plasma clearance, that is, the volume of plasma from which the drug is irreversibly and completely eliminated per unit time. For most nondepolarizing neuromuscular blockers, the process of distribution is more rapid than the process of elimination, and the initial rapid decline in plasma concentration is due primarily to distribution of the drug to tissues. An exception to this rule is mivacurium, which has such rapid clearance, because of metabolism by butyrylcholinesterase, that elimination is the principal determinant of the initial decline in plasma concentration.

After the initial process of drug distribution to tissues, the plasma concentration falls more slowly (the terminal phase). The rate of decrease in plasma concentration during this terminal phase is often expressed in terms of elimination half-life, which equals the natural logarithm of 2 divided by the rate constant of decline (i.e., the slope of the terminal phase). During this terminal phase, the concentration of drug in the tissue exceeds that in plasma, and the rate of decrease in plasma concentration is determined by two factors: the rate at which drug can move from tissues back into plasma and clearance of drug from plasma. In classic theory for neuromuscular blockers, the drug can move rapidly from tissues into plasma, and its elimination from plasma (i.e., clearance) is the rate-limiting step. For this reason, the terminal portion of the curve is often termed the elimination phase, even though the distribution of drug from tissues into plasma occurs continually throughout. The volume of distribution can also influence the terminal portion of the curve: the greater the volume of distribution, the slower the decline in plasma concentration.

The neuromuscular blockers are polar drugs, and their volume of distribution is classically thought to be limited to a volume roughly equivalent to a portion of the extracellular fluid space, namely, 150 to 450 mL/kg (see Tables 29-13 and 29-14).[124] With this model of drug distribution, the potential rate of drug movement from tissues to plasma exceeds the rate of elimination, and plasma clearance is the process that limits the rate of decline in plasma drug concentration. However, there is evidence that neuromuscular blockers are distributed more widely into tissues with low blood flow (e.g., connective tissue),[125] and the true volume of distribution of dTc has been estimated to be as high as 3.4 L/kg and its elimination half-life as long as 40 hours (compare with values in Tables 29-13 and 29-14).[126] Because the rate of drug movement from such tissues is less than that of plasma clearance, this becomes the limiting step in the rate of decline in plasma drug concentration. This phase becomes obvious only when drug is administered for many days or when sampling is continued for 24 to 96 hours after drug administration. In normal operating room use of neuromuscular blockers, the amount of drug that is

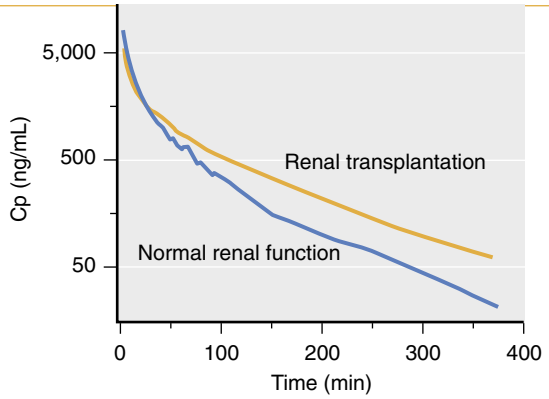


Figure 29-16 "Average" plasma concentration (Cp) versus time after a dose of 0.6 mg/kg rocuronium in patients with normal renal function (*blue line*) or patients undergoing renal transplantation (*yellow line*). *(From Szenohradszky J, Fisher DM, Segredo V, et al: Pharmacokinetics of rocuronium bromide (ORG 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. Anesthesiology 77:899-904, 1992.)*

distributed to this compartment does not affect clinical response to the drug. In conditions in which clearance of the neuromuscular blocker is reduced, such as renal or hepatic disease, the terminal portion of the plasma concentration-versus-time curve is most affected (see Fig. 29-14).[127] The rate of decline in plasma concentration is slowed, and recovery from paralysis is potentially delayed.[127] In conditions associated with an increased volume of distribution, such as renal or hepatic disease, early plasma concentrations of drug may be less than those observed when organ function is normal: with a greater volume of distribution, the plasma concentration should be less, whereas the total amount of a drug would be greater (Fig. 29-16). Decreased protein binding of a drug results in a larger distribution volume, but because the degree of protein binding of neuromuscular blockers is small, changes in protein binding will have minimal effect on their distribution.[128]

Recovery of neuromuscular function takes place as plasma concentrations decline, and the greater part of this decrease occurs primarily because of distribution. Thus, processes that primarily affect elimination of the drug, such as renal failure, may not be associated with prolonged duration of blockade.[129,130] However, as recovery comes to rely more on drug elimination than on distribution (i.e., from 25% to 75% or greater) or after the administration of larger or repeated doses, the duration of action may be prolonged.[123,131]

After the injection of a neuromuscular blocker, the plasma drug concentration immediately starts to decrease. The effect (neuromuscular blockade) takes approximately 1 minute to begin, increases initially, and does not start to recover for many more minutes despite the continually decreasing plasma concentration of drug. This discrepancy between plasma concentration and drug effect occurs because the action of neuromuscular blockers is not in plasma but at the neuromuscular junction. To produce paralysis, the drug must diffuse from plasma into the neuromuscular junction, and the effect is terminated later by diffusion of drug back into plasma (see Fig. 29-15). Thus, concentrations at the neuromuscular junction lag behind those in plasma, and they are lower during the onset of blockade and greater during recovery. The plasma concentration-effect relationship exhibits hysteresis; that is, for a given level of blockade, plasma concentrations are greater during onset than during recovery. For this reason, a concentration-effect relationship cannot be obtained simply by directly relating the plasma concentration to the level of neuromuscular blockade.

To overcome this problem, pharmacodynamic models have been developed to incorporate a factor for the delay caused by diffusion of drug to and from the neuromuscular junction.[84,120,132-143] This factor, k_{e0}, is the rate constant for equilibration of drug between plasma and the neuromuscular junction. By measuring plasma drug concentrations and neuromuscular blockade during both the onset and recovery phases and using the technique of simultaneous pharmacokinetic/pharmacodynamic modeling, it is possible to collapse the hysteresis in the plasma concentration-effect curve, estimate actual drug concentrations at the neuromuscular junction, and derive true concentration-effect relationships (Ce_{50} and k_{e0}) for the neuromuscular blockers (Table 29-5).[120]

Clinical Management

Neuromuscular blockers are used mainly to facilitate tracheal intubation and provide surgical relaxation. The intensity of neuromuscular blockade required varies with the surgical procedure. Important safety issues arise with the use of neuromuscular blockers: cardiovascular and respiratory side effects and the adequacy of recovery to normal neuromuscular function.

Several clinical alternatives to neuromuscular blockers are available that provide adequate surgical relaxation. It is important to keep them all in mind to avoid relying only on neuromuscular blockade to achieve a desired degree of relaxation. Such options include adjustment of the depth of general anesthesia, the use of regional anesthesia, proper positioning of the patient on the operating table, and proper adjustment of the depth of neuromuscular blockade. The choice of one or several of these options is determined by the estimated remaining duration of surgery, the anesthetic technique, and the surgical maneuver required.

Dosage

General Dosage Guidelines

It is important to select the proper dosage of a nondepolarizing neuromuscular blocker to ensure that the desired effect is achieved without overdosage (Tables 29-6 and 29-7). In addition to general knowledge of the guidelines, precise practice requires the use of a peripheral nerve stimulator to adjust the relaxant dosage for the individual patient. Overdosage must be avoided for two reasons: to limit the duration of drug effect to match the anticipated length of surgery and to avoid unwanted cardiovascular side effects.

Initial and Maintenance Dosage

The initial dose is determined by the purpose of administration. Traditionally, doses used to facilitate tracheal intubation are twice the ED_{95} (this also approximates four times the ED_{50}) (see Table 29-6). If the trachea has already been intubated without the use of a nondepolarizing blocker or with succinylcholine and the purpose is simply to produce surgical relaxation, a dose slightly less than the ED_{95} (see Table 29-7) should be given, with adjustment upward as indicated by responses evoked by peripheral

Table 29-5 Pharmacodynamic Parameters Derived by Simultaneous Pharmacokinetic/Pharmacodynamic Modeling

		Adductor Pollicis		
	Study Group	**Ce_{50}* (ng/mL)**	**k_{e0}† (min^{-1})**	**Reference**
Mivacurium				
Central link		57	0.169	132
Peripheral link		130	0.101	132
Rocuronium	Adult female: Propofol-remifentanil anesthesia, standard model	684	0.329	133
	Recirculatory model	876	0.129	133
	Volunteers: Propofol-fentanyl anesthesia	3510	0.405	134
	Infants	1190	0.25	135
	Children	1650	0.32	135
Cisatracurium, 0.075-3.0 mg/kg	Adults: Propofol-fentanyl anesthesia	126-158	0.07-0.09	135
Atracurium	Infants	363	0.19	137
	Children	444	0.16	137
	Young adults	449	0.13	138
	Elderly adults	436	0.12	138
	Standard model	359	0.12	139
	Threshold model	357	0.12	139
	Young adults	669‡	0.07	140
	Burn patients	2270‡	0.10	140
	No succinylcholine	454‡	0.07	84
	After succinylcholine	305‡	0.09	84
Vecuronium	Young adults	94	—	141
	Young adults	92	0.17	142
	Elderly adults	106	0.17	143
d-Tubocurarine	Normal renal function	370	0.13	120
	Renal failure	380	0.16	120
	Halothane, 0.5%-0.7%	360‡	0.09‡	143§
	Halothane, 1.0%-1.2%	220‡	0.12	143§
	Narcotic anesthesia	600‡	0.15‡	143§
Pancuronium	Young adults	88	—	141

*Ce_{50} is the concentration of each drug at the neuromuscular junction that produces a 50% decrease in the force of contraction or amplitude of the electromyogram of the adductor pollicis muscle after ulnar nerve stimulation.
†k_{e0} is the rate constant for equilibration of drug between plasma and the neuromuscular junction.
‡All groups different from each other.
§k_{e0} values calculated as 0.693/ $t_{½}k_{e0}$.

nerve stimulation. Downward adjustment of the initial dose is necessary in the presence of any of the potent inhaled anesthetics (see the subsection later on drug interactions).

To avoid prolonged residual paralysis, inadequate antagonism of residual blockade, or both, the main goal should be to use the lowest possible dose that will provide adequate relaxation for surgery. Management of individual patients should always be guided by monitoring with a peripheral nerve stimulator. In an adequately anesthetized and monitored patient, there is little reason to completely abolish twitch or TOF responses to peripheral nerve stimulation during maintenance of relaxation. Supplemental (maintenance) doses of neuromuscular blockers should be about one-fourth (in the case of intermediate- and short-acting neuromuscular blockers) to one-tenth (in the case of long-acting neuromuscular blockers) the initial dose and should not be given until there is clear evidence of beginning of recovery from the previous dose.

Maintenance of relaxation by continuous infusion of intermediate- and short-acting drugs can be performed and is useful to keep the relaxation smooth and to rapidly adjust the depth of relaxation according to surgical needs. The depth of blockade in each patient is kept moderate, if possible, to ensure prompt spontaneous recovery or easy reversal at the end of the procedure. Table 29-6 lists the approximate dose ranges that are usually required during infusion to maintain 90% to 95% blockade of the twitch (one twitch visible on TOF stimulation) under nitrous oxide–oxygen anesthesia supplemented with intravenous anesthetics. The infusion dosage is usually decreased by 30% to 50% in the presence of potent inhaled anesthetics.

Neuromuscular Blockers and Tracheal Intubation

The speed of onset of neuromuscular blockade is one of the requirements for rapidly securing the airway, and it is affected by several factors, including the rate of delivery of drug to the

Table 29-6 Guide to Nondepolarizing Relaxant Dosage (mg/kg) with Different Anesthetic Techniques*

	ED_{95} under N_2O/O_2	Dose for Intubation	Supplemental Dose after Intubation	Dosage for Relaxation	
				N_2O	Anesthetic Vapors†
Long-Acting					
Pancuronium	0.07	0.08-0.12	0.02	0.05	0.03
d-Tubocurarine	0.5	0.5-0.6	0.1	0.3	0.15
Intermediate-Acting					
Vecuronium	0.05	0.1-0.2	0.02	0.05	0.03
Atracurium	0.23	0.5-0.6	0.1	0.3	0.15
Cisatracurium	0.05	0.15-0.2	0.02	0.05	0.04
Rocuronium	0.3	0.6-1.0	0.1	0.3	0.15
Short-Acting					
Mivacurium	0.08	0.2-0.25	0.05	0.1	0.08
Continuous Infusion Dosage (μg/kg/min) Required to Maintain 90%-95% Twitch Inhibition under N_2O/O_2 with Intravenous Agents					
Mivacurium	3-15				
Atracurium	4-12				
Cisatracurium	1-2				
Vecuronium	0.8-1.0				
Rocuronium	9-12				

*The suggested dosages provide good intubating conditions under light anesthesia. Satisfactory abdominal relaxation may be achieved at the dosages listed after intubation without a relaxant or with succinylcholine. This table is intended as a general guide to dosage. Individual relaxant requirements should be confirmed with a peripheral nerve stimulator.

†The potentiation of nondepolarizing relaxants by different anesthetic vapors has been reported to vary 20% to 50%. Recent data suggest, however, that this variation may be much less, particularly in the case of intermediate- and short-acting relaxants. Therefore, for the sake of simplicity, this table assumes a potentiation of 40% in the case of all volatile anesthetics.

neuromuscular junction, receptor affinity, plasma clearance, and the mechanism of neuromuscular blockade (depolarizing versus nondepolarizing).[101,155,156] The speed of onset is inversely proportional to the potency of nondepolarizing neuromuscular blockers.[101,155] A high ED_{95} (i.e., low potency) is predictive of rapid onset of effect and vice versa (Fig. 29-17; Table 29-7). Except for atracurium,[157] the molar potency (the ED_{50} or ED_{95} expressed as μM/kg) is highly predictive of a drug's initial rate of onset of effect (at the adductor pollicis).[155] A drug's measured molar potency is the end result of many contributing factors: the drug's intrinsic potency (Ce_{50}—the biophase concentration resulting in 50% twitch depression), the rate of equilibration between plasma and the biophase (k_{e0}), the initial rate of plasma clearance, and probably other factors as well.[158] Rocuronium has a molar potency (ED_{95}) of 0.54 μM/kg, which is about 13% that of vecuronium and only 9% that of cisatracurium. Thus, rapid onset of rocuronium's effect (at the adductor pollicis) is not unexpected.

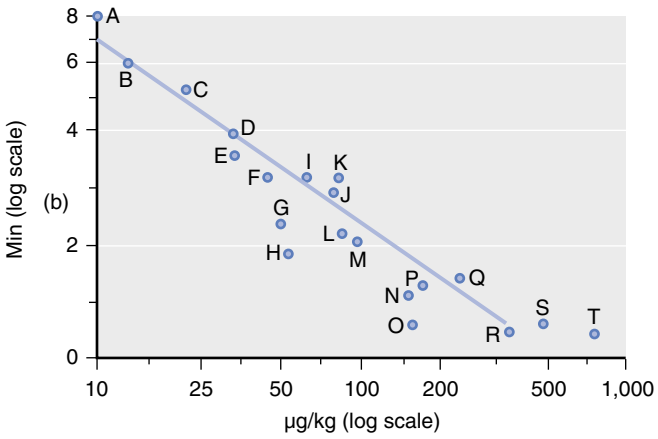


Figure 29-17 Linear regression of the onset of neuromuscular blockade (ordinate) versus potency of a series of steroidal relaxants studied in the cat model by Bowman and colleagues.[101] The data show that onset may be increased in compounds of low potency and encouraged the eventual development of rocuronium and rapacuronium (ORG 9487). A, pipecuronium; C, pancuronium; D, vecuronium.

Donati and Meistelman[156] proposed a model to explain this inverse potency-onset relationship. Nondepolarizing neuromuscular blockers of low potency (e.g., rocuronium) have more molecules to diffuse from the central compartment into the effect compartment. Once in the effect compartment, all molecules act promptly. Weaker binding of the low-potency drugs to receptors prevents buffered diffusion,[156] a process that occurs with more potent drugs. Buffered diffusion causes repetitive binding and unbinding to receptors, which keeps potent drugs in the neighborhood of the effector sites and potentially lengthens the duration of effect.

The times to 95% blockade at the adductor pollicis after administration of the ED_{95} dose of succinylcholine, rocuronium, vecuronium, atracurium, mivacurium, and cisatracurium are shown in Figure 29-18.[117,155,157] This illustration shows that the most potent compound, cisatracurium, has the slowest onset and that the least potent compound, rocuronium, has the most rapid onset.[117,155,157] Bevan[159] also proposed that rapid plasma clearance is associated with a rapid onset of action. The fast onset of succinylcholine's action is related to its rapid metabolism and plasma clearance.

Table 29-7 Pharmacodynamic Effects of Succinylcholine and Nondepolarizing Neuromuscular Blockers

	Anesthesia	Intubating Dose (mg/kg)	Approximate ED_{95} Multiples	Maximum Block (%)	Time to Maximum Block (min)	Clinical Duration* (min)	Reference
Succinylcholine	Narcotic or halothane	0.5	1.7	100	—	6.7	144
Succinylcholine	Desflurane	0.6	2	100	1.4	7.6	145
Succinylcholine	Narcotic or halothane	1.0	2	100	—	11.3	144
Succinylcholine	Desflurane	1.0	3	100	1.2	9.3	145
Succinylcholine	Narcotic	1.0	3	—	1.1	8	146
Succinylcholine	Narcotic	1.0	3	—	1.1	9	147
Succinylcholine	Isoflurane	1.0	3	100	0.8	9	148
Steroidal Compounds							
Rocuronium	Narcotic	0.6	2	100	1.7	36	149
Rocuronium	Isoflurane	0.6	2	100	1.5	37	148
Rocuronium	Isoflurane	0.9	3	100	1.3	53	148
Rocuronium	Isoflurane	1.2	4	100	0.9	73	148
Vecuronium	Isoflurane	0.1	2	100	2.4	41	148
Vecuronium	Narcotic	0.1	2	100	2.4	44	150
Pancuronium	Narcotic	0.08	1.3	100	2.9	86	151
Pancuronium	Narcotic	0.1	1.7	99	4	100	152
Benzylisoquinolinium Compounds							
Mivacurium	Narcotic	0.15	2	100	3.3	16.8	9
Mivacurium	Narcotic	0.15	2	100	3	14.5	149
Mivacurium	Halothane	0.15	2	100	2.8	18.6	153
Mivacurium	Narcotic	0.2	2.6	100	2.5	19.7	9
Mivacurium	Narcotic	0.25	3.3	100	2.3	20.3	9
Mivacurium	Narcotic	0.25	3.3	—	2.1	21	147
Atracurium	Narcotic	0.5	2	100	3.2	46	11
Cisatracurium	Narcotic	0.1	2	99	7.7	46	154
Cisatracurium	Narcotic	0.1	2	100	5.2	45	11
Cisatracurium	Narcotic	0.2	4	100	2.7	68	11
Cisatracurium	Narcotic	0.4	8	100	1.9	91	11
d-Tubocurarine	Narcotic	0.6	1.2	97	5.7	81	152

For atracurium and mivacurium, slower injection (30 seconds) is recommended to minimize circulatory effects.
*Time from injection of the intubating dose to recovery of twitch to 25% of control.

The onset of neuromuscular blockade is much more rapid in the muscles that are relevant to obtaining optimal intubating conditions (laryngeal adductors, diaphragm, and masseter) than in the muscle that is typically monitored (adductor pollicis) (see Fig. 29-4).[160] Thus, neuromuscular blockade develops faster, lasts a shorter time, and recovers more quickly in these muscles (Table 29-8).[26,160-163] These observations may seem contradictory because there is also convincing evidence that the median effective concentration (EC_{50}) for almost all drugs studied is between 50% and 100% higher at the diaphragm or larynx than it is at the adductor pollicis. Fisher and coworkers[164] explain this apparent contradiction by postulating more rapid equilibration (shorter $t_{½}k_{e0}$) between plasma and the effect compartment at these central muscles. This accelerated rate of equilibrium probably represents little more than differences in regional blood flow. Therefore, muscle blood flow rather than the drug's intrinsic potency may be more important in determining the onset and offset time of nondepolarizing neuromuscular blockers. More luxuriant blood flow (greater blood flow per gram of muscle) at the diaphragm or larynx would result in delivery of a higher peak plasma concentration of drug to the central muscle in the brief period before rapid redistribution is well under way.

Onset of blockade occurs 1 to 2 minutes earlier in the larynx than at the adductor pollicis after the administration of nondepolarizing neuromuscular blocking agents. The pattern of blockade (onset, depth, and speed of recovery) in the orbicularis oculi is similar to that in the larynx.[165] By monitoring the onset of neuromuscular blockade at the orbicularis oculi, one can predict the quality of intubating conditions. The onset of maximal blockade in the larynx also corresponds to the point at which the adductor pollicis begins to show palpable evidence of weakening. Furthermore, the return of thumb responses to normal suggests that the efferent muscular arc of the protective airway reflexes is intact.

Rapid Tracheal Intubation

Succinylcholine remains the drug of choice when rapid tracheal intubation is needed because it consistently provides muscle relaxation within 60 to 90 seconds. When succinylcholine is considered undesirable or contraindicated, the onset of action of

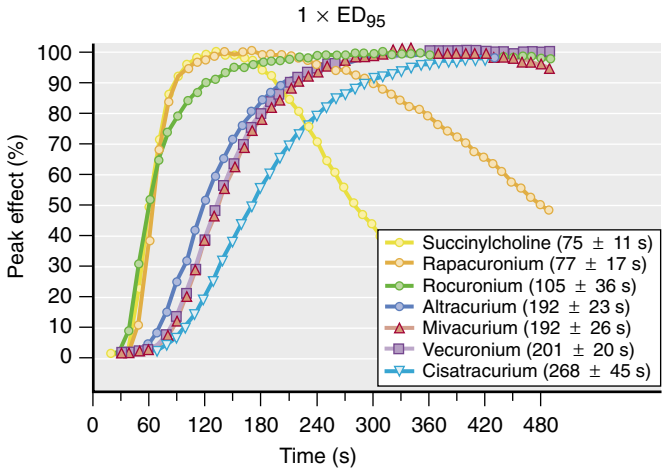


Figure 29-18 Percentages of peak effect after an ED_{95} of succinylcholine, rocuronium, rapacuronium, vecuronium, atracurium, mivacurium, and cisatracurium at the adductor pollicis muscle. Times (mean ± SD) in seconds to 95% of peak effect are shown in parentheses. *(Data from Kopman AF, Klewicka MM, Ghori K, et al: Dose-response and onset/offset characteristics of rapacuronium. Anesthesiology 93:1017-1021, 2000; Kopman AF, Klewicka MM, Kopman DJ, Neuman GG: Molar potency is predictive of the speed of onset of neuromuscular block for agents of intermediate, short, and ultrashort duration. Anesthesiology 90:425-431, 1999; and Kopman AF, Klewicka MM, Neuman GG: Molar potency is not predictive of the speed of onset of atracurium. Anesth Analg 89:1046-1049, 1999.)*

nondepolarizing neuromuscular blocking drugs can be accelerated by preceding the intubating dose with a priming dose of neuromuscular blocker,[166] by using high doses of an individual agent,[148] or by using combinations of neuromuscular blockers.[149] Although some combinations of mivacurium and rocuronium can achieve rapid onset without undue prolongation of action and without undesirable side effects,[149] combination therapy may not consistently result in rapid onset of effect.

The Priming Technique. Since the introduction of rocuronium, the use of priming has decreased considerably. Several groups of investigators have recommended that a small subparalyzing dose of the nondepolarizer (about 20% of the ED_{95} or about 10% of the intubating dose) be given 2 to 4 minutes before a large second dose for tracheal intubation.[166] This procedure, termed priming, has been shown to accelerate the onset of blockade for most nondepolarizing neuromuscular blockers by 30 to 60 seconds, which means that intubation can be performed within approximately 90 seconds of the second dose. However, the intubating conditions that occur after priming do not match those that occur after succinylcholine. Moreover, priming carries the risks of aspiration and difficulty swallowing, and the visual disturbances associated with subtle degrees of blockade are uncomfortable for the patient.[167]

The High-Dose Regimen for Rapid Tracheal Intubation. Larger doses of neuromuscular blockers are usually recommended when intubation must be accomplished in less than 90 seconds. High-dose regimens, however, are associated with a considerably prolonged duration of action and potentially increased cardiovascular side effects (see Table 29-7).[148,168] Increasing the dosage of rocuronium from 0.6 mg/kg (twice the ED_{95}) to 1.2 mg/kg (four times the ED_{95}) shortened the onset time of complete neuromuscular blockade from 89 ± 33 seconds (mean ± SD) to 55 ± 14 seconds but significantly prolonged the clinical duration (i.e., recovery of the first twitch of TOF [T1] to 25% of baseline) from 37 ± 15 minutes to 73 ± 32 minutes.[148]

Whatever technique of rapid-sequence induction of anesthesia and intubation is elected, the following four principles are important: (1) preoxygenation must be performed, (2) sufficient doses of intravenous drugs must be administered to ensure that the patient is adequately anesthetized, (3) intubation within 60 to 90 seconds must be considered acceptable, and (4) cricoid pressure should be applied subsequent to injection of the induction agent.

Low-Dose Relaxants for Tracheal Intubation

The low-dose technique is not suitable for rapid-sequence induction, but several studies have demonstrated that low doses of neuromuscular blocking drugs can be used for routine tracheal intubation. The use of low doses of neuromuscular blockers has advantages: (1) it shortens the time to recovery from

Table 29-8 Time Course of Action and Peak Effect at the Laryngeal Adductors and Adductor Pollicis

		Laryngeal Adductors			Adductor Pollicis			
Dose (mg/kg)	Anesthesia	Onset Time (sec)	Maximum Block (% Depression)	Clinical Duration (min)	Onset Time (sec)	Maximum Block (% Depression)	Clinical Duration (min)	Reference
Succinylcholine, 1.0	Propofol-fentanyl	34 ± 12	100 ± 0	4.3 ± 1.6	56 ± 15	100 ± 0	8 ± 2	161
Rocuronium, 0.25	Propofol-fentanyl	96 ± 6	37 ± 8	—	180 ± 18	69 ± 8	—	160
Rocuronium, 0.4	Propofol-fentanyl	92 ± 29	70 ± 15	—	155 ± 40	99 ± 3	24 ± 7	161
Rocuronium, 0.5	Propofol-fentanyl	84 ± 6	77 ± 5	8 ± 3	144 ± 12	98 ± 1	22 ± 3	160
Vecuronium, 0.04	Propofol-fentanyl	198 ± 6	55 ± 8	—	342 ± 12	89 ± 3	11 ± 2	26
Vecuronium, 0.07	Propofol-fentanyl	198 ± 12	88 ± 4	9 ± 2	342 ± 18	98 ± 1	22 ± 2	26
Mivacurium, 0.14	Propofol- alfentanil	137 ± 20	90 ± 7	5.7 ± 2.1	201 ± 59	99 ± 1	16.2 ± 4.6	162
Mivacurium, 0.2 mg	Propofol- alfentanil	89 ± 26	99 ± 4	10.4 ± 1.5	202 ± 45	99 ± 2	20.5 ± 3.9	163

Clinical duration is the time until T1 recovers to 25% of its control value. Values are means ± SD[161-163] or SEM.[26,160]

neuromuscular blockade and (2) it reduces the requirement for anticholinesterase drugs. Rocuronium has the shortest onset time of all the nondepolarizing neuromuscular blocking agents currently available.[160,161] The maximal effect of either 0.25 or 0.5 mg/kg of rocuronium at the laryngeal muscles occurs after 1.5 minutes.[160] This interval is shorter than the 3.3 minutes reported after the administration of equipotent doses of vecuronium (0.04 or 0.07 mg/kg)[26] and only slightly more than the 0.9 minute reported after 0.25 or 0.5 mg/kg of succinylcholine (see Table 29-8).[169]

With a better understanding of the multiple factors that contribute to satisfactory conditions for intubation, it is now possible to take full advantage of the onset profile for rocuronium. Intubating conditions are related more closely to the degree of neuromuscular blockade of the laryngeal adductor muscles than to the degree of blockade typically monitored at the adductor pollicis. Figure 29-19 demonstrates this principle.[158] Complete blockade at the larynx, diaphragm, or both may not be a prerequisite for satisfactory tracheal intubating conditions.

Kopman and associates[171] noted that 0.5 mg/kg of rocuronium (1.5 times the ED_{95}) provided very satisfactory conditions for intubation (25 intubations were rated excellent and 5 were rated good) in patients anesthetized with 12.5 µg/kg of alfentanil and 2.0 mg/kg of propofol if laryngoscopy were delayed for 75 seconds after drug administration. They estimated that 1.5 times the ED_{95} of rocuronium will produce at least 95% blockade in 98% of the population.[171] A similar or lower multiple of rocuronium's ED_{95} was shown to have a more rapid onset and shorter duration of action than atracurium[172] or cisatracurium.[112] The onset of cisatracurium's effect is too slow to provide good conditions for intubation in less than 2 minutes, even after a dose twice the ED_{95}.

In the vast majority of patients receiving 15 µg/kg of alfentanil followed by 2.0 mg/kg of propofol and 0.45 mg/kg of rocuronium, good to excellent conditions for intubation will be present 75 to 90 seconds after the completion of drug administration.

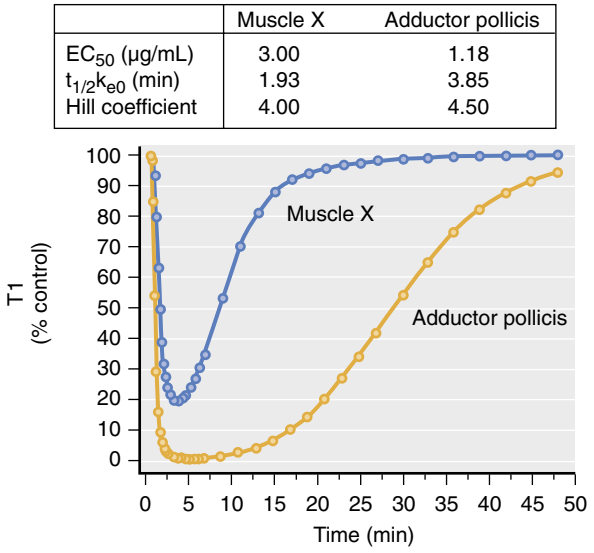


Figure 29-19 Computer simulation based on Sheiner's model[120] and data reported by Wierda and colleagues.[170] The ED_{95} of rocuronium at the adductor pollicis from this model is 0.33 mg/kg. Rocuronium, 0.45 mg/kg, is given as a bolus at time zero. Muscle X represents a muscle (such as the diaphragm or the laryngeal adductors) that is less sensitive to the effects of nondepolarizing relaxants than the adductor pollicis but has greater blood flow. In this example, the concentration of rocuronium producing a 50% block (EC_{50}) of muscle X is 2.5 times that of the adductor pollicis, but the half-life of transport between plasma and the effect compartment ($t_{1/2}k_{e0}$) of muscle X is only half as long. The rapid equilibration between plasma concentrations of rocuronium and muscle X results in more rapid onset of blockade of muscle X than the adductor pollicis. The greater EC_{50} at muscle X explains the faster recovery of this muscle than of the adductor pollicis from neuromuscular blockade. Lower blood concentrations of rocuronium must be achieved at the adductor pollicis than at muscle X before recovery begins. *(From Naguib M, Kopman AF: Low dose rocuronium for tracheal intubation. Middle East J Anesthesiol 17:193-204, 2003.)*

Metabolism and Elimination

The specific pathways of the metabolism (biotransformation) and elimination of neuromuscular blocking drugs are summarized in Table 29-9. Of the nondepolarizing neuromuscular blockers listed, pancuronium, pipecuronium, vecuronium, atracurium, cisatracurium, and mivacurium are the only ones that are metabolized or degraded. Nearly all nondepolarizing neuromuscular blocker molecules contain ester linkages, acetyl ester groups, and hydroxy or methoxy groups. These substitutions, especially the quaternary nitrogen groups, confer a high degree of water solubility with only slight lipid solubility. The hydrophilic nature of relaxant molecules enables easy elimination in urine by glomerular filtration, with no tubular resorption or secretion. Therefore, all nondepolarizing neuromuscular blockers show elimination of the parent molecule in urine as the basic route of elimination; those with a long duration of action thus have a clearance rate that is limited by the glomerular filtration rate (1 to 2 mL/kg/min).

Steroidal Compounds

Long-Acting Neuromuscular Blockers. Pancuronium is cleared largely by the kidney.[173] Its hepatic uptake is limited. A small amount (15% to 20%) is deacetylated at the 3-position in the liver, but this makes a minimal contribution to the total clearance. Deacetylation also occurs at the 17-position, but to such a small extent that it is clinically irrelevant. The three known metabolites have been studied individually in anesthetized humans.[151] The 3-OH metabolite is the most potent of the three, being approximately half as potent as pancuronium, and is the only one present in detectable concentrations in plasma. This metabolite has pharmacokinetics and a duration of action similar to those of pancuronium.[151] In addition, the 3-OH metabolite is most likely excreted largely by the kidney.[151] The parent compound and the 3-OH metabolite are also cleared in small amounts via a minor liver pathway. Total clearance is delayed, and the duration of action is significantly lengthened by severe disorders of renal or hepatic function.[129,174,175]

Intermediate-Acting Neuromuscular Blockers. Vecuronium, the 2-desmethyl derivative of pancuronium, is more lipid soluble than pancuronium because of absence of the quaternizing methyl group at the 2-position. It undergoes two to three times more metabolism than pancuronium does. Vecuronium is taken up into the liver by a carrier-mediated transport system[176] and then deacetylated at the 3-position by liver microsomes. About 12% of clearance of vecuronium occurs by conversion to 3-desacetylvecuronium,[177] and 30% to 40% is cleared in

Table 29-9 Metabolism and Elimination of Neuromuscular Blocking Drugs

Drug	Duration	Metabolism (%)	Elimination		Metabolites
			Kidney (%)	Liver (%)	
Succinylcholine	Ultrashort	Butyrylcholinesterase (98%-99%)	<2%	None	Monoester (succinyl monocholine) and choline; monoester metabolized much more slowly than succinylcholine
Gantacurium	Ultrashort	Cysteine (fast) and ester hydrolysis (slow)	?	?	Inactive cysteine adduction product, chloroformate monoester, and alcohol
Mivacurium	Short	Butyrylcholinesterase (95%-99%)	<5% (Metabolites eliminated in urine and bile)	None	Monoester and quaternary alcohol. The metabolites are inactive. They are most likely not themselves metabolized any further.
Atracurium	Intermediate	Hofmann elimination and nonspecific ester hydrolysis (60%-90%)	10%-40% (Metabolites eliminated in urine and bile)	None	Laudanosine, acrylates, alcohols, and acids. Although laudanosine has CNS-stimulating properties, the clinical relevance of this effect is negligible.
Cisatracurium	Intermediate	Hofmann elimination (77%?)	Renal clearance is 16% of total		Laudanosine and acrylates. Ester hydrolysis of the quaternary monoacrylate occurs secondarily. Because of the greater potency of cisatracurium, laudanosine quantities produced by Hofmann elimination are 5 to 10 times lower than in the case of atracurium, thus making this not an issue in practice.
Vecuronium	Intermediate	Liver (30%-40%)	40%-50% (Metabolites excreted in urine and bile, ≈40%)	50%-60%	The 3-OH metabolite accumulates, particularly in renal failure. It has about 80% the potency of vecuronium and may be responsible for delayed recovery in ICU patients.
Rocuronium	Intermediate	None	10%-25%	>70%	None
Pancuronium	Long	Liver (10%-20%)	85%	15%	The 3-OH metabolite may accumulate, particularly in renal failure. It is about two thirds as potent as the parent compound.
d-Tubocurarine	Long	None	80% (?)	20%	None

CNS, central nervous system; ICU, intensive care unit.

bile as parent compound.[127] Although the liver is the principal organ of elimination for vecuronium, the drug also undergoes significant (up to 25%) renal excretion, and this combined organ elimination gives it a clearance rate of 3 to 6 mL/kg/min.[177,178]

The principal metabolite of vecuronium, 3-desacetylvecuronium, is a potent (~80% of vecuronium) neuromuscular blocking drug in its own right. The metabolite, though, has slower plasma clearance and a longer duration of action than vecuronium does.[177] 3-Desacetylvecuronium has a clearance rate of 3.5 mL/kg/min, and renal clearance accounts for approximately a sixth of its elimination.[177] In patients in the ICU with renal failure, 3-desacetylvecuronium can accumulate and produce prolonged neuromuscular blockade.[179] Other putative metabolites are 17-desacetylvecuronium and 3,17-bisdesacetylvecuronium, neither of which occurs in clinically significant amounts.

Rocuronium is eliminated primarily by the liver, with a small fraction (~10%) eliminated in urine.[180] It is taken up into the liver by a carrier-mediated active transport system.[181] The putative metabolite, 17-desacetylrocuronium, has not been detected in significant quantities.

Benzylisoquinolinium Compounds

Short-Acting Neuromuscular Blockers. Mivacurium is hydrolyzed in plasma by butyrylcholinesterase to a monoester and an amino alcohol,[9] which are excreted in urine and bile. The metabolites are positively charged, thus making their entry into the central nervous system (CNS) unlikely. They show less than 1% of the neuromuscular blocking activity of the parent compound and do not affect the autonomic nervous system. Less than 5% is excreted in urine as the parent compound.

Mivacurium consists of three stereoisomers, and clearance rates for the two most pharmacologically active isomers, *cis-trans* and *trans-trans*, are approximately 100 and 50 to 70 mL/kg/min,

respectively.[99,182,183] These two isomers show elimination half-lives of 2 to 3 minutes.[99] The third stereoisomer, *cis-cis*, is present as only 4% to 8% of the mivacurium mixture and has less than 10% of the neuromuscular blocking potency of the other two isomers.[99] Consequently, even though it has a much longer elimination half-life (55 minutes) and lower clearance (~4 mL/kg/min) than the two other isomers, it does not contribute significantly to the duration of action of mivacurium.[99] This rapid enzymatic clearance of mivacurium accounts for its short duration of action,[9,99] which is much shorter than that of vecuronium and atracurium but about twice that of succinylcholine.[184] When butyrylcholinesterase activity is severely deficient, however, such as in the rare patients (1/3000) who are homozygous for genetically atypical enzymes, the duration of action of mivacurium is prolonged for up to several hours.[185-188]

Intermediate-Acting Neuromuscular Blockers. Theoretically, atracurium is metabolized by two pathways: Hofmann elimination and ester hydrolysis by nonspecific esterases. Hofmann elimination is a purely chemical process that results in loss of the positive charges by molecular fragmentation to laudanosine (a tertiary amine) and a monoquaternary acrylate, compounds that were thought to have no neuromuscular and little or no cardiovascular activity of clinical relevance.[189] Under the proper chemical conditions, however, these breakdown products may actually be used to synthesize the parent compound.

Because it undergoes Hofmann elimination, atracurium is relatively stable at pH 3.0 and 4°C and becomes unstable when injected into the bloodstream. Early observations of breakdown of the drug in buffer and plasma showed faster degradation in plasma, thus suggesting possible enzymatic hydrolysis of the ester groups. Further evidence suggested that this second pathway, ester hydrolysis, may be more important than originally realized in the breakdown of atracurium.[190] By pharmacokinetic analysis, Fisher and colleagues[191] concluded that a significant amount of clearance of atracurium may be accomplished by routes other than ester hydrolysis and Hofmann elimination. Hence, it appears that atracurium's metabolism is complicated and may not be completely understood.[191]

Laudanosine, a metabolite of atracurium, has CNS-stimulating properties. Unlike atracurium, laudanosine is dependent on the liver and kidney for its elimination and has a long elimination half-life.[192] Laudanosine concentrations are elevated in patients with liver disease[193] and those who have received atracurium for many hours in an ICU.[194] Laudanosine freely crosses the blood-brain barrier.[192] Beemer and coworkers[195] found that patients awakened at a 20% higher arterial concentration of thiopental when atracurium had been given; this was attributed to the CNS-stimulatory effect of laudanosine. These relatively low concentrations of laudanosine, however, did not influence an animal model of epilepsy[196] or lidocaine-induced seizures.[197] In the ICU, blood levels of laudanosine can be as high as 5.0 to 6.0 µg/mL.[186] Though not known in humans, the seizure threshold in animals ranges from 5.0 µg/mL in rabbits[198] to 17 µg/mL in dogs.[199] Thus, adverse effects are unlikely to occur with the use of atracurium in the operating room or ICU.

Laudanosine also has cardiovascular effects. In dogs, hypotension occurs at a blood concentration of about 6 µg/mL,[199] a level higher than that usually found in patients in the ICU. However, there is one case report of a patient who experienced severe hypotension and bradycardia while receiving atracurium, which resolved only when vecuronium was substituted.[200] Laudanosine enhances the stimulation-evoked release of norepinephrine,[201] a finding that may also partly account for its CNS-stimulating effect.

Atracurium is a mixture of 10 optical isomers. Cisatracurium is the 1R *cis*–1′R *cis* isomer of atracurium.[95] Like atracurium, cisatracurium is metabolized by Hofmann elimination to laudanosine and a monoquaternary acrylate.[202,203] In contrast, however, there is no ester hydrolysis of the parent molecule. Hofmann elimination accounts for 77% of the total clearance of 5 to 6 mL/kg/min. Twenty-three percent of the drug is cleared through organ-dependent means, with renal elimination accounting for 16% of this figure.[203] Because cisatracurium is about four or five times as potent as atracurium, about five times less laudanosine is produced, and accumulation of this metabolite is not thought to be of any consequence in clinical practice.

Long-Acting Neuromuscular Blockers. With these agents, there is no active metabolism of dTc. The kidney is the major pathway of elimination, with approximately 50% of a dose being eliminated through renal pathways. The liver is probably a secondary route of elimination. Therefore and because more suitable agents are available, these drugs are not indicated for use in patients with either renal[130] or hepatic failure.

Asymmetric Mixed-Onium Chlorofumarates (Gantacurium)

Gantacurium appears to be degraded by two chemical mechanisms, neither of which is enzymatic: (1) rapid formation of an apparently inactive cysteine adduction product, with cysteine replacing chlorine, and (2) slower hydrolysis of the ester bond adjacent to the chlorine substitution, presumably to inactive hydrolysis products (see Fig. 29-10).[105]

In summary, the only short-acting neuromuscular blocker currently available for clinical use, mivacurium, is cleared rapidly and almost exclusively via metabolism by butyrylcholinesterase, which results in much greater plasma clearance than with any other nondepolarizing neuromuscular blocker.[9] Neuromuscular blockers of intermediate duration, such as vecuronium, rocuronium, atracurium, and cisatracurium, have clearance rates in the range of 3 to 6 mL/kg/min because of multiple pathways of degradation, metabolism, and elimination. Atracurium is cleared two to three times more rapidly than the long-acting drugs.[123,193,204,205] Similar clearance values have been obtained for rocuronium[206-210] and cisatracurium.[202,203,211] Finally, the long-acting neuromuscular blockers undergo minimal or no metabolism, and they are eliminated largely unchanged, mostly by renal excretion. Hepatic pathways are less important in their metabolism.

Adverse Effects of Neuromuscular Blockers

Neuromuscular blocking agents seem to play a prominent role in the incidence of adverse reactions that occur during anesthesia. The Committee on Safety of Medicines in the United Kingdom reported that 10.8% (218 of 2014) of adverse drug reactions and 7.3% of deaths (21 of 286) were attributable to neuromuscular blocking drugs.[212]

Autonomic Effects

Neuromuscular blocking agents may interact with nicotinic and muscarinic cholinergic receptors within the sympathetic and

Table 29-10 Approximate Autonomic Margins of Safety of Nondepolarizing Neuromuscular Blockers*

Drug	Vagus†	Sympathetic Ganglia†	Histamine Release‡
Benzylisoquinolinium Compounds			
Mivacurium	>50	>100	3.0
Atracurium	16	40	2.5
Cisatracurium	>50	>50	None
d-Tubocurarine	0.6	2.0	0.6
Steroidal Compounds			
Vecuronium	20	>250	None
Rocuronium	3.0-5.0	>10	None
Pancuronium	3.0	>250	None

*Number of multiples of the ED_{95} for neuromuscular blockade required to produce the autonomic side effect (ED_{50}).
†In the cat.
‡In human subjects.

parasympathetic nervous systems and with nicotinic receptors at the neuromuscular junction.

Dose-response ratios to compare the neuromuscular blocking potencies of these agents (the ED_{95}) with their potencies in blocking vagal (parasympathetic) or sympathetic ganglionic transmission (the ED_{50}) can be constructed (Table 29-10). These ratios are termed the autonomic margin of safety of the relaxant in question. The higher the dose ratio, the lower the likelihood of or the greater the safety ratio for the occurrence of the particular autonomic effect. The side effect is considered absent (none) in clinical practice if the safety ratio is greater than 5; it is weak or slight if the safety ratio is 3 or 4, moderate if 2 or 3, and strong or prominent if the ratio is 1 or less.

These autonomic responses are not reduced by slower injection of the relaxant. They are dose related and additive over time if divided doses are given. If identical to the original dose, subsequent doses will produce a similar response; that is, no tachyphylaxis will occur. This is not the case, however, when the side effect of histamine release is in question. Cardiovascular responses secondary to histamine release are decreased by slowing the injection rate, and the response undergoes rapid tachyphylaxis. The autonomic effects of neuromuscular blocking drugs are summarized in Table 29-11.

Table 29-11 Clinical Autonomic Effects of Neuromuscular Blocking Drugs

Drug	Autonomic Ganglia	Cardiac Muscarinic Receptors	Histamine Release
Depolarizing Substance			
Succinylcholine	Stimulates	Stimulates	Slight
Benzylisoquinolinium Compounds			
Mivacurium	None	None	Slight
Atracurium	None	None	Slight
Cisatracurium	None	None	None
d-Tubocurarine	Blocks	None	Moderate
Steroidal Compounds			
Vecuronium	None	None	None
Rocuronium	None	Blocks weakly	None
Pancuronium	None	Blocks moderately	None

Histamine Release. Quaternary ammonium compounds such as neuromuscular blockers are generally weaker histamine-releasing substances than tertiary amines such as morphine are. Nevertheless, when large doses of certain neuromuscular blockers are administered rapidly, erythema of the face, neck, and upper part of the torso may develop, as well as a brief decrease in arterial pressure and a slight to moderate increase in heart rate. Bronchospasm in this setting is very rare. The clinical effects of histamine are seen when plasma concentrations increase to 200% to 300% of baseline values, and these effects involve chemical displacement of the contents of mast cell granules containing histamine, prostaglandin, and possibly other vasoactive substances.[213] The serosal mast cell, located in the skin and connective tissue and near blood vessels and nerves, is principally involved in the degranulation process.[213]

The side effect of histamine release is most often noted after administration of the benzylisoquinolinium class of muscle relaxants, although it has also been noted with steroidal relaxants of low potency. The effect is usually of short duration (1 to 5 minutes), is dose related, and is clinically insignificant in healthy patients. Hatano and associates[214] showed that the hypotensive cardiovascular response to 0.6 mg/kg of dTc in humans is prevented not only by antihistamines but also by nonsteroidal anti-inflammatory drugs (e.g., aspirin). These investigators concluded that the final step in dTc-induced hypotension is modulated by prostaglandins that are vasodilators.[214] This side effect can be reduced considerably by using a slower injection rate. It is also prevented by prophylaxis with combinations of $histamine_1$ and $histamine_2$ blockers.[215] If a minor degree of histamine release such as just described occurs after an initial dose of a neuromuscular blocker, subsequent doses will generally cause no response at all, as long as they are no larger than the original dose. This is clinical evidence of tachyphylaxis, an important characteristic of histamine release. A much more significant degree of histamine release occurs during anaphylactic or anaphylactoid reactions; these reactions are very rare.

Clinical Cardiovascular Manifestations of Autonomic Mechanisms

Hypotension. The hypotension seen with the use of atracurium and mivacurium is due to release of histamine, whereas dTc causes hypotension via histamine release and ganglion blockade.[216,217] The effects of dTc occur closer to the dose required to achieve neuromuscular blockade.[116] The safety margin for histamine release is about three times greater for atracurium and mivacurium than it is for dTc.[213,214,217] Rapid administration of atracurium in doses greater than 0.4 mg/kg and mivacurium in doses greater than 0.15 mg/kg has been associated with transient hypotension as a result of release of histamine (Fig. 29-20).

Tachycardia. Pancuronium causes a moderate increase in heart rate and, to a lesser extent, in cardiac output, with little or no change in systemic vascular resistance.[218] Pancuronium-induced tachycardia has been attributed to (1) vagolytic action,[218] probably secondary to inhibition of M_2 receptors, and (2) sympathetic stimulation that involves both direct (blockade of neuronal uptake of norepinephrine) and indirect (release of norepinephrine from adrenergic nerve endings) mechanisms.[219] In studies in humans, Roizen and colleagues[220] surprisingly found decreases in plasma norepinephrine levels after the administration of either pancuronium or atropine. They postulated that the increase in

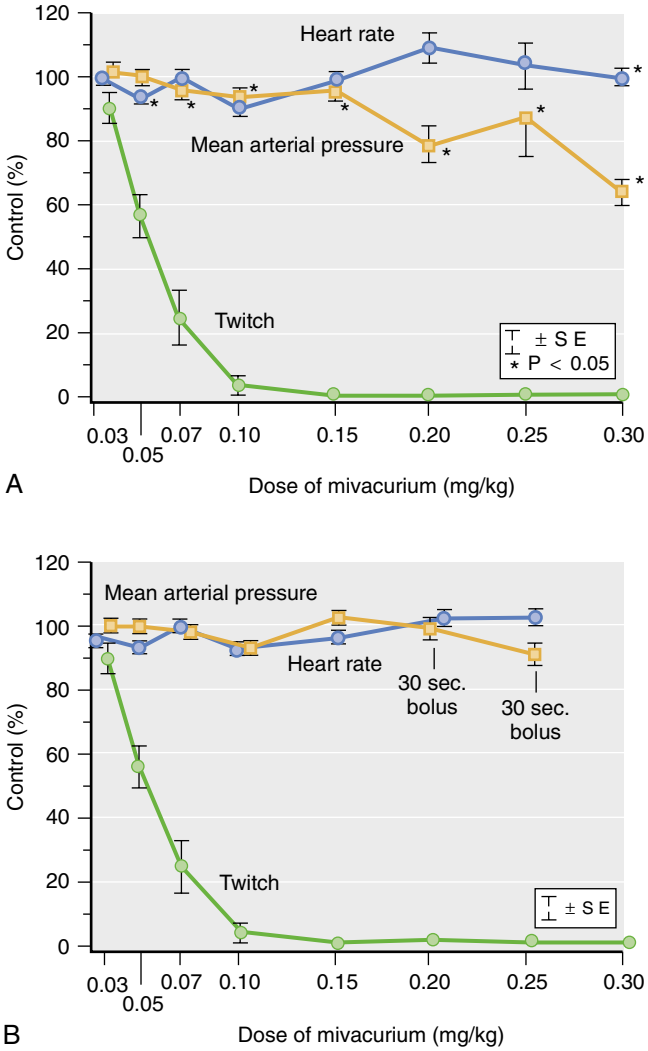


Figure 29-20 Dose response to mivacurium in patients under nitrous oxide–oxygen–opioid anesthesia. Maximum changes at each dose are shown; $n = 9$ subjects per group. **A,** With fast injection, a 15% to 20% decrease in arterial pressure occurred at 2.5 to 3 times the ED_{95} (0.20 to 0.25 mg/kg). **B,** The changes were less than 10% with a slower injection (30 seconds). *(From Savarese JJ, Ali HH, Basta SJ, et al: The cardiovascular effects of mivacurium chloride [BW B1090U] in patients receiving nitrous oxide–opiate–barbiturate anesthesia. Anesthesiology 70:386-394, 1989.)*

heart rate or rate-pressure product occurs because pancuronium (or atropine) acts through baroreceptors to reduce sympathetic outflow.[220] More specifically, the vagolytic effect of pancuronium increases the heart rate and, hence, blood pressure and cardiac output, which in turn influences the baroreceptors to decrease sympathetic tone. Support for this concept is provided by the fact that prior administration of atropine will attenuate or eliminate the cardiovascular effects of pancuronium.[218] However, a positive chronotropic effect that places emphasis on the vagolytic mechanism has not been found in humans.[221] The tachycardia seen with benzylisoquinolinium compounds is due to release of histamine.

DYSRHYTHMIAS. Succinylcholine and dTc actually reduce the incidence of epinephrine-induced dysrhythmias.[222] Possibly because of enhanced atrioventricular conduction,[223] the incidence of dysrhythmias caused by pancuronium appears to increase during halothane anesthesia.[218] Edwards and associates[224] observed a rapid tachycardia (more than 150 beats/min) that progressed to atrioventricular dissociation in two patients anesthetized with halothane who also received pancuronium. The only other factor common to these two patients was that both were taking tricyclic antidepressant agents.

BRADYCARDIA. Several case reports[225,226] have described the occurrence of severe bradycardia and even asystole after the administration of vecuronium or atracurium. All of these cases were also associated with opioid administration. Subsequent studies indicated that administration of vecuronium or atracurium alone does not cause bradycardia.[227] When combined with other drugs that do cause bradycardia (e.g., fentanyl), however, the nonvagolytic relaxants such as vecuronium, cisatracurium, and atracurium allow this mechanism to occur unopposed. Thus, the moderate vagolytic effect of pancuronium is often used to counteract opioid-induced bradycardia.

Respiratory Effects

The muscarinic cholinergic system plays an important role in regulating airway function. Five muscarinic receptors have been cloned,[228] three of which—M_1 to M_3—exist in the airways.[229] M_1 receptors are under sympathetic control, and they mediate bronchodilation.[230] M_2 receptors are located presynaptically (Fig. 29-21) at the postganglionic parasympathetic nerve endings, and they function in a negative-feedback mechanism to limit the release of acetylcholine. M_3 receptors, which are located postsynaptically (Fig. 29-21), mediate contraction of the airway smooth muscles (i.e., bronchoconstriction).[230] Nondepolarizing neuromuscular blockers have different antagonistic activities at both the M_2 and M_3 receptors.[231] For example, blockage of M_3 muscarinic receptors on airway smooth muscle inhibits vagally induced bronchoconstriction (i.e., causes bronchodilation), whereas blockage of M_2 receptors results in increased release of acetylcholine, which will act on M_3 receptors and cause bronchoconstriction.

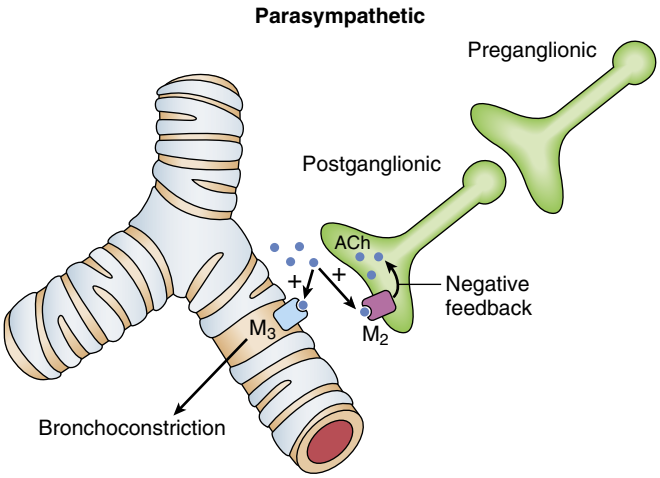


Figure 29-21 The muscarinic M_3 receptors are located postsynaptically on airway smooth muscle. Acetylcholine (ACh) stimulates M_3 receptors to cause contraction. M_2 muscarinic receptors are located presynaptically at the postganglionic parasympathetic nerve endings, and they function in a negative-feedback mechanism to limit the release of ACh.

The affinity of the compound rapacuronium to block M_2 receptors is 15 times higher than its affinity to block M_3 receptors.[231] This explains the high incidence (>9%) of severe bronchospasm[232-234] that was seen with this drug and resulted in its withdrawal from the market.

The administration of benzylisoquinolinium neuromuscular blocking drugs (with the exception of cisatracurium) is associated with histamine release, which may result in increased airway resistance and bronchospasm in patients with hyperactive airway disease.

Allergic Reactions

The frequency of life-threatening anaphylactic (immune-mediated) or anaphylactoid reactions occurring during anesthesia has been estimated to be between 1 in 1000 and 1 in 25,000 anesthetizations, with about a 5% mortality rate.[235,236] In France, the most common causes of anaphylaxis in patients who experienced allergic reactions were reported to be neuromuscular blocking drugs (58.2%), latex (16.7%), and antibiotics (15.1%).[237] Anaphylactic reactions are mediated through immune responses involving immunoglobulin E antibodies fixed to mast cells. Anaphylactoid reactions are not immune mediated and represent exaggerated pharmacologic responses in very rare and very sensitive individuals.

Neuromuscular blocking drugs contain two quaternary ammonium ions, which are the epitopes commonly recognized by specific immunoglobulin E.[238] Cross-reactivity has been reported between neuromuscular blocking drugs and food, cosmetics, disinfectants, and industrial materials.[238] Cross-reactivity is seen in 70% of patients with a history of anaphylaxis to a neuromuscular blocking drug.[237]

Steroidal compounds (e.g., rocuronium, vecuronium, pancuronium) result in no significant histamine release.[217] For example, four times the ED_{95} of rocuronium (1.2 mg/kg) causes no significant release of histamine.[239] Nevertheless, rocuronium and succinylcholine are reportedly associated with a 43.1% and 22.6% incidence of anaphylaxis in France.[237] Rose and Fisher[240] classified rocuronium and atracurium as having intermediate levels of risk for causing allergic reactions. They also noted that the increased number of reports of anaphylaxis with rocuronium is in line with the market share of that drug's use. Watkins[241] stated, "The much higher incidence of rocuronium reactions reported in France is currently inexplicable and is likely to remain so if investigators continue to seek a purely antibody-mediated response as an explanation of all anaphylactoid reaction presentations." There are currently no standards against which diagnostic tests (skin prick test, interdermal test, or immunoglobulin E testing) are performed, and new recommendations are still only in the proposal stage.[242] For instance, Laxenaire and Mertes[243] used a 1:10 dilution of rocuronium for interdermal skin testing, whereas Rose and Fisher[240] used a 1:1000 dilution. Levy and colleagues[244] showed that rocuronium in a 1:10 dilution can produce false-positive results on intradermal testing and suggested that rocuronium be diluted at least 100-fold to prevent such results. These authors also reported that high concentrations ($\geq 10^{-4}$ M) of both rocuronium and cisatracurium are capable of producing a wheal-and-flare response to intradermal testing, which was associated with mild to moderate mast cell degranulation in the cisatracurium group only.[244]

All neuromuscular blocking drugs can cause noncompetitive inhibition of histamine-*N*-methyltransferase, but the concentrations required for such inhibition far exceed those that would be used clinically, except in the case of vecuronium, with which the effect becomes manifested at 0.1 to 0.2 mg/kg.[245] This could explain the occurrence of occasional severe bronchospasm in patients after receiving vecuronium.[246]

Drug Interactions and Other Factors Affecting Response to Neuromuscular Blockers

A drug-drug interaction is an in vivo phenomenon that occurs when the administration of one drug alters the effects or kinetics of another drug. In vitro physical or chemical incompatibilities are *not* considered drug interactions.[247]

Many drugs have been shown to interact with neuromuscular blockers or their antagonists, or both, and it is beyond the scope of this chapter to review them all.[247,248] Some of the more important drug interactions with neuromuscular blockers and their antagonists are discussed in the following sections.

Interactions Among Nondepolarizing Neuromuscular Blockers

Mixtures of two nondepolarizing neuromuscular blockers are considered to be either additive or synergistic. Antagonistic interactions have not been reported in this class of drugs. Additive interactions have been demonstrated after the administration of chemically related agents, such as atracurium and mivacurium,[249] or after the coadministration of various pairs of steroidal neuromuscular blockers.[103] On the other hand, combinations of structurally dissimilar (e.g., a steroidal with a benzylisoquinolinium) neuromuscular blockers, such as pancuronium and dTc,[250] pancuronium and metocurine,[250] rocuronium and mivacurium,[149] or rocuronium and cisatracurium,[112] produce a synergistic response.

The administration of two neuromuscular blockers in combination was first introduced by Lebowitz and coworkers[250] in an attempt to reduce the cardiovascular side effects of neuromuscular blockers by giving smaller doses of each drug as a combination. An additional advantage (rapid onset and short duration) is noted for mivacurium-rocuronium combinations.[149] Although the precise mechanisms underlying a synergistic interaction are not known, hypotheses that have been put forward include the existence of multiple binding sites at the neuromuscular junction (presynaptic and postsynaptic receptors)[251] and the nonequivalence of binding affinities of the two α-subunits (α_H and α_L). Furthermore, inhibition of butyrylcholinesterase by pancuronium results in decreased plasma clearance of mivacurium and marked potentiation of the neuromuscular blockade.[252]

It should be noted that the pharmacodynamic response to the use of two different nondepolarizing blockers during the course of anesthesia depends not only on the specific drugs used

but also on the sequence of their administration.[253,254] Approximately three half-lives will be required for a clinical changeover (so that 95% of the first drug has been cleared) and for the duration of the blockade to begin to take on the characteristics of the second drug. After the administration of pancuronium, recovery from the first two maintenance doses of vecuronium is reportedly prolonged, although this effect becomes negligible by the third dose.[253] Similarly, Naguib and coauthors[249] noted that the mean duration of the first maintenance dose of mivacurium to 10% recovery of the first twitch was significantly longer after atracurium (25 minutes) than after mivacurium (14.2 minutes). However, the duration of the second maintenance dose of mivacurium after atracurium (18.3 minutes) was similar to that of mivacurium after mivacurium (14.6 minutes).

The apparent prolongation of action of the first maintenance dose of mivacurium administered after atracurium[249] and the prolongation reported with vecuronium after pancuronium[253,254] are not related to synergism. Combinations of atracurium and mivacurium[249] and vecuronium and pancuronium[103] are simply additive. However, this prolongation of the duration of action could be attributed to the relative concentrations of these drugs at the receptor site. Because most receptors remain occupied by the drug administered initially, the clinical profile depends on the kinetics or dynamics (or both) of the drug administered first rather than on those of the second (maintenance) drug. However, with further incremental doses of the second drug, a progressively larger proportion of the receptors are occupied by that drug, and its clinical profile becomes evident.

Interactions Between Succinylcholine and Nondepolarizing Neuromuscular Blockers

The interaction between succinylcholine and nondepolarizing neuromuscular blockers depends on the order of administration and the doses used.[86,255,256] Small doses of different nondepolarizing neuromuscular blockers administered before succinylcholine to prevent fasciculations have an antagonistic effect on the development of a subsequent depolarizing block produced by succinylcholine.[28,86] Therefore, it is recommended that the dose of succinylcholine be increased after the administration of a defasciculating dose of a nondepolarizing neuromuscular blocker.[28]

Studies on the effects of administration of succinylcholine before nondepolarizing neuromuscular blockers have produced conflicting results. Several investigators reported potentiation of the effects of pancuronium,[255] vecuronium, and atracurium[256] by prior administration of succinylcholine. In contrast, others found no significant influence of succinylcholine on the subsequent administration of pancuronium, rocuronium, or mivacurium.[86,257,258]

Interactions with Inhaled Anesthetics

Deep anesthesia induced with potent volatile anesthetics (in the absence of neuromuscular blockade) may cause a slight reduction in neuromuscular transmission, as measured by depression of sensitive indicators of clinical neuromuscular function, such as tetanus and TOF.[259] Inhaled anesthetics also enhance the neuromuscular blocking effects of nondepolarizing neuromuscular blockers. Inhaled anesthetics will decrease the dose of neuromuscular blockers needed, as well as prolong both the duration of action of the blocker and recovery from neuromuscular blockade,[260] depending on the duration of anesthesia,[259,261,262] the specific inhaled anesthetic,[263] and the concentration (dose) given.[264] The rank order of potentiation is desflurane > sevoflurane > isoflurane > halothane > nitrous oxide–barbiturate–opioid or propofol anesthesia (Fig. 29-22).[265-267]

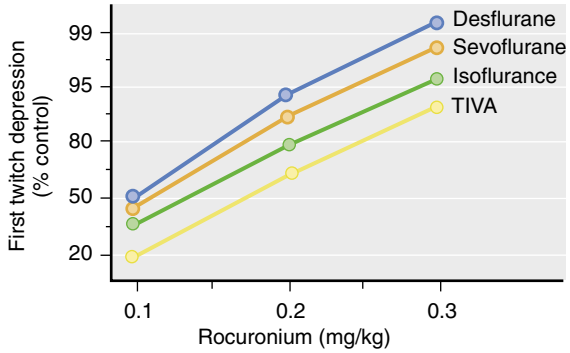


Figure 29-22 Cumulative dose-response curves for rocuronium-induced neuromuscular blockade during 1.5 minimum alveolar concentration (MAC) anesthesia with desflurane, sevoflurane, isoflurane, and total intravenous anesthesia (TIVA). *(From Wulf H, Ledowski T, Linstedt U, et al: Neuromuscular blocking effects of rocuronium during desflurane, isoflurane, and sevoflurane anaesthesia. Can J Anaesth 45:526-532, 1998, with permission from the Canadian Journal of Anaesthesia.)*

The greater clinical muscle-relaxing effect produced by less potent anesthetics is mainly due to their larger aqueous concentrations.[268] Desflurane and sevoflurane have low blood-gas and tissue-gas solubility, so equilibrium between the end-tidal concentration and the neuromuscular junction is reached more rapidly with these anesthetics than with older inhaled anesthetics.

The interaction between volatile anesthetics and neuromuscular blockers is one of pharmacodynamics, not pharmacokinetics.[143] The proposed mechanisms behind this interaction include (1) a central effect on α motoneurons and interneuronal synapses,[269] (2) inhibition of postsynaptic nAChRs,[270] and (3) augmentation of the antagonist's affinity at the receptor site.[268]

Interactions with Antibiotics

Most antibiotics can cause neuromuscular blockade in the absence of neuromuscular blocking agents. The aminoglycoside antibiotics, the polymyxins, and lincomycin and clindamycin primarily inhibit the prejunctional release of acetylcholine and also depress postjunctional nAChR sensitivity to acetylcholine. The tetracyclines, on the other hand, exhibit postjunctional activity only. When combined with neuromuscular blockers, the aforementioned antibiotics can potentiate neuromuscular blockade.[271] The cephalosporins and penicillins have not been reported to potentiate neuromuscular blockade. Because antagonism of neuromuscular blockade has been reported to be more difficult after the administration of aminoglycosides,[272] ventilation should be controlled until the neuromuscular blockade terminates spontaneously. Calcium should not be used to hasten the recovery of neuromuscular function for two reasons: the antagonism that it

produces is not sustained, and it may prevent the antibacterial effect of the antibiotics.

Temperature

Hypothermia prolongs the duration of action of nondepolarizing neuromuscular blockers.[273-275] The force of contraction of the adductor pollicis decreases by 10% to 16% per degree Celsius decline in muscle temperature below 35.2°C.[276,277] To maintain muscle temperature at or above 35.2°C, central temperature must be maintained at 36.0°C.[273] Recovery to 10% twitch height with 0.1 mg/kg of vecuronium increases from 28 minutes at a mean central temperature of 36.4°C to 64 minutes at 34.4°C.[273] The mechanism or mechanisms underlying this prolongation may be pharmacodynamic, pharmacokinetic, or both.[275] They include diminished renal and hepatic excretion, changing volumes of distribution, altered local diffusion receptor affinity, changes in pH at the neuromuscular junction, and the net effect of cooling on the various components of neuromuscular transmission.[273,278] Hypothermia decreases the plasma clearance and prolongs the duration of action of rocuronium and vecuronium.[275] Temperature-related differences in the pharmacodynamics of vecuronium have also been reported: k_{e0} decreases (0.023/min/°C) with lower temperature, suggesting slightly delayed equilibration of drug between the circulation and the neuromuscular junction during hypothermia.[275] The Hofmann elimination process of atracurium is slowed by a decrease in pH and especially by a decrease in temperature.[279] In fact, atracurium's duration of action is markedly prolonged by hypothermia.[274] For instance, the duration of action of a 0.5-mg/kg dose of atracurium is 44 minutes at 37°C but 68 minutes at 34.0°C.

Changes in temperature will also affect interpretation of the results of monitoring neuromuscular blockade. For example, the duration of action of vecuronium measured in an arm cooled to a skin temperature of 27°C is prolonged, and monitoring by post-tetanic count in that arm is unreliable.[280] In the same patient, TOF responses are different if the arms are at different temperatures, and correlation of responses in the two arms becomes progressively poorer as the temperature difference between the arms increases.[281]

The efficacy of neostigmine is not altered by mild hypothermia.[282-284] Hypothermia does not change the clearance, maximum effect, or duration of action of neostigmine in volunteers.[284]

Interactions with Magnesium and Calcium

Magnesium sulfate, given for the treatment of preeclampsia and eclamptic toxemia, potentiates the neuromuscular blockade induced by nondepolarizing neuromuscular blockers (see Chapter 69).[285,286] After a dose of 40 mg/kg of magnesium sulfate, the ED_{50} of vecuronium was reduced by 25%, the onset time was nearly halved, and the recovery time nearly doubled.[286] Neostigmine-induced recovery is also attenuated in patients treated with magnesium.[285] The mechanisms underlying the enhancement of nondepolarizing blockade by magnesium probably involve both prejunctional and postjunctional effects. High magnesium concentrations inhibit calcium channels at the presynaptic nerve terminals that trigger the release of acetylcholine.[14] Furthermore, magnesium ions have an inhibitory effect on postjunctional potentials and cause decreased excitability of muscle fiber membranes. In patients receiving magnesium, the dose of nondepolarizing neuromuscular blocker must be reduced and carefully titrated with a nerve stimulator to ensure adequate recovery of neuromuscular function at the end of surgery.

The interaction between magnesium and succinylcholine is controversial. However, more recent results suggest that magnesium antagonizes the block produced by succinylcholine.[287]

Calcium triggers the release of acetylcholine from the motor nerve terminal and enhances excitation-contraction coupling in muscle.[14] Increasing calcium concentrations decreased the sensitivity to dTc and pancuronium in a muscle-nerve model.[288] In hyperparathyroidism, hypercalcemia is associated with decreased sensitivity to atracurium and thus a shortened time course of neuromuscular blockade.[289]

Interactions with Lithium

Lithium remains the drug of choice for the treatment of bipolar affective disorder (manic-depressive illness). The lithium ion resembles sodium, potassium, magnesium, and calcium ions and may therefore affect the distribution and kinetics of all of these electrolytes.[290] Lithium enters cells via sodium channels and tends to accumulate within the cells.

By its activation of potassium channels, lithium inhibits neuromuscular transmission presynaptically and muscular contraction postsynaptically.[291] The combination of lithium and pipecuronium results in a synergistic inhibition of neuromuscular transmission, whereas the combination of lithium and succinylcholine results in additive inhibition.[291] Prolongation of neuromuscular blockade was reported in patients taking lithium carbonate and both depolarizing[282] and nondepolarizing neuromuscular blockers.[292] Only one report did not demonstrate prolongation of recovery from succinylcholine in patients receiving lithium.[293] In patients who are stabilized on lithium therapy and undergoing surgery, neuromuscular blockers should be administered in incremental and reduced doses and titrated to the degree of blockade required.

Interactions with Local Anesthetic and Antidysrhythmic Drugs

Local anesthetics act on the presynaptic, postsynaptic, and muscle membranes. In large intravenous doses, most local anesthetics block neuromuscular transmission; in smaller doses, they enhance the neuromuscular blockade produced by both nondepolarizing and depolarizing neuromuscular blockers.[294] The ability of neostigmine to antagonize a combined local anesthetic–neuromuscular blockade has not been studied. Procaine also inhibits butyrylcholinesterase and may augment the effects of succinylcholine and mivacurium by decreasing their hydrolysis by the enzyme.

In small intravenous doses, local anesthetics depress post-tetanic potentiation, and this is thought to be a neural prejunctional effect.[295] In larger doses, local anesthetics block acetylcholine-induced muscular contractions, which suggests that local anesthetics have a stabilizing effect on the postjunctional

membrane.[296] Procaine displaces calcium from the sarcolemma and thus inhibits caffeine-induced contracture of skeletal muscle.[297] Most of these mechanisms of action probably apply to all of the local anesthetics.

Several drugs used for the treatment of dysrhythmias augment the blockade induced by neuromuscular blockers. Single-fiber electromyography has disclosed that verapamil and amlodipine impair neuromuscular transmission in subjects without neuromuscular disease.[298] Clinical reports have suggested potentiation of neuromuscular block with verapamil[299] and impaired reversal of vecuronium in a patient receiving disopyramide.[300] However, the clinical significance of these interactions is probably minor.

Interactions with Antiepileptic Drugs

Anticonvulsants have a depressant action on release of acetylcholine at the neuromuscular junction.[301] Patients receiving chronic anticonvulsant therapy demonstrated resistance to nondepolarizing muscle blockers (except mivacurium[302] and probably atracurium as well),[301] as evidenced by accelerated recovery from neuromuscular blockade and the need for increased doses to achieve complete neuromuscular blockade. Clearance of vecuronium is increased twofold in patients receiving chronic carbamazepine therapy.[303] Some investigators, however, attribute this resistance to increased binding (i.e., decreased free fraction) of the neuromuscular blockers to α_1-acid glycoproteins or to upregulation of neuromuscular acetylcholine receptors (or to both mechanisms).[204] The latter could also explain the hypersensitivity seen with succinylcholine.[205] The slight prolongation of succinylcholine's action in patients taking anticonvulsants has few clinical implications. On the other hand, the potential hyperkalemic response to succinylcholine in the presence of receptor upregulation is of concern.

Interactions with Diuretics

In patients undergoing renal transplantation, the intensity and duration of dTc neuromuscular blockade is increased after a dose of furosemide (1 mg/kg intravenously).[306] Furosemide reduced the concentration of dTc required to achieve 50% twitch tension depression in the indirectly stimulated rat diaphragm and intensified the neuromuscular blockade produced by dTc and succinylcholine.[307] Furosemide appears to inhibit the production of cyclic adenosine monophosphate. In addition, the breakdown of adenosine triphosphate is inhibited, which results in reduced output of acetylcholine. Acetazolamide antagonizes the effects of anticholinesterases in the rat phrenic-diaphragm preparation.[308] However, in one report, 1 mg/kg of furosemide facilitated recovery of the evoked twitch response after pancuronium.[309] Chronic furosemide treatment had no effect on either dTc- or pancuronium-induced neuromuscular blockade.[310]

In contrast, mannitol appears to have no effect on nondepolarizing neuromuscular blockade. Moreover, increasing urine output by the administration of mannitol or other osmotic or tubular diuretics has no effect on the rate at which dTc and presumably other neuromuscular blockers are eliminated in urine.[126] However, this lack of effect on the excretion of dTc should not be surprising. Urinary excretion of all neuromuscular blockers that are long acting depends primarily on glomerular filtration. Mannitol is an osmotic diuretic that exerts its effects by altering the osmotic gradient within the proximal tubules so that water is retained within them. An increase in urine volume in patients with adequate glomerular filtration, therefore, would not be expected to increase the excretion of neuromuscular blockers.

Interactions with Other Drugs

Dantrolene (see Chapter 37), a drug used for the treatment of malignant hyperthermia, prevents release of calcium from the sarcoplasmic reticulum and blocks excitation-contraction coupling. Although it does not block neuromuscular transmission, the mechanical response to stimulation will be depressed, with subsequent potentiation of the nondepolarizing neuromuscular blockade.[88]

Azathioprine, an immunodepressant drug used in patients undergoing renal transplantation, has a minor antagonistic action on muscle relaxant–induced neuromuscular blockade.[311]

Steroids antagonize the effects of nondepolarizing neuromuscular blockers in both humans[312] and animals.[313] Possible mechanisms for this interaction include facilitation of acetylcholine release because of the effect of steroids on the presynaptic motor nerve terminal[314] and channel blockade of the nAChR.[315] Endogenous steroids act noncompetitively on nAChRs.[316] Prolonged treatment with a combination of corticosteroids and neuromuscular blocking drugs can result in prolonged weakness in critical care patients (see the later section "Neuromuscular Blockers and Weakness Syndromes in the Critically Ill").

Antiestrogenic drugs such as tamoxifen appear to potentiate the effects of nondepolarizing neuromuscular blockers.[317]

Recovery From Neuromuscular Blockade

In the 1970s, Ali and colleagues[318] described a TOF ratio of 0.60 as indicating adequate recovery of neuromuscular strength. Nonetheless, in 1997 a TOF ratio of 0.70 in unanesthetized volunteers was associated with difficulty speaking and swallowing, weakness of the facial musculature, visual disturbances, and inability to sit up without assistance.[319] Also in human volunteers, TOF ratios of 0.6 to 0.7 were associated with decreased upper esophageal tone and decreased coordination of the esophageal musculature during swallowing.[320,321] Fluoroscopic examination of these individuals demonstrated significant pharyngeal dysfunction resulting in a fourfold to fivefold increase in the risk for aspiration. With recovery of the TOF ratio to 0.9, esophageal tone and pharyngeal coordination returned toward baseline.[320,321]

Residual paralysis also decreases the hypoxic ventilatory drive (Fig. 29-23),[322,323] which is due to inhibition of the carotid body's neural response to hypoxia.[324] Vecuronium decreases carotid sinus nerve activity in response to hypoxia in a dose-related fashion, presumably through its interaction with nicotinic chemotransduction of the carotid body.

After the administration of nondepolarizing neuromuscular blocking drugs, adequate return of normal neuromuscular function must be present. Whether that degree of recovery is a

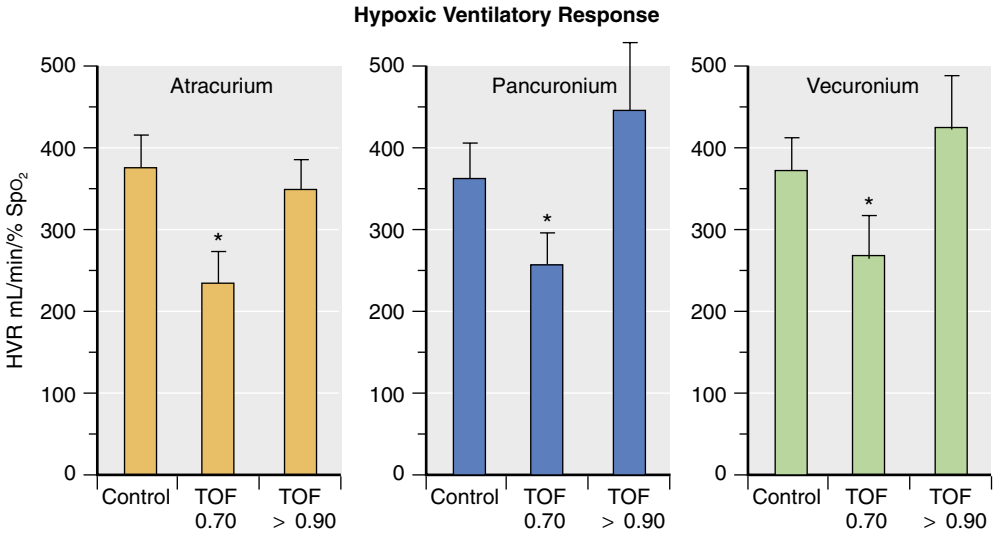


Figure 29-23 Hypoxic ventilatory response (HVR) before (control); during steady-state infusion (train-of-four [TOF] = 0.07) of atracurium, pancuronium, and vecuronium; and after recovery (TOF > 0.90). Data are presented as means ± SD. *$P < .01$. *(From Eriksson LI: Reduced hypoxic chemosensitivity in partially paralysed man. A new property of muscle relaxants? Acta Anaesthesiol Scand 40:520-523, 1996.)*

TOF ratio of 0.7, 0.8, or 0.9 has been an area of debate, and in a recent international guideline a TOF ratio of 0.9 was recommended as an end point for recovery from a nondepolarizing neuromuscular block. Certainly, the clinician's ability to quantify the degree of residual neuromuscular block is limited. Kopman and colleagues[319] work in volunteers demonstrated that when they could oppose their incisors to retain a tongue depressor, their TOF ratio was, on average, 0.8 and at least 0.68. This test of muscle strength, though, would have limited usefulness in tracheally intubated patients.

Recommendations for detection and prevention of residual neuromuscular blockade are summarized in Chapter 47.

Recovery from muscle relaxation caused by nondepolarizing neuromuscular blockers depends on several factors. Primarily, it depends on an increase in the acetylcholine concentration relative to that of the relaxant to overcome the competitive neuromuscular blockade. Although neostigmine will increase the acetylcholine concentration, ultimately, the muscle relaxant needs to be eliminated. The relative increase in acetylcholine concentration depends first on the ongoing movement of relaxant from the motor end plate into the central circulation and then on its elimination from the circulating blood volume so that it is not free to move into the synaptic cleft. Ultimately, recovery depends on elimination of the neuromuscular blocker from the body. Neuromuscular blockers may be eliminated through a host of mechanisms, including excretion as unchanged drug in urine, metabolism in the liver, enzymatic hydrolysis, and chemical breakdown. Although it has never been specifically examined, several groups of investigators have, through their ranges of recovery parameters, described wide interpatient variation in the spontaneous recovery of neuromuscular function.[325-327]

Several factors in addition to coexisting disease will affect the speed of spontaneous recovery of neuromuscular function. The presence of volatile anesthetics will potentiate any existing neuromuscular block and, presumably, cause recovery to be more prolonged.[328] If the anesthesiologist observes no or only minimal recovery of neuromuscular function in the presence of a volatile anesthetic, discontinuing or decreasing the concentration of that anesthetic should augment the recovery of neuromuscular function.

As will be discussed later in this section, acidosis, hypokalemia, hypothermia, and concomitant medications all potentiate residual neuromuscular blockade and render pharmacologic antagonism more difficult.

Antagonism of Residual Neuromuscular Blockade

Anticholinesterases act by inhibiting acetylcholinesterase (enzyme classification 3.1.1.7), which is a type B carboxylesterase. At the neuromuscular junction, acetylcholinesterase occurs in the asymmetric or A12 form and consists of three tetramers of catalytic subunits covalently linked to a collagen-like tail. Acetylcholinesterase has a powerful catalytic capacity: it can catalyze 4000 molecules of acetylcholine per active site per second. The active site lies deep inside the enzyme protein. Nearly half of the acetylcholine released is hydrolyzed across the synaptic cleft before reaching the nAChRs. For a detailed account of this enzyme, see the article by Soreq and Seidman.[329]

The active surface of acetylcholinesterase is best viewed as having two sites: the anionic site, which is concerned with binding and orienting the substrate molecule, and the esteratic site, which is responsible for the hydrolytic process. The existence of a second "anionic" site, known as the "peripheral" anionic site, has also been proposed. This topic has been reviewed by Silman and Sussman.[330]

Three anticholinesterases—neostigmine, pyridostigmine, and edrophonium—are used to antagonize residual neuromuscular blockade. They exert their effect primarily by inhibiting acetylcholinesterase and thus increasing the concentration of acetylcholine at the motor end plate. Neostigmine and pyridostigmine are oxydiaphoretic (acid-transferring) inhibitors of acetylcholinesterase. They transfer a carbamate group to acetyl-

cholinesterase and form a covalent bond at the esteratic site. Edrophonium is a prosthetic inhibitor that binds to the anionic site on the acetylcholinesterase by electrostatic attraction and to the esteratic site by hydrogen bonding. In addition, anticholinesterases may increase the release of acetylcholine from presynaptic nerve terminals, block neural potassium channels, and have a direct agonistic effect. For more details, see Bevan and colleagues.[331]

Major Determinants of the Speed and Adequacy of Recovery

Antagonism of nondepolarizing neuromuscular blockade is time dependent. Recovery occurs at a rate that depends primarily on five factors: (1) depth of the blockade when the antagonist is administered, (2) which anticholinesterase is administered, (3) dose of the anticholinesterase, (4) rate of spontaneous recovery from the neuromuscular blocker, and (5) concentration of inhaled anesthetic agent present during reversal.

Depth of the Blockade

Generally, more time is required to antagonize profound levels than lesser levels of blockade.[332] It is interesting that in a study by Bevan and coworkers,[333] antagonism of the blockade induced by doses of vecuronium or rocuronium that were 1.5 times the ED_{95} occurred at the same rate regardless of the timing of administration of 70 µg/kg of neostigmine. Neostigmine shortened the recovery time by approximately 40%, whether it was administered at the time of 1%, 10%, or 25% of spontaneous recovery. However, as shown in Figure 29-24, the time from administration of the neuromuscular blocker to TOF ratios of 0.7 and 0.9 did not decrease as the extent of spontaneous recovery at the time of neostigmine administration increased. Recovery to TOF ratios of 0.7 and 0.9 required, on average, 25 and 30 minutes, respectively. More specifically, should neostigmine be given during a profound (i.e., little or no response to peripheral nerve stimulation) neuromuscular block? Unfortunately, the answer is not clear. Thus, recommendations about the timing of administration of anticholinesterase are equivocal. Instinctively, many experts recommend not administering the anticholinesterase at the earliest degrees of recovery. Kirkegaard and associates[334] recently demonstrated that to recover to a TOF ratio of 0.7 within 10 minutes of administering neostigmine, three or four responses to TOF stimulation had to be present at the time of neostigmine administration. If only one response to TOF stimulation was present, recovery to a TOF ratio of 0.7 required up to 23 minutes.

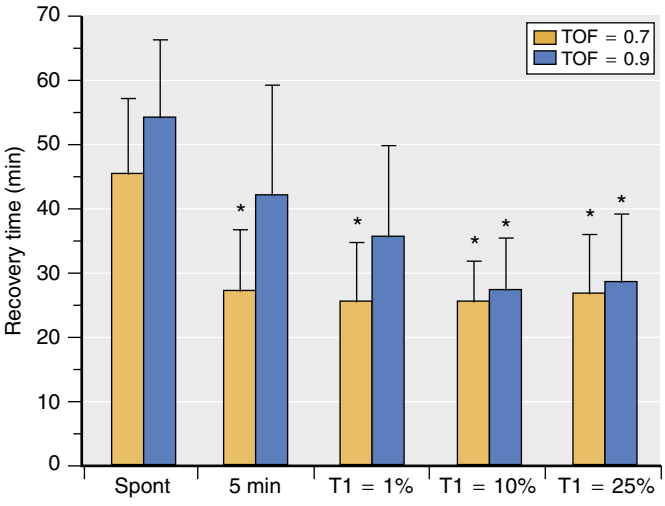


Figure 29-24 Recovery times (mean ± SD) after the administration of a single dose of 0.45 mg/kg (1.5 times the ED_{95}) rocuronium. In one group (Spont), spontaneous recovery was allowed. In the remaining groups, 70 µg/kg of neostigmine was administered 5 minutes after rocuronium or at 1%, 10%, and 25% recovery of the first twitch (T1) from its control value. *$P < .01$ versus spontaneous recovery. Note that the times to attain a train-of-four (TOF) ratio of 0.9 are significantly shorter when neostigmine was administered at T1 = 10% or 25% of control tension. *(From Bevan JC, Collins L, Fowler C, et al: Early and late reversal of rocuronium and vecuronium with neostigmine in adults and children. Anesth Analg 89:333-339, 1999.)*

The maximum antagonistic effect of neostigmine occurs in 10 minutes or less. If adequate recovery does not occur within this time, subsequent recovery is slow and requires ongoing elimination of the neuromuscular blocker from plasma. For profound vecuronium-induced blockade in which no twitch recovery has occurred, administration of 70 µg/kg of neostigmine produces an initial reversal that falls far short of adequate recovery.[327] Subsequent recovery occurs at the same rate as spontaneous recovery and is caused by the decrease in plasma concentration of vecuronium as the drug is eliminated.[327,335] Administration of a second dose of neostigmine has no further effect on recovery[327] because acetylcholinesterase is already maximally inhibited.

If the blockade at the time of neostigmine administration is sufficiently deep that adequate recovery does not occur within 10 minutes, the time at which full recovery of neuromuscular function will occur depends on the inherent duration of action of the neuromuscular blocker.[332] With drugs that have a long duration of action, this period of inadequate neuromuscular function can be 30 to 60 minutes or even longer, whereas with drugs that have an intermediate duration of action, it will be much shorter (e.g., 15 to 30 minutes).[336]

The Anticholinesterase Administered

Under the conditions of a moderate depth of blockade (such as two to three twitches palpable by TOF monitoring), the order of rapidity of antagonism of residual blockade by anticholinesterases is edrophonium > neostigmine > pyridostigmine.[337,338] For this reason and because of its lesser atropine requirement, edrophonium regained popularity as an antagonist during the 1980s.[327] However, Rupp and coworkers[339] found that edrophonium is not as effective as neostigmine in antagonizing profound blockade of more than 90% twitch depression (only one twitch palpable by TOF) whereas increasing the edrophonium dose from 0.5 to 1.0 mg/kg increased its efficacy. Neostigmine remains capable of more complete antagonism.[340] To be equivalent to 40 µg/kg of neostigmine as an antagonist of profound vecuronium blockade, 1.5 mg/kg of edrophonium must be administered.[330]

The relative potencies of edrophonium and neostigmine differ at various intensities of blockade (Fig. 29-25.).[341] Edrophonium becomes less potent relative to neostigmine as the depth of blockade becomes more intense. In other words, the dose-response curves are not parallel and become increasingly divergent as the depth of blockade intensifies. This difference indicates that edrophonium may be less effective than neostigmine when antagonizing very deep levels of blockade.

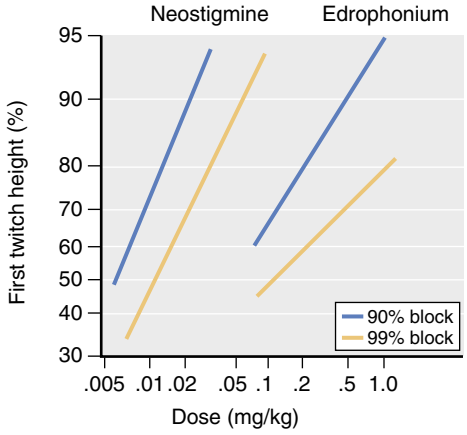


Figure 29-25 First twitch height (logit scale) versus dose (log scale) 10 minutes after the administration of neostigmine and edrophonium given at either 1% (99% block) or 10% (90% block) first twitch recovery. *(From Donati F, Smith CE, Bevan DR: Dose-response relationships for edrophonium and neostigmine as antagonists of moderate and profound atracurium blockade. Anesth Analg 68:13-19, 1989.)*

The Dose of Anticholinesterase

Larger doses of anticholinesterases should antagonize neuromuscular blockade more rapidly and more completely than smaller doses do. This relationship is true up to the point of the maximum effective dose, beyond which additional amounts of anticholinesterase will not produce any further antagonism. For neostigmine, this maximum effective dose is in the 60- to 80-µg/kg range,[327] and for edrophonium, it is in the 1.0- to 1.5-mg/kg range.[339,340]

Mixing or combining antagonists is not advisable. Neostigmine and edrophonium do not potentiate each other; in fact, their effects in combination may not even be additive.[342] Therefore, when inadequate reversal occurs, one should not be tempted to add a different anticholinesterase but should ensure only that the maximum dose of the original drug has been administered. Ventilation should then be supported until adequate neuromuscular function is achieved.

Rate of Spontaneous Recovery from the Neuromuscular Blocker

After administration of an anticholinesterase, two processes contribute to recovery of neuromuscular function. The first is the antagonism induced by the effect of the anticholinesterase at the neuromuscular junction; the second is the natural process of decrease in plasma concentration of the neuromuscular blocker (and hence its effect at the neuromuscular junction).[332,335] Therefore, the more rapid the elimination of the neuromuscular blocker, the faster the recovery of adequate neuromuscular function after the administration of an antagonist (Fig. 29-26).[343] A clear illustration of this principle is the difference in antagonism of the blockade induced by neuromuscular blockers with an intermediate duration of action versus those with a long duration. Plasma concentrations of drugs with an intermediate duration of action decrease more rapidly than those with a long duration of action,[141] and consequently, recovery of neuromuscular function is more rapid. Thus, the incidence of inadequate neuromuscular function in the postoperative period is less with intermediate-acting than with long-acting neuromuscular blockers.[336,344] This difference in speed of reversal between intermediate- and long-acting drugs is due to the effect of different rates of spontaneous recovery and not to a difference in response to neostigmine.[345] When neostigmine is administered to antagonize a stable level of blockade maintained by continuous infusion of either vecuronium or pancuronium, the rate and degree of recovery are similar to those achieved in the case of administration of each neuromuscular blocker alone.[345]

Even though mivacurium is no longer available in the United States, its pharmacology allows better understanding of basic pharmacology. The interaction between spontaneous recovery from and anticholinesterase-induced reversal of mivacurium's effect is more complex. The rate of spontaneous recovery from mivacurium-induced bockade is more rapid than that from any other nondepolarizing neuromuscular blocker. This is a result of its rapid hydrolysis by butyrylcholinesterase. Neostigmine-induced reversal of mivacurium is similar to or faster than that of atracurium.[184,346] During profound (<3% twitch recovery) mivacurium-induced blockade, the administration of neostigmine may prolong recovery.[347] Neostigmine has two major effects relevant to mivacurium. First, it inhibits acetylcholinesterase at the neuromuscular junction, thereby effectively increasing the acetylcholine concentration and facilitating recovery. Second, it inhibits butyrylcholinesterase, the enzyme responsible for metabolism of mivacurium, and slows the normally rapid decrease in the plasma concentration of mivacurium.[348] In contrast, edrophonium is a less potent inhibitor of butyrylcholinesterase[348] and should have little effect on the metabolism of mivacurium. Provided that there is 10% recovery of twitch response (one twitch in the TOF), either 20 to 40 µg/kg of neostigmine or 0.3 to 0.5 mg/kg of edrophonium will accelerate recovery from mivacurium.[346]

It has been suggested that routine administration of an anticholinesterase may often be omitted because spontaneous recovery from mivacurium's effect is so rapid. However, this strategy may lead to inadequate recovery and postoperative weakness unless at least 20 minutes is allowed for spontaneous recovery before the anticholinesterase is administered.[346]

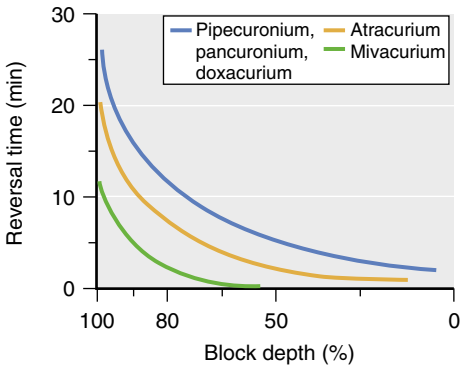


Figure 29-26 Comparative mean speed of antagonism by neostigmine of neuromuscular blockade induced by long-acting agents (doxacurium, pancuronium, pipecuronium), intermediate-acting drugs (atracurium and others), and the short-acting agent mivacurium. Antagonism is more rapid as processes of clearance increase (see text). *(From Savarese JJ: Reversal of nondepolarizing blocks: More controversial than ever?* In *Review Course Lectures, 67th Congress. Cleveland, OH, International Anesthesia Research Society, 1993.)*

Because mivacurium is metabolized by butyrylcholinesterase, administration of exogenous human butyrylcholinesterase can theoretically hasten recovery from mivacurium's effects. Administration of purified human cholinesterase does produce some antagonism of mivacurium-induced blockade,[349] but it is ineffective in profound blockade[348] and no better than edrophonium alone.[350] Administration of purified butyrylcholinesterase to patients who are genetically homozygous for atypical butyrylcholinesterase and have a prolonged blockade may be justified,[188] but this therapy is expensive and has not yet been tested adequately.

Concentration of Inhaled Anesthetic

Several studies have documented that antagonism of residual blockade is actually retarded by anesthetizing concentrations of anesthetic vapors.[351,352] For example, reversal of rocuronium by neostigmine under sevoflurane (and to a lesser extent, isoflurane) anesthesia occurred more slowly than under propofol anesthesia.[352] Sevoflurane may impede neostigmine-induced antagonism more than isoflurane does.[351] When compared with recovery from isoflurane anesthesia, recovery from that produced by desflurane or sevoflurane is prolonged.[343] Withdrawal of the anesthetic vapor at the end of surgery, with subsequent reduction of its enhancement of neuromuscular blockade, will speed pharmacologic reversal.[328]

Clinical Recommendations

When antagonizing deep levels of neuromuscular blockade (about 10% recovery or one twitch in response to TOF stimulation), larger doses of anticholinesterases (e.g., neostigmine, 35 µg/kg) should be administered and adequate time allowed for recovery of neuromuscular function. The time required for recovery to a TOF ratio of 0.7 will be approximately 60 minutes for the long-acting neuromuscular blocking drugs (pancuronium) and 30 minutes for the intermediate-acting ones (rocuronium). To antagonize lesser degrees of blockade, smaller doses of anticholinesterases may be administered, with additional anticholinesterase given if adequate recovery has not occurred in 10 minutes.

It is not advisable to administer additional anticholinesterase if maximal doses of edrophonium (1.5 mg/kg), neostigmine (70 µg/kg), or pyridostigmine (350 µg/kg) fail to antagonize the residual blockade.[340] Giving too much anticholinesterase to antagonize residual neuromuscular blockade may actually render patients weaker.[326,354,355] These doses inhibit acetylcholinesterase completely, and if they fail to fully antagonize the residual blockade, another likely cause of the inadequate antagonism should be sought. Some of these additional potential causes of inadequate antagonism of neuromuscular blockade are described in the following sections.

Acid-Base State

Both metabolic and respiratory acidosis may augment the blockade induced by a nondepolarizing neuromuscular blocker, but only respiratory acidosis prevents adequate antagonism.[338,356] The probability of achieving adequate antagonism of nondepolarizing neuromuscular blockade in the presence of significant respiratory acidosis (partial pressure of carbon dioxide in arterial gas >50 mm Hg) is low. Therefore, attempts to antagonize residual blockade may fail if a patient hypoventilates. Administration of narcotics to relieve pain may, by producing hypoventilation, increase the likelihood of this adverse event. Although metabolic acidosis might also be predicted to prevent antagonism by neostigmine, this hypothesis has not been substantiated.[338,356] Metabolic alkalosis, but not metabolic acidosis, prevents neostigmine's antagonism of dTc and pancuronium.[338,356,357] These results suggest that extracellular pH is not as important as changes in electrolyte concentrations and intracellular pH.

Electrolyte Imbalance

Few data are available on the effect of electrolyte imbalance on antagonism of a nondepolarizing neuromuscular blockade induced by neostigmine. Low extracellular concentrations of potassium enhance the blockade from nondepolarizing neuromuscular blockers and diminish the ability of neostigmine to antagonize the blockade. This effect is caused by the increase in end-plate transmembrane potential that results from a higher ratio of intracellular to extracellular potassium. Thus, a decrease in extracellular potassium causes hyperpolarization and produces resistance to depolarization. Patients with an imbalance in potassium may have other diseases or injuries that alter their response to neuromuscular blockers (e.g., patients with burns). In addition, severe dehydration will concentrate the neuromuscular blocker present in plasma, in effect decreasing the volume of distribution and increasing muscle relaxant activity. In an animal model of chronic hypokalemia, cats were given a diuretic without potassium supplementation for 15 days. Less pancuronium was required for neuromuscular blockade and more neostigmine was required for antagonism.[358] Even though the differences were small, the blockade was always antagonized completely. If we assume that this animal model approximates the clinical situation, changes in potassium appear to be of relatively minor consequence with respect to the clinical question of adequacy of reversal.

Other Factors

The calcium channel blocker verapamil will potentiate nondepolarizing neuromuscular blocking drugs and may render achieving adequate reversal difficult.[359,360] When attempting reversal of neuromuscular blockade in patients receiving verapamil, edrophonium may be more effective than neostigmine.[359,360] Other factors that may interfere with antagonism are hypothermia and the administration of antibiotics, particularly those of the aminoglycoside or polypeptide classes (see the section on drug interactions).[271] In the case of antibiotics, administration of an anticholinesterase may in fact deepen the blockade.

Side Effects of Anticholinesterases

Cardiovascular Effects

Because only the nicotinic effects of edrophonium, neostigmine, and pyridostigmine are desired, the muscarinic effects must be blocked by atropine or glycopyrrolate. Atropine induces its vagolytic effect much more rapidly than glycopyrrolate does. To minimize cardiovascular changes, atropine is better suited for administration with the rapid-acting edrophonium, and glycopyrrolate is better suited for administration with the slower-acting neostigmine and pyridostigmine.[361] In general, 7 to 10 µg/kg of atropine should be given with 0.5 to 1.0 mg/kg of edrophonium.[337] When cardiac dysrhythmias are a concern, glycopyrrolate may be

preferable to atropine,[362] and the anticholinesterases and anticholinergics should be administered more slowly (e.g., 2 to 5 minutes) to reduce the incidence and severity of disordered rhythm.

Nausea and Vomiting

Reports on the effect of anticholinesterase administration on postoperative nausea and vomiting are conflicting. Neostigmine has been implicated as a cause of postoperative nausea and vomiting,[363] but it has also been described as having antiemetic properties[364] and as having no effect on the incidence of postoperative nausea and vomiting.[365] A meta-analysis by Tramer and Fuchs-Bader[366] looked at the results of anticholinesterase administration in more than 1100 patients. They found a dose-response relationship for the incidence of nausea and vomiting after the administration of neostigmine: the highest incidence of vomiting after the administration of 1.5 mg of neostigmine was lower than the lowest incidence of vomiting after the administration of 2.5 mg of neostigmine. Discrepancies between the results of other studies may have been at least partly attributable to the use of different dosing regimens. Although vomiting occurs in 17% to 33% of patients after the administration of neostigmine, the authors did not recommend that all patients be allowed to recover spontaneously because of the risk for postoperative residual paralysis.[366] A more recent study demonstrated the hazards of not antagonizing residual neuromuscular blockade at least 2 hours after the administration of a dose twice the ED_{95} of vecuronium, rocuronium, or atracurium.[367]

Pharmacokinetics of Neostigmine, Pyridostigmine, and Edrophonium

The pharmacokinetics of edrophonium, neostigmine, and pyridostigmine is summarized in Table 29-12.[368-371] The data indicate several relevant clinical conclusions:

1. Pyridostigmine has a longer elimination half-life than that of the other anticholinesterases, which probably accounts for its longer duration of action.[368,369]
2. Comparison data on the elimination half-lives in patients with and without renal failure showed that renal excretion accounts for about 50% of the excretion of neostigmine and about 75% of the excretion of pyridostigmine and edrophonium. Renal failure decreases the plasma clearance of neostigmine, pyridostigmine, and edrophonium as much as, if not more than that of the long-acting neuromuscular blockers. Therefore, if proper doses of anticholinesterase drugs are given and overdoses of neuromuscular blockers are avoided, renal failure should not be associated with "recurarization."[368,369] This remote possibility is further diminished if the clinician restricts the relaxants used to the intermediate- or short-acting drugs in patients with renal failure.
3. Edrophonium was once thought to be an unsuitable antagonist in clinical practice because its duration of action was believed to be too short. However, when larger doses (e.g., 0.5 to 1.0 mg/kg) are given, sustained antagonism of nondepolarizing neuromuscular–induced blockade results.[372] In fact, the elimination half-life of edrophonium is similar to that of neostigmine and pyridostigmine (see Table 29-12).[370]

Mild hypothermia (i.e., 34°C to 35°C), which commonly occurs intraoperatively, affects the pharmacokinetics of neostigmine. Its clearance is decreased from 16.2 mL/kg/min at 36.5°C to 13.5 mL/kg/min at 34.5°C.[284] In addition, onset of the peak effect of neostigmine is delayed by mild hypothermia from 4.2 to 5.5 minutes.[284] If hypothermia has any influence on the efficacy of neostigmine-induced reversal, it is more likely to be due to the effect of temperature on the neuromuscular blocker (e.g., prolonged duration of action[273]) than to the pharmacology of neostigmine.

The pharmacokinetics of the anticholinesterases depends on several factors, including distribution, metabolism, and elimination. In the case of neostigmine, a carbamylated complex with acetylcholinesterase is formed, and it is the rate of dissociation of neostigmine from this complex (i.e., its metabolism) that is probably the major determinant of its duration of action. The decrease in the plasma concentration of neostigmine (i.e., its distribution and elimination) may not be as pertinent a determinant of its duration of action.

Table 29-12 Pharmacokinetics of Neostigmine (N), Pyridostigmine (P), and Edrophonium (E) in Patients without and with Renal Failure

	Without Renal Failure			With Renal Failure		
	N	P	E	N	P	E
Distribution half-life ($t_{½\alpha}$, min)	3.4	6.7	7.2	2.5	3.9	7.0
Elimination half-life ($t_{½\beta}$, min)	77	113	110	181	379	304
Volume of central compartment (L/kg)	0.2	0.3	0.3	0.3	0.4	0.3
Total plasma clearance (mL/kg/min)	9.1	8.6	9.5	4.8	3.1	3.9

Data from Cronnelly et al.[368,369] and Morris et al.[370,371]

Other Antagonists of Nondepolarizing Neuromuscular Blockade

Sugammadex

Sugammadex may be the most exciting drug in clinical neuromuscular pharmacology in the last 50 years. The combination of rocuronium and sugammadex could replace succinylcholine for rapid-sequence induction of anesthesia and completely eliminate residual paralysis in the postanesthetic recovery room.[373]

Sugammadex (ORG 25969) is the first selective relaxant binding agent (*su* refers to *su*gar, and *gammadex* refers to the structural molecule *gamma*-cyclo*dex*trin). A modified γ-cyclodextrin, sugammadex (Fig. 29-27) is a new type of reversal agent.[374] The three natural unmodified cyclodextrins consist of six, seven, and eight cyclic oligosaccharides (i.e., dextrose units joined through one to four glycosyl bonds) and are called α-, β-,

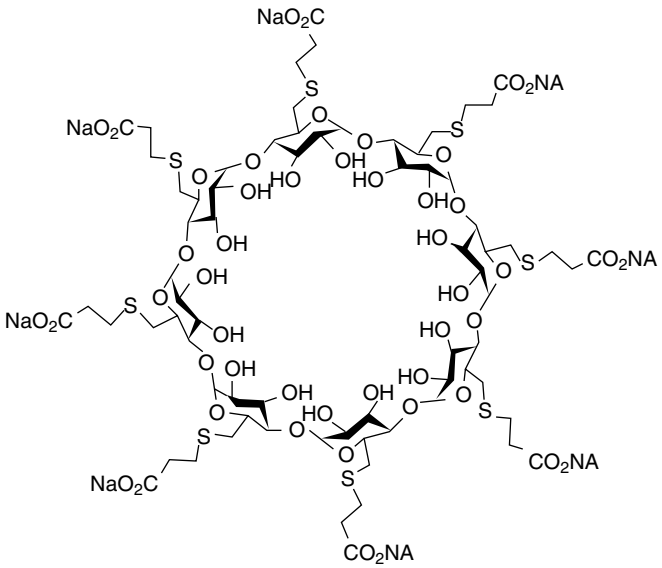


Figure 29-27 Structure of the synthetic γ-cyclodextrin sugammadex (ORG 25969).

and γ-cyclodextrin, respectively. Their three-dimensional structure resembles a hollow truncated cone or a doughnut. The structure has a hydrophobic cavity and a hydrophilic exterior because of the presence of polar hydroxyl groups. Hydrophobic interactions trap the drug in the cyclodextrin cavity (the "doughnut hole"), thereby resulting in the formation of a water-soluble guest-host complex. Although unmodified γ-cyclodextrin possesses a larger lipophilic cavity (7.5 to 8.3 Å) than any other cyclodextrin does, it is still not deep enough to accommodate the larger rigid structure of the rocuronium molecule. Therefore, the cavity was modified by adding eight side chains to extend it to 11 Å for better accommodation of the four hydrophobic steroidal rings of rocuronium and by adding negatively charged carboxyl groups at the end of the side chains to enhance electrostatic binding to the positively charged quaternary nitrogen of rocuronium (Fig. 29-28).[374,375] The stability of the rocuronium-sugammadex complex is the end result of an interplay of intermolecular forces (van der Waals forces), including thermodynamic (hydrogen bonds) and hydrophobic interactions.[376]

Sugammadex exerts its effect by forming very tight complexes in a 1 : 1 ratio with steroidal neuromuscular blocking agents (rocuronium > vecuronium ≫ pancuronium).[374] The guest-host complex exists in an equilibrium with a very high association rate and very low dissociation rate, so the complex is tight.[374] During rocuronium-induced neuromuscular blockade, intravenous administration of sugammadex results in rapid removal of free rocuronium molecules from plasma. This creates a concentration gradient favoring movement of the remaining rocuronium molecules from the neuromuscular junction back into plasma, where they are encapsulated by free sugammadex molecules. These molecules also enter tissues and form a complex with rocuronium. Therefore, the neuromuscular blockade of rocuronium is terminated rapidly by the diffusion of rocuronium away from the neuromuscular junction back into plasma. This results in an increase in the total plasma concentration of rocuronium (free and that bound to sugammadex).[377] Sugammadex therefore acts as a binding agent and has no effect on acetylcholinesterase or any receptor system in the body, thus eliminating the need for anticholinergic drugs and their undesirable side effects.

PHARMACOKINETICS. During an infusion of rocuronium to maintain a stable depth of neuromuscular blockade, administration of sugammadex increases the measured plasma concentration of rocuronium; the relaxant is redistributed from the effect compartment to the central compartment as it is encapsulated by sugammadex.[377] Recovery of muscle strength can occur despite increasing plasma concentrations of relaxant because the efficacy of sugammadex does not rely on renal excretion of the cyclodextrin-relaxant complex.[378]

When administered by itself to volunteers who had not received a neuromuscular blocking agent, 0.1 to 8.0 mg/kg of sugammadex had a clearance rate of 120 mL/min, an elimination half-life of 100 minutes, and a volume of distribution of 18 L.[379] Approximately 75% of a dose was eliminated in urine. The kinetics of sugammadex appears to be dose dependent in that clearance increases and the elimination half-life decreases as the dose of sugammadex increases from 0.15 to 1.0 mg/kg.[379]

In the absence of sugammadex, rocuronium is eliminated mainly by biliary excretion (>75%) and to a lesser degree by renal excretion (10% to 25%). Plasma clearance of sugammadex alone is approximately three times lower than that of rocuronium alone.[380] In volunteers, plasma clearance of rocuronium was decreased by a factor of greater than 2 after the administration of a 2.0-mg/kg or greater dose of sugammadex.[379] This decreased clearance occurs because the biliary route of excretion becomes unavailable for the rocuronium-sugammadex complex, and rocuronium clearance decreases to a value approaching the glomerular filtration rate (120 mL/min). Because of the soluble

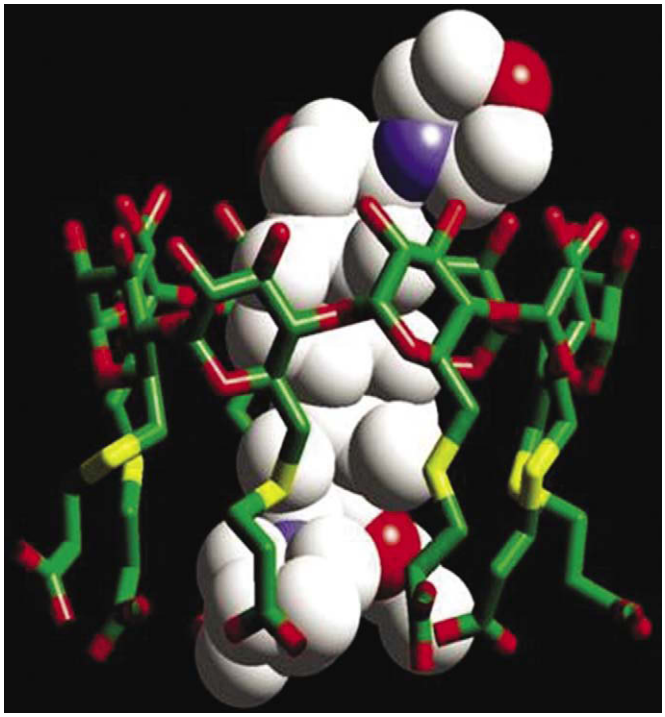


Figure 29-28 The sugammadex-rocuronium complex. *(From Bom A, Bradley M, Cameron K, et al: A novel concept of reversing neuromuscular block: Chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. Angew Chem 41:266-270, 2002.)*

nature of the rocuronium-cyclodextrin complex, urinary excretion of the complex is the major route of elimination of rocuronium. Renal excretion of rocuronium is increased by more than 100% after the administration of 4 to 8 mg/kg of sugammadex.[380]

As noted earlier, after the administration of sugammadex, the plasma concentration of free rocuronium decreases rapidly, but the total plasma concentration of rocuronium (both free and that bound to sugammadex) increases.[377]

Pharmacodynamics. In male volunteers, administration of 8 mg/kg of sugammadex 3 minutes after the administration of 0.6 mg/kg of rocuronium resulted in recovery of the TOF ratio to 0.9 within 2 minutes.[379] Decreasing the dose of sugammadex to 4 mg/kg resulted in recovery of the TOF ratio to 0.9 in less than 4 minutes.[379] Additionally, in surgical patients who were anesthetized with total intravenous anesthetic agents and had received 0.6 mg/kg of rocuronium, different doses of sugammadex or placebo were administered at reappearance of the second twitch of the TOF response.[381] Sugammadex decreased the median recovery time in a dose-dependent manner from 21.0 minutes in the placebo group to 1.1 minutes in the group given 4.0 mg/kg of sugammadex.[381]

Administration of sugammadex when the TOF count had returned to two detectable responses resulted in a dose-dependent recovery from the neuromuscular blockade induced by either rocuronium (0.60 mg/kg) or vecuronium (0.10 mg/kg).[382] After a dose of 4.0 mg/kg of sugammadex, the mean time to recovery of the TOF ratio to 0.9 was 1.1 minutes and 1.5 minutes after rocuronium and vecuronium, respectively. A sugammadex dose of 0.5 mg/kg is considered to be grossly inadequate for antagonism.[382-384]

One of the features that make sugammadex so different pharmacodynamically from the available anticholinesterases is that it takes effect more quickly and reliably than either neostigmine or edrophonium.[385] In a trial by Sacan and colleagues,[385] patients received 0.6 mg/kg of rocuronium, and neuromuscular blockade was maintained with supplemental doses of rocuronium given at reappearance of the second twitch in the TOF. The reversal agent—70 μg/kg of neostigmine, 1 mg/kg of edrophonium, or 4 mg/kg of sugammadex—was administered at least 15 minutes after the last dose of rocuronium. A 4-mg/kg dose of sugammadex reversed the rocuronium-induced neuromuscular blockade more rapidly than neostigmine or edrophonium did. The average time to achieve a TOF ratio of 0.9 was 10 times longer after the administration of neostigmine than it was after sugammadex (1044 versus 107 seconds) and three times longer after the administration of edrophonium (331 seconds) than after sugammadex. Although 5 of 20 patients in the neostigmine group and 2 of 20 patients in the edrophonium group achieved a TOF ratio of 0.9, all 20 in the sugammadex group achieved this degree of recovery. Furthermore, 5 minutes after the administration of edrophonium, none of the patients who had received edrophonium and 5% of those who had received neostigmine had recovered to a TOF ratio of 0.9, but all the patients in the sugammadex group had.[385] Hence, sugammadex appears to allow more complete recovery of neuromuscular function than the anticholinesterases do, and it does so more quickly than the more conventional agents. Unlike the case with neostigmine or edrophonium,[328,351,353] the choice of anesthetic agent (e.g., propofol versus sevoflurane) does not appear to influence the ability of sugammadex to antagonize rocuronium-induced neuromuscular blockade.[386]

Whereas there is a ceiling effect to what anticholinesterases can do[332] in that they cannot effectively antagonize profound levels of neuromuscular blockade, sugammadex has been shown to do so in trials.[384,387] Deep neuromuscular blockade (post-tetanic count of <10) was maintained for at least 2 hours in patients anesthetized with propofol–nitrous oxide–opioid anesthesia.[387] After spontaneous recovery of the second twitch of the TOF, different doses of sugammadex were administered; increasing the sugammadex dose from 0.5 to 4.0 mg/kg shortened the average recovery time to a TOF of 0.9 from 6.8 minutes (range, 4.8 to 11.4 minutes) to 1.4 minutes (range, 0.95 to 2.3 minutes), respectively.[387] Unexpectedly, the recovery time was longer (2.6 minutes[388]) with a 6.0-mg/kg dose.[387] The reason for this deviation is unclear.

Sugammadex produces rapid and effective reversal of even more profound rocuronium-induced neuromuscular blockade. In one study, sugammadex or placebo was administered 5 minutes after the administration of 1.2 mg/kg of rocuronium.[389] Increasing the dose of sugammadex to 16 mg/kg decreased the mean recovery time to a TOF ratio of 0.9 from 122.1 minutes (spontaneous recovery) to less than 2 minutes.[389]

In another study, patients were randomized to receive an intubating dose of 1.2 mg/kg of rocuronium followed 3 minutes later by 16 mg/kg of sugammadex or an intubating dose of 1.0 mg/kg of succinylcholine.[390] The mean time to 90% recovery of first twitch was significantly faster in the rocuronium-sugammadex group than it was in the succinylcholine group. The mean (± SD) time to 90% recovery of first twitch from the start of sugammadex administration was 2.9 minutes (1.7 minutes).[390] Therefore, the use of rapid-sequence induction with rocuronium can be facilitated by the presence of sugammadex. Administration of 1.2 mg/kg of rocuronium followed 3 minutes later by 16 mg/kg of sugammadex seems to provide a faster onset-offset profile than that seen with 1.0 mg/kg of succinylcholine (Fig. 29-29).[391]

Sugammadex is ineffective against succinylcholine and benzylisoquinolinium neuromuscular blockers such as mivacurium, atracurium, and cisatracurium[392] because it cannot form inclusion complexes with these drugs. Therefore, if neuromuscular blockade must be reestablished after using sugammadex, one of the benzylisoquinolinium neuromuscular blockers should be considered.

Side Effects. The ability of sugammadex to form complexes with steroidal and nonsteroidal compounds such as cortisone, atropine, and verapamil is probably clinically insignificant and is 120 to 700 times less than that of rocuronium.[393] In phase I and II studies, the most frequently reported side effects have been hypotension, coughing, movement, nausea, vomiting, dry mouth, parosmia (an abnormal sense of smell), a sensation of a changed temperature, and abnormal levels of *N*-acetyl-glucosaminidase in urine.[379,381,387] Patient movement with the administration of sugammadex may have been due to the unmasking of inadequate anesthesia rather than an adverse response to the reversal agent. In one study, prolongation of the corrected QT interval was noted in five subjects who received placebo and in three who received sugammadex.[379]

Cysteine

Gantacurium undergoes rapid degradation in plasma by chemical hydrolysis and inactivation by cysteine adduction (see Fig. 29-10),[105] which is a novel chemical mechanism of inactivation. Exogenous administration of cysteine can accelerate the

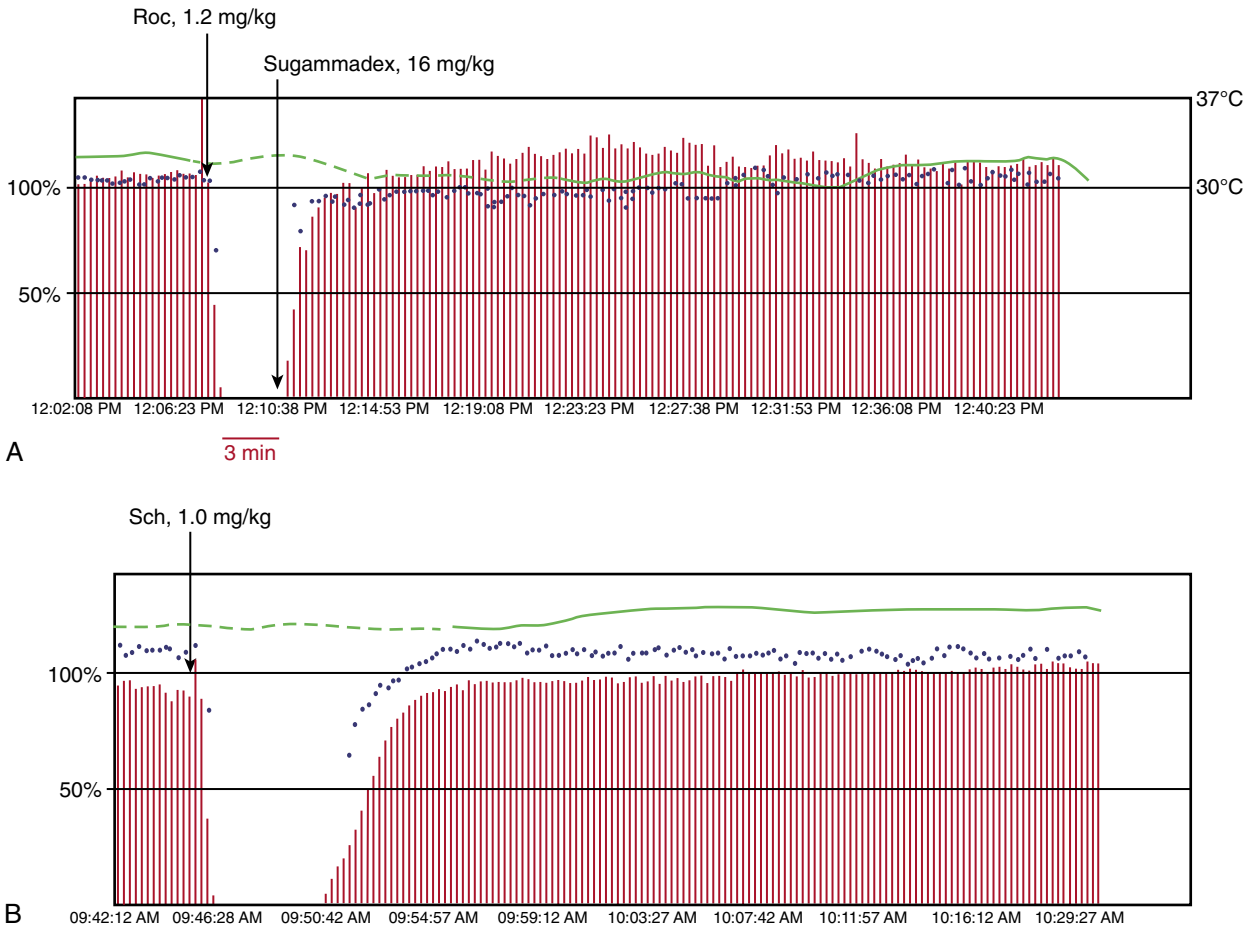


Figure 29-29 A, Recovery of twitch height and the train-of-four (TOF) ratio after the administration of 1.2 mg/kg of rocuronium, followed 3 minutes later by 16 mg/kg of sugammadex, both given intravenously. Recovery to a first twitch height (T1) of 90% and a TOF ratio of 0.94 occurred 110 seconds later. The onset-offset time with this sequence (i.e., time from the end of the injection of rocuronium until T1 recovery to 90%) was 4 minutes, 47 seconds. **B,** Effects of administering 1.0 mg/kg of succinylcholine (Sch) with spontaneous recovery to a T1 of 90% occurring after 9 minutes, 23 seconds. *(From Naguib M: Sugammadex: Another milestone in clinical neuromuscular pharmacology. Anesth Analg 104:575-581, 2007.)*

antagonism of gantacurium-induced neuromuscular blockade. As shown in Figure 29-30, after administration of a second 0.2-mg/kg dose of gantacurium, followed less than 1 minute later by 10 mg/kg of cysteine, complete recovery from neuromuscular blockade occurred within 4 minutes.

Special Populations

Pediatric Patients

Development of the neuromuscular junction is not complete at birth.[14] In humans, maturation of neuromuscular transmission probably occurs after the first 2 months of age. Nonetheless, neuromuscular blockers can be used safely in term and preterm infants.

Routine administration of succinylcholine to healthy children should be discontinued. In apparently healthy children, intractable cardiac arrest with hyperkalemia, rhabdomyolysis, and acidosis may occur after succinylcholine administration, particularly in patients with unsuspected muscular dystrophy of the Duchenne type.[394] In response to this report, the U.S. Food and Drug Administration and Glaxo-Wellcome have modified the package insert for succinylcholine to warn against the use of succinylcholine in children except for emergency control of the airway (see the section on complications of succinylcholine).

It is not apparent from older studies whether neonates are more sensitive than adults to nondepolarizing neuromuscular blockers.[395] More recent studies by Fisher and coworkers[137,396,397] on the pharmacokinetics and pharmacodynamics of neuromuscular blockers in infants, children, and adults, however, have made it possible to better understand the clinical pharmacology of these drugs in pediatric patients (see Chapter 82). Neonates and infants are more sensitive than adults to the neuromuscular blocking effects of dTc.[396] A lower plasma concentration of this neuromuscular blocker is required to achieve a desired level of neuromuscular blockade in these young patients. However, the dosage should not be decreased because infants have a larger volume of distribution. The increased volume of distribution and slower clearance (Fig. 29-31) contribute to a longer elimination half-life,[396,398]

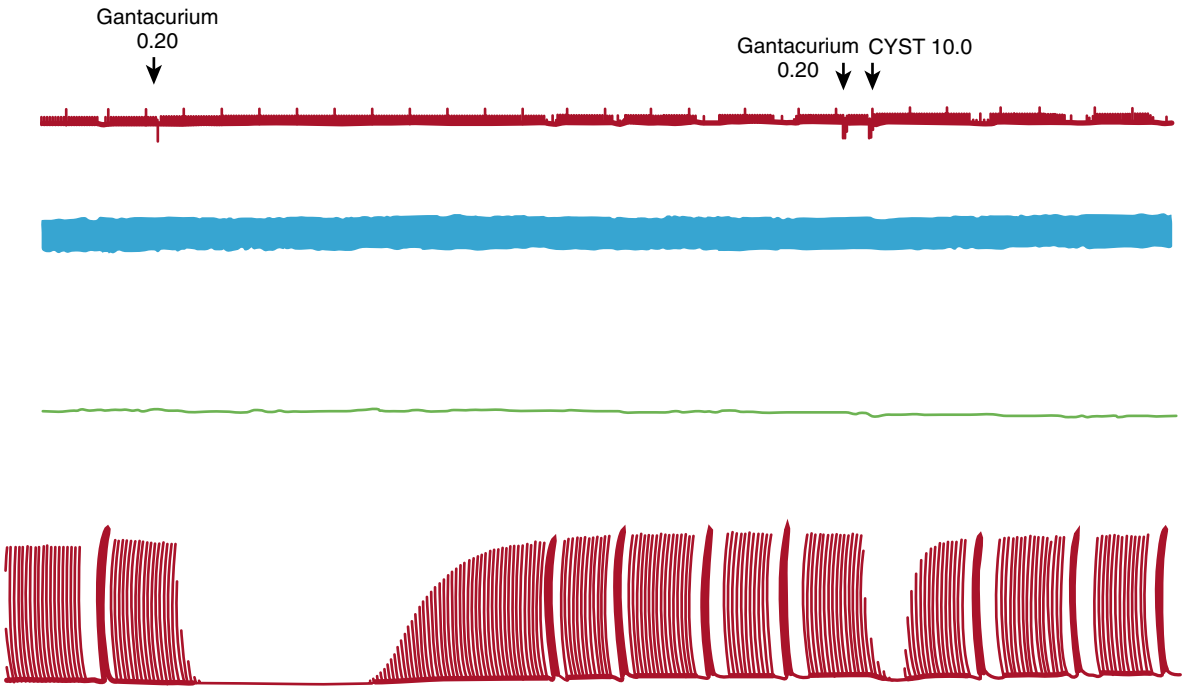


Figure 29-30 Twitch recording from a single monkey demonstrating complete spontaneous recovery from 3.2 times the ED_{95} of gantacurium, 0.2 mg/kg. Complete spontaneous recovery occurred within 10 minutes. Six minutes after complete recovery, a second dose of gantacurium, 0.2 mg/kg, was administered to this animal. Less than 1 minute later, 10 mg/kg of cysteine was administered. With cysteine administration, complete recovery occurred within 4 minutes of administering gantacurium. *(Courtesy of John J. Savarese.)*

which means that in infants, less frequent dosing (longer dosing intervals) of dTc may be required than in older children.

Atracurium, vecuronium, cisatracurium, rocuronium, and mivacurium are commonly administered to children. The popularity of these drugs in children most likely stems from the following points: minimal residual paralysis is seen in the postoperative period, and onset of action is faster in children than in adults.

Atracurium and vecuronium, in comparison, show very different kinetic and dynamic patterns in infants. As with the long-acting neuromuscular blockers, the sensitivity of infants to vecuronium is greater than it is in children (ED_{95} of 0.047 versus 0.081 mg/kg, respectively).[399] The increased duration of action in infants is most likely secondary to the increased volume of distribution of vecuronium because its clearance is unchanged.[397,398] Vecuronium therefore acts as a long-acting neuromuscular blocker in neonates.[397,398]

In contrast, the duration of action of atracurium is not significantly different in pediatric patients and adults.[400] As with vecuronium and dTc, the volume of distribution is increased in infants.[137] However, clearance of atracurium is also more rapid.[137] Therefore, the same dose (0.5 to 0.6 mg/kg) can be used in infants, children, and adults for tracheal intubation without any major difference between the three groups in its duration of action. In children, a dose of 0.1 mg/kg of cisatracurium has an onset of just over 2 minutes and a clinical duration of approximately 30 minutes during balanced or halothane anesthesia.[401] The calculated ED_{95} doses of cisatracurium in infants and children are 43

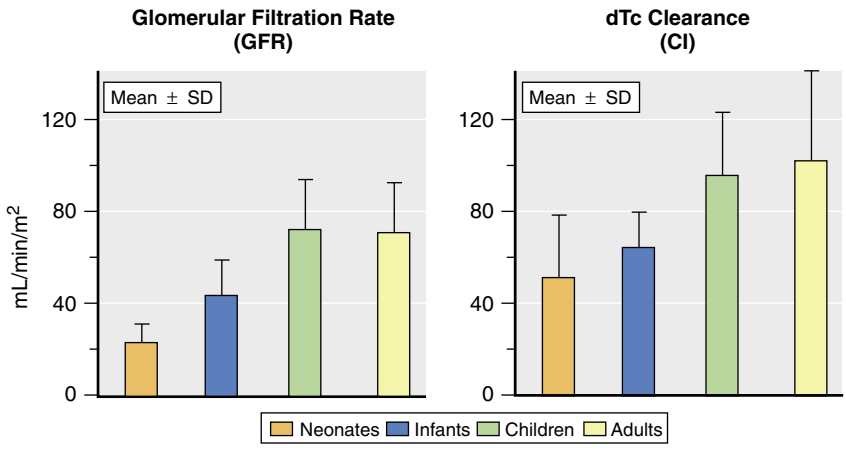


Figure 29-31 Correlation between age, glomerular filtration, and clearance of curare. *(From Fisher DM, O'Keeffe C, Stanski DR, et al: Pharmacokinetics and pharmacodynamics of d-tubocurarine in infants, children, and adults. Anesthesiology 57:203-208, 1982.)*

and 47 mg/kg, respectively.[402] The mean infusion rate necessary to maintain 90% to 99% neuromuscular blockade is also similar in infants and children.[402]

Rocuronium in adults is an intermediate-acting neuromuscular blocker with a fast onset of action, and this is also true in infants and children.[403,404] Its potency is greater in infants than in children, but its onset is faster in the latter age group.[404] In children, 0.6 mg/kg of rocuronium produces better conditions for rapid tracheal intubation than 0.1 mg/kg of vecuronium or 0.5 mg/kg of atracurium does.[403] As with adults, for rapid-sequence intubation (60 seconds) in the presence of a full stomach, a 1.2-mg/kg dose of rocuronium is suggested.

Antagonism of residual neuromuscular blockade in the case of the various nondepolarizers is similar in children and adults. Fisher and coauthors described some minor variations in the neostigmine and edrophonium dosage for pediatric patients. For example, the ED_{50} of neostigmine for antagonism of a dTc-induced 90% blockade of the adductor pollicis twitch was 22.9 μg/kg in adults versus 15.5 μg/kg in infants. In the case of edrophonium, the ED_{50} for antagonism of dTc-induced 90% blockade was 128 μg/kg in adults. In children, the ED_{50} was 233 μg/kg, and in infants it was 145 μg/kg.[405] The rate of recovery from intermediate- or short-acting neuromuscular blockers is faster than that from long-acting drugs in children.[333]

Neostigmine doses of 50 to 60 μg/kg or edrophonium doses of 500 to 1000 μg/kg should be used for antagonism of residual neuromuscular blockade in children. In all cases, tests of clinical recovery, such as head lift, leg lift, and cry, should be performed and documented for pediatric patients and adults.

Elderly Patients

The pharmacodynamics of neuromuscular blockers is altered in elderly patients (see Chapter 71). A number of physiologic changes that accompany the aging process, including decreases in total body water, increases in total body fat, decreases in hepatic and renal blood flow, and decreases in cardiac reserve, account for the altered responses of the elderly to neuromuscular blockers. A number of physiologic and anatomic changes at the neuromuscular junction also occur with aging. Such changes include an increase in the distance between the junctional axon and the motor end plate, flattening of the folds of the motor end plate, decreased concentration of acetylcholine receptors at the motor end plate, a reduction in the amount of acetylcholine in each vesicle in the prejunctional axon, and decreased release of acetylcholine from the preterminal axon in response to a neural impulse.[14] That is, the elderly and young adults have similar degrees of neuromuscular blockade at the same plasma concentration of a neuromuscular blocker. Rather, it appears that in the elderly, decreased splanchnic and renal blood flow, decreased glomerular filtration rate, and decreased hepatic function are responsible for the prolonged durations of action of most neuromuscular blockers. The greater depth of blockade with a given dose of relaxant in elderly patients than in young patients may also be due, in part, to altered volumes of distribution. The effect of aging alone, versus disease states often associated with the aging process, may be difficult to distinguish in identifying mechanisms of altered neuromuscular blocker action in the elderly.

Pancuronium,[406] vecuronium,[325,397] and rocuronium[208] all show altered pharmacodynamics and pharmacokinetics in elderly patients. Decreased clearance of each of these drugs from plasma explains their prolonged duration of action in these patients. These neuromuscular blockers depend on the kidney or the liver (or on both) for their metabolism and elimination.

In the case of drugs whose elimination is independent of hepatic or renal blood flow, pharmacokinetics and pharmacodynamics should be unaffected by age. This is true of atracurium, which depends on Hofmann elimination for its clearance.[138] Cisatracurium, which also undergoes Hofmann elimination, has a delayed onset of effect in elderly patients. The duration of action of the relaxant, however, appears to not be influenced by advanced age. The prolonged elimination half-life of the drug in the elderly is due to an increased volume of distribution. Clearance is not decreased with advanced age.

Butyrylcholinesterase activity in the elderly, though still in the normal range, is approximately 26% lower than it is in young adults.[407] Because mivacurium is metabolized by butyrylcholinesterase, its clearance is likely to be slightly reduced in the elderly; as a result, the duration of action of mivacurium is 20% to 25% longer in elderly patients,[408] and the infusion rate needed to maintain a stable depth of blockade is decreased.

In general, when maintaining neuromuscular blockade with nondepolarizing neuromuscular blockers in elderly patients, one can expect that with the exception of atracurium and cisatracurium, the dosing interval will be increased and fewer doses of neuromuscular blocker will be required to maintain the desired depth of neuromuscular blockade. The choice of drug and monitoring the depth of blockade are exceptionally important in this population because recovery of neuromuscular function is generally delayed in the elderly. Inadequate or incomplete recovery of muscle strength after the use of pancuronium is associated with an increased incidence of perioperative pulmonary complications in this patient population.[336]

Obese Patients

Reports on the effect of obesity on the pharmacodynamics of nondepolarizing neuromuscular blockade are conflicting. Although the duration of action of pancuronium is unaffected by a patient's weight,[409] obese patients recover more slowly from vecuronium-[410] or rocuronium-induced[411] neuromuscular blockade. These findings imply that elimination of these drugs is decreased. Recovery from atracurium-induced neuromuscular blockade, however, is not affected by obesity,[410] most likely because of lack of dependence on end-organ function for elimination.

Neuromuscular blockers should be administered to obese patients on the basis of about 20% more than lean body mass rather than on their actual body weight[412] to ensure that these patients are not receiving relative overdoses.

Severe Renal Disease

Renal failure influences the pharmacologic characteristics of nondepolarizing neuromuscular blockers either by decreased elimination of the drug or its metabolites via the kidney or by decreased activity of butyrylcholinesterase (Table 29-13). Consequently, the duration of action of neuromuscular blockers may be prolonged in patients with renal failure (see Chapters 65 and 67).

Table 29-13 Pharmacokinetics of Neuromuscular Blocking Drugs in Patients with Normal Renal Function or Renal Failure

	Plasma Clearance (mL/kg/min)		Volume of Distribution (mL/kg)		Elimination Half-life (min)		
	Normal Function	Renal Failure	Normal Function	Renal Failure	Normal Function	Renal Failure	Reference
Short-Acting Drugs							
Mivacurium isomers							183
Cis-trans	106	80	278	475	2.0	4.3	
Trans-trans	57	48	211	270	2.3	4.3	
Cis-cis	3.8	2.4a	227	244	68	80	
Intermediate-Acting Drugs							
Atracurium	6.1	6.7	182	224	21	24	204
	5.5	5.8	153	141	19	20	205*†
	10.9	7.8	280	265	17.3	19.7	413
Cisatracurium	5.2	—	31	—	—	—	203
Vecuronium	3.0	2.5	194	239	78	97	414
	5.3	3.1[a]	199	241	53	83[a]	415
Rocuronium	2.9	2.9	207	264[a]	71	97[a]	206
Long-Acting Drugs							
d-Tubocurarine	2.4	1.5	250	250	84	132	120
Pancuronium	74	20*	148	236*	97	475*	129†
	1.7	0.9	261	296*	132	257*	416

*Significant difference between normal renal function and renal failure.
†Values expressed as milliliters per minute, not weight adjusted.

Renal failure does not alter the sensitivity (dose-response relationship) of patients to the neuromuscular blocking action of pancuronium,[130] atracurium,[417] vecuronium,[418] or rocuronium.[419]

All long-lasting muscle relaxants are eliminated predominantly via the kidney, and renal failure is associated with reduced plasma clearance and an increased elimination half-life of these drugs as well.[107] As a consequence of these pharmacokinetic changes, the duration of neuromuscular blockade produced by these drugs is longer and more variable than in patients with normal renal function. Because of the potential for prolonged blockade and the availability of intermediate- and short-acting neuromuscular blockers, there is no longer any reason to recommend the use of the long-acting neuromuscular blockers in patients with renal failure.

The pharmacokinetics and duration of action of atracurium are unaffected by renal failure.[413,420] This lack of effect occurs in part because Hofmann elimination and ester hydrolysis[205] account for 50% of its total clearance.[191] The elimination half-life of laudanosine, the principal metabolite of atracurium, increases in renal failure.[413] Recent evidence suggests, however, that significant concentrations of laudanosine are not achieved during the administration of atracurium in the operating room setting.[413]

In patients with chronic renal failure, the duration of action of cisatracurium is not prolonged.[154] Hofmann elimination accounts for 77% of the total clearance of cisatracurium,[203] and renal excretion accounts for 16% of its elimination.[203] Clearance of the drug is slightly decreased (by 13%) in this patient population.

Vecuronium relies principally on hepatic, not renal, mechanisms for its elimination. However, its clearance is reduced and its elimination half-life is increased in patients with renal failure.[414,415] In one study, the duration of action of 0.1 mg/kg of vecuronium was both longer and more variable in patients with renal failure than in those with normal renal function.[415] In three other studies, the duration of action of 0.05 to 0.14 mg/kg of vecuronium was not prolonged by renal failure, but this result was probably due to the use of relatively small doses or inadequate sample sizes.[414] The principal metabolite of vecuronium, 3-desacetylvecuronium, has 80% of the neuromuscular blocking activity of vecuronium[177]; it may cause prolonged paralysis in patients with renal failure in the ICU.[179] In patients with renal failure, the duration of action and rate of recovery from vecuronium- or atracurium-induced neuromuscular blockade during surgery are similar.[421]

Plasma clearance of rocuronium may be decreased in patients with renal failure and its volume of distribution increased.[206] The duration of action of single and repeated doses, though, is not significantly affected.[419] When rocuronium is administered to patients with renal failure undergoing renal transplantation as opposed to patients with normal renal function, plasma clearance is unchanged (2.89 mL/kg/min), the volume of distribution is increased by 28%, and its elimination half-life is lengthened by 37% (see Fig. 29-16).[206]

Hepatobiliary Disease

Patients with hepatobiliary disease may exhibit prolonged blockade with pancuronium,[175] vecuronium,[127] rocuronium,[207,210] and mivacurium (see Chapters 66 and 67).[182] In the case of pancuronium,[175] vecuronium,[127] and mivacurium,[182] this prolonged action is associated with decreased plasma clearance of the drug. However, this relationship is not consistent, and many studies have described a reduction in clearance without a prolonged duration of action. In the case of atracurium, one study even demonstrated increased clearance in patients with cirrhosis, but the duration of action was normal.[193]

The influence of hepatobiliary disease on the pharmacokinetics of neuromuscular blockers is complex (Table 29-14). In

Table 29-14 Pharmacokinetics of Neuromuscular Blocking Drugs in Patients with Normal Liver Function or Hepatobiliary Disease

	Plasma Clearance (mL/kg/min)		Volume of Distribution (mL/kg)		Elimination Half-life (min)			
	Normal	Disease	Normal	Disease	Normal	Disease	Hepatic Pathology	Reference
Short-Acting Drugs								
Mivacurium isomers							Cirrhosis	182
Cis-trans	95	44*	210	188	1.53	2.48*		
Trans-trans	70	32*	200	199	2.32	11.1*		
Cis-cis	5.2	4.2	266	237	50.3	60.8		
Intermediate-Acting Drugs								
Atracurium	5.3	6.5	159	207*	21	22	Hepatorenal	417
	6.6	8.0*	202	282*	21	25	Cirrhosis	193
Cisatracurium	5.7	6.6*	161	195*	23.5	24.4	Transplantation-related	
Vecuronium	4.26	2.73*	246	253	58	848	Cirrhosis	127
	4.30	2.36*	247	206	58	98*	Cholestasis	422
	4.5	4.4	180	220	58	51	Cirrhosis	178
Rocuronium	2.79	2.41	184	234	87.5	96.0	Cirrhosis	207
	217	217	16.4	23.4*	76.4	111.5*	Mixed	209†
	296	189	151	264*	56	98*	Cirrhosis	423†
	3.70	2.66*	211	248	92	143*	Cirrhosis	210
Long-Acting Drugs								
Pancuronium	123	59*	261	307*	133	267*	Cholestasis	175†
	1.86	1.45*	279	416*	114	2088	Cirrhosis	174
	1.76	1.47	284	425*	141	224*	Cholestasis	424

*Significant difference between normal hepatic function and hepatobiliary disease.
†Values expressed as milliliters per minute or liters, not weight adjusted.

most studies, hepatic disease has been associated with an increased volume of distribution and, as a result, apparent resistance to the effect of dTc,[193] atracurium,[425] pancuronium,[423] and rocuronium.[426] The effect of hepatic disease on the pharmacokinetics of neuromuscular blockers (see Table 29-14) suggests that initial doses may need to be greater than those in patients with normal hepatic function but that once the desired level of blockade has been achieved, subsequent recovery may be slower. This is illustrated in the case of vecuronium, in which doses of up to 0.15 mg/kg have a normal duration of action[178,427] but a dose of 0.2 mg/kg results in prolonged action (see Fig. 29-14).[422]

Hepatic disease can alter the elimination of neuromuscular blockers by several mechanisms. The principal route of metabolism of pancuronium and vecuronium is deacetylation at the 3-position.[173] This metabolic process is presumed to occur in the liver because 10% to 20% of the total dose of pancuronium and 40% of that of vecuronium is found in the liver and bile as both parent drug and metabolite.[173] In hepatic disease, an increased plasma concentration of bile salts can reduce the hepatic uptake of pancuronium and vecuronium,[173] which may be an explanation for the decreased clearance of these drugs observed by some investigators.[174,175] Excretion of vecuronium is diminished in the presence of decreased hepatic function.[397] The duration of action of vecuronium is longer in these patients, and recovery is slower than in young healthy individuals.

Atracurium and cisatracurium share organ-independent modes of elimination.[189,202,203] As a consequence, their clearance should be little affected by hepatic disease. In fact and in contrast with that of all other neuromuscular blockers, plasma clearance of atracurium and cisatracurium is slightly increased in patients with liver disease (see Table 29-14).[193,211] Because elimination of atracurium and cisatracurium occurs outside of as well as from within the central compartment, it has been suggested that a larger volume of distribution should be associated with greater clearance.[203] In two studies,[193,211] the volume of distribution and clearance of the drugs increased with liver disease, thus lending support to this hypothesis.[203] The increased clearance of the relaxant in patients with liver disease is not reflected in a decrease in the drug's duration of action.[193,211]

One concern raised about administering atracurium to patients with hepatic disease was the possible accumulation of laudanosine. Although laudanosine relies principally on hepatic mechanisms for elimination, the concentrations encountered during liver transplantation are unlikely to be associated with clinical sequelae.[428]

In patients with hepatic disease (most commonly cirrhosis), the volume of distribution of rocuronium is increased,[207,209,210,426] and its clearance may be decreased.[210] The duration of action of rocuronium is prolonged in patients with hepatic disease,[207,210,426] and its onset may be prolonged.[207]

In patients with severe liver disease, butyrylcholinesterase activity is decreased because of decreased synthesis of the hepatic enzymes. Consequently, plasma clearance of the isomers of mivacurium is decreased by approximately 50% (see Table 29-14),[182] and its duration of action is prolonged and may be almost tripled.[182]

Burns

After a period of immobilization, burn injury causes upregulation of both fetal ($\alpha_2\beta\gamma\delta$) and mature ($\alpha_2\beta\varepsilon\delta$) nAChRs.[429] This upregulation of nAChRs is usually associated with resistance to nondepolarizing neuromuscular blockers and increased sensitivity to succinylcholine.[430] Causes of upregulation of nAChRs are listed in Box 29-1. A significant increase in the quantal content of evoked acetylcholine release is noted by 72 hours after scald injury in rats.[431] This also contributes to the resistance to nondepolarizing blockers in burn patients. In mice, thermal injury induces changes in diaphragm acetylcholinesterase with respect to total content and specific molecular forms.[432]

Resistance to the effects of nondepolarizing neuromuscular blocking drugs is usually seen in patients with burns over at least 25% of their total body surface area.[140,430] Recovery of neuromuscular function to preburn levels may take several months or even years after the burn injury.[433] The increase in serum potassium concentration that normally follows the administration of succinylcholine is markedly exaggerated in burned victims.[434] Potassium concentrations as high as 13 mEq/L have been reported to result in ventricular tachycardia, fibrillation, and cardiac arrest.[434] The magnitude of the hyperkalemic response does not appear to closely correlate with the magnitude of the burn injury. Potentially lethal hyperkalemia was seen in a patient with only an 8% total body surface area burn.[435] Succinylcholine has been safely administered within 24 hours of a burn injury. After this initial 24 hours, however, sufficient alteration in muscle response may have occurred, and the use of succinylcholine is best avoided.

The time course of abnormal muscle membrane function corresponds with that of the healing process. Once normal skin has regrown and any infection subsides, the normal acetylcholine receptor populations appear to return.[433] Normal responses to succinylcholine have been demonstrated in burn patients studied 3 years after injury.[433] The length of time during which a burn patient may be at risk for a hyperkalemic response is not well defined. A conservative guideline therefore would be to avoid the use of succinylcholine in patients 24 to 48 hours after a thermal injury and for at least 1 or 2 years after the burned skin has healed.

Box 29-1 Conditions Associated with Upregulation and Downregulation of Acetylcholine Receptors

- nAChR upregulation
  - Spinal cord injury
  - Stroke
  - Burns
  - Prolonged immobility
  - Prolonged exposure to neuromuscular blockers
  - Multiple sclerosis
  - Guillain-Barré syndrome
- nAChR downregulation
  - Myasthenia gravis
  - Anticholinesterase poisoning
  - Organophosphate poisoning

nAChR, nicotinic acetylcholine receptor.
From Naguib M, Flood P, McArdle JJ, Brenner HR: Advances in neurobiology of the neuromuscular junction: Implicatifons for the anesthesiologist. Anesthesiology 96:202-231, 2002, with permission from Anesthesiology.

Box 29-2 Reported Indications for the Use of Muscle Relaxants in the Intensive Care Unit

- Facilitate mechanical ventilation
  - Facilitation of endotracheal intubation
  - Enable patients to tolerate mechanical ventilation
  - High pulmonary inflation pressures, e.g., acute respiratory distress syndrome
- Hyperventilation for increased intracranial pressure
- Facilitate therapeutic or diagnostic procedures
- Tetanus
- Status epilepticus
- Reduce oxygen consumption
  - Abolish shivering
  - Reduce work of breathing

Neuromuscular Blockers and Weakness Syndromes in the Critically Ill

Neuromuscular blocking drugs are frequently used in conjunction with sedatives and analgesics in ICUs. Indications for the use of neuromuscular blockers in the ICU are outlined in Box 29-2. Few available data support their use, and evidence for a beneficial effect on pulmonary function or patient oxygenation is inconclusive.[436] Yet nondepolarizing neuromuscular blockers are commonly used for weeks in ICU patients, most of the time without monitoring and frequently at doses exceeding those used in the operating room.[437] The results of two surveys in the United States, including anesthesiologists and nurses with special certificates of competence in critical care, indicated that 98% of those surveyed use neuromuscular blocking drugs at least occasionally.[437]

Of particular concern in intensive care settings is the risk that paralyzed patients will receive inadequate analgesia and sedation.[438] This may be due to the fact that ICU nurses and physicians are unfamiliar with the pharmacology of neuromuscular blocking drugs.[437,438] For instance, pancuronium was thought to be an anxiolytic by 50% to 70% of ICU nurses and house staff, and 5% to 10% thought that it was an analgesic.[438] In the United Kingdom, the erroneous use of neuromuscular blockers as sedatives in intensive care was not uncommon in the 1980s.[439] Approximately 96% of ICU patients received neuromuscular blockers to aid mechanical ventilation in 1980. By 1986, their use had fallen to 16% of ventilated patients.[439] In the United States, neuromuscular blockers are used in less than 20% of all patients requiring mechanical ventilation.[437]

A prolonged ICU stay during critical illness is associated with disorders of neuromuscular function that contribute to morbidity, length of hospital stay, weaning difficulty, and prolonged rehabilitation.[440] Complications of long-term administration of

Box 29-3 Complications of Muscle Paralysis in the Intensive Care Unit

- Short-term use
  - Specific, known drug side effects
  - Inadequate ventilation in the event of ventilator failure or circuit disconnection
  - Inadequate analgesia and/or sedation
- Long-term use
  - Complications of immobility
    - Deep venous thrombosis and pulmonary embolism
    - Peripheral nerve injuries
    - Decubitus ulcers
  - Inability to cough
    - Retention of secretions and atelectasis
    - Pulmonary infection
- Dysregulation of nicotinic acetylcholine receptors
- Prolonged paralysis after stopping relaxants
  - Persistent neuromuscular blockade
  - Critical illness myopathy
  - Critical illness polyneuropathy
  - Combination of the above
- Unrecognized effects of drug or metabolites
  - Succinylcholine and metabolic acidosis/hypovolemia
  - 3-Desacetylvecuronium and neuromuscular blockade
  - Laudanosine and cerebral excitation

neuromuscular blockers in the ICU are outlined in Box 29-3. In the ICU, the duration of mechanical ventilation, sepsis, dysfunction of two or more organs, female sex, administration of steroids, and hypercapnia are known risk factors for the development of neuromuscular dysfunction. Syndromes of weakness in critically ill patients are relatively common and probably polymorphic in origin. In a retrospective study of 92 critically ill patients with clinically diagnosed weakness, electromyographic studies indicated that acute myopathy (critical illness myopathy) is three times as common as acute axonal neuropathy (critical illness neuropathy): 43% versus 13%, respectively.[440] The additional health care cost of one case of persistent weakness was estimated to be approximately $67,000.[441] Conditions to consider in the differential diagnosis of neuromuscular weakness in the ICU are listed in Box 29-4.

Critical Illness Myopathy

Lacomis and colleagues[442] suggested using the term "critical illness myopathy" (CIM) instead of the current terms used in the literature, such as acute quadriplegic myopathy,[443] acute (necrotizing) myopathy of intensive care, thick filament myopathy, acute corticosteroid myopathy, and critical care myopathy.

Most published reports of CIM in the ICU have focused on patients with status asthmaticus.[444] Affected individuals typically have been treated with corticosteroids and nondepolarizing neuromuscular blockers. Nevertheless, myopathy has also been documented in asthmatic patients and those with chronic lung disease without paralysis who received corticosteroids[445] and in critically ill patients with sepsis who received neither corticosteroids nor nondepolarizing neuromuscular blockers.[446] Animal studies have revealed that the number of cytosolic corticosteroid receptors is increased in immobilized muscles relative to contralateral controls.[447] It seems—at least in some patients—that prolonged immobility may be the key risk factor for myopathy in corticosteroid-treated patients[448] and that selective muscle atrophy is a result of changes in glucocorticoid sensitivity.[447]

Sepsis, immobility, and the catabolism associated with negative nitrogen balance may also result in myopathy.[14] Skeletal muscle hypoperfusion is noted in patients with severe sepsis despite normal or elevated whole blood oxygen delivery.[449] Antibodies to nAChRs have been demonstrated in a rodent model of sepsis.[450] Thus, myasthenia-like syndrome is also seen in critically

Box 29-4 Causes of Generalized Neuromuscular Weakness in the Intensive Care Unit

- Central nervous system
  - Septic or toxic-metabolic encephalopathy
  - Brainstem stroke
  - Central pontine myelinolysis
  - Anterior horn cell disorders (e.g., amyotrophic lateral sclerosis)
- Peripheral neuropathies
  - Critical illness polyneuropathy
  - Guillain-Barré syndrome
  - Porphyria
  - Paraneoplasia
  - Vasculitis
  - Nutritional and toxic
- Neuromuscular junction disorders
  - Myasthenia gravis
  - Lambert-Eaton myasthenic syndrome
  - Botulism
  - Prolonged neuromuscular junction blockade
- Myopathies
  - Critical illness myopathy
  - Cachectic myopathy
  - Rhabdomyolysis
  - Inflammatory and infectious myopathies
  - Muscular dystrophies
  - Toxic
  - Acid maltase deficiency
  - Mitochondrial
  - Hypokalemia
  - Hypermetabolic syndromes with rhabdomyolysis (e.g., neuroleptic malignant syndrome)

From Lacomis D: Critical illness myopathy. Curr Rheumatol Rep 4:403-408, 2002.

ill patients. Evidence of local immune activation by cytokine expression in skeletal muscle was reported in patients with CIM.[451]

The major feature of CIM is flaccid weakness that tends to be diffuse and sometimes also includes the facial muscles and diaphragm.[442] The clinical features of CIM overlap with those of critical illness polyneuropathy (CIP) and prolonged neuromuscular blockade.[442] Electrophysiologic studies and increases in serum creatine kinase concentration may differentiate neuropathy from myopathy.[442] Lacomis and coworkers[442] stated that "muscle biopsy should be considered if another myopathic process such as an inflammatory myopathy is suspected or if the histologic findings would affect management."

Critical Illness Polyneuropathy

The polyneuropathy seen in the critically ill has been termed "critical illness polyneuropathy (CIP)." It affects both sensory and motor nerves and occurs in 50% to 70% of patients with multisystem organ failure and systemic inflammatory response syndrome.[452] It has been postulated that systemic inflammatory response syndrome contributes to CIP by releasing cytokines and free radicals that damage the microcirculation of the central and peripheral nervous systems.[451] Dysregulation of the microcirculation may render the peripheral nervous system susceptible to injury.

No specific treatment of weakness syndromes in critically ill patients is available other than physical rehabilitation. Intravenous immunoglobulin and nerve growth factors appear to be promising in CIP syndrome. Recently, intensive insulin therapy during critical illness has been found to decrease the risk for CIP, and maintenance of blood glucose at or below 110 mg/mL in critically ill patients may reduce the risk for CIP.[453]

Outcomes after CIM and CIP appear to be similar.[440] The reported mortality rate of patients with CIP syndrome is about 35%. In one study, 100% (13 of 13) of the patients who survived had abnormal clinical or neurophysiologic findings 1 to 2 years after the onset of CIP syndrome, and quality of life was markedly impaired in all patients.[454]

Clinical Implications

Should Succinylcholine Be Used in ICU Patients?

It is likely that the upregulation of nAChRs induced by immobilization and by prolonged administration of nondepolarizing neuromuscular blockers contributes to (1) the higher incidence of cardiac arrest associated with the use of succinylcholine in ICU patients[455] and (2) increased requirements for nondepolarizing neuromuscular blockers in ICU patients.[456] Upregulation of nAChRs was noted in the muscles of deceased critically ill adults who had received long-term infusions of vecuronium.[455] Therefore, succinylcholine is best avoided in ICU patients in whom total body immobilization exceeds 24 hours.[14] In a survey in U.K. ICUs, 68.7% of respondents indicated that they would use succinylcholine in a clinical scenario suggestive of CIP.[457] This highlights the lack of awareness of the dangers associated with the use of succinylcholine in these patients.[457]

Should Nondepolarizing Neuromuscular Blockers Be Used in ICU Patients?

Nondepolarizing neuromuscular blocker–associated persistent weakness appears to be a distinct pathologic entity and is not simply a manifestation of weakness syndromes in the critically ill. In a prospective study, Kupfer and associates[458] showed a 70% incidence of persistent weakness in ICU patients who received neuromuscular blockers for more than 2 days versus a 0% incidence in similar ICU patients who did not receive a neuromuscular blocker. This is compelling evidence for the effects of nondepolarizing neuromuscular blockers in this complication.

Long-term weakness has been described after all commonly used nondepolarizing neuromuscular blockers.[179,459,460] The overall incidence of prolonged paralysis after long-term use of neuromuscular blockers is about 5%. Prolonged weakness developed in approximately 20% of patients who received neuromuscular blockers for more than 6 days,[459] in 15% to 40% of asthmatic patients who also received high-dose steroids,[444] and in 50% of patients with renal failure who received vecuronium.[179] Clinically, it appears that prolonged recovery from neuromuscular blockade occurs more frequently when steroidal neuromuscular blockers are used.[179,459]

However, prolonged weakness was also noted after the use of atracurium in ICU patients.[460] Furthermore, the use of atracurium has raised concern about its metabolite laudanosine. Laudanosine, also detected in the cerebrospinal fluid (CSF) of ICU patients given atracurium,[461] is an analeptic and can trigger seizures in animals.[462] The toxic dose in humans is not known, but there are case reports of patients having seizures while receiving atracurium, and laudanosine has not been ruled out as a cause of these seizures.[463-465] There is also evidence that laudanosine can activate neuronal nicotinic receptors.[466] Cisatracurium is a single isomer of atracurium, and because it is four to five times more potent than atracurium, it is given in smaller doses. Therefore, the risk of laudanosine-related adverse effects should be minimal.[199]

Nondepolarizing neuromuscular blockers are polar molecules and do not cross the blood-brain barrier readily, but vecuronium and its long-acting active metabolite 3-desacetylvecuronium have been detected in the CSF of patients in the ICU. The CNS effects of neuromuscular blockers and their metabolites in humans have not been well studied, but in rats, atracurium, pancuronium, and vecuronium injected into CSF will cause dose-related cerebral excitation culminating in seizures.[462] Cerebral excitation with consequent increased cerebral oxygen demand is undesirable in ICU patients at risk for cerebral ischemia. It has also been suggested that nondepolarizing neuromuscular blockers can gain access to nerves during systemic inflammatory response syndrome and thereby result in direct neurotoxicity.[462]

Combining corticosteroids and nondepolarizing neuromuscular blockers should be avoided. When nondepolarizing neuromuscular blockers are necessary, the use of a peripheral nerve stimulator is recommended, and periodic return of muscle function should be allowed. However, routine monitoring of neuromuscular function alone is insufficient in eliminating prolonged recovery and weakness syndromes in ICU patients.[467] Adjusting the dosage of neuromuscular blockers by peripheral nerve stimulation versus standard clinical dosing in critically ill patients reduces drug requirements, produces faster recovery of neuromuscular function, and results in a total cost savings of $738 per patient.[468] A recent study found that daily interruption of sedative-drug infusions decreases the duration of mechanical ventilation and length of stay in the ICU.[469] The effect of such an approach on weakness syndromes in ICU patients is unknown. When nondepolarizing neuromuscular blockers are used, the guidelines in Box 29-5 may help minimize the incidence of

Box 29-5 Recommendations for the Use of Neuromuscular Blockers in the Intensive Care Unit

Avoid the use of neuromuscular blockers by:
- Maximal use of analgesics and sedatives
- Manipulation of ventilatory parameters and modes

Minimize the dose of neuromuscular blocker:
- Use a peripheral nerve stimulator with train-of-four monitoring.
- Do not administer for more than 2 days continuously.
- Administer by bolus rather than infusion.
- Administer only when required and to achieve a well-defined goal.
- Continually allow recovery from paralysis.

Consider alternative therapies:
- Avoid vecuronium in female patients with renal failure.
- Use isoflurane in place of muscle relaxants in patients with severe asthma.
- Minimize the dose of steroid in patients with asthma.

complications. As stated in the clinical practice guidelines for sustained neuromuscular blockade in adult critically ill patients,[436] "*Independent of the reasons for using neuromuscular blockers, we emphasize that all other modalities to improve the clinical situation must be tried, using neuromuscular blockers only as a last resort.*"

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Charles B. Berde and Gary R. Strichartz

30 Local Anesthetics

Key Points

1. Local anesthetics block voltage-gated sodium channels and thereby interrupt initiation and propagation of impulses in axons, but they have a wide variety of other biologic actions, desirable and undesirable.
2. Currently available local anesthetics are of two chemical classes: aminoesters and aminoamides.
3. The low potency and lack of specificity of available local anesthetics are due in part to the very weak structural constraints at their binding site on the sodium channel. Most of their features derive from the requirement for high solubility and rapid diffusion in both aqueous environments and the lipid phases of biologic membranes.
4. Reversible protonation of the tertiary amine group tends to make local anesthetics less charged at more basic pH and more charged at neutral or acidic pH; the neutral base forms are more soluble in lipid environments, whereas the charged acid forms are more soluble in aqueous environments.
5. Aminoesters are metabolized primarily by plasma esterases, and aminoamides are metabolized primarily by hepatic cytochrome P450–linked enzymes.
6. The principal systemic toxicities of local anesthetics involve the heart (including atrioventricular conduction block, arrhythmias, myocardial depression, and cardiac arrest) and the brain (including agitation, lethargy, seizures, and generalized central nervous system depression). Hypoxemia and acidosis exacerbate these toxicities. Resuscitation after bupivacaine overdose is particularly difficult. Therefore, prevention of intravascular injection or overdose is crucial, and major nerve blockade should involve incremental, fractionated dosing.
7. Local anesthetics are directly toxic to nerve at the concentrations supplied in commercial solutions. Intraneural concentrations during regional anesthesia are generally (but not always) below a threshold for toxicity because of spread of solutions through tissues and diffusion gradients from injection sites into nerve. Injection into a constrained tissue space increases the risk for local toxicity.
8. Optimal use of local anesthetics in regional anesthesia requires an understanding of (1) the individual patient's clinical situation; (2) the location, intensity, and duration of regional anesthesia and analgesia required; (3) anatomic factors affecting deposition of drug near nerves; (4) proper drug selection and dosing; and (5) ongoing assessment of clinical effects after administration of a local anesthetic.
9. Recent efforts have led to the development of several new formulations for topical anesthesia. Single-stereoisomer (as opposed to a racemic mixture) formulations have been developed in an effort to reduce systemic toxicity and improve sensory selectivity.
10. Local anesthetics are increasingly being used for postoperative infusions and via both local and systemic administration for the management of chronic pain. Further research and development may lead to safe, more selective agents that will facilitate more prolonged administration in the setting of acute or chronic pain.

Local anesthesia results from the blockade of nerve impulses to abolish sensation. All currently available, clinically useful agents are either aminoesters or aminoamides. These drugs, when applied in sufficient concentration at the site of action, prevent conduction of electrical impulses by the membranes of nerve and muscle. In addition to blockade of impulses, local anesthetics can inhibit various receptors, enhance release of glutamate, and depress the activity of certain intracellular signaling pathways. When local anesthetic agents are given systemically, the functions of cardiac, skeletal, and smooth muscle, as well as transmission of impulses in the central and peripheral nervous systems and within the specialized conducting system of the heart, may all be altered. Local anesthetics may abolish sensation in various parts of the body by topical application, injection in the vicinity of peripheral nerve endings and major nerve trunks, or instillation within the epidural or subarachnoid spaces. Toxicity may be local or sys-

temic. The central nervous and cardiovascular systems are most commonly involved in acute clinical toxicity.

Basic Pharmacology

Chemistry

The Local Anesthetic Molecule

The typical local anesthetic molecule, exemplified by lidocaine and procaine (Fig. 30-1), contains a tertiary amine attached to a substituted aromatic ring by an intermediate chain that almost always contains either an ester (—C(=O)—O—) or an amide (—NHC(=O)—) linkage; local anesthetics may therefore be classified as aminoester or aminoamide compounds. The aromatic ring system gives a lipophilic (membrane-liking) character to its portion of the molecule, whereas the tertiary amine end is relatively hydrophilic, particularly since it is partially protonated and thus bears some positive charge in the physiologic pH range (Fig. 30-2). The structures of commonly administered local anesthetics are given in Table 30-1 and their physicochemical properties in Table 30-2.

Structure-Activity Relationships and Physicochemical Properties

The intrinsic potency and duration of action of local anesthetics are clearly dependent on certain features of the molecule.

Lipophilic-Hydrophilic Balance

The lipophilic versus hydrophilic character of a local anesthetic depends on the size of alkyl substituents on or near the tertiary amine and on the aromatic ring. "Lipophilicity" expresses the tendency of a compound to associate with membrane lipids, a property usually approximated by equilibrium partitioning into a hydrophobic solvent such as octanol.[1] Although octanol-buffer partition coefficients are comparable to membrane-buffer partition coefficients for the uncharged species of local anesthetics, they severely underestimate membrane partitioning for the charged, protonated species, octanol being a poor model for the polar regions near the membrane surface where local anesthetics are concentrated.[2] Here we use the term "hydrophobicity," expressed as octanol-buffer partitioning, to describe a physicochemical property of local anesthetics.

Compounds with a more hydrophobic nature are obtained by increasing the size of the alkyl substituents. These agents are more potent and produce longer-lasting blocks than their less hydrophobic congeners do.[3-5] For example, etidocaine, which has three more carbon atoms than lidocaine does in the amine end of the molecule, is four times as potent and five times as long lasting when compared by impulse blockade in the isolated sciatic nerve.

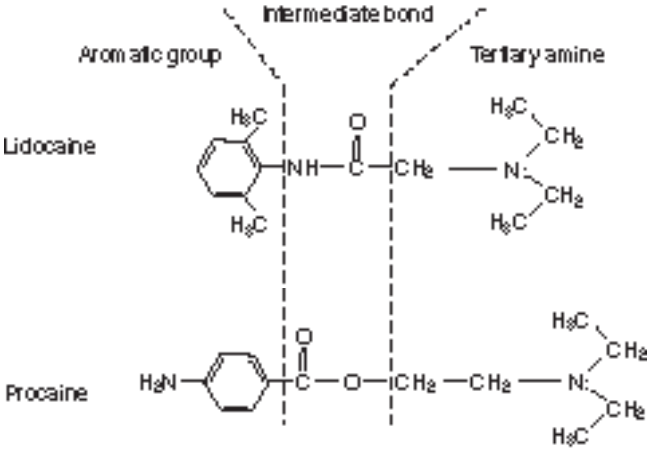


Figure 30-1 Structures of two local anesthetics, the aminoamide lidocaine and the aminoester procaine. In both drugs a hydrophobic aromatic group is joined to a more hydrophilic base, the tertiary amine, by an intermediate amide or ester bond.

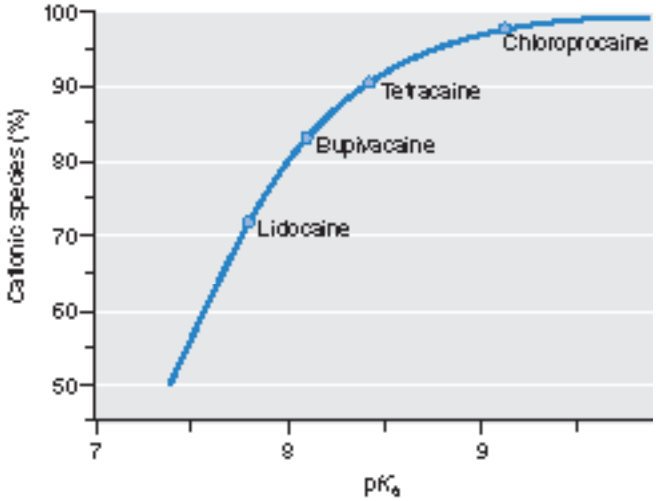


Figure 30-2 Fraction of local anesthetic in the protonated, cationic form of an aqueous solution at physiologic pH (7.4) as a function of the pK_a of the drug. Lidocaine, the drug with the lowest pK_a, has the smallest fraction of its molecules protonated, the largest in the neutral form, and vice versa for chloroprocaine, the local anesthetic with the highest pK_a. Individual drug molecules become protonated and deprotonated in thousandths of a second in solution.

Hydrogen Ion Concentration

Local anesthetics in solution exist in a very rapid chemical equilibrium between the basic uncharged form (B) and the charged cationic form (BH^+). At a certain hydrogen ion concentration ($\log_{10}^{-1}$ [–pH]) specific for each drug, the concentration of local anesthetic base in solution is equal to the concentration of charged cation. The logarithm of this hydrogen ion concentration is called pK_a. The relationship is defined by

$$\frac{[BH^+]}{[B]} = 10^{pK_a - pH} \quad (1)$$

pK_a values of local anesthetic agents in aqueous solution are listed in Table 30-2. The tendency to be protonated also

Table 30-1 Representative Local Anesthetics in Common Clinical Use

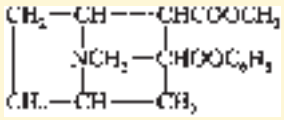
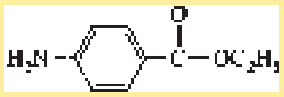
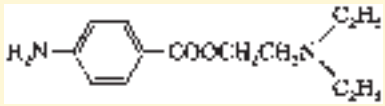
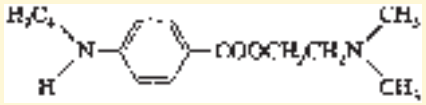
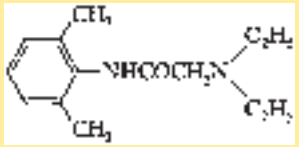
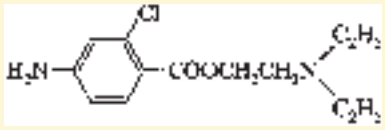
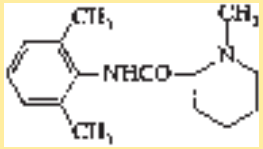
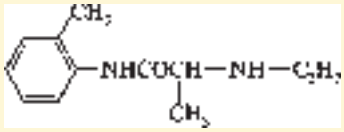
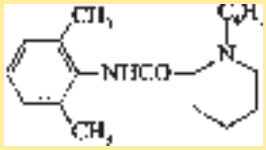
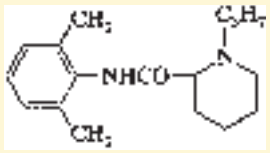
Generic* and Common Proprietary Name	Chemical Structure	Approximate Year of Initial Clinical Use	Main Anesthetic Use	Representative Commercial Preparation
Cocaine		1884	Topical	40 mg/mL solution
Benzocaine (Americaine)		1900	Topical	200 mg/mL
			Topical	200 mg/mL
Procaine (Novocain)		1905	Infiltration	10- and 20-mg/mL solutions
			Spinal	100-mg/mL solution
Dibucaine (Nupercaine)		1929	Spinal	0.667-, 2.5-, and 5-mg/mL solutions
Tetracaine (Pontocaine)		1930	Spinal	Niphanoid crystals—20- and 10-mg/mL solutions
Lidocaine (Xylocaine)		1948	Infiltration	5- and 10-mg/mL solutions
			Peripheral nerve blockade	10-, 15-, and 20-mg/mL solutions
			Epidural	10-, 15-, and 20-mg/mL solutions
			Spinal	50-mg/mL solution
			Topical	20 mg/mL jelly, viscous
			Topical	25, 50 mg/mL ointment
Chloroprocaine (Nesacaine)		1955	Infiltration	10-mg/mL solution
			Peripheral nerve blockade	10- and 20-mg/mL solutions
			Epidural	20- and 30-mg/mL solutions
Mepivacaine (Carbocaine)		1957	Infiltration	10-mg/mL solution
			Peripheral nerve blockade	10- and 20-mg/mL solutions
			Epidural	10-, 15-, and 20-mg/mL solutions

Table 30-1 Representative Local Anesthetics in Common Clinical Use—cont'd

Generic* and Common Proprietary Name	Chemical Structure	Approximate Year of Initial Clinical Use	Main Anesthetic Use	Representative Commercial Preparation
Prilocaine (Citanest)		1960	Infiltration	10- and 20-mg/mL solutions
			Peripheral nerve blockade	10-, 20-, and 30-mg/mL solutions
			Epidural	10-, 20-, and 30-mg/mL solutions
Bupivacaine (Marcaine)		1963	Infiltration	2.5-mg/mL solution
			Peripheral nerve blockade	2.5- and 5-mg/mL solutions
			Epidural	2.5-, 5-, and 7.5-mg/mL solutions
			Spinal	5- and 7.5-mg/mL solutions
Ropivacaine (Naropin)		1992	Infiltration	2.5- and 5-mg/mL solutions
			Peripheral nerve blockade	5- and 10-mg/mL solutions
			Epidural	5- and 7.5-mg/mL solutions

*USP nomenclature.
Modified from Covino B, Vassallo H: Local Anesthetics: Mechanisms of Action and Clinical Use. Orlando, FL, Grune & Stratton, 1976.

depends on environmental factors, such as temperature and ionic strength, and on the medium surrounding the drug. In the relatively apolar milieu of a membrane, the average pK_a of local anesthetics is lower than in solution.[6] This is chemically equivalent to saying that the membrane concentrates the base form of the local anesthetic more than it concentrates the protonated cation form.

The pH of the medium containing the local anesthetic influences drug activity by altering the relative percentage of the base and protonated forms. For example, in inflamed tissues the pH is lower than normal, and local anesthetics are more protonated than in normal tissue and thus penetrate the tissue relatively poorly (see later).

The relationship between pK_a and the percentage of local anesthetic present in the cationic form is shown in Figure 30-2. As described later, there are dual effects of pH on clinical effectiveness, depending on where the local anesthetic is injected and the importance of the base form for tissue penetration.

Anatomy of the Peripheral Nerve

Each peripheral nerve axon possesses its own cell membrane, the axolemma. Nonmyelinated nerves, such as autonomic postganglionic efferent and nociceptive afferent C fibers, contain many axons encased in a single Schwann cell sheath. In contrast, all large motor and sensory fibers are enclosed in many layers of myelin, which consists of the plasma membranes of specialized Schwann cells that wrap themselves around the axon during axonal outgrowth. Myelin greatly increases the speed of nerve conduction by insulating the axolemma from the surrounding conducting salt medium and forcing the "action current" generated by an impulse to flow through the axoplasm to the nodes of Ranvier, which are periodic interruptions in the myelin sheath where the active impulse is regenerated (Fig. 30-3). The Na^+ channels that serve generation and propagation of impulses are highly concentrated at the nodes of Ranvier of myelinated fibers[7] but are

Table 30-2 Relative in vitro Conduction-Blocking Potency and Physiochemical Properties of Local Anesthetic Drugs

Drug	Relative Conduction-Blocking Potency*	Physiochemical Properties	
		pK_a†	Hydrophobicity†
Low Potency			
Procaine	1	8.9	100
Intermediate Potency			
Mepivacaine	1.5	7.7	130
Prilocaine	1.8	8.0‡	129
Chloroprocaine	3	9.1	810
Lidocaine	2	7.8	366
High Potency			
Tetracaine	8	8.4	5822
Bupivacaine	8	8.1	3420
Etidocaine	8	7.9	7320

*Data derived from C fibers of isolated rabbit vagus and sciatic nerve.
†pK_a and hydrophobicity at 36°C; hydrophobicity equals the octanol-buffer partition coefficient of the base. Values are ratios of concentrations.
‡Values at 25°C.
From Strichartz GR, Sanchez V, Arthur GR, et al: Fundamental properties of local anesthetics. II. Measured octanol : buffer partition coefficients and pK_a values of clinically used drugs. Anesth Analg 71:158-170, 1990.

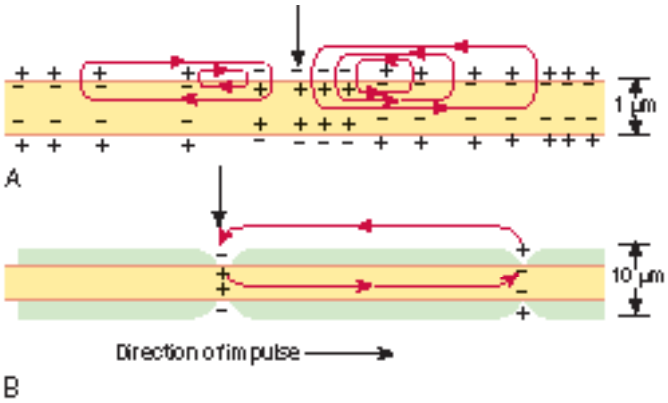


Figure 30-3 Pattern of "local circuit currents" flowing during propagation of an impulse in a nonmyelinated C fiber's axon (**A**) and a myelinated axon (**B**). During propagation of impulses, from left to right, current entering the axon at the initial rising phase of the impulse (*large vertical arrows*) passes through the axoplasm (local circuit current) and depolarizes the adjacent membrane. "Plus" and "minus" signs adjacent to the axon membrane indicate the polarization state of the axon membrane: negative inside at rest, positive inside during active depolarization under the action potential, and less negative in regions where local circuit currents flow. This ionic current passes relatively uniformly across the nonmyelinated axon, but in the myelinated axon it is restricted to entry at the nodes of Ranvier, several of which are simultaneously depolarized during a single action potential.

distributed all along the axon of nonmyelinated fibers (Fig. 30-3). A classification of peripheral nerves according to fiber size and physiologic properties is presented in Table 30-3.

A typical peripheral nerve consists of several axon bundles, or fascicles. Each axon has its own connective tissue covering, the *endoneurium*. Each fascicle of many axons is encased by a second connective tissue layer, the epithelial-like *perineurium*, and the entire nerve is wrapped in a loose outer sheath called the *epineurium* (Fig. 30-4). To reach the nerve axon, a local anesthetic molecule must traverse four or five layers of connective tissue or lipid membranous barriers, or both.

Structure of the Axonal Membrane

Biologic membranes consist of a molecular lipid bilayer containing proteins adsorbed on the surfaces, as well as embedded in or spanning the hydrocarbon core (Fig. 30-5). The character of the bilayer is determined by the phospholipids, which have long hydrophobic fatty acyl tails that lie in the center of the membrane, as well as by the polar hydrophilic head groups, which are usually composed of zwitterionic portions (containing positive and negative charges) that project into the cytoplasm or the extracellular

Table 30-3 Classification of Peripheral Nerves According to Anatomy, Physiology, and Function

Fiber Class	Subclass	Myelin	Diameter (µm)	Conduction Velocity (msec)	Location	Function	Susceptibility to Local Anesthetic Block
A	α	+	6-22	30-120	Efferent to muscles	Motor	++
	β	+	6-22	30-120	Afferent from skin and joints	Tactile, proprioception	++
	γ	+	3-6	15-35	Efferent to muscle spindles	Muscle tone	++++
	δ	+	1-4	5-25	Afferent sensory nerves	Pain, cold temperature, touch	+++
B		+	<3	3-15	Preganglionic sympathetic	Various autonomic functions	++
C	sC	–	0.3-1.3	0.7-1.3	Postganglionic sympathetic	Various autonomic functions	++
	dC	–	0.4-1.2	0.1-2.0	Afferent sensory nerves	Various autonomic functions Pain, warm temperature, touch	+

Modified From Bonica JJ: Principles and Practice of Obstetric Anesthesia and Analgesia. Philadelphia, FA Davis, 1967.

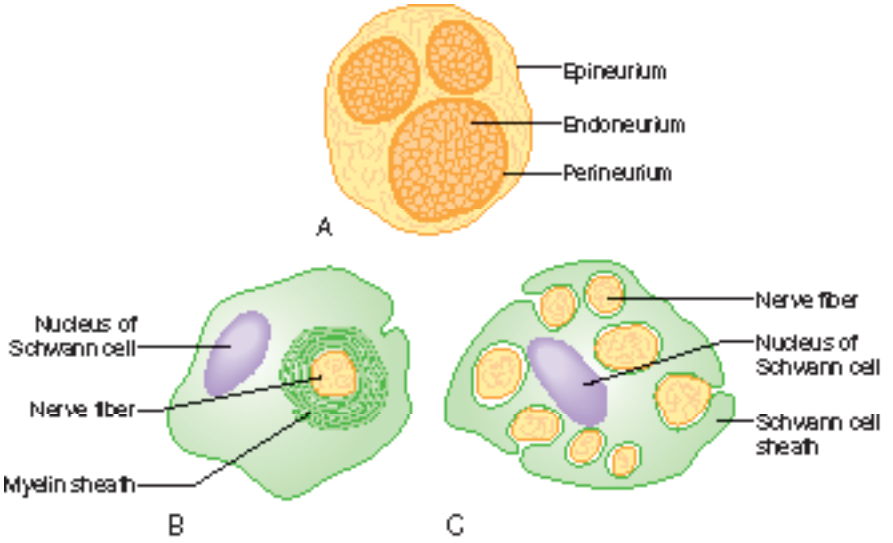


Figure 30-4 Transverse sections of a peripheral nerve (**A**) showing the outermost epineurium; the inner perineurium, which collects nerve axons in fascicles; and the endoneurium, which surrounds each myelinated fiber. Each myelinated axon (**B**) is encased in the multiple membranous wrappings of myelin formed by one Schwann cell, each of which stretches longitudinally more than approximately 100 times the diameter of the axon. The narrow span of axon between these myelinated segments, the node of Ranvier, contains the ion channels that support action potentials. Nonmyelinated fibers (**C**) are enclosed in bundles of 5 to 10 axons by a chain of Schwann cells that tightly embrace each axon with but one layer of membrane.

fluid. Within the membrane there is both lateral and rotational diffusion, which allows lipids and certain proteins to migrate in a fluid mosaic, but most membrane proteins are fixed within specific regions of a membrane, anchored by connections to specific proteins of the cell's cytoskeleton.[7]

A dynamic interaction exists between the cell's membrane and cytoplasm. Although we focus here on the channel-blocking actions of local anesthetics, it is noteworthy that many other cellular activities, including both metabolic and signal transduction pathways, are inhibited by these drugs.

Physiology of Nerve Conduction

The neural membrane is able to maintain a voltage difference of −60 to −90 mV between the intracellular medium and the cell's outside because at rest it is relatively impermeable to sodium ions but selectively permeable to potassium ions. The Na^+/K^+ pump, an active, energy-dependent mechanism, sustains the ion gradients that drive this potential difference by constant extrusion of sodium from within the cell in exchange for a net uptake of potassium, with adenosine triphosphate used as an energy source. Although the membrane is relatively permeable to potassium ions, an intracellular-to-extracellular potassium ratio of 150 to 5 mM, or 30:1, is maintained by active removal of potassium as it leaks passively across the plasma membrane.

The nerve at rest behaves largely as a "potassium electrode," according to the Nernst equation:

$$E_m \approx E_K = \left(\frac{-RT}{F}\right) \ln\left(\frac{[K^+]_i}{[K^+]_o}\right) \quad (2)$$

where E_m is the membrane potential, E_K is the potassium equilibrium potential, R is the gas constant, T is temperature (Kelvin), F

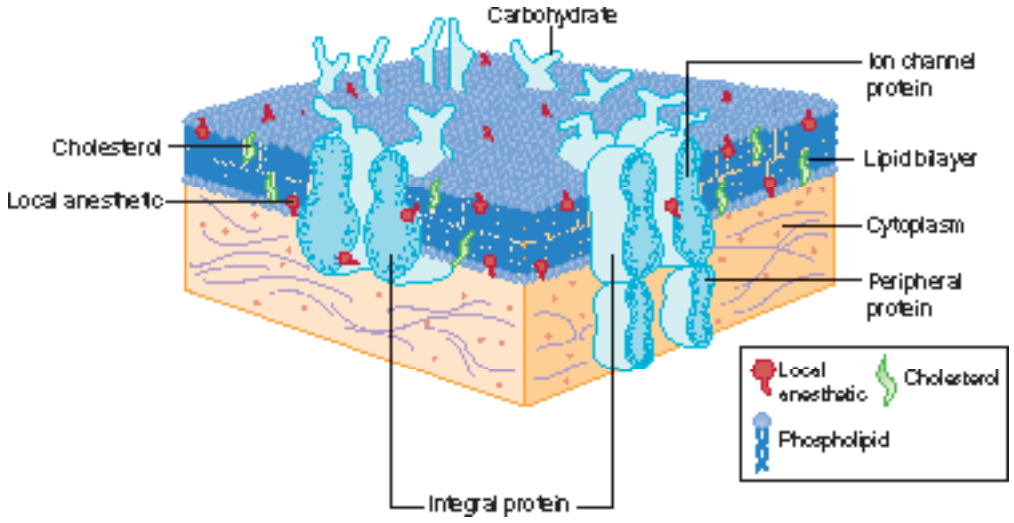


Figure 30-5 A typical plasma membrane has at its core the lipid bilayer, composed of phospholipids and cholesterol molecules (in about a 5:1 ratio) embedding the membrane integral proteins, which are most often glycosylated by extracellular carbohydrates and include receptors and ion channels essential for intercellular communication. "Peripheral proteins" regulate the functions of membrane proteins, chaperone them to the plasma membrane, and stabilize them in the cell through interactions with both the cytoskeleton and the extracellular matrix. Probable membrane locations and protein sites for local anesthetics are also shown.

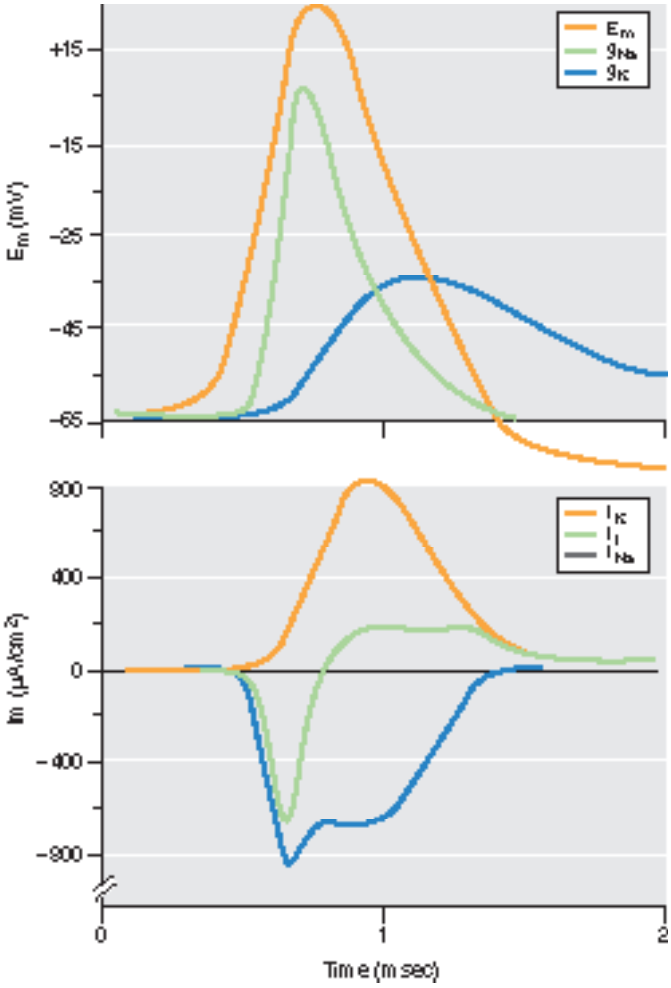


Figure 30-6 Membrane potential (E_m) and the voltage-gated ionic conductance of sodium (g_{Na}) and potassium (g_K), which determine the corresponding membrane currents Im (I_{Na} and I_K) during a propagated action potential. Modeled from the original studies of Hodgkin and Huxley on the squid giant axon (see Hodgkin[8]), these relationships hold for almost all invertebrate and vertebrate nerve fibers. The direction of the total ionic current (i_t), which is the sum of I_{Na} and I_K, is inward (negative values) for the depolarizing phase of the action potential and outward (positive values) for the repolarizing phase.

is Faraday's constant, and $[K^+]$ is the potassium ion concentration inside (i) and outside (o) the cell. For potassium, therefore,

$$E_K = -58 \log 30, \text{ or } -85.7 \text{ mV}$$

An opposite situation exists for Na^+, which is at higher concentration outside the cell and has a Nernst potential, E_{Na}, of about +60 mV. During an action potential, the nerve membrane transiently switches its higher permeability from K^+ to Na^+, thereby changing the membrane potential from negative to positive, and back again.[8] The progress of this potential change and the underlying events are graphed in Figure 30-6. They provide a basis for understanding local anesthetic conduction block.

Permeation of ions through membranes occurs via specialized proteins called ion channels.[9] The conformation of these channels is often sensitive to the membrane potential; both Na^+ and K^+ channels in nerve membranes are activated to an "open" conformation by membrane depolarization. Sodium channels, in addition, close to an "inactivated" conformation after their initial activation. A small membrane depolarization extending along an axon from a region of excited membrane, for example, will begin to open both Na^+ and K^+ channels. The Na^+ channels open faster, however, and the inwardly directed Na^+ current (see Fig. 30-6) depolarizes the membrane further, thereby leading to opening of more Na^+ channels and increasing the inward Na^+ current even further (Fig. 30-7). This sequence of events continues during the *depolarizing phase* until some of the Na^+ channels have become inactivated and enough of the K^+ channels have opened to change the balance of current and result in a net outward current that produces membrane *repolarization* (see Fig. 30-7). After one action potential, the concentrations of Na^+ and K^+ have changed little for the large myelinated fibers but by as much as 10% for the small, nonmyelinated axons. The Na^+ ions entering and K^+ ions leaving the cell as a result of this process are restored by the Na^+/K^+ pump.

Depolarizations too weak to activate enough Na^+ channels to produce a net inward current are below the membrane's excitability *threshold*. The precise value of the threshold varies in different regions of the cell and also changes with time. For example, directly after an impulse, when some Na^+ channels are still inactivated and some K^+ channels are still activated, the threshold is above its "resting" value and the membrane is "refractory" to stimulation. Over time, however, as Na^+ inactivation decays and K^+ channels return to their closed conformation, the original resting threshold value is restored.

The action potential is a wave of depolarization that is propagated along the axon by continuous coupling between excited and nonexcited regions of membrane. Ionic current (the action current) enters the axon in the excited, depolarized region and then flows down the axoplasm and exits through the surrounding membrane, thereby passively depolarizing this adjacent region (see Fig. 30-3). Although this *local circuit current* spreads away from the excited zone in both directions, the region behind the impulse, having just been depolarized, is absolutely refractory and propagation of impulses is thus unidirectional.

The local circuit current spreads rapidly along a length of insulated internode in a myelinated axon (see Fig. 30-3), and

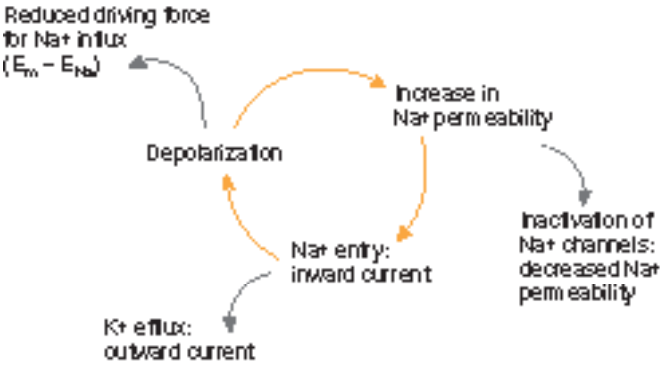


Figure 30-7 The action potential can be understood in terms of the cyclic relationships between factors contributing to the regenerative, depolarizing phase and the passive, repolarizing phase. *Positive* factors (*yellow arrows*) increase the rate of depolarization in a "positive-feedback loop," each element in the cycle favoring the subsequent one. *Negative* factors (*gray arrows*) decrease the depolarization rate by reducing or opposing the related positive factor, with efflux of K^+ eventually dominating the ionic flow and repolarizing the membrane.

many nodes of Ranvier in sequence are depolarized to threshold with little intervening delay. Single impulses do not jump from node to node as separate, discrete events; instead, active depolarization occurs simultaneously along several centimeters of the largest axons (see Fig. 30-3). Indeed, the local circuit current is so robust that it can skip past two completely nonexcitable nodes (e.g., blocked by local anesthetic) and successfully stimulate a third node. If excitability is partially reduced, such as by inhibition of some of the Na^+ channels, the amplitude of impulses in successive nodes falls decrementally, a process that can continue for many centimeters.[10,11] This situation probably occurs during certain phases of local anesthesia, as discussed later. However, when enough of the Na^+ channels are blocked, local circuit current fails to bring the adjacent resting region to threshold, and the impulse is fully extinguished.

Mechanism of Action of Local Anesthetics (Pharmacodynamics)

Active Form

Local anesthetic bases are poorly to sparingly soluble in water but are quite soluble in relatively hydrophobic organic solvents. Therefore, as a matter of chemistry (and to optimize shelf life), most of these drugs are formulated as hydrochloride salts. The pK_a of the drug and tissue pH determine the amount of drug that exists in solution as free base or as positively charged cation when injected into living tissue (see earlier). Furthermore, uptake of the drug by tissue, largely via lipophilic adsorption, will also alter its activity, both by shifting the effective pK_a downward, thereby favoring the neutral base form, and by limiting diffusion of the anesthetic away from the site of injection. Moderately hydrophobic local anesthetics block faster than either hydrophilic or highly hydrophobic ones, delivered at the same concentration, for the following reasons. Moderately hydrophilic molecules, such as lidocaine, are less bound to tissues than very hydrophobic drugs are (e.g., tetracaine) but are still more membrane permeant than very hydrophilic ones (e.g., 2-chloroprocaine). The highly hydrophobic local anesthetics, having higher intrinsic potencies (see Table 30-2), are therefore used in lower concentrations and their diffusion-controlled rate of onset is correspondingly reduced.

Which form of the local anesthetic, charged cation or neutral base, is actually responsible for blockade of impulses? More alkaline solutions of local anesthetics block nerve conduction more effectively. On sheath-free nerves, the rate of inhibition by tertiary amine anesthetics is greater at alkaline than at neutral external pH[12] because membrane permeation, favored by the base over the cationic species, determines the rate of access to the binding site. Direct control of axoplasmic pH (or internal perfusion with permanently charged quaternary amine homologs) shows that the dominant potency derives from the cationic species acting from the cytoplasmic surface.[13,14] The uncharged base also has intrinsic pharmacologic activity, however, which explains the effectiveness of benzocaine as a topical local anesthetic.

Electrophysiologic Effect of Local Anesthetics

The resting membrane potential of nerve is little affected by local anesthetics. As the concentration of local anesthetic applied to the nerve is increased, a decrease in the rate of depolarization and in the peak amplitude of the action potential occurs until the impulse is abolished. It is not possible, however, to derive data on the binding of local anesthetics to Na^+ channels from measurement of the changes in nerve impulses.

By using a "voltage-clamp" procedure, Na^+ currents and their inhibition by local anesthetics can be directly assayed (Fig. 30-8A). When the membrane of isolated neurons is rapidly depolarized to a constant value, the time course of ionic currents is observed. Sodium currents during one initial depolarization are reduced by subclinical doses of local anesthetic (e.g., 0.2 mM lidocaine) and totally abolished by clinical doses (e.g., 1% lidocaine, ≈40 mM). If the test depolarization is applied repeatedly, for example, at frequencies higher than 5 Hz (five pulses per second), the partially depressed (*tonically* inhibited) Na^+ current is further reduced incrementally for each pulse until a new steady-state level of inhibition is reached.[15,16] This frequency-dependent inhibition, also called *phasic inhibition*, is reversed when stimulation is slowed or stopped, and currents return to the level of tonic inhibition observed in the resting nerve. Paralleling the phasic inhibition of Na^+ currents in voltage-clamped membranes is a "use-dependent" blockade of action potentials during normal physiologic function (see Fig. 30-8B).

The potency of local anesthetics to produce tonic and phasic inhibition is similarly dependent on their structure, hydrophobicity, and pK_a. At its simplest, there appears to be a single binding site for local anesthetics on the Na^+ channel, with a "tonic" affinity at rest and increased "phasic" affinity occurring as a result of depolarization. The phasic blocking phenomenon can thus be used to reveal the true kinetics of binding of local anesthetic to the functional receptor, the Na^+ channel itself.

Phasic actions are a manifestation of the selective affinity of local anesthetics for conformations of the Na^+ channel that result from depolarization. Both "open" and "inactivated" states of the channel bind local anesthetics more avidly than the resting state does. Repeated depolarization thus increases the fraction of drug-bound channels; dissociation of these bound drug molecules is usually a slower process than the normal recovery from inactivation (see earlier) and results in the use-dependent accumulation of channels in the blocked condition and the phenomenon of phasic block.

By its selective binding to a channel state, the local anesthetic stabilizes that state. During phasic block, therefore, more inactivated channels become drug bound, and reciprocally, less activation can occur. This relationship between state-dependent affinities and modification of transitions among states through drug binding is known as the "modulated receptor" model.[17] Overall binding of anesthetic is increased by membrane depolarization for two reasons: *more binding sites become accessible* during activation (the "guarded receptor" model) and drug *dissociation* from inactivated channels *is slower* than from resting channels (the modulated receptor model).

The specific binding rates and affinities for the different conformations of the sodium channel depend on the particular local anesthetic drug. When the details of this dependence are

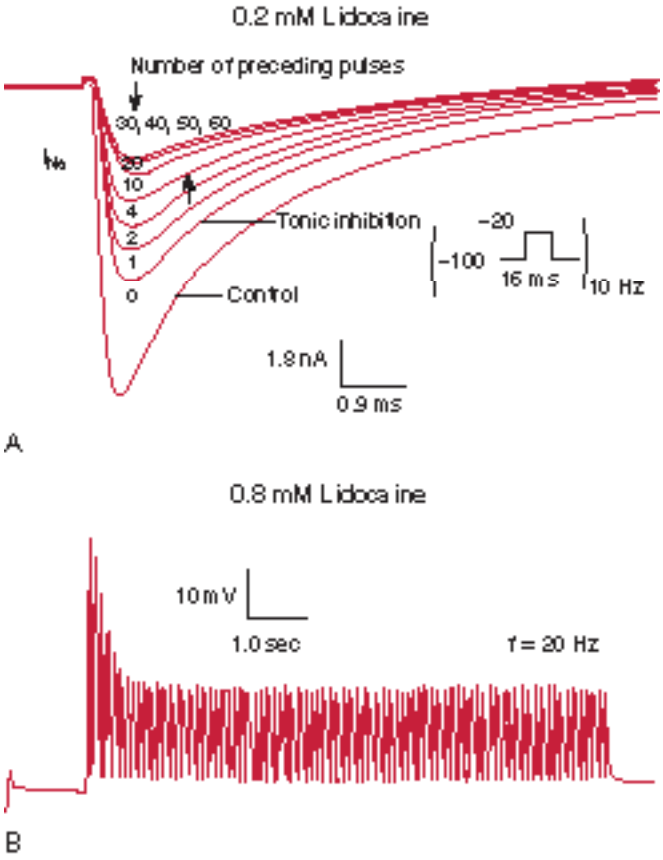


Figure 30-8 "Use-dependent" actions of local anesthetics on excitable membrane properties. **A,** Ionic Na^+ currents measured by a voltage-clamping technique are transiently activated by brief steps of depolarization applied infrequently ("tonic" test) or in a train at 10 times per second ("phasic" test, see E_m pattern in parentheses). After equilibration with 0.2 mM (0.005%) lidocaine, the currents measured tonically are reduced by about 30% from the control currents. Application of the "phasic" train of depolarizations results in a dynamic reduction of currents after each depolarization, with a steady-state value of phasic inhibition reached during the train of 75% of control currents. Recovery of currents to the tonic value occurs within a few seconds when phasic testing stops (not shown). **B,** Action potentials are also inhibited in a phasic manner by local anesthetics. After equilibration with 0.8 mM lidocaine (0.02%), the action potential is tonically reduced by about 20% from its amplitude in drug-free solution (not shown). Stimulation by a train at 20 stimuli per second induces a phasic inhibition that further reduces the amplitude by about 70% from the control value. As with the ionic currents (**A**), phasic inhibition of the action potential recovers rapidly when high-frequency stimulation stops.

correlated with the physicochemical properties of the drug and with the experimental conditions, they provide insight into the molecular features of the local anesthetic binding site.

The Nature of the Local Anesthetic Binding Site

Intentional mutation of specific amino acids of the Na^+ channel has allowed definition of regions that interact directly with local anesthetics. The major functional protein of the Na^+ channel (the α-subunit) is composed of four homologous "domains" (DI to DIV), each of which contains six helical regions (S1 to S6) that span the core of the membrane (Fig. 30-9A). Each domain also has a loop, termed the "P region," that links the extracellular ends of its S5 and S6 transmembrane segments; the P regions extend inward between the transmembrane regions such that when the α-subunit folds together, each P loop contributes a quarter of the cylindrical ion "selectivity pore," the narrowest passage of an open channel (see Fig. 30-9B). Voltage sensitivity derives from the positive charges located on S4 segments, which slide or swing "outward" in response to membrane depolarization. By linkages still unknown, this movement of S4 results in a conformational rearrangement of the S6 segments, which form the inner, cytoplasmic entry to the channel. Closed-to-open channel gating results from movement of the S6 segments, whereas inactivation gating results from binding of the cytoplasmic loop located between D-3 and D-4 to the cytoplasmic opening of the channel.

Local anesthetics bind in the "inner vestibule" of the closed Na^+ channel (see Fig. 30-9C). Amino acid mutations in the S6 segments of D-1, D-3, and D-4 all modify local anesthetic action, thus suggesting either that these regions form a "pharmocophore" small enough to simultaneously contact the drug at three surfaces or that the local anesthetic molecule moves rapidly among these three segments.

The rate constant for binding of local anesthetic to the closed Na^+ channel is larger for the more hydrophobic molecules, which suggest that drug molecules can reach the binding site (and depart from it) through a "hydrophobic" pathway. This path could be movement from the membrane phase laterally, into the channel, or through hydrophobic amino acid residues that limit access through a pathway in the closed pore. The slow block of closed and inactivated channels appears to use such a hydrophobic access and thus accounts for tonic inhibition.

The charged species of local anesthetics dissociates much more slowly from closed and inactivated Na^+ channels than the neutral form does, which suggests that an ionic bond may be involved in drug binding or that the charged molecule moves only slowly along the hydrophobic pathway.

In brief, hydrophobicity delivers the drug to the receptor and charge keeps it there.

Neurophysiologic Aspects of Phasic Inhibition

Different fiber types in the nerve are affected differently during local anesthesia. At least part of this difference arises from pharmacokinetic factors. At the onset of and during recovery from clinical block, in particular, longitudinal and radial diffusion of drug will produce concentration variations within and along the nerve. This variation is superimposed on the dynamic use-dependent inhibition to provide variable propagation, which depends on a fiber's geometry, position within the nerve, and functional as well as electrophysiologic properties.

Different fiber types are also differentially sensitive to local anesthetic blockade. In vivo experiments in which continuous superperfusion of peripheral nerve allows equilibration with drug and experiments in which a drug bolus is delivered by percutaneous injection,[18] analogous to clinical peripheral nerve block, show unequivocally that small myelinated axons (Aγ motor and Aδ sensory fibers) are the most susceptible to impulse annihilation. Next in order of block are the large myelinated (Aα and Aβ) fibers, and the least susceptible are the small, nonmyelinated C

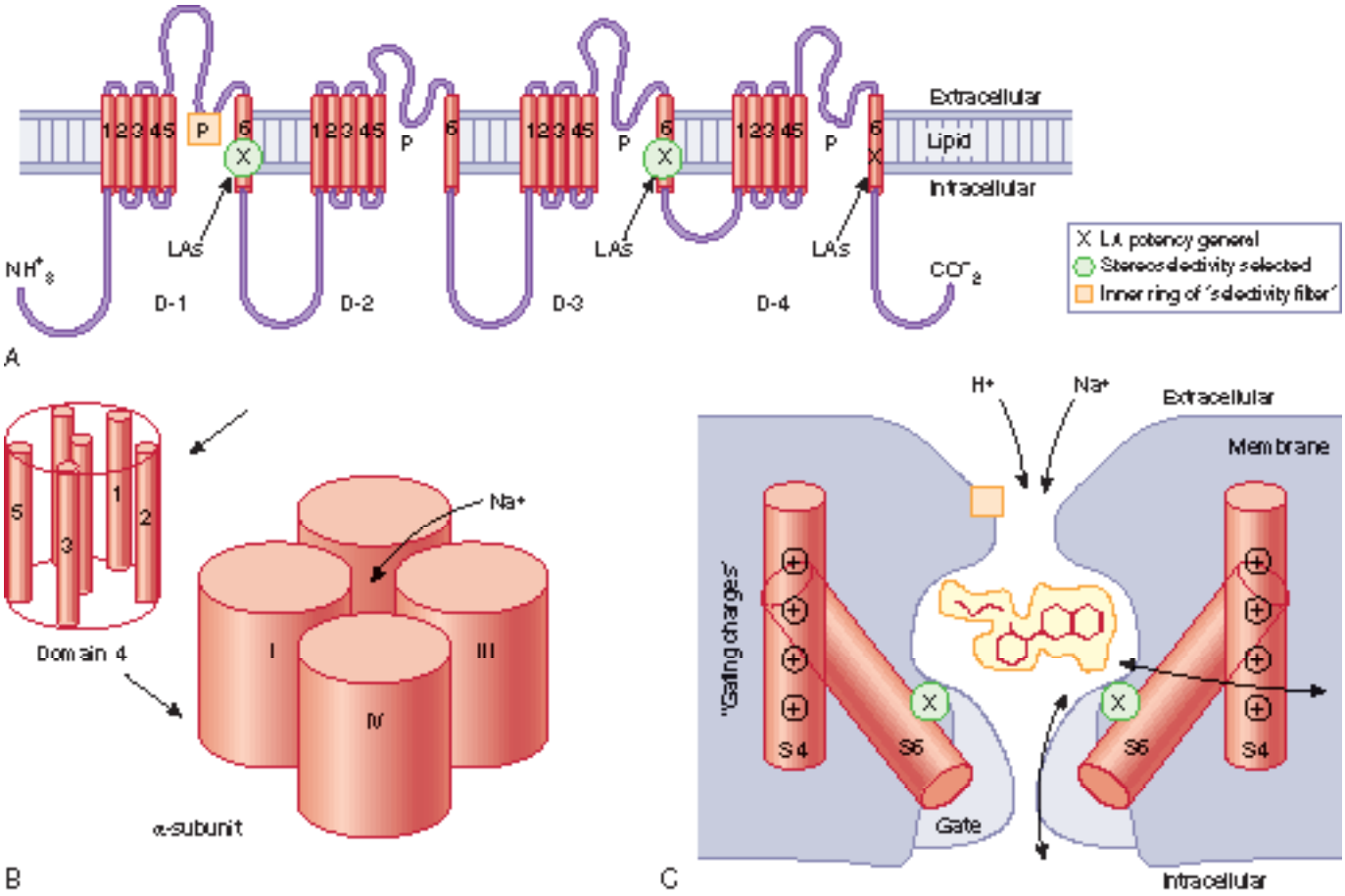


Figure 30-9 Structural features of the Na^+ channel that determine local anesthetic (LA) interactions. **A,** Consensus arrangement of the single peptide of the Na^+ channel α-subunit in a plasma membrane. Four domains with homologous sequences (D-1 through D-4) each contain six α-helical segments that span the membrane (S1 to S6). Each domain folds within itself to form one cylindrical bundle of segments, and these bundles converge to form the functional channel's quaternary structure (**B**). Activation gating leading to channel opening results from primary movement of the positively charged S4 segments in response to membrane depolarization (see panel **C**). Fast inactivation of the channel follows binding to the cytoplasmic end of the channel of part of the small loop that connects D-3 to D-4. Ions travel through an open channel along a pore defined at its narrowest dimension by the P region formed by partial membrane penetration of the four extracellular loops of protein connecting S5 and S6 in each domain. Intentional, directed mutations of different amino acids on the channel indicate residues that are involved in LA binding in the inner vestibule of the channel (X on S6 segments), at the interior regions of the ion-discriminating "selectivity filter (*square* on the P region), and also are known to influence stereoselectivity for phasic inhibition (*circle*, also on S6 segments). **C,** Schematic cross section of the channel speculating on the manner in which S6 segments, forming a "gate," may realign during activation to open the channel and allow entry and departure of a bupivacaine molecule by the "hydrophilic" pathway. The closed (inactivated) channel has a more intimate association with the LA molecule, whose favored pathway for dissociation is no longer between S6 segments (the former pore) but now, much more slowly, laterally between segments and then through the membrane, the "hydrophobic" pathway. Na^+ ions entering the pore will compete with the LA for a site in the channel, and H^+ ions, which pass very slowly through the pore, can enter and leave from the extracellular opening, thereby protonating and deprotonating a bound LA molecule and thus regulating its rate of dissociation from the channel.

fibers. In fact, in this last group, impulses in the slowest conducting population (conduction velocity of 0.5 to 0.8 msec) are the most resistant to local anesthetic.[18] The generalized notion that local anesthetics block the smallest fibers first or most is clearly wrong.

Selective Susceptibility of Na^+ Channel Isoforms

Ten different Na^+ channels have been physiologically identified and biochemically sequenced. At least four of them are found in peripheral neurons, some exclusively associated with nociceptive afferents. Obviously, it would be clinically advantageous to selectively inhibit these channels and thus prevent or reduce pain while sparing other functions. Although selective channel blockade has been attained with naturally occurring small peptide toxins,[19] relatively little selective blockade by local anesthetics has been reported,[20] probably because the local anesthetic pharmacophore is too similar among the different channel isoforms and the local anesthetic molecules themselves have several rotational axes, which makes them poor structural templates for selecting among static binding pockets.

Sodium Channel Isoforms in Human Diseases Characterized by Pain or Pain Insensitivity. Mutations in sodium channel isoform $Na_V1.7$ can produce disease states with either spontaneous pain[21,22] or profound and selective impairment of pain sensitivity.[23] Erythromelalgia is characterized by episodes of severe burning pain, predominantly in the feet and hands. In these subjects, pain is exacerbated by heat and relieved by cold. This disorder may occur as an isolated problem or can coexist

with certain rheumatologic disorders. In a small subgroup of these patients the disorder has a clear familial pattern with an autosomal dominant pattern of inheritance. A second autosomal dominant disorder characterized by spontaneous pain is known initially as "familial rectal pain disorder" or "paroxysmal extreme pain disorder." Recent molecular studies have shown that these disorders involve several distinct types of mutations in $Na_V1.7$ sodium channels.[21,22] When these channels are inserted into cells that lack sodium channels, they generate spontaneous, temperature-sensitive inward currents.

Perhaps even more remarkable is the recent report of several consanguineous families in Pakistan in which certain members exhibit profound insensitivity to pain while being neurologically normal in almost all other respects.[23] Genetic, biochemical, and electrophysiologic studies have demonstrated an autosomal recessive pattern of inheritance. Molecular studies have shown that these mutations are of the nonsense type and generate functionally impaired $Na_V1.7$ sodium channels; when placed into cell membranes in vitro, they fail to generate inward currents in response to depolarizing stimuli.

On the other hand, aberrant impulses, which are often considered the hallmarks of various diseases of excitable membranes such as abnormal repetitive firing in neuropathic pain or in certain types of inherited skeletal myotonia, are abolished by systemic lidocaine in doses that do not block normal propagating impulses. Conditions for the sensitivity of such impulses to local anesthetics, such as lidocaine, appear to result from the patterns of impulse spikes superimposed on slow membrane depolarizations caused by abnormal expression of Na^+ channels rather than from selective sensitivity of certain subtypes of channels to these drugs.[24]

Summary of Local Anesthetic Mechanisms

Impulse blockade by local anesthetics may be summarized by the following chronology[4]:

1. Solutions of local anesthetic are deposited near the nerve. Removal of free drug molecules away from this locus is a function of tissue binding, removal by the circulation, and local hydrolysis of aminoester anesthetics. The net result is penetration of the nerve sheath by the remaining free drug molecules.
2. Local anesthetic molecules then permeate the nerve's axon membranes and reside there and in the axoplasm. The speed and extent of these processes depend on a particular drug's pK_a and on the lipophilicity of its base and cation species.
3. Binding of local anesthetic to sites on voltage-gated Na^+ channels prevents opening of the channels by inhibiting the conformational changes that underlie channel activation. Local anesthetics bind in the channel's pore and also occlude the path of Na^+ ions.
4. During onset of and recovery from local anesthesia, impulse blockade is incomplete and partially blocked fibers are further inhibited by repetitive stimulation, which produces an additional, use-dependent binding to Na^+ channels.
5. One local anesthetic binding site on the Na^+ channel may be sufficient to account for the drug's resting (tonic) and use-dependent (phasic) actions. Access to this site may potentially involve multiple pathways, but for clinical local anesthetics, the primary route is the hydrophobic approach from within the axon membrane.
6. The clinically observed rates of onset and recovery from blockade are governed by the relatively slow diffusion of local anesthetic molecules into and out of the whole nerve, not by their much faster binding and dissociation from ion channels. A clinically effective block that may last for hours can be accomplished with local anesthetic drugs that dissociate from Na^+ channels in a few seconds.

Clinical Pharmacology

Successful use of regional anesthesia requires knowledge of the pharmacologic properties of the various local anesthetic drugs, as well as technical skill in performance of the nerve block. Local anesthetic requirements vary considerably, depending on factors such as the type of block, surgical procedure, and physiologic status of the patient.

Commonly used aminoester local anesthetics include procaine, chloroprocaine, tetracaine, and cocaine. Commonly used aminoamides include lidocaine, mepivacaine, prilocaine, bupivacaine (racemic and its levo-enantiomer), ropivacaine, and etidocaine. The ester and amide local anesthetics differ in their chemical stability, locus of biotransformation, and allergic potential. Amides are extremely stable, whereas esters are relatively unstable in solution. Aminoesters are hydrolyzed in plasma by cholinesterase enzymes, but the amides undergo enzymatic degradation in the liver. Two exceptions to this trend include cocaine, an ester that is metabolized predominantly by hepatic carboxylesterase,[25] and articaine, an amide local anesthetic widely used in dentistry that is inactivated by plasma carboxylesterase-induced cleavage of a methyl ester on the aromatic ring.

p-Aminobenzoic acid is one of the metabolites of ester-type compounds that can induce allergic-type reactions in a small percentage of patients. The aminoamides are not metabolized to *p*-aminobenzoic acid, and reports of allergic reactions to these agents are extremely rare.

General Considerations

Clinically important properties of the various local anesthetics include potency, speed of onset, duration of anesthetic action, and differential sensory/motor blockade. As previously indicated, the profile of individual drugs is determined by their physicochemical characteristics (see Table 30-2).

Anesthetic Potency

Hydrophobicity appears to be a primary determinant of intrinsic anesthetic potency[5] because the anesthetic molecule must penetrate into the nerve membrane and bind at a partially hydrophobic site on the Na^+ channel. Clinically, however, the correlation between hydrophobicity and anesthetic potency is not as precise as in an isolated nerve. For example, etidocaine is more potent than bupivacaine in an isolated nerve, whereas etidocaine is actually less potent than bupivacaine in vivo. Differences between in

vitro and in vivo potency may be related to a number of factors, including local anesthetic charge and hydrophobicity (which influence partitioning into and transverse diffusion across biologic membranes) and vasodilator or vasoconstrictor properties (which influence the initial rate of vascular uptake from injection sites into the central circulation).

Onset of Action

The onset of conduction block in isolated nerves is related to the physicochemical properties of the individual agents. In vivo latency is also dependent on the dose or concentration of local anesthetic used. For example, 0.25% bupivacaine possesses a rather slow onset of action, but increasing the concentration to 0.75% results in a significant acceleration of its anesthetic effect.[26] Chloroprocaine demonstrates a rapid onset of action in humans despite the fact that its pK_a is approximately 9, its proportion of charged molecules is high (97%), and thus its onset of action in isolated nerves is relatively slow. However, the low systemic toxicity of this agent allows its use in high concentrations (e.g., 3%). Therefore, the rapid onset of chloroprocaine in vivo may be related simply to mass diffusion because of the large number of molecules placed in the vicinity of peripheral nerves. In humans, 1.5% lidocaine produces a more rapid onset of epidural anesthesia than 1.5% chloroprocaine does[27]; however, 3% chloroprocaine results in more rapid onset than 2% lidocaine does.

Duration of Action

The duration of action of the various local anesthetics differs markedly. Procaine and chloroprocaine have a short duration of action. Lidocaine, mepivacaine, and prilocaine produce a moderate duration of anesthesia, whereas tetracaine, bupivacaine, ropivacaine, and etidocaine have the longest durations. For example, with procaine, the duration of brachial plexus blockade is 30 to 60 minutes, but up to approximately 10 hours of anesthesia (or at least analgesia) is common for brachial plexus blockade with bupivacaine or ropivacaine.[28]

In humans, the duration of anesthesia is markedly influenced by the peripheral vascular effects of the local anesthetic drugs. Many local anesthetics have a biphasic effect on vascular smooth muscle; at low concentrations these agents tend to cause vasoconstriction, whereas at higher, clinically administered concentrations, they cause vasodilation.[29] However, differences exist in the degree of vasodilator activity of the various drugs. For example, lidocaine is a more potent vasodilator than mepivacaine or prilocaine is. The effects of local anesthetics on vascular tone and regional blood flow are complex and vary according to concentration, time, and the particular vascular bed near the site of application, among other factors. As a practical example, the topical local anesthetic formulation EMLA (eutectic mixture of the local anesthetics lidocaine and prilocaine) vasoconstricts cutaneous vessels initially and through most of the first hour of application, but vasodilation is observed after 2 or more hours of application.

Differential Sensory/Motor Blockade

Another important clinical consideration is the ability of local anesthetic agents to cause differential inhibition of sensory and motor activity. Bupivacaine became popular in the 1980s for epidural blocks because it was better than the previously available long-acting agents (e.g., etidocaine) in producing adequate antinociception without profound inhibition of motor activity, particularly when dilute solutions are used. Bupivacaine is widely used epidurally for obstetric analgesia and postoperative pain management because it can provide acceptable analgesia with only mild muscle weakness, particularly when used for infusions in concentrations of 0.125% or less (also see Chapters 51, 69 and 87). When given by epidural bolus dosing, bupivacaine produces more effective sensory than motor blockade over a concentration range from 0.25% to 0.75%, whereas etidocaine produces almost equally effective sensory and motor blockade over this concentration range. Additional observations on the sensory selectivity of newer local anesthetics are detailed later in the section on chiral local anesthetics.

Traditional texts often state that small-diameter axons, such as C fibers, are more susceptible to local anesthetic block than larger-diameter fibers are. However, when careful measurements are made of single-impulse annihilation in individual nerve fibers, exactly the opposite differential susceptibility is noted (see earlier).[30,31] Repetitive stimulation, such as occurs during propagation of trains of impulses, produces a further, phasic inhibition of excitability, but it is unclear how this will affect a functionally selective failure of impulses. The length of drug-exposed nerve in the intrathecal space, imposed by anatomic restrictions, can perhaps explain clinically documented differential spinal or epidural blockade,[32] with longer drug-exposed regions yielding block by lower concentrations of local anesthetic.[33] However, this reasoning does not explain the functionally differential loss from peripheral nerve block. Other factors may include actual spread of the drug along the nerve or its selective ability to inhibit Na^+ channels over K^+ channels,[34] which in itself can produce a differential block because these channels are present in very different proportions in different types of nerves. As a result of these confounding factors, clinicians should be discouraged from making conclusions about fiber-type involvement in chronic pain syndromes based on the dose or concentration requirement for pain relief in diagnostic nerve blockade.[35]

Factors Influencing Anesthetic Activity in Humans

Dosage of Local Anesthetic

As the dosage of local anesthetic is increased, the probability and duration of satisfactory anesthesia increase and the time to onset of block is shortened. The dosage of local anesthetic can be increased by administering either a larger volume or a more concentrated solution. For example, increasing the concentration of epidurally administered bupivacaine from 0.125% to 0.5% while maintaining the same volume of injectate (10 mL) resulted in shorter latency, an improved incidence of satisfactory analgesia, and a longer duration of sensory analgesia.[36] The volume per se of anesthetic solution probably influences the spread of anesthesia. For example, 30 mL of 1% lidocaine administered into the epidural space produced a level of anesthesia that was 4.3 dermatomes higher than that achieved when 10 mL of 3% lidocaine was given.[37]

In selecting the volume and concentration for a specific block in a particular patient, clinicians must balance the risk of adverse effects from excessive dosing (systemic toxicity, excessive motor or autonomic blockade, etc.) against the increased risk of

block failure if an inadequate volume or concentration is chosen. The degree to which additional volume can compensate for imprecise needle placement varies among different blocks.

With the advent of very precise needle placement using ultrasound-guided blockade, it has become clear that the median effective volume for obtaining successful blockade can be achieved with smaller volumes than have been recommended from some previous clinical series based on traditional methods of needle localization. For example, in a recent dose-finding randomized trial for femoral nerve blockade, the median volumes for 50% or 95% success in obtaining dense sensory and motor block at 30 minutes under ultrasound guidance were 57% and 54% of the corresponding volumes with the use of nerve stimulation.[38] Interested readers will note the very wide confidence intervals found in this study and are encouraged to read recent work on some statistical design issues for dose-response studies involving all types of anesthetics.[39] As limited by toxicity considerations, the aim in most clinical situations should be to choose doses that provide high success rates; that is, a dose effective in 95% of patients (ED_{95}) is generally a more relevant guide to dose selection than an ED_{50} dose. We should not aim for failure 50% of the time.[40]

Addition of Vasoconstrictors

Vasoconstrictors, usually epinephrine (5 μg/mL or 1:200,000), are frequently included in local anesthetic solutions to decrease the rate of vascular absorption, thereby allowing more anesthetic molecules to reach the nerve membrane and thus improve the depth and duration of anesthesia, as well as to provide a marker for inadvertent intravascular injection.[41] Test dosing with epinephrine can generate false negatives and false positives. Some of these sources of error have been described for specific patient groups, such as adults and children under general anesthesia, parturients in labor, and patients receiving β-blockers. Despite these limitations, test dosing has utility in a wide range of clinical situations.[42]

Epinephrine in a concentration of 1:200,000 has been reported to provide the optimal degree of vasoconstriction when used with lidocaine for epidural or intercostal blockade.[43] Other vasoconstrictor agents, such as norepinephrine and phenylephrine, have been used but do not appear to be superior to epinephrine.

The extent to which epinephrine prolongs the duration of anesthesia depends on the specific local anesthetic used and the site of injection. Epinephrine will significantly extend the duration of both infiltration anesthesia and peripheral nerve blockade with shorter-duration agents (e.g., lidocaine); epinephrine produces mild intensification of blockade but only most modest prolongation of epidural or peripheral blocks with bupivacaine.[44] α_2-Adrenergic receptors in the spinal cord are known to activate endogenous analgesic mechanisms, and the increased depth of analgesic action produced by epinephrine and the α_2-agonist clonidine[45] with both epidural and intrathecal local anesthetics may arise from this pharmacodynamic mechanism and from the pharmacokinetic (vasoconstrictive) action.

Site of Injection

The most rapid onset but the shortest duration of action occurs after intrathecal or subcutaneous administration of local anesthetics. The longest latencies and durations are observed after brachial plexus blocks. For example, intrathecal bupivacaine will usually produce anesthesia within 5 minutes that will persist for 3 to 4 hours. However, when bupivacaine is administered for brachial plexus blockade, the onset time is approximately 20 to 30 minutes, and the duration of anesthesia (or at least analgesia) averages 10 hours.[28] These differences in the onset and duration of anesthesia and analgesia are due in part to the particular anatomy of the area of injection, which will influence the rate of diffusion and vascular absorption and, in turn, affect the amount of drug used for various types of regional anesthesia. In the subarachnoid space, for example, the lack of a nerve sheath around the spinal cord and deposition of the local anesthetic solution in the immediate vicinity of the spinal cord are responsible for the rapid onset of action, whereas the relatively small amount of drug used for spinal anesthesia probably accounts for the short duration of conduction block.

In contrast, the onset of brachial plexus blockade is slow because the anesthetic agent is usually deposited at some distance from the nerve and must diffuse through various tissue barriers before reaching the nerve membrane. The prolonged block with brachial plexus blockade may be related to several factors, including comparatively slow rates of vascular absorption from the brachial plexus sheath, larger doses of drug required for this regional anesthetic technique, and comparatively long segments of nerves exposed to local anesthetic.

Carbonation and pH Adjustment of Local Anesthetics

The addition of sodium bicarbonate to a solution of local anesthetic applied to an isolated nerve accelerates the onset and decreases the minimum concentration (C_m) required for conduction blockade.[46] Although the effect of carbon dioxide on local anesthetic activity is easily demonstrable in isolated nerve, controversy exists concerning the clinical utility of carbonated local anesthetic solutions.[47]

The addition of sodium bicarbonate to local anesthetic solutions has also been reported to decrease the onset time of conduction blockade.[47] An increase in the pH of the local anesthetic solution increases the amount of drug in the uncharged base form, which should enhance the rate of diffusion across the nerve sheath and nerve membrane and result in a more rapid onset of anesthesia. Alkalinization of solutions of bupivacaine or lidocaine accelerated the onset of brachial plexus and epidural blockade in some studies[47] but not others.[48]

Mixtures of Local Anesthetics

Mixtures of local anesthetics for regional anesthesia are sometimes used in an effort to compensate for the short duration of action of certain rapidly acting agents such as chloroprocaine and lidocaine and the long latency of longer-acting agents such as tetracaine and bupivacaine. Mixtures of chloroprocaine and bupivacaine theoretically offer significant clinical advantages because of the rapid onset and low systemic toxicity of chloroprocaine and the long duration of action of bupivacaine; however, clinical results in studies of combinations have been mixed.[49] In addition, the use of catheter techniques for many forms of regional anesthesia makes it possible to begin with a rapid-onset local anesthetic such as lidocaine, mepivacaine, or chloroprocaine and then follow with an infusion of either a shorter-acting or longer-acting local anesthetic thereafter. Conversely, clinicians should be cautioned to not use maximum doses of two local anesthetics in combination in the mistaken belief that their toxicities are independent.[50]

In the absence of additional data, the toxicities should be presumed to be additive.

Pregnancy

The spread and depth of epidural and spinal anesthesia are greater in pregnant than in nonpregnant women (also see Chapter 69). The effects of pregnancy on local anesthetic potency may reflect a combined effect of mechanical factors associated with pregnancy (i.e., dilated epidural veins decrease the volume of the epidural and subarachnoid spaces) and direct effects of hormones, especially progesterone, on the susceptibility of nerves to conduction blockade by local anesthetics per se.[51] Hormonal alterations are probably the more important of these two factors because greater spread of epidural anesthesia occurs during the first trimester of pregnancy,[52] before any gross change in vascular dimensions within the epidural or subarachnoid spaces. The dosage of local anesthetics should probably should be reduced in patients in all stages of pregnancy.

Choice of Local Anesthetic for Various Regional Anesthetic Procedures

On the basis of anatomic considerations, regional anesthesia may be divided into infiltration anesthesia, intravenous regional anesthesia, peripheral nerve blockade (including plexus blockade), central neural blockade, and topical anesthesia (also see Chapters 51, 52 , 53, 69, 70, 81, and 87). An additional method of local anesthetic injection, tumescent anesthesia, is included because it is widely used in office plastic surgery practice.

Infiltration Anesthesia

Any local anesthetic may be used for infiltration anesthesia. Onset of action is almost immediate for all agents after intradermal or subcutaneous administration; however, the duration of anesthesia varies (Table 30-4). Epinephrine will prolong the duration of infiltration anesthesia by all local anesthetic drugs, although this effect is most pronounced when epinephrine is added to lidocaine. The choice of a specific drug for infiltration anesthesia largely depends on the desired duration of action.

The dosage of local anesthetic required for adequate infiltration anesthesia depends on the extent of the area to be anesthetized and the expected duration of the surgical procedure. When large surface areas have to be anesthetized, large volumes of dilute anesthetic solutions should be used. These considerations are particularly important when performing infiltration anesthesia in infants and smaller children. As an example, consider a 4-kg infant receiving infiltration anesthesia with the maximum safe dose of lidocaine, 5 mg/kg. Dosing to 5 mg/kg × 4 kg permits 20 mg, which is 1 mL of a 2% solution or 4 mL of a 0.5% solution. Lidocaine is effective for infiltration in concentrations as dilute as 0.3% to 0.5%, so the more dilute solution can be used more safely to anesthetize a larger area.

Patients frequently experience pain immediately after subcutaneous injection of local anesthetic solutions, in part because of the acidic nature of these solutions. For example, neutralization of lidocaine solutions by the addition of sodium bicarbonate immediately before injection reduces pain on skin infiltration[53] and may improve onset (see earlier).

Intravenous Regional Anesthesia

Intravenous regional anesthesia involves the intravenous administration of a local anesthetic into a tourniquet-occluded limb (i.e., Bier block) (see Chapter 70).[54] The local anesthetic diffuses from the peripheral vascular bed to nonvascular tissue such as axons and nerve endings. Both the safety and the efficacy of this regional anesthetic procedure depend on interruption of blood flow to the involved limb and gradual release of the occluding tourniquet. Intravenous regional anesthesia has been used primarily for surgical procedures on the upper limbs. Shorter procedures on the foot can also be successfully performed under intravenous regional anesthesia. If a lower leg tourniquet is used, it should be applied well below the fibular neck to avoid pressure

Table 30-4 Infiltration Anesthesia

	Plain Solution			Epinephrine-Containing Solution	
Drug	**Concentration (%)**	**Max Dose (mg)**	**Duration (min)**	**Max Dose (mg)**	**Duration (min)**
Short Duration					
Procaine	1-2	500	20-30	600	30-45
Chloroprocaine	1-2	800	15-30	1000	30
Moderate Duration					
Lidocaine	0.5-1	300	30-60	500	120
Mepivacaine	0.5-1	300	45-90	500	120
Prilocaine	0.5-1	350	30-90	550	120
Long Duration					
Bupivacaine	0.25-0.5	175	120-240	200	180-240
Ropivacaine	0.2-0.5	200	120-240	250	180-240

over the superficial peroneal nerve; in general, use of an upper leg tourniquet is preferred over lower leg tourniquets.[55]

Lidocaine has been the drug used most frequently for intravenous regional anesthesia. Prilocaine, mepivacaine, chloroprocaine, procaine, bupivacaine, and etidocaine have also been used successfully. One might suppose a safety advantage with the aminoester-linked compounds because of their hydrolysis in blood; however, thrombophlebitis has been reported in several patients with chloroprocaine. Cardiovascular collapse has occurred after the use of bupivacaine for intravenous regional anesthesia, and this use of bupivacaine is discouraged.[56]

In general, approximately 3 mg/kg (40 mL of a 0.5% solution) of preservative-free lidocaine without epinephrine is used for upper extremity procedures. For surgical procedures on the lower limbs, 50 to 100 mL of a 0.25% lidocaine solution has been used.

Peripheral Nerve Blockade

Regional anesthetic procedures that inhibit conduction in fibers of the peripheral nervous system can be classified together under the general category of peripheral nerve blockade (also see Chapters 52 and 53). This form of regional anesthesia has been arbitrarily subdivided into minor and major nerve blocks. Minor nerve blocks are defined as procedures involving single nerve entities such as the ulnar or radial nerve, whereas major nerve blocks involve the blockade of two or more distinct nerves or a nerve plexus or the blockade of very large nerves at more proximal sites (i.e., the femoral and sciatic nerves).

Most local anesthetic drugs can be used for minor nerve blocks. The onset of blockade is rapid with most drugs, and the choice of drug is determined primarily by the required duration of anesthesia. A classification of the various drugs according to their duration of action is shown in Table 30-5. The duration of both sensory analgesia and motor blockade is prolonged significantly when epinephrine is added to the various local anesthetic solutions in some, but not all applications.[57]

In 1986, a technique of interpleural regional analgesia was described as an alternative to multiple intercostal nerve blocks.[58] This procedure involves the administration of local anesthetic solution into the pleural space, either by percutaneous placement or by placement through the open chest by the surgeon during thoracotomy. The risk of pneumothorax has varied in published case series. Although interpleural analgesia appears to be useful for unilateral postoperative analgesia after cholecystectomy, mastectomy, and nephrectomy, its efficacy for post-thoracotomy pain is doubtful.[59] This technique has been associated with extremely high plasma concentrations of anesthetic, with an associated risk of convulsions. Interpleural analgesia has also been used to provide analgesia for chronic pain conditions as diverse as upper extremity complex regional pain syndromes, pancreatitis, and cancer of the thorax and abdomen. In many centers, interpleural analgesia has largely been supplanted by thoracic epidural analgesia for the majority of thoracic and abdominal procedures.

Two related approaches for unilateral somatic blockade in the thorax are continuous extrapleural catheters[60] (placed by the surgeon through the chest dorsal to the parietal pleura) and continuous thoracic paravertebral somatic blockade.[61] One advantage of these two approaches over interpleural analgesia is that very little of the administered solution leaks out of the chest into chest tubes.

Brachial plexus blockade for upper limb surgery is the most common major peripheral nerve block technique. A significant difference exists between the onset times of various agents when these blocks are used (Table 30-6). In general, agents of intermediate potency exhibit a more rapid onset than the more potent compounds do. Onset times of approximately 14 minutes for lidocaine and mepivacaine have been reported versus approximately 23 minutes for bupivacaine. A variety of approaches to the brachial plexus are available; the choice among these approaches is dictated by several factors, including the site of surgery and the ability of the patient to tolerate spillover to other nerves, including the phrenic nerve; these considerations are detailed in Chapters 52, 53, and 70. Similarly, the lumbar plexus can be approached via several routes, including a posterior approach, an anterior perivascular "3 in 1" approach, and an anterior fascia iliaca compartment approach.[62]

The variation in duration of anesthesia after brachial plexus blockade is also considerably greater than that observed with other types of conduction block. For example, durations of anesthesia varying from 4 to 30 hours have been reported for bupivacaine. It is prudent to warn patients before a major nerve block about the possibility of prolonged sensory and motor block in the involved region, particularly when agents such as bupivacaine, levobupivacaine, and ropivacaine are used.

Table 30-5 Minor Nerve Blocks

		Plain Solutions		Epinephrine-Containing Solutions	
Drug	**Usual Concentration (%)**	**Usual Volume (mL)**	**Dosage (mg)**	**Average Duration (min)**	**Average Duration (min)**
Procaine	2	5-20	100-400	15-30	30-60
Chloroprocaine	2	5-20	100-400	15-30	30-60
Lidocaine	1	5-20	50-200	60-120	120-180
Mepivacaine	1	5-20	50-200	60-120	120-180
Prilocaine	1	5-20	50-200	60-120	120-180
Bupivacaine	0.25-0.5	5-20	12.5-100	180-360	240- 420
Ropivacaine	0.2-0.5	5-20	10-100	180-360	240-420

Also see Chapter 52.
Doses refer to 70-kg adults. For pediatric doses, see Chapter 81.

Table 30-6 Major Nerve Blocks

Drug with Epinephrine 1:200,000	Usual Concentration (%)	Usual Volume (mL)	Maximal Dose (mg)	Usual Onset (min)	Usual Duration (min)
Lidocaine	1-2	30-50	500	10-20	120-240
Mepivacaine	1-1.5	30-50	500	10-20	180-300
Prilocaine	1-2	30-50	600	10-20	180-300
Bupivacaine	0.25-0.5	30-50	225	20-30	360-720
Levobupivacaine	0.25-0.5	30-50	225	20-30	360-720
Ropivacaine	0.2-0.5	30-50	250	20-30	360-720

Also see Chapter 52. Doses listed refer to 70-kg adults receiving epinephrine-containing solutions. Doses should be reduced, as detailed in Chapter 81, for children, for patients with specific risk factors, and when non–epinephrine-containing solutions are used.

Central Neural Blockade

Any of the local anesthetic drugs may be used for epidural anesthesia (Table 30-7), although procaine and tetracaine are rarely used because of their long onset times (also see Chapter 51). Drugs of intermediate potency produce surgical anesthesia of 1 to 2 hours' duration, whereas long-acting drugs usually produce 3 to 4 hours of anesthesia. The duration of short- and intermediate-acting drugs is significantly prolonged by the addition of epinephrine (1:200,000), but the duration of long-acting drugs is only minimally affected by epinephrine. The onset of lumbar epidural anesthesia occurs within 5 to 15 minutes after the administration of chloroprocaine, lidocaine, mepivacaine, and prilocaine. Bupivacaine has a slower onset of action.

Bupivacaine bolus doses at a concentration of 0.125% produce adequate analgesia in many clinical settings with only mild motor deficits.[63] Continuous epidural infusions of bupivacaine as dilute as 0.0625% to 0.1% are useful for labor epidural analgesia, especially when administered in combination with opioids and other additives. Bupivacaine 0.25% may be used for more intense analgesia (particularly during combined epidural–light general anesthesia cases) with moderate degrees of motor block. Bupivacaine at concentrations of 0.5% to 0.75% is associated with a more profound degree of motor block, which makes these solutions most suitable for major surgical procedures, particularly when epidural anesthesia is not combined with general anesthesia. It should be emphasized that although high concentrations of local anesthetics may be appropriate for episodic bolus dosing for surgery, these concentrations (i.e., >0.2% for bupivacaine) should generally be avoided for continuous epidural infusions. Bolus injections produce much more cephalocaudad spread than infusions do. When concentrated bupivacaine solutions are used for infusions, they have the potential for excessive local effect with an associated risk for unwanted and very prolonged motor blockade. Etidocaine produces adequate sensory analgesia and profound, long-lasting motor block. Use of etidocaine has decreased in recent years, and at present it is primarily restricted to surgical procedures for which profound muscle relaxation is required.

Drugs available for subarachnoid administration are shown in Table 30-8.

Although lidocaine has long been used for spinal anesthesia as a 5% solution, recent studies of local anesthetic neurotoxicity have led some to question this practice; this issue is discussed later in the chapter in the section on the neurotoxicity of local anesthetics.

Tetracaine is available both as crystals and as a 1% solution, which may be diluted with 10% glucose to obtain a 0.5% hyperbaric solution. Hypobaric solutions of tetracaine (tetracaine in sterile water) may be used for specific operative situations, such as anorectal or hip surgery. Isobaric tetracaine obtained by mixing 1% tetracaine with cerebrospinal fluid or normal saline is useful for lower limb surgical procedures.

Bupivacaine is widely used as a spinal anesthetic, either as a hyperbaric solution at a concentration of 0.75% with 8.25% dextrose or by using the nearly isobaric 0.5% solution. Intrathecal

Table 30-7 Epidural Anesthesia

Drug with Epinephrine 1:200,000	Usual Concentration (%)	Usual Volume (mL)	Total Dose (mg)	Usual Onset (min)	Usual Duration (min)
Chloroprocaine	2-3	15-30	300-900	5-15	30-90
Lidocaine	1-2	15-30	150-500	5-15	
Mepivacaine	1-2	15-30	150-500	5-15	60-180
Prilocaine	1-3	15-30	150-600	5-15	
Bupivacaine	0.25-0.5	15-30	40-225	15-20	180-350
Levobupivacaine	0.25-0.75	15-30	40-250	15-20	180-350
Ropivacaine	0.2-0.75	15-30	40-250	15-20	180-350

Also see Chapter 51. Doses listed refer to 70-kg adults receiving epinephrine-containing solutions. Doses should be reduced, as detailed in Chapter 81, for children, for patients with specific risk factors, and when non–epinephrine-containing solutions are used.

Table 30-8 Spinal Anesthesia*

Drug	Usual Concentration (%)	Usual Volume (mL)	Total Dose (mg)	Baricity	Glucose Concentration (%)	Usual Duration (min)
Procaine	10.0	1-2	100-200	Hyperbaric	5.0	30-60
Lidocaine	1.5, 5.0	1-2	30-100	Hyperbaric	7.5	30-90
Mepivacaine	4	1-2	40-80	Hyperbaric	9.0	30-90
Tetracaine	0.25-1.0 0.25 1.0	1-4 2-6 1-2	5-20 5-20 5-20	Hyperbaric Hypobaric Isobaric	5.0	90-200 90-200 90-200
Dibucaine	0.25 0.5 0.06	1-2 1-2 5-20	2.5-5.0 5-10 3-12	Hyperbaric Isobaric Hypobaric	5.0	90-200 90-200 90-200
Bupivacaine	0.5 0.75	3-4 2-3	15-20 15-20	Isobaric Hyperbaric	 8.25	90-200 90-200
Levobupivacaine	0.5 0.75	3-4 2-3	15-20 15-20	Isobaric Hyperbaric		90-200 90-200
Ropivacaine	0.5 0.75	3-4 2-3	15-20 15-20	Isobaric Hyperbaric		90-200 90-200

*Dosing refers to a 70-Kg adult. Dosing may be reduced in pregnancy (see Chapter 69) and with advancing age (see Chapter 71). Pediatric dosing is detailed in Chapter 81.

bupivacaine possesses an anesthetic profile similar to that of tetracaine.[64]

The addition of vasoconstrictors may prolong the duration of spinal anesthesia; for example, the addition of 0.2 to 0.3 mg of epinephrine to lidocaine, tetracaine, or bupivacaine solutions will produce a 50% or greater increase in duration.[65,66] The duration of spinal anesthesia produced by tetracaine can also be increased to a similar extent by adding 1 to 5 mg of phenylephrine. The addition of epinephrine to bupivacaine or lidocaine may be more effective in prolonging the duration of spinal anesthesia in lumbosacral segments than in thoracic segments.

Topical Anesthesia

A number of local anesthetic formulations are available for topical anesthesia (Table 30-9), lidocaine, dibucaine, tetracaine, and benzocaine being the drugs used most commonly. In general, these preparations provide effective but relatively short durations of analgesia when applied to mucous membranes or abraded skin. Lidocaine and tetracaine sprays are commonly used for endotracheal anesthesia before intubation or for mucosal analgesia for bronchoscopy or esophagoscopy.

A variety of topical local anesthetic formulations have been developed to penetrate intact skin. EMLA, which is a eutectic mixture of 2.5% lidocaine base and 2.5% prilocaine base, is widely used for venipuncture, intravenous cannulation, skin grafting, and a range of other uses, including circumcision.[67-69] This preparation must be applied under an occlusive bandage for 45 to 60 minutes to obtain effective cutaneous anesthesia; longer application times increase the depth and reliability of skin analgesia. EMLA appears to be quite safe in neonates, and methemoglobinemia with the use of prilocaine is exceedingly uncommon. EMLA is more effective for newborn circumcision than placebo is but less effective than dorsal penile nerve block.[69,89] Several alternative topical local anesthetic formulations also are in use, including tetracaine gel[70] and liposomal lidocaine.[71] Physical methods to accelerate local anesthetic transit across skin, including iontophoresis, local heating, electroporation, and a variety of forms of needle-less pressure injection, may lead to more rapid onset of cutaneous analgesia.[72] Synera (originally studied as S-Caine) is a formulation of lidocaine and tetracaine that was developed with a heating element (activated by opening the package to initiate an oxygen-dependent exothermic reaction). This formulation has a rapid onset and evokes vasodilatation.[73]

Topical anesthesia through cut skin is commonly used in pediatric emergency departments for liquid application into lacerations that require suturing. Historically, this had been provided by a mixture of tetracaine, epinephrine (adrenaline), and cocaine, known as TAC.[74] TAC is usually supplied as tetracaine 0.5%, epinephrine 1:2000, and cocaine 10% to 11.8%, although studies suggest that more dilute concentrations may be almost equally effective and less likely to cause toxicity. The generally recommended safe maximum dose is 3 to 4 mL for adults or 0.05 mL/kg for children. TAC is ineffective through intact skin; in contrast, its rapid absorption from mucosal surfaces can lead to toxic, even fatal reactions.

Because of concerns regarding cocaine toxicity and the potential for diversion and abuse, several groups have investigated alternative cocaine-free topical preparations. Non–cocaine-containing formulations, especially lidocaine-epinephrine-tetracaine (LET) and tetracaine-phenylephrine, have largely supplanted TAC.[75] Similarly, otolaryngologists previously administered cocaine routinely as a solution or aerosol into the nasal passages to provide mucosal analgesia and vasoconstriction. In recent years, cocaine has increasingly been replaced for nasal application by the combined use of an α_1-adrenergic agonist (oxymetazoline or phenylephrine) and a local anesthetic such as 2% to 4% lidocaine, with more dilute solutions being recommended for infants and children (see Chapter 81). Systemic absorption of phenylephrine can cause severe hypertension and reflex bradycardia; oxymetazoline is associated with much less

Table 30-9 Various Preparations Intended for Topical Anesthesia

Anesthetic Ingredient	Concentration (%)	Pharmaceutical Application Form	Intended Area of Use
Benzocaine	1-5	Cream	Skin and mucous membrane
	20	Ointment	Skin and mucous membrane
	20	Aerosol	Skin and mucous membrane
Cocaine	4	Solution	Ear, nose, throat
Dibucaine	0.25-1	Cream	Skin
	0.25-1	Ointment	Skin
	0.25-1	Aerosol	Skin
	0.25	Solution	Ear
	2.5	Suppositories	Rectum
Cyclonine	0.5-1	Solution	Skin, oropharynx, tracheobronchial tree, urethra, rectum
Lidocaine	2-4	Solution	Oropharynx, tracheobronchial tree, nose
	2	Jelly	Urethra
	2.5-5	Ointment	Skin, mucous membrane, rectum
	2	Viscous	Oropharynx
	10	Suppositories	Rectum
	10	Aerosol	Gingival mucosa
Tetracaine	0.5-1	Ointment	Skin, rectum, mucous membrane
	0.5-1	Cream	Skin, rectum, mucous membrane
	0.25-1	Solution	Nose, tracheobronchial tree
EMLA	Lidocaine, 2.5 Prilocaine, 2.5	Cream	Intact skin
TAC	Tetracaine, 0.5 Epinephrine, 1:200,000 Cocaine, 11.8	Solution	Cut skin
LET	Lidocaine, 4% Epinephrine, 1:20,000 Tetracaine, 0.5%	Solution	Cut skin

EMLA, eutectic mixture of lidocaine and prilocaine; LET, lidocaine-epinephrine-tetracaine; TAC, tetracaine-epinephrine-cocaine.
Modified from Covino B, Vassallo H: Local Anesthetics: Mechanisms of Action and Clinical Use. Orlando, FL, Grune & Stratton, 1976, with permission.

systemic effect and has a considerably wider margin of safety. In our view, there is no clinical setting for which the benefits of cocaine clearly outweigh the potential risks when compared with alternative approaches involving combined administration of a local anesthetic and a topical vasoconstrictor such as oxymetazoline.

Tumescent Anesthesia

A technique of local anesthesia most commonly used by plastic surgeons during liposuction procedures involves the subcutaneous injection of large volumes of dilute local anesthetic in combination with epinephrine and other agents. Total doses of lidocaine ranging from 35 to 55 mg/kg have been reported to produce safe plasma concentrations, which may peak more than 8 to 12 hours after infusion.[76] Despite these seemingly huge doses, very good outcomes have been reported in several case series.[77] Conversely, there have been several case series of cardiac arrest and death during plastic surgical procedures in which multiple risk factors, including high local anesthetic concentrations and concomitant use of sedatives, may have contributed to the patients' instability and deterioration.[78] Factors governing uptake and clearance from this method of local anesthetic delivery deserve further study. Clinicians should exercise great caution when administering additional local anesthetics by infiltration or other routes for at least 12 to 18 hours after the use of this technique.

Systemic Local Anesthetics for Neuropathic Pain

A broad variety of local anesthetics, antiarrhythmics, anticonvulsants, and other Na^+ channel blockers are administered intravenously, orally, or both to relieve a number of forms of neuropathic pain (see Chapter 58).[79] Clinical results are unpredictable. Although successful responses from intravenous lidocaine are often taken as a positive indication for oral mexiletine, many patients find mexiletine difficult to tolerate. When the signs of neuropathic pain are reversed by lidocaine infusion, normal nociception and other sensory modalities are unaffected, suggesting that the neurophysiologic correlate of the disease has an unusually high susceptibility to these drugs, present in plasma at concentrations 50 to 100 times lower than that required to block normal impulses in peripheral fibers. Laboratory studies suggest

that ectopic impulse activity arising at a site of injury or elsewhere, such as the dorsal root ganglion, contributes to the neuropathic pain and that such impulses are particularly sensitive to use-dependent Na^+ channel blockers. It is noteworthy that relief of preexisting neuropathic pain, both clinically and in animal models,[80] can in some cases persist for days, weeks, or months after a single intravenous infusion of drug (e.g., lidocaine), far beyond the lifetime of the drug in vivo or any nerve block that it might affect. The mechanism of this remarkable action remains a mystery.

Pharmacokinetics

The concentration of local anesthetics in blood is determined by the amount injected, the rate of absorption from the site of injection, the rate of tissue distribution, and the rate of biotransformation and excretion of the specific drug.[81-83] Patient-related factors such as age, cardiovascular status, and hepatic function influence the physiologic disposition and resultant blood concentration of local anesthetics.

Absorption

The systemic absorption of local anesthetics is determined by the site of injection, dosage and volume, addition of a vasoconstrictor agent, and the pharmacologic profile of the agent itself.[81-83] Comparison of the blood concentration of local anesthetics after various routes of administration reveals that the anesthetic drug level is highest after intercostal nerve blockade, followed in order of decreasing concentration by injection into the caudal epidural space, lumbar epidural space, brachial plexus, and subcutaneous tissue.[83] When a local anesthetic solution is exposed to an area of greater vascularity, a greater rate and degree of absorption occur. This relationship is of clinical significance because use of a fixed dose of a local anesthetic agent may be potentially toxic in one area of administration but not in others. For example, the use of 400 mg of lidocaine without epinephrine for an intercostal nerve block results in an average peak venous plasma level of approximately 7 µg/mL, which is sufficiently high to cause symptoms of central nervous system (CNS) toxicity in some patients. By comparison, this same dose of lidocaine used for a brachial plexus block yields a mean maximum blood level of approximately 3 µg/mL, which is rarely associated with signs of toxicity.[83]

The maximum blood concentration of local anesthetic drugs is related to the total dose of drug administered for any particular site of administration. For most drugs there is a proportionality between the amount of drug administered and the resultant peak anesthetic blood concentration.

Local anesthetic solutions frequently contain a vasoconstrictor agent, usually epinephrine, in concentrations varying from 5 to 20 µg/mL. Epinephrine decreases the rate of vascular absorption of certain agents from various sites of administration and thus lowers their potential systemic toxicity. A 5-µg/mL concentration of epinephrine (1:200,000) significantly reduces the peak blood levels of lidocaine and mepivacaine irrespective of the site of administration. Peak blood levels of bupivacaine and etidocaine are minimally influenced by the addition of a vasoconstrictor after injection into the lumbar epidural space. However, epinephrine will significantly reduce the rate of vascular absorption of these drugs when they are used for peripheral nerve blocks such as brachial plexus blockade.

Differences also exist in the rate of absorption of various local anesthetics. In some studies, absorption of local anesthetics from the epidural space has appeared to involve both rapid and slow processes, as described by two-compartment models.[84]

Distribution

The systemic distribution of local anesthetics can be described sufficiently by a two-compartment model.[85] The rapid disappearance phase is believed to be related to uptake by rapidly equilibrating tissues (i.e., tissues that have high vascular perfusion). The slower phase of disappearance from blood is mainly a function of the particular compound.[85]

Local anesthetic drugs are distributed throughout all body tissues, but the relative concentration in different tissues varies. In general, more highly perfused organs show higher concentrations of local anesthetic drug than less well perfused organs do. Because local anesthetics are rapidly extracted by lung tissue, the whole blood concentration of local anesthetics decreases markedly as they pass through the pulmonary vasculature.[86]

Biotransformation and Excretion

The pattern of metabolism of local anesthetic agents varies according to their chemical classification. The ester, or procaine-like, drugs undergo hydrolysis in plasma by the pseudocholinesterase enzymes; clearance of chloroprocaine is especially rapid.[87,88]

The aminoamide drugs undergo enzymatic degradation primarily in the liver. Lidocaine is metabolized somewhat more rapidly than mepivacaine, which in turn is more rapidly metabolized than bupivacaine.[89-91]

Excretion of the metabolites of amide-type local anesthetics occurs via the kidney. Less than 5% of the unchanged drug is excreted via the kidney into urine.

Pharmacokinetic Alterations by Patient Status

Patient age may influence the physiologic disposition of local anesthetics (see Chapters 71 and 81). The half-life of lidocaine after intravenous administration averaged 80 minutes in human volunteers varying in age from 22 to 26 years, whereas volunteers 61 to 71 years of age demonstrated a significantly prolonged lidocaine half-life that averaged 138 minutes.[92]

Newborn infants have immature hepatic enzyme systems and hence prolonged elimination of lidocaine, bupivacaine, and ropivacaine.[93-95] Bupivacaine, for example, has a terminal elimination half-life in adults that averages around 3.5 hours. In neonates and some younger infants, terminal elimination half-lives may be as long as 8 to 12 hours. Prolonged elimination is particularly an issue for continuous infusions of local anesthetics in infants, and seizures have been associated with high bupivacaine infusion rates.[96] Based on analysis of these cases, a maximum infusion rate of 0.4 mg/kg/hr for prolonged bupivacaine infusions has been proposed for children and adults, whereas prolonged infusion

rates for neonates and young infants should not exceed 0.2 mg/kg/hr.[97] Even at 0.2 mg/kg/hr, plasma bupivacaine concentrations were found to be rising toward a toxic range in some younger infants after 48 hours.[98] Similarly, prolonged lidocaine infusions in neonates should not exceed 0.8 mg/kg/hr. The potential for toxicity with lidocaine infusions in neonates is also increased by the accumulation of its principal metabolite, monoethylglycinexylidide (MEGX), which can cause seizures. Chloroprocaine may offer unique advantages for epidural infusion in neonates in that it is rapidly cleared from plasma, even in preterm neonates.[99]

Decreased hepatic blood flow or impaired hepatic enzyme function can produce a substantial elevation of blood levels of the aminoamide local anesthetics. An average lidocaine half-life of 1.5 hours was reported in volunteers with normal hepatic function, whereas patients with liver disease demonstrated an average half-life of 5.0 hours.[100] The rate of disappearance of lidocaine from blood has also been shown to be markedly prolonged in patients with congestive heart failure.[101]

Toxicity

Local anesthetic drugs are relatively safe if administered in an appropriate dosage and in the correct anatomic location. However, systemic and localized toxic reactions can occur, usually as a result of accidental intravascular or intrathecal injection or administration of an excessive dose. In addition, specific adverse effects are associated with the use of certain drugs, such as allergic reactions to the aminoester drugs and methemoglobinemia after the use of prilocaine.

Systemic Toxicity

Systemic reactions to local anesthetics primarily involve the CNS and the cardiovascular system (also see Chapters 51 to 53 and 81). In general, the CNS is more susceptible to the actions of systemic local anesthetics than the cardiovascular system is, and thus the dose or blood level of local anesthetic required to produce CNS toxicity is usually lower than that resulting in circulatory collapse.

Central Nervous System Toxicity

The initial symptoms of local anesthetic–induced CNS toxicity are feelings of lightheadedness and dizziness followed frequently by visual and auditory disturbances such as difficulty focusing and tinnitus. Other subjective CNS symptoms include disorientation and occasional feelings of drowsiness. Objective signs of CNS toxicity are usually excitatory in nature and include shivering, muscular twitching, and tremors initially involving muscles of the face and distal parts of the extremities. Ultimately, generalized convulsions of a tonic-clonic nature occur. If a sufficiently large dose or rapid intravenous injection of a local anesthetic is administered, the initial signs of CNS excitation are rapidly followed by a state of generalized CNS depression. Seizure activity ceases, and respiratory depression and ultimately respiratory arrest may occur. In some patients CNS depression is seen without a preceding excitatory phase, particularly if other CNS depressant drugs have been administered.

CNS excitation may be the result of an initial blockade of inhibitory pathways in the cerebral cortex by local anesthetic drugs[102] but can also result from the net stimulation of release of glutamate, an excitatory amino acid neurotransmitter. Blockade of inhibitory pathways allows facilitatory neurons to function in an unopposed fashion, which results in an increase in excitatory activity leading to convulsions. A further increase in the dose of local anesthetic leads to inhibition of activity of both the inhibitory and facilitatory circuits, which results in a generalized state of CNS depression.

In general, a correlation exists between potency of the local anesthetic and intravenous CNS toxicity.[103] Convulsions caused by an inadvertent intravenous bolus of local anesthetic can generally be terminated by small intravenous doses of a benzodiazepine, such as midazolam, or by small intravenous doses of thiopental.

Respiratory or metabolic acidosis increases the risks for CNS toxicity from local anesthetics.[104]

Elevated $Paco_2$ enhances cerebral blood flow and thus the anesthetic is delivered more rapidly to the brain. In addition, diffusion of carbon dioxide into neuronal cells decreases intracellular pH, which facilitates conversion of the base form of the drugs to the cationic form. The cationic form does not diffuse well across the nerve membrane, so ion trapping will occur, which will increase the apparent CNS toxicity of local anesthetics.

Hypercapnia and acidosis also decrease the plasma protein binding of local anesthetic agents.[105] Accordingly, an elevation in $Paco_2$ or a decrease in pH will increase the proportion of free drug available for diffusion into the brain. On the other hand, acidosis increases the cationic form of the local anesthetic, which should decrease the rate of diffusion through lipoid barriers.

The clinical implication of this effect of hypercapnia and acidosis on toxicity deserves emphasis. Seizures produce hypoventilation and a combined respiratory and metabolic acidosis, which further exacerbates the CNS toxicity. In the setting of local anesthetic toxic reactions, it is essential to provide prompt assisted ventilation and circulatory support as needed to prevent or correct hypercapnia and acidosis and to prevent or correct hypoxemia, which also exacerbates CNS toxicity. Based on the preceding discussion, it should be apparent that clinicians performing major conduction blockade should make a routine practice of having the following ready at hand: monitoring equipment; an oxygen tank or wall oxygen outlet; airway equipment, including at minimum, a bag-mask circuit for delivery of positive-pressure ventilation; and drugs to terminate convulsions, such as midazolam, lorazepam, diazepam, or thiopental.

Cardiovascular System Toxicity

Local anesthetics can exert direct actions on both the heart and peripheral blood vessels, as well as indirect actions on the circulation by blockade of sympathetic or parasympathetic efferent activity.

Direct Cardiac Effects

The primary cardiac electrophysiologic effect of local anesthetics is a decrease in the rate of depolarization in the fast conducting tissues of Purkinje fibers and ventricular muscle.[106] This reduction in rate is believed to be due to a decrease in the availability of fast sodium channels in cardiac membranes. Action potential duration and the effective refractory period are also decreased by local anesthetics.

The electrophysiologic effects of various agents differ qualitatively. Bupivacaine depresses the rapid phase of depolarization (Vmax) in Purkinje fibers and ventricular muscle to a greater extent than lidocaine does. In addition, the rate of recovery from a use-dependent block is slower in bupivacaine-treated papillary muscles than in lidocaine-treated muscles. This slow rate of recovery results in incomplete restoration of Na^+ channel availability between action potentials, particularly at high heart rates. These differential effects of lidocaine and bupivacaine have been advanced as explanations of the antiarrhythmic properties of lidocaine and the arrhythmogenic potential of bupivacaine.

Electrophysiologic studies have shown that high blood levels of local anesthetics will prolong conduction time through various parts of the heart, as indicated on the electrocardiogram (ECG) by an increase in the PR interval and duration of the QRS complex. Extremely high concentrations of local anesthetics depress spontaneous pacemaker activity in the sinus node, thereby resulting in sinus bradycardia and sinus arrest.

All local anesthetics exert dose-dependent negative inotropic action on cardiac muscle[107]; the depression of cardiac contractility is roughly proportional to conduction blocking potency. Thus, bupivacaine and tetracaine are more potent cardiodepressants than lidocaine is.

Local anesthetics may depress myocardial contractility by affecting calcium influx and triggered release from the sarcoplasmic reticulum,[108] as well as by inhibiting cardiac sarcolemmal Ca^{2+} currents and Na^+ currents.

Direct Peripheral Vascular Effects

Local anesthetics exert biphasic effects on peripheral vascular smooth muscle.[109] Low concentrations of lidocaine and bupivacaine produced vasoconstriction in the cremaster muscle of rats, whereas high concentrations produced vasodilation in both isolated tissue models and in vivo.

Cocaine is the only local anesthetic that consistently causes vasoconstriction at all concentrations because of its ability to inhibit the uptake of norepinephrine by premotor neurons and thus to potentiate neurogenic vasoconstriction.

Comparative Cardiovascular Toxicity

All local anesthetics, but especially bupivacaine, can cause rapid and profound cardiovascular depression (also see Chapters 51 to 53 and 81). The cardiotoxicity of bupivacaine appears to differ from that of lidocaine in the following manner:

1. The ratio of the dosage required for irreversible cardiovascular collapse (CC) and the dosage that will produce CNS toxicity (convulsions) (i.e., the CC/CNS ratio) is lower for bupivacaine and etidocaine than for lidocaine.[110]
2. Ventricular arrhythmias and fatal ventricular fibrillation may occur more often after the rapid intravenous administration of a large dose of bupivacaine but far less frequently with lidocaine.[111,112] The CNS effects of local anesthetics may contribute to the generation of arrhythmias (see Chapter 61).[113]
3. A pregnant animal or patient may be more sensitive to the cardiotoxic effects of bupivacaine than a nonpregnant animal or patient[114] (see also Chapter 69). The 0.75% solution of bupivacaine is no longer recommended for use in obstetric anesthesia in the United States.
4. Cardiac resuscitation is more difficult after bupivacaine-induced cardiovascular collapse, and acidosis and hypoxia markedly potentiate the cardiotoxicity of bupivacaine.[115]

Many resuscitation drugs, including atropine, epinephrine, bretylium, lidocaine, amrinone, and phenytoin, have been used in animal studies and occasionally in humans for the treatment of bupivacaine overdose and cardiovascular collapse. In our view, beyond the established uses of epinephrine, vasopressin, and atropine in their designated steps in the advanced cardiac life support (ACLS) protocol[116] and beyond the use of Intralipid as detailed later, there is no established role for antiarrhythmic drugs or other traditional resuscitation drugs in the setting of bupivacaine-induced cardiac arrest. It is *not* recommended that bupivacaine-induced ventricular arrhythmias be treated with lidocaine or amiodarone.

The clinical implications for cardiac resuscitation after intravascular injection or overdose of local anesthetic are the following:

1. No medications are uniformly effective in facilitating resuscitation from bupivacaine-induced cardiac arrest or severe ventricular tachycardia (despite our recommendations regarding Intralipid later). Basic principles of cardiopulmonary resuscitation should be emphasized first, including attention to securing the airway, providing oxygenation and ventilation, and performing chest compressions if needed.
2. Because resuscitation after local anesthetic–induced circulatory collapse is so difficult, prevention of massive intravascular injection or excessive dosing is crucial.
3. Negative aspiration of the syringe does not always exclude intravascular placement. Incremental, fractionated dosing should be the rule for all patients undergoing major conduction blockade. Although changes on the ECG are not always present before circulatory collapse, they often are, and continuous attention to the ECG (including changes in QRS morphology, rate, rhythm, or ectopy) may be lifesaving by terminating injection before a lethal dose is administered.
4. Based on animal studies[117] and a growing number of human case reports,[118-120] we recommend that hospitals and clinics that perform major conduction blockade keep available for emergency use a supply of Intralipid 20%. If a patient experiences profound cardiovascular depression or circulatory arrest after the administration of bupivacaine, ropivacaine, or by extrapolation, other local anesthetics, then along with initiation of basic life support and the ACLS protocol we support the recommendation of Weinberg and colleagues[120] that a rapid bolus of Intralipid 20%, 1.5 mL/kg (or roughly 100 mL in adults), be administered without delay, followed if necessary by an infusion of 0.25 mL/kg/min for the next 10 minutes.

Chiral Local Anesthetics: Ropivacaine and Levobupivacaine

Commercial bupivacaine is a racemic mixture of (*R*)- and (*S*)-stereoisomers. In response to the problem of cardiovascular toxicity as a result of accidental intravenous injection of bupivacaine,

single enantiomers were developed in the hope that they would be potentially safer local anesthetics. Ropivacaine (Naropin)[121] and levo-(*S*)-bupivacaine (Chirocaine)[122] were formulated to exploit this stereoselectivity. Ropivacaine is a single (*S*)-stereoisomer that differs from levobupivacaine in the substitution of a propyl for the butyl group on the piperidine ring (see Fig. 30-2). With these designed changes in molecular structure, it was hoped that ropivacaine and levobupivacaine would be less intrinsically cardiotoxic. Conversely, it appears that the (*S*)-enantiomers of mepivacaine and bupivacaine are metabolized by the liver more slowly than the corresponding (*R*)-enantiomers, which would lead to somewhat greater systemic accumulation with prolonged infusions.[123]

The cardiovascular toxicity of local anesthetics is complex and involves direct effects on the myocardium, on vascular tissue (both smooth muscle and its neuronal supply), and on the central innervation of the heart. The very slow reversal of Na^+ channel blockade after a cardiac action potential, which is a hallmark of bupivacaine, is considerably faster with ropivacaine. In addition to these electrical differences, the negative inotropic potency of ropivacaine on isolated cardiac tissue appears to be considerably less than that of bupivacaine.[124,125] Both electrical and mechanical differences in the toxic profiles may arise from the selective inhibition of Ca^{2+} currents by bupivacaine.

Do the data support the claim of a greater therapeutic index for ropivacaine than bupivacaine, particularly with regard to cardiotoxicity? In clinical studies comparing potencies of ropivacaine and bupivacaine administered for brachial plexus[126] or lumbar epidural block,[127] the anesthetic profiles of the drugs were almost identical. A third study comparing lumbar epidural 0.5% bupivacaine with 0.75% ropivacaine also found no significant differences in motor or sensory effects between the drugs at these different concentrations.[128] Overall, it appears that ropivacaine is slightly less potent than (1:1.3 to 1:1.5) or equally potent as bupivacaine for regional anesthesia. In some laboratory animal studies and in some human studies, ropivacaine also produced blocks of shorter duration than those induced by bupivacaine. Other studies in animals and humans have found equal durations of sensory and motor block for the two drugs.

At the projected equipotent doses for nerve block, are the drugs equally toxic? The overall impression is that ropivacaine is less cardiotoxic than bupivacaine. Studies in animals have generally found that bupivacaine more readily produces conduction disturbances, cardiac collapse, or ventricular fibrillation than ropivacaine does and that aggressive cardiac resuscitation after an intentional intravenous bolus in dogs leads to effective reversal of the toxic effects far more frequently with ropivacaine than with bupivacaine.[129]

The greater safety of ropivacaine than bupivacaine may be related both to the reduced toxicity of the single (*S*)-isomer and to the difference between the propyl- and butyl-*N*-piperidine substituent. In contrast to bupivacaine, the cardiotoxic profile of ropivacaine in pregnant ewes is the same as the corresponding profile in nonpregnant ewes.[130]

Levobupivacaine has been studied in a range of clinical settings and sites of administration.[131-133] Although a number of publications have compared levobupivacaine with racemic bupivacaine and ropivacaine,[132,133] conclusions differ among studies regarding the relative potency and duration of block of these three drugs at different sites of administration with respect to sensory and motor end points. Clinicians should note that levobupivacaine is formulated as a weight percentage with regard to its free base content, whereas the weight percentage of most other local anesthetics is calculated on the basis of the hydrochloride salt.[134]

Acidosis and Hypoxia

As with CNS toxicity, hypercapnia, acidosis, and hypoxia potentiate the negative chronotropic and inotropic actions of lidocaine and bupivacaine in isolated cardiac tissue, and the combination of hypoxia and acidosis markedly potentiates the cardiodepressant effects of bupivacaine.[135] Hypoxia and acidosis also increased the frequency of cardiac arrhythmias and the mortality rate in sheep after the intravenous administration of bupivacaine. Hypercapnia, acidosis, and hypoxia occur very rapidly in some patients after seizure activity caused by the rapid accidental intravascular injection of local anesthetic agents.[136] Thus, the cardiovascular depression observed in some patients after the accidental intravenous injection of bupivacaine may be related in part to the effect of seizures producing acidosis and hypoxia and thereby leading to an exacerbation of bupivacaine's intrinsic cardiotoxicity.

Indirect Cardiovascular Effects

High levels of spinal or epidural blockade can produce severe hypotension. A follow-up study of closed claims of patients who suffered perioperative cardiac arrest confirmed previous reports of a series of cardiac arrests involving generally healthy patients undergoing spinal or epidural anesthesia.[137] These events frequently occurred in conjunction with high dermatomal levels of blockade, liberal use of sedatives, and progression to cardiac arrest after a period of hypotension accompanied by bradycardia, often involving delays in recognition of the problem, delays in instituting airway support (particularly in sedated patients), and delays in administration of direct-acting combined α- and β-adrenergic agonists, such as epinephrine. Whereas mild to moderate degrees of hypotension generally respond well to indirect-acting sympathomimetics such as ephedrine or incremental dosing of phenylephrine, the combination of severe hypotension and severe bradycardia under spinal anesthesia should in most clinical settings be treated promptly with incremental dosing of epinephrine, initially at doses of 0.1 to 1 μg/kg, or roughly 20- to 200-fold below those used in the ACLS cardiac arrest algorithm.

Methemoglobinemia

A unique systemic side effect associated with a specific local anesthetic is the development of methemoglobinemia after the administration of large doses of prilocaine.[138] In general, 600-mg doses are required for the development of clinically significant levels of methemoglobinemia in adults. Hepatic metabolism of prilocaine generates *O*-toluidine, which oxidizes hemoglobin to methemoglobin. Methemoglobinemia, if severe, may be treated by the intravenous administration of methylene blue. Standard dosing of the topical local anesthetic EMLA (a mixture of lidocaine and prilocaine) in term newborns produced minimal amounts of methemoglobin, and EMLA should be regarded as very safe in

the great majority of newborns. Risk may be increased in newborns with rare metabolic disorders or after the concomitant administration of other drugs that impair reduction of methemoglobin.

Allergies

Even though patients receiving local anesthetics may experience a range of local and systemic symptoms, prospective studies indicate that very few of these reactions are confirmed as allergic reactions.[139] Aminoester drugs such as procaine may produce allergic-type reactions more commonly than the aminoamides do, although even with aminoesters, the vast majority of reactions are not allergic. Aminoesters, unlike aminoamides, are derivatives of *p*-aminobenzoic acid, which is known to be allergenic. Some aminoamide solutions may contain a preservative, methylparaben, whose chemical structure is similar to that of *p*-aminobenzoic acid, but for most aminoamides, preservative-free solutions are available. Contamination of vials with latex antigen has been suspected in some allergic reactions, although it has been difficult to confirm. In the very rare patient for whom confirmed allergy to both aminoamides and aminoesters precludes their use for spinal anesthesia, meperidine can be considered as an alternative.[140]

Local Tissue Toxicity

All the clinically used aminoamide and aminoester local anesthetics can produce direct toxicity to nerves if they achieve sufficiently high intraneural concentrations. Conversely, in the great majority of clinical applications, no damage to nerves occurs. Although local anesthetics are usually packaged and injected at concentrations well above their physiologically effective range, in the process of delivery they are generally diluted sufficiently that no harm is done. If such dilution does not occur, however, long-term or permanent neural deficits do result. Thus, the application of 5% (200 mM) lidocaine in viscous, dense solutions through narrow intrathecal catheters has been associated with a high frequency of transient or longer-term radicular symptoms or even cauda equina syndrome.[141] Laboratory investigations have shown that such high concentrations of local anesthetics alone applied directly to bare nerve fibers produce an irreversible conduction block in less than 5 minutes.[142] Indeed, previous studies on ensheathed peripheral nerves in vivo had shown neurologic and histologic changes after infiltration of the space surrounding the nerve with local anesthetics at concentrations as low as 1% to 2%. Clinicians should be aware that the concentrations of formulated local anesthetic solutions are neurotoxic per se and that their dilution, in situ or in tissue, is essential for safe use. A recently published randomized trial has renewed interest in continuous spinal anesthesia,[143] and it may have a favorable risk-benefit ratio for selected high-risk patients.

In the late 1970s and early 1980s, prolonged sensory and motor deficits were reported in some patients after the epidural or subarachnoid injection of large doses of chloroprocaine.[144] Studies in animals have proved somewhat contradictory regarding the potential neurotoxicity of chloroprocaine.[145,146] Some studies suggest that the combination of low pH, sodium bisulfite, and inadvertent intrathecal dosing is responsible in part for the neurotoxic reactions observed after the use of large amounts of chloroprocaine solution; other studies have disputed this claim and note that chloroprocaine itself at high concentrations can also be neurotoxic,[145,146] but these concentrations are probably rarely achieved during properly positioned epidural anesthesia, as opposed to inadvertent spinal anesthesia. The currently available commercial solutions of chloroprocaine do not contain sodium bisulfite. This was initially replaced by ethylene glycol-bis-(β-aminoethyl ether)-*N*,*N*-tetraacetic acid (EGTA), a preservative and high-affinity calcium chelator that was occasionally reported to cause local muscle spasms after epidural administration. More recently, chloroprocaine has become available in an entirely preservative-free preparation. Chloroprocaine has unique utility in situations in which rapid plasma clearance is required to prevent excessive systemic accumulation of local anesthetic. Chloroprocaine has been given by epidural infusion to neonates and young infants in settings in which lidocaine and bupivacaine may not provide an effective therapeutic index,[99] and it has also recently become popular as a short-duration spinal anesthetic.

Single-shot spinal anesthesia with commonly recommended doses and concentrations of many different local anesthetics can produce more limited and transient neurologic symptoms (back pain, paresthesias, radicular pain, or hypoesthesia).[147] Some studies and systematic reviews have found that mepivacaine and lidocaine at a range of dilutions cause more frequent symptoms than bupivacaine and prilocaine do.[148] The risk of transient neurologic symptoms after spinal anesthesia was not diminished by dilution of lidocaine from 5% to 1%-2%. Differences in study design, method of questioning, and criteria for inclusion may be partially responsible for differences in the prevalence of radicular sequelae in various studies. Despite these differences in study design, a meta-analysis concluded that the pooled relative risk for transient neurologic symptoms after spinal anesthesia with lidocaine was 6.7-fold higher than with bupivacaine and 5.5-fold higher than with prilocaine.[148] The addition of vasoconstrictors to local anesthetic solutions may also increase risk.[149] Neurotoxicity appears to be unrelated to conduction block because tetrodotoxin, a highly potent blocker of sodium channels, can produce intense conduction blockade without histologic or behavioral signs of nerve injury.[150]

Intraoperative positioning also appears to be a risk factor. Patients undergoing surgery in the lithotomy position appear to be at increased risk for neurologic symptoms after either spinal or epidural anesthesia. It is unknown at present why this association produces increased risk; nerve compression or stretch or reduced perfusion pressure in the vasa nervorum may possibly exacerbate the toxicity from local anesthetics. The lithotomy position can produce neurologic sequelae and lower extremity compartment syndrome, particularly with prolonged surgery and use of the Trendelenburg position.[151]

Skeletal muscle changes have been observed after the intramuscular injection of local anesthetic agents such as lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine. In general, the more potent, longer-acting agents bupivacaine and etidocaine appear to cause more localized skeletal muscle damage than the less potent, shorter-acting agents lidocaine and prilocaine do. This

effect on skeletal muscle is reversible, and muscle regeneration occurs rapidly and is complete within 2 weeks after the injection of local anesthetic agents. Local anesthetic–induced myotoxicity may involve actions on mitochondria.[152]

Prolonged Infusions of Local Anesthetics and the Development of Long-Duration Local Anesthetics

Local anesthetics are increasingly being administered by continuous infusion for several days after surgery or for periods of weeks to months for the treatment of chronic malignant and nonmalignant pain (see also Chapters 58 and 87). With prolonged infusions there is the potential for delayed systemic accumulation and toxicity. Continuous bupivacaine infusions of up to 30 mg/hr in adults for as long as 2 weeks produced no overt CNS or cardiac toxicity despite total plasma bupivacaine concentrations in the range of 2 to 5 μg/mL in several patients.[153]

Several methods for producing long-duration nerve blockade are under investigation. Liposomal encapsulation can prolong nerve blockade, depending on the dose and the physical properties of the liposome (surface charge, size, lamellar structure).[154-156] Local anesthetics can be incorporated into biodegradable polymer microspheres for sustained release.[157] These preparations produce peripheral nerve blockade in animal models and human volunteers[158] ranging from 2 to 8 days, depending on the dose, site, and species. Because of the intrinsic neurotoxicity of all aminoamide and aminoester local anesthetics, there is likely to be some irreducible potential for neurotoxicity with most of these approaches to controlled release of aminoamide and aminoester local anesthetics in proximity to major nerve trunks. Thus, these formulations will have the most favorable risk-benefit ratio when used in nonprotective locations, such as intercostal nerve blockade, where prolonged numbness may be a benefit rather than a complication of the intervention. This risk is also likely to be less clinically important for infiltration analgesia.

Prolonged-duration local anesthesia also appears to be feasible with the use of site 1 sodium channel toxins in combination with either local anesthetics or adrenergics.[159] Other site 1 toxins have been used in humans in preliminary case series.[160] A combination of site 1 toxins with either local anesthetics or adrenergics results in prolongation of blockade and improvement in the therapeutic index.[159] Theoretically attractive features of site 1 toxins include their apparent lack of local tissue toxicity on nerves[150] or muscles[161] and their minimal effects on cardiac sodium channels.

Other drugs have been examined for use as local anesthetics, including tricyclic antidepressants,[162] although neurotoxicity may limit the clinical utility of this group of drugs.

It remains to be determined whether prolonged-duration local anesthetics will gain widespread use in clinical practice. If they prove to be safe and effective, they may have potential utility in intercostal blockade and wound infiltration, particularly for surgery on the thorax and abdomen, where protective sensation is comparatively less important than for limb surgery. If agents can be developed that last for weeks or longer, they may have additional applications in the management of chronic pain and cancer pain.

Biologic Mechanisms of Local Anesthetic Failure: Inflammation, Hyperalgesia, Tachyphylaxis, and Genetic Variants

Failure of local anesthesia is commonly ascribed to technical failure of delivery, insufficient volume or concentration of drug, or erroneous clinical decisions in selection of techniques. However, there are a number of clinical situations in which biologic processes contribute to failed local anesthesia, even with proper technique and drug selection. For example, in patients going to the dentist with infections such as a tooth abscess or severe pulpitis, failure rates of standard doses of local anesthetic have been reported to be as high as 70%. Local anesthetic failure at a site of inflammation appears to reflect a combination of pharmacokinetic factors and pharmacodynamic factors. Pharmacokinetic factors include (1) increased local blood flow leading to accelerated removal of drug from perineural injection compartments; (2) local tissue acidosis leading to a greater proportion of the drug in the hydrochloride form, which diffuses more poorly across biologic membranes; and (3) local tissue edema, which increases diffusion distances for drug into nerves. Pharmacodynamic factors include the effects of inflammation on both peripheral sensitization of nerves and central sensitization.[163,164] It is noteworthy that in the setting of an infected mandibular tooth, inferior alveolar nerve block (performed proximally at a site presumably remote from the infected area) also has an unexpectedly high failure rate.

Local anesthetics and regional anesthesia, in turn, can suppress components of inflammatory responses by a complex interplay of local, spinal, and systemic mechanisms.[165,166]

Apparent reductions in the effectiveness of local anesthetic infusions over time may be due to a number of causes unrelated to tolerance per se, including dislodgement of catheters and changes in the dermatomal origin or intensity of nociceptive input. In obstetric patients receiving epidural bolus injections, recurrence of pain before the next injection resulted in a reduction in the intensity and duration of blockade, whereas repeat injection before the return of pain prevented this rapidly occurring form of tolerance, or tachyphylaxis.[167] In postoperative patients, coadministration of systemic opioids prevented regression of segmental block in patients receiving thoracic epidural bupivacaine infusions.[168] Studies in rats suggest that both pharmacokinetic and pharmacodynamic mechanisms are involved. In a rat model, tachyphylaxis was linked to the development of hyperalgesia,[169] and drugs that inhibit hyperalgesia, including *N*-methyl-D-aspartate receptor antagonists and nitric oxide synthase inhibitors,[170] also prevented tachyphylaxis. Conversely, repeated sciatic injections of lidocaine resulted in reduced intraneural lidocaine content along with reduced duration of block.[171]

Occasional patients report that "local anesthetics don't work for me." Although this claim may reflect previous technical failures or a variety of other processes and patient- or procedure-specific factors, it is possible that in some cases these failures may involve genetic variation in local anesthetic responsiveness. For example, a subgroup of patients with the connective tissue disorder Ehlers-Danlos syndrome appears to have diminished responses to topical local anesthesia.[172]

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Fumito Ichinose and Warren M. Zapol

31 Nitric Oxide and Inhaled Pulmonary Vasodilators

Key Points

1. Endogenous nitric oxide (NO) is produced from oxygen and L-arginine by a group of enzymes called nitric oxide synthases with L-citrulline as a by-product.
2. Most of the effects of NO on the cardiovascular system are mediated by activation of the enzyme soluble guanylate cyclase, which catalyzes formation of the second messenger cyclic guanosine monophosphate (cGMP) from guanosine 5′-triphosphate. NO stimulates soluble guanylate cyclase to synthesize cGMP, which in turn activates cGMP-dependent protein kinase and thereby leads to vascular relaxation.
3. Because NO binds rapidly to hemoglobin with high affinity, the vasodilatory effect of inhaled NO is limited to the lung.
4. NO can be safely inhaled when delivered by facemask, nasal cannula, or an endotracheal tube.
5. According to a survey in 2000, 94% of pediatric cardiologists consider inhaled NO to be a clinically proven agent to test pulmonary vasoreactivity in the cardiac catheterization laboratory.[66]
6. Several clinical trials of inhaled NO in patients with acute lung injury demonstrated no effect on mortality or the duration of mechanical ventilation; however, the frequency of progression to severe respiratory failure from milder respiratory failure was decreased by inhaled NO in one study.[78]
7. Inhaled NO has been reported to ameliorate the postoperative pulmonary hypertension of congenital heart disease[91,92] and decrease the need for postoperative extracorporeal membrane oxygenation.[93]
8. The vasodilatory response to inhaled NO is variable in patients with valvular heart disease.[86,95] The variability in dilator response is likely to be related to the balance between pulmonary vascular remodeling and active vasoconstriction.
9. In contrast to therapy with intravenous vasodilators, which often cause systemic hypotension, inhaled NO has been shown in a small group of patients to selectively reduce peripheral vascular resistance and enhance right ventricular stroke work after cardiac transplantation.[98]
10. A trial of inhaled NO is recommended before consideration of implantation of a right ventricular assist device because this invasive procedure may be avoided if there is a salutary response to inhaled NO.[102]
11. Inhaled NO can combine with hemoglobin to form nitrosylhemoglobin, which is rapidly oxidized to methemoglobin. The enzyme methemoglobin reductase rapidly converts methemoglobin to hemoglobin in the red blood cell. Because neonates have reduced activity of this enzyme, they are at greater risk than adults for the development of significant methemoglobinemia after the inhalation of high levels of NO for a prolonged period.[142]

Pulmonary hypertension often complicates patient care intraoperatively, as well as in intensive care units (ICUs). Severe acute pulmonary hypertension may produce right ventricular (RV) failure. Pulmonary hypertension and RV failure may reduce left ventricular (LV) filling, decrease cardiac output, and lead to systemic hypotension. Decreased arterial blood pressure may compromise RV coronary perfusion at a time when RV end-diastolic pressure and RV myocardial oxygen consumption are increased because of increased RV wall tension, thereby leading to RV ischemia.[1] RV ischemia will exacerbate RV failure and cause a further reduction in cardiac output and blood pressure (Fig. 31-1). This vicious cycle may continue unless pulmonary artery pressure is reduced to permit increased RV ejection. Unfortunately, treatment of pulmonary hypertension with intravenous vasodilators may worsen the systemic hypotension. Inhalation of nitric oxide (NO) produces selective pulmonary vasodilation without reducing systemic arterial pressure in patients with acute or chronic pulmonary hypertension. Addi-

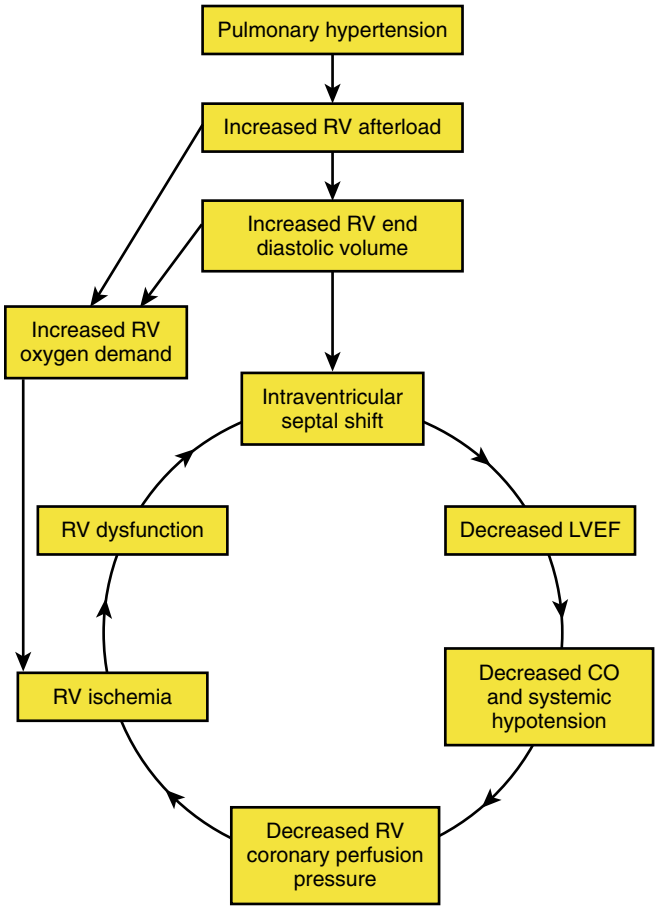

Figure 31-1 Vicious cycle of right ventricular (RV) failure triggered by pulmonary hypertension. CO, cardiac output; LVEF, left ventricular ejection fraction.

tionally, there are now a number of other experimental inhaled pulmonary vasodilators described in the literature that may provide potential alternatives to inhaled NO. In this chapter the theoretical background, current uses, and future therapeutic potential of inhaled NO and other inhaled pulmonary vasodilators are discussed.

Inhaled Nitric Oxide

Since recognition of NO as a key endothelial-derived vasodilator molecule in 1987, the field of NO research has expanded to encompass many areas of biomedical research. It is now well established that NO is an important signaling molecule throughout our body. Endogenous NO is produced from oxygen and L-arginine by a group of enzymes called nitric oxide synthases (NOSs) with L-citrulline as a by-product. Most of the effects of NO on the cardiovascular system are mediated by activation of the enzyme-soluble guanylate cyclase (sGC), which catalyzes formation of the second messenger cyclic guanosine monophosphate (cGMP) from guanosine 5′-triphosphate. Studies also indicate that NO may directly modulate other signaling systems. For example, recent evidence suggests that NO is directly involved in post-translational protein modification, including nitrosylation of proteins (Fig. 31-2).

A therapeutic potential for inhaled NO to act as a selective pulmonary vasodilator was demonstrated by Frostell and colleagues in 1991, who showed that breathing NO gas resulted in rapid and profound pulmonary vasodilation in an awake lamb model of pulmonary hypertension produced by infusion of a stable thromboxane analog (Fig. 31-3).[2] Because NO binds rapidly to hemoglobin (Hb) with high affinity, the vasodilatory effect of inhaled NO is limited to the lung. This is in sharp contrast to intravenously infused vasodilators, which often cause systemic vasodilation and lead to systemic arterial hypotension. This unique ability of inhaled NO to cause highly selective pulmonary vasodilation has prompted a large number of preclinical and clinical studies. The early pilot studies also demonstrated that inhaled NO therapy rapidly improves oxygenation without causing systemic hypotension in critically ill newborns with acute pulmonary hypertension (see Chapter 84).[3,4] Subsequently, the efforts of many research groups studying animals and patients led to approval of inhaled NO by the U.S. Food and Drug Administration in 1999 and by the European Medicine Evaluation Agency and European Commission in 2001.[5-8]

A number of studies now indicate that inhaled NO may play an important role in treating pulmonary hypertension in pediatric and adult patients with respiratory and cardiac failure, in determining the vasodilatory capacity of the pulmonary vas-

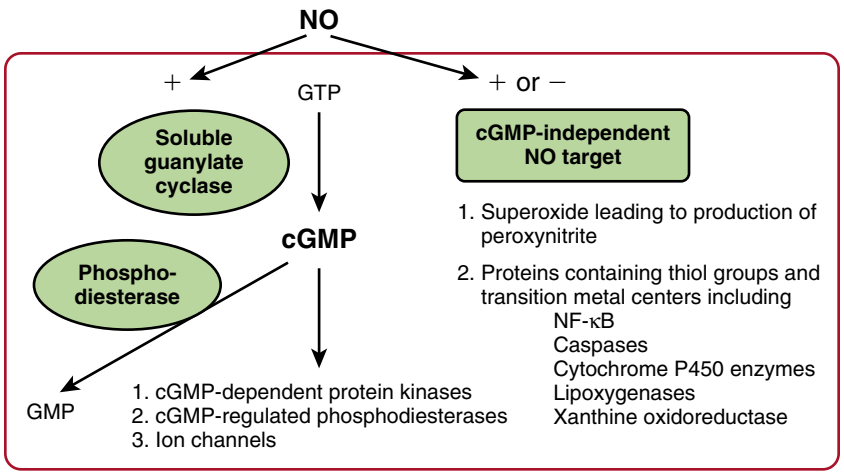

Figure 31-2 Nitric oxide (NO) signaling pathway. cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate.

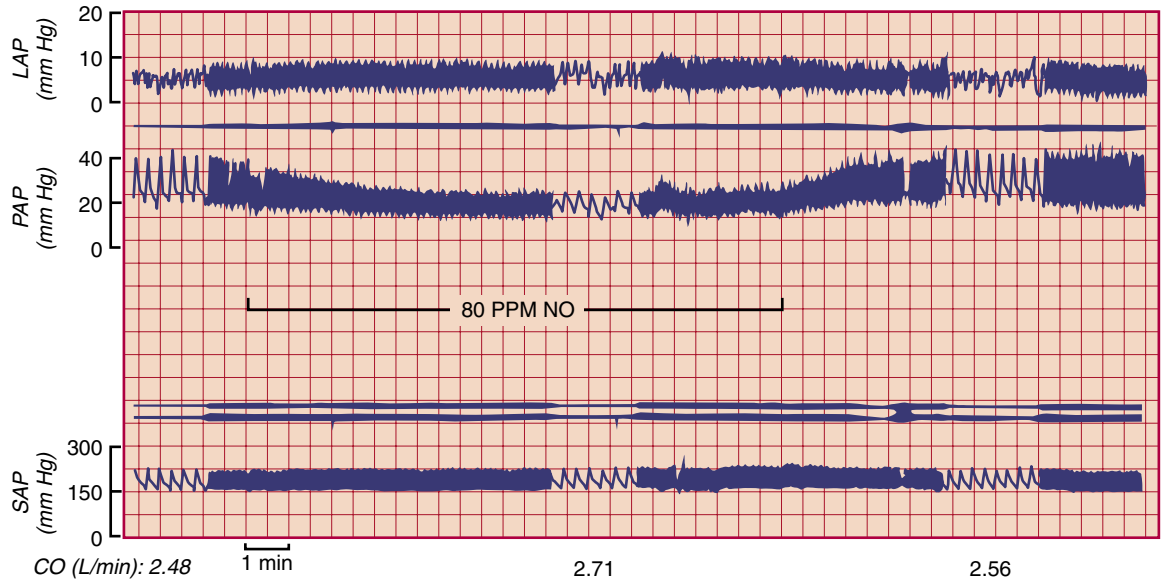

Figure 31-3 Effects of breathing nitric oxide (NO) at 80 ppm in a lamb with pulmonary hypertension induced by an infusion of U46619, a stable thromboxane analog. CO, cardiac output; LAP, left atrial pressure; PAP, pulmonary artery pressure; SAP, systemic artery pressure. Note that breathing NO decreased PAP without affecting LAP and SAP. *(From Frostell C, Fratacci MD, Wain JC, et al: Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 83:2038-2047, 1991, with permission.)*

cular bed, and perhaps in preventing the development of chronic lung disease in infants with lung injury.

Inhaled Nitric Oxide: Physical Properties, Methods of Administration, and Mechanism of Action

Chemistry of Nitric Oxide Gas

NO is a colorless and odorless gas that is only slightly soluble in water.[9] Atmospheric concentrations of NO usually range between 10 and 500 parts per billion by volume (ppb) but can exceed 1.5 parts per million (ppm) in areas of heavy traffic or lightning.[10] In the inhaled smoke of a burning cigarette, NO is produced by oxidation of nitrogen from the atmosphere and nitrogen-containing compounds in tobacco and can reach levels of 1000 ppm.[11] NO is unstable in air and undergoes spontaneous oxidation to form the more toxic nitrogen oxides (NO_2, N_2O_4, etc.). NO is therefore stored in cylinders diluted in an inert gas, usually nitrogen.

Delivery and Monitoring of Inhaled Nitric Oxide

NO can be safely inhaled when delivered by facemask, nasal cannula, or an endotracheal tube. It is important to carefully regulate the concentration of NO and its length of exposure to oxygen, which can be achieved with several commercially available systems. Although NO and NO_2 are more accurately measured by chemiluminescence devices, electrochemical detectors have proved adequate for the measurement of inhaled NO and are integrated components of several clinical delivery systems. Despite concern that ICU workers would passively inhale NO, this has not become a problem because levels of NO in ICU air remain quite low.[12]

Nitric Oxide/Cyclic Guanosine Monophosphate Signal Transduction System

After inhalation, NO diffuses rapidly across the alveolar-capillary membrane into the subjacent smooth muscle of pulmonary vessels (Fig. 31-4). NO stimulates sGC to synthesize cGMP, which in turn activates cGMP-dependent protein kinase and thereby leads to vascular relaxation. The physiologic actions of cGMP are limited by its hydrolysis to GMP and by export from the cell. A family of cyclic nucleotide phosphodiesterases (PDEs) is known to hydrolyze cyclic nucleotides. Of the 11 reported PDE isozymes, PDE5 is considered to be the most active cGMP-hydrolyzing PDE in smooth muscle (for review, see Rybalkin and associates[13]). PDE5 has high affinity for cGMP and is selectively inhibited by PDE inhibitors such as zaprinast, sildenafil, and verdenafil. In addition to its pulmonary vasodilating effects, inhaled NO has several other effects in the lung. For instance, inhaled NO has been shown to cause bronchodilation[14,15] and to possess anti-inflammatory[16] and antiproliferative[17] effects. NO can also elicit effects via cGMP-independent mechanisms, including interactions with heme-containing molecules (in addition to sGC) and with proteins containing reactive thiol groups.[18] NO interacts with the superoxide radical (O_2^-), which limits the bioavailability of NO and results in formation of the potent oxidant peroxynitrite ($ONOO^-$). In the presence of oxygenated Hb, NO is rapidly metabolized to nitrate with the formation of methemoglobin (MetHb). Within red blood cells, electron donors rapidly convert MetHb back to ferrous Hb.

Enhancement of Ventilation-Perfusion Matching by Inhalation of Nitric Oxide

The intrapulmonary distribution of blood flow and ventilation (ventilation-perfusion [$\dot{V}/\dot{Q}$] distribution) is a major determinant of the efficiency of transpulmonary oxygenation and determines the partial pressure of oxygen in arterial blood (Pao_2). In a normal, healthy lung, the majority of ventilated areas are well perfused (see also Chapter 15). The shunt from the right to the

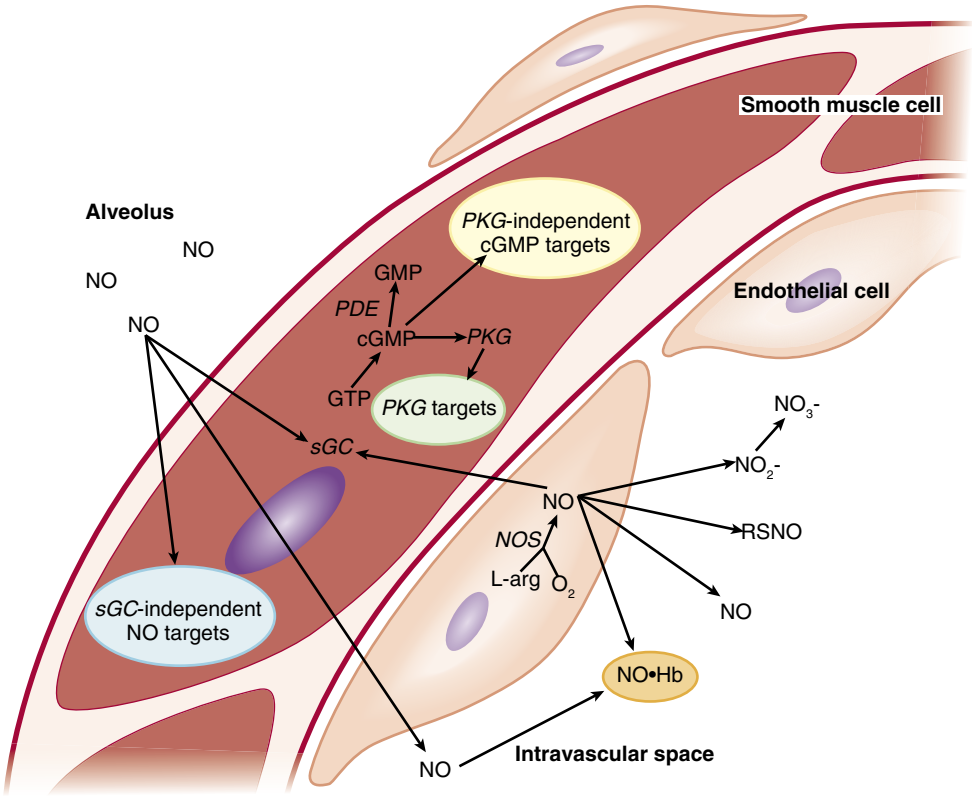

Figure 31-4 Schematic of the nitric oxide (NO) signaling pathway in the lung. NO, formed by endothelial cells or administered by inhalation, diffuses to vascular smooth muscle cells. Numerous targets of NO contribute to the wide variety of effects of this molecule on the cardiovascular system. One of the primary targets for NO is soluble guanylate cyclase (sGC). NO binds to the heme moiety of sGC and stimulates synthesis of the intracellular second messenger cyclic guanosine monophosphate (cGMP). cGMP interacts with a variety of targets, including ion channels, cGMP-regulated phosphodiesterases (PDEs), and cGMP-dependent protein kinases (PKGs). PKGs have been shown to phosphorylate various proteins in vascular smooth muscle cells. cGMP is metabolized to GMP by PDEs. On arrival in the bloodstream, the majority of NO rapidly binds to hemoglobin with high affinity, but small amounts of NO may remain to react with other molecules, including proteins. GTP, guanosine triphosphate; NOS, nitric oxide synthase; RSNO, S-nitrosothiol. *(From Ichinose F, Roberts JD, Zapol WM: Inhaled nitric oxide, a selective pulmonary vasodilator, current uses and therapeutic potential. Circulation 109:3106-3111, 2004, with permission.)*

left side of the circulation is mainly extrapulmonary (e.g., bronchial veins) and is less than 5% to 8% of cardiac output.[19] In a normal lung, local alveolar hypoxia constricts the vascular bed adjacent to hypoxic regions and redistributes blood flow toward lung regions with better ventilation and higher intra-alveolar Po_2. It has been proposed that inhaled NO amplifies this mechanism by increasing blood flow to well-ventilated lung areas, which may, in some diseases, cause increased vasomotor tone. This inhaled vasodilatory effect is in marked contrast to the effect of intravenously administered vasodilators, which produce diffuse dilation of the pulmonary vasculature, increase blood flow to areas of nonventilated lung, and thereby increase intrapulmonary shunting and reduce Pao_2. In contrast, inhaled NO should selectively improve the perfusion of ventilated regions and hence reduce intrapulmonary shunting and improve arterial oxygenation (Fig. 31-5). These beneficial effects of inhaled NO on intrapulmonary shunting and oxygenation have been demonstrated in some adult and pediatric patients with acute respiratory distress syndrome (ARDS).[20,21] Unfortunately, this effect can at times be transient.[22]

Clinical Use of Inhaled Nitric Oxide

Perinatal and Pediatric Uses of Inhaled Nitric Oxide

Nitric Oxide Is an Important Regulatory Molecule in the Perinatal Lung. Several studies indicate that NO has an important role in modulating pulmonary vascular resistance (PVR) at birth. For example, in the developing lungs of several animals, NOS and sGC expression and signaling increase late in gestation, are maximal in the postnatal period, and decrease in adults.[23-25] Moreover, because NOS inhibitors attenuate the reduction in PVR at birth,[26,27] it is likely that NO signaling plays a critical role in transition from the fetal to the newborn pulmonary circulatory system.

Many forms of newborn and infant lung disease are associated with endothelial cell injury and decreased NO/cGMP signaling. Studies in newborns suggest that premature constriction of the ductus arteriosus, septic mediators, and meconium aspiration all cause pulmonary endothelial cell injury. For example, in utero ligation of the ductus arteriosus in the fetal lamb causes flow-

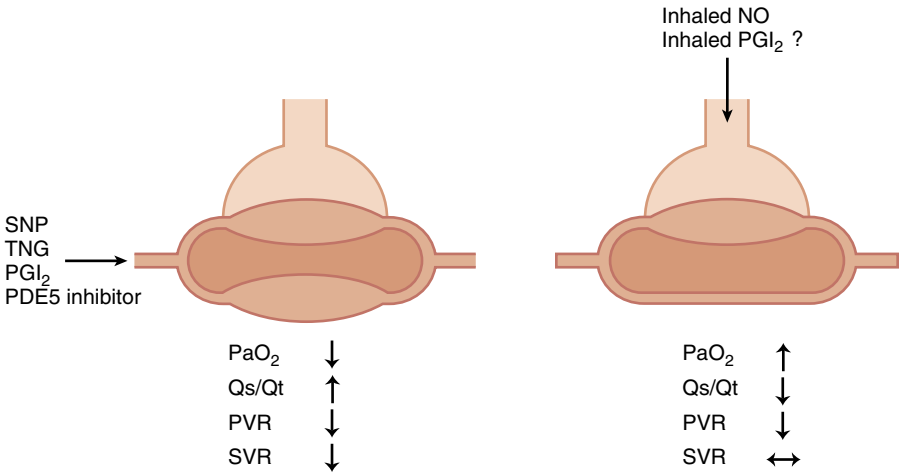

Figure 31-5 Diagram illustrating the differing pathophysiologic effects of inhaled pulmonary vasodilators and intravenous vasodilators. SNP, sodium nitroprusside; TNG, nitroglycerine; PGI_2, prostaglandin I_2; PDE5 inhibitor, phosphodiesterase 5 inhibitor; PaO_2, partial pressure of oxygen in arterial blood; Qs/Qt, right-to-left shunt fraction; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

induced endothelial cell dysfunction and decreases the expression of endothelial NOS (NOS3)[28] and vasorelaxation caused by NO.[29] Moreover, cardiac lesions, such as atrial and ventricular septal defects, atrioventricular canals, persistent ductus arteriosus, and transposition of the great vessels without a ventricular septal defect, cause endothelial cell injury, decrease NO-mediated pulmonary vasorelaxant activity, and lead to pulmonary hypertension.[30]

Accumulating evidence suggests that NO/cGMP signaling has an important role in regulating lung development. For example, in mildly hypoxemic newborn NOS3-deficient mice, alveolar development is severely inhibited in a manner that can be improved by inhalation of NO.[31,32] Furthermore, in perinatal models of pulmonary vascular disease, in which NO activity has been observed to be decreased, inhaled NO improves the development of peripheral pulmonary arteries.[33]

Experimental Studies of the Selective Pulmonary Vasodilator Effects of Inhaled Nitric Oxide in the Newborn. Several investigations in newborn animals have demonstrated that inhaled NO decreases pulmonary hypertension. For example, in fetal lambs with an intact placental circulation, inhaled NO decreased PVR.[34] Similarly, in newborn lambs with pulmonary vasoconstriction associated with hypoxemia, inhaled NO was observed to decrease PVR and increase lung cGMP levels in a manner that was not modified by acidosis.[35] Importantly, in the latter study inhaled NO did not cause systemic vasodilation, and breathing up to 80 ppm NO did not decrease either systemic vascular resistance or blood pressure.

Inhaled NO also reversed vasoconstriction in newborn animals with pulmonary vascular remodeling. In newborn lambs with pulmonary vascular disease induced by premature ligation of the ductus arteriosus and associated with muscularization of peripheral arteries in the lung periphery, inhaled NO caused dose-dependent vasodilatation and improved systemic oxygenation and survival rates.[36] Moreover, in lambs with lung hypoplasia caused by congenital diaphragmatic hernia, NO improved systemic oxygenation when inhaled after exogenous surfactant treatment or during partial liquid ventilation.[37] These latter findings suggest that lung volume recruitment is required for inspired NO to effectively reduce pulmonary vasoconstriction in models associated with lung hypoplasia.

Inhaled Nitric Oxide Can Attenuate Pulmonary Disease in Newborn Animals. In newborn rats, lung injury caused, for example, by sustained hypoxia or exposure to endothelial toxins results in pulmonary artery muscularization and hypertension similar to that observed in patients with pulmonary artery hypertension (PAH) and many forms of congenital heart disease. In these models, prolonged inhalation of NO has been reported to attenuate pulmonary vascular remodeling and RV hypertrophy in chronically hypoxic newborns.[33] Importantly, it appears that breathing NO can inhibit pulmonary vascular remodeling even in the absence of pulmonary hypertension. Roberts and colleagues reported that in newborn rats with monocrotaline-induced endothelial injury, inhaled NO decreased the abnormal proliferation of cells in the walls of pulmonary arteries and prevented abnormal pulmonary vascular remodeling even before the development of pulmonary hypertension.[17] These findings suggest that inhaled NO may play an important role in modifying the abnormal vascular development and secondary pulmonary hypertension of the injured newborn lung.

Lung injury decreases alveolar and pulmonary microvascular development in premature lambs and baboons and in newborn mice and rats.[38] Accumulating experimental evidence suggests that inhaled NO promotes the development of the injured maturing lung. For example, prolonged NO inhalation has been observed to increase alveologenesis in chronically ventilated premature baboons[39] and lambs.[40] Moreover, inhaled NO improves alveolar development in mice after hyperoxic lung injury.[41] The mechanisms responsible for the protective effects of inhaled NO in alveologenesis are unknown. Because studies suggest that the pulmonary vasculature importantly regulates alveolar development[42] and inhaled NO protects newborn lung vessels from injury,[33] it is possible that inhaled NO protects the lung via its effects on the microvasculature. This concept is supported by the observation that inhaled NO improves alveolarization in rat pups that have decreased microvascular development.[43] However, it is also possible that NO regulates the homeostasis of other cells or might modulate other signaling systems regulating or contributing to lung development.

Inhaled Nitric Oxide Increases Systemic Oxygenation in Hypoxemic Newborns with Pulmonary Hypertension. Pilot studies revealed that inhalation of NO increases systemic oxygenation in severely hypoxemic newborns with pulmonary hypertension (see Chapter 84).[3,4] The ability of inhaled NO to increase systemic oxygen levels was confirmed in several multicenter randomized controlled studies of term and near-term

babies with hypoxemia and pulmonary hypertension.[6,8,44] In one study, systemic oxygenation was observed to increase in nearly half of patients with severe persistent pulmonary hypertension of the newborn who received inhaled NO.[6] Importantly, the magnitude of the increase in oxygen levels in babies treated with inhaled NO was directly proportional to the degree of hypoxia before NO inhalation, and the increased systemic oxygenation of the NO-breathing infants was maintained in 75% of the patients. In another study, the optimal concentration of inhaled NO level was investigated[45]; although the maximum increase in systemic oxygenation was observed in babies breathing 80 ppm NO, as little as 5 to 20 ppm NO increased arterial oxygen levels above those measured in babies not breathing NO. Several studies have reported that inhaled NO decreases the need for extracorporeal membrane oxygenation (ECMO), an invasive procedure requiring systemic heparinization.[6,8,44]

Inhaled Nitric Oxide in Bronchopulmonary Dysplasia. Bronchopulmonary dysplasia (BPD) is an important chronic lung disease of prematurely born infants that results, in part, from the inhibition or disruption of normal pulmonary alveolar and microvascular development as a result of oxygen- and ventilator-induced lung injury.[46] Although an early study suggested that inhaled NO does not decrease the incidence of BPD,[47] a subsequent single-center trial involving 207 premature infants conducted by Schreiber and colleagues suggested that inhaled NO decreases the incidence of BPD and death in prematurely born infants.[48] These observations were supported by results from a later multicenter trial in which inhaled NO was noted to decrease the rate of BPD and death in premature infants with a birth weight of less than 1000 g.[49] In a more recent study of 793 newborns 34 weeks of gestational age or less, Kinsella and coauthors reported that inhaled NO decreased the incidence of BPD in the subset of 129 infants with a birth weight of at least 1000 g.[50] Furthermore, in another multicenter study of 582 premature infants with a birth weight of 1250 g or less in whom inhaled NO was commenced 7 to 21 days after birth, Ballard and coworkers reported that inhalation of NO improved survival and reduced the incidence of BPD.[51] Although these results are encouraging when considered together, additional studies need to be performed before the role of inhaled NO in preventing BPD can be defined.

Safety of Inhaled Nitric Oxide in the Newborn. Even though studies in newborns and infants suggest that prolonged inhalation of NO is safe,[52] the long-term pulmonary and extrapulmonary effects of inhaled NO are unknown. In particular, the effects of chronic NO inhalation on normal pulmonary cell proliferation and differentiation, as well as on alveolar and microvascular development, are unknown.

NO can increase cGMP levels in platelets and inhibit their function (reviewed by Schwarz and colleagues[53]). The potential of inhaled NO to alter platelet function[54] is of particular concern for immature infants because abnormal hemostatic activity might increase the incidence or evolution of intraventricular hemorrhage (IVH) and associated neurologic injury. In one study, breathing NO was associated with increased mortality and rates of IVH in infants weighing 1000 g or less.[49] Nevertheless, data from several other studies suggest that inhaled NO does not increase the incidence or severity of IVH in premature babies.[47,48,51] In fact, in one very large study of premature infants, inhaled NO was reported to decrease the frequency of IVH and its sequelae.[50]

It is uncertain whether the improvement in pulmonary disease in some premature babies who breathed NO is associated with improved neurologic development. In a European multicenter trial of nearly 100 premature babies, inhaled NO was not observed to affect the incidence of death or severe disability at 1 year corrected for postnatal age.[55] On the other hand, a more rigorous evaluation of older premature babies treated in another trial suggested that inhaled NO can improve neurologic outcomes.[56]

Uses of Inhaled Nitric Oxide in Adult Patients with Cardiopulmonary Diseases

Pulmonary Vasoreactivity Testing in the Cardiac Catheterization Laboratory. Demonstration of a positive response to vasodilating agents in patients with pulmonary hypertension correlates with an improved long-term clinical outcome and has been used to guide medical therapy (see Chapter 60).[57] Although a number of vasodilators, including intravenous prostacyclin and calcium channel blockers, have been used for diagnostic testing during cardiac catheterization, such circulating agents produce systemic vasodilation and increase intrapulmonary right-to-left shunting.[58] In contrast, recent studies indicate that inhaled NO is a safe and effective agent to determine the pulmonary circulation's capacity for vasodilation in pediatric[59] and adult patients[60,61] with pulmonary hypertension. In these patients, selective pulmonary vasodilation during NO breathing correlates with a subsequent response to oral and systemically active vasodilators.[62,63] Preoperative hemodynamic evaluation with oxygen and inhaled NO as opposed to a test with oxygen alone is suggested to more accurately identify patients with pulmonary hypertension who will be the most appropriate candidates for corrective cardiac surgery or transplantation.[64] In 1998, inhaled NO was the primary vasodilator used to test pulmonary vascular responsiveness in 32% of U.S. tertiary hospitals.[65] According to a survey in 2000, 94% of pediatric cardiologists consider inhaled NO to be a clinically proven agent to test pulmonary vasoreactivity in the cardiac catheterization laboratory.[66]

Treatment of Chronic Pulmonary Hypertension with Inhaled Nitric Oxide. Even though continuous administration of intravenous prostacyclin (epoprostenol) is associated with improved survival and exercise tolerance,[67] indwelling central venous catheters carry the risk of bacteremia. The feasibility of an ambulatory NO delivery system has been reported in a small number of patients with primary pulmonary hypertension.[68,69] The safety and efficacy of long-term domiciliary NO inhalation require investigation in larger patient populations. On the other hand, clinical trials with newer orally active vasodilators (bosentan,[70] beraprost,[71] and sildenafil[72]) in patients with primary pulmonary hypertension have reported promising results. Although these orally active medications are more convenient for ambulatory patients than intravenous or inhalation therapies are, inhaled NO may prove more effective than these agents. In addition, because these agents may cause systemic hypotension, inhaled NO may prove safer.

Treatment of Cardiogenic Shock Caused by Right Ventricular Myocardial Infarction. RV injury and dysfunction may complicate inferior myocardial infarction (MI) caused by right coronary artery occlusion. If coronary revascularization is delayed, cardiogenic shock may develop despite preserved LV function and is associated with a high frequency of mortality. In a small series of patients with cardiogenic shock

caused by right ventricular myocardial infarction (RVMI), Inglessis and colleagues reported that unloading the right ventricle by breathing 80 ppm NO acutely improved the cardiac index by approximately 25%.[73] In RVMI patients with a patent foramen ovale, treatment with inhaled NO markedly reduced right-to-left shunting and improved systemic oxygenation. Further studies are required to determine whether NO inhalation will decrease the morbidity and mortality associated with RVMI.

Acute Respiratory Distress Syndrome in Adults. In clinical studies of patients with severe ARDS, inhaled NO has been shown to produce selective pulmonary vasodilation,[20] decrease pulmonary capillary pressure[74] and pulmonary transvascular albumin flux,[75] and improve oxygenation (see Chapters 92 and 93).[20] Although these clinical studies, as well as a number of studies in animal models of acute lung injury, have demonstrated a physiologic benefit of inhaled NO therapy, subsequent clinical trials reported disappointing results. Two pilot trials were conducted in the United States. Both were randomized, unblinded, controlled, single-center studies with small sample sizes ($n = 40$ and $n = 30$) and demonstrated only transient improvements in oxygenation during the first 24 hours of treatment but no effect of inhaled NO on the mortality rate.[22,76] Subsequently, a randomized, double-blind, placebo-controlled trial of 177 patients (average entry $Pao_2/Fio_2 \approx 129$ mm Hg) treated with various concentrations of inhaled NO (1.25 to 80 ppm) versus placebo failed to find a difference in either the mortality rate or the number of days alive and off mechanical ventilation.[77] A prospective, randomized, unblinded European multicenter trial of inhaled NO in patients with acute lung injury ($n = 286$, average entry $Pao_2/Fio_2 \approx 105$ mm Hg) also demonstrated no effect on mortality or the duration of mechanical ventilation; however, the frequency of progression to severe respiratory failure from milder respiratory failure was decreased by inhaled NO.[78] Although renal failure was identified as a possible adverse effect of NO inhalation in the European trial, this finding remains unexplained and has not been confirmed in other clinical trials.

Several possible explanations why the physiologically beneficial effects of inhaled NO in ARDS were not translated into clinical outcome benefits have been offered: (1) because the majority of patients dying of ARDS suffer from multiple organ failure, the beneficial effects of a lung-selective therapy such as inhaled NO (e.g., improvement in gas exchange and reduced pulmonary artery pressure) may not alter the overall survival rate; (2) the beneficial effects of NO inhalation may be offset by toxic effects such as the formation of peroxynitrite in the presence of inflammation-produced superoxide; and (3) inhalation of NO has a narrow therapeutic range, and the effective dose may have changed over time as patients and their disease states vary.[79] Whether the subgroup of severely hypoxemic ARDS patients will respond more favorably to inhaled NO and have an improved clinical outcome has not yet been conclusively resolved.[80]

Chronic Obstructive Pulmonary Disease. Severe chronic obstructive pulmonary disease (COPD) is frequently complicated by pulmonary hypertension and hypoxemia. Systemic hypoxemia in COPD is primarily caused by ventilation-perfusion mismatching and not by intrapulmonary right-to-left shunting (as in ARDS). Hypoxic pulmonary vasoconstriction diverts venous blood flow to better ventilated lung regions, thereby improving arterial oxygenation. Although inhaled NO is a more potent pulmonary vasodilator than oxygen in patients with COPD, breathing inhaled NO admixed with air may produce vasodilation of poorly ventilated regions of the obstructed lung without receiving sufficient oxygen replenishment. Increasing blood flow with inhaled NO to these hypoventilated lung areas can reduce the transcutaneous arterial oxygen tension[81] and Pao_2.[82] However, when NO gas is breathed in combination with modest oxygen enrichment (1 L/min via facemask),[83] Pao_2 is increased to a greater extent than with oxygen therapy alone. Along these lines, a recent controlled, prospective randomized trial demonstrated that the combined use of supplemental oxygen and inhaled NO for a period of 3 months via a portable inspiratory pulsing device caused greater improvement in pulmonary hemodynamics than supplemental oxygen alone did without worsening the oxygenation of COPD patients.[84] Further studies are needed to determine the effect of long-term ambulatory breathing of pulsed NO and oxygen on the quality of life and mortality rate of patients with severe COPD.

Treatment of Perioperative Pulmonary Hypertension with Inhaled Nitric Oxide

Coronary Artery Bypass Grafting. Pulmonary hypertension often complicates the management of patients during and after cardiac surgery involving cardiopulmonary bypass (CPB) (see Chapter 60). A number of uncontrolled studies have demonstrated that 20 to 40 ppm inhaled NO effectively decreases pulmonary artery pressure after coronary artery bypass grafting (CABG), even in patients without significant preoperative pulmonary hypertension.[85-87] Although these results suggest a role for inhaled NO in treating transient pulmonary hypertension after CPB, whether inhaled NO can improve the clinically important outcomes of patients undergoing CABG is unknown. A large prospective randomized trial would be needed to define a role for inhaled NO in this patient population.

Congenital Heart Disease. Postoperative pulmonary hypertensive crises are an important cause of morbidity and mortality after congenital heart surgery[88,89] and may be precipitated by diminished NO bioavailability because of endothelial dysfunction.[30,90] PAH and subsequent heart failure are associated with certain types of congenital heart defects, particularly those characterized by increased pulmonary blood flow (e.g., ventricular septal defect and atrioventricular canal). Inhaled NO has been reported to ameliorate the postoperative pulmonary hypertension of congenital heart disease[91,92] and decrease the need for postoperative ECMO.[93] In a randomized double-blind study, Miller and colleagues examined the effects of the prophylactic use of inhaled NO in high-risk infants undergoing congenital heart surgery.[94] One hundred twenty-four patients were randomized before surgery, and inclusion in the study did not depend on the presence of pulmonary hypertension. They reported that when compared with placebo, infants who inhaled 10 ppm NO continuously after surgery until just before extubation had fewer pulmonary hypertensive crises and a shorter time to eligibility for extubation. These studies indicate that inhaled NO safely decreases postoperative pulmonary hypertension in patients after surgery for congenital heart disease. Further studies are needed to test if inhaled NO should be used in all patients after CPB for congenital heart disease surgery to decrease their perioperative morbidity and mortality.

Valvular Heart Disease. Patients with chronic mitral valve disease may have preoperative pulmonary hypertension caused by retrograde transmission of elevated left atrial pressure (see Chapter 60). After mitral valve repair or replacement,

pulmonary vascular remodeling and vasoconstriction may persist or slowly decrease. It has been reported that the vasodilatory response to inhaled NO is variable in patients with valvular heart disease.[86,95] The variability in dilator response is likely to be related to the balance between pulmonary vascular remodeling and active vasoconstriction. Treatment with inhaled NO after repair of valvular heart disease can relieve the vasoconstrictor component of pulmonary hypertension in these patients.[96] Whether inhaled NO can alter the clinical outcome of patients after valvular heart surgery is unknown.

Cardiac Transplantation. Pulmonary hypertension in cardiac transplant recipients is a major cause of right heart failure and early death. Goals in the management of acute RV failure include preservation of coronary perfusion through maintenance of systemic blood pressure and reduction of RV afterload by decreasing PVR.[97] In contrast to therapy with intravenous vasodilators, which often cause systemic hypotension, inhaled NO has been shown in a small group of patients to selectively reduce PVR and enhance RV stroke work after cardiac transplantation.[98] A positive pulmonary vasodilator response to inhalation of NO has been used as a criterion to select patients for cardiac transplantation.[99]

Insertion of Left Ventricular Assist Devices. RV dysfunction occurs in 20% to 50% of patients after insertion of a left ventricular assist device (LVAD).[100] The ability of the right ventricle to pump sufficient quantities of blood to the LVAD is critically related to the intrinsic contractility of the right ventricle and RV afterload, which is influenced by PVR. PVR is usually elevated in long-standing congestive heart failure and can be further increased in the early postoperative period by the effects of CPB. Inhaled NO has been shown to effectively decrease PVR in the setting of RV dysfunction after LVAD insertion.[101] A trial of inhaled NO is recommended before consideration of implantation of an RV assist device because this invasive procedure may be avoided if there is a salutary response to inhaled NO.[102] In a randomized, double-blind trial, Argenziano and coworkers demonstrated the hemodynamic benefits of inhaled NO (decreased pulmonary artery pressure and increased LVAD flow) in LVAD recipients with pulmonary hypertension.[103]

Treatment of Pulmonary Ischemia-Reperfusion Injury. Ischemia-reperfusion (I-R) injury is one of the major causes of early graft failure after lung transplantation. Adhesion and sequestration of activated leukocytes by activated pulmonary endothelium is believed to be an important mechanism of I-R injury. NO possesses anti-inflammatory properties, and inhaled NO has been shown to attenuate pulmonary I-R injury in preclinical studies.[104] Although two uncontrolled clinical studies suggested that inhaled NO may prevent lung I/R injury,[105,106] a small randomized, placebo-controlled study demonstrated that inhaling 20 ppm NO commencing 10 minutes after reperfusion did not affect the physiologic or clinical outcome of patients after lung transplantation.[107] Additional studies are required to define the therapeutic role of inhaled NO in patients in whom I-R injury develops after lung transplantation.

Experimental Methods to Improve the Efficacy of Inhaled Nitric Oxide

In an important fraction of patients, inhalation of NO fails to reduce PVR, improve oxygenation, or both. Moreover, because the pulmonary vasodilator effects of inhaled NO disappear after NO is discontinued, continuous therapy is required. Use of the lowest effective concentration of NO may decrease the risk for methemoglobinemia, augment matching of ventilation and perfusion, and theoretically, minimize lung toxicity. Based on an understanding of the NO/cGMP signal transduction system, several research groups have developed strategies to augment or prolong the efficacy of inhaled NO (or both). For example, inhibition of PDE5, the cGMP-specific PDE, by intravenous administration of zaprinast prolonged the pulmonary vasodilator effects of NO inhalation in awake adult lambs with U46619-induced pulmonary hypertension[108] and augmented the effects of inhaled NO in perinatal lambs with pulmonary hypertension induced by prenatal ligation of the ductus arteriosus.[109] Delivery of PDE5 inhibitors by inhalation also augmented and prolonged the efficacy of inhaled NO in adult lambs.[110,111] Steinhorn and colleagues have reported that reduction of NO scavenging by superoxide via superoxide dismutase can augment the efficacy of inhaled NO in neonatal pulmonary hypertension.[112] In studies of awake adult lambs with U46619-induced pulmonary hypertension, Evgenov and coauthors reported that agents that sensitize sGC to NO can augment and prolong the pulmonary vasodilator effects of inhaled NO.[113,114]

These observations in animal models have been extended to patients with pulmonary diseases. For example, sildenafil augmented and prolonged the pulmonary vasodilator effects of inhaled NO in patients with PAH secondary to pulmonary vascular disease[115] or congestive heart failure.[116] Importantly, sildenafil was also found to attenuate the pulmonary vascular rebound associated with discontinuing NO inhalation[117] and may facilitate weaning from NO gas in patients with cardiovascular instability.

Extrapulmonary Effects of Breathing Nitric Oxide

Because breathing NO decreased PVR without altering systemic blood pressure, it was initially proposed that the action of inhaled NO was limited to the lungs. It was hypothesized that any NO reaching the bloodstream would be rapidly scavenged by oxygenated Hb and lead to the production of nitrate and MetHb.[2] However, as early as 1993, evidence began to accumulate that inhalation of NO could inhibit platelet function.[54] Subsequently, studies describing a wide range of systemic effects of breathing NO were published, as summarized recently by McMahon and Doctor[118] and highlighted in Table 31-1. In this section, the ability of NO inhalation to decrease I-R injury is reviewed, and circumstances in which breathing NO can modulate systemic vascular tone are discussed. In addition, potential mechanisms by which inhaled NO may exert its systemic effects are outlined.

Inhaled Nitric Oxide and Platelet Function

The ability of NO-donor compounds to inhibit platelet function is well known, but the therapeutic application of their antithrombotic effects is limited by systemic hypotension. In 1993, Hogman and colleagues first reported that breathing NO (30 ppm) could prolong the bleeding time in rabbits and healthy human subjects.[54] Subsequent reports from multiple research groups presented conflicting data, with some investigators reporting that breathing NO increases the bleeding time in neonates and adults

Table 31-1 Biological Effects of Breathing Nitric Oxide with Selected Physiologic Impacts and Potential Therapeutic Applications

Biologic Effect	Impact	Therapeutic Application	References*
Pulmonary vasodilation	Reduction in pulmonary artery pressure	Pulmonary arterial hypertension	2
	Decrease in extrapulmonary right-to-left shunting and improved systemic oxygenation	Pulmonary hypertension of the newborn and congenital heart disease	3, 4, 91
	Decrease in RV afterload	RV failure after LVAD placement	103
		RVMI complicated by cardiogenic shock	73
		RV failure after cardiac surgery	85
Improved matching of lung ventilation and perfusion	Increased systemic oxygenation	Acute lung injury/pneumonia	20, 77, 78
		Chronic pulmonary disease	84
Pulmonary vascular and alveolar development	Decreased vascular SMC hyperplasia and increased alveolarization in the injured developing lung	Prevent or ameliorate pulmonary hypertension in infants with congenital heart disease and chronic lung disease in premature infants	32, 33, 39, 40
Systemic effects of breathing NO	Platelet inhibition	Decrease thrombosis after coronary thrombolysis (dogs)	54, 119
	Leukocyte inhibition	Improve mesenteric blood flow after ischemia and reperfusion (cats)	120
		Decrease infarct size in cardiac ischemia-reperfusion injury	121, 122
	Oxidization of extraerythrocytic hemoglobin	Decrease hemolysis-induced vasoconstriction and renal dysfunction (dogs)	123

*Representative references are included.
LVAD, left ventricular assist device; NO, nitric oxide; RV, right ventricular; RVMI, RV myocardial infarction; SMC, smooth muscle cell.
From Bloch KD, Ichinose F, Robert JD, Zapol WM: Inhaled NO as a therapeutic agent. Cardiovasc Res 75:339-348, 2007, with permission.

and others reporting that NO inhalation does not alter either the bleeding time or platelet function. Prolongation of the bleeding time raised the possibility of increased hemorrhagic complications in patients treated with inhaled NO, particularly neonates at increased risk for intracranial hemorrhage. On the other hand, the observation that breathing NO could decrease platelet function led other investigators to examine in animal models whether NO inhalation could be used to treat vascular diseases associated with platelet activation. For example, Semigran's group reported that in a canine model of coronary thrombosis after thrombolysis, breathing 20 and 80 ppm NO decreased platelet-mediated thrombosis,[119] an effect that was augmented by coadministration of inhibitors of type 5 PDE.[124] In addition, Lee and coworkers observed that breathing 80 ppm NO for 1 or 2 weeks decreased neointimal formation in rat carotid arteries subjected to balloon injury.[125] In both models, breathing NO did not prolong the bleeding time or cause systemic hypotension.

Inhaled Nitric Oxide and Ischemia-Reperfusion Injury of Extrapulmonary Organs

Observations that NO can form stable, biologically active adducts with protein thiol constituents led Kubes' group to examine whether inhaled NO could be used to deliver NO to peripheral tissues.[120] Studying postcapillary venules from cats subjected to intestinal I-R, these investigators observed that breathing 80 ppm NO, but not 20 ppm, prevented the reduction in blood flow, the increase in leukocyte activation (rolling, adherence, and migration), and vascular leakage. The investigators also observed that breathing NO prevented the arteriolar constriction and neutrophil activation induced by the administration of N^G-nitro-L-arginine methyl ester (L-NAME), a NOS inhibitor. Interestingly, because inhaled NO did not alter neutrophil activation or vascular leakage in endotoxin-challenged cats, the investigators proposed that inhaled NO does not affect peripheral tissues with abundant NO (produced by inducible NOS). In contrast, Neviere and coauthors reported that breathing NO (10 ppm) decreased adhesion of leukocytes to the mesenteric venular endothelium of endotoxin-challenged rats.[126] Furthermore, breathing NO prevented endotoxin-induced cardiac dysfunction and leukocyte accumulation. In a subsequent report, Kubes and associates reported that in contrast to NO-donor compounds, inhaled NO did not prevent the increase in mucosal permeability induced by intestinal I-R and suggested that the effects of breathing NO were limited to the vascular compartment.[127]

Based on these observations, Guery and colleagues evaluated the ability of breathing NO to preserve cardiac function after myocardial I-R injury.[128] Hearts from rats that had breathed air with or without 10 ppm NO for 4 hours were isolated and perfused. Coronary perfusion was stopped for 30 minutes, followed by reperfusion for 40 minutes. The investigators observed that pretreatment with inhaled NO led to improved systolic and diastolic function after ischemia and reperfusion. These findings were extended by Hataishi and colleagues, who examined the ability of breathing NO to decrease cardiac I-R injury in intact mice.[121] They observed that breathing NO for the final 20 minutes of ischemia and for 24 hours after reperfusion decreased MI size and improved systolic and diastolic function. Breathing 80 ppm NO decreased MI size similarly after 30, 60, or 120 minutes of ischemia. Breathing 40 and 80 ppm NO decreased myocardial I-R injury equally, but 20 ppm was not effective. Breathing NO decreased cardiac neutrophil accumulation, and leukocyte depletion prevented the beneficial effects of NO on MI size. Observations in rodents have recently been extended to a clinically relevant porcine model of cardiac I-R injury; Liu and colleagues reported that in pigs subjected to 50 minutes of cardiac ischemia and 4 hours of reperfusion, breathing 80 ppm NO decreased MI

size and improved myocardial perfusion.[122] The ability of inhaled NO to decrease cardiac I-R injury is further suggested by the observation that breathing NO decreased the release of cardiac enzymes in a small series of patients undergoing CPB.[129] Taken together with the observations of Fox-Robichaud and coworkers,[120] these results suggest that when inhaled, the concentrations of NO required to elicit systemic effects (in vivo) are greater than those required to directly elicit pulmonary vascular effects. Based on these considerations, a randomized clinical trial has been initiated to test whether breathing 80 ppm can decrease MI size in patients with ST-segment elevation MI.

Inhaled Nitric Oxide and Systemic Vascular Tone

Whether breathing NO can modulate systemic vascular tone remains controversial. Clinically significant systemic hypotension has not been observed in adults and babies with a wide variety of disorders treated with NO concentrations of up to 80 ppm. However, breathing 80 ppm NO has been reported to attenuate the ability of L-NAME to increase blood pressure in cats.[127] Cannon and colleagues reported that breathing 80 ppm NO increased forearm blood flow in healthy subjects treated by intrabrachial artery infusion of the NOS inhibitor L-NMMA.[130] In contrast, Hataishi and colleagues observed that breathing NO did not decrease SVR in L-NAME–treated mice or in mice congenitally deficient in NOS3.[131]

The ability of inhaled NO to decrease SVR is perhaps clearest in the case of the endothelial dysfunction associated with hemolysis. Studying dogs with free water–induced hemolysis, Minneci and associates observed that the presence of Hb in plasma induced hypertension and decreased creatinine clearance, probably via scavenging of endothelium-derived NO.[123] Breathing 80 ppm NO attenuated the hemolysis-induced hypertension and renal dysfunction by oxidizing free Hb to MetHb and preventing the scavenging of endogenous NO. The authors proposed that inhalation of NO may attenuate the hypertension, vascular disease, and prothrombotic state characteristic of diseases associated with hemolysis, such as sickle cell anemia.

How Does Inhaled Nitric Oxide Exert Its Systemic Effects?

With the exception of the case of hemolysis, the mechanisms by which NO, once inhaled, is able to induce responses in the periphery remain incompletely understood. One hypothesis is that during NO inhalation, blood cells, including white blood cells and platelets, are exposed to NO before scavenging of the gas by red blood cells and that NO-exposed blood cells are responsible for the systemic effects of inhaled NO. For example, exposure of platelets to NO in the pulmonary circulation may inhibit their activation at the site of vascular injury. However, this hypothesis does not fully account for the dilator effects of breathing NO seen in some vascular beds or the observations of Fox-Robichaud and coworkers,[120] who reported that inhaled NO did not alter the ability of feline blood leukocytes to bind to immobilized platelet monomers ex vivo.

An alternative hypothesis is that some of the inhaled NO escapes scavenging by Hb and is carried in a stable, bioavailable form to the periphery. Loscalzo's group proposed that endogenously synthesized NO reacts with low- and high-molecular-weight thiols in blood, including serum albumin.[132,133] These *S*-nitrosothiols can deliver NO to tissues distant from the site of its synthesis. Stamler and colleagues[132] observed that NO reacts with the thiol group on Cys93 of the Hb β-chain and that *S*-nitrosylation of Hb (SNO-Hb) is dependent on the oxygen tension enabling erythrocytes to load Hb in the rich oxygen environment of the lungs and release low-molecular-weight *S*-nitrosothiols in the relatively hypoxic periphery (reviewed by McMahan and Doctor[118]). NO can be oxidized in blood to nitrite, which regenerates NO in the presence of nitrite reductases, including deoxyhemoglobin (reviewed by Gladwin and colleagues[134]). Erythrocyte SNO-Hb and nitrite have both been implicated as potential mediators of the systemic vasodilation induced by tissue hypoxia. NO may also react with other plasma species that are subsequently capable of regenerating NO, including *N*-nitrosamines, iron-nitrosyls, and nitrated lipids.

Even before it was appreciated that breathing NO could selectively dilate the pulmonary vasculature, several research groups examined the metabolic fate of inhaled NO. In 1975, Oda and colleagues reported that inhalation of NO led to the formation of nitrosyl-Hb in the blood of mice, rats, and rabbits.[135] In 1987, Yoshida and Kasama reported that breathing ^{15}NO (145 ppm for 123 minutes) led to the formation of nitrosyl-Hb, nitrite, and nitrate.[136] More recently, Cannon and coworkers found that in healthy adults breathing 80 ppm NO, nitrosyl-Hb concentrations increased markedly, whereas nitrite increased modestly.[130] Arterial concentrations of both products were greater than venous levels, thus suggesting consumption in peripheral tissues. Cannon and colleagues did not detect an increase in plasma *S*-nitrosothiols or SNO-Hb. In contrast, Ng and coauthors reported that in cats, breathing 80 ppm NO increased plasma levels of *S*-nitrosoalbumin and nitrite, both of which were further increased in the setting of intestinal I-R.[137] Arterial levels of *S*-nitrosoalbumin were higher than venous levels, whereas the converse was true for nitrite levels, which suggested that *S*-nitrosoalbumin was consumed in the periphery and nitrite was generated.

The potential importance of nitrite as a mediator of inhaled NO's impact on I-R injury was highlighted in recent studies of Duranski and colleagues.[138] They observed that small increases in blood nitrite levels were sufficient to decrease I-R injury in the liver and heart. Moreover, in studies of murine I-R injury, Hataishi and coauthors[121] reported that breathing NO increased nitrite concentrations in plasma and blood to levels similar to those demonstrated to be effective by Duranski and associates.

Controversy regarding the identity of the circulating NO-derived products whose levels increase during inhalation of NO may be attributable to differences in the methods used to detect these products. Nonetheless, there appears to be a consensus that bioavailable NO derivatives contribute to the effects of breathing NO on the periphery. However, many questions remain, including the following: Do NO-derived products accumulate in tissues during the inhalation of NO? Are cGMP-dependent or cGMP-independent mechanisms responsible for the systemic effects of inhaled NO?

Safety Issues and Method of Administration

Prolonged inhalation of low levels of NO appears to be safe. The major clinical toxicity is due to the formation of NO_2 and methemoglobinemia. Nitrogen dioxide is rapidly converted to nitric acid in aqueous solution (acid rain) and is highly toxic to the respiratory tract. Increased airway reactivity has been reported

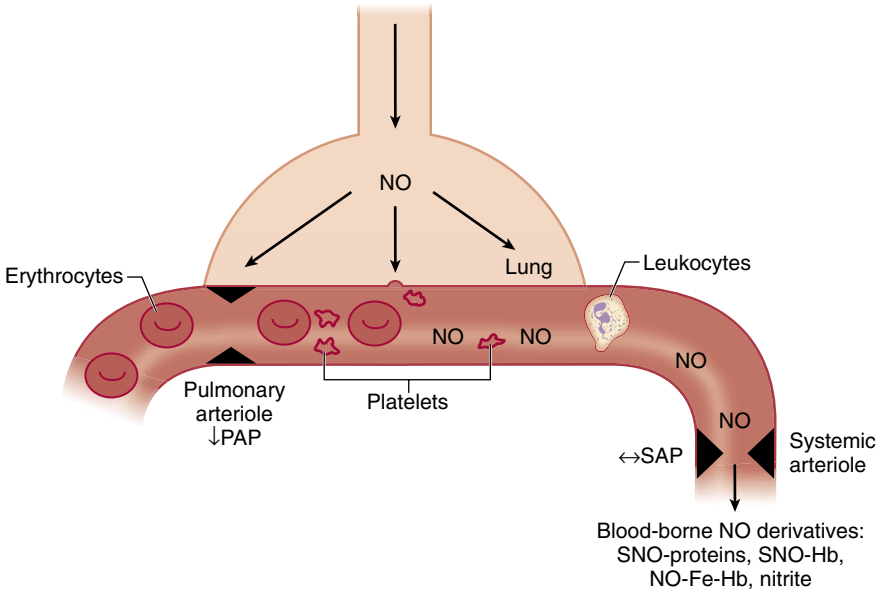

Figure 31-6 Inhaled nitric oxide (NO) is a selective pulmonary vasodilator with actions on the systemic vasculature. A schematic of an alveolar-capillary unit is presented in which the ability of inhaled NO to dilate pulmonary arterioles and reduce pulmonary artery pressure (PAP) is highlighted. Although inhaled NO does not dilate systemic arterioles or alter systemic arterial pressure (SAP) under normal conditions, inhaled NO does have systemic effects (described in text) that may be mediated by circulating cells exposed to NO in the lungs and blood-borne NO derivatives: SNO-proteins or *S*-nitroso proteins including SNO-albumin; SNO-Hb or S-nitroso-Hb (nitrosylated on Cys93 of the β-chain); NO-Fe-Hb or nitrosyl-Hb; and nitrite. *(From Bloch KD, Ichinose F, Robert JD, Zapol WM: Inhaled NO as a therapeutic agent. Cardiovasc Res 75:339-348, 2007, with permission.)*

in humans after exposure to as low as 1.5 ppm NO_2.[139] At higher inhaled NO_2 concentrations, pulmonary edema is the major toxicologic effect[140] and can result in rapid death after inhalation.[141]

Inhaled NO can combine with Hb to form nitrosyl-Hb, which is rapidly oxidized to MetHb. Rates of uptake and release of NO from ferrous (Fe^{2+}) Hb are 10^5- to 10^6-fold greater than those of oxygen. Tissue hypoxia can be produced at excessive circulating MetHb concentrations. In general, cyanosis does not appear until MetHb levels approach 15% to 20%, and clinical symptoms of hypoxia (such as fatigue and dyspnea) become significant at MetHb levels above 30% of the Hb concentration.[142] The enzyme MetHb reductase rapidly converts MetHb to Hb in red blood cells. Because neonates have reduced activity of this enzyme, they are at greater risk than adults for the development of significant methemoglobinemia after the inhalation of high levels of NO for prolonged periods.[142] Blood MetHb concentrations and inspired NO_2 concentrations were frequently monitored in clinical trials of inhaled NO in adults and neonates.[6,77,143,144] In a large number of adult (n = 120) and newborn patients (n = 351) pooled from several clinical trials, significant methemoglobinemia or NO_2 formation was uncommon in patients breathing NO at doses ranging from 1.25 to 80 ppm (see the summary table in the article by Steudel and coworkers).[19] If MetHb or NO_2 levels increased above predetermined limits, the concentration of inhaled NO was decreased. Discontinuation of NO administration because of excessive NO_2 or MetHb formation was necessary in only 3 of 471 patients (0.6%).

Inhaled NO has been demonstrated to be a selective pulmonary vasodilator in heart failure patients, although breathing NO can be accompanied by an elevation in LV filling pressure in patients with severe LV dysfunction.[58,145] Taken together with the in vitro experimental evidence of a direct negative inotropic action of NO,[146,147] these clinical observations led to concern that inhaled NO may exert clinically important negative inotropic effects in patients with impaired LV function. However, investigators learned that the elevation in LV filling pressure that occurs with breathing NO is due to the augmentation of filling into a relatively noncompliant left ventricle and is not caused by a negative inotropic effect.[148] This concept is supported by an observation in heart failure patients with mechanical LV assistance that inhaled NO increases LV filling pressure only when cardiac output is not assisted.[149] Nonetheless, it is important to be aware of the possibility that inhaled NO can produce pulmonary vasodilation and may overwhelm a failing left ventricle, thereby producing pulmonary edema.

Other Inhaled Pulmonary Vasodilators

Successful clinical use of inhaled NO as a selective pulmonary vasodilator prompted the search for other alternatives, at least in part because of the significant cost of inhaled NO therapy (e.g., $3000/day with a $12,000 monthly cap) in the United States.[150] A wide variety of intravenous vasodilators were clinically tested via the inhaled route, including prostacyclin (prostaglandin I_2 [PGI_2]),[151] milrinone,[152] nitroglycerin,[153] sodium nitroprusside,[154] PGE_1,[155] and iloprost, a stable analog of PGI_2.[156] It was expected that inhalation of intravenous vasodilators would maximize drug levels in the lung while minimizing their systemic effects (Fig. 31-6). Although encouraging results have been reported by some studies, especially with inhaled PGI_2 and iloprost, at the time of this writing, the efficacy and safety profile of these inhaled vasodilators have not been established. For instance, even though very brief exposure to inhaled PGI_2 has been reported to decrease PVR similar to inhaled NO,[157,158] PGI_2 is known to cause hypotension when large doses are inhaled.[158] The plasma half-life of PGI_2 is sufficiently long (5 minutes) to allow systemic effects, and systemic arterial levels of an active metabolite have been measured during the inhalation of even small doses of PGI_2. Furthermore, PGI_2 must be dissolved in a highly viscous and basic glycine diluent (pH = 10.5) that is associated with tracheitis,[159] interstitial pneumonia,[160] and ventilator valve malfunction.[161] Finally, although the drug cost associated with inhaled PGI_2 is claimed to be lower than that of inhaled NO, a robust cost comparison taking

into account the impact of prolonged therapy on overall cost has not been done. For example, if one therapy reduces ICU stay by 1 day or the need for an RV assist device or ECMO perfusion, the difference in drug cost would be incidental. Further studies appropriately designed to address these issues are needed to better define the role of other "less selective" inhaled pulmonary vasodilators.

Conclusion

Inhaled NO is the first vasodilator to produce truly selective pulmonary vasodilation. It is characterized by pulmonary vasoselectivity and it also raises arterial oxygenation and enhances pulmonary ventilation-perfusion matching by increasing blood flow to ventilated regions of the lung. A large number of laboratory and clinical research studies have been performed to delineate its biochemistry, physiology, side effects, and clinical efficacy in various diseases of children and adults. Nearly simultaneously, the clinical use of inhaled NO has become widespread. It is estimated that twenty thousand patients are treated with inhaled NO annually in the United States. During the past 16 years, inhaled NO has been used to treat pulmonary hypertension and hypoxemia in more than a hundred thousand pediatric and adult patients worldwide. For many it is lifesaving. The experimental use of inhaled NO continues to be a unique and fascinating approach to studying and treating diseases as diverse as acute rejection of a transplanted lung and sickle cell crisis. In evaluating this complex field, it is critical that our view not become colored by a single study of a particular disease state. As with most medical advances, it is the accumulation of a wide-ranging body of clinical research that will eventually determine the place of NO inhalation therapy in our therapeutic armamentarium for many diseases.

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32 Complementary and Alternative Therapies

Key Points

1. Despite lack of federal oversight, herbal medication use has increased dramatically in the overall population and particularly in preoperative patients.
2. Patients may not volunteer information unless they are specifically queried about herbal medication use.
3. Many commonly used herbs have side effects that affect drug metabolism, bleeding, and neuronal function.
4. Although stopping the use of herbal medication up to 2 weeks preoperatively can eliminate many of these problems, patients often arrive for surgery without a preoperative visit 2 weeks before surgery. Knowledge of specific interactions and metabolism of these herbs can provide practical guidelines to facilitate care.
5. Other complementary therapies, including acupuncture and music therapy, have become increasingly popular, although less is known about their effectiveness.

Complementary and alternative medicine (CAM) has implications for physicians in general but has particular importance for perioperative physicians because of complications associated with the use of certain therapies and their roles as anesthesia adjuvants. In 2002, 35% of Americans used CAM therapies.[1] Visits to CAM practitioners exceed those to American primary care physicians,[2] and CAM is even more widely used in Europe, where herbal medicines are more frequently prescribed than conventional drugs in many situations. Of particular relevance for anesthesiologists is that patients undergoing surgery appear to use CAM more than the general population does.[3,4]

Despite the public enthusiasm for CAM, scientific knowledge in this area is still incomplete and often confusing for practitioners and patients. One recent study confirmed poor knowledge of this subject among physicians.[5] Recommendations for clinicians are often based on small clinical trials, case reports, animal studies, predictions derived from known pharmacology, and expert opinion. Research is essential because CAM therapies are often widely adopted by the public before adequate data are available to support their safety and efficacy. In 1991, Congress established the Office of Alternative Medicine, which became the National Center for Complementary and Alternative Medicine within the National Institutes of Health in 1998. In 2006, more than twice as many CAM-related English-language research articles were published as in 1996.

Practices encompassed by CAM are heterogeneous and evolving as CAM therapies are integrated into conventional medicine (e.g., diet, exercise, behavioral medicine). CAM practices can be classified into five general categories (Box 32-1).[6] This chapter is not intended as a comprehensive review of CAM. Specific therapies relevant to anesthesia are discussed, and we focus primarily on herbal medicines. Nonherbal dietary supplements, acupuncture, and music are also examined.

Herbal Medicines

Preoperative use of herbal medicines has been associated with adverse perioperative events.[3] Surveys estimate that 22% to 32% of patients undergoing surgery use herbal medications.[7-9] As pharmacologically active agents, herbal medicines may affect the perioperative period through several mechanisms: direct effects (i.e., intrinsic pharmacologic effects), pharmacodynamic interactions (i.e., alteration of the action of conventional drugs at effector sites), and pharmacokinetic interactions (i.e., alteration of the absorption, distribution, metabolism, and elimination of conventional drugs). Because approximately 50% of herbal medicine users take multiple herbs concomitantly[8] and 25% of herbal medicine users take prescription drugs,[10] adverse effects are difficult to predict and attribute. For example, PC-SPES, a commercially available combination of eight herbs used by patients with prostate cancer, has been associated with thrombotic (i.e., deep venous thrombosis and pulmonary embolism) and hemorrhagic (i.e., anticoagulation from phytocoumarins) complications.[11]

Herbal medicines are associated with problems not usually found with conventional drugs.[12] Because herbal medicines are classified as dietary supplements, they are not subject to

Box 32-1 Five Major Categories of Complementary and Alternative Medicine

1. Alternative medical systems (e.g., homeopathic medicine, naturopathic medicine, traditional Chinese medicine, ayurveda)
2. Mind-body interventions (e.g., meditation; prayer; art, music, or dance therapy)
3. Biologically based treatments (e.g., herbal medicines, dietary supplements)
4. Manipulative and body-based methods (e.g., chiropractic manipulation, osteopathic manipulation, massage)
5. Energy therapies (e.g., acupuncture, electromagnetic fields, reiki, qi gong)

Adapted from the National Center for Complementary and Alternative Medicine. Available at http://nccam.nih.gov/health/whatiscam/ Accessed August 15, 2003.

preclinical animal studies, premarketing controlled clinical trials, or postmarketing surveillance. Under current law, the burden is shifted to the U.S. Food and Drug Administration (FDA) to prove products unsafe before they can be withdrawn from the market. Commercial herbal medicine preparations may have unpredictable pharmacologic effects resulting from inaccurate labeling, misidentified plants, adulterants, variations in natural potency, and unstandardized processing methods.

In this chapter we discuss the preoperative assessment and management of patients who use herbal medicines and examine nine herbal medicines that have the greatest impact on perioperative patient care: echinacea, ephedra, garlic, *Ginkgo biloba*, ginseng, kava, saw palmetto, St. John's wort, and valerian (Table 32-1). These nine account for 50% of the herbal medicines sold in the United States (Box 32-2).[13] Print and Internet resources for additional information on herbal medicines are provided in Table 32-2.

Preoperative Assessment and Management

Preoperative assessment should address the use of herbal medicines (see Chapter 34). However, 90% of anesthesiologists do not routinely ask about herbal medicine use.[14] Moreover, more than 70% of patients are not forthcoming about their herbal medicine use during routine preoperative assessment.[8] When a positive history of herbal medicine use is elicited, one in five patients is unable to properly identify the preparation being taken.[15] Patients should be asked to bring their herbal medicines and other dietary supplements with them at the time of the preoperative evaluation. A positive history of herbal medicine use should also prompt anesthesiologists to suspect the presence of undiagnosed disorders causing symptoms leading to self-medication. Patients who use herbal medicines may be more likely than those who do not to avoid conventional diagnosis and therapy.[16]

In general, herbal medicines should be discontinued preoperatively. When pharmacokinetic data for the active constituents in an herbal medication are available, the timeframe for preoperative discontinuation can be tailored. For other herbal medicines, 2 weeks is recommended.[17] However, in clinical practice because many patients require nonelective surgery, are not evaluated until the day of surgery, or are noncompliant with instructions to discontinue herbal medications preoperatively, they may take herbal medicines until the day of surgery. In this situation, anesthesia can usually proceed safely at the discretion of the anesthesiologist, who should be familiar with commonly used herbal medicines to avoid or recognize and treat complications that may arise. For instance, recent use of herbal medicines that inhibit platelet function (e.g., garlic, ginseng, *Ginkgo biloba*) may warrant specific strategies for procedures with substantial intraoperative blood loss (e.g., platelet transfusion) and those that alter the risk-benefit ratio of using certain anesthetic techniques (e.g., neuraxial blockade).

Preoperative discontinuation of all herbal medicines may not eliminate complications related to their use. Withdrawal of regular medications is associated with increased morbidity and mortality after surgery.[18] Alcoholics who abstain from drinking alcohol preoperatively may have poorer postoperative outcomes than those who continue drinking preoperatively.[19] The danger of abstinence after long-term use may be similar with herbal medicines such as valerian, which has the potential to produce acute withdrawal after long-term use.

Echinacea

Three species of echinacea, a member of the daisy family, are used for the prophylaxis and treatment of viral, bacterial, and fungal infections, particularly those of upper respiratory origin, although its efficacy in the latter is doubtful.[20] A recent meta-analysis

Box 32-2 Most Commonly Used Herbal Medicines in 2001

1. Echinacea*
2. *Ginkgo biloba**
3. Garlic*
4. Ginseng*
5. Saw palmetto*
6. Noni (*Morinda*)
7. St. John's wort*
8. Soy
9. Ephedra (ma huang)*
10. Milk thistle
11. Valerian*
12. Kava*
13. Grape seed extract
14. Green tea
15. Goldenseal
16. Primrose
17. Black cohosh root
18. Aloe
19. Bilberry
20. Cranberry

*Reviewed in this chapter.
Adapted from the Nutritional Business Journal's herbal and botanical U.S. consumer sales.[13]

Table 32-1 Clinically Important Effects, Perioperative Concerns, and Recommendations for Perioperative Discontinuation of Nine Commonly Used Herbal Medicines

Herbs (Common Names)	Pharmacologic Effects	Perioperative Concerns	Discontinue before Surgery
Echinacea (purple coneflower root)	Activation of cell-mediated immunity	Allergic reactions Decreases effectiveness of immunosuppressants Potential for immunosuppression with long-term use	No data
Ephedra (ma huang)	Increases heart rate and blood pressure through direct and indirect sympathomimetic effects	Risk of myocardial ischemia and stroke from tachycardia and hypertension Ventricular arrhythmias with halothane Long-term use depletes endogenous catecholamines and may cause intraoperative hemodynamic instability Life-threatening interaction with MAO inhibitors	24 hours
Garlic (ajo)	Inhibits platelet aggregation (may be irreversible) Increases fibrinolysis Equivocal antihypertensive activity	May increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	7 days
Ginkgo (duck-foot tree, maidenhair tree, silver apricot)	Inhibits platelet-activating factor	May increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	36 hours
Ginseng (American ginseng, Asian ginseng, Chinese ginseng, Korean ginseng)	Lowers blood glucose Inhibits platelet aggregation (may be irreversible) Increased PT/PTT in animals	Hypoglycemia May increase risk of bleeding May decrease anticoagulant effect of warfarin	7 days
Kava (awa, intoxicating pepper, kawa)	Sedation Anxiolysis	May increase sedative effect of anesthetics Increase in anesthetic requirements with long-term use unstudied	24 hours
Saw palmetto (dwarf palm, sabal)	Inhibits 5α-reductase Inhibits cyclooxygenase	May increase risk of bleeding	No data
St. John's wort (amber, goat weed, hardhay, hypericum, Klamath weed)	Inhibits neurotransmitter reuptake MAO inhibition unlikely	Induction of cytochrome P450 enzymes; affects cyclosporine, warfarin, steroids, and protease inhibitors; may affect benzodiazepines, calcium channel blockers, and many other drugs Decreased serum digoxin levels Delayed emergence	5 days
Valerian (all heal, garden heliotrope, vandal root)	Sedation	May increase sedative effect of anesthetics Benzodiazepine-like acute withdrawal May increase anesthetic requirements with long-term use	No data

MAO, monoamine oxidase; PT, prothrombin time; PTT, partial thromboplastin time.

showed echinacea's benefit in decreasing the incidence and duration of the common cold.[21] Its pharmacologic activity cannot be attributed to a single compound, although the lipophilic fraction, which contains alkylamides, polyacetylenes, and essential oils, appears to be more active than the hydrophilic fraction.

Echinacea had a number of immunostimulatory effects in preclinical studies.[22] Although no studies have specifically addressed interactions between echinacea and immunosuppressive drugs, expert opinion generally warns against the concomitant use of echinacea and these drugs because of the probability of diminished effectiveness.[22,23] Therefore, patients who may require perioperative immunosuppression, such as those awaiting organ transplantation, should be counseled to avoid echinacea. In contrast to its immunostimulatory effects with short-term use, long-term use of more than 8 weeks is accompanied by the potential for immunosuppression[23] and a theoretically increased risk for certain postsurgical complications such as poor wound healing and opportunistic infections.

Echinacea has also been associated with allergic reactions, including one reported case of anaphylaxis.[24] Therefore, echinacea should be used with caution in patients with asthma, atopy, or allergic rhinitis. Concern for potential hepatoxicity has also been raised, although documented cases are lacking.[25] In the absence of definitive information, patients with preexisting liver

Table 32-2 Printed and World Wide Web Sources of Herbal Medicine Information

Source	Comments
Physicians' Desk Reference for Herbal Medicines	
Commission E Monographs	
Textbook of Complementary and Alternative Medicine	
Center for Food Safety and Applied Nutrition, Food and Drug Administration: http://vm.cfsan.fda.gov/~dms/supplmnt.html	Clinicians should use this site to report adverse events associated with herbal medicines and other dietary supplements. Sections also contain safety, industry, and regulatory information
National Center for Complementary and Alternative Medicine, National Institutes of Health: http://nccam.nih.gov/	This site contains fact sheets about alternative therapies, consensus reports, and data bases
Agricultural Research Service, U.S. Department of Agriculture: www.ars-grin.gov/duke	The site contains an extensive phytochemical database with search capabilities
Quackwatch: www.quackwatch.com	Although this site addresses all aspects of health care, there is a considerable amount of information covering complementary and herbal therapies
National Council Against Health Fraud: www.ncahf.org	This site focuses on health fraud with a position paper on over-the-counter herbal remedies
HerbMed: www.herbmed.org	This site contains information on numerous herbal medications, with evidence for activity, warnings, preparations, mixtures, and mechanisms of action. There are short summaries of important research publications with Medline links
ConsumerLab: www.consumerlab.com	This site is maintained by a corporation that conducts independent laboratory investigations of dietary supplements and other health products

dysfunction should be cautious in using echinacea. Furthermore, because the pharmacokinetics of echinacea have not been studied, it may be prudent to discontinue this herb as far in advance of surgery as possible when compromise in hepatic function or blood flow is anticipated.

Ephedra

Ephedra, known as ma huang in Chinese medicine, is a shrub native to central Asia. It is used to promote weight loss, increase energy, and treat respiratory conditions such as asthma and bronchitis. Ephedra contains alkaloids, including ephedrine, pseudoephedrine, norephedrine, methylephedrine, and norpseudoephedrine.[26] Commercial preparations may be standardized to a fixed ephedrine content. Publicity about adverse reactions to this herb prompted the FDA to bar its sale in 2004, but ephedra is still widely available via the Internet.

Ephedra causes dose-dependent increases in blood pressure and heart rate. Ephedrine, the predominant active compound, is a noncatecholamine sympathomimetic that exhibits α_1, β_1, and β_2 activity directly at adrenergic receptors and indirectly by releasing endogenous norepinephrine (noradrenaline). These sympathomimetic effects have been associated with more than 1070 reported adverse events, including fatal cardiac and central nervous system complications.[27]

Although ephedrine is widely used as first-line therapy for intraoperative hypotension and bradycardia, the unsupervised preoperative use of ephedra raises certain concerns. Vasoconstriction and, in some cases, vasospasm of coronary and cerebral arteries may cause myocardial infarction and thrombotic stroke.[28] Ephedra may also affect cardiovascular function by causing hypersensitivity myocarditis characterized by cardiomyopathy with myocardial lymphocyte and eosinophil infiltration.[29] Long-term use results in tachyphylaxis from depletion of endogenous catecholamine stores and may contribute to perioperative hemodynamic instability. In these situations, direct-acting sympathomimetics may be preferred as first-line therapy for intraoperative hypotension and bradycardia. Concomitant use of ephedra and monoamine oxidase inhibitors can result in life-threatening hyperpyrexia, hypertension, and coma. Finally, continuous ephedra use has been documented as a very rare cause of radiolucent kidney stones.[30]

The pharmacokinetics of ephedrine has been studied in humans.[31,32] Ephedrine has an elimination half-life of 5.2 hours, with 70% to 80% of the compound excreted unchanged in urine. Based on the pharmacokinetic data and the known cardiovascular risks associated with ephedra, including myocardial infarction, stroke, and cardiovascular collapse from catecholamine depletion, this herb should be discontinued at least 24 hours before surgery.

Garlic

Garlic is one of the most extensively researched medicinal plants. It has the potential to modify the risk for atherosclerosis by reducing blood pressure, thrombus formation, and serum lipid and cholesterol levels.[33] These effects are primarily attributed to its sulfur-containing compounds, particularly allicin and its transformation products. Commercial garlic preparations may be standardized to a fixed alliin and allicin content.

Garlic inhibits platelet aggregation in vivo in a dose-dependent fashion. The effect of one of its constituents, ajoene, appears to be irreversible and may potentiate the effect of other platelet inhibitors such as prostacyclin, forskolin, indomethacin, and dipyridamole.[34] Although these effects have not been consistently demonstrated in volunteers, there is one case in the literature of an octogenarian in whom a spontaneous epidural hematoma developed that was attributed to continuous garlic use.[35] In addition to bleeding concerns, garlic has the potential to decrease systemic and pulmonary vascular resistance in laboratory animals, but this effect is marginal in humans.[36]

Although there are insufficient pharmacokinetic data on garlic's constituents, the potential for irreversible inhibition of platelet function may warrant discontinuation of garlic at least 7

days before surgery, especially if postoperative bleeding is a particular concern or other anticoagulants are given.

Ginkgo

Ginkgo is derived from the leaf of *Ginkgo biloba* and has been used for cognitive disorders, peripheral vascular disease, age-related macular degeneration, vertigo, tinnitus, erectile dysfunction, and altitude sickness. Studies have suggested that ginkgo may stabilize or improve cognitive performance in patients with Alzheimer's disease and multi-infarct dementia[37] but not in healthy geriatric patients.[38] The compounds believed to be responsible for its pharmacologic effects are the terpenoids and flavonoids. The two ginkgo extracts used in clinical trials are standardized to ginkgo-flavone glycosides and terpenoids.

Ginkgo appears to alter vasoregulation, act as an antioxidant, modulate neurotransmitter and receptor activity, and inhibit platelet-activating factor (PAF). Of these effects, inhibition of PAF raises the greatest concern for the perioperative period. Clinical trials in a small number of patients have not demonstrated bleeding complications, but four reported cases of spontaneous intracranial bleeding,[39-42] one case of spontaneous hyphema,[43] and one case of postoperative bleeding after laparoscopic cholecystectomy[44] have been associated with ginkgo use.

Terpenoids are highly bioavailable when administered orally. Glucuronidation appears to be part of the metabolism of flavonoids.[45] The elimination half-lives of the terpenoids after oral administration are between 3 and 10 hours.[46] Based on the pharmacokinetic data and the risk of bleeding in the surgical population, ginkgo should be discontinued at least 36 hours before surgery.

Ginseng

Among the several species used for their pharmacologic effects, Asian ginseng and American ginseng are the most commonly described. Ginseng has been labeled an "adaptogen" because it reputedly protects the body against stress and restores homeostasis.[47,48] Most pharmacologic actions are attributed to the ginsenosides, a group of compounds known as steroidal saponins. Commercially available ginseng preparations may be standardized to ginsenoside content.

Ginseng has a broad but incompletely understood pharmacologic profile because of the many heterogeneous and sometimes opposing effects of different ginsenosides.[49] The underlying mechanism appears to be similar to that classically described for steroid hormones. A potential therapeutic use for this herb lies in its ability to lower postprandial blood glucose in both type 2 diabetics and nondiabetics,[50] an effect that may create unintended hypoglycemia in patients who have fasted before surgery. There is concern about ginseng's effect on coagulation pathways. Ginsenosides inhibited platelet aggregation in vitro[51,52] and prolonged both the thrombin time and the activated partial thromboplastin time in rats.[53] One early study suggested that the antiplatelet activity of panaxynol, a constituent of ginseng, may be irreversible in humans.[54] Although ginseng may inhibit the coagulation cascade, in one case its use was associated with a significant decrease in warfarin anticoagulation.[55] A recent study in volunteers confirmed its ability to interfere with warfarin-induced anticoagulation.[56] Because warfarin is often used after orthopedic or vascular procedures, this drug interaction is more than theoretical in nature.

Studies of the pharmacokinetics of the ginsenosides Rg1, Re, and Rb2 in rabbits found elimination half-lives between 0.8 and 7.4 hours.[57] These data suggest that ginseng should be discontinued at least 24 hours before surgery. Because platelet inhibition by ginseng may be irreversible, it is probably prudent to discontinue ginseng use at least 7 days before surgery.

Kava

Kava is derived from the dried root of the pepper plant *Piper methysticum*. Kava has gained widespread popularity as an anxiolytic and sedative. The kavalactones appear to be the source of kava's pharmacologic activity.[58]

Because of its psychomotor effects, kava was one of the first herbal medications expected to interact with anesthetics. The kavalactones have dose-dependent effects on the central nervous system, including antiepileptic, neuroprotective, and local anesthetic properties. Kava may act as a sedative-hypnotic by potentiating inhibitory neurotransmission of γ-aminobutyric acid (GABA). The kavalactones increased barbiturate sleep time in laboratory animals.[59] This effect may explain the mechanism underlying the report of a coma attributed to an alprazolam-kava interaction.[60] Although kava has abuse potential, whether long-term use can result in addiction, tolerance, and acute withdrawal after abstinence has not been satisfactorily investigated. Continuous kava use may elevate γ-glutamyl transpeptidase levels, thus raising concern about hepatotoxicity.[61] With continuous use, kava produces "kava dermopathy," characterized by reversible scaly cutaneous eruptions.[62]

Peak plasma levels occur 1.8 hours after an oral dose, and the elimination half-life of kavalactones is 9 hours.[58] Unchanged kavalactones and their metabolites undergo renal and fecal elimination.[63] Pharmacokinetic data and the possibility for potentiation of the sedative effects of anesthetics suggest that kava should be discontinued at least 24 hours before surgery. Earlier discontinuation should be considered when surgical procedures are expected to compromise hepatic function or blood flow.

Saw Palmetto

Saw palmetto, which is used by more than 2 million men in the United States to treat symptoms associated with benign prostatic hypertrophy, is ineffective for this purpose.[64] The major constituents of saw palmetto are fatty acids and their glycerides (i.e., triacylglycerides and monoacylglycerides), carbohydrates, steroids, flavonoids, resin, pigment, tannin, and volatile oil. The pharmacologic activity of saw palmetto has not been attributed to a single compound.

The mechanism of action of saw palmetto is not known, but multiple mechanisms have been proposed.[65] In vitro data suggest that saw palmetto extract, like finasteride, inhibits 5α-reductase. However, results of in vivo studies have been inconsistent.[65] Other proposed mechanisms are inhibition of estrogen and androgen receptors, binding of autonomic receptors, blocking of prolactin receptor signal transduction, interference

with fibroblast proliferation, induction of apoptosis, inhibition of α_1-adrenergic receptors, and anti-inflammatory effects.

In a patient undergoing craniotomy, saw palmetto was associated with excessive intraoperative bleeding that required termination of the procedure.[66] This complication was attributed to saw palmetto's anti-inflammatory effects, specifically the inhibition of cyclooxygenase and subsequent platelet dysfunction. Because there are no pharmacokinetic data for saw palmetto, specific recommendations for preoperative discontinuation cannot be made.

St John's Wort

St John's wort is the common name for *Hypericum perforatum*. A multicenter clinical trial concluded that St John's wort is not effective in the treatment of major depression.[67] The compounds believed to be responsible for its pharmacologic activity are hypericin and hyperforin.[68] Commercial preparations are often standardized to a fixed hypericin content of 0.3%.

St John's wort exerts its effects by inhibiting reuptake of serotonin, norepinephrine, and dopamine.[69] Concomitant use of this herb with or without serotonin reuptake inhibitors may create a syndrome of central serotonin excess.[70] Although early in vitro data implicated monoamine oxidase inhibition as a possible mechanism of action, a number of later investigations have demonstrated that monoamine oxidase inhibition is insignificant in vivo.[71]

Use of St John's wort can significantly increase the metabolism of many concomitantly administered drugs, some of which are vital to the perioperative care of certain patients. There is induction of the cytochrome P450 3A4 isoform, with approximate doubling of its metabolic activity.[72] Interactions with substrates of the 3A4 isoform, including indinavir sulfate,[73] ethinylestradiol[74] and cyclosporine, have been documented. In one series of 45 organ transplant patients, St John's wort was associated with an average 49% decrease in blood cyclosporine levels.[75] Another group reported two cases of acute heart transplant rejection associated with this particular pharmacokinetic interaction.[76] Other P450 3A4 substrates commonly used in the perioperative period include alfentanil, midazolam, lidocaine, calcium channel blockers, and 5-hydroxytryptamine receptor antagonists. In addition to the 3A4 isoform, the cytochrome P450 2C9 isoform may also be induced. The anticoagulant effect of warfarin, a substrate of the 2C9 isoform, was reduced in seven reported cases.[74] Other 2C9 substrates include the nonsteroidal anti-inflammatory drugs. Furthermore, the enzyme induction caused by St John's wort may be more pronounced when other enzyme inducers, which could include other herbal medications, are taken concomitantly. St John's wort also affects digoxin pharmacokinetics.[77] A recent study in the rat showed that St John's wort could markedly alter intracellular accumulation of irinotecan and its major metabolite (SN-38) in hepatocytes and glucuronidation of SN-38.[78]

The single-dose and steady-state pharmacokinetics of hypericin, pseudohypericin, and hyperforin has been determined in humans.[79,80] After oral administration, peak plasma levels of hypericin and hyperforin are achieved in 6.0 and 3.5 hours, respectively, and their median elimination half-lives are 43.1 and 9.0 hours, respectively. Long half-life and altered metabolism of many drugs make concomitant use of St John's wort a particular risk in the perioperative setting. Pharmacokinetic data suggest that this herbal medication should be discontinued at least 5 days before surgery. Discontinuation is especially important in patients awaiting organ transplantation or in those who may require oral anticoagulation postoperatively. Moreover, these patients should be advised to avoid taking St John's wort postoperatively.

Valerian

Valerian (*Valeian officinalis*) is an herb native to temperate regions of the Americas, Europe, and Asia. It is used as a sedative, particularly in the treatment of insomnia, and virtually all herbal sleep aids contain valerian.[81] Valerian contains many compounds acting synergistically, but the sesquiterpenes are the primary source of valerian's pharmacologic effects. Commercially available preparations may be standardized to valerenic acid.

Valerian produces dose-dependent sedation and hypnosis.[82] These effects appear to be mediated through modulation of GABA neurotransmission and receptor function.[83] Valerian increased barbiturate sleep time in experimental animals.[84] In one patient, valerian withdrawal appeared to mimic an acute benzodiazepine withdrawal syndrome characterized by delirium, cardiac complications after surgery, and attenuation of the symptoms by administration of a benzodiazepine.[85] Based on these findings, valerian should be expected to potentiate the sedative effects of anesthetics and adjuvants that act at the GABA receptor, such as midazolam.

The pharmacokinetics of valerian's constituents has not been studied, although their effects are thought to be short lived. Abrupt discontinuation in patients who may be physically dependent on valerian risks benzodiazepine-like withdrawal. In these individuals, it may be prudent to taper this herbal medication with close medical supervision over the course of several weeks before surgery. If tapering is not feasible, physicians can advise patients to continue taking valerian up until the day of surgery. Based on the mechanism of action and a reported case of efficacy,[85] benzodiazepines can be used to treat withdrawal symptoms should they develop in the postoperative period.

Summary

Although the American Society of Anesthesiologists has no official standards or guidelines on the preoperative use of herbal medications, public and professional educational information released by this organization suggests that herbals be discontinued at least 2 to 3 weeks before surgery.[17,86] Our review of the literature favors a more targeted approach because in practice, evaluating patients 2 to 3 weeks before elective surgery may be impossible. Moreover, some patients require nonelective surgery or are noncompliant with instructions to discontinue herbal medications preoperatively. These factors and the extensive use of herbal medicines may mean that herbal medications are taken until the time of surgery. Pharmacokinetic data on selected active constituents indicate that some herbal medications are eliminated quickly and may be discontinued closer to the time of surgery.

Evidence-based estimates of herbal safety in the perioperative period are limited. One recent study of 601 patients who used traditional Chinese herbal medications suggested a low rate of potential serious complications.[87] Clinicians should be familiar

with commonly used herbal medications to recognize and treat any complications that may arise. Table 32-1 summarizes the clinically important effects, perioperative concerns, and recommendations for preoperative discontinuation of the nine herbal medications discussed in this chapter.

Nonherbal Dietary Supplements

Herbal medicines fall into the broader category of dietary supplements that also includes vitamins, minerals, amino acids, enzymes, and animal extracts. Data on the safety of these agents in the perioperative period are scant. High-dose vitamin use, particularly of the fat-soluble vitamins (i.e., A, D, E, and K), can be associated with acute and chronic toxicity. Glucosamine and chondroitin sulfate, which are used for joint disorders by many patients undergoing orthopedic procedures, have not been associated with perioperative complications, although chondroitin sulfate, which belongs to the same group of glycosaminoglycan molecules as heparin, may have minor anticoagulant effects.[88] Whether long-term chondroitin sulfate use can cause thrombocytopenia is unknown. Creatine, a dietary supplement used by athletes to enhance performance, has been associated with renal dysfunction in at least one case.[89] There are preliminary data that exogenous melatonin, a hormone produced by the pineal gland, may be useful in preventing and treating postoperative delirium.[90]

Acupuncture

Mechanism and General Practice

There has been interest in using acupuncture as an aid in diminishing preoperative anxiolysis to reduce intraoperative anesthetic requirements, in supporting cardiovascular function, in controlling postoperative pain, and in reducing postoperative ileus, nausea, and vomiting.[91]

Acupuncture is the stimulation of anatomic locations on the skin by a variety of techniques that can be classified as invasive (e.g., needles, injections) or noninvasive (e.g., transcutaneous electrical stimulation, pressure, laser). Needles inserted into the skin can be stimulated by manual manipulation, moxibustion (i.e., burning a substance to produce heat), pressure, laser, and electricity. There are Chinese, Japanese, Korean, French, and other acupuncture systems for identifying acupuncture points, but little research has compared these different systems. As a result, there are no standard or optimal acupuncture points. Practitioners consider acupuncture an art as much as a science.

The traditional theory of acupuncture is that it corrects disruptions in the flow of energy (i.e., qi) and restores the balance of dual forces (i.e., ying-yang) in the body. Data suggest that there is a scientific basis for acupuncture. Acupuncture stimulates high-threshold, small-diameter nerves leading to the activation of spinal cord, brainstem (i.e., periaqueductal gray area), and hypothalamic (i.e., arcuate) neurons, which trigger endogenous opioid mechanisms.[92] The effect of acupuncture analgesia can be reversed by naloxone.[93] Other mechanisms such as modulation of immune function,[94] inhibition of the inflammatory response,[95] regulation of neuropeptide gene expression,[96] and alterations in hormonal levels[97] have been proposed. The development of neuroimaging tools, such as positron emission tomography (PET)[98] and functional magnetic resonance imaging (fMRI),[99,100] make noninvasive studies of acupuncture's effects on human brain activity possible. Studies using PET have demonstrated that the thalamic asymmetry present in patients suffering from chronic pain was reduced after the patients underwent acupuncture treatment. Other studies, using fMRI, have pointed to relationships between particular acupoints and activation of the visual cortex.[101]

Many of the clinical acupuncture studies that have been published are of poor quality and suffer from insufficient sample size, high dropout rates, inadequate follow-up, and poorly defined illnesses, enrollment criteria, and outcome measures.[92] Acupuncture studies suffer from inherent methodologic problems, including difficulties in blinding patients and acupuncturists, using placebo or sham acupuncture, and choosing between different acupuncture techniques. One of the most promising indications for acupuncture is to prevent postoperative nausea and vomiting (PONV).

Acupuncture for Postoperative Nausea and Vomiting

PONV remains a significant problem that results in patient dissatisfaction, delayed discharge, unanticipated hospital admission, and the use of resources (see Chapter 86). Pharmacologic agents, the mainstay of management, have limited effectiveness, are associated with adverse effects, and can be costly. There is considerable interest in acupuncture for its potential to prevent PONV with minimal adverse effects and expense.

The evidence available suggests that when compared with placebo (e.g., sham acupuncture, no treatment), acupuncture prevents PONV.[91] Acupuncture appears to prevent PONV to approximately the same extent as pharmacologic agents do, including metoclopramide, droperidol, prochlorperazine, and ondansetron. A meta-analysis of studies published before 1998 showed that acupuncture and related techniques prevented PONV in adults, not children, with a calculated absolute reduction in risk of 20% to 25% (i.e., for every four or five patients treated, one case of PONV is avoided).[102] Several subsequent randomized, controlled trials suggested that acupuncture may also prevent PONV in the pediatric population[103-106]; another meta-analysis found that acupuncture was not useful for PONV prophylaxis in children after tonsillectomy.[107] P6 acupressure did not reduce PONV in women who underwent cesarean delivery with spinal anesthesia.[108]

Most PONV acupuncture studies use the P6 (i.e., Nei-Nuan or pericardium) acupuncture point, which is located between the palmaris longus and flexor carpi radialis muscle tendons, 4 cm proximal to the distal wrist crease and 1 cm below the skin (Fig. 32-1). Korean hand acupuncture may be equally effective.[109] Studies often differ on the acupuncture method: duration and timing of stimulation, unilateral versus bilateral stimulation, and type of stimulation (i.e., needles with or without additional stimulation, acupressure, transcutaneous electrical stimulation, cutaneous laser stimulation, injection of a 50% dextrose solution, or capsicum plaster). Data to compare the effectiveness, safety, and costs of different methods of stimulation are inadequate. It is

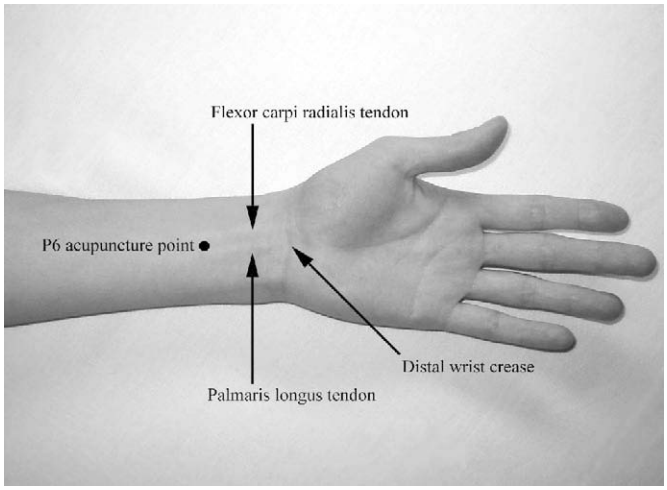

Figure 32-1 The P6 acupuncture point is located between the palmaris longus and flexor carpi radialis muscle tendons, 4 cm proximal to the distal wrist crease and 1 cm below the skin.

typically recommended that stimulation of the acupuncture point be initiated before induction of anesthesia.[110] However, some evidence suggests that postoperative stimulation may be just as or more effective.[111] In children, stimulation immediately before emergence and in the recovery room has been effective. Some anesthesiologists anecdotally report tapping a small needle cap or other piece of smooth plastic over the P6 point as an effective means of acupressure stimulation.

Music Therapy

Music may decrease preoperative anxiety, reduce intraoperative sedative and analgesic requirements, and increase patient satisfaction. Patient-selected music reduced patient-controlled sedative requirements during spinal anesthesia and analgesic requirements during lithotripsy.[112] Music in the preoperative area reduced anxiety without affecting physiologic measures of stress.[113] Music may be part of a low–sensory stimulation strategy to reduce anxiety and increase cooperation in children undergoing induction of anesthesia.[114] Music increased patient satisfaction and reduced systolic blood pressure during cataract surgery performed under a retrobulbar block.[115]

Conclusion

One of the fastest changing aspects of health care is the growing public and scientific interest in CAM. When taken preoperatively, some herbal medicines may adversely affect patient care. Surgery and anesthesia can usually proceed safely if potential complications are predicted and can be avoided. Preliminary data suggest that acupuncture and music may be useful adjuncts in the perioperative period. Although medical schools are beginning to incorporate CAM into their curricula, it is important for anesthesiologists already in practice to stay informed about these alternative therapies.

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Lee A. Fleisher

33 Risk of Anesthesia

Key Points

1. Perioperative risk is multifactorial and depends on the interaction of anesthesia-, surgery-, and patient-specific factors.
2. Anesthesia-related (and surgery-related) risk includes morbidity and mortality within 30 days, although shorter periods may be relevant, depending on the extent of surgery.
3. Anesthesia and the actions of anesthesiologists may completely or partially cause perioperative morbidity and mortality, but the actions of the anesthesiologist may also decrease or modify risk related to patient disease.
4. In the literature on anesthesia-related risk, rates of morbidity and mortality depend on the wide variety of definitions found.
5. Studies of anesthesia-related risk have found that postanesthesia respiratory depression is the major cause of death and coma totally attributable to anesthesia; this finding prompted the development of postanesthesia care units.
6. Research into anesthesia-related cardiac arrest has found it to be attributable to medication administration, airway management, and technical problems of central venous access.
7. Multivariate modeling using logistic regression equations can be used to determine factors associated with increased risk in the cohort and in individuals and has been used to develop risk indices such as the Cardiac Risk Index.
8. Surveys of maternal mortality suggest that the absolute rate of complications by anesthesia type has not decreased but that the increased use of regional anesthesia has led to improvements in outcome.
9. Medication-related and cardiovascular causes of cardiac arrest were the most common causes in the Pediatric Perioperative Cardiac Arrest Registry.
10. With increases in outpatient surgery, increased surveillance is required to ensure that appropriate procedures are performed in appropriate locations.

Much attention has been focused on the risks associated with anesthesia—surgery-related risks to the patient and occupational risks to the anesthesiologist. From the patient's perspective, it is important to provide an accurate assessment of the probability of complications and to study perioperative morbidity and mortality as a means of quality assurance to improve outcome. Numerous studies have attempted to define the probability of morbidity and mortality, with widely variable results. Risk indices have been developed to identify patients who have a higher probability of complications developing, and it has become evident that individual genetic makeup can affect outcome. In all these areas, as well as in clinical discussions with patients, the key issue is what risk are we attempting to define.

To determine the risk associated with anesthesia, multiple factors have to be entered into the equation. A myopic perspective could include only the morbidity and mortality that occur intraoperatively. From a quality assurance perspective, any death within 48 hours after the use of an anesthetic is evaluated for potential relevancy. Other investigators have evaluated 30-day morbidity and mortality as part of their estimation of anesthesia- and surgery-related risks. However, an important question is the period after anesthesia and surgery at which baseline risk returns to normal, although it is increasingly being recognized that events that take place during the perioperative period may have implications for quite a long time. From the perspective of a shorter timeframe, patients undergoing ambulatory surgery have been shown to have the lowest risk of death the day of surgery as opposed to 1 month later.[1] At the opposite end of the spectrum, asymptomatic release of cardiac enzyme in the perioperative period can have implications for months to years.[2,3] It is therefore important to define the time perspective when evaluating such studies (Table 33-1).

It is also important to differentiate the potential risk that is solely attributable to the administration of anesthesia from the risks that anesthesia may modify. Anesthesia has been touted as the one area of medicine that has achieved very low rates of

Table 33-1 Time Perspective of Anesthetic Morbidity and Mortality Studies

Study	Study Year	Time Perspective
Beecher and Todd	1954	All deaths on the surgical services
Dornette and Orth	1956	Deaths in the operating room or after failure to regain consciousness
Clifton and Hotten	1963	Any death under, attributable to, or without return of consciousness after anesthesia
Harrison	1978	Death within 24 hours
Marx, et al.	1973	Death within 5 days
Hovi-Viander	1980	Death within 3 days
Lunn and Mushin	1982	Death within 6 days
Tiret and Hatton	1986	Complications within 24 hours
Mangano, et al.	1996	Death within 2 years
Monk, et al.	2005	Death within 1 year

Adapted from Derrington MC, Smith G: A review of studies of anaesthetic risk, morbidity and mortality. Br J Anaesth 59:827, 1987.

medical error and complications when the rate of death directly attributable to anesthesia is considered. However, from a quality assurance perspective, a patient with coronary artery disease who experiences a perioperative myocardial infarction would have the primary cause of morbidity assigned to the disease, but tight heart rate control might have prevented the adverse outcome. In this situation, the perioperative infarction might be considered attributable to patient disease rather than the anesthesia, alternatively, it can be considered an event that is partially preventable by anesthesia care. Anesthesiologists must view perioperative organ protection as part of their goals to provide the highest quality of care and reduce perioperative risk. Another example is the use of regional anesthesia to reduce graft thrombosis in patients undergoing infrainguinal arterial reconstruction.[4,5] The importance of anesthesia care on perioperative risk may also be a reflection of the local risk associated with the surgery. For example, benefit from regional anesthesia was found in only two studies; the third study had a much lower rate of graft thrombosis that was not influenced by the type of anesthesia, suggesting that the benefit may be manifested only if the rate of complications is sufficiently large. Assessment of risk therefore depends on the rate of complications.

Traditionally, anesthesiologists and investigators have focused on issues of death and major morbidity such as myocardial infarction, pneumonia, and renal failure. It is becoming increasingly important to include outcomes that affect economic issues, quality of life, and satisfaction for the patient (Table 33-2). For example, a delay in or prevention of discharge home by nausea and vomiting is important from the perspective of economics and quality of life. Readmission to the hospital after outpatient surgery is an important component of outcome studies. Overall satisfaction with care is increasingly being included as an outcome. Further research is required to assess the influence of anesthesia care for nonmorbid outcomes and the importance of these outcomes from a patient-oriented perspective.

Many studies have also looked at what some investigators describe as surrogate end points. For example, nausea and vomiting that do not require treatment or do not delay discharge do not have the same impact as episodes that do affect these outcomes. Myocardial ischemia on the electrocardiogram is another example of a surrogate outcome that may not lead directly to overt morbidity. In determining the risk attributable to anesthesia, it is important to define the outcome of greatest significance.

Finally, many investigators as well as insurers, such as the Centers for Medicare and Medicaid Services, are now evaluating process measures. Examples of process measures include antibiotic timing (did the patient receive antibiotic within 1 hour before surgical incision). These measures are not the outcomes of interest, but there is sufficient evidence that improvement in compliance with these measures should decrease morbidity (e.g., surgical site infections) to warrant measurement and potentially payment for the action. Importantly, compliance with these measures are now publicly reported on websites such as www.hospitalcompare.hhs.gov.

Framework of Perioperative Risk

Perioperative risk is multifactorial and depends on the interaction of anesthesia-, patient-, and surgery-specific factors (Fig. 33-1). With respect to anesthesia, the effects of the agents and the skills of the practitioner are important. Similarly, the surgeon's skills and the surgical procedure itself affect perioperative risk. From the patient's perspective, the question remains whether coexisting disease raises the probability of complications to a level such that the benefit of the surgery is outweighed by the risk. Anesthesiologists frequently have focused on perioperative risk, but the patient is most concerned with management of the disease process. As the specialty focuses on its role in the 21st century, it is important to acknowledge the patient's perspective and desire to undergo procedures that prolong life or improve quality of life. Increasing the ability of the anesthesiologist to affect the decision-making process and overall risk is the future challenge.

Given these various goals, perspectives, and influences, this chapter attempts to define the current state of knowledge in this area. With the increasing interest in evidence-based medicine, it

Table 33-2 Examples of Common Outcome Measures

Outcome	Example
Mortality	
Morbidity	
Major	Myocardial infarction
	Pneumonia
	Pulmonary embolism
	Renal failure/insufficiency
	Postoperative cognitive dysfunction
Minor	Nausea
	Vomiting
	Readmission
Patient satisfaction	
Quality of life	

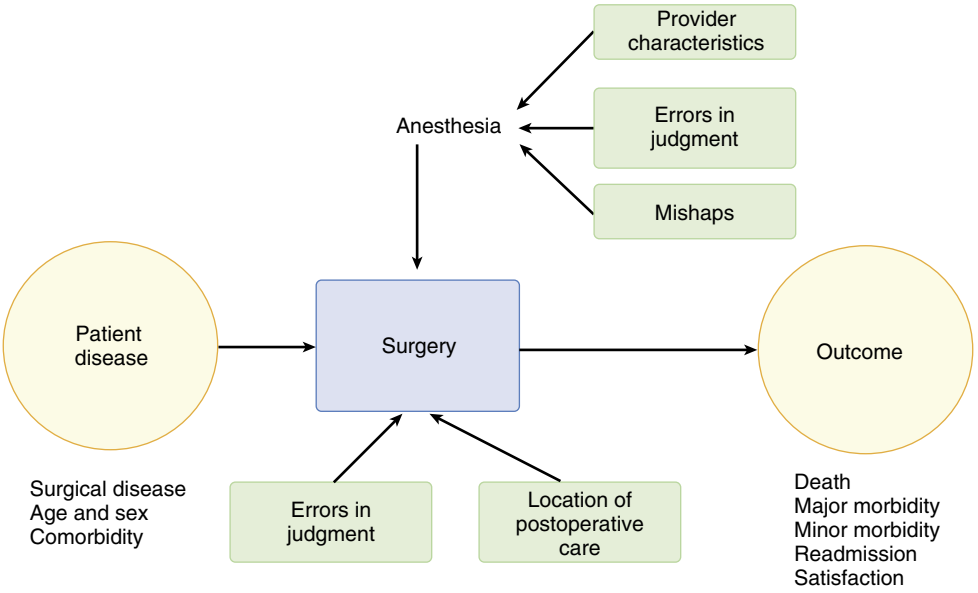

Figure 33-1 Representation of the influences of various components on poor perioperative outcomes. Surgical, anesthetic, and patient characteristics all contribute to outcome. Anesthesia-related contributions can include issues of judgment and mishaps, as well as characteristics of the provider. The surgical procedure itself affects outcome, as does the location of intraoperative and postoperative care.

is important to define what is known and not known. Because it would be unethical to compare operations performed with the use of an "ideal anesthetic" with those using a less ideal or no anesthetic, virtually all studies looking at the factors that contribute to perioperative mortality involve evaluations of large cohorts of patients. However, since the 1990s there have been several well-designed, randomized clinical trials to evaluate different anesthesia regimens, which has advanced the field. This chapter also reviews the literature, with an emphasis on the strength of the evidence for the conclusions.

Issues Related to Study Design

Types of Studies

To interpret the literature, it is important to understand the strengths and limitations of the various study designs. Prospective cohort studies involve the identification of a group of subjects who are monitored over time for the occurrence of an outcome of interest. The goal is to identify patients in whom the outcome develops. For studies of perioperative mortality, individual cases can be reviewed to determine the cause of mortality. Alternatively, data on all patients in the cohort can be obtained, and factors associated with the development of morbidity or mortality can be discerned. An example of a prospective cohort study to identify factors associated with perioperative cardiac morbidity and mortality is that of Goldman and colleagues,[6] which led to development of the Cardiac Risk Index.

Another example of a prospective cohort study is one in which patients with a known disease are studied for the development of predefined outcomes. Such studies provide the natural history of the disease. For example, studies of patients who have sustained a myocardial infarction could be important in determining optimal timing between occurrence of the infarct and surgery.

Although prospective cohort studies have important value in identifying risk factors for the outcome of interest, there are significant limitations. Selection of the cohort of interest can significantly affect the results obtained. The larger the cohort, the more the results can be generalized. A second bias is that many patients may be lost to follow-up. In perioperative studies, this may not be an important issue for short-term outcomes. The importance of a risk factor depends on the completeness of the data. For example, if the presence of severe angina were not included in the database, it could not be considered a risk factor, and other factors may appear to be more important.[6]

A specific example of a prospective cohort study is the randomized clinical trial. Randomized clinical trials represent the standard for evidence of causation. They have defined inclusion and exclusion criteria, treatment protocols, and outcomes of interest. They are usually single- or double-blinded (to patient and physician) studies and are designed to test the effect of a new drug or intervention. They are rarely used as a means of identifying risk, but they may be used to determine whether a risk factor is truly linked by a causal relationship or is simply an association. For example, hypothermia in the perioperative period has been associated with an increased incidence of perioperative ischemia, a surrogate marker for morbidity.[7] In a randomized clinical trial, the use of forced-air warming to maintain normothermia was associated with a significantly lower incidence of perioperative morbid cardiac events.[8] Randomized clinical trials directed at interventions that reduce the frequency of a given risk factor in the population are frequently performed after the results of a prospective cohort study to confirm the findings of an association between poor outcome and that factor.

Randomized clinical trials derive their strength from an evidence-based perspective because of their high degree of internal validity; the randomization scheme and the use of placebo (or accepted alternative treatments) provide strong evidence that the

results are related to the intervention. Importantly, these trials have a lower degree of external validity because the intervention may not behave in the same manner when it is diffused in a more heterogeneous population in which treatment is not defined. Additionally, low-risk complications in specific subsets of patients may not be detected in smaller randomized trials. For example, the cardiovascular complications of cyclooxygenase-2 inhibitors were not initially detected in the randomized trials.

Retrospective studies involve identification of patients who have sustained an outcome and definition of risk factors associated with the outcome. An example of a retrospective design is a case-control study. Case-control studies identify patients with the outcome of interest. Frequently, these patients are included as part of a prospective cohort study. The prevalence of a risk factor in patients with the outcome (i.e., cases) is compared with the prevalence of the risk factor in matched controls to maximize the efficiency and power of the results. The ratio of cases to controls can be varied to yield greater power with an increasing number of controls.

Case-control studies are subject to several biases. The exact definitions of cases and controls can influence the analysis. Frequently, patients are matched for age and gender, but other factors may play an important role. It is critical that the exposure precede the outcome, and a dose-response gradient further confirms the relationship.

Problems Inherent in Studying Anesthesia-Related Risk

Several issues related to studying anesthesia-related risk can affect the findings. For example, multiple definitions of perioperative mortality exist. In particular, the timeframe in which a death can be attributed to the surgery and delivery of anesthesia varies. Because in-hospital stays have shortened, many events related to surgery may occur after discharge. For this reason, the National Surgical Quality Improvement Project (NSQIP) requires 30-day follow-up on all patients to develop robust risk-adjusted models of morbidity and mortality. The issue of the time horizon is particularly important with ambulatory or short-stay surgery, for which recovery from anesthesia occurs at home. As we continue to monitor our patients for safety, it will be important to extend follow-up care beyond the traditional hospital setting, and many recent studies have included such an approach.

A major problem in any study of risk is the actual rate of complications in the population of interest. There are multiple sources of data for studying perioperative risk. Although some of the original studies used data from only one or a small group of institutions, such approaches may not be practical in the current era. As demonstrated throughout this chapter, most individuals believe that risk related to anesthesia has decreased over time, although this premise has been questioned.[9] For example, the rate of anesthesia-related mortality described in the Confidential Enquiry into Perioperative Deaths (CEPOD) of 1987 was 1 in 185,000 patients as opposed to the 1 in 2680 cases reported by Beecher and Todd about 30 years earlier.[10,11] In view of the current rate, any study would have to be enormous to detect anesthesia-related mortality. Such a study would require information from a large number of sites or data covering multiple years from a single institution. Because of concern in the United States regarding confidentiality and legal liability, a multicenter study of risk in unselected patients would be difficult to undertake. Such problems may not be inherent in other countries.

Another issue is the effect of the act of studying outcome. As in any study of risk, the actual rate of complications decreases as a result of increased observation. This is frequently observed as a lower than expected rate of complications in the placebo arm of a randomized, controlled trial.

An alternative approach is to identify bad outcomes and study them for patterns of error. For example, Cheney and colleagues[12] developed the American Society of Anesthesiologists (ASA) Closed Claims Study (ACCS). By obtaining the records of major events that led to legal litigation, they were able to identify factors that contributed to bad outcomes. With this methodology, selected morbidities that lead to litigation can be identified. The limitation of this methodology is that the actual rates of complications are not known; only the number of closed legal claims is identified. Cases that do not result in litigation are not included in the database.

Several attempts have been made to establish large epidemiologic databases. One example of such an approach has been the work of Mangano and the Multicenter Study of Perioperative Ischemia group with regard to cardiac surgery. This group used their database to evaluate issues such as the rate and importance of atrial fibrillation after cardiac surgery and the use of aspirin.[13,14] Other approaches include the development of cardiac surgery databases by the Society of Thoracic Surgeons, the U.S. Veterans Administration NSQIP, and the New England Collaborative Project.[15-18] These databases are used to define risk factors for poor outcome, to compare local with national complication rates, and as educational tools. Such databases currently include little or no information regarding anesthesia practice, although many anesthesia specialty societies are in discussion to develop independent databases or join with surgical groups to develop more robust databases. Even though these databases may provide extremely important information to improve care, the ability to generalize results to centers that do not have sufficient infrastructure to participate in such projects (e.g., smaller hospitals) is unknown.

This final issue—the institutional site of the surgery—may have other implications related to the pattern of care at a particular hospital. Although studies frequently categorize risk as related to anesthesia, surgery, or patient disease, postoperative care may have a profound impact on risk. For example, risk for pulmonary embolism may be related to nursing care and the frequency of patient ambulation after surgery.[19] The presence of an intensivist who makes daily rounds and higher nurse staffing ratios may also affect outcome.[20] Variations in the total care provided by a hospital, including anesthesiologists and surgeons, may significantly affect outcomes.

One advance in determining local complication rates is the development of hospital information systems. The use of computer databases in the assessment of risk began with Marx and colleagues[21] in the 1970s. These information systems are now nearly a requirement for survival of the hospital. The ability to query these systems will make large-scale studies of institutional risk much less burdensome in the future. Anesthesia information systems are increasingly becoming common. Reich and coworkers[22] used one such system to identify intraoperative hemodynamic abnormalities, including pulmonary hypertension, hypotension during cardiopulmonary bypass, and pulmonary

diastolic hypertension after cardiopulmonary bypass, as independent predictors of mortality, stroke, and perioperative myocardial infarction beyond the effects of other preoperative risk factors.

When extremely large sample sizes are needed, administrative databases may be among the most cost-effective approaches to this issue. Examples of administrative databases include Medicare claims files, private insurance company claims, and hospital electronic records. These databases include a small number of data points for an extremely large number of subjects. For example, the Medicare database includes financial data, disease codes (International Classification of Diseases, 9th revision [ICD-9]), and procedure codes (Current Procedural Terminology [CPT]) for each patient. It also includes information regarding the location of care and provider type. The Medicare claims file is being extensively used to provide benchmarks for rates of mortality and major complications after coronary bypass surgery.[23] Hospitals can compare their rates with those of neighboring and competing hospitals and may use these data as markers for quality of hospital care.[24,25] Silber and associates[26] took an alternative approach to the use of Medicare databases and evaluated perioperative factors that influence failure to rescue. Failure to rescue is the concept whereby the actual rate of complications associated with death is studied rather than the overall death and complication rate.[26] The underlying assumption is that higher quality of care results in a lower rate of fatal outcomes, even among patients who sustain complications. Importantly, the use of administrative databases to study outcomes should be considered as hypothesis generating rather than simply answering specific questions in the same manner as randomized controlled trials.

Mortality Related to Anesthesia

The first report of the delivery of anesthesia (ether) for an operative procedure took place in 1846. Only 2 years later, a death attributable to anesthesia was reported.[27] In that report, Hannah Greener died on induction with chloroform. Since that time there have been numerous investigations into the cause of anesthesia-related deaths. The first formal investigation of anesthesia-related deaths was published by John Snow in 1858.[28] Snow analyzed 50 deaths that occurred during chloroform anesthesia. At that time, mortality occurred principally in healthy patients undergoing minor procedures, suggesting that anesthesia was the principal cause of the mortality. Subsequent studies reported deaths of patients with significant comorbid conditions who were undergoing major surgical procedures; in these cases the cause of mortality was frequently multifactorial.

Surgery Without Anesthesia

Surgical procedures were carried out before the introduction of anesthetics. The key to success was the speed of the procedure, with successful amputations lasting only 30 seconds. Strong assistants and restraints were frequently required. Alternatively, decreased cerebral perfusion by means of bilateral carotid compression was used to decrease sensation during the procedure. Surgical procedures were associated with a significant risk of death and, at a minimum, were associated with severe pain. The development of anesthesia has been heralded as one of the great advances of modern medicine because it allowed surgery to advance.

Early Studies of Anesthesia-Related Mortality

One of the earliest systematic approaches to anesthesia-related risk occurred in 1935, when Ruth[29] helped establish the first anesthesia study commission to analyze perioperative deaths (Table 33-3). The commissioners relied on voluntary submission of cases and determined the cause of death by majority vote. Both

Table 33-3 Estimates of the Incidence of Mortality Related to Anesthesia before 1980

Study	Year	Number of Anesthetics	Primary Cause	Primary and Associated Cause
Beecher and Todd	1954	599,548	1:2680	1:1560
Dornette and Orth	1956	63,105	1:2427	1:1343
Schapira, et al.	1960	22,177	1:1232	1:821
Phillips, et al.	1960	—	1:7692	1:2500
Dripps, et al.	1961	33,224	1:852	1:415
Clifton and Hotton	1963	205,640	1:6048	1:3955
Memery	1965	114,866	1:3145	1:1082
Gebbie	1966	129,336	—	1:6158
Minuck	1967	121,786	1:6766	1:3291
Marx, et al.	1973	34,145	—	1:1265
Bodlander	1975	211,130	1:14,075	1:1703
Harrison	1978	240,483	—	1:4537
Hovi-Viander	1980	338,934	1:5059	1:1412

From Ross AF, Tinker JH: Anesthesia risk. *In* Miller RD (ed): Anesthesia, 3rd ed. New York, Churchill Livingstone, 1990.

these methodologies were deemed inadequate in subsequent years.

From a pragmatic standpoint, determining the cause of anesthesia-related mortality is important if information from the analysis can be used to improve subsequent care. This concept was best voiced by Sir Robert MacIntosh in 1948.[30] He stated that many anesthesia-related deaths were preventable and that improved education was the best means to avoid unnecessary mortality. He went so far as to suggest that all development of new drugs be halted for 5 years to direct more attention to training young anesthetists. He attempted to focus attention on postoperative care by suggesting that more deaths occurred after patients were returned to the ward than intraoperatively. His final comments were related to the need to establish a formal inquiry mechanism for determining the cause of any death because such an analysis could lead to improved practice. In many ways, the CEPOD was the culmination of such a philosophy.

A major advance in the analysis of anesthesia-related risk was the 1954 report by Beecher and Todd[10] of anesthesia-related deaths at 10 institutions. Their study included 599,548 anesthesia procedures. The overall chance of mortality from any cause was 1 per 75 cases. Anesthesia was the primary cause of mortality in 1 in 2680 procedures, and it was a primary or contributory cause of mortality in 1 in 1560 procedures. Surgical error in diagnosis, judgment, or technique was the primary cause of death in 1 in 420 cases, and patient disease was the primary cause in 1 in 95 cases.

Dornette and Orth[31] reported on deaths occurring in the operating room at their institution during a 12-year period from 1943 through 1954. The rate of mortality totally attributable to anesthesia was 1 in 2427 cases, and the rate of mortality totally or partially attributable to anesthesia was 1 in 1343 cases.

Dripps and colleagues[32] at the University of Pennsylvania surveyed their experience during the 10-year period from 1947 through 1957. They identified 1285 operative deaths (i.e., death within 30 days) in approximately 120,000 anesthesia procedures, for a gross mortality rate of 1.1%. This definition includes late deaths, in contrast to many studies that focused on the intraoperative period or the first 48 postoperative hours. After review of hospital records, the investigators determined whether anesthesia was definitely or possibly contributory to each death. Among patients who underwent spinal anesthesia, mortality definitely related to anesthesia occurred in 1 in 1560 procedures, and mortality definitely or possibly related to anesthesia occurred in 1 in 780 procedures. Among those who underwent general anesthesia, mortality was definitely related to anesthesia in 1 in 536 cases and definitely or possibly related in 1 in 259 cases. Mortality was correlated with physical status with use of the ASA physical status classification scoring system. The higher mortality figures than in other reports may be related to the higher physical acuity at this hospital. Importantly, deaths attributable to anesthesia did not occur in any of the 16,000 patients with ASA class 1 physical status.

Dripps and colleagues compared their data with those of Beecher and Todd. The principal intraoperative complications were hypotension and hypoxia. Virtually all patients who underwent spinal anesthesia had intraoperative complications, but postoperative complications were rare in this group. The investigators believed that anesthesia-related mortality had improved since the start of the study, mainly because of improvements in cardiac resuscitation, more rational transfusion therapy, standard use of recovery rooms, and efficient use of mechanical ventilators.

There were a number of reports from individual hospitals or a small group of hospitals during the subsequent 2 decades.[33] The Baltimore Anesthesia Study Committee[34] reviewed 1024 deaths occurring on the day of or the day after a surgical procedure to determine the potential contribution of anesthesia. This short period of observation (48 hours) contrasts with the 30-day period used by Dripps and coworkers. For each case reviewed, the committee determined whether anesthesia was the principal cause or one of several contributing factors. In 196 cases (19.2%), the committee voted that anesthesia management contributed to the death of the patient. Anesthesia was the principal cause of death in approximately one third of the cases (64 of 196), with one half of them being related to improper management of the anesthetic. The researchers estimated that operative mortality occurred in 4 per 10,000 operations by using these data and applying rates of surgery from the National Health Survey. In more than 50% of all cases studied, death occurred in the patient's room, which led the investigators to emphasize the need for routine use of postanesthesia care areas. In an attempt to educate practitioners and prevent duplication of preventable causes of death, each of the perioperative deaths was discussed.

Schapira and coauthors[35] reported on mortality occurring within 24 hours after surgery between the years 1952 and 1956 at Montefiore Hospital in New York. They ascribed 27 deaths to anesthesia, including 18 in which anesthesia was a primary cause and 9 in which it was contributory. The overall prevalence of death partially or totally attributable to anesthesia was 1 in 1232 procedures.

Clifton and Hotton[36] reported 162 deaths associated with anesthesia in 205,640 operations performed at the Royal Prince Alfred Hospital in Sydney, Australia, between 1952 and 1962. They calculated that the incidence of mortality totally attributable to anesthesia was 1 in 3955, that attributable to surgery was 1 in 2311, and that attributable to patient disease was 1 in 1996 procedures. One cause of postoperative mortality was respiratory insufficiency. The researchers argued that many of these complications would have been prevented by the use of a recovery unit. The potential safety advantages of a postanesthesia care unit (PACU) constituted a general theme in reports from the 1960s.

Dinnick[37] reported 600 deaths associated with anesthesia as part of a series of investigations sponsored by the Association of Anaesthetists in London. This represents the second report from this group since a committee was established to collect clinical data in 1949. The first report included a review of 1000 fatalities and concluded that "in the majority of the reports there were departures from accepted practice." The initial report, published in 1956, found that regurgitation or vomiting was the main factor leading to death, whereas the second report, published in 1964, found that low blood volume was more important. Underventilation was the second most common finding and it accounted for 25% of deaths.

Bodlander[38] provided a follow-up report of anesthesia-related mortality at the Royal Prince Alfred Hospital for the years 1963 to 1972. The incidence of mortality totally attributed to anesthesia decreased to 1 in 1702 cases, whereas anesthesia contributed to mortality in 1 in 502 cases as compared with 1 in 1208 for the years 1952 to 1962. The reduction in anesthesia-related deaths was attributed to an increase in the number of qualified staff and the degree of supervision.

Marx and colleagues[21] evaluated the incidence of death within 7 days after surgery in 34,145 consecutive patients at the Bronx Municipal Hospital Center between 1965 and 1969. A total of 645 patients died, and a death report form based on that developed by a committee of the New York Academy of Medicine was constructed. The deaths were then analyzed in relation to perioperative data available from a computer system. The patient's preexisting disease was considered to be the primary cause of death in 83% of cases, surgery in 10%, and anesthesia in only 4% (1 of 1265 cases). Although mortality rose progressively with age, physical status correlated best with the incidence of mortality.

Marx and colleagues also determined the relationship between type of anesthesia and mortality. Regional anesthesia was associated with the lowest incidence of death, local anesthesia with the highest; the incidence for general anesthesia was intermediate. Although this relationship was significantly different between groups, the difference appeared to be related to patient risk factors, a finding supported by a study by Cohen and coworkers.[39]

Farrow and associates[40,41] studied hospital mortality after 108,878 anesthesia procedures in Cardiff, Wales, between 1972 and 1977. The crude mortality rate was 2.2 per 100 patients. Mortality was greatest in patients older than 65 years. The mortality rate also increased with the severity of disease and the need for emergency operations.

Harrison[42] evaluated mortality associated with 240,483 anesthesia procedures performed between 1967 and 1976 at Groote Schuur Hospital in Cape Town, South Africa. Data were collected prospectively, beginning in 1956. Anesthesia was the cause of death or a major contributory factor in 0.22 cases per 1000 procedures, as opposed to 0.33 per 1000 operations in the previous 10 years. Anesthesia contributed to 2.2% of all the deaths associated with surgery. The most common causes of anesthesia-related mortality, in order of frequency, were hypovolemia, respiratory inadequacy after neuromuscular blockade, complications of tracheal intubation, and inadequate postoperative care. Although the improvement in anesthesia-related mortality could not be directly attributed to specific improvements in care, four specific changes did occur: continuing improvement in routine monitoring, an increase in the ratio of consultants to registrars (British system residents), a decrease in the case load per anesthesiologist, and the introduction of recovery rooms and intensive care units (ICUs).

Studies before 1980 demonstrated steady improvements in anesthesia-related mortality. Studies performed throughout the world focused on identifying causative factors for perioperative mortality. Several general themes emerged. Anesthesia represents a small but significant cause of perioperative mortality, perioperative respiratory complications represent a major complication, and elucidation of the causes of perioperative mortality and education about these causes should lead to improved outcomes.

Anesthesia-Related Mortality Studies after 1980

Whereas studies conducted before 1980 typically focused on one institution or a small group of institutions, studies since then have frequently been performed on a national basis. Improvements in anesthesia-related and overall mortality have made analysis of a single institution inadequate because of the small sample size. For example, Holland[43] reported deaths occurring within 24 hours after an anesthesia procedure in New South Wales, Australia. A committee of six anesthesiologists, three surgeons, an obstetrician, a general practitioner, and a medical administrator was established in 1960 and reviewed all such cases except those that occurred during a 3-year period between mid-1980 and mid-1983. Four categories were established to define the relationship of anesthesia to operative morbidity and mortality (Table 33-4). Between 1960 and 1985, information was available on 92% to 96% of all cases. The incidence of anesthesia-attributable deaths decreased from 1 in 5500 procedures performed in 1960 to 1 in 10,250 in 1970 and then to 1 in 26,000 in 1984. Based on these estimates, the investigators asserted that it was at least five times safer to undergo anesthesia in 1984 than in 1960, particularly for healthy individuals. A subsequent follow-up report stated that factors under the control of the anesthesiologist caused or contributed to perioperative mortality at a rate of 1 in 20,000 operations.[44] The latter study demonstrated a preponderance of male over female patients (1.7 : 1). The reason for this finding is unclear, although it confirms other reports. Importantly, 64% of the deaths were deemed inevitable, suggesting that only one third were preventable.

Table 33-4 Edwards Classification of the Relationship of Anesthesia to Operative Morbidity and Mortality

Category	Definition
I	When it is reasonably certain that the event or death was caused by the anesthetic agent or technique of administration or in other ways coming directly within the anesthetist's province
II	Similar to type I cases, but ones in which there is some element of doubt about whether the agent or technique was entirely responsible for the result
III	Cases in which the patient's adverse event or death was caused by the anesthetic and the surgical technique
IV	Events entirely referable to surgical technique

From Holland R: Anaesthetic mortality in New South Wales. Br J Anaesth 59:834, 1987.

The New South Wales study of anesthesia-related mortality evaluated the contribution of the anesthetist to perioperative mortality. Four groups of providers were identified: specialists, nonspecialists, certified registered nurse anesthetists (CRNAs), and residents. The absolute number of anesthesia-related deaths decreased in all groups but was most pronounced for nonspecialists. During the period 1960 through 1969, the resident medical officer frequently provided anesthesia. During this same period it was found that residents contributed significantly to the mortality observed in "good-risk" patients, which led to phasing out of the resident medical officer as a member of the anesthesia workforce.

Under the direction of the French Ministry of Health, Tiret and colleagues[45] carried out a prospective survey of complications associated with anesthesia in France between 1978 and 1982 from a representative sample of 198,103 anesthesia procedures chosen at random from hospitals throughout the country. The sample included a survey of 460 public and private hospitals. The investigators evaluated the occurrence of death or coma within 24

Table 33-5 Incidence of Complications Partially or Totally Related to Anesthesia

Complications	Partially Related	Totally Related	Total*
All complications	1:1887	1:1215	1:739
Death	1:3810	1:13,207	1:1957
Death and coma	1:3415	1:7924	1:2387

*Total number of anesthetics: 198,103.
From Tiret L, Desmonts JM, Hatton F, Vourc'h G: Complications associated with anaesthesia—A prospective survey in France. Can Anaesth Soc J 33:336-344, 1986.

hours after surgery. The opinion of the participating anesthesiologists and the National Committee of Assessors was determined, and the latter was accepted if there was disagreement. In the group studied, 268 patients had major complications, 67 patients died, and 16 patients suffered persistent coma. Death was totally related to anesthesia in 1 in 13,207 procedures and partially related in 1 in 3810 (Table 33-5). Sixty-two percent of the coma cases were deemed totally attributable to anesthesia, with the remainder being partially attributable to anesthesia. The French survey confirmed previous findings that major complications occur more frequently in older patients, those undergoing emergency operations, and those with more extensive comorbid conditions as measured by the ASA physical status classification.

One of the most important findings of the survey was that postanesthesia respiratory depression was the leading cause of death and coma that were totally attributable to anesthesia. Almost all the patients who had respiratory depression leading to a major complication had received narcotics and muscle relaxants that had not been reversed. They also reported a high incidence of anaphylactoid shock, which the investigators contended was caused primarily by the use of Althesin and succinylcholine. There was no category of drug overdose, which might have been a more appropriate label for some of these cases.

The study by Tiret and colleagues had the advantage of collecting data prospectively, thereby allowing more accurate estimation of overall mortality than many of the other studies completed. A major limitation of the study was that only deaths occurring within 24 hours after surgery were included, thus ignoring late deaths that were the direct result of intraoperative complications.

Tikkanen and Hovi-Viander[46] studied deaths associated with anesthesia and surgery in Finland and compared the results in 1986 with those collected in 1975. Mortality related to anesthesia decreased during the 9-year period; the incidence of anesthesia-related mortality was 0.15 per 10,000 procedures in 1986.

Lunn and coworkers[47-50] published two reports on anesthesia-related surgical mortality in the United Kingdom. When a death occurred in a hospital within 6 days after surgery, a questionnaire was sent to the patient's anesthetist and surgeon. For 59.3% of the 4034 reported deaths, both the surgeon and the anesthetist returned the forms. The replies were reviewed anonymously by two assessors, and differences of opinion were determined by arbitration. After review, further details were obtained if the reply indicated that anesthesia was at least partly responsible for the death. The second report was based on an analysis of 197 reports of death within 6 days after anesthesia during 1981. In this report, 43% of the deaths were found by the assessors to have nothing to do with anesthesia, 41% were partly attributable to anesthesia, and 16% were totally attributable to anesthesia. Of the 32 cases for which death was totally attributable to anesthesia, most were caused by faulty anesthesia technique or postoperative respiratory failure.

The pioneering work of Lunn and others led to the development of CEPOD, which assessed almost 1 million cases of anesthesia during a 1-year period in 1987 in three large regions of the United Kingdom. Unique to this study was the establishment of "crown privilege" by the government to allow total confidentiality:

> *The Secretary of State is satisfied that the disclosure of documents about individual cases prepared for the Enquiry into Perioperative Deaths would be against the public interest and would undermine the whole basis of a confidential study. The data or information sent to the Confidential Enquiry into Perioperative Deaths is therefore protected from subpoena …*

Deaths occurring within 30 days after surgery were included in the study. There were 4034 deaths in an estimated 485,850 operations, for a crude mortality rate of 0.7% to 0.8%. Surgery contributed totally or partially in 30% of all cases. Progression of the present disease contributed to death in 67.5% of the cases, and progression of an intercurrent disease was relevant in 44.3%. Anesthesia was considered the sole cause of death in only three individuals, for a rate of 1 in 185,000 cases, and anesthesia was contributory in 410 deaths, for a rate of 7 in 10,000 cases (Table 33-6).

There are several potential causes for the improvement in mortality between the CEPOD study and previous studies, including cases from the same group. One explanation is that improvement in care led to improvement in outcome. Many of the deaths that would previously have been classified as "anesthesia totally contributory" were later classified as "anesthesia partially contributory."

An important aspect of the CEPOD study was that it established anesthesia- and surgery-related factors that contributed to mortality. The five most common causes of death are shown in Table 33-7. Of the 410 perioperative deaths, there were 9 cases of aspiration or vomiting and 18 cases of cardiac arrest. A large proportion of elderly women had fractures of the femoral neck. The death rate was inversely related to the seniority of the operating surgeon and to preoperative preparation. The operating surgeon was a consultant in only 19% of the orthopedic cases as compared with 47% overall.

The CEPOD study also provided important information regarding anesthesia practice. Patients were seen preoperatively

Table 33-6 Death Totally Attributable to Each Component of Risk in the Confidential Enquiry into Perioperative Deaths

Component	Mortality Rate Contribution
Patient	1:870
Operation	1:2860
Anesthetic	1:185,056

Adapted from Buck N, Devlin HB, Lunn JL: Report of a Confidential Enquiry into Perioperative Deaths, Nuffield Provincial Hospitals Trust. London, The King's Fund Publishing House, 1987.

Table 33-7 Most Common Clinical Causes of Death in the Confidential Enquiry into Perioperative Deaths

Cause of Death	Percentage of Total
Bronchopneumonia	13.5
Congestive heart failure	10.8
Myocardial infarction	8.4
Pulmonary embolism	7.8
Respiratory failure	6.5

Adapted from Buck N, Devlin HB, Lunn JL: Report of a Confidential Enquiry into Perioperative Deaths, Nuffield Provincial Hospitals Trust. London, The King's Fund Publishing House, 1987.

in more than 80% of the cases but postoperatively in less than 50%. Although the electrocardiogram was monitored in 97% of cases, core temperature was assessed in only 7%. Muscle relaxants were used in more than 50% of the cases, but a nerve stimulator was used in only 14%.

The assessors concluded that avoidable factors were present in about 20% of the perioperative deaths. Contributing factors for anesthesiologists and surgeons tended to be failure to act appropriately with existing knowledge (rather than lack of knowledge), equipment malfunction, and fatigue. However, the researchers suggested that inadequate supervision was a problem and that no operation on a patient with an ASA physical status of class 4 or 5 should be performed without direct consultation with the appropriate anesthesia or surgical authority (Table 33-8).

Several large national studies have been published since the CEPOD. Pedersen and colleagues[51] performed a series of studies in the late 1980s in Denmark to look at factors attributable to anesthesia that led to serious morbidity or mortality. They performed a prospective study of 7306 anesthesia procedures. In a method similar to that used in earlier studies, three anesthetists reviewed the records of complications and determined whether the cause was attributable to anesthesia (no distinction was made between totally and partially contributing factors). Complications attributable to anesthesia occurred in 43 patients (1 in 170), and 3 patients (1 in 2500) died. Complications in the 43 patients, in order of incidence, included cardiovascular collapse in 16 (37%), severe postoperative headache after regional anesthesia in 9 (21%), and awareness under anesthesia in 8 (19%). The researchers determined that 37% of the anesthesia-related morbidity was preventable. The three deaths occurred in severely ill patients (ASA class 3 or greater physical status), and two of these deaths were judged to be preventable.

Cohen and coworkers[39] developed a methodology for studying the outcome of anesthesia in four teaching hospitals in Canada. They developed a new anesthesia record to serve as a data collection instrument. Research nurses reviewed all inpatient records within 72 hours after surgery, conducted interviews of the patients with a standardized instrument, and conducted a telephone survey of most of the outpatients. Assessment of the contribution of anesthesia to each complication was determined by using the classification of the New South Wales Committee on Anaesthesia Mortality (see Table 33-4). In a total of 6914 anesthesia procedures in adults, no deaths were directly attributable to anesthesia.

Lagasse[9] reviewed perioperative deaths (i.e., deaths occurring within 2 days after surgery) at a suburban university hospital network between 1992 and 1994 and an urban university hospital network between 1995 and 1999. There were a total of 347 deaths in 184,472 cases. Anesthesia-related mortality (i.e., death to which error by an anesthesia practitioner contributed) occurred in 1 in every 12,641 procedures in the suburban setting and in 1 in 13,322 procedures in the urban setting. Mortality increased with increasing ASA physical status (Fig. 33-2). In reviewing data over the previous decade, the investigators estimated that anesthesia-related mortality had remained stable at approximately 1 death per 13,000 procedures, with wide variation making it impossible to detect trends in anesthesia safety.

The Thai Anesthesia Incidents Study (THAI Study) consists of a prospectively defined cohort of patients who underwent anesthesia from February 1, 2003, to January 31, 2004 (N = 163,403).[52] The incidence of 24-hour perioperative death, death directly related to anesthesia, and death partially related to anesthesia per 10,000 anesthetics was 28.2 (95% confidence interval [CI], 25.7 to 30.8), 1.7 (95% CI, 1.1 to 2.3), and 4.0 (95% CI, 3.1 to 5.0), respectively. Of 462 deaths, 28 cases (6.1%) were directly related to anesthesia, 66 (14.3%) were partially related to anesthesia, 61 (3.3%) were related to surgery, 399 (86.4%) were

Table 33-8 Grade of Physician According to Time of Surgery in the Confidential Enquiry into Perioperative Deaths

	Anesthetist		Surgeon	
Grade	Day*	Night†	Day*	Night†
Consultant	50	25	45	34
Others	50	75	55	66

*Day represents Monday through Friday, 9 AM to 7 PM.
†Night represents Monday through Friday, 7 PM to 9 AM, and Saturday and Sunday.
Adapted from Buck N, Devlin HB, Lunn JL: Report of a Confidential Enquiry into Perioperative Deaths, Nuffield Provincial Hospitals Trust. London, The King's Fund Publishing House, 1987.

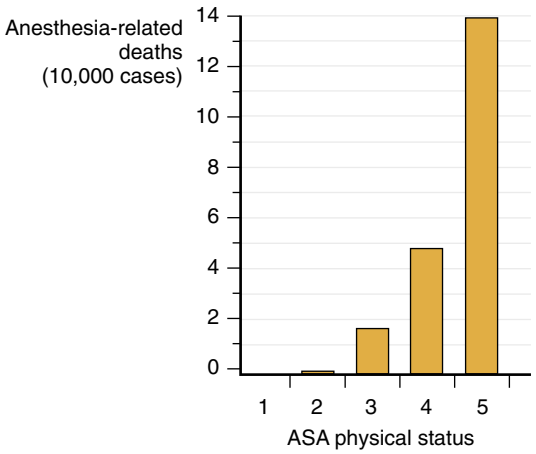

Figure 33-2 Relationship between the American Society of Anesthesiologists (ASA) physical status classification and perioperative mortality (within 2 days of surgery) related to anesthesia provided in urban and suburban institutions. *(Adapted from Lagasse RS: Anesthesia safety: Model or myth? A review of the published literature and analysis of current original data. Anesthesiology 97:1609, 2002.)*

related to patient disease, and 104 (22.5%) were related to the system or management.

Analysis of Intraoperative Cardiac Arrest

Rather than studying perioperative mortality associated with anesthesia, several studies have evaluated intraoperative fatal and nonfatal cardiac arrest (Table 33-9). In this situation there are sufficient numbers of complications to perform an analysis at a single institution. Keenan and Boyan[53] studied the incidence and causes of cardiac arrest related to anesthesia at the Medical College of Virginia during a 15-year period. A total of 27 cardiac arrests occurred during 163,240 procedures, for an incidence of 1.7 per 10,000 cases. Fourteen patients died, for an incidence of 0.9 per 10,000 cases. Pediatric patients had a threefold higher risk of arrest than adults did; emergency cases had a sixfold greater risk. Specific errors in anesthesia management could be identified in 75% of the cases, most commonly inadequate ventilation and absolute overdose of an inhaled anesthetic. The time of day did not appear to influence the rate of anesthesia-related cardiac arrest. From an educational perspective, the investigators identified progressive bradycardia preceding all but one arrest, suggesting that early identification and treatment may prevent complications.

Table 33-9 Cardiac Arrest Series When the Denominator is Greater Than 40,000 Anesthetics

Study	Years	Total No. of Anesthetics	Rate of Arrest
Hanks and Papper	1947-1950	49,728	1:2162
Ehrenhaft, et al.	1942-1951	71,000	1:2840
Bonica	1945-1952	90,000	1:6000
Blades	1948-1952	42,636	1:21,318
Hewlett, et al.	1950-1954	56,033	1:2061
Briggs, et al.	1945-1954	103,777	1:1038
Keenan and Boyan	1969-1978	107,257	1:6704 (P)
Cohen, et al.	1975-1983	112,721	1:1427 (C)
Tiret, et al.	1978-1982	198,103	1:3358 (C)
Tiret, et al.	1978-1982	198,103	1:11,653 (P)
Keenan and Boyan	1979-1988*	134,677	1:9620 (P)
Newland, et al.	1989-1999	72,959	1:14,493 (P)
Newland, et al.	1989-1999	72,959	1:7299 (C)
Olsson, et al.	1967-1984	250,543	1:33,000
Biboulet, et al.	1989-1995	101,769	1:7828
Kawashima, et al.	1994-1998	2,363,038	1:10,000 (P)
Sprung, et al.	1990-2000	518,294	1:20,000 (P)
Braz, et al.	1996-2005	53,718	1.9:10,000 (P)

C, contributory cause; P, primary cause.
*Because pulse oximetry was introduced in 1984, no "preventable respiratory" cardiac arrests have occurred.
Adapted from Brown DL: Anesthesia risk: A historical perspective. *In* Brown DL (ed): Risk and Outcome in Anesthesia, 2nd ed. Philadelphia, JB Lippincott, 1992.

Olsson and Hallen[54] studied the incidence of intraoperative cardiac arrest at the Karolinska Hospital in Stockholm, Sweden, from 1967 to 1984. A total of 170 arrests occurred in 250,543 anesthesia procedures performed. Sixty patients died, for a mortality rate of 2.4 per 10,000 procedures. After elimination of cases of inevitable death (e.g., rupture of a cerebral aneurysm, trauma), the rate of mortality caused by anesthesia was 0.3 per 10,000 procedures. The most common causes of anesthesia-related cardiac arrest were inadequate ventilation (27 patients), asystole after succinylcholine (23 patients), and postinduction hypotension (14 patients). The incidence of cardiac arrest increased with increasing severity of comorbid disease, as assessed by the ASA physical status classification. In evaluating the incidence of intraoperative cardiac arrest over time, there was a considerable decline between 1967 and 1984, coincident with the increased number of anesthesia specialists employed at the clinic.

Biboulet and colleagues[55] studied fatal and nonfatal cardiac arrests encountered during anesthesia and during the first 12 postoperative hours in the PACU or ICU in a single hospital in France. Eleven cardiac arrests related to anesthesia were identified in 101,769 anesthesia procedures (1.1 per 10,000). The mortality rate related to anesthesia was 0.6 per 10,000 cases. The major causes of death were anesthetic overdose, hypovolemia, and hypoxemia; 10 of the 11 cases had at least one human error, and all were classified as avoidable.

Newland and associates[56] reported anesthesia-related cardiac arrests during 72,959 procedures over a 10-year period in a teaching hospital in the United States. They judged that 15 of the 144 cardiac arrests were related to anesthesia (0.69 per 10,000 procedures), and in an additional 10 cases, anesthesia was considered contributory, for a total rate of 1.37 per 10,000 procedures (95% CI, 0.52 to 2.22). The risk of death from perioperative cardiac arrest that was attributable to anesthesia was 0.55 per 10,000 procedures. Most of the arrests were related to medication administration, airway management, or technical problems of central venous access.

Kawashima and colleagues sent confidential questionnaires to all Japan Society of Anesthesiologists Certified Training Hospitals every year from 1994 through 1998.[57] A total of 2,363,038 cases were documented over a 5-year period. The average yearly incidence of cardiac arrest during surgery that was totally attributable to anesthesia was 1.00 (95% CI, 0.88 to 1.12) per 10,000 cases. The average mortality per year in the operating room or within 7 postoperative days that was totally attributable to anesthesia was 0.21 (0.15 to 0.27) per 10,000 cases. The two principal causes of cardiac arrest totally attributable to anesthesia were drug overdose or selection error (15.3%) and serious arrhythmia (13.9%). Preventable human errors caused 53.2% of cardiac arrests and 22.2% of deaths in the operating room that were totally attributable to anesthesia. The outcomes of cardiac arrests totally attributable to anesthesia are shown in Table 33-10.

Sprung and colleagues studied patients who experienced cardiac arrest in the operating room, during transport to the PACU or ICU, or in the PACU after noncardiac surgery between 1990 and 2000.[58] Cardiac arrest occurred in 223 of 518,294 anesthesia procedures (4.3 per 10,000) during the study period. The frequency of arrest in patients receiving general anesthesia

Table 33-10 Cardiac Arrest Totally Attributable to Anesthesia During Anesthesia and Surgery and Its Outcomes, 1994-1998

		Outcomes				
	Number of Arrests	**Uneventful Recovery**	**Death in OR**	**Death within 7 Days**	**Vegetative State**	**Others**
5-year total	237	185	13	15	9	15
Incidence/10,000	1.00	0.78	0.05	0.08	0.04	0.06
95% CI	0.88- ≈1.12	0.66- ≈0.89	0.2- ≈0.08	0.02- ≈0.13	0.03- ≈0.05	0.02- ≈0.10
Ratio	100%	78.1%	5.5%	6.3%	3.8%	6.3%
95% CI		55.3- ≈100	1.7- ≈9.3	3.0- ≈9.7	2.5- ≈5.3	1.7- ≈11.0

N = 2,363,038.
CI, confidence interval; OR, operating room.
Reproduced with permission from Kawashima Y, Takahashi S, Suzuki M, et al: Anesthesia-related mortality and morbidity over a 5-year period in 2,363,038 patients in Japan. Acta Anaesthesiol Scand 47:809-817, 2003.

decreased over time (7.8 per 10,000 during 1990 to 1992; 3.2 per 10,000 during 1998 to 2000). The frequency of arrest during regional anesthesia (1.5 per 10,000) and monitored anesthesia care (0.7 per 10,000) remained consistent (Fig. 33-3). The hospital survival rate was 34.5%. Twenty-four patients (0.5 per 10,000) had cardiac arrest related primarily to anesthesia, 19 of whom (79.2%) survived to hospital discharge. The in-hospital mortality attributable to anesthetic-related cardiac arrest was 0.1 per 10,000 anesthetics. Given the small number of events, no relationship between the type of anesthesia and anesthetic-related cardiac arrest could be determined.

Braz and coworkers studied perioperative cardiac arrest that occurred during 53,718 anesthetics performed between 1996 and 2005 in a Brazilian teaching hospital.[59] One hundred eighty-six cardiac arrests (34.6 per 10,000) and 118 deaths (21.97 per 10,000) were reported. Major risk factors for cardiac arrest were neonates, children younger than 1 year and the elderly, male patients with ASA 3 or poorer physical status, emergency surgery, and general anesthesia. There were 18 anesthesia-related cardiac arrests (3.35 per 10,000), 10 totally attributed (1.86 per 10,000) and 8 partially related to anesthesia (1.49 per 10,000). There were six anesthesia-related deaths (1.12 per 10,000), three totally attributable and three partially related to anesthesia (0.56 per 10,000 in both cases). The main causes of anesthesia-related cardiac arrest were respiratory events (55.5%) and medication-related events (44.5%).

Perioperative Mortality and Morbidity in Outpatient Surgery

It is estimated that 60% of all surgical procedures are performed on an outpatient basis, and this percentage is increasing annually. The type and extent of surgical procedures performed in an outpatient setting are constantly changing, and procedures associated with greater perioperative risk are increasingly being performed on an outpatient basis (see Chapter 78). The value of overnight observation in a hospital setting as opposed to immediate discharge home has been studied for a number of surgical procedures. One of the first procedures advocated to be performed on an ambulatory basis was tonsillectomy. In 1968, a case series of 40,000 outpatient tonsillectomies with no deaths was reported.[60] Details on patient selection and length of postoperative monitoring were vague. Based on insurance company and state mandates, performance of tonsillectomy on an outpatient

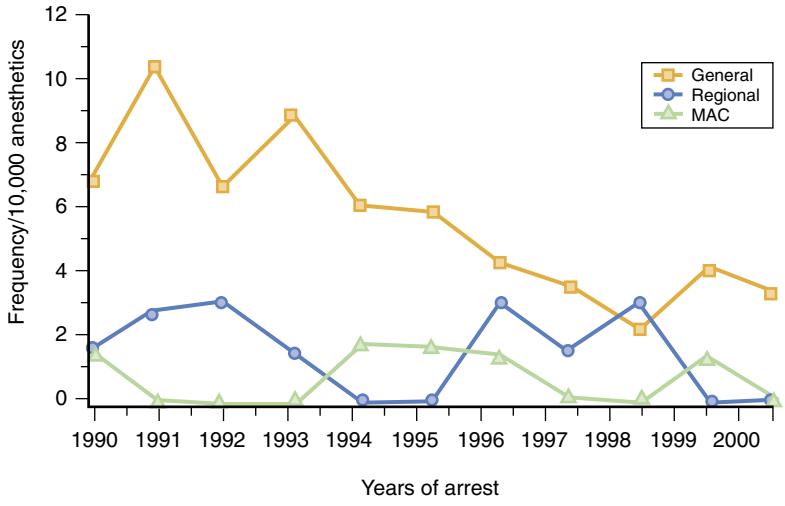

Figure 33-3 Frequency of cardiac arrest by calendar year and type of anesthesia. MAC, monitored anesthesia care. *(From Sprung J, Warner ME, Contreras MG, et al: Predictors of survival following cardiac arrest in patients undergoing noncardiac surgery: A study of 518,294 patients at a tertiary referral center. Anesthesiology 99:259-269, 2003.)*

basis became routine.[61] Beginning in the mid-1980s and continuing in the 1990s, a number of articles evaluated the risk associated with early discharge. For example, Carithers and colleagues[62] at Ohio State University analyzed 3000 tonsillectomies and argued that early discharge might be hazardous and economically unwarranted. The rate of readmission for active bleeding between 5 and 24 hours after surgery was reported to be between 0.2% and 0.5%.[63-66] Although the absolute rate of readmission is low, it represents a substantial risk for children. Whether the benefits of early discharge outweigh the risks is a decision society will have to make.

Another procedure being performed on an outpatient basis is mastectomy. An analysis of Medicare claims demonstrated that the rate of outpatient mastectomy increased from only two procedures reported to Medicare in 1986 to 10.8% of the mastectomies performed in this population in 1995.[67] The investigators compared the rate of readmission within 7 days after surgery for those who had the procedure performed on an inpatient basis versus those treated on an outpatient basis, with adjustment for the severity of disease. Simple mastectomies performed on an outpatient basis had a significantly higher rate of readmission than 1-day stays did, with an adjusted odds ratio (OR) of 1.84. There were 33.8 readmissions per 1000 cases for the outpatient surgeries as compared with 24.2 readmissions for surgeries with 1-day length of hospital stay. When compared with the group treated on an outpatient basis, there were significantly lower rates of readmission after 1-day stays for infection (4.1 versus 1.8 per 1000 cases), nausea and vomiting (1.1 versus 0 per 1000 cases), and pulmonary embolism or deep venous thrombosis (1.1 versus 0 per 1000 cases). Similarly, modified radical mastectomies performed on an outpatient basis had a significantly higher rate of readmission than 1-day stays did, with an adjusted OR of 1.72. The researchers suggested that patients who undergo the procedure on an outpatient basis may wait longer at home until seeking medical care and therefore may have more advanced symptoms initially.

Warner and colleagues[68] at the Mayo Clinic studied major morbidity and mortality occurring within 1 month after ambulatory surgery in 38,598 patients (see Chapter 78). Four patients died, two of myocardial infarction and two in an automobile accident (Fig. 33-4). The two deaths from myocardial infarction occurred at least 1 week after surgery and were not directly attributable to anesthesia. In view of the rate of mortality directly related to anesthesia described in the CEPOD study, no deaths would be expected in a study of this size.

Fleisher and coworkers[1] performed a claims analysis of patients undergoing 16 different surgical procedures in a nationally representative (5%) sample of Medicare beneficiaries for the years 1994 through 1999. A total of 564,267 procedures were studied, with 360,780 in an outpatient hospital, 175,288 in an ambulatory surgery center (ASC), and 28,199 in an office. On the day of surgery, no deaths occurred in the office, but 4 deaths occurred in the ASC (2.3 per 100,000) and 9 deaths occurred in the outpatient hospital (2.5 per 100,000). The 7-day mortality rate was 35 per 100,000 in the office setting, 25 per 100,000 in the ASC, and 50 per 100,000 in the outpatient hospital. The rate of admission to an inpatient hospital within 7 days was 9.08 per 1000 in the office, 8.41 per 1000 in the ASC, and 21 per 1000 in the outpatient hospital.

Fleisher and colleagues analyzed data from operations performed in hospital-based and freestanding ASCs in New York during 1997 that were obtained from the Agency for Healthcare Research and Quality's Healthcare Cost & Utilization Project.[69] Of the 783,558 patients eligible for inclusion in this study, 4351 were discharged directly for short-term hospitalization (1 in 180), and 19 died (1 in 41,240).

Chukmaitov and colleagues compared quality outcomes between ASCs and hospital-based outpatient departments in the state of Florida between the years 1997 and 2004.[70] They used 7- and 30-day mortality and unexpected hospitalization as the outcomes of interest in 12 surgical procedures. The importance of location of care varied by surgical procedure and the number of comorbid conditions included in the analysis. They postulated that the difference in outcomes between the two locations may be related to variations in organizational structure, processes, and strategies. The study, however, is flawed because of extreme selection bias and huge differences in available data between the ASC and hospital-based outpatient department setting. The differences in data sets were evaluated with a limited set and a set using all available data (which differed between settings). Not surprisingly, the results between settings changed with the two types of data.

Interest in performing surgery and providing anesthesia in office-based settings is increasing. There are no good data to determine the safety of such practice, although a number of high-profile cases have occurred in which patients have died during plastic surgery and during dental office procedures. Anesthesia and sedation are frequently provided by individuals other than anesthesiologists or nurse anesthetists in these settings, with reports of office nurses or even clerical help administering anesthetic agents.

There has been an attempt to quantify the incidence of complications in an office-based setting. The American Association for Ambulatory Plastic Surgery Facilities mailed a survey to their members to determine the incidence of complications occurring in office facilities.[71] The overall response rate was 57%. The findings showed that 0.47% of patients had at least one complication, including bleeding, hypertension, infection, and hypotension, and 1 in 57,000 patients died. Assuming that these are very minor procedures performed only on healthy individuals, a rate of mortality that is three times the current estimate for anesthesia-related complications is a concern. Further research and quality assurance mechanisms need to be in place before this practice is generalized. One of the problems inherent in an office-based setting is the inability to perform quality assurance reviews. For example, few surgeons or anesthesiologists would be willing to allow their "competitors" to review their complication rate unless mandated to perform such a review.

Vila and colleagues reviewed all adverse incident reports to the Florida Board of Medicine for procedure dates April 1, 2000, to April 1, 2002.[72] The numbers of office procedures performed during a 4-month period were used to estimate the total number of procedures. Adverse incidents occurred at a rate of 66 and 5.3 per 100,000 procedures in offices and ASCs, respectively. The death rate per 100,000 procedures performed was 9.2 in offices and 0.78 in ASCs. The relative risk for injury and death for procedures performed in the office versus ASCs was 12.4 (95% CI, 9.5 to 16.2) and 11.8 (95% CI, 5.8 to 24.1), respectively. The authors concluded that if all office procedures had been performed in ASCs, approximately 43 injuries and 6 deaths per year could have been prevented. In contrast, Coldiron and colleagues studied office-based surgery in Florida and showed that the greatest danger to patients lies not with surgical procedures in office-based settings per se but with cosmetic procedures that are

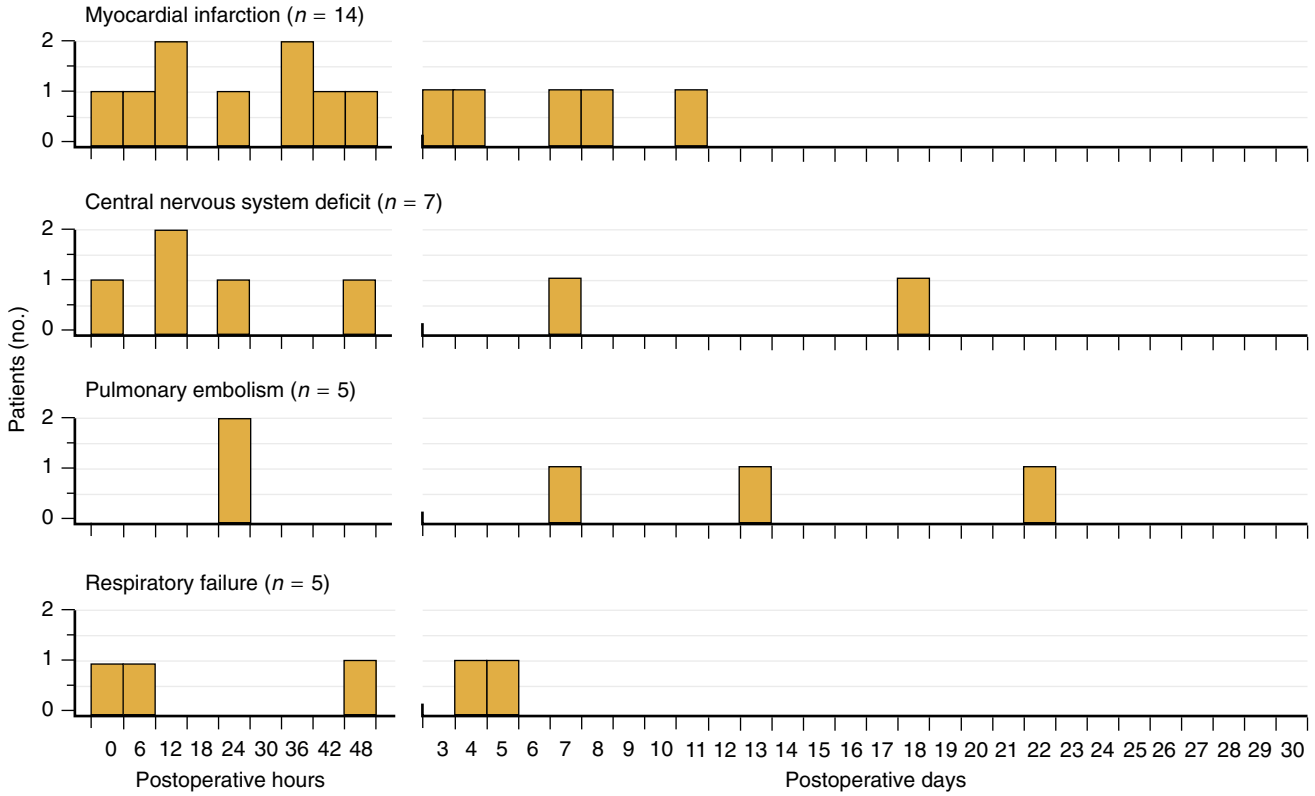

Figure 33-4 Timing of perioperative events in patients undergoing ambulatory surgery. Many of the events occurring within the first 48 hours are probably related to the stress of surgery. A subset of events occurring after this period may be related to background event rates. The overall rate of morbidity was lower than expected for a similar cohort of age-matched nonsurgical patients. *(From Warner MA, Shields SE, Chute CG: Major morbidity and mortality within 1 month of ambulatory surgery and anesthesia. JAMA 270:1437, 1993.)*

performed in office-based settings, particularly when under general anesthesia.[73] Several other groups have analyzed the Florida data and have been unable to document the increased risk in the office setting.[74,75]

Problems in evaluating the risk associated with outpatient surgery include the lack of any large database compiled from a diverse group of settings and the lack of uniform standards for quality assurance. Even though the Joint Commission accredits ASCs, as do two other organizations, accreditation is still not widespread and remains optional. Although ASCs have led the way in performing appropriate follow-up of their patients at home, such follow-up is not uniformly complete. As of 1998, only three states had established regulations for office-based settings, and these regulations vary greatly. The implications of the lack of regulation are unclear, but issues related to emergency plans and resuscitation equipment may be left to the discretion of the local personnel, potentially placing patients at risk.

The decision to perform a procedure in an ambulatory setting is based on the surgeon's preference and the insurance company's mandates. Frequently, a case series by a surgeon or review by an insurance company demonstrates that otherwise healthy individuals can undergo a given procedure safely in an outpatient setting. The need for subsequent medical attention or use of resources at home is not necessarily taken into account. This may lead to insurance company mandates that the procedure be performed in all patients in an ambulatory setting. The generalization from healthy individuals to patients with comorbid disease may not be justified in the absence of data to demonstrate its safety. As an advocate for the patient, the anesthesiologist should continue to evaluate the safety of such practices and determine when the risks of ambulatory surgery outweigh any potential benefits. It is also important to determine whether the insurance companies are in essence transferring the risk of undergoing surgery from the medical system to the patient.

Use of Anesthesia Information Management Systems

Use of computer databases has enhanced the ability of investigators to identify perioperative complications (see Chapter 4). In one of the earliest computer analyses of postanesthesia deaths, Marx and associates[21] identified 645 individuals who died within 7 days after surgery out of a total cohort of 34,145 consecutive surgical patients. More recently, anesthesia information systems have been installed in many operating rooms. The advantage of these systems is the ability to query very large sets of data; however, the limitation is that many of these systems do not link with data from outside the operating room or the PACU. Therefore, the risk related to anesthesia for most of these studies is restricted to intraoperative events. Currently, there are several initiatives to try to link these data, including linking multiple institutions, with validated postoperative data from the NSQIP or Society of Thoracic Surgeons database.

One of the first such analyses was performed by Sanborn and colleagues,[76] who used a computer anesthesia record to iden-

tify intraoperative incidents with high sensitivity and specificity. They were able to demonstrate that perioperative deaths occurred more frequently in patients who sustained an intraoperative incident than in those who did not.

Reich and colleagues used computerized anesthesia records to evaluate hemodynamic variables.[22] Among 2149 patients, there were 50 mortalities, 51 strokes, and 85 perioperative myocardial infarctions. By multivariate analysis they identified pulmonary hypertension, hypotension during cardiopulmonary bypass, and post–cardiopulmonary bypass pulmonary diastolic hypertension as independent predictors associated with mortality, stroke, and perioperative myocardial infarction over and above the effects of other preoperative risk factors.

Tremper's group at the University of Michigan used their home-grown information system to identify predictors of perioperative risk. For example, they queried 22,660 attempts at mask ventilation.[77] Limited or severely limited mandibular protrusion, abnormal neck anatomy, sleep apnea, snoring, and a body mass index of 30 kg/m^2 or greater were independent predictors of grade 3 or 4 mask ventilation and difficult intubation. In another publication, a total of 15,102 patients had a normal preoperative creatinine clearance and were undergoing noncardiac surgery.[78] Acute renal failure developed in 121 patients (0.8%), and 14 required renal replacement therapy (0.1%). Seven independent preoperative predictors were identified: age, emergency surgery, liver disease, body mass index, high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy. They found that acute renal failure was associated with increased 30-day, 60-day, and 1-year all-cause mortality.

Given the growth in the use of anesthesia information management systems and the ease of collecting large quantities of data and linking them to outcome, it is likely that many more studies documenting associations with outcome will be published.

Other Approaches to Discern the Root Cause of Morbidity and Mortality

The accumulating data clearly demonstrate that risk directly attributable to anesthesia has declined over time (see Chapter 5). The cause of this reduction in mortality is unclear. Numerous factors have been implicated in the improved outcome, including new monitoring modalities, new anesthetic drugs, and changes in the anesthesia workforce. However, it is difficult to document reduced risk related to any one factor (issues related to manpower are addressed later). Although the use of newer monitoring modalities, particularly pulse oximetry, would be expected to improve outcomes, no randomized trial has been able to document such a conclusion. This limitation supports the need for continued monitoring of complications and their root cause with studies such as the ACCS.

Studies similar to the CEPOD have not been performed in the United States, most likely because of the legal system, and information related to perioperative mortality must be obtained from other sources. The Professional Liability Committee of the ASA conducted a nationwide survey of closed insurance claims for major anesthesia mishaps. In the ACCS, fatal and nonfatal outcomes were reviewed. Among the fatal events, unexpected cardiac arrest during spinal anesthesia was observed in 14 healthy patients from the initial 900 claims.[79] The cases were analyzed in detail to identify patterns of management that might have led to the event. Two patterns were identified: oversedation leading to respiratory insufficiency and inappropriate resuscitation of high spinal sympathetic blockade.

Tinker and coworkers[80] queried the ACCS to determine the role of monitoring devices in the prevention of anesthesia mishaps. They reviewed 1097 anesthesia-related claims and determined that 31.5% of the negative outcomes could have been prevented by the use of additional monitors, primarily pulse oximetry and capnography. Injuries that were deemed preventable with additional monitoring resulted in dramatically more severe injury and cost of settlement than did those judged nonpreventable with additional monitoring. In nearly 90% (305 of 346) of the preventable cases, at least one clinical sign of abnormality was identified by the existing monitors.

Caplan and colleagues[81] reviewed the ACCS for respiratory events (Table 33-11). These claims represented the single largest class of injury (34%), with death or brain damage occurring in 85% of cases. They identified inadequate ventilation, esophageal intubation, and difficult tracheal intubation as the primary causes of respiratory events. Most of the outcomes were thought by the investigators to be preventable with better monitoring (Fig. 33-5). Although no randomized trial has demonstrated the value of pulse oximetry or capnography, an analysis of claims supports the value of such monitoring. This analysis also formed part of the basis for the guidelines and algorithm endorsed by the ASA Task Force on Management of the Difficult Airway.

The closed claims analysis has recently focused on such topics as monitored anesthesia care.[82] More than 40% of 121 claims associated with monitored anesthesia care involved death or permanent brain damage. Respiratory depression, after an absolute or relative overdose of sedative or opioid drugs, was the most common (21%, $n = 25$) of the complications.

A similar registry was developed by the Danish Patient Insurance Association.[83] For the period 1996 to 2004, 1256 files were related to anesthesia and 24 deaths were considered to be a result of the anesthetic procedure: 4 deaths were related to airway management, 2 to ventilation management, 4 to central venous catheter placement, 4 as a result of medication errors, 4 from infusion pump problems, and 4 after complications from regional blockade. Severe hemorrhage caused one death, and in one case the cause was uncertain.

Table 33-11 Distribution of Adverse Respiratory Events in the American Society of Anesthesiologists Closed Claims Study

Event	No. of Cases	Percentage of 522 Respiratory Claims
Inadequate ventilation	196	38
Esophageal intubation	94	18
Difficult tracheal intubation	87	17
Inadequate inspired oxygen concentration	11	2

From Caplan RA, Ward RJ, Posner K, Cheney FW: Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. Anesthesiology 68:5, 1988.

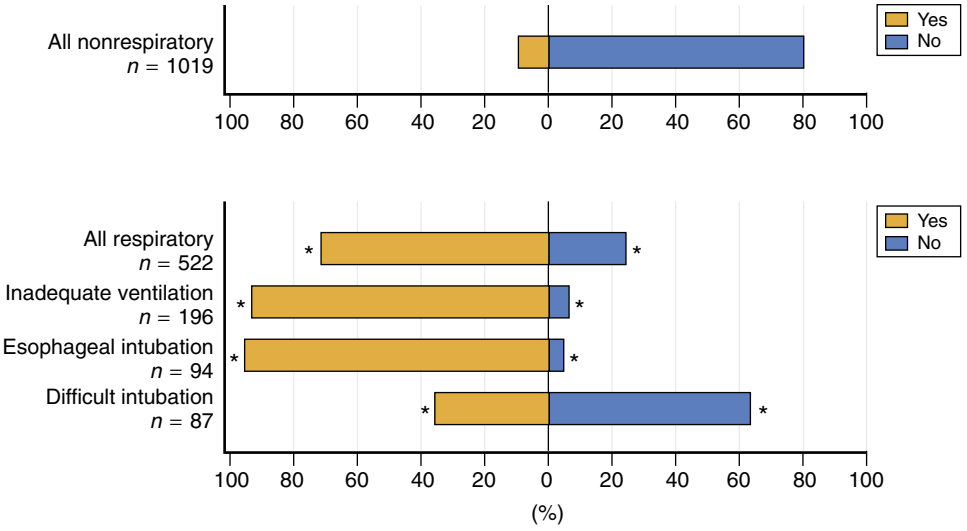

Figure 33-5 Relationship between adverse events in the American Society of Anesthesiologists Closed Claims Study and preventable complications. Preventable events related to respiratory complications were significantly more common than those related to all nonrespiratory complications. Of the respiratory complications, difficult intubation had the least number of preventable complications (*$P < .05$ versus nonrespiratory claims). *(From Caplan RA, Posner KL, Ward RJ, Cheney FW: Adverse respiratory events in anesthesia: A closed claims analysis. Anesthesiology 72:828, 1990.)*

Cooper and colleagues[84-86] approached the problem of sample size for determining perioperative morbidity by identifying critical incidents, which were defined as those that were preventable but could lead to undesirable outcomes. This definition included events that led to no or only transient effects in the patient. The investigation involved collecting data on anesthesia-related human errors and equipment failures from anesthesiologists, residents, and nurse anesthetists. In a series of reports, the authors identified frequent incidents, such as disconnections in breathing circuits, and causes of discovery of errors, such as intraoperative relief. They confirmed that equipment failure was a small cause of anesthesia mishaps (4%), whereas human error was dominant. They suggested that future studies of anesthesia-related mortality and morbidity should classify events according to a strategy for prevention rather than outcome alone.

The Australian Incident Monitoring Study was developed by the Australian Patient Safety Foundation and has been in existence since the early 1990s. It is a method of reporting and analyzing critical incidents so that corrective strategies can be implemented. Similar to the ACCS, there is no rate of occurrence, only an analysis of reported cases. Numerous reports have looked at the cause of critical incidents, including problems with ventilation, with vascular access, and in the PACU.[87-89]

Buffington and coworkers[90] studied the ability of attendees of an anesthesia meeting to identify five faults intentionally created in a standard anesthesia machine. A survey was distributed, and the answer sheets were scored with respect to the number of correct answers. Only 3.4% of the respondents found all five faults. The average number of faults detected was 2.2. The professional background of the participants did not influence the ability to find the faults; distributions were similar between physicians and CRNAs. There was a small improvement in fault-finding ability in those with more than 10 years of experience. Studies such as these highlight the problem of the practitioner's ability to identify conditions that may lead to anesthesia mishaps. Whether improved technology or education can reduce some basal level of mishaps is unknown.

Issues Associated with Anesthesia-Related Mortality

Most of the studies have focused on in-hospital and short-term mortality, but perioperative complications may be the events that directly lead to death. For example, a perioperative stroke or myocardial infarction may lead to death after the period of analysis. Even small myocardial infarctions or unstable angina during the perioperative period has been associated with worse long-term survival in several studies.[91,92] Should these "late" deaths be attributed to anesthesia complications for the purpose of such analyses? Results from several studies add to the dilemma. For example, Mangano and colleagues[93] performed a randomized clinical trial in which 7 days of perioperative β-blockade was compared with placebo in high-risk patients undergoing noncardiac surgery. They reported significantly improved survival at 6 months, which remained significant during the 2 years of follow-up. In a subsequent report regarding this trial, Wallace and coworkers[94] demonstrated that the improved survival in the group receiving β-blockade was associated with a significantly lower incidence of perioperative myocardial ischemia but no difference in perioperative cardiac events. The authors of the original study suggested that atenolol administration led to better plaque stabilization during the perioperative period, which resulted in improved long-term survival. If the hyperdynamic perioperative state is not well controlled, this theory suggests that more plaque becomes destabilized and progresses to acute occlusion and sudden death. If atenolol is not used and patients die within 6 months of surgery, should this be attributed to an error in anesthesia and perioperative management? Part of the answer relies on the strength of this study to support the conclusion that routine use of atenolol does result in improved long-term survival.

The potential effects of anesthesia on long-term survival were suggested by Monk and colleagues.[95] Multivariate Cox proportional hazards modeling identified three variables as signifi-

cant independent predictors of mortality: patient comorbidity (relative risk, 16.116), cumulative deep hypnotic time (bispectral index <45) (relative risk, 1.244/hr), and intraoperative systolic hypotension (relative risk, 1.036/min). They reported that cumulative deep hypnotic time and intraoperative hypotension were significant, independent predictors of increased mortality. Further work is required to determine whether these results reflect a true pathophysiologic link between perioperative management and long-term outcome or a simple statistical association.

Risks Related to the Patient

Perioperative morbidity and mortality increase with increasing patient comorbidity. The original ASA physical status scoring system was proposed in 1941 and included six categories.[96] It was intended to standardize terminology and allow statistical analysis of outcomes between sites.[97] The original classification avoided the inclusion of surgical variables and was restricted to preoperative patient characteristics. It was revised in 1961 by Dripps and colleagues[32] to five categories, which were then adopted by the ASA.

The simplest example of such a relationship is the incidence of mortality correlated with ASA physical status. In their original study of perioperative mortality, Dripps and coworkers demonstrated that mortality increased as the severity of comorbid disease increased, as assessed by the ASA physical status classification. Several investigators have re-evaluated the relationship between operative mortality and ASA physical status. Studies by Pedersen and Tiret and their colleagues demonstrated such relationships. Vacanti and coworkers[98] also demonstrated the relationship between increasing mortality and decreasing physical status in 68,388 cases.

In Canada, Cohen and colleagues[99] analyzed 100,000 anesthesia procedures and determined mortality within 7 days of surgery by using governmental vital statistics mortality data between the years 1975 and 1984. They established a computer database for each procedure that included age, preoperative conditions, ASA physical status, anesthesia technique, monitors, and other factors. The overall 7-day mortality rate was 71.04 deaths per 10,000 procedures. The mortality rate increased with advanced age, and it showed a marked increase in those older than 80 years. Rates were low for normal, healthy individuals and for those undergoing minor procedures. The investigators developed a multiple logistic regression model to determine the independent predictors of mortality. Significant risk markers for increasing mortality were advanced age, male gender, increasing physical status score, major or intermediate surgery, emergency procedure, having a complication in the operating room, narcotic anesthesia techniques, and having received only one or two anesthetic drugs (Table 33-12).

In an attempt to look at each of the categories of contributing factors independently, Cohen's group constructed receiver-operator characteristic curves. There was no increment in prediction of mortality beyond that based on characteristics of the patient plus surgery. Plots including "other" or anesthesia-related factors showed almost complete overlap with curves including only patient- and surgery-specific factors.

One of the limitations of the ASA physical status classification is that ranking is a subjective measure conferred by the practitioner rather than an objective measure determined by the presence of specific disease states. Owens and coworkers[100] evaluated this hypothesis by asking 255 anesthesiologists to classify 10 hypothetical patients. In six of the cases there was general agreement among the practitioners about classification of the patient; in the other four cases, opinion diverged. The key finding of this study was that the ASA physical status classification is "useful but suffers from a lack of scientific precision."

Rather than evaluating the risk of overall mortality, many studies have attempted to define the patient characteristics associated with morbidity and mortality related to a particular organ system. In evaluating the risk directly related to the patient's condition, it is important to understand the limitations of the methodology. All such studies evaluate the predictive value of a clinical

Table 33-12 Risk Factors Associated with Increased Odds of Dying within 7 Days for All Cases

Variable	All Procedures: Relative Odds of Dying within 7 Days	95% Confidence Limits
Patient Related		
Age (yr)		
60-79/<60	2.32	1.70-3.17
80+/<60	3.29	2.18-4.96
Sex (F/M)	0.77	0.59-1.00
Physical status score (3-5/1-2)	10.65	7.59-14.85
Surgery Related		
Major/minor	3.82	2.50-5.93
Intermediate/minor	1.76	1.24-2.5
Length of anesthesia (≤2 hr/<2 hr)	1.08	0.77-1.50
Emergency/elective	4.44	3.38-5.83
Other Factors		
Year of surgery (1975-1979/1980-1984)	1.75	1.32-2.31
Had a complication in the operating or recovery room (yes/no)	1.42	1.06-1.89
Anesthesia Related*		
Experience of the anesthetist (>600 procedures for ≥8 yr/<600 procedures for <8 yr)	1.06	0.82-1.37
Inhalation with narcotic/inhalation alone	0.76	0.51-1.15
Narcotic alone/inhalation alone	1.41	1.01-2.00
Narcotic with inhalation/inhalation alone	0.79	0.47-1.32
Spinal/inhalation alone	0.53	0.29-0.98
No. of anesthetic drugs (1-2/3+)	2.94	2.20-3.84

*All cases performed with the five most frequently used anesthetic techniques.
Adapted from Cohen MM, Duncan PG, Tate RB: Does anesthesia contribute to operative mortality? JAMA 260:2861, 1988.

or laboratory risk factor for a defined perioperative complication. In this approach, a cohort of individuals of interest is defined. In the optimal state the study is performed prospectively, and the outcome of interest is assessed in a rigorous, blinded fashion. Unfortunately, many of the studies focus on selected patients and include a retrospective design, methods that greatly limit their generalizability and validity. For example, many studies evaluating risk factors in vascular surgery patients include only patients who are referred for diagnostic testing rather than a consecutive series of patients.

Many studies have adopted the approach of defining a cohort of individuals, determining their clinical and laboratory risk factors, and using multivariate modeling to determine the factors associated with increased risk. Frequently, perioperative risk is used to define intraoperative and postoperative complications. A major limitation in the use of multivariate modeling for this purpose is the assumption that the intraoperative period is a "black box" and that care is not modified by knowledge of the risk factor (Fig. 33-6). However, anesthesiologists do modify their intraoperative care of high-risk patients in an attempt to reduce the risk. Changes in medical care over time and better knowledge about high-risk patients should result in a reduction of the risk related to specified clinical factors. For this reason, many of the indices developed previously may no longer have clinical validity.

In designing a multivariate risk index for perioperative morbidity and mortality, only factors that are included in the analysis and in the patient population of interest can be included in the final model. For example, if the population studied represents a unique referral bias, some risk factors may be overrepresented, and others may not be present in sufficient quantity to study. An example is unstable angina in the original Cardiac Risk Index developed by Goldman and colleagues.[6] Because patients with unstable angina are typically seen only for emergency surgery, that risk factor is rarely represented in many indices.

There are numerous specific disease states that increase perioperative risk. Cardiovascular disease has been the most extensively studied, with the goal of identifying patients at greatest risk for fatal and nonfatal myocardial infarction. One of the earliest attempts to define cardiac risk was performed by Goldman and colleagues at the Massachusetts General Hospital. They studied 1001 patients older than 45 years who were undergoing noncardiac surgery, excluding those who underwent transurethral resection of the prostate under spinal anesthesia. Using multivariate logistic regression, they demonstrated nine clinical factors associated with increased morbidity and mortality. Each of these risk factors was associated with a given weight in the logistic regression equation, which was converted into points in the index. An increasing number of points was associated with increasing perioperative cardiac morbidity or mortality.

There have been several attempts to validate the Goldman Cardiac Risk Index. Zeldin[101] prospectively determined the Cardiac Risk Index for 1140 surgical patients and reported that the overall accuracy of the index was as high as in the original study, although the rate of complications in the highest-risk group was less than originally reported. Larsen and coworkers[102] also found that the Cardiac Risk Index demonstrated good accuracy in 2609 consecutive unselected patients older than 40 years. Domaingue and colleagues[103] studied patients undergoing various vascular surgery procedures and reported a higher probability of major cardiac complications than that reported by Goldman and associates; however, they also demonstrated a higher rate of complications with increasing cardiac risk class. The validity of the Cardiac Risk Index is more controversial for vascular surgery patients. Jeffrey and colleagues[104] evaluated the rate of cardiac complications in 99 patients undergoing elective abdominal aortic surgery and demonstrated a similar pattern of increased overall complication rates with increasing cardiac risk. A higher percentage (7%) of patients in the lowest category in their study sustained a cardiac complication. White and associates[105] demonstrated the value of the Goldman Cardiac Risk Index for long-term survival after vascular surgery. Several other studies, however, were unable to demonstrate any relationship between the Cardiac Risk Index and perioperative cardiac complications, with a high incidence of complications found in patients with a Cardiac Risk Index of I or II.[106,107] When the ASA physical status classification was compared with the Goldman Cardiac Risk Index in a cohort of 16,277 patients undergoing noncardiac surgery,[108] both indices demonstrated predictive value, although the objective Goldman Cardiac Risk Index had little increased value over the more subjective ASA physical status classification.

Other investigators have attempted to develop risk indices. Detsky and coworkers[109] studied a cohort of individuals who were referred to an internal medicine service for preoperative evaluation. Many of the factors identified by Goldman were confirmed or slightly modified in the Detsky index, and angina was added to the risk factors. The researchers advocated the calculation of a pretest probability of complications based on the type of surgery, after which the Detsky Modified Risk Index is applied with the use of a nomogram. In this manner, the overall probability of complications can be determined as a function of the surgical procedure and patient disease. The Detsky index was advocated as the starting point for risk stratification in the American College of Physicians guidelines on preoperative evaluation.[110] In an

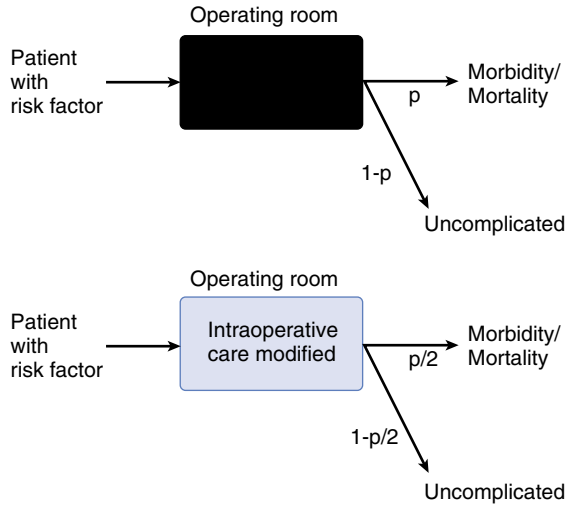

Figure 33-6 The concept of the black box for risk indices. In developing a risk index, patients with a specific risk factor enter the operating room and have a complication at a rate (p). If the anesthesiologist is aware of the importance of the risk factor and can modify care to reduce such risk (p/2), the risk factor may no longer be significant. If the risk factor is ignored, complications may again occur in such patients.

attempt to update the original index, Lee and colleagues[111] at the Brigham and Women's Hospital studied 4315 patients 50 years or older who were undergoing elective major noncardiac procedures in a tertiary care teaching hospital. Six independent predictors of complications were identified and included in a Revised Cardiac Risk Index: high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine level higher than 2.0 mg/dL. The rate of major cardiac complications increased with the number of risk factors.

Numerous risk indices for cardiac surgery have been developed. The goal has been to identify patients who are at greatest risk for adverse perioperative outcomes, not specifically anesthesia-related risk. Many of these indices focus on anatomic considerations for perioperative risk. They are extremely useful in risk adjustment to assess rates of mortality. For example, the state of New York annually publishes data on mortality rates associated with coronary bypass grafting by surgeon and by hospital.[112-114] For comparison of rates across institutions, risk figures must be adjusted so that institutions that perform predominantly high-risk surgery are not penalized.

Vanzetto and coworkers[115] performed a prospective evaluation in which an expanded number of clinical variables were identified in a cohort of patients undergoing major vascular surgery. Cardiovascular morbidity and mortality were determined prospectively in this population. An increasing number of clinical variables was associated with increasing perioperative risk. Most importantly, dipyridamole-thallium imaging was performed only in the subset of patients with two or more clinical variables, and the results of the test were not made available to the clinicians caring for the patients. In this well-performed study, the presence of thallium redistribution identified a cohort who had an incrementally greater perioperative risk than did those with negative scan results and a similar number of clinical variables.

As part of their study of anesthesia-related mortality, Pedersen and colleagues[51] evaluated the occurrence of cardiovascular and pulmonary complications. For a total of 7306 anesthesia procedures, they reported a 6.3% incidence of intraoperative or postoperative cardiovascular complications and a 4.8% incidence of intraoperative or postoperative pulmonary complications. Acute myocardial infarction occurred in 0.16% of the patients. The investigators evaluated a number of characteristics, including gender, age, presence of ischemic heart disease, duration of anesthesia, and type of surgery, and assessed their relationship to cardiovascular and pulmonary complications and overall mortality in the hospital (Table 33-13). Cardiopulmonary complications were associated with advanced age (>70 years), preoperative signs of ischemic heart disease with recent myocardial infarction, chronic heart failure, chronic lung disease, and abdominal surgery, particularly of an emergent nature. They observed that the use of pancuronium was associated with worse perioperative outcome, a finding reminiscent of the curare-related deaths of the 1940s and 1950s.

Numerous studies have evaluated the importance of single variables such as hypertension on perioperative risk. Goldman and Caldera[116] evaluated a cohort of patients undergoing noncardiac surgery under general anesthesia. Hypertension did not denote a group with increased perioperative risk, although the number of patients with diastolic blood pressure greater than 110 mm Hg was insufficient to draw any conclusions. This study highlighted the problems related to generalization of results in that many subsequent researchers have suggested that surgery be delayed in patients with a diastolic blood pressure greater than 110 mm Hg. In one of the few studies to demonstrate a relationship, Hollenberg and coworkers[117] identified hypertension and the presence of left ventricular hypertrophy as predictors of perioperative ischemia, but they did not consider their independent relationship to perioperative major morbidity.

Examples of prospective cohort studies to identify the risk associated with a particular clinical factor include studies of the rate of perioperative reinfarction in patients who had previously sustained a myocardial infarction. Traditionally, risk assessment for noncardiac surgery was based on the time interval between the myocardial infarction and surgery. Multiple studies have demonstrated an increased incidence of reinfarction if the myocardial infarction occurred within 6 months of surgery. With improvements in perioperative care, this difference has decreased.

The previous example of assessing risk illustrates the issue of changes in management over time. The importance of the intervening time interval may no longer be valid in the current era of thrombolytics, angioplasty, and risk stratification after acute myocardial infarction. Although many patients with myocardial infarction continue to have myocardium at risk for subsequent ischemia and infarction, in others, the critical area of coronary stenosis is totally occluded or widely patent. Patients should be evaluated from the perspective of their risk for ongoing ischemia. In their Guidelines for Perioperative Evaluation of Noncardiac Surgery, the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures[118] proposed that patients who have experienced a myocardial infarction within less than 30 days be considered the group at highest risk; after that period, risk stratification is based on disease severity and exercise tolerance.

Special Patient Groups

Obstetrics

Maternal mortality is rare, and the anesthesia-related component of maternal delivery represents only a small fraction of all maternal deaths, thus making study of this problem difficult or impossible in any one institution (see Chapter 69). A series of studies were performed between 1974 and 1985 to determine the rate of complications in the United States and England. One of the first reports included the period 1974 to 1978. Kaunitz and coauthors[119] reported an anesthesia-related death rate of 0.6 per 100,000 births with data from all 50 states. Endler and coworkers[120] studied births in Michigan between 1972 and 1984 and reported 15 maternal deaths in which anesthesia was the primary cause and 4 deaths in which anesthesia was contributory. This resulted in a rate of 0.82 anesthesia-related deaths per 100,000 live births. Eleven of the 15 deaths were associated with cesarean section. Obesity and emergency surgery were risk factors in many patients. Complications related to regional anesthesia were problems during the early part of the study, whereas failure to secure a patent airway was the primary cause of mortality in later years. There were no anesthesia-related maternal deaths in the final 2 years of the study. The incidence of anesthesia-related death was

Table 33-13 Factors Associated with Increased Perioperative Complications

Risk Factors	No. of Anesthetics (*N* = 7306)*	Cardiovascular Complications		Pulmonary Complications		Mortality in Hospital	
		%	Odds Ratio	%	Odds Ratio	%	Odds Ratio
Sex							
Female	4587	4.9		3.7		0.7	
Male	2634	8.8†	1.8	6.6†	1.8	2.2†	3.2
Age (yr)							
<50	3965	2.6		2.3		0.3	
50-90	2043	8.2		6.7		1.8	
70-79	886	14.3†		8.9		2.9†	
≥80	293	16.7†		10.2†		5.8†	
Ischemic heart disease	103	29.1†	6.5	8.7	1.9	2.9	2.5
Myocardial infarction							
>1 yr	125	20.8†		7.7		4.0†	
≤1 yr	26	38.5†		10.4†		7.7†	
Chronic heart failure	199	35.2†		15.1†	3.8	9.0†	9.9
Hypertension	380	11.8†	2.1	7.1†	1.6	1.3	1.1
Hypertension (SBP ≤90 mm Hg)	127	16.5†	2.5	17.3†	4.0	9.4†	9.8
Chronic obstructive lung disease	201	12.4†	2.1	12.4	3.0	5.0†	4.7
Renal failure	153	14.4†	2.2	11.8†	2.4	5.9†	5.2
Diabetes mellitus	141	9.2	1.5	7.1	1.5	2.1†	1.8
Neurologic disease	34	5.9	1.0	8.8†	1.9	2.9	2.4
Cancer	1257	7.0	1.1	5.5	1.2	1.1	1.0
Cancer (abdominal)	242	19.8†	3.2	19.4†	4.3	5.0†	5.4
Emergency surgery	2454	7.4†	1.3	6.3†	3.0	2.8†	3.2
Duration of anesthesia (min)							
<30	1774	1.2		0.6		0.1	
30-179	4621	6.8		4.5		1.3	
180-299	470	17.9†		13.4†		3.2†	
≥300	162	20.4†		30.2†		4.9†	
Minor surgery	4916	3.2		1.8		0.3	
Major surgery	2113	13.0†	4.1	10.6	5.8	3.1†	4.9
Total		6.3		4.8		1.2	

SBP, systolic blood pressure.
*The analysis shows the maximum number of patients in the various groups.
†$P < .05$ indicates a statistically significant higher rate of complications and mortality when compared with the rest of the total incidence.
From Pedersen T: Complications and death following anaesthesia: A prospective study with special reference to the influence of patient-, anaesthesia-, and surgery-related risk factors. Dan Med Bull 41:319, 1994.

markedly higher in black women, which the investigators suggested might have been related to an inability to detect cyanosis. Rochat and colleagues[121] studied 19 areas of the United States between 1980 and 1985 and reported 0.98 anesthesia-related deaths per 100,000 live births. They observed that maternal mortality did not decrease over the time of the study.

The Confidential Enquiry into Maternal Deaths in England and Wales has been assessing maternal deaths since 1952.[122] Records of all maternal deaths are sent to a district medical officer, who sends an inquiry form to all health practitioners involved in the care of these patients. These forms are evaluated by a senior obstetrician and an anesthesia assessor. Morgan[122] reported the maternal deaths from anesthesia between 1952 and 1981 (Table 33-14). The total maternal mortality rate decreased over time, but the percentage of deaths related to anesthesia increased, although the absolute number of deaths associated with anesthesia decreased. During the early years of the study, endotracheal intubation was rarely performed during obstetric anesthesia. Later reports advocated the use of endotracheal intubation after thiopental-suxamethonium, and technical difficulties with intubation were identified. The other major finding of this study was that the experience of the anesthetist in obstetric anesthesia was the most important factor in anesthesia-related maternal mortality.

Table 33-14 Maternal Mortality Figures Obtained from the Confidential Enquiry into Maternal Deaths in England and Wales

Years	Maternal Mortality per 1000 Total Births	Number of Deaths from Anesthesia	Percentage of True Maternal Deaths from Anesthesia	Percentage with Avoidable Factors
1952-1954	0.53	49	4.5	—
1955-1957	0.43	31	3.6	77
1958-1960	0.33	30	4.0	80
1961-1963	0.26	28	4.0	50
1964-1966	0.20	50	8.7	48
1967-1969	0.16	50	10.9	68
1970-1972	0.13	37	10.4	76
1973-1975	0.11	31	13.2	90
1976-1978	0.11	30	13.2	93
1979-1981	0.11	22	12.2	100

From Morgan M: Anaesthetic contribution to maternal mortality. Br J Anaesth 59:842, 1987.

Several studies have attempted to define the cause of anesthesia-related maternal deaths. Insight into the cause of maternal mortality can also be elicited from the ACCS. In 1991, Chadwick and coauthors[123] published a report of closed malpractice claims related to 190 obstetric cases—127 cesarean sections and 63 vaginal deliveries. The most frequent complications were maternal death and brain damage in the newborn. There were 15 maternal deaths in patients who underwent regional anesthesia and 26 in patients who had general anesthesia. Because the absolute number of patients who underwent each type of anesthesia was unknown, the risk attributable to anesthesia could not be determined, unlike the subsequent report from Hawkins and coworkers.[124]

Hawkins and associates[124] obtained data from the ongoing National Pregnancy Mortality Surveillance System of the Centers for Disease Control and Prevention. Using state data on births and fetal deaths from 1979 through 1990, three obstetric anesthesiologists reviewed the records to determine the possible risk related to anesthesia. A total of 129 women died of anesthesia-related causes during the study period, most (82%) during cesarean section, and the incidence decreased over time (Table 33-15). The decreased mortality rate appeared to be related to increased use of regional anesthesia. The primary cause of mortality was related to the type of anesthesia. For general anesthesia, 73% of the deaths were related to airway problems. Unlike the Confidential Enquiry into Maternal Deaths in England, the U.S. study lacked the extensive detail for each event, and the absolute cause of mortality therefore remained somewhat in doubt. In particular, the researchers acknowledge that general anesthesia may be used more often in patients with a higher acuity of disease, which may account for the higher mortality rate associated with its use. The availability of national databases should allow accurate tracking of mortality to ensure that appropriate quality assurance and quality improvement systems are in place.

Panchal and colleagues[125] conducted a retrospective case-control study using patients' records from a state-maintained anonymous database of all nonfederal Maryland hospitals that performed deliveries between 1984 and 1997 (Fig. 33-7). Variables studied included patient demographics and ICD-9 (Clinical Modification) diagnosis and procedure codes. Of the 822,591 hospital admissions for delivery during the 14-year study period, there were 135 maternal deaths. The most common diagnoses associated with mortality during hospital admission for delivery were preeclampsia or eclampsia (22.2%); postpartum hemorrhage or obstetric shock (22.2%); pulmonary complications (14%); blood clot or amniotic embolism, or both (8.1%); and anesthesia-related complications (5.2%).

Gibbs and coworkers[126] surveyed 1200 hospitals in 1981 and sent questionnaires to the chiefs of anesthesia and obstetrics. Anesthesiologists were available for obstetric anesthesia in only 21% of all hospitals and at night and on the weekends in just 15%. Hospitals with fewer than 500 deliveries per year had the most

Table 33-15 Numbers, Case Fatality Rates, and Risk Ratios of Anesthesia-related Deaths during Cesarean Section Delivery by Type of Anesthesia in the United States, 1979-1984 and 1985-1990

	Number of Deaths		Case-Fatality Rate		Risk Ratio	
Population	1979-1984	1985-1990	1979-1984	1985-1990	1979-1984	1985-1990
General	33	32	20.0* (95% CI, 17.7-22.7)	32.3* (95% CI, 25.9-49.3)	2.3 (95% CI, 1.9-2.9)	16.7 (95% CI, 12.9-21.8)
Regional	19	9	8.6† (95% CI, 1.8-9.4)	1.9† (95% CI, 1.8-2.0)	Referent	Referent

CI, confidence interval.
*Per million general anesthetics for cesarean section.
†Per million regional anesthetics for cesarean section.
Adapted from Hawkins JL, Gibbs CP, Orleans M, et al: Obstetric anesthesia work force survey, 1981 versus 1992. Anesthesiology 87:135, 1997.

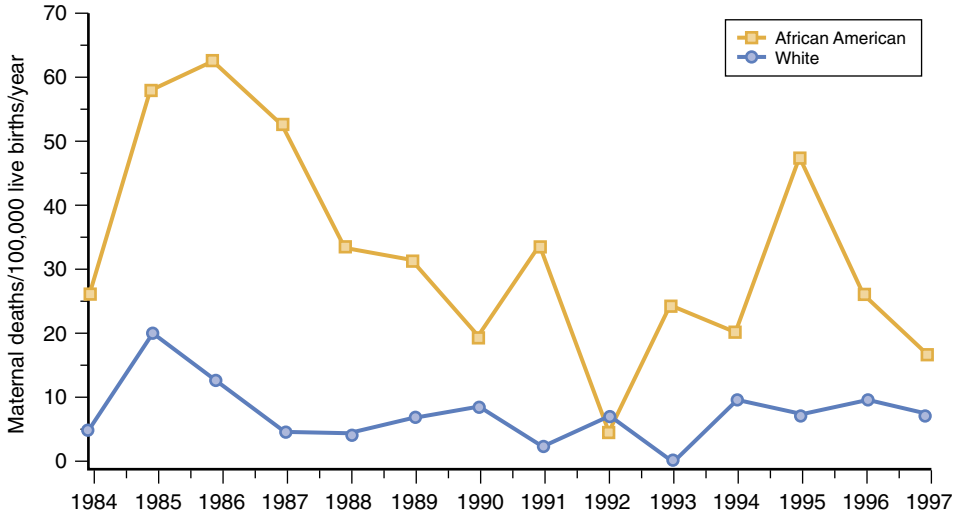

Figure 33-7 Delivery mortality ratios by race in Maryland, from 1984 to 1997, according to discharge summaries. *(From Panchal S, Arria AM, Labhsetwar SA: Maternal mortality during hospital admission for delivery: A retrospective analysis using a state-maintained database. Anesth Analg 93:134, 2001.)*

striking deficiencies in anesthesia personnel. Even for cases in which general anesthesia was provided for cesarean section, an anesthesiologist was involved in care only 44% of the time, whereas hospitals with greater than 1500 deliveries per year had an anesthesiologist present 85% of the time. The researchers did not evaluate the relationship between outcome and staffing models. The survey was performed again in 1992.[127] When compared with 1981, the researchers found a marked increase in the availability of labor analgesia and a decrease in the use of general anesthesia. In more than half of the anesthesia procedures for cesarean section, care was provided by nurse anesthetists without medical direction by an anesthesiologist. How these trends in staffing have affected maternal mortality requires further evaluation.

Mhyre and colleagues reviewed maternal mortality in Michigan between 1985 and 2003.[128] Of 855 pregnancy-associated deaths, 8 were related to anesthesia, and anesthesia was considered to be contributory in 7. All anesthesia-related deaths from airway obstruction or hypoventilation took place during emergence and recovery, not during induction of general anesthesia. Lapses in postoperative monitoring and inadequate supervision by an anesthesiologist seemed to contribute to more than half of the deaths.

Bloom and associates studied anesthesia-related morbidity and mortality as part of a prospective observational study conducted in women ($N = 37,142$) with singleton gestations undergoing cesarean delivery in the centers forming the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.[129] There was one maternal death, caused by failed intubation, in which the anesthetic procedure was directly implicated. Importantly, 93% received regional anesthesia.

Pediatrics

There are few studies of anesthesia-related risk in the pediatric population (see Chapters 81 to 84). Two themes emerge from these studies: very young infants are at increased risk, and anesthesia-related risk is reduced in centers with specialized pediatric anesthesia facilities. In the report by Beecher and Todd,[10] there was a "disproportionate number" of anesthesia-related deaths in children younger than 10 years.

Graff and colleagues[130] from the Baltimore Anesthesia Study Committee reported 335 operative deaths in the pediatric age group. Of these, 58 were thought to be primarily or partially attributable to anesthesia. The percentage of operative deaths attributable to anesthesia was relatively constant among age groups at 16.6% to 21.7%. The estimated anesthesia-associated mortality rate was 3.3 deaths per 10,000 operations for those younger than 15 years versus 0.6 for those between 15 and 24 years of age and 11.7 for those older than 64 years. More than half of the patients were categorized as ASA physical status class 1 or 2, suggesting that the majority of deaths occurred in children with good anesthesia risk. Most deaths occurred during tonsillectomy, which probably reflects the fact that tonsillectomy is the most common operation in this age group. The investigators attempted to determine the phase of the operation that was associated with highest risk. Improper management of the anesthetic accounted for approximately half of the cases. Respiratory complications (e.g., underventilation, aspiration of vomitus or blood) were apparent in 82% of the anesthesia-related deaths. The investigators suggested that female patients have a lower operative risk than male patients in all age groups.

Tiret and coauthors[131] published a study of pediatric anesthesia risk in 1988. They prospectively studied major anesthesia-related complications in pediatric patients in 440 hospitals in France between 1978 and 1982. There were 27 major complications in 40,240 cases, which included 12 cardiac arrests and 1 death. The incidence of major complications and cardiac arrest was significantly higher in infants than in older children. The rate of cardiac arrest related to anesthesia was highest in infants (19 per 10,000) and lowest in children (2.1 per 10,000). Most complications in infants involved the respiratory system and consisted predominantly of airway problems and aspiration. Older children experienced respiratory and cardiac complications, which occurred most frequently during induction and recovery.

Cohen and colleagues[132] studied 29,220 anesthesia procedures at the Winnipeg Children's Hospital. Data were collected

Table 33-16 Summary of Perioperative Events by Age Group*

	<1 Month (*n* = 361)	1-12 Months (*n* = 2544)	1-5 Years (*n* = 13,484)	6-10 Years (*n* = 7184)	11+ Years Event (*n* = 5647)
Any intraoperative event	14.96	7.31	7.10	12.22	9.69
Any recovery room event	16.61	7.23	12.20	14.88	15.23
Any postoperative event					
Minor event†	13.57	10.30	20.32	31.49	32.44
Major event‡	23.82	7.51	3.26	3.37	3.33
Any event§					
Among patients seen	48.89	25.92	37.50	50.52	51.33
Among all patients	41.55	23.47	33.16	45.04	45.78

*All figures are given as the percentage of events per total anesthetics.
†Includes nausea and vomiting, sore throat, muscle pain, headache, dental conditions, positional conditions, conditions involving extremities, eye conditions, croup, temperature, behavioral problems, thrombophlebitis, arterial line problem, awareness, and "other" problems.
‡Includes "other respiratory" conditions, cardiovascular disorders, nerve palsy, hepatic disorders, renal disorders, seizures, surgical complications, and death.
§Percentage of total anesthetics in which there was at least one event in the intraoperative, recovery room, or later postoperative period.
Adapted from Cohen MM, Cameron CB, Duncan PG: Pediatric anesthesia morbidity and mortality in the perioperative period. Anesth Analg 70:160, 1990.

from mid-1982 to 1987 and stored in a databank. Data on patients' coexisting medical conditions and postoperative follow-up were obtained within 72 hours. Complications included death, cardiac arrest, drug reactions, airway obstruction, and minor complications such as nausea and vomiting, arrhythmias, and sore throat. Neonates underwent a higher percentage of major vascular or cardiac and intra-abdominal procedures, and older children had a higher incidence of extremity procedures. Intraoperative cardiac arrest occurred most frequently in patients younger than 1 year (4 in 2901 procedures). Postoperatively, minor events such as nausea and vomiting were more common in older children, whereas respiratory events were more common in infants and younger children (Table 33-16). When compared with adult patients, children experienced different complications, which frequently extended well into the postoperative period. In a comparison of 2-year periods between 1982 and 1987, rates of intraoperative events were found to be stable, and the rate of postoperative complications decreased. The researchers suggested that identification of these problems could lead to changes in management that result in improved outcomes.

Flick and associates[132a] studied patients younger than 18 years who underwent surgery at the Mayo Clinic and experienced perioperative cardiac arrest between November 1, 1988, and June 30, 2005, A total of 92,881 anesthetics were administered during the study period, 4242 of which (5%) were for repair of congenital heart malformations. The incidence of perioperative cardiac arrest during noncardiac procedures was 2.9 per 10,000, and the incidence during cardiac procedures was 127 per 10,000. The incidence of perioperative cardiac arrest attributable to anesthesia was 0.65 per 10,000 anesthetics. The incidence of cardiac arrest and mortality was highest in neonates (0 to 30 days of life) undergoing cardiac procedures (incidence, 435 per 10,000; mortality, 389 per 10,000).

Investigators at the Children's Hospital of Boston used an established data registry that included all cardiac arrests from January 2000 through December 2005 related to surgery for congenital heart disease.[133] There were 41 cardiac arrests in 40 patients during 5213 anesthetics over the time period, for an overall frequency of 0.79%. Eleven cardiac arrests (26.8%) were classified as either likely ($n = 6$) or possibly related ($n = 5$) to anesthesia (21.1 per 10,000 anesthetics), but with no mortality; 30 were categorized as being related to the procedure.

In 1994, the Pediatric Perioperative Cardiac Arrest (POCA) Registry[134] was formed to determine the clinical factors and outcomes associated with cardiac arrest in anesthetized children. Institutions included in the registry submitted standardized data from each cardiac arrest occurring in an anesthetized child 18 years or younger. A total of 289 cardiac arrests occurred in the 63 institutions in the database during the first 4 years of the registry, 150 of which were judged to be related to anesthesia (1.4 per 10,000 anesthesia procedures), with a 26% mortality rate. Medication-related causes and cardiovascular causes of cardiac arrest were most common. Anesthesia-related cardiac arrest occurred most often in patients younger than 1 year and in patients with severe underlying disease. The goal of the registry is similar to that of the closed claims studies—to identify the causes in this unique population and thereby formulate preventive strategies.

An update from the POCA Registry was published in 2007.[135] From 1998 to 2004, 193 arrests (49%) were related to anesthesia. Medication-related arrests accounted for 18% of all arrests. Cardiovascular causes of cardiac arrest were the most common (41% of all arrests), with hypovolemia from blood loss and hyperkalemia from transfusion of stored blood being the most common identifiable cardiovascular causes (Fig. 33-8). Among respiratory causes of arrest (27%), airway obstruction from laryngospasm was the most common. Vascular injury incurred during placement of central venous catheters was the most frequent equipment-related cause of arrest. Cardiovascular and respiratory causes occurred most commonly in the surgical and postsurgical phases, respectively.

Geriatrics

Numerous studies have documented the importance of advanced age to perioperative risk (see Chapter 71). In many of the original studies on factors associated with perioperative mortality, the highest rates of death after surgery occurred in the youngest and the oldest patients. Age was implicated as one of the factors in the

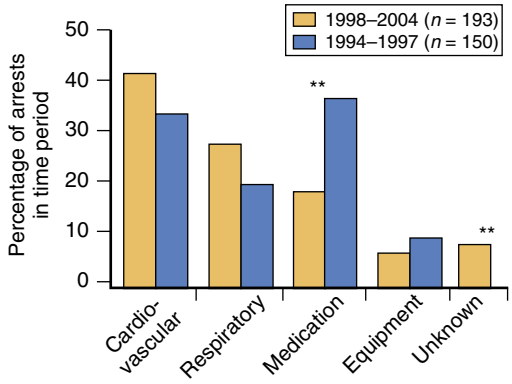

Figure 33-8 Causes of anesthesia-related cardiac arrest in in the Pediatric Perioperative Cardiac Arrest Registry from 1998 to 2004 versus 1994 to 1997. (**$P < .01$ 1998-2004 vs. 1994-1997 by Z test). *(From Bhananker SM, Ramamoorthy C, Geiduschek JM, et al: Anesthesia-related cardiac arrest in children: Update from the Pediatric Perioperative Cardiac Arrest Registry. Anesth Analg 105:344-350, 2007.)*

risk indices developed by Goldman, Detsky, and Pedersen. Age is predominantly analyzed as a dichotomous variable, with many studies focusing on age older than 70 years.

One of the issues regarding mortality rates in the geriatric population is the definition of this group. Multiple definitions have been used for advanced age, including patients older than 65, 70, 80, or 90 years. Denney and Denson[136] evaluated risk associated with surgery in patients older than 90 years. They suggested that the prevailing philosophy in 1972—that surgery might not be appropriate in this cohort in view of their high perioperative risk—was without objective supporting data. They reported 272 patients undergoing 301 operations at the University of Southern California Medical Center and found, contrary to their expectation, that the risk was more than justified in at least 70% of the nonagenarians. They reported that serious bowel obstruction was the only underlying comorbid condition associated with a prohibitive perioperative mortality rate (63%).

Djokovic and Hedley-Whyte[137] studied outcome after surgery in 500 patients older than 80 years at the Harvard University medical system. They found that mortality was predicted by ASA physical status classification, with greater comorbid conditions associated with increasing risk. Myocardial infarction was the leading cause of postoperative death. Patients without significant comorbid diseases (ASA class 1) had a mortality rate of less than 1%. The data suggest that surgery is safe in this cohort and that risk is not a function of age but of coexisting disease.

Del Guercio and Cohn[138] investigated the value of preoperative invasive monitoring in obtaining hemodynamic and cardiopulmonary variables for predicting operative risk in the elderly. A total of 148 consecutive patients older than 65 years were studied preoperatively in an ICU. Only 13.5% had normal physiologic measurements. Advanced and uncorrectable functional deficits were found in 63% of patients, and all in this group who underwent the planned operation died. This further supports the contention that coexisting disease, not age, is the risk.

An elderly patient presents a difficult issue for the anesthesiologist. Atherosclerosis increases with advancing age, and the heart muscle itself ages. Further preoperative evaluation in the elderly usually focuses on the identification of comorbid disease. Based on the accumulating evidence, these factors influence perioperative risk.

Risks Directly Related to the Anesthetic Drug

Numerous studies have evaluated the influence of the choice of anesthetic on outcome, a question that is discussed throughout this book. From a global perspective, there does not appear to be one best anesthesia technique. In a multivariate analysis by Cohen and coworkers[99] of 100,000 anesthesia procedures performed in Canada, the choice of drug did not provide any additional prognostic information for predicting mortality beyond that of patient disease and the surgical procedure. In univariate analysis, monitored anesthesia care did appear to be associated with worse outcomes, but this was attributable to its use in sicker patients (see Table 33-12).

One question that has plagued the anesthesia literature is the issue of inherent toxicity of anesthetics (see Chapter 24). There are important distinctions between undesirable side effects of anesthesia and true toxicity. In the initial reports of the mid-20th century, there was much concern about curare toxicity. Recent discussions of anesthetic toxicity have focused on halothane and sevoflurane. The issues for halothane were fulminant hepatic necrosis and death. The issue for sevoflurane was whether its metabolite compound A was nephrotoxic. After several case reports of hepatic necrosis after halothane anesthesia, a retrospective study of 856,500 anesthesia procedures at 34 institutions was undertaken.[139-141] In all but nine cases, hepatic necrosis could be explained by other causes. Of the remaining nine cases, only seven received halothane. Halothane could be associated with hepatitis and hepatic failure, but the incidence was very low.

Despite concern about the renal toxicity of sevoflurane (see Chapter 24), the overall safety of this drug has been sufficiently established for the U.S. Food and Drug Administration to allow its continued sale in the United States. Some laboratory studies have supported the contention that sevoflurane reacts with soda lime to form compound A and that this metabolite can lead to renal toxicity.[142,143] However, clinical studies have been unable to confirm this potentially detrimental effect.[144,145]

Numerous studies have attempted to define the "safest" anesthetic for high-risk patients. In the late 1980s, there was particular concern that isoflurane caused coronary steal in patients with coronary stenosis and collaterals and that this could result in myocardial ischemia.[146,147] A series of studies were conducted to evaluate the rate of perioperative cardiac morbidity and mortality in patients undergoing coronary artery bypass grafting to determine the importance of the agent used for general anesthesia.[148-151] All these studies demonstrated no difference in outcome, thus supporting the contention that there is no one safest anesthesia technique.

A series of randomized trials demonstrated improved outcome with regional rather than general anesthesia.[152] For lower extremity and pelvic surgery, regional anesthesia was associated with a lower incidence of graft thrombosis and deep venous thrombosis, as well as decreased bleeding. For vascular surgery patients, the primary finding was a lower incidence of graft thrombosis and need for reoperation in patients undergoing infrainguinal bypass surgery; however, the largest of these studies was unable to demonstrate any difference in outcome based on anesthesia technique.[4,153,154] The rate of this complication was low

in the total cohort in the largest trial, which made it impossible to detect any difference based on technique.

Rodgers and coworkers[152] published a large meta-analysis of regional versus general anesthesia. Neuraxial blockade was found to reduce postoperative mortality and other serious complications. The magnitude of some of these benefits remained uncertain. Discussion of regional versus general anesthesia is presented in Chapters 51 and 52.

Risks Related to Surgery

The surgical procedure itself significantly influences perioperative risk. In virtually every study performed, emergency surgery is associated with additional risk. For example, in the study of Goldman and colleagues,[6] emergency surgery was associated with the second highest weight (i.e., number of points) after active signs of congestive heart failure. In the same study, intrathoracic and abdominal procedures were determined to have higher risk.

In some cases, the risk related to surgery is a function of the underlying disease processes and the stress related to the surgical procedure. Cardiovascular surgery is associated with the highest risk of any procedure. The risks related to cardiac surgery are reviewed in Chapter 60. Vascular surgery is among the highest-risk group of noncardiac procedures. Although aortic reconstructive surgery has traditionally been considered the procedure with highest risk, infrainguinal procedures have shown a similar rate of cardiac morbidity in several studies.[155,156] In an attempt to analyze the cause of the high complication rate with a relatively peripheral procedure, L'Italien and associates[156] demonstrated that the extent of coronary artery disease is higher in patients undergoing infrainguinal procedures and most likely accounts for the excess morbidity and mortality.

Ashton and colleagues[157] evaluated perioperative morbidity and mortality in a cohort of patients at a Veterans hospital. Although vascular surgery was among the highest-risk procedures, amputation was associated with the highest in-hospital cardiac complication rate within this subgroup. This finding most likely represents the more severe nature of the cardiovascular disease in these patients and the prolonged hospitalization needed to facilitate recuperation. As in the study by Goldman and coworkers,[6] intra-abdominal, thoracic, and orthopedic procedures were associated with increased risk. In another report, Ashton and colleagues[158] evaluated the rate of perioperative myocardial infarction in patients undergoing transurethral resection of the prostate. Despite the high frequency of coronary artery disease in this population, the incidence of perioperative myocardial infarction was only 1%.

Numerous studies have evaluated the perioperative complication rate related to superficial procedures. Backer and associates[159] evaluated the rate of perioperative myocardial reinfarction in patients undergoing ophthalmologic surgery. They demonstrated that the rate of perioperative cardiac morbidity after ophthalmologic surgery was extremely low, even in patients with recent myocardial infarction. Virtually all studies have confirmed that ophthalmologic surgery is very safe under anesthesia.[160] Warner and colleagues[161] studied patients undergoing ambulatory surgery and reported no anesthesia-related deaths in more than 45,000 cases. A more complete discussion of the risk of anesthesia in the outpatient setting is provided earlier.

Eagle and associates[162] evaluated the contribution of coronary artery disease and its treatment to perioperative cardiac morbidity and mortality by surgical procedure. They evaluated patients enrolled in the Coronary Artery Surgery Study who had documented coronary artery disease and received medical therapy or coronary revascularization and then underwent noncardiac surgery during the subsequent 10-year period. Rates of perioperative myocardial infarction and death were determined, and the surgical procedures were divided into three broad categories. Major vascular surgery was associated with the highest risk, with a combined incidence of morbidity and mortality of greater than 5%. Procedures associated with a combined complication rate of 1% to 5% included intra-abdominal, thoracic, and head and neck operations. In all these cases, patients who had previously undergone coronary artery bypass grafting had a significantly lower combined morbidity and mortality rate than did those in the medically treated group. Low-risk procedures included breast, skin, urologic, and orthopedic surgery. These broad groups of surgical procedures were the basis for the definitions of surgical risk published in the guidelines on perioperative cardiovascular evaluation for noncardiac surgery by the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures.[163]

Risks Related to the Location of Surgery and Postoperative Monitoring

Perioperative risk varies among hospitals for major procedures such as coronary artery bypass grafting and abdominal aortic aneurysm repair (see Chapters 60 and 62).[164,165] Multiple studies have documented a relationship between surgical volume and mortality. Although surgical skill most certainly plays a role in the rate of complications and mortality, local factors may also play an important role. For example, low surgical volume may lead to less skilled anesthesia and postoperative care. The influence of each of these factors on overall morbidity and mortality is unknown.

Although the value of postoperative monitoring and care in an ICU has never been documented in a randomized clinical trial, many investigators have suggested that such care is one of the primary reasons for the improved morbidity and mortality in recent years. For patients undergoing major vascular surgery, several investigators have suggested that more intense postoperative monitoring could obviate the need for preoperative cardiac testing and revascularization.[163] One potential value of risk assessment is identification of patients who could benefit from referral to centers with more extensive perioperative resources. Patients with a low probability of perioperative morbidity and mortality could have surgery performed locally, and individuals at higher risk could receive benefit from transfer to a larger center.

Risks Related to the Anesthesia Provider

The added risk associated with the provider of anesthesia is an emotionally charged issue, particularly in the United States. Over the history of the specialty, various individuals have provided anesthesia, including anesthesiologists, general medical officers, residents, and CRNAs.

The importance of the anesthesiologist to outcome is best illustrated by the work of Slogoff and Keats.[166] They studied the association of perioperative myocardial ischemia and cardiac morbidity in patients undergoing coronary artery bypass grafting and found that perioperative myocardial infarction occurred significantly more frequently in patients with ischemia before the bypass operation. They then reported the rate of ischemia and infarction by anesthesiologist (identified by number). Anesthesiologist no. 7 had a significantly higher rate of complications than the average for the rest of the group. Operator technique or experience may affect risk. This observation parallels similar findings that surgical volume (and presumably experience) is associated with outcome.[167]

Arbous and coauthors reported a case-control study of major morbidity (coma) and mortality affecting a total of 869,463 procedures over a 1-year period in the Netherlands.[168] Eight hundred seven cases of coma or death within 24 hours of anesthesia were identified and matched by age and sex to randomly selected controls who underwent anesthesia temporally in close proximity to the matched case. The Hospital Characteristics Questionnaire, Procedure Questionnaire, and anesthesia and recovery records were used to examine the intraoperative and postoperative characteristics of cases and controls. Anesthesia practice in the Netherlands is described as a "flexible" system with one-on-one anesthesiologist coverage of induction and emergence, assisted by a nurse anesthetist or resident, and a two-on-one system during maintenance anesthesia, with a nurse or resident present in the room and an anesthesiologist in the vicinity. The authors elected to use multivariate analysis on data sets rather than match cases and controls for anesthesia/physical risk categories or the type of surgical procedure (or both).

Included in analysis were 807 cases and 883 controls. Cases and controls, however, were not comparable for ASA classification, and controls were more likely than cases to have undergone minor elective procedures during regular working hours. Cases more frequently underwent cardiac and major vascular procedures, and controls more often underwent orthopedic, urologic, and ophthalmologic procedures. Of 807 cases, 95% died within 24 hours, and 5% remained comatose, all of whom eventually died in the hospital. Postoperative mortality was 8.8% per 10,000 anesthetics, and postoperative coma occurred in 0.5% of 10,000 anesthetics. Confounding factors were, expectedly, ASA status, type of procedure, anesthetic technique, and hospital. Independent variables that were associated with decreased risk for coma and death in 24 hours were (1) anesthesia equipment check performed with a checklist (OR, 0.61); (2) direct availability of an anesthesiologist during maintenance anesthesia by phone, beeper, or walkie-talkie (OR, 0.46); (3) no change of anesthesiologist during the case (OR, 0.46); (4) presence of a full-time nurse anesthetist versus part-time anesthetist during maintenance anesthesia (OR, 0.41); (5) presence of two persons (anesthesiologist plus resident or nurse anesthetist) versus one person during emergence (OR, 0.69); (6) reversal of muscle relaxant (OR, 0.1); and (7) reversal of muscle relaxant and opioids (OR, 0.29).

This study is one of very few to attempt to identify practice characteristics rather than specific drugs or techniques that have an impact on anesthesia outcomes. The size of this study and the nonambiguity of outcomes followed are important characteristics. The study suffers from several significant problems, however. Study groups were not comparable in very important ways. The estimated incidence of underreporting of coma and death was 13% to 47%, and selective underreporting could have occurred. The finding that a change of anesthesiologist during maintenance anesthesia adversely affected patient outcomes contradicts findings in previous studies and requires further explanation. Confounding variables associated with a change of anesthesiologist during maintenance anesthesia could include case length and the time of day in which cases are performed. An intriguing finding is that practitioner characteristics affect outcomes (better outcomes with more availability of an anesthesiologist and better outcomes when nurse anesthetists practice full-time rather than part-time), and this finding warrants further follow-up.

Several studies have attempted to evaluate the complication rates and risks associated with various care provider models. Bechtoldt,[169] as a member of the North Carolina Anesthesia Study Committee, evaluated 900 perioperative deaths that occurred in an estimated 2 million anesthesia procedures performed in North Carolina between 1969 and 1976. Data were obtained from the medical examiner's report, routine death certificates, and a questionnaire completed by the person who administered the anesthetic. The committee concluded that 90 of these deaths were related to anesthesia. About half of the anesthesia-related deaths took place in the operating room, including 19 that occurred on induction. With information attained from a survey of hospitals, they then determined the relationship between mortality and anesthesia provider based on the total number of procedures administered by each group. The lowest rate of anesthesia-related deaths (1 per 28,166 procedures) occurred in patients who received anesthesia from an anesthesia care team (physician anesthesiologist and CRNA), and the highest rate (1 per 11,432 procedures) was associated with anesthesia administered by a dentist (1 per 11,432); the rate for the nurse anesthetist–only cohort was intermediate (1 per 20,723). The large number of cases in which the care provider was unknown and reliance on hospital estimates of the number of cases performed by each group made interpretation of this study difficult.

The Stanford Center for Health Care Research[170] also evaluated the impact of provider on outcome of care. They prospectively collected data from 8593 patients undergoing 15 surgical procedures over a 10-month period (May 1973 through February 1974). Using a risk adjustment methodology, the actual patient outcome was compared with that predicted by the patient's health status and operative procedure. The investigators reported that death plus severe morbidity was 11% higher than predicted in patients who received their care in a nurse anesthetist–only setting, 3% lower than predicted for physician-only care, and 20% lower than predicted for an anesthesia care team environment. Because of the small sample size, these findings did not reach statistical significance between groups.

The differences in outcome among anesthesia providers are extremely difficult to study from a methodologic standpoint. The impact of specific provider types may be greatest in specific situ-

ations. For example, there may be no difference in outcome for healthy individuals, particularly if no complications occur. In contrast, patients with significant comorbid diseases and those who sustain perioperative complications may benefit from having providers with specific skill sets. One way to study such issues is to evaluate the rate of survival after complications. Silber and colleagues[26] at the University of Pennsylvania studied the medical records of 5972 surgical patients randomly selected from 531 hospitals. They evaluated patient and hospital characteristics, including the number and type of physicians, board certification status, and ratio of care providers. The 30-day mortality rate correlated with patient characteristics. Failure to rescue (i.e., prevent death) after an adverse event was inversely associated with the proportion of board-certified anesthesiologists on staff in each facility. Improved perioperative survival was significantly associated with the presence of an increased number of board-certified anesthesiologists.

As a follow-up to this study, Silber and colleagues[171] used an administrative data set to compare the outcomes of surgical patients for whom anesthesia care was or was not personally performed or medically directed by an anesthesiologist. They analyzed all elderly patients in Pennsylvania who underwent general surgical or orthopedic procedures between 1991 and 1994. The 30-day mortality rate and the mortality rate after complications (i.e., failure to rescue) were lower when anesthesiologists directed anesthesia care, even after adjustment for patient and hospital characteristics. Interpretation of the study was limited because the undirected group was small and included a large percentage of procedures in which there was no bill submitted for anesthesia services, thus questioning the validity of the classification. Administrative data sets, such as Medicare claims, allow the investigator to study a large number of patients, but there are significant limitations related to the robustness of the data and potential uncontrolled confounding factors. Therefore, most investigators suggest that such studies are best at generating hypotheses rather than defining best practices.[172]

Silber and colleagues[173] used similar methodology to determine the importance of board certification on perioperative risk. Adjusted ORs for death (1.13; 95% CI, 1.00 to 1.26; $P < .04$) and for failure to rescue (1.13; 95% CI, 1.01 to 1.27; $P < .04$) were greater when care was delivered by noncertified, midcareer anesthesiologists.

Pine and coworkers evaluated mortality after eight specific surgical procedures.[174] Procedure-specific risk adjustment models (including institutional and geographic factors) were derived by stepwise logistic regression. Observed and predicted values by type of provider were not statistically significantly different. Hospitals without anesthesiologists had results similar to those where anesthesiologists provided or directed anesthesia care. The authors did not evaluate failure to rescue or cause of mortality.

Smith and associates[175] performed a systematic review of the available published studies through 2004 on the influence of anesthesia providers. They identified four studies, two smaller observational studies and the two previously described studies using administrative data sets. They concluded that all of the studies had potential confounding factors that limited the validity of the results and that the paucity of high-level primary evidence made it impossible to draw a conclusion regarding differences in patient safety as a function of provider type. Therefore, the relationship of patient outcomes to the type of anesthesia provider has not been conclusively demonstrated. Nurse anesthetists and other nonphysician providers are vital to the delivery of anesthesia care in the United States and elsewhere, and differences, if present, are small or restricted to specific situations.

Risks to the Anesthesiologist

Several potential risks to the anesthesiologist are related to the provision of care (see Chapter 101), including medicolegal risk, the risk of an allergic reaction, and the risk of a needlestick injury and transmission of disease from the patient to the practitioner. Medicolegal risks are described in Chapter 10.

It is increasingly becoming apparent that anesthesiologists are at risk for latex allergy, which can lead to a life-threatening reaction. Many anesthesiologists realize that they are sensitized to latex and apply appropriate precautions. The problem is that many sensitized individuals are asymptomatic. Brown and coworkers[176] studied 168 eligible anesthesiologists and nurse anesthetists working in the anesthesia department of The Johns Hopkins Hospital. The prevalence of latex allergy with clinical symptoms was 2.4% and that of latex sensitization without clinical symptoms was 10.1%. The prevalence of irritant or contact dermatitis was 24%. These data suggest that latex is an important problem to the anesthesiologist and that there is a need to transform the hospital to a latex-free environment.

There has always been concern that anesthesiologists are at risk for contracting a disease from a patient. In the past the risk was primarily hepatitis, but human immunodeficiency virus (HIV) is a greater concern today. In a review of the literature, Berry and Greene[177] reported that at least 20 different pathogens have been transmitted through accidental needlestick injuries.

Among anesthesia personnel in several studies conducted in the United States, hepatitis B seropositivity ranged from 12.7% to 48.6%, a rate at least four times greater than that in the general population.[178-180] The risk of hepatitis B infection after percutaneous exposure to antigen-positive blood is estimated to be 27% to 43%.[181] Development of the hepatitis B vaccine has substantially reduced this risk. Hepatitis C virus has been identified as a major cause of post-transfusion hepatitis. There have been several reports of occupationally acquired hepatitis in health care workers.[182] Because signs of chronic liver infection develop in up to 50% of infected individuals, this represents a potentially serious problem.

Among the greatest fears of health care workers is HIV infection. The risk of acquiring HIV is approximately 0.4% from a single percutaneous exposure to blood or bloody fluid from an HIV-infected patient.[183] There has been at least one case report of an anesthesiologist who was infected with HIV from a needlestick injury during insertion of a central venous catheter into an HIV-positive patient.[184]

Several strategies have been developed to reduce the transmission of communicable diseases (see Chapter 101). Although anesthesiologists traditionally think of the risk to the patient, they must now include the risk to themselves. Widespread adoption of universal precautions should reduce the rate of infection; however, anesthesiologists have not accepted these recommendations widely. In a study of nine hospitals, 59% of the contaminated percutaneous injuries were preventable.[185] In a theoretical model of the risk for HIV infection, it was estimated that the 30-year occupational risk was 0.10% to 0.22% in low-prevalence areas and

8.26% to 13% in high-prevalence areas.[186] The researchers suggested that double-gloving practices may lead to reduced risk.

Improving Anesthesia Safety

Over the past several decades there have been major initiatives to improve the safety of anesthesia. In 1984, Cooper, Kitz, and Ellison hosted the first International Symposium on Preventable Anesthesia Mortality and Morbidity in Boston. Approximately 50 anesthesiologists from around the world attended the meeting and, after much debate, established a series of definitions of outcome, morbidity, and mortality (Box 33-1). These meetings have been held every 2 years since the first symposium. The Anesthesia Patient Safety Foundation was established as a result of the Boston meeting. The society has been active in publishing widely circulated newsletters and awarding annual grants. Similar societies have been established in countries outside the United States, and a National Patient Safety Foundation has been created on the same model.

Starting with the ACCS, there has been much interest in establishing guidelines for the best and safest practice. Practice policies or guidelines are summations by clinicians of the available evidence about the benefits and risks of particular treatment plans. Guidelines are a method of codifying recommendations regarding the use of a given technology. Several types of recommendations fall into the general category of a practice parameter. A standard implies that a therapy or practice should be performed for patients with a particular condition. Standards are approved only if an assessment of the probabilities and utilities of the group indicate that the decision to choose the treatment or a strategy would be virtually unanimous. If a particular therapy or strategy is considered a standard, it is a cost-effective measure for those for whom it is being recommended. Standards are intended to be applied rigidly. The ASA has established standards for intraoperative monitoring, which were developed from safety guidelines adopted by the Harvard University hospital system. Guidelines are intended to be more flexible than standards, but they should be followed in most cases. Depending on the patient, the setting, and other factors, guidelines can and should be tailored to fit individual needs. Like standards, guidelines should be cost-effective methods. A number of specific guidelines have been adopted by the ASA for diverse issues such as a difficult airway,[187] use of the pulmonary artery catheter,[188] and use of blood components.[189] The goal is to define the evidence on which optimal practice can be based.

There is much interest in the use of anesthesia simulators to train and test individuals and their ability to react to simulated crises.[190-194] Standardized scenarios have been developed for making comparisons among individuals. Further research is required to determine how best to use this technology in anesthesia training and recertification. Further discussion of this topic can be found in Chapters 5, 6, and 7.

Box 33-1 Proposed Definitions from the 1994 International Symposium on Preventable Anesthesia Morbidity and Mortality

- Outcome
  - Normal
  - Abandoned procedure
  - Morbidity
  - Death
- Morbidity
  - An unplanned, unwanted, undesirable consequence of anesthesia
- Mortality
  - Death that occurs before recovery from the effects of a drug or drugs given to facilitate a procedure
  - Death that occurs during an attempt to relieve the pain of a condition
  - Death that results from an incident that occurs while the drugs are effective

Adapted from Pierce EC Jr: The 34th Rovenstine Lecture: 40 years behind the mask: Safety revisited. Anesthesiology 84:965, 1996.

Future Directions in Perioperative Risk

The impact of genetics on perioperative risk has been well known since elucidation of the inheritance pattern of malignant hyperthermia. With malignant hyperthermia, there is a clear link between the autosomal dominant disease and an adverse outcome after administration of an anesthetic.[195] Interest in evaluating the impact of genetic polymorphism on overall perioperative outcome is increasing, even if the link to anesthesia is less well defined. For example, apolipoprotein E_4 has been shown to modulate neurologic injury and recovery after a variety of acute ischemic insults, including coronary artery bypass grafting.[196] Polymorphism of the glycoprotein IIIa constituent of the platelet integrin receptor has also been correlated with postoperative cognitive decline.

Summary

The risks related to anesthesia have dramatically decreased over the past several decades. It is clear that death totally attributable to anesthesia is rare. Patient disease and the type and perhaps the location of surgical procedures have a greater effect on overall outcome. With these changes in risk, the anesthesiologist must now focus on nonmorbid outcomes, and there must be continued vigilance to maintain the high standards of hospital-based anesthesia in nonhospital settings. Finally, anesthesiologists should play a role in systems-based thinking to improve all aspects of care.

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34 Preoperative Evaluation

Key Points

1. The anesthesia preoperative evaluation is the clinical foundation and framework of perioperative patient management and can potentially reduce operative morbidity and enhance patient outcomes.
2. The fundamental purpose of preoperative evaluation is to obtain pertinent information regarding the patient's current and past medical history and to formulate an assessment of the patient's intraoperative risk and requisite clinical optimization.
3. Basic and complex medical diseases and syndromes that can potentially affect anesthesia perioperative management require the anesthesiologist to be clinically knowledgeable and current in many aspects of internal medicine.
4. Patients require preoperative diagnostic and laboratory studies that are consistent with their medical history, the proposed surgical procedure, and the potential for intraoperative blood loss. Routine preoperative testing cannot be justified and is costly and clinically inappropriate.
5. Preoperative patient education and individual discussion can significantly reduce patient anxiety and fears of the perioperative anesthesia process.
6. Under the clinical directorship of an anesthesiologist, the anesthesia preoperative evaluation clinic can enhance operating room efficiency, decrease day-of-surgery cancellations and delays, reduce hospital costs, and enhance the quality of patient care.
7. New and updated preoperative evaluation consensus and evidence-based guidelines published by multiple medical specialties have led to evaluation protocols for preparing patients for anesthesia and surgery.
8. Increasing regulatory and reporting requirements involving preoperative issues by agencies such as the Joint Commission on Accreditation of Healthcare Organizations require awareness and compliance by anesthesiologists.
9. Information technology and decision support systems in preoperative evaluation can enhance the quality of patient care and clinical management through electronic integration and standardization of patient data.
10. The anesthesiologist is the perioperative medical specialist and the only preoperative evaluation physician who can truly evaluate the risks associated with anesthesia, discuss these risks with the patient, and manage them intraoperatively.

Virtually every practicing anesthesiologist has experienced and contributed to the evolution of anesthesia's involvement in perioperative care. Furthermore, the rapid transformation from admission of the patient to the hospital the night before surgery to the morning of surgery has necessitated that preoperative evaluation be conducted in a different manner. Although the historical basic concept of preoperative evaluation and an anesthesia clinic is not new to anesthesia, what has occurred in this specialty is unique, remarkable, and revolutionary. Many anesthesiologists have essentially taken back from multiple medical specialties the primary responsibility, coordination, and recognition for assessment and optimization of preoperative risk in patients being prepared for surgery.

Some anesthesiologists have evolved into perioperative medical specialists by demonstrating their unique qualification of focused knowledge and experience to evaluate and successfully manage medical complexities related to anesthesia and surgery.[1,2] Anesthesia care is no longer limited to the operating room. Many departments of anesthesiology have even changed their official departmental titles to include anesthesia and "perioperative care."

This chapter on preoperative evaluation is intended to provide the reader with a comprehensive discussion of the basics and fundamental practice of preoperative assessment, as well as provide a review of new concepts, regulatory requirements, consensus guidelines, medical-legal responsibilities, and clinical options.

The Evolution in Preoperative Evaluation

Preoperative evaluation of a surgical patient for anesthesia increases the practitioner's awareness of the patient's medical condition and becomes the foundation of the individual patient's perioperative management plan. The fundamental purpose in preoperative evaluation is to obtain pertinent information regarding the patient's current and past medical history and to formulate an assessment of the patient's intraoperative risk.

Anesthesiologists preoperatively perform focused clinical examinations, develop a plan of medical intervention and optimization, reduce the patient's (and family's) anxiety and fears through education, discuss perioperative care and options for postoperative pain control, determine the appropriate laboratory tests and diagnostic studies to perform, discuss anesthesia risks, and obtain informed consent. The anesthesia preoperative evaluation can decrease surgical morbidity, minimize expensive delays and cancellations on the day of surgery, and increase perioperative efficiency. The practice of preoperative evaluation for anesthesia has changed. Fewer patients are admitted to the hospital before surgery unless their medical condition is unstable and requires optimization. Currently, approximately 80% of surgeries in the United States are performed on an outpatient or same-day admission basis, even including major neurosurgical, cardiac, and radical cancer procedures. The previous process of admitting the majority of patients to the hospital at least the day before is no longer financially supported or justified.

Although patients are still assessed for the first time by the anesthesiologist just before surgery, the trend toward preparing and evaluating patients in a preoperative program or "clinic" before the surgical date has increased. This has been especially important in patients with multiple medical risks and comorbid conditions. In other settings, the preoperative evaluation is completed for many patients by the surgeon (or designee) or primary care physician, and only patients at highest risk are referred for consultation by an anesthesiologist. In such circumstances, the anesthesia department must interact with the surgical departments to establish general protocols for acquiring the information needed to safely perform anesthesia or there could be a potential for an increased incidence of delays or cancellations at the time of surgery to obtain additional information or evaluation.

A change in the procedure and manner of preoperative evaluation requires the anesthesiologist to achieve a high level of efficiency and accuracy in assessment of the patient's history, physical examination, differential diagnosis, and planning of management. It presents the anesthesiologist with a formidable challenge from both an organizational and a clinical perspective because of a decreased amount of time available to evaluate often medically complex patients. Providing consistent quality and cost-effective preoperative preparation of patients is an important issue in perioperative patient management.

Both The Joint Commission (TJC) and the American Society of Anesthesiologists (ASA) have developed standards and requirements for preoperative anesthesia evaluation.[3] Recent and updated preoperative evaluation guidelines published by multiple medical specialties have led to protocols for evaluation in preparing patients for anesthesia and surgery. Several of the current practice guidelines challenge the historical manner of practicing anesthesia.

These guidelines require objective review, reasonable consideration, and possibly changes in the manner of customary anesthesia practice.[4] For example, the routine "nothing by mouth" (NPO) after midnight or 6 hours before surgery has been redefined by the ASA Task Force on Preoperative Fasting.[5] The American College of Cardiologists/American Heart Association (ACC/AHA) preoperative evaluation guidelines, recently updated in 2007, recommend proceeding with elective surgery in certain patients who have experienced a myocardial infarction (MI) in terms of weeks rather than months. Both these and other changes and challenges in anesthesia practice are reviewed and the implications discussed in this chapter.

If anesthesia and surgery were not associated with perioperative risk or adverse patient outcome, anesthesia preoperative evaluation and management would not be required. Although the incidence of patient morbidity and mortality has decreased in the past decades, many patients still have an abundance of fear and anxiety regarding anesthesia risk. We begin this preoperative chapter with a current review and identification of the concepts, evaluation, and goals in assessment of patient risk.

Preoperative Risk Assessment

The current ASA risk classification system was developed in 1941 by Meyer Saklad at the request of the ASA (Table 34-1). This classification was the first attempt to quantify the risk associated with anesthesia and surgery. Neither the type of anesthesia nor the location of the procedure or operation was considered in the development or as components of this risk classification. The system attempts to give a subjective and relative risk based only on the patient's preoperative medical history (i.e., no consideration of diagnostic studies). ASA physical status (ASA-PS) 2

Table 34-1 American Society of Anesthesiologists Physical Status Classification

ASA 1	Healthy patient without organic, biochemical, or psychiatric disease
ASA 2	A patient with mild systemic disease, e.g., mild asthma or well-controlled hypertension. No significant impact on daily activity. Unlikely to have an impact on anesthesia and surgery
ASA 3	Significant or severe systemic disease that limits normal activity, e.g., renal failure on dialysis or class 2 congestive heart failure. Significant impact on daily activity. Probable impact on anesthesia and surgery
ASA 4	Severe disease that is a constant threat to life or requires intensive therapy, e.g., acute myocardial infarction, respiratory failure requiring mechanical ventilation. Serious limitation of daily activity. Major impact on anesthesia and surgery
ASA 5	Moribund patient who is equally likely to die in the next 24 hours with or without surgery
ASA 6	Brain-dead organ donor

"E" added to the classification indicates emergency surgery.
Available from www.asahq.org.

patients are at higher risk than ASA-PS 1 patients, but only if undergoing the *same* operation. Most importantly, there is no attempt to *quantify* the risk, which hampers the ability to use this risk assessment tool for communicating meaningful expectations to patients and other caregivers.

Despite these limitations, some studies have corroborated an association of mortality and morbidity with ASA-PS scores. Studies have also shown a correlation between ASA-PS and unanticipated intensive care unit admissions, longer hospital stays for some procedures, and adverse cardiopulmonary outcomes. No correlation has been shown between ASA-PS class and cancellations, cost, unplanned admissions, and other perioperative complications, and traditionally, surgical risk has been considered more important than anesthetic risk. However, few studies have evaluated the effect of combining the risk inherent in the surgical procedure and the ASA-PS score. Among the first was the Johns Hopkins Risk Classification System, but this system focuses only on surgical risk. As surgery has evolved with innovations in minimally invasive and endoscopic techniques, a general anesthetic requiring instrumentation of the airway with associated significant physiologic perturbations may pose a significant and greater risk than the surgery itself to some extremely fragile individuals.

Even the location of the procedure may alter the risk. A study of ambulatory surgery in Medicare beneficiaries older than 65 years found no deaths on the day of surgery when the procedure was performed in a physician's office; 2.3 deaths per 100,000 performed in a freestanding ambulatory surgical center; and 2.5 deaths per 100,000 performed at an outpatient hospital. The 7-day mortality was 35 per 100,000, 25 per 100,000, and 50 per 100,000, respectively. Age older than 85 years, significant comorbidity, and the type of procedure predicted adverse events.[6]

Other specialties have developed risk assessment tools for patients undergoing anesthesia and surgery. One of the first was Goldman, who further advanced risk assessment by identifying risk factors and cardiac complications in patients undergoing noncardiac surgery. Several studies followed, culminating in one of the most widely used guidelines for assessment of the common, significant perioperative complication of cardiac morbidity and mortality associated with noncardiac surgery. The joint ACC/AHA guideline was first published in 1996 and updated in 2007.[7] This guideline combines patient and surgical risk but is specific only for cardiac complications. There is no comprehensive risk assessment tool available at the time of this writing.

The concept of risk associated with anesthesia (see Chapter 33) is unique in that rarely does the anesthetic itself offer benefit but merely allows others to do things that potentially offer benefit. The goals in assessing risk are to inform patients so that they can weigh their options and to identify opportunities to alter that risk. Analysis of the Australian Incident Monitoring Study (AIMS) database showed that 11.6% of reports identified inadequate or incorrect preoperative *assessment* (478 of 6271) or preoperative *preparation* (248/6271).[8] Of adverse events, 3.1% (197) were indisputably related to inadequate or incorrect preoperative assessment or preparation. Of these 197 patients, major morbidity occurred in 23, and 7 patients died. The investigators concluded that patient factors contributed only 1% of the time. More than half of the incidents were preventable; an additional 21% were possibly preventable. Unpreventable events accounted for just 5% of cases. Almost a quarter of the time, communication failure was cited as the most significant factor. Analysis of the first 2000 reports submitted to AIMS found a sixfold increase in mortality in patients who were inadequately assessed preoperatively.[9] In a different study of anesthetic-related perioperative deaths, 53 of 135 deaths involved inadequate preoperative assessment and management.

Many anesthesiologists perform preoperative evaluations, review diagnostic studies (chosen and ordered by someone else), discuss anesthetic risks, and obtain informed consent moments before patients undergo major, potentially life-threatening or disfiguring procedures. This choice offers little opportunity to optimize comorbid conditions or alter risk. The effects of extensive disclosure are stressful for patients and families at a time when they may be ill prepared to consider the implications rationally. An increase in preoperative anxiety probably affects postoperative outcomes because increased anxiety correlates with increased postoperative analgesic requirements and prolonged recovery and hospital stay. Anxiety impairs retention of information, with attendant medicolegal implications because of inadequate communication or discussion of the risks associated with anesthesia.

Some assessment of risk is important to prepare for anesthesia and the surgical procedure. Patients have a right to be informed during the consent process of possible complications and, if possible, be given some estimate of the chance of complications occurring. Identified modifiable risk factors such as poorly controlled hypertension or unstable ischemic heart disease should be addressed. Risk assessment is useful to compare outcomes, control costs, allocate compensation, postpone surgery until interventions improve risk, or assist in the difficult decision of canceling or recommending that a procedure not be done when the risks are too high. The need for special techniques, postoperative care in the intensive care unit, and special monitoring must be considered and planned for. Yet risk assessment, at its best, is hampered by individual patient variability.

Detecting Disease in Preoperative Evaluation

Several studies have proved the utility of the history and physical examination in determining diagnoses. A study of general medical clinic patients found that 56% of correct diagnoses were made with the history alone, which increased to 73% with the addition of physical examination. In patients with cardiovascular disease, the history establishes the diagnosis two thirds of the time, and physical examination contributes to a quarter of diagnoses. Diagnostic tests such as chest radiographs and electrocardiograms (ECGs) helped with only 3% of diagnoses, and special tests (e.g., exercise ECG) assisted with 6%. In patients with respiratory, urinary, and neurologic conditions, the history has also been shown to be the most important diagnostic method. The skill of performing a clinical examination derives from pattern recognition learned by listening to and seeing patients and assimilating the stories and outcomes of their illnesses. The diagnostic acumen of the physician is a result of the ability to integrate and develop an overall impression rather than just reviewing a compilation of facts.

Importance of the Preoperative Medical History

The variability of the medical history and the words that both patients and physicians use to describe symptoms is a common problem. Using lay language and recording symptoms in ordinary words leads to greater interobserver agreement between practitioners and can lessen communication errors, which are common obstacles in medical care. Common errors occur when diagnostic labels such as "angina" are written in the record when the patient actually complained of "chest pain." Conversely, true angina or cardiac ischemia/infarction is rarely described by a patient as chest *pain*. More likely, the patient will have complaints of tightness or squeezing, often in the upper part of the abdomen, shoulder, or neck. Therefore, medical interviewers should not be surprised that patients may deny ever having chest *pain* if this is the only noun used when inquiring about symptoms to elicit a history, thus missing a history of angina. Obtaining the patient's history is not simply asking questions but asking the right questions, frequently in a variety of ways, and interpreting and carefully recording the answers. Complete and thorough histories assist in planning appropriate and safe anesthesia care and are more accurate and cost-effective in establishing diagnoses than screening laboratory tests are.

Components of the Preoperative Medical History

The important components of the anesthesia history are shown in Figure 34-1. The form can be completed by the patient in person (paper or electronic version), via Web-based programs, through a telephone interview, or by anesthesia staff.

The classic "history of present illness, or HPI," as it relates to evaluation for anesthesia starts with the reason that the patient is having surgery and the planned procedure. Often one needs to inquire further about how the surgical condition developed and any previous therapies related to this problem. Current and past medical problems, previous surgeries and types of anesthesia, and any anesthesia-related complications need to be noted. Rarely is simply a notation of diseases or symptoms such as hypertension, diabetes mellitus, coronary artery disease (CAD), shortness of breath, or chest pain sufficient. Equally important in identifying the presence of a disease is to establish the severity, current or recent exacerbations, the stability, and previous treatment of the condition or planned interventions. The extent, degree of control, and activity-limiting nature of the problems are equally important. The patient's medical problems, previous surgeries, and response to questions will elicit further inquiry to establish a complete history.

Prescription and over-the-counter medications, including supplements and herbals, should be carefully recorded, along with dosages and schedules. Any recent but currently interrupted medications should be included because this may lead to recognition of important issues. It is necessary to inquire about allergies to drugs and substances such as latex or radiographic dye, with special emphasis on the specifics of the patient's response to the exposure. Frequently, patients claim an allergy to a substance when in reality the reaction was a common, expected side effect (e.g., nausea or vomiting with narcotics). Use of tobacco, alcohol, or illicit drugs should be documented. Quantitatively documenting tobacco exposure by pack-years (number of packs of cigarettes smoked per day times the number of years of smoking) is best. For example, if one has smoked two packs of cigarettes daily for the last 10 years, this is recorded as 20 pack/years of tobacco use.

A history of malignant hyperthermia (MH) or a suggestion of it (hyperthermia or rigidity during anesthesia) in either a patient or family member should be clearly documented to allow appropriate arrangements to be made before the day of surgery. A personal or family history of pseudocholinesterase deficiency should be identified preoperatively. Records from previous anesthesia may clarify an uncertain history.

A screening review of systems is especially useful to uncover symptoms that may lead to the establishment of previously undiagnosed conditions. During the review of systems for anesthesia purposes, special emphasis needs to be placed on airway abnormalities; a personal or family history of adverse events related to anesthesia; and cardiovascular, pulmonary, hepatic, renal, endocrine, or neurologic symptoms. Questioning the patient about snoring and daytime somnolence may suggest undiagnosed sleep apnea, which has implications for anesthesia management (see the section "Preoperative Evaluation of Patients with Obstructive Sleep Apnea" and Chapter 64). The presence of any two of the following increases the chance that a patient has sleep apnea:

- Snoring
- Daytime sleepiness
- Hypertension
- Obesity

A significant history of heartburn, especially with associated reflux or after a period of fasting comparable to what will occur preoperatively, is important. Women of childbearing age need to be prompted to recall their last normal menstrual period and their likelihood of being pregnant. This history is more reliable if the woman, especially if a minor child, is questioned in privacy.

Determination of the patient's cardiorespiratory fitness or functional capacity is useful in guiding additional preanesthetic evaluation and predicting outcome and perioperative complications.[7,10] Exercise or work activity can be quantified in metabolic equivalents of the task (METs), which refers to a measure of the volume of oxygen consumed during an activity (Table 34-2). One's ability to exercise is two-pronged in that better fitness decreases mortality through improved lipid and glucose profiles and reductions in blood pressure (BP) and obesity. Lack of exercise increases the risk for development of cardiac disease. Conversely, an inability to exercise may be the result of cardiopulmonary disease. Patients with peripheral vascular disease (PVD) will be limited by claudication, and those with ischemic heart disease may complain of shortness of breath or chest discomfort with exertion. Patients may not volunteer this information until asked why they cannot walk more than a certain distance or climb stairs. Several studies have shown that inability to perform average levels of exercise (4 to 5 METs) identifies patients at risk for perioperative complications (see Table 34-2).[7]

One should inquire about chest discomfort (pain, pressure, tightness), duration of the discomfort, precipitating factors, associated symptoms, and methods of relief. One should note diagnoses, diagnostic tests, therapies, and names of treating physicians.

Shortness of breath with exertion or when lying flat (orthopnea) or peripheral edema is important to note. Patients are asked about a history of heart murmurs and what diagnostic studies have been performed to evaluate a murmur. The cardinal symptoms of severe aortic stenosis are angina, heart failure, and syncope, although patients are much more likely to complain of a decrease in exercise tolerance and exertional dyspnea.

A general examination of all organ systems needs to be performed. For example, asking patients whether they have ever had problems with their heart, lungs, kidneys, liver, or nervous system, whether they have had cancer, anemia, or bleeding problems, or whether thay have ever been hospitalized for any reason will often prompt recall of medical problems. Similarly, obtaining a complete listing of previous surgeries can help complete the medical history. Finally, a review of records from primary care physicians, specialists, or the hospital can reveal issues that the patient may not recall.

The Preoperative Physical Examination

At a minimum, the preanesthetic examination should include vital signs (e.g., BP, heart rate [HR], respiratory rate, oxygen saturation), height, and weight. Body mass index (BMI) is calculated from height and weight and is more accurate than weight in establishing obesity. Online BMI calculators can be found at

Patient's name_____Age_____Sex_____Date of surgery_____

Planned operation _____Surgeon_____

Primary care doctor/phone #_____ Other physicians/phone #s_____

1. Please list **all operations** (and approximate dates)

a. _____ d. _____

b. _____ e. _____

c. _____ f. _____

2. Please list any **allergies** to medicines, latex or other (and your reactions to them)

a. _____ c. _____

b. _____ d. _____

3. Please list **all medications** you have taken in the last month (include over-the-counter drugs, inhalers, herbals, dietary supplements and aspirin)

Name of Drug	Dose and How Often	Name of Drug	Dose and How Often
a.		f.	
b.		g.	
c.		h.	
d.		i.	
e.		j.	

(Please check YES or NO and circle specific problems)	YES	NO
4. Have you taken steroids (prednisone or cortisone) in the last year?	☐	☐
5. Have you *ever* smoked? (Quantify in _____ packs/day for _____ years)	☐	☐
Do you still smoke?	☐	☐
Do you drink alcohol? (If so, how much?) _____	☐	☐
Do you use or have you ever used any illegal drugs? (we need to know for your safety)	☐	☐
6. Can you walk up one flight of stairs without stopping?	☐	☐
7. Have you had any problems with your heart? **(circle)** (chest pain or pressure, heart attack, abnormal ECG, skipped beats, heart murmur, palpitation, heart failure [fluid in the lungs], require antibiotics before routine dental care)	☐	☐
8. Do you have high blood pressure?	☐	☐
9. Have you had any problems with your lungs or your chest? **(circle)** (shortness of breath, emphysema, bronchitis, asthma, TB, abnormal chest x-ray)	☐	☐
10. Are you ill now or were you recently ill with a cold, fever, chills, flu or productive cough? Describe recent changes _____	☐	☐

Figure 34-1 Sample patient preoperative history form.

Continued

(Please check YES or NO and circle specific problems)	YES	NO
11. Have you or anyone in your family had serious bleeding problems? **(circle)** (prolonged bleeding from nosebleed, gums, tooth extractions, or surgery)	☐	☐
12. Have you had any problems with your blood (anemia, leukemia, sickle cell disease, blood clots, transfusions)?	☐	☐
13. Have you ever had problems with your: **(circle)**	☐	☐
Liver (cirrhosis, hepatitis, jaundice)?	☐	☐
Kidney (stones, failure, dialysis)?	☐	☐
Digestive system (frequent heartburn, hiatus hernia, stomach ulcer)?	☐	☐
Back, neck or jaws (TMJ, rheumatoid arthritis)?	☐	☐
Thyroid gland (underactive or overactive)?	☐	☐
14. Have you ever had: **(circle)**	☐	☐
Seizures, epilepsy, or fits?	☐	☐
Stroke, facial, leg or arm weakness, difficulty speaking?	☐	☐
Cramping pain in your legs with walking?	☐	☐
Problems with hearing, vision or memory?	☐	☐
15. Have you ever been treated for cancer with chemotherapy or radiation therapy? **(circle)**	☐	☐
16. Women: Could you be pregnant?	☐	☐
Last menstrual period began: _____		
17. Have you ever had problems with anesthesia or surgery? **(circle)** (severe nausea or vomiting, malignant hyperthermia (in blood relatives or self), prolonged drowsiness, anxiety, breathing difficulties, or problems during placement of a breathing tube)	☐	☐
18. Do you have any chipped or loose teeth, dentures, caps, bridgework, braces, problems opening your mouth, swallowing or choking? **(circle)**	☐	☐
19. Do your physical abilities limit your daily activities?	☐	☐
20. Do you snore?	☐	☐

21. Please list any medical illnesses not noted above:

_____

_____

_____

_____

22. Additional comments or questions for nurse or anesthesiologist?

_____

_____

Figure 34-1, cont'd

http://www.cdc.gov/nccdphp/dnpa/bmi/index.htm or http://www.nhlbisupport.com/bmi/. Formulas for calculating BMI are as follows:

English formula:

$$\text{BMI} = \left(\frac{\text{Weight in pounds}}{(\text{Height in inches}) \times (\text{Height in inches})} \right) \times 703$$

Metric formula:

$$\text{BMI} = \frac{\text{Weight in kilograms}}{(\text{Height in meters}) \cdot (\text{Height in meters})}$$

or

$$\text{BMI} = \left(\frac{\text{Weight in kilograms}}{(\text{Height in centimeters}) \times (\text{Height in centimeters})} \right) \times 10{,}000$$

A BMI of 40 or greater defines extreme obesity, obesity is defined as a BMI of 30 to 39.9, and an overweight person has a BMI of 25 to 29.9. An increased BMI is predictive of airway difficulties in some studies and one of many factors associated with the development of chronic diseases such as heart disease, cancer, and diabetes.[11]

Table 34-2 Metabolic Equivalents of Functional Capacity

MET	Functional Levels of Exercise
1	Eating, working at a computer, dressing
2	Walking down stairs or in your house, cooking
3	Walking 1-2 blocks
4	Raking leaves, gardening
5	Climbing 1 flight of stairs, dancing, bicycling
6	Playing golf, carrying clubs
7	Playing singles tennis
8	Rapidly climbing stairs, jogging slowly
9	Jumping rope slowly, moderate cycling
10	Swimming quickly, running or jogging briskly
11	Skiing cross country, playing full-court basketball
12	Running rapidly for moderate to long distances

From Jette M, Sidney K, Blumchen G: Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol 13:555-565, 1990.
MET, metabolic equivalent of the task. 1 MET = consumption of 3.5 mL O_2/min/kg of body weight.

Not infrequently, patients will have increased BP during the preoperative visit, even without a history of hypertension. This may be due to anxiety or missing doses of drugs because patients often do not take their medications before an appointment or procedure. This reading is probably not reflective of their usual control. Repeating the BP measurement, especially after the administration of anxiolytics if this is planned, obtaining previous readings from either medical records or asking patients what their "usual" BP measurements are, can be informative.

Inspection of the airway may be the single most important component of the physical examination from an anesthesiologist's perspective. Without specialized training in airway evaluation and management, including advanced techniques such as fiberoptic intubation, it is unlikely that nonanesthesiologists will be capable of performing an adequate assessment. See Box 34-1 for components of the airway examination.

All patients should have thorough documentation of an airway examination, whether in a preoperative evaluation clinic or immediately before surgery (see Chapter 50). The Mallampati classification is performed by having patients open the mouth widely and protruding the tongue completely forward. A tongue depressor is not used. In class I, the soft palate, fauces, entire uvula, and pillars are visualized; in class II, the soft palate, fauces, and a portion of the uvula; in class III, the soft palate and base of the uvula; and in class IV, the hard palate only. The evaluation should also document the status of teeth, range of motion of the neck, neck circumference (increasing size predicts difficulty with laryngoscopy), thyromental distance, body habitus, and pertinent deformities.[12] Because of the relatively high incidence of dental injuries during anesthesia, thorough documentation of preexisting tooth abnormalities is useful. A good time to discuss with patients variant options of airway management or techniques other than general anesthesia when applicable and prepare patients for possible awake fiberoptic intubation is after examination of the airway. When challenging airways are identified, advance planning ensures that the necessary equipment and skilled personnel are available.

Evaluation of the heart, lungs, and skin is necessary, as well as further focus on the organ systems involved with disease as reported by the patient. Auscultation of the heart and, when indicated, inspection of the pulses and peripheral and central veins and assessment for the presence of edema in the extremities may aid in developing a perioperative plan. One should auscultate for murmurs, rhythm disturbances, and signs of volume overload. Physical findings should focus on examination for third or fourth heart sounds, rales, jugular venous distention, ascites, hepatomegaly, and edema.

Observing whether the patient can walk up one to two flights of stairs can predict a variety of postoperative complications, including pulmonary and cardiac events and mortality, and aid in decisions regarding the need for further specialized testing such as pulmonary function tests (PFTs) or noninvasive cardiac stress testing.[13] This is frequently not practical, and a report by the patient is often sufficient.

The pulmonary examination should include auscultation for wheezing and decreased or abnormal breath sounds and notation of cyanosis or clubbing, use of accessory muscles, and effort of breathing.

A basic neurologic examination to document deficits in mental status, speech, cranial nerves, gait, and motor and sensory function may be indicated, depending on the surgical procedure and patient's history. For selective patients (e.g., those with deficits or disease or undergoing neurosurgery), a more extensive or focused neurologic examination is necessary to document specific preexisting abnormalities that may aid in diagnosis or interfere with positioning. Establishing a baseline allows comparison postoperatively for evaluation of new deficits and can aid in defense of potential malpractice claims of adverse events.

Obesity, hypertension, and large neck circumference (>17 inches in men, >16 inches in women, or >60 cm in anyone) predict an increased incidence of obstructive sleep apnea (OSA).[14] These same neck measurements also predict difficulty with mask ventilation and intubation. Intravenous access sites should be

Box 34-1 Components of the Airway Examination

- Length of the upper incisors
- Condition of the teeth
- Relationship of the upper (maxillary) incisors to the lower (mandibular) incisors
- Ability to protrude or advance the lower (mandibular) incisors in front of the upper (maxillary) incisors
- Interincisor or intergum (if edentulous) distance
- Tongue size
- Visibility of the uvula
- Presence of heavy facial hair
- Compliance of the mandibular space
- Thyromental distance with the head in maximum extension
- Length of the neck
- Thickness or circumference of the neck
- Range of motion of the head and neck

noted. If this is limited, one should discuss possible central line placement with the patient or arrange for assistance from interventional radiology. Auscultation for bruits is important in patients with a history of head and neck irradiation, stroke, or transient ischemic attack.

Preoperative Evaluation of Patients with Coexisting Disease

Many of these concerns and conditions, including intraoperative and postoperative anesthesia management, are discussed in greater detail in other chapters of this text. This section briefly reviews specific medical conditions that are commonly seen in preoperative evaluation and for which preoperative assessment and intervention are important. Identification of patients with these comorbid conditions often presents an opportunity for the anesthesiologist to intervene to lower risk. The following conditions are best managed before the day of surgery, which allows ample time for thoughtful evaluation, consultation, and planning of anesthesia care.

Cardiovascular Disease

Cardiovascular complications are the most common serious perioperative adverse event (see Chapter 33). It is estimated that cardiac morbidity will occur in 1% to 5% of unselected patients undergoing noncardiac surgery. In specific circumstances, perioperative interventions have been shown to modify cardiovascular morbidity and mortality.[7,15-17]

Hypertension

Hypertension, defined as two or more BP readings greater than 140/90 mm Hg, affects 1 billion individuals worldwide and increases with age. In the United States, 25% of adults and 70% of patients older than 70 years have hypertension, less than 30% are adequately treated, and 30% are undiagnosed. The degree of end-organ damage and morbidity and mortality correlate with the duration and severity of hypertension. Ischemic heart disease is the most common type of organ damage associated with hypertension. Each 20–mm Hg incremental elevation in systolic BP or 10–mm Hg incremental elevation in diastolic BP above 115/75 doubles the lifetime risk for cardiovascular disease in individuals 40 to 70 years of age. The odds ratio for an association between hypertension and perioperative cardiac risk is 1.31.[7,18] However, there is little evidence of an association between a preoperative BP reading of less than 180/110 mm Hg and perioperative cardiac risk. Heart failure, renal insufficiency, and cerebrovascular disease are common in hypertensive patients.

Preoperative evaluation identifies causes of hypertension, other cardiovascular risk factors, end-organ damage, and therapy. Paroxysmal hypertension or hypertension in young individuals should prompt a search for causes such as coarctation, hyperthyroidism, pheochromocytoma, or even illicit drug use such as cocaine, amphetamines, or anabolic steroids. (See the section "Pheochromocytoma" for further evaluation guidelines.) Physical examination focuses on the cardiovascular system, pulses, vital signs (BP needs to be repeated and previous records obtained to establish long-term values), the thyroid gland, and signs of volume overload. Asking about episodic tachycardia, palpitations, and syncope, measuring BP in both arms, listening for bruits, and assessing the pulses in both the upper and lower extremities are necessary if there is concern the patient may have more than essential hypertension. Testing should be determined by the history and physical examination. Patients with long-standing, severe (often based on the number and dosages of prescribed antihypertensive medications), or poorly controlled hypertension need an ECG and determination of blood urea nitrogen (BUN) and creatinine, depending on the surgical procedure. Those taking diuretics should have an evaluation of electrolytes. Patients with significant left ventricular hypertrophy (LVH), especially those with a strain pattern on the ECG, which is indicative of chronic ischemia, should have a careful assessment of symptoms and other risk factors for CAD. In the presence of heart failure or dyspnea of unknown origina, an echocardiogram may provide additional information that will modify management. LVH independently increases the risk for perioperative cardiac morbidity. Patients suspected of having hyperthyroidism require thyroid function tests.

It is generally recommended that elective surgery be delayed for severe hypertension (diastolic BP >115 mm Hg, systolic BP >200 mm Hg) until BP is less than 180/110 mm Hg. If severe end-organ damage is present, the goal should be to normalize BP *as much as possible* before surgery.[18] A careful history and physical examination to determine cardiac, neurologic, or renal disease is important (see appropriate sections of this chapter). Effective lowering of risk may require 6 to 8 weeks of therapy to allow regression of vascular and endothelial changes, but too rapid or extreme lowering of BP may increase cerebral and coronary ischemia; therefore, the benefits of delaying surgery for treatment must be weighed against the risks. The Antihypertensive and Lipid Lowering Treatment to Prevent a Heart Attack Trial (ALLHAT) showed that effective treatment of hypertension is not simply a matter of decreasing BP.[19] Thus, if surgery cannot be postponed, the goal is to not decrease chronically increased BP too rapidly. Severely elevated BP should be lowered over a period of several weeks. Studies suggest that hypotension intraoperatively is far more dangerous than hypertension.[18] For a BP lower than 180/110 mm Hg, there is no evidence to justify cancellation of surgery, although interventions preoperatively are appropriate. It is important to identify patients who have undiagnosed hypertension (although typically three separate occasions of increased BP in nonstressful situations are required to diagnosis true hypertension) and differentiate those who have poorly controlled hypertension from those who have episodic increased BP because of pain, anxiety, or stress.

Because the perioperative period is an excellent opportunity to alter the long- and short-term consequences of diseases, appropriate referral for future management is vital. Guidelines suggest that cardioselective β-blocker therapy is the best treatment preoperatively because of a favorable profile in lowering cardiovascular risk, although the Perioperative Ischemia Evaluation (POISE) trial has recently questioned the safety of starting these agents acutely.[7] The optimal time to start β-blocker therapy to achieve its benefit while minimizing risk is unknown. Even though diuretics are first-line therapies in most circumstances, starting them in the preoperative period is not generally a good idea because of the alterations in potassium (both hypokalemia and hyperkalemia) that may occur and the need for close moni-

toring and replacement. Calcium channel blockers (e.g., amlodipine, 5 to 10 mg daily) can be very effective. Frequently, anxiety increases BP, and therefore antianxiolytics can be used as adjunctive therapy. BP should not be lowered too rapidly. Continuation of antihypertensive treatment preoperatively is critical.

Ischemic Heart Disease

The goals of preoperative evaluation are to

- Identify the risk for heart disease based on risk factors (Fig. 34-2, Box 34-2)
- Identify the presence and severity of heart disease from symptoms, physical findings, or diagnostic tests
- Determine the need for preoperative interventions
- Modify the risk for perioperative adverse events

The basis of cardiac assessment is the history, physical examination, and ECG. Risk factors for CAD are as important or more important than symptoms of ischemia because CAD is not diagnosed in 40% of men and 65% of women before an acute coronary syndrome (unstable angina, acute MI, or sudden death) occurs. The traditional risk factors for CAD, such as smoking, hypertension, age, male gender, hypercholesterolemia, and family history, are not the same risk factors that are associated with an increased incidence of perioperative cardiac events (see Fig. 34-2 and Box 34-2). However, traditional risk factors are important in assessing the significance of chest pain, dyspnea, or an abnormal ECG. The Revised Cardiac Risk Index (RCRI; Box 34-2) has been validated in several studies as the best scoring system to predict

Box 34-2 Revised Cardiac Risk Index

High-risk surgery (intraperitoneal, intrathoracic, or suprainguinal vascular procedures)*
Ischemic heart disease (by any diagnostic criteria)
History of congestive heart failure
History of cerebrovascular disease
Diabetes mellitus requiring insulin†
Creatinine >2.0 mg/dL

*This risk factor is not considered a clinical predictor in the ACC/AHA 2007 guidelines for perioperative cardiac evaluation for noncardiac surgery.[7]
†This risk factor has been changed to simply diabetes mellitus in the ACC/AHA 2007 guidelines for perioperative cardiac evaluation for noncardiac surgery.[7]
From Lee TH, Marcantonio ER, Mangione CM, et al: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 100:1043-1049, 1999.

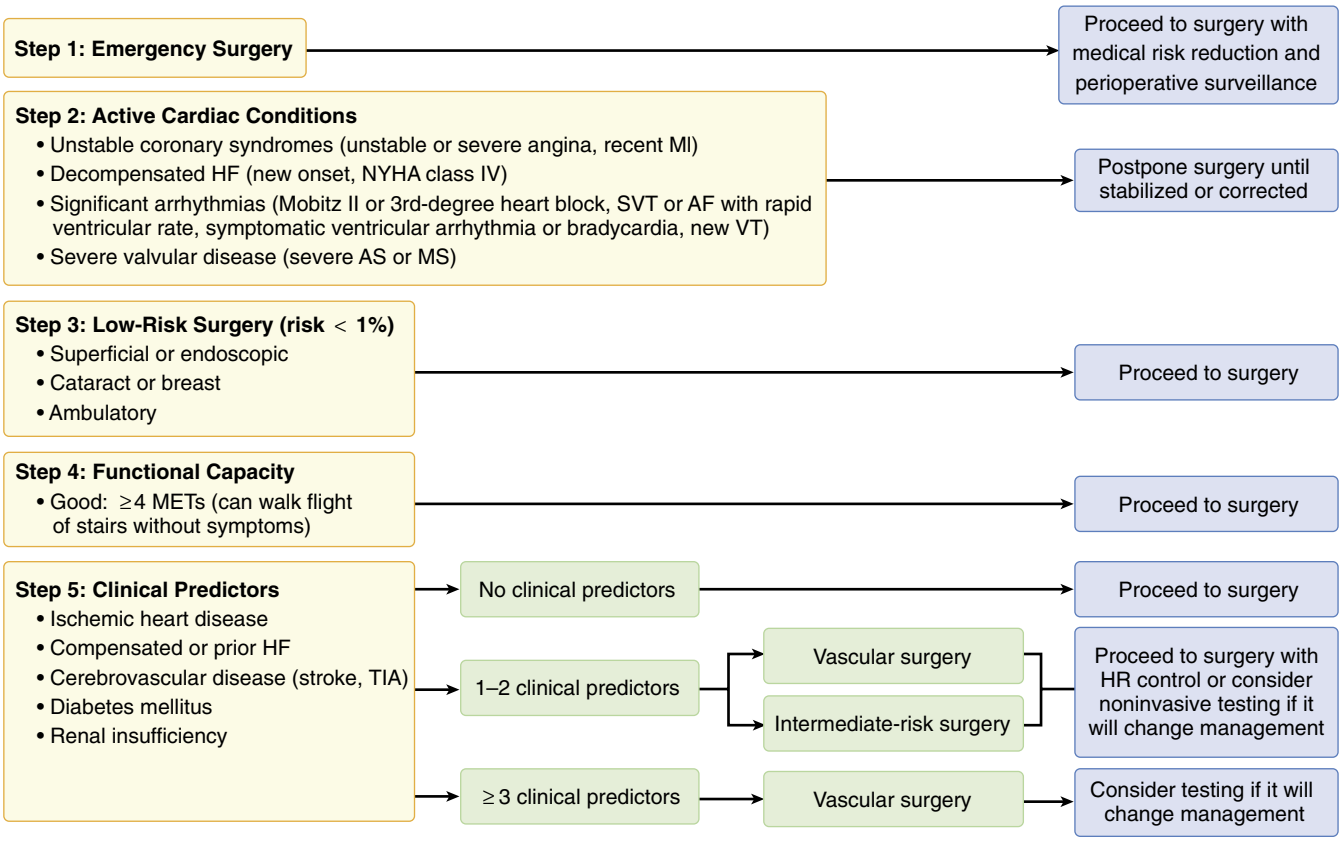


Figure 34-2 Simplified cardiac evaluation for noncardiac surgery. AF, atrial fibrillation; AS, aortic stenosis; HF, heart failure; HR, heart rate; METs, metabolic equivalents of the task; MI, myocardial infarction; MS, mitral stenosis; NYHA, New York Heart Association; SVT, supraventricular tachycardia; TIA, transient ischemic attack; VT, ventricular tachycardia. *(From Fleisher LA, Beckman JA, Brown KA, et al: ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. J Am Coll Cardiol 50:e159-e241, 2007. Available at http://www.acc.org/qualityandscience/clinical/guidelines/Periop_/ Accessed September 28, 2007.)*

perioperative cardiac risk in patients undergoing noncardiac surgery.[20] The most important risk factors for adverse events are a history of ischemic heart disease, heart failure, diabetes, cerebrovascular disease, and renal insufficiency; advanced age; and high-risk surgery, especially open vascular procedures.

One should inquire about chest discomfort (pain, pressure, tightness), the duration of the discomfort, precipitating factors, associated symptoms, and methods of relief. Regardless of symptoms, the most important prognostic indicators of heart disease and perioperative adverse events are risk factors. Shortness of breath with exertion is a common angina-equivalent. Dyspnea is nonspecific and can be a result of deconditioning, pulmonary disease, or heart failure. Dyspnea in patients with risk factors for CAD (see Fig. 34-2 and Box 34-2) may necessitate an investigation for ischemic heart disease. Women are particularly likely to have atypical symptoms of ischemic heart disease. One should note diagnoses, diagnostic tests, therapies, and names of treating physicians.

Patients with risk factors for CAD or symptoms suggestive of ischemia, including atypical ones such as dyspnea, need an ECG. Tait and colleagues suggested that routine preoperative ECGs are not indicated in patients without a history of cardiovascular disease and no significant risk factors.[21] An abnormal ECG is found in 62% of patients with known cardiac disease, in 44% of those with strong risk factors, but in only 7% of individuals younger than 50 years with no risk factors. Additionally, the specificity of an abnormality on the ECG in predicting postoperative cardiac adverse events is only 26%, and a normal ECG does not exclude cardiac disease.[22]

An ECG should not be ordered simply because of advanced age (see Chapter 71). Recommendations for age-based testing are derived from the high incidence of abnormalities found with advancing age. The frequency of Q-wave infarctions found only by ECG in men 75 years or older is about 0.5%. In an ambulatory surgical population, 43% of patients had an abnormal ECG, but only 1.6% had an adverse perioperative event and the preoperative ECG was of potential value in just half of those who had a complication. Only certain abnormalities on the ECG are important in preoperative assessment (e.g., Q waves, especially if recent; conduction abnormalities and arrhythmias), and one study found that just 2% of patients had one or both if a previous ECG did not show these abnormalities. Establishing a baseline for comparison is the most important reason to obtain an ECG preoperatively. However, if the rate of probable events is infrequent or the ECG is likely to be normal preoperatively, the yield lessens. If a previous ECG is available and there has been no change in symptoms or risk factors and no new physical findings, it is unlikely that a repeat ECG will be useful. The 2007 ACC/AHA guidelines on perioperative cardiovascular evaluation provide additional recommendations for preoperative resting ECGs (Box 34-3).[7]

Review of medical records and previous diagnostic studies, especially stress tests and catheterization results, should be performed if possible. In our experience, many patients are unaware of abnormalities or results not requiring revascularization. Frequently, a phone call to the primary care physician or cardiologist will yield important information and obviate the need for further testing or consultation. Consultation initiated by the preoperative physician should seek specific advice regarding diagnosis and status of the patient's condition. Asking specific questions such as "*Does this patient have CAD?*" or "*Is this patient optimized for planned radical nephrectomy?*" is the first step. Letters or notes stating "*cleared for surgery*" are not sufficient to design a safe anesthetic plan. A letter summarizing the medical problems and therapies, along with the results of diagnostic tests, should be requested.

Box 34-3 Recommendations for Preoperative Resting 12-Lead Electrocardiogram

Class I

A preoperative resting 12-lead ECG is recommended for patients with at least one clinical risk factor* who are undergoing vascular surgical procedures

A preoperative resting 12-lead ECG is recommended for patients with known congestive heart failure, peripheral arterial disease, or cerebrovascular disease who are undergoing intermediate-risk surgical procedures

Class IIa

A preoperative resting 12-lead ECG is reasonable in persons with no clinical risk factors who are undergoing vascular surgical procedures

Class IIb

A preoperative resting 12-lead ECG may be reasonable in patients with at least one clinical risk factor who are undergoing intermediate-risk operative procedures

Class III

Preoperative and postoperative resting 12-lead ECGs are not indicated for asymptomatic persons undergoing low-risk surgical procedures

Class I recommendations: the procedure *should* be performed; class IIa: it is reasonable to perform the preocedure; class IIb: the procedure may be considered; class III: the procedure should *not* be performed because it is not helpful.

*Clinical risk factors are listed in Box 34-2.

Adapted from Fleisher LA, Beckman JA, Brown KA, et al: ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. J Am Coll Cardiol 50:e159-e241, 2007. Available at http://www.acc.org/qualityandscience/clinical/guidelines/Periop_Fulltext_2007.pdf/ Accessed September 28, 2007.

The goal is to identify patients with heart disease who are at high risk for perioperative cardiac morbidity or mortality or those with modifiable conditions or risk. The guidelines for cardiac evaluation before noncardiac surgery published by the ACC/AHA have become the national standard of care. These guidelines were recently revised with a marked reduction in recommendations for preoperative noninvasive stress testing and revascularization.[7]

Step 1 in this guideline algorithm is to determine the urgency of the surgery. If emergency surgery does not allow further assessment, the focus needs to be placed on perioperative surveillance (e.g., serial ECGs, enzymes, monitoring) and risk reduction (e.g., HR control, statins, pain management). Clinical predictors, functional or exercise capacity, and level of surgical risk guide further diagnostic and therapeutic interventions.

Step 2 is to determine whether the patient has an active cardiac condition, such as acute MI, unstable or severe angina, decompensated heart failure, severe valvular disease (e.g., severe

aortic stenosis), or significant arrhythmias (e.g., ventricular tachycardia or atrial fibrillation with a rapid rate), that warrants postponement of all except lifesaving emergency procedures (e.g., ruptured aneurysms). After evaluating and treating these conditions according to the AHA/ACC guidelines, surgery may be considered if the benefits outweigh the risks. Traditionally, patients who experienced an MI within 3 to 6 months were considered high risk and surgery was delayed. More recent evidence and the ACC/AHA guidelines suggest that *acute* MI, defined as occurring within the past 7 days, should still be considered high risk and elective surgeries postponed. A *recent* MI, defined as occurring within the past 30 days (but more than 7 days) *with evidence of myocardium at risk* (generally based on persistent symptoms or results of stress testing), is also a high-risk condition. However, a recent (8 to 30 days previously) MI *without evidence of myocardium at risk* is considered an active cardiac condition and equivalent to any history of CAD.

Step 3 involves determination of the surgical risk or severity. Patients without active cardiac conditions who are undergoing low-risk surgery (reported cardiac risk generally <1%; endoscopic or superficial procedures, cataract, breast, or ambulatory surgeries) can proceed to surgery without further cardiac testing other than an ECG within 3 months.

Step 4 assesses the patient's functional capacity (see Table 34-2). Asymptomatic patients who are highly functional can proceed to surgery. The 2007 ACC/AHA guidelines use the RCRI (see Box 34-2) derived from a cohort study showing an incidence of major cardiac events of 0.4%, 0.9%, 7%, and 11% in patients with zero, one, two, or three risk predictors, respectively.[20] The RCRI medical conditions have been confirmed in independent studies as valid predictors of risk.[15]

Step 5 is the last and most complicated determination for patients with poor or indeterminate functional capacity. The presence and number of clinical predictors as shown in Box 34-2 drive the recommendations for and probable benefit of further cardiac testing. Patients with no clinical predictors proceed to surgery. Those undergoing vascular surgery with three or more clinical risk factors are the group most likely to benefit from further testing, but the ACC/AHA guidelines recommend further testing only "if it will change management." Patients with one or more clinical predictors undergoing intermediate-risk surgery (1% to 5% risk for cardiac complications, including orthopedic, intraabdominal, and intrathoracic procedures) or those with one or two risk factors undergoing vascular surgery can either proceed to surgery with HR control or undergo noninvasive testing if it will change management.

Chronic inflammatory conditions (e.g., rheumatoid arthritis, systemic lupus erythematosus [SLE]), chronic steroid use, and chest irradiation) increase the risk for CAD but have not been shown to be significant predictors of perioperative cardiac complications.[23,24] The substantial pullback of ACC/AHA recommendations advocating noninvasive stress testing and coronary revascularization before noncardiac surgery is due to the general lack of definitive benefit and risk reduction with this approach. The only randomized prospective study of revascularization (coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI] with stenting) versus medical management failed to show a difference in outcome. This study was performed in intermediate- to high-risk patients with known CAD undergoing major vascular surgery.[25] Numerous retrospective and observational studies have failed to show a benefit of coronary revascularization before noncardiac surgery. Noncardiac surgery soon after revascularization (CABG or PCI with or without stents) is associated with high rates of perioperative cardiac morbidity and mortality.[26] Factors to consider are the urgency of the noncardiac surgery (e.g., patients with cancer) and the potential long-term benefits of revascularization. Patients who need noncardiac surgery within the next year are not good candidates for implantation of drug-eluting stents, and if revascularization is absolutely necessary, these patients need to be considered for either CABG or PCI without stenting or with a bare metal stent.[27] See the section on recent coronary stents and antiplatelet agents.

Stress testing identifies CAD and its severity, but the positive predictive value for perioperative cardiac complications is generally only 5% to 25%.[28] The negative predictive value of noninvasive tests for predicting perioperative events generally approaches 100%, so these tests are typically more informative about a patient who will *not* have an event than one who will. However, studies of the predictive value of noninvasive testing predated the era of drug-eluting stents and the risk of perioperative acute thrombosis with these stents. Cardiac catheterization, which some consider the gold standard for evaluation of coronary lesions, does not absolutely risk-stratify patients.[29] This lack of prognostic value is partly due to the approximately 50% incidence of plaque rupture (with intermediate-sized plaque of 40% to 70% being most vulnerable to rupture) as the causative event during the perioperative period combined with the hypercoagulable state and the typical withdrawal of antiplatelet agents.

Exercise treadmill testing can be ordered for patients with normal ECGs who can exercise and are likely to achieve an adequate HR response (68% to 81% sensitivity and 66% to 77% specificity for finding ischemia).[7] Prognostic information such as functional capacity and the workload at which ischemia occurs predict outcome. The test result is adequate when the patient can exercise to at least greater than 85% of the target HR (the target HR is defined as 220 − age). The individual's ability to exercise and symptoms that limit activity, such as dyspnea, have long-term prognostic implications, even in those without evidence of ischemia.

Pharmacologic tests such as dobutamine echocardiography or nuclear perfusion imaging are necessary for patients unable to exercise, those with pacemakers or significant bradycardia, or those taking high-dose β-adrenergic blockers.[7]

A combination of exercise and imaging can be used in patients able to exercise who have significant abnormalities on the ECG that may interfere with the interpretation of ischemia via the ECG (e.g., LVH with a strain pattern, ST-T wave changes, or left bundle branch block [LBBB]). Exercise combined with perfusion imaging in patients with LBBB results in a high incidence of false-positive tests because of septal perfusion defects not caused by CAD.[7] For most patients, the choice of which pharmacologic test is immaterial. Dobutamine uncovers ischemia by increasing contractility, HR, and BP and may therefore not be the best test in patients with pacemakers, significant bradycardia, aortic or cerebral aneurysms, or poorly controlled hypertension. Adenosine radionucleotide imaging (one of the most common methods of nuclear stress testing) uses the vasodilatory properties of adenosine (stenotic vessels are maximally vasodilated at rest) and uptake of the radioisotope by viable myocardium. This type of test is not dependent on the HR response but may exacerbate bronchospasm in patients taking theophylline or reduce preload,

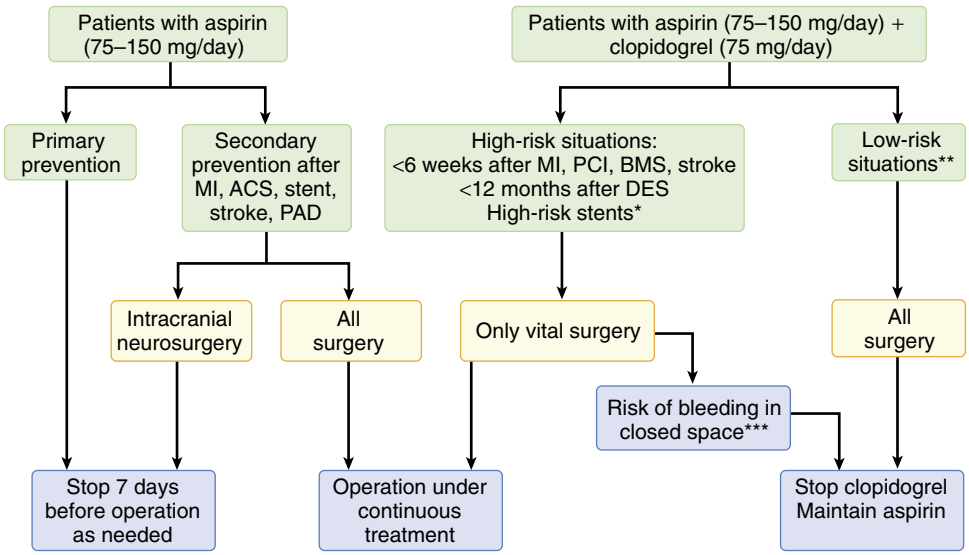
which may be dangerous in patients with severe aortic stenosis, hypertrophic cardiomyopathy (HCM), or carotid stenosis.

Echocardiography, combined with exercise or a pharmacologic agent, is used to look for wall motion abnormalities. Abnormalities present at rest (baseline) indicate scar tissue from previous infarction. Areas of myocardium that are normal at rest but show abnormalities with increased isotropy and chronotropy are consistent with stenotic lesions and limited blood flow. Similarly, nuclear imaging perfusion abnormalities at rest are consistent with infarction. Normal coronary arteries vasodilate with adenosine or exercise, and uptake of isotope is normal. Myocardium with limited blood flow will be normal at rest but show decreased uptake of isotope with exercise or administration of adenosine. Perioperative cardiac risk increases with increasing amounts of at-risk myocardium. If a patient has undergone a specific test in the past, it is most useful to obtain the same test for comparison.

Patients with ischemic heart disease require a complete blood count (CBC), and transfusion for anemia should be considered. In nonoperative settings but in populations with critical illness or chronic disease states associated with known CAD or risk factors for CAD, hemoglobin levels higher than 13.5 g/dL are associated with adverse outcomes.[30] A recent study suggests that even mild preoperative anemia increases postoperative mortality and cardiac morbidity in men but not in women.[31] Individuals with preoperative hematocrits between 39% and 51% had the lowest risk of adverse outcomes in this Veteran's Administration surgical population.

A thorough discussion of the optimal perioperative medical treatment of patients with ischemic heart disease can be found in Chapter 35. In brief, patients already taking statins and β-blockers need to have these drugs continued without interruption throughout the perioperative period. Those already taking β-blockers need their dosages adjusted to achieve an HR lower than 70 beats/min if at all possible. The optimal use of β-blockers in patients who are at significant risk for perioperative cardiac events and are currently not taking them in accord with national guidelines is controversial and discussed more fully in Chapter 35. Strong consideration should be given to continuing aspirin perioperatively or discontinuing for the shortest duration possible if used for secondary prevention of vascular events (Fig. 34-3).

By applying the ACC/AHA recommendations or using the predictive value of the RCRI and developing practice guidelines as shown in Figure 34-2, anesthesiologists in preanesthetic clinics are well positioned to risk-stratify patients, thus obviating the need for cardiac consultation. The preoperative period is an opportunity to identify patients with CAD who will benefit from long-term risk modification with statins, aspirin, exercise, and diet adjustment. Patients with symptoms consistent with ischemia (but without a diagnosis of CAD) or significant risk factors



*High-risk stents: long (>36 mm), proximal, overlapping, or multiple stent implantation, stents for chronic total occlusions, stents in small vessels or bifurcated lesions.
**Examples of low-risk situations: >3 months after BMS, stroke, uncomplicated MI, PCI without stenting.
***Risk of bleeding in closed space: intracranial neurosurgery, intra-medullary canal surgery, posterior eye chamber ophthalmic surgery. In these situations, the risk/benefit ratio of upholding vs withdrawing aspirin must be evaluated for each case individually; in case of aspirin upholding, early postoperative re-institution is important.

Figure 34-3 Algorithm for preoperative management of patients receiving antiplatelet therapy. ACS, acute coronary syndrome; BMS, bare metal stent; DES, drug-eluting stent; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention. *(From Chassot P-G, Delabays A, Spahn DR: Perioperative antiplatelet therapy: The case for continuing therapy in patients at risk of myocardial infarction. Br J Anaesth 99:316-328, 2007. Available at http://bja.oxfordjournals.org.)*

without medical management such as statins and aspirin may benefit from evaluation by a cardiologist regardless of whether they are having surgery. Preoperative evaluation should not simply focus on perioperative risk.

Heart Failure

Heart failure affects 4 to 5 million people (2% of the population) in the United States and is a significant risk factor for postoperative adverse events (see Chapter 60).[32] One in 100 individuals between 50 and 59 years of age has a 5% to 7% risk of perioperative cardiac complications, but those with decompensated failure have a 20% to 30% incidence. Heart failure may be due to systolic dysfunction (decreased ejection fraction because of abnormal contractility), diastolic dysfunction (elevated filling pressure because of abnormal relaxation but normal contractility and ejection fraction), or a combination. Diastolic failure accounts for almost half of all cases, but there is little science to guide perioperative care of these individuals. Hypertension is a cause of diastolic dysfunction, and LVH on an ECG should raise suspicion. Ischemic heart disease is the most common cause of systolic dysfunction in the United States (50% to 75% of cases). Cardiomyopathies occur from a variety of causes, including infectious causes (human immunodeficiency virus [HIV], coxsackievirus, influenza virus, adenovirus, Chagas' or Lyme disease), ischemia, stress, toxins, alcohol, the peripartum period, drugs (doxorubicin [Adriamycin], cocaine), muscular dystrophies, and idiopathic causes, which can be familial and inherited in an autosomal dominant or X-linked autosomal recessive pattern.

The preoperative evaluation history and physical examination focus on identifying and minimizing the effects of heart failure. Recent weight gain, complaints of shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough, peripheral edema, hospitalizations, and recent changes in management are all significant. Patients with decompensated heart failure feel as though they are "suffocating" or have "air hunger."[33] Angina or a history of CAD may indicate heart failure.

The physical examination focuses on finding third or fourth heart sounds, tachycardia, a laterally displaced apical pulse, rales, jugular venous distention, ascites, hepatomegaly, or peripheral edema. Classifying the patient's medical status according to the New York Heart Association (NYHA) categories is useful.[34]

NYHA Classification

Class I: no limitation of physical activity; ordinary activity does not cause fatigue, palpitations, or syncope
Class II: slight limitation of physical activity; ordinary activity results in fatigue, palpitations, or syncope
Class III: marked limitation of physical activity; less than ordinary activity results in fatigue, palpitations, or syncope; comfortable at rest
Class IV: inability to perform any physical activity without discomfort; symptoms at rest

Decompensated heart failure is considered a high-risk cardiac condition, and elective surgery should be postponed (see Fig. 34-2).[7] Brain naturetic peptide (BNP), which is released from the ventricles of the heart, can be useful in evaluating patients suspected of having decompensated heart failure.[35] In an emergency room study of patients with dyspnea, a plasma BNP level higher than 100 pg/mL diagnosed heart failure with a sensitivity, specificity, and predictive accuracy of 90%, 76%, and 83%, respectively. The plasma concentration of BNP correlated with NYHA functional class, with BNP levels ranging from 244 to 817 pg/mL corresponding to classes I to IV.[36] In patients undergoing noncardiac surgery, preoperative BNP levels predict cardiac complications and death.[37] An N-terminal pro-BNP level elevated to greater than 450 pg/mL in patients younger than 50 years and to greater than 900 pg/mL in patients 50 years or older is highly sensitive and specific for the diagnosis of acute failure. An N-terminal pro-BNP level less than 300 pg/mL has a 99% negative predictive value for acute heart failure. A study of patients undergoing vascular surgery showed that preoperatively elevated levels of N-terminal pro-BNP predicted cardiac events and mortality.[38]

A preoperative ECG plus determination of electrolytes, BUN, creatinine, and possibly BNP is indicated in all patients with or suspected of having heart failure. Digoxin levels should not be routinely measured unless toxicity under treatment or noncompliance is suspected. One should determine *trough* levels of digoxin, which is not always possible in a preoperative evaluation setting. Paroxysmal atrial tachycardia with a 2:1 atrioventricular (AV) block is pathognomonic of digoxin toxicity. Junctional tachycardia, ventricular ectopic beats, bigeminy, second-degree AV block, nausea, lethargy, altered color perception, and mental status changes or agitation are symptoms of digoxin toxicity. Chest radiography is useful in those suspected of pulmonary edema or decompensation. An objective measure of the left ventricular ejection fraction (LVEF), ventricular performance, and diastolic function with echocardiography is helpful if not previously performed, especially in patients with NYHA class III or IV heart failure. Normal LVEF is greater than 50%, mildly diminished is 41% to 49%, moderately diminished is 26% to 40%, and severely diminished is less than 25%. In patients with class III or IV heart failure, cardiology consultation would be useful before the patient undergoes general anesthesia or any intermediate- or high-risk procedure. Minor procedures under monitored anesthesia care may proceed as long as the patient's condition is stable.

Medical therapy, including β-blockers, hydralazine, nitrates, and digoxin, needs to be optimized and continued preoperatively. Angiotension-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics (including aldosterone antagonists such as spironolactone), and anticoagulants may be beneficial, even on the day of surgery. Selectively continuing or discontinuing these drugs depends on the volume and hemodynamic status of the patient, the degree of cardiac dysfunction, and the anticipated surgery and volume challenges. Continuing all medications for patients with severe dysfunction who are scheduled for minor procedures is probably best. The other extreme occurs when patients with well-compensated NYHA class I failure are scheduled for lengthy high-risk procedures with projected significant blood loss or fluid requirements; in this case it is best to discontinue potent diuretics on the morning of surgery. Short-acting calcium channel antagonists depress left ventricular function, worsen symptoms, and increase the risk for death. Some patients will have pacemakers or implantable cardiac defibrillators, which have special considerations perioperatively (see the section on devices for management of cardiac rhythm for recommendations and Chapter 43).

Unless truly an emergency and life preserving, surgery should be postponed in patients with decompensated or untreated heart failure. There is no consensus on how long after an acute

exacerbation patients remain at risk. Severely affected individuals or those with decompensation are best managed in concert with a heart failure specialist and may benefit from preoperative hospitalization for interventions designed to improve function.

Murmurs and Valvular Abnormalities

The quandary in the preoperative clinic is to determine the cause of cardiac murmurs and to distinguish between significant murmurs and clinically unimportant ones (see Chapter 60).[39] Functional murmurs occur as a result of turbulent flow across the aortic or pulmonic outflow tracts. These benign murmurs occur with high-outflow states such as hyperthyroidism, pregnancy, or anemia. However, noncardiologists or even cardiologists often cannot distinguish benign from pathologic murmurs. In elderly patients and those with risk factors for heart disease, other abnormal heart sounds, a history of rheumatic fever or anorectic drug use, evidence of volume overload, pulmonary disease, cardiomegaly, or an abnormal ECG, echocardiography should be considered (Box 34-4).[40] Although echocardiography may be useful in the diagnosis of many of these murmurs, the evaluation may not be required preoperatively if the information will not change management.

Diastolic murmurs are always pathologic and require further evaluation. Regurgitant disease is tolerated perioperatively much better than stenotic disease is. Heart failure in concert with any valvular disease is associated with a 20% risk of decompensation in the perioperative period. Murmurs are graded according to loudness: grade I, a faint murmur that can be heard with difficulty; grade II, faint but easily heard; grade III, moderately loud without a thrill; grade IV, loud with a palpable thrill; grade V, very loud but still needs a stethoscope (thrill present); and grade VI, murmur heard without a stethoscope. However, the usefulness of this distinction is debatable because severe lesions can be associated with soft murmurs and vice versa. The location of the murmur and changes in intensity with maneuvers guide diagnosis (Table 34-3). A Valsalva maneuver decreases filling of the right and left heart chambers and reduces the intensity of most murmurs, except those associated with mitral valve prolapse (MVP) and HCM. Standing will also increase the intensity of murmurs of MVP and HCM. Squatting increases venous return and afterload and therefore increases most murmurs, except those related to MVP and HCM. Asking the patient to repeatedly perform a handgrip will increase HR and afterload (increases BP) and will augment murmurs of mitral regurgitation and stenosis and aortic insufficiency but decrease aortic stenosis and HCM murmurs. All patients with murmurs require an ECG. In patients with significant abnormalities found by history, physical examination, or ECG, further evaluation by echocardiography or by a cardiologist should be considered (see Box 34-4).

Box 34-4 ACC/AHA Guideline Summary—Echocardiography in Asymptomatic Patients with Cardiac Murmurs*

Class I—There is evidence or general agreement (or both) that echocardiography is useful in asymptomatic patients with the following cardiac murmurs:

- Diastolic murmurs
- Continuous murmurs
- Late systolic murmurs
- Murmurs associated with ejection clicks
- Murmurs that radiate to the neck or back
- Grade 3 or louder systolic murmurs

Class IIa—The weight of evidence or opinion is in favor of the usefulness of echocardiography in asymptomatic patients with the following cardiac murmurs:

- Murmurs associated with other abnormal physical findings on cardiac examination
- Murmurs associated with an abnormal electrocardiogram or chest radiograph

Class III—There is evidence or general agreement (or both) that echocardiography is not useful in asymptomatic patients with the following murmurs:

- Grade 2 or softer midsystolic murmurs considered innocent or functional by an experienced observer

*These are indications for general evaluation but do not necessarily need to be performed preoperatively.

From Bonow, RO, Carabello, BA, Chatterjee, K, et al: ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease). J Am Coll Cardiol 48:e1, 2006.

Table 34-3 Descriptions of Murmurs Associated with Cardiac Abnormalities

Lesion	Location	Timing	Description
Aortic stenosis	Second parasternal interspaces	Midsystolic	Crescendo-decrescendo, radiates to the carotids; ± S_3, S_4; Valsalva and sustained handgrip exercise decrease intensity
Aortic insufficiency	Third and fourth parasternal interspaces	Holodiastolic	Decrescendo, blowing, high pitched, radiates to the carotids; Austin-Flint rumble at the apex; squatting, handgrip exercise, and leaning forward increase intensity
Mitral stenosis	Apex	Mid-diastolic	Opening snap; low-pitched rumble radiates to the axilla; squatting and handgrip exercise increase intensity
Mitral regurgitation	Apex	Holosystolic	High pitched, blowing, radiates to the axilla; loud S_3; standing decreases intensity; squatting and handgrip exercise increase intensity
Mitral valve prolapse	Apex	Late systolic	Crescendo, midsystolic click; Valsalva and standing increase intensity; squatting decreases intensity
Hypertrophic cardiomyopathy	Apex, lower left sternal border	Midsystolic	S_4, single S_2; Valsalva and standing increase intensity; squatting, passive leg raising, and handgrip exercise decrease intensity

Aortic Stenosis

Aortic stenosis, the most common valvular lesion in the United States, affects 2% to 4% of adults older than 65 years; severe stenosis is associated with high risk for perioperative complications.[7] Once considered a degenerative lesion associated with age or a congenital bicuspid valve, aortic stenosis is now thought to have much in common with ischemic heart disease and is an independent marker of CAD.[41] In patients with bicuspid valves, stenosis typically develops at a younger age (fourth and fifth decades of life); those with stenosis of the tricuspid valves are usually older than 60 years, but there is overlap.

Aortic *sclerosis*, which also causes a systolic ejection murmur similar to that of aortic stenosis, is present in 25% of people 65 to 74 years of age and in almost half of those older than 84 years.[41] Aortic sclerosis is associated with a 40% increase in risk for MI and a 50% increase in risk for cardiovascular death in patients without a history of CAD.[42] There is no hemodynamic compromise with aortic sclerosis.

The cardinal symptoms of severe aortic stenosis are angina, heart failure, and syncope, although patients are much more likely to complain of a decrease in exercise tolerance and exertional dyspnea. Aortic stenosis causes a systolic ejection murmur, best heard in the right upper sternal border and often radiating to the neck. There is delayed carotid upstroke and a paradoxically split S_2, and exercise will increase HR and decrease an aortic stenosis murmur. Patients with a previously undiagnosed murmur need an ECG, and an echocardiogram should be considered in patients with an abnormality on the ECG (see Box 34-4). Such abnormalities may consist of LVH, often with a strain pattern (ST-T wave changes), left axis deviation, or LBBB.

Aortic stenosis severity is based on the mean transvalvular pressure gradient and valve area (Table 34-4). The pressure gradient falls if the left ventricle begins to fail. Current guidelines recommend echocardiography annually for patients with severe aortic stenosis, every 2 years for moderate stenosis, and every 5 years for mild stenosis.[40] Patients with aortic stenosis are at risk for sudden death from arrhythmias, heart failure, and myocardial ischemia and infarction from concomitant CAD (high incidence) or a supply-demand mismatch. Patients with aortic sclerosis or stenosis need evaluation for CAD regardless of other risk factors. Those with severe or critical stenosis should not undergo noncardiac surgery (unless emergency and lifesaving) without a cardiology evaluation and careful consideration of risks or until valve replacement. Patients with moderate to severe aortic stenosis have an increased risk of bleeding (especially from gastrointestinal angiodysplasia). The cause appears to be an acquired von Willebrand syndrome resulting from mechanical disruption of von Willebrand multimers during turbulent blood flow through a narrowed valve. See the section "von Willebrand's Disease" for more details. An activated partial thromboplastin time (aPTT) is indicated. Prophylaxis for infective endocarditis in patients with aortic stenosis is no longer recommended.[43]

Table 34-4 Severity of Aortic Stenosis

Grade	Velocity of Aortic Jet (m/sec)	Mean Pressure Gradient (mm Hg)	Valve Area (cm^2)
Mild	<3	<25	≥1.5
Moderate	3-4	25-40	1.0-1.5
Severe	4-4.5	40-50	0.7-1.0
Critical	>4.5	>50	<0.7

Aortic Insufficiency

Insufficiency of the aortic valve occurs with true valvular disease affecting the leaflets, from aortic root dilation, or as a result of both. Rheumatic heart disease, a bicuspid valve, collagen vascular diseases, and endocarditis can all lead to valvular disease. Aortic root dilation can complicate ankylosing spondylitis, osteogenesis imperfecta, syphilis, hypertension, age-related degeneration, Marfan's syndrome, and collagen vascular diseases. Acute insufficiency with pulmonary edema and hypertension can occur with trauma, infection, or aortic dissection and is an emergency. The murmur of aortic insufficiency is described in Table 34-3. The intensity of the murmur does not correlate with the severity of regurgitation.[44] Patients typically have a widened pulse pressure (normal or elevated systolic BP and low diastolic BP) manifested as Corrigan's or water-hammer pulses (bounding carotid pulse with a rapid downstroke). de Musset's sign is a head bob with each heartbeat, Duroziez's sign is a systolic and diastolic bruit heard over the femoral artery when it is partially compressed, Quincke's pulses are capillary pulsations in the fingertips or lips, and Müller's sign is systolic pulsations of the uvula.

An ECG is needed and an echocardiogram should be considered if finding could change management (see Box 34-4); a chest radiograph may be useful. LVH with ST- and T-wave changes as a result of volume overload or underlying chronic ischemia may be present. Left atrial hypertrophy and left axis deviation along with premature atrial and ventricular contractions are not uncommon. Generally, chronic insufficiency is well tolerated in the perioperative period. Patients with good functional status and preserved left ventricular systolic function have a low risk of complications with anesthesia. Prophylaxis for infective endocarditis is no longer recommended.[43]

Mitral Stenosis

Mitral stenosis is much less common than aortic stenosis and is usually associated with a history of rheumatic heart disease. It can occur with aortic valvular disease or mitral regurgitation. A normal mitral valve has an area of 4 to 6 cm^2; stenosis is mild when the mitral valve area is 1.5 to 2.5 cm^2, moderate with an area of 1.1 to 1.5 cm^2, and critical when the area is 0.6 to 1.0 cm^2. A resting mean transvalvular gradient greater than 10 mm Hg also denotes severe stenosis. Symptoms typically occur 10 to 20 years after acute rheumatic fever and are often precipitated by pregnancy or illness. Unrecognized mitral stenosis is included in the differential diagnosis of pulmonary edema.

Preoperative evaluation includes determining whether the patient has a history of dyspnea, fatigue, orthopnea, pulmonary edema, and hemoptysis. These findings result from elevated left atrial pressure and decreased cardiac output. Atrial fibrillation can be due to a dilated left atrium, which can acutely precipitate failure and chronically cause thrombosis. Patients with atrial fibrillation require anticoagulation to avoid a left atrial thrombus. Tachycardia decreases cardiac output. Pulmonary hypertension and right heart failure may occur with significant stenosis. A loud S_2 suggests pulmonary hypertension. The characteristics of the murmur are described in Table 34-3. Sustained handgrip exercise increases HR and BP and may increase the murmur. Examination should look for rales and signs of right heart failure such as

jugular venous distention, peripheral edema, hepatomegaly, right ventricular heave, and ascites.

A preoperative ECG is necessary and an echocardiogram should be considered if it will change management (see Box 34-4). A chest radiograph should also be considered. β-Blockers are used to control HR, and antiarrhythmics prevent or control atrial fibrillation. These medications have to be continued preoperatively because HR needs to be controlled before surgery. Anticoagulation is managed in conjunction with the treating cardiologist and surgeon. Prophylaxis for infective endocarditis is no longer recommended.[43]

Mitral Regurgitation

Mitral regurgitation can be acute in the setting of ischemia or infarction or can be chronic and associated with mitral stenosis, mitral valve prolapse, collagen vascular diseases, or cardiomyopathies. The course is typically very gradual, and symptoms develop late and only after the development of left ventricular dysfunction. Preoperative symptoms are vague and often attributed to other causes. Fatigue, dyspnea, and atrial fibrillation can be present. Description of murmurs is presented in Table 34-3. A loud murmur associated with a thrill (grade ≥4) has a specificity of 91% for severe regurgitation but a sensitivity of 24%.[44] Severe regurgitation is rarely present with a grade 1 to 2 murmur; however, there is a wide range of severity with a grade 3 murmur. Chronic mitral regurgitation is generally well tolerated perioperatively unless other valvular lesions (e.g., mitral or aortic stenosis) or left ventricular dysfunction coexist. Prophylaxis for infective endocarditis is no longer recommended.[43]

Mitral Valve Prolapse

Also known as click-murmur or floppy valve syndrome, mitral valve prolapse is commonly diagnosed in young women during evaluation for atypical chest pain, palpitations, or syncope. Whether these symptoms are truly related is questionable. Interestingly, men older than 55 years with mitral valve prolapse are more likely to have regurgitation complications and are at greatest risk for infective endocarditis. The important issue preoperatively is to differentiate patients with clinically significant mitral valve degeneration and regurgitation from those with an incidental finding of prolapse or a click, which does not warrant further evaluation or change in management. Patients taking β-blockers for control of palpitations or atypical chest pain continue these medications perioperatively. Prophylaxis for infective endocarditis is no longer recommended.[43]

Tricuspid Regurgitation

Tricuspid regurgitation is a relatively common abnormality, but because it is usually asymptomatic and not audible on physical examination, it is most commonly noted by echocardiography performed for other reasons. A small degree of tricuspid regurgitation is present in approximately 70% of normal adults. Tricuspid regurgitation is most commonly caused by dilatation of the right ventricle and the tricuspid annulus. Right ventricular dilatation is caused by conditions that directly involve the right ventricle (ischemia, cardiomyopathy) or is due to pulmonary hypertension and elevated right ventricular systolic pressure. Tricuspid and mitral regurgitation often occurs together. Tricuspid regurgitation is less often due to processes that directly affect the tricuspid valve, such as Ebstein's anomaly (a congenital malformation), infective endocarditis, rheumatic fever, carcinoid syndrome, connective tissue disorders (Marfan's syndrome), myxomatous degeneration or prolapse (occurs in as many as 40% of patients with mitral valve prolapse), or injury from a pacemaker, central line, or implantable cardioverter-defibrillator (ICD) lead. Drugs such as the anorectics fenfluramine and phentermine and the dopamine agonist pergolide may cause tricuspid regurgitation by a mechanism similar to that seen with carcinoid syndrome. The aforementioned drugs are no longer available in the United States.

Tricuspid regurgitation is classically associated with a holosystolic murmur that is best heard at the right or left midsternal border or at the subxiphoid area. When the right ventricle is very enlarged, the murmur may even be appreciated at the apex. There is usually little radiation of the murmur, and a thrill is not palpable. However, the murmur of tricuspid insufficiency is often soft or absent, even when regurgitation is severe. Interventions that result in an increase in venous return (leg raising, exercise, hepatic compression) will augment the murmur of tricuspid regurgitation. The murmur may also become louder after a premature beat and prolonged diastole. In contrast, reducing venous return (by standing or with amyl nitrate) will diminish the intensity of the murmur. In patients with pulmonary hypertension, the intensity of the murmur may change with alterations in pulmonary artery pressure and therefore the right ventricle. Patients with (or suspected of having) pulmonary hypertension need to be managed in conjunction with a pulmonary hypertension specialist (see the section "Pulmonary Hypertension"). Prophylaxis for infective endocarditis is no longer recommended.[43] An echocardiogram should be considered if it will change management.

Hypertrophic Cardiomyopathy

Previously known as hypertrophic obstructive cardiomyopathy and before that as idiopathic hypertrophic subaortic stenosis, HCM can be familial. Patients with hypertrophic obstructive cardiomyopathy are often young and male and may be asymptomatic without murmurs. An ECG and echocardiogram should be considered if there is a personal or family history of syncope with exertion or sudden death or when a murmur consistent with this disorder is detected. Characteristics of the murmur are described in Table 34-3. A maneuver that decreases diastolic volume or increases contractility increases the intensity of the murmur. Passive leg raising and squatting decrease the intensity, and a Valsalva maneuver increases it. In an otherwise healthy nonhypertensive patient with LVH and ST-segment and T-wave abnormalities on an ECG, an echocardiogram should be considered.

Patients are at risk for sudden cardiac death probably from arrhythmias (see Box 34-4). Holter monitoring may be useful in some patients. Many patients are treated with β-blockers to decrease contractility; these medications are continued perioperatively. ICDs may be in place to prevent sudden death; see discussion in the appropriate section of this chapter. Prophylaxis for infective endocarditis is no longer recommended.[43]

Prosthetic Heart Valves

In patients with prosthetic valves, the most important issues preoperatively are determination of the underlying condition requiring replacement, the type of prosthesis, the need for anticoagulation, and the planned management of such patients in the perioperative period. Occasionally, patients will have valve-related hemolysis. The risk for thrombosis is greatest with multiple prosthetic

valves, followed by valves in the mitral position and then aortic valve replacements. Caged-ball valves (Starr-Edwards) have the highest risk, single tilting-disk valves (Björk-Shiley, Medtronic-Hall, Omnicarbon) have an intermediate risk, and the lowest risk is seen with bileaflet tilting-disk prostheses (St. Jude, CarboMedics, Edwards Duromedics). Bioprosthetic valves such as Carpentier-Edwards (porcine heterograft or pericardial) or Hancock (porcine) brands generally do not require long-term anticoagulation. The decision to stop anticoagulants, the duration off anticoagulants, and the need to "bridge" with a shorter-acting drug and the type of bridging agent (intravenous heparin or low-molecular-weight heparin [LMWH]) need to be made in conjunction with the treating cardiologist and surgeon. See the section on anticoagulation for a discussion of bridging.

Rhythm Disturbances and Electrocardiographic Abnormalities

Arrhythmias and conduction disturbances are common in the perioperative period (see also Chapter 42). Supraventricular and ventricular arrhythmias are associated with a greater risk of perioperative adverse events because of the arrhythmia itself and because they are markers for cardiopulmonary disease. Uncontrolled atrial fibrillation and ventricular tachycardia are high-risk clinical predictors, and elective surgery should be postponed until evaluation and stabilization are complete.[7] New-onset atrial fibrillation, symptomatic bradycardia, or high-grade heart block (second or third degree) identified in the preoperative clinic warrant consideration of postponement of elective procedurest and referral to cardiology for further evaluation. First-degree AV block is defined as a PR interval longer than 0.20 msec with an HR of 50 to 100 beats/min and is generally benign. Second-degree heart block occurs when the PR interval is prolonged greater than 0.20 msec, and eventually the atrial beat is blocked, which results in a dropped or missing QRS complex after a P wave. Two types of second-degree block exist. A Mobitz type I or Wenckebach block is more benign, rarely progresses to complete heart block, and responds to atropine. It is characterized by a progressive lengthening of the PR interval until the dropped beat occurs and is usually due to AV nodal delay. Mobitz type II results from an infranodal block, can progress to complete heart block, and is generally treated with a pacemaker unless secondary to a reversible cause such as ischemia or drugs. It is characterized by a fixed, prolonged PR interval that does not change before the dropped QRS complex. Third-degree or complete heart block is complete dissociation between the atrial and ventricular beats (P waves and QRS complexes) and requires a pacemaker unless a reversible source is identified. The ventricular beats in a patient with complete heart block are independent of the atria and should not be depressed. Two general factors are considered when determining the need for a pacemaker: an arrhythmia associated with symptoms and the location of the conduction abnormality. Syncope or near syncope associated with bradycardia or conduction delays is generally an indication for placement of a pacemaker. Disease below the AV node, in the His-Purkinje system, is more ominous and is suggested by a normal or minimally prolonged PR interval, a Mobitz type II block, and QRS abnormalities (bundle branch block, fascicular block, or both). Because disease in the His-Purkinje system is generally less stable, permanent pacemaker placement is likely to be beneficial. The indications for a pacemaker perioperatively are the same as those in nonsurgical patients (Box 34-5).[45]

Box 34-5 Indications for a Pacemaker

Class I Indications

- Sinus bradycardia with symptoms clearly related to the bradycardia (usually with a heart rate <40 beats/min or frequent sinus pauses)
- Symptomatic chronotropic incompetence
- Complete (third-degree) AV block*
- Advanced second-degree AV block (block of ≥2 consecutive P waves)
- Symptomatic Mobitz I or II second-degree AV block
- Mobitz II second-degree AV block with a widened QRS or chronic bifascicular block, regardless of symptoms

Class II Indications

- Sinus bradycardia (heart rate <40 beats/min) with symptoms suggestive of bradycardia but without a clear association between bradycardia and symptoms
- Sinus node dysfunction with unexplained syncope
- Chronic heart rates <30 beats/min in an awake patient

Class I conditions are those in which permanent pacing is definitely beneficial and effective, provided that the condition is not due to a transient cause. Class II conditions are those in which permanent pacing may be indicated but there is conflicting evidence or divergence of opinion (or both).

*Controversy exists concerning complete atrioventricular (AV) block without symptoms. The current ACC/AHA guidelines classify asymptomatic third-degree AV block with average awake ventricular rates of 40 beats/min or greater as a class IIa indication, although others recommend definite pacemaker placement.

From Gregoratos, G, Abrams, J, Epstein, AE, et al: ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: Summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). Circulation 106:2145-2161, 2002.

Bundle branch blocks are complete or incomplete and either right (RBBB) or left (LBBB). They result from aging or fibrosis of the conducting system, ischemia, pulmonary disease, radiation, or cardiomyopathies or can be normal variants. Traditionally, LBBB has been considered more ominous and has been shown to be associated with CAD and heart failure.[46,47] LBBB is strongly associated with CAD, and in a patient with a recent onset or no previous evaluation of LBBB, stress testing or cardiology consultation may be warranted. Obtaining a previous ECG for comparison can establish the stability. RBBB is likely to be congenital, a result of calcification and degeneration of the conduction system or secondary to pulmonary disease. Brugada's syndrome is a congenital disease characterized by RBBB with ST-segment elevation in the right precordial leads and is associated with a risk for sudden death and lethal arrhythmias. If the history and physical examination do not suggest significant pulmonary, congenital, or ischemic heart disease or Brugada's syndrome, no further evaluation is warranted because of an isolated RBBB. An RBBB in a patient with pulmonary symptoms (including pulmonary hypertension) may be suggestive of severe respiratory or vascular compromise and may warrant pulmonary evaluation and echocardiography if intermediate- or high-risk surgery is planned. If congenital heart disease, pulmonary hypertension (see the appropriate section in this chapter), or Brugada's

syndrome is suspected, cardiology consultation is indicated. LVH and ST-segment depression on a preoperative ECG are associated with a greater risk for MI and cardiac death perioperatively.[48] LVH may be associated with diastolic dysfunction and poorly controlled hypertension. Prolonged QT intervals should prompt an evaluation of electrolytes, magnesium, and calcium and a search for potentiating drugs. In a patient with a prolonged QT interval and syncope, near syncope, or a family history of sudden death, further evaluation should be considered.

Atrial Fibrillation

Atrial fibrillation occurs in elderly patients and those with thyrotoxicosis, valvular disease, and ischemic heart disease. It can be intermittent (paroxysmal), persistent (able to be cardioverted), or permanent (unable to be converted). Evidence suggests that rate control is more important than rhythm control. Patients with rapid ventricular rates (>100 beats/min) require control before elective surgery.[7] Patients with slow ventricular rates not caused by rate-controlling medications are at risk for sick sinus syndrome, need a careful history to uncover syncopal or near-syncopal episodes, and may need a Holter monitor. Most patients with atrial fibrillation will require long-term anticoagulation, which becomes an issue in the perioperative period. If they are being treated with only prophylactic therapy (no history of emboli or left atrial thrombi), bridging perioperatively is not cost-effective. Patients with atrial or ventricular thrombi or a previous history of thromboembolic events are at higher risk, and anticoagulant therapy is managed on a case-by-case basis in concert with the treating physician. β-Blockers, digoxin, and calcium channel blockers taken chronically to control rate or rhythm need to be continued perioperatively.

Supraventricular Arrhythmias

Supraventricular tachycardias result from rapidly firing ectopic atrial foci with rapid conduction via the AV node or from a reentry mechanism via accessory pathways. With a reentry mechanism the cycle self-perpetuates because conduction occurs down one pathway and up the other, with both the AV node–Purkinje system and the accessory pathway or pathways being involved. Various degrees of AV block may slow the ventricular rate. Wolff-Parkinson-White (WPW) syndrome is a classic supraventricular tachycardia with an accessory pathway but unique in that impulses can travel both retrograde and antegrade. Antegrade conduction over the accessory pathway results in a short PR interval (<0.12 msec) and slurring of the upstroke of the QRS, termed a delta wave. AV nodal–blocking drugs such as β-blockers, calcium channel blockers, and digoxin can paradoxically increase conduction over the accessory pathway and cause ventricular fibrillation. Lidocaine and procainamide are the preferred drugs to slow the tachycardia in patients with WPW syndrome. Certain patients may require ablation for long-term management of WPW syndrome, and this should be performed before elective surgery.

Ventricular Arrhythmias

Ventricular ectopics can be differentiated from atrial ectopics by a widen QRS (>0.12 msec) and lack of a P wave. The traditional grading system of Lown, organized by morphology (unifocal or multifocal), frequency (less than or greater than 30 beats/min), and other characteristics (couplets, R on T phenomenon), is limited in its ability to stratify risk. Classifying ventricular arrhythmias according to the type of rhythm disturbance and the presence of coexisting heart disease better predicts the risk for sudden death.

- Benign: isolated ventricular premature beats (VPBs) without heart disease
  - No need for further evaluation
  - No risk of sudden cardiac arrest
- Potentially lethal: greater than 30 VPBs/hr or nonsustained ventricular tachycardia with underlying heart disease
  - Requires cardiology evaluation with possible echocardiography, stress testing, catheterization, or electrophysiologic testing
  - Moderately high risk of sudden cardiac arrest; may benefit from an ICD
- Lethal: sustained ventricular tachycardia, ventricular fibrillation), syncope, or hemodynamic compromise associated with VPBs with underlying heart disease and often depressed cardiac function
  - Requires cardiology evaluation with possible stress testing, echocardiography, catheterization, or electrophysiologic testing
  - High risk of sudden cardiac arrest; likely to benefit from an ICD

Preoperative evaluation focuses on reversible causes such as hypokalemia, ischemia, acidosis, hypomagnesemia, drug toxicity, and endocrine dysfunction, which should be further evaluated and treated. Patients taking amiodarone are at risk for hypothyroidism and require thyroid function tests before surgery. Antiarrythmics should be continued perioperatively.

Cardiac Rhythm Management Devices: Pacemakers and Implantable Cardioverter-Defibrillators

More than 100,000 new cardiac rhythm management devices are implanted yearly in the United States. A complete discussion of the perioperative management of these devices can be found in Chapter 43.

Peripheral Vascular Disease

Also called peripheral arterial disease, PVD refers to aneurysmal or occlusive arterial disease of the extremities, visceral organs, head, neck, and brain. Many of these patients have disease secondary to tobacco abuse, diabetes, hyperlipidemia and hypertension, or combinations of these causes. Patients with Marfan's or Ehlers-Danlos syndrome may have aneurysmal disease without other risk factors. Renal insufficiency and cerebrovascular disease are frequent in this cohort of patients. Up to 75% of patients with PVD have CAD. In a study of 1000 consecutive patients scheduled for major vascular surgery, almost 60% had critical stenosis in at least one major coronary vessel. In addition, undiagnosed PVD (e.g., patients who smoke, are of increased age, have diabetes, or have cerebrovascular disease) should be considered when assessing patients scheduled for major surgery. Because claudication often limits functional capacity, symptoms of ischemic heart disease are often not apparent.

Determination of BP in both upper extremities and the presence or absence of peripheral pulses is important. Listening for bruits over the abdomen and femoral arteries or palpating for abdominal masses is part of the vascular examination but is rarely necessary preoperatively. BUN and creatinine should be determined before procedures involving injection of radiocontrast dye

(see the section "Contrast-Induced Nephropathy" for management to reduce risk). Many patients take aspirin or dipyridamole, a vasodilator with some antiplatelet effects that are reversible on discontinuation; its elimination half-life is approximately 10 hours. Therefore, stopping this drug 48 hours before surgery eliminates the antiplatelet effect. However, because dypyridamole is often combined with aspirin (Aggrenox), this drug must be stopped 5 to 7 days before surgery if complete reversal of its antiplatelet effects is desired, although the risks related to stopping antiplatelet medications must also be considered.

Pulmonary Disorders (See Chapter 59)

Asthma

Asthma is a chronic inflammatory disease characterized by obstruction of the airways that is partially or completely reversible with treatment or spontaneously.[49] Bronchoconstriction is precipitated by irritants (smoke), allergens, infections, medications, or instrumentation of the larynx, trachea, or bronchi. Asthma is classified as intermittent (mild) or persistent (mild, moderate, or severe) based on how frequently symptoms occur and whether they are sporadic or constant. Patients with mild, well-controlled asthma have no greater risk associated with anesthesia and surgery than normal individuals do.

Reporting of asthma should prompt further questioning about shortness of breath, chest tightness, coughing (especially nocturnal), recent exacerbations, therapy (especially the use of steroids, particularly within the previous year) or oxygen use, hospitalizations, and intubations. The patient's best exercise level is important information for assessment of risk. A history of previous exacerbations with anesthesia should be elicited. Patients with asthma are quite good at estimating their current status and breathing capacity when asked about what percentage they are presently at (100% being normal). Adequate and appropriate medical therapy must be determined. The quality of breath sounds, quantity of air movement, and degree of wheezing are important. The degree of wheezing does not always correlate with the severity of bronchoconstriction. With severe obstruction, airflow is dangerously restricted and wheezing diminishes. Observing the degree of accessory muscle use often gauges the severity of the bronchoconstriction. Determination of oxygen saturation by pulse oximetry is useful. Arterial blood gas analysis is not generally necessary unless the patient is having a severe acute exacerbation. Patients taking oral steroids need blood glucose checked and may require perioperative steroid supplementation.

Wheezing is a common symptom in asthmatics but is not specific for this disease. Patients with chronic obstructive pulmonary disease (COPD), gastroesophageal reflux disease, vocal cord dysfunction, tracheal or bronchial stenosis, cystic fibrosis, allergic bronchopulmonary aspergillosis, and heart failure may wheeze. Spirometry is the preferred diagnostic test, but a normal result does not exclude asthma. A methacholine challenge test or a trial of bronchodilator therapy is indicated if spirometry is normal but there is still a strong suspicion of asthma. PFTs have no perioperative predictive value but in rare instances may be useful to gauge the severity of disease or the adequacy of therapy. Typical findings on PFTs are reduced forced expiratory volume in 1 second (FEV_1) and normal to increased functional residual capacity (FVC).

A preoperative chest radiograph is necessary only for evaluation of infections or pneumothorax. Bronchodilators, inhaled and oral steroids, and antibiotics (if taken) need to be continued on the day of surgery. β-Agonists are the most useful prophylactic intervention to lower the risk for bronchospasm on induction of anesthesia. A short course of steroids (20 to 60 mg of prednisone daily for 3 to 5 days) preoperatively may be useful in any patient who is not at baseline and surgery must proceed.

Chronic Obstructive Pulmonary Disease

COPD includes chronic bronchitis and emphysema and is characterized by obstruction to airflow that is not fully reversible. It is often due to exposure to pollutants such as cigarette smoke or substances in the environment (air pollution, allergens, grain, dust, and coal), α_1-antitrypsin deficiency, chronic infections, and long-standing asthma. Chronic bronchitis is the presence of symptoms on most days for at least 3 months for 2 successive years or recurrent excessive sputum that severely impairs expiratory airflow. Dyspnea, coughing, wheezing, and sputum production are common features. An acute exacerbation is defined as an increase in symptoms that requires a change in management.

The preoperative history and physical examination for patients with COPD are similar to that for patients with asthma, but with additional emphasis on the change in amount of sputum, color, or other signs of infection. A barrel chest and pursed-lip breathing suggest advanced disease. Typically, FEV_1 is reduced because of obstructed airflow, but FVC is increased because of reduced airflow, loss of elasticity, and overexpansion. Diffusing capacity (D_{LCO}) is typically decreased, and its severity often correlates with the degree of hypoxia and hypercapnia, which in turn can predict the presence of pulmonary hypertension. However, PFTs have not been shown to predict perioperative outcome. Determination of oxygen saturation by pulse oximetry is appropriate to establish a baseline. Patients found to be hypoxic or using oxygen may benefit from further testing, including arterial blood gas determination. A chest radiograph is useful only when infection is suspected. An ECG may demonstrate right axis deviation, RBBB, or peaked P waves, which suggest pulmonary hypertension and possibly right ventricular changes in response to the chronic lung disease (see the section "Pulmonary Hypertension").

Restrictive Pulmonary Disorders

Restrictive lung disease is distinguished by a reduction in total lung capacity. Both pulmonary and extrapulmonary conditions cause restrictive disease. Pulmonary conditions include idiopathic interstitial pneumonia, interstitial lung disease related to connective tissue disease, lung resection, and pulmonary fibrosis. Extrapulmonary disorders are caused by chest wall limitations (kyphoscoliosis, obesity, ankylosing spondylitis), muscle dysfunction (muscular dystrophies, myasthenia gravis, paralyzed diaphragm), or pleural disease (mesothelioma, effusion, pneumothorax).

The preoperative medical history of associated diseases or symptoms prompts the directed evaluation. A chest radiograph and PFTs may be indicated to establish a diagnosis or evaluate acute or progressive worsening but are not routinely necessary preoperatively. FEV_1 and FVC are reduced proportionally, so the ratio is normal. These patients are at risk for pulmonary hypertension, which may not be diagnosed or communicated to caregivers because of overlapping symptoms with restrictive lung disease. See the section "Pulmonary Hypertension" for more details.

Dyspnea

Dyspnea is a subjective experience of breathing discomfort. It is a symptom of deconditioning, obesity, and disorders of ventilation, cardiac function, perfusion, and oxygen delivery. Dyspnea is associated with cardiac, pulmonary, hematologic, and neuromuscular diseases.

Patients with an insidious onset may not seek attention until quite late, and frequently they and their caregivers assume that the dyspnea is due to being "out of shape," although this should be a diagnosis of exclusion. The majority of patients with chronic dyspnea of unclear etiology have one of four diagnoses: asthma, COPD, interstitial lung disease, or cardiac dysfunction.

The important facts to determine are the onset, progression, precipitating factors, type and level of provocative activity, associated symptoms (chest pain, leg edema, syncope or near syncope, fatigue), other conditions (arthritis, connective tissue disease, cardiac disease, smoking), and drug or toxin exposure. Asking about the quality of dyspnea can differentiate causes. Dyspnea secondary to deconditioning is usually described as "heavy breathing," and one can often determine that the patient is actually describing fatigue more than true dyspnea. The bronchoconstriction in exacerbations of asthma is more commonly described as "tightness" or "air hunger," whereas patients with COPD complain of "not being able to take a deep breath" or "an increased effort to breathe." Patients with heart failure feel as though they are "suffocating" or have "air hunger."[33] Orthopnea (dyspnea while recumbent) suggests heart failure or sleep apnea. Coughing can be a symptom of heart failure, asthma, or COPD. Angina or a history of CAD may indicate heart failure. Anorexic drugs can cause pulmonary hypertension or valvular abnormalities. Connective tissue disease is associated with interstitial lung disease. On physical examination one should look for pallor, cyanosis, a "barrel" chest, rales, wheezing, crackles, murmurs, abnormal heart sounds or rhythms, an enlarged heart, tachycardia, jugular venous distention, joint involvement, clubbing, fibrotic skin changes, and edema. Patients with severe airflow obstruction may have pursed lips and a slow deep breathing pattern, and those with interstitial fibrosis or kyphoscoliosis typically have rapid shallow breathing.

The preoperative history and physical examination lead to accurate diagnoses in two thirds of cases. Initial testing may include an ECG, hematocrit (to exclude anemia), arterial blood gas analysis, thyroid function tests, a chest radiograph, spirometry, and oximetry at rest and while walking several feet. BNP levels may be useful. Most dyspnea patients with heart failure have BNP values higher than 400 pg/mL, whereas left ventricular dysfunction without exacerbation, pulmonary embolism, and cor pulmonale should be considered in dyspnea patients with plasma BNP concentrations between 100 and 400 pg/mL. Other testing depends on findings on these tests and is directed by the history and physical examination. Computed tomography scans and cardiopulmonary exercise testing are rarely necessary but can be useful if the aforementioned tests are not diagnostic.

Patients with Risk Factors for Postoperative Pulmonary Complications

Postoperative pulmonary complications develop in 5% to 10% of patients undergoing nonthoracic surgery and in 22% of high-risk patients. As many as one in four deaths occurring within a week of surgery are related to pulmonary complications, thus making it the second most common serious morbidity after cardiovascular adverse events.[50,51]

Established risk factors for an increased risk for pulmonary complications include the following[52]:

- History of cigarette use (current or >40 pack-years)
- ASA-PS scores higher than 2
- Age >70 years
- COPD
- Neck, thoracic, upper abdominal, aortic, or neurologic surgery
- Anticipated prolonged procedures (>2 hours)
- Planned general anesthesia (especially with endotracheal intubation)
- Albumin less than 3 g/dL
- Exercise capacity of less than two blocks or one flight of stairs
- BMI greater than 30

Surprisingly absent predictors in this list are asthma and results from arterial blood gas analysis or PFTs. The risk for complications is surprisingly low in patients with well-controlled asthma or those treated preoperatively with corticosteroids.[53] The risk is greater in asthmatics with recent exacerbations or a history of postoperative pulmonary complications or recent hospitalization or intubation for asthma. Arterial blood gas analysis is useful in predicting pulmonary function after lung resection surgery but does not predict risk for complications. The degree of airway obstruction, measured by FEV_1, is not predictive of pulmonary complications.[54] PFTs, arterial blood gas analysis, or chest radiographs should not be used routinely to predict the risk for postoperative pulmonary complications. PFTs may be indicated to diagnose disease (dyspnea caused by lung disease or heart failure?) or to assess management (can dyspnea or wheezing be improved further?) but should *not* be used as a risk assessment tool or to deny a beneficial procedure.[54]

Laboratory results and patient- and procedure-related determinants of risk for perioperative pulmonary complications have recently been reviewed in the literature.[55] Some of these factors can be modified to alter risk. The pulmonary status of patients with recent exacerbations or infections should be improved whenever possible. Prescriptions for antibiotics, bronchodilators, and steroids, referral to pulmonologists or internists, and postponing surgery are important in patients at high risk. Training patients preoperatively in lung expansion maneuvers, such as deep-breathing exercises and incentive spirometry, reduces pulmonary complications more than training postoperatively does. Additionally, a change in perioperative management, including altering the planned surgical procedure if possible, discussing alternatives to general anesthesia, especially when peripheral nerve blocks are an option, and educating the patient about the benefits of epidural pain management, may provide effective measures to decrease pulmonary complications.[56]

Patients Scheduled for Lung Resection

Most patients scheduled for lung resection surgery have underlying lung disease, and PFTs may be useful in predicting risk or excluding patients who may not have adequate pulmonary reserve after resection. This topic is covered more fully in Chapter 59.

Pulmonary Hypertension

Pulmonary hypertension may occur in isolation or with associated medical conditions and is classified into five groups (Box 34-6) according to the World Health Organization. Idiopathic

Box 34-6 Classification of Pulmonary Hypertension

Pulmonary Arterial Hypertension
Primary pulmonary hypertension
- Sporadic
- Familial

Associated with
- Collagen vascular disease
- Congenital shunts
- Portal hypertension
- Human immunodeficiency virus infection
- Drugs/toxins
- Persistent pulmonary hypertension of the newborn

Pulmonary Venous Hypertension
Left-sided heart disease

Extrinsic compression of central pulmonary veins

Pulmonary veno-occlusive disease

Pulmonary Hypertension Related to Lung Disease or Hypoxemia
Chronic obstructive pulmonary disease

Interstitial lung disease

Sleep-disordered breathing

Neonatal lung disease

Chronic exposure to high altitude

Pulmonary Hypertension Caused by Chronic Thromboembolic Disease
Pulmonary thrombosis or embolism

Sickle cell disease

Pulmonary Hypertension from Disorders Directly Affecting the Pulmonary Vasculature
Schistosomiasis

Sarcoidosis

Available from http://www.who.int/ncd/cvd/pph.html.

pulmonary arterial hypertension, formerly called primary pulmonary hypertension, is rare, but other forms are more common and occur with a variety of diseases, including cardiac, pulmonary, liver, thromboembolic, and collagen vascular disease. Pulmonary hypertension is associated with HIV infection, exposure to anorexics such as fenfluramine, chronic liver disease, especially if portal hypertension is present, and collagen vascular diseases, including scleroderma, SLE, and rheumatoid arthritis. Pulmonary hypertension is defined as a persistent elevation in mean pulmonary artery pressure greater than 25 mm Hg with a pulmonary artery occlusion pressure of less than 15 mm Hg. Occult pulmonary hypertension is more problematic than fully recognized disease because symptoms may be attributed to other diseases and perioperative decompensation may occur unexpectedly.

The manifestation of pulmonary hypertension is usually nonspecific, insidious, and associated with delayed diagnosis. Dyspnea is the initial symptom in 60% of patients but is present in 98% by the time of diagnosis. Dyspnea is nonspecific and associated with a multitude of conditions (see the section "Dyspnea"). Near syncope or syncopal episodes suggest severe disease. Hypoxia, hypercapnia, vasoconstrictors, and increased sympathetic tone (even from anxiety) increase pulmonary vascular resistance and lead to acute decompensation with right heart failure.

Patients with pulmonary arterial hypertension have a high rate of perioperative morbidity and mortality.[57] Mild pulmonary hypertension rarely affects anesthetic management, but moderate to severe disease increases the risk for right heart failure. Signs and symptoms of disease severity include[58]

- Dyspnea at rest
- Metabolic acidosis
- Hypoxemia
- Right heart failure (peripheral edema, hepatomegaly, jugular venous distention)
- History of syncope

Physical examination may reveal a split S_2 with a loud second component, right ventricular heave, a murmur of tricuspid regurgitation, ascites, hepatomegaly, jugular venous distention, and peripheral edema.

An echocardiogram is the screening test of choice and can used to estimate pulmonary artery pressure, assess right ventricular function, and identify left heart failure and valvular or congenital heart disease.[59] Patients with significant findings may require right and left heart catheterization, although the need for catheterization preoperatively depends on the surgical procedure. An ECG, chest radiograph, and echocardiogram are useful in patients with more than mild disease. Findings on the ECG include right axis deviation, RBBB, right ventricular hypertrophy, and tall R waves in leads V_1 and V_2. Right atrial hypertrophy and "P pulmonale" may be present in severe pulmonary hypertension, with peaked P waves most apparent in leads II, III, aVF, and V_1. Enlargement of the main pulmonary artery and a globular heart shape with loss of the retrosternal air space as a result of right ventricular dilation can be seen on the chest radiograph. Evaluators should inquire about a history of OSA, which can also be the cause of pulmonary hypertension.[60] A CBC with platelets, electrolytes, BUN, creatinine, and liver function tests (LFTs; may be elevated as a result of congestion or the use of bosentan) are needed.

Preoperatively, patients may be treated with diuretics, anticoagulants, calcium channel blockers, supplemental oxygen, sildenafil (a phosphodiesterase inhibitor), endothelin receptor antagonists (bosentan), and prostanoids (iloprost, epoprostenol). Some of these agents are given by continuous intravenous infusion, and even momentary interruption of therapy can be catastrophic. All drugs need to be continued preoperatively. Management of these patients in conjunction with a pulmonary hypertension specialist is advised.

Smokers and Those Exposed to Second-Hand Smoke

Exposure to tobacco, directly or through "second-hand" smoke, increases the risk for many perioperative complications. Smokers are more likely to experience wound infections, respiratory or airway complications (including oxygen desaturation), and severe coughing.[61] Smoking decreases macrophage function, negatively affects coronary flow reserve, and causes vascular endothelial dysfunction, hypertension, and ischemia. Smokers require longer hospital stays than nonsmokers do and often need postoperative intensive care admission.

The greatest benefit of smoking abstinence is probably realized only after several months of cessation. In studies reporting greater perioperative risk in recent quitters than in smokers, selection bias may have contributed to the results. Patients who were motivated to stop or advised to quit smoking may have been at greater risk because of health status. Soon after a patient quits smoking, carbon monoxide levels decrease, which improves oxygen delivery and utilization. Cyanide levels decrease, which benefits mitochondrial oxidative metabolism. Lower nicotine levels improve vasodilation, and many toxic substances that impair wound healing decrease. Patients without a history of ischemic heart disease who smoked shortly before surgery had significantly more episodes of rate-pressure product–related ST-segment depression than did nonsmokers, former smokers, or chronic smokers who did not smoke in the immediate preoperative period.[62]

A preoperative smoking cessation intervention in patients who underwent knee and hip replacement decreased rates of surgical site infection (SSI) from 23% in the conventional group to 4% in those who stopped smoking. The U.S. Public Health Service recommends that "*all* physicians should strongly advise every patient who smokes to quit because evidence shows that physician advice to quit smoking increases abstinence rates."[63] Nearly 70% of smokers want to quit.

Effective interventions include medical advice and pharmacotherapy, such as nicotine replacement therapy, which is safe in the perioperative period (see Chapter 35). Nicotine patches, gum, and lozenges are available without a prescription; nasal spray and buproprion (Wellbutrin) require prescriptions. Clonidine is also effective. Buproprion or clonidine should be started 1 to 2 weeks before an attempt at quitting; nicotine replacement therapy is effective immediately.[64] Individual and group counseling may increase rates of long-term abstinence. Many hospitals, insurance companies, and communities offer smoking cessation programs. Excellent resources are available on the Internet and from the U.S. government. Advice and guidelines are available at http://www.surgeongeneral.gov/tobacco/default.htm. Tobacco intervention training during medical school and residency can significantly improve the quality of physician counseling and rates of abstinence.

Endocrine Disorders (See also Chapter 35)

Diabetes Mellitus

Type 1 diabetes is an autoimmune disease that results in destruction of pancreatic insulin-producing (beta) cells; patients have an absolute deficiency of insulin but normal sensitivity to insulin, are at risk for ketoacidosis, and generally have an onset of disease at a younger age. Because of the often-difficult nature of control and the long duration of disease, by the time that these individuals reach adulthood, they are at increased risk for premature vascular disease, especially myocardial ischemia, even in the second decade of life. Type 2 diabetes is initially a result of insulin resistance, which with time can result in pancreatic "burnout," and is usually found in older, overweight adults. Using terms such as insulin dependent, non–insulin dependent, or adult onset is confusing and not recommended.

In the United States, approximately 20 million persons have diabetes, with 1 million new cases diagnosed each year. In as many as a third of patients, the disease is diagnosed only after significant diabetes-related complications develop. Unfortunately, the symptoms of diabetes are nonspecific, so the history, other than a family history of the disease, is not reliable in screening for the disease. However, patients who are overweight, have excessive abdominal fat (even if their BMI is normal), take steroids, or have polycystic ovarian syndrome are at increased risk. Certain ethnic groups (Native American, non-Hispanic black, Hispanic, and Asian American) have a higher incidence. Diabetes develops in females twice as commonly as in males.

Diabetics are at risk for multiorgan dysfunction, with renal insufficiency, stroke, peripheral neuropathy, autonomic dysfunction, and cardiovascular disease being most prevalent. Delayed gastric emptying, retinopathy, and reduced joint mobility occur in these patients. Diabetes is considered a CAD equivalent and an intermediate risk factor for perioperative cardiac complications, on a par with angina or a previous MI.[7] Diabetic patients without known coronary stenosis or angina have the same risk of myocardial ischemia or cardiac death as a nondiabetic with a previous MI.[65] Autonomic neuropathy is the best predictor of silent ischemia. Erectile dysfunction has been shown to be a strong predictor as well. Poorly controlled blood glucose and longer duration of disease also correlate with cardiac risk. See the section "Ischemic Heart Disease" and Figure 34-2 for further guidance on this topic.

Heart failure is twice as common in men and five times as common in women with diabetes as in those without diabetes. Poor glycemic control is associated with an increased risk for heart failure, and both systolic and diastolic dysfunction may be present. Diabetics are at increased risk for renal failure perioperatively and for postoperative infections. Recent studies suggest that tighter perioperative control may be warranted. Patients with poor preoperative management of glucose are likely to be more out of control intraoperatively and postoperatively. Aggressive management of hyperglycemia decreases postoperative complications.

Chronic kidney disease is usually asymptomatic until quite advanced. Diabetes is responsible for almost half of the patients requiring dialysis in the United States. The combination of hypertension, diabetes, and age older than 55 years accounts for more than 90% of patients with renal insufficiency. "Screening" for kidney disease is accepted practice in patients with diabetes. Patients with poorly controlled diabetes are at risk for the development of stiff joint syndrome with reduced cervical mobility, which may influence airway management.

The preoperative evaluation should focus on assessing organ damage and control of blood sugar. Cardiovascular, renal, and neurologic systems need close evaluation. Ischemic heart disease is often asymptomatic in diabetics. Inquiring about early satiety, erectile dysfunction, numbness in the hands and feet, and postprandial vomiting is important. Documenting pulses, skin breakdown, a sensory examination, and orthostatic vital signs (BP and HR both lying and standing) are important in most diabetics, especially those with long-standing disease or poor control. Patients with autonomic dysfunction or hypovolemia will have greater than a 20–mm Hg drop in systolic or greater than a 10–mm Hg decrease in diastolic BP pressure when assuming an upright position from recumbency.

A preoperative ECG plus determination of electrolytes, BUN, creatinine, and blood glucose is recommended for all diabetic patients. Frequently, patients are not fasting when evaluated in a preoperative clinic, and relying on reported glucose values is

problematic. If patients bring a diary of multiple glucose values at varying times of the day (preprandial and postprandial), one can estimate the adequacy of therapy. However, patients often will only randomly check AM fasting blood glucose, which is likely to be lower because of an overnight fast than glucose values obtained later in the day. The glycosolated hemoglobin (HbA_{1c}) level is not influenced by fasting and, if available, can identify those with poor control. The American Diabetes Association recommends a target HbA_{1c} of less than 7%. Suggestions for hypoglycemic medication management on the day of surgery are discussed in Chapter 35. The goals of perioperative diabetic management include avoidance of hypoglycemia and marked hyperglycemia. The American College of Endocrinologists position statement recommends a target fasting glucose level of less than 110 mg/dL in noncritically ill hospitalized patients.[66]

Thyroid Disease

Thyroid hormones are important for metabolism and its regulation. Mild to moderate dysfunction probably has minimal impact perioperatively. Significant hyperthyroidism or hypothyroidism appears to increase perioperative risk. Hyperthyroid patients may have tachycardia, arrhythmias, palpitations, tremors, weight loss, and diarrhea. Hypothyroid patients may be hypotensive, bradycardic, and lethargic and exhibit weight gain, depressed cardiac function, pericardial effusions, and an impaired ventilatory response to hypoxia and hypercapnia. Symptoms and findings of both hypothyroidism and hyperthyroidism can be subtle and nonspecific, especially in the elderly. Patients may have goiters with related symptoms such as dysphagia, dyspnea, wheezing, and orthopnea. Grave's ophthalmopathy or proptosis is more common in smokers. Patients taking amiodarone are at risk for hypothyroidism and require evaluation of thyroid function before surgery.

Determination of medical therapy is important. Patients with a history of chronic thyroid disease need thyroid function tests before surgery. If symptomatology and therapy have not changed, tests within the 6 month before surgery are generally adequate. Thyroid-stimulating hormone (TSH) assays are best to evaluate for hypothyroidism. Measuring both *free* triiodothyronine (T_3) and thyroxine (T_4) and TSH is useful in hyperthyroid patients and avoids the confusion of protein-binding effects seen with total hormone levels. Elective surgery should be postponed until patients are euthyroid. Surgery, stress, or illness can precipitate myxedema or thyroid storm in patients with untreated or severe thyroid dysfunction. Preoperative consultation with an endocrinologist should be considered if surgery is urgent in patients with clinical thyroid dysfunction. Hyperthryoid patients should be treated with β-blockers, antithyroid medications, and steroids if surgery is urgent. Chest radiography or computed tomography is useful to evaluate tracheal or mediastinal involvement by a goiter. Continuation of medications (thyroid replacement and antithyroid drugs such as propylthiouracil) on the day of surgery is important.

Parathyroid Disease

Parathyroid hormone regulates calcium, and most cases of hyperparathyroidism are discovered when an elevated calcium level is found incidentally during diagnostic testing. Primary hyperparathyroidism is caused by a primary disorder of the parathyroid glands (adenomas or hyperplasia). Secondary hyperparathyroidism is hyperplasia of the parathyroid gland caused by hyperphosphatemia and hypocalcemia from chronic renal failure. Tertiary hyperparathyroidism occurs when the parathyroid hyperplasia in secondary hyperparathyroidism functions autonomously and results in hypercalcemia. Hypercalcemia from parathyroid disease is associated with osteoporosis and bone loss. Rarely, the parathyroid glands can become so enlarged that they compromise the airway. Hypoparathyroidism is rare but can result from total parathyroidectomy. Hypercalcemia and hypocalcemia are discussed in the section on calcium disorders.

Hypothalamic-Pituitary-Adrenal Disorders

Corticotropin-releasing hormone is released by the hypothalamus and regulates adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, which in turn regulates cortisol from the adrenal cortex. A key component is the negative-feedback suppression by endogenous or exogenous glucocorticoids. Cortisol secretion varies with the circadian rhythm, being highest in the morning and with stress, fever, hypoglycemia, and surgery. Surgery is one of the most potent activators of the hypothalamic-pituitary-adrenal (HPA) axis. ACTH concentrations increase with incision and during surgery, but the greatest secretion of ACTH occurs during reversal of anesthesia, during extubation, and in the immediate postoperative period.

Excess adrenal hormone results from glucocorticoid treatment of disorders such as asthma or inflammatory diseases or from pituitary or adrenal tumors. Cushing's disease denotes the constellation of findings associated with a pituitary tumor; Cushing's syndrome refers to the same findings resulting from either an adrenal tumor or hyperplasia, ectopic ACTH from neoplasms, or exogenous steroids.

Preoperative findings on evaluation include significant hypertension, weight gain, myopathy, diabetes, moon facies, and a buffalo hump, which can influence airway management. Striae, virilization in females, and easy bruising are common. Exogenous steroids will suppress the adrenals, and the normal hypersecretion expected from stress or surgery will be blunted. Therefore, patients at risk will need "steroid coverage," which is discussed in Chapter 35. An ECG and electrolyte and glucose levels should be obtained preoperatively for most surgical procedures. Despite bruising easily, patients have normal coagulation profiles.

Adrenal insufficiency results from destruction of the pituitary or adrenal glands or from long-term administration of exogenous glucocorticoid. Tuberculosis and HIV infection can cause primary hypoadrenalism. Prednisone or its equivalent in doses of greater 20 mg/day for longer than 3 weeks suppresses the HPA axis. The HPA axis is not suppressed with doses of less than 5 mg/day of prednisone or its equivalent. Intermediate doses of steroids taken for longer than 3 weeks have equivocal effects on the HPA axis. The risk remains for up to 1 year after cessation of steroids. Patients with adrenal insufficiency exhibit weakness, weight loss, hypotension, orthostasis, hypovolemia, hyperpigmentation, and electrolyte abnormalities. Electrolytes and orthostatic vital signs should be evaluated.

Serum cortisol and plasma ACTH can establish the diagnosis and cause of adrenal insufficiency in most cases. If the serum cortisol concentration is inappropriately low and a simultaneous plasma ACTH concentration is very high, primary adrenal insufficiency (primary adrenal disease) is the cause. Secondary (pituitary disease) or tertiary (hypothalamic disease) insufficiency is the diagnosis if both the serum cortisol and plasma ACTH concentrations are inappropriately low. However,

in more urgent situations one may not be able to wait for the ACTH results, so an ACTH stimulation test can be performed unless the diagnosis has been ruled out by a basal serum cortisol value in the upper end of the reference range or higher.[67] Cosyntropin is synthetic ACTH and can be administered in either a high-dose or a low-dose test. The time of day is not important because in patients with adrenal insufficiency, the response to cosyntropin is the same in the morning and afternoon. A normal response to the high-dose (250 μg as an intravenous bolus) ACTH stimulation test is a rise in serum cortisol concentration, measured after 30 to 60 minutes, to a peak of 18 to 20 μg/dL or greater. Low-dose (1-μg intravenous bolus) ACTH causes a rise in cortisol of 17 to 22.5 μg/dL or greater after 20 to 30 minutes. For both tests, a subnormal response confirms the diagnosis of adrenal insufficiency, but further studies are necessary to establish the type and cause.

Preoperative electrolytes should be evaluated and an ECG obtained if appropriate. Patients continue steroids on the day of surgery and may need supplementation with additional doses (see the section on medication).

Aldosterone, which is produced by the adrenal cortex, regulates volume and electrolytes (absorption of sodium and chloride, secretion of potassium and hydrogen ions) and is controlled by renin-angiotensin, not the HPA axis.

Multiple Endocrine Neoplasia Syndromes

The multiple endocrine neoplasia (MEN) syndromes are rare, but recognition is important both for treatment and for evaluation of family members.[68] MEN type II (MEN II) is subclassified into three distinct syndromes: MEN IIA, MEN IIB, and familial medullary thyroid cancer. Inheritance of MEN I and II is autosomal dominant.

Hyperparathyroidism is the most common manifestation of MEN I, with almost 100% penetrance by 40 to 50 years of age. Hypersecretion of gastrin in MEN I in association with Zollinger-Ellison syndrome is often manifested as multiple peptic ulcers. The *MEN1* gene has been identified, and therefore testing for *MEN1* mutations is possible. There is little evidence that early, presymptomatic detection reduces morbidity or mortality in MEN I. Screening of asymptomatic family members can also be done by measurement of serum calcium because of the high penetrance of hyperparathyroidism in MEN I.

An undiagnosed pheochromocytoma can cause substantial morbidity or even death during surgery. It is important to consider this preoperative diagnosis as a component of possible MEN II and, if present, remove the tumor before eliminating other endocrine tumors. Extra-adrenal pheochromocytoma is rare in MEN II, but bilateral adrenal disease is common. It is unusual for pheochromocytoma to precede the development of medullary thyroid carcinoma or be the initial manifestation of MEN II.

Hyperparathyroidism in MEN IIA is often clinically occult. DNA testing is the optimal test in MEN II syndromes. In contrast to MEN I, in which the long-term benefit of early diagnosis by genetic screening is not well established, early diagnosis by screening of at-risk family members in MEN II kindreds is essential because medullary thyroid carcinoma is a life-threatening disease that can be cured or prevented by early thyroidectomy.

Please refer to the appropriate sections in this chapter for discussion of the preoperative evaluation of patients with thyroid, hyperparathyroid, and pituitary diseases and pheochromocytomas.

Pheochromocytoma

Tumors that arise from chromaffin cells of the adrenal medulla and sympathetic ganglia and secrete catecholamines are referred to as pheochromocytomas and extra-adrenal catecholamine-secreting paragangliomas (extra-adrenal pheochromocytomas), respectively.[69] The term "pheochromocytoma" is often used for both types of tumors because of similar clinical findings and therapies. Pheochromocytomas are discovered when patients have symptoms, a family history, or discovery of an incidental adrenal mass. Approximately 3% to 10% of adrenal incidentalomas prove to be pheochromocytomas. The classic triad of symptoms is episodic headache, sweating, and tachycardia. Paroxysmal hypertension occurs in half of the patients. Many of the rest have what appears to be essential hypertension. Approximately 5% to 15% of patients have normal BP.

Preoperative evaluation may demonstrate paroxysmal hypertension, which is a classic sign of pheochromocytoma; however, patients with this finding rarely have the disorder. Headache, which is variable in severity and duration, occurs in up to 90% of symptomatic patients. Sweating occurs in up to 60% to 70% of patients. Other symptoms include palpitations, dyspnea, weakness, and panic attacks (particularly with pheochromocytomas that produce an increase in epinephrine). Pallor, orthostatic hypotension, blurred vision, weight loss, polyuria, polydipsia, hyperglycemia, psychiatric disorders, cardiopulmonary dysfunction (especially with the initiation of β-adrenergic blockers), and dilated cardiomyopathy are due to excess catecholamines. Marked hypertension has also been reported.

Pheochromocytoma should be suspected in patients who have one or more of the following:

- Hyperadrenergic spells (nonexertional palpitations, diaphoresis, headache, tremor, pallor)
- Difficult-to-control hypertension
- A familial syndrome that includes catecholamine-secreting tumors (MEN II, neurofibromatosis 1, von Hippel-Lindau disease), often with bilateral disease
- A family history of pheochromocytoma
- An incidentally discovered adrenal mass
- Unusual BP response during anesthesia, surgery, or angiography
- Hypertension at a young age (e.g., <20 years old)
- Idiopathic dilated cardiomyopathy
- A history of gastric stromal tumor or pulmonary chondromas (Carney's triad)

Preoperative measurements of urinary and plasma fractionated metanephrines and catecholamines generally establishes the diagnosis. The history and physical examination focus on the cardiovascular system and evaluation of vital signs, orthostatic BP, and findings of heart failure. An ECG and determination of electrolytes, BUN, creatinine, and glucose should be performed in all patients. Computed tomography, echocardiography, and cardiac consultation may be useful. A complete discussion of the anesthetic implications can be found in Chapter 35.

Renal Disease

The type and degree of impairment are important. Patients with renal dysfunction have many associated comorbid conditions that

are generally related to the accompanying vasculopathy (see Chapters 18 and 45). Hypertension, cardiovascular disease, and electrolyte disturbances are most common. Chronic kidney disease (CKD) is defined as a decreased glomular filtration rate (GFR <60 mL/min/1.73 m^2) for at least 3 months or significant proteinuria. Chronic renal failure is defined as a GFR of less than 15 mL/min/1.73 m^2; acute renal failure (ARF) is a sudden decrease in renal function with a urine output of less than 0.5 mL/kg/hr. End-stage renal disease (ESRD) is loss of renal function for 3 or more months. Diabetes accounts for almost half of all cases of ESRD, hypertension for more than a quarter, and the combination of these plus age older than 55 years predicts more than 90% of cases. Polycystic kidney disease (autosomal dominant 90% of the time) is the causative factor in 10% of cases of ESRD and can be associated with intracranial aneurysms and mitral valve prolapse.

ARF may be reversible if precipitating factors are identified and corrected. Dividing ARF into prerenal, renal, and postrenal categories allows a systematic approach. Prerenal causes can often be differentiated by calculating the BUN-creatinine ratio. A ratio of 20 or greater suggests a prerenal cause, with hypovolemia or hypotension being most common. Fractional excretion of sodium (FE_{Na}) of less than 1% also suggests prerenal azotemia and can be calculated by the following formula:

$$FE_{Na} = \frac{P_{Cr}/U_{Cr}}{P_{Na}/U_{Na}}$$

Obstruction will result in dilated ureters and enlarged kidneys and is always in the differential diagnosis of ARF. Prompt identification with ultrasound leads to attempts to decompress the outflow tract. Rhabdomyolysis can cause ARF and is treatable.

GFR decreases with age, and the renal reserve of a normal 80-year-old is less than half that of a 40-year-old. The creatinine level is often not an accurate indicator of renal function, especially in elderly individuals. A doubling of serum creatinine from 0.8 to 1.6 mg/dL represents a halving of the GFR. The GFR can be reduced 50% or more without a rise in creatinine. Creatinine does not exceed the normal limits until the GFR has fallen below 50 mL/min. The Cockcroft-Gault formula can be used to estimate GFR:

$$\text{Creatinine clearance} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times (0.85 \text{ if female})}{72 \times \text{Serum creatinine (mg/dL)}}$$

Online calculators to estimate renal function are available at www.nephron.com. Calculation of an eGFR can be done in elderly patients, those with an elevated serum creatinine, or individuals with other risk factors for CKD.

Chronic renal disease is a significant risk factor for cardiovascular morbidity and mortality and is an ACC/AHA intermediate cardiac risk factor considered to be equal to angina, MI, or a history of known CAD. The annual incidence of death from CAD in patients with both diabetes and ESRD who require hemodialysis is 8.2%. A creatinine concentration of 2.0 mg/dL or higher should trigger an assessment of cardiac risk under the ACC/AHA guidelines, simplified in Figure 34-2.[7] See the section "Ischemic Heart Disease" for a more detailed discussion of these guidelines. Pericarditis, pericardial effusions, and diastolic and systolic dysfunction can be present. Valvular heart disease is common in patients undergoing maintenance dialysis. Abnormalities include valvular and annular thickening and, most significantly, calcification of the heart valves resulting in regurgitation or stenosis (or both).[70] Mitral and aortic valve calcifications (40% and 55% of patients, respectively) and stenosis (11% to 13%) occur. Valvular calcifications progress to stenosis at an accelerated rate in dialysis patients.[71] Systemic hypertension is almost ubiquitous but is generally easier to manage with initiation of dialysis. Pulmonary hypertension and increased cardiac output occur in many patients with an arteriovenous fistula.

Renal failure results in anemia from lack of erythropoietin production by the kidneys, but in the present era of aggressive erythropoietin replacement, many of these patients have normal or high hematocrits, which actually increases morbidity and vascular events.[30] Patients with CKD can have platelet dysfunction and increased bleeding despite a normal platelet count, prothrombin time (PT), and aPTT. Once on dialysis, patients are more prone to hypercoagulable states. Chronic metabolic acidosis is common but usually mild and compensated for by chronic hyperventilation. Patients may exhibit electrolyte and calcium abnormalities, pulmonary and peripheral edema, anemia, hypercholesterolemia, and hypoalbuminemia. Hyperkalemia is the most serious electrolyte disturbance. Hypocalcemia is common with dialysis, and eventually secondary and tertiary hyperparathyroidism develops. Chronically elevated troponin and creatine kinase levels are common in patients maintained on dialysis. Worsening renal function should be suspected in diabetics who have improved glycemic control or unexpected hypoglycemia because insulin is metabolized by the kidneys and has a prolonged duration of action with progressive renal dysfunction. Autonomic and peripheral (sensory and motor) neuropathies can occur.

Patients at risk for perioperative renal failure include those with preexisting renal insufficiency (the single strongest predictor) or diabetes, especially in combination, and those undergoing procedures with the administration of contrast medium. If all three conditions are present, the risk of renal failure may be as high as 12% to 50%. Preoperative identification of at-risk patients alters management, such as hydration, administration of sodium bicarbonate, a change in the type of contrast medium, and avoidance of hypovolemia (see Chapter 65). This may require admission preoperatively. Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX-2) inhibitors interfere with autoregulation of renal perfusion and should be avoided or discontinued in patients with or at risk for renal insufficiency. Cyclosporine and aminoglycoside antibiotics can cause renal insufficiency. ACEIs and ARBs prevent deterioration in patients with diabetes or renal insufficiency but may worsen function during hypoperfusion states.

Many drugs are metabolized or cleared by the kidneys. Drugs with particular implications for anesthesia and surgery are the LMWHs because there is no easy method of monitoring their anticoagulation effects. All the LMWHs available in the United States are cleared by the kidneys and are not removed during dialysis. Therefore, LMWH has a prolonged duration of action in patients with CKD. The risk of significant bleeding or hematomas with centroneuraxial anesthesia may be increased.

Preoperative evaluation of patients with renal insufficiency or failure should focus on the cardiovascular and cerebrovascular systems, fluid volume, and electrolyte status. The early stages of

CKD typically cause no symptoms. Inquiring about the cardiovascular systems (chest pain, orthopnea, paroxysmal nocturnal dyspnea), urine output, associated comorbid conditions, medications, and dialysis schedules is vital. Understanding changes in patient weight is one method of assessing volume status.

In patients with or at risk for renal disease (especially those with two of the following: diabetes, poorly controlled hypertension, advanced age), an ECG and determination of electrolytes, calcium, glucose, albumin, BUN, and creatinine should be performed if the results will have an impact on management. LVH (from hypertension), peaked T waves (hypokalemia), flattened T waves, and prolonged PR and QT intervals (hypokalemia) prompt further evaluation. A chest radiograph (infection or volume overload), echocardiogram (for murmurs or heart failure), and stress testing (see ACC/AHA guidelines) may be indicated in certain patients. Many of these patients will benefit from cardiology evaluation based on these tests as discussed earlier. Venous access or blood draws from the brachial, cephalic (antecubital), and central veins in the nondominant upper extremity should be avoided in patients who may need fistulas for dialysis in the future.

Preoperative renal replacement therapy (dialysis) schedules should be determined, with scheduling of surgery ideally within 24 hours after dialysis. In elective cases, dialysis is best performed within 24 hours of surgery but not immediately before because of acute volume depletion and electrolyte alterations. Dialysis is associated with fluid and electrolyte (sodium, potassium, magnesium, phosphate) imbalance and shifting of electrolytes between the intracellular and extracellular compartments. Dialysis should be performed to correct volume overload, hyperkalemia, and acidosis. Coordinating the scheduling of dialysis and elective surgery is an important aspect of preoperative care.

Contrast-Induced Nephropathy

Contrast-induced nephropathy is defined as a 25% rise in creatinine above baseline after the administration of a radiocontrast agent (see Chapter 79). Patients with diabetes and CKD are at greatest risk, although radiocontrast media causes a transient decrease in the GFR in most individuals. Renal failure requiring dialysis after contrast-induced nephropathy is associated with less than a 20% 2-year survival rate, and a third of patients die during the initial hospitalization.

Hepatic Disorders

Liver disease can affect hepatocytes, the biliary system, or both (see Chapters 17 and 66). Liver disease affects protein synthesis, including coagulation factors and albumin, drug and toxin metabolism, and bile regulation. Hepatocellular diseases, including viral, alcoholic, and autoimmune hepatitis or hepatocellular carcinoma, affect hepatocytes and synthetic function of the liver. Obstructive disorders, including choledocholithiasis and bile duct tumors (extrahepatic), primary biliary cirrhosis (intrahepatic), or primary sclerosing cholangitis (extrahepatic and intrahepatic), cause bile stasis. Most drug-induced liver disease and some forms of viral hepatitis affect both hepatocytes and the biliary system.

Hepatitis

Hepatitis is a term used to describe inflammation of hepatocytes and can be caused by drugs, alcohol, viruses (hepatitis A, B, C, D, and E), or autoimmune diseases. All of these conditions have acute and chronic phases that can progress to cirrhosis, which is irreversible fibrosis of the liver. Risk factors for hepatitis are alcohol use, sexual activity (multiple partners, sex industry workers, sex with sex industry workers, or men who have sex with men), intravenous drug use, blood transfusions before 1992, travel to underdeveloped countries, obesity, tattoos, and body piercing. Hepatitis A is caused by contaminated food or water or contact with an infected person and rarely progresses beyond the acute illness. A remote history of hepatitis A has no significance perioperatively. Hepatitis B is transmitted by sexual activity or contact with blood (rarely from transfusions since screening was implemented in 1986). It varies in severity but is much less common since the widespread use of vaccination against this virus. Hepatitis C is caused primarily by blood exposure (blood has been screened since 1992), most often in intravenous drug users. Many patients are unaware of infection because the acute phase is frequently asymptomatic but can advance to cirrhosis. Hepatitis D occurs only with hepatitis B, and hepatitis E is rare in developed countries. Alcoholic hepatitis generally occurs after at least 10 years of daily moderate to heavy alcohol intake (>3 drinks/day for women; >5/day for men) and may progress to cirrhosis. Autoimmune hepatitis primarily affects young women and has no known cause. Virtually any drug, as well as herbals and over-the-counter preparations, can cause hepatitis, including statins, isoniazid, and acetaminophen.

Obstructive Jaundice

Extrahepatic bile duct obstruction is caused by gallstones, tumors (pancreatic, gallbladder, bile duct, ampulla of Vater), or scarring. Patients may have jaundice, pruritus, and abdominal pain. Predictors of surgical mortality are a preoperative hemocrit of less than 30%, bilirubin concentration greater than 11 mg/dL, and malignancy, and death may occur in as many as 60% if all three are present.[72] Renal failure develops in up to 8% of these patients postoperatively, which may be lessened with administration of bile salts or lactulose.[73]

Miscellaneous Liver Diseases

Wilson's disease, hemochromatosis, and α_1-antitrypsin deficiency are less common than hepatitis, are hereditary, and commonly occur in members of the same family. Obesity can result in nonalcoholic steatohepatitis, also known as "fatty liver," which causes abnormal LFT results and can progress to fibrosis. Primary biliary cirrhosis is an autoimmune disorder that results in intrahepatic biliary obstruction; it occurs most frequently in middle-aged women and is associated with antimitochondrial antibodies. Primary sclerosing cholangitis destroys bile ducts, is most frequent in young males, is associated with inflammatory bowel disease but can be idiopathic, and may progress to cirrhosis. Acute illnesses such as sepsis, surgery, and anesthesia can cause hepatic dysfunction. Gilbert's syndrome is a benign familial disorder with mildly elevated bilirubin and has no perioperative significance.

Remote History of "Hepatitis"

Patients may recount a history of "having hepatitis" many years before but little other information is known. One must take a careful preoperative history to determine circumstances surrounding the onset (e.g., transfusions, travel, exposure to risky situations) and whether any sequelae of chronic liver disease are present. It is important to clarify whether the episode occurred

during or soon after surgery. Although halothane is rarely used in adults in the United States today, those who previously had halothane hepatitis may be at risk for cross-sensitivity to other fluorinated volatile agents with trifluoroacetyl metabolites (enflurane, isoflurane, desflurane).

Cirrhosis

Cirrhosis is the end result of most hepatotoxic conditions. Portal hypertension with splenomegaly, varices, ascites, and pleural effusions occur. The liver fails to synthesize proteins and clotting factors or clear toxins and drugs. Patients may have encephalopathy, bleeding, thrombocytopenia, and a prolonged PT and are at risk for renal insufficiency or failure. Pulmonary shunting may cause hypoxemia and pulmonary hypertension. Hepatorenal syndrome is the occurance of renal insufficiency in patients with hepatic disease in the absence of primary renal disease and may be related to hypoperfusion. Jaundiced patients are at particular risk for hepatorenal syndrome. Spontaneous bacterial peritonitis may develop in patients with ascites and increases perioperative mortality.

The Child-Turcotte-Pugh classification (Table 34-5) can predict perioperative morbidity and mortality. The Model for End-Stage Liver Disease (MELD) formula, which factors bilirubin, the international normalized ratio (INR), creatinine, and the cause of the liver disease, is used to select patients for transplantation, may be useful to predict risk for other surgery, and may do so better than the Child class.[74] Online calculators to determine MELD can be found at www.unos.org. Higher scores indicate more severe disease. One study showed that a MELD score lower than 14 predicted 77% of patients with poor outcomes.[74] Anemia increases postoperative mortality in patients with obstructive jaundice. One study did show that a serum albumin concentration of less than 2.1 mg/dL was a strong predictor of mortality in veterans undergoing major noncardiac surgery.[75]

Unexpected Increased Liver Function Test Values

Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reflect damage to hepatocytes, bilirubin measures the liver's ability to conjugate or excrete bile (or both), alkaline phosphatase rises with degradation of hepatic excretion (also from bone turnover and thus nonspecific for liver disease), and albumin and PT measure synthetic function of the liver. Only 1 in 700 preoperative patients is unexpectedly found to have liver disease, and the vast majority are not severe disorders. However, if abnormal LFT values are unexpectedly found, further testing or referral may be warranted. In patients with elevations in ALT or AST, screening for hepatitis with hepatitis A IgM antibody, hepatitis B surface and core antigens, hepatitis B surface antibody, and hepatitis C antibody can help in establishing a diagnosis. Elevated alkaline phosphatase or bilirubin with normal or mildly to moderately increased transaminases suggests obstruction of the biliary system, and abdominal ultrasound, computed tomography, and endoscopic retrograde cholangiopancreatography can establish a diagnosis.

Table 34-5 Child-Turcotte-Pugh Classification

	Points (For Each with a Maximum of 15)		
Parameter	**1**	**2**	**3**
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds over control)	<4	4-6	>6
Encephalopathy	None	Grade 1-2	Grade 3-4

Class A: <7 points; Class B: 7-9 points; Class C: >9 points.

All Forms of Liver Disease

The preoperative history often uncovers the cause of the liver disease, therapies, and associated complications. Important issues to explore include the cause and degree of hepatic dysfunction. Patients with liver disease may be asymptomatic or complain of fatigue, weight loss, dark urine, pale stools, pruritus, right upper quadrant pain, bloating, and jaundice. Weight and vital signs, including oxygen saturation, are needed. Physical examination may reveal jaundice, bruising, ascites, pleural effusions, peripheral edema, or hypoxia. The presence of encephalopathy, coagulopathy, ascites, volume overload, and infectivity needs to be determined and explored preoperatively. The bilirubin level is generally higher than 2.5 mg/dL before icterus can be seen in mucous membranes and sclerae. Examination may reveal hepatomegaly, splenomegaly, and altered mental status. New-onset or worsening encephalopathy prompts an evaluation for precipitating factors such as worsening liver disease, infection, drug effects, bleeding, or electrolyte disturbances.

In selected patients, preoperative evaluation may warrant further testing consisting of an ECG, CBC with platelet count, electrolytes, BUN, creatinine, LFTs, albumin, and PT. An ammonia level may be helpful in patients with encephalopathy. A chest radiograph may identify effusions. Coagulopathy can be a result of vitamin K deficiency caused by an inability to secrete bile (cholestatic disorders), deficiency of coagulation factors because of loss of synthetic function as a result of cirrhosis, or thrombocytopenia secondary to splenomegaly and portal hypertension.

Therapy to correct coagulopathy is directed at the cause. Vitamin K, fresh frozen plasma, or platelets are used to correct deficiencies. Vitamin K, 1 to 5 mg orally or subcutaneously daily for 1 to 3 days, may correct a prolonged PT and carries minimal risk. However, the coagulopathy in patients with synthetic failure will probably not correct with such measures, and performing a type and screen will prepare the patient for platelet and fresh frozen plasma transfusions with the goal of achieving a platelet count higher than 50,000/mm^3 and an INR less than 1.5, respectively. Correction of anemia is controversial but may limit renal dysfunction. Lactulose (30 mL orally every 6 hours for 3 days before surgery with the last dose given within 12 hours of surgery) or oral bile salts with intravenous hydration beginning the night before surgery may reduce perioperative progression of renal disease in patients at risk.[76] Reduction of ascites preoperatively may decrease the risk of wound dehiscence and improve pulmonary function. Sodium restriction (in diet and intravenous solutions), diuretics (especially spironolactone, which inhibits aldosterone), and even paracentesis are useful. If fluid is aspirated, it is important to analyze it for infection. Encephalopathy is frequently caused by an acute insult such as infection, gastrointestinal bleeding, hypovolemia, or sedatives. It is important to determine reversible factors and treat accordingly. Lactulose, 30 mL every 6 hours orally, is first-line therapy. Addressing nutritional deficiencies with enteral or parenteral supplementation

may have benefit, especially in alcoholic patients. Patients who abuse alcohol are at risk for neurologic deterioration if thiamine, folate, and vitamin B_{12} supplements are not provided, particularly when nutrition or glucose is given. These patients are also at risk for alcohol withdrawal syndromes (see the appropriate section).

Delaying elective surgery until after an acute episode of hepatitis or an exacerbation of chronic disease has resolved or until a diagnosis is established if hepatic dysfunction is newly detected is appropriate.[74] Elective surgery is contraindicated in patients with acute or fulminant liver disease, including alcoholic (mortality >55%), viral (mortality >10%), or undefined hepatitis. Perioperative risk in patients with chronic hepatitis or cirrhosis is predicted by its histologic severity (bridging or multilobular necrosis on biopsy), impairment of the synthetic and excretory functions of the liver, and portal hypertension (ascites, varices, bleeding).

Patients with severe liver disease have increased perioperative morbidity and mortality.[77] Perioperative management is discussed in Chapter 66. The most common adverse events are bleeding, infection, liver failure, and hepatorenal syndrome (renal failure in patients with portal hypertension but otherwise normal kidneys).

Hematologic Disorders

Anemia

Anemia may be a known problem or a suspected possibility based on a patient's history of underlying medical conditions or the reason for surgery. It is useful to determine the etiology, duration, and stability of the anemia, related symptoms, and therapy (especially transfusions), although the evaluation needs to consider the extent and type of surgery, the anticipated blood loss, and the patient's comorbid conditions that may influence oxygenation or be affected by hypoxia, such as pulmonary, cerebrovascular, or cardiovascular disease. Inquiring about a personal or family history of anemia is important.

The World Health Organization defines anemia as a hemoglobin level lower than 13 g/dL in adult men and less than 12 g/dL in adult women. The consequences of moderate levels of anemia and hemoglobin levels of 6.0 g/dL or higher in patients without CAD are minimal. The ASA Task Force on Blood Component Therapy concluded that red blood cells should not be transfused solely because of a hemoglobin level but rather because of risk for complications from inadequate oxygenation (see Chapter 55).[78] A recent Veteran's Affairs study suggests that even mild preoperative anemia increases postoperative mortality and cardiac morbidity, but only in men.[31] This study found that individuals with hematocrits between 39% and 51% had the lowest risk for adverse outcomes.

Preoperative patients at risk for anemia include those with a history of colon cancer, gastrointestinal or genitourinary bleeding, metrorrhagia, chronic infections, inflammatory diseases, nutritional deficiencies (including gastric bypass recipients), and a host of other conditions. Anemia is the most common preoperative hematologic disorder. An important component of the history and physical examination includes asking about palpitations, fatigue, chest pain, black or bloody stools, weight loss, pallor, murmurs, hepatospenomegaly, or lymphadenopathy.

Preoperative evaluation of patients with anemia or suspected anemia will benefit from a CBC. Generally, further evaluation should be done by a primary care physician or hematologist, but initial studies include a peripheral smear, determination of mean corpuscular volume (MCV), a reticulocyte count, and further testing such as iron studies, vitamin B_{12}, or folate levels, depending on the findings on the smear and the MCV. MCV, iron, and ferritin are low and total iron-binding capacity (TIBC) is high in iron deficiency anemia. MCV and TIBC are low or normal and iron and ferritin are normal or high in anemia associated with chronic disease. MCV is high and vitamin B_{12} or folate levels are low in macrocytic anemia associated with these deficiencies. Type and screening and preoperative transfusion may be necessary, depending on the level of anemia and anticipated surgical blood loss.

In special circumstances, such as a patient's refusal of perioperative blood transfusion or elective procedures with expected significant blood loss in anemic patients, postponement of surgery to treat with recombinant human erythropoietin and iron may be warranted.

Sickle Cell Disease

Sickle cell disease, a hereditary hemoglobinopathy with vaso-occlusion, is responsible for most of the associated complications. Patients homozygous for hemoglobin S (HbS) have disease and are at risk for major morbidity and a shortened life expectancy. Patients with SC disease have both HbS and HbC and a much less severe clinical course with moderate anemia. Heterozygous patients (HbS and HbA) have sickle cell trait and rarely have any consequences related to this condition. Preoperative assessment should focus on identification of organ dysfunction and acute exacerbations.[80] Patients may have renal insufficiency, splenomegaly, pulmonary hypertension and infarction, cerebrovascular accidents, and heart failure. They are at increased risk for infection because of splenic infarction. Frequent hospitalizations or a recent increase in hospitalizations, advanced age, preexisting infections, and pulmonary disease are predictive of perioperative vaso-occlusive complications.[79]

The preoperative history and physical examination should focus on the frequency, severity, and pattern of vaso-occlusive crises and the degree of pulmonary, cardiac, renal, and central nervous system damage. Pulse oximetry, hematocrit, measurement of BUN and creatinine, an ECG, and a chest radiograph should be considered. Additional testing (e.g., echocardiogram, arterial blood gases) may be needed in rare instances. Prophylactic transfusion may be beneficial, especially before intermediate- to high-risk cases. Preoperative prophylactic transfusion is controversial, and the decision to transfuse should be made in concert with a hematologist familiar with the disease. The Cooperative Study of Sickle Cell Disease concluded that preoperative transfusion was beneficial, although patients undergoing low-risk surgery had few complications even without transfusion.[80] Another study showed that a conservative transfusion regimen (decreasing HbS to <60% and hemoglobin to 10 g/dL) was as effective as a more traditional approach (transfusing to decrease HbS to <30% and hemoglobin to 10 g/dL). Additional benefits included fewer transfusion-related complications.[81]

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase deficiency is an X-linked hereditary Coombs-positive hemolytic anemia. Hemolysis occurs with exposure to drugs (antipyretics, nitrates, sulfonamides), infections, hypoxia, hypothermia, blood products, or stress. The

severity of the hemolysis varies among patients and the offending agent or condition. Steroids are usually effective. The preoperative history focuses on previous episodes of hemolysis, identification of predisposing factors, and determination of the current hematocrit.

Coagulopathies

Hypocoagulable states are either inherited disorders such as the hemophilias and thrombocytopenia or are acquired disorders secondary to liver disease, malnutrition, or drug exposure. To determine the diagnosis and risk of bleeding, one inquires about known diagnoses, tests, treatments, previous bleeding episodes, and family history. Asking about excessive bruising, prolonged bleeding after cuts, heavy menstrual cycles, and bleeding gums is sensitive but not specific. A *change* in one of these factors is more meaningful than a chronic history becauses what one individual considers excessive may actually be normal.

The preoperative evaluation inquires into excessive bleeding after previous procedures or childbirth, especially if transfusions were unexpectedly required; such bleeding is more definitive but not diagnostic. Petechiae, multiple bruises, hematomas, jaundice, and frank bleeding are important findings. Diagnostic testing may include a platelet count, CBC, PT, and aPTT. *Routine* screening for coagulopathies with a PT, aPTT, or a bleeding time without an indication is not indicated. If specific causes of bleeding are suspected or known, such as liver disease or malnutrition, targeted testing with liver enzyme, protein, and albumin levels and a PT is needed.

In the case of a prolonged PT without a history of warfarin use, the most common cause is laboratory error, liver disease, or malnutrition. One should first repeat the test. If the test is abnormal again, referral to a hematologist or the primary care physician or evaluation of liver enzymes and a hepatitis panel may be warranted, depending on the surgery. A trial of vitamin K (1 to 5 mg orally once a day for 3 days) can be initiated. A prolonged aPTT can result from both hypocoagulable and hypercoagulable conditions. The first step is to repeat the test and ascertain exposure to heparin. Even small amounts of heparin present in indwelling catheters, especially if the blood is drawn from that site, can prolong the aPTT. The most common cause of a prolonged aPTT other than heparin exposure is von Willebrand's disease (vWD), but other hemophilias discussed later can prolong the aPTT. Factor V Leiden, anticardiolipin antibody, and lupus anticoagulants, which result in increased clotting, cause prolongation of the aPTT. Further testing for a prolonged aPTT includes a repeat aPTT; an aPTT mixing study; lupus anticoagulant; evaluation of coagulation factors VII, IX, XI, and XII; and checking von Willebrand factor (vWF) antigen and ristocetin cofactor levels. A mixing study, in which normal blood is mixed with the subject's blood, will detect factor deficiencies (the aPTT will correct with this test) or inhibitors (the aPTT will not correct).

Hemophilias

Hemophilia A (factor VIII deficiency) and hemophilia B (or Christmas disease) are X-linked recessively inherited disorders that occur almost exclusively in males. Hemophiliacs have a prolonged aPTT and normal PT. The severity of bleeding varies among individuals but tends to be similar in relatives and is directly related to the degree of factor deficiency. Even mild trauma can result in significant hemorrhage. Orthopedic procedures account for 50% of operations in hemophiliacs because recurrent bleeding destroys joints. Hemophilia A accounts for 85% of all cases of hemophilia.

A hematologist should be involved in the perioperative care of these patients. A detailed plan to monitor and replace deficient factors is paramount. Typically, factors VIII and IX are maintained at 75% to 100% in the immediate perioperative period and then at 50% until any risk of bleeding is past. Each unit of recombinant or purified factor concentrate raises the factor level by 2% per kilogram. Intramuscular injections are to be avoided.

Von Willebrand's Disease

vWD is an inherited disorder of factor VIII and vWF that affects both genders. It is the most common congenital coagulopathy and is estimated to occur in 1% of individuals.[82] Several types (1, 2A, 2B, 2M, and 2N) are autosomal dominant, and type 3 is recessive. Factor VIII and vWF circulate as a complex, and vWD results from both quantitative and qualitative deficiencies. Most patients have a prolonged aPTT, but those with mild disease may have a normal aPTT. The most common cause of a prolonged aPTT in patients not taking heparin is vWD. vWD is diagnosed by measuring ristocetin cofactor (a functional assay for vWF that causes platelet aggregation in the presence of ristocetin), vWF antigen, and factor VIII. vWF is an acute-phase reactant that increases with certain conditions such as stress or surgery, which sometimes makes the diagnosis difficult. Most patients with vWD will have a history of bleeding, but in some the diagnosis will not be made until a second challenge to coagulation occurs, including major surgery or exposure to drugs such as aspirin or NSAIDs.

Involvement of a hematologist in the care of these patients is beneficial. Desmospressin (1-desamino-8-D-arginine vasopressin [DDAVP]) increases release of factor VIII, vWF, and plasminogen activator from endothelial cells. An intravenous dose of 0.3 μg/kg (given over a period of 15 to 30 minutes to avoid hypotension, flushing, and tachycardia) typically raises vWF threefold to fourfold. However, there is considerable variation among individuals, so vWF and factor VIII levels must be monitored. Desmopressin is available as a nasal spray and should not be given more frequently than every 48 hours to avoid depletion of endothelial stores. To avoid release of plasminogen activator by desmopressin, ε-aminocaproic acid or tranexamic acid is given. Desmopressin is contraindicated in patients with type 2B because it increases abnormal vWF and may result in thrombocytopenia. Cryoprecipitate or factor VIII concentrates containing vWF will replace abnormal vWF.

Thrombocytopenia

Thrombocytopenia is a platelet count lower than 150,000/mm^3 and results from decreased production, increased destruction, or sequestration. Malignancies, drugs, autoimmune disorders, preeclampsia, hereditary disease, and disseminated intravascular coagulation can cause thrombocytopenia. In patients found to have low platelet counts unexpectedly, first repeat the test, examine the peripheral smear, and collect blood for a platelet count in a tube without ethylenediaminetetraacetic acid (EDTA). EDTA is a chelating agent added to tubes commonly used for determination of the CBC because it prevents clotting. However, in some patients it causes clumping of platelets resulting in pseudothrombocytopenia.

Recent exposure to heparin raises the issue of heparin-induced thrombocytopenia (HIT), which generally occurs within

5 to 10 days after exposure to heparin.[83] HIT is an immune-mediated disorder with antibodies directed against platelets and can result in arterial or venous thrombosis, stroke, amputations, and death in up to 30% of patients. Immediate discontinuation of heparin and testing for heparin-induced platelet antibodies are indicated. LMWH is less likely than unfractionated heparin to cause HIT but is contraindicated in patients with HIT. Alternative anticoagulants are danaparoid sodium, lepirudin, and argatroban. Idiopathic thrombocytopenic purpura is a chronic autoimmune disorder with autoantibodies against platelets that results in increased destruction. Patients are treated with corticosteroids and splenectomy (to eliminate the major site of platelet removal). Patients often have minimal bleeding at even very low platelet levels, probably because of increased turnover and a predominance of young platelets.

Surgery can be performed safely in patients with platelet counts higher than 50,000/mm^3. The risk of bleeding is inversely related to platelet counts lower than 50,000/mm^3. Anemia, fever, infections, and drugs that affect platelet function increase bleeding at any platelet level. Centroneuraxial anesthesia is safe with platelet counts higher than 100,000/mm^3.[84] Patients with newly discovered thrombocytopenia may benefit from hematology consultation before elective surgery. One unit of platelets transfused typically raises the count by 10,000/mm^3.

Thrombocytosis

Thrombocytosis is a platelet count greater than 500,000/mm^3 and may be physiologic (exercise, pregnancy), primary (myeloproliferative disorder), or secondary (iron deficiency, neoplasm, surgery, chronic inflammation). Platelet counts greater than 1,000,000/mm^3 place patients at risk for thrombotic events such as stroke, MI, pulmonary and mesenteric emboli, and peripheral arterial and venous clots. Patients with primary thrombocytosis (essential thrombocythemia) have a bleeding tendency that is worsened by exposure to drugs such as aspirin. Older patients and those with a previous history of bleeding or thrombosis may be at increased risk. Hydroxyurea, anagrelide (these drugs decrease production, so 7 to 10 days is needed), or plasmapheresis (removes platelets, so the effect is immediate) may be used to lower the platelet count. Treatment of the underlying disorder of secondary causes of thrombocytosis usually results in normalization of the platelet count.

Polycythemia

Polycythemia is a hematocrit greater than 54% and can be primary (polycythemia vera) or secondary to chronic hypoxia (COPD, high altitude, congenital heart disease). A steep increase in blood viscosity, which is thrombogenic, occurs with hematocrits higher than 50%. High hematocrits are associated with increased atherosclerosis (carotid stenosis, stroke) and cardiovascular disease (heart failure, MI). There are contradictory reports on whether polycythemia increases perioperative risk. A recent study showed an increase in postoperative mortality in men but not women with hematocrits higher than 51%.[31] However, an earlier report found no increased perioperative complications in patients with secondary polycythemia.

The preoperative evaluation (history and physical examination) focuses on the pulmonary and cardiovascular systems. Examination for cyanosis, clubbing, wheezing, and murmurs is necessary. Oxygen saturation, an ECG, and possibly arterial blood gas analysis and a chest radiograph are needed in patients with polycythemia. An unexpected preoperative finding of polycythemia should prompt an investigation to find the cause and, if not readily apparent, the possibility of polycythemia vera.

Risk of Thromboembolism or Pulmonary Emboli

Fatal pulmonary embolism occurs in 0.1% to 0.8% of patients undergoing elective general surgery, 2% to 3% of patients having elective hip replacement, and 4% to 7% of patients undergoing repair of a fractured hip who do not receive prophylaxis. The risk for venous thrombosis is increased in patients with previous venous thromboembolism, obesity, varicose veins, diabetes, cancer, heart failure, pregnancy, paralysis, the presence of an inhibitor deficiency state, or age younger than 50 years.[85] Factor V Leiden is the most common cause of inherited thrombophilia (40% to 50% of cases). The prothrombin gene mutation and deficiencies in protein S, protein C, and antithrombin account for most of the remaining cases. The risk of perioperative venous thromboembolism depends on the surgical procedure (e.g., degree of invasiveness, trauma, and immobilization) and patient-related variables (e.g., inflammatory bowel disease, acute illness, smoking, malignancy, obesity, increasing age, previous thromboembolism, estrogen use, hypercoagulable state).[86] Primary thromboembolic prophylaxis is beyond the scope of this chapter, but it is important to risk-stratify patients preoperatively so that appropriate measures can be implemented on the day of surgery. Because of the high risk of thromboembolism in patients undergoing elective lower extremity joint replacement, these patients are often given a dose of warfarin the night before surgery. American Society of Regional Anesthesiologists guidelines specifically state that if a single dose of warfarin has been administered within the previous 24 hours, it is safe to perform neuraxial anesthesia.[87]

Recent arterial or deep venous thromboembolism (DVT) requires perioperative interventions or postponement of nonlifesaving procedures. Without anticoagulation, the risk for recurrent DVT within 3 months of a proximal DVT is approximately 50%. A month of warfarin treatment reduces the risk to 10%, and 3 months reduces it to 5%. Patients with a hereditary hypercoagulable state (e.g., antithrombin III or protein C or S deficiency, prothrombin gene mutation, Factor V Leiden), cancer, or multiple episodes of DVT are at higher risk indefinitely. Patients with nonvalvular atrial fibrillation who have had a previous cerebral embolism are also at higher risk. Patients with mechanical heart valves, especially multiple valves, are at risk for embolism. Risk is greater with mitral than with aortic valves. Surgery increases the risk for DVT, but there is no such evidence that surgery increases the risk for arterial embolism in patients with atrial fibrillation or mechanical valves.[84]

Preoperative evaluation determines whether "bridging" with either unfractionated heparin intravenously or LMWH subcutaneously as an outpatient (or not to bridge) is warranted for patients with mechanical heart valves or previous episodes of thromboembolism secondary to atrial fibrillation. The decision needs to be made in concert with the treating physician or a cardiologist.

The authors believe that elective surgery should be postponed in the first month after an episode of venous or arterial thromboembolism. If postponement is not possible, the patient should receive preoperative heparin while the INR is below 2.0.[84] Ideally, 3 months of anticoagulation is recommended before elective surgery. Typically, withholding warfarin for 5 days will allow

the PT/INR to fall to normal if the INR is chronically maintained between 2.0 and 3.0, the usual therapeutic targets. It may be necessary to withhold more doses if the INR is more prolonged or fewer doses if subtherapeutic. Therefore, it is necessary to check the INR during the preoperative visit to guide cessation of therapy. During the time without warfarin, patients may be at risk for recurrent thromboembolism, but the risk is relatively small in all but the highest-risk patients. It is controversial whether patients require "bridging" or heparin during this period. Previously, the only option was hospital admission for intravenous heparin therapy, which is costly. However, with the availability of LMWH, patients can receive subcutaneous (usually self-administered) LMWH at home without the need for monitoring.

Neurologic Disease

In patients with neurologic disease, a detailed history is required with a focus on recent events, exacerbations, or evidence of poor control of the medical condition. Information about previous investigations or therapy is important. A basic preoperative neurologic examination documenting deficits in mental status, speech, cranial nerves, gait, and motor and sensory function is important. This baseline determination allows comparison of new deficits postoperatively.

Cerebrovascular Disease

If a stroke or transient neurologic deficit has not been fully evaluated or has occurred recently, elective surgery should be considered pending complete evaluation because a history of stroke or symptoms of cerebrovascular insufficiency are strong predictors of perioperative stroke.[88] High-quality data are lacking on how soon after an event anesthesia and surgery are safe. The etiology and treatment guide further perioperative management. An embolic stroke from a patent foramen ovale (PFO) may require correction of the PFO or strict attention to avoidance of air emboli. A left atrial or ventricular thrombus or an embolic stroke secondary to atrial fibrillation or mechanical heart valves requires a minimum of 1 month and preferably 3 months of anticoagulation and possible bridging with short-acting anticoagulants for elective surgery.[84] Atrial fibrillation (either chronic or new onset) is a common cause of perioperative stroke, especially those occurring postoperatively, the most common time for stroke.[89]

Asymptomatic Bruit

A newly discovered carotid bruit requires a careful searching for symptoms of cerebral ischemia or transient ischemic attack, especially if the procedure is likely to involve manipulation of the neck or the patient has a potentially difficult airway. Frequently, patients will not have volunteered pertinent symptoms until specifically probed, especially if they were transient. Patients with risk factors for carotid atherosclerosis, including those who have undergone head and neck irradiation, especially at a younger age, need to be questioned specifically about amaurosis fugax, dysphagia, dysarthria, and other symptoms of cerebovascular insufficiency. One of the authors met a college professor in the preoperative clinic who was scheduled for an abdominal procedure and had a history of Hodgkin's lymphoma as a teenager. After a carotid bruit was ausculated, the patient confirmed receiving mantle irradiation for her lymphoma, but it took much probing to elicit a history of two transient episodes of slurred speech within the previous month. The patient was found to have 99% occlusion of her left internal carotid artery.

In patients who have truly asymptomatic bruits, significant carotid lesions are present 40% to 60% of the time, the risk of stroke in this group is 1% to 2% per year, and most strokes are preceded by transient symptoms.[90] A significant prospective, randomized multicenter trial found that patients with asymptomatic carotid stenosis of 60% or greater benefited from revascularization if they were considered good risk and the surgeon had a 3% or lower perioperative morbidity and mortality rate.[91] However, after reviewing the published data, a more recent Symposium on Cerebrovascular Diseases concluded that because progression rates are extremely slow and patients with carotid stenosis are at substantial risk for MI and vascular death, revascularization should be contemplated only in centers with low complication rates for medically stable patients, those expected to live at least 5 years with 80% or greater stenosis.[90] There is no evidence that truly asymptomatic bruits increase the risk for perioperative stroke. Carotid Doppler ultrasound studies are simple effective tools to evaluate at-risk patients who might benefit from further evaluation. Significant abnormalities on Doppler studies should prompt referral to a vascular surgeon or neurologist.

Seizure Disorder

The type and frequency of seizures (e.g., grand mal or absence) and the specifics of symptoms such as staring or focal findings are important to ascertain and document. Absence (previously petit mal) seizures may be particularly difficult to recognize because they lack generalized motor signs. More typical symptoms such as staring and obtundation may be misinterpreted as residual anesthetic effects in the postoperative period. Brain tumors, aneurysms, arteriovenous malformations (AVMs), classic epilepsy, drug toxicity, electrolyte disorders, infections, and vascular disease from arteriosclerosis, stroke, sickle cell disease, or SLE can all cause seizures.

Preoperative evaluation and documentation of anticonvulsants and the adequacy of seizure control are necessary. Routinely ordering tests for serum drug levels of anticonvulsant medications is not indicated unless toxicity is a concern or the patient is having breakthrough seizures. Patients with good control of seizures may have levels outside the therapeutic range, and the results may be confounded if the timing of administration of the drugs in relation to when the blood is drawn is not considered. Generally, trough levels are necessary for accurate interpretation. Medications to control seizures have multiple side effects (bone marrow suppression, macrocytic anemia, leukopenia, hyponatremia), and testing should be directed at suspected abnormalities. A CBC with a platelet count and electrolyte levels are most commonly obtained. Poorly controlled or new-onset seizures require consultation with a neurologist before proceeding with anything other than emergency surgery. Continuation of anticonvulsants in the perioperative period is necessary.

Multiple Sclerosis

Multiple sclerosis is thought to be an inflammatory immune disorder with two general patterns of disability: exacerbating-remitting and chronic progressive.[92] Symptomatology can include ataxia, motor weakness, sensory deficits, autonomic dysfunction, emotional lability, bladder or bowel dysfunction, and visual disturbances. Exacerbations can be triggered by stress, infections, the peripartum, and elevated temperatures. Varieties of treatments

have been evaluated, including steroids, immunosuppressants, monoclonal antibodies, plasmapheresis, benzodiazepines, and baclofen. Preoperatively, it is important to document the history and pattern of disease, including symptoms and physical deficits, with special emphasis on respiratory compromise. Medications and previous triggers are important. There has been no documented association with the type of anesthetic or particular anesthetic agents and exacerbation of disease. Regional anesthesia may offer advantages for patients with respiratory compromise or cognitive dysfunction. Detailed documentation of preexisting neurologic deficits is important. Determination of oxygen saturation is needed. Testing is directed toward possible medication effects (e.g., azathioprine can suppress bone marrow and affect liver function, cyclophosphamide may cause electrolyte abnormalities, and steroids can cause hyperglycemia) and associated disturbances (e.g., chest radiography and white blood cell count if pulmonary infection is suspected). Patients with minor, stable disease require no special testing. Medications are continued on the day of surgery.

Aneurysms and Arteriovenous Malformations

Cerebral and spinal vascular lesions consist of aneurysms and AVMs, which may be intact or ruptured, symptomatic, or an incidental finding (see Chapter 63). Patients with polycystic kidney disease, fibromuscular dysplasia, type IV Ehlers-Danlos syndrome, or a family history of aneurysms are at increased risk for aneurysms. An AVM may be large enough to cause a mass effect. Pregnancy increases the risk for aneurysmal and possibly AVM bleeding. Before rupture, most patients will have minimal symptoms other than headache or seizures, but it is important to document complaints in all patients. With rupture, altered mental status, syncope, increased intracranial pressure with the typical signs and symptoms, inappropriate secretion of antidiuretic hormone, and hemodynamic perturbations are common. Bradycardia, tachycardia, ectopic beats, and ST-T wave changes, often mimicking those seen with ischemia, are common. Significant cardiac dysfunction with depressed contractility and wall motion abnormalities can be present on echocardiography. Preoperatively, concomitant CAD or preexisting cardiomyopathy should be considered and it not be assumed that these changes are related only to the bleeding. A preoperative ECG with determination of electrolytes, glucose, BUN, and creatinine is necessary. Chest radiography and echocardiography may also be helpful.

Parkinson's Disease

Parkinson's disease is a degenerative disorder of the basal ganglia in which failure of dopamine secretion results in diminished inhibition of the extrapyramidal motor system.[93] Preoperative patients typically have diminution of spontaneous movements, rigidity (cogwheel rigidity is classic), resting tremor, masked facies, difficulty speaking and walking, and frequently depression and dementia. Autonomic dysfunction with orthostatic hypotension, excessive salivation, and difficulty regulating temperature also occurs.

Patients are at risk for pulmonary complications because of difficulty swallowing and altered mental status and have an increased risk of aspiration and dysfunction of ventilatory muscles. Replacement of dopamine with levodopa, often combined with carbidopa, anticholinergic agents, bromocriptine, amantadine, and selegiline, is standard treatment. Levodopa can cause dyskinesias (dystonic and myoclonic involuntary movements). Pergolide, a dopamine receptor agonist, was recalled in early 2007 because of an increased risk for mitral and aortic regurgitation.[94] Patients exposed to this drug need a careful examination for murmurs and, if present, require an ECG and may require an echocardiogram. Selegiline is a monoamine oxidase inhibitor that inhibits dopamine degradation. Metoclopramine, phenothiazines, and butyrophenones may exacerbate symptoms by interfering with dopamine.

Preoperative evaluation focuses on the pulmonary system and degree of disability, especially dysphagia and dyspnea. Determination of room-air saturation and orthostatic BP and HR is important. Significant pulmonary symptoms, especially symptoms of infection or if worsening, may require a chest radiograph, pulmonary consultation, and delay of the procedure for improvement. Patients who have taken pergolide need auscultation for murmurs and, if present, may benefit from an ECG and echocardiogram. Deep brain stimulators need to be deactivated before procedures in which electrocautery will be used. All parkinsonian medications are continued. Abrupt withdrawal of levodopa may exacerbate symptoms, epecially dysphagia and chest wall rigidity, or result in neuroleptic malignant syndrome (NMS). NMS is characterized by autonomic instability, altered mental status, rigidity, and fever.

Neuromuscular Junction Disorders

Myasthenia gravis is an autoimmune disorder of skeletal muscle neuromuscular junctions that is due to antibodies against nicotinic acetylcholine receptors.[95] It is characterized by muscle weakness that worsens with activity and improves with rest.

Preoperative evaluation determines whether the patient has clinical or progressive weakness that can be exacerbated by stress, infections, hypokalemia, medications (aminoglycoside antibiotics, propranolol, ciprofloxacin, clindamycin), and surgery. Cardiac and smooth muscles are unaffected. Thymic hyperplasia and tumors may be present. The thymus is located in the anterior mediastinum and, when enlarged, has implications related to anesthesia (see "Mediastinal Masses"). Cranial nerve and bulbar involvement is common with pharyngeal and laryngeal muscle weakness, which increases the risk for aspiration. Ocular symptoms (diplopia, ptosis) are usually present and are frequently the initial or only complaints. Ventilatory function can be compromised. Preoperative PFTs are indicated for severely affected individuals and may be useful in predicting who may require postoperative ventilation.[96] PFTs may be particularly helpful if patients are being considered for ambulatory surgery, especially in freestanding surgical centers. Other autoimmune diseases such as rheumatoid arthritis, polymyositis, and thyroid disorders are common in myasthenics. See the appropriate sections of this chapter for discussion of these topics.

Patients are treated by thymectomy and with anticholinesterase and immunosuppressant medications. Worsening symptoms may be due to deteriorating disease (a myasthenic crisis) or excessive anticholinesterase treatment (a cholinergic crisis). By using a short-acting anticholinesterase (edrophonium), the two can be distinguished; only a myasthenic crisis will improve with more anticholinesterase. Plasmapheresis and intravenous immunoglobulins have been used to treat myasthenic crises or prepare patients for surgery but require several days to weeks for improvement.

Preoperative patients taking azathioprine require a CBC and LFTs because of the bone marrow suppression and liver dysfunction associated with this drug. Patients treated with steroids

need an ECG and glucose determination and may require higher doses in the perioperative period. Even though anticholinesterases may cause bradycardia (necessitating a preoperative ECG) and salivation and alter the effects of neuromuscular blocking and reversal agents, they need to be continued to prevent a myasthenic crisis. Documentation of dosages and schedules and continuation of these medications up until the time of surgery are paramount. Avoidance of drugs that can exacerbate myasthenic symptoms is necessary. Management with a neurologist is important.

Lambert-Eaton syndrome is similar to myasthenia gravis and consists of muscle weakness, including oculobulbar involvement, and dysautonomia. It is caused by antibodies against voltage-gated calcium channels, which results in a decrease in acetylcholine. It is not associated with thymic abnormalities but is most common with malignancies; small cell lung cancer is the most frequent cause, but it also occurs with gastrointestinal tumors. The other distinguishing feature is that the muscle weakness classically improves with activity and is worse after inactivity. Therapies similar to that used for myasthenia, along with 3,4-diaminopyridine, a selective potassium channel blocker, are used and continued perioperatively. Preoperative evaluation and management are similar to that for myasthenia gravis.

Muscular Dystrophies and Myopathies

Muscular dystrophies and myopathies are inherited disorders of the neuromuscular junction (see Chapter 14). They share many similarities but have a few differences. Progressive skeletal muscle weakness commonly leading to respiratory failure and no effective therapy are the hallmarks of these disorders. Many have associated cardiomyopathies and possibly an association with MH. Duchenne's and Becker's muscular dystrophies are X-linked recessive disorders that occur in males. Patients have elevated creatine phosphokinase levels, often detected before the onset of symptoms. Males with a family history of Duchenne's or Becker's muscular dystrophy who have not been tested are considered at risk and require similar precautions as those with diagnosed disease. Cardiomyopathy and respiratory failure are common causes of death. Otherwise, normal female carriers may have dilated cardiomyopathy.

Preoperative evaluation for symptoms such as palpitations, dyspnea, chest pain, syncope, orthopnea, edema, aspiration, and pneumonia is important. Physical examination focuses on the cardiopulmonary system. An ECG, PFTs, and echocardiography are important in the preoperative evaluation.

Fascioscapulohumeral dystrophy is autosomal dominant, affects both genders, and causes a slowly progressive weakness of muscles of the shoulders and face. Cardiomyopathy is much less frequent than in the other dystrophies, but arrhythmias have been reported. Limb-girdle dystrophies have a variable inheritance and primarily affect the muscles of the shoulders and pelvis. Conduction abnormalities are present in some patients, although frank cardiomyopathies are less frequent. Inquiring about palpitations, syncope, and cardiac symptoms, examining patients as noted earlier for Duchenne's muscular dystrophy, and obtaining an ECG preoperatively are important.

Myotonic Dystrophies

Myotonia is prolonged contraction and delay of relaxation of muscles. It is a common symptom of several dystrophies, including classic myotonic dystrophy, congenital myotonic dystrophy, myotonia congenita, and central core disease. Myotonic dystrophy is the most common of these conditions and is an autosomal dominant inherited disorder that affects both genders. Congenital myotonic dystrophy is a severe form of this disease that is noted in infancy, often in the offspring of mothers with myotonic dystrophy.

Preoperative classic findings are severe muscle wasting, typically involving the face, hands, diaphragm, and pharyngeal, laryngeal, and pretibial muscles. Cold can trigger myotonia. The severity of disease is variable and it may not be apparent until the second to third decades of life, so a family history is important. Cardiomyopathies, arrhythmias, and conduction abnormalities are common, and some patients have cardiac valvular abnormalities. Cardiac involvement may not correlate with skeletal muscle atrophy or weakness. Patients require pacemakers once any evidence of second- or third-degree AV block develops, even if the patient is asymptomatic, because there may be unpredictably rapid progression of AV conduction disease. As a result of this potential for rapid progression, pacemaker placement is considered in these patients even with a first-degree AV block, regardless of symptoms. Aspiration with pneumonia and respiratory or cardiac failure are common. An increased risk for pulmonary complications postoperatively has been reported.[97]

Central core disease is a rare disorder consisting of a deficiency of mitochondrial enzymes. The name derives from the pathology of muscle biopsy specimens in which "cores" of abnormalities are apparent. Patients have proximal muscle weakness and scoliosis and may have cardiomyopathies. They are at risk for respiratory failure and aspiration, much like patients with myotonic dystrophy. Myotonia congenita is a hereditary disorder involving only skeletal muscles, is less severe, and does not cause cardiac abnormalities.

Patients with myotonia may be at increased risk for MH, although this is controversial. They may have similar findings as those with MH as a result of uncontrolled myotonic contraction with elevated metabolism and rhabdomyolysis.

Steroids, quinine, and procainamide may relieve myotonic contractions, but there is no cure for these diseases. These medications need to be continued perioperatively. The history and physical examination focus on the cardiopulmonary systems with special emphasis on findings of pulmonary infection, heart failure, palpitations, syncope, and conduction and valvular abnormalities. Preoperative testing includes an ECG and echocardiogram (except for patients with myotonia congenita), as well as a chest radiograph if acute symptoms of pulmonary disease are present. Any conduction abnormality on the ECG may benefit from cardiology consultation.

Central Nervous System Tumors

Pituitary tumors may be functioning (associated with endocrine abnormalities) or nonfunctioning and benign (adenomas are the most common pituitary lesion) or malignant (see Chapter 63).

Preoperative evaluation determines whether symptoms related to a mass effect of the tumor are present (e.g., headaches, visual field defects) or symptoms related to elevations in intracranial pressure are present (e.g., gait disturbances, vomiting, cranial nerve deficits, or bladder or bowel incontinence). Symptoms may be related to pituitary insufficiency (hypoadrenalism, hypothyroidism, or infertility being most common) or overactivity (Cushing's syndrome from tumors secreting ACTH; acromegaly from growth hormone secretion; hyperthyroidism from TSH production; gynecomastia, lactation, and sex hormone–

related changes from secretion of prolactin and gonadotropin [follicle-stimulating and luteinizing hormone]). These hormones are all produced by the anterior lobe of the pituitary and controlled via a feedback loop by the hypothalamus. The posterior pituitary stores and secretes vasopressin and oxytocin, which are synthesized in the hypothalamus. Cushing's syndrome results from excess cortisol production by the adrenals (stimulated by ACTH from the pituitary) and is discussed in the metabolic section of this chapter.

Acromegaly is caused by excess growth hormone and results in enlargement of connective tissue, bone, and visceral organs. On the preoperative physical examination, patients classically have an enlarged jaw (macrognathia), nose, feet, hands, and pharyngeal and laryngeal tissues, including the epiglottis and tongue (macroglossia). Patients have an increased incidence of both central sleep apnea and OSA, neuropathies from nerve entrapment, hypertension, LVH, diastolic dysfunction, and valvular abnormalities. CAD, heart failure, diabetes, hypothyroidism, and difficulty with mask ventilation, laryngoscopy, and intubation occur.

Preoperative solicitation and documentation of symptoms such as chest pain, dyspnea, snoring, numbness, polydipsia, headaches, and visual disturbances are important. Physical examination focuses on BP, airway features, murmurs, neurologic findings, and edema. Planning for difficult airway management plus discussion with the patient of possible awake fiberoptic intubation is necessary. An ECG, echocardiogram, electrolyte and glucose determination, and thyroid function tests are usually obtained.

TSH increases production of thyroid hormones (T_3 and T_4) by the thyroid gland. See the section "Thyroid Disease."

Posterior pituitary tumors result in failure to secrete vasopressin, also known as antidiuretic hormone, which regulates excretion of water by the kidneys. Deficiency of antidiuretic hormone results in excessive urine output from failure to reabsorb water and causes diabetes insipidus. These patients need estimation of volume status with orthostatic BP and HR measurement and electrolyte, BUN, and creatinine determination. Patients may have hypernatremia and volume depletion unless maintained on DDAVP.

Prolactin- and gonadotropin-secreting tumors have little impact on anesthetic management, but associated symptoms may alert clinicians to an undiagnosed pituitary tumor.

Patients with tumors or postpartum hemorrhage that cause pituitary insufficiency or those who have undergone resection of a pituitary tumor may require hormonal replacement such as steroids, thyroid medications, or DDAVP. It is important that these medications not be interrupted during the perioperative period. The preoperative history and physical examination should determine whether patients are adequately treated. Determining electrolyte, BUN, and creatinine levels and performing thyroid function tests and an ECG are necessary.

Intracranial tumors include gliomas (45% of tumors), such as glioblastoma multiforme, astrocytoma, ependymoma, medulloblastoma, and oligodendrocytoma, which are malignant and highly lethal. Benign meningiomas (15%) arise from the dura or meninges. Metastatic lesions (6%) are associated with virtually all types of malignancies. Schwannomas, craniophyaryngiomas, and dermoid tumors also occur. Most intracranial tumors are detected when symptoms related to a mass effect develop, patients have seizures, or they are found incidentally. Symptoms include headaches, stroke-like symptoms, vomiting, visual disturbances, altered cognitive function, and ataxia. If intracranial pressure becomes elevated, hypertension, bradycardia, arrhythmias, ECG abnormalities, and risk of brainstem herniation develop.

Careful questioning and documentation of neurologic deficits and symptomatology are important. For patients with metastatic lesions, issues pertaining to the primary malignancy or previous treatment need to be clarified. Continuation of steroids to decrease brain edema and anticonvulsant medications is essential.

Preoperative Evaluation of Patients with Psychiatric Disorders

Key issues in the preoperative assessment of patients with psychiatric disorders include assessing cognitive capacity, obtaining an accurate psychiatric history, evaluating the patient's capacity to give informed consent, and assessing the impact of psychotropic medications.[98]

Cognition is usually unimpaired in patients suffering from illnesses such as depression or schizophrenia and impaired in those suffering from disorders such as delirium, dementia, and autism. Orientation and memory should be assessed by the preoperative clinician to ensure that cognition is sufficient to obtain an accurate history and consent. Basic orientation to person, place, and time can be determined during the preoperative conversation or by looking at the way the patient has answered questions on forms. Mild cognitive impairment is frequently associated with mild dementia in elderly patients, who are at risk for postoperative delirium. More severe cognitive impairment raises issues regarding the reliability of the history and ability to obtain informed consent. Family members can aid by providing the history and countersigning consent forms.

Musculoskeletal and Connective Tissue Diseases

Deformities and chronic inflammation are key components of many of these disorders. The deformities need to be determined because of potential challenges in airway and regional anesthesia management. Chronic inflammation and associated vasculopathy with diseases such as rheumatoid arthritis, SLE, and scleroderma or systemic sclerosis often result in multiorgan dysfunction. The cardiovascular, pulmonary, renal, hematologic, integumentary, gastrointestinal, central, and peripheral nervous systems can all be involved.

Rheumatoid Arthritis

Rheumatoid arthritis affects up to 1% of the population (females more than males) and is a chronic autoimmune disorder primarily affecting the joints but often multiple systems.[99] Both large and small joints become inflamed, and severe deformity is possible, although the disease course varies dramatically. The temporomandibular joints and cricoarytenoid cartilage can be involved and result in limited mouth opening and hoarseness. Atlantodens subluxation and cervical spine instability can occur.

Subluxation is caused by laxity of the ligaments, not joint disease, and may be present in as many as 46% of patients.[100] Cervical spine diseases can occur without symptoms. Vasculitis or entrapment results in peripheral neuropathy. CAD, pericardial effusion, aortic regurgitation, and conduction abnormalities are frequently present.[101] The often severely limited functional status in these patients masks ischemic symptoms. Dyspnea, which can be an anginal equivalent, especially in women, may be confused with pulmonary symptomatology. Restrictive lung disease from decreased thoracic mobility, interstitial fibrosis, and pleural effusions may occur. Patients have an increased incidence of renal dysfunction from both vasculitis and chronic use of NSAIDs. Anemia, leukocytosis, and both thrombocytosis (from chronic inflammation) and thrombocytopenia (from splenomegaly) can be found. Rheumatoid nodules occur subcutaneously, usually over extensor joints, or in the lungs.

The preoperative history and physical examination are performed to document symptoms related to the many organ systems affected by rheumatoid arthritis (refer to appropriate sections of this chapter). Special detail needs to be given to the airway and to the neurologic, pulmonary, and cardiovascular systems. A careful history may elicit neurologic deficits, neck and upper extremity pain, and a crunching sound with neck movement. Patients who have neurologic deficits or symptoms or long-standing, severely deforming disease or who are scheduled to undergo procedures requiring manipulation of the cervical spine or special positioning, such as turning prone, require anteroposterior and lateral cervical spine radiographs with special flexion, extension, and open-mouth odontoid views.[100] Significant abnormalities (anterior atlas-dens interval >9 mm or posterior interval <14 mm) may benefit from consultation with a neurologist or neurosurgeon. However, the duration, severity, or symptoms of the disease do not correlate with cervical spine subluxation.

Preoperative documentation of deformities and neurologic deficits is important to establish a baseline level of function. For patients with significant hoarseness, referral to an otolaryngologist to assess mobility of the vocal cords and the degree of cricoarytenoid arthritis may be of benefit.[102] Acute or worsening pulmonary symptoms may trigger a need for pulse oximetry, chest radiographs, PFTs, or a pulmonary consultation (see the section "Pulmonary Disorders"). An ECG is always indicated, and abnormalities may prompt further testing or referral to a cardiologist, or both. Muffled heart sounds, pericardial rubs, and an enlarged heart detected by examination or on a chest radiograph together with low voltage on an ECG suggest a pericardial effusion, which can be evaluated with an echocardiogram. Many murmurs, especially if new, would benefit from further investigation (see Table 34-4 and Box 34-4). A CBC with a platelet count and determination of BUN and creatinine are indicated, except for the most minor of procedures.

Advanced planning for the management of identified or potential difficult airways is important. Discussion of regional anesthetic options and awake fiberoptic intubation is necessary. Continuation of steroids and chronic pain medications is optimal, but drugs with antiplatelet effects are generally discontinued and immunosuppressants may have to be temporarily stopped to allow normalization of blood counts. Patients with complex regimens and severe disease are best managed in concert with their rheumatologist or primary physician.

Ankylosing Spondylitis

Ankylosing spondylitis is a progressive inflammatory arthropathy that affects mainly the spine and sacroiliac joints.[103] It occurs primarily in males and can be accompanied by uveitis, peripheral arthritis, and vasculitis causing aortitis and aortic insufficiency. Restrictive lung disease can result from pulmonary fibrosis or poor chest wall movement secondary to joint fixation and kyphosis. Kyphosis can be so extreme that patients cannot face forward and are extremely difficult to intubate or even mask ventilate.

Preoperative evaluation by history and physical examination focuses on the skeletal and cardiopulmonary systems. A murmur warrants an ECG and may benefit from an echocardiogram. If ventilatory compromise is suspected or present, room-air pulse oximetry and a chest radiograph are necessary, as well as PFTs when appropriate. Acute processes must be managed preoperatively.

Patients taking NSAIDs require determination of BUN and creatinine levels, and a CBC with a platelet count and LFTs are indicated for those treated with leflunomide. Planning for airway management and discussion with the patient about the possibility of awake fiberoptic intubation are important. Peripheral nerve blocks are options, but centroneuraxial anesthesia is often unsuccessful because of severe spinal involvement.

Systemic Lupus Erythematosus

SLE is a systemic autoimmune disease predominately caused by vasculitis; it has a variable course, often with remissions punctuated by flares.[104] SLE affects mainly females and is typically more severe in African Americans than in other groups.

Preoperative evaluation determines whether the patient has chronic fatigue, weakness, respiratory compromise, fevers, and migratory arthritis affecting primarily the small joints of the hands and feet, which is common. Fevers may be a result of the disease itself or the frequent infections that develop because of the immune dysfunction and immunosuppressants used to treat the disease. Many patients have dermatologic conditions, including alopecia, the typical "butterfly rash" across the cheeks and nose, and photosensitivity. Vasospasm of the digits, dubbed Raynaud's phenomenon or disease, often with atrophy of the nails and fingernails, makes it difficult to obtain pulse oximetry readings.

Preoperative evaluation for interstitial lung disease, pleural effusions, frequent infections, and pulmonary hypertension is important and presents a significant concern. Pulmonary hypertension can result from interstitial lung disease, recurrent pulmonary emboli, or cardiomyopathy and carries a high risk of perioperative complications (see "Pulmonary Hypertension"). Cardiac involvement includes premature coronary artery arteriosclerosis, pericarditis, myocarditis, aseptic endocarditis, and pleural effusions.

Coronary vasculitis and cardiomyopathy may occur. Hypertension, frequently difficult to control, is almost ubiquitous. Neuropsychiatric manifestations consisting of cerebral vasculitis, stroke, cognitive dysfunction, seizures, peripheral neuropathy, headache, affective disorders, and carotid artery disease are common. Lupus nephritis is a common morbidity with a poor prognosis that frequently results in renal failure. Patients with SLE often have anemia and may have leukopenia and thrombocytopenia.

Antiphospholipid antibodies occur frequently and can result in a coagulopathy with recurrent episodes of venous and arterial thrombosis, including pulmonary emboli and stroke. Typically, the aPTT is prolonged in these patients. Antinuclear antibodies are present in most cases and can help establish a diagnosis, especially with atypical manifestations.

The preoperative history and physical examination must evaluate all major organ systems and identify medications. Patients with severe disease, exacerbations, or infections are best managed along with the physicians primarily responsible for their care or a rheumatologist. Detailed questioning regarding neurologic symptoms, coughing, dyspnea, chest pain, orthopnea, fever, the course of disease, and medications is paramount. Any history of thromboembolic events is important, but recent events regarding precipitating factors, type and duration of treatment, and severity of the event (e.g., pulmonary embolus or DVT) must be detailed so that one can plan discontinuation of anticoagulants and need for bridging. Because of the significant incidence of both cerebrovascular and coronary artery lesions in these patients, careful questioning about exercise capacity, atypical symptoms of ischemia, and any previous diagnostic studies such as computed tomography, magnetic resonance imaging, echocardiography, or stress testing may be revealing.

Systemic Sclerosis

Systemic sclerosis, previously known as scleroderma, is an autoimmune disease characterized by excessive fibrosis that occurs more commonly in females.[105] Raynaud's phenomenon is the most common occurrence besides skin thickening. Localized scleroderma involves just the skin without involvement of other organs. Limited cutaneous systemic sclerosis is "limited" to the skin of the face and upper extremities as the cutaneous manifestation, but with systemic involvement, the gastrointestinal tract (dysphagia, reflux) and lungs (interstitial lung disease, pulmonary hypertension) can be affected. Pulmonary hypertension is associated with a poor prognosis and increases perioperative risk (see "Pulmonary Hypertension").[106] Diffuse cutaneous systemic sclerosis causes generalized skin thickening and multiple end-organ damage. Myocardial fibrosis, pericarditis, heart failure, and coronary artery fibrosis or spasm can occur. Patients often have severe hypertension, renal failure, dysphagia, fatigue, weight loss, reflux, and right heart failure.

The preoperative history and physical examination focus on the organ systems as outlined in the section "Systemic Lupus Erythematosus," with special attention paid to signs or symptoms of pulmonary hypertension (see "Pulmonary Hypertension"). A careful history to elicit symptoms of pulmonary disease (cough, dyspnea) or cardiac disease (dyspnea, orthopnea, chest pain) is vital. A murmur of tricuspid regurgitation and a split second heart sound are suggestive of pulmonary hypertension. Because of the thickened and fibrosed skin, microstomia, limited neck mobility, poor dentition, and oropharyngeal lesions, airway examination and planning for management are essential. Dermal thickening, scarring, edema, and contractures make venous access and regional anesthesia challenging. Discussing central venous access, even arranging for interventional radiology to place intravenous lines, and explaining the possibility for awake fiberoptic intubation will help on the day of surgery.

Preoperatively, patients with systemic sclerosis need an ECG and determination of BUN and creatinine levels. A CBC with a platelet count is indicated in those taking immunosuppressants. A chest radiograph and PFTs can be useful when evaluating patients with symptoms (cough, dyspnea) or signs (rales, hypoxemia) of possible interstitial lung disease or pulmonary fibrosis. Echocardiography is useful to screen for pulmonary hypertension in patients suspected of having this significant end-organ complication. Calcium channel blockers to treat Raynaud's phenomenon, antihypertensive agents, and immunosuppressants need to be continued preoperatively.

Inherited Connective Tissue Disorders

Ehlers-Danlos syndrome, a disorder of collagen synthesis, consists of several subtypes that have various manifestations, but almost all are characterized by joint hypermobility. Type IV is one of the most serious because those affected may have vascular and skin fragility and are at risk for vascular and visceral rupture and pneumothorax. Patients with type VI Ehlers-Danlos syndrome have muscle weakness, scoliosis, ocular and skin fragility, and osteopenia.

Marfan's syndrome is characterized by tall stature, arachnodactyly (long digits), scoliosis, pectus excavatum, ascending aortic dilatation and even dissection, valvular disease (aortic insufficiency, mitral valve prolapse, mitral regurgitation), and arrhythmias. Ocular (ectopia lentis, strabismus, glaucoma) and pulmonary (blebs, spontaneous pneumothorax) complications can occur.[107] Patients may have retrognathia and high arched palates. Careful auscultation for the diastolic murmur of aortic insufficiency is important (see Table 34-3). An ECG, echocardiogram, and chest radiograph should be obtained if a murmur is detected and management will be changed.

The most distinguishing feature of osteogenesis imperfecta is the propensity of patients for fractures from extremely fragile bones. Patients may have blue sclerae, short stature, scoliosis, joint hypermobility, hearing loss, pulmonary complications, muscle weakness, mitral valve prolapse, aortic insufficiency, and platelet dysfunction. An ECG and echocardiogram are necessary if a murmur is detected.

Epidermolysis bullosa is distinguished by blistering, skin fragility, and scarring because of abnormal epidermal-dermal anchoring. Even obtaining a BP reading may cause skin blistering and breakdown.

Kyphoscoliosis

Kyphoscoliosis is a curvature of the spine both laterally and anteriorly and may involve the thoracic or lumbar regions, or both. It occurs alone as as a manifestation of other diseases, including collagen vascular disorders, Marfan's syndrome, neurofibromatosis, muscular dystrophies, and cerebral palsy, among others. Therefore, the preoperative evaluation is aimed at identifying coexisting abnormalities. Pulmonary and cardiac compromise can occur with severe thoracic deformity. Restrictive lung disease, pulmonary hypertension, tracheobronchial and cardiac compression, and heart failure are possible.

The preoperative history focuses on functional capacity and cardiopulmonary symptoms. The ability of the patient to lie supine and allow airway access and management needs to be determined. Vital signs and performance of pulse oximetry are important. Auscultation for rales, decreased air entry, murmurs, and additional heart sounds and examination for edema and jugular venous distention are crucial. An ECG and chest radiograph are needed, and if patients are scheduled for spine correction surgery, a CBC and type and screen are required. An

echocardiogram may be indicated if symptoms or signs of heart failure are present. Reversible lung disease or heart failure needs to be addressed and optimized before surgery.

Raynaud's Phenomenon

Raynaud's phenomenon or disease is an exaggerated vascular response to cold or emotional stress (thought to be due to stimulation of the sympathetic nervous system) that results in color changes of the digits.[108] It can be primary (idiopathic without a known cause) or secondary (associated with connective tissue diseases, autoimmune disorders, drugs, use of vibrating tools). It is estimated that more than 95% of patients with systemic sclerosis have Raynaud's phenomenon; 20% to 30% of patients with Sjögren's syndrome or SLE have it, but less than 5% of patients with rheumatoid arthritis. Raynaud's phenomenon most often affects the hands and typically results in a sudden onset of cold digits (fingers more common than toes) with sharply demarcated pallor or cyanosis. Cutaneous vasospasm is common in other sites such as the face and ears and can cause pain and numbness. Criteria for the diagnosis of primary disease include symmetric episodic attacks, no PVD, no tissue injury or gangrene, normal nail fold capillary examination, normal erythrocyte sedimentation rate, and a negative antinuclear antibody test. Primary Raynaud's phenomenon requires no special preoperative evaluation. Secondary disease should direct the assessment for associated disease states as outlined elsewhere in this chapter. It is important to distinguish Raynaud's phenomenon from PVD because of the difference in associated comorbid conditions. Calcium channel blockers are useful in many patients and need to be continued in the perioperative period.

Cancer/Tumors in Preoperative Patients

Cancer Patients

Patients with a history of cancer may have complications related to the disease or the treatment. Typically, patients will be aware of the side effects of treatment that they have experienced or are at risk of having. Asking them if any "unexpected complications" occurred or if chemotherapy or radiotherapy had to be interrupted because of adverse effects is important. A hypercoagulable state is common in patients with cancer, particularly those with advanced disease and primary brain tumors, ovarian adenocarcinoma, and pancreatic, colon, stomach, lung, prostate, and kidney cancer. Patients with cancer have a sixfold increased risk for thromboembolic events, and active cancer accounts for 20% of new episodes of thromboembolism (see "Risk of Thromboembolism or Pulmonary Emboli").

Preoperative evaluation should focus on evaluation of the heart, lungs, and neurologic and hematologic systems. Previous head and neck irradiation may cause carotid artery disease, hypothyroidism, or difficulty with airway management.[109] In these patients, auscultation for bruits, thyroid function tests, and carotid Doppler studies are recommended.

Mediastinal, chest wall, or left breast irradiation can cause pericarditis, conduction abnormalities, cardiomyopathy, valvular abnormalities, and premature CAD, even without traditional risk factors.[110] Therefore, younger patients who might not otherwise be expected to be at risk for heart disease but who have a history of radiation therapy for cancer should be assessed for symptoms of cardiac disease as part of the preoperative history and should have a preoperative ECG.

Cardiovascular disease is the second most common cause of mortality in survivors of Hodgkin's disease. One study found that 88% of patients had echocardiographic abnormalities 5 to 20 years after treatment, most of them asymptomatic. Treatment at a younger age increases the risk. Radiation exposure is not considered in the ACC/AHA guidelines for cardiac evaluation for noncardiac surgery but can be an important predictor of CAD.[110] A preoperative ECG, echocardiography, and stress testing may be indicated. Radiation pneumonitis can occur in those who have received irradiation of the lungs, breast, or mediastinum. A chest radiograph and oxygen saturation with pulse oximetry are indicated. PFTs may be needed.

Chemotherapy with doxorubicin can cause cardiomyopathy, bleomycin can produce pulmonary toxicity, vincristine and cisplatin may cause peripheral neuropathy, and cyclophosphamide may trigger hemorrhagic cystitis. Many agents cause renal and hepatic toxicity or suppress bone marrow, which may result in pancytopenia. Anemia is most common. A chest radiograph, CBC with platelets, determination of electrolytes, BUN, and creatinine, and LFTs may be indicated based on the type of chemotherapy.

Patients with hepatocellular cancer have a high incidence of chronic liver disease (see the appropriate section). One study found that almost 25% of patients with Child's class C disease (see Table 34-5) undergoing liver resection died in the hospital and almost 20% more died within the first month after discharge.[111] A CBC with platelets, electrolyte, BUN, creatinine, and albumin levels, LFTs, and PT are needed.

Intracranial neoplasms can be primary or metastatic and can be complicated by seizures, increased intracranial pressure with mental status changes, nausea, vomiting, gait disturbances, and hemodynamic alterations or neurologic deficits. Previous therapies, including radiation, steroids, and anticonvulsants, need to be determined. If the tumor is metastatic, the primary tumor site, the course of the illness, and complications of therapy are important. Cancers that typically metastasize to the brain include breast, colorectal, and lung cancer.

Preoperative neuroimaging, an ECG, and electrolytes and glucose levels are reviewed or obtained. Steroids and anticonvulsants are continued. Breast, colorectal, lung, head, and neck tumors commonly metastasize to bone and the liver. Bone lesions can result in hypercalcemia or pancytopenia. Pancytopenia, with anemia being most common, occurs with many cancers or with treatment of these cancers. Head and neck tumors or therapy for them (surgery, radiation) may cause difficulty with airway management and thyroid dysfunction. Lung cancer can compromise pulmonary function and cause airway problems or mediastinal masses (discussed later). Computed tomography scans of the head, neck, or chest may be indicated. Paraneoplastic syndromes can complicate almost any malignancy but are commonly associated with lung cancer. Hypercalcemia, inappropriate secretion of antidiuretic hormone, Lambert-Eaton or Cushing's syndrome (discussed in this chapter), and neuropathies may occur.

Preoperative patients who are chronically receiving opioids for cancer pain are likely to require greater than usual doses of medication for postoperative pain control. They should take their usual pain therapies the day of surgery with the exception of antiplatelet agents. Patients at risk for adrenal insufficiency should

be assessed with a corticotropin (ACTH) stimulation test (see "Hypothalamic-Pituitary-Adrenal Disorders") or should be considered for additional perioperative steroids. A preoperative ECG is indicated for patients who have received mediastinal, breast, or lung irradiation or doxorubicin. All patients with cancer require a preoperative CBC with platelets and determination of electrolytes, BUN, creatinine, and calcium. Patients who are significantly malnourished benefit from 7 to 10 days of enteral or parenteral nutrition before major surgery. Surgery is delayed to allow neutropenia and thrombocytopenia to resolve if possible. Type and screening and planning blood component replacement can avoid delays on the day of surgery.

Mediastinal Masses

Lymphomas, thymomas, teratomas, metastatic disease, and goiters can occur in the anterior mediastinal space. Anterior mediastinal masses can cause obstruction of the great vessels, including the aorta, pulmonary arteries and veins, and superior vena cava, as well as the heart, trachea, and bronchi. Evaluation of patients with a mediastinal mass can be found in Chapter 59.

Von Hippel-Lindau Disease

von Hippel-Lindau disease is an inherited, autosomal dominant syndrome manifested by a variety of benign and malignant tumors. The spectrum of associated tumors includes hemangioblastoma, retinal angioma, clear cell renal cell carcinoma, pheochromocytoma, and neuroendocrine tumors of the pancreas. Preoperative evaluation of these patients focuses on evaluation of renal function and determination of symptoms or diagnoses compatible with pheochromocytomas or neuroendocrine tumors (see the section "Pheochromocytoma"). A careful history and physical examination with vital signs, an ECG, and determination of electrolytes, BUN, creatinine, and glucose is necessary in all patients. Further testing is guided by the history and laboratory findings.

Carcinoid Tumors

Carcinoid tumors are rare neuroendocrine tumors that release mediators and typically occur in the gastrointestinal tract; they are the most common neoplasm of the appendix but are also found in the pancreas and bronchi.

Preoperatively, patients with carcinoid syndrome complain of flushing, tachycardia, arrhythmias, diarrhea, malnutrition, bronchospasm, and carcinoid heart disease caused by vasoactive amines (serotonin, norepinephrine, histamine, dopamine), polypeptides (bradykinin, somatostatin, vasoactive intestinal peptide, glucagon), and prostaglandins released by the tumors. The majority of patients are asymptomatic. The liver inactivates the bioactive products of carcinoid tumors, which is why patients with gastrointestinal tumors have manifestations of carcinoid syndrome only if they have hepatic metastases. Heart disease can involve endocardial fibrosis of the pulmonic and tricuspid valves and cause stenosis and regurgitation, respectively. Right heart failure with peripheral edema and hepatomegaly can occur. Carcinoid tumors occur in MEN I.

Preoperative diagnostic tests are guided by the history and physical findings such as dyspnea, orthopnea, wheezing, edema, arrhythmias, and murmurs. Patients with diarrhea need determination of orthostatic BP, electrolytes, BUN, and creatinine. Patients with cardiac involvement need an ECG, electrolye assay, and echocardiography. Malnourished patients need orthostatic BP determination, an ECG, and electrolyte and albumin levels. Elevated urinary 5-hydroxyindoleacetic acid levels and carcinoid heart disease increase perioperative adverse events.[112] H_1 and H_2 histamine receptor blockers, ketanserin (a serotonin receptor antagonist), and octreotide may be useful to block release or the effects of mediators.

Special Issues in Preoperative Evaluation

Patients with Upper Respiratory Infections

Analysis of the literature available on patients with upper respiratory infections and anesthesia provides guidelines to help ensure patient safety while minimizing unnecessary cancellations. Although children with active and recent upper respiratory infections have been shown to be at increased risk for postoperative respiratory complications, these complications are generally manageable and have not been associated with long-term sequelae. Tait and Malviya summarized the literature on patients with upper respiratory infections and have provided a useful practice algorithm.[113] According to this algorithm, afebrile patients with symptoms of an uncomplicated upper respiratory infection, including clear secretions, should be able to undergo surgery.

The preoperative evaluation distinguishes patients with more severe symptoms, including purulent secretions, productive cough, temperature higher than 38°C, or signs of pulmonary involvement, and elective surgery should be postponed for about 4 weeks. This period was suggested because airway hyperreactivity persists for several weeks after an upper respiratory infection and patients recovering from one have been shown to have a rate of complications similar to those who have acute symptoms. Additional risk factors that should be considered include a history of asthma, need for intubation, surgery on the airway, smoking history, and a history of prematurity in pediatric patients. In patients with severe symptoms, especially those with underlying conditions (e.g., significant asthma, heart disease, and immunosuppression) that may further compromise safe anesthesia, elective surgery should be postponed for at least 4 weeks as well.[113] Preoperative laboratory testing and chest films may not be helpful in the decision; patients with viral infections may not have elevated white blood cell counts, and chest film findings typically lag behind clinical symptoms in patients with lower respiratory infections.

The risk-benefit ratio in each individual case needs to be assessed. Most would agree that surgery in patients with mild uncomplicated upper respiratory infections should not be canceled and surgery in those with more severe symptoms should be postponed for 4 weeks. Management should include awareness and prevention of potential complications.

Preoperative Evaluation of Patients with a Transplanted Organ

The number of patients with transplanted organs requiring nontransplant surgery increases yearly. These patients present special

issues for preoperative evaluation because of concerns about transplant function, allograft denervation, immunosuppression, and post-transplant physiologic and pharmacologic issues (see Chapter 67). Close interaction with the transplant team is considered one of the most important steps in the perioperative care of these patients, and clinicians performing the preoperative assessment should ensure that the transplant care providers are aware of the upcoming procedure and be given an opportunity to make recommendations.

During the preoperative evaluation, the dosage regimen of all agents should be noted and patients should be instructed to continue taking all of these medications. However, these drugs can modify the pharmacology of many agents administered during the perioperative period. Impact on agents administered during anesthesia is discussed elsewhere and has been summarized in the literature.[114,115]

There are some general preoperative considerations in all transplant patients, as well as concerns specific to the type of organ transplanted.[116] In all transplant patients, the level of function of the transplanted organ and the presence of rejection should be evaluated. Immunosuppressant therapy results in hyperglycemia and adrenal suppression (steroids); risk of infection, hypertension, and renal insufficiency (steroids, cyclosporine, tacrolimus); and myelosuppresion with anemia, thrombocytopenia, and leukopenia (azathioprine, sirolimus). Because these patients are chronically immunosuppressed, the potential for infection should be considered in any preoperative evaluation. Although these patients are at higher risk for the development of infectious complications, there is no evidence suggesting that heightened antibiotic prophylaxis has any added benefit, and the usual preoperative recommendations should be followed. The need for "stress dose" supplementation in patients taking low-dose corticosteroids is controversial, although because of the low risks involved with this therapy, it is used frequently.

Careful cardiac evaluation is important in all transplant patients because the incidence of cardiovascular disease is increased. This is due to a variety of factors, including the association of organ failure with a number of cardiovascular risk factors, as well as the role of drug regimens, transplantation, and rejection episodes in creating new and worsened cardiovascular risk factors. Patients with heart transplants periodically undergo evaluation for CAD (stress testing or catheterization) and function (echocardiogram or multiple gated acquisition [MUGA]).

Renal function should be assessed preoperatively because chronic renal insufficiency is becoming a significant problem in recipients of other solid organs secondary to long-term use of immunosuppressive regimens. Although the effects of transplantation and immunosuppressive regimens on intravascular coagulation are controversial, DVT prophylaxis should be considered in all transplant patients.

Kidney transplant recipients present some specific issues. Despite the presence of a normal creatinine level, the average GFR is generally decreased. This predisposes patients to electrolyte abnormalities and altered drug metabolism, as reviewed in the articles referenced earlier. The risk for cardiovascular disease in renal transplant recipients is approximately twice that in the general population, and careful presurgical cardiac evaluation is essential. Nephrotoxic drugs, NSAIDs, and COX-2 inhibitors should be avoided in renal transplant recipients.

Liver transplant patients require careful evaluation of pulmonary function. Hepatopulmonary syndrome, which consists of intrapulmonary shunting caused by intrapulmonary vascular dilatation, can result in hypoxemia. These patients can also have ventilation-perfusion mismatching as a result of effusion, ascites, and diaphragmatic dysfunction. Diffusion abnormalities can result from interstitial pneumonitis and impaired hypoxic pulmonary vasoconstriction. In some cases, pretransplant pulmonary disturbances do not completely resolve after transplantation.

Lung transplant patients may require months to achieve peak pulmonary functional capacity. Because of exposure to the external environment, the transplanted lung is susceptible to infection and rejection. Lung transplant patients have a high rate of pulmonary infection, and the airway anastomosis is subject to risk of injury with intubation. Loss of the cough reflex and airway hyperresponsiveness may be present. These patients are also at increased risk for pulmonary edema. Preoperative pulmonary function testing can be extremely helpful.

Most of the issues relating to heart transplant patients evolve from the absence of autonomic innervation; specific drug effects are described in detail in the items referenced. The preoperative ECG may show two P waves, one from the native atria, which is not conducted, as well as one from the donor atria. The heart transplant lacks innervation, and thus ischemia is silent and autonomic reflexes are absent (lack of chronotropic response to exercise, anemia, or hypovolemia). Conduction abnormalities are common. Permanent pacemakers are required in a significant number of patients, and their function should be confirmed during preoperative assessment.

Preoperative Evaluation of Patients with Allergies

The patient's history of allergies and adverse drug reactions should be carefully documented in the preoperative record. True anaphylactic reactions should be distinguished from adverse side effects. The patient's definition of allergy may be very different from the true clinical definition, and patients may incorrectly think that previous perioperative difficulties are due to "allergies" to anesthetic or pain medications.

The incidence of true anaphylactic and anaphylactoid reactions during anesthesia is in the range of 1 in 6000; muscle relaxants account for 69% of these reactions, followed by latex (12%) and antibiotics (8%).[117] A careful history will allow avoidance of precipitating agents; premedication with histamine blockers and steroids is not generally recommended.

Anaphylactic reactions to amide local anesthetics are extremely rare. Allergies to preservatives such as para-aminobenzoic acid used with esters are more common. Patients may perceive, especially with dental procedures, adverse side effects from epinephrine in local anesthetic solutions as allergies, and this needs to be carefully distinguished. Similarly, true allergies to opioids are rare, and opioid side effects, such as nausea and emesis, may be misinterpreted as allergies. Skin testing can be used to determine the presence of a true allergy. Allergies to muscle relaxants are more common; there are no reports of anaphylaxis to volatile anesthetics.

Penicillin is the most common cause of anaphylaxis; however, of all who report an allergy, only about 10% to 20% actually have a true allergy. There is a small risk of cross reactivity with cephalosporins, but most of these reported reactions involve

rashes and not anaphylaxis. Anaphylactic reactions to solutions such as bacitracin or providone-iodine have only rarely been reported; contact dermatitis in association with these agents is a more common reaction.

The rate of latex sensitization continues to increase; however, as better ways of identifying at-risk patients are developed, the incidence of latex-induced anaphylaxis is decreasing.[118] Diagnosis of a latex allergy during preoperative evaluation is based on a careful history. Patients at risk for latex allergy include those with a history of multiple surgical procedures, health care workers, and those with atopic histories. When latex allergy is identified during the preoperative visit, the operative team should be notified in advance to ensure that all appropriate equipment is available. The ASA task force outlines in detail intraoperative considerations for these patients.[119]

The scientific status of multiple chemical sensitivity disorder is controversial. Patients with this disorder report chronic, diffuse, nonspecific symptoms with low levels of multiple chemical substances. Symptoms involve multiple organ systems and include fatigue, headache, memory loss, palpitations, and gastrointestinal symptomatology. The symptoms are not generally accompanied by biologic test abnormalities or changes on physical examination. This disorder is frequently associated with chronic fatigue syndrome and fibromyalgia.[120] Performing a preoperative evaluation on these patients can be extremely difficult because patients have significant concerns about the multiple exposures involved during the perioperative period and the impact on their symptomatology. Cultural, historical, and behavioral issues, possibly in combination with some as yet undetermined physiologic abnormalities, may be responsible for the genesis of this disorder. There are no specific treatments and no current recommendations regarding perioperative care of these patients.

Preoperative Evaluation of Morbidly Obese Patients

A morbidly obese patient presents a special set of preoperative risks (see Chapter 64). Obesity is associated with an increased incidence of risk factors, including diabetes and cardiovascular disease. These patients have a higher incidence of difficult tracheal intubation, decreased arterial oxygenation, increased gastric volume, decreased gastric pH, postoperative wound infection, pulmonary embolism, and sudden death.[121]

Obesity is an independent risk factor for heart disease. Hypertension, stroke, hyperlipidemia, osteoarthritis, diabetes mellitus, cancer, and obstructive sleep apnea (OSA) are more common in obese people. Obese individuals have increased oxygen consumption and work of breathing but decreased lung volume and capacity. They have LVH and often decreased functional capacity. They frequently complain of dyspnea, which may be related to cardiac or pulmonary insufficiency or deconditioning. They are at risk for nonalcoholic steatohepatitis, also known as "fatty liver," which results in elevated LFT values and can progress to fibrosis.

Preoperative evaluation should be directed toward coexisting diseases. Patients with extreme obesity are at risk for heart failure and pulmonary hypertension. Obesity-hypoventilation syndrome (OHS), also known as pickwickian syndrome, is distinct from OSA. OHS is associated with awake, chronic hypoxemia (Pa_{O_2} <65 mm Hg) without a diagnosis of COPD or primary lung disease. These patients have impaired central ventilatory drive. Drugs or methods of weight reduction (purging, diuretics, laxatives, gastric bypass procedures) may result in electrolyte abnormalities, vitamin deficiencies, malnutrition, anemia, and cardiopulmonary disorders. Fenfluramine and dexfenfluramine, unavailable since 1997, caused mainly regurgitant valvular lesions and pulmonary hypertension. It is recommended that anyone ever exposed to these drugs undergo a cardiovascular evaluation. An ECG and echocardiogram (frequently done in the past) are recommended for those suspected of having dysfunction.

The preoperative history and physical examination focus on the airway, a history of snoring or daytime sleepiness, the cardiopulmonary system, and vital signs, including pulse oximetry. The BP cuff needs to have a width of approximately two thirds that of the arm and a length to adequately encircle the extremity. Neck circumference predicts difficulty with intubation. Depending on the history and physical findings, additional testing may be indicated.

These patients also have an increased incidence of OSA, which can be associated with pulmonary and systemic hypertension, left and right ventricular hypertrophy, and an increased incidence of arrhythmias, MI, and stroke.[122]

Preoperative Evaluation of Patients with Obstructive Sleep Apnea

Sleep-disordered breathing affects up to 9% of middle-aged women and 24% of middle-aged men; less than 15% of these cases have been diagnosed. Asking patients whether they snore, about the intensity of their snoring and whether it bothers others, about observed awakenings or choking, about daytime sleepiness and whether it interferes with activities, and about falling asleep while driving can identify those with probable sleep apnea. OSA, the most common serious manifestation of sleep-disordered breathing, is caused by intermittent airway obstruction. OSA is characterized by total collapse of the airway with complete obstruction for more than 10 seconds. Obstructive hypopnea is partial collapse (30% to 99%) associated with at least 4% arterial oxygen desaturation. The severity of OSA is measured with the apnea-hypoxia index, or the number of apneic and hypopneic episodes per hour of sleep. Patients with severe OSA have more than 30 episodes per hour.

Cardiovascular disease is common in patients with OSA. These patients have an increased incidence of hypertension, atrial fibrillation, bradyarrhythmias, ventricular ectopy, endothelial damage, stroke, heart failure, pulmonary hypertension, dilated cardiomyopathy, and atherosclerotic CAD.[60] Mask ventilation, direct laryngoscopy, endotracheal intubation, and even fiberoptic visualization of the airway are more difficult in patients with OSA than in healthy patients (see Chapters 50 and 64). Patients with OSA are more sensitive to the respiratory depressant effects of opioids than individuals without OSA are.

Preoperative evaluation should focus on identifying patients at risk for OSA and improving associated comorbid conditions in those with OSA. Echocardiography may be indicated if heart failure or pulmonary hypertension is suspected. Many of these patients are obese, and even if not, many of the same issues

that apply to obese patients affect those with OSA. Patients should be instructed to bring their continuous positive airway pressure devices to the hospital on the day of surgery. Postoperative pain management and monitoring are critical.

Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

The HIV pandemic has spread to every country in the world. Acute infection with the virus causes a mononucleosis-like illness that progresses to chronic lymphadenopathy (lasting 3 to 5 years) and culminates in a cell-mediated immune deficiency characterized by opportunistic infections, malignancies such as Kaposi's sarcoma and non-Hodgkin's lymphoma, and death, usually secondary to infections, wasting, or cancer. Risk factors for HIV infection include sexual contact with an infected individual, blood-borne contamination, men who have sex with men, sexual workers, and those having contact with sexual workers. Most infection transmitted by blood exposure occurs in intravenous drug users, and infection via transfusion in the United States is rare (1 per 1.5 to 2 million blood transfusions). Mothers can transmit the disease to their infants, usually during breastfeeding or delivery.[123] Minority populations are at increased risk for HIV infection. Many patients infected with HIV are unaware of their status.

HIV can affect all organs and cause multiple complications. Myocarditis, dilated cardiomyopathy, valvular disease, pulmonary hypertension, pericardial effusions, and tamponade are possible. Antiretroviral-induced lipodystrophy causes CAD. Pulmonary infections with *Pneumocystis jiroveci*, *Mycobacterium avium* or *tuberculosis*, cytomegalovirus, and *Cryptococcus* are common and often drug resistant. Central nervous system tumors, infections, aseptic meningitis, and acquired immunodeficiency syndrome (AIDS)-related dementia occur, as well as lymphomas, Kaposi's sarcoma, cervical cancer, and lymphoid interstitial pneumonitis. Supraglottic or intraoral Kaposi's sarcoma may interfere with ventilation and intubation; non-Hodgkin's lymphoma can cause mediastinal masses. Dysphagia, diarrhea, esophagitis, and renal dysfunction can lead to malnutrition, dehydration, and electrolyte imbalance (hyponatremia and hyperkalemia are the two major electrolyte disorders). Acute tubular necrosis, glomerulonephritis, renovascular disease, and HIV-associated nephropathy with nephritic syndrome can be present. The nucleoside reverse transcriptase inhibitors (i.e., zidovudine, didanosine, stavudine, lamivudine, abacavir, emtricitabine) may cause lactic acidosis, electrolyte abnormalities, neuropathy, autonomic dysfunction, gastrointestinal upset, renal or hepatic dysfunction, and pancreatitis. Zidovudine can cause pancytopenia.

The preoperative evaluation may illicit a history of thrush, fever of unknown origin, chronic diarrhea, lymphadenopathy, or herpes zoster in more than one dermatome. In a relatively young, otherwise healthy individual, this should raise concern of HIV infection. The enzyme-linked immunosorbent assay (ELISA) is the primary screening test and is greater than 99% sensitive but has a high number of false-positive results. The Western blot technique is used to confirm ELISA results. Patients with known HIV infection will frequently require further evaluation, including an ECG, CBC with platelets, determination of electrolytes, BUN, and creatinine, LFTs, and a chest radiograph, depending on the surgical procedure. If malnourished or evidence of nephritic syndrome is present, measurement of albumin, total protein, and magnesium levels may be beneficial. Determining the $CD4^+$ lymphocyte cell count and viral load, which reflects the patient's immunologic status during the previous 3 months, can have prognostic value. A 13% mortality rate within 6 months of surgery has been reported when the $CD4^+$ count is less than $50/mm^3$ and a 0.8% mortality rate with $CD4^+$ counts greater than $200/mm^3$.[109] Antiretroviral therapy is continued perioperatively.

Evaluation of Patients with a History of Substance Abuse

A patient with a history of current or previous alcohol or drug addiction presents special challenges for the perioperative team (see Chapter 101). Although the prevalence of these addictions is significant (14% and 7%, respectively), there is limited information based on prospective clinical trials to guide perioperative management.[124]

The preoperative evaluation allows an opportunity to obtain a detailed history of addiction and recovery. Addictive disease is considered permanent, even in patients who have had long periods of abstinence. If a patient is in recovery, knowledge of the dosages and effects of medications used for maintenance of recovery is essential. Verification of all medication doses is vital. In a recovering patient, anxiety may be heightened as a result of concern about the possibility of both relapse into addiction and inadequate pain treatment because of the history of addiction. The patient should be assured during the preoperative interview that anxiety and pain will be adequately treated. Clinicians may have prejudicial attitudes and may lack the educational background to formulate appropriate plans for pain management. Pain medication may be inadequate and restricted because of concern about provoking a relapse. Identifying these at-risk patients during the preoperative evaluation and involving the acute pain service to assist in management may be helpful.

Patients who are actively abusing cocaine and amphetamines are at significant risk during anesthesia because of intraoperative hemodynamic instability. Urine testing (especially on the day of surgery) is appropriate to ensure the absence of abused substances in patients about to undergo procedures. Patients who are currently substance abusers have a variety of clinical manifestations, depending on the drug abused. Jage and Heid suggest classifying the substances into three categories: central nervous system depressors (e.g., heroin, alcohol, sedatives, hypnotics), stimulants (e.g., cocaine, amphetamines), and other psychotropic substances (e.g., cannabis).[125] The preoperative period should be used to plan for appropriate management. Heroin addicts may require substitution with methadone, and those addicted to alcohol, sedatives, or hypnotics may require stabilization with benzodiazepines. Discussion of regional techniques, avoidance of inadequate analgesia, and optimization of analgesia with nonopioids is essential. Inadequate analgesia can potentially activate addiction. All information and potential management plans should be clearly transmitted to members of the operative team.

Many addicts are polysubstance abusers, and psychiatric disorders are common comorbid conditions. Addicts may be at risk for a myriad of perioperative complications, including withdrawal, acute intoxication, altered tolerance of anesthetic and

opioid medications, infections, and end-organ damage.[126] Intravenous drug use should prompt an evaluation for cardiovascular, pulmonary, neurologic, and infectious complications such as endocarditis, abscesses, osteomyelitis, hepatitis, and HIV infection or AIDS. Alcohol abusers are specifically at risk for potentially life-threatening withdrawal with autonomic instability and hyperpyrexia. Cocaine and amphetamine addicts can have cerebrovascular accidents, cardiomyopathy, and arrhythmias. Additionally, cocaine and amphetamine inhibit the uptake of sympathomimetic neurotransmitters, increase BP, raise HR, and can cause paranoia, anxiety, seizures, angina, and MI (even in patients without CAD).[127] Long-term use causes ventricular hypertrophy, myocardial necrosis, and nasal septal perforation. Solvents can cause cardiac dysrhythmias, pulmonary and cerebral edema, diffuse cortical atrophy, and hepatic failure. Hallucinogens, including lysergic acid diethylamide (LSD), can cause autonomic dysregulation and paranoia. 3,4-Methylenedioxymethamphetamine (MDMA), commonly known as *ecstasy*, can cause excessive thirst, resulting in hyponatremia and pulmonary or cerebral edema.

Alcoholics are at risk for alcoholic hepatitis, cirrhosis, portal hypertension, cardiomyopathy, arrhythmias, seizures, neuropathies, dementia, Wernicke-Korsakoff syndrome (ataxia, cognitive dysfunction), and macrocytic anemia from vitamin deficiencies, delirium tremens, pneumonia, gastrointestinal bleeding, and coagulopathies secondary to either hepatic dysfunction or vitamin K deficiency. Marijuana can affect the cardiovascular and autonomic nervous systems and result in tachycardia, dysrhythmias, ECG abnormalities (T-wave and ST-segment changes), and increased cardiac output.

Patients who smoke marijuana are at the same risk as patients who smoke tobacco. Opioid (including heroin) users will have a tolerance to narcotics. It is important to document dosages of opioids taken, as well as any drugs to treat addiction such as methadone, clonidine, or buprenorphine (Suboxone or Subutex; with and without naloxone, respectively), a partial μ-agonist. Patients who are receiving opioid substitution therapy will experience normal pain responses to nociceptive stimuli and will require additional analgesia for control of postprocedure pain.[128]

Patients who use alcohol or prescription opioids to excess or illicit drugs may not give a reliable history. Vital signs, including temperature, are needed. Cocaine and amphetamines may raise BP and HR. Acute opioid use can slow the respiratory rate and cause lethargy and pinpoint pupils. Alcohol can often be detected by smell. Examination of venous access sites for signs of abscesses and skin and soft tissue infections is important. Auscultation for murmurs in intravenous drug users is essential. Symptoms and signs of heart failure or arrhythmias may be present in cocaine or alcohol abusers. Long-term use of alcohol causes liver dysfunction (see the appropriate section).

Preoperative testing depends on symptoms and findings from the history and physical examination. An ECG may be warranted in patients taking methadone because this drug can cause prolongation of the QT interval. It is important to ascertain whether and for how long patients can stop consuming alcohol or addictive drugs. In addition, more importantly, what happens when they do interrupt use? Does delirium tremens develop; do they have seizures or other signs of withdrawal? Ideally, patients with drug or alcohol dependence should be drug free well before elective surgery. Acute preoperative abstinence in alcoholics, however, has been associated with a poorer outcome postoperatively than if drinking is continued.[129] Preanesthesia clinic staff should be prepared to refer patients to addiction specialists or programs or prescribe medications to prevent withdrawal in the preoperative period if patients agree to abstinence.

Benzodiazepines are useful in preventing or treating alcohol withdrawal symptoms. Patients with a history of alcohol abuse who are taking disulfiram may have an altered response to sympathomimetic drugs; Hernandez and coworkers suggest that this agent be discontinued 10 days before surgery. If disulfram is continued, users can be sensitive to small amounts of alcohol (even from skin preparations or medications) and can experience flushing, nausea, and tachycardia. These authors also suggest that patients taking naltrexone for a history of alcohol or opioid abuse discontinue the drug 3 days before surgery. Patients taking SSRIs or methadone should continue maintenance doses. Marijuana users should be advised to avoid use at least 7 days before surgery because of its long half-life.[124]

Patients on methadone maintenance regimens continue the drug through the day of surgery. Because it may be difficult to overcome the analgesic agonist effect of Suboxone, it should be stopped 3 days before surgery. Patients may require substitution to avoid relapse of addiction during this period. Preoperative consultation with pain or addiction specialists (or both) may be useful for opioid abusers or patients taking methadone to combat addiction if the planned procedure will result in significant postoperative pain.

Preoperative Nutritional Evaluation

Patients who need surgery may be malnourished, either because of a chronic disease process (e.g., cancer or difficulty swallowing after a stroke) or because of a medical condition such as intermittent bowel obstruction (see Chapter 95). Malnutrition is associated with postoperative complications ranging from a prolonged hospital stay for patients undergoing total hip replacement to more major morbidity, such as wound breakdown, abscesses, infections, anastomotic breakdown, respiratory failure, and death.[130,131]

There is clear evidence that preoperative nutrition therapy in appropriate patients can reduce postoperative complications. TJC emphasizes the importance of preoperative nutritional evaluation and planning by requiring that nutritional screening be performed within 24 hours of admission, with full nutritional assessment in at-risk patients. Organizations must establish guidelines for nutrition screening and assessment that will identify patient characteristics known to be associated with nutrition problems and appropriately refer for planning. Reasonable agreement exists about predictive indicators of poor nutritional status: weight loss greater than 10% in the 6 months before surgery, change in dietary intake relative to normal, gastrointestinal symptoms that persist for longer than 2 weeks, decreased functional capacity (from lethargic to bedridden), and other physical factors such as loss of subcutaneous fat, muscle wasting, ankle edema, sacral edema, and ascites. Detsky and colleagues have incorporated these factors into the Subjective Global Assessment Scale.[132] The physical factors are rated as normal (0), mild (1+), moderate (2+), or severe (3+). Because of the high incidence of elective procedures that occur without previous admission, screening and assessment by TJC guidelines can be done either during the preoperative visit or during the first 24 hours of admission. This

makes it extremely difficult to implement preoperative nutrition support in patients who may benefit. Kudsk reported that in a group of patients undergoing gastrointestinal procedures, TJC-required assessments were performed in the vast majority of cases between 12 and 25 hours after surgery.[133] As a result, although the TJC mandate was met, the clinical team did not have the opportunity to provide preoperative nutrition support if indicated. Proper identification of at-risk patients would best be accomplished at the time of preoperative assessment and in an outpatient setting to allow time for implementation of preoperative nutrition plans.

The best places to look for loss of subcutaneous fat are the triceps region of the arms, the midaxillary line at the costal margin, the interosseous and palmar areas of the hand, and the deltoid region of the shoulder. Muscle wasting is best assessed in the quadriceps femoris and deltoid region. The nutritional status of patients can be classified A (well nourished), B (moderately malnourished; weight loss of 5% to 10% without stabilization or weight gain, poor dietary intake, and mild loss of subcutaneous tissue), or C (severely malnourished; ongoing weight loss of >10%, severe subcutaneous tissue loss, muscle wasting, and edema).

A serum albumin level of less than 3.5 g/dL in the general surgical population or less than 3.9 g/dL in patients who need total hip replacement is an accurate predictor of malnutrition.[130,131] Serum albumin less than 2.1 mg/dL was a strong predictor of mortality in veterans undergoing major noncardiac surgery.[75] The combination of history plus physical examination and serum albumin level provides slightly improved accuracy in predicting malnutrition than either indicator alone does.

When possible, nutritional status should be improved preoperatively in severely malnourished patients. Enteral nutrition is the preferred means, but if the gut cannot be used, total parenteral nutrition (TPN), though not without its own risks, is acceptable. In a Veterans Affairs study, severely malnourished patients who received TPN had fewer noninfectious complications than controls did (5% versus 43%), with no concomitant increase in infectious complications.[80]

Breastfeeding Patients

There is little science to guide recommendations for the safety of anesthetics and medications in the babies of mothers who breastfeed and receive these agents. For elective cases, women need to be advised to pump and store milk preoperatively, which can be used in the first 24 hours after administration of an anesthetic or for the duration of breast milk exposure to potentially harmful agents. The mother should discard milk produced within the first 24 hours after anesthesia and generally resume breastfeeding after this period. Very young or premature babies, especially those at risk for apnea, may have complications if the mother continues to take opioid or sedating drugs. Mothers should be advised to discuss with their child's pediatrician the safety of breastfeeding while taking medications.

Patients with Do-Not-Resuscitate Orders

Some patients scheduled for procedures will have advance directives or a do-not-resuscitate (DNR) status (see Chapter 97). In 1993 the ASA adopted guidelines for the care of these patients and updated them in 2001 (Box 34-7).[134] Frequently, in circumstances with DNR orders, care providers are focused on a procedure-directed approach (i.e., do not intubate, no resuscitative drugs), which is problematic in the perioperative period when much of anesthesia care involves this approach. It has been suggested that a better tactic would be to discuss DNR status in the context of anesthesia in a goal-directed approach (i.e., from the perspective of the patient's values and objectives, such as "quality-of-life" concerns).[135] The ideal time to discuss this emotional, complex issue is during the preoperative evaluation. It has been shown that short discussions in a preoperative clinic can foster dialogue among patients, their proxies, and physicians regarding advance directives concerning end-of-life care. A durable power of attorney was completed by 27% of intervention patients versus 10% of controls, and 87% of the intervention group discussed end-of-life care with the appropriate individuals versus 66% of the control group.[136]

Box 34-7 Do-Not-Resuscitate Orders in the Perioperative Period

Policies automatically suspending DNR orders or other directives that limit treatment before procedures involving anesthetic care may not sufficiently address a patient's rights to self-determination in a responsible and ethical manner. Such policies, if they exist, should be reviewed and revised, as necessary, to reflect the content of these guidelines.

1. Full Attempt at Resuscitation: The patient or designated surrogate may request full suspension of existing directives during anesthesia and the immediate postoperative period, thereby consenting to the use of any resuscitation procedures that may be appropriate to treat clinical events that occur during this time.
2. Limited Attempt at Resuscitation Defined with Regard to Specific Procedures: The patient or designated surrogate may elect to continue to refuse certain specific resuscitation procedures (e.g., chest compressions, defibrillation, or tracheal intubation). The anesthesiologist should inform the patient or designated surrogate about which procedures are (1) essential to the success of anesthesia and the proposed procedure and (2) which procedures are not essential and may be refused.
3. Limited Attempt at Resuscitation Defined with Regard to the Patient's Goals and Values: The patient or designated surrogate may allow the anesthesiologist and surgical team to use clinical judgment in determining which resuscitation procedures are appropriate in the context of the situation and the patient's stated goals and values. For example, some patients may want full resuscitation procedures to be used to manage adverse clinical events that are believed to be quickly and easily reversible but to refrain from treatment of conditions that are likely to result in permanent sequelae, such as neurologic impairment or unwanted dependence on life-sustaining technology.

From Committee on Ethics, American Society of Anesthesiologists: Ethical guidelines for the anesthesia care of patients with do not resuscitate orders, 2001. Available at http://www.asahq.org/publicationsAndServices/standards/09.html.

Pseudocholinesterase Deficiency

A personal or family history of pseudocholinesterase (specifically, butyrylcholinesterase) deficiency should be identified preoperatively (see Chapter 29). When patients report an "allergy to succinylcholine," one should suspect this disorder or MH. Inquiring whether the patient had to remain intubated postoperatively, was gravely ill, or required intensive care may help differentiate these disorders. Pseudocholinesterase activity may be reduced permanently because of abnormal genotypes or transiently altered because of disease, drug effects, parturition, or infancy. Patients should be educated that this enzyme also metabolizes ester-linked local anesthetics.

Preoperative records from previous anesthesia may clarify an uncertain history. A dibucaine number and plasma pseudocholinesterase, chloride, and fluoride levels should be obtained. The *dibucaine number* is a measure of the qualitative activity of pseudocholinesterase and is the percentage of inhibition of the enzyme by the local anesthetic dibucaine. Normal individuals are homozygous for the wild type, and their dibucaine number is 80 because their plasma cholinesterase is 80% inhibited by dibucaine. Those who are homozygous for the atypical genes have a dibucaine number of 20 because of 20% inhibition. Heterozygous individuals have a dibucaine number of 60 because of approximately 60% inhibition. The plasma cholinesterase level is a quantitative measure of this enzyme. Plasma cholinesterase should not be confused with cholinesterase activity, which is an assessment of erythrocyte or red blood cell cholinesterase. The combination of dibucaine number and plasma cholinesterase can differentiate genetic from nongenetic causes of prolonged apnea after the administration of succinylcholine. A transient decrease in pseudocholinesterase activity as a result of drug interactions or other identified reasons has been observed soon after episodes of suspected pseudocholinesterase deficiency, so diagnostic testing should be delayed at least 24 hours. Patients with known or suspected pseudocholinesterase deficiency should be urged to obtain proper identification (Web search for "medical alert identification").

Malignant Hyperthermia

A history of MH or a suggestion of it (hyperthermia or rigidity during anesthesia) in either a patient or family member should be clearly documented so that special arrangements can made before the day of surgery (see Chapter 37). Individuals are genetically predisposed to MH and are asymptomatic until exposed to triggering agents. Certain neuromuscular diseases are associated with a risk for MH, including Duchenne's, Becker's, and myotonic muscular dystrophies, King-Denborough syndrome, central core disease, periodic paralysis, osteogenesis imperfecta, myelomeningocele, and strabismus.

Residency Training in Preoperative Evaluation

The evolution of preoperative evaluation, as well as the anesthesiologist's role in this area, challenges training programs to educate practitioners who can function well in roles both inside and outside the operating room. Optimal preoperative assessment, as well as continued improvement, will rely on properly educating anesthesiologists in the skills of physical diagnosis and patient assessment, personnel and business management, and conducting and understanding outcome-based research in this area. It is unrealistic to expect the next generation of anesthesiologists to successfully manage administrative and clinical roles in perioperative medicine without adequate exposure during residency training. A survey of training programs published in 2001 revealed that although almost all program directors agreed that competency in preoperative evaluation was an important skill, less than half had a formal curriculum in this area, nearly 50% did not teach patient interview skills, and 39% of programs did not expose their residents to a preoperative clinic experience.[137] The American College of Graduate Medical Education (ACGME) has recognized the importance of adequate training in this area during anesthesia residency. Requirements have been amended and became effective in July 2008; requirements in preoperative education have been increased and more specifically defined.[138] During the 3 clinical anesthesia training years, 1 month must be spent in a preoperative evaluation clinic. This may occur in divided rotations not less than 1 week in length. Successive experiences must reflect increased responsibility and learning opportunities. Program objectives must include adequate training not only in the clinical aspect of preoperative assessment but also in interpersonal skills, effective communication, and business practices. Practice management, operating room management, and systems-based practice issues should be included in the curriculum.

Assessment of skills in this area requires a definition of objectives. Instruments for assessing resident performance in this area should be developed. A "Preanesthesia Consultation Scoring Checklist" has been developed that contains 37 items grouped into the domains of physician-patient relationship, medical history, physical examination, patient education, and preanesthesia records.[139] This instrument was shown to have high construct validity, moderate internal consistency, and high probability of inter-rater agreement. Analysis of the scores could reliably assess resident performance at the defined criteria. The development of similar instruments in conjunction with the institution of a specific curriculum in preoperative evaluation will be of great help in assessing resident performance, as well as in meeting ACGME requirements.

Meeting Regulatory and Reporting Requirements

Appropriate and safe clinical assessment includes elements that are considered standard of care medically, in addition to elements that are requirements mandated by outside agencies. These outside agencies may be those mandating practice for quality accreditation, such as the TJC. Agencies may mandate practice for payment, such as the Center for Medicare and Medicaid Services (CMS) or other agencies that provide payment based on practice or performance. A detailed discussion of the use of technology in the preoperative clinic to meet requirements will follow in a later section. Regulatory requirements may exist internally as well. Institutions generally develop practice guidelines or standards,

and it is incumbent on all practicing clinicians to abide by the standards of their respective institutions. A number of these standards involve preoperative care issues, and a number of requirements for accreditation by TJC involve preoperative issues. These requirements are described in detail in the TJC manual referenced and are available through the TJC website (www.jointcommission.org).

As far as the timing of preoperative assessment is concerned, TJC requires that the history and physical examination be completed within 30 days before the procedure and that a reassessment be done within the 24-hour period immediately preceding the surgery. No other TJC requirements exist regarding the timing of assessments, consents, or laboratory testing. It should be realized, however, that insurance payers might have specific requirements regarding the timing of assessments in relation to the surgical procedure and payment; providers may obtain information from their respective institutional compliance departments about the timing of assessments and payment by carrier. Hospital policies must ensure that patients have the right to refuse care, treatment, and services in accordance with the law. When the patient is not legally responsible, the surrogate decision-maker has the right to refuse care on the patient's behalf. To this end, the hospital must have a framework for ensuring that such advance directives are completed. TJC requires that the hospital document and have available to clinicians the patient's decision regarding such advance directives. The preoperative visit is an opportunity to supply the patient with information regarding advance directives, as well as to document the patient's wishes regarding such directives. TJC also requires that patients with special needs be assessed and these needs addressed. Such patients may be victims of abuse or neglect, alcohol or substance abusers, patients with significant emotional or behavioral disorders, and patients with specific nutritional needs. These assessments can be performed and documented at the time of the preoperative evaluation.

Many of these elements are documented as portions of the patient's nursing assessment, which TJC mandates be performed on each patient by a registered nurse. The preoperative history and physical examination may be performed by any licensed practitioner who is credentialed to do so. The anesthesia assessment may be performed by a physician or advanced practice nurse (nurse practitioner or certified registered nurse anesthetist) with appropriate training. TJC mandates that pain be assessed in all patients. A comprehensive pain assessment can be performed as part of the preoperative nursing or physician assessments. Establishing a baseline for the pattern of pain existing preoperatively is extremely important in formulating a postoperative care plan.

Patients who are taking significant amounts of narcotics and other pain relievers preoperatively can be identified and appropriate postoperative care plans formulated and communicated to the perioperative care team. TJC also supports a number of National Patient Safety Goals (NPSGs).[140] How an appropriate preoperative process can advance achievement of the 2007 NPSGs is illustrated in Table 34-6.

Table 34-6 Role of the Preoperative Clinic in Achieving National Patient Safety Goals

2007 National Patient Safety Goal	Preoperative Clinic Role
Improve the accuracy of patient identification	Use two patient identifiers when doing evaluation or testing; verify that all information on the operating room chart is correctly labeled
Improve the effectiveness of communication among caregivers	Communicate patient issues among multidisciplinary perioperative care providers Use a standardized list of abbreviations in the preoperative chart; eliminate the use of acronyms
Reduce the risk of health care–associated infection	Identify and transfer information to the operating room and postoperative areas regarding patients colonized with antibiotic-resistant organisms
Accurately and completely reconcile medications across the continuum of care	Begin a single accurate list of prescription and nonprescription medications and dosages that can follow the patient throughout the perioperative experience
Encourage patients' active involvement in their own care as a patient safety strategy	Perform patient and family education related to the upcoming procedure
Identify safety risks inherent in its patient population	Establish and implement a universal protocol to prevent wrong-sided procedures; verify sidedness at the time of preoperative assessment and correct errors

Preoperative Medical-Legal Issues

In a malpractice action involving preoperative professional negligence, the burden is on the plaintiff to show the generally recognized standard of medical care, deviation from that standard by the defendant, and that the deviation was the proximate cause of the patient's alleged injuries (see Chapter 10). Expert testimony is generally used to demonstrate the standard of care, as well as deviation from such standards. The ultimate decision of whether practice deviated from the standard of care should be a matter of fact, not opinion. However, in the preoperative area, many clinical "standards" are in actuality only guidelines based on general consensus or expert opinion, not on outcome data from large population-based studies. Compliance with the specific institutional guidelines, as well as with guidelines and standards set forth by credible groups such as the TJC and ASA, is heavily considered. The court generally accepts statements from these groups regarding definitions of standard of care. For example, there are a number of cases in which performance of preoperative assessment as defined by the TJC or guidelines for preoperative assessment as defined by the ASA have been placed into evidence as defining standard of care. Understanding the components of proper informed consent and establishing an effective system for obtaining consent are critical elements of the preoperative process. A review of legal decisions in this area by Raab has attempted to define appropriate parameters.[141] The absence of appropriate informed consent can result in consideration of the tort of battery. Lack of adequate informed consent has also been found to constitute the main cause of negligence, even when malpractice or substandard care cannot be proved. Courts apply either of two standards for adequate disclosure; one refers to what a reasonable clinician would consider important to the patient's decision (reasonable practitioner standard), and the other is whether the clini-

cian has disclosed what a prudent patient would need to know in order to make an intelligent decision (prudent patient standard). These are different legal concepts that are applied on a state-by-state basis. The law requires that nontrivial risks be disclosed; extremely rare complications need not be disclosed. As far as disclosure regarding risks associated with anesthesia is concerned, Raab believes that the risk of anesthesia-related death or severe injury in a patient whose health is otherwise reasonably good would be in the range of a rare consequence; however, most reasonable patients would still want to be aware of this. The signed consent form is documentation that such discussions have occurred. Raab thinks that the dilemma regarding informing patients of rare probabilities of anesthesia complications remains unsolved. With regard to surgical informed consent, a closed claims analysis has revealed that documentation of discussion in the surgeon's office notes was a significant factor in reducing indemnity risk, regardless of whether the actual consent form was signed by the surgeon, resident, or nurse practitioner.[142]

Clinicians may be concerned about liability in overordering or underordering preoperative testing. In general, clinicians are not held liable for errors in judgment; liability holds only when the testing rendered would be considered to fall below accepted standards of practice.[143] It is extremely difficult to decide what is standard of practice for routine preoperative laboratory testing because of numerous articles demonstrating lack of impact of routine preoperative screening tests on management. However, failure to order appropriate laboratory testing that would diagnose an important presurgical comorbidity would imply that the clinician had performed a substandard assessment. This emphasizes the importance of a complete and well-documented preoperative history and physical examination with testing geared toward comorbid diseases revealed by this evaluation. Routine screening batteries in the setting of inadequate evaluation would seem to put the clinician at a much greater risk of missing an important preoperative condition. A review of more than 400 diagnostic malpractice claims in the outpatient setting would support this view.[144] These investigators reported that the most common breakdowns in the diagnostic process were failure to obtain an adequate history or perform an adequate physical examination, failure to order a specific diagnostic test, failure to follow up on rest results, and incorrect interpretation of test results.

A clinician who has informed discussions with the presurgical patient and documents a proper history, physical examination, and anesthesia and nursing assessment in the chart would minimize medical-legal risk. Additionally, the clinician must provide chart evidence of discussions regarding consent, risks, and alternatives; orders of preoperative testing geared to the results of the patient's particular assessment, along with appropriate follow-up of the abnormalities documented; and notes that all the patient's questions were answered.

Information Technology and Decision Support Systems in Preoperative Evaluation

Decision support algorithms can suggest appropriate clinical management and preoperative testing based on factors documented in the patient's history and physical examination (see Chapter 4). These algorithms can be generated by clinical leadership and distributed as part of the educational and orientation process for the preoperative clinic providers. Appropriate use of clinical and testing algorithms by clinicians, even in the absence of computer-based prompts, has been demonstrated to decrease laboratory costs as a result of unnecessary or unreimbursed testing and consultations.[145]

Algorithms can be built into computer-based programs; integration with patient data stored as part of the hospital's electronic medical record would be particularly valuable. Because institutions frequently store data in programs using different platforms, there is often difficulty in attempting to integrate multiple data storage programs within a single institution and even greater difficulty in considering complete integration of patient data with commercially available systems.

Despite the potential benefits, there are a number of barriers to implementation of electronic preoperative systems. The lack of uniformity in coding medical conditions presents significant impediments to computer-based preoperative assessment systems. Coding of physician data is extremely complex, in contrast to computer recording of laboratory data. Most of the commercially available systems involve pull-down menus, which may or may not be consistent with the physician's thought processes. Pull-down menus may result in information being recorded where it "best fits" and therefore may not be completely accurate. The use of free text results in loss of the ability to generate a plan based on decision support and also prevents the use of aggregate data for reporting.

Coding needs to be recorded in such a way that the data can be used for individual patient billing, as well as in aggregate for reporting of quality performance measures. It will be difficult to demonstrate an impact of quality reporting programs on clinical outcomes until adequate physician coding through information technology can be achieved. Because of lack of this focus in coding, regulatory quality reporting programs have been shown to influence hospital improvement activities but have not been shown to have a positive impact on outcomes.[146]

Confidentiality issues in protecting computer-based data from interception are of great concern. Unlike paper-based records, computer-stored data have the potential for security risks as a result of inappropriate access to information on large numbers of patients. Proper policies and education of staff regarding privacy issues are essential. The Health Insurance Portability and Accountability Act (HIPAA) is legislation regarding the privacy of health care information and related transactions. HIPAA requirements from the Department of Health and Human Services are outlined in their website (www.hhs.gov/ocr/hipaa). Business partners of health care institutions, such as billing agencies and insurance companies, must comply with these regulations as well.

There is some concern that a change from manual to computer-based data entry during the patient visit would decrease the efficiency of established workflow patterns. The effect on the patient interview needs to be considered as well. Clinicians will need to ensure that the quality of the interview does not suffer as they divide their time between the computer terminal and the patient. The resource savings may not be demonstrated if information is merely being typed instead of written, thus again emphasizing the need for integration among platforms and reduction of requirements for free text entry. There is no evidence-

based literature demonstrating truly successful implementation, quality outcomes, and resource management with either commercially based or internally developed systems that address all of the necessary elements.

Groups such as Leapfrog and the National Surgical Quality Improvement Program have encouraged the development and use of such systems to record and report quality indicators and develop technologies to improve patient safety (www.leapfroggroup.org and www.acsnsqip.org). Because of the difficulties described with development and implementation of technology, adaption has been slow.[147] No "off-the-shelf" products are available, and no standards have been developed between vendors and institutions. Regulatory groups promote the ability of such systems to decrease errors and improve standardization and safety. Physicians are concerned about cost and the impact on workflow. The use of such systems may actually increase physician workload; one study estimated that computerized order entry would require 5% of a resident's weekly work hours.[148] Again, the ability of integration to allow medications already known in primary care and specialist's offices to be automatically entered into preoperative and order entry systems would vastly increase their appeal and efficiency.

Appropriate technology can address the TJC mandate regarding medicine reconciliation. According to this mandate, providers must enter an accurate single list of all prescription and nonprescription medications and dosages that starts at the time of entrance into the hospital for services. Development of such preoperative systems and incorporation into automated electronic perioperative information systems will aid in achieving efficient assessment before surgery. Acceptance of such systems and adequate patient and clinician use will require instruction, encouragement, and delineation of potential impact for improvement of the perioperative process.

Preoperative Involvement in Prevention of Surgical Site Infections

The preoperative visit provides an opportunity to intervene in the prevention of surgical site infections (SSIs). The Centers for Disease Control and Prevention (CDC) has used the National Nosocomial Infections Surveillance system to monitor nosocomial infections in acute care hospitals in the United States since 1970. Detailed information on this topic can be found on the CDC website (http://www.cdc.gov). In addition to considerable morbidity and mortality, SSIs significantly increase health care costs.[149] The CDC has developed standardized criteria for defining SSIs so that surveillance and comparisons can be done. Many institutions monitor the incidence of SSIs among various surgical services and procedures as a quality indicator. An analysis of one's own institutional performance and comparison with CDC benchmarks can yield extremely useful information. SSIs occurring after what would be defined by the CDC as clean surgery are probably due to certain factors, many of which can be identified during the preoperative visit (Box 34-8). The CDC recommends preoperative antiseptic showering. Preoperative showering with an antiseptic skin wash product is a well-accepted procedure for reducing skin bacteria, and showering on successive days with a skin antiseptic reduces counts progressively. However, there are no clear studies showing a direct independent relationship between preoperative antiseptic showering and a lower incidence of SSIs. Nevertheless, because of the CDC recommendation, many institutions instruct preoperative patients to perform these showers. At Brigham and Women's Hospital in Boston, patients undergoing non–mucous membrane surgery are given a skin antiseptic at the time of their preoperative clinic visit and instructed to take an antiseptic shower on each of the 2 days before the procedure. The preoperative visit can also provide an opportunity to ensure that appropriate SSI prophylaxis is ordered. If an institution establishes suggested guidelines, these algorithms can be followed and antibiotic orders written and available in the chart when the patient arrives for surgery, which would allow ample time for administration as indicated in the recommendations.

Box 34-8 Factors Influencing Surgical Site Infection after Clean Surgery

Patient Risk Factors
Age
Nutritional status
Diabetes
Obesity

Factors Associated with Preoperative Preparation
Preoperative antiseptic showering
Preoperative hair removal
Preoperative antibiotic prophylaxis

Factors Associated with the Procedure
Preoperative hand and arm antisepsis
Length of the procedure
Surgical technique

Infective Endocarditis Prophylaxis

The preoperative evaluation can also be used to identify patients in need of antibiotic prophylaxis to prevent subacute bacterial endocarditis. The recommendations by the AHA that were last published in 1997 were updated in 2006 and have included significant changes from the previous version. In this update the committee concludes that administration of antibiotics solely to prevent endocarditis is not recommended for patients undergoing a procedure on the genitourinary or gastrointestinal tract. Prophylaxis for dental procedures is recommended only for patients with underlying cardiac conditions associated with the highest risk of an adverse outcome from infective endocarditis. Infectious endocarditis is thought to be more likely to develop from frequent exposure to bacteremia associated with daily activities than from bacteremia associated with a dental, gastrointestinal, or gastrourinary procedure. The risk of antibiotic-associated adverse events and the cost-effectiveness of prophylactic therapy are such that the benefits are outweighed. Under these revised guidelines, many fewer patients will be candidates for prophylaxis.

The committee defined cardiac conditions associated with the highest risk for an adverse outcome from endocarditis. Such conditions include patients with prosthetic heart valves, unrepaired cyanotic congenital heart disease, congenital heart disease repaired with prosthetic devices for 6 months after the procedure (at which time endothelialization should have occurred), repaired congenital heart disease with residual defects, and cardiac transplantation with valvuloplasty. These are also the conditions for which prophylaxis during oral/dental procedures involving gingival manipulation or perforation of the oral mucosa are recommended, although the efficacy of such prophylaxis is unknown. Prophylaxis is recommended for the patients listed who are to undergo respiratory procedures that involve incision or biopsy of the mucosa. Prophylaxis for bronchoscopy is not recommended unless the procedure involves incision of the respiratory mucosa. Administration of prophylactic antibiotics solely to prevent endocarditis is not recommended for patients who undergo genitourinary or gastrointestinal procedures. Treatment is recommended if patients have an established infection or urinary tract colonization with enterococci. Antibiotics solely for the prevention of endocarditis are not recommended for patients with other cardiac conditions, including those with previous bypass surgeries or stents.

Prophylaxis for patients after total joint replacement was reviewed and an advisory statement issued in 2003. According to this advisory, patients with joint replacement who are undergoing high-risk procedures may need preventive antibiotics. This includes all patients during the first 2 years after joint replacement, immunocompromised/immunosuppressed patients, patients with inflammatory arthropathies such as rheumatoid arthritis and SLE, and patients with comorbid conditions, including previous prosthetic joint infections, malnourishment, hemophilia, HIV infection, insulin-dependent diabetes, and malignancy. The statements conclude that prophylaxis is not indicated for patients with pins, plates, or screws. The preoperative clinic visit can be an opportunity to identify those with joint replacements requiring prophylaxis and to ensure that appropriate orders are available at the time that the patient arrives for the procedure so that optimal timing of antibiotic administration can occur.

Recommended prophylaxis is amoxicillin, 2 g orally in adults and 50 mg/kg orally in children given 30 to 60 minutes before the procedure. This dose can be administered intravenously or intramuscularly if necessary. In patients allergic to penicillin, clindamycin (600 mg orally, intramuscularly, or intravenously in adults or 20 mg/kg orally, intramuscularly, or intravenously in children) can be used. Cephalexin (2 g orally in adults and 50 mg/kg orally in children) or cefazolin (1 g intramuscularly or intravenously in adults and 50 mg/kg intramuscularly and intravenously in children) can be used unless the patient has a history of anaphylaxis, angioedema, or urticaria with penicillin.

Preoperative Planning for Postoperative Pain Management

The preoperative evaluation provides an important opportunity to discuss and plan for the management of acute postoperative pain (see Chapter 87). Patients may be extremely concerned about this issue. Patients with chronic pain conditions need to have a plan for the management of acute pain in the setting of the chronic situation. In institutions that have an acute pain service, patients with particularly difficult management issues, patients taking large doses of analgesics, or patients with histories of analgesic abuse can be referred for consultation and appropriate perioperative managment. Patients can also be evaluated by the acute pain service postoperatively for management recommendations. In the absence of an acute pain service, the surgical service will generally be responsible for postoperative pain management.

TJC is particularly concerned that patients with pain issues be appropriately assessed and treated. A baseline pain assessment is an important part of any preoperative evaluation and is generally performed as part of the nursing assessment.[150] The preoperative pain standards in this regard state that patients have the right to appropriate assessment and management of pain and that pain must be assessed in all patients preoperatively.

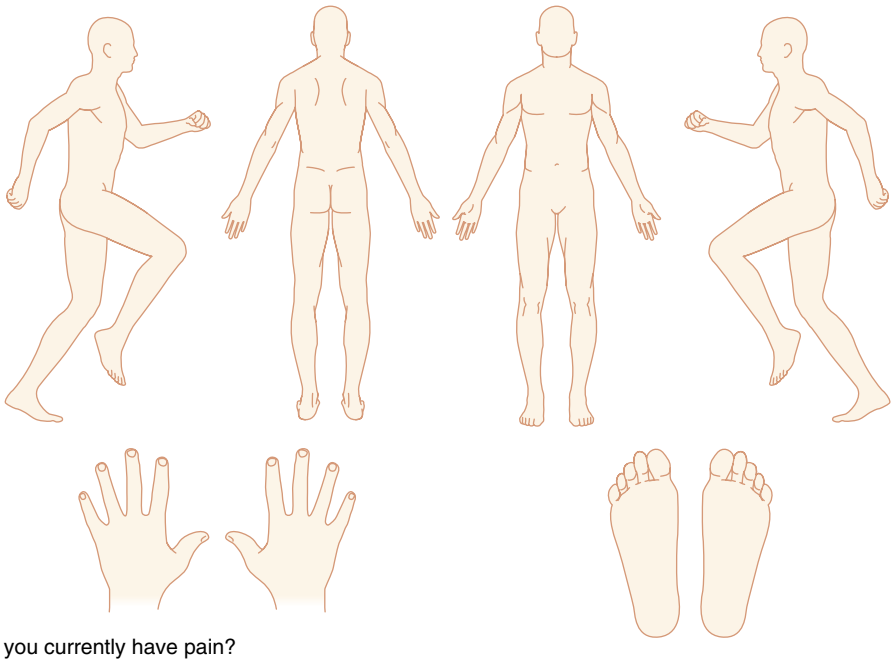
Standardization of pain measurement is difficult because of the subjective nature of the variable. Scales used fall into the categories of single-dimension scales, such as visual analog and numerical rating scales, and multidimensional scales, such as the McGill pain questionnaire.[151] Figure 34-4 shows one example used for pain assessment in a preoperative evaluation. The location of the pain is noted on the figure; the character, duration, and frequency are documented, and intensity is recorded with a numerical rating scale from 1 to 10, with 1 being no pain and 10 being the worst pain imaginable. If a numerical scale cannot be used, a scale using faces can be substituted. Use of these scales readily allows comparison when reassessments are performed postoperatively.

As part of the preoperative pain assessment, any information regarding previous and ongoing pain issues should be documented, including pain control methods that have worked or not worked in the past. Some understanding of patients' attitude toward pain medication (e.g., fear of addiction) is helpful. The exact dose of their current analgesic medications is essential. If patients take them as needed, how many are being used on average per day should be recorded.

Patients with chronic pain conditions present a special management problem. There is no reason to wean patients from pain medicine before surgery. If the patient's analgesic is an NSAID or COX-2 inhibitor, the patient may be told to discontinue use before surgery. If so, the patient may need to be given a different analgesic for pain control before the procedure. Patients should be told to take their usual morning doses of pain medicine. If the patient wears a fentanyl transdermal patch, it can be left on. It is important to inform the patient that care providers will do everything possible to maintain comfort postoperatively, but the expectation of having no pain should not be given. It should be expected that a chronic pain patient's requirement for pain medication will be increased postoperatively and should be managed accordingly. There are no useful algorithms for treatment of acute pain in chronic pain patients, and care needs to be individualized. A pain service consultation may be very useful in this situation, especially when the surgical staff is not familiar with complicated chronic pain regimens and alternative options.

Preoperative Use of Alternative and Complementary Therapies

A significant number of patients have been reported to use alternative and complementary therapies in the preoperative period (see Chapter 32). A survey of preoperative clinic patients demon-



Do you currently have pain?

☐ Yes ☐ No If Yes, location: _____

Character: ☐ sharp ☐ throbbing ☐ dull ☐ burning

Duration: _____

Frequency: _____

Intensity scale: _____

☐ Numeric

☐ Faces

What makes the pain better? _____

What makes the pain worse? _____

What is an acceptable pain level to you? _____

Figure 34-4 Pain/status/history form.

strated that 22% reported the use of herbal medications and 51% used vitamins.[152] Women and patients in the age range of 40 to 60 years were more likely to use herbal medicine. The most commonly used compounds, from highest to lowest, included echinacea, *Ginkgo biloba*, St. John's wort, garlic, and ginseng. The pediatric population has a significant amount of use as well, which varies with ethnic subgroup.[153] Use of nonprescribed dietary supplements was significantly higher in Hispanic than in white children (33% versus 9%).

Of concern is that unless specifically questioned, patients may not report the use of these nonprescription agents. In a group of patients awaiting cardiac surgery, 56% did not inform the anesthesiologists before surgery regarding the use of these products.[154] Because patients may fail to disclose the use of alternative therapies unless specifically questioned, it is difficult to make specific associations between potential drug and herb interactions. In addition, the U.S. Food and Drug Administration (FDA) does not have regulatory oversight of purity and other standards of these nonprescription medications. Many of the herbs sold are ineligible to be approved as a drug, and the FDA can take action only when a substance is determined to be unsafe.

The ASA has published two documents on dietary supplements, one for patients and one for providers.[155] Both these pamphlets are available through the ASA website. The ASA recommends discontinuation of all alternative therapies 2 weeks before elective procedures, although there are no definite data supporting this recommendation.

The impact of alternative therapies on perioperative outcome is unclear. In a Hong Kong cohort study, 80% of presurgical patients took self-prescribed traditional Chinese herbal medicines (TCHMs).[156] Despite the high use of alternative therapies in this group, there was no significant association between any type of TCHM and the occurrence of either intraoperative or postoperative events when adjusted for covariates. Patients who used TCHMs were more likely to have a preoperative event, including a prolonged aPTT and hypokalemia.

The most common potential adverse effects of herbal medicines in the perioperative period include impaired coagulation, cardiovascular side effects, electrolyte disturbances, and prolongation of the effects of anesthetic agents.[157] There is little information available about the epidemiology of perioperative events related to alternative therapies, and there is no agency currently

Box 34-9 Potential Adverse Effects of Alternative Therapies

Cardiovascular instability, including high blood pressure, tachycardia, angina, and atrial arrhythmias: saw palmetto, ginseng, black cohosh, St. John's wort

Thromboembolic events: saw palmetto, ginseng

Enhanced potential for bleeding: black cohosh, ginkgo, garlic, ginseng, ginger, chamomile, vitamin E

Prolongation of anesthesia: St. John's wort

Hypothyroidism: soy

Hyperthyroidism: triiodoacetic acid

Hepatotoxicity: echinacea, kava

Decreased effectiveness of HIV protease inhibitors: St. John's wort

Seizures: black cohosh

Enhanced effect of opioid analgesics: valerian, kava, chamomile

Inhibited effect of opioid analgesics: ginseng

responsible for overseeing manufacturing and safety, regulating sales, and reporting adverse events. Starting in 2005, TJC required that alternative therapies be considered like any other drug when documentation of patient medications is performed. Potential adverse effects of the more commonly used agents are summarized in Box 34-9. However, much of these data is based on anecdotal evidence, theoretical proposals, and case reports—not from good epidemiologic studies with large databases.[158,159] Further in vitro data, animal studies, and clinical epidemiologic studies are needed to assess the significance of these potential interactions.

A significant number of patients also report the use of nonherbal alternative therapies. The most common complementary and alternative therapies reported in a survey of preoperative patients were massage therapy (15%), herbal therapy (10%), relaxation (8%) and acupuncture (7%).[160]

Preoperative Laboratory and Diagnostic Studies

The value and outcome of preoperative diagnostic studies and testing have become a central issue in evaluating cost-effective health care in presurgical patients. It is estimated that up to $4.0 billion is spent annually in the United States on preoperative diagnostic and laboratory evaluation. The value of obtaining preoperative studies as a screening tool to detect disease and evaluate the stability of the patient's medical condition for anesthesia and surgery has been extensively published in the academic literature.[161] The concept of standardized testing in all presurgical patients regardless of age or medical condition is no longer considered medically appropriate. Unnecessary testing is inefficient and expensive, and it requires additional technical resources. Inappropriate studies may lead to costly evaluation of borderline or false-positive laboratory and diagnostic test abnormalities. This may result in unnecessary operating room delays, cancellations, and potential patient risk through additional testing and follow-up.

Patients require preoperative diagnostic and laboratory evaluation that is consistent with their medical history, the proposed surgical procedures, and the potential for intraoperative blood loss. Preoperative diagnostic and laboratory testing should be obtained for specific clinical indications that may increase perioperative risk and not simply because the patient is to undergo a surgical procedure. Consistent accuracy of diagnostic testing and the problems associated with false positives are reason enough to limit preoperative tests to specific indications. The sensitivity, specificity, reproducibility, and clinical predictive value of preoperative diagnostic studies have been comprehensively reviewed in previous editions of this chapter. It has been well documented in academic studies that routine preoperative screening tests in an asymptomatic healthy patient have no beneficial effect on surgical or anesthesia outcomes.

At many hospitals, the tradition has been that all preoperative tests and diagnostic studies be ordered by the surgeon or primary care physician. Frequently, these tests are obtained without a specific diagnostic focus other than a speculation that the anesthesiologist may "require them" to proceed with surgery and thus avoid delays and cancellations. Other reasons include routine screening for disease states, establishment of a diagnostic baseline, personal habit (using a "standard" checklist for all patients), physician reassurance, and a perceived medicolegal necessity "not to miss anything." This historical method of ordering preoperative laboratory tests as screening devices and to avoid cancellations and delays cannot be justified and is clinically inappropriate.

Nonselective laboratory testing and diagnostic studies result in significant cost to the hospital and expense for the patient.[162,163] Routine presurgical screening tests are no longer supported or reimbursed by Medicare and most private insurance carriers without specific indications. Implementation of changes is necessary to reduce these costs and enhance patient care. Anesthesiologists are the perioperative medicine experts and are best qualified to establish appropriate and necessary preoperative laboratory and diagnostic tests for intraoperative anesthesia management. Providing specific guidelines and education to physician colleagues and surgical services for recommended preoperative testing reduces costs, expedites patient care, and enhances the anesthesiologist's recognition as the perioperative physician specialist.

Several academic studies have demonstrated reductions in hospital cost for preoperative diagnostic evaluation when diagnostic testing is coordinated through the anesthesia preoperative evaluation clinic.[164,165] Preoperative diagnosis-based guidelines (Table 34-7) provide basic recommendations for perioperative management of patients with medical conditions that increase operative risk. These disease-specific guidelines are not intended as absolute or standard requirements. There are no consistent recommendations or protocols in anesthesia texts or the literature or by medical/anesthesia society consensus of what constitutes recommended laboratory and diagnostic studies in an asymptomatic healthy patient at any age. After 6 years of extensive discussion, The ASA Task Force on Preanesthesia Evaluation published recommendations in 2002 that testing and consultation be done on the basis of a reasonable expectation that the patient may have an abnormal value and that such a value will have an effect on the decision whether and how to provide care during perioperative

Table 34-7 Diagnosis-Based Preoperative Testing

Preoperative Diagnosis	ECG	CXR	Hct/Hb	CBC	Lytes	Renal	Glucose	Coag	LFTs	Drug Levels	Ca
Cardiac disease											
MI history	X				±						
Stable angina	X				±						
CHF	X	±									
HTN	X	±			X*	X					
Chronic atrial fibrillation	X									X†	
PVD	X										
Valvular heart disease	X	±									
Pulmonary disease											
Emphysema	X	±								X‡	
Asthma	(PFTs only if symptomatic; otherwise no tests required)										
Chronic bronchitis	X	±		X							
Diabetes	X				±	X	X				
Hepatic disease											
Infectious hepatitis								X	X		
Alcohol/drug induced								X	X		
Tumor infiltration								X	X		
Renal disease			X		X	X					
Hematologic disorders				X							
Coagulopathies				X				X			
CNS disorders											
Stroke	X			X	X		X			X	
Seizures	X			X	X		X			X	
Tumor	X			X							
Vascular/aneurysms	X		X								
Malignancy				X							
Hyperthyroidism	X		X		X						X
Hypothyroidism	X		X		X						
Cushing's disease				X	X		X				
Addison's disease				X	X		X				
Hyperparathyroidism	X		X		X						X
Hypoparathyroidism	X				X						X
Morbid obesity	X	±					X				
Malabsorption/poor nutrition	X			X	X	X	X				
Select drug therapies											
Digoxin (digitalis)	X				±					X	
Anticoagulants			X					X			
Dilantin										X	
Phenobarbital										X	
Diuretics					X	X					
Steroids				X			X				
Chemotherapy				X							
Aspirin/NSAID (no tests)											
Theophylline										X	

*Patients taking diuretics.
†Patients taking digoxin.
‡Patients taking theophylline.
X, obtain; ±, consider.
Ca, calcium; CBC, complete blood count; CHF, congestive heart failure; Coag, coagulation; CXR, chest x-ray; ECG, electrocardiogram; Hb, hemoglobin; Hct, hematocrit; HTN, hypertension; LFTs, liver function tests; Lytes, electrolytes; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PFTs, pulmonary function tests; PVD, peripheral vascular disease.

management.[3] Specific preoperative laboratory testing will be reviewed as follows, with an emphasis on diagnosis-based/clinical indications.

Complete Blood Count, Hemoglobin, and Hematocrit

The proposed surgical procedure and potential blood loss, together with individualized clinical indications, should determine the requirement for a blood count preoperatively. Primary clinical indications include a history of increased bleeding, hematologic disorders, renal disease, chemotherapy or radiation treatment, steroid or anticoagulant therapy, poor nutrition/malabsorption status, surgical procedures with anticipated high blood loss, and trauma.

Liver Function Testing

There is no routine preoperative anesthesia requirement for liver function testing. It should be based on a history of hepatic injury and physical examination findings. Primary clinical indications include a history of viral, alcohol, or drug-induced hepatitis, jaundice, cirrhosis, portal hypertension, biliary or gallbladder disease, hepatotoxic drug exposure, infiltration of tumor, certain immunologic disorders, and bleeding disorders.

Renal Function Testing

Tests of renal function measure the degree of renal tubular dysfunction and glomerular filtration. Primary clinical indications include patients with diabetes; hypertension; cardiac disease; dehydration; nausea and vomiting; anorexia; bulimia; increase fluid overload, such as in congestive heart failure, peripheral edema, or ascites; renal, hepatic, or cardiac impairment; hematuria; nocturia; polyuria; oliguria; anuria; and a history of renal transplantation.

Coagulation Testing

Clotting studies are not indicated as a routine preoperative evaluation, even in patients undergoing regional procedures, unless there is specific indication of a known or suspected coagulopathy. A careful history that includes drug therapies and physical examination will provide guidance if coagulation testing is indicated. Primary clinical indications include a history of a bleeding disorder or previous excessive intraoperative surgical bleeding, hepatic disease, poor nutritional status, and use of anticoagulants or other drugs that affect coagulation.

Urinalysis

There is no indication during preoperative anesthesia evaluation for routine urinalysis. Primary clinical indications could include a suspected urinary tract infection or unexplained fever or chills.

Pregnancy Test

Pregnancy testing is often determined by individual group practice protocols and can be based on the history and specific questions. Clinical indications can include the date of the last menstrual period, sexual activity, type or absence of birth control method, and patient or physician intuition.

The Electrocardiogram

The ECG is used to determine a previous history of MI, conduction/rhythm disturbances, ischemia, chamber hypertrophy, and metabolic/electrolyte disorders. Primary clinical indications preoperatively include a history of CAD or MI, hypertension, diabetes, congestive heart failure, chest pain, palpitations, abnormal valvular murmurs, peripheral edema, syncope, dizziness, dyspnea on exertion, shortness of breath, paroxysmal nocturnal dyspnea, and cerebrovascular disease. The ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation provide additional recommendations for preoperative resting ECGs (see Box 34-3).[7]

The Chest Radiograph

There is no routine indication to obtain a chest radiograph in preoperative evaluation. The chest radiograph should be used to assess concerned abnormalities that are present by history or physical examination. Primary clinical indications for a preoperative chest radiograph include auscultation of rales or rhonchi, advanced COPD and blebs, pulmonary edema, suspected pneumonia, pulmonary or mediastinal masses, tracheal deviation, aortic aneurysm, atelectasis, cardiomegaly, pulmonary hypertension, or dextrocardia.

Preoperative Pulmonary Function Assessment

PFTs are not considered routine for patients with a history of asthma, emphysema, or COPD. Patients with pulmonary diseases have often undergone pulmonary function testing through their primary care physician, obtainable as needed. Clinical examination and a careful history will indicate the patient's current respiratory status and the potential for anesthesia/surgical pulmonary compromise.

Preoperative PFTs can assess potential respiratory complications in patients undergoing surgical resection of the lung. PFTs determine the patient's pulmonary reserve and whether the patient may require postoperative chronic ventilation support. The specifics of preoperative pulmonary function testing in patients undergoing lung resection are reviewed in another section of this chapter.

The Preoperative Evaluation Clinic

Many anesthesia groups and major medical centers have developed preoperative evaluation programs and clinics with the goal

of enhancing operating room efficiency and the quality of patient care.[166,167] There are many variations in the staffing, structure, financial support, and daily operations of preoperative programs; however, all have a common goal of avoiding cancellations, delays, and adverse patient outcomes that could have been addressed before the day of surgery.

The development and implementation of a preoperative evaluation clinic depend on the daily volume of patients, the predominant medical patient acuity, the availability of facilities, the demographics of distance of the patient from the hospital, and a perioperative staff, hospital administrative, and anesthesia departmental commitment that supports changes.

It is essential that the anesthesiologist develop the leadership and management position in the preoperative evaluation program. When internal medicine departments and other medical specialties develop preoperative programs within hospitals, the anesthesiologist's role and expertise in perioperative patient management often become secondary. This can result in significant interdepartmental conflict and disagreement concerning a patient's evaluation, risk stratification, and optimal stability to proceed with anesthesia.

When patients are "cleared for surgery" by other specialties, this is often considered by the surgeon as evidence that the patient is appropriate and suitable for anesthesia. Unfortunately, this clearance is frequently provided with limited knowledge of current anesthesia practice and intraoperative patient management. The preoperative history, physical examination, and assessment by a medical specialist may not address specific anesthesia concerns of risk assessment[168,169] and patient optimization, thus providing the framework for potential surgical delays and cancellations. Additionally, patients may have had medications preoperatively withdrawn, changed, or added to their treatment in preparation for surgery, which further complicates intraoperative anesthesia management.

When cases are delayed or canceled by the assigned anesthesiologist on the day of surgery, it often creates significant frustration in the surgeon and patient. The anesthesiologist is the only specialist who can make the final determination of whether the patient is appropriate for anesthesia and whether the patient is stable to proceed. It is advantageous to accentuate this fact to hospital administrators and those who plan the development of a preoperative clinical program but remain uncertain regarding which speciality to support. Clinical studies have demonstrated that the anesthesiologist's leadership and direct clinical responsibility in a preoperative program will reduce hospital costs by decreasing operating room delays, cancellations,[164,170] and potential adverse intraoperative patient events.

Good outcomes depend strongly on awareness and planning. Anesthesia groups with a predominantly healthy outpatient and to-be-admitted population and hospital facilities with limited resources and staffing may be unable to evaluate all patients preoperatively before the day of surgery. This requires a means of screening patients and triaging them from the preoperative program in a manner that ensures a high level of accuracy in determining the patient's current health status. Accurate triaging results in time savings and avoidance of costly cancellation and delays on the day of surgery without compromising patient quality of care and outcomes.

One process of triaging involves having an anesthesia questionnaire (see Fig. 34-1) available in the surgeon's office, which could be filled out by the patient during the initial assessment by the surgeon. The questionare would be faxed to the group's anesthesia location before the surgical date. Reviewing the patient's medical history before the day of surgery, even by paper, reduces unresolved or unexpected medical concerns. A decision could then be made of whether the patient requires a formal preoperative consultation or could be evaluated on the day of surgery. A phone call by an anesthesiologist to a patient with a questionable medical history could clarify issues of concern. Another method of triaging patients to reduce the impact of unnecessary clinic evaluations would be to provide patients at the initial surgical visit with an anesthesia department Internet address where patients could fill out their medical questionnaire online for review.

Anesthesia groups with a larger number of medically complex presurgical patients may benefit from a more formal preoperative facility with multiple examination rooms, dedicated staffing, and a full-time operational system. The following sections describe the development and implementation of an anesthesia preoperative evaluation clinic with a focus on the necessary protocols, policies, and requirements for recognition, accomplishment, and success. Not every aspect of what is described becomes necessary. Various modifications and adaptations for individual practices, facility expansion, and financial support are expected.

Establishment of a successful anesthesia preoperative evaluation clinic requires interdepartmental commitment, collaboration, and financial support of several hospital disciplines.[164,171] The departments of anesthesia, surgery, nursing, and hospital administration must agree that a centralized preoperative clinic has value for the hospital, and each discipline must firmly support the necessary changes and operational goals of a preoperative evaluation clinic (Box 34-10).

Collaboration, Commitment, and Teamwork

The preoperative evaluation clinic is a visible partnership and collaboration between the departments of anesthesia, surgery, nursing, and hospital administration in achieving common goals as illustrated in Figure 34-5. It conveys the important concept that the development of this new clinical program is an integrated enterprise and requires obligation, sharing of endeavor, and financial responsibility.

Initially, surgeons may be reluctant to send patients to a newly developed anesthesia preoperative evaluation clinic. This hesitation stems from an unclear understanding of the supportive process, significance, and enhanced outcomes of a medical evaluation by an anesthesiologist. A surgeon's hesitation to send patients to the preoperative evaluation clinic can be reduced by identifying the clinical advantages of the preoperative program.

For example, informal assurances should be given to the surgical services that if a patient is evaluated in the preoperative program, the case will proceed to surgery without cancellation or delay by the assigned anesthesiologist, the only exception being illness or an adverse medical event between the time of evaluation and the time of the planned surgery. Cancellations and delays on the day of surgery can be a prominent source of aggravation and even antagonism for surgeons and patients and results in loss of revenue. Additionally, patients are often billed for hospital services although their actual surgical procedure was not performed.

Box 34-10 Operational Goals for a Preoperative Evaluation Clinic

Improve the client's perception of the preoperative evaluation experience by increasing personalized patient care, comfort, and convenience.

Provide a centralized site for preoperative evaluation.

Institute an anesthesia scheduling system for timely patient access and flow.

Ensure the presence of an anesthesiologist on site when patients are present.

Appoint a medical director to coordinate all activities.

Ensure the availability of medical records and surgical notes at the time of preoperative evaluation.

Decrease logistic shuffling of patients to multiple hospital service areas.

Integrate and coordinate services through on-site facilities for admission/registration, insurance authorization, laboratory tests, and electrocardiographic studies.

Improve the education of patients and families about the elements of their surgical procedure and the proposed anesthesia care, including postoperative pain control options.

Educate patients about what to expect regarding postoperative feeding and discharge needs.

Ensure and coordinate cost-effective ordering of preoperative laboratory and diagnostic studies.

Provide an anesthesia medical consultation service for evaluation of medically complex inpatients and outpatients.

Decrease the number of cancellations and delays in operative procedures on the day of surgery.

Enlist the skills of a nurse practitioner to assist in preoperative evaluation and patient/family education.

Develop protocols, policies, and clinical pathways.

Perform quality assurance reviews.

Maximize efficiency in operating room function and turnover time by coordinating all preoperative information at one location in the anesthesia preoperative evaluation clinic.

Enhance patient and surgeon satisfaction.

It is of paramount importance that anesthesia departmental practitioners discuss and agree on individual practice variations. Differences, such as at what fasting blood glucose level a surgical case would be canceled or what degree of preoperative hypertension is acceptable, require departmental clarification and agreement. If half the anesthesiologists would perform a particular surgical case with increased patient risk and the other half would cancel the case, the inconsistency demonstrated to the surgeon would foster a lack of support and reluctance to have patients evaluated, and essentially the clinic would be unsuccessful.

The anesthesia preoperative evaluation clinic can become a valued perioperative and hospital asset by providing consistent quality patient management and cost-effective outcomes that decrease surgical delays and cancellations. If a special medical concern related to anesthesia is identified before surgery, the preoperative program coordinates collecting the medical data, managing any additional workup or consultations, and discussing the case with the surgeon and the assigned anesthesiologist before the date.

Financial Concerns in Developing a Preoperative Clinic

Health care reforms have resulted in closer evaluation of the cost-benefit ratio and operational efficiency of many hospital programs.[172,173] Economic changes have decreased reimbursement and reduced the patient's length of stay in the hospital. At the same time there has been rapid advancement in outpatient services, especially in ambulatory surgery. The percentage of surgical patients entering the hospital as outpatients or admitted on the same day as surgery continues to increase and challenge perioperative personnel, especially the anesthesiologist.

Physicians are the primary decision-makers concerning the utilization of health care services. In preparing a patient for surgery, physicians are directly responsible for ordering virtually all of the patient's evaluations, including preoperative diagnostic testing and referral to specialists. Although health care continues to be in an active state of reform, it is frequently difficult for an individual physician or group to change the manner or routine of clinical practice patterns. There is increasing demand from hospitals and insurance carriers that providers demonstrate veri-

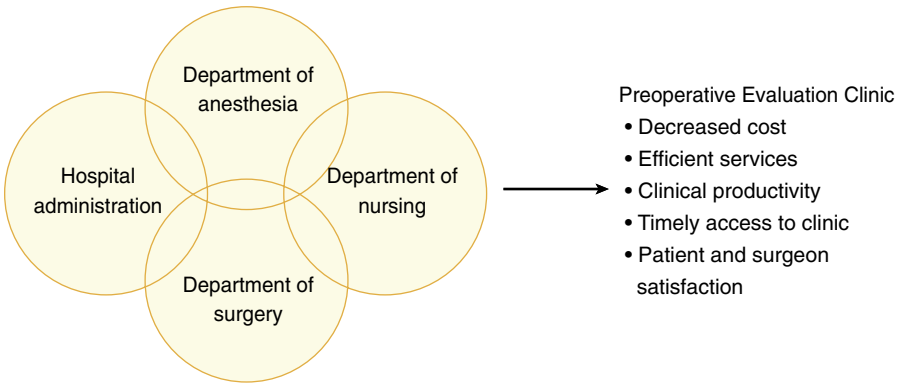


Figure 34-5 The anesthesia preoperative evaluation clinic is a constructive partnership toward common goals. Sharing of resources and budgetary costs is apportioned.

fiable evidence of decreasing costs while maintaining productivity and a high level of quality patient care.

Hospital support and financial contribution for a preoperative evaluation clinic will focus on price, quality, and value. Economic analysis of a proposed preoperative evaluation clinic is imperative to align administrative, operational, and financial support. It requires a documented comparison between the current preoperative resource utilization, costs, and outcomes (operating room delays, cancellations) with the projected preoperative evaluation clinic and anticipated operational improvements (decreased operating room delays, cancellations, enhanced operating room efficiency, etc.)

This document must be comprehensive and focused on opportunities for improvement. It is presented for hospital financial analysis in a business plan (Box 34-11) linked with academic publications demonstrating cost-effectiveness and outcomes in the preoperative clinic model. A preoperative clinic that offers no improvement and an increase in cost is unsuitable and economically detrimental to the hospital. Financial support for the anesthesia medical director is derived from both the department of anesthesia and hospital administration because the preoperative evaluation clinic is a hospital improvement–based program and can reduce hospital costs.

Facility Restructuring and Modernization

Focusing all preoperative clinical services into one hospital location establishes a center of visibility, competitiveness, and efficiency. The preoperative clinic should be regarded as a long-term investment for the hospital, physicians, and patients.

Facilities that have been developed at Stanford University Hospital are listed in Box 34-12 and are provided as an example of an extensive facility already in need of expansion because of increasing patient volume. However, not all hospital centers have the facilities or funding to construct a formal preoperative evaluation clinic. A compromise of sharing the preoperative clinic space with another medical specialty clinic could be beneficial in terms of staffing and reducing costs. The simplest of preoperative evaluation areas might be a private space in the presurgical holding area or the postanesthesia care unit as patient census decreases later in the day. Cross-trained staff from available resources such as the operating room or recovery room can assist in the preoperative evaluation program during downtime/low patient volume to process preliminary paperwork, obtain medical and outside records, record vital signs, collect laboratory specimens, and perform ECGs, for example.

The predominant costs of operating a preoperative evaluation clinic are essentially the number of staff per diem. Facility renovation can be costly or nominal. Material and supplies are usually minimal. A preoperative facility with a comfortable, low-stress patient waiting area is a positive investment in patient relationships. Patients often express their primary complaint with hospital services as waiting for excessive periods. A thoughtfully designed clinic facility enhances the patient's anesthesia experience.

Hospital administrators, surgeons, and other physicians will monitor performance of the preoperative evaluation clinic in terms of outcome measurements, personal observations, and value analysis. Achievement and success are often linked to renewed or additional financial support.

Quality assurance measurements and clinical benchmark indicators for the preoperative clinic should be entered into a database, which can then be used to determine performance standards and areas in need of improvement.[174,175] This information could measure, for example, operating room cancellation and delays, the specific causes, cost, and resource time loss. It provides the basis for operational changes and improvements in hospital service. Figure 34-6 is an example of a quality and service indicator form for a preoperative evaluation clinic.

Preoperative Standardization and Accuracy of Documentation

Standardization of the preoperative process is essential for both clinical and administrative reasons. Important reasons to encourage standardization in process and documentation are listed in Box 34-13.

Standardization maximizes reimbursement by ensuring accurate coding for the diagnosis-related group (DRG) and for preoperative testing. In many institutions, nonclinical personnel are used to review the preoperative history and physical assessment, from which comorbid conditions are coded to define the appropriate reimbursement level based on the surgical diagnosis and procedure. In some cases, a variety of clinicians in outside offices may be submitting preoperative history and physical assessments in nonstandard ways, thus making coding difficult. These assessments may focus on the surgical diagnosis and may not appropriately list all existing comorbid conditions. If an institution does not have a standardized process for preoperative recording of the history and physical examination, appropriate reimbursement for these issues may not be attained. This can be a major source of institutional revenue loss. In addition, a standardized process allows the clinician to accurately code for preoperative laboratory testing by diagnoses that can be reimbursed, as opposed to screening laboratory tests, which are no longer reimbursed by the CMS.

Standardization maximizes reimbursement by standardizing coding and data collection regarding pay-for-performance measures. Numerous strategies, including pay-for-performance measures, are being instituted across the country in an attempt to improve quality. Standardizing preoperative processes will allow the development and implementation of protocols so that the measures are met and appropriately documented. This is particularly important if implementation of these protocols is required before the day of the procedure. Presently, this could include implementing some of the national Surgical Care Improvement Project measures (e.g., appropriate perioperative β-blocker therapy).

Standardization allows the implementation of clinical algorithms based on best practice, which will optimize preoperative medical management and potentially reduce complications and ensure the best possible outcomes. Preoperative risk factors have been shown to be effective predictors of hospital cost.[176] Therefore, preoperative intervention to reduce risk could lead to significant cost savings. For example, despite the existing evidence, a significant number of patients who would be candidates for perioperative β-blockade are not receiving it at the time of the preoperative visit. There is inconsistent application of these guidelines by surgeons and referring physicians, thus again leading to

Box 34-11 Outline of a Business Plan for an Anesthesia Preoperative Evaluation Clinic (APEC)

The business plan provides or describes the following items:

I. An Executive Summary
One-paragraph summary of the proposed APEC program

II. Description of the APEC
Objective or mission of the APEC

Names of the proposed APEC medical director, department chair

Location within the hospital designated for the APEC (define an area, even if currently occupied)

Development stage (is there an existing preoperative program?)

Services of the APEC (see operational goals, Box 34-10)

Anesthesiology specialty information (i.e., anesthesiologists are the experts in operating room medicine and preoperative evaluation)

III. Analysis of General Factors Affecting Viability of the APEC
Volume and medical condition of preoperative patients (present a graph for past years)

Anticipated growth trends

Vulnerability to economic factors (e.g., fee-for-service payment is decreasing, managed care is increasing, hospitals need to decrease cost)

Technologic factors (e.g., anesthesia and surgical procedures are increasingly becoming more complex)

Regulatory issues (the APEC conforms to all local, state, and federal policies)

Financial considerations

IV. Definition of Target Markets
All outpatient and same-day admissions (i.e., increased smooth flow of a healthy patient through the health care system and educational processes, often starting in the surgical office)

Medically complex patient undergoing anesthesia and surgery

V. Discussion of Factors Relating to Competition
Competitive position of the APEC (the anesthesiologist is the operating room and preoperative medicine expert)

Barriers to entry (primary care physicians/consultants believe that they have sufficient specialty knowledge to clear patients for anesthesia and surgery)

Future competition

VI. Description of Effective Marketing Strategies
Increased visibility, which increases viability of the APEC

Use of hospital/health system news media to explain who anesthesiologists are and what they do

Formation of strategic partnerships with the departments of nursing and surgery and with the hospital/health system administration

Informal assurance that cases will be facilitated by anesthesia if seen in the APEC

Presentations at surgical, medical, gynecologic, pediatric, and administrative grand rounds (as well as others) and conferences

VII. Description of Operational Aspects of the APEC
Facilities (e.g., examination rooms, phlebotomy/electrocardiography room)

Equipment and supplies

Variable labor requirements (e.g., nurse practitioner, anesthesiologist)

Daily anticipated operations and flow

Quality assurance and utilization review

Management information systems

VIII. Description of Management and Organization of the APEC
Clinical and administrative director

Inclusion of the department of nursing and hospital administration

Organization management (presented in a flow chart)

IX. Description of the Developmental Goals of the APEC
Short-term goals (changes in clinical practice)

Long-term goals (e.g., renovation of facilities)

A time line (demonstrates a developmental plan)

The growth strategy (projection of 6-month, 1-year, and 5-year goals)

Evaluation of risk

X. Discussion of Financial Matters
Income statement (consider a facility fee, anesthesia medical consultation charge, projected hospital/health system cost savings, and market share enrichment)

Variable expenditures (e.g., APEC personnel and resources, facility housekeeping and supplies)

Balance sheet

Box 34-12 Facilities of the Anesthesia Preoperative Evaluation Clinic at Stanford University Hospital

- Five combination office and examination rooms
- A patient and family education room (preoperative teaching)
- A patient-centered media and video room
- A phlebotomy and electrocardiography room
- An on-site office for the medical director
- A registration and reception area
- On-site restroom facilities
- A large, comfortable patient lounge
- An area for admitting and financial services
- Approximately 2200 square feet for facilities
- Conference room and shared chart and computer support room

the question of accountability for the preoperative process. An anesthesia preoperative clinic can develop and standardize clinical presurgical evaluation policies and guidelines to coordinate the process of implementing appropriate protocols before the day of surgery. This could result in decreased cost for prolonged hospitalizations caused, for example, by perioperative cardiac complications. Providing algorithms for clinical practice in areas where outcome-based data are unavailable may result in the use of arbitrary parameters based on consensus opinion. An algorithm provided to clinical staff performing preoperative assessment is provided in Box 34-14.

A second example in which implementation of a preoperative protocol may reduce postoperative complications is protocols that address reduction of SSIs. A standardized preoperative process provides a means for instruction in this regard; for example, at the time of the preoperative visit, patients can be given antiseptic agents to shower with before surgery.

Standardized processes allow more accurate data collection for quality reporting. Hospitals may be contributing data on their operational results to organizations such as TJC, the National Surgical Quality Improvement Program, or the Institution for Health Care Improvement. In addition, state law may mandate reporting requirements. For example, in the state of Massachusetts, information on the preoperative, operative, and postoperative factors and outcomes of cardiac surgical patients must be collected in a standardized fashion and reported to the state.

Standardized processes help minimize complications caused by communication errors. Recent work shows that serious communication breakdowns occur throughout the continuum of surgical care.[177] In a review of surgical malpractice claims, 81 communication breakdowns occurred in a total of 444 cases. Of these breakdowns, 38% involved problems with communication of preoperative information. Ambiguity about responsibility was a commonly associated factor. Standardization of documentation would improve transfer of care from preoperative clinicians to the operative team. Responsibility for dealing with abnormalities identified during the preoperative assessment could be clearly delineated.

Information Management and Centralization

For a patient's surgery to proceed without delay, all required paperwork and information must be present. At many hospitals, the surgeon's history and physical examination, operation consent form, laboratory test results, nursing operating room admission form, and anesthesia preoperative notes must be present in the patient's chart before entering the operating room.

The preoperative evaluation clinic can coordinate, process, and centralize all patient presurgical information in the medical chart. A simple checklist of required content can reduce delays and increase operating room efficiency by correcting problems before the day of surgery.

Because patients from out of the local area may be staying in hotels or with family or friends, it is important that a "day before surgery" local/cellular phone number be recorded in the presurgical chart so that the patient can be contacted before surgery. The preoperative staff telephones patients on the evening before surgery to ensure compliance with arrival time, to reinforce instructions, and to answer any questions. This contact by telephone avoids day-of-surgery delays and potential cancellations.

Accuracy of preoperative records is imperative, with multiple health care professionals, regulatory agencies, and occasionally the legal profession reading and reviewing medical entries. Preoperative issues that result in misinterpretation of intended documentation or physician orders can be a factor in adverse patient outcome and potential legal responsibility. Box 34-15 reviews preoperative evaluation documentation fundamentals and concerns.

Box 34-13 Importance of Preoperative Process Standardization

- Standardization maximizes reimbursement by diagnosis-related group and for preoperative testing by standardization and accuracy of documentation in the preoperative assessment.
- Standardization maximizes reimbursement by standardizing coding and data collection regarding pay-for-performance measures.
- Standardization allows the implementation of clinical algorithms based on best practice, which will optimize preoperative medical management and potentially reduce complications and ensure the best possible outcomes.
- Standardized care protocols and optimization of clinical care with a potential impact on reduction of complications can reduce the cost of admission and length of stay.
- Standardized processes allow more accurate data collection for quality reporting.
- Standardized processes help minimize complications caused by communication errors.

(Addressograph)

Preop Program
Quality & Service Indicator Form

Today's date: _____

Date of surgery: _____

• Anesthesia evaluator: _____ Referring clinic: _____

• Scheduled appointment: ☐ Yes ☐ No

• Arrived ± 30 minutes of appt. time: ☐ Yes ☐ No

• Patient triaged out: ☐ Yes ☐ No

• Patient chart available: ☐ Yes ☐ No ☐ Ordered

• Time first seen in preop clinic: _____ (military time)

• Time in preop program < 90 minutes: ☐ Yes ☐ No

Evaluator
(Military Time)

Time in: _____

Time out: _____

Pt. Level: _____

Teach: Yes ( ) No ( )

TOTAL

Visit time in: _____

Visit time out: _____

If No, cause of delay in preop program:

☐ No chart

☐ Outside records/tests did not arrive with patient
Time to find old/recent: ☐ ECG ☐ Chest X-ray ☐ MUGA ☐ PFTs ☐ ECHO ☐ Stress test ☐ Lab work

☐ Complex history, No H&P, start from the beginning for history

☐ Lab order problems/changes ☐ Call resident

☐ Wait to clear patient's ECG

☐ Consult with medical director

☐ Medical director not available, find appropriate person

☐ Contact outside source for additional information

☐ Patient arrived after 5:00 P.M.

☐ Patient had surgery recently, chart not available, start all over with information

☐ Clinical complication that could postpone or cancel surgery

☐ Language barrier w/interpreter ☐ Language barrier w/NO interpreter

☐ Physical disabilities

☐ Teaching

☐ Nursing assessment forms

☐ Solved problems unrelated to anesthesia; explain: _____

☐ Cardiac surgical team not available

Comments: _____

Figure 34-6 Preoperative program quality and service indicator form. ECG, electrocardiogram; ECHO, echocardiography.

Structure and Activities of the Preoperative Evaluation Clinic

The daily operations of an anesthesia preoperative clinic will vary according to patient volume, acuity of the patient's medical conditions, availability of facilities, and employee resources. However, a generalized operational structure can be suggested by examining several preoperative clinic models currently in practice.

Centers with a large volume of patients should have their patients formally scheduled in the clinic before the day of evaluation so that medical records and appropriate outside information would be available. The surgeon's office should schedule the anesthesia clinic appointment at the same time that the operating room case is booked. Flexibility in scheduling appointments is needed in the clinic to accommodate patients with urgent surgical requirements and those residing outside the local hospital area.

The anesthesia evaluator interviews and examines the patient, obtains historical medical information and outside records (via facsimile and phone as needed), and determines the appropriate diagnostic, laboratory, ECG, and other evaluation requirements. Phlebotomy, ECG, and hospital admitting/insurance registration are available in the preoperative clinic. Such centralization of multiservices provides a significant convenience to patients, who no longer must search for multiple hospital locations to complete preoperative requirements. It also centralizes all

Box 34-14 Algorithm for Preoperative Clinical Assessment

A. Assess Surgical Risk:

High risk (>5%)
- Aortic surgery
- Major vascular surgery
- Peripheral vascular surgery
- Prolonged procedures with fluid shifts*

Moderate risk (1% to 5%)
- Head and neck surgery
- Intraperitoneal and intrathoracic surgery
- Carotid endarterectomy
- Orthopedic surgery
- Prostate surgery

Low risk (1%)
- Superficial procedures
- Cataract surgery
- Breast surgery

B. Assess Functional Status

Low functional status: METs less than 4, unable to climb two flights of stairs, or inability to assess functional status

Acceptable functional status: METs greater than 4 or able to climb two flights of stairs without symptoms

C. Assess Stability

1. Does the patient have shortness of breath that is not due to pulmonary disease?
2. Does the patient have a history of syncope that has not been investigated?
3. Does the patient have a change in the pattern of chest pain or a history of chest pain that has not been investigated?
4. Does the patient have an increase in leg swelling, rales on lung examination, or new leg swelling that has not been investigated?
5. Does the patient have a history of paroxysmal nocturnal dyspnea or orthopnea that has not been investigated or has worsened?

D. Decision for Referral Based on A, B, C:

With a "yes" answer to any of the questions in C, consider referral to the PCP or cardiology regardless of functional status or surgical risk

If the answer to questions 1 to 5 is "no" and functional status is low, consider referral to cardiology only if the surgery is very high risk

If the answer to questions 1 to 5 is "no" and functional status is adequate, the patient does not warrant referral based on stability

Consider Cardiology Evaluation:
- Pacemaker not checked within 6 months
- Automatic implanted cardioverter-defibrillator not checked within 3 months
- History of positive exercise tolerance test without follow-up (Bruce <6 minutes, >4 segments with perfusion abnormalities)
- New left bundle branch block
- Atrial fibrillation (new or old) with a ventricular rate greater than 120 beats/min
- New T-wave inversions or new ST elevations or depressions greater than 2 mm
- New atrial fibrillation
- Second-degree atrioventricular block with a wide QRS complex (not investigated)
- New pathologic Q waves consistent with myocardial infarction
- Prolonged QT (>520 msec)

Consider Primary Care Evaluation
- New anemia (hematocrit less than 30% with unknown cause)
- Diastolic blood pressure greater than 110 mm Hg
- Glycohemoglobin greater than 8.5
- Wheezing on physical examination
- Potassium less than 3.2
- Platelet count less than 100,000, cause unknown or not investigated
- New hyperthyroidism
- Abnormal urinalysis suggestive of urinary tract infection
- Unexplained coagulation abnormalities
- New murmur

*Mastectomy with reconstruction, major bowel resection with colectomy, major lung resection procedures, hip revision, major back surgery, pelvic debulking.
METs, metabolic equivalents of the task; PCP, primary care provider.

hospital data into one chart, which remains in the preoperative evaluation clinic area until the time of surgery.

The patient's ECG is assessed during the clinic visit, and laboratory test results are evaluated at the end of each clinic day, with follow-up of abnormal findings as needed. In this manner, significant abnormalities can be addressed immediately, and if needed, cancellation of a surgical case would occur before the day of surgery.

One of the fundamental goals of the preoperative evaluation clinic is patient perioperative education to increase awareness and comfort by decreasing anxiety and fear. A nurse educator specifically trained in perioperative teaching discusses in detail the forthcoming surgical/hospital process with each patient and family member.

Enhanced Operating Room Efficiency and Outcomes

Appropriate utilization of perioperative services yields net benefits to the hospital and achieves a cost-benefit framework. Unnecessary surgical delays result in increased cost to the hospital and reduce operating room efficiency. The preoperative evaluation

Box 34-15 Preoperative Documentation and Concerns

Legibility of records. Poor handwriting results in misinterpretation or failure to implement important orders preoperatively.

Entries that are not signed or the signature is illegible. Print your last name and beeper/contact number.

All preoperative evaluation entries must be dated and timed in the document.

Do not black-out, obliterate, or white-out an error. Place one line through the entry, initial, and write "error."

Document all phone calls, time, and date to consulting physicians with their name and specifically what was discussed.

Note HIPAA* guidelines regarding unapproved abbreviations, which can result in patient medication and treatment errors.

If the patient has an abnormal diagnostic test result, document it and indicate what follow-up is planned. If you order a laboratory test, chest radiograph, electrocardiogram, or any test, you are responsible for knowing the results, follow-up, or referral if needed. Document it in the chart.

*Health Insurance Portability and Accountability Act.

program focuses on patient management and preparation for a smooth transition to surgery.

In one study on start times of the first case of the day, 91% of patients evaluated in the preoperative evaluation clinic entered the operating room by 6:50 AM for 7:30 AM start times. Delays were considered the exception rather than the customary occurrence. The operating room day ends earlier with decreased cost and overtime staffing when delays and problems are minimized. The preoperative evaluation clinic can establish a standard of efficient clinical services, including a contribution to on-time starts, decreased delays, and increased patient and surgeon satisfaction.

Although there are defined costs in developing and maintaining a preoperative evaluation clinic, a comparison with previous outcomes clearly demonstrates the clinic's utility, performance, and an improvement in operating room efficiency in terms of energy, time, and money.

Patient Education and Patient Satisfaction

The benefits of an effective preoperative evaluation process on efficiency have been well documented; however, there is limited information on the benefit of these clinics to the patient's experience. The use of patient satisfaction has been advocated as a unique clinical end point and as an indicator of the quality of the health care provided. Fung and Cohen believed that this outcome could be more insightful than the use of rare major outcomes such as death or common minor outcomes such as pain and nausea, which can be influenced by many other factors. Patient education and patient satisfaction with the preoperative process are closely linked. In work using an internally generated patient satisfaction questionnaire to assess satisfaction with all elements of the preoperative evaluation, the subscale that involved information and communication had the highest correlation with the overall satisfaction subscale.[178] Providing good patient education may facilitate patients' involvement in their care, give them a sense of control over the process, and contribute to increased patient satisfaction. Consumerism and transparency in quality measures, with patient satisfaction being one of these quality measures, are becoming ever more important issues in health care. Measuring patient satisfaction with the various elements of the preoperative process is essential to evaluate success and plan process improvement. Although health care leaders realize the importance of feedback systems, they often do not use the information they receive to pinpoint opportunities for change and correction.[166,179] Gail Scott provides tools and techniques that would allow feedback on the preoperative process to drive improvement.[179] These techniques are summarized in Box 34-16.

Most currently available surveys used by hospitals, such as the commonly used Press Ganey survey, reflect the overall perioperative experience. These standard questions are not effective at discerning patient satisfaction with particular elements of the preoperative process. For this reason, studies have developed internal questionnaires to measure this. Studies using this questionnaire (Box 34-17) show successful evaluation of preoperative process improvement. As noted, in this study the subscale that involved information and communication had the highest correlation with the overall satisfaction subscale. The authors conclude that the clinical and functional aspects of the preoperative evaluation visit have a significant impact on patient satisfaction, with information and communication versus the total amount of time

Box 34-16 Using Feedback to Drive Preoperative Process Improvement

Raise awareness; make sure that everyone in the organization understands the focus of process improvement.

Create measurable targets and goals (e.g., decreasing wait time).

Set service expectations and standards of behavior.

Allow direct service providers (frontline staff) access to hear feedback and input into problem solving.

Develop skills. Teach staff members customer service skills such as interviewing, dealing with difficult people, and conflict management.

Identify and remove barriers. Policies that do not make sense need to be eliminated.

Develop and support teams and relationships.

Listen to your customers: surveys, interviews, comments, shadowing.

Do not forget internal customers; obtain feedback from other teams and departments in the organization.

Share feedback in ways that teach. Eliminate an environment of blame.

Box 34-17 Sample Preoperative Satisfaction Questionnaire

Your feedback is important to us in assessing our services and helping us make changes. Please rate the quality of the services you received during your visit to the Pre-Admitting Test Center. To indicate your answer, just fill in the circle. *Please do not "check" or "X" circles.*

What Type of Surgery Are You Having?

○ Orthopedic	○ Neurosurgery	**Use these ratings:**
○ Thoracic	○ Ear, nose, throat/ophthalmology	*Poor*
○ Cardiac	○ Gynecology	*Fair*
○ General surgery	○ Urology	*Good*
○ Plastic	○ Other/Don't know	*Very Good*
		Excellent

Please rate the following about your visit to the Weiner Center for Preoperative Evaluation (CPE):

1. Explanation of the CPE process by your surgeon's office _____.
2. Ease of locating the CPE in the hospital _____.
3. How clearly the CPE receptionist explained what would happen during your visit _____.
4. Courtesy and efficiency of the CPE receptionist _____.
5. Length of time you spent waiting to be seen _____.
6. If you called the CPE, how promptly and efficiently were your questions answered _____.

Visit with the Anesthesia Care Provider

1. Courtesy and respect you were given by your anesthesia provider _____.
2. Explanation of your options and plan for anesthesia _____.
3. Amount of time spent with the anesthesia provider _____.

Visit with a Nurse or Nurse Practitioner

1. Courtesy and respect you were given by your nurse/nurse practitioner_____.
2. Explanation of your planned operation _____.
3. Amount of time spent with the nurse/nurse practitioner _____.
4. Explanation of how you should prepare for your surgery _____.

Visit with Laboratory/X-Ray Technicians

1. Courtesy and respect you were given by the lab and x-ray technicians _____.
2. Skill of the lab and x-ray technicians _____.

Other

1. Overall, how would you rate the care and service you received in the CPE? _____.
2. To what degree were your questions answered clearly and completely? _____.
3. After your CPE visit, how prepared do you feel for your surgery? _____.
4. If you submitted information to the CPE over the Internet, such as medical history, how would you rate the service? _____.

spent being the most positive and negative components, respectively. Of note is that after the preoperative visit, the vast majority of patients felt appropriately prepared for their upcoming procedure regarding education and communication of information (Box 34-17).

It is the role of the preoperative staff to educate the patient about issues regarding anesthesia, surgery, and the perioperative experience and to address specific patient anxieties about the procedure. A variety of ways to provide this have been evaluated, including direct communication, written information, videos, and websites. When comparing a face-to-face interview with an interview plus a brochure or a video, patients in the group receiving an interview plus a video had the highest scores in patient satisfaction and information gain.[167] An Internet tool may be a viable way for patients to receive information about their particular upcoming procedure, as well as to express concerns and formulate questions without the pressure of a rushed preoperative visit. Past studies have shown that patients may in fact be more likely to provide more information and reveal more problems, especially social and psychiatric issues, at a computer interface instead of to a health care provider.[180] By being aware of patient concerns, the visit can be tailored to better meet the needs of the patient. Time that would otherwise be spent trying to extract information from the patient can be used instead to answer patient questions more comprehensively, build rapport, and decrease stress.

How best can education be provided and patient concerns addressed? To answer this requires some understanding of what concerns patients have regarding their anesthetic and surgical experience. A number of studies have been reviewed to understand this information. Failure to wake up from an anesthetic has

consistently been shown to be a major concern. Younger patients and women tend to express more anxiety regarding their anesthesia. Some practitioners believe that informing patients of all possible risks in detail will serve only to increase anxiety. Several studies have shown that more information does not necessarily decrease anxiety. It may be more important to identify subgroups of patients and focus the information toward the patient's coping style. A British study showed that although there was no correlation between the level of information provided preoperatively and patient anxiety, there was a strong correlation between patients' satisfaction with the amount of information provided and decreased anxiety. Identifying patient subgroups that may benefit from specific educational methodologies and providing this education to these subgroups in a cost-effective manner remain a challenge. In addition, optimal skills in the practitioner providing the patient education must be ensured. Diverse levels of educator experience can result in inconsistent patient information. Skill levels and core competencies in providing patient education must be established.

Preoperative patient education has been demonstrated to be a factor in reducing postoperative pain. Egbert found reduced narcotic requirements and reduced length of stay in patients who had intensive preoperative instruction about pain. Reduction in length of stay and postoperative medication was also shown in patients undergoing spinal surgery for back pain who received teaching sessions before surgery. In patients undergoing CABG, the group receiving information plus coping preparations had a lower incidence of postoperative hypertension, although this study did not show a decrease in length of stay or postoperative narcotic requirements.

In addition, patients who are taught to use a pain scale during the preoperative visit can more effectively self-report pain postoperatively.[181] Preoperative education can also provide an opportunity for intervention to improve patient lifestyle, such as an introduction to smoking cessation programs.

Optimal preoperative patient education can influence a number of factors that affect overall operating room efficiency. For example, appropriate preoperative fasting and medication orders can be given, thereby preventing delays and cancellations. An adequate discussion of informed consent during the clinic visit prevents delays in the preoperative holding area to address these issues. The preoperative visit can ensure that the patient receives adequate bowel preparation and stoma care instructions, and patients undergoing day surgery can be educated regarding the requirement for transportation home.

Preoperative Fasting Status

Preoperative fasting recommendations have been made to reduce the occurrence of pulmonary aspiration. The ASA has published practice guidelines for preoperative fasting based on the evidence available.[5] The task force supports a fasting period of 2 hours for clear liquids in all patients. The volume of liquid ingested is less important than the type of liquid ingested. A fasting period of 4 hours for neonates and infants receiving breast milk and 6 hours for those receiving formula and solids is recommended. For noninfants, a fasting period of 6 hours after a light meal and 8 hours after a meal that includes fried or fatty foods is recommended. These guidelines recommend that the preoperative evaluation include assessment of factors that may increase the risk for aspiration, including gastrointestinal motility disorders, the potential for difficult airway management, and diabetes mellitus. Separate fasting guidelines are not provided for patients with these and other conditions that may increase the risk of regurgitation and pulmonary aspiration. There is great diversity among institutions in the current practice patterns for preoperative fasting, with many being more conservative than the ASA guidelines would suggest.[182]

There is agreement among most institutions in this study that ingestion of clear fluids up to 2 to 3 hours before anesthesia is acceptable. There is diversity regarding solids, with many institutions still restricting intake of solids after midnight.

Role of the Medical Consultant in Preoperative Evaluation

The use of medical consultation for preoperative patients will vary by institution, depending on the level of expertise in perioperative medicine of the clinicians performing preoperative assessments. The comfort level of the preoperative staff in interpreting ECGs and in ordering and interpreting stress testing and echocardiograms will have a major influence on the amount of consultation requested, as demonstrated by Tsen and colleagues. Park has summarized the recommendations for preoperative cardiology consultation in a 2003 review.[183] This analysis suggests that anesthesiologists need consultation for a significant number of patients with cardiac disease who are undergoing noncardiac surgery.[184] However, as Kleinman states in the accompanying editorial, the level of expertise of the cardiology consultant over and beyond that of the requesting anesthesiologist is related to the immediate management of acute coronary syndromes.

As a perioperative physician, the anesthesiologist should have adequate expertise to quantify and manage perioperative risk. For example, in the one generally accepted effective intervention of perioperative β-blockade, a cardiologist is not needed to provide this therapy. In Kleinman's opinion, the cardiologist's major role is in the perioperative management of acute coronary syndromes and in long-term management of chronic medical conditions. There seems to be little agreement among cardiologists, anesthesiologists, and surgeons regarding the purposes and utility of consultation; a review of 55 consecutive cardiology consultations suggests that most give little advice that truly affects management.[169] When requesting a cardiology or any specialty consultation, the anesthesiologist should ask specific questions regarding the information desired to increase the value of the consultation and perioperative management.

The anesthesiologist is the final physician who questions and determines the patient's appropriateness and stability for surgery. There can be considerable frustration and tension in the presurgical holding area when a patient's surgery is delayed or canceled just before entering the operating room. Essential diagnostic studies such as a cardiac stress test or specific laboratory tests may not have been obtained. A perioperative risk concern may not have been evaluated by the specialty consultation. To avoid day-of-surgery delays and cancellations by the anesthesiol-

ogist, some surgeons have developed a pattern of obtaining more medical specialty consultations than are necessary or appropriate. When the anesthesiologist is involved in the determination of whether a medical consultation is needed, overall numbers of specialty consultations decrease—a substantial savings in cost and time.[164]

Role of the Preoperative Clinic in Guiding Intraoperative Management Choices

The role of preoperative evaluation is to provide data and guidance so that the team managing the case on the day of the procedure can make appropriate choices. It is inappropriate for clinic providers or any preoperative consultant to make ultimate decisions regarding a specific type of anesthesia to be provided. Possible options that depend on the type of procedure, patient comorbid conditions, and patient preference should be discussed. Documentation in the final anesthesia assessment should include a statement that the options have been discussed with the patient and any patient preference noted. The patient should be informed that the final decision regarding the anesthetic plan would be made by the team managing the case. The preoperative clinician should provide ample opportunity for the patient to have any questions or concerns regarding anesthetic options addressed. Patients are often concerned that they are not speaking with the anesthesia clinician who will be providing their care. They should be reassured that all information obtained in the clinic is transferred and reviewed by the team and that they will have a chance to speak with their actual care providers on the day of surgery if additional questions arise.

Additionally, should a high-risk case warrant the skills of a specialty anesthesiologist, this assessment and request can be facilitated through the preoperative evaluation clinic before the day of surgery. A personal discussion the day before surgery between the preoperative evaluator and anesthesiologist assigned a difficult case or airway enhances the perioperative management plan and avoids operating room delays, cancellations, and potential adverse outcomes.

Summary

The practice of anesthesiology has changed.[185,186] The expanding role of the anesthesiologist outside the operating room has redefined our specialty in the hospital and with our physician colleagues with regard to our clinical expertise, effectiveness, and contribution to quality patient care.

Anesthesiologists have noticeably evolved from a specialty practicing only inside the operating rooms to an acknowledged position as perioperative medicine specialists who comprehensively evaluate and manage patients preoperatively, intraoperatively, and through their postoperative pain requirements. Frequently this occurs in formalized hospital service programs or anesthesia preoperative/pain management clinics. The anesthesiologist's visibility and leadership position in perioperative patient management has enhanced hospital opportunities, leadership recognition, and the viability of our specialty.

Anesthesiologists need to be clinically knowledgeable and skilled in assessing patients in the preoperative period, whether it be in an evaluation clinic setting before the day of surgery or at the bedside immediately before induction of anesthesia. Preparation for anesthesia and surgery can be straightforward or complex and difficult. Medicine is increasingly fragmented and extremely specialized. Patients are getting older and living longer with chronic diseases. Surgical technologies, procedures, and settings where anesthesia is administered, as well as regulatory requirements, are constantly changing and requiring anesthesiologists to accept expanding perioperative responsibilities.

Guidelines and evidence-based medicine practices are being developed and updated frequently. Virtually all disease states have an impact on perioperative patients and their care. Anesthesiologists can collaborate with primary care providers, physician extenders, and specialists, but none can truly evaluate the risks associated with anesthesia, discuss these risks with patients, or manage them perioperatively other than a physician trained in anesthesiology.

Although health care changes, regulatory issues, consensus guidelines, and medical developments will occur, the primary purpose of preoperative evaluation will never change. The anesthesia preoperative evaluation is the clinical foundation and framework of perioperative patient management and can potentially reduce operative morbidity and enhance patient outcome.

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35 Anesthetic Implications of Concurrent Diseases

Key Points

1. The history and physical examination most accurately predict the risks and the likelihood of changes in monitoring or therapy.
2. For diabetic patients, end-organ dysfunction and the degree of glucose control in the perioperative and periprocedural periods are the critical issues with regard to risk.
3. The key to managing blood glucose levels in diabetic patients perioperatively is to set clear goals and then monitor blood glucose levels frequently enough to adjust therapy to achieve these goals.
4. Obesity is associated with multiple comorbid conditions, including diabetes, hyperlipidemia, and cholelithiasis, but the primary concern is derangements of the cardiopulmonary system.
5. Obstructive sleep apnea is important to recognize because of the increased sensitivity to and the consequence of depressing the effects of hypnotics and opioids on airway muscle tone and respiration, as well as the difficulty with laryngoscopy and mask ventilation.
6. Although no controlled, randomized prospective clinical studies have been performed to evaluate the use of adrenergic receptor blocking drugs in patients undergoing resection of pheochromocytoma, the preoperative use of such drugs is generally recommended.
7. For patients with hypertension, we recommend the routine administration of all drugs preoperatively except angiotensin-converting enzyme inhibitors and angiotensin II antagonists.
8. Evaluation of a patient with cardiovascular disease depends on clinical risk factors, the extent of surgery, and exercise tolerance.
9. In patients with pulmonary disease, the following should be assessed: dyspnea, coughing and the production of sputum, recent respiratory infection, hemoptysis, wheezing, previous pulmonary complications, smoking history, and physical findings.
10. In patients with pulmonary disease, several strategies have been suggested, including cessation of smoking 8 weeks or more before surgery.
11. Risk factors for perioperative renal dysfunction include advanced age, congestive heart failure, previous myocardial revascularization, diabetes, and elevated baseline creatinine.
12. The main concern for a patient with renal disease is making it worse and thereby increasing the chance for renal failure, coma, and death.
13. Mild perioperative anemia may be significant only in patients with ischemic heart disease.
14. Careful management of chronic drug administration can include questions about the effects and side effects of alternative as well as prescription drugs.

This chapter reviews many conditions requiring special preoperative and preprocedure evaluation, intraoperative or intraprocedure management, or postprocedure care with particular focus on preprocedure care for those with increased waist size (see Chapter 64). Patients undergoing surgery move through a continuum of medical care to which a primary care physician, an internist or pediatrician, an anesthesiologist, and a surgeon, radiologist, or obstetrician-gynecologist contribute to ensure the best outcome possible. No aspect of medical care requires greater cooperation among physicians than does performance of a surgical operation or complex procedure involving multiple specialists and the perioperative care of a patient. Moreover, nowhere else can counseling make so huge a difference in so many lives. Because over 40% of medical costs are occasioned by tobacco use, physical inactivity, and poor food choices, the anesthesiologist has an important role in initiating change while assessing and ameliorating risk. We spend twice as much as developed Europe on medical care, largely because we in the United States have twice the incidence of chronic disease.[1] However, costs in the United States and the world will increase dramatically if we and other physicians do not

use preoperative and other similar situations to influence patient lifestyle choices. The importance of integrating physicians' expertise is even greater within the context of the increasing life span of our population.[2] As the number of the elderly and the very old (those >85 years) grows, so does the need of surgical patients for preoperative consultation to help plan for comorbidity and multiple drug regimens, knowledge of which is crucial to successful patient management (also see Chapter 71). At a time when medical information is encyclopedic, it is difficult, if not impossible for even the most conscientious anesthesiologist to keep abreast of the medical issues relevant to every aspect of perioperative or periprocedure patient management. This chapter reviews such issues with primary emphasis on the anesthesiologist providing preoperative evaluation and care rather than transferring these responsibilities to other providers.

As with "healthy" patients (also see Chapter 34), it is the history and physical examination that most accurately predict not only the associated risks but also the likelihood that a monitoring technique or change in therapy will be beneficial or necessary for survival. This chapter emphasizes instances in which specific information should be sought in history taking, physical examination, or laboratory evaluation. Although controlled studies designed to confirm that optimizing a patient's preoperative or preprocedure physical condition would result in lower morbidity have not been performed for most diseases, it is logical to assume that such is the case. Studies showing the benefits of optimizing specific preprocedure conditions are highlighted. The fact that such preventive measures would cost less than treating the morbidity that would otherwise occur is an important consideration in a cost-conscious and soon cost-restricted environment.

Minimally invasive procedures such as cataract extraction, magnetic resonance imaging (MRI), or diagnostic arthroscopy, performed in conjunction with the best current anesthetic practices, may pose no greater risk than daily living does and thus might not be considered an opportunity for special evaluation. Nonetheless, preanesthetic and preprocedure evaluations have provided information that has led to changes in health care plans for more than 15% of all American Society of Anesthesiologists (ASA) class I and II patients (and for >20% of all patients in general) at the University of Florida (Gibby GL, et al., personal communication). Although these changes in care plans were attributable to data found by history taking and observation (the most common being gastric reflux, diabetes mellitus requiring insulin, asthma, and suspected difficult endotracheal intubation), no data show that patient outcome was improved by such changes. Nevertheless, logic caused practitioners to alter plans for such patients in ways that would optimize operating room schedules and decrease costs. Examples would be administering a β-adrenergic blocking drug, aspirin, or a statin (or any combination) the night before rather than delaying surgery to do so on the morning of surgery; administering a histamine type 2 (H_2) antagonist 1 to 2 hours before and an oral antacid immediately before entry into the operating room; ensuring the availability of equipment to measure blood glucose levels; obtaining a history of the patient's diabetic course and treatment from the primary care doctor, as well as from the patient; and performing a fiberoptic laryngoscopic examination or procuring additional skilled attention. Counseling to begin walking even 5 days in advance of surgery anecdotally reduces perioperative complications and speeds return to typical behavior. Thus, even if preoperative and preprocedure evaluation might not alter the outcome in an important way, its ability to decrease cost by reducing unwarranted laboratory testing and delays in obtaining treatment and equipment perceived to be beneficial (and medicolegally required) would be substantial and would warrant its use.

The following conditions are discussed in this chapter:

1. Diseases involving the endocrine system and disorders of nutrition (we have put this first because of its increasing importance to care)
2. Diseases involving the cardiovascular system
3. Disorders of the respiratory and immune system (including a tobacco cessation counseling plan—Breathe Free)
4. Diseases of the central nervous system (CNS), neuromuscular diseases, and mental disorders
5. Diseases involving the kidney, infectious diseases, and disorders of electrolytes
6. Diseases involving the gastrointestinal (GI) tract or the liver
7. Diseases involving hematopoiesis and various forms of cancer
8. Diseases of aging or those that occur more commonly in the aged, as well as chronic and acute medical conditions requiring drug therapy (also see Chapter 71).

Role of the Primary Care Physician or Consultant

The role of the primary care physician or consultant is not to select or suggest anesthetic or surgical methods but rather to optimize the patient's preoperative and preprocedure status regarding conditions that increase the morbidity and mortality associated with surgery and to alert the anesthesia care team about these conditions.

Quotations and a box in a Medical Knowledge Self-Assessment Program published by the leading organization representing internists, the American College of Physicians, highlight this role for the consultant[2]:

> *Effective interaction with colleagues in other specialties requires a thorough grounding in the language and science of these other disciplines as well as an awareness of basic guidelines for consultation [Box 35-1]. The consulting internists' role in perioperative care is focused on the elucidation of medical factors that may increase the risks of anesthesia and surgery. Selecting the anesthetic technique for a given patient, procedure, surgeon, and anesthetist is highly individualized and remains the responsibility of the anesthesiologist rather than the internist.*

Optimizing a patient's preoperative and preprocedure condition and counseling a patient about needed future lifestyle changes such as walking, food choices, and tobacco cessation are cooperative ventures between the anesthesiologist and the internist, pediatrician, surgeon, or family physician. If the primary care physician cannot affirm that the patient is in the very best physical state attainable (for that patient), the anesthesiologist and physician should do what is necessary to optimize that condition. Failure to consult with the primary care physician preoperatively

Box 35-1 Guidelines for Consultation Practice

Complete a prompt, thorough, generalist-oriented evaluation.

Respond specifically to the question or questions posed.

Indicate clearly the perioperative importance of any observations and recommendations outside the area of initial concern.

Provide focused, detailed, and precise diagnostic and therapeutic guidance.

Emphasize verbal communication with the anesthesiologist and surgeon, particularly to resolve complex issues.

Avoid chart notations that unnecessarily create or exacerbate regulatory or medicolegal risk.

Use frequent follow-up visits in difficult cases to monitor clinical status and compliance with recommendations.

From American College of Physicians: Medical consultation. *In* Medical Knowledge Self-Assessment Program IX, Part C, Book 4. Philadelphia, American College of Physicians, 1992, p 939.

or before a complex procedure is as risky as not checking the oxygen in the spare tanks. In fact, statements that describe the preoperative and preprocedure physical condition of the patient (e.g., "This patient is in optimum shape" and "I believe the mitral stenosis is more severe than the slight degree of mitral insufficiency") are much more useful to the anesthesiologist than statements that suggest overall clearance ("cleared for surgery") or perioperative procedures ("prevent hypoxia and hypotension"). Knowing the patient's waist size and exercise capacity is much more important than learning that his T waves did not flip by the time he completed his stress test (knowing his maximum metabolic equivalents of the task [METs] and heart rate recovery from a stress test are very useful).

Primary care physicians can prepare and treat a patient to provide optimal conditions for daily life. However, they do not have the depth of understanding of the anesthesiologist regarding the physiologic changes brought on by surgery and the manipulations in function that must be made to facilitate surgery and procedures and optimize perioperative and periprocedure outcomes. One example would be the induction of some degree of prerenal azotemia in a patient with congestive heart failure (CHF) by the primary care physician. The intravascular volume depletion associated with prerenal azotemia may make a cardiac patient more comfortable in daily life but would predispose that patient to hypovolemic problems during and after surgery and complex procedures. Thus, even though it would be desirable for the primary care physician to start the process of preparing the patient for the needs of surgery or complex procedures, this activity would not be compatible with the current state of knowledge or functioning of the vast majority of primary care physicians. Although such education is more readily available and of better quality than in previous decades[3-5] and although Fleisher, Goldman, Charlson, and their coworkers and even cardiologic organizations have provided considerable data regarding the importance of this aspect of care,[6-8] the training, knowledge, and ability of primary care physicians are still very deficient in this aspect of consultation. Without understanding the physiologic changes that occur perioperatively, it is difficult to prescribe the appropriate therapy. It is therefore part of the anesthesiologist's job to instruct the patient's consultants about the type of information needed from the preoperative and preprocedure consultation.

Diseases Involving the Endocrine System and Disorders of Nutrition

Pancreatic Disorders

Preoperative and Preprocedure Diabetes Mellitus

This section makes nine major points regarding diabetes:

1. The number of people known to be diabetic has more than tripled in 17 years in the United States to 25 million and is increasing substantially in the world. This growth has been fueled by the rise in type 2 diabetes caused by waist gain in the adult and now pediatric population (also see Chapter 82).
2. Diabetes itself may not be as important to perioperative outcome as its end-organ effects are (see point 4 for exceptions). Although the presence of diabetes has long been assumed to increase perioperative risk, results from epidemiologic studies may not support this assumption in patients not requiring management in the intensive care unit (ICU). These studies segregated the effects of diabetes per se on the organ system from the effects of the complications of diabetes (e.g., cardiac, nervous system, renal, and vascular disease) and the effects of old age and the accelerated aging that diabetes causes. Even in patients requiring ICU management, long-standing diabetes does not appear to be as important an issue as the end-organ dysfunction that exists and the degree of glucose control in the perioperative/periprocedure and ICU periods.[9-14]
3. Because diabetes represents at least two disease processes, its perioperative management may differ between these processes.
4. The Diabetes Control and Complication Trial for type 1 diabetics, the U.K. Prospective Diabetes Study for type 2 diabetics, The Advance Studies, and the Kumamoto studies all show that chronic tight control of blood sugar and blood pressure (BP), along with physical activity, results in a major delay in microvascular complications and perhaps indefinite postponement in type 2 diabetic patients.[15,16] However, current debate centers on the benefit associated with tight control in the perioperative period and on the benefit-risk ratio. Evidence indicates that tight control of blood glucose might be of benefit for pregnant diabetics (and their future offspring) (also see Chapter 69), for diabetics undergoing cardiopulmonary bypass (also see Chapter 60), for those with (global) CNS ischemia (also see Chapters 13 and 63), and for patients requiring postoperative or postprocedure care in an ICU. Little evidence indicates that perioperative tight control is of substantial benefit to any other group; moreover, the benefit-risk ratio of tight control has not been examined for any other group of patients.[9-14]

5. Different regimens permit almost any degree of perioperative control of blood glucose levels, but the tighter the control desired, the more frequently blood glucose levels must be monitored. Three treatment regimens are outlined later.
6. The major risk factors for diabetics undergoing surgery are the end-organ diseases associated with diabetes: cardiovascular dysfunction, renal insufficiency, joint collagen tissue abnormalities (limitation in neck extension,[17] poor wound healing), inadequate granulocyte production, and neuropathies.[9-19] Thus, a major focus of the anesthesiologist should be the preoperative and preprocedure evaluation and treatment of these diseases to ensure optimal preoperative and preprocedure conditions.
7. Regional anesthesia may be indicated to facilitate some procedures (also see Chapter 52). The following considerations should be kept in mind regarding the use of regional anesthesia for diabetic patients. Local anesthetic requirements are lower and the risk of nerve injury is higher in diabetic patients.[20] In addition, combining local anesthetics with epinephrine may pose an even greater risk for ischemic or edematous nerve injury (or both) in diabetics.
8. Nosocomial infection rates are probably decreased with outpatient surgery; the frequency of complications may be decreased in diabetics most at risk by either tight control of blood glucose or intense postoperative care, or both.
9. Both forms of diabetes cause accelerated aging (also see Chapter 71). Thus, the risks involved in caring for someone with diabetes are similar to those for someone much older, that is, someone who has a much higher physiologic age (or "RealAge").[21-23]

Non–insulin-dependent (type 2) diabetics account for more than 95% of the over 25 million diabetics in the United States. At the current rate of growth, there will be 300 million diabetics in the world in 2010. These individuals tend to be overweight, relatively resistant to ketoacidosis, and susceptible to the development of a hyperglycemic-hyperosmolar nonketotic state. The diagnosis of diabetes is made with a fasting blood glucose level greater than 110 mg/dL (6.1 mmol/L), and impaired glucose tolerance is diagnosed if the fasting level is less than 110 mg/dL (6.1 mmol/L) but greater than 100 (5.5). Plasma insulin levels are normal or increased in type 2 diabetics but are relatively low for the level of blood glucose. This hyperinsulinemia by itself is postulated to cause accelerated cardiovascular disease.

Diabetes mellitus is a heterogeneous group of disorders that have the common feature of a relative or absolute lack of insulin. The disease is characterized by a multitude of hormone-induced metabolic abnormalities, by diffuse microvascular lesions, and by long-term end-organ complications. Diabetes can be divided into two very different diseases that share these end-organ abnormalities. Type 1 diabetes is associated with autoimmune diseases and has a concordance rate of 40% to 50% (i.e., if one of a pair of monozygotic twins had diabetes, the likelihood that the other twin would have diabetes is 40% to 50%). In type 1 diabetes, the patient is insulin deficient and susceptible to ketoacidosis if insulin is withheld. In type 2, the concordance rate is 100% (i.e., genetic material is both necessary and sufficient for the development of type 2 diabetes). How markedly the aging and end-organ effects of these genes are expressed is based on lifestyle choices of food and physical activity. These patients are not susceptible to the development of ketoacidosis in the absence of insulin, and they have peripheral insulin resistance. Gestational diabetes develops in more than 3% of all pregnancies and increases the risk for type 2 diabetes to 17% to 63% within 15 years.

Type 1 and type 2 diabetes differ in other ways as well. Contrary to long-standing belief, patient age does not allow a firm distinction between type 1 and type 2 diabetes; type 1 diabetes can develop in an older person, and clearly, type 2 diabetes can develop in overnourished children. A diabetes-producing variant of Coxsackie B4 virus has been isolated from the pancreas of a patient who died of diabetic ketoacidosis (type 1 diabetes). This virus was also recovered from mice bred to be diabetes prone after inoculation of the virus had produced hyperglycemia and pancreatic beta cell necrosis coincident with rising antibody titers. Thus, the intrinsic genetic "vulnerability" in insulin-dependent type 1 diabetes mellitus may consist of a diminished capacity of beta cells to survive exposure to potentially damaging extrinsic agents. Type 1 diabetes is associated with a 15% prevalence of other autoimmune diseases, including Graves' disease, Hashimoto's thyroiditis, Addison's disease, and myasthenia gravis.

The common orally administered drugs can be classified into six groups in the sulfonylurea class of antidiabetic medications: tolazamide (Tolinase), tolbutamide (Orinase), and the newer sulfonylureas glyburide (Micronase), glipizide (Glucotrol), gliclazide (Diamicron), and glimepiride (Amaryl). Some of these medications have a longer blood glucose–lowering effect that persists for 24 hours or more and fewer drug-drug interactions. Oral hypoglycemic drugs may produce hypoglycemia for as long as 50 hours after intake (chlorpropamide [Diabinese] has the longest half-life). Other drugs and drug classes that fit into the category of hypoglycemic agents include the biguanide metformin, which decreases hepatic glucose output and may increase peripheral responsiveness to glucose (and is associated with lactic acidosis if the patient becomes dehydrated); the α-glucosidase inhibitors acarbose and miglitol, which decrease glucose absorption; the thiazolidinediones (such as pioglitazone), which increase peripheral responsiveness to insulin; and meglitinides and other noninsulin secretagogues such as repaglinide (Prandin), nateglinide (Starlix), and sitagliptin (Januvia). Recent experience with rosiglitazone (Avandia) for control of blood sugar makes one question whether examination of the mechanism or end-organ effects may lead to the best outcome for patients. Nevertheless, physicians advocating tight control of blood sugar levels usually give insulin to "maturity-onset" insulin-dependent diabetic patients twice a day or even more frequently.

Insulin-dependent diabetics tend to be young, nonobese, and susceptible to the development of ketoacidosis. Plasma insulin levels are low or nonmeasurable, and therapy requires insulin replacement. Patients with insulin-dependent diabetes experience an increase in their insulin requirements in the postmidnight hours, which may result in early-morning hyperglycemia (dawn phenomenon). This accelerated glucose production and impaired glucose utilization are due to nocturnal surges in secretion of growth hormone (GH). Normal patients and diabetics taking insulin have steady-state levels of insulin in their blood. (Unfortunately, traditional values for insulin pharmacokinetics are derived from studies designed as though the diabetic received only one shot of insulin in a lifetime.) Absorption of insulin is highly variable and dependent on the type and species of insulin, the site of administration, and subcutaneous blood flow. Nevertheless, attainment of a steady state is dependent on periodic

administration of the preparations received by the patient. Thus, it seems logical to perioperatively continue the combinations of preparations that the patient had been receiving chronically after examining the patient's blood glucose monitoring logbook for the degree of control. (In our clinical experience, erratic control can foreshadow perioperative hypoglycemia.)

Acute complications in diabetic patients include hypoglycemia and diabetic ketoacidosis, as well as hyperglycemic, hyperosmolar, nonketotic coma. Diabetic patients are also subject to a series of long-term complications that lead to considerable morbidity and premature mortality, including cataracts, neuropathies, retinopathy, and angiopathy involving peripheral and myocardial vessels. The leading cause of the blindness associated with renal failure in the United States is diabetes. Many of these complications will bring the diabetic patient to surgery. The evidence that hyperglycemia itself accelerates these complications or that tight control of blood sugar levels decreases the rapidity of progression of microangiopathic disease is becoming more definitive.[24]

Glucose itself may be toxic because high levels can promote nonenzymatic glycosylation reactions leading to the formation of abnormal proteins that may decrease elastance and wound-healing tensile strength. The decrease in elastance is responsible for the stiff joint syndrome and for the fixation of the atlanto-occipital joint that makes intubation difficult. Furthermore, elevations in glucose may increase the production of macroglobulins by the liver, thereby increasing blood viscosity, and may promote intracellular swelling by favoring the production of nondiffusible, large molecules (e.g., sorbitol). Newer drug therapies (e.g., aldose reductase inhibitors) aim to decrease intracellular swelling by inhibiting the formation of such large molecules.

Studies on the long-term outcome of type 1 and type 2 diabetics indicate that tight control of blood glucose and blood sugar substantially prevents such complications (Table 35-1).[15,16]

Perioperative management of a diabetic patient may affect the surgical outcome. Physicians advocating tight control of blood glucose levels point to the evidence of increased wound-healing tensile strength and decreased wound infections in animal models of diabetes (type 1) under tight control and the development of infections, renal failure, other serious complications, and death in patients requiring intensive care.[9-14]

Infections account for two thirds of postoperative complications and about 20% of perioperative deaths in diabetic patients. Experimental data suggest that many factors can make a diabetic patient vulnerable to infection. Many alterations in leukocyte function have been demonstrated in hyperglycemic diabetics, including decreased chemotaxis and impaired phagocytic activity of granulocytes, as well as reduced intracellular killing of pneumococci and staphylococci.[25] Keeping glucose levels in the vicinity of 150 mg/dL appears to maintain the ability of immunoglobins to form complexes. When diabetic patients are treated aggressively and blood glucose levels are kept below 270 mg/dL, the phagocytic function of granulocytes is improved and intracellular killing of bacteria is restored to nearly normal levels.[25]

Diabetic patients experience more infections in clean wounds than nondiabetics do. In a review of 23,649 surgical patients, the rate of wound infection in clean incisions was 10.7% for diabetics versus 1.8% for nondiabetics.[26] In addition, hyperglycemia may worsen the neurologic outcome after intraoperative cerebral ischemia.

Blood glucose levels may affect neurologic recovery after a global ischemic event. In a study of 430 consecutive patients resuscitated after out-of-hospital cardiac arrest, mean blood glucose levels were higher in patients who never awakened (341 ± 13 mg/dL) than in those who did awaken (262 ± 7 mg/dL).[27] Among patients who awakened, those with persistent neurologic deficits had higher mean glucose levels (286 ± 15 mg/dL) than those without deficits did (251 ± 7 mg/dL). These results are consistent with the finding that hyperglycemia during a stroke is associated with poorer short- and long-term neurologic outcomes. Although several questions remain, the likelihood that blood glucose is a determinant of brain damage after global ischemia is supported by the vast majority of animal studies after global CNS ischemia and by most, but not all studies after focal CNS ischemia. The preponderance of data after CNS ischemia indicates that levels of glucose higher than 150 or 250 mg/dL have an adverse effect on CNS recovery. Until better data are available, many will argue that a diabetic patient about to undergo surgery in which hypotension or reduced cerebral blood flow may occur should have a blood glucose level below 200 mg/dL during a period of cerebral ischemia. Some special situations may also influence how tightly one should manage a patient's glucose level, such as surgery requiring cardiopulmonary bypass, surgery in pregnant patients, and emergency surgery in patients with diabetic ketoacidosis or hyperosmolar nonketotic coma.

Diabetics undergoing coronary artery bypass grafting (CABG) in 1980 had a perioperative mortality rate of 5% versus 1.5% for nondiabetics.[28] In this study and in most other studies of diabetic patients undergoing CABG, important additional risk factors or confounding variables were not considered, including the incidence and extent of hypertension, ventricular dysfunction, and CHF or the severity of coronary artery disease.

The aforementioned study of 340 diabetics and 2522 nondiabetics undergoing CABG in 1980 demonstrated only a moderate increase in operative mortality for diabetics (1.8% versus 0.6%).[28] In the postbypass phase, patients with diabetes were found to require inotropic therapy and intra-aortic balloon

Table 35-1 Tight Control of Blood Glucose Levels Reduces Chronic Complications in Type 1 Diabetic Patients

	Type 1 Diabetic Patients	
Measure and Results	**Group Undergoing Intensive Control of Blood Glucose**	**Control Group**
Measurement of blood glucose levels	≥4/day	1/day
Insulin injections	≥3/day or an insulin pump was used	1-2/day
Diet	Special diet	Usual diabetic diet
Physician office visits	1-4/mo	Once every 3 mo
Results after 6 yr		
Diabetic retinopathy	70% less than control	
Treatment needed for retinopathy	50% less than control	
Significant nephropathy	50% less than control	
Neuropathy	60% less than control	

Modified from Reichard P, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 329:304-309, 1993.

pump support five times more frequently than nondiabetics did. This increased need for therapy in diabetics is due to several possible factors. Diabetics with angina have more extensive coronary artery disease than nondiabetic patients do. They are also more likely to have hypertension, cardiomegaly, diffuse hypokinesis, and previous myocardial infarction (MI). Insulin-dependent diabetics with coronary artery disease, impaired stress responses, and autonomic nerve dysfunction appear to have stiffer ventricles with a large increase in left ventricular end-diastolic pressure than matched nondiabetic controls do.[29] During cardiopulmonary bypass, hypothermia and stress reactions decrease the response to insulin and result in marked hyperglycemia (even when the perfusate and intravenous solutions do not contain glucose) (also see Chapter 60). Administration of washed cells has been advocated for small individuals because acid citrate dextrose– or adenine-supplemented blood can result in significant hyperglycemia. These changes are exaggerated in diabetic patients, and administration of insulin may have little effect until rewarming is achieved. Inotropic drugs are ineffective in maintaining cardiac contractility, although filling pressures, sinus rhythm, serum electrolytes, and arterial blood gases were adequate. Blood sugar levels were elevated in each case. After intravenous infusion of insulin, effective myocardial contractions returned and allowed easy and rapid weaning from bypass. The effect of glucose levels on neurologic outcome during cardiopulmonary bypass is both unclear and controversial.

Many diabetics requiring emergency surgery for trauma or infection have significant metabolic decompensation, including ketoacidosis. Frequently, little time is available for stabilization of the patient, but even a few hours may be sufficient for correction of any fluid and electrolyte disturbances that are potentially life threatening. It is futile to delay surgery in an attempt to eliminate ketoacidosis completely if the underlying surgical condition will lead to further metabolic deterioration. The likelihood of intraoperative cardiac arrhythmias and hypotension resulting from ketoacidosis will be reduced if intravascular volume depletion and hypokalemia are at least partially treated.

Insulin therapy is initiated with a 10-unit intravenous bolus of regular insulin, followed by continuous insulin infusion. The rate of infusion is determined most easily if one divides the last serum glucose value by 150 (or 100 if the patient is receiving steroids, has an infection, or is considerably overweight [body mass index ≥35]). The actual amount of insulin administered is less important than regular monitoring of glucose, potassium, and pH. Because the number of insulin binding sites is limited, the maximum rate of decline in glucose is fairly constant and averages 75 to 100 mg/dL/hr, regardless of the dose of insulin.[30] During the first 1 to 2 hours of fluid resuscitation, the glucose level may fall more precipitously. When serum glucose reaches 250 mg/dL, the intravenous fluid should include 5% dextrose.

The volume of fluid required for therapy varies with the overall deficit; it ranges from 3 to 5 L and may be as high as 10 L. Despite losses of water in excess of losses of solute, sodium levels are generally normal or reduced. Factitious hyponatremia caused by hyperglycemia or hypertriglyceridemia may result in this seeming contradiction. The plasma sodium concentration decreases by about 1.6 mEq/L for every 100-mg/dL increase in plasma glucose above normal. Initially, normal saline is infused at a rate of 250 to 1000 mL/hr, depending on the degree of volume depletion and cardiac status. Some measure of left ventricular volume should be monitored in diabetics who have a history of myocardial dysfunction. About a third of the estimated fluid deficit is corrected during the first 6 to 8 hours and the remaining two thirds over the next 24 hours.

The degree of acidosis is determined by measurement of arterial blood gases and detection of an increased anion gap (also see Chapter 49):

$$Na^+ - (Cl^- + HCO_3^-)$$

Acidosis with an increased anion gap (≥16 mEq/L) in an acutely ill diabetic may be caused by ketones in ketoacidosis, lactic acid in lactic acidosis, increased organic acids from renal insufficiency, or all three problems. In ketoacidosis, plasma levels of acetoacetate, β-hydroxybutyrate, and acetone are increased. Plasma and urinary ketones are measured semiquantitatively with Ketostix and Acetest tablets. The role of bicarbonate therapy in diabetic ketoacidosis is controversial. Myocardial function and respiration are known to be depressed at a blood pH below 7.0 to 7.10, yet rapid correction of acidosis with bicarbonate therapy may result in alterations in CNS function and structure. These alterations may be caused by (1) paradoxical development of cerebrospinal fluid and CNS acidosis from rapid conversion of bicarbonate to carbon dioxide and diffusion of the acid across the blood-brain barrier, (2) altered CNS oxygenation with decreased cerebral blood flow, and (3) the development of unfavorable osmotic gradients. After treatment with fluids and insulin, β-hydroxybutyrate levels decrease rapidly, whereas acetoacetate levels may remain stable or even increase before declining. Plasma acetone levels remain elevated for 24 to 42 hours, long after blood glucose, β-hydroxybutyrate, and acetoacetate levels have returned to normal; the result is continuing ketonuria.[30] Persistent ketosis with a serum bicarbonate level less than 20 mEq/L in the presence of a normal glucose concentration is an indication of the continued need for intracellular glucose and insulin for reversal of lipolysis.

The most important electrolyte disturbance in diabetic ketoacidosis is depletion of total-body potassium. Deficits range from 3 to 10 mEq/kg body weight. Serum potassium levels decline rapidly and reach a nadir within 2 to 4 hours after the start of intravenous insulin administration. Aggressive replacement therapy is required. The potassium administered moves into the intracellular space with insulin as the acidosis is corrected. Potassium is also excreted in urine because of the increased delivery of sodium to the distal renal tubules that accompanies volume expansion. Phosphorus deficiency in ketoacidosis as a result of tissue catabolism, impaired cellular uptake, and increased urinary losses may give rise to significant muscular weakness and organ dysfunction. The average phosphorus deficit is approximately 1 mmol/kg body weight. Replacement is needed if the plasma concentration decreases below 1.0 mg/dL.[30]

Glucotoxicity

Chronic tight control of blood glucose has been motivated by a theoretical concern about four potential glucotoxicities, plus the results from three major randomized outcome studies involving diabetic patients.[9-17]

1. Glucose itself may be toxic because high levels can promote nonenzymatic glycosylation reactions that lead to the formation of abnormal proteins. These proteins may weaken endothelial junctions and decrease elastance, which is responsible for the stiff joint syndrome (and difficult intu-

bation secondary to fixation of the atlanto-occipital joint), as well as decrease wound-healing tensile strength.
2. Furthermore, elevations in glucose may increase macroglobulin production by the liver (which would increase blood viscosity) and promote intracellular swelling by favoring the production of nondiffusible, large molecules (such as sorbitol). Some drug therapies (e.g., aldose reductase inhibitors) endeavor to decrease intracellular swelling by inhibiting the formation of such large molecules.
3. Glycemia also disrupts autoregulation. Glucose-induced vasodilation prevents target organs from protecting against increases in systemic BP. A glycosylated hemoglobin level of 8.1% is the threshold at which the risk for microalbuminuria increases logarithmically. A person with type 1 diabetes who has microalbuminuria of greater than 29 mg/day has an 80% chance of experiencing renal insufficiency. The threshold for glycemic toxicity differs for various vascular beds. For example, the threshold for retinopathy is a glycosylated hemoglobin value of 8.5% to 9.0% (12.5 mmol/L or 225 mg/dL), and that for cardiovascular disease is an average blood glucose value of 5.4 mmol/L (96 mg/dL). Thus, different degrees of hyperglycemia may be required before different vascular beds are damaged, or certain degrees of glycemia are associated with other risk factors for vascular disease. Another view is that perhaps severe hyperglycemia and microalbuminuria are simply concomitant effects of a common underlying cause. For instance, diabetics in whom microalbuminuria develops are more resistant to insulin, insulin resistance is associated with microalbuminuria in first-degree relatives of type 2 diabetics, and persons who are normoglycemic but subsequently have clinical diabetes are at risk for atherogenesis before the onset of disease.

Tight control retards all these glucotoxicities and may have other benefits in retarding the severity of diabetes itself.[9-17,31]

Thus, management of intraoperative glucose might be influenced by specific situations, such as the type of operation, pregnancy,[32] and the expected global CNS insult; the bias of the patient's primary care physician; or the type of diabetes. Type 1 diabetic patients definitely need insulin and might be considered candidates for tight control of blood glucose levels. Type 2 diabetic patients have insulin, and current data indicate that they do not benefit from tight perioperative control unless they need intensive care.[9-14]

The key to managing blood glucose levels perioperatively in diabetic patients is to set clear goals and then monitor blood glucose levels frequently enough to adjust therapy to achieve these goals. Three regimens that afford various degrees of perioperative control of blood glucose levels are discussed in the following sections.

Classic "Non–Tight Control" Regimen

Aim: To prevent hypoglycemia, ketoacidosis, and hyperosmolar states.

Protocol:

1. On the day before surgery, the patient should be given nothing by mouth (NPO) after midnight; a 13-oz glass of clear orange juice should be at the bedside or in the car for emergency use.
2. At 6 AM on the day of surgery, infuse a solution of intravenous fluids containing 5% dextrose through plastic cannulas at a rate of 125 mL/hr/70 kg body weight.
3. After starting the intravenous infusion, give half the usual morning insulin dose (and the usual type of insulin) subcutaneously.
4. Continue 5% dextrose solutions through the operative period and give at least 125 mL/hr/70 kg body weight.
5. In the recovery room, monitor blood glucose concentrations and treat on a sliding scale.

Such a regimen has been found to meet its goals.

"Tight Control" Regimen 1

Aim: To keep plasma glucose levels at 79 to 120 mg/dL. Maintenance of such levels may improve wound healing and prevent wound infections, improve neurologic outcome after global or focal CNS ischemic insults, or improve weaning from cardiopulmonary bypass.

Protocol:

1. On the evening before surgery, determine the preprandial blood glucose level.
2. Through a plastic cannula, begin an intravenous infusion of 5% dextrose in water at a rate of 50 mL/hr/70 kg body weight.
3. "Piggyback" an infusion of regular insulin (50 units in 250 mL or 0.9% sodium chloride) to the dextrose infusion with an infusion pump (Fig. 35-1). Before attaching this piggyback line to the dextrose infusion, flush the line with 60 mL of infusion mixture and discard the flushing solution. This approach saturates insulin binding sites on the tubing.

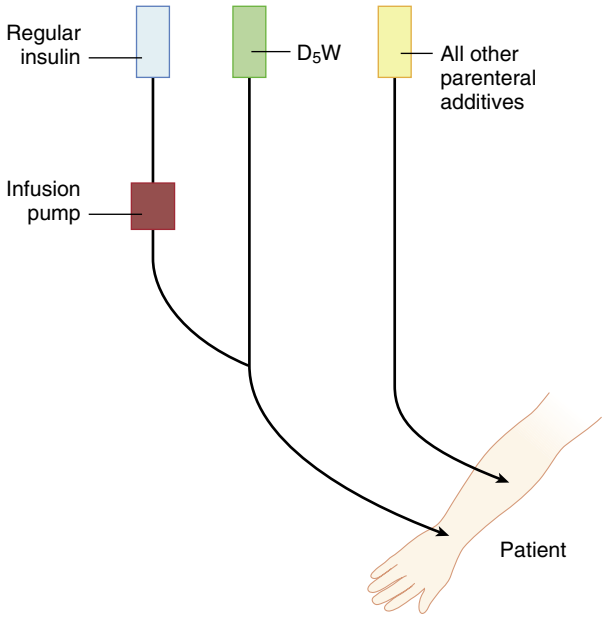


Figure 35-1 Arrangement of intravenous lines for infusion of regular insulin in a regimen tightly controlling blood glucose levels in diabetic patients undergoing surgery. D_5W, 5% dextrose in water.

4. Set the infusion rate by using the following equation: Insulin (U/hr) = plasma glucose (mg/dL)/150. (*Note*: The denominator should be 100 if the patient is taking corticosteroids, e.g., 10 mg of prednisolone a day or its equivalent, not to include inhaled steroids, or has a body mass index of ≥35.)
5. Repeat blood glucose measurements every 4 hours as needed, and adjust insulin appropriately to obtain blood glucose levels of 100 to 200 mg/dL.
6. On the day of surgery, intraoperative fluids and electrolytes are managed by continued administration of non–dextrose-containing solutions, as described in steps 3 and 4.
7. Determine the plasma glucose level at the start of surgery and every 1 to 2 hours for the rest of the 24-hour period. Adjust the insulin dosage appropriately.

Although we have not found it necessary to treat hypoglycemia (i.e., blood glucose levels <50 mg/dL), we have been prepared to do so with 15 mL of 50% dextrose in water. In such circumstances, the insulin infusion would be terminated. This regimen has been found to accomplish its objectives, with the exception of such tight goals for blood glucose, even in very "brittle" diabetics (i.e., those extremely resistant to treatment) given high doses of steroids.

"Tight Control" Regimen 2

Aim: Same as for Tight Control Regimen 1.

Protocol:

1. Obtain a "feedback mechanical pancreas" and set the controls for the desired plasma glucose regimen.
2. Institute two appropriate intravenous lines.

This last regimen may well supersede all others if the cost of a mechanical pancreas can be reduced and if control of hyperglycemia is shown to make a meaningful difference perioperatively; it has superseded all others in many ICUs and for good reason (Table 35-2).[11-13]

Table 35-2 Therapy for 1548 Postsurgical Diabetics in the Leuven Intensive Care Unit Study*

	Intensive Glucose Therapy (80-110 mg/dL)	Conventional Glucose Therapy (180-200 mg/dL)
Death in the ICU	4.6%	8.0%
After 5 days in the ICU	10.6%	20.2%
First 5 ICU days	1.7%	1.8%
All deaths	7.2%	10.9%
>14 days in the ICU	11.4%	15.7%
>14 days ventilated	7.5%	11.9%
Rx dialysis	4.8%	8.2%
Polyneuropathy	28.7%	51.9%

*Decreased complication rates and improved survival were observed in the group treated by tight control.

Diabetes and Accelerated Physiologic Aging

Adverse perioperative outcomes have repeatedly and substantially correlated with the age of the patient,[6,7,21-23,33] and diabetes does cause physiologic aging. When one translates the results of the Diabetes Control and Complications Trials into age-induced physiologic changes, a type 1 diabetic who has poor control of blood sugar ages approximately 1.75 years physiologically for every chronologic year of the disease and 1.25 years if blood sugar has been controlled tightly.[21-23] A type 2 diabetic ages about 1.5 years for every chronologic year of the disease and about 1.06 years with tight control of blood sugar and BP.[16,21-23,34] Thus, when providing care for a diabetic patient, one must consider the associated risks to be those of a person who is much older physiologically. That is, a diabetic's physiologic age ("RealAge") is considerably higher than that person's calendar age just by virtue of having the disease.[2]

The increased prevalence of obesity and lack of physical exercise seem to be major contributors to the increased prevalence of type 2 diabetes. As with type 1 diabetes, tight control of blood sugar, increased physical activity, and reduction in weight appear to reduce the accelerated aging associated with type 2 diabetes and even to substantially delay appearance of the disease and aging from it (Box 35-2).[21-23,34] Although such a reduction in aging should reduce the perioperative risk for diabetic patients, no controlled trials have confirmed this theory.

Other Conditions Associated with Diabetes

Diabetes is associated with microangiopathy (in retinal and renal vessels), peripheral neuropathy, autonomic dysfunction, and infection. Diabetics are often treated with angiotensin-converting enzyme (ACE) inhibitors, even in the absence of gross hypertension, in an effort to prevent the effects of disordered autoregulation, including renal failure.[15,16,35]

Before surgery, assessment and optimization of treatment of the potential and potent end-organ effects of diabetes are at least as important as assessment of the diabetic's current overall metabolic status. The preoperative evaluation of diabetics is also discussed in Chapter 34.

If one is to believe the few studies we have, the presence of autonomic neuropathy makes the operative period more hazardous and the postoperative period crucial to survival. Evidence of autonomic neuropathy might be routinely sought before surgery. Patients with diabetic autonomic neuropathy are at increased risk for gastroparesis (and consequent aspiration) and for intraoperative and postoperative cardiorespiratory arrest. Data indicate that diabetics who exhibit signs of autonomic neuropathy, such as early satiety, lack of sweating, lack of pulse rate change with inspiration or orthostatic maneuvers, and impotence, have a very high incidence of painless myocardial ischemia[19,36] and gastroparesis. Some investigators have successfully used 10 mg of metoclopramide preoperatively to facilitate gastric emptying of solids (Fig. 35-2). Interference with respiration or sinus automaticity by pneumonia or by anesthetics, pain medications, or sedative drugs appears to be the precipitating cause in most cases of sudden cardiorespiratory arrest. Measuring the degree of sinus arrhythmia or beat-to-beat variability provides a simple, accurate test for significant autonomic neuropathy. The difference between the maximum and minimum heart rate on deep inspiration is normally 15 beats/min but is 5 beats/min or less in all patients who sustained cardiorespiratory arrest.[19,36]

Box 35-2 The YOU Docs Plan for Reversing the Aging from Type 2 Diabetes and Metabolic Syndrome*

We or you have told us of tests and measurements that indicate you have type 2 diabetes or metabolic syndrome. Don't be alarmed; you can control the genes that predispose you to such so that this syndrome will not be as much problem to you in the future. BUT YOU HAVE TO DO IT—it is not your docs or your mother, IT IS UP TO YOU TO CONTROL YOUR GENES.

Because you have been diagnosed with type 2 diabetes or these syndromes, you can begin getting healthier by reducing your weight. Without a doubt, diabetes can be as damaging to your health as an annoyed anaconda. However, if you can hit these goals and even gradually decrease your waist size and your weight (aim for 2 pounds a week for the first 4 weeks, then 1 pound a week for 4 weeks, then 1 pound every month—after all you didn't get this big all at once), you'll decrease the aging effects of diabetes or metabolic syndrome by 80%, perhaps even more. Here's what has worked for our typical patient with your physique and tests and how to lose the weight and waist:

1. Avoid all white food—we're talking icing and white bread, not cauliflower.
2. Walk 30 minutes a day, no matter what.
3. Get a buddy and a plan for making YOU-turns: If you can walk 30 minutes every day and call (or e-mail) a support person each day after you've walked, you can lose the weight and have the waist you want, at least that's what review of weight and waist loss from over 190,000 buddy pairs tells us. So get a buddy you tell you walked daily and who will call you to check up if you do not call her within 15 minutes of your usual time (her's work better as buddies than him's). Have a plan for when you slip up—because you will. Here's a three-step approach for getting back on the right path:
   - Relax and say something positive to steer yourself back on course. Be confident that you can overcome the slip.
   - Do something physical right away—for instance, take a brisk walk or do a yoga pose. I recommend the downward-facing dog posture. This will help you refocus, take a deep breath, and remind yourself of your goals.
   - Eat something nutritious. Certain foods—such as carrots and apples—can help counteract stress, probably because they're crunchy and a touch sweet. You could choose a crisp vegetable, too. Whatever it is, make this the nutritious food "YOU-turn" to whenever you're stressed.
4. Once you have walked 30 minutes a day for 30 consecutive days, learn to lift weights and then integrate a resistance training program for 20 minutes three times a week into your weekly routine (you can download one for free at www.realage.com/youdocs); start with the beginner level no matter what your age.
5. Measure your waist around your belly button every Sunday. Suck in (you will anyway). Aim to lose an inch a month.
6. Get a blood pressure monitor and take it every Sunday. Your goal is 115/75.
7. Avoid the five aging foods: all added sugars and syrups, including all high-fructose corn syrup; saturated fats (four-legged plus palm or coconut oil) and *trans*-fats (blends or partially hydrogenated fats); and any grain except 100% whole grain, especially if it's one of the first five ingredients listed on a label.
8. Have as much fruit—whole, not fruit mixes or canned—and veggies as you want. By the way, Fruit Loops doesn't cut it.
9. Eat half an ounce of nuts—6 walnut halves, 12 almonds, or 20 peanuts—8 minutes before each meal, followed by a glass of water 4 minutes later.
10. Make eating automatic. I know I've said this before, but if you can train yourself—over 2 weeks or longer—to eat the right foods and make the right activity choices, you'll reprogram your body so that gradually eating right and exercising becomes a habit, one you'll do automatically. One tip for making your eating automatic is to have the same foods every day for two meals, say breakfast and lunch, and vary only one meal, such as dinner. Perhaps you're thinking "No one could do that." In fact, I practice what I preach by eating steel cut oatmeal for breakfast everyday. You can even prepare a week's worth of oats in advance to save time.
11. Inform and work with your primary care doctor. Keep taking your antidiabetic medications (and all others such as anti–high blood pressure medications), but follow your blood sugar and blood pressure closely. Our typical patients have to reduce antidiabetic medications and insulin after about 2 weeks and gets rid of them by the time they have lost 15% to 20% of the excess waist and weight they have gained since age 18 (women) or age 21 (men). Moreover, that reduction in medications occurs for their anti–high blood pressure medications too.

*The Type II Diabetes Disease Reversal plan is copywritten by the YOU Docs in *YOU On a Diet: The Owner's Manual for Waist Management* (Free Press, 2006 in the United States), reprinted here by permission of the copyright owner and offered to all who want to use it—feel free to copy and hand to patients (as long as credit is given).

Other characteristics of patients with autonomic neuropathy include postural hypotension with a decrease in BP of more than 30 mm Hg, resting tachycardia, nocturnal diarrhea, and dense peripheral neuropathy. Diabetics with significant autonomic neuropathy may have impaired respiratory responses to hypoxia and are particularly susceptible to the action of drugs that have depressant effects. These patients may warrant very close, continuous cardiac and respiratory monitoring for 24 to 72 hours postoperatively, although such logical treatment has not been tested in a rigorous, controlled trial.[19] In the absence of autonomic neuropathy, we would favor outpatient surgery for a diabetic (Table 35-3).

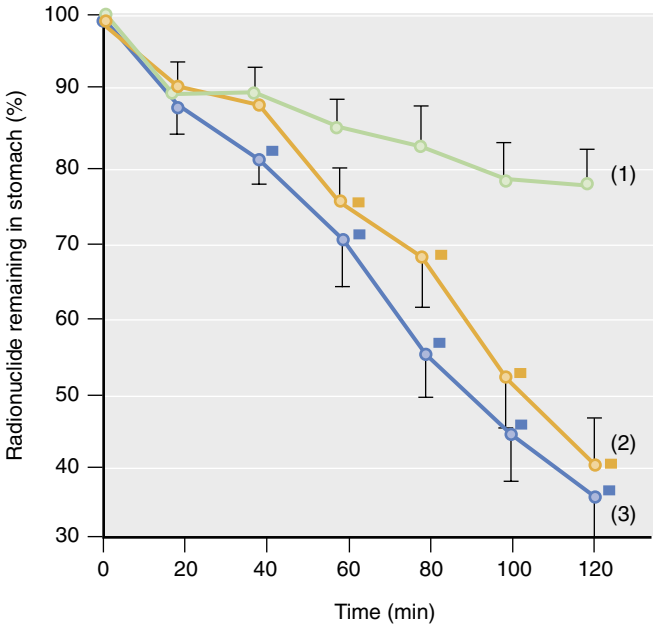


Figure 35-2 Gastric emptying time (mean ± SD) of a solid test meal in three groups of patients: diabetics (line 1), diabetics given metoclopramide (10 mg intravenously) 1.5 hours before the test meal (line 2), and nondiabetics (line 3). *(From Wright RA, Clemente R, Wathen R: Diabetic gastroparesis: An abnormality of gastric emptying of solids. Am J Med Sci 289:240, 1985.)*

Anticipated Newer Treatments of Diabetes

At least three major changes in the care of diabetic patients have made it to the clinical trial stage:

- Implanted (like a pacemaker) glucose analyzer with electronic transmission to a surface (watch) monitor
- New islet transplantation medication that makes islet cell transplants much more successful and rejection medication less hazardous
- Medications such as INGAP (islet neogenesis–associated protein) peptide, which may cause regrowth of normally functioning islet cells (without needing transplantation)

One can imagine how some of these treatments may radically change the therapies used in the perioperative period. If regrowth of islets becomes common, type 1 diabetes could all but disappear; if implanted minute-to-minute glucose reading is possible, tight control may be much easier and more expected.

Insulinoma and Other Causes of Hypoglycemia

Hypoglycemia in persons not treated for diabetes is rare. Hypoglycemia in nondiabetics can be caused by such diverse entities as pancreatic islet cell adenoma or carcinoma, large hepatoma, large sarcoma, alcohol ingestion, use of β-adrenergic receptor blocking drugs, haloperidol therapy, hypopituitarism, adrenal insufficiency, altered physiology after gastric or gastric bypass surgery, hereditary fructose intolerance, ingestion of antidiabetic drugs, galactosemia, or autoimmune hypoglycemia.[37] The last four entities cause postprandial reactive hypoglycemia. Because restriction of oral intake prevents severe hypoglycemia, the practice of keeping the patient NPO and infusing small amounts of a solution containing 5% dextrose greatly lessens the possibility of perioperative postprandial reactive hypoglycemia. The other causes of hypoglycemia can cause serious problems during the perioperative period.[37]

Symptoms of hypoglycemia fall into two groups: adrenergic excess (tachycardia, palpitations, tremulousness, or diaphoresis) and neuroglycopenia (headache, confusion, mental sluggishness, seizures, or coma). All these symptoms may be masked by anesthesia, so blood glucose levels should be determined frequently in such patients to ensure that hypoglycemia is not present. Because manipulation of an insulinoma can result in massive insulin release, this tumor should probably be operated on only at centers equipped with a mechanical pancreas. Perioperative use of the somatostatin analog octreotide, which suppresses insulin release from such tumors, appears to make the perioperative period a logarithm safer in anecdotal experience.

Disorders of Nutrition, Including Obesity

Hyperlipoproteinemia, Hyperlipidemia, and Hypolipidemia

Hyperlipidemia may result from obesity, estrogen or corticoid therapy, uremia, diabetes, hypothyroidism, acromegaly, alcohol ingestion, liver disease, inborn errors of metabolism, or pregnancy. Hyperlipidemia may cause premature coronary or peripheral vascular disease or pancreatitis.

Data showing that coronary events can be reduced by treating individuals with even normal levels of low-density cholesterol (LDL) cholesterol with the "statins"—drugs that raise high-density cholesterol (HDL) and lower LDL cholesterol levels—resulted from a decade of rapid progress in preventing reinfarction in high-risk patients.[38-40] Secondary prevention efforts were successful when these high-risk patients stopped smoking, reduced their BP, controlled stress, increased physical activity, and used aspirin, folate, β-blocking drugs, angiotensin inhibitors, diet, and other drugs to reduce their levels of LDL and increase their levels of HDL.

Table 35-3 Should a Diabetic Be an Outpatient or a Morning Admittance Patient?

Outpatient If	Morning Admittance Patient If
Can evaluate the history in advance	Cannot evaluate the history
End-organ disease does not require monitoring	End-organ disease requires invasive monitoring
Prehydration is available	Needs careful prehydration or is unnecessary
No CNS ischemia or planned cardiopulmonary bypass	CNS ischemia is present or cardiopulmonary bypass is planned
Not pregnant	Pregnant
Patient or vested home "mate" can determine blood glucose level	Patient cannot determine blood glucose level
Has vested home "mate"	No vested individual
Can take temperature or look for "red" wound	Cannot take temperature or look for "red" wound
Plan higher admission rate (no data)	Social care network is unsuitable

Although controlling the diet remains a major treatment modality for all types of hyperlipidemia, the drugs fenofibrate and gemfibrozil, which are used to treat hypertriglyceridemia, can cause myopathy, especially in patients with hepatic or renal disease; clofibrate is also associated with an increased incidence of gallstones. Cholestyramine binds bile acids, as well as oral anticoagulants, digitalis drugs, and thyroid hormones. Nicotinic acid causes peripheral vasodilation and should probably not be continued through the morning of surgery. Probucol (Lorelco) decreases the synthesis of apoprotein A-I; its use is associated on rare occasion with fetid perspiration or prolongation of the QT interval (or both) and sudden death in animals.

The West of Scotland Coronary Prevention Study and its congeners produced convincing evidence that drugs in the "statin" class (3-hydroxy-3-methylglutaryl–coenzyme A [HMG-CoA] reductase inhibitors) prevent the morbidity and mortality related to arterial aging and vascular disease, as well as their consequences, such as coronary artery disease, stroke, and peripheral vascular insufficiency.[39] Thus, the statins—lovastatin (Mevacor), pravastatin (Pravachol), simvastatin, fluvastatin, atorvastatin (Lipitor), and rosuvastatin (Crestor)—are mainstays of therapy.

However, the report of Downs and coworkers[39] from the Air Force/Texas Coronary Atherosclerosis Prevention Study went further. It showed a 37% reduction in the risk for first acute major coronary events in patients who had no risk factors and normal (average) LDL cholesterol levels. In this study lovastatin did not alter mortality rates, but that had been true for many early short-term trials with the statins. Although much of the effect of the statins has been attributed to their lipid-lowering effects, at least 40% of the effect of statins is modification by them of endothelial function, inflammatory responses, plaque stability, and thrombogenicity (Steven Nissen, MD, personal communcation). The report of Downs and colleagues broadened the use of statins, and they remain mainstays of therapy for hyperlipidemia. Statins are drugs that block HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis. Their use is occasionally accompanied by liver dysfunction, CNS dysfunction, and severe depression not related to the high cost of each drug and its cogeners. Other drugs that reduce LDL and increase HDL cholesterol and decrease triglycerides are docosahexaenoic acid (DHA, an ω-3 fatty acid) and niacin. Recent data indicate that statins also provide the substantial benefit of reversing inflammation in arteries, as evidenced by their ability to decrease highly specific C-reactive protein and pull cholesterol from plaque.[41]

Hypolipidemic conditions are rare diseases often associated with neuropathy, anemia, and renal failure. Although anesthetic experience with hypolipidemic conditions has been limited, some specific recommendations can be made: continuation of caloric intake and intravenous administration of protein hydrolysates and glucose throughout the perioperative period.

Obesity

Although many conditions associated with obesity (diabetes, hyperlipidemia, cholelithiasis, gastroesophageal reflux disease, cirrhosis, degenerative joint and disk disease, venous stasis and thrombotic/embolic disease, sleep disorders, and emotional and altered body image disorders) contribute to chronic morbidity in the obese, the main concerns for the anesthesiologist have been the same for more than 4 decades—derangements of the cardiopulmonary system (also see Chapter 64).

Morbid obesity with minimal or no coexisting pulmonary conditions (e.g., no obesity-hypoventilation syndrome or chronic obstructive pulmonary disease [COPD]) will be referred to as "simple" obesity. In simple obesity, the pathophysiology of mild alterations in daytime gas exchange and pulmonary function may also result from compression and restriction of the chest wall and diaphragm by excess adipose tissue.[42] Typically, in the obese, the expiratory reserve volume and functional residual capacity are most affected and reduced to 60% and 80% of normal, respectively. Morbid obesity and its perioperative implications are also discussed in Chapters 34 and 64.

Other Eating Disorders: Anorexia Nervosa, Bulimia, and Starvation

Many endocrine and metabolic abnormalities occur in patients with anorexia nervosa, a condition characterized by starvation to the point of 40% loss of normal weight, hyperactivity, and a psychiatrically distorted body image. Many anorectic patients exhibit impulsive behavior, including suicide attempts, and intravenous drug use is much more common than in the general population. Acidosis, hypokalemia, hypocalcemia, hypomagnesemia, hypothermia, diabetes insipidus, and severe endocrine abnormalities mimicking panhypopituitarism need attention before anesthesia and surgery. Similar problems occur in bulimia (bulimorexia), a condition that may affect as many as 50% of female college students[43] and is even unintentionally present in many elderly.[44] As in severe protein deficiency (kwashiorkor), anorexia nervosa and bulimia may be accompanied by alterations on the electrocardiogram (ECG), including a prolonged QT interval, atrioventricular (AV) block, and other arrhythmias; sensitivity to epinephrine; and cardiomyopathy.[43] Total depletion of body potassium makes the addition of potassium to glucose solutions useful; however, fluid administration can precipitate pulmonary edema in these patients. Esophagitis, pancreatitis, and aspiration pneumonia are more frequent in these patients, as is delayed gastric emptying. Thus, invasive monitoring (radial artery and pulmonary artery catheterization) may be indicated for anorectic, bulimic, and malnurtured patients requiring emergency surgery. Elective surgery should probably be delayed until the abnormalities are treated.

Hyperalimentation (Total Parenteral or Enteral Nutrition)

Hyperalimentation (i.e., total parenteral nutrition [TPN]) consists of concentrating hypertonic glucose calories in the normal daily fluid requirements (also see Chapter 95). The solutions contain protein hydrolysates, soybean emulsions (i.e., Intralipid), or synthetic amino acids (or any combination of these ingredients). The major benefits of TPN or enteral nutrition have been fewer complications postoperatively and shorter hospital stays for patients scheduled to have no oral feeding for 7 days or who were malnourished preoperatively.[45,46] Starker and colleagues[47] found that the response to TPN, as monitored by serum albumin levels, predicted the postoperative outcome. The group demonstrating a rise in serum albumin with TPN had diuresis, weight loss, and fewer complications (1 of 15 patients) than did the group that gained weight and had a decrease in serum albumin (8 of 16 patients had 15 complications) (Fig. 35-3). These data are echoed by those in the Veterans Administration (VA) studies, which

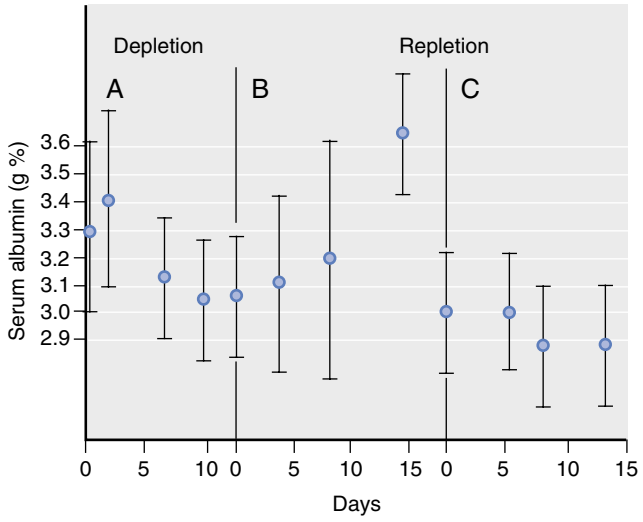


Figure 35-3 The response to hyperalimentation A, (repletion), as measured by variation in serum albumin levels, predicted the outcome of surgery. Patients who responded (B) to nutritional support with increased albumin levels had a significantly better outcome than did those whose albumin level did not increase (C). See the text for a more complete explanation. *(Adapted from Starker PM, Group FE, Askanazi J, et al: Serum albumin levels as an index of nutritional support. Surgery 91:194, 1982.)*

reported that the serum albumin level was one of the most powerful predictors of perioperative outcome.[45]

The major complications of hyperalimentation are sepsis and metabolic abnormalities. The central lines used for TPN require application with an absolutely aseptic technique and should not be used routinely as an intravenous route for drug administration. Major metabolic complications of TPN relate to deficiencies and the development of hyperosmolar states. Complications of hypertonic dextrose can develop if the patient has insufficient insulin (diabetes mellitus) to metabolize the sugar or if insulin resistance occurs (e.g., because of uremia, burns, or sepsis).

A gradual decrease in the infusion rate of TPN prevents the hypoglycemia that can occur on abrupt discontinuance. Thus, the infusion rate of TPN should be decreased the night before anesthesia and surgery or be continued throughout the operation at its current rate. The main reason for slowing or discontinuing TPN before anesthesia is to avoid intraoperative hyperosmolarity secondary to accidental rapid infusion of the solution or hypoglycemia if the infusion is discontinued because of high levels of endogenous insulin and lower levels of glucose present in the usual crystalloid solutions.[45] Hypophosphatemia is a particularly serious complication that results from the administration of phosphate-free or phosphate-depleted solutions for hyperalimentation. The low serum phosphate level causes a shift of the oxygen dissociation curve to the left. The resulting low 2,3-diphosphoglycerate and adenosine triphosphatase levels mean that cardiac output must increase for oxygen delivery to remain the same. Hypophosphatemia of less than 1.0 mg/dL of blood may cause hemolytic anemia, cardiac failure, tachypnea, neurologic symptoms, seizures, and death. In addition, long-term TPN is associated with deficiencies in trace metals such as copper (refractory anemia), zinc (impaired wound healing), and magnesium.

For these reasons, one author (M.F.R.) has adopted the following practices. Infusion of TPN or enteral nutrition is reduced beginning the night before surgery, and a 5% or 10% dextrose solution is substituted preoperatively. If serum glucose, phosphate, and potassium concentrations (measured preoperatively) are abnormal, they are restored to within normal limits. Strict asepsis is maintained. Conversely, one should continue infusing the TPN solution by using a pump system or enteral nutrition while strictly maintaining its normal rate and asepsis, administering all fluids through a different intravenous site, and performing a rapid-sequence induction of anesthesia (for those who received enteral nutrition).

Adrenocortical Malfunction

Three major classes of hormones—androgens, glucocorticoids, and mineralocorticoids—are secreted by the adrenal cortex. For each class, an excess or a deficiency of hormone produces a characteristic clinical syndrome. The widespread use of steroids can also make the adrenal cortex unable to respond normally to the demands placed on it by surgical trauma and subsequent healing. The increase in unindicated (scanning) computed tomography (CT) abdominal imaging procedures has meant that many adrenal masses have unfortunately been discovered only incidentally. These adrenal "incidentalomas," as they are termed because they were initially thought a nuisance discovered by unindicated body scans, have proved more serious. As many as 30% are hormonally active; in one recent review of 2000 such masses, 82% were not hormonally active, 5.3% proved to be cortisone-secreting adenomas, 5.1% were pheochromocytomas, 4.7% were adrenal carcinomas, 2.5% were unsuspected metastatic disease, and 1% were aldosterone-secreting adenomas. Incidentalomas may therefore require serious pursuit. Several points relative to adrenal cortical management deserve attention.

Controlled comparisons of the perioperative management of patients who have disorders of adrenal function are lacking, although we use steroids more and more commonly, with the results of some controlled trials available for specific uses. However, a review of the possible pathophysiologic changes in the adrenal cortex and techniques for their management should enable us to improve the perioperative care of patients with adrenal abnormalities.

Physiologic Properties of Adrenocortical Hormones

Androgens

Androstenedione and dehydroepiandrosterone, weak androgens arising from the adrenal cortex, constitute major sources of androgen in women (and have gained prominence for their use or abuse by baseball players seeking to hit more home runs). Excess secretion of androgen causes masculinization, pseudopuberty, or female pseudohermaphroditism. With some tumors, androgen is converted to an estrogenic substance, in which case feminization results. No special anesthetic evaluation is needed for such patients. Some congenital enzyme defects that cause androgen abnormalities also result in glucocorticoid and mineralocorticoid abnormalities that should be evaluated before surgery. Most of these patients are treated with exogenous glucocorticoids and mineralocorticoids and consequently require supplementation of these hormones perioperatively (see later).

Glucocorticoids

The principal glucocorticoid, cortisol, is an essential regulator of carbohydrate, protein, lipid, and nucleic acid metabolism. Cortisol exerts its biologic effects through a sequence of steps initiated by binding of hormone to stereospecific intracellular cytoplasmic receptors. This bound complex stimulates nuclear transcription of specific mRNA molecules. These molecules are then translated to give rise to proteins that mediate the ultimate effects of hormones.

Most cortisol is bound to corticosterone-binding globulin (CBG, transcortin). It is the relatively small amounts of unbound cortisol that enter cells to induce actions or to be metabolized. Conditions that induce changes in the amount of CBG include liver disease and nephrotic syndrome, both of which result in decreased circulating levels of CBG, and estrogen administration and pregnancy, which result in increased CBG production. Total serum cortisol levels may become elevated or depressed under conditions that alter the amount of bound cortisol, and yet the unbound, active form of cortisol is present in normal amounts. The most accurate measure of cortisol activity is the level of urinary cortisol—that is, the amount of unbound, active cortisol filtered by the kidney.

The serum half-life of cortisol is 80 to 110 minutes. However, because cortisol acts through intracellular receptors, pharmacokinetic data based on serum levels are not good indicators of cortisol activity. After a single dose of glucocorticoid, serum glucose is elevated for 12 to 24 hours; improvement in pulmonary function in patients with bronchial asthma can still be measured 24 hours after glucocorticoid administration. Treatment schedules for glucocorticoid replacement are therefore based not on the measured serum half-life but on the well-documented prolonged end-organ effect of these steroids. Hospitalized patients requiring chronic glucocorticoid replacement therapy are usually treated twice daily, with a slightly higher dose given in the morning than in the evening to simulate the normal diurnal variation in cortisol levels. For patients who require parenteral "steroid coverage" during and after surgery (see later paragraphs), administration of glucocorticoid every 12 hours is appropriate.[48] The relative potencies of glucocorticoids are listed in Table 35-4. Cortisol is inactivated primarily in the liver and is excreted as 17-hydroxycorticosteroid. Cortisol is also filtered and excreted unchanged into urine.

The synthetic glucocorticoids vary in their binding specificity in a dose-related manner. When given in supraphysiologic doses (>30 mg/day), cortisol and cortisone bind to mineralocorticoid receptor sites and cause salt and water retention and loss of potassium and hydrogen ions. When these steroids are administered in maintenance doses of 30 mg/day or less, patients require a specific mineralocorticoid for electrolyte and volume homeostasis. Many other steroids do not bind to mineralocorticoid receptors, even at high doses, and have no mineralocorticoid effect (see Table 35-4).

Secretion of glucocorticoids is regulated by pituitary adrenocorticotropic hormone (ACTH). ACTH is synthesized from a precursor molecule (pro-opiomelanocortin) that is metabolized to form an endorphin (β-lipotropin) and ACTH. Episodic secretion of ACTH has a diurnal rhythm that is normally greatest during the early morning hours in men, later in women, and is regulated at least in part by light-dark cycles. Its secretion is stimulated by release of corticotropin-releasing factor (CRF) from the hypothalamus. (An abnormality in the diurnal rhythm of corticoid secretion has been implicated as a cause of so-called jet lag.) Cortisol and other glucocorticoids exert negative feedback at both the pituitary and hypothalamic levels to inhibit the secretion of ACTH and CRF. If the CRF- or ACTH-producing cells are destroyed, the adrenal gland takes more than 30 days to atrophy to the point where acute administration of exogenous ACTH will cause almost no adrenal responsiveness.

Table 35-4 Relative Potencies and Equivalent Doses for Commonly Used Glucocorticoids

Steroids	Relative Glucocorticoid Potency	Equivalent Glucocorticoid Dose (mg)
Short Acting		
Cortisol (hydrocortisone)	1.0	20.0
Cortisone	0.8	25.0
Prednisone	4.0	5.0
Prednisolone	4.0	5.0
Methylprednisolone	5.0	4.0
Intermediate Acting		
Triamcinolone	5.0	4.0
Long Acting		
Betamethasone	25.0	0.60
Dexamethasone	30.0	0.75

Data from Axelrod L: Glucocorticoid therapy. Medicine (Baltimore) 55:39, 1976.

Mineralocorticoids

Aldosterone, the major mineralocorticoid secreted in humans, comes from the zona glomerulosa of the adrenal cortex and causes reabsorption of sodium and secretion of potassium and hydrogen ions, thereby contributing to electrolyte and volume homeostasis. This action is most prominent in the distal renal tubule but also occurs in the salivary and sweat glands. The major regulator of aldosterone secretion is the renin-angiotensin system. Juxtaglomerular cells in the cuff of renal arterioles are sensitive to decreased renal perfusion pressure or volume and, consequently, secrete renin. Renin splits the precursor angiotensinogen (from the liver) into angiotensin I, which is further converted by a converting enzyme, primarily in the lung, to angiotensin II. Angiotensin II binds to specific receptors to increase mineralocorticoid secretion, which is also stimulated by an increased potassium concentration and, to a lesser degree, by ACTH.

Adrenocortical Hormone Excess

Glucocorticoid Excess

Glucocorticoid excess (Cushing's syndrome) resulting from either endogenous oversecretion or chronic treatment with glucocorticoids at higher than physiologic doses produces a moon-faced plethoric individual with a centripetal distribution of fat (truncal obesity and skinny extremities), thin skin, easy bruising, and striae. Muscle wasting is common, but the heart and diaphragm are usually spared. A test for this syndrome is to ask the patient

Table 35-5 Clinical Features of Hyperadrenalism (Cushing's Syndrome) and Hypoadrenalism

Cushing's Syndrome	Hypoadrenalism
Central obesity	Weight loss
Proximal muscle weakness	Weakness, fatigue, lethargy
Osteopenia at a young age	Muscle and joint pain and back pain
Hypertension	Postural hypotension and dizziness
Headache	Headache
Psychiatric disorders	Anorexia, nausea, abdominal pain, constipation, diarrhea
Purple striae	
Spontaneous ecchymoses	
Plethoric facies	
Hyperpigmentation	Hyperpigmentation
Hirsutism	
Acne	
Hypokalemic alkalosis	Hyperkalemia, hyponatremia
Glucose intolerance	Occasional hypoglycemia
Kidney stones	Hypercalcemia
Polyuria	Prerenal azotemia
Menstrual disorders	
Increased leukocyte count	

to get up from a chair without using the hands. An inability to do so indicates proximal muscle weakness consistent with Cushing's syndrome. These patients often have osteopenia as a result of decreased formation of bone matrix and impaired absorption of calcium. Fluid retention and hypertension (because of increases in renin substrate and vascular reactivity caused by glucocorticoid) are common. Such patients may also have hyperglycemia and even diabetes mellitus from inhibition of peripheral use of glucose, as well as anti-insulin action and concomitant stimulation of gluconeogenesis (Table 35-5).

The most common cause of Cushing's syndrome is the administration of glucocorticoids for such conditions as arthritis, asthma, and allergies.[49] In these conditions, the adrenal glands atrophy and cannot respond to stressful situations (e.g., the preoperative and preprocedure period) by secreting more steroid. Thus, additional glucocorticoids may be required perioperatively (see the later section "Patients Taking Steroids for Other Reasons"). Spontaneous Cushing's syndrome may be caused by pituitary production of ACTH (65% to 75% of all spontaneous cases), which is usually associated with pituitary microadenoma, or by nonendocrine ectopic ACTH production (principally by tumors of the lung, pancreas, or thymus).[50] Ten percent to 20% of cases of spontaneous Cushing's syndrome are caused by an ACTH-independent process, either an adrenal adenoma or carcinoma.

Special preoperative and preprocedure considerations for patients with Cushing's syndrome include regulating diabetes and hypertension and ensuring that intravascular fluid volume and electrolyte concentrations are normal. Ectopic ACTH production may cause marked hypokalemic alkalosis. Treatment with the aldosterone antagonist spironolactone will stop the potassium loss and help mobilize excess fluid. Because of the high incidence of severe osteopenia and the risk of fractures, meticulous attention must be paid to positioning of the patient. In addition, glucocorticoids are lympholytic and immunosuppressive and thus increase the patient's susceptibility to infection. The tensile strength of healing wounds decreases in the presence of glucocorticoids, an effect that is at least partially reversed by the topical administration of vitamin A.

Specific considerations pertain to the surgical approach for each cause of Cushing's syndrome. For example, nearly three fourths of cases of spontaneous Cushing's disease result from a pituitary adenoma that secretes ACTH. One author's (M.F.R.) perioperative treatment of patients who have Cushing's disease and a pituitary microadenoma differs from that of patients who have a pituitary adenoma associated with amenorrhea and galactorrhea. A patient with Cushing's disease is inclined to bleed more easily and (on the basis of anecdotal evidence) tends to have higher central venous pressure (CVP). Thus, during transsphenoidal tumor resection in such patients, the practice is to routinely monitor CVP and maintain it at the low end of the normal range. In other cases of transsphenoidal resection of microadenoma, such monitoring is needed only infrequently.

Ten percent to 15% of patients with Cushing's syndrome exhibit adrenal overproduction of glucocorticoids from an adrenal adenoma or carcinoma. If either unilateral or bilateral adrenal resection is planned, we normally begin administering glucocorticoids at the start of resectioning of the tumor. Despite the absence of definitive studies, we normally give 100 mg of hydrocortisone hemisuccinate or hydrocortisone phosphate every 24 hours intravenously. We reduce this amount over a period of 3 to 6 days until a maintenance dose is reached. Beginning on day 3, the surgeons that we have worked with most also give a mineralocorticoid, 9α-fluorocortisol (0.05 to 0.1 mg/day). In certain patients, both steroids may require several adjustments. This therapy continues if the patient has undergone bilateral resection. For a patient who has undergone unilateral adrenal resection, therapy is individualized according to the status of the remaining adrenal gland. The incidence of pneumothorax in open adrenal resection approaches 20%; the diagnosis of pneumothorax is sought and treatment is begun before the wound is closed. This problem has almost vanished with use of the laparoscopic technique, which means that patients who need open resection merit even closer postoperative scrutiny.

Bilateral adrenalectomy in patients with Cushing's syndrome is associated with a high incidence of postoperative complications and a perioperative mortality rate (greater than that of even cardiac surgery) of 5% to 10%; it often results in permanent mineralocorticoid and glucocorticoid deficiency. Ten percent of patients with Cushing's syndrome who undergo adrenalectomy have an undiagnosed pituitary tumor. After reduction of high levels of cortisol by adrenalectomy, the pituitary tumor enlarges. These pituitary tumors are potentially invasive and may produce large amounts of ACTH and melanocyte-stimulating hormone, thereby increasing pigmentation.

Adrenal tumors are at least 85% incidentalomas—that is, discovered incidentally during screening (and largely unindicated) CT scans. Nonfunctioning adrenal adenomas are found in patients on autopsy, ranging from 1% to 32% in different series. Functioning adenomas are generally treated surgically; often, the

contralateral gland resumes functioning after several months. Frequently, however, the effects of carcinomas are not cured by surgery. In such cases, administration of inhibitors of steroid synthesis, such as metyrapone or mitotane (*o,p′*-DDD[2,2-bis(2-chlorophenyl4-chlorophenyl)-1,1-dichloroethane]), may ameliorate some symptoms but may not improve survival. These drugs and specific aldosterone antagonists may aid in reducing symptoms in the case of ectopic ACTH secretion if the primary tumor proves unresectable. Patients given these adrenal suppressants are also prescribed chronic glucocorticoid replacement therapy (i.e., the goal of therapy is complete adrenal suppression). These patients should be considered to have suppressed adrenal function, and glucocorticoid replacement should be increased perioperatively.

Mineralocorticoid Excess

Excess mineralocorticoid activity (common with glucocorticoid excess because most glucocorticoids have some mineralocorticoid properties) leads to potassium depletion, sodium retention, muscle weakness, hypertension, tetany, polyuria, inability to concentrate urine, and hypokalemic alkalosis. These symptoms constitute primary hyperaldosteronism, or Conn's syndrome (a cause of low-renin hypertension because renin secretion is inhibited by the effects of the high levels of aldosterone).

Primary hyperaldosteronism is present in 0.5% to 1% of hypertensive patients who have no other known cause of hypertension. Primary hyperaldosteronism most often results from unilateral adenoma, although 25% to 40% of patients have been found to have bilateral adrenal hyperplasia. Intravascular fluid volume, electrolyte concentrations, and renal function should be restored to within normal limits preoperatively by administering the aldosterone antagonist spironolactone. The effects of spironolactone are slow in onset and increase for 1 to 2 weeks. A patient who has a serum potassium level of 2.9 mEq/L may have a total-body potassium deficit of as little as 40 mEq or as much as 400 mEq. Frequently, at least 24 hours is required to restore potassium equilibrium. A normal serum potassium level does not necessarily imply correction of a total-body deficit of potassium. In addition, patients with Conn's syndrome have a high incidence of hypertension and ischemic heart disease; hemodynamic monitoring should be appropriate for the degree of cardiovascular impairment.

A retrospective anecdotal study indicated that intraoperative hemodynamic status was more stable when BP and electrolytes were controlled preoperatively with spironolactone than when other antihypertensive drugs were used. However, the efficacy of optimizing the perioperative status of patients who have disorders of glucocorticoid or mineralocorticoid secretion has not been clearly established. We have assumed that gradual restoration of a normal condition is good medicine and that it would decrease perioperative morbidity and mortality.

Adrenocortical Hormone Deficiency

Glucocorticoid Deficiency

Withdrawal of steroids or suppression of synthesis by steroid therapy is the leading cause of underproduction of corticosteroids. Management of this type of glucocorticoid deficiency is discussed in the later section "Patients Taking Steroids for Other Reasons." Other causes of adrenocortical insufficiency include defects in ACTH secretion and destruction of the adrenal gland by autoimmune disease, tuberculosis, hemorrhage, or cancer; some forms of congenital adrenal hyperplasia (see previous discussion); and administration of cytotoxic drugs.

Primary adrenal insufficiency (Addison's disease) is associated with local destruction of all zones of the adrenal cortex and results in both glucocorticoid and mineralocorticoid deficiency if the insufficiency is bilateral; common symptoms and signs are listed in Table 35-5. Autoimmune disease is the most common cause of primary (nonexogenous) bilateral ACTH deficiency in the United States, whereas tuberculosis is the most common cause worldwide. Tuberculosis is associated with decreased adrenal function but large adrenal glands, as is also common in sarcoidosis, histoplasmosis, amyloidosis, metastatic malignancy, and adrenal hemorrhage. Destruction or partial destruction by trauma and by human immunodeficiency virus (HIV) and other infections, such as cytomegalovirus, mycobacteria, and fungi, is being recognized more frequently.

An increasingly common cause of adrenal insufficiency associated with large adrenal glands is heparin-induced thrombocytopenia, which might be considered in every patient who has received heparin and has hypotension.

Autoimmune destruction of the adrenals may be associated with other autoimmune disorders, such as some forms of type 1 diabetes and Hashimoto's thyroiditis. Enzymatic defects in cortisol synthesis also cause glucocorticoid insufficiency, compensatory elevations in ACTH, and congenital adrenal hyperplasia. Because adrenal insufficiency usually develops slowly, such patients are subject to marked pigmentation (from excess ACTH trying to stimulate an unproductive adrenal gland) and cardiopenia (apparently secondary to chronic hypotension).

Secondary adrenal insufficiency occurs when ACTH secretion is deficient, often because of a pituitary or hypothalamic tumor. Treatment of pituitary tumors by surgery or radiation therapy may result in hypopituitarism and subsequent adrenal failure.

If unstressed, glucocorticoid-deficient patients usually have no perioperative problems. However, acute adrenal crisis (addisonian crisis) can occur when even a minor stress is present (e.g., upper respiratory infection). Preparation of such a patient for anesthesia and surgery should include treatment of hypovolemia, hyperkalemia, and hyponatremia. Because these patients cannot respond to stressful situations, it was traditionally recommended that they be given a stress dose of glucocorticoids (about 200 mg hydrocortisone/70 kg body weight/day) perioperatively. However, Symreng and colleagues[51] gave 25 mg of hydrocortisone phosphate intravenously to adults at the start of the operative procedure, followed by 100 mg intravenously over the next 24 hours. Because using the minimum drug dose that would produce an appropriate effect is desirable, this latter regimen seems attractive. Such a regimen has proved to be as successful as a regimen using maximum doses (about 300 mg hydrocortisone per 70 kg body weight per day—see the later section "Patients Taking Steroids for Other Reasons"). Thus, we now recommend giving 100 mg of hydrocortisone phosphate intravenously every 24 hours.

Mineralocorticoid Deficiency

Hypoaldosteronism, a less common condition, can be congenital or can occur after unilateral adrenalectomy or prolonged administration of heparin. In addition, it can also be a consequence of long-standing diabetes and renal failure. Nonsteroidal inhibitors of prostaglandin synthesis may also inhibit renin release and exacerbate this condition in patients with renal insufficiency.

Plasma renin activity is below normal and fails to increase appropriately in response to sodium restriction or diuretic drugs. Most symptoms are caused by hyperkalemic acidosis rather than hypovolemia; in fact, some patients are hypertensive. These patients can have severe hyperkalemia, hyponatremia, and myocardial conduction defects. These defects can be treated successfully by administering mineralocorticoids (9α-fluorocortisol, 0.05 to 0.1 mg/day) preoperatively. Doses must be carefully titrated and monitored to avoid an increase in hypertension.

Patients Taking Steroids for Other Reasons

Perioperative Stress and the Need for Corticoid Supplementation

Many experimental studies and other reports (mostly anecdotal) concerning the adrenal responses of normal patients to the perioperative period, as well as the responses of patients taking steroids for other diseases, indicate the following:

1. Perioperative stress is related to the degree of trauma and the depth of anesthesia. Deep general or regional anesthesia causes the usual intraoperative glucocorticoid surge to be postponed to the postoperative period.
2. A few patients with suppressed adrenal function will have perioperative cardiovascular problems if they do not receive supplemental steroids perioperatively.
3. Although on occasion a patient who chronically takes steroids becomes hypotensive perioperatively, only rarely has this event been documented sufficiently to implicate glucocorticoid or mineralocorticoid deficiency as the cause.
4. Acute adrenal insufficiency occurs only rarely but can be life-threatening.
5. There is little risk in giving these patients steroid coverage equivalent to 100 mg of hydrocortisone hemisuccinate perioperatively.

In a well-controlled study of glucocorticoid replacement in primates, the investigators clearly defined the life-threatening events that can be associated with inadequate perioperative corticosteroid replacement.[48] This study further defined the physiologic and hemodynamic consequences of inadequate cortisol replacement; an alternative dose regimen is suggested that has stood the test of a decade and has altered management methods to possibly improve patient safety. In this study, adrenalectomized primates and sham-operated controls were maintained on physiologic doses of steroids for 4 months. The animals were then randomly allocated to groups that received subphysiologic (a 10th of the normal cortisol production), physiologic, or supraphysiologic (10 times the normal cortisol production) doses of cortisol for 4 days preceding abdominal surgery (cholecystectomy). Hemodynamic variables were measured by means of arterial and pulmonary artery catheters. The animals were maintained on their randomized dosage schedules during and after surgery. The group given subphysiologic doses of steroid perioperatively had a significant increase in postoperative mortality. Death rates for the physiologic and supraphysiologic replacement groups were the same and did not differ from the rate for sham-operated controls. Death in the subphysiologic replacement group was related to severe hypotension associated with a significant decrease in systemic vascular resistance and a reduced left ventricular stroke work index. Filling pressures of the heart were unchanged when compared with those in control animals. There was no evidence of hypovolemia or severe CHF. Despite the low systemic vascular resistance, the animals did not become tachycardic. All these responses are compatible with the previously documented interaction of glucocorticoids and catecholamines and thus suggest that glucocorticoids mediate catecholamine-induced increases in cardiac contractility and maintenance of vascular tone.

The investigators used a sensitive measure of wound healing involving accumulation of hydroxyproline. All treatment groups, including the group given supraphysiologic doses of glucocorticoids, had the same capacity for wound healing. Furthermore, perioperative administration of supraphysiologic doses of corticosteroids produced no adverse metabolic consequences.

This well-conducted study confirms several long-standing intuitive impressions concerning patients who have inadequate adrenal function as a result of either underlying disease or administration of exogenous steroids. Inadequate replacement of corticosteroids perioperatively can lead to addisonian crisis and death. Administration of supraphysiologic doses of steroids for a short time perioperatively caused no discernible complications. However, at least theoretical negative consequences can occur when large doses of steroids are given (see later). It is clear that inadequate corticosteroid coverage can cause death. What is not so clear is what dose of steroid should be recommended for replacement therapy. The authors of the previously discussed study on monkeys were reluctant to recommend simple physiologic steroid replacement doses for human patients perioperatively.[48] We never supplement perioperatively with a dose lower than what the patient has already been receiving.

Which patients definitely need supplementation? If in doubt, how can a patient's need for glucocorticoid supplementation be determined? Because the risk is low, we normally provide supplementation for any patient who has received steroids within a year.[48,51] Data indicate that topical application of steroids (even without the use of occlusive dressings) can suppress normal adrenal responses for as long as 9 months to 1 year (Table 35-6).

How can one determine when adrenal responsiveness has returned to normal? The morning plasma cortisol level does not reveal whether the adrenal cortex has recovered sufficiently to ensure that cortisol secretion will increase adequately to meet the demands of stress. Inducing hypoglycemia with insulin has been advocated as a sensitive test of pituitary-adrenal competence but is impractical and probably a more dangerous practice than simply administering glucocorticoids. If the plasma cortisol concentration is measured during acute stress, a value of greater than 25 μg/dL assuredly (and a value >15 μg/dL probably) indicates normal pituitary-adrenal responsiveness. In another test of pituitary-adrenal sufficiency, the baseline plasma cortisol level is determined. Then, 250 μg of synthetic ACTH (cosyntropin) is given, and plasma cortisol is measured 30 to 60 minutes later. An increase in plasma cortisol of 6 to 20 μg/dL or more is normal.[52,53] A normal response indicates recovery of pituitary-adrenal axis function. A lesser response usually indicates pituitary-adrenal insufficiency, possibly requiring perioperative supplementation with steroids.

It is unusual for laboratory data defining pituitary-adrenal adequacy to be available before surgery. Rather than delay surgery or test most patients, we assume that any patient who has taken steroids at any time during the preceding year has sup-

Table 35-6 Recovery of Hypothalamic-Pituitary-Adrenal Function after Withdrawal of Steroids

Recovery Time (mo)	Plasma 17-Hydroxycorticoid Values	Plasma ACTH Values	Adrenal Response to Exogenous ACTH	Response to Metyrapone
1	Low*	Low	Low	Low
2-5	Low	High†	Low	Low
6-9	Normal	Normal	Low	Low
>9	Normal	Normal	Normal	Normal

*Various subjective manifestations of mild adrenal insufficiency occur during this stage.
†The diurnal rhythm of plasma concentrations is qualitatively normal during this stage.
ACTH, adrenocorticotropic hormone.
Data from Graber AL, Ney RI, Nicholson WE, et al: Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids. J Clin Endocrinol Metab 25:11, 1965.

pressed pituitary-adrenal function and will require perioperative supplementation.

Under perioperative conditions, the adrenal glands secrete 116 to 185 mg of cortisol daily. Under maximum stress, they may secrete 200 to 500 mg/day. Good correlation exists between the severity and duration of the operation and the response of the adrenal gland. "Major surgery" would be represented by procedures such as laparoscopic colectomy and "minor surgery" by procedures such as herniorrhaphy. In one study of 20 patients during major surgery, the mean maximal concentration of cortisol in plasma was 47 µg/dL (range, 22 to 75 µg/dL). Values remained above 26 µg/dL for a maximum of 72 hours after surgery. During minor surgery, the mean maximal concentration of cortisol in plasma was 28 µg/dL (range, 10 to 44 µg/dL).

Although the precise amount required has not been established, we usually intravenously administer the maximum amount of glucocorticoid that the body manufactures in response to maximal stress (i.e., approximately 200 mg/day of hydrocortisone phosphate per 70 kg body weight). For minor surgical procedures, we usually give hydrocortisone phosphate intravenously, 100 mg/day per 70 kg body weight. Unless infection or some other perioperative complication develops, we decrease this dose by approximately 25% per day until oral intake can be resumed. At this point, the usual maintenance dose of glucocorticoids can be administered.

Risks of Supplementation

Rare complications of perioperative steroid supplementation include aggravation of hypertension, fluid retention, inducement of stress ulcers, and psychiatric disturbances. Although data are not available to assess the incidence of the following risks, two common complications of short-term perioperative supplementation with glucocorticoids are described in the literature: abnormal wound healing and an increased rate of infections. This evidence is inconclusive, however, because it relates to acute glucocorticoid administration and not to chronic administration of glucocorticoids with increased doses at times of stress. In contrast to some studies that suggest a deleterious effect of perioperative glucocorticoid administration on wound healing in rats, a study involving primates suggests that high doses of glucocorticoids, administered perioperatively, do not impair sensitive measures of wound healing.[48] Other data are not conclusive regarding a short-term increase in supplementation. However, an overall assessment of these results suggests that short-term perioperative supplementation with steroids has a small, but definite deleterious effect on wound healing that is perhaps partially reversed by topical administration of vitamin A.

Information regarding the risk of infection from perioperative glucocorticoid supplementation is also unclear. In many studies of chronic patient use and supplementation, no increased risk of serious infections was reported with chronic use alone. Data indicate that the risk of infection in a patient chronically taking steroids is real, but these data are inadequate to conclude that perioperative supplementation with steroids increases that risk.

Adrenal Cortex Function in the Elderly

Production of androgens by the adrenal gland progressively decreases with age (also see Chapter 71). This decrease in androgen activity has no known implications for anesthesia. Plasma levels of cortisol are unaffected by increasing age. Levels of CBG are also unaffected by age, which suggests that a normal fraction of free cortisol (1% to 5%) is present in elderly patients. Several investigators have noted a progressively impaired ability of aged patients to metabolize and excrete glucocorticoids. In normal individuals, the quantity of 17-hydroxycorticosteroids excreted is reduced by half by the seventh decade. This decreased excretion undoubtedly reflects the reduced renal function that occurs with aging. When excretion of cortisol metabolites is expressed as a function of creatinine clearance, the age difference disappears. Further reductions in cortisol clearance may be due to impaired hepatic metabolism of circulating cortisol.

The rate of secretion of cortisol is 30% lower in the elderly. This reduced secretion may be an appropriate compensatory mechanism for maintaining a normal cortisol level in the face of decreased hepatic and renal clearance of cortisol. It is important to the anesthesiologist that the reduced cortisol production can be overcome during periods of stress and that even the very elderly (those older than 100 years) display an entirely normal adrenal response to the administration of ACTH and to stresses such as hypoglycemia.

Both underproduction and overproduction of glucocorticoids are generally considered diseases of younger individuals. The highest incidence of Cushing's disease of either pituitary or adrenal origin occurs during the third decade of life. The most common cause of spontaneous Cushing's disease is benign pituitary adenoma. However, in patients older than 60 years in whom Cushing's disease develops, the most likely cause is adrenal carcinoma or ectopic ACTH production from tumors usually located in the lung, pancreas, or thymus.

Adrenal Medullary Sympathetic Hormone Excess: Pheochromocytoma

Less than 0.1% of all cases of hypertension are caused by pheochromocytomas, or catecholamine-producing tumors derived from chromaffin tissue.[54] Nevertheless, these tumors are clearly important to the anesthetist inasmuch as 25% to 50% of hospital deaths in patients with pheochromocytoma occur during induction of anesthesia or during operative procedures for other causes.[55] Though usually found in the adrenal medulla, these vascular tumors can occur anywhere, such as in the right atrium, the spleen, the broad ligament of the ovary, or the organs of Zuckerkandl at the bifurcation of the aorta. Malignant spread, which occurs in less than 15% of pheochromocytomas, usually proceeds to venous and lymphatic channels with a predisposition for the liver. This tumor is occasionally familial or part of the pluriglandular-neoplastic syndrome known as multiple endocrine adenoma type IIa or type IIb and is manifested as an autosomal dominant trait. Type IIa consists of medullary carcinoma of the thyroid, parathyroid adenoma or hyperplasia, and pheochromocytoma. What used to be called type IIb is now often called pheochromocytoma in association with phakomatoses such as von Recklinghausen's neurofibromatosis and von Hippel-Lindau disease with cerebellar hemangioblastoma. Frequently, bilateral tumors are found in the familial form. Localization of tumors can be achieved by MRI or CT, metaiodobenzylguanidine (MIBG) nuclear scanning, ultrasonography, or intravenous pyelography (in decreasing order of combined sensitivity and specificity).

Symptoms and signs that may be solicited before surgery or procedures and are suggestive of pheochromocytoma are excessive sweating; headache; hypertension; orthostatic hypotension; previous hypertensive or arrhythmic response to induction of anesthesia or to abdominal examination; paroxysmal attacks of sweating, headache, tachycardia, and hypertension; glucose intolerance; polycythemia; weight loss; and psychological abnormalities. In fact, the occurrence of combined symptoms of paroxysmal headache, sweating, and hypertension is probably a more sensitive and specific indicator than any one biochemical test for pheochromocytoma (Table 35-7). Despite more than 2000 articles in the literature about pheochromocytoma, little is known about what factors in care affect perioperative morbidity.[56,57]

Although no controlled, randomized, prospective clinical studies have investigated the value of preoperative and preprocedure use of adrenergic receptor blocking drugs, the use of such drugs is generally recommended before surgery. These drugs probably reduce the complications of hypertensive crisis, the wide BP fluctuations during manipulation of the tumor (especially until venous drainage is obliterated), and the myocardial dysfunction that occurs perioperatively. A reduction in mortality associated with resection of pheochromocytoma (from 40% to 60% to the current 0% to 6%) occurred when α-adrenergic receptor blockade was introduced as preoperative and preprocedure preparatory therapy for such patients.[56-60]

α-Adrenergic receptor blockade with prazosin or phenoxybenzamine restores plasma volume by counteracting the vasoconstrictive effects of high levels of catecholamines. This re-expansion of fluid volume is often followed by a decrease in hematocrit. Because some patients may be very sensitive to the effects of phenoxybenzamine, it should initially be given in doses of 20 to 30 mg/70 kg orally once or twice a day. Most patients usually require 60 to 250 mg/day. The efficacy of therapy should be judged by the reduction in symptoms (especially sweating) and stabilization of BP. For patients who have carbohydrate intolerance because of inhibition of insulin release mediated by α-adrenergic receptor stimulation, α-adrenergic receptor blockade may reduce fasting blood sugar levels. For patients who exhibit ST-T changes on the ECG, long-term preoperative and preprocedure α-adrenergic receptor blockade (1 to 6 months) has produced ECG and clinical resolution of catecholamine-induced myocarditis.[56,57,59-63]

β-Adrenergic receptor blockade with propranolol is suggested for patients who have persistent arrhythmias or tachycardia[56,57,59-63] because these conditions can be precipitated or aggravated by α-adrenergic receptor blockade. β-Adrenergic receptor blockade should not be used without concomitant α-adrenergic receptor blockade lest the vasoconstrictive effects of the latter go unopposed and thereby increase the risk for dangerous hypertension.

The optimal duration of preoperative therapy with phenoxybenzamine has not been studied. Most patients require 10 to 14 days, as judged by the time needed to stabilize BP and ameliorate symptoms. On the basis of our experience, this is a minimal period.[59,60,63] Because the tumor spreads slowly, little is lost by waiting until medical therapy has optimized the patient's preop-

Table 35-7 Characteristics of Tests for Pheochromocytoma

			Likelihood Ratio	
Test/Symptoms	**Sensitivity (%)**	**Specificity (%)**	**Positive Result***	**Negative Result†**
Vanillylmandelic acid excretion	81	97	27.0	0.20
Catecholamine excretion	82	95	16.4	0.19
Metanephrine excretion	83	95	16.6	0.18
Abdominal computed tomography	92	80	4.6	0.10
Concurrent paroxysmal hypertension, headache, sweating, and tachycardia‡	90	95	18.0	0.10

*The ratio representing the likelihood of a positive result is obtained by dividing the sensitivity by 1 and then subtracting the specificity.
†The ratio representing the likelihood of a negative result is obtained by subtracting the sensitivity from 1 and then dividing by the specificity.
‡Data for concurrent paroxysmal symptoms are best estimates from available data.
Modified from Pauker SG, Kopelman RI: Interpreting hoofbeats: Can Bayes help clear the haze? N Engl J Med 327:1009, 1992.

erative condition. Accordingly, we recommend using the following criteria:

1. No in-hospital BP reading higher than 165/90 mm Hg should be evident for 48 hours before surgery. We often measure arterial BP every minute for 1 hour in a stressful environment (our postanesthesia care unit). If no BP reading is greater than 165/90, this criterion is considered satisfied.
2. Orthostatic hypotension should be present, but BP on standing should not be lower than 80/45 mm Hg.
3. The ECG should be free of ST-T changes that are not permanent.
4. No more than one premature ventricular contraction (PVC) should occur every 5 minutes.

Other drugs, including prazosin, calcium channel blocking drugs, clonidine, dexmedetomidine, and magnesium, have also been used to achieve suitable degrees of α-adrenergic blockade before surgery.

Although specific anesthetic drugs have been recommended, we believe that optimal preoperative preparation, gentle induction of anesthesia, and good communication between the surgeon and anesthesiologist are most important. Virtually all anesthetic drugs and techniques (including isoflurane, sevoflurane, sufentanil, remifentanil, fentanyl, and regional anesthesia) have been used with success. In fact, all drugs studied are associated with a high rate of transient intraoperative arrhythmias.[59] One author (M.F.R.) has avoided desflurane because it may precipitate non-neurogenic catecholamine release. No good data indicate that these biases are appropriate.

Because of ease of use, there is a preference to give phenylephrine hydrochloride (Neo-Synephrine) or dopamine for hypotension and nitroprusside for hypertension. Phentolamine (Regitine) has too long an onset and duration of action. Occasionally (five times in >80 pheochromocytoma resections), we have used a β-adrenergic blocking agent (esmolol is now the preferred agent) for severe tachycardia without hypertension or volume depletion. Painful or stressful events such as intubation often cause an exaggerated stress response in less than perfectly anesthetized patients who have pheochromocytoma. This response is caused by release of catecholamines from nerve endings that are "loaded" by the reuptake process. Such stresses may result in catecholamine levels of 200 to 2000 pg/mL in normal patients. For a patient with pheochromocytoma, even simple stress can lead to blood catecholamine levels of 2000 to 20,000 pg/mL. However, infarction of a tumor, with release of products onto peritoneal surfaces, or surgical pressure causing release of products can result in blood levels of 200,000 to 1,000,000 pg/mL—a situation that should be anticipated and avoided (ask for a temporary stay of surgery, if at all possible, while the rate of nitroprusside infusion is increased). Once the venous supply is secured and if intravascular volume is normal (as measured by pulmonary wedge pressure or echocardiography), normal BP usually results. However, some patients become hypotensive and occasionally require massive infusions of catecholamines. On rare occasion, patients remain hypertensive intraoperatively. Postoperatively, about 50% remain hypertensive for 1 to 3 days—and initially have markedly elevated but declining plasma catecholamine levels—at which time all but 25% become normotensive. It is important to interview other family members and perhaps advise them to inform their future anesthetist about the potential for such familial disease.

Hypofunction or Aberration in Function of the Sympathetic Nervous System (Dysautonomia)

Disorders of the sympathetic nervous system include Shy-Drager syndrome, Riley-Day syndrome, Lesch-Nyhan syndrome, Gill's familial dysautonomia, diabetic dysautonomia, and the dysautonomia of spinal cord transection.

Although individuals can function well without an adrenal medulla, a deficient peripheral sympathetic nervous system occurring late in life poses major problems for many facets of life; nevertheless, perioperative sympathectomy or its equivalent has been recommended by some.[64-70] A primary function of the sympathetic nervous system appears to be regulation of BP and intravascular fluid volume during changing of body position. Common features of all the syndromes of hypofunctioning of the sympathetic nervous system are orthostatic hypotension and decreased beat-to-beat variability in heart rate. These conditions can be caused by deficient intravascular volume, deficient baroreceptor function (as also occurs in carotid artery disease[71]), abnormalities in CNS function (as in Wernicke or Shy-Drager syndrome), deficient neuronal stores of norepinephrine (as in idiopathic orthostatic hypotension[72] and diabetes), or deficient release of norepinephrine (as in traumatic spinal cord injury[73]). These patients may have an increased number of available adrenergic receptors (a compensatory response) and an exaggerated response to sympathomimetic drugs. In addition to other abnormalities, such as retention of urine or feces and deficient heat exchange, hypofunctioning of the sympathetic nervous system is often accompanied by renal amyloidosis. Thus, electrolyte and intravascular fluid volume status should be evaluated preoperatively. Because many of these patients have cardiac abnormalities, intravascular fluid volume might be assessed preoperatively with a Swan-Ganz catheter or intraoperatively via transesophageal echocardiography rather than measurement of CVP.

Inasmuch as functioning of the sympathetic nervous system is not predictable in these patients, we generally use slow, gentle induction of anesthesia and treat sympathetic excess or deficiency by infusing, with careful titration, drugs that directly constrict (phenylephrine) or dilate (nitroprusside) blood vessels or that stimulate (isoproterenol) or depress (esmolol) the heart rate. We prefer these drugs to agonists or antagonists, which may indirectly release catecholamines. A 20% perioperative mortality rate for 2600 patients after spinal cord transection has been reported, thus indicating that such patients are difficult to manage and deserve particularly close attention.

After reviewing 300 patients with spinal cord injuries, Kendrick and coworkers[74] concluded that autonomic hyperreflexia syndrome does not develop if the lesion is below spinal dermatome T7. If the lesion is above that level (splanchnic outflow), 60% to 70% of patients experience extreme vascular instability. The trigger to this instability, or a mass reflex involving noradrenergic and motor hypertonus,[75] can be a cutaneous, proprioceptive, or visceral stimulus (a full bladder is a common initiator). The sensation enters the spinal cord and causes a spinal reflex, which in normal persons is inhibited from above. Sudden increases in

Table 35-8 Biochemical Measurements of Thyroid Function That Account for Variation in Production of Thyroid-Binding Globulin

	Examples of Normal Thyroid Status					
	FT_4E	=	**T_4**	×	**THBR**	**TSH**
Normal	0.19 (0.12-0.25)	=	0.6 (0.4-0.9)	×	31% (25%-35%)	0.2 (0.2-0.8)
During use of oral contraceptives	0.19	=	1.3	×	15%	0.3
During use of corticosteroids	0.18	=	0.3	×	60%	0.3

FT_4E is the free T_4 (thyroxine) estimate. It is usually obtained by multiplying the total T_4 concentration (the free amount and the amount bound to protein) by the thyroid hormone–binding ratio (THBR, formerly called the resin T_3 uptake). THBR is a measure of the bound thyroid hormone–binding protein. TSH is the thyroid-stimulating hormone secreted by the pituitary in the negative feedback loop. (TSH increases when FT_4E is low in hypothyroidism.)

BP are sensed in the pressure receptors of the aorta and carotid sinus. The resulting vagal hyperactivity produces bradycardia, ventricular ectopia, or various degrees of heart block. Reflex vasodilation may occur above the level of the lesion and result in flushing of the head and neck. Two new techniques to help reduce acute injury or aid in repair (high-dose DHA and acute cooling) may also have anesthetic implications, but reports of these effects, if any, have not been published.

Depending on the length of time since spinal cord transection, other abnormalities may occur. Acutely (i.e., <3 weeks from the time of spinal injury), retention of urine and feces is common and, by elevating the diaphragm, may impair respiration. Disimpaction of the intestine alleviates this respiratory problem. Hyperesthesia is present above the lesion; reflexes and flaccid paralysis are present below the lesion. The intermediate period (3 days to 6 months) is marked by a hyperkalemic response to depolarizing drugs.[76] The chronic phase is characterized by return of muscle tone, a Babinski sign, and frequently, the occurrence of hyperreflexia syndromes (e.g., mass reflex, see earlier).

Thus, in addition to meticulous attention to perioperative intravascular volume and electrolyte status, the anesthesiologist should know—by history taking, physical examination, and laboratory data—the status of the patient's myocardial conduction (as revealed by the ECG), the status of renal functioning (by noting the ratio of creatinine to blood urea nitrogen [BUN]), and the condition of the respiratory muscles (by determining the ratio of forced expiratory volume in 1 second [FEV_1] to forced vital capacity [FVC]) (also see Chapter 44). The anesthesiologist may also obtain a chest radiograph if atelectasis or pneumonia is suspected on the basis of history taking or the physical examination. Temperature control, the presence of bone fractures or decubitus ulcers, and normal functioning of the urination and defecation systems must be assessed. Confirmation of the latter prevents postoperative pneumonia or atelectasis caused by high positioning of the diaphragm.

Thyroid Dysfunction

The major thyroid hormones are thyroxine (T_4), a prohormone product of the thyroid gland, and the more potent 3,5,3-triiodothyronine (T_3), a product of both the thyroid and extrathyroidal enzymatic deiodination of T_4. Under normal circumstances, approximately 85% of T_3 is produced outside the thyroid gland. Production of thyroid secretions is maintained by secretion of thyroid-stimulating hormone (TSH) in the pituitary, which in turn is regulated by secretion of thyrotropin-releasing hormone (TRH) in the hypothalamus. Secretion of TSH and TRH appears to be negatively regulated by T_4 and T_3. Many believe that all effects of thyroid hormones are mediated by T_3 and that T_4 functions only as a prohormone.

Because T_3 has greater biologic effect than T_4 does, one would expect the diagnosis of thyroid disorders to be based on levels of T_3. However, this is not usually the case. The diagnosis of thyroid disease is confirmed by one of several biochemical measurements: levels of free T_4 or total serum concentrations of T_4 and the "free T_4 estimate." This estimate is obtained by multiplying total T_4 (free and bound) by the thyroid-binding ratio (formerly called resin T_3 uptake) (Table 35-8). Free T_4 can be accurately measured by many laboratories. Direct measurement of free T_4 obviates the need to account for changes in binding protein synthesis and affinity caused by other conditions. The T_3-binding ratio measures the extra quantity of serum protein-binding sites. This measurement is necessary because thyroxine-binding globulin (TBG) is abnormally high during pregnancy, hepatic disease, and estrogen therapy (all of which would elevate the total T_4 level) (Box 35-3). Reliable interpretation of measurements of the total hormone concentration in serum necessitates

Box 35-3 Factors Influencing Serum Levels of Thyroxine-Binding Globulin

Conditions Increasing Serum Levels
Use of oral contraceptives
Pregnancy
Use of estrogen
Infectious hepatitis
Chronic active hepatitis
Neonatal state
Acute intermittent porphyria
Inherited conditions

Conditions Decreasing Serum Levels
Testosterone
Use of corticosteroids
Severe illness
Cirrhosis
Nephrotic syndrome
Inherited conditions

data on the percentage of bound hormone. The thyroid hormone–binding ratio test provides this information. In this test, I-labeled T_3 is added to a patient's serum and allowed to reach an equilibrium binding state. A resin is then added that binds the remaining radioactive T_3. Resin uptake is greater if the patient has fewer TBG-binding sites. In normal patients, resin T_3 uptake (the thyroid hormone–binding ratio) is 25% to 35%. When serum TBG is elevated, the thyroid hormone–binding ratio is diminished (see Table 35-8). When serum TBG is diminished, as in nephrotic syndrome, in conditions in which glucocorticoids are increased, or in chronic liver disease, the thyroid hormone–binding ratio is increased.

The free T_4 estimate and the free T_3 estimate are frequently used as measures of a patient's serum T_4 and T_3 hormone concentration. To obtain these estimates, the concentration of total serum T_4 or total serum T_3 is multiplied by the measured thyroid hormone–binding ratio. Values of these two indices are normal in the event of a primary alteration in binding but not with an alteration in secretion of thyroid hormone.

Hyperthyroidism can be diagnosed by measuring levels of TSH after the administration of TRH. Although administering TRH normally increases TSH levels in blood, even a small increase in the T_4 or T_3 level in blood abolishes this response. Thus, a subnormal or absent serum TSH response to TRH is a very sensitive indicator of hyperthyroidism. In one group of disorders involving hyperthyroidism, serum TSH levels are elevated in the presence of elevated levels of free thyroid hormone.

Measurement of the α-subunit of TSH has been helpful in identifying the rare patients who have a pituitary neoplasm and who usually have increased α-subunit concentrations. Some patients are clinically euthyroid in the presence of elevated levels of total T_4 in serum. Certain drugs, notably gallbladder dyes, propranolol, glucocorticoids, and amiodarone, block the conversion of T_4 to T_3, thereby elevating T_4 levels. Severe illness also slows this conversion. Levels of TSH are often high in situations in which the rate of conversion is decreased. In hyperthyroidism, cardiac function and responses to stress are abnormal; return of normal cardiac function parallels the return of TSH levels to normal.

Hyperthyroidism

Although hyperthyroidism is usually caused by the multinodular diffuse enlargement in Graves' disease (also associated with disorders of the skin or eyes, or both), it can also occur with pregnancy, thyroiditis (with or without neck pain), thyroid adenoma, choriocarcinoma, or TSH-secreting pituitary adenoma. Five percent of women have thyrotoxic effects 3 to 6 months postpartum and tend to have recurrences with subsequent pregnancies. Major manifestations of hyperthyroidism are weight loss, diarrhea, warm moist skin, weakness of large muscle groups, menstrual abnormalities, osteopenia, nervousness, jitteriness, intolerance to heat, tachycardia, cardiac arrhythmias, mitral valve prolapse, and heart failure. When the thyroid is functioning abnormally, the entity most threatened is the cardiovascular system. When diarrhea is severe, dehydration should be corrected preoperatively. Mild anemia, thrombocytopenia, increased serum alkaline phosphatase, hypercalcemia, muscle wasting, and bone loss frequently occur in hyperthyroidism. Muscle disease usually involves the proximal muscle groups; it has not been reported to cause respiratory muscle paralysis. In the apathetic form of hyperthyroidism (seen most commonly in persons older than 60 years), cardiac effects dominate the clinical picture. Signs and symptoms include weight loss, anorexia, and cardiac effects such as tachycardia, irregular heart rhythm, atrial fibrillation (in 10%), heart failure, and occasionally, papillary muscle dysfunction.

Although β-adrenergic receptor blockade can control the heart rate, its use is fraught with hazard in a patient already experiencing CHF. However, a decreasing heart rate may improve heart-pumping function. Thus, hyperthyroid patients who have fast ventricular rates, who are in CHF, and who require emergency surgery are given esmolol guided by changes in pulmonary artery wedge pressure and their condition. If slowing the heart rate with a small dose of esmolol (50 μg/kg) does not aggravate the heart failure, we administer more esmolol. We believe that we should aim to avoid imposing surgery on any patient whose thyroid function is clinically abnormal. Therefore, we believe that only "life or death" emergency surgery should preclude making the patient pharmacologically euthyroid, a process that can take 2 to 6 weeks. Evaluation of hyperthyroidism is also covered in Chapter 34. Antithyroid medications include propylthiouracil and methimazole, both of which decrease the synthesis of T_4 and may enhance remission by reducing TSH receptor antibody levels (the primary pathologic mechanism in Grave's disease). Propylthiouracil also decreases the conversion of T_4 to the more potent T_3. However, the literature indicates a trend toward preoperative preparation with propranolol and iodides alone.[77] This approach is quicker (i.e., 7 to 14 days versus 2 to 6 weeks); it shrinks the thyroid gland, as does the more traditional approach; it decreases conversion of the prohormone T_4 into the more potent T_3; and it treats symptoms but may not correct abnormalities in left ventricular function. Regardless of the approach, antithyroid drugs should be administered chronically and on the morning of surgery. If emergency surgery is necessary before the euthyroid state is achieved, if subclinical hyperthyroidism progresses without adequate treatment, or if hyperthyroidism gets out of control during surgery, intravenous administration of esmolol, 50 to 500 μg/kg, could be titrated to restore a normal heart rate (assuming the absence of CHF) (see earlier). In addition, intravascular fluid volume and electrolyte balance should be restored. However, administering propranolol or esmolol does not invariably prevent "thyroid storm."

No controlled study has demonstrated clinical advantages of any anesthetic drug over another for surgical patients who are hyperthyroid. A review of cases performed at the University of California, San Francisco, from 1968 to 1982 revealed that virtually all anesthetic drugs and techniques[78] have been used without adverse effects even remotely being attributable to the drug or technique. Furthermore, although some investigators have recommended that anticholinergic drugs (especially atropine) be avoided inasmuch as they interfere with the sweating mechanism and cause tachycardia, atropine has been given as a test for the adequacy of antithyroid treatment. Because patients are now subjected to operative procedures only (or almost only) when euthyroid, the traditional "steal" of a heavily premedicated hyperthyroid patient (so commonly found in the iodine-deficient locales surrounding the Lahey, Mayo, and Cleveland clinics) in the operating room has vanished.

A patient with a large goiter and an obstructed airway can be handled in the same way as any other patient with problematic airway management. Preoperative medication should avoid excessive sedation, and an airway should be established, often with the patient awake. A firm armored endotracheal tube is preferable

and should be passed beyond the point of extrinsic compression. It is most useful to examine CT scans of the neck preoperatively to determine the extent of compression. Maintenance of anesthesia usually presents little difficulty. Postoperatively, extubation should be performed under optimal circumstances for reintubation in the event that the tracheal rings have been weakened and the trachea collapses.

Of the many possible postoperative complications (nerve injury, bleeding, and metabolic abnormalities), "thyroid storm" (discussed later), bilateral recurrent nerve trauma, and hypocalcemic tetany are the most feared. Bilateral recurrent laryngeal nerve injury (secondary to trauma or edema) causes stridor and laryngeal obstruction as a result of unopposed adduction of the vocal cords and closure of the glottic aperture. Immediate endotracheal intubation is required, usually followed by tracheostomy to ensure an adequate airway. This rare complication occurred only once in more than 30,000 thyroid operations at the Lahey Clinic. Unilateral recurrent nerve injury often goes unnoticed because of compensatory overadduction of the uninvolved cord. However, we often test vocal cord function before and after this surgery by asking the patient to say "e" or "moon." Unilateral nerve injury is characterized by hoarseness and bilateral nerve injury by aphonia. Selective injury to the adductor fibers of both recurrent laryngeal nerves leaves the abductor muscles relatively unopposed, and pulmonary aspiration is a risk. Selective injury to the abductor fibers leaves the adductor muscles relatively unopposed, and airway obstruction can occur. Bullous glottic edema, an additional cause of postoperative respiratory compromise, has no specific cause or known preventive measure.

The intimate involvement of the parathyroid gland with the thyroid gland can result in inadvertent hypocalcemia during surgery for thyroid disease. Complications related to hypocalcemia are discussed in the later section "Hypocalcemia."

Because postoperative hematoma can compromise the airway, neck and wound dressings are placed in a crossing fashion (rather than vertically or horizontally) and should be examined for evidence of bleeding before a patient is discharged from the recovery room.

Thyroid Storm

"Thyroid storm" is the name for the clinical diagnosis of a life-threatening illness in a patient whose hyperthyroidism has been severely exacerbated by illness or surgery. Thyroid storm is characterized by hyperpyrexia, tachycardia, and striking alterations in consciousness. It can thus be manifested very similarly to malignant hyperthermia, pheochromocytoma, or neuroleptic malignant syndrome. No laboratory tests are diagnostic of thyroid storm, and the precipitating (nonthyroidal) cause is the major determinant of survival. Therapy can include blocking the synthesis of thyroid hormones by administering antithyroid drugs, blocking the release of preformed hormone with iodine, meticulous attention to hydration and supportive therapy, and correcting the precipitating cause. Blocking the sympathetic nervous system with reserpine, α- and β-receptor antagonists, or α_2-agents may be exceedingly hazardous and requires skillful management and constant monitoring of the critically ill patient.

Thyroid dysfunction, either hyperthyroidism or hypothyroidism, develops in more than 10% of patients treated with the antiarrhythmic agent amiodarone.[79] Approximately 35% of the drug's weight is iodine, and a 200-mg tablet releases about 20 times the optimal daily dose of iodine. This iodine can lead to reduced synthesis of T_4 or increased synthesis. In addition, amiodarone inhibits the conversion of T_4 to the more potent T_3.

Patients receiving amiodarone might be considered to be in need of special attention preoperatively and may even require special attention to anesthesia, not just because of the arrhythmia that led to such therapy but also to ensure that no perioperative dysfunction or surprises occur because of unsuspected thyroid hyperfunction or hypofunction.[80] Many patients with amiodarone-induced thyrotoxicosis receive steroids for a period, another area of questioning that might be triggered by the use of amiodarone in a preoperative patient.

Hypothyroidism

Hypothyroidism is a common disease that has been detected in 5% of a large population in Great Britain, in 3% to 6% of a healthy older population in Massachusetts, and in 4.5% of a medical clinic population in Switzerland. The apathy and lethargy that often accompany hypothyroidism frequently delay its diagnosis, so the perioperative period may be the first opportunity to spot many such hypothyroid patients. However, hypothyroidism is usually subclinical, serum concentrations of thyroid hormones are in the normal range, and only serum TSH levels are elevated. The normal range of TSH is 0.3 to 4.5 mU/L, and TSH values of 5 to 15 mU/L are characteristic of this entity. In such cases, hypothyroidism may have little or no perioperative significance. However, a retrospective study of 59 mildly hypothyroid patients found that more hypothyroid patients than control subjects required prolonged postoperative intubation (9 of 59 versus 4 of 59) and had significant electrolyte imbalances (3 of 59 versus 1 of 59) and bleeding complications (4 of 59 versus 0 of 59).[81] Because only a small number of charts were examined, these differences did not reach statistical significance. In another study, overt hypothyroidism later developed in a high percentage of patients with a history of subclinical hypothyroidism.[82,83] Thus, a previous history of subclinical hypothyroidism may indicate the need to search for and be concerned about the possibility of overt hypothyroidism.

In the less frequent occurrences of overt hypothyroidism, the relative lack of thyroid hormone results in slow mental functioning, slow movement, dry skin, arthralgias, carpal tunnel syndrome, periorbital edema, intolerance to cold, depression of the ventilatory responses to hypoxia and hypercapnia, impaired clearance of free water with or without hyponatremia, "hung-up reflexes," slow gastric emptying, sleep apnea,[84] and bradycardia. In extreme cases, cardiomegaly, heart failure, and pericardial pleural effusions are manifested as fatigue, dyspnea, and orthopnea. Hypothyroidism is often associated with amyloidosis, which may produce an enlarged tongue, abnormalities of the cardiac conduction system, and renal disease. Hypothyroidism decreases the anesthetic requirement slightly. The tongue may be enlarged in a hypothyroid patient even in the absence of amyloidosis, and such enlargement may hamper endotracheal intubation.

A rising TSH level is the most sensitive indicator of failing thyroid function. Ideal preoperative and preprocedure management of hypothyroidism consists of restoring normal thyroid status: we routinely administer the normal dose of levothyroxine the morning of surgery, even though these drugs have long half-lives (1.4 to 10 days). (Levothyroxin is the preferred therapy because it allows the controlling enzyme systems to regulate TSH secretion, as well as conversion to T_3.) Reduced GI absorption of levothyroxine may occur with the coadministration of cholestyramine or aluminum hydroxide, iron, a high-bran meal, or sucral-

fate or colestipol. For patients in myxedema coma requiring emergency surgery, liothyronine can be given intravenously (with fear of precipitating myocardial ischemia, however) while supportive therapy is undertaken to restore normal intravascular fluid volume, body temperature, cardiac function, respiratory function, and electrolyte balance.

Treating hypothyroid patients with symptomatic coronary artery disease poses special problems and may require compromises in the general practice of preoperatively restoring euthyroidism with drugs. Although both levothyroxine and esmolol may be given, adequate amelioration of both ischemic heart disease and hypothyroidism may be difficult to achieve. The need for thyroid therapy must be balanced against the risk of aggravating the anginal symptoms. One review suggested early consideration of coronary artery revascularization.[85] It advocated initiating thyroid replacement therapy in the ICU soon after the patient's arrival from the operating room and myocardial revascularization surgery. However, several deaths from arrhythmia and CHF, as well as cardiogenic shock with infarction, have occurred while patients who were not given thyroid therapy were awaiting surgery. Thus, true emergency coronary artery revascularization should be considered in patients with both severe coronary artery disease and significant hypothyroidism.

In hypothyroidism, respiratory control mechanisms do not function normally. However, the response to hypoxia and hypercapnia and clearance of free water become normal with thyroid replacement therapy. Drug metabolism is anecdotally reported to be slowed, and awakening times from sedatives are reported to be prolonged during hypothyroidism. However, few formal studies and none in humans of the pharmacokinetics and pharmacodynamics of sedatives or anesthetic drugs have been published. These concerns disappear when thyroid function is normalized preoperatively. Addison's disease (with its relative steroid deficiency) is more common in hypothyroidism, and some endocrinologists routinely treat noniatrogenic hypothyroid patients with stress doses of steroids perioperatively because both conditions are commonly caused by autoimmune responses. The possibility that this steroid deficiency exists should be considered if the patient becomes hypotensive perioperatively. Body heat mechanisms are inadequate in hypothyroid patients, so temperature should be monitored and maintained, especially in patients requiring emergency surgery. Because of an increased incidence of myasthenia gravis in hypothyroid patients, it may be advisable to use a peripheral nerve stimulator to guide administration of muscle relaxants (see Chapter 29).

Thyroid Nodules and Carcinoma

More than 90% of thyroid nodules are benign, yet identifying malignancy in a solitary thyroid nodule is a difficult and important procedure. Male patients and patients with previous radiation therapy to the head and neck have an increased likelihood of malignant disease in their nodules. Often, needle biopsy and scanning are sufficient for the diagnosis, but occasionally, excisional biopsy is needed. Papillary carcinoma accounts for more than 70% of all thyroid carcinomas. Simple excision of lymph node metastases appears to be as efficacious for patient survival as radical neck procedures. Follicular carcinoma accounts for about 15% of thyroid carcinomas, is more aggressive, and has a less favorable prognosis.

Medullary carcinoma, the most aggressive form of thyroid carcinoma, is associated with a familial occurrence of pheochromocytoma, as are parathyroid adenomas. For this reason, a history might be obtained from patients who have a surgical scar in the thyroid region so that the possibility of occult pheochromocytoma can be ruled out.

Disorders of Calcium Metabolism

The three substances that regulate serum concentrations of calcium, phosphorus, and magnesium—parathyroid hormone (parathyrin, PTH), calcitonin, and vitamin D—act on bone, kidney, gut, and their own receptors (the last has led to an important advance in treatment in the last few years). Calcium excess in blood is due to either malignancy or hyperparathyroidism in more than 90% of patients.[86] PTH stimulates bone resorption, inhibits renal excretion of calcium, and increases conversion to active vitamin D, three conditions that lead to hypercalcemia. Calcitonin can be considered an antagonist to PTH. Through its metabolites, vitamin D aids in the absorption of calcium, phosphate, and magnesium from the gut and facilitates the bone resorptive effects of PTH. Secretion of PTH is modulated through the calcium-sensing receptor on the cell surface of parathyroid cells. An increase in ionized calcium stimulates this receptor, which causes a decrease in PTH secretion. Recognition of this effect has led to re-evaluation of the therapy for hyperparathyroidism inasmuch as a drug upregulating this receptor's sensitivity reduces PTH levels and the presence of increased calcium in over 60% of people who have elevated calcium levels from this cause.[87]

Hyperparathyroidism and Hypercalcemia

Primary hyperparathyroidism occurs in about 0.1% of the population, most commonly begins in the third to fifth decades of life, and occurs two to three times more frequently in women than men. Primary hyperparathyroidism usually results from enlargement of a single gland, commonly an adenoma and very rarely a carcinoma. Hypercalcemia almost always develops.

Calcium is the chief mineral component of the body; it provides structure to the skeleton and performs key roles in neural transmission, intracellular signaling, blood coagulation, and neuromuscular functioning. Ninety-nine percent of the 1000 g of calcium present in the average human body is stored in the bone mineral reservoir. The normal total serum calcium level is 8.6 to 10.4 mg/dL, as measured in most laboratories. Fifty percent to 60% is bound to plasma proteins or is complexed with phosphate or citrate. The value is dependent on the albumin level, with a decline of 0.8 mg/dL for each 1-g/dL drop in albumin. Binding of calcium to albumin is dependent on pH: binding decreases with acidic pH and increases with alkaline pH. It should be noted that serum calcium and not ionized calcium decreases with decreases in albumin levels. Although ionized calcium is the clinically significant fraction, the cost and technical difficulties of stabilizing the electrodes used for measurement have limited the available assays. Nevertheless, PTH and vitamin D_3 work to keep the level stable within 0.1 mg/dL in any individual.

Many of the prominent symptoms of hyperparathyroidism are a result of the hypercalcemia that accompanies it. Regardless of the cause, hypercalcemia can produce any of a number of symptoms, the most prominent of which involve the renal, skeletal, neuromuscular, and GI systems—anorexia, vomiting, constipation, polyuria, polydipsia, lethargy, confusion, formation of renal calculi, pancreatitis, bone pain, and psychiatric abnormalities. Free intracellular calcium initiates or regulates muscle con-

traction, release of neurotransmitters, secretion of hormones, enzyme action, and energy metabolism.

Nephrolithiasis occurs in 60% to 70% of patients with hyperparathyroidism. Sustained hypercalcemia can result in tubular and glomerular disorders, including proximal (type II) renal tubular acidosis. Polyuria and polydipsia are common complaints.

Skeletal disorders related to hyperparathyroidism are osteitis fibrosa cystica, simple diffuse osteopenia, and osteoporosis. The rate of bone turnover is five times higher in patients with hyperparathyroidism than in normal controls. Patients may have a history of frequent fractures or complain of bone pain, the latter especially in the anterior margin of the tibia.

Because free intracellular calcium initiates or regulates muscle contraction, neurotransmitter signaling, hormone secretion, enzyme action, and energy metabolism, abnormalities in these end organs are often symptoms of hyperparathyroidism. Patients may experience profound muscle weakness, especially in proximal muscle groups, as well as muscle atrophy. Depression, psychomotor retardation, and memory impairment may occur. Lethargy and confusion are frequent complaints.

Peptic ulcer disease is more common in these patients than in the rest of the population. Production of gastrin and gastric acid is increased. Anorexia, vomiting, and constipation may also be present.

Approximately a third of all hypercalcemic patients are hypertensive, but the hypertension usually resolves with successful treatment of the primary disease. Neither hypertension nor minimally invasive surgery seems to alter the perioperative risk associated with surgery in such patients in comparison to the usual hypertensives.[88,89] Even octogenarians with asymptomatic hyperparathyroidism can be operated on without mortality and with morbidity no different from that in younger individuals, thus encouraging the use of parathyroidectomy as preventive therapy.[89,90] Long-standing hypercalcemia can lead to calcifications in the myocardium, blood vessels, brain, and kidneys. Cerebral calcifications may cause seizures, whereas renal calcifications lead to polyuria that is unresponsive to vasopressin.

The most useful confirmatory test for hyperparathyroidism is a radioimmunoassay for PTH. In fact, two recent changes have radically reduced anesthesia involvement in the care of patients with primary hyperparathyroidism. One, the drug class that modulates the calcium-sensitive PTH cell receptor and thereby decreases calcium levels, the calcimimetics, has been discussed (earlier) and its use emphasized in older individuals (see later). The other is to use minimally invasive approaches after imaging procedures with just local anesthesia or a cervical plexus block—as with thyroidectomy.[91,92] Most surgeons now performing minimally invasive parathyroid removal monitor PTH levels intraoperatively to determine whether they have resected the causative adenoma. In hyperparathyroid patients, hormone levels are abnormal for a given level of calcium. The level of inorganic phosphorus in serum is usually low, but it may be within normal limits. Alkaline phosphatase is elevated if considerable skeletal involvement is present.

Glucocorticoid administration reduces the level of calcium in blood in many other conditions that cause hypercalcemia, but not usually in primary hyperparathyroidism. In sarcoidosis, multiple myeloma, vitamin D intoxication, and some malignant diseases, all of which can cause hypercalcemia, administration of glucocorticoids may lower serum calcium levels through an effect on GI absorption. This effect occurs to a lesser degree in primary hyperparathyroidism.

Hypercalcemia may also occur as a consequence of secondary hyperparathyroidism in patients who have chronic renal disease. When phosphate excretion decreases as a result of lower nephron mass, serum calcium levels fall because of deposition of calcium and phosphate in bone. Secretion of PTH subsequently increases, which causes the fraction of phosphate excreted by each nephron to increase. Eventually, the chronic intermittent hypocalcemia of chronic renal failure leads to chronically high levels of serum PTH and hyperplasia of the parathyroid glands—one of the entities termed secondary hyperparathyroidism.

What should be done for asymptomatic patients with primary hyperparathyroidism or even ones with secondary hyperparathyroidism? This question has become the subject of a major controversy, for which no definitive answer exists. Symptomatic primary hyperparathyroidism in those younger than 50 years or with serum calcium levels more than 1 mg/dL above the upper limit of normal, a 30% or greater reduction in the glomerular filtration rate (GFR), or severe bone demineralization is usually treated surgically. If the patient refuses surgery or if other illnesses make surgery inadvisable, medical management with the new calcimimetic cinacalcet has made management much more feasible. The difficulty with such management is that the hyperfunctioning parathyroid glands secrete more hormone as the serum calcium concentration is lowered—as though the calcium set point for feedback regulation of PTH secretion had been raised.

Patients with moderate hypercalcemia who have normal renal and cardiovascular function present no special preoperative and preprocedure problems. The ECG can be examined preoperatively and intraoperatively for shortened PR or QT intervals (Fig. 35-4). Because severe hypercalcemia can result in hypovolemia, normal intravascular volume and electrolyte status should be restored before commencement of anesthesia and surgery.

Management of hypercalcemia preoperatively should include (even in urgent or emergency situations) treatment of the underlying cause—a frequent strategy in malignancy-associated hypercalcemic patients coming to surgery. Antitumor therapy preoperatively for both malignant and nonmalignant causes of hypercalcium can include hydration and diuresis to increase urinary calcium excretion. Restoration of intravascular volume, augmentation and excretion of urinary sodium (with saline infusion), and administration of diuretics (furosemide is commonly used) generally increase urinary calcium excretion substantially. Infusion rates of 200 to 400 mL/hr preoperatively are commonly used, but monitoring is needed to avoid fluid overload, especially since many patients have compromised cardiac pumping ability. Other complications of these interventions include hypomagnesemia and hypokalemia.

In emergency situations, vigorous expansion of intravascular volume usually reduces serum calcium to a safe level (<14 mg/dL); administration of furosemide is also often helpful in these situations. Phosphate should be given to correct hypophosphatemia because it decreases calcium uptake into bone, increases calcium excretion, and stimulates breakdown of bone. Hydration and diuresis, accompanied by phosphate repletion, suffice in the management of most hypercalcemic patients. Other measures to decrease reabsorption of bone include the bisphosphonates pamidronate sodium (90 mg intravenously) and zoledronate

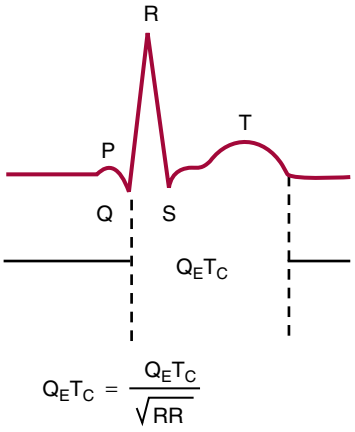


Figure 35-4 Measurement of the QTc interval (properly termed Q_ET_c to indicate that it begins with the start of the Q wave, lasts throughout the QT interval, ends with the end of the T wave, and is corrected for heart rate). RR is the RR interval in seconds. *(From Hensel P, Roizen MF: Patients with disorders of parathyroid function. Anesthesiol Clin North Am 5:287, 1987.)*

(4 mg intravenously), salmon calcitonin (100 to 400 units every 12 hours), and plicamycin (15 to 25 µg/kg intravenously).

Calcitonin lowers serum calcium levels through direct inhibition of bone resorption. It can decrease serum calcium levels within minutes after intravenous administration. Side effects include urticaria and nausea. It is so rapid acting that it can be used to reduce calcium levels while waiting for hydration and a bisphosphonate to take effect. Dialysis can also be used when appropriate.

It is especially important to know whether the hypercalcemia has been chronic because serious cardiac, renal, or CNS abnormalities may have resulted.

Hypocalcemia

Hypocalcemia (caused by hypoalbuminemia, hypoparathyroidism, hypomagnesemia, hypovitaminosis D, hungry bones after correction of hyperparathyroidism, anticonvulsant therapy, citrate infusion, or chronic renal disease) is not usually accompanied by a clinically evident cardiovascular disorder. The most common cause of hypocalcemia is hypoalbuminemia. In true hypocalcemia (i.e., when the free calcium concentration is low), myocardial contractility is affected. That is, myocardial contractility varies directly with levels of blood ionized calcium, although contractility decreased only 20% when ionized calcium levels changed from 1.68 to 1.34 mmol/L. The clinical signs of hypocalcemia are clumsiness; convulsions; laryngeal stridor; depression; muscle stiffness; paresthesia (oral and perioral); parkinsonism; tetany; Chvostek's sign; dry scaly skin, brittle nails, and coarse hair; low serum concentrations of calcium; prolonged QT intervals; soft tissue calcifications; and Trousseau's sign.

Hypocalcemia delays ventricular repolarization, hence increasing the QTc interval (normal, 0.35 to 0.44 second). With electrical systole prolonged, the ventricles may fail to respond to the next electrical impulse from the sinoatrial node, and a 2:1 heart block results. Prolongation of the QT interval is a moderately reliable ECG sign of hypocalcemia, not for the population as a whole, but for the individual patient.[93] Thus, monitoring the QT interval as corrected for the heart rate (see Fig. 35-4) is a useful, but not always accurate means of monitoring hypocalcemia in any individual patient. CHF may also occur with hypocalcemia, but this is rare. Because CHF in patients with coexisting heart disease is reduced in severity when calcium and magnesium ion levels are restored to normal, these levels may be normalized before surgery in a patient with impaired exercise tolerance or signs of cardiovascular dysfunction; normalization can be achieved intravenously over a 15-minute period if absolutely necessary.[94,95] Sudden decreases in blood levels of ionized calcium (as with chelation therapy) can result in severe hypotension.

Patients with hypocalcemia may have seizures. They may be focal, jacksonian, petit mal, or grand mal in appearance, indistinguishable from such seizures in the absence of hypocalcemia. Patients may also have a type of seizure called cerebral tetany, which consists of generalized tetany followed by tonic spasms. Therapy with standard anticonvulsants is ineffective and may even exacerbate these seizures (by an anti–vitamin D effect). In long-standing hypoparathyroidism, calcifications may appear above the sella; these calcifications represent deposits of calcium in and around small blood vessels of the basal ganglia. They may be associated with a variety of extrapyramidal syndromes.

The most common cause of acquired hypoparathyroidism is surgery on the thyroid or parathyroid glands. Other causes include autoimmune disorders, therapy with iodine 131, hemosiderosis or hemochromotosis, neoplasia, and granulomatous disease. Idiopathic hypoparathyroidism has been divided into three categories: an isolated persistent neonatal form, branchial dysembryogenesis, and autoimmune candidiasis related to multiple endocrine deficiency.

Pseudohypoparathyroidism and pseudopseudohypoparathyroidism are rare hereditary disorders characterized by short stature, obesity, rounded face, and shortened metacarpals. Patients with pseudohypoparathyroidism have hypocalcemia and hyperphosphatemia despite high serum levels of PTH. These patients have a deficient end-organ response to PTH as a result of abnormalities in G-protein function.

Because treatment of hypoparathyroidism is not surgical, hypoparathyroid patients who come to the operating room are those who require surgery for an unrelated condition. Their calcium, phosphate, and magnesium levels should be measured both preoperatively and postoperatively. Patients with symptomatic hypocalcemia might be treated with intravenous calcium gluconate before surgery. Initially, 10 to 20 mL of 10% calcium gluconate may be given at a rate of 5 mL/min. The effect on serum calcium levels is of short duration, but a continuous infusion with 10 mL/min of 10% calcium gluconate in 500 mL of solution over a period of 6 hours helps keep serum calcium at adequate levels. Magnesium and phosphate levels may require normalization as well to normalize cardiovascular and nervous system function.

The objective of therapy is to bring the symptoms under control before surgery and anesthesia. For patients with chronic hypoparathyroidism, the objective is to keep the serum calcium level in the lower half of the normal range. A preoperative and preprocedure ECG is useful for maintaining the QTc interval. The preoperative and preprocedure QTc value may be used as a guide to the serum calcium level if rapid laboratory assessment is not possible. Changes in the calcium level may alter the duration of muscle relaxation, so such alterations might be monitored by using a twitch monitor in these (as well as all other) patients.

The intimate involvement of the parathyroid gland with the thyroid gland can result in unintentional hypocalcemia during

surgery for diseases of either organ. Because of the affinity of their bones for calcium, this relationship is crucial in patients with advanced osteitis. Internal redistribution of magnesium, calcium, or both ions may occur (into "hungry bones") after parathyroidectomy and cause hypomagnesemia, hypocalcemia, or both conditions. Because the tendency to tetany increases with alkalosis, hyperventilation is usually assiduously avoided. The most prominent manifestations of acute hypocalcemia are distal paresthesias and muscle spasm (tetany). Potentially fatal complications of severe hypocalcemia include laryngeal spasm and hypocalcemic seizures. The clinical sequelae of magnesium deficiency include cardiac arrhythmias (principally ventricular tachyarrhythmias), hypocalcemic tetany, and neuromuscular irritability independent of hypocalcemia (tremors, twitching, asterixis, and seizures).

In addition to monitoring total serum calcium or ionized calcium postoperatively, one can test for the Chvostek and Trousseau signs. (Note that serum calcium and not ionized calcium is dependent on the albumin level, with a decline of about 0.8 mg/dL for each 1-g/dL drop in serum albumin level.) Because the Chvostek sign can be elicited in 10% to 15% of patients who are not hypocalcemic, an attempt should be made to elicit it preoperatively to ensure that its appearance is meaningful. The Chvostek sign is a contracture of the facial muscles produced by tapping the ipsilateral facial nerves at the angle of the jaw. The Trousseau sign is elicited by applying a BP cuff at a level slightly above the systolic level for a few minutes. The resulting carpopedal spasm, with contraction of the fingers and inability to open the hand, stems from the increased muscle irritability in hypocalcemic states, aggravated by ischemia produced by the BP cuff.

Osteoporosis

Fifty percent of women older than 65 years sustain an osteoporotic fracture. (Because men are living longer, osteoporosis has become an increasing problem for them too, and recent reports indicate a 15% per decade hip fracture rate for men older than 65 years).[93] Men with COPD (even without steroid treatment) are at high risk for vertebral fractures and thus might be allowed to position and move themselves onto and off surgical tables. Furthermore, in either gender, each vertebral fracture is associated with a 10% decrease in lung capacity. Diagnosis and treatment of these conditions have increased with routine use of dual-energy x-ray absorptiometry (DEXA) or quantitative ultrasonography. Because "T" and "Z" scores were developed to relate changes in white postmenopausal women to those at age 21, care must be used in interpreting the results. Known risk factors include age, relative lifetime estrogen deficiency (late menarche, amenorrhea, early menopause, nulliparity), deficiency of dietary calcium, tobacco use, increased aerobic exercise in combination with decreased weight-bearing exercise, decreased weight-bearing exercise by itself, use of soft drinks, and Asian or white ancestry. Although therapy for osteoporosis (use of biphosphates, bone mineral depositors, weight-bearing exercises, calcium, vitamin D, estrogen, and now designer estrogens that may be useful for men such as Evista) does not have major known implications for anesthesia care,[96-98] bone fractures in such patients have occurred on movement to and from an operating table. Recombinant PTH and calcitonin are also used, but again, no reports of perioperative interactions have been prominent. Thus, the precautions mentioned earlier for hyperparathyroid patients relative to self-positioning and careful positioning may be useful.

Pituitary Abnormalities

Anterior Pituitary Hypersecretion

The anterior pituitary gland (or master endocrine gland) consists of five identifiable types of secretory cells (and the hormones that they secrete): somatotrophs (GH), corticotrophs (ACTH), lactotrophs (prolactin), gonadotrophs (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), and thyrotrophs (TSH). Secretion of these pituitary hormones is largely regulated by a negative-feedback loop by hypothalamic regulatory hormones and by signals that originate from the target site of pituitary action. Six hypothalamic hormones have been characterized: dopamine, the prolactin-inhibiting hormone; somatostatin, the GH release– inhibiting hormone; GH-releasing hormone (GHRH); corticotropin-releasing hormone (CRH); gonadotropin-releasing hormone (GnRH or LHRH); and TRH. Most pituitary tumors (>60%) are hypersecretory and are classified according to the excess production of a specific anterior pituitary hormone.

The three most common disorders of pituitary hypersecretion are those related to excesses of prolactin (amenorrhea, galactorrhea, and infertility), ACTH (Cushing's syndrome), or GH (acromegaly). In addition to knowing the pathophysiologic processes of the disease involved, the anesthesiologist must determine whether the patient recently underwent air pneumoencephalography (almost obsolete, but still used rarely). If so, nitrous oxide should not be used to lessen the risk of intracranial hypertension from gas collection. CT or MRI of the sella has largely replaced neuroencephalography, but as stated, the latter is still performed.

Preoperative evaluation of patients with acromegaly is found in Chapter 34. More than 99% of cases of acromegaly are attributable to pituitary adenoma (or use of recombinant GH for unapproved aging prevention, which it does not do as of current data). Thus, the primary treatment of acromegaly is transsphenoidal surgery (or withdrawal of drug) and symptomatic treatment of the carpal tunnel or other syndromes provoked. If the pituitary tumor is not totally removed, patients are often offered external pituitary irradiation. In the case of suprasellar extension, conventional transfrontal hypophysectomy is often performed. The dopaminergic agonist bromocriptine can lower GH levels, but the long-term follow-up with this drug is not favorable. Octreotide, a long-acting analog of somatostatin, now given in depot form about once a month, produces effective palliation in 50% of patients. Other medical therapies such as pegvisomant or somatostatin analogs are also medications that have been tried before surgery.

Difficulty with endotracheal intubation should be anticipated in an acromegalic patient; lateral neck films or CT scans of the neck and direct or indirect visualization can identify patients with subglottic stenosis or an enlarged tongue, mandibles, epiglottis, or vocal cords. If placement of an arterial line is necessary, a brachial or femoral site may be preferable to a radial site.[99]

Anterior Pituitary Hypofunction

Anterior pituitary hypofunction results in deficiency of one or more of the following hormones: GH, TSH, ACTH, prolactin, or gonadotropin. Preoperative and preprocedure preparation of patients who are chronically deficient in ACTH and TSH is dis-

cussed in Chapter 34. No special preoperative and preprocedure preparation is required for a patient deficient in prolactin or gonadotropin; deficiency in GH, however, can result in atrophy of cardiac muscle, a condition that may necessitate preoperative and preprocedure cardiac evaluation. Nonetheless, anesthetic problems have not been documented in patients with isolated GH deficiency. Acute deficiencies are another matter.

Acute pituitary deficiency is often caused by bleeding into a pituitary tumor. In surgical specimens of resected adenomas, as many as 25% show evidence of hemorrhage. These patients often have acute headache, visual loss, nausea or vomiting, ocular palsy, disturbances of consciousness, fever, vertigo, or hemiparesis. In such patients, rapid transsphenoidal decompression should be accompanied by consideration of replacement therapy, including glucocorticoids, and treatment of increased intracranial pressure.

Obstetric anesthesiologists are often aware of these pituitary failure problems (also see Chapter 69); Sheehan's syndrome is the clinical manifestation of pituitary infarction associated with hypotension after or during obstetric hemorrhage. Conditions that strongly suggest this diagnosis are failure to start postpartum lactation, increasing fatigue, cold intolerance, and especially hypotension unresponsive to volume replacement and pressors.

Posterior Pituitary Hormone Excess and Deficiency

Secretion of vasopressin or antidiuretic hormone (ADH) is enhanced by increased serum osmolality or the presence of hypotension. Inappropriate secretion of vasopressin, without relation to serum osmolality, results in hyponatremia and fluid retention. This inappropriate secretion can result from a variety of CNS lesions; from drugs such as nicotine, narcotics, chlorpropamide, clofibrate, vincristine, vinblastine, and cyclophosphamide; and from pulmonary infections, hypothyroidism, adrenal insufficiency, and ectopic production from tumors. Preoperative and preprocedure management of a surgical patient with inappropriate secretion of vasopressin includes appropriate treatment of the causative disorders and restriction of water. Occasionally, drugs that inhibit the renal response to ADH (e.g., lithium or demeclocycline) should be administered preoperatively to restore normal intravascular volume and electrolyte status.

Most of the clinical features associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) are related to hyponatremia and the resulting brain edema; such features include weight gain, weakness, lethargy, mental confusion, obtundation, and disordered reflexes and may culminate in convulsions and coma. This form of edema rarely leads to hypertension.

Recently, it has been recognized that 10% to 20% of long-distance and marathon runners have SIADH with increased vasopressin secretion. Because such people not infrequently undergo surgical treatment of injuries, SIADH symptoms and laboratory evaluation might be routine for that group as well.

SIADH should be suspected in any patient with hyponatremia who excretes urine that is hypertonic relative to plasma. The following laboratory findings further support the diagnosis:

1. Urinary sodium >20 mEq/L
2. Low serum levels of BUN, creatinine, uric acid, and albumin
3. Serum sodium <130 mEq/L
4. Plasma osmolality <270 mOsm/L
5. Urine hypertonic relative to plasma

Noting the response to water loading is a useful way of evaluating patients with hyponatremia. Patients with SIADH are unable to excrete dilute urine even after water loading. Assay of ADH in blood can confirm the diagnosis. Too vigorous treatment of chronic hyponatremia can result in disabling demyelination.[100,101] The increase in serum sodium should not be greater than 1 mEq/L/hr[100,101] (see discussion of hyponatremia in the later section "Electrolyte Disorders").

Patients with mild to moderate symptoms of water intoxication (and worse outcomes are seen in children, those with hypoxic episodes, and menstruant women) can be treated with restriction of fluid intake to about 500 to 1000 mL/day. Patients with severe water intoxication and CNS symptoms may need vigorous treatment consisting of intravenous administration of 200 to 300 mL of a 5% saline solution over a period of several hours, followed by fluid restriction.

Treatment should be directed at the underlying problem. If SIADH is drug induced, use of the drug should be withdrawn. Inflammation should be treated with appropriate measures, and neoplasms should be managed by surgical resection, irradiation, or chemotherapy, whichever is indicated.

No drugs are available that can suppress release of ADH from the neurohypophysis or from a tumor. Phenytoin (Dilantin) and narcotic antagonists such as naloxone and butorphanol have some inhibiting effect on physiologic ADH release but are clinically ineffective in patients with SIADH. Drugs that block the effect of ADH on renal tubules include lithium, which is rarely used because its toxicity often outweighs its benefits, and demethylchlortetracycline in doses of 900 to 1200 mg/day. The latter drug interferes with the ability of the renal tubules to concentrate urine, thereby causing excretion of isotonic or hypotonic urine and lessening the hyponatremia. Demethylchlortetracycline can be used in ambulatory patients with SIADH when it is difficult to restrict fluids.

When a patient with SIADH comes to the operating room for any surgical procedure, fluids are managed by measuring central volume status by CVP, pulmonary artery lines, or the cross-sectional left ventricular area at end-diastole on transesophageal echocardiography and by frequent assays of urine osmolarity, plasma osmolarity, and serum sodium, including the period immediately after surgery. Despite the common impression that SIADH is frequently seen in elderly patients in the postoperative period, studies have shown that the patient's age and the type of anesthetic used have no bearing on the postoperative development of SIADH. It is not unusual to see several patients in the neurosurgical ICU suffering from this syndrome. The diagnosis is usually one of exclusion. Patients with SIADH generally require only fluid restriction; very rarely is hypertonic saline needed.

Lack of ADH, which results in diabetes insipidus, is caused by pituitary disease, brain tumors, infiltrative diseases such as sarcoidosis, head trauma (including trauma after neurosurgery), or lack of a renal response to ADH. The last can occur as a result of such diverse causes as hypokalemia, hypercalcemia, sickle cell anemia, obstructive uropathy, and renal insufficiency. Preoperative or preprocedure treatment of diabetes insipidus consists of restoring normal intravascular volume by replacing urinary

losses, administering desmopressin nasally, and giving daily fluid requirements intravenously.

Perioperative management of patients with diabetes insipidus is based on the extent of the ADH deficiency. Management of a patient with complete diabetes insipidus and a total lack of ADH does not usually present any major problem as long as the side effects of the drug are avoided and the presence of the condition is known before surgery. Just before surgery, the patient is given the usual dose of DDAVP (desmopressin acetate) intranasally or an intravenous bolus of 100 mU of aqueous vasopressin, followed by a constant infusion of 100 to 200 mU/hr.[2] The dose is usually adjusted to permit the daily breakthrough polyuria that avoids the iatrogenic syndrome of SIADH. We have found it useful to continue that dosing regimen perioperatively in all ambulatory patients who can take fluid orally in the postoperative period. All the intravenous fluids given intraoperatively should be isotonic to reduce the risk of water depletion and hypernatremia. Plasma osmolality should be measured every hour, both intraoperatively and immediately after surgery. If plasma osmolality rises well above 290 mOsm/L, hypotonic fluids can be administered; the rate of the intraoperative vasopressin infusion can be increased to greater than 200 mU/hr.

For patients who have a partial deficiency of ADH, it is not necessary to use aqueous vasopressin perioperatively unless plasma osmolality rises above 290 mOsm/L. Nonosmotic stimuli (e.g., volume depletion) and the stress of surgery usually cause the release of large quantities of ADH perioperatively. Consequently, these patients require only frequent monitoring of plasma osmolality during this period.

Because of side effects, the dose of vasopressin should be limited to that necessary for control of diuresis. The oxytoxic and coronary artery–constricting properties of vasopressin make this limit especially applicable to patients who are pregnant or have coronary artery disease.

Another problem for anesthesiologists is the care of patients who come to the operating room with a vasopressin drip for the treatment of bleeding from esophageal varices. This treatment is less common since the advent of laser therapy for varices. However, when vasopressin is given, the vasoconstrictive effect of vasopressin on the splanchnic vasculature is used to decrease bleeding. Such patients are often volume depleted and may have concomitant coronary artery disease. Because vasopressin has been shown to markedly decrease oxygen availability, primarily as a result of decreased stroke volume and heart rate, monitoring of tissue oxygen delivery may be useful. In patients with a history of angina pectoris who received a combination of cimetidine and vasopressin for esophageal varices, bradyarrhythmias and AV block have occurred. This effect indicates that the combination of cimetidine and vasopressin could be deleterious to the heart because of the combined negative inotropic and arrhythmogenic effects of the two drugs.

Diseases Involving the Cardiovascular System

Hypertension

Analysis of the perioperative treatment of hypertension is important because of the prevalence of the condition (30% of the general population in the United States), the great risk in perioperative care of a hypertensive patient, and the high cost of unnecessary delays in surgery (also see Chapter 34). The controversy centers around two issues. Does inadequate control of hypertension result in complications that could be prevented with some control? How much control of BP is needed and for how long? That is, does overzealous control just create unnecessary postponements of elective surgery or, worse, predispose the patient to exaggerated adverse drug reactions and greater hemodynamic instability than not so zealous control does?

Because of the controversy regarding the appropriateness of preoperative treatment of hypertension, the original articles that stimulated this controversy have been evaluated fully in previous editions.

Several schools of thought exist, the two oldest represented by studies conducted by Prys-Roberts and colleagues[102] in 1971 and by Goldman and Caldera[103] in 1979. Several other studies (Bedford and Feinstein,[104] Asiddao et al.,[105] Stone et al.,[106] Flacke et al.,[107] Ghignone et al.,[108] Tuman et al.,[109] Ellis et al.,[110] Mangano et al.,[111] Pasternack et al.[112]) have also been cited. Weksler and colleagues[113] studied 989 chronically treated hypertensive patients who underwent noncardiac surgery with diastolic BP between 110 and 130 mm Hg and no previous MI, unstable or severe angina pectoris, renal failure, pregnancy-induced hypertension, left ventricular hypertrophy, previous coronary revascularization, aortic stenosis, preoperative dysrhythmias, conduction defects, or stroke.[113] The control group had their surgery postponed and remained in the hospital for control of BP, and the study patients received 10 mg of nifedipine intranasally. No statistically significant differences in postoperative complications were observed, thus suggesting that this subset of patients without significant cardiovascular comorbid conditions can proceed with surgery despite elevated BP the day of surgery.

Only one study has directly assessed the relationship between cardiovascular disease and preoperative isolated systolic hypertension. In a multicenter study of patients undergoing CABG, the presence of isolated systolic hypertension has been associated with a 30% increased incidence of perioperative cardiovascular complications when compared with normotensive individuals, but no study has addressed the importance of isolated systolic hypertension in noncardiac surgery.[114] Unfortunately, each of these studies has deficiencies that prevent the establishment of a definitive answer to this question.

Recommendations

Although preoperative systolic BP is a significant predictor of postoperative morbidity, no data definitively establish whether preoperative treatment of hypertension reduces perioperative risk. Until a definitive study is performed (and that would unfortunately be extremely difficult to do), we recommend letting the weight of evidence guide preoperative treatment of a patient with hypertension. Such treatment would be based on three general beliefs: (1) the patient should be educated regarding the importance of lifelong treatment of hypertension, even isolated systolic hypertension; (2) perioperative hemodynamic fluctuations occur less frequently in treated than in untreated hypertensive patients (as demonstrated by Prys-Roberts and colleagues[102] and confirmed by Goldman and Caldera[103] and Mangano and associates,[111]); and (3) hemodynamic fluctuations have some relationship to morbidity. The data of Pasternack and colleagues[112] and Weksler and associates[113] imply that rapid correction of BP or prevention of increases in heart rate may be all that is needed. However, data from animals that had declining renal function with acute reduc-

tions in arterial BP accentuate the risks of such reductions.[115] Even though other epidemiologic data confirm these risks,[116,117] the hazards of BP fluctuations and acute hypertension may be serious in an untreated hypertensive subject.[118] Modern drug therapy for hypertension appears to reduce these risks but does so for many with a decrement in quality of life that causes many patients to avoid such medications.[119] Specific racial differences need to be considered before treatment (African Americans respond less well to β-adrenergic receptor blocking drugs and ACE inhibitors but as well to calcium channel antagonists as whites do).[120]

We use preoperative data to determine the individualized range of values that we consider tolerable by a particular patient during and after surgery. That is, if BP is 180/100 mm Hg and the heart rate is 96 beats/min on admission with no signs or symptoms of myocardial ischemia, we feel confident that the patient can tolerate these levels during surgery. If during the night BP decreases to 80/50 mm Hg and the heart rate to 48 beats/min and the patient does not wake with signs of a new cerebral deficit, we believe that the patient can safely tolerate such levels during anesthesia. Therefore, on the basis of preoperative data, we derive an individualized set of values for each patient. We then try to keep cardiovascular variables within that range and, in fact, plan before induction what therapies to use to accomplish that goal (e.g., administration of more/less anesthesia, nitroglycerin or nitroprusside/dopamine, dobutamine, phenylephrine, propranolol/isoproterenol, or atropine). We believe that this type of planning is especially important for a patient with suspected cardiovascular disease and relatively unimportant for a totally healthy patient. We do not know for certain that keeping cardiovascular variables within an individualized range of acceptable values improves the surgical outcome, but we do believe that such a plan reduces morbidity. For example, the POISE study demonstrated that acute β-blocker administration resulted in an increased incidence of stroke and death that was associated with an increased rate of hypotension.[121]

Preoperative Administration of All Antihypertensive Drugs

We routinely administer all antihypertensive drugs preoperatively, except ACE inhibitors or angiotensin II antagonists (AIIAs), which we tailor to the individual patient. Coriat and colleagues[122] found that ACE inhibitors were associated with hypotension in 100% of patients during induction versus about 20% in whom ACE inhibitors were withheld on the morning of surgery. Bertrand and coworkers performed a prospective randomized study in which it was demonstrated that more severe hypotensive episodes requiring vasoconstrictor treatment occur after induction of general anesthesia in patients chronically treated with an AIIA and receiving the drug on the morning before surgery than in those in whom AIIAs were discontinued on the day before surgery.[123] Kheterpal and colleagues performed a propensity-matched analysis of 12,381 noncardiac surgery cases.[124] Patients with chronic ACE inhibitor/angiotensin receptor blocker and diuretic therapy showed more periods with a mean arterial BP lower than 70 mm Hg, periods with a 40% decrease in systolic BP, periods with a 50% decrease in systolic BP, and vasopressor boluses than patients receiving diuretic therapy alone did. If these drugs are continued, vasopressin is the drug of choice for refractory hypotension. Although the long-term adverse effects of withholding therapy on the morning of surgery were not assessed, we withhold therapy until either oral fluid is able to be consumed (ambulatory patients) or we can convert to intravenously or nasogastrically administered alternatives (patients who remain NPO postoperatively). We even administer the patient's chronic diuretics on the morning of surgery because the major effect of diuretics after 1 week of therapy is arteriolar vasodilation and assessment of urine output may be inaccurate if the diuretic is abruptly discontinued on the morning of surgery.

Ischemic Heart Disease

Preoperative evaluation of a patient with ischemic heart disease (also see Chapter 60) and a discussion of the American Heart Association/American College of Cardiology (AHA/ACC) guidelines can be found in Chapter 34.[125]

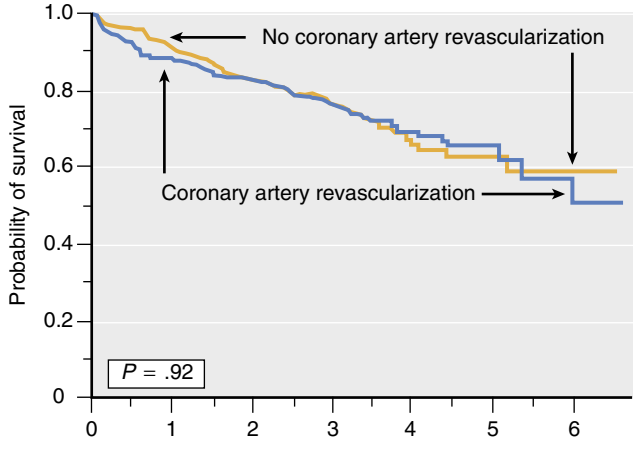
Role of Coronary Artery Bypass Graft or Percutaneous Coronary Interventions before Noncardiac Surgery

Coronary revascularization has been suggested as a means of reducing perioperative risk before noncardiac surgery. Previous retrospective evidence has shown that prior successful preoperative revascularization may decrease postoperative cardiac risk twofold to fourfold in patients undergoing elective vascular surgery.[126,127] The strongest retrospective evidence comes from the Coronary Artery Surgery Study (CASS) registry, which enrolled patients from 1978 to 1981. Operative mortality in patients with CABG performed before noncardiac surgery was 0.9% but was significantly higher at 2.4% in patients without previous CABG. However, there was a 1.4% mortality rate associated with the CABG procedure itself. Eagle and colleagues reported on a long-term analysis of patients entered into CASS.[128] They studied patients assigned to medical or surgical therapy for coronary artery disease for over 10 years who subsequently underwent 3368 noncardiac operations in the years after assignment of coronary treatment. Intermediate-risk surgery such as abdominal, thoracic, or carotid endarterectomy was associated with a combined morbidity and mortality rate of 1% to 5% and a small but significant improvement in outcome in patients who had previously undergone revascularization. The most significant improvement in outcome occurred in patients who underwent major vascular surgery such as abdominal or lower extremity revascularization. However, this observational study did not randomize patients and was undertaken in the 1970s and 1980s, before significant advances in medical, surgical, and percutaneous coronary strategies.[128] Landesberg and coauthors retrospectively reviewed long-term outcomes in 578 major vascular procedures.[129] By multivariate analysis, age, type of vascular surgery, presence of diabetes, previous MI, and moderate to severe ischemia on preoperative thallium scanning (PTS) independently predicted mortality, and preoperative coronary revascularizaton predicted improved survival. Long-term survival after major vascular surgery was significantly improved if patients with moderate to severe ischemia on PTS underwent selective coronary revascularization.

The benefit of percutaneous coronary intervention (PCI) before noncardiac surgery has also been examined in several cohort studies. Posner and colleagues used an administrative data set of patients who underwent PCI and noncardiac surgery in Washington State.[130] They matched patients with coronary disease who were undergoing noncardiac surgery with and without previous PCI and looked at cardiac complications. In this nonrandomized design, they noted a significantly lower rate of 30-day

cardiac complications in patients who underwent PCI at least 90 days before the noncardiac surgery. Importantly, however, PCI within 90 days of noncardiac surgery did not improve outcome. Although the explanation for these results is unknown, they may support the notion that PCI performed "to get the patient through surgery" may not improve perioperative outcome because cardiac complications may not occur in patients with stable or asymptomatic coronary stenosis. PCI may actually destabilize coronary plaque, which becomes manifest in the days or weeks after noncardiac surgery. Godet and associates studied a cohort of 1152 patients after abdominal aortic surgery in which 78 patients underwent PCI.[131] In the PCI group, the observed percentages of patients with a severe postoperative coronary event (9.0%; 95% confidence interval [CI], 4.4 to 17.4) or death (5.1% [95% CI, 2.0 to 12.5]) were not significantly different from the expected percentages (8.2% and 6.9%, respectively), which was confirmed by propensity analysis. PCI did not seem to significantly limit cardiac risk or death after aortic surgery.

Several randomized trials have now addressed the value of testing and CABG or PCI (or both) in a subset of patients. McFalls and colleagues reported the results of a multicenter randomized trail in the VA Health System in which patients with documented coronary artery disease on coronary angiography, excluding those with left main disease or a severely depressed ejection fraction (<20%), were randomized to CABG (59%) or percutaneous transluminal coronary angioplasty (PTCA) (41%) versus routine medical therapy.[132] At 2.7 years after randomization, mortality in the revascularization group was not significantly different (22%) from that in the no-revascularization group (23%) (Fig. 35-5). Within 30 days after the vascular operation, postoperative MI, defined by elevated troponin levels, occurred in 12% of the revascularization group and 14% of the no-revascularization group (P = .37). The authors suggested that coronary revascularization is not indicated in patients with stable coronary artery disease, and their results further support the lack of efficacy of PCI or CABG for single- or double-vessel disease before noncardiac surgery. However, in a follow-up analysis, Ward and coauthors reported improved outcome in the subset who underwent CABG versus PCI.[133] Poldermans and colleagues randomized 770 patients about to undergo major vascular surgery and considered to have intermediate cardiac risk, defined as the presence of one or two cardiac risk factors, to either undergo further risk stratification with stress imaging or proceed directly to surgery.[134] All patients received bisoprolol with a targeted heart rate of 60 to 65 beats/min initiated before and continued after surgery. The 30-day incidence of cardiac death and nonfatal MI was similar in both groups (1.8% in the no-testing group versus 2.3% in the tested group). The conclusion of the authors was that further risk stratification in this group of patients considered to be at intermediate risk based on clinical history alone was unnecessary as long as perioperative β-blockers were used and that testing only delayed necessary vascular surgery. In a pilot study, Poldermans and associates tested patients with more than three risk factors; 101 (23%) showed extensive ischemia and were randomly assigned to revascularization (n = 49) or no revascularization.[135] Revascularization did not improve 30-day outcome; the incidence of the composite end point was 43% versus 33% (odds ratio [OR], 1.4; 95% CI, 0.7 to 2.8; P = .30). In addition, no benefit during 1-year follow-up was observed after coronary revascularization (49% versus 44%; OR, 1.2; 95% CI, 0.7 to 2.3; P = .48).



Years	1	2	3	4	5	6
No. at risk						
Revascularization	226	175	113	65	18	7
No revascularization	229	172	108	55	17	12

Figure 35-5 Long-term survival in patients randomized to coronary revascularization or routine care in patients with coronary artery disease on angiography and undergoing major vascular surgery in the Coronary Artery Revascularization Prophylaxis trial. *(Reproduced with permission from McFalls EO, Ward HB, Moritz TE, et al: Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 351:2795-2804, 2004.)*

One issue in interpreting the results is that the length of time between coronary revascularization and noncardiac surgery most likely has an impact on its protective effect and potential risks. Back and coworkers studied 425 consecutive patients undergoing 481 elective major vascular operations at an academic VA Medical Center.[136] Coronary revascularization was classified as recent (CABG <1 year; PTCA <6 months) in 35 cases (7%), prior (CABG >1 year and ≤5 years; PTCA >6 months and ≤2 years) in 45 cases (9%), and remote (CABG ≥5 years; PTCA ≥2 years) in 48 cases (10%). Outcomes in patients with previous PTCA were similar to those after CABG (P = .7). Significant differences in adverse cardiac events and mortality were found between patients with CABG performed within 5 years or PTCA within 2 years (6.3%, 1.3%, respectively), individuals with remote revascularization (10.4%, 6.3%), and nonrevascularized patients stratified at high risk (13.3%, 3.3%) or intermediate/low risk (2.8%, 0.9%). The authors concluded that previous coronary revascularization (CABG <5 years; PTCA <2 years) may provide only modest protection against adverse cardiac events and mortality after major arterial reconstruction.

PCI using coronary stenting poses several special issues. Kaluza and associates reported on the outcome of 40 patients who underwent prophylactic coronary stent placement less than 6 weeks before major noncardiac surgery requiring general anesthesia.[137] There were seven MIs, 11 major bleeding episodes, and 8 deaths. All deaths and MIs, as well as 8 of the 11 bleeding episodes, occurred in patients subjected to surgery less than 14 days after stenting. Four patients expired after undergoing surgery 1 day after stenting. Wilson and colleagues reported on 207 patients who underwent noncardiac surgery within 2 months of stent placement.[5] Eight patients died or suffered an MI, all of whom were among the 168 patients who had surgery 6 weeks after stent placement. Vincenzi and coworkers studied 103 patients and reported that the risk of suffering a perioperative cardiac event

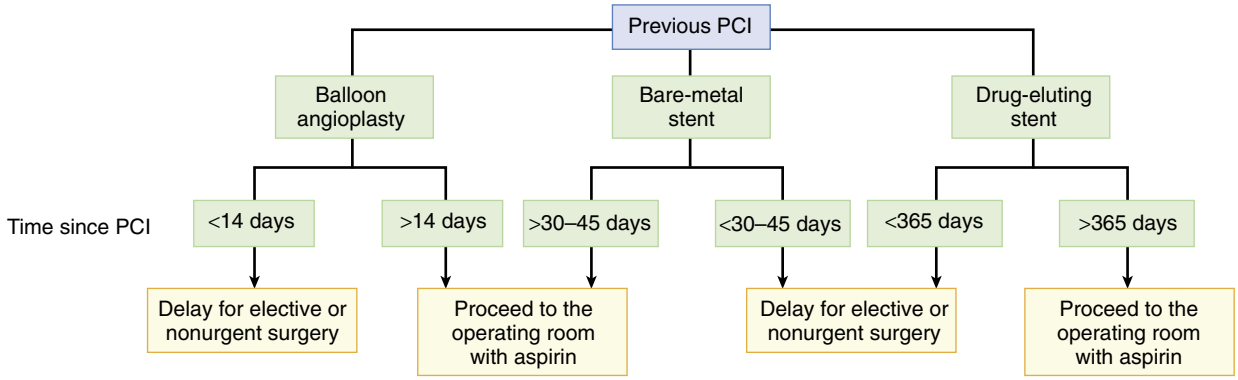


Figure 35-6 Recommendation for management of a patient with a previous percutaneous coronary intervention (PCI) from the American Heart Association/American College of Cardiology. *(Reproduced with permission from Fleisher LA, Beckman JA, Brown KA, et al: ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 116(17): e418-e499, 2007.)*

was 2.11-fold greater in patients with recent stents (<35 days before surgery) than in those who underwent PCI more than 90 days before surgery.[138] Leibowitz and associates studied a total of 216 consecutive patients who underwent PCI within 3 months of noncardiac surgery (PTCA, 122; stent, 94).[139] A total of 26 patients (12%) died, 13 in the stent group (14%) and 13 in the PTCA group (11%), a nonsignificant difference. The incidence of acute MI and death within 6 months was not significantly different (7% and 14% in the stent group and 6% and 11% in the PTCA group, respectively). Significantly more events occurred in the two groups when noncardiac surgery was performed within 2 weeks of PCI. Based on the accumulating data, elective noncardiac surgery after PCI, with or without stent placement, should be delayed for 4 to 6 weeks.

Drug-eluting stents may represent an even greater problem during the perioperative period based on case reports. Nasser and coauthors described two patients with in-stent thrombosis occurring 4 and 21 months after the implantation of sirolimus-eluting stents.[140] Several reports suggest that drug-eluting stents may represent an additional risk over a prolonged period (up to 12 months), particularly if antiplatelet agents are discontinued.[141] The new guidelines suggest continuing aspirin therapy in all patients with a coronary stent and discontinuing clopidogrel for as short an interval as possible for patients with bare-metal stents in place for less than 30 days or drug-eluting stents for less than 1 year (Fig. 35-6).

Summary of Preoperative and Intraoperative Factors That Correlate with Perioperative Morbidity

Summarizing a large number of studies, we list the following preoperative findings as conditions that correlate with perioperative morbidity and that can be corrected before surgery:

Table 35-9 Cardiovascular Disease Classification Chart

Class	New York Heart Association Functional Classification	Canadian Cardiovascular Society Functional Classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity such as walking or climbing stairs does not cause angina. Angina with strenuous or rapid prolonged exertion at work or recreation
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Slight limitation of ordinary activity. Ordinary walking or climbing stairs rapidly, walking uphill, and walking or stair climbing after meals or in the cold, in wind, under emotional stress, or only for a few hours after awakening. Walking more than two blocks on a level surface or up more than one flight of stairs at a normal pace and under normal conditions
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	Marked limitation of ordinary physical activity. Walking one or two blocks on a level surface and climbing more than one flight of stairs under normal conditions
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Inability to carry out physical activity without discomfort—anginal syndrome *may* be present at rest

Modified from Wong DH, Weber EC, Schell MJ, et al: Factors associated with postoperative pulmonary complications in patients with severe COPD. Anesth Analg, 80: 276, 1995.

1. Recent MI[91,119,142-144]
2. Severe CHF (i.e., sufficiently severe to produce rales, an S_3 gallop, or distention of the jugular vein)[91,111,130,137,142,145-164]
3. Severe angina (see Table 35-9 for classification of the severity of angina)[137,142,145-152]
4. Heart rhythm other than sinus[142,145,153,154]
5. Premature atrial contractions[142]
6. More than five PVCs per minute (although unconfirmed in later studies)[142]
7. Chronic renal insufficiency
8. BUN levels higher than 50 mg/dL or potassium levels below 3.0 mEq/L[142,148,149,155]

Preoperative factors that correlate with perioperative risk but cannot be altered include (1) old physiologic or chronologic age (perioperative risk increases with age),* (2) significant aortic stenosis,[142,155,169] (3) emergency surgery,[91,142,145,147,153-155,165] (4) cardiomegaly,[142,145,147,153-156] (5) history of CHF,[91,142,145-147,153-158,160-163,170,171] (6) angina (or a history of angina or ischemia) on the ECG,[91,111,142,145-147,153,154,157-162,170,172] (7) abnormal ST-segment or inverted or flat T waves on the ECG,[8,142,145,154] or abnormal QRS complex on the ECG,[142] and (8) a significant mitral regurgitant murmur.[142,155]

Significant intraoperative factors that correlate with perioperative risk and that may be avoided or altered are (1) unnecessary use of vasopressors,[173,174] (2) unintentional hypotension[120,142,175] (this point is controversial, however, because some investigators have found that unintentional hypotension does not correlate with perioperative morbidity[174]), (3) hypothermia,[176] (4) too low or too high a hematocrit,[177,178] and (5) lengthy operations.[142]

Significant intraoperative factors that correlate with perioperative morbidity and probably cannot be avoided are (1) emergency surgery and (2) thoracic or intraperitoneal surgery or above-the-knee amputations.[142,145-147,153-155,157-159,161,162,168,170,171]

Although the evidence for these factors is fairly substantial, virtually no data are derived from prospective randomized studies indicating that treatment of the aforementioned conditions reduces perioperative risk in patients with ischemic heart disease. Nevertheless, all logic dictates that such treatment does reduce risk. Thus, the goal in giving anesthesia to patients with ischemic heart disease is to achieve the best preoperative condition obtainable by treating conditions that correlate with perioperative risk. The next step is to intraoperatively monitor for conditions that correlate with perioperative risk and, by careful attention to detail, avoid circumstances that lead to perioperative risk. Although local anesthesia may reduce perioperative risk, epidemiologic studies do not indicate any significant differences in perioperative morbidity in patients with ischemic heart disease who are given local anesthesia as opposed to general anesthesia.

Preoperative and Preprocedure Therapy

The only way known to increase oxygen supply to the myocardium of patients with coronary artery stenosis is to maintain diastolic BP, hemoglobin concentration (Fig. 35-7), and oxygen saturation. The main goal of anesthesia practice for these patients has been to decrease the determinants of myocardial oxygen demand, heart rate, ventricular wall tension, and contractile performance and improve plaque stabilization. Thus, medical management designed to preserve all viable myocardial tissue may include the following:

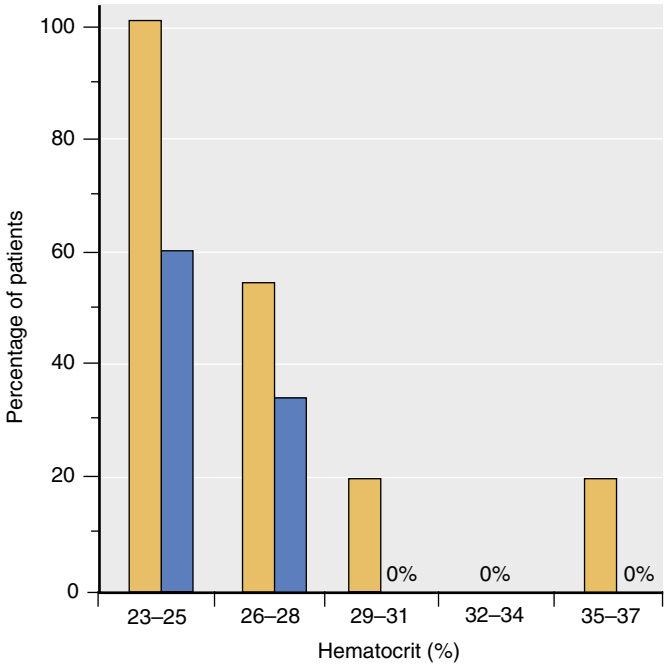


Figure 35-7 Relationship of postoperative myocardial ischemia (*yellow bars*) and morbid cardiac events (*blue bars*) to hematocrit for 27 high-risk patients undergoing infrainguinal arterial bypass. *(Data from Nelson AH, Fleisher LA, Rosenbaum SH: The relationship between postoperative anemia and cardiac morbidity in high risk vascular patients in the ICU. Crit Care Med 21:860, 1993.)*

1. Continuation of β-adrenergic receptor blocking drugs (propranolol, atenolol, esmolol, or metoprolol) to avoid β-blocker withdrawl leading to increased contractility and heart rate. Multiple studies have demonstrated improved outcome in patients given perioperative β-blockers, especially if the heart rate is controlled.[179,180] However, newer studies have demonstrated that β-blockers may not be effective if the heart rate is not well controlled or in lower-risk patients.[181-183] Recently, the POISE trial was published in which 8351 high-risk β-blocker–naive patients were randomized to high-dose continuous-release metoprolol versus placebo.[121] There was a significant reduction in the primary outcome of cardiovascular events along with a 30% reduction in the MI rate, but a significantly increased rate of 30-day all-cause mortality and stroke. The current ACC/AHA guidelines on perioperative β-blockade advocate that perioperative β-blockade is a class I indication and should be used in patients previously taking β-blockers and those with a positive stress test undergoing major vascular surgery, although acute administration without titration may be associated with harm (Table 35-10).
2. Vasodilation (with nitroglycerin or its "long-acting" analogs nitroprusside, hydralazine, or prazosin) to decrease ventricular wall tension may be beneficial, although there are currently no randomized trials that support the prophylactic use of these agents.[110-112] The use of Swan-Ganz catheters[159,184] and transesophageal echocardiography for this type of patient is described in Chapters 40 and 41, and the

*See references 22, 23, 142, 145, 148, 153, 154, 157, 158, 164-168.

Table 35-10 Recommendations for Perioperative β-Blocker Therapy Based on Published Randomized Clinical Trials

Surgery	No Clinical Risk Factors	One or More Clinical Risk Factors	CHD or High Cardiac Risk	Patients Currently Taking β-Blockers
Vascular	Class IIb; level of evidence: B	Class IIa; level of evidence: B	Patients found to have myocardial ischemia on preoperative testing: class I; level of evidence: B* Patients without ischemia or no previous test: class IIa; level of evidence: B	Class I; level of evidence: B
Intermediate risk	…	Class IIb; level of evidence: C	Class IIa; level of evidence: B	Class I; level of evidence: C
Low risk	…	…	…	Class I; level of evidence: C

Ellipses (…) indicate that data were insufficient to determine a class of recommendation or level of evidence.
*Applies to patients found to have coronary ischemia on preoperative testing.
CHD, coronary heart disease.
Reproduced with permission from Fleisher LA, Beckman JA, Brown KA, et al: ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery." Circulation 116(17):e418-e499, 2007.

intraoperative management of patients with ischemic heart disease is discussed in further detail in Chapters 60 and 62 and in recent guidelines.[125]

3. Aspirin, statins, exercise, and diet. These choices seem to be indicated in many patients. Briefly, we believe that drugs given chronically (e.g., antihypertensive medications and some ACE inhibitors) should be continued through the morning of surgery (see earlier). The topic of chronic drug therapy is discussed in more detail in the last section of this chapter.

Valvular Heart Disease

Major alterations in the preoperative management of patients with valvular heart disease have been made regarding the use of anticoagulant therapy and are now based on the causes of the disease. Preoperative and intraoperative management of patients with valvular heart disease is discussed in Chapters 34 and 60.

The prognosis and, presumably, the perioperative risk for patients with valvular heart disease depend on the stage of the disease. Although stenotic lesions progress faster than regurgitant lesions do, regurgitant lesions secondary to infective endocarditis, rupture of the chordae tendineae, or ischemic heart disease can be rapidly fatal. Left ventricular dysfunction is common in the late stage of valvular heart disease.

Preoperative maintenance of drug therapy can be crucial; for example, a patient with aortic stenosis can deteriorate rapidly with the onset of atrial fibrillation or flutter because the atrial contribution to left ventricular filling can be critical in maintaining cardiac output. One of the most serious complications of valvular heart surgery and valvular heart disease before surgery is cardiac arrhythmia. Conduction disorders and chronic therapy with antiarrhythmic and inotropic drugs are discussed elsewhere in this chapter. The reader is referred elsewhere in this book (Chapter 83) or to other sources[185] for discussion of the management of a child with congenital heart disease who is undergoing noncardiac surgery.

Preoperative Antibiotic Prophylaxis for Endocarditis

Patients who have any form of valvular heart disease, as well as those with intracardiac (ventricular septal or atrial septal defects) or intravascular shunts, should be protected against endocarditis at the time of a known bacteremic event. Endocarditis has occurred in a sufficiently significant number of patients with hypertrophic cardiomyopathy (subvalvular aortic stenosis, asymmetric septal hypertrophy) and mitral valve prolapse to warrant the inclusion of these two conditions in the prophylaxis regimen.

Is endotracheal intubation associated with bacteremia? Bacteremia occurs after the following events: dental extraction, 30% to 80%; brushing of teeth, 20% to 24%; use of oral irrigation devices, 20% to 24%; barium enema, 11%; transurethral resection of the prostate (TURP), 10% to 57%; upper GI endoscopy, 8%; nasotracheal intubation, 16% (4 of 25 patients); and orotracheal intubation, 0% (0 of 25 patients). There are new guidelines from the AHA that are substantially different from those published in 2006.[186] There is also an update in 2008 from the AHA/ACC on endocarditis in patients with valvular heart disease, with changes from the 2006 document shown in Table 35-11.[187]

Cardiac Valve Prostheses and Anticoagulant Therapy and Prophylaxis for Deep Venous Thrombosis

In patients with prosthetic valves, the risk of increased bleeding during a procedure in a patient receiving antithrombotic therapy has to be weighed against the increased risk of thromboembolism caused by stopping the therapy. Common practice in patients undergoing noncardiac surgery with a mechanical prosthetic valve in place is cessation of anticoagulant therapy 3 days before surgery. This timeframe allows the international normalized ratio to fall to less than 1.5 times normal. The oral anticoagulants can then be resumed on postoperative day 1. Using a similar protocol, Katholi and colleagues found no perioperative episodes of thromboembolism or hemorrhage in 25 patients.[188] An alternative approach in patients at high risk for thromboembolism is conversion to heparin during the perioperative period. The heparin can then be discontinued 4 to 6 hours before surgery and resumed shortly thereafter. Current prosthetic valves may have a lower

Table 35-11 Changes Related to Endocarditis Prophylaxis: AHA/ACC Guidelines on Valvular Heart Disease

2006 VHD Guideline Recommendations	2008 VHD Focused Update Recommendations	Comments
Class I	**Class IIa**	
1. Prophylaxis against infective endocarditis is recommended for the following patients: • Patients with prosthetic heart valves and patients with a history of infective endocarditis (*level of evidence: C*) • Patients who have complex cyanotic congenital heart disease (e.g., single-ventricle states, transposition of the great arteries, tetralogy of Fallot) (*level of evidence: C*) • Patients with surgically constructed systemic pulmonary shunts or conduits (*level of evidence: C*) • Patients with congenital cardiac valve malformations, particularly those with bicuspid aortic valves, and patients with acquired valvular dysfunction (e.g., rheumatic heart disease) (*level of evidence: C*) • Patients who have undergone valve repair (*level of evidence: C*) • Patients who have hypertrophic cardiomyopathy when there is latent or resting obstruction (*level of evidence: C*) • Patients with MVP and auscultatory evidence of valvular regurgitation and/or thickened leaflets on echocardiography* (*level of evidence: C*)	1. Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: • Patients with prosthetic cardiac valves or prosthetic material used for cardiac valve repair (*level of evidence: B)* • Patients with previous infective endocarditis (*level of evidence: B*) • Patients with CHD (*level of evidence: B*) • Unrepaired cyanotic CHD, including palliative shunts and conduits (*level of evidence: B*) • Completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure (*level of evidence: B*) • Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (both of which inhibit endothelialization) (*level of evidence: B*) • Cardiac transplant recipients with valve regurgitation as a result of a structurally abnormal valve (*level of evidence: C*)	Modified recommendation (changed class of recommendation from I to IIa, changed text). There are no class I recommendations for infective endocarditis prophylaxis
Class III		
1. Prophylaxis against infective endocarditis is not recommended for the following patients: • Patients with isolated secundum atrial septal defect (*level of evidence: C*) • Patients 6 or more months after successful surgical or percutaneous repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (*level of evidence: C*) • Patients with MVP without MR or thickened leaflets on echocardiography* (*level of evidence: C*) • Patients with physiologic, functional, or innocent heart murmurs, including patients with aortic valve sclerosis as defined by focal areas of increased echogenicity and thickening of the leaflets without restriction of motion and a peak velocity of less than 2.0 m/sec (*level of evidence: C*) • Patients with echocardiographic evidence of physiologic MR in the absence of a murmur and with structurally normal valves (*level of evidence: C*) • Patients with echocardiographic evidence of physiologic TR and/or pulmonary regurgitation in the absence of a murmur and with structurally normal valves (*level of evidence: C*)	1. Prophylaxis against infective endocarditis is not recommended for nondental procedures (such as transesophageal echocardiography, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection (*level of evidence: B*)	Modified recommendation (changed text)

*This footnote is obsolete. Please see 2006 VHD Guideline (3) for footnote text.
CHD, congestive heart disease; MR, mitral regurgitation; MVP, mitral valve prolapse; TR, tricuspid regurgitation; VHD, valvular heart disease.
From Nishimura RA, Carabello BA, Faxon DP, et al: ACC/AHA 2008 guideline update on valvular heart disease: Focused update on infective endocarditis: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 118:887-896, 2008.

incidence, and the risk associated with heparin may outweigh its benefit in the perioperative setting. According to the AHA/ACC guidelines, heparin can usually be reserved for those who have had a recent thrombus or embolus (arbitrarily within 1 year), those with demonstrated thrombotic problems when previously off therapy, those with a Björk-Shiley valve, and those with more than three risk factors (atrial fibrillation, previous thromboembolism, hypercoagulable condition, and mechanical prosthesis).[189] A lower threshold for recommending heparin should be considered in patients with mechanical valves in the mitral position, in whom a single risk factor would be sufficient evidence of high risk. Subcutaneous low-molecular-weight heparin offers an alternative outpatient approach.[190] It is appropriate for the surgeon and cardiologist to discuss the optimal perioperative manage-

ment for such a patient, including a review of the most recent guidelines.[191]

Regional anesthetic techniques might be avoided, although this issue is controversial.[192] Many practitioners do not hesitate to use regional anesthesia in the face of prophylaxis for deep venous thrombosis.[193-195] However, epidural hematoma has been associated with anticoagulant therapy in many reports. Large retrospective reviews of outcome after epidural or spinal anesthesia, or both, during or shortly before initiation of anticoagulant therapy with heparin have not reported neurologic dysfunction related to hematoma formation in any patient.[196,197] This paucity of damaging epidemiologic evidence, though reassuring, does not reduce the need for frequent evaluation of neurologic function and a search for back pain in the perioperative period after regional anesthesia in any patient receiving any clotting function inhibitor, including aspirin.[192,198-200] The risk of regional anesthesia concurrent with prophylaxis for deep venous thrombosis with heparin is greater with the use of low-molecular-weight heparin. (Heparin-induced thrombocytopenia has been treated successfully with intravenous immunoglobulin.[194]) The American Society of Regional Anesthesia and Pain Management has issued a consensus statement on the use of regional anesthesia in anticoagulated patients.[201] They suggest that the decision to perform spinal or epidural anesthesia/analgesia and the timing of catheter removal in a patient receiving antithrombotic therapy should be made on an individual basis, with the small though definite risk of spinal hematoma weighed against the benefits of regional anesthesia for a specific patient.

Deep venous thrombosis is so common in postoperative patients that almost 1% of postsurgical patients die of fatal pulmonary embolism (Table 35-12).[202] Because of this high mortality risk, prophylaxis against deep venous thrombosis has attained widespread acceptance; thus, prophylaxis often begins with 5000 units of heparin given subcutaneously 2 hours before surgery.[202-204] Other trials have shown equal effect with external pneumatic compression.[203,205] Persuading surgeons to use this technique may provide greater assurance in using regional anesthesia. Such an option, however, is not available for patients

Table 35-12 Incidence of Deep Venous Thrombosis and Fatal Pulmonary Embolism

	Incidence of		
Type of Surgery	**Deep Venous Thrombosis (%)**	**Proximal Deep Venous Thrombosis (%)**	**Fatal Pulmonary Embolism (%)**
General			
Age >40 yr	10	<1	0.1
Age >60 yr	10-40	3-15	0.8
Malignancy	50-60		
Thoracic	30		
Vascular			
Aortic repair	26		
Peripheral	12		
Urologic			
Open prostatectomy	40		
TURP	10		
Other urologic	30-40		
Major gynecologic			
With malignancy	40		
Without malignancy	10-20		
Neurosurgery			
Craniotomy	20-80		
Laminectomy	4-25		1.5-3.0
Orthopedic			
Total-hip replacement	40-80	10-20	1.0-5.0
Hip fracture	48-75		1.0-5.0
Tibial fracture	45		
Total knee	60-70	20	1.0-5.0
Head, neck, chest wall	11		
Medical			
Acute myocardial infarction	30	6	
Stroke	60-75		
Acute spine injury	60-100		
Other bed bound	26		

TURP, transurethral resection of the prostate.

with a prosthetic valve. New recommendations are available from the American College of Chest Physicians for prophylaxis against venous thromboembolism.[235a]

Another problem that can arise is managing a pregnant patient with a prosthetic valve during delivery. It is recommended that warfarin be replaced by subcutaneous heparin during the peripartum period. During labor and delivery, elective induction is advocated with discontinuance of all anticoagulant therapy, as indicated for the particular valve prosthesis (discussed earlier).[206]

Auscultation of the prosthetic valve should be performed preoperatively to verify normal functioning (Fig. 35-8).[207] Abnormalities in such sounds warrant preoperative consultation and verification of functioning.

Cardiac Conduction Disturbances: Cardiac Arrhythmias

Bradyarrhythmias, especially if profound or associated with dizziness or syncope, are generally managed with pacemakers (also see Chapters 34, 43, and 61). However, chronic bifascicular block (right bundle branch block with a left anterior or posterior hemiblock or a left bundle branch block with combined left anterior and posterior hemiblocks), even when only a first-degree heart block is present, can progress to complete heart block and sudden perioperative death on rare occasion. In six studies, less than 2% of the approximately 266 patients with bifascicular block progressed to complete heart block perioperatively.[208] On the other hand, these patients have a high 5-year mortality rate (160 of 554 patients, or 29%). Most of the deaths were related to tachyarrhythmias or MI—events not usually preventable by traditional pacemakers.[209] Thus, the presence of a bifascicular block on the ECG should make the anesthesiologist more worried about associated coronary artery disease or left ventricular dysfunction. Nevertheless, these patients rarely have complete heart block perioperatively. Therefore, prophylactic preoperative insertion of temporary pacing wires for bifascicular block does not seem warranted. However, a central route can be established in advance in the event that a temporary pacemaker needs to be inserted (most operating rooms do not rely on transthoracic pacing, although such might be attempted if available).[210] The actual pacemaker equipment and appropriate personnel should be immediately available and tested regularly because symptomatic heart block does occur perioperatively in more than 1% of patients. One study appears to have confirmed this rate of at least 1% for patients undergoing cardiac surgery.[211] One percent of patients in whom a pacing pulmonary artery catheter was not inserted preoperatively subsequently required pacing before cardiopulmonary bypass. By contrast, 19% of patients who had such a catheter in place underwent cardiac pacing before cardiopulmonary bypass. Predictors of the need for pacing included previous symptomatic bradyarrhythmia, a history of transient complete AV block, and aortic valve disease.

More than five PVCs per minute on preoperative examination correlates with perioperative cardiac morbidity.[142,147,153,154] To the classic criteria for treating PVCs (the presence of R-on-T couplets, the occurrence of more than three PVCs per minute,

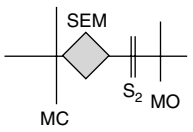
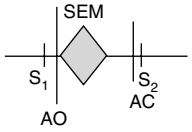
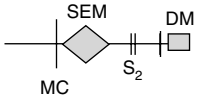
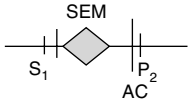
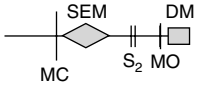
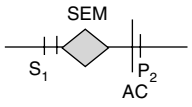
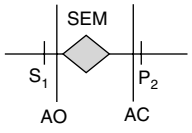
Prosthesis Type	Mitral Prosthesis	Acoustic Characteristics	Aortic Prosthesis	Acoustic Characteristics
Ball valves		1) A_2–MO Interval 0.07–0.11 sec. 2) MV > MC 3) II-III/VI Systolic ejection murmur (SEM) 4) No diastolic murmur		1) S_1–AO Interval 0.07 sec. 2) AO > AC 3) II/VI harsh SEM 4) No diastolic murmur
Disk valves		1) A_2–MO Interval 0.05–0.09 sec. 2) MO is rarely heard 3) II/VI is usually heard 4) II-III/VI diastolic rumble is usually heard		1) S_1–AO Interval 0.04 sec. 2) AO is uncommonly heard AC is usually heard 3) II/VI SEM is usually heard 4) Occasional diastolic murmur
Porcine valves		1) A_2–MO Interval 0.01 sec. 2) MO is audible 50% 3) I-II/VI apical SEM 50% 4) Diastolic rumble 1/2–2/3		1) S_1–AO Interval 0.03–0.08 sec. 2) AO is uncommonly heard AC is usually heard 3) II/VI SEM in most 4) No diastolic murmur
Bileaflet valve (St. Jude)				1) AO and AC commonly heard 2) A soft SEM is common

Figure 35-8 Summary of the normal acoustic characteristics of valve prostheses according to type and location. A_2, aortic second sound; AC, aortic valve closure sound; AO, aortic valve opening sound; DM, diastolic murmur; MC, mitral valve closure sound; MO, mitral valve opening sound; MV, mitral valve; P_2, pulmonary second sound; S_1, first heart sound; S_2, second heart sound; SEM, systolic ejection murmur. *(Redrawn from Smith ND, Raizada V, Abrams J: Auscultation of the normally functioning prosthetic valve. Ann Intern Med 95:594, 1981.)*

and multifocality of PVCs) must be added frequent (>10/hr over a 24-hour period) and repetitive ventricular beats. Electrophysiologic and programmed ventricular stimulation studies are being used to indicate and guide treatment of patients with ischemic heart disease or recurrent arrhythmias and survivors of out-of-hospital cardiac arrest. Although such patients are often treated with antiarrhythmic therapy, attention to their underlying condition should be a focus of our preoperative management. Chronic antiarrhythmic therapy is discussed in the last section of this chapter. Torsades de pointes is an arrhythmia characterized by episodes of alternating electrical polarity such that the major vector of the QRS complex seems to alternate around an isoelectric line. The hallmark enabling differential diagnosis from ventricular tachycardia is the unusual response of this arrhythmia to commonly used antiarrhythmic drugs. That is, the use of drugs that prolong the QT interval (e.g., quinidine, procainamide, disopyramide, some of the antihistamines, and the antipsychotic phenothiazines) may well make the arrhythmia more frequent or of longer duration. Reports of the sudden occurrence of torsades de pointes during surgery have been rare in the anesthesia literature. Immediate therapy consists of the administration of magnesium or electrical cardioversion, followed by overdrive cardiac pacing or the administration of β-adrenergic agonists and discontinuation of drugs that prolong the QT interval.

Premature atrial contractions and cardiac rhythm other than sinus also correlate with perioperative cardiac morbidity.[142,153] These arrhythmias may be more a marker of poor cardiovascular reserve than a specific cause of perioperative cardiac complications.

Pre-excitation syndrome is the name for supraventricular tachycardias associated with AV bypass tracts.[212] Successful treatment, which is predicated on an understanding of the clinical and electrophysiologic manifestations of the syndrome, consists of either catheter ablation techniques[209] or surgery using preoperative and intraoperative techniques that avoid release of sympathetic and other vasoactive substances and therefore tachyarrhythmias.[213,214] Anesthesia for electrophysiologic procedures is discussed in Chapter 61.

Disorders of the Respiratory and Immune Systems

General Preoperative and Preprocedure Considerations

Pulmonary complications after procedures requiring anesthesia are as common as cardiovascular complications—even more common if deep venous thrombosis is included. Moreover, pulmonary complications are equally or more important to the patient and health system in terms of morbidity, mortality, length-of-stay extension, and cost.

Although little may seem to have changed in the preoperative preparation of patients with respiratory disease, this impression is not true. Major changes in drug therapy have occurred, and appreciation of the effects of smoking and sleep apnea on perioperative and chronic care has increased.[215-232] (Preoperative and preprocedure identification and perioperative care of patients with sleep apnea are discussed in the earlier section on obesity and in Chapter 64.)

The main purpose of preoperative testing is to identify patients at risk for perioperative complications so that appropriate perioperative therapy can be instituted to foster return to functional status. Preoperative assessment can also establish baseline function and the feasibility of surgical intervention. Whereas numerous investigators have used pulmonary function tests to define inoperability or high-risk versus low-risk groups for pulmonary complications, few have been able to demonstrate that the performance of any specific preoperative or intraoperative measure, save perhaps smoking cessation and physical activity such as a walking program, reliably decreases perioperative pulmonary morbidity or mortality. Because routine preoperative pulmonary testing and care are discussed extensively in Chapters 44 and 59, the current discussion is limited to an assessment of the effectiveness of this type of care.

In fact, few randomized prospective studies indicate an outcome benefit of preoperative preparation, and we do not even have such for smoking cessation or walking—only epidemiologic data; a larger cohort has implied a benefit of intraoperative and postoperative pain therapy techniques (usually planned preoperatively).[227-232] Stein and Cassara[228] randomly allocated 48 patients to undergo preoperative therapy (cessation of smoking, administration of antibiotics for purulent sputum, and use of bronchodilating drugs, postural drainage, chest physiotherapy, and ultrasonic nebulizer) or no preoperative therapy. The no-treatment group had a mortality of 16% and morbidity of 60%, as opposed to 0% and 20%, respectively, for the treatment group. In addition, the treatment group spent an average of 12 postoperative days in the hospital as compared with 24 days for the 21 survivors in the no-treatment group.

Collins and colleagues[233] prospectively examined the benefits of preoperative antibiotics, perioperative chest physiotherapy and therapy with bronchodilating drugs, and routine postoperative analgesia (morphine) on postoperative respiratory complications in patients with COPD. Of these therapies, only preoperative treatment with antibiotics had a beneficial effect.

Warner and coworkers[234] collected data retrospectively about smoking history and prospectively (concurrently) about pulmonary complications for 200 patients undergoing CABG. These investigators documented that 8 weeks or more of smoking cessation was associated with a 66% reduction in postoperative pulmonary complications. Smokers who stopped for less than 8 weeks actually had an increase (from 33% for current smokers to 57.1% for recent quitters) in the rate of one or more of the six complications surveyed: purulent sputum with pyrexia; need for respiratory therapy care; bronchospasm requiring therapy; pleural effusion or pneumothorax (or both) necessitating drainage; segmental pulmonary collapse, as confirmed by radiography; or pneumonia necessitating antibiotic therapy. Others have found that both shorter and longer periods of cessation of smoking were needed before achieving cardiovascular[235] and hematologic benefit.[236] Of note, Bluman and associates[237] performed a retrospective chart review of 410 patients undergoing noncardiac surgery at a VA hospital. Current smoking was associated with a nearly sixfold increase in risk for a postoperative pulmonary complication. Reduction in smoking within 1 month of surgery was not associated with a decreased risk for postoperative pulmonary complications. Nakagawa and coauthors also reported higher pulmonary complication rates in patients undergoing pulmonary

surgery who quit within 4 weeks of surgery than in current smokers or those who had stopped smoking for more than 4 weeks.[238] The fact that anesthesiologists rarely see their patients 4 weeks or more before surgery presents a dilemma: if one is unable to advise the patient to stop smoking 8 weeks or more before surgery, is it preferable for the patient to continue smoking? Perhaps these data will further support the implementation of preoperative and preprocedure assessment clinics in which anesthesiologists are able to advise and counsel patients about risk reduction.

At the Cleveland Clinic we have embarked on an active campaign motivated by several articles[239,240] and the ASA's efforts to use the preprocedure time of heightened awareness of health to try to motivate each patient who smokes to quit smoking as soon as recovery from surgery has begun. In the first 7 months we referred more than 1000 patients (of about 5000 admitted smokers) to a "breath free" clinic that follows a low-cost Web-based doctor-supervised process (Box 35-4) and succeeded in helping over 50% of those who kept their initial appointment successfully quit. Although that rate is lower than rates in patients self-referred and self-reported to websites that use the same protocol (Oprah.com and Real Age.com—where we have more than 120,000 self-reported successful quitters), we consider the effort worthwhile. Many fewer patients (about 100) have decided to quit before surgery (L. Skolaris and I. Hasan, personal communication).

When Skolnick and coworkers[226] studied 602 children prospectively, exposure to passive smoking (as measured by urinary cotinine, the major metabolite of nicotine) correlated directly with airway complications. Children with the least exposure to passive smoke had the fewest complications. Second-hand smoke may be a model for particulate air pollution with PM 2.5 particles, which have immediate and long-term effects in increasing lung dysfunction and inflammatory stimuli throughout the body.[241,242] In this sense, reducing particulate and diesel exhaust exposure in the 2 weeks before surgery might make sense, but such a hypothesis has not been tested (and outpatient surgery centers off busy freeways might prove to make such subtle inhibition of healing secondary to diesel particles an appropriate site to study).

As for things to do, Celli and associates[243] performed a randomized prospective controlled trial of intermittent positive-pressure breathing (IPPB) versus incentive spirometry and deep-breathing exercises in 81 patients undergoing abdominal surgery. The groups exposed to a respiratory therapist (regardless of the treatment given) had more than a 50% lower incidence of clinical complications (30% to 33% versus 88%) and shorter hospital stays than the control group did. Thus, this third prospective study indicates that outcome improves when there is any concern about

Box 35-4 You Tool: Breathe Free Program

Smoking Cessation Plan*

One of the most powerful addictions isn't bridal reality shops; it's cigarette smoking. Here, in our Breathe Free Program, developed with Daniel Seidman, MD, and the Cleveland Clinic team, we're going to teach you how to stop the addiction so that you can gain back the 8 to 13 years you've taken off your life (half in length and half in disability and illness) through those nasty sticks. Yes, you get a do-over here too and can make yourself younger even if you've burned your fingers with 20 cigarettes every day.

Step 1: Assess Yourself

Answer the following questions to see if you've lost control of your smoking behavior and it's turned into a full-fledged dependence.

1. **Have you smoked every day for at least the past several weeks?**
2. **Do you experience any of the following withdrawal symptoms after you stop or reduce your amount of smoking ("withdrawal symptoms can begin within a few hours of cessation")?**
   - Depressed mood
   - Insomnia
   - Irritability, frustration, or anger
   - Anxiety
   - Difficulty concentrating
   - Restlessness
   - Decreased heart rate
   - Increased appetite or weight gain
3. **Do you experience significant distress because of the symptoms in Question 2? Do you avoid social or work obligations—or leave in the middle of these obligations—because of significant distress or discomfort from not smoking?**

   If you answer "yes" to Question 1, "yes" to at least four of the symptoms in Question 2, and/or "yes" to Question 3, then you have a problem and may even meet the psychiatric definition for nicotine withdrawal. Knowing this can help build your commitment to change and to learning to breathe free.
4. **In the past year, was there a day you didn't smoke at all—not even a puff?**

   If you answered "yes," think about how you did it and how you then went back to smoking. Try to learn from what worked and what didn't.

   If you answered "no," don't despair. The movie in your head about how impossible breaking free from smoking will be probably is greatly exaggerated. With proper use of medicines and a good behavioral plan, it's possible to break free of smoking. We know, we helped over 700 people individually and over 80,000 using our Web-based programs (see oprah.com or realage.com). If you follow our plan and have a buddy to help, we believe your chance of success is over 60% each time you try—so three tries will get you to over a 90% chance of success.

*The Breath Free plan is copywritten by the YOU Docs in *YOU Being Beautiful: The Owner's Manual to Outer and Inner Beauty* (Free Press, 2008, United States), reprinted here by permission of the copyright owner and offered to all who want to use it—feel free to copy and hand to patients (as long as credit is given).

Box 35-4 You Tool: Breathe Free Program—cont'd

5. **Do you continue to smoke despite having a tobacco-caused medical problem such as bronchitis or COPD (chronic obstructive pulmonary disease)?**

   If you answered "yes," consider that almost all smokers are well aware of the medical problems associated with smoking. After all, they are listed on every pack you smoke. Even when told it is a matter of life and death, many continue to smoke after having a heart attack, lung surgery, or oral cancer removed. This behavior mystifies your loved ones and even leaves you, the smoker, bewildered, yet this is a hallmark of addiction and distinguishes it from "bad habits," which also involve automatic behavior. The difference is that bad habits predictably don't cause real and serious life consequences—a 20-can-a-day diet cola habit doesn't invariably result in troubles, nor does picking your nose.

6. **Do you get less of an effect—of pleasure or satisfaction—from the same number of cigarettes each day?**

7. **Do you continue to smoke, even though you enjoy only 10% to 20% of the cigarettes you light up?**

   If you answered "yes" to Questions 6 and 7, know that many people get sick of their addiction over time, especially after age 40. What was social and fun becomes rote habit with less pleasure than advertised. Keeping this in mind can motivate you to move forward with breathing free.

8. **Do you still enjoy smoking most or all of the time?**

   If you answered "yes," ask yourself if it would be nice to shed the burden of guilt and shame you carry from smoking? Remember, this is your body, and there is only one available for each customer. So even with all the new replacement parts available, you still can't protect your body from all the pollution in the cigarette smoke.

9. **Do you feel anxious and nervous, and has this continued every day for the past 2 weeks?**

   If you answered "yes," you may have more anxiety about getting through your breathe-free day—the day you go completely tobacco free. In that case, you may need to pay extra attention to the next step—working on preparation, confidence building, and motivation.

10. **Do you feel sad and blue, and has this continued every day for the past 2 weeks?**

    If you answered "yes," you may have more emotional discomfort after getting through your breathe-free day. You may also need to carefully review with your doctor nicotine withdrawal symptoms and the use of successful strategies to learn to live well without tobacco.

Step 2: Do the Prep Work

You're about to make a big change, one that requires some planning. Give yourself a month (31 days) to do all the prep work.

- **Promise yourself**: Make a personal pact with yourself to quit.
- **Set a quit date:** Make it at least a month from today
- **Take the Breathe Free Pledge:** See below.

As of _____, my official "Quit Date," I pledge to commit to breathing free!

My reasons for quitting smoking: _____ _____.

I have found a buddy I will call daily: _____ _____.

I recognize that this may be one of the greatest challenges of my life, but I also know that breathing free is the best decision I can make to protect and improve my health. Upon signing this contract, I make a commitment to myself to breathe free and free myself from the limitations placed on me by my addiction.

I don't know what will happen or how difficult it will be, but I can get help from _____ _____, and I have decided to (check one):

___ 1. Walk for 30 days and try nicotine patches (21 or 22 mg if I smoke a pack a day or so) and bupropion (100 mg twice a day—a reduced dose of Zyban) plus my buddy

___ 2. Use nicotine patches (or nicotine gum or nicotine oral inhaler) alone (plus my buddy)

___ 3. Use varenicline (Chantix) alone (plus my buddy)

I also know that staying smoke free (not having "just one") after the initial breathe-free period is important, and I have asked my friends and family to support me and not smoke around me. I will also continue to talk daily to my buddy for at least 6 months, and then I'll become a buddy to others.

By committing to a life of breathing free, I will ensure a healthier future for myself, and I will protect the well-being of my loved ones and everyone around me who will no longer be exposed to the dangers of second-hand smoke. I know that I am not only motivated but also committed and willing to make the effort to become a nonsmoker.

I deserve to give myself the healthiest life possible and breathe free!

- **Think of the three biggest reasons why you're quitting**: Write them on a card that you can carry with you and look at several times each day.
- **Be restrictive**: Eliminate smoking in two or three situations that usually prompt you to smoke.
- **Cut back**: Reduce the number of cigarettes you smoke to one pack a day or less.
- **Go cheap**: Change to a less desirable brand of cigarettes.
- **Need a light**: Discard your lighter and matches.
- **Misplace your cigarettes:** Carry them in a different place than you usually do.
- **Role-play**: Spend a little time each day imagining yourself in stressful situations in which you are not smoking.

(Continued)

Box 35-4 You Tool: Breathe Free Program—cont'd

Do the following four things, which will make quitting easier and could be the keys to your success.

- **Start walking 30 minutes a day—every day.**

Before you actually stop smoking, you have to establish another behavior—walking 30 minutes a day, every day—in its place. No excuses—you miss a day, you reset the clock to day 0. That is because another behavior takes at least 30 days to form. However, after a month of walking, you'll have two of the things you need to stick with our plan: more physical stamina and greater mental discipline.

- **Find a quitting buddy**.

Don't quit alone. We know from experience that everyone needs to be encouraged by someone—and your buddy is that someone. However, you shouldn't be the only one relying on other people; try to find a support partner who needs you as much as you need him or her.

- **See if you're covered**.

More and more insurance plans are offering some level of coverage for quit-smoking efforts. Ask your insurance company about its coverage. If your aren't insured, ask your HR department—many cover the cost (about $600 for 6 months—it really is cheaper than a pack a day, but we know dollars spent for medical expenses and smoking are usually segregated in smokers' minds and hearts).

- **Schedule a checkup.**

Quitting smoking is physically and mentally stressful, and you want to be sure you have no conditions that might interfere with the tools, techniques, and medications suggested in this program. So talk to your doctor about the following prescriptions to help you stop smoking:

1. Bupropion (Zyban or Wellbutrin) in 100-milligram tablets—one twice a day. Bupropion is an anticraving drug (it's also an antidepressant at higher doses) that can help you make the transition from smoker to quitter. It can interact with other medications, so make sure your doctor's aware of any drugs you're taking, particularly for high blood pressure or seizure disorders.
2. Nicotine patches. Talk with your doctor to figure out what strength would be best for you—for a one-pack-a-day habit it's usually 22 milligrams.

Quitting day is almost here—it's time to start getting your body ready to fight future cravings.

- **Start taking bupropion.** On day 30, 2 days before you'll actually stop smoking, take one tablet in the morning.
- **Keep taking bupropion**. On day 31, take one bupropion tablet in the morning.

Step 3: Break the Habit

Today's the day you stop smoking. If you've done the prep work, you're ready.

- **On day 32, QUIT**: Throw away all your cigarettes, and get rid of all ashtrays and any other smoking-related objects.
- **Put on a nicotine patch**. Place one on your arm, chest, or thigh (you'll be doing this daily for a while).
- **Take your bupropion**: One in the morning and one at night.

Here are your daily to-do's for days 33 through 61.

- **Take two**: Increase your bupropion to two tablets a day—one in the morning and another in the evening.
- **Patch up**: Put on a new one every day (and don't forget to take the old one off).
- **Keep walking**: Every day for 30 minutes.
- **Reach out**: Check in with your buddy.
- **Drink up**: Have as much coffee or water as you wish.

Step 4: Enjoy Life as an Ex-Smoker

Making it through a month without smoking is a huge accomplishment. It's time to celebrate the new YOU! Here are some to-do's for day 62 and beyond.

- **Breathe in**: Enjoy how quitting has made your lungs happier.
- **Push yourself**: Use your newfound vitality to start a strength-building routine. But take it slow; don't increase your physical activity by more than 10% a week.
- **Love life without the patch**: Every 2 months, decrease the dose of your nicotine patch by a third. Your goal is to be patch free after 6 months.
- **Say bye-bye bupropion**: But make it a slow goodbye. At 5 months, decrease your bupropion to one tablet in the evening, and aim to be off it entirely by your 8-month anniversary. Tip: Just in case you feel a craving, for the rest of your life carry one bupropion tablet with you at all times so that you can take it if you need to.

lung function on the part of someone knowledgeable in maneuvers designed to clear lung secretions.

Bartlett and coworkers[244] randomly assigned 150 patients undergoing extensive laparotomy to one of two groups. One group received preoperative instruction in and postoperative use of incentive spirometry (10 times per hour). The other group received similar medical care but no incentive spirometry. Only 7 of 75 patients using incentive spirometry had postoperative pulmonary complications, as opposed to 19 of 75 in the control group. However, other studies have not shown a benefit for specific treatments or have been too contaminated with bias to have a clear result emerge. Lyager and colleagues[245] randomly assigned 103 patients undergoing biliary or gastric surgery to receive either incentive spirometry with preoperative and postoperative chest physiotherapy or only preoperative and postoperative chest physiotherapy. No difference in the postoperative course or pulmonary complications was found between the two groups. Other studies have shown a specific benefit (i.e., above that provided by routine care) for chest physiotherapy and IPPB. These studies are usually poorly controlled, not randomized, or retrospective in design (or any combination of the three); these deficiencies probably substantially bias the results toward finding a benefit in

Table 35-13 Grade of Dyspnea Caused by Respiratory Problems (Assessed In Terms of Walking on a Level Surface at a Normal Pace)

Category	Description
0	No dyspnea while walking on a level surface at a normal pace
I	"I am able to walk as far as I like, provided I take my time"
II	Specific (street) block limitation ("I have to stop for a while after one or two blocks")
III	Dyspnea on mild exertion ("I have to stop and rest while going from the kitchen to the bathroom")
IV	Dyspnea at rest

Modified from Boushy SF, Billing DM, North LB, et al: Clinical course related to preoperative pulmonary function in patients with bronchogenic carcinoma. Chest 59:383, 1971.

reducing postoperative pulmonary complications. Although randomized prospective studies showed no benefit or actual harm from chest physiotherapy and IPPB on the resolution of pneumonia or postoperative pulmonary complications, the four studies cited earlier[228,233,243,244] and numerous retrospective studies strongly suggest that preoperative evaluation and treatment of patients with pulmonary disease actually decrease perioperative respiratory complications, even if only by causing a change in anesthetic techniques.

Recent meta-analyses have suggested a benefit of anesthetic and pain management with respect to respiratory outcomes. Rodgers and associates reviewed 141 trials involving 9559 patients who had been randomized to receive neuraxial blockade or general anesthesia. Overall mortality was significantly lower in the neuraxial blockade group (2.1% versus 3.1%). The relative risk of pneumonia in the neuraxial group was 0.61 (CI, 0.48 to 0.81), and the relative risk of respiratory depression was 0.41 (CI, 0.23 to 0.73).[227]

Not all studies demonstrate beneficial effects of pretreatment. In afebrile outpatient ASA class I and II children with no lung disease or findings who underwent noncavitary, nonairway surgery lasting less than 3 hours, neither albuterol nor ipratropium premedication decreased adverse events.[246]

Evaluation of dyspnea is especially useful and thus warrants discussion here (for a review of specific pulmonary function tests that identify high-risk groups, see Chapter 44). Boushy and coworkers[247] found that grades of preoperative dyspnea correlated with postoperative survival. (Grades of respiratory dyspnea are provided in Table 35-13.) Mittman[248] demonstrated an increased risk of death after thoracic surgery, from 8% in patients without dyspnea to 56% in patients who were dyspneic. Similarly, Reichel[249] found that no patients died after pneumonectomy if they were able to complete a preoperative treadmill test for 4 minutes at the rate of 2 mph on level ground. Other studies have found that the history and physical examination of an asthmatic subject can also predict the need for hospitalization.[217] Wong and colleagues[250] found that the risk index (Table 35-14) correlated with postoperative pulmonary complications. Other than dyspnea, what preoperative conditions make postoperative respiratory complications more likely? (See also Chapter 34.)

Arozullah and associates developed the first validated multifactorial risk index for postoperative respiratory failure, defined as mechanical ventilation for more than 48 hours after surgery or reintubation and mechanical ventilation after postoperative extubation.[251] In a prospective cohort study of 181,000 male veterans as part of the National Veterans Administration Surgical Quality Improvement Program, seven factors independently predicted risk (Table 35-15). With increasing numbers of risk factors present, the rate of complications increased from 0.5% (class 1) to 26.6% (class 4). Arozullah and colleagues subsequently developed a risk index for postoperative pneumonia by using data on 160,805 patients undergoing major noncardiac surgery and validated the index by using data on an additional 155,266 patients.[252] Patients were divided into five risk classes by using risk index scores (Table 35-16). Pneumonia rates were 0.2% in those with 0 to 15 risk points, 1.2% in those with 16 to 25 risk points, 4.0% in those with 26 to 40 risk points, 9.4% in those with 41 to 55 risk points, and 15.3% in those with more than 55 risk points.

Preoperative evaluation of patients with pulmonary disease can be found in Chapters 34 and 44. Despite the lack of definitive data establishing the efficacy of preoperative pulmonary testing and therapy, we recommend the following approach:

1. Eradicate acute infections and suppress chronic infections by using appropriate diagnostic measures and antibiotic treatment.
2. Relieve bronchospasm by using inhaled corticosteroids and bronchodilating drugs and document such relief with measurements of FEV_1 (also see Chapter 44).

Table 35-14 Classification of Risk of Pulmonary Complications for Thoracic and Abdominal Procedures

Category	Points*
I. Expiratory spirogram	
A. Normal (% FVC + [% FEV_1/FVC] > 150)	0
B. % FVC + (% FEV_1/FVC) = 100-150	1
C. % FVC + (% FEV_1/FVC) < 100	2
D. Preoperative FVC > 20 mL/kg	3
E. Postbronchodilator FEV_1/FVC < 50%	3
II. Cardiovascular system	
A. Normal	0
B. Controlled hypertension, myocardial infarction without sequelae for more than 2 yr	0
C. Dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, dependent edema, congestive heart failure, angina	1
III. Nervous system	
A. Normal	0
B. Confusion, obtundation, agitation, spasticity, discoordination, bulbar malfunction	1
C. Significant muscular weakness	1
IV. Arterial blood gases	
A. Acceptable	0
B. $Paco_2$ >50 mm Hg or Pao_2 <60 mm Hg on room air	1
C. Metabolic pH abnormality >7.50 or <7.30	1
V. Postoperative ambulation	
A. Expected ambulation (minimum, sitting at bedside) within 36 hr	0
B. Expected complete bed confinement for ≥36 hr	1

Modified from Wong DH, Weber EC, Schell MJ, et al: Factors associated with postoperative pulmonary complications in patients with severe COPD. Anesth Analg 80:276, 1995.

Table 35-15 Preoperative Predictors of Postoperative Respiratory Failure

Variable	Odds Ratio (95% Confidence Interval)
Type of surgery	
Abdominal aortic aneurysm	14.3 (12.0-16.9)
Thoracic	8.14 (7.17-9.25)
Neurosurgery, upper abdominal, or peripheral vascular	4.21 (3.80-4.67)
Neck	3.10 (2.40-4.01)
Other surgery*	1.00 (reference)
Emergency surgery	3.12 (2.83-3.43)
Albumin <0.30 g/L	2.53 (2.28-2.80)
Blood urea nitrogen >0.30 mg/dL	2.29 (2.04-2.56)
Partially or fully dependent status	1.92 (1.74-2.11)
History of COPD	1.81 (1.66-1.98)
Age (yr)	
≥70	1.91 (1.71-2.13)
60-69	1.51 (1.36-1.69)
<60	1.00 (reference)

*Other surgeries include ophthalmologic, ear, nose, mouth, lower abdominal, extremity, dermatologic, spine, and back surgery.
COPD, chronic obstructive pulmonary disease.
From Arozullah AM, Daley J, Henderson WG, et al: Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Ann Surg 232:242-253, 2000, with permission.

3. In patients with bronchial asthma, consider the administration of corticosteroids beginning at least 48 hours before surgery in patients with a significant history of bronchospastic disease to achieve the maximal effect at the time of surgery. No randomized data support such an approach, but studies have not shown an increase in the risk for respiratory infection or wound complications.[253]
4. Institute measures to improve sputum clearance and familiarize the patient with respiratory therapy equipment (incentive spirometry) and postural drainage maneuvers. Initiate practice coughing and deep-breathing exercises.
5. Treat uncompensated right ventricular heart failure and heart rate with digoxin, diuretics, oxygen, and drugs that decrease pulmonary vascular resistance (e.g., hydralazine).[254]
6. The use of low-dose heparin prophylactically to decrease the incidence of venous thrombosis (and pulmonary emboli) has been the standard.[255,256] More recently, the use of low-molecular-weight heparin and intermittent compression stockings has become the standard for high-risk patients.[235a,255,256]
7. Identify and treat suspected or diagnosed sleep apnea with continuous positive airway pressure (CPAP), biphasic positive airway pressure (BiPAP), or other measures as indicated earlier (in the section "Disorders of Nutrition, Including Obesity").
8. Encourage reduction or cessation of smoking at least 4 weeks and preferably 8 weeks or more before surgery.[234,239,240]

Specific Diseases

Pulmonary Vascular Diseases

Pulmonary vascular diseases include pulmonary hypertension secondary to heart disease (postcapillary disorders), parenchymal lung disease (pulmonary precapillary disorders), pulmonary embolism, and cor pulmonale from COPD.[257] Optimal preoperative management of these conditions requires treatment of the underlying disease.[257-259] Because pulmonary embolism can be particularly difficult to diagnose, it is crucial to be especially alert to the possibility of this disease. The clinical findings of pulmonary emboli are not always present or specific for the diagnosis. The history may include tachypnea, dyspnea, palpitations, syncope, chest pain, or hemoptysis. Physical examination can reveal a pleural rub, wheezing, rales, a fixed and split second heart sound, right ventricular lift, or evidence of venous thrombosis, none of which are present in most patients. If the ECG shows an

Table 35-16 Postoperative Pneumonia Risk Index

Preoperative Risk Factor	Point Value
Type of surgery	
Abdominal aortic aneurysm repair	15
Thoracic	14
Upper abdominal	10
Neck	8
Neurosurgery	8
Vascular	3
Age	
80 yr	17
70-79 yr	13
60-69 yr	9
50-59 yr	4
Functional status	
Totally dependent	10
Partially dependent	6
Weight loss >10% in past 6 mo	7
History of chronic obstructive pulmonary disease	5
General anesthesia	4
Impaired sensorium	4
History of cerebrovascular accident	4
Blood urea nitrogen level	
<2.86 mmol/L (0.8 mg/dL)	4
7.85-10.7 mmol/L (22-30 mg/dL)	2
≥10.7 mmol/L (≥30 mg/dL)	3
Transfusion >4 U	3
Emergency surgery	3
Steroid use for chronic condition	3
Current smoker within 1 yr	3
Alcohol intake >2 drinks/day in past 2 wk	2

From Arozullah AM, Khuri SF, Henderson WG, et al: Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Ann Intern Med 135:847-857, 2001, with permission.

S_1Q_3 pattern, spiral CT or lung perfusion scans can be obtained to rule out the diagnosis of pulmonary emboli. A high degree of suspicion is necessary to warrant angiography and anticoagulation or fibrinolytic therapy. If possible, the reactivity of the pulmonary vasculature should be determined, for it may be enhanced or decreased by such drugs as nifedipine, hydralazine, nitroglycerin, prazosin, tolazoline, phentolamine, sildenafil citrate, and nitric oxide. Monitoring of pulmonary artery pressure is often required; preoperative measures should be undertaken to ensure that the patient is not exposed to conditions that elevate pulmonary vascular resistance (e.g., hypoxia, hypercapnia, acidosis, lung hyperinflation, hypothermia)[260] or that decrease blood volume (prolonged restriction of fluid intake) or systemic vascular resistance.

Infectious Diseases of the Lung

Preoperative evaluation and treatment should follow the basic guidelines outlined in the introduction to this section and Chapter 34; treatment of the underlying disease should be completed before all but emergency surgery is performed.

Even though elective surgery should be postponed whenever infectious diseases of the lung are present, patients undergoing emergency surgery often have nosocomial infections and immunocompromised systems. The predominant pathogens for nosocomial pneumonia are gram-negative bacilli, *Staphylococcus aureus*, *Haemophilus influenzae*, anaerobes, and pneumococci. Furthermore, tuberculosis increased rapidly in the late 1980s and in the 1990s, probably because of reactivation in patients infected with HIV. Increased funding and directly observed antituberculosis therapy have more than offset immigrant and travel risk to cause it to decrease recently. Tuberculosis leads to chronic pulmonary and systemic symptoms. Affected patients may have malaise, headache, fever, hemoptysis, and extrapulmonary diseases affecting the skin, cervical lymph nodes, kidneys, pericardium, and meninges. Active disease is treated with four-drug therapy: isoniazid, pyrazinamide, ethambutol or streptomycin, and rifampin for 9 months. Therapy should probably be started before surgery. Management of these emergency patients (many of whom have adult respiratory distress syndrome) before they are brought to the operating room might include initiation of anti-infective therapy, optimization of fluid status and gas exchange, and therapy for the underlying pathophysiologic process.

Chronic Diseases of the Lung

Treatment of COPD (reactive airways) may include the use of β-adrenergic drugs, parasympatholytic agents (especially for exercise-induced asthma), systemic or inhaled corticosteroids, and leukotriene antagonists. An estimated 5% of the population has bronchospasm. Some investigators recommend using inhaled bronchodilators as first-line drugs and reducing the dose of inhaled steroids, such as beclomethasone dipropionate, budesonide, mometasone, or fluticasone, which are inactivated after absorption. However, in large doses, these "inhaled" steroids can suppress adrenal function, and supplemental systemic corticosteroids may be needed at times of stress (see earlier discussion under the section "Adrenocortical Malfunction"). Preoperative assessment must include gaining knowledge of drug regimens and their effects and education of the patient regarding proper use of an inhaler (Box 35-5) because these drugs can interact dangerously with anesthetics (see the last section of this chapter) or can be used inappropriately and therefore produce side effects without maximum benefit.[215-225] No known interaction between the inhaled anticholinergic ipratropium bromide and muscle relaxants has been reported. Patients can feel fine at rest but must be tested by exercise or spirometry to document the degree of current bronchospasm. Furthermore, a symptomatic response to bronchodilators in an asymptomatic patient may not predict whether the patient responds to bronchodilator therapy. An estimated 10% of asthmatic patients exhibit sensitivity to aspirin and may react not only to compounds containing aspirin but also to tartrazine, yellow dye No. 5, indomethacin, other nonsteroidal anti-inflammatory drugs, and aminopyrine.[261]

Box 35-5 Procedures for Correct Use of a Metered-Dose Inhaler

Remove the cap and hold the inhaler upright.

Shake the inhaler.

Tilt the head back slightly and exhale steadily to functional residual capacity.

Position the inhaler by using a spacer between the actuator and the mouth.

Press down on the inhaler while taking a slow, deep breath (3 to 5 seconds).

Hold the full inspiration for at least 5 and up to 10 seconds, if possible, to allow the medication to reach deeply into the lungs.

Repeat inhalations as directed. Waiting 1 minute after inhalation of the bronchodilator may permit subsequent inhalations to penetrate more deeply into the lungs and is necessary to ensure proper delivery of the dose. Rinse your mouth and expectorate after using the inhaler.

Cystic fibrosis is characterized by dilatation and hypertrophy of the bronchial glands, mucous plugging of the peripheral airways, and frequently, bronchitis, bronchiectasis, and bronchiolectasis. For all these conditions, the measures recommended earlier in this section, as well as appropriate hydration to allow mobilization of secretions, constitute optimal preprocedure therapy.

Surgical resection is the primary therapy for non–small cell carcinomas (e.g., adenocarcinoma, squamous cell carcinoma, and large cell carcinoma). These carcinomas account for 75% of all lung carcinomas, 12% of all malignant tumors, and 20% of all cancer deaths in the United States.[262] Success of surgery can be predicted by the stage of the tumor.

The combination of chemotherapy and radiation therapy is the current treatment of choice for small cell carcinomas of the lung.[263] Oat cell (small cell) carcinoma of the lung and bronchial adenomas are known for their secretion of endocrinologically active substances, such as ACTH-like hormones. Squamous cell cancers in the superior pulmonary sulcus produce Horner's syndrome, as well as characteristic pain in areas served by the eighth cervical nerves and first and second thoracic nerves. These tumors are now treated with preoperative radiation; surgical resection leads to an almost 30% "cure" rate.

Anaphylaxis, Anaphylactoid Responses, and Allergic Disorders Other Than Those Related to Lung Diseases and Asthma

Anaphylactic and Anaphylactoid Reactions

Anaphylaxis is a severe life-threatening allergic reaction. *Allergic* applies to immunologically mediated reactions, as opposed to those caused by pharmacologic idiosyncrasy, by direct toxicity or drug overdosage, or by drug interaction.[264-266] Anaphylaxis is the typical immediate hypersensitivity reaction (type I). Such reactions are produced by immunoglobulin E (IgE)-mediated release of pharmacologically active substances. These mediators in turn produce specific end-organ responses in the skin (urticaria), the respiratory system (bronchospasm and upper airway edema), and the cardiovascular system (vasodilation, changes in inotropy, and increased capillary permeability). Vasodilation occurs at the level of the capillary and postcapillary venule and leads to erythema, edema, and smooth muscle contraction. This clinical syndrome is called *anaphylaxis*. By contrast, *anaphylactoid reaction* denotes an identical or very similar clinical response that is not mediated by IgE or (usually) an antigen-antibody process.[265,266]

In anaphylactic reactions, an injected or inhaled (or injested) substance—usually drugs, food, or insect venom—can serve as the allergen itself. Low-molecular-weight agents are believed to act as haptens that form immunologic conjugates with host proteins. The offending substance, regardless of whether it is a hapten, may be the parent compound, a nonenzymatically generated product, or a metabolic product formed in the patient's body. When an allergen binds immunospecific IgE antibodies on the surface of mast cells and basophils, histamine and eosinophilic chemotactic factors of anaphylaxis are released from storage granules in a calcium- and energy-dependent process.[265,266] Other chemical mediators are rapidly synthesized and subsequently released in response to cellular activation. These mediators include slow-reacting substance of anaphylaxis, which is a combination of three leukotrienes; other leukotrienes[265,266]; kinins; platelet-activating factors; adenosine; chemotactic factors; heparin; tryptase; chymase; and prostaglandins, including the potent bronchoconstrictor prostaglandin D_2, eosinophil growth and activating factors, mast cell growth factors, and proinflammatory and other factors that contribute to the IgE isotype switch.

The end-organ effects of the mediators produce the clinical syndrome of anaphylaxis. Usually, a first wave of symptoms, including those caused by vasodilation and a feeling of impending doom, is quickly followed by a second wave as the cascade of mediators amplifies the reactions. In a sensitized patient, onset of the signs and symptoms caused by these mediators is usually immediate but may be delayed 2 to 15 minutes or, in rare instances, as long as 2.5 hours after the parenteral injection of antigen.[267,268] After oral administration, manifestations may occur at unpredictable times.

Mast cell proliferation, together with severe progressive inflammation, contributes to the worsening of symptoms that occurs even after an allergen load is no longer present. The antigen present in cells and lymphocytes, as well as activated mast cells, starts to induce the production of cytokines. These proinflammatory cytokines recruit more inflammatory cells, which leads to tissue edema and mediates a second wave of mast cell degranulation. This second wave can promote the recurrence of severe symptoms 6 to 8 hours later and necessitates, some believe, at least 8 hours of continued ICU-like observation.

In addition, there are multiple effector processes by which biologically active mediators can be generated to produce an anaphylactoid reaction. Activation of the blood coagulation and fibrinolytic systems, the kinin-generating sequence, or the complement cascade can produce the same inflammatory substances that result in an anaphylactic reaction. The two mechanisms known to activate the complement system are called classical and alternative. The classical pathway can be initiated through IgG or IgM (transfusion reactions) or plasmin. The alternative pathway can be activated by lipopolysaccharides (endotoxin), drugs (Althesin), radiographic contrast media,[269] membranes (nylon tricot membranes for bubble oxygenators), cellophane membranes of dialyzers, vascular graft material,[270] latex or latex-containing products,[271,272] and perfluorocarbon artificial blood. The most common agents responsible for intraoperative anaphylaxis are muscle relaxants.[272] However, latex accounts for a significant number of these reactions, and the incidence of intraoperative anaphylaxis caused by latex is increasing. It is now probably the second most important cause of intraoperative anaphylaxis. In addition, histamine can be liberated independent of immunologic reactions.[273] Mast cells and basophils release histamine in response to chemicals or drugs. Most narcotics can release histamine[273] and produce an anaphylactoid reaction, as can radiographic contrast media,[269] *d*-tubocurarine, and thiopental. What makes some patients susceptible to release of histamine in response to drugs is unknown, but hereditary and environmental factors may play a role.

Intravenous contrast material is probably the most frequently used agent that causes anaphylactoid reactions. Because diagnostic (skin and other) tests are helpful only in IgE-mediated reactions, pretesting is not useful for contrast reactions. Pretreatment with diphenhydramine, cimetidine (or ranitidine), and corticosteroids has been reported to be useful in preventing or ameliorating anaphylactoid reactions to intravenous contrast material[269,274] and perhaps to narcotics. Unfortunately, very large doses of steroids (1 g of methylprednisolone intravenously) may be necessary to obtain a beneficial effect.[275] The efficacy of large-dose steroid therapy has not been confirmed. Other common substances associated with anaphylactic or anaphylactoid reactions that might merit preoperative therapy include antibiotics, volume expanders, and blood products (Table 35-17).[265] The anesthesiologist should be prepared preoperatively to treat an anaphylactic or anaphylactoid response.

In some cases, a patient with a history of an anaphylactic or anaphylactoid reaction must receive a substance suspected of producing such a reaction (e.g., iodinated contrast material). In addition, some patients have a higher than average likelihood of having a reaction, thus warranting well-planned pretreatment and therapy for possible anaphylactic and anaphylactoid reactions.[269]

Minimizing Risks Preoperatively

Although virtually all evidence on this subject is merely anecdotal, enough consistent thought recurs through the literature to justify proposing an optimal approach to these problems. First, predisposing factors should be sought; patients with a history of atopy or allergic rhinitis should be suspected of being at risk. Because anaphylactic and anaphylactoid reactions to contrast media occur 5 to 10 times more frequently in patients with a previously suspected reaction, consideration should be given to the administration of low-osmotic agents and both H_1 and H_2 receptor antagonists for 16 to 24 hours before exposing these

Table 35-17 Incidence of Anaphylactic or Anaphylactoid Reactions to Some Common Agents

Agent	Incidence
Plasma protein	
Plasma protein derivative	0.019
Human serum albumin	0.011
Dextran 60/75	0.069
Dextran 40	0.007
Hydroxyethyl starch	0.085
Penicillin	0.002*
Chymopapain	0.3-1.5

*Fatal reactions.
Data modified from Levy JH, Roizen MF, Morris JM: Anaphylactic and anaphylactoid reactions: A review. Spine 11:282, 1986; and Moss J, McDermott DJ, Thisted RA, et al: Anaphylactic/anaphylactoid reactions in response to Chymodiactin (chymopapain). Anesth Analg 63:253, 1984.

patients to a suspected allergen. H_1 receptor antagonists appear to require this much time to act on the receptor. Volume status can be optimized,[265] and perhaps large doses of steroids (1 g of hydrocortisone) should also be administered before exposing patients to agents associated with a high incidence of anaphylactic or anaphylactoid reactions.[275] Older patients and patients taking β-adrenergic blocking drugs present special problems; they are at higher risk of having complications from both pretreatment (especially vigorous hydration) and therapy for anaphylactic reactions (glucagon is useful here) and are less responsive to treatment regimens.[276] One approach is to avoid drugs likely to trigger anaphylactic or anaphylactoid reactions or alter the treatment protocol for this group. Drawing blood for later analysis, especially of tryptase, can be useful in clarifying the diagnosis.[277]

With the increasing incidence of latex hypersensitivity, attempts have been made to make much of the operating room environment latex free; however, costs and preferences have resulted in the continued use of latex-containing gloves in many hospitals. Nonetheless, more hospitals are totally latex free. In allergic patients, care should be taken to ensure that no latex-containing products are present in the operating room.

Primary Immunodeficiency Diseases

Primary immunodeficiency diseases are usually manifested early in life as recurrent infections. Along with survival achieved with antibiotic and antibody treatment have come new prominent features: cancer and allergic and autoimmune disorders. Hereditary angioneurotic edema is an autosomal dominant genetic disease characterized by episodes of angioneurotic edema involving the subcutaneous tissues and submucosa of the GI tract and airway and often manifested as abdominal pain. These patients have a functionally impotent inhibitor or deficiency of an inhibitor to complement component C1. Treatment of an acute attack is supportive because epinephrine, antihistamines, and corticosteroids often fail to work. Plasma transfusions have been reported to resolve attacks or make them worse (theoretically by supplying either C1 esterase inhibitor or previously depleted complement components). The severity of attacks can be prevented or decreased by drugs that are either plasmin inhibitors (e.g., ε-aminocaproic acid [EACA] and tranexamic acid) or androgens (e.g., danazol). Because trauma can precipitate acute attacks, prophylactic therapy with danazol, intravenous EACA, plasma, or all three is recommended before elective surgery. Reports have also described the successful use of a partially purified C1 esterase inhibitor in two patients.

Most of the 1 in 700 persons who have selective IgA deficiency (i.e., <5 mg/dL) have repeated serious infections or connective tissue disorders. These infections commonly involve the respiratory tract (e.g., sinusitis, otitis) or GI tract (manifested as diarrhea, malabsorption, or both). If the patient has rheumatoid arthritis, Sjögren's syndrome, or systemic lupus erythematosus, the anesthetist should consider the possibility of isolated IgA deficiency. However, patients with this disorder can be otherwise healthy. Because antibodies to IgA may develop in these patients if previously exposed to IgA (as might occur from a previous blood transfusion), subsequent blood transfusions can cause anaphylaxis, even when they contain washed erythrocytes. Transfusions should therefore consist of blood donated by another IgA-deficient patient.

Many immunomodulators are now being given to augment cancer treatments[278]; no interactions between these modulators, no effects on the incidence of immune reactions during anesthesia, and no interactions with anesthetic effects have been reported except those regarding immune-suppressing drugs (see the last section of this chapter).

Immunonutrition[271] is increasingly being used preprocedurally by patients and prescribed by providers to decrease inflammatory responses. Whereas excellent data on the benefits of probiotics in changing the intestinal mileau to decrease inflammation can be found, limited data are available on their effects on periprocedural recovery or outcomes.

Diseases of the Central Nervous System, Neuromuscular Diseases, and Psychiatric Disorders

Evaluation of a patient with neurologic or psychiatric disease can be found in Chapter 34. Information gathered from the history that would warrant further investigation includes a previous need for postoperative ventilation in a patient without inordinate lung disease, which would indicate the possibility of metabolic neurologic disorders such as porphyria, alcoholic myopathy, other myopathies, neuropathies, and neuromuscular disorders such as myasthenia gravis. Other historical information warranting further investigation would be the use of drugs such as steroids; guanidine; anticonvulsant, anticoagulant, and antiplatelet drugs; lithium; tricyclic antidepressants; phenothiazines; and butyrophenones.

Although preoperative treatment of most neurologic disorders has not been reported to lessen perioperative morbidity, knowledge of the pathophysiologic characteristics of these disorders is important in planning intraoperative and postoperative management. Thus, preoperative knowledge about these disorders and their associated conditions (e.g., cardiac arrhythmias with Duchenne's muscular dystrophy or respiratory and cardiac muscle weakness with dermatomyositis) may reduce perioperative morbidity. A primary goal of neurologic evaluation is to determine the site of the lesion in the nervous system. Such localization to one of four levels (supratentorial compartment, poste-

rior fossa, spinal cord, peripheral nervous system) is essential for accurate diagnosis and appropriate management. (Disorders accompanied by increased intracranial pressure and cerebrovascular disorders are discussed in Chapters 13 and 63.)

Coma

Little is known about specific anesthetic or perioperative or periprocedural choices that alter outcome for a comatose patient, but as for all other conditions, it is imperative to know the cause of the coma so that drugs can be avoided that might worsen the condition or that might not be metabolized because of organ dysfunction. First, the patient should be observed. Yawning, swallowing, or licking of the lips implies a "light" coma with major brainstem function intact. If consciousness is depressed but respiration, pupillary reactivity to light, and eye movements are normal and no focal motor signs are present, metabolic depression is likely. Abnormal pupillary responses may indicate hypoxia, hypothermia, local eye disease, or drug intoxication with belladonna alkaloids, narcotics, benzodiazepines, or glutethimide; pupillary responses may also be abnormal, however, after the use of eye drops. Other metabolic causes of coma include uremia, hypoglycemia, hepatic coma, alcohol ingestion, hypophosphatemia, myxedema, and hyperosmolar nonketotic coma. Except in extreme emergencies, such as uncontrolled bleeding or a perforated viscus, care should be taken to render the patient as metabolically normal as possible before surgery. This practice and documenting the findings on the chart preoperatively lessen any confusion regarding the cause of intraoperative and postoperative problems. However, too rapid correction of uremia or hyperosmolar nonketotic coma can lead to cerebral edema, a shift of water into the brain as a result of a reverse osmotic effect caused by dysequilibrium of the urea concentration.

The physical examination can be extremely helpful preoperatively in assessing the prognosis. Arms flexed at the elbow (i.e., decorticate posture) imply bilateral hemisphere dysfunction but an intact brainstem, whereas extension of the legs and arms (bilateral decerebrate posture) implies bilateral damage to structures at the upper brainstem or deep hemisphere level. Seizures are often seen in patients with uremia and other metabolic encephalopathies. Hyperreflexia and upward-pointing toes suggest a structural CNS lesion or uremia, hypoglycemia, or hepatic coma; hyporeflexia and downward-pointing toes with no hemiplegia generally indicate no structural CNS lesion.

Epileptic Seizures

Epileptic seizures result from paroxysmal neuronal discharges of abnormally excitable neurons. Six percent to 10% of individuals younger than 70 years will experience a seizure at some time during their lifetime. Fifty percent to 70% of patients with one seizure will never have another. However, 70% of people with two seizures will have an epileptic focus, be candidates for antiseizure medications, and be subject to withdrawal seizures after anesthesia if such medications are not continued.[279] A seizure is the term for the clinical event defined as a paroxysmal alteration in neurologic function caused by a synchronous, rhythmic depolarization of brain cortical neurons. Epilepsy is the condition manifested by recurrent, unprovoked seizures. Sometimes syncopal episodes can be mistaken for seizures, especially when interviews are compressed in the short timeframe of a preoperative visit. We believe that each patient who gives a history of recent undiagnosed syncope or seizure should be seen by a specialist in this field before proceeding with anesthesia because anesthesia can provoke these conditions (see later).[280] Twenty-five percent of patients with a seizure have a normal electroencephalogram (EEG) when interictal. Thus, a negative EEG does not indicate that someone with a seizure will not have a withdrawal seizure when emerging from anesthesia. Seizures can be generalized (arising from deep midline structures in the brainstem or thalamus, usually without an aura or focal features during the seizure), partial focal motor, or sensory (the initial discharge comes from a focal unilateral area of the brain, often preceded by an aura). As with cerebrovascular accidents and coma, knowing the origin may be crucial to understanding the pathophysiologic processes of the disease and to managing the intraoperative and postoperative course.

Epileptic seizures can arise from discontinuation of sedative-hypnotic drugs or alcohol, use of narcotics, uremia, traumatic injury, neoplasms, infection, congenital malformation, birth injury, drug use (e.g., amphetamines, cocaine), hypercalcemia or hypocalcemia, blood in the ventricle or hypoxia, and vascular disease and vascular accidents. Thirty percent of epileptic seizures have no known cause. Most partial seizures are caused by structural brain abnormalities (secondary to tumor, trauma, stroke, infection, and other causes).

An epileptic patient requires no special anesthetic management other than that for the underlying disease. Most authorities believe that anticonvulsant medications should be given in the therapeutic range[279-281] and continued through the morning of surgery, even in pregnant women; they should also be given postoperatively, even in mothers who plan to breast-feed, according to guidelines published by the American Academy of Neurology. Many of the epileptic drugs, including phenytoin, carbamazepine, and phenobarbiturate, alter the hepatic metabolism of many drugs and induce cytochrome P450 enzyme activity. Drug-drug interactions are much less problematic with the newer epileptic drugs such as gabapentin and topirimate.[279] Appropriate treatment of status epilepticus may include general anesthesia.[281] In one controlled trial, phenobarbital was more rapidly effective in controlling status epilepticus than was diazepam followed by phenytoin.[281] The frequency of side effects and required tracheal intubation was similar for both regimens. High concentrations of enflurane (especially with hyperventilation) can be associated with EEG evidence of epileptic activity and tonic-clonic movements. These seizures, however, do not appear to have serious sequelae. Enflurane anesthesia does not seem to increase seizure activity in patients with a history of convulsive disorders, and it even suppresses seizures induced by electroshock, pentylenetetrazole, strychnine, picrotoxin, or bemegride. Thus, other than the use of current drug therapy and heeding precautions taken for the underlying disease, no known changes in perioperative management seem to be indicated.

Infectious Diseases of the Central Nervous System, Degenerative Disorders of the Central Nervous System, and Headache

Many degenerative CNS disorders have been traced to slowly developing viral diseases or even the presence of certain proteins

or viral particles ("prions"). No special perioperative anesthetic considerations appear to apply for infectious disorders of the CNS other than those for increased intracranial pressure and avoidance of occupational exposure and transmission of disease to health care workers (also see Chapter 101). The appropriate prophylactic measures to take if one comes in contact with meningococcal disease or other infectious CNS diseases are still not well established. The use of *H. influenzae* type b vaccine has made meningitis an adult disease.[282]

Parkinson's disease is a degenerative disorder of the CNS that may or may not be caused by a virus. Clinically, Parkinson's disease, chronic manganese intoxication, phenothiazine or butyrophenone toxicity, Wilson's disease, Huntington's chorea, traumatic boxing injury, the effects of street drug toxins such as methylphenyltetrahydropyridine (MPTP), and carbon monoxide encephalopathy all have similar initial features: bradykinesia, muscular rigidity, and tremor.

Newer therapies have been developed to arrest or even reverse the progression of Parkinson's disease. Therapy is directed at (1) increasing the neuronal release of dopamine or the receptor's response to dopamine, (2) stimulating the receptor directly with bromocriptine and lergotrile, (3) implanting dopaminergic tissue, or (4) decreasing cholinergic activity. New therapies using the monoamine oxidase inhibitor (MAOI) deprenyl or adrenal medullary transplants to slow the progression of disease appear promising,[283,284] and even treatment with high-dose coenzyme Q10 seems to be strikingly beneficial.[22] Experience with deprenyl in the perioperative milieu is insufficient to make proscriptions about its use. Anticholinergic agents have been the initial drugs of choice because they decrease tremor more than muscle rigidity. Dopamine does not pass the blood-brain barrier, so its precursor L-dopa (levodopa) is used. Unfortunately, L-dopa is decarboxylated to dopamine in the periphery and can cause nausea, vomiting, and arrhythmia. These side effects are diminished by the administration of α-methylhydrazine (carbidopa), a decarboxylase inhibitor that does not pass the blood-brain barrier. Refractoriness to L-dopa develops, and it is now debated whether the drug should be used only when symptoms cannot be controlled with other anticholinergic medications. "Drug holidays" have been suggested as one means of restoring the effectiveness of these compounds, but cessation of such therapy may result in a marked deterioration of function and need for hospitalization. Therapy for Parkinson's disease should be initiated before surgery and be continued through the morning of surgery; such treatment seems to decrease drooling, the potential for aspiration, and ventilatory weakness.[285,286] Reinstituting therapy promptly after surgery is crucial,[280,283-287] as is avoiding drugs such as the phenothiazines and butyrophenones (droperidol), which inhibit the release of dopamine (and perhaps alfentanil) or compete with dopamine at the receptor.[285] Carbidopa/levodopa in low doses (20 to 200 mg nightly versus the usual 60 to 600 mg/day for Parkinson's disease) is commonly used in the nonparkinsonian restless leg syndrome of the elderly (present in 2% to 5% of individuals older than 60 years). This drug too should be given the night before and the night immediately after surgery. Clozapine (a benzodiazepine) does not appear to worsen the movement disorders of Parkinson's disease and has been used postoperatively to stop levodopa-induced hallucinations.

Dementia, a progressive decline in intellectual function, can be caused by treatable infections (e.g., syphilis, cryptococcosis, coccidioidomycosis, Lyme disease, tuberculosis), depression (a trial of antidepressants is indicated in most patients), side effects of medications (digitalis has slowed brain function more than the heart rate), myxedema, vitamin B_{12} deficiency, chronic drug or alcohol intoxication, metabolic causes (liver and renal failure), neoplasms, partially treatable infections (HIV), untreatable infections (Creutzfeldt-Jakob syndrome), or decreased acetylcholine in the cerebral cortex (Alzheimer's disease). This last condition occurs in more than 0.5% of Americans.[288-291] Although these patients are often given cholinergic agonists, controlled trials of these drugs have not as yet shown major significant benefit.[289,290,292] Gingko has been advocated and has improved subjective symptoms in 37% of patients versus 23% of those given placebo. Although later controlled trials have failed to confirm its benefit in early Alzheimer's disease or in healthy elderly individuals, gingko is still popular. However, the prevalence of Alzheimer's disease and the desperation of the patients and their families have now widened such therapies. Cholinergic medications have been shown to improve functioning in patients with Alzheimer's disease.[293] These families often desire surgery, but the interactions of these drugs and therapies with perioperative analgesic and anesthetic drug therapies are not well established. There is one case report of intraoperative bradycardia in such patients with two cholinergic drugs.[294] Based on basic science research, there is some concern about a link between Alzheimer's disease, postoperative cognitive dysfunction, and inhaled agents.[295] Several investigators have demonstrated β-amyloid deposition in animals exposed to inhaled anesthetics.[296-298] Further research is required to determine whether this link is clinically relevant in humans. Most reversible dementias are either drug-induced delirium or depression.[289,290,299] At present, early results with stimulation at "threshold testing" are promising and seem to stimulate dendritic regrowth and may reverse some or much of the cognitive decline. Such computer programs and games are in early testing. Creutzfeldt-Jakob disease has been transmitted inadvertently by surgical instruments and corneal transplants; the causative virus or protein particle is not inactivated by heat, disinfectants, or formaldehyde.

More than 90% of patients with chronic recurring headaches are categorized as having migraine, tension, or cluster headaches. The mechanism of tension or cluster headaches may not differ qualitatively from that for migraine headaches; all may be manifestations of labile vasomotor regulation.[300] A headache is said to be migraine if it is characterized by four of the following five "POUNDing" conditions: if it is Pulsating, if it lasts One day or more, if it is Unilateral, if there is Nausea, and if it Disturbs daily activities.[301]

Treatment of cluster and migraine headaches centers on the use of serotonin drugs such as sumatriptan or ergotamine and its derivatives.[300-302] Other drugs that may be effective are propranolol, calcium channel inhibitors, cyproheptadine, prednisone, antihistamines, tricyclic antidepressants, phenytoin, and diuretic drugs, as well as biofeedback. Giant cell arteritis, glaucoma, and all the meningitides, including Lyme disease, are other causes of headache that might benefit from treatment before surgery.[303] No other special treatment is indicated preoperatively for a patient who has a well-delineated cause for the headaches. Acute migraine attacks can sometimes be terminated by ergotamine tartrate aerosol or by injection of sumatriptan or dihydroergotamine mesylate intravenously; general anesthesia has also been used. We normally continue all prophylactic headache medicine, although the decision to continue aspirin through the morning of surgery is usually left to the surgeon.

Back Pain, Neck Pain, and Spinal Canal Syndromes

Acute spinal cord injury is discussed earlier in the section on autonomic dysfunction. Although it is a common problem, little is written about the anesthetic management of syndromes related to herniated disks, spondylosis (usually of advancing age), and the congenital narrowing of the cervical and lumbar canal that gives rise to symptoms of nerve root compression. One report stresses the importance of the vascular component in the mechanism of damage to the spinal cord and, hence, the theoretical desirability of slight hypertension perioperatively.[304] Another report suggests the use of awake intubation, a fiberoptic bronchoscope, and monitoring of evoked potentials.[305] Other than the commonsense approach of seeking neurologic consultation or, if necessary, using awake positioning of patients in a comfortable position before emergency root decompression procedures, no special procedures appear to be necessary.

Demyelinating Diseases

Demyelinating diseases constitute a diffuse group of diseases ranging from those with uncertain cause (e.g., multiple sclerosis, where genetic, epidemiologic, and immunologic factors are probably all involved and interferon beta appears to be a promising treatment[306]) to those that follow infection, vaccination (e.g., Guillain-Barré syndrome), or antimetabolite treatment of cancer. Therefore, demyelinating diseases can have very diverse symptoms. Apparently, there is a risk of relapse of these diseases immediately after surgery. Because relapse may occur as a result of rapid electrolyte changes in the perioperative period, such changes might be avoided. In addition, perioperative administration of steroids has been advocated as a protective measure.[99] Although there are concerns about the use of neuraxial anesthesia in these patients, epidural anesthesia has been administered without problems.[307] Multiple sclerosis and demyelinating diseases in general are the most common cause of nontraumatic disability in young adults. The age-adjusted survival rate is 80% of that of unaffected individuals, or put another way, the average patient with multiple sclerosis ages 1.2 years for every year with the disease. However, the variability of the disease makes this average rate of aging almost meaningless. Thus far, no mode of treatment has been shown to alter most of these disease processes, although ACTH, steroids, interferon beta, glatiramer acetate (Copaxone), and plasmapheresis may ameliorate or abbreviate a relapse, even alter disease progression, especially progression of multiple sclerosis and (if started within 2 weeks of onset) Guillain-Barré syndrome.[308] Such an effect is consonant with the hypothesis of an immunologic disorder being the cause of these diseases. Care should be taken to avoid succinylcholine in these patients because of the risk of hyperkalemia

Sleep apnea may be considered a demyelinating or degenerative CNS disease or a peripheral disease of obesity, depending on its etiology. Both types (central and peripheral causes) appear to be increasingly common and are present in more than 5% of elderly African Americans. Preprocedure and preoperative identification of patients and therapy for sleep apnea are discussed in Chapter 64.

Metabolic Diseases

Included in the category of metabolic diseases is nervous system dysfunction secondary to porphyrias, alcoholism, uremia, hepatic failure, and vitamin B_{12} deficiency. The periodic paralysis that can accompany thyroid disease is discussed under "Neuromuscular Disorders" (see later).

Alcoholism or heavy alcohol intake is associated with acute alcoholic hepatitis (also see Chapter 66), the activity of which declines as alcohol is withdrawn; with myopathy and cardiomyopathy, which can be severe; and with withdrawal syndromes. Within 6 to 8 hours of withdrawal, the patient may become tremulous, a state that usually subsides within days or weeks. Alcoholic hallucinosis and withdrawal seizures generally occur within 24 to 36 hours. These seizures are generalized grand mal attacks; when focal seizures occur, other causes should be sought. Delirium tremens usually appears within 72 hours of withdrawal and is often preceded by tremulousness, hallucinations, or seizures. These three symptoms, combined with perceptual distortions, insomnia, psychomotor disturbances, autonomic hyperactivity, and in a large percentage of cases, another potentially fatal illness (e.g., bowel infarction or subdural hematoma), are components of delirium tremens. This syndrome is now treated with benzodiazepines. Nutritional disorders of alcoholism include alcoholic hypoglycemia and hypothermia, alcoholic polyneuropathy, Wernicke-Korsakoff syndrome, and cerebellar degeneration. In alcoholic patients (i.e., those who drink at least two six packs of beer or 1 pint of whiskey per day or the equivalent), emergency surgery and anesthesia (despite alcoholic hepatitis) are not associated with worsening abnormalities in liver enzymes. In addition, about 20% of alcoholic patients also have COPD. A patient who has a history of alcohol abuse therefore warrants careful examination of many systems for quantification of preoperative physical status.

Although hepatic failure can lead to coma with high-output cardiac failure, unlike uremia, it does not lead to chronic polyneuropathy. Uremic polyneuropathy is a distal symmetric sensorimotor polyneuropathy that may be improved by dialysis. The use of depolarizing muscle relaxants in patients with polyneuropathies has been questioned (also see Chapter 29). We believe that patients who have a neuropathy associated with uremia should not be given succinylcholine because of a possible exaggerated hyperkalemic response.

Pernicious anemia caused by vitamin B_{12} deficiency may result in subacute combined degeneration of the spinal cord; the signs are similar to those of chronic nitrous oxide toxicity. Both pernicious anemia and nitrous oxide toxicity are associated with peripheral neuropathy and disorders of the pyramidal tract and posterior column (which governs fine motor skills and the sense of body position). Combined-system disease can also occur without anemia, as can nitrous oxide toxicity in dentists and nitrous oxide abusers. Patients with vitamin B_{12} deficiency and anemia, if treated with folate, improve hematologically but progress to dementia and severe neuropathy. It may thus be prudent to give an intramuscular injection of 100 μg of vitamin B_{12} or 800 μg orally before giving folate to a patient who has signs of combined-system degeneration.[309]

The porphyrias are a constellation of metabolic diseases that result from an autosomally inherited lack of functional enzymes active in the synthesis of hemoglobin. Figure 35-9 sche-

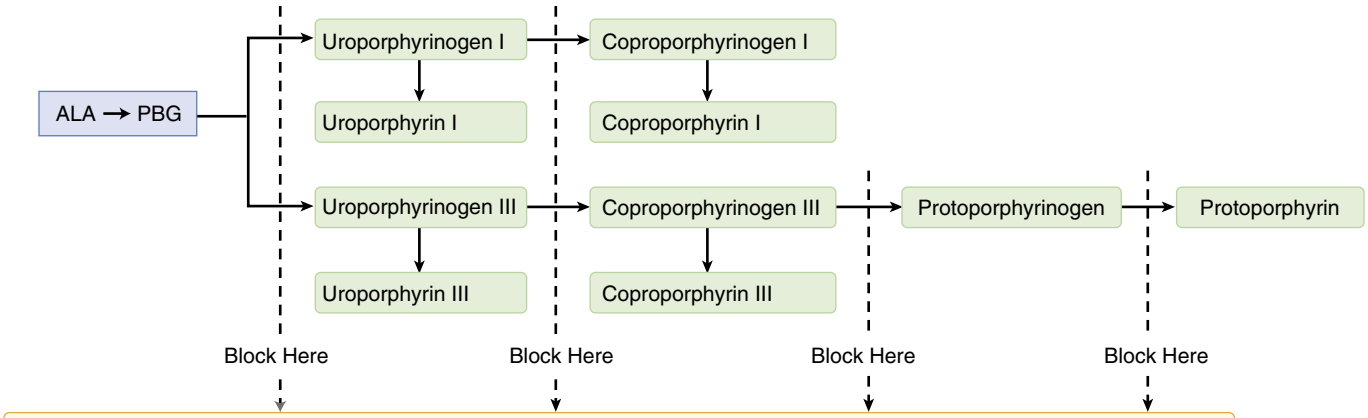
matically depicts the abnormalities that result from these enzyme deficits. It is important to note that type 1, 3, and 4 porphyrias can cause life-threatening neurologic abnormalities. These conditions are characterized by the presence of aminolevulinic acid (ALA) or porphobilinogen (or both) in urine; these substances do not occur in porphyria cutanea tarda, a disease that does not incur neurologic sequelae.[310] In acute intermittent porphyria, the typical pattern consists of acute attacks of colicky pain, nausea, vomiting, severe constipation, psychiatric disorders, and lesions of the lower motor neuron that can progress to bulbar paralysis. Certain drugs can induce the enzyme ALA synthetase and thereby exacerbate the disease process.[311-313] Such sensitizing drugs include barbiturates, meprobamate, chlordiazepoxide, glutethimide, diazepam, hydroxydione, phenytoin, imipramine, pentazocine, birth control pills, ethyl alcohol, sulfonamides, griseofulvin, and ergotamine preparations. Patients often have attacks during infection, fasting, or menstruation. Administration of glucose suppresses ALA synthetase activity and prevents or ablates acute attacks. Drugs used in anesthetic management that are reported to be safe for patients with porphyria include neostigmine (Prostigmin), atropine, gallamine, succinylcholine, *d*-tubocurarine, pancuronium, nitrous oxide, procaine, propofol, propanidid, etomidate, meperidine, fentanyl, morphine, droperidol, promazine, promethazine, and chlorpromazine.[311-313] Although ketamine has been used, postoperative psychoses attributable to the disease may be difficult to distinguish from those possibly caused by ketamine. In addition, although ketamine and etomidate are reported to be safe in humans, they seem to be porphyrinogenic in rats. Propofol has been used without provoking porphyria in at least two susceptible patients.[311,312]

Neuromuscular Disorders

Neuromuscular disorders consist of conditions affecting any major component of the motor unit: motor neuron, peripheral nerve, neuromuscular junction, and muscle. Neuropathies may involve all components of the nerve, thereby producing sensory, motor, and autonomic dysfunction, or only one component. Myopathies may involve only the proximal or distal muscles, or both.

Myasthenia gravis (also see Chapter 34) is a disorder of the muscular system caused by partial blockade or destruction of nicotinic acetylcholine receptors by IgG antibodies. The severity of the disease correlates with the ability of antibodies to decrease the number of available acetylcholine receptors.[314] Treatment of myasthenia is usually begun with anticholinesterase drugs, but in moderate and severe disease, treatment progresses to steroids and thymectomy.[314,315] Immunosuppressive drugs and plasmapheresis are initiated if the more conservative measures fail, and intravenous immunoglobulin, a rapid-onset therapy, is reserved for acute exacerbations and myasthenic crises.[314,315]

One major problem for the anesthesiologist involves the use of muscle relaxants and their reversal.[316] Because much of the care of myasthenia gravis patients involves tailoring the amount



Diagnosis:	Acute intermittent porphyria	Porphyria cutanea tarda	Coproporphyria (hereditary porphyria)	Variegate porphyria
In urine:	ALA PBG	Uroporphyrin	ALA PBG	ALA PBG
Neurologic sequelae:	Yes	No	Yes	Yes
Drug sensitization:	Yes	No	Yes	Yes

Figure 35-9 Schematic depiction of the functional enzyme deficits that occur in some of the porphyrias. ALA, aminolevulinic acid; PBG, porphobilinogen.

of anticholinesterase medication to the maximal muscle strength of the patient, derangement of the course of the patient during surgery could necessitate reassessment of the drug dosage. For that reason, several researchers recommend withholding all anticholinergic drugs for 6 hours before surgery and reinstituting medication postoperatively with extreme caution because the sensitivity of these patients to such drugs may have changed. In addition, there has been some concern that anticholinergic drugs may lead to a high incidence of bowel anastomotic leaks in patients who have undergone bowel anastomosis. Small doses of succinylcholine can be used to facilitate endotracheal intubation; tiny doses of nondepolarizing drugs can be used for intraoperative relaxation not achieved by regional anesthesia or volatile anesthetics. Controlled ventilation is frequently required for at least 24 to 48 hours postoperatively, although immediate extubation has become more common.[315-317] Postoperative ventilation is especially important in cases involving myasthenia gravis of more than 6 years' duration, COPD, a daily pyridostigmine requirement of 750 mg in association with significant bulbar weakness, and vital capacity of less than 40 mL/kg.[317]

Lambert-Eaton syndrome (myasthenic syndrome) is characterized by proximal limb muscle weakness and is associated with antibodies directed against the voltage-gated calcium channels in presynaptic nerve terminals. Strength or reflexes may increase with repetitive effort. Affected patients exhibit decreased release of acetylcholine at the neuromuscular junction. Guanidine therapy enhances the release of acetylcholine from nerve terminals and improves strength. Men with this syndrome generally have small cell carcinoma of the lung or other malignancy, whereas women often have malignancy, sarcoidosis, thyroiditis, or a collagen-related vascular disease. In addition, these patients have increased sensitivity to both depolarizing and nondepolarizing muscle relaxants.[318] Lambert-Eaton syndrome is also associated with an autonomic nervous system defect manifested by gastroparesis, orthostatic hypotension, and urinary retention.

Dermatomyositis and polymyositis are characterized by proximal limb muscle weakness with dysphagia. These conditions are associated with malignancy or collagen-related vascular disease and often involve respiratory and cardiac muscle.

Periodic paralysis is another disease in which sensitivity to muscle relaxants increases. Periodic weakness starts in childhood or adolescence and is precipitated by rest after exercise, sleep, cold, surgery, or pregnancy. Hypokalemic and hyperkalemic forms exist and are associated with cardiac arrhythmias. Like thyrotoxic periodic paralysis, these hypokalemic and hyperkalemic forms usually spare the respiratory muscles. Anesthetic management consists of minimizing stress and maintaining normal fluid and electrolyte status and body temperature.[318-321]

Muscular dystrophy patients now survive into their late twenties or early thirties, and their preoperative evaluation is reviewed in Chapter 34. Because the disease involves the muscles themselves and not their innervation, conduction anesthesia cannot produce adequate relaxation of tonic muscles. Gastric dilation has also been reported to be a problem, as has malignant hyperthermia. As with the other forms of muscular dystrophy, most problems in myotonic dystrophy arise from cardiac arrhythmias and inadequacy of the respiratory muscles.[322] For all the forms of muscular dystrophy, as for all the neuropathies (discussed earlier), there have been problems related to exaggerated release of serum potassium after the administration of depolarizing muscle relaxants (also see Chapter 29).

Malignant hyperthermia (also see Chapter 37) in the patient or in a relative of the patient merits careful history taking and at least consideration of performing a test for susceptibility to the condition. Prophylaxis with intravenous dantrolene sodium (Dantrium) may also be warranted. In some cases, malignant hyperthermia has been associated with recognizable musculoskeletal abnormalities such as strabismus, ptosis, myotonic dystrophy, hernias, kyphoscoliosis, muscular dystrophy, central core disease, and marfanoid syndrome. Appropriate preparation for a patient with previous masseter spasm, or trismus, is a matter of considerable debate. We prepare for malignant hyperthermia (i.e., we ensure a contaminant-free machine, use nontriggering agents, and have a malignant hyperthermia cart in the room) but do not routinely perform muscle biopsy or prescribe dantrolene prophylaxis.[323,324] Malignant hyperthermia occurs most frequently in children and adolescents, the incidence being 1 in 14,000 administrations of anesthetic. The incidence increases to 1 in 2500 patients requiring squint surgery.

Down Syndrome

Down syndrome (trisomy 21) occurs once in 1000 live births. It is associated with congenital cardiac lesions such as endocardial cushion defects (40%), ventricular septal defects (27%), patent ductus arteriosus (12%), and tetralogy of Fallot (8%), and prophylactic antibiotics should be used before predictable bacteremic events. Down syndrome is also associated with upper respiratory infections, with atlanto-occipital instability (in about 15% of patients,[325-328] in whom it is asymptomatic in most cases, but it is recommended that all patients be treated as though they have atlanto-occipital instability) and laxity of other joints, with thyroid hypofunction (50%), with an increased incidence of subglottic stenosis, and with enlargement of the tongue (or a decreased oral cavity size for a normal-sized tongue).[327,329] No abnormal responses to anesthetics or anesthetic adjuvants have been substantiated. A reported sensitivity to atropine has been disproved, although administration of atropine to any patient given digoxin for atrial fibrillation should be done with extreme care.[329] Examination for the conditions associated with Down syndrome should precede surgery.

Preoperative Prediction of Increased Intracranial Pressure during Neurosurgery

Symptoms and signs of increased intracranial pressure include morning headache or headache made worse by coughing, nausea, vomiting, disturbances in consciousness, history of large tumors, tumors involving the brainstem, neck rigidity, and papilledema. Patients with these signs, large ventricles (as seen on radiography or images of the brain), or edema surrounding supratentorial tumors should be considered at risk for intraoperative intracranial hypertension. These patients may benefit from preoperative treatment or anesthetic management that assumes this possibility (also see Chapter 63).[330]

Other preoperative considerations for patients with neurologic disease that can cause intracranial hypertension are the associated hypoventilation and hypoxia in patients who have severe hemiplegia and the presence of subarachnoid bleeding or other forms of intracranial hemorrhage (especially likely in

women given heparin who have two or more cerebral infarcts noted on CT). Many strokes or transient ischemic attacks have a possible cardiac origin (59 of 184 patients).[331,332] The drugs used to prevent cerebral arterial spasm—calcium channel blockers—are discussed in the last section of this chapter.

Mental Disorders

Perhaps the most important preoperative consideration for patients with mental disorders, in addition to developing rapport, is understanding their specific drug therapy and its effects and side effects. More than 15% of all adult patients undergoing surgery are taking one of these therapies or have recently been taking one of these therapies. Lithium, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), other antidepressants that defy classification such as bupropion, phenothiazines, butyrophenones, and MAOIs are used in these patients.[333] These drugs have potent effects and side effects that are discussed in the last section of this chapter.

Renal Disease, Infectious Diseases, and Electrolyte Disorders

One may ask why preoperative preparation of a patient with renal disease is discussed in the same section as preoperative preparation of a patient with an infectious disease. Although it is commonly recommended that no surgery except emergency or curative (e.g., drainage of an abscess) operations be performed in patients with infectious disease, it has become evident that renal insufficiency can be caused by antimicrobial drugs[334] and that sepsis, not shock, is probably the leading cause of acute postoperative renal failure. The anesthesiologist has an important role to play in preventing the onset and consequences of renal failure and its initiators. The linking of renal failure to electrolyte disorders is more obvious: the kidney is the primary organ for regulating body osmolality and fluid volume and has a major role in excretion of the end products of metabolism. In performing these functions, the kidney becomes intimately involved in the excretion of electrolytes.

A patient with renal insufficiency whose own kidneys are still functioning is distinct not only from a patient with end-stage renal disease whose renal functions are provided by dialysis but also from a patient who has a transplanted kidney. These three groups of patients require very different preoperative preparation. In addition, acute changes in renal function present quite a different problem than do chronic alterations in function. Certain renal diseases require different preoperative preparation than others, but generally, renal disease of any origin presents the same preoperative problems (also see Chapters 18, 34, and 45).

Renal Disease

Causes and Systemic Effects of Renal Disorders

Nephrotic syndrome may develop in patients with glomerular diseases without disturbing tubular function. The soundness of tubular function is an important consideration because tubular dysfunction with attendant uremia presents quite different problems than glomerular disease with only nephrotic syndrome does. This is not to minimize the adverse effects of glomerular disease; nephrotic syndrome consists of massive proteinuria and consequent hypoalbuminemia. The resulting reduction in plasma oncotic pressure diminishes plasma volume and calls forth compensatory mechanisms that result in retention of sodium and water. As a result, a common clinical finding in nephrotic syndrome is edema. Thus, patients with nephrotic syndrome may have excess total-body water and decreased intravascular volume. In addition, diuretics are often given in an attempt to decrease edema. Although serum creatinine and creatinine clearance estimations have limitations as indices of the GFR (inulin clearance is still the gold standard), these measurements are, for now, the most readily available to the anesthesiologist. Plasma creatinine levels reflect endogenous muscle catabolism and dietary intake, as well as urinary excretion. Urinary excretion depends on both filtration and secretion by the kidney. Drugs that are commonly used in the preoperative and perioperative periods can distort this measure of glomerular filtration: cimetidine and trimethoprim interfere with secretion by increasing plasma creatinine and decreasing creatinine clearance without altering filtration. It should also be remembered that the commonly used methods for measuring creatinine have a 95% confidence limit of greater than 20% for a GFR higher than 30 mL/min. Thus, a normal creatinine level of 1.3 mg/dL might give a measured value ranging from 1.0 to 1.5 mg/dL.

Furthermore, in patients with nephrotic syndrome in whom renal tubular function has been preserved, hypovolemia appears to be a significant cause of deteriorating tubular renal function.[335-337] Consequently, we advocate the same intense preoperative, intraoperative, and postoperative fluid management for patients with nephrotic syndrome as we do for patients with diminished tubular function. Admittedly, no randomized study has shown that close control of intravascular volume status in these groups of patients preserves renal tubular function (or any other measure of perioperative morbidity) to a greater degree than less rigid control does.

Uremia, the end result of renal tubular failure (i.e., failure of the concentrating, diluting, acidifying, and filtering functions) is manifested in many ways. Changes occur in the cardiovascular, immunologic, hematologic, neuromuscular, pulmonary, and endocrine systems, as well as in bone. These alterations are ascribed either to the toxic end products of protein metabolism or to an imbalance in functioning of the kidney. As the number of functioning nephrons diminishes, the still-functioning nephrons attempt to increase some solute and body composition preservation functions at the expense of other functions, such as excretion of phosphate. The accumulation of phosphate increases PTH levels, which in turn produces osteodystrophy. Osteodystrophy can be managed by (1) restriction of dietary phosphate, (2) the use of gels (e.g., aluminum hydroxide or carbonate) that bind with intestinal phosphate, (3) calcium supplementation, or (4) parathyroidectomy.

Certain alterations in patients with uremia, such as neuropathy, are most logically attributed to an accumulation of toxic metabolites. Peripheral neuropathy is most often sensory and involves the lower extremities, but it may also be motor; peripheral neuropathies are frequently improved with hemodialysis and can be dramatically reversed with transplantation. The use of

depolarizing muscle relaxants in patients with peripheral neuropathy is controversial and is discussed in the section on neuropathies. Tubular function is commonly assessed by acidifying and concentrating capabilities.[338] Although such tests are crude, these capabilities are usually readily assessed by measuring urine pH and specific gravity. Better assessment of renal blood flow, for the purpose of improving renal blood flow and its distribution, is promised by the use of contrast-enhanced ultrasound in the operating room.[339] Along with the altered volume status and cardiac complications in uremic patients, autonomic neuropathy may contribute to hypotension during anesthesia. Atherosclerosis is often accelerated in uremic patients; hypertension, with its attendant consequences, is very common.

Cardiac failure (especially episodic failure) frequently occurs in uremic patients because of the presence of many adverse conditions: anemia with increasing myocardial work, hypertension, atherosclerosis, and altered volume status. Pericarditis can be manifested by pericardial rub alone or by pain (with or without hemorrhage). Cardiac tamponade should be ruled out on the basis of clinical features and by echocardiography if this diagnosis is seriously suspected preoperatively. In addition, cardiac tamponade should be treated or planned for preoperatively.

If anemia is present, its severity generally parallels the degree of uremia; chronically uremic patients seem to adapt well to anemia. No hard data have substantiated the need to give a preoperative blood transfusion to a chronically uremic patient, even when the preoperative hematocrit is as low as 16 or 18 vol%. Even in nonuremic patients in an ICU, a randomized trial was unable to demonstrate improved outcome with a liberal transfusion strategy,[340] and transfusions increase the risk for immune system compromise (also see Chapter 55).[341] Thus, one of the major historical reasons for not transfusing blood in patients with end-stage renal disease has been disproved by this finding: data show that the more blood transfusions a transplant recipient receives before transplantation, the greater the chance that the transplant will function successfully.[342] This immunosuppressive effect of transfusions is now routinely used in transplantation. However, the development of recombinant human erythropoietin has obviated the need for transfusions in chronically uremic patients. Balancing of the immunosuppressive use of blood transfusions versus the benefits of erythropoietin and the risks of transfusion remains to be determined. In uremic patients, coagulation and platelet adhesiveness may be abnormal and factor III activity decreased. Even uremic patients not given corticosteroids or immunosuppressive drugs may demonstrate abnormal immunity, perhaps warranting increased attention regarding procedures that lessen patient cross-contamination.

Uremic patients exhibit a wide variety of metabolic and endocrinologic disorders in addition to hyperparathyroidism, including impaired carbohydrate tolerance, insulin resistance, type IV hyperlipoproteinemia, autonomic insufficiency, hyperkalemia, and anion-gap acidosis (caused by an inability of the kidneys to reabsorb filtered bicarbonate and excrete sufficient ammonium into urine). Furthermore, the excretion and pharmacokinetics of drugs are different in uremic patients than in normal patients. In addition, complications of hemodialysis include nutritional deficiencies, electrolyte and fluid imbalances, and mental disorders. Because these conditions can lead to serious perioperative morbidity, they should be evaluated before surgery. No data, however, have substantiated the hypothesis that preoperative optimization of these metabolic and endocrinologic disorders reduces perioperative risk in uremic patients.

As with uremic patients, preoperative optimization of volume status is paramount in patients with kidney stones, and both are affected by carbohydrate intolerance.[343,344] Seventy-five percent of all kidney stones are composed of calcium oxalate. Patients with these stones frequently take diuretic drugs, consume calcium- and citrate-rich foods, and restrict salt intake. Prevention of dehydration by institution of intravenous fluid therapy along with restricted oral intake of protein may be as important for these patients as it is for those with struvite or uric acid stones. Struvite stones often result from urinary infection. Uric acid stones can be prevented by treatment with allopurinol, by preoperative hydration, or by alkalization of urine. Acidosis may contribute to stone formation. Again, optimal intravascular volume status is important in preventing stones and preserving renal function. More thorough discussion of renal function and physiology is provided in Chapter 18. Chapter 65 deals with the complexities of managing patients for renal surgery and other urologic procedures.

Creatinine clearance in conjunction with free water clearance appears to be the most accurate way of quantifying, for pharmacokinetic purposes, the degree of decreased renal function (also see Chapter 18).[344] For a patient with stable renal function, creatinine clearance, which is a rough estimate of GFR, can be approximated by noting the serum creatinine level: a doubling of the creatinine level represents a halving of the GFR. Thus, a patient with a stable serum creatinine level of 2 mg/dL would have a GFR of approximately 60 mL/min. A stable serum creatinine level of 4 mg/dL would accompany a GFR of approximately 30 mL/min, and a stable serum creatinine level of 8 mg/dL would accompany a GFR of 15 mL/min or less. When pregnancy and considerable edema are not present and the serum creatinine level is stable, the following formulas can be used to estimate creatinine clearance and free water clearance.[344-346]

$$\text{Creatinine clearance} = \frac{(140 - \text{Age}[\text{yr}]) \times \text{Body weight}\,(\text{kg})}{72 \times \text{Serum creatinine}\,(\text{mg/dL})}$$

$$\text{Free water clearance} = \text{Urine flow}\,(\text{mL/hr}) - \frac{\text{Urine osmolality}\,(\text{mOsm/L}) \times \text{Urine flow}\,(\text{mL/hr})}{\text{Plasma osmolality}\,(\text{mOsm/L})}$$

Note that renal function must be stable. Unstable renal function is often associated with changes in serum creatinine levels that lag by several days. Although knowing the serum creatinine level is more useful than knowing the BUN level, the latter provides some information, as discussed in the next section.

Free water clearance is a measure of renal concentrating ability and is normally −25 to +100 mL/hr; it becomes more positive in renal insufficiency states. It may also become more positive in patients who have a head injury or high blood alcohol levels or in those undergoing aggressive fluid infusion or administration of diuretics.[345]

Patients with Insufficient but Functioning Kidneys

One of the greatest challenges for the anesthesiologist is presented by patients with insufficient renal function whose renal function

must be preserved during surgery. Additionally, the presence of chronic renal failure is associated with higher rates of perioperative cardiac morbidity, which may warrant further evaluation for the presence of occult coronary artery disease.[346] The many uremic symptoms and great perioperative morbidity associated with uremia can probably be avoided by attention to detail in the preoperative and perioperative management of patients with insufficient, but still functioning kidneys.[335-337]

First, studies demonstrate that acute postoperative renal failure is associated with an extremely high mortality rate.[347] There are multiple risk factors for the development of perioperative renal dysfunction, the most important of which include preexisting renal disease, heart surgery involving cardiopulmonary bypass or aortic surgery involving cross-clamping of the thoracic or abdominal aorta, and ongoing sepsis. In a systematic review of 28 studies by Novis and colleagues, preoperative renal risk factors such as increased serum creatinine, increased BUN, and preoperative renal dysfunction were repeatedly found to predict postoperative renal dysfunction.[345] Mangano and coworkers performed a prospective cohort study of 2222 patients with or without concurrent vascular surgery.[347] They identified five independent preoperative predictors of renal dysfunction: age 70 to 79 years (relative risk [RR], 1.6; 95% CI, 1.1 to 2.3) or age 80 to 95 years (RR, 3.5; CI, 1.9 to 6.3), CHF (RR, 1.8; CI, 1.3 to 2.6), previous myocardial revascularization (RR, 1.8; CI, 1.2 to 2.7), type 1 diabetes mellitus (RR, 1.8; CI, 1.1 to 3.0) or preoperative serum glucose levels exceeding 16.6 mmol/L (RR, 3.7; CI, 1.7 to 7.8), and preoperative serum creatinine levels of 124 to 177 µmol/L (RR, 2.3; CI, 1.6 to 3.4).

Moreover, acute perioperative renal failure is most likely to occur in patients who have renal insufficiency before surgery, are older than 60 years, and have preoperative left ventricular dysfunction.[345,347] Proper hydration before surgery probably decreases the mortality after acute renal failure induced by radiocontrast agents.[337] Clues regarding the presence of hypovolemia or hypervolemia should be sought from the history and physical examination (e.g., weight loss or gain, thirst, edema, orthostatic hypotension and tachycardia, flat neck veins, dry mucous membranes, decreased skin turgor). In seriously ill patients, insertion of a pulmonary artery catheter will permit more precise monitoring of intravascular fluid volume. Other causes of deterioration in function in chronic renal insufficiency are low cardiac output or low renal blood flow (in prerenal azotemia, whether because of cardiac failure or fluid depletion from diuretic drugs, BUN often increases disproportionately to increases in creatinine), urinary tract infection, use of nephrotoxic drugs, hypercalcemia, and hyperuricemia. These conditions and drugs should be avoided; if any of these conditions exist, they should be treated preoperatively.

To preserve normal renal function, infusion of saline, mannitol, furosemide, or low-dose dopamine has been recommended.[348-350] However, these therapies should be initiated with caution because saline infusions and mannitol can lead to fluid overload and myocardial damage; in addition, diuretic drugs given intraoperatively can produce postoperative hypovolemia, which worsens renal function. Very high concentrations of mannitol may also cause acute renal failure.[351] A meta-analysis of 58 trials involving the use of dopamine for renal protection/treatment, only 17 of which were randomized, was unable to demonstrate any benefit from the use of low-dose dopamine.[352] Maintenance of normal intravascular fluid volume can be guided by pulmonary capillary wedge pressure and has prevented impairment of renal function after open abdominal aortic reconstruction, even when urinary volumes were low.[353] Fenoldopam is a dopamine analog that causes natriuresis and increases renal blood flow and urine output. Several small studies have reported renoprotective effects of fenoldopam in patients undergoing cardiopulmonary bypass and infrarenal aortic aneurysm repair.[354-356]

Anesthetic drugs have been studied in patients with renal insufficiency. In a randomized trial, general anesthesia with desflurane or isoflurane did not exacerbate renal insufficiency.[357] Despite concern that sevoflurane leads to the production of compound A, which impairs renal functioning, a randomized trial of low-flow sevoflurane versus low-flow isoflurane anesthesia in patients with stable renal insufficiency did not demonstrate any difference in any measured renal function parameter.[358]

Patients Undergoing Dialysis

Patients with chronic (and at times acute) renal failure require renal replacement therapy, including conventional intermittent hemodialysis, peritoneal dialysis, and continuous renal replacement therapy (CRRT). CRRT includes a wide variety of techniques whose perioperative management has recently been reviewed (Table 35-18).[359] Although the primary indication for CRRT is acute renal failure, it can also be used for fluid clearance, correction of electrolyte abnormalities, and management of metabolic acidosis. It can be used in surgical patients without significant hemodynamic abnormalities. These patients may return to the operating room and their assessment and management may be complicated by the underlying disease and the use of systemic anticoagulation to prevent filter and circuit clotting. In patients undergoing intermittent treatment with hemodialysis or peritoneal dialysis, the procedure is discontinued before entering the operating room. For CRRT, the anesthesiologist must determine the appropriateness of discontinuing the therapy. With short procedures, the therapy can almost always be stopped and the arterial and venous ends of the circuit connected and run in the bypass mode. CRRT can also be used to manage fluids during surgery by changing the dialysate. If CRRT is continued, its effect on drug dosing must be recognized. In addition to effects on renal elimination of drugs, there are effects from changes in protein binding and volume of distribution, as well as drug removal effects from membrane permeability, membrane surface area, the ultrafiltration rate, and the dialysate flow rate.

Because a patient undergoing dialysis has already lost natural renal functioning, the emphasis in preoperative assessment shifts toward protecting other organ systems and optimally maintaining vascular access sites for cannulation. Usually, this does not require invasive monitoring. Emphasis is placed on intravascular fluid volume and electrolyte status, which can be ascertained by knowing when the patient last underwent dialysis, how much weight was normally gained or lost with dialysis, whether the fluid loss was peritoneal or intravascular, and what electrolyte composition the blood was dialyzed against. Although preoperative dialysis may benefit patients who have hyperkalemia, hypercalcemia, acidosis, neuropathy, and fluid overload, the resulting dysequilibrium between fluid and electrolytes can cause problems. Because hypovolemia induced by dialysis can lead to intraoperative hypotension, we try to avoid weight and fluid

Table 35-18 Characteristics of Renal Replacement Therapy

Renal Replacement Therapy	Blood Pump	Replacement Fluid (RF)/Dialysate (D)	Intraoperative Use
Conventional intermittent hemodialysis	Yes	D	No
Peritoneal dialysis	No	D	No
Slow continuous ultrafiltration	Yes/no	None	Yes
Continuous arteriovenous hemodialysis	No	D	No
Continuous arteriovenous hemodiafiltration	No	RF/D	No
Continuous venovenous hemofiltration	Yes	RF	Yes
Continuous venovenous hemodialysis	Yes	D	Yes
Continuous venovenous hemodiafiltration	Yes	RF/D	Yes

From Petroni KC, Cohen NH: Continuous renal replacement therapy: Anesthetic implications. Anesth Analg 94:1288-1297, 2002, with permission.

reduction in patients undergoing preoperative dialysis. In addition, hypopnea has been found to occur during and after dialysis when the dialysate contained acetate. Avoiding an acetate bathing solution may prevent this cause of hypoventilation.

Patients Who Have Received a Renal Transplant

More than 175,000 patients have received renal transplants (versus 300,000 currently undergoing dialysis in the United States). Approximately 50% are still alive, although a third must undergo dialysis (approximately 60,000 patients are now awaiting transplantation).[360] When these patients have subsequent surgery, the status of their renal function must be determined (i.e., whether they have normal renal function, insufficient but still functioning kidneys, or end-stage renal disease requiring hemodialysis). Descriptions of side effects from immunosuppressive drugs should also be sought. The drugs used preoperatively and intraoperatively to prevent acute rejection themselves have serious side effects that encourage close monitoring of blood glucose and cardiovascular function.[342,361] Because renal transplantation greatly increases the risk of infection, it is very important to avoid invasive monitoring and prevent patient cross-contamination.

Drugs in Patients with Renal Failure

Patients with renal azotemia have a threefold or higher risk of having an adverse drug reaction than those with normal renal function do.[362-364] The risk is increased by two conditions. (1) Excessive pharmacologic effects result from high levels of a drug or its metabolite (e.g., the metabolite of meperidine) in blood because of physiologic changes in target tissues induced by the uremic state. An example would be excessive sedation in a uremic patient with standard blood levels of sedative-hypnotic drugs. (2) Excessive administration of electrolytes with drugs also increases the risk of having an adverse drug reaction. For example, penicillin standardly has 1.7 mEq of potassium per 1 million units.[362-364] Administration of standard doses of drugs that depend on renal excretion for their elimination can result in drug accumulation and enhanced pharmacologic effect. Bennett and associates[362] have provided dosing guidelines for many drugs used by anesthesiologists for patients with and without renal failure. For example, patients with end-stage renal disease required significantly higher propofol doses to achieve the clinical end point of hypnosis than patients with normal renal function did.[364]

Infectious Disease

Because it is commonly recommended that no surgery except emergency or essential surgery (e.g., drainage of an abscess) be performed when an acute infectious disease is present and because renal insufficiency can be caused by antimicrobial drugs,[334,336,337] renal function and organ damage from renal insufficiency should be assessed preoperatively when infectious disease is present. Prophylactic administration of antibiotics (see Table 35-11) helps prevent sepsis from bacteremic interventions.[365] If therapeutic levels of an antibiotic are achieved and a reduction in fever occurs (presumably because of decreased levels of interleukin-2 released), spinal anesthesia might be considered by the anesthesiologist (using benefit-risk judgments) when an acute infectious disease is present.[366]

Sepsis is a leading cause of postoperative morbidity,[334,337] probably through a decrease in systemic vascular resistance related to activation of the complement system and other mediators. Thus, attention to the effects of antibiotic drugs must be supplemented by attention to intravascular volume status.[334-337,367,368] The degree of impairment of the infected organ and its effect on anesthesia should be assessed. For instance, endocarditis merits examination of volume status; antibiotic and other drug therapy and side effects[369]; myocardial function; and renal, pulmonary, neurologic, and hepatic function—organ systems that can be affected by endocarditis.

Although all surgery except emergency or essential operations is proscribed when an acute infectious disease is present (also see the section on upper respiratory infections in the pulmonary section of this chapter), many such diseases (e.g., influenza and pneumococcal pneumonia) and even inflammatory conditions are becoming less frequent because of successful immunization recommendations and programs.[370] Furthermore, even though acute infections are less common, surgery in patients with chronic viral diseases such as hepatitis and HIV infection is more frequent. Many of these patients may also harbor opportunistic infections such as tuberculosis or may have other systemic problems. Whether anesthesia or surgery, or both, exacerbates these infections or their systemic manifestations is not clear.

At least two other considerations merit preoperative consideration: patient isolation to prevent contamination of the

patient and health care providers. Both concerns are real and are the focus of at least several published volumes. Nosocomial infection is a major source of postsurgical morbidity and has been radically reduced by consistent practices such as hand washing.[371,372] Acquired immunodeficiency syndrome (AIDS) and many forms of hepatitis (A, B, and C) appear to be due to viral infections but require direct contact with blood or body fluids. Screening for specific viruses or for the chronic end-organ effects of these viruses[373] is now being done to reduce the risk of infection to both recipients and health care personnel during blood transfusions. The usual precautions appear to be largely effective, but the risk is considerable if these precautions are not followed meticulously.[374]

Electrolyte Disorders

Disorders of calcium, magnesium, and phosphate balance were discussed in the section on diseases involving the endocrine system and disorders of nutrition (also see Chapters 34 and 49).

Hyponatremia and Hypernatremia

Electrolyte disorders are usually detected by determining the levels of electrolytes in serum. These concentrations reflect the balance between water and electrolytes. The osmolality of all body fluids is normally maintained within the narrow physiologic range of 285 to 290 mOsm/kg H_2O by integration of three key processes: thirst, release of ADH, and responsiveness of the medullary collecting ducts to ADH. Because of the permeability of biologic membranes, intracellular osmolality and extracellular osmolality are almost always equal and can be estimated by the following formula:

$$2[NA^+](mEq/L) + \frac{[Glucose](mg/dL)}{18} + \frac{[BUN](mg/dL)}{2.8} = mOsm/kg$$

This formula will become easier to calculate when we convert fully to the Système International d'Unités (metric system) because millimoles (mmol) can be substituted for mg/(factor) in the above formula to read

$$2[Na^{2+}] + [Glucose] + [BUN] = mOsm/kg$$

with concentrations expressed in millimoles per liter (mmol/L). Although secretion of ADH is tightly controlled by osmotic stimuli at 285 to 290 mOsm/kg, the osmotic threshold for thirst is high (300 mOsm/kg), thus making this sign an important guide to volume deficiency.

Hyponatremia is perhaps the third most common fluid electrolyte abnormality in hospitalized patients. (Magnesium deficiency occurs in as many as 25% [see Chapter 54] and potassium deficiency, discussed later in this section, in as many as 10%.) Hyponatremia can occur in isotonic, hypertonic, or hypotonic forms. For example, isotonic hyponatremia can develop in protein or liquid accumulation states such as myeloma. Hypertonic hyponatremia can be present with hyperglycemia or with infusions of glycine (as in the TURP syndrome[375]). Hypotonic hyponatremia is the largest classification and is subdivided according to the status of the extracellular fluid into hypovolemic, isovolumic, or hypervolemic hypotonic hyponatremia. All three types require that excretion of renal water be impaired despite continued intake of dilute fluid. Common causes of hypovolemic hypotonic hyponatremia (Box 35-6) are GI losses[376] (vomiting, diarrhea), third-space losses (diuretics or salt-wasting nephropathy), or adrenal insufficiency. Hypervolemic hypotonic hyponatremic states complicate severe cardiac failure,[377] cirrhosis, nephrotic syndrome, or renal failure and are characterized by retention of sodium with disproportionately larger amounts of water.

The more common isovolumic hypotonic hyponatremia is caused by retention of water without sodium. Because edema is not usually clinically apparent, such patients appear isovolumic. Edema is most often caused by SIADH, which in turn may be caused by CNS or pulmonary tumors or dysfunction. Secretion of ADH increases with age, thus rendering the elderly more prone to hyponatremia. Drugs that potentiate the secretion of ADH (tricyclic antidepressants and vincristine) or its effects on the medullary collecting duct system in the kidney (nonsteroidal anti-inflammatory drugs and chlorpropamide) or that have similar effects (oxytocin) may be more likely to cause hyponatremia in the elderly. To establish the diagnosis of SIADH, the physician should determine that the patient is free of renal and cardiac dysfunction, has normal adrenal and thyroid function, and is normovolemic. Urine osmolality would then be found to exceed 100 mOsm/kg, serum osmolality would be low, and urine sodium excretion would be higher than 20 mEq/L (20 mOsm/L).

Disturbances in serum sodium therefore reflect alterations in glucose metabolism, renal function, or accumulation of body water. The last can be affected by disturbances in thirst, release of ADH, and renal function. Thus, hyponatremia reflects a relative excess of free water and can occur when total-body sodium

Box 35-6 Types and Causes of Hypotonic Hyponatremia*

Hypovolemic
Gastrointestinal losses
- Vomiting
- Diarrhea

Skin losses

Third-space losses

Lung losses

Renal losses
- Diuretics
- Renal damage
- Urinary tract obstruction

Adrenal insufficiency

Isovolemic
Syndrome of inappropriate secretion of antidiuretic hormone

Renal failure

Water intoxication

Hypokalemia

Dysfunctional osmostat

Hypervolemic
Congestive heart failure

Nephrosis

Liver dysfunction

*Serum osmolality less than 280 mOsm/L.

increases (as in edematous disorders), when total-body sodium is normal (as in excess of free water because of SIADH), or when total-body sodium decreases (as occurs with too aggressive use of diuretic drugs). Definition of the cause defines the treatment. For instance, water restriction is the mainstay of therapy for SIADH. Administration of demeclocycline is another option that corrects SIADH by inducing a reversible nephrogenic diabetes insipidus. The anesthesiologist is faced with the question of what levels of electrolytes require treatment before anesthesia. Although slowly developing hyponatremia usually produces few symptoms, the patient may be lethargic and apathetic. Chronic hyponatremia is better tolerated than acute hyponatremia because of mechanisms regulating intracellular fluid volume that alleviate brain edema; the loss of other solutes from cells decreases the osmotic movement of water into cells. Nonetheless, severe chronic hyponatremia (i.e., serum sodium levels <123 mEq/L) can cause brain edema.

By contrast, acute hyponatremia may be manifested by severe symptoms requiring emergency treatment: profound cerebral edema with obtundation, coma, convulsions, and disordered reflexes and thermoregulatory control.[99,100,378] Depending on the cause and relative total sodium and water content, treatment can range from the administration of hypertonic saline or mannitol (with or without diuretic drugs) to restriction of fluids or administration of other drugs.[99,100,378] Because neurologic damage may develop if the serum sodium concentration is increased too rapidly, the rate of increase should not exceed 1 mEq/L/hr.[99,100,378] After the serum sodium concentration has reached 125 mEq/L, therapy may consist of water restriction; more rapid correction may result in CNS demyelination.[99,100,378] In hyponatremic patients who have excess total-body water secondary to SIADH, serum levels can be corrected by giving furosemide, 1 mg/kg, and hypertonic saline to replace the loss of electrolytes in urine.[99,100,378] The diagnosis of SIADH is discussed earlier in this chapter (see the section "Pituitary Abnormalities").

Neither acute nor chronic hyponatremia necessitates restoration of serum sodium to normal levels; brain swelling usually disappears at a serum sodium level of 130 mEq/L. This leaves us with the question of what levels of serum sodium make anesthesia more risky. Because no data exist to answer this question, to allow for some error in caring for patients, we have arbitrarily chosen a flexible concentration of 131 mEq/L as the lower sodium limit for elective surgery.

Hypernatremia occurs much less commonly than hyponatremia. It is often iatrogenic in origin (e.g., it can be caused by failure to provide sufficient free water to a patient who is unconscious or who has had a recent stroke-induced deficit of the thirst mechanism) and can occur in the presence of low, normal, or excess total-body sodium. The primary symptoms of hypernatremia relate to brain cell shrinkage. Because too rapid correction of hypernatremia can lead to cerebral edema and convulsions, correction should be made gradually. Again, with no data to support this stance, we believe that all patients undergoing surgery should have serum sodium concentrations of less than 150 mEq/L before anesthesia.

Hypokalemia and Hyperkalemia

Hypokalemia and hyperkalemia are also discussed in Chapters 34 and 54. The relationship between the measured potassium concentration in serum and total-body potassium stores can best be described with a scattergram. Only 2% of total-body potassium is stored in plasma (4200 mEq in cells and 60 mEq in extracellular fluid). In normal persons, 75% of the 50 to 60 mEq/L of total-body potassium is stored in skeletal muscle, 6% in red blood cells, and 5% in the liver. Thus, a 20% to 25% change in potassium levels in plasma could represent a change in total-body potassium of 1000 mEq or more if the change were chronic or as little as 10 to 20 mEq if the change were acute.

As with serum sodium levels,[99,100,378] acute changes in serum potassium levels appear to be less well tolerated than chronic changes. Chronic changes are relatively well tolerated because of the equilibration of serum and intracellular stores that takes place over time to return the resting membrane potential of excitable cells to nearly normal levels.

Hyperkalemia can result from factitious elevation of potassium (as in red blood cell hemolysis); excessive exogenous potassium from sources such as salt substitutes or, in large amounts, bananas; cellular shifts in potassium (as a result of metabolic acidosis, tissue and muscle damage after burns, use of depolarizing muscle relaxants, or intense catabolism of protein); and decreased renal excretion (as occurs in renal failure, renal insufficiency with trauma, and therapy with potassium-sparing diuretic drugs, especially when combined with ACE inhibitors or mineralocorticoid deficiency).[379-381] Factitious hyperkalemia can occur when a tourniquet is left on too long or even by simple fist clenching.[382]

The major danger in anesthetizing patients who have disorders in potassium balance appears to be abnormal cardiac function—that is, both electrical disturbance[379] and poor cardiac contractility. Hyperkalemia lowers the resting membrane potential of excitable cardiac cells and decreases the duration of the myocardial action potential and upstroke velocity. This decreased rate of ventricular depolarization, plus the beginning of repolarization in some areas of the myocardium while other areas are still undergoing depolarization, produces a progressively widening QRS complex that merges with the T wave into a sine wave on the ECG.

Above a potassium level of 6.7 mEq/L, the degree of hyperkalemia and the duration of the QRS complex correlate well.[379] This correlation is even better than the correlation between the serum potassium level and T-wave changes. Nevertheless, the earliest manifestations of hyperkalemia are narrowing and peaking of the T wave. Though not diagnostic of hyperkalemia, T waves are almost invariably peaked and narrow when serum potassium levels are 7 to 9 mEq/L. When serum potassium levels exceed 7 mEq/L, atrial conduction disturbances appear, as manifested by a decrease in P-wave amplitude and an increase in the PR interval. Supraventricular tachycardia, atrial fibrillation, PVCs, ventricular tachycardia, ventricular fibrillation, or sinus arrest may all occur.

The ECG and cardiac alterations associated with hyperkalemia are potentiated by low serum levels of calcium and sodium. Intravenous administration of saline, bicarbonate, glucose with insulin (1 U/2 g glucose), and calcium can reverse these changes by shifting some extracellular potassium into the cell.

β-Adrenergic stimuli also cause redistribution of potassium into the cell. Indeed, the plasma potassium concentration measured in samples immediately before surgery is usually 0.2 to 0.8 mEq/L lower than that measured during the less stressful period 1 to 3 days before surgery.[383] β-Adrenergic receptor blocking drugs such as propranolol can be used to prevent such an

effect preoperatively. A β-adrenergic receptor stimulating agent (20 mg of nebulized albuterol for a 70-kg patient) can be used to treat hyperkalemia when it occurs; it decreases potassium levels 1.0 mEq/L within 30 minutes, and its effect lasts 2 hours.[384] Although nebulized β_2-agonists effectively lower plasma potassium concentrations by stimulating sodium- and potassium-dependent adenosine triphosphatase, this therapy should be used as an adjunct to rather than a substitute for more established measures. Kayexalate (sodium polystyrene sulfonate) enemas can be given to bind potassium in the gut in exchange for sodium. Dialysis against a hypokalemic solution will also decrease serum potassium levels. However, in a hyperkalemic patient, hypoventilation can be dangerous during anesthesia because each 0.1 change in pH can produce a 0.4- to 1.5-mEq/L change in serum potassium levels in the opposite direction. For example, if pH decreases from 7.4 to 7.3, serum potassium levels could increase from 5.5 to 6.5 mEq/L.

Hypokalemia can be caused by inadequate intake of potassium, excessive GI loss (through diarrhea, vomiting, nasopharyngeal suctioning, chronic use of laxatives, or ingestion of cation exchange resins, as in certain wines), excessive renal loss (because of the use of diuretic drugs, renal tubular acidosis, chronic chloride deficiency, metabolic alkalosis, mineralocorticoid excess, excessive ingestion of licorice, use of antibiotics, ureterosigmoidostomy, and diabetic ketoacidosis), and shifts of potassium from extracellular to intracellular compartments (as occurs in alkalosis, insulin administration, administration of a β-adrenergic agonist or stress, barium poisoning, and periodic paralysis). As with hyperkalemia, knowledge of the cause of the potassium deficiency and appropriate preoperative evaluation and treatment of that cause may be as important as treatment of the deficiency itself. Also like hyperkalemia, hypokalemia may reflect small or vast changes in total-body potassium. Acute hypokalemia may be much less well tolerated than chronic hypokalemia. The major worrisome manifestations of hypokalemia pertain to the circulatory system, both the cardiac and peripheral components. In addition, chronic hypokalemia results in muscle weakness, hypoperistalsis, and nephropathy.

Cardiovascular manifestations of hypokalemia include autonomic neuropathy, which results in orthostatic hypotension and decreased sympathetic reserve; impaired myocardial contractility; and electrical conduction abnormalities, which can result in sinus tachycardia, atrial and ventricular arrhythmias, and disturbances in intraventricular conduction that can progress to ventricular fibrillation. In addition to arrhythmias, the ECG shows widening of the QRS complex, ST-segment abnormalities, progressive diminution of the T-wave amplitude, and a progressive increase in the U-wave amplitude. Surawicz[379] found these changes to be invariably present when serum potassium levels decreased to below 2.3 mEq/L. Although U waves are not specific for hypokalemia, they are sensitive indicators of the condition. Replenishing the total-body potassium deficit for a depletion reflected by a serum deficit of 1 mEq/L (e.g., from 3.3 to 4.3 mEq/L) may require 1000 mEq of potassium. Even if this amount could be given instantaneously (and it should not be replenished at a rate exceeding 250 mEq/day), it would take 24 to 48 hours to equilibrate in all tissues. Potassium-depleted myocardium is unusually sensitive to digoxin, calcium, and most important, potassium. Rapid potassium infusion in a hypokalemic patient can produce arrhythmias as severe as those produced by hypokalemia itself.[385] One potential strategy to prevent hypokalemia from anxiety and stress includes premedication with clonidine.[386]

Thus, the decision to proceed with surgery and anesthesia in the face of acute or chronic depletions or excesses of potassium depends on many factors.[387-392] It is essential to know the cause and treatment of the underlying condition creating the electrolyte imbalance and the effect of that imbalance on perioperative risk and physiologic processes. The urgency of the operation, the degree of electrolyte abnormality, the medications given, the acid-base balance, and the suddenness or persistence of the electrolyte disturbance are all considerations. For example, one small study of patients undergoing vascular access procedures with preoperative potassium levels of greater than 6 mmol/L demonstrated no adverse outcomes.[390] Similarly, in a cohort study in which 38 patients had a preoperative potassium level higher than 5.5 mEq/L, there were no dysrhythmias or major morbidity associated with the use of succinylcholine.[391]

Retrospective epidemiologic studies attribute significant risk to the administration of potassium (even chronic oral administration).[387] In one study, 1910 of 16,048 consecutive hospitalized patients were given oral potassium supplements. Of these 1910 patients, hyperkalemia contributed to death in 7, and the incidence of complications of potassium therapy was 1 in 250. Armed with such data, many internists do not prescribe oral potassium therapy for patients given diuretic drugs. Yet these patients frequently become moderately hypokalemic.[393] Modest hypokalemia occurs in 10% to 50% of patients given diuretic drugs. Should surgery be delayed to subject such patients to the risks of potassium therapy?

Three studies investigated whether modest hypokalemia was a problem by prospectively seeking arrhythmias on the ECGs of patients who had various preoperative levels of potassium.[388,389,392] No difference in the incidence of arrhythmias occurred in 25 normokalemic ($K > 3.4$ mEq/L) patients, 25 moderately hypokalemic ($K = 3$ to 3.4 mEq/L) patients, and 10 severely hypokalemic ($K < 2.9$ mEq/L) patients.[388] Wahr and coauthors studied 2402 patients undergoing elective CABG and reported that a serum potassium level less than 3.5 mmol/L was a predictor of serious perioperative arrhythmia (OR, 2.2; 95% CI, 1.2 to 4.0), intraoperative arrhythmia (OR, 2.0; 95% CI, 1.0 to 3.6), and postoperative atrial fibrillation/flutter (OR, 1.7; 95% CI, 1.0 to 2.7).[392] The inability of the eye to pick up these changes—or even the inability of Holter recordings for short periods (which seem not to have been used in this study)—points to the need for confirming studies.

Other studies indicate that modest hypokalemia can have severe consequences.[393,394] Holland and coworkers[394] treated 21 patients with 50 mg of hydrochlorothiazide twice a day for 4 weeks. These patients had a history of becoming hypokalemic during diuretic therapy; none of them had cardiac disease or was taking other medications. Before and after diuretic therapy, 24-hour ambulatory ECGs were recorded. This study is also subject to the limitations of Holter monitoring. Ventricular ectopy, including complex ventricular ectopy (multifocal PVCs, ventricular couplets, ventricular tachycardia), developed in 7 of the 21 patients (33%). Potassium repletion decreased the number of ectopic ventricular beats per patient from 71.2 to 5.4/hr. Apparently, some patients are sensitive to even minor potassium depletion. In the Multiple Risk Factor Intervention Trial involving 361,662 patients, more than 2000 of whom were treated for hypertension with

diuretics, the reduction in serum potassium after diuretic therapy was greater in those with PVCs.[393] Although we recommend that hypokalemic patients be given potassium supplements, the merit of this practice is unclear.

Our personal criteria for preoperative potassium therapy are as follows. As a rule, all patients undergoing elective surgery should have normal serum potassium levels. However, we do not recommend delaying surgery if the serum potassium level is above 2.8 mEq/L or below 5.9 mEq/L, if the cause of the potassium imbalance is known, and if the patient is in otherwise optimal condition. This range of safe potassium levels is arbitrary and has changed from 3.3 in 1979, to 3.1 in 1986, to 2.9 in 1990 on the lower side and from 5.6 in 1979, to 5.7 in 1986, to 5.9 in 1990 on the upper side as more data have become available on the safety of preoperative hypokalemia and the dangers of replacing potassium in a hospital environment.[387] We subject all patients with end-stage renal failure to dialysis (using the same arbitrary safe range) before all surgical procedures except truly emergency ones (as in instances of imminent exsanguination). In studies on dogs in 1978, Tanifuji and Eger[395] determined the relationships between electrolyte status and anesthetic requirements that may require intraoperative consideration: hyponatremia and hypoosmolality decreased the minimum alveolar concentration (MAC), hypernatremia increased MAC, and hyperkalemia did not affect the anesthetic requirement.

Gastrointestinal and Liver Diseases

Gastrointestinal Disease

Preoperative Search for Diverse Associated Disorders in Gastrointestinal Disease

Although preoperative preparation of the GI tract is usually the responsibility of the surgeon and although the GI tract frequently does not need to be extensively evaluated by the anesthesiologist, GI disease can and often does cause derangements in many or all other systems. Such disturbances can affect the safety of anesthesia for the patient. Thus, the anesthesiologist may need to not only optimize the patient's condition through extensive preoperative preparation but also have knowledge of disease processes and their effects to guide the patient smoothly through the perioperative period. The major advances of correcting fluid and electrolyte disorders and optimizing nutritional status before surgery now allow surgery to be performed in patients with GI disease previously deemed to be at too great a risk and may have lessened the risk for others.[45-47,396] Still, in patients with GI disease, thorough assessment of intravascular fluid volume, electrolyte concentrations, and nutrition is essential, including an evaluation of the supervening side effects of these therapies (e.g., hypophosphatemia from parenteral nutrition, hyperkalemia or cardiac arrhythmias from too vigorous treatment of hypokalemia, and CHF from too rapid or too vigorous treatment of hypovolemia).

In addition to the vast alterations in fluids, electrolytes, and nutrition that can occur with such diverse GI diseases as neoplasms and pancreatitis, patients with GI disorders can have gastroesophageal reflux disease,[397] bowel obstruction, vomiting, or hypersecretion of acid. These effects may merit rapid induction of anesthesia with the application of cricoid pressure or awake endotracheal intubation, preoperative nasogastric suctioning, or preoperative use of histamine receptor blocking agents. Clotting abnormalities may need to be corrected because fat-soluble vitamin K (often malabsorbed) is necessary for the synthesis of factors V, VII, IX, and X in the liver (also see Chapter 56). Liver disease is often associated with GI disease and, if severe enough, can also result in a deficiency of clotting factors synthesized by the liver.

Other factors should be remembered in the perioperative management of any patient with GI disease. First, closed spaces containing gas expand by absorbing nitrous oxide. Such expansion can lead to ischemic injury, rupture of GI viscera, or both. Second, GI surgery predisposes the patient to sepsis; sepsis and decreased peripheral vascular resistance can lead to massive fluid requirements, cardiac failure, and renal insufficiency. Recently, the surgical site infection rate has been declining. This decrease may be attributable to the use of better technique, more appropriate prophylactic timing and use of antibiotics, better nutrition, less invasive (laparoscopic and endoscopic) surgery, maintenance of normothermia, or surgical resection of even solid tumors.[398-402] Third, patients with GI disease may have many other associated disorders not directly related to the GI tract. For example, they may be anemic from deficiencies in iron, intrinsic factor, folate, or vitamin B_{12}. They may also manifest neurologic changes from combined-system disease. Respiration may be impaired because of heavy cigarette smoking, peritonitis, abscess, pulmonary obstruction, previous incisions, aspiration, or pulmonary embolism (as occurs with ulcerative colitis or with thrombophlebitis in the bedridden). These patients may also have hepatitis, cholangitis, side effects from antibiotic drugs or other medications, massive bleeding with anemia and shock, or psychological derangements.

Because GI disease can be accompanied by so many diverse associated disorders, the clinician must clearly search for involvement of other systems and preoperatively assess and treat such disorders appropriately. Discussion of two specific diseases, ulcerative colitis and carcinoid tumor, will highlight the importance of involvement of other systems in GI disease.

Ulcerative Colitis and Carcinoid Tumors as Examples of Gastrointestinal Disease Affecting Other Systems

Patients with ulcerative colitis often have psychological problems. They may also have phlebitis; deficiencies in iron, folate, or vitamin B_{12}; anemia; or clotting disorders caused by malabsorption. They may be malnourished or dehydrated or have electrolyte abnormalities. In addition, ulcerative colitis can be accompanied by massive bleeding, bowel obstruction or perforation or toxic megacolon causing respiratory compromise, hepatitis, arthritis, iritis, spondylitis, or diabetes secondary to pancreatitis.

The site of origin of carcinoid tumors in more than 75% of patients is the GI tract. Within the GI tract, carcinoid tumors have been documented to occur from the esophagus to the rectum. The most frequent site is the appendix, but carcinoids in this location rarely, if ever metastasize or produce carcinoid syndrome. Tumors arising in the ileocecal region have the highest incidence of metastases. Carcinoid tumors originating from sites other than the GI tract, such as the head and neck, lung, gonads, thymus, breast, and urinary tract, have also been reported. Cardiac involvement, though frequently reported, is usually limited to right-sided valvular and myocardial plaque formation.[403]

Not all patients with carcinoid tumors have symptoms attributable to secretion of hormone by the tumor. Some can, however, and unexpected carcinoid can be manifested during surgery by hypersecretion of gastric fluid. The most comprehensive series in the literature indicates that only 7% of patients have carcinoid syndrome, which typically consists of flushing, diarrhea, and valvular heart disease. Of those with the syndrome, approximately 74% have cutaneous flushing; 68%, intestinal hypermotility; 41%, cardiac symptoms; and 18%, wheezing. Factors influencing symptoms include the location of the tumor and the specific hormones produced and secreted. Although it is generally believed that if patients do not exhibit carcinoid syndrome, the tumors are not producing serotonin (5-hydroxytryptamine [5-HT]), but such may not be the case. Approximately 50% of patients with carcinoid tumors of the GI tract demonstrate evidence of 5-HT production as manifested by elevated urinary levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolic product of 5-HT. Carcinoid syndrome is usually associated with ileal carcinoid tumors that have metastasized to the liver. Presumably, the liver clears mediators released from the tumor. Impairment of this clearing ability by the metastatic tumor results in carcinoid syndrome.

Most patients with carcinoid tumors and increased urinary 5-HIAA have typical carcinoid tumors originating from the midgut (ileum or jejunum). These patients excrete only small amounts of 5-hydroxytryptophan (5-HTP). Patients with atypical carcinoid tumors that originate in the foregut (bronchus, stomach, and pancreas) excrete large amounts of 5-HT and 5-HTP, as well as moderately higher amounts of 5-HIAA.

Although it is generally agreed that 5-HT is responsible for the diarrhea experienced by patients with carcinoid tumors, other neurohumoral agents may contribute to the flushing and hypotension, including dopamine, histamine, and some of the neuropeptides such as substance P, neurotensin, vasoactive intestinal peptide, and somatostatin.

The net physiologic effect of circulating 5-HT represents a composite of both direct action (mediated by 5-HT receptors) and indirect action (mediated through modulation of adrenergic neurotransmission). The existence of several subtypes of 5-HT receptors may account for the different effects of 5-HT on various serotonin-sensitive tissue beds. Indirect actions are effected through alterations in catecholamine release and depend on the level of circulating 5-HT.

5-HT has little if any direct effect on the heart. With elevated levels, however, positive chronotropic and inotropic myocardial effects may occur, mediated by the release of noradrenaline (norepinephrine). Effects of serotonin on the vasculature include both vasoconstriction and vasodilation.

Alterations in GI function attributed to 5-HT include increased motility and net intestinal secretion of water, sodium chloride, and potassium. 5-HT reportedly causes bronchoconstriction in many animals, but rarely in humans. Asthmatics are a possible exception. Carcinoid tumors are frequently manifested as diarrhea with fluid and electrolyte abnormalities. Because these tumors secrete vasoactive substances, patients can exhibit hypotension or hypertension along with the flush associated with release of vasoactive substances. Vasoactive substances can be released from the tumor by any number of substances, including catecholamines. Until the 1990s, management of patients with this tumor was a real challenge for the anesthesiologist. Thus, anesthesiologists of that era had to tread a fine line between avoiding substances known to release 5-HT (e.g., *d*-tubocurarine and morphine) and inducing anesthesia so light that painful stimuli activate a sympathetic stress response.[404] The anesthesiologist also needed to be ready and able to treat hypotension, decreased peripheral vascular resistance, bronchospasm, and hypertension. α-Adrenergic receptor blockade with the phenothiazines, butyrophenones, or phenoxybenzamine and β-adrenergic receptor blockade with propranolol have been advocated to prevent catecholamine-mediated release of vasoactive substances. These practices, however, can lead to hypotension. Nevertheless, the difficulty in managing carcinoid syndrome seemed to change with the availability of a somatostatin analog. In fact, somatostatin is now such a powerful inhibitor of the release of peptides from carcinoid tumors and an inhibitor of the peptic effects on receptor cells that it is the therapy of choice for preoperative, intraoperative, and postoperative management of carcinoid symptoms and crises.[404,405] In cardiac surgical patients there has been a reduction in mortality over time, and vasopressors were shown to be safe in conjunction with octreotide.[406] However, the ease of management of most patients[404,405,407-410] should not lull the anesthesiologist into being unprepared—in fact, somatostatin has caused problems of its own and has failed to prevent severe hypotension and bronchospasm.[411,412]

In patients with severe hypotension that is not treatable with somatostatin, the drug of choice is either angiotensin or vasopressin. (Angiotensin is not commercially available in the United States.) However, the vasoactive substances released by carcinoid tumors cause fibrosis of the heart valves that often results in pulmonic stenosis or tricuspid insufficiency. To increase cardiac output in a patient with tricuspid insufficiency, the anesthesiologist should avoid drugs or situations that increase pulmonary vascular resistance (e.g., angiotensin, vasopressin, acidosis, hypercapnia, hypothermia). In addition, the production of large amounts of 5-HT (equal to 200 mg/day of 5-HIAA) can lead to the development of niacin deficiency with pellagra (as occurs with diarrhea, dermatitis, and dementia).

Acute elevation of plasma kinin activity in carcinoid patients has been postulated for many years as the explanation for the symptoms of carcinoid syndrome. The physiologic effects of kinins are known to include vasodilation of smaller resistance vessels and stimulation of the release of histamine from mast cells. The latter action potentiates their own vasodilating properties and further reduces systolic and diastolic BP. In addition, increases in vascular permeability may lead to edema. Kinins are not known to affect the myocardium directly.

Steroids have been effective in treating the symptoms of bronchial carcinoid tumors. Although prophylactic preoperative administration and intraoperative therapeutic use have been described, controlled studies of beneficial effects are lacking. Aprotinin, like steroids, inhibits the kallikrein cascade. This drug is capable of blocking the proteinase activity of kallikrein, and some reports have described a dramatic clinical response.

A subset of patients with symptoms of carcinoid syndrome excrete histamine at increased levels in their urine. Histamine causes vasodilation of small blood vessels, which leads to flushing and decreased total peripheral resistance. Histamine is known to cause bronchoconstriction, particularly in patients with bronchial asthma and other pulmonary diseases. Its role in carcinoid bronchospasm, if any, is uncertain. Histamine receptor blocking drugs have been used with some success in alleviating the flushing associated with carcinoid syndrome. H_2 antagonism alone was

found to be just as effective as combination therapy in preventing symptoms; pure H_1 antagonism, however, was ineffective. These therapies have been relegated to a second-line defense since the use of somatostatin.

Catecholamines aggravate the symptoms of carcinoid syndrome, presumably by stimulating release of hormone by the tumor. The mechanism by which this release occurs remains obscure. Adrenergic receptors have not been demonstrated in carcinoid tumors, nor do these tumors usually have neural innervation. Perhaps adrenergic stimuli work through their mechanical effects on the gut and vessels to stimulate the release of tumor products. Treatment of patients with carcinoid tumors by means of α- and β-adrenergic antagonists has been beneficial in ameliorating flushing in some instances but ineffective in others.

The results of prospective studies on somatostatin to ameliorate the symptoms of carcinoid syndrome have been dramatic. Somatostatin appears to be a major advancement in the treatment of carcinoid syndrome.

It might logically be concluded that preoperative preparation of a patient with carcinoid syndrome would be similar to that for a patient with pheochromocytoma: titration of adrenergic, histaminic, and serotonergic receptor blocking drugs to maximum effect while monitoring intravascular volume status and adding somatostatin before surgery. Although this approach is logical, preoperative symptoms do not correlate with perioperative symptoms, and only the last two therapeutic options (optimization of intravascular fluid status and administration of somatostatin) are most effective.

Bronchospasm with or without flushing also develops in many patients when vasoactive substances are released. Thus, a patient with carcinoid tumor may be well or may be severely incapacitated by pulmonary, neurologic, nutritional, fluid, electrolytic, or cardiovascular disturbances. Therefore, although the GI system in itself may not require extensive preoperative preparation, GI disease can cause disturbances in any or all other systems that require extensive preoperative preparation to optimize the patient's condition plus preoperative knowledge of physiology and the effects of diseases to guide patients through the perioperative period smoothly. In addition, the anesthesiologist's understanding of the nature of the surgery probably aids in determining the system involvement caused by the GI disorder.

Another perioperative consideration is that patients with GI diseases (perhaps even more so than those with other diseases) have had to endure the psychosocial trauma of having to live with their disease for long periods or the necessity of facing such a prospect.[413] They need emotional support and holistic kindnesses as much as, if not more than others, without sacrificing scientific rigor in the treatment of their condition. Obtaining relevant psychological data while gathering medical information, sitting (not standing) while taking the history, and empathizing with the patient about how difficult it must be to accomplish tasks with this disease (stressing accomplishments, we have found) legitimize the physician's interests in and support of the patient's pain and other psychosocial issues. The time spent sitting and talking with the patient also allows the anesthesiologist to discuss options for pain therapy with the patient, why systemic morphine might be avoided in a patient with a fresh bowel anastomosis,[414] and other issues that show the anesthesiologist to be both a competent physician and particularly concerned with that patient's well-being. In addition to an appreciation of the organic effects of their disease, attention to emotional support of these patients perioperatively presents opportunities to use one's full skills as a physician to bring about healing.

Liver Disease

What are the risks of giving anesthesia to patients with acute liver disease who require emergency surgery? What are the risks of giving anesthesia to patients with chronic impairment of liver function? What can be done to minimize these risks? Although one might think that the experiences gained from providing anesthesia for liver transplantation would answer many of these questions, there is a substantial difference between optimizing cardiovascular function to meet the needs of a new liver (e.g., supply of nutrients) and maintaining liver function in a diseased liver. Because hepatic function and physiology are discussed in Chapter 17 and the preoperative evaluation is reviewed in Chapter 34, we will mention only that the liver performs many functions: it synthesizes substances (e.g., proteins, clotting factors), detoxifies the body of both drugs and the products of normal human metabolism, excretes waste products, and stores and supplies energy.

Hematologic Disorders and Oncologic Disease

Hematologic Disorders

Anemia and Polycythemia

Chapters 55 and 57 discuss the evidence that normovolemic anemia or polycythemia increases perioperative morbidity. The results indicate that knowledge and pretreatment of polycythemia might decrease perioperative morbidity and mortality.

Except for patients with ischemic heart disease (see later), no such evidence exists for normovolemic anemia.[415] Thus, there are no specific preoperative routines for anemia itself, except regarding patients who have or are likely to have ischemic heart disease (as determined by risk factors).[416-418] For these patients, hematocrits above or below 29% to 34% were found in two separate studies to be associated with increased episodes of myocardial ischemia after vascular surgery (Fig. 35-10).[178] For patients at risk for current ischemic heart disease, data indicate that transfusion to a hematocrit level of 29% to 34% may be appropriate (also, see the earlier section on cardiovascular diseases).[419,420] It should be remembered that anemia is a reduction in circulatory erythrocyte mass below the range of values considered normal for persons of the same sex at the same location (age older than 6 months, race, and ethnic background do not explain anemia). Each erythrocyte lives for approximately 120 days; therefore, replacement of 15 to 20 mL of senescent cells needs to be accomplished in the absence of diseases that destroy or cause loss of blood cells. Moreover, the symptoms of anemia—headache, weakness, exertional dyspnea, and loss of endurance—do not provide much information about the severity, rapidity of onset, and cardiorespiratory effects of the underlying cause of the anemia.

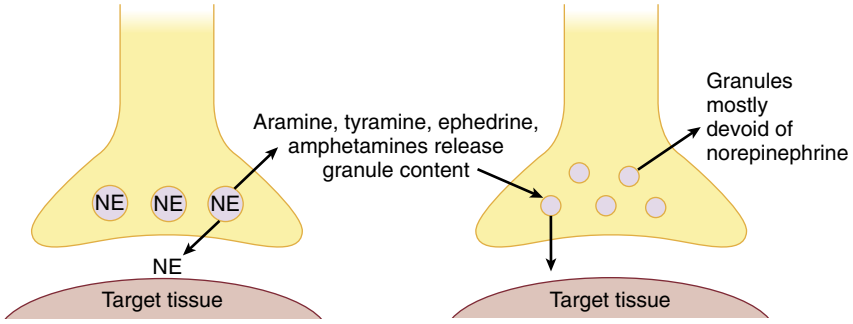


Figure 35-10 Antihypotensive drugs such as metaraminol (Aramine), tyramine, and ephedrine create their effect by releasing catecholamines from granules of the nerve terminal. Therefore, when treatment with drugs such as methyldopa, reserpine, or guanethidine depletes store of norepinephrine (NE) in the granules, little NE remains for release, and the antihypotensive drugs have been rendered ineffective.

Furthermore, because anemia can be a hallmark of many other diseases possibly affecting perioperative anesthetic management, the preoperative presence of anemia requires a search for and treatment of the underlying cause. For instance, anemia could indicate renal insufficiency or a drug reaction, both of which could alter anesthetic management. For this reason, the cause of the anemia should be known preoperatively. Similarly, polycythemia can be a primary disease (e.g., polycythemia vera), or it can be secondary to smoking, the use of diuretic drugs, chronic use of androgens, hypoxia, or other forms of chronic lung/heart disease. Phlebotomies are quite effective for patients with mild polycythemia. Cerebral blood flow improves when the hematocrit is kept below 45%. No prospective controlled study has been performed on humans regarding a possible decrease in perioperative morbidity or wound healing[178,416-418] as a result of perioperative treatment of anemia or polycythemia, although a National Institutes of Health–sponsored trial in hip fracture patients is ongoing. The time of most danger to the patient may be the early recovery room period, during which time oxygen delivery to the lungs is perhaps at its worst.[178] Options for alternatives to blood therapy are discussed in Chapters 55 and 57.

Erythropoietin is one of the substances necessary for normal production of red blood cells. Production and secretion of erythropoietin from the peritubular cells of the kidney are stimulated by tissue hypoxia. Signal transduction of this hypoxic stimulus depends on a heme-containing oxygen-sensing protein that mediates changes in the stability of messenger RNA from chromosome 7 in erythropoietin-producing cells. Erythropoietin triggers quiescent, early erythroid progenitor cells into cycle by acting like a mitogen and facilitating differentiation into late committed erythroid progenitor cells. In normoxic individuals, synthesis of erythropoietin is not stimulated until the concentration of hemoglobin falls below 10.5 g/dL. In severe anemia, erythropoietin levels can increase more than 1000-fold. Iron, folic acid, and vitamin B_{12} are also needed for normal maturation of erythrocytes. Several forms of anemia present special situations, such as sickle cell anemia, hereditary spherocytosis, and the autoimmune hemolytic anemias.

Sickle Cell Anemia and Related Hemoglobinopathies

The sickle cell syndromes constitute a family of hemoglobinopathies caused by abnormal genetic transformation of amino acids in the heme portion of the hemoglobin molecule. The sickle cell syndromes arise from a mutation in the β-globin gene that changes the sixth amino acid from valine to glutamic acid. A major pathologic feature of sickle cell disease is the aggregation of irreversibly sickled cells in blood vessels. The molecular basis of sickling is the aggregation of deoxygenated hemoglobin B molecules along their longitudinal axis.[421] This abnormal aggregation distorts the cell membrane and thereby produces a sickle shape. Irreversibly sickled cells become dehydrated and rigid and can cause tissue infarcts by impeding blood flow and oxygen to tissues.[421-424] Some have challenged this hypothesis, with several studies showing enhanced adhesion of sickled erythrocytes to vascular endothelium.[425] Some other abnormal hemoglobins interact with hemoglobin S to various degrees and give rise to symptomatic disease in patients heterozygous for hemoglobin S and one of the other hemoglobins such as the hemoglobin of thalassemia (hemoglobin C).

Three tenths of 1% of the African American population in the United States have sickle cell–thalassemia disease (hemoglobin SC); these patients also have end-organ disease and symptoms suggestive of organ infarction. For these patients, perioperative considerations should be similar to those for patients with sickle cell disease (hemoglobin SS), discussed later.

Whereas 8% to 10% of African Americans have the sickle cell trait (hemoglobin AS), 0.2% are homozygous for sickle cell hemoglobin and have sickle cell anemia. Sickle cell trait is a heterozygous condition in which the individual has one βS globin gene and one βA globin gene, which results in the production of both hemoglobin S and hemoglobin A, with a predominance of hemoglobin A. Sickle cell trait should not be considered a disease because hemoglobin AS cells begin to sickle only when the oxygen saturation of hemoglobin is below 20%. No difference has been found between normal persons (those with hemoglobin AA) and those with hemoglobin AS regarding survival rates or the incidence of severe disease, with one exception: patients with hemoglobin AS have a 50% increase in pulmonary infarction. However, single case reports of a perioperative death and a perioperative brain infarct in two patients with hemoglobin AS disease do exist, and a report of death believed to be due to aortocaval compression during general anesthesia that resulted in a sickling crisis does exist.[426] The need for exchange transfusion before cardiac surgery has been debated.[427,428] Frequent measurement of oxygen

saturation (pulse oximetry) in multiple areas of the body is recommended, including the ear and toe in pregnant patients.[426] A retrospective review of exercise in military recruits showed that soldiers with sickle cell trait had a higher risk for sudden death after extreme exertion during basic training than did black soldiers with only hemoglobin A—32 per 100,000 versus 1 per 1,000,000.[429] Although this magnitude of increase may not seem great, the vasoactive responses of the perioperative period can be similar to those of moderate to extreme exertion.

The pathologic end-organ damage that occurs in sickle cell states is attributable to three processes: the sickling or adhesion (or both) of cells in blood vessels, which causes infarcts and subsequent tissue destruction secondary to tissue ischemia; hemolytic crisis secondary to hemolysis; and aplastic crises that occur with bone marrow exhaustion, which can rapidly result in severe anemia. Logic dictates that patients currently in crisis not undergo surgery except for extreme emergencies, and then only after an exchange transfusion.[423,425-429]

Because sickling is increased with lowered oxygen tensions, acidosis, hypothermia, and the presence of more desaturated hemoglobin S, current therapy includes keeping the patient warm and well hydrated, giving supplemental oxygen, maintaining high cardiac output, and not creating areas of stasis with pressure or tourniquets. Meticulous attention to these practices in periods when we do not usually pay most careful attention (i.e., waiting in the preinduction area) or when gas exchange may be most unmatched to the cardiovascular-metabolic demands (early postoperative period) may be important in lessening morbidity. Even following these measures routinely, with no special emphasis placed on the periods described, succeeded in reducing mortality to 1% in several series of patients with sickle cell syndromes.[426,429,430] Retrospective review of patient charts led the authors of those studies to conclude that at most, a 0.5% mortality rate could be attributed to the interaction between sickle cell anemia and anesthetics.

Can this rate be decreased?[422,430] Several investigators have advocated using partial exchange transfusions perioperatively. In children with sickle cell anemia and acute lung syndromes, partial exchange transfusion improved clinical symptoms and blood oxygenation. In addition, serum bilirubin levels decreased in patients with acute liver injury. Clinical improvement of pneumococcal meningitis and cessation of hematuria in papillary necrosis also accompanied exchange transfusion.[422] The goal of exchange transfusion is to increase the concentration of hemoglobin A to 40% and the hematocrit to 35%. The 40% figure is an arbitrary one because no controlled studies have established a threshold ratio of hemoglobin A to hemoglobin S that would render blood unable to sickle in vivo. To achieve the 40% ratio in a 70-kg adult, about 4 units of washed erythrocytes would have to be exchanged; the system is inexpensive but efficient.

The possible decrease in preoperative morbidity after partial exchange transfusion has not been compared with the risks of exchange, except in two studies,[424,431] in which the risks of exchange were found to exceed the benefits. In the first study, a retrospective review of 82 surgical procedures performed between 1978 and 1986 in 60 patients, no advantage was noted for preoperative exchange transfusion, as measured by a decrease in postoperative complications.[431] (However, only the sickest may have received exchange transfusions because patients were not randomly allocated to exchange or nonexchange groups.) A slight increase in postoperative atelectasis requiring treatment was seen in patients given preoperative transfusions. More than 50% of the patients given transfusions had a postoperative complication. Patients who began with a hematocrit higher than 36% had a lower rate of complications.[431] In the second study, a randomized comparison of aggressive versus conservative transfusion practices in 551 patients (604 operations), perioperative sickling complications were not different between groups, and transfusion-related complications were substantially less in the conservative group.[424] Therefore, our recommendation is to pay meticulous attention to preventing conditions that increase sickling or that cause infection and to limit exchange transfusion to crisis situations. Perhaps giving higher concentrations of enriched oxygen to patients undergoing laparoscopic procedures should also become routine. Induction of hyponatremia has been shown to abort acute sickle cell crisis; however, this treatment has not gained widespread acceptance. Other conditions are common in sickle cell syndromes: pulmonary dysfunction with increased shunting, renal insufficiency, gallstones, small MIs, priapism, stroke, aseptic necrosis of bones and joints, ischemic ulcers, retinal detachment as a result of neovascularization, and complications of repeated transfusions.

In thalassemia, globin structures are normal, but because of gene deletion, the rate of synthesis of either the α- or β-chains of hemoglobin (α- and β-thalassemia, respectively) decreases.[432-434] Two copies of the gene that codes for the α-globin chain are located on chromosome 16. Deletion of all four of these genes causes cell death in utero, and three deletions cause severe chronic hemolysis and a shortened life span. "α-Thalassemia-1 (trait)" occurs when two genes have been deleted and mild anemia results; "α-thalassemia-2 (silent)" occurs when the two genes have been deleted but no mild anemia or microcytosis results. In α-thalassemia trait, the hemoglobin A_2 level is normal. β-Thalassemia is associated with an excess of α-chains, which denature developing erythrocytes, thereby leading to their premature death in marrow or to shortened survival in the circulation. An elevated hemoglobin A_2 level is the hallmark of β-thalassemia trait, a common cause of mild anemia and microcytosis. Bone marrow transplantation and pharmacologic manipulation of hemoglobin F synthesis are being tried in these hemoglobinopathies, as is direct gene replacement therapy. These therapies seem to be promising in even reversing liver failure from previous iron overload.[435] These syndromes are common in Southeast Asia, India, and the Middle East and in people of African descent.

In thalassemia, facial deformity from erythropoietin-stimulated ineffective erythropoiesis (ineffective because of a genetic inability to produce useful hemoglobin) has been reported to make endotracheal intubation difficult.[432,433] This one case report[433] has not been amplified, and there are no reports of this complication in patients with sickle cell anemia. However, the anemia associated with these syndromes often produces a compensatory hyperplasia of the erythroid marrow, which in turn is associated with severe skeletal abnormalities.[432-434]

Cytoskeletal Anemias (Hereditary Spherocytosis and Elliptocytosis), Enzyme-Deficient Anemias, and Autoimmune Hemolytic Anemias

Congenital abnormalities of the erythrocyte membrane are becoming better understood. In elliptocytosis and hereditary spherocytosis, the membrane is more permeable to cations and more susceptible to lipid loss when cell energy is depleted than is the membrane of a normal red blood cell. Both hereditary sphe-

rocytosis (present in 1 in 5000 people) and hereditary elliptocytosis are inherited as autosomal dominant traits. In both disorders, defects in the membrane are thought to result from a mutation of spectrin, a structural protein of the membrane cytoskeleton.[436] Although the therapeutic role of splenectomy in these diseases is not fully defined, in severe disease, splenectomy is known to improve the shortened life span of the red blood cell 100% (from 20 to 30 days to 40 to 70 days). Because splenectomy predisposes the patient to gram-positive septicemia (particularly pneumococcal), perhaps patients should be given pneumococcal vaccine preoperatively before predictable bacteremic events. No specific problems related to anesthesia have been reported for these disorders.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency (a gender-linked recessive trait) is also reported to occur in approximately 8% of African American men.[437] Young cells have normal activity, but older cells are grossly deficient when compared with normal cells. A deficiency in G6PD results in hemolysis of the erythrocyte and the formation of Heinz bodies. Red cell hemolysis can also occur with intercurrent infections or after the administration of drugs that produce substances requiring G6PD for detoxification (e.g., methemoglobin, glutathione, and hydrogen peroxide). Drugs to be avoided are sulfa drugs, quinidine, prilocaine, lidocaine, antimalarial drugs, antipyretic drugs, nonnarcotic analgesics, vitamin K analogs, and perhaps sodium nitroprusside.

The autoimmune hemolytic anemias include cold antibody anemia, warm antibody anemia (idiopathic), and drug-induced anemia.[438-440] Cold antibody hemolytic anemias are mediated by IgM or IgG antibodies, which at room temperature and below cause red blood cells to clump. When these patients are given blood transfusions, the cells and all fluid infusions must be warm, and body temperature must be meticulously maintained at 37°C if hemolysis is to be prevented. Warm antibody (or "idiopathic") hemolytic anemia is a difficult management problem characterized by chronic anemia, the presence of antibodies active against red blood cells, a positive Coombs test, and difficulty crossmatching blood. For patients undergoing elective surgery, autologous transfusions, predeposit of blood with or without erythropoietin stimulation,[441] and blood from rare Rh-negative red blood cell donors or the patient's first-degree relatives (or both) can be used. In emergency situations, the possibility of autotransfusion, splenectomy, or corticosteroid treatment should be discussed with a hematologist knowledgeable in this area.

Drug-induced anemias have three mechanisms. In receptor-type hemolysis, a drug (e.g., penicillin) binds to the membrane of the red blood cell, and the complex stimulates the formation of an antibody against the complex. In "innocent bystander" hemolysis, a drug (e.g., quinidine, sulfonamide) binds to a plasma protein, thereby stimulating an antibody (IgM) that cross-reacts with an erythrocyte. In autoimmune hemolysis, the drug stimulates the production of an antibody (IgG) that cross-reacts with the erythrocyte. Drug-induced hemolytic anemias generally cease when therapy with the drug ends. In emergency situations, the least incompatible cells available should be used for blood transfusion.

Granulocytopenia

Granulocyte mechanisms have undergone experimental elaboration in the last decade, partly because of the molecular biologic revolution: in addition to erythropoietin (discussed earlier), more than 14 hemolymphopoietic growth factors or cytokines have been characterized biochemically and cloned genetically. These growth factors interact with cell-surface receptors to produce their major actions (Table 35-19).[442] Use of the colony-stimulating factors has permitted more intense oncologic treatment. The few reports related to their perioperative effects detail the unfavorable adverse consequences that such therapies can have on gas exchange when adverse immunologic effects occur.[443]

In patients who have fewer than 500 granulocytes per milliliter of blood and established sepsis, the use of growth factor and granulocyte transfusion has been shown to prolong life.[444-446] Although bone marrow transplantation is being used increasingly, complications usually occur after transplantation, not on harvesting of cells (at which time the anesthesiologist who is not involved in critical care is most frequently involved). Abnormal results on pulmonary function testing before bone marrow transplantation seem to predict complications after transplantation, but not so strongly as to preclude transplantation.[447]

Platelet Disorders

Although inherited platelet disorders are rare, acquired disorders are quite common and affect at least 20% of all patients in medical and surgical ICUs, with infections and drug therapies being the leading causes (also see Chapter 55).[448] Both acquired and inherited platelet conditions cause skin and mucosal bleeding, whereas defects in plasma coagulation produce deep tissue bleeding or delayed bleeding. Perioperative treatment of inherited platelet disorders (e.g., Glanzmann's thrombasthenia, Bernard-Soulier syndrome, Hermansky-Pudlak syndrome) consists of platelet transfusions. EACA has recently been used successfully (experimentally, 1 g/70 kg four times daily) to decrease perioperative bleeding in thrombocytopenic patients. The much more common acquired disorders may respond to one of several therapies (see Chapter 55). Immune thrombocytopenias, such as those associated with lupus erythematosus, idiopathic thrombocytopenic purpura, uremia, hemolytic-uremic syndrome, platelet transfusions, heparin, and thrombocytosis, may respond to steroids, splenectomy, plateletpheresis, eradication of *Helicobacter pylori*, or alkylating agents or may require platelet transfusions, plasma exchange, whole blood exchange, or transfusion; sometimes these disorders do not respond to anything.[194,449,450] Traditionally, splenectomy is performed when steroid therapy fails or reaches a dosage that poses unacceptable risks of toxicity. Newer agents such as anti-D immune globulin and rituximab may induce desirable remissions in idiopathic thrombocytopenic purpura without splenectomy.

Thrombotic thrombocytopenic purpura is a rare disorder of unknown cause. Despite various therapies, this disorder carries a very high mortality rate. However, the introduction of plasmapheresis has improved response rates dramatically in patients with this disease. One uncontrolled study implies that the benefit lies not only in improvement of the hematologic picture but also in prevention of adult respiratory distress syndrome, a leading cause of death in these patients.[450] In that study, early institution of plasmapheresis improved oxygenation.

By far the largest number of platelet abnormalities consists of drug-related defects in the aggregation and release of platelets. Aspirin irreversibly acetylates platelet cyclooxygenase, the enzyme that converts arachidonic acid to prostaglandin endoperoxidases. Because cyclooxygenase is not regenerated in the circulation within the life span of the platelet and because this enzyme is

Table 35-19 Major Effects of Hemolymphopoietic Growth Factors/Cytokines

Cytokine	Other Names	Biologic Effects
Erythropoietin		Erythrocyte production
Interleukin-3 (IL-3)	Multicolony-stimulating factor Stem cell–activating factor Persisting cell-stimulating factor Hemopoietin-2	Stimulates proliferation and differentiation of granulocyte, macrophage, eosinophil, mast cell, megakaryocyte, and T- and B-cell lineage and early myeloid stem cells. Interacts with erythropoietin to stimulate erythroid colony formation, stimulates proliferation of AML blasts, and stimulates histamine release by mast cells
Granulocyte colony-stimulating factor (G-CSF)	Differentiation factor MGI-2	Stimulates granulocyte lineage proliferation and differentiation. Acts on early myeloid stem cells, especially in association with other factors; synergizes with IL-3 to stimulate megakaryocyte colony formation. Increases neutrophil phagocytes and antibody-dependent cell-mediated cytotoxicity. Releases neutrophils from bone marrow and is chemotactic for neutrophils and monocytes. Enhances phagocytosis and antibody dependent cell-mediated cytotoxicity and oxidative metabolism of neutrophils. Stimulates monocyte killing of *Mycobacterium avium-intracellulare* and *Candida* species, tumoricidal activity of monocytes, antibody-dependent cell-mediated cytotoxicity, and expression of cell-surface proteins
Granulocyte-macrophage colony-stimulating factor (GM-CSF)		Stimulates granulocyte, macrophage, and megakaryocyte proliferation and differentiation, early myeloid stem cells, and—in the presence of erythropoietin—erythropoiesis. Enhances the cytotoxic and phagocytic colony-stimulating factor activity of neutrophils against bacteria, yeast, parasites, and antibody-coated tumor cells. Increases surface expression of neutrophil adhesion proteins and enhances eosinophil cytotoxicity, macrophage phagocytosis, and basophil histamine release. Amplifies IL-2–stimulated T-cell proliferation and stimulates B-cell lines to proliferate
Colony-stimulating factor-1	Macrophage colony-stimulating factor	Stimulates predominantly macrophage-monocyte proliferation and differentiation with lesser effects on granulocytes. Acts synergistically with other factors on earlier myeloid stem cells. Stimulates macrophage phagocytosis, killing, migration, antitumor activity, and metabolism. Stimulates secretion of plasminogen activator, G-CSF, interferon, IL-3, or tumor necrosis factor by peritoneal macrophages
Interleukin-1 (α and β)	Endogenous pyrogen Hemopoietin-1 Osteoclast-activating factor Lymphocyte-activating factor	Induces synthesis of acute-phase proteins by hepatocytes. Activates resting T cells, cofactor for T- and B-cell proliferation. Chemotactic for monocytes and neutrophils. Induces production of growth factors, including G-CSF, GM-CSF, IL-6, CSF-1, IL-3, and interferon by many cells. Radioprotective in mice
Interleukin-2	T-cell growth factor	Growth factor for T cells, activates cytotoxic T lymphocytes, promotes synthesis of other cytokines, enhances natural killer cell function
Interleukin-4	B-cell–stimulating factor-1 B-cell differentiation factor (BCDF) IgG induction factor	Enhances antibody production (IgG and IgE) and upregulates class II MHC molecules and Fc receptors on B cells. Costimulant with anti-IgM antibodies for induction of DNA synthesis in resting B cells. Stimulates growth of activated T cells. In the presence of IL-3, enhances mast cell growth; with G-CSF, enhances granulocytes of GM colony formation; and with erythropoietin and/or IL-1, stimulates erythroid and megakaryocyte colony formation
Interleukin-5	Eosinophil differentiation factor (EDF) T-cell–replacing factor (TRF) B-cell growth factor-II (BCGF-II) B-cell differentiation factor (BCDF)	Enhances antibody production (IgA). Promotes proliferation and IgG secretion by B-cell lines and induces hapten-specific IgG secretion in vitro by in vivo–primed B cells. Promotes differentiation by normal B cells. Stimulates eosinophil production and differentiation (GM-CSF and IL-3 act synergistically with IL-5 to stimulate eosinophil proliferation and differentiation). Enhances synthesis of IL-2 receptors
Interleukin-6	B-cell–stimulating factor-2 (BSF-2) Interferon-β_2 T-cell activation factor Hybridoma growth factor	B-cell differentiation and IgG secretion. T cells activated to cytotoxicity. Synergizes with IL-3 on early marrow myeloid stem cells and stimulates proliferation and differentiation of granulocytes, macrophages, eosinophils, mast cells, and megakaryocytes, as well as platelet production (may be a thrombopoietin)
Interleukin-7	Lymphopoietin-1	Stimulates pre–B-cell production. Stimulates T-cell proliferation
Interleukin-8*	Neutrophil-activating factor T-cell chemotactic factor	Inflammatory mediator; stimulates activation of neutrophils
Interleukin-9		Stimulates erythroid colony formation and proliferation of a megakaryocyte cell line
Interleukin-10	Cytokine synthesis– inhibiting factor	Inhibits cytokine production by T_H1 cells
Interleukin-11		Stimulates B-cell, megakaryocyte, and mast cell lineages
C-kit ligand	Mast cell factor Stem cell factor Hemolymphopoietic growth factor-1	Acts on relatively early stem cells synergistically with other cytokines. Stimulates pre-B cells

*Not considered a true growth factor but included here for completeness.
AML, acute myeloblastic leukemia; MHC, major histocompatibility complex; T_H1, first of the thymus-derived cells.
Modified from Quesenberg PJ, Schafer AI, Schreiber AD, et al: Hematology. *In* American College of Physicians: Medical Knowledge Self-Assessment. Philadelphia, American College of Physicians, 1991, p 374.

essential for the aggregation of platelets, one aspirin tablet may affect platelet function for a week. All other drugs that inhibit platelet function (e.g., vitamin E, indomethacin, sulfinpyrazone, dipyridamole, tricyclic antidepressant drugs, phenothiazines, furosemide, steroids) do not inhibit cyclooxygenase function irreversibly; these drugs disturb platelet function for only 24 to 48 hours. If emergency surgery is needed before the customary 8-day period for platelet regeneration after aspirin therapy or if the 2-day period for other drugs has not elapsed, administration of 2 to 5 units of platelet concentrates will return platelet function in a 70-kg adult to an adequate level and platelet-induced clotting dysfunction to normal. Only 30,000 to 50,000 normally functioning platelets per milliliter is needed for normal clotting. Because low-dose aspirin therapy (<650 mg/day) allows aspirin to be gone from the body 24 hours after the last dose and because the body makes 70,000 platelets/mL blood per day, a 48-hour period after the last aspirin in minidose therapy should be sufficient time for platelet aggregation to become normal. This may be the period that must pass to avoid platelet transfusions and their associated risks. One platelet transfusion will increase the platelet count from 4000 to 20,000/mL blood; the platelet half-life is about 8 hours.

Heparin-induced thrombocytopenia can develop within hours on re-exposure to heparin in a previously sensitized patient. Lepirudin and argatroban are direct thrombin inhibitors effective as therapy for heparin-induced thrombocytopenia.[451]

Major risk factors for thrombosis include factor V Leiden and prothrombin 20210A mutations, elevated plasma homocysteine, and the antiphosphoid antibody syndrome.[452,453] Clinicians facing these challenging patients might seek expert local consultation for help with management. This issue is discussed more fully in Chapter 56.

Hemophilia and Related Clotting Disorders

Abnormalities in blood coagulation as a result of defects in plasma coagulation factor are either inherited or acquired. Inherited disorders include X-linked hemophilia A (a defect in factor VIII activity), von Willebrand's diseases (defect in the von Willebrand component of factor VIII), hemophilia B (a sex-linked deficiency of factor IX activity), and other less common disorders. The sex-linked origin of some of these disorders means that hemophilia occurs almost exclusively in the male offspring of female carriers; men do not transmit the disease to their male offspring.

In elective surgery, levels of the deficient coagulation factor should be assayed 48 hours before surgery and the level restored to 40% of normal before surgery. One unit of factor concentrate per kilogram of body weight normally increases the factor concentration by 2%. Thus, in an individual essentially devoid of activity, administration of 20 U/kg body weight would be required as an initial dose. Because the half-life is 6 to 10 hours for factor VIII and 8 to 16 hours for factor IX, approximately 1.5 U/hr/kg of factor VIII or 1.5 U/2 hr/kg of factor IX should be given. Additional administration of factors VIII and IX should be guided by the activity of the clotting factors for about 6 to 10 days postoperatively.[454-456]

These factors are available in various preparations; the newer genetically engineered von Willebrand factor, cryoprecipitate, which contains 20 U/mL, is obtained from regular donors (the risk of hepatitis being 1 in 200 for 5-mL lots) or from fresh frozen plasma (which contains 1 U/mL). Some risk of transmitting hepatitis and AIDS accompanies transfusion but, with better testing, much less than formerly.[457-460] Current screening of blood for aspartate or alanine aminotransferase levels is believed to result in a much lower risk of hepatitis C and even AIDS from transfusion. Theoretically, antigenic testing for HIV should further decrease the risk of transmission by blood products. Heat treatment is also reported to reduce the risk substantially. Factor IX, but not factor VIII is contained in prothrombin complex concentrates; however, these concentrates may contain activated clotting factors, which can lead to disseminated intravascular coagulation (DIC) and a high risk for hepatitis. In addition, although EACA or tranexamic acid is sometimes administered as a fibrinolytic inhibitor, these substances carry with them a significant risk for DIC. Additional hazards of modern therapy include acute and chronic hepatitis, AIDS, hypersensitivity reactions, psychic trauma, chronic pain with narcotic addiction, and inhibition of factors, especially VIII.

An antibody that inactivates factor VIII or IX (fresh frozen plasma fails to increase clotting factor activity after incubation with the patient's plasma) develops in approximately 10% of patients with either hemophilia A or B. These acquired anticoagulants are usually composed of IgG, are poorly removed by plasmapheresis, and are variably responsive to immunosuppressive drugs. The use of prothrombin complex concentrates can be lifesaving but carries the risk of DIC and hepatitis.

Vitamin K deficiency is discussed in the section on liver disease. To review, vitamin K–dependent clotting factors (II, VII, IX, and X) require vitamin K for the postsynthetic addition of γ-carboxyl groups to glutamate residues; administration of vitamin K or fresh frozen plasma can correct these deficiencies.

Patients who come to the operating room after having received many units of blood (as in massive GI bleeding) may have deficient clotting. This impaired clotting is initially caused by depletion of platelets, which occurs after approximately 10 to 15 units of blood has been given, and later, by depletion of coagulation factors (see Chapter 56). Treatment of these deficiencies can be corrected with platelet concentrates—each concentrate is normally suspended in 50 mL of fresh plasma; thus, coagulation factors are also replaced.

Urokinase, streptokinase, and tissue plasminogen activator (t-PA) have been used to treat pulmonary embolism, deep venous thrombosis, stroke, and arterial occlusive disease. These drugs accelerate the lysis of thrombi and emboli, in contrast to heparin, which may prevent, but not dissolve a thrombus. Bleeding complications associated with these fibrinolytic agents are the result of dissolution of hemostatic plugs and can be quickly reversed by discontinuing the medication and replenishing plasma fibrinogen with cryoprecipitate or plasma. However, cryoprecipitate and plasma are seldom needed preoperatively because the fibrinolytic activity of urokinase and streptokinase usually dissipates within 1 hour of discontinuing their administration. Nonetheless, insufficient data have accumulated to prescribe the ideal preoperative preparation and intraoperative management of hemostasis in patients recently treated with urokinase, streptokinase, or t-PA. Postponing surgery for three half-lives of the drug (increases in plasmin activity in blood can be assayed for ≥4 to 8 hours) may not be possible, and meticulous observation of the operative field for hemostasis may not suffice.[461,462] The process may be even more complex in a vascular or cardiac patient who requires heparin administration intraoperatively. To correct the fibrinogen deficiency in these patients, some clinicians administer fibrinogen

before surgery and EACA at heparin administration. We usually delay or avoid giving EACA until heparin is administered in an effort to minimize the risk for thrombosis.

Desmopressin is now being tried in operations associated with high blood loss as a routine measure to decrease bleeding and transfusion requirements. Desmopressin therapy began as treatment of platelet dysfunction in von Willebrand's disease but has since expanded to routine use in patients undergoing cardiovascular surgery and frequent use in other high–blood loss operations. This increased use was prompted by the finding that desmopressin decreases bleeding and transfusion requirements.[463] Whether the side effects of desmopressin exceed its benefits remains to be determined and will probably influence how routine its administration becomes.

The problem of patients taking oral anticoagulants is discussed in the cardiovascular section of this chapter.[193-200,202-205] Regional anesthetic techniques might be avoided in patients given anticoagulant drugs.[193-200,202-205] Whether these regional techniques should also be avoided in patients treated prophylactically with low-dose subcutaneous heparin has not been studied. The effects of heparin sulfate can be reversed by titrating protamine, with the activated clotting time used as a guide.

Pharmacologic research is searching for specific molecular subtypes of heparin that have different anticoagulant potencies, binding affinities for antithrombin III, antithrombotic effects, and platelet-aggregating effects (see the pulmonary section in this chapter on prophylaxis for deep venous thrombosis). The search is on for a "new" heparin preparation that will block thrombosis without causing clinical bleeding (see earlier). Such a development might change our ways of monitoring clotting function. As of now, the new heparins appear to increase the risk for epidural hematoma. Determining the bleeding time, platelet count, partial thromboplastin time, and prothrombin time will identify almost all problems in patients with a suspected clotting or bleeding disorder (also see Chapter 56). As explained in Chapter 34, these screening tests should probably not be obtained for asymptomatic patients.

Oncologic Disease

Patients with malignant tumors may be otherwise healthy or may be desperately ill with nutritional, neurologic, metabolic, endocrinologic, electrolyte, cardiac, pulmonary, renal, hepatic, hematologic, or pharmacologic disabilities. Thus, determining the other disabilities accompanying malignant tumors requires evaluation of all systems. Abnormalities frequently accompanying such tumors include hypercalcemia either by direct bone invasion or by ectopic elaboration of PTH or other bone-dissolving substance, uric acid nephropathy, hyponatremia (especially with small cell, or oat cell, carcinoma of the lung), nausea, vomiting, anorexia and cachexia, fever, tumor-induced hypoglycemia, intracranial metastases (10% to 20% of all cancers), peripheral nerve or spinal cord disorders, meningeal carcinomatosis, toxic neuropathies secondary to anticancer therapy, and paraneoplastic neurologic syndromes (dermatomyositis, Eaton-Lambert syndrome, myopathies, and distal neuropathies).

Many patients with malignant tumors are given large doses of analgesics and should be kept comfortable during the perioperative period. Avoiding drug dependence is of no practical importance in terminally ill patients.[464] Marijuana (tetrahydrocannabinol) depresses the CNS vomiting center and may be more effective than the phenothiazines or butyrophenones in suppressing the nausea associated with cancer and its therapy; marijuana decreases anesthetic requirements 15% to 30%. Immunomodulators, stimulating factors or cytokines, gene identification,[465,466] and drugs for treating side effects (e.g., midazolam or ondansetron) have given new hope for safer, more effective therapy with fewer limiting side effects. The effect of ondansetron in preventing vomiting and the effect of midazolam in preventing "memory-stimulated vomiting" have been important additions. The NK-1 antagonists have also been approved for treatment in oncologic patients."

The toxicity of cancer chemotherapy is related to the drugs used and the dose. For radiation therapy, damage occurs when the following doses are exceeded: lungs, 1500 rad; kidneys, 2400 rad; heart, 3000 rad; spinal cord, 4000 rad; intestine, 5500 rad; brain, 6000 rad; and bone, 7500 rad. The toxicities of biologic and immunomodulating therapies are related to the change in immune function that they cause. Alkylating agents cause bone marrow depression, including thrombocytopenia, as well as alopecia, hemorrhagic cystitis, nausea, and vomiting. The alkylating agents, including cyclophosphamide and mechlorethamine, can act as an anticholinesterase and prolong neuromuscular blockade.[467] The antineoplastic alkaloid vincristine produces peripheral neuropathy and SIADH, and vinblastine produces myelotoxicity. Cisplatin is also associated with peripheral neuropathy and severe nausea. Nitrosoureas can produce severe hepatic and renal damage, as well as bone marrow toxicity, myalgia, and paresthesia. Folic acid analogs such as methotrexate have been linked to bone marrow depression, ulcerative stomatitis, pulmonary interstitial infiltrates, GI toxicity, and occasionally, severe liver dysfunction. Fluorouracil and floxuridine, both pyrimidine analogs, cause bone marrow toxicity, megaloblastic anemia, nervous system dysfunction, and hepatic and GI alterations. Purine analogs (mercaptopurine, thioguanine) have bone marrow depression as their primary toxic effect. Anthracycline antibiotics (doxorubicin, daunorubicin, mithramycin, mitomycin C, bleomycin) can all cause pulmonary infiltrates; cardiomyopathy (especially doxorubicin and daunorubicin); myelotoxicity; and GI, hepatic, and renal disturbances.

The wisdom of anesthetizing patients given bleomycin has been questioned. A retrospective study by Goldiner and coauthors[468] reported postoperative deaths in five consecutive patients given bleomycin. All five patients died of postoperative respiratory failure. Using the same anesthetic technique, Goldiner and coworkers[468] then anesthetized 12 patients, limited the inspired oxygen concentration to 22% to 25% perioperatively, and replaced much of the blood loss with colloids rather than crystalloids. None of the 12 patients died. These investigators postulated that bleomycin caused epithelial cell edema that progressed to necrosis of type I alveolar cells, leakage of fluid into the alveolar space, and the formation of "hyaline membranes" similar to that associated with oxygen toxicity. Goldiner and colleagues[468] believe that this pathophysiologic similarity indicates a possible synergistic relationship between oxygen and bleomycin. However, LaMantia and coworkers[469] retrospectively analyzed the changes in 16 patients undergoing surgery after bleomycin therapy. Thirteen patients were given oxygen at inspired concentrations of 37% to 45%. No instances of postoperative respiratory failure occurred. Animal data do not support this effect of bleomycin in altering the toxicity of hyperoxia.[470] Thus, data are currently available to

support all practices regarding administration of oxygen to patients given bleomycin. We prefer to keep inspired oxygen concentrations at the lowest level that provides adequate tissue oxygenation. When in doubt about side effects in patients undergoing cancer chemotherapy, our practice is to seek advice from two experts.

Patients Given Drug Therapy for Chronic and Acute Medical Conditions

A steadily increasing number of potent drugs are being used to treat disease, and the average hospitalized patient receives more than 10 drugs. Many drugs have side effects that might make anesthesia more risky or patient management more difficult. Knowing the pharmacologic properties and potential side effects of commonly used drugs helps the anesthesiologist avoid pitfalls during anesthesia and surgery.

The first step in avoiding these pitfalls is to obtain a drug history from the patient, including vitamins, herbs, and supplements.[21-23,471,472] Then, for every drug, medicine, and over-the-counter preparation that the patient is using, the anesthesiologist should know the name, classification of drug, diseases and conditions for which it is prescribed, and common side effects. Having this knowledge before surgery helps the anesthesiologist avoid making mistakes that might turn minor side effects into life-threatening situations. If necessary, the anesthesiologist should return to the patient's bedside (or telephone outpatients) to search for signs or symptoms of these effects. Unnecessary drugs should be discontinued for at least three and preferably five half-lives of the drugs. This period should be longer if metabolites of the drug have activity and longer half-lives. For essential or beneficial drugs, the optimal dose should be determined in consultation with the treating physician; the optimal dose is that maximizing the ratio of therapeutic value to the risk of drug toxicity. Side effects should be sought and either corrected preoperatively or at least planned for in anesthetic management. For instance, if a patient is made hypokalemic with diuretic drugs, hypokalemia might be corrected before surgery; an additional tactic would be to avoid hyperventilation during surgery (see the earlier section on hypokalemia). This line of reasoning and planning is best done at least 1 week before surgery. Ideally, the surgeon, internist, primary care practitioner, and anesthesiologist should communicate regarding these topics well in advance of surgery. Understanding the side effects of chronic drug therapy that affect the sympathetic nervous system requires some knowledge of the basic pharmacologic characteristics of the sympathetic nervous system (see Chapter 12).

Pharmacologic Processes in the Sympathetic Nervous System

It is important to remember several points related to the pharmacology of the sympathetic nervous system when considering chronic drug therapy.

Norepinephrine, dopamine, and epinephrine exert their physiologic effect by interacting with an appropriate receptor at the target tissue. The primary receptor acts through intermediary messenger systems (including cyclic 3′,5′-adenosine monophosphate [cAMP] or G-stimulatory or G-inhibitory proteins, or both) or can change the conformation (and hence the affinity for ligands) of bordering or neighboring receptors. These bordering or neighboring receptor effects may account for many of the multitude of effects associated with catecholamines.

The action of sympathomimetic substances is terminated through an unusual process: the nerve ending uses an active reuptake system to recapture most of the norepinephrine from the target tissue (see Chapter 12). Obviously, blockage of this system permits more norepinephrine to remain free to produce physiologic effects. In addition to this reuptake system, two enzymes transform catecholamines metabolically: monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT).

Antihypertensive Drugs

Many antihypertensive drugs and almost all mind-altering drugs affect sympathetic neuronal storage, uptake, metabolism, or release of neurotransmitters. For instance, the antihypertensive drug reserpine depletes the granules of norepinephrine, epinephrine, and dopamine in both the brainstem and periphery. Depletion of transmitters in sympathetic nerve endings renders drugs such as ephedrine and metaraminol ineffective because these drugs act primarily by releasing catecholamines (see Fig. 35-10). Guanethidine and guanadrel deplete granular norepinephrine and affect only the peripheral sympathetic system. In amounts used clinically, reserpine decreases MAC by 20% to 30%, whereas guanethidine has no effect on anesthetic requirements. In addition to causing a lack of response to indirect-acting vasopressors, reserpine can cause denervation supersensitivity and hyperresponsiveness (with hypertension or tachycardia, or both) to the usual doses of direct-acting sympathetic amines such as phenylephrine (Neo-Synephrine), isoproterenol, norepinephrine, epinephrine, and dopamine.[471,472] Thus, in patients who have been treated with drugs that alter sympathetic neurotransmitter release, uptake, metabolism, or receptor function, some problems may occur: hypotension, hypertension, and bradycardia should be treated by titrating doses of direct-acting vasoconstrictors such as phenylephrine, vasodilators such as nitroprusside, or chronotropic drugs such as atropine, isoproterenol, or dopamine.

Another group of antihypertensive drugs consists of "false neurotransmitters." False neurotransmitters replace norepinephrine in the granules at the nerve ending. α-Methyldopa (Aldomet) becomes α-methyldopamine, which is further metabolized to α-methylnorepinephrine (Fig. 35-11). In some nerve endings and for some receptors, α-methyldopamine or α-methylnorepinephrine is more potent than dopamine or norepinephrine as dopaminergic or α-adrenergic receptor stimulants. However, at most nerve endings, the false neurotransmitters are less potent stimulants; this lower degree of stimulation is one means by which their antihypertensive action is produced. Alternatively, α-methyldopa may act by stimulating the brainstem sympathetic nervous system. When this system antagonizes the peripheral sympathetic nervous system, the activity of the latter decreases and BP is reduced. Through its central effect, α-methyldopa decreases anesthetic requirements 20% to 40%.

In addition to altering the response to exogenously administered vasopressors, these neurotransmitter-depleting drugs can

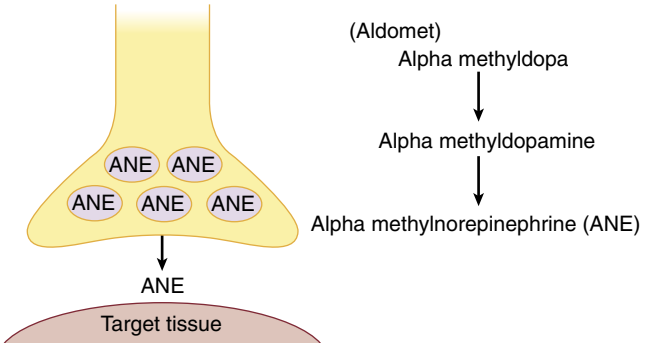


Figure 35-11 In the granules of the nerve terminal, α-methyldopa (Aldomet) is converted enzymatically to α-methyldopamine by the same enzyme that converts dopa to dopamine. α-Methyldopamine is converted to α-methylnorepinephrine by the same enzyme that converts dopamine to norepinephrine.

also produce side effects: psychic depression, nightmares, drowsiness, nasal stuffiness, diarrhea, bradycardia, and orthostatic hypotension with impotence (reserpine).[473-475] Guanethidine and guanadrel can cause orthostatic hypotension, bradycardia, asthma, diarrhea, and inhibition of ejaculation. α-Methyldopa is associated with drowsiness, orthostatic hypotension, bradycardia, diarrhea, acute or chronic hepatitis, cirrhosis, and autoimmune hemolytic anemia (i.e., a positive Coombs test result).[472] Because of these side effects, ACE inhibitors (captopril, enalapril, lisinopril, enalaprilat, and ramipril) and angiotensin II receptor blockers are being used increasingly as first-line drugs and appear to improve the quality of life of patients taking antihypertensive drugs. One of the angiotensin II receptor blockers—valsartan—when combined with a diuretic, actually increases libido in both men and women while decreasing BP. However, ACE inhibitors and angiotensin II receptor blockers may be associated with more peripheral vasodilation and hypotension on induction of anesthesia than sympatholytics are. Added to this group are the ACE receptor blocking agents. These last two classes of drugs are associated with such severe hypotension with standard anesthetic induction that we discontinue or at least consider discontinuing the use of these drugs preoperatively (see earlier).

Catecholamine or sympathetic receptor blocking drugs affect the three major types of catecholamine receptors: α-adrenergic, β-adrenergic, and dopaminergic. The existence of subdivisions (e.g., β_1 and β_2) suggested the possibility that some drugs would be found to affect only one set of receptors. For example, terbutaline is used more frequently than isoproterenol because terbutaline is said to exert a preferential effect on α_2-receptors (i.e., dilation of bronchial smooth muscle), thereby avoiding the cardiac stimulation produced by drugs that stimulate β_1-receptors. In fact, the selectivity is dose related. At a certain dose, a direct β_2-receptor stimulating drug will affect only those receptors but, at a higher dose, will stimulate both β_1- and β_2-receptors. The effect of a given dose varies with each patient. A certain dose may stimulate β_1- and β_2-receptors in one patient but neither receptor in another patient. More and more selective blocking drugs are being developed in hope of widening the margin between β_1- and β_2- and α-adrenergic effects. Ultimately, however, even more selectivity is desired. It would be advantageous to be able to decrease the heart rate without changing myocardial contractility or to increase contractility without changing the heart rate. Such is the goal of much drug research and the development of dobutamine and fenoldopam. However, to date, all such selectivity appears to be dose related, even for dobutamine.

Metoprolol (Lopressor) and atenolol (Tenormin) (both β_1-adrenergic receptor blocking drugs) and propranolol, betaxolol, timolol, esmolol, pindolol, oxprenolol, acebutolol, carteolol, penbutolol, and nadolol are widely available β-adrenergic receptor blocking drugs used for chronic therapy in the United States. Because nadolol has poor lipid solubility, it has a long elimination half-life (17 to 24 hours) and does not cross the blood-brain barrier readily. Although selective β-adrenergic receptor blocking drugs should be more appropriate in patients with increased airway resistance or diabetes, this advantage is apparent only when low doses are used. The use of β-adrenergic receptor blocking drugs has become widespread because these drugs treat everything from angina and hypertension to priapism and stage fright. These drugs appear to decrease morbidity and mortality in patients who have initially survived MI[476,477] and may increase perioperative survival in selected patients (see the earlier section on cardiovascular disease).

Smulyan and colleagues[478] studied the problems of long-term propranolol hydrochloride therapy in adult patients who must undergo abdominal surgery. Because these patients cannot take oral medications postoperatively for many days, they must be protected against perioperative sympathetic stimulation and the propranolol withdrawal syndrome. It is therefore common to develop intravenous β-blocker protocols for patients chronically taking these agents, although it is important to recognize the risk of β-blockers. The hypotensive and bradycardic effects of propranolol and general anesthesia appear to be additive. Because of its shorter half-life (3 to 10 minutes), esmolol has replaced propranolol in critical care (including anesthesia) settings because errors in therapy or side effects, such as increased airway resistance, vanish much more quickly than if propranolol were administered.[479] Propranolol does not affect anesthetic requirements, and one would expect the same lack of effect from other "pure" β-adrenergic receptor blocking drugs.

α-Adrenergic receptor blocking drugs include phentolamine, prazosin, terazosin, doxazosin, phenoxybenzamine, the phenothiazines, and the butyrophenones (e.g., droperidol). Dopaminergic receptor antagonists include the antischizophrenic drugs (phenothiazines and butyrophenones) and metoclopramide. The receptor blocking drugs inhibit the action of sympathomimetic drugs at the receptor in a dose-related fashion. Thus, propranolol lowers BP by blocking the tendency of norepinephrine and epinephrine to increase the rate and force of contractions of the heart (and perhaps their tendency to increase the secretion of renin as well). To overcome this blockade, one need only provide more β-receptor stimulating drug. Thus, high doses of vasopressors may be needed to increase BP in a patient given large doses of propranolol.

When administration of β-adrenergic receptor blocking drugs is terminated, sympathetic stimulation often increases, as though the body had responded to the presence of these drugs by increasing sympathetic neuron activity. Thus, propranolol and nadolol (to name just two) withdrawal can be accompanied by a hyper–β-adrenergic condition that increases myocardial oxygen

demands. Administering propranolol or metoprolol can cause bradycardia, CHF, fatigue, dizziness, depression, psychoses, bronchospasm, and Peyronie's disease. The POISE study emphasizes the concerns that inadequate titration of these agents can lead to stroke or increased mortality.[121] Side effects of dopaminergic receptor blocking drugs are discussed later in this chapter. Prazosin (Minipress), terazosin, and oxazocin are α_1-adrenergic receptor blocking drugs used to treat hypertension, ischemic cardiomyopathy, receding hairlines, and benign prostatic hypertrophy because they dilate both veins and arteries and reduce sphincter tone. These drugs are associated with vertigo, palpitations, depression, dizziness, weakness, and anticholinergic effects.

Some sympathomimetic drugs stimulate α-adrenergic receptors in the brainstem. Clonidine (Catapres), a drug with a half-life of 12 to 24 hours, guanabenz, and guanfacine (Tenex) are α_2-adrenergic receptor stimulants. Presumably, α_2-adrenergic agonists, including clonidine, guanabenz, and guanfacine, chronically lower BP through the central brainstem adrenergic stimulation referred to previously. They may also be used chronically to treat opiate, cocaine, food, and tobacco withdrawal. Occasionally, withdrawal from clonidine can precipitate a sudden hypertensive crisis, analogous to that occurring on withdrawal from propranolol, and cause a hyper–β-adrenergic condition. The degree of hypertensive crisis after clonidine withdrawal is now being debated. (Although intravenous clonidine is not available in the United States, a skin patch of clonidine is being used preoperatively to ablate sympathomimetic responses perioperatively.) Tricyclic antidepressant drugs and presumably phenothiazines and the butyrophenones interfere with the action of clonidine. Although administration of a butyrophenone (e.g., droperidol) to a patient taking clonidine, guanabenz, or guanfacine chronically could theoretically precipitate a hypertensive crisis, none has been reported. Clonidine administration can be accompanied by drowsiness, dry mouth, orthostatic hypotension, bradycardia, and impotence. Acute clonidine or dexmedetomidine administration decreases anesthetic requirements by at least 40% to 60%; chronic administration decreases requirements by 10% to 20%.[480,481] Because of the relative safety of these drugs and their ability to decrease anesthetic requirements, block narcotic-induced muscle rigidity, and provide pain relief, their popularity preoperatively, intraoperatively, and in ICU sedation is increasing dramatically.[480-484]

Three other classes of antihypertensive drugs affect the sympathetic nervous system indirectly: diuretics, arteriolar dilators, and slow (calcium) channel blocking agents. Thiazide diuretic drugs are associated with hypochloremic alkalosis, hypokalemia, hyperglycemia, hyperuricemia, and hypercalcemia. The potassium-sparing diuretic drug spironolactone is associated with hyperkalemia, hyponatremia, gynecomastia, and impotence. All diuretic drugs can cause dehydration. The thiazide diuretics and furosemide appear to prolong neuromuscular blockade. The arteriolar dilator hydralazine can cause a lupus-like condition (usually with renal involvement), nasal congestion, headache, dizziness, CHF, angina, and GI disturbances. Such a syndrome is nonexistent with the other direct vasodilator on the U.S. market, minoxidil.

The slow-channel calcium ion antagonists ("calcium channel blocking drugs") inhibit the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. Such inhibition reduces the heart rate (negative chronotropy); depresses contractility (negative inotropy); decreases conduction velocity (negative dromotropy); and dilates coronary, cerebral, and systemic arterioles (Fig. 35-12).[485] Verapamil, diltiazem, and nifed-

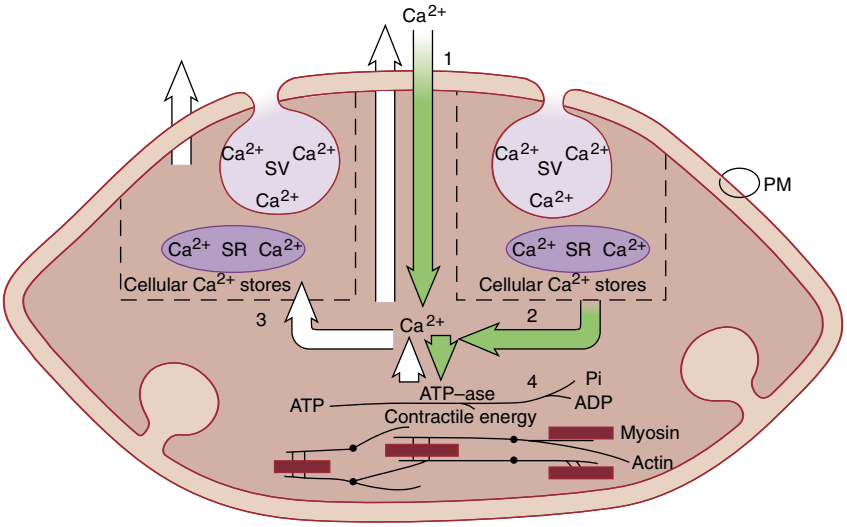


Figure 35-12 Schematic drawing of a smooth muscle cell showing calcium flux and possible sites of interference by halothane and nifedipine. The concentration of calcium (Ca^{2+}) in the cytoplasm increases (*green arrows*) because of entry through the plasma membrane (PM) and release from surface vesicles (SV) or the sacroplasmic reticulum (SR). When the concentration of cytoplasmic Ca^{2+} is sufficiently high, adenosine triphosphate (ATP) is activated. Splitting of ATP by adenosine triphosphatase (ATPase) into phosphatidylinositol (Pi) and adenosine diphosphate (ADP) provides the interaction and contraction of actin filaments and myosin particles constituting muscle fibers. The concentration of cytoplasmic Ca^{2+} decreases (*white arrows*) with the return of Ca^{2+} to cellular stores and the extracellular transport of Ca^{2+}. Both halothane and nifedipine probably (1) inhibit the entry of Ca^{2+} and (2) may also interfere with cytoplasmic Ca^{2+} flux by reducing the release of Ca^{2+} by the SR, by (3) reducing storage and reuptake, or by (4) blocking ATPase or the contractile mechanism (or both). *(Redrawn from Tosone SR, Reves JG, Kissin I, et al: Hemodynamic responses to nifedipine in dogs anesthetized with halothane. Anesth Analg 62:903, 1983.)*

ipine all produce such effects, but to varying degrees and apparently by similar, but different mechanisms. These mechanisms relate to the three different classes of calcium channel antagonists that they represent: the phenylalkyl amines, the benzothiazepines, and the dihydropyridines, respectively. Nifedipine is the most potent of the three as a smooth muscle dilator, whereas verapamil and diltiazem have negative dromotropic and inotropic effects and vasodilating properties. Diltiazem has weak vasodilating properties when compared with nifedipine and has less of an AV conduction effect than verapamil does. Thus, verapamil and diltiazem can increase the PR interval and produce AV block. In fact, reflex activation of the sympathetic nervous system may be necessary during the administration of diltiazem, and especially during verapamil therapy, to maintain normal conduction. Clearly, verapamil and diltiazem must be titrated very carefully when a patient is already taking a β-adrenergic receptor blocking drug or when adding β-blocking drugs to a patient already taking verapamil or diltiazem.

The use of calcium channel blocking drugs has several important implications for anesthetic management.[485-487] First, the effects of inhaled and narcotic anesthetics and nifedipine in decreasing systemic vascular resistance, BP, and contractility may be additive. Similarly, verapamil and anesthetics (inhaled anesthetics, nitrous oxide, and narcotics) increase AV conduction times and additively decrease BP, systemic vascular resistance, and contractility. Second, verapamil and presumably the other calcium channel blocking drugs have been found to decrease anesthetic requirements by 25%. These drugs can produce neuromuscular blockade, potentiate both depolarizing and nondepolarizing neuromuscular blocking drugs, and in at least one type of myopathy (Duchenne's muscular dystrophy), even precipitate respiratory failure. Finally, because slow-channel activation of calcium is necessary to cause spasms of cerebral and coronary vessels, bronchoconstriction, and normal platelet aggregation, these drugs may have a role in treating ischemia of the nervous system, bronchoconstriction, and unwanted clotting disorders perioperatively. All three drugs are highly protein bound and may displace or be displaced by other drugs that are also highly protein bound (e.g., lidocaine, bupivacaine, diazepam, disopyramide, and propranolol). Adverse consequences can be minimized by titrating the inhaled or narcotic drug to the hemodynamic and anesthetic effects. By monitoring for side effects, the anesthetist can prevent them from becoming serious (S. Slogoff and coworkers, personal communication). Hemodynamic, but not electrophysiologic changes can usually be reversed by administering calcium. Reversal of the electrophysiologic effects may occur if "industrial" doses of β-adrenergic agonists are given.

Mood-Altering Drugs

Mood-altering drugs are the most frequently prescribed medications in the United States.[474,475] They include MAOIs, SSRIs, phenothiazines, tricyclic antidepressant drugs, other antidepressants that fail previous drug category classification such as bupropion, and drugs of abuse such as cocaine. MAOIs, which include isocarboxazid (Marplan), phenelzine (Nardil), pargyline (Eutonyl), tranylcypromine (Parnate), and deprenyl, bind irreversibly to the enzyme MAO, thereby increasing intraneuronal levels of amine neurotransmitters (serotonin, norepinephrine, dopamine, epinephrine, octopamine). This increase is associated with an antidepressant effect, an antihypertensive effect, an antinarcoleptic effect, elevation of liver enzymes, and delayed onset of Parkinson's disease (deprenyl). Because two forms of the enzyme (MAO-A and MAO-B) are selective in vitro for substrate (MAO-A is selective for serotonin, dopamine, and norepinephrine; MAO-B for tyramine and phenylethylamine), presumably MAOIs selective for MAO-A or MAO-B would have different effects.[488] This is not known for certain inasmuch as deprenyl (selegiline [Eldepryl]), an MAO-B–selective drug, improves a dopamine deficiency state, parkinsonism.

Interactions between MAOIs and a variety of foods and drugs containing indirect-acting sympathomimetic substances such as ephedrine or tyramine (found especially in aged cheeses) can occur for as long as 2 weeks after the last dose of MAOI is given. The most serious effects of this interaction are convulsions and hyperpyrexic coma (particularly after narcotics).

Anesthetic management of a patient given an MAOI can be chaotic; for this reason it is widely accepted practice to discontinue MAOIs at least 2 to 3 weeks before any planned operation.[474,475,488-492] An alternative point of view has been expressed regarding severely psychotic patients or emergency surgery.[488,493-495] Clearly, the risk of discontinuing MAOIs must be weighed against the risk of suicidal tendencies in some patients deprived of MAOIs. There are no reported experiences of interactions between narcotics and deprenyl, so judgments about possible worsening of Parkinson's disease and continuing MAOIs have no basis in data. It should be noted that severe reactions have occurred when too short an interval existed between the administration of MAOIs and tricyclic antidepressants. Emergency surgery on patients given MAOIs can be punctuated by hemodynamic instability. A regional block can be attempted as treatment of postoperative pain to avoid having to give narcotics. Cases of hyperpyrexic coma after the administration of most narcotics have been reported in humans, and animal studies document a 10% to 50% incidence of hyperpyrexic coma in animals pretreated with MAOIs and then given a variety of narcotics.[474,475,488-492] These reactions appear to be treated best by therapy supporting vital functions.

Alternative drugs for the treatment of severe depression include the tricyclic antidepressant drugs: amitriptyline (Elavil, Endep), imipramine (Tofranil, Presamine), desipramine (Norpramin), doxepin (Adapin, Sinequan), nortriptyline (Aventyl), fluoxetine (Prozac), trazodone (Desyrel), bupropion (Wellbutrin), and others.[474,475] Tricyclic antidepressant drugs also block the reuptake of neurotransmitters and cause their acute release. Given chronically, these drugs decrease stores of noradrenergic catecholamines. Tricyclic antidepressant drugs also produce side effects similar to those of atropine (dry mouth, tachycardia, delirium, urinary retention) and can cause changes on the ECG (changes in the T wave, prolongation of the QRS complex, bundle branch block or other conduction abnormalities, or PVCs). Although arrhythmias induced by tricyclic antidepressants have been treated successfully with physostigmine, bradycardia has sometimes occurred.[474,475] Drug interactions with tricyclic antidepressants include those related to blockade of the reuptake of norepinephrine (such as interference with the action of guanethidine) and fatal arrhythmias after halothane and pancuronium.[496,497] Such interactions, though predictable for a population of patients, may not alter a patient's threshold for arrhythmias. The newer antidepressants (the SSRIs) can also have serious side effects. Fluoxetine, a tricyclic that also has an SSRI effect, causes nausea,

vomiting, headaches, nervousness, and possibly paranoia and ideas of suicide more commonly than the other tricyclics do[474,475]; however, it is less likely to cause anticholinergic effects or orthostatic hypotension. Bupropion may cause nausea, vomiting, seizures, agitation, tremor, excitement, and increased motor activity, but it only rarely causes anticholinergic effects or orthostatic hypotension. Discontinuing drugs can cause withdrawal symptoms or precipitate recurrence of psychiatric illness. Switching between drugs for depression can cause hyperpyrexia and coma. Thus, switching before surgery should not be requested casually.[474,475]

The effectiveness of phenothiazines and butyrophenones in schizophrenia suggests a dopamine receptor blocking action. In addition, these drugs possess varying degrees of parasympathetic stimulation and ability to block α-adrenergic receptors. The phenothiazines include chlorpromazine (Thorazine, Chlor-PZ), promazine (Sparine), triflupromazine (Vesprin), fluphenazine (Prolixin), trifluoperazine, prochlorperazine (Compazine), and many others. The butyrophenones include droperidol and haloperidol (Haldol). Both the phenothiazines and butyrophenones produce sedation, depression, and antihistaminic, antiemetic, and hypothermic responses. They are also associated with cholestatic jaundice, impotence, dystonia, and photosensitivity. Other side effects associated with phenothiazines include orthostatic hypotension (partly as a result of α-adrenergic blockade) and abnormalities on the ECG such as prolongation of the QT or PR intervals, blunting of T waves, depression of the ST segment, and on rare occasion, PVCs and torsades de pointes.[474,475,496,497] Although few data are available on the antidepressant drugs selective for serotonin (the SSRIs), occasional case reports of severe hypotension and cardiac arrest with severe bradycardia have been presented in abstract form.

Several important drug interactions are noteworthy for the phenothiazine derivatives. The effects of CNS depressants (especially narcotics and barbiturates) are enhanced by the concomitant administration of phenothiazines. In addition, the CNS seizure threshold is lowered by the administration of phenothiazines, which should be avoided in patients who are epileptic or withdrawing from any drug that depresses the CNS. The antihypertensive effects of guanethidine and guanadrel are blocked by tricyclic antidepressant drugs and the phenothiazines.[472] Lithium carbonate is used to treat manic depression, but it is more effective in preventing mania than relieving depression. In excitable cells, lithium mimics sodium and decreases the release of neurotransmitters both centrally and peripherally. Lithium prolongs neuromuscular blockade and may decrease anesthetic requirements because it blocks brainstem release of norepinephrine, epinephrine, and dopamine.

Psychoactive drugs such as the amphetamines (including methamphetamines and their smokable derivative in crystal form known as "ice") and cocaine acutely release norepinephrine, epinephrine, and dopamine and block their reuptake. Taken chronically, they deplete nerve endings of these neurotransmitters.

Drugs that appear to increase central α-adrenergic release increase anesthetic requirements, whereas drugs that appear to decrease central α-adrenergic release decrease anesthetic requirements. (This may not be the mechanism by which they alter anesthetic requirements, but it is a convenient way of remembering the alteration.) Drugs that affect only the β-adrenergic receptors do not alter anesthetic requirements.

Sympathomimetic Drugs

Many antiasthmatic drugs (bronchodilators) such as terbutaline, aminophylline, and theophylline are sympathomimetic drugs that can interact with volatile anesthetics to cause cardiac arrhythmias (also see Chapter 16). Halothane (and to some degree most other volatile anesthetics) sensitizes the myocardium to exogenous catecholamines.[498,499] Sensitization means that the minimum dose of exogenous epinephrine administered intravenously that is needed to produce PVCs would be lower in patients anesthetized with halothane than in awake patients.

How much epinephrine is safe to give when halothane is the anesthetic? Katz and Bigger[498] reported that the administration of 0.15 mL/kg of a 1:100,000 epinephrine solution per 10-minute period (not to exceed 0.45 mL/kg of a 1:100,000 solution per hour) was safe. Several studies have shown that lidocaine given with epinephrine affords extra protection and that enflurane and isoflurane are less sensitizing than halothane. Xanthines are effective bronchodilators because they produce β-adrenergic stimulation in two ways: they cause the release of norepinephrine[500,501] and also inhibit the breakdown of cAMP,[502] the mediator of many of the actions of β-adrenergic receptor agonists. Phosphodiesterase catalyzes the breakdown of cAMP. Thus, inhibition of phosphodiesterase by theophylline increases the concentration of cAMP. Marcus and associates[500] and Westfall and Flemming[501] showed that at least 40% of the inotropic effects of aminophylline are due to its ability to release norepinephrine directly.

Plasma theophylline levels of 5 mg/L are needed to reduce abnormally high airway resistance. No further beneficial effects are obtained when levels exceed 20 mg/L; instead, toxic effects appear. Theophylline (aminophylline is a combination of 85% theophylline and 15% ethylenediamine) is metabolized largely by the liver, with less than 10% being excreted unchanged in urine. The average half-life is 4.4 ± 1.15 hours in adults, and clearance is 1.2 mL/min/kg. Significant liver disease or pulmonary edema can decrease clearance of the drug by half and by a third, respectively.

An interaction between aminophylline and halothane appears to be a frequent, predictable occurrence: of 16 dogs anesthetized with 1% halothane and given high-dose bolus injections of aminophylline, 12 had ventricular arrhythmias and 8 had ventricular tachycardia or fibrillation. Thus, it is advisable to wait three drug half-lives after the last dose of aminophylline is given (i.e., approximately 13 hours in normal individuals) before using halothane to anesthetize an asthmatic patient. Using another anesthetic that is a bronchodilator but is less likely to predispose the patient to catecholamine-induced arrhythmias (e.g., enflurane, isoflurane, or sevoflurane) or using inhaled or systemic steroids started several days in advance might be alternatives in patients requiring aminophylline or other exogenous sympathomimetic drugs before or during surgery.

Other Drugs

Drugs other than those discussed earlier in this chapter have implications for anesthetic management. The therapies that have been discussed include anticoagulants and fibrinolytics (in the hematologic section), endocrinologic preparations excluding

birth control pills but including corticosteroids (in the section on endocrinologic disease), antihypertensive drugs (earlier in this section and in the section on cardiovascular diseases), anticonvulsant drugs (in the section on neurologic disorders), and cancer chemotherapeutic agents (in the section on oncology).

Antiarrhythmic Drugs

Antiarrhythmic drugs include local anesthetics (lidocaine, procaine), anticonvulsant (phenytoin) or antihypertensive (propranolol) drugs, calcium channel blocking drugs, or primary antiarrhythmic drugs. These drugs are classified into five major categories: local anesthetics that alter phase 0 and phase 4 depolarization (quinidine, procainamide, and flecainide), local anesthetics that affect only phase 4 depolarization (lidocaine, tocainide, phenytoin, encainide), β-adrenergic receptor antagonists, antiadrenergic drugs (bretylium, disopyramide, amiodarone), and calcium entry blockers. These drugs are discussed elsewhere in this chapter. A useful reference with suggestions about drug therapy for cardiac arrhythmias and monitoring of side effects was published by the *Medical Letter on Drugs and Therapeutics*.[503] A lack of adverse reports does not indicate that all these drugs should be continued through the time of surgery; pharmacokinetic studies have not yet determined whether anesthesia (or anesthesia with specific agents) alters the volume of distribution or clearance of these drugs to an extent sufficient to warrant changing the dosage or dosage schedule in the perioperative period. The dearth of reports on this subject may be due to a lack of significant drug interaction or to a lack of awareness that untoward events could be caused by such an interaction.

The pharmacologic characteristics of the various antiarrhythmic drugs can affect anesthetic management. Disopyramide is similar to quinidine and procainamide in its antiarrhythmic effectiveness. Disopyramide is excreted mainly by the kidneys, but hepatic disease increases its half-life. This drug often produces anticholinergic effects, including tachycardia, urinary retention, and psychosis. Hepatitis has also been reported to have occurred after its use.[503] Little is known of the interaction of bretylium with anesthetics. Because bretylium blocks the release of catecholamines, chronic therapy with this drug has been associated with hypersensitivity to vasopressors.[503] Quinidine is dependent on the kidneys for excretion, can produce vagolytic effects that can decrease AV block, and is associated with blood dyscrasias and GI disturbances.[503] Most of the antiarrhythmic drugs enhance nondepolarizing neuromuscular blockade. Reports have confirmed this enhancement for quinidine, phenytoin, lidocaine, procainamide, and propranolol.[504-512] Amiodarone, an antiadrenergic drug used to treat recurrent supraventricular and ventricular tachycardia, causes thyroid dysfunction as a result of the large amount of iodine in its structure (see the section on thyroid disorders earlier in this chapter), as well as peripheral neuropathy, and has been associated with hypertension, bradyarrhythmias, and reduced cardiac output during anesthesia.[513] The drug has a half-life of 29 days, and its pharmacologic effects persist for over 45 days after discontinuance.[514] No data document such an effect for depolarizing muscle relaxants.

Antibiotics

Many antibacterial agents are nephrotoxic or neurotoxic (or both), and many prolong neuromuscular blockade (also see Chapter 29).[506-512] The only antibiotics devoid of neuromuscular effects appear to be penicillin G and the cephalosporins.[511] Most enzyme-inducing drugs do not increase the metabolism of enflurane or isoflurane. However, isoniazid appears to induce the microsomal enzymes responsible for the metabolism of at least enflurane, thereby increasing the possibility of fluorine-associated renal damage after enflurane.[515] Appropriate antibiotic prophylaxis for surgery requires a knowledge of the probability of infection for that type of surgical procedure and, if the incidence of infection warrants, the use of a drug regimen directed against the most likely infecting organisms.[516]

Digitalis

Digitalis preparations have a limited margin of safety, and the risk of toxicity increases with hypokalemia.[517] Although there is good rationale for administering digoxin prophylactically before surgery,[518] we generally avoid doing so because potassium concentrations can fluctuate widely during anesthesia as a result of fluid shifts, ventilatory acid-base derangements, and adjuvant treatments and because intraoperative arrhythmias caused by digitalis toxicity may be difficult to differentiate from those having other sources. Digitalis intoxication can be manifested by such diverse cardiac arrhythmias as junctional escape rhythm, PVCs, ventricular bigeminy or trigeminy, junctional tachycardia, paroxysmal atrial tachycardia with or without block, sinus arrest, sinus exit block, Mobitz type I or II block, or ventricular tachycardia.[517] However, anesthetics appear to protect against digitalis toxicity, at least in animal studies.[519-522] A titrated cardioversion technique using at first 10- and then 20-, 30-, 40-, 50-, 75-, 100-, 150-, and 200-J doses resulted in safe cardioversion in the presence of digitalis and propofol or midazolam hypnosis.[523] For patients in atrial fibrillation, the ventricular response should guide the choice of dose of digitalis.

Medications for Glaucoma

Medications for glaucoma include two organophosphates: echothiophate and isoflurophate (also see Chapter 75). These drugs inhibit serum cholinesterase, which is responsible for the hydrolysis and inactivation of succinylcholine and ester-type local anesthetics such as procaine, chloroprocaine, and tetracaine.[524,525] These ester-type local anesthetics should be avoided in patients treated with eye drops containing organophosphate. Table 35-20 lists other medications related to anesthesia and their side effects (from the National Registry for Drug-Induced Ocular Side Effects, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97201; 503-279-8456).

Magnesium, Cimetidine, and Oral Contraceptives

Although information on drugs long used in therapy is old, it is still pertinent and useful to review for these old "standby" drugs. Magnesium is given to treat eclampsia; it can cause neuromuscular blockade by itself and potentiates neuromuscular blockade by both nondepolarizing and depolarizing muscle relaxants. Cimetidine reduces hepatic blood flow and inhibits enzymatic degradation of drugs by the liver. Thus, higher blood levels and prolonged elimination half-lives may result when drugs that are metabolized by the liver (e.g., lidocaine, procaine, some narcotics, and propranolol) are given to patients taking cimetidine chronically or acutely.[526,527] The risk of postoperative venous thrombosis increases when oral contraceptives are used preoperatively. Although some authorities recommend changing from oral con-

Table 35-20 Common Ophthalmologic Drugs and Their Anesthetically Important Interactions

Drug (Trade Name)	Toxicities and Specific Treatments
Glaucoma: Primary goal is to reduce IOP by Miotics and epinephrine: increase outflow of aqueous humor β-Blockade and carbonic anhydrase inhibitors: reduce production of aqueous humor Osmotic drugs: transiently decrease volume	
Miotics Parasympathomimetics Pilocarpine (Adsorbocarpine, Isopto Carpine, Pilocar, Pilocel) Carbachol	
Acetylcholinesterase inhibitors Physostigmine Demecarium Isoflurophate (Floropryl) Echothiophate (Echodide, Phospholine)	Tox: Hypersalivation, sweating, N/V, bradycardia, hypotension, bronchospasm, CNS effects, coma, respiratory arrest, death Rx: Atropine, pralidoxime (Protopam) Ix: Succinylcholine—prolonged apnea (drugs must be discontinued 4 wk before)
Epinephrine (Epitrate, Murocoll, Mytrate, Epifrin, Glaucon, Epinal, Eppy)	Tox: (rare) Tachycardia, PVCs, HTN, headache, tremors Ix: Avoid drugs that sensitize to catecholamines, e.g., halothane
β-Blockers Timolol (Timoptic) Betaxolol (Betoptic) Levobunolol (Betagan)	Tox: J-blockade with bradycardia, exacerbation of asthma, CNS depression, lethargy, confusion Synergy noted with systemic drugs
Carbonic anhydrase inhibitors Acetazolamide (Diamox) Dichlorphenamide (Daranide, Oratrol) Ethoxzolamide (Cardrase, Ethamide) Methazolamide (Neptazane)	Tox: Anorexia, GI disturbances, "general miserable feeling" and malaise, paresthesias, diuresis, hypokalemia (transient), renal colic and calculi, hyperuricemia, thrombocytopenia, aplastic anemia, acute respiratory failure in patients with COPD
Osmotic drugs Glycerin (Glyrol, Osmoglyn) Isosorbide (Ismotic) Urea (Urevert, Ureaphil) Mannitol (Osmitrol)	Tox: Dehydration, hyperglycemia, nonketotic hyperosmolar coma (rare). Fatalities with mannitol secondary to CHF or intracranial bleeding Urea may cause thrombosis
Intraocular acetylcholine (Miochol)	Tox: Hypotension, bradycardia Rx: Atropine
Mydriatics and cycloplegics: Provide pupillary dilatation and paralysis of accommodation Anticholinergics block muscarinic receptors; paralyzing in iris α-Adrenergics contract the dilator of the iris	
Anticholinergics Atropine (Atropisol, Bufopto, Isopto Atropine) Cyclopentolate, alone (Cyclogyl) or with phenylephrine-homatropine (Cyclomydril) Scopolamine tropicamide (Homatrocel, Isopto Homatropine, Isopto Hyoscine, Murocoll #19, Mydriacyl)	Tox: Dry mouth, flushing, thirst, tachycardia, seizure, hyperactivity, transient psychosis, rare coma, and death Rx: Physostigmine
α-Adrenergics Phenylephrine (Efricel, Mydfrin, Neo-Synephrine) Hydroxyamphetamine (Paredrine)	Tox: Tachycardia, HTN, PVCs, myocardial ischemia, agitation

CHF, congestive heart failure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HTN, hypertension; IOP, intraocular pressure; Ix, interaction; N/V, nausea and vomiting; PVCs, premature ventricular contractions; Rx, treatment; Tox, toxicity.

traceptives to topical methods of birth control 2 to 4 weeks before surgery, no controlled study has determined whether birth control pills should be discontinued before surgery or the resulting incidence of pregnancy. Moreover, year-long pellets make discontinuation impractical for some. Other authorities recommend preventing venous thromboembolism by using low-dose heparin, guided by a determination of efficacy and cost-effectiveness. In addition, estrogens with micronized progestins are effective at reducing all-cause mortality for at least the first 10 years after menopause.[22,23,528] Thus, the uncertainty surrounding prophylaxis

for heart disease (created by the dilemma of long-term benefit versus the short-term risk of thromboembolism) needs better data for resolution.

Interrupting a Drug Regimen before Surgery

If a drug is needed for treatment preoperatively, it should be continued through surgery. One of us (M.F.R.) provides patients and other professionals with a detailed list (Box 35-7) that we supply through our preanesthesia and preprocedure assessment clinic. It must often be specifically requested because many patients and nurses perceive the NPO directive to include drugs.[529,530] The only exception to this general rule of not altering preoperative drug therapy might pertain to (1) MAOIs, (2) anticoagulants and fibrinolytic drugs (e.g., clopidogrel [Plavix]) if surgical hemostasis is needed, (3) nicotinic acid, (4) dosage adjustments for insulin and corticosteroids, (5) ACE inhibitors and receptor antagonists (angiotensin II receptor blocking drugs), and (6) drugs for erectile dysfunction (i.e., sildenafil [Viagra], vardenafil [Levitra], tadalafil [Cialis], or similar drugs). These recommendations require that the anesthesiologist be aware of the pharmacologic characteristics, interactions, and anesthetic implications of drugs described earlier in this chapter.

When in doubt about a disease or a drug, we consult the following textbooks: *Harrison's Principles of Internal Medicine*; *Anesthesia and Uncommon Diseases: Pathophysiologic and Clinical Correlations*; *Anesthesia and Co-Existing Disease*; *Essence of Anesthesia Practice*; *Anesthetic Implications of Congenital Anomalies in Children*; *Pharmacology and Physiology in Anesthetic Practice*; and *Goodman and Gilman's The Pharmacologic Basis of Therapeutics*. It is then wise to consult two experts on the drug or disease and determine who is best able to care for the patient. The

Box 35-7 Preoperative and Preprocedure Medication Instruction Guidelines (PPAC Form 5)

Instruct patients to take the following medications with a small sip of water EVEN IF OTHERWISE NPO:

Antihypertensive medications—Continue on the day of the operation or procedure

Diuretics—Continue on the day of the operation or procedure

Cardiac medications (e.g., digoxin)—Continue on the day of the procedure

Antidepressant, antianxiety, and psychiatric medications—Continue on the day of the operation or procedure

Thyroid medications—Continue on the day of the operation or procedure

Birth control pills—Continue on the day of the operation or procedure

Eye drops—Continue on the day of the operation or procedure

Heartburn or reflux medications (e.g., Prilosec, Zantac)—Continue on the day of the operation or procedure

Narcotic pain medications—Continue on the day of the operation or procedure

Antiseizure medications—Continue on the day of the operation or procedure

Asthma medications—Continue on the day of the operation or procedure

Steroids (oral and inhaled)—Continue on the day of the operation or procedure

Statins (e.g., Zocor, Lipitor)—Continue on the day of the operation or procedure

Aspirin—Usually continue; discontinue 7 days before plastic surgery and surgery on the retina

COX-2 inhibitors—Continue on the day of the operation or procedure unless the surgeon specifies (usually concerned about bone healing)

NSAIDs—Usually continue; discontinue 48 hours before plastic surgery and surgery on the retina

Vitamins, iron, Premarin—Discontinue on the day of the operation or procedure

Topical medications (e.g., creams and ointments)—Discontinue on the day of the operation or procedure

Oral hypoglycemic drugs—Discontinue on the day of the operation or procedure

Insulin—For all patients, discontinue all regular or combination (70/30 preparations) insulin on the day of the operation or procedure. Type 2 diabetics should discontinue all insulins of any type. Type 1 diabetics should take a small amount (usually a third) of their usual AM long-acting insulin (e.g., Lente or NPH) on the day of the operation or procedure. Type 1 diabetics should not take any short-acting insulin, such as regular insulin, on the day of the procedure. Patients with an insulin pump should continue their basal rate only.

Viagra, Levitra, Cialis, or similar drugs—Discontinue 36 hours before surgery

Warfarin (Coumadin)—Discontinue 4 days before surgery except for patients undergoing cataract surgery without a bulbar block

Plavix (clopidogrel)—Discontinue 7 days before surgery except for vascular patients or those undergoing cataract surgery

Herbals and nonvitamin supplements—Discontinue 7 days before surgery

MAOIs—Patients taking these antidepressant medications need an anesthesia consultation before surgery (preferably 3 weeks before surgery)

COX, cyclooxygenase; MAOIs, monoamine oxidase inhibitors; NPO, nothing by mouth; NSAIDs, nonsteroidal anti-inflammatory drugs.

expert who is best qualified should be observed while attending to the patient, not only preoperatively and intraoperatively but also postoperatively. It is important to remember that few prospective controlled studies have shown that any preoperative technique, treatment, or management decreases perioperative risk. However, common sense and foreknowledge of potential pitfalls, as well as diligence in avoiding these pitfalls, should reduce avoidable perioperative complications.

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Lydia Cassorla and Jae-Woo Lee

36 Patient Positioning and Anesthesia

Key Points

1. Patient positioning is a major responsibility that is shared by the entire operating room team. A balance between optimal surgical positioning and patient well-being is sometimes required.
2. Many patient positions that are used for surgery result in undesirable physiologic consequences, including significant cardiovascular and respiratory compromise. Anesthetics blunt natural compensatory mechanisms, rendering surgical patients vulnerable to positional changes.
3. Peripheral nerve injury, although rare, accounted for 18% of cases in the 1990-1994 American Society of Anesthesiologists (ASA) Closed Claims Database, second only to death. Peripheral nerve injury is often a result of patient positioning. The mechanisms of injury are stretching, compression, and ischemia.
4. Ulnar neuropathy is the most common postoperative nerve injury, followed by injury to the brachial plexus, lumbosacral nerve roots, and spinal cord.
5. Not all postoperative neuropathies, including ulnar neuropathy, are currently explainable and may not be entirely preventable. Many postoperative ulnar nerve deficits do not seem to be related to intraoperative patient position because they appear days after surgery.
6. The ASA issued a Practice Advisory in 2000 for the prevention of perioperative peripheral neuropathies. Only 6 of 509 studies reviewed met the standard, however, for a scientifically proven relationship between intervention and outcome.
7. Postoperative visual loss is a rare but devastating complication that is associated with the prone position. The causes are multifactorial and incompletely understood.
8. Anesthetics administered outside classic operating rooms present special challenges with regard to patient positioning because of equipment limitations and differences in the work environment and culture.

Anesthesiologists share a critical responsibility for the proper positioning of patients in the operating room. Positions deemed optimal for surgery often result in undesirable physiologic changes, such as hypotension from impaired venous return to the heart or oxygen desaturation owing to ventilation-perfusion mismatching. In addition, peripheral nerve injuries during surgery remain a significant source of perioperative morbidity.[1-3]

Proper positioning requires the cooperation of anesthesiologists, surgeons, and nurses to ensure patient well-being and safety while providing surgical exposure. During anesthesia care, whenever possible, patients should be placed in a position that they would tolerate when awake. Jewelry and hair ornaments are removed. Padded surfaces, lumbar support, and natural joint position are optimal. The head should remain midline without substantial extension or flexion whenever possible. At no time should pressure on the eyes occur. Because surgeons wish to have optimal exposure, and positions may be maintained for long periods, prevention of complications often requires compromise and judgment. The duration of more extreme positions, if such are necessary, should be limited as much as possible. Expected tilting of the operating room table during surgery should be anticipated before draping, and the patient should be secured accordingly. Use of safety straps and prevention of a patient fall are fundamental.

Cardiovascular Concerns

Complex arterial, venous, and cardiac physiologic responses have evolved to blunt the effects of positional changes on arterial blood pressure and maintain perfusion to vital organs. Central, regional, and local mechanisms are involved. This is particularly important for humans who maintain an upright posture, owing to the vertical distance from the heart to the brain and its need for constant perfusion.

Normally, as an individual reclines from an erect to a supine position, venous return to the heart increases as pooled blood from the lower extremities redistributes toward the heart. Preload, stroke volume, and cardiac output are augmented. The resultant

increase in arterial blood pressure activates afferent baroreceptors from the aorta (via the vagus nerve) and within the walls of the carotid sinuses (via the glossopharyngeal nerve) to decrease sympathetic outflow and increase parasympathetic impulses to the sinoatrial node and myocardium. The result is a compensatory decrease in heart rate, stroke volume, and cardiac output. Mechanoreceptors from the atria and ventricle also are activated to decrease sympathetic outflow to muscle and splanchnic vascular beds. Lastly, atrial reflexes are activated to regulate renal sympathetic nerve activity, plasma renin, atrial natriuretic peptide, and arginine vasopressin levels.[4] As a result, systemic arterial blood pressure is maintained within a narrow range during postural changes in the unanesthetized setting.

General anesthesia, muscle relaxation, positive-pressure ventilation, and neuraxial blockade interfere with venous return to the heart, arterial tone, and autoregulatory mechanisms, rendering patients under anesthesia especially vulnerable to relatively uncompensated circulatory effects of changes in position. The use of spinal or epidural anesthesia causes a significant sympathectomy across all affected dermatomes, independent of the presence of general anesthesia, reducing preload and potentially blunting cardiac response if the sympathetic output to the heart is affected (see Chapter 51). Positive-pressure ventilation increases mean intrathoracic pressure, diminishing the venous pressure gradient from peripheral capillaries to the right atrium. Because small pressure gradients are active in the venous circulation, this may significantly affect cardiac filling and consequently cardiac output. Positive end-expiratory pressure increases mean intrathoracic pressure further, as do conditions associated with low lung compliance, such as airways disease, obesity, ascites, and light anesthesia. Venous return and cardiac output may be compromised further.[5]

For these reasons, arterial blood pressure is often particularly labile immediately after the initiation of anesthesia and during patient positioning. It is crucial for the anesthesiologist to anticipate, monitor, and treat these effects, and to assess the safety of positional changes for each patient. Blood pressure should be measured frequently after induction of anesthesia or initiation of neuraxial blockade. It is often necessary to increase intravenous fluid administration, adjust the level of anesthesia, or administer vasopressors during this hemodynamic transition. Temporary use of head-down positions may be helpful. Sometimes a delay in repositioning of the patient for surgery may be necessary until systemic blood pressure reaches an acceptable level of homeostasis. Interruptions in monitoring to facilitate positioning or turning of the operating room table must be minimized during this dynamic period. Patient positioning is always secondary to patient safety.

Pulmonary Concerns

Anesthetized patients who are breathing spontaneously have a reduced tidal volume and functional residual capacity and an increased closing volume compared with the nonanesthetized state. Positive-pressure ventilation with muscle relaxation may ameliorate ventilation-perfusion mismatches under general anesthesia by maintaining adequate minute ventilation and limiting atelectasis. The diaphragm assumes an abnormal shape, however, owing to the loss of muscle tone, and is displaced less in the dependent portions of the lung.[6] This decreases ventilation-perfusion matching and consequently arterial Po_2. Patients undergoing neuraxial anesthesia lose abdominal and thoracic muscle function in affected dermatomes, but diaphragmatic function is retained if general anesthesia and muscle relaxation are not concurrently administered. In addition to these effects of anesthesia, patient position has distinct effects on pulmonary function. In particular, any position that limits movement of the diaphragm, chest wall, or abdomen may increase atelectasis and intrapulmonary shunt.

Spontaneous ventilation results from small negative intrathoracic pressure shifts during inspiration owing to diaphragmatic displacement and chest wall expansion. This pressure decrease also promotes venous return to the thorax by reducing the pressure in the great veins and right atrium compared with the periphery. Normal distribution of ventilation is determined by the excursion of the diaphragm, movement of the chest wall, and compliance of the lung. When an individual shifts from standing to supine, functional residual capacity decreases owing to cephalad displacement of the diaphragm. The relative contribution to ventilation of the chest wall compared with the diaphragm decreases from 30% to 10%. With spontaneous ventilation in either position, diaphragmatic movement is greatest adjacent to the most dependent portions of the lung, helping to bring new ventilation to the zones of the lung that are preferentially perfused. The preferential perfusion of the dependent portions is dominated by gravity; however, other factors, such as pulmonary vascular length, also may be important. Perfusion seems to follow a central-to-peripheral spectrum in each lobe that is maintained with changes in cardiac output.[7-9]

The prone position has been used to improve respiratory function in patients with adult respiratory distress syndrome.[10] In anesthetized patients, the prone position has advantages over the supine position with regard to lung volumes and oxygenation without adverse effects on mechanics,[11,12] including obese[13] and pediatric patients (see Chapter 82).[14] When patients are prone, weight should be distributed to the thoracic cage and bony pelvis, allowing the abdomen to move with respiration, as outlined subsequently.

Specific Positions

Supine

The most common position for surgery is the supine, or dorsal decubitus position (Fig. 36-1). Because the entire body is close to the level of the heart, hemodynamic reserve is best maintained. Because compensatory mechanisms are blunted by anesthesia, however, even a few degrees of head-down (Trendelenburg) position or head-up (reverse Trendelenburg) position are sufficient to cause significant cardiovascular changes.

Associated Arm Position

In a supine patient, one or both arms may be abducted out to the side or adducted (tucked) alongside the body. It is recommended that upper extremity abduction be limited to less than 90 degrees to minimize the likelihood of brachial plexus injury by caudad pressure in the axilla from the head of the humerus.[15] The hand

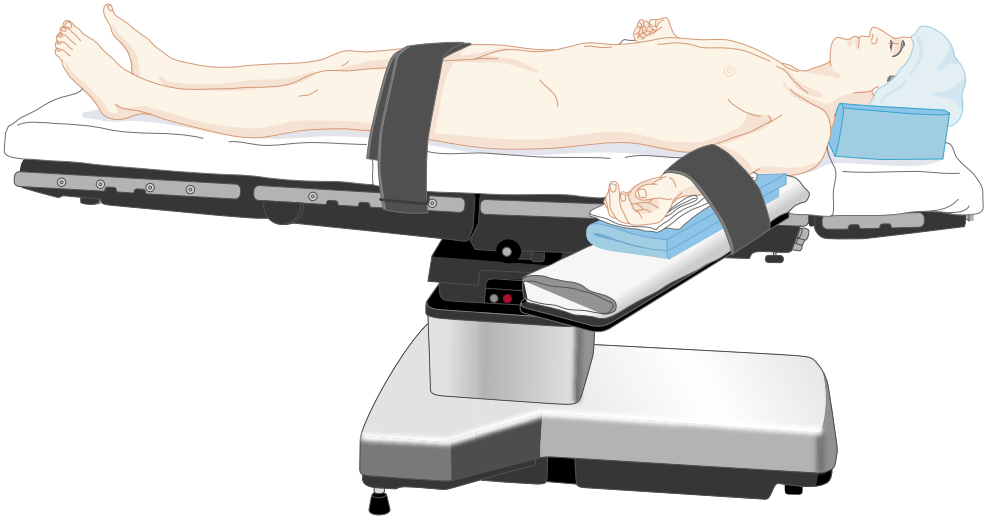

Figure 36-1 Supine position. Note the asymmetry of the base of the table, placing the patient's center of gravity over the base if positioned in the usual direction.

and forearm are either supinated or kept in a neutral position with the palm toward the body to reduce external pressure on the spiral groove of the humerus and the ulnar nerve (Fig. 36-2).[16-18] When the arms are adducted, they are usually held alongside the body with a "draw sheet" that passes under the body and over the arm, and is then tucked directly under the torso (not the mattress) to ensure that the arm remains properly placed next to the body. Alternatively, in surgeries in which access to the chest or abdomen is not necessary, curved arm cradles may be used. In all cases, the arms are placed in a neutral position.[16] The elbows and any protruding objects, such as intravenous fluid lines and stopcocks, are padded (Fig. 36-3).

Variations of the Supine Position

Several variations of the supine position are frequently used. The *lawn chair position,* in which the hips and knees are slightly flexed (Fig. 36-4), reduces stress on the back, hips, and knees, and is better tolerated by patients who are awake or undergoing monitored anesthesia care. In addition, because the legs are slightly above the heart, venous drainage from the lower extremity is facilitated. Also, the xiphoid to pubic distance is decreased, reducing the tension on the ventral abdominal musculature and easing closure of laparotomy incisions. Proper positioning of the patient's hips on the operating room table and several modifications to the table are required to achieve this position. Typically, the back of

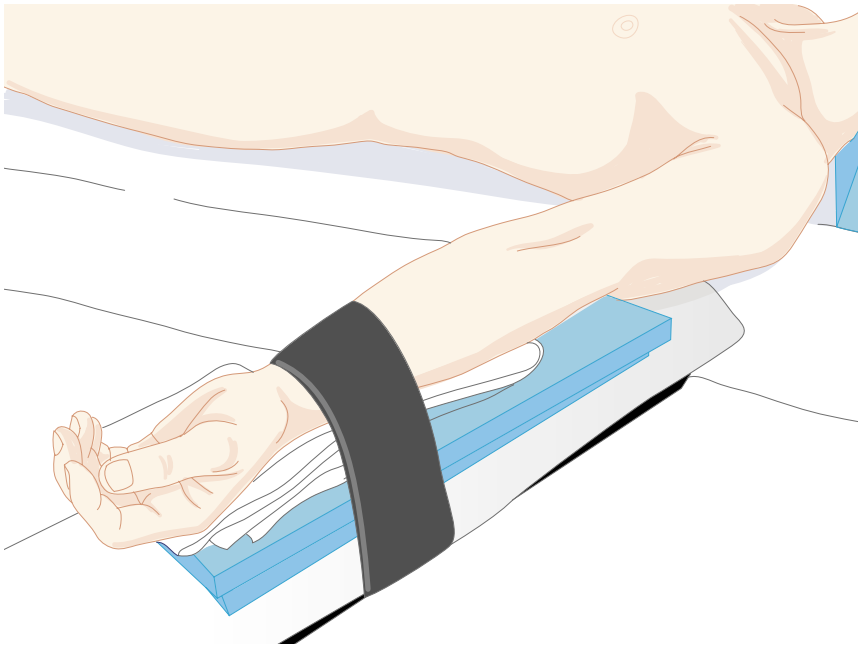

Figure 36-2 Arm position on arm board. Abduction of arm should be limited to less than 90 degrees whenever possible. The arm is supinated, and the elbow is padded.

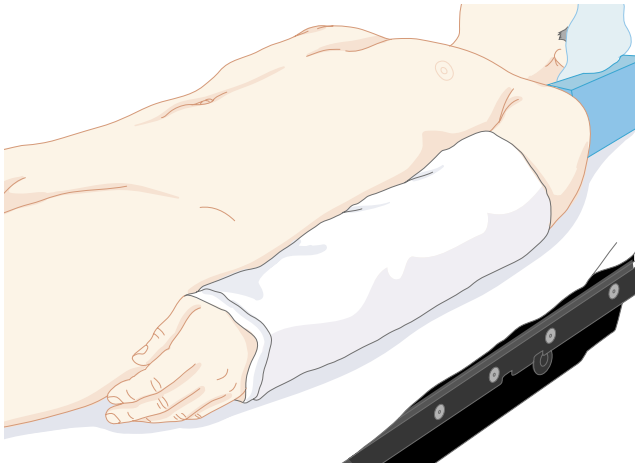

Figure 36-3 Arm tucked at patient's side. Arm in neutral position with palm to hip. The elbow is padded, and one needs to ensure that the arm is supported.

the bed is raised, the legs below the knees are lowered to an equivalent angle, and a slight Trendelenburg tilt is used to level the hips with the shoulders, if desired. These modifications reduce venous pooling in the legs and permit an arm board or table to be parallel with the floor if desired for upper extremity surgery.

The *frog-leg position,* in which the hips and knees are flexed, and the hips are externally rotated with the soles of the feet facing each other, allows access to the perineum, medial thighs, genitalia, and rectum. Care must be taken to minimize stress and postoperative pain in the hips and prevent dislocation by supporting the knees appropriately.

Tilting a supine patient head down, the *Trendelenburg position* (Fig. 36-5), is often used to increase venous return during hypotension, to improve exposure during abdominal and laparoscopic surgery, and to prevent air emboli and facilitate cannulation during central line placement. It is linked by name to a 19th century German surgeon, Trendelenburg, who described its use for abdominal surgery. Nonsliding mattresses are recommended to prevent the patient from sliding cephalad. Shoulder braces are not recommended because of considerable risk of compression injury to the brachial plexus.

The Trendelenburg position has significant cardiovascular and respiratory consequences. The head-down position increases central venous, intracranial, and intraocular pressures. Prolonged head-down position also can lead to swelling of the face, conjunctiva, larynx, and tongue with an increased potential for postoperative upper airway obstruction. The cephalic movement of abdominal viscera against the diaphragm also decreases functional residual capacity and pulmonary compliance. In spontaneously ventilating patients, the work of breathing increases. In mechanically ventilated patients, airway pressures must be higher to ensure adequate ventilation. The stomach also lies above the glottis. Endotracheal intubation is often preferred to protect the airway from pulmonary aspiration related to reflux and to reduce atelectasis. Because of the risk of edema to the trachea and mucosa surrounding the airway during surgeries in which patients have been in the Trendelenburg position for prolonged periods, it may be prudent to verify an air leak around the endotracheal tube or visualize the larynx before extubation.

Reverse Trendelenburg position (head-up tilt) (see Fig. 36-5) is often employed to facilitate upper abdominal surgery by shifting the abdominal contents caudad. This position is increasingly popular because of the growing number of laparoscopic surgeries. Caution is advised to prevent patients from slipping on the table, and more frequent monitoring of arterial blood pressure may be prudent to detect hypotension owing to decreased venous return. In addition, the position of the head above the heart reduces perfusion pressure to the brain and should be taken into consideration when determining optimal blood pressure.

In all positions in which the head is at a different level than the heart, the effect of the hydrostatic gradient on cerebral arterial and venous pressures should be carefully considered in terms of cerebral perfusion pressure. Careful documentation of any potential arterial pressure gradients is especially prudent.



Figure 36-4 Lawn chair position. Flexion of the hips and knees decreases tension on the back.

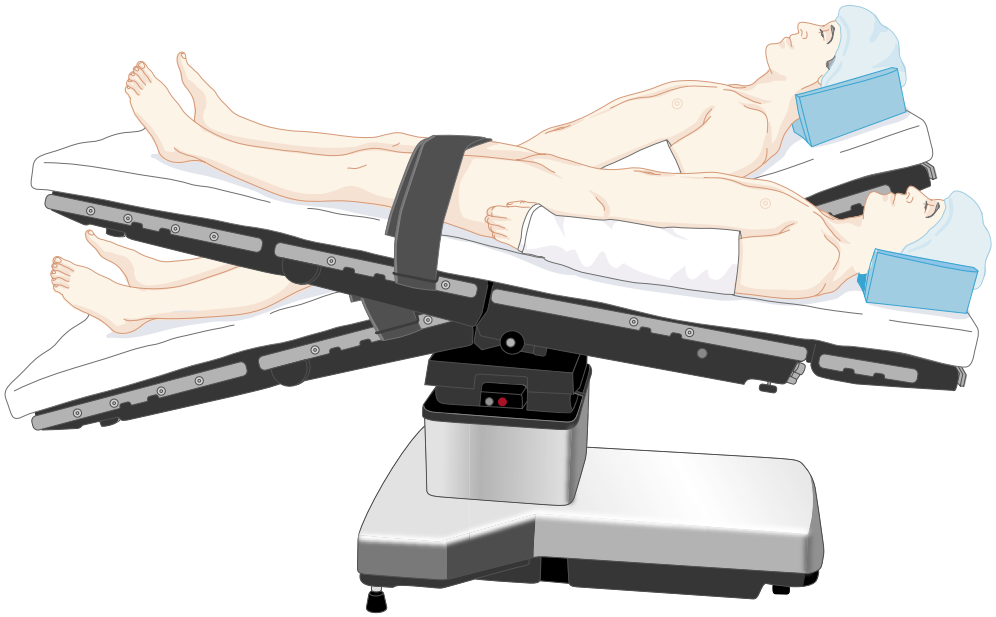

Figure 36-5 Trendelenburg position and reverse Trendelenburg position. Shoulder braces should be avoided to prevent brachial plexus compression injuries.

Complications

Pressure alopecia resulting from ischemic hair follicles is related to prolonged immobilization of the head with its full weight falling on a limited area, usually the occiput. Lumps, such as those caused by monitoring cable connectors, should not be placed under head padding because they may create focal areas of pressure. Hypothermia and hypotension during surgery, such as during cardiopulmonary bypass, may increase the incidence of this complication. Consequently, it is prudent to cushion the head well, and if possible during prolonged surgery, periodic rotation of the head to redistribute the weight may be considered.

Backache may occur in the supine position as the normal lumbar lordotic curvature, particularly the tone of the paraspinous musculature, is lost during general anesthesia with muscle relaxation or a neuraxial block. Consequently, patients with extensive kyphosis, scoliosis, or a previous history of back pain may require extra padding of the spine or slight flexion at the hip and knee. Tissues overlying all bony prominences, such as the heels and sacrum, must be padded to prevent soft tissue ischemia owing to pressure, especially during prolonged surgery.[19]

Peripheral nerve injury (discussed in detail subsequently) is a complex phenomenon with a multifactorial etiology. The American Society of Anesthesiologists (ASA) published a practice advisory in 2000 to help prevent perioperative neuropathies.[16] Ulnar neuropathy is the most common lesion. Although there is no direct evidence that positioning or padding alone can prevent perioperative ulnar neuropathies, the committee has recommended, as mentioned earlier, to limit arm abduction in a supine patient to less than 90 degrees at the shoulder with the hand and forearm either supinated or kept in a neutral position. Regardless of the position of the upper extremities, maintaining the head in a relatively midline position can help minimize the risk of stretch injury to the brachial plexus.[20]

When patients are very heavy, caution is advised when placing them in reverse axis on the operating room table (see Chapter 64). The base of the operating room table is asymmetric, with the torso over the foot of the table. Patients are often positioned with the torso over the open side of the table, however, to improve surgical access or to permit use of equipment such as C-arm x-ray devices. This positioning places the heaviest part of the body and the patient's center of gravity opposite the weighted foot of the table, with substantial leverage. The operating room table can tilt and tip over if sufficient weight is placed away from the base, particularly if extensions are used, or the bed is tilted in the Trendelenburg position. Operating room table weight limits differ substantially with regard to normal and reverse positioning and should be strictly observed.

Lithotomy

The classic lithotomy position is frequently used during gynecologic, rectal, and urologic surgeries. The hips are flexed 80 to 100 degrees from the trunk, and the legs are abducted 30 to 45 degrees from the midline. The knees are flexed until the lower legs are parallel to the torso, and the legs are held by supports or stirrups, usually "candy cane," knee crutch, or calf support style (Figs. 36-6, 36-7, and 36-8). The foot section of the operating room table is lowered. If the arms are on the operating table alongside the patient, the hands and fingers may lie near the open edge of the lowered section of the table. When raising the foot of the table at the end of surgery, strict attention to the position of the hand must be paid to avoid a potentially disastrous crush injury to the fingers (Fig. 36-9). For this reason, positioning the arms on armrests far from the table hinge point is recommended at all times when patients are in the lithotomy position.

Initiation of the lithotomy position requires coordinated positioning of the lower extremities by two assistants to avoid torsion of the lumbar spine. Both legs should be raised together, flexing the hips and knees simultaneously. The lower extremities should be padded to prevent compression against the stirrups. After the surgery, the patient must be returned to the supine posi-

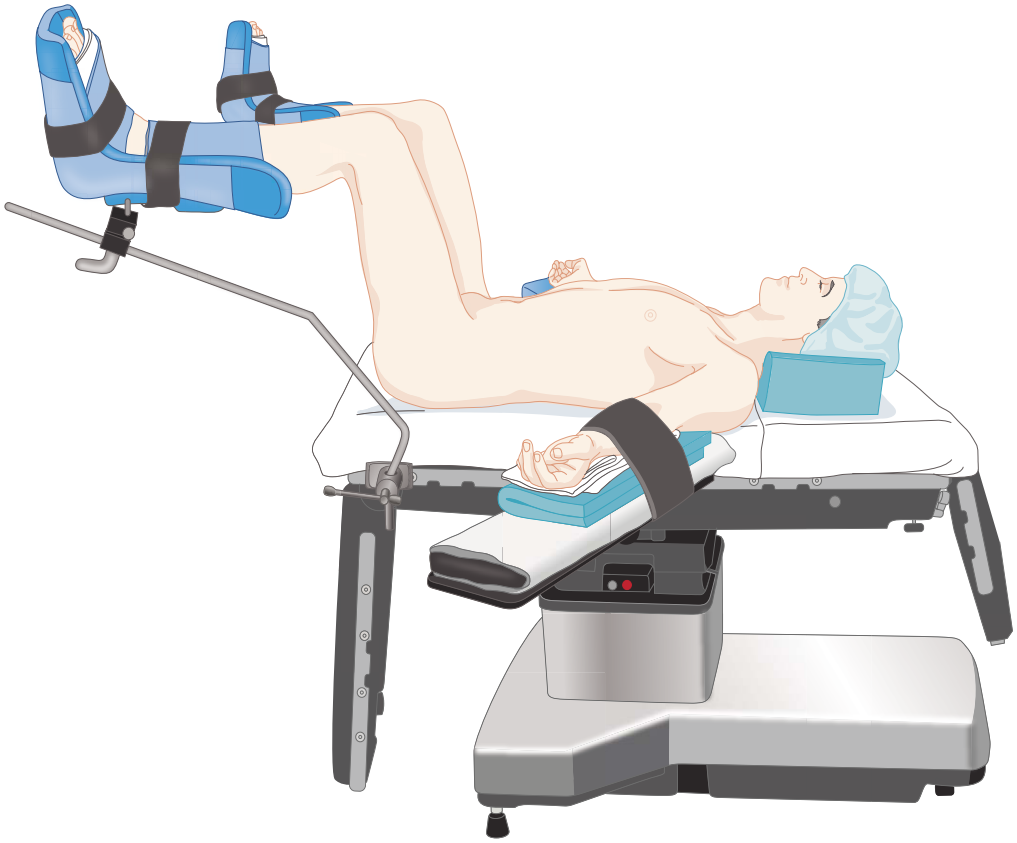

Figure 36-6 Lithotomy position. Hips are flexed 80 to 100 degrees with lower leg parallel to body. Arms are on armrests away from hinge point of foot section.

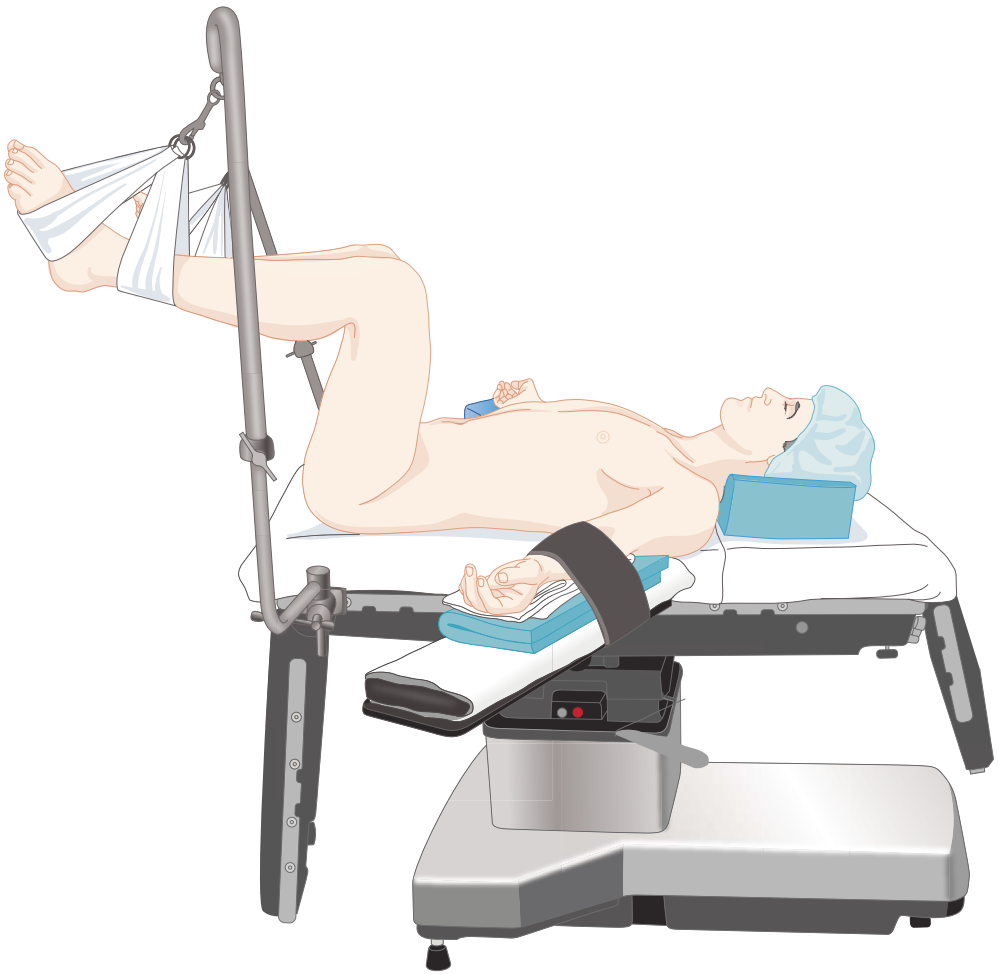

Figure 36-7 Lithotomy position with “candy cane” supports.

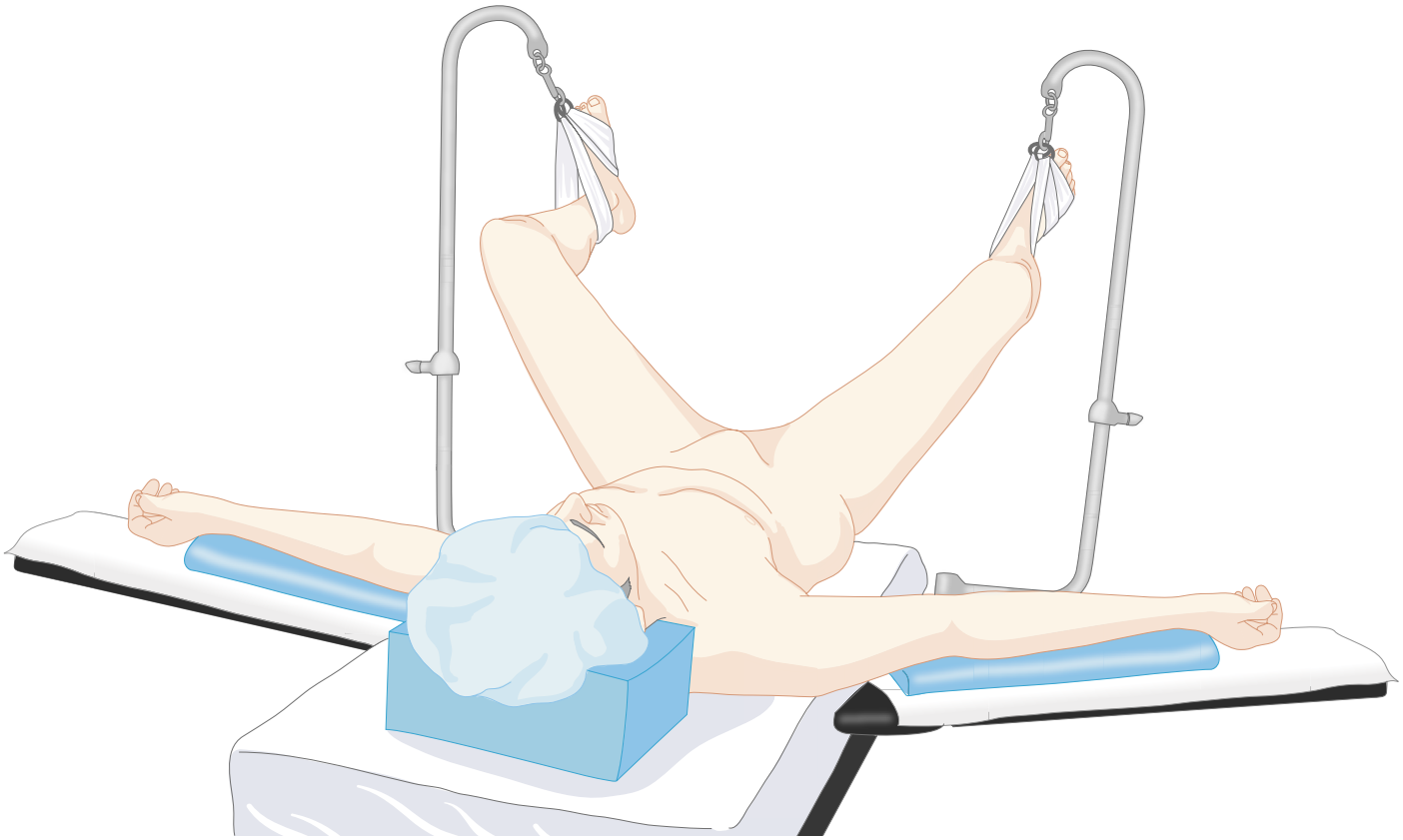

Figure 36-8 Lithotomy position with correct position of "candy cane" stirrups well away from lateral fibular head.

tion in a coordinated manner. As mentioned, the hands should be positioned to prevent entrapment in any moving or articulating sections of the operating room table. The legs should be removed from the holders simultaneously, knees brought together in the midline, and the legs slowly straightened and lowered onto the operating room table.

The lithotomy position also may cause significant physiologic changes. When the legs are elevated, preload increases, causing a transient increase in cardiac output and, to a lesser extent, cerebral venous and intracranial pressure in otherwise healthy patients. In addition, the lithotomy position causes the abdominal viscera to displace the diaphragm cephalad, reduc-

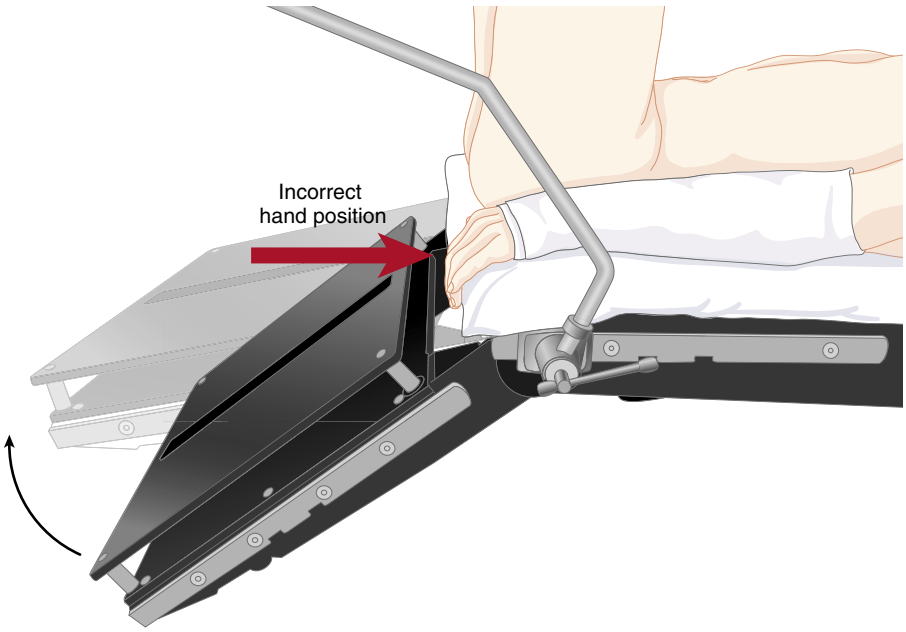

Figure 36-9 Improper position of arms in lithotomy position with fingers at risk for compression when the lower section of the bed is raised.



Figure 36-10 Lateral decubitus position. Note flexion of lower leg, padding between legs, and proper support of both arms.

ing lung compliance and potentially resulting in a decreased tidal volume. If obesity or a large abdominal mass is present (tumor, gravid uterus), abdominal pressure may increase significantly enough to obstruct venous return to the heart. Lastly, the normal lordotic curvature of the lumbar spine is lost in the lithotomy position, potentially aggravating any previous lower back pain.[21]

In a retrospective review of 198,461 patients undergoing surgery in the lithotomy position from 1957 to 1991, injury to the common peroneal nerve was the most common lower extremity motor neuropathy, representing 78% of nerve injuries. A potential cause of the injury was the compression of the nerve between the lateral head of the fibula and the bar holding the legs. When the candy cane stirrups are used, special attention must be paid to avoid compression (see Fig. 36-8). The injury was more common with patients who had low body mass index, recent cigarette smoking, or prolonged duration of surgery.[22] In a prospective review of 991 patients undergoing surgery in the lithotomy position from 1997 to 1998, there were no motor neuropathies in the lower extremity, although paresthesias in the distribution of the obturator, lateral femoral cutaneous, sciatic, and peroneal nerves were found.[23]

Lower extremity compartment syndrome is a rare complication associated with the lithotomy position. It occurs when perfusion to an extremity is inadequate, resulting in ischemia, edema, and extensive rhabdomyolysis from increased tissue pressure within a fascial compartment. In a large retrospective review of 572,498 surgeries, the incidence of compartment syndromes was higher in the lithotomy (1 in 8720) and lateral decubitus (1 in 9711) positions compared with the supine (1 in 92,441) position. Long surgical procedure time was the only distinguishing characteristic of the surgeries in which patients developed lower extremity compartment syndromes.[24] Compartment pressures have been studied in the lithotomy position and found to increase over time. It is recommended to lower the legs to the level of the body periodically if surgery extends beyond several hours.[25-27]

Lateral Decubitus

The lateral decubitus position (Fig. 36-10) is used most frequently for surgery involving the thorax, retroperitoneal structures, or hip. The patient rests on the nonoperative side and is balanced with anterior and posterior support, such as bedding rolls or a deflatable beanbag, and a flexed dependent leg. The arms usually are positioned in front of the patient. The dependent arm rests on a padded arm board perpendicular to the torso. The nondependent arm is often supported over folded bedding or suspended with an armrest or foam cradle. If possible, the arm should not be abducted more than 90 degrees. For some high thoracotomies, the nondependent arm may need to be elevated above the shoulder plane for exposure; however, vigilance is warranted to prevent neurovascular compromise.

The act of positioning a patient in the lateral decubitus position requires the cooperation of the entire operating room staff to prevent potential injuries. The patient's head must be kept in a neutral position to prevent excessive lateral rotation of the neck and stretch injuries to the brachial plexus. Additional head support may be required (Fig. 36-11). The dependent ear should be checked to avoid folding and undue pressure. It is advised to verify that the eyes are securely taped before repositioning if the patient is asleep. The dependent eye must be checked frequently for external compression.

To avoid compression injury to the dependent brachial plexus or vascular compression, an "axillary roll" (generally a liter bag of intravenous fluid) is frequently placed just caudal to the dependent axilla (Fig. 36-12). This roll should never be placed *in* the axilla. Its purpose is to ensure that the weight of the thorax is borne by the chest wall caudal to the axilla and avoid compression of the axillary contents. Many practitioners do not use a roll if the deflatable beanbag is used to cradle the torso. Regardless of the technique, the pulse should be monitored in the dependent arm for early detection of compression to axillary neurovascular structures. Vascular compression and venous engorgement in the dependent arm may affect the pulse oximetry reading, and a low

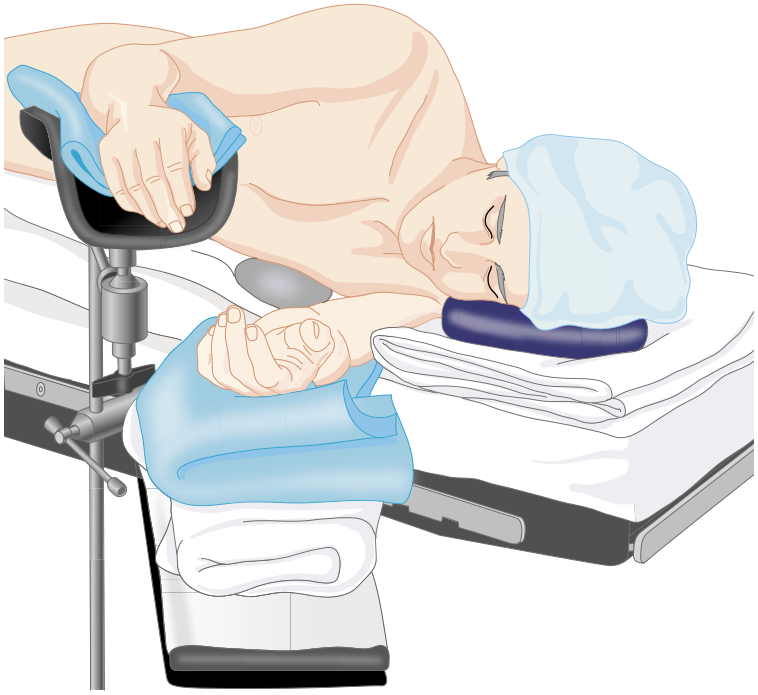

Figure 36-11 Lateral decubitus position showing placement of arms and head. Note additional padding under headrest to ensure alignment of head with spine. Headrest should be kept away from dependent eye.

saturation reading may be an early warning of compromised circulation. Hypotension measured in the dependent arm may be due to axillary arterial compression, so it is useful to retain the ability to measure blood pressure in both arms. When a kidney rest is used, it must be properly placed under the dependent iliac crest to prevent inadvertent compression of the inferior vena cava. Finally, a pillow or other padding is generally placed between the knees with the dependent leg flexed to minimize excessive pressure on bony prominences and stretch of low extremity nerves.

The lateral decubitus position also is associated with pulmonary compromise.[28] In a patient who is mechanically ventilated, the combination of the lateral weight of the mediastinum and disproportionate cephalad pressure of abdominal contents on the dependent lung favors overventilation of the nondependent lung. At the same time, pulmonary blood flow to the underventilated, dependent lung increases owing to the effect of gravity. Consequently, ventilation-perfusion matching worsens, potentially affecting gas exchange and ventilation.

The lateral decubitus position is preferred during pulmonary surgery and one-lung ventilation. The minute ventilation of the dependent lung is usually increased when the nondependent lung is collapsed. The increase in minute ventilation combined with decreased compliance owing to positioning may exacerbate further the airway pressure required to achieve adequate ventilation. Head-down tilt in the lateral position

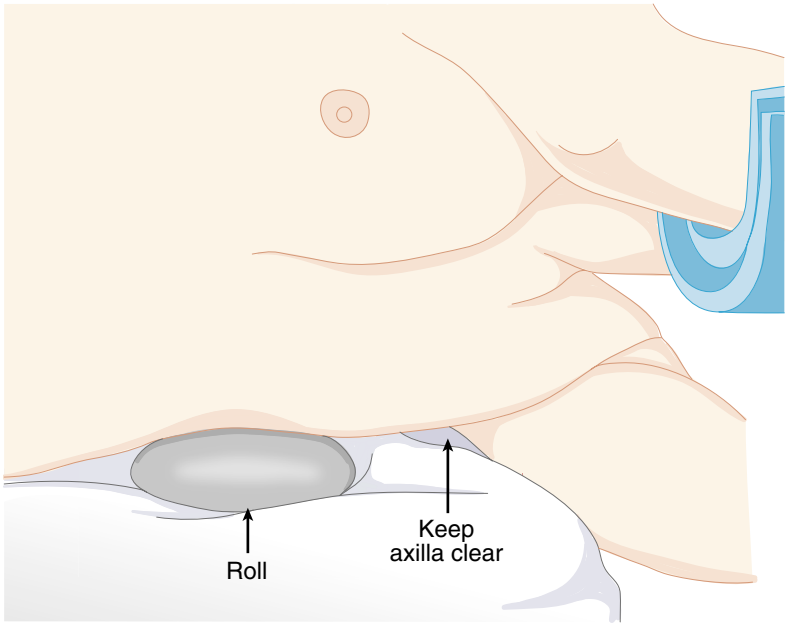

Figure 36-12 Use of axillary roll in lateral decubitus position. Roll, in this case a bag of intravenous fluid, is placed well away from axilla to prevent compression of the axillary artery and brachial plexus.

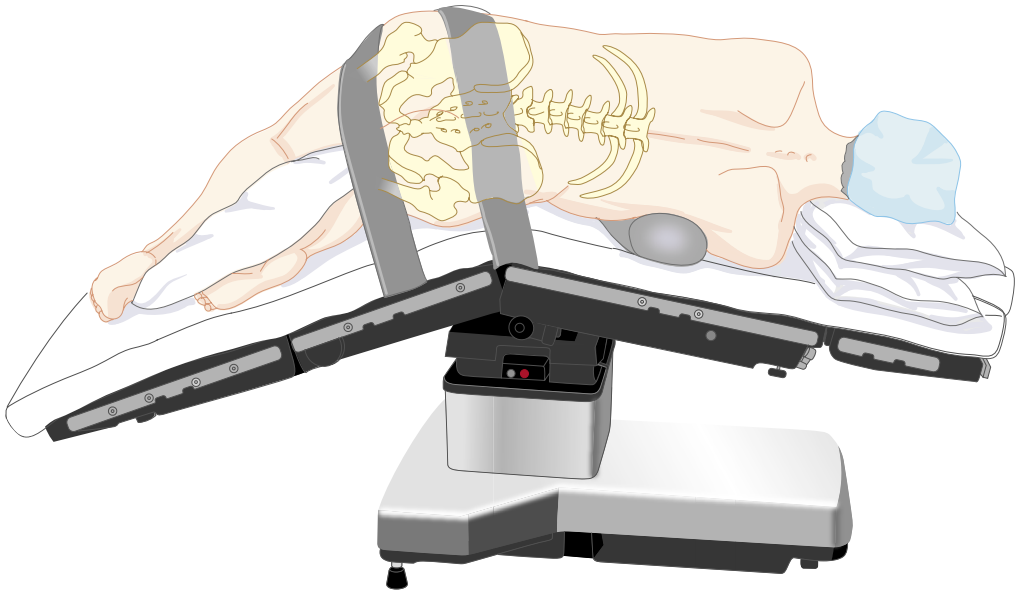

Figure 36-13 Flexed lateral decubitus position. Point of flexion should lie under iliac crest, rather than the flank or lower ribs, to optimize ventilation of the dependent lung.

worsens pulmonary function still further, increasing shunt fraction.[29]

Patients may be flexed while in the lateral position to spread the ribs during thoracotomies or improve exposure of the retroperitoneum for renal surgeries. The point of flexion, and the kidney rest if raised, should lie under the iliac crest rather than the flank or ribcage to minimize compression of the dependent lung (Fig. 36-13). This position is often accompanied by a component of reverse Trendelenburg positioning, creating the potential for venous pooling in the lower body. For these reasons, use of the flexed, lateral position is discouraged when not actively needed for surgical exposure.

Prone

The prone or ventral decubitus position (Fig. 36-14) is used primarily for surgical access to the posterior fossa of the skull, the posterior spine, the buttocks and perirectal area, and the lower extremities. As with the supine position, if the legs are in plane with the torso, hemodynamic reserve is maintained; however, if there is any significant lowering of the legs or tilt of the entire table, venous return may be decreased or augmented accordingly. Pulmonary function may be superior to the supine or lateral decubitus positions if there is no significant abdominal pressure, and the patient is properly positioned.[30,31] The legs should be



Figure 36-14 Prone position with Wilson frame. Arms are abducted less than 90 degrees whenever possible. Pressure points are padded, and chest and abdomen are supported away from the bed to minimize abdominal pressure and preserve pulmonary compliance. Soft head pillow has cutouts for eyes and nose and a slot to permit endotracheal tube exit. Eyes must be checked frequently.

padded and flexed slightly at the knees and hips. The head may be supported face-down with its weight borne by the bony structures or turned to the side.

Both arms may be positioned to the patient's sides and tucked in the neutral position as described for a supine patient, or placed next to the patient's head on arm boards—sometimes called the prone "superman" position. Extra padding under the elbow is needed to prevent compression of the ulnar nerve. The arms should not be abducted greater than 90 degrees to prevent excessive stretching of the brachial plexus, especially in patients with the head turned. Finally, elastic stockings and active compression devices are needed for the lower extremities to minimize pooling of the blood, especially with any flexion of the body.

When general anesthesia is planned, the patient is first intubated on the stretcher, and all intravascular access is obtained as needed. The endotracheal tube is well secured to prevent dislodgment and loosening of tape owing to drainage of saliva when prone. With the coordination of the entire operating room staff, the patient is turned prone onto the operating room table, keeping the neck in line with the spine during the move. The anesthesiologist is primarily responsible for coordinating the move and for repositioning of the head. An exception might be cases in which rigid pin fixation is used, and the surgeon holds the pin frame. It is recommended to disconnect blood pressure cuffs and arterial and venous lines that are on the side that rotates furthest to avoid dislodgment, although some clinicians prefer to disconnect all lines and monitors before moving. Pulse oximetry usually can be maintained if applied to the "inside" arm, and full monitoring should be reinstituted as rapidly as possible. Endotracheal tube position and adequate ventilation are reassessed immediately after the move.

Head position is crucial. The patient's head may be turned to the side when prone if neck mobility is adequate. As in the lateral decubitus position, the dependent eye must be checked frequently for external compression. In addition, in patients with cervical arthritis or cerebrovascular disease, lateral rotation of the neck may compromise carotid or vertebral arterial blood flow or jugular venous drainage. In most cases, the head is kept in a neutral position using a surgical pillow, horseshoe headrest, or Mayfield head pins. Numerous commercially available pillows are specially designed for the prone position. Most, including disposable foam versions, support the forehead, malar regions, and the chin, with a cutout for the eyes, nose, and mouth (see Fig. 36-14). The face is not always visible, however, making eye checks more difficult. Mirror systems are available to facilitate intermittent visual confirmation that the eyes are unimpinged, although direct visualization or tactile confirmation of at least the initial appearance is prudent (Fig. 36-15).

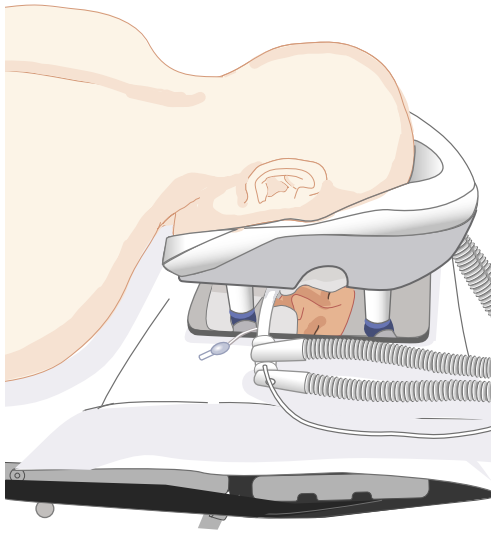

Figure 36-15 Mirror system for prone position. Bony structures of head and face are supported, and monitoring of eyes and airway is facilitated with a plastic mirror.

The horseshoe headrest supports only the forehead and malar regions and allows excellent access to the airway, but it is more rigid and potentially dangerous if the head moves (Figs. 36-16 and 36-17). Mayfield rigid pins support the head without any direct pressure on the face, allow access to the airway, and hold the head firmly in one position that can be finely adjusted for optimal neurosurgical exposure (Fig. 36-18). Rigid pin fixation is rarely used outside cranial or cervical spine surgeries. When properly applied, the pins cause significant periosteal stimulation. A high degree of vigilance also is necessary to prevent patient movement when the head is held in rigid pins; skidding out of pins can result in scalp lacerations or cervical spine injury. Because horseshoe and pin headrests attach to adjustable articu-

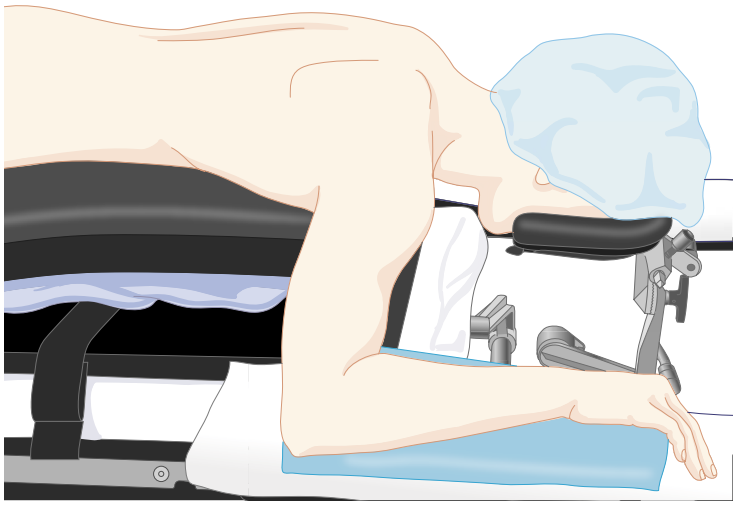

Figure 36-16 Prone position with horseshoe adapter. Head height is adjusted to position neck in a natural position.

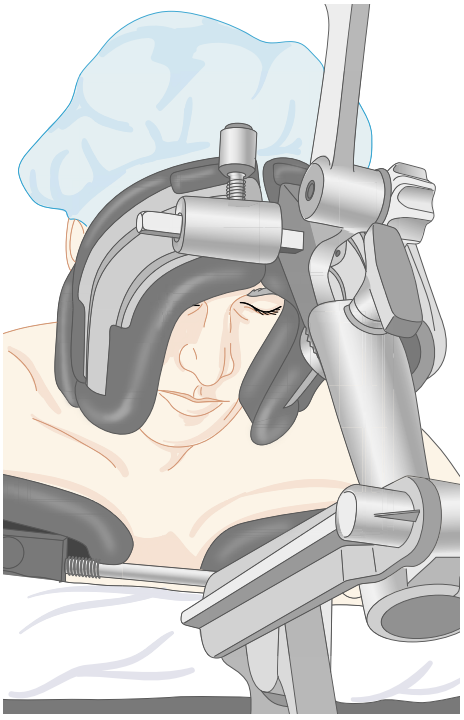

Figure 36-17 Prone position, face seen from below. Horseshoe adapter permits superior access to airway and visualization of eyes. Width may be adjusted to ensure proper support by facial bones.

lating supports, any slippage or failure of this bracketing device may lead to complications if the head suddenly drops.

Regardless of the technique employed to support the head, the eyes, face, and airway must be checked periodically to ensure that the weight is borne only by the bony structures, and that there is no pressure on the eyes. Proper position is verified frequently and noted in the anesthetic record. The face should be rechecked if any patient motion occurs during surgery, or if the table is significantly repositioned. The prone position is a risk factor for perioperative visual loss, which is discussed in detail subsequently.

Because the abdominal wall is easily displaced, external pressure on the abdomen may elevate intra-abdominal pressure in the prone position. This elevated pressure compromises respiration and transmits elevated venous pressures to the abdominal and spine vessels, including the epidural veins. During spinal surgery, low venous pressure is desirable to minimize bleeding and facilitate surgical exposure. External pressure on the abdomen may push the diaphragm cephalad, decreasing functional residual capacity and pulmonary compliance, and increasing peak airway pressure. Abdominal pressure also may impede venous return through compression of the inferior vena cava. For these reasons, careful attention must be paid to the ability of the abdomen to hang free and to move with respiration.

The thorax is generally supported by firm rolls or bolsters placed along each side from the clavicle to the iliac crest. Multiple commercial rolls and bolsters are available, including the Wilson frame (see Fig. 36-14), Jackson table, Relton frame, and the Mouradian/Simmons modification of the Relton frame. All devices serve to minimize abdominal compression by the operating room table and maintain normal pulmonary compliance. To prevent tissue injury, pendulous structures (e.g., male genitalia and female breasts) should be clear of compression; the breasts should be placed medial to the bolsters. The lower portion of each roll or bolster must be placed under its respective iliac crest to prevent pressure injury to the genitalia and the femoral vasculature.[32] The prone position presents special risks for morbidly obese patients, whose respiration is already compromised, and who may be difficult to reposition quickly. Sometimes it may be necessary to discuss alternative positioning options with the surgeon to ensure patient safety.

Sitting

The sitting position, although infrequently used because of the perception of risk from venous and paradoxical air embolism, offers advantages to the surgeon in approaching the posterior

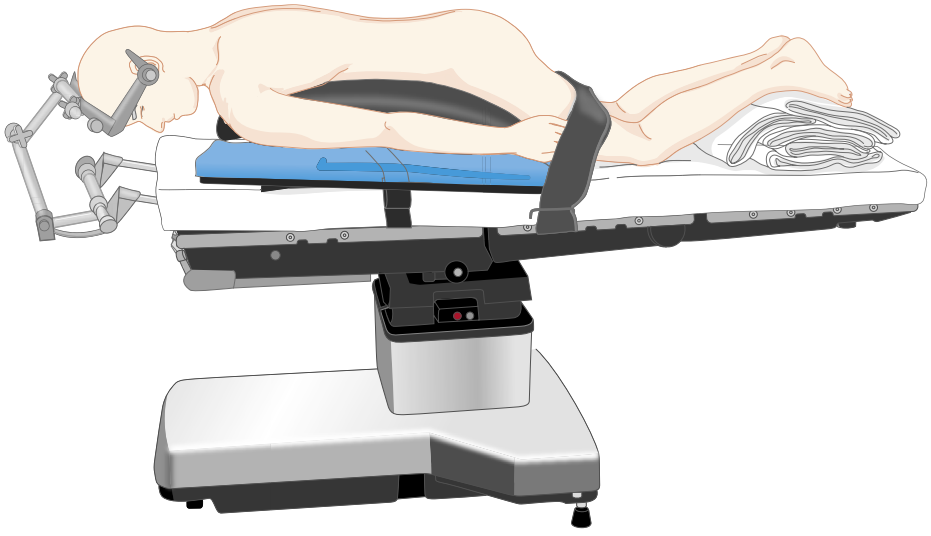

Figure 36-18 Prone position with Mayfield head pins. Rigid fixation is provided for cervical spine and posterior intracranial surgeries. Head position may include neck torsion or flexion that affects endotracheal tube position.



Figure 36-19 "Sitting" position with Mayfield head pins. This is actually a modified recumbent position as the legs are kept as high as possible to promote venous return. Arms must be supported to prevent shoulder traction. In a commonly used variation they are padded and rest on the abdomen, as illustrated in Figure 63-8. Note that the head holder support is preferably attached to the back section of the table so that the patient's back may be adjusted or lowered emergently without first detaching the head holder. If the head holder is connected to the thigh section of the table this cannot be done.

cervical spine and the posterior fossa (Fig. 36-19). The main advantages of the sitting position over the prone position for neurosurgical and cervical spine surgeries are excellent surgical exposure, decreased blood in the operative field, and, possibly, reduced perioperative blood loss.[33] The main advantages to the anesthesiologist are superior access to the airway, reduced facial swelling, and improved ventilation, particularly in obese patients. A variation of the sitting position, the beach chair position is increasingly used for shoulder surgeries, including arthroscopic procedures (Fig. 36-20). Its attraction to the surgeon is superior access to the shoulder from the anterior and posterior aspect, and potential for great mobility of the arm at the shoulder joint.

The head may be fixed in pins for neurosurgery or taped in place with adequate support for other surgeries. Because gravity is pulling the arms caudad, they must be supported to the point of slight elevation of the shoulders to avoid traction on the shoulder muscles and potential stretching of upper extremity neurovascular structures. The knees are usually slightly flexed for balance and to reduce stretching of the sciatic nerve, and the feet are supported and padded.[34]

The hemodynamic effects of placing a supine patient in the sitting position are dramatic. Because of the pooling of blood into the lower body under general anesthesia (see earlier), patients are particularly prone to hypotensive episodes. Incremental positioning and the use of intravenous fluids, vasopressors, and appropriate adjustments of anesthetic depth can reduce the degree and duration of hypotension. Elastic stockings and active leg compression devices can help maintain venous return.

Head and neck position has been associated with complications during surgery to the posterior spine or skull in the sitting position. Excessive cervical flexion has numerous adverse consequences. It can impede arterial and venous blood flow, causing hypoperfusion or venous congestion of the brain. It may impede normal respiratory excursion. Excessive flexion also can obstruct the endotracheal tube and place significant pressure on the tongue, leading to macroglossia. Generally, maintaining at least two fingers' distance between the mandible and the sternum is recommended for a normal-sized adult, and patients should not be positioned at the extreme of their range of motion.[35] Extra caution with neck flexion is advised if transesophageal echocardiography (TEE) is used for air embolism monitoring because the esophageal probe lies between the flexed spine and the airway and endotracheal tube, adding potential for compression of laryngeal structures and the tongue.

Because of the elevation of the surgical field above the heart, and the inability of the dural venous sinuses to collapse because of their bony attachments, the risk of venous air embolism is a constant concern. Arrhythmia, desaturation, pulmonary hypertension, circulatory compromise, or cardiac arrest may occur if sufficient quantities are entrained. If the foramen ovale is patent, even small amounts of venous air may result in a stroke or myocardial infarction owing to paradoxical embolism. TEE has shown some degree of venous air in most patients studied during neurosurgery in the sitting position (≤100%).[36,37] Because of the risk of paradoxical embolus, screening contrast echocardiography to investigate the patency of the interatrial septum is



Figure 36-20 Sitting position adapted for shoulder surgery. This is sometimes called the "beach chair position". Arms must be supported to prevent stretching of the brachial plexus.

often performed before sitting position intracranial or cervical spine surgery. Septal patency may not always be detected, however. Adequate hydration and early detection of entrained air with the use of TEE or precordial Doppler ultrasound may decrease the incidence and severity of venous air embolism.[36]

Peripheral Nerve Injury

Peripheral nerve injury remains a serious perioperative complication and a significant source of professional liability despite the low incidence (approximately 0.11% of 81,000 anesthetic procedures reviewed from 1987 to 1993).[38] Injuries occur when peripheral nerves are subjected to stretch, ischemia, or compression during surgery.[39] Because sensation is blocked by unconsciousness or regional anesthesia, early warning symptoms of pain and the normal spontaneous repositioning are absent. In 1984, the ASA developed a Closed Claims Project to evaluate adverse anesthetic outcomes from the closed claims files of 35 U.S. liability insurance companies. Since the initial report in 1990, the incidence of nerve injury has remained essentially constant, representing 18% of all claims during 1990 through 1994, second only to death (22%).[1-3] Among the total 670 claims filed, ulnar neuropathy remained the most frequent site of injury (28%), followed by the brachial plexus (20%), lumbosacral nerve root (16%), and spinal cord (13%) (Table 36-1).

The distribution of nerve injuries has changed significantly over time. Ulnar neuropathy decreased from 37% in 1980-1984 to 17% in the 1990s, and spinal cord injury increased from 8% in 1980-1984 to 27% in 1990s. Spinal cord injury and lumbosacral nerve root neuropathy were predominantly associated with regional anesthesia. Epidural hematoma and chemical injury represented 29% of the known mechanisms of injury among the claims filed. The injuries probably were related to the use of neuraxial block in anticoagulated patients and the increased usage of blocks for chronic pain management (Table 36-2).[3,40,41]

With the exception of spinal cord injury, the mechanism of nerve injury remains largely unknown. Most injuries, particularly injuries to nerves of the upper extremity, such as the ulnar nerve and brachial plexus, occurred in the presence of adequate positioning and padding. Because of the significant morbidity associated with peripheral nerve injury, in 2000 the ASA published a practice advisory for the prevention of peripheral neuropathies.[16] The advisory was not based on scientific evidence, but the consensus of a consultant expert group. Only 6 of 509 positioning studies reviewed "… exhibited sufficiently acceptable methods and analyses that provided a clear indication of the relationships between interventions and outcomes of interest" (Table 36-3).

Because of the paucity of clear data on the causes and the prevention of peripheral injuries, individual practices vary with regard to specific padding and positional details. Prolonged duration is a risk factor. Good sense would avoid positions that permit stretching of the nerves and pressure to anatomic locations known

Table 36-1 Nerve Injury Claims in the American Society of Anesthesiologists Closed Claims Database

Nerve	No. Claims in Current Database (*N* = 4183)	% of Total (*N* = 670)	No. Claims since 1990 Report	% of Total since 1990 (*N* = 445)
Ulnar	190	28	113	25
Brachial plexus	137	20	83	19
Lumbosacral nerve root	105	16	67	15
Spinal cord	84	13	73	16
Sciatic*	34	5	23	5
Median	28	4	19	4
Radial	18	3	13	3
Femoral	15	2	9	2
Other single nerves	43	6	35	8
Multiple nerves	16	2	10	2
Total	*670*	*100*	*445*	*100*

*Includes peroneal nerve.
From Cheney FW, Domino KB, Caplan RA, et al: Nerve injury associated with anesthesia. Anesthesiology 90:1064, 1999.

to carry nerves prone to injury, such as the ulnar cubital tunnel and the peroneal nerve coursing over the fibular head. Whenever possible, the patient's position should appear as natural as possible. Padding and support should distribute weight over as wide an area as possible; however, no padding material has been shown to be superior. It also is important to anticipate the additional effects of anesthesia and muscle relaxation.

In a retrospective study of 1000 consecutive spine surgeries that used somatosensory evoked potential (SSEP) monitoring, five arm positions were compared with regard to SSEP changes in the upper extremities. A modification of arm position reversed 92% of upper extremity SSEP changes. The incidence of position-related upper extremity SSEP changes was significantly higher in the prone superman (7%) and lateral decubitus (7.5%) positions compared with the supine arms out, supine arms tucked, and prone arms tucked positions (1.8% to 3.2%). Reversible SSEP changes were not associated with postoperative deficits (see Chapter 46).[42]

Ulnar Nerve

The etiology of perioperative ulnar neuropathy is complex and incompletely understood. The ulnar nerve lies in a superficial

Table 36-2 Most Common Nerve Injuries in American Society of Anesthesiologists Closed Claims Database after 1990

Injury	Recommendations for Prevention
Ulnar nerve (25%)	Avoid excessive pressure on postcondylar groove of humerus Keep hand and forearm either supinated or in neutral position
Brachial plexus (19%)	Avoid the use of shoulder braces in patients in Trendelenburg position (use nonsliding mattresses) Avoid excessive lateral rotation of head either in supine or prone position Limit abduction of the arm to <90 degrees in supine position Avoid placement of high axillary roll in decubitus position—keep roll out of axilla Use ultrasound to find internal jugular vein for central line placement
Spinal cord (16%) and lumbosacral nerve root (15%)	Be aware that the fraction of spinal cord injuries is increasing, probably in relation to use of epidural catheters for pain management Follow current guidelines for regional anesthesia in anticoagulated patients*
Sciatic and peroneal (5%)	Minimize time of surgery in lithotomy position Use two assistants to coordinate simultaneous movement of both legs to and from lithotomy position Avoid excessive flexion of hips, extension of knees, or torsion of lumbar spine Avoid excessive pressure on peroneal nerve at the fibular head
Median (4%) and radial (3%)	Be aware that 25% of injuries to the median and radial nerves were associated with axillary block, and 25% of injuries were associated with traumatic insertion or infiltration of an intravenous line

*Horlocker TT, Wedel DJ, Benzon H, et al: Regional anesthesia in the anticoagulated patient: Defining the risks (The Second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain Med 28:172-197, 2003.
Data from references 1-3.

Table 36-3 Summary of American Society of Anesthesiologists Task Force Consensus Findings on Prevention of Perioperative Peripheral Neuropathies

Preoperative Assessment
When judged appropriate, it is helpful to ascertain that patients can comfortably tolerate anticipated operative position
Upper Extremity Positioning
Arm abduction should be limited to 90 degrees in supine patients; patients who are positioned prone may comfortably tolerate arm abduction >90 degrees
Arms should be positioned to decrease pressure on the postcondylar groove of the humerus (ulnar groove). When arms are tucked at the side, a neutral forearm position is recommended. When arms are abducted on armboards, either supination or a neutral forearm position is acceptable
Prolonged pressure on radial nerve in spiral groove of humerus should be avoided
Extension of elbow beyond a comfortable range may stretch median nerve
Lower Extremity Positioning
Lithotomy positions that stretch hamstring muscle group beyond a comfortable range may stretch sciatic nerve
Prolonged pressure on peroneal nerve at fibular head should be avoided
Neither extension nor flexion of hip increases risk of femoral neuropathy
Protective Padding
Padded armboards may decrease risk of upper extremity neuropathy
Use of chest rolls in laterally positioned patients may decrease risk of upper extremity neuropathies
Padding at elbow and at fibular head may decrease risk of upper and lower extremity neuropathies
Equipment
Properly functioning automated blood pressure cuffs on upper arms do not affect risk of upper extremity neuropathies
Shoulder braces in steep head-down positions may increase risk of brachial plexus neuropathies
Postoperative Assessment
Simple postoperative assessment of extremity nerve function may lead to early recognition of peripheral neuropathies
Documentation
Charting specific positioning actions during care of patients may result in improvements of care by (1) helping practitioners focus attention on relevant aspects of patient positioning, and (2) providing information that continuous improvement processes can use to effect refinements in patient care

From ASA Task Force on Prevention of Perioperative Peripheral Neuropathies: Practice advisory for the prevention of perioperative peripheral neuropathies. Anesthesiology 92:1168-1182, 2000.

position at the elbow. Although the incidence is low, the morbidity associated with ulnar neuropathy can be severe. In a prospective study among 1502 patients undergoing noncardiac surgery, 7 patients developed perioperative ulnar neuropathy, of which 3 patients had residual symptoms after 2 years.[43] The neuropathy, if permanent, results in the inability to abduct or oppose the fifth finger, diminished sensation in the fourth and fifth fingers, and eventual atrophy of the intrinsic muscle of the hands creating a claw-like hand.

Previously, injury was thought to be associated with hyperflexion of the elbow and compression by the operating room table of the nerve at the condylar groove and the cubital tunnel against the posterior aspect of the medial epicondyle of the humerus. The current consensus is that the etiology of ulnar nerve palsy is multifactorial and not always preventable. In a large retrospective review of perioperative ulnar neuropathy lasting longer than 3 months, the onset of symptoms occurred more than 24 hours postoperatively in 57% of patients, 70% were male, and 9% experienced bilateral symptoms. Very thin or obese patients were at increased risk, as were patients on prolonged postoperative bed rest. There was no association with intraoperative patient position or anesthetic technique.[44]

The Closed Claims Project also showed that perioperative ulnar neuropathy occurred predominantly in men, in an older population, and with a delayed onset (median of 3 days).[3] Although most ulnar damage claims were associated with general anesthesia, payment also was made for claims where the patient had been awake or sedated during regional anesthesia involving the lower extremity. In a prospective study of medical patients who did not undergo surgical procedures, 2 of 986 patients developed ulnar neuropathy.[45] The large predominance of ulnar injury in men may be explained by anatomic differences. Men have a more developed and thickened flexor retinaculum with less protective adipose tissue and a larger (1.5 ×) tubercle of the coronoid process that can predispose to nerve compression in the cubital tunnel.[46,47] Other risk factors, including diabetes mellitus, vitamin deficiency, alcoholism, cigarette smoking, and cancer, need further studies to be substantiated. In the ASA Closed Claims Project, only 9% of ulnar injury claims had an explicit mechanism of injury, and, in 27% of claims, the padding of the elbows was explicitly stated.[3] It has become accepted that postoperative ulnar nerve palsy can occur without any apparent cause, even when padding and positioning of the patient's arm were done carefully and documented in the anesthetic record.[18]

Brachial Plexus

The brachial plexus is susceptible to injury from stretching or compression because of its long superficial course in the axilla between two points of fixation, the vertebra and the axillary fascia, in association with the mobile clavicle and humerus (Fig. 36-21). The patient often complains of sensory deficit in the distribution of the ulnar nerve. Injury is most commonly associated with arm abduction greater than 90 degrees, lateral rotation of the head, asymmetric retraction of the sternum for internal mammary artery dissection during cardiac surgery, and direct trauma. To avoid brachial plexus injury, patients ideally should be positioned with the head midline, arms kept at the sides, the elbow mildly flexed, and the forearm supinated.

In cardiac surgery patients requiring median sternotomy, brachial plexus injury has been specifically associated with the C8-T1 nerve roots. In a prospective study in which the incidence of injury was 4.9%, the authors found that 73% of the injuries occurred on the same side as the internal jugular vein cannulation.[48] Among noncardiac surgery patients, the incidence is reported to be 0.02%.[49] In the ASA Closed Claims Project, 16% of brachial plexus injuries occurred during a regional block, particularly the axillary block.[3]

Brachial plexus injury also is associated with direct compression, particularly with the use of shoulder braces in patients undergoing surgery in the Trendelenburg position. The nerves are vulnerable to compression as they pass between the clavicle and

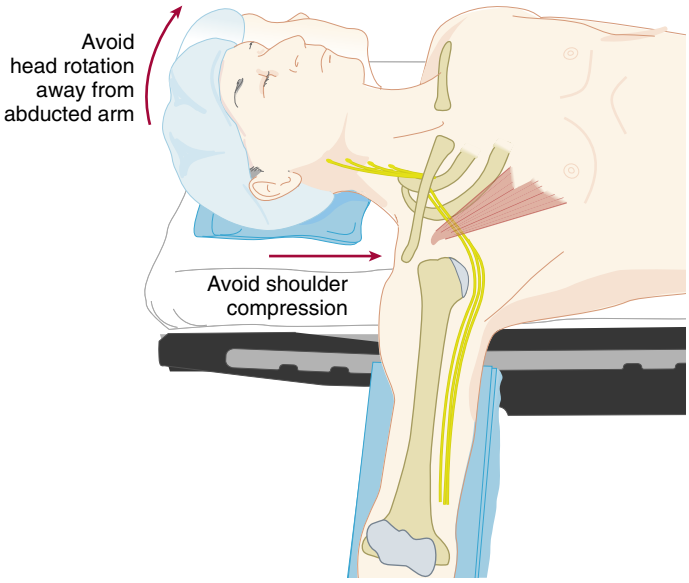

Figure 36-21 The brachial plexus is vulnerable to stretch and compression. Arm abduction is limited to less than 90 degrees whenever possible. Excessive head rotation, especially away from an abducted arm, should be avoided. Shoulder braces should be avoided because they may cause direct compression of the plexus medially between the clavicle and first rib, or laterally below the head of the humerus.

the first rib. Medial placement of the braces can compress the proximal roots, and lateral placement of the braces can stretch the plexus by displacing the shoulders (see Fig. 36-21). The patient with injury often complains of painless motor deficit in the distribution of the radial and median nerves. In the ASA Closed Claims Project, 10% of brachial plexus injuries were directly attributed to patient positioning. Of those, one half involved the use of shoulder braces in patients in the Trendelenburg position.[3] Consequently, nonsliding mattresses should be used in place of shoulder braces.

Other Upper Extremity Nerves

Although quite rare, the radial nerve can be injured from direct pressure as it traverses the spiral groove of the humerus in the lower third of the arm. The injury often manifests as a wrist drop with an inability to abduct the thumb or extend the metacarpophalangeal joints. Isolated median nerve injury most often occurs during the insertion of an intravenous needle into the antecubital fossa in an anesthetized patient where the nerve is adjacent to the medial cubital and basilic veins. Patients with this injury are unable to oppose the first and fifth digits and have decreased sensation over the palmar surface of the lateral three and a half fingers. In an evaluation of the ASA Closed Claims database from 1970 to 2001, Liau[50] found that peripheral intravenous and arterial line insertion accounted for 2.1% of all claims filed, particularly among patients undergoing cardiac surgery where the arms are tucked and the lines are not visible for inspection. Nerve injury accounted for 17% of intravenous line complications second only to skin slough or necrosis (28%) and swelling, inflammation, and infection (17%).

Lower Extremity Nerves

Injuries to the sciatic and common peroneal nerves occur most often in the lithotomy position. Because of its fixation between the sciatic notch and the neck of the fibula, the sciatic nerve can be stretched with external rotation of the leg. Hyperflexion of the hips or extension of the knees also can aggravate nerve stretch in this position. The common peroneal nerve, a branch of the sciatic nerve, can be damaged from the compression of the nerve between the head of the fibula and the frame of the leg support. Most often, patients who sustain injury complain of a foot drop and the inability to extend the toes in a dorsal direction or evert the foot.

In a prospective study of 991 patients undergoing surgery under general anesthesia in the lithotomy position, the incidence of lower extremity neuropathies was 1.5%, with injuries to the sciatic and peroneal nerves representing 40% of the cases. Symptoms were predominantly paresthesia with onset within 4 hours of surgery and resolution generally within 6 months. No motor deficits were noted, but in a previous retrospective study, the same authors found the incidence of severe motor disability in patients undergoing surgery in the lithotomy position to be 1 in 3608.[22,23]

Injury to the femoral or obturator nerves generally occurs during lower abdominal surgical procedures with excessive retraction. The obturator nerve also can be injured during a difficult forceps delivery or by excessive flexion of the thigh to the groin. A femoral neuropathy manifests with decreased flexion of the hip, decreased extension of the knee, or a loss of sensation over the superior aspect of the thigh and medial/anteromedial side of the leg. An obturator neuropathy manifests with inability to adduct the leg with decreased sensation over the medial side of the thigh.

Perioperative Eye Injury and Visual Loss

Although quite rare (incidence of 0.056% in one retrospective review),[51] perioperative eye injuries are a source of significant morbidity and liability (see Chapter 90). In the ASA Closed Claims database, eye complications constituted 3% of all claims and were associated with greater monetary settlements compared with nonocular injuries.[3]

Corneal abrasion is the most common type of perioperative eye injury and is associated with direct trauma to the cornea from facemasks, surgical drapes, or other foreign objects. Corneal abrasion also can be associated with decreased basal tear production or swelling of the dependent eye in patients in the prone position. Patients complain of pain associated with a foreign body sensation in the eye on awakening from surgery. This injury also can occur from a dried section of cornea. Symptoms are generally transient, and treatment comprises supportive care and antibiotic ointment to prevent bacterial infection.

In a prospective study of 671 patients undergoing nonocular surgery, 4.2% of patients reported a new onset of blurred vision lasting at least 3 days after surgery. For most patients, the symptoms resolved within 2 months without complication; 1% required visits to eye care providers.[52] Precautionary measures to reduce the incidence of corneal abrasion include early and careful

taping of the eyelids after induction of anesthesia, care regarding dangling objects when leaning over patients, and close observation as patients awaken. Before they are completely awake, patients often try to rub their eye or nose with pulse oximeter probes, armboards, and intravenous lines attached, inadvertently endangering their eyes.

Postoperative visual loss is a devastating complication that has been associated with specific surgeries and patient risk factors (see Chapter 90). Risk varies with type of surgery. The incidence varies from a range of 1 in 60,965 to 1 in 125,234 for patients undergoing noncardiac, nonocular surgeries[51,53] to 0.06% to 0.113% for patients undergoing cardiac surgery with cardiopulmonary bypass,[54,55] and 0.09% for patients undergoing spine surgery in the prone position.[56] Ischemic optic neuropathy (ION) and, to a lesser extent, central retinal arterial occlusion from direct retinal pressure are the conditions most sited as potential causes. Perioperative factors associated with an increased risk of ION include prolonged hypotension, long duration of surgery especially in the prone position, large blood loss, large crystalloid use, anemia or hemodilution, and increased intraocular or venous pressure from the prone position.[57,58] Intraocular pressure increases in the dependent eye in the lateral decubitus position as well.[59] Patient risk factors associated with ION include hypertension, diabetes, atherosclerosis, morbid obesity, and tobacco use. With the exception of obvious external compression of the eyes, however, the cause of perioperative visual loss seems to be multifactorial in nature with no consistent underlying mechanism.

In 1999, the ASA Committee on Professional Liability established the ASA Postoperative Visual Loss Registry to understand the complication better. By 2005, 131 cases were reported to the registry, of which 73% of reported cases involved patients undergoing spine surgeries, and 9% involved cardiac surgery.[60-62] Of 93 patients with postoperative visual loss after prone spine surgery, Lee and colleagues[62] reported that 89% were diagnosed with ION, predominantly posterior, and 11% were diagnosed with central retinal artery occlusion. In patients who were diagnosed with ION, 66% had documented bilateral involvement, of which 42% had eventual improvement in vision, although often clinically insignificant. Compared with central retinal artery occlusion, patients with ION had significantly higher anesthetic duration (9.8 ± 3.1 hours versus 6.5 ± 2.2 hours), estimated blood loss (median 2 L versus 0.75 L), and crystalloid infusion (9.7 ± 4.7 L versus 4.6 ± 1.7 L). Patients with ION also were relatively healthy (64% ASA class I and II), and 73% were men.[62]

In 2006, the ASA issued a practice advisory for perioperative visual loss associated with spine surgery. No definite recommendations were made concerning the issue of induced hypotension, use of vasopressors, or transfusion threshold owing to the multifactorial nature and the low incidence of the injury. Despite a lack of direct evidence, several suggestions were made for "high risk" patients undergoing complex spine surgery, as follows:[63]

- Discuss the possibility of staging the spine surgery in consultation with the surgeon.
- Avoid excessive increase in intraocular pressure from head position below the body and external compression of the abdomen or chest. Keep the head neutral.
- Use colloids along with crystalloids to maintain intravascular volume. Consider placement of a central venous line for monitoring preload.
- For patients who are anticipated preoperatively to undergo procedures that are prolonged, have substantial blood loss, or both, consider informing the patients of a small, unpredictable risk of perioperative visual loss.

Additional recommendations include frequent eye checks, which may help prevent central retinal artery occlusion, although the required frequency has not been established, and careful attention to factors related to oxygen delivery, including oxygen tension and maintenance of adequate intravascular volume and cardiac output.[64]

Until the causative factors of this devastating type of injury are better defined, it is likely that debate regarding patient management strategies will continue. With regard to patient positioning, the anesthesiologist should be aware that intraocular pressures are elevated in the dependent eye in the lateral position and both eyes in the prone position in the absence of any external pressure. It is sensible to avoid external eye pressure at all times, to document eye checks frequently, and to limit time in the prone position whenever possible.

Evaluation and Treatment of Perioperative Neuropathies

When a nerve injury becomes apparent postoperatively, it is essential to perform and document a directed physical examination to correlate the extent of sensory or motor deficits with the preoperative examination and any intraoperative events. Whether or not an etiology is suspected, it is prudent to seek neurologic consultation to define the neurogenic basis, localize the site of the lesion, and determine the severity of injury for guiding prognostication.[65,66] With proper diagnosis and management, most injuries resolve; however, months to years may be required.[39]

For motor neuropathy, an electromyogram can be performed to determine the exact location of the injury. An electromyogram involves recording the electrical activity of muscle from a needle electrode inserted within it. If present, abnormalities may point to the affected component within the motor unit, which consists of the anterior horn cell, its axon and neuromuscular junctions, and the muscle fibers that it innervates. Certain findings are suggestive of denervation, including the presence of abnormal spontaneous activity in the resting muscle (fibrillation potentials and positive sharp waves, which result from muscle irritability) and increased insertion activity. Insertion activity increases within a few days of muscle denervation, whereas abnormal spontaneous activity takes 1 to 4 weeks to develop, depending on the distance from the nerve lesion to the muscle. From a medicolegal standpoint, the presence of abnormal spontaneous activity in the acute setting may suggest the nerve injury was present preoperatively. In addition, depending on the pattern of abnormalities, an electromyogram may distinguish between radiculopathies, plexopathies, and neuropathies.

For anesthesiologists, nerve conduction studies may be more useful to evaluate potential peripheral nerve injuries, such as ulnar neuropathy. Nerve conduction studies permit the assessment of motor and sensory nerves. To evaluate motor integrity, the nerve is stimulated supramaximally at two points along its course, and a recording is made of the electrical response of one

of the muscles that it innervates. The size of the muscle action potential provides an estimate of the number of motor axons and muscle fibers that are activated by the stimulus. For sensory conduction studies, the nerve fiber is stimulated supramaximally at one point, and the sensory nerve action potential is recorded from another point. The latency of the response can be interpreted as a reflection of the number of functioning sensory axons. Nerve conduction studies are useful for several reasons because they may reveal the presence of a subclinical polyneuropathy that made the individual nerves more susceptible to injury, and help distinguish between axon loss and demyelination, which has significant implications regarding course and overall prognosis.

Most sensory neuropathies are generally transient and require only reassurance to the patient with follow-up, whereas most motor neuropathies include demyelination of peripheral fibers of a nerve trunk (neurapraxia) and generally take 4 to 6 weeks for recovery. Injury to the axon within an intact nerve sheath (axonotmesis) or complete nerve disruption (neurotmesis) can cause severe pain and disability. When reversible, recovery often takes 3 to 12 months. Interim physical therapy is recommended to prevent contractures and muscle atrophy.[65,66]

If a new sensory or motor deficit is found postoperatively, electrophysiologic evaluation by a neurologist within the first week may provide useful information concerning the characteristic and temporal pattern of the injury. Another examination after 4 weeks, when enough time has elapsed for the electrophysiologic changes to evolve, provides more definitive information about the site, nature, and severity of the nerve injury. Regardless, electrophysiologic testing must be interpreted within the clinical content for which it was obtained. No single test can define the etiology of injury.

Anesthesia outside the Operating Room

Anesthesia care providers are increasingly involved with procedures performed for gastrointestinal endoscopy, cardiac catheterization, interventional radiology, neuroradiology, and magnetic resonance imaging/computed tomography, and for office-based procedures (see Chapter 79).[67] Anesthesia care may be requested specifically because a patient is not expected to tolerate the position required for the procedure owing to comorbidities, such as congestive heart failure, pulmonary disease, or morbid obesity. Additionally, positions that are generally safe for patients who are awake may pose serious risks to patients under anesthesia.

Vigilance is particularly important outside the operating room to maintain patient safety because of the less familiar environment, lack of positioning equipment, and variability in staff and nursing training with regard to patient positioning. Many locations do not routinely have safety straps or arm supports available. Diagnostic tables may not lend themselves to established intraoperative solutions to patient positioning challenges. The ability to institute Trendelenburg positioning to augment venous return and cardiac output rapidly is often lacking. In some settings, such as magnetic resonance imaging, the anesthesiologist is not in direct proximity to the patient, and vigilance is more difficult.

Currently, the number of claims in the ASA Closed Claims database for injury during anesthesia care outside the operating room is very small (33 versus 4291 claims for intraoperative surgical anesthesia). Of these claims, 54% were associated with death; 63% were associated with substandard care (predominantly owing to inadequate monitoring); and 58% involved monitored anesthesia care among patients who were ASA class III to V, most of whom were at the extremes of age.[68] In such an environment, where practice patterns have often evolved in the context of nonanesthetized patients, the anesthesiologist is primarily responsible for verifying the safety of each patient's position, and for implementing guidelines for patients under anesthesia.

Summary

The positioning of patients under anesthesia care is a major responsibility requiring great attention to detail and constant vigilance. Rapid positioning and optimal surgical exposure are virtues that may be appreciated instantly, but the potential for lasting harm to patients from improper positioning and physiologic compromise must be kept in mind. Each position has significant physiologic effects on ventilation and circulation. In addition, despite increased awareness, position-related complications, including peripheral nerve injuries, remain a significant source of patient morbidity. Anesthesiologists, surgeons, and nurses must work together when positioning patients to ensure their comfort and safety in addition to the desired surgical exposure. Ideally, the final position should appear natural: a position that the patient would comfortably tolerate if awake and unsedated for the anticipated duration of the procedure.

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37 Neuromuscular Disorders and Malignant Hyperthermia

Key Points

1. Dystrophin, along with dystrophin-associated glycoproteins, is involved in sarcolemmal stability. Its defects are responsible for Duchenne's muscular dystrophy (DMD) and Becker's muscular dystrophy (BMD).
2. Whereas the risk for a malignant hyperthermia (MH) mutation in DMD/BMD patients is similar to that in the general population, the incidence of MH-like anesthetic events has been reported to be 0.002 with DMD and 0.00036 with BMD.
3. Succinylcholine is contraindicated in DMD/BMD patients because of the risk of rhabdomyolysis and hyperkalemia as a result of their unstable sarcolemmal membrane.
4. The majority of complications in patients with myotonic dystrophy (MD) were found to be pulmonary related. Pulmonary complications of MD are the result of hypotonia, chronic aspiration, and central and peripheral hypoventilation.
5. Although patients with sodium channel pathology have often been considered to be susceptible to MH, there is no increased risk for MH in these patients.
6. MH is an anesthetic-related disorder of increased skeletal muscle metabolism. It is an inherited condition and it occurs in swine and humans.
7. Skeletal muscle accounts for approximately 40% of body weight; its increased metabolism therefore has a profound effect on whole-body metabolism.
8. Signs of MH, including tachycardia, increased expired CO_2, muscle rigidity, and increased temperature, are related to the increased metabolism.
9. The abnormal function of the ryanodine receptor of skeletal muscle in MH causes barely controlled concentration of calcium within the cell when it is not exposed to triggering agents.
10. The added loss of control of intracellular calcium on exposure to triggering agents or heat stress leads to marked metabolic stimulation within the cell to provide extra adenosine triphosphate to drive the calcium pumps that restore calcium to its reservoirs (e.g., sarcoplasmic reticulum, mitochondria, extracellular fluid).
11. Dantrolene markedly attenuates myoplasmic Ca^{2+} concentrations and thereby restores metabolism to normal, with reversal of the signs of metabolic stimulation.
12. MH is inherited; one mutation accounts for all porcine MH, whereas more than 130 mutations account for human MH.
13. Evaluation of persons susceptible to MH includes contracture of a skeletal muscle biopsy specimen with halothane and caffeine and evaluation of DNA to identify mutations. Only DNA testing is needed to evaluate swine MH.
14. Future MH goals include advancement of genetic evaluations in North American and European medical programs and stronger finances to support genetic studies, identification of the mode of action of dantrolene, determination of the immediate cause of triggering of MH, and the development of effective, nondestructive tests for MH susceptibility.

Neuromuscular disorders, although rarely encountered in routine anesthetic practice, are a group of disorders that challenges both perioperative management and intensive care.

In this chapter, diseases that affect the normal function of peripheral nerves, the neuromuscular junction, and muscles are described. Although such diseases are thought to be rare, the number of patients that a clinician may encounter is increasing annually because of better medical care, increasing longevity, and possibly other yet unidentified factors. As a rule, neuromuscular disorders have significant potential to interact with an improper anesthetic plan, and all affected patients require special perioperative attention for anesthetic management. In this area, the armamentarium of invasive and noninvasive diagnostic tools is being developed, especially in genetics. Also covered in this

chapter is malignant hyperthermia (MH). This fulminant syndrome is elicited by the administration of triggering anesthetic agents, such as a volatile anesthetic or a depolarizing neuromuscular blocking agent. MH has been and continues to be a life-threatening complication of anesthesia if the diagnosis is not made promptly and treatment is not begun in a timely fashion. Unlike other disorders described in this chapter, MH has virtually no characteristic phenotype before exposure to the triggering agent and is truly an example of the interaction of genes and environment.

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disorder characterized by T-cell–mediated autoantibodies against myelin and a subsequent inflammatory response within the central nervous system (CNS: brain and spinal cord). Thus, MS is a disorder of the myelinated part of the axon that leads to secondary nerve conduction failure. The disease affects mainly women, primarily between 20 and 40 or 45 and 60 years of age. Although the etiology is unknown, it has been speculated that MS is caused by environmental factors combined with a genetic predisposition. Naturally, researchers have focused on identifying key events and the genetic origin of the disorder to provide diagnostic and possibly also therapeutic tools for the management of MS patients.

Patients with MS frequently report paresthesias, muscle weakness, and sensory disturbances. Typically, there is a localized or, late in the course of disease, generalized muscle weakness with the legs affected more than the arms. In severe cases, respiration may be involved with the development of hypoxemia. Diplopia and other cranial nerve–dependent impairments are early and frequent signs, along with sensory abnormalities and sometimes disturbed bowel and bladder function. As a rule, symptoms are closely related to the site affected within the CNS, and the amount of symptoms is related to the extent of sclerosing CNS plaque. Notably, MS can be associated with impaired autonomic function, which may lead to adverse reactions to sympathomimetic drugs.[1]

Diagnosis of MS is currently based on a combination of clinical and laboratory tests, including cerebrospinal fluid (CSF) antibody analysis and radiology (detection of CNS plaque by magnetic resonance imaging). Medication consists of various combinations of immunosuppression modalities.

Anesthetic Considerations. It has been speculated that general anesthesia and surgery may increase the risk for aggravation of MS.[2] At present, there is no general consensus on this matter, and patients should therefore be informed of the potential for aggravated symptoms in the postoperative period. In general, preoperative chronic immunosuppressive medication should be continued during the perioperative period. Patients with MS are sensitive to physical (pain, fever, infection) and emotional stress, which makes it more likely that symptoms will be intensified in the perioperative period. Great care must be exercised to minimize changes in body temperature, fluid homeostasis, and central hemodynamics (preload, afterload) and to maintain respiration. Although intravenous induction agents and volatile anesthetics have been used safely, it is wise to avoid administering depolarizing neuromuscular blocking drugs to MS patients. MS-induced denervation or misuse myopathy may lead to a risk for succinylcholine-induced hyperkalemia, which can result in fatal cardiac arrhythmias (see also Chapter 29). Use of nondepolarizing neuromuscular blockers appears to be safe. Regional anesthesia, including epidural application of low concentrations of local anesthetics, has been used in MS patients. Spinal anesthesia exacerbates symptoms in MS and is therefore not recommended for MS patients by most authorities. Notably, postpartum worsening of MS symptoms is noted in 20% of females (also see Chapter 69). The need for postoperative care is dependent on the preoperative symptoms, type of surgery, and status of the patient at the end of the surgical procedure. In this context, MS patients with severe weakness and respiratory distress, including pharyngeal dysfunction, may need extended postoperative care, such as noninvasive respiratory support and intense physiotherapy, to avoid further impairment of their pulmonary function.

Motor Neuron Disorders

Motor neuron disorders involve either the upper or the lower motor neurons of the cerebral cortex, brainstem, and spinal cord. Some forms are mixed, whereas others have predominately upper or lower motor neuron involvement. Amyotrophic lateral sclerosis (ALS) is the most common disease within this group and involves both upper and lower motor neurons. Other examples of motor neuron disease are Kennedy's disease (spinobulbar muscular atrophy), Friedreich's ataxia (mixed upper and lower motor neurons), and spinal muscular atrophy (lower motor neurons).

ALS (Lou Gehrig's disease) is characterized by progressive and variable loss of motor neurons within the cerebral cortex, medullary nuclei of cranial nerves, and nuclei of the ventral horn in the spinal cord. Degenerative loss of these neurons leads to progressive muscle weakness, muscle atrophy, and loss of neuronal mass in these locations. Sensory functions, including intellectual capacity and cognition, as well as bowel and bladder function, are not usually affected in ALS.

ALS has an incidence of about 2 in 100,000, and onset of the disease usually takes place around 40 to 50 years of age, with males more often affected than females. Most cases are sporadic, but rare familial forms (autosomal dominant and recessive forms) do exist. The underlying mechanism or mechanisms for this selective and progressive motor neuronal death are thus far unclear, but it has recently been suggested that superoxide dismutase mutations may have a key role in the increased formation of free radicals seen in subsets of patients. The diagnosis is made by electrophysiology (electromyography [EMG] and electroneurography) and by neurologic examination, which demonstrates early spastic weakness of the upper and lower extremities, typical subcutaneous muscle fasciculations, and bulbar involvement affecting pharyngeal function, speech, and the facial muscles. No curative treatment is currently available, and patients are therefore treated symptomatically.

Anesthetic Considerations. Bulbar involvement in combination with respiratory muscle weakness leads to a risk for aspiration and pulmonary complications. Notably, these patients may have increased sensitivity to the respiratory depressant effects of sedatives and hypnotics. There are reports of sympathetic hyperreactivity and autonomic failure.[3] Succinylcholine should be avoided because of the risk for hyperkalemia as a result of denervation and immobilization. Nondepolarizing neuromuscu-

lar blocking agents may cause prolonged and pronounced neuromuscular blockade and hence should be used with great caution.[4] General anesthesia combined with epidural anesthesia has been used without complications.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an acute inflammatory polyneuritis caused by an immunologic reaction. Although the etiology is unknown, in many cases a timely association with a viral (influenza-like) or bacterial infection or even lymphomatous disease can be demonstrated.[5] Symmetric peripheral flaccid muscle weakness and sensory loss develop. The lower extremities are affected first, after which the disease progresses to the upper extremities and cranial nerve–innervated muscles in some cases. Importantly, patients may also have autonomic involvement that could lead to sudden fatal cardiac and circulatory collapse. The diagnosis is made after careful neurologic examination, clinical electrophysiology, and CSF analysis. CSF analysis may show a typical increase in CSF protein in combination with a normal cell count, which is a classic sign of the disease. Treatment focuses on respiratory support, nutritional support, and early initiation of plasmapheresis.

Anesthetic Considerations. Succinylcholine should not be used because of the risk of hyperkalemia. Nondepolarizing muscle relaxants are not contraindicated but should be avoided as a result of the increased sensitivity and risk for prolonged muscle weakness in the postoperative period. The risk for autonomic dysfunction, respiratory failure, and aspiration may require assisted or mechanical ventilation, even in the postoperative period. Great care should be taken to maintain circulatory stability, including adequate cardiac preload and afterload. Careful hemodynamic monitoring is therefore essential in these patients. General anesthesia can be used; however, the combination of general anesthesia and epidural anesthesia is more controversial.[6] Although regional anesthesia is not contraindicated, there are reports of an association between GBS and epidural anesthesia.[7]

Hereditary Motor-Sensory Neuropathies, including Charcot-Marie-Tooth Disease

Hereditary motor-sensory neuropathies include a spectrum of peripheral neurologic disorders, among which Charcot-Marie-Tooth (CMT) disease is often listed. They are caused by a specific mutation in one of several myelin genes that results in defects in myelin structure, maintenance, and formation. Hereditary motor-sensory neuropathies have been classified into seven types and multiple subtypes according to the age at onset, mode of inheritance, predominately involved muscle groups, and genotypes.[8,9] CMT types 1 and 2 are the most common hereditary peripheral neuropathies, with an estimated prevalence of 40 per 100,000.[9] Patients with CMT disease typically experience slow and progressive distal muscle weakness and wasting. Damage to sensory axons may also lead to sensory loss resulting in frequent tripping and falls. Neuropathic pain may develop in some patients. CMT patients usually have normal life expectancy. CMT type 3, also known as Dejerine-Sottas disease, is a very severe condition with an early onset of hypotonia during infancy. Nerve conduction velocity is typically significantly reduced to less than 10 msec.[9] The genetic inheritance pattern for CMT disease is heterogeneous.

Anesthetic Considerations. The anesthesia experience in patients with CMT disease is limited because of the small number of cases. Major considerations include the use of hypnotic agents, muscle relaxants, volatile agents, and neuraxial techniques. CMT type 1 patients have been reported to have significantly increased sensitivity to thiopental at induction that correlates with the severity of both motor and sensory defects. However, total intravenous anesthesia (TIVA) has been performed successfully in a number of cases without any reported problems.[10-12]

Because of the reduced number of acetylcholine receptors, sensitivity to nondepolarizing muscle relaxants is elevated and the response to succinylcholine is also reduced.[13] Although succinylcholine has been used without adverse effect,[14,15] the risk of an exaggerated hyperkalemic response may be sufficient to preclude it from being used in patients with suspected muscular denervation.[15] Prolonged neuromuscular blockade with vecuronium has been reported.[16] As a result of the large variety of disabilities in this patient group, careful baseline assessment of neuromuscular status should be conducted before the use of nondepolarizing neuromuscular relaxants. Normal response to atracurium and mivacurium has been demonstrated.[17,18] Both TIVA and volatile anesthetics have been used safely in CMT patients in a series of cases.[14] Neuraxial techniques for obstetric procedures have been reported to generally be successful in CMT patients.[19-22] However, the use of regional anesthesia can be controversial given that the possible complications may exacerbate the neurologic symptoms.[23] Similar medicolegal concerns may apply to the surgical and anesthesia positioning of CMT patients because of the sensory deficits and limb deformities.

Duchenne's Muscular Dystrophy and Becker's Muscular Dystrophy

Duchenne's muscular dystrophy (DMD) is the most common and severe type of muscular dystrophy, with an incidence of 1 per 3500 live male births[24] and a total male prevalence of about 50 to 60×10^{-6}.[25] Becker's muscular dystrophy (BMD) is relatively rare and has an incidence of about 1 in 18,000 live male births and a prevalence of 23.8×10^{-6}.[25] Both DMD and BMD are X-linked recessive diseases. The defect is located on the short arm of the X chromosome at the Xp21 region, which contains the gene for the large protein Dp427, also known as dystrophin. The dystrophin gene is 2500 kilobases long with more than 70 exons.[25] Dystrophin is distributed not only in skeletal, cardiac, and smooth muscle but also in the brain.[26] Because of the large size of the dystrophin gene, spontaneous new mutations are common and account for a third of new cases.[27]

The most common form of mutation is a deletion within the gene (65% to 70% of cases of DMD and >80% of BMD). Duplication and point mutations are responsible for the rest. It

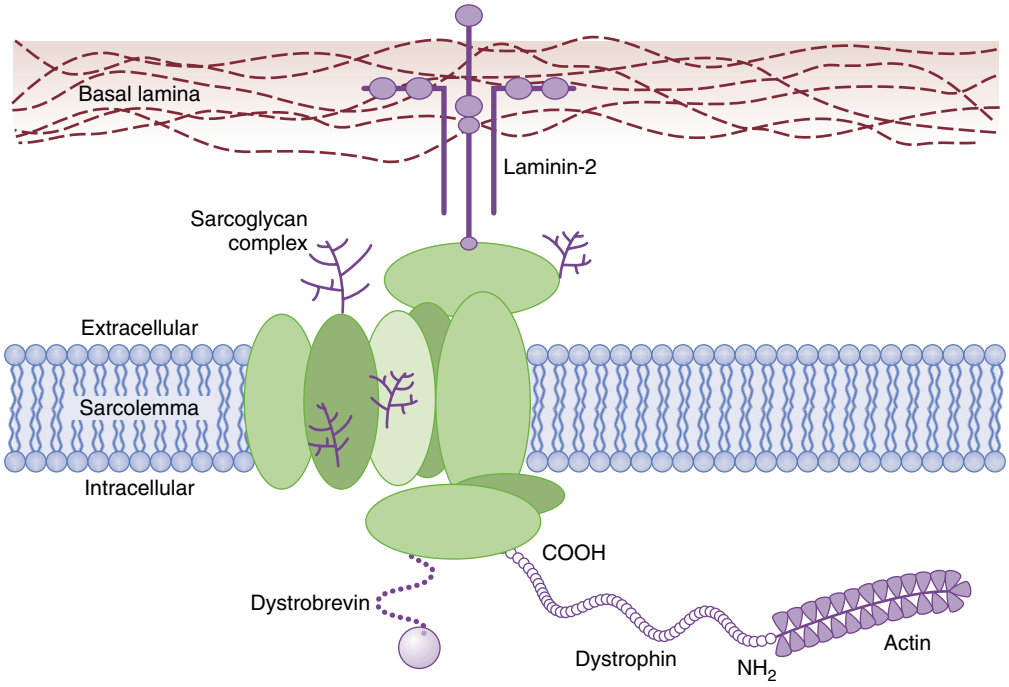

Figure 37-1 Diagram of the cell-surface and cytoskeleton protein complex.

also appears that there are "hot spots" within the first 20 exons and in the central region of the gene (exons 45 to 55) where deletion and duplication are likely to occur.[25] Female cases of DMD have been reported with the 45,X and 46,XX karyotypes. The disease mechanism for the female 46,XX karyotype was thought to be preferential loss of the paternal X chromosome by postzygotic nondisjunction and manifestation of the DMD gene from the maternal X chromosome in muscle cells.[28] BMD is usually milder in severity than DMD because disruption of the translation process occurs in the relatively distal part of the gene, which leads to a reduced amount of truncated dystrophin protein.[25,29]

Dystrophin, along with dystrophin-associated glycoproteins (DAGs), is involved in sarcolemmal stability. Dystrophin is responsible for maintenance of muscle membrane integrity despite the fact that it accounts for only approximately 0.002% of the protein in striated muscle.[30] Dystrophin aggregates and links to actin (at its N terminus) and the DAG complex (at its C terminus) to form a stable structure that interacts with laminin in the extracellular matrix (Fig. 37-1). Lack or dysfunction of dystrophin leads to cellular and membrane instability, with progressive leakage of intracellular components and elevation of creatine phosphokinase (CPK) levels. Eventually, damaged muscle cell units are invaded by macrophages and destroyed. Current study suggests that cytotoxic T cells are probably the culprit. Consequently, clinical pseudohypertrophy of the muscle occurs when the dead muscle shells are replaced by fibrofatty infiltrates. Loss of muscle units accounts for the weakness and contracture.[26]

Both DMD and BMD are characterized by progressive weakness and wasting of predominantly the proximal musculature. Pseudohypertrophy of the calves and other muscle groups is common. As the more severe of the two diseases, DMD tends to be symptomatic early in life. Seventy-four percent of children with DMD were found to manifest the disease by 4 years of age.[24] DMD patients do not usually begin to walk until they are about 18 month of age or later. The initial clinical findings include a waddling gait, frequent falling, and difficulty climbing stairs because of proximal muscle weakness in the pelvic girdle. The classic Gower maneuver describes rising from a sitting to a standing position with the help of both arms. Patients may also show weakness in the shoulder girdle and trunk erectors that leads to thoracolumbar scoliosis. The earlier the onset of disease, the more rapid the disease course. In most cases, children with DMD are unable to walk by the age of 9 to 11. Proximal deep tendon reflexes in the upper extremities and patella may also disappear despite the lack of denervation.[29] Nevertheless, the tendo Achillis reflex remains intact even in later stages of the disease. Sixty percent of patients will have pseudohypertrophy of the calves, and 30% will have macroglossia. Some may also suffer from pain in the calves with activity. The intellectual impairment that can be associated with the disease was thought to be related to limitation of educational opportunities. However, with equalization of educational opportunities, psychometric studies have revealed a significantly lower average intelligence quotient in DMD patients than in healthy groups.[31] This implies a possible effect of dysfunctional dystrophin in the brain on learning. Death in patients with DMD is commonly due to cardiopulmonary compromise in their 30s.[24] BMD is a mild form of DMD. The mutation that causes BMD produces dystrophin that retains partial function. The onset of symptoms occurs in the second or third decade of life. As a result, the life span of BMD patients can reach the early 40s. Pneumonia is the most common cause of death (Fig. 37-2).[29]

The heart is also affected to various degrees, depending on the stage of the disease and the type of mutation. Cardiac degeneration is due to replacement of myocardium by connective tissue or fat, which leads to dilated cardiomyopathy.[32] Cardiac involvement starts early in the course of the disease, although clinical

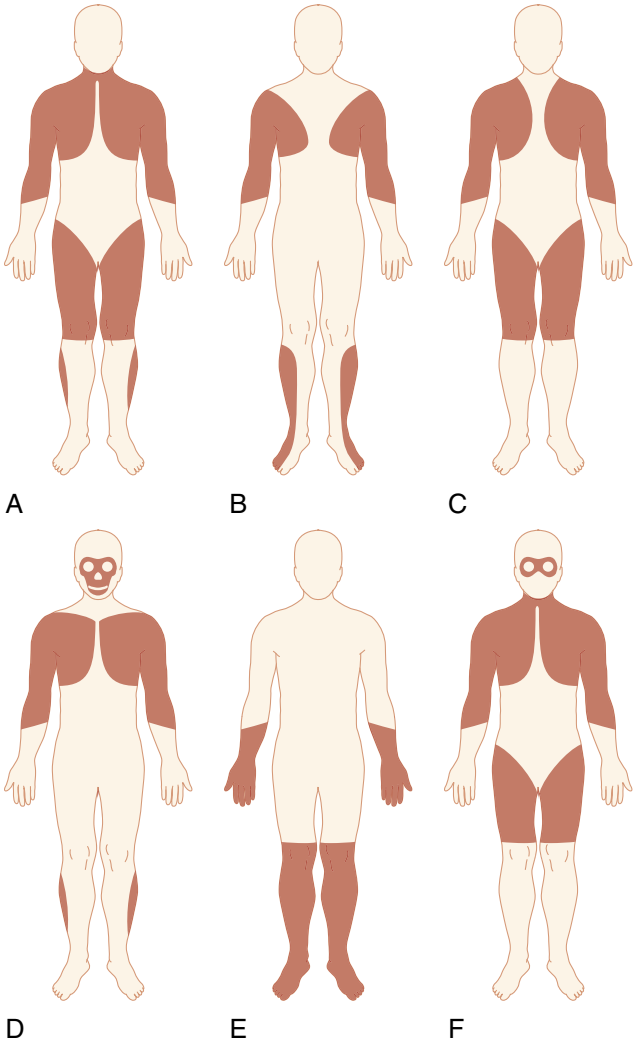

Figure 37-2 Distribution of predominant muscle weakness in different types of dystrophy: **A,** Duchenne type and Becker type; **B,** Emery-Dreifuss; **C,** limb girdle; **D,** facioscapulohumeral; **E,** distal; and **F,** oculopharyngeal. *(Redrawn from Emery AE: The muscular dystrophies. BMJ 317:991-995, 1998.)*

signs are not usually obvious in the early stage. No correlation has been established between the severity of cardiac disease and the severity of skeletal disease. Studies at necropsy have shown that the cardiomyopathy in DMD involves the posterobasal and contiguous lateral left ventricular walls as initial and primary sites of myocardial dystrophy in the absence of small vessel coronary artery disease in these areas.[33] Typical initial manifestations on the electrocardiogram (ECG) in DMD and BMD are sinus tachycardia, tall R waves in the right precordial leads, prominent left precordial Q waves, increased QT dispersion, and inverted T waves from scarring of the posterobasal portion of the left ventricle. Initially, echocardiography is normal or shows regional wall motion abnormalities in areas of fibrosis. With the spreading of fibrosis, left ventricular dysfunction can be seen and ventricular arrhythmias frequently occur as well. In the final stages of the disease, systolic dysfunction may lead to heart failure and sudden death. Subclinical or clinical cardiac involvement is present in about 90% of DMD/BMD patients, but it is the cause of death in only 20% of DMD and 50% of BMD patients. Angiotensin-converting enzyme inhibitors are recommended in early stages of the disease, and β-blockers may be an additional option if indicated.[32]

Pulmonary insufficiency is a leading cause of morbidity and mortality in DMD.[34] Usually, expiratory muscle function is affected first because of the early onset of abdominal muscle weakness. By contrast, inspiratory muscle function is relatively preserved in the first decade, implying sparing of the diaphragm.[35] Vital capacity (VC) increases in the first decade because of overall body growth, plateaus in early adolescence, and then declines dramatically as the diaphragmatic weakness progresses.[35] Other measured lung volumes such as inspiratory reserve volume and total lung capacity (TLC) follow the same pattern. A disproportionate loss of VC and TLC relative to the respiratory muscle dysfunction results in part from additional factors, such as altered chest wall and lung mechanics, modifications in the distribution of surfactant, micro-atelectasis, and local fibrosis secondary to recurrent pneumonia.[35] Scoliosis further impairs pulmonary function. On average, for each 10 degrees of thoracic scoliosis curvature, forced vital capacity (FVC) decreases by 4%.[30] In 90% of patients, a curvature of greater than 20 degrees develops 3 to 4 years after they are wheelchair bound. Respiratory failure inevitably occurs in the second decade of life and is the most common cause of death.[36]

Diagnosis and Differential Diagnosis. Chronic elevation of the serum CPK level is a general indication of muscle disease. Three serum tests showing elevated CPK levels obtained 1 month apart is diagnostic of muscular dystrophy. CPK represents leakage of enzyme from muscle cells and does not correlate with severity of the disease. CPK could reach 50 to 300 times the normal value in early stages of the disease. The level tends to decrease with the loss of muscle mass. Elevation of the MB fraction of creatine kinase (CK) precludes its use as a marker for cardiac injury.[29] EMG can be supportive of the diagnosis; however, it can be very difficult to perform on children. Muscle biopsy, followed by immunostaining or Western blot analysis for dystrophin, is recommended for diagnostic testing. Multiple polymerase chain reaction is also useful in detecting more than 98% of the existing deletions.[26] The result is usually available within 24 hours, which may render muscle biopsy, the old "gold standard," obsolete.

Anesthetic Considerations. Patients with DMD and BMD may require anesthesia for muscle biopsy, correction of scoliosis, release of contractures, and exploratory laparotomy for ileus,[29] as well as for dental[37] and obstetric[38] procedures. As the natural course of the disease progresses, the risk of surgery increases concomitant with the increased comorbid conditions associated with the later phase of the disease. However, perioperative complications are not proportional to the severity of the disease. They occur even in mildly affected patients. Consequently, patients should undergo careful preoperative consultation and evaluation.

Fifty percent to 70% of patients with muscular dystrophy demonstrate some cardiac abnormality, although it is clinically significant in only 10%.[29] Preoperative cardiology assessment with an ECG and echocardiography is essential. Continuous cardiac Holter monitoring is necessary if an arrhythmia is captured on the ECG or the patient describes symptoms that can be related to cardiac arrhythmias. Echocardiography will demonstrate mitral valve prolapse in 10% to 25% of patients. It may also show posterobasilar hypokinesis in a thin-walled ventricle and a

slow relaxation phase with normal contraction characterizing the cardiomyopathy seen in DMD.[29] However, echocardiography may not always reflect the ability of the diseased myocardium to respond to perioperative stress. Stress echocardiography using angiotensin to detect latent heart failure and identify inducible contraction abnormalities has been advocated.[39]

An estimated 30% of deaths in individuals with DMD are due to respiratory causes.[40] Therefore, careful preoperative pulmonary assessment is important. Webster demonstrated that the manual muscle strength test has a strong statistical correlation with all of the timed functional tests. Peak expiratory flow was not only easy to perform but also correlated statistically with all timed functional tests.[41] The correlation was not significant for VC or forced expiratory volume in 1 second (FEV_1).

Intraoperatively, in terms of airway management, patients with DMD and BMD may have decreased laryngeal reflexes and prolonged gastric emptying time, which increases the risk for aspiration.[42] Decreased ability to cough up the accumulation of oral secretions predisposes muscular dystrophy patients to postoperative respiratory tract infections.[29] Masseter spasm is also a possible complication during induction of anesthesia in these patients.[43] Preparedness for a difficult airway is necessary, especially in patients with potential airway problems.

Postoperatively, DMD patients are at an increased risk for respiratory compromise.[44] Retrospective reviews have indicated that the incidence of prolonged postoperative ventilation (>36 hours) was greatest in DMD patients who had a preoperative FVC of less than 40% of the predicted value.[45,46] Preoperative pulmonary function studies are valuable in determining the postoperative course. Patients with a VC of greater than 30% of the predicted value can usually be extubated immediately after surgery.[29] Sleep apnea may also compound the condition and contribute to the development of pulmonary hypertension. Continuous positive airway pressure and bilevel positive airway pressure have been demonstrated to be effective in the management of postoperative respiratory depression. Delayed pulmonary insufficiency may occur up to 36 hours postoperatively despite the apparent recovery of skeletal muscle strength.[47]

Reports have suggested a relationship between DMD/BMD and MH, but this association is not based on good rational grounds. Whereas the risk for an MH mutation in DMD/BMD patients is similar to that of the general population, the incidence of MH-like anesthetic events has been reported to be 0.002 with DMD and 0.00036 with BMD.[48] Unexplained cardiac arrest[43,49] and acute heart failure[50] have been reported in DMD/BMD patients. Succinylcholine is contraindicated in these patients because of the potential for rhabdomyolysis and hyperkalemia as a result of their unstable sarcolemmal membrane. Succinylcholine-induced hyperkalemia during acute rhabdomyolysis is more likely to result in cardiac arrest and unsuccessful resuscitation than is the potassium efflux resulting from upregulation of acetylcholine receptors in burn patients.[47] The use of nondepolarizing muscle relaxants is usually accompanied by an increase in both maximal effect and duration of action.[51] Narcotics can be used, but small incremental dosing and short-acting medications are recommended given the respiratory depression associated with these medications. Because of reports of inadvertent reactions to volatile anesthetics,[29] TIVA has become more popular.[52] However, consideration needs to be given to the myocardial status of the patient when propofol or barbiturates are used because they may lead to profound hypotension and reduced organ perfusion.[29,53] Regional anesthesia may be a good alternative to general anesthesia in that it avoids the risk of triggering agents and respiratory depression and enables the use of local anesthetics for postoperative analgesia. It may also facilitate chest physiotherapy.[54]

Limb-Girdle Muscular Dystrophy

Limb-girdle muscular dystrophy (LGMD) is a group of disorders with heterogeneous causes. To date, at least 18 genes have been identified as being responsible for this disease, with 7 being autosomal dominant and 11 autosomal recessive.[55] Mutations within the same gene may result in different phenotypes that sometimes are not consistent with LGMD. Proximal muscle (shoulder or pelvic) girdle weakness is the characteristic feature of this group of diseases. Given the marked genetic heterogeneity, clinical manifestations of the disease vary. Autosomal recessive forms are about 10 times more common than autosomal dominant forms. Fukutin-related protein (*FKRP*) and calpain 3 (*CAPN3*) gene mutations have been associated with LGMD. In addition, a number of other disorders not strictly included under LGMD in this classification may have LGMD-like phenotypes.[55] Sporadic cases of LGMD have been reported in the anesthesia literature.[56-58] General approaches to these patients are the same as those for DMD/BMD.

Myotonic Dystrophy

Myotonic dystrophy (MD) is an inherited muscular disorder characterized by progressive muscle weakness and wasting. Two types of MD result from a mutation in either the dystrophia myotonica–protein kinase (*DMPK*) gene, located on chromosome 19q13.3 (MD1, also known as Steinert's disease), or the CysCysHisCys (CCHC)-type zinc finger, nucleic acid binding protein (*CNBP*) gene, located on chromosome 3q21 (MD2).[59] The incidence of MD is 1 in 8000. MD1 is by far the most common of the two types and accounts for about 98% of all cases. MD1 is caused by expansion of a CTG trinucleotide repeat in the *DMPK* gene and is inherited in an autosomal dominant manner.[60] Typical signs and symptoms include muscle weakness and wasting (most prominent in the cranial and distal limb musculature), periodic myotonia, progressive myopathy, insulin resistance, defects in cardiac conduction, neuropsychiatric impairment, cataracts, testicular atrophy, and frontal balding in males. The typical cranial muscle weakness and wasting are manifested not only in the facial, temporalis, masseter, and sternocleidomastoid muscles but also in the vocal cord apparatus. Mitral valve prolapse is found in 20% of patients.[47] The severity of the disease is related to the number of extra trinucleotide repeats.[61] MD1 patients may also have mildly elevated CK levels. Myotonic discharges can be identified on EMG, as well as an inability to relax from a handgrip. During pregnancy, the symptoms may be exacerbated. Uterine atony and retained placenta may also complicate vaginal delivery. First-degree atrioventricular heart block is a common finding on the ECG before the onset of symptoms.[47]

MD2 is also called proximal myotonic myopathy. Intron 1 of the *CNBP* gene contains a complex repeat motif,

(TG)n(TCTG)n(CCTG)n, and expansion of the CCTG repeat was determined as the cause of MD2. Patients with MD2 suffer from myotonia (90% of those affected), muscle dysfunction (82% weakness, pain, and stiffness), and less commonly, cardiac conduction defects, iridescent posterior subcapsular cataracts, insulin-insensitive type 2 diabetes mellitus, and testicular failure.[62]

Anesthetic Considerations. General considerations for MD are similar to those for other muscular dystrophies. Mathieu and coworkers conducted a retrospective study on the anesthetic and surgical complications of MD. The majority of complications were found to be pulmonary related and significantly more frequent in patients undergoing upper abdominal operations and those with severe disability, as assessed by the presence of proximal limb weakness.[63] The pulmonary complications of MD are the result of hypotonia, chronic aspiration, and central and peripheral hypoventilation.[29] Smooth muscle atrophy, which leads to poor gastric motility, when coupled with a diminished cough reflex, promotes aspiration. Succinylcholine will produce contractions lasting for several minutes, thus making intubation and ventilation a challenge. These contractions are not antagonized by nondepolarizing muscle relaxants. Other agents, including methohexital, etomidate, propofol, and even neostigmine, may also induce myotonic reactions. Short-acting nondepolarizing muscle relaxants or avoidance of relaxation is therefore advised.[29] Triggering factors, such as hypothermia, shivering, and mechanical or electrical stimulation, may cause a myotonic reaction.[64] The reaction can be treated with phenytoin (4 to 6 mg/kg/day) or quinine (0.3 to 1.5 g/day).[29] Furthermore, MD patients can be very sensitive to anesthetic agents, with hypersomnolence and CO_2 retention sometimes being observed. Careful titration with relatively short-acting anesthetic agents may be beneficial. Close cardiac monitoring is required for MD patients. Pacing equipments should be readily available because a third of first-degree atrioventricular blocks may not respond to atropine.[29] All patients should be treated as though they have both cardiomyopathy and conduction defects.

Myotonia Congenita

Myotonia congenita (MC) is a congenital form of muscular dystrophy characterized by uncontrolled temporary skeleton muscle excitability as a result of mutations in the muscle chloride channel gene (*CLCN1*). There are two forms of MC, one with autosomal dominant and the other with recessive inheritance. The former is also known as Thomsen's disease and the later as Becker's myotonia. The myotonia in MC patients is usually initiated by a forceful muscle contraction, particularly after rest for at least 10 minutes. The myotonic muscle stiffness then becomes increasingly obvious after a second and third short, but forceful contraction. Further contractions usually dampen the myotonia.[65]

Thomsen's disease was the first myotonic disease to be described. Patients may have a hypertrophic and athletic appearance. The sign of percussion myotonia is described as an indenting-appearing myotonia triggered by tapping the muscle. Lid lag is common and muscle stretch reflexes are normal.[65] Myotonia symptoms in Becker's myotonia usually start at 10 to 14 years of age or even later and are more severe than those of Thomsen's disease. Becker's myotonia may be associated with severe generalized stiffness resulting in falling. It can frequently be misdiagnosed as epilepsy. Antiepileptic medications do improve the symptoms, however.[65]

Anesthetic Considerations. As with many muscle diseases, there have been reports that MC patients are predisposed to MH, but as is the case for almost all of them, there are no data to support this hypothesis.[66-68] However, depolarizing muscle relaxant can lead to severe masseter spasm in MC patients. Generalized spasm involving the respiratory and skeletal muscles has been reported.[66] The findings resemble those of MH, so dantrolene is sometimes administered.[65] Because dantrolene is an inhibitor of calcium release from the sarcoplasmic reticulum (SR), it can usually abolish the myotonia effectively.[66,67] Some believe that local anesthetics and class Ib antiarrhythmic drugs such as lidocaine should be used for myotonic reactions rather than dantrolene.[69] Because shivering in the operating room can trigger the myotonic reaction, MC patients should be kept normothermic during surgery.[65]

Myotubular Myopathy

Myotubular myopathy (MTM) is pathologically defined by the presence of centrally placed nuclei in the majority of extrafusal muscle fibers, an appearance resembling fetal myotubes during normal muscle development. Consequently, MTM is also called centronuclear myopathy (CNM).[70] However, MTM now mostly refers to the X-linked form of the disease, whereas CNM is used for the autosomal form.[70]

MTM and CNM are rare. The estimated incidence of MTM is 1 in 50,000 newborn males.[70] MTM has been linked to the myotubularin (*MTM1*) gene on Xq28. Pregnancy is often complicated by polyhydramnios and reduced fetal movements. Affected males typically have severe floppiness and weakness and respiratory distress at birth. Cardiac muscles are not generally involved. The patient usually has a normal response to pain, but tendon reflexes are absent. The long-term prognosis for MTM is extremely poor.[70] In patients who survive the first year of life, most are either completely or partially ventilator dependent.[71] These patients often have abnormal liver function.[71] Both autosomal recessive and autosomal dominant forms have been observed in CNM patients. Its clinical features include respiratory distress, hypotonia, bulbar weakness, ophthalmoplegia, ptosis, and facial diplegia. Although the exact genetic mechanism is not fully understood, the *MTM1*, myotubularin-related protein (*MTMR2*), and myotubularin-related phosphatase (*MTMR3*) genes have been implicated.[70] Pathologically, MTM and CNM share a similar characteristic histologic feature: predominantly type 1 fiber with centrally placed nuclei seen on hematoxylin-eosin staining of formalin-fixed, paraffin-embedded tissue.[70]

Anesthetic Considerations. Reports of anesthesia for patients with MTM are sparse.[72-77] Nontriggering general anesthesia has been used because of the unfounded concern of possible susceptibility to MH. Agents such as propofol, fentanyl, remifentanil, and nitrous oxide have been used successfully without adverse effects.[72-77] The possibility of a prolonged effect of nondepolarizing muscle relaxants has been suggested with mechanomyography.[72-77] However, in reality, intubation of such patients may not require any muscle relaxant because of their hypotonic state. Costi and van der Walt suspected that the defect in MTM

is distal to the neuromuscular junction,[73] whereas Dorchies and coworkers suggested that muscle in MTM might be intrinsically normal, with myotubularin-deficient motor neurons involved in development of the disease.[78]

Metabolic Myopathies

Two major energy sources for muscle exist: glycogen and fatty acid. Glycogen serves as a dynamic, but limited reservoir of glucose, mainly stored in skeletal muscle and liver. Glycogen storage disorders (GSDs) are a group of metabolism disorders caused by enzyme deficiency or dysfunction. They reduce effective glucose storage by interfering with normal glycogen synthesis and degradation. Synthetic errors cause decreased normal glycogen, whereas degradation errors tend to block the breakdown of glycogen. Subsequently, hypoglycemia and accumulation of glycogen in tissues could occur as a result of substrate use. There are more than 12 types of GSD that are assigned Roman numerals based on the enzyme deficiencies. Types I and II are discussed here.

Glycogen Storage Disease Type I

The incidence of GSD I is approximately 1 in 100,000 live newborns.[79] The incidence in non-Ashkenazi Jews from North Africa may be as high as 1 in 5420 people.[79] The defective enzyme causing the disease is glucose-6-phosphatase, which is the enzyme that converts glucose 6-phosphate (G6P) to glucose in the liver. Type Ia (von Gierke's disease) is due to a deficiency in G6P hydrolase (catalytic subunit) activity and accounts for more than 80% of cases. Types Ib (G6P transporter deficiency), Ic, and Id represent allelic defects in the translocase associated with G6P. Their inheritance is autosomal recessive. The G6P gene (*G6PC*) encoding the hydrolase resides at 17q21, with the gene encoding G6P translocase (*G6PT*) located at 11q23. Mutations responsible for GSD I have been described in both type Ia and Ib patients.[79]

Impaired glycogenolysis results in accumulation of glycogen and G6P in the liver, kidney, intestine, skeletal muscle, and heart and is manifested as hepatomegaly, renomegaly, proximal tubular dysfunction, and diarrhea.[80] Fasting hypoglycemia is the initial manifestation of the disease. As a result, upregulation of the synthesis and transport of counter-regulatory hormones, such as glucagon, cortisol, catecholamines, and growth hormone, becomes obvious and leads to the release of pyruvate, lactate, and free fatty acid. Lipid deposition in lean tissues such as the liver, skeletal muscle, cardiac muscle, and pancreas results in lipotoxicity and organ failure, including pulmonary hypertension, steatohepatitis, end-stage renal disease, insulin resistance, cardiac contractile dysfunction, and pancreatic beta cell failure.[79] For type Ib disease, specific problems such as neutropenia and neutrophil dysfunction are prominent. Patients may have recurrent infections and inflammatory bowel disease.[81]

Anesthesia Considerations. Anesthesia case reports for GSD I patients are rare.[82,83] Patients with GSD I diseases should be given intravenous glucose-containing fluid preoperatively when they have fasted. Lactate-containing solutions should be avoided because these patients are not able to convert the lactic acid to glycogen.[29] Patients need to be monitored frequently to avoid hypoglycemia.

Glycogen Storage Disease Type II (Acid Maltase Deficiency)

The incidence of acid maltase deficiency (AMD) is estimated to be 1 in every 14,000 to 40,000 births. Its inheritance is autosomal recessive with a few exceptions.[84,85] Mutations of the acid maltase gene on chromosome 17q25 cause deficiency of lysosomal acid maltase (acid α-1,4-glucosidase).[85] Cases of AMD have been arbitrarily classified into three groups—infantile, childhood, and adult—according to the age at onset or death, rate of progression, and tissue-organ involvement.[85]

Acid maltase is a lysosomal enzyme that catalyzes the one-way hydrogenation of glycogen to G6P and is found in all tissues, including skeletal and cardiac muscle.[86] Consequently, glycogen accumulates within the muscle tissues of maltase-deficient patients. Infantile AMD, also known as Pompe's disease, is usually manifested within the first few months of life as rapidly progressive weakness and hypotonia and enlargement of the tongue, heart, and liver. Massive amounts of glycogen (8% to 15% of the wet weight of the tissue) accumulate in the heart, liver, and skeletal muscle, with relatively smaller deposits in smooth muscle, eyes, kidneys, endothelial cells, lymphocytes, brain, and spinal cord. Accumulation of glycogen in cardiac muscle leads to cardiac failure in the infantile form.[85] Echocardiography demonstrates marked thickening of the interventricular septum and posterior left ventricular wall, left ventricular outflow obstruction, and trabecular hypertrophy.[85] Ventricular wall thickness may be increased to up to 25 mm.[87] Wolff-Parkinson-White syndrome has been reported.[88] The signs and symptoms of infantile AMD may resemble those of DMD. Death usually results from cardiorespiratory decompensation within several years of disease progression.[89]

Childhood AMD occurs in infancy to early childhood and is manifested by clinical signs of myopathy. Respiratory muscles tend to be selectively affected. Calf enlargement can also occur. The disease progresses relatively slowly in this form, with a few patients surviving beyond the second decade of life.[85] Tongue, heart, and liver enlargement occur infrequently.[90] However, involvement of vascular smooth muscle is more severe than in the infantile form. There has been a report of extensive glycogen deposition in the arterial wall causing basilar aneurysms.[90]

Adult AMD usually occurs after age 20 and is characterized by slow progressive myopathy or symptoms of respiratory failure.[85] The weakness in proximal muscles is more prominent than the weakness in distal muscles. A third of adult AMD patients suffer from respiratory failure with a restrictive pattern. Weakness in the diaphragm causes extensive atelectasis. VC may be significantly reduced.[85]

Anesthetic Considerations. Anesthesia reports in AMD patients are rare.[91-94] Isolated intraoperative cardiac arrest during halothane anesthesia in infantile AMD has been documented.[94] Despite the problem noted with halothane, enflurane[92] and sevoflurane[93] have been used without complications. Theoretically, total intravenous general anesthesia with propofol may cause a reduction in afterload leading to an increased risk for

myocardial ischemia. This may become significant when the patient is tachycardic.[93]

Subendocardial ischemia may occur in patients with a thickened ventricular wall and result in higher left ventricular end-diastolic pressure at lower ventricular volume.[93,95] Close cardiac monitoring is therefore necessary. A central venous or pulmonary artery catheter is not essential in patients who are normovolemic without preexisting heart failure.[93] Adequate filling pressure and normal to high systemic vascular resistance (SVR) are required to ensure effective coronary perfusion.[93] Ketamine has been used successfully in a number of cases because of its ability to maintain SVR and contractility. Respiratory failure and muscle weakness are the other concerns for anesthesiologists. A spectrum of uses of muscle relaxants from none[92] to atracurium[91] to rocuronium[93] have been attempted. Low-dose rocuronium, 0.5 mg/kg, with close monitoring of neuromuscular function and adequate use of reversal agents, has been sufficient to prevent prolonged postoperative weakness.[93] Depolarizing agents should be avoided because of the potential risk of hyperkalemia and rhabdomyolysis.[93,94]

Mitochondrial Myopathies

Mitochondrial diseases refer to defects in the five main steps of mitochondrial metabolism: substrate transport, substrate utilization, the Krebs cycle, the electron transport chain, and oxidation-phosphorylation coupling.[96] However, the term *mitochondrial myopathy* has been reserved for disorders caused by defects in the respiratory chain.[96] The respiratory chain is composed of five multimeric complexes (I to V) embedded in the inner mitochondrial membrane, plus two small mobile electron carriers, coenzyme Q_{10} (CoQ_{10}) and cytochrome *c*, for a total of more than 80 proteins,[96] among which 13 are encoded by mitochondrial DNA (mtDNA) and all others by nuclear DNA (nDNA). mtDNA is different from nDNA in several aspects: (1) mtDNA is circular and contains no intron, (2) it has larger numbers of copies than nDNA does and a much higher spontaneous mutation rate, and (3) its inheritance is maternal. Diagnosis of mitochondrial diseases is difficult because of their clinical heterogeneity.

Primary mtDNA mutations may include point mutations in polypeptide, tRNA, or rRNA encoding regions and large-scale rearrangements, duplications, or deletions.[97] Some of the common conditions caused by point mutations include myoclonic epilepsy with ragged-red fibers (MERRF); mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); neuropathy, ataxia, and retinitis pigmentosa (NARP); maternally inherited Leigh's syndrome; and Leber's hereditary optic neuropathy (LHON).[96] Sporadic large-scale mutations may lead to Kearns-Sayre syndrome, progressive external ophthalmoplegia, and Pearson's syndrome.[96] nDNA mutations can cause deficiencies in complexes I to IV and CoQ_{10} of the electron transport chain.[96]

Mitochondrial myopathy is estimated to have an incidence of 1 in 4000.[98] Among all the mitochondrial functions, abnormalities in electron transport and oxidative phosphorylation are the most common causes of mitochondrial myopathies.[99] Mitochondrial myopathies are characterized by proximal muscle weakness with increased lactic acid and positive muscle biopsy for mitochondrial cytopathy.[100] The hallmark of mitochondrial myopathies is the "ragged red fiber" when muscle biopsy specimens are stained with modified Gomori trichrome stain,[101] and specific defects in the activity of these enzymes have been demonstrated in patients with mitochondrial disease.[102] Fatigue and poor stamina are prominent clinical features. Movement disorders such as ataxia, dystonia, myoclonus, chorea, athetosis, and tremors have also been described as being due to mitochondrial abnormalities.[102]

Anesthetic Considerations

Preoperative Evaluation. Given the heterogeneous types of mitochondrial disease, patients with mitochondrial disease will need a comprehensive preoperative evaluation with a particular focus on neurologic, cardiac, respiratory, musculoskeletal, endocrinopathic, and metabolic compromise (also see Chapters 34 and 35). An ECG and echocardiogram should be considered in patients with signs and symptoms of cardiomyopathy or conduction defects (or both). Although normal lactate and glucose levels cannot rule out mitochondrial diseases, laboratory studies consisting of glucose, electrolytes with anion gap, complete blood count, blood urea nitrogen, lactate, pyruvate, ammonia, CK, biotinidase, acyl carnitines, and blood and urine amino and organic acids could be used as initial investigation for suspected mitochondrial disorders.[103] Further workup should include an erythrocyte sedimentation rate, glycosylated hemoglobin (HbA_{1C}), liver and renal profiles, thyroid function tests, arterial blood gas, and urinanalysis.[98,102] Multidisciplinary consultation with special laboratory and imaging studies may be required.[102]

Induction and Maintenance of Anesthesia. Anesthesia has a significant impact on mitochondrial function. Both barbiturates and propofol inhibit complex I of the electron transport chain.[103] Local anesthetics have been demonstrated to disrupt oxidative phosphorylation and decrease the bioenergetic capacity of mitochondria.[103] Sensitivity to intravenous barbiturates and etomidate has been reported.[104,105] However, midazolam,[106] thiopental,[107] propofol,[108,109] remifentanil,[110] and ketamine[109] have all been used safely. Premedication should avoid respiratory depression caused by impaired respiratory responses to hypoxemia. Volatile agents such as halothane, isoflurane, and sevoflurane have been shown to inhibit complex I.[103] This direct inhibition of mitochondrial electron transport system enzymes and altered mitochondrial bioenergetics in the heart were thought to be the mechanism of cardiac preconditioning by volatile anesthetics.[111,112] Inhaled sevoflurane has been widely used for induction because of its low pungency.[100] In some cases, halothane[106] and isoflurane[106,113] have also been used. Isoflurane has been recommended as the agent of choice in patients with Kearns-Sayre syndrome because rhythm disturbances have been reported with halothane in such patients.[106,113] In addition, artificial pacing capability is recommended when dealing with this specific subset of patients.[100] With use of the bispectral index, higher sensitivity to volatile agents has been suggested in children with mitochondrial diseases, especially with dysfunction of complex I.[114] However, its methodology has been criticized.[115] A decreased minimum alveolar concentration of halothane in patients with mental retardation has also been reported.[116]

Despite no real evidence and the fact that volatile anesthetics are frequently the anesthetic of choice when muscle relaxants are considered, several papers have expressed concern that these myopathies are associated with increased sensitivity to MH. This conclusion is not supported by any data. Increased sensitivity to

nondepolarizing muscle relaxants has been documented for mivacurium,[117] atracurium,[118] and rocuronium.[118,119] In contrast, normal responses to depolarizing and nondepolarizing neuromuscular blockers such as pancuronium,[120] vecuronium,[121] and atracurium[108,122] are also reported. Although muscle relaxants are not absolutely contraindicated based on current literature and research, it is necessary for anesthesia practitioners to administer depolarizing or nondepolarizing neuromuscular blockers with caution to patients with mitochondrial diseases and to use neuromuscular monitoring (see Chapter 47).[98]

Nonsteroidal anti-inflammatory drugs[100] and regional techniques consisting of local,[100,123] spinal,[124] and epidural administration have been reported. However, it is suggested that regional anesthesia be performed when neurologic abnormalities of the spinal cord and peripheral nerves have definitely been ruled out.[124] Importantly, coagulation function should be assessed because of the possibility of hepatic dysfunction.[100]

Opioids should be used with caution because of the increased risk for respiratory depression and their potential to induce respiratory acidosis in addition to the underlying metabolic acidosis.[100] Because patients with mitochondrial diseases have dysfunctional aerobic metabolism, any increase in the basic metabolic rate should be prevented.[102] Shivering, hypoxia, fasting, and hypotension in such patients may exacerbate the lactic acidosis and should therefore be avoided.[125] Finally, the increased postoperative infection rate in patients with mitochondrial diseases may be due to low hepatic mitochondrial activity, phagocytosis by Kupffer cells, and decreased activity of the reticuloendothelial system.[126]

Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction. Autoantibodies against the α-subunit of the muscle-type nicotinic acetylcholine receptor destroy acetylcholine receptors of the neuromuscular junction and cause classic transmission failure with muscle weakness and fatigue. Sparing of other α-subunits of neuronal-type nicotinic acetylcholine receptors provides an explanation for the lack of autonomic or CNS involvement of the disease. The incidence of MG varies between geographic regions, being 1.2 per million in Japan and about 14 per 100,000 in some areas of the United States.[127,128] In younger age groups, females are affected more often than males are, whereas in elderly age groups (>60 years), males are more frequently affected.

There is a striking association between MG and hyperplasia of the thymus, with more than 70% of MG patients having thymus hyperplasia and 10% having thymomas.[128] MG may also be seen as a part of a paraneoplastic syndrome.[128]

Typically, patients first report bulbar symptoms consisting of diplopia and ptosis. The bulbar symptoms are often followed by unevenly distributed muscle weakness and fatigue of the extremities and face. Speech and chewing may be affected, as well as pharyngeal function and coordination of swallowing, with a subsequent increased frequency of aspiration of oral contents. The muscle weakness is often exacerbated during exercise and throughout the course of the day. Apart from the patchy distribution of muscle weakness, symptoms may also vary from day to day, and there may be periods of remission of varying duration.

The diagnosis of MG is made by neurologic examination and testing of the tendency to fatigue and exhibit increased weakness during exercise or repeated contractions. The diagnosis can be confirmed by the Tensilon test (administration of an anticholinesterase, e.g., edrophonium). Improvement is usually seen within 5 minutes after administration of the drug and lasts for about 10 minutes. In addition, electrophysiologic evaluation is often performed and shows a classic decrement in the compound muscle action potential after repetitive nerve stimulation.

Anesthetic Considerations. Ideally, careful neurologic consultation in addition to preoperative evaluation should be performed on MG patients with the aim of optimizing drug therapy and preparing for postoperative care. Pulmonary function tests may be indicated to determine the need for mechanical ventilation postoperatively.[117] As a general rule, patients should keep taking their anticholinesterase medication and be informed about the possibility of postoperative ventilator support. Succinylcholine can be used if needed for rapid tracheal intubation. However, patients with MG might need larger than normal doses (1.5 to 2.0 mg/kg body weight) because of the decreased number of functional acetylcholine receptors.[129] On the other hand, as a result of the decrease in cholinesterase activity achieved by anticholinesterase treatment, neuromuscular blocks with succinylcholine or mivacurium are frequently prolonged.[130,131] Nondepolarizing neuromuscular blockers can be used in patients with MG but should be given with caution because their effects are highly unpredictable and the distribution of muscle weakness is often uneven. Consequently, monitoring of neuromuscular function with a peripheral nerve stimulator is not always reliable in MG patients, and dosing of any nondepolarizing muscle relaxant should be increased in small increments corresponding to 0.1 to 0.2 times the 95% effective dose (ED_{95}) until the desired neuromuscular blocking effect is achieved. Perioperative anticholinesterase treatment will modify the response to reversal agents because of the already existing acetylcholinesterase block, and in some cases, recovery of neuromuscular function after the administration of a reversal agent has been reported to be prolonged.[132]

Potent volatile anesthetics have been used successfully in MG patients. Because of the impaired margin of safety at the neuromuscular junction, a volatile anesthetic usually provides adequate muscular paralysis to allow most surgical procedures to be performed without the need for a neuromuscular blocking agent. Epidural and spinal anesthesia can be used in MG patients, provided that muscle function and ventilation are carefully monitored perioperatively, as for general anesthesia. For a more detailed review, see Baraka[133] and Abel and Eisenkraft.[134]

Eaton-Lambert Myasthenic Syndrome

Eaton-Lambert myasthenic syndrome (ELMS) is an immune-mediated channelopathy caused by decreased release of acetylcholine as a result of autoantibodies against presynaptic voltage-gated calcium channels and other presynaptic elements.[135] Patients with ELMS have muscle weakness and fatigability, generally of the proximal limb muscles, with the lower extremities affected more often than the extraocular and bulbar muscle

groups. The syndrome is frequently part of a paraneoplastic phenomenon, usually combined with small cell lung carcinoma. Unlike MG, patients with ELMS are usually worse in the morning with gradual improvement throughout the day. Improvement of muscle function with exercise is due to the accumulation of presynaptic calcium and subsequent improved release of acetylcholine.[136] A minority of patients exhibit autonomic dysfunction. The diagnosis of ELMS is made by careful physical examination combined with clinical electrophysiology showing the typical facilitation of motor action potential with high-frequency nerve stimulation (30 to 50 Hz). Anticholinesterase treatment has little effect on patients with ELMS. Plasmapheresis, immunoglobulin therapy, and 3,4-diaminopyridine (DAP) result in transient improvement.

Anesthetic Considerations. As in patients with MG, those with ELMS should be carefully evaluated for the risk of postoperative respiratory failure and the need for prolonged respiratory monitoring in the postoperative period. Sensitivity to depolarizing and nondepolarizing neuromuscular blocking agents is usually increased. In patients treated with DAP or an anticholinesterase agent, reversal of neuromuscular blockade may be ineffective.

Periodic Paralysis (Hyperkalemic and Hypokalemic)

Hyperkalemic periodic paralysis (HyperPP) is an autosomal dominant disorder first described by Tyler and associates in 1951.[65] It is characterized by attacks of flaccid weakness associated with increased serum potassium.[137] A potassium-rich meal or rest after strenuous exercise may precipitate an attack. Stressful situations may also provoke the onset of paralysis. The paralysis may last for 15 minutes to an hour, with decreased tendon reflexes. In the interictal state, HyperPP is usually associated with mild myotonia that does not impede voluntary movements.[65]

The pathogenesis of HyperPP involves mutations in the voltage-gated sodium channel NaV1.4 of mature muscle fibers; such mutations lead to pathologically increased sodium current and an increased tendency of the muscle fiber to become depolarized.[65,137] Influx of sodium into the muscle is accompanied by simultaneous efflux of potassium and hyperkalemia. Mutant channels exhibit sustained sodium currents that lead to prolonged membrane depolarization, causing myotonia followed by membrane desensitization (or inactivation) and resulting in paralysis. In HyperPP patients, serum CK can be elevated, sometimes 5 to 10 times above the normal limit, whereas serum sodium and potassium levels are normal in the interictal state.[65]

Hypokalemic periodic paralysis (HypoPP) is characterized by a decrease in potassium levels in blood. Attacks of HypoPP can be triggered by rigorous exercise, stress, high-carbohydrate or high-salt meals, pregnancy, menstruation, hypothermia, or drugs such as insulin.[138,139] EMG does not usually show myotonia.[137] The severity of attacks is usually greater than those occurring in patients with HyperPP. HypoPP is an autosomal dominant disease with higher penetration in males. The disease is due to loss of function of one of the two different ion channel types: CaV1.1 and NaV1.4.[137] The most common muscle groups affected are those in the arms and legs; however, the disorder can also affect swallowing and respiratory muscles, which can be fatal in severe cases.[140] The diagnosis of HypoPP is made by laboratory testing demonstrating hypokalemia during attacks and normokalemia between attacks.

Anesthetic Considerations. Potassium, cholinesterase inhibitors, and depolarizing muscle relaxants will aggravate the myotonia in HyperPP patients.[65] Prolonged muscle weakness has been reported when succinylcholine is used.[141] Although one third of patients had no signs of myotonia,[142] masseter spasm and respiratory and skeletal muscles stiffness could still occur during intubation and ventilation.[65] Therefore, neostigmine and succinylcholine should be contraindicated in HyperPP patients. Ideally, all patients with HyperPP need to be admitted preoperatively so that proper preoperative fasting can be accompanied by the administration of dextrose-containing potassium-free maintenance fluid.[143] Postoperatively, HyperPP patients may remain paralyzed for up to several hours. Preventive measures such as maintaining normal body temperature and low serum potassium levels and avoiding hypoglycemia are helpful in limiting such paralysis.[144] Although patients with sodium channel pathology have often been considered to be susceptible to MH, there is no increased risk for MH in these patients.[145] General anesthesia with and without nondepolarizing muscle relaxants has been shown to have satisfactory outcomes.[141,143,144,146] Regional techniques may also be appropriate for this patient group.[142,146] Abortion of the hyperkalemic attack may be accomplished by administering glucose, insulin, epinephrine, and calcium supplements, or alternatively, glucagon may be used. β-Adrenergic treatment with metaproterenol has also been shown to prevent attacks and facilitate recovery.[143]

Management of HypoPP patients should focus on avoiding triggers and medications causing shift of potassium. General anesthesia, postoperative stress, glucose-containing intravenous solutions, and long-acting neuromuscular blockers are associated with postoperative paralytic events.[138] Epidural analgesia has been shown to reduce both pain-related hyperventilation and serum catecholamines, thereby minimizing changes in serum potassium levels.[138] The sympathomimetic effect of epinephrine-containing local anesthetics may also precipitate hypokalemia.[138]

Malignant Hyperthermia

MH is a pharmacogenetic clinical syndrome that in its classic form occurs during anesthesia with a volatile halogenated alkane such as halothane and the depolarizing muscle relaxant succinylcholine. Clinical MH produces rapidly increasing body temperature (by as much as 1°C/5 min) and extreme acidosis as a result of acute loss of control of intracellular calcium levels and compensatory uncontrolled increases in skeletal muscle metabolism that may proceed to severe rhabdomyolysis. Although MH was initially associated with a mortality rate of 70%, earlier diagnosis and the use of dantrolene have reduced the mortality to less than 5%. Current cases of MH are restricted in severity because of diagnostic awareness, early detection through end-expired carbon dioxide, use of less potent anesthetic triggers, and administration of drugs that attenuate its progression. Wilson and colleagues[147] first used the term *malignant hyperthermia* in print in 1966. A Danish survey[148] reported an incidence of fulminant MH of one case per 62,000 anesthetics administered when triggering agents

were not used, but the number of suspected cases was one per 4500 anesthetics administered when triggering agents were administered. Public education and communication in the United States are provided by a layman's organization, Malignant Hyperthermia Association of the United States (MHAUS, 11 E. State Street, P.O. Box 1069, Sherburne, NY 13460-1069; telephone: 1-607-674-7901; fax: 1-607-674-7910; e-mail: info@mhaus.org; website: www.mhaus.org), and by emergency consultation with the MH Hotline (1-800-MHHYPER, or 1-800-644-9737). The North American MH Registry, a professional subsidiary of MHAUS, collates findings from muscle biopsy centers in Canada and the United States and provides access to specific patient data through the hotline or its director Dr. Barbara Brandom (North American MH Registry of MHAUS, Room 7449, Department of Anesthesiology, Children's Hospital, University of Pittsburgh, 3705 Fifth Avenue at DeSoto St., Pittsburgh, PA, 15213-2583; telephone: 1-888-274-7899; fax: 1-412-692-8658; e-mail: bwb@pitt.edu).

Between 50% and 80% of genotyped patients who have had a clinical MH syndrome and a positive muscle biopsy have had their disease linked to 1 of more than 110 mutations in the type 1 ryanodine receptor (RyR1; SR Ca^{2+} release channel) gene and 2 mutations in the L-type Ca^{2+} channel CaV1.1.[149] The genetics of MH and the related abnormal function of RyR1, the dihydropyridine receptor (DHPR), and associated proteins are being investigated at the molecular biologic level, with a porcine model and several new mouse models providing intricate details about the etiology of the disorder. Parallel studies in humans are limited by scarce material for scientific study and are complicated by the fact that phenotypes within a genotype vary as a result of genetic, epigenetic, and environmental modifiers. In vitro muscle biopsy testing remains the only "approved" stand-alone screening test currently available in the United States and elsewhere.

History

Between 1915 and 1925, one family experienced three anesthetic-induced MH deaths with rigidity and hyperthermia and was puzzled for decades regarding the cause of these deaths. MH susceptibility (MHS) was eventually confirmed in three descendants by in vitro muscle biopsy tests.[150] In 1929, Ombrédanne[151] described anesthesia-induced postoperative hyperthermia and pallor in children accompanied by significant mortality but did not detect any familial relationships. Critical worldwide attention to MH began in 1960, when Denborough and Lovell[152] reported a 21-year-old Australian with an open leg fracture who was more anxious about anesthesia than about surgery because 10 of his relatives had died during or after anesthesia. Lovell initially anesthetized him with the then-new agent halothane, halted it when signs of MH appeared, successfully treated the symptoms and aborted the syndrome, and subsequently used spinal anesthesia. Further evaluations by George Locher in Wausau, Wisconsin, and Beverly Britt in Toronto, Canada, led to the discovery that MH risk was indeed familial.[153] It was also found that the cause of the syndrome was the result of skeletal muscle involvement rather than central loss of temperature control by the recognition of increased muscle metabolism or muscle rigidity early in the syndrome, low-threshold contracture responses, and elevated CK values.[154]

Interestingly, a similar syndrome was discovered in swine inbred with breeding patterns designed to produce a rapid growth rate and superior muscle development (e.g., Landrace, Pietrain, Duroc, Poland, China). *Porcine stress syndrome*,[155] which is associated with increased metabolism, acidosis, rigidity, fever, and death from rapid deterioration of muscle and results in pale, soft, exudative pork,[156] can be triggered by any stress, such as separation, shipping conditions, weaning, fighting, coitus, or preparation for slaughter, and had become a significant problem for meat production. In 1966, Hall and coworkers[157] reported that a syndrome that appeared to be identical to MH could be induced in stress-susceptible swine by the administration of halothane and succinylcholine. The cause of this syndrome in pigs was discovered to be a single missense mutation in *RYR1*, and all susceptible swine have the same Arg615Cys mutation in the SR calcium release channel RyR1.[158]

In 1975, Harrison[159] described the efficacy of dantrolene in preventing and treating porcine MH, which was rapidly confirmed in humans by a multihospital evaluation of dantrolene used to treat anesthetic-induced episodes.[160] Today, dantrolene still remains the primary basis for successful MH therapy.

Physiology and Pathophysiology of Excitation-Contraction Coupling and Malignant Hyperthermia

MH is a syndrome caused by dysregulation of excitation-contraction (EC) coupling in skeletal muscle. Normal muscle contraction is initiated by nerve impulses arriving at the neuromuscular junction (i.e., the motor end plate) that trigger the release of acetylcholine from the nerve terminal. Acetylcholine activates cation channels on the muscle membrane essential for initiating action potentials that propagate rapidly along the surface membrane of the muscle. Invaginations of the surface membrane (transverse or T tubules) act as conduits to rapidly and uniformly direct action potentials deep within the myofibrils, where they are transduced by a "voltage sensor," the slow voltage-gated Ca^{2+} channels (DHPRs). In response to membrane depolarization, the voltage sensor then undergoes a conformational change that is mechanically transmitted to the Ca^{2+} release channels (RyR1) concentrated in the junctional face of the SR. The mechanical coupling of DHPRs and RyR1 channels that occurs at specialized junctions (*triadic junctions*) is essential for initiating release of Ca^{2+} stored within the SR. Release of SR Ca^{2+} causes the free, intracellular Ca^{2+} concentration to increase from 10^{-7} to about 10^{-5} M. The Ca^{2+} binds to proteins (troponin C and tropomyosin) in the thin filament to expose the myosin binding sites on actin that activate the thick filament (myosin) and cause muscle contraction. The whole process is called EC coupling. Intracellular Ca^{2+} pumps (i.e., sarcoplasmic/endoplasmic reticulum Ca^{2+}-adenosine triphosphatase [ATPase], or SERCA pumps) rapidly propel Ca^{2+} actively back into the SR, and muscle relaxation begins when the Ca^{2+} concentration falls below 10^{-6} M and ends when the resting myoplasmic Ca^{2+} concentration is restored to 10^{-7} M. Because both contraction and relaxation are energy-related processes that consume adenosine triphosphate (ATP), knowing the molecular events contributing to EC coupling and the associated relaxation is essential to understanding the cause of MH (Fig. 37-3). Clinical and laboratory data from swine and

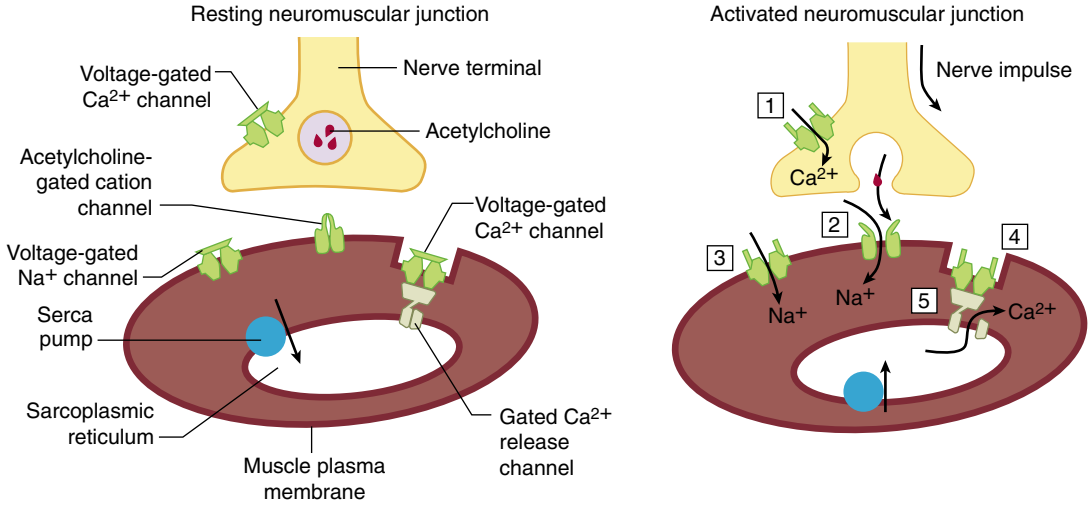

Figure 37-3 Key ion channels involved in neuromuscular transmission and excitation-contraction coupling. Nerve impulses arriving at the nerve terminal activate voltage-gated Ca^{2+} channels (1). The resulting increase in cytoplasmic Ca^{2+} concentration is essential for the exocytosis of acetylcholine. Binding of acetylcholine to postsynaptic nicotinic cholinergic receptors activates an integral nonselective cation channel that depolarizes the sarcolemmal membrane (2). Depolarizing the sarcolemma to threshold activates voltage-gated Na^+ channels (3), which propagate action potential impulses deep into the muscle through the transverse tubule system. Within the transverse tubule system, L-type voltage-gated Ca^{2+} channels sense membrane depolarization and undergo a conformational change (4). A physical link between the α_1-subunit and the ryanodine receptor is thought to be the means by which the signal is transferred to the sarcoplasmic reticulum to induce the release of stored Ca^{2+} (5). *(Adapted from Alberts B, Bray D, Lewis J, et al: Molecular Biology of the Cell, 3rd ed. New York, Garland Press, 1994.)*

humans indicate that the fulminant MH syndrome is associated with a persistent increase in intracellular Ca^{2+}.[161-164] The increased activity of pumps and exchangers trying to correct the increase in Ca^{2+} causes a need for ATP, which in turn produces heat. Thus, the end result is hyperthermia. The rigidity that is frequently seen during a fulminant MH episode is the result of the inability of the Ca^{2+} pumps and transporters to reduce the unbound myoplasmic Ca^{2+} below the contractile threshold. Dantrolene is therapeutic because it reduces the concentration of myoplasmic Ca^{2+}. However, the pathway by which dantrolene lowers myoplasmic Ca^{2+} is complex and still not fully understood.

Malignant Hyperthermia Is the Result of Abnormal Function of Muscle Calcium Release Units

Ryanodine receptors (RyRs), which in muscle are synonymous with the junctional foot protein/SR calcium release channel, are so named because they specifically bind the toxic plant alkaloid ryanodine.[165,166] There are three RyR isoforms encoded by three genes located on human chromosomes 19q13.1, 1q42.1-q43, and 15q14-q15, the "skeletal" (RyR1), "cardiac" (RyR2), and "brain" (RyR3) isoforms, respectively. Each functional RyR consists of four identical subunits (≈5000 amino acids each), and each subunit binds with an accessory protein, calstabin 1 (FK506 12-kd binding protein [FKBP12]). The total mass of the tetramer exceeds 2 megadaltons. Thus, it is one of the largest known proteins and the largest known channel in mammalian species. Evidence of direct coupling of CaV1.1 and RyR1 has been demonstrated by expressing chimeric CaV1.1/CaV1.2 cDNA dysgenic myotubes that lack constitutive expression of either Ca^{2+} channel protein.[167,168] Such studies have provided compelling evidence that the cytoplasmic region between repeats II and III (i.e., cytosolic II-III loop) contains a stretch of 46 amino acids (L720 to Q765) that are essential for engaging bidirectional signaling with RyR1.[169]

In the last 5 years our understanding of EC coupling has increased significantly by identifying protein-protein interactions that regulate both the release and sequestration of Ca^{2+} within skeletal muscle. The elemental unit of function has been named the Ca^{2+} release unit (CRU), and it is localized within junctional regions of T-tubule and SR membranes.[170] The CRU is a macromolecular assembly of interacting proteins that participate in tightly regulating EC coupling. RyR1 is a high-conductance channel that regulates release of SR Ca^{2+} and is the central component of the CRU. The functional RyR1 physically interacts with tetrads composed of four voltage-activated CaV1.1 subunits within the T-tubule membrane to engage bidirectional signaling. Proteins localized within the triad junction that interact with either or both RyR1 and CaV1.1 include Homer 1, which physically binds and functionally couples target proteins, calstabin 1, triadin, junctin, Mg29, junctophilin 1 and 2, calsequestrin, calmodulin, the catalytic and regulatory subunits of protein kinase A, and protein phosphatase 1 (for review see elsewhere[171-174]), and it is likely that this list is not complete. There is experimental support that mutations found in RyR1 ($_{MH}$RyR) alter protein-protein interactions in the CRU.[175-177]

In the presence of certain chemical substances, MH mutations in RyR1 or DHPR cause severe dysregulation of RyR1 channel function. This can be seen in vitro as heightened sensitivity to volatile anesthetics, 4-chloro-*m*-cresol, caffeine, ryanodine, and potassium depolarization.[178-180] Chemically induced dysfunction of the RyR1 complex appears to be the principal cause of triggering uncontrolled skeletal muscle metabolic acidosis (aerobic and glycolytic), rigidity, and hyperkalemia, but the mechanisms governing the syndrome are unclear.

Two essential cations greatly shape the kinetics and magnitude of Ca^{2+} release in response to depolarizing triggers: Ca^{2+} itself and Mg^{2+}. The normal RyR1 complex responds to Ca^{2+} in a biphasic manner. First, Ca^{2+} activates the channel in a graded

manner between 100 nM and 100 μM, whereas higher concentrations inhibit channel activity.[181,182] This biphasic action is thought to occur via binding of Ca^{2+} to two classes of regulatory sites on RyR1, a high-affinity stimulatory site and a low-affinity inhibitory site.[173] Mg^{2+}-induced inhibition is the second important physiologic regulator of RyR1 activity in skeletal muscle.[183,184] Mg^{2+} inhibits RyR1 in a cooperative manner ($n_H \approx 2$; 50% inhibitory concentration [IC_{50}] ≈ 650 μM). It is likely that Mg^{2+} acts by competing with Ca^{2+} at its activator sites and by binding to yet unidentified low-affinity inhibitory sites.[185,186] Possibly, MH mutations introduce allosteric instability into the RyR1 complex that leads to a reduction of inhibition rather than directly altering the binding properties of Ca^{2+} or Mg^{2+}, or both, at the activator or inhibitor sites. Therefore, hypersensitivity to pharmacologic agents is likely to be closely tied to altered responses to physiologic ligands. However, whether MHS channels are primarily hyposensitive to inhibition by Mg^{2+} [187,188] or Ca^{2+} (or both), are hypersensitive to activation by Ca^{2+}, or exhibit altered sensitivities in both directions to both ions remains controversial. Recent studies have also pursued the "leaky channel" hypothesis by examining SR preparations from homozygous R615C MHS pigs and heterozygous R163C and C512S mice; they observed a significantly lower Ca^{2+} loading capacity (38%, 23%, and 22% lower than matched wild type mice, respectively) primarily mediated by the presence of leaky channels that remain active even with 100-nM extravesicular Ca^{2+}.[189,190] These direct measures of MHS RyR1 channel dysfunction are consistent with intracellular calcium measurements made in MHS muscles, myotubes, and myoball preparations and in dyspedic myotubes expressing $_{MH}$RyR1s, all of which have been shown to have chronically elevated resting cytoplasmic $[Ca^{2+}]_i$.[177,179,191] Dirksen and coworkers demonstrated that cells expressing the CaV1.1 R1086H MHS mutation have enhanced RyR1 sensitivity to activation by endogenous (voltage sensor) and exogenous (caffeine) activators.[192-196]

Some experimental evidence suggests that long-range interdomain interactions between regions of RyR1 are involved in channel regulation by stabilizing protein conformations critical for normal channel transitions.[197]

Factors Other Than Ryanodine Receptor Abnormalities

Other cellular processes can affect MH episodes. It has been demonstrated that concurrent administration of nondepolarizing neuromuscular blocking drugs at the same time as triggering agents can delay or prevent the onset of clinical MH syndrome. Pretreatment of MH-susceptible pigs with sufficient nondepolarizing neuromuscular blocking agent to completely abolish muscle twitch elicited by electrical stimulation of the nerve prevented halothane from triggering the clinical syndrome for 90 minutes, the longest time point tested.[198] However, in the continued presence of halothane, when function of the neuromuscular junction was restored by administration of the cholinesterase inhibitor neostigmine, clinical MH was triggered immediately. This suggested a close relationship between functional neuromuscular junctions or depolarization of the sarcolemma (or both) and the clinical syndrome.

Recently, it has been shown that sarcolemmal excitation-coupled Ca^{2+} entry (ECCE) is sensitive to the conformation of the RyR1 and is enhanced by several mutations in RyR1, including MH mutations.[171,176,199] This enhancement is responsible for the observation that MHS muscles are more sensitive to depolarization with KCl. Although the sarcolemmal channel responsible for ECCE has not yet been identified, it is one target for dantrolene's reduction of muscle contraction in response to both electrical and KCl depolarization.[175] In addition to ECCE, classic store-operated capacitive Ca^{2+} entry pathways similar to the store-operated Ca^{2+} entry (SOCE) seen in nonexcitable cells[200] have been shown to be present in skeletal muscle[201-203] and could be more active in MHS muscles as a response to chronic store depletion. Such a SOCE channel has also been suggested to be a target for dantrolene.[204] Together, these data suggest that $_{MH}$RyRs or $_{MH}$CaV1.1 and possibly $_{MH}$Csq1 or another $_{MH}$CRU protein could assume a conformation that enhances Ca^{2+} entry via ECCE or SOCE (or both). This enhanced entry, when combined with decreased sensitivity of $_{MH}$RyRs to Ca^{2+} and Mg^{2+} inhibition, could provide cellular conditions that heighten sensitivity to triggering agents and perpetuate the fulminant clinical MH syndrome.

Dantrolene

Dantrolene is the only drug that has been shown to be effective in reversing the symptoms of MH. Preadministration of dantrolene will also prevent the development of fulminant MH in homozygous pigs or heterozygous MH mice when exposed to a triggering stimulus. Dantrolene sodium is a hydantoin derivative (1-[5-(4-nitrophenyl)-2-furanyl]methylene]imino]-2,4-imidazolidinedione) that does not block neuromuscular transmission but causes muscle weakness by direct muscular action. The properties of dantrolene have been closely correlated with its ability to reduce efflux of Ca^{2+} from the SR in vitro. Dantrolene (20 μM) counteracts the effect of reduced Mg^{2+} inhibition in MH-affected muscle.[61] Dantrolene (20 μM) can inhibit the enhanced sensitivity to caffeine seen in MH muscles, and both dantrolene and its water-soluble analog azumolene (150 μM) have been shown to reduce depolarization-induced release of Ca^{2+}, both in muscle and in triadic vesicles.[205] The idea that dantrolene suppresses SR Ca^{2+} release as a result of direct interactions with RyR1 is somewhat controversial. Paul-Pletzer and associates[206] demonstrated that [^{3}H]azidodantrolene specifically labels the amino terminus of RYR1 defined by the 1400–amino acid residue N-terminal calpain digestion fragment of RYR1. More detailed analysis further localized the [^{3}H]azidodantrolene binding site to a single domain containing the core sequence corresponding to amino acid residues 590 through 609 of RyR1.[206] However, to date we lack evidence of a direct action of dantrolene on single RyR1 channels studied in lipid bilayers, even in the presence of calstabin 1, ATP, and activating concentrations of Ca^{2+}, suggesting that dantrolene's main action is to alter key protein-protein interactions.

Genetics

RYR1 mutations have been found in 50% to 80% of patients and relatives who are labeled MH susceptible by positive contracture tests and in almost all families with central core disease (CCD) and King-Denborough syndrome. More than 143 missense mutations and 8 deletions associated with MH have thus far been detected. Another 29 missense mutations are associated with CCD and multiminicore disease in patients with unknown MH testing status.[149] Interestingly, 40% of missense *RYR1* mutations occur at CpG dinucleotide sequences. Five other loci (17q21-24, 1q32, 3q13, 7q21-24, and 5p) have been linked to families with

positive contracture tests and an unusual response to anesthesia and have been designated MHS loci 2 through 6, respectively. However, of these five, the only gene that has been shown to be associated with MH is *CACNL1A3*,[207] which codes for CaV1.1 (the α_{1S}-subunit of DHPR), in the MHS3 locus. Two causative mutations in this gene are linked to less than 1% of MHS families worldwide. In some of the other loci, all genes within the locus have been ruled out as causing susceptibility to MH. Hence for practical reasons, the *RYR1* gene remains the primary target for current clinical genetic analysis.

Distribution of *RYR1* Mutations

The missense mutations associated with MHS, CCD, or in some cases both, are dispersed throughout the coding region of the *RYR1* gene, and all allow transcription of a protein that is putatively functional.[149,208] Until recently, it was thought that most *RYR1* mutations were clustered in three "hot spots": between amino acid residues 35 and 614 (MH/CCD region 1), between amino acid residues 2163 and 2458 (MH/CCD region 2) in the myoplasmic foot region of the protein, and between amino acids 4643 and 4898 in the carboxyl-terminal transmembrane loop or pore region (MHS/CCD region 3)[209] (Fig. 37-4). It appears that the supposition that there were "hot spots" was simply due to bias in sample analysis inasmuch as the missense mutations associated with MH or CCD (or both) are scattered over 54 of the 107 exons of *RYR1*. Approximately 41% of reported MH mutations are found in multiple families. CCD mutations are predominantly found in the C-terminal region of the gene (exons 85 to 103), and only 10 mutations (17%) have been described in more than one family: R4861H ($n = 14$), V4849I ($n = 9$), I4898T ($n = 7$), L4824P ($n = 4$), A4940T ($n = 4$), G4638D ($n = 3$), R4893W ($n = 3$), R4861C ($n = 2$), R4893Q ($n = 2$), and G4899E ($n = 2$).

MH and CCD have been reported in Western populations predominantly, but more likely than not this is incorrect and the result of the manner and frequency in which cases are reported. The true ethnic distribution of MH and CCD is difficult to ascertain. It does appear that the associated mutations are clustered in a given region of the world, but the distribution and frequency appear to be somewhat population specific. In the United Kingdom, 69 *RYR1* mutations have been discovered, 25 of which are found in only a single family. G2434R is found in approximately 40% of the 434 mutation-positive MH families investigated in the United Kingdom, with the next most common mutations being T2206M (10%) and G341R (8%). In Switzerland, V2168M and I2336H are the predominant mutations,[210] and in Germany, R163C (MH and CCD), R614C (MH), T2206M (MH), G2434R (MH), and R2454H (MH) have each been detected in five or more independent cases.[211,212] G341R and R614C are common in France,[213] and R614C has also been found in several MH families from Italy[213] and Canada.[214] G341R has been found frequently in Belgium.[213] The mutation common to Europe and North America is G2434R, which occurs in 4% to 7% of European and 5.5% of North American families.[215] Single-family mutations are the most common mutations reported in Japanese, Chinese, Taiwanese, Australian, and New Zealand MH families,[216-218] but it is likely that this may reflect the small number of cases investigated there. Because genetic screening in European and North American studies has predominantly targeted only regions 1 and 2 of the original hot spots in the gene, the absence of *RYR1* mutations in some of the screened population could be explained by

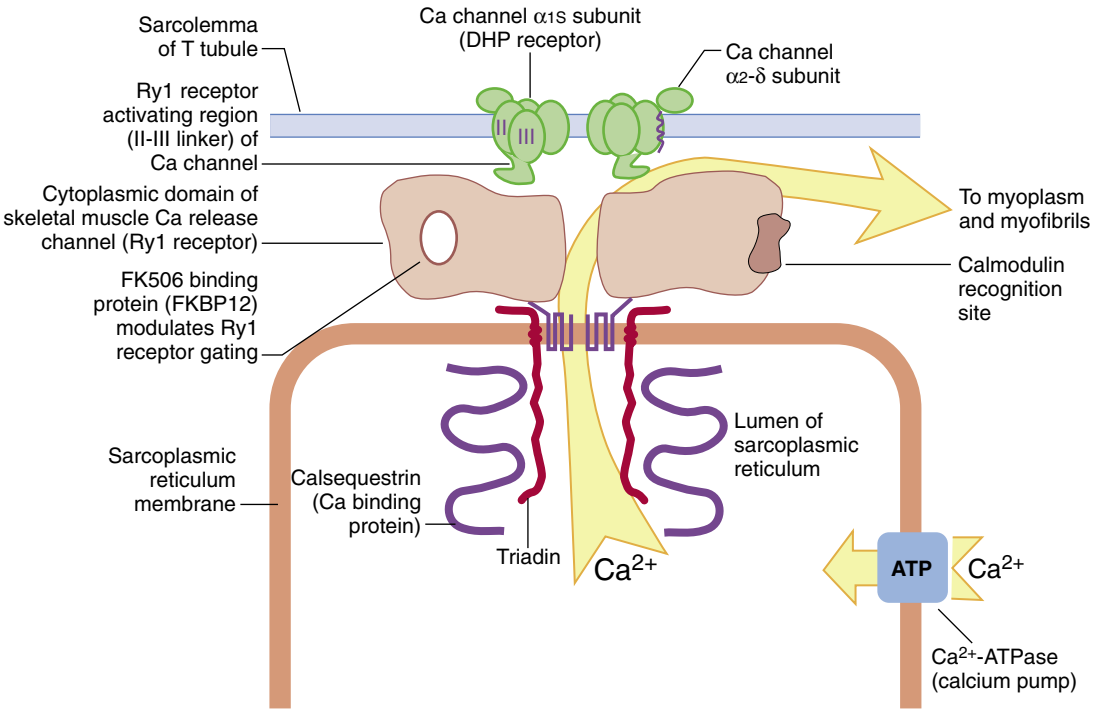

Figure 37-4 Schematic representation of the triad junction of skeletal muscle shows the junctional foot protein (ryanodine [Ry1] receptor) and its associated proteins. In skeletal muscle, the α_{1S}-subunit of the dihydropyridine receptor (DHPR) participates in excitation-contraction coupling. These physical links transmit essential signals across the narrow gap of the triadic junction that activate the Ry1 receptor and release Ca^{2+} from the sarcoplasmic reticulum. *(Adapted from Pessah IN, Lynch C III, Gronert GA: Complex pharmacology of malignant hyperthermia. Anesthesiology 84:1275, 1996.)*

RYR1 mutations located outside these two regions or by involvement of other genes.

Inheritance and Penetrance of Malignant Hyperthermia

Inheritance of human MH can no longer be considered to be solely autosomal dominant with variable penetrance because more than one MH-linked mutation has been identified in some probands and families. Six nonconsanguineous families harbor at least two *RYR1* mutations that have both been linked to MHS, and in two families one is an *RYR1* mutation and the second is a *CaV1.1* mutation.[219] Although MHS homozygotes are common in affected pigs, they are rare in human and transgenic mouse populations. The known MHS homozygous humans appear clinically normal but exhibit stronger responses to IVCT and caffeine/halothane contracture tests (CHCTs) than heterozygous individuals do.[220-223] Homozygosity of two MH mutations in "hot spot" 1 leads to perinatal lethality in mice.[189,190] Double heterozygous individuals do not appear to show any additive effect of the second mutation on IVCT.[219]

Discordance between Genetic and IVCT/CHCT Malignant Hyperthermia Testing

Discordance has confounded linkage analysis worldwide. Examples include MHN patients carrying an *RYR1* mutation associated with MH and MHS patients who do not carry the familial *RYR1* mutation. Several explanations are possible, the most likely being that IVCT/CHCT is not clinically precise and that the thresholds for IVCT or CHCT are inexact. This would lead to errors in determining whether a patient was MHN or MHS. A second possibility is variable penetrance with possible allelic silencing,[224] and a third is that individuals with discordance have mutations in other unknown genes or modifier genes that affect the function of RyR1 and its phenotypic penetrance. The rarity of large kindreds with MH makes linkage analysis and understanding variability in clinical manifestations difficult. Robinson and associates demonstrated by the transmission disequilibrium test (TDT) that loci on chromosomes 5 and 7 and, to a lesser extent, loci on chromosomes 1 and 7 influence susceptibility to MH.[213]

Guidelines for Genetic Screening

In 2000, the European MH group[225] formulated guidelines for *RYR1* mutation screening with linkage data to other loci for some MH families, but all MH investigators emphasized the vital role of IVCT in the diagnosis of MH. These guidelines for screening have reduced the number of relatives requiring contracture testing without increasing the risk of misdiagnosis[226,227] and include the following: (1) confirmation of MHS in a family member (preferably a proband) by IVCT before genetic testing; (2) use of 15 *RYR1* mutations characterized by in vitro functional assays for the genetic protocol; (3) confirmation of MHS and omission of IVCT if a causative mutation is detected in a first-degree relative; and (4) need for performance of IVCT before MHN is diagnosed if a familial mutation is not detected in a first-degree relative.

Only a small number of MH-susceptible families have been investigated extensively in North America by phenotyping, linkage analysis, and screening of specific genes. Collaborative protocols over the past several years between MH biopsy centers and molecular biologists have screened 209 unrelated MHS subjects for mutations in the *RYR1* gene (see "Distribution of *RYR1* Mutations").

A recent consensus meeting agreed to the following: (1) limitations of genetic testing include low sensitivity because of the diversity of mutations and genes; (2) the *RYR1* gene is the primary focus for genetic testing, but further studies are required for more complete understanding of the relationship between mutations and susceptibility; (3) guidelines for referral and education are needed to establish clinical testing in a Clinical Laboratories Improvement Act (CLIA)—certified laboratory; and (4) a North American MH *RYR1* Mutation Panel was not changed from the original panel set out in 2002 (Table 37-1).

Fulminant Malignant Hyperthermia

Fulminant MH is rare. Acute episodes of MH depend on four variables: a genetic (perhaps rarely acquired) predisposition, the absence of inhibiting factors, the presence of an anesthetic or nonanesthetic trigger, and the presence of environmental factors that could potentiate the action of one or more of the other three variables.

Anesthetic Triggering

Anesthetic drugs that trigger MH include ether, halothane, enflurane, isoflurane, desflurane, sevoflurane, and depolarizing muscle relaxants, the only currently used of which is succinylcholine. Desflurane and sevoflurane appear to be less potent triggers than halothane and produce a more gradual onset of MH.[228,229] The onset may be explosive if succinylcholine is used. MH-susceptible swine were traditionally screened by induction with a volatile anesthetic, which led to pronounced hind limb rigidity within 5 minutes, frequently sooner.[230] Prior exercise even an hour before induction of anesthesia increased the severity and hastened the onset of rigidity in swine.[230] Similarly, in the new knock-in mouse models, the onset of limb rigidity after commencing exposure to volatile anesthetics is very rapid. There are also several modifying factors that are more likely to be present in humans than in pigs or mice and can alter (or even prevent) the onset of clinical MH. Mild hypothermia and preadministration of barbiturates, tranquilizers, propofol, or nondepolarizing neuromuscular blockers delay or prevent the onset of MH[163,230-232] in MH-susceptible humans, thus making them respond less predictably than swine or MH knock-in mice. There have been many instances in which fulminant MH has been reported in patients who have previously tolerated potent triggers without difficulty.[233] Why this occurs is unknown, but it is likely to be related to prior or concurrent administration of drugs that prevent or delay onset of the syndrome, as described earlier, or unknown environmental influences that help provoke the positive incident. Thus, onset of the syndrome in humans is extremely variable both in initial symptoms and in the time of onset of the syndrome. Its onset is so variable that making the diagnosis in the setting of a clinical anesthetic can be quite difficult. Although not perfect, the clinical grading scale developed by Larach and colleagues[234] is a useful way for clinicians to retrospectively determine whether a patient who responded abnormally to anesthesia is in any way likely to actually have had a clinical MH episode. However, MH is most easily diagnosed prospectively by vigilance, recognizing its signs and symptoms, and knowing how to treat the syndrome.

Table 37-1 Findings of the North American Malignant Hyperthermia Mutation Panel, 2002

Exon	Mutation*	RyR1 Amino Acid Change	No. of Families in North America†	Estimated Incidence in Europe (%)	Phenotype
6	C487T	R163C	2	2-7	MHS, CCD
9	G742A	G248R	2 (11)	2	MHS
11	G1021A	G341R	1	6-17	MHS
17	C1840T	R614C	6 (42)	4-45	MHS
39	C6487T	R2163C	2	4	MHS
39	G6488A	R2163H	0	1	MHS, CCD
39	G6502A	V2168M	1	8	MHS, CCD
40	C6617T	T2206M	2	One family	MHS
44	Deletion	ΔG2347	2	0	MHS
44	G7048A	A2350T	1	0	MHS
45	G7303A	G2434R	9 (54)	4-10	MHS
45	G7307T	R2435H	1	2.5	MHS, CCD
46	G7361A	R2454H	4	One family	MHS
46	C7372	R2458C	0	4	MHS
46	G7373A	R2458H	0	4	MHS
101	G14582A	A4861H	0	Multiple families	CCD
102	T14693C	I4898T	0	Multiple families	MHS, CCD

*Criteria for the 17 mutations: (1) they occur in more than one family in North America or Europe, and (2) previous testing of a sequence variant shows that it is not a polymorphism.
†Data collaboration of the Uniformed Services University of the Health Sciences, Thomas Jefferson University, Wake Forest University, University of California, Davis, and Barrow Neurological Institute indicates those also found in Canada (e.g., for exon 45, four families with the mutation G2434R were found in Canada).
CCD, central core disease; MHS, malignant hyperthermia susceptibility; RyR1, ryanodine receptor type 1.

The two classic clinical manifestations of fulminant MH syndrome may start in one of the following two scenarios.

1. Rigidity after induction with thiopental and succinylcholine but successful intubation, followed rapidly by the symptoms listed after scenario 2
2. Normal response to induction of anesthesia and uneventful anesthetic course until onset of the following symptoms:
   - Unexplained sinus tachycardia or ventricular arrhythmias, or both
   - Tachypnea if spontaneous ventilation is present
   - Unexplained decrease in O_2 saturation (because of a decrease in venous O_2 saturation)
   - Increased in end-tidal P_{CO_2} with adequate ventilation (and in most cases unchanged ventilation)
   - Unexpected metabolic and respiratory acidosis
   - Central venous desaturation
   - Increase in body temperature above 38.8°C with no obvious cause

The usually muted onset of MH (scenario 2) is in most cases detected quickly by the development of tachycardia, increased levels of expired carbon dioxide, and muscle rigidity. It can be delayed for several reasons and may not be overt until the patient is in the recovery room. Once initiated, the course of MH can be rapid. When clinical signs such as increased expired carbon dioxide, muscle rigidity, tachycardia, and fever suggest MH, more than one abnormal sign must be observed before making the diagnosis because according to a meta-analysis of many reported cases, a single adverse sign does not usually indicate MH.[234] The mechanism by which anesthetics and depolarizing muscle relaxants trigger MH is unsolved, *but* it cannot be ignored that they are etiologic agents and that early diagnosis is critical for successful treatment.

During a fulminant MH episode, triggering agents cause affected subjects to undergo a very large increase in aerobic and anaerobic metabolism that results in intense production of heat, carbon dioxide, and lactate and an associated respiratory and metabolic acidosis.[230,235] These reactions markedly alter whole-body acid-base balance and temperature and are magnified as temperature increases because skeletal muscle makes up 40% of the body mass. Whole-body rigidity occurs in almost all susceptible pigs and mice, as well as in most humans. Temperature may exceed 43°C (109.4°F), P_{aCO_2} may exceed 100 mm Hg, and arterial pH (pH_a) may decrease well below 7.00. The increased permeability of skeletal muscle results in increased serum levels of potassium, ionized calcium, CK (although MH-related changes in serum CK do not differ overall from changes in CK observed during surgery[236]), myoglobin, and serum sodium.[230] Sympathetic hyperactivity is responsible for the cardinal sign of MH—tachycardia—which occurs early as an indication of increased metabolism. With metabolic exhaustion, cellular permeability increases along with whole-body edema, including acute cerebral edema. As MH progresses untreated, disseminated intravascular

coagulation and cardiac or renal failure may develop. It is important to note that MH is a disorder of increased muscle metabolism and, despite its name, need not involve increased temperature! For example, if heat loss is greater than production or if cardiac output plummets early, central temperature will not increase.

Awake Triggering: Exercise and Heat

Whether MH can be triggered in humans in the absence of a triggering agent is controversial. Porcine environmental stress such as exercise, heat, anoxia, apprehension, and excitement triggers fulminant MH (see "History").[230,235] These responses are related to muscle movement or to increased temperature. Increased ambient temperature triggers fulminant MH in two strains of MH mice.[190,191] Epidemiologic studies have shown that exercise-induced symptoms, including rhabdomyolysis, occur more frequently in MHS patients[237]; an Arg401Cys *RYR1* mutation was present in three cases of exercise-induced rhabdomyolysis.[216] Other reports are largely anecdotal and relate heat stroke, sudden and unexpected death, unusual stress and fatigue, or myalgias to possible awake MH episodes. Stresses associated with these episodes include exercise and environmental exposure to volatile nonanesthetic vapors.[238-240]

Malignant Hyperthermia–Associated Syndromes

Masseter Spasm ("Thiopental-Succinylcholine or Halothane-Succinylcholine Rigidity"). Masseter spasm is defined as jaw muscle rigidity in association with limb muscle flaccidity after the administration of succinylcholine. The masseter and lateral pterygoid muscles contain slow tonic fibers that can respond to depolarizing neuromuscular blockers with a contracture.[241,242] This is manifested clinically on exposure to succinylcholine as an increase in jaw muscle tone, well defined by van der Spek and associates.[243] There is a spectrum of responses: a tight jaw that becomes a rigid jaw and then a very rigid jaw (Fig. 37-5). This jaw rigidity may occur even after pretreatment with a "defasciculating" dose of a nondepolarizing relaxant. If there is rigidity of other muscles in addition to trismus, the association with MH is absolute; anesthesia should be halted as soon as possible and treatment of MH begun. However, in more than 80% of patients with trismus but no rigidity of other muscles, it is a variant found in normal patients. If trismus occurs, proper monitoring should include end-expired CO_2, examination for pigmenturia, and arterial or venous blood sampling for CK, acid-base status, and electrolyte levels, particularly potassium. Although scientifically unproven, it is thought that the initial tightness of the jaw and its duration may predict the gravity of the response. For patients with "jaws of steel," the procedure should be halted, especially if the condition persists for more than several minutes. If the jaw is slightly resistant to opening, the anesthesiologist may continue anesthesia with proper monitoring. If the jaw is moderately tight and distinctly a problem, there are two choices: halt the procedure or continue with nontriggering agents. Any suggestion of MH should prompt MH therapy, including administration of dantrolene.

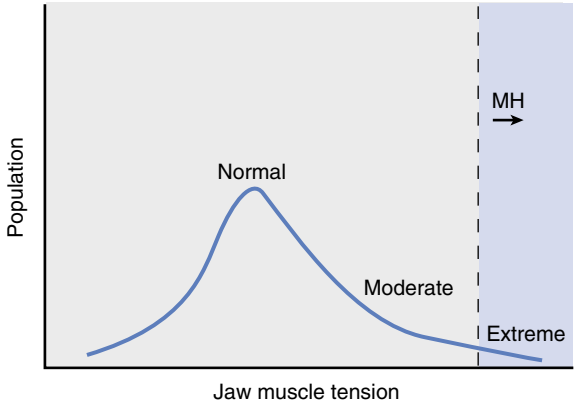

Figure 37-5 Succinylcholine usually increases jaw muscle tone slightly. In some patients this increase is moderate, and in very few, the effect is extreme (i.e., "jaws of steel"). As many as 50% of this latter group may be susceptible to malignant hyperthermia (MH). Somewhere in the area of the declining curve is the boundary for the MH population.

Diagnosis in the Operating Room and Postanesthesia Care Unit

As stated earlier, fulminant MH is rare, and early signs of clinical MH may be subtle. These signs must be distinguished from other disorders with similar signs (Box 37-1). When the diagnosis is obvious (i.e., fulminant MH or succinylcholine-induced rigidity with rapid metabolic changes), marked hypermetabolism and heat production occur, and there may be little time left for specific therapy to prevent death or irreversible morbidity. If the syndrome begins with slowly increasing end-tidal CO_2 (defined earlier), specific therapy can await a complete clinical workup before treatment. In general, MH is not expected to occur when no triggers are administered (see "Anesthesia for Susceptible Patients"). When volatile anesthetics or succinylcholine is used, MH should be suspected whenever there is an unexpected increase in end-expired CO_2, undue tachycardia, tachypnea, arrhythmias, mottling of the skin, cyanosis, increased temperature, muscle rigidity, sweating, or unstable blood pressure. If any of these occur, signs of increased metabolism, acidosis, or hyperkalemia must be sought. Analysis of arterial blood gases demonstrates metabolic acidosis and may show respiratory acidosis if the patient is unable to increase ventilation as metabolism increases. O_2 and CO_2 change more markedly in the central venous compartment than in arterial blood; therefore, end-expired or venous CO_2 levels more accurately reflect whole-body stores. Venous carbon dioxide, unless the blood drains an area of increased metabolic activity, should have P_{CO_2} levels of only about 5 mm Hg greater than that of expected or measured $Paco_2$. In small children, particularly those without oral food or fluid for a prolonged period, the base deficit may be 5 mEq/L because of their smaller energy stores. Any patient suspected of having an MH episode should be reported to the North American Registry via the rare disease protocol (American Medical Record Association [AMRA]), available from the MHAUS website at http://www.mhaus.org/.

Box 37-1 Mimics of Malignant Hyperthermia Disorder

Alcohol therapy for limb arteriovenous malformation
Contrast dye
Cystinosis
Diabetic coma
Drug toxicity or abuse
Environmental heat gain more than loss
Equipment malfunction with increased carbon dioxide
Exercise hyperthermia
Freeman-Sheldon syndrome
Heat stroke
Hyperthyroidism
Hypokalemic periodic paralysis
Intracranial free blood
Muscular dystrophies (Duchenne's, Becker's)
Myotonias
Neuroleptic malignant syndrome
Osteogenesis imperfecta
Pheochromocytoma
Prader-Willi syndrome
Rhabdomyolysis
Sepsis
Ventilation problems
Wolf-Hirschhorn syndrome

Treatment

Acute therapy for MH can be summarized as follows: (1) Discontinue all anesthetic agents and hyperventilate with 100% oxygen. Normal ventilation is that required to remove metabolic carbon dioxide. With increased aerobic metabolism, normal ventilation must increase. However, carbon dioxide production is also increased because of neutralization of fixed acid by bicarbonate; hyperventilation removes this additional CO_2. (2) Administer dantrolene (2.5 mg/kg intravenously [IV] to a total dose of 10 mg/kg IV) every 5 to 10 minutes until symptoms subside. (3) Administer bicarbonate (2 to 4 mEq/kg IV) to correct the metabolic acidosis with frequent monitoring of blood gases and pH. (4) Control fever by administering iced fluids, cooling the body surface, cooling body cavities with sterile iced fluids, and if necessary, using a heat exchanger with a pump oxygenator. Cooling should be halted at 38°C to 39°C to prevent inadvertent hypothermia. (5) Monitor urinary output and establish diuresis to protect the kidney from probable myoglobinuria. (6) Further therapy is guided by blood gases, electrolytes, temperature, arrhythmia, muscle tone, and urinary output. Treatment of hyperkalemia with glucose and insulin should be slow. The most effective way to lower serum potassium is reversal of MH by effective doses of dantrolene. (7) Analyze coagulation studies (e.g., international normalized ratio, platelet count, prothrombin time, fibrinogen, fibrin split or degradation products).

Discontinuation of the trigger may be adequate therapy for acute MH if the onset is slow or if exposure was brief. Dantrolene is packaged in 20-mg bottles with sodium hydroxide for a pH of 9 to 10 (otherwise it will not dissolve) and with mannitol (converts the hypotonic solution to isotonic). The initial dose should be 2.5 mg/kg dantrolene reconstituted in sterile water and administered intravenously. Dantrolene *must* be reconstituted in sterile water rather than salt solutions or it will precipitate. Dantrolene has a half-life of at least 10 hours in children and adults.[244,245] At therapeutic concentrations, dantrolene may prolong the need for intubation and assisted ventilation. Aside from cholestasis during long-term (>3 weeks) therapy, dantrolene has no serious side effects.

The clinical course will determine further therapy and studies. Dantrolene should probably be repeated at least every 10 to 15 hours (its half-life) for at least one and possibly several doses. Recrudescence of MH can approach 50%, usually within 6.5 hours.[246,247] When indicated, calcium and cardiac glycosides may be used safely. They can be lifesaving during persistent hyperkalemia. Permanent neurologic sequelae, such as coma or paralysis, may occur in advanced cases, probably because of inadequate cerebral oxygenation and perfusion for the increased metabolism and because of the fever, acidosis, hypo-osmolality with fluid shifts, and potassium release. Slow voltage-gated calcium channel blockers do not increase porcine survival.[248,249] If uncertain at any time, the physician should contact the MH Hotline to verify treatment and report the case with an AMRA form.

Anesthesia for Susceptible Patients

Safe anesthetics consist of nitrous oxide, barbiturates, etomidate, propofol, opiates, tranquilizers, and nondepolarizing muscle relaxants. Potent volatile anesthetics and succinylcholine must be avoided, even in the presence of dantrolene. There are anecdotal reports that some human patients have experienced a hypermetabolic state despite these precautions, but they have always responded favorably to the administration of intravenous dantrolene. Preoperative dantrolene is never needed because the use of nontriggering agents is almost always associated with uneventful anesthesia. Regional anesthesia is safe and may be preferred. Amide anesthetics such as lidocaine were once considered dangerous in susceptible patients because they were thought to induce or worsen muscle contractures in vitro as a result of their effect of increasing calcium efflux from the SR. Porcine and human studies have consistently demonstrated the lack of danger of amide anesthetics. Before use for MH-susceptible patients, anesthetic machines may be "cleansed" of potent volatile agents by removal or sealing of the vaporizers, changing the soda lime, perhaps replacing the fresh gas outlet hose, and using a disposable circle with a flow of 10 L/min for 5 minutes.[250,251]

The anesthesiologist should confidently discuss anesthetic care with MH-susceptible patients and assure them that all will be done to avoid difficulties with MH and that the appropriate drugs, knowledge, and skills are immediately at hand if any problems occur. Many of these patients have undergone procedures uneventfully, such as dental analgesia and obstetric anesthesia, before the diagnosis of susceptibility was made. The patient can enter the therapeutic environment in a reassured, relaxed, and

comfortable state. Outpatient procedures are feasible in most environments; the time of discharge depends on the usual outpatient criteria.

Any facility using MH triggers on an inpatient or outpatient basis should have dantrolene available immediately.

Evaluation of Susceptibility

Evaluation of susceptibility includes a history and physical examination to detect any subclinical abnormality. A genealogy with specific information about anesthetic exposure and agents can estimate the likelihood of exposure to triggering agents. Blood CK values, when determined in a resting, fasting state without recent trauma, reflect muscle membrane stability. When the CK level is elevated in a close relative of a person with known MHS, the relative may be considered to have MHS without contracture testing. If the CK level is normal on several occasions, there is no predictive value, and contracture studies are necessary. The patient must travel to the test center for surgical biopsy to ensure viability and accurate results. Muscle biopsy contracture studies, performed at about 30 centers around the world, involve exposure to halothane, caffeine, halothane plus caffeine, and ryanodine.[225] 4-Chloro-*m*-cresol may add to precision.[176] It is also important to note that contracture responses are sometimes positive in patients with myopathies that bear no direct relationship to MH and therefore may not indicate susceptibility. Dantrolene must be avoided before biopsy because it masks the response to contracture-producing drugs. After a patient is diagnosed as being MH susceptible, DNA testing for mutations should follow. When a mutation is detected, other relatives with that mutation should be considered to be MH susceptible without the need for an invasive contracture test, and they need not travel to a testing center (see "Genetics").

Advice should be given to susceptible patients. Precautions are necessary in regard to general anesthesia, and triggers include all potent volatile agents and succinylcholine. Awake episodes are uncommon, and if not experienced before diagnosis, they are an unlikely problem. The true predictive value (i.e., percentage of positive results that are true positives) or efficiency (i.e., percentage of all results that are true, whether positive or negative) of contracture testing in determining susceptibility in the general population cannot be estimated because of the selection process that has been used to date for testing (i.e., limited to those with anesthesia reactions who do not have any other muscle disease pathology). False-positive results from cautious interpretation or decreased specificity are masked because the patient will never be exposed to triggering agents. A promising innovative in vivo human application involves physiologically based microdialysis infusion of caffeine or halothane into muscle of MH-susceptible patients to trigger exaggerated localized changes in acid-base balance.[252-256] White blood cells express MH mutations and provide a substrate for genetic analysis.[257-261] Nuclear magnetic resonance has promise,[262,263] but it is difficult to standardize a stress, such as forearm ischemia, that can differentiate susceptible from normal tissue.

Summary

MH is a subclinical myopathy featuring an eerie and erratic metabolic mayhem that is unmasked on exposure to potent volatile anesthetics or succinylcholine. Skeletal muscle acutely and unexpectedly increases its myoplasmic Ca^{2+} concentration, thereby leading to increased oxygen consumption and lactate production and resulting in greater heat production, respiratory and metabolic acidosis, muscle rigidity, sympathetic stimulation, and increased cellular permeability. MH-susceptible skeletal muscle differs from normal muscle in that it is always closer to loss of control of Ca^{2+} concentration within the muscle fiber, and it can involve a generalized alteration in cellular or subcellular membrane permeability. This is an EC coupling defect resulting from an alteration in protein-protein interaction in the CRU. It is a homozygous, single point mutation of *RYR1* in swine and a heterozygous disorder in humans, in whom there may also be a modification of RyR1 protein function by interacting structures, membranes, or enzymes. Diagnosis rests on acute awareness of the signs and symptoms of this syndrome, of which hyperthermia is a late sign. Specific treatment is administration of dantrolene to lower muscle Ca^{2+} levels; symptomatic treatment consists of reversal of the acid-base and temperature changes. Evaluation of affected families is guided by analysis of drug-induced muscle contractures (by European IVCT and North American CHCT protocols) and genetic testing of DNA samples. General or regional anesthesia is safe for patients susceptible to MH, provided that care is taken to specially prepare the anesthesia machine and avoid all potent volatile anesthetics and succinylcholine if a general anesthesia technique is chosen. Research on MH has yielded insight into the physiology of metabolism and into the molecular biology of genetic muscle disorders. Challenges remaining include identification of all genetic mutations responsible for human MH, elucidation of the mechanism that links exposure to subsequent loss of control of Ca^{2+}, development of noninvasive and nondestructive testing for susceptibility, and determination of the mode of action of dantrolene.

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James Szocik, Steven J. Barker, and Kevin K. Tremper

38 Fundamental Principles of Monitoring Instrumentation

Key Points

1. Accuracy and precision are different. Accuracy is how close a value is to the true value. Precision is how repeatable the measurements are. An inaccurate, but precise monitor can be recalibrated to be accurate, but an imprecise monitor cannot be improved.
2. Filtering can improve the signal display, but it also can result in smoothing and loss of information.
3. A signal can be extracted from noise by repeated measurements because the noise is random over time, but the signal is not.
4. Electrical signals can be converted from analog to digital. Conversion can introduce some artifacts, but can allow for greater storage and analysis capabilities.
5. Invasive pressure monitors are affected by damping and resonance. Damping leads to distortion, signal loss, and reduction of peak values. Resonance can lead to amplification and overestimation of the peak value.
6. Pulse oximetry combines analysis of optical plethysmography and absorption analysis with empirical data to produce an estimate of Sao_2.
7. Wavelength and frequency are related to the speed of the wave by the following formula: speed = wavelength × frequency. Shorter wavelengths improve the resolution of light and ultrasound measurements.
8. Flow measurements are among the most difficult to obtain and usually involve indirect measures. (For example, a temperature change or pressure decrease is measured, and a flow value is derived. A small error in the initial measurement leads to a much larger error in the derived flow value.)

Why Fundamental Principles Are Important

Patient monitoring has been a key aspect of anesthesiology since its beginnings as a medical specialty. As anesthesiology has grown more sophisticated and complex, so have the monitors and the data that they produce. The anesthesiologist's senses of sight, hearing, and touch, at first expanded with the stethoscope, sphygmomanometer, and electrocardiograph, are now supplemented by the pulse oximeter, expired gas analyzer, evoked potential monitor, and transesophageal echocardiograph, to name a few. The complexity of some of these devices can be intimidating, and the anesthesiologist may be tempted to regard them as incomprehensible "black boxes" that provide clinical data. To do so, however, would be to shirk an important part of the anesthesiologist's clinical responsibility. Anesthesiologists must be able not only to understand and interpret the data from the monitors, but also to anticipate and recognize errors associated with their use. Anesthesiologists cannot accomplish this goal without understanding how these devices work.

This chapter provides an understanding of the scientific principles underlying the design and function of the most commonly used monitors. Some concepts of basic physics are defined first, followed by more detailed descriptions of the principles and their monitoring applications. The text and figures explain these principles predominantly in a qualitative manner. For readers desiring a more quantitative explanation, the relevant physics and equations are provided in the appendices to this chapter.

Basic Principles

Nature of Physics and Measurement

Physics is the science of matter and energy and interactions between the two—that is, it is the study of everything in the physical universe. Physics encompasses everything from the motions and inner workings of the atom to those of galaxies. Physics is quantitative, and mathematics is the language of physics. Newton and Leibnitz invented "the calculus" as a mathematical tool for

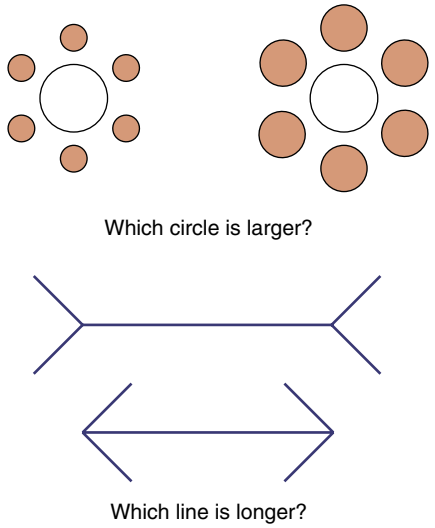


Figure 38-1 Optical illusions. We perceive the circles to be different sizes because we infer the size by relative dimension. The closeness of the smaller circles makes the inner circle appear smaller, and vice versa. The lines appear to be different sizes because we use straight-line perspective to estimate size and distance. This illusion reportedly does not work in cultures where straight lines are not used. Our internal perceptions lead us to err in estimating size and length. In the same way, the internal programming of our monitors can lead us to misinterpret results.

expressing and studying the laws of physics. Our monitors are also quantitative. Before we can discuss and understand the complexity of modern anesthetic monitors, we must quantitatively define what we are attempting to measure and understand the limitations of measurement.

We measure and monitor mass and energy: how much of a substance is present and in what energy state. Much of what we desire to monitor is outside the range of human physical senses. We must make measurements in this insensible realm with devices that enhance or extend our senses. Just as the senses have limitations and can be "fooled" under certain circumstances (Fig. 38-1), our physiologic monitors are limited by their design and can be fooled under some conditions. Intelligent users of these devices must understand their basic design assumptions to predict when they are likely to produce erroneous data.

Accuracy and Precision of Measurements

All measurements have errors. Error is usually determined by the comparison of a measurement with a "gold standard" of that measure. All measurements, even the so-called gold standards, are subject to errors with respect to reproducibility. From a clinician's perspective, a physiologic measurement is dependable only if it is accurate to the degree required for clinical decision making.

Systemic blood pressure can be measured in several ways. We can listen to Korotkoff sounds by the use of a sphygmomanometer cuff and stethoscope; we can rely on an oscillometric automated noninvasive blood pressure device, or if we need continuous measurement, we may place an intra-arterial cannula.[1] Each of these techniques provides slightly different arterial blood pressure values, and each has different sources of error. Our choice of method may be determined by accuracy or by our needs for the frequency of the data and the ease of retrieving these data. An automatic oscillometric device is usually chosen over manual auscultatory measurements for ease of acquisition and reproducibility. Two individuals taking auscultatory blood pressure measurements may hear the Korotkoff sounds at slightly different points and record different blood pressures. The required accuracy of a clinical monitor is determined by the smallest change in the measured variable that could affect a clinical decision. The requirements for "absolute accuracy" (is the measured value correct?) may be different from the requirements for "relative accuracy" (does the measured value follow trends?).

A pulse oximeter estimates arterial hemoglobin oxygen saturation by measuring light absorbance. The pulse oximeter saturation estimate, Spo_2, is compared with the hemoglobin oxygen saturation determined from analysis of an arterial blood sample by a laboratory carbon monoxide oximeter, Sao_2. Some errors are associated with arterial blood sampling and in vitro analysis of the sample by the carbon monoxide oximeter. Nevertheless, the carbon monoxide oximeter is considered to be the gold standard in this comparison of methods.

The pulse oximeter's saturation value can be compared with that of the carbon monoxide oximeter by the determination of bias and precision, as recommended by Bland and Altman (Fig. 38-2).[2] Bias is the average difference between simultaneous values from the two methods, or the systematic error. If a pulse oximeter reads an average of 5% higher than the carbon monoxide oximeter, it has a bias of 5%, and we can adjust for that systematic error by recalibrating the device. Precision is the standard deviation of the difference between the two measurements, and it quantifies the random error, or "scatter." A higher value for precision indicates a larger random error. (This statistic may be more appropriately called "imprecision.") If the random error is too large, the device may not be clinically useful. We can adjust for systematic error (bias) by recalibration, but there is no way to adjust for random error.

Measurement of Mass

Measurement is the determination of a physical quantity. A "dimension" is a specific category or type of physical quantity, such as mass, length, time, energy, or any of their derivatives. Units are specific ways of measuring a given dimension. Examples of units are the meter (length), second (time), kilogram (mass), ampere (current), and degree Kelvin (temperature). Describing a measurement without defining the unit is meaningless. A 30° day in Fahrenheit is literally freezing; a 30° day in Celsius is hot. Units can be base units or derived units. There are seven base units (meter, kilogram, second, ampere, degree-Kelvin, mole, and candela) in the SI (*Système International* [International System of Units]) system used in science, from which multiple other units can be derived.

When we "weigh" a patient, we are determining the force of gravity acting on the patient's mass. We generally mean this to be on the earth's surface, but the concept of weight is applicable to other locations. (On the surface of Jupiter, a 70-kg man would weigh 12 times his Earth weight, but his mass would still be 70 kg.) Because force = mass × acceleration due to gravity (Newton's second law), we *balance* the force on the patient with a known mass to determine the patient's "weight" (the SI units of force or weight are "Newtons") and mass (kg) (Fig. 38-3). The concept of balancing forces applies to multiple other monitoring

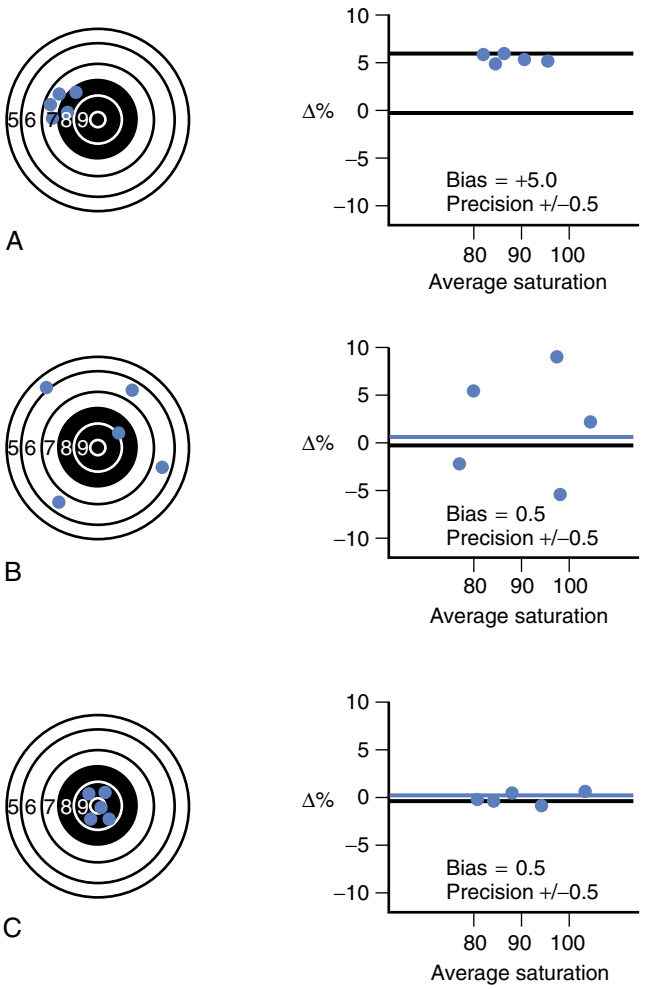


Figure 38-2 Accuracy and precision. The bias plot is a way to compare two different methods of measuring the same variable. **A-C,** Examples are plotted above on the right for saturation values, blood analysis versus pulse oximetry. It is a plot of the difference between the two measurements being compared versus the average of those two measurements. **A,** If one method constantly measures slightly higher than the other by a consistent value, it has a positive bias. If it has only slight variation around that bias, it is said to have very low random error (or precision, which equals the standard deviation of the differences). **B,** The values are randomly scattered, such that the average difference is near zero, but the precision value is very large. This large random error makes the device unusable because calibration would not improve this random error. **C,** The optimal device has a bias near zero and a very small precision (standard deviation of the differences). No amount of calibrating or "sighting in" could cause the device in **B** to become more accurate because the error is randomly scattered.

modalities. When we measure the central venous pressure using a simple manometer, we are observing the balance of forces between the patient's venous pressure and the force of gravity acting on a fluid column (Fig. 38-4). When the same pressure is measured electronically, we are "balancing" a Wheatstone bridge (a system of resistors used to determine an unknown resistance) (Fig. 38-5).

Measurement of Energy

Energy can exist in many different forms. Even matter is related to energy, mathematically defined by Einstein's famous $E = mc^2$

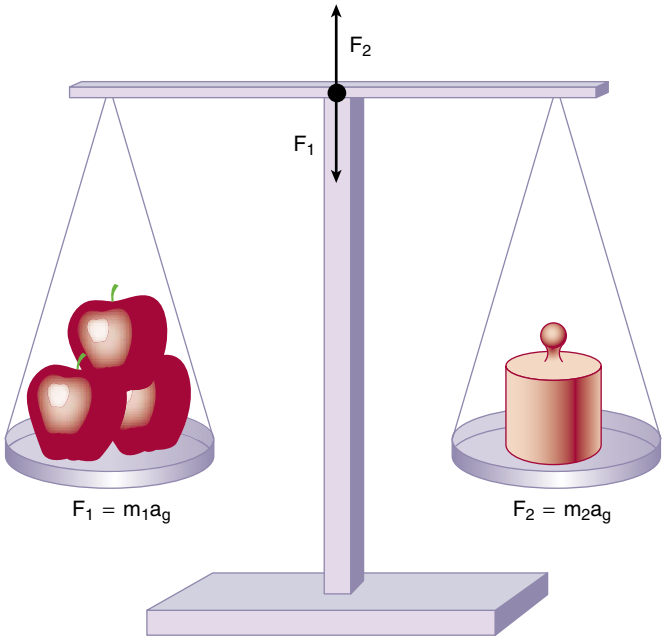


Figure 38-3 Balance. A scale is in balance when the forces are equal and in opposite directions. The force of gravity on the unknown mass of fruit is balanced by the known standard masses on the opposite side of the balance. $F_1 = F_2$, hence $m_1\ a_g = m_2\ a_g$; because $a_g = a_g$, $m_1 = m_2$ (a_g = acceleration due to gravity).

equation; that is to say, matter and energy are different forms of the same "stuff." In the absolute sense, usually reserved for thermonuclear weapons, atomic reactors, and the sun, matter can be converted into energy, and vice versa. If a 1-kg mass were completely converted to energy by means of $E = mc^2$, it would yield 8.987×10^{16} J (Table 38-1).The energy of motion is described as kinetic energy ($KE = \frac{1}{2}\ mv^2$). Temperature is a form of kinetic

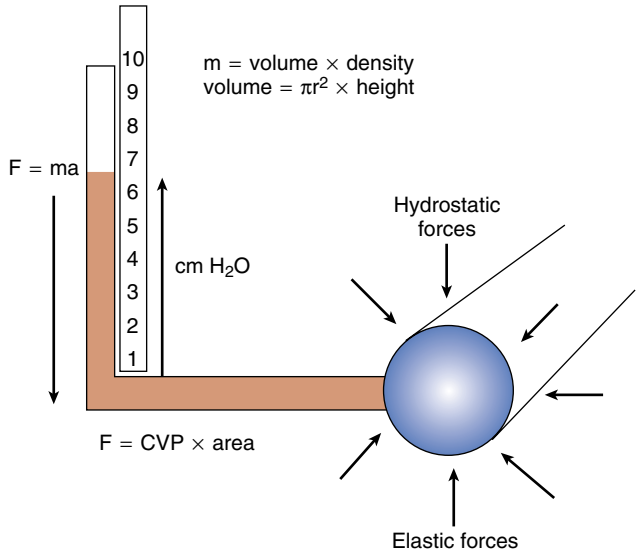


Figure 38-4 Manometer. A water manometer uses a balance of forces. In this case, the downward pressure of the fluid, as determined by its density and height, balances the upward pressure of the central venous system, caused by hydrostatic and elastic recoil forces. CVP, central venous pressure; F, force.

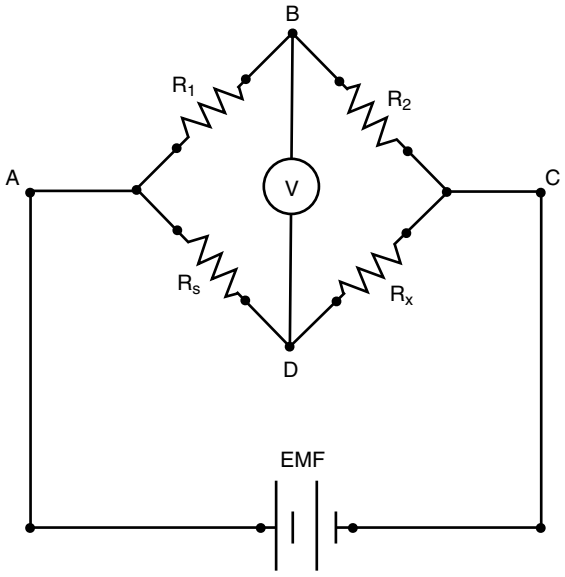


Figure 38-5 Wheatstone bridge. A Wheatstone bridge is an electronic circuit designed so that an unknown resistance can be calculated by knowing two sets of variables: (1) the voltage drop across the bridge and (2) the other resistances in the circuit (see Appendix 3).

energy at the molecular level. Acoustic energy (sound) is a wave of pressure energy transmitted through matter. Light is a form of electromagnetic energy. Potential energy is stored energy and can be of many forms, including gravitational, chemical, pressure, and electromagnetic. The fundamental law of conservation of energy (energy and matter can neither be created nor destroyed, only changed from one form to another) is at the core of understanding many anesthetic monitors.

Table 38-1 Comparison of Energy Levels of Common and Uncommon Events

Event	Energy
1-kg mass falling 1 m on Earth	9.8 J
Heart beat	10 J (at rest, 60 beats/min, 10 W)
Internal defibrillation for ventricular fibrillation	30 J
Maximum output of surface defibrillator	360 J
1 kcal	4186 J
Car battery	1.8 mJ = 1.8×10^6 J
1 kg of fat	3.8×10^7 J
Ton of TNT	4.2×10^9 J
Atomic bomb (Hiroshima)	15 kilotons = $15 \times 10^3 \times 4.2 \times 10^9$ J = 6.3×10^{14} J
Hydrogen bomb	1 megaton = 4.2×10^{15} J
1 kg converted completely to energy	8.987×10^{16} J
The sun (4.2×10^9 kg matter/sec)	3.8×10^{26} J/sec

Modified from Hecht E: Physics: Algebra/Trig. Pacific Grove, CA, Brooks/Cole, 1994.

Signal Processing and Information Theory

When a quantity varies over time, it can be said to contain a "signal." Recording of vital signs and patient data, first begun a century ago by Cushing,[3] is a primitive form of signal analysis. To quote Cushing[4]:

> *In all serious or questionable cases the patient's pulse and blood-pressure, their usual rate and level having been previously taken under normal ward conditions, should be followed throughout the entire procedure, and the observations recorded on a plotted chart. Only in this way can we gain any idea of physiological disturbances—whether given manipulations are leading to shock, whether there is a fall of blood-pressure from loss of blood, whether the slowed pulse is due to compression, and so on.*

Often the signals (the energy or concentration of matter) we are interested in monitoring are too small for our senses to define changes adequately. We must either concentrate or amplify the signal. Often, this information is "transduced" or changed from one form to another for amplification and processing. An old-style gramophone is a good example: The information stored in the shape of the record groove moves a needle attached to a mica diaphragm (the reproducer), which is connected to a sound horn. The mechanical vibrations are reproduced as longitudinal sound waves. These sound waves enter the human ear, contact onto the ear drum, causing it to vibrate, which moves the ossicular chain, resulting in an amplification of the pressure at the oval window, transmitted through the fluid of the inner ear where the appropriate hair cell resonates and generates a neural signal (transduction) (Fig. 38-6). This process is analogous to the process by which our arterial pressure transducers work (Fig. 38-7).

Data Processing

When an analog signal (e.g., voltage versus time) is amplified, the background noise and the desired signal are amplified (Fig. 38-8). Various techniques can be used to enhance the signal-to-noise ratio. Most pulse oximeters assume that a patient's pulse rate is between 30 and 300 beats/min. The instrument filters out any pulsations that occur at frequencies less than 30 or greater than 300 (see the section on alternating current, capacitors, and impedance and Fig. 38-25). Filtering can remove the noise that is outside of this frequency range, improving our ability to discern the signal of interest. Improper filtering can destroy the true signal. In some cases, a desired periodic signal can be repeated and summated, and the accompanying random noise becomes a smaller fraction of the signal. Evoked potentials are an excellent example of this process of "ensemble averaging." The evoked response signal for a single stimulus is actually much smaller than the random noise, but this signal is nearly identical after each stimulus. By summing the potentials after many stimuli, we reinforce the evoked response signal, but not the noise (Fig. 38-9).

Finally, the waveform of any periodic signal can be represented by a summation of sinusoidal waves, called a "Fourier

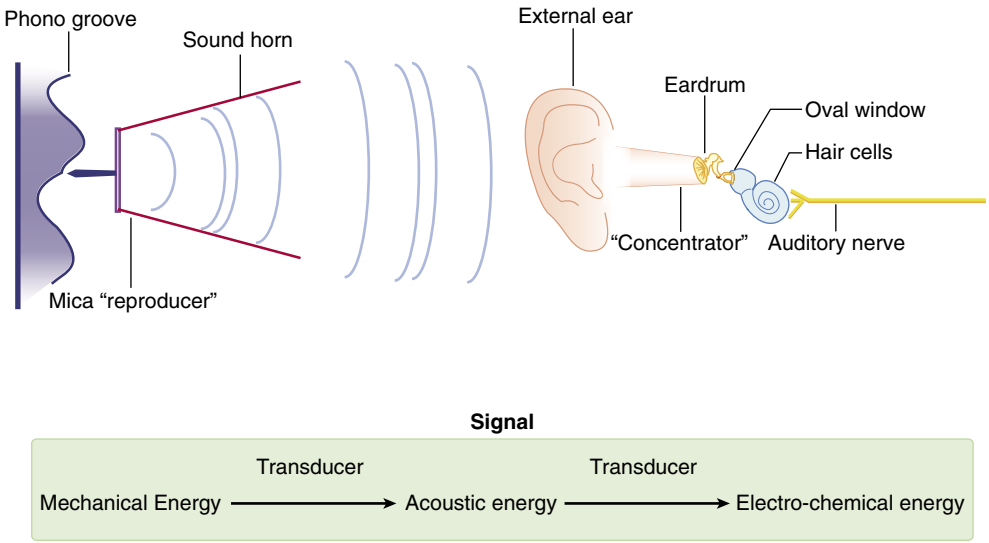


Figure 38-6 Transduction in mechanical and biologic systems. Mechanical energy of the winding mechanism causes the cylinder of the phonograph to rotate. The bumps and curves in the cylinder then move the needle, converting that energy into acoustic energy (a longitudinal wave). The mechanical vibrations are reproduced as longitudinal sound waves. These sound waves enter the human ear, contact the ear drum, causing it to vibrate, which moves the ossicular chain, resulting in an amplification of the pressure at the oval window, transmitted through the fluid of the inner ear where the appropriate hair cell resonates and generates a neural signal (transduction). Loss of hair cells leads to deafness, most commonly in the higher frequency range as one ages. This is analogous to a monitor lacking sensitivity in the desired range.

series" (Fig. 38-10).[5] The component sine waves can be described by their frequency and amplitude (or power, which is proportional to the square of the amplitude). A waveform originally expressed as amplitude versus time is transformed into a plot of power versus frequency (Fig. 38-11). The resulting plot, called the "power spectrum," is a common form for displaying and interpreting some types of waveform data, such as the electroencephalogram (see Chapter 39).

Errors in Signal Analysis

We have all seen movies where car wheels appear to be rotating backward while the car is moving forward. This is the result of a specific type of error, called "aliasing," which occurs when the sampling frequency is too slow to capture the rapid variations of the true signal (Fig. 38-12). Aliasing also can happen with ultrasound, where the display may show echoes from objects that do not actually exist.

In mechanical systems, such as the conventional liquid-filled tubing and pressure transducer for measuring arterial blood pressure, frictional forces can dampen the signal. The signal also can be distorted by resonant amplification, where the energy of the signal is temporarily stored in the compliance of the tubing, and then released (see Appendix 4) (Fig. 38-13). If the display rate is too fast, we also can miss important signals. The systolic pressure variation (alteration in systolic blood pressure with positive-pressure ventilation)[6,7] has been used to determine volume

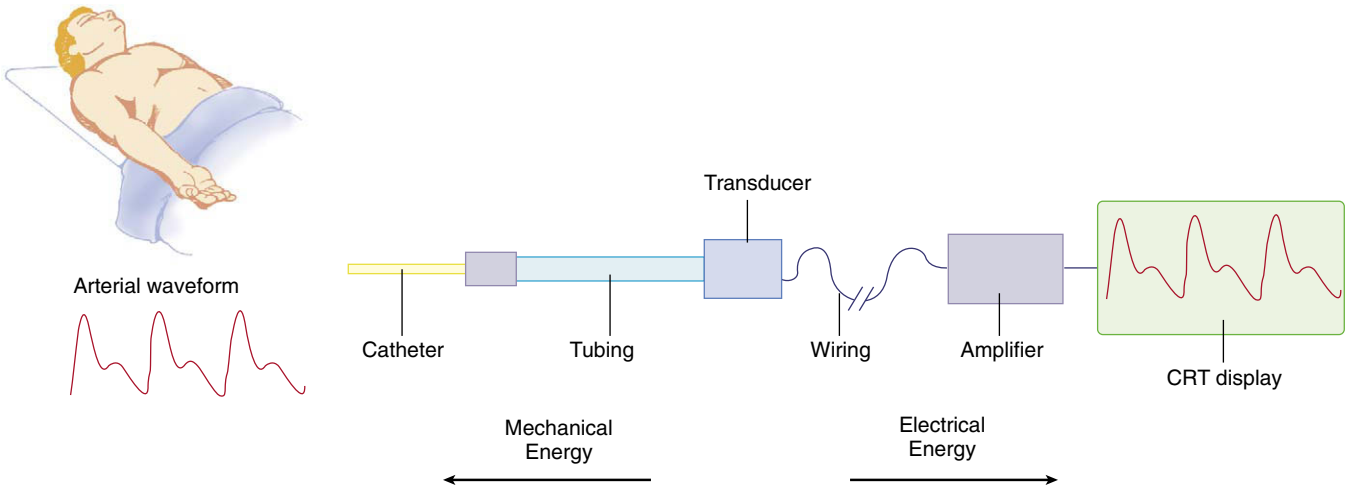


Figure 38-7 Transducer. A transducer changes a signal from one form of energy to another. A common transducer in anesthesia changes mechanical energy (e.g., an arterial pulse) into electrical energy, which is then displayed as time versus amplitude on an LCD or CRT display. Microphones and speakers are also examples of transducers.

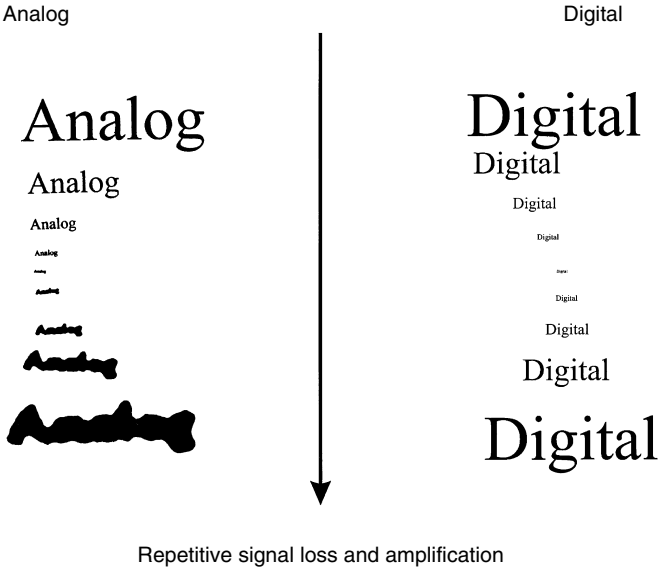


Figure 38-8 Digital and analog signal processing. The analog signal shows distortion and loss of fidelity as it is reduced and then amplified. The digital signal shows no such loss. To create the analog example, a copy machine was used to shrink the text and then enlarge it. For the digital signal, the font size was reduced, the text copied, and the process reversed.

responsiveness in hypotension. Because this change happens much more slowly than the heart rate, and because many displays employ "auto-gain"—that is, they control the size of the display to maintain a constant waveform amplitude (e.g., the plethysmograph display of most pulse oximeters)—the systolic pressure variation has been clinically neglected for many years.

With modern data recording and storage, Cushing's original rationale of correlating changes in patient physiology to intra-

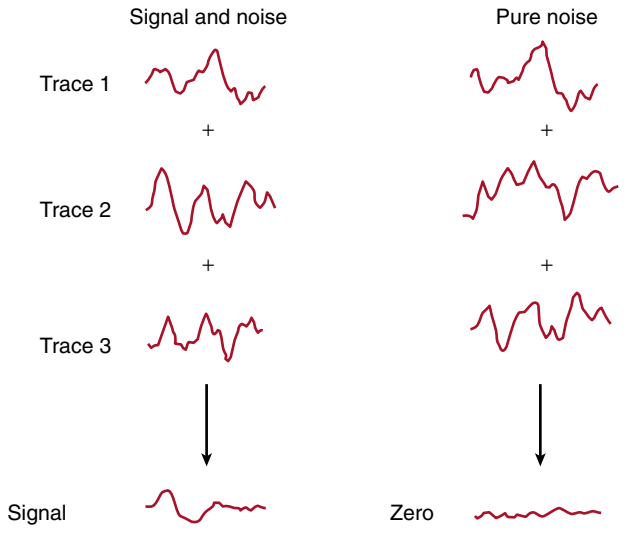


Figure 38-9 Somatosensory evoked potentials. A background signal can be separated from random noise by repeatedly adding the signals. The noise (random) is equally likely to be positive or negative; adding positive and negative yields zero with multiple summations.

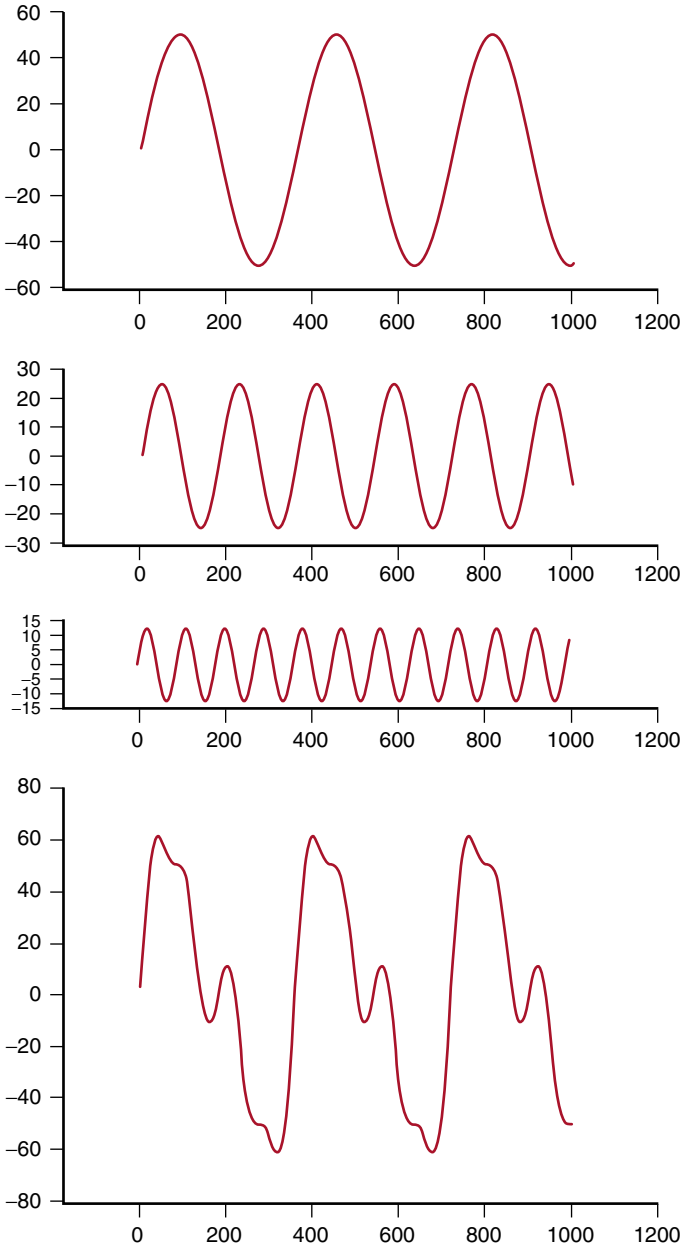


Figure 38-10 Fourier series. This pseudoarterial waveform was generated by adding the three sine waves with the following characteristics, y = 50 sinx, y = 25 sin2x, y = 12 sin4x.

operative events can now be applied to entire populations as well as individuals. The original signal, whether an observed pupillary sign, palpated pulse, transduced pressure, or auscultated breath sound, that was integrated by the anesthesiologist, interpreted (is this real or is it artifact?), and charted (data storage) can now be processed automatically. This point is important because it introduces new possibilities in monitoring (trends, signals, feedback to user) and new pitfalls. Imagine an anesthesia record that would alert you to future potential physiologic issues from currently monitored data and predictive algorithms, that is, an intelligent

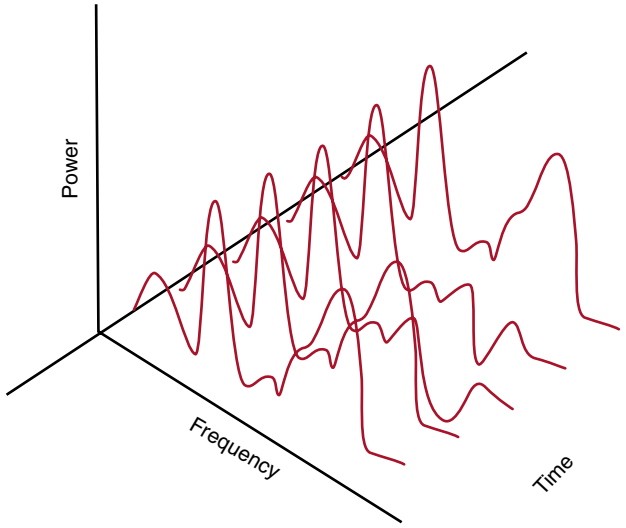


Figure 38-11 Spectral arrays. A compressed spectral array can display the frequency on the *x* axis and power on the *y* axis. A number of these can be aligned with time as a third axis, giving an indication of changes in power over time.

anesthesia record. New problems are introduced by such technology, including security, potential loss of data (loss of not only a single chart or data point, but of all the charts), and erroneous signal processing (imagine a faulty algorithm denying you the very information Cushing sought to use to improve patient care).

Pressure Measurement

Principles of Pressure Measurement

With some of the basics of measurement behind us, we can now work through an example of clinical measurement. As part of a clinical examination, we can note the distention of the jugular vein. What are we really doing? We are visualizing the reflection of light off of the patient's skin changing as the underlying structure (the jugular vein) fills and collapses. But what are the physics of this distention? If we were to insert a clear tube into the vein and hold the tube vertical with respect to gravity, we would observe the mass of blood in the tube raised a certain distance (centimeters) against the force of gravity by the central venous pressure until a balance point is reached. Energy is lost in the work done in raising the fluid column, distending the tubing, and frictional losses. The actual venous pressure is slightly greater than we can reasonably measure. Despite these limitations, a liquid manometer is a simple and effective way to determine central venous pressure.

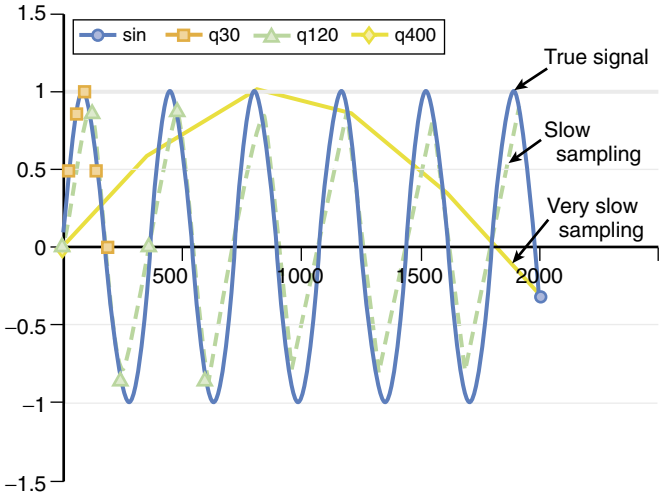


Figure 38-12 Aliasing. Improper sampling leads to an erroneous waveform. A slower sampling rate results in a change in the amplitude and wavelength.

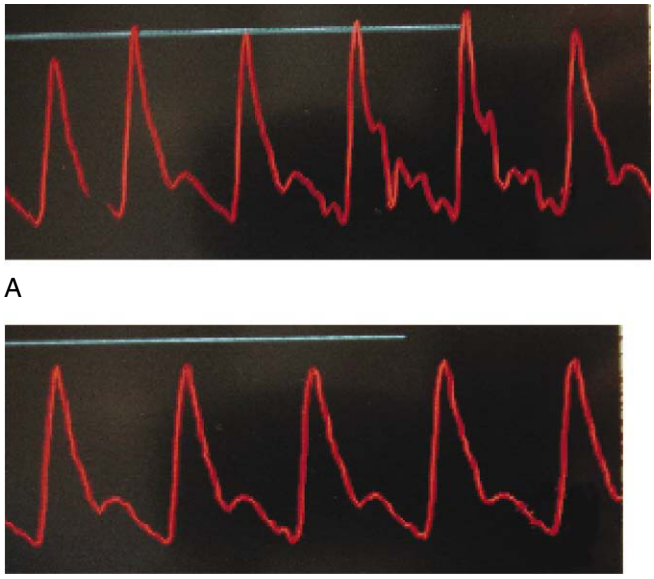


Figure 38-13 Arterial waveform resonance. **A,** A peaked arterial waveform indicating some resonance with overestimation of the systolic blood pressure. **B,** The same patient when damping is added to the system.

The units of pressure measurement can tell us something about how the measurement is made. We commonly define pressure in terms of millimeters of mercury (mm Hg), centimeters of water (cm H_2O), pounds per square inch (psi), or atmospheres (atm). What we have measured in our clear manometer tube is a pressure in centimeters of blood. Given that the content of blood in the tube can vary, we need to have more standard units than centimeters of patient blood. To do so, we must understand the physics of the manometer. The density of a fluid is its mass per unit volume, which has SI units of kilograms per cubic meter (kg/m^3) or, more commonly, grams per milliliter (g/mL). The pressure exerted by a liquid column of height z and density ρ is simply ρgz (see Appendix 2 for derivation). If the manometer liquid is mercury, which has a density of 13,600 kg/m^3 (13.6 g/mL), the manometer pressure in pascals (the SI unit of pressure) is:

$$P\,(\text{Pa}) = 13{,}600 \cdot 9.8 \cdot z\,(\text{m}) = 1.333 \cdot 105 \cdot z\,(\text{m})$$

Because these large numbers are awkward, we often express P in kilopascals (kPa) and z in mm Hg:

$$P\,(kPa) = 0.1333z\,(mm\ Hg)$$

A useful reference for the various pressure units in use today is the pressure of the earth's atmosphere at sea level, called "1 atmosphere" or 1 atm:

$$\begin{aligned} 1\ atm &= 101.3\ kPa \\ &= 760\ mm\ Hg = 29.92\ inches\text{-}Hg \\ &= 14.7\ psi \\ &= 988\ cm\ H_2O \end{aligned}$$

If a fluid-filled catheter is connected to the circulatory system of a patient, the height of the fluid in the manometer determines the mean pressure at the tip of the catheter. If the pressure measured is central venous pressure, we can use these data to infer right ventricular preload. For slowly changing pressures, a water or mercury manometer is simple and dependable (see Fig. 38-4). The manometer cannot respond quickly to rapid changes in pressure because of its inertia; that is, the mass of the liquid column resists rapid changes in height.

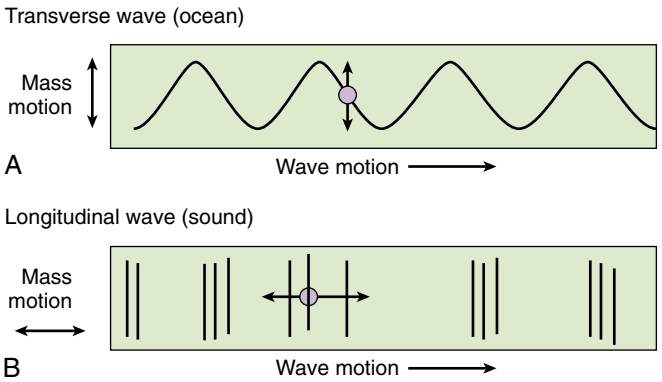


Figure 38-15 Transverse and longitudinal waves. **A,** In transverse waves (e.g., ocean waves), the particles move perpendicular to the motion of the wave. **B,** In longitudinal waves (e.g., sound waves), the particles move back and forth in the direction of the wave. The actual matter in either wave does not move much. The energy transfers without mass transfer. In arterial systems, this can clarify the fact that pressure does not equal flow.

Dynamic Pressure Measurement (Transducer)

Accurate measurement of a rapidly changing pressure signal, such as arterial blood pressure, is more difficult and complex. There are many characteristics of the arterial pressure versus time waveform (Fig. 38-14) that we might wish to determine. Systolic, diastolic, and mean arterial pressures are given by the maximum, minimum, and average pressure values during the cardiac cycle. In addition, we can measure the maximum upward slope of the waveform during systole, which is related to the speed of ventricular ejection. An abnormally rapid downslope after aortic valve closure (indicated by the dicrotic notch) suggests possible aortic insufficiency. The details of the pressure-time waveform and its maxima and minima are important to the clinician. Despite our display of the waveform on a vertical axis, it is important to remember that the arterial pressure is not a transverse wave (similar to a wave on the ocean), but a longitudinal wave (similar to a sound wave or a pulse transmitted through a coiled spring) (Fig. 38-15).

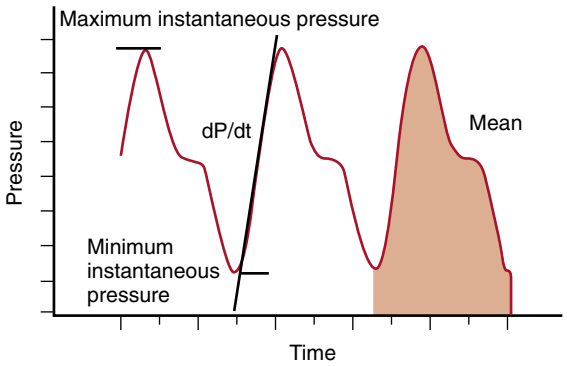


Figure 38-14 Arterial waveform. Systolic pressure is defined as the instantaneous maximal pressure; diastolic, the instantaneous minimum pressure; and mean, the average pressure over a cycle. dP/dT refers to the upstroke of the arterial pressure (i.e., the rate of pressure generation). The mean pressure is estimated as the diastolic plus ⅓ the pulse pressure (systolic-diastolic) when only the systolic and diastolic pressures are known.

A modern pressure transducer is a device that changes either electric resistance or capacitance in response to changes in pressure on a solid-state device. The variable transducer electric resistance is placed in a circuit involving three known resistances (Wheatstone bridge [see Fig. 38-5]; see Appendix 3), and the change in resistance is converted into electric voltage. The moving part of the transducer itself is very small and has little mass. It is not clinically or commercially practical to place the transducer in direct contact with arterial blood (although one manufacturer has done exactly this), so we use a liquid-filled tube to connect the intra-arterial catheter to the external pressure transducer. This system of a fluctuating driving pressure (i.e., the arterial pressure being measured), a liquid-filled tube, and a pressure transducer is mechanically equivalent to the mass-spring harmonic oscillator shown in Figure 38-16. The mass (m) represents the mass of the fluid in the tubing. The spring represents the elasticity of the tubing and transducer. The damper, shown schematically as a piston moving in oil, represents the friction generated by the fluid moving to and fro in the tubing.

A more commonly encountered harmonic oscillator is that of a car driving down a bumpy dirt road (see Fig. 38-16). In this case, the oscillating driving pressure is provided by the bumps in the road, which force the car wheels to oscillate up and down. The car springs are analogous to the compliance of the arterial pressure tubing, and the car's shock absorbers, which oppose motion of the wheel in either direction, are analogous to the friction of the fluid moving back and forth in the fluid-filled tube. Depending on the frequency of the bumps (i.e., driving pressure frequency), the system can either suppress the bumpy road or may initiate dramatically increased oscillations. The frequency of the driving force that causes maximal amplification of the signal is called the natural or resonant frequency (Fig. 38-17). The degree of amplification is directly related to the mass and inversely related to the amount of friction present; for large amounts of

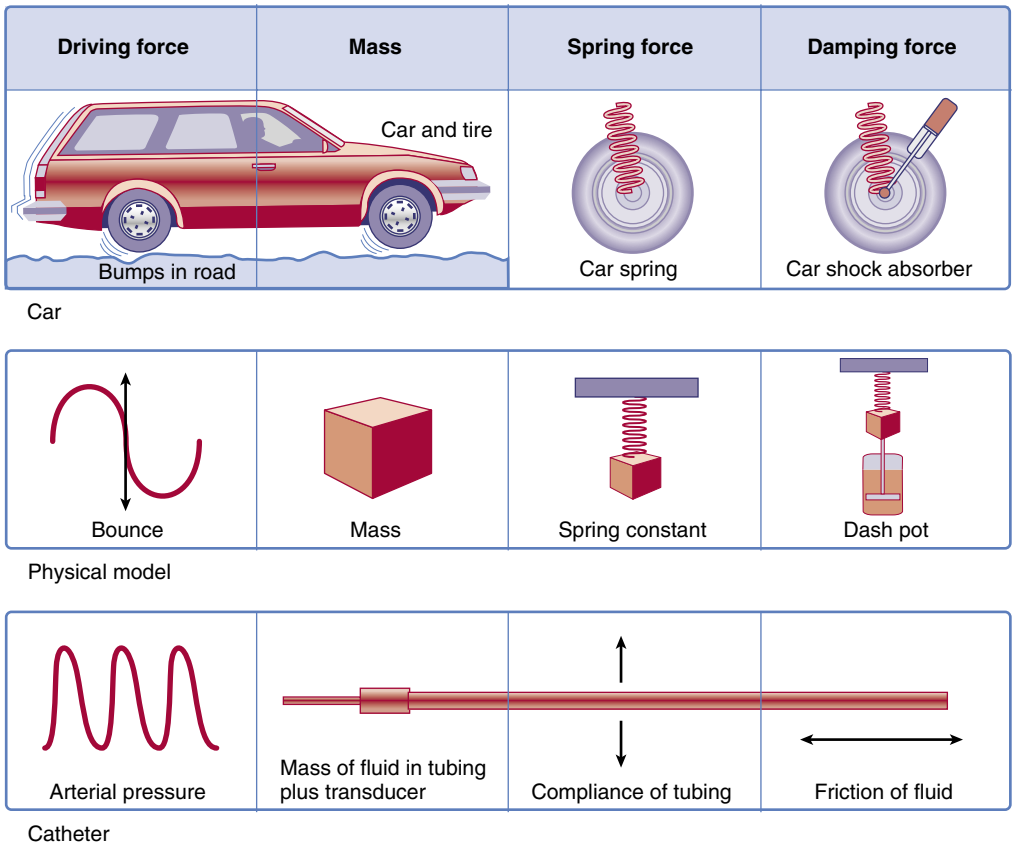


Figure 38-16 Damping and resonance. Pressure measured in an invasive arterial catheter can overshoot or amplify the actual blood pressure. This phenomenon is referred to as the dynamic frequency response of the fluid-filled arterial line and transducer system. This phenomenon has a physical model, which can generate an equation to predict the output pressure response, depending on the frequency of the input pressure and several physical parameters of the system. In the physical model, the driving pressure (the arterial blood pressure) acts on a mass (the fluid within the arterial pressure tubing), pushing it up and down against a spring, which stores energy (the compliant pressure tubing), and a dash pot, which opposes motion in either direction (the resistance of the fluid as it moves to and fro within the pressure tubing). Depending on the input frequency, the output may go through an amplification as it reaches a specific frequency, known as the resonant frequency of the system. There is a common phenomenon noted when a car drives along a bumpy dirt road. In this situation, the driving force is the bumps in the road, which act on the tire. The car spring is equivalent to the compliance to the pressure tubing, and the shock absorber corresponds to the resistance of fluid moving back and forth in the arterial line. The mass of the fluid is analogous to the mass of the front of the car. You may have experienced the phenomenon in which you reach a certain speed as you are driving along a bumpy road when the front of the car starts to oscillate with increasing amplitude. If you speed up or slow down, this phenomenon disappears. The car bounces highest when you have reached the resonant frequency of this harmonic oscillator. (See Appendix 4 for a detailed mathematical description of this process.)

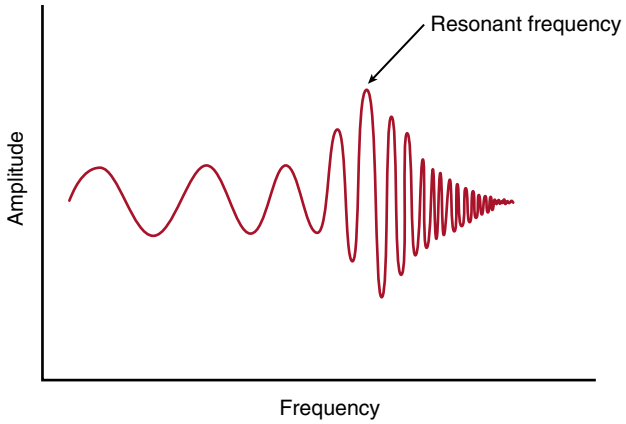


Figure 38-17 Amplitude and frequency. As the frequency increases, the amplification can increase to a maximum, and then the signal becomes attenuated. *(Adapted from Sykes MK, Vickers MD, Hull CJ: Principles of Measurement and Monitoring in Anesthesia and Intensive Care, 3rd ed. Oxford, Blackwell, 1991.)*

friction, attenuation rather than amplification occurs (see Appendix 4).

To visualize this concept intuitively, hang a weight on the end of a rubber band while holding the upper end of the band in your hand. If you move your hand up and down slowly, the weight follows your hand movements almost exactly. As you increase the frequency of your hand oscillations, the weight begins to "lag" behind your hand, and the amplitude of the weight movement begins to increase. As you approach the natural frequency of this simple system, you will observe the phenomenon of "resonance," when the amplitude of the weight motion becomes very large. If you try different rubber bands and weights, you will find that stiffer bands or smaller weights yield higher natural frequencies. The same is true of our fluid-coupled pressure transducer system. Stiffer (i.e., less compliant) tubing or a shorter length of tubing (less mass) produces higher natural frequencies in this system; that is, it requires a much higher pulse rate before amplification.

To minimize the potential of amplification of the real arterial pressure, the system should have noncompliant (i.e., stiff) tubing, and the total mass of liquid in the system should be minimized, which can be accomplished by having small-diameter tubing and as short a length as possible. In most clinical systems, the natural resonant frequency is 10 to 15 Hz, which is much higher than the primary frequency of the arterial waveform (the heart rate is 60 to 120 beats/min or 1 to 2 Hz). The arterial waveform is not a sine wave, however; it is the more complex shape shown in Figure 38-10 and is composed of a summation of sine waves of frequencies that are various multiples of the heart rates—a Fourier series. The higher frequency components of the arterial waveform (higher harmonics) are the ones that are closer to the natural frequency of the system and are amplified. This is why we see a "whip" in the waveform when the peak systolic pressure and the initial upstroke are amplified significantly above the true systolic pressure, even though the heart rate itself is not near the resonant frequency. Theoretically, mean arterial pressure should be the same because this amplification of systolic pressure also produces a reduction in diastolic pressure (see Appendix 4).

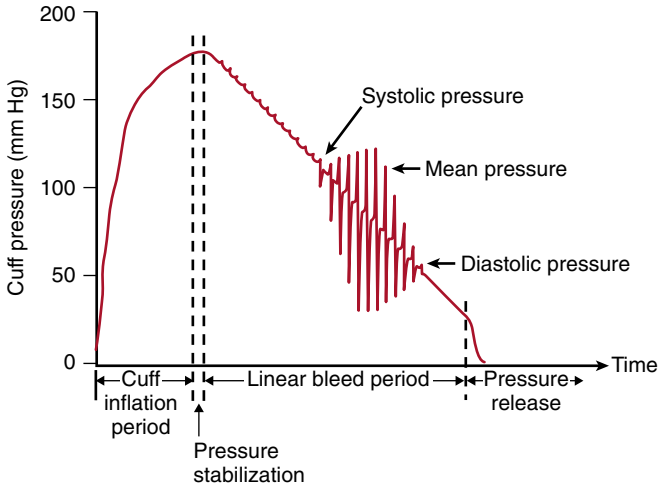


Figure 38-18 Noninvasive blood pressure measurement. Using the signal from the arterial pulse, oscillometric blood pressure measurements are obtained by determining the point at which the signal is first detected, its maximal amplitude, and the signal decay rate. *(Adapted from Ehrenwerth J, Eisenkraft J: Anesthesia Equipment: Principles and Applications. St. Louis, Mosby-Year Book, 1993.)*

Signal-Processed Pressure Measurement (Noninvasive Blood Pressure Monitor)

Systolic pressure can be estimated by noting return of the flow pulse after occlusion of the brachial artery by a cuff. The return of flow can be detected by (1) simple palpation of the radial artery, (2) recording with a Doppler device over the radial artery, or (3) the use of a pulse oximeter. Most anesthesiologists are familiar with the loss of pulse oximeter signal when the noninvasive blood pressure monitor is cycling.

Automated noninvasive blood pressure monitoring devices used in operating rooms employ a more sophisticated application of this principle. These devices monitor the oscillating signal generated in the cuff by the arterial pressure changes. The cuff first inflates to above systolic pressure, at which point the signal and oscillations are abolished. Then the cuff slowly deflates in a stepwise fashion. The pressure at which the oscillating pressure signal first appears is interpreted as the systolic pressure. The signal increases in amplitude as the cuff pressure decreases. The point at which the signal is at maximal amplitude is interpreted as mean arterial pressure. As cuff pressure decreases further, the oscillations drop off rapidly. Diastolic pressure is mathematically inferred from the systolic and mean values (Fig. 38-18).[8]

Errors can be introduced in the same manner as for manual auscultation of Korotkoff sounds: Too small or too large a cuff requires a higher or a lower pressure to occlude arterial flow, and stiff atherosclerotic arteries are resistant to compression. External compression caused by patient motion or the surgeon leaning on the blood pressure cuff can cause pressure oscillations that are not related to arterial pressure and may result in an erroneous reading, most commonly a higher diastolic pressure. Mercury sphygmomanometers are being phased out of use in some countries and hospitals, which leads to questions regarding the accuracy and precision of alternative devices, such as the aforementioned automated noninvasive blood pressure monitors and aneroid sphygmomanometers.[9,10]

Measurements Using Sound Energy (Longitudinal Pressure Wave)

Principles of Sound

Sound waves are small fluctuations in pressure, density, and velocity that can propagate through matter of any form: solid, liquid, or gas (see Fig. 38-15). In contrast to electromagnetic waves such as light (see the section on light), sound cannot propagate in a vacuum. The commonly used unit of sound, the decibel (dB), is not an SI unit, but a logarithmic ratio of the sound energy referenced to 20 μPa (or 0.0002 millibar), the threshold of normal human hearing.

Sound has been used for many years in medical diagnosis and monitoring. It can be used as a diagnostic method in two ways: passive and active. In a passive examination, the sounds generated by the patient are studied. The basic examination of this type uses the stethoscope. In an active examination, acoustic energy is transmitted into the patient, and the resulting interaction of this energy with the patient is analyzed for information. Both types of examination use the same physical principles.

In 1842, Doppler first described the apparent change in pitch of a sound that occurred when either the source of the sound or the listener was moving.[11] This "Doppler effect" now has several applications in patient monitoring, including precordial and esophageal Doppler ultrasound monitoring of local blood velocities or cardiac output.

When a sound source is moving toward the listener, the apparent pitch increases, and vice versa. The exact amount of frequency shift depends on whether the listener or the sound source is moving (Fig. 38-19; see Appendix 7). Because changes in the frequency of sine waves can be measured precisely, the Doppler principle provides a very accurate method of measuring

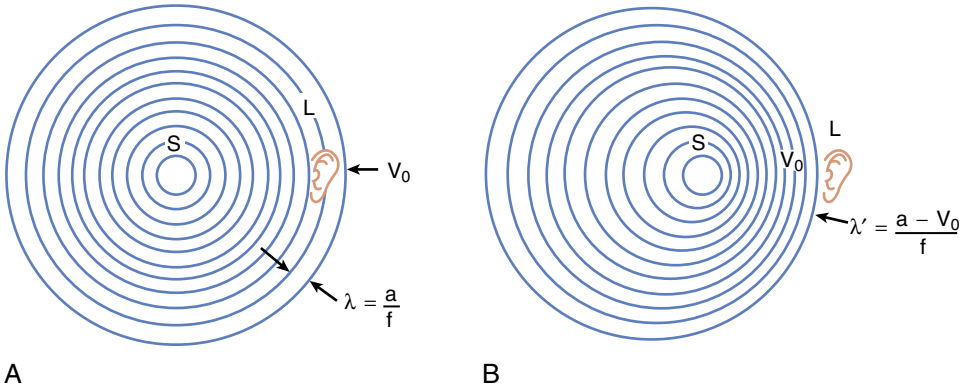


Figure 38-19 Doppler effect. **A,** When a listener is moving toward a stationary sound source, the frequency increases because the listener transverses more waves per unit time than a stationary listener. **B,** When a sound source is moving toward a stationary listener, the wave fronts "stack up," causing an apparent increased frequency.

the velocities of moving sound reflectors. At the high frequencies often used (>5 MHz), objects as small as red corpuscles can scatter enough sound for detection.

Passive Sound Examination (Stethoscope)

Vibrations, such as those caused by the closing and opening of heart valves or air moving through the respiratory passages, travel through the body as sound waves. Sound is conducted better and more rapidly in liquids than in gases. Bronchial breath sounds are heard better when the bronchi are surrounded by lung consolidation. When sound waves reach a sudden change in density (e.g., a liquid-gas interface), some of the energy is reflected.

Some simple facts about sound waves can facilitate an understanding of the reflection and scattering process in the body. First, all sound waves can be represented as a summation of sinusoidal waves of various frequencies and amplitudes. This process of Fourier or power spectral analysis was discussed earlier in this chapter. A note from a musical instrument consists of a sine wave at the "fundamental frequency" plus many "harmonics" at multiples of this frequency. The fundamental frequency describes the pitch of the tone: middle C is standardized at 256 Hz, for example.

All of these many frequencies propagate at the same speed, the speed of sound (called "a"). For ideal gases, the speed of sound is proportional to the square root of temperature. The speed of sound in air at room temperature is 344 msec, or 1129 ft/sec or 770 miles/hr (mph). At an altitude of 13,000 m (40,000 ft), where the standard air temperature is −57°C, the speed of sound is only 295 msec, or 661 mph. The speed of sound is much higher in liquids than in gases. The speed of sound through water at 15°C is 1450 m/sec. This value also approximates the speed of sound through most of the solid parts of the human body. In other solids, the speed of sound varies greatly, with a range of 54 m/sec in rubber to 6000 m/sec in granite. Reflection of sound occurs at interfaces where the product of the density and the speed of sound ($\rho \times a$) changes suddenly. Larger changes in this "acoustic impedance" result in greater reflection and less transmission. In the human body, the largest changes in acoustic impedance occur at gas-tissue boundaries: the lungs and the gastrointestinal tract. Reflection of sound by the lungs makes it difficult to auscultate heart tones through an air-filled, emphysematous chest. For the same reason, a transthoracic echocardiograph provides less detail than the transesophageal technique; in the former case, the lungs are in the way.

The first attempts to gather information about the inside of the patient by using sound involved placing one's ear directly on the patient. Although this procedure had many limitations, it led to the development of the modern stethoscope, which is based on the physical principles of sound transmission. The stethoscope uses a large diaphragm to transmit and concentrate the sound energy. The bell acts as an amplifier and a low-pass filter to transmit low-frequency diastolic rumbles. The physics of stethoscopy were described in depth by Rappaport and Sprague.[12]

In a simple stethoscopic examination, errors are introduced by "signal processing," that is, lack of experience or appropriate knowledge on the part of the listener. Because it is a nonpowered, nontechnologic device (the energy levels come from the phenomena themselves), an esophageal or precordial stethoscope has unique value in being a continuous monitor during power outages. Physical limits to the technique include airspace disease (in itself an informational finding), inability to place the monitor appropriately, and lack of quantifiable data.

Active Sound Examination (Percussion, Echo, Doppler)

The earliest "active" acoustic diagnostic technique was percussion of the chest wall. A skilled clinician can use this method to detect consolidation of the lungs, pleural effusion, and a few other chest pathologies. Although based on transmission and reflection of sound, percussion is purely qualitative and is unable to localize pathologic changes accurately. Modern ultrasound improves on percussion by using shorter wavelength sound waves and quantitative detection of their reflections (echoes). The spatial resolution of an examination is limited by the wavelength of the sound used (Fig. 38-20). Using ultrasound at frequencies in the megahertz (10^6 cycles/sec) range allows resolution of much smaller objects. The wavelength of 1-MHz sound waves in solid tissue is about 1.5 mm, whereas the wavelength of a 256-Hz tone (middle C) in tissue is 5.7 m.

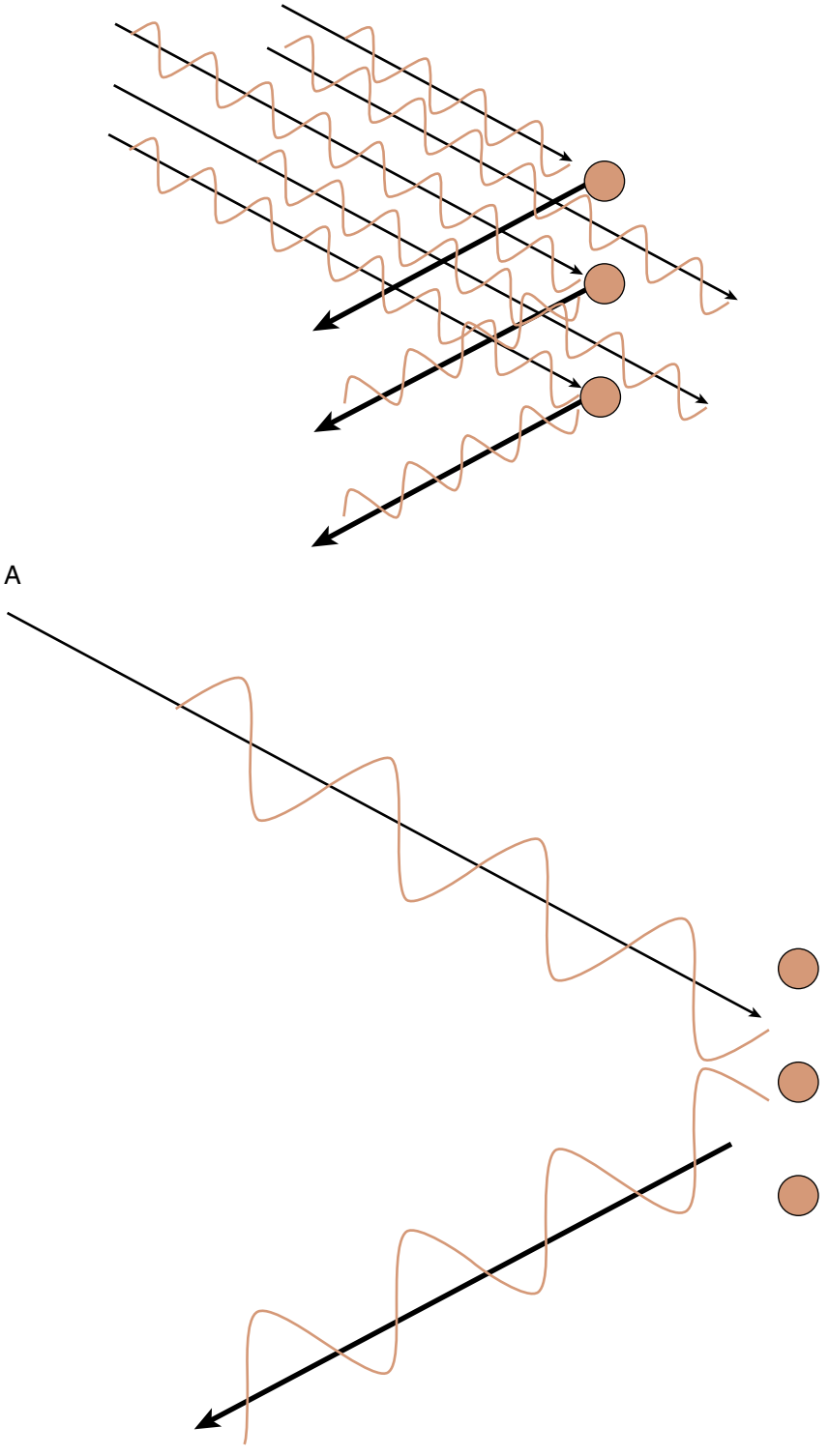


Figure 38-20 Wave size and resolution. Wave reflection depends on the relative size of waves and objects. For small objects, small waves are needed for good reflection and resolution. **A,** The object size is large relative to the wave size, resulting in good spatial resolution. **B,** The object size is small relative to the wavelength, leading to poor resolution of the objects. This principle also applies to light waves. Electron microscopes can resolve smaller objects than light microscopes because the wavelengths used are smaller. Imagine running an unsharpened pencil over a fine (1-mm grid) or coarse (1-cm grid) screen. The pencil sticks in the larger holes, while passing over the smaller ones. Sharpening the pencil to a point improves the resolution.

With the use of esophageal transducers, echocardiography has become a popular intraoperative monitoring technique.[13,14] Sound waves in the 2- to 10-MHz range are transmitted toward the heart in short bursts or pulses. After each pulse, the transducer passively listens to the reflected echoes from various tissues. The ability to place the transducer in the esophagus is advantageous because sound does not have to pass through airspaces or bone on its way to and from the heart. The speed of sound through the heart and surrounding soft tissues is a nearly constant 1540 msec. Exact measurement of the elapsed time between transmission of the pulse and receipt of the echo provides the distance to the reflecting structure. The sound beam from the transducer is projected in a narrow "searchlight" pattern, so the exact direction of reflecting structures also is known.

The Doppler effect is used in echocardiography to determine the presence and degree of valvular regurgitation by converting the Doppler shift of sound waves reflected from erythrocytes into a color display (see Appendix 7; also see Chapter 41). Cardiac output also can be estimated from descending thoracic aortic blood velocity by using a Doppler technique. These devices estimate the blood flow in the descending aorta and ignore flow to the head and arms. They calibrate descending aortic flow to cardiac output by assuming a constant proportional relationship between the two flows.[15]

Measurements Using Electric Energy (Transverse Wave) (see also Chapter 100)

Principles of Electricity

Most monitors and other anesthesiology apparatus use the basic principles of electricity and magnetism. Nearly all transducers use some form of electric energy as their output, and the subsequent data processing and display are entirely electric. We review some basic electromagnetic principles in this section by using examples from medical equipment. Electromagnetic waves, including light, are transverse waves, meaning that the electric and magnetic field vectors are oriented perpendicular to the direction of wave propagation. In contrast to sound, these waves require no media in which to propagate.

Static Electricity

Electricity is a manifestation of a property called "charge" that is inherent in matter. The charge can be negative, positive, or neutral. Static electricity involves charges at rest: Like charges repel one another, whereas opposite charges attract. What we usually mean by the word "electricity" involves the flow of charges, or electric current. Current flows in one direction in direct-current (DC) electronic devices and alternates back and forth in alternating-current (AC) devices.

The SI unit of charge is the coulomb, and the smallest quantum of charge is the charge of an electron (1.6×10^{-19} Coulomb), which is equal but opposite to the charge of a proton. (More recently discovered subatomic particles called "quarks" actually have smaller charges, but this is beyond the scope of this chapter and not relevant to medicine.) An electrostatic force is exerted between two charged objects and is directly proportional to the product of the two charges and inversely proportional to the square of the distance between them:

$$F = k \times q_1 \times q_2 / r^2 \text{—Coulomb's law} \quad (1)$$

This force is attractive when the charges are of opposite sign, and repulsive when they are of the same sign. In a Nobel Prize–winning experiment, Millikan determined the charge of an electron by suspending charged oil drops between two horizontal charged plates such that the electrostatic force balanced the gravitational force, and the drops were held in midair (Fig. 38-21). Approximately 20 years later in 1940, Millikan's son developed one of the earliest infrared ear oximeters, the forerunner of the pulse oximeter (see the section on the pulse oximeter).

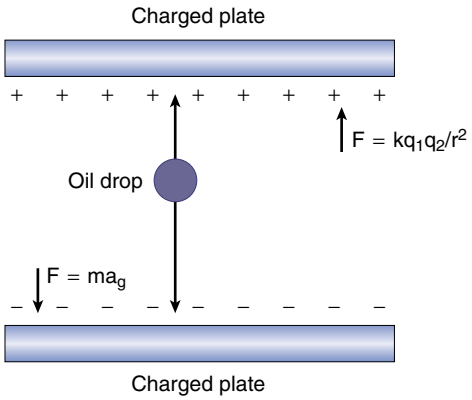


Figure 38-21 Electric force. The quantity of charge on an electron was determined by balancing the electric force on an oil drop against the gravitational force on the same drop. $F_1 = kq_1\, q_2/r^2 = F_2 = m_1\, a_g$.

Direct Current

Just as mechanical energy may be stored as potential energy, electric energy can be stored as a "potential difference." A common analogy is to compare electric potential difference with water pressure (Fig. 38-22 and Table 38-2). The potential difference (V) between points *A* and *B* is defined as the work required to move a unit charge from *A* to *B*. The SI unit of potential difference is the volt; the term *voltage* is often used for potential difference. Charges can move easily through conductors, but they do not move well through insulators, also called "dielectrics." If a potential difference (V) exists between *A* and *B,* and these two points are connected by a conductor, charges will flow between them and produce an electric current (I).

The SI unit of current is the coulomb per second, called the "ampere." If points *A* and *B* are separated by an insulator, no current will flow until the potential difference becomes so great that a breakdown of the insulator occurs. If *A* and *B* are separated by dry air, no current will flow until the potential difference reaches 3000 V/mm. At this very large potential gradient, air ionizes and becomes a conductor, and a current flows in the form of a visible (and audible) spark. To generate a spark between two electrodes 1 cm apart, one must create a potential difference of 30,000 V. The spark plugs in a car have an electrode gap of about 0.8 mm, requiring at least 2400 V from the ignition coil to generate a spark. Lightning is a larger manifestation of the same phenomenon.

A battery is a chemical cell that produces a nearly constant potential difference between two electrodes, which is called "electromotive force (EMF)". The battery can provide a continuous source of electrons, or current, to flow through any conducting circuit connected between its electrodes. Flow of electricity is opposed by resistance, analogous to resistance in water pipes. In most materials, resistance (R) is related to voltage (V) and current flow (I) in the following manner:

$$V = IR \quad (2)$$

This relationship is called Ohm's law, and materials that follow this behavior are called "ohmic" materials. This example is analogous to hemodynamic flow, in which the pressure decrease across the systemic vasculature (mean arterial pressure—central

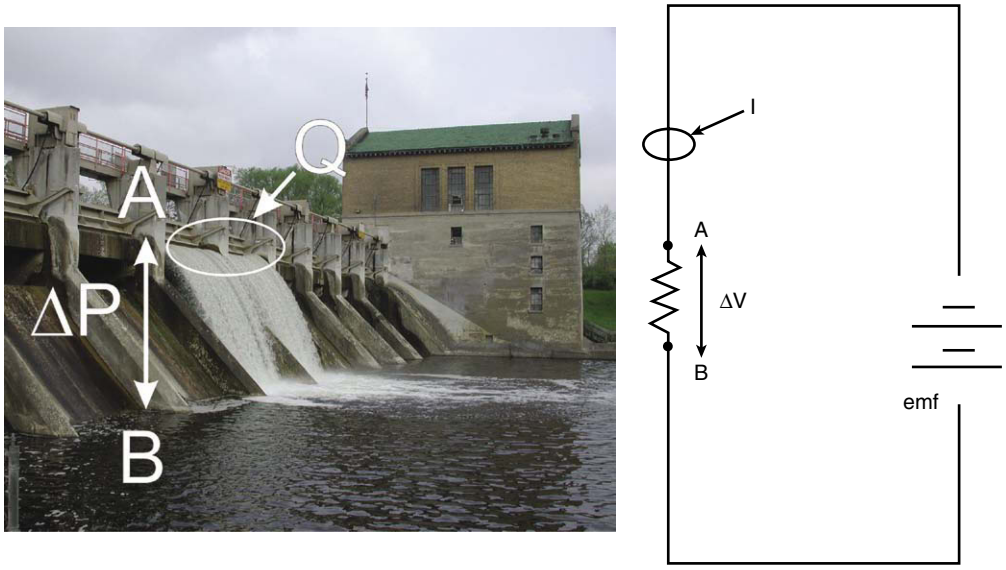


Figure 38-22 Water and electricity. The pressure drop over the dam (*A* to *B*) is analogous to the voltage drop over the resistance (*A* to *B*) (e.g., light bulb). The amount of flow (width of water) (*Q*) is analogous to the current (*I*). Both falling water and electric potential can do work, as evidenced by the use of dams to generate electricity and electricity to pump water.

venous pressure) equals cardiac output times systemic vascular resistance:

$$\Delta P = CO \times SVR \quad (3)$$

The power (i.e., rate of work; see discussion earlier in this chapter) required to produce an electric current is the product of voltage and current: P = VI. By combining this formula with Ohm's law (V = IR), we have $P = I^2R = V^2/R$. If we double the current through a fixed resistance (R), we use four times the original power. This power loss in resistors is dissipated as heat, which is the reason why nearly all electric devices become warm during use. The filament in an incandescent light bulb is merely a resistor that becomes so hot from ohmic heating that it glows, or radiates light.

A capacitor is a device that stores charge (Q) in direct proportion to the potential difference (V) between its two electrodes: Q = CV. The proportionality constant (C) is called "capacitance," which is measured in SI units of farads (1 farad = 1 coulomb/volt). When a capacitor is connected to a battery, current flows until the capacitor is charged to the point that the potential across the capacitor equals the EMF of the battery: V = Q/C = EMF (Fig. 38-23). When we push the "charge" button of a cardiac defibrillator, this kind of circuit is activated to charge a capacitor to the desired level. As shown in Figure 38-23B, time is required to charge a capacitor. For a large capacitor, more time is required. It takes longer to charge a defibrillator to 200 J than to 50 J.

Table 38-2 Comparison of Hydrodynamic and Electrical Energy Commonly Encountered

Water	Electricity	Energy
Squirt gun	Static electric spark	High pressure, low flow, low energy
Garden hose	House current	Moderate pressure, moderate flow, moderate energy
	Car battery	Low pressure, moderate flow, moderate energy
River flood		Low pressure, huge flow, huge energy
Fire hose	High tension wires	High pressure, high flows
	Lightning	High pressure, high flow

Alternating Current

In an AC circuit, the current and the voltage fluctuate rapidly (Fig. 38-24). There are many important differences between AC and DC power. The voltage in common AC "house power" fluctuates sinusoidally at a frequency of 60 Hz (50 Hz in Europe). We characterize the amplitude of such a fluctuating voltage by its root mean square (RMS), that is, the square root of the time average of V^2. For AC house power, V_{RMS} = 115 V (230 V in Europe). Current in an AC system also is constantly changing and is likewise measured as an RMS value.

AC circuits have three forms of impedance: resistance (R), capacitance (C), and inductance (L). An inductor is a circuit element whose impedance, called "inductive reactance," increases with the frequency (f) of the current fluctuations ($R_L = 2\pi fL$). Conversely, the impedance of a capacitor, called "capacitive reactance," decreases with increasing frequency ($R_C = \frac{1}{2}\pi fC$). Inductors tend to block high frequencies, whereas capacitors tend to block low frequencies (Fig. 38-25). This principle is used in stereo systems to direct the signal to either the "woofer" (low-frequency speaker) or the "tweeter" (high-frequency speaker). In medical instruments, inductance and capacitance circuits can be used to "filter" the signal (e.g., decreasing the amount of 60-Hz interference from AC wiring).

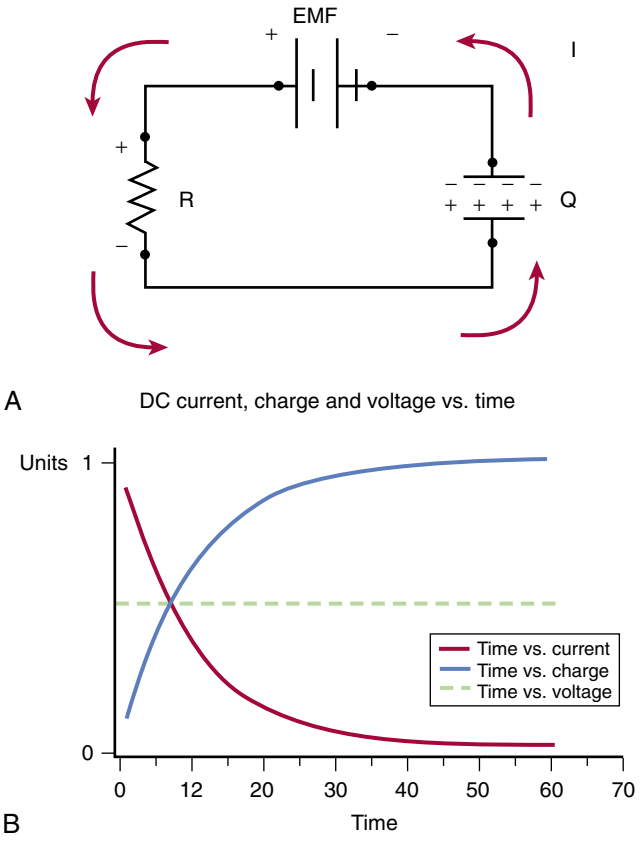


Figure 38-23 Resistance and capacitance in a direct-current circuit. **A,** Under direct current, the resistance impedes flow, resulting in a voltage decrease across the resistance. The capacitor allows current to flow until the charge builds on the capacitor. **B,** Under direct current, the voltage is constant over time, and the current flow decreases as the charge on the capacitor increases. This type of circuit is used to charge a defibrillator.

Passive Electric Examination (Electrocardiograph, Electroencephalograph)

Now that some of the basics of electricity have been described, we can discuss the electrocardiograph (ECG) and the electroencephalograph (EEG), where the sources of EMF are the heart and the brain (see Chapters 40 and 42). Electric potentials on biologic surfaces are too small to observe directly and must be amplified and processed before display. ECG potentials on the skin are in the 1-mV range, and EEG potentials are near 0.1 mV.

Figure 38-26 illustrates why electric potentials on biologic surfaces are so small. The heart generates an electric signal as a result of the synchronous depolarization and repolarization of multiple cells. The electric potentials generated by the heart are measured between two skin electrodes, *A* and *B*. As the figure shows, there are multiple effective resistances and capacitances in the tissues between the EMF source and the measuring electrodes. These impedances reduce the magnitude of the voltage signal at the skin. The "shunt" resistors R_3, R_4, and R_5 combined with the "series" resistors R_1, R_2, and R_3 form what is called a "voltage divider network." Lower values of shunt resistance or higher values of series resistance result in smaller voltages at the skin. The capacitance of the skin (C_s) also acts to attenuate the low-frequency components and distort the waveform. Skin resistance, which may be a megaohm (10^6 ohms) for dry skin, can be reduced to a few hundred ohms by conductive gels.

If a DC voltage is applied between two body surface electrodes, current flows through the tissues between them. Although the electric current in metals consists entirely of electron flow, in tissues, positive and negative ions migrate. Negative ions tend to accumulate at the positive electrode (the anode), and positive ions accumulate at the negative electrode (the cathode). This collection of anions and cations near each electrode creates its own EMF, which opposes the EMF that set up the original current. The current decreases, so the effective impedance between the electrodes increases. This phenomenon, called "polarization of electrodes," has two harmful effects. First, the increased impedance from polarization can attenuate the ECG signal for several seconds after defibrillation or DC cardioversion. Such attenuation could be misinterpreted as a lack of electric activity and result in inappropriate administration of a second shock. The second consequence of prolonged application of DC voltage is accumulation of a local concentration of toxic ions near electrode sites, a condition that can cause burns or tissue necrosis.

A partial solution to the problem is the use of a nonpolarizable electrode, such as a silver and silver chloride combination.

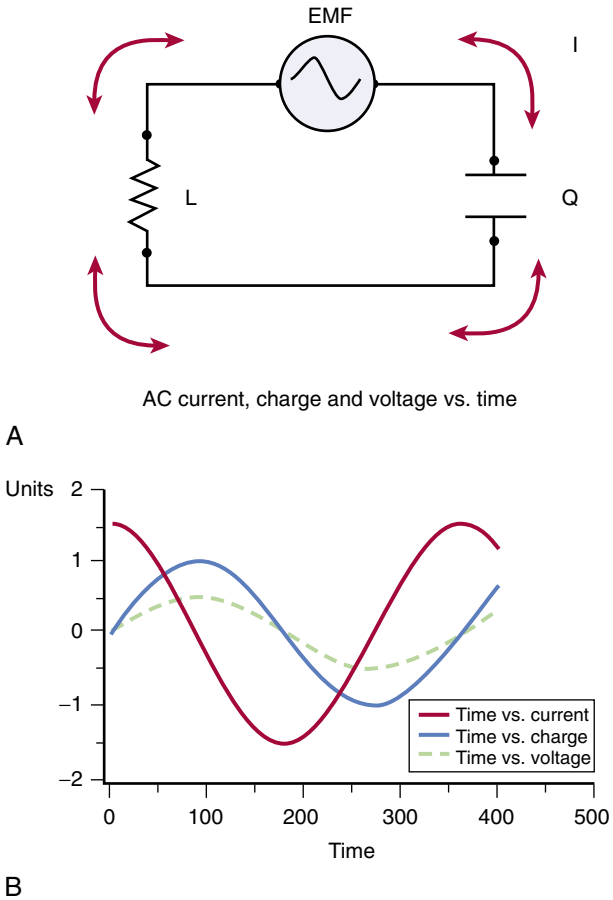


Figure 38-24 Resistance and capacitance in an alternating-current (AC) circuit. **A,** In an AC circuit, in contrast to a direct-current circuit, the capacitor does not block current flow. **B,** The capacitor and resistance act to shift the phase of the AC current. Current changes lag behind voltage changes. EMF, electromotive force.

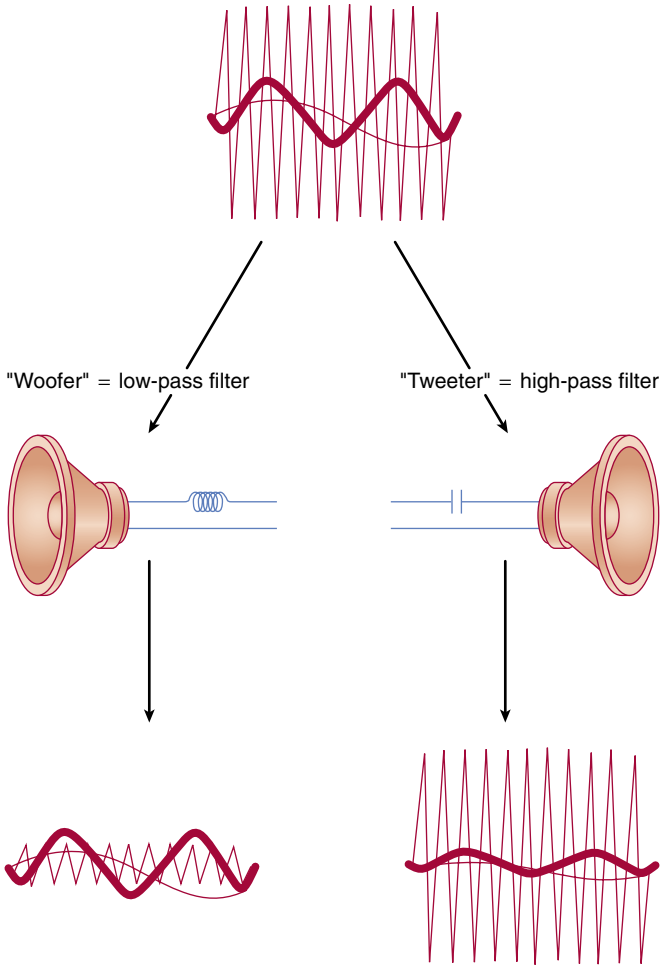


Figure 38-25 Woofer and tweeter. Stereo speakers use resistors to act as an impedance to high-frequency components of sound, allowing only the bass frequencies to pass on to the woofer speaker. Capacitors are used as a high-pass filter to allow only the high frequencies to get to the tweeter. By a similar process, 60-Hz interference from electrical appliances can be decreased. *(From Hecht E: Physics: Algebra/Trig. Pacific Grove, CA, Brooks/Cole, 1994.)*

This electrode can act as a source of, or "sink," for anions and cations, minimizing the accumulation of ions. Most disposable ECG electrodes now use such materials. Even these electrodes are nonpolarizable for only a limited time, however, and the application of prolonged DC voltage between any tissue electrodes must be avoided.

Similar problems complicate measurements of the EEG, but in this case, the raw signal is one tenth the amplitude of the ECG: 100 µV versus 1 mV. The spontaneous EEG provides eight or more channels of surface voltage versus time data, which is of limited use for monitoring in the operating room. For rapid interpretation and diagnosis, the amplitude versus time data are usually transformed into plots of amplitude (or power) versus frequency. This process of power spectral analysis was discussed in the section on signal processing. The EEG power spectrum facilitates rapid diagnosis of hemisphere asymmetries and changes in frequency content that accompany either deep anesthesia or cerebral hypoxia. "Bispectral density" is another method of analyzing the raw EEG that determines levels of correlation (or degree of "phase-locking") between various frequency components in the power spectrum. Another derived parameter is the "burst-suppression ratio," which is the percentage of time during which the EEG amplitude is less than +5 µV. Both of these last two derived quantities have been related to depth of anesthesia in clinical studies (see Chapter 39).

Active Electric Examination (Neuromuscular Block Monitor, Somatosensory Evoked Potentials)

A muscle twitch can be elicited by generating a 0.2- to 0.3-msec pulse of current to depolarize a peripheral motor nerve. This motor nerve conducts the impulse to the muscle, where a twitch is generated. We can understand the "in-use" failings of this device by following the path of the signal. We must start with an adequate power source (no power = no twitch). If the coupling of the electrodes to the patient is poor (i.e., if the electrodes are dry or good skin contact is not made), the circuit will have high resistance, and very little current will flow (see earlier discussion and equation 8), resulting in a diminished twitch. The simplest way to be certain that this monitor is functioning properly is to perform a positive control (see the desired response of thumb twitch before the chosen drug is given) and a negative control (see the twitch disappear in response to administered drug) (see Chapters 46 and 47).

Evoked potential (evoked response) monitors can determine the status of multiple parts of the sensory nervous system by measuring the central nervous system response to a discrete sensory stimulus. The stimulus can be auditory, optical, or peripheral somatosensory. The amplitude of the evoked response measured at the skin can be very small—less than 1 µV in the case of acoustic cortical potentials. This very small signal is in a "sea" of spontaneous EEG (>100-µV amplitude) signals. We resort to a signal enhancement technique called "ensemble averaging." Rather than trying to measure the small response to a single stimulus, we average the responses from hundreds (or thousands) of stimuli. Because the evoked responses that we seek occur consistently at the same time after the known stimulus, this averaging process

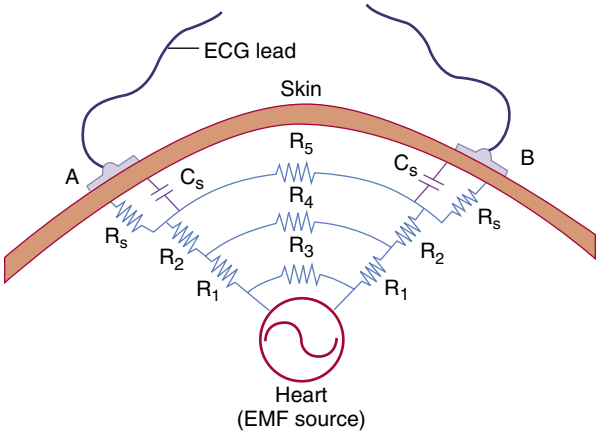


Figure 38-26 Why the electrocardiograph (ECG) is so small. Multiple resistances and capacitances in the body decrease the potential and distort the waveform before the electromotive force (EMF) reaches the surface.

reinforces the signal from the evoked response, and the random "noise" tends to cancel itself. In this way, we commonly measure signals whose amplitude is roughly 1% the amplitude of the background noise (see Fig. 38-9).

Whenever charged particles are moving, a magnetic field is generated in a direction perpendicular to the motion. Paramagnetism is a form of magnetism exhibited only in specific substances in the presence of an external magnetic field. Oxygen is a paramagnetic gas. This property is used to measure inspired and expired oxygen concentrations—chemical methods such as fuel cell amperometric sensors and polarographic electrodes are too slow to respond. In a fast responding paramagnetic oxygen sensor, 100% oxygen can exert a pressure of 3 Pa in a 2.4-T magnetic field.

Measurement Using Light Energy

Principles of Light

What we commonly refer to as light is electromagnetic radiation in the visible range of wavelengths. Every substance with a temperature greater than absolute zero emits electromagnetic radiation, called "black body radiation." This radiation is characterized by a frequency and wavelength that are related by the speed of light: frequency = speed of light ÷ wavelength (c = speed of light = 3×10^8 m/sec or 186,400 miles/sec or 7.5 times around the earth's circumference in 1 second, in a vacuum). High energies or temperatures are associated with high frequencies and short wavelengths, such as those of gamma rays and x-rays. As wavelength increases to the micron range, ultraviolet radiation proceeds to visible light (approximately 0.5 to 0.8 μ), and at larger wavelengths, infrared is followed by microwaves and radio waves with wavelengths in the kilometer range.

Electromagnetic waves and sound waves have some important differences. The particles in motion in sound waves are in the same direction as the propagation (longitudinal waves), whereas in electromagnetic waves, the electric and magnetic fields are perpendicular to the direction of propagation (transverse waves). Sound waves can propagate only through matter, whereas electromagnetic waves propagate through a vacuum without attenuation. The speed of light is about 1 million times faster than the speed of sound in sea-level air. If an observer is moving relative to a sound source, measurement of the speed of sound depends on the observer's own motion, but the speed of light is the same to any observer in any frame of reference. This last statement is the basic premise of Einstein's special theory of relativity. In the high-frequency range of the electromagnetic spectrum are two forms of ionizing radiation: x-rays and gamma rays. These high-frequency waves are capable of knocking electrons out of their orbits and can cause cell injury and death or ontogenesis. Gamma rays are commonly emitted by decaying radioactive nuclei.

Visible light and infrared light have several properties common to all electromagnetic radiation. Light represents a form of energy that, when passing through matter, may be reflected, transmitted, or absorbed. Although light itself cannot be stored, it can be converted into some other form of energy, such as electricity, chemical energy, and heat. In addition, light can be generated from other forms of energy, including heat (incandescent), electric (gas discharge), and chemical (photoluminescent) energy.

Light as a Multifunctional Tool: Beer-Lambert Law

When light passes through matter, it is transmitted, absorbed, or reflected. The relative absorption or reflection of light at different wavelengths is used in several monitoring devices to estimate the concentrations of dissolved substances (e.g., carbon dioxide in respiratory gas and hemoglobin in plasma). This type of measurement is called spectrophotometry and is based on the Beer-Lambert law of absorption, which states that if a known intensity of light illuminates a chamber of known dimensions, the concentration of a dissolved substance can be determined if the incident and transmitted light intensity is measured:

$$I_t = I_i e^{-dC\alpha} \quad (4)$$

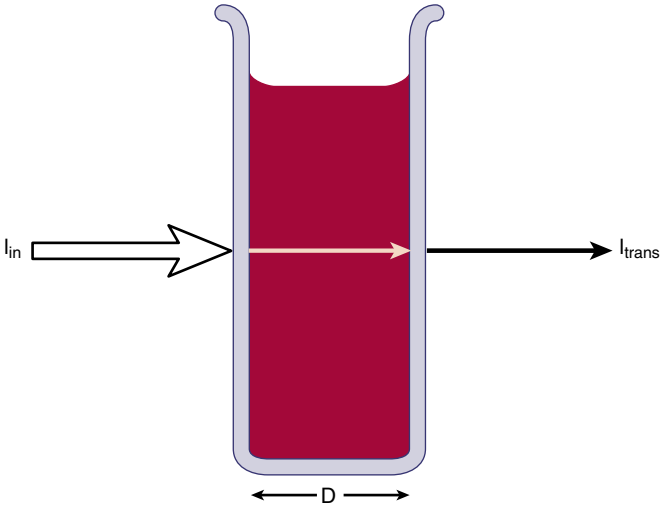
Solved for C:

$$C = \left(1/d\alpha\right)\ln\left[I_i/I_t\right] \quad (5)$$

where C is the concentration of the dissolved substance, d is the path length of the light *a*, and α is an absorption constant for the dissolved substance at the light wavelength used. I_i and I_t are the incident and transmitted light intensity. The unknown C is inversely proportional to d and directly proportional to the log of the ratio of I_i to I_t (Fig. 38-27). Red and infrared light (wavelength 0.6 to 1 μ) are generally used because the constituents of interest to anesthesiologists (anesthetic agents, carbon dioxide, hemoglobin) absorb light within that range. Red and infrared light can penetrate soft tissues and may be used to measure the concentrations of hemoglobin species in vivo (see the section on pulse oximeters). Infrared light is absorbed by small molecules only if they have bonds and are asymmetric; in other words, their molecules have a dipole moment. Nitrogen, oxygen, and helium cannot be measured by infrared light. Another limitation of infrared light is that it is absorbed by ordinary glass; the measurement chambers for these devices must be made of sapphire or other infrared-permeable materials.

Simple Absorbance Monitors (Capnometer, Anesthetic Analyzer)

Capnometers, capnographs, and anesthetic gas analyzers all use the Beer-Lambert law to analyze constituents of the respiratory gas stream (see Chapter 25). A capnometer measures and displays only discrete values of partial pressure of carbon dioxide (P_{CO_2}), such as the end-tidal value. A capnograph provides a continuous plot of P_{CO_2} in the airway versus time. The physical design of capnometers is divided into two categories: mainstream and sidestream. In mainstream capnometers, the light absorption chamber is placed directly in the airway, and the light source shines through the chamber, with carbon dioxide being measured during inspiration and expiration directly. Advantages of this technique are a very fast response time and no problems with clogging of the sampling tubes, which is a disadvantage of sidestream capnometers. Disadvantages of the mainstream geometry include the



$I_{trans} = I_{in}e^{-(D \times C \times a_\lambda)}$

I_{trans} = intensity of light transmitted

I_{in} = intensity of incident light

D = distance light is transmitted through the liquid

C = concentration of solute (oxyhemoglobin)

a_λ = extinction coefficient of the solute (a constant)

Figure 38-27 Cuvette. Light entering the cuvette is reflected and absorbed. The concentration of substances absorbing and reflecting light can be determined by measuring the amount of light entering and exiting the system.

necessity of having a potentially heavy, expensive infrared measurement device placed directly in the airway at the endotracheal tube, and the unavailability of devices that can measure anesthetic agents and carbon dioxide.

The most commonly used devices in the operating room are sidestream capnometers. A thin sampling tube is attached to the airway near the endotracheal tube, and samples are aspirated at 200 to 400 mL/min into the measurement chamber, which is located within the monitor itself. The advantages of this method are the opposite of the disadvantages of the mainstream capnometers; the sampling tube is lightweight, and the device can be used to measure carbon dioxide and anesthetic agents. Disadvantages of sidestream capnometers relate mostly to the delayed response time and potential clogging of the aspiration tubing.[16]

Anesthetic agent analyzers and capnographs function by the same physical principles, but with different wavelengths of light being used (Fig. 38-28). The light absorbances of a mixture of gases can interfere with each other, so compensations are built into current devices.

Processed Absorbance Monitors (Pulse Oximeter)

Oximeters are devices that use light absorbance measurements to determine the concentration of various species of hemoglobin. One of the first in vivo oximeters was a noninvasive monitor used in aviation research during World War II. This device transilluminated tissue (the earlobe) with light of two wavelengths. One wavelength was sensitive to changes in oxyhemoglobin, and the other was not. In effect, the earlobe acted as a test tube containing the suspended hemoglobin. For a review of the development of pulse oximetry, the reader is referred to the excellent article by Severinghaus and Astrup.[17]

Before specific engineering problems are discussed, we need to define what we wish to measure. Adult blood usually contains four species of hemoglobin: oxyhemoglobin (HbO_2), reduced hemoglobin (Hb), methemoglobin (metHb), and carboxyhemoglobin (COHb). The latter two are abnormal hemoglobins (called "dyshemoglobins"), and are normally present in only small amounts. Each of these hemoglobin species has a different light absorption profile. Figure 38-29 illustrates the different absorption constants for each hemoglobin species light from red to infrared light. Fractional hemoglobin saturation ($O_2Hb\%$) is defined as the ratio of HbO_2 to total hemoglobin:

$$O_2Hb\% = HbO_2 / \left(HbO_2 + Hb + metHb + COHb\right)$$

Measuring this quantity in the presence of metHb and COHb requires at least four wavelengths of light, which yield four simultaneous Beer-Lambert equations to solve for the four hemoglobin species. Because metHb and COHb do not contribute to oxygen transport, functional saturation is defined as the ratio of HbO_2 to HbO_2 plus reduced hemoglobin:

$$Sao_2 = HbO_2 / \left(HbO_2 + Hb\right)$$

Although functional saturation depends explicitly on only HbO_2 and Hb, four light wavelengths are still required to measure it in the presence of significant concentrations of COHb and metHb.[18,19] If the concentrations of metHb and COHb are zero, $O_2Hb\%$ and Sao_2 become identical.

The pulse oximeter performs substantial signal processing of optically transduced physiologic data. Although the physical

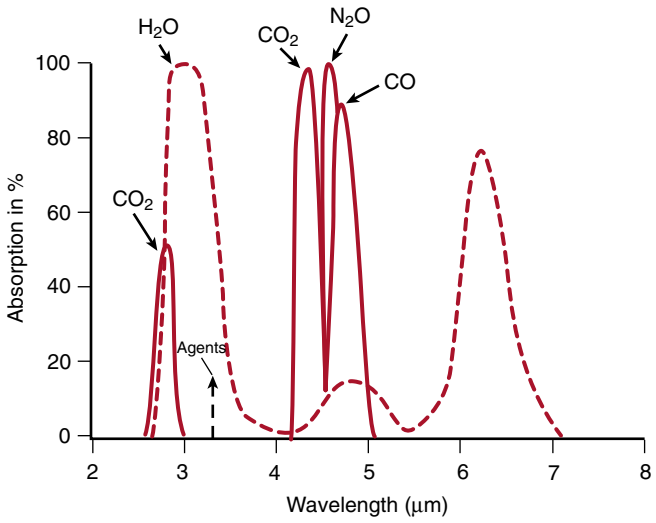


Figure 38-28 Absorption spectra of some gases and materials important to anesthesia. The absorption is not constant over wavelengths. It is important to choose the proper wavelength to measure. Also, when multiple substances are present, it is still possible to measure their concentrations, provided that enough wavelengths are available. (The solution becomes one of multiple equations with multiple unknowns.) *(From Gravenstein JS, Paulus DA, Hayes TJ: Capnography in Clinical Practice. Boston, Butterworths, 1989.)*

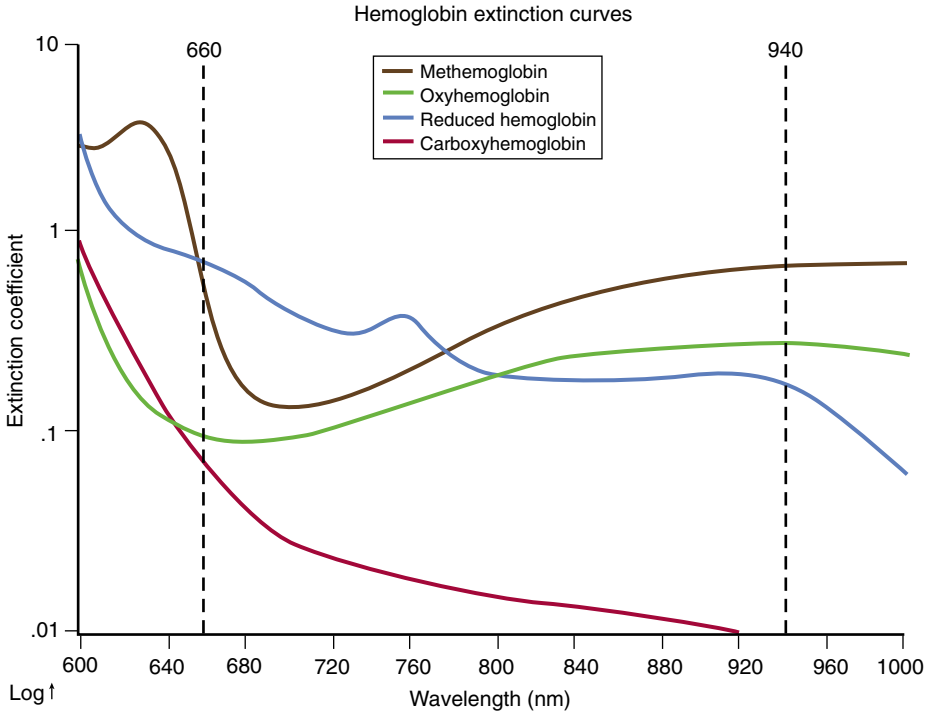


Figure 38-29 Hemoglobin extinction curves. Pulse oximetry uses the wavelengths of 660 nm and 940 nm because these are available in solid state emitters (not all wavelengths are able to be emitted from diodes). Carboxyhemoglobin and oxyhemoglobin absorb equally at 660 nm, and so both read as Sao_2 to a conventional pulse oximeter. In addition, methemoglobin and reduced hemoglobin share absorption at 660 nm and interfere with correct Sao_2 measurement. *(Courtesy of Susan Manson, Biox/Ohmeda, Boulder, CO, 1986.)*

principle governing pulse oximetry is straightforward, application of this principle to produce a clinically useful device involves significant engineering problems.[18,20] The remainder of this section describes the physical and physiologic problems of pulse oximeter design and the engineering solutions to these problems. The discussion is divided into basic design and management of signal artifacts.

Basic Design of Pulse Oximeters

Noninvasive in vivo oximeters measure red and infrared light transmitted through and reflected by a tissue bed. Accurate estimation of Sao_2 by this method entails several technical problems. There are many light absorbers in the transmitted light path other than arterial hemoglobin (e.g., skin, soft tissue, and venous and capillary blood). The pulse oximeter accounts for the effects of absorption of light by tissue and venous blood by assuming that only arterial blood pulsates. Figure 38-30 schematically illustrates the series of absorbers in a typical sample of living tissue. At the top of the figure is the AC component, which represents absorption of light by the pulsating arterial blood. The DC (baseline) component represents absorption of light by the tissue bed, including venous, capillary, and nonpulsatile arterial blood. Pulsatile expansion of the arteriolar bed increases the light path length (see equations 4 and 5), increasing absorbency. Conventional pulse oximeters (including all commercial pulse oximeters until 2005) use only two wavelengths of light, typically 660 nm (red light) and 940 nm (near-infrared light). The pulse oximeter first determines the fluctuating or "AC" component of absorbance at each wavelength and then divides this value by the nonfluctuating or "DC" component to obtain the "pulse-added absorbance," which is independent of the incident light intensity. The oximeter then calculates the ratio (R) of the two pulse-added absorbances (one for each wavelength)[18]:

$$R = \left(AC\ 660/DC\ 660\right)/\left(AC\ 940/DC\ 940\right) \qquad (6)$$

Finally, the value of R (often called the "ratio of ratios") is related to the displayed saturation estimate Spo_2 by a "look-up table" programmed into the oximeter's software. The tables used in all commercial pulse oximeters are based on experimental studies in healthy human volunteers. Although each manufactur-

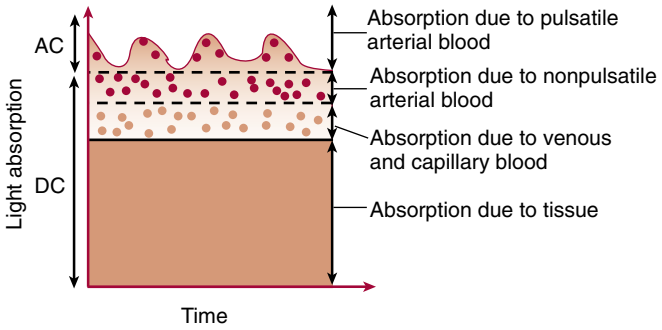


Figure 38-30 Pulse oximetry signals. A primary difficulty with pulse oximetry is that the pulsatile signal is small compared with the total absorbance of the ear or finger being examined. Pulsatile flow is needed to determine the Sao_2. AC, alternating current; DC, direct current. *(Adapted from Ohmeda Pulse Oximeter model 3700 Service Manual.)*

er's exact calibration curve is proprietary, these curves are very similar. When the ratio of red-to-infrared pulse-added absorbance is 1.0, the displayed Spo_2 is approximately 85%. This fact has clinical implications that are discussed in the next section.

Signal Artifact Management

One of the most difficult engineering problems in pulse oximetry is identification of the fluctuating absorbance pattern of arterial blood in a sea of electromagnetic and other artifacts. Artifacts have four major sources: ambient light, low perfusion (weak pulse, low AC-to-DC signal ratio), venous blood pulsations (caused by patient motion, among other things) and additional light absorbers in the blood (e.g., dyshemoglobins, intravenous dyes). All these sources of artifacts produce a low signal-to-noise ratio, resulting in either erroneous Spo_2 values or no value at all.

The photodiodes used in the sensor to detect light cannot differentiate one wavelength of light from another. The detector does not know whether the light received originates from the red (660 nm) light-emitting diode (LED), the infrared (940 nm) LED, or the room lights. This problem is solved in most pulse oximeters by alternating the red and infrared LED sources. The red LED is turned on first, and the photodiode detector produces a current resulting from the red LED plus the room lights. Next, the red LED is turned off, and the infrared LED is turned on. The photodiode signal then represents the infrared LED plus the room lights. Finally, both LEDs are turned off, and the photodiode generates a signal from the room lights alone. This sequence is repeated hundreds of times per second. In this way, the oximeter attempts to eliminate light interference even in a quickly changing background of room light.[18] Some sources of fluctuating light can cause problems despite this clever design. Artifact from ambient light can be minimized simply by covering the sensor with an opaque shield.

Another engineering problem is that of a low AC-to-DC signal ratio, or low perfusion. When a small pulsatile absorbance signal is detected, the conventional pulse oximeter amplifies the signal and estimates saturation from the ratio of the amplified absorbances. In this way, the pulse oximeter can estimate saturation values of Spo_2 for a wide range of patients who generate different amplitudes for pulsatile absorbance. As with a radio receiver, when a weak signal is amplified, the background noise, or "static," also is amplified. At the highest amplifications (which can be up to 1 million times), some pulse oximeters may "analyze" this noise signal and generate an Spo_2 value from it. Because the noise is usually equal in the red and the infrared signals, the ratio of the two is often near unity (1.0), which yields a displayed saturation of approximately 85%.

This problem could be shown in early pulse oximeters by placing a piece of paper in the sensor between the photodiode and the LED. Some early models amplified the background noise while searching for a pulse until they eventually displayed a pulse and saturation value for the piece of paper. To prevent this type of artifact, many manufacturers have now incorporated minimum values for the signal-to-noise ratio, below which the device displays no value for Spo_2. Some oximeters also display a low signal strength error message; in addition, many display a plethysmographic wave for visual identification of noise.

Patient motion, causing venous pulsations with a high AC-to-DC signal ratio, may be the most difficult artifact to eliminate. Engineers have tried several approaches to this problem, beginning with simply increasing the signal averaging time. If the device averages its measurements over a longer period, the effect of an intermittent artifact is usually less. This longer averaging period also slows the response time to an acute change in Sao_2, however, and it may result in "frozen" Spo_2 values being displayed when the true saturation is rapidly changing. Most pulse oximeters now allow the user to select one of several time-averaging modes. In addition, some manufacturers use more sophisticated algorithms to identify and reject spurious signals.

One innovation aimed at reducing motion artifact is based on the premise that motion causes pulsations of venous blood within the tissue bed. Conventional pulse oximetry cannot distinguish venous pulsations from those of arterial blood; large low-reading errors or loss of signal can result. In the newer signal-processing algorithm developed by Masimo, Inc. (Irvine, CA), the oximeter computes a venous "noise reference signal," which is common to both light wavelengths. The noise reference is subtracted from the total signal, and a "true" arterial signal is left. This is one of five "parallel engine" algorithms that Masimo SET (Signal Extraction Technology) uses simultaneously to find the most reliable Spo_2 value for the current signal conditions. Tests in human volunteers and preliminary clinical studies indicate that this new technology represents an improvement in pulse oximeter performance in low signal-to-noise ratio situations.[21,22]

More recently, Masimo has brought to market the first multiwavelength pulse oximeter: the Rainbow Rad-57 Pulse CO-oximeter. This device employs eight light wavelengths rather than the usual two, making it capable of measuring COHb and MetHb, in addition to the conventional Spo_2 value and pulse rate. The first human volunteer study of this instrument shows that it can measure COHb with an uncertainty of ±2%, and MetHb with an uncertainty of ±0.5%.[23]

Other in vivo oximeters have been developed to measure light reflected by living tissue in an attempt to determine hemoglobin saturation in specific organs. Using reflected rather than transmitted light adds complexity because the path lengths of the light through the tissue may be varied and tortuous, making calibration difficult. Nevertheless, a signal reflected from living tissue may produce useful information regarding the average saturation of the hemoglobin within that tissue.[24] A cerebral oximeter may be able to measure mean brain hemoglobin saturation, which reflects the intracerebral balance among venous, arterial, and capillary blood, and the oxygenation of all three.

Measurement of Temperature

Principles of Temperature

Moving matter contains energy. Even stationary objects are moving at the atomic level. This kinetic energy of molecules and atoms is described as temperature. When all molecular motion (translational, vibrational, and rotational) ceases, the substance is said to be at a temperature of absolute zero—the lowest possible temperature. This temperature is equivalent to −273°C, and is defined as 0°K. This state provides a reference point for all temperature measurements, which in all thermodynamic calculations must be expressed in degrees Kelvin.

Heat is a form of internal kinetic energy that can flow between two contacting bodies that are at different temperatures.

The amount of heat required to increase the temperature of 1 g of a given substance by 1°C is called the specific heat of that substance. The calorie, a common heat unit, is the amount of heat required to increase the temperature of 1 g of water from 14.5°C to 15.5°C. One calorie is equivalent to 4.184 J of energy. When we refer to calories in terms of the calories in the food that we eat or the calories that we expend while exercising, we are actually referring to kilocalories, or thousands of calories (also called "kitchen calories"). The total amount of heat energy in an object depends on its specific heat, its temperature, and its mass. Although a cup of 60°C coffee is much "hotter" than a 30°C swimming pool, the coffee contains much less total thermal energy than the pool does. The same is true for potential energy stored as pressure potential or electric potential. A small container at high pressure may have less potential energy than a larger container at lower pressure (see Chapter 48).

Temperature Monitors (Thermometer, Thermistor, Thermopile, Liquid Crystal)

Three techniques are commonly used for measuring temperature: based on expansion of a material as its temperature increases, based on changes in electric properties with temperature, and based on optical properties of a material. As heat is added to most substances (gases, liquids, or solids), motion of the molecules increases, and the volume of the material increases at constant pressure. Depending on the material, this expansion can be calibrated directly to changes in temperature. Liquids are most commonly used, such as mercury because its effective range extends from its freezing point of −39°C to approximately 250°C.[25] Mercury thermometers have two disadvantages. First, they require 2 to 3 minutes for complete thermal equilibration (mercury is a liquid metal with a high specific heat). Second, they are enclosed in a glass tube, which may break and cause injuries.[26] Thermometers based on the expansion of gas (Bourdon tube) or metal (bimetallic strip) are frequently used in thermostats because they also respond slowly to transient changes in temperature.

Electric techniques for measuring temperature can be subdivided into three categories: resistance thermometers, thermistors, and thermocouples. Resistance thermometers operate on the principle that the electric resistance of metals increases with temperature. These devices most frequently use a platinum wire as the temperature-sensitive resistor, a battery, and a galvanometer to measure current, which can be calibrated to temperature. The platinum wire is incorporated into a Wheatstone bridge circuit, which accurately measures very small changes in resistance (see Fig. 38-5).

Compared with a platinum thermometer, a thermistor is a semiconductor that displays the opposite behavior with regard to electric resistance. As the thermistor is heated, its resistance decreases. Thermistors, being solid-state devices, can be manufactured in extremely small sizes and have a fast response to change in temperature (i.e., little heat is needed to increase their temperature). Most of the temperature probes used in anesthesia, from the ones at the end of pulmonary artery catheters to esophageal probes, are thermistors. Physical problems with thermistors are few: Cracked or broken wires lead to high resistance and incorrect temperature readings. More common problems are poor probe placement and misinterpretation of the resulting value (e.g., placing an esophageal probe in the oropharynx and measuring airway temperature rather than core temperature). Thermocouples are conductors that generate a voltage in response to a temperature gradient.

The optical properties of materials can be used to measure temperature in two ways: (1) the infrared "black body" emissions of an object can be measured by using a device known as a thermopile, and the emission can be converted to temperature, and (2) a liquid crystal "matrix" can be placed in direct contact with the desired zone, and an optical change can be observed (a change in color). The most commonly encountered example of infrared temperature measurement involves the tympanic membrane temperature monitor used in recovery rooms, pediatrics, and hospital wards.[27] The infrared detector produces an electric signal that is proportional to the fourth power of the difference in absolute temperatures of the objects. The following formula describes this phenomenon: $Q_{1,2} = K (T_1^4 - T_2^4)$, where $Q_{1,2}$ is net heat transfer (W/cm^2), K is the Stefan-Boltzmann constant, and T_1 and T_2 are the absolute temperatures of the two objects (°K).

In theory, this method of measuring the core temperature should be accurate. In practice, improper placement and lack of calibration, but not ear canal cerumen, contribute to real-world errors.[28-30] Additionally, the probe is large for intraoperative use.

Liquid crystal measures of temperature (found in "mood rings") are often used for skin temperature monitoring. Just as the molecules in a liquid crystal watch display change their optical properties with a small electric current, becoming polarized and dark, the molecules in a liquid crystal temperature device change their optical properties with temperature, resulting in a rainbow of colors. The crystal matrix is sensitive to pressure and temperature. (By touching an LCD display panel, one can note the visual rainbow of changing colors.) The reported clinical accuracy of liquid crystal devices varies.[31,32]

Measurement of Flow

Principles of Flow

Although conceptually one of the easier measurements to understand as volume or mass movement over time, flow is actually not easy to measure. We must clearly distinguish between fluid flow and fluid velocity, which are often confused. Flow (Q) refers to the volume of fluid passing a particular surface area per unit of time; its SI units are cubic meters per second (m^3/sec), but in medicine, it is more commonly measured in mL/sec or L/min. Fluid velocity (U) is simply the speed of the fluid at a particular point in space, measured in msec. By analogy, imagine a multilane freeway: the speed (velocity) of individual cars may vary depending on the lane; the flow is the number of cars passing a point per minute.

Mass and Volume Flow Meters (Urometer, Volumeter)

Flow can be measured directly, by diverting the flow into a measuring chamber. We can measure the mass or volume of fluid flowing per unit time by catching the fluid in a container and either weighing it or measuring its volume. The common urom-

eter for measuring urine volume is an example. The volumeter used in North American Drager anesthesia machines also measures aliquots of volume integrated over time to measure tidal and minute volume (Fig. 38-31).[33]

Dilutional Flow Meters (Thermodilution, Fick Principle)

Volume and mass flow also can be measured by dilutional techniques. If some measurable indicator (a bolus of dye, a thermal pulse, oxygen consumption, carbon dioxide production) is injected into a flow, and its concentration is measured as a function of time at a point downstream, the volume flow (Q) can be calculated by integration. The most common medical application is determination of cardiac output by the pulmonary artery thermodilution method (see Appendix 6). Errors associated with these methods involve using the wrong injectate volume (too small a volume resulting in an overestimate of flow) or an error in temperature measurement (see the section on temperature).

"Continuous" thermodilution cardiac output using an electric heating coil to warm the pulmonary artery blood removes errors associated with fluid injectate techniques but introduces the need to average the smaller signal over a longer time interval. Additionally, there is an upper limit to warming the blood without cellular damage, so signal quality is reduced in febrile patients.[34] A slightly different approach is to measure the electric current required to maintain a constant temperature at the catheter tip. This is the principle of a constant temperature hot wire anemometer (used to measure gas flows in wind tunnels and in some anesthesia machines) applied to cardiac output.

The rate of carbon dioxide production or oxygen consumption can be used to measure cardiac output by modifications of the Fick equation (see Appendix 6). When using these variables, a change in metabolic rate can lead to errors in cardiac output measurement.

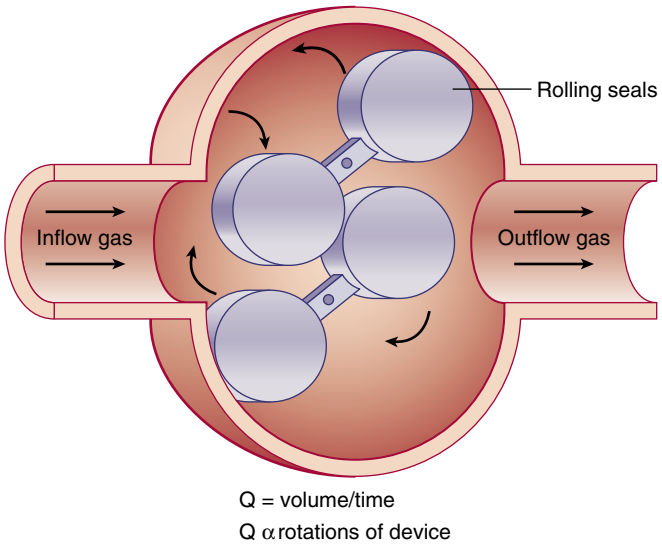


Figure 38-31 Volumeter. Flow can be described as volume over time. This design of flow meter allows gas to pass in only small aliquots, each of which turns a counter to measure the amount flowing past. When divided by time, this results in a flow measurement. *(Adapted from Ehrenwerth J, Eisenkraft J: Anesthesia Equipment: Principles and Application. St. Louis, Mosby-Year Book, 1993.)*

Velocity and Pressure Flow Meters (Venturi, Pitot)

Flowing fluids in tubes generate velocity and pressure, which can be used to measure the flow indirectly. Pressure in fluids can be thought of as a form of potential energy, as described earlier. Kinetic energy in fluids is expressed in terms of flow, the bulk movement of fluid with a given direction and magnitude. The potential energy of pressure can be converted into the kinetic energy of flow; for example, the hydrostatic pressure generated by gravity acting on a vertical column of liquid can be transformed into flow by opening a valve at the bottom of the column. Pressure and flow also can change independently. With the human circulatory system used as an example, a healthy young trauma patient in hypovolemic shock can have normal blood pressure, but low blood flow with high systemic vascular resistance. A septic patient can have very low blood pressure accompanied by high blood flow and low systemic vascular resistance (high-output septic shock). The total mechanical energy of a moving fluid is the sum of the kinetic (flow) energy and the potential (pressure) energy (see Table 38-2).

A pressure gradient (changing pressure in a particular spatial direction) exerts a force on the fluid, and the fluid tends to accelerate in the direction of decreasing pressure. Pressure gradient is only one of the forces that commonly act on fluids; other forces include gravity (discussed earlier) and viscous force or friction. If these other forces are negligible, and the fluid is incompressible (i.e., a liquid with constant density), the equation of motion (F = ma) can be integrated to yield:

$$P + \tfrac{1}{2}\rho U^2 = P_0 \qquad (7)$$

where P is pressure, ρ is fluid density, U is the magnitude of the fluid velocity, and P_0 is a constant called the "stagnation pressure" (see Appendix 5). This form of the Bernoulli equation tells us that pressure decreases as velocity increases in a frictionless flow, and vice versa. This equation dispells the common misconception that pressure always decreases in the direction of flow. In the flow inside a tube (a pipe or a large vein) of gradually increasing diameter, fluid velocity (U) decreases in the downstream direction as the diameter and cross-sectional area of the tube increase. As U decreases, equation 5 tells us that P increases in the direction of flow. This example shows the relationship of potential and kinetic energy in fluids: As the kinetic energy of this tube flow decreases (U^2 falls) in the flow direction, the potential energy increases (P rises) by an equal amount. The total energy remains constant because we have assumed no friction.

Flow can be determined by measuring the average velocity of the fluid across the tube. In laminar tube flow (Fig. 38-32A), the velocity profile has a parabolic shape, with the highest velocity at the center line and the fluid at the walls being stationary. In turbulent tube flow, the velocity profile is "flattened" as shown in Figure 38-32B.

The Bernoulli equation applies to a specific subset of frictionless flows, as described earlier. Many flows important to anesthesiologists do not follow the Bernoulli equation. Most com-

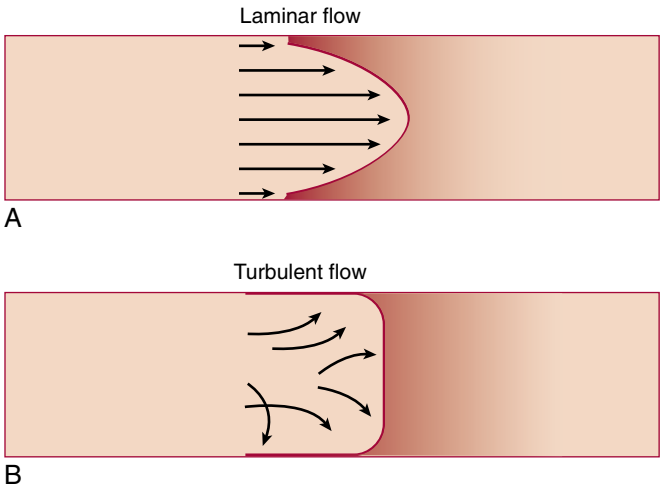


Figure 38-32 Laminar and turbulent flow. **A,** In a smooth-walled tube at low flow rates (i.e., small pressure gradients), the flow rate is laminar; that is, flow moves smoothly in concentric circles, with the centermost area having the greatest flow velocity and the area nearest the wall of the tube being virtually stationary. **B,** As flow rate (and pressure gradient) increases, the flow transitions from laminar to turbulent. Instead of a neatly ordered flow, the velocities are more randomly distributed, energy is dissipated as heat, and the energy needed for a given flow rate increases. Many factors govern this transition, including size of the tube, viscosity of the fluid, flow rate, and pressure gradient. These factors are combined in the determination of the Reynolds number (see Appendix 5).

monly, the flow that we desire to measure is not laminar, but turbulent. The transition from laminar to turbulent flow depends on the type of fluid, the speed of the flow, and the shape of the flow. The fluid factors are combined in a dimensionless ratio called the "Reynolds number (Re)":

$$Re = \rho UL/\mu \quad (8)$$

where ρ is the density of the fluid, U is the mean flow velocity, L is a characteristic dimension (length) of the flow, and μ is the viscosity of the fluid. For a given flow geometry (e.g., flow through a tube of circular cross-section), transition from laminar to turbulent flow occurs at a critical value of Re. In straight, smooth, circular tubes, transition from laminar to turbulent flow occurs at Re of approximately 2100 (see Appendix 5).

A Venturi tube is a circular tube with a gradual contraction and expansion in diameter, in contrast to the sudden contraction-expansion of an orifice flow meter (Fig. 38-33). Because the contraction is smooth and gradual, the Bernoulli equation (equation 7) applies to this geometry. For conservation of mass and energy to apply, as we restrict the flow by narrowing the tube, the speed *increases*; the pressure on the walls *decreases* to keep the total energy (the "stagnation pressure" of the Bernoulli equation) constant. The total mass flow on both sides of the contraction must be equal (we have not created or lost any matter). If we measure the pressure difference between the widest and the narrowest parts of the Venturi tube, we can solve the Bernoulli equation for velocity (see Appendix 5). The Venturi tube derives fluid velocity (U) from the pressure difference, not volume flow (Q). The Venturi tube is used in many industrial applications and is used on some aircraft to measure speed.

To have a measurable pressure gradient, there must be some resistance in the fluid path. The lower the rate of flow, the

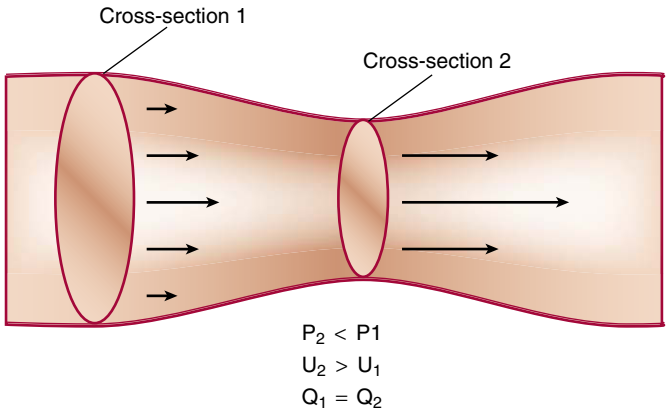
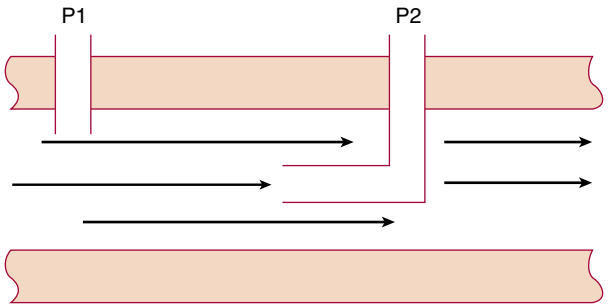


Figure 38-33 Venturi tube. By measuring the pressure difference between two points in a laminar flow, the average flow velocity can be determined because the mass flow and total energy (minus frictional losses) must be the same (see Appendix 5).

greater the resistance must be to generate the same pressure gradient. In respiratory applications, pediatric flow meters have too much resistance (owing to lower flows) to use in adults, and adult flow meters do not generate enough resistance to give an adequate signal (pressure change) in pediatric patients. A variable resistance flow meter has been devised (Ohmeda 7900/Aisys (GE Healthcare, Madison, WI) wherein the orifice is a flap that moves as the flow increases. No simple equation or relationship exists between the pressure above and below the restriction; this flow meter must be empirically calibrated, and the calibration curve for each sensor must be stored electronically.

A Pitot tube is a cylindric tube whose open end is pointed directly into the flow, that is, "upstream" (Fig. 38-34). The pressure measured in the Pitot tube approximates the stagnation pressure, given earlier by equation 7. If we independently measure the static pressure p (the p_1 side port in the Fig. 38-34) at the same location, and we know the fluid density ρ, we can easily solve equation 7 for the fluid velocity U. The Pitot tube derives velocity U, not volume flow Q. The Pitot tube is simple and reliable, and is used



$$Q^2 \alpha (P_2 - P_1)$$

$$Q \alpha \sqrt{(P_2 - P_1)}$$

Figure 38-34 Pitot tube. As flows increase, wall pressure decreases as a result of the Bernoulli principle. The Pitot tube measures the difference in pressure from the middle of the flow to the wall and converts this to a flow measurement (see Appendix 5). *(Adapted from Ehrenwerth J, Eisenkraft J: Anesthesia Equipment: Principles and Applications. St. Louis, Mosby-Year Book, 1993.)*

on most aircraft to measure their speed. In anesthesia, the Pitot tube is used in Datex Ultima monitors (GE Healthcare, Helsinki, Finland). To measure gas flow in two directions, the Datex monitor incorporates two Pitot tubes, one facing in each direction. Additionally, the monitor samples gas composition to correct for the density and viscosity of the gas mixture.

Balance-of-Pressure Flow Meters (Thorpe Tube, Bourdon Tube)

If flow in a tube passes through a sudden restriction such as an orifice, the volume flow Q is proportional to the area of the orifice and the square root of the pressure drop through the orifice. (The Bernoulli equation does not apply to this flow geometry.) This is the principle of all orifice flow meters, including the rotameter of an anesthesia machine (see Appendix 5).

The most common flow meter seen by anesthesiologists is the floating bobbin rotameter on the anesthesia machine, the Thorpe tube (Fig. 38-35). This variable-orifice flow meter uses a balance of forces to determine pressure change and measure flow. When the flow meter valve is opened, the flow of gases through the annular orifice between the bobbin and the tapered glass tube provides a force to raise the bobbin. As the bobbin rises, the area of the annular gap between the bobbin and the tube increases as a result of the taper of the tube. As the area of this gap (orifice) increases, the pressure change across the bobbin decreases because the pressure change across an orifice is inversely proportional to the square of the orifice area. The bobbin ceases its upward motion at an equilibrium point when the downward force of gravity (weight of the bobbin) is balanced by the upward pressure force. The height of the bobbin in the tube is directly related to the gas flow. Although this flow meter is simple in principle, its application becomes more complex when the flow in the tube changes from laminar to turbulent as velocity and diameter increase. For mathematical derivations, see Appendix 5.

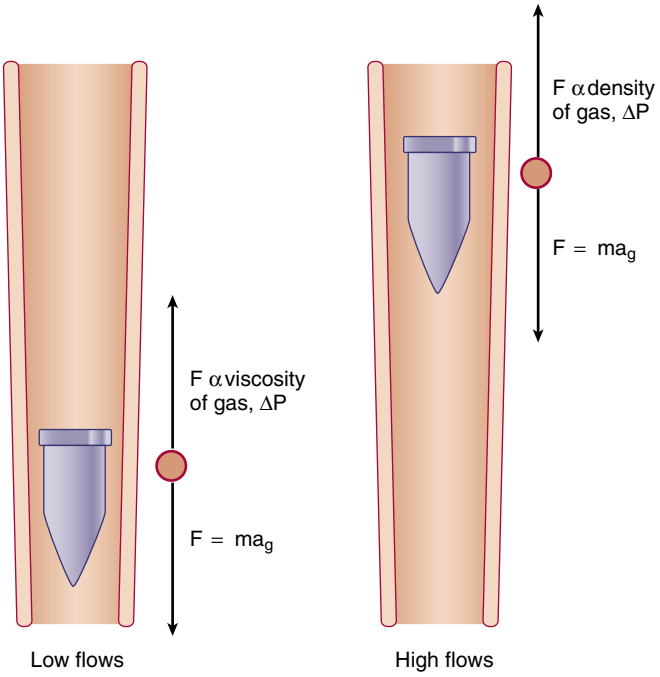


Figure 38-35 Thorpe tube flow meter. At low flows, viscosity of gas predominates, and the flows balance when the gravitational attraction equals the pressure gradient across the equivalent orifice. At higher flows, density takes over, and the balance is the same except for the formula determining pressure (acts like an orifice) (see Appendix 5).

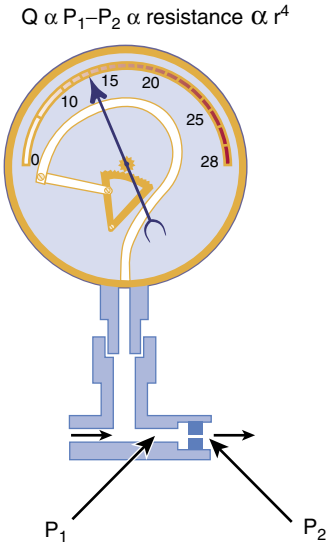


Figure 38-36 Bourdon tube flow meter. In contrast to the Thorpe tube, which has a constant pressure, but a variable orifice, the Bourdon tube has a constant orifice, but a variable pressure. The tube uncoils under the high back pressure. This drawback makes it unsuitable for use in low-pressure respiratory systems. It receives much use in portable oxygen tanks, however. If the orifice is increased in radius, the flow meter will under-read actual flow. If the orifice is dirty (i.e., decreased radius), the flow will be overestimated. *(From Mushin WW, Jones PL: Physics for the Anaesthetist, 4th ed. Oxford, Blackwell, 1987.)*

Another flow meter, the Bourdon tube (Fig. 38-36), keeps the orifice constant and allows the pressure to vary. As flow Q increases, the gradient of P_1 to P_2 increases and causes the flattened metal tube to uncoil and move the pointer.

Kinetic Energy Flow Meters (Wright Spirometer)

Vanes or propellers placed in a confined flow turn at a rate proportional to the volume flow if there is no friction in the propeller bearings. Various vane spirometers (Fig. 38-37) (e.g., Wright spirometer) work by this principle. These devices tend to be less accurate at very high and low flow rates because of frictional forces.

Summary of Flow Measurement

Every method of measuring flow has its particular limitations and uncertainties. Because gases are not always pure with a known, constant density, flow meters based on the Bernoulli equation (equation 7) are subject to errors. Any device inserted into a fluid flow can disturb the flow by its presence. A rotating vane spirom-

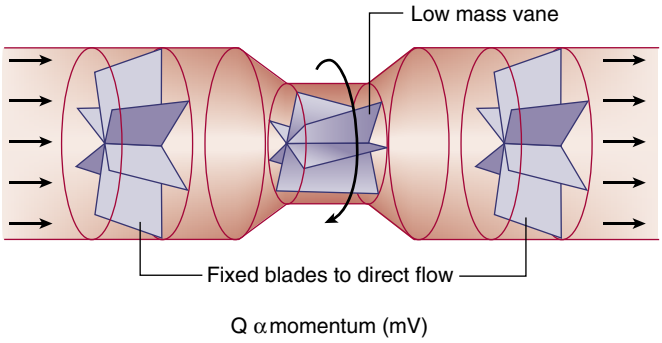


Figure 38-37 Vane spirometer. Moving gases contain kinetic energy. This can be sampled by a rotating "windmill" in the gas stream. *(Adapted from Ehrenwerth J, Eisenkraft J: Anesthesia Equipment: Principles and Applications. St. Louis, Mosby-Year Book, 1993.)*

eter may reduce the gas flow at high flow rates because of internal friction. Several methods of flow or fluid velocity measurement depend on a pressure measurement (Pitot tube, Venturi tube, orifice flow meter); the flow measurement is no more accurate than the pressure measurement.

Conclusion

New monitors are being developed almost continuously, but new physical principles are revealed only rarely. The science of physics is a constant effort to understand, simplify, and predict the behavior of the universe in quantitative terms. The terms and principles outlined here will be referred to multiple times in subsequent chapters.

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Appendix 1

Distance versus Time under Constant Acceleration: Equivalence of Potential and Kinetic Energy

Velocity (v) is the rate at which distance is changing; that is, it is the time derivative of distance:

$$\mathbf{v} = d\mathbf{x}/dt \quad (1)$$

The variable v is in boldface type to indicate that it is a vector: it has magnitude and direction. Distance **x** is a vector pointing from the origin to the present location of the particle or object; it is called the "position vector." Time (t) is a scalar; it has magnitude, but no direction and is in plain type.

Acceleration (**a**) is the time rate of change of velocity. It is the time derivative of the velocity vector, or the second derivative of distance with respect to time:

$$\mathbf{a} = d\mathbf{v}/dt = (d/dt)(d\mathbf{x}/dt) = d^2\mathbf{x}/dt^2 \quad (2)$$

If an object starts with zero velocity ($\mathbf{v} = 0$) at time zero ($t = 0$) and then accelerates with constant acceleration (a), its velocity at time t will be simply $\mathbf{v} = \mathbf{a}t$. To calculate the distance traveled by the object between time $t = 0$ and time t, we must divide the time interval 0 to t into a series of very small intervals, each of time length dt. The distance traveled during the interval dt is simply the velocity at that time multiplied by the time interval:

$$d\mathbf{x} = \mathbf{v}dt = (\mathbf{a}t)dt \quad (3)$$

In the second step, we have substituted the constant acceleration relationship $\mathbf{v} = \mathbf{a}t$ from above. Now to compute the total distance traveled, we must sum the distance from all of the small dt time intervals that occur between 0 and t:

$$\mathbf{x} = \Sigma(\mathbf{a}t)dt \quad (4)$$

If we allow the length of the time interval dt to approach zero, the summation process becomes the integral with respect to time from time zero to time t:

$$\mathbf{x} = \int \mathbf{v}dt = \int (\mathbf{a}t)dt = \frac{1}{2}\mathbf{a}t^2 \quad (5)$$

An object starting from rest at $t = 0$ and moving with constant acceleration (**a**) will move a distance $\frac{1}{2}\ \mathbf{a}t^2$ in time t. If this is a falling object (in a vacuum, where there is no air resistance), $a = g = 9.8$ msec^2, and the distance formula becomes:

$$\mathbf{x} = \frac{1}{2}gt^2 = (4.9)t^2 \quad (6)$$

In the first second, the object falls 4.9 m; at the end of 2 seconds, it has fallen 19.6 m; after 3 seconds, 44.1 m; and so on.

The kinetic energy (KE) of a moving object is

$$KE = \frac{1}{2}mv^2 \quad (7)$$

where m is the mass of the object, and v is the magnitude of its velocity (also called speed). Note that v used in this sense is in plain type, not boldface. Consider again the falling object that started at position $x = 0$ at time $t = 0$ and falls a distance h:

$$h = \frac{1}{2}gt^2, \text{ or}$$

$$t = \sqrt{(2h/g)} \quad (8)$$

Because velocity $v = at = gt$, we have by substitution from equation 8:

$$V = gt = g\sqrt{(2h/g)} = \sqrt{(2gh)} \quad (9)$$

The kinetic energy is given by:

$$KE = \frac{1}{2}mv^2 = \frac{1}{2}m(2gh) = mgh \quad (10)$$

Now let us consider the work required to lift the fallen object back to its original height of h. Work is defined as the force exerted times the distance over which the force acts: $W = Fd$. The force of gravity acting on our object is $F_g = mg$, so the work required to lift it the distance (h) back to $x = 0$ is:

$$W = Fd = (mg)d = mgh \quad (11)$$

The work required to restore the object equals the kinetic energy possessed by the object at the bottom of its fall, $KE = W = mgh$. When we lift the object from $x = h$ back to $x = 0$, we have increased its potential energy (PE) by the amount mgh. This potential energy can be converted to kinetic energy by allowing the object to fall the distance h. This type of potential energy, called gravitational potential, has a value that clearly depends on where we locate the origin of our coordinates, $x = 0$. It is the change in potential energy, however, and not its absolute value, that the potential energy/kinetic energy balances:

$$\Delta KE = -\Delta PE \quad (12)$$

The change in kinetic energy is equal to and of opposite sign to the change in potential energy.

Appendix 2

Physics of Hydrostatic Pressure

A liquid manometer is a simple and reliable means of monitoring pressures that do not change rapidly. It simply uses the weight of a measured vertical column of liquid to balance the pressure exerted against the bottom of the column. We have defined weight as the force exerted by gravity on a mass (m): $F_g = mg$. To determine the weight of a column of liquid of known dimensions (the manometer in Fig. 38-4), we must first know the density (mass per unit volume) of the liquid. Density has dimensions of m/L^3, and the SI units are kilograms per cubic meter (kg/m^3). Because liquids are almost incompressible, their density is influenced little by pressure (but affected by temperature). The density of water at room temperature is 997.8 kg/m^3, or 1 g/cm^3.

The pressure (p) exerted by the bottom of the vertical column of liquid in a manometer (see Fig. 38-4) is determined as

follows. If the cross-sectional area of the liquid cylinder is A, and the height of the cylinder is z, its volume is V = Az. If the liquid has a density of ρ, the mass of the column is:

$$m = \rho V = \rho Az \quad (1)$$

Its weight is:

$$W = mg = \rho Azg \quad (2)$$

The liquid column exerts a force equal to its weight on its base, whose surface area is A, creating the following pressure on the surface:

$$p = \text{force}/\text{area} = \rho Azg/A = \rho gz \quad (3)$$

The pressure exerted by the manometer is independent of its cross-sectional area (A); it depends on only the density of the working fluid and the vertical height of the column. If we know the liquid density, measurement of the column height (z) allows us to calculate the pressure (p). If the working fluid is mercury (e.g., sphygmomanometers), the density is 13,680 kg/m^3 (13.68 g/cm^3, or 13.68 times the density of water). The relationship of pressure to height of the column is:

$$p = \rho gz = (13{,}600\ \text{kg}/\text{m}^3)(9.8\ \text{N}/\text{kg})(z)$$
$$p[\text{N}/\text{m}^2] = 133{,}300(z) \quad (4)$$

The unit of pressure newton/meter^2 (N/m^2) is called the pascal (Pa). Because a pascal is a small unit of pressure, we usually use kilopascals (10^3 Pa or kPa). If we express p in kPa and z in mm Hg (rather than meters), equation 4 becomes:

$$p[\text{kPa}] = 0.1333(z)[\text{mm}] \quad (5)$$

Appendix 3

Wheatstone Bridge

The Wheatstone bridge is a network of four resistors connected as shown in Figure 38-5, with a battery or direct-current voltage source (electromotive force) connected between *A* and *C* and a voltmeter (V) connected between *B* and *D*. The bridge is said to be "balanced" when the voltmeter reads zero potential difference between points *B* and *D*. From Ohm's law (V = IR), it is easy to show that balance occurs when $R_x = R_s \times (R_2/R_1)$. If R_s is an adjustable standard resistor, and R_1 and R_2 are fixed known resistors, the balanced bridge provides a very precise means of determining R_x, the unknown resistance. This principle has many applications in biomedical engineering, including strain gauge pressure transducer measurements. In this case, the transducer itself is the unknown resistance R_x.

Appendix 4

Amplification Artifact of a Fluid Tube/Transducer Pressure Wave

The amplification artifact of a fluid tube/transducer pressure waveform can be calculated if a few properties of the system are known. The most relevant part of this solution is the response amplitude, which is plotted against the driving frequency (f) in Figure 38-17. This figure shows some important properties of fluid-coupled transducers and other harmonic oscillators. One of these properties is the existence of a resonant frequency, f_0, which is defined as follows:

$$f_0 = \frac{1}{2}\pi\sqrt{k/m} \quad (1)$$

m is the mass of the system, and k is the elasticity, or spring constant.

As we increase the amount of damping (i.e., friction; c is the friction constant), we observe a decrease in the peak amplitude at resonance, and the frequency at which the peak occurs decreases slightly. The damping coefficient (z) is defined as follows:

$$z = c/\sqrt{2km} \quad (2)$$

Although the arterial pressure waveform is not actually sinusoidal, Figure 38-16 shows the most important characteristics of the pressure transducer response. Any combination of catheter, tubing, and transducer can be characterized by two quantities: a resonant frequency (f_0) and a damping coefficient (z). Gardner measured these quantities for many transducer and tubing systems and found that most systems have resonant frequencies of 10 to 20 cycles/sec or Hz and damping coefficients of 0.2 to 0.3. For clinical systems, the maximum amplification factor (ratio of transducer output to input waveform amplitude) at resonance is near 2.5.

If the resonant frequency is 10 Hz (600 cycles/min), one might conclude that amplification plays little role in the clinical range of pulse rates, which are 5 to 10 times smaller. The arterial pressure waveform is not a sine wave, however. It can be represented as a summation of sine waves (a Fourier series) with frequencies up to many times the pulse rate. These higher harmonic frequencies are amplified most and yield the spiked appearance of a poorly processed arterial waveform. Depending on the shape of the actual arterial pressure wave, this distortion can introduce a 20% to 40% "overshoot" error in systolic blood pressure readings. Even worse, this error depends on the pulse rate, so an error determined for a particular patient at the beginning of administration of an anesthetic may not remain constant.

From this discussion, we can easily predict how to optimize the performance of a pressure transducer system. First, the resonant frequency (f_0) should be as high as possible. The value for k

in equation 1 should be large (i.e., the spring should be "stiff"), and the value for m should be small (i.e., the cannula and pressure tubing should be as stiff and inelastic as possible). To minimize the mass of the moving fluid, the tubing should be short in length and small in diameter. Judging from plots of amplitude versus frequency/resonant frequency at different damping coefficients, the optimal damping coefficient would be 0.4 to 0.5. One also should carefully eliminate air bubbles from the system because they add elasticity and friction, lowering the resonant frequency. In a clinical system, one can determine the approximate f_0 and z of a transducer system if graphic output is available. If the high-pressure flush is turned on and then quickly turned off at a high chart speed (50 mm/sec), the tracing oscillates through several cycles at a frequency near f_0. The damping coefficient can be found by determining the ratio of amplitudes of successive peaks on the tracing. This is a practical example of how fundamental principles of mechanics can be used to predict and optimize the performance of monitoring systems. These concepts of mechanics recur in other sections of this chapter.

Appendix 5

Flow Meters, Bernoulli's Principle, Laminar and Turbulent Flow

The equations governing the motion of fluids are expressions of Newton's second law, F = ma. Forces associated with fluids fall into three major categories: (1) gravity, (2) pressure, and (3) friction. In the example using manometers, the gravitational force per unit volume of fluid is simply ρg, acting in the vertical direction. Pressure forces are the result of differences in pressure from one point to another and are expressed mathematically as the negative of the pressure gradient. (A pressure gradient is a vector in the direction of the maximal rate of pressure increase, with magnitude equal to the pressure derivative in that direction.) Friction is proportional to viscosity, the physical property of a fluid that relates shear stress to rate of strain:

$$P_0 = p + \frac{1}{2}\rho U^2 + \rho g z \quad (1)$$

Equation 1 shows the relationship between velocity and pressure of a fluid in a flow that meets the conditions described. For flows in tubes, the manometer technique provides an easy method of measuring mean pressure. The simplest flow meters apply a combination of these two principles to a tube of changing cross-sectional diameter. The Venturi flow meter shown in Figure 38-33 consists of a tube of varying cross-sectional area that has two ports for measurement of pressure. The Bernoulli equation for points 1 and 2 in the figure becomes:

$$P_1 + \frac{1}{2}\rho {U_1}^2 = P_2 + \frac{1}{2}\rho {U_2}^2 \quad (2)$$

Here, the gravity terms have canceled out because the tube is horizontal, but these terms are usually negligible for gas flows in any direction.

The volume of the fluid flow (Q) (also called flux) at both locations must be the same because no fluid is entering or leaving through the tube walls. The dimensions and SI units for the volume of fluid flow are L^3/t and m^3/sec. This volume is determined at each cross-section of the tube by multiplying the average velocity (U) by the cross-sectional area (A):

$$Q = U_1 A_1 = U_2 A_2 \quad (3)$$

Assuming that A_1, A_2, P_1, and P_2 are known, we now have two equations for the two unknowns U_1 and U_2. Solving these for the velocity U_1 produces:

$$U_1 = \sqrt{\left[2\left(P_1 - P_2\right)/\rho\left(1 - {A_1}^2/{A_2}^2\right)\right]} \quad (4)$$

To find the volume of the flow (Q), we multiply this result by A_1. Velocity is proportional to the square root of the pressure drop, or the pressure change varies as velocity is squared. For a given U_1, or the magnitude of flow velocity, the pressure drop varies as the square of the ratio of the areas, or the fourth power of the ratio of the diameters. If we choose an A_2 greater than A_1, equation 4 implies that P_2 is greater than P_1. In this case, the pressure increases in the direction of flow, a change that initially seems contrary to intuition.

The bobbin flow meters (also called variable-orifice flow meters) in anesthesia machines use a similar principle. These devices consist of a slightly tapered vertical tube and a bobbin or ball that fits inside the tube (see Fig. 38-35). The cross-sectional area of the ring-shaped gap between the bobbin and the tube wall is proportional to the height of the bobbin. Because changes in the cross-sectional area of flow are abrupt rather than gradual (as in Fig. 38-33), the Bernoulli equation does not accurately describe this type of flow. The flow above the bobbin (i.e., downstream) is highly turbulent, and turbulence is a condition that dissipates kinetic energy into heat. Introduction of the empirical constant C_d enables one to use the same formulation as in equation 4:

$$Q = C_d A \sqrt{\left[2\left(P_1 - P_2\right)\right]/\rho} \quad (5)$$

and

$$P_1 - P_2 = \left(\frac{1}{2}\rho Q^2\right)\Big/\left(C_d{}^2 A^2\right) \quad (6)$$

where C_d is a dimensionless constant called the "discharge coefficient." This constant varies with the shape of the orifice and with the value for another dimensionless parameter, the Reynolds number (Re). Re, the overall ratio of inertial forces to viscous forces in a particular flow, is determined as follows:

$$Re = \rho U L/\mu \quad (7)$$

where U is mean flow velocity, L is a characteristic length for the flow (in our flow meter, L is the diameter of the tube), and μ is the viscosity of the fluid. The dimension for viscosity is M/LT. The value for Re is important to any fluid flow because it determines some of the most important characteristics of the flow. The transition from laminar, or "smooth," flow to turbulent flow is determined by the shape of the flow and Re. Flow in a long, straight, smooth-walled tube becomes turbulent at an Re value of approxi-

mately 2100. Flow through an abrupt orifice, such as that of the flow meter in Figure 38-36, becomes turbulent at an Re value of less than 100.

Returning now to the function of the flow meter, one can see that as gas flows upward through the tapered tube, the bobbin begins to rise. As the bobbin rises, the cross-sectional area of the orifice (A) increases because of the taper of the tube; the drop in pressure ($P_1 - P_2$) decreases. The bobbin reaches an equilibrium position for a given volume of flow (Q) when the pressure lifting the bobbin is exactly equal to the weight of the bobbin. In this type of flow meter, the pressure difference is fixed by the bobbin weight, and the area of the orifice varies with the volume of the flow—hence the name "variable-orifice flow meter." Equations 5 and 6 show that calibration of these flow meters depends on the density and the viscosity of the gas: density (ρ) appears explicitly, and viscosity (μ) appears in the dependence of Cd on Re. If we use the wrong gas in a particular flow meter, equations 5 and 6 and the viscosity and density of the new gas enable us to predict the change in calibration.

Appendix 6

Measurement of Cardiac Output by Thermal Dilution and Mass Flow Technique

A commonly used method of measuring blood flow is dilutional calculation—dye or thermal dilution. These methods are simply mass or energy balances that determine the volume of fluid that has been diluted by adding a volume of dye or a given thermal energy. If you have a bucket of water at room temperature (25°C), and you want to determine the volume of water in the bucket, you could add a known volume of water at a known temperature. If 100 mL of water at 35°C is added to the bucket, and the final temperature is 27°C, the unknown volume can be calculated by balancing the heat energy associated with the dilutional process, assuming that no heat is lost to the environment. This dilutional process can be used to measure blood flow by completing this same heat balance measured over time. Thermodilution cardiac output measurements can have significant error as a result of the many assumptions associated with the technique, such as rapid injection of the thermodilution injectate; accurate temperature and volume of the injected fluid; constant known heat capacity of blood, which in reality is a function of the hematocrit value; and little heat loss to the lung.

Thermistor probes are most commonly used for clinical monitoring of patient temperature because they are inexpensive, small, and flexible. For these reasons, the thermistor probe also is used to measure cardiac output determined by the thermodilution technique. Computation of cardiac output performed in this manner is, in effect, a heat balance for the right side of the heart. (Heat balance is a method of accounting for all heat in a process or change involving transfer of heat.) The technique consists of quick injection of a known volume of a sterile solution (usually 10 mL of 5% dextrose in water) into the right side of the heart, while a sensor notes the temperature of the blood in the pulmonary artery. It is assumed that the cold injected solution equilibrates thermally with the blood as it perfuses the pulmonary artery, but that the solution does not acquire heat from other tissues. The following equation is the solution of this heat balance:

$$CO = \left[\rho i Ci Vi\left(T_b - T_i\right)(60Cr)\right] \Big/ \left[\left(\rho_b C_b \int_0^\infty T_b(t)dt\right)\right] \qquad (1)$$

where CO is cardiac output (L/min), ρ_i and ρ_b are the densities of the injectate and blood, C_i and C_b are the heat capacities of the injectate and blood, V_i is the volume of the injectate, T_b and T_i are the temperature of the blood and the injectate, *Cr* is a computational constant that corrects for the increasing temperature of the injectate, and the integration is the area under the thermodilution curve. Because the injectate warms as it is injected through the catheter before mixing with the blood, the correction factor Cr is applied to the equation.

The same principle of balance used for temperature determination of cardiac output can be applied to oxygen or carbon dioxide (CO_2) balance as well. Classically, oxygen balance is used as described by Fick. Measurement of oxygen consumption and content is cumbersome, and a modification of the Fick equation using CO_2 production is used. NICO is a new partial rebreathing method using the following equation:

$$Q = \dot{V}_{CO_2} \Big/ \left(C\bar{V}_{CO_2} - Ca_{CO_2}\right) \qquad (2)$$

Cardiac output (Q) is simply the expired CO_2 divided by the arterial-venous difference in CO_2. Assuming that Q does not change, the equations for CO_2 elimination must be the same with or without rebreathing, where *N* indicates normal breathing, and *R* indicates rebreathing. By rearranging the equations, cardiac output is the ratio of the change in elimination of CO_2 divided by the change in arterial CO_2 content. Arterial CO_2 content is derived from the slope of end-tidal pressure of CO_2 (P_{ETCO_2}):

$$Q = \dot{V}_{CO_{2N}} \Big/ \left(C\bar{V}_{CO_{2N}} - Ca_{CO_{2N}}\right) = \dot{V}_{CO_{2R}} \Big/ \left(C\bar{V}_{CO_{2R}} - Ca_{CO_{2R}}\right) = \frac{\Delta \dot{V}CO_2}{\Delta CaCO_2} \qquad (3)$$

We can see that potential errors are induced by violations of the following assumptions: (1) change in Q during the measurement period, (2) change in metabolic rate and production of CO_2, and (3) change in ventilation. As a trend analysis, patients with chronic obstructive lung disease, in which the absolute value of $PaCO_2$ is widely different from P_{ETCO_2}, may have an absolute error in Q determination by this method, but the relative changes should track.

Appendix 7

Ultrasound

The simplest sound wave to represent mathematically is a sinusoidal wave propagating in one dimension:

$$p' = p_0 \sin\left[(2\pi/\lambda)(x - at)\right] \quad (1)$$

where p' is the pressure fluctuation, λ is the wavelength (distance between waves), x is the coordinate in the direction of propagation, and *a* is the speed of propagation, or the speed of sound.

The amplitude of a sound wave is measured by the root mean square value of the pressure fluctuations. This value is called the sound pressure level (SPL). Because the range of SPL values is often very wide, a logarithmic scale is used:

$$SPL = 20\log\left(p^*/P_0\right) \quad (2)$$

where p^* is the root mean square pressure fluctuation, and P_0 is a reference pressure chosen as the lowest sound pressure detectable by the human ear. This pressure representing the threshold of hearing is 2×10^{-8} kPa at a sound frequency of 2 kHz (2000 cycles/sec). The units in this SPL scale are called decibels. A sound pressure of 2×10^{-8} kPa corresponds to an SPL of 0 dB, the lowest audible sound level [$(p^*/P_0 = 1$; log (1) = 0)]. Quiet conversation has an SPL of approximately 40 to 50 dB, or a pressure 10 to 300 times that of the threshold of hearing.

When sound waves encounter a sudden change in the properties of the conducting medium, some of the sound is transmitted through the new medium, and some of it is reflected, or "scattered," in many directions. Although the mathematics of this process are complex, one conclusion is readily apparent: The greater the mismatch in density and compressibility between the two media, the more sound that is reflected. The quantity that best determines the degree of reflection at an interface between two media is the ratio (R) of the products of density (ρ) and the speed of sound (a) through the two media:

$$R = (\rho_1 a_1)/(\rho_2 a_2) \quad (3)$$

We can easily see that the greatest acoustic mismatch in the body occurs between solid tissues and the lungs. The density and the speed of sound are much lower in the air-filled lungs than in solid tissues. Ultrasonography cannot "look" through the lungs at tissues or organs on the other side. The second greatest mismatch occurs between soft tissues and bone, the latter having a much higher ρa than the former. In 1842, Doppler first described the apparent change in pitch of a sound that occurred when either the source of the sound or the listener was moving. This Doppler effect now has several applications in patient monitoring, including precordial and esophageal Doppler ultrasound devices that measure local blood velocities or cardiac output. If a sound source radiating a frequency (f) is stationary, and the listener is moving (see Fig. 38-19A), the wavelength of the waves can be determined by the equation:

$$\lambda = a/f \quad (4)$$

because the time between wave fronts is 1/f, and the waves are moving at the speed of sound (a). If the listener moves toward the source at speed V_0, the velocity of the listener relative to the moving wave fronts is $(a + V_0)$. The number of wave fronts that the listener encounters per unit time is:

$$f' = \text{velocity}/\text{distance between waves} = (a + V_0)/\lambda \quad (5)$$

Because the sound frequency for a stationary listener is $f = a/\lambda$ (equation 4), the frequency f' heard by the moving listener becomes:

$$f' = (a + V_0)/\lambda = f + \left(V_0/\lambda\right) = f + \left(V_0 f/a\right) = f\left[1 + \left(V_0/a\right)\right] \quad (6)$$

The apparent frequency of the listener is increased by the factor $[1 + (V_0/a)]$. A listener moving toward the source at half the speed of sound hears a frequency 1.5 times that of a stationary listener.

Now consider a stationary listener and a source moving at speed V_0, as shown in Figure 38-19B. The wave fronts are no longer concentric circles; they are more closely spaced in the direction that the source is moving. If the frequency of the sound emitted at the source is f, the source moves a distance V_0/f during each vibration. The wavelength in the direction of motion is shortened by V_0/f and becomes $l = (a - V_0)/f$. The waves themselves are traveling at speed a, so the frequency heard by the stationary listener is:

$$f' = a/\lambda' = af/(a - V_0) = f\left[1/\left(1 - V_0/a\right)\right] \quad (7)$$

If the source is moving at half the speed of sound toward the listener, the apparent frequency doubles. Compare this situation with the preceding one in which the listener is moving, and the apparent frequency increases by only 50%. Doppler ultrasound systems combine the two situations shown in Figure 38-19. The initial acoustic source is a stationary transducer, and the sound from this device is scattered from a moving target (e.g., red blood cells). The scattered sound returns to a stationary listener—the receiving transducer. In effect, the target is a moving listener hearing a stationary source; the target re-radiates the sound as a moving source toward a stationary listener. The frequency heard by the receiving transducer is obtained by combining equations 6 and 7:

$$f' = f\left[\frac{1 + V/a}{1 - V/a}\right] \quad (8)$$

In this example, we have assumed that the target is moving toward the ultrasound transducers at speed V. If the target is moving at half the speed of sound, the observed frequency is increased by a factor of 3. Because changes in the frequency of sine waves can be measured precisely, the Doppler principle provides an accurate method of measuring the velocity of moving sound reflectors. At the high frequencies often used (ε5 MHz), objects as small as red corpuscles can scatter enough sound for detection.

Ultrasound imaging is exceptionally complex. For simplicity's sake, recall the submarine movies wherein the sonar operator calls out "range 2000 yards, bearing 36 degrees." These two parameters are crucial in describing some of the math of ultrasound.

The first factor to consider is the maximal range of the ultrasound, which is described by the following relationship:

$$r_{max} = cT/2 \quad (9)$$

That is, the maximal range equals the speed of sound in tissue (≈1540 msec) multiplied by time T between pulses divided by 2. A further limitation is the fact that the energy dissipates in the tissue. (You need to tap harder when percussing to detect deeper structures). For deeper penetration into tissues, one requires

higher energies and slower pulse rates. Wavelength and frequency are related in the following manner:

$$\lambda = c/f \quad (10)$$

where f is the frequency, λ is the wavelength, and c is the speed of sound.

Next, we need to consider the axial resolution (is the enemy destroyer 2000 yards distant, or 2005?) and the annular resolution (is the bearing 36 or 38 degrees?). Sound in tissue spreads out in a bandwidth around a fundamental frequency. To determine the necessary bandwidth for an axial resolution of 2 mm, the following rough approximation holds:

$$B = 2c/\Delta r \quad (11)$$

where Δr is the axial resolution. We need a bandwidth of 1.54 MHz to get an axial resolution of 2 mm.

For annular resolution (Δθ), the beam spreads out the farther it goes from the source. Without deriving the mathematics, two factors determine annular resolution—the frequency and the aperture. Aperture size is limited to a size that fits into or onto a human. A 1-degree error at a 1-cm range increases at a 10-cm range: circumference = 2πr: $\frac{1}{360} \times 2 \times \pi \times 1 = 0.17$ mm; at 10 cm, circumference = 1.7 mm.

Adrian W. Gelb, Kate Leslie, Donald R. Stanski, and Steven L. Shafer

39 Monitoring the Depth of Anesthesia

Key Points

1. The definition of "depth of anesthesia" has constantly evolved since the first demonstration of clinical anesthesia in the 1840s. The changing definitions have revolved around the available drugs used to provide anesthesia and the body of knowledge on their effects in humans.
2. Anesthesia is not a single pharmacologic process. It is a complex interaction of multiple stimuli, diverse responses, and the drug-induced probability of nonresponsiveness to the stimuli.
3. Anesthesia can be defined by hypnotic (unconsciousness) and analgesic (pain relief) components. The hypnotic component can be created by intravenous and inhaled anesthetics, whereas the analgesic component can be created by opioids and local anesthetics. Some drugs, such as ether, nitrous oxide, and ketamine, provide both hypnotic and analgesic components to some degree.
4. Hypnotics, when given alone, allow significant hemodynamic response to intense noxious stimuli. Opioids, when given alone, do not guarantee consistent unconsciousness or lack of movement response to intense noxious stimuli. The combination of the two can result in predictable unconsciousness and lack of hemodynamic response to intense noxious stimuli.
5. The interaction of the hypnotic and analgesic components can be characterized by a three-dimensional surface with hypnotic concentration on the *y* axis, analgesic concentration on the *x* axis, and the probability of nonresponse on the *z* axis.
6. Characterization of the three-dimensional surface requires precise stimuli to be applied and specific responses to be measured at defined effect-site concentrations of the hypnotic and analgesic.
7. The specific stimuli-response pairs used to define anesthetic depth range from easily suppressed responses to mild stimulation, such as the verbal response to a verbal command, to difficult-to-suppress responses to intense stimuli, such as the hemodynamic response to intubation.
8. The interaction of hypnotics and analgesics is generally synergistic.
9. Current clinical anesthesia involves the physician carefully observing the clinical response to defined stimuli and then adjusting the hypnotic or analgesic dosage (or both) by using the synergistic interaction to achieve the clinical goals of hemodynamic control, lack of awareness, and rapid, safe induction and emergence.
10. The hypnotic effects of the intravenous and inhaled anesthetics can be measured with empirically derived indices calculated from the electroencephalogram (EEG).
11. EEG-based indices of hypnotic drug effect correlate with hypnotic-induced sedation, amnesia, loss of consciousness, and reduced cerebral metabolic rate.
12. A consequence of inadequate anesthetic depth is intraoperative awareness. The incidence of awareness in healthy patients is approximately 0.1% and can increase to 1.0% to 1.5% in higher-risk patient populations.
13. There is emerging evidence that intraoperative monitoring of the hypnotic component of an anesthetic regimen may significantly decrease the risk of awareness associated with anesthesia. However, it does not totally eliminate the risk.
14. Maintenance of a high steady-state concentration of a volatile anesthetic may reduce the risk of awareness if the consequences of a high concentration can be tolerated by the patient.

A corollary to the aphorism "if you don't know where you are going, then any road will do" is that if you don't know what anesthesia is, any monitor of anesthetic depth will do. What is anesthesia? Anesthesiologists have multiple inconsistent definitions of the anesthetic state and hold strong opinions on how to measure it. Fortunately, an integrated, quantitative concept of the anesthetic state can now be built on the incremental knowledge developed since the introduction of anesthesia more than a century ago. As our understanding of the anesthetic state has advanced, so has our ability to control it pharmacologically and monitor it in real time.

The chapter is divided into four sections. The first reviews evolving definitions of depth of anesthesia. Anesthesia will be defined in terms of two fundamental pharmacologic components, the hypnotic effect and the analgesic effect, with clinical anesthesia requiring both components. The second section reviews memory and awareness, critical components of anesthetic depth. The third reviews basic pharmacologic concepts that are linked to depth of anesthesia. The last section discusses electrophysiologic approaches to assessing depth of anesthesia, including the influence of specific drugs on electrophysiologic approaches. The perspective of the authors is that anesthesia is a pharmacologically induced state that renders patients insensitive to surgery. Because pharmacology is inextricably linked to defining and measuring anesthetic depth, the pharmacology of hypnotics and opioids is discussed from different perspectives in each section. There is unavoidable overlap because monitoring the depth of anesthesia, the focus of this chapter, means monitoring the pharmacologic effects of the drugs used to render patients insensate.

Definitions of Anesthetic Depth

In a 1987 editorial, Prys-Roberts[1] examined clinical components truly relevant to the depth of anesthesia. He began by observing that depth of anesthesia is difficult to define because anesthetists have approached the issue in terms of the drugs available to them rather than the patient's needs during surgery. Prys-Roberts believed that the noxious stimulation of surgery induces a variety of reflex responses that may be independently modulated. One important observation was that pain is the conscious perception of noxious stimulation. Thus, he defined anesthesia as a state of drug-induced unconsciousness in which the patient neither perceives nor recalls noxious stimulation. The loss of consciousness is an all-or-none phenomenon. By this definition, there can be no variable depth of anesthesia. The patient is either conscious or unconscious.

Prys-Roberts defined noxious stimulation as a mechanical, chemical, thermal, or radiation-induced trespass causing potential or actual cell damage. Figure 39-1 shows the somatic and autonomic responses to noxious stimulation. Noxious stimulation arises from somatic or visceral tissue, and responses can be somatic or autonomic. Somatic responses include both sensory and motor activity. A sensory response is perception of pain. Low concentrations of inhaled or intravenously administered anesthetics can eliminate pain, particularly in combination with opioids, but they allow a motor response. The motor response to noxious stimuli is typically an all-or-none withdrawal of the stimulated part. This is the same concept that Eger and colleagues[2] used more than 4 decades earlier when they defined the minimum

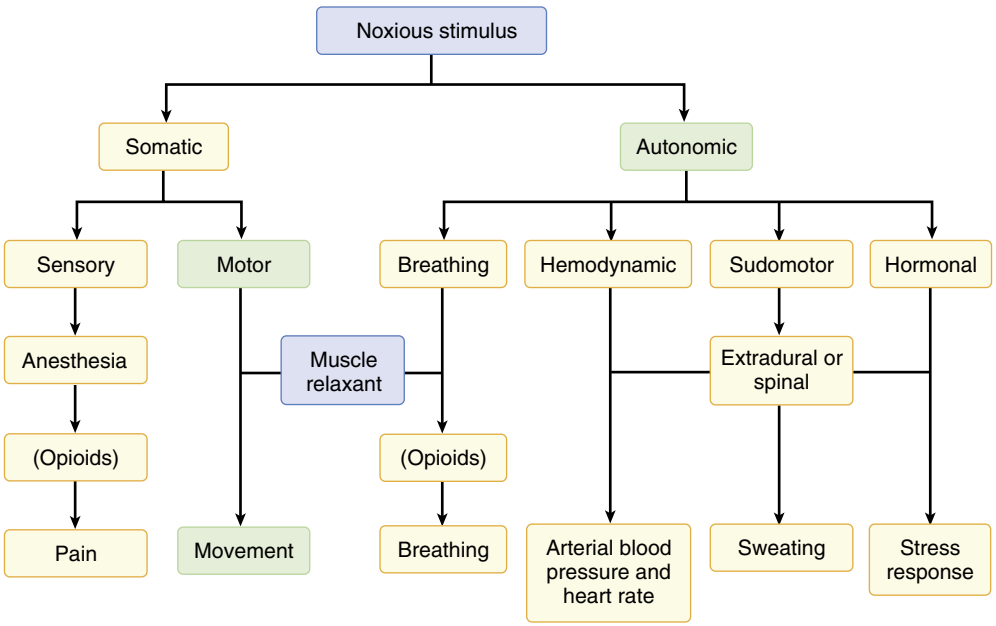

Figure 39-1 Depth of anesthesia can be defined by suppression of the clinically relevant responses to noxious stimuli, as proposed by Prys-Roberts. The figure is read from left to right and from top to bottom to see the order in which reflex responses are suppressed by anesthetic drugs. *(Modified from Prys-Roberts C: Anaesthesia: A practical or impossible construct? [editorial] Br J Anaesth 59:1341, 1987.)*

alveolar concentration (MAC) as the drug concentration that blocked movement in response to noxious stimulation.

Prys-Roberts divided autonomic responses into four categories: breathing, hemodynamic, sudomotor, and hormonal. The ventilatory response may occur even if there is no somatic motor response to surgical stimulation. A higher concentration is required to suppress the breathing response than is required to suppress the somatic response to noxious stimuli.

The hemodynamic response consists of autonomic responses to noxious stimuli, namely, increased sympathetic tone, which elevates arterial blood pressure and the heart rate. The sudomotor response consists of sweating, whereas the hormonal response consists of catecholamines and corticosteroids.

Prys-Roberts considered pain relief, muscle relaxation, and suppression of autonomic activity to be discrete pharmacologic effects. Some drugs can produce all these end points. Others produce only one or two. The only feature common to most anesthetics is suppression of sensory perception and production of unconsciousness. He considered the inclusion of muscle relaxation in the definition of the anesthetic state to be illogical and confusing. Although muscle relaxation is necessary for laryngoscopy and surgical access, it is neither a component of anesthesia nor an alternative to adequate anesthesia.

In a 1993 editorial, Kissin[3] expanded, refined, and further contributed to the definition of anesthesia. Similar to Prys-Roberts, Kissin began by indicating that a wide spectrum of pharmacologic actions via different drugs can be used to create the anesthetic state. Such pharmacologic actions include analgesia, anxiolysis, amnesia, unconsciousness, and suppression of somatic motor, cardiovascular, and hormonal responses to the stimulation of surgery. Kissin stated that the spectrum of effects that constitutes the state of general anesthesia should not be regarded as several components of anesthesia resulting from one anesthetic action but, rather, regarded as representing separate pharmacologic actions, even if the anesthesia is produced by one drug. Kissin then reviewed a series of investigative studies and concepts that supported his hypothesis:

1. Several groups of drugs (benzodiazepines, opioids, α_2-agonists) that induce anesthesia by acting on specific receptors can have their anesthetic effects reversed by the administration of a specific receptor antagonist.
2. There is growing understanding that the molecular mechanisms of general anesthesia are more specific than was suggested by the previous unitary hypothesis of anesthesia.
3. The rank order of effects for two important goals of anesthesia (hypnotic effect and blockade of somatic motor response to noxious stimuli) can be different for different classes of anesthetics. Opioids induce blockade of movement response to noxious stimulation before hypnosis occurs. For intravenous anesthetics, the opposite occurs.
4. When studies of anesthetic interactions are undertaken, the type of interaction (synergism, antagonism, summation) for one component of anesthesia may differ from that of another component.
5. Classic theories of anesthesia, based on the unitary nonspecific mechanisms of anesthetic action, suggest that one anesthetic may be freely replaceable by another and that the effects of anesthetic combinations should be additive. This appears to be true for inhaled anesthetics,[4] but most combinations of intravenous anesthetic drugs are synergistic for hypnotic effects, a finding that suggests diverse drug targets for drug-induced hypnosis.

If one understands general anesthesia as a spectrum of separate pharmacologic actions that vary according to the goals of anesthesia, certain conclusions can be made regarding the measurement of anesthetic potency and depth of anesthesia. Kissin stated that the "diversity of pharmacological actions that in combination provide anesthesia make[s] it almost impossible to determine the potency of different actions with one measure."[3]

A Modern Definition of the Anesthetic State

What is Anesthesia?

The sine qua non of the anesthetized state is unconsciousness or the lack of thought processing. The crux of the difficulty in defining "anesthetic depth" is that unconsciousness cannot be measured directly. What can be measured is response to stimulation. Does the patient respond to command? Does the response to incision suggest conscious perception? Does the heart rate or blood pressure go up in response to surgical manipulation? Does the patient remember events, conversations, or pain? As observed by Prys-Roberts, anesthesia is nonresponsiveness. The "depth" of anesthesia is determined by the stimulus applied, the response measured, and the drug concentration at the site of action that blunts responsiveness.

The state of consciousness can be assessed clinically with tools such as the Modified Observer Assessment of Alertness/Sedation (MOAA/S) scale (Table 39-1).[5] As defined later in this chapter, the state of consciousness can be inferred, although not directly measured, by analysis of information on the electroencephalogram (EEG). This can be done with either spectral techniques, such as the bispectral index (BIS) or with evoked potentials, such as auditory evoked potentials (AEPs). These indices do not directly measure unconsciousness or unresponsiveness. However, we know through extensive validation that these measures are predictive of the likelihood of response, provided that the anesthetic state has been induced with the drugs used to calibrate the electrophysiologic measure.

Nonresponsiveness can be induced by deep sleep or by 2% isoflurane. What distinguishes the nonresponsiveness of the anesthetic state from the nonresponsiveness of normal sleep is the stimulus intensity required to penetrate the state of nonrespon-

Table 39-1 Modified Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
5	Responds readily to name spoken in a normal tone
4	Lethargic response to name spoken in a normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Box 39-1 Components Needed to Define Depth of Anesthesia

Afferent stimulus
Efferent response
Equilibrated concentrations of analgesic drugs
Equilibrated concentrations of hypnotic drugs
Equilibrated concentrations of other relevant drugs (e.g., β-blockers, muscle relaxants, local anesthetics)
Interaction surface relating the drug concentrations to the probability of the given response to the given stimulus

siveness and rouse the brain to conscious perception. The hypnotic drugs used in anesthesia (propofol, thiopental, inhaled anesthetics, ketamine) are each capable of producing such profound central nervous system (CNS) depression that even the most painful surgical stimulus cannot rouse the patient from a state of near-total nonresponsiveness. However, if the painful surgical stimulus can be attenuated before reaching the cortical level, the dose required to maintain the state of nonresponsiveness can be reduced.

Attenuation of surgical stimulation is the function of systemic analgesics (e.g., opioids) and local anesthetics. The interaction between analgesics and hypnotics is thus fundamental to understanding and defining anesthetic depth. Box 39-1 indicates the components of defining the depth of anesthesia used in the remainder of this chapter.

Extending ideas proposed by Glass in 1998,[6] consciousness can be perceived as the balance between depression and excitation within the cortex (Fig. 39-2, upper right). The cortex is primarily depressed by hypnotics, although opioids and nitrous oxide also have sedating properties that depress the cortex. Cortical depression promotes unconsciousness. These effects are opposed by ambient stimulation (e.g., loud music, a hard cold operating table) and the excitatory effects of pain projected on the cortex.

Figure 39-2 also shows the influence of opioids, nitrous oxide, and local anesthetics in preventing noxious stimulation from reaching the cortex. Systemic opioids act on the midbrain and thalamus,[7] although spinal actions are also critical for their analgesic effects.[8] Neuraxial opioids clearly act primarily on the spinal cord. Local anesthetics act either at the spinal cord (for neuraxial blocks) or on peripheral nerves (e.g., nerve blocks and local infiltration). Nitrous oxide exerts some of its analgesic effects through spinal mechanisms,[9,10] as well as the midbrain,[11] but for simplicity we will lump nitrous oxide with opioids at the midbrain. The net effect of analgesic and local anesthetics is to attenuate the transmission of painful sensation to the cortex, thereby reducing the amount of hypnotic required to obtain a state of nonresponsiveness.

Pharmacologic View of the Anesthetic State

Figure 39-3 reduces the model in Figure 39-2 to a highly simplified pharmacologic view.[12] The subcortical actions in Figure 39-2 have been compressed to a single site of action in the lower left of Figure 39-3, and all analgesics, including nitrous oxide, local anesthetics, and opioids, have been compressed to just "opioids." The simplification produces a mathematically tractable pharmacologic structure and may provide insight into the interaction between analgesics and hypnotics on consciousness and responsiveness.

In Figure 39-3, painful stimuli arrive in the lower left. Opioids (and all other analgesics) attenuate the painful stimulus.

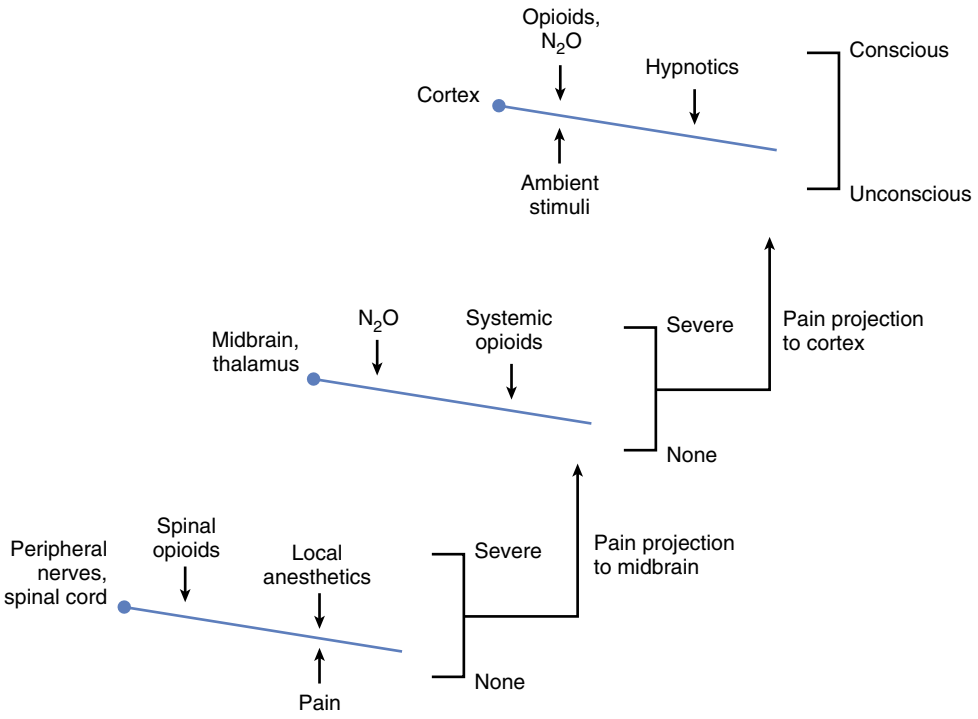

Figure 39-2 Stylized view of the interaction between hypnotics, which depress consciousness, and analgesics, which suppress noxious stimuli.

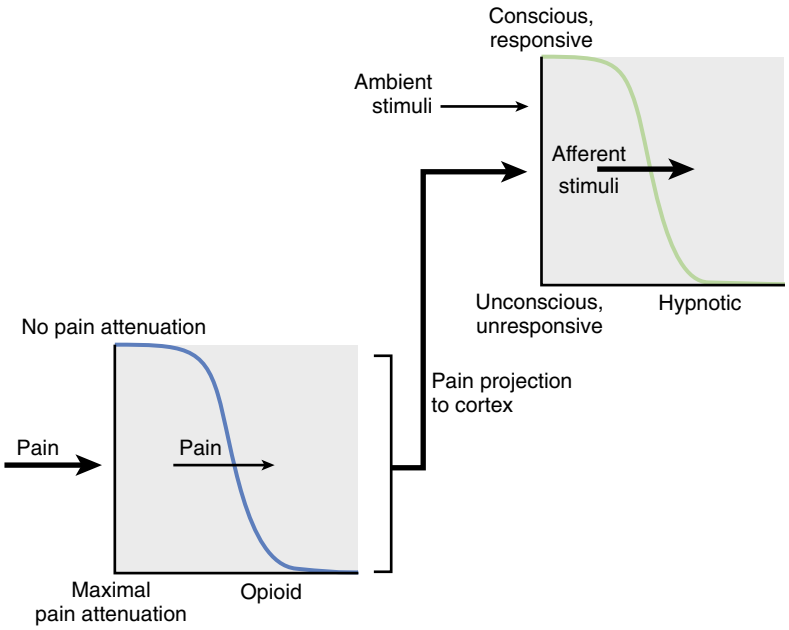

Figure 39-3 Pharmacologic interpretation of the interaction between hypnotics and analgesics. All measures of responsiveness appear in the upper right as "unconsciousness, unresponsive" which lumps the cortical and subcortical responses.

The magnitude of the stimulus affects both the magnitude of the output and the apparent potency of the opioids. Another way of saying this is that it takes more opioid to attenuate a powerfully painful stimulus than a moderately painful stimulus. This has repeatedly been demonstrated, as shown in Figure 39-4.[13] Pharmacologically, the effect of "opioids" on attenuating the pain signal can be expressed by using a standard sigmoid Emax pharmacodynamic equation:

$$\text{Pain out} = \text{Pain in} \cdot \left(1 - \frac{\text{Opioid}^{\gamma}}{\text{Opioid}^{\gamma} + \left[\text{Opioid}_{50} \cdot \text{Pain in}\right]^{\gamma}}\right)$$

in which "pain in" is the afferent painful stimulus, "pain out" is the efferent painful stimulus transmitted to the cortex, "opioid" is the steady-state opioid concentration, "opioid$_{50}$" is the equilibrated opioid concentration associated with 50% attenuation of the "pain in" for an afferent pain intensity of 1, and γ is the steepness of the opioid concentration-versus-response relationship. Opioid$_{50}$ is multiplied by "pain in" to reflect the decreased potency of opioids in attenuating severe pain, as shown in Figure 39-4.

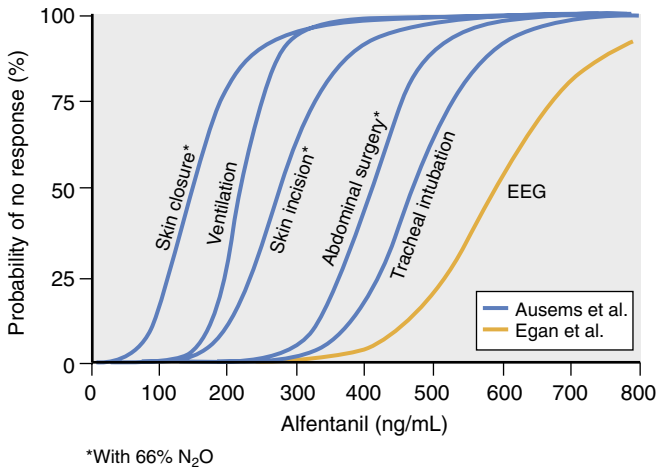

Figure 39-4 The effect of increasingly painful stimulation on the opioid concentration-versus-response relationship.[13] As pain intensity increases, the apparent potency of the opioids decreases. EEG, electroencephalogram.

In Figure 39-3 the output of the attenuated noxious stimulation is projected to the cortex, where the CNS-arousing characteristics of pain are balanced by the CNS-depressant effects of hypnotics. The pharmacologic expression of this would be

$$\text{Probability of responsiveness} = 1 - \frac{\text{Hypnotic}^{\eta}}{\text{Hypnotic}^{\eta} + \left[\text{Hypnotic}_{50} \cdot \text{Stimulus in}\right]^{\eta}}$$

where "stimulus in" is the "pain out" projecting from lower structures plus the ambient stimulation, "hypnotic" is the steady-state concentration of the sedative-hypnotic, "hypnotic$_{50}$" is the concentration associated with a 50% probability of nonresponsiveness when the "stimulus in" equals 1, and η is the steepness of the hypnotic concentration–versus–probability of nonresponsiveness relationship.

This cascading model of drug effect produces the response surface shown in Figure 39-5. The *x* and *y* axes in Figure 39-5 are the equilibrated concentrations of opioid and hypnotic, respectively, The *z* axis in Figure 39-5 is the probability of nonresponsiveness. This surface has the fundamental properties of the opioid-hypnotic relationship. Near the origin for drug concentrations, labeled "1" on the surface, there is no chance of nonresponsiveness, and the patient is probably wide awake. In fact, the floor of the figure indicates that there is a minimum amount of drug that must be given before the patient has any chance of nonresponsiveness. On the other side of the surface, labeled "2", there is enough opioid and hypnotic to ensure virtually no chance of response. The red line in the middle of the surface, labeled "5", is the 50% isobole. This line shows the opioid and hypnotic concentrations associated with a 50% probability of responsiveness. It extends from the curve for the hypnotic-versus-response relationship in the absence of opioids on the far left, labeled "3," to

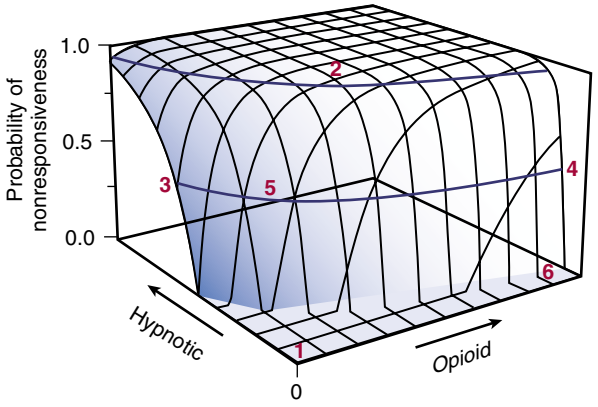

Figure 39-5 Relationship between opioid and hypnotic drug concentrations and the probability of nonresponsiveness. 1, No chance of nonresponsiveness; 2, no chance of response; 3, hypnotic-versus-response relationship in the absence of opioids; 4, hypnotic-versus-response relationship in the presence of large doses of opioids; 5, area of maximum synergy between opioids and hypnotics; 6, in the absence of opioids even profound levels of opioids cannot suppress response; *blue line* in the middle of the surface, the 50% isobole; *blue curve* at the top of the surface, 95% isobole.

the hypnotic-versus-response relationship in the presence of large quantities of opioids on the right, labeled "4." The relationship between hypnotics and opioids is highly synergistic in that when the drugs are used in combination (for example, at the point labeled "5"), it takes far less of either drug than would be the case were the opioids or hypnotics used alone. The model predicts that some hypnotic is required to achieve the anesthetized state. In the absence of a hypnotic, even profound levels of opioids are unable to produce a state of nonresponsiveness, as can be seen at point "6" on the surface.[14-17] However, a modest amount of opioid profoundly reduces the concentration of hypnotic necessary for nonresponsiveness, as seen at point "5." Beyond this, additional opioid has only modest effect in further reducing the hypnotic dose required for a drug effect. The corollary is that large doses of hypnotic are required in the absence of an opioid.[18-20] The blue curve at the top of the surface is the 95% isobole. This curve defines the opioid and hypnotic combinations associated with a 95% probability of nonresponsiveness. Because the surface is very steep, as soon as there is a modest probability of nonresponsiveness, a modest increase in drug concentration is all that is required to move from a 50% chance of nonresponsiveness to a 95% chance of nonresponsiveness.

Figure 39-5 shows that the model of the anesthetic state presented in Figure 39-2 generates a pharmacologic response surface that is very much like those seen in virtually all drug interaction trials.[21]

The ability of inhaled anesthetics to induce immobility in response to noxious stimulation is mediated by the spinal cord, not the cortex.[22,23] Experimentally, the interaction between inhaled anesthetics and opioids in preventing movement response to noxious stimulation[24] resembles Figure 39-5. As such, a pharmacologic model of the effect of opioids on MAC would resemble Figure 39-3 except that the response end point (movement) is mediated by the spinal cord rather than the cortex.

Experimental Characterization of the Anesthetic State

To quantify anesthetic depth, we must be rigorous about the definition of the *z* axis in Figure 39-5, the probability of nonresponsiveness. Consider the matrix of stimuli and responses shown in Figure 39-6. Stimuli can be roughly divided into benign and noxious. Benign stimuli are not physically painful. Thus, responses to benign stimuli are readily suppressed by hypnotics alone, with minimal need for analgesic drugs. Noxious stimuli are physically painful, and thus responses to noxious stimuli are more readily suppressed in the presence of analgesics. Skin incision appears somewhat in the middle of noxious stimuli, being more stimulating than electrical pain but much less stimulating than laryngoscopy and intubation. Figure 39-6 represents the noxious stimuli in approximately increasing order of intensity.

Figure 39-6 shows 10 responses in approximate rank order of difficulty to suppress and 14 stimuli of approximately increas-

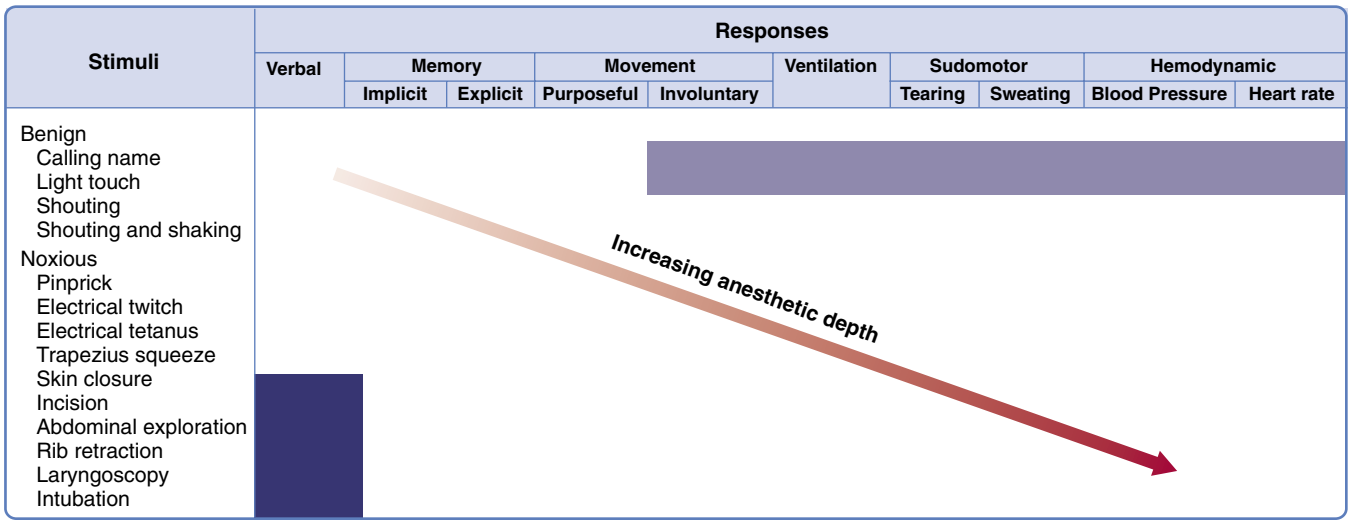

Figure 39-6 Matrix of relevant stimuli and responses. Stimuli are in approximately increasing order of noxiousness. Responses are in approximately increasing order of difficulty of suppression. As the cells progress from left to right and from top to bottom, increasingly larger doses of anesthetic drug are required to suppress the given response to the given stimulus.

ing intensity. The grayed-out cells have been removed as being clinically uninteresting, which leaves 122 cells to define anesthetic depth. If we wanted to fully characterize the ability of isoflurane and fentanyl to create a state of nonresponsiveness for each of the listed responses to any of the listed stimuli, we would need to characterize the response surface (i.e., Fig. 39-5) for each clinically relevant cell! With so many choices of stimuli and interactions, it is not surprising that anesthesiologists cannot agree on a simple definition of anesthetic depth.

Fortunately, it is not necessary to characterize the response to every stimulus. If we characterize the response to a benign stimulus, such as shaking and shouting, and several noxious stimuli, such as electrical tetanus, incision, laryngoscopy, and intubation, we will have captured the clinically relevant range of benign and noxious stimulation.

To our matrix of stimuli and responses we must add the matrix of hypnotics and opioids. Commonly used hypnotics include the anesthetic vapors halothane, isoflurane, sevoflurane, and desflurane and the intravenous hypnotics propofol, thiopental, etomidate, and midazolam. Commonly used opioids include fentanyl, alfentanil, sufentanil, remifentanil, morphine, meperidine, hydromorphone, methadone, tramadol, and piritramide. With 8 hypnotics and 10 opioids, there are 80 combinations. Eighty combinations times 122 interactions yields 9760 combinations of opioids, hypnotics, stimuli, and responses. To this we must then add the influence of age, disease, genetics, and other factors. Clearly, it is impossible to create response surfaces to characterize how opioids and hypnotics produce a state of nonresponsiveness for all possible combinations of drugs, patients, stimuli, and responses.

Fortunately, there are powerful generalizations that provide clinical insight and tractable experimental design. The most important is that for any stimulus-response pair, the depth of anesthesia is the probability of nonresponse. Specifically, *the depth of anesthesia is the drug-induced probability of nonresponse to stimulation, calibrated against the strength of the stimulus and the difficulty of suppressing the response*. Anesthetic depth ranges from fully awake (i.e., verbally responsive to a simple command) to a 100% probability of nonresponse for a difficult-to-suppress (e.g., tachycardia) to a profoundly noxious stimulation (e.g., intubation). Thus, a fully integrated view of anesthetic depth requires consideration of the components shown in Box 39-1.

Figure 39-7 shows an experimentally tractable and clinical useful distillation of the matrix of stimuli and responses from Figure 39-6. The matrix has been reduced to three stimuli, calling name, incision, and intubation, and three responses, verbal response, purposeful movement, and hemodynamic response. Within three of the cells are representative opioid-hypnotic interaction surfaces. As seen in the cells, verbal response to name calling is readily suppressed by hypnotics, with only modest effect from opioids. The middle surface shows that suppression of movement in response to incision requires more hypnotic and opioid to suppress than does a verbal response to a patient's name being called. Additionally, the vertical probability axis stretches for the more profound stimuli to indicate that a 100% chance of nonresponse to incision is a more profound level of drug effect than is a 100% chance of nonresponse to calling the patient's name. Suppressing the most refractory response, hypertension and tachycardia, to the most profound stimulus, intubation, requires yet more opioid and hypnotic. As demonstrated by Figure 39-7, anesthetic depth ranges from a 100% chance of a verbal response to a verbal command (wide awake, no drug) to enough opioid and hypnotic to provide a 100% chance of no hemodynamic response to intubation.

MAC creates a unifying principle of anesthetic depth for the inhaled anesthetics. Although each inhaled anesthetic has some pharmacologic peculiarities, in general they have parallel dose-response curves across drugs (e.g., isoflurane versus sevoflurane versus desflurane) and across stimuli-response pairs. Examples are the inhaled concentration associated with response to

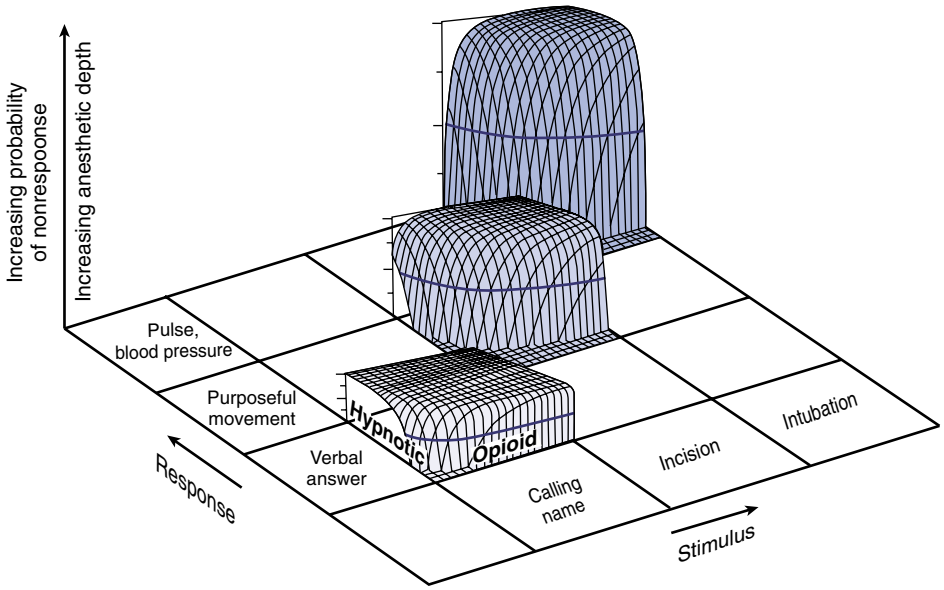

Figure 39-7 The role of opioid and hypnotics in the stimulus-response relationship for three stimuli of increasing intensity and three increasingly difficult responses to suppress. Each cell would have its own opioid-hypnotic interaction surface, and three are displayed. The vertical axis is the probability of nonresponse. Verbal nonresponsiveness to name calling is readily suppressed, even at light levels of anesthesia. In contrast, profound levels of anesthesia are required to suppress the hemodynamic response to intubation.

verbal stimulation (MAC-awake),[25] movement to incision (MAC), and hemodynamic response to incision (MAC-BAR).[26] Thus, by knowing the relative values of MAC, one can infer the relative values of the other stimulus-response relationships. There is less similarity among the intravenous hypnotics. Fortunately, the only intravenous drugs regularly used to maintain the anesthetic state are propofol and midazolam, which limits the number of clinically interesting intravenous anesthetic combinations.

Fentanyl, alfentanil, sufentanil, and remifentanil appear to differ mainly in potency and time course of drug effect, despite conflicting reports of pharmacologic idiosyncrasies for each member of the fentanyl series. Morphine, meperidine, hydromorphone, and methadone appear to differ in potency and intrinsic efficacy and have a slightly reduced maximum analgesic effect than the fentanyl series of opioids does. These latter four drugs also have their own pharmacologic quirks, particularly meperidine, which has only a limited role as an analgesic in contemporary practice.

Nitrous oxide is not only the oldest of the anesthetic drugs still in common use but also remains one of the least well understood. It has properties of hypnotics, with a MAC that slightly exceeds 1 atm,[27] as well as potent analgesic properties. Although the interaction of nitrous oxide with opioids,[28] inhaled anesthetics,[29] and propofol,[30] has been characterized, no studies have gathered enough data to generate the response surfaces needed to fully understand the interactions of this nearly ubiquitous anesthetic drug.

Fundamental Relationships That Characterize the Anesthetic State

Based on the simplifying assumptions just stated, we can comprehend anesthetic depth by understanding a limited number of prototypical drug combinations: isoflurane-fentanyl, isoflurane-nitrous oxide, nitrous oxide-fentanyl, propofol-fentanyl, propofol-nitrous oxide, midazolam-nitrous oxide, and midazolam-fentanyl. For each of these combinations, characterization of the response surface for a handful of stimuli and responses, as suggested in Figure 39-7, would allow understanding of current clinical practice and provide for definition of the full range of anesthetic depth:

1. Loss of response to shouting and shaking:
   a. Any response is considered, (i.e., "MAC-awake")
2. Loss of response to electrical tetanus:
   a. Verbal response or purposeful movement
   b. Any autonomic (hemodynamic or sudomotor) response
   c. Any memory response
3. Loss of response to an intermediate stimulus (incision, trapezius muscle squeeze):
   a. Purposeful movement (i.e., "MAC")
   b. Any autonomic (hemodynamic or sudomotor) response (i.e., "MAC-BAR")
   c. Any memory response
4. Loss of response to laryngoscopy/intubation:
   a. Purposeful movement
   b. Any autonomic (hemodynamic or sudomotor) response
   c. Any memory response
5. The concentration-versus-EEG response relationship in the absence of stimulation

We now have a matrix of just 11 stimuli-versus-response relationships. Multiplied by our seven prototypical drug combinations yields 77 response surfaces, from which we can infer the rest of the surfaces through scaling based on the MAC for inhaled drugs and C_{50} (concentration associated with a 50% probability of drug effect) for intravenous drugs and the relative rankings of stimuli and responses. Moreover, the combinations range from light anesthesia with modest stimulation and easily attenuated responses, found in the upper left corner of Figure 39-6, to deep anesthesia with profound stimuli and very difficult-to-ablate responses, found in the lower right corner of Figure 39-6.

Figure 39-8 shows examples of response surfaces for a modest and a profound stimulus. These interaction surfaces are based on the same model as the interaction surface shown in Figure 39-5, differing only in the intensity of the afferent painful signal. We find the same pattern when we examine real data. Figure 39-9 shows response surfaces for the potentiation of isoflurane by fentanyl (left)[16] and for the potentiation of propofol by alfentanil (right).[17] The shapes of these curves are not exactly like

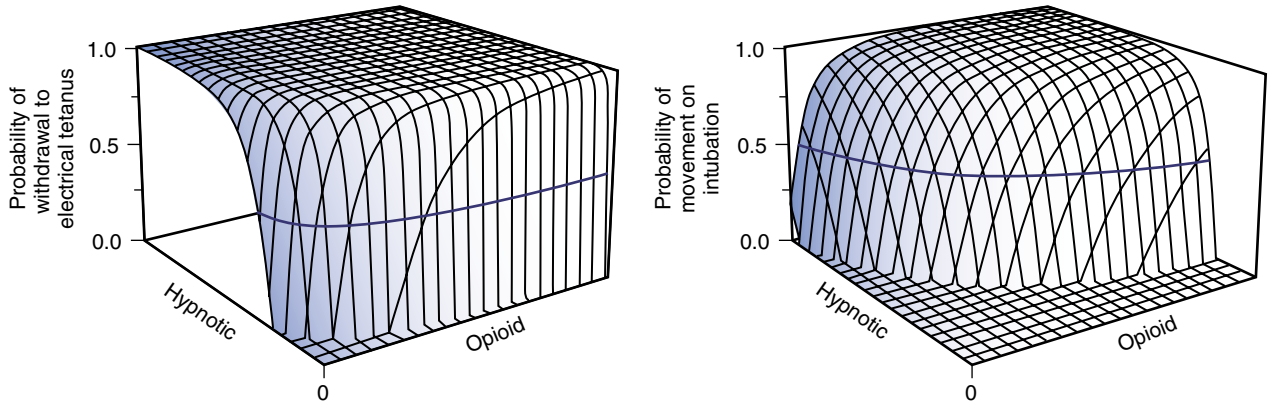

Figure 39-8 Examples of response surfaces for a modest stimulus on the *left* (withdrawal to electrical tetanus) and a profound stimulus on the *right* (movement response to intubation) based on the model shown in Figure 39-5 with differing intensity of the afferent painful signal. The figure on the *left* shows a relatively mild stimulus-response combination, whereas the figure on the *right* shows a profoundly noxious stimulus-response combination.

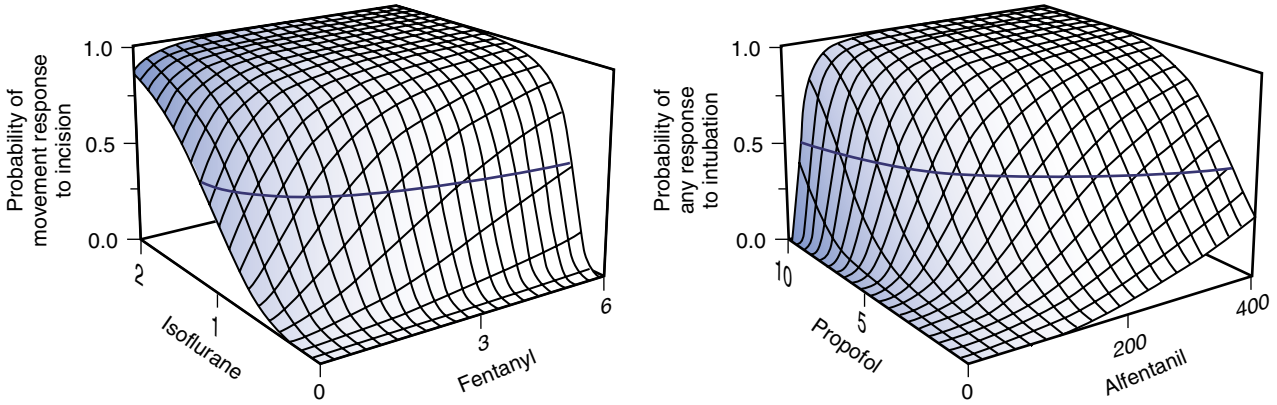

Figure 39-9 The *left* image shows the response surface for reduction in the minimum alveolar concentration of isoflurane by fentanyl.[16] The *right* image shows the interaction of propofol with alfentanil on blunting all responses to intubation.[17] Both figures demonstrate the intrinsic synergy between opioids and hypnotics in producing unresponsiveness.

the shapes derived from our hypnotic-opioid interaction model because (1) the investigators were interested only in characterizing the interaction at the 50% response level and thus did not gather enough data to characterize the upper and lower edges of either curve and (2) the mathematical function was logistic regression, which has several shortcomings as a model of drug interaction. Nevertheless, the figures demonstrate the intrinsic synergy between opioids and hypnotics in producing unresponsiveness, as well as the tendency for more profoundly noxious stimulation (e.g., intubation) to generate more synergy between the analgesic and hypnotic components of anesthesia.

Given our broad definition of anesthetic depth as providing nonresponsiveness to a wide range of stimuli-response pairs (see Fig. 39-6), one might wonder what drugs constitute "anesthetics"? Drugs are defined by their actions, and "anesthesia" is too nonspecific to characterize a drug effect. Because creation of a state of nonresponsiveness ("anesthesia") involves so many drug actions, the term "anesthetic" should not be used to suggest a particular drug class. In particular, "anesthetics" should not be used to describe drugs that suppress consciousness inasmuch as these drugs are more accurately termed "hypnotics." The one exception might be "inhaled anesthetics" because the drugs in this class (halothane, isoflurane, desflurane, and sevoflurane) suppress most of the responses to noxious stimuli.

Awareness and Memory

A spectrum of cognitive activity, including awareness, unconscious memory formation, and dreaming, has been reported during the administration of drugs that are intended to induce and maintain general anesthesia (Fig. 39-10). In addition, a range of physical and physiologic responses have been reported that may indicate perception of painful stimulation, whether conscious or unconscious. The nomenclature used to describe these phenomena has been varied and confusing. In this chapter we use the following widely accepted definitions (Box 39-2).

Awareness

Awareness during anesthesia is an important clinical problem that sometimes results in disabling psychological sequelae for the patient.[34] Although substantial improvements in prevention and treatment of awareness have been made in recent decades, further reductions are hopefully possible through improved training, continuing education, and perioperative care.

Incidence of Awareness

Measuring the Incidence of Awareness

No "cast-iron" method of measuring the incidence of awareness is available because awareness is a subjective cognitive experience that may not be completely understood by the patient or revealed by the patient to the interviewer.[35] Nevertheless, a consensus has developed about an acceptable form of questioning that is based on the questions first used by Brice, Hetherington, and Utting[36] published in 1970:

1. What was the last thing you remembered happening before you went to sleep?

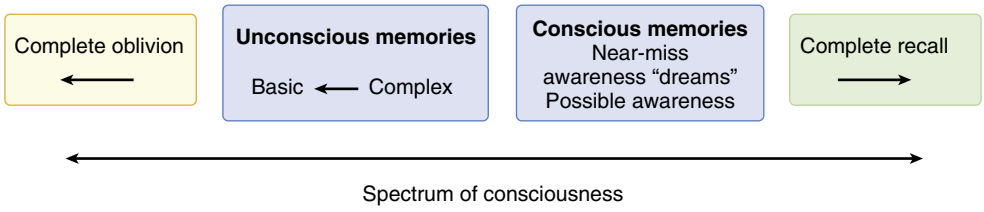

Figure 39-10 Spectrum of cognitive activity reflecting the pharmacologic activity of drugs that induce and maintain the anesthetized state, including awareness, unconscious memory formation, and dreaming.

Box 39-2 Definitions of Awareness and Memory

Awareness—Postoperative recall of events occurring during general anesthesia[31]

Amnesic wakefulness—Responsiveness during general anesthesia without postoperative recall[31]

Dreaming—Any experience (excluding awareness) that patients are able to recall postoperatively that they think occurred during general anesthesia and that they believe is dreaming[32]

Explicit memory—Conscious recollection of previous experiences ("awareness" is evidence of explicit memory)[33]

Implicit memory—Changes in performance or behavior that are produced by previous experiences but without any conscious recollection of those experiences ("unconscious memory formation" during general anesthesia)[33]

2. What is the first thing you remembered happening on waking?
3. Did you dream or have any other experiences while you were asleep?

Abouleish and Taylor[37] modified the Brice questionnaire to the form most commonly used in subsequent studies:

1. What was the last thing you remembered before going to sleep?
2. What was the first thing you remembered on waking?
3. Do you remember anything between going to sleep and waking?
4. While you were sleeping during the operation, did you dream?

An important feature of the modified questionnaire is that it includes a direct question about memory of intraoperative events without making any suggestion about what form these memories might take. A direct question is desirable inasmuch as previous research has suggested that patients may not volunteer information about their awareness episode.[38] In addition, patients should be questioned on more than one occasion postoperatively to maximize the likelihood of detecting all cases of awareness. Residual anesthetic effects, preoccupation with immediate postoperative problems such as pain, and memory suppression as a result of post-traumatic stress disorder[39] (PTSD) may inhibit patients from reporting their awareness experience at an early postoperative interview.

Clinicians should note that the modified Brice questionnaire has been administered to tens of thousands of patients in quality assurance audits and research projects without reports of undue distress to patients, thereby making it a useful tool for their routine postoperative rounds.

Studies of the Incidence of Awareness

Case reports of awareness date from the first demonstration of ether anesthesia by William Morton in 1846. Although the demonstration was deemed a success—because the patient was unresponsive during surgery—it was later revealed that the patient recalled part of the procedure. Patients continued to experience awareness in subsequent decades, but it was not until the introduction of curare into anesthetic practice in 1942 that the modern era of awareness began. The use of muscle relaxants allowed anesthesiologists to administer lower doses of volatile anesthetic agents because they were no longer relying on them to prevent movement during surgery. Case reports of recall of intraoperative paralysis began to appear. In the first prospective study, published by Hutchinson in 1960, a 1.2% incidence of awareness was reported.[40]

Many cohort studies and randomized trials have been published subsequently, the largest of which are presented in Table 39-2. This table reveals a 10-fold decrease in the incidence of awareness in the last 50 years, from about 1% to about 0.1%. In these recent studies, patients undergoing high-risk surgery were included in the mix and a substantial proportion received muscle relaxants. Most patients were attending tertiary referral centers where anesthesia was provided by qualified anesthesiologists and nurse anesthetists, as well as practitioners in training. Patients were asked a direct question about awareness and in two studies were interviewed more than once.

Several other recent studies have reported a substantially different incidence of awareness. Enlund and Hassan[52] did not identify any episode of awareness in 5216 patients undergoing minor surgery at a surgery center. A "high-dose" propofol-opioid protocol without muscle relaxants was administered to 93% of the patients. These patients were interviewed once at discharge from the postanesthesia care unit with the modified Brice questionnaire. The authors and others[62] questioned whether the patient mix, anesthesia protocol, and timing or number of interviews were responsible for the absence of awareness. Pollard and coauthors[33] also reported a low incidence of awareness in 87,361 patients undergoing all types of surgery (six cases [0.0068%]). Four of the aware patients were having cardiac surgery (incidence of 0.12% in cardiac surgery patients). This study was conducted in a tertiary referral hospital (56% of patients) and seven community hospitals and surgery centers (44% of patients). Anesthesia was administered by qualified nurse anesthetists and anesthesiologists using volatile anesthetic–based protocols. The authors and others[63,64] questioned whether the data collection method, which did not include a direct question about recall of events during surgery, the patient population, the absence of anesthesia providers in training, and the anesthetic protocols were responsible for the low incidence of awareness.

In contrast, several recent studies have reported higher rates of awareness. Chaiwat and colleagues[54] reported five cases of awareness in 802 American Society of Anesthesiologists (ASA) class 1 and 2 patients (0.62%) undergoing elective noncardiac, nonobstetric surgery in a Thai tertiary referral center. Volatile-based anaesthesia with muscle relaxants was administered. A cogent reason for each of the cases was present (i.e., inadequate anesthetic delivery, cardiovascular instability, increased anesthetic requirement). Errando and colleagues[61] recently reported 39 cases of awareness in 3921 patients (1%) undergoing noncardiac surgery at a tertiary referral center in Spain. The patients were enrolled between 1995 and 2001, and critically ill and traumatized patients were excluded. A higher incidence of awareness was reported in patients whose anesthesia was maintained with propofol (1.1%) or nitrous oxide (5%) than in patients maintained with a volatile anesthetic (0.59%).

Many studies have sought to determine the incidence of awareness in specific patient groups. These studies report an

Table 39-2 Prospective Cohort Studies of Awareness in Adult Patients

Year	Patients	*N*	Interviews	Incidence (%)	Type of anesthesia	Reference
1960	General surgery*	656	1	1.2	N_2O based and volatile based combined	Hutchinson[40]
1971	Obstetric surgery	880	1	3.3; 0.2	N_2O based versus volatile based	Crawford[41]
1975	General surgery	490	1	1	N_2O based and volatile based combined	Wilson[42]
1985	Cesarean section	777	1	6; 1	Low versus higher dose volatile based	Crawford[42a]
1991	General surgery	1000	1	0.2	Not stated	Liu[43]
1991	Cesarean section	3076	1	1.3; 0.4	Low- versus higher-dose thiopental/volatile	Lyons[44]
1993	Cardiac surgery	700	1	1.1	Volatile based	Phillips[45]
1993	Noncardiac surgery	1727	1	0.3	Propofol based	Sandin[46]
1997	General surgery	1000	3	0.2	Propofol based	Nordstrom[47]
1998	General surgery	2612	1	0.4	Volatile based and propofol based combined	Ranta[48]
1998	Cardiac surgery	617	1	0.3	Volatile based	Dowd[49]
2000	Noncardiac surgery	11,785	3	0.18; 0.10	Volatile based; muscle relaxant versus no muscle relaxant	Sandin[50]
2000	Nonobstetric surgery	10,811	1	0.11	Not stated	Myles[51]
2002	Minor general surgery	5216	1	0	Propofol based	Enlund[52]
2002	Cardiac surgery	929	1	0.5	Not stated	Ranta[53]
2002	General surgery	802	1	0.62	Volatile based	Chaiwat[54]
2004	High risk of awareness	2463	3	0.89; 0.16	Volatile based and propofol based; routine care or BIS guided	Myles[55]
2004	Nonobstetric surgery	19,575	2	0.13	Not stated	Sebel[56]
2004	General surgery	4945	3	0.04	Volatile based (all BIS monitored)	Ekman[57]
2005	All surgery	126,078	1	0.08	Volatile based	Rungreungvanich[58]
2007	All surgery	87,361	2	0.0068	Volatile-based	Pollard[33]
2007	Cesarean section	763	2	0.26	(33% BIS monitored)	Paech[59]
2008	High risk of awareness	1941	3	0.2; 0.2	Volatile based; end-tidal agent monitoring guided versus BIS guided	Avidan[60]
2008	Noncardiac surgery	3921	3	1.1; 0.59; 5	Propofol based, volatile based or N_2O based	Errando[61]

*General surgery corresponds to nonobstetric, noncardiac surgery.
BIS, bispectral index.

increased risk in patients undergoing cardiac surgery,[65] trauma surgery,[66,67] cesarean section,[44,59] airway endoscopic surgery,[68,69] and pediatric surgery[70,71] (although these incidences have also decreased over time). The reasons that these patients may be more at risk for awareness are discussed in the following paragraphs.

Risk Factors for Awareness

Awareness results from an imbalance between anesthetic requirement and anesthetic delivery. This imbalance may be summarized under three main headings:

Normal Requirement—Low Delivery

Inadequate delivery of anesthesia to patients with a normal anesthetic requirement is a common cause of awareness and one that exposes anesthesiologists to peer review, media attention, and litigation.[72,73]

Historically, anesthesia was commonly maintained with nitrous oxide supplemented by residual premedication and induction drugs—a technique associated with a greater than 1% incidence of awareness.[40] Appreciation of this fact resulted in increased use of volatile anesthetics and opioids and a decline in the incidence of awareness, particularly during cesarean section. Similarly, for cardiac surgery, high doses of opioids with or without an adjuvant hypnotic were favored because of stable patient hemodynamics. Unfortunately, however, responsiveness to noxious stimulation was ablated and a high risk of awareness was reported.[65,74] Influential commentary that questioned whether opioids were really capable of producing general anesthesia,[75] as well as a desire for rapid tracheal extubation ("fast tracking"), led to a change in practice and a reduced risk of awareness.[68]

Errors in knowledge, judgment, vigilance, or technical expertise can lead to inadequate anesthetic delivery during any type of general anesthesia.[76-78] However, inhaled and intravenous anesthetics each have their unique problems. During anesthesia with inhaled agents, awareness can result from vaporizer, anesthetic circuit, or end-tidal anesthetic gas monitor malfunctions

that lead to inadequate delivery of nitrous oxide or volatile anesthetic agents (or both).[78] Interruptions in delivery of volatile anesthetics when moving patients from anesthetic induction rooms to operating rooms may also have contributed to the historical incidence of awareness, especially in children.[31,70,71] During intravenous anesthesia, problems in every part of the system from the syringe driver to the site of intravenous access have been reported.[76,79] However, despite early concern about an increased incidence of awareness during propofol-maintained anesthesia,[80] only the Errando study identified a risk,[61] with other studies failing to confirm this risk.[52]

Low Requirement—Very Low Delivery

Delivering adequate anesthesia to patients with a low anesthetic requirement or low cardiovascular reserve presents a particular challenge. For example, pregnant women have a lower anesthetic requirement than nonpregnant women do.[81,82] However, concern about uterine contractility, placental blood flow, and neonatal respiratory depression makes anesthesiologists cautious about anesthetic delivery during cesarean section. The incidence of awareness during cesarean section was particularly high when nitrous oxide–based anesthesia was the norm. Recently, however, the risk of awareness appears to have diminished because of supplementation with volatile anesthetics and possibly the advent of EEG-based monitors.

Patients with low perfusion states as a result of hypovolemia or cardiac failure have a lowered anesthetic requirement, but the anesthetic doses required for adequate anesthesia may still be greater than those that can be tolerated by the cardiovascular system. The result is a higher incidence of awareness in cardiac[65,77] and trauma surgery patients.[66,67] This issue applies particularly to young cardiac and trauma patients, in whom the discrepancy between the vigor of the brain and the cardiovascular system is greatest.

High Requirement—Normal Delivery

Anesthetic requirements may be higher than usual in patients who are tolerant of sedative or analgesic drugs, such as alcohol, benzodiazepines, and opioids (unless the patient is acutely intoxicated, in which case anesthetic requirements may be lower).[54] In addition, there is normal variability in the population with respect to anesthetic requirements. Some patients have multiple episodes of awareness or have family members who have suffered awareness, thus suggesting a genetic etiology.[38,54] Recent evidence also links increased anesthetic requirements to the phenotype of red hair[83] and to childhood.[71] Finally, women recover more rapidly from anesthesia than men do, which potentially increases their risk of awareness if anesthetic delivery becomes inadequate.[84,85]

Preventing Awareness

The incidence of awareness has decreased substantially over recent decades, possibly because of the recognition that awareness has significant consequences for patients and their anesthesiologists and that some anesthetic techniques are associated with increased risk. Nevertheless, further reductions are hopefully possible through further training, continuing education, and perioperative care (Fig. 39-11).

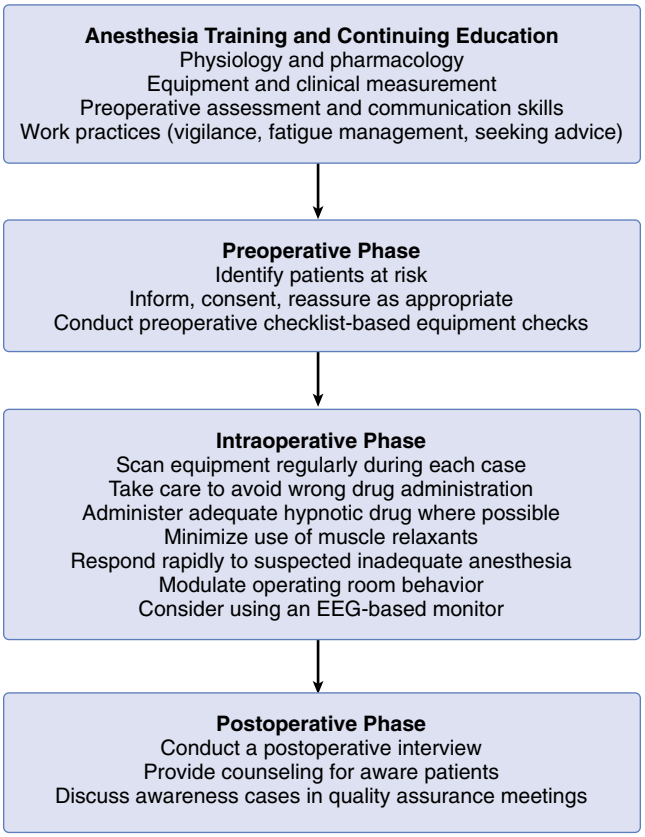

Figure 39-11 Steps to reduce intraoperative awareness by integrating training with perioperative vigilance. EEG, electroencephalogram.

Identifying Patients at Risk

An ASA task force recently promulgated a Practice Advisory that combined an evidence-based approach with expert opinion and open forum commentary.[34] The consensus was that a preoperative interview may be useful in identifying patients at increased risk for awareness and that patients at increased risk should be informed of the possibility of awareness preoperatively.[61] To elicit a past history of awareness, direct questioning may be required.[86]

Reducing Intraoperative Risk

A thorough checklist-based evaluation of equipment should be adhered to preoperatively.[61] During anesthesia, anesthesiologists should develop the habit of scanning drug delivery systems regularly to specifically detect inadequate delivery (e.g., leakage of propofol or air entrainment). Special care should be taken to avoid incorrect drug administration (e.g., giving a muscle relaxant instead of midazolam before induction).[73] Sufficient hypnotic should be administered when possible, and muscle relaxants should be avoided unless required. There should be a rapid response to suspected inadequate anesthesia because memories can take some seconds or minutes to be encoded. This response may include increasing delivery of hypnotic drug, reducing nociception by halting surgery and administering analgesics, and speaking reassuringly to the patient.[86]

Awareness cannot be directly measured as it occurs because by definition, it relies on postoperative recall of intraoperative events.[33] Traditional clinical signs such as movement, tachycardia, hypertension, pupillary responses, and lacrimation are thought to be unreliable predictors of awareness, but they

should still be monitored in every patient and treated on their merits.[35,37,54,55,61,86,87]

The utility of the BIS (Aspect Medical Systems, Inc.) in preventing awareness has been investigated in three large studies. Ekman and colleagues[88] conducted a prospective cohort study in Swedish patients undergoing noncardiac surgery under relaxant general anesthesia with routine BIS monitoring. Patients were interviewed three times with a modified Brice questionnaire. The incidence of awareness was significantly reduced in the BIS-monitored group in comparison to a historical control group without BIS monitoring (0.04% versus 0.18%; $P = .038$).

Myles and coworkers[55] conducted an international randomized controlled trial in 2463 patients at high risk of awareness who were undergoing all types of surgery under relaxant general anesthesia (the B-Aware Trial). Patients were randomized to receive BIS-guided anesthesia (BIS titrated to 40 to 60) or routine care and were interviewed three times with a modified Brice questionnaire. The overall incidence of awareness was 0.5%. There were two confirmed cases of awareness in the BIS-guided group and 11 confirmed cases in the control group (odds ratio, 0.18; 95% confidence interval, 0.02 to 0.84; $P = .022$). Awareness was not predicted from clinical signs in any case. The authors concluded that BIS monitoring is warranted in patients at high risk for awareness undergoing relaxant general anesthesia.

Recently, Avidan and coauthors[60] reported the results of a single-center randomized controlled trial in 1941 patients at higher risk for awareness who were undergoing all types of surgery under relaxant general anesthesia. Patients were randomized to receive BIS-guided anesthesia (BIS titrated to 40 to 60) or end-tidal anesthetic gas (ETAG) concentrations of 0.7 to 1.3 MAC and were interviewed three times with a modified Brice questionnaire. The overall incidence of awareness was 0.2%. There were two cases of awareness in each group (absolute difference, 0%; 95% confidence interval, −0.56% to 0.57%). The authors concluded that their results did not support routine BIS monitoring. Subsequently, it has been shown that the study was underpowered to confirm a difference inasmuch as the incidence of awareness was much lower than anticipated by the sample size calculation, the patients were at relatively low risk, and ETAG concentrations in the 0.7 to 1.3 MAC range are likely to prevent awareness (if the hemodynamic consequences can be tolerated by the patient).[89] In fact, adequate power to detect a difference between BIS and ETAG would have required a group size of more than 9000 patients.[90] Although it is not possible to draw a conclusion about the relative effectiveness of BIS and ETAG from this study, Avidan and coworkers have provoked a discussion about whether ETAG-guided anesthesia is a viable means of preventing awareness.[60] This hypothesis awaits confirmation by a suitably designed trial.

Overall, the current evidence indicates that BIS monitoring may reduce but not eliminate the risk of awareness.[91,92] Failure to respond adequately to changes in the index (i.e., allowing sustained BIS values above the recommended range),[55,60] failure to recognize the possibility of misleading values or artifact,[93,94] and the possibility that awareness may occur at BIS values within the recommended range[55,60] are all reasons why awareness may still occur in BIS-monitored patients. Furthermore, no specific data exist for the other available EEG-based monitors. On this basis, the ASA taskforce concluded that "the decision to use a brain function monitor should be made on a case-by-case basis by the individual practitioner for selected patients (e.g., light anesthesia)."[34] This analysis should also take into account the potential cost of using this technology to prevent a relatively rare complication of anesthesia.[55,60,95]

Consequences of Awareness

Earlier reports on the psychological consequences of awareness were based on retrospective study designs in which patients were identified by advertisement, referral, or analysis of closed claims.[35,72,96] These studies illustrated the distress that may result from an awareness episode but did not confirm the spectrum of symptoms or the incidence of PTSD. More recently, Lennmarken and colleagues[97] audited the incidence of psychological sequelae in 18 prospectively identified awareness cases. Three weeks after the episode, all patients appeared to be coping well and follow-up was discontinued. Two years later, two patients could not be contacted, one had died, and six refused to be interviewed. Of the nine interviewed patients, four were severely disabled by PTSD and another three reported more minor symptoms. These authors suggested that the incidence of PTSD could be greater than 50% inasmuch as avoidance of medical situations is one of the signs of PTSD. Subsequently, this group of researchers reported a contrasting result.[38] They asked 2681 consecutive patients whether they had been aware in the past and identified greater emotional stress in the few days after the episode than later (incidence of late psychological symptoms, 33%). They concluded that the study methodology may influence the result.

Risk factors for PTSD in the awareness setting have not been identified. Commentators have suggested that memory of the pain of surgery and an unsympathetic response from caregivers may contribute.[35,97] The psychological literature suggests that peritraumatic dissociation is a predictor of the severity of posttraumatic symptoms.[39] Further research is required in this area.

An episode of awareness may have consequences for the anesthesiologist as well. Most patients who suffer an awareness episode do not proceed to litigation or generate unwanted attention from the media or regulatory authorities. One could hope that good communication and patient support may prevent not only adverse patient sequelae but also lawsuits.[98] The ASA Closed Claims Project provides a valuable analysis of cases that have proceeded to litigation in the United States. In the period 1990 to 2001, 55 claims were made, substandard care was identified in 47% of cases, and 46% were settled with a patient payment (median payment, $41,210 [substantially lower than the median payment for other general anesthesia claims]).[98] It is difficult to say whether the recent attention paid to awareness[34] and the advent of EEG-based monitoring[55] will increase or decrease the liability for awareness in the future.

Unconscious Memory Formation During Anesthesia

Whether patients can form unconscious memories during anesthesia and whether these memories matter are interesting questions and ones that have occupied researchers for the last 40 years.[99] In the first systematic study of this subject, Levinson[100] staged a mock crisis during anesthesia and then hypnotized the patients to determine whether unconscious memories of the crisis had been retained. No patient had active recall of events occurring during anesthesia, but under hypnosis, 4 of the 10 patients could recount the crisis accurately. However, this study

and subsequent ones[99] were confounded by the inability to discount inadequate anesthesia or reduce the influence of active recall when testing for unconscious memory.

Since the mid-1990s, investigators have more carefully controlled anesthetic depth by using EEG-based monitoring and have used perceptual priming tests that measure explicit and implicit memory in a single test involving the process dissociation paradigm.[101] These studies revealed that unconscious memories are retained if anesthesia is relatively light or variable in depth and word presentation occurs during surgery.[102-104] For example, Lubke and coworkers[102] investigated patients in whom general anesthesia was induced for trauma surgery by using the word stem completion test and process dissociation paradigm. The number of stem completions with words presented during surgery ("hits") increased with increasing BIS values, and implicit memory was demonstrated at BIS values of less than 60. Stonell and coauthors[103] reported successful priming at BIS values greater than 50, whereas Deeprose and colleagues[104] reported priming at mean BIS values of 42. In contrast, Kerssens and colleagues[105] targeted a similar BIS range but achieved a lot less fluctuation in BIS values (1% versus 8% to 11% in the previously mentioned studies[103,104]). They could not demonstrate any unconscious memory formation. This study emphasizes that excursions into light planes of anesthesia appear to be necessary for memory formation.

Finally, does unconscious memory formation during anesthesia have any consequences for the patient? In the psychological literature, priming has been reported to enhance existing tendencies—this is the foundation of subliminal advertising techniques. However, there is no evidence yet that unconscious memory formation has adverse or even therapeutic effects after general anesthesia. Nevertheless, we should avoid making comments during anesthesia that we do not want our patients to hear.[106]

Dreaming During Anesthesia

Dreaming during anesthesia is a commonly reported and fascinating phenomenon that nevertheless remains poorly understood. The incidence of dreaming during anesthesia varies according to the age and sex of the patients, the type of anesthesia, and the timing of the postoperative interview. Dreaming is more commonly reported by younger patients[107,108] and after propofol-based,[108] opioid-based,[36] or ketamine-based[109] anesthesia. If an interview is conducted at emergence from anesthesia, about 25% of patients will report that they have been dreaming.[108] However, if the interview is delayed until discharge from the postanesthesia care unit, the incidence falls to around 6%.[55]

Early reports of dreaming were often suggestive of near-miss awareness: (1) "A patient dreamed that he was at a fairground and someone was throwing darts at his stomach,"[110] (2) "A patient dreamt that the pages of a heavy book were being slowly turned over at regular intervals,"[40] and (3) "A patient dreamed of a party at a public house in which there was a generous supply of gin and the anaesthetist was the landlord!"[36] It was also reported that dreaming patients exhibited more signs of light anesthesia, were more likely to report awareness, and were less likely than nondreaming patients to have been BIS monitored.[36,107,111]

Subsequent studies suggested, however, that most dreaming is not related to inadequate anesthesia and may occur during recovery. Leslie and coworkers[108] conducted a prospective cohort study of 300 young healthy patients undergoing relaxant general anesthesia for noncardiac surgery. No difference in median BIS values during surgery between dreamers and nondreamers was reported. The form and content of the dreams were suggestive of the dreams of sleep onset, and the authors postulated that dreaming was occurring during physiologic sleep (a hypothesis that awaits confirmation).

Almost all dreaming during anesthesia is harmless, unimportant, and quickly forgotten. Only dreams that worry the patient or that are suggestive of awareness should receive further attention. These patients should receive similar follow-up to patients with frank recall of intraoperative events.[108]

Hypnotics, Analgesics, and Anesthetic Depth

Inhaled Anesthetics

Movement Response and the MAC Concept

Purposeful movement of a body part in response to noxious stimuli has been extensively used as a clinical sign of anesthesia. Using this movement to quantitate anesthetic response induced by potent inhaled anesthetics, Eger, Merkel, and their colleagues[2,112] defined MAC as the minimum alveolar concentration of inhaled anesthetic required to prevent 50% of subjects from "gross purposeful movement" in response to a skin incision. As suggested by the definition, "minimum" is a slight misnomer, and "median" would probably have been a better descriptor. Readers are referred to the excellent review articles that document development of the MAC concept and its many applications in anesthesia.[113,114]

The MAC concept has three basic components: (1) an all-or-none (quantal) movement response must occur after applications of a "supramaximal" noxious stimulus; (2) end-tidal concentrations of anesthetic in the alveoli, considered an equilibrated sample site, are used as an indication of the concentration of anesthetic in the brain; and (3) MAC is a unifying concept of inhaled anesthetic potency.

For determination of MAC in humans, the standard noxious stimulus has been the initial surgical skin incision.[2] Skin incision represents a reproducible noxious stimulation. There has been no systematic examination of other perioperative surgical stimuli (e.g., peritoneal traction) representing more profound surgical manipulation than skin incision or endotracheal intubation. For determination of MAC in animals, the standard stimulus has been application of a surgical clamp to the base of the tail. After examining other noxious stimuli in dogs, Eger and colleagues[2] concluded that tail clamping represented the most noxious stimulation that was experimentally reproducible and not excessively traumatic.

A second component of the MAC concept involves use of the alveolar concentration of an anesthetic as an indication of drug concentration. The steady-state (i.e., equilibrated) partial pressures of inhaled anesthetics must be identical in all body tissues, such as alveoli, blood, and brain. Thus, the measured end-tidal partial pressure of an inhaled anesthetic (representative of the alveolar concentration) is in direct proportion to the underlying concentration in the brain at steady state. Because the brain

is so well perfused relative to its mass, it is possible to achieve an equilibration among end-tidal, alveolar, arterial, and brain anesthetic partial pressures within 15 minutes of exposure to a constant end-tidal anesthetic concentration.[115]

A third component of MAC is that it has served as a unifying measure of inhaled anesthetic potency. This has resulted in the concept of MAC fractions or MAC multiples for end points other than movement response to skin incision. Stoelting and colleagues determined the MAC of an anesthetic that would allow opening of the eyes on verbal command during emergence from anesthesia ("MAC-awake").[116] This stimulation is less intense than surgical skin incision, and response occurs at lower concentrations of anesthetic than movement to skin incision does. Generally, the MAC-awake values are a third to a fourth of the MAC values for surgical incision. Yakaitis and coworkers[117] determined the MAC of an inhaled anesthetic that would inhibit movement and coughing during endotracheal intubation ("MAC-intubation"). Intubation is significantly more stimulating than skin incision, with higher concentrations of inhaled anesthetic required to eliminate movement response. Finally, Roizen and associates[118] investigated the MAC of anesthetics necessary to prevent an adrenergic response to skin incision ("MAC-BAR"), as measured by the concentration of catecholamine in venous blood. When one examines the values for (1) MAC-awake, (2) MAC–skin incision, (3) MAC-intubation, and (4) MAC-BAR, one sees a family of concentration-versus-response curves that characterize the hypnotic effects of inhaled anesthetics relative to defined clinical stimuli.

Zbinden and colleagues undertook a comprehensive examination of the effects of different noxious stimuli on the purposeful movement response with isoflurane.[119] Twenty-six healthy surgical patients were administered only isoflurane with adequate inspired/end-tidal equilibration. Multiple noxious stimuli were applied at varying end-tidal isoflurane concentrations. From the resulting data, the authors were able to define a family of concentration-versus-response curves for different noxious stimuli, as displayed in Figure 39-12. The percent end-tidal isoflurane concentrations that resulted in a 50% probability of no movement response for different stimuli were as follows: verbal responsiveness, 0.37%; trapezius muscle squeeze, 0.84%; laryngoscopy, 1.0%; 50-Hz electrical tetanus, 1.03%; skin incision, 1.16% (MAC, by definition); and laryngoscopy with intubation, 1.76%. This study demonstrates how varying clinical stimuli require different isoflurane concentrations to prevent a clinical response and can be used to define a concentration-versus-response relationship for the hypnotic effects of isoflurane. When different inhaled anesthetics are compared, the ratio of MAC–skin incision to MAC-intubation or MAC-awake is relatively constant.

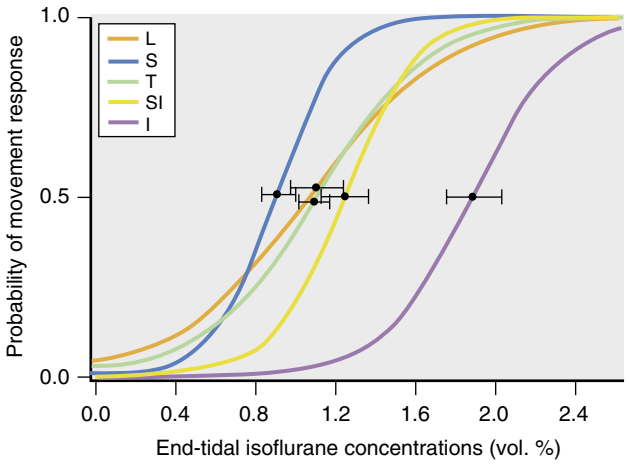

Figure 39-12 Logistic regression analysis of the end-tidal isoflurane concentration relative to the predicted probability of no movement response for different noxious stimuli. *Bars* indicate the 95% confidence intervals the end-tidal concentration with a 50% probability of response. I, laryngoscopy/intubation; L, laryngoscopy; S, trapezius muscle squeeze; SI, skin incision; T, tetanic nerve stimulation. *(Modified from Zbinden AM, Maggiorini M, Petersen-Felix S, et al: Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. I. Motor reactions. Anesthesiology 80:253-260, 1994.)*

Table 39-3 Factors that Affect Minimum Alveolar Concentration

Effect on MAC	Factors (Study Subjects)
Decrease	Hypothermia (animals) Severe hypotension (animals) Advanced age (humans) Opioids, ketamine (humans, animals) Chronic administration of amphetamine (animals) Reserpine, α-methyldopa (animals) Cholinesterase inhibitors (animals) Intravenous local anesthetics (humans, animals) Pregnancy (animals) Hypoxemia (Pa_{O_2} < 40 mm Hg) (animals) Anemia (animals) α_2-Agonists (animals, humans)
Increase	Hyperthermia (animals) Hyperthyroidism (animals) Alcoholism (humans) Acute administration of dextroamphetamine (animals) Young age (humans, animals)
No effect	Duration of anesthesia (humans, animals) Sex (human, animals) Metabolic acid-base status (animals) Hypercapnia and hypocapnia (humans, animals) Isovolemic anemia (animals) Hypertension (animals)

Other drugs used in anesthesia increase the apparent potency of inhaled anesthetics by decreasing the anesthetic requirement, as measured by a reduction in MAC. Numerous altered physiologic states (e.g., aging) also change the apparent potency of inhaled anesthetics. Several review articles have described the many studies applying the MAC concept to the clinical practice and science of anesthesia.[38] Table 39-3 summarizes the results of these studies regarding the factors that affect MAC.

Much of the previous research on MAC assumed that the lack of movement response from inhaled anesthetics was due to anesthetic effects on the central, cortical brain tissues. This assumption has been challenged. In 1993, Rampil and coworkers demonstrated in decorticate rats that the spinal cord was the primary site mediating immobility for inhaled anesthetics.[22] Antognini and Schwartz also drew the same conclusions from experiments in goats with isolated brain/body perfusion.[23] These investigators demonstrated that the MAC value for the goat was

Table 39-4 Hemodynamic Response to Defined Noxious Stimuli Under Isoflurane Anesthesia

Stimulus	End-Tidal Concentration That Suppresses Movement In 50% of Patients (ET_{50}) (Percent atm)	Change in Systolic Blood Pressure for Patients at ET_{50} (mm Hg)	Change in Heart Rate for Patients at ET_{50} (Beats/min)
Trapezius muscle squeeze	0.90	9	5
Electrical tetanus	1.10	15	15
Laryngoscopy	1.07	23	17
Skin incision	1.24	34	35
Laryngoscopy and intubation	1.87	53	36

ET, end-tidal concentration.

approximately twice as large when only the brain was exposed to isoflurane than when both the brain and spinal cord were exposed to the anesthetic.

Other Clinical Responses

Responses other than purposeful movement have been investigated as possible clinical measures of the depth of anesthesia: the rate and volume of ventilation in spontaneously breathing subjects, eye movement, the diameter and reactivity of pupils to light, heart rate, arterial blood pressure, and autonomic signs such as sweating. It has not been possible to use these clinical signs to generate uniform measures of the depth of anesthesia for inhaled anesthetics. Although some clinical signs do correlate with depth of anesthesia for certain inhaled anesthetics, the same cannot be said for other inhaled anesthetics.[120]

We have previously noted that the hemodynamic response is harder to suppress than movement. This was particularly well demonstrated by Zbinden and colleagues[121] in a systematic study of the hemodynamic response to different noxious stimuli at increasing isoflurane concentrations. In 26 healthy surgical patients receiving different equilibrated end-tidal concentrations of isoflurane, the following noxious stimuli were applied, several of them on multiple occasions: trapezius muscle squeeze, 50-Hz electrical tetanus, laryngoscopy, laryngoscopy with intubation, and skin incision. With continuous recording of intra-arterial hemodynamics, acute increases in heart rate and systolic blood pressure were recorded and related to the isoflurane concentration and presence or absence of purposeful movement. Table 39-4 presents the absolute increase in systolic blood pressure and heart rate at the isoflurane end-tidal concentration that had a 50% probability of no purposeful movement for that specific stimulus. As stated earlier, different noxious stimuli result in different degrees of hemodynamic response. There is a relative rank order of the degree of hemodynamic response, with laryngoscopy and intubation being the most intense stimuli. Multiple regression analysis demonstrated that the type of stimulation had the most influence on the increase in blood pressure, with the isoflurane concentration being the least important. Figure 39-13 presents the baseline systolic blood pressure and subsequent increase in systolic pressure at a measured isoflurane concentration for subjects receiving a skin incision. Increasing isoflurane concentration did not prevent the increase in systolic blood pressure, even at very high end-tidal concentrations. Rather, increasing isoflurane concentration only decreased the prestimulation systolic

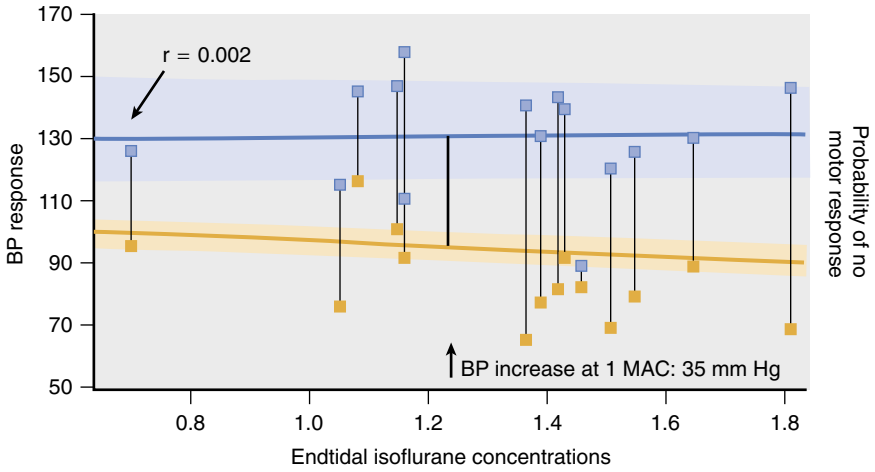

Figure 39-13 Response of systolic blood pressure (BP, in mm Hg) to skin incision as a function of end-tidal isoflurane concentration. Yellow squares, systolic blood pressure before stimulation; Blue squares, systolic blood pressure after stimulation; *lower oblique line*, regression line to systolic BP before stimulation (r = –0.46); *upper line*, regression line to systolic BP after skin incision (r = 0.0002); *shaded area*, 95% confidence interval for regression lines; *vertical arrow*, median effective isoflurane concentration for the motor response of the stimulation pattern. The *shaded areas* represent the linear regression relationship of isoflurane concentration versus prestimulus and poststimulus systolic BP. MAC, minimul alveolar concentration. *(From Zbinden AM, Maggiorini M, Petersen-Felix S, et al: Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. I. Motor reactions. Anesthesiology 80:253-260, 1994.)*

pressure such that the noxious stimuli returned systolic pressure closer to the normal, awake values.

The clinical implications of these data relative to judging anesthetic depth from the hemodynamic response for inhaled anesthetics are significant. When used as a sole agent, even in high concentrations, isoflurane is unable to suppress hemodynamic responses to noxious stimuli. Rather, the hemodynamic control seen with high isoflurane concentrations occurs as a result of a decrease in the prestimulation hemodynamic baseline. Thus, although hemodynamic responses are the most commonly used clinical measures to judge inhaled anesthetic depth of anesthesia, the scientific basis for such application is tenuous.

Zbinden's work is important evidence that isoflurane provides hypnotic effects with minimal analgesic effect, as judged by the profound hemodynamic response to noxious stimuli in the presence of 1.8 MAC isoflurane. In clinical practice, additional drugs are commonly used with inhaled anesthetics. Daniel and colleagues[26] examined how fentanyl (0 to 3 µg/kg) and 60% nitrous oxide alter the heart rate, mean arterial blood pressure, and catecholamine response (components of MAC-BAR) during desflurane and isoflurane anesthesia. Fentanyl, 1.5 µg/kg, reduced MAC-BAR for desflurane from 1.3 to 0.4 MAC and for isoflurane from 1.3 to 0.55 MAC. Increasing the fentanyl dose to 3 µg/kg did not cause further change in MAC-BAR values for both inhaled anesthetics. Figure 39-14 shows an interaction surface for fentanyl and isoflurane based on modifying the model reported by McEwan to increase C_{50} in the absence of fentanyl by 1.3 and adjusting the isoflurane C_{50} in the presence of an effect-site fentanyl concentration of 1.36 ng/mL (corresponding to a 1.5-µg/kg bolus) to 0.4 MAC. The red arrow shows the reduction in MAC-BAR demonstrated by Daniel and coworkers.[26] It is clear from the figure that additional opioid would not be expected to yield further significant reductions in MAC-BAR. This study suggests that the addition of analgesic components, such as nitrous oxide and fentanyl, can prevent the sympathetic stimulation and hemodynamic responses seen with noxious surgical stimuli when inhaled anesthetics are used.

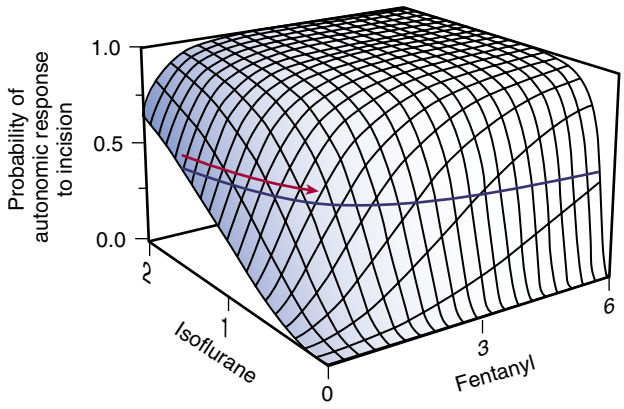

Figure 39-14 Interaction surface for fentanyl and isoflurane reflecting suppression of the autonomic response. The surface is based on the isoflurane interaction reported by McEwan and colleagues,[16] but modified to increase the C_{50} of isoflurane in the absence of fentanyl by 1.3 minimum alveolar concentration (MAC) and adjusting the isoflurane C_{50} in the presence of an effect-site fentanyl concentration of 1.36 (corresponding to a 1.5-µg/kg bolus) to 0.4 MAC, as reported by Daniel and coauthors.[26] The *red arrow* shows the reduction in MAC-BAR demonstrated by Daniel and coworkers.[26]

Intravenously Administered Hypnotics

Traditionally, intravenous hypnotics were used for induction of anesthesia as a single intravenous bolus. The introduction of propofol allowed these drugs to be infused for maintenance of anesthesia, where assessment of depth of anesthesia becomes more relevant.

Assessing Depth During Induction of Anesthesia

Induction of anesthesia often consists of a rapid intravenous bolus injection of an intravenous hypnotic (e.g., propofol, thiopental, etomidate). Plasma concentrations peak within a half to 1 minute and decline rapidly on redistribution of the drug. The rapidly changing plasma concentrations cause a corresponding fluctuation in the degree of CNS depression. Depth of anesthesia increases rapidly (causing loss of consciousness), peaks, and then decreases as plasma concentrations decline. CNS depression lags behind plasma concentrations and is manifested as hysteresis on curves plotting effect against plasma concentration. All the concepts discussed earlier regarding non–steady-state conditions produced by rapid administration of a drug make assessment of the relationship of plasma concentration and depth of anesthesia difficult, if not impossible, during bolus intravenous administration.

Clinical end points useful in assessing depth of anesthesia during induction include loss of verbal responsiveness, loss of eyelid reflex, and loss of corneal reflex. Typical stimulation occurring during induction of anesthesia includes laryngoscopy and intubation, which are profoundly noxious stimuli. Frequently, response to these two procedures cannot be eliminated completely with just the intravenously administered hypnotic. In one study, administration of thiopental (6 mg/kg) was followed by an average increase in systolic blood pressure of 53 mm Hg on laryngoscopy and intubation.[122] In another study, administration of thiamylal (4 mg/kg) was followed by an increase in mean arterial blood pressure from 92 mm Hg (control) to 136 mm Hg on laryngoscopy.[123] Because most intravenous hypnotics do not provide significant analgesia, the hemodynamic response to major noxious stimuli is great, even when large doses are given. Thus, assessment of depth of anesthesia with clinically relevant noxious stimuli such as laryngoscopy and intubation requires the concurrent administration of other analgesic drugs (opioids or nitrous oxide) to provide reasonable and clinically acceptable hemodynamic control.

Assessing Depth During Maintenance of Anesthesia

Becker[124] presented one of the first studies that quantified the relationship between plasma concentrations of an intravenous anesthetic (in this case, thiopental) and clinical measures of depth of anesthesia.

Hung and coauthors[125] proposed a conceptual approach that used clinical measures to examine intravenous anesthetic pharmacodynamics. A target controlled infusion of thiopental rapidly achieved and then maintained a low (10 to 40 µg/mL) and then high (40 to 90 µg/mL) thiopental concentration in 26 surgical patients. After allowing 5 minutes for blood-brain equilibration, increasingly noxious stimuli (verbal command, 50-Hz electrical tetanus, trapezius muscle squeeze, laryngoscopy, and intubation) were applied at 1-minute intervals until the patient responded verbally or moved purposefully. The approach sepa-

rated the increasing levels of thiopental required to block increasingly noxious stimulation.

Kazama and colleagues[19] examined the pharmacodynamics of propofol alone and then of propofol with fentanyl by using the defined noxious stimuli/movement responses that Hung and coworkers[125] used for thiopental and the hemodynamic methodology developed by Zbinden and associates[121] for isoflurane. These results are shown in Figure 39-15. Verbal response was easily suppressed by propofol, whereas the response to intubation was the most difficult to suppress. Tetanus, incision, and laryngoscopy were similarly noxious in this paradigm. Kazama and colleagues also found that addition of a steady-state fentanyl concentration of 1 or 3 ng/mL minimally decreased the amount of propofol required to suppress verbal response but profoundly decreased the amount of propofol required to suppress the response to tetanus, laryngoscopy, skin incision, and intubation.[19] Similar to what Zbinden and associates[121] described for isoflurane, the addition of fentanyl to propofol attenuated the increases in systolic blood pressure in a dose-dependent manner. The conceptual methodology used by Kazama and coworkers allows characterization of anesthetic depth by using multiple, defined noxious stimuli, as discussed previously in this chapter, and supports the intellectual framework for anesthetic depth shown in Figure 39-7.

Quantitation of clinical depth of anesthesia for the combination of an opioid and intravenous anesthetic was reported by Vuyk and coauthors.[126] Using the pharmacodynamic methodology developed by Ausems and colleagues,[28] the interaction of a constant plasma concentration of propofol (in place of nitrous oxide) was examined as the alfentanil was titrated to clinical responses. Propofol exhibited a significant interaction with alfentanil, thus decreasing the total dose of alfentanil and the alfentanil plasma concentrations needed for adequate anesthesia. Table 39-5 indicates how the total dose of alfentanil needed decreased from 22.8 mg with 66% nitrous oxide to 10.3 mg with a steady-state propofol plasma concentration of 4 µg/mL. The mechanism of this decreased dose requirement was marked potentiation of alfentanil such that the alfentanil plasma concentrations needed to achieve the same degree of pharmacologic effect were two to four times lower with propofol.

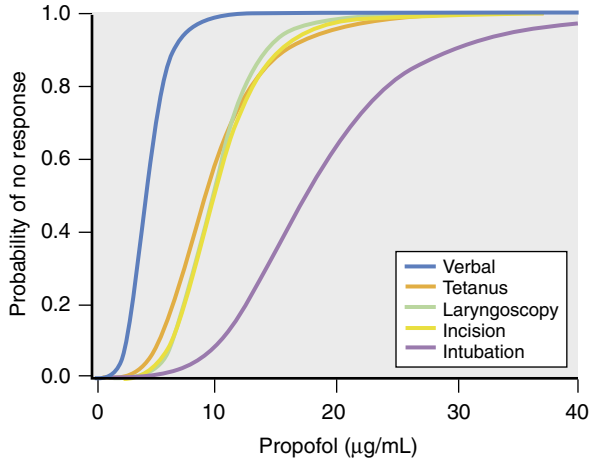

Figure 39-15 Propofol concentration-versus-response relationship for five clinically relevant stimuli: verbal, electrical tetanus, laryngoscopy, incision, and intubation. *(From Kazama T, Ikeda K, Morita K: Reduction by fentanyl of the Cp_{50} values of propofol and hemodynamic responses to various noxious stimuli. Anesthesiology 87:213-227, 1997.)*

Table 39-5 Interaction of Propofol and Nitrous Oxide with Alfentanil in Lower Abdominal Surgery

	Alfentanil Cp_{50} (ng/mL) in Conjunction with	
Event	**Propofol**	**Nitrous Oxide**
Steady-state propofol or nitrous oxide concentration	4.0 ± 0.6 µg/mL (range, 3.2 to 4.9)	66%
Intubation	92 ± 20*	429 ± 42*
Skin incision	55 ± 16*	101 ± 16*
Intra-abdominal dissection	66 ± 38†	206 ± 65†
Total alfentanil dose (mg)	10.3 ± 6.1†	22.8 ± 6.4†

*± standard error.
†± standard deviation.
Modified from Vuyk J, Lim T, Engbers FH, et al: Pharmacodynamics of alfentanil as a supplement to propofol or nitrous oxide for lower abdominal surgery in female patients. Anesthesiology 78:1036-1045, 1993.

In a subsequent study, Vuyk and colleagues used this same methodology, but they randomized the surgical subjects to a range of constant propofol blood concentrations.[17] With blood propofol concentrations increasing from 2 to 10 µg/mL, the alfentanil Cp_{50} decreased from 170 to 25 ng/mL for laryngoscopy, from 280 to 23 ng/mL for intubation, from 259 to 9 ng/mL for opening of the peritoneum, and from 209 to 16 ng/mL for the intra-abdominal surgical stimulus. With plasma alfentanil concentrations increasing from 10 to 150 ng/mL, the propofol Cp_{50} for regaining of consciousness decreased from 3.8 to 0.8 µg/mL. This study confirms the profound, synergistic interaction of propofol with alfentanil. Vuyk and colleagues used computer simulations of their gathered data to suggest that the optimal blood propofol and plasma alfentanil concentrations that allow the most rapid recovery from intraoperative anesthesia occur at 3.5 and 85 ng/mL, respectively. An editorial[127] comment on this study provided more general guidelines for using the quantitative interaction of propofol and alfentanil to design dosing regimens for total intravenous anesthesia.

Opioids

As indicated earlier, large intravenously administered doses of thiopental or propofol are ineffective at eliminating the hemodynamic response to highly noxious stimuli such as laryngoscopy and intubation (also see Chapter 27).[19,122,123] Fentanyl decreases the anesthetic requirement for thiopental or propofol by providing antinociceptive effects that the intravenous hypnotics do not provide.[19,128] Although not absolutely necessary to achieve the end points shown in Figure 39-6, as Figure 39-7 suggests, opioids are typically combined with hypnotic drugs to create the state of nonresponsiveness we recognize as anesthesia.

Opioids as Complete Anesthetics

In 1947, Neff and associates[129] used meperidine as an intravenous supplement to nitrous oxide/oxygen anesthesia. The later use of opioids without the concurrent use of hypnotics coincided with

the development of cardiac surgery and intensive care during the 1970s. Providing anesthesia for patients with severe valvular or congenital heart disease without causing cardiovascular collapse was difficult before the introduction of high-dose opioid anesthesia. These early cardiac surgery patients were extremely ill and had little or no circulatory reserve. During the late 1960s, Lowenstein and coauthors[130] noted the hemodynamic stability of patients undergoing mechanical ventilation who were given frequent large doses of intravenous morphine to suppress respiration in the intensive care units. This observation encouraged Lowenstein and coworkers to become the first to administer morphine (0.5 to 3.0 mg/kg) as the only "anesthetic" drug. The resulting cardiovascular stability in acutely ill patients with acquired valvular heart disease was impressive. As cardiac surgery advanced in methodology, patients with ischemic heart disease began to undergo surgical anesthesia. Unfortunately, morphine anesthesia was less satisfactory for these patients, in whom hypertension, tachycardia, and awareness developed during surgery.[130]

In 1978, Stanley and Webster[131] introduced the use of high-dose fentanyl for cardiac anesthesia. This technique minimized the undesirable effects of morphine on induction (hypotension) and provided better hemodynamic stability in patients with good ventricular function and ischemic heart disease. As clinical experience with fentanyl increased, however, investigators found that even enormous doses of fentanyl could not reliably produce the anesthetic state, as defined in Figure 39-7, for the most potent stimuli and difficult-to-suppress responses.[132] This discovery demonstrated that opioids are not "anesthetics," but only potent analgesics and weak hypnotics, as suggested by Figure 39-2.

Many studies confirm this finding. Wynands and colleagues[14] used moderate to large doses of fentanyl (50 to 150 µg/mL) only, with no other anesthetic drugs (no hypnotic component), and measured plasma concentrations at defined surgical stimuli (intubation, skin incision, sternotomy, aortic root dissection) in patients undergoing coronary surgery with good ventricular function. In approximately 20% of patients, extremely high plasma concentrations of fentanyl (15 ng/mL) did not eliminate hemodynamic responses, defined as a 20% increase in systolic blood pressure. These results have been confirmed by Hynynen and colleagues[133] and Philbin and associates.[134]

Murphy and Hug[135] measured the ability of fentanyl to decrease enflurane MAC in dogs. They first anesthetized the dogs with enflurane and determined MAC. Fentanyl was then infused at progressively higher rates to obtain a constant steady-state plasma concentration of fentanyl in each animal. After each increase in infusion rate, enflurane MAC was determined again. Murphy and Hug found that even very high plasma concentrations of fentanyl (20 ng/mL) did not decrease enflurane MAC beyond 60% to 70% of its initial value (Fig. 39-16). That is, there was a ceiling to the enflurane-sparing effect. Morphine, sufentanil, and alfentanil also decrease enflurane MAC and have a similar ceiling effect in dogs.[136-138]

McEwan and colleagues undertook similar studies in humans and characterized the decrease in isoflurane MAC with varying constant fentanyl plasma concentrations achieved with a computer-driven infusion pump.[16] Movement response to initial skin incision was examined relative to end-tidal isoflurane concentrations. McEwan and coworkers[16] found the results in humans to be very similar to those observed by Hug and colleagues in dogs. Isoflurane MAC decreased 39% at a steady-state fentanyl plasma concentration of 1 ng/mL and 63% at a fentanyl plasma concentration of 3 ng/mL. Increasing fentanyl plasma concentrations to more than 3 ng/mL produced a minimal further reduction in isoflurane MAC. The maximal reduction in MAC was 82% at a steady-state fentanyl plasma concentration of 10.6 ng/mL. Similar MAC reduction results have been obtained with other inhaled anesthetics (desflurane, sevoflurane) and other opioids (alfentanil, sufentanil, remifentanil).[6,139]

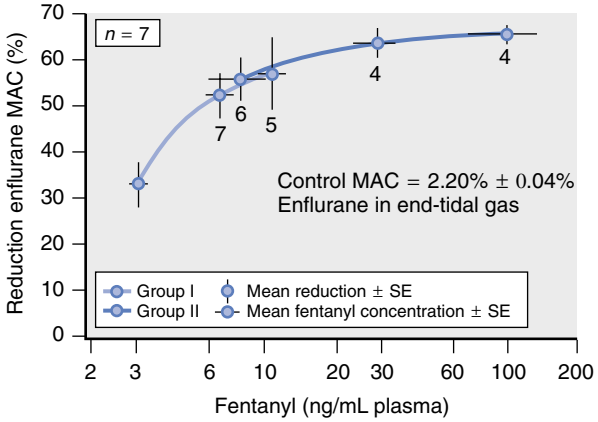

Figure 39-16 Percent reduction in enflurane minimum alveolar concentration (MAC) as a function of the plasma concentrations of fentanyl. Each point represents the mean concentration (± SEM) for fentanyl in plasma and the average percent (± SEM) reduction in enflurane MAC. Numbers of dogs below the vertical standard error bars indicate the numbers per data point. SE, standard error. *(From Murphy MR, Hug CC Jr: The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 57:485-488, 1982.)*

Similar results are found when other end points of inhaled anesthetics and opioid interactions are examined, including MAC-awake and MAC-BAR[118,140,141]: a ceiling effect of the opioid occurs at defined steady-state plasma concentrations.

Clinical Signs of Inadequate Anesthesia and Plasma Concentration of Opioids

Ausems and colleagues[142] used pharmacodynamic modeling concepts to relate clinical signs of inadequate opioid anesthesia to plasma concentrations of the drug. In their study paradigm, patients were premedicated with a benzodiazepine, anesthesia was induced with alfentanil (150 µg/kg), and the trachea was intubated with the aid of succinylcholine. Anesthesia was maintained with 70% nitrous oxide and a variable-rate infusion of alfentanil. The infusion was titrated to the following clinical end points: (1) systemic arterial blood pressure increased to greater than 15 mm Hg higher than the patient's normal value; (2) heart rate exceeding 90 beats/min in the absence of hypovolemia; (3) somatic responses, such as body movements (minimal muscle paralysis allowed physical movement), swallowing, coughing, grimacing, or opening of the eyes; and (4) autonomic signs of inadequate anesthesia (e.g., lacrimation, flushing, or sweating). If any clinical signs occurred, the infusion rate was increased 25 to 50 µg/kg/hr, and a small bolus dose (7 µg/kg) was given. Good hemodynamic control was possible in all subjects. If no clinical signs occurred, however, the infusion rate was decreased at regular 15-minute intervals.

Figure 39-17A shows the relationship between the plasma concentration of alfentanil and response/no response for three clinical end points: intubation, skin incision, and skin closure. Figure 39-17B shows the individual subject curves for the proba-

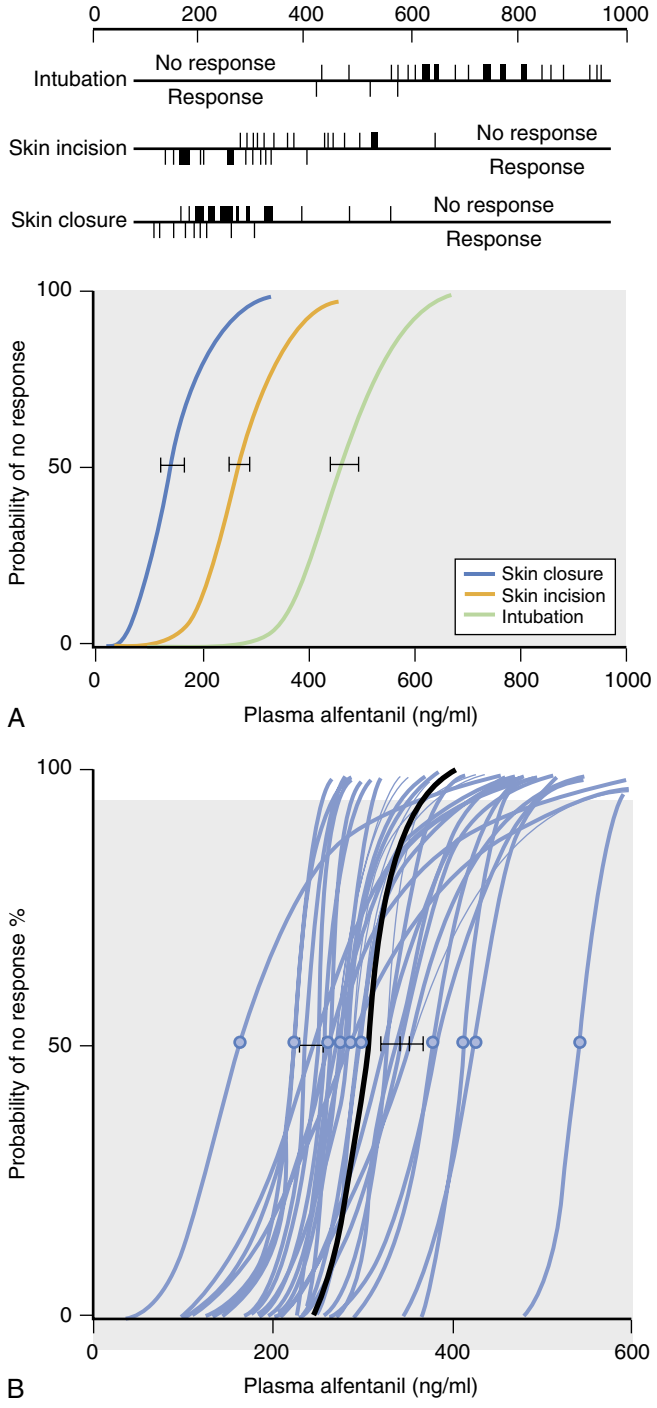

Figure 39-17 **A,** Relationship between the plasma concentration of alfentanil and response/no response at three specific events of short duration. The quantal data are characterized by logistic regression in the lower panel, ± standard error for Cp_{50}, which is the alfentanil plasma concentration associated with a 50% probability of no response. **B,** Plasma concentration of alfentanil versus the probability of no response for each of 34 patients during the intra-abdominal phase of lower abdominal surgery. *Circles* represent the Cp_{50} values, and the *black line* represents the average response of the 34 patients. (***A,*** *From Ausems ME, Hug CC Jr, Stanski DR, Burm AG: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. Anesthesiology 65:362-373, 1986;* ***B,*** *from Ausems ME, Vuyk J, Hug CC Jr, Stanski DR: Comparison of computer-assisted infusion versus intermittent bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. Anesthesiology 68:851-861, 1988.)*

bility of no response during surgery. Attenuating the response to intubation required significantly higher plasma concentrations of alfentanil than attenuating the response to skin incision did. Cp_{50} values for these clinical responses are shown in Table 39-6.

Remifentanil is the newest opioid in the fentanyl family and has a unique ester bond that is susceptible to hydrolysis by nonspecific blood and tissue esterases, which results in very rapid metabolism. Minto and colleagues[143,144] quantitated the population pharmacokinetics and dynamics of this opioid by using simulation techniques to develop dosing guidelines. Drover and Lemmens[145] applied the opioid anesthetic depth concepts developed by Ausems and coworkers[28] to define therapeutic plasma concentrations of remifentanil in surgical patients.

The approach to opioid administration presented by Ausems and colleagues[28] provides useful insight into the clinical assessment of depth of anesthesia. Overdosage with opioids cannot be judged intraoperatively in a paralyzed patient. Only at the end of anesthesia, when spontaneous ventilation should occur, does one know whether administration of opioids has been excessive. To prevent overdosage, Ausems and coworkers[28] proposed titrating the alfentanil infusion rate to clinical effect to find the lowest possible effective rate of opioid administration. Once the infusion rate associated with hemodynamic responsiveness (i.e., "light anesthesia") has been determined, one increases the rate slightly to provide an adequate analgesic component to achieve a nonresponsive state. Intermittent intravenous bolus administration of opioids is not as efficient as variable-rate infusion when titrating plasma concentrations of opioids to clinical effect.[142] The steep slope of the concentration-versus-response curve for alfentanil (Fig. 39-17B) demonstrates that a small increase in the plasma concentration of the drug rapidly converts an inadequate anesthetic state (100% probability of response to stimuli) to an adequate anesthetic state. Because of moderate variability in the pharmacokinetics of alfentanil, this process of titrating the infusion rate against clinical effect and pharmacodynamics is necessary for each patient. Egan and Shafer have referred to this concept as "surfing" the concentration-versus-response curve.[146] This concept is nearly ideal for remifentanil because of the rapid and

Table 39-6 Cp_{50} Values for Perioperative Events and Intraoperative Manipulation Associated with Three Types of Surgical Procedures During Alfentanil Anesthesia

Event	Cp_{50} (ng/mL)
Single events	
Intubation	475 ± 28*
Skin incision	279 ± 20
Skin closure	150 ± 23
Spontaneous ventilation	233 ± 13
Intraoperative manipulation	
Breast surgery (n = 12)	270 ± 63†
Lower abdominal (n = 14)	309 ± 44
Upper abdominal (n =11)	412 ± 135

*Standard error of the estimated value for the parameter.
†Values are presented as means ± SD.
Cp_{50}, plasma concentration of a drug producing a 50% chance of suppressing response to the given stimulus.
From Ausems ME, Vuyk J, Hug CC Jr, Stanski DR: Comparison of computer-assisted infusion versus intermittent bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. Anesthesiology 68:851-861, 1988.

predictable pharmacokinetic profile along with rapid blood-brain equilibration.[143]

Electrophysiologic Monitoring

(see also Chapter 46)

Spontaneous Electroencephalogram

The realization that anesthetic drugs alter the EEG dates back to the discovery that the brain produces electrical activity. In 1875, Caton used chloroform to convince himself that the electrical oscillations from the brain were indeed biologic in origin.[147] During the 1920s and 1930s, when electronic amplifiers allowed recording of these small voltages through the skull, Berger measured the influence of chloroform on the EEG.[148] In 1937, Gibbs and coauthors reported that anesthetics changed EEG activity from low-voltage fast waves to high-voltage slow waves and postulated that the EEG could be used to measure the effects of anesthesia.[149] In 1952, Faulconer demonstrated with ether that the depth of anesthesia, based on recognition of EEG patterns, correlated with the arterial concentration of ether.[150] He also demonstrated that the presence of nitrous oxide lowered the arterial concentration of ether necessary to produce a given effect on the EEG.

Hypnotic general anesthetics produce a biphasic EEG effect that was first described by Martin and colleagues.[151] With light anesthesia, there is EEG desynchronization and increased frequency associated with the excitement phase. This is followed by progressive synchronization, slowing, and an initial increased amplitude eventually leading to burst suppression with lengthening periods of EEG silence. With induction of anesthesia the topographic distribution also changes from occipital dominance to frontal dominance. Loss of spatial localization may occur with arousal.

The EEG can be considered a measure of the depth of anesthesia for several reasons:

1. It represents cortical electrical activity derived from summated excitatory and inhibitory postsynaptic activity, which in turn is the result of subcortical events, including those that pass through subcortical thalamic nuclei.
2. Cerebral blood flow and cerebral metabolism are related to the degree of EEG activity.[152]
3. Anesthetic drugs affect cerebral blood flow, metabolism, and EEG patterns.
4. Surgical stimulation affects cerebral blood flow, metabolism, and the EEG.

The EEG is thus a continuous, responsive, noninvasive indicator of cerebral function even when the patient is unconscious and unresponsive.

Noxious stimulation during inadequate anesthesia generally causes EEG activation. Peripheral noxious stimuli reach the brain through afferent systems that pass through the ascending reticular activating systems of the brainstem. These systems regulate cerebral function and thus affect the underlying EEG pattern. Noxious stimuli can cause three types of changes in the EEG:

1. Desynchronization with the appearance of 20- to 60-Hz fast rhythms (EEG activation)
2. The appearance of 6- to 10-Hz spindles
3. Bursts of 1- to 3-Hz slow waves[153]

These EEG patterns vary with individual anesthetics and with the nature of the stimulation, and there is a distinct drug plasma concentration that blocks responses to noxious stimulation.[154,155]

Early studies concluded that the EEG was not a meaningful measure of the depth of anesthesia. Galla and colleagues examined raw EEG signals for 43 patients and correlated EEG patterns with clinical signs of anesthesia.[156] A discrepancy seemed to exist between the clinical signs and EEG patterns, especially during induction and emergence. During induction, clinical signs indicated that the patients were more lightly anesthetized than the EEG patterns suggested, whereas on emergence, clinical signs indicated greater anesthetic depth.

Although recording of raw EEG signals involves accumulating a large amount of information and EEG tracings, current computer analysis techniques can summarize and distill the EEG into a condensed, descriptive format (the "processed" EEG).[157,158] Levy investigated processed EEG signals during induction and before cardiopulmonary bypass.[159] He examined a series of univariate descriptors, including median frequency (the frequency below which 50% of the EEG power is located) and spectral edge (the frequency below which 95% of the EEG power is located). He concluded that the multimodal EEG activity observed in 64% of cases precluded the use of single univariate parameters to describe the anesthetic state.

Clinical assessment of the depth of anesthesia did not correlate well with EEG patterns but suggested that some patterns may be useful trend monitors. Drummond and colleagues examined five numeric descriptors derived from the processed EEG during imminent arousal (spontaneous movement, coughing, or eye opening) from isoflurane/nitrous oxide anesthesia.[160] These authors determined the threshold value for each parameter that best predicted imminent arousal. Although several parameters (median frequency, spectral edge 90% frequency, total power, and frequency band ratio) predicted imminent arousal with a sensitivity of 90% and specificities of 82% to 90%, none of the EEG descriptors could serve as a completely reliable, sole predictor of imminent arousal. Long and coworkers undertook a similar analysis using either isoflurane or fentanyl anesthesia.[161] For isoflurane anesthesia, these investigators found that awakening was always presaged by an abrupt overall decrease in power in the 1- to 4-Hz frequency range (decrease in delta power). During emergence from fentanyl/nitrous oxide anesthesia, obvious change in the overall EEG power spectrum was not noted; however, the same numeric EEG descriptors that were predictive of awakening from isoflurane also occurred during emergence from fentanyl. These two studies concluded that consistent trends in the EEG can be expected to occur with changing depth of anesthesia, with the available EEG descriptors providing potentially useful trend information regarding the changing depth of anesthesia. However, the sensitivity and specificity of the available parameters are such that no one parameter can serve as the sole indicator of anesthetic depth.

Dwyer and colleagues examined the power spectrum of the EEG in surgical patients receiving 0.6 to 1.4 MAC isoflurane-only anesthesia with skin incision.[162] A second group of volunteers

received 0.15 to 0.45 MAC isoflurane with memory testing. Different time-dependent EEG frequency parameters (e.g., spectral edge, median frequency) were examined relative to the clinical measures. The authors found that isoflurane caused some decrease in EEG activity. However, no difference in EEG parameters was found between subjects who moved and those who did not move with skin incision. In volunteers receiving low-dose isoflurane, memory of the information presented did not correlate with values of any EEG parameter. The authors concluded that the EEG parameters examined did not predict depth of anesthesia as defined by response to surgical skin incision, response to verbal command, or development of memory.

The previously described clinical research attempting to relate EEG effects to clinical anesthetic depth resulted in inconclusive findings. When single anesthetic drugs are examined under defined conditions, it has been possible to demonstrate unambiguous relationships between EEG parameters and anesthetic drug concentrations and to use pharmacokinetic and pharmacodynamic modeling concepts to link drug concentrations to EEG drug effects.[163] Application of the EEG to measure clinical depth of anesthesia failed previously for several reasons:

1. A lack of understanding of the effects of interactions of several concurrently administered anesthetic drugs on the EEG
2. No standard approach to choosing an optimal EEG parameter
3. No clear definition of a "gold standard" for measurement and assessment of the clinical depth of anesthesia

Multiparameter Electroencephalographic Monitoring

In the 1990s, Aspect Medical Systems undertook an integrated research effort to develop the EEG as a measure of anesthetic depth. The Aspect EEG monitor, or the BIS, quantitates anesthetic effects on the brain, specifically, the hypnotic component of anesthesia. Other devices have followed this example but have used somewhat different approaches to EEG analysis (see later). Manufacturers differ in their willingness to disclose all the details of the algorithms, but they typically follow principles similar to those used by Aspect. In terms of clinical evaluation, the volume of literature on the BIS far exceeds that of any other device.

The common principles are shown in Figure 39-18:

1. The devices present a continuous EEG parameter, the specific index, that ranges from an awake, no-drug-effect value of 95 to 100 to 0 with no detectable EEG activity.
2. Multiple EEG signal–processing approaches that capture incremental information not captured with traditional approaches based on a single signal-processing approach, such as fast Fourier transformation, are used simultaneously.
3. Multiple clinically relevant measures (movement, hemodynamics, lash reflex, response to verbal command, recall, and drug concentration) were gathered in volunteers and patients with concurrent EEG data as part of the validation process.
4. Advanced multivariate statistical data analysis was used to correlate the components of the multiple EEG signal–processing approaches with the clinical data to create the univariate parameter.
5. Prospective clinical evaluation of the index is performed at multiple institutions under varying anesthetic and surgical conditions.
6. The indices measure the hypnotic components of the anesthetic and are relatively insensitive to the analgesic (e.g., opioid) components of an anesthetic.
7. Prospective clinical trials demonstrate that the monitors can improve the outcome of an anesthetic regimen.
8. Simple hardware and sensors were developed and are commercially available to facilitate capture of high-quality signals despite the noisy electrical environment of the operating room.

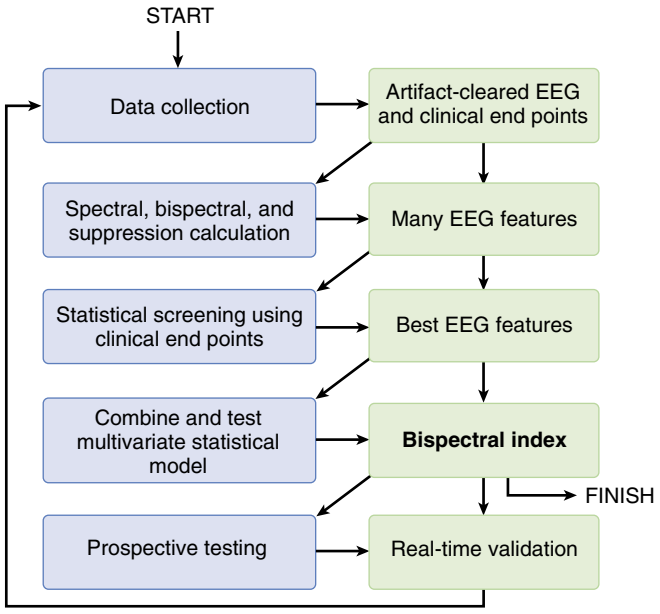

Figure 39-18 Key steps used during development of the bispectral index algorithm. Statistical modeling was used to identify the best features of the electroencephalogram (EEG) for recognition of clinical end points. The circular path notes that the process was iterative. *(From Kelley SD: Monitoring Level of Consciousness during Anesthesia and Sedation. Aspect Medical Systems, 2003.)*

Electroencephalographic Signal Processing

Most EEG signal processing has previously involved a form of spectral analysis that examines the EEG signal during a small slice of time (epoch) as a function of frequency. The frequency analysis decomposes the EEG signal into a series of sine waves by Fourier analysis. Because the signal is digitally sampled, Fourier analysis is performed by a mathematical transformation called the discrete Fourier transformation. The discrete Fourier transformation calculates the phase and amplitude of discrete sine waves at frequencies ranging from 0 to half the sampling frequency in increments of 1/x (x is the number of seconds in each "epoch" or segment of the EEG signal). The frequency of each sine wave is the number of cycles per second, although the mathematics of the discrete Fourier transformation necessarily calculate only uniformly spaced frequencies. The amplitude is half the peak-to-

peak voltage. The phase angle describes the time offset of the sine wave relative to the start of the epoch.

The conventional output of the discrete Fourier analysis is a spectral histogram showing the frequency and amplitudes of the sine waves in the underlying EEG signal. The phase information is typically ignored. Fourier analysis assumes that the signal pattern is constant during the epoch. Thus, it poorly handles signals that abruptly change during an epoch, such as burst suppression.

In "bispectral" analysis, the phase information is not ignored, and a more complex algorithm incorporates the phase information to look for evidence of phase coupling among frequency bands, such as bicoherence. Bispectral analysis was originally developed by the statistician John Tukey[164] and found one of its first applications in submarine warfare.[165] The anatomic, electrophysiologic, and clinical meaning of EEG phase relationships is unknown. However, the general notion is that an awake brain has multiple signal generators working independently and hence displays little synchronization. With progressive drug-induced loss of consciousness, fewer independent signal generators are active, and thus the resulting EEG is more likely to reflect coupling between signal generators. In addition, several useful techniques that promote noise suppression beyond what is possible with conventional spectral analysis are used.[166] Thus, the analyses provide additional information about the EEG signal than is captured by traditional spectral analysis approaches in which only frequency and amplitude are considered.

The Bispectral Index

Bispectral EEG signal processing has been reviewed by Rampil[166] and by Sigl and Chamoun.[167] Johansen and Sebel reviewed the clinical development of BIS monitoring.[168] Its development and validation are described here in some detail because it has the largest literature describing its development and it serves to illustrate the path that other devices would have to follow.

The BIS is a complex, proprietary EEG parameter developed by Aspect Medical Systems. In 1996, the U.S. Food and Drug Administration approved the commercially available version as a monitor of anesthetic effect on the brain. Figure 39-18 displays the conceptual process whereby Aspect took EEG and clinical data from approximately 1500 subjects and 5000 hours of EEG signal gathered under a broad range of anesthetic regimens. The EEG was processed by first removing high- and low-frequency artifacts, electrocardiographic signals, pacemaker spikes, eye blinks, wandering baseline, and interference by alternating current. The EEG data were then analyzed by three different approaches: Fourier spectral analysis, bispectral analysis, and time domain analysis (Fig. 39-19). Time domain analysis was used to characterize burst suppression (seen at a BIS value of less than 40) and isoelectricity. The EEG was smoothed across the power spectrum and bispectrum by using a moving average. The analysis then examined the degree of beta or high frequency (14 to 30 Hz), the amount of low-frequency synchronization, and the

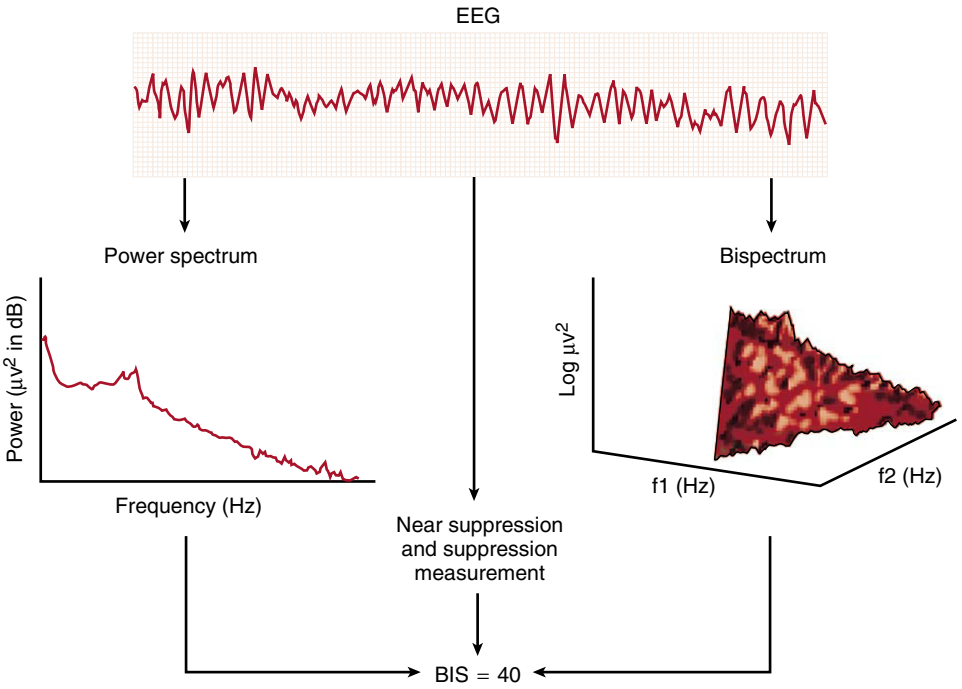

Figure 39-19 Schematic diagram of signal processing paths integral to generating a single bispectral index (BIS) value. After digitization and artifact rejection, original electroencephalographic (EEG) epochs undergo three primary paths of analysis: power spectral analysis, bispectral analysis, and time-based analysis for suppression/near suppression to look for key EEG features. The BIS algorithm, based on statistical modeling, combines the contributions of each of the identified features to generate the scaled BIS. *(From Kelley SD: Monitoring Level of Consciousness during Anesthesia and Sedation. Aspect Medical Systems, 2003.)*

presence of fully or nearly suppressed periods (i.e., isoelectric signal). The algorithm to determine the relative weighting in the final calculation of the BIS value (0 to 100) involved performing a multivariate statistical analysis, similar to semilinear canonic correlation, on the aforementioned EEG data relative to a clinical database that was gathered from multiple different clinical studies over the past 15 years.[169] As prototype versions of the BIS were developed over a period of several years, subsequent clinical testing was used to improve and refine the algorithms and components of the EEG parameter. The BIS algorithm was adapted to handle burst suppression EEG, to minimize the initial activation of the EEG seen with some anesthetic drugs, and to optimally use the components of Fourier analysis and bispectrum analysis. Thus, the BIS is a complex parameter composed of a combination of time domain, frequency domain, and higher-order spectral components derived from clinical data that measure the hypnotic component of an anesthetic.[166] Over the past decade, the BIS parameter has been modified on the basis of new data about the EEG response to novel anesthetic drugs and drug combinations, as well as to incorporate new signal collection and noise rejection technology. This is important to bear in mind as one reviews studies performed years apart.

The initial studies with early versions of the BIS algorithm in the early 1990s attempted to correlate the BIS to predict movement in response to skin incision with the use of isoflurane/oxygen,[167] propofol/nitrous oxide,[170] or propofol/alfentanil anesthesia.[171] In the first major clinical evaluation of the BIS technology, a large, multicenter study by Sebel and colleagues randomized 300 patients into two groups.[172] Both groups received an anesthetic regimen designed so that approximately half of all patients would move at skin incision. In the control group, the BIS was passively recorded and not used for titration. In the BIS-titrated group, drug concentrations were increased to produce a BIS value of less than 60. In the control group, the BIS was a mean of 66 ± 19 (standard deviation [SD]) with a 43% movement rate. In the BIS-adjusted group, the BIS was lower, a mean of 51 ± 9 (SD) with a significantly lower movement rate of 13%. In this multicenter trial, some centers used primarily opioids with nitrous oxide, whereas others used propofol or isoflurane as the primary anesthetic. The study also found that reliability of the BIS was strongly influenced by anesthetic technique. When hypnotic drugs such as propofol or isoflurane are used as the primary anesthetic, changes in the BIS correlate with the probability of a movement response to skin incision. When opioid analgesics are used at higher doses, the correlation to patient movement became much less significant. This information, when linked to the understanding that purposeful movement upon skin incision reflects the spinal action of anesthetics instead of their cortical effects,[22,23] provided fundamental understanding of how development of the BIS algorithm had to be focused on the hypnotic components of anesthesia, specifically, the clinical measures of consciousness and memory. A subsequent series of studies described in the following paragraphs provided the data and clinical understanding to create the current algorithm to calculate the BIS.

Glass and coworkers designed a study to examine the relationship among BIS, measured drug concentrations, and increasing levels of sedation when the anesthetic drugs propofol, midazolam, isoflurane, and alfentanil were given to volunteers in a controlled manner.[173] Data from this study were used to further optimize the BIS algorithm. Seventy-two volunteers received a single drug at four or five defined, increasing target plasma concentrations that ultimately created an unconscious subject. The BIS, arterial drug or end-tidal concentrations, and subjective sedation and memory scores were measured. The BIS was significantly correlated to measured drug concentrations, as well as clinical measures of sedation. None of the alfentanil patients lost consciousness and had minimal change in the BIS, a finding confirming that the BIS is not sensitive to low concentrations of opioid analgesics. Fifty percent and 95% of the volunteers were unconscious at BIS values of 67 and 50, respectively.

Liu and colleagues demonstrated in 26 surgical subjects that the BIS accurately tracked the degree of clinical sedation with intermediate (4 mg) to large (20 mg) doses of midazolam given during regional anesthesia.[174] Response to a loud voice corresponded to a BIS of 87 ± 6 (SD) and a 40% probability of recall. A deeper end point, lack of response to mild prodding, corresponded to a BIS value of 81 ± 8 (SD) and resulted in complete lack of recall. When midazolam created an unresponsive subject, the mean BIS value was 69.2 ± 13.9 (SD). Similar results were found by these investigators for propofol when given under regional anesthesia[175] and were reported by Katoh and coworkers with low, sedating doses of sevoflurane and also with higher, anesthetic concentrations in 69 surgical patients.[176] Both the BIS and end-tidal sevoflurane concentrations were correlated to clinical sedation scores of the patients. The BIS decreased almost linearly from a median value of 95 to 45 with an end-tidal sevoflurane concentration increasing from 0.2% to 1.4%. Sevoflurane concentrations greater than 1.4% produced a limited further reduction in the BIS.

Flaishon and colleagues examined the behavior of the BIS when surgical patients were given a single intravenous bolus of propofol, 2 mg/kg, or thiopental, 4 mg/kg, with concurrent muscle relaxants.[177] The isolated arm technique was used to identify loss and then return of consciousness. No patient with a BIS value of less than 58 was conscious; a BIS value of less than 65 signified a less than 5% probability of return of consciousness within 50 seconds.

A more detailed examination of memory and response to command was undertaken by Kearse and associates during propofol/nitrous oxide sedation with BIS monitoring.[178] These investigators found a strong association between the BIS and response to command, whether the command consisted simply of a uniform voice asking a volunteer to move a hand or foot or incorporated graded and then varied stimuli. The relationship between the BIS and responsiveness scores remained consistent over time and with increases or decreases in propofol concentrations. No subject was responsive when the BIS was less than 57.

Clinically, a unilateral self-adhesive frontotemporal montage provided by the proprietary BIS sensor is used. The monitor displays the BIS number, a single channel of raw EEG signals, and an index of activity on the electromyogram (EMG). Current devices can be seen at http://www.aspectmedical.com/. A BIS value of less than 55 is recommended during general anesthesia.

Entropy

Because the EEG displays chaotic or nonlinear behavior, it seems reasonable to apply methods from the theories of nonlinear dynamics. Entropy is used in chemistry to describe the microstates of gases and liquids and the ability of atoms to move in

multiple directions (i.e., the amount of disorder). As a substance changes from a solid to a liquid to a gas, the mobility and potential for interaction among atoms increases and entropy also increases. The converse applies in going from a gas to a solid.

In 1948, Claude Shannon applied these concepts to information theory such that entropy described the complexity, irregularity, or unpredictability of a signal.[179] A pure sinusoidal wave would have an entropy of zero because it is regular and predictable, whereas a wave containing hugely variable frequencies (e.g., noise) would have very high entropy. Unfortunately, as originally described by Shannon, entropy is not normalized to the total power, so there is great interindividual variation. This limits clinical use because one wants the same index value to indicate a similar depth of anesthesia among patients.

There are multiple entropy algorithms, but only spectral entropy has been used in a commercially available device, the GE Healthcare Entropy Module (formerly Datex-Ohmeda M-Entropy), which was commercially released in 2003. The exact algorithm was published in 2004 and is in the public domain.[180,181] The algorithm uses the time domain (i.e., burst suppression) and frequency domain from Fourier analysis and then also applies the Shannon function to the frequency data. This approach has been termed "time-frequency balanced spectral entropy."

The facial EMG has a frequency range (approximately >20 Hz) that overlaps with the "traditional" EEG (0.8 to 32 Hz), thereby confounding analysis of cortical activity. The facial EMG changes with level of consciousness and the use of neuromuscular blocking drugs. EMG analysis was briefly and unsuccessfully tried as a depth-of-anesthesia monitor.[182,183] Some authorities have the impression that the EMG may be more related to analgesia requirements. Datex-Ohmeda tried to exploit this by creating two indices, State Entropy (SE) and Response Entropy (RE). SE is computed from the EEG in the 0.8- to 32-Hz range and should encompass mainly the hypnotic elements of the EEG, whereas RE is computed from 0.8 to 47 Hz, which includes a significant amount of the facial EMG.[180] Thus when EMG activity is low, SE and RE should be the same, but with arousal and an increase in facial EMG, RE should increase. The initial clinical studies with this device showed that it produced results comparable to those of the BIS when tested with intravenous and inhaled hypnotic anesthetics.[184-186]

The GE Entropy Module uses the same unilateral self-adhesive frontotemporal sensor as the BIS but specifically made for the GE product (i.e., they are not interchangeable). The module works only with GE monitoring systems with the appropriate software loaded. The SE, RE, and a single channel of the raw EEG are displayed on the same screen as the other monitored variables. The displayed SE range is 0 (isoelectric EEG) to 91 (fully awake), and the RE range is 0 to 100. The anesthetic range is 40 to 60, and the manufacturer recommends that SE outside this range may require a change in hypnotic dosing, whereas if the SE is in this range but the RE is more than 10 above the SE, more analgesic may be required. Good substantiation of this recommendation is lacking.

Patient State Index

The Patient State Index (PSI) from Physiometrix, Inc., also incorporates a proprietary algorithm. In addition to using time, frequency, and phase information, the PSI also uses spatial information as EEG dominance changes with induction of anesthesia from occipital to frontal and with arousal.[187,188] A self-adhesive five-lead bilateral frontotemporal montage is used that provides greater spatial analysis than can be achieved with a unilateral montage. Development of the algorithm involved extensive use of EEG databases[189] and is illustrated in Figure 39-20. Development of the PSI has recently been reviewed.[190] Figure 39-21 shows the complexity of analyses continuously performed in the process of updating the PSI. Similar complexity occurs with most such monitors. Initial studies show it to be comparable to the BIS in tracking sedation levels.[191,192]

The portable monitor displays the PSI, with 25 to 50 being the anesthetic range. The index is shown as the current number, as well as the trend, which is color-coded to indicate whether it is in the anesthetic range, too light, or too deep. In addition, there are qualitative indicators of the EMG, artifacts, and burst suppres-

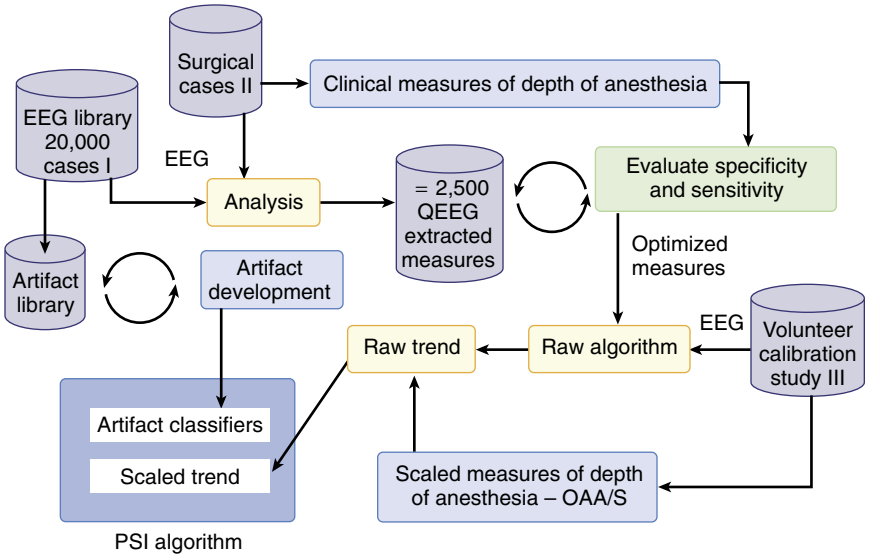

Figure 39-20 Algorithm used to develop the Patient State Index (PSI). EEG, electroencephalogram; OAA/S, Observer Assessment of Alertness/Sedation scale; QEEG, quantitative EEG. *(From Drover DR, Ortega R: Patient State Index. Best Pract Res Clin Anaesthesiol 20:121-128, 2006.)*

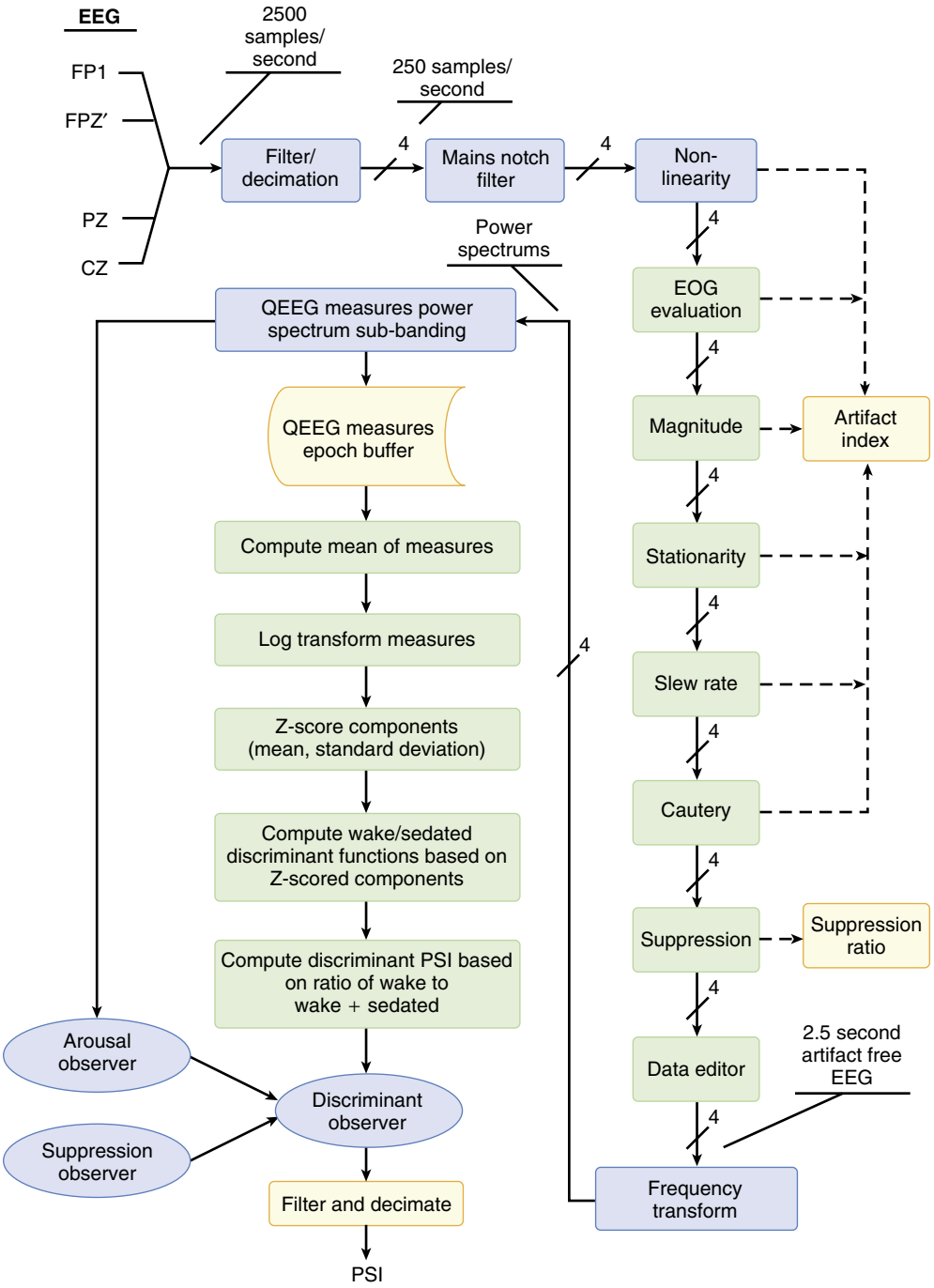

Figure 39-21 The Patient State Index (PSI) involves a series of steps that consider both the linear and nonlinear spectral components of the electroencephalogram (EEG). EOG, electro-oculogram; QEEG, quantitative electroencephalogram. *(From Drover DR, Ortega R: Patient State Index. Best Pract Res Clin Anaesthesiol 20:121-128, 2006.)*

sion. Other optional displays include four channels of EEG and the digital spectral array, an alternative way of showing frequency data.

Narcotrend

The Narcotrend monitor takes a somewhat different approach to EEG analysis by using a categorization system initially developed for analyzing the sleep EEG. In 1937, Loomis and coworkers categorized the sleep EEG into characteristic patterns labeled A to E.[193] This pattern was extended to include substages and made more appropriate for anesthesia with stages labeled A to F.[194] After artifact rejection, multiple time and frequency domain analyses are used to derive the most appropriate anesthetic stage. Initial validation also involved testing a large data set of EEGs during anesthesia. Early clinical studies found the Narcotrend to be similar to the BIS.[195-197]

This monitor uses standard electrocardiography electrodes rather than a proprietary electrode strip. The monitor displays a single channel of raw EEG, the Narcotrend stage indicated by a capital letter and a numerical subscript (e.g., D_2), the power spectrum, and the trend of the stages.

Other EEG-Based Devices

There is a steady increase in the number of devices emerging on the market. Although they differ in display format, size, electrodes, and other features, they are to a greater or lesser extent similar in principle to the devices described earlier. Examples include the SNAP Index (Viasys Healthcare, Madison, WI) and Cerebral State Monitor (Danmeter, Odense, Denmark).

Evoked Responses as Monitors of the Depth of Anesthesia

Sensory, including auditory, stimulation produces a low-amplitude signal, or evoked response, within the CNS. This evoked response can be separated by means of computer signal-averaging techniques from the underlying, spontaneous EEG. The ability to evoke a response is a measure of the functional integrity of the pathways between the sensory receptor and the neural generator of peaks in the evoked response waveform. Because evoked responses are sensitive to anesthetic drugs, they have been investigated as possible measures of anesthetic drug effect and depth of anesthesia.[198]

Recording of evoked responses involves recording EEG epochs synchronized to the repetitive sensory stimuli. Computer techniques extract the evoked potential from the underlying EEG. Typically, the algorithm requires 100 to 1000 stimuli to confidently extract the evoked potential from the underlying EEG signal. Therefore, the evoked response represents a time-versus-voltage relationship that can be quantitated by measuring the poststimulus latency and interpeak amplitudes in the waveform. Evoked response methodology has been reviewed in detail.[199]

Many investigations have been performed with evoked potentials, with special emphasis on midlatency auditory evoked potentials (MLAEPs).[198,200-203] MLAEPs have been shown to be significantly affected by anesthetic hypnotic drugs in a graded, reversible, and nonspecific manner. Specifically, the amplitudes (microvolts) and the latency (milliseconds) of the waves Pa and Nb have been examined. Hypnotic anesthetic drugs decrease the amplitudes and increase the latencies of these two waves. Opioids in clinically relevant concentrations produce minimal changes in MLAEPs.[204]

Measuring MLAEPs can be inconvenient, and this may have limited their clinical use to date. Limitations include the following:

1. Considerable time needed to produce a response, 0.5 to 5 minutes
2. Complex setup, with MLAEPs typically requiring more than 5 minutes of patient preparation
3. Need for intact hearing
4. Lack of a univariate parameter calibrated to the anesthetic state

Kenny and colleagues addressed some of these limitations by introducing a new MLAEP parameter, the AEP index, based on a proprietary algorithm.[205,206] The AEP index simplifies interpretation of the MLAEP waveforms, but it still requires significant time for the signal-averaging process. Jensen and coworkers developed a new adaptive method for extracting the MLAEP from the EEG signal that involves an autoregressive model with an exogenous input (ARX) to allow extraction of the AEP signal within 15 to 25 sweeps of 110-msec duration; the process results in only a 6-second delay.[207] This concept has been incorporated into a commercial device that calculates the A-Line ARX Index (AAI) from the fast-extracted MLAEP waveform analysis (A-Line Monitor, Danmeter A/S, Odense, Denmark). The AAI, like the BIS, ranges from 100 (awake) to 0 (deep hypnotic effect), and the recommended surgical anesthesia range is 15 to 25. The software has recently been updated and the current iteration, the AEP monitor/2, also uses EEG-derived data to supplement the AEP data.[208]

In clinical studies the A-Line performed comparably to the BIS and other EEG-based monitors but did not demonstrate advantages that would outweigh the nuisance of ear plugs and continuous high-frequency clicking sounds in patients' ears.[209-211]

Clinical Interpretation and Effects of Drugs on Electrophysiologic Monitors

All of the currently available devices have adopted a scale of 0 to 100, where 0 represents an isoelectric EEG and 100 represents an awake patient. The documentation for these monitors recommends specific ranges for wakefulness, sedation, light anesthesia, deep anesthesia, and excessive anesthesia. The clinical ranges are not identical across devices, so care is required when using or comparing different devices. For example, the BIS "anesthesia" range is 40 to 60, whereas the PSI "anesthesia" range is 25 to 50. Figure 39-22 displays the numerical value of the BIS from 0 to 100 relative to clinical end points and the underlying EEG signal.

After administration of a hypnotic drug, the index decreases from awake values of 80 to 100 as the patient's level of consciousness undergoes a series of transitions. At a device's threshold index of anesthesia, the probability of consciousness is low. The "anesthesia" range reflects adequate hypnotic effect for loss of consciousness with reasonably rapid recovery to consciousness. Like all electrophysiologic measures, in each patient one must correlate the clinical state to the reported value to adjust for variability between patients. Figure 39-23 displays the relationship between the BIS value and the probability of response to voice or the probability of explicit memory recall during propofol anesthesia.[212] Response to verbal command is preserved at lower BIS values than explicit recall is.

A limited number of studies examined the relationship of the BIS to direct measures of brain function. Alkire[213] studied the correlation between the cerebral metabolic rate, as measured by positron emission tomography, and the BIS during propofol and isoflurane anesthesia. Volunteers served as their own controls. After baseline measurements, volunteers received increasing amounts of propofol or isoflurane until they were unconscious (BIS values of 30 to 50). This study demonstrated a linear relation-

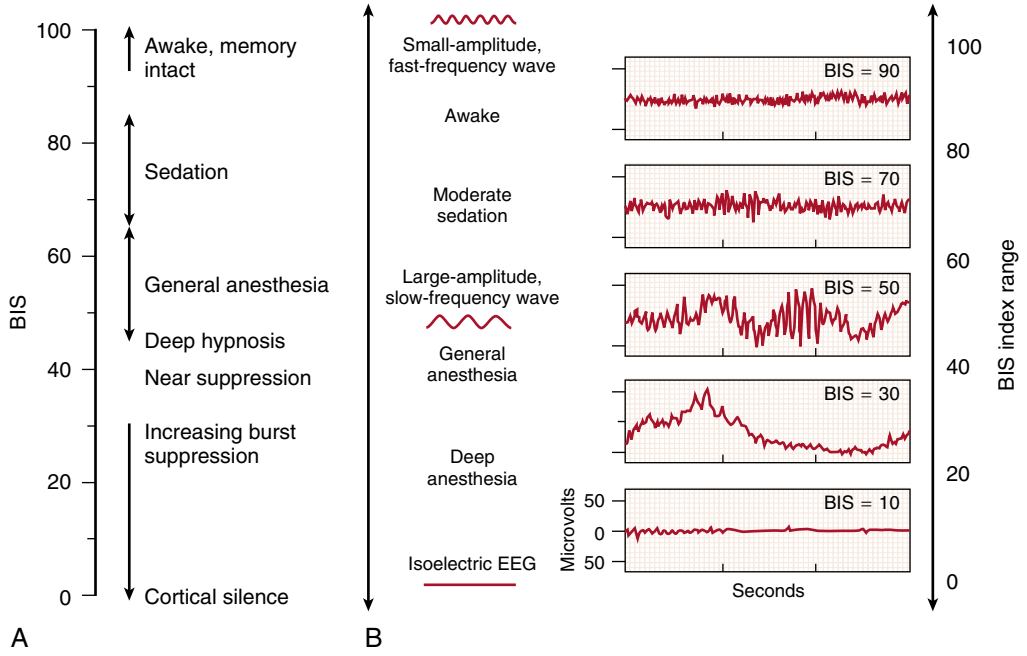

Figure 39-22 **A,** Clinical correlations of the bispectral index (BIS). Maintaining the BIS value of 45 to 60 during general anesthesia appears to ensure unconsciousness with a hypnotic/opioid anesthetic technique while providing for rapid emergence. **B,** Changes on the electroencephalogram (EEG) observed with increasing depth of anesthesia. (***A,*** *Adapted from Johansen JW, Sebel PS: Development and clinical application of electroencephalographic bispectrum monitoring. Anesthesiology 93:1336-1344, 2000;* ***B,*** *from Kelley SD: Monitoring Level of Consciousness during Anesthesia and Sedation. Aspect Medical Systems, 2003.)*

ship between decreasing BIS and a reduction in cerebral metabolic rate (r = −0.81), indicating a physiologic link between the EEG and the cerebral metabolic response to hypnotic drugs.

Ludbrook and colleagues examined the relationship between propofol brain concentrations, as estimated by simultaneous arterial/jugular bulb venous blood sampling during propofol induction of anesthesia, cerebral blood flow, and BIS measurements.[214] Although significant intersubject variability was seen, calculated propofol brain concentrations and BIS values correlated closely. Similar results have been found by using the estimated propofol or sevoflurane effect-site concentration. There is high correlation in the prediction probability of BIS, entropy, and effect-site propofol concentration, but differences between the devices are not of clinical significance.[185,186]

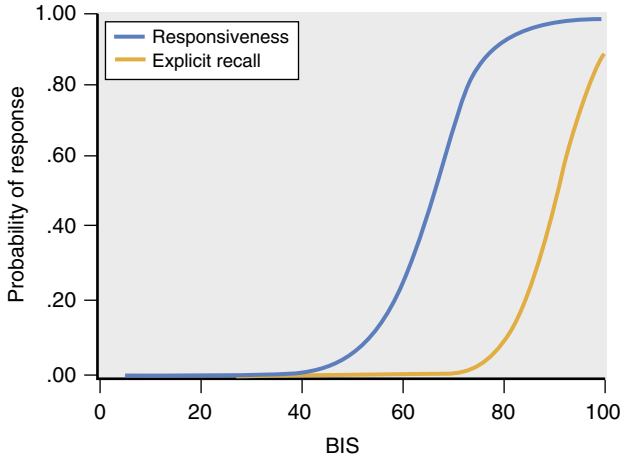

Figure 39-23 Reduction in verbal responsiveness to command (*blue line*) and memory (*yellow line*) with decreased bispectral index (BIS) values during propofol anesthesia. BIS values less than 60 are associated with 0 probability of awareness. *(Iselin-Chaves IA, Flaishon R, Sebel PS, et al: The effect of the interaction of propofol and alfentanil on recall, loss of consciousness, and the bispectral index. Anesth Analg 87:949-955, 1998.)*

Hypnotics

The relationship between depth-of-anesthesia indices and commonly used hypnotics such as midazolam, propofol, isoflurane, sevoflurane, and desflurane has been assessed in both patients and volunteers. The approach is to use stepwise increases in drug concentration and correlate this with a clinical sedation grading scale such as MOAA/S (see Table 39-1).[5] The MOAA/S scale requires stimulating the subject, which may change the depth-of-anesthesia index. Whether the index is recorded before or after stimulation is not always reported.

Studies of all currently available devices show a good relationship with the MOAA/S scale for commonly used hypnotics.[173-176,190,209,210,215-220] Indeed, such a relationship is a requirement for regulatory approval and integral for development of the software (see earlier). The relationship between sedation and the derived electrophysiologic index does not seem to be influenced by age in adults.[221] Although the average index tracks the sedation scale well at steady state, there is huge interindividual variation, particularly during non–steady-state conditions such as induction and emergence.[222] While awake, the index may range from 70 to 100, but once anesthetized, the index might be in the range of 25 to 65. Schnider and colleagues reported an extreme example in a patient with genetically determined low-voltage EEG.[223] This otherwise unremarkable volunteer had a baseline BIS of 40, which paradoxically increased with the administration of xenon. Thus,

intersubject variability in the EEG requires assessment of awake values before titration of hypnotic to a given target EEG index.

Opioids

Early studies demonstrated that low concentrations of opioids did not change the BIS response during propofol or inhaled anesthesia.[172,173] Iselin-Chaves and coworkers performed a volunteer study that examined sedation score and the presence/absence of recall during stepped increases in propofol and propofol with alfentanil (50 or 100 ng/mL).[212] The BIS, sedation, and memory function were highly correlated, and the BIS value was not affected by the low alfentanil concentration.

A similar limited interaction has also been found with remifentanil[224] and sufentanil.[225] In contrast, Koitabashi and associates found that the addition of increasing doses of remifentanil reduced BIS for the same propofol dose.[226] Struys and colleagues examined the propofol estimated effect-compartment concentration needed to prevent response to verbal stimulation, eye lash reflex, and tetanic stimulation in patient volunteers given one of three remifentanil target concentrations: 0, 2, or 4 ng/mL.[215] BIS and the AAI were monitored as well. The indices decreased monotonically as propofol was increased. For both indices, the value at loss of response was higher with each successive dose of remifentanil; specifically, with remifentanil the volunteers were "asleep" with less propofol and at higher BIS or AAI. This relates to the definition of anesthetic depth at the beginning of the chapter. Struys and colleagues required a stimulus to assess anesthetic depth, and interpretation of the index from the processed EEG requires consideration of the opioid and hypnotic component together.

Ferenets and coworkers used a similar paradigm to study entropy and complexity measures, including spectral entropy, approximate entropy, Higuchi fractal dimension, Lempel-Ziv complexity, relative [beta] ratio, and the SyncFastSlow measure.[227] They found that the effect of remifentanil was critically dependent on the frequency range used for the calculations, which may further explain the conflicting literature on opioids and depth-of-anesthesia devices.

Bouillon and colleagues used response surface modeling to assess the likelihood of response, BIS, and approximate entropy.[12] Figure 39-24 shows the synergy between propofol and remifentanil on the probability of response to laryngoscopy (A) and the additive effects of propofol and remifentanil effect on the BIS (B). Most critically, the trajectory lines on figure B show the trajectory of equipotent combinations of propofol and remifentanil for probabilities of no response to laryngoscopy ranging from 5% to 95%. Because the interaction on the BIS has a different shape from the interaction on the probability of nonresponse to noxious stimulation, the "right" BIS value for any desired probability of nonresponse is a function of the relative amounts of propofol and remifentanil. If the drugs are used at the point of maximum interaction, the "right" BIS value associated with nonresponse will be higher than if the drugs are not well balanced and synergy is reduced.

Most commercially available monitors have been calibrated for the combination of opioids and hypnotics, as suggested by Figure 39-24. The commercially available indices are therefore most accurate when used with anesthesia consisting of a low or moderate dose of opioid and a hypnotic drug (volatile inhaled anesthetic, intravenous anesthetic) titrated to the average anesthetic range of the monitored index. When using high doses of opioids it is important to provide an adequate dose of hypnotic to guarantee lack of awareness.[228]

Nitrous Oxide

Most studies suggest that nitrous oxide given in concentrations of up to 70% has minimal effect on the BIS. Rampil and coworkers demonstrated in volunteers that nitrous oxide concentrations of up to 50% alter the spectral content of the EEG with surprisingly little change in the BIS.[229] However the subjects did not exhibit CNS depression at these concentrations. In a different study, 70% nitrous oxide produced unconsciousness but still did not alter the BIS.[230] The addition of nitrous oxide to a hypnotic, even up to 70%, may reduce the BIS, have no effect, or increase it.[231-233] The effect of nitrous oxide appears to be dependent on the monitor used. Soto and colleagues found that neither BIS nor PSI demon-

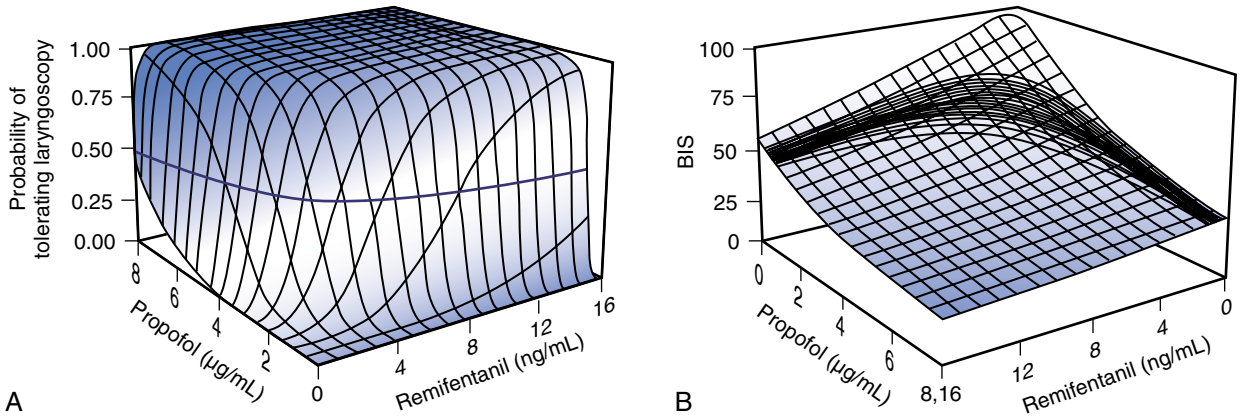

Figure 39-24 **A,** Interaction between propofol and remifentanil for a decreased probability of response to laryngoscopy based on the model shown in Figure 39-3. **B,** Interaction between propofol and remifentanil for their effects on the bispectral index (BIS); additivity is demonstrated. The trajectory lines show the BIS values at equipotent combinations of propofol and remifentanil for 5% to 95% probabilities of no response to laryngoscopy based on **A.** *(From Bouillon TW, Bruhn J, Radulescu L, et al: Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology 100:1353-1372, 2004.)*

strated a change in index but SE did when nitrous oxide was added or removed.[234]

Ketamine

The dissociative anesthetic ketamine produces excitatory effects on the EEG. Ketamine doses that create unresponsiveness (0.25 to 0.5 mg/kg) did not change the BIS.[235]

When ketamine is used with propofol, an additive anesthetic interaction occurs[24] that is not reflected in the BIS,[236] and the response to ketamine may differ by device used.[237] Thus, the addition of ketamine to an anesthetic complicates interpretation of the processed EEG, again emphasizing the need to consider the clinical circumstance and drugs used when interpreting a "depth-of-anesthesia" index.

Interaction with Muscle Relaxants

The algorithms used in the currently available devices all, to a greater or lesser extent, include some EMG activity inasmuch as EMG and EEG frequencies overlap at values greater than 30 Hz. Indeed, the GE Entropy device deliberately includes EMG in the belief that it may be an index of need for analgesia (see earlier). Muscle relaxants may confound the accuracy of devices in relation to the depth of anesthesia (also see Chapter 29). Ekman and coworkers[238] recently found that BIS and AAI responses to noxious stimulation were affected by the degree of neuromuscular block and that the block did not affect the indices in the absence of noxious stimulation.

Fluctuating muscle tension and tonic input from muscle spindles contribute to CNS arousal. As a result, muscle relaxants may deepen anesthesia by reducing neural traffic.[239] Multiple studies have demonstrated an effect of muscle relaxants in appearing to deepen anesthesia.[240-242] The most bizarre was the study by Messner and associates, in which awake volunteers (the investigators themselves) received succinylcholine with no hypnotic (!) and the BIS decreased to as low as 33.[243] Reversal of muscle relaxation can also change the amount of EMG activity and influence the monitor.[244]

Not all studies have demonstrated an effect of muscle relaxants.[245] The differences among studies probably reflect the algorithm being used,[246] which may change among iterations of the same device. Additionally, deep anesthesia at baseline may already have eliminated much of the EMG activity.[247]

Other Drugs

Drugs that affect the sympathetic nervous system may influence depth-of-anesthesia devices. Infusion of a β-blocker such as esmolol can also alter the BIS in some studies. Johansen found that during stable propofol/alfentanil anesthesia, a 30-minute infusion of esmolol (1-mg/kg bolus, 250 μg/kg/min) decreased the BIS from 37 ± 6 (SD) to 22 ± 6.[248] Discontinuation of esmolol reversed these changes. In other studies there was no effect of the β-blocker when there was no stimulation, but the increase in BIS with intubation was attenuated.[249,250] Epinephrine also has an effect on arousal and BIS. Andrzejowski and colleagues established a stable level of propofol sedation (OAA/S = 2) and then gave a bolus of 15 μg of epinephrine.[251] The sedation level increased (OAA/S = 4) and the BIS rose on average by 13. These studies indicate that there is a complex interaction among β-receptors, level of arousal, and BIS during anesthesia. β-Adrenoreceptor blockade can alter the EEG arousal response to noxious stimuli even when inadequate analgesia is present and can decrease the BIS during adequate clinical anesthesia. The effect of dexmedetomidine on depth-of-anesthesia monitors has not yet been well studied. Initial studies indicate that the BIS performs appropriately, whereas auditory responses do not change substantially.[252,253]

Response to Noxious Stimulation

Guignard and associates examined the response of the BIS to laryngoscopy and tracheal intubation during propofol administration with and without remifentanil.[254] Hemodynamics, movement response, and BIS were measured. With propofol at a target effect-site concentration of 4 μg/mL, the BIS decreased to a mean of approximately 45. Intubation increased the BIS to a mean of 70. When computer-controlled infusion of remifentanil was added to achieve target effect-site concentrations of 2 to 16 ng/mL, the interaction of remifentanil on BIS values was obvious. Before intubation, these remifentanil concentrations did not change the BIS values during propofol hypnosis. Progressively increasing concentrations of remifentanil blunted the increase in BIS after intubation. Remifentanil target effect-site concentrations of 8 and 16 ng/mL resulted in a minimal increase in the BIS, hemodynamic stability, and no purposeful movement. This study demonstrated that significant noxious stimuli given with only a hypnotic present (e.g., propofol, inhaled anesthetics) will result in a significant hemodynamic response with an increase in BIS values. The addition of adequate opioid analgesia results in hemodynamic control and less or no change in the BIS value. Ropcke and colleagues demonstrated similar EEG activation and an increase in BIS values when desflurane only (no opioids) was given to surgical patients during intra-abdominal surgery.[255] They demonstrated that in unstimulated patients before the initiation of surgery, a desflurane end-tidal concentration of 2.2% was needed to achieve a mean BIS value of 50. The desflurane end-tidal concentration needed to achieve a BIS value of 50 increased to 6.8% during intra-abdominal noxious surgical stimulation. The authors did not examine whether opioid analgesia would change the response observed with desflurane. A study in volunteers subjected to different combinations of propofol and remifentanil and progressively increasing stimulation (shouting, shaking, laryngoscopy) found that BIS, entropy, spectral edge 95, measured drug concentrations, and predicted drug concentrations all had a very good prediction probability for hypnosis but barely acceptable prediction probability for airway manipulation.[216]

Epidural anesthesia can also decrease the amount of hypnotic anesthetic needed for sedation. Hodgson and Liu have shown that the end-tidal concentration of sevoflurane needed to achieve a BIS value of 50 was 0.59% in patients receiving a lidocaine epidural for surgical procedures, whereas a sevoflurane end-tidal concentration of 0.92% was needed to achieve a BIS value of 50 in patients receiving general anesthesia or general anesthesia with an intravenous infusion of lidocaine to match the plasma concentrations achieved during the epidural anesthetic.[256] This study demonstrates that the deafferentation induced by regional anesthesia results in supraspinal effects that change hypnotic anesthetic requirements.

Studies such as these show that EEG activation is dependent on the amount of neural traffic. Processed EEG indices are good indicators of hypnosis at a given amount of stimulation but may not accurately predict the changes that will occur when

stimulation changes. The behavioral, hemodynamic, and EEG response to painful stimuli can be prevented by adequate analgesia.

Clinical Utility of Depth-of-Anesthesia Devices

Drug Titration

Depth-of-anesthesia devices primarily measure the effects of hypnotics on the EEG. The synergistic interaction of opioids on clinical end points (hemodynamics, movement responses) is more profound than reflected by the EEG. As a result, these devices are most accurate when used with anesthesia consisting of a low or moderate dose of opioid analgesic and a hypnotic drug (volatile inhaled anesthetic, intravenous anesthetic).

Clinical use involves separating the hypnotic and analgesic components of an anesthetic regimen. The concept entails titration of the hypnotic component to the anesthetic range that is associated with a high probability of unconsciousness. A small to moderate amount of analgesic (opioid) decreases the noxious input to the CNS, thus providing hemodynamic stability and decreasing the probability of response.

The anesthesiologist must continuously evaluate the clinical and monitored responses to the surgical stimulation. During intense surgical stimulation, if the index increases or the patient exhibits movement and hemodynamic responses (or both), the anesthesiologist should respond by increasing the hypnotic component to lower the index if it is elevated. Incremental opioid should be given to increase the analgesic component until movement and hemodynamics are controlled. As the end of the anesthetic regimen approaches, the hypnotic component should be decreased to allow the index to increase. These devices therefore add another monitored parameter but in no way relieve the anesthesiologist of the need to use clinical judgment and to be vigilant at all times to ensure that patients are adequately anesthetized.

Drug Consumption, Costs, and Recovery

Several studies have examined the clinical and economic outcome benefits of BIS monitoring in routine surgery. Gan and colleagues[257] studied 302 subjects receiving a propofol/alfentanil/nitrous oxide anesthetic regimen in four different institutions. Half the subjects were randomized to "standard practice" whereby the propofol and alfentanil were titrated to provide stable anesthesia with the fastest possible recovery. The BIS was recorded in this group but not displayed to the practitioner. The remaining subjects received "standard practice plus BIS monitoring." In this group, propofol infusions were titrated to achieve a target BIS value between 45 and 60 during surgery and 60 to 75 during the final 15 minutes of anesthesia. Patients in the BIS group required significantly lower normalized propofol infusion rates (134 versus 116 μg/kg/min), were extubated significantly sooner (11.2 versus 7.3 minutes), had a higher percentage of patients oriented on arrival in the recovery room (43% versus 23%), and had more rapid discharge from the recovery room. This study demonstrated that titrating propofol with BIS monitoring during balanced anesthesia decreased propofol use and significantly improved recovery with no difference in intraoperative conditions.

Song and colleagues[258] presented similar findings with inhaled anesthetics. Sixty surgical patients were randomized to receive desflurane or sevoflurane with 65% nitrous oxide and low doses of fentanyl. Half the patients were randomized to standard practice in which the inhaled anesthetic was titrated according to clinical end points and judgment. The second group had the volatile anesthetic titrated to a BIS value of 60. During the maintenance period, BIS values were significantly lower in the standard-treatment group (mean of 42), a finding suggesting deeper anesthesia than in the BIS-titrated group with a mean of 60. Volatile anesthetic use in the BIS-titrated group was 30% to 38% lower than in the control group. Similarly, times to verbal responsiveness were 30% to 55% shorter in the BIS-titrated group. This study demonstrated that titrating desflurane and sevoflurane with the use of BIS monitoring decreased utilization of the drugs and contributed to faster emergence from anesthesia.

A meta-analysis of 11 trials involving 1380 patients found that BIS monitoring reduced drug consumption by 19%, nausea and vomiting by 6%, and recovery room time by 4 minutes.[259] The cost saving from drugs was offset by the cost of the monitoring electrodes, so the actual cost was 5.55 U.S. dollars higher in the monitored group. A recent review for the Cochrane Database of 20 studies with 4056 patients found that BIS monitoring reduced drug consumption and shortened recovery times by 2 to 8 minutes.[260] Similar results have been found with other devices.[261,262] Although it seems the devices can save on drug costs and time in the early recovery period, the overall benefit from a cost and time perspective is probably modest.

Outcome

The relationship of anesthetic management to patient morbidity and mortality has generally focused on the immediate perioperative period. Information on the effects of anesthetic management on long-term postoperative mortality rates is limited. Monk and coworkers monitored the BIS in 1064 patients undergoing general anesthesia for major elective surgery (excluding cardiac and intracranial procedures) lasting at least 2 hours.[263] The anesthetic technique was not controlled, and the anesthesiologist was blind to the BIS values. The authors examined the incidence of death at 1 year. Independent predictors of mortality were comorbid conditions (relative risk [RR] of 16), cumulative deep hypnotic time with a BIS value less than 45 (RR of 1.24), and systolic hypotension (RR of 1.03). There are many concerns with this study, including the fact that it has not been replicated nor has the outcome parameter "cumulative deep hypnotic time" been validated.

Lindholm and colleagues looked at mortality within 2 years of surgery in 4087 surgical patients monitored with the BIS.[264] They found that the duration of a BIS value less than 45 was statistically associated with increased 1- and 2-year postoperative mortality (hazard ratio, 1.13 and 1.18, respectively) if preexisting malignancy was not included among the covariates. Importantly, when preexisting malignancy was included among the covariates, the hazard ratio was reduced to 1.08 and did not reach statistical significance. They concluded that the linkage of a BIS value lower than 45 to postoperative mortality is "very weak in comparison with co-morbidity as assessed by ASA physical score, the preexisting malignancy status at surgery, and age," and a causal relationship, if any, can only be assessed in a prospective randomized trial.

Conclusions

Anesthetic depth can be defined as the drug-induced probability of nonresponse to stimulation, calibrated against the strength of the stimulus and the difficulty of suppressing the response. This definition requires that multiple different stimuli and responses are measured at precisely defined drug concentrations to permit estimation of the full drug-versus–probability of nonresponse surface for clinically important stimuli. There is no one stimulus and response measurement that will capture depth of anesthesia in a clinically or scientifically meaningful manner. The anesthesiologist must understand a complex matrix of stimuli, responses, and "anesthetic" drugs, including their pharmacodynamic (and generally synergistic) interactions. This definition captures the nature of routine clinical care whereby anesthesiologists observe a series of stimuli ranging from talking to the patient preoperatively to intubation to skin incision. They also observe a range of responses ranging from verbal response to movement to tachycardia and hypertension, and they calibrate these observations of stimuli and responses against the drugs used to reduce the probability of response by constantly adjusting the administered dose to achieve the desired anesthetic depth.

Our definition of "depth of anesthesia" identifies two critical components to maintain the anesthetic state: hypnosis from drugs such as propofol or the inhaled anesthetics and analgesia from opioids or nitrous oxide. We demonstrate the scientific evidence that profound degrees of hypnosis in the absence of analgesia will not prevent the hemodynamic responses to profoundly noxious stimuli and that profound degrees of analgesia do not guarantee unconsciousness. However, the combination of hypnosis and analgesia suppresses the hemodynamic response to noxious stimuli and guarantees unconsciousness. The synergy between hypnotics and analgesics is used every day by every anesthesiologist in clinical practice. We also demonstrate that this concept can be captured with a three-dimensional interaction surface (hypnotic concentration on the *y* axis, analgesic concentration on the *x* axis, probability of nonresponsiveness for defined stimuli on the *z* axis) that can be accurately estimated with available clinical data for currently used anesthetic drugs.

Awareness during anesthesia is an important clinical problem that sometimes results in prolonged disabling psychological sequelae for the patient. Comprehensive understanding of the sciences underpinning anesthesia, thorough preoperative evaluation and preparation, careful intraoperative observation, and postoperative debriefing may help reduce the incidence of awareness and the severity of its consequences. Unconscious memory formation and dreaming remain fascinating but probably harmless phenomena.

There are now many electrophysiologic monitors that can be used to assess the magnitude of the drug-induced changes in the EEG and evoked responses and help guide titration of anesthetics. Of these, the BIS is the most extensively validated. These monitors correlate well with the effects of hypnotics (particularly propofol, thiopental, and inhaled anesthetics) on memory, sedation, and consciousness but should always be used in conjunction with clinical assessment of the patient, the stimulus, and the drugs used. Titration guided by the BIS decreases the incidence of intraoperative awareness. An electrophysiologic measure of analgesia is not currently available.

There is considerable room for the development of additional technology and pharmacologic insight into measures of the depth of anesthesia. The opioid/hypnotic concentration-versus-response surface has not been characterized for many stimulus-response pairs. There are many additional drug interactions that might be profitably characterized (e.g., opioids versus α_2-adrenergic agonists), as well as higher-dimensional drug interactions (e.g., three-drug interaction surfaces). There are cells in the stimulus-response matrix for which only poor EEG predictors exist (e.g., movement with opioid/nitrous oxide anesthesia, ketamine). There are important responses that are poorly understood (e.g., inflammatory, humeral, neurophysiologic, and psychological responses). Our definition of anesthetic depth, as well as measurement of anesthetic depth, will expand as the matrix of stimuli, responses, and drugs that influence the probability of nonresponse expands with new research and new knowledge.

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40 Cardiovascular Monitoring

Key Points

1. Although a stethoscope should be present in every anesthetizing location, continuous stethoscopy is an insensitive method for early detection of untoward hemodynamic events.
2. Most automated noninvasive blood pressure measuring devices use an oscillometric measurement technique and rarely cause complications. Caution should be exercised in patients who cannot complain of arm pain, those with irregular rhythms that force repeated cuff inflation, and individuals receiving anticoagulant therapy.
3. Direct arterial pressure monitoring should be widely used in operative patients with severe cardiovascular diseases or those undergoing major surgical procedures that involve significant blood loss or fluid shifts.
4. The Allen test for palmar arch collateral arterial flow is not a reliable method to predict complications from radial artery cannulation. Despite the absence of anatomic collateral flow at the elbow, brachial artery catheterization for perioperative blood pressure monitoring is a safe alternative to radial or femoral arterial catheterization.
5. The accuracy of a directly recorded arterial pressure waveform is determined by the natural frequency and damping coefficient of the pressure monitoring system. Optimal dynamic response of the system will be achieved when the natural frequency is high, thereby allowing accurate pressure recording across a wide range of damping coefficients.
6. Rather than the common placement at the midaxillary line, the preferred position for alignment (or "leveling") of external pressure transducers is approximately 5 cm posterior to the sternomanubrial junction. When using external transducers and fluid-filled monitoring systems, this transducer location will eliminate confounding hydrostatic pressure measurement artifacts.
7. Because of wave reflection and other physical phenomena, arterial blood pressure recorded from peripheral sites has a wider pulse pressure than central aortic pressure does.
8. Dynamic measures of cardiac preload, such as systolic pressure variation and pulse pressure variation, are better predictors of volume responsiveness than static indicators such as central venous pressure (CVP) or pulmonary capillary wedge pressure.
9. Selecting the best site, catheter, and method for safe and effective central venous cannulation requires that the physician consider the purpose of the catheterization, the patient's underlying medical condition, the intended operation, and the skill and experience of the physician performing the procedure. Right internal jugular vein cannulation is favored by most anesthesiologists because of its consistent, predictable anatomic location and its relative ease of access intraoperatively.
10. Methods to reduce mechanical complications from central venous catheters include the use of ultrasound vessel localization, venous pressure measurement before insertion of large catheters, and radiographic confirmation that the catheter tip rests outside the pericardium and parallel to the walls of the superior vena cava.
11. When using CVP as a measure of intravascular volume, the influences of ventricular compliance and intrathoracic pressure must be taken into consideration. In general, a trend in CVP values or its change with therapeutic maneuvers is more reliable than a single measurement. Important pathophysiologic information can be obtained by careful assessment of the CVP waveform morphology.
12. Of the many complications of central venous and pulmonary artery catheters, catheter misuse and data misinterpretation are among the most common.
13. Pulmonary artery wedge pressure is a delayed and damped reflection of left atrial pressure. The wedge pressure provides a close estimate of pulmonary capillary pressure in many cases but may underestimate capillary pressure when postcapillary pulmonary vascular resistance is increased, as in patients with sepsis.

14. Use of central venous, pulmonary artery diastolic, or pulmonary artery wedge pressure as an estimate of left ventricular preload is subject to many confounding factors, including changes in diastolic ventricular compliance and juxtacardiac pressure.
15. Most randomized prospective clinical trials have failed to show that pulmonary artery catheter monitoring results in improved patient outcome. Reasons cited for these results include misinterpretation of catheter-derived data and failure of hemodynamic therapies that are guided by specific hemodynamic indices.
16. Thermodilution cardiac output monitoring, the most widely used clinical technique, is subject to measurement errors introduced by rapid intravenous fluid administration, intracardiac shunts, and tricuspid valve regurgitation.
17. Mixed venous hemoglobin oxygen saturation is a measure of the adequacy of cardiac output relative to body oxygen requirements. It is also dependent on arterial hemoglobin oxygen saturation and hemoglobin concentration.
18. Newer methods of cardiac output monitoring, including esophageal Doppler and pulse contour analysis, allow beat-to-beat estimation of left ventricular stroke volume and measurement of other cardiovascular variables.

Introduction to Cardiovascular Monitoring: Focused Physical Examination

Although cardiovascular monitors receive prime emphasis, the fundamental basis for circulatory monitoring remains in the eyes, hands, and ears of the anesthesiologist. In many ways, the clinician's senses capture more information than even the most sophisticated electronic monitors do. Combined with knowledge, experience, and sound clinical judgment, the clinician's senses offer an integrated, panoramic view of the patient's condition, made even more valuable by an understanding of the clinical context present. Whereas electronic instruments accurately and monotonously collect huge volumes of quantitative data, the clinician plays a vital role in patient monitoring by integrating, evaluating, and interpreting these data.[1] Just as inspection, palpation, and auscultation are the cornerstones of physical examination of the cardiovascular system, these same clinical procedures are fundamental elements of perioperative cardiovascular monitoring. However, they must be adapted and focused on the unique requirements of surgical and critically ill patients, and their limitations must be recognized.

Many standard physical means of assessing the circulation are used throughout an operation. For many healthy patients undergoing minor procedures, these physical signs provide a considerable fraction of the total cardiovascular monitoring. For higher-risk patients and longer, more complicated operations, the extent of supplemental electronic monitoring grows accordingly. However, careful physical assessment still provides the clinician with an all-important backup system to confirm or refute information derived from other monitoring devices. The most obvious, perhaps trivial, example is a patient whose electrocardiogram (ECG) shows asystole. Detection of a normal pulse by direct palpation focuses the anesthesiologist on correcting the monitoring artifact rather than initiating cardiopulmonary resuscitation.

Early advances in cardiovascular assessment beyond basic physical examination were not readily accepted into medical practice. Around 1900, the introduction of sphygmomanometry to measure blood pressure was criticized because it would weaken clinical acuity by blunting the senses and acute perceptions of the clinician. Even stethoscopy had its critics, simply on the basis that it placed the physician at greater distance from the patient.

Palpation of the pulse and its rate and character should not be forgotten in the perioperative setting. Environmental constraints in the operating room may dictate which pulses are accessible for monitoring, but they also provide unique opportunities for pulse monitoring during surgery. For example, during cardiac surgery the beating heart may be observed directly, and palpation of the ascending aorta by the surgeon provides a useful estimate of aortic blood pressure. In fact, the surgeon's evaluation of any arterial pulse within the surgical field should be considered whenever severe hemodynamic instability develops.

Clinical evaluation of venous pressure during anesthesia is technically difficult because of unusual patient positions, positive-pressure mechanical ventilation, and lack of access to observe the neck veins. However, early recognition of venous obstruction in an extremity or in the head and neck may have important clinical consequences. Not only might this observation herald hemodynamic problems for the patient, but communicating these observations to the operating surgeon should also allow timely correction of contributing surgical factors.

Given that the cardiovascular system is responsible for the transport of substrates and by-products to and from all organ systems, monitoring end-organ function can be used to assess the adequacy of cardiovascular performance. Inspection of mucous membranes, skin color, and skin turgor can reveal pertinent clues about hydration, oxygenation, and perfusion. Additional simple clinical techniques include empirical estimation of fluid deficits and blood loss, measurement of urine output, and detection of altered mental status. Unfortunately, interpretation of these clinical signs and symptoms is often confounded by preexisting organ dysfunction and the direct effects of anesthetic drugs on organs. As a result, use of these clinical assessment tools is of limited value in many anesthetized or critically ill patients. Frequently, additional cardiovascular monitoring techniques are required.

Stethoscopy

Although Laennec is credited with introducing the stethoscope into general medical practice in 1818, nearly a century elapsed before Harvey Cushing proposed in 1908 that the stethoscope be used as a routine cardiopulmonary monitoring device during surgery.[2] For many years thereafter, intraoperative monitoring with either a precordial or an esophageal stethoscope became the

most common simple method for monitoring ventilation and circulation in anesthetized patients.

Stethoscopy provides a simple and reliable means of listening to heart and breath sounds continuously throughout an operation. The most common equipment used for precordial stethoscopy consists of a heavy metal bell or accumulator attached to a length of rubber or plastic extension tubing and a custom-molded monaural plastic earpiece. Electronically amplified stethoscopes have been designed to improve the quality and clarity of heart and breath sounds but have not supplanted standard inexpensive mechanical devices in everyday practice.[3] Though minimally invasive and practical only for patients receiving general endotracheal anesthesia, the esophageal stethoscope provides monitoring benefits not available with its precordial cousin. Clear breath sounds and distinct heart sounds are audible in most patients when the tip of the stethoscope is positioned 28 to 30 cm from the incisors, and esophageal temperature can be measured with an incorporated thermistor.[4] Although use of the esophageal stethoscope is generally without significant risk, rare complications include hypoxemia from unintended tracheobronchial placement or compression of the membranous posterior portion of the trachea in small infants, loss down the esophagus, detachment of the acoustic cuff, and distortion of surgical anatomy in the neck. Placement of the esophageal stethoscope may also cause pharyngeal or esophageal trauma and interfere with nasogastric tube positioning or transesophageal echocardiography.

Despite the purported value of the precordial or esophageal stethoscope for basic monitoring of patient safety, its widespread application in clinical practice has diminished in recent years.[5,6] This decline may be driven by the routine use of pulse oximetry, capnography, and other electronic monitors that have become ubiquitous.[7] As a practical matter, clinicians may not recognize changing heart or breath sounds as readily as might be expected because of reliance on more modern electronic devices, distraction, or operating room noise. These practice patterns appear to be borne out by the 1993 Australian Incident Monitoring Study, which noted that a stethoscope was used in only 5% of the 1256 critical incidents reported and was the first monitor to detect the morbid incident—cardiac arrest—in only one instance.[5] As a result, the current role of intraoperative stethoscopy as a continuous monitor has become limited to special applications (e.g., pediatric anesthesia) and to institutions with insufficient resources to purchase electronic monitors.

Heart Rate Monitoring

The simplest and least invasive form of cardiac monitoring remains measurement of the heart rate. Under most circumstances in modern anesthesia practice, electronic devices are used to continuously monitor this vital sign and provide an important guide to the influence of anesthetics and surgical stimuli on the patient's condition. The ability to estimate the heart rate quickly with a "finger on the pulse" is a skill as important as this expression is common.

Although any monitor that measures the period of the cardiac cycle can be used to determine the heart rate, the ECG is the most common method used in the operating room (see Chapter 42). Measurement of the heart rate by ECG begins with accurate detection of the R wave and measurement of the R-R interval. The digital value displayed for the heart rate is generated from an algorithm designed to count and average a certain number of beats and then display a number that is updated every 5 to 15 seconds.[8] As a result, transient dysrhythmias may have little impact on the displayed digital heart rate value (Fig. 40-1).

Occasionally, the clinician must check electrode attachment, increase signal gain on the ECG, or select alternative ECG leads to improve the accuracy of heart rate monitoring. Most monitors allow manual adjustment of the threshold or sensitivity for R-wave detection and recognition of electronic pacing spikes. In the operating room, ECG artifacts are common, particularly those caused by the electrosurgical unit. The ECG trace should always be inspected visually to confirm the numeric value for the heart rate displayed on the monitor. In addition, the arterial pressure waveform or the pulse oximeter plethysmograph should be used to confirm the pulse rate in these instances.

Electrical interference in the ECG trace may arise from sources other than the electrosurgical unit. Power line noise appears as a 60-Hz artifact and may be eliminated by selecting narrower-bandpass ECG filters, including a 60-Hz notch filter. Other artifacts result from muscle twitching and fasciculations, as well as from various medical devices, including lithotripsy machines, cardiopulmonary bypass equipment, and fluid warmers.[9] Paced rhythms can produce problems with measurement of the heart rate on the ECG. When tall pacing spikes are present, the monitor may misinterpret these high-amplitude signals as R waves and miscalculate the heart rate. Tall T waves may produce the same artifact when the monitor mistakenly

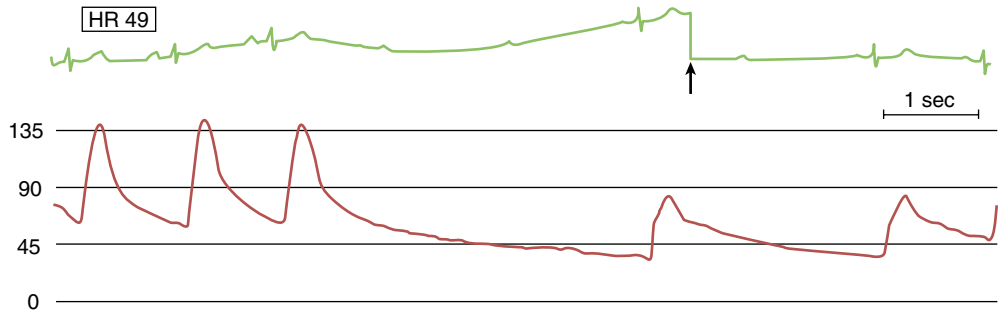


Figure 40-1 Digital heart rate (HR) displays may fail to warn of dangerous bradyarrhythmias. Direct observation of the electrocardiogram (ECG) and the arterial blood pressure traces reveals a complete heart block and a 4-second period of asystole, whereas the digital display reports an HR of 49 beats/min. Note that the ECG filter (*arrow*) corrects the baseline drift so that the trace remains on the recording screen. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 13-2.)*

counts these T waves as R waves. These problems may be ameliorated by decreasing ECG gain, adjusting the sensitivity for detection of R waves, changing the ECG lead to one with a smaller pacing spike or T-wave amplitude, or selecting pacing detection modes that distinguish pacing spikes from other ECG features.

Pulse Rate Monitoring

The distinction between heart rate and pulse rate centers on whether a given electrical depolarization and systolic contraction of the heart (heart rate) generate a palpable, peripheral arterial pulsation (pulse rate). Pulse deficit describes the extent to which the pulse rate is less than the heart rate. Such deficit is typically seen in patients with atrial fibrillation, in which short R-R intervals compromise cardiac filling during diastole and result in reduced stroke volume and an imperceptible arterial pulse. The most extreme example of a pulse deficit is electrical-mechanical dissociation, or pulseless electrical activity, seen in patients with cardiac tamponade, extreme hypovolemia, and other conditions in which cardiac contraction does not generate a palpable peripheral pulse.

Most monitors report heart rate and pulse rate separately. The former is measured from the ECG trace and the latter is determined from a selectable pulse source. The pulse oximeter plethysmograph trace is the most common source for measurement of the pulse rate, but it may be of poor quality in patients with severe arterial occlusive disease or marked peripheral vasoconstriction. In addition to indicating the pulse rate, this waveform may also provide supplementary diagnostic clues to cardiovascular function[10,11] (see systolic pressure variation in the later section "Arterial Pressure Monitoring for Prediction of Volume Responsiveness"). Other pulse rate sources include the directly measured arterial pressure waveform and automatic noninvasive blood pressure (NIBP) monitors, which determine the pulse rate from the pressure oscillations detected by the surrounding cuff. Pulse rate monitoring and heart rate monitoring complement one another. Although monitoring both may seem redundant, such redundancy is intentional and being applied to modern computerized monitoring algorithms to reduce measurement errors and false alarms.[12]

Arterial Blood Pressure Monitoring

Like the heart rate, blood pressure is a fundamental cardiovascular vital sign and a critical part of monitoring anesthetized or seriously ill patients. The importance of monitoring this vital sign is underscored by the fact that standards for basic anesthetic monitoring mandate measurement of arterial blood pressure at least every 5 minutes in all anesthetized patients.[13]

Techniques for measuring blood pressure fall into two major categories: indirect cuff devices and direct arterial cannulation and pressure transduction. These methods differ most notably in terms of the physical signal being monitored and their level of invasiveness. Although direct arterial blood pressure measurement is the reference standard against which other methods are compared, even this technique can yield spurious results. Consequently, blood pressure measured in clinical practice with different techniques often yields significantly different values.[14]

Indirect Measurement of Arterial Blood Pressure

Manual Intermittent Techniques

Most indirect methods of measuring blood pressure rely on a sphygmomanometer similar to the one first described by Riva-Rocci in 1896.[15] This apparatus included an arm-encircling inflatable elastic cuff, a rubber bulb to inflate the cuff, and a mercury manometer to measure cuff pressure. Riva-Rocci described the measurement of systolic arterial blood pressure by determining the pressure at which the palpated radial arterial pulse disappeared as the cuff was inflated.

A commonly used variation of the Riva-Rocci method, termed the "return-to-flow technique," records the pressure during cuff deflation at which the pulse reappears and is detected by palpation. When the patient has a finger pulse oximeter or an indwelling arterial catheter in the ipsilateral arm, return to flow can be detected by reappearance of the plethysmographic or arterial pressure waveforms. Return-to-flow methods provide a simple, rapid estimation of systolic blood pressure during urgent situations but do not allow measurement of diastolic blood pressure.

To measure both systolic and diastolic arterial pressure, the most widely used intermittent manual method is the auscultatory technique, originally described by Korotkoff in 1905.[16] Using a sphygmomanometer, cuff, and stethoscope, Korotkoff measured blood pressure by auscultating sounds generated by arterial blood flow. These sounds are a complex series of audible frequencies produced by turbulent flow beyond the partially occluding cuff. The pressure at which the first Korotkoff sound is heard is generally accepted as systolic pressure (phase I). The character of the sound progressively changes (phases II and III), becomes muffled (phase IV), and is finally absent (phase V). Diastolic pressure is recorded at phase IV or V. However, phase V may never occur in certain pathophysiologic states such as aortic regurgitation.[17]

A fundamental shortcoming of the auscultatory method of blood pressure measurement is its reliance on blood flow to generate Korotkoff sounds. Pathologic or iatrogenic causes of decreased peripheral blood flow, such as cardiogenic shock or high-dose vasopressor infusion, can attenuate or obliterate the generation of sound and result in significant underestimation of blood pressure.[18] In contrast, low compliance of the tissues underlying the cuff, as encountered in a shivering patient, will require an excessively high cuff-occluding pressure and produce "pseudohypertension." A similar situation exists in patients with severe calcific arteriosclerosis, whose noncompressible arteries may be palpated distal to a fully inflated cuff (positive Osler sign).[17]

Other common sources of error during intermittent manual blood pressure measurement include selection of an inappropriate cuff size and excessively rapid cuff deflation. The optimal cuff should have a bladder length that is 80% and a width at least 40% of arm circumference.[17] The cuff should be applied snugly, with the bladder centered over the artery and any residual air squeezed out. Although too large a cuff will generally work well and produce little error, use of cuffs that are too small will result in overestimation of blood pressure.[17] The cuff deflation rate is another impor-

tant variable that influences manual blood pressure measurement. The decrease in cuff pressure should proceed slowly enough for the Korotkoff sounds to be detected and properly assigned to the current pressure in the cuff. Failure to identify the initial Korotkoff sounds will result in a falsely low measurement of blood pressure.

Automated Intermittent Techniques

Many limitations of manual intermittent blood pressure measurement have been overcome by automated NIBP devices, which are now used widely. In addition, automated NIBP devices provide audible alarms and can transfer data to a computerized information system. However, the greatest advantage of automated NIBP devices over manual methods of blood pressure measurement is that they provide frequent, regular blood pressure measurements and free the operator to perform other vital clinical duties.

Most automated NIBP devices are based on oscillometry, a technique first described by Marey in 1876.[17] In this method, variations in cuff pressure resulting from arterial pulsations during cuff deflation are sensed by the monitor and used to determine arterial blood pressure values. The pressure at which the peak amplitude of arterial pulsations occurs corresponds closely to directly measured mean arterial pressure (MAP), and values of systolic and diastolic pressure are derived from proprietary formulas that examine the rate of change of the pressure pulsations.[19,20] Consequently, systolic and diastolic values are less reliable than MAP values.[17] Systolic pressure is typically identified as the pressure at which pulsations are increasing and are at 25% to 50% of maximum. Diastolic pressure is the most unreliable oscillometric measurement and is commonly recorded when the pulse amplitude has declined to a small fraction of its peak value (Fig. 40-2).

Although oscillometry is used primarily in automated NIBP measurement, the same principles may be applied to determine blood pressure manually with a standard cuff and aneroid manometer. If the cuff is deflated slowly until the needle on the aneroid gauge begins to flicker or oscillate, the corresponding pressure value provides a close estimate of systolic blood pressure. Like the return-to-flow technique, "manual oscillometry" can be performed quickly, with only one hand on the inflation bulb and pressure relief valve and observing the aneroid gauge needle for the onset of oscillation.

In clinical practice, oscillometric automated NIBP measurement has focused largely on pressure measured from the upper part of the arm. If a patient's surgical procedure or medical condition requires that the cuff be applied to the calf, ankle, or thigh, an appropriately sized cuff must be used.

Other methods using a variety of sensing techniques, including Doppler, photo-oscillometry, and motion of the arterial wall, have also been described for automated intermittent NIBP measurement.[21] Although these methods have been found to measure blood pressure with reasonable accuracy under limited clinical circumstances, they all require additional sensing transducers, their accuracy in critically ill patients is uncertain, and consequently, none has supplanted the standard oscillometric technique.

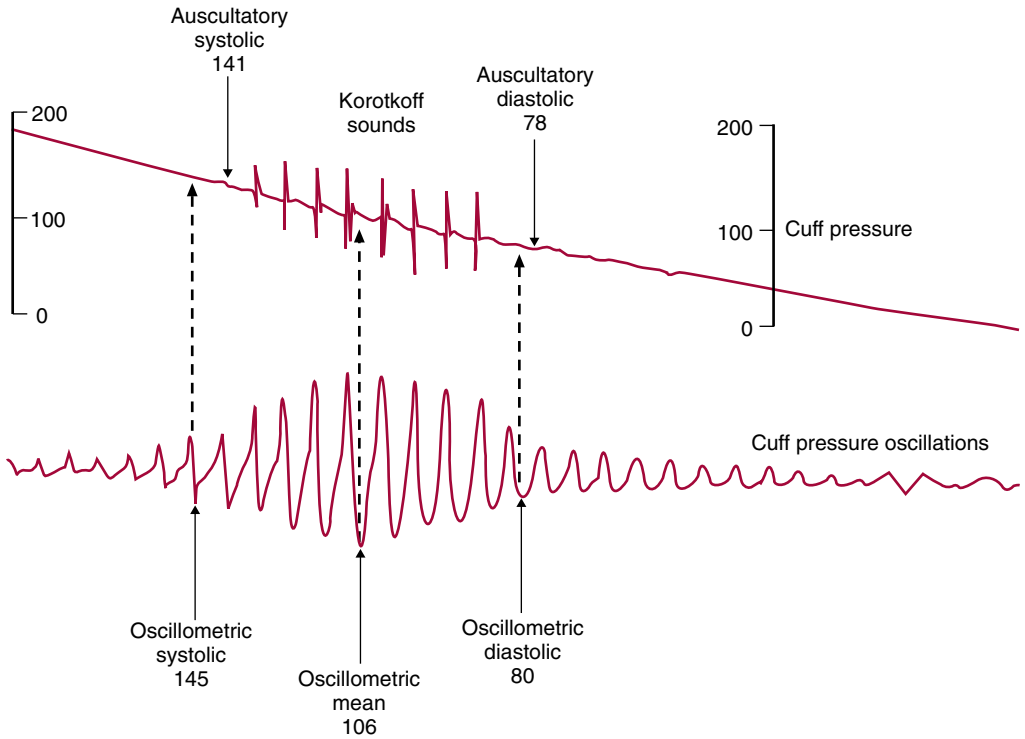


Figure 40-2 Comparison of blood pressure measurements via Korotkoff sounds and oscillometry. Oscillometric systolic blood pressure is recorded at the point where cuff pressure oscillations begin to increase, mean pressure corresponds to the point of maximal oscillations, and diastolic pressure is measured at the point where the oscillations become attenuated. Note the correspondence between these measurements and the Korotkoff sounds that determine auscultatory systolic and diastolic pressure. *(From Geddes LA: Cardiovascular Devices and Their Applications. New York, John Wiley, 1984, Fig. 34-2. Reprinted by permission of John Wiley & Sons, Inc.)*

Even though automated NIBP measurements have been shown to closely approximate directly measured arterial pressure in controlled clinical settings, numerous investigations underscore the disagreement that often exists when direct and indirect pressure measurements are compared, particularly when techniques are compared under changing hemodynamic conditions.[14,17] Standards for performance of automated NIBP devices have been advanced by the Association for the Advancement of Medical Instrumentation, the British Hypertension Society, and other organizations. These standards generally require accuracy within 5 mm Hg with respect to reference methods.[17,21] However, the clinical performance of an NIBP monitor should be evaluated by other criteria, including the number of outlier values, duration of discrepancies, magnitude of individual errors, and performance under variable clinical conditions.[21]

Complications of Noninvasive Blood Pressure Measurement

Although automated blood pressure measurement techniques are considered noninvasive and relatively safe, complications have been reported, including rare severe events such as compartment syndrome (Box 40-1).[22] These morbid events occur more often after prolonged periods of excessively frequent cycles of cuff inflation/deflation and are due to trauma or impaired distal limb perfusion. Other factors that may contribute include cuff misplacement across a joint or repeated attempts to determine blood pressure in the presence of an artifact-producing condition such as involuntary muscle tremors. Caution should be exercised when using these monitors in patients with depressed consciousness, preexisting peripheral neuropathies, arterial or venous insufficiency, or irregular cardiac rhythms, as well as in those receiving anticoagulant or thrombolytic therapy.

Automated Continuous Techniques

Advances in microprocessor and servomechanical control technology have enabled noninvasive techniques to provide a reasonable representation of the arterial pressure waveform and nearly continuous assessment of blood pressure without resorting to direct arterial cannulation. One such device measures finger blood pressure with an arterial volume-clamp method designed and first reported by Penaz in 1973.[23] Although several clinical investigators have demonstrated reasonable accuracy of finger blood pressure as a surrogate for intra-arterial pressure measurements, a number of factors have precluded more widespread application of this technology.[24] In many circumstances, finger blood pressure monitoring will not reflect brachial arterial pressure. In addition, finger arteries are prone to spasm with the potential for distal ischemia, hand position will influence pressure values, and blood sampling cannot be performed without indwelling catheters.

Box 40-1 Complications of Noninvasive Blood Pressure Measurement

- Pain
- Petechiae and ecchymoses
- Limb edema
- Venous stasis and thrombophlebitis
- Peripheral neuropathy
- Compartment syndrome

Other automatic continuous noninvasive techniques have been used to measure blood pressure by applying technologies based on arterial wall displacement, pulse transit time, arterial tonometry, and other methods. All techniques have limitations, including the need for calibration, sensitivity to motion artifact, and limited applicability in critically ill patients.[17,21,25] It remains unclear whether any noninvasive technique will reduce the need for direct arterial pressure monitoring or whether these methods will replace automated intermittent oscillometry as the standard NIBP monitoring method in anesthesia and critical care.

Direct Measurement of Arterial Blood Pressure

Arterial cannulation with continuous pressure transduction and waveform display remains the accepted reference standard for blood pressure monitoring despite the fact that it is more costly, has the potential for more complications, and requires more technical expertise to initiate and maintain than noninvasive monitoring does. There are a number of reasons why clinicians should use this form of invasive pressure monitoring (Box 40-2). First and foremost, direct arterial pressure monitoring should be used when moment-to-moment blood pressure changes are anticipated and rapid detection is vital. These conditions typically apply to patients with preexisting severe cardiovascular disease or hemodynamic instability or when the planned operative procedure is likely to cause large, sudden cardiovascular changes, rapid blood loss, or large fluid shifts. The Australian Incident Monitoring Study of 1993 confirmed the superiority of direct arterial pressure monitoring over indirect monitoring techniques for the early detection of intraoperative hypotension.[26]

In addition to continuous blood pressure monitoring, arterial catheterization provides reliable vascular access for frequent blood sampling and allows monitoring of blood pressure when NIBP measurement is impossible (as during nonpulsatile cardiopulmonary bypass). Perhaps the most underemphasized value of direct arterial pressure monitoring is that analysis of the arterial pressure waveform may provide many important diagnostic clues to the patient's condition. More than a half-century ago, Eather and colleagues emphasized these diagnostic insights in a paper that first introduced and advocated direct monitoring of "arterial pressure and pressure pulse contours" in anesthetized

Box 40-2 Indications for Arterial Cannulation

- Continuous, real-time blood pressure monitoring
- Planned pharmacologic or mechanical cardiovascular manipulation
- Repeated blood sampling
- Failure of indirect arterial blood pressure measurement
- Supplementary diagnostic information from the arterial waveform
- Determination of volume responsiveness from systolic pressure or pulse pressure variation

patients.[27] Some of these diagnostic insights are readily apparent and commonly sought, such as identification of the arterial dicrotic notch to guide proper timing for intra-aortic balloon counterpulsation, whereas others are more subtle, such as recognition of excessive variation in systolic blood pressure as a sign of hypovolemia.[28]

Percutaneous Radial Artery Cannulation

The radial artery is the most common site for invasive blood pressure monitoring in anesthesia and critical care because it is technically easy to cannulate and complications are uncommon, in part because of the good collateral circulation of the hand.[29] Slogoff and coauthors described the results of radial artery cannulation in 1700 cardiovascular surgical patients who underwent the procedure without ischemic complications despite evidence of radial artery occlusion after decannulation in more than 25% of the patients.[30]

Before attempting radial artery cannulation, many clinicians assess the adequacy of collateral flow to the hand by performing a modified Allen test. This bedside examination, originally described by E. V. Allen in 1929, provided a technique to assess arterial stenosis in the hands of patients with thromboangiitis obliterans.[31] To perform the Allen test, the examiner compresses the radial and ulnar arteries and asks the patient to make a tight fist to exsanguinate the palm. The patient then opens the fist while avoiding hyperextension of the wrist or fingers, and as occlusion of the ulnar artery is released, the color of the open palm is observed. Normally, the palm will show a striking flush in several seconds; severely reduced ulnar collateral flow is present when the palm remains pale for more than 10 seconds.

Although the Allen test is often used to identify patients at high risk for ischemic complications from radial artery catheterization, the predictive value of this test is uncertain. Numerous reports of permanent ischemic sequelae note that a normal Allen test result was present before catheterization.[32] In contrast, there are many descriptions of uncomplicated radial artery catheterization despite the presence of an abnormal Allen test result before the procedure.[30] In recent years, the radial artery has been used safely as an access site for coronary stenting or excised and used as a graft for coronary bypass surgery, even in individuals with abnormal Allen test results.[33,34] Although most patients show radial artery dominance with respect to overall hand perfusion, total radial artery occlusion does not appear to compromise distal perfusion, perhaps because of collateral recruitment.[34] Furthermore, Allen test results bear little relation to distal blood flow, as measured by fluorescein dye injection or photoplethysmography. Although it is obviously of great importance that the clinician minimize the chance of significant distal ischemia from arterial pressure monitoring, the Allen test cannot be relied on to avoid this adverse outcome.

Consistent, successful radial artery cannulation should be easily achievable with attention to a number of procedural details. The wrist and hand are immobilized in mild dorsiflexion and secured with the wrist resting across a soft pad. Excessive dorsiflexion of the wrist should be avoided because of the possibility of attenuating the pulse. The course of the radial artery proximal to the wrist is identified by gentle palpation, the skin is prepared with an antiseptic, and a local anesthetic is injected intradermally and subcutaneously alongside the artery. Arterial catheterization can then be performed with a standard intravenous catheter or an integrated guidewire-catheter assembly designed for this purpose. A recent educational video provides greater detail about this standard procedure.[35]

Once the catheter is fully advanced into the vessel lumen, the radial artery is occluded by applying proximal pressure, the needle is removed, the monitoring system pressure tubing is fastened to the catheter, an appropriate sterile dressing is applied, and the apparatus is taped and secured to the wrist. Although a soft armboard can be used to maintain the wrist in an anatomically neutral position during arterial pressure monitoring, extreme wrist dorsiflexion should always be avoided because it may lead to median nerve injury.[36,37]

Some clinicians choose the "transfixion" technique for arterial cannulation, in which the front and back walls of the artery are punctured intentionally, the needle is removed from the catheter, and the catheter is withdrawn into the vessel lumen. Although it is unnecessary to place an additional hole in the back wall of the radial artery for successful cannulation, the technique per se does not appear to influence the success rate or incidence of postcannulation complications.

Other aids to arterial cannulation include the use of ultrasound imaging to guide catheter insertion.[38] This may be particularly helpful when standard placement attempts by palpation have failed. Although some authors have suggested that ultrasound or guidewire-based techniques will improve success rates of arterial cannulation, it appears that this is more a function of operator experience and personal preference.[39]

Alternative Arterial Pressure Monitoring Sites

If the radial arteries are unsuitable for monitoring pressure, several alternative cannulation sites are available. The *ulnar artery* is cannulated with a technique much like that described for the radial artery.[40] Even in circumstances in which previous attempts to cannulate the ipsilateral radial artery have failed, the ulnar artery may be cannulated safely.[30]

Although in theory the *brachial artery* does not have the anatomic benefit of the collateral circulation present in the hand, clinical trials have confirmed the safety of this cannulation site. Bazaral and coauthors reported the use of more than 3000 brachial artery catheters in patients undergoing cardiac surgery over a 3-year period, with only one patient requiring postoperative thrombectomy and no untoward sequelae.[41] A slightly longer catheter is preferred for the brachial site because of the need for the catheter to traverse the elbow joint. Other peripheral arteries occasionally chosen for monitoring pressure include the *dorsalis pedis*, *posterior tibial*, and *superficial temporal arteries*. The dorsalis pedis and posterior tibial arteries are generally reserved for pediatric applications.

The *axillary artery* provides another site for long-term pressure monitoring. Advantages include patient comfort, mobility, and access to a central arterial pressure waveform. Complications appear to be infrequent and similar in incidence to radial and femoral artery catheterization.[42] If the axillary approach is chosen, the left side is preferred over the right because the axillary catheter tip will lie distal to the aortic arch and great vessels. Clinicians should be aware, however, that the risk of cerebral embolization is increased whenever more centrally located arterial catheters are used.

The *femoral artery* is the largest artery commonly selected for monitoring blood pressure, and it appears to have a safety record comparable to that of other sites.[42] As with axillary artery pressure monitoring, the femoral artery waveform more closely

resembles aortic pressure than do waveforms recorded from peripheral sites. When compared with radial artery catheterization, the risk of distal ischemia after femoral artery cannulation may be reduced because of the large diameter of the artery, but atherosclerotic plaque embolization is more likely during initial guidewire and catheter placement. Catheterization of the femoral artery is best achieved with a guidewire technique. The operator must be careful to puncture the femoral artery below the inguinal ligament, thereby limiting the risk of arterial injury causing uncontained hemorrhage into the pelvis or peritoneum, a potentially catastrophic complication.[43]

Complications of Direct Arterial Pressure Monitoring

Widespread application of invasive arterial pressure monitoring in anesthesia and intensive care is related, no doubt, to the extremely good safety record of this technique. Large clinical investigations confirm the low incidence of long-term complications after radial artery cannulation, in particular, the small risk of distal ischemia, which is probably less than 0.1%.[29,30,42] Although vascular complications from radial artery cannulation are uncommon, factors that may increase risk include vasospastic arterial disease, previous arterial injury, thrombocytosis, protracted shock, high-dose vasopressor administration, prolonged cannulation, and infection.[44,45]

Additional rare, but serious complications have been reported after arterial cannulation (Box 40-3). In most cases there were technical problems during catheter placement or confounding medical problems such as shock or coagulopathy. The Australian Incident Monitoring Study provides some noteworthy observational data on the incidence and types of complications of blood pressure monitoring.[26,46] Of 2000 untoward clinical events reported in this investigation, only 13 were related to peripheral arterial cannulation, less than the number associated with central venous or peripheral venous cannulation (18 and 33 incidents, respectively). Five of these 13 cases involved equipment faults or misassembly, in 3 cases the arterial line was mistaken for an intravenous line and used for injection of drugs, in 3 cases the arterial line was either disrupted or kinked, in 1 case a fragment of guidewire broke off inside the patient, and in only 1 instance did transient vasospasm follow radial artery cannulation. A second report from this study noted that direct pressure monitoring failed or gave misleading results in 10 instances, including 5 in which there was either incorrect calibration, incorrect interpretation of the pressure display, or unrecognized subclavian artery stenosis. These data suggest that most complications of direct arterial pressure monitoring can be attributed to equipment misuse. This serves to highlight the importance of having a backup system readily available for manual measurement of blood pressure.

Box 40-3 Complications of Direct Arterial Pressure Monitoring

- Distal ischemia, pseudoaneurysm, arteriovenous fistula
- Hemorrhage, hematoma
- Arterial embolization
- Local infection, sepsis
- Peripheral neuropathy
- Misinterpretation of data
- Misuse of equipment

Technical Aspects of Direct Blood Pressure Measurement

Direct measurement of arterial blood pressure requires that the pressure waveform from the cannulated artery be reproduced accurately on the bedside monitor. Not surprisingly, the displayed pressure signal is influenced significantly by the measuring system, including the arterial catheter, extension tubing, stopcocks, flush devices, transducer, amplifier, and recorder.[47]

Blood pressure monitoring systems used in the operating room and intensive care units are described as underdamped, second-order dynamic systems.[47-49] These fluid-filled systems may be modeled after mass-spring systems that demonstrate simple harmonic motion and exhibit similar behavior that depends on the physical properties of elasticity, mass, and friction. These three properties determine the system's operating characteristics, termed the *frequency response* or *dynamic response*, which in turn are characterized by two important system parameters, *natural frequency* (f_n, ω) and *damping coefficient* (ζ, Z, α, D). The natural frequency of the monitoring system quantifies how rapidly the system oscillates, and the damping coefficient quantifies the frictional forces that act on the system and determine how rapidly it comes to rest. Both parameters may be estimated or measured at the bedside, and they dramatically influence the appearance of the recorded pressure waveform.

Natural Frequency, Damping Coefficient, and Dynamic Response of Pressure Monitoring Systems

The arterial blood pressure waveform is a periodic complex wave that can be reproduced by Fourier analysis, which recreates the original complex pressure wave by summing a series of simpler sine waves of different amplitudes and frequencies.[50,51] The original pressure wave has a characteristic periodicity termed the *fundamental frequency*, which is equal to the pulse rate. Although the pulse rate is reported in beats per minute, fundamental frequency is reported in cycles per second or hertz (Hz).

The sine waves that sum to produce the complex wave have frequencies that are multiples or harmonics of the fundamental frequency. A crude arterial waveform that displays a systolic upstroke, systolic peak, dicrotic notch, and so forth can be reconstructed with reasonable accuracy from two sine waves, the fundamental frequency, and the second harmonic (Fig. 40-3). If the original arterial pressure waveform contains high-frequency components such as a steep systolic upstroke, higher-frequency sine waves (and more harmonics) are needed to provide faithful reconstruction of the original pressure waveform. As a general rule, 6 to 10 harmonics are required to provide distortion-free reproduction of most arterial pressure waveforms.[50,52] Hence, accurate blood pressure measurement in a patient with a pulse rate of 120 beats/min (2 cycles/sec or 2 Hz) requires a monitoring system dynamic response of 12 to 20 Hz. The faster the heart rate and the steeper the systolic pressure upstroke, the greater the dynamic response demands on the monitoring system.

If the monitoring system has a natural frequency that is too low, frequencies in the monitored pressure waveform will overlap the natural frequency of the measurement system. As a result, the system will resonate and pressure waveforms recorded on the monitor will be exaggerated or amplified versions of true intra-arterial pressure (Fig. 40-4). This phenomenon is the familiar

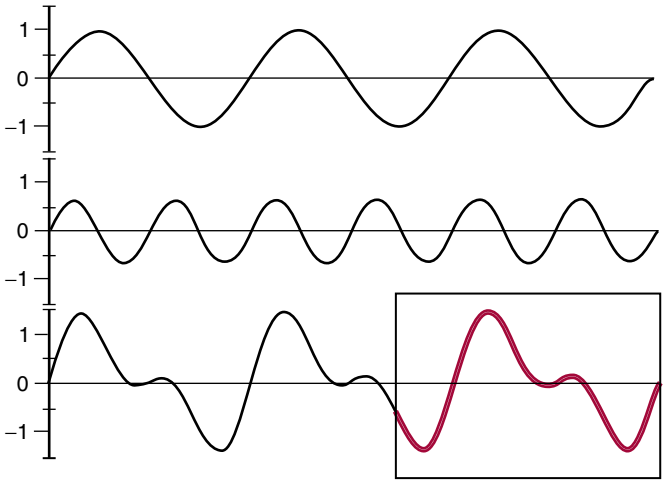


Figure 40-3 Arterial blood pressure waveform produced by summation of sine waves. The fundamental wave (*top*) added to 63% of the second harmonic wave (*middle*) results in a pressure wave (*bottom*) that resembles an arterial blood pressure waveform (*box*). *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 9-1.)*

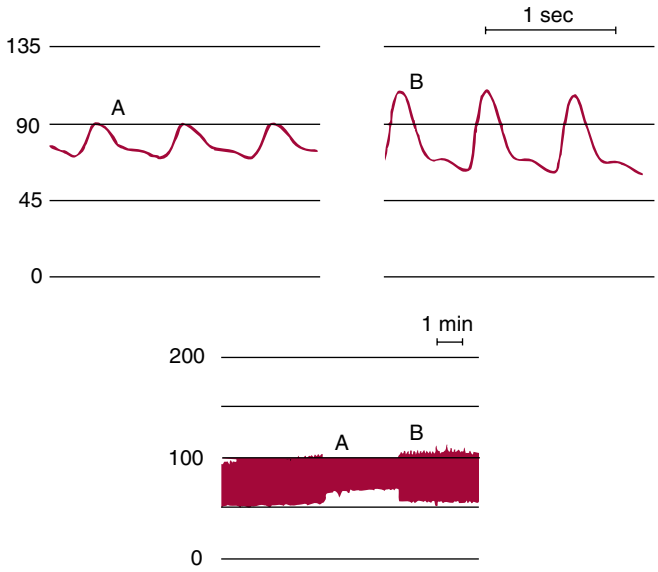


Figure 40-5 Overdamped arterial pressure waveform. The overdamped pressure waveform (A) shows a diminished pulse pressure when compared with the normal waveform (B). The slow-speed recording below demonstrates a 3-minute period of damped arterial pressure. Despite the damped pressure waveform, mean arterial pressure remains unchanged during this period. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 9-3.)*

arterial pressure waveform that displays overshoot, ringing, or resonance. In these instances, the recorded systolic blood pressure overestimates true intra-arterial pressure.

In addition to a sufficiently high natural frequency, the bedside monitoring system must also have an appropriate damping coefficient. An overdamped arterial pressure waveform is recognized by its slurred upstroke, absent dicrotic notch, and loss of fine detail. Severely overdamped pressure waves display a falsely narrowed pulse pressure, although MAP may remain reasonably accurate (Fig. 40-5). In contrast, underdamped pressure waveforms display systolic pressure overshoot and contain additional artifacts produced by the measurement system that are not part of the original intravascular pressure wave (see Fig. 40-4). It is a mistake to attach physiologic significance to these small artifactual waves produced by an underdamped monitoring system that continues to ring or oscillate abnormally in response to the input pressure signal.

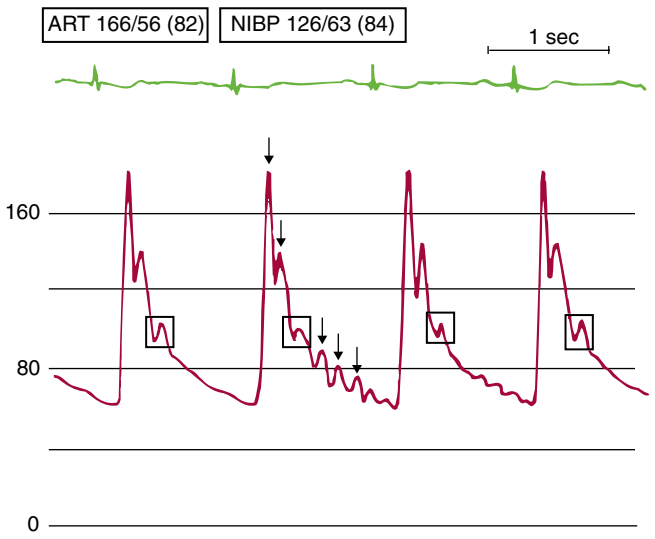


Figure 40-4 Underdamped arterial pressure waveform. Systolic pressure overshoot and additional small, nonphysiologic pressure waves (*arrows*) distort the waveform and make it hard to discern the dicrotic notch (*boxes*). Digital values displayed for direct arterial blood pressure (ART, 166/56; mean, 82 mm Hg) and noninvasive blood pressure (NIBP, 126/63; mean, 84 mm Hg) show the differences in pressure measurement that arise because of an underdamped arterial pressure waveform. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig 9-4.)*

Most catheter-transducer systems are underdamped but have an acceptable natural frequency that exceeds 12 Hz. If the system's natural frequency is lower than 7.5 Hz, the pressure waveform is often distorted, and no amount of damping adjustment can restore the monitored waveform to adequately resemble the original waveform.[47] If, on the other hand, the natural frequency can be increased sufficiently (e.g., 24 Hz), damping will have minimal effect on the monitored waveform, and faithful reproduction of intravascular pressure is achieved more easily (Figs. 40-6 and 40-7). In other words, the lower the natural frequency of the monitoring system, the more narrow the range of damping coefficients that can be tolerated to ensure faithful reproduction of the pressure wave. For example, if the monitoring system's natural frequency is 10 Hz, the damping coefficient must be between 0.45 and 0.6 for accurate monitoring of the pressure waveform. If the damping coefficient is too low, the monitoring system will be underdamped, resonate, and display factitiously elevated systolic blood pressure; if the damping coefficient is too high, the system will be overdamped, systolic pressure will be falsely decreased, and fine detail in the pressure trace will be lost.

From these considerations it follows that a pressure monitoring system will have optimal dynamic response if its natural frequency is as high as possible.[51] In theory, this is best achieved by using short lengths of stiff pressure tubing and limiting the

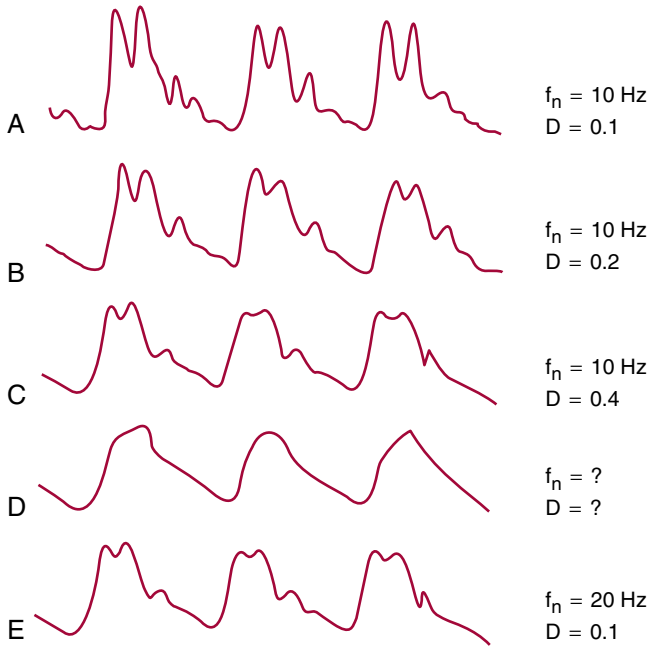


Figure 40-6 Interaction between damping coefficient (D) and natural frequency (f_n) in pressure waveform recordings. **A,** An underdamped pressure waveform (f_n = 10 Hz; D = 0.1) displays small artifactual waves and systolic pressure overshoot. **B,** A small increase in D (0.2) diminishes these artifacts. **C,** Critical damping (D = 0.4) provides an accurate pressure waveform even though f_n remains low. **D,** Overdamping results in loss of fine detail and precludes determination of f_n or D. **E,** Increased f_n (20 Hz) allows a low D (0.1) to have minimal impact on waveform morphology. Notice the similarities between waveforms **C** and **E**. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 9-7.)*

number of stopcocks and other monitoring system appliances. Blood clots and air bubbles trapped and concealed in stopcocks and other connection points will have similar adverse influences on the system's dynamic response. As a general rule, adding air bubbles to monitoring systems will not improve their dynamic response because any increase in system damping is always accompanied by a decrease in natural frequency. Somewhat paradoxically, monitoring system resonance may increase and cause even greater systolic pressure overshoot (Fig. 40-8).

To assess the amount of distortion existing in a pressure monitoring system, the fast-flush test provides a convenient bedside method for determining the system's dynamic response.[47,49,51] To perform this test, the fast-flush valve is opened briefly, and the resulting flush artifact is examined. Natural frequency is inversely proportional to the time between adjacent oscillation peaks. It can be calculated as 1 cycle/1.7 mm × 25 mm/sec = 14.7 cycles/sec (14.7 Hz) (Fig. 40-9). Monitoring systems with shorter oscillation cycles will have higher natural frequencies.[51]

The damping coefficient is related to the amplitudes of successive oscillation peaks. The amplitude ratio thus derived indicates how quickly the measuring system comes to rest. The damping coefficient can be calculated mathematically, but it is usually determined graphically from the amplitude ratio.[47,51] For example, if the amplitudes of two successive oscillation cycles are 24 and 17 mm, the amplitude ratio is 17/24, or 0.71. This corresponds to a damping coefficient of 0.11 based on the graphic solution (Fig. 40-9). Note that the monitoring system illustrated has an adequate natural frequency (approximately 15 Hz) but is underdamped (damping coefficient of 0.11), and one would expect to find systolic pressure overshoot in such a system.

Although the technical requirements for accurate blood pressure measurement are well known, these conditions are often unmet in routine clinical practice. Schwid examined the frequency response of 30 radial artery catheter-transducer systems used in routine intensive care monitoring.[53] Mean values (± SD) for natural frequency (14.7 ± 3.7 Hz) and damping coefficient (0.24 ± 0.07) were worse than values typically reported for measurements made under laboratory conditions, instead falling in the underdamped response region reported by Gardner.[47] Furthermore, the range of frequency responses (10.2 to 25.3 Hz) and damping coefficients (0.15 to 0.44) measured in this setting suggests that distortion of the arterial waveform is common in clinical practice, particularly systolic arterial pressure overshoot resulting from an underdamped system (see Fig. 40-7).

Components of Pressure Monitoring Systems

Arterial pressure monitoring systems have a number of components, beginning with the intra-arterial catheter and including extension tubing, stopcocks, in-line blood sampling set, pressure transducer, continuous-flush device, and electronic cable connecting the bedside monitor and waveform display screen. The stopcocks in the system provide sites for blood sampling and allow the transducer to be exposed to atmospheric pressure to establish a zero reference value. Needleless blood sampling ports and in-line aspiration systems permit drawing of blood without the use of sharp needles and allow aspirated waste blood to be

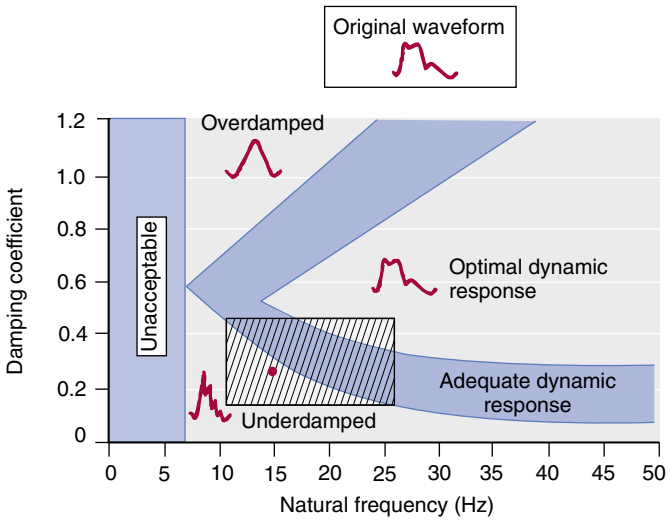


Figure 40-7 Interaction between damping coefficient and natural frequency. Depending on these two system parameters, catheter tubing-transducer systems fall into one of five different dynamic response ranges. Systems with an optimal dynamic response will faithfully record the most demanding pressure waveforms, whereas those with an adequate dynamic response will accurately record most pressure waveforms seen in clinical practice. Overdamped and underdamped systems introduce artifacts characteristic of these technical limitations. Systems with a natural frequency of less than 7 Hz are considered unacceptable. The *rectangular crosshatched box* indicates the ranges of damping coefficients and natural frequencies commonly encountered in clinical pressure measurement systems. The point within the box shows the mean values of 30 such systems recorded by Schwid.[53] *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Figs.9-6, 9-8, and 9-11.)*

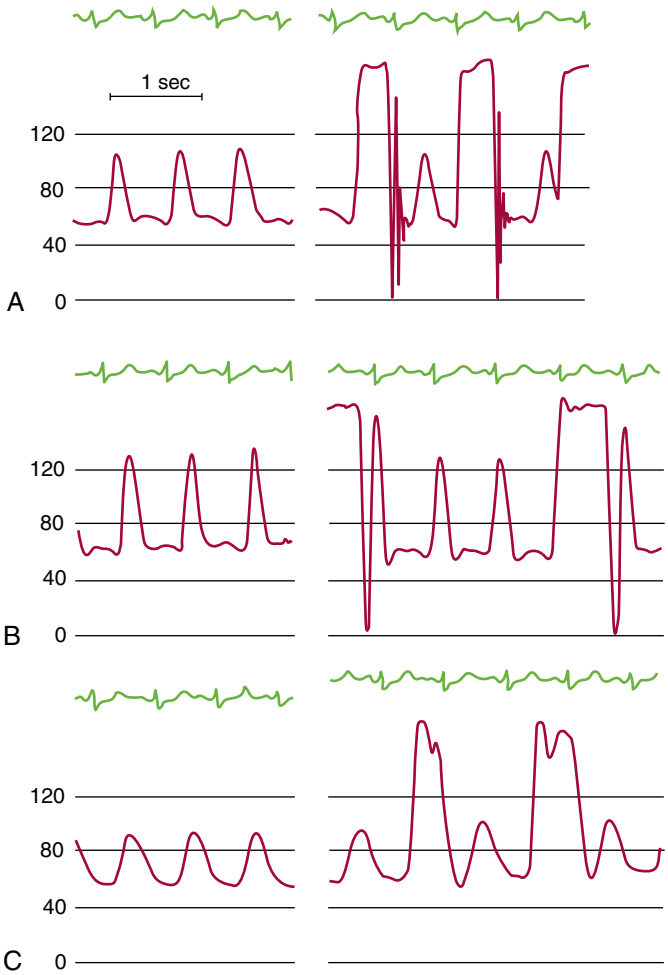


Figure 40-8 Effect of small air bubbles within arterial pressure monitoring systems. Arterial pressure waveforms are displayed, along with superimposed fast-flush square-wave artifacts. **A,** The original monitoring system has an adequate dynamic response (natural frequency, 17 Hz; damping coefficient, 0.2). **B,** A small 0.1-mL air bubble added to the monitoring system produces a paradoxical increase in arterial blood pressure. Note the decreased natural frequency of the system. **C,** A larger 0.5-mL air bubble further degrades the dynamic response and produces spurious arterial hypotension. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 9-14.)*

returned to the patient within a convenient closed system. Modifications such as these are intended to reduce the incidence of needle injury and decrease waste of the patient's blood during sampling. However, these additional features may degrade the dynamic response of the monitoring system and further exacerbate systolic arterial pressure overshoot.

The flush device provides a continuous, slow (1 to 3 mL/hr) infusion of saline to purge the monitoring system and prevent thrombus formation within the arterial catheter. Dextrose solutions should not be used because flush contamination of sampled blood may cause serious errors in blood glucose measurement.[54] A dilute concentration of heparin (1 to 2 units heparin/mL saline) has been added to the flush solution to further reduce the incidence of catheter thrombosis, but this practice increases the risk for heparin-induced thrombocytopenia and should be avoided. The flush device not only ensures continuous slow flushing of the line and catheter but also includes a spring-loaded valve for periodic, high-pressure flushing. This rapid flushing is used to purge the extension line of blood after an arterial sample has been taken or to restore the dynamic response characteristics of the pressure monitoring system, which will otherwise slowly deteriorate over time.[55]

Transducer Setup: Zeroing and Leveling

Before initiating patient monitoring, the pressure transducer must be zeroed, calibrated, and leveled to the appropriate position on the patient. The initial step in this process is to expose the transducer to atmospheric pressure by opening the adjacent stopcock to air, pressing the zero pressure button on the monitor, and

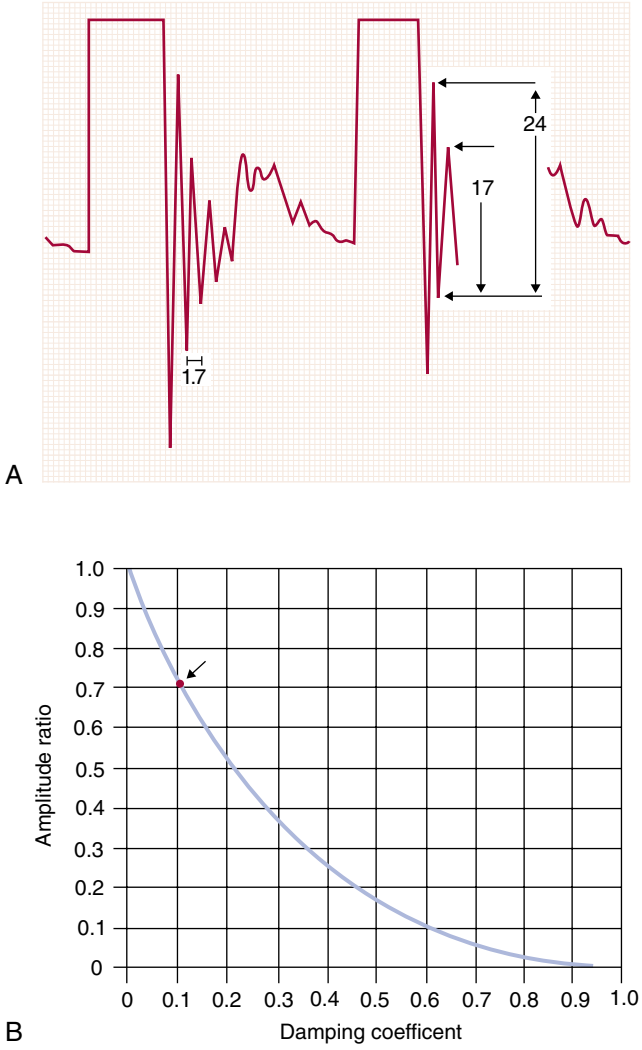


Figure 40-9 Clinical measurement of natural frequency and damping coefficient. **A,** Two square-wave fast-flush artifacts interrupt an arterial pressure waveform recorded on standard 1-mm grid paper at a speed of 25 mm/sec. Natural frequency is determined by measuring the period of one cycle of adjacent oscillation peaks (1.7 mm). The damping coefficient is determined by measuring the heights of adjacent oscillation peaks (17 and 24 mm). From these measurements a natural frequency of 14.7 Hz and an amplitude ratio of 0.71 may be calculated. See text for greater detail. **B,** Relationship between amplitude ratio and damping coefficient. The amplitude ratio determined in the fast-flush test in **A** corresponds to a damping coefficient of 0.11. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Figs.9-9 and 9-10.)*

thereby establishing the zero pressure reference value. The transducer now has a reference—ambient atmospheric pressure—against which all intravascular pressures are measured. This process underscores the fact that all pressures displayed on the monitor are referenced to atmospheric pressure outside the body. Although clinicians generally refer to "zeroing the transducer," the transducer is actually exposed to atmospheric pressure through an open stopcock affixed to the transducer. To be precise, it is this air-fluid interface at the level of the stopcock that is the zero pressure locus. This point must be aligned with a specific position on the patient to ensure the correct transducer level.

When a significant change in pressure occurs, the zero reference value can be rechecked quickly by opening the stopcock and noting that the pressure value on the bedside monitor is still zero.[52] Occasionally, a faulty transducer, cable, or monitor will cause the zero baseline to drift. Though uncommon with modern monitoring components, this zero drift artifact must be identified to avoid important diagnostic errors.[56,57]

Historically, calibration of the transducer was the next step after zeroing. Calibration is an adjustment in system gain to ensure accurate transducer measurement relative to a known reference pressure value. Though traditionally calibrated against a mercury manometer, current disposable pressure transducers meet accuracy standards established by the Association for the Advancement of Medical Instrumentation and the American National Standards Institute.[56] As a result, bedside calibration of the transducer is no longer performed. Nonetheless, on rare occasion, despite successful transducer zeroing, the measured blood pressure values seem erroneous, and a malfunctioning pressure transducer, cable, or monitor must be suspected and replaced.[57]

The final step in transducer setup is to adjust the pressure monitoring zero point to the appropriate level relative to the patient. Note that transducer zeroing and leveling are two distinct procedures. Zeroing exposes the transducer to ambient atmospheric pressure through an open stopcock. Leveling assigns this zero reference point to a specific position on the patient's body. Although precise location of the zero reference level is essential for accurate monitoring of blood pressure, it is also critically important for measurement of cardiac filling pressures, where a small absolute error in pressure measurement will cause a large relative error.

Arterial pressure transducers should be placed at a level that will best estimate aortic root pressure. In a supine patient, pressure transducer levels are often adjusted to the midchest position in the midaxillary line. However, based on physical principles and measurement of the uppermost fluid levels in the cardiac chambers, Courtois and associates have shown that cardiac filling pressures will be overestimated by as much as 7 mm Hg when transducers are leveled to the midchest rather than a position approximately 5 cm posterior to the sternal border.[58] This preferred (more anterior) transducer location obviates the confounding effect of hydrostatic pressure on cardiac filling pressure measurements. Inasmuch as this transducer location will provide the most accurate measurement of left ventricular pressure, the same transducer level is optimal for arterial blood pressure measurement. Other investigators have confirmed that leveling of pressure transducers to the midchest position will cause overestimation of cardiac filling pressure and presumably aortic root pressure.[59]

In some circumstances, the clinician may choose to adjust the arterial transducer level to a different position on the body. It is critically important to recognize that when this is done, the pressure is being measured at the level of the transducer and not at the level of the aortic root. For example, during sitting neurosurgical operations, if the arterial pressure transducer is raised to a level even with the patient's ear to approximate the location of the circle of Willis, the clinician is measuring blood pressure at the level of the brain and must recognize that the aortic root pressure is higher (by an amount equal to the vertical difference in height between the pressure transducer and the aortic root). Whenever the level of the pressure transducer is adjusted, there is no need to rezero the transducer because atmospheric pressure changes little over the few inches of height adjustment.

Common errors in blood pressure measurement occur when pressure transducers are fixed to an intravenous pole and the height of the patient's bed is adjusted. Raising the height of the bed relative to the transducer will cause overestimation of blood pressure, whereas lowering the patient below the transducer will cause underestimation of blood pressure.

Proper interpretation of blood pressure measurements from a patient in the lateral decubitus position requires an understanding of the distinction between zeroing and leveling pressure transducers and the differences between noninvasive and invasive blood pressure measurement (Fig. 40-10). When a patient is in the lateral decubitus position, one arm is higher than the heart (and aortic root) and the other arm is lower. Regardless of whether direct arterial pressure is measured from the right or the left arm, as long as the pressure transducer remains fixed at the level of the heart, the location of the arms has no influence on the measured arterial pressure. However, noninvasive cuff blood pressure measurements will be different in the two arms, higher in the dependent (down) arm and lower in the nondependent (up) arm (see Fig. 40-10). Note that if the arterial pressure transducers were attached to the arms rather than fixed at the level of the heart, pressures recorded from the right and left radial artery catheters would equal those recorded by the ipsilateral noninvasive cuffs and would be higher in the dependent arm than in the nondependent arm.

Normal Arterial Pressure Waveforms

Direct arterial pressure monitoring in anesthetized patients began nearly 60 years ago.[27] In that early era, arterial pulse waveform analysis was noted to provide useful diagnostic information, but somewhat surprisingly, modern physicians pay little attention to the morphology and detail of the arterial pressure waveform. O'Rourke and Gallagher attribute this change in practice to the reliance on cuff sphygmomanometry, which provides "numbers which came to be linked in a simplistic way to cardiac strength (systolic pressure) and arteriolar tone (diastolic pressure). Pseudoscience had arrived with (these) numbers. … Even when monitored directly in operating theatres and critical care areas, anesthetists and intensivists show little interest in the waveform and base their judgments on values of systolic, diastolic and mean pressure."[60]

Because clinicians today benefit from the widespread availability of high-resolution, multicolored monitor displays, renewed interest in waveform analysis should expand clinical monitoring capabilities.[28] Appreciation of the diagnostic clues provided by the direct arterial pressure waveform requires full understanding of normal waveform components, their relationship to the cardiac cycle, and differences in waveforms recorded from different sites in the body.

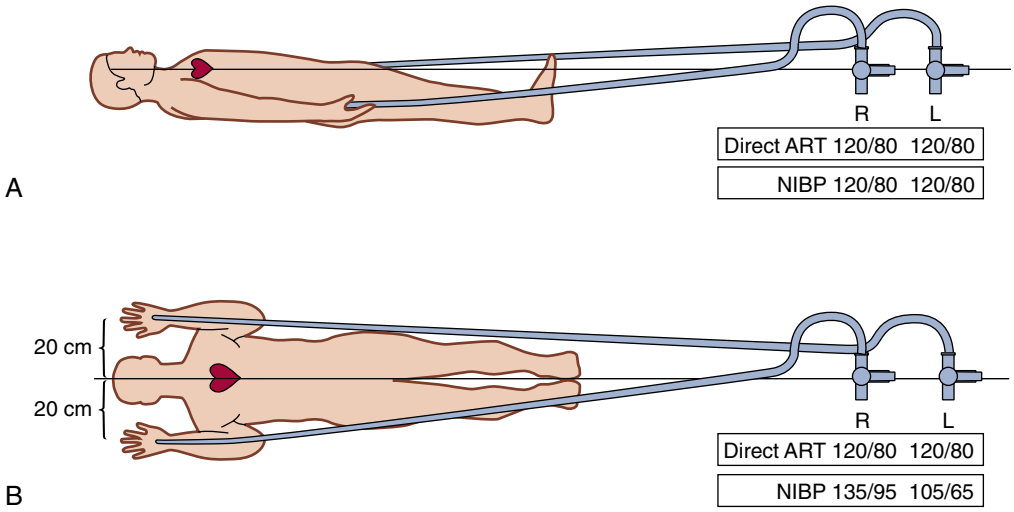


Figure 40-10 Effect of patient position on the relationship between direct arterial blood pressure (ART) and indirect noninvasive blood pressure (NIBP) measurements. **A,** In a supine patient, pressures measured from the right (R) or left (L) arms by either technique will be the same. **B,** In the right lateral decubitus position, ART recorded directly from the right and left radial arteries will remain unchanged as long as the respective pressure transducers remain at heart level. However, NIBP will be higher in the dependent right arm and lower in the nondependent left arm. Differences in NIBP are determined by the positions of the arms above and below the level of the heart and are equal to the hydrostatic pressure differences between the level of the heart and the respective arm. A 20-cm difference in height produces a 15–mm Hg difference in pressure. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 9-22.)*

The systemic arterial pressure waveform results from ejection of blood from the left ventricle into the aorta during systole, followed by peripheral arterial runoff of this stroke volume during diastole (Fig. 40-11). The systolic components follow the ECG R wave and consist of a steep pressure upstroke, peak, and decline and correspond to the period of left ventricular systolic ejection. The downslope of the arterial pressure waveform is interrupted by the dicrotic notch, then continues its decline during diastole after the ECG T wave, and reaches its nadir at end-diastole. The dicrotic notch recorded directly from the central aorta is termed the *incisura* (from the Latin, "a cutting into"). The incisura is sharply defined and is undoubtedly related to closure of the aortic valve.[61] In contrast, the peripheral arterial waveform generally displays a later, smoother dicrotic notch that only approximates the timing of aortic valve closure and depends more on properties of the arterial wall. Note that the systolic upstroke of the radial artery pressure trace does not appear for 120 to 180 msec after inscription of the ECG R wave (see Fig. 40-11). This interval reflects the sum of times required for spread of electrical depolarization through the ventricular myocardium, isovolumic left ventricular contraction, opening of the aortic valve, left ventricular ejection, transmission of the aortic pressure wave to the radial artery, and finally, transmission of the pressure signal from the arterial catheter to the pressure transducer.

The bedside monitor displays numeric values for the systolic peak and end-diastolic nadir pressures. Measurement of mean pressure is more complicated and depends on the algorithm used by the monitor. In simplest terms, MAP is equal to the area beneath the arterial pressure curve divided by the beat period and averaged over a series of consecutive heartbeats. Although MAP is often estimated as diastolic pressure plus one third times pulse pressure, this estimate is valid only at slower heart rates because the proportion of the cardiac cycle spent in diastole decreases during tachycardia.[62]

One of the most important features of the arterial pressure waveform is the phenomenon of distal pulse amplification. Pressure waveforms recorded simultaneously from different arterial sites will have different morphologies because of the physical characteristics of the vascular tree, namely, impedance and harmonic resonance[21,60] (Fig. 40-12). As the arterial pressure wave travels from the central aorta to the periphery, the arterial upstroke

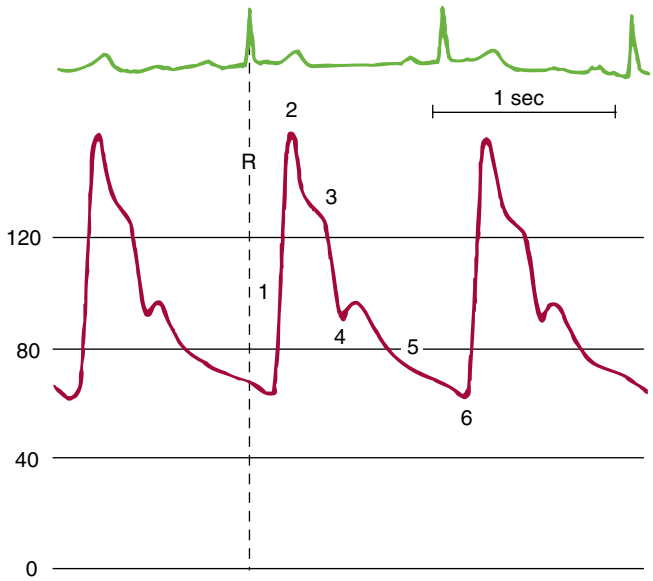


Figure 40-11 Normal arterial blood pressure waveform and its relationship to the electrocardiographic R wave. 1, Systolic upstroke; 2, systolic peak pressure; 3, systolic decline; 4, dicrotic notch; 5, diastolic runoff; 6, end-diastolic pressure. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 8-1.)*

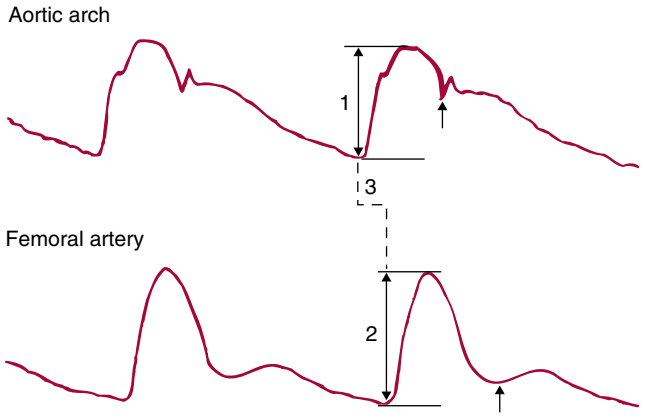


Figure 40-12 Distal pulse wave amplification of the arterial pressure waveform. When compared with pressure in the aortic arch, the more peripherally recorded femoral artery pressure waveform demonstrates a wider pulse pressure (compare 1 and 2); a delayed upstroke (3); a delayed, slurred dicrotic notch (compare *arrows*); and a more prominent diastolic wave. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 8-4.)*

becomes steeper, the systolic peak becomes higher, the dicrotic notch appears later, the diastolic wave becomes more prominent, and end-diastolic pressure becomes lower. Thus, when compared with central aortic pressure, peripheral arterial waveforms have higher systolic pressure, lower diastolic pressure, and wider pulse pressure. Furthermore, there is a delay in arrival of the pressure pulse at peripheral sites, so the systolic pressure upstroke begins approximately 60 msec later in the radial artery than in the aorta. Despite morphologic and temporal differences between peripheral and central arterial waveforms, MAP in the aorta is just slightly greater than MAP in the radial artery.

Pressure wave reflection is the predominant factor that influences the shape of the arterial pressure waveform as it travels peripherally.[60] As blood flows from the aorta to the radial artery, mean pressure decreases only slightly because of little resistance to flow in the major conducting arteries. At the arteriolar level, mean blood pressure falls markedly as a result of the dramatic increase in vascular resistance at this site. This high resistance to flow diminishes pressure pulsations in small downstream vessels but acts to augment upstream arterial pressure pulses because of pressure wave reflection.[63] These intrinsic vascular phenomena determine the shape of the arterial pulse wave recorded from different sites in the body, in both health and disease. For example, elderly patients have reduced arterial distensibility, which results in early return of reflected pressure waves, increased pulse pressure, a late systolic pressure peak, and disappearance of the diastolic pressure wave (Fig. 40-13).

From these considerations it becomes evident that the morphology of the arterial waveform and the precise values of systolic and diastolic blood pressure vary throughout the body under normal conditions in otherwise healthy individuals. Perhaps of even greater importance, the relationship between central and peripheral arterial pressure varies with age and is altered by various physiologic changes, pathologic conditions, and pharmacologic interventions.

Arterial Blood Pressure Gradients

In addition to the normal physiologic phenomena that exert subtle influences on the arterial pressure waveform, a number of pathophysiologic conditions cause exaggerated arterial pressure gradients in the body. Frank and coworkers demonstrated that 21% of patients undergoing peripheral vascular surgery had a blood pressure difference between the two arms that exceeded 20 mm Hg.[64] In view of the prevalence of this problem, when blood pressure is lower in one arm than in the other or when the pulses are weaker on one side, one should never insert an arterial catheter on the side with the weaker pulse because determination of blood pressure from this site will probably underestimate true aortic pressure. In addition to atherosclerosis, other pathologic conditions such as arterial dissection or embolism preclude accurate monitoring of pressure from the affected sites.

Unusual patient positions during surgery may produce regional arterial compression, and surgical retraction, particularly during cardiothoracic operations, can produce local vascular compression.[65,66] The nature of the operative procedure is always an important determinant of the appropriate site for monitoring arterial pressure. Operations requiring placement of a descending thoracic aortic cross-clamp may interrupt arterial flow to the left subclavian artery and its tributaries in the left arm, as well as branches of the aorta beyond the clamp. In these cases, blood pressure monitored from the right arm best estimates aortic root pressure and carotid arterial pressure and is used to guide anesthetic management. In addition, pressure may be monitored simultaneously from a femoral artery in an attempt to estimate perfusion pressure to vital organs distal to the aortic cross-clamp.

Various pathophysiologic disturbances may produce generalized arterial pressure gradients in the body and should be considered when choosing a site for monitoring arterial pressure. Large differences in peripheral and central arterial pressure may be seen in patients in shock. Femoral artery systolic pressure may exceed radial artery systolic pressure by more than 50 mm Hg in septic patients who require vasopressor infusions, an observation that has significant therapeutic implications for the management of critically ill patients.[67] Other vasoactive drugs, anesthetics (particularly neuraxial blockade), and changes in patient temperature produce pressure gradients that alter the relationship between central and peripheral arterial pressure measurements.[21] During hypothermia, thermoregulatory vasoconstriction causes radial

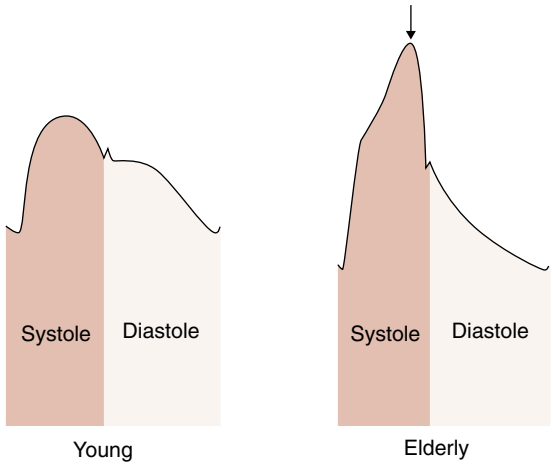


Figure 40-13 Impact of pressure wave reflection on arterial pressure waveforms. In elderly individuals with reduced arterial distensibility, early return of reflected waves increases pulse pressure, produces a late systolic pressure peak (*arrow*), and attenuates the diastolic pressure wave.

artery systolic pressure to exceed femoral artery systolic pressure, whereas during rewarming, vasodilation reverses this gradient and causes radial artery pressure to underestimate femoral artery pressure.[68]

Large differences between central and peripheral arterial blood pressure have also been described in cardiac surgical patients undergoing cardiopulmonary bypass (Fig. 40-14). Shortly after initiation of cardiopulmonary bypass, mean radial artery pressure is lower than mean femoral artery pressure, and this difference seems to persist during the bypass procedure.[69] Furthermore, in the initial minutes after bypass, radial arterial pressure continues to be lower than central aortic pressure, often by more than 20 mm Hg.[70] In most patients, these pressure differences persist after bypass for only several minutes and resolve within an hour, but occasionally these pressure gradients are still present during the postoperative period.

Abnormal Arterial Pressure Waveforms

Detailed examination of the morphologic features of individual arterial pressure waveforms can provide important diagnostic clues to a variety of pathologic conditions (Table 40-1). *Aortic stenosis* produces a fixed obstruction to left ventricular ejection that results in reduced stroke volume and an arterial pressure waveform that rises slowly (*pulsus tardus*), peaks late in systole, and is small in amplitude (*pulsus parvus*) (Fig. 40-15A and B). A distinct shoulder, termed the *anacrotic notch*, often distorts the pressure upstroke, and the dicrotic notch may not be discernible. These features make the arterial pressure waveform appear overdamped.

In *aortic regurgitation*, the arterial pressure wave displays a sharp rise, wide pulse pressure, and low diastolic pressure as a result of runoff of blood into the left ventricle and the periphery during diastole. Because of the large stroke volume ejected from the left ventricle in this condition, the arterial pressure pulse may have two systolic peaks (*bisferiens pulse*) (see Fig. 40-15C). These peaks represent separate percussion and tidal waves, the former resulting from left ventricular ejection and the latter arising from the periphery as a reflected wave. In *hypertrophic cardiomyopathy*, the arterial pressure waveform assumes a peculiar bifid shape termed a "spike-and-dome" configuration. After an initial sharp pressure upstroke that results from rapid left ventricular ejection in early systole, arterial pressure falls rapidly as dynamic left ventricular outflow obstruction develops during midsystole and is followed by a late systolic reflected wave, thereby creating the characteristic double-peaked waveform (see Fig. 40-15D).

Observation of arterial waveform patterns over consecutive heartbeats provides an additional set of diagnostic clues. *Pulsus alternans* is recognized by the alternating beats of larger

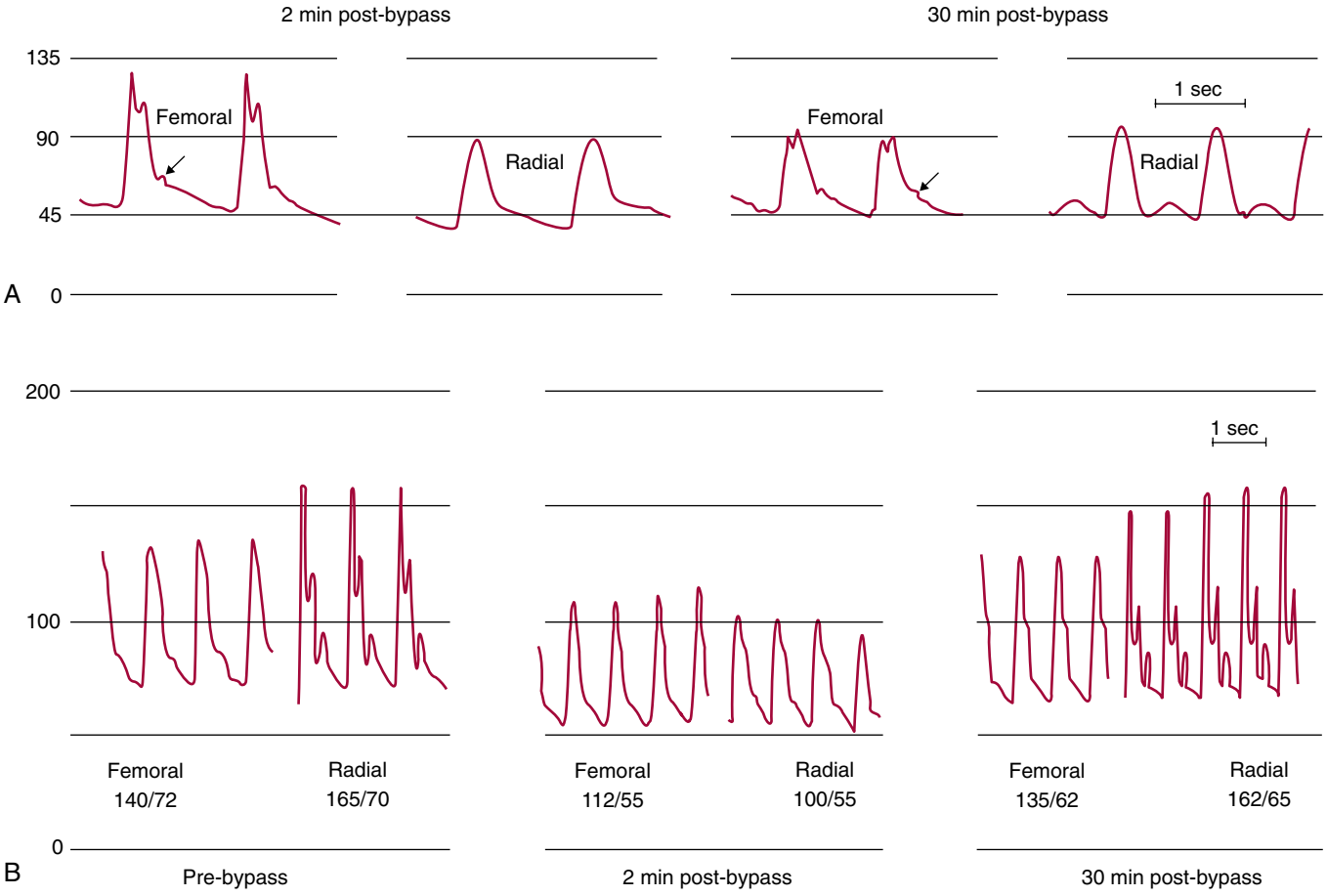


Figure 40-14 Arterial pressure gradients after cardiopulmonary bypass. **A,** Femoral and radial artery pressure traces recorded 2 minutes after bypass, when radial artery pressure underestimates the more centrally measured femoral artery pressure, and 30 minutes later, when radial and femoral arterial pressure has been equalized and radial pressure has assumed a more typical morphology. Note that the dicrotic notch (*arrows*) is visible in the femoral pressure trace after bypass but not initially in the radial pressure trace. **B,** Femoral and radial artery pressure traces recorded before cardiopulmonary bypass, 2 minutes after bypass, and 30 minutes after bypass. Note the changing relationship between femoral and radial artery pressure measurements (in mm Hg) at these different times.

Table 40-1 Arterial Blood Pressure Waveform Abnormalities

Condition	Characteristics
Aortic stenosis	Pulsus parvus (narrow pulse pressure) Pulsus tardus (delayed upstroke)
Aortic regurgitation	Bisferiens pulse (double peak) Wide pulse pressure
Hypertrophic cardiomyopathy	Spike-and-dome pattern (midsystolic obstruction)
Systolic left ventricular failure	Pulsus alternans (alternating pulse pressure amplitude)
Cardiac tamponade	Pulsus paradoxus (exaggerated decrease in systolic blood pressure during spontaneous inspiration)

and smaller pulse pressures (Fig. 40-16A). In general, it is considered to be a sign of severe left ventricular systolic dysfunction, often noted in patients with advanced aortic stenosis. Pulsus alternans should be distinguished from the bigeminal pulse that arises from a bigeminal rhythm, usually ventricular bigeminy. Both abnormalities create an alternating pulse pressure in the arterial pressure waveform, but the rhythm is regular in pulsus alternans.

Pulsus paradoxus is an exaggerated inspiratory fall in systolic arterial pressure that exceeds 10 to 12 mm Hg during quiet breathing (see Fig. 40-16B).[71,72] The term is confusing because a small inspiratory reduction in blood pressure is a normal phenomenon and pulsus paradoxus is not truly paradoxical, but rather an exaggeration of the normal inspiratory decline in blood pressure. Pulsus paradoxus is a characteristic, almost universal finding in cardiac tamponade that occurs in many patients with pericardial constriction. It is said to occur in patients with airway obstruction, bronchospasm, dyspnea, or any condition characterized by large swings in intrathoracic pressure. However, in cardiac tamponade, pulse pressure and left ventricular stroke volume decrease during inspiration, in contrast to the blood pressure changes observed in patients with forced breathing patterns and exaggerated changes in intrathoracic pressure, in whom pulse pressure is relatively unchanged.[73]

The arterial pressure waveform provides diagnostic clues in other unusual physiologic states, such as for proper timing of intra-aortic balloon counterpulsation (Fig. 40-17A). During nonpulsatile cardiopulmonary bypass, minor variations in blood pressure created by the arterial roller head allow calculation and confirmation of the adequacy of systemic blood flow[28] (see Fig. 40-17B).

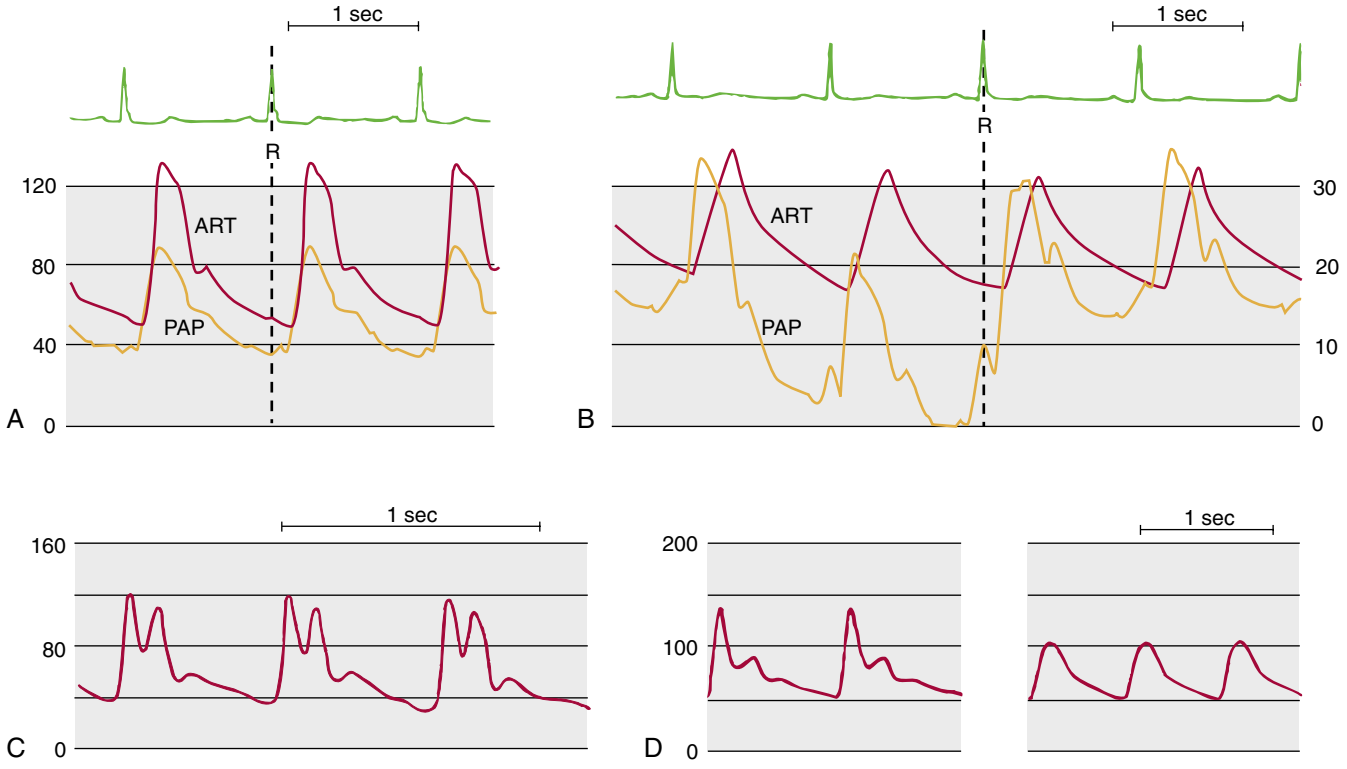


Figure 40-15 Influence of pathologic conditions on arterial pressure (ART) waveform morphology. **A,** *Normal* ART and pulmonary artery pressure (PAP) waveform morphologies demonstrating the similar timing of these waveforms relative to the electrocardiographic R wave. **B,** In *aortic stenosis*, the ART waveform is distorted and demonstrates a slurred upstroke and delayed systolic peak. These changes are particularly striking in comparison to the normal PAP waveform. Note the beat-to-beat respiratory variation in the PAP waveform. See text for greater detail. For **A** and **B,** the ART scale is on the *left* and the PAP scale is on the *right*. **C,** *Aortic regurgitation* produces a bisferiens pulse and a wide pulse pressure. See text for greater detail. **D,** The arterial pressure waveform in *hypertrophic cardiomyopathy* shows a peculiar "spike-and-dome" configuration. The pressure waveform assumes a more normal morphology after surgical correction of this condition. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Figs.3-3, 17-21, and 17-24.)*

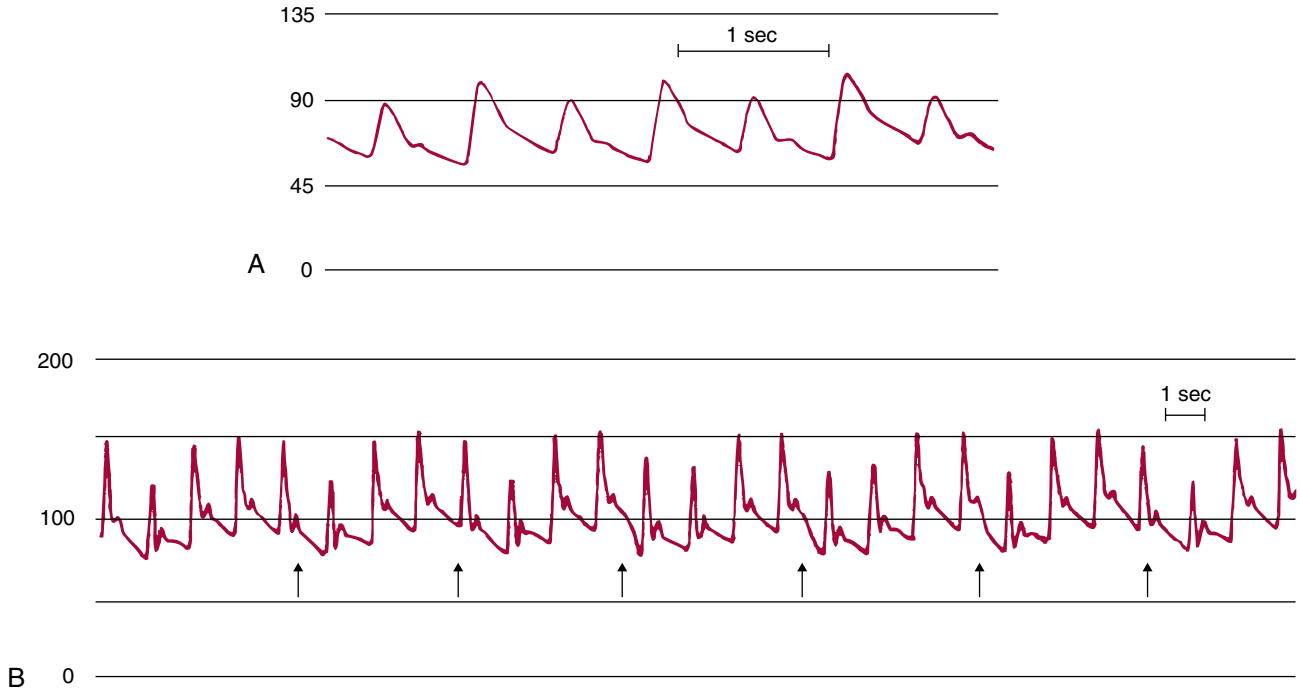


Figure 40-16 Beat-to-beat variability in arterial pressure waveform morphologies. **A,** *Pulsus alternans*. **B,** *Pulsus paradoxus*. The marked decline in systolic arterial pressure and pulse pressure during spontaneous inspiration (*arrows*) is characteristic of cardiac tamponade. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 18-10.)*

Arterial Pressure Monitoring for Prediction of Volume Responsiveness

The starting point for hemodynamic resuscitation begins with optimizing cardiac preload. The limitations of static indicators of preload, such as central venous pressure (CVP), have been increasingly recognized because of the many factors that confound their interpretation.[74] Newer dynamic markers of volume responsiveness have been described that provide more useful information for determining appropriate end points for fluid resuscitation. Variations in arterial blood pressure observed during positive-pressure mechanical ventilation are the most widely studied of these dynamic indicators. These changes in blood pressure are readily observed on the bedside monitor in patients who are receiving direct arterial blood pressure monitoring, and they result from the changes in intrathoracic pressure and lung volume that occur during the respiratory cycle.

During positive-pressure inspiration, increasing lung volume compresses and displaces the pulmonary venous reservoir and propels blood into the left heart chambers, thereby increasing left ventricular preload. Simultaneously, the increase in intrathoracic pressure reduces left ventricular afterload. The increase in left ventricular preload and decrease in afterload produce an increase in left ventricular stroke volume and an increase in systemic arterial pressure. In most patients the preload effects are more important, but in patients with severe left ventricular systolic failure, the reduction in afterload plays an important role in increasing left ventricular ejection. At the same time that left heart filling is increasing during early inspiration, the rising intrathoracic pressure causes a decrease in systemic venous return and right ventricular preload. The increased lung volume may also increase pulmonary vascular resistance (PVR) slightly and thereby increase right ventricular afterload. These effects combine to reduce right ventricular ejection during inspiration. During early expiration, the reduced right ventricular stroke volume that occurred during inspiration crosses the pulmonary vascular bed and leads to reduced left ventricular filling. As a result, left ventricular stroke volume falls and systemic arterial blood pressure decreases. This cyclic variation in systemic arterial pressure may be measured and quantified as the *systolic pressure variation* (SPV).

SPV is often subdivided into inspiratory and expiratory components by measuring the increase (Δ Up) and decrease (Δ Down) in systolic pressure in relation to the end-expiratory, apneic baseline pressure (Fig. 40-18). In a mechanically ventilated patient, normal SPV is 7 to 10 mm Hg, with Δ Up being 2 to 4 mm Hg and Δ Down being 5 to 6 mm Hg.[75] The greatest clinical use of SPV has been for the early diagnosis of hypovolemia.[76] In both experimental animals and patients, hypovolemia causes a dramatic increase in SPV, particularly the Δ Down component. An increase in SPV, particularly in Δ Down, may herald hypovolemia, even in patients in whom arterial blood pressure is maintained near normal levels by compensatory arterial vasoconstriction.

In a heterogeneous group of intensive care patients, Marik demonstrated that a large SPV (>15 mm Hg) was highly predictive of low pulmonary artery wedge pressure (PAWP) (<10 mm Hg).[77] Using echocardiography to measure the left ventricular cross-sectional area as a surrogate for preload, Coriat and colleagues found Δ Down to be better than wedge pressure as a predictor of preload.[78] Other uses of SPV focus on changes in the Δ Up portion of the arterial pressure trace. Just as Δ Down may

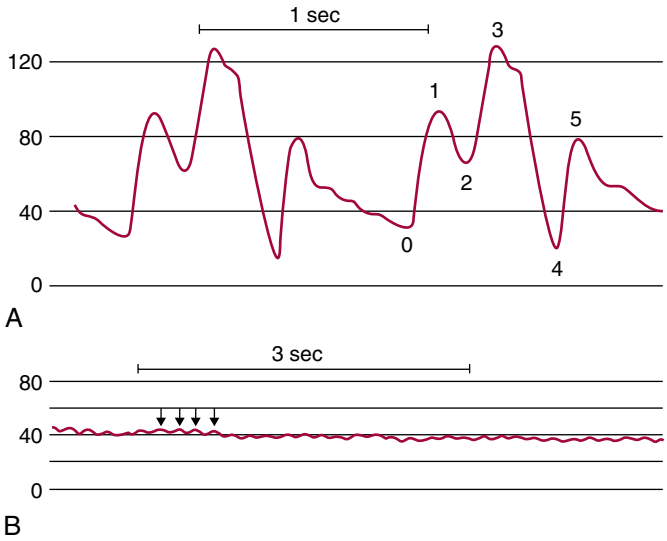


Figure 40-17 Unusual arterial pressure waveforms. **A,** *Intra-aortic balloon counterpulsation* with a 1:2 balloon-assist ratio produces a characteristic change in the arterial pressure waveform. Four cardiac cycles are shown, two with balloon assistance and two without. 0, Unassisted end-diastolic pressure; 1, unassisted systolic pressure; 2, dicrotic notch; 3, assisted or augmented diastolic pressure; 4, end-diastolic or presystolic dip; 5, assisted systolic pressure. Effective afterload reduction by the intra-aortic balloon is evidenced by the presystolic dip pressure (4) lower than the unassisted end-diastolic pressure (0) and the assisted systolic pressure peak (5) lower than the unassisted systolic pressure peak (1). **B,** Arterial pressure waveform during *cardiopulmonary bypass*. Small phasic pressure variations (*arrows*) result from the mechanical action of the bypass roller pump. The bypass pump flow rate may be estimated by measuring these pulsations. Nineteen pulsations are recorded in a 3-second time interval. In this case, the pump configured with ⅜-in tubing has an effective stroke volume of 27 mL. The pump flow rate may be calculated as follows: (19 pulsations/3 sec) × (1 pump revolution/two pulsations) × (27 mL/revolution) × (60 sec/min) = 5130 mL/min. This calculated pump flow rate should equal the flow rate displayed on the pump console (i.e., 5.2 L/min). *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Figs.20-3 and 19-8.)*

reveal changes in cardiac preload, the Δ Up portion of the arterial pressure trace may provide clues to the afterload dependence of the left ventricle.

As a dynamic indicator of cardiac preload, SPV and Δ Down provide valuable clinical information beyond that provided by static preload indicators such as CVP or PAWP. It appears that the magnitude of blood pressure variation accurately predicts patients who will subsequently respond to a volume challenge by increasing stroke volume and cardiac output. Using receiver-operator curve analysis, Tavernier and coworkers showed that when compared with PAWP or left ventricular end-diastolic area, Δ Down was a far better indicator of volume responsiveness.[79]

Another dynamic marker of volume responsiveness is *pulse pressure variation* (PPV), defined as the maximal difference in arterial pulse pressure measured over the course of the positive-pressure respiratory cycle divided by the average of the maximal and minimal pulse pressure[80,81] (Fig. 40-19). Normal PPV should not exceed 13%.[82] In addition to SPV and PPV, new pulse contour methods for measurement of cardiac output (see later) allow online measurement of variations in left ventricular stroke volume, so-called *stroke volume variation* (SVV). Like the other related dynamic indicators of volume responsiveness, normal SVV is approximately 10%, and greater variability accurately predicts a positive response to a fluid challenge.[83] Another approach to assessing fluid responsiveness has focused on the respiratory cycle–induced variation in the pulse plethysmogram, but this physiologic signal is even more subject to confounding influences than the arterial blood pressure waveform is.[82,84]

Despite rapidly accumulating evidence of the value of SPV and PPV and their related measures as accurate predictors of cardiac preload, they have not found widespread clinical adoption for a number of reasons. The original description of this method required transient interruption of mechanical ventilation to identify an apneic baseline for measurement of Δ Down and Δ Up.[75] Newer monitors use computerized algorithms to measure and display SPV or PPV continuously, but these automated measures are not yet routinely available in standard bedside monitors.[85,86]

A number of additional factors have precluded the wider application of SPV and PPV for monitoring volume responsiveness. The magnitude of blood pressure variation observed in any patient will be influenced by positive-pressure ventilation parameters, including tidal volume and peak inspiratory pressure. SPV and PPV cannot be used reliably in patients with cardiac arrhythmias or significant changes in chest wall or lung compliance. As noted earlier, respiratory cycle–induced variations in arterial pressure are not solely related to changes in left ventricular preload but depend in part on afterload influences. Although it is clear that the magnitude of SPV and PPV predict fluid responsiveness, precise threshold values remain uncertain, and the variety of techniques described have not been standardized.[83] Perhaps most important, all these measures have been validated only in mechanically ventilated patients and are not applicable to

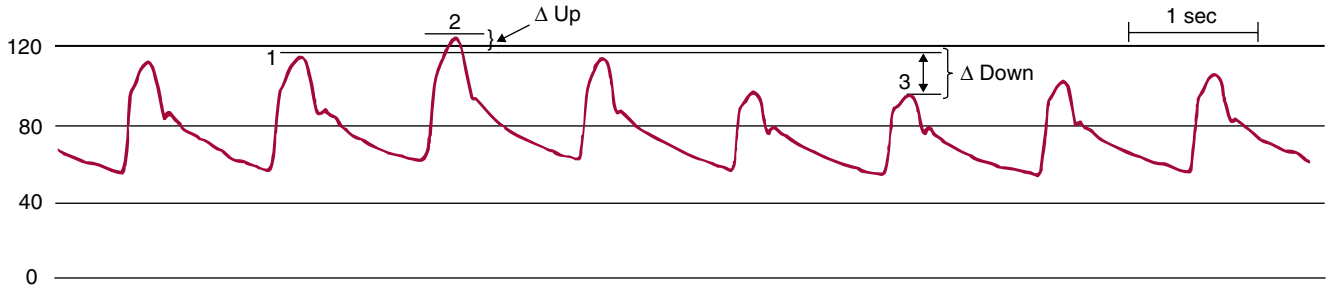
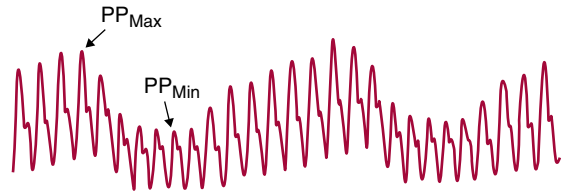


Figure 40-18 Systolic pressure variation. When compared with the systolic blood pressure recorded at alpha (1), a small increase occurs during positive-pressure inspiration (2, Δ Up), followed by a decrease (3, Δ Down). Normally, total systolic pressure variation does not exceed 10 mm Hg. In this instance, the large Δ Down indicates hypovolemia even though systolic arterial pressure and the heart rate are relatively normal. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 16-16.)*



Note: The arterial blood pressure tracing is not drawn to scale

$PP_{Max} = 150 - 70 = 80$
$PP_{Min} = 120 - 60 = 60$
$PPV = (PP_{Max} - PP_{Min})/([PP_{Max} + PP_{Min}]/2)$
$PPV = 80 - 60/([80 + 60]/2) = 29\%$

Figure 40-19 Pulse pressure variation. Pulse pressure variation (PPV) is calculated as the difference between the maximal (PP_{Max}) and minimal (PP_{Min}) pulse pressure values during one mechanical respiratory cycle, divided by the average of these two values. (Note that the arterial blood pressure trace is drawn for illustrative purposes and not to scale.)

spontaneously breathing subjects, thereby precluding their use in many anesthetized and critically ill patients.

Central Venous Pressure Monitoring

Indirect assessment of CVP through physical examination of the neck veins is a fundamental aspect of cardiovascular assessment, but one that has many shortcomings. The jugular veins may be impossible to identify in up to 20% of patients, and the bedside diagnosis of low, normal, or high CVP is often inaccurate, particularly in critically ill patients.[87,88] This problem is compounded in the perioperative period, when visualization of the neck veins is further obscured and abrupt changes, sometimes of great magnitude, are not uncommon. As a result, direct measurement of CVP is frequently necessary in hemodynamically unstable patients and those undergoing major operations.

Central Venous Cannulation

Cannulation of a large central vein is the standard clinical method for monitoring CVP and is also performed for a number of additional therapeutic interventions, such as providing secure vascular access for the administration of vasoactive drugs or to initiate rapid fluid resuscitation. Frequently, the central venous location is the only site available for intravenous access of any kind. Patients at risk for venous air emboli may have central venous catheters placed for aspiration of entrained air. In addition, central venous access is required to initiate transvenous cardiac pacing, temporary hemodialysis, or pulmonary artery catheterization for more comprehensive cardiac monitoring (Box 40-4).

The decision to perform central venous cannulation before or after induction of anesthesia is guided most often by individual patient and physician preferences or institutional practice. One should consider abandoning attempts at preoperative central venous cannulation in any patient who becomes overly sedated or uncooperative during the procedure and proceed with inducing anesthesia and obtaining secure control of the airway. At that point, further attempts at gaining central vascular access are appropriate.

Choosing the Catheter, Site, and Method of Central Venous Cannulation

Central venous catheters come in a variety of lengths, gauges, composition, and lumen number.[89,90] These characteristics vary according to the purpose of the catheterization, whether for CVP monitoring or other therapeutic indications and whether intended for short- or long-term use. This makes it critical for the physician to choose the best catheter for any given application. Seven-French, 20-cm multiport catheters that allow monitoring of CVP and infusion of drugs and fluids simultaneously are the most common.[91] It should be noted that rapid fluid resuscitation is more efficient with short, large-bore intravenous catheters inserted peripherally because the smaller diameter of each individual lumen and the overall catheter length increase resistance to flow significantly. For example, according to the manufacturer's product specifications, the maximal flow rate of the 16-gauge lumen of a standard 7-Fr, 20-cm central venous catheter is a quarter that of a 16-gauge, 3-cm intravenous catheter in a large peripheral vein.

A popular alternative method for multilumen central venous access uses a large introducer sheath with an integrated T-connector sidearm for multiple drug infusions combined with a single-lumen catheter inserted through the hemostasis valve for continuous CVP monitoring. Although use of these larger introducer sheaths is not free of complications, they do allow rapid placement of a pacing wire or pulmonary artery catheter (PAC) for more intensive monitoring should the need arise.

Selecting the best site for safe and effective central venous cannulation ultimately requires consideration of the indication for catheterization (pressure monitoring versus drug or fluid administration), the patient's underlying medical condition, the clinical setting, and the skill and experience of the physician performing the procedure. In patients with severe bleeding diatheses, it is best to choose a puncture site at which bleeding from the vein or adjacent artery is easily detected and controlled with

Box 40-4 Indications for Central Venous Cannulation

- Central venous pressure monitoring
- Pulmonary artery catheterization and monitoring
- Transvenous cardiac pacing
- Temporary hemodialysis
- Drug administration
  - Concentrated vasoactive drugs
  - Hyperalimentation
  - Chemotherapy
  - Agents irritating to peripheral veins
  - Prolonged antibiotic therapy (e.g., endocarditis)
- Rapid infusion of fluids (via large cannulas)
  - Trauma
  - Major surgery
- Aspiration of air emboli
- Inadequate peripheral intravenous access
- Sampling site for repeated blood testing

local compression. In such a patient, an internal or external jugular approach would be preferable to a subclavian site. Likewise, patients with severe emphysema or others who would be severely compromised by pneumothorax would be better candidates for internal jugular than subclavian cannulation because of the higher risk with the latter approach. If transvenous cardiac pacing is required in an emergency situation, catheterization of the right internal jugular vein is recommended because it provides the most direct route to the right ventricle. Trauma patients with their necks immobilized in a hard cervical collar are best resuscitated via a femoral or subclavian approach; the latter may be used even more safely if the risk of pneumothorax is obviated by prior placement of a thoracostomy tube. The physician must recognize that the length of catheter inserted to position the catheter tip properly in the superior vena cava will vary according to puncture site, being slightly (3 to 5 cm) greater when the left internal or external jugular veins are chosen versus the right internal jugular vein.[92] Finally, a physician's personal experience undoubtedly plays a significant role in determining the safest site for central venous cannulation, particularly when the procedure is performed under urgent or emergency circumstances.

Since its introduction into clinical practice in the late 1960s, percutaneous puncture of the right internal jugular vein has been the method preferred by anesthesiologists for central venous cannulation.[93-95] Reasons for this preference include consistent, predictable anatomic location of the internal jugular vein, readily identifiable and palpable surface landmarks, and a short, straight course to the superior vena cava. An internal jugular vein catheter is highly accessible during most surgical procedures and has a rate of successful placement of approximately 90% to 99%.[94,96]

Right Internal Jugular Vein Cannulation

Many different techniques for internal jugular vein cannulation have been described, although the "central" approach described by Daily and colleagues is among the most popular and is described with minor modifications here.[97] Careful positioning will make the patient comfortable, improve identification of surface landmarks, and increase the likelihood of success. The patient is placed in the supine position with the head turned slightly to the left to expose the right side of the neck and keep the chin from interfering with the procedure. Pillows that cause the neck to be flexed should be removed, but forceful neck extension or extreme leftward rotation of the head should be avoided because this alters cervical vascular anatomy and may cause the internal jugular vein to overlie the carotid artery, thereby increasing the risk for carotid arterial puncture.[98] Anatomic landmarks, including the sternal notch, clavicle, and sternocleidomastoid muscle, should be identified before skin preparation and draping for the sterile procedure because these landmarks are more easily appreciated before they are covered by the sterile drape (Fig. 40-20). The patient should be calm, sedated, receiving supplemental oxygen if necessary, and monitored with an ECG, blood pres-

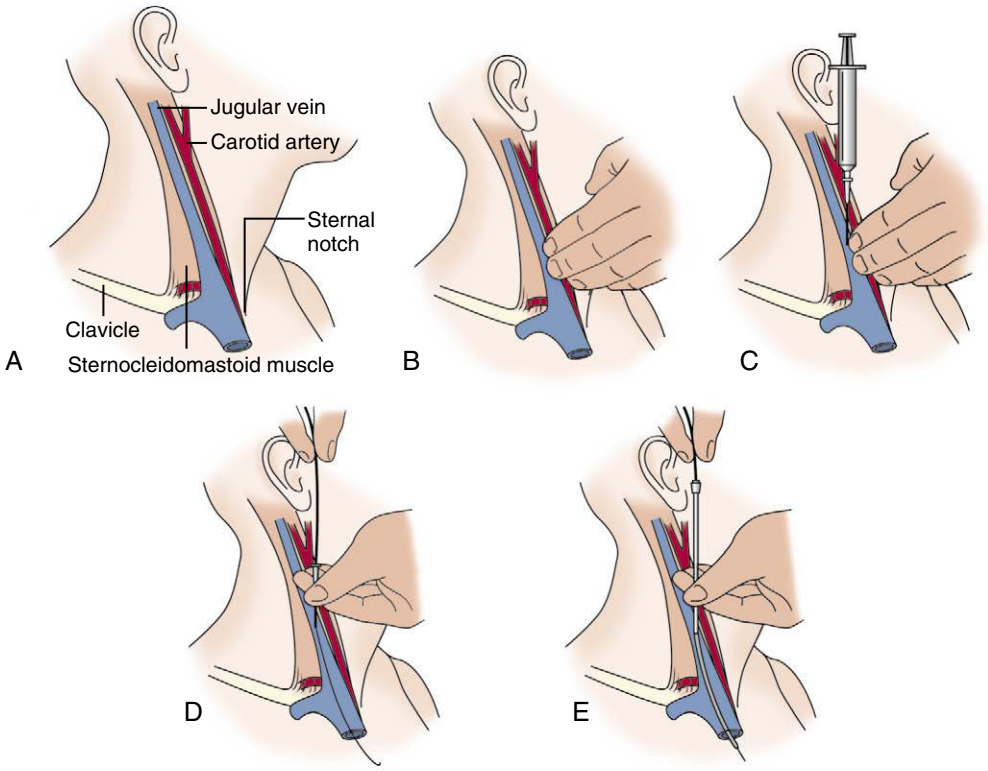


Figure 40-20 Technique for central venous cannulation of the right internal jugular vein. **A,** Important surface landmarks are identified. **B,** The course of the internal carotid artery is palpated. **C,** The internal jugular vein is punctured at the apex of the triangle formed by the two heads of the sternocleidomastoid muscle, with the needle tip directed toward the ipsilateral nipple. **D,** A guidewire is introduced through the thin-walled needle into the vein. **E,** The central venous cannula is inserted over the guidewire while making sure that the proximal end of the guidewire protrudes beyond the catheter and is controlled by the operator.

sure monitor, and pulse oximeter. Because of the frequency and serious morbidity of infectious complications from central venous catheterization, strict aseptic technique is required. Formal guidelines to reduce these complications have been published by the Centers for Disease Control and Prevention and provide prudent recommendations that should be followed during all catheterizations.[99]

Good aseptic technique begins with hand washing before the procedure. A mask, cap, sterile gloves, and gown should always be used, regardless of the procedural setting. The skin is cleaned widely from earlobe to clavicle to sternal notch, preferably with 2% chlorhexidine, an agent that has been shown to be superior to the more traditional 10% povidone-iodine.[99,100] Aseptic preparation is completed with the application of a large sterile drape that provides maximal barrier precautions, preferably a full-body drape.

Under these sterile conditions, the relevant anatomy is again identified, particularly the course of the carotid artery in the neck. The internal jugular vein lies in the groove between the sternal and clavicular heads of the sternocleidomastoid muscle, lateral and slightly anterior to the carotid artery in most cases. In many patients, venous pulsations from the internal jugular vein are observed directly within this groove and further identify the approximate site for skin puncture. An assistant then places the patient in a slight head-down (Trendelenburg) position to increase jugular vein diameter in the neck. This step may be omitted in a hypervolemic, dyspneic patient. The intended skin is anesthetized by subcutaneous infiltration of a local anesthetic solution (typically 1% lidocaine) with a 25-gauge needle if the patient is awake. Venipuncture then proceeds with a 22-gauge, 1½-inch (3.8-cm) finder needle mounted on a 5-mL syringe (see Fig. 40-20). The needle is inserted at the apex of the triangle formed by the two heads of the sternocleidomastoid muscle, at an angle of approximately 30 degrees from the plane of the skin, and directed toward the ipsilateral nipple. Gentle aspiration will identify the jugular vein when dark venous blood enters the syringe. Although use of the small finder needle is an extra step in this procedure, it presumably increases the margin of safety because unintentional puncture of the carotid artery with this small needle is less likely to result in significant bleeding and hematoma formation.[101] If blood is not aspirated as the finder needle is advanced and then withdrawn, additional needle passes may locate the internal jugular vein by fanning laterally in a small arc from the point where the needle enters the skin. If the vein is not located after several needle passes, the finder needle is withdrawn completely and checked for patency, the anatomy is reassessed, and the puncture may then proceed with the needle entering the skin several millimeters closer to the palpated carotid pulse but still directed in a sagittal or slightly lateral direction. One should resist the temptation to explore with a medial or leftward direction of the finder needle when this technique is being used because such exploration will increase the likelihood of unintentional puncture of the carotid artery.

After the internal jugular vein is located with the finder needle, the needle is gently withdrawn while the skin and surface anatomy remain fixed by the left hand. The vein is then punctured with an 18-gauge, 2½-inch (6.4-cm), thin-walled needle attached to a 5-mL syringe along the same track used with the finder needle while keeping in mind the three-dimensional location and depth of the identified internal jugular vein. It is not uncommon for the lumen of the jugular vein to be compressed as this larger thin-walled needle is advanced and both the front and back walls pierced almost simultaneously.[102,103] Consequently, the thin-walled needle should be inserted only slightly beyond the expected depth of the vein and then slowly withdrawn while maintaining gentle aspiration on the syringe. As such, venous entry of the needle is recognized during needle withdrawal by the sudden return of free-flowing venous blood.

Many individuals choose to substitute a 2-inch, 18-gauge intravenous catheter for the 18-gauge thin-walled needle for venipuncture. In this method, the catheter is advanced over the needle and into the vein immediately after blood is seen returning into the barrel of the syringe. Although this catheter can be advanced completely into the vein, it may be kinked or occluded, thereby making it more difficult to differentiate pulsatile arterial blood flow from unintentional arterial puncture. It is vital to confirm the intravenous location of this catheter. The color of the aspirated blood is examined, and it may be compared with a simultaneously obtained arterial sample, although this technique is not completely reliable.[104] A safer method is to manually transduce the pressure by attaching sterile intravenous extension tubing to the catheter and observing the fluid column.[104,105] When using this technique, it is important to allow the blood to fill more than 30 cm of the tubing and then raise it vertically and observe a fall in the column of blood. This excludes the possibility of a kinked catheter or the catheter tip abutting the arterial wall, either of which may mask an arterial puncture. Continuous pressure transduction of the thin-walled needle has been advocated as an even better method of detecting arterial puncture and preventing arterial cannulation.[96,106] Although none of these measures are foolproof, they may provide a greater margin of safety and reduce the rate of serious complications resulting from unintentional cannulation of the carotid artery with a large-bore catheter.

Once successful venipuncture is confirmed, the hub of the thin-walled needle or catheter is fixed with the fingers of the left hand, the syringe is detached, and venous blood should be observed to drip from the needle hub. A guidewire (usually 0.032 or 0.035 inch) with either a J-shaped tip or a soft, flexible straight end is inserted through the needle. The wire should advance easily into the vein with little resistance. The ECG is monitored continuously to detect arrhythmias, which are common if the wire tip is inserted too far and contacts the wall of the right atrium or ventricle.[107] From this point in the procedure, it is critical that the clinician maintain control over the guidewire and monitor its depth of insertion and continued sterility.

The puncture site is enlarged with a No. 11 scalpel blade to accommodate the greater size required for the intended catheter. A firm, tapered-tip vessel dilator may be inserted to dilate the subcutaneous tissues around the guidewire and allow a larger catheter to pass smoothly without damage to the tip of the catheter. (When an introducer sheath is to be used, the dilator and sheath form a single unit, and this separate dilation step is usually omitted.) The vessel dilator is removed, and the central venous catheter is inserted over the guidewire while countertraction on the skin is maintained. Again, the clinician must be attentive to the guidewire and ensure that a sufficient length protrudes from the catheter hub before advancing the catheter into the vein so that the wire may be extracted easily. The catheter is inserted to an appropriate depth that will place the tip in the superior vena cava, above its junction with the right atrium. This depth is typically 15 to 18 cm if the catheter is placed via the technique described. The guidewire is then withdrawn, the catheter is

attached by a Luer-Lok connector to monitoring or infusion tubing and secured in place, and sterile dressing is applied. Antibiotic ointment should not be applied to the insertion site because it may increase the risk of catheter colonization with multidrug-resistant bacteria or *Candida*.[108,109]

In patients at risk for major intraoperative blood loss and hemodynamic instability, two central venous catheters may frequently be required. Some physicians advocate double cannulation of the same central vein (usually the right internal jugular) with two catheters in close proximity. With this technique, a guidewire is introduced into the internal jugular vein by the standard method. Then, before catheter placement, a second jugular venipuncture is performed, approximately 1 to 2 cm cephalad or caudad, and a second guidewire is introduced into the vein. Placing appropriate catheters over each guidewire and securing them at the skin in the normal fashion complete the procedure. Although limited evidence suggests that the incidence of major complications with this double-cannulation technique is no greater than with single central venous catheterization, it is not clear whether this approach is safer than central venous cannulation in two separate central veins.[110] Serious complications of the double-cannulation technique include facial vein avulsion, catheter entanglement, and catheter fracture.[111,112] Double central venous cannulation must be reserved for patients whose needs for venous access and hemodynamic monitoring cannot be met through single cannulation.

Alternative Central Venous Cannulation Sites

Left Internal Jugular Vein

Cannulation of the left internal jugular vein may be accomplished with a technique similar to the one described earlier, although several anatomic details make the left side less attractive than the right. The cupola of the pleura is higher on the left, thereby theoretically increasing the risk for pneumothorax. The thoracic duct may be injured during the procedure as it enters the venous system at the junction of the left internal jugular and subclavian veins.[113] The left internal jugular vein is often smaller than the right and demonstrates a greater degree of overlap of the adjacent carotid artery during head rotation.[114] Catheters inserted from the left side of the patient must traverse the innominate (i.e., left brachiocephalic) vein and enter the superior vena cava perpendicularly, and their distal tips may impinge on the right lateral wall of the superior vena cava and thereby increase the potential for vascular injury. (This anatomic disadvantage pertains to all left-sided catheterization sites and highlights the need for radiographic confirmation of proper catheter location.) Furthermore, there is less familiarity with the technique simply because clinicians cannulate the left internal jugular vein much less often, a situation that results in more adverse events and morbidity.[98,115]

Subclavian Vein

The subclavian vein is an important site for central venous cannulation and is particularly popular among surgeons and other physicians who place central venous catheters for emergency volume resuscitation and long-term intravenous therapy or dialysis rather than for shorter-term monitoring purposes.[116,117] Advantages of subclavian venous cannulation include a lower risk of infection than with internal jugular or femoral sites, ease of insertion in trauma patients who may be immobilized in a cervical collar, and increased patient comfort, especially for long-term intravenous therapy such as hyperalimentation and chemotherapy.[99,118]

For subclavian central access, the patient is placed in a slight head-down position with the arms fully adducted and the head turned slightly away. A small roll is placed between the shoulder blades to expose the infraclavicular area fully. The skin is punctured 2 to 3 cm caudad to the midpoint of the clavicle, far enough from its inferior edge to avoid downward angulation of the needle as it is inserted just beneath the posterior surface of the clavicle. The needle tip is directed toward the suprasternal notch, which may be constantly identified by the fingers of the operator's other hand. Again, the needle is always advanced with gentle negative pressure exerted against the plunger of the syringe. If the subclavian vein is not entered in the first pass, the needle may be withdrawn and a second pass attempted in a slightly more cephalad direction while ensuring that the needle continues to hug the undersurface of the clavicle as it is advanced and avoiding the tendency to increase the downward angulation of the needle. Once the subclavian vein is punctured, catheterization proceeds in a manner similar to that described for jugular vein catheterization.

Several important technical details must be followed to ensure successful subclavian vein cannulation and avoid complications, particularly pneumothorax. Venipuncture generally proceeds without first identifying the vein with a smaller-gauge finder needle because the depth of the subclavian vein is often beyond the reach of the standard 1½-inch, 22-gauge finder needle. A thin-walled needle is preferred over an 18-gauge catheter/needle assembly because the catheter would be very easily kinked as it courses under the clavicle, thereby precluding both confirmation of venous puncture and passage of the guidewire. Of greatest importance, however, the clinician should resist the temptation to make multiple needle passes if the subclavian vein is not punctured on the second or third attempt. It is clear that complications from this procedure, particularly the incidence of pneumothorax and subclavian artery puncture, are directly related to the number of attempts.[117,119] Bilateral attempts at subclavian venipuncture are highly discouraged because of the serious morbidity of bilateral pneumothorax and the difficulty detecting and treating injury to the subclavian artery. Perhaps to an even greater degree than with internal jugular vein cannulation, the safety of subclavian venous line placement rests in the experience of the operator. In more practiced hands, the incidence of complications should be low, with pneumothorax developing in less than 2% and arterial puncture in less than 5% of cases.[117,119]

External Jugular Vein

Both the right and left external jugular veins provide a safe, albeit somewhat problematic alternative to internal jugular or subclavian vein cannulation. Because the external jugular veins are superficial, they allow central venous cannulation with essentially no risk of pneumothorax or unintended arterial puncture. In most instances, it is best to use an 18-gauge catheter rather than the thin-walled needle to introduce the guidewire because of the tortuous course of the external jugular vein and the frequent need to manipulate the guidewire repeatedly to guide it into the superior vena cava. A J-tipped guidewire should always be used because it may be advanced under the clavicle and into the central circulation more successfully than a straight-tipped wire.[120,121] When the guidewire does not advance as desired and appears to be moving peripherally into the subclavian vein, abducting the

ipsilateral shoulder beyond 90 degrees before advancing the wire may facilitate central venous passage. Alternatively, the patient's ipsilateral arm is placed at the side and an assistant applies mild caudad traction on the shoulder to straighten the course of the external jugular vein while the wire is advanced. Essentially the only factors that preclude use of the external jugular veins for CVP monitoring are an inability to visualize and cannulate the vessel in the neck and to advance a catheter into the central circulation. Care should be taken to not use excessive force when advancing catheters and stiff dilators into the external jugular vein because the sharp angle that this vein makes with the subclavian vein may increase the risk for venous injury. Unfortunately, problems with successful placement occur in approximately 20% of patients, thus limiting more widespread application of this technique.[104,122]

Femoral Vein

Femoral vein cannulation provides a useful site for CVP monitoring when the more common jugular and subclavian sites are not accessible, as is commonly the case in patients with burns or trauma, during surgical procedures that involve the head, neck, and upper part of the thorax, or during cardiopulmonary resuscitation. Use of the femoral vein obviates many of the common complications of central venous catheterization, specifically pneumothorax, but it does carry the risk of femoral artery and, more rarely, femoral nerve injury. Femoral venipuncture is performed below the inguinal ligament just medial to the palpated femoral arterial pulse in a manner similar to that used for femoral artery cannulation. Either a long (40 to 70 cm) catheter is positioned, under ECG or fluoroscopic guidance, in the inferior vena cava close to the cavoatrial junction or a shorter (15 to 20 cm) catheter is inserted from the femoral vein into the common iliac vein.[123,124] Both techniques provide intra-abdominal venous pressure measurements that appear to agree closely with pressures measured in the superior vena cava in mechanically ventilated, critically ill adults.[123,124] It is not clear whether this correlation remains valid in patients who are breathing spontaneously, those with elevated intra-abdominal or intrathoracic pressure, or those not in the supine position. Disadvantages of the femoral venous route include an increased risk of thromboembolic and infectious complications, as well as vascular injury, which may lead to intra-abdominal or retroperitoneal hemorrhage.[125] Moreover, catheters inserted at the femoral site generally preclude ambulation during recovery.

Axillary and Other Peripheral Veins

In patients with extensive, severe burn injuries, the axillary region is often spared and provides a useful site for either arterial or venous pressure monitoring.[126] Standard 20-cm CVP catheters placed in the axillary veins, approximately 1 cm medial to the palpated axillary artery, allow measurement of pressure from the superior vena cava. Even more distal pressures measured from peripheral veins in the hand and forearm may provide a reasonably accurate estimate of CVP in selected surgical patients.[127] Modified volumetric infusion pumps can even measure in-line peripheral venous pressure without the need for additional transducers and monitoring equipment.[128] Although this method of measuring CVP incurs no risk beyond that associated with placing any standard peripheral intravenous catheter, it has not been validated widely and cannot replace central venous cannulation in most circumstances.

Peripherally inserted central venous catheters (*PICCs*) have become a popular alternative to centrally inserted catheters in patients requiring long-term intravenous therapy. Advantages of a PICC include bedside placement under local anesthesia, an extremely low risk of major insertion-related complications, and safe placement by nonphysicians (i.e., registered nurses and physician assistants). This technique may be particularly cost-effective because it eliminates the need for a minor operative procedure in patients who require a Hickman or Broviac central venous catheter.[129] Venous access for a PICC is obtained through an antecubital vein, preferably the basilic vein, which is generally more successfully catheterized than the cephalic vein because of its more linear course. Early reports described only modest success positioning PICCs in an appropriate central location, as well as considerable risk for venous thrombosis, but improvements in catheter design and insertion technique now result in successful placement and few complications in most patients.[129-131] Most PICCs are placed for long-term therapeutic indications (chemotherapy or parenteral nutrition) and use very flexible, nonthrombogenic silicone catheters. Less commonly, a standard polyurethane 40-cm intravenous catheter is inserted peripherally and advanced to a central location for short-term infusion of vasoactive drugs or monitoring of CVP or pulmonary artery pressure (PAP). CVP recorded via PICCs is slightly higher than the pressure measured with centrally inserted catheters, but this difference is clinically insignificant.[132] When these standard long venous catheters are inserted from an antecubital vein, the catheter tip may advance into the heart as the arm is abducted, thereby increasing the risk for cardiac perforation or arrhythmias.[133,134] Whenever a PICC line is in place, the clinician should exercise caution when placing any additional central venous catheters because of the risk of shearing the PICC line within the central venous circulation.

Ultrasound-Guided Central Venous Cannulation

First described in 1984, ultrasound-guided placement of central venous catheters has proved beneficial in most settings, including the intensive care unit and the operating room.[135,136] Available evidence suggests that fewer needle passes are required for successful venous cannulation when two-dimensional ultrasound guidance is used. In addition, most investigators have shown that ultrasound guidance reduces the time required for catheterization, increases overall success rates, and results in fewer complications.[137,138] The benefit is most evident when the internal jugular vein rather than the subclavian or femoral vein is cannulated, when inexperienced rather than experienced operators perform the procedure, and for adult rather than pediatric patients. Based on this evidence, the Agency for Healthcare Research and Quality has listed the use of real-time ultrasound guidance for central venous catheterization as 1 of 11 practices to improve health care.[139] Nonetheless, the use of ultrasound for placement of central venous catheters continues to be low. Recent surveys show that both house staff physicians at one academic tertiary care center and a group of practicing American anesthesiologists routinely use ultrasound for central venous cannulation less than 15% of the time.[93,140] Some aspects of the use of ultrasound for placement of all central venous access remain controversial. It is still largely unknown whether the additional equipment and manipulation associated with real-time ultrasound guidance may increase the rate of catheter-related infections or whether the increased dependence on this technology by

trainees will prove detrimental in clinical settings in which it may be unavailable.

Ultrasound guidance can be used in several different ways during central venous catheterization. For example, Doppler ultrasound transforms the sound waves reflected from the moving red blood cells into an amplified audio signal that can be used to locate the artery and vein before or during cannulation.[135] Two-dimensional ultrasound can be used to confirm vessel location and patency and mark the skin, and then the catheterization can proceed in the usual fashion. Alternatively, the technology can be incorporated into the procedure itself to give real-time visualization of vessel cannulation, a method that is coming to replace the more limited, "one-look" technique.[141]

Real-time, two-dimensional ultrasound guidance for internal jugular vein cannulation requires a 7.5- to 10-MHz transducer protected by a sterile sheath. The operator holds the ultrasound probe in the nondominant hand to obtain a view of the target vessel. The vein and artery appear as two circular black structures on the ultrasound image. The vein is identified by anatomic location and by its compressibility. The artery appears mildly pulsatile (Fig. 40-21). When using ultrasound guidance, either transverse (short axis) or longitudinal (long axis) views are adequate. In general, the transverse view is easier to learn and allows simultaneous identification of the artery and vein, whereas the longitudinal view allows visualization of the needle tip at all times, which may reduce perforation of the posterior wall of the vein.[142] After positioning the vein in the center of the ultrasound screen, the vessel is punctured under direct vision with the 18-gauge needle of choice. The technique then proceeds as in the standard landmark technique described earlier, but with confirmation of the intravenous location of the guidewire with a longitudinal view before proceeding with dilation of the vessel.

Ultrasound imaging of the subclavian vessels is more difficult and often hampered by the patient's body habitus and probe configuration. When using ultrasound to guide cannulation of the subclavian vein, the transducer is placed in the infraclavicular groove at the level of the middle or lateral third of the clavicle, and the axillary vein and artery are imaged as they exit the bony canal formed by the clavicle and the first rib.[143] The artery is most commonly cephalad to the vein and noncompressible, and it does not vary in size with respiration. Either a transverse or longitudinal view can be obtained and used to guide needle insertion.[144] Another approach has been described in children in which the probe is placed in the supraclavicular space to obtain a longitudinal view of the subclavian vein while cannulation is performed via the usual infraclavicular route.[145]

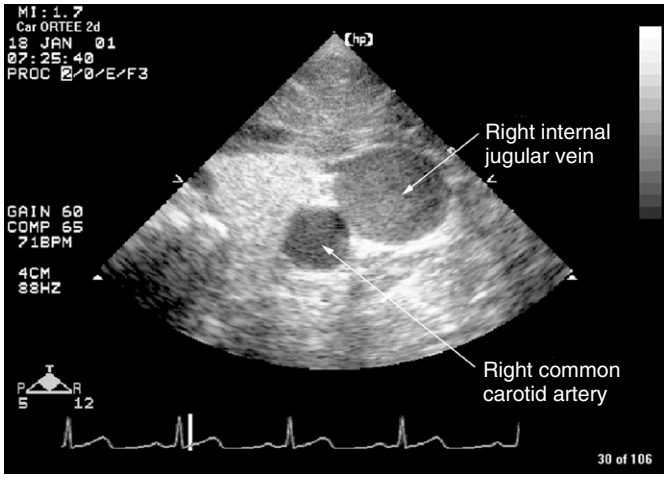


Figure 40-21 Transverse-plane ultrasound image showing the right internal jugular vein and its typical anatomic position anterior and lateral to the right common carotid artery.

Confirming Catheter Position

Central venous catheters placed in the operating room are commonly used for the duration of the surgical procedure without radiologic confirmation of the location of the catheter tip. Before monitoring or infusion commences, aspiration of blood should confirm the intravenous location of each lumen of a multilumen catheter and remove any residual air from the catheter-tubing system. After surgery, however, the position of the catheter tip must be confirmed radiographically. Catheter tips located within the heart or below the pericardial reflection of the superior vena cava increase the risk for cardiac perforation and fatal cardiac tamponade. Ideally, the catheter tip should lie within the superior vena cava, parallel to the vessel walls, and be positioned *below* the inferior border of the clavicles and *above* the level of the third rib, the T4 to T5 interspace, the azygos vein, the tracheal carina, or the takeoff of the right mainstem bronchus.[146,147] Using fresh human cadavers, Albrecht and colleagues recently confirmed that the tracheal carina was always above the pericardial reflection on the superior vena cava, thus suggesting that catheter tip should always be located superior to this radiographic landmark.[148]

Complications of Central Venous Pressure Monitoring

Complications of central venous cannulation are increasingly being recognized as major sources of morbidity, with more than 15% of patients experiencing some sort of related adverse event.[125] Although serious immediate complications are infrequent when these procedures are performed by well-trained, experienced clinicians, infectious complications are common, and the use of CVP catheters continues to result in significant morbidity and mortality. Complications are often divided into mechanical, thromboembolic, and infectious causes (Box 40-5).

Mechanical Complications of Central Venous Catheterization

The incidence of complications depends on a number of factors, including the catheter insertion site and the patient's medical condition. Large retrospective and observational studies provide the best estimates of the incidence and frequency of complications. In general, *unintended arterial puncture* is the most common acute mechanical complication, with an incidence ranging from 1.9% to 15%.[149] Many of these injuries result in localized hematoma formation, but on rare occasion even small-gauge needle punctures may lead to serious complications such as arterial thromboembolism.[150]

If arterial puncture with a small needle occurs during central venous cannulation, the needle should be removed and external pressure applied for several minutes to prevent hematoma formation. When unintentional carotid artery cannulation occurs, it can usually be managed conservatively by removing the catheter, applying local compression to the puncture site, and monitor-

Box 40-5 Complications of Central Venous Pressure Monitoring

- Mechanical
  - Vascular injury
    - Arterial
    - Venous
    - Hemothorax
    - Cardiac tamponade
  - Respiratory compromise
    - Airway compression from hematoma
    - Tracheal, laryngeal injury
    - Pneumothorax
  - Nerve injury
  - Arrhythmias
  - Subcutaneous/mediastinal emphysema
- Thromboembolic
  - Venous thrombosis
  - Pulmonary embolism
  - Arterial thrombosis and embolism (air, clot)
  - Catheter or guidewire embolism
- Infectious
  - Insertion site infection
  - Catheter infection
  - Bloodstream infection
  - Endocarditis
- Misinterpretation of data
- Misuse of equipment

ing the patient's airway and neurologic status. A vascular surgeon should be consulted promptly to help manage the complication. Only under exceptional circumstances should the catheter be allowed to remain in the vessel because of a high risk for arteritis, thrombus formation, and cerebral embolization.[151]

Vascular injuries from central venous catheterization have a range of clinical consequences. The most common minor complications are localized hematoma or injury to the venous valves.[152] More serious complications include perforation into the pleural space or mediastinum resulting in hydrothorax, hemothorax, hydromediastinum, hemomediastinum, chylothorax, or any combination of these sequelae.[113,153-156] Other catastrophic and thankfully rare vascular injuries have been reported, including aortic perforation and avulsion of the facial vein.[111,157] Delayed vascular complications after central venous catheterization are uncommon but should be considered consequences of this procedure. A number of these delayed complications have been described in the literature, including aortoatrial fistula, venobronchial fistula, carotid artery–internal jugular vein fistula, and pseudoaneurysm formation.[158-161]

The most important life-threatening vascular complication of central venous catheterization is *cardiac tamponade* resulting from perforation of the intrapericardial superior vena cava, right atrium, or right ventricle and subsequent hemopericardium or unintentional pericardial instillation of intravenous fluid.[162] This injury was the second most common complication related to central venous catheters in an analysis of the American Society of Anesthesiologists Closed Claims Project in 2004.[163] Cardiac tamponade resulted in death in 81% of cases in this report and often had a delayed manifestation (1 to 5 days), thus indicating that this complication is related to catheter maintenance and use more often than to the vascular access procedure itself. Most reports document the avoidable nature of this catastrophic event and highlight that patients are predisposed to this complication when central venous catheter tips are malpositioned within the heart chambers or abutting the wall of the superior vena cava at a steep angle. This latter position can be recognized radiographically as a gentle curvature of the catheter tip within the superior vena cava.[164] These observations emphasize that objective confirmation of proper catheter tip location is mandatory, regardless of whether the catheter is inserted from a central or peripheral site. In fact, many early reports of catheter-related cardiovascular perforation suggested that peripheral catheters may be associated with an unusually high risk for this complication because arm abduction may cause the catheter tip to advance into a dangerous location within the heart.[133,165] When cardiac tamponade is caused by catheter-induced cardiac perforation, symptoms develop suddenly, so a high index of suspicion is required if severe hypotension occurs in any patient with a central venous catheter in place. Cardiac arrhythmias may provide an early clue to intracardiac location of the catheter tip.[134] Occasionally, both posteroanterior and lateral chest radiographs, as well as injection of radiopaque contrast material, are required to locate the catheter tip precisely.[166]

Pneumothorax is often cited as the most common complication of subclavian vein cannulation, although it appears that unintended arterial puncture is actually more frequent.[46,119] Mansfield and coauthors reported a 1.5% incidence of pneumothorax and a 3.7% incidence of arterial puncture in 821 patients who underwent attempted subclavian vein cannulation.[119] Pneumothorax is even less frequent with the internal jugular approach. Shah and coworkers reported a 0.5% incidence of pneumothorax in their series of nearly 6000 internal jugular catheterizations.[149] This estimate is most likely high because these patients had undergone sternotomy for cardiac surgery, a procedure that may have been responsible for the pneumothorax in many cases. Small pneumothoraces may be managed conservatively, whereas tube thoracostomy is the best treatment for larger air collections or pneumothorax in patients receiving positive-pressure mechanical ventilation or scheduled for major surgery. The physician must always be prepared for the possibility of tension pneumothorax and its adverse hemodynamic sequelae. In addition to pneumothorax, other respiratory tract injuries have been reported after central venous catheterization, including subcutaneous and mediastinal emphysema, tracheal perforation, and rupture of an endotracheal tube cuff.[167]

Nerve injury is another potential complication of central venous cannulation. Damage may occur to the brachial plexus, stellate ganglion, phrenic nerve, or vocal cords.[168,169] In addition, chronic pain syndromes have been attributed to this procedure.[170]

Thromboembolic Complications of Central Venous Catheterization

Catheter-related thrombosis varies according to the site of central venous catheterization and occurs in as many as 21.5% of patients with femoral vein catheters and 1.9% of those with subclavian vein catheters.[118] Catheters that are positioned low in the right atrium may be more prone to thrombus formation, possibly because of mechanical irritation of the right atrial endocardium

by the catheter.[171] Thrombi that form at the catheter tip or adhere to the endocardium have the potential to become a nidus for infection, cause superior vena cava syndrome, or embolize into the pulmonary circulation.[172,173] Occasionally, surgical removal is required.[174]

In addition to thromboembolism, other reported embolic complications of central venous catheterization include embolism of portions of the catheter or guidewire and air embolism.[175,176] Almost invariably, these problems are the result of misuse of equipment, thus highlighting the need for proper education and training of nurses and physicians responsible for the use of these devices.

Infectious Complications of Central Venous Catheterization

By far the most common major late complication of central venous cannulation is *infection*. Bloodstream infections occur in approximately 5% of patients with standard central venous catheters and thus lead to an estimated 150,000 to 250,000 cases of catheter-related bacteremia or fungemia annually.[99,177] Given that the crude mortality of patients with nosocomial bloodstream infections is approximately 35% and the cost of these infections can exceed $50,000 per episode, even basic strategies to reduce this complication appear to be both cost-effective and lifesaving.[177,178]

As previously noted, the starting point for prevention of infection is meticulous attention to aseptic technique.[179] When more long-term central venous access is anticipated, the subclavian site is preferred because use of the jugular or femoral veins carries a higher risk for infection.[118,180] Multilumen catheters may carry a higher risk for infection than single-lumen catheters, although the added clinical functionality of such catheters often mandates their use.[99,125] Catheters are made from materials such as silicone, polyvinyl chloride, Teflon, and polyurethane. Furthermore, catheters of the same material may be manufactured differently, which influences their surfaces and the frequency of bacterial adherence to the surface.[181] Heparin-bonded central venous catheters have been shown to reduce the incidence of catheter-related thrombosis and infection in children and adults.[182] Incorporation of antimicrobial treatments onto the catheter surface, such as combinations of chlorhexidine and silver sulfadiazine or monocycline and rifampin, have been shown to reduce rates of catheter colonization and bloodstream infection.[177,183] The added expense has prevented more widespread adoption of these catheters, although an analysis has suggested their cost-effectiveness in settings in which the rate of catheter-related infection remains high (>3.3 per 1000 catheter-days).[184] The use of catheters with a silver-impregnated subcutaneous cuff has not been shown to be beneficial.[185] A chlorhexidine gluconate–impregnated sponge dressing has been shown to reduce catheter colonization in infants and children but does not reduce the rate of catheter-associated bloodstream infections.[186,187] Current guidelines from the Centers for Disease Control and Prevention do not support routine catheter site changes or scheduled changes over a guidewire and instead provide other detailed recommendations for catheter management to reduce the risk for infectious complications.[99]

Other Complications of Central Venous Catheterization

Miscellaneous other adverse sequelae of central venous cannulation have been reported (see Box 40-5), and although their incidence is not clearly known, most appear to be uncommon. All physicians performing these procedures should be familiar with them, particularly since many of these complications are related to *operator error*.[46,188]

Use of *guidewires*, *vessel dilators*, and *large-bore catheters* carries certain additional risks that mandate meticulous attention to technique. The proximal tip of the guidewire must remain under the physician's control at all times to avoid inserting the wire too far into the heart and thus causing arrhythmias or potentially losing the guidewire within the circulation.[175,189] By design, vessel dilators are stiffer than the catheters and may cause significant trauma if inserted forcefully or farther than necessary to dilate the subcutaneous tissue tract from skin to vein.[190] Large-bore introducer sheaths and multilumen catheters have become popular because of their clinical utility, yet their size may increase the risk for cannulation-associated trauma, hemorrhage from unrecognized line disconnections, and major venous air embolism. Not only may air be entrained during initial cannulation, but improperly connected large-bore cannulas may pose an additional risk because of the large site for entry of air directly into the central venous circulation.[176,191]

Although many complications of CVP monitoring relate to equipment misuse, the frequency of complications caused by misinterpretation of data remains unknown. It is extremely likely, however, that clinicians misinterpret CVP measurements and have suboptimal understanding of CVP monitoring, just as has been demonstrated repeatedly for PAP monitoring (see discussion later). Safe and effective use of CVP monitoring requires a detailed understanding of cardiovascular physiology, normal CVP waveforms, and common pathologic abnormalities in these measurements.

Physiologic Considerations for Central Venous Pressure Monitoring: Diastolic Pressure-Volume Relationships and Transmural Pressure

Cardiac filling pressures are monitored to estimate cardiac filling volumes, which in turn determine the stroke output of the left and right ventricles. According to the Frank-Starling principle, the force of cardiac contraction is directly proportional to end-diastolic muscle fiber length at any given level of intrinsic contractility or inotropy. This muscle fiber length or preload is proportional to end-diastolic chamber volume. Even though it would be ideal to monitor cardiac chamber volumes continuously in critically ill patients, this goal remains elusive in clinical practice.

When a cardiac filling pressure is measured as a surrogate for estimating cardiac volume, one must not assume that these two variables always change in direct proportion or even in the same direction. In fact, the diastolic pressure-volume relationship in cardiac muscle is not linear, but rather curvilinear, with a progressively steeper slope at higher volumes (Fig. 40-22).[192,193] This diastolic pressure-volume relationship is one limb of a pressure-volume loop that describes the relationship between pressure and volume for the left or right ventricle during an entire cardiac cycle. When a ventricle is operating along the flat portion of its diastolic filling curve, a significant increase in filling volume or preload results in a small increase in filling pressure. In contrast,

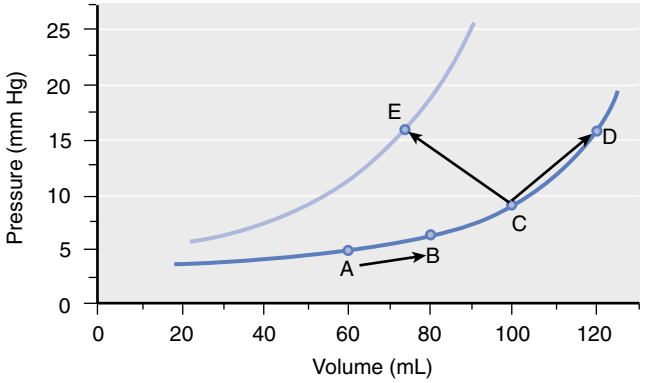


Figure 40-22 Ventricular diastolic pressure-volume relationship. Along the flat portion of the curve, a 20-mL increase in ventricular volume causes a small increase in ventricular pressure (A to B). In contrast, the same increase in volume along the steep portion of the ventricular filling curve causes a marked increase in filling pressure (C to D). Another problem associated with the use of filling pressure as a surrogate for filling volume arises when shifts in the pressure-volume relationship occur. At point C, ventricular volume is 100 mL and ventricular pressure is 8 mm Hg. An increase in filling pressure to 15 mm Hg may accompany either an increased volume (D) or decreased volume (E). The latter occurs when ventricular compliance changes and shifts the ventricular diastolic pressure-volume relationship up and to the left. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 15-2.)*

the same increase in filling volume causes a significant increase in filling pressure when the ventricle is operating on the steep portion of its curve.[194] An even more confusing situation arises when the diastolic pressure-volume relationship of the ventricle changes, for example, with the onset of myocardial ischemia. Rather than moving along the same diastolic pressure-volume curve, the ventricle now shifts to a different, steeper curve, where somewhat paradoxically, an increase in filling pressure may accompany a decrease in filling volume.[195] As in this example, not only can one not assume that a given measured change in cardiac filling pressure reflects a proportional change in ventricular preload, it cannot even be assumed that diastolic pressure and volume change in a similar direction.[195]

The relationship between ventricular volume and filling pressure depends on the portion of the pressure-volume curve over which the patient's heart is operating and the shape or slope of the curve. Commonly termed ventricular compliance, this change in pressure for a given change in volume ($\Delta P/\Delta V$) is actually the reciprocal of compliance and is more accurately termed ventricular elastance, distensibility, or stiffness.[196] A patient with an abnormally stiff ventricle will have a greater change in end-diastolic pressure for any given change in end-diastolic volume, and the converse is true for a patient with an abnormally compliant ventricle. By definition, diastolic dysfunction is present when changes in ventricular pressure are abnormally elevated for any given change in ventricular volume.

The ventricular diastolic pressure-volume relationship is influenced by the intrinsic properties of the ventricle, such as the passive mechanical characteristics of cardiac muscle, chamber geometry, and relaxation. In addition, external forces exerted by the pericardium, the adjacent ventricle, the coronary vasculature, and pleural pressure will further influence ventricular pressure-volume relationships.[197,198] One should not equate cardiac filling pressures with filling volumes when patients are functioning over wide ranges of their diastolic pressure-volume curve or under conditions in which diastolic stiffness is abnormal or changing rapidly.

In general, all intravascular pressures measured in clinical practice are referenced to ambient atmospheric pressure. Indeed, the first step in pressure transducer setup is to zero the transducer by exposing it to atmospheric pressure and assigning this pressure a value of zero by pressing the zero pressure button on the monitor (see "Technical Aspects of Direct Blood Pressure Measurement"). Thus, a cardiac filling pressure of 10 mm Hg is 10 mm Hg higher than ambient atmospheric pressure. Does this pressure value accurately represent the distending force across the cardiac chamber wall at end-diastole?

To answer this question, one needs to consider transmural pressure. The cardiac chambers are all contained within the pericardium and thorax. Changes in pressure in the structures surrounding the heart will influence pressures recorded within the heart. Transmural pressure is the difference between chamber pressure and juxtacardiac or pericardial pressure. This transmural pressure determines ventricular preload, end-diastolic volume, or fiber length. The same measured filling pressure, referenced to atmospheric pressure, can be associated with markedly different transmural pressures and chamber volumes, depending on whether juxtacardiac pressure is high or low. Although juxtacardiac pressure can be ignored under some circumstances, marked alterations in pleural and pericardial pressure occur commonly and must be considered when any cardiac filling pressure is interpreted. Transmural pressure is always the pressure of physiologic interest. Because juxtacardiac pressure is not measured routinely, one must always consider that the measured central venous pressure, referenced to ambient atmosphere, may be a poor estimate of transmural pressure.[194,199]

Cardiac filling pressures are measured directly from a number of sites in the vascular system. CVP monitoring is the least invasive method, followed by monitoring of PAP and left atrial pressure (LAP). Proper interpretation of all cardiac filling pressures requires knowledge of normal values for these pressures, as well as pressures in the cardiac chambers, the great vessels, and other measured and derived hemodynamic variables (Table 40-2).

Normal Central Venous Pressure Waveforms

Strictly speaking, CVP is the pressure measured at the junction of the venae cavae and the right atrium and reflects the driving force for filling the right atrium and ventricle. Because the large veins of the thorax, abdomen, and proximal extremities form a compliant reservoir for a sizable percentage of total blood volume, CVP is highly dependent on intravascular blood volume and the intrinsic vascular tone of these capacitance vessels. In other words, CVP or right atrial pressure in part reflects the relationship of blood volume to the capacity of the venous system.[200] In addition, CVP also reflects the functional capacity of the right ventricle. Based on the Frank-Starling mechanism, higher right heart filling pressures are required to maintain ventricular stroke output when ventricular contractility is impaired. Thus, in clinical practice, CVP monitoring is used for assessment of blood volume and right heart function.[201] Normal CVP in an awake, spontaneously breathing patient ranges between 1 and 7 mm Hg.

Table 40-2 Normal Cardiovascular Pressures

Pressure	Average (mm Hg)	Range (mm Hg)
Right Atrium		
a wave	6	2-7
v wave	5	2-7
Mean	3	1-5
Right Ventricle		
Peak systolic	25	15-30
End-diastolic	6	1-7
Pulmonary Artery		
Peak systolic	25	15-30
End-diastolic	9	4-12
Mean	15	9-19
Pulmonary Artery Wedge		
Mean	9	4-12
Left Atrium		
a wave	10	4-16
v wave	12	6-21
Mean	8	2-12
Left Ventricle		
Peak systolic	130	90-140
End-diastolic	8	5-12
Central Aorta		
Peak systolic	130	90-140
End-diastolic	70	60-90
Mean	90	70-105

Table 40-3 Central Venous Pressure Waveform Components

Waveform Component	Phase of Cardiac Cycle	Mechanical Event
a wave	End diastole	Atrial contraction
c wave	Early systole	Isovolumic ventricular contraction, tricuspid motion toward the right atrium
v wave	Late systole	Systolic filling of the atrium
h wave	Mid to late diastole	Diastolic plateau
x descent	Mid systole	Atrial relaxation, descent of the base, systolic collapse
y descent	Early diastole	Early ventricular filling, diastolic collapse

Mechanical events during the cardiac cycle are responsible for the sequence of waves seen in a typical CVP trace. The CVP waveform consists of five phasic events, three peaks (a, c, v) and two descents (x, y) (Table 40-3, Fig. 40-23).[202,203] The most prominent wave is the *a wave* of atrial contraction, which occurs at end-diastole after the ECG P wave. Atrial contraction increases atrial pressure and provides the "atrial kick" to fill the right ventricle through the open tricuspid valve. Atrial pressure decreases after the a wave as the atrium relaxes. This smooth decline in pressure is interrupted by the *c wave*. This wave is a transient increase in atrial pressure produced by isovolumic ventricular contraction, which closes the tricuspid valve and displaces it toward the atrium. The c wave always follows the ECG R wave because it is generated during the onset of ventricular systole. (Note that the c wave observed in a jugular venous pressure trace might have a slightly more complex origin. This wave has been attributed to early systolic pressure transmission from the adjacent carotid artery and may be termed a carotid impact wave.[204] Because jugular venous pressure also reflects right atrial pressure, however, this c wave probably represents both arterial [carotid impact] and venous [tricuspid motion] origins.) Atrial pressure continues its decline during ventricular systole because of continued atrial relaxation and changes in atrial geometry produced by ventricular contraction and ejection. This is the *x descent*, or systolic collapse in atrial pressure. The *x* descent can be divided into two portions, x and x′, corresponding to segments before and after the c wave. The last atrial pressure peak is the *v wave*, which is caused by venous filling of the atrium during late systole while the tricuspid valve remains closed. The v wave usually peaks just after the ECG T wave. Atrial pressure then decreases, thereby inscribing the *y descent*, or diastolic collapse, as the tricuspid valve opens and blood flows from atrium to ventricle. (A final compo-

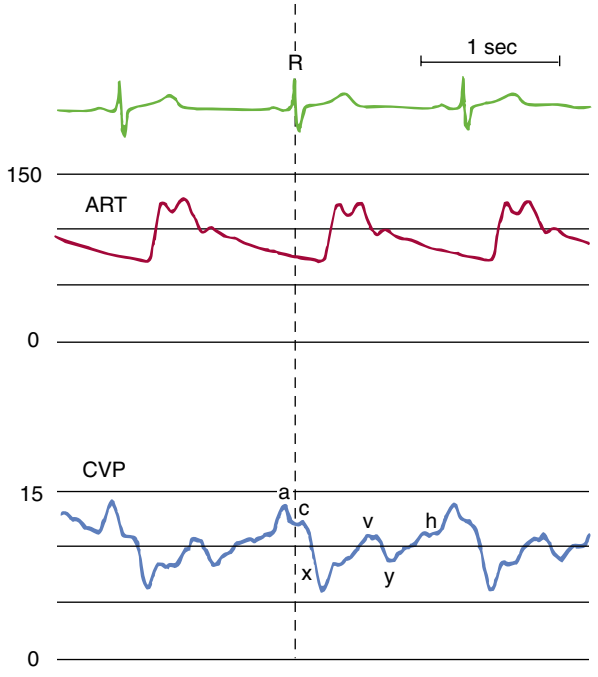


Figure 40-23 Normal central venous pressure (CVP) waveform. The diastolic components (y descent, end-diastolic a wave) and the systolic components (c wave, x descent, end-systolic v wave) are all clearly delineated. A mid-diastolic plateau wave, the h wave, is also seen because the heart rate is slow. Identification of the waveform is aided by timing the relationship between individual waveform components and the electrocardiographic R wave. Waveform timing using the arterial (ART) pressure trace is more confusing because of the relative delay in systolic arterial pressure upstroke. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 2-5.)*

nent of the CVP waveform, the *h wave*, occasionally appears as a pressure plateau in mid to late diastole. The h wave is not normally seen unless the heart rate is slow and venous pressure is elevated.[204,205]) In summary, the normal venous waveform components may be remembered as follows: the a wave results from atrial contraction; the c wave results from closure of the tricuspid valve and isovolumic right ventricular contraction; the x descent is the systolic decrease in atrial pressure caused by atrial relaxation; the v wave results from ventricular ejection, which drives venous filling of the atrium; and the y descent is the diastolic decrease in atrial pressure caused by flow across the open tricuspid valve.

In relation to the cardiac cycle and ventricular mechanical actions, the CVP waveform can be considered to have three systolic components (c wave, x descent, v wave) and two diastolic components (y descent, a wave). By recalling the mechanical actions that generate the pressure peaks and troughs, it is easy to identify these waveform components properly by aligning the CVP waveform and the ECG trace and using the ECG R wave to mark end-diastole and the onset of systole. When the radial artery pressure trace is used for timing of the CVP waveform instead of the ECG, confusion may arise because the arterial pressure upstroke occurs nearly 200 msec after the ECG R wave (see Fig. 40-23). This normal physiologic delay reflects the times required for spread of electrical depolarization through the ventricle (~60 msec), isovolumic left ventricular contraction (~60 msec), transmission of the rise in aortic pressure to the radial artery (~50 msec), and transmission of the rise in radial artery pressure through fluid-filled tubing to the transducer (~10 msec).[61,206]

The normal CVP peaks are designated systolic (c, v) or diastolic (a) according to the phase of the cardiac cycle in which the wave begins. However, one generally identifies these waves not by their onset or upstroke but rather by the location of their peaks. For instance, the a wave generally begins and peaks in end-diastole, but the peak may appear delayed to coincide with the ECG R wave, especially in a patient with a short PR interval. In this instance the a and c waves merge, and this composite wave is termed an a-c wave. Designation of the CVP v wave as a systolic event may be even more confusing. Although ascent of the v wave begins during late systole, the peak of the v wave occurs during isovolumic ventricular relaxation, immediately before opening of the atrioventricular valve and the y descent. Consequently, the most precise description would be that the v wave begins in late systole but peaks during isovolumic ventricular relaxation, the earliest portion of diastole. For clinical purposes, it is simplest to consider the v wave to be a systolic wave.

Although three distinct CVP peaks (a, c, v) and two troughs (x, y) are discernible in the normal venous pressure trace, heart rate changes and conduction abnormalities alter this pattern. A short ECG PR interval causes fusion of the a and c waves, and tachycardia reduces the length of diastole and the duration of the y descent, which causes the v and a waves to merge. In contrast, bradycardia causes each wave to become more distinct, with separate x and x′ descents visible and a more prominent h wave. Although there are circumstances in which other pathologic waves may be evident in the CVP trace, one should resist the temptation to assign physiologic significance to each small pressure peak because many will arise as artifacts of fluid-filled tubing-transducer monitoring systems. It is more useful to search for the expected waveform components, including those characteristic of the pathologic conditions suspected.

Abnormal Central Venous Pressure Waveforms

Various pathophysiologic conditions may be diagnosed or confirmed by examination of the CVP waveform (Table 40-4). One of the most common applications is rapid diagnosis of cardiac arrhythmias.[207] In *atrial fibrillation*, the a wave disappears and the c wave becomes more prominent because atrial volume is greater at end-diastole and the onset of systole as a result of the absence of effective atrial contraction (Fig. 40-24A). Occasionally, atrial fibrillation or flutter waves may be seen in the CVP trace when the ventricular rate is slow. Isorhythmic *atrioventricular dissociation* or *junctional* (*nodal*) *rhythm* (see Fig. 40-24B) alters the normal sequence of atrial contraction before ventricular contraction. Instead, atrial contraction now occurs during ventricular systole when the tricuspid valve is closed, thereby inscribing a tall "cannon" a wave in the CVP waveform. Absence of normal atrioventricular synchrony during ventricular pacing (see Fig. 40-24C) can be identified in a similar fashion by searching for cannon waves in the venous pressure trace. In these instances, the CVP waveform helps diagnose the cause of the arterial hypotension; loss of the normal end-diastolic atrial kick may not be as evident in the ECG trace as it is in the CVP waveform.

Right-sided valvular heart diseases alter the CVP waveform in different ways.[208] *Tricuspid regurgitation* produces abnormal systolic filling of the right atrium through the incompetent valve (Fig. 40-25A). A broad, tall systolic c-v wave results, beginning in early systole and obliterating the systolic x descent in atrial pressure. The CVP trace is said to be ventricularized and resembles right ventricular pressure. Note that this regurgitant wave differs in onset, duration, and magnitude from a normal v wave caused by end-systolic atrial filling from the venae cavae. In patients with tricuspid regurgitation, right ventricular end-diastolic pressure is

Table 40-4 Central Venous Pressure Waveform Abnormalities

Condition	Characteristics
Atrial fibrillation	Loss of a wave Prominent c wave
Atrioventricular dissociation	Cannon a wave
Tricuspid regurgitation	Tall systolic c-v wave Loss of x descent
Tricuspid stenosis	Tall a wave Attenuation of y descent
Right ventricular ischemia	Tall a and v waves Steep x and y descents M or W configuration
Pericardial constriction	Tall a and v waves Steep x and y descents M or W configuration
Cardiac tamponade	Dominant x descent Attenuated y descent
Respiratory variation during spontaneous or positive-pressure ventilation	Measure pressures at end-expiration

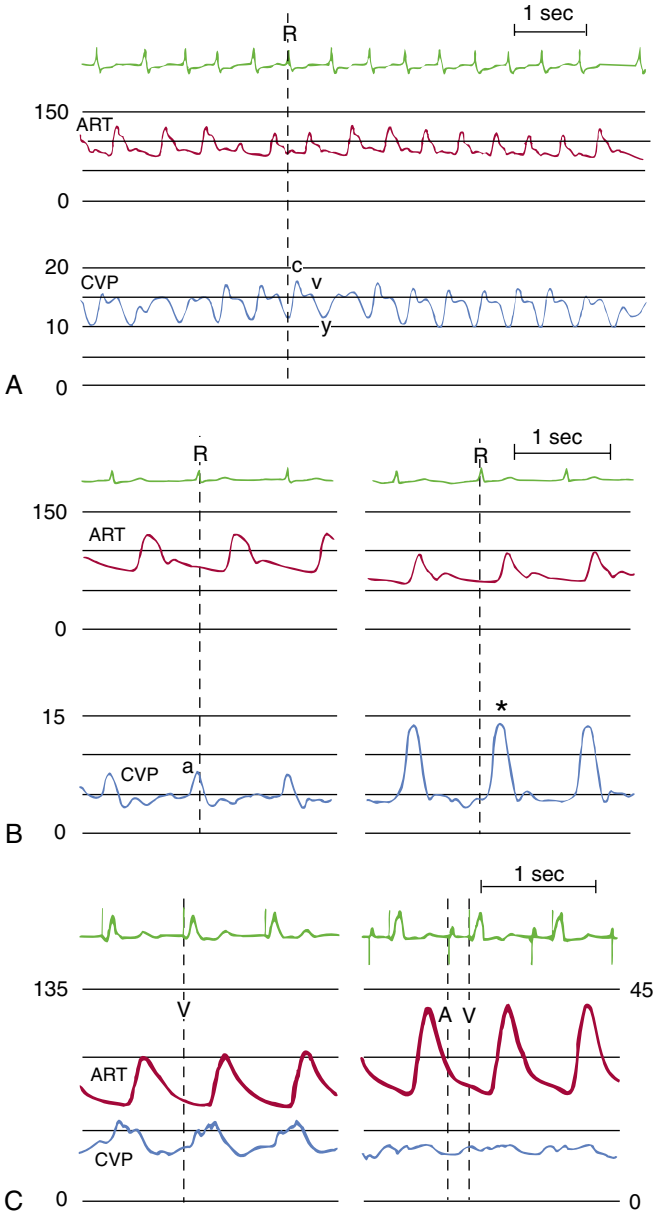


Figure 40-24 Changes in central venous pressure (CVP) caused by cardiac arrhythmias. **A,** Atrial fibrillation. Note the absence of the a wave, a prominent c wave, and a preserved v wave and y descent. This arrhythmia also causes variation in the electrocardiographic (ECG) R-R interval and left ventricular stroke volume, which can be seen in the ECG and arterial pressure (ART) traces. **B,** Isorhythmic atrioventricular dissociation. In contrast to the normal end-diastolic a wave in the CVP trace (*left panel*), an early systolic cannon wave is inscribed (*, *right panel*). Reduced ventricular filling accompanying this arrhythmia causes decreased arterial blood pressure. **C,** Ventricular pacing. Systolic cannon waves are evident in the CVP trace during ventricular pacing (*left panel*). Atrioventricular sequential pacing restores the normal venous waveform and increases arterial blood pressure (*right panel*). The ART scale is shown on the *left*; the CVP scale is on the *right*. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Figs.14-1, 14-5, and 14-6.)*

overestimated by the numeric display on the bedside monitor, which reports a single mean value for CVP. Instead, right ventricular end-diastolic pressure is best estimated by measuring CVP at the time of the ECG R wave, before the regurgitant systolic wave (see Fig. 40-25A). Unlike tricuspid regurgitation, *tricuspid stenosis* produces a diastolic defect in atrial emptying and ventricular filling (see Fig. 40-25B). Mean CVP is elevated, and a pressure gradient exists throughout diastole between the right atrium and ventricle. The a wave is unusually prominent and the y descent is attenuated as a result of the impaired diastolic egress of blood from the atrium. Other conditions that reduce right ventricular compliance, such as right ventricular ischemia, pulmonary hypertension, or pulmonic valve stenosis, may produce a prominent end-diastolic a wave in the CVP trace but do not attenuate the early diastolic y descent. CVP waveform morphology changes in other characteristic ways in the presence of pericardial disease and right ventricular infarction. These patterns are

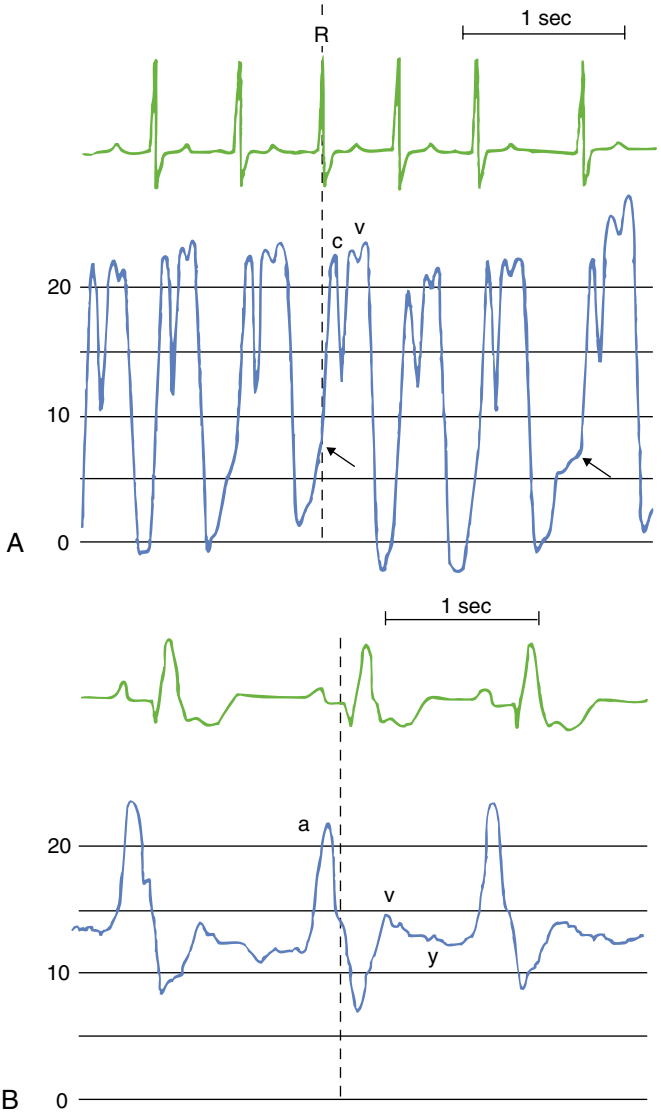


Figure 40-25 Changes in central venous pressure (CVP) in tricuspid valve disease. **A,** Tricuspid regurgitation increases mean CVP, and the waveform displays a tall systolic c-v wave that obliterates the x descent. In this example the a wave is not seen because of atrial fibrillation. Right ventricular end-diastolic pressure is estimated best at the time of the electrocardiographic R wave (*arrows*) and is lower than mean CVP. **B,** Tricuspid stenosis increases mean CVP, the diastolic y descent is attenuated, and the end-diastolic a wave is prominent. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Figs. 17-3 and 17-15.)*

best interpreted in conjunction with monitoring of PAP, which is discussed later.

Perhaps the most important application of CVP monitoring is to provide an estimate of the adequacy of circulating blood volume and right ventricular preload. As noted earlier, transmural CVP is the pressure of physiologic interest, although in clinical practice we measure and record pressures referenced to ambient atmospheric pressure. Consequently, accurate interpretation of CVP requires the physician to consider the alterations in intrathoracic or juxtacardiac pressure that occur during the respiratory cycle.[194,199] During spontaneous breathing, inspiration causes a decrease in pleural and juxtacardiac pressure, which is transmitted, in part, to the right atrium and lowers CVP (Fig. 40-26A). This same decrease in pleural pressure will influence other measured central vascular pressures in similar fashion. Note a subtle, but critically important observation about the measurement of central vascular pressures. Although CVP measured relative to atmospheric pressure decreases during the inspiratory phase of spontaneous ventilation, transmural CVP, the difference between right atrial pressure and juxtacardiac pressure, may actually increase slightly as more blood is drawn into the right atrium. The opposite pattern is observed during positive-pressure ventilation, in which inspiration increases intrathoracic pressure while raising the measured CVP but decreases transmural CVP because the elevated intrathoracic pressure reduces venous return (see Fig. 40-26B). As mentioned earlier, transmural pressures are rarely measured in clinical practice because of difficulty assessing juxtacardiac or intrathoracic pressure. Instead, end-expiratory values for cardiac filling pressures should be recorded in all patients to provide the best estimate of transmural pressure. At the end of expiration, intrathoracic and juxtacardiac pressures approach atmospheric pressure regardless of ventilatory status, and the CVP values will coincide (see Fig. 40-26). Proper pressure values can also be determined by visual inspection of the CVP waveform on a calibrated monitor screen or paper recording. This facilitates comparison of CVP values (and other cardiac filling pressures) obtained from the same patient under varying patterns of ventilation, a common situation in anesthesia and critical care.

Not only can individual CVP waveforms provide unique diagnostic clues about the circulation, but trends in CVP over time may also be useful in estimating fluid or blood loss and guiding replacement therapy. It is important to remember that there is a significant range of normal values and that a small change in CVP may reflect a significant alteration in circulating blood volume and right ventricular preload. Additional useful information may be derived from examining how a fluid bolus simultaneously alters CVP and other variables of clinical interest, such as blood pressure, urine output, and so forth.

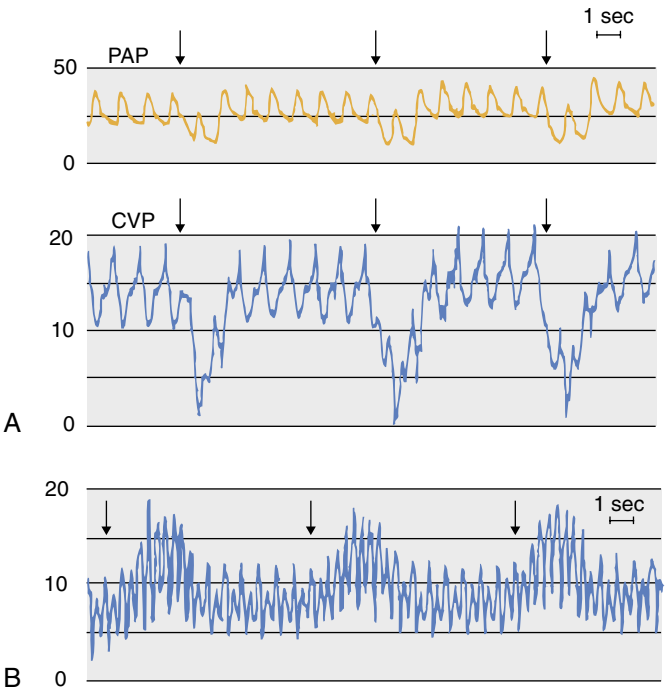


Figure 40-26 Respiratory influences on the measurement of central venous pressure (CVP). **A,** During spontaneous ventilation, the onset of inspiration (*arrows*) causes a reduction in intrathoracic pressure, which is transmitted to both the CVP and pulmonary artery pressure (PAP) waveforms. CVP should be recorded at end-expiration (mean CVP, 14 mm Hg). **B,** During positive-pressure ventilation, the onset of inspiration (*arrows*) causes an increase in intrathoracic pressure. CVP is still recorded at end-expiration (mean CVP, 8 mm Hg). *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Figs. 16-1 and 16-2.)*

Pulmonary Artery Catheter Monitoring

In 1970, Swan, Ganz, and colleagues introduced pulmonary artery catheterization into clinical practice for hemodynamic assessment of patients with acute myocardial infarction.[209,210] These catheters allowed accurate measurement of important cardiovascular physiologic variables at the bedside, and their popularity soared. By the mid-1990s, estimated annual PAC sales in the United States approached 2 million catheters, with an estimated cost associated with their use in excess of $2 billion each year.[211]

The PAC provides measurements of several hemodynamic variables that many clinicians, including experts in intensive care, cannot predict accurately from standard clinical signs and symptoms.[212] However, it remains uncertain whether PAC monitoring leads to improved patient outcome.[213]

Pulmonary Artery Catheterization

PACs can be placed from any of the central venous cannulation sites described earlier, but the right internal jugular vein is preferred because it provides the most direct route to the right heart chambers. The procedure is conducted in a manner similar to that for central venous cannulation. However, before PAC insertion, a slightly larger skin nick is made to accommodate a large-bore introducer sheath with a hemostasis valve at its outer end and a side-arm extension for intravenous access. A tapered-tip, stiff dilator stylet is placed inside an introducer sheath to facilitate passage into the vein. Utmost care must be exercised when introducing this large dilator-cannula assembly by advancing it only to the depth required to enter the vein and then threading the introducer into the vein. Finally, the guidewire and dilator are removed, and the introducer sheath is sutured in place.

The standard PAC has a 7.0- to 9.0-Fr circumference, is 110 cm in length marked at 10-cm intervals, and contains four

internal lumens. The distal port at the catheter tip is used for monitoring of PAP, whereas the second is 30 cm more proximal and is used for monitoring of CVP. The third lumen leads to a balloon near the tip, and the fourth houses wires for a temperature thermistor, the end of which lies just proximal to the balloon.

The steps in placing a PAC require the aid of a skilled assistant. Before insertion, the PAC is passed through a sterile sheath that attaches to the hub of the introducer and allows sterile manipulation of PAC position during use. The assistant attaches the distal and proximal port hubs to pressure transducers and flushes them to ensure proper function and exclude air from the system. The balloon is tested by filling it completely with 1.5 mL of air from a volume-limited syringe to ensure symmetry of expansion and patency. The air-filled balloon at the tip of the catheter serves to "float" the catheter forward with blood flow through the right heart chambers and into its proper position in the pulmonary artery.

It is important to check the assembly for proper function. When the tip of the PAC is held near heart level, the recorded pressure should be 0 mm Hg, thus confirming that the transducer was correctly adjusted at the beginning of the procedure. The catheter tip is then raised up straight to create a 30-cm-tall vertical fluid column, which should produce a pressure of 22 mm Hg (equivalent to 30 cm H_2O) on the bedside monitor.

The PAC is then inserted through the hemostasis valve of the introducer to a depth of 20 cm or approximately 5 cm beyond the tip of the introducer sheath. A characteristic CVP waveform should be visible. The gentle curvature of the PAC should be oriented to point just leftward of the sagittal plane (the 11-o'clock position as viewed from the patient's head) to facilitate passage through the anteromedially located tricuspid valve. The balloon is inflated and the catheter is advanced into the right atrium; through the tricuspid valve, right ventricle, and pulmonic valve; into the pulmonary artery; and finally into the wedge position. Characteristic waveforms from each of these locations confirm proper catheter passage and placement (Fig. 40-27).

After PAWP is measured, the balloon is deflated and the PAP waveform should reappear. Wedge pressure may be obtained as needed by reinflating the balloon and allowing the catheter to float distally until pulmonary artery occlusion occurs again. The clinician must recognize that the tip of the PAC advances to a smaller pulmonary artery each time that the balloon is inflated to measure wedge pressure. In some patients the PAC may migrate distally even without balloon inflation. This problem is more common during cardiopulmonary bypass because of the repeated cardiac manipulations and temperature changes, which alter the stiffness of the catheter.[214] Consequently, proper catheter position must be ensured throughout the monitoring period by frequent observation of the pressure waveform. If a PAWP trace appears without balloon inflation or with only partial balloon inflation, the balloon should be deflated and the catheter withdrawn several centimeters to reduce the risk of pulmonary vascular injury. Although the external protective sleeve covering the PAC is intended to maintain sterility during these minor adjustments, the sleeve does not preclude contamination. Therefore, PACs should be manipulated only as necessary to maintain a proper safe location.[215]

Additional Guidelines for Placement of Pulmonary Artery Catheters

From a right internal jugular vein puncture site, the right atrium should be reached when the PAC is inserted 20 to 25 cm, the right ventricle at 30 to 35 cm, the pulmonary artery at 40 to 45 cm, and the wedge position at 45 to 55 cm. When other sites are chosen for catheter placement, additional distance is required, typically an extra 5 to 10 cm from the left internal jugular and left and right external jugular veins, 15 cm from the femoral veins, and 30 to 35 cm from the antecubital veins.[216] These distances serve only as a rough guide, and waveform morphology must always be verified and catheter position confirmed with a chest radiograph as soon as practical. The tip of the PAC should be within 2 cm of the cardiac silhouette on a standard anteroposterior chest film.[217]

Keeping in mind these typical distances helps avoid complications caused by unintended catheter loops and knots within the heart. If a right ventricular waveform is not observed after inserting the catheter 40 cm, coiling in the right atrium is likely. Similarly, if a pulmonary artery waveform is not observed after inserting the catheter 50 cm, coiling in the right ventricle has probably occurred. The balloon should be deflated, the catheter withdrawn to 20 cm, and the PAC floating sequence repeated.

Although the right internal jugular vein is the primary site for catheterization of the pulmonary artery, failure to achieve venous cannulation or other medical and surgical considerations may require the use of alternative sites. For cardiac surgery, the

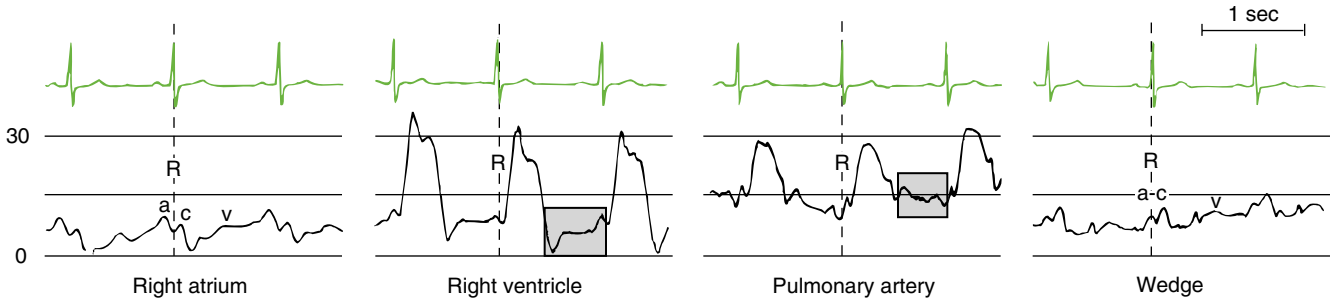


Figure 40-27 Characteristic waveforms recorded during passage of the pulmonary artery catheter. Right atrial pressure resembles a central venous pressure waveform and displays a, c, and v waves. Right ventricular pressure shows higher systolic pressure than seen in the right atrium, although the end-diastolic pressures are equal in these two chambers. Pulmonary artery pressure shows a diastolic step-up when compared with ventricular pressure. Note also that right ventricular pressure increases during diastole whereas pulmonary artery pressure decreases during diastole (*shaded boxes*). Pulmonary artery wedge pressure has a similar morphology to right atrial pressure, although the a-c and v waves appear later in the cardiac cycle relative to the electrocardiogram. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 3-1.)*

left internal jugular vein is often the second choice because a PAC inserted by the subclavian route may be compressed and kinked under the clavicle, thus making it extremely difficult to withdraw or advance after sternotomy.[219]

Regardless of the intended surgical procedure, whenever one plans to insert a PAC through the left internal jugular, subclavian, and particularly the external jugular veins, the more tortuous course of these vessels may make it difficult to advance the large-bore introducer sheath fully into the vessel. This is not a problem as long as the introducer cannula is withdrawn slightly to maintain a position in the vein that allows unimpeded intravenous infusion and free aspiration of venous blood. Frequently, the introducer cannula needs to remain in this partially inserted position while the PAC is introduced through its hemostasis valve. Because the tip of the PAC is more flexible and smaller than the tip of the introducer, the PAC might advance easily and completely into the central vein and right atrium. The PAC balloon may then be inflated and the procedure completed in the normal fashion with the PAC serving as the de facto guidewire. Occasionally, the introducer sheath must remain partially or completely withdrawn to avoid acute angulation and kinking of the PAC as it leaves the sheath and enters the central vein.[218,219]

After successful venous cannulation, if attempts to advance the PAC to the right ventricle prove difficult, the physician should consider whether this difficulty might result from abnormal venous anatomy. The most common abnormality of the systemic veins is persistence of the left superior vena cava, which is present in approximately 0.1% to 0.2% of the general population and 2% to 9% of patients with other forms of congenital heart disease.[220,221] A persistent left superior vena cava descends along the left mediastinum and empties into a dilated coronary sinus. As a result of its benign nature, virtually all cases are asymptomatic and discovered incidentally at the time of failed central venous or pulmonary artery catheterization. Because a normal right superior vena cava is present in most of these patients, the anomaly is recognized only when attempted PAC placement proceeds from a left-sided vein. More rarely, difficult PAC placement is encountered during attempted right-sided venous cannulation because the right superior vena cava is absent as well. In these cases, the right internal jugular vein joins the persistent left superior vena cava by a bridging innominate vein. A rare form of atrial septal defect, termed *unroofed coronary sinus*, may also be encountered in these patients and provide coronary sinus–left atrial communication and the potential for a PAC to enter the left atrium and systemic circulation.[221] With any of these venous anomalies, advancement of the PAC into the coronary sinus may disclose an unexpected pressure waveform, coronary sinus pressure. This waveform has characteristics of both the downstream right atrial pressure and an indirectly transmitted, dampened left ventricular pressure waveform.

A few additional points might aid successful positioning of the PAC. The air-filled balloon tends to float to nondependent regions as it passes through the heart into the pulmonary vasculature. Consequently, positioning a patient head down will aid flotation past the tricuspid valve, and tilting the patient onto the right side and placing the head up will encourage flotation out of the right ventricle.[222] Deep inspiration during spontaneous ventilation will increase venous return and right ventricular output transiently and may facilitate catheter flotation in a patient with low cardiac output. On occasion, a catheter may be floated to proper position when stiffened by injecting 10 to 20 mL of an iced solution through the distal lumen. Finally, a catheter that is initially difficult to place may be positioned easily when hemodynamic conditions change, as commonly occurs after induction of general anesthesia and initiation of positive-pressure ventilation.

Complications of Pulmonary Artery Catheter Monitoring

Complications of PAC use may be divided into several groups: those resulting from catheter placement, those associated with the in vivo presence of the catheter, and those resulting from catheter use and misuse. For the most part, problems encountered during catheter placement are the same for both PAP and CVP monitoring (see Box 40-5). However, catheterization of the right ventricle and pulmonary artery causes complications uniquely associated with PACs (Box 40-6).

When all adverse effects from PAC use are considered, including self-limited arrhythmias observed during catheter insertion, it appears that minor complications occur in more than 50% of catheterized patients.[211] However, major morbidity specifically attributable to PAC use is uncommon.[223] In both an initial exhaustive review of the literature and in its 2003 update, the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization emphasized that the reported incidence of complications from PAC monitoring varies widely, although it seems that serious complications occur in 0.1% to 0.5% of PAC-monitored surgical patients.[211] In 1984, Shah and coworkers reported the use of PACs in 6245 patients undergoing cardiac and noncardiac operations.[149] Quite remarkably, only 10 patients (0.16%) had serious complications resulting in morbidity and only 1 patient (0.016%) died as a result of pulmonary artery catheterization. Furthermore, a 1998 European report of PAC use in 5306 patients undergoing cardiac surgery confirmed this low incidence of major morbidity, with injury to the right ventricle or pulmonary artery occurring in only 4 patients (0.07%).[224] Finally, only 1 of 2000 adverse events reported in the Australian Incident Monitoring Study of 1993 involved the use of a PAC, in contrast to 64 adverse events involving access to the arterial or venous

Box 40-6 Complications of Pulmonary Artery Catheter Monitoring

- Catheterization
  - Arrhythmias, ventricular fibrillation
  - Right bundle branch block, complete heart block
- Catheter residence
  - Mechanical, catheter knots
  - Thromboembolism
  - Pulmonary infarction
  - Infection, endocarditis
  - Endocardial damage, cardiac valve injury
  - Pulmonary artery rupture
  - Pulmonary artery pseudoaneurysm
- Misinterpretation of data
- Misuse of equipment

systems.[46] However, it is important to acknowledge that although these large studies indicate a low incidence of serious complications attributable to the use of PACs, the frequency of complications in a particular clinical setting or patient group remains unknown.

Arrhythmias are the primary complication observed during pulmonary artery catheterization. In fact, self-limited atrial or ventricular arrhythmias are so common during PAC passage through the heart that most clinicians do not consider them complications, but instead confirmation that the PAC is traversing the cardiac chambers appropriately. Shah and associates observed transient premature ventricular contractions in 68% and atrial dysrhythmias in 1.3% of their catheterized patients.[149] Of greater clinical significance, persistent ventricular dysrhythmias requiring treatment occurred in only 3.1% of patients, none of whom suffered prolonged hemodynamic instability. Although the balloon-tipped PAC is less arrhythmogenic when it strikes the endocardium than a standard intravenous catheter or transvenous pacing wire is, PACs have been reported to induce sustained atrial fibrillation, ventricular tachycardia, and even ventricular fibrillation.[222,224,225]

Prophylactic use of intravenous lidocaine before pulmonary artery catheterization is not effective in reducing ventricular ectopy.[226] When such problems arise, the balloon should be deflated and the catheter withdrawn to the right atrium. When hemodynamically significant dysrhythmias develop hours or even days after placement, it is unlikely that the PAC is responsible. However, the position of the catheter tip should always be checked by observation of the pressure waveform and chest radiograph to identify catheters that have migrated back into the right ventricle.

As the PAC passes through the right ventricle and strikes the interventricular septum, transient right bundle branch block occurs in up to 5% of patients.[227,228] This is of no clinical significance except in patients with preexisting left bundle branch block. In these patients, complete heart block may be precipitated, although this is rare. Shah and coworkers catheterized 113 patients with preexisting left bundle branch block, and complete heart block developed in only 1 patient (0.9%).[149] In a different population of 47 high-risk patients with left bundle branch block, many of whom had acute myocardial infarction or heart failure, Morris and colleagues inserted 82 PACs without a single episode of complete heart block for the initial 24-hour period.[227] However, transcutaneous pacing equipment, an external pulse generator, and a temporary transvenous pacing wire or pacing PAC should be readily available as a precaution, especially since the onset of heart block in this setting may be delayed.

A dizzying array of mechanical problems have been reported with PACs or introducer sheaths since their introduction into clinical use. In the setting of cardiac surgery, PACs may be damaged by surgical instruments or become entrapped in sutures or bypass cannulas.[149,229-231] Whenever right heart structures are involved, it is prudent to ensure free movement of the PAC before chest closure. Sternal retraction during cardiac surgery may pose other problems, particularly when the PAC is inserted via the external jugular or subclavian route. The PAC may kink as it exits the introducer sheath and makes an acute angle between the sheath and vessel wall.[218,219] These mechanical difficulties should be suspected whenever there is a damped appearance of the monitored pressure trace or difficulty infusing fluids or withdrawing blood through one of the catheter lumens.

Although gross structural defects in the catheter itself should be recognized by inspection of the catheter before insertion, more subtle manufacturing problems may escape detection. Some, such as communications between the PAP, CVP, and balloon inflation lumens, may be suspected only when the data are contradictory or inconsistent.[232,233]

PACs may dislodge temporary transvenous pacing wires, become entangled with other cardiac catheters, or form knots within the heart.[234,235] Arnaout and coauthors reported a PAC knot around the tricuspid valve chordae tendineae that resulted in severe tricuspid valve regurgitation after catheter removal.[234] Catheter knots should be suspected when there is difficulty withdrawing a PAC, and the diagnosis may be confirmed by chest radiography. Knots may be untied by radiologists with the use of intravascular snares and fluoroscopic guidance.[236] If the knot has already been drawn tight, surgical exploration and removal are usually required.

Although the incidence of thromboembolic complications is increased in patients who require PAC monitoring for longer periods, thrombi have been detected on PACs within hours of placement.[237] When drugs such as aprotinin and ε-aminocaproic acid are used to reduce perioperative bleeding, the risk of thrombus formation on the PAC may be increased.[238,239] Although heparin bonding to the external surface has unquestionably reduced the thrombogenicity of PACs, it does not entirely eliminate the possibility.[237,240] Fortunately, major pulmonary embolism is a rare occurrence.[241]

The incidence of PAC-related infection increases after 3 days of continuous monitoring and in patients with preexisting sepsis.[242] The most catastrophic of these infections is endocarditis, most often of the right-sided valves.[243,244] Using sophisticated microbiologic techniques in 297 critically ill patients, Mermel and associates demonstrated a 22% incidence of local infection of the introducer sheath but only a 0.7% incidence of bacteremia related to the PAC.[245] In view of these findings, it is not surprising that scheduled PACs changes do not reduce the risk for bloodstream infection, particularly when the catheter is changed over a guidewire.[246] However, cannulation at a new site carries a significant risk of vascular complications. The specific risks and benefits must be weighed in each patient.

In addition to infectious injury, mechanical injury may also result from PAC use.[243,244] In a series of 55 autopsies of patients who had been monitored with a PAC, Rowley and colleagues identified right-sided endocardial lesions in 53%.[243] Even though both severe tricuspid regurgitation and severe pulmonic regurgitation have been reported, these complications of PAC use are rare.[234,244,247] Using color flow Doppler echocardiography, Sherman and coworkers demonstrated that placement of a PAC caused a slight increase in the magnitude of tricuspid regurgitation, but in no instances did the PAC lead to severe right-sided valvular insufficiency.[248]

Pulmonary artery rupture, the most deadly but also the most preventable of complications, occurs in approximately 0.02% to 0.2% of catheterized patients and appears to carry a mortality rate of 50%.[149,249] Several factors appear to increase the risk for this catastrophic event, including hypothermia, anticoagulation, and advanced age, although many reported cases involve heart transplant procedures.[249-251] Pulmonary hypertension may also possibly predispose patients to arterial injury during balloon inflation because of the increased gradient between proximal arterial and distal wedge pressure or because pulmonary hyper-

tension distends the pulmonary vasculature and causes the PAC to wedge in a distal, less compliant vessel.[252]

Several mechanisms of pulmonary artery injury have been proposed and investigated, including forceful inflation of the PAC balloon and chronic erosion by the catheter tip abutting the vessel wall or eccentric balloon inflation forcing the uncushioned catheter tip through the vessel wall.[251,253] Regardless of the precise mechanism by which pulmonary arterial injury occurs, case reports highlight that this complication often results from suboptimal catheter insertion and management techniques. Procedural errors include unnecessary catheter manipulation, excessive insertion depth, unrecognized persistent wedge pressure, prolonged balloon inflation, or improper balloon inflation with liquid rather than air.[252-254] It is critical that the clinician recognize artifactual "overwedged" pressure recordings that indicate peripheral location of the PAC tip or impaction against the vessel wall and correct this problem immediately by withdrawing the catheter into the proximal pulmonary artery (see later).

The hallmark of catheter-induced pulmonary artery rupture is hemoptysis, which may cause life-threatening exsanguination or hypoxemia. Less commonly, occult hypotension or respiratory compromise may develop. If the visceral pleura fails to contain the bleeding, free rupture into the pleural space produces a large hemothorax. When time allows, a chest radiograph helps make the diagnosis by revealing the hemothorax or a new infiltrate near the tip of a distally positioned PAC. Although its initial appearance may be confused with catheter-related pulmonary infarction, its pattern of resolution and clinical course differentiate these diagnoses. In confusing cases the diagnosis may be made by performing a wedge angiogram, in which radiopaque dye injected through the wedged PAC will extravasate into the pulmonary parenchyma and thus identify the site of arterial disruption.[250]

Treatment of pulmonary artery rupture focuses on resuscitation and immediate control of the hemorrhage. Specific therapeutic steps are highly individualized, depending on the setting. The first priority is ensuring adequate oxygenation and ventilation, which may require endobronchial intubation with either a single- or double-lumen endotracheal tube to selectively ventilate and protect the unaffected lung. In addition, positive end-expiratory pressure (PEEP) applied to the affected lung may help control hemorrhage.[255] Any anticoagulation should be reversed unless the patient must remain on cardiopulmonary bypass and bronchoscopy is performed to localize and control the site of bleeding. A bronchial blocker may be guided into the involved bronchus to tamponade the bleeding and prevent contamination of the uninvolved lung.[256] Management of the PAC itself is more controversial. Some experts recommend removing the catheter, but others suggest leaving the PAC in place to monitor PAP and guide antihypertensive therapy targeted at lowering this pressure and reducing bleeding.[257,258] Others have suggested that the PAC balloon may be carefully reinflated and the catheter floated into the involved pulmonary artery to occlude the bleeding arterial segment as a temporizing measure.[256] Although these techniques may be effective in some cases, many patients will require definitive surgical therapy, such as oversewing the involved pulmonary artery or resecting the involved segment, lobe, or lung.[250,256] In addition, some authors have recommended distant follow-up with angiography to rule out pseudoaneurysm formation in those managed conservatively because of the high morbidity associated with secondary hemorrhage.[249,256,259,260]

A more insidious but possibly more common complication of PAC use is misinterpretation of data.[261,262] Although the magnitude of the problem is not clear, there is reason to believe that there are widespread knowledge deficits among practitioners who use PACs. In 1990, Iberti and coauthors reported the results of a 31-question multiple-choice examination taken by 496 resident and staff physicians in the medicine, surgery, and anesthesiology departments in 13 North American medical centers. The authors found a poor overall level of knowledge of PACs, as evidenced by a mean score of only 67% correct answers. Although higher scores were demonstrated by individuals with more training and more experience inserting and using catheter-derived information, none of these factors ensured a high level of knowledge.[263] These results have been duplicated in a variety of other specialty care groups.[264] It is especially concerning that PAWP measurement was performed incorrectly by 30% to 50% of the clinicians in these studies and that educational programs failed to improve performance.[265,266] Taken together, these observations highlight the fact that effective use of PACs requires a great deal of expertise and clinical experience and that even measuring the most fundamental PAC-derived variable, namely, wedge pressure, is a complicated endeavor.[267]

Physiologic Considerations for Pulmonary Artery Catheter Monitoring: Prediction of Left Ventricular Filling Pressure

Pulmonary artery catheterization allows measurement of a variety of hemodynamic variables, including cardiac output, mixed venous oxygen saturation, and most important, pulmonary artery diastolic and wedge pressure. These values, in turn, are used to estimate left ventricular filling pressure and, in combination with other clinical information, help guide administration of fluid and vasoactive drugs.

When a PAC floats to the wedge position, the inflated balloon isolates the distal pressure-monitoring orifice from upstream PAP. A continuous static column of blood now connects the wedged PAC tip to the junction of the pulmonary veins and left atrium. Thus, wedging the PAC, in effect, extends the catheter tip to measure the pressure at the point at which blood flow resumes on the venous side of the pulmonary circuit. Because resistance in the large pulmonary veins is negligible, PAWP provides an accurate, indirect measurement of both pulmonary venous pressure and LAP.[50,268]

Pulmonary artery diastolic pressure (PADP) is often used as an alternative to PAWP to estimate left ventricular filling pressure. This is acceptable in normal circumstances because when pulmonary venous resistance is low, the pressure in the pulmonary artery at the end of diastole will equilibrate with downstream pressure in the pulmonary veins and left atrium.[269,270] From a monitoring standpoint, PADP has the added advantage of being available for continuous monitoring, whereas PAWP is measured only intermittently.

For PADP or PAWP to be valid estimates of left ventricular filling pressure, the column of blood connecting the tip of the wedged catheter and the draining pulmonary vein must be continuous and static. At the microcirculatory level, this channel consists of pulmonary capillaries that are subject to external compression by surrounding alveoli. West and colleagues described a

three-zone model of the pulmonary vasculature based on the gravitationally determined relationships between relative pressure in the pulmonary arteries, the pulmonary veins, and the surrounding alveoli.[271] This model provides useful insight into conditions when PAC measurements are erroneous.

In West zone 1, alveolar pressure exceeds that in both the pulmonary artery and the pulmonary veins, whereas in zone 2, it is intermediate between these two pressures (Fig. 40-28). A PAC positioned in both zone 1 and 2 will be highly susceptible to alveolar pressure, and measurements will reflect alveolar or airway pressure rather than left ventricular filling pressure. As such, the tip of the PAC must lie in zone 3 for PAWP measurements to be accurate. In most clinical settings, a supine position of the patient favors zone 3 conditions, a finding that has been confirmed by radiographic studies.[272] However, when patients are placed in the lateral or semi-upright position, zone 2 may expand significantly. In general, zones 1 and 2 become more extensive when LAP is low, when the PAC tip is located vertically above the left atrium, or when alveolar pressure is high. Clues to an incorrectly positioned catheter include absence of normal PAWP a and v waves, marked respiratory variation in PAWP, and a PADP that exceeds the PAWP measurement without excessively tall a or v waves visible on the trace.[49]

Normal Pulmonary Artery and Wedge Pressure Waveforms

As the balloon-tipped PAC is floated to its proper position in the pulmonary artery, characteristic pressure waveforms are recorded (see Fig. 40-27). In the superior vena cava or right atrium, a CVP waveform should be observed, with its a, c, and v waves and low mean pressure. At this point the PAC balloon is inflated and the catheter advanced until it crosses the tricuspid valve to record right ventricular pressure, which is characterized by a rapid systolic upstroke, a wide pulse pressure, and low diastolic pressure. The PAC next enters the right ventricular outflow tract and floats past the pulmonic valve into the main pulmonary artery. Premature ventricular beats are common during this period as the balloon-tipped catheter strikes the right ventricular infundibular wall. Entry into the pulmonary artery is heralded by a step-up in diastolic pressure and a change in waveform morphology.

On occasion it may be difficult to distinguish right ventricular pressure from PAP, particularly if only the numeric values for these pressures are examined. However, careful observation of the pressure waveform by focusing on the diastolic pressure contours allows differentiation. During diastole, PAP will fall because of interruption of flow during pulmonic valve closure, while simultaneously, pressure in the right ventricle will increase because of filling from the right atrium (see Fig. 40-27).[216]

Under normal conditions, the PAP upstroke slightly precedes the radial artery pressure upstroke because of the longer duration of left ventricular isovolumic contraction, as well as the time required for propagation of the pressure wave to a distal monitoring site. As a practical matter, though, the pulmonary and systemic arterial pressure waveforms appear to overlap on the bedside monitor (Fig. 40-29). Understanding these temporal relationships is critically important for proper interpretation of abnormal pulmonary artery and wedge pressure waveforms, particularly when tall v waves are present (see later).

As noted previously, wedge pressure is an indirect measurement of pulmonary venous pressure and LAP and should therefore resemble these venous waveforms, with characteristic a and v waves and x and y descents. However, because of interposition of the pulmonary vascular bed between the PAC tip and left atrium, wedge pressure is a delayed representation of LAP.[268] On average, 160 msec is required for the LAP pulse to traverse the pulmonary veins, capillaries, arterioles, and arteries. As a consequence of this delay, the wedge pressure a wave appears to follow the ECG R wave in early ventricular systole even though the a wave is an end-diastolic event (see Fig. 40-29).

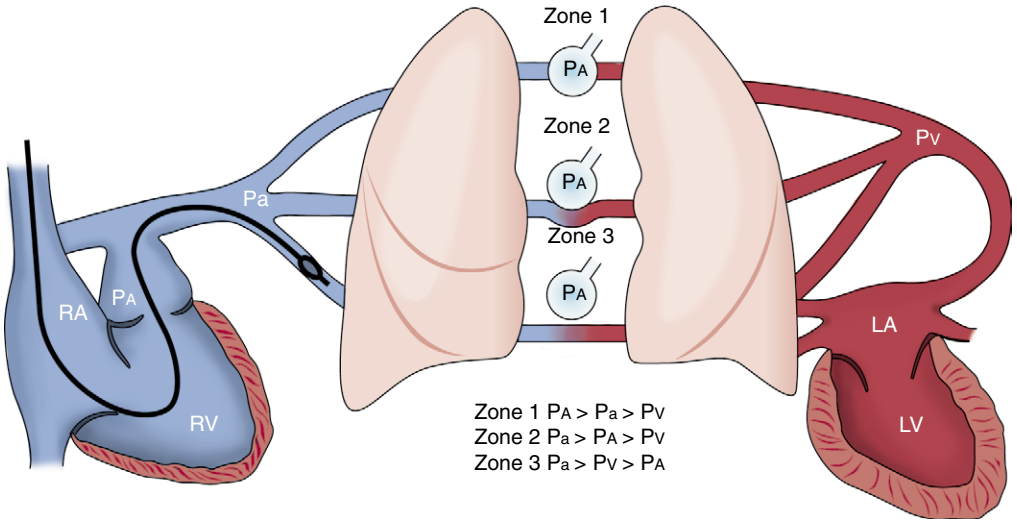


Figure 40-28 The tip of the pulmonary artery catheter must be wedged in lung zone 3 to provide an accurate measure of pulmonary venous (Pv) or left atrial (LA) pressure. When alveolar pressure (PA) rises above Pv in lung zone 2 or above pulmonary arterial pressure (Pa) in lung zone 1, wedge pressure will reflect alveolar pressure rather than intravascular pressure. LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 6-10.)*

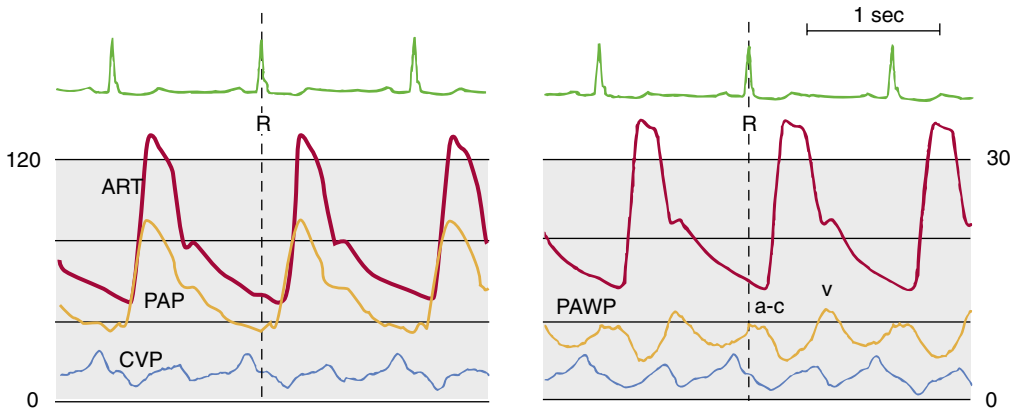


Figure 40-29 Temporal relationships between normal systemic arterial pressure (ART), pulmonary artery pressure (PAP), central venous pressure (CVP), and pulmonary artery wedge pressure (PAWP). Note that the PAWP a-c and v waves appear to occur later in the cardiac cycle than their counterparts on the right side of the heart seen in the CVP trace. The ART scale is on the *left*; the PAP, CVP, and PAWP pressure scales are on the *right*. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 3-3.)*

To recognize prominent a or v waves in the wedge pressure trace, it is not always necessary to inflate the PAC balloon. Because the PCWP trace reflects pressure waves transmitted in retrograde fashion from the left atrium, these waves will not normally be visible within the antegrade PAP waves produced by right ventricular ejection. In the setting of prominent a or v waves, the PAP trace becomes a composite wave that reflects both retrograde and antegrade components. Tall left atrial a or v waves will distort the normal PAP waveform appearance, with the a wave inscribed at the onset of the systolic upstroke and the v wave distorting the dicrotic notch (Fig. 40-30).[268,273] Once these waves are identified by wedging the PAC and comparing the PAP and PAWP traces, it is wise to "follow" the "wedge pressure" a and v waves in the unwedged PAP trace rather than repeatedly inflating the balloon.

In summary, PAWP measured with a balloon-tipped PAC provides a delayed, damped estimate of LAP by measuring the pressure near the junction of the pulmonary veins and the left atrium. Mean wedge pressure should be lower than mean PAP; otherwise, blood would not flow in an antegrade direction. The PAWP waveform should display small but visible a and v waves if the pressure trace is displayed with sufficient gain and resolution on the monitor screen.

Left Atrial Pressure, Pulmonary Artery Wedge Pressure, and Pulmonary Capillary Pressure

The most common technique for monitoring LAP during cardiac surgery involves catheterization of the left atrium with a thin catheter introduced through the right superior pulmonary vein and secured with a purse-string suture. The catheter is brought out through the skin beneath the xiphoid process and attached to a closed pressure monitoring system. Because LAP monitoring is discontinued simply by withdrawing the left atrial catheter through the skin, transseptal methods for LAP monitoring during surgery have been proposed to reduce the risk of bleeding after catheter removal.[274]

Today, direct LAP monitoring has largely been supplanted by PAC monitoring, no doubt because the latter provides a wider array of hemodynamic data. Furthermore, PAWP generally provides an excellent estimate of LAP after cardiac surgery.[275,276] On the other hand, there are a host of pathophysiologic conditions that alter the relationships between PADP, PAWP, and LAP and lead to erroneous measurements and potential clinical errors (see later).

Direct LAP monitoring continues to be particularly useful in pediatric patients undergoing complex congenital heart surgery, in part because of technical difficulties in this patient population. Gold and coauthors reported complications from left-sided monitoring occurring in only 0.68% of 2393 catheters.[277] However, direct access to the left heart chambers carries the grave risk of air and particulate embolization to the systemic circulation, especially during routine flushing of the lines.

Catheter removal may result in bleeding, the most common complication from LAP catheters. Consequently, these lines must be removed before the mediastinal chest drains, and if attempted withdrawal is met with resistance, surgical re-exploration is required. More unusual complications include catheter entrapment in mechanical aortic or mitral valve prostheses, fistulas between the right superior pulmonary vein and the right mainstem bronchus, and embolization of catheter fragments.[277-279]

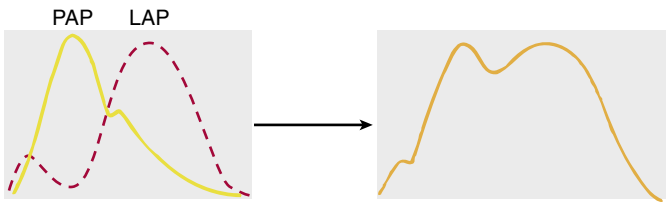


Figure 40-30 Tall left atrial pressure (LAP) a and v waves transmitted in a retrograde direction through the pulmonary vasculature distort the antegrade pulmonary artery pressure (PAP) waveform. The LAP a wave distorts the systolic upstroke, and the v wave distorts the dicrotic notch. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 4-10.)*

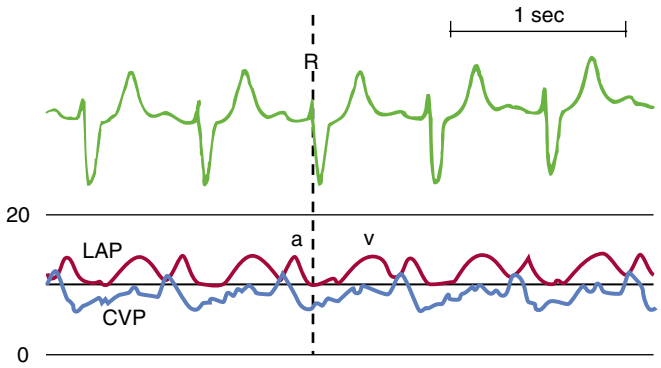


Figure 40-31 Normal temporal relationships between the electrocardiographic, central venous pressure (CVP), and left atrial pressure (LAP) traces. The LAP and CVP waveforms have nearly identical morphologies, although the CVP a wave slightly precedes the LAP a wave. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 2-9.)*

Normal LAP waveforms resemble those from CVP catheters, although there are a few subtle morphologic distinctions. Because atrial depolarization originates in the sinoatrial node located at the junction of the superior vena cava and the right atrium, the right-sided a wave appears slightly earlier than the left-sided a wave (Fig. 40-31). Although the a wave is the most prominent pressure peak in a normal CVP trace, the v wave is often taller than the a wave in a normal LAP waveform, thus suggesting that atrial contraction is stronger on the right than the left and that the left atrium is less distensible than the right.[61] Finally, the interval between atrial and ventricular contraction is approximately 40 msec longer on the right than on the left.[61] Consequently, a and c waves are seen as separate waves in a right atrial pressure trace, whereas on the left they merge into a composite a-c wave. In the PAWP waveform, the c wave is obscured even further by the damping effect of the lung vasculature.

The terms *pulmonary artery wedge pressure* and *pulmonary artery occlusion pressure* are used interchangeably and refer to the same measurement obtained from the tip of a PAC after balloon inflation and flotation to the wedged position. However, pulmonary capillary pressure must not be confused with wedge pressure or LAP, nor should the term *pulmonary capillary wedge pressure* be used at all. The hydrostatic pressure in the pulmonary capillaries that causes edema formation according to the Starling equation is different from LAP. This is the pressure that must exceed LAP to maintain antegrade blood flow through the lungs. Although the magnitude of the difference between pulmonary capillary pressure and wedge pressure is generally small, it can increase markedly when resistance to flow in the pulmonary veins is elevated.[280] In most situations, the major component of PVR occurs at the precapillary, pulmonary arteriolar level. However, rare conditions such as pulmonary veno-occlusive disease may cause a marked increase in postcapillary resistance to flow. Similar situations arise in conditions that disproportionately increase pulmonary venous resistance, such as central nervous system injury, acute lung injury, hypovolemic shock, endotoxemia, and norepinephrine infusion.[273,274] Under these conditions, measurement of wedge pressure will underestimate pulmonary capillary pressure substantially and thereby underestimate the risk of hydrostatic pulmonary edema. Although pulmonary capillary pressure may be measured at the bedside by analyzing the decay in the PAP trace after PAC balloon inflation, these techniques have not been adopted widely in clinical practice.[281,282] To avoid confusion, the phrase "pulmonary capillary wedge pressure" should be abandoned because it is imprecise and misleading.

Abnormal Pulmonary Artery and Wedge Pressure Waveforms

PAC monitoring is subject to the same technical artifacts inherent in all invasive pressure monitoring techniques, as well as some additional problems unique to this method.[253,283,284] Because the PAC is longer and passes through the cardiac chambers, it is more prone to distortions from clot or air bubbles, and motion-related artifacts are more problematic. Artifactual pressure spikes may be distinguished from the underlying physiologic pressure waveform by their unique morphology and timing.

At the onset of systole, tricuspid valve closure accompanied by right ventricular contraction and ejection resulting in excessive catheter motion are responsible for the most common PAC trace artifact.[283,285] Note that this pressure artifact occurs simultaneous with the CVP c wave and may produce either an artificially low pressure or a pressure peak. If the monitor detects this inappropriate pressure nadir, it may erroneously be designated as PADP (Fig. 40-32). Repositioning the PAC often solves the problem.

Another common artifact in PAC pressure measurement occurs when the balloon is overinflated and occludes the lumen orifice. This phenomenon is termed *overwedging* and is usually caused by distal catheter migration and eccentric balloon infla-

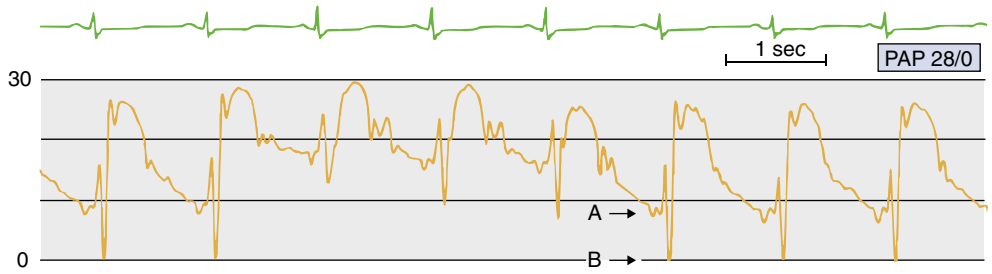


Figure 40-32 Artifactual pressure peaks and troughs in the pulmonary artery pressure (PAP) waveform caused by catheter motion. The correct value for pulmonary artery end-diastolic pressure is 8 mm Hg (A), although the monitor digital display erroneously reports the PAP as 28/0 mm Hg (B). *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 5-6.)*

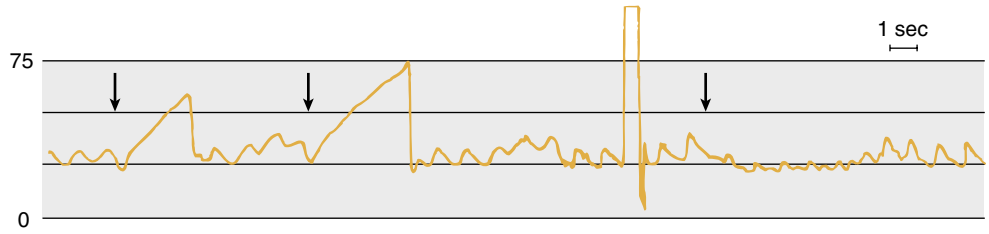


Figure 40-33 Overwedging of the pulmonary artery (PA) catheter causes artifactual waveform recordings. The first two attempts to inflate the PA catheter balloon (first *two arrows*) produce a nonpulsatile increasing pressure caused by an occluded catheter tip. After the catheter is withdrawn slightly, balloon inflation allows proper wedge pressure measurement (*third arrow*). Before the third attempt at balloon inflation, the PA pressure lumen is flushed, which restores the appropriate pulsatile pressure detailed to the PA and wedge pressure waveforms on the right side of the trace. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 5-7.)*

tion, which forces the catheter tip against the vessel wall. The catheter now records a gradually rising pressure produced by the continuous flush system and builds up pressure against the obstructed distal opening (Fig. 40-33). For a catheter that has migrated to a more distal position, it is possible for overwedging to occur without balloon inflation. Note that the overwedged pressure is devoid of pulsatility, is higher than expected, and rises continuously to the flush pressure. Such a pattern should arouse suspicion and prompt corrective action.

As emphasized earlier, with each PAC balloon inflation and wedge measurement, the catheter tip migrates distally. When a wedge pressure tracing appears during partial balloon inflation, it suggests that the PAC is inappropriately located in a smaller, distal branch of the pulmonary artery. The catheter should be withdrawn before overwedging results in vascular injury or pulmonary infarction.

Pathophysiologic conditions involving the left-sided cardiac chambers or valves produce characteristic changes in the pulmonary artery and wedge pressure waveforms. One of the characteristics of these waveforms is the tall v wave of mitral regurgitation. Unlike a normal wedge pressure v wave produced by late systolic pulmonary venous inflow, the prominent v wave of mitral regurgitation begins in early systole. Mitral regurgitation causes fusion of the c and v waves and obliteration of the systolic x descent because the isovolumic phase of left ventricular systole is eliminated as a result of retrograde ejection of blood into the left atrium.[208] Because the prominent v wave of mitral regurgitation is generated during ventricular systole, mean wedge pressure overestimates left ventricular filling pressure. Consequently, in cases of severe disease, left ventricular end-diastolic pressure is best estimated by measuring wedge pressure before onset of the regurgitant v wave (Fig. 40-34). Although mean wedge pressure exceeds left ventricular end-diastolic pressure in patients with severe mitral regurgitation, mean wedge pressure remains a good approximation for mean LAP. Retrograde pressure reflected by the regurgitant v wave contributes to left atrial hypertension and the subsequent risk of hydrostatic pulmonary edema.

When large v waves are present in the wedge pressure trace, it is critically important to recognize them and be able to distinguish the wedged from the unwedged pressure waveform. At first glance, a wedge trace with a tall systolic v wave resembles a typical unwedged PAP trace, but closer observation reveals a number of discriminating details. The PAP upstroke is steeper and slightly precedes the systemic arterial pressure upstroke, whereas a wedge tracing with a prominent v wave has a more gradual upstroke that begins after the radial artery pressure upstroke. Furthermore, the wedge pressure v wave reaches its peak later in the cardiac cycle, after the ECG T wave, as opposed to the simultaneous systemic and pulmonary arterial peaks (see Fig. 40-34).[208,286] Another distinguishing feature in patients with severe mitral regurgitation is the unusual morphology of the pulmonary artery waveform itself. The larger the v wave, the more the regurgitant v wave distorts the pulmonary artery waveform by giving it a bifid appearance and obscuring the normal end-systolic dicrotic notch (see Fig. 40-34).[273] Through recognition of these subtle but important diagnostic details, a clinician may assess the wedge pressure v wave by observing the unwedged PAP trace. This would eliminate the need for repeated balloon inflation and avoid the potential for catastrophic arterial rupture.

A close look at left atrial pressure-volume relationships helps explain the apparently paradoxical coexistence of severe mitral regurgitation and a normal PAWP trace.[287,288] Three factors determine whether mitral regurgitation produces a prominent v wave in the left atrial or wedge pressure traces: left atrial volume (often termed the patient's "volume status"), left atrial compliance, and regurgitant volume (Fig. 40-35). Given that the left atrial

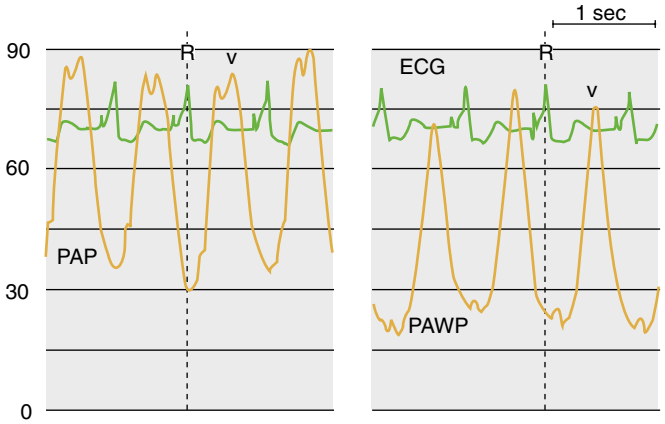


Figure 40-34 Severe mitral regurgitation. A tall systolic v wave is inscribed in the pulmonary artery wedge pressure (PAWP) trace and also distorts the pulmonary artery pressure (PAP) trace, thereby giving it a bifid appearance. The electrocardiogram (ECG) is abnormal because of ventricular pacing. Left ventricular end-diastolic pressure is estimated best by measuring PAWP at the time of the electrocardiographic R wave, before onset of the regurgitant v wave. Note that mean PAWP exceeds left ventricular end-diastolic pressure in this condition. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 17-11.)*

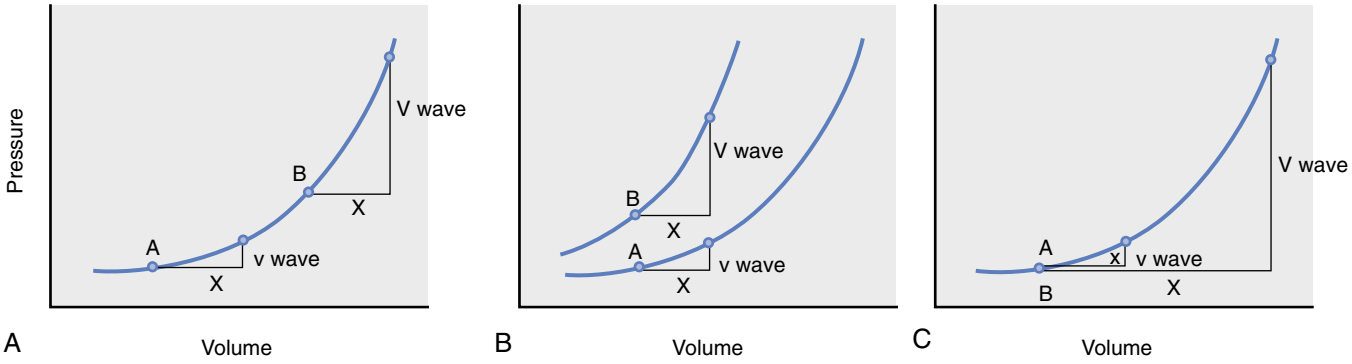


Figure 40-35 V wave height as an indicator of the severity of mitral regurgitation. Left atrial pressure-volume curves describe the three factors that determine v wave height. **A,** Influence of left atrial volume. For the same regurgitant volume (x), the left atrial v wave will be taller if baseline atrial volume is greater (point B versus point A). **B**, Influence of left atrial compliance. For the same regurgitant volume (x), the left atrial *v* wave will be taller if baseline atrial compliance is reduced (point B versus point A). **C,** Influence of regurgitant volume. Beginning at the same baseline left atrial volume (points A and B), if regurgitant volume increases (X versus x), the left atrial pressure v wave will increase (V versus v). *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 17-13.)*

pressure-volume relationship is not linear, the same volume of regurgitation will result in a variable increment in systolic pressure, depending on the preexisting atrial volume at the onset of systole. Furthermore, the nature of that relationship is dependent on the compliance (i.e., stiffness) of the left atrium. Although the total regurgitant volume of blood entering the left atrium will influence the height of the v wave, this clearly is not the only determinant of v wave magnitude. This may explain why patients with acute mitral regurgitation tend to have tall wedge pressure v waves—they have smaller, stiffer left atria with poorer compliance than patients with long-standing disease do. It is not surprising that wedge pressure v waves are neither sensitive nor specific indicators of the severity of mitral regurgitation, and the height of these waves should not be used in such a manner.[287] Prominent wedge pressure v waves may exist in the absence of mitral regurgitation when LAP is high, as might occur when the left atrium is compressed.[289] Tall v waves are also seen commonly in patients with hypervolemia, congestive heart failure, and ventricular septal defects.[287] Note that the giant v waves observed in patients with ventricular septal defects are not caused by retrograde flow, but rather excessive antegrade systolic flow into the left atrium as a result of the intracardiac shunt.[290]

In contrast to mitral regurgitation, which distorts the systolic portion of the wedge pressure waveform, mitral stenosis alters its diastolic aspect. In this condition, the holodiastolic pressure gradient across the mitral valve results in an increased mean wedge pressure, a slurred early diastolic y descent, and a tall end-diastolic a wave. Similar hemodynamic abnormalities are seen in patients with left atrial myxoma or whenever there is obstruction to mitral flow. Diseases that increase left ventricular stiffness (e.g., left ventricular infarction, pericardial constriction, aortic stenosis, and systemic hypertension) produce changes in wedge pressure that partly resemble those seen in mitral stenosis. In these conditions, mean wedge pressure is increased and the trace displays a prominent a wave, but the y descent remains steep because there is no obstruction to flow across the mitral valve during diastole. Because patients with advanced mitral stenosis often have coexisting atrial fibrillation, the a wave will not be present in many of these cases (Fig. 40-36).[208]

Myocardial ischemia may be detected with the PAC in several ways. Ischemia itself impairs left ventricular relaxation and thus results in diastolic dysfunction, a pattern particularly characteristic of demand ischemia associated with tachycardia or induced by rapid atrial pacing.[195,291,292] Impaired ventricular relaxation results in a stiffer, less compliant left ventricle, which leads to increased left ventricular end-diastolic pressure. Not only does this in turn increase left atrial and wedge pressure, but the morphology of these waveforms changes as well, with the phasic a and v wave components becoming more prominent as diastolic filling pressure increases.[293-295] Although myocardial ischemia will often be detectable as a rise in pulmonary artery diastolic, mean, or systolic pressure, these changes are generally less striking than the accompanying change in wedge pressure and the new appearance of tall a and v waves (Fig. 40-37). In patients with left ventricular ischemia, the tall wedge pressure a wave is produced by end-diastolic atrial contraction into a stiff, incompletely relaxed left ventricle.[296] Although the diastolic dysfunction accompanying myocardial ischemia leads to an increase in left ventricular end-diastolic pressure, this elevation in pressure often coexists with decreased left ventricular end-diastolic volume or preload.[195] The dissociation between filling pressure and filling volume in this condition must be appreciated to avoid diagnostic and therapeutic errors.

Myocardial ischemia also produces a characteristic pattern of left ventricular systolic dysfunction. Systolic dysfunction is the hallmark of supply ischemia, which is caused by a sudden reduction or cessation of coronary blood flow to a region of the myocardium.[292,297] With severe systolic dysfunction, changes in global left ventricular contractile performance may be detected by hemodynamic monitoring. As the ejection fraction falls significantly, left ventricular end-diastolic volume and pressure rise, and systemic arterial hypotension and elevated pulmonary diastolic and wedge pressure develop.[298] A more common hemodynamic manifestation of myocardial ischemia occurs when left ventricular geometry is distorted or when the region of ischemic myocardium underlies a papillary muscle and results in acute mitral regurgitation.[299] This form of mitral regurgitation is often termed "papillary muscle ischemia" or "functional mitral regurgitation." As noted earlier, PAC monitoring is particularly well suited to detect this event by revealing the onset of new regurgitant v waves in the pulmonary artery or wedge pressure traces (see Fig. 40-34).

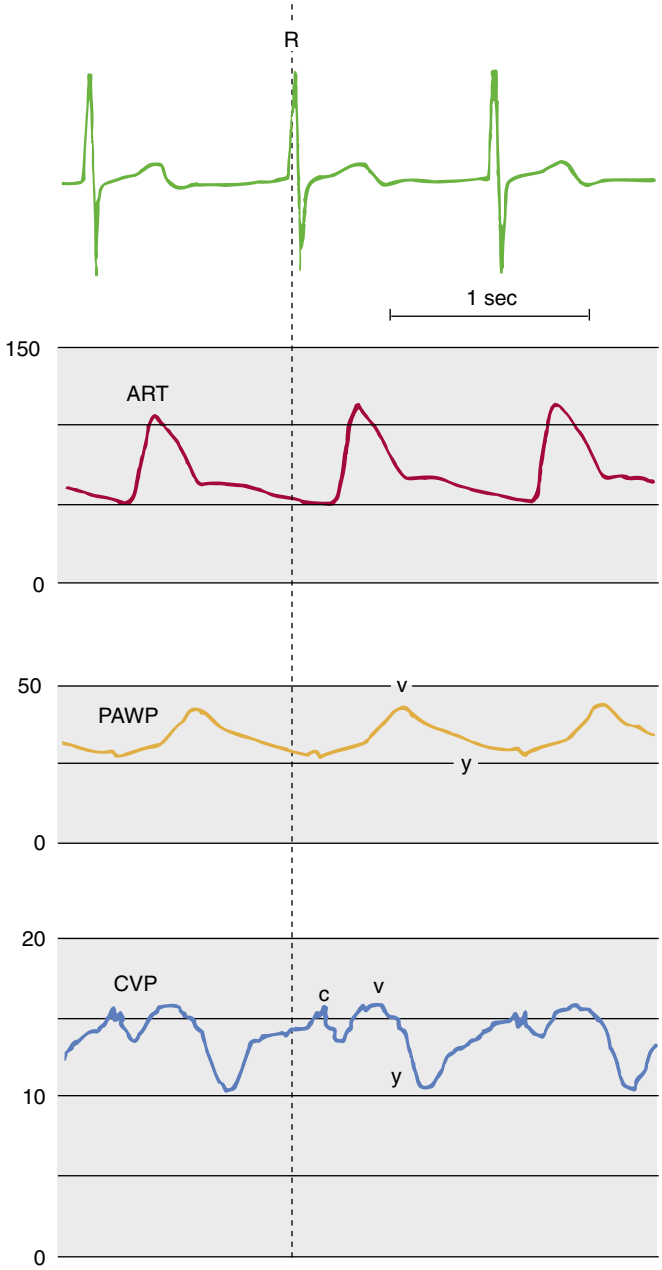


Figure 40-36 Mitral stenosis. Mean pulmonary artery wedge pressure (PAWP) is increased (35 mm Hg) and the diastolic y descent is markedly attenuated. Compare the slope of the y descent in the PAWP trace with the y descent in the central venous pressure (CVP) trace. In addition, compare this PAWP y descent with the PAWP y descent in mitral regurgitation (see Fig 40-34). A waves are not seen in the PAWP or CVP traces because of atrial fibrillation. ART, arterial blood pressure. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998,: Fig. 17-19.)*

Whether the PAC should be used in high-risk patients as a supplemental monitor for detection of myocardial ischemia remains controversial.[295,300-302] None of the current methods for detecting perioperative myocardial ischemia are perfectly sensitive or specific. Although patients with left ventricular ischemia are likely to have higher mean wedge pressure than those without ischemia, these differences are small and may be difficult to detect clinically.[295] Furthermore, clear quantitative threshold values for mean wedge pressure or a and v wave peak pressures that are diagnostic of ischemia have not been identified, perhaps because of the wide variations found in normal patients. Consequently, when a PAC is used to diagnose myocardial ischemia, the best approach is to integrate the PAC data with other clinical data.[303]

Right ventricular ischemia produces characteristic PAC trace patterns that may be helpful in diagnosis and management. Just as left ventricular ischemia increases PAWP, right ventricular ischemia increases CVP. In fact, this is one of the few situations in which CVP may be higher than wedge pressure. In addition, CVP waveforms may display a prominent a wave resulting from right ventricular diastolic dysfunction and a prominent v wave resulting from ischemia-induced tricuspid regurgitation.[304,305] This particular CVP waveform is described as having an M or W configuration, which refers to the tall a and v waves and interposed steep x and y descents. Severe pulmonary artery hypertension may also result in right ventricular ischemia and dysfunction and increases in CVP, but this can be distinguished from primary right ventricular dysfunction in that the PAP and calculated PVR are normal in primary ventricular failure.

The CVP waveform in right ventricular infarction is similar to that in restrictive cardiomyopathy or pericardial constriction, including elevated mean pressure, prominent a and v waves, and steep x and y descents.[306] The cardinal feature common to these conditions is impaired right ventricular diastolic compliance, often termed "restrictive physiology." In restrictive cardiomyopathy and right ventricular infarction, diastolic dysfunction impairs ventricular relaxation and decreases wall compliance, whereas in pericardial constriction, also termed constrictive pericarditis or pericardial restriction, cardiac filling is limited by the rigid, often calcified pericardial shell. Impaired venous return decreases end-diastolic volume, stroke volume, and cardiac output. Despite reduced cardiac volumes, cardiac filling pressures are markedly elevated and equal in all four chambers of the heart at end-diastole (Fig. 40-38). Although PAC monitoring reveals this pressure equalization, the characteristic M or W configuration is more apparent in the CVP trace, most likely because of the damping effect of the pulmonary vasculature on left-sided filling pressures.[307-309]

Another hallmark of pericardial constriction is observed in the right and left ventricular pressure traces. These traces demonstrate rapid, but short-lived early diastolic ventricular filling, which produces a diastolic "dip-and-plateau" pattern or "square root sign."[72,310] In some cases, particularly when the heart rate is slow, a similar waveform pattern may be noted in the CVP trace: a steep y descent (the diastolic dip) produced by rapid early diastolic flow from the atrium to the ventricle, followed by a mid-diastolic h wave (the plateau) from the interruption in flow imposed by the restrictive pericardial shell (see Fig. 40-38).

Like pericardial constriction, cardiac tamponade impairs cardiac filling, but in the case of tamponade, a compressive pericardial fluid collection produces this effect. This fluid collection results in a marked increase in CVP and reduced diastolic volume, stroke volume, and cardiac output. Despite many similar hemodynamic features, tamponade and constriction may be distinguished by the different CVP waveforms seen in these two conditions. In tamponade, the venous pressure waveform appears more monophasic and is dominated by the systolic x pressure descent. The diastolic y pressure descent is attenuated or absent because early diastolic flow from the right atrium to the right ventricle is impaired by the surrounding compressive pericardial

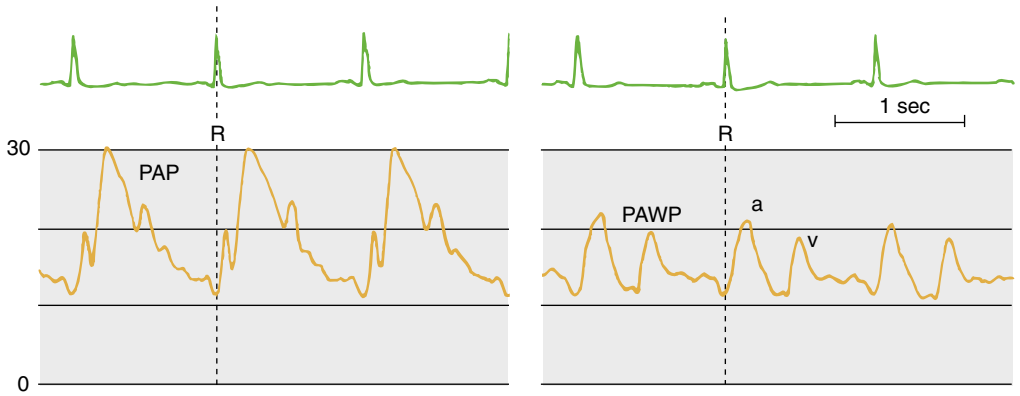


Figure 40-37 Myocardial ischemia. Pulmonary artery pressure (PAP) is relatively normal and mean pulmonary artery wedge pressure (PAWP) is only slightly elevated (15 mm Hg). However, PAWP morphology is markedly abnormal, with tall a waves (21 mm Hg) resulting from the diastolic dysfunction seen in this condition. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 12-4.)*

fluid collection (Fig. 40-39).[307,311,312] Clearly, other clinical and hemodynamic clues help identify these diagnoses, such as the presence of *pulsus paradoxus*, an almost invariable finding in cardiac tamponade (see Fig. 40-16).[313] Coexisting abnormalities such as tachycardia, arrhythmias, and atrial contractile failure may complicate interpretation of these waveforms. On occasion, localized pericardial constriction may simulate valvular stenosis, and hypovolemia may lower cardiac filling pressure to within the normal range and confound the diagnosis.

Probably the single most important waveform abnormality or interpretive problem in PAC monitoring is discerning the correct pressure measurement in patients who are receiving *positive-pressure ventilation* or who have labored spontaneous respiration or other causes of greatly increased intrathoracic pressure. Just as in the case of CVP monitoring, transmural cardiac filling pressures are best estimated when end-expiratory pressure values are recorded (see the earlier section "Physiologic Considerations for Central Venous Pressure Monitoring: Diastolic Pressure-Volume Relationships and Transmural Pressure"). During positive-pressure ventilation, inspiration increases pulmonary artery and wedge pressure. By measuring these pressures at end-expiration, the confounding effect of this inspiratory increase in intrathoracic pressure is minimized (Fig. 40-40).[199] Forceful inspiration during spontaneous ventilation has the opposite effect, but again, measurement of these pressures at end-expiration eliminates this confounding factor. Bedside monitors are designed with algorithms that aim to identify and report the numeric values for end-expiratory pressures but are notoriously inaccurate.[314,315] The most reliable method for measuring central vascu-

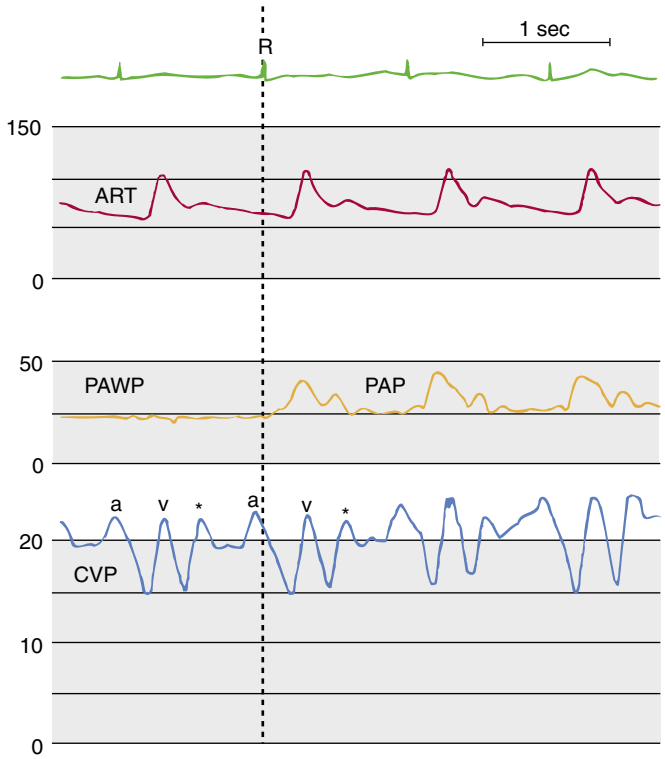


Figure 40-38 Pericardial constriction. This condition causes elevation and equalization of diastolic filling pressure in the pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), and central venous pressure (CVP) traces. The CVP waveform reveals tall a and v waves with steep x and y descents and a mid-diastolic plateau wave (*) or h wave. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 18-1.)*

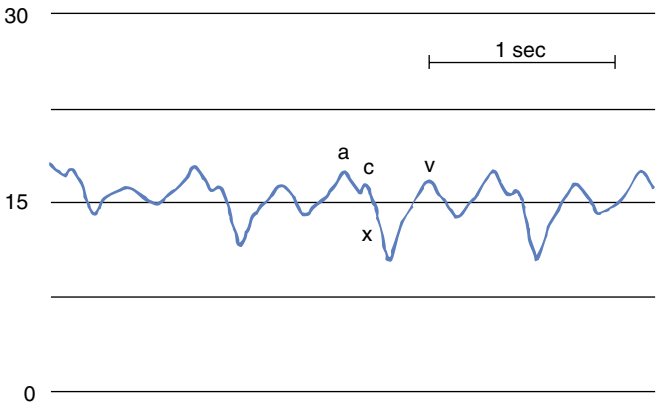


Figure 40-39 Cardiac tamponade. The central venous pressure waveform shows increased mean pressure (16 mm Hg) and attenuation of the y descent. Compare with Figure 40-38. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 18-5.)*

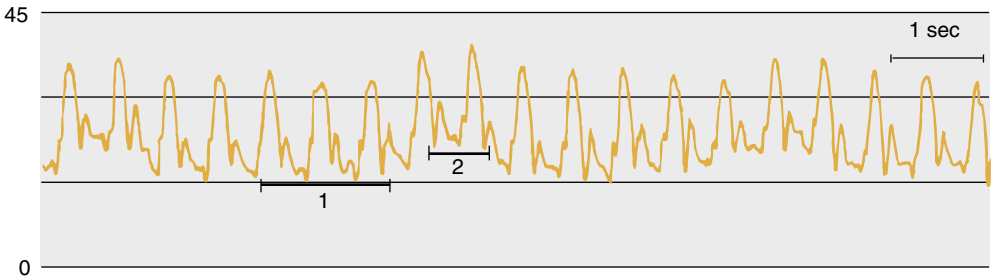


Figure 40-40 Influence of positive-pressure mechanical ventilation on pulmonary artery pressure. Pulmonary artery pressure should be measured at end-expiration #1, 15 mm Hg) to obviate the artifact caused by positive pressure inspiration (#2, 22 mm Hg). Compare with Figure 40-26. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 16-3.)*

lar pressures at end-expiration is examination of the waveforms on a calibrated monitor screen or paper recording.[315,316]

Use of Central Vascular Pressures to Estimate Left Ventricular Preload

A detailed understanding of the relationship between left ventricular filling pressure and preload is important for clinically meaningful interpretation of PAC-derived data. Although surrogates such as PADP and PAWP are used as measures of left ventricular filling, many factors influence the relationship between filling pressure and chamber volume. For example, a PAWP of 20 mm Hg is somewhat higher than normal, but depending on its interpretation and the clinical setting, different treatments would be indicated. Proper interpretation of this filling pressure depends on juxtacardiac pressure and ventricular compliance. Most commonly, a wedge pressure of 20 mm Hg is assumed to mean that juxtacardiac pressure and ventricular compliance are normal and the diagnosis is hypervolemia, with increased left ventricular end-diastolic volume causing the increased PAWP. However, different conclusions are reached if juxtacardiac pressure is increased by certain condition, including tamponade, constriction, or positive-pressure ventilation. Furthermore, a wedge pressure of 20 mm Hg may mean that ventricular compliance is decreased, such as might occur with diastolic dysfunction secondary to myocardial ischemia, hypertrophy, or cardiomyopathy (Fig. 40-41).

Determining an ideal central vascular pressure is often a clinical challenge. At the extremes of high and low, the appropriate intervention is more obvious. Unfortunately, things are rarely so clear-cut in critically ill patients, and the optimal wedge pressure must often be chosen empirically. A fluid challenge may be useful in determining the optimal pressure by comparison with the baseline hemodynamics of the particular patient. An intravenous bolus of crystalloid or colloid solution (250 to 500 mL) is given over a period of 15 minutes, and the change in wedge pressure is measured. Small increases in wedge pressure after the fluid challenge (e.g., <3 mm Hg) suggest that the ventricle is operating on the flat portion of its diastolic filling curve, whereas large increases in wedge pressure (e.g., ≥7 mm Hg) suggest that the steep portion of the curve has been reached and that little further increase in stroke volume and cardiac output can be achieved without a substantial risk of producing hydrostatic pulmonary edema.[50,315]

Clinicians have recognized for years that CVP is a poor indicator of volume status for a variety of reasons.[317,318] The diastolic pressure-volume curves for the left and right ventricles are different even in healthy individuals, with the left ventricle being less compliant. Although investigators have shown that CVP, PADP, and PAWP all vary in the same direction, the more important question is whether small changes in CVP are clinically meaningful or even reliably detectable.[319,320]

The shared septum of the left and right ventricles, as well as the presence of the pericardium, leads to further interpretive problems in the use of CVP for assessing ventricular preload. Ventricular interdependence and pericardial constraint couple changes in right and left ventricular function such that a primary change in right ventricular filling may produce a secondary change in left ventricular filling by altering its diastolic pressure-volume relationship.[198,321] For example, acute pulmonary artery hypertension increases right ventricular end-diastolic volume and pressure, shifts the ventricular septum leftward, and increases left ventricular end-diastolic pressure while simultaneously decreasing left ventricular end-diastolic volume because of a shift

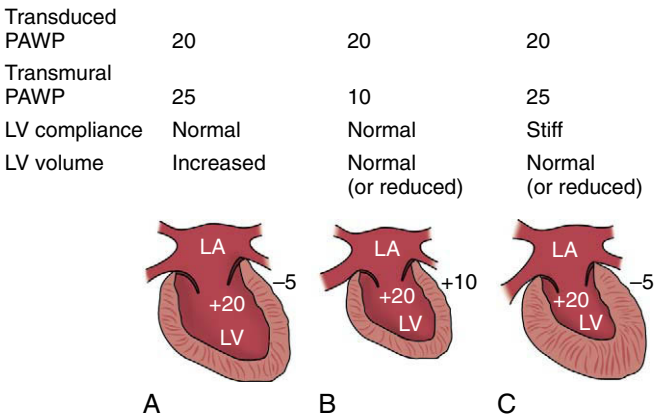


Figure 40-41 Influence of juxtacardiac pressure and ventricular compliance on left ventricular (LV) preload. There are three interpretations of increased transduced pulmonary artery wedge pressure (PAWP, 20 mm Hg). **A,** Juxtacardiac pressure (–5 mm Hg) and LV compliance are normal, transmural PAWP is increased (25 mm Hg), and LV volume is increased. **B,** Juxtacardiac pressure is increased (+10 mm Hg), LV compliance is normal, transmural PAWP is decreased (10 mm Hg), and LV volume is normal or decreased. **C,** Juxtacardiac pressure is normal, LV compliance is decreased, transmural PAWP is increased (25 mm Hg), and LV volume is normal or decreased. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 15-8.)*

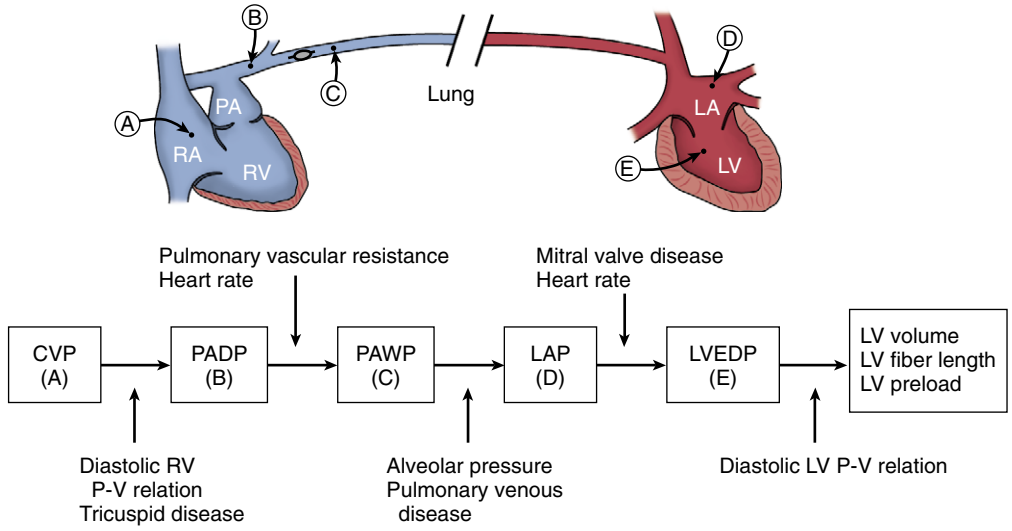


Figure 40-42 Anatomic and physiologic factors that influence the relationships between various measures of left ventricular (LV) filling and true LV preload. The further upstream filling pressure is measured, the more confounding factors may influence the relationship between this measurement and LV preload. CVP, central venous pressure; LA, left atrium; LAP, left atrial pressure; LVEDP, left ventricular end-diastolic pressure; PA, pulmonary artery; PADP, pulmonary artery diastolic pressure; PAWP, pulmonary artery wedge pressure; P-V, pressure-volume; RA, right atrium, RV, right ventricle. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 15-5.)*

in the left ventricular pressure-volume relationship to a steeper, stiffer curve. Conversely, primary changes on the left side can adversely affect the right heart structures in similar ways.

Finally, numerous additional factors may alter the relationship between CVP and left ventricular preload (Fig. 40-42).[194] The further upstream from the left ventricle one records the "filling pressure," the greater the multitude of factors that conspire to nullify the relationship between the monitored pressure and left ventricular preload. In view of these considerations, it should be no surprise that reliance on CVP to estimate left ventricular preload in critically ill patients is poorly placed.

Predicting Left Ventricular End-Diastolic Pressure

The first reason to measure wedge pressure is that it estimates pulmonary capillary pressure and as such offers a measure of the hydrostatic pressure within the pulmonary capillaries that largely controls the formation of pulmonary edema. Although wedge pressure and capillary pressure are not identical, changes in PAWP and capillary pressure generally mirror each other.

The second purpose for measuring wedge pressure is to estimate filling of the left ventricle. The end-diastolic wedge pressure after atrial contraction best predicts left ventricular end-diastolic filling pressure or preload.[315] Left ventricular end-diastolic pressure is measured at the Z-point (the point at which the slope of the left ventricular pressure upstroke changes, approximately 50 msec after the ECG Q wave and generally coinciding with the ECG R wave) (Fig. 40-43).[61]

PAC Underestimation of Left Ventricular End-Diastolic Pressure

When a PAC is used to estimate left ventricular filling pressure, there are a number of situations in which this pressure is either underestimated or overestimated (Tables 40-5 and 40-6, respectively). Left ventricular diastolic dysfunction leading to decreased ventricular compliance is the most common cause of underestimation of left ventricular end-diastolic pressure.[322] The atrial contribution to left ventricular end-diastolic volume and pressure is normally less than 20%, but with diastolic dysfunction, it may approach 50%.[296] Under these conditions, the wedge pressure a wave will be unusually prominent and will provide a close estimate of left ventricular end-diastolic pressure, but the mean wedge pressure will underestimate left ventricular filling (see Fig. 40-37).[269] In patients with aortic regurgitation, abnormal diastolic left ventricular filling from the aorta occurs as soon as left ventricular pressure falls below aortic pressure and continues after left atrial contraction and closure of the mitral valve. Left ventricular diastolic pressure continues to rise until end-diastolic pressure is reached at the onset of mechanical systole. Because mitral valve closure occurs before end-diastole, mean PAWP and the wedge pressure a wave both underestimate left ventricular end-diastolic pressure.[269]

In the presence of pulmonic regurgitation, diastolic flow from the proximal pulmonary artery becomes bidirectional, moving both antegrade into the left atrium and retrograde into the right ventricle. When right ventricular diastolic pressure is lower than LAP, pulmonary artery diastolic flow seeks the lower-pressure pathway toward the right ventricle, and PADP will underestimate PAWP, LAP, and left ventricular end-diastolic pressure.[323]

When PVR is normal, there is no pressure gradient across the pulmonary vascular bed at the end of diastole, and PADP equilibrates with the downstream LAP. However, when right ventricular systole is delayed because of right bundle branch block, PAP continues to fall with the x or systolic descent in LAP. In such circumstances, PADP may underestimate left ventricular end-diastolic pressure by as much as 7 mm Hg.[324]

Under normal conditions, inflation of the PAC balloon to measure wedge pressure interrupts antegrade blood flow through

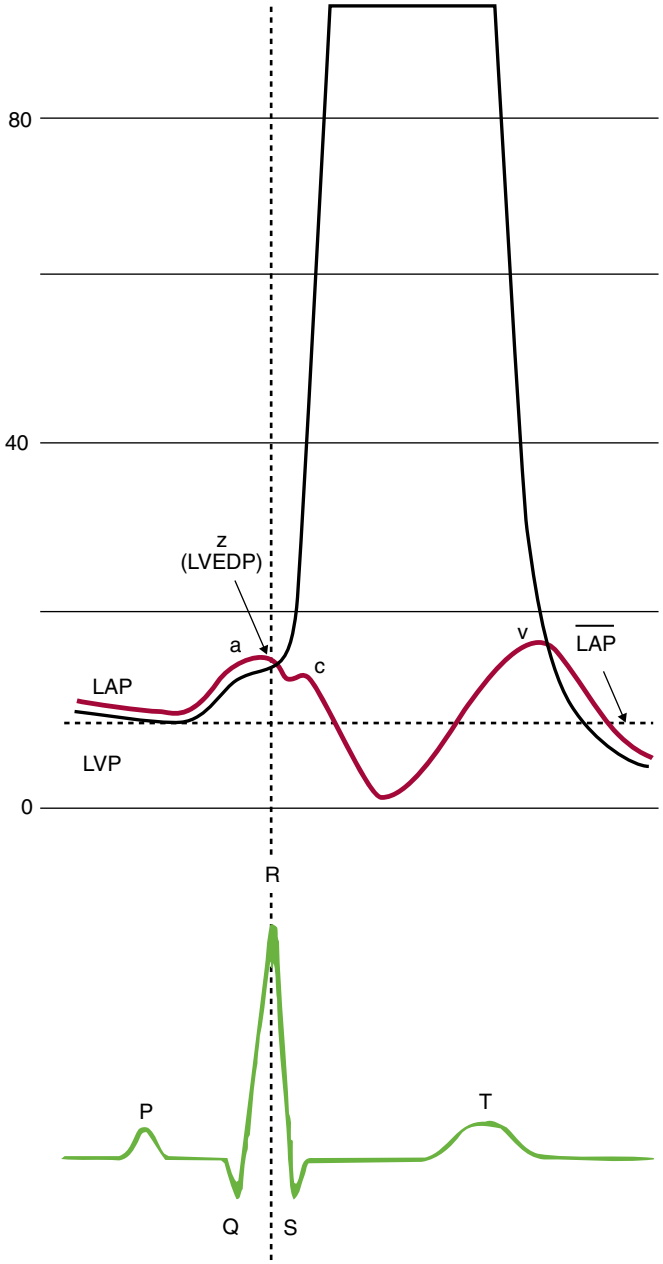


Figure 40-43 Relationship between left atrial pressure (LAP) and left ventricular end-diastolic pressure (LVEDP). LVEDP is measured at the Z-point on the left ventricular pressure (LVP) trace at the time of the electrocardiographic R wave. Mean LAP (9 mm Hg) underestimates LVEDP (15 mm Hg), but the LAP a wave pressure peak closely estimates LVEDP. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 6-1.)*

a small section of the lung and has no measurable effect on total pulmonary blood flow or left heart filling. However, after pneumonectomy and in other rare conditions that markedly decrease the pulmonary vascular bed, balloon inflation may occlude a significant portion of the remaining pulmonary vascular cross-sectional area. Mechanical obstruction of pulmonary blood flow ensues and causes increased CVP, as well as decreased LAP, cardiac output, and systemic blood pressure.[325] Therefore, because inflation of the PAC balloon for measurement of wedge pressure leads to obstruction of pulmonary blood flow, the measured wedge pressure underestimates the left atrial and left ventricular end-diastolic pressures that existed before balloon inflation.

Table 40-5 Underestimation of Left Ventricular End-Diastolic Pressure

Condition	Site of Discrepancy	Cause of Discrepancy
Diastolic dysfunction	Mean LAP < LVEDP	Increased end-diastolic a wave
Aortic regurgitation	LAP a wave < LVEDP	Mitral valve closure before end-diastole
Pulmonic regurgitation	PADP < LVEDP	Bidirectional runoff for pulmonary artery flow
Right bundle branch block	PADP < LVEDP	Delayed pulmonic valve opening
After pneumonectomy	PAWP < LAP or LVEDP	Obstruction of pulmonary blood flow

LAP, left atrial pressure; LVEDP, left ventricular end-diastolic pressure; PADP, pulmonary artery diastolic pressure; PAWP, pulmonary artery wedge pressure. Modified from Mark JB: Predicting left ventricular end-diastolic pressure. *In* Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 59.

PAC Overestimation of Left Ventricular End-Diastolic Pressure

Respiratory influences on the pulmonary artery and wedge pressure traces are the most common cause of overestimation of left ventricular end-diastolic pressure (see Table 40-6). Mechanical ventilation with PEEP poses a particular problem inasmuch as it may expand zone 1 or zone 2 lung conditions and allow PAWP to be influenced by alveolar pressure. In general, mechanical ventilation with PEEP increases wedge pressure by an amount less

Table 40-6 Overestimation of Left Ventricular End-Diastolic Pressure

Condition	Site of Discrepancy	Cause of Discrepancy
Positive end-expiratory pressure	Mean PAWP > mean LAP	Creation of lung zone 1 or 2 or pericardial pressure changes
Pulmonary arterial hypertension	PADP > mean PAWP	Increased pulmonary vascular resistance
Pulmonary veno-occlusive disease	Mean PAWP > mean LAP	Obstruction to flow in large pulmonary veins
Mitral stenosis	Mean LAP > LVEDP	Obstruction to flow across the mitral valve
Mitral regurgitation	Mean LAP > LVEDP	Retrograde systolic v wave raises mean atrial pressure
Ventricular septal defect	Mean LAP > LVEDP	Antegrade systolic v wave raises mean atrial pressure
Tachycardia	PADP > mean LAP > LVEDP	Short diastole creates pulmonary vascular and mitral valve gradients

LAP, left atrial pressure; LVEDP, left ventricular end-diastolic pressure; PADP, pulmonary artery diastolic pressure; PAWP, pulmonary artery wedge pressure. Modified from Mark JB: Predicting left ventricular end-diastolic pressure. *In* Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 59.

than half the value of PEEP applied (i.e., 10 cm H_2O PEEP will raise wedge pressure less than 5 cm H_2O or 4 mm Hg).[50,326] However, the ratio of chest wall compliance to lung compliance has a significant impact on the relationship between PEEP and its effect on PAWP, and simple mathematical methods to adjust for this effect are not adequate.[50,321,327] Alternative methods to correct for PEEP, such as measuring pleural pressure, are cumbersome and not generally used. Prolonged discontinuation of PEEP before measuring wedge pressure is to be discouraged. Not only might circulatory dynamics change dramatically as a result of rebound central hypervolemia caused by translocation of blood into the core, but respiratory gas exchange may also deteriorate and be slow to recover.[50] As an alternative, Pinsky and coworkers found that transient airway disconnection for 2 to 3 seconds in patients receiving mechanical ventilation with PEEP allowed measurement of nadir wedge pressure, which proved to be a better and safer way to estimate left ventricular filling pressure at higher levels of PEEP.[327] When wedge pressure measurement did not change after abrupt airway disconnection, the on-PEEP wedge pressure measurement accurately reflected left ventricular filling pressure. However, when wedge pressure decreased after airway disconnection, the nadir wedge pressure reached within 3 seconds provided a more accurate measurement. Studying patients with adult respiratory distress syndrome, Teboul and colleagues found that PAWP closely estimates left ventricular end-diastolic pressure at all levels of PEEP up to 20 cm H_2O.[328] This relative microvascular "protection" from the effects of PEEP presumably occurred because of the marked increase in lung stiffness seen in these patients.

When the pulmonary vasculature is normal, pulmonary blood flow ceases at end-diastole, and PADP equals LAP. However, if PVR increases, PAP equilibration with downstream pressure does not occur. Under these conditions, the pulmonary vascular bed begins to resemble the systemic vasculature, where a large pressure gradient between systemic arterial pressure and right atrial pressure persists at end-diastole. Therefore, in the presence of pulmonary arterial hypertension, PADP overestimates PAWP, LAP, and left ventricular end-diastolic pressure.[329]

In contrast to the precapillary pulmonary vasoconstriction that exists in patients with pulmonary arterial hypertension, postcapillary obstruction to flow in the pulmonary veins may occur in the rare condition pulmonary veno-occlusive disease. Patients with this condition have normal LAP, but some disagreement exists about whether these patients have normal or elevated PAC-derived wedge pressure measurements.[50,330,331] In part, these different observations may relate to whether the PAC has been wedged successfully because the wedge position may be difficult to obtain in these patients or in some instances the measured wedge pressure may be recorded from a totally occluded vascular channel. The most important factor, however, is whether the patient has predominantly small-vein occlusion or large-vein occlusion. Obstruction to flow in the small pulmonary veins narrows the static column of blood connecting the wedged PAC tip with the flowing column in the larger pulmonary veins. Given that the partial obstruction involves only the static column, wedge pressure will measure normal left atrial and pulmonary venous pressure because there is no pressure drop across this partially obstructed vascular segment in the absence of flow. Conversely, large-vein obstruction creates a pressure gradient across the large veins as blood flows in these vessels toward the left atrium. In this instance, wedge pressure will detect an increased pulmonary venous pressure and overestimate left atrial and ventricular diastolic pressure.[50,330,331] This model of pulmonary vein obstruction is consistent with the observations of Zidulka and Hakim, who measured wedge pressure in both large and small pulmonary arteries.[332] Other conditions may mimic the hemodynamic features of pulmonary veno-occlusive disease, including mediastinal fibrosis and intrathoracic or atrial tumors that obstruct pulmonary venous flow near the left atrium.

Mitral stenosis obstructs blood flow between the left atrium and left ventricle, and consequently LAP will exceed left ventricular pressure throughout diastole. Furthermore, all upstream pressures recorded by the PAC will overestimate left ventricular end-diastolic pressure as a result of the valvular obstruction. Because the pressure gradient across the mitral valve is directly related to flow, PADP and PAWP will overestimate left ventricular filling pressure even more when transmitral flow is increased by tachycardia or elevated cardiac output.[333]

LAP is increased in mitral regurgitation because of the abnormal leakage of blood across the incompetent valve during systole, and left ventricular end-diastolic pressure is better approximated by measuring wedge pressure before onset of the regurgitant c-v wave (see Fig. 40-34).[334] In contrast to patients with mitral stenosis, in whom LAP exceeds left ventricular pressure throughout diastole, patients with mitral regurgitation have appropriate diastolic equilibration of atrial and ventricular pressure. The problem in mitral regurgitation is choosing the appropriate end-diastolic, pre–v wave pressure to use as an estimate for left ventricular end-diastolic pressure. Mean PAWP will overestimate left ventricular end-diastolic pressure in any patient whose wedge pressure displays tall systolic v waves, including those with ventricular septal defect and left ventricular failure.[287,290]

When tachycardia develops, the duration of diastole is shortened. At both the mitral and pulmonary vascular levels, pressure gradients develop as diastole progressively shortens.[335,336] Consequently, PADP overestimates mean PAWP, which in turn overestimates left ventricular end-diastolic pressure. Patients in atrial fibrillation will have more complete equilibration of PADP and left ventricular end-diastolic pressure during longer R-R intervals. Consequently, these beats should be chosen to provide the best estimate of left ventricular end-diastolic pressure and preload.

Additional Features of Pulmonary Artery Catheters

The popularity of PACs is largely due to the fact that they are multipurpose and provide a wide range of supplementary features for therapeutic and diagnostic applications. Some catheters have a third lumen, which is often used as an additional venous infusion line that opens either 20 or 30 cm from the catheter tip. Others have specific modifications designed for monitoring continuous cardiac output, right heart function, or mixed venous oximetry, thereby vastly expanding the types of physiologic information available to those caring for critically ill patients. Specialized PACs also allow temporary endocardial pacing or intracardiac ECG recording and may even have combinations of electrodes permanently implanted along its length to allow bipolar ventricular, atrial, or atrioventricular pacing.[337] Other models have a special lumen that opens in the right ventricle, through which a

thin bipolar wire may be introduced for endocardial ventricular pacing, or have separate atrial and ventricular lumens for passage of two pacing wires for bichamber sequential pacing.[338]

Pulmonary Artery Catheterization and Outcome Controversies

Pulmonary artery catheterization has stimulated a great deal of vigorous controversy. It is an expensive, invasive technique that is widely used but still not proven to improve patient outcome. The PAC controversy has been fueled in part by strongly worded editorials written by prominent physicians debating whether PAC use should be suspended pending scientific proof of its efficacy.[339-341] Although similar controversies have surrounded the use of other widely adopted, highly technical clinical monitoring techniques such as electronic fetal monitoring, physicians who use PACs should especially appreciate the uncertainties surrounding PAC monitoring and be fully informed of the evidence that must guide patient selection.[342,343]

In 2003, the American Society of Anesthesiologists published an updated practice guideline for pulmonary artery catheterization that included a current exhaustive review of the scientific evidence for the clinical effectiveness of PAC monitoring.[211] The inconsistent findings of the many studies in the literature were striking, with evidence both supporting and refuting the benefits of this technique.[213,301,344-346] A great amount of the published literature concerning the use of PACs had been plagued by problems in study design (lack of randomization, small sample size), lack of standardization, and heterogeneity of both patients and clinical settings (medical versus surgical, cardiac surgery patients versus patients with acute congestive heart failure). Furthermore, even within a given clinical setting there is little consensus on which hemodynamic parameters are the most relevant to obtain from use of the PAC and no agreement on appropriate therapeutic interventions in response to specific findings.

Perhaps the most provocative of the early studies was published by Connors and colleagues, who examined the association between PAC use during the first 24 hours of intensive care and subsequent survival.[347] This prospective cohort study included 5735 patients in five teaching hospitals as part of a larger 9000 patient cohort.[348,349] Entry into the study required predicted 6-month mortality in excess of 50%. Patients who were in the PAC-monitored group were judged to be sicker by every measurement recorded, although to the extent statistically possible, the authors used case-matching analyses and applied a propensity score to adjust for these confounding medical covariates. These patients had increased mortality, increased length of hospital stay, and increased cost. Moreover, there was no subgroup of patients who appeared to benefit from PAC monitoring. Publication of this study was accompanied by a strongly worded editorial calling for a moratorium on PAC use or initiation of a randomized controlled trial to define its efficacy.[339]

In the intervening years, a great deal of work and energy have been devoted to determining whether patients are being helped or harmed by the use of PACs. Fortunately, a series of large, randomized, adequately powered studies have been published that specifically address this issue. Three trials enrolling a total of 3468 patients showed no effect on mortality or on hospital or intensive care unit length of stay despite a higher incidence of adverse events.[213,350,351] These complications were most commonly infection or "insertion-related" events. These trials included medical and surgical patients, elderly and high-risk patients, and those with severe heart failure. These findings were confirmed by two meta-analyses of 11 and 13 published randomized, controlled trials involving PAC use.[352,353]

Some investigators have even been able to show a treatment benefit from PAC use in selective populations, a finding that helps guide future use and research. A review of 53,312 patients from the National Trauma Data Bank showed no mortality benefit in those treated with PACs in the group as a whole. However, in patients with an injury severity scale score greater than 25, those who arrived at the hospital in severe shock, or those older than 60 years, mortality was decreased significantly.[354] In a mixed medical and surgical population, patients with Acute Physiology and Chronic Health Evaluation (APACHE) scores less than 25 showed increased mortality when treated with PACs, whereas those with scores higher than 31 showed significant benefit.[355]

Indications for Pulmonary Artery Catheterization

The most recent recommendations governing the use of PACs are the American Society of Anesthesiologists practice guideline published in 2003.[211] The task force considered PAC monitoring to be appropriate in surgical patients undergoing procedures associated with a high risk of complications from hemodynamic changes (e.g., cardiac surgery) or patients with advanced cardiopulmonary diseases that would place them at increased risk for adverse perioperative events. Furthermore, the specific practice setting, as well as the proficiency and experience of clinicians, should be considered.

PAC use must be tailored to the degree of risk for the patient and the risk posed by the procedure itself. For example, a patient with advanced ischemic cardiomyopathy who needs lower extremity amputation under regional anesthesia would not warrant PAC monitoring, whereas a patient with stable ischemic heart disease scheduled for extensive abdominal cancer resection may benefit from perioperative use. Furthermore, the individual practice setting must be considered.[211] Keats has termed this feature "the role of environment in the outcome of operation," by which he means important unmeasurable aspects of the clinical setting, including, but not limited to technical skill and experience.[356] Clearly, all physicians and nurses using a PAC must have the requisite knowledge and skills to use it safely and effectively. Unfortunately, this is a goal that eludes objective definition and remains unattained by current postgraduate training programs.[266]

Several important points should be kept in mind when indications for PAC monitoring are being considered. First, uses of the catheter are different in different patient populations. For example, whereas acute titration of fluids and inotropic agents is most relevant in the perioperative period, in the heart failure population, fine management of oral medications or delineation of drug combinations may be most important. Use of the catheter should be timely; that is, it should not be withheld until irreversible injury has occurred and therapies would be futile. Patients arriving in shock may benefit from immediate PAC placement, whereas others may warrant "watchful waiting." In addition, no

catheter should be placed unless the data will be used. Finally, it is of the utmost importance to consider the clinical expertise and experience of those manipulating the catheter and interpreting the data.

It seems a reasonable conclusion from the bulk of published research that PAC use should be limited, although a moratorium on use is ill advised. Use should be reserved to centers with significant experience and expertise. Moreover, PACs should generally be used to monitor and guide therapy in patients at high risk for hemodynamic instability, those who are judged more critically ill by a variety of clinical means, and those who are in shock, especially if older than 60 years.

There remains a great deal of uncertainty and controversy surrounding PAC use. Among the many measurements and calculations possible from a PAC, there is little consensus on which is the most meaningful and useful. Furthermore, therapies based on these findings have not been systematically studied or validated. Indeed, the variations in PAC design have moved so far beyond simple wedge pressure measurement that the PAC is becoming as much a physiologic monitor as it is a hemodynamic one. A PAC itself has no capacity to benefit and only limited risk. However, the potential for adverse outcomes from therapies based on PAC measurements is tremendous. This is the direction that future research needs to take.

Cardiac Output Monitoring

Aside from its pressure monitoring capabilities, one of the more important features of the PAC is its ability to measure cardiac output via the thermodilution method. Cardiac output is the total blood flow generated by the heart, and in a normal adult at rest it ranges from 4.0 to 6.5 L/min. Measurement of cardiac output provides a global assessment of the circulation, and when combined with other hemodynamic measurements (heart rate, arterial blood pressure, CVP, PAP, and PAWP), it allows calculation of additional important circulatory variables such as systemic vascular resistance (SVR), PVR, and ventricular stroke work (Table 40-7).

Three factors have driven efforts to measure cardiac output in clinical practice. The first is the recognition that in many critically ill patients, low cardiac output leads to significant morbidity and mortality.[357] In addition, clinical assessment of cardiac output is often inaccurate; for example, seriously ill patients with decreased cardiac output might have normal systemic arterial blood pressure.[358] Finally, newer techniques for measurement of cardiac output are less invasive than PAC monitoring and thus might provide benefit to many patients without the attendant risks associated with invasive monitoring.[358-360] The advantages and disadvantages of each technique must be appreciated for proper clinical application.

Thermodilution Cardiac Output Monitoring

The thermodilution technique has become the de facto clinical standard for measuring cardiac output because of its ease of implementation and extensive clinical experience with its use in various settings. It is a variant of the *indicator dilution* method, in which a known amount of a tracer substance is injected into the bloodstream and its change in concentration measured over time at a downstream site (see Chapter 38 for more details). For thermodilution, (negative) heat is injected, and change in temperature downstream is measured.

Table 40-7 Normal Hemodynamic Values

	Average	Range
Cardiac output (L/min)	5.0	4.0-6.5
Stroke volume (mL)	75	60-90
Systemic vascular resistance		
Wood units	15	10-20
Dynes•sec/cm^5	1200	800-1600
Pulmonary vascular resistance		
Wood units	1	0.5-3
Dynes•sec/cm^5	80	40-180
Arterial oxygen content (mL/dL)	18	16-20
Mixed venous oxygen content (mL/dL)	14	13-15
Mixed venous oxygen saturation (%)	75	70-80
Arteriovenous oxygen difference (mL/dL)	4	3-5
Oxygen consumption (mL/min)	225	200-250

In practical terms, a fixed volume of iced or room-temperature fluid is injected as a bolus into the proximal (right atrial) lumen of the PAC, and the resulting change in pulmonary artery blood temperature is recorded by a thermistor at the catheter tip. As in all other forms of cardiovascular monitoring, it is important to have a real-time display of the thermodilution curve resulting from each cardiac output measurement.[361] This allows the clinician to discern artifacts that would invalidate the cardiac output measurement, such as unstable blood temperature, recirculation, or incomplete indicator injection. Usually, a series of three cardiac output measurements performed in rapid succession are averaged to provide a more reliable result. When only a single injection was used to determine cardiac output, a difference between sequential cardiac output measurements of 22% was required to suggest a clinically significant change. In contrast, when three injections were averaged to determine the thermodilution measurement, a change greater than 13% indicated a clinically significant change in cardiac output.[362]

Even when carefully performed, some studies have found that thermodilution cardiac output measurements may not agree with other reference methods.[363,364] However, few complications are directly attributable to the technique itself, and monitoring the trend in cardiac output is probably more clinically useful than emphasizing any absolute value.

Sources of Error in Thermodilution Cardiac Output Monitoring

Several important technical issues and potential sources of error must be considered to interpret thermodilution cardiac output measurements properly (Box 40-7).[361] The thermodilution technique measures right ventricular output. In the face of an *intracardiac shunt*, right ventricular and left ventricular output will not be equal. In patients with left-to-right shunts, early recirculation of the thermal indicator can be seen to distort the downward slope of the thermodilution curve, and in patients with right-to-

Box 40-7 Factors Influencing the Accuracy of Thermodilution Cardiac Output Measurement

- Intracardiac shunts
- Tricuspid or pulmonic valve regurgitation
- Inadequate delivery of thermal indicator
  - Central venous injection site within the catheter introducer sheath
  - Warming of iced injectate
- Thermistor malfunction from fibrin or a clot
- Pulmonary artery blood temperature fluctuations
  - Post–cardiopulmonary bypass status
  - Rapid intravenous fluid administration
- Respiratory cycle influences

left shunt, some of the injected indicator will bypass the thermistor and result in overestimation of left ventricular cardiac output.

Patients with *tricuspid* or *pulmonic valve regurgitation* pose additional problems for thermodilution cardiac output measurement because of recirculation of the indicator across the incompetent valve. In patients with severe tricuspid regurgitation, the thermodilution curves have an abnormally prolonged decay time, and the measured cardiac output may be inaccurate. Unfortunately, there is no simple method to correct for this problem. In the presence of significant tricuspid regurgitation, thermodilution cardiac output techniques are simply unreliable, either underestimated or overestimated, depending on the severity of valvular regurgitation and the magnitude of the cardiac output.[361,365]

Other technical problems with thermodilution cardiac output measurement are caused by *inadequate delivery of the thermal indicator*. Mishandling of an iced injectate syringe can warm the solution and reduce the signal of the thermal indicator administered. In addition, fibrin or blood clot on the PAC tip may lead to *thermistor malfunction* and result in spurious cardiac output values.

Unrecognized *fluctuation in blood temperature* may also influence cardiac output measurement. In most patients, pulmonary artery blood temperature falls rapidly in the initial minutes *after cardiopulmonary bypass* when the rewarmed body core redistributes the heat gained at the end of bypass. Because of this progressive decline in central core and pulmonary artery blood temperature, the thermal baseline is unstable. Thermodilution cardiac output measurements made in the minutes after bypass are notoriously unreliable, most often leading to marked underestimation of true cardiac output.[366] Other inaccuracies in thermodilution cardiac output measurement occur when pulmonary artery blood temperature changes because of *rapid fluid infusion*.[367] Either overestimation or underestimation of cardiac output occurs, depending on the timing of the additional fluid bolus.

The choice of iced (0°C) or room-temperature injectate has been examined in detail to determine the preferred method for accurate measurement of cardiac output. Although the size of the thermal bolus (and hence the signal-to-noise ratio) is increased when an iced injectate is used, this indicator is more time-consuming, expensive, and cumbersome to prepare than a room-temperature injectate is. Because several groups have demonstrated equivalent accuracy in cardiac output determinations when iced and room-temperature injectates are compared, it appears that room-temperature injectate is preferred for almost all clinical applications.[368] In adults, an injectate volume of 10 mL should be used, whereas in children, an injectate volume of 0.15 mL/kg is recommended.[361]

One of the more controversial issues in standard bolus thermodilution cardiac output monitoring is the proper timing of measurement in relation to the *respiratory cycle*, particularly in patients receiving positive-pressure mechanical ventilation. Because the stroke output of the right ventricle varies as much as 50% during the respiratory cycle, the limited "sampling" of right ventricular stroke volumes measured with the bolus thermodilution technique may lead to widely variable measurements of cardiac output, depending on the point during the respiratory cycle when the measurements are performed.[369] Although reproducibility of consecutive measurements improves markedly when the bolus injections are synchronized to the same phase of the respiratory cycle, accurate measurement of average cardiac output is achieved more reliably by making multiple injections during the different phases of the respiratory cycle and then averaging the results.[361,369]

Continuous Thermodilution Cardiac Output Monitoring

Newer technologies applied to PAC monitoring allow nearly continuous cardiac output (CCO) monitoring with a warm thermal indicator.[370,371] In brief, small quantities of heat are released from a 10-cm thermal filament incorporated into the right ventricular portion of a PAC, approximately 15 to 25 cm from the catheter tip, and the resulting thermal signal is measured by the thermistor at the tip of the catheter in the pulmonary artery. The heating filament is cycled on and off in a pseudorandom binary sequence, and cardiac output is derived from cross-correlation of the measured pulmonary artery temperature with the known sequence of heating filament activation.[371] Typically, the value displayed for cardiac output is updated every 30 to 60 seconds and represents the average value for the cardiac output measured over the previous 3 to 6 minutes. In a laboratory investigation examining how CCO measurements responded to unstable hemodynamic conditions, such as hemorrhage and fluid resuscitation, Siegel and colleagues showed that changes in CCO were markedly slower than changes detected by ultrasonic flow probe, blood pressure, or mixed venous oxygen saturation.[372] In view of these inherent time delays, the PAC CCO method should be considered a continual rather than a continuous real-time monitor.

In general, the CCO method appears to have good agreement with standard bolus thermodilution cardiac output measurements or electromagnetic flow probe techniques.[370,373] In a small, multicenter study, Mihm and associates found that CCO provided a clinically reliable measurement in a group of 47 intensive care unit patients.[370] The device performed well in patients with a wide range of cardiac output (1.6 to 10.6 L/min) and core temperature (33.2°C to 39.8°C), and the method showed no deterioration in performance over the 72-hour monitoring period. Reproducibility and precision appear to be better with the CCO method than with the standard bolus thermodilution techniques,

probably because of the fact that the continuous method displays a time-weighted average cardiac output value as opposed to a single instantaneous measurement.[374,375]

The CCO PAC has been widely accepted into clinical use for a number of practical reasons. Although these catheters are more expensive than standard PACs, obviating the need for bolus injections reduces nursing workload and the potential risk of fluid overload or infection. Furthermore, because the CCO PAC provides a cardiac output value that is an average derived over the previous several minutes, the beat-to-beat variations in stroke volume that occur during a single respiratory cycle are all equally represented. As a result, cardiac output measured by the CCO method may provide a more accurate measurement of global cardiac output in patients receiving positive-pressure mechanical ventilation.

However, like cold bolus thermodilution techniques, warm thermal CCO has certain methodologic pitfalls that must be recognized and avoided. The CCO computer and catheter require a significant amount of time to warm up and may work poorly in an environment with a great deal of thermal noise, such as the cardiac operating room. As already emphasized, CCO monitors have an inherent 5- to 15-minute delay in responding to abrupt changes in cardiac output, and the magnitude of this delay depends on the type of physiologic perturbation, as well as the CCO computer monitor algorithm.[372] Although modifications of CCO algorithms provide a "STAT Mode" rapid response time, acute changes in cardiac output are still detected more slowly by CCO monitoring than by other methods, such as direct arterial pressure or mixed venous oximetry. In effect, the CCO technique involves a fundamental tradeoff between rapid response time and overall accuracy of measurement. Standards for these performance characteristics have not been defined but must balance the response time against the stability of the displayed value and its immunity from thermal noise.[374]

Mixed Venous Oximetry Pulmonary Artery Catheter

Although the formal Fick cardiac output method is not widely applied in clinical practice, the physiologic relationships described by the Fick equation form the basis for another PAC-based monitoring technique termed *continuous mixed venous oximetry*. Rearrangement of the Fick equation reveals the four determinants of mixed venous hemoglobin saturation:

$$S\bar{v}O_2 = SaO_2 - \frac{\dot{V}O_2}{\dot{Q} \times 1.36 \times Hb} \quad (1)$$

where $S\bar{v}O_2$ = mixed venous hemoglobin saturation (%)
SaO_2 = arterial hemoglobin saturation (%)
$\dot{V}O_2$ = oxygen consumption (mL O_2/min)
$\dot{Q}$ = cardiac output (L/min)
Hb = hemoglobin concentration (g/dL)

To the extent that arterial hemoglobin saturation, oxygen consumption, and hemoglobin concentration remain stable, mixed venous hemoglobin saturation may be used as an indirect indicator of cardiac output. For example, when cardiac output falls, tissue oxygen extraction increases and the mixed venous blood will have a lower oxygen content and lower hemoglobin oxygen saturation. However, as noted in this equation, mixed venous hemoglobin saturation also varies directly with arterial hemoglobin concentration and saturation and inversely with oxygen consumption. When any of these other variables change significantly, one cannot assume that a change in mixed venous hemoglobin saturation results solely from a change in cardiac output. Although these considerations may confound the use of mixed venous hemoglobin saturation as an indicator of cardiac output, monitoring this variable provides more comprehensive information about the balance of oxygen delivery and consumption by the body—not just the raw cardiac output, but also the adequacy of that cardiac output.[376]

Although mixed venous hemoglobin saturation may be determined by intermittent blood sampling from the pulmonary artery, a specially designed PAC can provide this information reliably and continuously. Fiberoptic bundles incorporated into the PAC determine the hemoglobin saturation in pulmonary artery blood based on the principles of reflectance oximetry using either a two- or three-wavelength system. A special computer connected to this PAC displays the mixed venous hemoglobin saturation continuously. The technology is typically incorporated into the standard PAC or the CCO PAC, in the latter case providing both CCO and venous oximetry data.

Technical problems with continuous mixed venous oximetry are generally limited to improper positioning of the PAC tip against the vessel wall or inaccurate calibration.[377] Multi-wavelength fiberoptic technology and reflection intensity algorithms help reduce wall artifacts caused by spurious reflections from a PAC thrombus or the pulmonary arterial walls. These catheters are calibrated at the bedside before use but may also be calibrated in vivo from a pulmonary artery blood gas sample if the mixed venous saturation values are questionable. Most clinical trials comparing PAC-derived continuous venous oximetry values with laboratory analysis of pulmonary artery blood samples have shown good agreement between techniques.[378] It is important to remember that mixed venous oxygenation is a global, whole-body measurement. Therefore, regionally inadequate blood flow and tissue oxygen delivery (such as limb or intestinal ischemia) can coexist with a normal or a high mixed venous oximetry value.

The continuous mixed venous oximetry PAC may be used to measure thermodilution cardiac output and arterial and mixed venous oxygen content values and thereby calculate oxygen consumption by rearrangement of the Fick equation. However, values for oxygen consumption derived from these measurements generally underestimate direct oxygen consumption measured by mass spectrometry, metabolic cart, or water-sealed spirometry.[379]

Oxygen delivery may also be calculated as shown in Equation 2:

$$\dot{D}O_2 = \dot{Q} \cdot CaO_2 \quad (2)$$

where $\dot{D}O_2$ = oxygen delivery (mL/min)
$\dot{Q}$ = cardiac output (dL/min)
CaO_2 = oxygen content of arterial blood (mL O_2/dL blood)

Many physicians have used these derived measures of oxygen consumption and oxygen delivery to guide the treatment of critically ill patients, although the success of this "goal-oriented therapy" in improving patient outcomes is still inconclusive. However, a recent randomized study in patients undergoing

cardiac surgery has shown better outcome in patients randomized to protocol-driven interventions aimed at achieving mixed venous oxygen saturation higher than 70% (and blood lactate <2 mg/dL).[380] Similarly, optimizing central venous oxygen saturation (measured in superior vena cava blood) has been shown to improve outcome in patients with early sepsis[381] and in high-risk surgical patients.[382]

It is important to note that these studies have used strict protocol-driven therapeutic interventions. A large Veterans Affairs observational trial of 3265 cardiac surgical patients noted that 49% of patients received continuous mixed venous oximetry PACs and that use of this catheter was associated with increased cost but no better outcome than achieved in the standard PAC group.[383] In this study, however, no protocol was used to guide therapeutic interventions based on monitoring results.

Right Ventricular Ejection Fraction Pulmonary Artery Catheters

Although cardiovascular monitoring has focused predominantly on left ventricular performance, in some instances, right ventricular dysfunction may be the more important factor limiting circulation. Patient populations at increased risk for right ventricular dysfunction include those with chronic obstructive pulmonary disease, adult respiratory distress syndrome, pulmonary hypertension, and right ventricular ischemia and infarction.[384] Standard techniques are available for monitoring right ventricular performance in patients with acute myocardial infarction involving the right ventricle. PAC monitoring in patients with right ventricular infarction often reveals the characteristic hemodynamic patterns described earlier. However, accurate evaluation of right ventricular performance has proved more complicated. In patients with severe respiratory failure, for example, the confounding effects of mechanical ventilation with high levels of PEEP have made interpretation of cardiac filling pressures difficult and, in some cases, misleading.[385]

Measurement of right ventricular ejection fraction (RVEF) with a specially designed PAC offers another method for evaluating right ventricular function. This method uses a standard PAC equipped with a rapid-response thermistor that detects and quantifies the small changes in pulmonary artery blood temperature that occur with each heartbeat, in a manner somewhat analogous to a standard CCO PAC. The cardiac output computer measures the residual fraction of thermal signal after each heartbeat and derives RVEF.[386] Clearly, all factors that confound standard thermodilution cardiac output measurement will also interfere with accurate determination of RVEF. In addition, because the temperature changes measured by the RVEF PAC are small beat-to-beat changes, the method will not work if the ECG R waves cannot be detected accurately, the R-R interval is short because of tachycardia, or the cardiac rhythm is irregular.[377] Comparison of PAC-based RVEF measurements with angiographic or nuclear techniques has yielded mixed results in terms of accuracy, but this may reflect, in part, the absence of a widely accepted reference standard for this measurement.[386,387] Intraoperative use of the RVEF PAC has focused primarily on detection of right ventricular dysfunction in patients with coronary artery disease undergoing surgical revascularization. Reduced RVEF has been noted after cardiopulmonary bypass, particularly in patients with preexisting right coronary artery obstruction.[388] However, RVEF is an extremely load-dependent measurement of right ventricular performance, and the clinician must keep this fact in mind to interpret this measurement properly.[377,389] Clinical use of the RVEF PAC appears to have found its greatest application to date in critically ill patients, especially those with respiratory failure.[389,390] In these applications, the measurement of greatest interest has been right ventricular end-diastolic volume, which is derived mathematically from RVEF:

$$\text{RVEDV} = \frac{\text{SV}}{\text{RVEF}} \tag{3}$$

where RVEDV = right ventricular end-diastolic volume (mL)
SV = stroke volume (mL)
RVEF = right ventricular ejection fraction

Right ventricular end-diastolic volume appears to correlate better with cardiac output than standard preload measurements such as CVP or PAWP do.[390,391] These findings are not surprising given all the interpretive problems associated with monitoring cardiac filling pressure previously discussed. It should be kept in mind, however, that the better correlation between right ventricular end-diastolic volume and cardiac output may result from the mathematical coupling of measurements because both are derivatives of stroke volume determined with the PAC. Furthermore, as in the case of standard PAC monitoring, the benefit of RVEF PAC monitoring in terms of patient outcome remains unproven.[392]

Pulmonary Artery Catheter–Derived Hemodynamic Variables

The cardiovascular system is often modeled as an electrical circuit, with the relationship between cardiac output, blood pressure, and resistance to flow related in a manner similar to Ohm's law:

$$\text{SVR} = \frac{\text{MAP} - \text{CVP}}{\text{CO}} \times 80$$
$$\text{PVR} = \frac{\text{MPAP} - \text{PAWP}}{\text{CO}} \times 80 \tag{4}$$

where SVR = systemic vascular resistance (dyne·sec·cm^{-5})
PVR = pulmonary vascular resistance (dyne·sec·cm^{-5})
MAP = mean arterial pressure (mm Hg)
CVP = central venous pressure (mm Hg)
MPAP = mean pulmonary artery pressure (mm Hg)
PAWP = pulmonary artery wedge pressure (mm Hg)
CO = cardiac output (L/min)

Normal values for SVR and PVR are given in Table 40-7. Note that these calculations of SVR and PVR are based on a hydraulic fluid model that assumes continuous laminar flow through a series of rigid pipes.[393] These calculations also use atrial pressure as the downstream pressure for systemic or pulmonary flow, with CVP used for right atrial pressure in the SVR calculation and PAWP used for LAP in the PVR calculation. Alternative methods to calculate resistance ignore the effect of these downstream pressures. For the systemic circulation, total resistance may be calculated from MAP and cardiac output alone, and for

the pulmonary circulation, total pulmonary resistance describes the ratio of mean PAP and cardiac output.

All these resistance formulas oversimplify the behavior of the cardiovascular system to a tremendous degree. A more physiologic model of the systemic circulation considers the vasculature to be a series of collapsible vessels with intrinsic tone. This model, also called the *vascular waterfall*, describes a critical closing pressure in the downstream end of the circuit that exceeds right atrial pressure and serves to limit flow—an effective downstream pressure that is higher than the right atrial pressure used in the SVR formula. Detailed consideration of these issues is beyond the scope of this discussion and is available from other sources.[394,395] The important point for clinicians, though, is that therapy focused on fine adjustment of SVR may be very misleading and should be avoided.

Additional problems arise in considering the pulmonary vasculature and using the formulas just presented as a measure of resistance to flow through the lung. The pulmonary vasculature is more compliant than the systemic vasculature, and marked increases in pulmonary blood flow may not produce any significant increase in PAP. In addition, flow usually ceases at end-diastole in the low-resistance pulmonary circuit.[396] Thus, changes in PVR may result from intrinsic alterations in pulmonary vascular tone (constriction or dilation) or vascular recruitment or from rheologic changes. For the pulmonary circuit, a better approach to evaluating changes in PVR may be to examine the end-diastolic gradient between PADP and PAWP (Fig. 40-44).[397]

Another set of common calculations derived from standard hemodynamic variables adjusts these measurements for the patient's body surface area (BSA) in an attempt to normalize these measurements for patients of different size. BSA is generally determined from a standard nomogram based on height and weight. The most commonly indexed variables are the cardiac index (cardiac index = cardiac output/BSA) and stroke volume index (stroke volume index = stroke volume/BSA). On occasion, SVR and PVR are indexed as well (SVR index = SVR/BSA; PVR index = PVR × BSA). In theory, normalizing hemodynamic values through "indexing" should help clinicians determine appropriate normal physiologic ranges to help guide therapy. Unfortunately, there is little evidence that these additional calculations provide valid normalizing adjustments. BSA is a biometric measurement with an obscure relationship to blood flow, and it does not adjust for variations between individuals based on age, sex, body habitus, or metabolic rate.[398] Although it is important to be aware of a patient's size and medical history when interpreting and treating changes in any of the measured or calculated hemodynamic variables, it is not appropriate to target therapy solely at achieving normal indexed values.

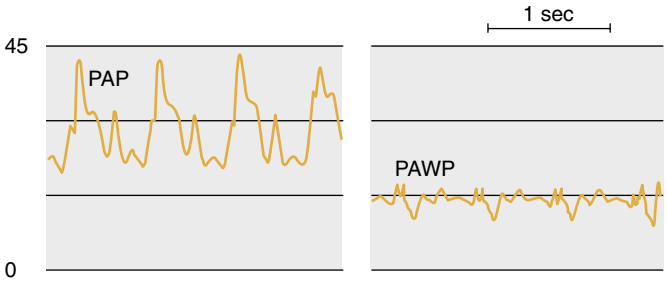


Figure 40-44 Pulmonary hypertension. The increased gradient across the pulmonary vasculature causes pulmonary artery diastolic pressure to exceed pulmonary artery wedge pressure (PAWP). PAP, pulmonary artery pressure. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, Fig. 6-11.)*

Other Methods for Monitoring Cardiac Output and Perfusion

Ultrasound-Based Methods for Monitoring Cardiac Output

All of the ultrasound-based methods for monitoring cardiac output use the Doppler principle. When ultrasound waves strike moving objects, these waves are reflected back to their source at a different frequency, termed the *Doppler shift frequency*, which is directly related to the velocity of the moving objects and the angle at which the ultrasound beam strikes these objects. For measurement of blood flow, the red blood cells flowing through a major artery serve as the moving objects targeted by the ultrasound beam. To measure blood flow velocity, the Doppler equation is rearranged to solve for velocity:

$$v = \frac{f \times c}{2f_0 \times \cos\theta} \quad (5)$$

where v = velocity of red blood cell targets
f = Doppler shift frequency
f_0 = transmitted ultrasound beam frequency
θ = angle between the ultrasound beam and the vector of red blood cell flow
c = velocity of ultrasound in blood (approximately 1570 m/sec)

In general, determining blood flow velocity requires just a single measurement, the Doppler shift frequency, because the velocity of ultrasound in blood and the transmitted ultrasound frequency are known and cos θ is assumed to equal 1 as long as the angle of insonation is small. This assumption requires that the ultrasound beam be oriented as much as possible in a direction that is parallel to the flow of blood. For example, for angles of less than 20 degrees, cos θ will be greater than 0.94, thereby introducing an error of less than 6% in calculation of cardiac output. Once the Doppler shift frequency is measured and blood flow velocity is calculated, stroke volume can be determined from Equation 6:

$$SV = v \cdot ET \cdot CSA \quad (6)$$

where SV = stroke volume (mL)
v = spatial average velocity of blood flow (cm/sec)
ET = systolic ejection time (sec)
CSA = cross-sectional area of the vessel (cm^2)

Several different ultrasound-based methods can be used to measure cardiac output, each using slightly different equipment and measuring blood flow from a different site in the body.

Suprasternal Doppler Cardiac Output Monitoring

This method was developed to measure blood flow velocity in the distal aortic arch with an ultrasound transducer applied to the

suprasternal notch.[399] Although the suprasternal Doppler cardiac output technique showed reasonable agreement with the thermodilution method, it is relatively labor intensive, requires a fair degree of experience and expertise, and cannot be accomplished in a significant number of critically ill medical and surgical patients.[399,400] Because it provides only an intermittent measurement at best, clinical acceptance of this method was limited.

Esophageal Doppler Cardiac Output Monitoring

The evolution of Doppler techniques into practical clinical monitoring tools required an ultrasound transducer that could be positioned and left in place for continuous monitoring without the need for repeated adjustments or time-consuming measurements by the physician or ultrasonographer. Such a transducer was incorporated into the tip of a standard esophageal stethoscope to allow continuous monitoring of cardiac output by interrogating the blood flow profile in the descending thoracic aorta. In brief, the Doppler probe is inserted into the esophagus to a depth of approximately 35 cm from the incisors. Probe position is adjusted to optimize the audible Doppler flow sound from the descending aorta. In most patients, optimal probe tip position is at the T5-T6 vertebral interspace or the third sternocostal junction because the esophagus and the descending aorta lie in close proximity and run essentially parallel to one another at this location.[401] The ultrasound transducer is mounted at a fixed angle that is anatomically defined and known by the cardiac output computer. This angle is then used to correct the resulting Doppler shift frequency to provide an accurate velocity measurement.

Several limitations of the esophageal Doppler technique must be appreciated by the physician to avoid pitfalls in interpretation of data. This monitoring method interrogates blood flow in the descending thoracic aorta and therefore measures only a fraction of total cardiac output. To report total cardiac output, either the esophageal Doppler measurement must be "calibrated" by some alternative method or an empirically determined correction constant of 1.4 must be used.[402] This constant is accurate for most patients but does not apply universally, especially in the presence of conditions that redistribute blood flow, such as pregnancy, aortic cross-clamping, and post–cardiopulmonary bypass status.[401,403] In addition, the diameter of the descending aorta is either measured by using A-mode ultrasound or calculated on the basis of the patient's age, sex, height, and weight via a nomogram.[404] When calculated, it is assumed that the diameter of the descending aorta does not change throughout the cardiac cycle.[405] Moreover, the technique is likely to be inaccurate in the presence of aortic valve stenosis or regurgitation or in patients with thoracic aortic disease, it is not easily applied in nonintubated patients, and it cannot be used in individuals with esophageal pathology. Finally, like all ultrasound techniques, the acoustic window needed to acquire the Doppler signal may not be adequate in some individuals, thereby precluding use of this method.

Advantages of the esophageal Doppler monitoring technique include its ease of use, minimal invasiveness, and inherent safety. It appears that limited experience is needed for clinical success—as few as 10 to 12 cases for accurate application of the technique.[401] In a recent review describing 25 clinical trials in which esophageal Doppler cardiac output measurement was compared with PAC thermodilution measurements, it was noted that the Doppler cardiac output values correlated well with the thermodilution measurements and showed minimal overall bias and good tracking of directional changes in thermodilution cardiac output with low intraobserver and interobserver measurement variability.[401]

The esophageal Doppler method has enjoyed renewed popularity.[402,406] Current devices provide a clear visual display of the spectral Doppler waveform, but they also calculate and display additional hemodynamic variables, including peak blood flow velocity, flow acceleration, and heart rate–corrected flow time (Fig. 40-45). Some studies have shown that these additional measures provide useful information about left ventricular preload, contractility, and SVR.[402,407] One of the more important values of the monitor may be focusing clinical attention on optimizing stroke volume rather than total cardiac output. Indeed, in critically ill patients, complications may be better predicted by low stroke volume than by low cardiac output.[408] Several studies have shown that volume resuscitation guided by maximizing esophageal Doppler–measured stroke volume in moderate-risk surgical patients reduces perioperative morbidity and shortens hospital stay.[409-411]

Bioimpedance Cardiac Output Monitoring

The technique of bioimpedance cardiac output monitoring was first described by Kubicek and colleagues and is based on changes in electrical impedance of the thoracic cavity occurring with ejection of blood during cardiac systole.[412] Their original formula relates these bioimpedance measurements to stroke volume:

$$SV = \frac{\rho L^2}{Zo^2} \times VET \times \max \frac{dZ}{dt} \qquad (7)$$

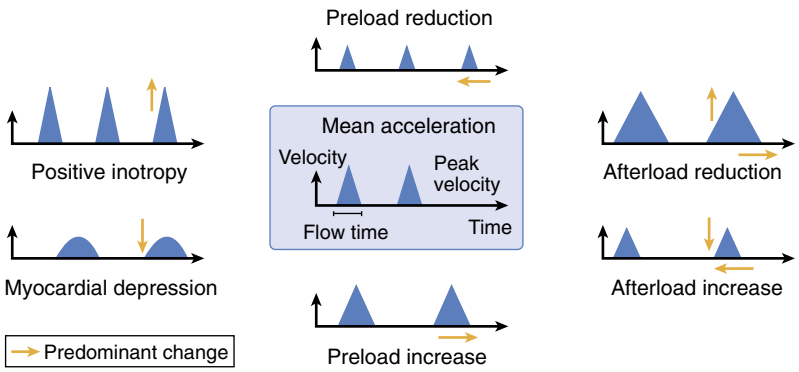


Figure 40-45 Spectral Doppler tracings of aortic blood flow recorded with esophageal Doppler cardiac output monitoring. The velocity-time waveform shape reflects alterations in contractility (mainly affecting peak velocity and mean acceleration), preload (mainly affecting systolic flow time corrected for heart rate [FTc]), and afterload (which affects FTc, mean acceleration, and peak flow velocity). *(Modified with permission from Singer M: Esophageal Doppler monitoring of aortic blood flow: Beat-by-beat cardiac output monitoring. Int Anesthesiol Clin 31:99-125, 1993.)*

where SV = stroke volume
ρ = specific resistivity of blood
L = thoracic length
Zo = basal thoracic impedance
VET = ventricular ejection time

$\max \frac{dZ}{dt}$ = maximum rate of impedance change during systolic upstroke

For performing the measurements, disposable electrodes are applied to the skin surface along the sides of the neck and lateral aspect of the lower part of the thorax, and a continuous small electrical current is applied across the chest. Patient height, weight, and gender are used to calculate the volume of the thoracic cavity. Bioimpedance cardiac output is computed for each cardiac cycle and continuously displayed as an average value over several heartbeats.

Although many studies suggest that the bioimpedance method is accurate in healthy volunteers, its reliability deteriorates in critically ill patients, including those with sepsis, increased lung water, aortic regurgitation, and electronic cardiac pacing.[413-415] More recent changes in signal processing techniques have improved the accuracy of thoracic bioimpedance measurements and might increase its clinical acceptance.[416]

Partial CO_2 Rebreathing Cardiac Output Monitoring

Another method of monitoring cardiac output that does not require pulmonary artery catheterization is the partial CO_2 rebreathing technique.[417,418] Because of the difficulty encountered in the standard Fick method involving measuring oxygen consumption and mixed venous hemoglobin saturation, this new technique is based on a restatement of the Fick equation for carbon dioxide elimination rather than oxygen uptake:

$$\dot{Q} = \frac{\dot{V}_{CO_2}}{C\bar{v}_{CO_2} - Ca_{CO_2}} \quad (8)$$

where $\dot{Q}$ = cardiac output
$\dot{V}_{CO_2}$ = rate of carbon dioxide elimination
$C\bar{v}_{CO_2}$ = carbon dioxide content of mixed venous blood
Ca_{CO_2} = carbon dioxide content of arterial blood

This method uses the change in CO_2 production and end-tidal CO_2 concentration in response to a brief, sudden change in minute ventilation. With a specially designed breathing system and monitoring computer, this measurement is easily performed in any tracheally intubated patient. Every 3 minutes a computer-controlled pneumatic valve intermittently increases dead space for a 50-second period, thereby causing partial rebreathing of exhaled gases. Changes in end-tidal CO_2 in response to the rebreathing are used to calculate cardiac output by a differential version of the Fick equation for carbon dioxide. The attractive features of this method are that it is entirely noninvasive, it can be performed every few minutes, and the brief episodes of rebreathing pose no substantial risk to most patients, with end-tidal CO_2 measurements increasing by less than 3 mm Hg. However, as currently designed, this technique requires tracheal intubation for accurate measurement of exhaled gases. Furthermore, changing patterns of ventilation may have an unpredictable influence on the measurement. As with all Fick-based techniques, the partial CO_2 rebreathing method measures pulmonary capillary blood flow as an indicator of total cardiac output and thus requires correction for pulmonary shunt.

The initial clinical trials suggested reasonably good agreement between the partial rebreathing CO_2 cardiac output method and other techniques such as thermodilution. However, as with most of these newer monitoring methods, the clinical trials are small and mainly focused on specific patient groups, particularly coronary artery bypass patients.[419] At present, the clinical role of this technique is primarily focused on short-term intraoperative applications or mechanically ventilated postoperative patients.

Lithium Dilution Cardiac Output Monitoring

The lithium dilution technique is another cardiac output monitoring method that derives its fundamental basis from indicator dilution principles.[420] In brief, after an intravenous bolus injection of a small dose of lithium chloride, an ion-selective electrode attached to a peripheral arterial catheter measures the lithium dilution curve, from which cardiac output is derived. Preliminary investigations suggest that this technique is accurate when compared with standard thermodilution methods or electromagnetic flowmetry.[421,422] As originally described, the technique required a central venous catheter for injection of lithium, but recent studies indicate comparable accuracy with peripheral intravenous bolus administration of the lithium indicator.[423] Thus, the technique seems to provide a method for accurate cardiac output measurement in a wide variety of critically ill patients who only have peripheral intravenous and arterial catheters.

Transpulmonary Thermodilution Cardiac Output

For transpulmonary thermodilution measurement, ice-cold saline is injected into a central line and the change in temperature is measured in a large peripheral artery (femoral, axillary, or brachial artery) via a special arterial catheter equipped with a thermistor.[424] Several studies have shown adequate correspondence to standard thermodilution cardiac output.[425,426] Because the measurement lasts over several cardiac cycles, respiratory effects on stroke volume are averaged and eliminated, in contrast to standard thermodilution.[427] Mathematical derivation from the thermodilution curve can produce two additional clinically useful indices: extravascular lung water, which is a measure of pulmonary edema,[428,429] and intrathoracic blood volume, which is a measure of preload. Several studies have found this index to be a better measure of cardiac preload than traditional measurements such as CVP or PAWP.[430,431]

Pulse Contour Cardiac Output Monitoring

In an attempt to provide continuous measurement of cardiac output, a number of techniques have focused on analysis of the arterial pulse pressure waveform. These methods, generally termed *pulse contour cardiac output*, determine the cardiac output from computerized analysis of the arterial pressure waveform

recorded from an arterial catheter or even a noninvasive finger blood pressure waveform.[432,433] Pulse contour methods offer the potential for continuous, beat-to-beat monitoring of cardiac output. In addition, the change in stroke volume from beat to beat can be used to evaluate volume status in ventilated patients.[434]

However, several disadvantages exist.[435] First, baseline calibration with a known cardiac output is required to account for individual differences in vascular resistance, impedance, and wave reflectance. Additionally, recalibration is required every 8 to 12 hours to account for changes in vasculature characteristics over time. A reasonably well-defined arterial pressure waveform is needed for accurate identification of systole and diastole, a condition that might not exist in patients with severe tachycardia or dysrhythmia.

Although early studies comparing these techniques showed fairly poor agreement with other cardiac output measurements, more recent clinical trials in surgical patients have shown that the pulse contour methods provide an acceptable level of accuracy.[433,436,437]

Gastric Tonometry

Gastric tonometry aims at monitoring gastric circulation as an early indication of splanchnic hypoperfusion.[438] A balloon-tipped tube is inserted into the stomach, and the saline or air in the balloon is allowed to equilibrate with the CO_2 in the gastric lumen. Intermittently, the saline or air is aspirated and the CO_2 level is measured. With the development of gastric hypoperfusion, clearance of CO_2 from the gastric mucosa decreases while CO_2 production increases from titration of acid released by anaerobic metabolism. The CO_2 from the mucosa diffuses freely to the gastric lumen and is detected by the tonometry.

Several studies have shown that gastric mucosal CO_2 and pH are a predictor of post-trauma or perioperative complications or death.[439-441] Furthermore, several studies have shown that therapy guided by gastric tonometry can improve clinical outcome in critically ill or perioperative patients.[442,443]

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Daniel P. Vezina, Ken B. Johnson, and Michael K. Cahalan

41 Transesophageal Echocardiography

Key Points

1. One of the category I indications for transesophageal echocardiography (TEE) is evaluation of intubated, hemodynamically unstable patients.
2. Guidelines expected in 2009 will probably recommend the use of TEE during all cardiac and other major surgical procedures in which severe hemodynamic instability is anticipated.
3. The speed of sound in the heart is assumed to be constant at 1540 m/sec.
4. The higher the transducer frequency, the better the image quality, but the more limited the depth of penetration.
5. Doppler echocardiography is used to measure the velocity of blood in the cardiac chambers and across the valves.
6. The modified Bernoulli equation transforms velocities into pressure gradients. Pressure gradient = $4V^2$, where V = velocity in m/sec.
7. Continuous wave Doppler measures high velocities but does not precisely identify their location.
8. Pulsed wave Doppler permits measurement of velocities at an exact location but is limited in its ability to measure high velocities.
9. Color Doppler codes for flow: blue away from the probe, red toward the probe (BART).
10. The abbreviated TEE examination will be adequate for the practice of basic TEE as defined by the 1996 SCA/ASA TEE guidelines.
11. TEE has been shown to be more sensitive than electrocardiography for the intraoperative detection of myocardial ischemia.

Transesophageal echocardiography (TEE) is the most powerful cardiovascular diagnostic technique available in the practice of perioperative medicine today. Thousands of published reports document its vital role in the determination of hemodynamics, detection of myocardial ischemia, evaluation of cardiovascular pathology, and assessment of cardiac surgical plans and results. With the information provided by TEE, anesthesiologists, surgeons, and intensivists can alter therapy to decrease morbidity and increase the survival of surgical patients. No other diagnostic technique has had such an impact on the practice of anesthesia and critical care. This chapter reviews the published literature documenting TEE's role in perioperative care after presenting a brief summary of TEE's history, its underlying physical principles, and the techniques required to perform it.

History

In 1976, Dr. Leon Frazin and colleagues published the results of studies using an esophageal M-mode transducer and thereby introduced the concept of transesophageal echocardiography.[1] Subsequently, Matsumoto and associates used M-mode TEE to study left ventricular (LV) function during cardiovascular surgery.[2] However, M-mode echocardiography provides too limited a view of spatial relationships to be practical for intraoperative monitoring or real-time decision-making. In the early 1980s, investigators led by Hanrath introduced a two-dimensional (2D), phased-array transducer mounted on the tip of a flexible gastroscope, and TEE's intraoperative potential became apparent.[3] However, wide adoption of TEE did not occur until the mid-1980s, when TEE transducer design was refined and color flow Doppler became commercially available. With these advances, TEE could provide the high-resolution, real-time images of structure and blood flow that we use on a daily basis today. However, the original single-plane and subsequent biplane TEE probes limited the potential imaging planes. Multiplane TEE using a rotatable 2D transducer within the probe tip resolved these limitations substantially and remains the current standard of practice.

Along with advances in probe technology, ultrasound manufacturers improved image compression algorithms, high-density digital storage, and broadband communication networks, which

has revolutionized the storage and processing of TEE images. Secure digital servers have replaced videotape libraries of clinical studies, thereby resulting in vastly faster access to and fidelity of stored images, and after decades of work on real-time three-dimensional (3D) imaging, it is finally a reality. Its impact on clinical practice remains to be determined, but we predict that it will simplify and speed mastery of the assessment of valvular anatomy and pathology.[4]

Practice Guidelines for Transesophageal Echocardiography

In 1992, the American Society of Echocardiography (ASE) Committee for Physician Training in Echocardiography published its guidelines for training in TEE.[5] They are based on previous recommendations for training in transthoracic echocardiography (TTE) and are directed at training for TEE in both operative and nonoperative applications. These guidelines require the trainee to attain at least an intermediate level of training in echocardiography and perform and interpret no less than 50 supervised TEE examinations. In 1996, a joint task force of the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists (SCA) published guidelines for perioperative TEE that defined two levels of practice: basic and advanced.[6] Anesthesiologists with basic training in perioperative TEE "should be able to use TEE for indications that lie within the customary practice of anesthesiology" and "must be able to recognize their limitations in this setting and request assistance, in a timely manner, from a physician with advanced training." Anesthesiologists with advanced training in perioperative TEE "should, in addition to the above, be able to exploit the full diagnostic potential of TEE in the perioperative period." These guidelines broadly defined the general principles for training in perioperative TEE, including cognitive and technical objectives. In addition, the guidelines delineated three categories of evidence-based indications for TEE, including category I indications, in which TEE was judged to frequently be useful in improving clinical outcomes in patients with hemodynamic instability, valvular pathology, cardiac source of emboli, and aortic pathology (Box 41-1). These indications were based on available data in 1995 when the task force wrote the guidelines. In 2007, the task force was reconvened to update the guidelines. Publication of their recommendations is expected in 2009. Based on the information available today, we anticipate a recommendation that TEE be used in all patients undergoing cardiac or thoracic aortic surgery and in other surgical patients in whom known or suspected cardiovascular pathology might result in significant hemodynamic, pulmonary, or neurologic compromise.

In 1999, a joint task force of the ASE and SCA published recommendations for a comprehensive TEE examination.[7] These recommendations described in detail the 20 TEE cross sections included in the comprehensive examination. In 2002, a joint task force of the ASE and SCA used the principles and recommendations published in the aforementioned guidelines to formulate guidelines for training in perioperative TEE, including the prerequisite medical knowledge and training, echocardiographic knowledge and skills, training components and duration, training environment and supervision, and equivalence requirements for postgraduate physicians already in practice.[8] A minimum number of cases are delineated; however, these numbers are less important than the depth and diversity of the clinical experience and the quality of training. Like previous published guidelines, these guidelines provide training recommendations for a basic and an advanced level of perioperative echocardiography. Unlike previous guidelines, these guidelines do not specify the duration of training. Instead, they emphasize the goals of training and the number and diversity of cases required to meet these goals (Table 41-1). The time required for perioperative training will vary markedly depending on the volume and diversity of the affiliated cardiac surgical program.

The American Heart Association (AHA), American College of Cardiology (ACC), ASE, and other professional organizations have issued other guidelines that involve TEE. In 2003, the AHA, ACC, and ASE published practice guidelines for the clinical use of echocardiography, including intraoperative and critical care TEE applications.[9] Their class I indications are essentially the

Box 41-1 Indications for Perioperative Transesophageal Echocardiography

Category I indications: Supported by the strongest evidence or expert opinion; TEE is frequently useful in improving clinical outcomes in these settings and is often indicated, depending on individual circumstances, for the following:

Intraoperative evaluation of acute, persistent, and life-threatening hemodynamic disturbances in which ventricular function and its determinants are uncertain and have not responded to treatment

Intraoperative use in valve repair

Intraoperative use in congenital heart surgery for most lesions requiring cardiopulmonary bypass

Intraoperative use in repair of hypertrophic obstructive cardiomyopathy

Intraoperative use for endocarditis when preoperative testing was inadequate or extension of infection to perivalvular tissue is suspected

Preoperative use in unstable patients with suspected thoracic aortic aneurysms, dissection, or disruption who need to be evaluated quickly

Intraoperative assessment of aortic valve function during repair of aortic dissections with possible aortic valve involvement

Intraoperative evaluation of pericardial window procedures

Use in the intensive care unit for unstable patients with unexplained hemodynamic disturbances, suspected valve disease, or thromboembolic problems (if other tests or monitoring techniques have not confirmed the diagnosis or patients are too unstable to undergo other tests)

Adapted with permission from Practice guidelines for perioperative transesophageal echocardiography. A report by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography. Anesthesiology 84:986-1006, 1996.

Table 41-1 Recommendations for Basic and Advanced Perioperative Echocardiography

	Basic*	Advanced*
Minimum number of examinations†	150	300
Minimum number personally performed‡	50	150
Program director qualifications	Advanced perioperative echocardiography training	Advanced perioperative echocardiography training plus at least 150 additional perioperative TEE examinations
Program qualifications	Wide variety of perioperative applications of echocardiography	Full spectrum of perioperative applications of echocardiography

*Totals for basic training may be counted toward advanced training provided that the basic training was completed in an advanced training environment.
†Complete echocardiographic examinations interpreted and reported by the trainee under appropriate supervision; may include transthoracic studies recorded by qualified individuals other than the trainee.
‡Comprehensive intraoperative transesophageal echocardiographic examinations personally performed, interpreted, and reported by the trainee under appropriate supervision.
Adapted from Cahalan MK, Abel M, Goldman M, et al: American Society of Echocardiography and Society of Cardiovascular Anesthesiologists task force guidelines for training in perioperative echocardiography. Anesth Analg 94:1384-1388, 2002.

same as those listed in Box 41-1. In 2005, the ASE published its recommendations for indications and performance guidelines for pediatric TEE, including intraoperative applications,[10] and in 2007, the ACC, ASE, and multiple other societies issued their appropriateness criteria (i.e., summary of proven indications) for TTE and TEE. However, in this publication, intraoperative applications were explicitly excluded.

Properties of Ultrasound

To noninvasively visualize structures inside the body, ultrasound machines generate an imperceptible vibration within a transducer that, when put next to tissue surfaces, vibrates the surrounding tissue (muscle, blood, fat, or bone). During vibration, particles within the tissue compress and then spread apart. This dual process is called *compression* and *rarefaction*. The sequence of compression and rarefaction is described by sine waves and is characterized in terms of wavelength, frequency, amplitude, and propagation velocity (Fig. 41-1).

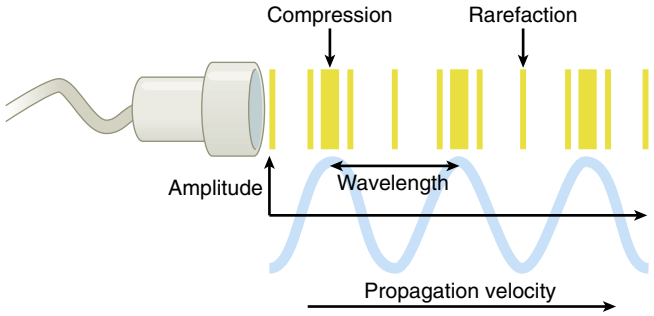


Figure 41-1 Illustration of terms used to describe transmission of ultrasound energy from a transducer into adjacent tissue. As ultrasound vibrations enter surrounding tissue, particles within the tissue compress and then spread apart (compression and rarefaction). Sine waves are used to characterize the sequence of compression and rarefaction, wavelength is the distance between two peaks of the sine wave, amplitude is a measure of tissue compression, and propagation velocity is the speed of the ultrasound wave within tissue.

Wavelength is the distance between two peaks of the sine wave. Wavelengths used in ultrasound are measured in millimeters. *Frequency* is the number of cycles that occur in 1 second. One cycle per second is defined as 1 hertz (abbreviated Hz). Ultrasound is sound with frequencies higher than the audible range for humans, or greater than 20,000 cycles per second (20 kHz). Frequencies typically used for sonographic imaging are 2 to 10 mega hertz (MHz). Wavelength is inversely related to frequency.

Amplitude is a measure of tissue compression. Amplitude represents the *loudness* of an ultrasound wave. Amplitude can vary over a large range and is described by decibels (dB). Decibels is a logarithmic transformation that allows large amplitudes to be presented next to small amplitudes (i.e., 1000 and 0.001) on the same display. A rule of thumb is that a 6-dB change is equivalent to doubling or halving of the amplitude.

Propagation velocity describes the speed of an ultrasound wave traveling through tissue. In blood it is 1540 m/sec. The relationship between propagation velocity, frequency, and wavelength is described by Equation 1:

$$\text{Propagation velocity} = \text{Frequency} \cdot \text{Wavelength} \qquad (1)$$

Assuming that propagation velocity is constant, the wavelength for any frequency can be calculated (Table 41-2).

Transducers, typically made of quartz or titanate ceramic, use crystals that exhibit the piezoelectric effect. With electricity,

Table 41-2 Relationship Among Frequency, Wavelength, and Depth of Penetration

Frequency	Wavelength	Depth of Penetration (200-400 × Wavelength)	Approximate Resolution (2 × Wavelength)
3.5 MHz	0.44 mm	9-18 cm	0.9 mm
5.0 MHz	0.31 mm	6-12 cm	0.6 mm
6.0 MHz	0.26 mm	5-10 cm	0.5 mm
7.5 MHz	0.21 mm	4-8 cm	0.4 mm

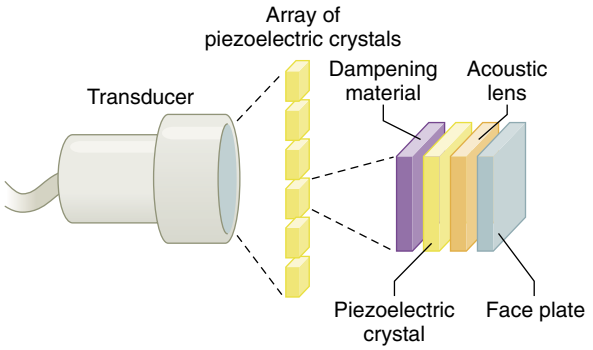


Figure 41-2 Illustration of an array of piezoelectric crystals contained within an ultrasound transducer. When pulsed with alternating current, piezoelectric crystals "ring" much like a bell. The crystal continues to vibrate after an electrical pulse has ended. To achieve a crisper pulse, a backing material is applied to the crystal to *dampen* the ring after the pulse has ended. To optimize transmission from the crystal into tissue, an *acoustic lens* focuses the ultrasound beam and an *impedance-matching face plate* improves conductance of ultrasound from the transducer into tissue.

the crystal vibrates and emits ultrasound. The reverse also holds: When ultrasound waves strike a piezoelectric crystal and make it vibrate, the crystal generates electricity. Thus, the same crystals can serve as emitters and receivers of ultrasound. The *frequency* of vibration is determined by the thickness of the piezoelectric crystal. To refine and control the emitted ultrasound beam, several layers of material are placed adjacent to the crystal (Fig. 41-2).

Transducer Frequency, Image Resolution, and Depth of Penetration

Echocardiography uses ultrasound waves with frequencies of 2.5 to 7.5 million cycles/sec (MHz). Important relationships between transducer frequency, depth, and resolution include (1) the slower the frequency, the greater the depth of penetration at the expense of resolution, and (2) the faster the frequency, the greater the resolution at the expense of depth of penetration (Table 41-3). Frequencies greater than 7.5 MHz are not used because they produce wavelengths too short for adequate penetration into tissue (an exception would be epiaortic scanning). Penetration is limited to about 200 to 400 times the wavelength. Resolution is limited to about twice the wavelength.

Image resolution is characterized in terms of axial, elevational, lateral, and temporal resolution. Axial resolution is resolution along the length of an ultrasound beam. It is a function of transducer frequency and pulse width. Long wavelengths (slow frequency) have deeper tissue penetration but are unable to resolve objects that are close together along the ultrasound beam scan line. Short wavelengths (fast frequency) do the opposite. Similarly, short-duration pulses improve and long pulses worsen axial resolution. Elevational resolution refers to the thickness of the ultrasound image: typically 8 to 10 mm.

Lateral resolution is a function of ultrasound beam formation. The initial segment (near field) of an ultrasound beam is columnar, and the length is dependent on transducer width and wavelength. Beyond the near field, the beam diverges (far field). Divergence is also a function of transducer frequency. As the frequency rises, the near field gets longer and the divergence angle decreases. For example, for transducer frequencies of 3.5 and 7 MHz, the divergence angles are 26 and 12 degrees, respectively. As the transducer width gets smaller, the angle of divergence gets larger. The lack of lateral resolution at greater depths accounts for blurring of the image in the far field (Fig. 41-3A and B).

Another descriptor of lateral resolution is the grating lobe. A grating lobe is a diverging ultrasound beam that emerges from the transducer along with the main ultrasound beam. The angle of the diverging grating lobe is determined by the spacing between the crystals in a transducer array. At angles at which the path length of an ultrasound wave between the two adjacent transducer crystals differs by one wavelength, a grating lobe is formed (Fig. 41-4).

An example of a grating lobe artifact is a properly positioned pulmonary artery catheter that appears to go through the aorta. The artifact appears as an echo-dense archlike object that traverses structures within the heart and is at equal distance from the transducer throughout the image. In this example, a diverging ultrasound beam from a grating lobe is reflected back to the transducer. The ultrasound machine cannot differentiate between reflected ultrasound from the main beam and the grating lobe beam.

Temporal resolution is the ability to accurately locate moving structures at a particular instant in time. The more images displayed per second (frame rate), the better the temporal resolution. A typical frame has 128 lines in a 90-degree 2D image. If the depth is set to 20 cm, the time required for sampling one line is 260 μsec. To scan all 128 lines requires 33 msec. In 1 second, the sector is scanned 30 times. To image moving structures inside the heart, a frame rate of at least 30 frames/sec is required. Decreasing

Table 41-3 Clinical Features of Pulsed Wave, Continuous Wave, and Color Flow Doppler

Doppler Technique	Advantages	Disadvantages	Clinical Uses
Pulsed wave	Measures blood flow velocities at selected areas of interest 3-5 mm wide along the ultrasound scan line	Cannot measure fast blood flow velocities (>1 m/sec) because of aliasing	To measure blood flow velocities through the pulmonary veins and mitral valve and in low-flow areas within the heart
Continuous wave	Detects blood flow velocities up to 7 m/sec (not subject to the Nyquist limit)	Cannot identify location of the peak velocity along the ultrasound scan line	To measure blood flow velocities through the aorta, aortic valve, stenotic valve lesions, and regurgitant valvular jets
Color flow	Presents the spatial relationships between structure and blood flow	Like pulsed wave Doppler, cannot measure fast blood flow velocities because of aliasing	To enhance recognition of valvular abnormalities, aortic dissections, and intracardiac shunts

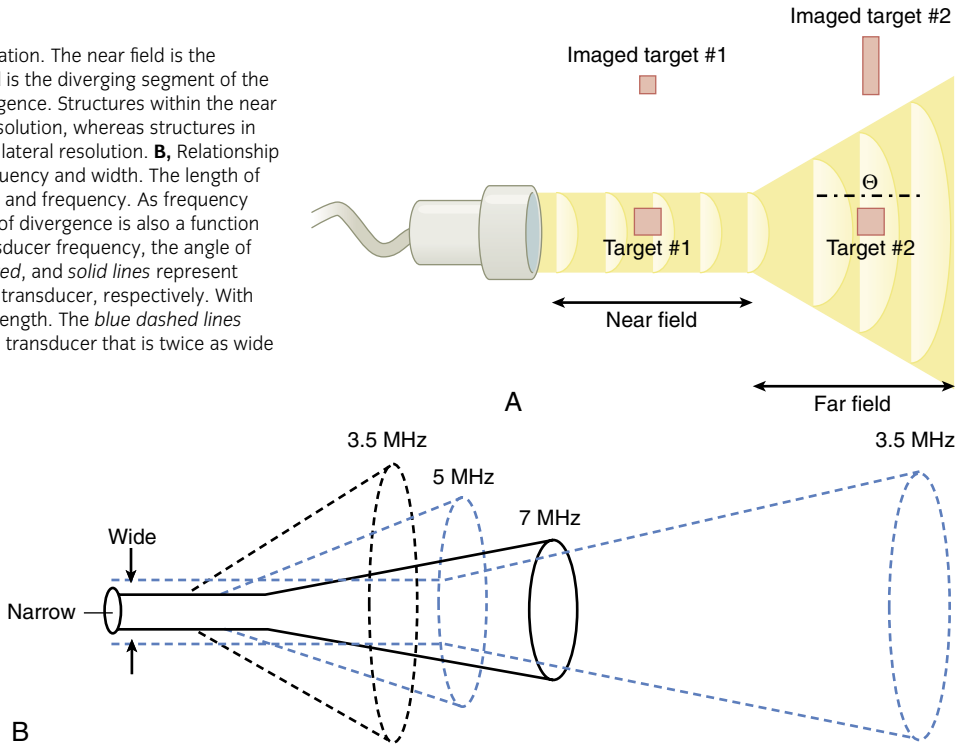


Figure 41-3 **A,** Near- and far-field beam formation. The near field is the columnar portion of the beam and the far field is the diverging segment of the beam. Theta (Θ) represents the angle of divergence. Structures within the near field (target 1) are imaged with crisp lateral resolution, whereas structures in the far field (target 2) are imaged with blurred lateral resolution. **B,** Relationship between near-field length and transducer frequency and width. The length of the near field is a function of transducer width and frequency. As frequency increases, the near field lengthens. The angle of divergence is also a function of transducer frequency. With increasing transducer frequency, the angle of divergence decreases. The *black dashed*, *dotted*, and *solid lines* represent beam divergence for a 3.5-, 5.0-, and 7.0-MHz transducer, respectively. With wider transducers, the near field increases in length. The *blue dashed lines* represent the near and far fields for a 3.5-MHz transducer that is twice as wide as the narrow transducer.

image depth will improve temporal resolution. Ultrasound machines allow the operator to zoom in on a region of interest within the 2D display. This function redistributes the number of scan lines used to generate a full 2D image into a smaller region of interest and thereby improve temporal resolution.

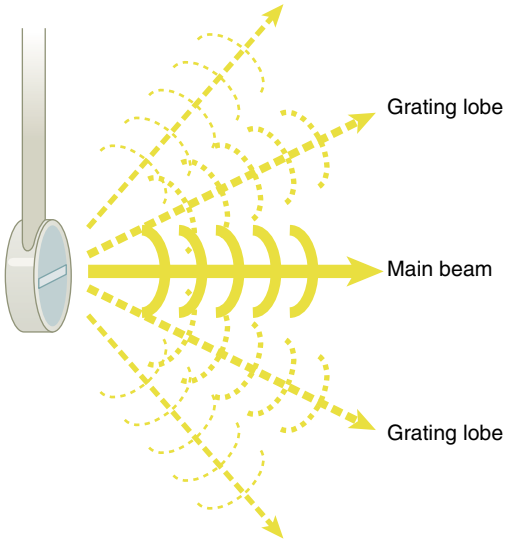


Figure 41-4 The main ultrasound beam (*solid line*) emitted from a transducer is accompanied by a series of grating lobes (*dotted lines*). The grating lobes are a phenomenon of beam formation that is a function of the array of piezoelectric crystals within the transducer. At certain angles from the main beam, the ultrasound wave from each crystal within the array is exactly one wavelength behind the wavelength from the adjacent crystal. This generates a grating lobe. The clinical implications of grating lobes are that highly echogenic objects such as a Swan-Ganz catheter or a mitral valve prosthesis can "appear" to be locations within the heart (i.e., the aorta) that are incorrect.

As ultrasound waves penetrate tissue, signal strength is attenuated. *Attenuation* is a function of tissue *absorption* (ultrasound energy converted to heat), *divergence* of ultrasound energy as it moves away from the transducer, *reflection*, and *scattering* (Fig. 41-5). Absorption is dependent on tissue type. For example, air absorbs more ultrasound energy than bone does, but bone absorbs more than blood or water does. A term used to describe absorption is half-power distance, which is the distance required

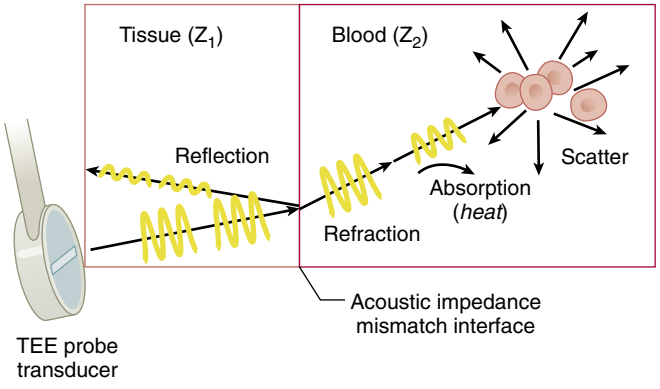


Figure 41-5 Diagram of specular reflection, refraction, absorption, scatter, and acoustic impedance. As ultrasound waves strike an interface between two different tissue types, some of it is reflected and the remainder passes through. The reflected ultrasound wave has a trajectory angle equal to the incident angle. Refraction refers to deflection of the ultrasound beam as it travels from one tissue type to another. Scattering occurs when an ultrasound wave strikes a structure that is less than one wavelength in lateral dimension (a red blood cell). Absorption represents the amount of ultrasound energy that dissipates as heat. Acoustic impedance refers to the resistance that an ultrasound wave meets when traveling though tissue. Acoustic impedance (Z) is defined as the product of tissue density and propagation velocity.

to decrease the ultrasound energy by 50%. The half-power distances for air, bone, blood, and water are 0.08, 0.8, 15, and 380 cm, respectively.

As ultrasound waves strike an interface between two different tissue types, some of it is reflected and the remainder passes through. Just as light is reflected from a mirror, the reflected ultrasound wave has a trajectory angle equal to the incident angle. The amplitude of reflected ultrasound waves is decreased by 40 to 60 dB (100- to 1000-fold). Ultrasound waves that pass through to adjacent tissue are subject to *refraction*. Refraction refers to deflection of the ultrasound beam as it travels from one tissue type to another. An example of refraction is distortion of an image of an object when partially submerged in a fish tank or swimming pool. Refraction can bend ultrasound beams and thus make objects appear in locations where they do not exist. Scattering occurs when an ultrasound wave strikes a structure that is less than one wavelength in lateral dimension (a red blood cell). The scattered ultrasound energy is radiated in all directions.

Acoustic impedance refers to the resistance that an ultrasound wave meets when traveling though tissue. It is a function of tissue density and is defined by Equation 2:

$$\text{Acoustic impedance (Z)} = \text{Tissue density} \cdot \text{Propagation velocity} \quad (2)$$

The greater the tissue density, the faster the ultrasound beam moves through the tissue. For example, ultrasound waves are much slower in air (330 m/sec), faster in blood (1540 m/sec), and very fast in bone (4080 m/sec). The extent of ultrasound beam reflection is a function of the difference in acoustic impedance between two adjacent tissues. The larger the difference in acoustic impedance, the more ultrasound energy will be reflected. Bone–soft tissue and air–soft tissue interfaces reflect most of the ultrasound beam. Imaging structures deep to these interfaces is difficult.

Mismatches in acoustic impedance and attenuation are important to consider in imaging the heart with TEE. For example, the upper aortic arch is difficult to visualize from the esophagus because of interposition of the air-filled trachea. In addition, most of the ultrasound energy that does make it to the trachea-tissue interface is reflected as a result of the large difference in acoustic impedance between air and tissue.

Basic Principles of Image Optimization: Gain, Depth, and Focus

Gain is used to amplify low-amplitude ultrasound waves reflected back to the transducer. Gain represents how well the ultrasound system *listens*. It can be used to offset the large-amplitude signals returned from proximal structures from the low-amplitude signals returned from distant structures. Many ultrasound machines have a series of sliding controls called *time gain compensation* controls that allow the operator to adjust the gain at a given depth. One temptation when structures are not readily visualized in the brightly lit operating room is to turn up the gain. Although gain increases structure brightness, it comes at the cost of amplifying background noise. A better approach is to brighten the display screen settings and keep gain at normal settings.

In echocardiography, the crystals emit very short pulses of ultrasound (0.5 to 3 µsec containing two wavelengths) and receive or "listen" for the reflected ultrasound for 250 to 500 µsec. The *pulse repetition frequency* (PRF) is the number of pulses that leave and return to the transducer in a single second. As image depth is increased, the time required to reach the target depth and return increases. Thus, the number of cycles that can be completed within 1 second is reduced. The opposite also holds: as imaging depth decreases, PRF increases. PRF is also described in hertz; it is audible and ranges from 1 to 10 kHz.

Early echocardiography displays used this principle to map out the depth of structures within the heart. The first echocardiograms, "motion" or "M-mode" studies, were one-dimensional views of cardiac structures produced by single-crystal transducers with the results traced on moving photosensitive paper. Today, M-mode echocardiography is used principally to view rapidly moving structures, such as valve leaflets, because M-mode transducers can produce up to 1800 images/sec (Fig. 41-6). However, M-mode images reveal only a small portion of the heart at one time, thus making orientation and interpretation of spatial relationships difficult.

To generate 2D images, ultrasound machines were configured to sequentially redirect the beam over an area (sector) of interest. Transducers contain a row of piezoelectric crystals (a linear array). By introducing a small delay in the firing of adjacent crystals in the array (a phased array), the ultrasound machine is able to steer the resultant ultrasound beam. Hence, by varying the time delay between crystals, ultrasound machines are able to steer

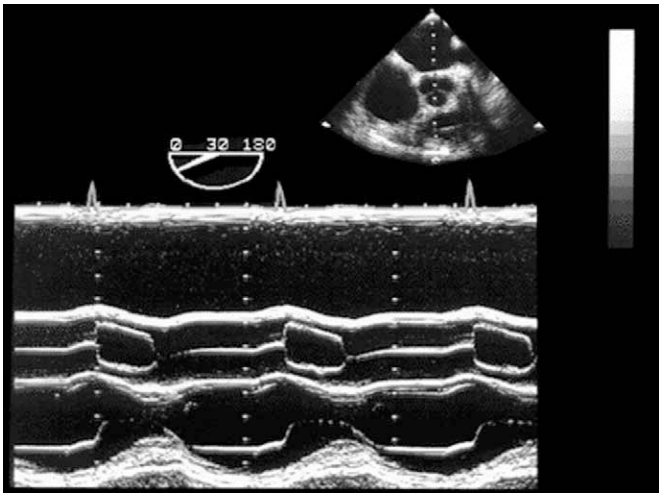


Figure 41-6 M-mode transesophageal echocardiogram of a normal aortic valve. For reference, a single frame (stop action) of the two-dimensional cross section is shown at the top right of the figure. The *dotted vertical line* through the two-dimensional echocardiogram depicts the single line of sampling provided by the M-mode echocardiogram over time (the horizontal axis for the lower two thirds of the figure). The electrocardiogram defines systole and diastole. Note in the middle of the M-mode image the three tilted *rectangles* connected by the slightly *undulating line*. These rectangles and lines are formed by the motion of the leaflets of the aortic valve as they open and close during the cardiac cycles shown. From top to bottom in this M-mode echocardiogram, the structures indicated by the *white lines* are the posterior wall of the left atrium (just under the electrocardiogram), the posterior wall of the aortic annulus, the aortic valve (as described above), the anterior wall of the aortic annulus, a pulmonary artery catheter, and the myocardium of the right ventricular outflow tract. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

the beam through a sector of interest (typically a 90-degree sector). Although 2D techniques produce only about 30 images/sec, definition in two dimensions provides an enormous advantage in recognizing anatomic and pathologic landmarks (Fig. 41-7). Images are displayed in "real time" on a monitor screen and digitally recorded for later review. In a similar fashion to steering the ultrasound beam, the *focal depth* of an ultrasound beam can be adjusted by triggering the piezoelectric crystals to concentrate the ultrasound beam at a desired depth (Fig. 41-8). The focal depth is typically set at or just below the structure of interest in a 2D image.

The advance from 2D to real-time 3D echocardiography has proved difficult. The time needed to acquire the requisite 2D images, the computing challenge of collating them into 3D images, and the display challenge of depicting 3D images on a 2D video screen all contributed to the difficulty. Matrix-array transducers solved the image acquisition problem. Typically, they contain over 3000 imaging elements and electronically rotate the 2D ultrasound beam through 180 degrees in milliseconds to acquire the requisite 2D images in a fraction of the time possible with mechanically rotated multiplane transducers. Computing power and commercially patented display algorithms solved the other problems (Fig. 41-9).[11]

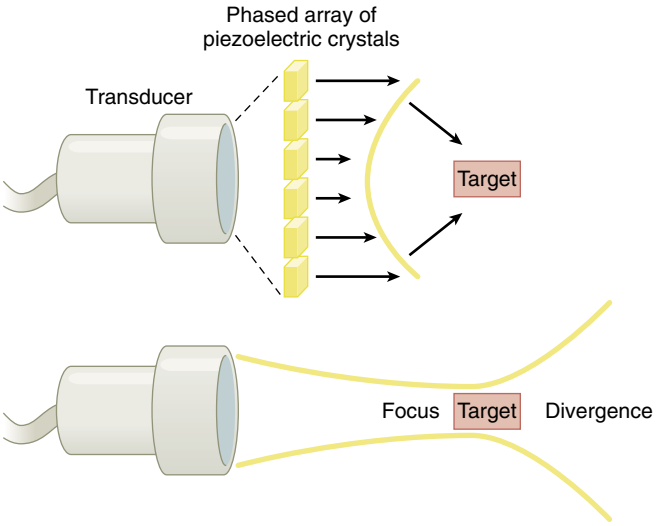


Figure 41-8 Schematic illustration of phasing the start of an array of piezoelectric crystals to focus an ultrasound beam. Crystals are sequentially fired from the outer edge to the middle of the array. The resultant concave wave converges at a point some distance from the transducer. The focal distance from the transducer is a function of the time delay between firing crystals from the edge to the middle of the array.

Integration of Flow and Structure

Christian Doppler, a physicist, studied a band playing a specific pitch on a moving train. He observed a change in pitch as the train passed by. In this experiment he characterized the relationship between train velocity and frequency (pitch), known as the Doppler shift. When applied to echocardiography, Doppler shift provides a significant enhancement to 2D imaging. With Doppler, blood flow velocity can be measured as blood flows through structures inside the heart. The ultrasound that bounces off moving red blood cells is reflected back to the transducer at a slightly different frequency than that emitted from the transducer. The shift in frequency allows the ultrasound machine to estimate blood flow velocity and direction of flow. Blood flow toward a transducer increases the frequency and vice versa with blood flowing away from the transducer. Doppler shifts are between 20 and 2000 Hz (within the audible range). Many ultrasound machines allow the user, if interested, to listen to the Doppler shift.

One important feature of assessing Doppler shift is the intercept angle (i.e., θ). To get the most accurate estimate of red blood cell speed, Doppler shift should be measured with an ultrasound beam that travels in the direction of blood flow. As the intercept angle deviates from zero degrees, blood flow will be underestimated. To compensate for this, the cosine of θ is used to account for the sampling angle. Most ultrasound machines

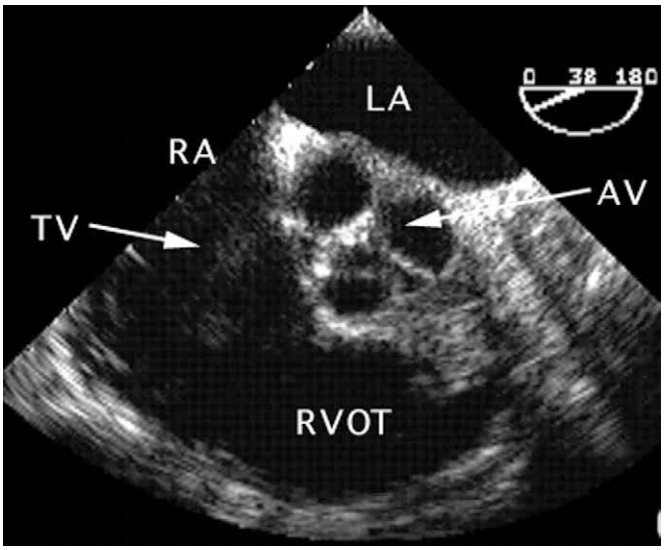


Figure 41-7 Stop-action short-axis two-dimensional cross section of a normal aortic valve (AV). This midesophageal view of the AV reveals the morphology of the three cusps of this normal valve. LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract; TV, tricuspid valve. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

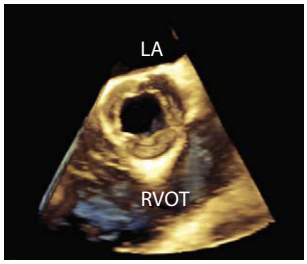


Figure 41-9 Stop-action image of a short-axis three-dimensional cross section of a normal aortic valve during systole. The partially open leaflets of aortic valve are seen in the center of the figure. Shadowing and color variation are used to depict the actual three-dimensional contours and shape of the valve and surrounding structures. In stop-action mode, these techniques are not as effective as when the real-time images are displayed. LA, left atrium; RVOT, right ventricular outflow tract.

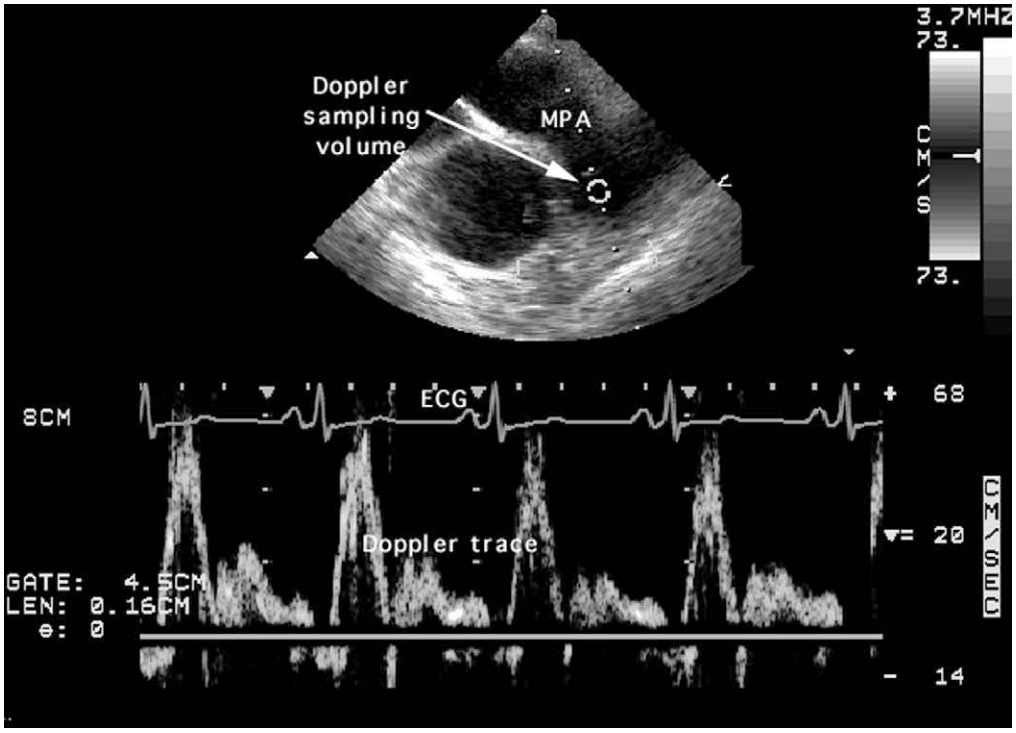


Figure 41-10 Pulsed wave Doppler echocardiogram of the main pulmonary artery (MPA). At the top of the echocardiogram is a still-frame image of the two-dimensional cross section used to position the Doppler sampling volume (*broken circle* at point of *white arrow*). On the bottom two thirds of the echocardiogram is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume. The electrocardiogram (ECG) provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. Flow velocities above this line are positive (i.e., toward the transducer) to a maximum of 68 cm/sec. Flow below this line is negative (i.e., away from the transducer) to a maximum of –14 cm/sec. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

ignore the cosine term (assume that $\theta = 0$ and cosine $\theta = 1$). At angles of 20, 30, and 60 degrees, Doppler shift will underestimate the velocity by 6%, 13%, and 50%, respectively. An intercept angle of up to 30 degrees is usually acceptable.

Doppler shifts are presented in three ways: pulsed wave Doppler (PWD), continuous wave Doppler (CWD), and color flow Doppler (CFD). The clinical features of each are presented in Table 41-3. With PWD, a small sampling volume (cursor) is placed in an area of interest within a 2D image. The transducer generates a pulse of ultrasound and then switches to the receive mode and awaits the arrival of a reflected portion of the ultrasound pulse from the sampling area (Fig. 41-10). The ultrasound machine then measures the frequency shift (or Doppler shift) to estimate the speed of blood cells in the sample volume.

One limitation of PWD is that it may be too slow to capture the velocity of fast-moving blood cells. This phenomenon is known as *aliasing*. An example of aliasing is when one watches the spokes on a wagon wheel in a western movie. As velocity increases, the movie camera detects an increase in rotational velocity of the wheel up to a point, and then the wheel appears to start spinning backward. As rotational velocity increases beyond the movie camera's sample rate, the wheel appears to be slowing down even though in reality it is speeding up.

The limit at which the sampling rate fails to accurately capture the true velocity is called the *Nyquist limit*. The sampling frequency, in this example the movie camera's sampling rate, must be at least twice the speed of the rotational velocity of the wagon wheel. With PWD, if the velocity of blood flow exceeds the Nyquist limit for the PRF (defined as PRF/2), blood flow will appear to reverse direction (Fig. 41-11).

For PWD, the maximal detectable velocity is a function of depth and transducer frequency. For depth, the farther the ultrasound pulse has to travel, the slower the maximal detectable velocity. For transducer frequency, the faster the frequency, the slower the maximal detectable velocity. To minimize aliasing with PWD, the slowest transducer setting is used. Aliasing of PWD occurs at blood flow velocities greater than 0.8 to 1.0 m/sec. Normal flow within the heart may reach 1.4 m/sec and pathologic flow up to 6 m/sec. To measure such velocities, CWD is needed.

CWD uses two sets of separate crystals: one to continuously emit ultrasound and one to continuously receive it. CWD has an infinite PRF, which eliminates the problem of aliasing (Fig. 41-12). However, this infinite pulse repetition rate allows insufficient time for the first pulse to return to the transducer before the next is emitted. Consequently, the ultrasound machine cannot precisely define the location of the moving blood cells.

CFD is based on PWD and uses multiple sample volumes along a scan line. The operator selects an area of interest ("color sector"). Scan lines are sequentially scanned through this sector. Blood flow velocity measurements are taken at several points along each scan line. A color code is used to depict flow toward (red) and away (blue) from the transducer; lighter and darker shades of red and blue, respectively, denote relatively faster and slower velocities. Continuous color maps of flow are superimposed on gray-scale cross-sectional echocardiograms. CFD has the same limitations as described previously for PWD. The

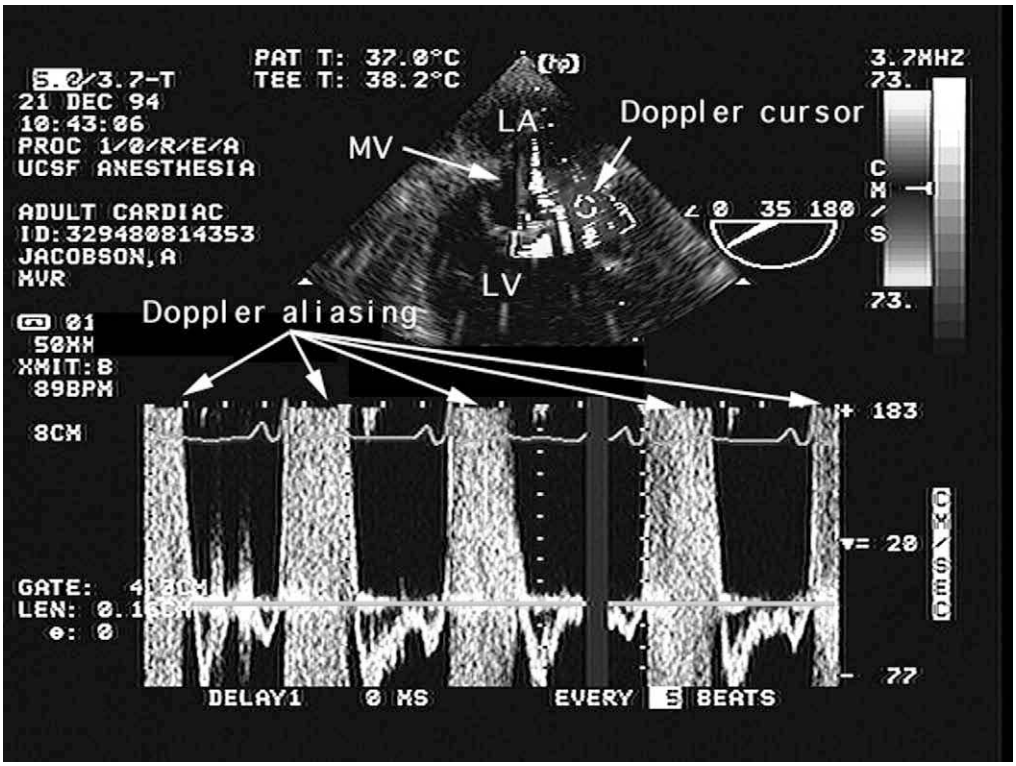


Figure 41-11 Pulsed wave Doppler (PWD) echocardiogram with aliasing at high velocities. PWD measurement of blood flow velocities in a mitral valve (MV) orifice during four cardiac cycles is shown. At the top of the figure is a still-frame image of the two-dimensional cross section used to position the Doppler sampling volume (indicated by the Doppler cursor–labeled *arrow*). On the bottom two thirds of the figure is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume. The electrocardiogram provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. Flow velocities above this line are positive (i.e., toward the transducer) to a maximum of 183 cm/sec. Flow velocities below this line are negative (i.e., away from the transducer) to a maximum of –77 cm/sec. This tracing documents significant mitral regurgitation (the positive systolic velocities) but does not measure the peak velocity of regurgitant flow because it is beyond the Nyquist limit—the systolic velocities off the top of the scale are said to alias; that is, they go off scale and wrap around into the domain of negative velocities. LA, left atrium; LV, left ventricle. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

maximal blood velocity that can be detected with CFD is a function of sector depth and PRF. PRF is considerably longer with CFD because of the numerous series of samples taken throughout the sector of interest, so the Nyquist limit is typically lower than with PWD.

Two aliasing patterns are easily recognized. The first is "normal" aliasing, in which the area of apparent flow reversal forms one or more broad, relatively homogeneous color surfaces (Fig. 41-13). Blood flow velocities within a normal heart often produce this type of aliasing because they exceed the Nyquist limit for color Doppler (0.6 to 0.8 m/sec). The second type of aliasing results from disturbed or turbulent flow within the heart (e.g., mitral regurgitation) and is never normal (Fig. 41-14). When the ultrasound machine detects two different velocities within the same small sample volume (as a result of disturbed flow), it displays a mixture, or mosaic, of colors. In most cardiovascular abnormalities these mosaics form jetlike configurations and are called "color jets." Minimizing the color sector area or reducing the distance between the transducer and the sector (or both) increases the overall PRF and thus allows an increase in the maximal measurable flow velocity before aliasing occurs. When evaluating color jets caused by valvular regurgitation, jet size is affected markedly by the Nyquist limit and gain settings. To facilitate consistent interpretation, the ASE recommends using a Nyquist limit (aliasing velocity) of 50 to 60 cm/sec and a color gain that just eliminates random color speckle from nonmoving regions.[12]

Tissue Doppler

Tissue Doppler imaging is a relatively new use of PWD technology adapted to measure myocardial velocity instead of blood flow velocity.[13] During normal LV contraction, the mitral annulus descends toward the apex of the heart. Tissue Doppler imaging measures the velocity of this descent (S_m), and S_m correlates with traditional measures of LV function, including ejection fraction and the rate of rise in LV systolic pressure (dP/dt).[14,15] In addition, S_m decreases in the presence of myocardial ischemia and responds as expected with changes in inotropy.[16,17] The four-chamber cross-sectional view is best for measuring S_m; the sampling volume is placed at the lateral insertion point of the mitral valve into the left ventricle and the cross section is aligned so that the sampling cursor is directly parallel to the motion of the annulus. S_m is an easy and reproducible measurement. However, like fractional area change and fractional shortening, it should be interpreted with caution when preload changes. Ama and associates tested its load dependence in 42 hemodynamically stable patients with normal

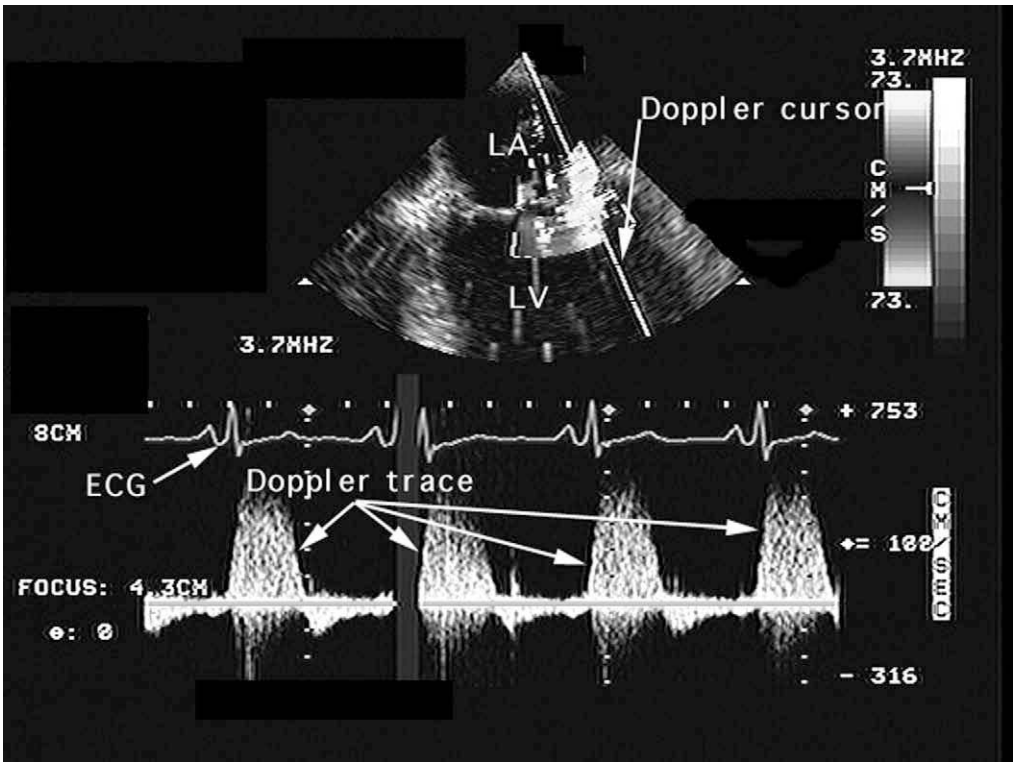


Figure 41-12 Continuous wave Doppler (CWD) measures high-velocity flow without aliasing. CWD measurement of blood flow velocities in a mitral valve orifice during four cardiac cycles is shown. At the top of the figure is a still-frame image of the two-dimensional cross section used to position the Doppler sampling cursor (the *diagonal white line*). On the bottom two thirds of the figure is the display in white of all the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring anywhere along that cursor. The electrocardiogram (ECG) provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. Flow velocities above this line are positive (i.e., toward the transducer) to a maximum of 753 cm/sec. Flow velocities below this line are negative (i.e., away from the transducer) to a maximum of –316 cm/sec. This tracing documents significant mitral regurgitation (the positive systolic velocities) with a peak blood flow velocity of approximately 5 m/sec (each *white dot* on the vertical axis equals 100 cm/sec or 1 m/sec). LA, left atrium; LV, left ventricle. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

segmental LV function after coronary surgery. S_m did not change significantly in response to a 20% increase or decrease in mean arterial pressure induced by phenylephrine or nitroglycerin. However, it increased significantly when preload was augmented by rapid infusion of colloid.[18] In summary, S_m is less dependent on afterload than fractional area change and fractional shortening are but, like these other two measures, remains critically dependent on preload. The few measures of LV function that appear to be independent of both preload and afterload (e.g., preload-recruitable stroke work) are not practical for clinical use.

Equipment Design and Operation

TEE probes are a marvel of engineering: a miniaturized echocardiographic transducer (about 40 mm long, 13 mm wide, and 11 mm thick) mounted on the tip of a gastroscope. Typically, the transducer is a phased-array configuration with 64 piezoelectric elements operating at 3.7 to 7.5 MHz. With sequential firing of the elements and an acoustic lens in the transducer housing, the ultrasound waves are formed into a 90-degree beam approximately 2 to 10 mm in thickness that emanates at right angles to the transducer. Like standard gastroscopes, two rotary knobs ("wheels") control movement of the tip of the scope. One wheel anteflexes and retroflexes the transducer (i.e., moves the transducer toward and away from the heart). The other wheel flexes the transducer rightward and leftward (Fig. 41-15).

Currently, most multiplane transducers use the same transducer technology but mount the transducer on a rotating device that allows it to spin on its axis from 0 to 180 degrees within the tip of the gastroscope (transducer housing). Because cardiac structures and blood flow are not precisely aligned relative to the transducer, this design has significantly refined imaging capability. Matrix transducers accomplish the same rotation of the beam but do so electronically (i.e., without mechanically moving the transducer). The size of the probes has been decreased for pediatric application by reducing the number of crystals, and probes are now small enough for use in infants and neonates.

Ultrasonographs contain high-powered computers capable of initiating the ultrasound beam and processing the returning data. A series of electronic transforms (some guarded commercial secrets) produce the real-time images displayed on the video screen. All ultrasonographs share common technical aspects, including gain, depth, and Doppler controls. However, the differences in technical aspects between manufacturers and even between models from the same manufacturer are sufficiently great to prevent formulation of any universal operating instruc-

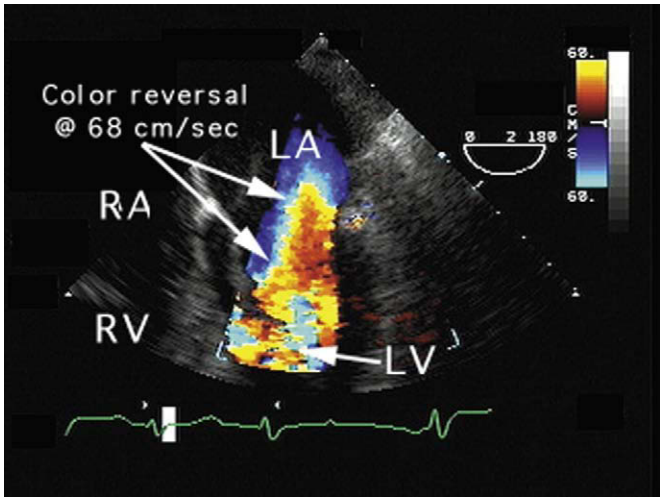


Figure 41-13 "Normal" color Doppler aliasing. In this echocardiogram, "normal" color Doppler aliasing is seen because laminar flow of blood through the mitral valve and into the left ventricle (LV) exceeds the Nyquist limit (68 cm/sec in this example—see the color reference icon at the upper right of the figure), thereby resulting in reversal of the color coding of flow direction. Notice that this color reversal occurs across fairly broad, regular areas and not in a random or point-by-point fashion as occurs with turbulent flow (always abnormal). In this example, follow the blue flow from high in the left atrium (LA) as it accelerates into the mitral orifice, and notice how color Doppler depicts the increasing flow velocities: the blue color becomes lighter and lighter until the Nyquist limit is reached. Color reversal then occurs, with light blue becoming yellow. Just at that reversal point, the velocity equals the Nyquist limit, in this example 68 cm/sec. Subsequent reversals may occur at that limit or multiples of that limit. RA, right atrium; RV, right ventricle. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

tions. Fortunately, detailed instructions for each model are available in the operator's manual supplied with each ultrasonograph. Alternatively, cardiac sonographers are often excellent sources of instruction in the operation of these machines.

Basic Transesophageal Examination

Before performing TEE, the operator must determine that the benefits of TEE outweigh the risks. Except in the presence of esophageal disease or injury, the risk is quite low. Absolute contraindications include previous esophagectomy, severe esophageal obstruction, esophageal perforation, and ongoing esophageal hemorrhage. Relative contraindications include an esophageal diverticulum, varices, fistula, and previous esophageal surgery, as well as a history of gastric surgery, mediastinal irradiation, unexplained swallowing difficulties, and other conditions that might be worsened by placement and manipulation of the TEE probe.

In some studies, TEE is associated with a low incidence of oral and pharyngeal injuries (0.1% to 0.3%), but in other studies, the incidence of postoperative gastrointestinal complaints did not differ significantly from that in comparable patients who had not undergone TEE.[19,20] Uncontrolled studies have reported a 0.1% to 12% incidence of transient hoarseness after TEE. Serious pharyngeal or esophageal injury after TEE has been reported but is rare.[21] Two case reports indicate the possibility of TEE-associated splenic injury.[22,23] Among 10,218 patients (European multicenter study) undergoing TEE (primarily outpatients), esophageal perforation occurred in 1, who subsequently died; autopsy revealed a malignant tumor invading the esophagus.[24] Although bacteremia during TEE is uncommon, endocarditis has been reported in outpatients.[25,26] Endocarditis from intraoperative TEE has not been reported, and the risk is probably near zero because antibiotics are usually administered for prevention of surgical wound infection. In infants, TEE has a low complication rate, but even an appropriately sized TEE probe may obstruct the airway distal to the endotracheal tube or compress the descending aorta.[27]

Once the patient is anesthetized and the trachea securely intubated, the contents of the stomach are suctioned. Gentle massage of the left upper quadrant of the abdomen during suctioning may help remove air, which can otherwise degrade the imaging. The patient's neck is then extended and the well-lubricated TEE probe is introduced into the midline of the hypopharynx with the transducer side facing anteriorly. Usually, with minimal force the probe will pass blindly into the esophagus, especially if the neck is extended. If the probe does not pass blindly, a laryngoscope is used to lift the larynx anteriorly and the probe is placed into the esophagus under direct vision. During insertion or withdrawal of the transducer, the controls of the gastroscope must be in the neutral or relaxed position to allow the transducer to follow the natural course of the esophagus, thereby potentially minimizing the chance for injury.

Because of time constraints and relatively narrow diagnostic goals, anesthesiologists often perform a more limited intraoperative examination than described in the ASE/SCA's task force recommendation for a comprehensive TEE examination (see the

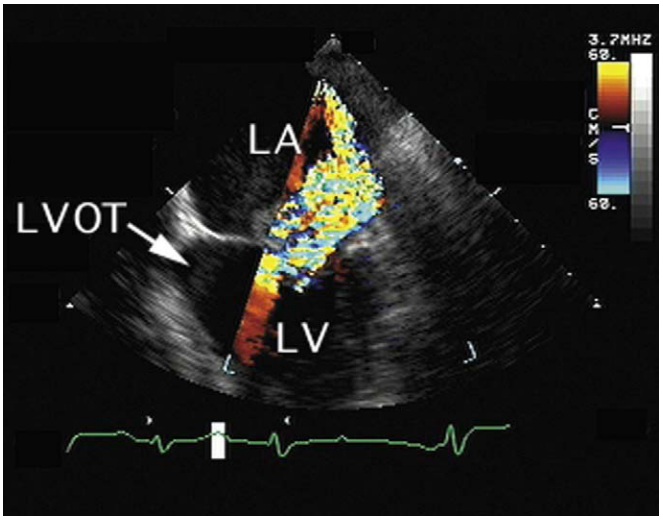


Figure 41-14 Color Doppler aliasing depicting turbulent flow. In this echocardiogram, color Doppler reveals aliasing caused by severe mitral regurgitation: a broad-based systolic color jet emanating from the mitral valve and extending far into the left atrium (LA). This jet is composed of a mosaic of colors mixed in a seemingly random, point-by-point fashion because the jet results from the turbulent flow of mitral regurgitation. Turbulence is never normal in the heart, and thus mosaic jets such as the one shown here are highly valuable diagnostic signs of underlying pathology. LV, left ventricle; LVOT, left ventricular outflow tract. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

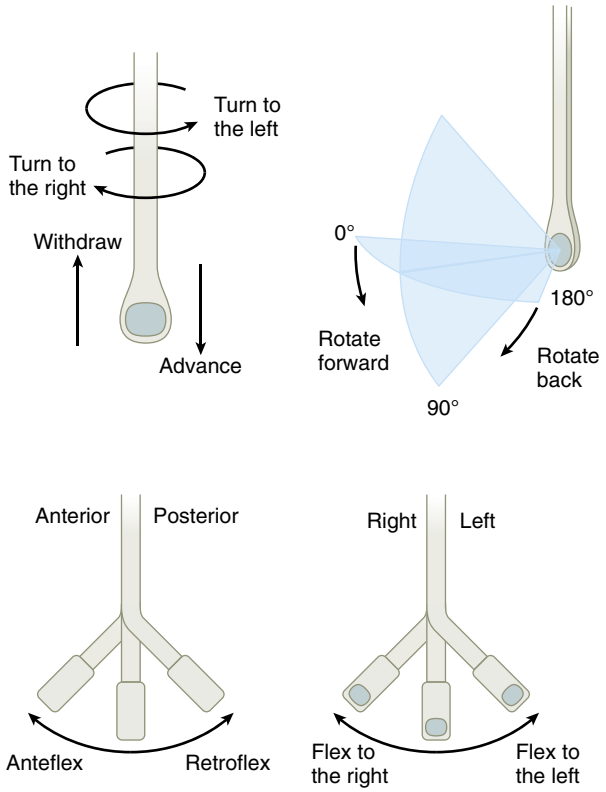


Figure 41-15 Terminology used to describe transesophageal echocardiography probe movements. *(Reproduced with permission from Shanewise JS, Cheung AT, Aronson S, et al: ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: Recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. Anesth Analg 89:870-884, 1999.)*

subsequent section).[7,28] However, even when time is critical, the examination performed should allow at least the basic applications of TEE as outlined in the 1996 guidelines for perioperative TEE: detection of markedly abnormal ventricular filling or function, extensive myocardial ischemia or infarction, large air embolism, severe valvular dysfunction, large cardiac masses or thrombi, large pericardial effusions, and major lesions of the great vessels.[6] A minimum of eight different cross sections drawn from the 20 cross sections delineated in the comprehensive examination are required to meet these diagnostic goals. Four of the cross sections are imaged in both 2D and color Doppler to assess valvular function. The next paragraph describes the probe manipulations required to achieve these cross sections. The reader should review Figure 41-15 to understand the terms used in this description.

After the TEE probe is introduced safely into the esophagus, it is advanced to the midesophageal (ME) level (28 to 32 cm measured at the upper incisors), and the aortic valve (AV) is imaged in the short axis (SAX) by turning the probe, adjusting its depth in the esophagus, and rotating the multiplane transducer 25 to 45 degrees until the three cusps of the valve are seen as being approximately equal in size and shape (Fig. 41-16H). Image depth is set at 10 to 12 cm as required to position the AV in the center of the video screen. This cross section is ideal for detection of aortic stenosis. This and all subsequent cross sections are digitally recorded. Next, the probe is turned slightly to position the AV in the center of the video screen, and then the multiplane angle is rotated forward to 110 to 130 degrees to bring the long axis (LAX) of the AV in view (see Fig. 41-16I). This cross section is best for detection of ascending aortic abnormalities, including type I aortic dissection. Color Doppler is used for assessment of AV competence. For detection of valvular stenosis and regurgitation, the Nyquist limit is set to 50 to 60 cm/sec.[12] Next, Doppler is discontinued and the probe is turned rightward until the ME bicaval cross section comes into view (see Fig. 41-16L). This cross section is usually seen best at a multiplane angle between 90 and 110 degrees and is ideal for assessing caval abnormalities, as well as compression of the right atrium from anteriorly located masses or effusions and compression of the left atrium from posteriorly located masses or effusions. In addition, the bicaval cross section may reveal collections of air located anteriorly in the left or right atrium, as well as the structure of the interatrial septum, including the foramen ovale. Next, the multiplane angle is rotated back to 60 to 80 degrees and the probe is turned leftward just past the AV to bring the ME right ventricular (RV) inflow and outflow cross section into view (see Fig. 41-16M). Usually, an image depth of 12 to 14 cm is required to position the RV outflow tract in the center of the video screen. This cross section reveals RV contractile function, the outflow tract, and pulmonary valve function with the application of color Doppler. Next, the transducer is rotated back to 0 degrees and the probe advanced 4 to 6 mm into the esophagus and gently retroflexed until all four cardiac chambers are visualized (ME four-chamber cross section) (see Fig. 41-16A). Rotating the transducer 10 to 15 degrees will often enhance the view of the tricuspid annulus. Usually, an image depth of 14 to 16 cm is required to include the LV apex in the sector scan. In 2D imaging, the free wall of the right ventricle and the lateral and septal LV wall segments are evaluated for contractile function. With color Doppler, both the mitral and tricuspid valves are assessed. Stenotic and regurgitant lesions can be diagnosed accurately. During this assessment, image depth is decreased to 10 to 12 cm to afford a magnified view of the valves and color Doppler flow patterns. Next, color Doppler is discontinued, the left ventricle is positioned in the center of the screen, and the multiplane angle is rotated forward to 90 degrees to bring into view the ME two-chamber cross section (see Fig. 41-16B). Image depth is returned to 14 to 16 cm. This cross section is best for revealing the function of the basal and apical segments of the anterior and inferior LV walls, as well as anterior and inferior pericardial collections. When air emboli collect in the left ventricle, they can generally best be seen in this view as very echogenic areas located along the anterior apical endocardial surface. The transducer is then rotated forward to 135 degrees to reveal the ME LAX cross section, which is best for assessment of the anteroseptal and posterior wall segments for contractile LV function (see Fig. 41-16C). Together, the ME four-chamber, two-chamber, and LAX cross sections reveal all 16 segments of the left ventricle (Fig. 41-17). However, the next and last of the basic cross sections provides a second look at the midventricular segments, as well as other benefits. To achieve this cross section, the transducer is rotated back to 0 degrees, the left ventricle is centered in the screen, and the probe is advanced 4 to 6 cm into the stomach. It is then gently flexed anteriorly to reveal the transgastric (TG) SAX cross section (see Fig. 41-16D). This cross section is ideal for monitoring LV filling and contractile function. All major coronary arteries supplying the myocardium are viewed in this cross section. Moreover, changes in preload cause greater changes

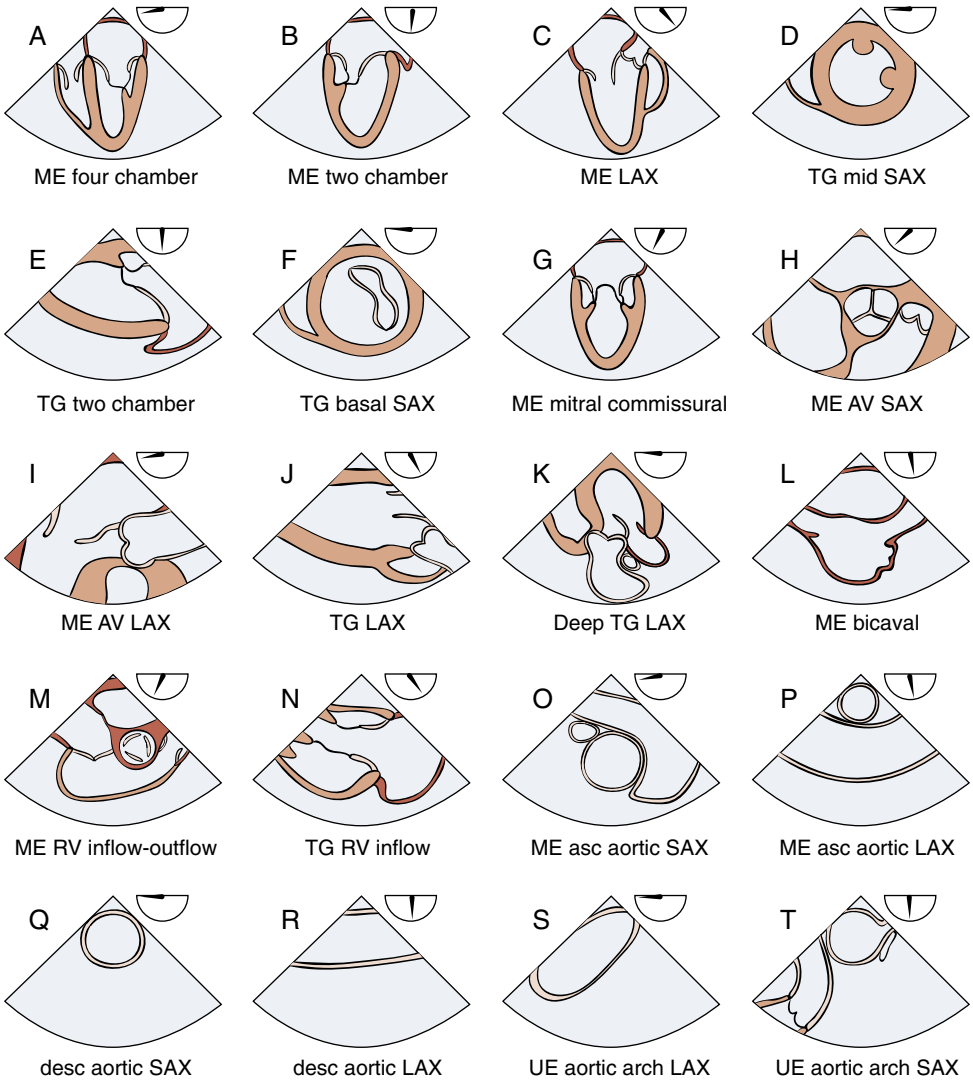


Figure 41-16 Transesophageal echocardiography cross sections in a comprehensive examination. Twenty standard cross sections and their abbreviated names are depicted by the line drawings. The text describes the probe manipulations required to produce each of these cross sections. *(Reproduced with permission from Shanewise JS, Cheung AT, Aronson S, et al: ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: Recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. Anesth Analg 89:870-884, 1999.)*

in the LV SAX than in the LAX dimension, and movement of the probe from this cross section is readily apparent inasmuch as the papillary muscles provide prominent landmarks. Because this cross section is used to judge filling and ejection, image depth is consistently set to 12 cm so that the size and function of the heart can easily be judged relative to previously examined hearts.

Comprehensive Transesophageal Examination

In addition to the 8 cross sections described in the preceding paragraph, 12 other cross sections are required to complete the comprehensive perioperative TEE examination delineated in the 1999 ASE/SCA task force recommendations.[7] When time permits or the diagnostic questions require, the comprehensive examination can be completed in any order deemed most appropriate by the operator. Shanewise and colleagues described an examination sequence based on anatomic structures, and the reader is referred to this very detailed reference for one excellent approach.[7] However, when a single individual is responsible for anesthetic care and the TEE examination, the comprehensive examination is completed as time permits after the basic examination has been recorded. When such is the case, the operator can use 3 of the 8 basic cross sections as takeoff points for the other 12 cross sections, thus making completion of the comprehensive examination a relatively easy sequence to remember and quick to perform.

With the probe positioned for the AV SAX cross section, the other six cross sections of the aorta are easily achieved. First, the probe is withdrawn slowly 1 to 3 cm while keeping the aorta in the center of the video screen to view the ascending aorta in SAX (see Fig. 41-16O). As the probe is withdrawn, the operator progressively views more superior SAX cross sections of the aorta beginning with the sinotubular junction until the image is lost

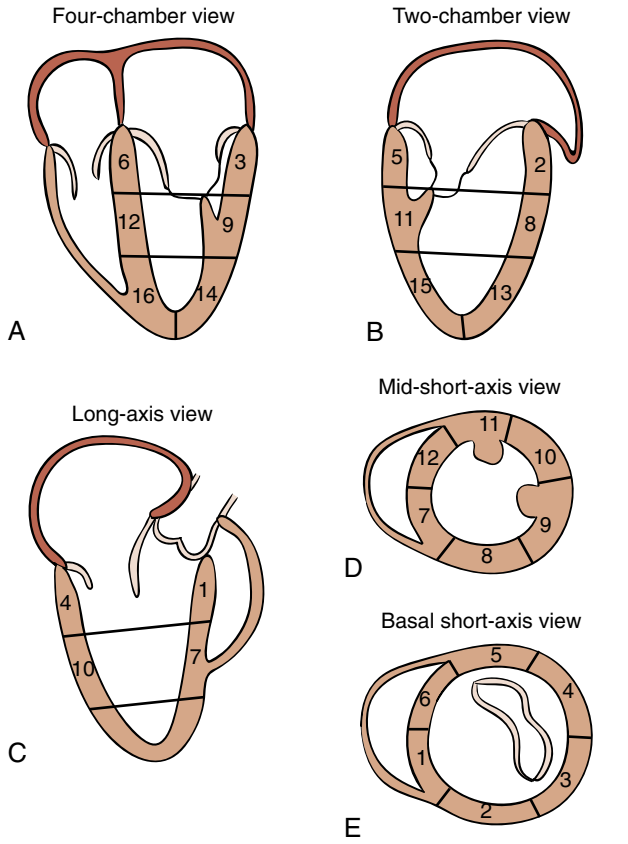


Figure 41-17 Five transesophageal echocardiography cross sections with myocardial segments identified. A total of 16 myocardial segments are identified and named according to standards adopted by the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. *(Reproduced with permission from Shanewise JS, Cheung AT, Aronson S, et al: ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: Recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. Anesth Analg 89:870-884, 1999.)*

because of interposition of the trachea between the esophagus and aorta. Next, the multiplane angle is rotated forward to 100 to 120 degrees and advanced slowly 1 to 3 cm while keeping the aorta in the center of the video screen to view the ascending aorta in LAX (see Fig. 41-16P). These two cross sections are ideal for assessment of pathology of the ascending aorta, such as type I aortic dissection and aortic atheromas. However, the most superior aspect of the aorta is rarely seen, including the takeoff of the innominate artery, because of the aforementioned tracheal interposition. Next, the transducer is returned to 0 degrees, the image depth decreased to 6 cm, and the probe turned leftward past the cardiac structures to reveal the descending aorta in SAX (see Fig. 41-16Q). The probe is withdrawn and advanced with the aorta maintained in the center of the screen until the entire descending aorta has been examined in SAX. This maneuver is repeated with the transducer at 90 degrees to examine the descending aorta in LAX (see Fig. 41-16R). Next, the transducer is returned to 0 degrees and the probe withdrawn until the distal aortic arch in LAX comes into view (see Fig. 41-16S). Rotating the transducer to 90 degrees reveals the distal arch in SAX (see Fig. 41-16T). The probe is turned leftward until the aorta just disappears from view and then turned slowly rightward to identify the takeoff of the left subclavian artery (well seen in most patients) and the left carotid (well seen in a minority of patients). These cross sections of the descending aorta and distal aortic arch reliably reveal dissections and atheromatous disease.

With the probe positioned for the ME four-chamber cross section, the ME mitral commissural cross section is easily achieved by centering the coaptation point of the mitral valve in the center of the video screen and rotating the multiplane angle forward to about 60 degrees (see Fig. 41-16G). This maneuver positions the ultrasound beam parallel to the closure line of the mitral leaflets and completes the LAX examination of the mitral valve. Although a detailed discussion of mitral leaflet structure and function is beyond the scope of this chapter, Figure 41-18 summarizes an excellent approach to this challenging task.[29]

With the probe positioned for the TG mid SAX, the remaining five cross sections of the comprehensive examination are achieved easily in most patients. First, the left ventricle is centered in the video screen and the multiplane angle is rotated forward to 90 degrees to reveal the TG two-chamber cross section (see Fig. 41-16E). Although this cross section reveals the same structures as the ME two-chamber cross section, the viewing angle is orthogonal to the former viewing angle, and as a result, subvalvular structures are seen better. Next, the transducer is rotated to 100 to 120 degrees to reveal the TG LAX cross section (see Fig. 41-16J). Again, this cross section reveals the same structures as the ME LAX, but the TG LAX permits a more parallel alignment of the ultrasound beam with blood flow through the LV outflow track and AV. Next, the TG RV inflow cross section is achieved by returning the probe to the TG mid SAX position, turning it rightward until the right ventricle is centered in the video screen, and then rotating the multiplane angle to 100 to 120 degrees to bring the RV apex into view (see Fig. 41-16N). This cross section is ideal for viewing the RV inferior free wall. Next, the TG basal SAX is achieved by returning the probe to the TG mid SAX, releasing the flexion of the probe, withdrawing 1 to 2 cm, and then flexing the probe gently until the orifice of the mitral valve is seen in SAX (Fig. 41-16F). This cross section can prove vital in determining the precise location of mitral regurgitation.[29] Finally, the TG deep LAX cross section is achieved by returning the probe to the TG mid SAX position, releasing the flexion of the probe, advancing it 6 to 8 cm into the stomach, fully flexing it once in the stomach, gently withdrawing it until minimal resistance is met at the gastroesophageal junction, and then slightly turning it leftward or rightward to reveal the LV outflow tract and AV (Fig. 41-16K). Usually, this cross section does not resolve structures as well as the ME LAX does, but it provides optimal beam alignment for Doppler interrogation of the LV outflow tract and AV. Frequently, this cross section is the most difficult of the cross sections to visualize. If a few gentle attempts fail to accomplish it, it should be abandoned.

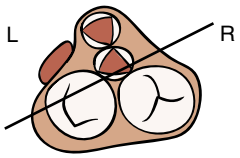
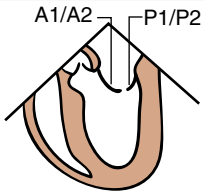
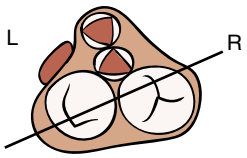
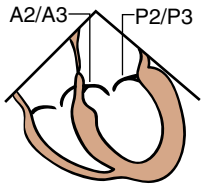
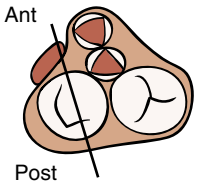
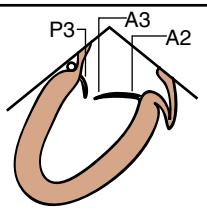
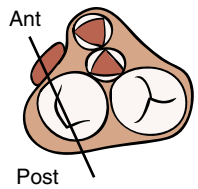
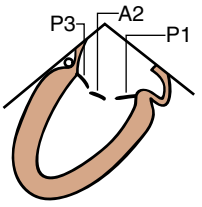
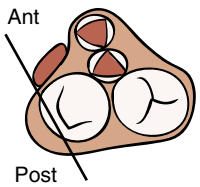
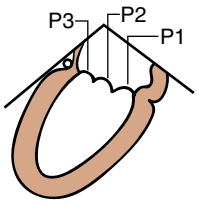
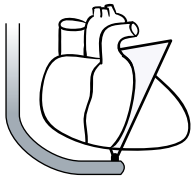
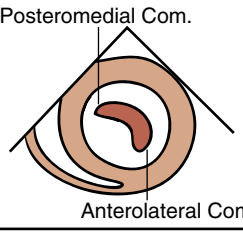
5-Chamber Allows localization of pathology to the anterior or posterior leaflet. Specific scallops difficult to identify based only on this view, but generally shows anterior elements of the valve.		
4-Chamber Allows localization of pathology to the anterior or posterior leaflet. Specific scallops difficult to identify based only on this view, but generally shows posterior elements of the valve.		
2-Chamber Anterior Shows a long anterior leaflet (A2/A3) and a short segment of the posterior leaflet (P3). Note that the part of the anterior leaflet that coapts with the P3 scallop is the A3 segment.		
2-Chamber Mid Three scallops and two coaptation points are seen: P3, P1, and a variable amount of A2, which disappears during diastole.		
2-Chamber Posterior No coaptation point seen. The plane cuts through the posterior leaflet only. Usually demonstrates mostly P2, with some P1 and P3.		
Short Axis This view is most useful with color Doppler to localize the site of regurgitation. However, it rarely demonstrates the nature of the pathology.		

Figure 41-18 A systematic examination of the mitral valve is depicted. In this examination, the mitral valve is viewed in multiple cross sections to delineate the leaflet anatomy. The five-chamber cross section is accomplished by withdrawing the probe slightly from the standard four-chamber cross section until the left ventricular outflow track is in view. The *center column* shows the planes of the different cross sections as viewed from directly above the base of the heart. The two-chamber anterior, mid, and posterior cross sections are variations on the standard two-chamber cross section that are accomplished by turning the probe from the patient's right to left. P1, P2, and P3 refer to the three scallops of the posterior mitral leaflet, and A1, A2, and A3 refer to the juxtaposed segments of the anterior mitral leaflet. The *right column* shows the leaflet segments seen in the corresponding cross section. *(Reproduced with permission from Lambert AS, Miller JP, Foster E, et al: Improved evaluation of the location and mechanism of mitral valve regurgitation with a systematic transesophageal echocardiography examination. Anesth Analg 88:1205-1212, 1999.)*

Basic Transthoracic Examination

In patients with an unsecured airway, TTE is easier to perform than TEE because TTE is entirely noninvasive. TTE uses frequencies lower (1 to 3 MHz) than TEE does to penetrate the greater distances inherent in the transthoracic technique, but all previously discussed modalities (M-mode, spectral Doppler, color Doppler, and tissue Doppler) can be performed with TTE. Transthoracic cardiac probes are significantly different from the linear probes used to identify superficial vascular structures and nerve bundles. Thus, the probes used for ultrasound-guided nerve

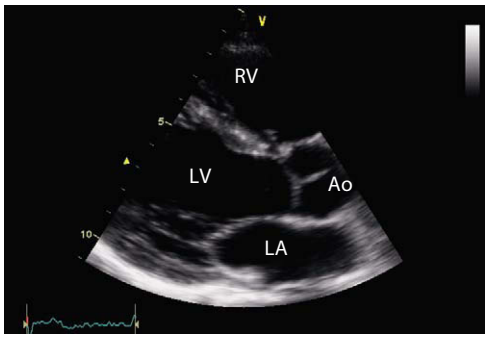


Figure 41-19 Transthoracic parasternal long-axis two-dimensional cross section of a normal heart. This cross section reveals a small triangular segment of the right ventricle on the upper section of the display and left ventricular chamber (LV), the left atrium (LA), and the aortic root (Ao) in the middle section of the display. This cross section shows the same tomographic view as with the midesophageal long-axis view described in the transesophageal examination (see Fig. 41-16C). RV, right ventricle.

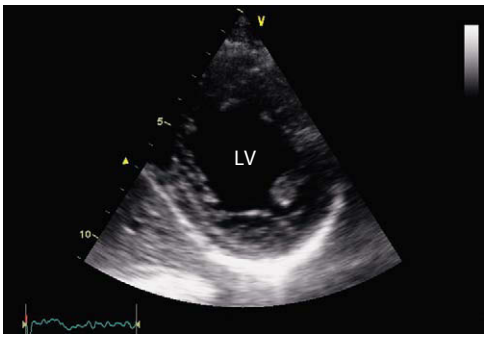


Figure 41-20 Transthoracic parasternal short-axis two-dimensional cross section of a normal heart. This cross section reveals a small part of the crescent-shaped right ventricle at the top of the display and the left ventricle (LV) in a short-axis view in the rest of the image. This cross section shows the same tomographic view as with the transgastric short-axis view described in the transesophageal examination (see Fig. 41-16D).

blocks and vascular access are not appropriate for TTE. TTE uses three standard "windows" (soft tissue points that avoid interposition of bone between the transducer and heart): parasternal (PS), apical (AP), and subcostal (SC). The next paragraphs describe the probe manipulations required at these windows to achieve the TTE cross sections.

The examination begins with the patient turned halfway onto the left side with the left arm elevated alongside the head. Optimal imaging requires ultrasound gel between the probe and chest wall. Patients should be warned of the cold sensation of the gel on the skin. The parasternal long-axis (PS LAX) cross section is acquired first (Fig. 41-19) by placing the probe on the left side of the sternum at the level of the fourth intercostal space and directing the ultrasound beam toward the patient's right shoulder. Appropriate adjustment of image depth (15 to 18 cm), rotation, and angulation of the transducer reveals a small triangular segment of the right ventricle on the upper section of the display and the LV chamber, left atrium, and aortic root in the middle section of the display. This cross section shows the same tomographic view as the ME LAX described in the TEE examination (see Fig. 41-16C). Like the ME LAX, the PS LAX cross section permits assessment of the structure and function of the AV, mitral valve, and basal segments of the anteroseptum and the posterior wall of the left ventricle. Sclerocalcific changes in the AV and reduction of cusp excursion are seen with aortic stenosis. Reduction of motion of the anterior leaflet of the mitral valve during diastole can be an indication of mitral stenosis, LV dilation, LV dysfunction, elevated filling pressure, or any combination of these pathologies. In this cross section, color Doppler allows the diagnosis of stenotic and regurgitant lesions of both atrioventricular valves. Next, the parasternal short-axis (PS SAX) cross section is obtained (Fig. 41-20) by rotating the transducer 90 degrees clockwise and angling it inferiorly toward the left hip until the right ventricle appears as a crescent-shaped structure at the top of the display and the left ventricle in SAX is viewed at the bottom. This cross section shows the same tomographic view as the TG SAX described in the TEE examination (see Fig. 41-16D). In the absence of segmental dysfunction in the apical or basal segments of the heart, LV and RV size and contractile function can be assessed accurately from the PS SAX cross section.

The next cross sections are acquired from the apical window by placing the transducer in the fourth or fifth intercostal space lateral to the nipple line with the transducer marker (the notch or other landmark on the transducer indicating beam orientation) pointing toward the floor. Appropriate adjustment of the rotation and angulation of the transducer reveals the apical four-chamber (AP-4C) cross section (Fig. 41-21) with the apex of the heart on the top of the display and the right and left atria on the bottom. This cross section shows the same tomographic view as with the ME four-chamber cross section described in the TEE examination (see Fig. 41-16A). The AP-4C cross section reveals the size and global contraction of the ventricles, as well as the segmental function of their lateral walls and interventricular septum. Color Doppler of the tricuspid and mitral valves facilitates the diagnosis of valvular stenosis and regurgitation. In addition, the right upper pulmonary vein is visualized, and PWD estimates of flow there can help in fluid management (see the subsequent section on ventricular diastolic function). The next cross section is the apical two-chamber (AP-2C) view, which is acquired by rotating the transducer 60 degrees counterclockwise

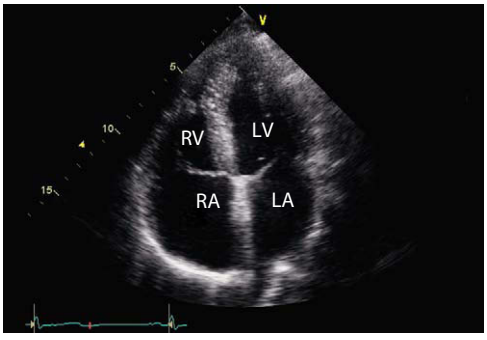


Figure 41-21 Transthoracic apical four chamber two-dimensional cross section of a normal heart. This cross section reveals the apex of the heart on the top of the display and the right and left atria (RA, LA) on the bottom. This cross section shows the same tomographic view as with the midesophageal four-chamber view described in the transesophageal examination (see Fig. 41-16A). LV, left ventricle; RV, right ventricle.

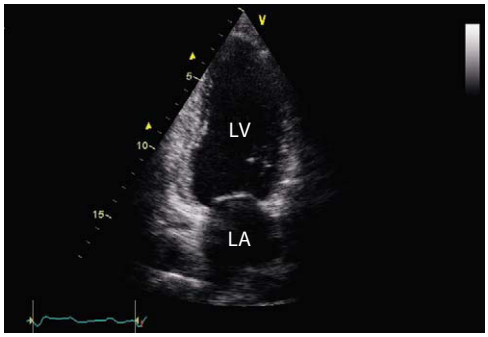


Figure 41-22 Transthoracic apical two-chamber two-dimensional cross section of a normal heart. This cross section reveals the left ventricle (LV) on the top (apex) and middle of the display and the left atrium (LA) on the bottom. This cross section shows the same tomographic view as with the midesophageal two-chamber view described in the transesophageal examination (see Fig. 41-16B).

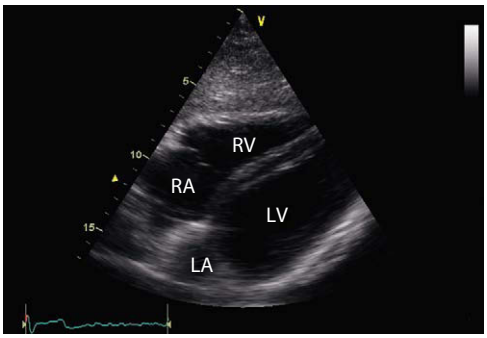


Figure 41-24 Transthoracic subcostal four-chamber two-dimensional cross section of a normal heart. The liver occupies the upper third of the display and the heart the lower two thirds. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

(Fig. 41-22). This cross section shows the same tomographic view as the ME two-chamber cross section described in the TEE examination and reveals segmental function of the anterior and inferior walls of the left ventricle (see Fig. 41-16B). The last apical cross section is the apical long-axis (AP LAX) view (Fig. 41-23), which is obtained by rotating the transducer counterclockwise another 60 degrees until the LV outflow tract and AV are seen in the bottom of the display. This cross section shows the same tomographic view as with the ME LAX described in the TEE examination (see Fig. 41-16C). The AP LAX provides an ideal vantage point for Doppler quantification of aortic stenosis and regurgitation because of the parallel direction of the ultrasound beam and blood flow.

The last two cross sections are acquired from the subcostal window with the patient in the supine position. The transducer is positioned flat under the right costal ridge next to the xiphoid appendix and pointed toward the patient's left shoulder with the transducer marker pointing leftward. The subcostal four-chamber (SC-4C) view is seen (Fig. 41-24), with the upper third of the display occupied by the liver and the heart below. RV free wall contractility and hemodynamically significant pericardial effusion are assessed best from this view. Finally, the subcostal inferior vena cava (SC IVC) cross section is obtained by rotating the transducer 90 degrees counterclockwise (Fig. 41-25). The IVC is seen on the left side of the display as a rectangular echolucent structure inside the liver connecting to the right atrium. This view allows assessment of right-sided filling pressure by evaluating the size and collapsibility of the IVC in spontaneously breathing patients.[30]

When TEE is impracticable and cardiovascular status must be evaluated reliably, these basic TTE cross sections can provide much of the same information as TEE does and thereby extend the benefits of echocardiography to many more surgical and critical care patients than when only TEE is available. We predict that TTE will become the stethoscope of the future for cardiovascular anesthesiologists and other perioperative physicians who regularly care for critically ill patients.

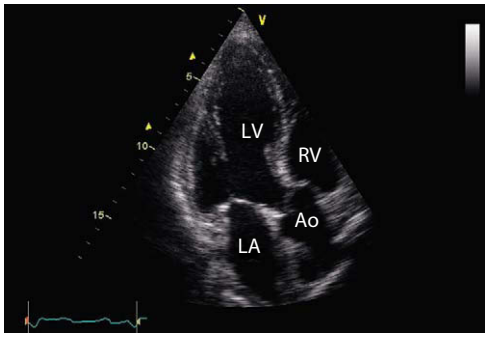


Figure 41-23 Transthoracic apical long-axis two-dimensional cross section of a normal heart. This cross section reveals the left ventricle (LV) at the top (apex) and middle of the display and the left ventricular outflow tract and aortic valve at the bottom of the display. This cross section shows the same tomographic view as with the midesophageal two-chamber view described in the transesophageal echocardiographic examination (see Fig. 41-16C). Ao, aorta; LA, left atrium; RV, right ventricle.

Assessment of Hemodynamics

Evaluation of Ventricular Filling

TEE reveals changes in LV preload more reliably than filling pressure. In 30 patients scheduled for cardiac surgery, Cheung and

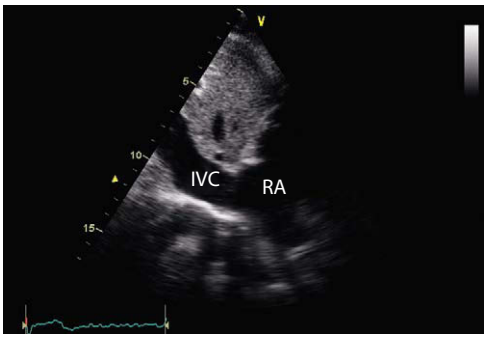


Figure 41-25 Transthoracic inferior vena cava (IVC) two-dimensional cross section of a normal heart. The IVC is seen on the left side of the display as a rectangular echolucent structure inside the liver connecting to the right atrium (RA).

colleagues removed 15% of each patient's blood volume in six equal aliquots before bypass.[31] TEE demonstrated a significant decrease in cross-sectional area at end diastole (EDA) after removal of the first aliquot (about 200 mL) and a linear decrease with subsequent aliquots. Pulmonary artery occlusion and central venous pressure also declined but correlated poorly with EDA. In most adults, an EDA of less than 12 cm^2 indicates hypovolemia, but values between 12 and 15 cm^2 may not because of variations in patient size and diastolic compliance. However, when a volume challenge increases EDA, stroke volume also increases.[32] Although quantitative TEE measurements of ventricular preload are well validated as noted earlier, they are tedious and impractical to perform intraoperatively. Instead, clinicians assess LV filling and function subjectively with the "trained eye." This approach is a valid method to guide fluid administration, and in patients with concentric hypertrophy, it may identify the need for higher than normal filling pressure to achieve optimal LV filling and function.[33]

In addition to estimating LV filling volume, TEE provides practical ways to estimate LV filling pressure. Placing the Doppler cursor at the junction of the left atrium and left superior pulmonary vein, Kuecherer and associates demonstrated that a systolic fraction of flow of less than 55% was a specific and sensitive sign of left atrial pressure greater than 15 mm Hg. This sign is easily detected as predominance of flow during diastole (Figs. 41-26 and 41-27).[34] Significant mitral regurgitation, the presence of non–sinus rhythm, and extremes of cardiac output affect pulmonary venous flow and therefore limit this application of TEE. Alternative methods have been described that obviate these limitations.[35,36] Accordingly, TEE cannot estimate left atrial pressure precisely but can reliably identify clinically significant elevations.

Estimation of Cardiac Output

Real-time TEE images of LV filling and ejection permit qualitative, immediate detection of extreme changes in cardiac output. However, TEE can quantify cardiac output more precisely by measuring both the velocity and the cross-sectional area of blood flow at appropriate locations in the heart or great vessels. The product of these measurements is stroke volume. Appropriately performed TEE estimates of cardiac output should fall within 0.3 to 0.8 L/min of thermodilution estimates, except in patients with severe tricuspid regurgitation, in whom thermodilution may underestimate output.[37,38]

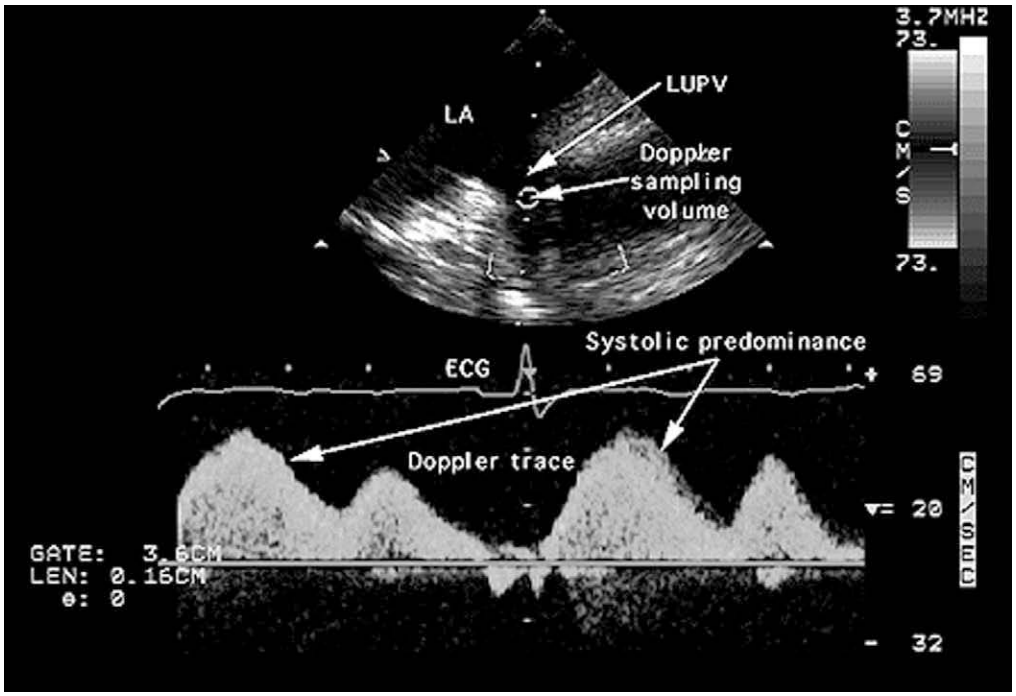


Figure 41-26 Pulsed wave Doppler measurement of normal blood flow velocities in the left upper pulmonary vein. At the top of the figure is a still-frame image of the two-dimensional cross section used to position the Doppler sampling volume (*broken circle* at point of *arrow*). On the bottom two thirds of the figure is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume. The electrocardiogram (ECG) provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. Flow velocities above the *bold line* are positive (i.e., toward the transducer) to a maximum of 69 cm/sec. Flow below the *bold line* is negative (i.e., away from the transducer) to a maximum of –32 cm/sec. In this patient with normal left atrial pressure, systolic predominance of flow is evident; that is, more flow enters the atrium during the period of ventricular systole than during ventricular diastole as evidenced by the greater peak and average flow velocities during systole than during diastole. LA, left atrium; LUPV, left upper pulmonary vein. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

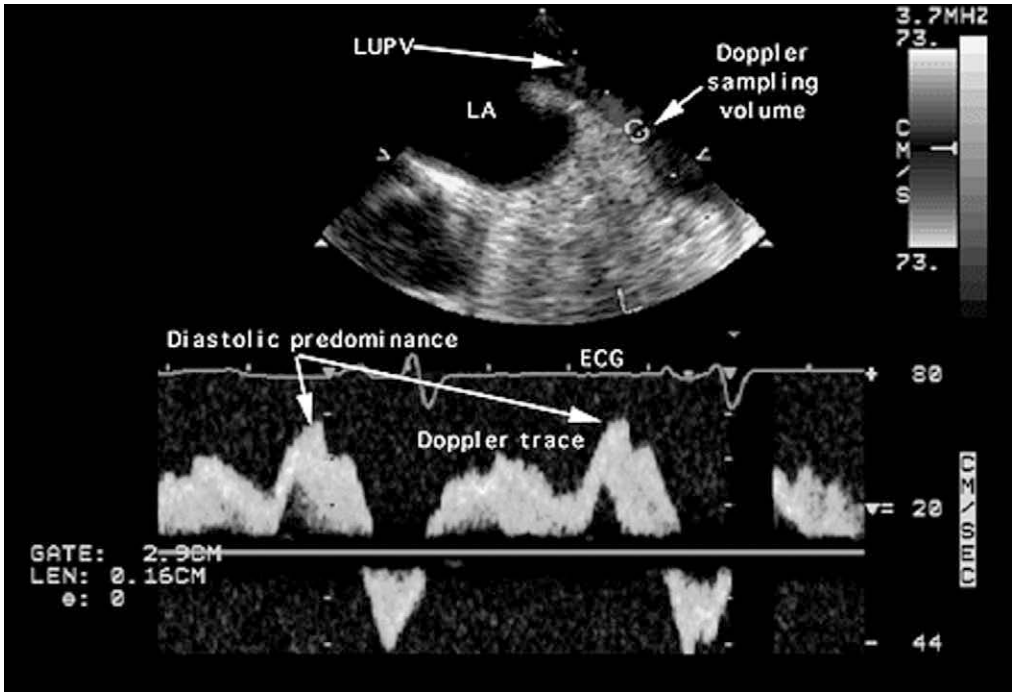


Figure 41-27 Pulsed wave Doppler measurement of blood flow velocities in the left upper pulmonary vein (LUPV) in a patient with abnormally high left atrial pressure. At the top of the figure is a still-frame image of the two-dimensional cross section used to position the Doppler sampling volume (*broken circle* at point of *arrow*). On the bottom two thirds of the figure is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume. The electrocardiogram (ECG) provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. Flow velocities above the *bold line* are positive (i.e., toward the transducer) to a maximum of 80 cm/sec. Flow below the *bold line* is negative (i.e., away from the transducer) to a maximum of –44 cm/sec. In this patient with abnormally high left atrial pressure, diastolic predominance of flow is evident; that is, more flow enters the left atrium (LA) during the period of ventricular diastole than during ventricular systole as evidenced by the greater peak and average flow velocities during diastole than during systole. The negative flow velocities are due to atrial contraction pushing blood back into the pulmonary vein. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

Assessment of Ventricular Systolic Function

Fractional area change (FAC) during systole is a commonly used measure of global LV function. It is measured by using the simple formula (EDA − ESA)/EDA, where EDA is the cross-sectional area at end diastole and ESA is the cross-sectional area at end systole. Marked changes in FAC are apparent by simply viewing the real-time images. Thus, severe LV depression is easy to detect with TEE. Although FAC correlates reasonably well with other approximations of ventricular function, significant limitations apply. First, TEE often underestimates the LV LAX (it foreshortens the left ventricle). Second, the midventricular SAX view may be a poor guide to overall ventricular ejection if other areas of the ventricle have markedly different function. Third, FAC, like other traditional echocardiographic indices of systolic function, is load dependent: changes in preload and afterload markedly alter FAC without changing the intrinsic function of the ventricle.

Measurement of RV function is more difficult than LV function because of the right ventricle's complex shape and response to changes in loading. However, severe RV dysfunction is not difficult to recognize. The hallmarks are severe hypokinesis or akinesis of the RV free wall, enlargement of the right ventricle so that it exceeds the size of the left ventricle, and a change in shape of the right ventricle from crescent to round. When RV dysfunction is due to acute pulmonary hypertension, as occurs in pulmonary embolism, the intraventricular septum flattens or bulges leftward.

Assessment of Ventricular Diastolic Function

Approximately a third of patients with symptomatic heart failure have normal LV systolic function. Their heart failure is due to diastolic dysfunction: abnormal diastolic relaxation and filling. TEE is an ideal tool for assessment of diastolic function because of its unobstructed view of the mitral valve and pulmonary veins.[39] Normal flow across the mitral valve in diastole has an early higher-velocity component generated by atrial pressure and ventricular relaxation (E wave on the Doppler echocardiogram) and a second lower-velocity component generated by atrial contraction (A wave). At slower heart rates, these two waves are separated by a period of relatively little flow (diastasis). Three severities of diastolic dysfunction are diagnosed by the combination of flow patterns in the mitral valve and pulmonary veins (Fig. 41-28).[40] The least severe is "impaired relaxation," which is characterized by a decrease in E-wave velocity, a decrease in the deceleration of early filling (seen as decreased slope of the E wave and termed "deceleration time"), and an increase in A-wave velocity to greater than E-wave velocity, thereby reversing the E-to-A ratio. In

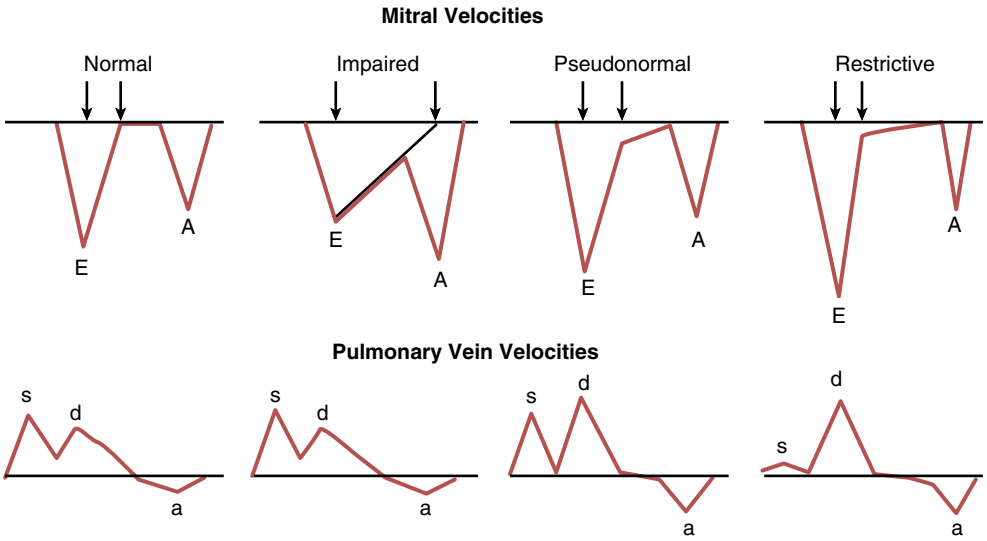


Figure 41-28 Line drawings representing simultaneous transesophageal pulsed wave Doppler recordings from the mitral annulus and right upper pulmonary vein are shown for normal, impaired, pseudonormal, and restrictive left ventricular diastolic function. The *solid black line* represents the slope of the E-wave velocity. From the start of the line at the inflection point of the E wave until its intercept at the base line is the deceleration time. This time is depicted in each of the mitral velocity drawings by *black arrows*. Please see text for further details. *(Adapted From Zile MR, Brutsaert DL: New concepts in diastolic dysfunction and diastolic heart failure: Part I: Diagnosis, prognosis and measurements of diastolic function. Circulation 105:1387-1393, 2002.© 2002 American Heart Association, Inc.)*

impaired relaxation, left atrial pressure is normal, and therefore so is the pattern of pulmonary venous flow: the S wave is greater than the D wave. The second and more severe degree of diastolic dysfunction is termed "pseudonormal" and is characterized by return of the normal E-to-A ratio because of a pathologic increase in left atrial pressure that results in abnormal pulmonary venous flow: the D wave is greater than the S wave. One simple way to confirm that the mitral flow pattern is pseudonormal and not normal is to transiently reduce left atrial filling with a Valsalva maneuver. If diastolic function is pseudonormal, the E-to-A ratio will transiently reverse, with A being greater than E. If diastolic function is normal, the normal ratio of E greater than A will persist and both waves will decrease in size. The third and most severe degree of diastolic dysfunction is termed "restrictive" and is characterized by very high E-wave velocity, a short deceleration time, and low A-wave velocity. In restrictive diastolic function, left atrial pressure is very high and results in a very small S wave and large D wave in the pulmonary veins. Patients with this pattern have a poor prognosis and suffer symptoms of congestive heart failure regardless of their systolic function.[41]

Transesophageal Echocardiography During Life-Threatening Hypotension

Ultimately, hypotension has only two possible causes: inadequate cardiac output or inappropriately low systemic vascular resistance. TEE is remarkably well suited for addressing this differential diagnosis. During severe hypotension, qualitative TEE estimates of ventricular filling and function serve as practical guides for the administration of fluids, inotropes, and vasopressors. An experienced observer can differentiate severe ventricular dysfunction from other life-threatening causes of hypotension. In severe LV failure, ventricular filling (as assessed by end-diastolic area) is increased and ejection is decreased, whereas in inappropriately low systemic vascular resistance, ventricular filling is usually normal or slightly decreased and ejection is markedly increased. Hypovolemia is easily recognized as a marked decrease in ventricular filling and a marked increase in ejection. Although inappropriately low systemic vascular resistance, severe aortic regurgitation, severe mitral regurgitation, and ventricular septal defects can manifest the same LV filling and ejection pattern on the TG SAX cross section, distinguishing these causes of hypotension is not difficult with the use of other cross sections and color Doppler. A dramatic example of the use of TEE in hypotensive patients is provided by a study of 60 consecutive patients with severe, persistent hypotension after cardiac surgery despite intensive therapy guided by invasive monitors.[42] TEE confirmed the presumed etiology of the hypotension in only 30 of these patients. In two patients, TEE revealed unsuspected cardiac tamponade and in six others unsuspected hypovolemia. In five patients, TEE prevented unnecessary reoperations by proving that tamponade was not present despite hemodynamic data suggesting that it was. In another study, unstable cardiac surgical patients in the operating room ($n = 57$) or intensive care unit ($n = 83$) underwent emergency TEE.[43] Based on TEE findings alone, 22 of these patients underwent urgent surgical interventions. The average time to diagnosis was 11 minutes. In still another study involving critically ill surgical patients, TEE proved to be more cost-effective than TTE because the latter so often fails to reveal diagnostic images.[44] Moreover, TEE has prognostic value in hypotensive, critically ill patients: when it reveals nonventricular causes of hypotension (e.g., valvular or pericardial), patients are twice as likely to survive as those with other causes of hypotension.[45] Even in the setting of prolonged cardiopulmonary resuscitation, TEE may reveal crucial diagnostic information.[46]

Detection of Myocardial Ischemia

Within seconds after the onset of myocardial ischemia, affected segments of the heart cease contracting normally. In 50 patients undergoing cardiovascular surgery, new intraoperative segmental wall motion abnormalities (SWMAs) diagnostic of myocardial ischemia (see later) occurred in 24 patients and ischemic ST-segment changes in only 6.[47] In three patients who sustained intraoperative myocardial infarction, SWMAs developed in the corresponding area of myocardium and persisted until the end of surgery, but only one of these three had ischemic ST-segment changes intraoperatively. Subsequent studies in comparable patients confirmed these advantages of TEE over electrocardiographic monitoring.[48] Moreover, when multiple TEE cross sections are monitored (not just the one cross section as was done in the aforementioned studies), the detection rate of SWMAs more than doubles.[49] Limitations of TEE in the detection of ischemia should be recognized. When an area of myocardium is clearly in view, segmental contraction can be difficult to evaluate if the heart rotates or translates markedly during systole or if discoordinated contraction occurs because of bundle branch block or ventricular pacing. Consequently, a valid system for assessment of SWMAs must evaluate both regional endocardial motion and myocardial thickening. Marked worsening of segmental wall motion and wall thickening (in the absence of similar global changes) is required to make the diagnosis of ischemia; even experts do not consistently interpret less pronounced changes. Not all SWMAs are indicative of myocardial ischemia. Myocarditis, myocardial infarction, and myocardial stunning also cause SWMAs. In coronary surgery, differentiating infarction, stunning, and ischemia is vitally important. When TEE reveals LV wall thickness of less than 0.6 cm, an old infarction in that thinned area is almost certain.[50] If inotropic stimulation improves the segmental motion of an SWMA, stunning, not ischemia, is likely.[51] One other cause of SWMA is severe hypovolemia in patients with preexisting SWMAs.[52] However, with the exception of myocardial stunning and severe hypovolemia as noted earlier, a sudden, severe decrease in segmental contraction is almost certainly due to myocardial ischemia.

Transesophageal Echocardiography in Cardiac Surgery

New Diagnoses

TEE can reveal new diagnostic findings before incision that prompt changes in surgical management (also see Chapter 60). In one prospective study of 474 consecutive patients undergoing coronary artery surgery, the surgical plan was changed in 3.4% of patients based on TEE.[53] In a different prospective study involving 3245 patients, the surgical plan was changed in 14% of patients based on TEE; the most common new finding prompting change was the discovery of a patent foramen ovale.[54] In a third prospective study involving 5016 patients, pre-bypass information from TEE led to modification of the surgical procedure in 27% of patients undergoing coronary surgery and 11% undergoing valvular surgery.[55] The divergent findings in these three studies are due to different patient populations, utilization criteria for TEE (selected versus consecutive use), and surgical practices, especially the treatment of patent foramen ovale and ischemic mitral regurgitation. Hemodynamic changes caused by general anesthesia alter the degree of mitral regurgitation (usually lessening it), thereby complicating surgical decision-making. Restoring intraoperative blood pressure with phenylephrine to preoperative levels improves the concordance between preoperative and intraoperative assessment of mitral regurgitation, but discrepancies remain.[56] In coronary surgery patients, even mild mitral regurgitation identified by intraoperative TEE predicts a significantly greater likelihood of death or hospitalization for heart failure over the subsequent 3 years than in coronary surgical patients without mitral regurgitation.[57] However, no definitive data are available to determine whether surgical repair of mild mitral regurgitation during coronary surgery is worth the added acute risk. Numerous case reports document that TEE can detect other problems necessitating changes in perioperative management, including intracardiac shunts and masses, great vessel obstruction, pulmonary embolism, and other conditions.

Aortic Diseases

TEE may have a crucial role in surgical diseases of the aorta. In a study of 160 consecutive patients with suspected thoracic aortic injury after blunt chest trauma, TEE was diagnostically superior to and faster than aortography for detection of the injury.[58] In a different study, TEE reliably distinguished between subadventitial disruptions, which require emergency surgery, and intimal tears, which do not.[59] In acute aortic dissection, TEE has proved superior to aortography and computed tomography.[60] It is associated with a shorter time to diagnosis, less morbidity (renal dysfunction and neurologic events), and shorter hospital stays than aortography is.[61] Though marginally less specific than magnetic resonance imaging (MRI) for some dissections (those originating in the aortic arch, where TEE imaging is partially obstructed by the trachea), TEE requires less time and expense than MRI or any other comparably reliable alternative.[62] Moreover, TEE can delineate the mechanisms and severity of associated aortic regurgitation and thereby identify patients in whom valve repair is likely to be successful.[63] Similarly, TEE-detected aortic atheromas have important implications. In 130 patients older than 65 years undergoing coronary artery bypass grafting, TEE detection of protruding atheroma of the ascending aorta proved to be the only independent predictor of stroke.[64] When these atheromas are detected by TEE, alteration of the aortic cannulation technique or increasing blood pressure during cardiopulmonary bypass may reduce the incidence of stroke.[65,66] Although TEE is not as sensitive as epiaortic scanning for detection of atheromas of the aortic arch, it is a good screening tool: if TEE reveals no significant atheromas in the ascending or descending aorta, none are likely to be present in the arch.[67] When intraoperative TEE reveals severe atheromatous disease of the aorta, off-pump coronary surgery results in a lower risk of death and stroke than on-pump surgery does.[68,69]

Valvular Diseases

TEE has profoundly affected valvular heart surgery by providing the surgical team with a definitive evaluation of their intervention while still in the operating room, where any needed revisions can be accomplished immediately. In 205 consecutive patients undergoing posterior mitral leaflet quadrangular resection (the most common mitral repair technique) for the treatment of mitral regurgitation, TEE revealed immediate failures in 24 patients (11.7%).[70] In 20 of these patients, TEE identified the mechanism of the failure and guided immediate further repair, and 1 patient required valve replacement. In a different study, 437 patients underwent mitral valve repair by a variety of techniques.[71] During a mean follow-up period of 29 months, 41 patients (9.4%) required a reoperation for failure of the repair. Successful initial repair as assessed by intraoperative TEE was the most important predictor of repair durability. Systolic anterior motion (SAM) of the mitral leaflet as diagnosed by intraoperative TEE is a known complication of mitral repair surgery. In a third study of 2076 patients undergoing mitral repair, TEE identified this complication in 174 patients (8.4%).[72] Four of these patients required immediate reoperation to relieve severe persistent SAM. In the others, it was managed medically. During a median follow-up period of 5.4 years, echocardiograms were available for 93 of these patients. SAM was present in 13 of them, and in 4 patients it was severe enough to cause partial LV outflow tract obstruction. Thus, when TEE reveals SAM immediately after mitral repair, it can be managed medically in most patients by preload augmentation, arterial vasoconstriction, β-blockade, or any combination of these treatments. During valve replacement surgery, TEE reliably detects periprosthetic leaks (surprisingly common). Although moderate or severe periprosthetic leaks should almost always undergo immediate repair, almost half of the small leaks resolve with the administration of protamine. However, surgically correctable prosthesis malfunction occurs in other patients and will be missed without the use of TEE. In a study of 417 patients undergoing valve replacement, immediate surgical correction was required in 15 patients (3.6%): periprosthetic leak ($n = 8$), immobilized leaflet ($n = 4$), coronary obstruction ($n = 2$), and xenograft incompetence ($n = 1$).[73]

Although a comprehensive review of valvular assessment is beyond the scope of this chapter, a brief overview of the most commonly used techniques should prepare the reader to fulfill at least the requirements for basic TEE practice so that gross valvular dysfunction can be recognized. The degree of aortic stenosis is appreciated easily in the ME AV SAX cross section, where the extent of leaflet opening can be estimated visually or measured directly by planimetry.[74] Severe stenosis is characterized by marked thickening of the leaflets and severely reduced leaflet motion (valve opening area of <1 cm^2). In the deep TG LAX cross section, CWD allows reliable estimation of the gradient across the AV (Fig. 41-29).[75] In severe stenosis, the peak instantaneous gradient will exceed 64 mm Hg (CWD velocity exceeding 4 m/sec), provided that cardiac output has not been markedly compromised. Noteworthy is the fact that the echocardiographically derived AV gradient may be higher than the peak-to-peak gradient reported from a catheterization study because the latter does not measure the instantaneous gradient as Doppler echocardiography does. Additional information on the morphology of the AV, including the dimensions of the annulus, sinotubular junction, and ascending aorta, can be garnered from the ME AV LAX cross section. The degree of aortic regurgitation is appreciated best in this cross section. With color Doppler positioned over the leaflets and outflow tract, aortic regurgitation is recognized as a color jet emanating from the valve during diastole. Even modest degrees of aortic regurgitation can be clinically significant during cardiac surgery and produce LV distention during cardiopulmonary bypass and diminish the effectiveness of antegrade cardioplegia.[76] Mild regurgitation is characterized by a narrow-based, diastolic color jet (<2 mm at its origin in the valve) that occupies less than a third of the cross-sectional area of the LV outflow tract and extends minimally into the left ventricle (1 to 2 cm). Moderate regurgitation is a broader-based, diastolic color jet (3 to 5 mm) occupying less than two thirds of the cross sectional area of the LV outflow tract and extending moderately into the left ventricle (3 to 5 cm). Severe regurgitation is a broad-based, diastolic color jet (>5 mm) occupying the entire LV outflow tract and extending well into the left ventricle (Table 41-4).

The presence and severity of mitral stenosis are determined easily with TEE on the ME four-chamber, two-chamber, commissural, or LAX cross section (or any combination of these views), as well as the basal TG SAX cross section. 2D imaging reveals thickened leaflets that dome toward the left ventricle and open poorly. Color Doppler reveals laminar flow acceleration into the stenotic orifice and a turbulent jet emerging into the ventricle (Fig. 41-30). PWD and CWD traces display a characteristic flow pattern consisting of increased peak and mean velocities (Fig. 41-31). Mathematical calculation from these traces, such as pressure half-time, are the most precise methods to assess the severity of mitral stenosis, and formulas for these evaluations are built into the software of virtually every ultrasonograph.[77] In addition to the signs just noted, severe mitral stenosis always causes marked left atrial enlargement and left atrial spontaneous contrast. Spontaneous contrast is a swirling, smokelike appearance of 1- to 2-mm densities not attributable to exogenously administered

Table 41-4 Simplified Grading for Aortic Insufficiency*

	Jet Width at Origin (mm)	Jet Area (% LVOT)	Jet Depth into the LV (cm)
Mild	<2	<33	1-2
Moderate	3-5	<66	3-5
Severe	>5	100	>5

*Diastolic jet width is assessed with color Doppler in the ME AV LAX view at the closure point of the aortic valve (the origin of the regurgitant jet). The transducer should be repositioned until the origin of the jet is clearly imaged. Failure to image the origin of the jet may lead to overestimation of its severity. The diastolic jet area is assessed with color Doppler. % LVOT is the percentage of the LVOT occupied by the plume of the color jet (the area of turbulent flow depicted by the mosaic of color pixels). This parameter is markedly affected by aortic diastolic pressure. Failure to adjust color or two-dimensional gains correctly may lead to underestimation or overestimation of the severity of the regurgitation. Color gain should be set just below the level that results in random color sparkle, and two-dimensional gains should be set at the minimum levels allowing adequate visualization of cardiac structures. Diastolic jet depth is assessed with color Doppler. The length of penetration of the jet from the LVOT into the LV is estimated in centimeters. This parameter is also markedly affected by aortic diastolic pressure and gain settings.
LV, left ventricle; LVOT, left ventricular outflow tract.
From Cahalan MK: Intraoperative Transesophageal Echocardiography: An Interactive Text and Atlas. New York, Churchill Livingstone, 1996.

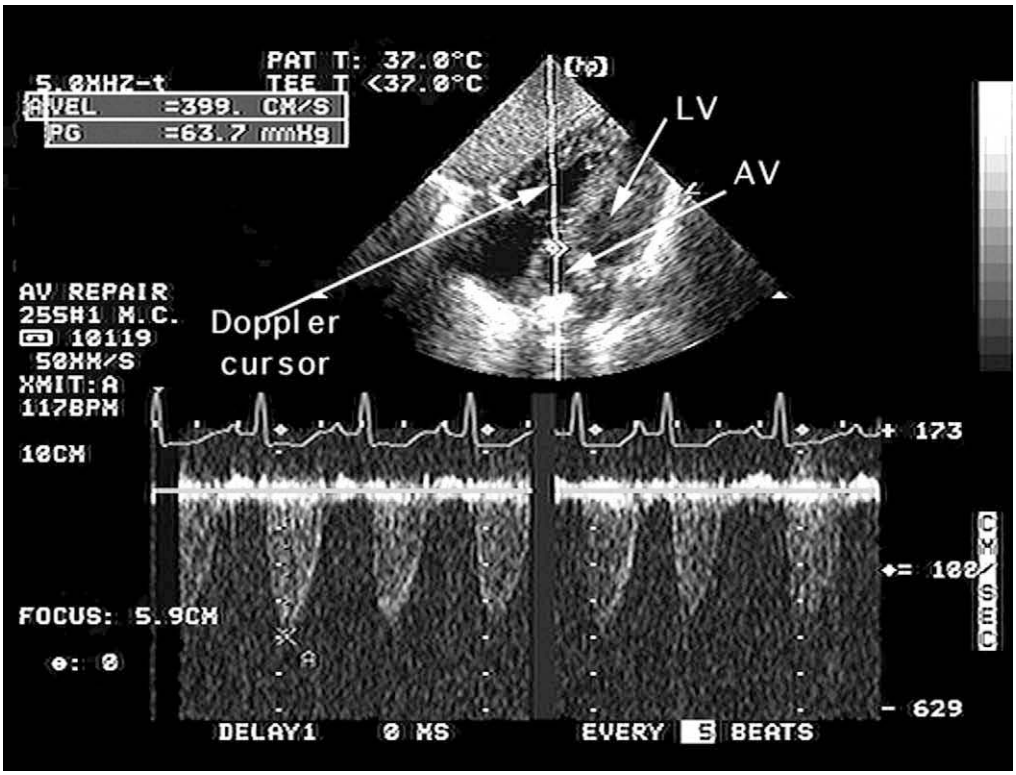


Figure 41-29 Continuous wave Doppler measurement of blood flow velocities immediately above the aortic valve (AV) during seven cardiac cycles. At the top of the figure is a still-frame image of the two-dimensional cross section used to position the Doppler sampling cursor (the *diagonal white line*). On the bottom two thirds of the figure is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring anywhere along that cursor. The electrocardiogram provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. With this Doppler alignment, all flow velocities are negative (i.e., away from the transducer). The Doppler scale has been set to a maximum of –629 cm/sec, and this tracing documents significant aortic stenosis: a peak blood flow velocity of approximately 4 m/sec (each *white dot* on the vertical axis equals 100 cm/sec or 1 m/sec), corresponding to a peak gradient across the AV of 64 mm Hg. LV, left ventricle. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

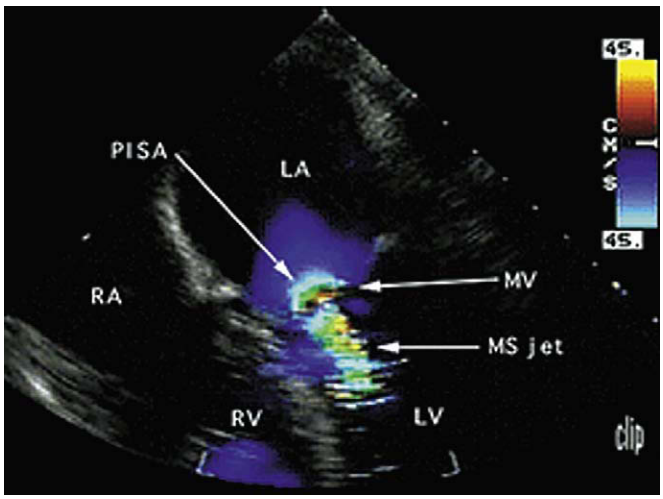


Figure 41-30 This four-chamber echocardiogram reveals a thickened and narrowed mitral valve (MV) indicative of mitral stenosis (MS). Color Doppler demonstrates (1) acceleration of blood flow into the stenotic valve (a light blue semicircular area immediately above the valve [PISA (proximal isovelocity surface area)]), (2) a narrow color jet across the valve itself, and (3) a 1- by 4-cm color jet extending from the undersurface of the valve into the left ventricle (LV). LA, left atrium; RA, right atrium; RV, right ventricle. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

contrast agents but to aggregation of red cells in areas of low flow. Whenever left atrial enlargement and spontaneous contrast are noted, thrombus in the left atrium and, in particular, the left atrial appendage should be suspected and investigated carefully.

The presence and severity of mitral regurgitation are evaluated from the same cross sections used for evaluation of mitral stenosis and with the same grading strategy used for aortic regurgitation (Table 41-5). Mild regurgitation is characterized by a narrow-based, systolic color jet (<2 mm at its origin in the valve) that occupies less than 25% of the left atrial cross-sectional area and extends less than half the distance to the posterior wall of the left atrium. Moderate regurgitation is a broader-based, systolic color jet (3 to 5 mm at its origin in the valve) occupying less than 50% of the left atrial cross-sectional area and extending 50% to 90% of the distance to the posterior wall of the left atrium. Severe regurgitation is a broad-based, systolic color jet (>5 mm) occupying most of the left atrium and extending into the pulmonary veins and left atrial appendage (Fig. 41-32). Eccentrically directed jets of mitral regurgitation that hug the wall of the atrium are generally associated with more severe valvular regurgitation than their cross-sectional area might suggest (see Fig. 41-32). Moreover, eccentrically directed jets usually point away from the defective leaflet (i.e., laterally directed jets are typically associated with anterior leaflet defects and medially directed jets with posterior leaflet defects), provided that the mechanism of regurgitation is leaflet prolapse or flail.[78] Severe mitral regurgitation is invariably

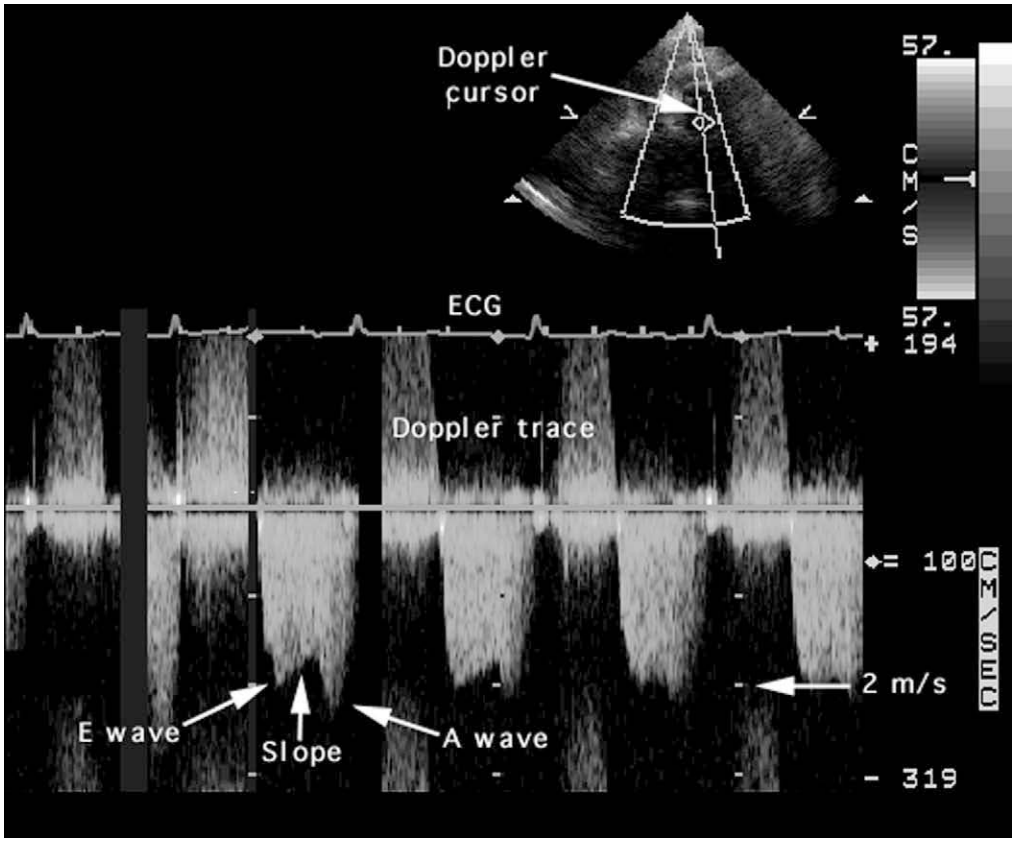


Figure 41-31 Continuous wave Doppler measurement of blood flow velocities through a stenotic mitral valve. At the top of the figure is a still-frame image of the four-chamber cross section used to position the Doppler cursor. On the bottom two thirds of the figure is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring anywhere along that cursor. The electrocardiogram (ECG) is shown for timing purposes, and the *bold horizontal line* running through the Doppler tracing is the baseline (zero flow) for the flow velocities. Velocities displayed above the baseline are positive and represent flow toward the transducer. These velocities are due to mitral regurgitation and are so high they exceed the scale used in this example. Velocities displayed below the baseline are negative and represent flow away from the transducer. These velocities are due to severe mitral stenosis and average about 2 m/sec, indicative of a 16 mm Hg gradient across the mitral valve. Also note how slowly flow velocity decreases after the peak of the E wave (i.e., the Slope). The pressure half-time can be calculated from this slope and is markedly increased in the presence of severe mitral stenosis. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

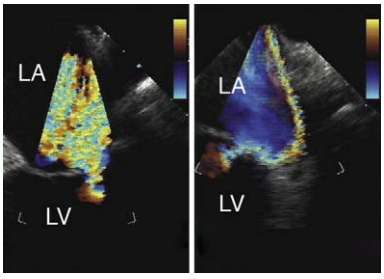


Figure 41-32 Two honed-down stop-action four-chamber transesophageal echocardiograms demonstrating severe mitral regurgitation. The one on the *left* reveals a large color jet depicting turbulent flow emanating from the center of the mitral valve at its coaptation point. The mechanism of the regurgitation in this patient is annular dilatation. Notice the broad base of the jet at the level of the valve leaflet and the extent of the jet's penetration into the left atrium (LA). The stop-action echocardiogram on the *right* reveals another broad-based jet with eccentric direction indicative of prolapse of the anterior leaflet of the mitral valve. Wall-hugging jets such as this one have a small cross-sectional area because much of their energy is absorbed by the wall of the atrium. LV, left ventricle.

associated with systolic reversal of pulmonary venous inflow (Fig. 41-33).[79] The general guidelines listed earlier are widely used, but many more criteria have been described for assessment of mitral regurgitation.[12] Of most importance, the degree of regurgitation is exquisitely dependent on LV loading conditions. For practical purposes, quantitative measures of regurgitation, such as the regurgitant orifice area based on the theory of proximal isovelocity surface area, are less often used in operating rooms because of time restriction.

Pulmonary and tricuspid valve pathology is assessed in a fashion analogous to that described previously for the aortic and mitral valves.

Coronary Disease

In a study of 82 high-risk patients undergoing coronary artery surgery, the investigators used staged blinding of the cardiac surgeons and anesthesiologists at critical points during surgery to document the clinical impact of TEE. After these clinicians docu-

Table 41-5 Simplified Grading for Mitral Regurgitation*

	Jet Width at Origin (mm)	Jet Area (% LA_a)	Jet Depth (% LA_d)
Mild	>2	<25	<50
Moderate	3-5	25-50	50-90
Severe	>5	<50	>100

*Systolic jet width is assessed with color Doppler in the five- or four-chamber view at the closure point of the mitral valve (the origin of the regurgitant jet). The transducer should be repositioned until the origin of the jet is clearly imaged. Failure to image the origin of the jet may lead to overestimation of its severity. Systolic jet area is assessed with color Doppler in the five- or four-chamber view. % LA_a is the percentage of the LA_a occupied by the plume of the color jet (the area of turbulent flow depicted by the mosaic of color pixels). This parameter is markedly affected by left ventricular systolic pressure. Failure to adjust color or two-dimensional gains correctly may lead to underestimation or overestimation of the severity of the regurgitation. Color gain should be set just below the level that results in random color sparkle, and two-dimensional gains should be set at the minimum levels allowing adequate visualization of cardiac structures. Systolic jet depth is assessed with color Doppler in the five- or four-chamber view. % LA_d is the depth of penetration of the jet into the left atrium expressed as a percentage of the distance from the mitral annulus to the posterior wall of the left atrium. This parameter is also markedly affected by left ventricular systolic pressure. In severe mitral regurgitation, the regurgitant jet may extend into one or more pulmonary veins and cause transient reversal of pulmonary venous blood flow.
From Cahalan MK: Intraoperative Transesophageal Echocardiography: An Interactive Text and Atlas. New York, Churchill Livingstone, 1996.

mented their planned management at each stage, the TEE results were revealed and led to at least one significant change in anesthetic management in 51% of patients and surgical management in 33% of patients, including additional unplanned or revised grafts (15%) and unplanned valve procedures (20%).[80] These high-risk patients had postoperative infarction and mortality rates below predicted (1% versus 3% predicted, difference not statistically significant). In the study noted in the section earlier involving 457 consecutive patients undergoing coronary artery surgery, TEE identified 71 new findings in 13% of patients. The new finding resulted in a change in surgical management in 6% of patients. After bypass, surgical management, including graft evaluation or revision and mitral repair, was initiated in 10 patients.

Congenital Heart Surgery

Pediatric TEE probes are used in infants as small as 3 kg (also see Chapter 83). Stevenson and coauthors reported that intraoperative TEE reliably detected residual cardiac defects in 17 (7.4%) of 230 consecutive patients undergoing congenital heart surgery.[81] These patients were reoperated on immediately for revision of the residual defects. However, a subsequent publication from the same center reported that the number of residual defects missed

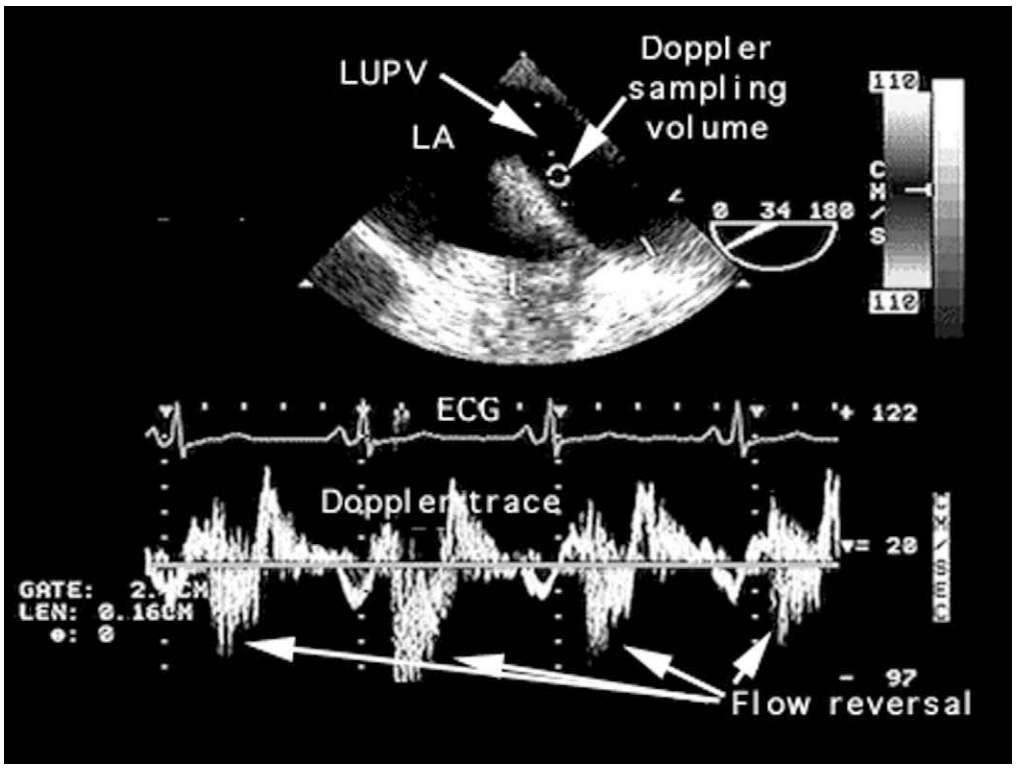


Figure 41-33 Pulsed wave Doppler measurement of blood flow velocities in the left upper pulmonary vein (LUPV). At the top of the figure is a still-frame image of the two-dimensional cross section used to position the Doppler sampling cursor (*broken circle* at point of *arrow*). On the bottom two thirds of the figure is a display of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring in the LUPV. The electrocardiogram (ECG) is shown for timing purposes, and the *bold horizontal line* running through the Doppler tracing is the baseline (zero flow) for the flow velocities. Velocities displayed above the baseline are positive and represent flow toward the transducer (in this case, into the left atrium [LA]). Velocities displayed below the baseline are negative and represent flow away from the transducer (in this case, into the LUPV). This Doppler tracing documents systolic flow reversal (normally it is positive, that is, toward the LA in systole) and confirms the presence of severe mitral regurgitation. *(Reproduced with permission from Cahalan MK: Intraoperative Transesophageal Echocardiography. An Interactive Text and Atlas. New York, Churchill Livingstone, 1997.)*

by intraoperative TEE increased from 2% to 13% when the attending anesthesiologist and not a separate echocardiographer performed TEE.[82] This study generated considerable controversy. Although it does not resolve the issue of whether a separate echocardiographer is required to perform TEE adequately in patients undergoing congenital heart repair, it does amply demonstrate that patients can suffer severe consequences when intraoperative TEE is not expertly performed, interpreted, and acted on. In this study, the deaths of seven patients may have been related to the delayed recognition of residual defects. With progress in pediatric congenital heart surgery, more and more children with palliated congenital heart disease will survive to adulthood and undergo cardiac and other kinds of surgery. For an excellent update on TEE in adult congenital heart disease, please see the recent review by Russell and associates.[83]

Other Cardiac Diseases and Applications

In addition to use in valve repair, congenital heart surgery, and thoracic aortic surgery and in hemodynamically unstable patients, the 1996 ASA/SCA guidelines identify intraoperative use of TEE during surgery for hypertrophic cardiomyopathy, endocarditis, and pericardial window procedures as category I indications.[6] Subsequent publications have documented the critical role that TEE may provide in minimally invasive cardiac surgery and in placement of cardiac support devices.[84,85] Thousands of other published reports have documented that TEE can reveal virtually any significant morphologic or functional pathology of the heart. TEE is particularly sensitive for abnormalities involving the left atrium and mitral valve, including masses, thrombi, and emboli, because of the proximity of the left atrium and mitral valve to the TEE transducer. In contrast, pathologies of the RV and LV apex are less reliably detected. TEE is exquisitely sensitive to air embolism, and as a result, even insignificant amounts of air in the circulation give rise to impressive densities on the video display. Currently, accurate estimation of the amount of air in the circulation is impossible with TEE. However, large amounts typically opacify the involved chambers until collections (very bright densities) are formed in the most superiorly positioned parts of the chambers (e.g., the anterior endocardial surface of the left ventricle in a supine patient). Pulmonary emboli may be seen with TEE if they lodge proximal to the bifurcation of the main pulmonary artery.

Transesophageal Echocardiography in Noncardiac Surgery and Critical Care

TEE has many of the same applications in noncardiac surgical patients and critically ill patients as in cardiac surgical patients (also see Chapter 91). Numerous case reports and case series have documented the impact that it can have on patient management and outcome. In our practice, the leading indications are hemodynamic instability and massive blood loss, where TEE has a vital role in determining the etiology of the instability (see the previous section on this topic) and in guiding volume resuscitation.[86,87] In the intensive care unit, TEE has similar applications, and these have been reviewed recently.[88,89]

Data Storage, Documentation, and Quality Assurance

Traditionally, echocardiograms were stored on videotape and written reports of the results were placed in the patient's medical record. Currently, digital recording of individual cardiac cycles or multiple cycles is the standard. The resulting "loops" are transported via hospital networks or the Internet to secure servers, where the studies can be retrieved rapidly. The SCA has published guidelines for TEE reporting (http://www.scahq.org/sca3/peri_op_report4-02.rtf) and a recommended report form (http://www.scahq.org/sca3/TEEREPORfin4-02.rtf).

The ASE and SCA have published guidelines for continuous quality improvement (CQI) in perioperative echocardiography.[90] However, even relatively simple CQI interventions may produce dramatic results in the consistency of image acquisition and storage.[28] Periodic expert review of TEE interpretations is essential if practitioners are to reach and maintain their diagnostic potential. Collaboration between the departments of anesthesiology and cardiology is one approach to this review process that minimizes the duplication inherent in the formation of independent CQI programs.

Certification

The SCA and ASE formed the National Board of Echocardiography (www.echoboards.org). This new board offers a written examination and certification in perioperative echocardiography. The written examination is open to all licensed physicians. Certification requires additional documented experience for physicians who completed their training before 2009. For physicians completing their training after 2009, certification will require fellowship training in perioperative echocardiography (http://www.echoboards.org/certification/pte/reqs.html).

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Zak Hillel and Giora Landesberg

42 Electrocardiography

Key Points

1. Electrocardiographic monitoring is mandatory and a standard of care.
2. Electrocardiography permits detection of electrical disturbances that may influence the mechanical function of the heart.
3. With carefully selected lead combinations, most arrhythmias and myocardial ischemic events can be detected in the perioperative setting.
4. Appropriate diagnosis of arrhythmias and ischemia will allow proper and effective treatment.

The electrocardiogram (ECG) was first invented by William Einthoven in 1901, who used a string galvanogram for his recordings. This time-honored and relatively simple tool remains, even today, a mainstay in clinical cardiac diagnosis and therapy. In the perioperative setting, electrocardiography serves two main functions: diagnosis and monitoring. In the preoperative period, the standard 12-lead ECG is performed mainly for risk assessment. It is used to provide information on the patient's baseline (chronic) cardiac status with regard to myocardial ischemia and conduction or rhythm abnormalities as part of the whole preoperative clinical assessment. Occasionally, the preoperative ECG may reveal acute or new abnormalities, especially when dealing with urgent or emergency operations, and in such cases comparing current with previous ECGs is of extreme importance. During and after surgery the ECG is used mainly for monitoring to detect changes in rate and rhythm or myocardial ischemia. With many patients undergoing surgery with pacemakers or implantable cardiac defibrillators in place, the ECG enables the anesthesiologist to monitor the proper function of these devices during the surgical procedure. Perioperative management of these devices is described in Chapter 43. During cardiac surgery, both myocardial ischemia and different types of arrhythmia are common, especially after separation from cardiopulmonary bypass. Proper diagnosis and management of intraoperative ischemia and arrhythmias are part of the expertise of the anesthesiologist. A postoperative 12-lead ECG is often obtained in patients at high cardiac risk when new ischemic or rhythm changes are suspected. In all these scenarios, a good understanding of the principles of interpretation of the ECG is vital for the clinical anesthesiologist. This chapter is intended to cover most aspects of interpretation of the ECG, with special emphasis on issues relevant to anesthesia and perioperative care.

Electrocardiographic Lead Systems

Standard Recording Electrodes and Leads

The small electric currents produced by the electrical activity of cardiac muscle spread an electrical field throughout the body that behaves as a volume conductor, which allows it to be recorded at various sites on the surface of the body as electrocardiographic signals. The electrical potentials reaching the skin are recorded by electrodes (leads) placed at specific locations, and the output of these leads is amplified, filtered, and displayed on various electronic devices. There are two types of electrocardiographic leads: *bipolar* and *unipolar*. A bipolar lead consists of two electrodes placed at different sites to measure the difference in potential between them. Unipolar leads measure the "absolute" electrical potential at one site in relation to a *reference*, or *remote site*, at which the potential is deemed to be zero. The standard clinical ECG includes recordings from 12 leads. These 12 leads include three *bipolar* (leads I, II, and III), six *unipolar precordial* (leads V_1 through V_6), and three *modified unipolar limb leads* (the augmented limb leads aVR, aVL, and aVF) (Table 42-1).

Standard Electrocardiographic Recordings

The ECG is normally recorded on special paper consisting of grids of horizontal and vertical lines. Distances between vertical lines represent time intervals, whereas distances between hori-

Table 42-1 Location of electrodes and lead connections for the standard 12-lead electrocardiogram and additional leads

Lead Type	Positive Input	Negative (Reference) Input
Bipolar Limb Leads		
Lead I	Left arm	Right arm
Lead II	Left leg	Right arm
Lead III	Left leg	Left arm
Augmented Unipolar Limb Leads		
aVR	Right arm	Left arm plus left leg
aVL	Left arm	Right arm plus left leg
aVF	Left leg	Left arm plus left arm
Precordial Leads		
V_1	Right sternal margin, 4th intercostals space	Wilson central terminal
V_2	Left sternal margin, 4th intercostal space	Wilson central terminal
V_3	Midway between V_2 and V_4	Wilson central terminal
V_4	Left midclavicular line, 5th intercostal space	Wilson central terminal
V_5	Left anterior axillary line	Wilson central terminal
V_6	Left midaxillary line	Wilson central terminal

Adapted from Zipes DP, Libby P, Bonow R, Braunwald E: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia, WB Saunders, 2005.

zontal lines represent voltage. The lines are 1 mm apart, with every fifth line intensified. The speed of the paper is standardized to 25 mm/sec. On the horizontal axis, 1 mm represents 0.04 second, and 0.5 cm represents 0.20 second. On the vertical axis, 10 mm represents 1 mV. On every recording, a 1-cm (1-mV) calibration mark should indicate that the ECG is appropriately calibrated.

Normal Electrical Activity

P Wave

Under normal circumstances, the sinoatrial (SA) node has the most rapid spontaneous depolarization rate and is therefore the dominant cardiac pacemaker. From the SA node, the impulse normally spreads to the atrioventricular (AV) node through one left-sided and two right-sided pathways. The P wave is the result of normal depolarization of the atria, and identification of this wave is important for determination of normal sinus rhythm. The anatomically anterior right atrium is activated earlier, and only later does the signal shift posteriorly as activation proceeds over the left atrium. Therefore, the P wave in the right precordial leads (V_1 and, occasionally, V_2) is commonly biphasic, a positive deflection followed by a negative one, whereas in the lateral leads, the P wave is upright and reflects right-to-left spread of the activation front.

PR Interval

The PR interval is the temporal bridge between atrial and ventricular activation, during which the AV node, the bundle of His, the bundle branches, and the intraventricular conduction systems are activated (Fig. 42-1). Most of the conduction delay during this segment is due to slow conduction within the AV node. The normal PR interval is 120 to 200 msec in duration.

Myocardial Activation—The QRS Complex

The QRS complex is the manifestation of left and right ventricular muscle depolarization. Its pattern in each electrocardiographic lead represents the sum of all electrical forces emanating from the wavefront propagation of ventricular electrical excitation aimed in the direction of that lead. Ventricular excitation spreads within several milliseconds from the bundle branches to the His-Purkinje fibers, which are dispersed broadly throughout the entire endocardial surfaces of both ventricles. Excitation of the Purkinje–ventricular muscle junctions in the endocardium then proceeds by conduction from muscle cell to muscle cell to activate the entire ventricle thickness toward the epicardium. The normal pattern of activation of the ventricles starts in the interventricular septum with a vector oriented from left to right in the frontal plane and anteriorly in the horizontal plane (as determined by the anatomic position of the septum within the chest). This produces an initial small positive R wave in the right-sided leads (aVR and V_1) and small negative waves (septal q waves—less than 30 to 40 msec) in the left-sided leads (I, aVL, V_5, and V_6). Subsequent QRS complex elements reflect activation of the free walls of the left and right ventricles. Because the right ventricular muscle mass is considerably smaller than that of the left ventricle, the QRS primarily represents left ventricular (LV) activity with its main vector proceeding from right to left in the axial plane and anterior followed by posterior vectors in the horizontal plane (R wave followed by a small S wave in the left-sided leads). The

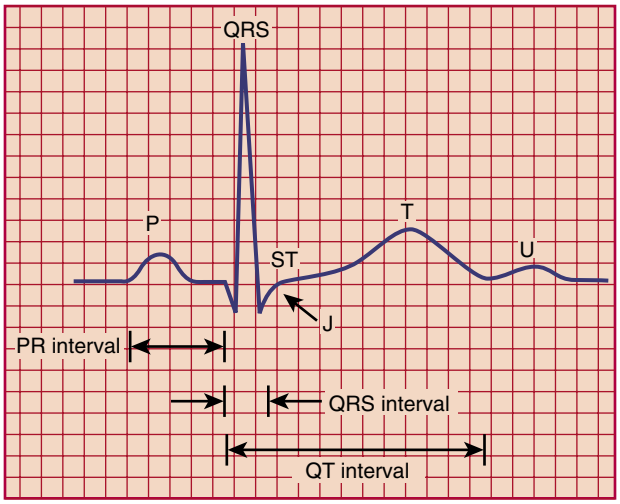

Figure 42-1 Waves and intervals of a normal electrocardiogram. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 6th ed. St Louis, CV Mosby, 1999; and Zipes DP, Libby P, Bonow R, Braunwald E: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia, WB Saunders, 2005.)*

main vector of the QRS complex in the frontal plane serves to calculate the electrical axis of the heart, which is normally between −30 and +90 degrees. An axis more negative than −30 degrees is called *left axis deviation*, and an axis higher than +90 degrees is termed *right axis deviation*. The duration of the normal QRS complex is less than 120 msec.

ST Segment and T Wave

Repolarization of the ventricles generates the ST segment and T wave. Repolarization, like activation, occurs in a characteristic geometric pattern. Because the endocardial action potential lasts longer than that of its overlying epicardium, repolarization of the epicardium often starts earlier than in the endocardium. However, under normal conditions, there are regional differences in electrical recovery properties of the ventricles, and the transmural gradients predominantly determine the ST patterns.

Normally, there is concordance between the orientation of the QRS complex and the T wave, with both deflecting in the same direction. The junction of the QRS and the ST segment is called the J junction. The QT interval—the duration from the Q wave to the end of the T wave—is highly dependent on heart rate, and formulas have been developed to calculate the corrected QT interval (QTc), which if prolonged may be associated with serious ventricular arrhythmias. The T wave is sometimes followed by a small U wave, which may be associated with hypokalemia or hypomagnesemia (see Fig. 42-1). An example of a normal 12-lead electrocardiogram is shown in Figure 42-2.

The Abnormal Electrocardiogram

Atrial Abnormality

Initiation of atrial electrical activation from a site other than the SA node occurs in one of two ways: either as an escape rhythm if the normal SA nodal pacemaker slows or fails or as an accelerated atrial ectopic rhythm if the automaticity of the ectopic site is associated with a rate higher than the SA node. Ectopic atrial activation is often manifested by an abnormal morphology of the P wave (different from the native P). Most commonly, negative P waves are seen in the leads where the P wave is normally upright (leads I, II, aVF, and V_4 through V_6), with or without shortening of the PR interval. The exact site of an ectopic atrial pacemaker is usually of little clinical significance except that left-sided atrial ectopy is seen more often in association with LV or left heart valvular abnormalities, whereas right-sided ectopy is more common in patients with chronic obstructive lung disease or other causes of right heart dysfunction.

Ventricular Hypertrophy and Enlargement

Left ventricular hypertrophy (LVH) or enlargement produces changes throughout the QRST complex. The most characteristic change is increased voltage of the QRS complex: tall R waves in the left-sided leads (I, aVL, V_5, and V_6) and deep S waves in the right-sided leads (V_1 and V_2). ST-segment and T-wave amplitudes can be normal or increased. ST-segment depression with downsloping from a depressed J point and inverted asymmetric T waves are common in long-standing and severe LVH. Similarly, a QRS duration prolonged beyond 110 msec reflects the longer duration of activation of the thickened ventricular wall. Many sets of diagnostic electrocardiographic criteria for LVH have been developed, although their diagnostic importance in the era of echocardiography has obviously diminished. For example, Sokolow and Lyon found the following voltage criteria to correlate best with postmortem pathologic findings of LVH: SV_1 + (RV_5 or RV_6) > 3.5 mV or RaVL > 1.1 mV (or both) (Fig. 42-3).

Right ventricular hypertrophy is manifested on the ECG by abnormally tall R waves in the rightward-directed leads (aVR, V_1, and V_2), reversal of normal R-wave progression in the precordial leads, deep S waves with abnormally small R waves in the left-sided leads (I, aVL, V_5, and V_6), and marked right axis deviation (>110 degrees). Chronic obstructive pulmonary disease can lead to right ventricular hypertrophy, changes in the position of the heart within the chest, and hyperinflation of the lungs. Acute right ventricular pressure overload, such as that caused by pulmonary embolism, can produce a characteristic pattern on the ECG: a QR or qR pattern in the right-sided leads, an $S_1Q_3T_3$ pattern, and an acute incomplete or complete right bundle branch block (RBBB). However, even the classic $S_1Q_3T_3$ pattern occurs in only about 10% of cases of acute pulmonary embolism (Fig. 42-4).

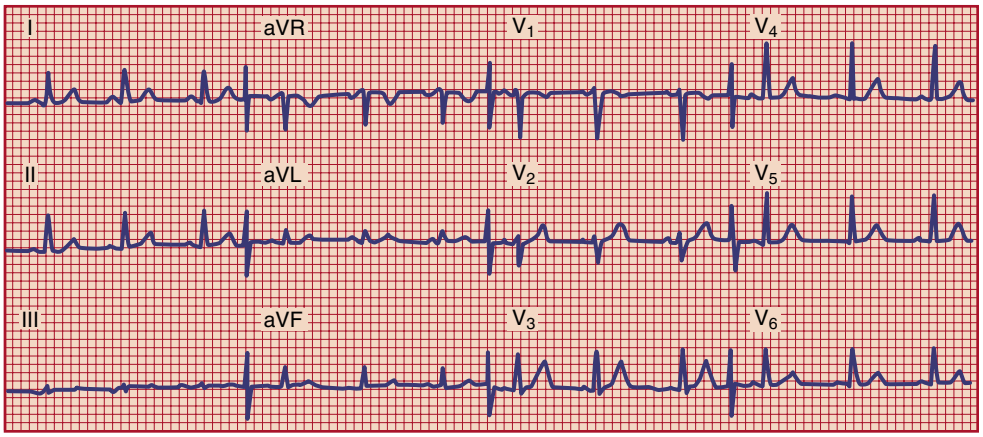

Figure 42-2 Example of a normal 12-lead electrocardiogram. *(From Zipes DP, Libby P, Bonow R, Braunwald E: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia, WB Saunders, 2005.)*

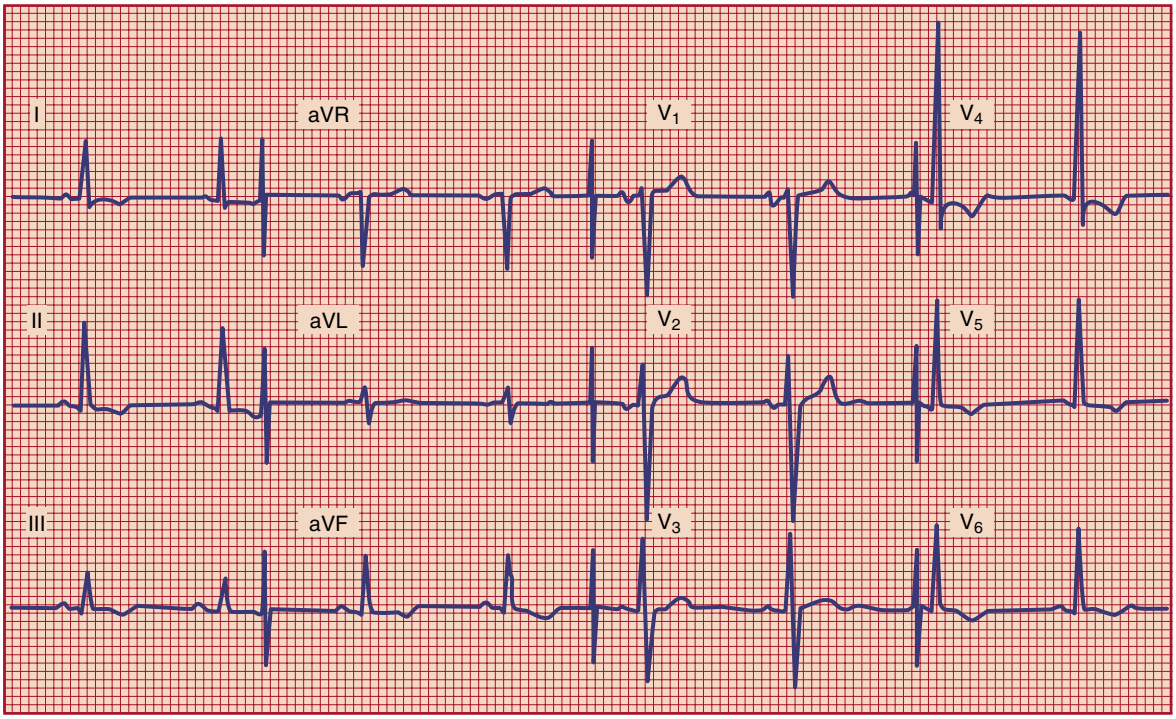

Figure 42-3 Left ventricular hypertrophy on electrocardiography. Tall R waves on the left-sided leads and deep S waves on the right-sided ones, down-sloping ST-segment depression and T-wave inversion opposite the main R-wave axis, and a biphasic p wave signify left atrial abnormality. *(From Zipes DP, Libby P, Bonow R, Braunwald E: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia, WB Saunders, 2005.)*

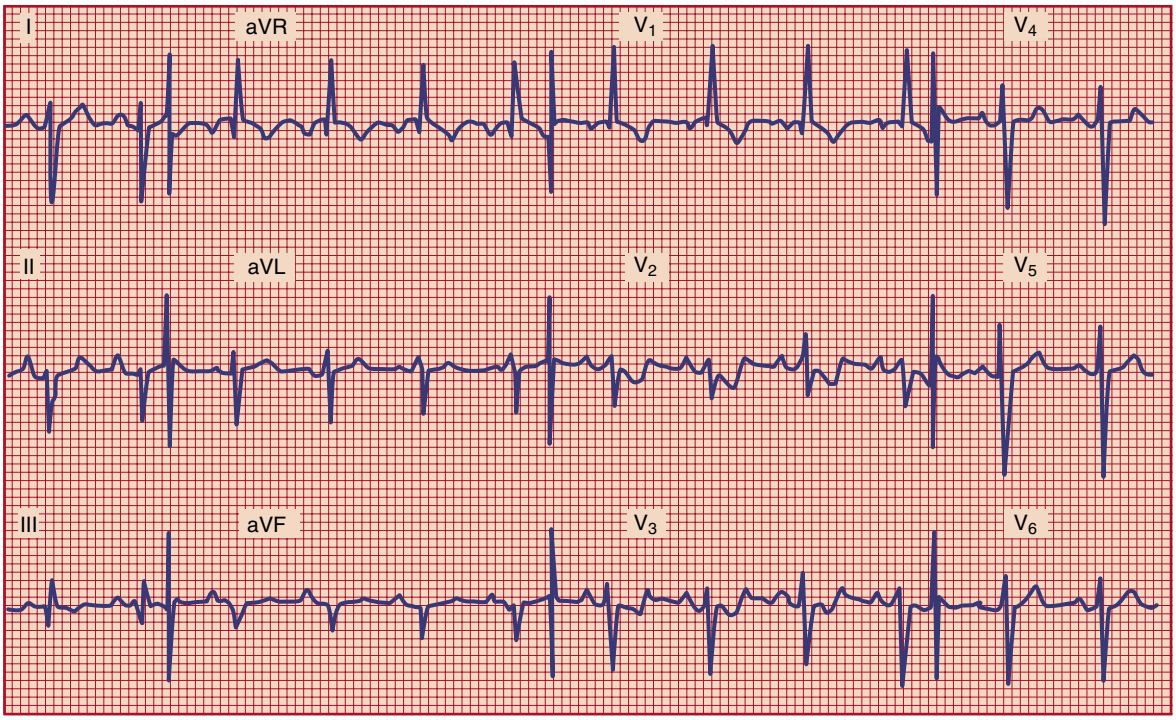

Figure 42-4 Severe right ventricular hypertrophy indicated by tall R waves on the right-sided leads, deep S waves on the left-sided leads, and T-wave inversions on the right-sided leads ($S_1Q_3T_3$).

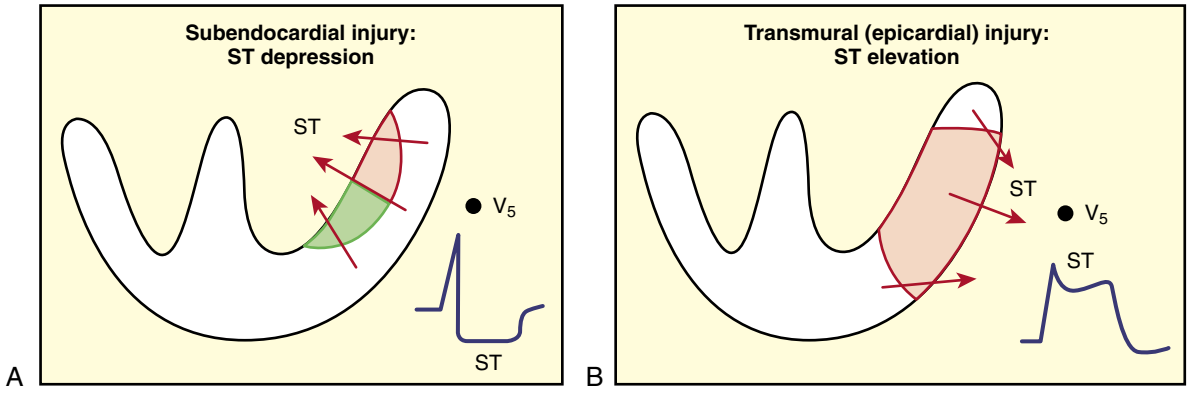

Figure 42-5 Patterns of injury currents. **A,** Acute subendocardial, ST-depression type. **B,** Transmural, ST-elevation type (ischemia). *(From Zipes: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed.)*

Myocardial Ischemia

The ST-T segment, representing myocardial repolarization, is the component of the ECG most sensitive to acute myocardial ischemia. ST elevation, which may be accompanied by tall positive (hyperacute) T waves, indicates transmural ischemia and is most often the result of acute coronary artery occlusion caused by either coronary thrombosis or vasospasm (Prinzmetal's variant angina). Reciprocal ST depression may appear in the contralateral leads. Ischemia confined to the subendocardial area is usually denoted by ST-segment depression. Subendocardial, ST depression–type ischemia typically occurs during episodes of symptomatic or asymptomatic ("silent") stable angina pectoris. It is characteristic of ischemia occurring during exercise, tachycardia, or a pharmacologic stress test in patients with significant but stable coronary artery disease (CAD) (Fig. 42-5).

Myocardial Infarction

With prolonged ischemia, there is a risk of developing myocardial necrosis or myocardial infarction (MI). The electrocardiographic manifestation of MI includes decreased R-wave amplitude and pathologic Q waves (>1 mm in depth and >40 msec in duration), which may develop as a result of loss of electromotive forces in the infarcted area. Transmural infarctions are more likely to culminate in pathologic Q waves, whereas subendocardial (nontransmural) infarcts are less likely to produce Q waves. However, pathologic studies have shown such a wide overlap between the two entities and their electrocardiographic expression that "Q-wave" or "non–Q-wave" infarction is not synonymous with transmural or nontransmural infarction. Pathologic Q waves usually develop days after the onset of acute MI, and once they develop, they infrequently disappear and serve as an indicator of the location of the infarction. Persistent T-wave inversion may also be the only sign of chronic ischemia and recent or old MI. Pathologic Q waves with ST elevation that persists for weeks or longer after MI correlate strongly with severe myocardial mechanical dysfunction, akinesis, or ventricular aneurysm.

Electrocardiographic leads demonstrating ST-T changes or Q waves may help define the location and the coronary artery responsible for the ischemia or MI. For example, precordial leads V_1 to V_3 correspond to the anteroseptal or apical walls of the left ventricle; leads V_4 to V_6 to the apical or lateral LV walls (Fig. 42-6); leads II, III, and aVF to the inferior LV wall (Fig. 42-7); and the

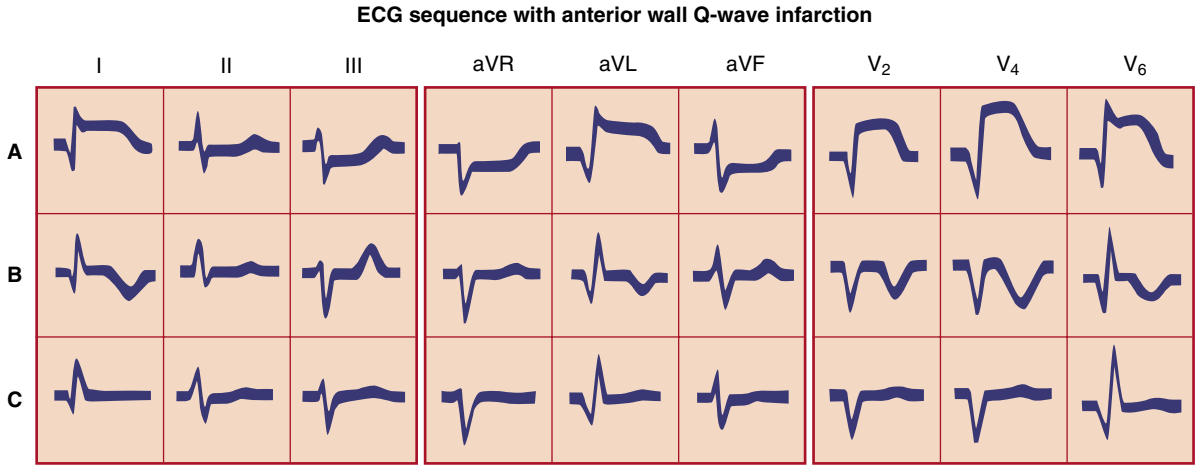

Figure 42-6 Acute, ST-elevation–type anterior wall myocardial infarction. **A,** Acute phase: ST elevations and new Q waves. **B,** Evolving phase: deep T-wave inversions. **C,** Resolving phase: partial or complete regression of the ST-T changes (and sometimes Q waves). Notice the reciprocal ST-T changes in the inferior leads (II, III, and aVF). *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 7th ed. St Louis, CV Mosby, 2006.)*

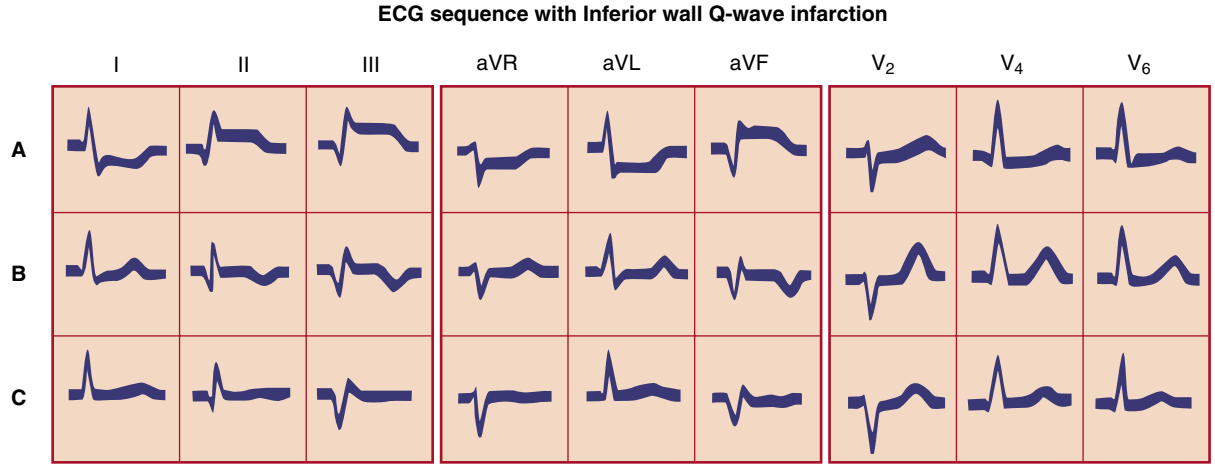

Figure 42-7 Inferior wall myocardial infarction. **A,** Acute phase: ST elevations and new Q waves. **B,** Evolving phase: deep T-wave inversions. **C,** Resolving phase: partial or complete regression of the ST-T changes (and sometimes Q waves). Notice the reciprocal ST-T changes in the anterior leads (I, aVL, and V_2). *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 7th ed. St Louis, CV Mosby, 2006.)*

right-sided leads to the right ventricle. Posterior wall infarction induces ST elevation or Q waves in leads placed over the left side and back (V_7 to V_9), and reciprocal ST depression or tall R′ waves may develop in leads V_1 to V_3.

Electrolyte Abnormalities

The ECG is affected not only by structural or functional myocardial abnormalities but also by numerous metabolic and electrolyte aberrations (see Chapter 54).

CALCIUM. Hypercalcemia shortens and hypocalcemia prolongs phase 2 of the action potential duration, thus leading to abbreviation or prolongation of the QT interval, respectively. Severe hypercalcemia (e.g., total serum Ca^{2+} >15 mg/dL) causes a decrease in T-wave amplitude or T-wave inversion, and hypercalcemia may produce a high-takeoff ST segment in leads V_1 and V_2 simulating acute ischemia.

POTASSIUM. Hyperkalemia leads to a distinctive sequence of changes on the ECG, starting with narrowing and peaking of the T wave and shortening of the QT interval. Progressive hyperkalemia causes widening of the QRS complex, a low P-wave amplitude, and prolongation of the PR interval with the possibility of a second- to third-degree AV block (Fig. 42-8). Severe hyperkalemia results in sine-wave ventricular flutter and eventually asystole. Hypokalemia, in contrast, may cause ST depression, flattened T waves, and a prominent U wave that may sometimes exceed the amplitude of T waves. Hypokalemia prolongs repolarization and leads to long QT(U) syndrome, which predisposes to a torsades de pointes–type ventricular fibrillation.

MAGNESIUM. Mild to moderate hypermagnesemia or hypomagnesemia is not associated with specific changes on the ECG. Yet severe hypermagnesemia can cause AV and intraventricular conduction disturbances, including complete heart block and cardiac arrest (Mg^{2+} >15 mEq/L). Hypomagnesemia is often associated with hypocalcemia or hypokalemia

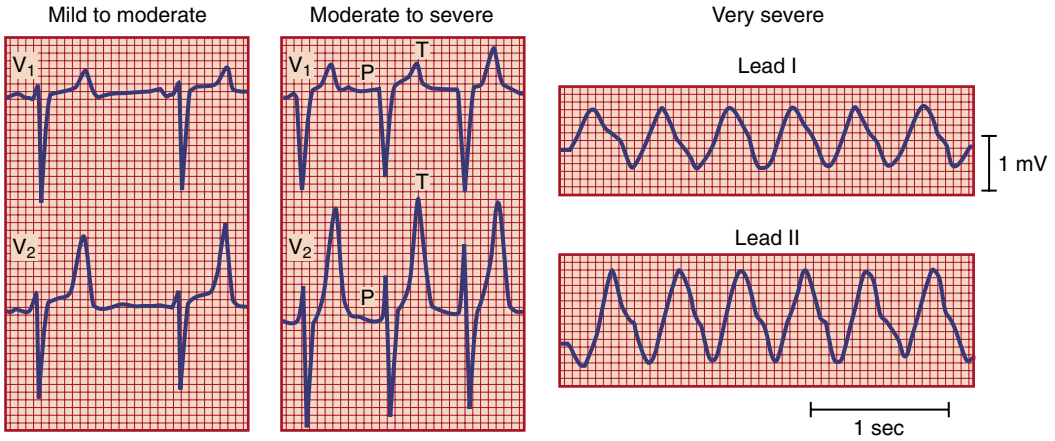

Figure 42-8 Electrocardiographic signs of hyperkalemia. The earliest change with hyperkalemia is peaking ("tenting") of the T waves. With progressive increases in the serum potassium concentration, the QRS complexes widen, the P waves decrease in amplitude and may disappear, and finally a sine-wave pattern leads to asystole unless emergency therapy is initiated. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 7th ed. St Louis, CV Mosby, 2006.)*

and may predispose to long QT(U) syndrome and torsades de pointes.

Electrocardiographic Monitoring Systems

Noise Filtering

Low-Frequency Filtering. All electrocardiographic monitors use filters to narrow the signal bandwidth in an attempt to reduce environmental artifacts and improve signal quality. Low-frequency noise, such as that produced by respiration or any other patient motion, causes the tracing to wander above and below the baseline. Therefore, low-frequency filters are used in electrocardiographic monitoring. The heart rate in beats per minute forms a rough lower bound for the frequency content in hertz (Hz, cycles per second). Because heart rates below 40 beats/min (0.67 Hz) are uncommon, traditional low-frequency analog filters are used to cut signals off at frequencies below 0.5 Hz. However, such filters introduce considerable distortion on the ECG, particularly with respect to the level of the ST segment. It results in phase nonlinearities in areas of the electrocardiographic signal where frequency content and wave amplitude change abruptly, as occurs where the end of the QRS complex meets the ST segment. The 1975 American Heart Association (AHA) recommendations included a 0.05-Hz low-frequency cutoff for diagnostic electrocardiography. This recommendation preserves the fidelity of repolarization, but it does not eliminate the problem of baseline drift. Current modern digital filtering provides more sophisticated methods to achieve a higher cutoff for low-frequency filtration without the phase distortions seen with analog filtering. Thus, current AHA recommendations[1] to reduce artifactual distortion of the ST segment are that the low-frequency cutoff should be (1) 0.05 Hz for monitors with analog filters and (2) 0.67 Hz or lower for monitors and electrocardiographic recording devices with linear digital filters and zero phase distortion.

High-Frequency Filtering. High-frequency filters are needed to reduce distortions from muscle fasciculations, tremors, and electromagnetic interference from other electrical equipment. Older monitors used a 40-Hz filter to reduce the interference from electrical current. However, the higher the frequencies contained in the filtered signal, the more accurate the measurement of rapid upstroke velocity, peak amplitude, and waves of short duration. A high-frequency cutoff of 100 Hz was considered adequate by the AHA in 1975 to maintain diagnostic accuracy during visual inspection of the ECG, even though it has long been recognized that higher-frequency components of the QRS complex may have clinical significance in patients with various forms of heart disease. According to current AHA recommendations, an upper frequency cutoff of at least 150 Hz is required to accurately measure routine duration and amplitudes in adults, adolescents, and children, and an upper frequency cutoff of 250 Hz is more appropriate for infants.

Most modern electrocardiographic monitors allow the operator a choice of several bandwidths. The actual filter frequencies tend to vary among manufacturers. One manufacturer allows a choice of three different filtering modes: (1) a diagnostic mode with a bandwidth of 0.05 to 130 Hz for adults and 0.5 to 130 Hz for neonates, (2) a monitoring mode with a bandwidth of 0.5 to 40 Hz for adults and 0.5 to 60 Hz for neonates, and (3) a filter mode with a bandwidth of 0.5 to 20 Hz. The importance of bandwidth selection for detection of perioperative myocardial ischemia was evaluated by Slogoff and coworkers, who showed that the position of the ST segment was similar in all systems using the lower filter limit (0.05 Hz) recommended by the AHA.[2]

Three-Electrode Electrocardiographic Monitoring

In contrast to the standard 12-lead ECG, in which the four limb electrodes are placed on the wrists and ankles, electrode placement for continuous cardiac monitoring is on the torso to reduce artifacts from limb movement, as well as to avoid tethering the patient. Therefore, the right and left arm (RA/LA) electrodes are placed in the infraclavicular fossae close to the right and left shoulders, respectively, and the left leg (LL) electrode is placed below the rib cage on the left side of the abdomen. The ground or reference electrode (RL), if present, can be positioned anywhere, but it is usually placed on the right side of the abdomen.

The three-electrode system is the simplest and most common mode of electrocardiographic monitoring in operating rooms and intensive care units (ICUs). It allows monitoring of three bipolar leads by recording the potential difference between each of three pairs of electrodes: lead I (positive electrode, LA; negative electrode, RA), lead II (positive electrode, LL; negative electrode, RA), lead III (positive electrode, LL; negative electrode, LA), or other modified chest leads.[3] Three-electrode monitoring is usually good enough to track the heart rate, detect R waves for synchronized direct-current (DC) shock in cardioversion, and detect ventricular fibrillation. However, it is inadequate for diagnosing more complex arrhythmias, such as distinguishing between RBBB and left bundle-branch block (LBBB) or between ventricular tachycardia (VT) and supraventricular tachycardia (SVT) with aberrant ventricular conduction, for which a "true" V_1 lead is necessary. The three-electrode system is also inadequate for ST-segment monitoring because it does not provide multilead monitoring or precordial leads, which are frequently the most sensitive for detecting ischemia. The older literature[4] suggested that modified chest leads such as CS_5 (RA electrode placed under the right clavicle and LA electrode placed in the V_5 position) or CB_5 (RA electrode over the center of the right scapula and LA electrode in the V_5 position) may be suitable for detection of anterior wall myocardial ischemia; however, these leads are currently considered not accurate enough and are not recommended for monitoring myocardial ischemia.

Five-Electrode Electrocardiographic Monitoring

In the five-electrode monitoring system, the four limb electrodes, LA, RA, LL, and RL placed at their corresponding monitoring locations, allow any of the six limb leads to be obtained (leads I, II, III, aVR, aVL, and aVF), and a fifth chest electrode can be placed in any of the standard V_1 through V_6 locations (Fig. 42-9).

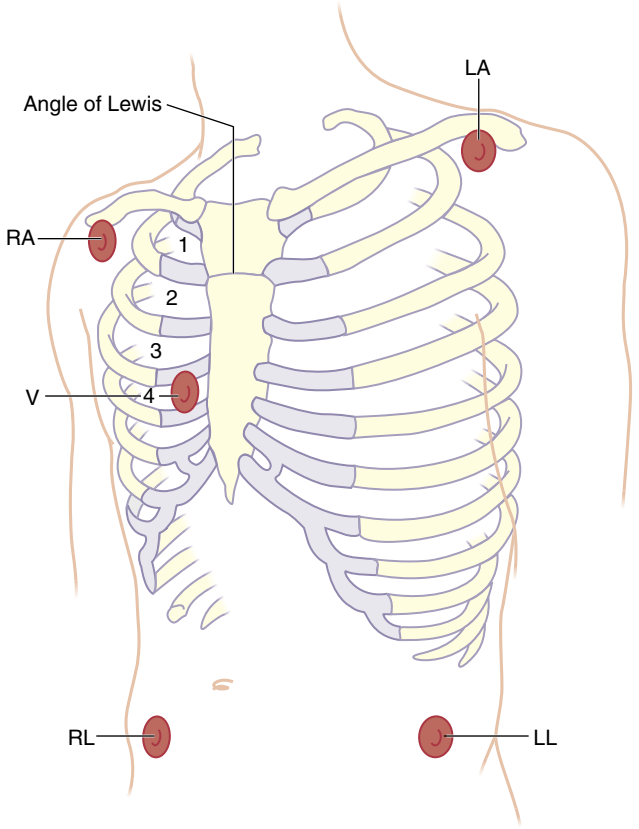

Figure 42-9 Commonly used five-electrode lead system that allows recording any of the six limb leads plus one precordial (V) lead. Shown here is lead placement for recording V_1. A limitation of this system is that only one precordial lead can be recorded. *(From Drew BJ, Califf RM, Funk M, et al: Practice standards for electrocardiographic monitoring in hospital settings: An American Heart Association Scientific Statement from the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young. Circulation 110:2721-2746, 2004.)*

V_1 is the preferred lead for special arrhythmia monitoring, whereas the other precordial leads, especially V_3 to V_5, are the preferred leads for ischemia monitoring. The five-electrode monitoring system is currently the standard for monitoring patients with suspected perioperative myocardial ischemia. Differences in sensitivity and specificity among the different electrocardiographic leads in detecting myocardial ischemia are discussed later.

Ten-Electrode, Twelve-Lead Electrocardiographic Monitoring

Mason and Likar in 1966 introduced a variation on positioning the standard limb electrodes of the 12-lead ECG during exercise stress testing to minimize artifacts in the limb leads caused by movement.[5] In this design, the RA and LA electrodes were attached to the right and left infraclavicular fossae, and the LL electrode was attached to the left iliac fossa. The RL electrode could be placed anywhere but was usually placed on the right iliac fossa for symmetry. Studies have shown that although the limb lead QRS complexes are slightly different in amplitude and axis and the precordial leads may also vary slightly from the standard 12-lead recording, the ST-segment measurements during exercise stress testing were only incidentally affected when the Mason and Likar 12-lead electrocardiographic system was used as compared with the standard 12-lead ECG.[6] A major advantage of cardiac monitors using the Mason-Likar 12-lead system is that ST-segment monitoring software has been developed to analyze all 12 leads and to sound an alarm for ST-segment changes, regardless of whether multiple leads are being displayed on the bedside or central monitor. Therefore, if lead II is being displayed but the patient has a transient ischemic event involving lead V_5, an ST alarm would be triggered. Not all manufacturers who offer the Mason-Likar lead system perform full 12-lead ST-segment analysis, nor do they store all 12 leads for printing at a later time. Another advantage of the Mason-Likar lead system is that more than one precordial lead can be displayed at the same time. The disadvantage of the system for cardiac monitoring is that 10 electrodes are required and the 6 precordial electrodes often interfere with diagnostic (e.g., echocardiography, chest radiography) and emergency (defibrillation sites) procedures. In addition, the precordial sites are difficult to maintain on patients with large breasts or hirsute chests (Fig. 42-10).

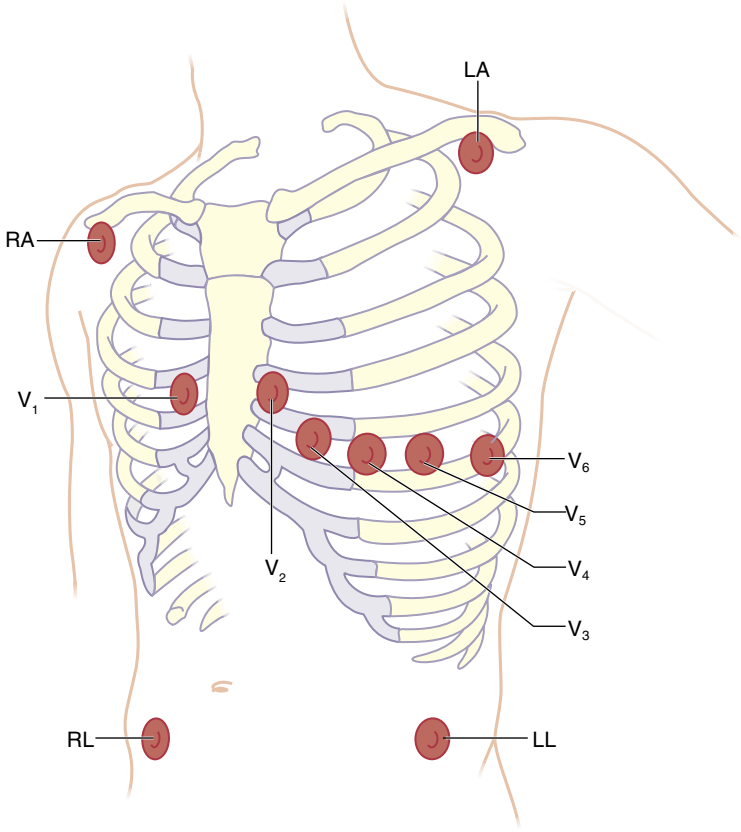

Figure 42-10 Mason-Likar 12-lead electrocardiographic (ECG) system. Anatomic locations for precordial leads are the same as for recording a standard 12-lead electrocardiogram, except that the limb leads are relocated from standard 12-lead ECG positions on the wrists and ankles to the torso. *(From Drew BJ, Califf RM, Funk M, et al: Practice standards for electrocardiographic monitoring in hospital settings: An American Heart Association Scientific Statement from the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young. Circulation 110:2721-2746, 2004.)*

Holter Monitoring

Holter monitoring, originally a cardiologist's tool, has been used by a number of anesthesiologists to document the perioperative incidence of arrhythmias or ischemia. In Holter monitoring, electrocardiographic information from two or three bipolar leads is recorded by a miniature recorder. Up to 48 hours of electrocardiographic signals can be collected. Subsequently, the data are processed via a playback system, and the electrocardiographic signals are analyzed. On most modern systems, the playback unit includes a dedicated computer for rapid analysis and automatic recognition of arrhythmias and ischemia.

A significant early obstacle to the widespread use of conventional Holter monitoring in the perioperative period was the delayed, retrospective analysis and interpretation. This limitation was to some extent overcome by real-time Holter monitors, which both record specific electrocardiographic segments for later playback and also analyze the rhythm and ST segment in real time to alert the user to an acute event.[7,8] Despite significant technical progress, Holter monitoring devices continue to be limited primarily to clinical investigations.

Interpretation and Management of Arrhythmias

There is little doubt that during prolonged visual electrocardiographic monitoring on a video display, arrhythmias may go undetected. It has been demonstrated long ago that coronary care unit staff failed to detect serious ventricular arrhythmias in 84% of their patients.[9] Subsequently, computerized monitors have been designed for the automatic detection of arrhythmias in an attempt to increase the rate of detection of abnormal, potentially dangerous rhythms. These monitors use proprietary sophisticated algorithms such as pattern recognition, measurements of QRS width, onset, offset, and amplitude, and calculations of area to classify complexes into morphologic families.[10,11] Most monitors are capable of detecting potentially fatal arrhythmias such as severe bradycardia or asystole and dangerous tachyarrhythmias such as VT or ventricular fibrillation. Yet no published study has evaluated the accuracy, sensitivity, and specificity of these automated, real-time arrhythmia detection monitors. It has been shown, though, that detection of clinically important arrhythmias in the cardiac ICU improves significantly if a nurse watches the monitor and pays attention to the alarms.[12] Thus, today's computerized monitoring systems still have not achieved the level of accuracy sufficient to eliminate the need for human surveillance; the alarms must be recognized and the ECG interpreted and acted on by a knowledgeable person in a timely fashion.

Diagnosis of Arrhythmias

Arrhythmias are common during and after surgery and have numerous causes. Postoperative dysrhythmias are most likely to occur in patients with structural heart disease. The initiating factor for an arrhythmia after surgery is usually a transient insult such as hypoxemia, cardiac ischemia, catecholamine excess, or electrolyte abnormality.[13] Using perioperative Holter recordings, Mahla and colleagues[14] evaluated how anesthesia and surgery affect the course of ventricular dysrhythmias (premature ventricular beats and repetitive forms of ventricular beats: couplets and nonsustained VT) noted preoperatively in patients with structural heart disease undergoing noncardiac surgery. They concluded that the frequency of ventricular dysrhythmias was not associated with adverse cardiac outcomes. The incidence of perioperative dysrhythmia in patients with an adverse outcome (8%) did not differ from the incidence in those with a good outcome. Patients undergoing cardiac surgery obviously have a higher incidence of cardiac dysrhythmias. The incidence of new-onset atrial fibrillation after cardiac surgery approaches 33%, such arrhythmias are associated with a worse outcome.[15] Several major factors contribute to the development of perioperative arrhythmias:

1. *General anesthetics*: Volatile anesthetics, such as halothane or enflurane, produce arrhythmias, probably by a reentrant mechanism.[16] Halothane also sensitizes the myocardium to endogenous and exogenous catecholamines. Drugs that block the reuptake of norepinephrine, such as cocaine and ketamine, can facilitate the development of epinephrine-induced arrhythmias (see Chapter 23). In contrast, volatile anesthetics may have an antifibrillatory effect in response to acute coronary occlusion and reperfusion, at least in a canine model.[17] Sevoflurane may cause severe bradycardia and nodal rhythm when used in high concentrations during induction in infants,[18] and desflurane may prolong the QTc within the first minute of anesthesia in patients with a normal heart.[19]
2. *Local anesthetics*: Regional anesthesia by central neuraxial blockade, the goal of spinal or epidural anesthesia, may be associated with profound, albeit transient pharmacologic sympathectomy. This phenomenon may cause parasympathetic nervous system dominance leading to mild to very severe bradyarrhythmias, especially when the blockade extends to very high thoracic levels (see Chapter 51). Inadvertent intravascular injection of a large dose of local anesthetic may lead to asystole and cardiac arrest, which are very difficult to treat.[20] One proposed treatment is the administration of 20% Intralipid.[21,22]
3. *Abnormal arterial blood gases or electrolyte levels*: Excessive hyperventilation, particularly in the presence of low serum potassium levels, may precipitate severe cardiac arrhythmias.[23] Alterations in blood gases or electrolytes may lead to arrhythmias by producing reentrant mechanisms or by altering the phase 4 depolarization of conduction fibers. Electrolyte disturbances associated with cardiopulmonary bypass can also result in intraoperative arrhythmias (see Chapters 54 and 60).
4. *Endotracheal intubation*: This maneuver may be the most common cause of arrhythmias during surgery and is frequently associated with hemodynamic disturbances by eliciting autonomic reflexes (see also Chapter 50).
5. *Autonomic reflexes*: Vagal stimulation may produce sinus bradycardia and allow ventricular escape mechanisms to occur. It may also produce AV block or even asystole. These reflexes may be related to traction on the peritoneum or direct pressure on the vagus nerve during carotid surgery (see Chapter 62). During jugular vein cannula-

tion, stimulation of the carotid sinus by palpation of the neck can lead to bradyarrhythmias. Specific reflexes, such as the oculocardiac reflex, can also produce severe bradycardia or asystole.

6. *Central nervous system stimulation and dysfunction of the autonomic nervous system*: Many electrocardiographic abnormalities can occur in patients with intracranial disease, especially subarachnoid hemorrhage. These abnormalities are most commonly ST-T wave changes and may easily mimic myocardial ischemia and infarction (see Chapter 63).[24] The mechanism of these arrhythmias appears to be related to changes in autonomic nervous system tone.
7. *Preexisting cardiac disease*: This is probably the most common background for arrhythmias during anesthesia and surgery.[25] Patients with a preexisting tendency for atrial or ventricular arrhythmias are more likely to exhibit them during or after surgery in response to perioperative stress or secondary to acute withdrawal of oral antiarrhythmic medications, most commonly β-blockers.
8. *Central venous cannulation*: Insertion of catheters or wires into the central circulation frequently leads to arrhythmias (see Chapter 40).
9. *Surgical manipulation of cardiac structures*: Arrhythmias are frequently observed during insertion of atrial sutures or placement of venous cannulas for cardiopulmonary bypass during cardiac surgery (see Chapters 60 and 83). They are usually self-limited and cease at the end of manipulation.
10. *Location of surgery*: Dental surgery is often associated with arrhythmias because profound stimulation of the sympathetic and parasympathetic nervous systems frequently occurs.[26] Junctional rhythms are often seen and may be caused by stimulation of the autonomic nervous system by the fifth cranial nerve. The oculocardiac reflex leads to severe bradycardia in response to traction on the rectus muscles of the orbit. This reflex, which is mediated by the trigeminal nerve as the afferent limb and the vagus nerve as the efferent limb, is especially sensitive in *neonates* and children and common during strabismus operations.

After an arrhythmia is recognized, does it produce a hemodynamic disturbance, what type of treatment is required, and how urgently should therapy be instituted? Treatment should be initiated promptly if the arrhythmia results in marked hemodynamic impairment. Prompt treatment should also be instituted if the arrhythmia is a precursor for a more severe arrhythmia (e.g., frequent multifocal ventricular premature beats [VPBs] with an R-on-T phenomenon can lead to ventricular fibrillation). Immediate attention is required for arrhythmias in a patient with underlying cardiac disease (e.g., any tachycardia in a patient with mitral valve stenosis, aortic valve stenosis, or ischemic heart disease). Arrhythmias can be classified by heart rate or by anatomic origin within the heart. By heart rate criteria, arrhythmias can be broken down into three categories: bradyarrhythmias (heart rate <60 beats/min), tachyarrhythmias (heart rate >100 beats/min), and conduction blocks (at any heart rate). The anatomic origin of an arrhythmia can be ventricular, supraventricular, junctional, or elsewhere. Diagnosis and treatment of arrhythmias can be simplified by using the following checklist when looking at an electrocardiographic display:

1. What is the heart rate?
2. Is the rhythm regular?
3. Is there one P wave for each QRS complex?
4. Is the QRS complex normal?
5. Is the rhythm dangerous?
6. Does the rhythm require treatment?

The following is analysis of some common intraoperative arrhythmias.

Sinus Bradycardia

Sinus bradycardia is diagnosed when the pacemaker site is in the sinus node but the rate is slower than normal. Etiologic factors include drug effects, acute inferior MI, hypoxia, vagal stimulation, and high sympathetic blockade. Sinus bradycardia accounts for roughly 11% of intraoperative arrhythmias.

1. *Heart rate*: Slower than 60 beats/min. In patients maintained on chronic β-blocker therapy, it is defined as a heart rate of less than 50 beats/min.
2. *Rhythm*: Regular, except for occasional escape beats from other pacemaker sites.
3. *P/QRS*: Ratio of 1 : 1.
4. *QRS complex*: Normal morphology.
5. *Significance*: Heart rates lower than 40 beats/min are poorly tolerated, even in healthy patients, and should be evaluated on the basis of their effect on cardiac output. Treatment is recommended if hypotension, ventricular arrhythmias, or signs of poor peripheral perfusion are observed. Sinus bradycardia may be part of the sick sinus syndrome in which sinus node dysfunction can precipitate bradycardia, heart block, tachyarrhythmia, or alternating bradyarrhythmia and tachyarrhythmia.[27]
6. *Treatment*: Usually none is necessary. When treatment is deemed necessary, the following approach may be considered: (1) atropine, 0.5 to 1.0 mg by intravenous bolus repeated every 3 to 5 minutes, up to 0.04 mg/kg or approximately a 3.0-mg total dose for the average 75-kg male patient; (2) ephedrine, 5 to 25 mg by intravenous bolus; (3) dopamine or dobutamine (if blood pressure is adequate), 5 to 20 μg/kg/min by intravenous infusion; (4) epinephrine, 2 to 10 μg/min by intravenous infusion; (5) isoproterenol, 2 to 10 μg/min by intravenous infusion. Temporary transcutaneous or transvenous pacing may be necessary for severe, drug-refractory sinus bradycardia. Immediate institution of transcutaneous pacing is especially important in symptomatic patients.

Sinus Tachycardia

The pacemaker site in patients with sinus tachycardia is in the sinus node, and the rate is faster than normal. Sinus tachycardia is the most common arrhythmia in the perioperative period. It occurs with such frequency that it is not included in most studies of the incidence of arrhythmias. Common causes include pain, inadequate anesthesia, hypovolemia, fever, hypoxia, hypercapnia, heart failure, and drug effects.

1. *Heart rate*: Faster than 100 beats/min in adult patients and may be as high as 170 beats/min. Patients with significant CAD may not tolerate heart rates even as low as 70 to 80 beats/min, and subendocardial ischemia can develop. Similarly, patients with severe mitral or aortic stenosis may be sensitive to even moderate increases in heart rate.
2. *Rhythm*: Regular.
3. *P/QRS*: Ratio of 1:1.
4. *QRS complex*: Normal but there may be associated ST-segment depression with severe increases in heart rate and resulting myocardial ischemia.
5. *Significance*: Prolonged tachycardia in patients with underlying heart disease can precipitate MI and congestive heart failure (CHF) as a result of the increased myocardial work required and decreased myocardial oxygen supply because of decreased diastolic coronary perfusion time. A major diagnostic problem is encountered when the heart rate is 150 beats/min because this is a common rate for sinus tachycardia, paroxysmal atrial tachycardia, or atrial flutter with a 2:1 block. These three arrhythmias can sometimes be distinguished by the use of carotid sinus massage or intravenous administration of edrophonium or adenosine phosphate.
6. *Treatment*: The underlying disorder should be treated. Hypovolemia and light anesthesia are the most common causes. In patients with ischemic heart disease in whom tachycardia develops, β-adrenergic blockers should be used judiciously to prevent myocardial ischemia regardless of whether ST-segment changes are present. Hypovolemia or other causes should also be addressed in these patients.

Sinus Arrhythmia

In sinus arrhythmia, the impulses arise from the SA node, and the rhythm is characterized by a variable rate. The PR interval is normal, as is the QRS complex. Most commonly, but not invariably, the rate increases with inspiration and decreases with expiration. This arrhythmia occurs more often in children than in adults. The heart rate is 60 to 100 beats/min, the rhythm is irregular, the P/QRS ratio is 1:1, and the QRS complex has normal morphology. Sinus arrhythmia has little clinical significance, is considered a normal finding, and requires no treatment.

Atrial Premature Beats

An ectopic pacemaker site in the left or right atrium initiates an atrial premature beat (APB). The shape of the P wave is different from the usual SA node P wave and may be inverted. The PR interval may be shorter or longer than normal, depending on the site of the ectopic focus and the refractoriness of the AV nodal pathway. The APB spreads through the AV node and ventricular conduction system and, in retrograde fashion, reaches the SA node and resets the sinus pacemaker. The interval from the APB to the next sinus beat is therefore a normal sinus cycle (i.e., no compensatory pause). The absence of a compensatory pause is an important distinguishing feature between APBs and VPBs. Occasionally, APBs may find part of the ventricular conduction system refractory, in which case they travel down an aberrant pathway and create an abnormal QRS complex. They are then called APBs with aberrant ventricular conduction and can easily be confused with VPBs. Because the recovery period of the right ventricular conduction system is longer than that of the left, the most common form of aberration appears as an RBBB. Helpful points in differentiating APBs with aberrant ventricular conduction from VPBs include (1) the presence of a preceding P wave, usually abnormally shaped; (2) an RBBB configuration of the QRS complex; (3) the presence of an rsR′ ventricular complex in V_1; and (4) the finding that the initial vector forces are identical to the preceding beat, which is usually the opposite with a VPB. Other characteristics of APBs are as follows:

1. *Heart rate*: Variable, depending on the frequency of the APBs.
2. *Rhythm*: Irregular.
3. *P/QRS*: Usually 1:1. The P waves have various shapes and may even be lost in the QRS or T waves. Occasionally, the P wave is so early that it finds the ventricle refractory, and a nonconducted beat occurs.
4. *QRS complex*: Usually normal unless ventricular aberration is present.
5. *Significance*: In one study, APBs represented 10% of all intraoperative arrhythmias. They have little clinical significance, but frequent APBs may lead to other, more serious supraventricular arrhythmias or may be a sign of digitalis intoxication.
6. *Treatment*: Rarely necessary.

Paroxysmal Supraventricular Tachycardia

Paroxysmal SVT (PSVT) is characterized by a rapid regular rhythm, generally with a narrow QRS complex and lacking the normal SA node P wave. Inclusion of tachycardias involving the AV node (Fig. 42-11) allows a useful classification of tachycardias as being caused by reentry in the AV node, by apparent or concealed accessory AV pathways, or less often, by SA node reentry. Ectopic atrial or ectopic nodal tachycardias are among the less frequent SVTs. Inappropriate or persistent sinus tachycardia is another variant. PSVT rhythms are usually abrupt in onset and termination. PSVT is easily distinguished from rapid atrial fibrillation, which is an irregular rhythm, and from rapid atrial flutter, which has flutter waves.

1. Heart rate: 130 to 270 beats/min.
2. *Rhythm*: Usually regular unless the impulse originates from multiple atrial foci.
3. *P/QRS*: 1:1 relationship, although the P wave may often be hidden in the QRS complex or T wave.
4. *QRS complex*: Generally normal, but ST-T changes indicative of ischemia may be observed. Aberration of ventricular conduction may occur and complicate the differential diagnosis with VT. SVT may also be confused with sinus tachycardia, atrial flutter, and atrial fibrillation. In differentiating these rhythms, carotid sinus massage or edrophonium (5 to 10 mg given intravenously) was traditionally used. More recently, adenosine (6 to 12 mg by intravenous bolus) has been used to slow the rate by transiently enhancing the normal degree of AV block or to terminate the arrhythmia.[28] Esophageal electrocardiographic leads may also be helpful to better define atrial activity.[29]

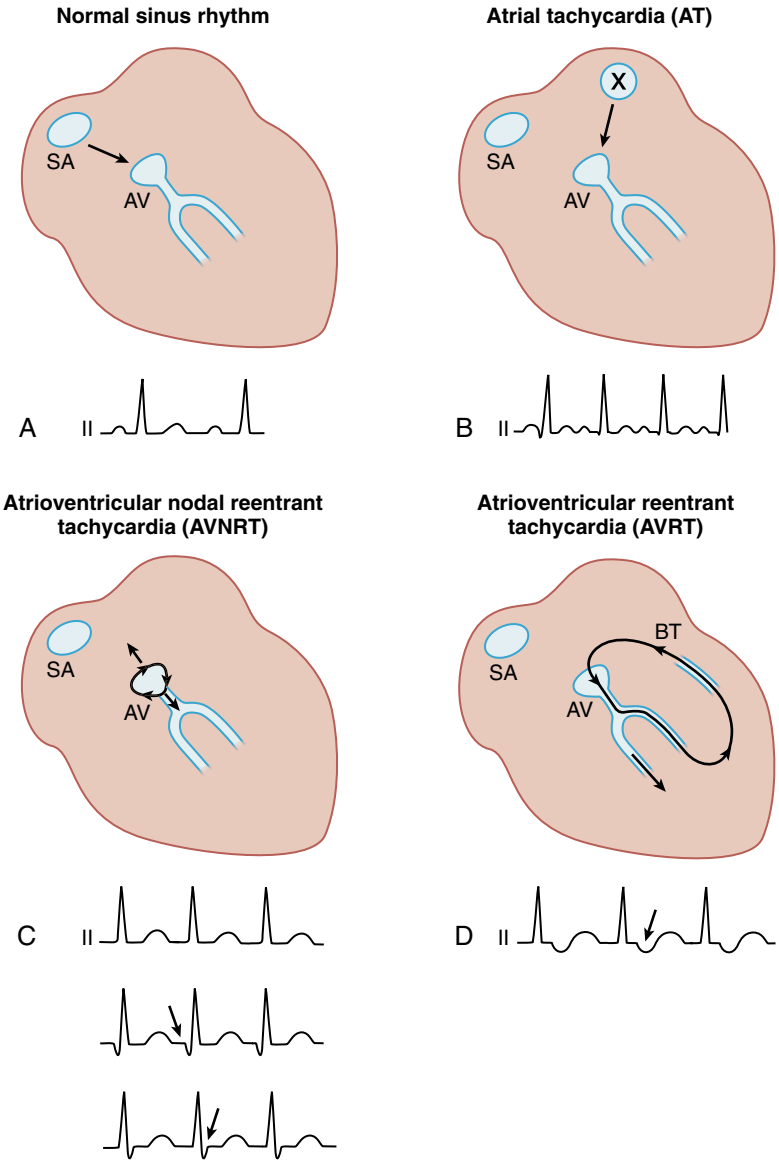

Figure 42-11 Major types of paroxysmal supraventricular tachycardia. **A,** Normal sinus rhythm. **B,** Atrial tachycardia. A focus (X) outside the sinoatrial (SA) node fires off automatically at a rapid rate. **C,** Atrioventricular (AV) nodal reentrant tachycardia. The cardiac stimulus originates as a wave of excitation that spins around the AV nodal (junctional) area. As a result, retrograde P waves may be buried in the QRS or appear immediately before or just after the QRS complex (*arrows*) because of nearly simultaneous activation of the atria and ventricles. **D,** A similar type of reentrant (circus-movement) mechanism may occur with a bypass tract (BT) of the type found in Wolff-Parkinson-White syndrome. This mechanism is referred to as atrioventricular reentrant tachycardia (AVRT). Note the negative P wave (*arrow*) in lead II, somewhat after the QRS complex. (With AVRT, the P wave in lead II may be negative or isoelectric.) *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 7th ed. St Louis, CV Mosby, 2006.)*

5. *Significance*: PSVT can be seen in 5% of normal young adults and in patients with Wolff-Parkinson-White syndrome or other pre-excitation syndromes. During anesthesia, PSVT accounts for up to 2.5% of all arrhythmias. This arrhythmia has no association with any intrinsic heart disease or systemic illness. When a patient is anesthetized, PSVT can be precipitated by changes in autonomic nervous system tone, by drug effects, or by intravascular volume shifts and can produce severe hemodynamic deterioration. Sometimes the PSVT may be associated with AV block because of the fast atrial rate and slow AV conduction. PSVT with a 2:1 block represents digitalis intoxication in many patients.
6. *Treatment*: Even though this arrhythmia is not usually associated with hemodynamic deterioration, the following can be undertaken to treat it:
   a. Vagal maneuvers such as carotid sinus massage should be applied only to one side.[30]
   b. Adenosine, which is the drug of choice, is given by 6-mg rapid (2 seconds) intravenous bolus, preferably through an antecubital or central vein. If no response is elicited, second and third doses of 12 to 18 mg of adenosine may be administered by rapid intravenous bolus.[31]
   c. Verapamil (2.5 to 10 mg given intravenously) terminates AV nodal reentry successfully in about 90% of cases.[32] Unlike adenosine, verapamil has the advantage of providing long-term relief.
   d. Amiodarone (150-mg infusion over a 10-minute period for the loading dose) is a recent addition.[33]
   e. Esmolol (1 mg/kg by bolus and 50 to 200 mg/kg/min by infusion) has been shown to be effective.[34]
   f. Edrophonium or neostigmine can be given by intravenous bolus.[35]
   g. Phenylephrine (100 µg by intravenous bolus) is administered if the patient is hypotensive.[36]
   h. Intravenous digitalization is performed with one of the short-acting digitalis preparations: ouabain (0.25 to 0.5 mg given intravenously) or digoxin (0.5 to 1.0 mg given intravenously).[36]

i. Rapid overdrive pacing may be done in an effort to capture the ectopic focus.[37]
j. Synchronized cardioversion may be performed with incremental doses of energy of 100, 200, 300, and 360 J, preferably after light sedative premedication.[38] Electrode catheter ablation with radiofrequency energy has evolved as the definitive, long-term treatment of most persistent AV reentrant or focal atrial SVTs.[39]

Atrial Flutter

Atrial flutter most commonly represents a macro-reentrant arrhythmia that circulates in a specific manner in the right atrium (i.e., counterclockwise rotation as viewed in the angiographic left anterior oblique view). Because it is associated with very fast heart rates, it is generally accompanied by AV block. Classic sawtooth flutter waves (F waves) are usually present (Fig. 42-12). The characteristics of atrial flutter are as follows:

1. *Heart rate*: The atrial heart rate is 250 to 350 beats/min with a ventricular rate of about 150 beats/min (2:1 or varying AV conduction block).
2. *Rhythm*: The atrial rhythm is regular. The ventricular rhythm may be regular if a fixed AV block is present or irregular if a variable block exists.
3. *P/QRS*: Usually there is a 2:1 block with an atrial rate of 300 beats/min and a ventricular rate of 150 beats/min, but it may vary between 2:1 and 8:1. F waves are best seen in leads V_1 and II and the esophageal lead.
4. *QRS complex*: Normal. T waves are lost in the f waves.
5. *Significance*: Atrial flutter does not always indicate severe heart disease. It can be seen in patients with CAD, mitral valve disease, pulmonary embolism, hyperthyroidism, cardiac trauma, cancer of the heart, and myocarditis.
6. *Treatment*: Pharmacologic or synchronized DC cardioversion, when indicated, should be performed only after careful consideration or evaluation of a possible thromboembolic event. Initial treatment should consist of control of the ventricular response rate with drugs that slow AV node conduction:

a. β-Blockers such as esmolol (1 mg/kg by intravenous bolus) or propranolol.
b. Calcium channel blockers such as verapamil (5 to 10 mg given intravenously) or diltiazem.[40] β-Blockers and calcium channel blockers are also effective as pharmacoprophylaxis for the prevention of postoperative atrial tachyarrhythmias after thoracic and cardiac surgery.[41]

If the ventricular response is excessively rapid or hemodynamic instability is present, or both, the following guidelines should be used:

c. Synchronized DC cardioversion starting at a relatively high energy of 100 J and gradually increasing to 360 J is indicated.
d. The class III antiarrhythmic agent ibutilide (Corvert, 1 mg in 10 mL saline or 5% dextrose in water [D_5W] infused slowly intravenously over a 10-minute period) has been documented to convert atrial flutter to sinus rhythm in most patients with relatively new-onset atrial flutter.[42] This may be repeated once, and although it is highly effective, life-threatening torsades de pointes (discussed later) may occur hours after ibutilide administration, thus making 4- to 8-hour monitoring after treatment highly desirable.
e. Procainamide (5 to 10 mg/kg for the intravenous loading dose, infused no faster than 0.5 mg/kg/min) may rarely be used in an attempt to restore sinus rhythm after the ventricular response has been adequately controlled.[43]
f. Amiodarone (150-mg intravenous loading dose infused over a 10-minute period, followed by 1 mg/min intravenously for 6 hours, a 0.5-mg/min intravenous infusion for 18 hours, and then a reduced intravenous dose or switching to an oral dose) has recently been shown to be effective.

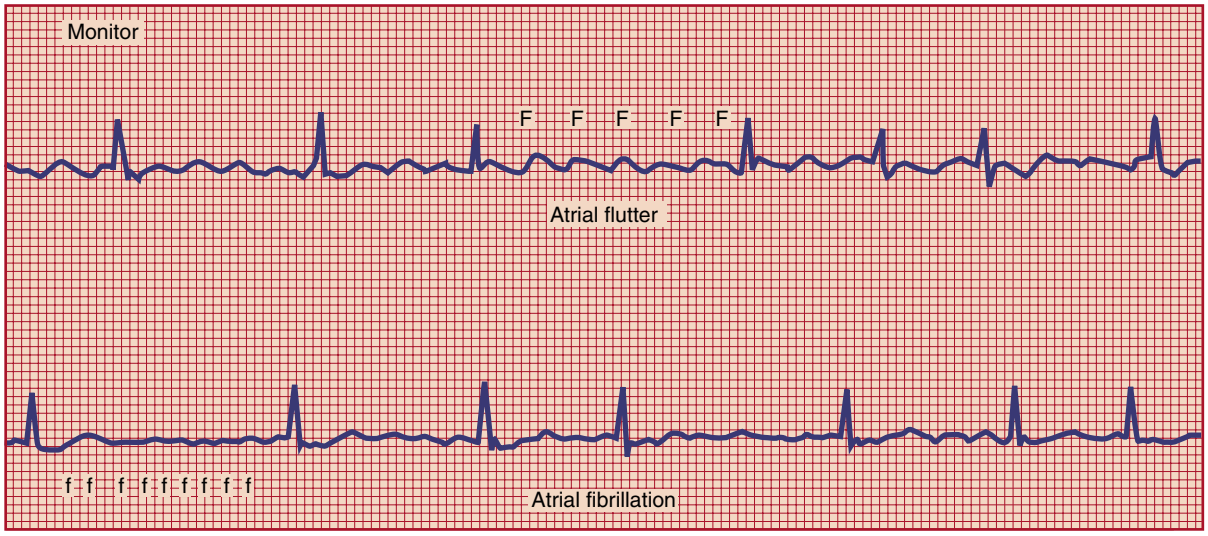

Figure 42-12 Atrial flutter and fibrillation. Notice the "sawtooth" waves (F waves) with atrial flutter and the irregular fibrillatory waves (f waves) with atrial fibrillation. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 7th ed. St Louis, CV Mosby, 2006.)*

Atrial Fibrillation

Atrial fibrillation is an excessively rapid and irregular atrial focus with no P waves appearing on the ECG; instead, fine fibrillatory activity is seen (f waves, see Fig. 42-12). This is the most commonly encountered irregular rhythm. It is often described as irregularly irregular and may be associated with a pulse deficit. Its characteristics are as follows:

1. *Heart rate*: The atrial rate is 350 to 500 beats/min, and the ventricular rate is 60 to 170 beats/min.
2. *Rhythm*: Irregularly irregular.
3. *P:QRS*: The P wave is absent and replaced by f waves or no obvious atrial activity at all.
4. *QRS complex*: Normal.
5. *Significance*: The causes of atrial fibrillation are similar to those of atrial flutter. This rhythm is often associated with significant cardiac disease; however, idiopathic, paroxysmal atrial fibrillation has become increasingly recognized. The clinical significance and treatment of atrial fibrillation are similar to that for atrial flutter, except for two important considerations. The loss of atrial "kick" from inefficient contraction of the atria may reduce ventricular filling and significantly compromise cardiac output. After 24 to 48 hours, atrial fibrillation may be associated with the development of atrial thrombi, possibly resulting in pulmonary or systemic embolization.

   Atrial fibrillation is the most common postoperative arrhythmia and has significant consequences on patient health. Postoperative atrial fibrillation complicates up to 8% of all noncardiac surgeries, between 3% and 30% of noncardiac thoracic surgeries, and between 16% and 46% of cardiac surgeries. It has been associated with increased morbidity, mortality, and longer, more costly hospital stays. The risk of atrial fibrillation after cardiac and noncardiac surgery may be affected by several epidemiologic and intraoperative factors, as well as by the presence of preexisting cardiovascular and pulmonary disorders. It is typically a transient, reversible phenomenon that may develop in patients who possess an electrophysiologic substrate for the arrhythmia that is present before or as a result of surgery. Numerous studies support the efficacy of β-blockers in the prevention of postoperative atrial fibrillation. Perioperative administration of amiodarone, sotalol, nondihydropyridine calcium channel blockers, and magnesium sulfate has also been associated with a reduction in the occurrence of atrial fibrillation.[44]
6. *Treatment*:
   a. *Acute atrial fibrillation*: Treatment of acute atrial fibrillation is very similar to that for atrial flutter. Primary attention should be focused on controlling the ventricular response, especially with the administration of diltiazem or esmolol intravenously. Ibutilide may restore sinus rhythm, but it is less effective than in the treatment of flutter. Synchronized DC cardioversion should be relied on in patients with pronounced hemodynamic instability. However, if fibrillation is present for longer than 48 hours, attempts to restore sinus rhythm may be associated with a heightened risk for thromboembolism. In a patient with a normal coagulation profile, adequate anticoagulation for 3 to 4 weeks should be considered before attempting to restore sinus rhythm. Alternatively, transesophageal echocardiographic examination to rule out atrial thrombi may be substituted. New developments in electrophysiologic techniques for ventricular defibrillation consisting of biphasic current shocks have shown superiority to the conventional monophasic current techniques (discussed later). However, data regarding the efficacy of biphasic shocks for conversion of atrial fibrillation are still emerging. A randomized, double-blind, multicenter trial by the BiCard investigators[45] demonstrated that for the cardioversion of atrial fibrillation, a biphasic shock waveform has greater efficacy, requires fewer shocks and lower delivered energy, and results in less dermal injury than a monophasic shock waveform does. These results mirror those seen in the ventricular fibrillation trials.
   b. *Long-term therapy*: Long-term therapy for atrial fibrillation varies and depends on factors such as whether the arrhythmia is constant or paroxysmal, the nature of the underlying heart disease, and the state of ventricular function or hemodynamic stability or reserve. In an older individual or in the setting of specific risk factors (e.g., hypertension, diabetes mellitus, severe LV systolic dysfunction), anticoagulation with warfarin (Coumadin) should be strongly considered. When control of ventricular response is difficult with standard agents (e.g., β-blockers, calcium channel blockers, digitalis), electrode catheter ablation of the AV junction and permanent pacemaker insertion have seen increased use. This method is not a curative, merely a rate-controlling procedure. It also produces a regular ventricular contraction rhythm. For patients who are in and out of atrial fibrillation, implanted atrial defibrillators that function much like their ventricular counterparts (see Chapter 43) were considered a therapeutic option. Today, these devices see very limited application. The current "curative" electrophysiologic procedure is transseptal pulmonary vein isolation via radiofrequency catheter ablation (see Chapter 61).[46]

      In the absence of coronary artery disease or significant LV systolic dysfunction, class Ic antiarrhythmic agents (i.e., flecainide or propafenone) have become the agents of choice.[47] Use of class Ia drugs (i.e., quinidine, procainamide, and disopyramide) has sharply diminished because of concern about their significant proarrhythmic function and their systemic and organ side effects. Use of antiarrhythmic drugs that block repolarizing potassium currents (i.e., sotalol[48] and amiodarone[49]) has gained popularity for the suppression of atrial fibrillation in individuals with significant structural heart disease. Sotalol, however, has much lower efficiency in converting atrial fibrillation than class Ic agents do. New class III agents show good efficacy in converting atrial fibrillation. Ibutilide converts rapidly, can be effective in up to 50% of cases,[50] and is more effective than sotalol or procainamide. All of the drugs mentioned for treating atrial fibrillation have significant adverse cardiovascular effects, torsades de pointes (ventricular fibrillation), CHF, bradycardia, and hypotension being the most prominent.[51]

Junctional Rhythms

The AV node itself and sites just above and below it can act as pacemakers. It makes sense to consider this ectopic activity as arrhythmias of the AV junction. The resultant P wave is abnormal and, depending on the position of the ectopic pacemaker, may be very close to, buried in, or after the QRS complex. Depending on the rate of fire of the ectopic pacemaker, the resultant rhythm is nodal premature; nodal quadrigeminy, trigeminy, or bigeminy; nodal rhythm; or nodal tachycardia.

1. *Heart rate*: Variable, 40 to 180 beats/min (i.e., nodal bradycardia to junctional tachycardia).
2. *Rhythm*: Regular.
3. *P/QRS*: 1 : 1, but there are three varieties:
   a. *High nodal rhythm*: The impulse reaches the atrium before the ventricle; the P wave therefore precedes the QRS but has a shortened PR interval (0.1 second).
   b. *Mid nodal rhythm*: The impulse reaches the atrium and the ventricle at the same time. The P wave is lost in the QRS.
   c. *Low nodal rhythm*: The impulse reaches the ventricle first and then the atrium, so the P wave follows the QRS complex.
4. *QRS complex*: Normal, unless altered by the P wave.
5. *Significance*: Junctional rhythms are common in patients under anesthesia (about 20%), especially with halogenated anesthetic agents. Junctional rhythms frequently decrease blood pressure and cardiac output by about 15%, but they can decrease it up to 30% in patients with heart disease.[52]
6. *Treatment*: Usually, no treatment is required, and the rhythm reverts spontaneously. If hypotension and poor perfusion are associated with the rhythm, treatment is indicated. Atropine, ephedrine, or isoproterenol can be used in an effort to increase the activity of the SA node so that it will take over as the pacemaker. Dual-chamber electrical pacing at a rate faster than a slow nodal rhythm is another option.

Ventricular Premature Beats

VPBs result from ectopic pacemaker activity arising below the AV junction. The VPB originates in and spreads through the myocardium or ventricular conducting system, thereby resulting in a wide (>0.12-second), bizarre QRS complex. The ST segment usually slopes in the direction opposite the main deflection of the QRS complex. There is no P wave associated with a VPB, but retrograde depolarization of the atria or blocked sinus beats may obscure the diagnosis.

The most important entity in the differential diagnosis is APB with aberrant ventricular conduction. The distinction should be made whenever possible.

Although an APB normally reaches the SA node and resets the sinus rhythm, such an occurrence is rare when the ectopic pacemaker is in the ventricle. A VPB often blocks the next depolarization from the SA node, but the following sinus beat occurs on time. The result is a fully compensatory pause consisting of the interval from the VPB to the expected normal QRS, which is blocked at the AV node, plus a normal sinus interval.

VPBs are common during anesthesia, where they account for 15% of observed arrhythmias. They are much more common in anesthetized patients with preexisting cardiac disease. Other than heart disease, known etiologic factors include electrolyte and blood gas abnormalities, drug interactions, brainstem stimulation, and trauma to the heart.

1. *Heart rate*: Depends on the underlying sinus rate and frequency of the VPBs.
2. *Rhythm*: Irregular.
3. *P/QRS*: No P wave with the VPB.
4. *QRS complex*: Wide and bizarre, with a width of more than 0.12 second. If it is of an RBBB nature, prominent R forces are present in V_1. If it is an LBBB in appearance, notching of the S wave and less acute downward sloping of the ST segment are common.
5. *Significance*: The new onset of VPBs must be considered a potentially serious event because in certain clinical situations, the arrhythmia may progress to VT or ventricular fibrillation. Such situations include coronary artery insufficiency, MI, digitalis toxicity with hypokalemia, and hypoxemia. VPBs are more likely to precede ventricular fibrillation if they are multiple, multifocal, or bigeminal; occur near the vulnerable period of the preceding ventricular repolarization (i.e., R-on-T phenomenon)[53]; or appear in short-long-short coupling sequences. VPBs are markers, not the cause of more severe arrhythmias.
6. *Treatment*: In most patients, VPBs (occurring as single, bigeminy, or trigeminy but excluding nonsustained VT) do not need to be treated, particularly if the patient does not have an acute coronary syndrome, and treatment is generally dictated by the presence of symptoms attributable to the VPBs. The first step in treatment is to correct any underlying abnormalities such as decreased serum potassium or low arterial oxygen tension. If the arrhythmia is of hemodynamic significance or if it is believed to be a harbinger of worse arrhythmias, lidocaine is the treatment of choice, with an initial bolus dose of 1.5 mg/kg. Recurrent VPBs can be treated with a lidocaine infusion at 1 to 4 mg/min; additional therapy includes esmolol, propranolol, procainamide, quinidine, disopyramide, atropine, verapamil, or overdrive pacing.

Ventricular Tachycardia

The presence of three or more sequential VPBs defines VT. Diagnostic criteria include the presence of fusion beats, capture beats, and AV dissociation. The specific morphologic appearance of the QRS complex may also be helpful in distinguishing VT from other arrhythmias. VT is classified by its duration and morphology. In duration, nonsustained VT lasts three beats and up to 30 seconds, and sustained VT lasts 30 seconds or longer. With monomorphic morphology, all complexes have the same pattern, and with polymorphic morphology, complexes constantly change patterns. Polymorphic VT with a long QTc is also called "torsades de pointes."

The characteristics of VT are as follows:

1. *Heart rate*: 100 to 200 beats/min.
2. *Rhythm*: Generally regular, but may be irregular if the VT is paroxysmal.

3. *P/QRS*: Usually there is no fixed relationship because VT is a form of AV dissociation in which the P waves can be seen marching through the QRS complex.
4. *QRS complex*: Wide, more than 0.12 second in width, with similar morphologic criteria in lead V_1 as for VPB.
5. *Significance*: Acute onset is life threatening and requires immediate treatment.
6. *Treatment*: If the patient is hemodynamically stable, amiodarone administered as one or more intravenous doses of 150 mg in 100 mL saline or D_5W over a period of 10 minutes, followed by an intravenous infusion of 1 mg/min for 6 hours and 0.5 mg/min thereafter, is the recommended current treatment (maximum intravenous dose, 2.2 g/24 hr). Although amiodarone is associated with substantially less hypotension than bretylium is, hypotension and bradycardia are its main side effects. Amiodarone's pharmacologic effects persist for more than 45 days. Lidocaine and procainamide have been used in the past with varying degrees of success to treat VT. Synchronized cardioversion is the indicated nonpharmacologic intervention in any wide-complex tachycardia, whether monomorphic VT or a wide-complex SVT. Polymorphic VT with a normal QT interval is treated with amiodarone and cardioversion. Metabolic abnormalities and drug toxicity must be considered and treated. Polymorphic VT with a prolonged QT interval is a more serious rhythm disturbance, and the recommended current treatment is an intravenous infusion of 1 g of magnesium administered over a 2- to 3-minute period. Precipitating metabolic or toxic causes should be treated. Overdrive pacing may also be helpful in this setting (Fig. 42-13).

Ventricular Fibrillation

Ventricular fibrillation is an irregular rhythm that results from a rapid discharge of impulses from one or more ventricular foci or from multiple wandering reentrant circuits in the ventricles. The ventricular contractions are erratic and are represented on the ECG by bizarre patterns of various size and configuration. P waves are not seen. Important causes of ventricular fibrillation include myocardial ischemia, hypoxia, hypothermia, electric shock, electrolyte imbalance, and drug effects (Fig. 42-14).

Its characteristics are as follows:

1. *Heart rate*: Rapid and grossly disorganized.
2. *Rhythm*: Totally irregular.
3. *P/QRS*: None seen.
4. *QRS complex*: Not present.

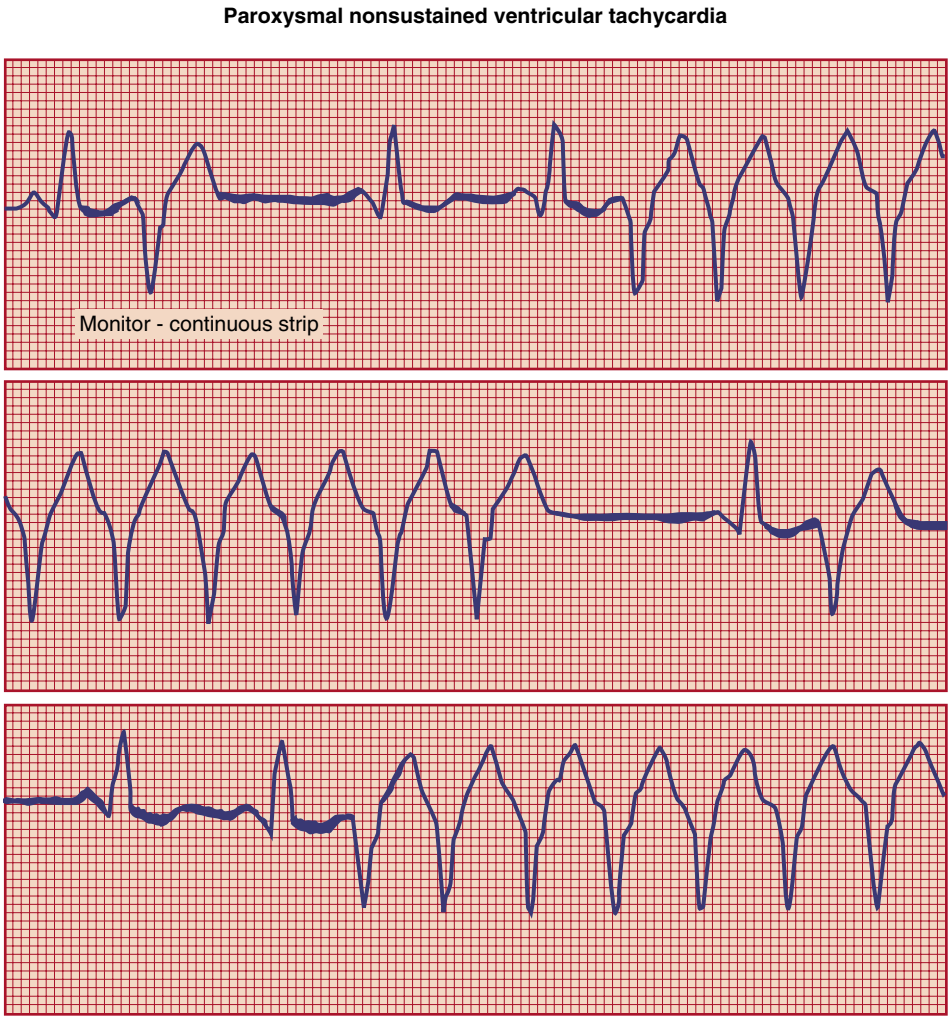

Figure 42-13 Short bursts of ventricular tachycardia. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 7th ed. St Louis, CV Mosby, 2006.)*

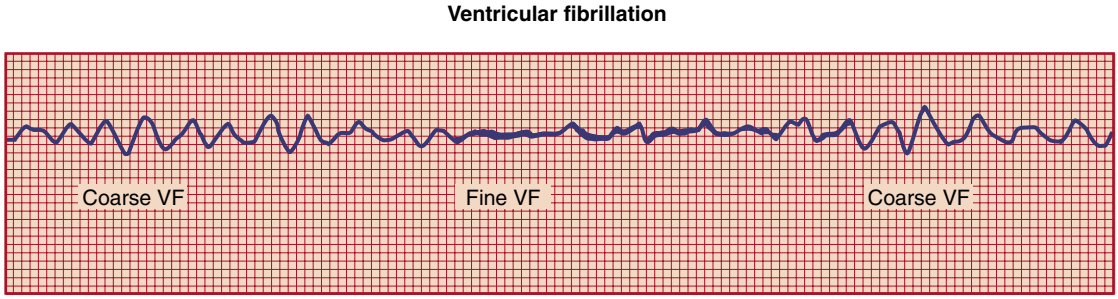

Figure 42-14 Ventricular fibrillation (VF) in the form of coarse and fine waves. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 7th ed. St Louis, CV Mosby, 2006.)*

5. *Significance*: There is no effective cardiac output, and life must be sustained by artificial means, such as external cardiac massage.
6. *Treatment*:
   a. Cardiopulmonary resuscitation must be initiated immediately, and then defibrillation must be performed as rapidly as possible. Asynchronous external defibrillation should be performed with a DC defibrillator using incremental energies in the range of 200 to 360 J. The introduction of biphasic (and rectilinear) transthoracic shocks has reduced the energy levels required and increased the efficacy of ventricular defibrillation. In a prospective, randomized, multicenter trial conducted by the ZOLL investigators,[54,55] 120 J of biphasic current was superior to 200 J of monophasic current, especially in patients with increased chest wall impedance.
   b. Early administration of 1 g of magnesium sulfate may facilitate defibrillation. In some instances, epinephrine has been used for coarsening the fibrillation to facilitate defibrillation. Vasopressin has been added as a drug for the treatment of ventricular fibrillation. The vasopressin dose is a single 40-unit intravenous bolus. Subsequent administration of epinephrine should be delayed for at least 5 minutes after vasopressin. Supportive pharmacologic therapy may include lidocaine, amiodarone, bretylium, procainamide, phenytoin, or esmolol.
   c. Torsades de pointes, which may mimic ventricular fibrillation or VT, is a life-threatening arrhythmia that occurs in the presence of disturbed repolarization (hence its association with prolonged QT intervals).[56] Discontinuation of drugs that predispose to prolongation of the QT interval and correction of electrolyte abnormalities are essential in the treatment of torsades de pointes. Acute therapy may include defibrillation, 1 to 2 g of intravenous magnesium sulfate, intravenous isoproterenol, and overdrive pacing.[57]

Conduction Defects

Conduction defects are most often chronic, are present on the baseline preoperative ECG, and represent the underlying disease state of the myocardium or conduction system. However, conduction defects may be observed for the first time during surgery and anesthesia. They can occur as a result of simple manipulation, such as passage of a pulmonary artery catheter through the right ventricle, but they can also be a manifestation of myocardial ischemia. Because high-grade (second- and third-degree AV blocks) conduction defects often have deleterious effects on hemodynamic performance, intraoperative recognition is important.

Three types of conduction system blocks are possible: SA block, AV heart block, and intraventricular conduction block. The His bundle ECG used by cardiologists has greatly improved the understanding of conduction through the heart. In an SA block, the block occurs at the sinus node. Because atrial excitation is not initiated, P waves are not found on the ECG. The next beat can be a normal sinus beat, a nodal escape beat, or a ventricular escape beat.

The second type of heart block is an AV heart block, or AV block, which may be incomplete or complete. First- and second-degree AV blocks are generally considered incomplete, whereas a third-degree AV block is considered to be a complete heart block. First-degree AV block is often found in healthy hearts, but it is also associated with CAD or digitalis administration. It is characterized by a PR interval longer than 0.21 second. All atrial impulses progress through the AV node to the Purkinje system. This form of heart block ordinarily requires no treatment. Second-degree AV block is associated with the conduction of some of the atrial impulses to the AV node and into the Purkinje system. It is further subdivided into two specific types. A Mobitz type I block, or a Wenckebach block, is characterized by progressive lengthening of the PR interval until an impulse is not conducted and the beat is dropped (Fig. 42-15). This form of block is relatively benign and often reversible, and it does not require a pacemaker. It may be caused by digitalis toxicity or MI and is usually transient. A Mobitz type I block reflects disease of the AV node.

The other form of second-degree heart block is a Mobitz type II block, which may reflect disease of the bundle of His and Purkinje tissues, especially when the QRS complex is broad. In this, the less common and more serious form of second-degree heart block, dropped beats occur without any progressive lengthening of the PR interval (Fig. 42-16). This type of block has a serious prognosis because it frequently progresses to a complete heart block and may require pacemaker insertion before major surgical procedures.

Third-degree AV block, also called a complete heart block, occurs when all electrical activity from the atria fails to progress into the Purkinje system. The atrial and ventricular contractions have no relationship with each other, although each chamber

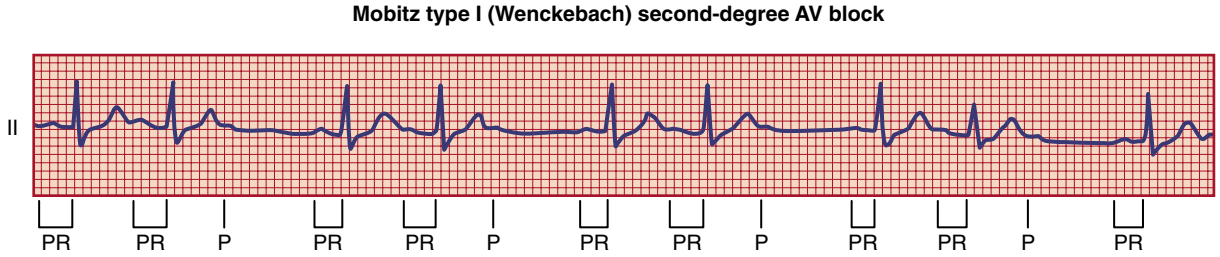

Figure 42-15 A Mobitz type I (Wenckebach) block produces a characteristically syncopated rhythm with grouping of the QRS complexes (group beating). Notice the progressive increase in PR intervals, with the third sinus P wave in each sequence not followed by a QRS complex. AV, atrioventricular. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 7th ed. St Louis, CV Mosby, 2006.)*

contracts regularly. The ventricular rate is approximately 40 beats/min. The QRS complex may be normal if the pacemaker site is in the AV node, but it is usually widened to longer than 0.12 second when the pacemaker site is located in the ventricle (Fig. 42-17). The heart rate is usually too slow to maintain adequate cardiac output, and syncope or Adams-Stokes syndrome may occur, as well as heart failure. These patients generally require insertion of a transvenous endocardial or epicardial pacemaker to increase their heart rate and cardiac output.

Intraventricular blocks

Under normal conditions, activation of the left ventricle spreads simultaneously through both the left anterior and left posterior fascicles. Blockage or even a modest delay in conduction in one of these fascicles results in sequential rather than simultaneous activation of the corresponding sites and produces characteristic abnormal patterns on the ECG.

Left Anterior Fascicular Block. The left bundle branch of the bundle of His itself bifurcates distally into two fascicles, the anterior and posterior fascicles. A left anterior fascicular block (LAFB) is relatively common because of the delicate structure of the left fascicle. It causes delayed activation of the anterosuperior LV wall and is characterized by marked (−45- to −90-degree) left axis deviation. LAFB may occur in persons without overt cardiac disease but is it found mainly in patients with a wide range of diseases of the myocardial and conduction system, such as CAD or LVH. It has minimal to no independent prognostic significance.

Left Posterior Fascicular Block. A left posterior fascicular block (LPFB) is considerably less common than an anterior fascicular block because of the thicker structure of the right fascicle. It is also at a less vulnerable location near the LV inflow tract. LPFB results in delayed activation of the inferoposterior aspect of the left ventricle, and the electrocardiographic features of LPFB are marked right axis deviation (>120 degrees). LPFB can occur in patients with almost any cardiac disease but is unusual in otherwise healthy people. As in the case of LAFB, the overall QRS duration remains normal (<120 msec) (Fig. 42-18).

Left Bundle Branch Block. Caused by a serious delay or block of the main left bundle branch or both of its two fascicles, an LBBB results in a prolonged QRS duration, abnormal QRS complex, and ST-T wave abnormalities. A basic requirement is a QRS duration of 120 msec or longer. There is also a broad, sometimes notched R wave in the left-sided leads (I, aVL, V_5, V_6) with deep S waves in the right precordial leads and absent septal Q waves. The QRS axis is highly variable. It can be normal or devi-

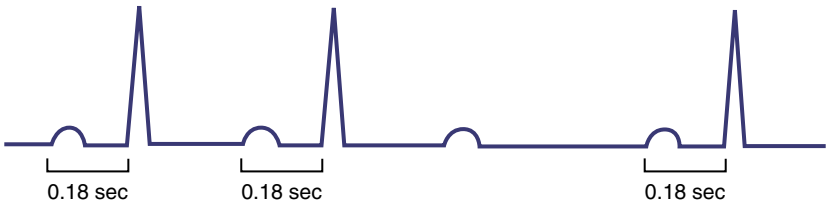

Figure 42-16 Mobitz type II atrioventricular block. Notice that the PR intervals remain constant as long as the QRS is not dropped, as in Mobitz type I. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 7th ed. St Louis, CV Mosby.)*

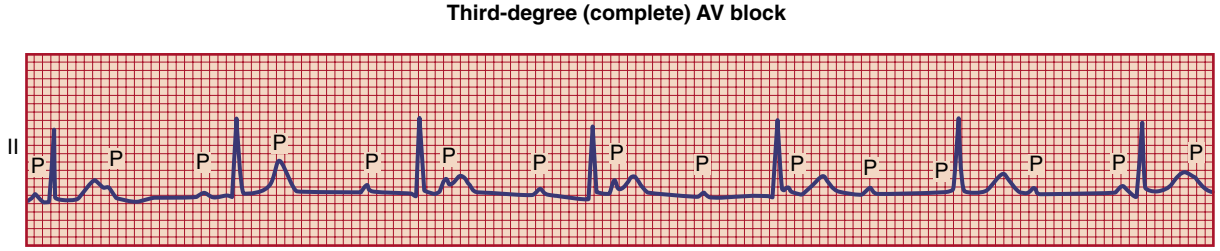

Figure 42-17 A complete heart block with underlying sinus rhythm is characterized by independent atrial (P) and ventricular (QRS complex) activity. The atrial rate is almost always faster than the ventricular rate. The PR intervals are completely variable. AV, atrioventricular. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 7th ed. St Louis, CV Mosby, 2006.)*

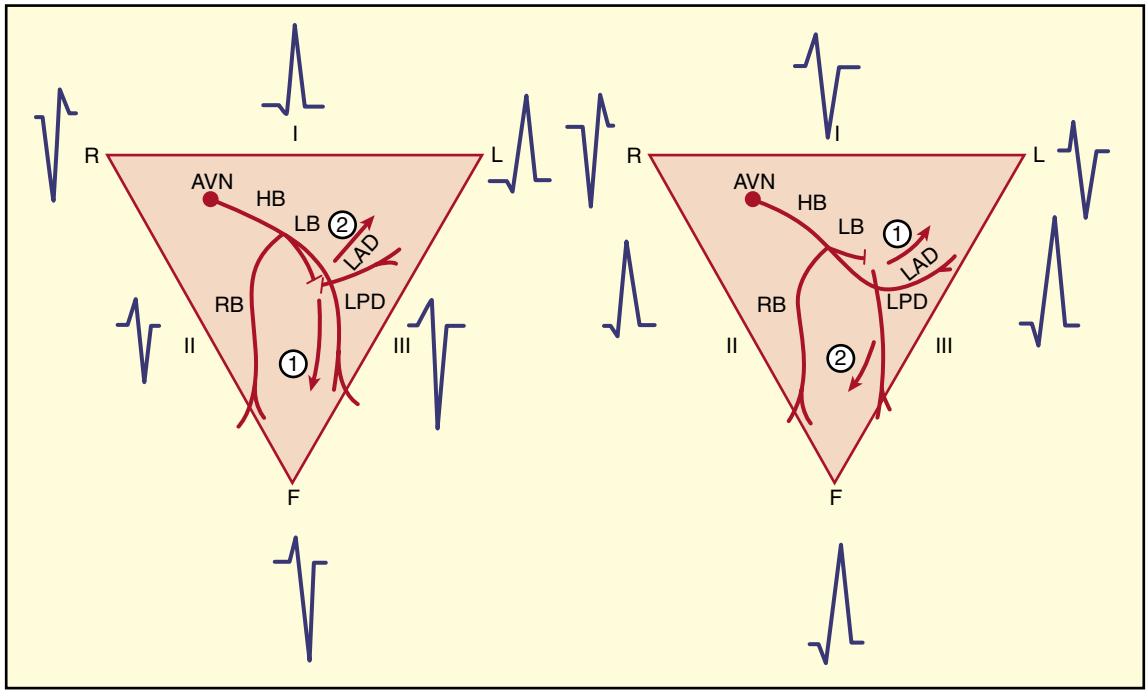

Figure 42-18 Diagrammatic representation of fascicular blocks in the left ventricle. Interruption of the left anterior fascicle (*left*) results in an initial inferior (1) followed by a dominant superior (2) direction of activation (negative in lead II and positive in leads I and aVL). Interruption of the left posterior fascicle (*right*) results in an initial superior (1) followed by a dominant inferior (2) direction of activation (negative in lead I and positive in leads II and III). AVN, atrioventricular node; HB, His bundle; LAD, left anterior descending artery; LB, left bundle; LPD, left posterior descending artery; RB, right bundle. *(Courtesy of C. Fisch, M.D.; From Zipes DP, Libby P, Bonow R, Braunwald E: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia, WB Saunders, 2005.)*

ated to the left or even the right. The ST-T waves are usually discordant with the direction of the QRS complex. LBBB is an ominous prognostic sign and has associated survival rates as low as 50%, probably reflecting the severity of the underlying cardiac disease. The QRS duration correlates inversely with the LV ejection fraction and is one of the criteria for current ventricular resynchronization therapy (biventricular pacing).

LBBB obscures or simulates other patterns on the ECG. In the presence of LBBB, the diagnosis of LVH, acute ischemia, or MI may be difficult or impossible (Fig. 42-19).

Right Bundle Branch Block. An RBBB is caused by a conduction delay anywhere in the right-sided intraventricular conduction system. The high prevalence of RBBB corresponds to the relative fragility of the right bundle branch, as suggested by the development of RBBB after minor trauma produced by right ventricular catheterization. The electrocardiographic manifestation of RBBB consists of prominent and notched R waves with rsr′, rsR′, or rSR′ on the right-sided leads and wide S waves on the left-sided leads, along with QRS prolongation (≥120 msec). If the QRS duration is not prolonged, it is termed an incomplete RBBB. As with LBBB, the ST-T waves are discordant with the QRS complex.

RBBB is common in the general healthy population without clinical evidence of structural heart disease and has no prognostic significance in this group. However, in patients with organic heart disease, new onset of RBBB does predict a higher rate of CAD, CHF, and mortality (Fig. 42-20).

Trifascicular blocks usually consist of one of the foregoing bilateral bundle branch blocks (i.e., RBBB plus LAFB or LPFB), in addition to a prolonged PR interval. Bundle of His ECGs are necessary to determine whether the AV conduction disturbance is localized in the AV node or whether it is distal and possibly represents an incomplete fascicular block in the last remaining fascicle.

Electrocardiographic Criteria for Acute Myocardial Ischemia

ST Depression–Type Ischemia

The criteria most accepted for detecting myocardial ischemia on continuous electrocardiographic monitoring are those established and validated during exercise stress testing.[58] During stress testing and with acute subendocardial ischemia, the electrical forces responsible for the ST segment are deviated toward the inner layer of the heart, thereby causing depression of the ST segment. With acute transmural (epicardial) ischemia, the electrical forces in the ischemic area are deviated toward the outer layer of the heart, thereby causing ST-segment elevation in the overlying leads (see Fig. 42-5). As the heart rate increases, the J point, or junctional up-sloping depression, occurs normally. In patients with myocardial ischemia, however, the ST segment typically becomes horizontal (flattens) as the severity of ischemia increases. With progressive exercise or tachycardia during ischemia, the ST-segment depression may worsen, the ST segment may become down sloping, even causing T-wave inversion in more than one lead, and angina may develop. In about 10% of patients, especially asymptomatic ones, ischemia may appear only in the recovery phase after exercise.

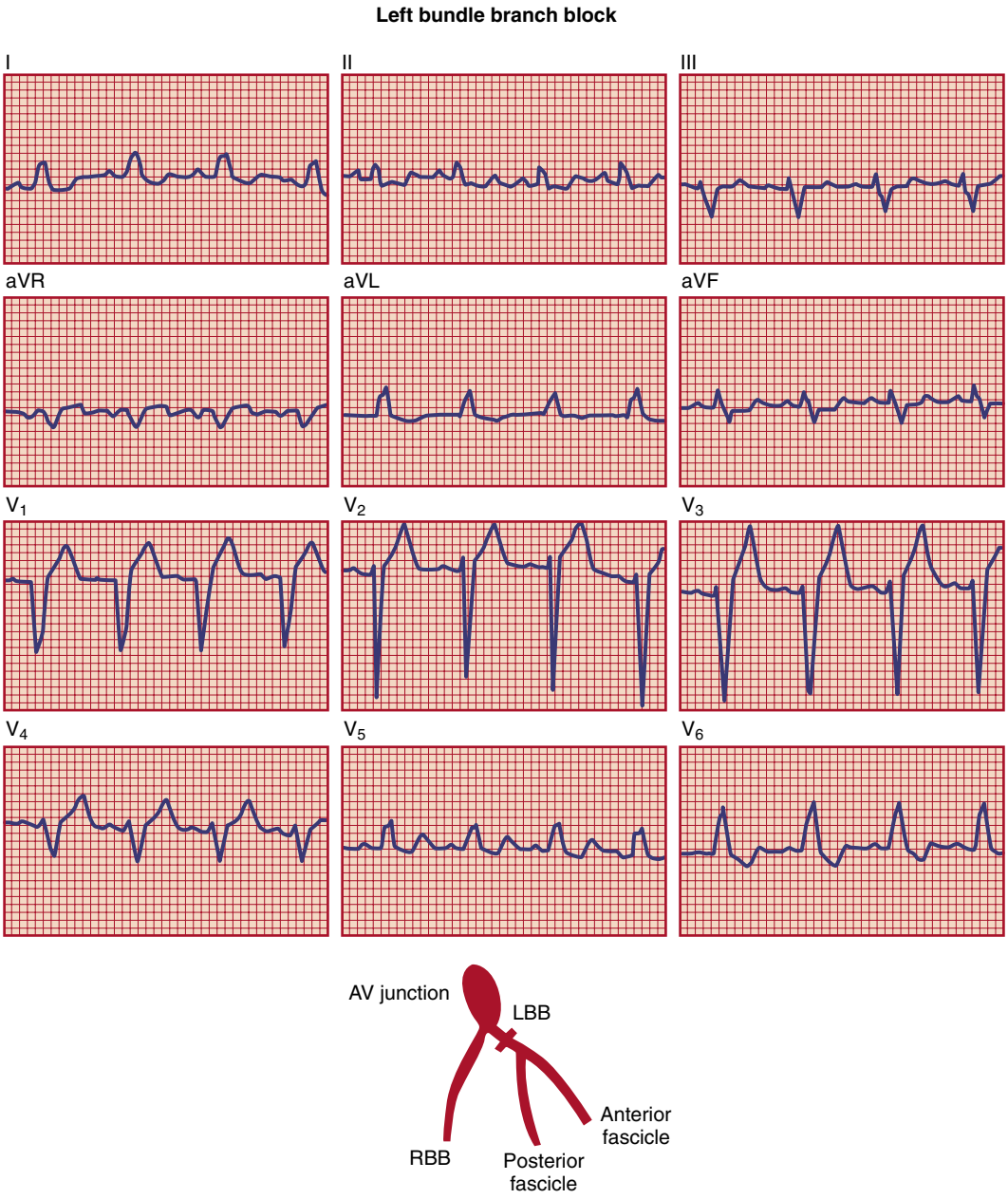

Figure 42-19 Left bundle branch (LBB) block with a characteristic wide QS complex in lead V_1 and a wide R wave in lead V_6 with slight notching at the peak. The inverted T waves in leads V_5 and V_6 (secondary T-wave inversions) are also characteristic of an LBB block. AV, atrioventricular; RBB, right bundle branch. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach, 7th ed. St Louis, CV Mosby, 2006.)*

The criteria established for stress-induced ischemia are 1 mm (0.1 mV) or more of horizontal or down-sloping ST-segment depression measured 60 to 80 msec after the J point in at least three consecutive beats with a stable baseline. The ST depression may be accompanied by T-wave flattening or inversion. Junctional or J-point depression is normal during exercise. In addition, a *rapidly up-sloping* ST segment (>1 mV/sec) that is also *depressed less than 0.15 mV* (1.5 mm) is considered normal. In patients with *slowly up-sloping* ST-segment depression in which the ST segment is *depressed 0.15 mV (1.5 mm) or more* at J+80 msec, the slowly up-sloping ST depression may signify CAD (Figs. 42-21 and 42-22).

Some patients have preexisting ST-segment abnormalities from previous MI, bundle branch blocks, or LVH that make ST-segment interpretation more difficult. In these patients, additional horizontal or down-sloping ST-segment depression of 1 mm or greater from baseline is required to be considered myocardial ischemia. Causes of ST-segment changes other than myocardial ischemia include drugs (most notably digitalis), temperature changes, hyperventilation, and positional changes. The distribution of ST depression–type ischemia correlates poorly with the specific location of CAD.

ST Elevation–Type Ischemia

ST-segment elevation in a non–Q-wave lead is very uncommon during stress testing; it occurs in approximately 1% of patients

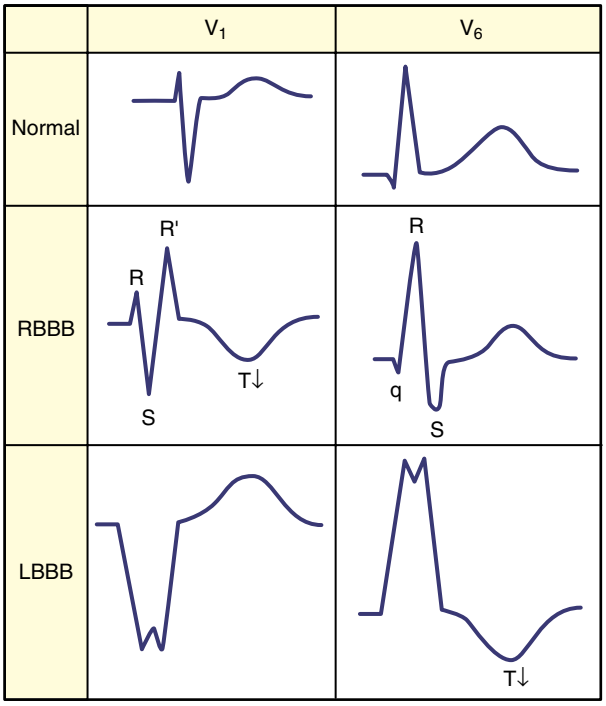

Figure 42-20 Comparison of QRST changes in left bundle branch block (LBBB) versus right bundle branch block (RBBB). *(From Zipes: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed; and Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.)*

with CAD and suggests transmural myocardial ischemia caused by coronary vasospasm or high-grade coronary narrowing. The electrocardiographic site of ST-segment elevation is relatively specific for the myocardial territory involved, in contrast to ST depression–type ischemia. ST elevation occurring during exercise testing in electrocardiographic leads with pathologic Q waves does not indicate myocardial ischemia but does correlate with reduced LV function and a worse prognosis.

T-Wave Changes

T-wave morphology is largely influenced by body position, respiration, hyperventilation, and drug therapy, as well as by myocardial ischemia/necrosis. Therefore, T-wave changes not accompanied by significant ST-segment displacement rarely signify myocardial ischemia. Pseudonormalization of T waves (inverted at rest, becoming upright during exercise) may in rare instances also be a marker for myocardial ischemia. In a meta-analysis that included 147 reports of patients who underwent both angiography and exercise testing, the sensitivity and specificity of the exercise electrocardiographic stress test for detection of CAD were 68% and 77%, respectively.[59]

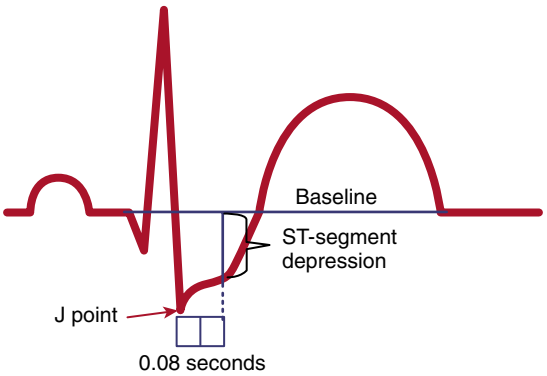

Figure 42-21 Illustration demonstrating how the ST-segment deviation is measured at 80 msec after the J point (J+80 msec).

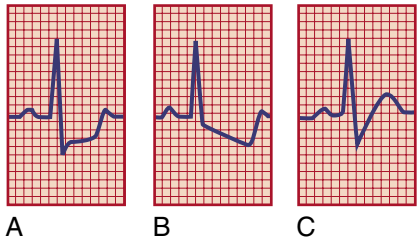

Figure 42-22 Horizontal ST depression (**A**) and down-sloping (**B**) ST depression—indicative of myocardial ischemia. Up-sloping ST depression (**C**) may be a normal finding.

Real-Time Myocardial Ischemia Monitoring

Real-time ST-segment analysis first appeared in cardiac monitoring in the mid-1980s, and currently this feature is standard in most electrocardiographic monitors. On some monitors, ST-segment analysis is automatic when a five-electrode system is used. However, the five-electrode monitoring system with automatic ST-segment analysis is primarily used by anesthesiologists in the operating room but widely underused postoperatively in the postanesthesia care unit or ICU. A recent study has shown that even among coronary care units, fewer than than 50% of clinicians routinely use ST-segment monitoring for the detection of myocardial ischemia in patients admitted with acute coronary syndromes.[60] Chief among the reasons for underuse of ST analysis are (1) a high number of false alarms, (2) lack of education on how to use the technology, and (3) what to do in response to ST alarms. In addition, there are no published randomized clinical trials to determine whether the addition of computerized ST-segment ischemia monitoring improves outcomes in patients with acute coronary syndromes or in postsurgical patients.[12]

The algorithm for ST-segment analysis is relatively simple. In each electrocardiographic lead, the computer determines the voltage of the ST segment at 60 or 80 msec after the J point (termed J+60 or J+80 msec) and compares it with the isoelectric point measured normally during the PR interval. One millimeter of ST-segment deviation is equivalent to a 100-mV difference. The changes in ST-segment level over time in each lead are displayed as ST-segment trends. To overcome problems of noise and artifacts, most monitors use filters to exclude erroneous or abnormal beats on the ECG. Averaging processes are used to calculate the mean ST-segment level over a period of 8 to 15 beats. Current monitors automatically detect the J point and calculate the J+60 msec ST-segment level. However, they also allow the operator to manually adjust the J point and the ST-segment measurement point in patients with abnormal patterns on the ECG.

One major advantage of continuous ST-segment monitoring over serial 12-lead ECGs is that the electrodes stay in place and do not vary as standard 12-lead ECGs may do between different measuring sessions. However, for improved diagnostic accuracy of ST-segment monitoring, the following points should be recognized:

1. Changes in body position may cause ST-segment changes and lead to false ST-segment deviations. However, these positional ST-segment changes are almost always accompanied by changes in QRS and therefore can easily be distinguished from true ST-segment deviations. In addition, returning the patient to the supine position may help distinguish true from positional ST-segment deviation. Changes in position of the heart in the mediastinum were also shown to affect the ST segment. Mark and coworkers[61] observed that placement of a Canadian sternal retractor during cardiac surgery was associated with a reduction in V_5 R-wave amplitude from 15 ± 1 to 10 ± 1 mm. Simultaneously, V_5 S-wave amplitude and absolute ST-segment deviation were reduced from 3.5 ± 0.4 to 1.7 ± 0.3 mm and from 0.50 ± 0.04 to 0.39 ± 0.05 mm, respectively (Table 42-2). These investigators concluded that inclusion of an R-wave gain factor may improve perioperative electrocardiographic ischemia monitoring.
2. Many patients with CAD do not have perfectly isoelectric ST segments. Early repolarization (a normal variant), intraventricular conduction delays, ventricular hypertrophy, digitalis, and nonspecific ST-T wave abnormalities may cause baseline ST-segment abnormalities. It is therefore important to tailor the ST alarm trending to the patient's baseline ST level. Many current cardiac monitors with ST-segment monitoring software allow clinicians to set alarm parameters manually. If alarm parameters are set 1 to 2 mm around the isoelectric (0 μV) line rather than at the patient's baseline ST level, frequent false alarms will occur. It is recommended that alarm parameters be set 1 mm above and below the baseline ST level in patients at high risk for ischemia. It should also be remembered that underlying electrocardiographic abnormalities may hinder ST analysis in about 10% of patients. Such abnormalities include hypokalemia, digitalis, LBBB, Wolff-Parkinson-White syndrome, LVH with strain, and acute pericarditis. In these patients, other modalities for diagnosis of myocardial ischemia should be considered, such as transesophageal echocardiography.
3. Most cardiac monitors with ST-segment monitoring software provide displays of ST-segment trends in a single lead or summated leads. Although such graphic trends are convenient for quick identification of potential ischemic events, it is of paramount importance to also print the electrocardiographic tracing in question to confirm that the ST-segment changes are the result of ischemia rather than a transient arrhythmia (e.g., an accelerated ventricular rhythm or a new bundle branch block) or other abnormality of the electrocardiographic complex, which can lead to inaccurate calculation.

Electrocardiographic Lead Sensitivity for Detecting Perioperative Myocardial Ischemia

During the perioperative period, electrocardiographic monitoring most commonly identifies stress-induced, ST-segment depression–type ischemia. Such electrocardiographic changes do not provide information about the location of the ischemic myocardial area. In contrast, ST-segment elevation indicating transmural ischemia, seen particularly during cardiac surgery, provides useful information about the myocardial segment and coronary perfusion territory responsible for the ischemic episode. Because the majority of modern patient-monitoring systems do not monitor all 12 electrocardiographic leads simultaneously, selecting which chest leads to monitor is of great importance, particularly in noncardiac surgery. During exercise stress testing, investigators have identified leads V_4 and V_5 as the most sensitive leads to detect exercise-induced ischemia (90% to 100% sensitivity).[62] London and colleagues[63] studied high-risk patients undergoing noncardiac surgery and showed that the greatest sensitivity for ischemia was obtained with lead V_5 (75%), followed by lead V_4 (61%). Combining leads V_4 and V_5 increased the sensitivity to 90%, whereas with the standard lead II and V_5 combination, the sensitivity was only 80%. They also suggested that if three leads (II, V_4, and V_5) could be examined simultaneously, the sensitivity would rise to 98%. More recently, Landesberg and associates[64] monitored continuous 12-lead ST-segment changes greater than 0.2 mV from baseline in a single lead, or greater than 0.1 mV in two contiguous leads at J+60 msec, lasting longer than 10 minutes in patients undergoing major vascular surgery. Troponins were used as markers for MI. They showed that in fact leads V_3 and V_4 were more sensitive than V_5 in detecting perioperative ischemia

Table 42-2 Electrocardiographic Changes during Sternal Retractor Placement in 83 Patients

Variable	Period	Mean ± SEM	*n* Increase	*n* Decrease	χ^2	*P*
V_5 RWA	Baseline	15.1 ± 0.8	—	—	—	—
	Retractor	9.9 ± 0.7	9	69	44.6	.001
V_5 SWA	Baseline	3.5 ± 0.4	—	—	—	—
	Retractor	1.7 ± 0.3	3	59	48.8	.001
V_5 ST-ABS	Baseline	0.05 ± 0.04	—	—	—	—
	Retractor	0.40 ± 0.05	20	51	12.68	.001

n, number of patients showing the indicated change; RWA, R-wave amplitude; ST-ABS, absolute value of ST displacement; SWA, S-wave amplitude; χ^2, comparison between *n* increase and *n* decrease.
Adapted from Mark JB, Chein GL, Steinbrook RA, et al: Electrocardiographic R-wave changes during cardiac surgery. Anesth Analg 74:26, 1992.

(87%, 79%, and 66%, respectively). Among the patients who experienced MI, V_4 was the most sensitive for ischemia (83.3%), followed by V_3 and V_5 (75% each). Combined monitoring of two of these leads (e.g., V_3 and V_5) increased the sensitivity to about 97%.[62] It was also demonstrated that on average, the baseline, preanesthesia ST segment was above the isoelectric point in V_1 through V_3 and below isoelectric in V_5 through V_6. Lead V_4 was closest to the isoelectric level on the baseline ECG, thus rendering it most suitable for detection of ischemia. Lead V_4 also detects ischemia earlier and shows a greater ST-segment deviation. These main findings were corroborated by Martinez and colleagues,[65] who also used the same method to monitor postoperative ischemia in ICU patients after major vascular surgery.

For patients with acute coronary syndromes (e.g., those with atherosclerotic plaque disruption), the recommendation is to monitor limb lead III and leads V_3 and V_5 as the most sensitive combination for detection of ischemia.[66] Monitoring of a right-sided precordial lead (V_4R) may be of benefit in patients with occlusive disease of the right coronary artery,[67] as might inspection of posterior leads (V_7 to V_9) in patients with suspected posterior ischemia.

It is commonly believed that monitoring for intraoperative myocardial ischemia is unnecessary in neonates. Whereas electrocardiographic lead systems for adults are concerned with detection of ischemia and arrhythmias, neonatal electrocardiographic monitoring has focused on recognition of arrhythmias alone. The results of some studies, however, suggest that the neonatal heart is more susceptible to ischemia than the adult heart is.[68] These studies have demonstrated the importance of calibrated electrocardiographic monitoring in neonates with congenital heart disease (see Chapter 83).

Perioperative Myocardial Ischemia and Infarction

Perioperative monitoring for myocardial ischemia in patients undergoing cardiac or noncardiac surgery started about 30 years ago. In 1980, Tinker[69] noted the importance of intraoperative ST-segment monitoring via lead V_5 and that large fluctuations in systolic blood pressure, heart rate, or hypothermia with postoperative shivering are associated with ischemia. Coriat and colleagues,[70] pioneers in using Holter monitoring in patients undergoing major vascular surgery, showed that the presence of intraoperative ischemia on Holter monitoring was strongly associated with the severity of preoperative angina pectoris. Slogoff and Keats[71] first demonstrated in 1985 an association between intraoperative ischemia and postoperative MI. They demonstrated that MI detected before induction of anesthesia or before the onset of cardiopulmonary bypass during coronary artery bypass graft surgery is strongly associated with ischemia on Holter monitoring. Several studies using perioperative (preoperative, intraoperative, and postoperative) Holter monitoring in patients undergoing major vascular surgery showed that early postoperative tachycardia-induced silent myocardial ischemia was frequent after vascular surgery and significantly associated with postoperative clinical ischemic events.[72-74] Mangano and coworkers[75] (1990) demonstrated that postoperative Holter-detected ischemia was common (41%) and predictive of adverse postoperative cardiac events, with a ninefold increase in the odds of postoperative cardiac morbidity and mortality when compared with intraoperative or preoperative ischemia.

Table 42-3 summarizes all the studies that were published in the English literature on perioperative ischemia and postoperative cardiac morbidity after major noncardiac surgery.[76-90] Altogether, these studies included more than 2400 patients. The majority of the studies involved major vascular surgery and Holter monitoring for detection of perioperative ischemia (except for the studies by Landesberg and colleagues, which used continuous on-line 12-lead electrocardiographic monitoring). The data revealed that perioperative ischemia was common in high-risk patients, with an incidence between 24% and 63%, and was almost exclusively ST depression consistent with ischemia (97% to 100%). The average postoperative MI rate in these studies was 3.9% (range, 0.6% to 15%), the majority of which were non–Q-wave infarctions (66% to 100%). The incidence of all ischemic postoperative cardiac events was 7.3% (range, 3% to 37%), and the average mortality was 1.04% (range, 0% to 2.8%). Another important observation was that the duration of postoperative ischemia was strongly associated with postoperative ischemic cardiac events. Patients with prolonged, often long hours of postoperative ST depression–type ischemia were likely to experience postoperative MI and elevated serum troponin levels, whereas short episodes of ischemia (<30 minutes) were unlikely to culminate in MI.[87] Additional studies have shown that perioperative ischemia is associated not only with early but also with long-term (5 years) postoperative morbidity and mortality.[88,91]

Examples of Perioperative Ischemia and Infarction

Example 1. Frank and coauthors[76] published one of the first and most detailed cases of postoperative cardiac mortality related to heart rate–induced prolonged postoperative ST depression–type ischemia detected on Holter monitoring. A patient who underwent lower extremity arterial bypass surgery was monitored with a Holter monitor before, during, and after the operation. His records show that he had heart rate–related silent myocardial ischemia preoperatively that subsided intraoperatively, immediately after anesthesia was instituted, only to recur as soon as the patient woke up from surgery. Figure 42-23 shows the ischemia worsening progressively after surgery until the patient died suddenly 10 hours after the operation. The ST depression–type ischemia of this patient occurred at a relatively low heart rate of 80 to 85 beats/min and in the absence of significant alterations in blood pressure. Two snapshots of electrocardiographic disclosure are presented at around 12 midnight: one at a heart rate of approximately 90 beats/min, which showed deep ST-segment depression, and the other a short while later with temporary slowing of the heart rate to around 60 beats/min, which showed almost complete but transient resolution of the ST depression. Although cardiac markers were not measured and no data were provided on myocardial function by echocardiography, it is very suggestive that the patient died as a result of prolonged, silent, heart rate–related ST depression–ischemia, which was at least temporarily reversible by slowing his heart rate (Fig. 42-23).

Example 2. A 70-year-old patient with a history of CAD (treated by coronary artery bypass grafting 7 years earlier), reduced LV function, insulin-dependent diabetes mellitus, and

Table 42-3 (Part 1) Studies Published in the English Literature on Perioperative Ischemia and Postoperative Cardiac Morbidity after Major Noncardiac Surgery

Publication	N	Type of Surgery	Patients with Ischemia (%)	Patients with Any Ischemic Event (%)	Postoperative Ischemic Cardiac Events in Patients with Ischemia on Continuous Electrocardiographic Monitoring				
					Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Relative Risk (%)
McCann and Clements,[72] J Vasc Surg, 1989	50	Vascular	38	8	100	62	21	100	Indefinite
Ouyang et al.,[73] Am J Cardiol, 1989	24	Vascular	63	37.5	89	37.5	53	89	4.8
Pasternack et al.,[74] J Vasc Surg, 1989	200	Vascular	50.5	4.5	100	36.5	7.1	100	Indefinite
Frank et al.,[75] J Clin Anesth, 1990	1	Vascular							
Mangano et al., N Engl J Med, 1990,[76] J Am Coll Cardiol, 1991[77]	474	Major noncardiac	41	3.2	85.7	82	13.9	99	8.6
Pasternack et al.,[78] J Vasc Surg, 1992	385	Vascular	46	4.9	84.2	68.8	13.3	98.8	11.7
Raby et al.,[79] JAMA, 1992	115	Vascular	30.4	13.9	87.5	69.5	40	97.5	16
Marsch et al.,[80] Anesthesiology, 1992	52	Hip arthroplasty	31	6 (11.5)	50	69.2	18.7	91.6	2.25
Landesberg et al.,[81] Lancet, 1993	151	Vascular	48	8.6	84.6	52.3	15.3	97.4	6
Andrews et al.,[82] J Vasc Med Biol, 1994	145	Vascular	24.8	4.1	100	75.2	16.7	100	Indefinite
Ganz et al.,[83] Am Heart J, 1994	1	Vascular							
Fleisher et al.,[84] J Clin Anesth, 1995	145	Major noncardiac	26	6.2	77.8	74.5	18.9	98.1	10.2
Wallace et al.,[85] Anesthesiology, 1998	101	Major noncardiac	34	11.0	?				
Groves et al.,[86] Br J Anaesth, 1999	82	Thoracotomy	24	10.9	55.5	75.6	25	93.5	3.8
Rapp et al.,[87] Acta Anaesthesiol Scand, 1999	20	Vascular	40	15	100	60	37.5	100	Indefinite
Gauss et al.,[88] Anesthesiology, 2001	204	Major noncardiac	1.5 with ischemia >30 min	8.6	18.75	96.3	100	83.5	6.1
Landesberg et al.,[89,90] J Am Coll Cardiol, 2001, 2003	447	Major Vascular	14.7 with ischemia >10 min	9.2	92.7	85.2	57.6	99.2	73

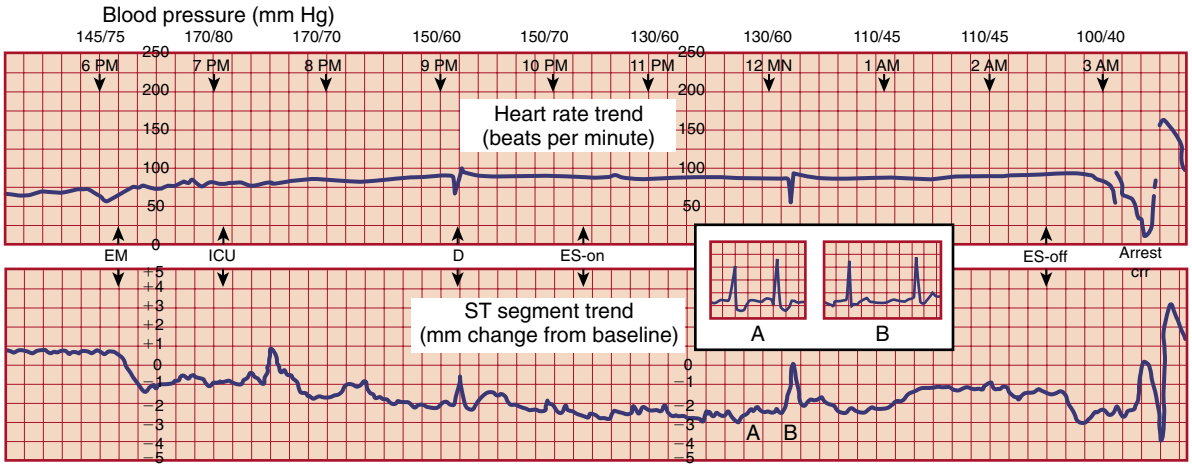

Figure 42-23 Heart rate and ST trends from emergence of anesthesia (EM) to cardiac arrest. CPR, cardiopulmonary resuscitation; D, brief decrease in heart rate; ES-on/off, start/end of esmolol infusion; ICU, intensive care unit admission. *(From Frank SM, Beattie C, Christopherson R, et al: Perioperative rate-related silent myocardial ischemia and postoperative death. J Clin Anesth 2:326-331, 1990.)*

Table 42-3 (Part 2)

Publication	% with ST Depression	Postoperative Ischemia Duration (hr)		Postoperative MI		Cardiac Mortality (%)	Electrocardiographic Leads Monitored
		Patients without MI	Patients with MI	%	% with non-Q MI		
McCann and Clements,[72] J Vasc Surg, 1989	Not specified			4	Not specified	4	Modified V_5
Ouyang et al.,[73] Am J Cardiol, 1989	100	Median = 1.05 (0.08-9.0) min		8.3	Not specified	0	2 inferior + 2 anterior
Pasternack et al.,[74] J Vasc Surg, 1989	Only ST depression was studied	2.9 ± 8.3	11.5 ± 13.1	4.5	Not specified	0.5	Single MC_5
Frank et al.,[75] J Clin Anesth, 1990	ST depression		>10 hr			100	L_2, V_5
Mangano et al., N Engl J Med, 1990,[76] J Am Coll Cardiol 1991[77]	98	1.3 ± 3.3		2.5	Not specified	1.3	CC_5 and MC_5
Pasternack et al.,[78] J Vasc Surg, 1992	Only ST-depression was studied	2.98 ± 8.76	8.1 ± 10.1	4.9	Not specified	1.3	Single CM_5
Raby et al.,[79] JAMA, 1992	Only ST-depression was studied	0.36 (0.02-4.7)		7.8	Not specified	2.6	Not specified
Marsch et al.,[80] Anesthesiology, 1992	100	Not specified		0.5	Not specified	0	CM_3, CM_5, aVF
Landesberg et al.,[81] Lancet, 1993	97	0.56 ± 0.36	8.44 ± 7.84 (>2 hr)	4.0	84	0	Modified V_4, V_5, aVF
Andrews et al.,[82] J Vasc Med Biol, 1994	Only ST-depression was studied		All were >2 hr	0.68	Not specified		Inferior and lateral leads
Ganz et al.,[83] Am Heart J, 1994	ST depression		> 12 hr			100	
Fleisher et al.,[84] J Clin Anesth, 1995	99.3		All were >30 min	6.2	100	0.68	Modified V_3, V_5
Wallace et al.,[85] Anesthesiology, 1998	100	4.7 ± 6.0		2	Not specified	2	CC_5, CM_5, ML
Groves et al.,[86] Br J Anaesth, 1999	Not specified	Not specified		4.8		2.4	V_2, V_5
Rapp et al.,[87] Acta Anaesthesiol Scand, 1999	100	4.3 ± 3.8	28.8 ± 26.9; >5.8 hr	15 (by cTn)	100	0	CC_5, CM_5
Gauss et al.,[88] Anesthesiology, 2001	100	Not reported	>30 min	3 (by cTn)	66	0	V_4, V_5
Landesberg et al.,[89,90] J Am Coll Cardiol, 2001, 2003	99	0.85 ± 0.81	6.26 ± 6.1	3.6 (by cTn)	100	0.4	12-lead ECG

cTn, cardiac troponin; ECG, electrocardiogram; MI, myocardial ischemia.

peripheral vascular disease exhibited prolonged myocardial ischemia and infarction immediately after carotid endarterectomy. On arrival at the operating room the patient was connected to a continuous, 12-lead electrocardiographic monitor with online ST-segment analysis. During surgery no ischemia was observed (Fig. 42-24). Immediately after surgery and on emergence from anesthesia, significant ST depression occurred in association with a moderate increase in heart rate to a maximum of 102 beats/min, in accordance with vague pain in his jaw. The ischemic ST-segment changes lasted 193 minutes, after which the ECG reverted completely to its baseline. Nevertheless, an increase in troponin I to 10.2 ng/mL was measured 6 hours after surgery and up to 32.1 ng/mL on the morning after surgery (see Fig. 42-24).[90] The figure insert depicts all 12-lead electrocardiographic complexes during peak ischemia superimposed on their baseline, preoperative pattern. Significant ST depression occurred in all the

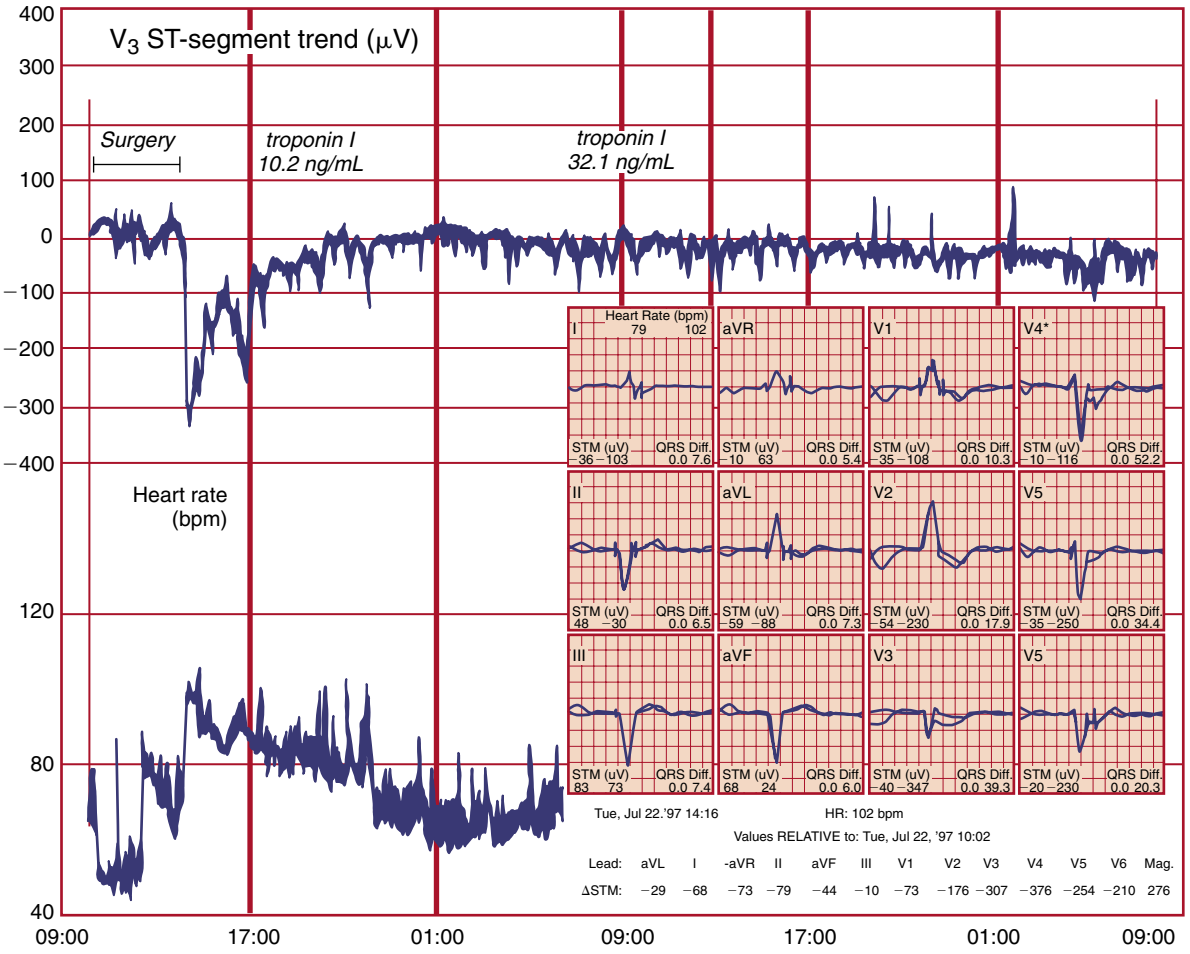

Figure 42-24 Lead V_3 ST-segment and heart rate trends in a patient with prolonged (193 minutes) postoperative ST-segment depression and troponin elevation. The *insert* shows the 12-lead electrocardiographic complexes at peak ischemia superimposed on their baseline patterns.

chest leads and was deepest in lead V_4 (−3.7 mm at peak ischemia). It is interesting to notice the marked abnormality of this patient's baseline ECG (LVH, RBBB, left anterior hemiblock, and baseline ST-T changes). Despite these baseline abnormalities on the ECG, the continuous ST trend monitoring in 12 leads combined with the marked troponin I elevation strongly suggests that the patient had prolonged (>3 hours) ischemia that culminated in elevation of troponin and MI.

EXAMPLE 3. A 65-year-old patient was admitted for surgery because of an asymptomatic abdominal aortic aneurysm (7 cm) and exhibited prolonged postoperative ischemia and infarction with chronic total occlusion of a coronary artery. His past medical history was significant for hypertension, mild obesity (85 kg), and smoking until 12 years before admission. He had no clinical history of ischemic heart disease, but because of shortness of breath on climbing stairs, a preoperative thallium scan was performed (Fig. 42-25) and demonstrated a moderate to severe, large reversible defect in the entire LV anterior wall.

On echocardiography, the size and function of both ventricles were normal with moderate mitral regurgitation. In light of the thallium scan findings, the patient underwent preoperative coronary angiography (Fig. 42-26), which showed total ostial occlusion of the left anterior descending artery with retrograde filling through a large collateral from the right coronary artery.

Based on these findings, a decision was made to proceed to surgery without coronary revascularization. The patient was given bisoprolol (β_1-selective blocker), 50 mg daily for a month, before he returned for surgery (aortobifemoral bypass).

As in the previous example, this patient was monitored during and after surgery by continuous 12-lead electrocardiography with on-line ST-segment monitoring. Intraoperatively, the heart rate was 50 to 70 beats/min, and no significant ST-segment changes were observed. However, immediately at the end of surgery and extubation, significant ST-depression consistent with ischemia developed in association with an increase in heart rate to a maximum of 98 beats/min (Fig. 42-27) and blood pressure of 155/86. Intravenous esmolol and labetalol were administered immediately, and the ischemia subsided within 15 minutes. The patient was transferred extubated and comfortable to the ICU under continuous infusion of esmolol. In the ICU, the doses of esmolol had to be escalated gradually because of a persistent increase in heart rate. Postoperative pain was managed with the epidural catheter. Nevertheless, 5 hours after the end of surgery, severe ST depression recurred in the entire anterior wall. The ischemia lasted longer than 5 hours and responded poorly to β-adrenergic blocking agents (see Fig. 42-27). The patient became delirious and shortness of breath developed. Treatment included intravenous diuretics and a slow

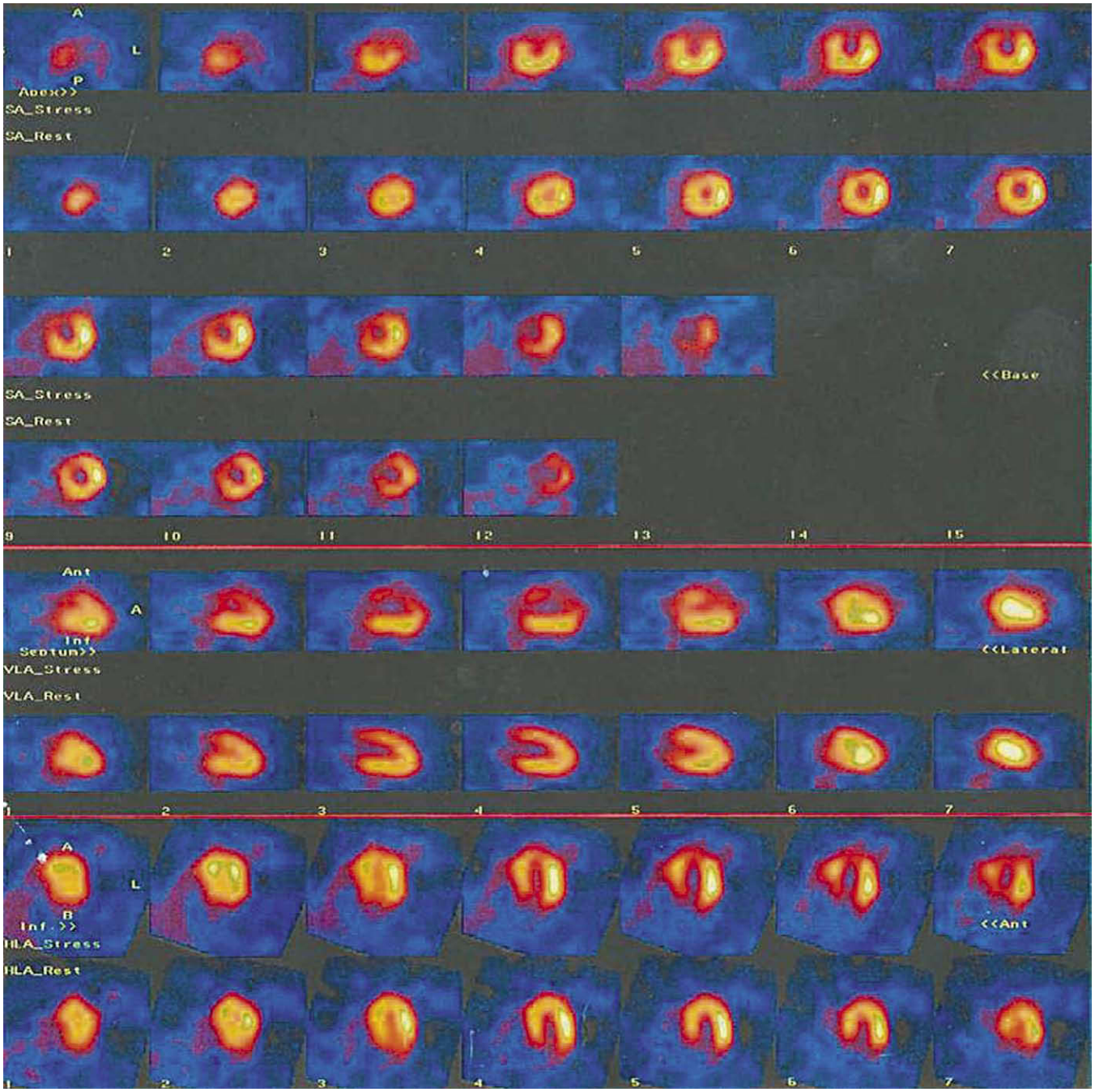

Figure 42-25 Preoperative dipyridamole-thallium single photon emission computed tomography scan of a patient scheduled for abdominal aortic surgery. A moderate to severe reversible defect is present in the entire anterior wall.

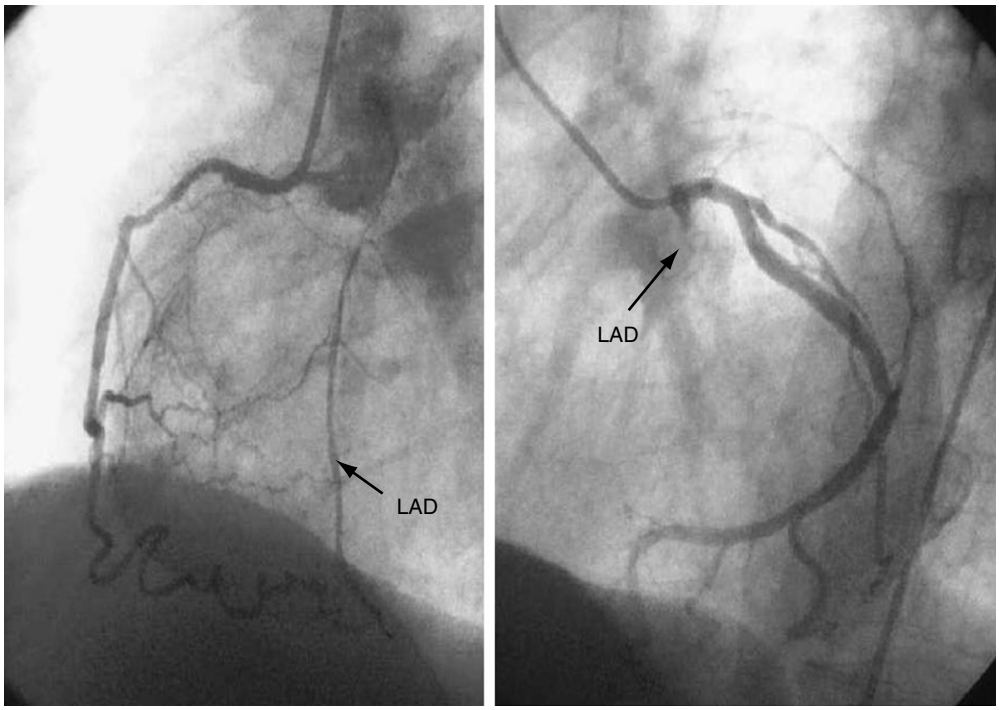

Figure 42-26 Coronary angiogram of the patient in Figure 42-25 showing chronic total ostial occlusion of the left anterior descending (LAD) artery with excellent filling of the distal LAD artery by a collateral from the right coronary artery. A possible mild stenosis is also noted in the first marginal coronary artery.

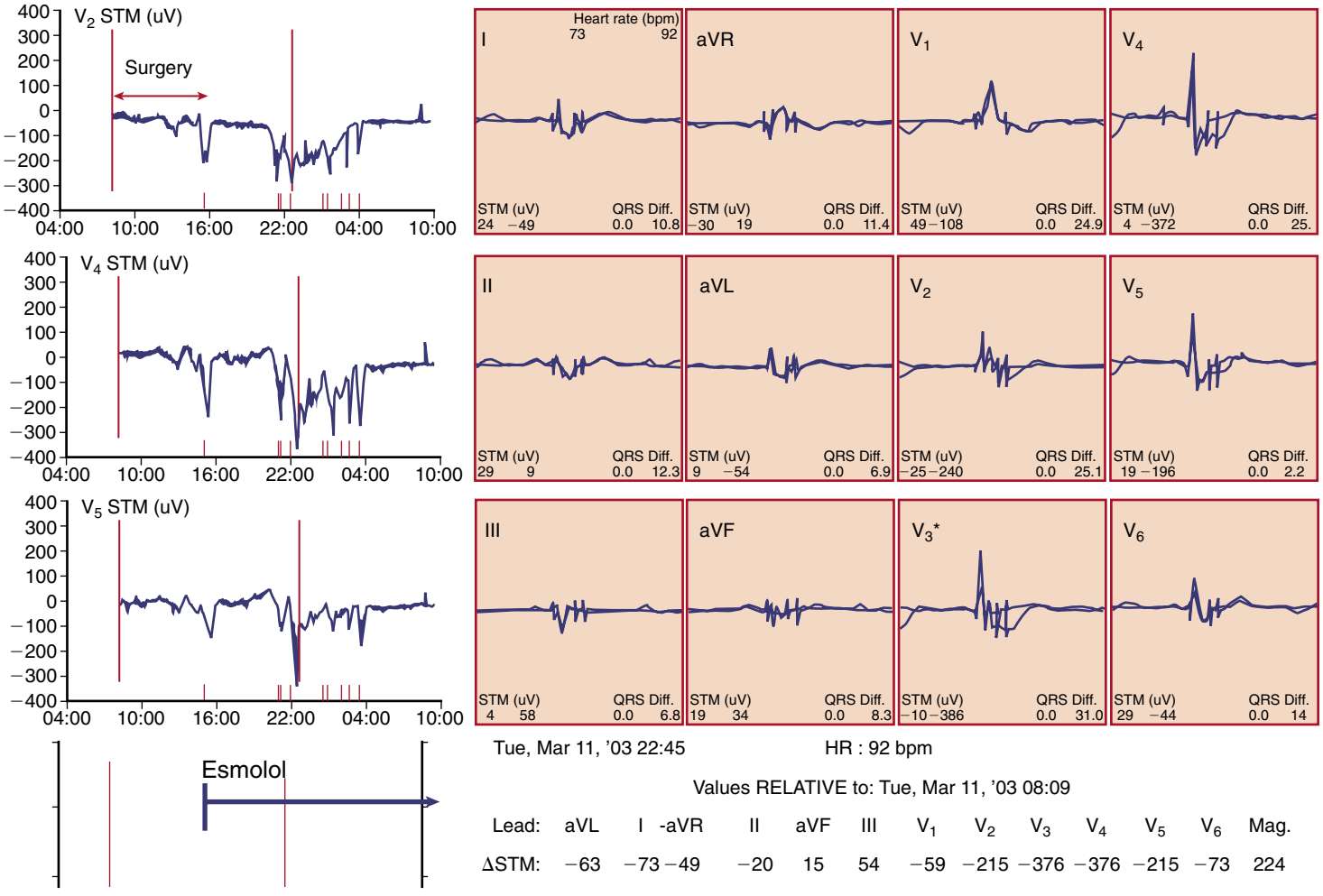

Figure 42-27 Perioperative ST-segment and heart rate trends are demonstrated in the *left panels*. All 12-lead electrocardiographic complexes during peak ischemia, superimposed over the corresponding baseline (preoperative) complexes, are demonstrated in the *right panels*. The ST-segment trends show two episodes of ST-depression–type ischemia: a short episode of 15 minutes immediately at the end of surgery, followed by a 5-hour period of no ischemia and then another long episode of ST depression lasting more than 5 hours. Ischemia is evident in all anterior leads but is maximal in V_3 and V_4.

infusion of packed red blood cells. Twenty-fours hours after the end of surgery, the ischemic electrocardiographic changes regressed almost completely to normal, yet serum troponin T levels increased to 0.64 ng/mL and remained elevated for another 5 days.

This unique case demonstrates that postoperative MI may occur as a result of prolonged stress-induced ST depression–type ischemia in the presence of stable CAD with chronic total coronary artery occlusion of one coronary artery and no rupture of coronary plaque.

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Marc A. Rozner

43 Implantable Cardiac Pulse Generators: Pacemakers and Cardioverter-Defibrillators

Key Points

Preoperatively

1. Identify the generator manufacturer and whether the generator is a pacemaker or defibrillator.
2. Have the pacemaker or defibrillator interrogated by a competent authority shortly before administration of the anesthetic.
3. Obtain a copy of this interrogation. Ensure that the device will pace the heart.
4. Consider replacing any device near its elective replacement period in a patient scheduled to undergo either major surgery or surgery within 25 cm of the generator.
5. Determine the patient's underlying rate and rhythm, which then determines the need for backup (external) pacing support.
6. Identify the magnet rate and rhythm, if any.
7. Program minute ventilation rate responsiveness off, if present.
8. Program all rate enhancements off.
9. Consider increasing the lower rate limit to optimize oxygen delivery to tissues for major cases.
10. Disable antitachycardia therapy if a defibrillator is present.

Intraoperatively

1. Monitor cardiac rhythm with pulse oximetry (plethysmography) or arterial waveform analysis.
2. Ask the surgeon to operate without the monopolar electrosurgical unit (ESU).
3. Use a bipolar ESU if possible; if not possible, a pure cut is better than "blend" or "coag."
4. Place the ESU return pad so that electricity is prevented from crossing the generator-heart circuit, even if the pad must be placed on the distal part of the forearm and the wire covered with sterile drape.
5. If the ESU causes ventricular oversensing and pacer quiescence, limit the period or periods of asystole.

Postoperatively

1. Have the device interrogated by a competent authority immediately postoperatively. Some rate enhancements can be reinitiated, and the optimum heart rate and pacing parameters should be determined. Note that any patient with disabled antitachycardia therapy must be monitored until the antitachycardia therapy is restored.

Adapted from the ASA Practice Advisory for Perioperative Management of Patients with a Pacemaker or Defibrillator.

Battery-operated pacing devices were introduced by C. W. Lillehei (a cardiothoracic surgeon) and Earl Bakken (an electrical technician) in 1958, just 4 years after invention of the transistor. In 1960, Wilson Greatbatch, an engineer in Buffalo, New York, created the first implantable battery-powered device in his barn.[1] The natural progression of pacemaker (PM) developments led to invention of the implantable cardioverter-defibrillator (ICD*) around 1980 by Michael Morchower (of Baltimore). First approved by the U.S. Food and Drug Administration (FDA) in 1985, implantation of ICDs required a thoracotomy, a significant operation in a patient with poor heart function. Advances in electronic miniaturization, as well as improvements in battery technology, have led to the development of very small (10-mL volume), but electronically complicated, programmable pacing devices.

Technologic advances (transvenous lead placement, antitachycardia* pacing [ATP] capability, miniaturization permitting

*Although many authors and references identify this device as an "automatic implantable cardioverter-defibrillator or AICD," the term "AICD" is a brand name originally owned by CPI-Cardiac Pacemakers, Inc., which was acquired by Guidant Medical Corporation and is now a part of Boston Scientific (Natick, MA). The term "PCD" (for "Programmable Cardioverter-Defibrillator") belongs to the Medtronic Corporation (Minneapolis, MN).

*The terms *antibradycardia* and *antitachycardia* will be used throughout this chapter. Antibradycardia refers to pacing to maintain a minimum rate. Thus, conventional PMs are antibradycardia devices. Antitachycardia refers to therapy delivered in the setting of tachycardia, and it is designed to reduce the underlying heart rate.

pectoral pocket placement, and multiple-chamber, rate-responsive antibradycardia pacing) and numerous survival benefits[2,3] have led to increases in the use of ICDs. These changes in ICD implantation and indications have two important results for health care providers. First, a pectoral (rather than abdominal) pocket ICD with pacing capability might be mistaken, by virtue of pacing "spikes" on the surface electrocardiogram, for a (non-ICD) PM. At many centers, electrocardiograms are obtained from patients who have "PMs" with use of a magnet. Because some ICDs from Boston Scientific/Guidant Medical/CPI can undergo permanent deactivation of antitachycardia therapy with magnet placement, this mistake could leave a patient unprotected[4] and possibly result in death.[5] Second, pacing functions in an ICD often respond to external stimuli (magnet placement, electromagnetic interference [EMI]) differently than a PM does. These issues are addressed later in this chapter. Additionally, all ICDs now perform permanent cardiac pacing, so the issues in the sections on pacing will apply to ICD care as well. Distinguishing a conventional PM from an ICD can be accomplished by examining the right ventricular (RV) lead system on a chest radiograph (Fig. 43-1). A chest radiograph can also be used to identify the generator manufacturer (Fig. 43-2).

Pacemaking and defibrillation systems have a remarkable record for reliability, but they can and do fail. Maisel and colleagues reviewed FDA records for PM and ICD failures (death or explantation because of malfunction other than battery depletion) for the period 1990 to 2002. Even though the nature of this reporting scheme promotes under-reporting of problems, for these 12 years, 2.25 million PMs were implanted, with 8,834 (0.4%) confirmed (and reported) malfunctions and 30 deaths. For ICDs, 415,780 were implanted, with 8,489 (2%) confirmed malfunctions and 31 deaths.[6] Thus, every patient with a cardiac generator should undergo regular in-office follow-up. For appropriately selected devices, telephone checks can be used to identify battery depletion (PM and ICD) or detection of tachycardia (ICD), but telephone checks cannot ensure adequacy of pacing capture and sense safety margins at this time. For PMs, nationally published guidelines recommend at least a telephone check every 1 to 3 months, depending on implant duration.[7] No such guidelines exist for ICD follow-up, although most ICD manufacturers recommend follow-up periods not to exceed 4 months.

Issues also develop and lead to "notices," "product advisories," or "recalls" from the various manufacturers, which might affect perioperative care. For example, Guidant has 46,000 ICDs with potentially defective magnet sensors that could prevent delivery of shock or ATP. Their recommended action was to permanently disable the magnet switch by programming. An ICD thus programmed will therefore deliver a shock even with a magnet in place (Fig. 43-3).[8] The Sprint Fidelis ICD lead series from Medtronic will report ventricular activity in the absence of true electrical systoles (oversensing), which can result in failure to pace or inappropriate delivery of shock,[9] and Guidant has one such lead with similar issues (Model 0156) (Fig. 43-4).

The complexity of PMs and ICDs, as well as the multitude of programmable parameters, limits the number of generalizations that can be made about the perioperative care of a patient with an implanted pulse generator. Population aging, continued enhancements in implantable technology, and new indications for implantation of cardiac devices continue to drive the growing number of implants. The American Society of Anesthesiologists has taken note of these issues and is developing a Perioperative Practice Advisory[10]; the "Key Points" reflect this advisory. Practice guidelines have been issued by the American College of Cardiology (ACC) (hereafter called the ACC guidelines),[11] the American Heart Association (AHA), and the Heart Rhythm Society (formerly the North American Society of Pacing and Electrophysiology [NASPE]).[12] Reviews can also be found in a number of journals.[13-15]

Patients with an implanted cardiac pulse generator often have significant comorbid disease in addition to their cardiac rhythm disturbance. Our ability to care for these patients requires attention to both their medical and psychological problems. We also need an understanding of their pulse generator, its function, and its probable idiosyncrasies in the operating or procedure room.

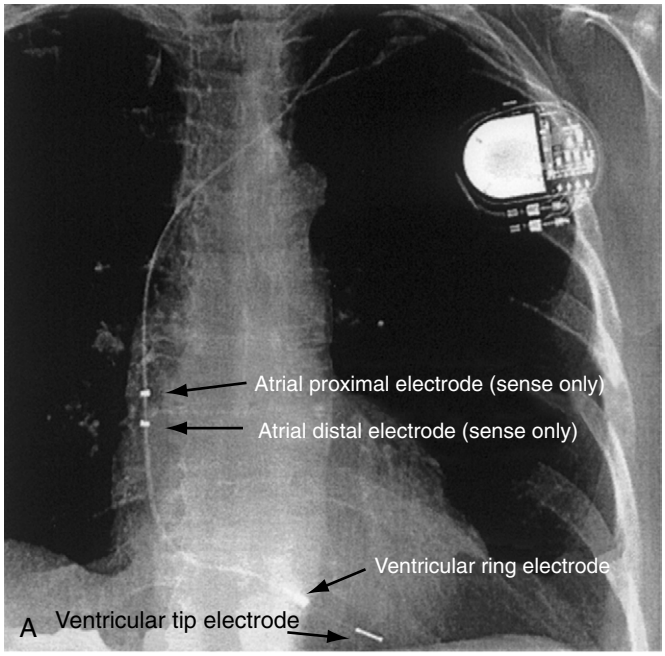
Finally, not all electronic generators implanted in the chest are cardiac devices, and devices resembling cardiac pulse generators are being implanted at increasing rates for indications unrelated to cardiac issues. When implanted in the pectoral position (the usual place for current cardiac generators), these noncardiac devices can be mistakenly identified as cardiac generators.[16] Pulse generator implantation has been approved by the FDA for pain control, thalamic stimulation to control Parkinson's disease, phrenic nerve stimulation to stimulate the diaphragm in paralyzed patients, and vagus nerve stimulation to control epilepsy and depression.[17] Vagus nerve stimulation is also under consideration for the treatment of heart failure[18] and perhaps obesity. Thus, when evaluating a patient with any pulse generator, one must now determine whether the pulse generator will be pacing the heart, stimulating the central nervous system, stimulating the spinal cord, or stimulating the vagus nerve.

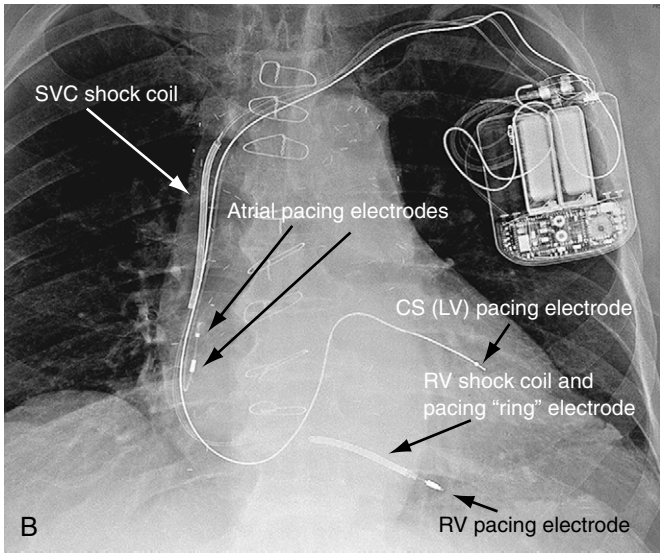
Pacemakers

PM manufacturers report that more than 2,500 generators have been manufactured by more than 26 named entities over the past 40 years. Currently, more than 250,000 adults and children in the United States undergo new PM placement each year, and nearly 2 million patients have PMs today. Many factors lead to confusion regarding the behavior of a device and the perioperative care of a patient with a device, especially since case reports, textbooks, and literature reviews have not kept pace with technologic developments.

A pacemaking system consists of an impulse generator and a lead or leads to carry the electrical impulse to the patient's heart. Leads are connected to the heart's chambers through the vena cava (transvenous leads) or are directly sewn onto the surface of the heart (epicardial leads). Leads can be unipolar (one electrode per lead), bipolar (two electrodes per lead), or multipolar (multiple electrodes and wires contained within one lead with connections in multiple chambers) (see Fig. 43-1A). Because two electrodes are required to complete a circuit, the second electrode in a unipolar configuration will be the metal generator case. Use of the case as an electrode requires that the generator pocket be devoid of gas, and electrical continuity has reportedly been disrupted by the use of nitrous oxide.[19]

PMs with unipolar leads seem to be more sensitive to the effects of EMI, and these systems produce larger "spikes" on an analog-recorded electrocardiogram. Most PM systems (except many Autocapture devices from St. Jude Cardiac Rhythm Management, Sylmar, CA) pace in bipolar mode because bipolar





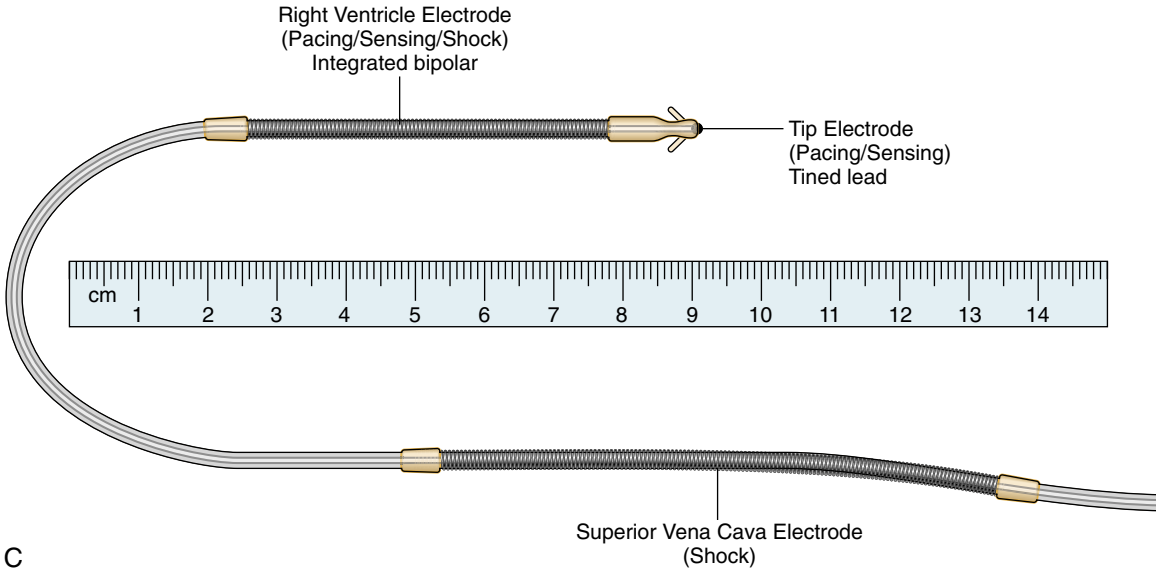


Figure 43-1 A conventional single lead pacemaker, an implantable cardioverter-defibrillator (ICD), and a right ventricular (RV) defibrillator lead are shown to assist in determination of the type of system on chest radiography. **A,** Conventional pacemaker with one quadripolar lead that provides atrial and ventricular sensing and ventricular pacing. This chest radiograph shows a number of features of a modern pacing system. The generator is located in the left pectoral region. The single lead enters the subclavian vein under the clavicle but superficial to the first rib (a common site for lead problems, although no problem is demonstrated here). This device has two electrodes positioned within the right atrium that can provide sensing to detect intrinsic atrial activity. The ventricular portion of the lead shows the classic bipolar pattern with a ring electrode just proximal to the tip electrode, and these electrodes can be used for sensing intrinsic ventricular activity, as well as depolarizing the ventricle. This particular system is a VDD pacemaking system, and this configuration is placed into patients with a functioning atrioventricular node. The system cannot be used to depolarize the atrium. Because the surface electrocardiogram will often demonstrate ventricular pacing that tracks the atrial activity, inspection of the surface electrocardiogram often produces an erroneous diagnosis of a dual-chamber (DDD) pacemaker. **B,** Defibrillator system with biventricular pacing capability. Note that three leads are placed: a conventional bipolar lead to the right atrium, a multipolar lead terminating in the right ventricle, and a unipolar lead to the coronary sinus (CS). The presence of a "shock" conductor in the right ventricle (called a "shock coil") distinguishes a defibrillation system from a conventional pacing system. Many ICDs have an additional shock coil in the superior vena cava (SVC). Typically, the SVC shock coil is electrically identical to the defibrillator case (called the "can"). When the defibrillation circuitry includes the ICD case, it is called "active can configuration." This particular system is designed to provide "resynchronization therapy" in the setting of dilated cardiomyopathy with a prolonged QRS interval (and frequently with a prolonged PR as well). The bipolar lead in the right atrium will perform both sensing and pacing function. Likewise, the tip electrode in the right ventricle along with the shock coil performs RV pacing and sensing function. When the second RV pacing electrode is merged with the shock coil, the lead is called "integrated bipolar" because unipolar RV pacing is not permitted in an ICD system. The lead in the CS depolarizes the left ventricle (LV). Failure to depolarize one of the ventricles might result in ventricular oversensing (and inappropriate antitachycardia therapy) in an ICD. **C,** Integrated bipolar RV defibrillator lead. The tip of this lead becomes enmeshed in the RV trabeculae (called a "tined" lead) rather than engaging the myocardial wall with a screw ("active fixation"). This particular lead has an SVC shock coil as well.

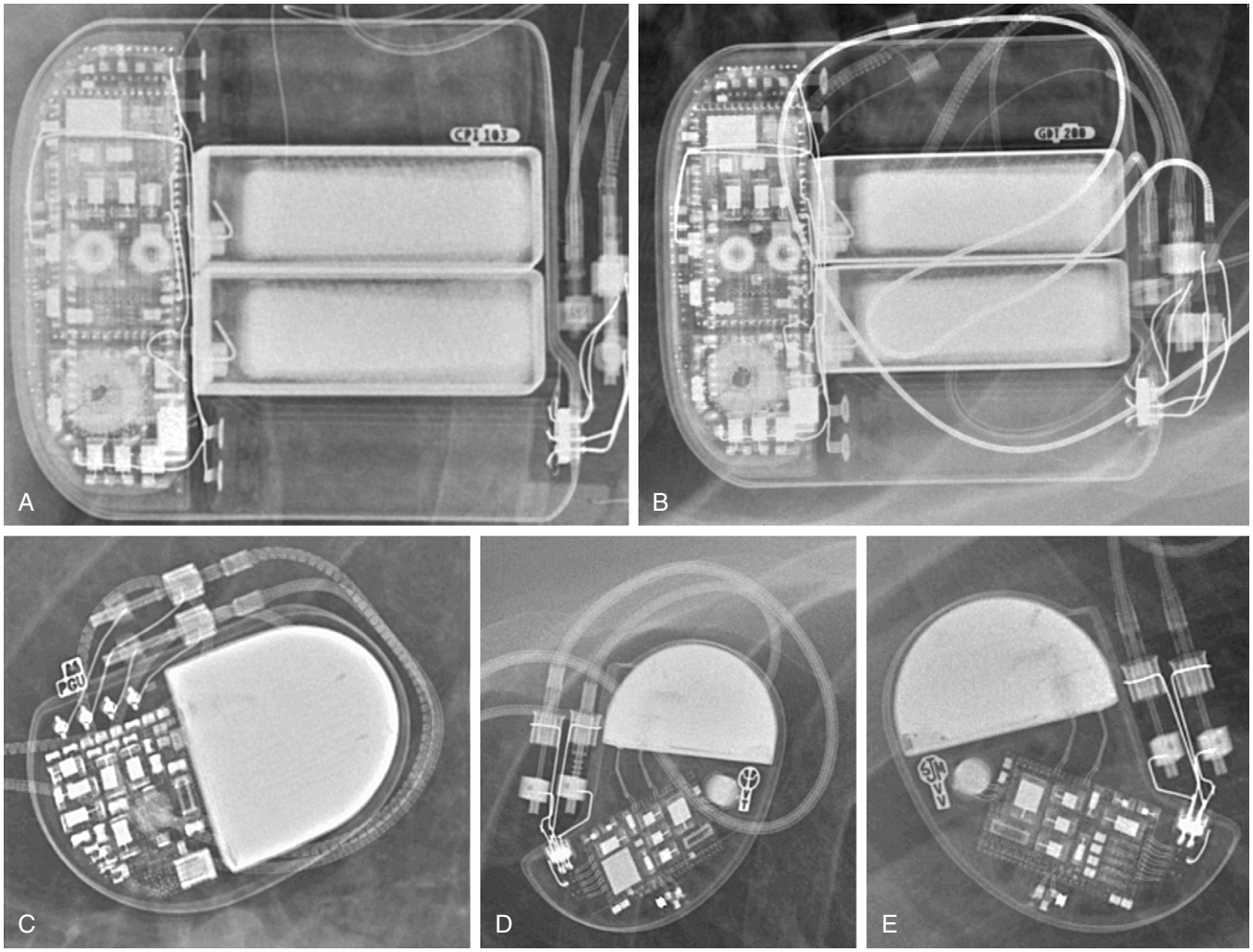
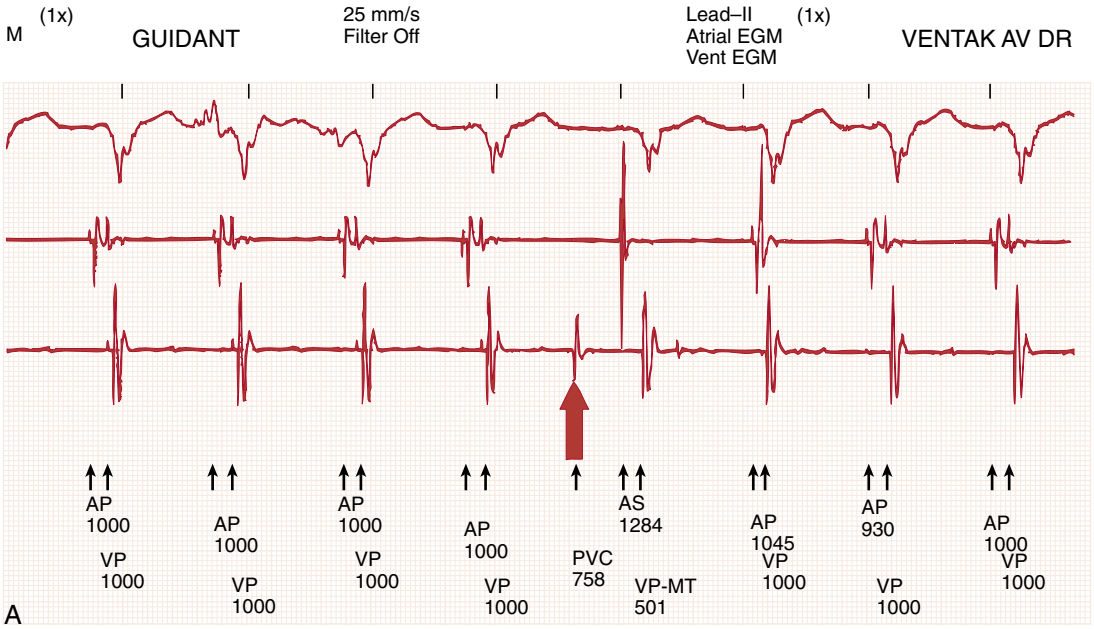


Figure 43-2 Radiographic identifiers for some generator manufacturers. Pacemaker and implantable cardioverter-defibrillator generators can be identified from operative dictations, patient cards, or some chest radiographs. Using digital x-ray equipment with postprocessing zoom capability, corporate x-ray logo identifiers from CPI (**A**), Guidant (**B**), Medtronic (**C**), Pacesetter (**D**), and St. Jude Medical (**E**) are shown. Not shown: BOS is the new Boston Scientific logo.

Setup

	INITIAL VALUE	PRESENT VALUE
Magnet		
*Enable magnet use		Off
*Change tachy mode with magnet		
Beeper		
Beep during capacitor charge		Off
Beep on sensed and paced ventricular events		Off
Beep when ERI is reached		On

Figure 43-3 Magnet mode setup from a Guidant Contak Renewal 3 HE model H179. This implantable cardioverter-defibrillator (ICD) is part of an "Urgent Medical Device Safety Information and Corrective Action" letter to physicians from the Guidant Corporation on June 23, 2005, in which a magnet switch problem was announced. The corrective action was designed to permanently disable the magnet switch by programming. As a result, this ICD will not disable shock therapy in response to magnet placement. According to the notice, approximately 46,000 Guidant ICDs were affected and should have their magnet switch permanently disabled. Note the line below the magnet switch report called "Change tachy mode with magnet." With magnet function operative in many Boston Scientific/Guidant Medical/CPI ICDs, enabling this setting allows permanent deactivation of ICD function with the application of a magnet for more than 30 seconds (see text).



ICD Model: Gem III VR 7231
Serial Number

Apr 26,2005 14:12:05
9971 Software Version 5.0
Copyright Medtronic, Inc. 2000

Status Report **Page 1**

Last interrogation: Apr 11, 2005 15:06:25

Battery Voltage

(ERI = 2.55 V, EOL = 2.40 V)
Apr 26, 2005 14:04:43
Voltage 2.97V

Last Capacitor Formation*

Dec 31, 2004 20:24:36
Charge Time 6.08 sec
Energy 0.0 – 30.0J

Last Charge

Dec. 31, 2004 20:24:36
Charge Time 6.08 sec
Energy 0.0 – 30.0J

Device Status

Charge Circuit is OK.

*Minimum Auto Cap Formation interval is 4 months

Lead Impedance

Apr 26, 2005 03:00:05
V. Pacing 444 ohms
Defibrillation (HVB) 13 ohms

Last High Voltage Therapy

May 21, 2002 09:14:00
Measured Impedance 56 ohms
Delivered Energy 20.2 J
Waveform Biphasic
Pathway AX > B

Sensing Integrity Counter

Since Apr 11, 2005 15:18:06
120–130 ms V-V intervals 875
(if > 300 counts, check for sensing issues)

B

Figure 43-4 Ventricular oversensing from damaged leads. **A,** A real-time telemetry recording from a Guidant implantable cardioverter-defibrillator (ICD) with a Guidant 0156 right ventricular (RV) defibrillation lead reports a spontaneous ventricular (*arrow*) event that was not present on the surface electrocardiogram (ECG), termed ventricular oversensing. In this ICD, the pacing function was DDD (lower rate, 60 beats/min; atrioventricular delay, 180 msec), and this patient was dependent on the ICD pacing function for his ventricular systoles. The top tracing is the surface ECG, the second tracing is the intracardiac atrial electrogram (EGM), and the third tracing is the intracardiac ventricular EGM. Along the bottom is the "marker channel," which shows the pacemaker's interpretation of events—AP is atrial pace, AS is atrial sense, VP is ventricular pace, and the inappropriate ventricular sensed event is labeled "PVC" because it occurs after a ventricular event without an intervening atrial event. Note that this oversensing has prolonged the RR interval between the fourth and fifth ventricular systoles because this patient is dependent on the pacing function for his ventricular systoles. In a pacing-dependent patient, this type of oversensing can lead to asystole. It can also provoke inappropriate antitachycardia therapy (i.e., shock) in a patient with native ventricular activity because these oversensed events can increase the apparent heart rate count to the ICD. **B,** A patient with a single-chamber Medtronic ICD and a Medtronic Sprint Fidelis RV defibrillation lead was found to have a significant ventricular oversensing issue at interrogation 4/26/05 before his head and neck surgery. In this case the ICD is reporting 875 "short RR intervals" (note the *arrow*) since the previous interrogation 15 days earlier (4/11/05). These data are consistent with a lead fracture causing intermittent "make-break" contacts. In this case, new counts began accumulating 12 minutes after the previous interrogation was complete. More than 100 counts per month is considered a problem; indications to replace the lead include ventricular oversensing in a pacing-dependent patient or high rate detection triggered by this inappropriate oversensing.

Table 43-1 NASPE/BPEG Revised (2002) Generic Pacemaker Code (NBG)

Position I: Pacing Chamber(s)	Position II: Sensing Chamber(s)	Position III: Response(s) to Sensing	Position IV: Programmability	Position V: Multisite Pacing
O = none	**O** = none	**O** = none	**O** = none	**O** = none
A = atrium	**A** = atrium	**I** = inhibited	**R** = rate modulation	**A** = atrium
V = ventricle	**V** = ventricle	**T** = triggered		**V** = ventricle
D = dual (A + V)	**D** = dual (A + V)	**D** = dual (T + I)		**D** = dual (A + V)

The generic pacemaker code.[20] This code, initially published in 1983, was last revised in 2002 in an effort to keep current with technologic developments in the pacing field. The NBG code is a joint project by the North American Society of Pacing and Electrophysiology (NASPE) (the "N") and the British Pacing and Electrophysiology Group (BPEG) (the "B"). The "G" stands for generic.

pacing usually requires less energy. Bipolar sensing is more resistant to interference from muscle artifacts or stray electromagnetic fields. Frequently, bipolar electrodes can be identified on the chest film because they will have a ring electrode 1 to 3 cm proximal to the lead tip (see Fig. 43-1A). Note, however, that generators with bipolar leads can be programmed to the unipolar mode for pacing, sensing, or both.

Pacemaker Codes

No discussion of PMs can take place without an understanding of the generic PM code, which has been published by the NASPE and British Pacing and Electrophysiology Group (BPEG). This code (NBG*) was initially published in 1983 and was last revised in February 2002.[20] It describes the basic behavior of the pacing device (Table 43-1). PMs also come with a variety of terms generally unfamiliar to the anesthesiologist, many of which are shown in the glossary at the end of this chapter.

The first two positions of this code (chambers paced, chambers sensed) seem relatively straightforward. Although early PMs provided only ventricular support, current models can provide pacing in the atria and ventricles, and these devices can also be programmed to determine intrinsic activity in these chambers as well. The code does not describe the array of diagnostic data that can be accumulated by these devices.

Probably the most confusing aspect of the NBG code is the third position (response to the sensed event). Most PMs are programmed either to the DDD mode (dual-chamber pacing and sensing, both triggered and inhibited mode) or the VVI mode (for single-chamber, ventricular pacing in the inhibited mode). Two other modes frequently found are VDD (ventricular pacing with dual-chamber pacing in the triggered and inhibited mode) and DDI (dual-chamber pacing and sensing, but inhibited mode only). In the United States, atrial-only PM placement (AAI mode) is unusual, but these devices are implanted in patients with sinus node disease in other countries. This third position describes the following behavior:

D (**Dual**): DDD pacing provides atrioventricular (AV) synchrony. In the DDD setting, atrial pacing will take place in the "inhibited" mode; that is, the pacing device will emit an atrial pulse if no sensed atrial event (or intervening ventricular event because any ventricular event will reset atrial timing) takes place within the appropriate timeframe. In DDD or VDD devices, once an atrial event has occurred (whether native or paced), the pacing device will ensure that a ventricular event follows (up to the upper tracking rate [UTR, see "Glossary"]).

I (**Inhibited**): The appropriate chamber is paced unless intrinsic electrical activity is detected during the pacing interval. For the DDI mode, AV synchrony is provided only when the atrium is paced. If intrinsic atrial activity is present, no AV synchrony is provided by the pacing function.

T (**Triggered**): The pacing device will emit a pulse only in response to a sensed event. The triggered mode is used when the device is being tested.

The modes VDD and DDI deserve further comment. VDD pacing is used for a patient with AV nodal dysfunction but intact and appropriate sinus node behavior. VDD pacing is accomplished with a single lead that incorporates atrial sensing electrodes and ventricular conductors that can both pace and sense (see Fig. 43-1A). A VDD device has no atrial pacing capability. As a result, in a patient who depends on atrial contraction to augment cardiac output, events that result in VVI pacing (e.g., sinus rate below the programmed rate, battery depletion) or asynchronous ventricular pacing (e.g., magnet placement in many devices, EMI) can lead to deteriorating hemodynamics.[21,22]

DDI pacing is indicated for a patient who has a dual-chamber pacing device and also has episodes of paroxysmal atrial dysrhythmia (e.g., paroxysmal atrial fibrillation). DDI pacing prevents high ventricular rates (i.e., pacing at the UTR) that could result from attempted tracking of the atrial arrhythmia, and it provides AV synchrony only when the atrium is paced. Many DDD programs will enter the DDI mode on detection of high (programmable) atrial rates (called mode switch, automatic mode switch, or atrial tachy response, depending on the manufacturer). When the mode switches to DDI, perturbations (such as very high [>400/min] atrial rates, EMI from the electrosurgical unit [ESU], or magnet placement and removal) might revert the PM back to DDD pacing, with the resultant appearance of AV pacing or ventricular pacing at the UTR (see "Pacemaker Magnets").

Rate modulation (the fourth position) also remains a poorly understood concept. Because some patients cannot increase their heart rate in response to increased oxygen demand (chronotropic incompetence), PM manufacturers have devised a number of mechanisms to detect "patient exercise," such as sensors that detect vibration, respiration, and pressure (Box 43-1). As the sensor detects "exercise," it increases the pacing rate

*The NBG code is a joint project from the NASPE (the "N") and the BPEG (the "B"). The "G" stands for generic. NASPE reorganized as the Heart Rhythm Society (HRS) in 2004.

Box 43-1 Rate Modulation (Activity) Sensors Available or Under Investigation

Currently Approved in the United States
- Vibration sensor
- Motion sensor
- Minute ventilation (bioimpedance sensor)
- QT interval (Vitatron only)
- Right ventricular pressure (Biotronik only)

Under Investigation
- Right ventricular stroke volume
- Blood pH
- Blood temperature
- Mixed venous oxygen sensor
- Systolic time intervals
- Evoked response
- Intracardiac Impedance

Of the types of sensors used to detect exercise in a patient with a cardiac pacemaker, five are currently approved in the United States, although many others are under investigation. Some devices have two sensors and can be programmed for cross-checking to prevent increases in heart rate from spurious causes. Minute ventilation sensors are very sensitive to stray electromagnetic interference, and patients have been inappropriately treated for pacemaker-driven tachycardias as a result. There is very little perioperative experience with right ventricular pressure sensors at this time. Most pacemaker experts recommend that rate modulation be programmed to "OFF" in the perioperative period to prevent confusion between an intrinsic tachycardia versus a pacemaker-induced tachycardia (for example, see Schwartzenburg and colleagues[23]).

(termed "sensor-indicated rate"). As the exercise tapers, this sensor-indicated rate returns to the programmed lower rate. The sensitivity of these sensors to their exercise signals and the rates of change in pacing are programmable features in current generators. Activation of rate response algorithms resulting in an increased pacing rate in the operating room, whether from vigorous chest wall skin preparation, pressure on the generator, or EMI in a minute ventilation device, has led to inappropriate treatment and patient harm.[24,25]

With the 2002 revision of the NBG, the fifth column describes multisite pacing functionality (it had been used to describe antitachycardia functions, but this scheme has been abandoned and a generic defibrillator code has been established). Atrial multisite pacing might prevent atrial fibrillation,[26] and ventricular multisite pacing is an acceptable means of pacing patients with dilated cardiomyopathy (DCM).[27-29]

Pacemaker Indications

Indications for permanent pacing are shown in Box 43-2 and are reviewed in detail elsewhere.[30] Classically, antibradycardia pacing treats patients with sinus node disease (improper impulse formation) and AV node disease (improper impulse conduction). Pacing can be used to reduce the outflow tract obstruction in hypertrophic obstructive cardiomyopathy (HOCM) in both adults and children because paced ventricular conduction takes place in a left bundle branch pattern (the left ventricular [LV] septum depolarizes after the other segments rather than as an early systolic event).[31] Finally, in August 2001, devices were approved by the FDA for three-chamber pacing (right atrium, both ventricles) to treat DCM.[32] This pacing modality can also be called cardiac resynchronization therapy (CRT) or biventricular (BiV) pacing. To accomplish LV pacing, a pacing lead is placed into the coronary sinus (see Fig. 43-1B) or sewn onto the LV free wall. In patients with a significant RV-to-LV activation time, loss of capture in a ventricle can lead to ventricular overcounting with resultant inappropriate antitachycardia therapy in those with a DCM-pacing defibrillator.[33,34]

Pacing for HOCM and DCM requires careful attention to pacer programming. To be effective in these patients, the PM must provide the stimulus for ventricular depolarization, and AV synchrony must be preserved.[35] PM inhibition or loss of pacing (e.g., from native conduction, atrial irregularity, ventricular irregularity, development of junctional rhythm, or EMI) can lead to deteriorating hemodynamics in these patients.

BiV pacing might cause inappropriate lengthening of the QT interval in susceptible patients, and this lengthening has been reported to be associated with torsades de pointes.[36] As a result of this report, prudent anesthesiologists should ensure adequate access to rapid defibrillation for patients with BiV pacing accomplished without an ICD.

Pacemaker Magnets

Despite oft-repeated folklore, most PM manufacturers warn that magnets were never intended to treat PM emergencies or prevent the effects of EMI. Rather, magnet-activated switches were incorporated to produce pacing behavior that demonstrates remaining battery life and, sometimes, pacing threshold safety factors.

Placement of a magnet over a generator might produce no change in pacing because *not all pacemakers switch to a continuous asynchronous mode when a magnet is applied*. Moreover, not all models from a given company behave the same way. Possible effects of magnet placement are shown in Table 43-2.[37-39] In some devices magnet behavior can be altered by programming, whereas in others, magnet behavior can be completely eliminated by programming.

Box 43-2 Pacemaker Indications

Symptomatic diseases of impulse formation (sinus node disease)

Symptomatic diseases of impulse conduction (disease of the atrioventricular node)

Long QT syndrome

Hypertrophic obstructive cardiomyopathy*

Dilated cardiomyopathy*

Indications for permanent pacing are listed. Most patients with pacemakers currently fall into the first two categories (sinus or atrioventricular nodal disease).

*Requires 100% ventricular pacing to be effective. Thus, short atrioventricular delays (around 120 to 150 msec) are programmed.

Table 43-2 Pacemaker Magnet Behavior

Pacemaker Company		Magnet Mode Designation	Explanation
Biotronik (except INOS and DROMOS)		AUTO	If battery okay, 10 asynchronous events at 90 beats/min, then returns to original programmed mode, without rate responsiveness. Pacing is at the lowest available rate (LRL, sleep rate, or hysteresis rate). If battery at ERI, 10 asynchronous events at 80 beats/min in the VOO mode, then either VDD (dual-chamber) or VVI (single-chamber) pacing at 11% lower than the lowest available rate. For any dual-chamber mode (DDD, DDI, or VDD), the AV delay shortens to 100 msec while the magnet is in place
		ASYNCH	Asynchronous pacing at 90 beats/min if battery okay. At ERI, 80 beats/min (single-step change) in the VOO mode regardless of original programming. For any dual-chamber mode (DDD, DDI, or VDD), the AV delay shortens to 100 msec while the magnet is in place
		SYNCH	If battery okay, pacing in original programmed mode, without rate responsiveness. Pacing is at the lowest available rate (LRL, sleep rate, or hysteresis rate). If battery at ERI, either VDD (dual-chamber) or VVI (single-chamber) pacing at 11% lower than the lowest available rate. For any dual-chamber mode (DDD, DDI, or VDD), the AV delay shortens to 100 msec while the magnet is in place
Boston Scientific/Guidant Medical/CPI		ASYNCH	Asynchronous pacing at 100 beats/min if okay, 85 beats/min at ERI (single-step change). The Insignia model has an intermediate step at 90 beats/min at IFI. For Triumph and Prelude models, see Medtronic pacemakers, below
		OFF	No change, magnet is ignored. OFF is the magnet mode after a "power on reset," which can occur secondary to EMI
		EGM mode	No change in pacing. Magnet application initiates data collection
Medtronic			Asynchronous pacing at 85 beats/min if okay, SSI at 65 beats/min regardless of original programming if ERI detected (single-step change). Most Medtronic pacemakers emit one or more ventricular pulses during the first 3-7 asynchronous events (which might be at a rate of 100 beats/min) at a reduced pulse width or voltage to demonstrate the adequacy of ventricular pacing output. Also, Medtronic pacemakers default to SSI pacing at 65 beats/min, without rate responsiveness, on detection of ERI, regardless of whether a magnet is present
St. Jude Medical (not including Telectronics)	"SJM" x-ray logo	Battery Test	Asynchronous pacing at 98.6 beats/min gradually decreasing to <86.3 beats/min at ERI
		OFF	No magnet response
		Event snapshots	No change in pacing. Magnet application causes pacemaker to collect data. Identity and Entity models lack this feature
		Event snapshots + Battery Test	For a magnet placed 2 seconds, pacing mode and rate are unchanged and the device stores an EGM. If the magnet is placed ≥5 seconds, the Battery Test mode (see above) is activated. Identity and Entity models lack this feature
	Pacesetter x-ray logo (ψ)	Battery Test	Asynchronous pacing, with rate depending on the specific model. In general, a pacing rate of less than 90 beats/min should prompt further evaluation
		OFF	No magnet response
		VARIO mode (present in some models)	VARIO results in a series of 32 asynchronous pacing events. The rate of the first 16 paces reflects battery voltage, which gradually declines from 100 to 85 beats/min at ERI. The next 15 paces are used to document the ventricular pacing capture safety margin. The rate will be 119 beats/min with gradually declining pacing voltage. The 16th pace of this group is at no output. The next pace restarts the 32-event sequence. The 32-event sequence repeats as long as the magnet remains in place

The effect or effects of appropriately placing a magnet over a pacemaker are shown. Column 1 shows the pacemaker manufacturer. If the magnet response is programmable, column 2 shows the various programmable modes available. The first mode shown for a company is the default mode. Column 3 shows the effect on pacing therapy for the magnet mode shown in column 2. Unless otherwise specified, asynchronous pacing takes place, without rate responsiveness, in the chambers originally programmed. Thus, a dual-chamber program would result in DOO pacing, and a single-chamber program would result in VOO pacing (unless an atrial device is used, which would be AOO), and a biventricular, dual-chamber device would be DOOOV.

AV, atrioventricular; EGM, electrogram; EMI, electromagnetic interference; EOL, end of life—the device should be replaced immediately; ERI, elective replacement indicator—the device should be replaced promptly; IFI, intensified follow-up interval—the device needs monthly battery checks; LRL, lower rate limit—the programmed lower rate, or set point, of the pacemaker; SSI, single-chamber, inhibited mode—if implanted for ventricular pacing, SSI = VVI; for an atrial pacemaker, SSI = AAI.

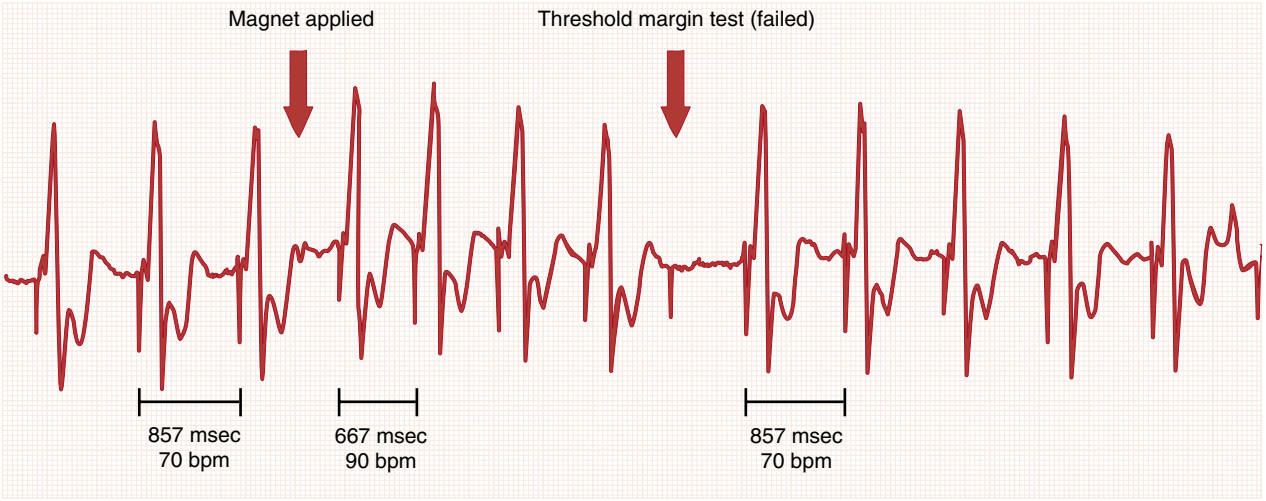


Figure 43-5 Threshold margin test (TMT) demonstrating an inadequate safety margin for pacing. Application of a magnet to some pacemakers will produce asynchronous pacing in which one or more pacing stimuli are emitted with reduced ventricular pacing voltage, pulse width, or both. This sequence is used to determine, without formal pacemaker interrogation, the adequacy of pacing energy settings. In this electrocardiographic strip from an Intermedics device, the patient was being paced in the VVI mode at a rate of 70/min (equal to 857-msec intervals). On application of the magnet, this pacemaker produced four intervals (five pacing stimuli) of asynchronous pacing at a rate of 90/min (667-msec intervals), thus demonstrating adequate battery voltage for this device (pacemaker response to magnet placement is dependent on the manufacturer and sometimes the programming). At the fifth pacing stimulus after magnet application, the pacemaker performs a TMT by reducing the stimulus pulse width to 50% of the programmed value (equal to 50% of programmed energy). Failure of this stimulus to produce ventricular systole (i.e., failure to capture) demonstrates a dangerously low safety margin for ventricular pacing because pacing pulse width should be at least three and generally four times the threshold for capture. After these five initial stimuli, Intermedics pacemakers then pace asynchronously at the programmed lower rate (70 in this case) for 60 additional cycles. On completion of these 64 cycles (65 stimuli), Intermedics pacemakers return to programmed values and ignore the magnet.

For all generators, calling the manufacturer remains the most reliable method of determining magnet response and using this response to predict remaining battery life (phone numbers for device manufacturers are shown in Appendix 2). As battery voltage falls, the magnet response can be used to detect the following:

IFI (Intensified follow-up required)—the device must be checked frequently (approximately every 4 weeks for most models).
ERI (Elective replacement indicator)—the device is nearing the end of its useful life and should be electively replaced.
EOL (End of life)—the device has insufficient battery power remaining and should be replaced immediately.

Upon application of a magnet, some devices perform a "threshold margin test" (TMT). In this test, one or more of the PM pulses are reduced in amplitude, pulse width, or both in an attempt to gauge the safety margin for pacing voltage. Loss of capture on these TMT pulses indicates an inadequate safety margin for pacing (Fig. 43-5). Some devices from St. Jude Medical (formerly Pacesetter) with the Siemens "Vario" feature will reduce the ventricular pacing energy over 16 cycles to demonstrate the pacing threshold. As a result, many pacing cycles can take place at insufficient energy for ventricular capture, which can produce periods of asystole while the magnet is applied.[40]

Occasionally, PM-mediated tachycardia (PMT) can ensue on removal of the magnet from a dual-chamber PM (Fig. 43-6). These PMTs result from retrogradely conducted P waves during asynchronous ventricular pacing, most commonly when the magnet rate is lower than the patient's intrinsic rate. These retrograde P waves are then "tracked" by a dual-chamber device (DDD, VDD modes only), which results in pacing at the UTR. Each paced ventricular cycle results in another retrograde P wave, thereby producing tachycardia. Should this behavior be observed, it can be subverted by reapplication and then removal of the magnet. Some devices can be programmed to recognize these PMTs and will periodically omit one ventricular pacing pulse or lengthen one AV delay cycle during UTR pacing.

In addition, as noted earlier, a patient with a dual-chamber device that has detected a rapid atrial rate and has "mode-switched" to prevent UTR pacing could have the mode switch reset upon application and removal of the magnet. These patients will then undergo UTR pacing until criteria are met to return to the mode-switch function. Distinguishing PMT caused by retrograde P waves from UTR pacing caused by rapid atrial rates (before mode-switch entry) can be very difficult. In general, though, mode switch secondary to rapid atrial rates will take place within 10 to 15 seconds, and PMT from retrograde P waves is quite persistent.

For generators with programmable magnet behavior (Boston Scientific/Guidant Medical/CPI, Pacesetter, St. Jude Medical, Telectronics, Biotronik), only interrogation with a programmer can reveal the current settings. Many manufacturers publish a generator reference guide, although not all of these guides list all magnet idiosyncrasies.

Preanesthetic Evaluation and Pacemaker Reprogramming

Preanesthetic management of a patient with a PM includes evaluation and optimization of coexisting disease (also see Chapter 34).

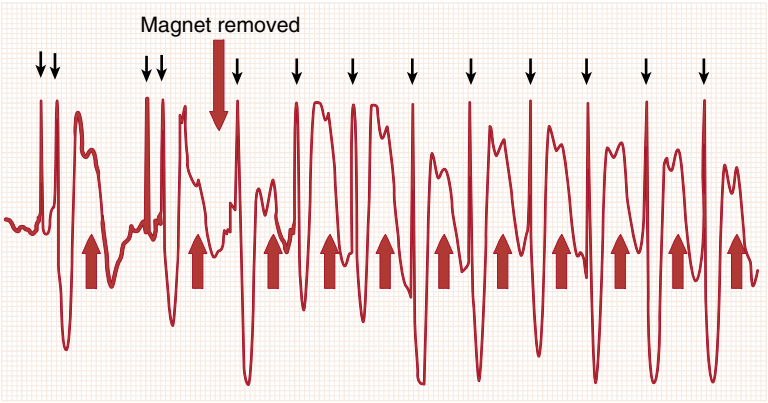


Figure 43-6 Pacemaker-mediated tachycardia (PMT) after removal of the magnet from a pacemaker. This patient had a dual-chamber pacemaker implanted for atrioventricular (AV) nodal disease, and she was pacemaker dependent for ventricular activity. She had a sinus rate of 75/min before application of the magnet with appropriate ventricular pacing (strip not shown). Her programmed AV delay is 200 msec. With magnet application, her pacemaker produced asynchronous AV sequential pacing (DOO mode) at a rate of 60/min. This strip is from an electrocardiographic recorder that enhances the pacemaker artifact with *black*, *downward arrows*. Because the asynchronous "magnet" rate of this device is lower than her intrinsic atrial rate, many of the atrial pacing stimuli were applied during an atrial refractory period (called functional noncapture). A consequence of atrial noncapture can be retrograde AV nodal conduction with depolarization of the atria after depolarization of the ventricle or ventricles. The retrograde P waves are shown with the *red upward arrows*. While the magnet is applied, this retrograde depolarization of the atria is ignored. Shortly after the magnet was removed (shown), there was a paced ventricular event, followed by retrograde AV nodal conduction. With the ensuing depolarization of the atria from this retrograde conduction, the pacemaker sensed an atrial event and responded by pacing the ventricle 200 msec later. Yet another retrograde P wave appears, and each pace in response to a retrograde P wave created yet another ventricular pace. The result is a PMT at the upper tracking rate (programmed here to 130/min) of the pacemaker. PMT from retrograde AV nodal conduction can occur in any DDD or VDD device with magnet removal, a premature ventricular contraction, or a noncaptured atrial pace. Treatment of this PMT should be reapplication of the magnet. Some pacemakers can be programmed to eventually delay one AV cycle when pacing at the upper tracking limit to "break" PMT.

ACC guidelines suggest that cardiac testing (stress tests, echocardiograms) be dictated by the patient's underlying disease, medications, symptomatology, interval from last testing, and planned intervention.[11]

No special laboratory tests or radiographs are needed for patients with a conventional PM. Chest films rarely depict lead problems, not all devices have radiographic markings, and a standard chest radiograph can exclude the generator or its markings. However, a patient with a BiV PM or ICD might need a chest film to document the position of the coronary sinus lead, especially if central line placement is planned. Currently, there are no data or guidelines regarding placement of a central line in the setting of a coronary sinus lead, and because these leads have no fixation, they might be more easily dislodged than a standard PM or ICD lead. In fact, in early studies, spontaneous dislodgement of the coronary sinus lead was detected in more than 11% of patients.[41,42]

Important features of preanesthetic device evaluation are shown in Appendix 1. Current NASPE and Medicare guidelines include telephone evaluation every 4 to 12 weeks (depending on device type and age) and at least one direct evaluation (i.e., device interrogation with a programmer) at least once per year.[7] In abstract form, Rozner and coauthors reported significant noncompliance with these guidelines in 161 consecutive patients, as well as the need to replace 5% of PMs preoperatively for battery depletion.[43] Telephone evaluation provides some assurance of battery longevity, but it does not provide rigorous evaluation of the pacemaking system. ACC guidelines recommend timely, preoperative interrogation of every PM.[11]

For current PMs, interrogation with a programmer remains the most reliable method for evaluating battery voltage, battery impedance, lead performance, and adequacy of the current settings. Special attention should be paid to patients from countries where PMs might be reused[44] because battery life (typically 5 to 7 years) might not be related to length of implantation in the current patient. For any PM with battery voltage less than 2.6 V or battery impedance (where available) greater than 3000 Ω, the company should be consulted about the possible need for elective replacement of the device before surgery.

Appropriate reprogramming (Box 43-3) is the safest way to avoid intraoperative problems, especially if monopolar "Bovie" electrosurgery will be used. Many PM manufacturers stand ready to assist with this task (see Appendix 2 for company telephone numbers). However, interrogation of any generator with or without reprogramming requires a medical prescription and supervision by an appropriately trained physician.[52] Hospital guidelines and policy should reflect the need for a competent physician to review and validate any care delivered by a company representative.

Reprogramming a PM to asynchronous pacing at a rate more rapid than the patient's underlying rate usually ensures that no oversensing during EMI will take place, thus protecting the patient. However, there is one case report involving a Telectronics device that would open its output circuitry (i.e., no pacing stimuli would be delivered) in the presence of high-voltage EMI.[53] Furthermore, at our institution we have observed two PMs in DOO mode decrease their rate during use of an ESU for monopolar coagulation, presumably because of high battery current drain.

Reprogramming a device *will not* protect the device from internal damage or reset caused by EMI. Additionally, setting a device to asynchronous mode causes the PM to ignore premature atrial or ventricular systoles, which could have the potential to create a malignant rhythm in a patient with significant structural compromise of the myocardium.[54]

In general, rate responsiveness and other "enhancements" ("afib" suppression [formerly dynamic atrial overdrive], hystere-

sis, managed ventricular pacing, sleep rate, AV search, and so on) should be disabled by programming to prevent misinterpretation of the cardiac rhythm.[46,55] Note that for many Guidant and CPI devices, Guidant Medical recommends increasing the pacing voltage to "5 V or higher" in any case in which an ESU will be used. Few cardiologists follow this recommendation, but there are reports of pacing threshold changes during both intrathoracic[56] and nonchest surgery,[57] as well as in patients with significant noncardiac acute disease.[58]

Special attention must be given to any device with a minute ventilation (bioimpedance) sensor (Box 43-4) because inappropriate tachycardia has been observed secondary to mechanical ventilation,[25,47] monopolar "Bovie" electrosurgery,[47,61,62] and connection to an electrocardiographic monitor with respiratory rate monitoring.[48-50,59,60,63] Sometimes this PMT has led to inappropriate, unsuccessful pharmacologic treatment of the tachycardia[25] with subsequent patient injury.[24]

Intraoperative (or Procedure) Management of Pacemakers

Although no special monitoring or anesthetic technique is required for a patient with a cardiac generator, attention must be given to a number of concerns (also see Chapters 40 and 60). First, electrocardiographic monitoring of a patient must include the ability to detect pacing discharges. Currently, most electrocardiographic monitors in both the operating room and the intensive care unit perform digital acquisition and analysis of electrocardiographic signals, and they are subject to considerable interference from a variety of sources.[64] In their default settings, these monitors often filter the pacing artifacts, and no pacing "spikes" will be shown. This filtering must be disabled so that the monitor will "paint" pacing spikes onto the display. Even with the filtering disabled, however, pacing artifacts do not always appear. Atrial signals are weak, and current monitors do a poor job detecting them. Moreover, because many digital monitors analyze only one lead for these signals (and then "paint on" artifacts on every lead), placement of the electrocardiographic leads can markedly affect the detection axis.* In practice, when a patient with known pacing is monitored, sometimes changing the "analysis" lead on the monitor will result in the appearance of pacing signals. Unfortunately, when the PM artifact filter is disabled, EMI, especially from use of a monopolar ESU, can lead to inappropriate "painting" of pacing artifacts on the monitor (Fig. 43-7).[65]

Second, patient monitoring must include the ability to ensure that paced electrical activity is converted to mechanical

Box 43-3 Situations Probably Requiring Pacemaker Reprogramming

Any rate-responsive device—see text (problems are well known[23,45] and have been misinterpreted with the potential for patient injury[46-49]; the Food and Drug Administration has issued an alert regarding devices with minute ventilation sensors[50]—see Box 43-4)

Special pacing indication (hypertrophic obstructive cardiomyopathy, dilated cardiomyopathy, pediatric patients)

Pacemaker-dependent patients

Major procedure in the chest or abdomen

Rate enhancements present that should be disabled

Special procedures (see text)

Lithotripsy

Transurethral resection

Hysteroscopy

Electroconvulsive therapy

Succinylcholine use

Magnetic resonance imaging (generally contraindicated by device manufacturers)[51]

In some situations and for certain patients, a pacemaker should be reprogrammed either to avoid potential patient injury or to prevent a pacemaker rhythm that could be confused with pacemaker malfunction.

Box 43-4 Pacemakers with Minute Ventilation (Bioimpedance) Sensors

ELA Medical
- Brio (212, 220, 222)
- Chorus RM (7034, 7134)
- Opus RM (4534)
- Rhapsody (2530)
- Symphony (2250, 2550)
- Talent (130, 213, 223)

Boston Scientific/Guidant Medical/CPI
- Pulsar (1172, 1272)
- Pulsar Max (1170, 1171, 1270)
- Pulsar Max II (1180, 1181, 1280)
- Insignia Plus (1194, 1297, 1298)

Medtronic
- Kappa 400 series (KDR401, KDR403, KSR401, KSR403)

Telectronics/St. Jude
- Meta (1202, 1204, 1206, 1230, 1250, 1254, 1256)
- Tempo (1102, 1902, 2102, 2902)

Pacemakers with minute ventilation (bioimpedance) sensors frequently respond to electromagnetic interference (EMI) with pacing at the upper sensor rate.[48,49] These tachycardias can also be produced by connection to an operating room electrocardiographic monitor because many of these devices inject electrical signals through the electrocardiographic leads to determine the respiratory rate or lead disconnection.[59,60] In 1998, the U.S. Center for Devices and Radiologic Health issued a safety alert calling for the deactivation of any minute ventilation (bioimpedance) sensor before exposing a patient to a potential source of EMI or connection to medical devices.[50]

*Most monitors manufactured since 2005 have much improved capability to detect and display pacing artifacts, although they still filter these high-frequency signals in their default setup mode.

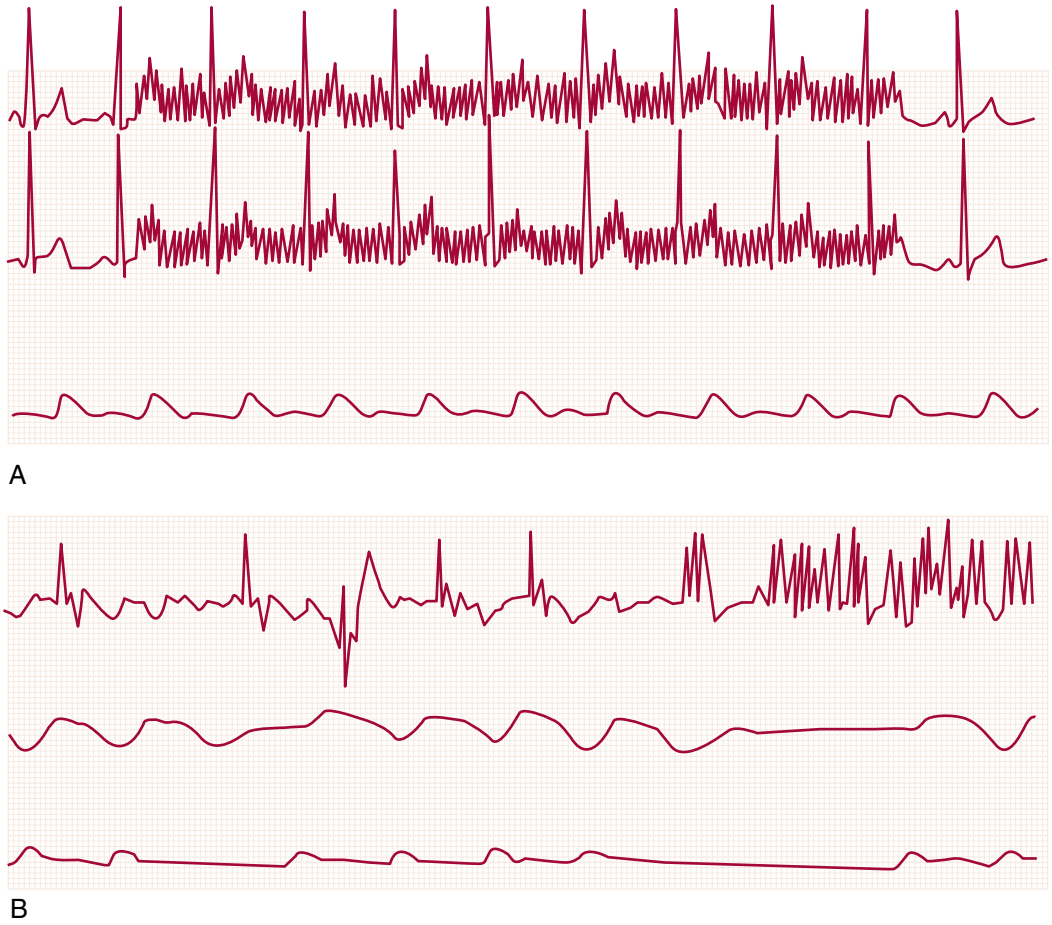


Figure 43-7 Disabling the pacemaker artifact filter on a digitally processed electrocardiographic monitor results in the "painting" of environmental noise (EMI) as pacemaker artifacts. **A,** Effects of "Cut" monopolar electrosurgical unit (ESU) application. Here, the patient's underlying rate exceeded the pacemaker's programmed lower rate limit, and no pacing took place. However, activation of the ESU in the "Cut" mode produced sufficient electromagnetic noise that the monitor began "painting" pacemaker artifacts at a rate of about 20 Hz. The *top tracing* is the electrocardiographic (ECG) lead II, the *middle tracing* is ECG lead V_5, and the *bottom tracing* is the invasive arterial pressure waveform. **B,** The effects of "Coagulation" ESU application produced ventricular oversensing with pacemaker inhibition and left this patient with compromised cardiac output. There is also evidence of inappropriate monitor "painting" of pacemaker artifacts from the EMI. The *top tracing* is ECG lead II, the *middle tracing* is the pulse oximeter plethysmogram, and the *bottom tracing* is the invasive arterial pressure waveform. *(From Rozner MA: Review of electrical interference in implanted cardiac devices. Pacing Clin Electrophysiol 26:923-925, 2003. Used by permission.)*

systole. Mechanical systole is best evaluated by pulse oximetry plethysmography, or arterial pressure waveform display.

Third, there remains limited published perioperative experience with intraoperative BiV pacing at this time. These patients often have ejection fractions of less than 30%, and they depend on pacing in both ventricles to improve their cardiac output. Loss of ventricular pacing from any cause (AV dyssynchrony [atrial fibrillation, atrial flutter, appearance of junctional rhythm], myocardial ischemia, acid-base disturbance, change in pacing threshold, ESU interference, etc.) can cause an immediate decrease in cardiac output. With the exception of transesophageal echocardiography, no beat-to-beat monitoring of cardiac output has demonstrated any utility in detecting loss of BiV pacing behavior. Patients with HOCM pacing can be dependent on ventricular pacing to limit LV outflow tract obstruction.

Fourth, some patients might need an increased pacing rate during the perioperative period to meet an increased oxygen demand. This subject is often not addressed. PM patients reportedly experience postoperative morbidity and mortality frequently,[66] and failure to address tissue oxygen demands and cardiac output needs might contribute to this problem.

Fifth, appropriate equipment must be on hand to provide backup pacing or defibrillation (or both) if needed. Cardiac generators, although hardy, occasionally perform some untoward maneuver or fail, even in the absence of EMI.[67] Acceptable, but inappropriate behavior of a PM or ICD can create an inhospitable situation. Even a properly working, dual-chamber PM can produce R-on-T pacing, especially in the setting of junctional rhythm or premature ventricular contractions (Fig. 43-8).

The medical team caring for a patient with an implanted cardiac pulse generator must understand that the patient has been deemed needy of this device by a physician who is an expert in the diagnosis and management of cardiac rhythm issues. Few anesthesiologists are qualified to contradict this diagnosis, yet some persist in providing an anesthetic without appropriate backup pacing and defibrillation equipment on hand.

Monopolar "Bovie" ESU use remains the principal intraoperative issue for patients with a PM. Between 1984 and 1997, the



Figure 43-8 Normal dual-chamber pacemaker timing can produce R-on-T pacing. **A,** This strip demonstrates functional ventricular undersensing of a premature ventricular contraction (PVC) with resultant R-on-T pace leading to torsades de pointes. This patient had a dual-chamber pacemaker in the DDD mode with a programmed lower rate of 70/min (R-R interval of 857 msec) and atrioventricular (AV) delay of 200 msec. With these parameters, the pacemaker will pace the atrium 657 msec after any previous ventricular event. Atrial pacing is labeled "A" and ventricular pacing is labeled "V." The *top tracing* is electrocardiographic (ECG) lead II, the *middle tracing* is ECG lead V_5, and the *bottom tracing* is the invasive arterial blood pressure waveform. Approximately 660 msec after the first QRS (1) on the strip (which was adequately sensed by the pacemaker), an atrial stimulus is emitted. At 200 msec after this atrial pace, a ventricular stimulus is emitted and appears to depolarize the ventricle (2). About 660 msec later (3), the patient experienced a PVC. Because the pacemaker was preparing to emit the atrial stimulus, it had disabled its ventricular sensing element and failed to sense this PVC (termed *functional undersensing*). At 200 msec after the atrial stimulus, no ventricular event had been sensed, so the pacemaker emitted a ventricular stimulus on the T wave. Because the ventricle was in a refractory period from the PVC, there was no depolarization of the ventricle (called *functional noncapture*). At 660 msec from this attempted V-pace, the pacemaker again paces the atrium (4), and it appears that the next V-pace captures the ventricle. At point 5 there is a repeat of the events at point 3; that is, the pacemaker disabled its sensing elements in preparation to pace the atrium and failed to detect the PVC. This time, however, the V-pace on the T wave produced torsades de pointes. **B,** This strip was obtained from a Medtronic programmer during interrogation of a Kappa 700 dual-chamber pacemaker. The *top tracing* is ECG lead II, and the *bottom tracing* is the "marker channel," which shows the pacemaker's interpretation of events. This pacemaker was programmed to the DDD mode with a lower rate of 60/min. The AV delay was 200 msec. As a result, after any ventricular event, the pacemaker will emit an atrial pulse at 800 msec if no intervening atrial or ventricular event takes place. This patient had a junctional rhythm at 75/min (corresponding to an R-R interval of 800 msec), so the pacemaker emitted an atrial pulse just as the junctional event occurred. Because the pacemaker disables its ventricular sensing element when emitting the atrial pulse, it failed to detect the ventricular event and emitted the ventricular pulse 200 msec later, on the T wave. This inappropriate pacing takes place every other cycle because every other junctional event is sensed around 600 msec after the previous ventricular pace. Decreasing the AV delay will decrease the likelihood of pacing during the vulnerable period of the ventricle. AP is an atrial pace, VP is a ventricular pace, and VS is a ventricular sensed event. The third complex deserves comment. The pacemaker sensed this ventricular event as it re-enabled its sensing element, and the pacemaker cannot tell whether the sensed event is a true ventricular depolarization or an "echo" of the atrial pace. When a signal from the ventricle is sensed within 30 to 90 msec after an atrial pace, many pacemakers immediately emit a ventricular pacing stimulus. Called a "ventricular safety pace," this pacing stimulus is designed to protect the patient from inappropriate sensing of the atrial signal by the ventricular channel, which would then inhibit the ventricular output. The safety pace is emitted at 110 msec to prevent R-on-T pacing. This feature is also called "nonphysiologic AV delay" by some manufacturers. R-on-T pacing can be appropriate (but not ideal) behavior of a DDD or DDI pacemaker in the setting of PVCs, as well as a junctional rhythm. It can also be seen with atrial or ventricular undersensing.

FDA was notified of 456 adverse events with pulse generators, 255 from electrosurgery, and a "significant number" of device failures.[68] A monopolar ESU is more likely to cause problems than a bipolar ESU, and PMs with a unipolar electrode configuration are more sensitive to EMI than those with bipolar configurations are.[69] The most common effect of an ESU on pacing function is ventricular oversensing, which causes pacing inhibition (see Fig. 43-7B). Sometimes the generator detects significant EMI and begins pacing asynchronously at the programmed lower rate. This behavior is called "noise reversion mode pacing," even though the PM does not actually change "modes." Noise reversion is not present in some ICDs and is programmable in others.

Magnet placement during electrosurgery might prevent aberrant PM behavior, and it might allow reprogramming of an older (pre-1990) generator. Note that some generators cannot be programmed in the presence of a magnet (for example, devices from Boston Scientific, Guidant, and CPI). Newer generators are believed to be relatively immune to spurious reprogramming as a result of EMI, although they can undergo a reset condition that will probably alter the programmed settings.[70]

If a monopolar ESU is to be used, the electrosurgical current-return pad (often misidentified as the "grounding pad") must be placed to ensure that the ESU current path does not cross the pacemaking system. Some authors recommend placement of this pad on the shoulder for head and neck procedures or on the distal part of the arm (with sterile draping of the wire) for breast and axillary procedures.[69,71] Procedures using only a monopolar ESU or with special EMI pacing ramifications include the following:

Lithotripsy—The cardiac generator must be excluded from the lithotripter field. If the lithotripter triggers its output on the sensed electrocardiographic "R" wave, atrial pacing should be disabled to prevent the lithotripter from inappropriately firing on the atrial pacing artifact (also see Chapter 65).

Transurethral Resection and Uterine Hysteroscopy—Transurethral resection of the bladder or prostate and hysteroscopic procedures generally use a monopolar ESU, and device reprogramming might be needed to prevent PM oversensing with resultant PM inhibition. A resectoscope that includes the current-return electrode on the shaft (the irrigation medium will be normal saline) might limit EMI to the generator but has not been carefully tested in this environment (also see Chapter 65).

Magnetic Resonance Imaging (MRI)—Without special care, MRI is contraindicated by most device manufacturers, and deaths have been reported. According to physicians' manuals from most manufacturers, MRI might lead to magnet switch closure (magnet mode activation), reprogramming, inappropriate high-rate pacing, generator damage, myocardial injury, or generator movement within the pocket causing pain, lead failure, or arrhythmia. Nevertheless, safe performance of MRI in qualified patients with PMs and ICDs has been reported[72,73] (also see Chapter 79).

Electroconvulsive Therapy—Electroconvulsive therapy might require a nonsensing (asynchronous) mode to prevent myopotential-induced oversensing with resultant PM inhibition.[74]

Nerve Stimulator Testing/Therapy—Nerve stimulators can cause PM oversensing with resultant PM inhibition[75] and cardiac arrest.[76] Nerve stimulators have been used intraoperatively to inhibit undesired cardiac pacing[23] or arrest the cardiac rhythm for placement of an endovascular stent.[77] In patients with an ICD, inappropriate detection of neuromuscular stimulators, transcutaneous electrical nerve stimulation, and chiropractic electrical muscle stimulation as ventricular tachycardia (VT) or ventricular fibrillation (VF) has been reported.[78,79] Nerve stimulators can also interfere with electrocardiographic monitoring of PM artifacts.[65] Like ESU current, the electrical path for nerve stimulator current should not cross the generator system or the chest[80] (also see Chapter 47).

Succinylcholine or Etomidate Use—Reports of myopotential problems on administration of succinylcholine[81] or etomidate[82] have been published. In the case of succinylcholine, muscle fasciculations might have caused ventricular oversensing with resultant PM inhibition, but this report is difficult to interpret. No electrocardiographic tracings were published, and the PM was damaged during a subsequent defibrillation. Using programmers, I have witnessed succinylcholine administration to more than 50 patients with PMs or defibrillators without finding any myopotential oversensing. The etomidate issue is also not clear because there were other issues with the particular PM.[83] However, myopotential oversensing (in the absence of succinylcholine) has been observed to interfere with PM function[84] or cause inappropriate ICD therapy[85] (also see Chapter 29).

Pacemaker Failure

PM failure has three causes: generator failure, lead failure, or failure of capture. Generator failure is rare in a device that has previously been evaluated and not near the end of useful battery life, unless the generator (or leads) is struck directly by the ESU. Lead failure, also unusual but reported during patient repositioning,[86] can result in undersensing (intrinsic activity is not detected), oversensing ("detection" of events unrelated to intrinsic activity), or failure to deliver sufficient energy to the myocardium to produce depolarization (termed loss of capture). Myocardial changes that lengthen the refractory period or increase the energy requirement for depolarization (failure to capture) can result from myocardial ischemia/infarction, acid-base disturbance, electrolyte abnormalities, or abnormal antiarrhythmic drug levels.

The response to PM failure depends on the clinical situation: a patient with a perfusing rhythm and stable vital signs can be observed while a plan is made to correct the problem. For a patient with inadequate perfusion, the following steps can be attempted (while cardiopulmonary resuscitation is in progress when appropriate):

1. A magnet can be applied if the PM is known to revert to an asynchronous mode, which will also eliminate sensing behavior in these devices. For many of the St. Jude Autocapture devices with magnet mode enabled, magnet application might increase pacing amplitude and restore capture. Devices from ELA Medical (Denver, CO) typically increase their pacing amplitude when a magnet is applied. Some PMs perform threshold margin testing upon magnet placement, which can further reduce pacing.[38]

2. Temporary pacing can be initiated, and it can be transthoracic (transcutaneous), transvenous, or transesophageal. Transesophageal (atrial) pacing requires a functional atrium and AV node for ventricular activation, so it is contraindicated in patients with atrial fibrillation or flutter. It is also generally contraindicated in the presence of a permanent PM (or ICD).

In the setting of external pacing, the electrocardiogram can be misinterpreted because the PM artifacts are large in comparison to the QRS complexes (Fig. 43-9A). Successful ventricular pacing has been reported with transesophageal PMs, but it remains unreliable[87] and produces inferior hemodynamics when compared with atrial pacing (Fig. 43-9B). Note that any external pacing might further

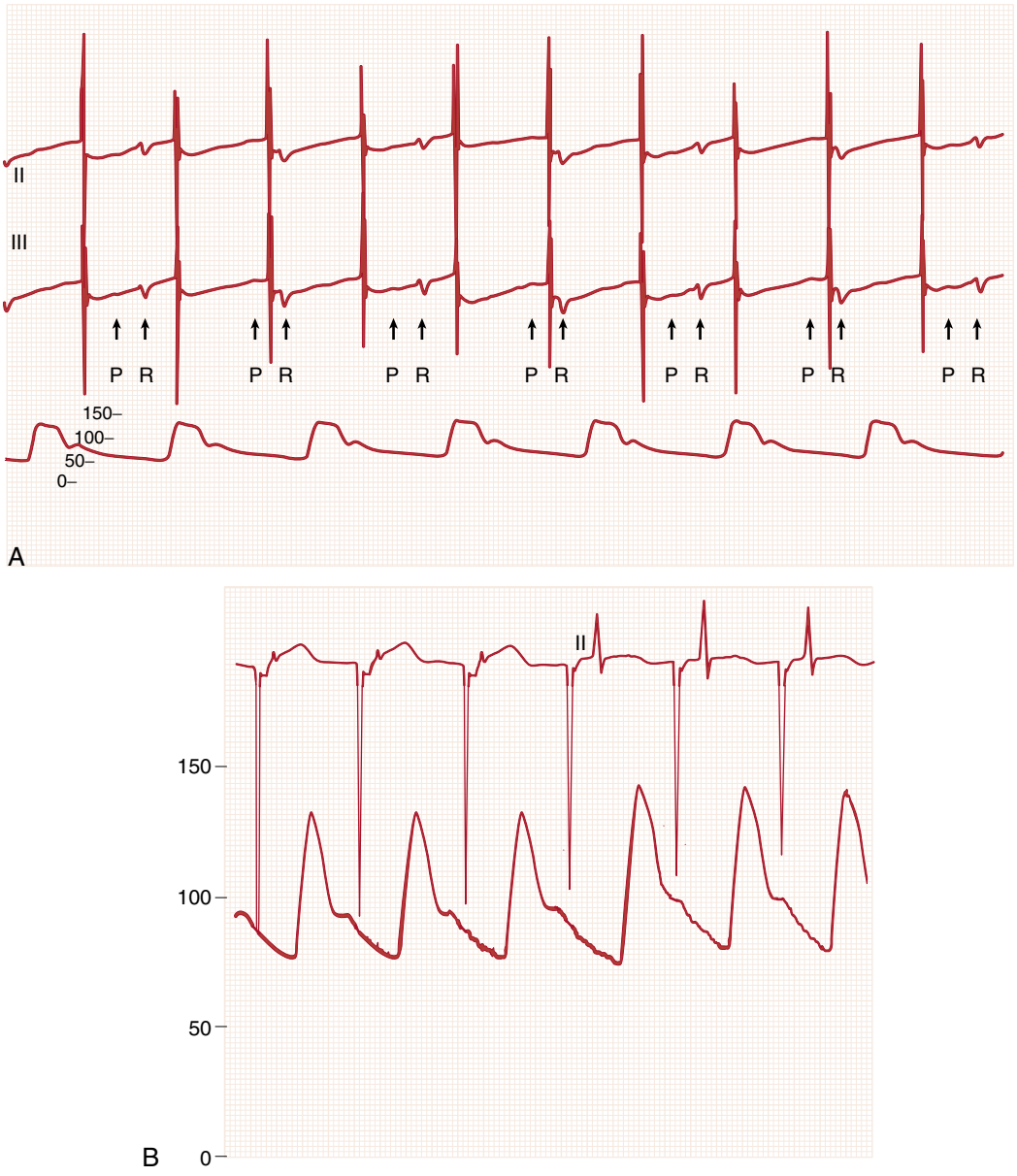


Figure 43-9 Issues with a transesophageal atrial pacemaker (TAP). **A,** Improper placement of a TAP demonstrating atrial noncapture. The *top recording* is electrocardiographic (ECG) lead II, the *middle recording* is ECG lead III, and the *bottom recording* is the invasive arterial pressure waveform. Sinus bradycardia with evidence of tissue underperfusion developed in this 72-year-old man. A TAP (CardioCommand, Tampa, FL) was placed, and the large ECG artifacts at 75/min were misinterpreted by personnel and the ECG monitor as ventricular systoles (capture). This patient has a sinus rate of 50/min with a first-degree atrioventricular block (PR interval of 280 msec). The patient's native atrial (P) and ventricular (R) depolarizations are noted. The arterial pressure waveform confirms pacing noncapture. **B,** Direct ventricular activation with a transesophageal pacemaker. The *top recording* is ECG lead II, and the *bottom recording* (enhanced vertical scale) is the invasive arterial pressure waveform. This strip is from an obese 61-year-old woman with diabetes and hypertension undergoing transsphenoidal hypophysectomy. Shortly after induction, sinus bradycardia at 37 beats/min and mild hypotension developed. A transesophageal pacemaker was placed but advanced too far into the esophagus. This strip was recorded during "pullback." The ventricle was directly activated in the first four events, with a resultant wide-complex QRS and average blood pressure of 135/75 mm Hg. On pullback, the atrium was activated, the QRS returned to a narrow complex, and blood pressure increased to 143/80 mm Hg. Except for the bradycardia, this patient had a normal heart and did not have a permanently placed generator.

inhibit PM output at energies that will not produce myocardial capture.[88]

3. Sympathomimetic drugs can decrease depolarization threshold or increase chronotropicity (or both). Epinephrine (0.5 to 1 μg/min) or dopamine (5 to 20 μg/kg/min) should be considered. Isoproterenol (0.5 μg/min) is often recommended but not widely available and is complicated by hypotension. Antimuscarinic drugs (atropine, glycopyrrolate) might be helpful.
4. Causes of myocardial ischemia should be sought and corrected. Myocardial ischemia can substantially increase the energy required for ventricular capture.[89]
5. Disturbances in electrolyte balance, antiarrhythmic drug levels, and acid-base equilibrium should be investigated and corrected. Potassium, calcium, and magnesium abnormalities can raise depolarization thresholds. In addition, potassium flux, ionized calcium levels, and acid-base equilibrium can be affected by hyperventilation and hypoventilation.
6. If none of the measures just presented succeed, consideration should be given to placement of epicardial leads by the surgical staff.

Postanesthesia Pacemaker Evaluation

A PM that was reprogrammed for the perioperative period should be reset appropriately. For non-reprogrammed devices, most manufacturers recommend interrogation to ensure proper functioning and acceptable remaining battery life if any electrosurgery was used. The ACC guidelines now recommend a postprocedure interrogation (also see Chapter 85).[11] Consideration should be given to increasing the lower paced rate in a chronotropically incompetent patient if increased cardiac output will benefit the patient during convalescence.

Implantable Cardioverter-Defibrillators

The development of an implantable, battery-powered device able to deliver sufficient energy to terminate VT or VF represents a major medical breakthrough for patients with a history of ventricular tachydysrhythmias. These devices reduce deaths in the setting of malignant ventricular tachydysrhythmias,[90,91] and they clearly remain superior to antiarrhythmic drug therapy.[92] Initially approved by the FDA in 1985, more than 60,000 devices will be implanted in the United States this year, and industry sources report that more than 250,000 patients have these devices today. Furthermore, results from the Sudden Cardiac Death–Heart Failure Trial (SCD-HeFT—showing that prophylactic placement of an ICD is superior to drug therapy in any patient with an ejection fraction less than 0.35 and *without* evidence of arrhythmic inducibility) have led to a significant increase in the number of patients for whom ICD therapy is indicated.[93]

A considerable number of technologic advances have been applied since the first ICD was placed, including substantial miniaturization (pectoral pocket placement with transvenous leads is the norm), as well as battery improvements that now permit permanent pacing with these devices. Thus, one could easily confuse a pectoral ICD for a PM.

Table 43-3 NASPE/BPEG Generic Defibrillator Code (NBD)

Position I: Shock Chambers(s)	Position II: Antitachycardia Pacing Chamber(s)	Position III: Tachycardia Detection	Position IV: Antibradycardia Pacing Chamber(s)*
O = none	**O** = none	**E** = electrogram	**O** = none
A = atrium	**A** = atrium	**H** = hemodynamic	**A** = atrium
V = ventricle	**V** = ventricle		**V** = ventricle
D = dual (A + V)	**D** = dual (A + V)		**D** = dual (A+V)

The NBD code is a joint project from the North American Society of Pacing and Electrophysiology (NASPE) (the "N") and the British Pacing and Electrophysiology Group (BPEG) (the "B").[94] The "D" stands for defibrillator.
*For robust identification, position IV is expanded into its complete NBG code. For example, a biventricular pacing-defibrillator with ventricular shock and antitachycardia pacing functionality would be identified as VVE-DDDRV, assuming that the pacing section was programmed DDDRV. Currently, no hemodynamic sensors have been approved for detection of tachycardia (position III).

Like PMs, ICDs have a four-place generic code (NBD*) to indicate lead placement and function, as shown in Table 43-3.[94] The most robust form of identification, called the "label form," expands the fourth character into its component generic PM code (NBG).

Newer ICDs (since 1993) have many programmable features, but essentially they measure each cardiac R-R interval and categorize the rate as normal, too fast (short R-R interval), or too slow (long R-R interval). When the device detects a sufficient number of short R-R intervals within a certain period (all programmable), it will begin an antitachycardia event. The internal computer will choose ATP (less energy use, better tolerated by patient) or shock, depending on the manifestation and device programming. If shock is chosen, an internal capacitor is charged. Charging time is dependent on the desired output, and it can be 6 to 15 seconds for a maximum shock. Charging time is lengthened by lower battery voltage, time from last charge,† and lower temperature.

Most ICDs can be programmed to "reconfirm" VT or VF after charging to prevent inappropriate shock therapy. Some ICDs can be programmed to begin ATP immediately on initiating a charge cycle. Typically, ICDs deliver 6 to 18 shocks per event. Once a shock is delivered, no further ATP will take place. Despite considerable improvement in detection of ventricular dysrhythmias, more than 10% of shocks are for rhythms other than VT or VF.[95,96] Supraventricular tachycardia (SVT) remains the most common etiology of inappropriate shock therapy,[97,98] and causes of inappropriate shock have been reviewed elsewhere.[99] Program-

*The NBD code is a joint project from the NASPE (the "N") and the BPEG (the "B"). The "D" stands for defibrillator.

†The capacitor in an ICD "deforms" during inactivity, which leads to increased time needed to charge the capacitor. To mitigate the effects of deformation, all ICDs perform nontherapeutic charging of their capacitor (called "reforming") at a programmable periodic interval (usually 1 to 6 months).

mable features in current ICDs to differentiate VT from a tachycardia of supraventricular origin (SVT) include the following[100]:

1. Onset criteria—in general, the onset of VT is abrupt, whereas the onset of SVT has a sequentially shortening R-R interval.
2. Stability criteria—in general, the R-R interval of VT is relatively constant, whereas the R-R interval of atrial fibrillation with rapid ventricular response is quite variable.
3. QRS width criteria—in general, the QRS width in SVT is narrow (<110 msec), whereas the QRS width in VT is wide (>120 msec).
4. "Intelligence" in dual-chamber devices attempting to associate atrial activity with ventricular activity.
5. Morphology waveform analysis with comparison to stored historical templates.

Note that once the R-R interval becomes sufficiently short for detection of VF, most ICDs will begin a shock sequence. As noted earlier, once the device delivers any shock therapy, no further ATP will take place.

An ICD with antibradycardia therapy capability will begin pacing when the R-R interval is too long. In July 1997, the FDA approved devices with sophisticated dual-chamber pacing modes and rate-responsive behavior for ICD patients who need permanent pacing (about 20% of ICD patients). Because of the DAVID study, which suggested that DDD pacing in a patient without a clear need for dual-chamber pacing decreases survival when compared with single-chamber device placement,[101] many electrophysiologists are programming long (>250 msec) AV delays in these patients to limit ventricular pacing. As noted previously, however, long AV delays can lead to R-on-T pacing (see Fig. 43-8A). In addition, many ICD manufacturers have designed algorithms to limit ventricular pacing. Some of these algorithms allow dropped QRS events, which can resemble a second-degree Mobitz II block or malfunction of the pacing system.

ICD Indications

Initially, ICDs were placed for hemodynamically significant VT or VF (Box 43-5). Newer indications associated with sudden death include patients awaiting heart transplantation[102] and those with long QT syndrome,[103] Brugada syndrome (right bundle branch block, ST-segment elevation in leads V_1 to V_3), and arrhythmogenic RV dysplasia.[104,105] Studies suggest that ICDs can be placed prophylactically (i.e., used for primary prevention) to prevent sudden death in young patients with hypertrophic cardiomyopathy,[106] as well as in post–myocardial infarction patients with an ejection fraction less than 30%,[93] but they are of no benefit after coronary artery bypass grafting. Three-chamber ICDs have been approved by the FDA for patients with DCM, and ICDs are in clinical trial for patients with HOCM who have experienced VT or VF.

Box 43-5 Indications for Implantable Cardioverter-Defibrillators

Ventricular tachycardia

Ventricular fibrillation

Brugada syndrome (right bundle branch block, ST-segment elevation in V_1 to V_3)

Arrhythmogenic right ventricular dysplasia

Long Q-T syndrome

Hypertrophic cardiomyopathy

Prophylactic use in a patient who has a cardiomyopathy (CM) without electrophysiologic testing to justify placement: MADIT II (ejection fraction [EF] <30%, ischemic CM),[93] MUSTT (EF <40%, ischemic CM with unsustained ventricular tachycardia),[92] SCD-HeFT (EF <35% and causing CM).[3]

ICD Magnets

Like PMs, magnet behavior in ICDs can be altered by programming. Most devices will suspend tachydysrhythmia detection (and therefore therapy) when a magnet is appropriately placed to activate the magnet switch. Some devices from Angeion, Boston Scientific, CPI, Guidant, Pacesetter, St. Jude Medical, or Ventritex can be programmed to ignore magnet placement, and some Guidant ICDs have had their magnet function permanently disabled because of a magnet switch issue (e.g., see Fig. 43-3).[8]

Depending on programming, antitachycardia therapy in some Boston Scientific/Guidant Medical/CPI devices can be permanently disabled by magnet placement for 30 seconds, and as noted earlier, some patients have been discovered with their ICD antitachycardia therapy unintentionally disabled.[4,5] In Boston Scientific/Guidant Medical/CPI devices, if the magnet mode is enabled and the ICD is enabled for antitachycardia therapy, the ICD will emit beeps synchronized to R waves to signify adequate placement of the magnet and suspension of tachyarrhythmia detection (hence disabling therapy). If the ICD emits a constant tone, antitachycardia therapy has been programmed to "off," regardless of magnet placement. Depending on programming, ICDs from Boston Scientific/Guidant Medical/CPI can toggle between activated and inactivated states with 30 seconds of magnet application. Thus, to re-enable therapy, the magnet must be removed and then replaced until the constant tone reverts to beeps synchronized to R waves. Subsequent removal of the magnet then returns the antitachycardia therapy to the enabled state. Any Boston Scientific/Guidant Medical/CPI device that emits either beeps or constant tones while a magnet is placed will have its antitachycardia therapy disabled during the magnet session.

To ensure correct magnet placement on its devices, Medtronic marketed a device called the "Smart Magnet." Manufacturing ceased around 2005 because not many were sold. This battery-powered instrument contains a magnet and a radiofrequency (RF) receiver. All Medtronic generators broadcast RF destined for the programmer on magnet placement, and the Smart Magnet detects this RF transmission and illuminates the "found" light when an ICD is under the magnet. Medtronic recommends that the Smart Magnet be taped to the patient. Note that during the occurrence of EMI, transmission from the ICD to the Smart Magnet can be interrupted, and the ICD "found" light often turns off. In this setting, though, the ICD remains disabled because it is the physical presence of the magnet rather than the RF communication that disables the antitachycardia therapy.

In general, magnets will not affect ICD antibradycardia pacing mode or rate (except ELA [rate change] and Telectronics

Guardian 4202/4203 [disabled]). Intermedics devices transiently change the pacing rate (VVI mode) to reflect battery voltage. Interrogating the device and calling the manufacturer remain the most reliable method for determining magnet response.

Preanesthetic Evaluation and ICD Reprogramming

In addition to evaluating and optimizing any comorbid disease in ICD patients, I believe that every ICD should undergo preoperative interrogation. These devices store considerable data regarding the occurrence of dysrhythmias. Because ATP is well tolerated, most patients are not aware of this intervention. For any patient scheduled to undergo an elective procedure, the onset of new dysrhythmias probably warrants investigation of the problem before the procedure (Fig. 43-10).

Determination of the need for elective replacement of an ICD because of battery depletion is more complicated than with PMs. Because some ICDs can have multiple battery cells, predicting battery depletion based on battery voltage is difficult. In general, however, the manufacturer should be consulted for any device with a "charging time" in excess of 12 seconds.

Most ICDs should have their antitachycardia therapy disabled before the use of any device that causes EMI. Use of a monopolar ESU can produce inappropriate shocks. Casavant and associates found a stored electrogram sequence in an ICD suggesting that it had misinterpreted use of a monopolar ESU during dermatologic facial surgery as VF,[107] and Figure 43-11 shows VT detection that occurred during surgery. Additionally, there is one report of a central line guidewire interacting with the RV lead that led to a short-circuit shock and subsequent failure of the ICD.[108]

The comments in the pacing section (including Appendix 1 and Box 43-3) apply here for any ICD with antibradycardia pacing. Many ICDs have no noise reversion behavior, so ESU-induced ventricular oversensing might lead to nonpacing in a patient who is dependent on the ICD for pacing.

Intraoperative (or Procedure) Management of ICDs

At this time, no special monitoring (because of the ICD) is required for a patient with an ICD. Electrocardiographic monitoring and the ability to deliver external cardioversion or defibrillation must be present during the time of ICD disablement. Should cardioversion or defibrillation be needed, the defibrillator pads should be placed so that they avoid the pulse generator to the greatest extent possible. Nevertheless, one should remember that the patient, not the ICD, is being treated. The recommendations in the section "Intraoperative (or Procedure) Management of Pacemakers" apply here as well.

No special anesthetic techniques have been championed for patients with an ICD. Most of these patients will have severely depressed systolic function, dilated ventricular cavities, and significant valvular regurgitation. Thus, the choice of anesthetic technique should be dictated by the underlying physiologic derangements that are present. Conflicting data have been published regarding the choice of anesthetic agent or agents and changes in defibrillation threshold (DFT). In 1993, Gill and coworkers examined DFT in dogs and concluded that neither halothane nor isoflurane changed the DFT in open chest defibrillation when compared with pentobarbital infusion.[109] However, Weinbroum and associates evaluated DFTs in humans during ICD implantation and found that halothane, isoflurane, and fen-

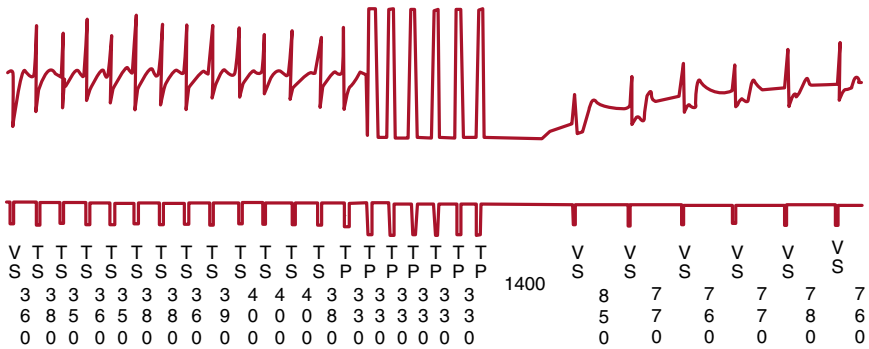


Figure 43-10 Unexpected ventricular tachycardia (VT) with antitachycardia pacing was found in this patient during her preoperative visit. A 65-year-old woman with a history of VT had undergone implantation of a Medtronic single-chamber defibrillator about 8 months previously. She had not had any dizziness or syncopal episodes since placement of an implantable cardioverter-defibrillator (ICD). Interrogation of her device in the preoperative center revealed VVE-VVI programming, along with an episode of tachycardia at 150 to 162 beats/min that was detected by the ICD as VT. The ICD delivered a six-beat burst of antitachycardia pacing at 182 beats/min, which converted the tachycardia back to sinus rhythm. No backup pacing was needed after the VT was terminated. The *upper tracing* is a digitized ventricular electrogram that was stored in the ICD during the tachycardic event. The *lower tracing* is the "marker channel," which reports the interpretation of each event by the ICD. The numbers below the marker channel represent the interval (in milliseconds). The rate is calculated by dividing the interval into 60,000 msec/min. TD marks the final event that starts therapy, TS represents an interval in the VT zone, TP is an antitachycardia pace event, and VS is an intrinsic ventricular depolarization with a rate that is neither too fast (short interval) nor too slow (long interval). This device was set to detect VT as 16 consecutive ventricular events with a rate between 146 and 200 per minute and to deliver antitachycardia pacing at 84% of the last R-R interval (the last interval was 400 msec, so antitachycardia pacing was delivered at a rate of 182/min (330 msec).

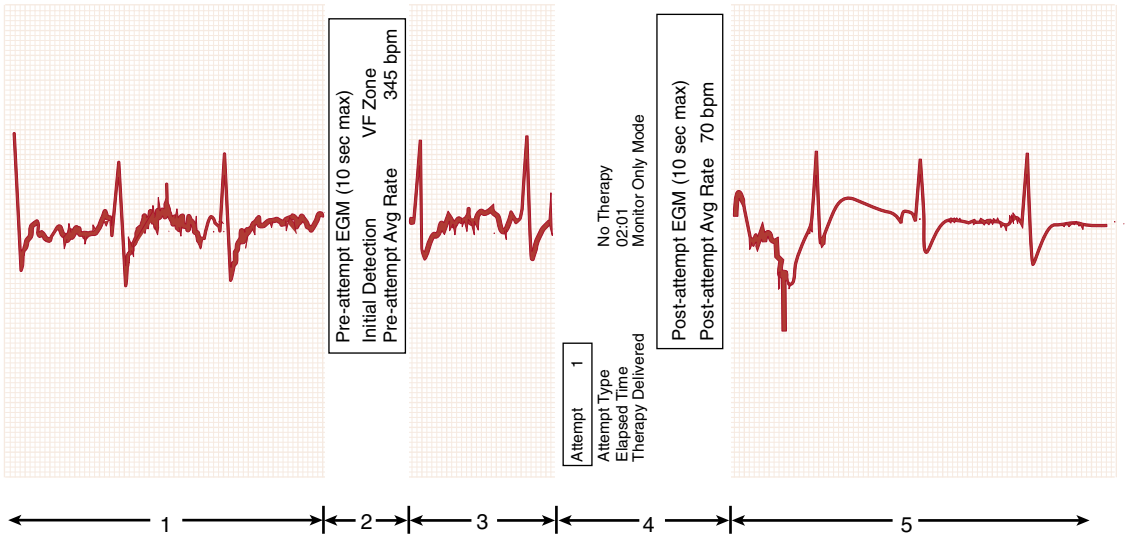


Figure 43-11 Electromagnetic interference (EMI) from the monopolar electrosurgery unit (ESU; "Bovie") caused an implantable cardioverter-defibrillator (ICD) to detect ventricular fibrillation (VF). This stored electrogram (EGM) was one of 73 found at the end of a 4-hour surgical procedure in which considerable monopolar electrosurgery was used. This patient had a Guidant Medical ICD in the VOE-VVI mode. The patient's ICD had been placed in a "monitor only" mode before surgery. As a result, the ICD recorded any instance of ventricular dysrhythmia that would have triggered therapy, but it could not actually deliver therapy. From left to right, (1) the EGM demonstrates a ventricular rate of 70/min, but with considerable noise on the baseline; (2) a VF event was declared for the detected heart rate of 345/min, and the ICD charged its capacitor; (3) the ICD was programmed to "reconfirm before shock," and the ventricular rate remains 70/min with noise on the baseline; (4) again, the noise caused the ICD to believe that the patient remained in VF, and the ICD would have delivered a shock, except that it was programmed to "monitor only"; and (5) because the noise is gone (the ESU had stopped), the ICD declares the event over after "successful" defibrillation.

tanyl increased the DFT.[110] Even with these increases, though, the increased DFTs were still substantially lower than the maximum energy generally available in ICDs, and these increases would not have been noted under the usual testing conditions.

Postanesthesia ICD Evaluation

The ICD must be reinterrogated and re-enabled, and deaths from failure to re-enable an ICD have been reported.[5] All recorded events should be reviewed and counters should be cleared. The pacing parameters must be checked and reprogrammed as necessary.

Summary

Electronic miniaturization has permitted the design and use of sophisticated electronics in patients who have need for artificial pacing or automated cardioversion/defibrillation of their heart. These devices are no longer confined to merely keeping the heart beating between a minimum rate (pacing function) and a maximum rate (ICD functions); they are now being used as therapy to improve a failing heart.

Both aging of the population and our ability to care for a patient with increasingly complex disease suggest that we will be caring for many more patients with these devices, and we must be prepared for this situation. Safe and efficient clinical management of these patients depends on our understanding of implantable systems, indications for their use, and the perioperative needs that they create.

Glossary

Afib Suppression (formerly Dynamic Atrial Overdrive)—A programmable rate enhancement for PMs that increases the pacing rate in response to the presence of intrinsic atrial activity. Afib suppression is designed to pace the atrium at a rate just above the intrinsic rate to prevent atrial fibrillation.[111] It should be disabled before an anesthetic to prevent high pacing rates.

Atrioventricular Delay—The time that a dual-chamber system waits after detecting (or initiating) an atrial event before pacing the ventricle. Some generators shorten this time as the heart rate increases (termed "rate-adaptive AV delay" or "dynamic AV delay"). Some generators can be programmed to extend the AV delay to search for intrinsic conduction ("search AV delay"). Some generators will prolong an AV delay after any atrial event when the last ventricular event was intrinsic ("AV delay hysteresis"). In a patient with a conducting AV node, the sensed AV delay will be slightly longer than the "PR" interval on the surface electrocardiogram (see Fusion Beat and Pseudofusion Beat) because the ventricular sensing element is attached to the apex of the right ventricle and the depolarization takes place only after RV activation (typically >60 msec after activation of the AV node).

Automatic Rate—see Lower Rate Limit.

Bipolar Lead—An electrode with two conductors. Bipolar pacing typically uses less energy than unipolar pacing does, and it will produce smaller artifacts on analog monitors. Bipolar sensing is more resistant to oversensing from muscle artifact or stray electromagnetic fields. Most pacing generators can be programmed to a unipolar mode (separate settings for pacing and sensing), even in the presence of bipolar electrodes.

Electrogram Storage Mode (EGM Mode)—Passive acquisition and internal storage of electrocardiographic data for diagnostic purposes while pacing (or monitoring) with programmed parameters. A PM programmed to enter the EGM mode on application of a magnet will not demonstrate asynchronous pacing behavior.

Fusion Beat (FB)—A PM spike delivered shortly before native depolarization of the ventricle that alters the morphology of the QRS, often misdiagnosed as undersensing. With an FB, the pacing stimulus is delivered after activation of the AV node, but before the sensing element detects the PM-induced depolarization. It is similar to pre-excitation of the ventricle seen in Lown-Ganong-Levine syndrome or Wolff-Parkinson-White syndrome. Confirmation of appropriate sensing behavior can be made by lengthening the sensing interval (i.e., lengthening the AV delay). Fusion beats suggest, but should not be used to confirm ventricular capture. See also Pseudofusion Beat.

Generator—Device with a power source and circuitry to produce an electrical impulse designed to be conducted to the heart. Typically, pacing generators are placed in a pectoral pocket, and leads are inserted into the right atrium, right ventricle, or both. Since 1995, however, ICDs have also been approved for pectoral pocket placement.

Hysteresis—If present, the amount by which the patient's intrinsic rate must fall below the programmed rate before the generator begins pacing. Some pacers periodically decrease the pacing rate to search for resumption of intrinsic activity (called "search hysteresis"). These functions, when present, can mimic PM malfunction.

Implantable Cardioverter-Defibrillator (ICD) Mode—Designation of chambers shocked, chambers paced for antitachycardia pacing, method of tachycardia detection, and chambers paced for antitachycardia therapy. Table 43-3 shows the NASPE/BPEG generic ICD code.

Lower Rate Limit (LRL, also **Automatic Rate** or **Programmed Rate**)—The lowest sustained regular rate at which the generator will pace. Typically, the device begins pacing when the patient's intrinsic rate falls below this value.

Oversensing—Detection of undesired signals that are interpreted as cardiac activity. Oversensing can lead to PM-driven tachycardia (pacing device, DDD mode with atrial oversensing and ventricular tracking), ventricular pause (pacing device with electrosurgically induced ventricular oversensing leading the pacer to "detect" ventricular activity), or inappropriate shock (defibrillator, event oversensing).

Pacing Mode—The designation of chambers paced, chambers sensed, sensing response, rate responsiveness, and antitachyarrhythmia function for a PM system. Table 43-1 shows the NASPE/BPEG generic PM code.

Programmed Rate—see Lower Rate Limit

Pseudofusion Beat (PFB)—A PM spike delivered shortly after native depolarization without alteration of the QRS morphology. PFBs are often misdiagnosed as undersensing, and they result from the position of the sensing electrode relative to the depolarizing wave front (see "Fusion Beat"). Confirmation of appropriate sensing behavior can be achieved by lengthening the sensing interval (i.e., decreasing the program rate [atrial FB] or lengthening the AV delay [ventricular PFB]). PFB cannot be used to confirm electronic capture.

Rate Enhancements—Features such as rate-adaptive AV delay (shortens the AV delay with increasing heart rate), AV search hysteresis (lengthens/shortens the AV delay to produce intrinsic AV conduction), suppression of atrial fibrillation (also called dynamic atrial overdrive—increases the lower rate on appearance of native atrial depolarization so that nearly constant atrial pacing is produced but at a rate only slightly higher than the patient's intrinsic rate), rate smoothing (limits changes in ventricular paced rates caused by changes in atrial rates; rising and falling rate limits can be programmed), sleep rate (see later), ventricular rate regulation (similar to rate smoothing but used to prevent atrial fibrillation), and hysteresis (see earlier). Each of these enhancements can produce pacing/nonpacing that can mimic PM dysfunction, and these enhancements should be programmed "OFF" before delivery of any anesthetic.

Rate Modulation—The ability of the generator to sense the need to increase the heart rate in response to patient activity. Mechanisms include (1) a mechanical sensor in the generator to detect motion or vibration, (2) electronic detection of the QT interval (shortens during exercise), (3) transthoracic impedance to measure changes in respiration, and (4) a sensor or sensors for central venous blood temperature or oxygen saturation (see Box 43-1). Some generators now incorporate multiple sensors. The pacing rate determined by the rate modulation algorithm is called the "Sensor Indicated Rate."

Sensor Indicated Rate—The pacing rate determined by the sensor in a PM programmed to a rate-responsive mode (the fourth character of NBG = "R").

Sleep Rate (also **Circadian Rate**)—The rate (lower than the Programmed Rate) at which the pacing generator will pace during programmed "nighttime" hours.

Undersensing—Failure to detect a desired event.

Unipolar Lead—An electrode with only one conductor. Some devices with bipolar leads are programmed to the unipolar lead mode. Systems with unipolar leads produce larger spikes on the electrocardiogram than bipolar leads do. Systems with unipolar leads use the generator case as the second conductor.

Upper Sensor Rate (**USR**, also **Upper Activity Rate** [**UAR**])—The maximum rate to which a rate-modulated PM can drive the heart. The USR is not affected by the UTR because when the USR becomes active, the PM is pacing the atrium.

Upper Tracking Rate (**UTR**, also called **Upper Rate Limit** [**URL**])—PMs programmed to the VDD or DDD mode cause the ventricles to track atrial activity. Should an atrial tachyarrhythmia develop, such as supraventricular tachycardia, atrial fibrillation, or atrial flutter, the generator acts to limit ventricular pacing. When the atrial rate exceeds the UTR, the generator can change mode (i.e., switch to DDI) or introduce a second-degree AV block. Second-degree blocks can be Mobitz type I (Wenckebach) or Mobitz type II, depending on a variety of programmed settings within the PM.

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Appendix 1

Preanesthetic Pulse Generator (Pacemaker, Implantable Cardioverter-Defibrillator) Evaluation

Determining the indication for and date of initial device placement
Identifying the type of device (pacemaker, implantable cardioverter-defibrillator) and manufacturer
Determining the patient's underlying rhythm and rate (if any)
Identifying the number and types of leads
Determining the last generator test date and battery status
Obtaining a history of generator events (if any)
Obtaining the current program information (device interrogation), including mode, rate, and rate enhancements
Ensuring that generator discharges become mechanical systoles with adequate pacing safety margins
Ensuring adequate safety margin for sensing events (if intrinsic events are present)
Ensuring that magnet detection is enabled (magnet behavior and rate should be recorded)
Determining whether the pacemaker should be reprogrammed, depending on pacemaker dependency, surgery type and location, need for increased heart rate, and other factors

The preanesthetic pacemaker evaluation should consist of device interrogation. The above statements can be fashioned into a request to the cardiologist or pacemaker service. Note that for implantable cardioverter-defibrillators, the term "generator events" includes a history of antitachycardia therapy

Appendix 2

Pulse Generator Company Phone Numbers

AM Pacemaker Corp (Boston Scientific)	800-227-3422	Edwards Pacemaker Systems (Medtronic)	800-325-2518
Angeion	**800-264-2466**	**ELA Medical**	**800-352-6466**
Arco Medical (Boston Scientific)	800-227-3422	**Boston Scientific**	**800-227-3422**
Biotronik	**800-547-0394**	**Intermedics (Boston Scientific)**	**800-227-3422**
Boston Scientific	**800-227-3422**	**Medtronic**	**800-505-4636**
Cardiac Control Systems	Unavailable	**Pacesetter (St. Jude Medical)**	**800-722-3774**
Cardio Pace Medical, Inc. (Novacon)	Unavailable	Siemans—Elema (St. Jude Medical)	800-722-3774
Cardiac Pacemakers, Inc.—CPI (Boston Scientific)	**800-227-3422**	**Telectronics Pacing (St. Jude Medical)**	**800-722-3774**
Cook Pacemaker Corp.	800-245-4715	**Ventritex (St. Jude Medical)**	**800-722-3774**
Coratomic (Biocontrol Technology)	Unavailable	Vitatron (Medtronic)	800-328-2518
Cordis Corporation (St. Jude Medical)	800-722-3774		
Diag/Medcor (St Jude Medical)	800-722-3774		

Companies in bold text market implantable cardioverter-defibrillators.

Stephen M. Eskaros, Peter J. Papadakos, and Burkhard Lachmann

44 Respiratory Monitoring

Key Points

1. Hypoxemia is caused by reduced P_{IO_2}, hypoventilation, increased ventilation-perfusion ($\dot{V}/\dot{Q}$) heterogeneity, increased shunt, and diffusion nonequilibrium. Hypercapnia is almost always due to hypoventilation.
2. During mechanical ventilation in the operative and intensive care settings, hypoxemia is most often due to increased $\dot{V}/\dot{Q}$ heterogeneity and shunt.
3. A clinically useful approximation to the alveolar gas equation for O_2 is given by $P_{AO_2} = (P_B - 47) \times F_{IO_2} - 1.2 \times P_{CO_2}$. Exchange of O_2 and CO_2 takes place independently in the lung.
4. The alveolar-arterial (A-a) gradient increases with age and supplemental O_2. The P_{aO_2}/F_{IO_2} and A/a ratios typically do not change with increased age or inspired O_2.
5. When derangements in gas tensions are noted on arterial blood gas analysis, it is important to verify that the sample was obtained and analyzed in an appropriate and timely manner.
6. Refinements and further studies on continuous intravascular blood gas monitors may one day lead to widespread routine use of these devices.
7. Pulse oximetry is a rapid, reliable indicator of oxygenation status in surgical and critically ill patients. Newer oximeters feature reduced capability for errors attributable to motion artifact and hypoperfusion.
8. Multiwavelength pulse oximeters are commercially available and allow measurement of carboxyhemoglobin and methemoglobin. Pulse oximetry may one day prove to be a reliable noninvasive monitor of volume status and fluid responsiveness.
9. A sudden decrease in P_{ETCO_2} usually results from a circuit disconnection, airway obstruction, abrupt decrease in cardiac output, or pulmonary embolism. P_{ETCO_2} is not always a reliable approximation of P_{aCO_2}, particularly during general anesthesia or in the critically ill.
10. Mapping of pressure-volume curves in patients with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) can provide valuable information about lung mechanics and help guide positive end-expiratory pressure (PEEP) and tidal volume settings. Sustained high airway pressure is needed to open collapsed alveoli, and PEEP stabilizes the recruited lung units.
11. Computed tomography has greatly increased our understanding of the complicated interaction between PEEP and lung recruitment in ARDS. Electrical impedance tomography may in the future emerge as a useful bedside monitor of lung recruitment, pulmonary edema, and respiratory mechanics.
12. Recruitment strategies and low–tidal volume ventilation have been shown to improve outcomes in ARDS and ALI. High-frequency ventilators are safe and effective in refractory ARDS and may some day prove to be the ideal mode of lung protective ventilation.

Gas Exchange

The realization that gas exchange takes place in the lung was made by the ancients. However, not until the 18th century, when oxygen was discovered by Joseph Priestley, did Lavoisier ascertain the true purpose of breathing: the biochemical combustion of carbon and oxygen to carbon dioxide, a process known as respiration.[1] More than 200 years later, the exact mechanisms by which the respiratory system takes up oxygen and eliminates carbon dioxide are still being debated.

Alveolar Gases

A practicable method for directly sampling and analyzing alveolar air was first described by Haldane and Priestly in 1905.[2] Because of the inaccuracies and technical difficulty involved in

direct sampling, efforts to develop indirect methods of determining the composition of alveolar air ensued. Subsequently, many equations describing the concentration of alveolar gases have been derived, with a wide range of accuracy and complexity. All are based simply on the law of conservation of mass and derive from the universal alveolar air equation:

$$\text{Alveolar fraction of gas X} = \frac{(\text{Inspired fraction of X} \pm \text{Output or uptake of X})}{\text{Alveolar ventilation}}$$

(i.e., output for CO_2, uptake for O_2) (1)

The equation in this form is only approximate and requires corrections to account for differences in expired and inspired minute volume, discussed later. Moreover, because of the inhomogeneous nature of the lung, the partial pressures calculated should be interpreted as *averages* of various alveolar concentrations present in heterogeneous gas exchange units. Put simply, the gas concentrations in each alveolus are probably different, and values obtained from the equation represent the mean of all alveoli.

In the case of O_2, solving the universal equation for uptake $\left(\dot{V}_{O_2}\right)$ yields a general Fick equation that can be solved for alveolar O_2:

$$\dot{V}_{O_2} = \dot{V}_A\left(F_{IO_2} - F_{AO_2}\right) \quad (2)$$

$$F_{AO_2} = \left(F_{IO_2} - \dot{V}_{O_2}\right)/\dot{V}_A \quad (3)$$

where F_{AO_2} is the alveolar O_2 fraction, F_{IO_2} is the inspired fraction, and $\dot{V}_A$ is alveolar ventilation in volume per minute. In other words, the amount of O_2 in alveoli is equal to the difference between the amount inspired and the amount taken up by pulmonary capillaries (conservation of mass). Multiplying through by dry barometric pressure ($P_{B_{dry}}$) to obtain partial pressures, Equation 3 becomes

$$P_{AO_2} = P_{B_{dry}}\left(F_{IO_2} - \dot{V}_{O_2}/\dot{V}_A\right) \quad (4)$$

where $P_{B_{dry}}$ = barometric pressure − saturated water vapor pressure.

It is most clear in this form of the equation that P_{AO_2} is influenced only by four variables: barometric pressure, fraction of inspired O_2, uptake of O_2, and alveolar ventilation.[3]

The same manipulations of the universal equation yield a formula for determining alveolar CO_2:

$$P_{ACO_2} = P_{B_{dry}}\left(F_{ICO_2} + \dot{V}_{CO_2}/\dot{V}_A\right) \quad (5)$$

Note that CO_2 output must be *added* to the inspired concentration to obtain P_{ACO_2}. However, because F_{ICO_2} is usually zero and $\dot{V}_{CO_2}$ is relatively constant, it is clear that P_{ACO_2} is dependent mainly on one factor, alveolar ventilation, to which it is inversely proportional:

$$P_{ACO_2} = c\left(1/\dot{V}_A\right) \quad (6)$$

where c is a constant. This approximation becomes less accurate in clinical situations in which CO_2 output can be appreciably elevated, as with fever, sepsis, or shivering.[4]

Perhaps the simplest and most widely used approximation of the alveolar gas equation was derived by Riley and colleagues[5] and relates P_{AO_2} and P_{ACO_2} in the following way:

$$P_{AO_2} = P_{IO_2} - P_{ACO_2}/R \quad (7)$$

where R is the respiratory exchange ratio defined as $\dot{V}_{CO_2}/\dot{V}_{O_2}$ and relates CO_2 output to O_2 uptake. Normally, the ratio is relatively constant at 0.8 (i.e., 0.8 mol CO_2 produced for every 1 mol O_2 consumed), and the equation becomes

$$P_{AO_2} = P_{IO_2} - 1.25 \times P_{ACO_2} \quad (8)$$

Note that the term P_{ACO_2}/R in Equation 7 replaces the term $\left(P_{B_{dry}} \cdot \dot{V}_{O_2}\right)/\dot{V}_A$ from Equation 4. Because P_{ACO_2} can be assumed to be equal to P_{aCO_2} based on the Enghoff modification and R relates O_2 uptake to CO_2 output, P_{ACO_2}/R is essentially an indirect measure of O_2 uptake and is much easier to accurately calculate than $\dot{V}_{O_2}/\dot{V}_A$.[6]

A common misconception from the appearance of P_{CO_2} in Equations 7 and 8 is that P_{AO_2} is directly influenced by changes in P_{ACO_2}. Rather, exchange of O_2 and CO_2 takes place independently in the lung, and P_{AO_2} is influenced by only the four aforementioned factors. The apparent influence of P_{ACO_2} on P_{AO_2} is actually reflective of a change in minute ventilation or O_2 consumption, more obvious in Equation 4. For example, as alveolar ventilation decreases, P_{aCO_2} rises and P_{AO_2} will decrease according to Equation 8 as a result of the reduced alveolar ventilation. There is no "displacement" or direct alteration of O_2 by CO_2.[6,7]

Despite being quite adequate for clinical use, the Riley equation does not account for small differences in expired and inspired gas volume because of (1) the respiratory exchange ratio (less CO_2 output than O_2 uptake at a ratio of 4:5) and (2) respired inert gases not being in equilibrium with blood (such as during nitrous oxide induction or washout). An equation proposed by Filley and coworkers[8] corrects for this difference and does not entail calculation of R, which can be higher than the normal 0.8 in certain clinical settings, such as with metabolic acidosis or overfeeding:

$$P_{AO_2} = P_{IO_2} - P_{ACO_2}\left[\left(P_{IO_2} - P_{EO_2}\right)/P_{ECO_2}\right] \quad (9)$$

Though more accurate, it is more cumbersome than the Riley equation in that mixed expired gas concentrations must be measured. This equation should be used, for example, when calculating shunt fraction because precise P_{AO_2} values are imperative.[3]

Arterial Gases

Exchange of gases between alveoli and blood occurs at the pulmonary capillaries. Arterial blood is formed by mixture of this pulmonary capillary blood with the mixed venous shunt fraction. Thus, three major factors influence the efficiency of this exchange and the resultant arterial gas tensions: $\dot{V}/\dot{Q}$ matching, alveolar diffusion capacity, and shunt fraction. Along with hypoventilation and low P_{IO_2}, derangements in any of these factors result in arterial hypoxemia (Box 44-1). Some determination of the cause of the hypoxemia can be made by evaluation of the A-a O_2 gradient; problems with gas exchange increase the gradient, whereas it is normal in hypoxemia because of low P_{IO_2} or hypoventilation. The A-a gradient is usually elevated in a patient breathing supplemental oxygen. Two other indices of oxygenation that remain unchanged with fluctuating F_{IO_2} are the P_{AO_2}/F_{IO_2} and a/A ratios (normally 350 to 500 mm Hg and 0.8 to 0.85, respectively).

Box 44-1 Five Causes of Hypoxemia and the Associated Alveolar-to-Arterial (A-a) O_2 Gradient

Normal A-a O_2 Gradient
- Hypoventilation
- Reduced P_{IO_2}

Increased A-a O_2 Gradient
- Increased $\dot{V}/\dot{Q}$ heterogeneity
- Increased shunt
- Diffusion limitation

The extent to which these factors affect the makeup of arterial blood differs for CO_2 and O_2 because they have different arteriovenous gradients and diffusing capacities. CO_2 is estimated to have a diffusing capacity 20 to 30 times greater than that of O_2,[9] and its exchange is therefore minimally affected by derangements in alveolar membrane diffusion and $\dot{V}/\dot{Q}$ mismatching. The narrower arteriovenous gradient of CO_2 (≈6 mm) versus O_2 (~60 mm) leads to less profound effects of venous shunt on arterial P_{CO_2}. Except in extreme circumstances there is little evidence that impaired diffusion of O_2 or CO_2 across the alveolar membrane occurs to any clinically significant extent, so this is not discussed further in this chapter.

$\dot{V}/\dot{Q}$ Mismatch

In normal subjects, resting minute ventilation is roughly 4 L/m and pulmonary blood flow is 5 L/m, which results in a ventilation-to-perfusion ratio of roughly 0.8 for the entire lung.[10] This would represent the $\dot{V}/\dot{Q}$ ratio of each alveolus if ventilation and perfusion were uniformly distributed in the lung. In reality, distribution is not uniform, and ratios range anywhere from zero (shunt) to infinity (dead space ventilation). For example, alveoli in dependent lung regions are better perfused than those in the apices and therefore have lower $\dot{V}/\dot{Q}$ ratios.[11] Ventilation is usually more evenly distributed throughout the lung than blood flow is, so impaired oxygenation of arterial blood is most often due to derangements in perfusion.

$\dot{V}/\dot{Q}$ mismatching results in hypoxemia for two reasons. First, more blood tends to flow through alveoli with low $\dot{V}/\dot{Q}$, such as dependent lung.[9] Thus, when $\dot{V}/\dot{Q}$ scatter increases, flow through alveoli with low $\dot{V}/\dot{Q}$ (and therefore low P_{O_2}) is greater than flow through areas of high $\dot{V}/\dot{Q}$, which causes a disproportionately large effect from the areas of low $\dot{V}/\dot{Q}$ and hence a reduction in P_{aO_2}. The second reason is due to the nature of oxyhemoglobin (HbO_2) dissociation. Alveoli with high $\dot{V}/\dot{Q}$ are on the plateau portion of the curve, where shifts in P_{AO_2} have little effect on O_2 content. These new areas of high (or higher) $\dot{V}/\dot{Q}$ introduced by scatter are unable to compensate for the new areas of low $\dot{V}/\dot{Q}$, which are on the steep portion of the curve and therefore more profoundly affected by changes in P_{AO_2} (Figs. 44-1 and 44-2).

Shunt

One extreme of $\dot{V}/\dot{Q}$ mismatch is a right-to-left shunt ($\dot{V}/\dot{Q}$ = 0), the other extreme being dead space ventilation ($\dot{V}/\dot{Q}$ = infinity). Normally, a small shunt fraction (<3% of cardiac output) exists because of drainage of bronchial and thebesian venous blood into the left heart.[7] However, as a result of the steep arterio-

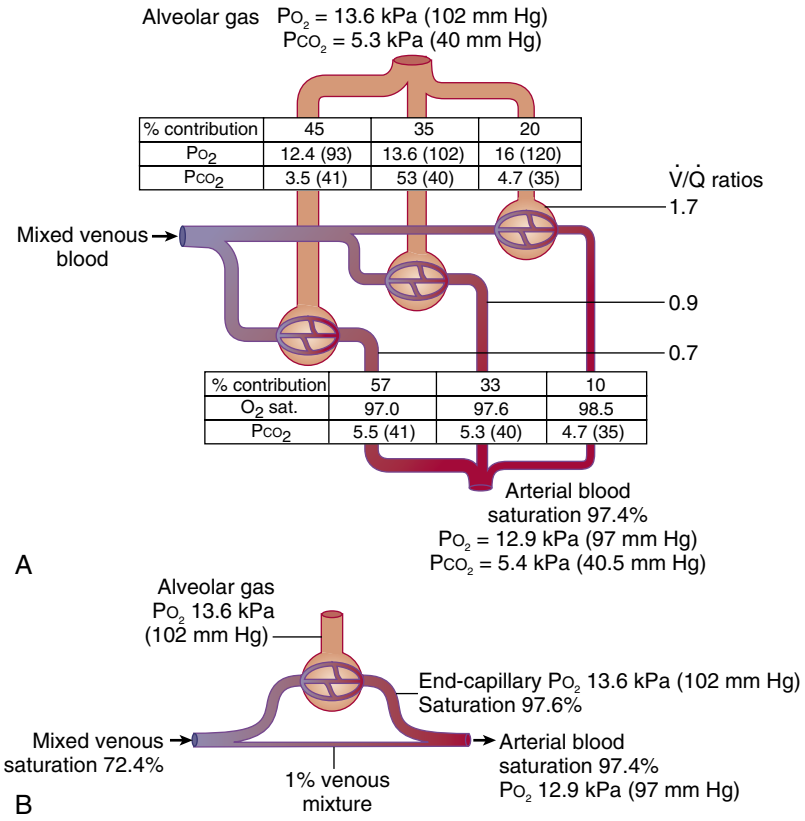

Figure 44-1 Alveolar-to-arterial P_{O_2} difference caused by scatter of $\dot{V}/\dot{Q}$ ratios and its representation by an equivalent degree of venous admixture. **A,** Scatter of $\dot{V}/\dot{Q}$ ratios corresponding roughly to the three zones of the lung in a normal upright subject. Mixed alveolar gas P_{O_2} is calculated with allowance for the contribution of gas volumes from the three zones. Arterial saturation is similarly determined and P_{O_2} derived. There is an alveolar-arterial P_{O_2} difference of 0.7 kPa (5 mm Hg). **B,** Theoretical situation that would account for the same alveolar-to-arterial P_{O_2} difference caused solely by venous admixture. This is a useful method of quantifying the functional effect of scattered $\dot{V}/\dot{Q}$ ratios but should be carefully distinguished from the actual situation. *(From Lumb AB: Nunn's Applied Respiratory Physiology, 6th ed. Philadelphia, Elsevier/Butterworth Heinemann, 2005.)*

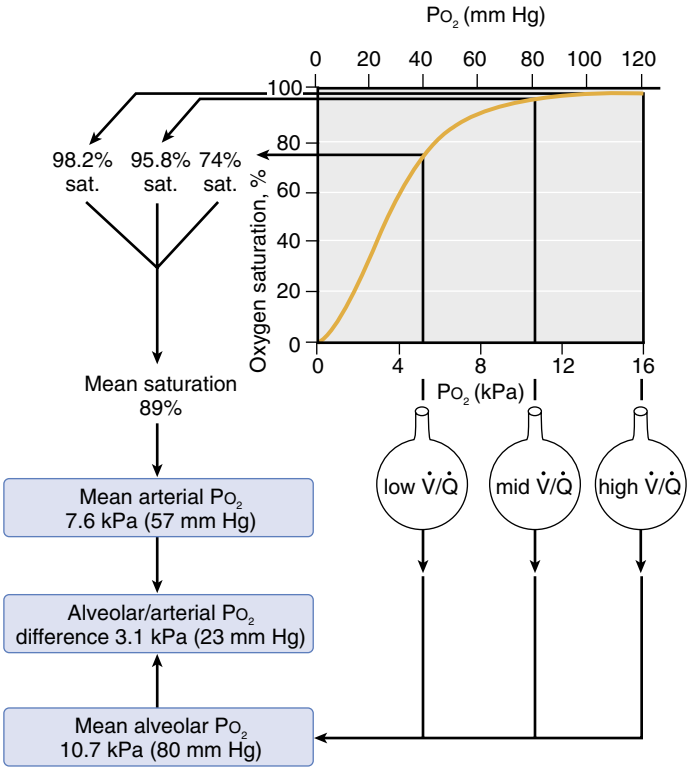

Figure 44-2 Alveolar-arterial P_{O_2} difference caused by scatter of $\dot{V}/\dot{Q}$ ratios resulting in oxygen tensions along the upper inflection of the oxygen dissociation curve. The diagram shows the effect of three groups of alveoli with P_{O_2} values of 5.3, 10.7, and 16.0 kPa (40, 80, and 120 mm Hg). Ignoring the effect of the different volumes of gas and blood contributed by the three groups, mean alveolar P_{O_2} is 10.7 kPa. However, because of the shape of the dissociation curve, the saturation of blood leaving the three groups is not proportional to their P_{O_2}. The mean arterial saturation is in fact 89%, and P_{O_2} is therefore 7.6 kPa. The alveolar-arterial P_{O_2} difference is thus 3.1 kPa. The actual difference would be somewhat greater because gas with a high P_{O_2} would make a relatively greater contribution to alveolar gas and blood with a low P_{O_2} would make a relatively greater contribution to arterial blood. In this example, a calculated venous admixture of 27% would be required to account for the scatter of $\dot{V}/\dot{Q}$ ratios in terms of the measured alveolar-arterial P_{O_2} difference at an alveolar P_{O_2} of 10.7 kPa. *(From Lumb AB: Nunn's Applied Respiratory Physiology, 6th ed. Philadelphia, Elsevier/Butterworth Heinemann, 2005.)*

venous P_{O_2} gradient, this shunt is partly responsible for the normal A-a O_2 gradient of 5 to 10 mm Hg found in children and young adults breathing room air. Shunt introduced by these circulations can increase to 10% of cardiac output in the presence of severe bronchial disease and aortic coarctation.[9] The normal heterogeneity of $\dot{V}/\dot{Q}$ throughout the lung is the other contributor to the baseline A-a gradient. The gradient increases with age, probably secondary to increased closing capacity and $\dot{V}/\dot{Q}$ scatter.[7]

Pathologic right-to-left shunting of blood occurs in areas of atelectasis or airway blockage, as in acute lung injury (ALI) or pneumonia. Alveoli are collapsed or unventilated but continue to be perfused. Venous drainage from lung tumors also constitutes a pathologic shunt. If hypoxic pulmonary vasoconstriction (HPV) fails to adequately limit blood flow to these regions, hypoxemia occurs. Indeed, inhaled anesthetics are known to cause attenuation of HPV, and induction of general anesthesia (GA) causes immediate development of atelectasis (see Chapter 15).[12,13] Both phenomena are probably contributors to the 5% to 10% shunt found in patients undergoing GA with mechanical ventilation.[10]

Calculating Shunt Fraction and Dead Space

A simplified but useful three-compartment lung model aids in approximating what fraction of cardiac output $(\dot{Q}_T)$ constitutes shunt $(\dot{Q}_S)$ and what fraction of tidal volume (V_T) constitutes dead space ventilation $(\dot{V}_{DS})$. Commonly known as the Riley approach, the lung is considered as though it were made up of three compartments at the three extremes of $\dot{V}/\dot{Q}$ matching: (1) a shunt compartment with perfused but unventilated alveoli, (2) a dead space compartment with ventilated but unperfused alveoli, (3) and an ideal compartment with normally distributed ventilation and perfusion (Fig. 44-3).

As discussed earlier, the lung is actually composed of many compartments with a wide distribution of $\dot{V}/\dot{Q}$ ratios, and this as an oversimplified but clinically useful model.

The shunt fraction $(\dot{Q}_S/\dot{Q}_T)$ can be calculated by using the Berggren shunt equation to compare the O_2 content of mixed venous $(C\bar{v}O_2)$, pulmonary capillary $(Cc'O_2)$, and arterial (CaO_2) blood:

$$\dot{Q}_S/\dot{Q}_T = (Cc'O_2 - CaO_2)/(Cc'O_2 - C\bar{v}O_2) \quad (10)$$

In a normal subject with capillary O_2 saturation close to 100%, the following approximation can be made

$$\dot{Q}_S/\dot{Q}_T = (1 - SaO_2)/(1 - S\bar{v}O_2) \quad (11)$$

where $S\bar{v}O_2$ and SaO_2 are mixed venous and arterial O_2 saturation, respectively.

It is important to note that the fraction calculated in Equation 10 is not a *true* shunt (intrapulmonary shunt through alveoli

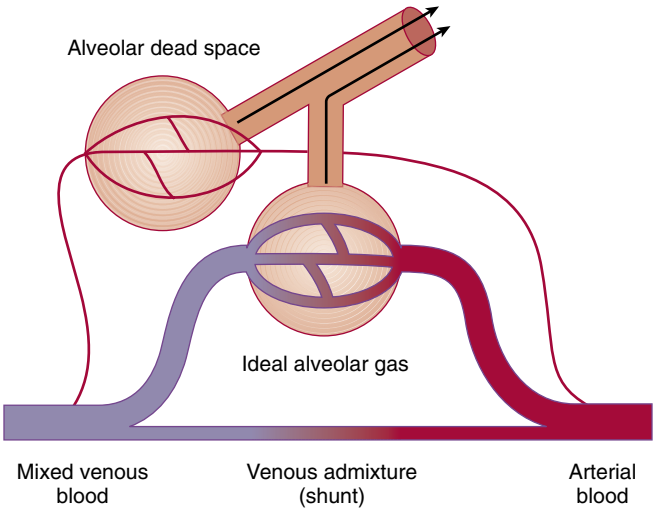

Figure 44-3 Three-compartment (Riley) model of gas exchange. The lung is imagined to consist of three functional units consisting of alveolar dead space, "ideal" alveoli, and venous admixture (shunt). Gas exchange occurs only in the "ideal" alveoli. The measured alveolar dead space consists of true alveolar dead space together with a component caused by $\dot{V}/\dot{Q}$ scatter. The measured venous admixture consists of true venous admixture (shunt) together with a component caused by $\dot{V}/\dot{Q}$ scatter. Note that "ideal" alveolar gas is exhaled contaminated with alveolar dead space gas, so it is not possible to sample "ideal" alveolar gas. *(From Lumb AB: Nunn's Applied Respiratory Physiology, 6th ed. Philadelphia, Elsevier/Butterworth Heinemann, 2005.)*

with zero $\dot{V}/\dot{Q}$) but should be thought of as a *total* shunt because it includes intracardiac and physiologic shunting and the contribution of areas with relatively low (shuntlike) but nonzero $\dot{V}/\dot{Q}$. Thus, the model is unable to predict how much each of these factors contributes to the calculated shunt because they all introduce undersaturated blood into the arterial circulation. It is though that breathing 100% O_2 eliminates the *shuntlike* contribution by fully saturating capillary blood in low-$\dot{V}/\dot{Q}$ alveoli, but it appears instead that these regions may progress via resorption atelectasis into areas of true shunt.[14] Making the distinction between true shunt and shuntlike regions caused by low $\dot{V}/\dot{Q}$ may be clinically important, particularly for anesthesiologists, in that reduced $\dot{V}/\dot{Q}$ has been shown to be more predictive of postoperative hypoxemia than increased shunt is.[10] Techniques allowing more accurate distinction between the components of calculated shunt and dead space have been developed and are described later.

A method has been derived to estimate shunt fraction without sampling arterial or mixed venous blood.[15] Arterial oxygen content is calculated from measured hemoglobin (Hb) and Spo_2, and Po_2 is obtained from the alveolar gas equation by using end-tidal Pco_2 as an estimate of $Paco_2$. Mixed venous O_2 content is estimated by assuming a fixed arterial–to–mixed venous O_2 gradient. Estimates of shunt fraction obtained by this method are expectedly somewhat imprecise (±16%) when compared with invasive measurements but are adequate for clinical use.

The dead space component in the three-compartment gas exchange model can be calculated with the Bohr equation:

$$V_{DS}/V_T = \left(Paco_2 - Peco_2\right)/Pao_2 \qquad (12)$$

where Peo_2 is the mixed expired Pco_2

The fraction calculated includes anatomic, alveolar, and apparatus (i.e., breathing circuit) dead space, which together represent *physiologic* dead space.

As with the shunt calculation described earlier, dead space determined by the equation is not *true* dead space because it includes an indeterminate contribution from relatively underperfused or *dead space–like* alveoli with high $\dot{V}/\dot{Q}$ (see Fig. 44-3). Another limitation of the model is that alterations in cardiac output or Hb concentration can lead to different calculated values of shunt fraction, even when actual $\dot{V}/\dot{Q}$ ratios have not changed. A substantial rise in cardiac output will increase $S\bar{v}o_2$ and cause a subsequent rise in the O_2 content of shunted blood and therefore arterial blood (Fig. 44-4). The calculated shunt fraction would decrease without an actual decrease in percent shunt by volume.

Distinguishing between Shunt and Altered $\dot{V}/\dot{Q}$ as the Cause of Impaired Oxygenation

In 1974, Wagner and coauthors described a technique known as multiple inert gas elimination (MIGET), which allows plotting of pulmonary ventilation and perfusion against the $\dot{V}/\dot{Q}$ ratio for a large number of lung compartments (rather than just three compartments as in the Riley approach), all with different $\dot{V}/\dot{Q}$ ratios.[14] Six inert tracer gases with widely varying blood solubility are infused intravenously and allowed to reach steady state. Arterial and mixed expired gas concentrations are measured, and the mixed venous concentration is calculated via the Fick principle. Retention-solubility and excretion-solubility curves are created and then translated into a continuous plot of perfusion against $\dot{V}/\dot{Q}$ and ventilation against $\dot{V}/\dot{Q}$, respectively, in relation to the heterogeneous spectrum of $\dot{V}/\dot{Q}$ ratios present throughout the lung. A host of other variables can be accurately measured, including intrapulmonary shunt and alveolar dead space. The technique is cumbersome and the numerical analyses rather complicated for routine use, but studies using the technique have been invaluable to our understanding of gas exchange in intensive care unit (ICU)[16] and surgical[17,18] settings. Figure 44-5 shows a typical plot in awake patients, with the development of shunt, increased dead space, and $\dot{V}/\dot{Q}$ scatter on induction of GA. Increasing shunt detected by multiple inert gas elimination (MIGET) has been correlated with increasing atelectasis noted on chest computed tomography (CT).[19] Distinguishing between true shunt and low $\dot{V}/\dot{Q}$ can also be performed noninvasively by simultaneously plotting Sao_2 versus Pio_2 (Fig. 44-6). Increasing shunt shifts the curve downward, whereas reducing $\dot{V}/\dot{Q}$ below the normal 0.8 shifts the curve rightward. The figure schematically shows the long-established observation that hypoxemia caused by true shunt is minimally responsive to increased Pio_2, in contrast to hypoxemia caused by $\dot{V}/\dot{Q}$ mismatch. As mentioned, $\dot{V}/\dot{Q}$ reduction detected by a rightward shift of the curve intraoperatively has been shown to correlate with hypoxemia up to 30 hours postoperatively. The technique may help identify patients at risk for postoperative hypoxemia and in need of supplemental O_2 and closer monitoring. It can also be used in patients with chronic lung disease to determine whether additional O_2 may be needed during air travel or at altitude.[10]

Blood Gas Analysis

Measurement of Blood Gas Tensions

The basic design that modern blood gas analyzers still use today was introduced by Severinghaus and Bradley in 1958.[20] Designed by Leland Clark in 1953,[21] the Po_2 electrode is a platinum probe bathed in an electrolyte solution and separated from the sample (blood) by an O_2 permeable membrane. Oxygen molecules pass from blood through the membrane and are reduced to hydroxyl ions. Po_2 is proportional to the current generated by this reduction reaction. Similarly, the Stow/Severinghaus Pco_2 electrode is a pH-sensitive glass probe bathed in a bicarbonate solution and encased by a CO_2 permeable membrane. Pco_2 is proportional to the H^+ generated as CO_2 reacts with water to form H^+ and HCO_3^-. Severinghaus and Astrup have provided a detailed history of the development of blood gas analysis (BGA).[22,23]

Temperature Correction

Modern blood gas analyzers measure blood gas tensions at 37°C. Because patients rarely have a temperature of exactly 37°C, blood samples must be heated or cooled to 37°C for analysis. Heating a blood sample decreases pH, gas solubility, and Hb affinity for O_2 and CO_2. Thus, as the blood from a hypothermic patient (say 35°C) is heated and analyzed at 37°C, more gas becomes dissolved in solution and the measured Po_2 and Pco_2 will be higher than at 35°C. Raising the temperature also increases the H^+ concentration and would give a falsely low pH in a hypothermic patient. Modern analyzers use one of a number of algorithms to automatically correct pH and blood gas tensions for temperature, and Box 44-2 provides the formulas approved by the National Committee

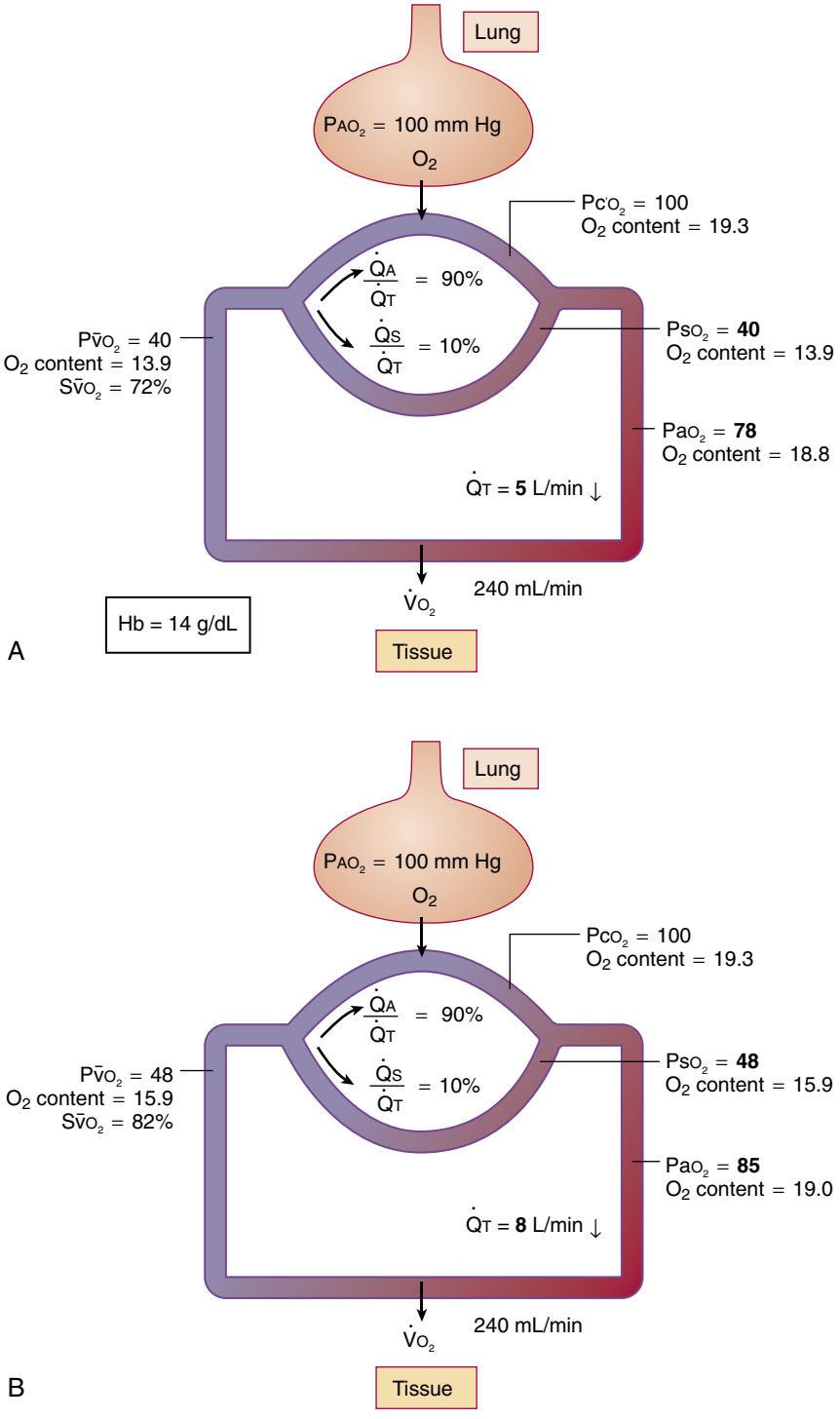

Figure 44-4 Effect of cardiac output on P_{O_2}. **A,** Arterial and mixed venous O_2 tension and content are shown at a cardiac output of 5 L/min. **B,** Assuming constant $\dot{V}_{O_2}$, an increase in cardiac output to 8 L/min increases P_{aO_2} from 78 to 85 mm Hg because $S_{\bar{v}O_2}$ increases at higher cardiac output. The resulting increase in O_2 content of the shunted blood (here assumed to be 10% of cardiac output) then raises the arterial O_2 content and P_{aO_2}. P_{O_2} values are in mm Hg, and O_2 content is in mL/dL.

for Clinical Laboratory Standards (NCCLS). The corrections are all rather slight, and there is little evidence to suggest that temperature-corrected values are clinically more useful than 37°C values. Two approaches, pH-stat and alpha-stat, have been used to manage pH in hypothermic patients undergoing cardiopulmonary bypass. The alpha-stat approach lets pH rise naturally into the alkalotic range as the patient is cooled, and pH-stat maintains normal pH and presumably cerebral perfusion by adding CO_2. Data favoring either approach are very limited.

Artifactual Changes in Arterial Blood Gas Values

Delay in analyzing a blood sample after it is drawn can artifactually change the measured pH and gas tensions. Storing a sample longer than 20 minutes can cause a significant elevation in P_{CO_2} and reduction in P_{O_2} and pH, probably secondary to cellular metabolism. Leukocytosis and thrombocytosis accelerate these

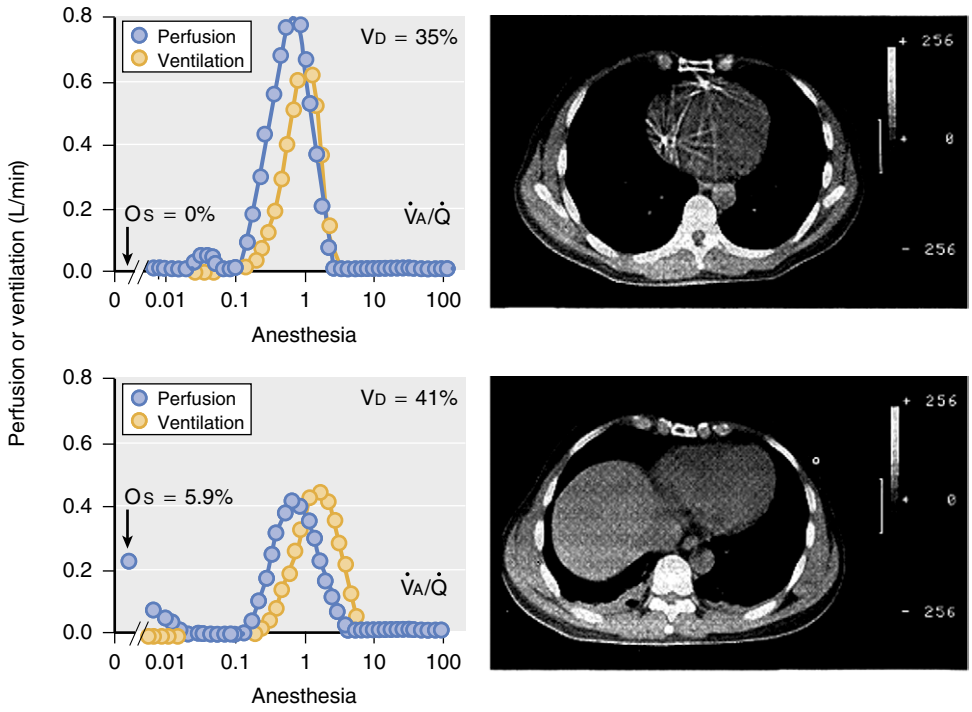

Figure 44-5 Ventilation-perfusion ($\dot{V}_A/\dot{Q}$) distribution and computed tomography in a supine subject. **Left,** $\dot{V}_A/\dot{Q}$ distribution in an awake (*top*) and anesthetized (*bottom*) subject. Note the appearance of a pulmonary shunt and an increase in $\dot{V}_A/\dot{Q}$ mismatch during general anesthesia with mechanical ventilation. **Right,** Computed tomography of the chest just above the top of the right diaphragm. Note the appearance of densities in the dependent lung regions during anesthesia. V_D, volume of distribution. *(Redrawn from Gunnarsson L, Tokics L, Gustavsson H, et al: Influence of age on atelectasis formation and gas exchange impairment during general anesthesia. Br J Anaesth 66:423-432, 1991.)*

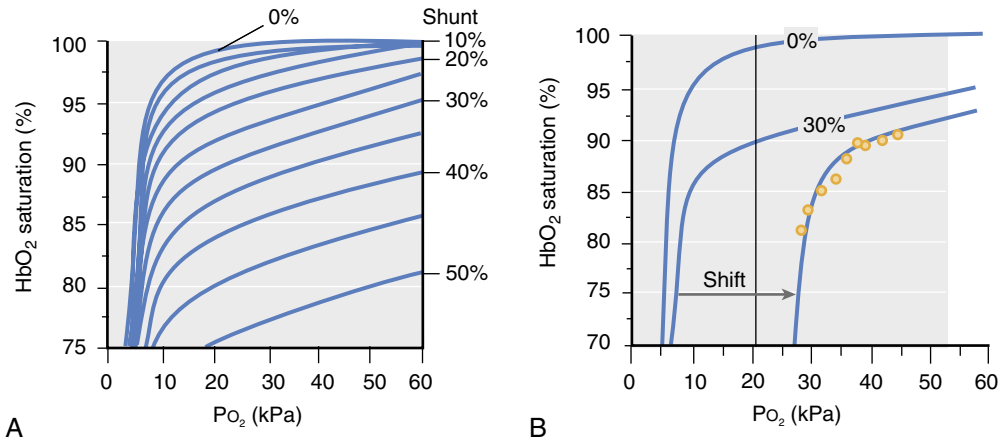

Figure 44-6 Hemoglobin-oxygen (HbO_2) saturation versus inspired partial pressure of oxygen (P_{O_2}). The curves are plotted by changing inspired P_{O_2} in stepwise fashion. **A,** Series of theoretical curves obtained by calculating the effect of different degrees of right-to-left shunt. Increasing shunt displaces the curves downward. **B,** The curve on the *left* of the graph (0%) is from a normal subject. The *middle* curve (30%) represented a 30% right-to-left shunt from the 30% curve seen in **A**. The curve on the *right* of this graph is from a patient undergoing thoracotomy for esophageal surgery. The points cannot be fitted by any of the shunt curve, but the fit is quite good when the 30% curve is shifted to the right. This implies a combination of shunt and $\dot{V}_A/\dot{Q}$ mismatch. *(Adapted from Jones JG, Jones SE: Discriminating between the effect of shunt and reduced $\dot{V}_A/\dot{Q}$ on arterial oxygen saturation is particularly useful in clinical practice. J Clin Monit Comput 16:337, 2000.)*

Box 44-2 Algorithms for Correction to Body Temperature of Blood Gas Tensions Measured at 37°C

pH

$\Delta pH/\Delta T = -0.0146 + 0.0065\ (7.4 - pH_m)$

$\Delta pH/\Delta T = -0.015$

$\Delta pH/\Delta T = -0.0147 + 0.0065\ (7.4 - pH_m)$*

$\Delta pH/\Delta T = -0.0146$

Pco_2

$\Delta \log_{10} Pco_2/\Delta T = 0.019$*

$\Delta \log_{10} Pco_2/\Delta T = 0.021$

Po_2

$$\Delta \log_{10} Pco_2/\Delta T = \left(\frac{0.0252}{0.234(Po_2/100)^{3.88}+1}\right)+0.00564$$

$$\Delta \log_{10} Pco_2/\Delta T = 0.0052+0.27\left[1-10^{-0.13(100-SAo_2)}\right]$$

$$\Delta \log_{10} Pco_2/\Delta T = \frac{5.49\times10^{-11}\ Po_2^{3.88}+0.071}{9.72\times10^{-9}\ Po_2^{3.88}+2.3}$$*

$$\Delta \log_{10} Pco_2/\Delta T = \frac{0.012(Po_{2m}/714)+(So_2/100)}{(1-So_2/100)(Hb/0.6)+0.073}$$

$Po_{2m}/714+So_2/100(1-So_2/100)(Hb/0.6)$

$So_2 \le 95\%$: $\Delta \log_{10} Pco_2/\Delta T = 0.31$

$So_2 > 95\%$: $\Delta \log_{10} Pco_2/\Delta T = 0.032 - 0.0268e^{(0.35So_2-30)}$

*National Committee for Clinical Laboratory Standards (NCCLS)-approved standard.

Hb, blood hemoglobin concentration in g/dL; pH_m and Po_{2m}, pH and Po_2 values measured at an electrode temperature of 37°C; Po_2, partial pressure of oxygen in mm Hg; So_2, percent hemoglobin-oxygen (HbO_2) saturation; T, temperature in degrees centigrade (°C).

Data from Ashwood ER, Kost G, Kenny M: Temperature correction of blood-gas and pH measurements. Clin Chem 29:1877, 1983; and Siggaard-Andersen O, Wimberley PD, Gothgen I, Siggaard-Andersen M: A mathematical model of the hemoglobin-oxygen dissociation curve of human blood and of the oxygen partial pressure as a function of temperature. Clin Chem 30:1646, 1984.

changes.[24] Because red cells do not contain mitochondria, this phenomenon is not observed in polycythemia. However, anaerobic glycolysis can generate lactic acid and reduce pH. Placing the sample in ice immediately after it is obtained can maintain its stability, and addition of sodium fluoride or cyanide can inhibit cellular O_2 consumption.[24] The presence of air bubbles in the sample syringe can falsely elevate Po_2 but has little effect on pH and Pco_2. Syringes are usually heparinized to prevent coagulation.

Transcutaneous Blood Gas Monitoring

Although the turnaround time for obtaining Po_2 with traditional blood gas analyzers has drastically decreased since their inception, the ability to assess a patient's oxygenation status even more rapidly and easily has obvious advantages. One alternative is to measure gas tensions at the bedside transcutaneously. This technology relies on the tendency of capillary Po_2 to approximate arterial Po_2 when skin is warmed, which causes blood flow to exceed the amount required for local O_2 consumption. O_2 from capillaries diffuses through the warmed skin, where it is analyzed by a Clark-type electrode adhered to it. Though useful in infants, transcutaneous gas monitoring has many limitations despite good agreement of Po_2 values with traditional BGA.[25] Peripheral vascular disease or vasoconstriction can generate erroneous values. Cutaneous hypoxia caused by reduced cardiac output will give falsely decreased Po_2 readings. These devices must be calibrated frequently, have a relatively slow response time, and can cause skin burns with prolonged application.

In-Line Blood Gas Monitoring

Continuous intra-arterial pH measurement was accomplished as early as 1927 with antimony electrodes. Shortly after Clark developed his Po_2 electrode in 1956, the first continuous intravascular blood gas monitoring (CIBGM) devices were developed. Early devices consisted of electrochemical sensors and were essentially modified Clark electrodes. Problems with these devices included excessive drift, lack of reliability, large size, and interference from anesthetic gases. Later, Lubbers and Opitz, using a technology known as fluorescence quenching, created fiberoptic probes to continuously measure Po_2 and Pco_2, which they named *optodes*.[26] Absorbance-based fiberoptic sensors were also developed. Only two single-parameter devices became commercially available: the Continucath 1000 electrochemical Po_2 sensor for adults and the Neocath (Biomedical Sensors, High Wycomb, UK) O_2 sensor for neonatal umbilical artery placement.

Advances in the design of single-parameter systems inevitably led to the development of multiparameter devices capable of measuring pH, Pco_2, Po_2, and temperature. Most are pure optode systems, with the Paratrend 7 being the only hybrid optode-electrode system. The upgraded Paratrend 7+ replaced the Clark Po_2 electrode with an optode, thus making it a pure optode system (Fig. 44-7).

Agreement between sensor and traditional BGA measurements can be quantified by use of the Bland-Altman calculation

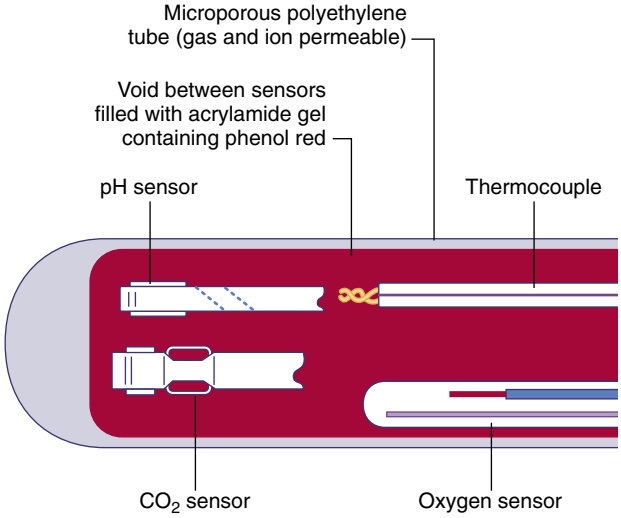

Figure 44-7 Cross section of the Paratrend 7 sensor tip. *(Courtesy of Biomedical Sensors, High Wycombe, UK.)*

of *bias* and *precision*.[27] Bias is the difference between mean values obtained by standard methods (BGA) and those obtained with the new device being tested. Precision is the standard deviation of these differences and measures reproducibility of the results.

Like their predecessors, newer probes remain fragile and continue to exhibit motion artifact, wall effect (decreased Po_2 readings because of contact with the arterial wall), and thrombogenicity. Their accuracy diminishes with insufficient blood flow to the cannulated artery. Moreover, despite encouraging in vitro and animal studies, results from clinical trials have not consistently been as favorable. Data for Pco_2 and pH measurements are impressive, but studies have found poor agreement of sensor Po_2 measurements with those obtained by BGA in elevated Po_2 ranges.[28,29] Weiss and colleagues found accurate results with minimal drift in all parameters up to 10 days after insertion in pediatric patients, but the O_2 sensor required frequent calibration.[30] Several published studies on the clinical performance of various CIABGM devices are summarized in Table 44-1.

Despite its limitations, CIABGM has many theoretical advantages over traditional BGA, although no outcome studies have proved these advantages (Box 44-3). Use of CIABGM in cardiac, thoracic, orthopedic, and transplant surgery may lead to earlier detection of severe blood gas and acid-base derangements.[35,36] Detection of Po_2 changes after cement implantation during hip replacement has been accomplished with this technology.[33] It has been validated for use in anesthesia and intensive care in pediatric patients.[32] Further technologic refinements, outcome studies, and data on cost-effectiveness are necessary for CIABGM to have widespread application in anesthesia and critical care.

Box 44-3 Advantages of a Continuous Intra-arterial Blood Gas Monitoring System over Intermittent Blood Gas Analysis

- Availability of continuous data
- Earlier detection of deleterious events
- Potential for trend analysis
- Decreased blood loss
- Decreased laboratory turnaround time
- Decreased exposure of staff to potentially infected blood

From Venkatesh B: In-line blood gas monitoring. *In* Papadakos PJ, Lachmann B (eds): Mechanical Ventilation: Clinical Applications and Pathophysiology. Philadelphia, Elsevier, 2008.

Oxygen Saturation

Although traditional BGA remains the standard modality for determining oxygen content, an alternative is to measure oxygen saturation (So_2). It can provide rapid and clinically useful information about oxygenation status.

Co-oximetry

The co-oximeter is a traditional blood gas analyzer that is also capable of measuring concentrations of HbO_2, reduced hemoglobin (HbR), carboxyhemoglobin (COHb), and methemoglobin (MetHb). Each of these species has unique absorption spectra, and corresponding wavelengths of light are used to analyze a small blood sample. It is currently the gold standard for measuring Sao_2. Results are usually obtained in less than 2 minutes.

Transcutaneous Oximetry

The principle of transcutaneous oximetry is similar to that of transcutaneous gas tension monitoring, but Sao_2 is measured instead of Po_2. Two wavelengths of light are used to measure quantities of oxygenated and deoxygenated blood to give an estimate of Sao_2, provided that the blood being analyzed is mostly arterial and other Hb species are absent. Two-wavelength ear oximeters were developed and used in practice more than 60 years ago.[37] Robert Shaw patented an eight-wavelength ear oximeter in 1972, and a device using this technology was marketed in the late 1970s by Hewlett Packard. Problems with size and reliability of data prevented its widespread use.

Pulse Oximetry

Some of the problems with transcutaneous oximetry were solved with the invention of pulse oximetry. Though first developed in Japan in the early 1970s, it was not until a decade later that its routine use began. Pulse oximetry works by analyzing the pulsatile arterial component of blood flow, thereby ensuring that arterial saturation (Spo_2) rather than venous saturation is being measured (Fig. 44-8). Two wavelengths of light are used, usually

Table 44-1 Results from Some Published Studies on Clinical Performance of Continuous Intra-arterial Blood Gas Monitoring

Investigator(s)	Device	Number of Patients	Clinical Setting and Insertion Site	pH Bias ± Precision (pH Units)	Pco_2 Bias ± Precision (mm Hg)	Po_2 Bias ± Precision (mm Hg)
Ganter[29]	Paratrend 7+	23	OR: thoracoscopic surgery (radial)	–0.01 ± 0.06	3 ± 9	–20 ± 86
Coule et al.[31]	Paratrend 7+	50 (Ped)	ICU (radial/femoral)	0.00 ± 0.04	0.38 ± 4.8	0.75 ± 25
Weiss et al.[30]	Paratrend 7	24 (Ped)	ICU (radial/femoral)	0.005 ± 0.03	–1.8 ± 6.3	1.2 ± 24
Venkatesh et al.[33]	Paratrend 7	10	OR: hip replacement (radial)	0.02 ± 0.03	0.53 ± 1.8	1.2 ± 20
Larson et al.[34]	PB 3300	29	OR/ICU (radial)	0.01 ± 0.04	1.2 ± 3.3	0.3 ± 9

ICU, intensive care unit; OR, operating room; Ped, pediatric.

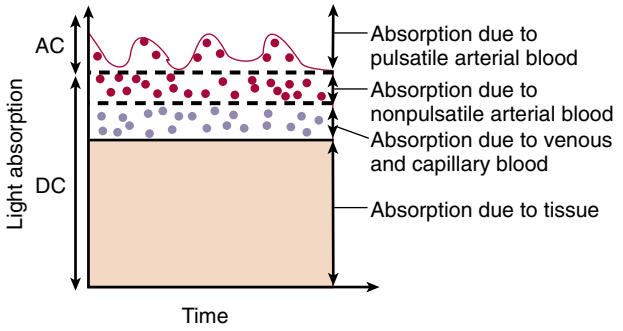

Figure 44-8 Principle of pulse oximetry. Light passing through tissue containing blood is absorbed by tissue and by arterial, capillary, and venous blood. Usually, only the arterial blood is pulsatile. Light absorption may therefore be split into a pulsatile component (AC) and a constant or nonpulsatile component (DC). Hemoglobin O_2 saturation may be obtained by application of Equation 19. *(Data from Tremper KK, Barker SJ: Pulse oximetry. Anesthesiology 70:98, 1989.)*

660 nm (red) and 940 nm (infrared), because oxygenated and deoxygenated blood each absorb light quite differently at these wavelengths. At 660 nm, HbO_2 absorbs less light than HbR does, whereas the opposite is observed with infrared light. Two diodes emitting light of each wavelength are placed on one side of the probe and a photo diode that senses the transmitted light on the opposite side. The amount of light absorbed at each wavelength by the pulsatile arterial component (AC) of blood flow can be distinguished from baseline absorbance of the nonpulsatile component and surrounding tissue (DC). The ratio R is calculated by the oximeter as follows and is empirically related to O_2 saturation:

$$R = \left(AC_{660}/DC_{660}\right)\Big/\left(AC_{660}/DC_{660}\right) \qquad (13)$$

A calibration curve (Fig. 44-9) is derived from R and laboratory measurements of arterial oxygen saturation in healthy volunteers and the algorithm stored in the oximeter. Modern devices

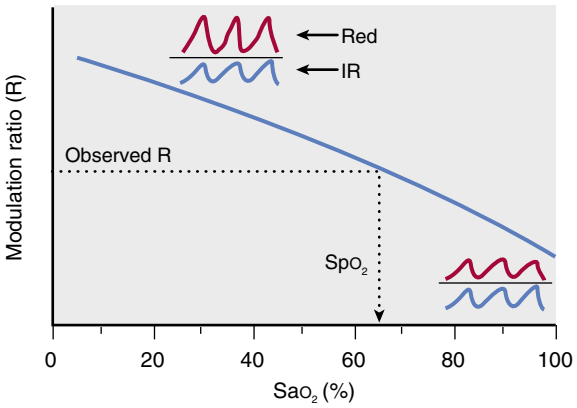

Figure 44-9 Red/infrared modulation ratio (R) versus oxygen saturation (Sao_2). At high Sao_2 (*right* side of the graph), the pulse amplitude (or modulation) of the red signal is less than that of the infrared signal, whereas the reverse is true at low Sao_2. Pulse oximeters measure R, the ratio of red to infrared pulse amplitudes (see Equation 13), and estimate Sao_2 by applying the calibration curve (*solid line*) as depicted by the *dashed line* and *arrow*. *(From Mannheimer PD: The light-tissue interaction of pulse oximetry. Anesth Analg 105(6 Suppl):S10-S17, 2007.)*

are calibrated against laboratory Sao_2 down to 70% saturation, and lower saturations are determined by extrapolation of the curve. Thus, pulse oximeters cannot be calibrated by the user, and their reliability is dependent on the quality of signal processing and the stored calibration curve.

Accuracy of Pulse Oximetry

Because of its impressive accuracy, reliability, and convenience, pulse oximetry has become one of the most important technologic developments in clinical monitoring. Several studies comparing co-oximetry and pulse oximetry report substantial agreement between Spo_2 and Sao_2 over a wide range of Sao_2 values.[38,39]

Errors in Pulse Oximetry

Because Spo_2 measurements are averaged over a few seconds to provide readings, there is some degree of delay in response time. Hypothermia, low CO, and vasoconstriction secondary to drugs or peripheral hypoxia all increase bias, imprecision, and response time for hypoxic episodes (Table 44-2).[40] This appears to be more common with finger probes than with ear or forehead monitoring (Fig. 44-10).[41] Motion artifact and hypoperfusion are the most common causes of Spo_2 inaccuracy,[42,43] both of which are less problematic with newer oximeters. Caution is advised in using pulse oximetry to not make inferences about gas exchange. Spo_2 should not be used to assess the adequacy of ventilation because Sao_2 is only minimally affected by changes in Pco_2 (via the Bohr effect). In addition, when Po_2 is high, large decreases in oxygen tension produce only small changes (if any) in Sao_2 and may not be detected with pulse oximetry (see Fig. 44-2).

Anemia, with an Hb concentration as low as 2.3 g/dL, has little or no effect on Spo_2 readings when Sao_2 is normal,[44] but underestimation of Sao_2 has been observed during hypoxemia.[45] Because MetHb substantially absorbs both red and infrared light, falsely low Spo_2 readings are generated when actual Sao_2 is above 85%, and readings are falsely high when actual Sao_2 is below 85%. Spo_2 invariably reads 85% when very large amounts of MetHb are present.[46] Conversely, COHb absorbs very little infrared light, but it is very similar to HbO_2 in its red light absorbance. Oximeters using only two wavelengths therefore cannot distinguish between HbCO and HbO_2, and the presence of HbCO produces falsely elevated Spo_2 readings. Erroneous Spo_2 readings can be caused by structural hemoglobinopathies,[47,48] as well as by a host of other factors, many of which are summarized in Table 44-2.

Recent Advances in Pulse Oximetry

Error Correction. Motion sensitivity and signal loss secondary to hypoperfusion are two of the more common errors that occur with pulse oximetry. These inaccuracies have been reduced with the recent advances in signal analysis that have been incorporated into units from a number of manufacturers.[49] Several studies suggest that newer units can detect hypoxemic episodes more reliably than their predecessors can under these conditions.[50,51] Indeed, one study reported that during hypoperfusion or excessive motion, oximeters using this technology give accurate Sao_2 readings in 92% of cases in which older monitors failed.[52]

Multiwavelength Pulse Oximeters. Because only two wavelengths of light are used in traditional pulse oximeters, the presence of additional Hb species cannot be detected, which may result in erroneous readings. Using principles from both pulse

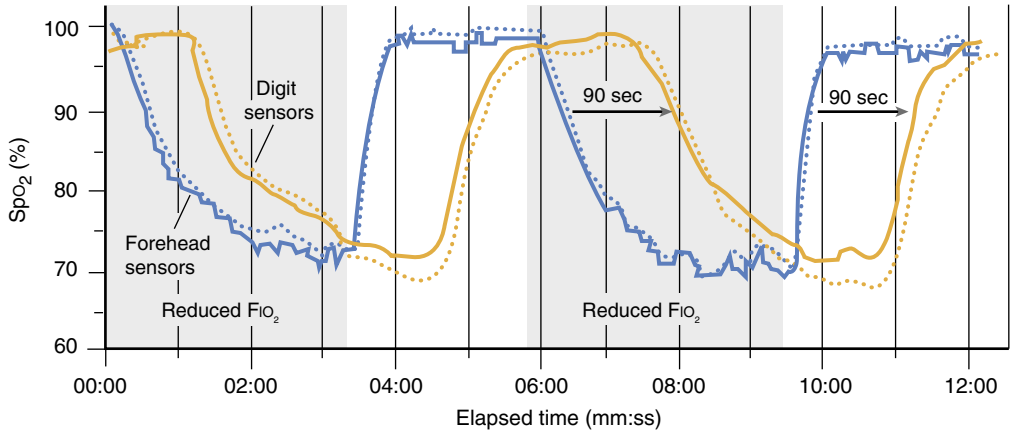

Figure 44-10 Effect of pulse oximeter probe replacement on delay from onset of hypoxemia to a drop in measured Spo_2. During cold-induced peripheral vasoconstriction in normal volunteers, the onset of hypoxemia was detected more quickly with an oximeter probe on the forehead than on the finger. Other studies have shown a similar advantage for pulse oximeter probes placed on the ear. *(From Bebout DE, Mannheimer PD, Wun C-C: Site-dependent differences in the time to detect changes in saturation during low perfusion. Crit Care Med 29:A115, 2002.)*

oximetry and co-oximetry, the first eight-wavelength pulse oximeter capable of measuring several species of Hb has become commercially available and may prove to be a major advance in oxygen monitoring. The Massimo Rad-57 (Massimo Corp, Irvine, CA) gained Food and Drug Administration (FDA) clearance in 2006 and boasts the ability to accurately measure MetHb and COHb, in addition to all the features of conventional pulse oximetry. Two large studies comparing measurements from the unit with conventional co-oximetry in emergency department patients have produced equivocal results, with one reporting a significant number of false-positive readings.[53,54] One smaller study in healthy volunteers reported good agreement between oximeter and laboratory measurements,[55] and other investigations to determine accuracy of the device are ongoing.

Reflectance Pulse Oximetry. The technology was developed to combat problems with signal transmission during hypoperfusion and for use when a transmission path is unavailable. Probes are commonly placed on the forehead, where motion artifact and hypoperfusion tend to be less of a problem than with other sites.[56] Forehead probes are commercially available and appear to detect hypoxemia more quickly than ear or finger probes do.[41] The light-emitting and light-sensing diodes are on the same side of the probe instead of opposite sides as in traditional pulse oximetry, and the reflected light from the tissue bed is analyzed. Indeed, reflectance oximetry has been used to monitor fetal oxygen saturation with scalp probes and been shown to decrease surgical intervention in the face of non-reassuring fetal status.[57] Esophageal probes have been designed and have shown success in measuring Spo_2 during cardiothoracic surgery when finger probes have failed.[58] The investigators reported minimal bias and narrow limits of agreement when compared with finger probes used in the study. Monitoring of gastric Spo_2 as an indicator of splanchnic perfusion has also shown promise.[59] Excessive edema, poor skin contact, and motion artifact are the most common sources of error in reflectance oximetry. Artifacts have also been shown to occur with probe placement directly over a pulsating superficial artery.[60]

Clinical Applications of Pulse Oximetry

Pulse oximetry is arguably most useful as an early warning sign of hypoxemia. Because this is of paramount importance in the surgical setting, pulse oximetry became a standard of care in anesthesia practice in 1986. In a large study comparing intraoperative pulse oximeter use with standard care, 80% of anesthesiologists felt more comfortable when using pulse oximetry.[61] It is interesting to note that despite its widely accepted value, there is little evidence that pulse oximetry affects outcomes in anesthesia,[62] and a study evaluating postsurgical patients did not demonstrate that routine Sao_2 monitoring reduces mortality, cost of hospitalization, or ICU transfer.[63]

Perioperative. In a randomized, controlled study of 200 surgical patients, Moller and colleagues found a reduced incidence of hypoxemia intraoperatively and in the postanesthesia care unit (PACU) when pulse oximetry was used. In the recovery room, patients in the oximeter group on average received higher FIO_2 and more naloxone, had a longer stay, and were discharged with supplemental O_2 more frequently.[64] The same group later conducted a study looking at postoperative complications with and without intraoperative pulse oximetry in 20,802 patients. No overall difference was found in complication rate, outcome, mean hospital stay, or in-hospital death between the groups, even though hypoxemia and hypoventilation were detected more frequently when pulse oximetry was used.[64] However, post hoc analysis of this trial suggests that pulse oximetry may have decreased the incidence of myocardial ischemia.[62] A number of studies report detection of hypoxemia several days postoperatively with pulse oximetry.[65,66] Intrapartum fetal pulse oximetry in the presence of a non-reassuring fetal heart rate is associated with a reduction in operative interventions.[57] The peak effects of analgesia may correlate with hypoxemia, so monitoring of patients receiving narcotics may be important to prevent adverse cardiac events.[67]

Critically Ill. The complicated pathophysiologic milieu of critical illness is such that many monitoring devices can produce inaccurate data in this patient population. Pulse oximetry, on the other hand, appears to maintain its reliability. Jubran and Tobin found that pulse oximeters accurately estimate Sao_2 in critically ill patients when Sao_2 is greater than 90% (bias, 1.7%; precision, ±1.2%) but are less accurate when Sao_2 falls below 90%.[68] An Spo_2 of 92% was indicative of adequate oxygenation when titrating O_2 in white patients. In black patients, however, significant hypoxemia was commonly present with an Spo_2 of

Table 44-2 Artifacts in Pulse Oximetry

Factor	Effect
Toxic Alterations in Hemoglobin	
Carboxyhemoglobin (COHb)	Slight reduction of the assessment of oxygen saturation (Sao_2) by pulse oximetry (Spo_2) (i.e., overestimates the fraction of hemoglobin available for O_2 transport)
Cyanmethemoglobin	Not reported
Methemoglobin (MetHb)	At high levels of MetHb, Spo_2 approaches 85%, independent of actual Sao_2
Sulfhemoglobin	Not reported (affects CO oximetry by producing a falsely high reading of MetHb)
Structural Hemoglobinopathies	
Hemoglobin F	No significant effect
Hemoglobin H	No significant effect (i.e., overestimates the fraction of hemoglobin available for O_2 transport)
Hemoglobin Köln	Artifactual reduction in Spo_2 of 8% to 10%
Hemoglobin S	No significant effect
Hemoglobin Replacement Solutions	
Diaspirin cross-linked hemoglobin	No significant effect
Bovine polymerized hemoglobin (oxygen carrier-201)	No significant effect
Dyes	
Fluorescein	No significant effect
Indigo carmine	Transient decrease
Indocyanine green	Transient decrease
Isosulfan blue (patent blue V)	No significant effect at low dose; prolonged reduction in Spo_2 at high dose
Methylene blue	Transient, marked decrease in Spo_2 lasting up to several minutes; possible secondary effects as a result of effects on hemodynamics
Hemoglobin Concentration	
Anemia	If Sao_2 is normal, no effect; during hypoxemia with Hb values less than 14.5 g/dL, progressive underestimation of actual Sao_2
Polycythemia	No significant effect
Other Factors	
Acrylic fingernails	No significant effect
Ambient light interference	Bright light, particularly if flicker frequency is close to a harmonic of the light-emitting diode switching frequency, can falsely elevate the Spo_2 reading
Arterial O_2 saturation	Depends on manufacturer; during hypoxemia, Spo_2 tends to be artifactually low
Blood flow	Reduced amplitude of pulsations can hinder obtaining a reading or cause a falsely low reading
Henna	Red henna, no effect; black henna, may block light sufficiently to preclude measurement
Jaundice	No effect; multiwavelength laboratory oximeters may register a falsely low Sao_2 and falsely high COHb and MetHb
Motion	Movement, especially shivering, may depress the Spo_2 reading
Nail polish	Slight decrease in Spo_2 reading, with greatest effect using blue nail polish, or no change
Sensor contact	"Optical shunting" of light from source to detector directly or by reflection from skin results in falsely low Spo_2 reading
Skin pigmentation	Small errors or no significant effect reported; deep pigmentation can result in reduced signal
Tape	Transparent tape between sensor and skin has little effect; falsely low Spo_2 has been reported when smeared adhesive is in the optical path
Vasodilatation	Slight decrease
Venous pulsation (e.g., tricuspid insufficiency)	Artifactual decrease in Spo_2

92%, and an Spo_2 of 95% was needed to ensure adequate oxygenation. After cardiac surgery, use of pulse oximetry has been shown to increase detection of hypoxemic episodes and decrease the number of arterial BGAs performed in the ICU.[69]

New and Future Applications

Analysis of the plethysmographic waveform generated by pulse oximeters has been advocated as a means of assessing volume status, fluid responsiveness, and a number of other clinical variables.[70,71] Respiratory variations in systolic pressure (dPs) and arterial pulse pressure (dPp) have been shown to be accurate indicators of volume status and fluid responsiveness in mechanically ventilated patients (Fig. 44-11).[72] Pulse pressure variation may predict fluid responsiveness more reliably than the use of dPs can. Such analyses require placement of an arterial catheter and are not always practical. Recently, variation in the pulse oximeter plethysmograph (dPOP) amplitude was shown to be a reliable noninvasive surrogate for dPp because both parameters are dependent on

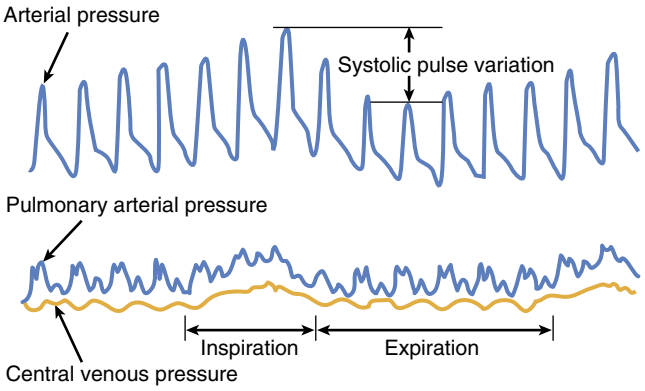

Figure 44-11 Cyclic variation of vascular pressures during positive-pressure ventilation. Inspiratory reduction in preload leads to reduced left ventricular volume after a lag phase of a few heartbeats because of pulmonary vascular transit time. The inspiratory decrease in left ventricular volume results in decreased stroke volume and systolic blood pressure during expiration. Similar variations in amplitude can be noted in pulse oximeter waveforms. *(From Nanchal R, Taylor RW. Hemodynamic monitoring.* In *Papadakos PJ, Lachmann B [eds]: Mechanical Ventilation: Clinical Applications and Pathophysiology. Philadelphia, Elsevier, 2008.)*

stroke volume.[73] In a study of patients under GA, Cannesson and colleagues found that baseline dPOP was correlated with percent change in cardiac index induced by volume expansion.[74] Similar results were obtained in a separate study on critically ill septic patients.[75] The authors of these trials concluded that dPOP can predict response to fluid administration and quantifies the effect of volume expansion on a number of hemodynamic parameters. To elucidate where the oximeter probe should be placed to best detect these variations, Shelley and colleagues analyzed plethysmographic waveforms from finger, ear, and forehead probes in patients undergoing positive-pressure ventilation during surgery, as well as in spontaneously breathing patients.[76] Their results suggest that the ear and forehead may be better monitoring sites than the finger for detection of variation in respiratory waveform. Because error and artifact correction in most commercial pulse oximeters can obscure the often subtle respiratory variations, unaltered plethysmographic waveforms are needed for such analyses.

Many other novel applications of pulse oximetry in anesthetic practice have been studied. Mowafi found that dPOP may be a better indicator of intravascular test dose injection during epidural placement than traditional hemodynamic markers are (i.e., heart rate and blood pressure).[77] A 10% decrease in POP indicated intravascular injection with 100% sensitivity, specificity, positive predictive value, and negative predictive value. Sensitivities using heart rate and blood pressure change as criteria were 85% to 95%. Changes in perfusion index (defined as AC_{940}/DC_{940}) have been used as confirmation of epidural placement and as an indicator of painful stimulus under anesthesia.[78,79] Many modern oximeters are programmed to measure perfusion index.

Mixed Venous Monitoring

Shock represents an imbalance between oxygen demand, delivery, and utilization at the tissue level. Monitoring of mixed venous oxygen saturation ($S\bar{v}O_2$) can give insight into the adequacy of this balance. It can be calculated by rearranging the Fick equation for O_2:

$$S\bar{v}O_2 = SaO_2 - \dot{V}O_2/(Hb \times 1.39 \times CO) \quad (14)$$

From this equation, it is clear that decreased $S\bar{v}O_2$ can be caused by low SaO_2, low Hb, or low cardiac output, all of which decrease oxygen delivery (DO_2), or by increased O_2 consumption ($\dot{V}O_2$). These variables are related in the following way:

$$\dot{V}O_2 = DO_2 \cdot ERO_2 \quad (15)$$

where ERO_2 is the extraction ratio (%) of O_2.

If oxygen delivery to tissue falls and consumption is to remain constant, oxygen extraction by tissues must increase. Blood returning to the right heart will therefore have a reduced O_2 content and $S\bar{v}O_2$. Thus, a reduced $S\bar{v}O_2$ is suggestive of global tissue hypoxia, which often precedes multiorgan failure and death.[80] Increased anaerobic metabolism as evidenced by increased lactate levels ensues and is associated with increased mortality.[81] These processes are usually under way as $S\bar{v}O_2$ approaches 40%. A pulmonary artery catheter is required to measure mixed venous saturation, and continuous monitoring can be performed with a catheter that incorporates a fiberoptic bundle. A superior vena cava sample obtained from a central venous catheter is often used as a surrogate for mixed venous saturation when a pulmonary artery catheter is impractical or unavailable.[82]

Shock of any etiology can cause the aforementioned turn of events, and a low $S\bar{v}O_2$ sheds no light on the cause of the global hypoxia. As mentioned, low $S\bar{v}O_2$ may not always be secondary to impaired delivery but may be due to increased oxygen consumption in the face of fever, thyrotoxicosis, and other conditions (Fig. 44-12). Moreover, a normal $S\bar{v}O_2$ is not necessarily indicative of adequate tissue oxygenation. Although cardiogenic and hypovolemic shock is very often associated with low $S\bar{v}O_2$, it can be normal or elevated in shock secondary to severe sepsis or hepatic failure because these conditions are frequently associated with microvascular dysfunction and impaired oxygen extraction by tissues. DO_2 is often elevated in these states.

In a novel application of continuous $S\bar{v}O_2$ measurement, pulse oximetry combined with $S\bar{v}O_2$ monitoring has been used in patients with acute respiratory failure to continuously monitor shunt fraction and adjust ventilator settings accordingly.[82] The authors of this study adjusted continuous positive airway pressure (CPAP) levels to obtain the lowest shunt fraction and showed that use of this method results in CPAP settings similar to those obtained by conventional means. Though somewhat invasive, the technique was found to be cost-effective and accurate in titrating CPAP in this subset of patients.

Tissue Oxygenation

The goal of optimizing pulmonary gas exchange is to ultimately optimize oxygenation at the cellular level. Analysis of alveolar, arterial, and venous gases is used in conjunction with clinical indices of tissue function (i.e., urine output, mental status) to make inferences about the state of affairs in cells. Oxygen is transported from alveoli with a PO_2 of around 100 mm Hg down a steep gradient, known as the oxygen cascade, to its final site of utilization, the mitochondrion, where PO_2 is estimated to be less

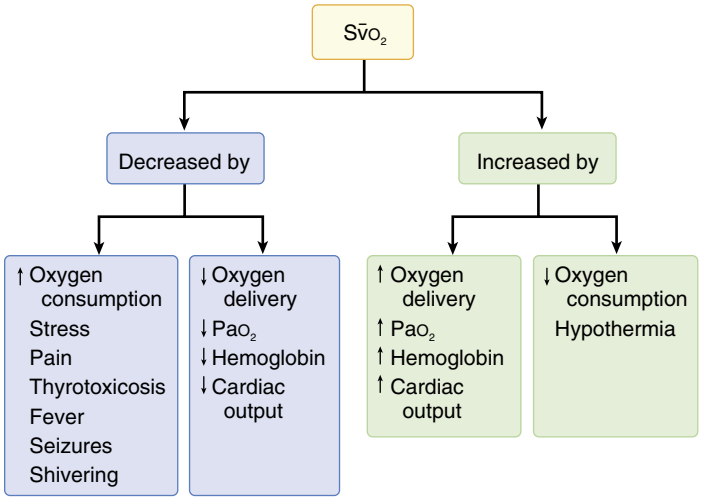

Figure 44-12 Causes of changes in mixed venous oxygen saturation. *(From Nanchal R, Taylor RW. Hemodynamic monitoring.* In *Papadakos PJ, Lachmann B [eds]: Mechanical Ventilation: Clinical Applications and Pathophysiology. Philadelphia, Elsevier, 2008.)*

than 1 mm Hg. Mitochondria from skeletal muscle appear to maintain their function with a Po_2 as low as 0.1 mm Hg.[83]

Unlike arterial Po_2 measurements, which should be nearly equal regardless of the artery sampled, Po_2 varies considerably within a particular organ or tissue bed because blood flow and O_2 consumption are not uniform but vary from point to point within the tissue. Because O_2 diffuses down a gradient from arterioles to mitochondria, measurements may also vary depending on where along this pathway a reading is obtained. Thus, it is generally thought that a distribution of Po_2 measurements across the tissue must be obtained to best describe its oxygenation status. Because of variable O_2 supply and demand, normal Po_2 levels and distributions differ from organ to organ.

A variety of methods have been devised to directly measure oxygen tensions and concentrations within tissues, and it has been an area of intense research for several decades. Most of the technologic advances have been made in the laboratory and have yet to be proved practical in the clinical setting.

Polarography is the current standard modality for measuring tissue oxygenation. It has the best resolution of all the available technology. Similar in principle to laboratory BGA, a Clark or needle-type electrode is inserted into tissue (rather than a blood sample), and Po_2 is proportional to the current generated as oxygen is reduced. Oxygen tension as low as 0.1 mm Hg can be resolved quite accurately. Though too invasive for routine clinical use, the technology is commercially available and has found application in neurosurgery and oncology.[84,85]

Near-infrared spectroscopy is a noninvasive system capable of measuring the oxygenation state of hemoglobin, myoglobin, and mitochondrial cytochromes.[86] The ability to monitor the oxygenation status of cytochromes along the electron transport chain will probably prove to be the best estimate of cellular oxygenation. Up to four wavelengths of light are applied to tissue, and the scattered light is returned via fiberoptic cables to the monitor for analysis. The technology has been incorporated into devices capable of measuring blood O_2 saturation in the brain, which have been commercially available for some 20 years.[87] Resolution is inferior to that of polarography, and problems with calibration and interference have limited its widespread use. Images can be obtained depicting changes in Hb concentration, but the resolution is poor.

A number of new systems for measuring tissue oxygenation are under laboratory investigation and have yet to reach commercial availability. Such systems include phosphorescence, fluorescence, electron paramagnetic resonance oximetry, and nuclear magnetic resonance spectroscopy. A number of reviews detailing all of these techniques have been compiled.[87]

Expired Gas Analysis

The ability to rapidly measure concentrations of inspired and expired gas is of paramount importance in anesthetic practice. Most anesthesia machines are equipped with oxygen sensors on the inspiratory limb of the circuit to help ensure that an adequate supply of oxygen is delivered to the patient at all times. Expired gas analysis is used to make inferences about blood concentrations and depth of anesthesia. Several systems are available for the measurement of gas tensions in exhaled air.

Mass Spectrometry

Mass spectrometry is a technique by which concentrations of gas particles in a sample can be determined according to their mass-charge ratio. A gas sample is passed through an ionizer and molecules become positively charged ions. Because all of the ions generated carry the same positive charge, this allows separation of particles based solely on mass. A detector then counts the number of ions of each mass, and the results are translated into concentrations. Measurements are quite reliable and can be obtained in fractions of a second.

Clinical use of mass spectrometry for expired gas analysis began in respiratory care units in the mid-1970s. They were introduced into operating rooms and anesthesia practice shortly thereafter. Because of their size and complexity, hospitals often connected many operating rooms to a single spectrometer and had the results relayed back to the anesthesiologist. The convenience plus low cost of infrared analyzers has largely phased mass spectrometry out of clinical use.

Infrared Absorption

Presently, most expired gas analyzers used in anesthesia involve infrared absorption. A gas sample is collected in a chamber through which infrared light is passed, and gas tensions are derived based on the intensity of the transmitted light. Today's infrared gas analyzers are capable of measuring all anesthetic agents currently in use, as well as CO_2 and N_2O. Oxygen does not absorb infrared light and therefore must be measured by other means, such as electrochemical or paramagnetic analysis.

Electrochemical Analysis

The same principles allowing electrochemical determination of oxygen in blood or tissue can be used to measure Po_2 in a mixture of gas. Polarographic (Clark type) electrodes, which require an applied voltage, or galvanic cells (most common) can be used for this purpose. In either arrangement, the amount of current generated as oxygen is reduced is proportional to the amount of oxygen present in the gas mixture, thus providing reliable estimates of Po_2 electrochemically. These sensor types are often used to measure inspired oxygen concentrations in anesthesia machines and conventional ventilators. Response time is somewhat slow and the method is rarely used for expired gas analysis.

Paramagnetic Analysis

Because the oxygen molecule has magnetic properties, its behavior in a magnetic field can be used to determine the concentration of oxygen in a gaseous mixture. Some newer anesthesia machines (e.g., Datex Ohmeda S/5) have incorporated paramagnetic oxygen analyzers capable of measuring oxygen in both the inspired and expired limbs of the circuit. Paramagnetic devices boast a longer life span and faster response time than electrochemical cells do.

Measurement of Nitric Oxide

Nitric oxide (NO) is a potent pulmonary vasodilator and has been used for a number of years to improve oxygenation in the face of acute respiratory distress syndrome (ARDS) and severe pulmonary hypertension (see also Chapter 31). It is produced endogenously and has multiple physiologic functions, including neurotransmission, regulation of vascular tone, and mediation of inflammation. Studies have identified NO as a marker of airway eosinophil activation, and exhaled levels are elevated in a number of inflammatory airway diseases such as asthma and chronic obstructive pulmonary disease (COPD).[88] Elevation of exhaled NO is greater than 90% specific for the diagnosis of asthma in both children and adults.[89,90] NO_2, the toxic oxidation product of NO, can accumulate with prolonged treatment or if stored NO is exposed to oxygen. Although accumulation of harmful levels is rare, NO_2 is known to cause pulmonary toxicity even at relatively low concentrations. Thus, an ideal NO analyzer would also have the ability to accurately measure NO_2 levels to avoid delivery or accumulation of toxic levels of this by-product. As the diagnostic and therapeutic use of NO has increased, methods to accurately quantify inhaled and exhaled concentrations of both NO and NO_2 have been sought.

Continuous measurement of inhaled NO has traditionally been accomplished with the use of electrochemical sensors. NO is oxidized to nitric acid, and its concentration is proportional to the current generated by the reaction. A number of electrochemical NO sensors have been independently evaluated and are reported to be quite accurate in measuring inhaled NO and NO_2.[91,92] The electrodes are sensitive to water vapor, and prolonged exposure can shorten the life span of the sensor and promote inaccurate readings. Accuracy also begins to wane at concentrations below 1 part per million (ppm), thus making them inappropriate for measurement of exhaled concentrations, which are typically in the parts-per-billion (ppb) range. Moreover, the slow response time of electrochemical sensors prevents their use for single-breath and exhaled NO analysis.

Because it is normally exhaled in very low concentrations, NO in expired air can be measured only with mass spectrometry or a process known as chemiluminescence. These analyzers, currently the most commonly used, have a shorter response time and can detect less than 1 ppb NO and NO_2. Wide variations in exhaled NO readings have been reported with chemiluminescence analyzers, and NO_2 levels may be underestimated in the presence of high oxygen concentrations.[93,94] Unstable instrument temperature, varying expiratory flow rate, and interference are some of the factors that may explain these variations.[95] Another study comparing four analyzers found that only the most rapid device provided accurate analysis in a continuous flow system and that the other three overestimated low levels and underestimated high levels.[96] A mid-infrared laser spectroscopy system has been developed that may eliminate some of the problems encountered with chemiluminescence analyzers by simultaneously measuring CO_2. It has shown promise in a small study comparing its results with typical exhaled NO levels.[95]

Waveform Analysis of Expired Respiratory Gases

Capnographs

Changes in the shape of the expired CO_2 waveform in an intubated patient can provide very useful monitoring information. Capnometry is the measurement of expired CO_2 and has become increasingly popular as a diagnostic tool in a number of settings. It is now the confirmation method of choice in anesthesia for proper placement of an endotracheal tube. CO_2 concentration is usually measured by infrared absorption with either a mainstream or sidestream capnometer. Measurements can then be plotted against time or exhaled volume to generate a *capnograph*. Capnography has found many useful clinical applications, and in 1998 it was adopted by the American Society of Anesthesiologists as standard care for all general anesthetics administered.

Mainstream versus Sidestream

The major difference between sidestream and mainstream capnometry is location of the sensor. However, this seemingly minor

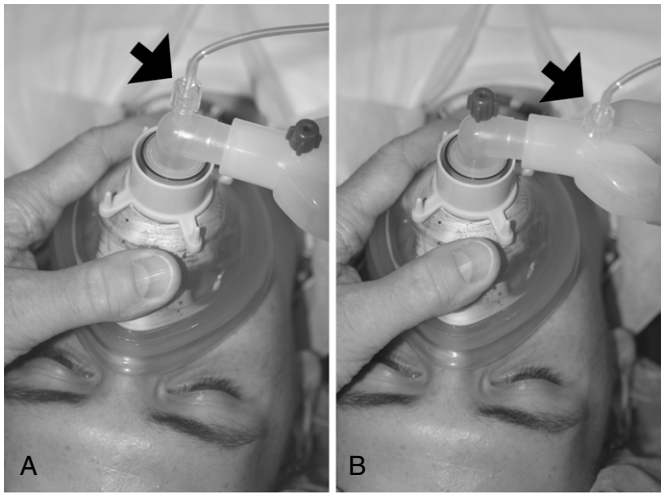

Figure 44-13 Sidestream sampling port placement. **A,** To minimize the effects of breathing circuit dead space, attachment of the sampling port should be as close to the patient as possible (*arrow*). **B,** Placement of the port as shown (*arrow*) can cause artifactual lowering of the end-tidal measurement.

difference plays a major role in the complexity, accuracy, and response time of each system.

SIDESTREAM. In sidestream capnometry, a fixed volume of gas is continuously sampled from the circuit. The sampled gas is aspirated through nylon or Teflon tubing into the measuring cell and then released into the atmosphere or returned to the circuit through a second tube (Fig. 44-13). Sampling should take place as close to the patient as possible to minimize the effects of circuit dead space, and the rate is usually adjusted to between 50 and 500 mL/min. It is imperative that the sampling rate be adjusted properly. Erroneous measurements will be obtained if the sampling rate exceeds the expiratory flow rate and causes inspired gas to be sampled. Hypoventilation may occur if the sampling flow exceeds fresh gas flow. Particular attention should be paid to this factor in the pediatric setting, in which expired and fresh gas flow can be quite low. Oxygen masks or nasal cannulas can be adapted to allow CO_2 monitoring (Fig. 44-14). The respiratory rate can be monitored adequately, but P_{ETCO_2} measurements may be falsely low unless the sample tubing is placed close to the nostril. Cannulas specifically designed to allow P_{ETCO_2} monitoring while administering O_2 have been developed and are commercially available.

There are several sources of potential error in sidestream capnometry. Water vapor condenses in the sample tubing and often accumulates in the measuring chamber. Liquids and particulate matter can also enter the measuring cell and produce erroneous readings. Most systems incorporate filters and water traps to help minimize these factors. Response time is delayed because gas samples must travel to the measuring cell through the sample tubing. Such delay can be minimized by using short tubing with a small lumen and high sample flow rates. The somewhat complicated sampling system and tubing connections provide multiple sites for damage or gas leakage. CO_2 can diffuse out of sample tubing and cause falsely low readings. Longer tubing and slower sampling rates increase this error, and nylon appears to be less permeable to CO_2 than other commonly used materials are.

MAINSTREAM. Mainstream capnometers incorporate the infrared sensor into the circuit very close to the endotracheal tube. Consequently, many of the problems with sidestream capnometry have been eliminated. CO_2 is measured directly in the circuit and no gas is subtracted, thus obviating the need for a complicated sampling system. The effects of breathing circuit and sample tubing dead space are minimized and the response time is therefore faster with mainstream systems. They are often used in the pediatric population, where circuit dead space can be more significant and response time is more critical. The measuring chamber must be warmed to about 40°C to prevent condensation of water vapor on the sensor window. Care must be taken to avoid skin contact with the chamber. It is somewhat heavy, and the

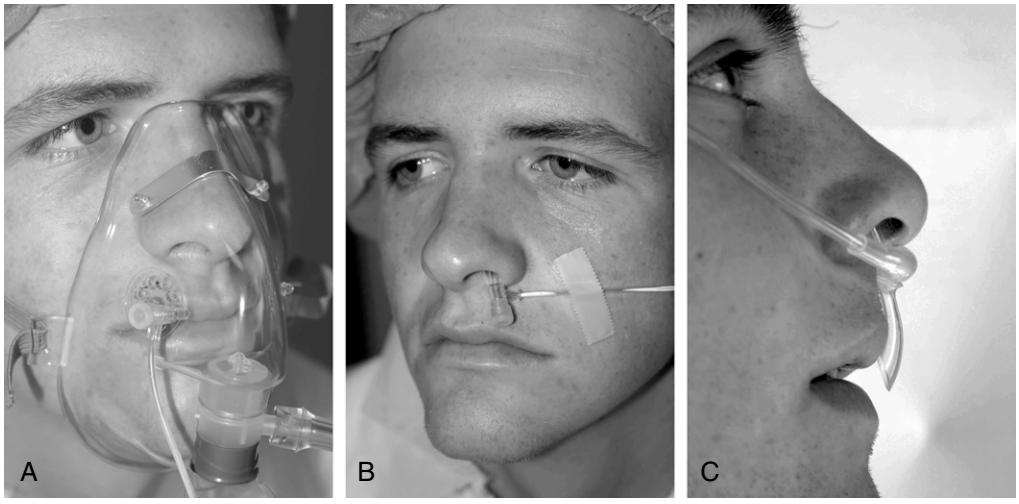

Figure 44-14 Monitoring a spontaneously breathing patient with a sidestream capnometer. **A,** Attachment of the sampling line to a non-rebreathing mask usually provides waveforms adequate for monitoring the respiratory rate, but end-tidal CO_2 tension (P_{ETCO_2}) is low because of mixing within the mask. **B,** Placement of a sample probe close to a nostril increases the accuracy of P_{ETCO_2} measurement. **C,** A specially designed probe (Oridion, Needham, MA) samples exhaled gas from the nose and mouth for assessing exhaled gas from mouth breathers. A second port in the same device can be used to administer supplemental oxygen.

circuit should be inspected frequently to avoid kinking of the endotracheal tube. Mainstream capnometers require frequent calibration, usually daily, and are prone to soiling with saliva or mucus because of their close proximity to the patient.

Time versus Volume Capnographs

TIME. The most commonly used type of capnograph plots P_{CO_2} versus time. The tracing is traditionally divided into an inspiratory phase and three (sometimes four) expiratory phases (Fig. 44-15):

Phase 0: inspiratory phase
Phase I: dead space and little or no CO_2
Phase II: mixture of alveolar and dead space gas
Phase III: alveolar plateau, with the peak representing end-expiratory (end-tidal) CO_2 (P_{ETCO_2}).

In patients with normal lung function, P_{ETCO_2} generally underestimates P_{aCO_2} by 1 to 5 mm Hg because of the presence of a small amount of alveolar dead space.[7] Factors that increase alveolar dead space will widen this gradient and increase the slope of phase III. During anesthesia there is often increased alveolar dead space caused by reduced cardiac output and decreased perfusion of the lung apices.[97] It is therefore not surprising that studies under anesthesia have found the P_{ETCO_2}-P_{aCO_2} gradient to be slightly elevated at 5 to 10 mm Hg.[98] An extreme example of acutely increased alveolar dead space is pulmonary embolism. Thus, an abruptly decreased P_{ETCO_2} with ventilation held constant is often indicative of a sudden decrease in cardiac output or pulmonary embolism. Other common causes of a widened gradient include obstructive lung disease, smoking, and advanced age. Examples of commonly encountered capnographic waveforms are shown in Figure 44-16.

The slope of the alveolar plateau (phase III) can also be increased in obstructive airway disease or during prolonged expiration. Two explanations for this phenomenon have generally been forwarded. First, obstructed (slow) lung units with low $\dot{V}/\dot{Q}$ and high P_{CO_2} empty slower and later than "fast" alveoli with normal $\dot{V}/\dot{Q}$ and low P_{CO_2}. This is manifested as a linear upsloping of phase III instead of the typical "plateau." Second, as lung volume decreases during exhalation and CO_2 excretion from capillaries remains constant, P_{CO_2} slowly rises throughout expiration and causes an upsloping plateau (Fig. 44-17).[99] Accordingly, even a person with completely normal lungs can have an upsloping plateau during prolonged expiration. End-tidal CO_2 therefore approximates *peak* alveolar CO_2, whereas P_{aCO_2} can be thought of as average alveolar P_{CO_2}.

At the terminal end of the phase III plateau, a sharp rise in P_{CO_2} is sometimes observed and is referred to as phase IV. Although its exact cause is unknown, this rise is thought to occur when closing capacity is reached and small airways close, usually

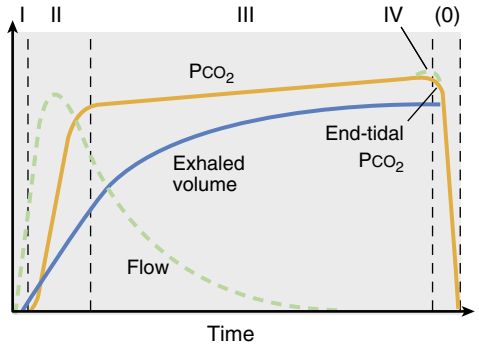

Figure 44-15 Time and volume capnographs. **A,** Expired P_{CO_2} versus time (i.e., standard time capnogram). The waveform is conventionally subdivided into phases. During phase I, exhaled gas from the large airways has a P_{CO_2} of 0. Phase II is the transition between airway and alveolar gas. Phase III (i.e., alveolar plateau) is normally flat, but in the presence of $\dot{V}_A/\dot{Q}$ mismatching, it has a positive slope. The downslope of the capnogram at the onset of inspiration is usually referred to as phase 0, but sometimes there is a terminal increase in the slope associated with the onset of airway closure (*dashed line* labeled IV). The P_{CO_2} value at the end of exhalation is referred to as the end-tidal P_{CO_2} (P_{ETCO_2}). Also shown are the exhaled gas flow rate and volume.

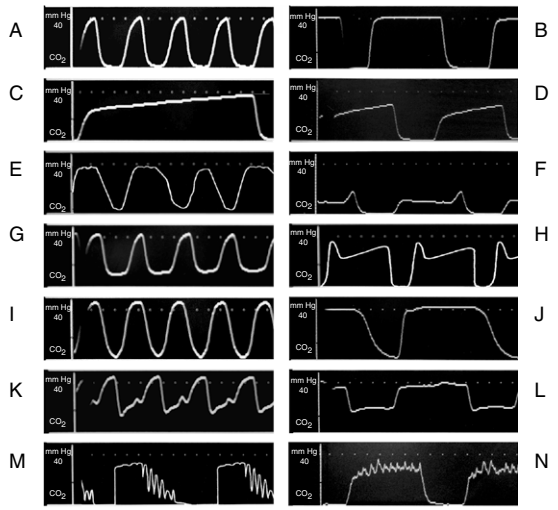

Figure 44-16 Examples of capnograph waves. **A,** Normal spontaneous breathing. **B,** Normal mechanical ventilation. **C,** Prolonged exhalation during spontaneous breathing. As CO_2 diffuses from mixed venous blood into alveoli, its concentration progressively rises (see Fig. 44-17). **D,** Increased slope of phase III in a mechanically ventilated patient with emphysema. **E,** Added dead space during spontaneous ventilation. **F,** Dual plateau (i.e., tails-up pattern) caused by a leak in the sample line. The alveolar plateau is artifactually low because of dilution of exhaled gas with air leaking inward. During each mechanical breath the leak is reduced because of higher pressure within the airway and tubing, thus explaining the rise in CO_2 concentration at the end of the alveolar plateau. This pattern is not seen during spontaneous ventilation because the required increase in airway pressure is absent. **G,** Exhausted CO_2 absorbent producing an inhaled CO_2 concentration greater than zero. **H,** Double peak in a patient with a single lung transplant. The first peak represents CO_2 from the transplanted (normal) lung. Exhalation of CO_2 from the remaining (obstructed) lung is delayed, thereby producing the second peak. **I,** Inspiratory valve stuck open during spontaneous breathing. Some backflow into the inspired limb of the circuit causes a rise in the level of inspired CO_2. **J,** Inspiratory valve stuck open during mechanical ventilation. The "slurred" downslope during inspiration represents a small amount of inspired CO_2 in the inspired limb of the circuit. **K** and **L,** Expiratory valve stuck open during spontaneous breathing and mechanical ventilation, respectively. Inhalation of exhaled gas causes an increase in inspired CO_2. **M,** Cardiogenic oscillations, when seen, usually occur on sidestream capnographs of spontaneously breathing patients at the end of each exhalation. Cardiac action causes to-and-fro movement of the interface between exhaled and fresh gas. The CO_2 concentration in gas entering the sampling line therefore alternates between high and low values. **N,** Electrical noise resulting from a malfunctioning component. The seemingly random nature of the signal perturbations (about three per second) implies a nonbiologic cause.

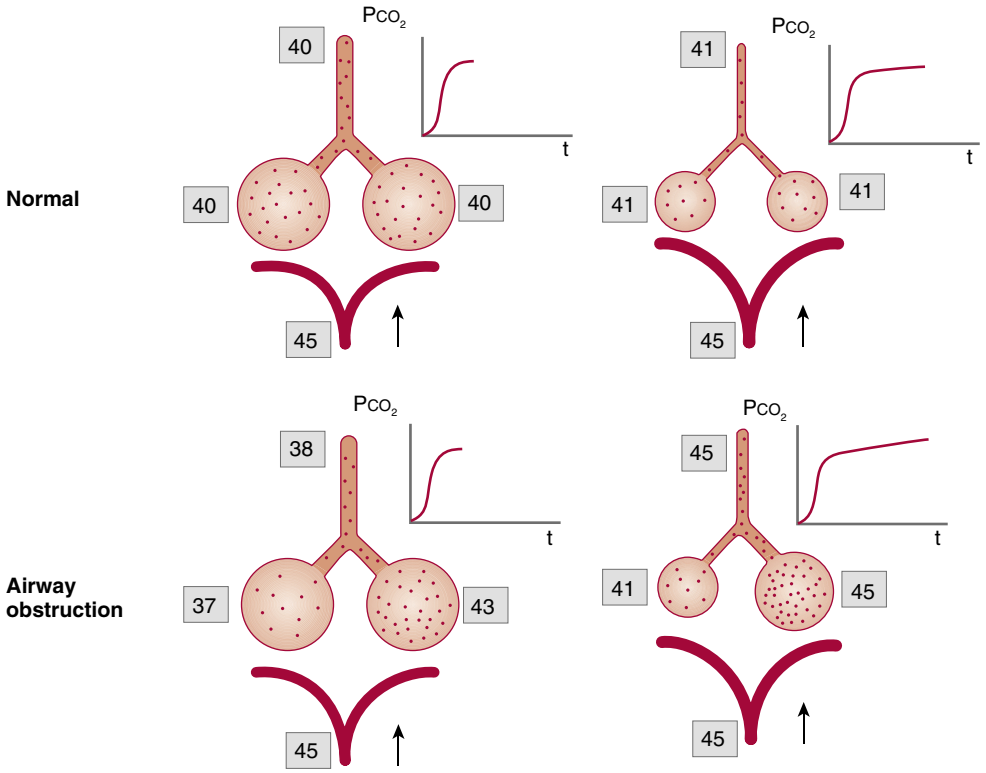

Figure 44-17 Mechanisms of airway obstruction producing an upsloping phase III capnogram. In a normal, healthy person (*upper panel*), there is a narrow range of $\dot{V}_A/\dot{Q}$ ratios with values close to 1. Gas exchange units therefore have similar P_{CO_2} and tend to empty synchronously, and the expired P_{CO_2} remains relatively constant. During the course of exhalation, alveolar P_{CO_2} slowly rises as CO_2 continuously diffuses from blood. This causes a slight increase in P_{CO_2} toward the end of expiration, and this increase can be pronounced if the exhalation is prolonged (see Fig. 44-16C). In a patient with diffuse airway obstruction (*lower panel*), the airway pathology is heterogeneous, with gas exchange units having a wide range of $\dot{V}_A/\dot{Q}$ ratios. Well-ventilated gas exchange units, with gas containing lower P_{CO_2}, empty first; poorly ventilated units, with higher P_{CO_2}, empty last. In addition to the continuous rise in P_{CO_2} mentioned previously, there is a progressive increase caused by asynchronous exhalation.

after prolonged expiration. These small airways may supply lung units with little CO_2 for various reasons, and their closure would therefore allow CO_2-rich gas from other lung units to abruptly reach the upper airway. Bhavani-Shankar and colleagues favor a different explanation and state that well-ventilated, open lung units have an upsloping increase in P_{CO_2} whereas P_{CO_2} in poorly ventilated, closure-prone units increases linearly. When poorly ventilated airways close, the pattern from well-ventilated units predominates and the slope of the plateau rises suddenly.[99] This concept is nicely cartooned at capnography.com in the phase IV section.

To summarize, any condition that increases alveolar dead space or $\dot{V}/\dot{Q}$ heterogeneity will increase the slope of phase III. This includes acute and chronic airway obstruction, and prolonged expiration in a normal subject can also generate this pattern. Sometimes this slope is so significant that the reported P_{ETCO_2} actually exceeds Pa_{CO_2}. This has been observed during anesthesia in obese patients and in 50% of both normal infants and pregnant women.[100] It is probably secondary to reduced thoracic compliance and functional residual capacity (FRC), increased cardiac output, and increased CO_2 production.[101] High mixed venous CO_2 tension and malignant hyperthermia have also been reported to cause a negative Pa_{CO_2}-P_{ETCO_2} gradient.[102] In such cases, P_{ETCO_2} is clearly not an accurate estimate of Pa_{CO_2}, and the average alveolar P_{CO_2} obtained from a volume capnograph may be more indicative of Pa_{CO_2}.[103]

Volume. A volume capnograph is obtained by plotting expired P_{CO_2} versus exhaled gas volume, usually obtained with a spirometer or pneumotachometer. There is no inspiratory phase in a volume capnograph, and the curve is divided into three expiratory phases. Several measurements that are not possible with time capnography can be made, such as partitioning of dead space components. The area under the P_{CO_2} curve is the total volume of CO_2 (V_{CO_2}) exhaled for that single breath. Dividing this value by the total exhaled tidal volume (V_T) gives the fraction of expired CO_2 (F_{ECO_2}), and the product of this fraction and barometric pressure yields a value for mixed expired P_{CO_2} (P_{ECO_2}). The Enghoff-modified Bohr equation can then be used to determine total (physiologic) dead space ($V_{DS_{phys}}$ or $V_{DS_{tot}}$) (Figs. 44-18 and 44-19):

$$V_{DS_{tot}} = V_T\left[\left(Pa_{CO_2} - P_{ECO_2}\right)/Pa_{CO_2}\right] \quad (16)$$

Once $V_{DS_{tot}}$ has been determined, subtracting the anatomic dead space ($V_{DS_{anat}}$) derived from the capnograph (see Fig. 44-18) yields the alveolar dead space component ($V_{DS_{alv}}$):

$$V_{DS_{alv}} = V_{D_{tot}} - V_{DS_{anat}} \quad (17)$$

Alternatively, alveolar dead space can be calculated by replacing P_{ECO_2} in the Bohr equation with *average* alveolar P_{CO_2} ($P_{A'CO_2}$), which can be derived from the volume capnograph[104]:

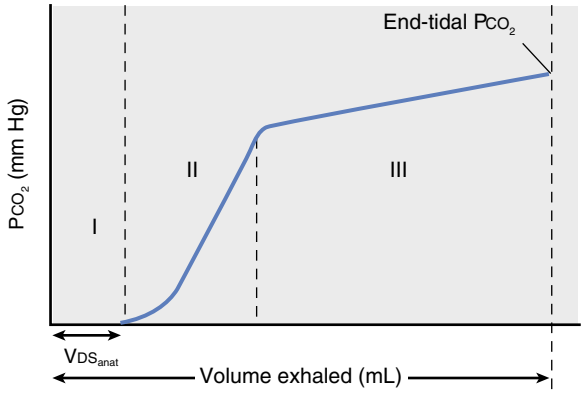

Figure 44-18 Volume capnograph: single-breath CO_2 ($SBCO_2$) curve. The horizontal axis of the graph represents expiratory/inspiratory tidal volume and is generally divided into three areas: I, the anatomic dead space volume ($V_{DS_{anat}}$); II, the transitional phase II volume; and III, the phase III alveolar volume. The sum of these values is the tidal volume. The vertical axis represents the concentration of CO_2. P_{CO_2}, partial pressure of carbon dioxide. *(From Pilbeam SP, Cairo JM: Mechanical Ventilation: Physiological and Clinical Applications, 4th ed. St. Louis, Elsevier, 2006.)*

$$V_{DS_{alv}} = (V_T - V_{DS_{anat}}) / \left[\left(Pa_{CO_2} - P_{A'CO_2} \right) / Pa_{CO_2} \right] \quad (18)$$

Capnography has been used to titrate positive end-expiratory pressure (PEEP) settings inasmuch as narrowing of the Pa_{CO_2}-P_{ETCO_2} gradient suggests reduced alveolar dead space and shunt fraction as a result of alveolar recruitment and improved $\dot{V}/\dot{Q}$ matching. These changes are often subtle or absent on a time capnograph and may be detectable only with volume capnography.[100] It has been suggested that an incompetent inspiratory valve and rebreathing during mechanical ventilation may require volume capnography to be detected reliably.[105] The technique may also be better than time capnography for the diagnosis of pulmonary embolism.[106]

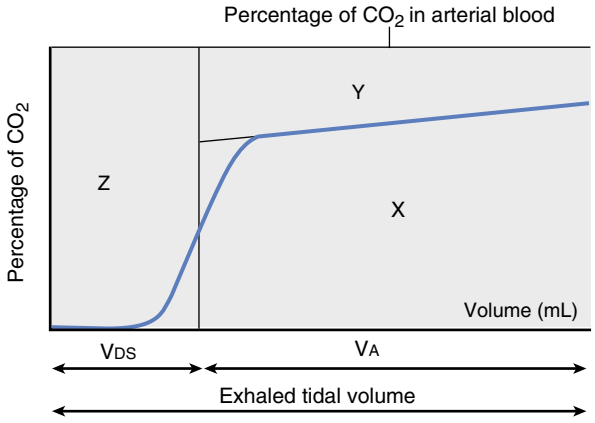

Figure 44-19 Volume capnograph: graph of the percentage of carbon dioxide (%CO_2) (*y* axis) and volume (*x* axis). A *horizontal line* drawn at the top of the curve represents %CO_2 in arterial blood. Three distinct regions are established. Area X represents the actual CO_2 exhaled in one breath (assuming that no CO_2 is rebreathed), area Y is the amount of CO_2 that is not eliminated because of alveolar dead space, and area Z is the amount of CO_2 not eliminated because of anatomic dead space. The ratios of these areas are the same as in the relationship seen in the Bohr equation: $(Pa_{CO_2} - P_{ECO_2})/Pa_{CO_2} = (Y + Z)/(X + Y + Z)$. P_{ECO_2}, mixed expired P_{CO_2}; V_A, alveolar volume; V_{DS}, dead space volume.

Additional Clinical Applications of Capnography

In addition to those outlined in the preceding sections, capnography has a host of clinical applications. Monitoring of P_{ETCO_2} can be invaluable during mechanical ventilation in the operating room and ICU to make inferences about cardiovascular status, Pa_{CO_2} trends, and adequacy of ventilation. Disappearance of the capnograph waveform may warn of cardiovascular collapse or massive airway obstruction, but it is most often due to disconnection or a large leak in the circuit. Capnography has been used to assess the efficacy of chest compressions during cardiopulmonary resuscitation and even to verify proper placement of enteric feeding tubes.[107]

Errors

Various disease states discussed previously may cause overestimation or underestimation of Pa_{CO_2} with use of P_{ETCO_2}. Condensation of water vapor in the sample tubing and measuring cell can elevate the reported P_{CO_2} slightly. Warming these pieces of equipment plus avoiding the use of drying agents in the sample line reduces this error. Capnometers may underreport true P_{ETCO_2} at higher respiratory rates. Exhausted CO_2 absorbent increases inspired CO_2, and failure to recognize such depletion may lead to suspicion of rebreathing from other causes.

Pulmonary and Chest Wall Monitoring

Pressure-Volume Curve Analysis

Lung mechanics can be severely impaired in a number of respiratory disorders. Monitoring changes in mechanical function of the lung is vital in developing a safe and effective support strategy in the face of respiratory failure. In a mechanically ventilated patient, construction of pressure-volume (PV) curves can provide important information about mechanics and help guide ventilator management. A *dynamic* PV curve is one that is constructed during gas flow, whereas *static* curves are derived when flow is absent. Techniques for constructing static curves were introduced in the mid-1970s and soon thereafter were shown to be useful in determining the cause of acute respiratory distress (Fig. 44-20). In recent years, the PV relationship has been studied extensively as a means of determining optimal PEEP and tidal volume in ARDS and ALI.

Static Curve

A static curve is constructed by using the ventilator or a large syringe to deliver known tidal volumes, and patients must be sedated and paralyzed for an optimal study. The resultant plateau (P_{plat}) and peak inspiratory pressures (P_{pk}) are recorded after each breath to allow determination of both static (C_{stat}) and dynamic (C_{dyn}) compliance. Because C_{stat} is calculated by using plateau

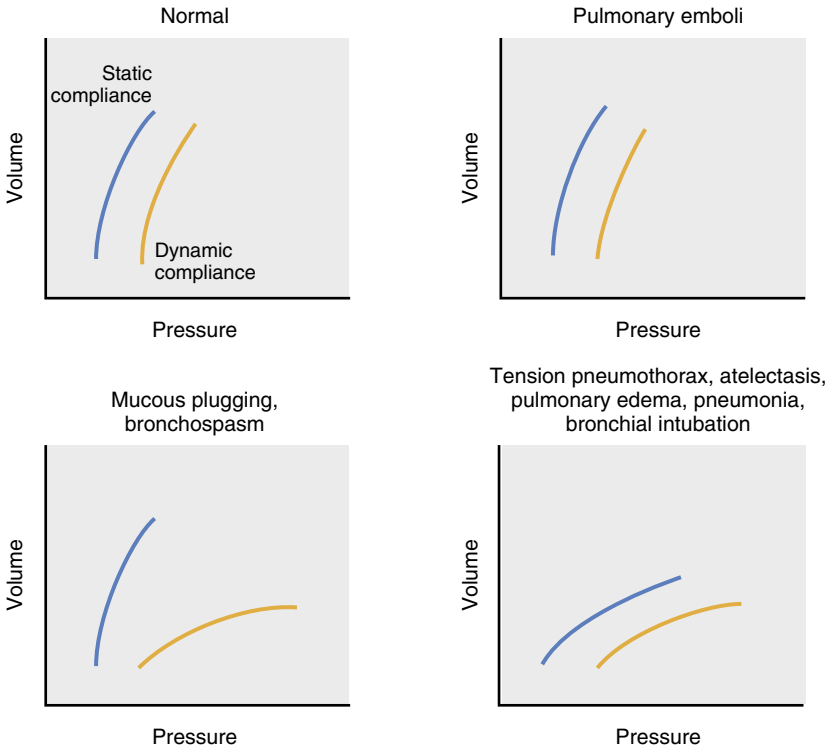

Figure 44-20 Pressure-volume curves reflecting changes in static and dynamic compliance (C_{stat} and C_{dyn}) during mechanical ventilation. Under normal conditions, the C_{stat} and C_{dyn} curves are similar. Because pulmonary emboli do not affect resistance or compliance, neither curve changes with this condition. With mucous plugging or bronchospasm, airway resistance (Raw) increases, the C_{dyn} curve shifts to the right and flattens (more pressure is required), and the C_{stat} curve remains unchanged. With conditions that reduce lung compliance (C_L), both curves shift to the right and flatten. *(From Bone RC: Monitoring ventilatory mechanics in acute respiratory failure. Respir Care 28:597-604, 1983.)*

pressure, it is mainly influenced by chest wall and alveolar elastic recoil:

$$C_{stat} = V_T / (P_{plat} - PEEP) \quad (19)$$

C_{dyn} is derived by using P_{pk} and therefore takes airway and circuit resistance into account as well:

$$C_{dyn} = V_T / (P_{pk} - PEEP) \quad (20)$$

In patients with normal lung function, the static PV curve is usually linear, and C_{stat} ranges from 50 to 100 mL/cm H_2O (Fig. 44-21). In disorders such as ARDS and ALI, where compliance can be substantially decreased, the curve becomes sigmoidal or S shaped.[108,109] Upper (UIP) and lower (LIP) inflection points can often be identified. The LIP, sometimes called P_{flex}, signifies an abrupt increase in compliance and is thought to result from the sudden recruitment of a large number of alveoli. The plateau pressure at which the LIP occurs is often referred to as the *opening pressure* of the lung. Overdistention of alveoli begins to occur once a critical volume (or pressure) is reached, marked by the UIP. Maintaining airway pressures between the LIP and UIP is therefore believed by many to prevent derecruitment and overdistention of alveoli, both of which contribute to ventilator-induced lung injury.[108,109] Using this reasoning, PEEP would be set slightly above the LIP to keep recruited alveoli open.[110] Indeed, this approach has been shown to result in earlier weaning from the ventilator, less release of inflammatory cytokines, and a trend toward reduced mortality in ARDS patients.[108,111]

Despite positive results using the LIP and UIP to guide PEEP and V_T settings, recent evidence suggests that the LIP does not correlate with the pressure at which recruited alveoli will begin to close, known as the *critical closing pressure*.[112,113] A probable explanation is that contrary to previous thought, recruitment has been shown to occur along the entire PV curve, independent of the LIP and UIP. Thus, setting PEEP above the LIP is not always beneficial and may instead increase the risk for overdistention and barotrauma.[114] Direct measures of appropriate response may be more suitable in determining the best PEEP level (see "Analysis of the Level of PEEP").

Once the lung has been fully recruited, a deflation curve can be drawn by stepwise deflation of the lung, similar to mapping of the inspiratory limb. As lung volume decreases, critical closing

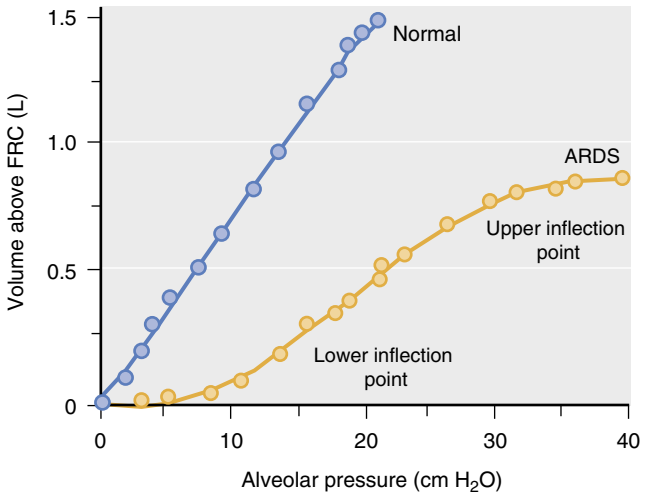

Figure 44-21 Example of a static, inspiratory pressure-volume curve of the respiratory system in a patient with acute respiratory distress syndrome (ARDS) versus a healthy subject. Upper (about 30 cm H_2O) and lower (about 10 cm H_2O) inflection points are present in the patient with ARDS. FRC, functional residual capacity. *(From Hess DR, Kacmarek RM: Essentials of Mechanical Ventilation, 2nd ed. New York, McGraw-Hill, 2002.)*

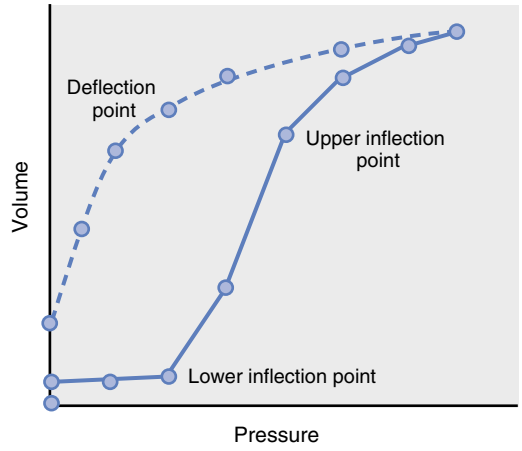

Figure 44-22 Pressure-volume relationship of the lung showing the inflation (*solid line*) and the deflation limb (*dashed line*). Note the clear difference in lung volume between both limbs at identical pressure (hysteresis). *(From van Kaam AHLC: Neonatal mechanical ventilation.* In *Papadakos PJ, Lachmann B [eds]: Mechanical Ventilation: Clinical Applications and Pathophysiology. Philadelphia, Elsevier, 2008.)*

pressure is reached, and a *deflection* point appears on the curve corresponding to a rapid decrease in compliance and closure of a large number of lung units (Fig. 44-22). Because compliance improves during inflation as lung units are recruited, higher volumes are observed at the same pressure during deflation than during inflation, a phenomenon referred to as *hysteresis*. Accordingly, critical closing pressure will be lower than opening pressure, and setting PEEP slightly above the deflection point rather than the LIP may provide superior alveolar stabilization with less risk of overdistention and ventilator-induced lung injury.[115,116] A number of recent studies suggest that the LIP does not reliably indicate the pressure at which maximal alveolar derecruitment occurs.[112,117] In addition, there is mounting evidence that using the deflation limb rather than the inflation limb of PV curves to guide ventilation may improve gas exchange and mechanics, often at lower mPaw and PEEP levels.[118,119] Therefore, although the presence of an LIP on the PV curve indicates a *need* for lung recruitment, the deflection point may be more valuable in determining the amount of PEEP required to prevent alveolar collapse. Evaluating deflation C_{stat} in this manner to determine closing pressure is at least as effective as monitoring Pao_2 for selection of the optimum PEEP level.[115,116] Moreover, recruitment maneuvers have been shown to be quite safe and are less injurious than allowing shear stress damage associated with derecruitment to proceed unchecked.[120,121]

Static PV curves can also be obtained from a single breath delivered slowly (2 to 3 L/m) until a predetermined pressure is reached and are referred to as slow-flow or quasi-static PV loops. The curves derived are comparable to those obtained with typical static techniques, but the deflation limb is often difficult to acquire.[122,123] Several modern ventilators have incorporated this capability. The Hamilton Galileo ventilator allows selection of the desired flow rate for the PV study, and an interactive curve is then displayed on the monitor, usually within 30 seconds.

Dynamic Curve

A number of ventilators are capable of mapping dynamic PV curves during tidal breaths delivered with normal gas flow. Newer ventilators automatically display the curve with each tidal volume. Though useful in following general trends in compliance, identification of inflection points is more difficult on dynamic PV curves. Several factors can alter the loop from breath to breath, and using dynamic curves for determination of optimal V_T and PEEP is not generally recommended.[122]

Analysis of the Level of PEEP

Application of PEEP has long been known to improve lung mechanics and gas exchange in many forms of acute respiratory failure. Appropriate PEEP increases FRC, decreases pulmonary edema, and maintains the patency of airways and recruited alveoli. It is important to note that PEEP does not recruit the lung; rather, it is sustained high pressure that reopens closed alveoli and airways, and PEEP stabilizes these recruited lung units. A host of tools and parameters described in this chapter have been used by clinicians to evaluate PEEP settings, including capnography, titration to the best Pao_2/Sao_2 ratio, continuous $S\bar{v}o_2$ and shunt monitoring, PV curve analysis, and others. None have unequivocally been shown to result in superior outcome. Consequently, there is no consensus on a single method of titrating and evaluating clinical response to PEEP. More than 30 years ago it was noted that the PEEP level resulting in maximum O_2 delivery also produced optimal compliance while minimizing dead space and shunt fraction.[124] The authors coined the phrase "optimum" PEEP to refer to that producing the maximum improvement in pulmonary function with minimal hemodynamic compromise. Recent trials have shown that during a derecruitment study, measuring C_{stat} may be as useful and more cost-effective than measuring Pao_2 in determining closing pressure and guiding PEEP selection.[115,116] Nowadays most clinicians use one of these two parameters to set PEEP after the recruitment maneuver. Inflection points on PV curves are not always easy to identify, and a decrease in Pao_2 rather than C_{stat} should be used to identify closing pressure in such cases.

Patients under GA are prone to compression atelectasis in dependent lung regions (see Fig. 44-5).[125] Thus, it is tempting to apply PEEP to all patients undergoing surgery with mechanical ventilation to prevent this atelectasis. It has been shown that application of PEEP during GA can attenuate and reverse dependent atelectasis but does not improve gas exchange.[126] A study comparing normal and obese subjects also found that application of PEEP during GA did not alter gas exchange in normal patients, but some improvement was noted in the obese population.[127] Thus, there is no evidence to support routine use of PEEP during GA. However, these studies did not use recruitment maneuvers, and a trial by Tusman and colleagues showed that alveolar recruitment can improve oxygenation during GA (see also Chapter 15).[128] In addition, PEEP combined with recruitment maneuvers has been shown to provide a sustained increase in Pao_2 and lung volume in mechanically ventilated postsurgical patients.[128,129]

Analysis of Lung Recruitment

The importance of early lung recruitment in respiratory failure and ARDS has been well documented.[130] Lung-protective ventilation in ARDS via frequent recruitment maneuvers results in improved 28-day survival, earlier weaning from mechanical ven-

tilation, and less barotrauma than with conventional ventilation strategies.[111] Effective recruitment is performed by applying sustained high airway pressure, usually for 30 to 90 seconds. Many successful techniques, all using essentially these same principles, have been described.[131,132] Recruitment maneuvers are typically well tolerated, with no significant hemodynamic deterioration or inflammatory response.[133,134] Although improvements in pulmonary compliance and oxygenation are indicative of successful recruitment, direct methods of quantifying and monitoring lung recruitment are emerging.

Computed Tomography

Technologic advances in CT have made it a valuable tool for studying ARDS and lung recruitment. It has been used in numerous studies to evaluate the effects of a wide range of variables on alveolar recruitment and stabilization.[135] Recently, Gattinoni and colleagues performed a trial to examine whether measuring the amount of recruitable lung by CT could help predict how the lung would respond to PEEP after recruitment. They concluded that a higher amount of recruitable lung was correlated with a positive response to PEEP whereas PEEP was of little benefit and perhaps detrimental in patients with less recruitable lung measured by CT.[136] This conclusion was in line with previous studies showing that PEEP results in hyperinflation and increased stress in normal lung regions when the amount of recruitable lung is low.[137] Quantitative CT analysis of potentially recruitable lung may therefore be useful in determining the best PEEP level, but further studies are needed on the practicality of routine use. CT was instrumental in the discovery that lung recruitment occurs throughout inspiration and not solely around the LIP of the PV curve.[138]

Electrical Impedance Tomography

A new and exciting form of monitoring of pulmonary function may be electrical impedance tomography (EIT).[139,149] It is a noninvasive and radiation-free technique based on the measurement of electric potentials at the chest wall surface. Within a particular cross-sectional plane, harmless electrical currents are driven across the thorax in a rotating pattern to generate a potential gradient at the surface, which is then transformed into a two-dimensional image of the distribution of electrical impedance within the thorax. The dynamic behavior and the qualitative information extracted from EIT images look similar to that reported in dynamic studies (Fig. 44-23).[141,142]

This technology may be an excellent assessment tool for easy bedside use to evaluate alveolar lung recruitment, pulmonary embolism, lung water, and other lung pathology. The importance of lung recruitment in both the operating room and the ICU has clearly changed the practice of mechanical ventilation.

Amato's group in Brazil recently completed a validation study of EIT.[142] It is an easy bedside tool to evaluate mechanical ventilation with immediate feedback. EIT devices may, in the future, easily detect selective intubation, pneumothorax, and alveolar atelectasis. Titration of PEEP may someday be evaluated in real time, with EIT used instead of waiting for BGA, radiologic studies, and CT scans. This technology may one day be integrated into the bedside monitor or into closed-loop mechanical ventilators.

Inspiratory Pressure Monitoring

Impaired respiratory muscle function from fatigue or neuromuscular disorders can contribute to respiratory failure and difficulty weaning from mechanical ventilation. Measurement of maximum inspiratory pressure (MIP), also called negative inspiratory force, gives a useful bedside appraisal of respiratory muscle strength. It can be performed on intubated and nonintubated patients by attaching a pressure manometer to the endotracheal tube or a noninvasive mouthpiece. Alternatively, use of a one-way valve that allows exhalation only has been described, although it is quite uncomfortable for the patient.[143] Normal MIP is about −90 cm H_2O but can range between −50 and −120 cm H_2O. To obtain accurate measurements, MIP should be measured after maximal expiration because the diaphragm can generate the greatest pressure at residual volume. Studies have demonstrated that inability to generate MIP more negative than −20 cm results in tidal volumes that are insufficient for generating a strong cough. Moreover, this cutoff has been shown to result in weaning failure with

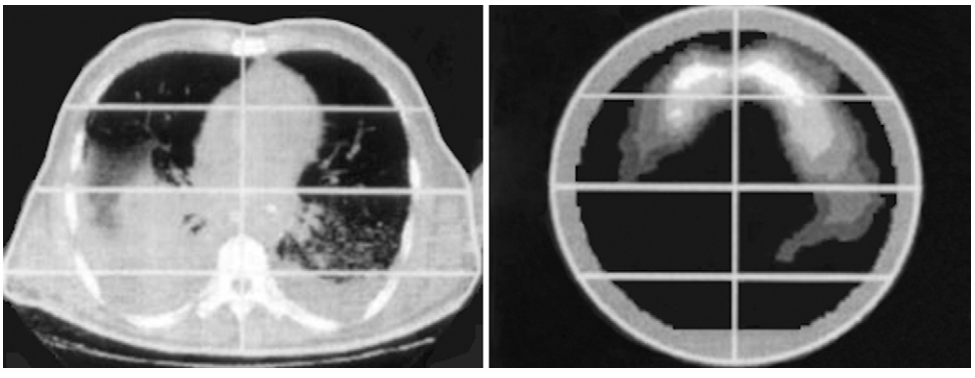

Figure 44-23 Comparison of a computed tomographic (CT) scan and an electrical impedance tomographic (EIT) image during mechanical ventilation of a patient with acute lung injury. The *gray* and *white* areas in the EIT image reflect areas with change in impedance (volume changes) and correlate with well-inflated areas on the CT scan. There is no impedance change on the EIT scan in the dorsal area, where atelectasis is present on the CT scan. *(From Wolf GK, Arnold JH: High-frequency oscillatory ventilation for adult acute respiratory distress syndrome: A decade of progress. Crit Care Med 33(Suppl):S163-S169, 2005.)*

a negative predictive value of 1.[144] Though not yet a firmly established predictor of weaning outcome, MIP is useful in determining whether patient weakness or neuromuscular dysfunction is playing a role in unsuccessful weaning trials.

Esophageal Monitoring

Transpulmonary pressure, rather than peak or plateau pressure, is the most important determinant of alveolar distention and is defined as alveolar pressure (PA) minus pleural pressure (Ppl).[145] Thus, true distending pressure of the lung cannot be measured without determination of Ppl. Direct measurement of Ppl is clinically impractical, but it can be estimated quite reliably in upright patients by measuring pressure in the distal third of the esophagus. The esophagus is a fairly passive structure and the third part is very close to the pleural space, thus allowing transmission of pleural pressure to an intraesophageal pressure monitor.[146] A balloon-tipped catheter is typically used, and this technique is considered the standard modality for evaluating inspiratory effort and work of breathing (WOB). In the supine position, this relationship is less predictable because gravitational forces cause compression of the esophagus and dependent lung, thereby skewing the measurements.

Placement of a second balloon catheter into the stomach allows simultaneous measurement of gastric pressure and provides a means of obtaining a host of useful information about respiratory mechanics. For example, transdiaphragmatic pressure monitoring can be performed to assess diaphragmatic contraction. As the diaphragm contracts and the domes descend, negative Ppl (or Pes) should coincide with positive abdominal pressure (or Pg) generating transdiaphragmatic pressure. Inability of the diaphragm to contract properly results in loss of transdiaphragmatic pressure and has been observed after uncomplicated upper abdominal surgery (Fig. 44-24). Diaphragmatic fatigue and phrenic nerve palsy elicit a similar pattern.[147] This can also be observed clinically inasmuch as impaired diaphragmatic activity is associated with paradoxical inward movement of the abdomen during inspiration.

Work of Breathing

The work involved in normal respiration, often referred to as *work of breathing (WOB)*, usually requires minimal energy expenditure. Work is defined as the force needed to move a mass times the distance moved: $W = F \times d$. In the respiratory system, it represents the pressure (or force) needed to inspire a certain volume of gas: $WOB = P \times V$. With respiratory compromise, WOB can be quite high, as much as 40% of total oxygen consumption (normally <5%). WOB can be estimated by measuring pressure and volume changes from a PV curve. Total work is the area enclosed by the curve (integral of pressure and volume). Thus, the larger the loop, the greater the WOB (Fig. 44-25). However, studies indicate that mechanical work calculated in this manner may underestimate true WOB and is weakly correlated with the $\dot{V}O_2$ of respiratory muscles. Alternatively, many clinicians believe that the *pressure-time product* (PTP) is the most accurate measure of work performed by the diaphragm during inspiration and better correlates with $\dot{V}O_2$[148] because the PTP takes isometric contraction of the diaphragm into account, which consumes additional O_2. Increases in PTP indicate stronger diaphragmatic contraction and vice versa. Calculation of PTP requires measurement of transdiaphragmatic pressure as outlined earlier and is not routinely performed. Occlusion pressures (P_{100}) measured with a dedicated valve system or conventional ventilator have also been shown to correlate with WOB.[148,149]

Closed-Loop Analysis

Closed-loop ventilation involves computer-based real-time interpretation of respiratory mechanics with continuous adjustment of the level of support delivered to the patient.[150] Any change in mechanics or patient effort is detected and a new breathing pattern is initiated by the ventilator. Ventilator dyssynchrony and WOB are minimized. Moreover, erroneous or unsafe settings could potentially be minimized with a system that continuously regulates ventilator support based on real-time assessment of the

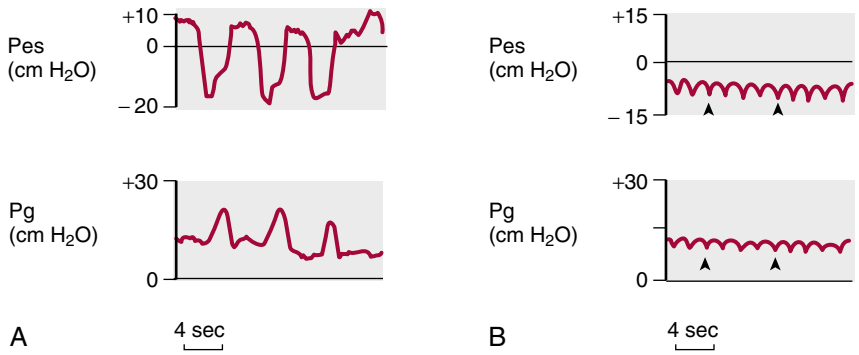

Figure 44-24 Examples of transdiaphragmatic pressure monitoring. **A,** Simultaneous esophageal (Pes) and gastric (Pg) pressure waveforms during tidal breathing in a normal individual. Negative esophageal (and therefore pleural) pressure swings are accompanied by positive gastric pressure waves indicative of the development of transdiaphragmatic pressure during inspiration. **B,** The same waveforms in a patient with phrenic nerve palsy (and therefore absent diaphragmatic contraction). Negative intrathoracic pressure swings (*arrowheads*) are accompanied by gastric pressure swings in the same direction. Intrathoracic pressure changes are directly transmitted through a passive diaphragm. These changes can also be observed in the early postoperative period in patients who have undergone upper abdominal surgery. *(From Brown KA, Hoffstein V, Byrick RJ: Bedside diagnosis of bilateral diaphragmatic paralysis in a ventilator-dependent patient after open-heart surgery. Anesth Analg 64:1208, 1985.)*

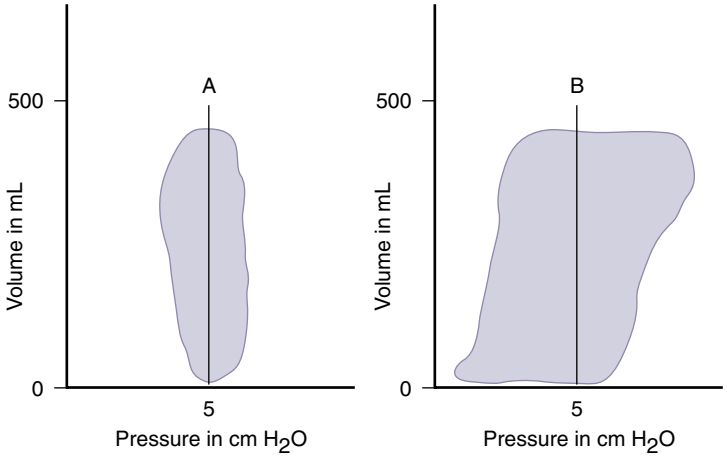

Figure 44-25 Work of breathing (WOB) during continuous positive airway pressure (CPAP). WOB in this figure is the integral of airway pressure and tidal volume. Loop A is an example of a freestanding CPAP system. Spontaneous breaths occur clockwise, inspiration to expiration. Loop B is CPAP through a ventilator demand valve system. Breathing occurs clockwise. *(Redrawn from Hirsch C, Kacmarek RM, Stanek K: Work of breathing during CPAP and PSV imposed by the new generation mechanical ventilators: A lung model study. Respir Care 36:815–828, 1991; and Kirby RR, Banner MJ, Downs JB: Clinical Applications of Ventilatory Support. New York, Churchill Livingstone, 1990.)*

patient. Table 44-3 summarizes the four commercially available closed-loop systems. A study was performed to compare ARDS and COPD patients ventilated with a closed-loop mode termed *adaptive support ventilation* (ASV) available on the Hamilton Galileo ventilator. The authors found that on average, ARDS patients received lower tidal volumes with a higher respiratory rate than COPD patients did.[151] This would be expected and desired based on current knowledge of mechanics and the importance of low–tidal volume ventilation in ARDS. Moreover, the results support the possibility that closed-loop ventilation with ASV can appropriately tailor ventilation based on respiratory mechanics. It is highly conceivable that closed-loop ventilator modes may one day prove to be safer and more convenient than traditional mechanical ventilation.

Apnea Monitoring

The postoperative period is often characterized by episodes of apnea and hypoxemia. Paradoxical breathing and other ventilatory disturbances can also occur frequently. Though more common with narcotic administration, residual effects of other anesthetic agents can play a role in the cause of these disturbances. They are often subtle and are more likely to be noticed with continuous respiratory monitoring as opposed to intermittent observation.[152] A wide variety of continuous apnea monitoring systems have been developed. Most methods detect changes in chest wall movement, gas exchange, or gas flow to make inferences about changes in respiratory pattern.

Movement of the chest wall is most commonly detected by transthoracic impedance. The technology is usually incorporated into the electrocardiographic (ECG) monitoring system. A small current is passed between two ECG leads, and chest wall movement is detected by a change in impedance to the current induced by the motion. Respiratory inductive plethysmography (RIP) is another method of apnea detection that monitors chest movement. The chest and abdomen are encircled by one or more coils that measure changes in their cross-sectional area occurring with respiration. Inductance of the bands depends on the area that they enclose and thereby allows detection of respiratory movements. A technique called photoplethysmography (PPG) also relies on detection of anatomic changes induced by breathing. Infrared PPG sensors placed near upper extremity veins can detect cyclic changes in venous blood flow occurring with respiration.[153] Respiratory muscle electromyography has also been used as a means of monitoring respiration. A limitation common to all these techniques is that respiratory efforts during episodes of obstructive apnea may be interpreted as normal respirations despite absent gas flow.[154] Monitoring of gas flow and exchange may therefore be a more reliable indicator of adequate respiration.

Table 44-3 Main Characteristics of Proportional Assist Ventilation (PAV), Neurally Adjusted Ventilatory Assist (NAVA), Knowledge-Based System (KBS), and Adaptive Support Ventilation (ASV)

	PAV	NAVA	KBS	ASV
Principle	P_{insp} proportional to $flow_{insp}$	P_{insp} proportional to EMG_{dia}	P_{insp} to maintain RR in comfort zone	P_{insp} and RR to minimize WOB
Breath type	Spontaneous	Spontaneous	PSV	PSV, PCV, P-SIMV
Sedated patients	No	No	No	Yes
Active patients	Yes	Yes	Yes	Yes
Automatic weaning	No	No	Yes	Yes

EMG_{dia}, diaphragmatic electromyographic activity; $Flow_{insp}$, inspiratory flow; PCV, pressure-controlled ventilation; P-SIMV, pressure-controlled intermittent mandatory ventilation; PSV, pressure-support ventilation; RR, respiratory rate; WOB, work of breathing.
From Wysocki M, Brunner JX: Closed-loop ventilation: An emerging standard of care? Crit Care Clin 23:223-240, 2007.

Apnea monitoring systems that rely on airflow detection may be a more sensitive alternative to monitors of patient movement. In a study comparing transthoracic impedance and a nasal-oral airflow system in the PACU, Wiklund and colleagues found that impedance monitoring failed to detect apneic episodes more frequently than flow detection did.[154] False alarm rates were similar between the two groups. Hök and associates studied an acoustic airflow monitoring system and reported that it was more sensitive in detecting episodes of apnea and hypoventilation than pulse oximetry was.[155] Another acoustic airflow sensor was compared with a thoracic impedance system by Werthammer and colleagues.[155a] Of 26 apneic episodes observed by direct observation, the airflow sensor detected all 26, whereas only 7 episodes were detected by the impedance monitor. Other airflow monitors detect respiration by measuring changes in humidity. Tatara and Tsuzaki studied a device called a rapid-response hygrometer that monitors changes in humidity at the nostril and can measure respiratory rates of up to 60 breaths per minute.[156] Respiratory phases could be identified almost 2 seconds faster than with capnography. The development of fiberoptic humidity-based systems has also been described.[157,158]

Because end-tidal CO_2 monitoring and pulse oximetry can rapidly detect derangements in gas exchange, they may prove to be the most dependable options for apnea monitoring. In a study of more than 4000 apneic episodes from overnight polysomnograms, detection of apnea by pulse oximetry was compared with manual detection, such as airflow or respiratory movement.[158a] Only 1.32% of apneic episodes were reportedly missed by pulse oximetry, whereas manual devices missed 7.9% of apnea events. Although end-tidal CO_2 monitoring can be performed easily and accurately on intubated patients, measurements from a mask or nasal cannula are often unreliable. However, the respiratory rate is usually reported accurately, and trends in P_{ETCO_2} can be monitored with these devices. As pulse oximetry and capnography systems become more portable and inexpensive, their use for apnea monitoring will probably continue to grow. Large outcome studies may be needed to demonstrate the possible superiority of one system over another.

Lung Water Analysis

Many disease states can cause abnormal accumulation of extravascular lung water (EVLW), commonly known as pulmonary edema. Clinicians have long been aware of the severe cardiac and respiratory insufficiency that pulmonary edema can cause, yet it remains unclear whether accurately quantifying it can guide management in a way that ultimately improves outcome. Nonetheless, investigators continue to seek simple and reliable methods for detecting and quantifying EVLW, and many advances have been made in recent years. Research in this field is complicated by the fact that gravimetry, which requires analysis of postmortem lung weight, remains the standard for EVLW measurement.[159,160] As a result, much of the data evaluating new techniques come from animal studies.

Radiographic Methods

The chest radiograph is the most widely used test to screen for pulmonary edema. Under ideal conditions, obtaining a chest film allows semiquantitative measures of EVLW, as well as determination of its distribution and possible etiology. Even under such conditions, sensitivity is rather poor; a 30% to 35% increase in EVLW is needed before radiographic changes consistent with pulmonary edema can be detected on the chest film.[161] In typical critical care settings, where image quality and acquisition technique can vary greatly, it is estimated that a 100% increase in EVLW may be needed to produce observable radiographic changes. Moreover, weak correlation of EVLW measurements between chest radiography and other established methods has been observed in the ICU environment.[159]

CT has been increasingly studied in recent years as a means of quantification of EVLW. In animal experiments, CT densitometry could detect an increase in EVLW by as little as 50%.[162] Using thin-section CT, Scillia and colleagues found that significant hypoxemia secondary to pulmonary edema may not develop until the increase in EVLW approaches the 200% to 300% range.[163] Lack of portability and high radiation exposure limit the use of CT for serial EVLW measurement. Research continues on a number of other imaging modalities, including ultrasonography,[164] positron emission tomography,[165] nuclear magnetic resonance,[166] and EIT,[167] but none have been incorporated into routine clinical use.

Indicator Dilution Methods

Quantification of EVLW via double indicator dilution curves was first described more than 50 years ago. More recently, a transpulmonary thermodilution technique that uses cold saline as a single indicator has been described. Although controversy exists over the accuracy of dilution techniques, many studies report excellent reproducibility and correlation with gravimetric methods.[159] One study using transpulmonary thermodilution reported that changes in EVLW of as little as 10% to 20% can be detected with high sensitivity.[168] Both techniques are somewhat invasive and require placement of arterial and central venous catheters. Although early devices were quite cumbersome, currently available systems are relatively safe and easy to implement and allow bedside measurements to be obtained.

Despite recent improvements in a number of the aforementioned modalities, chest radiography remains the only tool widely integrated into clinical practice. A probable explanation is that studies have suggested potential clinical utility in precise EVLW analysis, but none have shown that obtaining such measurements facilitates decision-making or improves patient outcome.

Monitoring High-Frequency Ventilation

Recent data on the benefits of low–tidal volume, high-PEEP ventilation in ARDS have prompted a search for the optimal lung protective mode of ventilation. First introduced in the late 1950s, high-frequency ventilation (HFV) offers an alternative to conventional ventilation in patients with ARDS and ALI. HFV is characterized by rapid delivery of small tidal volumes and maintenance of high mean airway pressure.[169] Whereas routine use in adults is a fairly recent trend, trials in preterm infants with neonatal res-

piratory distress syndrome began almost 20 years ago.[170] Clear evidence of outcome benefit with HFV versus conventional ventilation is lacking, but numerous studies have implied that HFV may reduce the risk for ventilator-induced lung injury,[171] improve oxygenation,[172] and be as safe as conventional ventilation in ARDS.[173] The FDA has defined HFV as any form of ventilation that delivers a respiratory rate greater than 150 breaths/min. Although several forms of HFV have evolved since its development, the most widely used method in both adults and pediatric patients is high-frequency oscillatory ventilation (HFOV). Other modes include high-frequency jet ventilation (HFJV), high-frequency flow interruption (HFFI), and high-frequency percussive ventilation (HFPV). Before the widespread availability of HFV modes, a conventional ventilator was used to deliver low tidal volumes with high frequency, a technique that became known as high-frequency positive-pressure ventilation (HFPPV).

Because mechanisms of gas exchange during HFV differ from those regulating conventional ventilation, standard monitoring equipment may not provide accurate data. Fortunately, the reliability of pulse oximetry in assessing oxygenation status with other modes of ventilation seems to extend to HFV. Early studies showed a correlation between airway pressure and gas exchange efficiency during HFJV, with higher peak and driving pressures resulting in lower $Paco_2$ and higher Pao_2. Monitoring $Petco_2$ conventionally during HFV produces unreliable measurements for a number of reasons, but mainly because of difficulty obtaining undiluted, CO_2-rich gas samples.[174,175] Though useful in monitoring conventional ventilation, the concept of "end-tidal" CO_2 is altogether misguided in HFV because no inspiratory or expiratory phases are identifiable on capnographic waveforms.[176] Moreover, the likelihood that expired CO_2 tensions accurately reflect $Paco_2$ is low in patients requiring HFV inasmuch as alveolar dead space and intrapulmonary shunting can be extensive.[174]

Despite its limitations, studies have demonstrated the ability of capnometry to provide accurate $Paco_2$ estimates during HFV. A common technique is to interrupt or slow the ventilator down to deliver a normal breath. CO_2 tensions measured with intermittent capnography have been shown to agree well with simultaneously obtained $Paco_2$ values.[177] The accuracy of capnometric Pco_2 readings may also depend on where the sample is obtained. Gas sampled from the distal tip of the endotracheal tube seems to provide more valid approximations of $Paco_2$ than sampling proximally does.[176] However, these measurements must also be obtained intermittently. In an effort to eliminate this problem and others associated with expired gas analysis during HFV, Berkenbosch and Tobias studied the accuracy of continuous transcutaneous CO_2 monitoring in this setting. When compared with $Paco_2$ values from BGA obtained simultaneously, bias and precision were only 2.1 and 2.7 mm Hg, respectively.[174] Studies by these authors and other investigators have also demonstrated that transcutaneous CO_2 monitoring may approximate $Paco_2$ better than $Petco_2$ in both adults and children undergoing mechanical ventilation.[178,179] Although the technique has gained a footing in pediatric critical care, transcutaneous O_2 and CO_2 monitoring in adults will probably increase in popularity as refinements to this technology continue to be made.

As the potential benefits of HFV continue to be elucidated, investigators have sought practical techniques for bedside monitoring of lung mechanics, recruitment, and regional aeration. Portable chest radiography has been shown to be a poor tool for assessing lung morphology in ARDS.[179,180] CT has proved useful for such analyses but continues to be limited by portability issues. Recently, some investigators have focused on EIT and RIP as modalities that may be able to provide accurate lung volume measurements at the bedside during HFV.[181,182] RIP has been used experimentally to construct PV curves during HFV and thereby determine optimal lung volume and pressure settings.[183,184] In the first infant study of this kind, Tingay and colleagues used the open-lung concept to recruit lung and then map the deflation limb of the PV curve.[185,186] The authors concluded that RIP could be used during HFOV to construct satisfactory deflation curves. Ventilation along the deflation limb resulted in greater lung volume and oxygenation, often with lower distending pressure requirements, than did ventilation on the inflation limb (Fig. 44-26). This was in line with previous animal studies demonstrating improved mechanics and oxygenation with deflation limb ventilation after recruitment.[117] An earlier infant trial using single-occlusion compliance measurements failed to demonstrate the utility of PV curves in optimizing lung volume during HFV, but neither recruitment maneuvers nor deflation limb ventilation had been used.[187] EIT has the advantage of providing information about global and regional changes in lung volume, as well as continuous imaging of changes in impedance (and probably volume) occurring throughout the respiratory cycle. Bedside availability would potentially allow clinicians to detect aeration changes in real time and reverse them by adjusting ventilation parameters.[182]

Estimation of pulmonary mechanics during HFV has most often been accomplished by the conventional passive techniques described earlier. This practice has raised concern among some authors, who argue that technical aspects of these strategies may exacerbate derecruitment and provide inadequate information about lung parenchyma.[187] In the study by Tingay and colleagues, passive deflation was not used for PV analysis, and derecruitment was further prevented by avoiding full deflation of the lung below closing pressure. Others suggest that the high frequencies and flow rates associated with HFV currently limit the feasibility of obtaining accurate dynamic measurements. Thus, efforts have been undertaken to identify safe alternatives for reliably assessing lung compliance and determining optimal airway pressure during

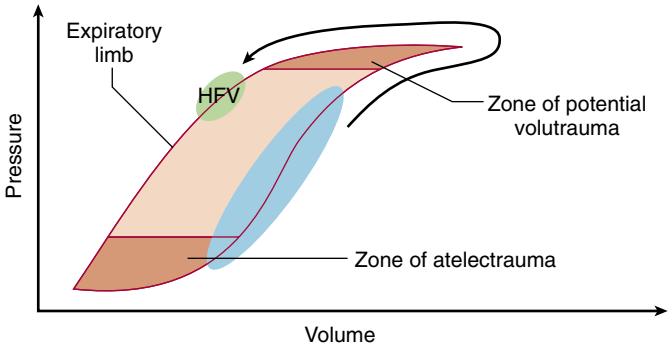

Figure 44-26 Pressure-volume curve depicting the "open lung" concept using high-frequency ventilation (HFV). Potential lung injury is reduced when ventilation of the lung is shifted onto the expiratory portion of the curve by aggressive lung recruitment. Lung volume is then maintained with high mean airway pressure and small tidal volumes. *(From Singh JM, Stewart TE: High-frequency ventilation.* In *Fink MP, Abraham E, Vincent JL, et al [eds]: Textbook of Critical Care, 5th ed. Philadelphia, Elsevier, 2005.)*

HFV. The oscillatory pressure ratio (OPR), defined as the ratio of pressure swings at the distal and proximal ends of the endotracheal tube, was shown to be inversely related to lung compliance in an animal model of ALI.[188] The mPaw setting resulting in the lowest OPR also generated the best lung compliance and oxygenation. Titrating mPaw to a minimal OPR may therefore prove to be a reliable, noninvasive means of optimizing lung mechanics and oxygenation during HFV. The low-frequency forced oscillation technique is another experimental monitor that allows partitioning of lung mechanics into airway and parenchymal components, as well as determination of chest wall impedance.[189] Monitoring chest vibration can provide a crude indicator of changes in compliance during HFOV. Oscillator power is often titrated to generate vibrations from the clavicle down to the midportion of the thigh, and a change in pattern may signal the development of an obstruction, pneumothorax, or worsening mechanics of any etiology.

Monitoring the Respiratory System in Transport

Intrahospital transport of critically ill and mechanically ventilated patients becomes necessary in a number of situations (see Chapter 79). The need for diagnostic or surgical procedures is among the most frequent reasons for patient transport. A number of studies have reported on the high number of transports that critically ill patients require.[190] Children and trauma victims seem to require more frequent transportation for diagnostic purposes than other critically ill patients do. Not surprisingly, intrahospital transport of this tenuous patient population can be fraught with problems ranging from simple equipment malfunction to major disasters such as anoxic brain injury and even death. Studies report a widely varying incidence of adverse events during transportation of critically ill patients. Complex and numerous pieces of equipment are often necessary to safely perform the transfer. One study looking at 125 transports from the ICU found a 34% incidence of equipment-related adverse events, the most common being ECG lead disconnection and monitor power failure.[190]

Lack of agreed-upon monitoring techniques and definitions of "adverse events" partly explains the wide discrepancy in reported incidence. Moreover, few outcome studies comparing monitoring strategies during transport have been performed. It has long been observed, however, that transport of critically ill patients may put them at increased risk for cardiovascular and respiratory compromise, both during and after transport.[191] A higher incidence of gas exchange deterioration and even pneumonia has been reported after intrahospital transport.[192,193] Arrhythmias, hypotensive episodes, and blood gas derangements are not uncommon. Studies in trauma patients have revealed widely variable heart rate and blood pressure during transportation for diagnostic procedures.[194] Thus, a continually displayed electrocardiogram and blood pressure must be available during transport of all critically ill patients. In addition, pulse oximetry should be used in light of its high reliability in forewarning of hypoxemia and deterioration in gas exchange. A good rule of thumb is to monitor critically ill patients at least as closely during transport as deemed necessary within the ICU before transport. Complications are reduced when personnel trained to deal with the intricacies of intrahospital transport are available.[195] Emergency cardiovascular drugs should be available for postoperative transport of all hemodynamically unstable and critically ill subjects. Preparation of equipment and medication checklists before transport can help ensure readiness for any untoward events. The receiving location should confirm before transport that it has the equipment and necessary staff in place to receive the patient.

Transport of a mechanically ventilated patient presents the inherent risks of airway loss and further derangements in gas exchange. Equipment and medications needed to establish and maintain a secure airway must accompany such patients during any transfer. The presence of adequate oxygen supply with properly functioning low-pressure alarms should be verified during pretransport preparation. Many authors advocate the use of a mechanical ventilator rather than manual ventilation devices for intrahospital transport because more variability in pH and CO_2 tension has been observed with the use of manual devices.[196] A higher incidence of significant Pa_{O_2}/F_{IO_2} deterioration may also be associated with manual versus mechanical ventilation ($P = .056$).[196] In a blinded study using capnography, Tobias and associates noted a high incidence of unintentional hyperventilation when using manual devices during the intrahospital transfer of intubated pediatric patients.[197] Similar findings have been noted in adults, and tighter control of Pa_{CO_2} can be achieved if P_{ETCO_2}[198] or V_T is monitored during manual ventilation. These findings have led many experts to recommend P_{ETCO_2} monitoring in addition to standard monitoring for high-risk patients requiring a more optimal level of ventilation.

Obvious contraindications to the transport of critically ill patients include an inability to provide adequate oxygenation and ventilation during transport or at the receiving location. Unstable hemodynamics or an inability to adequately monitor cardiovascular status throughout the trip should prompt postponement or cancellation. The risk-benefit ratio should be considered before all transports to help determine whether a trip is truly warranted; performing such analyses may be the most effective way of avoiding adverse events during transportation. Indeck and coworkers found that 68% of patients transferred from a trauma unit for diagnostic testing experienced serious physiologic changes whereas only 24% of the transfers resulted in significant modification of patient management.[199] The development of increasingly sophisticated portable devices has provided a bedside alternative for many diagnostic and therapeutic procedures.

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45 Renal Function Monitoring

Key Points

1. Perioperative acute renal failure (ARF), although uncommon, is associated with extremely high morbidity and mortality rates.
2. The mechanism for perioperative ARF is complex and most commonly involves multiple factors such as ischemia/reperfusion, inflammation, and toxins.
3. Repeated direct perioperative assessment of renal hemodynamics, tubular function, or pathogenesis of perioperative renal dysfunction is impractical; therefore, indirect assessments, such as serum creatinine trends, are the best practical currently available perioperative tool to assess renal function.
4. Intraoperative urine formation depends on a number of factors and is an insensitive and unreliable method for assessing postoperative risk of renal dysfunction.
5. Serum chemistries and urine indices such as blood urea nitrogen, creatinine, fractional excretion of sodium, and free water clearance are generally late indicators of renal function deterioration and do not enable the clinician to clearly delineate the cause of renal failure.
6. Creatinine clearance is the most sensitive and specific clinical method for determining renal function, but it is limited by time and measurement restrictions.
7. Early biochemical markers for renal function hold promise and are a current focus for research that may soon lead to new tests able to provide prompt clinical information.

Acute kidney injury (AKI) characterized by rapid decline in glomerular filtration and accumulation of nitrogenous waste products (blood urea nitrogen [BUN] and creatinine) is a common medical problem occurring in 5% and 30% of all hospital and intensive care unit (ICU) patients, respectively.[1] AKI is also a serious perioperative complication for patients undergoing major surgery (Fig. 45-1).[2-10] Disentangling the clinical effects of AKI from those of other conditions (e.g., sepsis) is difficult because renal impairment rarely presents in isolation in critically ill patients. However, a prevailing observation is that AKI itself portends poor prognosis, not only owing to the loss of renal function and potential for excessive volume and solutes but also from the ineffective clearance of "uremic toxins," such as inflammatory mediators,[11-13] and the numerous potentially life-threatening complications related to impaired renal function, including sepsis, respiratory failure, gastrointestinal hemorrhage, and central nervous system dysfunction. Acute renal failure (ARF) requiring dialysis develops in 1% to 7% of patients after cardiac or major vascular surgery (Fig. 45-2) and is strongly associated with morbidity and mortality (Fig. 45-3) (see Chapters 60 and 62).[14-17] The mortality rate of ARF was 91% during World War II, 68% in the Korean War, and 67% in the Vietnam War. Today, depending on associated comorbidities, postoperative renal failure is responsible for up to 60% mortality in the postoperative period.[3,4,7,8] ARF in the presence of no other comorbidities has a 10% to 40% mortality rate, whereas ARF in the ICU setting carries a 50% to 80% mortality rate (see Chapter 91).[18] Perioperative renal failure accounts for one half of all patients requiring acute dialysis.[18]

The overall reported frequency of ARF among all patients admitted to the hospital is 1%[19] and may increase to 2% to 5%[3,20] during hospitalization. The incidence of perioperative ARF requiring dialysis has remained largely unchanged since it was first described over 40 years ago[21,22]; however, recognition of this disorder is increasing[9] and reinvigorated efforts to reduce its occurrence are underway as medical populations shift toward older and more critically ill patients undergoing increasingly higher-risk procedures (see Chapter 71). An emerging strategy to reduce the incidence of perioperative renal failure involves improvement of renal function monitoring to allow prompt recognition of the onset of ARF in the operative and critical care setting.

Perioperative renal failure, for example, has long been defined as the need for postoperative dialysis; however, this is by no means the only tool that has been used as a marker to describe acute changes in kidney well-being. In one review of 28 studies,[23] no two definitions for perioperative ARF were the same. Because the implications of needing postoperative dialysis are quite

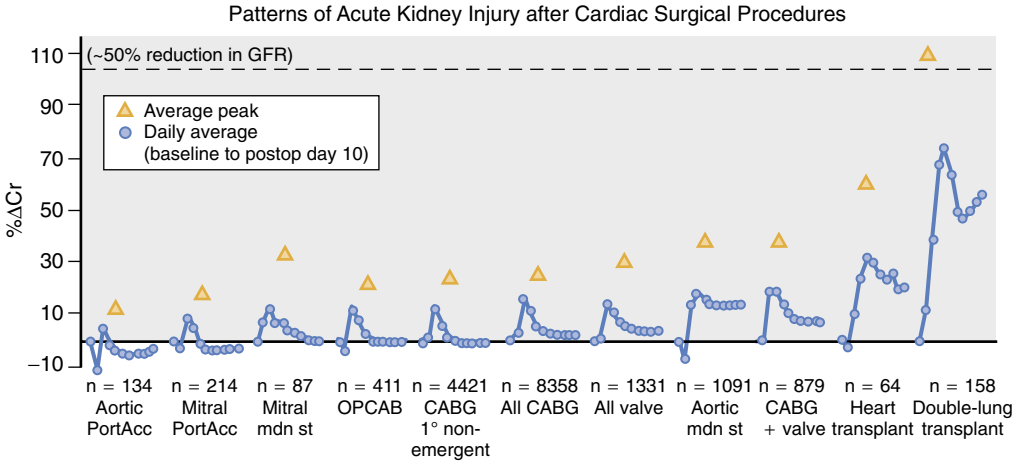

Figure 45-1 Average daily (*circles*) and unadjusted average peak (*triangles*) serum creatinine values for the first 10 days after several different cardiac surgery procedures, represented as change relative to preoperative serum creatinine.[118,334-340] The average peak value considerably exceeds the highest average daily value for each procedure because creatinine peaks on different days for different patients. % ΔCr, peak fractional serum creatinine rise; Aortic PortAcc, minimally invasive parasternotomy aortic valve replacement; Mitral PortAcc, port access mitral valve surgery; Mitral mdn st, median sternotomy mitral valve surgery; OPCAB, off-pump coronary artery bypass surgery; CABG, coronary artery bypass surgery 1° nonemergent; Aortic mdn st, median sternotomy aortic valve replacement. (*Used with permission from Stafford-Smith M, Patel U, Phillips-Bute B, et al: Acute kidney injury and chronic kidney disease after cardiac surgery. Adv Chronic Kidney Dis 15:157-177, 2008.*)

different for a patient starting with normal baseline function than one starting near the brink of filtration failure, even the usefulness of dialysis as a marker of outcome has been questioned.[24] Recent research efforts have been directed toward developing a universally accepted standard for describing AKI or renal failure.[25-32]

Although ischemic causes have long been believed to be primarily responsible for perioperative ARF,[33,34] lack of success with this paradigm in developing renoprotective strategies,[35] combined with accumulating evidence that postoperative renal dysfunction possesses characteristics of multiple types of AKI,[36,37] has resulted in a reevaluation of the pathophysiology of this disorder. Much can be learned from the many settings beyond ischemia-reperfusion where specific types of AKI occur; examples include contrast-associated nephropathy, pigment nephropathy (e.g., hemoglobin, myoglobin), cholesterol embolism (atheroembolism) nephropathy, aminoglycoside nephropathy, norepinephrine-induced nephropathy, and as part of the sepsis/systemic inflammatory response syndrome. In these examples, the disorder describes the renal pathophysiology and strategies to prevent or attenuate each condition are interventions directed specifically toward the cause. Animal studies of such "pure" nephropathies treated with logical renoprotective interventions often demonstrate success; unfortunately, this has rarely extended to equivalent renoprotection in human perioperative studies. However, it makes sense that a specific treatment for a "pure" nephropathy applied nonselectively to a mixture of nephropathies, variably expressed in different patients, would be unsuccessful. Protection from one perioperative nephropathy may even add

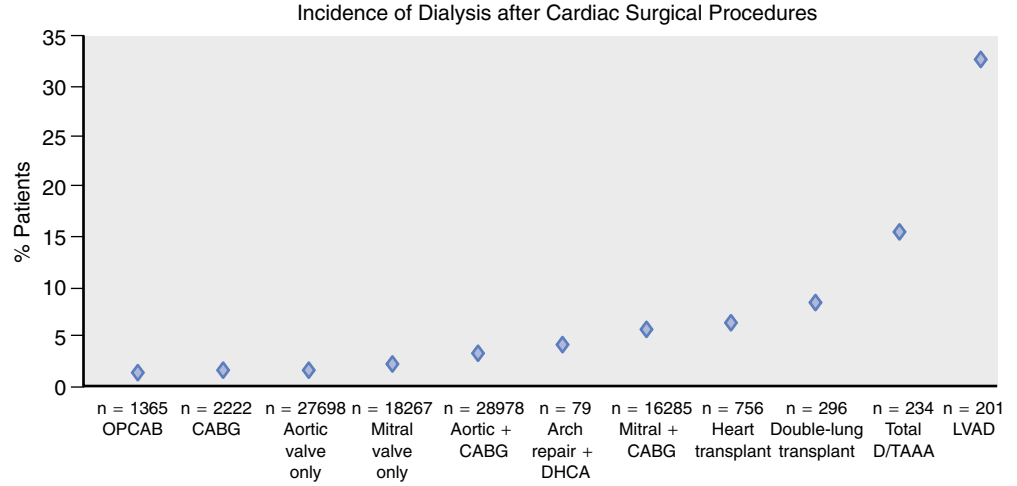

Figure 45-2 Rate of new-onset dialysis differs significantly for various surgical procedures.[4,341-348] OPCAB, off-pump coronary artery bypass surgery; CABG, coronary artery bypass surgery; DHCA, deep hypothermic circulatory arrest; D/TAAA, descending/thoracoabdominal aortic aneurysm; LVAD, left ventricular assist device. (*Used with permission from Stafford-Smith M, Patel U, Phillips-Bute B, et al: Acute kidney injury and chronic kidney disease after cardiac surgery. Adv Chronic Kidney Dis 15:157-177, 2008.*)

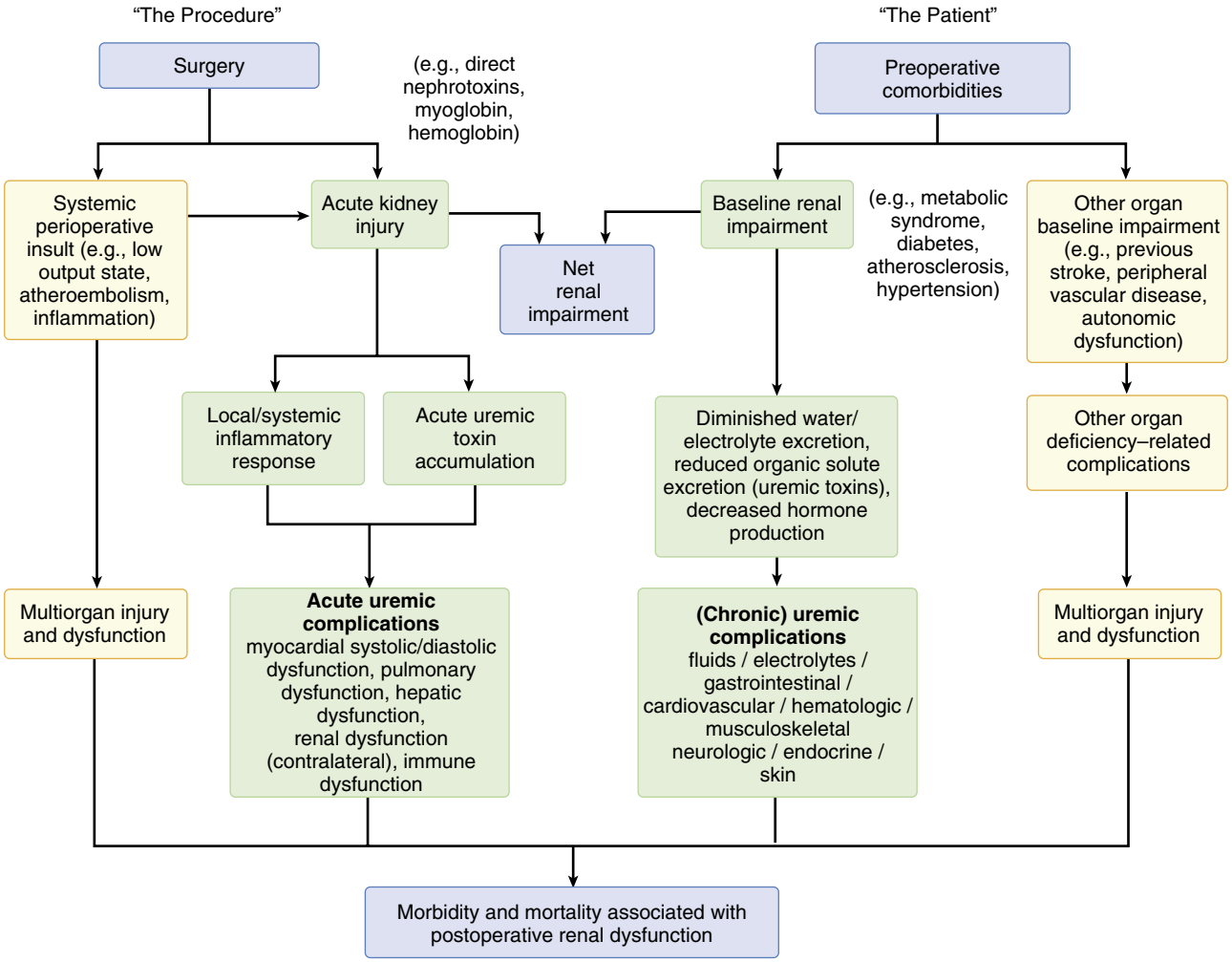

Figure 45-3 Procedural and patient factors related to surgery contributing to risk of perioperative acute kidney injury (AKI) and postoperative morbidity and mortality. Of note, although AKI contributes to this risk, a significant part of this association must also be attributed to other very serious conditions that can cause injury, such as sepsis, that themselves are major sources of adverse outcome. (*Modified with permission from Stafford-Smith M, Patel U, Phillips-Bute B, Shaw A, Swaminathan M: Acute kidney injury and chronic kidney disease after cardiac surgery. Adv Chr Kid Dis 15:157-177, 2008.*)

risk for another type; for example, augmenting renal blood flow (RBF) may attenuate ischemia-reperfusion injury while delivering more atheroemboli and inflammatory mediators. Evidence continues to grow supporting the idea that postoperative AKI is a mosaic of several "pure" nephropathies, each of varying importance for a particular patient and procedure, suggesting that only individualized renoprotection strategies, guided by timely point-of-care renal function monitoring, will be helpful in developing effective renoprotection strategies. Hence, advances in renal function monitoring are currently a major focus in the search for improved renal protection and risk stratification strategies for AKI (see Chapter 18).

Renal Physiology

The kidneys are mesoderm-derived, bean-shaped retroperitoneal organs and weigh approximately 150 g each. They are the most highly perfused major organs in the body, representing only 0.4% of body weight but receiving an impressive 25% of cardiac output; as a comparison, "at rest" blood flow to the kidneys is eightfold greater per gram of tissue than blood flow to muscle during heavy exercise. Notably, renal artery blood flow is not primarily linked to metabolic demand; it is this "excess" blood flow that allows filtration of plasma at rates as rapid as 125 to 140 mL/min in adults. However, autoregulatory reflexes do exist that regulate renal perfusion; these are myogenic and tubular-glomerular reflexes that exist to "protect" the glomeruli from damage due to pressure overload by restricting RBF at higher pressures (e.g., >80 mm Hg).[38,39] However, the kidneys may not receive a luxury supply of nutrients and oxygen, because marked regional differences in blood flow within the kidney paradoxically make some areas (i.e., the medulla) very vulnerable to ischemic injury. Cortical blood flow exceeds outer and inner medullary perfusion by 3- and 20-fold per gram of tissue, respectively.[40] Although there is strong evidence that paracrine regulation of oxygen delivery is important in the medulla, little is known about the specifics of this process.[41]

Gross Anatomy and Internal Architecture

A detailed description of the anatomy of the kidney can be obtained elsewhere.[42] In simple terms, the internal morphology of the kidney parenchyma is highly organized, including a deep medullary region and superficial cortical layer. The medulla is further subdivided into inner and outer regions. Tightly packed nephrons are tubular structures that contain specialized segments including the glomerulus, proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting duct (Fig. 45-4). The collecting ducts feed urine to the renal pelvis, which empties into the ureter and goes on to the bladder. Each kidney contains approximately 1 million nephrons. The loops of Henle and collecting ducts are found in the deeper parts of the kidney (medulla). Two types of nephrons are differentiated by glomerular location into cortical (85%) and juxtamedullary (15%) types; only the latter have loops of Henle that course deep into the medulla and participate in *countercurrent exchange,* a mechanism that makes possible the formation of highly concentrated urine.

Vascular Anatomy

A single *renal artery* enters at the kidney hilum and then divides many times, ultimately producing *arcuate arteries* that pass along the boundary between cortex and outer medulla (see Fig. 45-4).[41] Arcuate arteries give rise to *interlobular arteries* that branch toward the outer kidney surface, passing through the cortex as they produce numerous *afferent arterioles,* which in turn supply a *capillary tuft* to each glomerulus. The glomerular capillary tuft is the barrier where plasma elements are filtered and pass from the vascular to tubular space. Specialized negatively charged fenestrated capillary endothelial cells and tubular epithelial cells (podocytes) separated by a basement membrane allow approximately 25% of plasma volume to pass into the glomerulus (Bowman's capsule); normally, only elements smaller than 60 to 70 kDa are small enough to be filtered. Many disease conditions cause abnormalities of this interface and allow much larger proteins and even red blood cells to pass through; this manifests as either nephrotic syndrome (proteinuria > 3.5 g/24 hr) or glomerulonephritis (proteinuria and hematuria). As the vascular tuft exits the glomerulus, capillaries merge and become the *efferent arteriole.* Subsequent branches of the afferent arterioles become *peritubular capillaries* to nourish the tubules. Peritubular capillaries receive reabsorbed fluids and solutes from tubular cells before rejoining to form *venules.* Peritubular vessels of juxtamedullary glomeruli are known as *vasa recta* and accompany the loops of Henle deep into the medulla. The venous system of the kidney runs parallel and close to the arterial vasculature, finally returning blood to the inferior vena cava through the *renal vein.* Vascular supply to the kidney is strictly segmental, and embolic arterial or venous obstruction affects renal tissue in a "pizza wedge" parenchymal distribution involving all cortical and medullary tubular elements of affected nephrons.

Medullary hypoxia is a key concept that refers to the low oxygen levels that exist in the renal medulla, even during normal resting conditions. Sodium and water reabsorption depend on the hypertonicity of the medullary interstitium. The countercurrent multiplier system in the loop of Henle is a critical component of the kidney's ability to excrete or conserve salt and water.

The apparent overabundance of blood flow to the cortex is designed to maximize flow-dependent functions, such as glomerular filtration and tubular reabsorption. In the medulla, blood flow and oxygen reserve are restricted by a tubulovascular anatomy specifically designed for urinary concentration. The tubules carrying blood to the medulla are arranged in a hairpin-loop pattern to allow a countercurrent exchange of solute between the ascending and the descending limbs of the hairpin loop.[43] The osmotic gradient in the deeper portions of the medulla requires active transport of sodium in the thick ascending loop of Henle and limited blood flow through the medullary vessels to prevent washout of the solutes in those deeper tubules. To maintain this concentration gradient in the thick ascending limb, high energy demand (i.e., active sodium transport) must be coupled with low oxygen delivery.

Factors necessary to allow countercurrent exchange and create a urea gradient conspire to make normal medullary Po_2 very low (e.g., 10 to 20 mm Hg); these include high oxygen demand from active solute transport and sluggish blood supply (5% to 10% of RBF). Average blood flow is 5.0 mL/g/min and 0.03 mL/g/min for the cortex and medulla, respectively, and the oxygen extraction ratio (i.e., oxygen consumption over oxygen delivery) is 0.18 and 0.79 for the cortex and medulla, respectively. The descending vasa recta are vasoactive arteriolar microvessels that are anatomically positioned to regulate total and regional blood flow to the outer and inner medulla.[43] Normally, the partial pressure of oxygen is about 50 mm Hg in the cortex and 8 to 15 mm Hg in the medulla, making the thick ascending loop of Henle most vulnerable to tissue hypoxia. Medullary oxygen delivery is made more inefficient by the unique hairpin loop anatomy of the loops of Henle and vasa recta that allows "oxygen escape" from entering to exiting capillaries (see Fig. 45-4).[44,45] This precarious arrangement underpins some of the specialized homeostatic abilities of the kidney, particularly the formation of concentrated urine, but also underlies the extreme vulnerability of the renal medulla to ischemic injury.[46]

The high metabolic requirement of the thick ascending loop of Henle in a hypoxic environment makes it especially vulnerable to injury associated with an imbalance in oxygen supply and demand.[47,48] Hypoxic perfusion of an isolated kidney preparation has demonstrated that the cells of the thick ascending limb of the loop of Henle in the medulla are extremely vulnerable to hypoxic damage.[48] Most recent available evidence suggests specific roles for prostaglandins (mediated by cyclooxygenase-2 receptors), angiotensin II, bradykinin, adenosine, nitric oxide (generated by nitric oxide synthase type 3), norepinephrine, and vasopressin in the paracrine autoregulation of medullary blood flow.[41] An adenosine receptor–mediated renal *ischemic preconditioning reflex* has been characterized, but the relevance of this to humans is unknown.[49-51]

Normal Function

The "resting" kidney continuously regulates body composition by processing plasma filtrate to keep fluid volume, osmolarity, acidity, and numerous electrolytes within narrow limits. Every 3 minutes a plasma volume equivalent to a 12-oz soft drink is filtered, and all but 1% (4 mL) is returned to circulation; the remnant is urine. Tightly regulated through tubular processing are extracellular solutes, including sodium, potassium, hydrogen ion, bicarbonate,

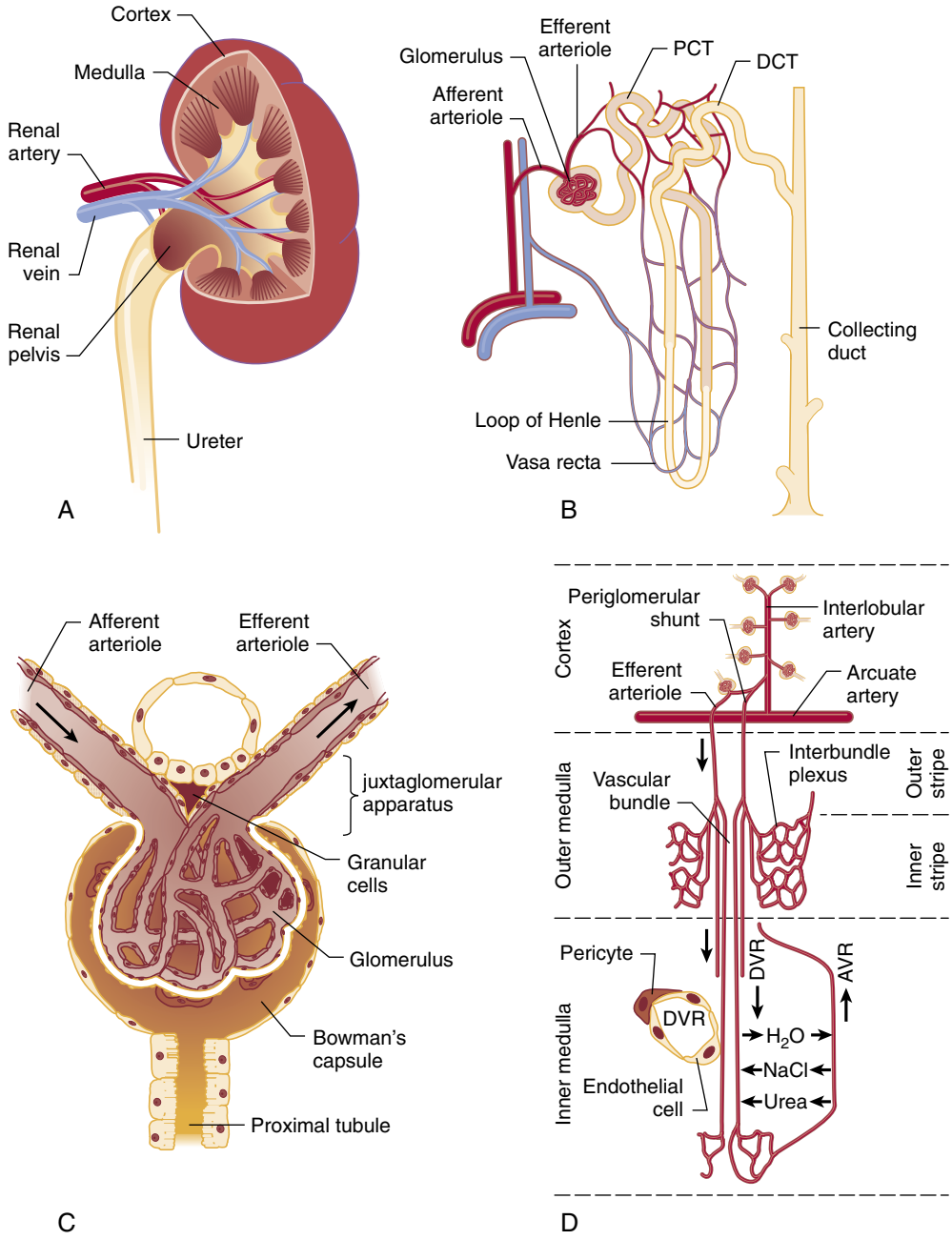

Figure 45-4 A, The internal structure of the kidney includes the vasculature, cortex and medulla regions, and urinary tract structures. **B,** The functional unit of the kidney is the nephron. **C,** The glomerulus is the site where plasma filtration occurs; approximately 20% of plasma entering the glomerulus will pass through the specialized capillary wall into Bowman's capsule and enter the tubule to be processed and generate urine. **D,** The vascular anatomy of the kidney is highly organized, and the medullary microcirculation is part of the mechanism that permits countercurrent exchange.[41] AVR, ascending vasa recta, DVR, descending vasa recta. PCT, proximal convoluted tubule; DCT, distal convoluted tubule. (***A*** *from http://www.nida.nih.gov/consequences/kidney/. Accessed February 17, 2008;* ***B*** *from http://www.pathology.vcu.edu/education/PathLab/pages/renalpath/rpsrhome.htm from Lecture 1. Accessed February 17, 2008;* ***C*** *from http://www.besthealth.com/besthealth/bodyguide/reftext/images/Nephron.jpg. Accessed February 17, 2008. Used with permission from Pallone TL, Zhang Z, Rhinehart K: Physiology of the renal medullary microcirculation. Am J Physiol Renal Physiol 284:F253-F266, 2003.*)

and glucose. The kidney also generates ammonia and eliminates metabolic and nitrogenous wastes, including creatinine, urea, and bilirubin, as well as toxins and many classes of drugs. Finally, the kidneys generate glucose and secrete circulating hormones that influence erythrocyte generation, systemic blood pressure, and calcium homeostasis.

High concentrations of aldosterone stimulate reabsorption of sodium and water, primarily in the distal tubule and the collecting ducts. Aldosterone is produced by the adrenal cortex in response to the feedback from the renin-angiotensin-aldosterone system, simplified as follows. Reduced delivery of sodium to the macula densa causes release of renin from the granular cells of

the juxtaglomerular apparatus. Renin catalyzes the release of angiotensin I from angiotensinogen. Angiotensin I is then transformed to angiotensin II in the lungs, catalyzed by angiotensin-converting enzyme. Angiotensin II stimulates the production of aldosterone.

Antidiuretic hormone (ADH, vasopressin) acts primarily on the collecting ducts to increase water reabsorption. ADH is released from the posterior pituitary gland in response to increased blood osmolarity, which stimulates osmoreceptors in the hypothalamus. ADH release is also influenced by stress and increased partial pressure of arterial carbon dioxide.[52] A high level of ADH results in the excretion of small volumes of concentrated urine. ADH is inhibited by stimulation of atrial baroreceptors or increased atrial volume.[53]

Atrial natriuretic peptide causes systemic vasodilation and promotes renal excretion of sodium and water by increasing glomerular filtration.[54] Atrial natriuretic peptide is secreted by the cardiac atria and other organs in response to increased intravascular volume. It decreases systemic blood pressure by relaxing vascular smooth muscle, reducing sympathetic stimulation, and inhibiting the renin-angiotensin-aldosterone system. The kidney also synthesizes prostaglandins, which regulate the influence of other hormones. During hemodynamic instability and increased adrenergic stimulation, for example, prostaglandin E_2 decreases the vasoconstrictive effect of angiotensin II on the afferent arterioles and preserves RBF. Inhibition of prostaglandin synthesis during normal states of hydration, renal perfusion, and sodium balance does not affect renal function. When the kidney is confronted with a vasoconstricted state, such as hypotension and hypovolemia, however, the presence of renal prostaglandins is essential for preserving adequate RBF. Patients taking nonsteroidal anti-inflammatory drugs are at risk during conditions of impaired circulatory status because these agents inhibit cyclooxygenase activity, an important enzyme in the prostaglandin synthesis pathway, thereby rendering the kidney (afferent arteriole) susceptible to the systemic vasoconstrictive effect of angiotensin II and other catecholamines normally secreted to preserve intravascular volume and perfusion pressure.

Interaction between the urinary bladder, the kidney, and the ureters influences urine production.[55] General anesthesia decreases the rate of ureteral contractility.[56] The autonomic nervous system also plays an important role in ureteral function and consequently in urine formation.[55] Cholinergic agonists generally increase the frequency and the force of ureteral contraction. Drugs that act primarily on adrenergic receptors tend to stimulate ureteral activity, whereas agents that primarily activate adrenergic receptors tend to inhibit ureteral activity. Histamine stimulates ureteral activity. In a variety of preparations, morphine increases ureteral tone. In humans, irregular peristaltic contractions occur with retroperitoneal inflammation resulting from appendicitis, regional enteritis, ulcerative colitis, and peritonitis.[57]

A gross summary of plasma processing by the kidney involves glomerular filtration (~120 mL/min); subsequently, up to two thirds of the water and electrolytes is quickly returned to the circulation through active transport processes by the proximal convoluted tubule. Two thirds of remaining tubular contents is more sluggishly reabsorbed in the loop of Henle and distal convoluted tubule. Finally, more water is reabsorbed from the remaining effluent in the collecting ducts (5-10 mL/hr) as it passes to larger urine collecting structures (1-2 mL/min).

The Pathophysiology of Ischemic Acute Kidney Injury

The sources of perioperative insults to the kidney are extensively reviewed elsewhere.[37] Two primary contributing mechanisms are ischemia-reperfusion and nephrotoxic effects, with three notable sources of insult common to many surgical procedures where postoperative AKI is prevalent: hypoperfusion, inflammation, and atheroembolism. Several other less common sources of renal insult may contribute in selected patients (e.g., rhabdomyolysis, drug-related).

Ischemic renal failure related to shock or severe dehydration is always preceded by an early compensatory phase of normal renal adaptation (e.g., pre-prerenal failure) followed by a condition termed *prerenal azotemia* in which the kidney maximizes activities at the expense of retention of nitrogenous end products to preserve the internal environment through extreme retention of solutes and water (Fig. 45-5). Prerenal azotemia precedes 70% of general community-acquired ARF.[19,20] Although prerenal azotemia is ominous and typically accompanied by oliguria (<0.5 mL/kg/hr), it is reversible and sometimes jokingly referred to as "acute renal success" (i.e., the kidney is succeeding in maintaining homeostasis). At a critical tilting point, as conditions go beyond the compensatory mechanisms that maintain renal perfusion, ischemia leads to irreversible renal cell necrosis.[58,59] This event is called *acute tubular necrosis* and represents the "pure" form of ischemic nephropathy. The terms *acute tubular necrosis, vasomotor nephropathy,* and *ischemic tubular injury* are often used interchangeably in the literature. Notably, several other "pure" nephropathies exist that can themselves cause ARF; these include pathophysiologies related to inflammation, pigments (hemoglobin, myoglobin), and contrast dye. Other types of "pure" nephropathy do not involve the typical pattern of prerenal azotemia and oliguria. Importantly, most cases of perioperative ARF are the result of numerous renal insults, rather than being due to one "pure" source (Fig. 45-6).

Interruption of blood flow to kidneys for more than 30 to 60 minutes results in ARF and irreversible cell damage. The kidneys receive 1000 to 1250 mL/min of blood, or 3 to 5 mL/min/g of tissue for the average adult, and this amount far exceeds that needed to provide the kidney's intrinsic oxygen requirement. Intracortical blood flow may not be evenly distributed (see Fig. 45-4).[60] Because the renal cortex contains most of the glomeruli and depends on oxidative metabolism for energy, ischemic hypoxia injures the renal cortical structures, particularly the pars recta of the proximal tubules. As ischemia persists, the supply of glucose and substrates continues to decrease; glycogen is consumed, and the medulla, which depends to a greater extent on glycolysis for its energy sources, becomes more adversely affected. Early cell changes are reversible, such as the swelling of cell organelles, especially the mitochondria. As ischemia progresses, lack of adenosine triphosphate interferes with the sodium pump mechanism, water and sodium accumulate in the endoplasmic reticulum of tubular cells, and the cells begin to swell. In irreversible ARF, several pathologic changes occur. Swelling of tubular epithelial cells leads to formation of bullae, which protrude into the tubular lumen distal to the cell; necrosis of tubular cells results in abnormal membrane permeability; structural changes in the glomerular epithelium may decrease glomerular filtration; and

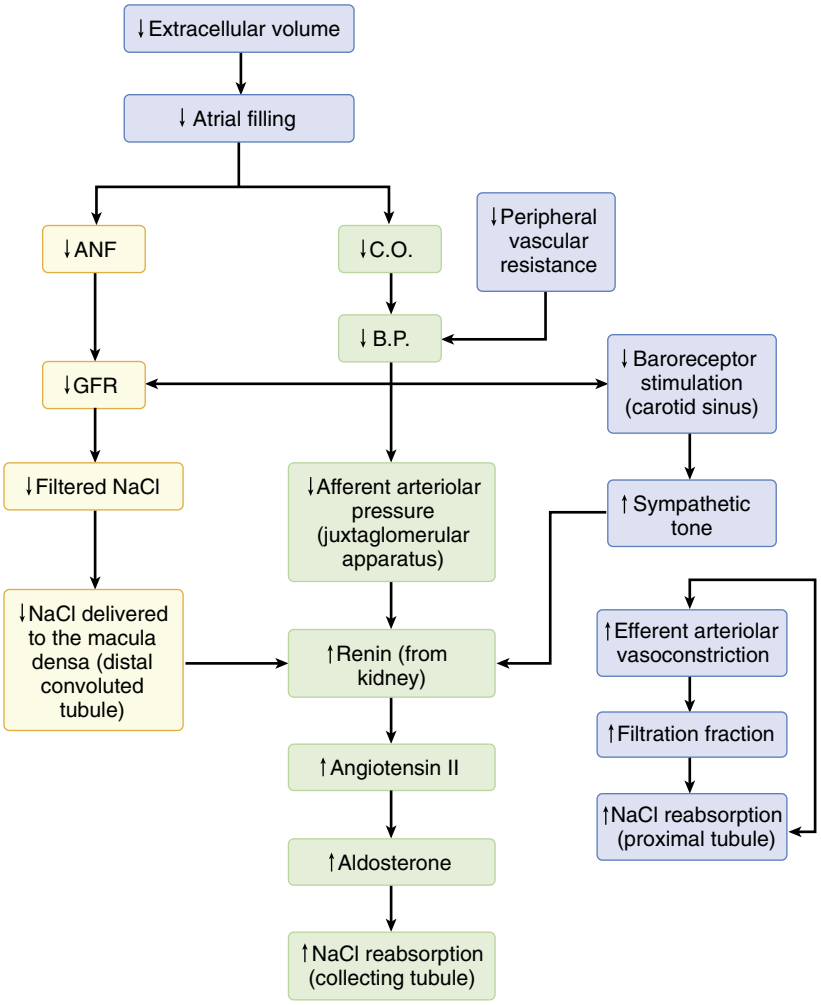

Figure 45-5 Mechanism for renal sodium and volume regulation in response to decreased extracellular volume (e.g., hypovolemia, hemorrhage). ANF, atrial natriuretic factor; B.P., blood pressure; C.O., cardiac output; GFR, glomerular filtration rate; NaCl, sodium chloride.

constriction of intrarenal arteries and arterioles may further reduce glomerular blood flow.

Onset of tubular damage usually occurs within 25 minutes of ischemia as the microvilli of the proximal tubular cell brush borders begin to change. Within an hour, they slough off into the tubular lumen and membrane bullae protrude into the straight portion of the proximal tubule. After a few hours, intratubular pressure rises, and tubular fluid backflows passively. Within 24 hours, obstructing casts appear in the distal tubular lumen. Even when RBF is completely restored after 60 to 120 minutes of ischemia, long-lasting vasoconstriction means that glomerular filtration rate (GFR) will not improve to baseline levels for an extended period.[61]

Lesions created during ischemia-induced ARF are unevenly distributed among nephrons. In contrast, lesions from nephrotoxin-induced failure are more evenly distributed among all nephrons. Proximal tubular obstruction of the tubular lumen with necrotic cell casts is characteristic.[62] After restoration of blood flow, intrarenal vascular resistance is high because of cell swelling and ischemic damage, and flow is as much as 50% below control values.[61] As blood flow becomes inadequate to support glomerular filtration, urine flow ceases and toxic substances accumulate in the urine and renal parenchyma. Other factors contributing to the increased risk of renal failure include the interference of certain drugs (e.g., nonsteroidal anti-inflammatory drugs) with autoregulation and preservation of blood flow to strategic regions of the kidney, drug-induced membrane damage, or mitochondrial uncoupling, causing an inefficient use of oxygen. Toxic substances (e.g., aminoglycosides) and oxygen deprivation cause depletion of adenosine triphosphate due to low blood flow.

Anesthesia, Surgery, and Normal Renal Function

Notably, the importance of oliguria (<0.5 mL/kg/hr) as a predictor of AKI is very limited in the perioperative setting (Fig. 45-7).[63] Anesthesia and surgery influence normal renal function primarily through changes in GFR.[64] Fluctuations in blood pressure have a major effect on RBF and glomerular filtration.[65,66] Anesthetic interventions, whether involving volatile agents, intravenous drugs, or regional blocks, generally reduce blood pressure and cardiac output, thereby diminishing RBF, leading to decreased glomerular filtration and urine formation.[67] Commonly used premedications can similarly influence urine output.[68] Narcotics and barbiturates, for example, cause a small decrease in GFR and urine volume.

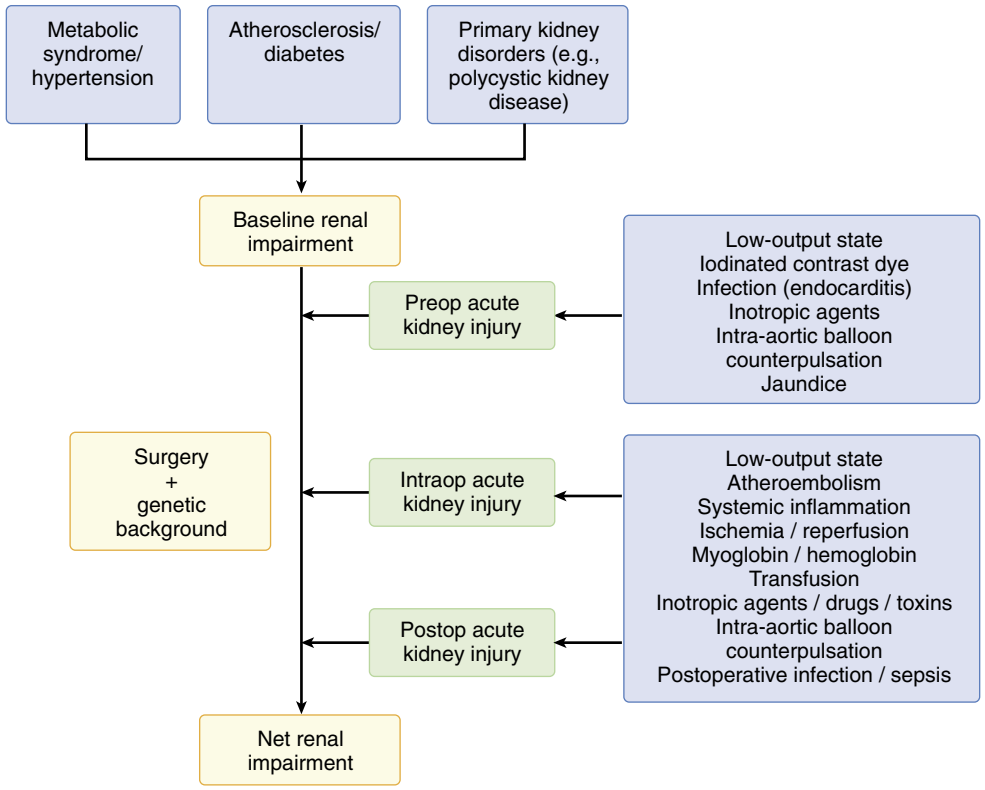

Figure 45-6 Perioperative clinical risk factors that predict risk of postoperative kidney injury and chronic kidney disease.

Surgical and anesthetic interventions may have autonomic consequences, such as increasing circulating catecholamines, that also reduce glomerular filtration by altering renal vascular resistance and decreasing RBF. The normal physiology of the kidney includes a role of adrenergic receptors in modulating vasoconstrictor (alpha 1) and vasodilating (alpha 2) effects, respectively. In animal models, infusion of norepinephrine is a well-described source of renal vasoconstriction and reduction in glomerular filtration[69,70]; this effect also appears to be relevant to human physiology.[71] The perioperative stress response to major surgery, particularly related to neurosurgical procedures, can further reduce urine output by increasing circulating ADH levels.[72,73]

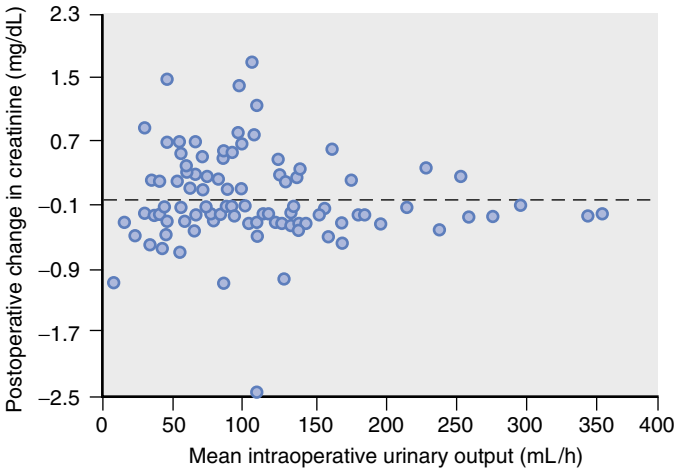

Figure 45-7 Low hourly urine flow (<0.5 mL/kg/hr) is a marker in some widely used criteria to diagnose AKI but is not a meaningful assessment to make this diagnosis in the immediate perioperative period. The lack of association of urine output with postoperative renal complications is exemplified by data in the figure comparing postoperative urine output and postoperative change in serum creatinine after aortic surgery. (*Used with permission from Alpert RA, Roizen MF, Hamilton WK, et al: Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. Surgery 95:707-711, 1984.*)

Effects of Regional Anesthesia

Regional anesthetics and the kidneys interact in a complex manner that varies according to the underlying cardiovascular, renal, fluid, and electrolyte status of the patient (see Chapters 51 and 52).[74] Epidural and spinal anesthesia reduce systemic and renal vascular sympathetic tone.[75] Spinal cord segments T4 through L1 contribute to the sympathetic innervation of the renal vasculature, which is mediated by sympathetic fibers from the celiac and renal plexus.[76,77] Autonomic blockade above the fourth thoracic level also blocks cardioaccelerator sympathetic innervation to the heart. If neuraxial blockade reduces blood pressure and cardiac output, it will reduce RBF, with matching reductions in glomerular filtration and urine output. Suleiman and colleagues[78] demonstrated in healthy volunteers that RBF is unchanged during epidural anesthesia with a T6 sensory block. In their study, mean arterial pressure remained above 70 mm Hg and RBF never decreased below 6% of the baseline level.

The effect of neuraxial blockade varies not only on the level of sympathetic block but also the presence of underlying disease. In all perioperative settings, renal filtration and urine formation

depend on the net sum of numerous endogenous effects, including circulating catecholamines, autonomic blockade, ADH, angiotensin, dopamine, vasopressin, prostaglandin, atrial natriuretic peptide, endothelin, and nitric oxide. Superimposed on endogenous factors are surgical and anesthetic interventions, such as aortic cross-clamping, cardiopulmonary bypass (CPB), diuretics, and vasoactive infusions (e.g., vasopressin, dopaminergic and adrenergic agonists).

Urine volume and free water clearance may decrease during spinal anesthesia as a result of increased ADH secretion. Increased renal sympathomimetic activity decreases RBF through α-adrenergic mediation and increases renin release through β-adrenergic innervation directly or by interaction with the renal tubular macula densa and the baroreceptor reflex mechanism.[79-82] Of note, thoracic epidural anesthesia has been shown to increase RBF and urine output in animal models of endotoxic shock.[83]

Two recent large reviews on epidural anesthesia have findings that relate to perioperative renal outcomes. Moraca and colleagues[81,82] conducted a meta-analysis and reported on the association of thoracic epidural anesthesia with improved surgical outcomes in part attributable to reduction of perioperative morbidity, including blunting of stress response, attenuating infections, reduced ileus, reduced blood loss, and reduction in ARF. Liu and Wu[80] reviewed 18 meta-analyses, 10 reviews, eight randomized controlled trials, and two observational studies on epidural analgesia and found that the data support the ability of epidural analgesia to reduce cardiovascular and pulmonary complications, including renal morbidity after major vascular surgery on high-risk patients.

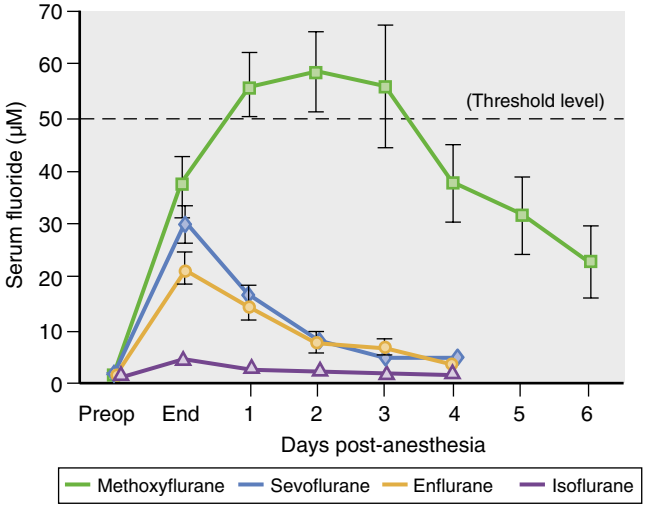

Figure 45-8 The nephrotoxic effect of the older volatile inhaled anesthetics are attributed to the liberation of inorganic fluoride when they are metabolized. Methoxyflurane-related AKI was related to threshold circulating fluoride levels greater than 50 μM/L. Levels of inorganic fluoride do not correlate as closely with the risk of AKI for modern volatile anesthetics such as sevoflurane. (*Used with permission from Mazze RI: Methoxyflurane revisited: tale of an anesthetic from cradle to grave. Anesthesiology 105:843-846, 2006.*)

Effects of Inhaled Anesthetics

There is a well-recognized nephrotoxic effect of the older volatile inhaled anesthetics that has been attributed to the liberation of inorganic fluoride when they are metabolized (see Chapter 24).[84] Methoxyflurane (no longer used clinically) and enflurane, when employed for prolonged periods (9.6 minimum alveolar concentration [MAC] hours), lead to significant generation of inorganic fluoride.[84-87] Increased serum levels of inorganic fluoride caused polyuric renal insufficiency.[84,85] Approximately 100 published cases of renal failure and 20 renal-related deaths attest to the significance of methoxyflurane-related nephrotoxicity.[84]

Because sevoflurane metabolism is similar to enflurane in regard to liberation of free fluoride ions,[84,88-91] (Fig. 45-8) concerns were raised during development that this agent may also impair the ability of the kidneys to concentrate urine.[89,92] Methoxyflurane studies indicated that AKI was likely to occur with circulating fluoride levels greater than 50 μM/L.[84,86] This presumed toxic threshold was extrapolated to the study of other halogenated anesthetic agents, including enflurane and sevoflurane (see Fig. 45-8). Notably, mean plasma fluoride levels in volunteers are approximately twice as high with sevoflurane as enflurane and 43% of volunteers receiving sevoflurane have plasma fluoride levels that exceed 50 μM/L. Healthy patients receiving 9 MAC hours of sevoflurane anesthesia have serum fluoride levels averaging 36.6 ± 4.3 μM/L.[88,93] However, relative to methoxyflurane, high fluoride levels with sevoflurane are short-lived, peaking 2 hours after the end of anesthesia and dropping by 50% within 8 hours. Despite high fluoride levels with sevoflurane, volunteers have no impairment in their ability to concentrate urine in response to desmopressin, whereas 20% of volunteers receiving enflurane have transient concentrating deficits on day 1 but not day 5 post exposure.[93] To interpret these findings, investigators postulate that intrarenal production of fluoride ion may be more important for nephrotoxicity than circulating plasma fluoride levels.[91] The intrarenal metabolism of methoxyflurane is fourfold greater than the intrarenal metabolism of sevoflurane.

Other explanations for differences in the renal effects of volatile agents were sought, including evaluation of variation in nephrotoxic compounds generated when an inhaled anesthetic agent interacts with carbon dioxide absorbents. In breathing circuit systems at high temperature and low flow rates, carbon dioxide absorbents degrade sevoflurane, creating fluoromethyl-2,2-difluoro-1-(trifluoroethyl) vinyl ether, also known as compound A. Metabolism of compound A includes conjugation in the liver with glutathione and then modification in the kidney by an enzyme (cysteineconjugate β-lyase). Some compound A metabolites can cause renal injury, characterized by diuresis, glycosuria, proteinuria, and elevated serum BUN and creatinine levels. AKI by this mechanism in experimental models is a function of the degree and duration of exposure to compound A,[94] with well-defined exposure thresholds in rats for injury (50-114 ppm for 3 hours) and death (331 for 3 hours, 203 for 6 hours, or 127 ppm for 12 hours).[95] However, a disparity exists between the results in rats and humans that may be due to differences in compound A processing; of the four recognized pathways for metabolism, three do not involve renal β-lyase nor result in kidney toxicity. Humans have 10- to 30-fold less renal β-lyase enzyme activity compared with rats, which may account for the absence of kidney injury from sevoflurane in humans. One study[96] compared the safety of low-flow sevoflurane and isoflurane anesthesia in patients having prolonged surgeries (>6 hr). The average MAC hours in both groups was similar, and the

average compound A concentration in the sevoflurane group was 20 ± 7 ppm. Markers of renal injury, including BUN, creatinine, *N*-acetyl-β-D-glucosaminidase (NAG), and alanine aminopeptidase, were increased similarly in all groups during the prolonged exposure to the volatile anesthetics.

The concentrations of compound A possible with sevoflurane during anesthesia has been evaluated in human volunteers.[97] Fresh carbon dioxide absorbent was used, and 1.25 MAC sevoflurane was given (without nitrous oxide) for 8 hours. Compound A levels approached 50 ppm, and 24-hour urine collections were analyzed for 3 consecutive days after exposure. Urinary glutathione S-transferase (GST) and other highly sensitive markers of tubular damage after nephrotoxic and ischemic insults were measured.[98] The investigators reported transient elevations of urinary protein, albumin, glucose, α-GST, and π-GST in patients receiving sevoflurane. Interestingly, no such increases were observed after similar exposure to desflurane. A multicenter study[99] involving 73 elective surgical procedures lasting 2 to 8 hours compared the safety and efficacy of low flow (less than 2 L/min) sevoflurane to isoflurane. Fresh carbon dioxide absorbent was used for all cases, and nitrous oxide was not permitted. Sevoflurane use averaged 3.6 MAC hour, and compound A levels were as high as 223 ppm (mean 79 ± 54 ppm). No differences were found in urine albumin, glucose, protein, or osmolality between treatment groups. Moreover, within the sevoflurane group, there were no significant correlations between compound A levels and BUN, creatinine, or urinary excretion of protein, glucose, NAG, α-GST, or π-GST.[99]

Despite the fact that 7% to 15% of patients receiving sevoflurane may have (short-lived) circulating levels of fluoride in excess of 50 μM/L and/or significant exposure to compound A, adverse renal effects do not seem to occur.[84] While explanation for the apparent safety of sevoflurane in the presence of nephrotoxins is not completely understood, some have proposed that the source of methoxyflurane-related renal injury may even be some other metabolic "villain" than fluoride or compound A that is unique to methoxyflurane metabolism, such as dichloroacetic acid.[100] Potential benefits of sevoflurane to the kidney have been described. In patients undergoing cardiac surgery, preconditioning with sevoflurane has been reported to decrease biochemical markers for renal (as well as myocardial) dysfunction.[101] Seventy-two patients scheduled for coronary artery bypass graft surgery (CABG) were randomly assigned to preconditioning conditions (oxygen-air versus sevoflurane 4%) during the first 10 minutes of CPB. Sevoflurane preconditioning significantly decreased postoperative release of brain natriuretic peptide and plasma cystatin C concentrations compared with oxygen-air.

Perioperative Hemodynamic Instability and Renal Function

An early compensated phase of renal adaptation in response to decreased glomerular blood flow with oliguria is sometimes referred to as "pre-prerenal failure" or "acute renal success."[58] When compensatory mechanisms are overwhelmed, accumulation of nitrogenous waste ensues (e.g., blood urea nitrogen) and prerenal failure. Renal clearance is determined by the delivery of waste products to the kidney (i.e., RBF) and by the kidney's ability to extract them (i.e., glomerular filtration).

In animal models, RBF is interrupted mechanically or pharmacologically; flow reduction by more than 50% is followed by a timed episode of complete renal ischemia (e.g., 40 to 60 minutes); and the consequent functional and histologic lesion, laboratory, and pathologic features resemble significant AKI without the need for dialysis. A number of theories have been proposed to explain the pathogenesis of hemodynamically mediated AKI. Although an extreme reduction in RBF is clearly necessary,[34,102] the unpredictable degree of AKI after hypotension suggests that it is not always sufficient. Even with decreased glomerular perfusion, a series of compensatory mechanisms can still preserve renal filtration.[58] Salt and water retention can restore intravascular volume and fractional tubular reabsorption. At a given level of cardiac output, intrarenal factors affect the ratio of renal-to-systemic vascular resistance, thereby influencing the fraction of cardiac output received by the kidneys. At the glomerular capillary, plasma is separated into a protein-free ultrafiltrate and a nonfiltered portion. Normally, the filtration fraction (i.e., relationship of glomerular filtration to renal plasma flow) is about 0.2. Initially, the filtration fraction is maintained by efferent arteriolar constriction. Unabated, the mechanisms that influence efferent arteriolar vasoconstriction ultimately may influence afferent arteriolar vasoconstriction. The resulting decrease in filtration fraction is the hallmark of postischemic AKI.[58] Ischemic tubular damage may be exacerbated further by an imbalance between oxygen supply and demand. Most vulnerable to the imbalance are the thick ascending tubular cells of the loop of Henle in the medulla.[48,102-105]

Microsphere, xenon washout, and angiographic techniques have shown that outer cortical blood flow decreases in ischemic models of AKI.[106-108] Because 85% to 90% of RBF is normally distributed to cortical glomeruli, the finding of cortical pallor and RBF redistribution away from cortex suggests that redistribution may contribute to the functional lesions of AKI. In some cases, the return of perfusion to the cortex has correlated with a return of renal function.[107] The theory that intrarenal distribution of blood flow away from the outer cortex to the inner medulla decreases oxygen supply while increased tubular reabsorption of solute increases oxygen demand is further supported by studies of renal energetics during AKI.[109-111] A decrease in the glomerular filtration, and consequently in the energy requirement for tubular reabsorption, may be a mechanism by which the kidney reduces energy demands before energy supply is critically limited.

Other Perioperative Perturbations and Renal Function

Whereas aortic cross-clamping above the renal arteries has obvious influence on glomerular filtration, infrarenal aortic cross-clamping and declamping also has significant indirect effects on glomerular filtration and urine formation through changes in myocardial function, sympathetic activity, neuronal and hormonal activity (e.g., renin and angiotensin production), intravascular volume, and systemic vascular resistance.[112] During standard CPB, cardiorenal relationships are approximately as expected;

RBF falls to 12% to 13% of total pump flow and is predicted by flow rate and perfusion pressure; however, only mean pressure correlates with urine output.[65,66] The intactness of myogenic and tubular-glomerular autoregulatory feedback has not been evaluated during CPB.[38,39]

ARF after aortocoronary bypass surgery continues to be a devastating complication that is associated with multiorgan dysfunction, increased resource utilization, high cost, and increased mortality (see Chapters 60 and 62).[2-10] Annually, 1 million patients worldwide have coronary revascularization with use of CPB with approximately 77,000 patients a year developing postoperative AKI, among which approximately 14,000 require dialysis for the first time.[4] The mechanism of perioperative AKI during cardiac surgery appears to be multifactorial, involving preoperative and intraoperative risk factors, including preexisting renal dysfunction, diabetes, ventricular dysfunction, older age, hypertension, microembolic and macroembolic processes, inflammatory mediators, prolonged CPB time, sensitivity to sympathetic stimulation, perturbation in renovascular resistance and flow,[3,8,113] and hypertension subtype (namely, pulse pressure hypertension).[2]

The importance of CPB has been evaluated in numerous studies of postoperative AKI between patients undergoing off-pump and on-pump coronary revascularization surgeries[114-124] with no conclusive evidence that CPB directly contributes to postoperative AKI. In a recent multicenter study of patients undergoing cardiac surgery, independent and significant risk factors for AKI were age older than 75 years, preoperative congestive heart failure, prior history of myocardial infarction, preexisting renal disease, intraoperative use of multiple inotropes, intraoperative insertion of intra-aortic balloon pump, and extended duration of CPB (>2 hr). In addition, preoperative pulse pressure (systolic minus diastolic) greater than 40 mm Hg had an incremental and progressive relationship with renal risk, such that for every additional 20-mm Hg increment in pulse pressure there was an additive odds ratio of 1.49 (CI, 1.17 to 1.89; $P = .001$). In this large study, with a high incidence of AKI (4.8%) in both the derivation (n = 2381) and validation (n = 2402) cohorts, AKI was nearly two times and renal-related death three times more common in patients with a pulse pressure greater than 80 mm Hg.

Genetic variants are an established predictor of chronic kidney disease (e.g., renal transplant nephropathy) and explain twofold to threefold more variation in postoperative AKI than standard clinical risk factors alone.[125,126] A handful of candidate polymorphisms known to affect inflammation and vasoconstriction have been studied, and several demonstrate strong associations with postcardiac surgery AKI.[126,127] The most clinically relevant genetic findings to date identify co-possession of the IL-6 572C and angiotensinogen (AGT) 842C polymorphisms in whites (9% of patients) as a predictor of an approximately fourfold greater than average peak creatinine rise after coronary revascularization (121%) (Fig. 45-9) and may have potential as a preoperative screening tool if validated in other populations. In African Americans, a similar, but statistically less robust finding, co-possession of the endothelial nitric oxide synthase (eNOS) 894T and angiotensin-converting enzyme deletion polymorphisms, also predicts a large creatinine rise (162.5%) (see Fig. 45-9). This compelling evidence of a genetic basis for postoperative AKI has come from analysis of a relatively small number of candidate genetic variants.

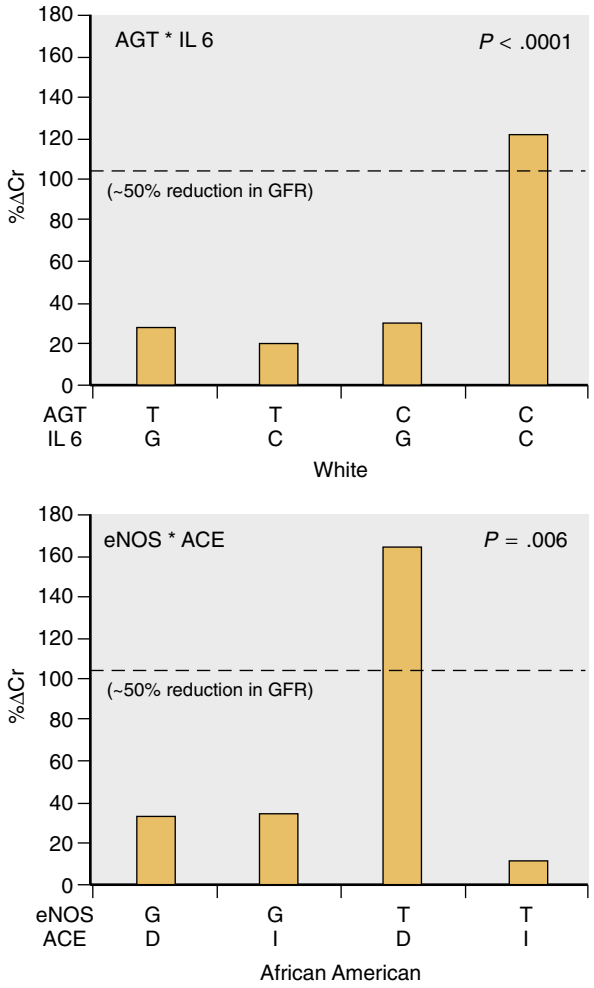

Figure 45-9 AKI after cardiac surgery is better predicted by knowledge of genetic variants than by standard clinical risk factors alone. Common gene polymorphism combinations predict increased risk; angiotensinogen (AGT) 842T→C and interleukin (IL) -6 572G→C in whites; endothelial nitric oxide synthase (eNOS) 894G→T and angiotensin-converting enzyme (ACE) insertion/deletion (I/D) in African Americans. % ΔCr, peak fractional serum creatinine rise; GFR, glomerular filtration rate. (*Used with permission from Stafford-Smith M, Podgoreanu M, Swaminathan M, et al: Association of genetic polymorphisms with risk of renal injury after coronary artery bypass graft surgery. Am J Kidney Dis 45:519-530, 2005.*)

Monitors of Renal Function

In patients with perioperative AKI, one of the major challenges to optimal perioperative management and early intervention has been the absence of tools for early recognition of subtle AKI. Traditional renal failure monitoring tools typically are insensitive until less than 40% of normal functioning nephrons remain (Fig. 45-10); this leaves only a small margin of renal function before uremic symptoms are apparent, when less than 5% of normal functioning nephrons remain.[58]

The highest standard for evidence of perioperative renal preservation is the avoidance of renal replacement therapy and reduced mortality. For example, optimal postoperative management of hyperglycemia in critically ill patients reduces the incidence of dialysis and improves survival.[128] Unfortunately, most

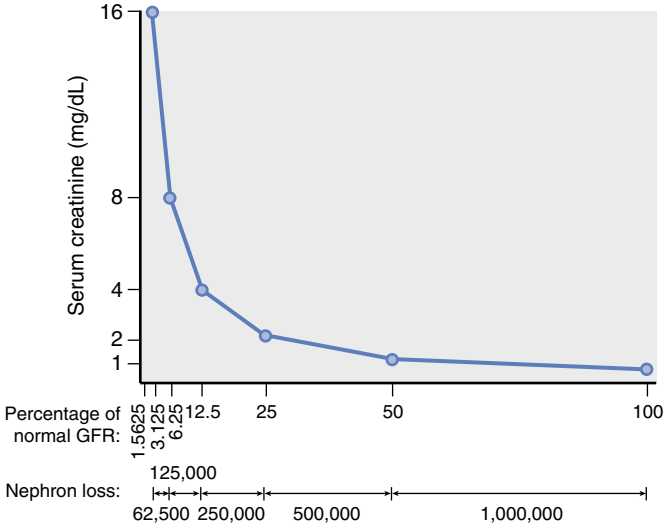

Figure 45-10 The inverse logarithmic relationship between serum creatinine concentration (*y* axis) and relative reductions in glomerular filtration rate (GFR) and approximate nephron loss (*x* axis). The nonlinear relationship means that serum creatinine level is not markedly increased until there is a 75% reduction in GFR (e.g., 120 to 30 mL/min). (*Modified from Faber MD, Kupin WL, Krishna G, Nairns RG: The differential diagnosis of ARF. In Lazarus JM, Brenner BM [eds]: ARF, 3rd ed. New York, Churchill Livingstone, 1993, p 133.*)

studies do not have sufficient sample size to show differences in mortality or dialysis rates and instead employ surrogates.

Most commonly, renal preservation is measured using secondary surrogate end points as markers for dialysis and death. Secondary measures most commonly reflect changes in glomerular filtration after surgery rather than renal failure requiring dialysis; peak filtration impairment is compared with a critical threshold or to renal function at baseline. Although most markers of renal filtration impairment based on serum creatinine have been validated through their association with postoperative mortality, there is little consensus on a standard assessment modality[129]; one review of 28 controlled perioperative studies found no two reports with the same AKI or ARF criteria.[23] Many studies present a variety of markers of AKI to describe an effect.[130]

Renal function is monitored indirectly. Among obstructive causes that may initiate ARF, an occluded or kinked urinary catheter must be eliminated as a source of oliguria. Toxic causes of ARF include antibiotics (e.g., aminoglycosides, amphotericin B) or radiocontrast agents. For example, with aminoglycosides, nephrotoxicity is poorly correlated with kidney tissue or plasma levels of the drug but is markedly augmented by concomitant volume depletion or liver cirrhosis.[20] In contrast, the likelihood of AKI correlates with baseline renal impairment and the amount of radiocontrast material injected, particularly when the contrast volume to creatinine clearance ratio is greater than 6.0.[131] The vigilance of the anesthesiologist is the first monitor required for preserving renal function.

The monitoring of renal function possible during the perioperative period is highly related to perioperative timing, postoperative disposition, and operative procedure. Unlike the postoperative/critical care setting where renal monitoring can involve periodic evaluation of kidney function under relatively stable conditions, intraoperative renal monitoring involves a briefer more unstable period, often involving significant blood loss, major fluid shifts, wide hemodynamic fluctuations, and even direct compromise to renal artery blood flow; all of these factors undermine the steady state so essential to most standard tests of renal function, such as creatinine clearance. The anesthesiologist often relies on indirect variables, such as urine volume, to assess renal perfusion. Unfortunately, urine output does not reliably reflect glomerular filtration and renal function under intraoperative conditions. Even knowledge of renal artery blood flow is not particularly informative, because increased flow mandates increased filtration and active transport demands, as well as increased oxygen delivery. As previously discussed, a monitor of balanced supply/demand of regional renal perfusion, particularly in the renal medulla, would be an ideal, although currently unavailable, direct monitoring tool. The best tools currently available intraoperatively are indirect hemodynamic monitors that can assist in optimizing conditions consistent with kidney well-being, such as ensuring adequate intravascular volume (i.e., preload), cardiac performance, and systemic perfusion. Serum chemistries and urinary indices may enable the assessment of adequate distribution of cardiac output to the kidneys themselves.

Indirect Markers of Optimal Renal Perfusion and Function

Nonoperative epidemiologic studies show a pattern for the development of renal failure that commonly involves the combination of severe dehydration with chronic renal conditions. For example, the combination of diabetes mellitus and volume depletion increases the chance of developing ARF by 100-fold.[20] The most practical preoperative methods to assess volume status are by standard preoperative history and physical examination and by evaluating changes in blood pressure in response to changing conditions. An awake patient normally does not have significant orthostatic changes in blood pressure unless he or she is dehydrated, whereas a similarly dehydrated anesthetized patient may demonstrate paradoxical arterial pulse changes with positive-pressure inspiration.[132]

Oxygen Delivery: Blood Gas, Acid-Base Balance, and Hematocrit

Severe arterial hypoxemia to a partial pressure of arterial oxygen (Pao_2) value of less than 40 mm Hg is associated with decreased RBF and renal vasoconstriction.[133,134] It appears that systemic hypoxia can produce antidiuresis and antinatriuresis independent of renal nerve innervation.[135] Capnometry may be a useful monitor because hypercarbia has been associated with decreased RBF in patients requiring mechanical ventilation.[136] Animal studies indicate that oxygen supply demand inequalities are exaggerated and medullary hypoxia is extreme during CPB, effects that last well beyond separation from circulatory support.[137]

The effects of anemia on the kidney have been most studied in the context of CPB management. When crystalloid/colloid solutions are used to prime an extracorporeal circuit, initiation of CPB obligates an acute drop of approximately 30% in oxygen-carrying capacity. Animal studies endorse moderate hemodilution (hematocrit 20%-30%) as renoprotective during CPB through

reduction of blood viscosity and improved regional blood flow.[138,139] However, although hematocrits less than 20% during CPB are commonly accepted clinically (extreme hemodilution), recent studies have linked very low hematocrit values with adverse outcome.[140-142] Several large retrospective studies identify lowest hematocrit during CPB as a predictor of postoperative AKI and renal failure.[130,143-145] Ironically, one alternative to tolerating extreme CPB hemodilution, transfusion, has also been considered risky for the kidney.[143,145]

Swaminathan and colleagues found an independent association of lowest CPB hematocrit (range, 22% to 24%) with postoperative AKI in a retrospective study of 1404 CABG surgery patients, a risk that was increased for obese patients.[143] These authors also observed a relationship between transfusion with renal impairment. In a similar study of AKI, Habib and colleagues[130] identified a near sigmoid-shaped detrimental CPB hematocrit "elbow" effect below 24%, even after adjustment for transfusion and extended CPB duration. Finally, Karkouti and colleagues evaluated the incidence of dialysis relative to lowest CPB hematocrit in 9080 cardiac surgery patients, noting a hematocrit less than 21% to be detrimental, compared with 21% to 25%, with a 2.3-fold increased risk of dialysis.[144] Interestingly, high hematocrits (>25%) were also associated with an increased risk for dialysis in this study. Although these studies endorse efforts to prevent extreme hemodilution during CPB, and guidelines for transfusion have been described,[146] support for transfusion as a treatment for all but the most extreme anemia (<15%)[147,148] is more controversial.[149]

Systemic Perfusion: Systolic Arterial and Pulse Pressure

Large multicenter epidemiologic studies have identified a relationship between markers of abnormal central aortic compliance, such as preoperative isolated systolic hypertension (>160 mm Hg) and wide pulse pressure hypertension (>40 mm Hg),[2,8,150] and postoperative AKI and dialysis. Preexisting systolic hypertension predicts a 40% greater risk, and wide pulse pressure also predicts postoperative AKI such that in cardiac surgery patients for every additional 20–mm Hg increment in pulse pressure greater than 40 mm Hg there is an OR of 1.49 (CI, 1.17 to 1.89; $P = .001$).

The systolic component of blood pressure is determined by stroke volume and the rate of ventricular ejection, whereas the pulsatile component of blood pressure is governed by the relationships among stroke volume, ventricular ejection, viscoelastic properties of large arteries, and peripheral vascular resistance. Pulse pressure is an index of the effects of large artery stiffness and the rate of pressure on propagation and reflection within the arterial tree. Early return of reflected arterial waves during late systolic rather than early diastolic pressure (from increased propagation velocity in stiff vessels) increases systolic blood pressure (i.e., afterload) and decreases diastolic blood pressure (i.e., perfusion pressure). It is likely that perfusion pressure and risk of perioperative renal dysfunction are linked by the preexisting capacity of the vasculature to compensate for low pressure as it determines flow. Those with a predisposition to low flow due to abnormal central aortic compliance may represent patients who require higher pressure to maintain adequate flow and minimize renal risk compared with normotensive patients.

RBF during CPB is not autoregulated and varies with pump flow rates and blood pressure.[65] However, CPB hypotension is not equivalent to hypotension with hemorrhagic shock or low cardiac output states, because low pressure during CPB is rarely associated with low flow. Fischer and colleagues retrospectively compared CPB flow rates and perfusion pressures in a case-control analysis of three groups of patients with normal baseline renal function who postoperatively either required dialysis (n = 44), sustained a renal injury without requiring dialysis (n = 51) or had no renal impairment (n = 48).[151] These authors noted that, on average, greater renal injury was associated with longer bypass durations, lower flows, and longer periods with CPB pressure less than 60 mm Hg. A serious limitation of this study is the potential for confounding CPB variables and known renal risk factors. In contrast, several large retrospective studies that accounted for known risk factors in evaluating perfusion management did not link low CPB blood pressure (with maintained flow) with postoperative AKI.[152-155]

RBF is affected by renal artery stenosis. In a retrospective study of 798 aortocoronary bypass patients whose cardiac catheterization procedures routinely included renal angiogram, Conlon and colleagues found that 18.7% of patients had at least 50% stenosis of one renal artery (9 patients had > 95% renal artery stenosis bilaterally).[156] However, in a multivariable logistic regression analysis there was no association of the presence or severity of renal artery stenosis with postoperative AKI.

Intravascular Volume Status: Central Venous Pressure, Pulmonary Capillary Wedge Pressure, Left Atrial Pressure, and Left Ventricular End-Diastolic Area

The decision to use any monitor should depend on the patient's functional cardiac reserve status and the extent of the proposed surgical insult. Although maintaining adequate cardiac output is necessary for maintaining adequate RBF, it may not guarantee adequate flow. Intravascular volume monitoring techniques must include caution to identify physiologic conditions that influence their validity as a reflection of preload in a particular patient (see Chapters 16, 18, 40, and 88). Monitoring central venous pressure to assess preload involves assumptions about normal left and right ventricular function, pulmonary vascular resistance, and mitral, pulmonary, and tricuspid valve function. Similarly, monitoring pulmonary artery pressure or pulmonary capillary wedge pressure assumes normal left ventricular compliance, mitral valve function, and normal airway pressure.

Direct measurements of left atrial pressure may offer insight into the kidney pressure-flow relationship because left atrial hypotension is a powerful stimulus for renal vasoconstriction.[85] Despite equivalent reductions in cardiac output and arterial blood pressure, RBF decreases much more when left atrial pressure is decreased (e.g., hemorrhagic shock) compared with when left atrial pressure is increased (e.g., cardiogenic shock).[157] Left atrial pressure receptors modulate renal vasoconstriction through release of atrial natriuretic peptide, a hormone secreted by the cardiac atria in response to intravascular volume expansion.[158] Atrial natriuretic hormone acts on the arterial and venous systems, the adrenals, and the kidneys to reduce intravascular volume and decrease blood pressure.[54] Within the kidney, the hormone

increases hydraulic pressure in the glomerular capillaries through afferent arteriolar dilation and efferent arteriolar vasoconstriction. Atrial natriuretic peptide reduces blood pressure by relaxing smooth muscle and reducing sympathetic vascular stimulation and also inhibits renin and aldosterone secretion, causing renal vasodilation, natriuresis, and diuresis.[54]

Intraoperatively, one of the most direct ways to monitor intravascular volume may be by direct assessment of the left ventricular end-diastolic area with transesophageal echocardiography.[159,160] In addition, assessment of adequate cardiac function through pulse oximetry, acid-base assessment, cardiac output monitoring, and left ventricular fractional area of change as a surrogate for ejection fraction contribute to evidence of normovolemia and renal perfusion (see Chapters 16, 18, 40, and 88).[161] However, monitoring with invasive devices, such as pulmonary artery catheters, arterial cannulas, and transesophageal echocardiography, has never been demonstrated to reduce the incidence of ARF.

Blood Flow: Cardiac Output and Esophageal Doppler Ultrasonography–Guided "Fluid Optimization"

The electrocardiogram is essential to detect the depolarization-repolarization changes consistent with the electrolyte abnormalities of renal dysfunction and to monitor for normal rate and rhythm. The synchronized atrial kick preceding ventricular contraction may contribute significantly to cardiac output in the patient with a noncompliant left ventricle. Transesophageal echocardiography 2D and renal arterial Doppler waveform images, primarily of the left kidney, can be used to assess changes in pulsatility and resistive indices and qualitatively describe RBF changes over time.[162,163]

Many believe that dehydration, hypovolemia, and blood loss are major contributors to perioperative renal dysfunction.[164] An update to enhance traditional, somewhat unreliable guides to fluid administration (e.g., central venous pressure) is the concept of "guided fluid optimization." The principle behind fluid optimization is to maximize tissue-oxygen delivery by achieving a maximum stroke volume, typically achieved by esophageal Doppler ultrasonography–monitored fluid boluses.[165] Some randomized studies have evaluated fluid optimization, a strategy that leads to increased perioperative volume administration for almost all patients, and reported improved outcomes such as shorter hospital stays.[166] In contrast, other studies have studied restrictive fluid regimens and also reported improved outcomes without evidence of increased ARF, despite decreases in perioperative urine output.[167,168] A systematic review of over 80 perioperative fluid management randomized trials concluded that current evidence does not allow evidence-based recommendations of one type of fluid over another or on the optimal amount of fluid to be administered for fluid replacement in elective surgical procedures but recommended strict avoidance of fluid overload.[169] Others have described the disastrous and unpredictable occurrence of acute pulmonary edema related to postoperative fluid retention.[170] There is insufficient evidence on which to base judgments on the importance of fluid selection and management strategies on perioperative renal function.[165,169]

Autoregulation and Distribution of Cardiac Output to the Kidneys

Standard cardiorenal relationships identify cardiac output and perfusion pressure as major predictors of RBF, whereas pressure alone correlates with urine output.[65,66] As previously mentioned, renal artery autoregulatory reflexes are *not* influenced by metabolic need and serve to "protect" the glomeruli from overload by restricting blood flow at higher pressures (e.g., >80 mm Hg).[38,39] Renal reflexes guided by different stimuli are the afferent and efferent arteriolar myogenic and tubular-glomerular feedback reflexes and the paracrine reflexes of the medullary microcirculation.

The fraction of cardiac output perfusing the kidneys depends on the ratio of renal vascular resistance to systemic vascular resistance.[58] In general, the response to renal hypoperfusion involves three major regulatory mechanisms that support renal function: (1) afferent arteriolar dilation increases the proportion of cardiac output that perfuses the kidney; (2) efferent arteriolar resistance increases the filtration fraction; and (3) hormonal and neural responses improve renal perfusion by increasing intravascular volume, thereby indirectly increasing cardiac output. The afferent arterioles react to reductions in perfusion pressure by relaxing their smooth muscle elements to decrease renal vascular resistance. Decreased solute delivery to the macula densa in the cortical portion of the thick ascending loop of Henle results in relaxation of the juxtaposed afferent arteriolar smooth muscle cells, improving glomerular perfusion and filtration.

The kidney produces vasodilator prostaglandins to counteract the effects of systemic vasoconstrictor hormones such as angiotensin II.[171] In a state of low cardiac output when systemic blood pressure is preserved by the action of systemic vasopressors, RBF is not depressed because the effect of the vasopressors is blunted within the kidney.

A selective increase in efferent arteriolar resistance decreases glomerular plasma flow, thereby preserving GFR. Glomerular filtration is augmented because capillary pressure upstream from the site of vasoconstriction tends to rise. This mechanism enables the kidney to offer high organ vascular resistance to contribute to the maintenance of systemic blood pressure without compromising its function of filtration. Studies using specific inhibitors of angiotensin II have shown that efferent arteriolar resistance largely results from the action of angiotensin II.[172] At low concentrations, norepinephrine has a vasoconstricting effect on efferent arterioles, indicating that the adrenergic system may also be important for maintaining the renal compensatory response.[173]

Evidence supports the notion that reductions in cardiac output are accompanied by the release of vasopressin and by increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system. These regulatory mechanisms to preserve RBF conserve salt and water. The control of blood delivery to the kidney, the fraction of plasma filtered, and the amount of volume returned to the systemic circulation are determined by regulatory mechanisms within the kidney that attempt to preserve filtration function during compromised circulation.

One study reported the normal response to hemorrhage in otherwise healthy patients, describing a 30% reduction in RBF

with a decrease in mean perfusion pressure from 80 to 60 mm Hg.[174] Changes known to occur at the initiation of CPB include greater reduction in renal than systemic perfusion, loss of RBF autoregulation, and stress hormone and inflammatory responses known to be harmful to the kidney.[65,175,176] These effects may explain why the duration of CPB independently predicts post–cardiac surgery renal impairment.[3,4,177,178] Notably, during experimental CPB, medullary Po_2 drops from typically low levels to unmeasurable levels.[137]

Laboratory Tests of Serum and Urine as Markers of Renal Function

An ideal glomerular filtration monitor for perioperative AKI recognition would be accurate, point-of-care, simple, brief, and inexpensive and, in addition, should have confirmed links with AKI-related outcomes (e.g., mortality). Although no such test exists, trends in repeated serum creatinine determinations (relative or absolute changes), alone or integrated into estimates of GFR, are currently the most used clinical tool for this purpose.[179-181]

Although traditional tests are useful in identifying kidney failure, an inherent limitation of almost all currently available tools is the obligate delay between the *onset* of AKI and the *diagnosis* of AKI. One striking difference between management of AKI and acute myocardial infarction (AMI) is the lack of *early biomarkers* for AKI to guide prompt recognition and intervention when tissue is threatened (i.e., AMI—troponin, creatinine kinase-MB). Thus, one of the primary priorities of the largest current collaborative initiative, the AKI network (AKIN),[30] is to explore the existence and value of early AKI biomarkers. Therefore, the following discussion will be categorized into traditional diagnostic tools that provide only delayed recognition of AKI and the currently expanding field of early biomarkers for AKI.

Traditional (Delayed) Biomarkers of Acute Kidney Injury

Biomarkers for renal failure and acute tubular necrosis, which are reviewed next, include urine volume, urine specific gravity, urine osmolality, serum creatinine level, serum blood urea nitrogen level, urine-to-plasma creatinine ratio, urine-to-plasma urea ratio, urine sodium level, fractional excretion of sodium (FE_{Na}), free water clearance, creatinine clearance, inulin clearance, and RBF (Table 45-1).

Table 45-1 Biomarkers of Kidney Function*

- Serum creatinine
  - Analysis tools
    - Baseline to peak postoperative fractional change
    - Peak in-hospital postoperative
    - Maximum change baseline-to-peak
    - ARF definitions
    - STS definition
    - AKIN criteria[30]
    - RIFLE criteria[31]
    - Modified contrast nephropathy
- Creatinine clearance
  - Estimates
    - Cockroft-Gault equation[180]
    - MDRD equation[181]
  - Direct measures
    - 24-hr urine collection
    - 2-hr urine collection
  - Analysis tools
    - Nadir postoperative
    - Baseline-to-nadir postoperative
    - Baseline-to-nadir postoperative fractional change
- Glomerular filtration rate
- Inulin clearance
- Iohexol clearance
  - Analysis tools
    - Nadir postoperative
    - Baseline-to-nadir postoperative
    - Baseline-to-nadir postoperative fractional change
- Urine volume
  - Analysis tools
    - AKIN criteria[30]
    - RIFLE criteria[31]
- Blood urea nitrogen
- Urine specific gravity
- Urine osmolality
- Urine-to-plasma creatinine ratio
- Urine-to-plasma urea ratio
- Urinary sodium
- Fractional excretion of sodium
- Free water clearance
- Renal blood flow

*Traditional biomarkers of kidney function primarily focus on measurements or estimates of function for comparison to expected normal values. With regard to diagnosis of prerenal azotemia and acute kidney injury, these tools typically provide information to confirm a diagnosis as long as 48 hours after the event.
STS, Society of Thoracic Surgeons; AKIN, AKI Network; MDRD, Modification of Diet in Renal Disease (study).

Urine Volume

Although recorded religiously, intraoperative urine output remains a controversial perioperative marker of renal function. Whereas the presence of urine (regardless of amount) confirms blood flow to the kidney, urine flow rate is an indirect parameter of renal function, and many nonrenal factors directly and profoundly influence urine production. Multiple studies have shown no correlation between urine volume and histologic evidence of acute tubular necrosis, GFR, creatinine clearance, or changes from preoperative to postoperative levels of BUN and creatinine levels in patients with burn injury,[182] trauma,[183,184] or shock status or in those undergoing cardiovascular surgery.[63,185,186] Alpert and colleagues observed oliguric aortic surgery patients (urine flow < 0.125 mL/kg/hr) given either additional crystalloid solution, intravenous mannitol, furosemide, or no intervention[63] and found no correlation between intraoperative mean or lowest hourly urine output and subsequent AKI (see Fig. 45-7).

In contrast to the intraoperative setting, significant prolonged preoperative or postoperative oliguria (<0.5 mL/kg/hr for > 6 hr) is more predictive and even diagnostic of AKI; for example, oliguria has been incorporated into the AKIN and RIFLE AKI criteria.[30,31] The kidney concentrates the ultrafiltrate so that at maximal concentration, a minimum of 400 to 500 mL of urine is

required to clear the daily obligatory nitrogenous wastes.[187] Among the factors that influence tubular excretion of solute and water are local and systemic levels of renin, aldosterone, and ADH. In the operating room, patients are often hemodynamically unstable; decreased blood volume or cardiac output, fluctuating hormone levels (e.g., aldosterone, renin, ADH), nervous system reflexes, and increased catecholamine concentrations, added to the effects of general anesthesia, can alter GFR. The data do not support oliguria as a reliable intraoperative sign of pending renal dysfunction.[63,182-187] Notably, the lack of correlation of immediate perioperative oliguria with AKI requires further incorporation into recent consensus statements developed primarily by nephrologists and critical care physicians as one of the criteria to diagnose AKI, such as the RIFLE and AKIN criteria.[30,31]

Urine Specific Gravity

Urine specific gravity reflects the mass of 1 mL of urine compared with 1 mL of distilled water. Normal values range between 1.001 and 1.035. In settings of poor perfusion or prerenal azotemia, urine specific gravity is high (e.g., 1.030), reflecting the kidney's ability to conserve sodium and water. With loss of concentrating ability due to acute tubular necrosis, urine specific gravity resembles plasma osmolarity (i.e., 1.010). Specific gravity is a surrogate for osmolarity (normal range, 50 to 1000 mOsm/kg). Unfortunately, when substances that raise specific gravity without significantly changing osmolarity are present in large amounts (e.g., glucose, protein, contrast dye) (Table 45-2), high urine specific gravity can provide misleading reassurance that renal concentrating ability is preserved.[188,189] The ability of the kidneys to concentrate urine after water deprivation is impaired in elderly patients, also making urine specific gravity an unreliable test.

Urine Osmolality

Osmolality is a measure of the number of osmotically active particles in solution in the solvent phase. It is one of the major forces that move fluid throughout the body, especially in the kidney. Theoretically, urine osmolality is physiologically superior to urine specific gravity as a test of renal function; however, the same substances and conditions that render urine specific gravity a nonspecific test can also affect the reliability of urine osmolality (see Table 45-2). A defective urinary concentrating mechanism tends to be one of the most consistent and lasting tubular defects of ARF.

Table 45-2 Substances and Conditions Affecting Urine Specific Gravity and Urine Osmolality

Proteins
Glucose
Mannitol
Dextran
Diuretics
Advanced age
Extremes of age
Radiographic contrast media
Antibiotics (e.g., carbenicillin)
Hydrometer calibration
Detergents
Temperature
Hormonal imbalances

The sensitivity and specificity of urine osmolality as a test for predicting or distinguishing acute tubular necrosis from prerenal azotemia are clinically inadequate.[186,190-195] With values greater than 500 mOsm, the positive predictive value for diagnosing prerenal azotemia ranges from 60% to 100%. With a value less than 350 mOsm, the positive predictive value for diagnosing acute tubular necrosis ranges from 69% to 95%.

Serum Creatinine Concentration

In spite of all its limitations, the serum creatinine concentration remains the most used clinical tool to assess renal function. However, due to its nonlinear relationship with changes in renal function (see Fig. 45-10), variability among individuals, and susceptibility to changes unrelated to changes in GFR (e.g., cimetidine, trimethoprim, acetylcysteine),[196,197] elevation of serum creatinine concentration is only somewhat reliable as a sign of renal dysfunction, and GFR may be reduced by as much as 75% before elevations reach abnormal levels.[198]

Creatinine, a cyclic anhydride of creatine, is a small molecule (113 daltons) that is continuously released during skeletal muscle protein catabolism. Muscle mass, which is smaller in women and declines with age, directly predicts creatinine release. Curiously, age- and gender-related differences in GFR are well matched with differences in creatinine release such that normal serum creatinine levels vary little with age or between genders (Fig. 45-11). Creatinine levels in body fluids (e.g., plasma, serum, urine) are also easy and inexpensive to measure. These properties have made serum creatinine a mainstay as a marker of steady-state changes in renal filtration.

Developing a consensus definition of AKI has been a recent focus. A consensus opinion from the Acute Kidney Injury Network asserts that the term *AKI* be used to represent the entire spectrum of ARF.[30] The AKIN definition, a 1.5-fold or 0.3 mg/dL (≥ 26.4 μmol/L) creatinine rise within a 48-hour period or more than 6 hours of oliguria (<0.5 mL/kg/hr), is a modification of its predecessor, the Acute Dialysis Quality Initiative (ADQI) Group so-called RIFLE criteria.[31] Specific to cardiac surgery is the Society of Thoracic Surgeons' definition of ARF as at least a twofold creatinine rise to a value exceeding 2.0 mg/dL or new dialysis or both.[25] Another commonly used AKI definition requires creatinine rise to exceed 25% or 0.5 mg/dL (44 μmol/L).[26,37]

Whereas creatinine has many advantages as a marker of changes in filtration function, its many drawbacks continue to fuel the search for a more ideal marker of renal filtration. In conditions such as the perioperative period where steady state is difficult to ascertain, serum creatinine may fail to accurately reflect the magnitude of nephron loss, and relative changes in serum creatinine may be more important than whether a value lies within or outside the normal range. Because creatinine production is proportional to muscle mass, many chronically ill, malnourished, elderly patients have serum creatinine values in the normal range, despite reduced renal concentrating ability and GFR. Conversely, many critically ill patients at risk for developing ARF may have high metabolic rates because of hyperalimentation, sepsis, or post-traumatic states. Higher metabolic rates mean higher nitrogenous waste production requiring greater than average RBF and urine flow rates to maintain normal serum creatinine concentration. Because creatinine is excreted by glomerular filtration and tubular secretion, as the GFR decreases the tubular secretion becomes a progressively more important fraction of creatinine excretion, such that creatinine clearance

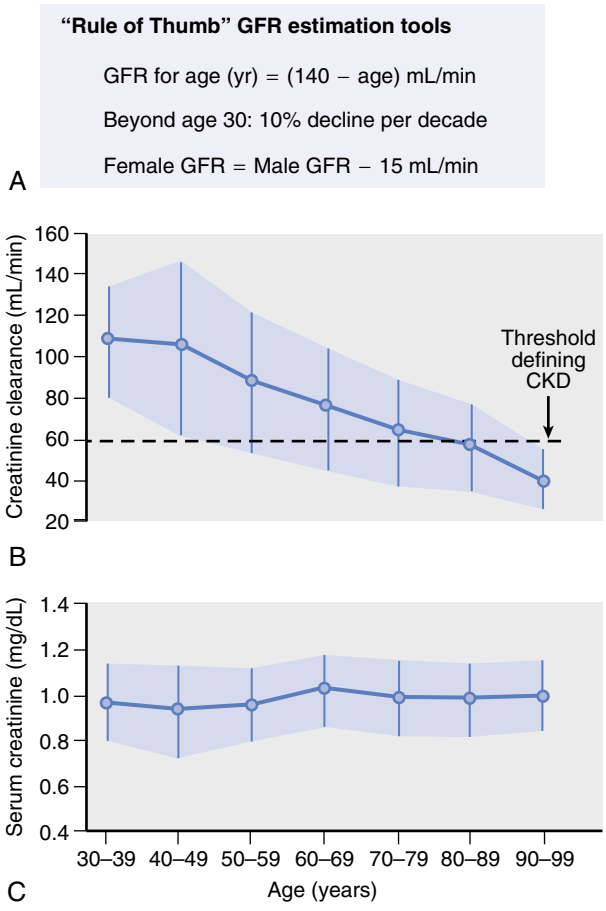

Figure 45-11 Several "rule of thumb" tools exist to estimate normal glomerular filtration rate (GFR) values based on age and gender (**A**). Creatinine clearance approximates but overestimates GFR due to creatinine secretion from the proximal renal tubule. Notably, owing to the similarity in rate of decline of GFR and creatinine release related to age (**B**), and based on gender, normal serum creatinine values remain remarkably similar throughout life (**C**). Notably, by the fifth decade some individuals, and by the ninth decade most individuals, with serum creatinine values in the normal range have GFR values reflecting chronic renal dysfunction (<60 mL/min). CKD, chronic kidney disease. (*Modified with permission from Davies DF, Shock NW: Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. J Clin Invest 29:496-507, 1950.*)

overestimates the GFR by 50% to 100% if the true GFR is less than 15 mL/min.[198,199] Postoperative rise of serial serum creatinine measurements do not definitively identify AKI sometimes for several days after cardiac or noncardiac surgery.[32,200] Nonetheless, the serum creatinine concentration remains a useful, inexpensive, and, so far, unsurpassed clinical tool particularly to reflect *trends* of change in renal filtration function and predict outcome, even during the perioperative period.[179,201,202]

Blood Urea Nitrogen

BUN remains widely used to assess renal function but possesses few of the characteristics of an "ideal" substance. A product of protein metabolism, BUN level is increased by high protein intake, blood in the gastrointestinal tract, and accelerated catabolism (e.g., in traumatized or septic patients). The normal range is 8 to 20 mg/dL. Because urea is synthesized in the liver, hepatic dysfunction decreases urea production and, therefore, BUN concentration. BUN concentration fails in a key criterion as a reliable estimate of the GFR. Although urea is freely filtered at the glomerulus, it is reabsorbed to a large and variable extent. The reabsorption of urea is greater, approximately 60% of the filtered load, when urinary flow is low; only about 40% is reabsorbed when flow is high. In addition, perioperative hemodilution (e.g., CPB) may affect circulating BUN levels.

It was believed that combining BUN and serum creatinine levels would provide more reliable information than using either alone. If ratios of BUN to serum creatinine exceeded 20:1, for example, dehydration was suspected.

Urine-to-Plasma Creatinine Ratio

The urine-to-plasma creatinine index was first introduced in 1950 by Bull and colleagues[203] as a method of evaluating patients with acute tubular necrosis. It was determined retrospectively that patients whose urine-to-plasma creatinine levels rose above 10 after having been below 10 were no longer at serious risk for "uncontrolled mineral and water loss." This index was introduced primarily as a prognostic aid and not as a diagnostic test.

The sensitivity and specificity of the urine-to-plasma creatinine index are unfortunately clinically unreliable for diagnosing acute tubular necrosis and prerenal azotemia.[204] Miller and coworkers[191] concluded that the index was not useful, except in extreme situations, because of significant overlap between groups. Espinel and Gregory[192] prospectively studied 87 patients (61 with acute tubular necrosis or prerenal azotemia) and concluded that the urine-to-plasma creatinine ratio might be a useful indicator of acute tubular necrosis if the ratio was less than 10 and that it might be an indicator of prerenal azotemia if the ratio was less than 40. However, a significant overlap in values was found for 33% of patients.

Urine-to-Plasma Urea Ratio

In 1959, Perlmutter and colleagues[205] proposed that the ratio between urine and serum urea nitrogen levels could differentiate prerenal azotemia from acute tubular necrosis. These investigators thought that a ratio of greater than 14 was associated with transient oliguria and that a ratio of less than 10 was associated with acute tubular necrosis. In 1965, Eliahou and Bata[190] reported that the urine-to-blood urea ratio might not be useful for diagnosis in all cases. Subsequently, Chisholm and associates[206] confirmed that the urine-to-plasma urea ratio was often misleading in the diagnosis of uremia.

Urea production is not constant and is affected by many nonrenal variables.[207] Variables include sudden increases or decreases in protein intake, states of increased protein catabolism (i.e., trauma, infections, hyperthermia, or corticosteroid therapy), gastrointestinal bleeding, and liver dysfunction. Because urea levels can vary tremendously independent of renal function, it is not surprising that knowing the urine-to-plasma urea ratio does not make it possible to differentiate between prerenal azotemia and acute tubular necrosis.

Urinary Sodium Concentration

With decreasing perfusion, the normally functioning kidney conserves sodium and water. The factors affecting this phenomenon are numerous and include heterogenicity of nephrons, secretion of aldosterone, secretion of ADH, diuretic therapy, saline content

of intravenous infusion solutions, sympathetic neural tone, and sodium-avid states (e.g., congestive heart failure, cirrhosis). It is traditionally accepted that a urinary sodium level of less than 20 mEq suggests prerenal azotemia and that a level of greater than 40 mEq indicates acute tubular necrosis.

The reported sensitivity and specificity of urinary sodium levels for diagnosis of acute tubular necrosis and prerenal azotemia suggest that the levels can be used for diagnosis of approximately one half of the patients with acute tubular necrosis.[186,191-193,203,208,209] Considering the complex physiology of sodium homeostasis, it is not surprising that levels of urinary sodium are unreliable indicators of prerenal azotemia or acute tubular necrosis. The test is nonspecific because a significant overlap exists between the diagnostic categories and because urinary sodium measurement tends to correlate more with volume and type of resuscitation fluid than with renal function.[184]

Fractional Excretion of Sodium

Failure of avid sodium reuptake by the kidney in the setting of dehydration manifests by increased urine sodium and is the principle underpinning the utility of FE_{Na} as a diagnostic tool. A sodium excretion value of less than 1% compared with greater than 1% often enables differentiation between prerenal azotemia and acute tubular necrosis, particularly in the presence of oliguria.[210] The FE_{Na} was first described by Espinel[208]; it represents the fraction of sodium excreted versus that filtered by the kidneys. Handa and Morrin[204] had previously described the "renal failure ratio," which is a derivative of the excreted fraction of filtered sodium. The only difference between the two is that in determining renal failure ratio the plasma sodium level is assumed to be constant. FE_{Na} is calculated as follows:

$$FE_{Na} = \frac{\text{Excreted Na}}{\text{Filtered Na} \cdot 100} = \frac{U_{Na}P_{Cr}}{\left(U_{Cr}P_{Na} \cdot 100\right)}$$

where P_{Cr} is the plasma creatinine level, P_{Na} is the plasma sodium level, U_{Cr} is the urinary creatinine level, and U_{Na} is the urinary sodium level.

At first, investigators reported that FE_{Na} permitted clear differentiation between prerenal azotemia and acute tubular necrosis.[191-193,208] However, subsequent case reports cast doubt on the sensitivity and specificity of FE_{Na} as a useful discriminator between these conditions.[208,209,211-213] Brown[211] suggested that the FE_{Na} was diagnostic of acute tubular necrosis but was of little or no value for the early prediction of renal failure. Brosius and Lau[212] showed that early determinations of the FE_{Na} were more likely to be misleading than later determinations, indicating that the measurement was unlikely to be helpful in the early diagnosis of acute tubular necrosis. Shin and colleagues[210] concluded that knowing the FE_{Na} was useful only when oliguria was already present. However, because this indicator is usually observed later in the course of renal disease than the changes in creatinine or free water clearance, the FE_{Na} is not a highly valuable tool for predicting imminent renal failure and is rarely used now for this purpose.[214,215]

Free Water Clearance

Water that contains no solutes is considered "free water." Thus, compared with normal isosmotic plasma, hyperosmotic urine can be considered to represent the clearance of a negative amount of free water (i.e., avid water retention). Normal free water clearance (C_{H2O}) in the setting of dehydration can be as high as −25 to −20 mL/hr, whereas free water clearance of −15 to +15 mL/hr reflects incipient renal dysfunction. Free water clearance is a measure of the kidney's ability to dilute or concentrate urine as necessary to maintain homeostasis and is determined using the following equation:

$$C_{H2O} = UV - \left(U_{Osm} \times UV / P_{Osm}\right)$$

where UV is urine volume, U_{Osm} is urinary osmolality, and P_{Osm} is plasma osmolality.

Jones and Weil[216] assessed the sensitivity of free water clearance and concluded that serial measurements predicted the patients who would experience progressive renal dysfunction.[186] However, Rosenberg and coworkers[184] found no correlation between renal function and free water clearance in a prospective study of 69 trauma and sepsis patients. After studying 38 ICU patients, Baek and associates[217] concluded that ARF was diagnosed 1 to 3 days sooner with free water clearance than by other clinical and laboratory diagnostic criteria (creatinine clearance was not measured). These investigators recommended sequential measurements of free water clearance as an early indicator of ARF.

In a retrospective study of 675 trauma victims, Shin and colleagues[183] found free water clearance alone was not sufficient for the early detection of renal dysfunction. However, these authors found free water clearance greater than 20 mL/hr combined with a creatinine clearance less than 25 mL/min identified a high-risk group. However, in a prospective study of postoperative patients,[210] these same authors concluded that free water clearance was not as sensitive as creatinine clearance for predicting ARF in trauma patients. The same substances and conditions that decrease the usefulness of urine osmolality for indicating renal failure can similarly decrease the usefulness of free water clearance (see Table 45-2).[218]

Creatinine Clearance

Substances used to assess GFR through their clearance from the circulation are presumed to have certain "ideal" properties, including a steady supply to the circulation, free glomerular filtration, and neither reabsorption or excretion by the tubules. As previously mentioned, creatinine partially fails these criteria, owing to its minimal secretion from the proximal tubule; however, because "gold standard" methodologies such as inulin, ^{51}Cr-EDTA, or ^{99m}Tc-DTPA clearance are expensive and cumbersome, creatinine clearance continues to be the most commonly used direct measurement of renal filtration function. Creatinine clearance is the volume of plasma that the kidneys can completely clear of creatinine per minute and is measured by calculating the amount of creatinine reaching the urine during a period of time (urine volume and urine creatinine concentration) and comparing it with the concentration of creatinine in the blood. Measurements of creatinine clearance are most useful to quantify renal reserve.

Precise measurements of creatinine clearance require collection of timed urine samples using the following formula:

$$GFR = UV/P$$

where U is the urinary concentration of creatinine (mg/dL), V is the volume of urine (mL/min), and P is the plasma concentration (mg/dL). The major limitation in the determination of creatinine clearance is the necessity of collecting urine accurately. Although

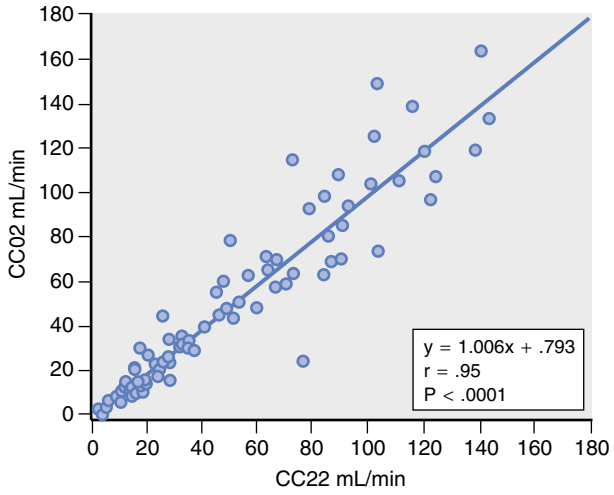

Figure 45-12 Correlation between the 2-hour creatinine clearance (CC02) and the 22-hour creatinine clearance (CC22). (*Adapted from Sladen RN, Endo E, Harrison T: Two-hour versus 22-hour creatinine clearance in critically ill patients. Anesthesiology 67:1013-1016, 1987.*)

reasonable correlation between 2-hour and 24-hour creatinine clearance (R = 0.85) has been reported for patients in ICUs (Fig. 45-12),[219,220] it remains true that the longer the urine collection period, the more accurate is the calculation of creatinine clearance. Changing hydration of the patient invalidates short-term determinations of the GFR, as does failure to record urine volume accurately. The error in calculation of creatinine clearance can vary from 10% to 27%, depending on the accuracy of urine collection,[221] body weight, surface area, and normal day-to-day variations. Another significant drawback is that for the patient with ARF a test that requires 24-hour urine collection is often impractical.

Perioperatively, creatinine clearance can be estimated by integrating serum creatinine values with other patient characteristics.[180] However, the dynamic changes in renal function and rapid fluid shifts typical of the surgical period often compromise precise measurement of renal glomerular filtration rate at this time. Until more precise validated perioperative markers are available, many believe that serum creatinine–derived markers are at least as accurate (and less expensive) than other more invasive tests.[179,201,202] A variety of algorithms have been developed to estimate creatinine clearance from a single steady-state serum creatinine value during conditions; these formulas are usually developed through modeling using data from large nonsurgical populations and require knowledge of factors that influence creatinine generation (gender, age, body weight). Of the many predictive tools that exist, the Cockcroft-Gault equation has been the most validated and durable.[180] The Cockcroft-Gault equation calculates estimated GFR (eGFR) based on patient gender, age (years), weight (kg), and serum creatinine (Cr) (mg/dL):

$$\text{Cockcroft-Gault eGFR}\left(\text{mL/min}\right) = \left(140-\text{age}\right)\times\text{weight}\left(\text{kg}\right)/\left(\text{Cr}\times 72\right)$$
$$\left(\times 0.85 \text{ for females}\right)$$

More recently, an estimating method from the Modification of Diet in Renal Disease (MDRD) study that adds knowledge of ethnicity (black versus nonblack) to standard components of the Cockcroft-Gault equation may improve accuracy.[181]

An abbreviated MDRD formula is available that can estimate GFR measured in mL/min/1.73 m^2

$$\text{GFR} = 186\times\left(\text{serum creatinine}\left[\text{mg/dL}\right]\right)^{-1.154}\times\left(\text{age}\right)^{-0.203}$$
$$\left(\times 0.742 \text{ for females}\right)$$
$$\left(\times 1.210 \text{ for blacks}\right)$$

However, even the most detailed MDRD eGFR equation under ideal conditions correlates poorly with GFR determined using "gold standard" tools, with a 30% or greater error in 10% patients and more than a 50% deviation in 2%.[181]

When Shin and associates[183] retrospectively reviewed the records of 26 patients who had acute tubular necrosis, they concluded that the diagnosis was likely to be made in patients who had a creatinine clearance of less than 25 mL/min and a free water clearance of greater than 15 mL/hr. In a follow-up study of 40 trauma patients who underwent surgery, these researchers[210] concluded that creatinine clearance of less than 25 mL/min alone permitted the early detection of renal dysfunction in patients with the potential for development of renal failure and that free water clearance was not as sensitive.

So-called Starling forces are important in understanding the factors that affect glomerular filtration. Glomerular filtration is governed by the following equation:

$$\text{GFR} = K_f\times\left(P_{GC}-P_{BC}-P_{PO}\right)$$

where GFR is the glomerular filtration rate or the rate at which fluid is filtered through the glomerular capillaries into the Bowman capsule, K_f is the glomerular filtration coefficient or the factor that considers the permeability and surface area of the glomerular basement membrane, P_{GC} is the glomerular capillary pressure, P_{BC} is the pressure in the Bowman capsule, and P_{PO} is the plasma oncotic pressure.

Acute changes in GFR, and consequently in urine formation, are commonly caused by changes in glomerular capillary pressure. For example, events that reduce plasma flow rates reduce the hydraulic pressure of glomerular capillaries and favor decreased ultrafiltration whereas events that increase plasma flow rate have the opposite effect. Theoretically, varying concentrations of plasma proteins may influence urine formation and the GFR. As the concentration of proteins in plasma decreases, the oncotic pressure and the oncotic force opposing ultrafiltration also decrease. Conversely, an increase in oncotic pressure reduces the GFR. This effect is most likely offset by the oncotic force of plasma proteins (e.g., albumin), which enables adequate intravascular volume to be maintained. However, in one series,[222] patients resuscitated with albumin after massive transfusion had more renal dysfunction than those resuscitated with saline.

Intravenous fluid choices are associated with increased renal risk in some studies of postoperative AKI. When the impact of normal saline-based intravenous fluid replacement was evaluated and compared with lactated Ringer's solution (i.e., albumin 5% in normal saline, hetastarch in normal saline, or lactated Ringer's solution), renal function indices (i.e., creatinine clearance, serum creatinine, and urine output) were all inferior in the normal saline-based vehicle groups.[223] The patients receiving lactated Ringer's solution were more likely to exhibit a hypercoagulable

state.[223] Outcome data, however, did not enable a distinction between albumin and normal saline as a fluid replacement option. Volume expansion using hydroxyethyl starch (HES) preparations is associated with AKI in critically ill and surgical patients in several retrospective reports.[224-227] In a randomized study of 129 patients with septic shock or severe sepsis that received either 3% gelatin or 6% HES, peak serum creatinine and the frequency of ARF and oliguria was higher in the HES group.[228] In the same study, a multivariable analysis also identified the use of HES as an independent predictor of ARF. In contrast, Boldt and colleagues found no evidence of increased renal risk in two small perioperative randomized studies of surgical patients receiving either gelatin or 6% HES.[229,230] Recent studies have focused on the contents of the solutions supporting the HES preparations and their potential to influence the development of metabolic hyperchloremic acidosis and variations in renal outcome.

Use of saline or saline-based colloid solutions in perioperative patients is commonly associated with the acid-base abnormality metabolic hyperchloremic acidosis. In a randomized, blinded trial, 47 elderly patients undergoing major surgery received 6% HES suspended in either 0.9% sodium chloride (HESPAN, B. Braun Medical, Inc., Irvine, CA) or a balanced salt solution (Hextend, BioTime, Inc., Berkeley, CA) (see Chapters 71 and 88). None of the patients receiving the balanced salt-based solution but two thirds of those receiving sodium chloride developed hyperchloremic metabolic acidosis ($P < .0001$).[231] In addition, in the saline group, gastric tonometry identified a larger increase in the CO_2 gap ($P = .04$), suggesting poorer splanchnic perfusion. Some have speculated that this metabolic abnormality may be a relevant modifier of perioperative renal vulnerability.[232] Increased chloride levels and acidosis can reduce RBF and GFR, increase afferent arteriolar tone, and alter renin release.[233,234] The avoidance of saline and the development of metabolic hyperchloremic acidosis may prove to be an important modifier of renal risk.

In general, the GFR is determined by the rate of glomerular plasma flow (as it influences ultrafiltration pressure), systemic oncotic pressure, glomerular hydraulic pressure differences, and an ultrafiltration coefficient. The ultrafiltration coefficient is the product of glomerular capillary hydraulic permeability and total surface area available for filtration. The filtration rate across a capillary bed is, therefore, the product of surface area, pressure gradients, and permeability. Hydrostatic pressures are normally maintained higher in glomerular capillaries than in other capillary beds by a delicate balance of preglomerular and postglomerular vascular tone in arterioles. The permeability of the glomerular capillary wall is equal for substances with molecular masses up to 5000 to 6000 daltons and decreases to almost zero at 60,000 to 70,000 daltons.[235] Metabolic wastes and essential nutrients are filtered freely, and larger proteins, such as albumin and immunoglobulin G, are filtered in trace amounts or not at all. The glomerulopathic process in diabetes,[236] for example, results from all of the factors that cause sustained increase in glomerular pressure and flow. Hyperglycemia induces a state of extracellular fluid volume expansion, structural hypertrophy of the kidney, and altered glucoregulatory and vasoregulatory hormone action. These hemodynamic consequences of hyperglycemia lead to renal vasodilation and increased plasma flow rate. The increase of plasma flow causes increased glomerular transcapillary flux of plasma proteins. The elevation in glomerular flow (i.e., pressure) also alters the permeability and selectivity of the glomerular basement membrane, resulting in increased protein filtration. The increased transglomerular flux of plasma proteins leads to their accumulation in the mesangium, which further propagates glomerulosclerosis.

Inulin Clearance

Glomerular filtration is an important index of renal function. Because the tubule reabsorbs most of the water filtered through the glomerulus, urine volume cannot be used to measure GFR. For measurement, a substance is required that is filtered through the glomerulus at the same rate as water and is excreted in the urine (i.e., neither reabsorbed nor secreted). The amount of such a substance filtered is then equal to the amount eliminated in the urine and can be determined from the product of the substances' concentration in plasma and the amount of plasma water filtered.

Inulin, a polymer of fructose with a molecular mass of 5200 daltons that is found in Jerusalem artichokes, dahlias, and chicory, has been used to measure GFR because it is filtered freely in the glomerulus, not reabsorbed or secreted, and is excreted in the urine. Purified inulin is expensive and difficult to measure. However, since its introduction in 1934, inulin clearance has been considered the standard for measurement of GFR.[237] To assess inulin clearance, the clinician administers a priming dose of inulin intravenously, followed by a continuous infusion calculated to maintain constant blood concentrations. After an equilibration period (usually 1 hour), clearance measurements are obtained. Urine is collected (typically with a Foley catheter), and venous blood samples are obtained at the midpoint of each clearance period. The longer the clearance period, the less likely is the introduction of error from incomplete voiding. The standard formula for calculation of clearance is as follows:

$$C_I = (U_I V)/P_I$$

where U_I and P_I are the urine and plasma concentrations of inulin, C_I is the rate of inulin clearance, and V is the urine flow rate.

Whereas inulin clearance is considered a "gold standard" tool to measure GFR in clinical practice, the endogenous substance creatinine is used to measure clearance. Creatinine is a smaller substance than inulin and is not an ideal substance for measuring clearance because a small amount is secreted under normal conditions. Although creatinine clearance may exceed inulin clearance, the clearance of endogenous creatinine approximates that of inulin and has proved to be a reasonable measure of GFR.[238] The creatinine-to-inulin clearance ratio is almost identical in healthy infants, children, and adults. In subjects with moderate to severe renal insufficiency, however, the creatinine-to-inulin clearance ratio is increased.[239] Increased secretion and clearance of creatinine in patients with renal insufficiency may, therefore, result in overestimates of true GFR.

Urea (molecular mass of 60 daltons) cannot be used to estimate GFR because, under normal conditions, it is filtered and reabsorbed. More importantly, urea clearance changes with the state of hydration; for example, under conditions of dehydration, urea clearance is significantly less than inulin clearance.

Renal Blood Flow

Although it is certainly true that an extended period of renal artery clamping (e.g., 30-40 min) sufficient to cause blood flow to cease is also sufficient to cause ischemic AKI, it is simplistic to assume that moderate increases and decreases in renal artery

blood flow are good and bad for the kidney, respectively. Regional variations in perfusion result in a precarious balance between oxygen supply and demand in some renal tissues, particularly in the inner renal medulla. Notably, high levels of RBF also oblige high levels of oxygen demand to facilitate active transport of sodium and other solutes back into the circulation. Unfortunately, RBF is a very poor indicator of the adequacy of regional medullary perfusion and oxygen delivery. Despite an overwhelming number of clinical trials failing to demonstrate the value of the dopaminergic agonist effects of low dose intravenous dopamine (3-5 μg/kg/min) that include increased renal artery blood flow as renoprotective[240,241] and many editorials discouraging its use,[242,243] this strategy continues to be popular with some clinicians.[244,245]

Interest in RBF as a predictor of renal function was first stimulated in 1947 when Trueta and associates[246] introduced the concept of cortical ischemia and attributed the pathogenesis of ARF to increased blood flow through the medulla. Supporting evidence for this view has since been offered by many investigators who measured RBF distribution with various methods.[247-250] Perhaps nephrons in the outer cortex are "salt losers" and those in the inner cortex are "salt retainers." If this is true, salt-retaining states should occur with the selective reduction of RBF to the superficial cortex, and these states may or may not be accompanied by a rise in RBF to the deep cortex.[222,250]

It is essential to understand how hypovolemia affects distribution of RBF. Activation of the sympathetic nervous system and possibly the renin-angiotensin system reduces RBF and GFR. Despite well-maintained arterial blood pressure, blood flow may decrease to one third of its normal level but still significantly exceed the intrinsic oxygen needs of the kidney. Constriction of afferent arterioles becomes sufficient to reduce the hydrostatic pressure in glomerular capillaries to levels inadequate for maintenance of normal filtration. Only when hypovolemia or hemorrhage is extreme does this extend to adverse effects on the metabolic function of the kidney itself. As RBF decreases further, arteriolar vasoconstriction leads to ischemia and morphologic damage.

Renal arteriographic and xenon washout studies in patients with ARF have shown selected, profound reduction in RBF.[249] Arteriography reveals severe attenuation of the intrarenal arterial tree, inability to visualize cortical vessels, absence of a normal cortical nephrogram, and striking reduction in the velocity of contrast dye as it passed through the kidney. These same patients have no bleeding from the cortex during open renal biopsy. The xenon washout studies also show that the usual transit of xenon through the cortex (indicating cortical perfusion) that is usual in the normal kidney is absent in acute oliguria. Renal cortical perfusion at one third of its normal level, involving constriction of the afferent arterioles, appears sufficient to impair renal function.

The understanding that distribution of RBF is nonhomogeneous, the recognition of nephron structure and functional heterogenicity, and the suggestion that changes in the zonal distribution of RBF affect renal salt and water homeostasis have focused investigators on developing improved techniques to measure intrarenal blood flow.[250] Methods to measure distribution of RBF in humans include the clearance of para-aminohippurate, indicator dilution, renocortical tissue Po_2, radiolabeled tracers, Doppler ultrasonography, and external gas-washout techniques. Owing to the risks and limitations associated with these techniques their clinical use has been limited.

Any nontoxic substance cleared by the kidney and not metabolized may be used to measure RBF by application of the Fick principle, whereby renal plasma flow (RPF) is calculated as follows:

$$RPF = UV/(A - RV)$$

where U is urinary concentration, V is urine flow rate, A is arterial plasma concentration, and RV is renal venous plasma concentration. RBF is then calculated from the following formula:

$$RBF = RPF/(1 - Hematocrit)$$

The volume of plasma from which the kidney can extract and excrete a specific substance in a given time is the renal clearance of the substance. An ideal substance for measuring renal plasma flow would be completely eliminated from the plasma in one pass through the renal circulation due to filtration at the glomerulus without any further tubular metabolism. Para-aminohippurate is a substance that almost meets these criteria. The practical advantage of measuring the extraction of para-aminohippurate is that its renal extraction is approximately 90% in humans after one passage. Measurement of RBF is based on the assumption that cortical extraction is 100% and that extraction in the medulla is 0%; therefore, it has been assumed that the nonextracted fraction (10%) should reflect the fraction of blood flowing through the medulla. However, experimental evidence shows that cortical extraction is not 100%,[251] casting doubt on the accuracy of intrarenal blood flow assessment with extraction techniques. Other limitations of the extraction technique include the requirement for a high rate of urine flow, a steady state for 15 to 30 minutes, and the sampling of systemic arterial and renal venous blood.

Indocyanine green, which is bound to albumin in plasma, has been used in the indicator dilution method with densitometry. The indicator dilution method necessitates catheterization of a renal artery and vein. Although attempts have been made to measure renocortical (fast) and medullar (slow) blood flows separately from dye dilution curves, no convincing results have been produced.[252] Measurement of RBF by a continuous thermodilution technique, which requires renal venous cannulation and continuous injection of normal saline, has been proposed.[253] Measurements have correlated with calculated RBFs derived from clearance techniques in patients after cardiac catheterization; however, only total RBF is measured with the thermodilution technique.

Tissue oxygen pressure is measured with a multiwire surface Po_2 electrode and temperature probe. This polarographic Clark-type electrode has multiple platinum microelectrodes arranged in an array in the center of the tissue contact area, with a polarographic silver anode positioned at its circumference. The probe is placed directly on the renal cortex and measures changes in local tissue Po_2, which is an indirect indicator of renal surface perfusion.[254-256] However, this device measures only outer cortical RBF changes. Because ischemic insults to the kidney are associated with a marked decrease in blood flow to the outer cortex, a redistribution of blood flow to the juxtamedullary glomeruli in the inner cortex and medulla is presumed.

Monitoring of urinary oxygen tension, as an indicator of medullary oxygen tension, has been examined as a method for assessing renal function.[257-260] Drops in urine Po_2 after CPB predict creatinine rise after cardiac surgery,[261] a finding possibly

related to the strong correlation between medullary and urine oxygen levels observed in animal models.[137] Although urine Po_2 measured in the ureter provides a good "online" estimate of medullary Po_2 in a pig model of CPB, this technology has not been evaluated in humans.[137] Urine samples exposed to the atmosphere during collection from bladder catheters provide artificially high urine Po_2 values because samples are easily contaminated with oxygen from room air. Another problem with measuring urinary oxygen tension or saturation is that bladder wall oxygen tension differs considerably from urine measurements.

External krypton-85 and xenon-133 clearance are techniques that can estimate RBF per gram of tissue from gas clearance.[262] The gas-washout technique requires selective catheterization of the renal artery and is usually performed in conjunction with arteriography. Alternatively, the renal artery can be punctured intraoperatively for injection. After injection, the gas diffuses rapidly into the renal tissue, theoretically equilibrating in tissue and blood. The renal washout curve is then assessed by external counting. The reliability of washout methods in some circumstances has been questioned.[263]

Qualitative and semi-quantitative evaluation of renal perfusion can be obtained with a gamma camera recording of the transit of a radiopharmaceutical tracer through the kidney. Qualitative evaluation of renal perfusion consists of the visual assessment of the serial images and comparative assessment of the first transit of tracer from the aorta (or iliac-renal artery) to the kidney. Among the limitations associated with the renogram is movement of the radiopharmaceutical (injected intravenously as a bolus) before it reaches the kidney, necessitating that the pharmacokinetic model contain all the possible exchange compartments between the kidney and the plasma for accurate analysis of the tissue radioactivity curve. The presence of low urine flow rates, dilated pelvic caliceal cavities, or severely reduced renal function may also cause difficulties for test interpretation. In general, the information that can be derived from the renogram includes renal clearance (as a fraction of the radioisotope to blood volume) and blood flow of the two kidneys relative to each other.[264] Because the results obtained are comparative, lesions are revealed only when they have asymmetric distribution.

Intraoperative transesophageal echocardiography 2D and renal arterial Doppler waveform images, primarily of the left kidney, can be used to assess changes in pulsatility and resistive indices and qualitatively describe RBF changes over time.[162] Typically, an interlobar artery is selected for evaluation. The anatomic course and relationships of the vessel allow easy recognition on subsequent serial scans in the same patient; the vessel is large enough to assume laminar flow throughout its length; and the angle of the ultrasound beam can generally be minimized to assume maximum Doppler frequency shift. Renal vascular resistance can be assessed by the pulsatility index.[265] The lower the pulsatile index, the less resistance there is to flow. The value is derived by dividing the difference between systolic maximum height and diastolic minimum height of the waveform by its mean height. Change in flow velocity can be assessed from a change in the mean frequency shift. The frequency shift is proportional to the mean velocity of blood flow within the vessel multiplied by the cosine of the angle between the ultrasound beam and the direction of flow. The angle is assumed to be close to zero. With this method, only blood flow velocity in large interlobar arteries and resistance can be assessed. The duplex Doppler ultrasound technique may provide a unique opportunity to demonstrate the effects of drugs on the renal vasculature and to predict the onset of pending renal failure or transplanted kidney rejection. Overall, this technique should provide an opportunity for measuring relative changes in large vessel flow velocity but not in absolute RBF.

Contrast ultrasonography has been used to image RBF.[266-269] The microbubbles produced by ultrasonic cavitation (i.e., sonication) are smaller than red blood cells and, in passing with them through the microcapillary vascular bed, reflect an echo beam to permit direct ultrasonic imaging of tissue volume and flow. Sonicated microbubbles have been shown to exhibit intracavitary velocities comparable to those of red blood cells, as observed by Doppler ultrasound techniques. Modest correlations have been found between calculated RBF assessed by contrast ultrasonography and direct flow assessment.[269]

Although not evaluated in surgical patients, a novel approach to the recognition of AKI is scintigraphic functional magnetic resonance imaging that can characterize abnormal kidney physiology, including glomerular filtration rate, tubular concentration, transit, blood volume, perfusion, inflammation, and even hypoxia.[163]

Novel (Early) Biomarkers of Acute Kidney Injury

Disappointing progress in care for AKI has prompted a strategic reevaluation of research in this area and fueled a rebirth of interest in old early indicators and a search for new "early biomarkers."[270,271] While early biomarkers are as yet some of the least validated tools in clinical AKI management, a very large research initiative is underway.[270-280] A unifying theme is the goal of providing information to facilitate prompt intervention strategies to improve care of AKI. While a few of the new tools represent attempts to find a substitute "ideal" creatinine-like substance to use in estimates of renal filtration (e.g., cystatin C), most markers take advantage of one of the three early consequences of AKI: tubular cell damage, tubular cell dysfunction, and the adaptive stress response of the kidney. The hope is that prompt biomarker information will allow timely AKI risk identification, surveillance (i.e., recognition of "pre-AKI" states such as pre-renal azotemia), diagnosis, and prognosis. Strategic approaches to improve the usefulness of early biomarkers have included combining tests to create focused panels for specific AKI concerns. Test panels could address issues such as the timing of onset, grade of a problem, and even the type of AKI (e.g., ischemic versus inflammatory). For example, in children developing AKI after cardiac surgery, one early biomarker (neutrophil gelatinase-associated lipocalin) increases 25-fold within 2 hours of surgery, facilitating diagnosis of AKI 2 days sooner than by serum creatinine values,[281] whereas another biomarker (urinary IL-18) rises 4 to 6 hours postoperatively and persists for more than 48 hours (Fig. 45-13).[282] In septic AKI, elevated levels of urinary IL-18 and two other markers (platelet-activating factor and urinary sodium hydrogen exchanger isoform-3) precede overt kidney failure by as much as 48 hours.[271] Urinary IL-18 levels in this study also differentiated septic from nonseptic AKI. A collection of the most promising biomarkers are presented here, including classes reflecting impaired renal filtration, tubular cell damage (tubular enzymuria), tubular cell

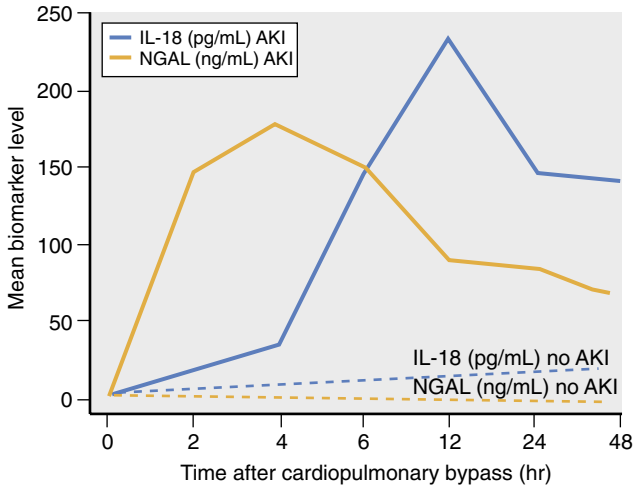

Figure 45-13 Pattern of early biomarkers urinary IL-18 and NGAL after CPB in 55 cardiac surgery patients with and without criteria for AKI diagnosed 48 to 72 hours postoperatively (defined as a peak rise in serum creatinine concentration greater than 50% of baseline). IL, interleukin; NGAL, neutrophil gelatinase-associated lipocalin. (*Used with permission from Parikh CR, Mishra J, Thiessen-Philbrook H, et al: Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int 70:199-203, 2006.*)

dysfunction (tubular proteinuria), and adaptive responses of the kidney to stress (Table 45-3).

New Filtration-Based Markers of Renal Dysfunction

Examples of the search for a replacement for creatinine include cystatin C, proatrial natriuretic peptide(1-98) (proANP[1-98]), and tryptophan glycoconjugate. Cystatin C is a member of the cystatin "superfamily" of cysteine proteinase inhibitors and is produced by all nucleated cells at a constant rate. Cystatin C has been available clinically for more than 15 years and can be determined rapidly. Much like creatinine, cystatin C accumulates in the circulation with renal impairment and can be used as a marker of glomerular filtration. But cystatin C has theoretical advantages over creatinine, particularly as an indicator of mild chronic renal failure.[270,283,284] Equivalent to creatinine clearance, cystatin C clearance can be calculated using the Larsson equation.[285] Cystatin C outperformed creatinine in detecting AKI after cardiac and renal transplantation surgery in a small number of studies, although these studies have received valid criticism.[270,286] In one cardiac surgery study, serum creatinine peaked on day 3 while cystatin C peaked on day 2,[286] although another cardiac surgery study did not see such a clear-cut difference in timing.[287] Studies have linked rises in cystatin C with mortality in congestive heart failure and acute coronary syndrome patients,[288,289] validating cystatin C as a marker of important change in renal function, something notably lacking for many of the new early AKI biomarkers. However, there are concerns with the usefulness of cystatin C compared with creatinine.[290] Interindividual variability in steady-state cystatin C levels is much greater compared with creatinine (75% versus 7%). In addition, conditions such as malignancy, human immunodeficiency virus infection, corticosteroid, or thyroid hormone therapy are associated with increased serum levels without changes in renal function.[270] Finally, three studies in critically ill patients have questioned the prognostic ability of cystatin C in this setting.[270]

ProANP(1-98) is the remnant of the prohormone that remains when α–atrial natriuretic peptide is generated.[270] ProANP(1-98) disappears from the blood largely due to renal clearance and is, therefore, suitable to assess glomerular filtration. Although numerous studies of this substance have been performed in patients with chronic renal disease, understanding of this substance in AKI is limited to a single study.[291] In this investigation of 29 septic patients, proANP(1-98) was a better predictor for the occurrence of ARF than cystatin C. In addition, proANP(1-98) levels were four times higher in nonsurvivors.

Tryptophan glycoconjugate 2-(α-mannopyranosyl)-L-tryptophan is a novel circulating marker of glomerular filtration that is excreted independent of muscle mass and tubular secretion.[292] The behavior of this substance is very similar to that of inulin, making it an "ideal" substance to assess glomerular filtration; however, unfortunately measurement is currently prohibitively labor intensive and expensive.

Table 45-3 Early Biomarkers* of Acute Kidney Injury

Filtration-Based Markers of Renal Dysfunction
Cystatin C
Proatrial natriuretic peptide (1-98)
Tryptophan glycoconjugate
Biomarkers Reflecting Renal Tubular Cell Damage (Tubular Enzymuria)
α-Glutathione S-transferase
π-Glutathione S-transferase
β-*N*-Acetyl-β-D-glucosaminidase
γ-Glutamyl transpeptidase
Alkaline phosphatase
Lactate dehydrogenase
Ala-(Leu-Gly)-aminopeptidase
Proximal renal tubular epithelial antigen
Urinary sodium hydrogen exchanger isoform 3
Biomarkers Reflecting Renal Tubular Cell Dysfunction (Tubular Proteinuria)
α_1-Microglobulin
β_2-Microglobulin
Albumin
Adenosine deaminase binding protein
Renal tubular epithelial antigen-1
Retinol binding protein
Lysozyme
Ribonuclease
IgG
Transferrin
Ceruloplasmin
Lambda and kappa light chains
Urinary total protein
Biomarkers Reflecting the Renal Stress Response
Neutrophil gelatinase-associated lipocalin
Urinary interleukin-18
Platelet-activating factor
Kidney injury molecule-1
Cysteine-rich protein 61

*New early biomarkers are being developed to promptly provide information to improve risk stratification, surveillance, diagnosis, and prognostic information about acute kidney injury.

Biomarkers Reflecting Renal Tubular Cell Damage (Tubular Enzymuria)

Renal tubular cells contain enzyme proteins that are highly specific to their location within the kidney and even tubule region, making detected enzyme leakage from damaged tubular cells into urine an appealing target for early biomarker discovery. Many tubular enzyme tests have been available for years, but only recently has their clinical use been seriously considered. Segmental involvement and ultrastructural origin of AKI is known, for example, with α and π isomers of glutathione *S*-transferase (GST), which are cytosolic enzymes from proximal and distal tubular cells, respectively. *N*-acetyl-β-D-glucosaminidase (NAG) is a proximal tubular lysosomal enzyme. General brush border injury is reflected by other markers including γ-glutamyl transpeptidase (γ-GT), alkaline phosphatase, and Ala-(Leu-Gly)-aminopeptidase. The concentration of many of these substances measured soon after a renal stress, normalized relative to urine creatinine, appears able to differentiate AKI from other conditions. In a study of 26 critically ill patients, Westhuyzen and colleagues found that by testing for several tubular enzymes twice daily, detection of AKI was accelerated by 12 hours to 4 days compared with serum creatinine. [293] These authors speculated that low expense and easy automated assays for γ-GT and alkaline phosphatase made these enzyme tests appealing for identifying AKI in random urine samples. In a study of proximal renal tubular epithelial antigen (HRTE-1) urine levels from 36 normal subjects and 51 patients with renal conditions (acute tubular necrosis [ATN]), chronic nephropathies, prerenal azotemia), 79% of ATN patients had abnormal concentrations, whereas all other subjects had normal levels.[193] As a diagnostic test, HRTE-1 had 90% and 81% discrimination in differentiating ATN versus chronic nephropathies and ATN versus prerenal azotemia, respectively.

NAG is the most commonly used investigational urinary enzyme assay for assessment of renal disease and the detection of nephrotoxicity. Unlike a number of unstable enzymes excreted into the urine, NAG remains suitable for clinical diagnosis of renal disease. Increased NAG activity detected in urine is a sensitive test for renal tubular damage[294]; its molecular mass precludes filtration by the glomerulus, and it is neither absorbed nor secreted by the tubules. Any increase in urinary concentration of NAG may be considered a marker for tubular damage. The value of NAG as a diagnostic test is further enhanced by its presence in a number of isoenzyme forms. The relative amount of each isoenzyme varies at different stages of renal disease.

A number of analytical methods are available for the determination of urinary NAG, including fluorometric, colorimetric, spectrophotometric, and dipstick tests. Each of these methods is tedious, and this limits its clinical application. Low levels of NAG are excreted by normal individuals, and assay procedures must be sensitive enough to overcome the endogenous inhibitor urea.[295] Another factor to overcome is variation from urine collection that occurs over time. Factoring the enzyme activity with creatinine concentration over the same urine flow collection period is a reasonable approach for this problem.[296] In general, the sensitivity and reproducibility of the fluorometric method, when it is performed correctly, is excellent, but the equipment necessary is not commonly available in laboratories.

The colorimetric technique overcomes the limitations of the fluorometric technique by the incorporation of a calibrant for easy interlaboratory comparison and access in most clinical chemistry laboratories, with modification for use with spectrophotometric analysis.[297] A dipstick method exists for detection of NAG in the urine.[298] The NAG strip incorporates a biochemical derivative that releases a blue-violet color on hydrolysis but requires up to 30 minutes from the addition of reagents. Unfortunately, if the sample is contaminated with blood or bilirubin, results from this test can be misleading. Besides pigmented material in urine, a concentrated urine specimen that is high in urea also renders the test inaccurate.

Perhaps the most interesting discovery regarding urinary NAG for detection of renal disease is that there appears to be isoenzyme specificity for various types of pathology.[299] NAG is the most active lysosomal hydrolase and is normally found in tissues as two major forms: A and B. These major forms differ in their subunit composition. Traditionally, the main clinical interest in these isoenzymes had been their use in the detection of two autosomal recessive disorders: Tay-Sachs disease and Sandhoff disease. In 1970, Price and colleagues[300] reported that the B form increased in a urinary pattern of NAG after surgical trauma. Since that time it has been appreciated that the relative amount of the B form increased (i.e., the ratio of A to B forms decreased) compared with urine in the normal population. Automated methods for separation of NAG isoenzymes allow the pattern of excretion to be compared in various disease states. Of interest to the anesthesiologist is that evidence suggests that after major surgery the percentage of an intermediate isoenzyme (I) increases in the urine.[301] Smaller increases in the I form were also observed in rejection of renal transplants. Rejection was more strongly associated with a decrease in the A/B ratio in a cohort of renal transplant patients. No change in the isoenzyme profile was found in stable transplant patients, whereas reversible rejection was characterized by an increase in the I form and a decrease in the relative amount of the A form present. When a patient did not respond to treatment, the I and the B forms were elevated but levels of the A form decreased.[302]

Different nephrotoxic drugs or conditions appear to produce characteristic urinary NAG isoenzyme profiles. For example, the B and I forms are elevated after administration of aminoglycosides. Total urinary and serum NAG activity also has been reported to increase in diabetic patients. Overall, NAG activity in the urine reflects the activity of the disease or severity of the damage. Serial monitoring is, therefore, most useful because relative change over time is the most useful way to interpret the results. The NAG-to-creatinine ratio is a more sensitive and specific marker for renal tubular dysfunction. It is useful to express NAG as a ratio of urinary creatinine to minimize dilutional or concentration effects. The lack of sensitive, simple, inexpensive, and efficient methods is the limiting factor for widespread clinical use of NAG monitoring. Another urinary enzyme, clusterin, may prove to be more specific than NAG[303] for evaluating nephrotoxicity caused by aminoglycoside use while remaining equally sensitive.

Other urinary constituents can detect cytotoxic and abnormal processes in specific regions of the nephron. α-GST is found principally in the proximal convoluted tubules, and π-GST is found principally in the distal convoluted tubule. Ala-(Leu-Gly)-aminopeptidase and γ-GT excretion are specific markers for proximal tubular brush border injury. Of note, although enhanced urinary excretion of tubular enzymes can signal damaged tubular cells, it can also reflect an increased turnover of tubular cells or some other metabolic disturbance; thus, the signals of early, irreversible disease may not always be distinguished from the noise

of biologic variability and use of these markers should be applied with appropriate caution. In addition, their validation compared to clinically important outcomes, such as dialysis or mortality, has received little attention.

Urinary sodium hydrogen exchanger isoform-3 (NHE-3) is the isoform of the Na^+/H^+ exchanger present in the apical membrane of proximal tubular cells and responsible for the majority of Na^+ uptake and H^+ excretion by the kidney.[304] NHE-3 is found in the urine with tubular injury, and levels can be estimated from semiquantitative immunoblots of the urine membrane fraction. In a study of 54 critically ill patients and 14 controls, NHE-3 was only seen with tubular injury and, when normalized to urinary creatinine, was six times higher with ATN than prerenal azotemia, without overlap.[305] In addition, urinary NHE-3 was not present with intrinsic ARF other than ATN, and the normalized level correlated with serum creatinine rise in patients with tubular injury.

Biomarkers Reflecting Renal Tubular Cell Dysfunction (Tubular Proteinuria)

When small proteins are filtered by the glomerulus, binding and endocytic reuptake in the proximal tubule normally returns these substances to the body through a megalin-mediated transport system. So-called tubular proteinuria results from functional impairment of this process and the escape of small proteins into the urine. Endogenous low-molecular-weight (LMW) proteins that are normally taken up in this way include β_2- and α_1-microglobulin, albumin, adenosine deaminase binding protein, renal tubular epithelial antigen-1, retinol binding protein, lysozyme, ribonuclease, IgG, transferrin, ceruloplasmin, lambda and kappa light chains, and urinary total protein. Appearance of any of these substances in the urine heralds abnormal proximal nephron function consistent with AKI. However, enthusiasm for LMW protein markers as perioperative tools to diagnose AKI has been reduced, particularly with cardiac surgery, by the confusion that can occur when an antifibrinolytic agent is used.[306] Lysine and its analog (e.g., ε-aminocaproic acid, tranexamic acid) specifically block renal binding sites, causing a profound but reversible inhibition of LMW protein reuptake (Fig. 45-14) [307]; the effect is transient and apparently benign but so potent that urine LMW protein measurement after a small dose of intravenous lysine has been proposed as a tool for estimating GFR.[307] The serine protease inhibitor antifibrinolytic drug aprotinin is a small protein and does not inhibit tubular reuptake but is itself metabolized by the same renal transport system as LMW proteins.[308] Although the influence of aprotinin on renal processing of LMW proteins has not been examined, α_1-microglobulinuria without change in serum creatinine has been reported in cardiac surgical patients after use of this agent.[309]

β_2-Microglobulin is a subunit of the class I antigen of the major histocompatibility complex and is structurally homologous to immunoglobulins.[310] Its mass is 11,600 daltons, it is freely filtered from plasma by the renal glomerulus, and more than 99.9% reabsorbed in the proximal tubule. β_2-Microglobulin is measured by radioimmunoassay and immunodiffusion techniques.[311] Specific limitations to its use include its unstable nature in urine of pH 5.5 or below, thereby precluding its use for patients with concomitant urinary tract infection or pyuria. Its degradation by proteolysis is affected by temperature, and its measurement requires a sophisticated laboratory that precludes widespread clinical use. α_1-Microglobulin is filtered at the glomerulus and is

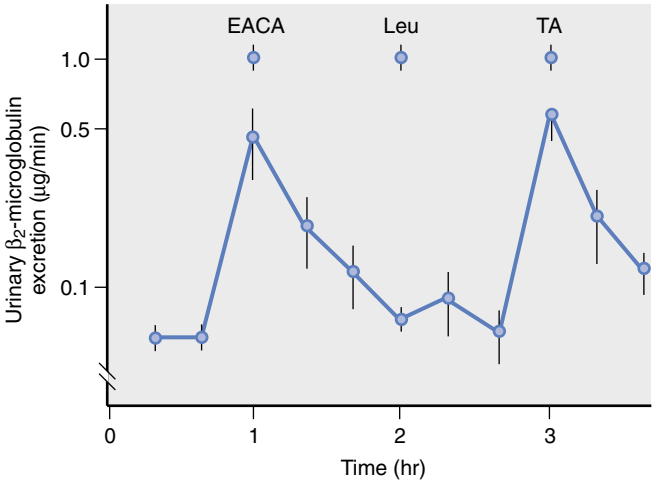

Figure 45-14 Spillage of low-molecular-weight proteins, such as β_2-microglobulin, into the urine, also known as tubular proteinuria, is a poor early biomarker of AKI when lysine analog antifibrinolytic agents are being used.[306] In volunteers, significant but transient increases in urinary β_2-microglobulin levels occur after injection with ε-aminocaproic acid (EACA) and tranexamic acid (TA), but not injection of an unrelated amino acid, leucine (Leu).[307] This potent but transient effect reflects inhibition of normal small protein reuptake by the proximal tubule transport system. (*Modified with permission from Mogensen CE, Solling K: Studies on renal tubular protein reabsorption: Partial and near complete inhibition by certain amino acids. Scand J Clin Lab Invest 37:477-486, 1977.*)

95% reabsorbed at the proximal tubule, thereby indicating proximal tubular dysfunction when present in the urine.[1,312,313]

Lysozymuria, an increase of the enzymatic protein lysozyme in urine, occurs if the serum level is elevated above the normal renal threshold (45 mg/mL) or when renal tubular function is impaired.[314] The normal urinary lysozyme level is less than 1.9 mg/mL, and a level greater than 5 mg/mL is regarded as evidence for significant renal tubular damage. Elevated serum levels of lysozyme may be a consequence of renal failure as well as a marker for it. Because white blood cells have a high concentration of lysozyme, urinary tract infections may also lead to elevated serum levels.

Biomarkers Reflecting the Renal Tubular Cell Response to Stress

Examples of markers that assess the response of the kidney to stress include neutrophil gelatinase–associated lipocalin (NGAL), urinary interleukin-18, platelet-activating factor, kidney injury molecule-1, and cysteine rich protein-61. NGAL is a small protease-resistant polypeptide. Although its role remains largely obscure, NGAL infusion in mice attenuates AKI after renal ischemia.[315] A transcriptome-wide interrogation for genes induced very early after renal ischemia identified NGAL as a protein generated by ischemic renal tubular cells.[316] NGAL appears in kidney parenchyma within 1 hour and in urine of cardiac surgery patients within 2 hours after injury (see Fig. 45-13), earlier than traditional markers,[282,317] and elevated levels are highly predictive of postoperative AKI.[281] Although NGAL demonstrates great promise as an early AKI biomarker, a notable limitation is the high variability among patients in baseline values. Like many early biomarkers, NGAL requires validation as a useful clinical tool in a wide variety of clinical settings and correlation with important outcomes.

Inflammation is a central aspect of the pathophysiology of AKI. Cytokines and adhesion molecules mediate injury in the

kidney, and levels of urinary cytokines such as interleukin-18 (IL-18) and platelet-activating factor have been assessed as early biomarkers of AKI. IL-18 is an inflammatory mediator of ischemic acute tubular necrosis in animals.[318] In human studies, a cross-sectional study comparing a variety of renal conditions with AKI found increased urinary IL-18 level to be a good discriminator between AKI patients and those with prerenal azotemia, urinary tract infections, chronic renal insufficiency, and nephrotic syndrome.[319] This study found that a cut-off urinary IL-18-to-serum creatinine ratio of 500 pg/mg creatinine had sensitivity and specificity of 85% and 88% for the diagnosis of ATN, respectively. Another study in critically ill patients with adult respiratory distress syndrome found that urinary IL-18 levels predicted AKI and mortality risk.[318] Interestingly, in this report, urinary IL-18 levels were significantly higher in septic than nonseptic AKI patients, despite similar serum creatinine concentrations. In one study of cardiac surgery patients, increased urinary IL-18 levels within 6 hours postoperatively predicted subsequent diagnosis of AKI by traditional criteria (see Fig. 45-13).[282] Other plasma and urinary cytokines, such as IL-8, IL-10, IL-1 receptor antagonist, and tissue necrosis factor soluble receptor-2, are less studied but have been shown to correlate with proximal tubular dysfunction.[1]

Platelet-activating factor is a phospholipid mediator of inflammation also known to participate in the pathophysiology of AKI.[271] In a study of 12 critically ill patients with septic shock and AKI, blood and urinary concentrations of platelet-activating factor correlated with several standard clinical and laboratory parameters related to ARF.[320]

Kidney injury molecule-1 (KIM-1) is a transmembrane protein expressed at low levels in normal kidney that is markedly upregulated in proximal renal tubular cells in response to ischemic or nephrotoxic AKI.[271] Increases in rat urine KIM-1 levels correlate with increases in serum creatinine values.[321,322] In a study of humans with ARF, KIM-1 expression is markedly increased in renal biopsy samples with ATN and accompanied by elevated urine KIM-1 levels.[323] In this study, urine KIM-1 was also a better predictive tool than γ-GT and AP.[323] KIM-1 appears in urine within 12 hours of AKI and remains elevated; however, to date there are no published data to correlate the extent of damage with KIM-1 levels. KIM-1 also appears in the urine before a rise in serum creatinine level with cisplatin or high-dose folic acid nephrotoxicity.[270] Measurement of KIM-1 in urine requires Western blot analysis and quantification by enzyme-linked immunosorbent assay.

Cysteine-rich protein-61 (CYR61) is a heparin-binding protein that is secreted by injured tissues, including the kidney, and is involved in tissue growth and repair.[316] In an animal model, CYR61 was expressed in renal tissue within 1 hour and detected in urine 3 to 6 hours after ischemia, peaking in urine 6 to 9 hours after injury. The CYR61 gene is upregulated more than 10-fold after renal ischemic injury.[324] Notably, CYR61 does not appear in animals with prerenal azotemia.

Preoperative Evaluation of Renal Function

The greater the magnitude and duration of the surgical insult and the number of acute and chronic risk factors, the greater is the likelihood of perioperative renal compromise and the need for preoperative identification of renal function (see Chapters 34 and 35). In patients with inadequate blood flow, injury is commonly caused by the added risk of drugs, by abnormal hemodynamics, or by preexisting disease.[325] Studies have shown that 12% to 14% of patients who develop acute renal insufficiency during hospitalization do so after radiographic procedures requiring use of a contrast agent. If preexisting renal insufficiency exists, progressive deterioration in renal function occurs in 42% of cases, with a poor prognosis if dialysis is required.[326] Risk factors, such as volume depletion, aminoglycoside use, radiocontrast dye exposure, use of nonsteroidal anti-inflammatory drugs, septic shock, and pigmenturia all contribute to the development of ARF. It appears that the combined interaction of these multiple acute risk factors is central in the pathogenesis of ARF (see Fig. 45-6).[20] Patients with preexisting renal insufficiency, for example, are especially prone to develop ARF that requires dialysis as a result of cardiovascular surgery. Similarly, diabetic patients with renal insufficiency are especially vulnerable to radiocontrast agents. Of course, part of this association is due to the insensitivity of standard tools such as serum creatinine to loss of renal function (see Fig. 45-10), leaving limited reserve and only a small further loss in renal function required to push an individual to the brink of dialysis. Some key determinants of postoperative renal function are preoperative renal function, maintenance of appropriate intravascular volume, and normal myocardial function.[23]

The potential value of understanding the genetic makeup of patients has yet to be fully explored and is likely to be important (see earlier discussion). Genetic variants are an established predictor of chronic kidney disease (e.g., renal transplant nephropathy), and early perioperative studies in cardiac surgery patients have already identified genetic factors that explain twofold to threefold more variation in postoperative AKI compared with standard clinical risk factors alone.[125,126]

In addition to intrinsic renal disease, several extrinsic variables influence the outcome of renal function tests: intracellular and extracellular volume, cardiovascular function, and neuroendocrine factors.[327,328] Advanced age also markedly decreases renal function reserve. GFR, normally about 125 mL/min in a young adult, decreases to about 80 mL/min at 60 years of age and to 60 mL/min at 80 years (see Fig. 45-11). Although not necessarily the primary cause for end-stage renal disease, hypertension in up to 85% of patients with renal failure is a major risk factor for the high cardiovascular morbidity that occurs.[329] The role of metabolic syndrome in contributing to end-stage renal disease is also becoming more apparent.[330]

In addition to its contribution to renal failure in hypertensive nephrosclerosis resulting from essential hypertension and hyperfiltration in diabetic nephropathy, hypertension also contributes to the loss of renal function associated with aging. Preoperative isolated systolic blood pressure hypertension and wide pulse pressure (i.e., the difference between systolic and diastolic blood pressure) are strong independent predictors of postoperative renal dysfunction.[150,331] It appears that an increase in conduit vessel stiffness with inadequate flow during low-pressure states contributes to increased preoperative renal dysfunction and hemodialysis-dependent renal failure.

Urinalysis provides qualitative information that must be interpreted cautiously. Hematuria (i.e., more than one or two red blood cells per high-power field in a concentrated sediment)

suggests glomerular disease or, in a trauma patient, injury to the kidneys or the lower urinary tract. A urine test result that is positive for blood in the absence of red blood cells suggests the presence of free hemoglobin or myoglobin in the urine. Pyuria (i.e., more than four white blood cells per high-power field) suggests urinary tract infection. Although urine may normally contain hyaline and granular casts, cellular casts represent a pathologic condition. Red blood cell casts suggest interstitial nephritis, including pyelonephritis. Urinary pH, although difficult to interpret on a spot urine sample, may assist in the diagnosis of some acid-base disturbances. The pH of urine tends to be more acidic when factors that initiate failure are prerenal rather than postrenal. The presence of proteinuria on a routine dipstick examination may be normal, or it may suggest severe renal disease. In a concentrated urine sample, trace or 1+ proteinuria is a nonspecific finding, whereas 3+ or 4+ proteinuria suggests glomerular disease. The existence of glucosuria without hyperglycemia indicates proximal tubular damage.

Serum creatinine levels offer rapid but inexact estimates of creatinine clearance. Acute elevations of serum creatinine levels occur in approximately 5% of all hospitalized patients and in up to 20% of patients in intensive care units.[32] The incidence increases directly with the severity of trauma and the degree of injury or disease. The incidence and severity of ARF usually are greater when the preoperative serum creatinine level is greater than 2 mg/dL[332]; however, an isolated serum creatinine measurement is an unreliable indicator of GFR when renal function is changing. There is an inverse logarithmic relationship between GFR and serum creatinine concentration (see Fig. 45-10). Decreasing the rate by one half results in twice the serum creatinine level. For example, a patient with a baseline serum creatinine level of 0.6 mg/dL who develops contrast nephropathy sufficient to reduce the number of glomeruli and filtration rate by one half would have a serum creatinine level of 1.2 mg/dL, still in the normal range. Thus, a trend in serum creatinine values is always more useful than a single serum creatinine measurement to evaluate renal function reserve, particularly when changes are anticipated. The measurement of creatinine clearance may constitute the best overall indicator of GFR, although this index also has limitations. In one study, more than one half of 131 critically ill patients had normal values for urine output, BUN, and serum creatinine but had reduced creatinine clearance. Creatinine clearance was the best predictor of mortality among these patients compared with the other measures of renal function.[333] Although serum creatinine level may be a more reliable measure of glomerular function than the BUN level, the simultaneous determination of BUN and serum creatinine levels offers a more complete evaluation of renal function than either determination alone. Ordinarily, the BUN-to-creatinine ratio is approximately 10, and if the BUN level is approximately 10 times as great as the serum creatinine level, the clinician may conclude that the measurements are probably correct. Conversely, if the ratio deviates significantly from 10, the clinician should consider the nonrenal factors influencing the BUN level or serum creatinine level or both. All three measurements (i.e., BUN, serum creatinine level, and creatinine clearance) require careful interpretation.

Summary

In patients with, or at risk for developing, AKI the perioperative management continues to be challenging. Numerous factors contribute to the heterogeneous condition referred to as perioperative AKI, but insults collectively combine through ischemic and toxic mechanisms. The recent revision of mission in the research community in regard to the investigation of AKI will likely lead to rapid developments in the field of renal function monitoring, including "early biomarker" tests or panels of tests that aid in risk prediction, identification of patients with conditions that precede AKI, such as prerenal azotemia, and the diagnosis and prognosis of AKI. The major hope is that improvements in monitoring will translate into better prevention, treatment, and outcome from AKI, something that has been disappointingly absent over the past half century since the problem of perioperative ARF was first described. As understanding of renal function and AKI evolves, traditional tests, such as serum creatinine, are being questioned as to allow sufficiently early intervention to improve the care of patients with AKI. The introduction of new "early biomarker" tests and even preoperative genetic testing may contribute significant advances to renal function monitoring. That this information will improve the prognosis of AKI is hoped for but not known. Meanwhile, serum creatinine continues to be the mainstay of most renal function monitoring strategies.

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46 Neurologic Monitoring

Key Points

1. There are four key principles of intraoperative neurologic monitoring.
2. The pathway at risk during the surgical procedure must be amenable to monitoring.
3. If evidence of injury to the pathway is detected, there must be some intervention possible.
4. If changes in the neurologic monitor are detected, and no intervention is possible, although the monitor may be of prognostic value, it does not have the potential to provide direct benefit to the patient from early detection of impending neurologic injury.
5. The monitor must provide reliable and reproducible data.
6. There are few randomized prospective studies evaluating the efficacy of neurologic monitoring modalities.
7. Based on clinical experience and nonrandomized studies, practice patterns for use of neurologic monitoring have emerged.
8. There are procedures for which monitoring is recommended and used by most centers
9. There are procedures for which monitoring is used frequently in some centers, but not in others.
10. There are procedures for which there is no clear clinical experience or evidence indicating that monitoring is useful at all (experimental use).
11. There are procedures in which monitoring is used selectively for patients believed to be at higher-than-usual risk for intraoperative neurologic injury.

Neurologic monitoring in the context of anesthesia care for a patient spans a wide spectrum of techniques, diverse procedures, and various intraoperative or even postoperative settings. Techniques for monitoring fall into two broad categories: techniques to assess metabolic integrity of the nervous system, which typically entail either global or regional determinations of blood flow or oxygenation, or techniques to assess functional integrity, which likewise may be global or focused on specific anatomic components of the nervous system.

The procedures and settings in which neurologic monitoring is typically applied all share the characteristic that changes in the monitored parameters can be corrected or minimized by either modifying the surgical approach or manipulating parameters under the control of the anesthesiologist. Monitored procedures range from procedures where monitoring dictates the surgical approach, such as localization of the motor strip during tumor surgery or the neurologic examination during an "awake" craniotomy, to procedures that by their nature put parts of the nervous system at increased risk.

In many procedures that require neurologic monitoring, the surgical target overlaps with the site of action of drugs a patient receives. The anesthesiologist and the surgeon need to be aware not only of limitations inherent in individual monitoring techniques, but also of nonsurgical factors that influence the monitoring results. The monitoring approach ideally should anticipate nonsurgical factors by providing a degree of redundancy that helps distinguish a localized surgical trespass from a systemic event.

For some procedures, neurologic monitoring is a marker of the quality of care and is routinely employed because outcome data support its use. Examples include correction of scoliosis and resection of vestibular schwannomas. More frequently, the approach to monitoring is based on local conventions and surgical expectations. In this latter case, monitoring utility depends even more on a good understanding of the technique's capabilities and limitations by anesthesiologists and surgeons and on their mutual collaboration to allow corrective action in the face of changing signals or to prevent false alarms that disrupt surgery.

This chapter first discusses individual monitoring modalities in isolation so that the clinician can appreciate the inherent strengths and weaknesses of each. Subsequent sections apply this information by describing suitable approaches to various clinical settings that combine and integrate individual techniques to optimize neurologic outcome for patients. The chapter ends with a brief discussion of how neurologic monitoring is believed to be useful today, and where more work is needed to determine whether monitoring has a role in surgical patients in the future.

Monitoring Modalities

Monitors of Adequacy of Nervous System Blood Flow

Adequacy of cerebral blood flow (CBF) can be monitored by two principal methods. The first method assesses blood flow itself with the implicit assumption that "normal" flow provides adequately for the metabolic needs of the brain. The second approach assesses oxygen delivery either locally or globally with the implicit assumption that "normal" values at the site of measurement are reflective of adequate blood supply throughout the central nervous system (CNS). To illustrate the limitations imposed by such implicit assumptions, let us examine global or hemispheric CBF in the context of a patient's disease process.

In normal brain, values of hemispheric CBF of approximately 50 mL/100 g/min reflect adequate oxygen delivery for maintaining structural integrity and function. Values of less than 20 to 25 mL/100 g/min are associated first with failure of function and on further decrease with structural damage.[1] In neurosurgical patients, structural integrity and function may be altered by disease processes and anesthetics, which have an impact on the interpretation of measured CBF. A CBF of 40 mL/100 g/min in a patient in barbiturate coma after resection of an arteriovenous malformation may represent hyperemia (because metabolic demand is very low), whereas the same CBF in a patient with a mass lesion may reflect a modest decrease in cerebral perfusion pressure secondary to increasing intracranial pressure.

Global Blood Flow Monitoring Techniques (Noninvasive)

Intravascular Tracer Compounds. Direct measurement of CBF is possible by determining kinetics of washin or washout, or both, of an inert tracer compound, a method originally described by Kety and Schmidt.[2] The most widely used measurement technique involves administration of a radioactive isotope of xenon (^{133}Xe), followed by measurement of the radioactivity washout with gamma detectors placed over specific areas of the brain. Depending on the number of detectors, this method can provide a spatial resolution of 4 cm. In normal brain, flow at different depths may be inferred from the early washout, which should reflect high-perfusion cortical gray matter, and late washout from low-perfusion deeper white matter.

Drawbacks of the method are the patient's exposure to radioactive compounds and the need for externally placed and potentially cumbersome detector equipment, which may interfere with surgery itself in the case of intracranial surgery. Focal areas of hypoperfusion may be missed because of underlying or overlying adequate flow, a phenomenon described as "look-through."[3] Despite these shortcomings, ^{133}Xe washout has been used at a few major centers for intraoperative monitoring during operations such as carotid endarterectomy.[4-8] Modern variations of the same concept are mean transit time determinations of intravascular contrast agents during neuroimaging for determining locoregional blood flow[7,8] or a double-indicator technique for determining global CBF.[9] All these techniques share the limitation of providing a snapshot of CBF in time instead of continuous monitoring.

Transcranial Doppler Ultrasound. Transcranial Doppler (TCD) ultrasound is a technique that infers CBF from measurements of the blood flow velocity in the large conducting arteries of the brain. The TCD probe transmits pulses of sound waves through the thin temporal bone in a variation of the pulsed wave Doppler technique with which anesthesiologists may be familiar from echocardiography. When these sound waves are reflected off the red blood cells back toward the TCD probe, the velocity of the reflected sound waves is changed because the blood cells themselves are in motion toward or away from the probe. This phenomenon is known as the "Doppler shift," and is directly related to flow velocity and flow direction of the blood cells. Blood flow is faster during systole and in the center of a vessel and slower in diastole and near the vessel wall. TCD records a spectrum of flow velocities, whose outline resembles an arterial waveform tracing. These concepts are illustrated in Figure 46-1.

Intraoperatively, TCD measurements are most commonly and easily made by continuous monitoring of the middle cerebral artery for the purpose of detecting either significant changes in flow velocity or the presence of particulate emboli. As a diagnostic study, in addition to the middle cerebral artery, the anterior cerebral, anterior communicating, posterior cerebral, and posterior communicating arteries can be examined through the temporal bone window. The basilar, ophthalmic, and internal carotid arteries also can be insonated through the foramen magnum (TCD probe at the back of the flexed neck) (basilar artery), the closed eyelid (with reduced sound energy) (ophthalmic artery), and near the angle of the jaw (internal carotid artery). An important limitation of TCD results from the fact that most of the examination is done through the temporal bone, which may be thick enough to preclude an adequate examination in 10% to 20% of patients.[10,11]

Two assumptions that are intuitive and plausible, but ultimately unproven, must be made for TCD-measured blood flow velocity to have a direct relationship to CBF. First, blood flow velocity is directly related to blood flow only if the diameter of the artery where the flow velocity is measured and the measurement angle of the Doppler probe remain constant. In practical terms, the difficulty with this assumption lies in finding a means to affix the TCD probe in a way that prevents dislodgment or movement during monitoring. The second assumption requires that CBF in the basal arteries of the brain is directly related to cortical CBF. Because TCD monitoring is typically done mainly using the middle cerebral artery, this assumption may be invalid if collateral blood flow by leptomeningeal collaterals from anterior and posterior cerebral artery territories is adequate. Although these two assumptions constrain the utility of TCD as a standalone monitor of CBF, the changes in flow velocity seen in typical applications (discussed subsequently) are large enough to provide useful clinical information.

More importantly, TCD is the only continuous neurologic monitoring technique that provides early warning for hyperperfusion and for the number of emboli delivered to the brain during various phases of an operation. Because of their high echogenicity, emboli show up in the TCD spectrum as high-intensity transient signals (HITSs) (see Fig. 46-1) and are easily identified as brief beeps or chirps within the background of the Doppler sounds.

Jugular Bulb Venous Oxygen Saturation. The degree of oxygen extraction by an organ can be monitored by following the

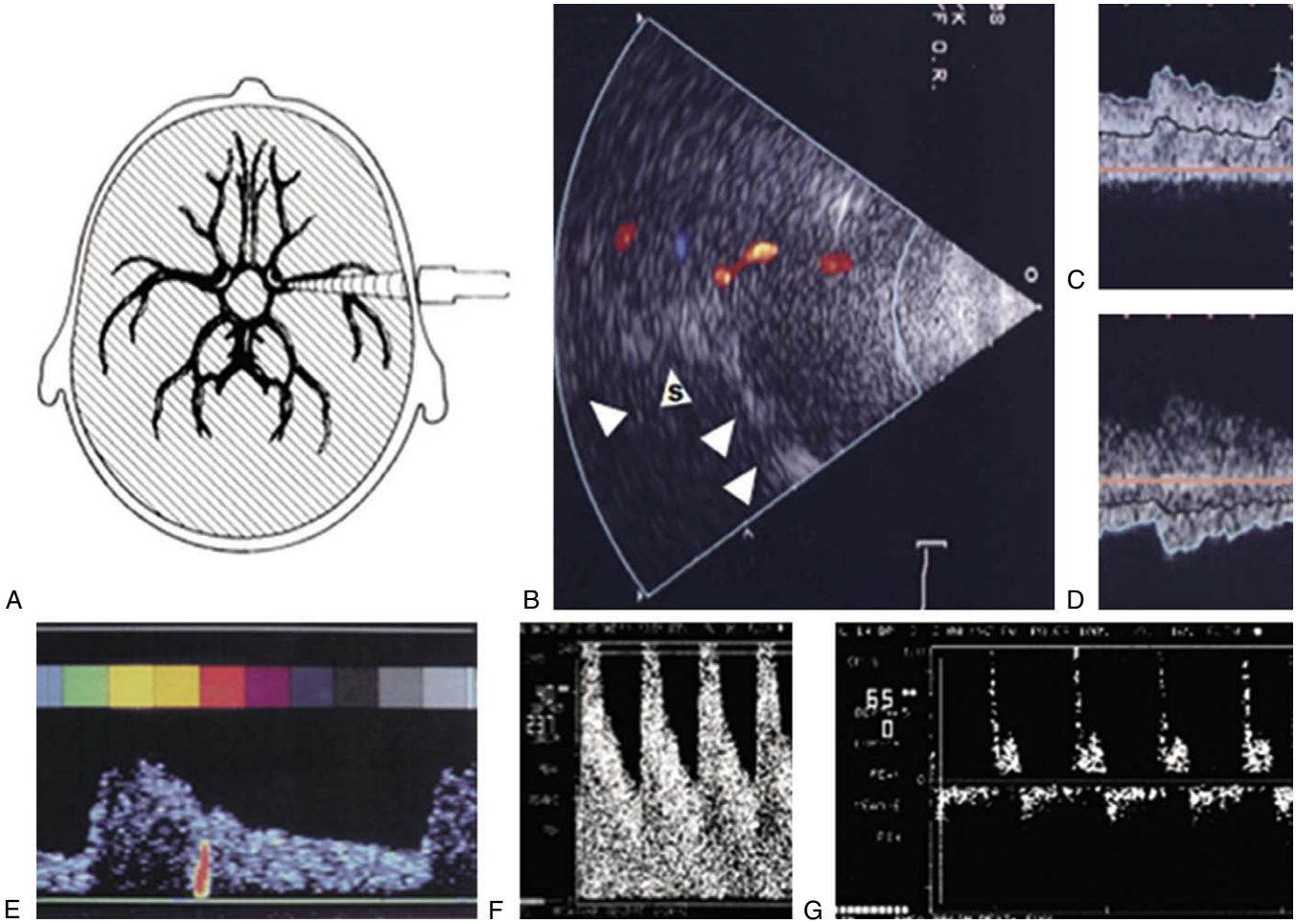

Figure 46-1 **A,** Transcranial Doppler monitoring is done by insonating the arteries at the base of the brain through a thin part of the temporal bone. **B,** If this is done with an imaging probe, some intracranial structures, such as the cerebral peduncles (*white triangles*) or the sella complex (*white triangle labeled "S"*), can be visualized. The Doppler signals originate from the right middle, right anterior, and left anterior cerebral arteries. **C,** Normal Doppler spectrum obtained from the middle cerebral artery. **D,** Doppler profile of the bifurcation of the terminal internal carotid artery as it branches into the middle cerebral artery (flowing toward the transducer) and the anterior cerebral artery (flowing away). This flow signal can be obtained if the transducer is focused as shown in **A**. **E-G,** Examples of three clinical applications of transcranial Doppler. **E,** Emboli are highly echogenic and show up as high-energy transient signals (HITS). On the audible output, these emboli are easily noticed as brief beeps or chirps. **F,** Doppler profile of a middle cerebral artery in a patient with severe vasospasm after an aneurysmal subarachnoid hemorrhage (compare with **C**). **G,** Transcranial Doppler examination consistent with intracranial circulatory arrest. There is a brief systolic inflow followed by retrograde flow during diastole.

oxygen saturation of the mixed venous blood that drains that organ. In the case of the brain, jugular bulb venous oxygen saturation ($Sjvo_2$) is believed to measure the degree of oxygen extraction and to represent the balance between cerebral oxygen supply and demand. To monitor $Sjvo_2$, a fiberoptic catheter is placed in a retrograde fashion into the jugular bulb through the internal jugular vein under fluoroscopic guidance. The fiberoptic bundle emits near-infrared light and records light reflected back to the catheter, a technique known as "reflectance oximetry." Because near-infrared light can travel several centimeters in tissue and is mostly absorbed by hemoglobin, it is possible to determine the oxygen saturation of the surrounding tissue (i.e., the jugular venous blood). Correct tip placement is crucial to minimize admixture of extracranial venous blood. To decrease the risk of complications, usually only one side is monitored.

Several theoretical limitations of the technique must be borne in mind to interpret $Sjvo_2$ values and trends properly. Although nearly all blood from the brain drains via the jugular veins, intracranial mixing of venous blood is incomplete and may result in differences between right-sided and left-sided measurements. The dominant jugular vein (i.e., the right for most patients) drains predominantly cortical venous blood, whereas the contralateral jugular vein drains more of the subcortical regions.[12] Despite such regional differences, $Sjvo_2$ must be considered a monitor of global cerebral oxygenation because inadequate perfusion to a focal brain region may not decrease $Sjvo_2$ values below the normal range of 55% to 75%. Because $Sjvo_2$ represents the balance between supply and demand, interpretation of the absolute value of $Sjvo_2$ must take the clinical circumstances into account.

Cerebral Oximetry. Cerebral oximetry is a noninvasive technique that, similar to $Sjvo_2$ monitoring, uses reflectance oximetry to measure the oxygen saturation of the tissues underneath the sensor. Typically, two sensors are applied to both sides of the forehead. The light passes not only through parts of the frontal

brain, but also through the overlying skull and scalp. Contamination of the oximetry signal by extracranial blood sources is a serious concern, although the use of two sensing diodes with different distances from the light source within one sensor patch and adjustments of the algorithm of the oximeter may minimize this problem.[13,14]

Because two thirds to four fifths of the cerebral blood volume is venous blood, cerebral oximetry determines predominantly "local venous oxygen saturation."[15] It can be expected that in the face of cerebral ischemia, oximetry values decrease as a result of increased oxygen extraction, well before function fails, or permanent neuronal damage ensues. The simplicity of its use and the familiarity with the principles of treating decreases in systemic mixed venous oxygen saturation have made cerebral oximetry a popular trend monitor in operations that potentially cause decreases in blood flow to the vessels of the head. There are some significant limitations, however, of the use of cerebral oximetry during such procedures. First, adequacy of global cerebral perfusion is inferred from measurements over the frontopolar brain. Second, normative data on normal values or expected changes for cerebral oximetry are largely absent, but preoperative application of the sensors allows the start of a trend in conjunction with a neurologic baseline examination.

An example of how these limitations play out is provided by a study of the use of cerebral oximetry during 100 carotid endarterectomies in awake patients.[16] Cerebral oximetry was able to identify 97.4% of patients with adequate CBF as indicated by the absence of clinical symptoms. The monitor frequently indicated inadequate CBF, defined as a 20% decrease in cerebral oxygen saturation from the preclamp baseline, although the patient had no clinical symptoms of inadequate CBF. The false-positive rate of 66.7% may simply illustrate the fact that oxygen extraction increases before function fails. The real problem is that the lower limit for acceptable regional oxygen saturation is unknown in a large population of patients.[17] The value may be different from patient to patient, and addition of anesthetic drugs that influence cerebral metabolism may confuse the picture further.

Tissue-Level Blood Flow Monitoring Techniques (Invasive)

Tissue-level monitoring for the brain is by definition invasive. All monitors in current clinical or research use are implanted through a burr hole, extend either into the white matter or ventricular system, and typically use a bolt for stabilization. They all share a 1% to 2% risk of bleeding, infection, or ischemia owing to the implantation procedure.[18] A second shared feature is their limited spatial resolution (i.e., each monitoring probe monitors only a limited area of brain surrounding the probe). When these monitors were first developed, there was considerable debate regarding the optimal placement of the device given such limited spatial resolution. Based on today's appreciation for the impact of secondary neurologic insults on the ultimate outcome, there is growing agreement that tissue-level monitoring is best performed in morphologically and functionally normal tissue that is part of the penumbra or vulnerable zone of interest.[19-21] Placing a blood flow monitor into the brain tissue supplied by an aneurysm-carrying artery in the setting of a subarachnoid hemorrhage maximizes, but does not ensure, the chances of early detection of vasospasm.

Of the tissue-level monitors, two have undergone sufficient refinement to be in wider clinical use. They represent the two principal modes of assessing adequate blood flow—assessing CBF through thermal diffusion monitoring or assessing oxygen delivery through tissue partial pressure of oxygen (Po_2) monitoring.

Thermal Diffusion Cerebral Blood Flow Monitoring. Thermal diffusion CBF monitoring is based on the idea that the rate at which heat dissipates in a tissue depends on the tissue's thermal conductive properties and the blood flow in that area. Because thermal conduction properties remain constant, changes in heat dissipation reflect changes in blood flow and can be expressed quantitatively in the conventional units of CBF as mL/100 g/min. In practice, the probe consists of a thin catheter with two thermistors placed 5 mm apart (Fig. 46-2). When inserted, both thermistors are located in subcortical white matter. The proximal or passive thermistor measures brain temperature, whereas the distal or active thermistor is heated to 2°C above the temperature measured by the passive thermistor. The power required to sustain the 2°C temperature difference is directly proportional to CBF. The initial rate of propagation of the thermal field is used to establish the fixed conductive component of heat transfer.

The acute performance of this technology has been validated against stable xenon computed tomography (CT) in patients with head injury and performed well across a wide range of CBF

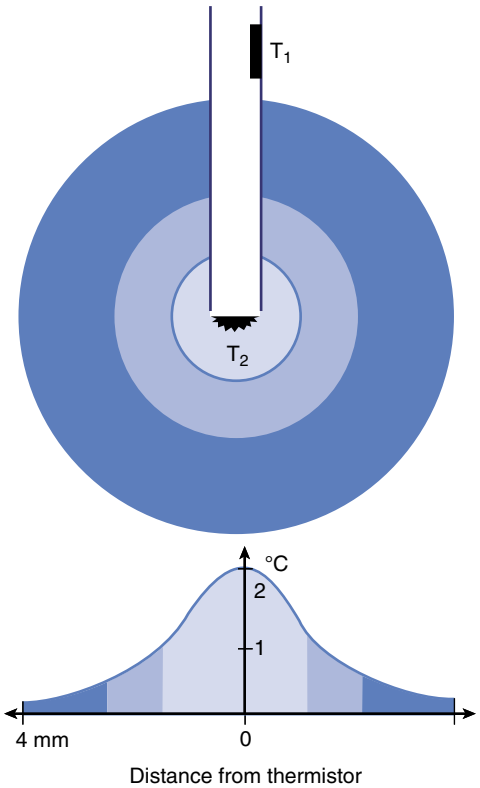

Figure 46-2 Thermal diffusion measurement of cerebral blood flow. The probe is placed in the subcortical white matter. It contains a passive thermistor (T_1) that measures brain temperature and is located outside of the area influenced by the active thermistor. The active thermistor (T_2) is heated to 2°C above brain temperature. The energy required to maintain that increase in temperature is proportional to cerebral blood flow.

values in a sheep model of hypercarbia, hyperventilation, and cardiac arrest.[22] In continuous clinical use, the probe shows some drift and recalibrates at regular intervals.[23] To avoid thermal tissue injury, measurement is automatically suspended if the passive thermistor measures a brain temperature of 39.1°C. Because fever is a frequent complication, particularly in patients with severe brain disease, the inability to monitor during a febrile episode may constitute a true limitation of the technique.

Tissue Partial Pressure of Oxygen Monitoring. Localized monitoring of tissue Po_2 is based on an oxygen-sensitive electrode originally described by Clark.[24] The diffusion of oxygen molecules through an oxygen-permeable membrane into an electrolyte solution causes an electric current that is proportional to Po_2. Currently available catheter-based electrodes provide stable recording conditions over long periods. Similar to regional CBF probes, they are placed into the subcortical white matter.

Most of the data on brain tissue oxygen levels ($P_{Br}O_2$) comes from studies in patients with head trauma. Comparison with stable xenon CT for assessment of CBF shows good correlation between $P_{Br}O_2$ and CBF.[25,26] Similarly, the time course of changes in $P_{Br}O_2$ after traumatic brain injury resembles that of CBF.[27,28] Critics of the technique argue that $P_{Br}O_2$ values are highly influenced by the partial pressure of arterial oxygen (Pao_2) and are merely an elaborate indicator of the quality of patient ventilation. This view is supported by the observation that increasing the fraction of inspired oxygen (Fio_2) increases $P_{Br}O_2$, but likely represents an oversimplification.[29] Concurrent microdialysis studies have shown that increasing Fio_2 not only increases $P_{Br}O_2$, but also decreases tissue lactate levels, suggesting a true improvement in the metabolic milieu of the brain tissue itself.[30,31]

Monitors of Nervous System Function

The most commonly used monitors of function are the electroencephalogram (EEG), sensory evoked responses (SERs), motor evoked responses, and the electromyogram (EMG). The EEG is a surface recording of the summation of excitatory and inhibitory postsynaptic potentials spontaneously generated by the pyramidal cells in the cerebral cortex. The signals are very small, and each recording electrode records only information generated directly beneath the electrode. Monitoring the EEG is usually directed toward one or more of four perioperative uses. First, the EEG is used to help identify inadequate blood flow to the cerebral cortex caused by either a surgically induced or anesthetic-induced reduction in blood flow or retraction on cerebral tissue. Second, the EEG may be used to guide an anesthetic-induced reduction of cerebral metabolism either in anticipation of a loss of CBF or in the treatment of high intracranial pressure, when a reduction in CBF and blood volume is desired. Third, the EEG may be used to predict neurologic outcome after a brain insult. Finally, the EEG may be used to gauge the depth of the hypnotic state of the patient under general anesthesia (see Chapter 39).

More than 50 years of experience monitoring the EEG has led to many known correlations of EEG patterns with clinical states of the normal and pathologic cerebral cortex. The electroencephalographer can accurately identify consciousness, unconsciousness, seizure activity, stages of sleep, and coma. In the absence of significant changes in anesthetic technique, the electroencephalographer also can accurately identify inadequate oxygen delivery to the brain (from either hypoxemia or ischemia). By using high-speed computerized EEG analysis and statistical methods, EEG patterns in the continuum from awake to deeply anesthetized are becoming, with few exceptions, much better understood. In addition, computer advances have made possible high-speed mathematic manipulation of the EEG signal to present the data in a manner more suitable to continuous trends for use during surgical or anesthetic monitoring.

Evoked potentials are electric activity generated in response to either a sensory or a motor stimulus. Measurements of evoked responses may be made at multiple points along an involved nervous system pathway. The evoked responses are generally smaller than other electric activity generated in nearby tissue (muscle or brain) and are readily obscured by these other biologic signals. In the case of SERs, repeated sampling and sophisticated electronic summation and averaging techniques are needed to extract the desired evoked potential signal from background biologic signals. Motor evoked responses are generally larger and commonly do not require averaging.

SERs are the most common type of evoked potentials monitored intraoperatively. During the last 2 decades, much research has been done on the use of intraoperative motor evoked potentials (MEPs). Although routine use of MEP monitoring is still not widespread, it is becoming more so. There are three basic types of sensory evoked responses: somatosensory evoked potentials (SSEPs), brainstem auditory evoked potentials (BAEPs), and visual evoked potentials (VEPs).

The SSEP is produced by electrically stimulating a peripheral (or rarely cranial) nerve. Responses may be recorded proximally over the stimulated nerve, the spinal cord, and the cerebral cortex. The recorded responses assess the function of the peripheral nerve, the posterior and lateral aspects of the spinal cord, a small portion of the brainstem, the ventral posterolateral nucleus of the thalamus, the thalamocortical radiation, and a portion of the sensory cortex. The BAEP is usually produced by a series of rapid, loud clicks applied directly to the external auditory canal. Responses are most commonly recorded from electrodes applied to the scalp, although more invasive direct recordings from auditory structures and nerves may also be made. BAEPs assess function of the auditory apparatus itself; cranial nerve VIII; the cochlear nucleus; and a small area of the rostral brainstem, the inferior colliculus, and the auditory cortex. The VEP is produced by flash stimulation of the retina. Recordings are made from cortically placed electrodes and assess visual pathways from the optic nerve to the occipital cortex.

MEP responses are generated most commonly by the application of a transcranial train of electric stimuli, and responses are recorded at various points along the spinal column, peripheral nerve, and innervated muscle. Electric stimuli to activate motor tracts also may be applied at the level of the spinal cord, but this method of stimulation is controversial (see later), with research suggesting that the response, as it is currently recorded, is at best a mixed response and at worst primarily a sensory response. Magnetic stimuli also may be applied transcranially or at the level of the spinal cord, but use of magnetic stimulation is much less common than electric stimulation, primarily for technical reasons involving fixation of the magnet to the patient to avoid shifts in magnetic field application, which would significantly alter responses. MEPs assess the integrity of the descending motor

pathway through the internal capsule, the brainstem, the spinal cord, the peripheral nerve, and finally the muscle itself. The ability to record MEPs from some patients with cerebral palsy indicates that normal functional organization of the motor cortex cannot be inferred from MEPs.

Electroencephalogram

Basic Unprocessed Electroencephalogram Concepts. The EEG is produced by a summation of excitatory and inhibitory postsynaptic potentials produced in cortical gray matter. Because the EEG signal is generated only by postsynaptic potentials and is much smaller than action potentials recorded over nerves or from the heart, extreme care must be taken when placing electrodes to ensure proper placement and excellent contact with the skin to avoid significant signal loss. Alternatively, subdermal needle electrodes may be used, particularly when sterile application of an electrode close to a surgical field is necessary. When electrodes are applied directly to the surface of the brain, impedance is minimized by close electrode contact and saturation of the area with an electrolyte solution.

EEG electrodes generally are placed according to a mapping system that relates surface head anatomy to underlying brain cortical regions. The placement pattern of recording electrodes is called a montage. Use of a standard recording montage permits anatomic localization of signals produced by the brain and allows development of normative EEG patterns and comparison of EEG recordings made at different times. The standard EEG "map" is called the 10-20 system for EEG electrode placement (Fig. 46-3). This system is a symmetric array of scalp electrodes placed systematically based on the distance from the nasion to the inion and from the pretragal bony indentations associated with both temporomandibular joints. Based on 10% or 20% of these distances, recording electrodes are placed systematically over the frontal (F), parietal (P), temporal (T), and occipital (O) regions at increasing distances from the midline. Left-sided electrodes are given odd number subscripts, and right-sided electrodes are given even number subscripts. Increasing numbers indicate an increasing distance from the midline. Midline electrodes are designated with a "z" subscript. The standard diagnostic EEG uses at least 16 channels of information,[32] but intraoperative recordings have been reported using 1 to 32 discreet channels.

The intraoperative EEG is most commonly recorded from electrodes placed on the scalp. Recordings also may be made from electrodes placed on the surface of the brain (electrocorticography), or from microelectrodes placed transcortically to record from individual neurons (e.g., during surgery for Parkinson's disease).[33,34] The EEG signal is described using three basic parameters: amplitude, frequency, and time. Amplitude is the size, or voltage, of the recorded signal and ranges commonly from 5 to 500 μV (versus 1 to 2 mV for the electrocardiogram signal). Because neurons are irreversibly lost during the normal aging process, EEG amplitude decreases with age. Frequency can be thought of simply as the number of times per second the signal oscillates or crosses the zero voltage line. Time is the duration of the sampling of the signal; this is continuous and real time in the standard paper or digital EEG, but is a sampling epoch in the processed EEG (see later).

Normal Electroencephalogram. Normal patterns seen on the EEG vary among normal individuals, but are consistent enough to allow for accurate recognition of normal and pathologic patterns. The usual base frequency in an awake patient is the beta range (>13 Hz). This high-frequency and usually low-amplitude signal is common from an alert attentive brain and may be recorded from all regions. With eye closure, higher amplitude signals in the alpha frequency range (8 to 13 Hz) seen best in the occipital region appear (Fig. 46-4). This "eyes closed" resting pattern is the baseline awake pattern used when anesthetic effects on the EEG are described. When events that lead the brain to produce higher frequencies and larger amplitudes occur, the EEG is described as "activated," and when slower frequencies are produced (theta = 4 to 7 Hz, and delta = <4 Hz), the EEG is said to be "depressed." The EEG in a sleeping patient may contain all of these frequencies at various times. The slower frequencies occur during deep natural sleep with "sleep spindles" (Fig. 46-5), but during light sleep or rapid eye movement (REM) sleep, the EEG becomes activated, and the eye muscle EMG appears on the EEG.

In the normal EEG in awake and asleep patients, patterns recorded from corresponding electrodes on each hemisphere are symmetric in terms of frequency and amplitude, the patterns are predictable if clinical states are known, and spike (epileptic) waveforms are absent. In most cases, normal EEG patterns are associated with normal underlying brain function in awake and anesthetized patients.

Abnormal Electroencephalogram. General characteristics of the "abnormal" EEG include asymmetry with respect to frequency, amplitude, or both, recorded from corresponding electrodes on each hemisphere, and patterns of amplitude and

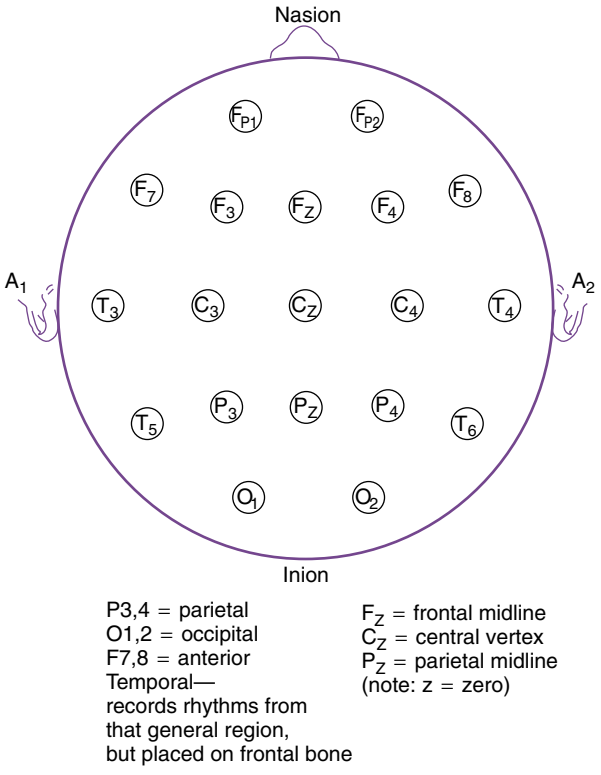

Figure 46-3 International 10-20 system of electrode placement for recording electroencephalogram and sensory evoked responses. *(From Hughes JR: EEG in Clinical Practice, 2nd ed. Newton, MA, Butterworth-Heinemann, 1994.)*

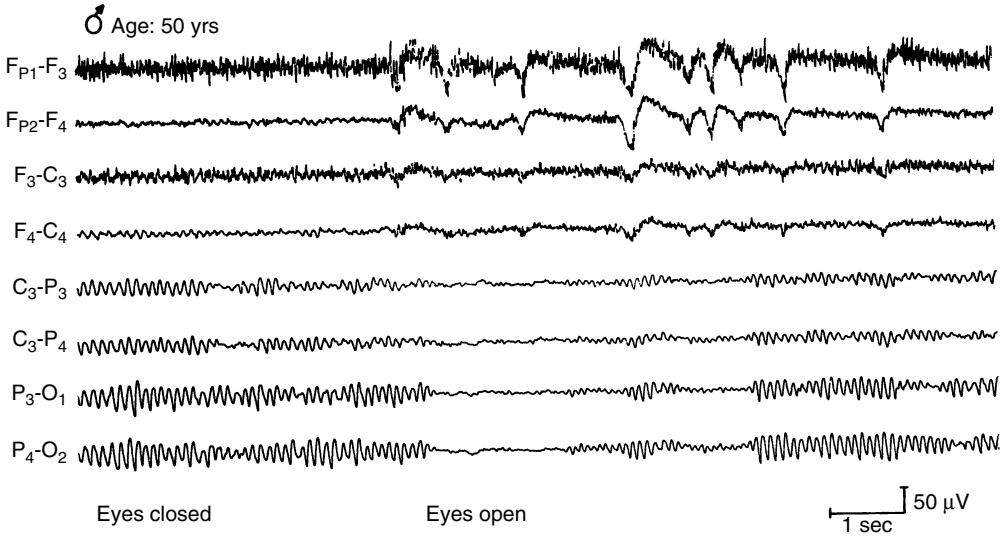

Figure 46-4 The loss and return of α activity as the eyes open and close can be seen. The large spikes are muscle artifact.

frequency that are unpredictable or unexpected in the normal recording. These abnormal patterns reflect either anatomic or metabolic alterations in the underlying brain. Regional asymmetry can be seen with tumors, epilepsy, and cerebral ischemia or infarction. Epilepsy may be recognized by high-voltage spike and slow waves, whereas cerebral ischemia manifests first with EEG slowing with preservation of voltage. Further slowing and loss of voltage occurs as ischemia becomes more severe. Factors affecting the entire brain may produce symmetric abnormalities of the signal. Identifying pathologic abnormal patterns in the global EEG signal is very important, although sometimes quite difficult, in the clinical situation. Many of the normal global pattern changes produced by anesthetic drugs are similar to pathologic patterns produced by ischemia or hypoxemia. Control of anesthetic technique is very important when the EEG is being used for clinical monitoring of the nervous system.

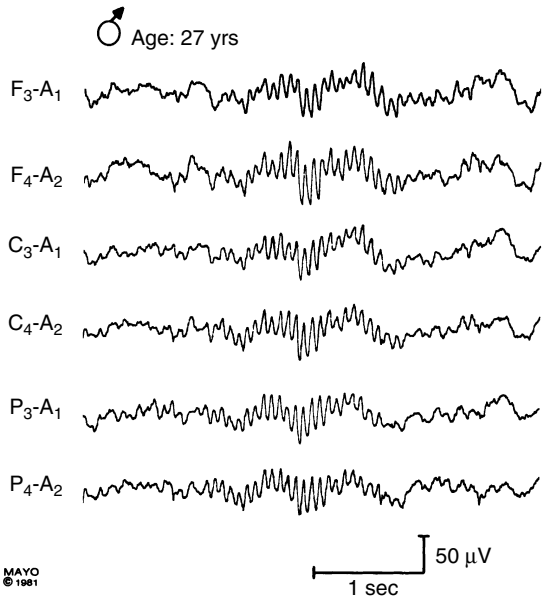

Figure 46-5 Characteristic sleep spindles in normal sleep are shown in the center.

Processed Electroencephalogram Concepts. Interpretation of the standard paper EEG tracing is a science and an art. Until the last quarter of the 20th century, the paper EEG was used during intraoperative monitoring with the technologist relying on memory of the baseline and on experience to determine when significant EEG changes occurred. This qualitative approach was used simply because the waveforms could not be described mathematically in a time frame that would make such information of any practical use. Computer hardware has dramatically improved in speed and size, and real-time signal processing is now possible and commonly used.

Numerous limitations are introduced when moving from the raw EEG domain to the processed EEG domain. First, artifact is processed in many cases along with desired signal leading to a perfectly believable processed EEG display that is materially incorrect. Second, the standard 16-channel EEG montage provides more information than can be practically analyzed or displayed by most processed EEG monitors and perhaps more than is needed for routine intraoperative use. Most available processed EEG devices used by anesthesiology personnel use four or fewer channels of information—translating to at most two channels per hemisphere. Processed EEG devices generally monitor less cerebral territory than a standard 16-channel EEG. Third, some intraoperative changes are unilateral (e.g., regional ischemia owing to carotid clamping), and some are bilateral (e.g., EEG depression by bolus administration of an anesthetic). Display of the activity of both hemispheres is necessary to delineate unilateral from bilateral changes. An appropriate number of leads over both hemispheres is needed. Most early studies validating intraoperative EEG monitoring used continuous visual inspection of a 16- to 32-channel analog EEG by an experienced electroencephalographer—such monitoring was considered the gold standard.[35,36] Adequate studies comparing the processed EEG with fewer channels with this gold standard across multiple uses and operations have not been done, although limited data using processed EEG

monitoring during carotid surgery suggest that two- or four-channel instruments would detect most significant changes,[37,38] provided that the electrodes are appropriately placed over watershed areas of blood supply.

Devices. Two basic forms of EEG processing are used currently: power analysis and bispectral analysis. Power analysis uses Fourier transformation to convert the digitized raw EEG signal into component sine waves of identifiable frequency and amplitude. The raw EEG data, which is a plot of voltage versus time, is converted to a plot of frequency and amplitude versus time. Many commercially available processed EEG machines display power (voltage or amplitude squared) as a function of frequency and time. These monitors display the data in two general forms, either compressed spectral array or density spectral array. In compressed spectral array, frequency is displayed along the *x* axis, and power is displayed along the *y* axis with height of the waveform equal to the power at that frequency. Time is displayed along the *z* axis. Tracings overlap each other, with the most recent information in front (Fig. 46-6). Density spectral array also displays frequency along the *x* axis; time is displayed along the *y* axis, and power is reflected by the density of the dots at each frequency. Each display format provides the same data, and choice depends on the preference of the user.

Many changes that occur during anesthesia and surgery are reflected as changes in amplitude, frequency, or both. These changes can be clearly seen in these displays if adequate and appropriate channels are monitored. Power analysis has been used clinically for many years as a diagnostic tool during procedures with risk for intraoperative cerebral ischemia, such as carotid endarterectomy and cardiopulmonary bypass (CPB). Power analysis has proven to be a sensitive and reliable monitor in the hands of experienced operators using an adequate number of channels. In addition, parameters obtained from power analysis have been investigated as monitors for depth of anesthesia.[39-42] Although earlier attempts to use parameters derived from power analysis for assessment of anesthetic depth were largely unsuccessful, these same parameters are now used to varying degrees with much more success as a part of different algorithms (including BIS [Bispectral Index Score] and PSI [Patient State Index]) to measure hypnotic states.

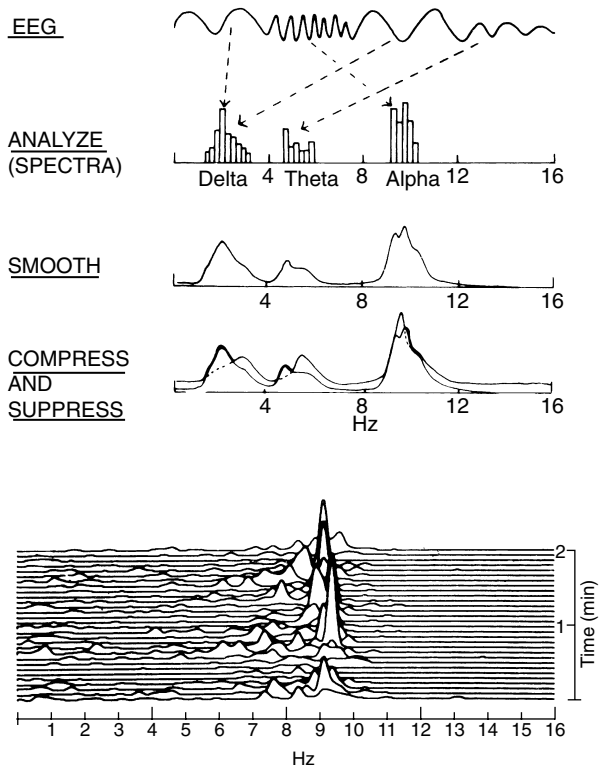

Figure 46-6 Diagram of technique used to generate compressed spectral array. Example at the bottom of the figure shows compressed spectra of the α rhythm from a normal subject. *(From Stockard JJ, Bickford RG: The neurophysiology of anaesthesia. In Gordon E [ed]: A Basis and Practice of Neuroanesthesia. New York, Elsevier, 1981, p 3.)*

Data Acquisition Period. An important consideration in the processed EEG is time. The standard paper or digital EEG is continuous in real time. The processed EEG samples data over a given time period (epoch), processes the data, and then displays information in various formats. There is a relationship between epoch length and spectral resolution. If a long epoch length is chosen, the waveform can be described precisely, but the time required for data processing is long and not real time. If a short length of data is sampled, analysis may be done in near real time, but the epoch chosen for analysis may not be representative of the overall waveform (i.e., the condition of the patient). There also may be insufficient data points for meaningful Fourier transformation. This issue, as related to the use of intraoperative EEG for analysis of anesthetic depth, has been studied by Levy.[43] A longer epoch may produce less epoch-to-epoch variability and allow more precise description of frequency and power; however, the longer epoch increases the delay before new information is processed and displayed, reducing the amount and timeliness of information available for clinical decision making. In studying EEG epochs of 2 to 32 seconds, Levy[43] concluded that 2-second epochs are appropriate during general anesthesia. Many commercially available devices have used 2-second epoch lengths, updated at varying user-selected intervals. With better and faster computers, continuous monitoring of 2-second epochs and now even longer epochs is possible.

Evoked Potentials

Basic Concepts Common to All Modalities. EEG signals provide information about cortical function, but little to no information about subcortical neural pathways crucial to normal neurologic function. Intraoperative monitoring of SERs has gained increasing popularity over the last 25 years because it provides the ability to monitor the functional integrity of sensory pathways in an anesthetized patient undergoing surgical procedures placing these pathways at risk. Because motor pathways are often adjacent anatomically to these sensory pathways or supplied by the same blood vessels, or both, function of motor pathways may be inferred, albeit imperfectly, from the function of these sensory pathways. Today, MEPs are ideally monitored together with SERs to provide direct information about function of motor pathways.

Sensory Evoked Responses. SERs are electric CNS responses to electric, auditory, or visual stimuli. SERs are produced by stimulating a sensory system and recording the resulting electric responses at various sites along the sensory pathway

up to and including the cerebral cortex. Because of the very low amplitude of SERs (0.1 to 10 μV), it is often impossible to distinguish SERs from other background biologic signals, such as the EEG or EMG, which may be considered in this case undesirable "noise." To extract the SER from the background noise, the recorded signal is digitized, and signal averaging is applied. With this technique, signal recording is time-locked to the application of the sensory stimulus. During intraoperative median nerve SER monitoring, after nerve stimulation at the wrist, only signal information occurring less than 50 msec after the stimulus is recorded. The SER occurs at a constant time after the stimulus application; other electric activity, such as spontaneous EEG, occurs at random intervals after the sensory stimulus. The averaging technique improves the SER signal-to-noise ratio by eliminating random elements and enhancing the SER. This enhancing effect increases directly with the square root of the number of responses added into the averaged response.

SER recordings are of two general types determined by the distance of the recording electrode from the neural generator of the evoked response. SERs recorded from electrodes close to the neural generators (within approximately 3 to 4 cm in the average adult) are termed "near-field potentials."[44] Near-field potentials are recorded from electrodes placed very close to the actual signal generator site,[45] and the morphology is directly affected by electrode location.[44] Far-field potentials are recorded from electrodes located a greater distance from the neural generator and are conducted to the recording electrode through a volume conductor (brain, cerebrospinal fluid, and membranes). As a result, it is more difficult to locate the source of the recorded signal (the current spreads diffusely throughout the conducting medium), and the electrode position has little effect on the morphology of the recorded evoked potential.[44,45] As the distance between the recording electrode and the neural generator increases, the recorded SER becomes smaller. More responses have to be averaged to record far-field potentials (several thousand) than near-field potentials (50 to 100).[44,45]

SERs also may be described as cortical or subcortical in origin. Cortical SERs are generated by the arrival at the cortex of the volley of action potentials generated by stimulating the sensory system. Because they are recorded as a near-field potential, they are typically easy to identify by elapsed time, waveform morphology, and amplitude. Subcortical responses may arise from many different structures depending on the type of response, including peripheral nerves, spinal cord, brainstem, thalamus, cranial nerves, and others. Cortical SERs are usually recorded from scalp electrodes placed according to the standard 10-20 system for EEG recordings (see Fig. 46-3). Subcortical evoked responses also may be recorded as far-field potentials from scalp electrodes or, as appropriate, from electrodes placed over the spinal column or peripheral nerve.

Evoked potentials of all types (sensory or motor) are described in terms of latency and amplitude (Fig. 46-7). Latency is defined as the time measured from the application of the stimulus to the onset or peak (depending on convention used) of the response. The amplitude is simply the voltage of the recorded response. According to convention, deflections below the baseline are labeled "positive (P)," and deflections above the baseline are labeled "negative (N)." Because amplitude and latency change with recording circumstances, normal values must be established for each neurologic monitoring laboratory, and may differ from values recorded in other laboratories.

SERs used for intraoperative monitoring include SSEPs, BAEPs, and rarely VEPs. For all these techniques, cortical recording electrodes are placed on the scalp, using the same standard 10-20 system as for recording the EEG, whereas recordings for subcortical and peripheral signals are placed in various standardized anatomic locations. The surgical incision and the need for sterility may necessitate nonstandard electrode placements. Such deviations must be considered when interpreting baseline and subsequent SERs. In the case of MEPs, stimulating electrodes also are placed according to the 10-20 system of electrode placement, but over motor cortex instead. Recording electrodes may be

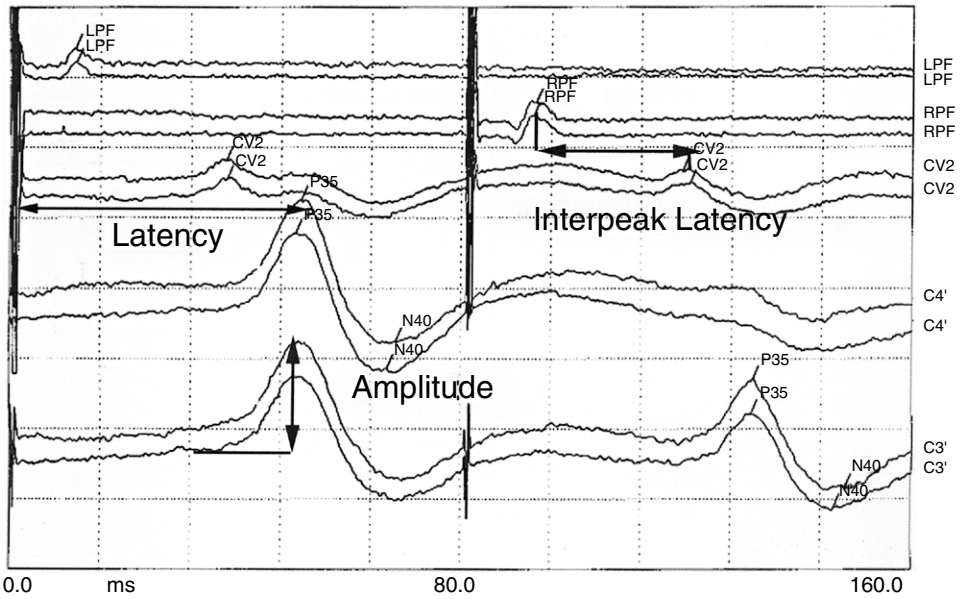

Figure 46-7 Sensory evoked responses are described in terms of latency and amplitude. Interpeak latency is the measured time between two peaks. Interpeak latency may be measured between two peaks in the same channel or between peaks in different channels (shown in figure). Note that the polarity of peaks is displayed contrary to standard convention (see text).

placed over the spinal column, peripheral nerve, and (most commonly) innervated muscle.

Intraoperative changes in evoked responses, such as decreased amplitude, increased latency, or complete loss of the waveform, may result from surgical trespass, such as retractor placement or ischemia, or they may reflect systemic changes, such as changes in anesthetic drug administration, temperature changes, or hypoperfusion. When these changes are detected and considered to be significant, the surgeon or anesthesiologist can make changes to relieve or lessen the insult to the monitored pathway (and presumably surrounding neural structures). Interventions by the anesthesiologist are directed at improving perfusion to the nervous tissue at risk and include increasing arterial blood pressure, especially if induced hypotension is used, or if the patient's pressure has decreased to below the preoperative level; transfusion, if significant anemia is present; volume expansion; augmentation of cardiac output; and normalization of arterial blood gas tensions if indicated. Changes in evoked potentials after retractor placement during a craniotomy or after compression of the blood supply to the spinal cord from spinal column distraction promptly allow the surgeon and the anesthesiologist to make appropriate changes to the operative procedure and anesthetic management that may prevent or minimize any postoperative neurologic deficit (Fig. 46-8).

Tolerance limits for degree of change in evoked response signals or duration of complete loss of waveform before permanent neurologic dysfunction occurs are not clearly defined, and this problem is especially true for transcranial MEPs. Such ambiguity is common among intraoperative monitors. Although we do know that increased frequency and duration of ST segment depression during coronary bypass surgery is associated with an increased risk of perioperative infarction, exact limits for degree and duration of ST segment depression for surgery do not exist, and likely vary significantly from patient to patient. The same problem may be exhibited with neurologic monitors.

Many centers using intraoperative SER monitoring define decreases in amplitude of 50% or more from baseline associated with a less than 10% prolongation in latency as clinically significant SER changes. Uncorrected, such changes are associated in clinical series and in case reports with onset of new postoperative neurologic deficits. As a result, such changes are immediately investigated. In practice, any SER changes directly associated with a surgical event are considered clinically significant, however, even if the magnitude of change is less than just described. Changes in SER that do not progress to complete loss of the waveform are less likely to be associated with a major new postoperative neurologic deficit. Complete loss of the SER waveform intraoperatively without recovery is highly likely to be associated with a major new deficit. If the SER recovers either spontaneously or after intraoperative interventions, the likelihood of neurologic injury depends on the procedure, the duration of the SER loss, and on whether the SER is mainly used to judge integrity of

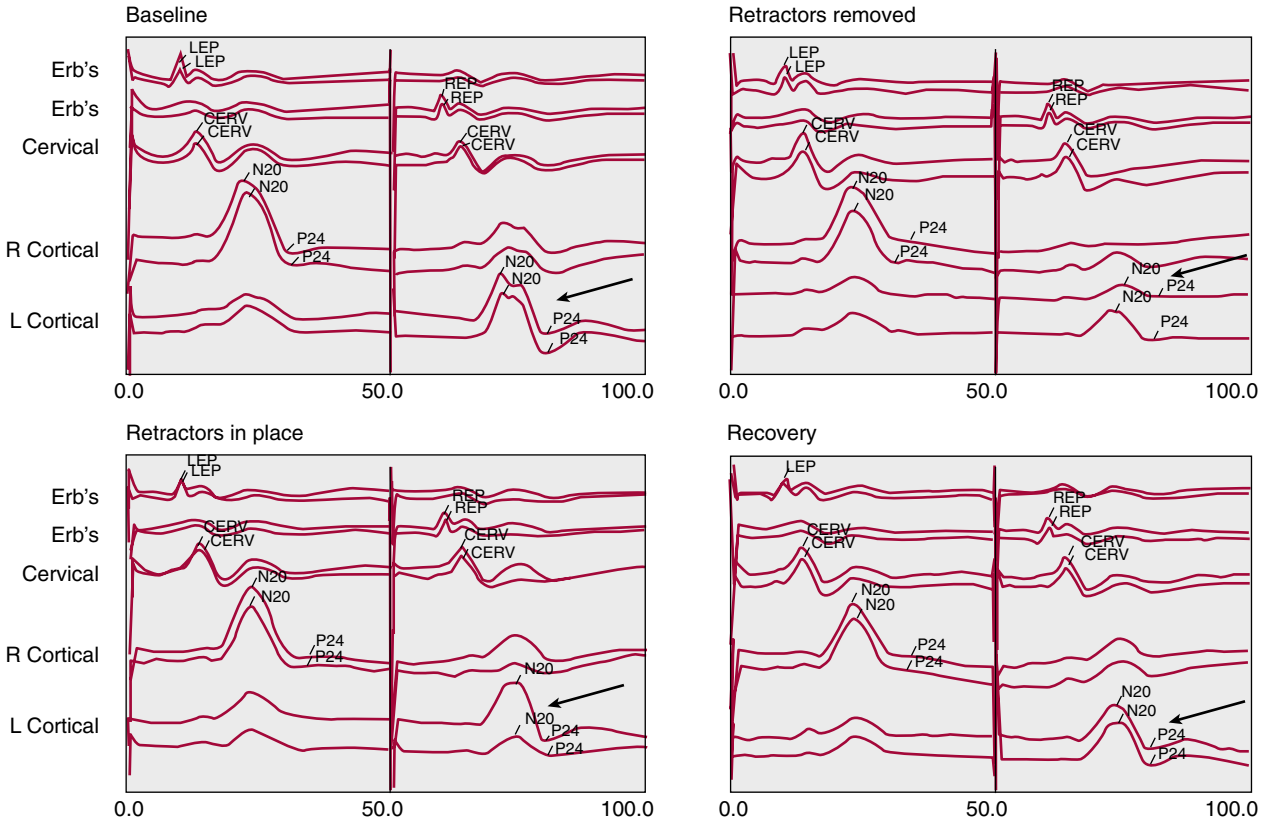

Figure 46-8 Somatosensory evoked potentials during an aneurysm clipping. Responses generated by the cortex at risk are indicated by *arrows*. Baseline, after retractor placement, after retractor removal, and recovery traces are shown. The initial evoked response change occurred 4 minutes after retractor placement. Note loss of voltage of cortical evoked response caused by inadvertent compression of the middle cerebral artery.

adjacent unmonitored structures. In one study of aortic vascular surgery in which SSEPs were monitored, loss of the SSEP waveform for less than 15 minutes was not associated with a new permanent neurologic deficit, whereas complete loss of the SSEP for longer periods was increasingly likely to reflect permanent neurologic injury, even if the response recovered completely to its intraoperative baseline during surgery.[46]

One of the most important principles of recording SERs intraoperatively is that reproducible, reliable tracings must be obtained at baseline before any intervention likely to cause changes in the evoked response. If good quality tracings with identifiable waveforms cannot be recorded and reproduced at baseline, evoked response monitoring would be of little use in monitoring the integrity of the CNS intraoperatively. If significant variability exists, or waveforms are difficult to identify, it would be impossible intraoperatively to distinguish SER changes that are clinically significant from a preexisting baseline variability of waveforms. When good, reproducible responses cannot be recorded at baseline, monitoring should not be used for clinical decision making.

Somatosensory Evoked Potentials. SSEPs are recorded after electric stimulation of a peripheral mixed nerve. Stimulation is provided most commonly with surface electrodes (e.g., electrocardiogram electrodes) placed on the skin above the nerve or with fine needle electrodes. A square wave stimulus of 50 to 250 μsec duration is delivered to the peripheral nerve, and the intensity is adjusted to produce a minimal muscle contraction. Increasing the stimulus intensity beyond the sum of the motor and sensory threshold does not influence the amplitude or latency of the recorded evoked potential. On a practical basis, however, many laboratories do not establish SSEP monitoring until after the patient is already anesthetized and paralyzed. In these cases, stimulus intensity is increased until no further increase in response size occurs at any recording site, typically constant current stimulation of 20 to 50 mA. For comparison, consider supramaximal stimulation used for the neuromuscular blockade monitor, commonly 80 mA. The rate of stimulation varies from 1 to 6 Hz. The common sites of stimulation include the median nerve at the wrist, the common peroneal nerve at the knee, and the posterior tibial nerve at the ankle.[47]

SSEP responses consist of short-latency and long-latency waveforms. Cortical short-latency SSEPs are most commonly recorded intraoperatively because they are less influenced by changes in anesthetic drug levels. The pathways involved in the generation of upper extremity short-latency SSEPs include large-fiber sensory nerves with their cell bodies in the dorsal root ganglia and central processes traveling rostrally in the ipsilateral posterior column of the spinal cord synapsing in the dorsal column nuclei at the cervicomedullary junction (first-order fibers), second-order fibers crossing and traveling to the contralateral thalamus via the medial lemniscus, and third-order fibers from the thalamus to the frontoparietal sensorimotor cortex. These primary cortical evoked responses, which are recordable with most anesthetic techniques, result from the earliest electric activity generated by the cortical neurons and are thought to arise from the postcentral sulcus parietal neurons. The longer latency secondary cortical waves are thought to arise in the association cortex. These responses have much greater variability in an awake patient,[45] habituate rapidly on repetitive stimulation,[44] and are only poorly reproducible during general anesthesia. Cortical SSEPs other than the primary cortical response are not monitored or interpreted intraoperatively because they are severely altered by general anesthesia.[44]

Although most evidence indicates that upper extremity evoked potentials are conducted rostrally in the spinal cord via dorsal column pathways, much data suggest that lower extremity SSEPs are conducted substantially by the lateral funiculus.[48] Stimulation of the posterior tibial nerve or common peroneal nerve at or above motor threshold activates group I fibers that synapse and travel rostrally through the dorsal spinocerebellar tract. After synapsing in nucleus Z at the spinomedullary junction, the pathway crosses and projects onto the ventral posterolateral thalamic nucleus.[49] Studies with dogs, cats, and monkeys support the concept that lower extremity SERs are conducted in all quadrants of the spinal cord, but primarily in the dorsal lateral funiculus.[50,51] This pathway difference is important because the dorsal lateral funiculus is supplied primarily by the anterior spinal artery, the artery that also supplies the descending motor pathway and neurons in the spinal cord. Manipulations, such as distraction of the spinal column to correct scoliosis, which may secondarily compress or distort radicular blood supply to the anterior spinal cord, should cause changes in the SSEP in the event blood supply is reduced to critical levels. This hypothesis is verified by the very low, but not zero, incidence of postoperative paraplegia on awakening without any intraoperative changes in SSEPs.

For SSEP recordings with median nerve stimulation, recording electrodes (usually electrocardiogram pads) are first placed at Erb's point, just above the midpoint of the clavicle. This point overlies the brachial plexus, and signals recorded here assure the clinician that the stimulus is actually being delivered properly to the patient. The next electrode (either an electrocardiogram pad or a gold cup electrode) is placed midline posteriorly over the neck at level of the second cervical vertebra, relatively near the dorsal column nuclei. Signals recorded here ensure proper transmission of the response from the peripheral nervous system into the spinal cord and rostral along the spinal cord to the lower medulla. The final electrodes (gold cup electrodes or needle electrodes) are placed on the scalp overlying the sensory (parietal) cortex contralateral to the stimulated limb. Signals recorded here ensure the integrity of the pathway through the brainstem, thalamus, and internal capsule, and may assess adequacy of CBF in this area of the cortex.[52-56]

To record SSEPs after posterior tibial nerve stimulation, electrodes (electrocardiogram pads) are placed first over the popliteal fossa to ensure proper stimulus delivery to the nervous system. Electrodes also may be placed over the lower lumbar spine to ensure proper transmission of the signal into the spinal cord itself, but this site is not commonly used because of the proximity of sterile surgical incisions. Cervical spine and scalp recording electrodes are placed in a similar fashion as described previously, although different locations may be used as required by the placement of the surgical incision. More invasive recording methods, such as epidural electrodes, also may be used intraoperatively.

Purported generators for short-latency SSEPs are listed in Table 46-1 and shown in Figure 46-9.[44,47] Induction of anesthesia and use of different recording electrode locations (montage), necessitated by the surgical incision, may significantly alter the appearance of the SSEP. In these cases, attribution of a particular generator to a given wave on the tracing may be quite difficult. During neurologic monitoring, such precision is not needed, and

Table 46-1 Generators of Somatosensory Evoked Potentials after Median Nerve Stimulation

Peak	Generators
N9 (EP)	Brachial plexus*
N11	Posterior columns or spinal roots
N13/P13	Dorsal column nuclei*
N14, 15	Brainstem or thalamus
N19/P22	Parietal sensory cortex*

*Indicates sites commonly recorded during surgery. All other waveforms indicated are not commonly monitored.

recorded waveforms are compared with tracings obtained at baseline and during earlier portions of the surgical procedure. After lower limb stimulation, absolute latencies are increased because of the greater distance the response to stimulation must travel along the peripheral sensory nerve and spinal cord. Interpeak latencies (see Fig. 46-7) also are evaluated to assess specific conduction times, such as N9 to N14 conduction time, reflecting transmission time from the brachial plexus to brainstem, or N14 to N19 conduction time, reflecting transmission time between the dorsal column nuclei and the primary sensory cortex.[57]

Brainstem Auditory Evoked Potentials. BAEPs are produced in the diagnostic laboratory by delivering repetitive clicks or tones via headphones. Headphones are not practical for surgical monitoring of neurosurgical procedures, and click stimuli are delivered using foam ear inserts attached to stimulus transducers (Fig. 46-10). Stimulus intensity is usually set at 60 to 70 dB above the patient's click-hearing threshold, although, practically speaking, many intraoperative laboratories establish monitoring after induction of anesthesia and instead begin with a stimulus intensity of 90 dB nHL (normal hearing level). The duration of the click is approximately 100 μsec, and the stimulus is given usually 10 to 15 times per second. Clicks are delivered using different "polarities"—that is, the click may cause initial movement of the tympanic membrane away from the transducer (rarefaction) or toward the transducer (condensation). Use of these two different methods commonly produces very different waveforms, amplitudes, and latencies in individual patients, and the method that produces the largest reproducible response is chosen. If stimulus artifact is a serious problem, clicks of alternating polarity may be used to decrease the artifact, but the waveforms produced are an average of those produced by either stimulating technique alone and may be more difficult to monitor.

Rate and intensity of stimulus delivery affect BAEPs.[44,58] Unilateral stimulation is used because responses from the other ear, which may remain normal during surgery, may obscure any abnormal responses from the monitored ear. Recording electrodes (usually gold cup electrodes) are placed on the lobe of the stimulated ear and on the top of the head (vertex).[58] White noise commonly may be delivered to the contralateral ear to prevent bone conduction from stimulation of the monitored ear from producing an evoked response from the contralateral ear. On average, 500 to 2000 repetitions are required because BAEPs recorded from the scalp are far-field potentials and extremely small (often <0.3 μV).[44,58]

Peaks in recordings of BAEPs are labeled I through VII; the purported neural generators for these peaks and the auditory pathway are shown in Figure 46-11. The anatomic auditory pathway would predict that BAEP monitoring would be most useful for surgical procedures in the posterior fossa that risk hearing or structures in the upper medulla, pons, and midbrain. As with other SERs, amplitude, absolute latencies, and interpeak latencies are evaluated to assess integrity of the auditory system,

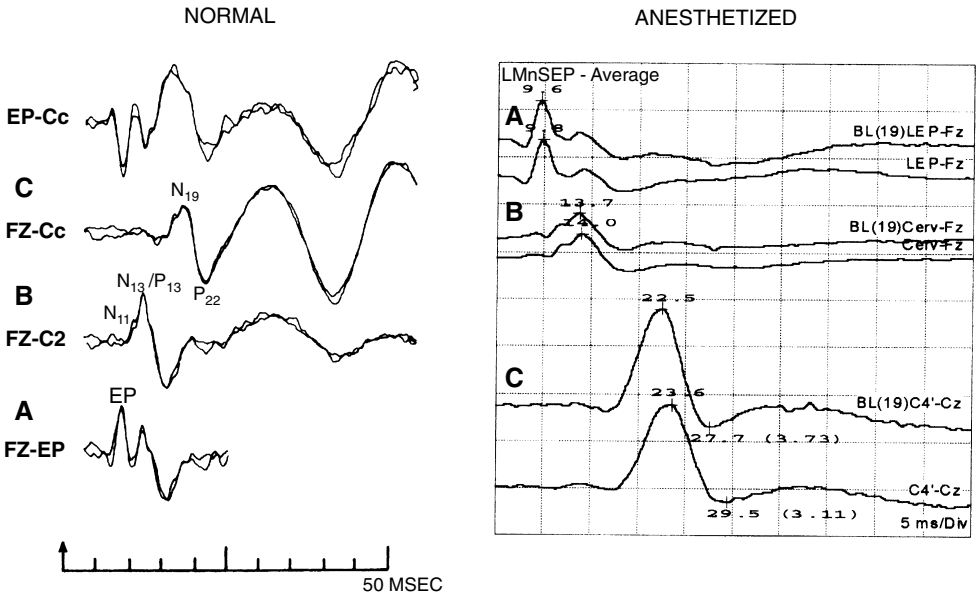

Figure 46-9 Short-latency somatosensory evoked potentials produced by stimulation of the median nerve at the wrist. The ability to identify each of the labeled peaks shown in the tracing from the awake patient is compromised by the anesthetic state and use of different recording electrode locations (**A** to **C**). Corresponding tracings are labeled with the same letter. *(From Chiappa KH, Ropper AH: Evoked potentials in clinical medicine. N Engl J Med 306:1205, 1982.)*

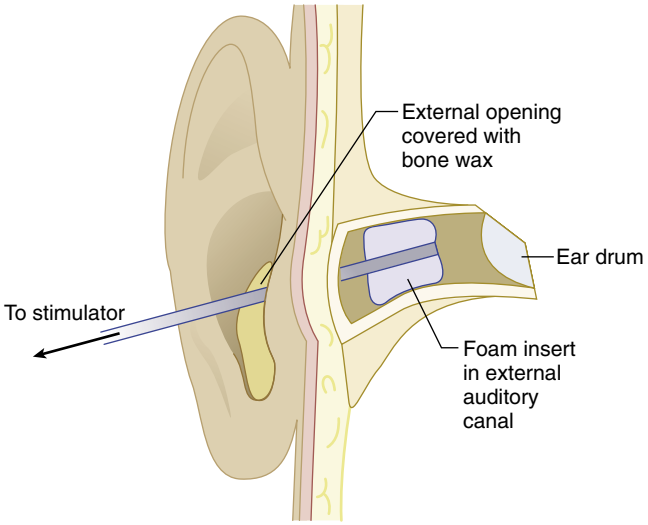

Figure 46-10 Schematic of brainstem auditory evoked potential stimulating apparatus. Loud click stimuli are delivered directly to the eardrum through the ear insert.

localize the functional defect when it occurs, and assess peripheral and central conduction times. Because waves VI and VII are inconsistent and variable, they are not routinely monitored,[58] and most articles reporting use of BAEP for surgical monitoring in the operating room monitor waves only up to wave V.[59-61]

Visual Evoked Potentials. VEPs are recorded after monocular stimulation with recording electrodes over the occipital, parietal, and central scalp.[60] Flash stimulation of the retina using light-emitting diodes embedded in soft plastic goggles through closed eyelids or as needed via contact lenses with built-in light-emitting diodes is provided. VEPs are cortical SERs, which vary with the type of stimulus, part of the retina stimulated, degree of pupil dilation, and patient's attention level.[44] Because some of these factors change commonly and even constantly during the course of every anesthetic, VEPs would be expected to be highly variable during surgery even when no surgical trespass on the visual system occurs. VEPs are the least commonly used evoked response monitoring technique intraoperatively.

Motor Evoked Potentials. MEPs are generated most commonly by the application of a transcranial train of electric stimuli, and responses are recorded at various points along the spinal column, peripheral nerve, and innervated muscle.

Transcranial Motor Evoked Potentials. Monitoring of the integrity of the motor tracts within the spinal cord is a technique with great potential benefit, and even during the relative short history of MEP monitoring, there are reported cases of loss of MEPs with preservation of the SSEP.[62-67] This technique has potential applications in spinal surgery, in which transmission across the operative field can be assessed, and in aortic surgery, with the potential for impairment of the blood supply to the vulnerable anterior spinal cord. Relative to SER monitoring, MEP monitoring is quite invasive and, in the case of transcranial stimulation, uses much higher stimulus intensity (≥400 V).

Several variants of MEP monitoring exist. The first method involves transcranial stimulation, either electric or magnetic. During transcranial electric MEP monitoring, stimulating electrodes (usually small, metallic screw-type electrodes similar to those used in fetal monitoring) are placed into the scalp overlying the motor cortex, and a train of electric stimuli (usually around 400 to 500 V) is applied to the scalp. This stimulation definitely activates muscles of mastication, and bite-blocks must be placed to prevent serious damage to the tongue during stimulation. During magnetic stimulation, a powerful magnetic stimulator is placed on the scalp over the motor cortex. Magnetic stimulation is more difficult for two reasons. First, the magnetic stimulator must be fixed to the head to prevent movement because even a slight movement of the stimulator can substantially alter the

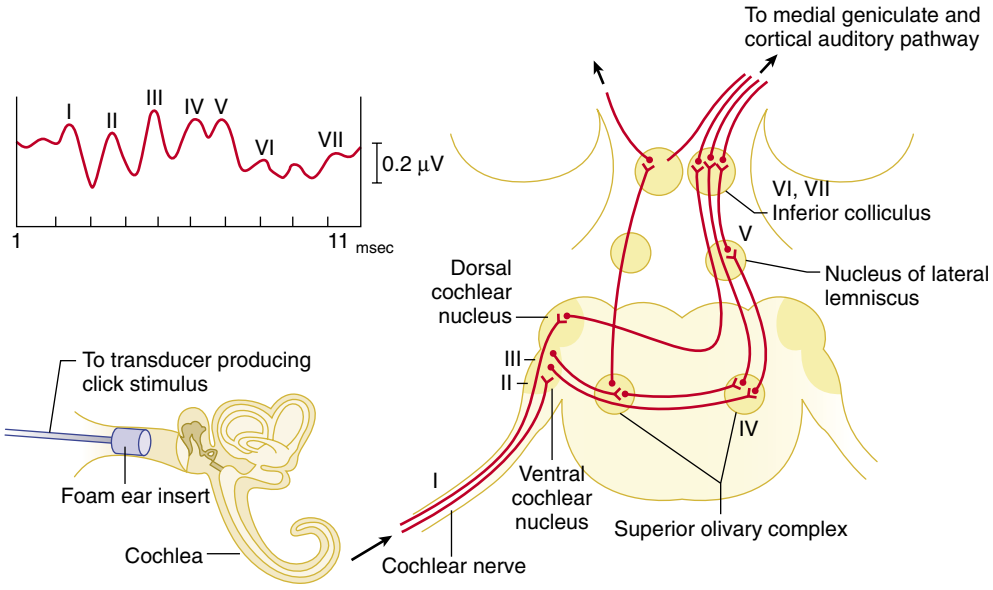

Figure 46-11 Schematic of auditory neural pathway. The brainstem auditory evoked potential is initiated by stimulation of the cochlea with a broadband click stimulus given via an ear insert in the external auditory canal. Neural generators of the brainstem auditory evoked potential peaks are shown.

stimulus applied to the motor cortex. Second, the stimulator is quite large and cannot practically be used intraoperatively if a craniotomy is performed. Brief repetitive applications of electric current or a strong magnetic field induce current in the motor cortex and produce an MEP.

These transcranial stimulating methods also may activate surrounding cortical structures and subcortical white matter pathways (sensory and motor). Distal antidromic propagation of the transcranially applied stimulus is blocked by synapses in all of the ascending sensory pathways. The stimulus is propagated easily orthodromically via descending motor pathways. The evoked responses may be recorded over the spinal cord, the peripheral nerve, and, most commonly, the muscle itself. To enhance the MEP, these responses may be averaged in the same manner as SERs, but averaging is almost always unnecessary.

Spinal Motor Evoked Potentials. Another method of producing the MEP involves electric stimulation of the spinal cord itself above the area of the cord at risk during surgery. Responses may be recorded over the distal spinal cord, peripheral nerve, and muscle.[68-70] Responses are recorded distally, usually over the peripheral nerve, and profound surgical muscle relaxation is used to prevent gross movement during surgery. This type of MEP is called a "neurogenic" MEP. Initially, investigators believed that this response, recorded over a peripheral nerve in the lower extremity (typically the tibial nerve in the popliteal fossa), was generated by stimulation of the descending motor tracts, activation of the anterior horn cells, and propagation of the nerve action potential via the peripheral nerve. Multiple clinical trials were conducted using this technique and comparing results of MEP monitoring with the SSEP with good results.[68-70] These responses also have the advantage that they do not show the same sensitivity to anesthetics that SSEPs do and may be recorded with any anesthetic technique.

Subsequent studies in animals and humans[71] have shown that neurogenic MEPs are, at best, mixed responses with a significant component of an antidromically conducted response along the sensory pathway. Stimulation of the dorsal column results in an antidromically conducted recordable signal peripherally because the somesthetic system does not synapse in the dorsal root ganglion, and fibers pass directly from the dorsal column through the cell body in the ganglion into the peripheral nerve. Because of this problem, use of neurogenic MEP monitoring has decreased significantly, replaced by the more invasive transcranial stimulation techniques, which produce responses that are exclusively produced by activation of the motor system.

Electromyography. Intraoperative monitoring of EMG responses generated by cranial and peripheral motor nerves allows early detection of surgically induced nerve damage and assessment of level of nerve function intraoperatively. In these cases, the ability of a nerve to produce a response in the innervated muscle is used to assess the health of a cranial or peripheral nerve at risk during surgery. Recordings are made from either surface (electrocardiogram or gold cup) electrodes or needle electrodes placed directly in the innervated muscle of interest. The most experience with this monitoring modality has been obtained during facial nerve monitoring.

EMG monitoring may be either active or passive. During active monitoring, a cranial or peripheral nerve is stimulated electrically, and the evoked EMG (compound muscle action potential) response from the muscle is recorded. Stimulation of the nerve proximal to the operative area or tumor can be used to assess functional integrity of the nerve.[72] Nerve function also may be assessed by noting the intensity of nerve stimulus needed to evoke a muscle response and by the morphology of the compound muscle action potential. Nerve function may be monitored passively during surgery with continuous recording of all generated responses from innervated muscle groups. "Popcorn" EMG discharges are produced by simple, benign contact with the monitored nerve. Response trains are produced with more significant nerve irritation. Neurotonic discharges are produced by significant nerve irritation or damage or both (Fig. 46-12).[72] These EMG responses, when they reach a certain voltage threshold, are usually converted into audible signals that provide immediate feedback to the surgeon and warn of impending nerve damage in real time. Real-time feedback is key because density and frequency of neurotonic discharges may correlate with degree of postoperative nerve dysfunction, as shown by data obtained from patients undergoing resection of acoustic tumors.[73]

Intraoperative monitoring of the motor component of other cranial nerves also has been successfully performed. EMG monitoring of the trigeminal nerve can be accomplished with electrodes placed over or in the temporalis or masseter muscles. Trigeminal nerve motor monitoring has been used during nerve section for tic douloureux to ensure preservation of the motor branch of the trigeminal nerve and in combination with facial nerve monitoring during resection of large posterior fossa lesions.[72] Using recording electrodes placed in or over the trapezius or sternocleidomastoid muscles, the spinal accessory nerve has been successfully monitored during resection of large meningiomas, glomus jugulare tumors, and neck carcinomas.[72] EMG monitoring of the hypoglossal nerve with needle electrodes placed in the tongue has been infrequently used for large posterior fossa lesions and clivus tumors.[72] Although EMG monitoring of the eye muscles can be performed using tiny hook wires for recording, it is rarely used.

Monitoring of peripheral motor nerves has been performed by placing needle electrodes in or over the muscles innervated by

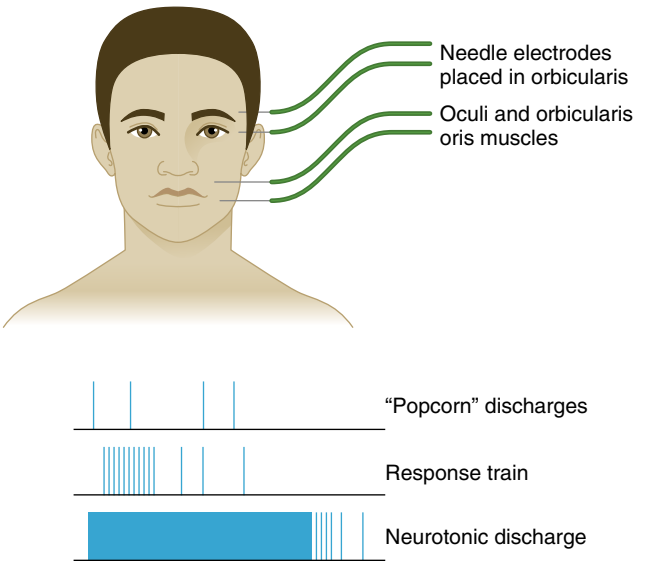

Figure 46-12 Schematic of facial nerve monitoring and typical responses seen during surgery.

nerves that traverse the operative area and are at risk from the planned surgical procedure. Auditory feedback from EMG monitoring can warn the surgeon of unexpected surgical trespass of the nerve, help locate a nerve within the field (e.g., during untethering of the spinal cord), and localize the level of any conduction block or delay. Because radiculopathies have been reported to occur after spine surgery, EMG monitoring of peripheral nerves has been used in patients undergoing spine surgery to decrease the risk of nerve root injury during the procedure.[72]

Clinical Applications of Neurologic Monitoring

Neurovascular Surgery (also see Chapter 63)

Extracranial Neurovascular Surgery: Carotid Vascular Surgery (Monitors: EEG, SSEPs, TCD, Cerebral Oximetry)

Electroencephalogram. The use of the EEG as a monitor of the adequacy of CBF during carotid endarterectomy has been established for many years. In a large series of patients undergoing carotid endarterectomy at the Mayo Clinic,[36] the EEG was compared with regional CBF using the ^{133}Xe washout method. This study validated the EEG as an indicator of the adequacy of regional CBF.

Normal CBF in gray and white matter averages 50 mL/100 g/min. With most anesthetic techniques, the EEG begins to become abnormal when CBF decreases to 20 mL/100 g/min. The threshold for EEG changes apparently is much lower (8 to 10 mL/100 g/min), however, when isoflurane is used.[74] Cellular survival is not threatened until CBF decreases to 12 mL/100 g/min (lower with isoflurane). The difference in blood flow between when the EEG becomes abnormal and the blood flow at which cellular damage begins to occur provides a rational basis for monitoring the EEG during carotid surgery. In many cases, prompt detection of EEG changes may allow intervention (e.g., shunting, increasing cerebral perfusion pressure) to restore CBF before onset of permanent neurologic damage. Standard hemodynamic monitoring provides no direct information about the adequacy of CBF. Blood pressure is not a specific indicator of the adequacy of CBF. Significant hypotension is not predictably associated with EEG evidence of cerebral ischemia. Severe anemia and decreases in oxygen saturation also decrease oxygen delivery. EEG activity becomes abnormal when increased blood flow cannot compensate for decreased arterial oxygen content.

Serious intraoperative reduction in cerebral oxygen supply may result from surgical factors (e.g., carotid cross-clamping) that are usually beyond the anesthesiologist's control, and from factors that the anesthesiologist can correct. Reduction in CBF produced by hyperventilation, hypotension, or temporary occlusion of major blood vessels may be corrected by reducing ventilation, by restoring normal blood pressure, or, in the case of temporary vessel occlusion, by increasing blood pressure above normal. Because the EEG may readily detect cerebral ischemia, continuous EEG monitoring may be used to evaluate the effectiveness of therapy instituted to correct ischemia.

If monitoring of the EEG could be proved scientifically to reduce the incidence of stroke during carotid vascular surgery, EEG monitoring would be established as a standard of care. Definitive data showing stroke reduction do not yet exist, however, and given the number of patients required to power a trial that would show a reduction in stroke rate from 2% to 1%, such studies are unlikely to be funded or forthcoming. What data are available do not provide a basis to recommend universal use of EEG monitoring during carotid surgery. In a large series of patients undergoing carotid endarterectomy with selective shunting who were monitored with 16-channel unprocessed EEG, no patient awakened with a new neurologic deficit that was not predicted by EEG.[75] Transient, correctable EEG changes were not associated with stroke. Persistent changes were associated with stroke. This study had no comparison group, however, analyzing stroke rate when EEG monitoring was not used during surgery.

In the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial, retrospective comparison of patients receiving EEG monitoring and patients not receiving EEG monitoring failed to show a significant difference in outcome.[76,77] Because the EEG detects reductions in CBF that would not otherwise be apparent in unmonitored patients, and permits intervention that may correct the problem (usually placing a shunt or increasing blood pressure), EEG monitoring should logically be useful in reducing the incidence of stroke when selective shunting is used. Data available from studies at this time bring us no closer to resolving this question, however, than we were 30 years ago. Advocates of monitoring and individuals who believe monitoring is of no value can cite multiple studies supporting each viewpoint.

Even more difficult to prove is that EEG monitoring is useful when all patients are shunted during carotid clamping. Such monitoring has detected correctable shunt malfunction, and investigators have described hypotension-related EEG changes in patients with critical stenoses and poor collateral circulation.[78] Advocates of selective shunting based on EEG (or other monitoring) criteria claim that inserting a shunt unnecessarily through a region of diseased vessel would surely increase embolization. A multicenter study of 1495 carotid endarterectomies provides some evidence that shunting of patients without evidence of decreased cerebral perfusion increases the incidence of stroke more than sixfold.[79] Although this study and other more recent studies[80-82] advocate that selective shunting using some form of monitoring of the adequacy of CBF should improve perioperative stroke rate, an analysis by the Cochrane Stroke Group[83] failed to show sufficient evidence to advocate for routine shunting, selective shunting, or even no shunting at all. Until compelling studies addressing this issue are done, it is unlikely that EEG monitoring during carotid vascular surgery would become a standard method.

Processed EEG also has been used during carotid vascular surgery. Two issues affect the efficacy and reliability of processed EEG as a monitor for cerebral ischemia. First, what is the minimum number of channels (or areas of the brain) to be monitored? The 16-channel unprocessed EEG is a reliable and sensitive monitor for intraoperative cerebral ischemia during carotid endarterectomy. In a series of more than 2000 patients monitored with 16-channel EEG at the Mayo Clinic, there were no false-negative EEGs[75]; in other words, no patient had undetected intraoperative cerebral injury. In operating rooms where carotid surgery is performed, however, 16-channel EEG monitored by a dedicated technician is unavailable. Processed EEG using less than 16 channels is used much more commonly. Clinical experience and clinical

investigations suggest that four channels (two per side) are the minimum number of channels for adequate sensitivity and specificity.[37] When a limited number of channels were compared with 16-channel EEG monitoring, 100% sensitivity and specificity were obtained using 2 channels per hemisphere, provided that those channels monitored the middle cerebral artery territory. These results were obtained with a frontoparietal channel combined with a frontotemporal channel.[37]

The second issue is the experience level of the observer monitoring the processed EEG. Is a dedicated, experienced technician or electroencephalographer needed? In a study addressing this question, the 16-channel unprocessed EEG monitored by a dedicated technician was compared with a processed EEG reviewed by three anesthesiologists of differing levels of experience with processed EEG.[38] The three anesthesiologists interpreted the tracings without knowledge of the case. They were presented only with the written trace with an indication of the point at which the carotid artery was clamped. In these cases, the most important interpretation pitfall to avoid is the "false-negative" pattern. If the clinician interprets the EEG as showing adequate CBF when in fact it does not, the surgeon may fail to shunt an ischemic patient. A false-positive result may be less of a problem because that patient is not ischemic but is given a shunt anyway. In this case, only the risk of emboli from the "unnecessary" shunt is incurred. The positive predictive value of the anesthesiologist correctly interpreting the trace as unchanged after clamping was 91% to 98%, which indicates that the device can be used by novice interpreters with fair accuracy to determine the presence of cerebral ischemia at the time of carotid occlusion. In this study, the review by the anesthesiologist was not done during the course of the procedure, but rather "off line," and does not address the issue of whether an anesthesiologist providing the intraoperative anesthetic management of the patient can provide adequate monitoring of the processed EEG simultaneously.

EEG monitoring has limitations. Despite the data available from the Mayo Clinic, immediately evident postoperative strokes have been reported in patients without any evidence of EEG changes intraoperatively. In our experience, such strokes result from emboli via the lenticulostriate arteries to subcortical structures that do not generate or affect the EEG, but are critically involved in the descending motor pathway. Overall, such events are rare.

Should the patient undergoing carotid endarterectomy have EEG monitoring? That question cannot be answered based on any available data. EEG monitoring provides information about CBF that would not otherwise be available. The clinician has an opportunity to intervene to increase inadequate blood flow when it occurs. Anecdotally, many clinicians have found such monitoring useful and use it routinely. Population studies do not support routine use, and it is up to the clinician to decide whether to use it.

Somatosensory Evoked Potentials. SSEP monitoring also has been used to gauge adequacy of CBF to the cerebral cortex and subcortical pathways during carotid vascular surgery.[56,84,85] SSEPs have been found in the laboratory to have a similar but slightly lower threshold for failure compared with the EEG. SSEPs are generally intact until the cortical blood flow decreases to less than 15 mL/100 g/min.[54] In a few comparison studies with the EEG, a similar sensitivity and specificity for postoperative neurologic function was found. These studies involved few patients, however, and are inadequate to support the hypothesis that SSEP monitoring may substitute for EEG monitoring of the adequacy of CBF.[84-86] Logic also would suggest that changes in SSEP are unlikely, for example, with ischemia involving the anterior portions of either the frontal or temporal lobe, which could readily be detected by an appropriately placed EEG electrode. Finally, a more recent meta-analysis does not support the use of SSEPs during carotid vascular surgery as a sole monitor of neurologic function.[87] There is even less outcome evidence to support the use of SSEPs during carotid surgery than there is for the EEG, but the authors and others have found SSEPs to be useful as a simultaneous monitor with EEG to detect subcortical ischemia.

Transcranial Doppler. TCD monitoring during carotid vascular surgery is based on measurement of two primary parameters—blood flow velocity in major conducting arteries leading to the cerebral cortex (most commonly middle cerebral artery) and the number of emboli detected in the same artery. The hypothesis justifying the use of this monitoring during carotid vascular surgery has two components: blood flow velocity correlates with CBF, and increasing numbers of emboli increase the likelihood of emboli related cerebral ischemia or stroke. The first component has not been well tested and shows variable results. An early study in a small group of patients undergoing carotid surgery did not show good correlation between CBF and blood flow velocity.[88] Subsequent studies in patients with varying intracranial pathology have yielded mixed results.[89-92]

The correlation between CBF and TCD-measured blood flow velocity remains good over time only when the artery being insonated does not change diameter, and when cortical blood flow in the distribution of the measured artery does not have significant collateral sources of blood flow. The relationship between emboli count and stroke is better established with multiple studies conducted in the preoperative, intraoperative, and postoperative periods indicating that higher emboli counts are associated with higher stroke risk and warrant intervention.[93-99]

Intraoperative use of TCD has not been widely adopted for many reasons. As previously noted, good TCD signals cannot be obtained in many individuals who could benefit from monitoring. Also, TCD probe motion during surgery causes major problems with loss of signal or with angle of insonance–induced changes in the relationship between blood flow velocity and blood flow. Nonetheless, multiple series of carotid endarterectomies with TCD monitoring have been reported with good success, quoting a critical blood flow velocity reduction around 50% as indicative of inadequate CBF requiring intervention (shunt or increased blood pressure or both).[93-99] There are no good outcome data supporting TCD use intraoperatively, but data regarding emboli count and risk of stroke suggest that if technical issues with probe attachment to the patient can be overcome, TCD may be useful as a predictor of impending stroke in the preoperative, postoperative, and perhaps intraoperative periods.

Cerebral Oximetry (Near-Infrared Spectroscopy). Near-infrared spectroscopy (NIRS) is an attractive monitor because of its ease of application and lack of training required for interpretation. The hypothesis governing its use is very simple: As oxygen delivery to the brain decreases, oxygen extraction from arterial blood increases, and the oxygen saturation in cerebral venous blood decreases. NIRS applied to cerebral monitoring measures

the oxygen saturation in the cerebral venous blood in the prefrontal cortex and promptly detects increases in oxygen extraction resulting from decreased oxygen delivery. Multiple case reports and series document the use of cerebral oximetry during neurovascular surgery, but several major questions surrounding use of NIRS during carotid surgery remain unanswered.

The first and most important question is what degree of decrease in oxygen saturation can be tolerated before intervention is necessary. Because most interventions involve some risk (e.g., shunt → emboli, increased BP → myocardial ischemia), the answer to this question is important. The answer does not yet exist, however, and may vary from patient to patient. Two more recent studies showed that in awake patients, the saturation value at which any patient would develop symptoms varied from patient to patient,[100,101] and an absolute value that required shunting could not be determined. Another study showed that cerebral oxygen saturation decreased before the EEG developed changes, and the authors used this observation to claim superiority for NIRS monitoring of the brain during carotid surgery.[102] This finding should not be surprising, however, because function of the brain (in this case, electric function) does not fail until increased extraction of oxygen no longer meets metabolic demands for the tissue. If metabolic demands are being met by increased extraction, it is unclear that intervention is needed.

Finally, a study by Friedell and colleagues[103] compared NIRS with EEG and SSEP monitoring during carotid surgery. In 24 of 323 patients, significant differences were observed between NIRS and monitors of electric function. Seventeen patients showed no changes in electric function with significant decreases in cerebral oxygen saturation. In seven patients, no change in cerebral oxygen saturation occurred despite significant change in the EEG and SSEP. These data in combination with the data from studies in awake patients suggest that use of NIRS alone during carotid vascular surgery may be inappropriate.

Intracranial Neurovascular Surgery (Monitors: SSEPs)

Somatosensory Evoked Potentials. SSEPs have been extensively studied during cerebral aneurysm surgery. During these procedures, the surgical incision and brain retraction precludes placement of scalp or brain surface electrodes that could detect cerebral ischemia in at-risk cortex. Recording electrodes placed on the surface of the brain have been used successfully, but they are commonly considered "in the way" by neurosurgeons. Scalp electrodes may be placed easily for SSEP monitoring, although the recording montage is frequently not the same as that used in an awake patient.

For aneurysms involving the anterior cerebral circulation, SSEP monitoring has an excellent, but not perfect, record for predicting postoperative neurologic function. Most patients without surgically induced SSEP changes during surgery awaken with an unchanged neurologic examination. Patients with significant SSEP changes that do not revert to normal awaken with a new neurologic deficit. Patients with SSEP changes that return to normal after a significant intraoperative change may show at least a transient postoperative deficit, with the severity and duration increasing as the duration of the SSEP change increases. Many authors have reported significant utility of SSEP monitoring in detecting improper aneurysm clip placement (see Fig. 46-8) and in guiding intraoperative blood pressure management, particularly in patients already showing or at significant risk for vasospasm after subarachnoid hemorrhage.[55,104-109] The same success cannot be reported, however, for posterior circulation aneurysms. In these cases, many areas of the cortex and subcortical structures are at risk for damage that cannot be monitored at all by somatosensory pathway function. A significant false-negative monitoring pattern exists for these patients, but changes can still be detected when a surgical insult is sufficiently severe to involve large portions of the brain.[110-113]

Supratentorial Intracranial Nonvascular Surgery (Monitors: Awake Patient, EEG, SSEPs)

During supratentorial procedures, neurologic monitoring can contribute to the precise localization of structures that need to be preserved or conversely supplement the anatomic information provided by imaging with functional data. Three techniques fall under this category: (1) Awake craniotomy can be a suitable approach for the resection of tumors and seizure foci. (2) Intraoperative electrocorticography (i.e., the recording from strategically placed subdural electrodes) is used to target more closely the resection of seizure foci. (3) Localization of the central sulcus and by extension the precentral motor cortex is sometimes helpful, if these structures have been displaced by a tumor.

The most comprehensive approach to the problem of functional localization of brain structures that need to be preserved to achieve a good outcome is to perform entire segments of a supratentorial craniotomy in an awake patient, who is undergoing repeated neurologic examinations targeted to assess the eloquent area at risk. Such procedures are typically divided into exposure, mapping, and resection phases, and can be done with the patient entirely awake or awake only during periods when the neurologic examination needs to be assessed.[114] Common to all these approaches is the need for meticulous locoregional anesthesia of the scalp at the craniotomy site and the pin sites of the head holder.[115] A second requirement is a patient who is well informed about the awake parts of the procedure and willing and able to cooperate. Dexmedetomidine, propofol, and remifentanil are the agents most frequently incorporated into the anesthetic regimens for awake craniotomy.[116] Complications of awake craniotomy include nausea and vomiting, respiratory problems, and "tight" brain, but are typically mild and occur in less than 10% of cases in experienced centers. Seizures triggered by cortical stimulation can be stopped by the application of iced saline to the exposed cortex or a small amount of barbiturate or propofol.

Seizure Focus Localization Surgery

Patients with epilepsy who have seizures that generalize from an anatomically distinct focus may benefit greatly from the surgical resection of that seizure focus.[117] Precise localization of a seizure focus is important for achieving the therapeutic objective of seizure control and for minimizing complications from the resection. With sensitive magnetic resonance tomography techniques, neuronavigation, and recordings of typical seizure activity in the awake patient after placement of subdural and depth electrodes, the anatomic location and the appropriate extent of the resection frequently can be determined preoperatively.[118] These developments have diminished the role of intraoperative recordings from the epileptogenic zone using electrocorticography.[119]

Neurologic monitoring during such a resection is performed using two different techniques. First, activity of the seizure focus can be recorded through electrocorticography. Second, eloquent brain areas next to the seizure focus can be monitored during an awake craniotomy as described in the previous section. Electrocorticography is done by placing a grid of subdural electrodes onto the exposed brain surface and recording spontaneous electric activity. Electrocorticography is constrained by several limitations. The time for such recordings is limited to a few minutes; recordings are limited to interictal discharges, which may not correlate with the epileptogenic focus; and recordings need to be obtained from a brain that is under the effects of general anesthetic agents, which alter the EEG.

To provide good conditions during the recording, the level of anesthesia is lightened (e.g., by use of a strict nitrous-narcotic technique or low concentrations of volatile agents). Provocative techniques, such as hyperventilation or administration of a small dose of methohexital, may be useful to activate the seizure focus. Intraoperative seizure mapping requires the involvement of an expert electroencephalographer familiar with this technique.

Motor Strip Localization

Electrophysiologic monitoring of the somatosensory system in anesthetized patients can provide a simple anatomic guide to the location of the rolandic fissure, which separates the parietal primary sensory and frontal primary motor cortex. The fissure is located by recording cortical SSEPs from a subdural strip electrode that is placed perpendicular to the presumed location of the fissure. The exact location of the fissure is characterized by a reversal in the polarity of the primary cortical response between the electrodes straddling the fissure, as illustrated in the clinical example in Figure 46-13.

Posterior Fossa Surgery (Monitors: BAEPs, Cranial Nerve Monitoring, SSEPs, MEPs)

Beside the cerebellum, the posterior fossa contains within the narrow space of the brainstem many crucial neural structures, including ascending and descending sensorimotor pathways; cranial nerve nuclei; cardiorespiratory centers; the reticular activating system; and the neural networks that underlie crucial protective reflexes, such as eye blink, swallowing, gag, and cough. Posterior fossa surgery is not undertaken lightly, and even small injuries can leave significant neurologic deficits. Although some of these neural structures, such as the sensory or auditory pathway, can be monitored consistently, intraoperative integrity of other neural structures is frequently only inferred from the well-being of neighboring structures amenable to monitoring.

Microvascular Decompression of Cranial Nerves V, VII, and IX

Microvascular decompression is done most frequently for trigeminal neuralgia (cranial nerve V) in patients who present acceptable medical risks for a posterior fossa craniotomy. More rarely, the same approach is used to treat hemifacial spasm or neurovascular compromise of lower cranial nerves. The surgery entails dissecting along the intracranial portion of the nerve, identifying offending blood vessels that encroach on the nerve, and placing an insulating Teflon pad between vessel and nerve. The surgery risks ischemic damage to perforating vessels coming off the offending arteries and cerebellar retraction–related damage to cranial nerves. The facial and vestibulocochlear nerves are at particular risk for stretch-induced injury caused by medial retraction of the cerebellum. Retraction-induced stretch produces a prolongation of the interpeak latency between peaks I and V of the BAEP waveform, ultimately leading to a complete loss of all waves beyond wave I (Fig. 46-14). Failure to release retraction in a timely manner results in postoperative hearing loss. Such monitoring increases the chances for preserved hearing after microvascular decompression.[120-124]

Vestibular Nerve Schwannoma

Vestibular nerve schwannomas are the most common tumors located in the cerebellopontine angle. Because of the common origin of the cochlear component of cranial nerve VIII and the essentially identical intracranial trajectory of the facial nerve, hearing loss and facial nerve palsy are concerns during surgical resection of these tumors. Size and preoperative auditory function are the best predictors of postoperative hearing.[125] For tumors up to about 2 to 3 cm in size, monitoring of BAEPs can increase the chances of preserving hearing.[126] In addition to BAEPs, the facial nerve is monitored through spontaneous and stimulated EMG. Prospective trials have shown a higher percentage of patients with a functional facial nerve 1 year after surgery if facial nerve monitoring was used as previously described. Tonic discharges warn of impending damage caused by stretch or heat (bovie). Sharp section of the nerve may elicit no discharge, and neuromuscular blockade may eliminate the ability to monitor. If the course of the nerve is displaced by the tumor, the surgeon can map its course with a hand-held stimulator and real-time auditory feedback.

Other Posterior Fossa Neoplasms

Monitoring for operations on other neoplasms located in the brainstem typically is individualized to each particular case or to the particular surgical approach. EMG may be recorded not only from the territory of the facial nerve, but also from the tongue to monitor the hypoglossal nerve, and from the glottis through electrodes embedded into a specialized endotracheal tube to monitor the vagus nerve. Such a setup can be used to map the floor of the fourth ventricle functionally, if it is distorted by a tumor.[127] Such monitoring may be insufficient to preserve vital reflexes because only the efferent limb of these reflexes is monitored by recording EMG from innervated muscle.

Use of neurologic monitoring for brainstem ischemia, although done in some centers, is not well documented or supported by clinical studies. Global well-being of the brainstem may be monitored by combining multiple modalities of evoked potentials, such as BAEPs, SSEPs, and MEPs. Each modality monitors a function whose integrity would be considered important in its own right for the functional outcome of an individual patient. As illustrated in Figure 46-15, the cross-section monitored by combining all these modalities still leaves out crucial areas. Given that perfusion occurs through perforating vessels, it is easy to see that monitoring may indicate that all is well or, more likely, that a therapeutic intervention was helpful in restoring function, when clinically the patient is still left with a significant deficit. This occurrence invalidates neither monitoring nor the therapeutic

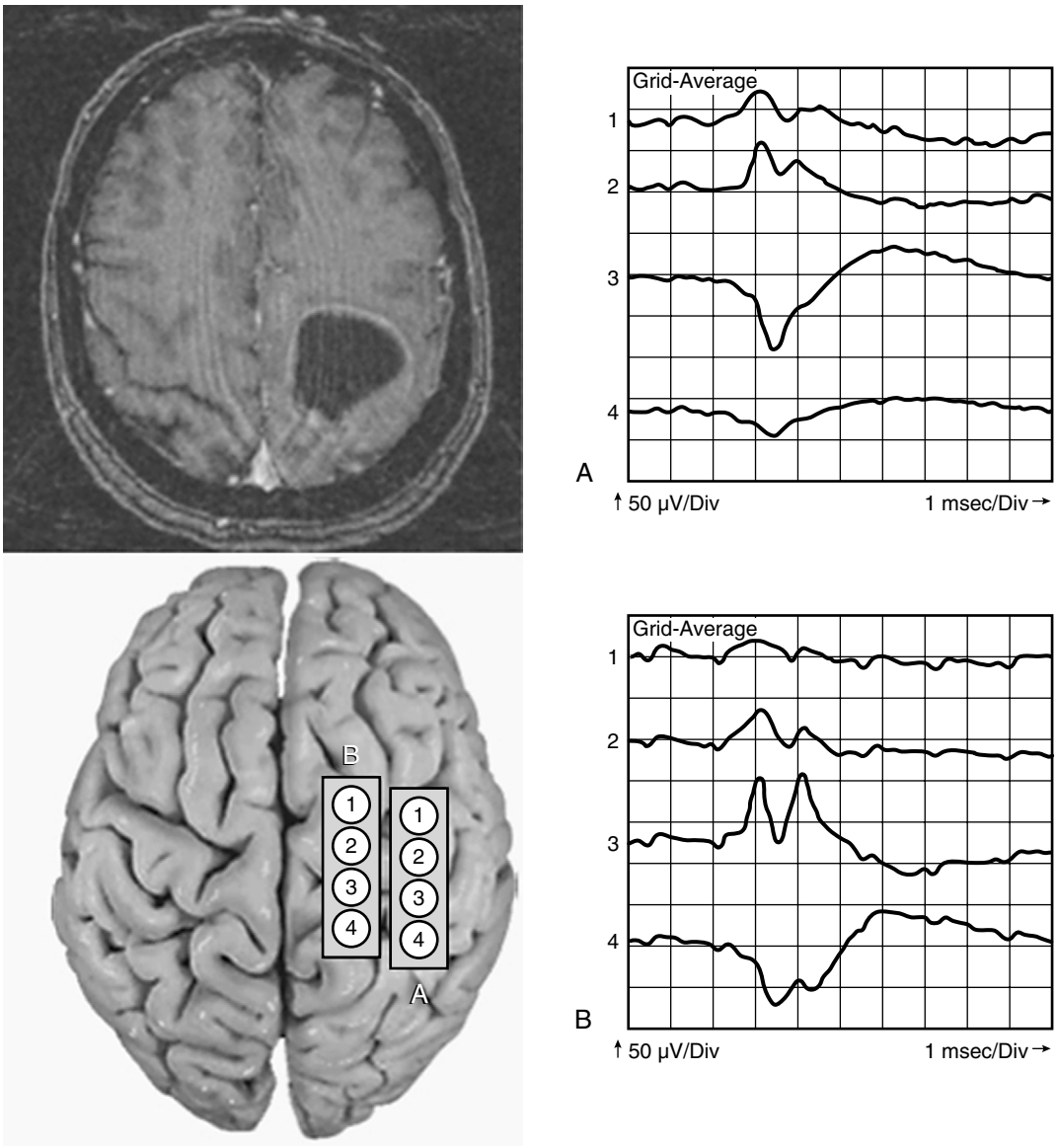

Figure 46-13 Intraoperative localization of the rolandic fissure separating the primary sensory and motor cortex. The clinical example is from a patient with a large parietal tumor shown in the scan. Two of the recordings made from a four-contact subdural electrode strip are shown. The relative positions of the strip electrode are labeled B and A. In recording A, the primary cortical response from the electrodes anterior to the rolandic fissure shows an upward deflection, whereas the response from electrodes posterior to the fissure shows a downward deflection. Moving the strip electrode anterior (recording B) moves this "phase reversal" between electrodes 3 and 4.

intervention, but indicates only that the monitored pathway was not located in an area at risk from the surgical procedure. Because of such obligatory "false-negatives," few studies address the utility of such monitoring. Because each individual monitoring modality comes with its own constraints, such an approach typically requires a dedicated neurophysiologist for interpretation and troubleshooting.

Spinal Column and Spinal Cord Surgery (Monitors: SSEPs, MEPs, EMG)

Intraoperative monitoring of SSEPs has been used most extensively in patients undergoing surgical procedures involving the spinal column or spinal cord, or both. Extensive experience has been gained in patients who have decompressive laminectomies or who have undergone corrective procedures for scoliosis. Intraoperative changes in SSEPs have been noted in 2.5% to 65% of patients undergoing surgical procedures on the spine or spinal cord.[128-131] When these changes are promptly reversed either spontaneously or with interventions by the surgeon or anesthesiologist (e.g., lessening the degree of spine straightening in scoliosis surgery or increasing arterial blood pressure), the patients most often have preserved neurologic function postoperatively. When these changes persisted, however, the patients most often awakened with worsened neurologic function.

False-negative (rare) and false-positive (common) results have been reported with SSEP monitoring during spine surgery. Patients with intact SSEPs throughout the procedure have awak-

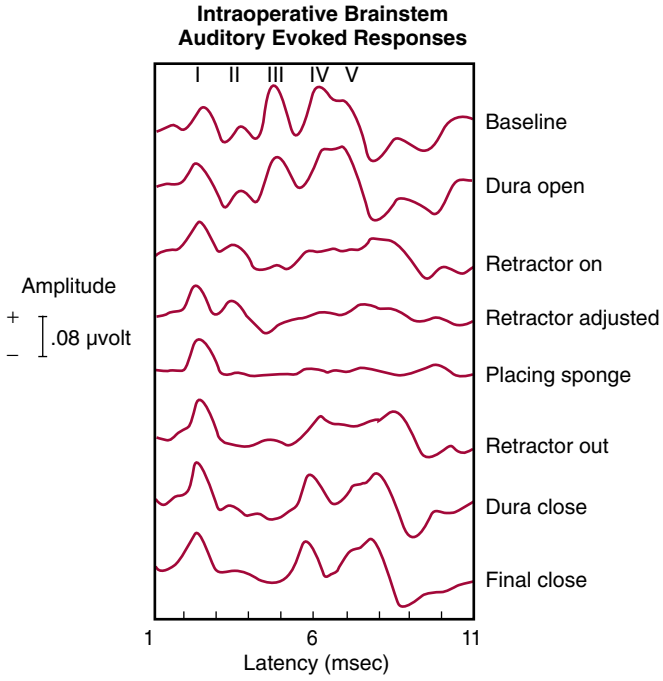

Figure 46-14 Intraoperative monitoring of brainstem auditory evoked responses during microvascular decompression. The baseline recording shows the typical five waves of the brainstem auditory evoked potential response. Intraoperative events are designated to the right of each trace. Placement of the retractor causes a severe increase in latency of wave V even after adjustment of retraction. During placement of the sponge, all waves subsequent to wave I, which originates in the inner ear, are nearly completely lost. Removal of the retractor causes brainstem auditory evoked potentials to revert toward baseline.

ened with a new significant neurologic deficit, but the total reported incidence of this finding is far less than 1% of all cases monitored. Patients with no postoperative neurologic deficit commonly experience significant changes in intraoperative SSEPs.[131] This monitoring pattern is most commonly caused by failure to control for other, nonpathologic factors that may alter the SSEP. Overall, the reliability of properly performed SSEP monitoring to predict the postoperative sensory and motor function has been reported to be excellent.[44,130,132] Motor tracts are not directly monitored by SSEPs, however. In addition, the blood supply to the dorsal columns of the spinal cord, which carries all of the upper extremity SSEPs and at least a portion of the lower extremity SSEPs, is derived primarily from the posterior spinal arteries. The blood supply to motor tracts and neurons is derived primarily from the anterior spinal artery. It is possible for a significant motor deficit to develop postoperatively in patients with intact SSEPs throughout the operative course. Such events have been reported.[133,134]

In operations on the spinal column and after acute spinal cord injury, the sensory and motor changes generally correlate well[44]; however, in patients with neurologic dysfunction after thoracic aortic vascular surgery, frequently posterior spinal cord function (proprioception, vibration, light touch) is left intact when motor and other sensory functions (pain, temperature) are impaired. This result occurred in 32% of patients with neurologic injury after aortic aneurysm repair in one series,[135] with similar results in many other series. Intraoperative SSEP monitoring in these patients carries a significant risk for false-negative results, and as a result, such monitoring is not widely used.

Multiple anecdotal reports and an increasing number of case series suggest that MEP monitoring during surgery on the spine or its blood supply is useful. Several series have reported significant changes in MEPs without changes in SSEPs. These series suggest that combined use of SSEP monitoring and MEP monitoring may eliminate false-negative monitoring patterns during spine surgery.[136-141] In the case of monitoring paraplegia risk during thoracoabdominal aneurysm surgery, the literature shows mixed but improving support for the use of MEP monitoring. Two earlier studies suggested that MEPs may not be as effective as hoped. The first study recorded MEPs from the lumbar spinal cord in dogs produced by transcranial electric stimulation.[135] Elmore and associates[142] found that these spinally recorded potentials did not accurately predict postoperative motor function. In a second study, Reuter and colleagues[143] recorded MEPs at the spinal cord and the peripheral nerve level in dogs produced by transcranial electric stimulation. They also found that the spinally recorded responses were inaccurate in predicting motor function postoperatively. The peripheral nerve responses disappeared in all animals and were not present 24 hours later regardless of whether the animal could move its lower extremities.

These studies suggest that the spinally recorded MEP likely represents a response generated by the descending corticospinal tract. This white matter pathway is resistant to ischemia compared

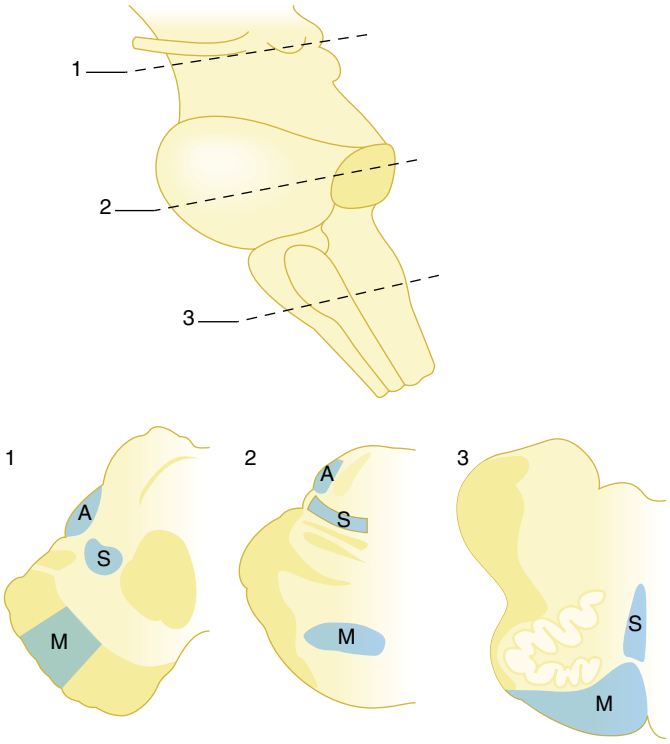

Figure 46-15 Monitoring of the brainstem with evoked potentials. Evoked potentials monitor specific tracts that encompass defined areas in the brainstem. This is shown in three transverse sections approximately at the levels indicated in the drawings. The areas directly monitored by a given modality are indicated in *blue* and labeled M (motor), S (somatosensory), and A (auditory). Conclusions about the well-being of the remainder of the brainstem are made by inference from the monitored areas.

with the more metabolically active anterior horn cells (gray matter). Recovery of this white matter–generated MEP response could occur after reperfusion of the cord, whereas the gray matter might not recover. Responses recorded from the peripheral nerve would reflect postsynaptic anterior horn cell function, but lower extremity ischemia occurring after aortic cross-clamping may preclude recording this or the response from muscles during surgery.

More recent clinical series have shown much greater success with MEP monitoring during aortic vascular surgery in correctly detecting inadequate spinal cord blood flow and in improving operative outcome. The technique has proven useful, particularly when operative strategies such as reimplantation of crucial intercostal vessels based on results of MEP monitoring, alteration of spinal cord perfusion pressure (blood pressure increase or cerebrospinal fluid drainage or both), spinal cord cooling, and other methods are used.[144-153] Although this monitoring technique holds promise in aortic surgery, much more clinical work is needed before MEP monitoring during aortic surgery becomes widely accepted and used.

Peripheral Nerve Surgery (Monitors: EMG, Nerve Action Potential)

Neurologic monitoring for surgeries involving peripheral nerves can be done in two different settings. In the first, the peripheral nerve is intact, but threatened by the surgery. Examples would be an intrinsic nerve tumor, such as a schwannoma or an extensive soft tissue tumor, particularly if it displaces the normal anatomic course of a nerve. Monitoring of spontaneous and stimulated muscle responses from muscle groups innervated by the nerve in question can be used to guide the resection. Spontaneous EMG discharges can be generated by stretch or compression of the nerve, by local heating from electrocautery, or from ischemia. Two caveats apply to the monitoring of spontaneous EMG. First, the neuromuscular junction is part of the monitored pathway, and muscle relaxation decreases/abolishes the sensitivity of monitoring in a dose-dependent manner. Second, sharp section of the nerve may not result in a noticeable discharge. To search out the course of the nerve intraoperatively, the surgeon may stimulate the wound area with a hand-held probe and listen for stimulated EMG or palpate for muscle contraction. The underlying concept should be familiar to anesthesiologists from the use of nerve stimulators in regional anesthesia.

A variation of this technique of monitoring that is gaining popularity is monitoring of pedicle screw placement during spinal instrumentation with the aim of avoiding nerve root injuries owing to malpositioned pedicle screws.[154,155] Typically, the shank of an implanted pedicle screw is stimulated repetitively with increasing current to determine the threshold for eliciting a dermatomal compound muscle potential. Because thresholds vary among cervical, thoracic, and lumbar spine, and between healthy and diseased nerve roots, this technique is currently not universally regarded as useful, but shows some promise.[156]

A second setting where monitoring of peripheral nerves is used is in patients with prolonged weakness and sensory loss after nerve injury undergoing nerve exploration.[157] The aim is to determine whether nerve reconstruction may improve outcome. The area of the lesion is determined by preoperative nerve conduction studies. Intraoperatively, the nerve is first stimulated proximal to the lesion, and a recording of the nerve action potential is made directly from the nerve distal to the lesion, as illustrated in Figure 46-16. If there is nerve conduction across the lesion, lysis of scar is performed, and the incision is closed. Natural recovery by means of axonal regrowth produces the best outcome. If conduction does not occur across the lesion, resection of the damaged nerve and nerve cable grafting is performed.[158-160]

Non-neurologic Surgery That Risks Damage to the Central Nervous System (Monitors: EEG, TCD, Cerebral Oximetry, $SjvO_2$)

Cardiopulmonary Bypass

Electroencephalogram. In humans, changes that occur with the institution of cardiopulmonary bypass (CPB) may alter the EEG via multiple different mechanisms. Plasma and brain levels of anesthetic drugs may be altered by CPB or by anesthetic drugs commonly given at the institution of CPB, alterations in arterial carbon dioxide tension and blood pressure may occur, and hemodilution with hypothermic perfusate nearly always occurs. These effects, all of which may produce EEG changes similar to pathologic changes seen with ischemia, make it difficult to interpret EEG changes occurring around the time of institution of CPB.

Levy and others[161,162] have tried to distinguish the normal effects of hypothermia from other events occurring at the institution of and conclusion of CPB. Initially, Levy concluded that only a qualitative relationship could be determined, but later, with the use of a much more sophisticated EEG analysis technique (approximate entropy), EEG changes associated with changes in temperature could be quantified.

Chabot and colleagues in Boston[163] and Edmonds and colleagues in Louisville[164] have attempted to use quantitative (processed, multiple-channel) EEG during CPB to detect cerebral hypoperfusion and relate these changes to postoperative neurologic function. In addition, some minimal work has been done with intervention after detection of cerebral hypoperfusion using quantitative EEG. Such monitoring techniques have not been widely adopted because although the data seem promising, only a few patients have been studied, and there are very few corroborating studies. In addition, this type of monitoring is extremely costly in time, personnel, and equipment costs, and given the lack of convincing outcome data, the cost-to-benefit ratio is unclear at best. Some other investigators failed to show any convincing relationship between intraoperative EEG parameters and postoperative neurologic function, especially in small infants and children.[165,166] Much work remains to be done studying use of the processed, quantitative EEG to provide information for clinical management of patients during CPB. None of the currently available studies and recommendations would support an evidence-based justification for their routine application.

Transcranial Doppler. TCD also has been used to monitor the cerebral circulation during CPB. Anecdotal reports and case series document the use of TCD for determining adequacy of CBF, detection of emboli, and detection of improper cannula placement.[167] Only very limited outcome data exist, and use of

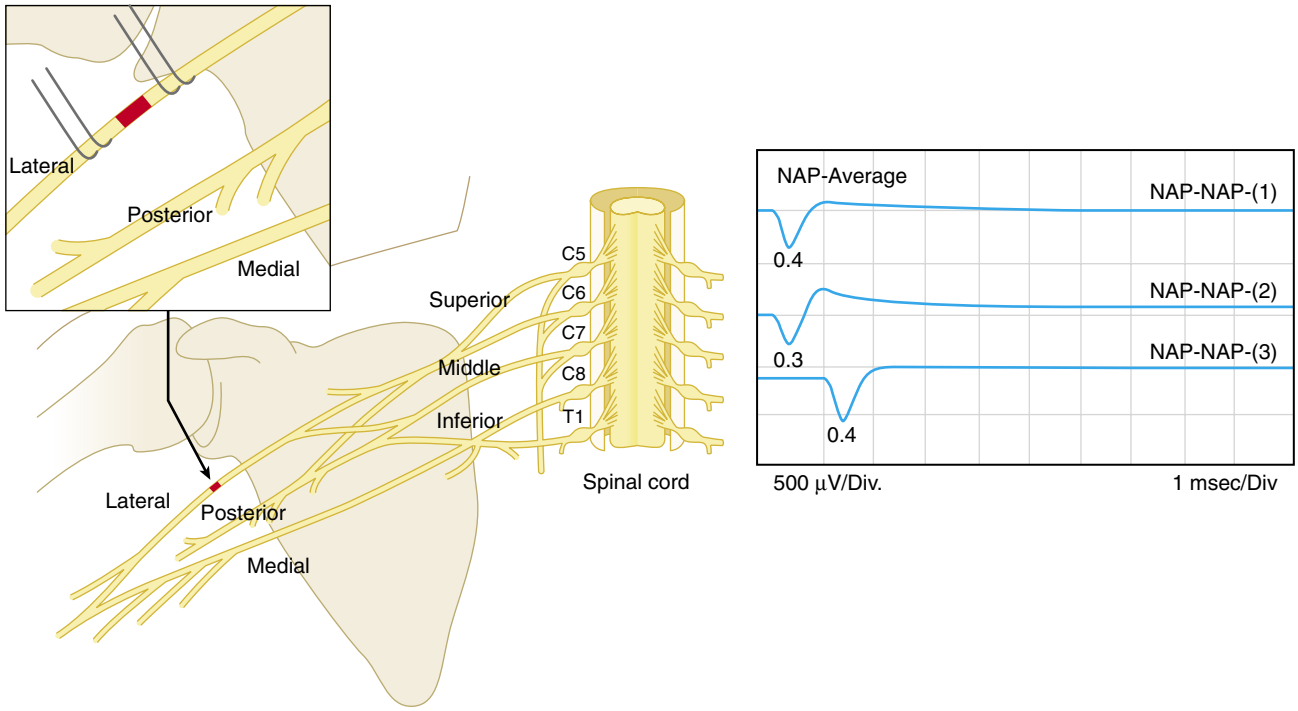

Figure 46-16 Recording a nerve action potential during a brachial plexus exploration. The site of the injury on the lateral fascicle is indicated in *red*. As shown in the *inset,* the surgeon places hook electrodes on either side of the exposed part of the nerve. If the injury is limited to an axonotmesis, proximal stimulation will result in a distal nerve action potential similar to the ones shown in the recording to the right. The delay in the response in the third tracing is simply due to a change in technical settings.

TCD during CPB does not stand up to evidence-based examination, primarily because of lack of information. Probe placement instability and inability to obtain signals in some patients also have limited the use of this monitor intraoperatively.

Cerebral Oximetry and Jugular Venous Oxygen Saturation. As is the case with EEG monitoring during CPB, there are multiple case reports and several series that advocate the use of NIRS or $Sjvo_2$ as indicators of adequate perfusion of the brain during CPB.[168,169] Incorrect placement of CPB cannulas has been detected clinically and in laboratory studies. One more recent series of patients undergoing CPB for coronary bypass surgery showed a higher incidence of major organ system dysfunction and longer hospital stays in patients with lower baseline and intraoperative cerebral oxygen saturation values.[170] The same questions exist for this application of NIRS, however, as do for the use of NIRS during carotid vascular surgery. Use of NIRS during CPB, although it provides information that would not otherwise be available, does not stand up to evidence-based examination, and much more work is needed before NIRS can be recommended as a standard of care during CPB.

$Sjvo_2$ is very invasive. Although data from case reports and studies suggest that $Sjvo_2$ may have utility in detecting inadequate CBF, lack of outcome data, lack of clearly defined critical values at different temperatures during CPB, and availability of more noninvasive modalities (EEG, cerebral oximetry) have resulted in only limited use of this monitoring method during CPB. Based on current information, no neurologic monitoring techniques either alone or in combination are clearly useful in improving outcome during surgery requiring CPB. Further research is needed before the cost in personnel and in equipment of neurologic monitoring during CPB can be justified.

Intensive Care Applications of Neurologic Monitoring (Monitors: EEG, Evoked Potentials, TCD, $Sjvo_2$)

Secondary injury to the CNS has been recognized in past decades as a major modifiable risk factor in patients with CNS disease. Aneurysmal subarachnoid hemorrhage, stroke, and traumatic brain injury are examples of CNS insults in which secondary injury has important implications for the ultimate functional outcome.[171-173] The same diseases frequently result in a primary insult to the CNS that severely constrains the utility of the clinical neurologic examination because of the need for mechanical ventilation and sedation. Many techniques of neurologic monitoring discussed earlier also have been used in the intensive care unit. Generally, however, techniques that require continued presence of skilled technologists, such as monitoring of evoked potentials, are prohibitively expensive and of less practical value than techniques that can be performed as a daily examination, or techniques that provide data easily integrated into the intensive care frame of mind. Along with monitoring, some of the techniques discussed previously also can provide important prognostic information in comatose patients and guide decision making.

Cerebral Ischemia

Cerebral ischemia is an important cause of secondary injury to the CNS. It can be difficult to detect in patients who are either

comatose or sedated, but can occur even in the face of an adequate cerebral perfusion pressure.[174,175] Three techniques may provide intensivists with additional information about cerebral perfusion. None of the monitors is considered "standard of care." As with all monitors, the impact of the monitor on outcome depends on the quality of the therapeutic interventions that result from integration of the additional data into the clinical management of a given patient.

$SjvO_2$ monitoring is used most extensively in the intensive care unit to monitor patients with traumatic brain injury. The data have been used to guide blood pressure and ventilatory management to optimize blood flow. $SjvO_2$ monitoring has had a major effect on ventilatory management of head-injured patients and has significantly reduced the routine use of hyperventilation in neurosurgical patients.[176-180] $SjvO_2$ values of less than 50% generally indicate cerebral ischemia. Increases in $SjvO_2$ may occur in response to therapy, or may be an ominous sign if the increase is caused by falling demand because of neuronal death.

Similar to $SjvO_2$ monitoring, monitoring of $P_{Br}O_2$ and blood flow is used most frequently in patients with traumatic brain injury. $P_{Br}O_2$ performs well in clinical practice. Decreases to less than 10 to 15 mm Hg are associated with worsening outcome,[27,180] whereas $P_{Br}O_2$-targeted treatment strategies may improve outcome.[181] The data for thermal diffusion CBF are not as comprehensive, perhaps reflecting the slightly less robust technology.[182] Nonetheless, in the setting of subarachnoid hemorrhage, thermal diffusion CBF less than 15 mL/100 g/min showed a sensitivity of 90% and a specificity of 75% for detecting symptomatic vasospasm.[19]

TCD is widely used in the intensive care unit to document the presence and severity of cerebral vasospasm after subarachnoid hemorrhage. As the major cerebral arteries narrow, flow velocity within the lumen must increase if blood flow is to be maintained. Such narrowing occurs 12 to 24 hours before the onset of clinical symptoms, allowing therapy to be initiated before the onset of clinical symptoms.[183-187] Mean flow velocities of more than 120 cm/sec seem to correlate well with angiographic vasospasm,[188,189] although intracranial pressure and concurrent therapy with hypertensive hypervolemic hemodilution modify the flow velocity. The latter two factors result in characteristic changes of the TCD waveform, however, preserving the utility of the examination.

Prognosis in Coma and Determination of Brain Death.

EEG monitoring may help to assess the clinical course and the prognosis of comatose patients. Assessment of prognosis must be separated from the insult that precipitated the coma by more than 24 hours. If not, the EEG may reflect predominantly the effect of the insult and may not predict prognosis. More than 24 hours after the insult, spontaneous sustained burst suppression correlates strongly with severe irreversible brain injury.[190] Absence of EEG variability portends a high likelihood of persistent vegetative state or death,[190,191] whereas spontaneous variability, reactivity to external stimuli, and typical sleep patterns are associated with more favorable outcomes.[192-194]

A specific indication for EEG monitoring is the therapeutic induction of a coma by barbiturate administration. Because neither blood nor cerebrospinal fluid concentrations of barbiturates reliably predict burst suppression and near-maximal reduction in cerebral metabolic rate of oxygen consumption,[195] and because barbiturate administration usually requires an increase in cardiovascular support, documentation of a burst suppression pattern on EEG allows the use of the minimal effective dose of barbiturate.

Similar to EEG, evoked potential studies have a place in predicting prognosis in comatose patients. The presence of normal SSEPs bilaterally is an excellent prognostic sign, whereas the absence of any SSEP cortical response is a poor prognostic indicator. The degree of bad outcome can be predicted by BAEPs. Intact and normal BAEPs with absent cortical SSEPs predict a best outcome of a chronic vegetative state. Outcome may be worse, however, because BAEPs commonly deteriorate later with rostral-to-caudal deterioration. Absent BAEP responses beyond wave I predict a high likelihood of brain death. Present but abnormal SSEPs are associated with outcomes intermediate between good/high function and a chronic vegetative state.[196-205]

TCD also has been used in the intensive care unit as an aid to the diagnosis of brain death. As intracranial pressure increases, the pulsatility of the TCD waveform increases, accentuating the systolic peak and diminishing flow during diastole. With further increases in intracranial pressure, a characteristic to-and-fro pattern of flow is established, which is consistent with clinical brain death.[206] TCD studies are easily performed at the bedside and can minimize the need for unnecessary transports of the patient for definitive radiologic studies.

Nonsurgical Factors Influencing Monitoring Results

Anesthesia and the Electroencephalogram

Anesthetic drugs affect the frequency and amplitude of EEG waveforms. Although each drug class and each specific drug has some specific, dose-related EEG effects (Table 46-2), some basic anesthesia-related EEG patterns may be described. Subanesthetic doses of intravenous and inhaled anesthetics usually produce an increase in frontal beta activity and abolish the alpha activity normally seen in the occipital leads in an awake, relaxed patient with the eyes closed. As the patient actually goes to sleep with general anesthesia, the brain waves become larger in amplitude and slower in frequency. In the frontal areas, small beta activity seen in an awake patient slows to the alpha range and increases in size. In combination with the loss of the occipital alpha activity, this phenomenon produces the appearance of a "shift" of the alpha activity from the posterior cortex to the anterior cortex. Further increases in the dose of the inhalation or intravenous agent produce further slowing of the EEG, and some agents have the capability to suppress EEG activity totally (see Table 46-2). Other agents never produce burst suppression or an isoelectric EEG, despite increasing dose, either because they are incapable of completely suppressing the EEG (e.g., opioids, benzodiazepines) or because cardiovascular toxicity of the drug (e.g., halothane) prevents administration of a large enough dose.

Intravenous Anesthetic Drugs

Barbiturates, Propofol, and Etomidate. Despite widely varying potencies and durations of action, barbiturates, propofol, and etomidate produce similar EEG patterns (Fig. 46-17 shows

Table 46-2 Anesthetic Drugs and Electroencephalogram (EEG)

Drug	Effect on EEG Frequency	Effect on EEG Amplitude	Burst Suppression?
Isoflurane			Yes, >1.5 MAC
Subanesthetic	Loss of alpha, ↑ frontal beta	↑	
Anesthetic	Frontal 4-13 Hz activity	↑	
Increasing dose >1.5 MAC	Diffuse theta and delta → burst suppression → silence	↑ → 0	
Desflurane	Similar to equi-MAC dose of isoflurane	Similar to equi-MAC dose of isoflurane	Yes, >1.5 MAC
Sevoflurane	Similar to equi-MAC dose of isoflurane	Similar to equi-MAC dose of isoflurane	Yes, >1.5 MAC
Nitrous oxide (alone)	Frontal fast oscillatory activity (>30 Hz)	↑, especially with inspired concentration >50%	No
Enflurane			Yes, >1.5 MAC
Subanesthetic	Loss of alpha, ↑ frontal beta	↑	
Anesthetic	↑ frontal 7-12 Hz activity	↑	
Increasing dose >1.5 MAC	Spikes/spike and slow waves → burst suppression; hypocapnia → seizures	↑↑ → 0	
Halothane			Not seen in clinically useful dosage range
Subanesthetic	↑ frontal 10-20 Hz activity	↑	
Anesthetic	↑ frontal 10-15 Hz activity	↑	
Increasing dose >1.5 MAC	Diffuse theta, slowing with increasing dose	↑	
Barbiturates			Yes, with high doses
Low dose	Fast frontal beta activity	Slight ↑	
Moderate dose	Frontal alpha frequency spindles	↑	
Increasing high dose	Diffuse delta → burst suppression → silence	↑↑↑ → 0	
Etomidate			Yes, with high doses
Low dose	Fast frontal beta activity	↑	
Moderate dose	Frontal alpha frequency spindles	↑	
Increasing high dose	Diffuse delta → burst suppression → silence	↑↑ → 0	
Propofol			Yes, with high doses
Low dose	Loss of alpha, ↑ frontal beta	↑	
Moderate dose	Frontal delta, waxing/waning alpha	↑	
Increasing high dose	Diffuse delta → burst suppression → silence	↑↑ → 0	
Ketamine			No
Low dose	Loss of alpha, ↑ variability	↑↓	
Moderate dose	Frontal rhythmic delta	↑	
High dose	Polymorphic delta, some beta	↑↑ (beta is low amplitude)	
Benzodiazepines			No
Low dose	Loss of alpha, increased frontal beta activity	↑	
High dose	Frontally dominant delta and theta	↑	
Opiates			No
Low dose	Loss of beta, alpha slows	↔ ↑	
Moderate dose	Diffuse theta, some delta	↑	
High dose	Delta, often synchronized	↑↑	
Dexmedetomidine	Moderate slowing, prominent spindles	↑↑	No

*delta = <4 Hz frequency; theta = 4-7 Hz frequency; alpha = 8-13 Hz frequency; beta = >13 Hz frequency.
MAC, minimum alveolar concentration.

EEG effects of thiopental). These drugs all follow the basic anesthesia-related EEG pattern described previously with initial EEG activation (see Fig. 46-17A), followed by dose-related depression. As the patient loses consciousness, characteristic frontal spindles are seen (see Fig. 46-17B), which are replaced by polymorphic 1- to 3-Hz activity (see Fig. 46-17C) as the drug dose is increased. Further increases in dose result in lengthening periods of suppression interspersed with periods of activity (burst suppression). With a very high dose, EEG silence results. All of these drugs have been reported to cause epileptiform activity in humans, but epi-

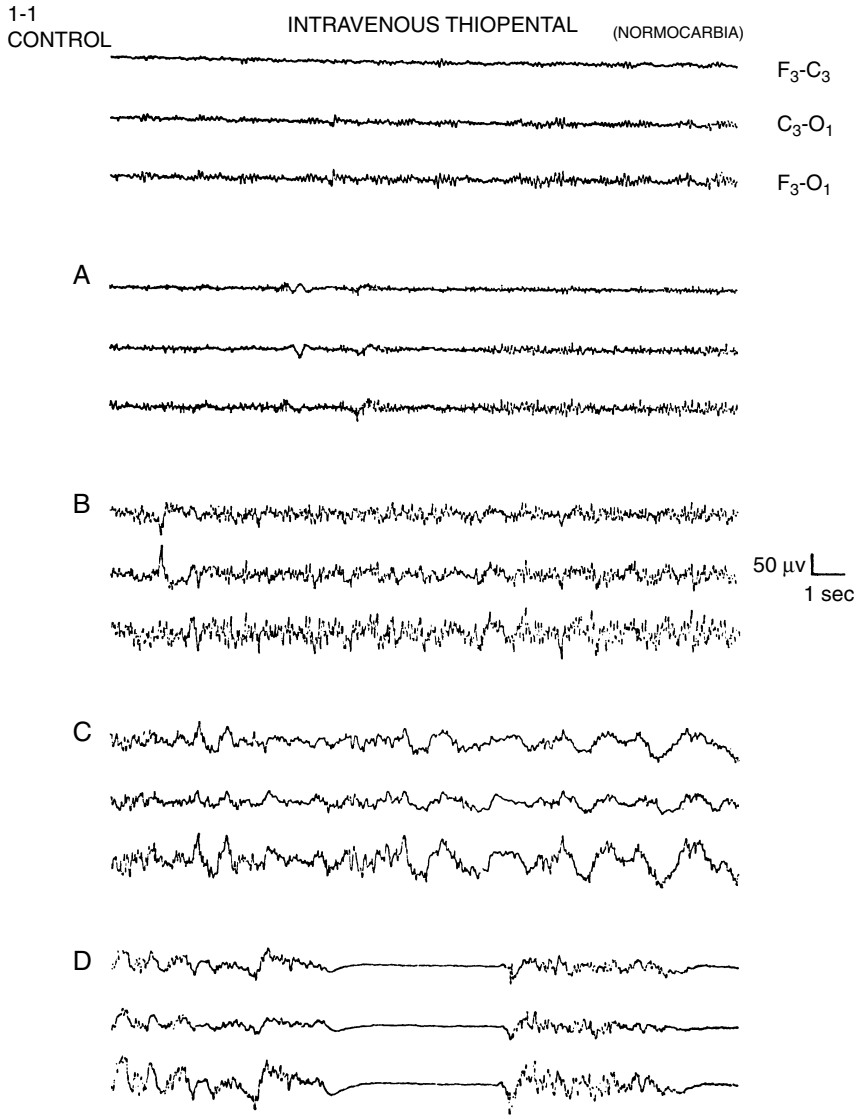

Figure 46-17 Electroencephalogram effects of intravenous administration of thiopental in humans. **A,** Rapid activity. **B,** Barbiturate spindles. **C,** Slow waves. **D,** Burst suppression. *(From Clark DL, Rosner BS: Neurophysiologic effects of general anesthetics. Anesthesiology 38:564, 1973.)*

leptiform activity is clinically significant only after methohexital and etomidate when given in subhypnotic doses.

Ketamine. Ketamine does not follow the basic anesthesia-related EEG pattern. Anesthesia with ketamine is characterized by frontally dominant rhythmic, high-amplitude theta activity. Increasing doses produce intermittent polymorphic delta activity of very large amplitude interspersed with low-amplitude beta activity.[207] Electrocortical silence cannot be produced with ketamine. EEG activity may be very disorganized and variable at all doses. This disorganization of the EEG with ketamine is responsible for the failure of the bispectral index to be useful in looking at the effect of ketamine on consciousness. Recovery of normal EEG activity even after a single bolus dose of ketamine is slow compared with barbiturates. There is no information available about the relationship between emergence reactions after ketamine and the EEG. Ketamine also has been associated with increased epileptiform activity.[207]

Benzodiazepines. Despite varying potencies and durations of action, benzodiazepines also follow the basic anesthesia-related EEG pattern. As a class, however, these drugs are incapable of producing burst suppression or an isoelectric EEG.

Opioids. As a class, opioids do not follow the basic anesthesia-related EEG pattern. Opioids generally produce a dose-related decrease in frequency and increase in amplitude of the EEG. If no further doses of opiates are given, alpha and beta activity return as drug redistribution occurs. The rapidity of return depends on the initial dose and on the drug. Remifentanil is associated with the most rapid return to normal.[208] Complete suppression of the EEG cannot be obtained with opioids. Epileptiform activity occurs in humans and in animals receiving large to supraclinical doses of opioids. Sharp wave activity is common after induction of anesthesia with fentanyl, with 20% of patients showing this phenomenon after 30 µg/kg; 60%, after 50 µg/kg; 58%, after 60 µg/kg; and 80%, after 70 µg/kg. Alfentanil bolus has

been used clinically to activate seizure foci during epilepsy surgery.[209] This epileptiform activity is mainly noted in the frontotemporal region.[210]

Dexmedetomidine. Dexmedetomidine is being increasingly used for sedation in the operating room and in the intensive care unit. EEG studies of patients undergoing sedation with dexmedetomidine alone show patterns similar to those seen in normal human sleep with increased slow-wave activity and sleep spindles prominent.[211] Burst suppression or an isoelectric EEG pattern cannot be produced even with high doses of the drug. Level of sedation with dexmedetomidine can be effectively monitored using processed EEG parameters and has been reported using bispectral index and entropy techniques.[212]

Inhaled Anesthetics

Nitrous Oxide. Used alone, nitrous oxide causes a decrease in amplitude and frequency of the dominant occipital alpha rhythm. With the onset of analgesia and depressed consciousness, frontally dominant fast oscillatory activity (>30 Hz) is frequently seen.[213] This activity may persist to some extent for 50 minutes after discontinuation of nitrous oxide. When nitrous oxide is used in combination with other agents, it increases the effects that would be associated with the agent alone clinically and with respect to the EEG pattern seen.

Isoflurane, Sevoflurane, Enflurane, Halothane, and Desflurane. Potent inhaled anesthetics follow the basic anesthesia-related EEG pattern. Isoflurane initially causes an activation of the EEG followed by a slowing of the EEG activity that is more marked with increasing dose. Isoflurane begins to produce periods of EEG suppression at 1.5 minimum alveolar concentration (MAC), which become longer with increasing dose until electric silence is produced at 2 to 2.5 MAC. Isolated epileptiform patterns sometimes can be seen during intersuppression activity at 1.5 to 2 MAC isoflurane.[214] Sevoflurane causes similar dose-dependent EEG effects. Equi-MAC concentrations of sevoflurane and isoflurane cause similar EEG changes.[215] Epileptiform activity has been induced by administration of sevoflurane in patients without epilepsy, and seizure activity on EEG, but not clinical seizure activity, has been reported in pediatric patients with a history of epilepsy during induction of anesthesia with sevoflurane.[216,217] Despite these observations, sevoflurane, similar to other inhalation agents, is not suitable for use during electrocorticography for localization of seizure foci.[218] EEG patterns seen with enflurane are similar to the patterns seen with isoflurane except that epileptiform activity is considerably more prominent. At 2 to 3 MAC, burst suppression is seen, but virtually all intersuppression activity consists of large spike/wave pattern discharges. Hyperventilation with high concentrations of enflurane increases the length of suppression, decreases the duration of bursts, but increases the amplitude and main frequency component of the intersuppression epileptiform activity. Frank EEG seizures also may occur with enflurane that produce the same cerebral metabolic effects as pentylenetetrazol, a known convulsant.

Halothane also produces EEG patterns similar to those of isoflurane, but dosages of halothane that would produce burst suppression in the EEG (3 to 4 MAC) are associated with profound cardiovascular toxicity. Desflurane produces EEG changes similar in nature to equi-MAC concentrations of isoflurane. In limited clinical studies, there has been no evidence of epileptiform activity with desflurane, despite hyperventilation and 1.6 MAC dosage,[219] and desflurane has been used as a treatment of refractory status epilepticus.[220]

Clinical studies have shown that the EEG effects of inhalational anesthetic agents are influenced by age and baseline EEG characteristics. Older patients and patients with EEG slowing at baseline were more sensitive to the EEG effects of isoflurane and desflurane. As anesthesia was deepened, similar EEG pattern changes were noted, but these changes occurred at lower end-tidal anesthetic concentrations.[221]

Anesthesia and Sensory Evoked Responses

Volatile Anesthetics

Multiple drugs used in the perioperative period can influence the ability to monitor SERs accurately (Table 46-3). A more recent review provides the interested clinician with a detailed analysis of all drug effects on SERs,[222] which is beyond the scope of this chapter. Table 46-3 does not quantify drug effects, but rather lists whether an individual drug is capable of producing a change in any part of an evoked response that could be mistaken for a surgically induced change. A "no" designation in this table does not mean that there are no effects of a given drug on SERs. The "no" designation indicates that any effects that do occur would not be called clinically significant by *clinicians experienced in intraoperative monitoring*. Several general concepts (Table 46-4) help the clinician who is trying to determine the best choice of drugs for use during monitored cases.

The volatile anesthetics isoflurane, sevoflurane, desflurane, enflurane, and halothane have similar effects in differing degrees on all types of SERs. VEPs are the most sensitive to the effects of volatile anesthetics, and BAEPs are the most resistant to anesthetic-induced changes. Spinal and subcortical SSEP responses are significantly less affected than cortical potentials.[223-225]

SSEPs, because they are the most widely used intraoperative SER technique, are the most completely studied with respect to the effects of anesthetic drugs. The effects of the currently used volatile agents on cortical SSEPs are dose-dependent increases in latency and conduction times and a decrease in amplitude of cortically, but not subcortically recorded signals.[223-227] When comparing the different volatile agents, studies have reported conflicting results.[223,225] One study suggests that halothane has a greater impact on cortical SSEPs than either isoflurane or enflurane,[225] whereas another published report supports a greater effect produced by enflurane and isoflurane than halothane.[223] None of these differences are clinically important and may be ignored by the practicing clinician. With respect to the newer agents, desflurane and sevoflurane seem to have qualitatively and quantitatively similar effects on SERs as isoflurane.[228-232] In neurologically normal patients, 0.5 to 1 MAC of any of the potent inhaled agents in the presence of nitrous oxide is compatible with monitoring of cortical SSEPs (Figs. 46-18, 46-19, and 46-20).[223,227] Neurologically impaired patients may show a significantly greater sensitivity to inhaled agents, even to the point of not tolerating any recordable level of inhaled agent. Generally, better monitoring conditions are obtained, however, with narcotic-based anesthetics with less than 1 MAC total (nitrous oxide plus potent agent) end-tidal inhaled anesthetic concentration.

Table 46-3 Ability of an Individual Anesthetic Drug to Produce a Change in Sensory and Motor Evoked Potentials That Could Be Mistaken for a Surgically Induced Change

	SSEPs		BAEPs		VEPs		Transcranial MEPs	
Drug	**LAT**	**AMP**	**LAT**	**AMP**	**LAT**	**AMP**	**LAT**	**AMP**
Isoflurane	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Enflurane	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Halothane	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Nitrous oxide*	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Barbiturates	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Etomidate	No	No	No	No	Yes	Yes	No	No
Propofol	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Droperidol	No	No	No	No	—	—	Yes	Yes
Diazepam	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Midazolam	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Ketamine	No	No	No	No	Yes	Yes	No	No
Opiates	No	No	No	No	No	No	No	No
Dexmedetomidine	No	No	No	No	No	ND	ND	No

Note: This table is not quantitative in any way. "Yes" or "no" designations indicate whether an individual drug is capable of producing an effect on any portion of the evoked response that could be mistaken for a surgically induced change.
*Increases the effect of the agent(s) with which it is used.
(p): Use of this drug and any dose may render this type of monitoring impossible for a signifieant period of time.
AMP, amplitude; BAEPs, brainstem auditory evoked potentials; LAT, latency; MEPs, motor evoked potentials; ND, no data available from the literature; SSEPs, somatosensory evoked potentials; VEPs, visual evoked potentials.

The volatile anesthetics result in increases in latency of BAEPs without significantly affecting the amplitude.[227,233-235] Volatile anesthetics cause increases in latency and decreases in amplitude in the early (middle latency) cortical responses after auditory stimulation,[234] however, and these middle latency responses are now being used to monitor the hypnotic component of general anesthetics.[32] Adequate monitoring of BAEPs is possible with any clinically useful concentrations of inhaled agents (with or without nitrous oxide) (Figs. 46-21 and 46-22).[227,233-236]

Use of the volatile agents during monitoring of VEPs results in dose-dependent increases in latency with or without changes in amplitude.[227,237-240] Isoflurane results in dose-dependent increases in latency and decreases in amplitude up to 1.8% in 100% oxygen, at which time the waveform is lost.[227,237] Enflurane in the absence of hypocarbia also leads to decrease in amplitude.[237] Halothane causes increases in latency without changes in amplitude.[238,239] Although the data from these studies seem valid, the results are not clinically relevant because the variability of VEPs in anesthetized patients is so great that satisfactory monitoring, in the opinion of many experts, is impossible using any anesthetic technique.

Although volatile anesthetics cause significant changes in the SER waveforms, it is possible to provide adequate monitoring intraoperatively in the presence of anesthetic doses of volatile anesthetics. Doses of agents causing significant depression of the

Table 46-4 Guidelines for Choosing Anesthetic Techniques During Procedures in Which Sensory Evoked Responses Are Monitored

1. Intravenous agents have significantly less effect than "equipotent" doses of inhaled anesthetics
2. Combinations of drugs generally produce "additive" effects
3. Subcortical (spinal or brainstem) sensory evoked responses are very resistant to the effects of anesthetic drugs. If subcortical responses provide sufficient information for the surgical procedure, anesthetic technique is not important, and effects on cortically recorded responses may be ignored

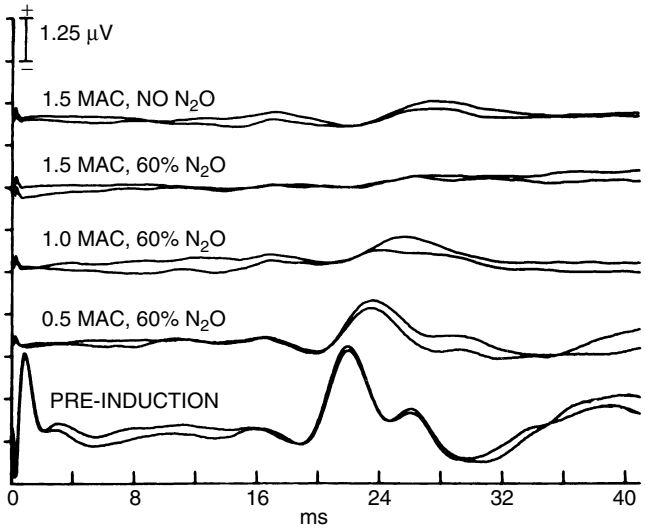

Figure 46-18 Representative somatosensory evoked potential cortical responses (C-3, C-4-FPz) at various minimum alveolar concentration (MAC) levels of isoflurane. *(From Peterson DO, Drummond JC, Todd MM: Effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans. Anesthesiology 65:35, 1986.)*

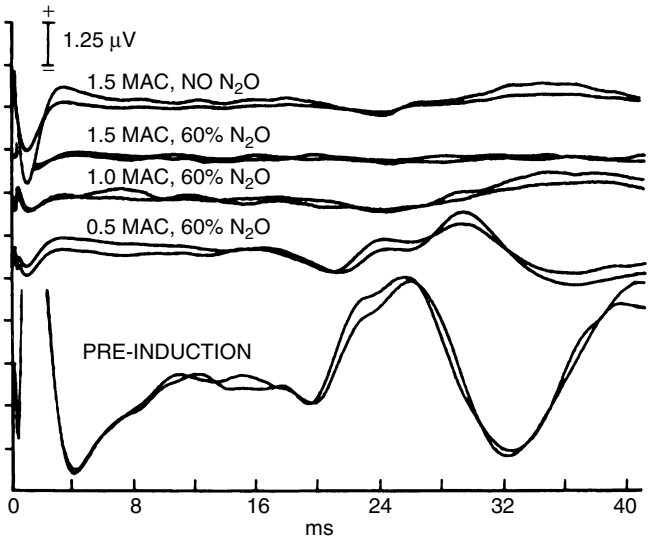

Figure 46-19 Representative somatosensory evoked potential cortical responses (C-3, or C-4-FPz) at various minimum alveolar concentration (MAC) levels of enflurane. *(From Peterson DO, Drummond JC, Todd MM: Effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans. Anesthesiology 65:35, 1986.)*

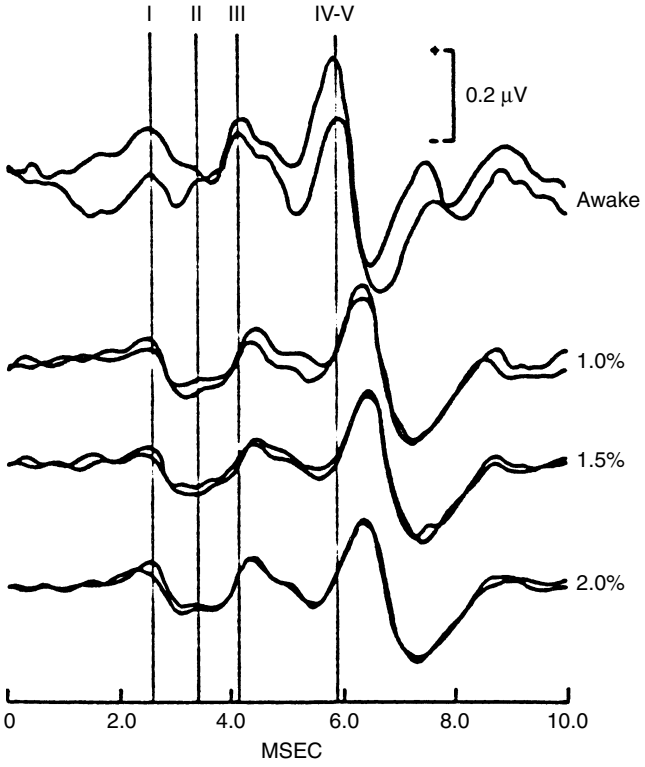

Figure 46-21 Influence of isoflurane alone on brainstem auditory evoked potential in a typical subject. Latency of peaks III and IV to V increased at 1.0%, but stabilized with increasing anesthetic depth. *(From Manninen PH, Lam AM, Nicholas JF: The effects of isoflurane–nitrous oxide anesthesia on brainstem auditory evoked potentials in humans. Anesth Analg 64:43, 1985.)*

response to be monitored must be prevented. In the authors' experience, end-tidal concentrations of inhaled agents totaling greater than 1.3 MAC have a dose-related, increasing probability of obliterating cortical SSEPs even in neurologically normal patients. Equally important, anesthetic concentration should not be changed during the critical periods of intraoperative monitoring. Critical periods are defined as periods in which surgical interventions are most likely to result in damage to neurologic tissue and changes in the SERs. Because the volatile anesthetic-induced changes in SERs are dose-dependent, increasing anesthetic dosage at a crucial point in the operative procedure can result in confusing changes in the SERs that potentially may be caused by the anesthetic, the surgical procedure, or both. The appropriate intervention is difficult to determine.

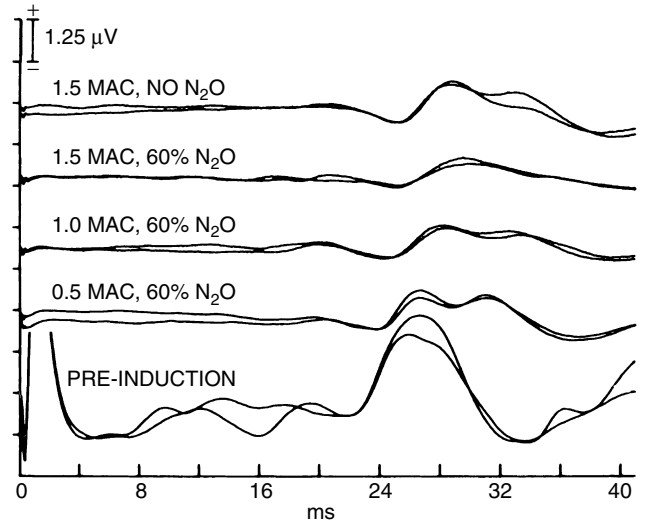

Figure 46-20 Representative somatosensory evoked potential cortical responses (C-3, C-4-FPz) at various minimum alveolar concentration (MAC) levels of halothane. *(From Peterson DO, Drummond JC, Todd MM: Effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans. Anesthesiology 65:35, 1986.)*

As with the volatile anesthetics, nitrous oxide causes differing effects on the SERs depending on the sensory system monitored. It causes decreases in amplitude without significant changes in latency in SSEPs when used alone or when added to a narcotic-based or volatile anesthetic.[223,224,241] The addition of nitrous oxide to a maintenance volatile anesthetic during the monitoring of BAEPs causes no further change.[233] Likewise, use of nitrous oxide alone causes no change in BAEPs, unless gas accumulates in the middle ear.[241] Use of nitrous oxide alone results in an increase in latency and a decrease in amplitude in VEPs, but when it is added to a volatile anesthetic technique, it causes no further changes in VEPs.[237,241]

Intravenous Agents

The effects of barbiturates on SERs have been studied in animal models and in humans. Increasing doses of thiopental in patients result in progressive dose-dependent increases in latency, decreases in amplitude of SSEPs, and progressive increases in latency of wave V in BAEPs. The changes in SSEPs are more pronounced than the changes in BAEPs, and waveforms beyond the initial primary cortical response are quickly obliterated. This finding is consistent with the theories that barbiturates affect synaptic transmission more than axonal conduction. Early wave-

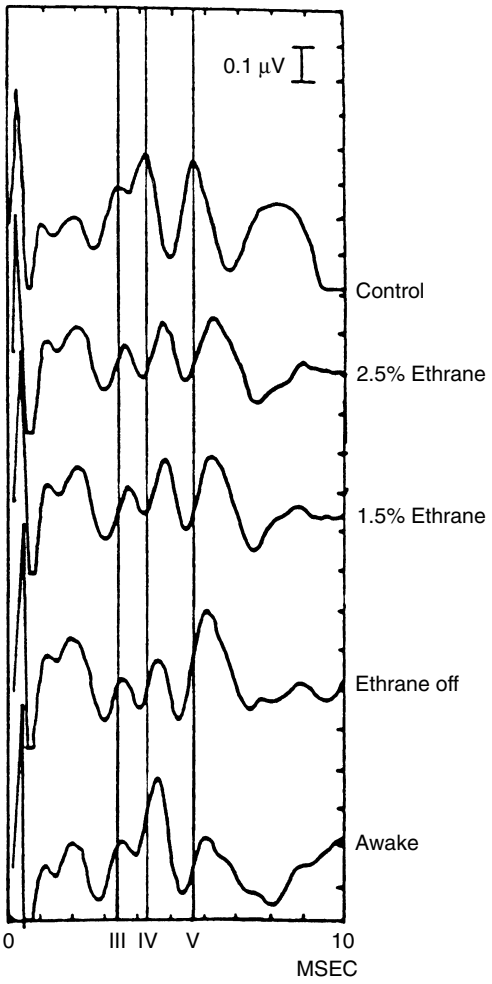

Figure 46-22 Brainstem auditory evoked potential recording obtained in one patient at different enflurane (Ethrane)-inspired concentrations. *(From Dubois MY, Sato S, Chassy J, et al: Effects of enflurane on brainstem auditory evoked responses in humans. Anesth Analg 61:898, 1982.)*

forms in SERs result primarily from axonal transmission, and later waves depend on multisynaptic pathways in addition to axonal transmission. At doses of thiopental far greater than doses producing an isoelectric EEG, adequate monitoring of early cortical and subcortical SSEPs and BAEPs was preserved.[242] Other barbiturate compounds show similar effects. Somatosensory and auditory SERs were never obliterated even at doses greater than those causing complete suppression of spontaneous EEG activity.[243] This observation is important, especially when attempting to monitor the adequacy of CBF during cerebrovascular surgery when the patient has been given large, "protective" doses of barbiturates. The EEG is isoelectric and not helpful for monitoring. The early cortical SSEP waveforms are still preserved, however, and may be very helpful in determining adequacy of CBF. Preserved ability to monitor SSEPs in head-injured patients receiving therapeutic thiopental infusions has been shown.[244] VEPs are much more sensitive to barbiturates. Low barbiturate doses obliterate all except the earliest waveforms. The early potentials persisted with increases in latency even to very high pentobarbital doses.[245] Except for VEPs, adequate perioperative monitoring of SERs is possible even in the presence of high-dose barbiturate therapy as long as the effects of the drug (increased latency with moderately decreased amplitude) are considered.

After bolus administration and intravenous infusions, etomidate causes increases in latency of all waves and prolongation of central conduction time in SSEPs. In contrast to virtually all other commonly used anesthetics, etomidate causes increases in amplitude of the cortical SSEP.[246,247] This effect may be due to an alteration in the balance of inhibitory and excitatory influences or an increase in the irritability of the CNS. This effect seems to be present in the cortex, but not in the spinal cord.[247] Etomidate infusions have been used to enhance SSEP recording in patients when it was impossible to obtain reproducible responses at the beginning of intraoperative monitoring because of the patients' pathology (Fig. 46-23). Following baseline responses that could not be monitored, the etomidate augmentation of the SSEP allowed adequate monitoring and detection of intraoperative

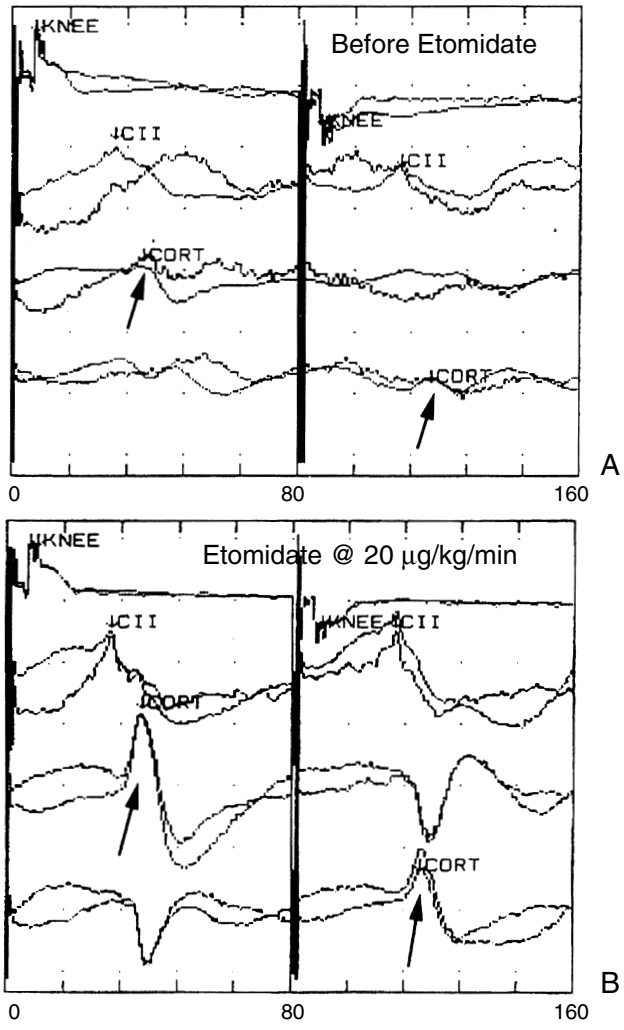

Figure 46-23 Effects of etomidate on somatosensory evoked potential. **A,** The *top tracings* were obtained from a mildly mentally impaired patient with severe kyphoscoliosis during the early maintenance phase of anesthesia using isoflurane and fentanyl. **B,** The *bottom tracings* were obtained after discontinuing isoflurane and instituting an etomidate infusion at 20 μg/kg/min. Note dramatically increased amplitude and clarity of the signal in the cortical channels (marked by *arrows*), which both are recorded with the same amplification scale.

events leading to compromise of the spinal cord.[247] The effects of etomidate on BAEPs are dose-dependent increases in latency and decreases in amplitude that are not clinically significant.[248]

Droperidol in premedicant doses has been shown to have varying effects on SSEPs. In most patients, decreases in amplitude and loss of late waves were noted. In a few patients, increases in amplitude were noted. In all patients, conduction time was prolonged.[249] Effects were not clinically significant. Benzodiazepines also can cause changes in SERs.[250,251] Diazepam causes increases in latency and decreases in amplitude of SSEPs, increases in latency in the cortical response after auditory stimulation, and no change in BAEPs.[250,251] Midazolam causes decreases in amplitude without changes in latency of SSEPs.[246]

Generally, opioids cause small dose-dependent increases in latency and decreases in amplitude of SSEPs. These changes are not clinically significant. Effects on amplitude are more variable than the latency increases.[252,253] Even at large doses of fentanyl (60 μg/kg), reproducible SSEPs can be recorded.[253] Other opiates cause similar dose-dependent changes in SSEPs.[252,254] Opioids can be used even in high doses in patients requiring intraoperative SSEP monitoring without impairment of ability to monitor neurologic function adequately. Opioid-induced changes must be taken into account, however, when evaluating the recordings. Large intravenous bolus administration of opioids should be avoided at times of potential surgical compromise to neurologic function to prevent confusing the interpretation of SEP changes if they develop. BAEPs were resistant to doses of fentanyl of 50 μg/kg with no changes observed in absolute latency, interpeak latency, or amplitude.[255]

Based on several case reports and small series, dexmedetomidine seems to be compatible with all types of evoked potential monitoring (including MEPs), and does not produce changes that would be mistaken for a surgically induced change. Data are limited, and large studies are lacking entirely. As the use of this drug increases, more data should become available, but at this time, use of dexmedetomidine does not seem to be problematic.

Anesthesia and Motor Evoked Potentials

Except in the case of neurogenic MEPs, effects of anesthetics are surprisingly profound, particularly on MEP recordings from muscle produced by either single pulse transcranial electric or especially magnetic stimulation (see Table 46-3).[256-261] Anesthetic techniques typically used by most anesthesiologists for spine surgery would produce prohibitive depression of the MEP.[262,263] Investigators showed in several studies that intravenous agents produce significantly less depression, and techniques using any of a combination of ketamine, opiates, etomidate, and propofol have been described.[264-270] The authors have had excellent experience with a combination of propofol and remifentanil, which also is supported in the literature.

Anesthetic effects on MEP responses recorded at spinal levels seem to be less serious. When responses are recorded from muscle, neuromuscular blocking agents should be monitored quantitatively, maintaining T1 twitch height at around 30% of control values to prevent excessive movement during the operation.[136,257] When responses are not recorded from muscle, profound relaxation is desirable because gross muscle movement produced by MEP stimulation is eliminated, facilitating the surgical procedure. More recent studies using rapid trains of stimuli with transcranial electric and magnetic stimulus techniques have produced responses that are more resistant to the effects of anesthetic agents, and more "traditional" techniques using inhaled agents and narcotics may be used.[271-273] Most studies support the use of total intravenous anesthesia as preferable to techniques using nitrous oxide or potent inhaled agents, however. Precise control of the anesthetic and avoidance of boluses during critical monitoring periods seem to be even more important than for SSEPs, and active cooperation of the anesthesia care team is essential for good, reproducible results. Figure 46-24 shows the dramatic effect of introduction of 0.3 MAC isoflurane to a total intravenous technique using propofol and remifentanil.

Pathophysiologic Effects on the Electroencephalogram

Hypoxia

Hypoxia may produce inadequate delivery of oxygen to the cerebral cortex generating EEG, and changes similar to those occurring with ischemia result. Initially, hypoxemia may not result in any EEG changes because the brain can increase blood flow to compensate. When the hypoxemia becomes severe enough, further increases in flow are impossible, and EEG changes occur. "Slowing" of the EEG during hypoxia is a nonspecific global effect. Fast frequencies are lost, and low frequencies dominate. Eventually, the EEG is abolished as the brain shuts down electric activity and diverts all oxygen delivered to maintenance of cellular integrity.

Hypotension

In a normal, awake patient, significant levels of hypotension seem to be needed to cause the earliest of CNS signs, as measured by discrimination tests such as the flicker-fusion test. This test examines the flicker rate at which the observer perceives the light to be continuous. In the early days of deliberate hypotension, this test was part of the preoperative evaluation to judge how far the pressure could be reduced during the operation. Clear signs of confusion and inability to concentrate or respond properly to simple commands generally represent very low levels of cerebral perfusion when caused by hypotension because the normal cerebral circulation has a large capacity to vasodilate and maintain normal flow in the face of significant hypotension.

The EEG changes associated with even this level of hypotension are not dramatic, although they are clear by comparison with a previously active recording. Herein lies the problem with using intraoperative EEG to determine whether a given level of hypotension has resulted in brain ischemia. EEG changes are not very pronounced and are bilateral. These changes also are nearly identical to the changes caused by increasing doses of many anesthetic drugs. EEG changes associated with hypotension can be detected, but when the hypotension is induced slowly and associated with changes in anesthetic drugs (e.g., use of isoflurane to reduce blood pressure), the changes are very difficult to interpret. EEG changes associated with acute, severe hypotension such as may be caused by sudden arrhythmias are easier to read. Many patients undergoing surgery do not have a normal cerebral circulation, however. In these individuals, even mild hypotension may result in significant cerebral ischemia. In these individuals, moni-

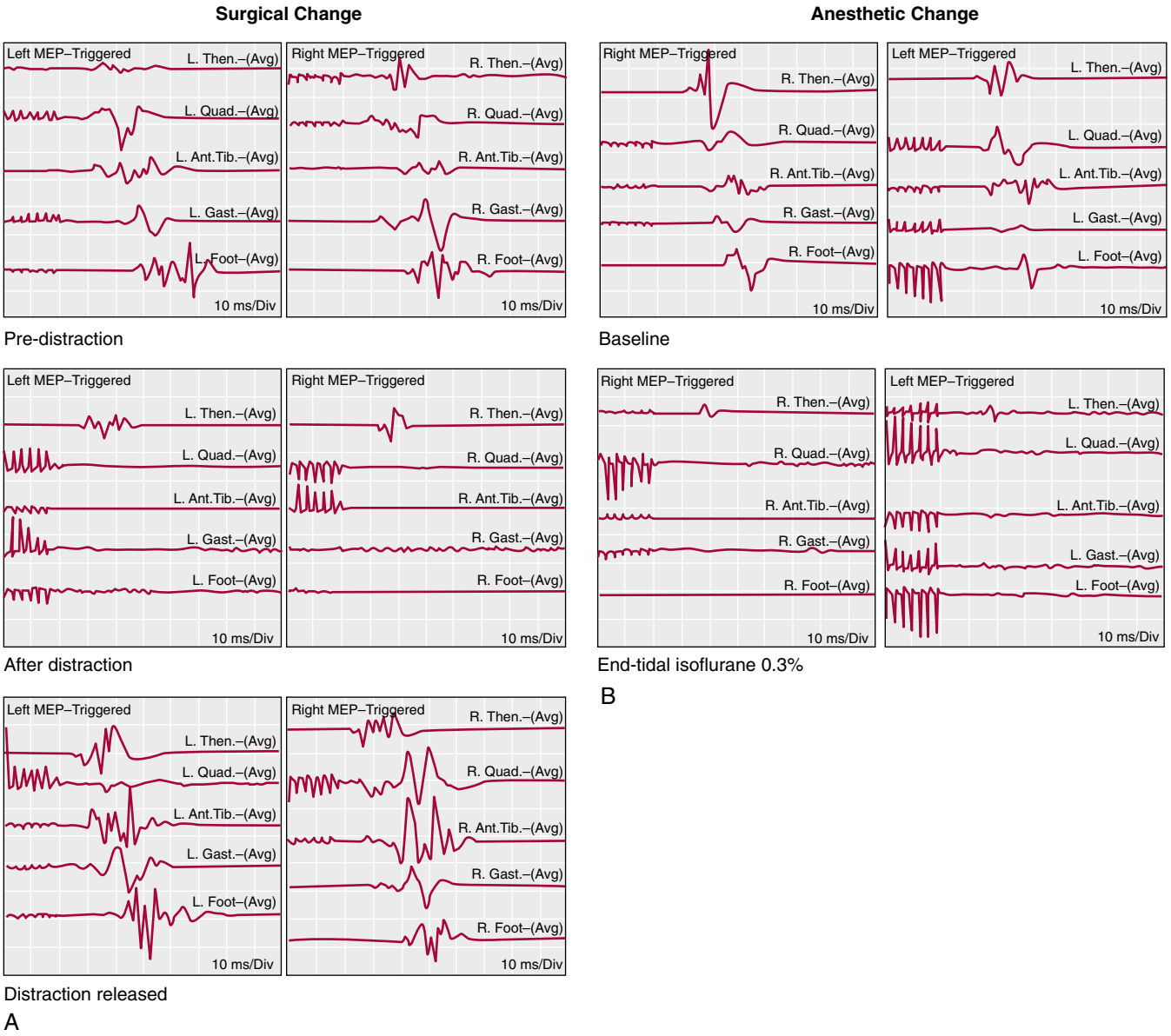

Figure 46-24 A, Transcranial electrical motor evoked potential recording showing surgically induced change during spine surgery (scoliosis repair). **B,** Motor evoked potential with an anesthetic-induced change. Note similarity of the change pattern except that in the anesthetic-induced change, the responses in the upper extremity also changed. Left-sided and right-sided responses are shown on the corresponding panel. A single upper extremity response is shown (*top tracing*) in each panel. Responses from four muscle groups in each lower extremity are shown directly below.

toring the EEG during planned hypotension may be helpful, provided that other causes of similar EEG changes may be carefully controlled. There remains little literature to support the use of EEG monitoring during hypotension, but in our opinion, when the EEG is being monitored (e.g., during carotid surgery), EEG changes secondary to hypotension really do represent cerebral ischemia of a significant degree and should be considered an important finding.

Hypothermia

During cooling on CPB, the total power and peak power frequency of the high-frequency band were highly correlated with temperature using Fourier analysis and spectral edge data; however, there was significant variability between subjects, especially during cooling.[274] Complete EEG suppression usually develops at 15°C to 18°C. Levy and colleagues[162] showed an improved ability to quantify the effects of hypothermia on the EEG using an EEG processing technique known as "approximate entropy."

Hypercarbia and Hypocarbia

Hypocapnia is known to activate excitable seizure foci, and in rare cases may produce EEG evidence of cerebral ischemia even in awake subjects.[275] Hypercapnia, unless severe and associated with hypoxemia, has only indirect effects secondary to increased CBF. In an anesthetized patient, hypercarbia-associated increases in

CBF may have similar effects to the effects seen with increasing end-tidal tension of volatile anesthetics.[276]

Untoward Events

One of the suggested reasons for monitoring the brain of an anesthetized patient is to enable detection of injuries to the nervous system that would not be otherwise apparent. Although there are hundreds of such case reports in the literature and many in the authors' experience, cost-effectiveness of such monitoring is unclear. In a more recent case at the authors' institution, severe EEG changes occurred at the beginning of a carotid endarterectomy, before surgical incision, and were unassociated with any other vital sign changes or hypotension. Immediate angiography revealed acute carotid occlusion and completely changed the operation performed with this patient, and the patient recovered completely. There are intraoperative events that could lead to CNS insult, which, if detected early, could be rapidly reversed or treated to prevent permanent injury. Given the rarity of such events, however, it is extremely unlikely that such monitoring would be shown to be beneficial in any foreseeable randomized trial. If the "at-risk" patient could be identified preoperatively, perhaps the EEG or other types of neuromonitoring could be useful in detecting untoward CNS events during anesthesia, such as a new stroke after elective general surgery.

Physiologic Factors Influencing Sensory Evoked Responses

Numerous physiologic variables, including systemic blood pressure, temperature (local and systemic), and blood gas tensions, can influence SEP recordings. With decreases in mean arterial blood pressure to below levels of cerebral autoregulation owing to either blood loss or vasoactive agents, progressive changes in SERs have been noted. SSEP changes observed are progressive decreases in amplitude until loss of the waveform with no changes in latency.[277,278] BAEPs are resistant to even profound levels of hypotension (mean arterial pressure of 20 mm Hg in dogs).[277] Cortical (synaptic) function necessary to produce cortical SERs seems to be more sensitive to hypoperfusion than spinal cord or brainstem, nonsynaptic transmission.[278] Rapid decreases in blood pressure to levels above the lower limit of autoregulation also have been associated with transient SSEP changes of decreased amplitude that resolve after several minutes of continued hypotension at the same level.[279] Reversible SSEP changes at systemic pressures within the normal range have been observed in patients undergoing spinal distraction during scoliosis surgery. These changes resolved with increases of systemic blood pressure to slightly above the patient's normal pressure, suggesting that the combina-

Table 46-5 Current Practices in Neurologic Monitoring

Procedure	Monitors	Current Practice
Carotid endarterectomy	Awake patient neurologic examination, EEG, SSEP, TCD	NIH recommends use of one of these four available monitors.
	CO	Threshold value not determined, inadequate normative population data
Scoliosis surgery	SSEP	Monitoring recommended, and may substitute for wake-up testing
	Wake-up test	Largely abandoned in centers using electrophysiologic monitoring. Monitoring is not continuous and false-negative monitoring patterns have been reported.
	MEP	Increased clinical use now that transcranial electrical stimulation is FDA approved. Useful in combination with SSEP
Acoustic neuroma	Facial nerve monitor	Facial nerve monitoring recommended
	BAEP	BAEP shows some clinical evidence of improved outcome in some procedures.
Intracranial aneurysm clipping	SSEP, EEG	Used routinely in some centers; limited clinical data on outcome, but appears clinically useful during anterior circulation procedures
Cranial nerve V decompression	BAEP	Used in some centers, reduces hearing loss
Cranial nerve VII decompression	BAEP	Data from small series show improved hearing preservation
Supratentorial mass lesions	SSEP	Used in some centers in selected high-risk procedures
Infratentorial mass lesions	BAEP/SSEP	BAEP to detect retractor-related cranial nerve VIII injury; SSEP in rare, high-risk lesions adjacent to ascending sensory pathways
Decompression of spinal stenosis	SSEP	Used in some centers in high-risk procedures (more often cervical)
Spinal cord trauma	SSEP/MEP	Used in some centers in high-risk procedures
Cardiopulmonary bypass	EEG, TCD, $SjvO_2$, CO	Used routinely in some centers, actively studied, but no outcome data as of yet
Aortic coarctation	SSEP	Used routinely in a few centers, no widespread acceptance
Aortic aneurysm repair	SSEP	Used routinely in a few centers, no widespread acceptance
	MEP	Used routinely in a few centers, no widespread acceptance

BAEP, brainstem auditory evoked potential; CO, cerebral oximetry; EEG, electroencephalogram; FDA, U.S. Food and Drug Administration; MEP, motor evoked potential; NIH, National Institutes of Health; $SjvO_2$, jugular bulb venous oxygen saturation; TCD, transcranial Doppler.

tion of surgical manipulation with levels of hypotension generally considered "safe" could result in spinal cord ischemia.[280]

Changes in temperature also affect SERs. Hypothermia causes increases in latency and decreases in amplitude of cortical and subcortical SERs after all types of stimulation.[281-283] Hyperthermia also alters SERs, with increases in temperature leading to decreases in amplitude in SSEPs and loss of SSEPs at 42°C during induced hyperthermia.[284]

Changes in arterial blood gas tensions have been reported to alter SERs, probably in relation to changes in blood flow or oxygen delivery to neural structures.[285,286] Hypoxia produces SSEP changes (decreased amplitude) similar to the changes seen with ischemia.[286] Decreased oxygen delivery associated with anemia during isovolemic hemodilution results in progressive increases in latency of SSEPs and VEPs that become significant at hematocrits less than 15%. Changes in amplitude were variable until very low hematocrits (approximately 7%) were reached, at which point the amplitude of all waveforms decreased.[287]

Summary

Regardless of the type of intraoperative neurologic monitor, several principles must be observed for neurologic monitoring to provide potential benefit to the patient. First, the pathway at risk during the surgical procedure must be amenable to monitoring. Second, if evidence of injury to the pathway is detected, there must be some intervention possible. If changes in the neurologic monitor are detected, and no intervention is possible, although the monitor may be of prognostic value, it does not have the potential to provide direct benefit to the patient from early detection of impending neurologic injury. Third, the monitor must provide reliable and reproducible data. If the data have a high degree of variability in the absence of clinical interventions, their utility for detecting clinically significant events is limited.

This chapter has reviewed the most common clinically used intraoperative neurologic monitors. Ideally, clinical studies would provide outcome data on the efficacy of a neurologic monitor in a given procedure to improve neurologic outcome. Although there is a wealth of clinical experience with many of these monitoring modalities, there is little in the way of randomized prospective studies evaluating the efficacy of neurologic monitoring. Based on clinical experience with neurologic monitoring and nonrandomized clinical studies in which neurologic monitoring is used and generally compared with historical controls, practice patterns for use of neurologic monitoring have developed. In certain procedures, neurologic monitoring is recommended and used by most centers; in other procedures, monitoring is used almost routinely in some centers, but not in others; and in some procedures, there is no clear clinical experience or evidence that would indicate that monitoring is useful at all (experimental use). Finally, there are procedures in which monitoring is used selectively for patients believed to be at higher-than-usual risk for intraoperative neurologic injury. Table 46-5 provides a summary of current clinical practice.

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Jørgen Viby-Mogensen

47 Neuromuscular Monitoring

Key Points

1. Residual postoperative neuromuscular blockade causes decreased chemoreceptor sensitivity to hypoxia, functional impairment of the pharyngeal and upper esophageal muscles, impaired ability to maintain the airway, and an increased risk for the development of postoperative pulmonary complications.
2. It is difficult and often impossible to exclude with certainty clinically significant residual curarization by clinical evaluation of recovery of neuromuscular function.
3. Absence of tactile fade in the response to train-of-four (TOF) stimulation, tetanic stimulation, and double-burst stimulation does not exclude significant residual blockade.
4. Adequate recovery of postoperative neuromuscular function cannot be guaranteed without objective neuromuscular monitoring.
5. Good evidence-based practice dictates that clinicians should always quantitate the extent of neuromuscular blockade by objective monitoring.
6. To exclude clinically significant residual neuromuscular blockade, the TOF ratio, when measured mechanically or by electromyography, must exceed 0.9.
7. Total twitch depression during surgery should be avoided. Whenever possible, one or two TOF responses should be maintained.
8. Antagonism of the neuromuscular block with a cholinesterase inhibitor should not be initiated before at least two or preferably three or four responses to TOF stimulation are observed.
9. If sufficient recovery (TOF ≥ 0.9) has not been documented objectively at the end of the surgical procedure, the neuromuscular block should be antagonized.

Quite often, the degree of neuromuscular blockade during and after anesthesia is evaluated with clinical criteria alone. However, clinically significant residual neuromuscular blockade (i.e., paralysis) may persist postoperatively.[1,2] Objective monitoring of the degree of neuromuscular block during and after anesthesia should reduce the problems of residual neuromuscular blockade.[3,4]

In awake patients, muscle power can be evaluated by tests of voluntary muscle strength, but during anesthesia and recovery from anesthesia this is not possible. Instead, the clinician uses clinical tests to assess muscle power directly and to estimate neuromuscular function indirectly (muscle tone; feel of the anesthesia bag as an indirect measure of pulmonary compliance, tidal volume, and inspiratory force). All these tests, however, are influenced by factors other than the degree of neuromuscular blockade. Therefore, whenever more precise information regarding the status of neuromuscular functioning is desired, the response of muscle to nerve stimulation should be assessed. This procedure also takes into account the considerable variation in individual response and sensitivity to muscle relaxants.

This chapter reviews the basic principles of peripheral nerve stimulation and the requirements for effective use of nerve stimulators. It also describes the response to nerve stimulation during depolarizing (phase I and phase II) and nondepolarizing neuromuscular blockade. Finally, methods of evaluating evoked neuromuscular responses with and without the availability of recording equipment are discussed.

Types of Peripheral Nerve Stimulation

Neuromuscular function is monitored by evaluating the muscular response to supramaximal stimulation of a peripheral motor nerve. Two types of stimulation can be used: electrical and magnetic. Electrical nerve stimulation is by far the most commonly used method in clinical practice and is described in detail in this chapter. In theory, magnetic nerve stimulation has several advantages over electrical nerve stimulation.[5,6] It is less painful and does not require physical contact with the body. However, the equipment required is bulky and heavy, it cannot be used for train-of-four (TOF) stimulation, and it is difficult to achieve

supramaximal stimulation with this method. Therefore, magnetic nerve stimulation is very seldom used in clinical anesthesia.

Principles of Peripheral Nerve Stimulation

The reaction of a single muscle fiber to a stimulus follows an all-or-none pattern. In contrast, the response of the whole muscle depends on the number of muscle fibers activated. If a nerve is stimulated with sufficient intensity, all fibers supplied by the nerve will react, and the maximum response will be triggered. After administration of a neuromuscular blocking drug, the response of the muscle decreases in parallel with the number of fibers blocked. The reduction in response during constant stimulation reflects the degree of neuromuscular blockade.

For the preceding principles to be in effect, the stimulus must be truly maximal throughout the period of monitoring; therefore, the electrical stimulus applied is usually at least 20% to 25% above that necessary for a maximal response. For this reason the stimulus is said to be supramaximal; however, supramaximal electrical stimulation hurts, which is not a concern during anesthesia, but during recovery the patient may be awake enough to experience the discomfort of nerve stimulation. Therefore, some researchers advocate stimulation with submaximal current during recovery. Although several investigations indicate that testing of neuromuscular function can be reliably performed postoperatively with submaximal stimulation,[7,8] the accuracy of such monitoring is unacceptable with low current.[9]

Patterns of Nerve Stimulation

For evaluation of neuromuscular function, the most commonly used patterns of electrical nerve stimulation are single-twitch, TOF, tetanic, post-tetanic count (PTC), and double-burst stimulation (DBS).

Single-Twitch Stimulation

In the single-twitch mode of stimulation, single supramaximal electrical stimuli are applied to a peripheral motor nerve at frequencies ranging from 1.0 Hz (once every second) to 0.1 Hz (once every 10 seconds) (Fig. 47-1). The response to single-twitch stimulation depends on the frequency at which the individual stimuli are applied. If the rate of delivery is increased to greater than 0.15 Hz, the evoked response will gradually decrease and settle at a lower level. As a result, a frequency of 0.1 Hz is generally used. Because 1-Hz stimulation shortens the time necessary to determine supramaximal stimulation, this frequency is sometimes used during induction of anesthesia; however, the apparent time of onset and length of neuromuscular blockade depend on the pattern and duration of stimulation. Therefore, results obtained with 1-Hz single-twitch stimulation cannot be compared with results obtained by using, for instance, 0.1-Hz single-twitch stimulation or TOF stimulation.[10]

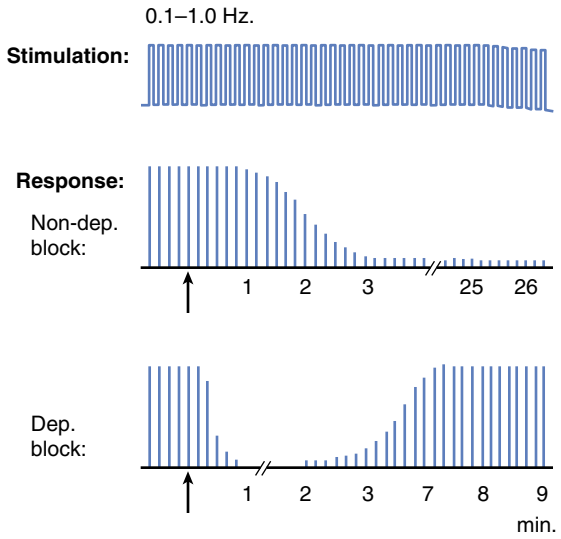


Figure 47-1 Pattern of electrical stimulation and evoked muscle responses to single-twitch nerve stimulation (at frequencies of 0.1 to 1.0 Hz) after injection of nondepolarizing (Non-dep.) and depolarizing (Dep.) neuromuscular blocking drugs (*arrows*). Note that except for the difference in time factors, no differences in the strength of the evoked responses exist between the two types of block.

Train-of-Four Stimulation

In TOF nerve stimulation, introduced by Ali and associates[11,12] during the early 1970s, four supramaximal stimuli are given every 0.5 second (2 Hz) (Fig. 47-2). When used continuously, each set (train) of stimuli is normally repeated every 10th to 20th second. Each stimulus in the train causes the muscle to contract, and "fade" in the response provides the basis for evaluation. That is, dividing the amplitude of the fourth response by the amplitude of the first response provides the TOF ratio. In the control response (the response obtained before the administration of a muscle relaxant), all four responses are ideally the same: the TOF

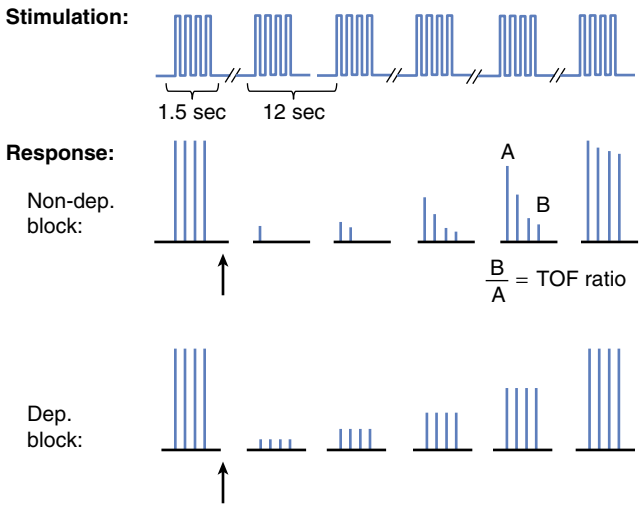


Figure 47-2 Pattern of electrical stimulation and evoked muscle responses to TOF nerve stimulation before and after injection of nondepolarizing (Non-dep.) and depolarizing (Dep.) neuromuscular blocking drugs (*arrows*).

ratio is 1.0. During a partial nondepolarizing block, the ratio decreases (fades) and is inversely proportional to the degree of blockade. During a partial depolarizing block, no fade occurs in the TOF response; ideally, the TOF ratio is approximately 1.0. Fade in the TOF response after injection of succinylcholine signifies the development of a phase II block (discussed later in the section on depolarizing neuromuscular blockade).

The advantages of TOF stimulation are greatest during nondepolarizing blockade because the degree of block can be read directly from the TOF response even though a preoperative value is lacking. In addition, TOF stimulation has some advantages over tetanic stimulation: it is less painful and, unlike tetanic stimulation, does not generally affect the degree of neuromuscular blockade.

Tetanic Stimulation

Tetanic stimulation consists of very rapid (e.g., 30-, 50-, or 100-Hz) delivery of electrical stimuli. The most commonly used pattern in clinical practice is 50-Hz stimulation given for 5 seconds, although some investigators have advocated the use of 50-, 100-, and even 200-Hz stimulation for 1 second. During normal neuromuscular transmission and a pure depolarizing block, the muscle response to 50-Hz tetanic stimulation for 5 seconds is sustained. During a nondepolarizing block and a phase II block after the injection of succinylcholine, the response will not be sustained (i.e., fade occurs) (Fig. 47-3).

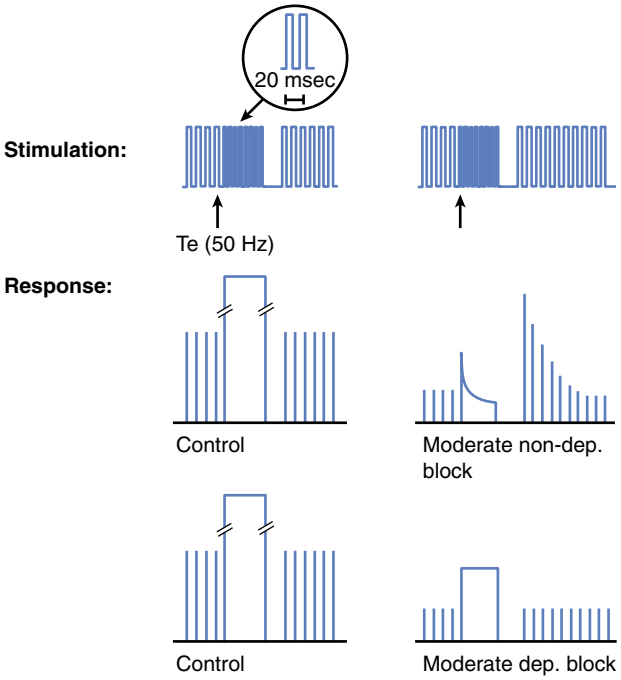


Figure 47-3 Pattern of stimulation and evoked muscle responses to tetanic (50-Hz) nerve stimulation for 5 seconds (Te) and post-tetanic twitch stimulation (1.0-Hz) (*arrows*). Stimulation was applied before the injection of neuromuscular blocking drugs and during moderate nondepolarizing (non-dep.) and depolarizing (dep.) blocks. Note the fade in the response to tetanic stimulation, plus the post-tetanic facilitation of transmission during nondepolarizing blockade. During depolarizing blockade, the tetanic response is well sustained, and no post-tetanic facilitation of transmission occurs.

Fade in response to tetanic stimulation is normally considered a presynaptic event; the traditional explanation is that at the start of tetanic stimulation, large amounts of acetylcholine are released from immediately available stores in the nerve terminal. As these stores become depleted, the rate of acetylcholine release decreases until equilibrium between mobilization and synthesis of acetylcholine is achieved. Despite this equilibrium, the muscle response caused by tetanic stimulation of the nerve at, for example, 50 Hz is maintained (given normal neuromuscular transmission) simply because the acetylcholine released is many times greater than the amount necessary to evoke a response. When the "margin of safety"[13] at the postsynaptic membrane (i.e., the number of free cholinergic receptors) is reduced by nondepolarizing neuromuscular blocking drugs, a typical reduction in twitch height is seen with a fade during, for instance, repetitive stimulation. In addition to this postsynaptic block, nondepolarizing neuromuscular blocking drugs may also block presynaptic neuronal-type acetylcholine receptors, thereby leading to impaired mobilization of acetylcholine within the nerve terminal.[14] This effect substantially contributes to fade in the response to tetanic (and TOF) stimulation. Although the degree of fade depends primarily on the degree of neuromuscular blockade, fade also depends on the frequency (Hz) and the length (seconds) of stimulation and on how often tetanic stimuli are applied. Unless these variables are kept constant, results from different studies using tetanic stimulation cannot be compared.

During partial nondepolarizing blockade, tetanic nerve stimulation is followed by a post-tetanic increase in twitch tension (i.e., post-tetanic facilitation of transmission) (see Fig. 47-3). This event occurs because the increase in mobilization and synthesis of acetylcholine caused by tetanic stimulation continues for some time after discontinuation of stimulation. The degree and duration of post-tetanic facilitation depend on the degree of neuromuscular blockade, with post-tetanic facilitation usually disappearing within 60 seconds of tetanic stimulation. Post-tetanic facilitation is evident in electromyographic, acceleromyographic, and mechanical recordings during partial nondepolarizing neuromuscular blockade. In contrast, post-tetanic twitch potentiation, which sometimes occurs in mechanical recordings before any neuromuscular blocking drug has been given, is a muscular phenomenon that is not accompanied by an increase in the compound muscle action potential.

Tetanic stimulation is very painful and therefore not normally acceptable to an unanesthetized patient. Furthermore, especially in the late phase of neuromuscular recovery, tetanic stimulation may produce lasting antagonism of neuromuscular blockade in the stimulated muscle such that the response of the tested site may no longer be representative of other muscle groups.[15]

Traditionally, tetanic stimulation has been used to evaluate residual neuromuscular blockade but is too painful to use in an unanesthetized patient. Except in connection with the technique of PTC (see later), tetanic stimulation has very little place in everyday clinical anesthesia. If the response to nerve stimulation is recorded, all the information required can be obtained from the response to TOF nerve stimulation. In contrast, if the response to nerve stimulation is evaluated only by tactile evaluation[16,17] or by eye (Viby-Mogensen and colleagues, unpublished observation), even experienced observers are unable to judge the response of tetanic stimulation with sufficient certainty to exclude residual neuromuscular blockade.

Post-Tetanic Count Stimulation

Injection of a nondepolarizing neuromuscular blocking drug in a dose sufficient to ensure smooth tracheal intubation causes intense neuromuscular blockade of the peripheral muscles. Because no response to TOF and single-twitch stimulation occurs under these conditions, these modes of stimulation cannot be used to determine the degree of blockade. It is possible, however, to quantify intense neuromuscular blockade of the peripheral muscles by applying tetanic stimulation (50 Hz for 5 seconds) and observing the post-tetanic response to single-twitch stimulation given at 1 Hz starting 3 seconds after the end of tetanic stimulation.[18] During intense blockade, there is no response to either tetanic or post-tetanic stimulation (Fig. 47-4). However, when the intense neuromuscular blockade dissipates and before the first response to TOF stimulation reappears, the first response to post-tetanic twitch stimulation occurs. As the intense block dissipates, more and more responses to post-tetanic twitch stimulation appear. For a given neuromuscular blocking drug, the time until return of the first response to TOF stimulation is related to the number of post-tetanic twitch responses present at a given time (i.e., the PTC) (Fig. 47-5).[18-22]

The PTC method is mainly used to assess the degree of neuromuscular blockade when there is no reaction to single-twitch or TOF nerve stimulation, as may be the case after injection of a large dose of a nondepolarizing neuromuscular blocking drug. However, PTC can also be used whenever sudden movements must be eliminated (e.g., during ophthalmic surgery). The necessary level of blockade of the adductor pollicis muscle to ensure paralysis of the diaphragm depends on the type of anesthesia and, in the intensive care unit, on the level of sedation. To ensure elimination of any bucking or coughing in response to tracheobronchial stimulation, neuromuscular blockade of the peripheral muscles must be so intense that no response to post-tetanic twitch stimulation can be elicited (PTC 0) (Fig. 47-6).[19-23]

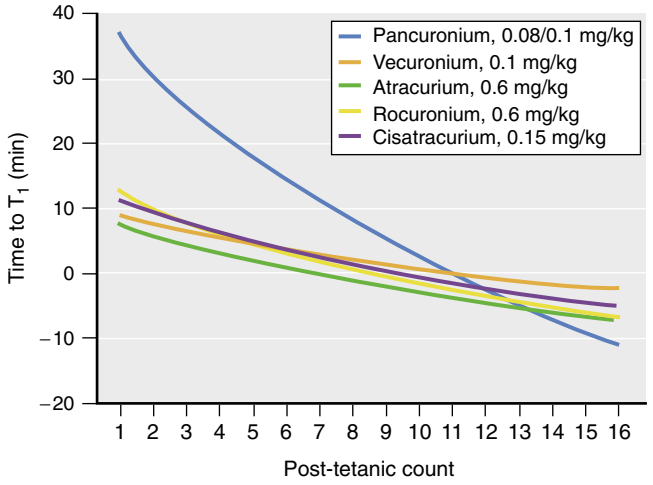


Figure 47-5 Relationship between the post-tetanic count and time when onset of train-of-four (T_1) is likely to be elicited for various neuromuscular blocking agents. *(From El-Orbany MI, Joseph JN, Salem MR: The relationship of post-tetanic count and train-of-four responses during recovery from intense cisatracurium-induced neuromuscular blockade. Anesth Analg 97:80, 2003.)*

The response to PTC stimulation depends primarily on the degree of neuromuscular blockade. It also depends on the frequency and duration of tetanic stimulation, the length of time between the end of tetanic stimulation and the first post-tetanic stimulus, the frequency of the single-twitch stimulation, and also (probably) the duration of single-twitch stimulation before tetanic stimulation. When the PTC method is used, these variables should be kept constant. In addition, because of possible antagonism of neuromuscular blockade in the hand, tetanic stimulation should not be performed more often than every 6 minutes.[18] If the hand muscles undergo antagonism of neuromuscular blockade while the rest of the body is still paralyzed, the hand muscles are no longer useful for monitoring.

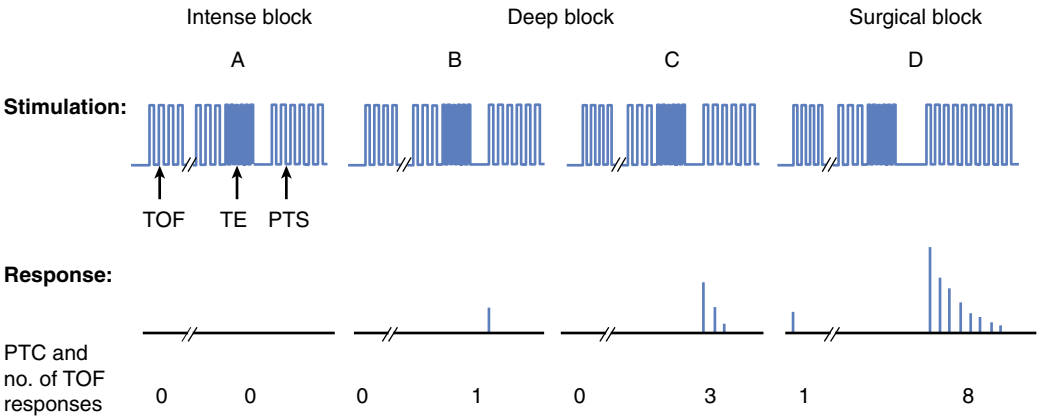


Figure 47-4 Pattern of electrical stimulation and evoked muscle responses to train-of-four (TOF) nerve stimulation, 50-Hz tetanic nerve stimulation for 5 seconds (TE), and 1.0-Hz post-tetanic twitch stimulation (PTS) during four different levels of nondepolarizing neuromuscular blockade. During intense blockade of peripheral muscles (**A**), no response to any of the forms of stimulation occurs. During less pronounced blockade (deep blockade, **B** and **C**), there is still no response to TOF stimulation, but post-tetanic facilitation of transmission is present. During surgical blockade (**D**), the first response to TOF appears and post-tetanic facilitation increases further. The post-tetanic count (see text) is 1 during very deep block (**B**), 3 during less deep block (**C**), and 8 during surgical (or moderate) block (**D**).

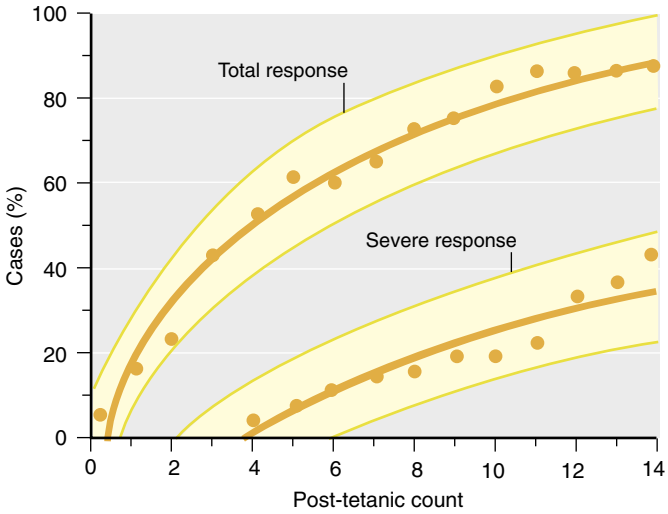


Figure 47-6 Relationship between the rate of muscle response to stimulation of the tracheal carina and the degree of neuromuscular blockade of peripheral muscles, as evaluated by post-tetanic count (PTC). The subjects were 25 patients anesthetized with thiopental, nitrous oxide, and fentanyl and given vecuronium (0.1 mg/kg) for tracheal intubation. For comparison, the first response to train-of-four stimulation usually occurs when the PTC is approximately 10 (range, 6 to 16). The carina was stimulated with a soft sterile rubber suction catheter introduced via the endotracheal tube. The total response consisted of mild responses plus severe responses. A mild response was said to occur if stimulation of the carina induced only slight bucking that did not interfere with surgery. A severe response was said to occur if stimulation elicited bucking that interfered with surgery and required intervention. Elimination of severe responses requires an intense neuromuscular blockade; PTC must be less than 2 to 3, and elimination of all reactions requires that PTC be 0. *(From Fernando PUE, Viby-Mogensen J, Bonsu AK, et al: Relationship between post-tetanic count and response to carinal stimulation during vecuronium-induced neuromuscular blockade. Acta Anaesthesiol Scand 31:593, 1987. Copyright 1987, Munksgaard International Publishers, Ltd. Copenhagen, Denmark.)*

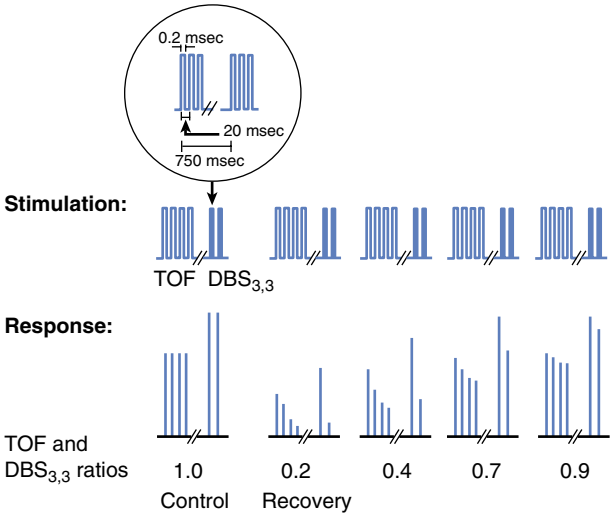


Figure 47-7 Pattern of electrical stimulation and evoked muscle responses to train-of-four (TOF) nerve stimulation and double-burst nerve stimulation (i.e., three impulses in each of two tetanic bursts, $DBS_{3,3}$) before injection of muscle relaxants (control) and during recovery from nondepolarizing neuromuscular blockade. The TOF ratio is the amplitude of the fourth response to TOF divided by the amplitude of the first response. The $DBS_{3,3}$ ratio is the amplitude of the second response to $DBS_{3,3}$ divided by the amplitude of the first response. (See text for further explanation.)

Double-Burst Stimulation

DBS consists of two short bursts of 50-Hz tetanic stimulation separated by 750 msec. The duration of each square wave impulse in the burst is 0.2 msec (Fig. 47-7). Although the number of impulses in each burst can vary, DBS with three impulses in each of the two tetanic bursts ($DBS_{3,3}$) is most commonly used.[24-26]

In nonparalyzed muscle, the response to $DBS_{3,3}$ is two short muscle contractions of equal strength. In a partly paralyzed muscle, the second response is weaker than the first (i.e., the response fades) (see Fig 47-7). Measured mechanically, the TOF ratio correlates closely with the $DBS_{3,3}$ ratio. DBS was developed with the specific aim of allowing manual (tactile) detection of small amounts of residual blockade under clinical conditions,[24] and during recovery and immediately after surgery, tactile evaluation of the response to $DBS_{3,3}$ is superior to tactile evaluation of the response to TOF stimulation.[26,27] However, as shown in Figure 47-8, absence of fade in the manually evaluated response to $DBS_{3,3}$ (and TOF) does not exclude residual neuromuscular blockade.[28]

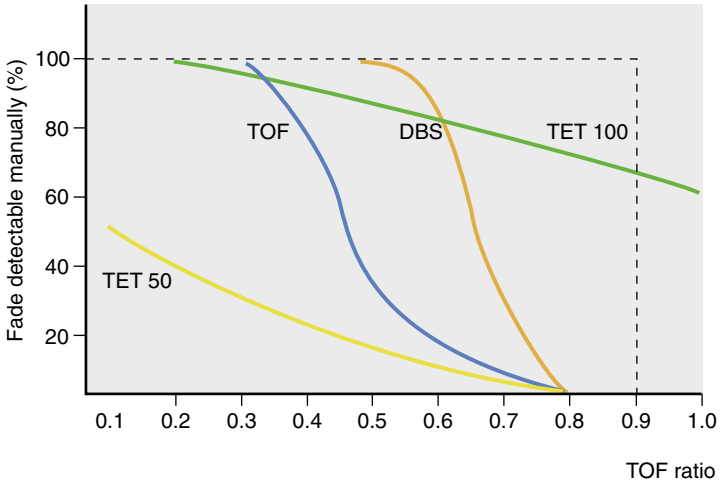


Figure 47-8 Fade detectable by feel in the response to train-of-four (TOF), double-burst stimulation ($DBS_{3,3}$), and 50- and 100-Hz tetanic stimulation (TET 50 and TET 100) in relation to the true TOF ratio, as measured mechanically. The axis indicates the percentage of instances in which fade can be felt at a given TOF ratio.[17,25,26] It appears that it is not possible to exclude residual neuromuscular block by any of the methods, regardless of whether a TOF ratio of 0.7 or 0.9 is taken to reflect adequate recovery of neuromuscular function. (See text for further explanation.)

The Nerve Stimulator

Although many nerve stimulators are commercially available, not all meet the basic requirements for clinical use. The stimulus should produce a monophasic and rectangular waveform, and the length of the pulse should not exceed 0.2 to 0.3 msec. A pulse exceeding 0.5 msec may stimulate the muscle directly or cause repetitive firing. Stimulation at a constant current is preferable to stimulation at a constant voltage because current is the determinant of nerve stimulation. Furthermore, for safety reasons, the nerve stimulator should be battery operated, include a battery check, and be able to generate 60 to 70 mA, but not higher than 80 mA. Many commercially available stimulators can deliver just 25 to 50 mA and provide a constant current only when skin resistance ranges from 0 to 2.5 kΩ. These limitations are a disadvantage; during cooling, skin resistance may increase to approximately 5 kΩ, which may cause the current delivered to the nerve to fall below the supramaximal level and lead to a decrease in the response to stimulation. As a result, the anesthesiologist may misjudge the degree of neuromuscular blockade. Ideally, the nerve stimulator should have a built-in warning system or a current level display that alerts the user when the current selected is not delivered to the nerve.

The ideal nerve stimulator should have other features as well. The polarity of the electrodes should be indicated, and the apparatus should be capable of delivering the following modes of stimulation: TOF (as both a single train and in a repetitive mode, with TOF stimulation being given every 10 to 20 seconds), single-twitch stimulation at 0.1 and 1.0 Hz, and tetanic stimulation at 50 Hz. In addition, the stimulator should have a built-in time constant system to facilitate PTC. The tetanic stimulus should last 5 seconds and be followed 3 seconds later by the first post-tetanic stimulus. If the nerve stimulator does not allow objective measurement of the response to TOF stimulation, at least one DBS mode should be available, preferably $DBS_{3,3}$. Single-twitch stimulation at 1 Hz is useful during initiation of monitoring because it shortens the time necessary to determine supramaximal stimulation. Most investigators agree that there is no need for tetanus at 100 or 200 Hz because 50-Hz tetanic stimulation stresses neuromuscular function to the same extent as maximal voluntary effort does. Furthermore, in contrast to 100- and 200-Hz stimulation, 50-Hz tetanic stimulation does not cause fatigue (fade) in nonparalyzed muscle.

The Stimulating Electrodes

Electrical impulses are transmitted from stimulator to nerve by means of surface or needle electrodes, the former being the more commonly used in clinical anesthesia. Normally, disposable pregelled silver or silver chloride surface electrodes are used. The actual conducting area should be small, approximately 7 to 11 mm in diameter.[29] Otherwise, the current produced in the underlying nerve may not be adequate. The skin should always be cleansed properly and preferably rubbed with an abrasive before application of the electrodes. When a supramaximal response cannot be obtained with surface electrodes, needle electrodes should be used. Although specially coated needle electrodes are commercially available, ordinary steel injection needles can be used. The needles should be placed subcutaneously but never in a nerve.

Sites of Nerve Stimulation and Different Muscle Responses

In principle, any superficially located peripheral motor nerve may be stimulated. In clinical anesthesia, the ulnar nerve is the most popular site; the median, posterior tibial, common peroneal, and facial nerves are also sometimes used. For stimulation of the ulnar nerve, the electrodes are best applied to the volar side of the wrist (Fig. 47-9). The distal electrode should be placed about 1 cm proximal to the point at which the proximal flexion crease of the wrist crosses the radial side of the tendon to the flexor carpi ulnaris muscle. The proximal electrode should preferably be placed so that the distance between the centers of the two electrodes is 3 to 6 cm (see Fig. 47-9). With this placement of the electrodes, electrical stimulation normally elicits only finger flexion and thumb adduction. If one electrode is placed over the ulnar groove at the elbow, thumb adduction is often pronounced because of stimulation of the flexor carpi ulnaris muscle. When this latter placement of electrodes (sometimes preferred in small children) is used, the active negative electrode should be at the wrist to ensure maximal response. Polarity of the electrodes is less crucial when both electrodes are close to each other at the volar side of the wrist; however, placement of the negative electrode distally normally elicits the greatest neuromuscular response.[30] When the temporal branch of the facial nerve is stimulated, the negative electrode should be placed over the nerve, and the positive electrode should be placed somewhere else over the forehead.

Because different muscle groups have different sensitivities to neuromuscular blocking agents, results obtained for one muscle cannot be automatically extrapolated to other muscles. The diaphragm is among the most resistant of all muscles to both depo-

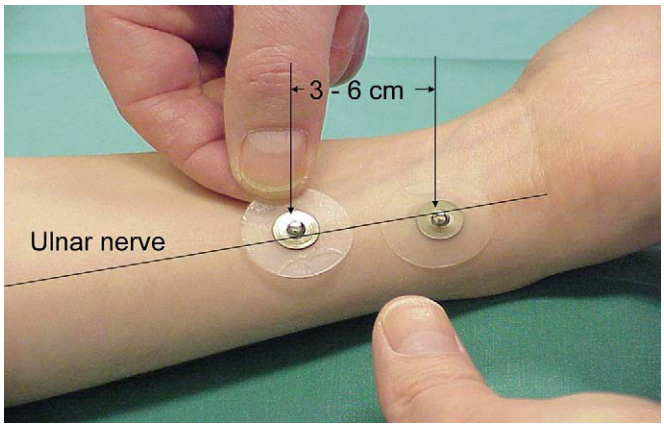


Figure 47-9 Stimulating electrodes with the appropriate contact area in the correct position over the ulnar nerve of the left forearm. *(From Fuchs-Buder T, Claudius C, Skovgaard LT, et al: Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: The Stockholm revision. Acta Anaesthesiol Scand 51:789, 2007.)*

larizing[31] and nondepolarizing neuromuscular blocking drugs.[32] In general, the diaphragm requires 1.4 to 2.0 times as much muscle relaxant as the adductor pollicis muscle for an identical degree of blockade (Fig. 47-10).[32] Also of clinical significance is that onset time is normally shorter for the diaphragm than for the adductor pollicis muscle and the diaphragm recovers from paralysis more quickly than the peripheral muscles do (Fig. 47-11).[33] The other respiratory muscles are less resistant than the diaphragm, as are the larynx and the corrugator supercilii muscles.[34-36] Most sensitive are the abdominal muscles, the orbicularis oculi muscle, the peripheral muscles of the limbs, and the geniohyoid, masseter, and upper airway muscles.[37-40] From a practical clinical point of view, it is worth noting that (1) the response of the corrugator supercilii to facial nerve stimulation reflects the extent of neuromuscular blockade of the laryngeal adductor muscles and abdominal muscles better than the response of the adductor pollicis to ulnar nerve stimulation does[34,41] and (2) the upper airway muscles seem to be more sensitive than the peripheral muscles.[37,38] Although three investigations using acceleromyography have indicated small differences in the response to TOF nerve stimulation in the arm (adductor pollicis muscle) and the leg (flexor hallucis brevis muscle), these differences are probably of little clinical significance.[42,43]

Even though the precise source of these differences is unknown, variations in acetylcholine receptor density, acetylcholine release, acetylcholinesterase activity, fiber composition, innervation ratio (number of neuromuscular junctions), blood flow, and muscle temperature may be possible explanations.

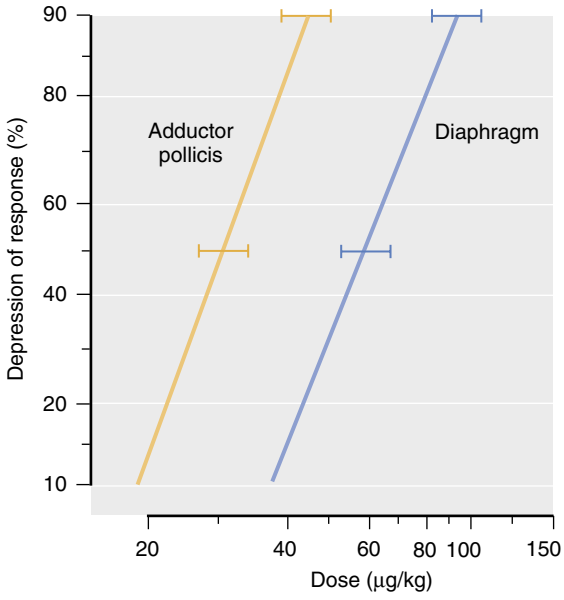


Figure 47-10 The mean cumulative dose-response curve for pancuronium in two muscles shows that the diaphragm requires approximately twice as much pancuronium as the adductor pollicis muscle for the same amount of neuromuscular blockade. The depression in muscle response to the first stimulus in train-of-four nerve stimulation (probit scale) was plotted against dose (log scale). The force of contraction of the adductor pollicis was measured on a force-displacement transducer; response of the diaphragm was measured electromyographically. *(From Donati F, Antzaka C, Bevan DR: Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans. Anesthesiology 65:1, 1986.)*

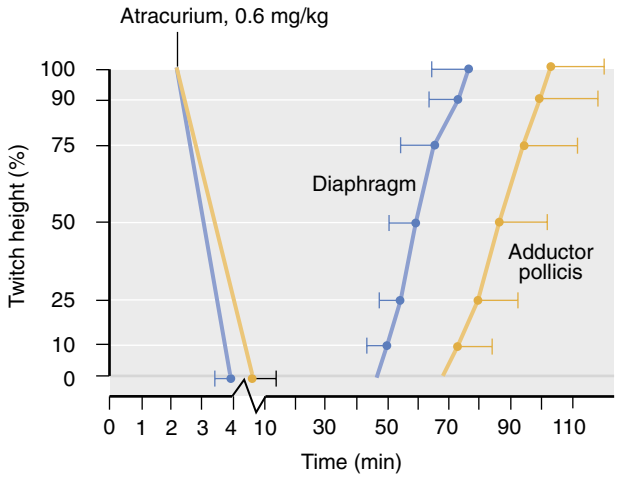


Figure 47-11 Evolution of twitch height (mean ± SD) of the diaphragm (*blue circles*) and the adductor pollicis muscle (*yellow circles*) in 10 anesthetized patients after the administration of atracurium, 0.6 mg/kg. *(From Pansard J-L, Chauvin M, Lebrault C, et al: Effect of an intubating dose of succinylcholine and atracurium on the diaphragm and the adductor pollicis muscle in humans. Anesthesiology 67:326, 1987.)*

In assessing neuromuscular function, use of a relatively sensitive muscle such as the adductor pollicis of the hand has both disadvantages and advantages. Obviously, during surgery it is a disadvantage that even total elimination of the response to single-twitch and TOF stimulation does not exclude the possibility of movement of the diaphragm, such as hiccupping and coughing. PTC stimulation, however, allows evaluation of the intense blockade necessary to ensure total paralysis of the diaphragm. On the positive side, the risk of overdosing the patient decreases if the response of a relatively sensitive muscle is used as a guide to the administration of muscle relaxants during surgery. In addition, during recovery, when the adductor pollicis has recovered sufficiently, it can be assumed that no residual neuromuscular blockade exists in the diaphragm or in other resistant muscles.

Recording of Evoked Responses

The choice of recording method is a practical decision. Five methods are available: measurement of the evoked mechanical response of the muscle (mechanomyography [MMG]), measurement of the evoked electrical response of the muscle (electromyography [EMG]), measurement of acceleration of the muscle response (acceleromyography [AMG]), measurement of the evoked electrical response in a piezoelectric film sensor attached to the muscle (piezoelectric neuromuscular monitor [P_ZEMG], and phonomyography [PMG]).

Mechanomyography

A requirement for correct and reproducible measurement of evoked tension is that the muscle contraction be isometric. In clinical anesthesia, this condition is most easily achieved by measuring thumb movement after the application of a resting tension

of 200 to 300 g (a preload) to the thumb. When the ulnar nerve is stimulated, the thumb (the adductor pollicis muscle) acts on a force-displacement transducer. The force of contraction is then converted into an electrical signal, which is amplified, displayed, and recorded. The arm and hand should be rigidly fixed, and care should be taken to prevent overloading of the transducer. In addition, the transducer should be placed in correct relation to the thumb (i.e., the thumb should always apply tension precisely along the length of the transducer). It is important to remember that the response to nerve stimulation depends on the frequency with which the individual stimuli are applied and that the time used to achieve a stable control response may influence subsequent determination of the onset time and duration of blockade.[29] Generally, the reaction to supramaximal stimulation increases during the first 8 to 12 minutes after commencement of the stimulation. Therefore, in clinical studies, recording of the control response (before injection of muscle relaxant) should not be made until the response has stabilized for 8 to 12 minutes or a 2- or 5-second 50-Hz tetanic stimulation has been given.[44] Even then, twitch response often recovers to 110% to 150% of the control response after paralysis with succinylcholine. This increase in response, thought to be caused by a change in the contractile response of the muscle, normally disappears within 15 to 25 minutes.

Although numerous methods for mechanical recording of evoked mechanical responses exist, not all meet the criteria outlined.

Electromyography

Evoked EMG records the compound action potentials produced by stimulation of a peripheral nerve. The compound action potential is a high-speed event that for many years could be picked up only by means of a preamplifier and a storage oscilloscope. Modern neuromuscular transmission analyzers are able to make on-line electronic analyses and graphic presentations of the EMG response.

The evoked EMG response is most often obtained from muscles innervated by the ulnar or the median nerves. Stimulating electrodes are applied as in force measurements. Although both surface and needle electrodes may be used for recording, no advantage is obtained by using the latter. Most often, the evoked EMG response is obtained from the thenar or hypothenar eminence of the hand or from the first dorsal interosseous muscle of the hand, preferably with the active electrode over the motor point of the muscle (Fig. 47-12). The signal picked up by the analyzer is processed by an amplifier, a rectifier, and an electronic integrator. The results are displayed either as a percentage of control or as a TOF ratio.

Two new sites for recording the EMG response have been introduced: the larynx and the diaphragm.[45,46] By using a noninvasive disposable laryngeal electrode attached to the tracheal tube and placed between the vocal cords, it is possible to monitor the onset of neuromuscular blockade in the laryngeal muscles. Thus far, however, the method is mainly of interest in clinical research when investigating onset times of the laryngeal muscles. In paravertebral surface diaphragmatic EMG, the recording electrodes are placed on the right of vertebrae T12/L1 or L1/L2 for monitoring the response of the right diaphragmatic crux to transcutaneous stimulation of the right phrenic nerve at the neck.[45-47] As is the case with surface laryngeal EMG, surface diaphragmatic EMG is mainly of interest in clinical research because of difficulties connected with stimulation of the phrenic nerve transcutaneously at the neck.

Evoked electrical and mechanical responses represent different physiologic events. Evoked EMG records changes in the electrical activity of one or more muscles, whereas evoked MMG records changes associated with excitation-contraction coupling and contraction of the muscle as well. For these reasons, the results obtained with these methods may differ.[48,49] Although evoked EMG responses generally correlate well with evoked mechanical responses,[50] marked differences may occur, especially in the response to succinylcholine and in the TOF ratio during recovery from a nondepolarizing block.[48-50]

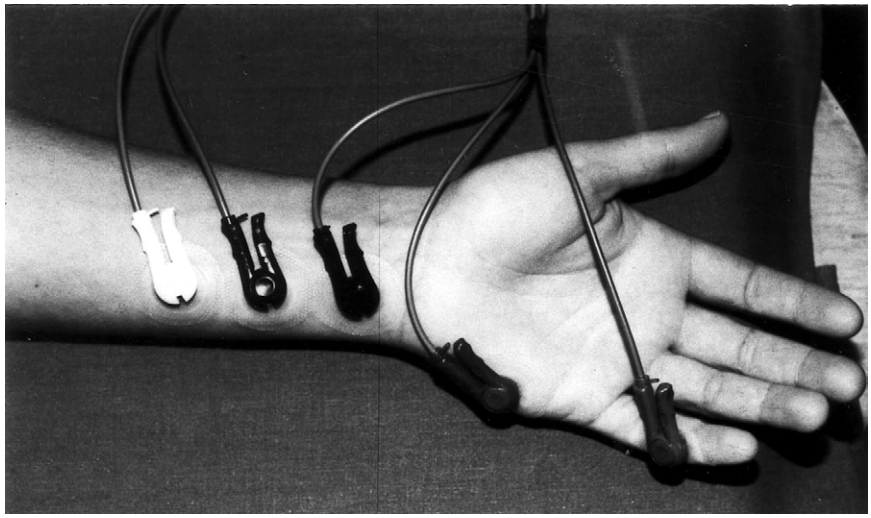
In theory, recording of evoked EMG responses has several advantages over recording of evoked mechanical responses. Equipment for measuring evoked EMG responses is easier to set up, the response reflects only factors influencing neuromuscular transmission, and the response can be obtained from muscles not accessible to mechanical recording. However, evoked EMG does entail some difficulties. Although high-quality recordings are possible in most patients, the results are not always reliable. For one thing, improper placement of electrodes may result in inadequate pickup of the compound EMG signal. If the neuromuscular transmission analyzer does not allow observation of the actual waveform of the compound EMG, determining optimal placement of the electrodes is difficult. Another source of unreliable results may be that fixation of the hand with a preload on the thumb might be more important than is generally appreciated[50] inasmuch as changes in the position of the electrodes in relation to the muscle may affect the EMG response. In addition, direct muscle stimulation sometimes occurs. If muscles close to the stimulating electrodes are stimulated directly, the recording electrodes may pick up an electrical signal even though neuromuscular transmission is completely blocked. Another difficulty is that the EMG response often does not return to the control value. Whether this situation is the result of technical problems, inadequate fixation of the hand, or changes in temperature is unknown (Fig. 47-13). Finally, the evoked EMG response is very sensitive to electrical interference, such as that caused by diathermy.

Acceleromyography

The technique of AMG is based on Newton's second law: force equals mass times acceleration.[51] If mass is constant, acceleration is directly proportional to force. Accordingly, after nerve stimulation, one can measure not only the evoked force but also acceleration of the thumb.

AMG uses a piezoelectric ceramic wafer with electrodes on both sides. Exposure of the electrode to a force generates an electrical voltage proportional to acceleration of the electrode. Consequently, when an accelerometer is fixed to the thumb and the ulnar nerve is stimulated, an electrical signal is produced whenever the thumb moves. This signal can be analyzed in a specially designed analyzer[52] or perhaps displayed on a recording system. At least one detached monitor based on measurement of acceleration is commercially available: the TOF-Watch (Organon, part of Schering-Plough Corp.) (Fig. 47-14).

AMG is a simple method of analyzing neuromuscular function, both in the operating room and in the intensive care



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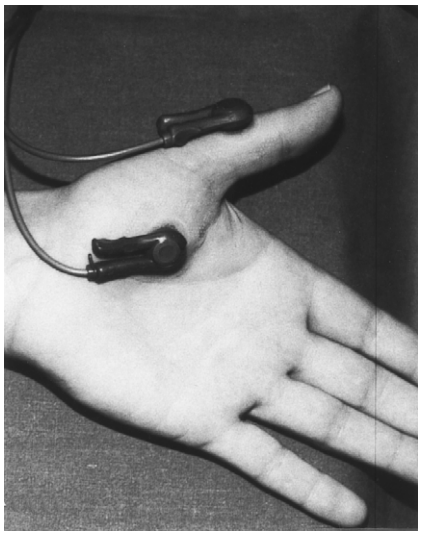

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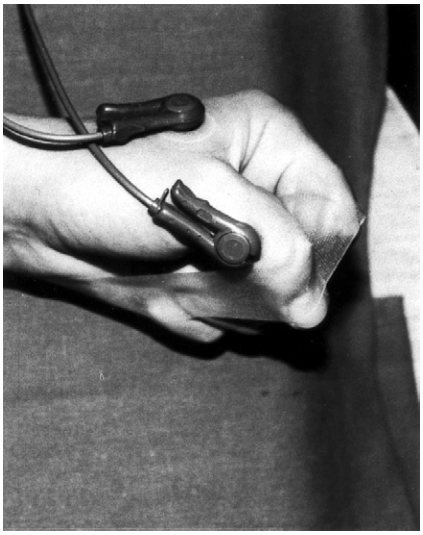

C

Figure 47-12 Electrode placement for stimulation of the ulnar nerve and for recording of the compound action potential from three sites of the hand. **A,** Abductor digiti minimi muscle (in the hypothenar eminence). **B,** Adductor pollicis muscle (in the thenar eminence). **C,** First dorsal interosseus muscle. *(Courtesy of Datex-Ohmeda, Helsinki, Finland.)*

unit. However, although good correlation exists between the TOF ratio measured by this method and the TOF ratio measured with a force-displacement transducer or EMG,[51,53,54] measurements made via AMG are not directly comparable with results obtained by the other two methods.[54-58] When AMG is used with a free-moving thumb, as originally suggested,[51] wide limits of agreements in twitch height (T1) and TOF ratio and differences in the onset and recovery course of blockade between AMG and MMG have been found. Moreover, the AMG control TOF ratio is consistently higher than when measured with a force-displacement transducer. In accordance with this, several studies have indicated that when using AMG, the TOF ratio indicative of sufficient postoperative neuromuscular recovery is 1.0 rather than 0.9 as when measured by MMG or EMG in the adductor pollicis muscle.[2,17,59,60]

One reason for the wide limits of agreement between AMG and MMG is probably and paradoxically connected with one of the originally claimed advantages of the method, that fixation of the hand could be reduced to a minimum as long as the thumb could move freely.[51] However, in daily clinical practice it is often not possible to ensure that the thumb can move freely and that the position of the hand does not change during a surgical procedure. The evoked response may therefore vary considerably. Several solutions have been proposed, and on-going clinical research indicates that the use of an elastic preload on the thumb may improve the agreement between results obtained with AMG and MMG (Fig. 47-15). Despite these reservations, it is my opinion that AMG at the thumb is a valuable clinical tool that when used with intelligence, may eliminate the problem of postoperative residual neuromuscular blockade.[61,62]

When the thumb is not available for monitoring during surgery, some clinicians prefer to monitor the AMG response of the orbicularis oculi or the corrugator supercilii in response to facial nerve stimulation.[41] However, neuromuscular monitoring of both these sites with AMG is subject to large uncertainty regarding the extent of paralysis, and it therefore cannot be recommended for routine monitoring. It provides only a rough estimate of the degree of block of the peripheral muscles.[63,64]

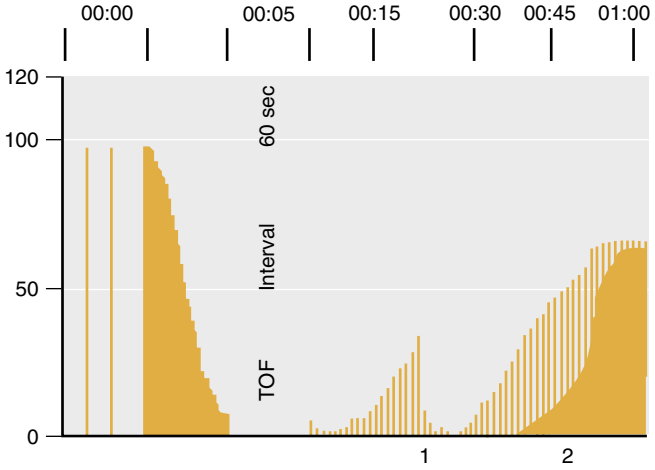

Figure 47-13 Evoked electromyographic printout from a Relaxograph. Initially, single-twitch stimulation was given at 0.1 Hz, and vecuronium (70 µg/kg) was administered intravenously for tracheal intubation. After approximately 5 minutes, the mode of stimulation was changed to train-of-four (TOF) stimulation every 60 seconds. At a twitch height (first twitch in the TOF response) of approximately 30% of control (marker 1), 1 mg of vecuronium was given intravenously. At marker 2, 1 mg of neostigmine was given intravenously, preceded by 2 mg of glycopyrrolate. The printout also illustrates the common problem of failure of the electromyographic response to return to the control level. *(Courtesy of Datex-Ohmeda, Helsinki, Finland.)*

Piezoelectric Neuromuscular Monitors

The technique of the piezoelectric monitor is based on the principle that stretching or bending a flexible piezoelectric film (e.g., one attached to the thumb) in response to nerve stimulation generates a voltage that is proportional to the amount of stretching or bending.[65,66] At least two devices based on this principle are available commercially: the ParaGraph Neuromuscular Blockade Monitor (Vital Signs, Totowa, NJ) and the M-NMT MechanoSensor, which is a part of the Datex AS/3 monitoring system (Datex-Ohmeda, Helsinki, Finland) (Fig. 47-16).

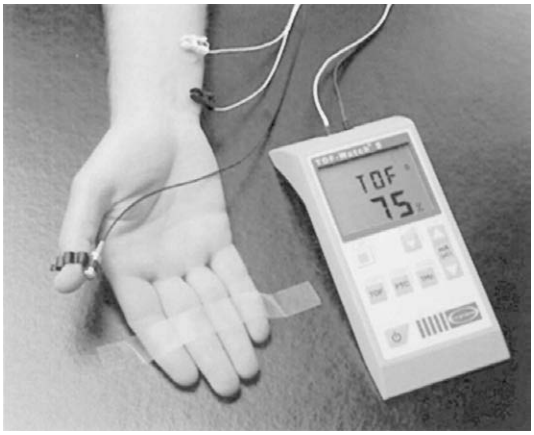

Figure 47-14 TOF-Watch (Organon, part of Schering-Plough, Corp.). This neuromuscular transmission monitor is based on measurement of acceleration with a piezoelectric transducer.[51,52] Note that the transducer is fastened to the thumb and the stimulating electrodes. On the display of the TOF-Watch, the train-of-four (TOF) ratio is given in percentage.

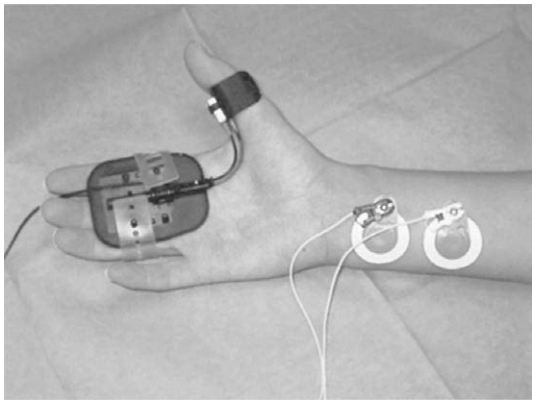

Figure 47-15 Hand adaptor (elastic preload) for the TOF-Watch transducer (Organon, part of Schering-Plough, Corp.).

Few studies have evaluated the function of these monitors.[65-67] The scarce data indicate a good relationship between results obtained with P_ZEMG, AMG, and MMG, but also wide limits of agreement between the methods. Therefore, although P_ZEMG may be a valuable clinical tool, the values obtained in an individual patient with this method may vary from those obtained with MMG or AMG.

Phonomyography

PMG (acoustic myography) is a relatively new method of monitoring neuromuscular function.[68-72] Contraction of skeletal muscles generates intrinsic low-frequency sounds, which can be recorded with special microphones. This method has been evaluated for clinical and research purposes. Several reports indicate good correlation between evoked acoustic responses and those obtained with more traditional methods of recording, such as MMG, EMG, and AMG. However, it is uncertain whether PMG will ever be used for monitoring neuromuscular blockade during routine anesthesia. What does make PMG interesting, however, is that in theory the method can be applied not only to the adductor pollicis muscle but also to other muscles of interest such as the diaphragm, larynx, and eye muscles. In addition, the ease of application is attractive.

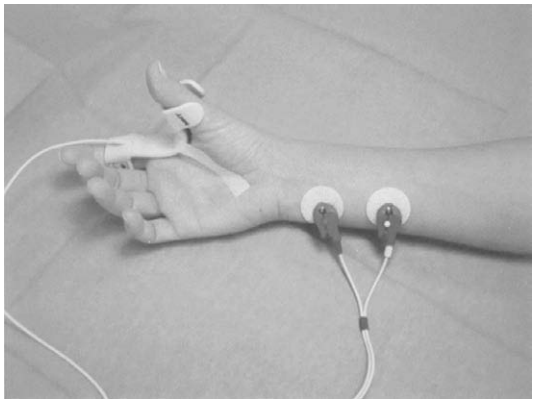

Figure 47-16 Datex-Engstrøm M-NMT MechanoSensor (a piezoelectric neuromuscular monitor).

For further information on recording evoked responses, the reader is referred to guidelines for good clinical research practice in pharmacodynamic studies of neuromuscular blocking drugs, published in *Acta Anaesthesiologica Scandinavica*.[29]

Evaluation of Recorded Evoked Responses

Nerve stimulation in clinical anesthesia is usually synonymous with TOF nerve stimulation. Therefore, the recorded response to this form of stimulation is used to explain how to evaluate the degree of neuromuscular blockade during clinical anesthesia.

Nondepolarizing Neuromuscular Blockade

After injection of a nondepolarizing neuromuscular blocking drug in a dose sufficient for smooth tracheal intubation, TOF recording demonstrates four phases or levels of neuromuscular blockade: intense blockade, deep blockade, moderate or surgical blockade, and recovery (Fig. 47-17).

Intense Neuromuscular Blockade

Intense neuromuscular blockade occurs within 3 to 6 minutes of injection of an intubating dose of a nondepolarizing muscle relaxant, depending on the drug and the dose given. This phase is also called the "period of no response" because no response to any pattern of nerve stimulation occurs. The length of this period varies, again depending primarily on the duration of action of the muscle relaxant and the dose given. The sensitivity of the patient to the drug also affects the period of no response.

Deep Neuromuscular Blockade

Intense neuromuscular blockade is followed by a period of deep block, characterized by absence of response to TOF stimulation, but presence of post-tetanic twitches (i.e., PTC ≥ 1; compare with Figure 47-4). Although it is not possible during this phase to determine exactly how long deep neuromuscular blockade will last, correlation does exist between PTC stimulation and the time until reappearance of the first response to TOF stimulation (see Fig. 47-5).

Moderate or Surgical Blockade

Moderate or surgical blockade begins when the first response to TOF stimulation appears. This phase is characterized by a gradual return of the four responses to TOF stimulation. Furthermore, good correlation exists between the degree of neuromuscular blockade and the number of responses to TOF stimulation. When only one response is detectable, the degree of neuromuscular blockade (the depression in twitch tension) is 90% to 95%. When the fourth response reappears, neuromuscular blockade is usually 60% to 85%.[73,74] The presence of one or two responses in the TOF pattern normally indicates sufficient relaxation for most surgical procedures. During light anesthesia, however, patients may move, buck, or cough. Therefore, when elimination of sudden movements is crucial, a deeper block (or a deeper level of anesthesia) may be necessary. The deep block can then be evaluated by PTC (see Fig. 47-6).

Antagonism of neuromuscular blockade with a cholinesterase inhibitor should not normally be attempted when the blockade is intense or deep because reversal will often be inadequate, regardless of the dose of antagonist administered.[75] Furthermore, after the administration of large doses of muscle relaxants, reversal of the block to clinically normal activity is not always possible if only one TOF response is present. In general, antagonism with cholinesterase inhibitors should not be initiated before at least two and preferably three or four responses are observed.

Recovery

Return of the fourth response in the TOF heralds the recovery phase. During neuromuscular recovery, a reasonably good correlation exists between the actual TOF ratio measured by MMG and clinical observation, but the relationship between the TOF ratio and signs and symptoms of residual blockade varies greatly

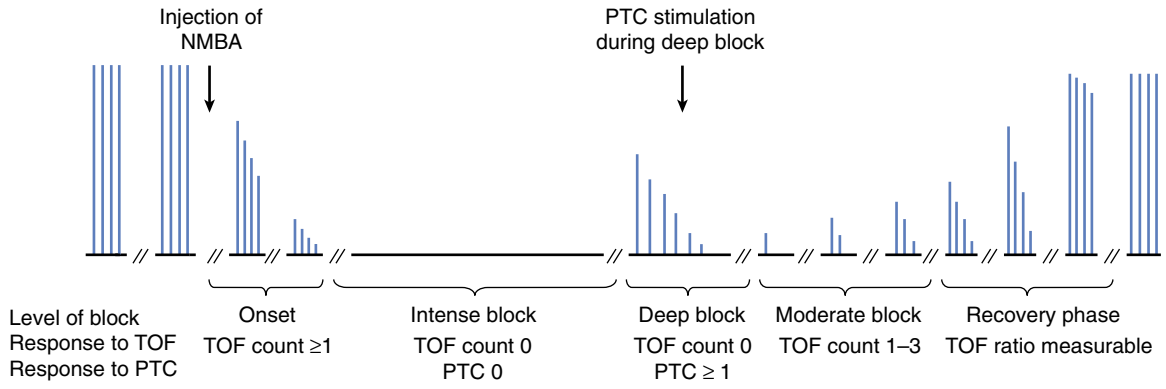

Figure 47-17 Levels of block after a normal intubating dose of a nondepolarizing neuromuscular blocking agent (NMBA) as classified by post-tetanic count (PTC) and train-of-four (TOF) stimulation. During intense (profound) block, there are no responses to either TOF or PTC stimulation. During deep block, there is response to PTC but not to TOF stimulation. Intense (profound) block and deep block together constitute the "period of no response to TOF stimulation." Reappearance of the response to TOF stimulation heralds the start of moderate block. Finally, when all four responses to TOF stimulation are present and a TOF ratio can be measured, the recovery period has started. *(From Fuchs-Buder T, Claudius C, Skovgaard LT, et al: Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: The Stockholm revision. Acta Anaesthesiol Scand 51:789, 2007.)*

among patients.[75] When the TOF ratio is 0.4 or less, the patient is generally unable to lift the head or arm. Tidal volume may be normal, but vital capacity and inspiratory force will be reduced. When the ratio is 0.6, most patients are able to lift their head for 3 seconds, open their eyes widely, and stick out their tongue, but vital capacity and inspiratory force are often still reduced. At a TOF ratio of 0.7 to 0.75, the patient can normally cough sufficiently and lift the head for at least 5 seconds, but grip strength may still be as low as about 60% of control.[76] When the ratio is 0.8 and higher, vital capacity and inspiratory force are normal.[12,77-79] The patient may, however, still have diplopia and facial weakness (Table 47-1).[75]

In clinical anesthesia, a TOF ratio of 0.70 to 0.75, or even 0.50, has been thought to reflect adequate recovery of neuromuscular function.[79] However, the TOF ratio, whether recorded mechanically or by EMG, must exceed 0.80 or even 0.90 to exclude clinically important residual neuromuscular blockade.[40,50,59,80-85] Moderate degrees of neuromuscular blockade decrease chemoreceptor sensitivity to hypoxia and thereby lead to insufficient response to a decrease in oxygen tension in blood.[80,81,83,85] Moreover, residual blockade (TOF < 0.90) is associated with functional impairment of the pharyngeal and upper esophageal muscles, which most probably predisposes to regurgitation and aspiration of gastric contents.[40] Recently, Eikerman and colleagues documented that partial neuromuscular blockade, even to a degree that does not evoke dyspnea or oxygen desaturation, may decrease inspiratory upper airway volume and can evoke partial inspiratory airway collapse.[86] Accordingly, residual blockade (TOF < 0.70) caused by the long-acting muscle relaxant pancuronium is a significant risk factor for the development of postoperative pulmonary complications (Table 47-2 and Fig. 47-18).[82] Even in volunteers without sedation or impaired consciousness, a TOF ratio of 0.9 or less may impair the ability to maintain the airway.[76] Adequate recovery of neuromuscular function requires return of an MMG or EMG TOF ratio to 0.90 or greater, which cannot be guaranteed without objective neuromuscular monitoring.[61,62,87-90]

Table 47-1 Clinical Signs and Symptoms of Residual Paralysis in Awake Volunteers After Mivacurium-Induced Neuromuscular Blockade

Train-of-Four Ratio	Signs and Symptoms
0.70-0.75	Diplopia and visual disturbances
	Decreased handgrip strength
	Inability to maintain apposition of the incisor teeth
	"Tongue depressor test" negative
	Inability to sit up without assistance
	Severe facial weakness
	Speaking a major effort
	Overall weakness and tiredness
0.85-0.90	Diplopia and visual disturbances
	Generalized fatigue

From Kopman AF, Yee PS, Neuman GG: Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. Anesthesiology 86:765, 1997.

Table 47-2 Relationship between Train-of-Four Ratio at the First Postoperative Recording and Postoperative Pulmonary Complications*

	Pancuronium (*n* = 226)			Atracurium or Vecuronium (*n* = 450)		
	No. of Patients	Patients with POPC		No. of Patients	Patients with POPC	
		n	%		*n*	%
TOF ≥ 0.70	167	8	4.8	426	23	5.4
TOF < 0.70	59	10	16.9†	24	1	4.2

*Results from a prospective, randomized, and blinded study of postoperative pulmonary complications (POPC) in a total of 691 adult patients undergoing abdominal, gynecologic, or orthopedic surgery and receiving either pancuronium, atracurium, or vecuronium.[82] In 4 of the 46 patients with POPC (1 in the pancuronium group and 3 in the atracurium and vecuronium groups), the train-of-four (TOF) ratio was not available. Because there were no significant differences in the two groups of patients given the intermediate-acting muscle relaxants, the data from these groups are pooled.
†$P < .02$ versus patients in the same group with a TOF ratio of 0.70 or greater.

Depolarizing Neuromuscular Blockade (Phase I and II Blocks)

Patients with normal plasma cholinesterase activity who are given a moderate dose of succinylcholine (0.5 to 1.5 mg/kg) undergo a typical depolarizing neuromuscular block (phase I block; i.e., the response to TOF or tetanic stimulation does not fade, and no post-tetanic facilitation of transmission occurs). In contrast, some patients with genetically determined abnormal plasma cholinesterase activity who are given the same dose of succinylcholine undergo a nondepolarizing-like block characterized by fade in the response to TOF and tetanic stimulation and the occurrence of post-tetanic facilitation of transmission (Fig. 47-19). This type of block is called a phase II block (dual, mixed, or desensitizing block). In addition, phase II blocks sometimes occur in genetically normal patients after repetitive bolus doses or a prolonged infusion of succinylcholine.

From a therapeutic point of view, a phase II block in normal patients must be differentiated from a phase II block in patients with abnormal cholinesterase activity. In normal patients, a phase II block can be antagonized by administering a cholinesterase inhibitor a few minutes after discontinuation of succinylcholine. In patients with abnormal genotypes, however, the effect of intravenous injection of an acetylcholinesterase inhibitor (e.g., neostigmine) is unpredictable. For example, neostigmine can potentiate the block dramatically, temporarily improve neuromuscular transmission, and then potentiate the block or partially reverse the block, all depending on the time elapsed since administration of succinylcholine and the dose of neostigmine given. Therefore, unless the cholinesterase genotype is known to be normal, antagonism of a phase II block with a cholinesterase inhibitor should be undertaken with extreme caution. Even if neuromuscular function improves promptly, patient surveillance should continue for at least 1 hour.

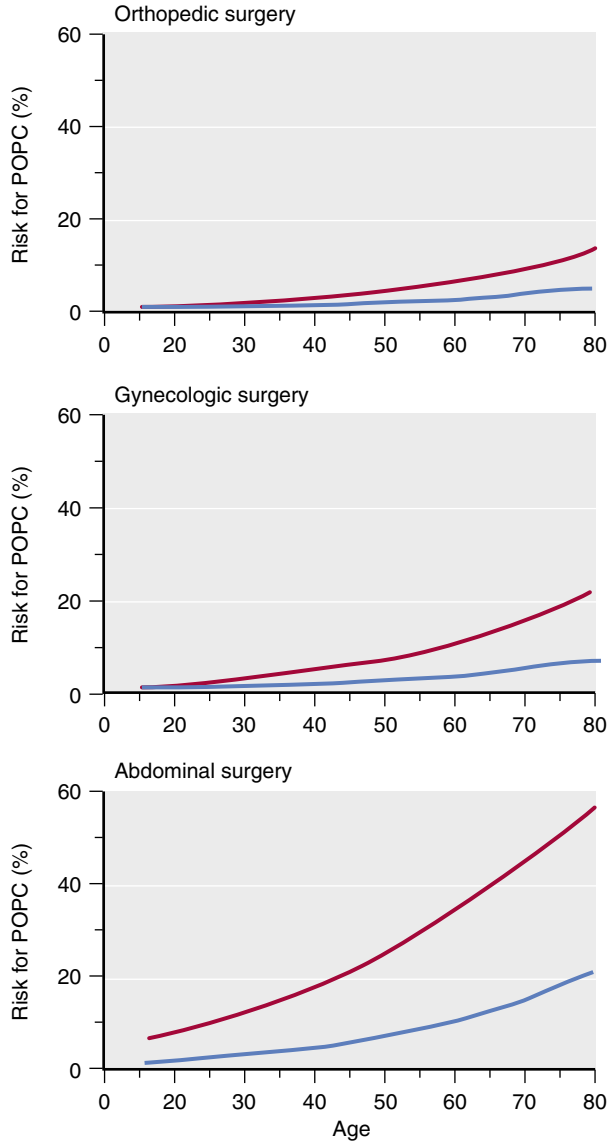

Figure 47-18 Predicted probabilities of a postoperative pulmonary complication (POPC) in different age groups in orthopedic, gynecologic, and major abdominal surgery with a duration of anesthesia of less than 200 minutes. The *red lines* represent patients with residual neuromuscular block (train-of-four [TOF] < 0.70) after the administration of pancuronium; the *blue lines* represent patients with a TOF of 0.70 or greater after the administration of pancuronium, as well as all patients after the administration of atracurium and vecuronium, independent of the TOF ratio at the end of anesthesia.[82]

Use of Nerve Stimulators Without Recording Equipment

Whenever a neuromuscular blocking drug is administered to a patient, tactile or visual evaluation of the evoked response is still the most common form of clinical neuromuscular monitoring. The following is a description of how this is best done.

First, for supramaximal stimulation, careful cleansing of the skin and proper placement and fixation of electrodes are essential. Second, every effort should be taken to prevent central cooling, as well as cooling of the extremity being evaluated. Both central and local surface cooling of the adductor pollicis muscle may reduce twitch tension and the TOF ratio.[91-93] Peripheral cooling may affect nerve conduction, decrease the rate of release of acetylcholine and muscle contractility, increase skin impedance, and reduce blood flow to muscles, thus decreasing the rate of removal of muscle relaxant from the neuromuscular junction. These factors may account for the occasional very pronounced difference in muscle response between a cold extremity and the contralateral warm extremity.[94] Third, when possible, the response to nerve stimulation should be evaluated by feel and not by eye, and the response of the thumb (rather than response of the fifth finger) should be evaluated. Direct stimulation of the muscle often causes subtle movement of the fifth finger when no response is present at the thumb. Finally, the different sensitivities of various muscle groups to neuromuscular blocking agents should always be kept in mind. Figure 47-20 shows which modes of nerve stimulation can be used at various perioperative times.

Use of a Peripheral Nerve Stimulator During Induction of Anesthesia

The nerve stimulator should be attached to the patient before induction of anesthesia but should not be turned on until after the patient is unconscious. Single-twitch stimulation at 1 Hz may be used initially when seeking supramaximal stimulation. However, after supramaximal stimulation has been ensured and before muscle relaxant is injected, the mode of stimulation should be changed to TOF (or 0.1-Hz twitch stimulation). Then, after the response to this stimulation has been observed (the control response), the neuromuscular blocking agent is injected. Although the trachea is often intubated when the response to TOF stimulation disappears, postponement of this procedure for 30 to 90

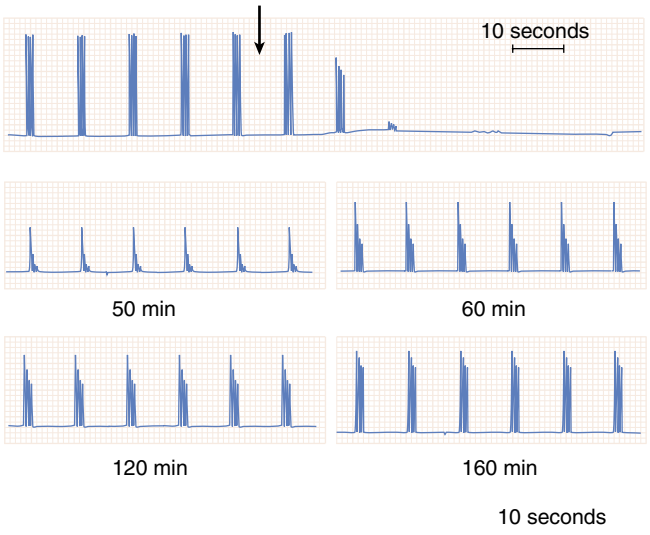

Figure 47-19 Typical recording of the mechanical response (Myograph 2000) to train-of-four ulnar nerve stimulation after injection of 1 mg/kg of succinylcholine (*arrow*) in a patient with genetically determined abnormal plasma cholinesterase activity. The prolonged duration of action and the pronounced fade in the response indicate a phase II block.

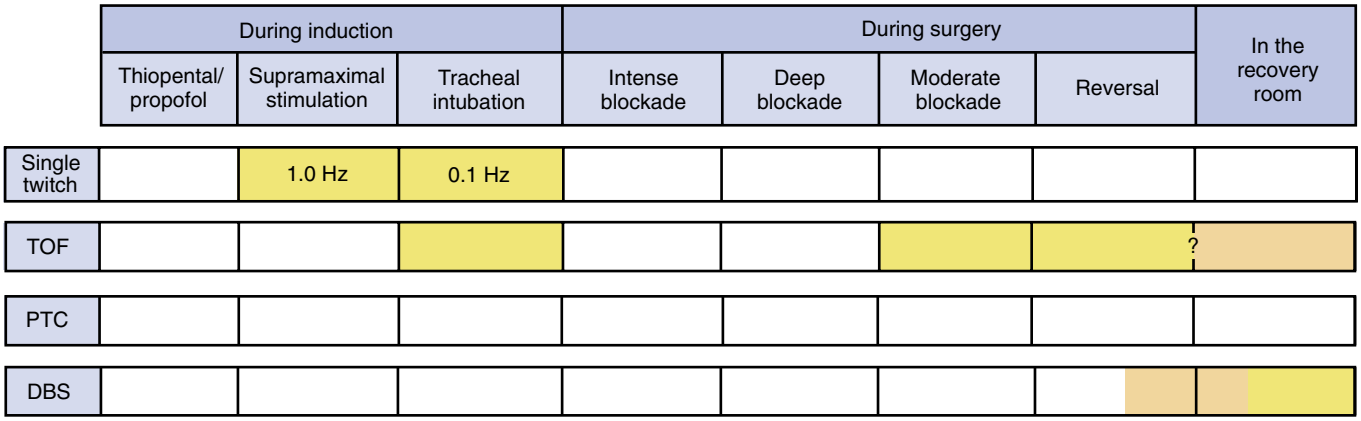

Figure 47-20 Diagram showing when the different modes of electrical nerve stimulation can be used during clinical anesthesia. *Dark areas* indicate appropriate use and *light areas*, less effective use. Modes of nerve stimulation are train-of-four (TOF) stimulation; post-tetanic count (PTC); double-burst stimulation (DBS); and the question mark (?), indicating that TOF is less useful in the recovery room unless measured with mechanomyography, electromyography, or acceleromyography. (See text for further explanation.)

seconds, depending on the muscle relaxant used, usually produces better conditions.

Use of a Peripheral Nerve Stimulator During Surgery

If tracheal intubation is facilitated by the administration of succinylcholine, no more muscle relaxant should be given until the response to nerve stimulation reappears or the patient shows other signs of returning neuromuscular function. If plasma cholinesterase activity is normal, the muscle response to TOF nerve stimulation reappears within 4 to 8 minutes.

When a nondepolarizing neuromuscular drug is used for tracheal intubation, a longer-lasting period of intense blockade usually follows. During this period of no response to TOF and single-twitch stimulation, the time until return of response to TOF stimulation may be evaluated by PTC (see Fig. 47-5).

For most surgical procedures requiring muscle relaxation, twitch depression of approximately 90% will be sufficient, provided that the patient is adequately anesthetized. If a nondepolarizing relaxant is used, one or two of the responses to TOF stimulation can be felt. However, because the respiratory muscles (including the diaphragm) are less sensitive to neuromuscular blocking agents than the peripheral muscles are, the patient may breathe, hiccup, or even cough at this depth of blockade. To ensure paralysis of the diaphragm, neuromuscular blockade of the peripheral muscles must be so intense that the PTC is zero in the thumb.

An added advantage of keeping the neuromuscular blockade at a level of one or two responses to TOF stimulation is that antagonism of the block is facilitated at the end of surgery.

Use of a Peripheral Nerve Stimulator during Reversal of Neuromuscular Blockade

Antagonism of nondepolarizing neuromuscular blockade with a cholinesterase inhibitor such as neostigmine should probably not be initiated before at least two responses to TOF stimulation are present or before obvious clinical signs of returning neuromuscular function are seen. Certainly, reversal of neuromuscular blockade will not be hastened and may possibly be delayed by giving neostigmine when no response to peripheral nerve stimulation is present. Conversely, to achieve rapid reversal (within 10 minutes) to a TOF ratio of 0.7 in more than 90% of patients, three and preferably four responses should be present at the time of neostigmine injection.[95] To achieve a TOF ratio of 0.9 in all patients with this method is not possible, but critical episodes of postoperative residual blockade should be an infrequent occurrence.[96]

During recovery of neuromuscular function, when all four responses to TOF stimulation can be felt, an estimation of the TOF ratio may be attempted. However, manual (tactile) evaluation of the response to TOF stimulation (see Fig. 47-8) is not sensitive enough to exclude the possibility of residual neuromuscular blockade.[25,88,97] Greater sensitivity is achieved with $DBS_{3,3}$, but even absence of manual fade in the $DBS_{3,3}$ response does not exclude clinically significant residual blockade.[27] Therefore, manual evaluation of responses to nerve stimulation should always be considered in relation to reliable clinical signs and symptoms of residual neuromuscular blockade (Box 47-1).

When to Use a Peripheral Nerve Stimulator

At some institutions, nerve stimulators are used routinely whenever a neuromuscular blocking drug is administered. In most cases, the response is evaluated by touch, and only in selected cases are the responses recorded. Many anesthesiologists do not agree with extensive use of nerve stimulators and argue that they manage quite well without these devices. However, the question is not how little an experienced anesthetist can manage with but rather how to ensure that all patients receive optimal treatment.

In daily clinical practice, significant residual blockade can be excluded with certainty only if objective methods of neuromuscular monitoring are used.[61,62] In my opinion[3] and those of others,[4] good evidence-based practice dictates that clinicians

Box 47-1 Clinical Tests of Postoperative Neuromuscular Recovery

Unreliable

Sustained eye opening

Protrusion of the tongue

Arm lift to the opposite shoulder

Normal tidal volume

Normal or nearly normal vital capacity

Maximum inspiratory pressure less than 40 to 50 cm H_2O

Most Reliable

Sustained head lift for 5 seconds

Sustained leg lift for 5 seconds

Sustained handgrip for 5 seconds

Sustained "tongue depressor test"

Maximum inspiratory pressure 40 to 50 cm H_2O or greater

should always quantitate the extent of neuromuscular recovery by objective monitoring. At a minimum, the TOF ratio should be measured during recovery whenever a nondepolarizing neuromuscular block is not antagonized.[3]

However, in many departments clinicians do not have access to equipment for measuring the degree of block. How then to evaluate and, as far as possible, exclude a clinically significant postoperative block? First, long-acting neuromuscular blocking agents should not be used. Second, the tactile response to TOF nerve stimulation should be evaluated during surgery. Third, if possible, total twitch suppression should be avoided. The block should be managed so that there is always one or two tactile TOF responses. Fourth, the block should be antagonized at the end of the procedure, but reversal should not be initiated before at least two and preferably three or four responses to TOF stimulation are present. Fifth, during recovery, tactile evaluation of the response to DBS is preferable to tactile evaluation of the response to TOF stimulation because it is easier to feel fade in the DBS than in the TOF response. Sixth, the clinician should recognize that absence of tactile fade in both the TOF and DBS responses does not exclude significant residual blockade.[28,87,88,97] Finally, reliable clinical signs and symptoms of residual blockade (see Box 47-1) should be considered in relation to the response to nerve stimulation.

In view of the uncertainty connected with the use of clinical tests of postoperative neuromuscular recovery and tactile evaluation of the response to nerve stimulation, at a minimum, every anesthesia department and every recovery room should have at least one apparatus for recording evoked responses. Whether the functioning of such a neuromuscular transmission analyzer is based on EMG, MMG, AMG, P_ZEMG, or PMG is not crucial, as long as the physician knows how to use the apparatus in question.

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Daniel I. Sessler

48 Temperature Regulation and Monitoring

Key Points

1. General anesthetics decrease the thresholds (triggering core temperatures) for vasoconstriction and shivering by 2°C to 3°C.
2. Anesthetic-induced impairment of thermoregulatory control, combined with a cool operating room environment, makes most patients hypothermic.
3. The major initial cause of hypothermia in most patients is core-to-peripheral redistribution of body heat.
4. Neuraxial anesthesia impairs both central and peripheral thermoregulatory control and is associated with substantial hypothermia.
5. Large randomized trials have proved that even mild hypothermia (i.e., 1.5°C to 2.0°C) causes adverse outcomes, including a threefold increase in morbid myocardial outcomes, a threefold increase in risk for wound infection, coagulopathy and need for allogeneic transfusion, prolonged recovery, and prolonged hospitalization.
6. Body temperature should be monitored in patients undergoing surgery lasting longer than 30 minutes, and core temperature should be maintained at 36°C or higher whenever possible. Forced-air warming currently offers the best combination of high efficacy, low cost, and remarkable safety.

Mammals and birds are homeothermic and require a nearly constant internal body temperature. When internal temperature deviates significantly from normal, metabolic functions usually deteriorate, and death may result. The thermoregulatory system generally maintains core body temperature within a few tenths of a degree centigrade of "normal," which is about 37°C in humans. Anesthetic-induced inhibition of thermoregulation combined with exposure to a cold operating room environment makes most unwarmed patients hypothermic. In recent years, major outcome studies have shown that mild hypothermia (≈1°C to 2°C): (1) triples the incidence of morbid cardiac outcomes, (2) triples the incidence of surgical wound infections, (3) increases surgical blood loss and the need for allogeneic transfusion by about 20%, and, (4) prolongs postanesthesia recovery and the duration of hospitalization. An understanding of normal and anesthetic-influenced thermoregulation will facilitate prevention and management of these and numerous other temperature-related complications.

Normal Thermoregulation

Thermoregulation is based on multiple, redundant signals from nearly every type of tissue. Processing of thermoregulatory information occurs in three phases: *afferent thermal sensing*, *central regulation*, and *efferent responses*.

Afferent Input

Information on temperature is obtained from thermally sensitive cells throughout the body. Cold-sensitive cells are anatomically and physiologically distinct from those that detect warmth. Warm receptors increase their firing rates when temperature increases, whereas cold receptors do so when temperature decreases. Cutaneous warm receptors rarely depolarize at normal skin temperatures and are probably important only during heat stress. The actual sensors appear to be a recently discovered class of transient receptor potential (TRP) protein receptors.[1]

Cold signals travel primarily via Aδ nerve fibers, and warm information, by unmyelinated C fibers, although there is some overlap.[2] C fibers also detect and convey pain sensation, which is why intense heat cannot be distinguished from sharp pain. Most ascending thermal information traverses the spinothalamic tracts in the anterior spinal cord, but no single spinal tract is critical for conveying thermal information. Consequently, the entire anterior cord must be destroyed to ablate thermoregulatory responses.

The hypothalamus, other parts of the brain, the spinal cord, deep abdominal and thoracic tissues, and the skin surface each

contribute roughly 20% of total thermal input to the central regulatory system.[3]

Central Control

Temperature is regulated by central structures (primarily the hypothalamus) that compare integrated thermal input from the skin surface, neuraxis, and deep tissues with *threshold* temperatures for each thermoregulatory response. Although integrated by the hypothalamus, most thermal information is "preprocessed" in the spinal cord and other parts of the central nervous system. This hierarchic arrangement presumably developed when the evolving thermoregulatory control system co-opted previously existing mechanisms (e.g., shivering from muscles previously used for posture and locomotion). Some thermoregulatory responses can be mounted by the spinal cord alone.[4] For example, animals and patients with high spinal cord transection regulate temperature better than might be expected.

The slope of response intensity versus core temperature defines the *gain* of a thermoregulatory response. Response intensity no longer increasing with further deviation in core temperature identifies the *maximum intensity*. This system of thresholds and gains is a model for a thermoregulatory system that is further complicated by interactions between other regulatory responses (i.e., vascular volume control) and time-dependent effects.

How the body determines absolute threshold temperatures is unknown, but the mechanism appears to be mediated by norepinephrine, dopamine, 5-hydroxytryptamine, acetylcholine, prostaglandin E_1, and neuropeptides. The thresholds vary daily in both sexes (circadian rhythm) and monthly in women by approximately 0.5°C. Exercise, food intake, infection, hypothyroidism and hyperthyroidism, anesthetic and other drugs (including alcohol, sedatives, and nicotine), and cold and warm adaptation all alter threshold temperatures.

Control of autonomic responses is approximately 80% determined by thermal input from core structures (Fig. 48-1).[5] In contrast, a large fraction of the input controlling behavioral responses is derived from the skin surface. The *interthreshold range* (core temperatures *not* triggering autonomic thermoregulatory responses) is a few tenths of a degree centigrade.[6] This range is bounded by the sweating threshold at its upper end and by vasoconstriction at the lower end. Because energy cost and nutrients are conserved without excessive autonomic control within this range, some animals such as camels and desert rats use this strategy extensively and exhibit core temperature changes of up to 10°C each day. However, most mammals—including humans—normally regulate core temperature tightly.

Both sweating and vasoconstriction thresholds are 0.3°C to 0.5°C higher in women than in men, even during the follicular phase of the menstrual cycle (first 10 days).[7] These differences are even greater during the luteal phase.[8] Central thermoregulatory control is apparently intact even in somewhat premature infants.[9] In contrast, thermoregulatory control is sometimes impaired in the elderly.[10]

Efferent Responses

The body responds to thermal perturbations (body temperatures differing from the appropriate threshold) via effector mechanisms that increase metabolic heat production or alter environmental heat loss. Each thermoregulatory effector has its own threshold and gain, so there is an orderly progression of responses and response intensities in proportion to need. In general, energy-efficient effectors such as vasoconstriction are maximized before metabolically costly responses such as shivering are initiated. Figure 48-2 shows the normal values for the major autonomic response thresholds.

Effectors determine the ambient temperature range that the body will tolerate while maintaining a normal core temperature. When specific effector mechanisms are inhibited (e.g., when shivering is prevented by the administration of muscle relaxants), the

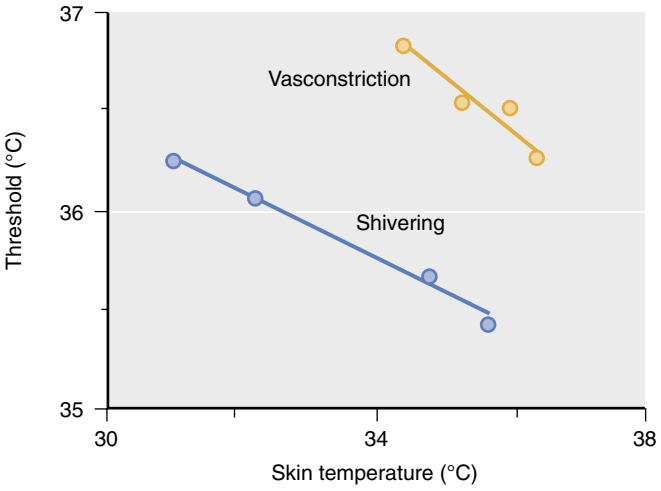

Figure 48-1 There is a linear relationship between mean skin temperature and the core temperature triggering vasoconstriction and shivering. Skin temperature contributes about 20% to control of each thermoregulatory defense. *(From Cheng C, Matsukawa T, Sessler DI, et al: Increasing mean skin temperature linearly reduces the core-temperature thresholds for vasoconstriction and shivering in humans. Anesthesiology 82:1160-1168, 1995.)*

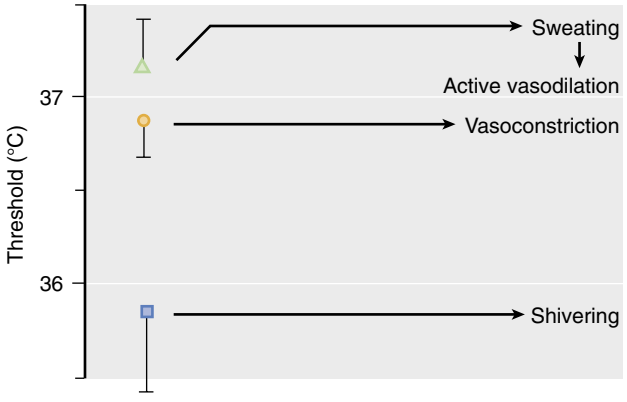

Figure 48-2 A core temperature below the threshold for response to cold provokes vasoconstriction, nonshivering thermogenesis, and shivering. A core temperature exceeding the hyperthermic threshold produces active vasodilation and sweating. No thermoregulatory responses are initiated when the core temperature is between these thresholds; these temperatures identify the interthreshold range, which in humans is usually only about 0.2°C. *(Threshold data from Lopez M, Sessler DI, Walter K, et al: Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans. Anesthesiology 80:780-788, 1994.)*

tolerable range is decreased. Still, temperature will remain normal unless other effectors cannot compensate for the imposed stress. Quantitatively, *behavioral regulation* is the most important effector mechanism. Behavioral compensations include dressing appropriately, modifying environmental temperature, assuming positions that oppose skin surfaces, and voluntary movement.

Infants regulate their temperature remarkably well. In contrast, advanced age, infirmity, or medications can diminish the efficacy of thermoregulatory responses and increase the risk for hypothermia. For example, decreased muscle mass, neuromuscular diseases, and muscle relaxants all inhibit shivering, which increases the minimum tolerable ambient temperature. Similarly, anticholinergic drugs inhibit sweating, which decreases the maximum tolerable temperature.

Cutaneous vasoconstriction is the most consistently used autonomic effector mechanism. Metabolic heat is lost primarily via convection and radiation from the skin surface, and vasoconstriction reduces this loss. Total digital skin blood flow is divided into nutritional (mostly capillary) and thermoregulatory (mostly arteriovenous shunt) components.[11] The arteriovenous shunts are anatomically and functionally distinct from the capillaries supplying nutritional blood to the skin (thus vasoconstriction does not compromise the needs of peripheral tissues).

Control of blood flow through arteriovenous shunts tends to be "on" or "off." In other words, the gain of this response is high, with digital flow increasing from trivial to maximal levels after changes in core temperature of only a few tenths of a degree centigrade. Local α-adrenergic sympathetic nerves mediate constriction in the thermoregulatory arteriovenous shunts, and flow is minimally affected by *circulating* catecholamines. Roughly 10% of cardiac output traverses the arteriovenous shunts; consequently, shunt vasoconstriction increases mean arterial pressure approximately 15 mm Hg.[12]

Nonshivering thermogenesis increases metabolic heat production (measured as whole-body oxygen consumption) without producing mechanical work. It doubles heat production in infants[13] but increases it only slightly in adults.[14] The intensity of nonshivering thermogenesis increases in linear proportion to the difference between mean body temperature and its threshold. Skeletal muscle and brown fat tissue are the major sources of nonshivering heat in adults. The metabolic rate in both tissues is controlled primarily by norepinephrine released from adrenergic nerve terminals and is further mediated locally by an uncoupling protein.[15]

Sustained shivering augments metabolic heat production by 50% to 100% in adults. This increase is small in comparison to that produced by exercise (which can, at least briefly, increase metabolism by 500%) and thus is surprisingly ineffective. Shivering does not occur in newborn infants and probably is not fully effective until children are several years old. The rapid tremor (up to 250 Hz) and unsynchronized muscular activity of thermogenic shivering suggest no central oscillator. However, superimposed on the fast activity, there is usually a slow (4 to 8 cycles/min), synchronous "waxing-and-waning" pattern that presumably is centrally mediated.[16]

Sweating is mediated by postganglionic, cholinergic nerves.[17] It thus is an active process that is prevented by nerve block or administration of atropine.[18] Sweating is the only mechanism by which the body can dissipate heat in an environment exceeding core temperature. Fortunately, the process is remarkably effective, with 0.58 kcal dissipated per gram of evaporated sweat.

Active vasodilation is apparently mediated by nitric oxide.[19] Because active vasodilation requires intact sweat gland function, it is also largely inhibited by nerve blockade. The threshold for active vasodilation is usually similar to the sweating threshold, but the gain may be less. Consequently, maximum cutaneous vasodilation is generally delayed until core temperature is well above that provoking maximum sweating intensity.

Thermoregulation During General Anesthesia

Behavioral regulation is not relevant during general anesthesia because patients are unconscious and frequently paralyzed. All general anesthetics tested thus far markedly impair normal autonomic thermoregulatory control and cause slightly elevated warm-response thresholds, whereas cold-response thresholds are markedly reduced. Consequently, the interthreshold range is increased from its normal value near 0.3°C to about 2°C to 4°C.[20-24] The gain and maximum intensity of some responses remain normal,[7] whereas others are reduced by general anesthesia.[25,26]

Response Thresholds

Propofol,[20] alfentanil,[21] and dexmedetomidine[22] all produce a slight linear increase in the sweating threshold combined with a marked and linear decrease in the vasoconstriction and shivering thresholds. Isoflurane[24] and desflurane[23] also slightly increase the sweating threshold; however, they decrease the cold-response threshold nonlinearly. Consequently, the volatile anesthetics inhibit vasoconstriction and shivering less than propofol does at low concentrations but more than propofol does at typical anesthetic doses. In all cases (except during meperidine[27] and nefopam[28] administration), vasoconstriction and shivering decrease synchronously and thus maintain their normal approximate 1°C difference.

The dose-dependent response thresholds for four anesthetic drugs are shown in Figure 48-3. The combination of increased sweating thresholds and reduced vasoconstriction thresholds increases the interthreshold range about 20-fold, from its normal value near 0.2°C to approximately 2°C to 4°C. Temperatures within this range do *not* trigger thermoregulatory defenses, and patients are thus by definition poikilothermic within this temperature range.

Isoflurane,[24] desflurane,[23,25] enflurane,[29] halothane,[30] and the combination of nitrous oxide and fentanyl[31] decrease the vasoconstriction threshold 2°C to 4°C from its normal value near 37°C. The dose dependence is nonlinear; that is, greater concentrations produce disproportionate threshold reductions. The shivering thresholds decrease synchronously. In contrast, these drugs increase the sweating threshold only slightly.

Clonidine synchronously decreases cold-response thresholds[32] while slightly increasing the sweating threshold.[33] Nitrous oxide decreases the vasoconstriction[34] and shivering[35] thresholds less than equipotent concentrations of volatile anesthetics do. In

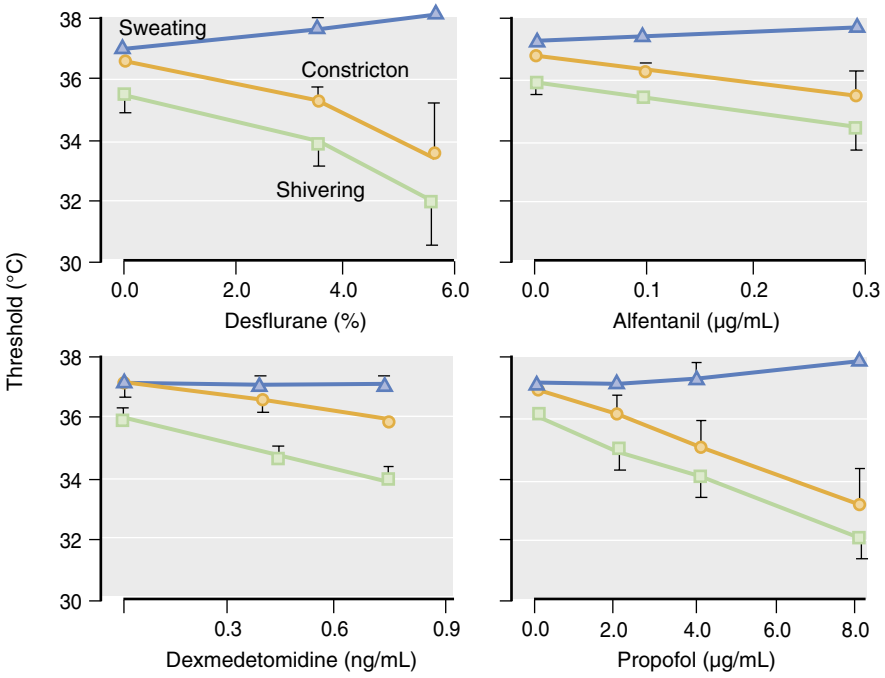

Figure 48-3 Major autonomic thermoregulatory response thresholds in volunteers given desflurane, alfentanil, dexmedetomidine, or propofol. All the anesthetics slightly increase the sweating threshold (triggering core temperature) while markedly and synchronously decreasing the vasoconstriction and shivering thresholds. Standard deviation bars smaller than the data markers have been deleted. *(From Annadata RS, Sessler DI, Tayefeh F, et al: Desflurane slightly increases the sweating threshold, but produces marked, non-linear decreases in the vasoconstriction and shivering thresholds. Anesthesiology 83:1205-1211, 1995; Kurz A, Go JC, Sessler DI, et al: Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. Anesthesiology 83:293-299, 1995; Talke P, Tayefeh F, Sessler DI, et al: Dexmedetomidine does not alter the sweating threshold, but comparably and linearly reduces the vasoconstriction and shivering thresholds. Anesthesiology 87:835-841, 1997; and Matsukawa T, Kurz A, Sessler DI, et al: Propofol linearly reduces the vasoconstriction and shivering thresholds. Anesthesiology 82:1169-1180, 1995.)*

contrast, midazolam only slightly impairs thermoregulatory control.[36,37] Painful stimulation slightly increases the vasoconstriction thresholds[29]; consequently, thresholds will be somewhat lower when surgical pain is prevented by simultaneous local or regional anesthesia.

Responses in Infants and the Elderly

Thermoregulatory vasoconstriction is comparably impaired in infants, children, and adults given isoflurane[38] or halothane (Fig. 48-4).[39] In contrast, the vasoconstriction threshold is about 1°C less in patients aged 60 to 80 years than in those between 30 and 50 years (see Chapters 69, 71, 82, and 84).

Nonshivering thermogenesis does not occur in anesthetized adults,[40] but it is an important thermoregulatory response in animals and human infants. However, nonshivering thermogenesis in animals is inhibited by volatile anesthetics,[41] and it fails to increase the metabolic rate in infants anesthetized with propofol (Fig. 48-5).[42]

Gain and Maximum Response Intensity

Both the gain and maximum intensity of sweating remain normal during isoflurane[7] and enflurane anesthesia.[43] However, the gain of arteriovenous shunt vasoconstriction is reduced threefold during desflurane anesthesia (Fig. 48-6),[25] even though the maximum vasoconstriction intensity remains normal.[44]

Shivering is rare at surgical levels of general anesthesia, which is consistent with its threshold being roughly 1°C less than the vasoconstriction threshold.[20-24] (Vasoconstriction usually prevents additional hypothermia,[45] so even unwarmed patients rarely become cold enough to shiver.) Nonetheless, shivering can be induced by sufficient active cooling.

Gain and maximum shivering intensity remain normal during both meperidine and alfentanil administration.[46] Gain also remains nearly intact during nitrous oxide administration, although maximum intensity is reduced.[47] Isoflurane changes the macroscopic pattern of shivering to such an extent that it is no longer possible to easily determine gain. The drug does, however, reduce maximum shivering intensity.[26]

In summary, sweating is the best preserved major thermoregulatory defense during anesthesia. Not only is the

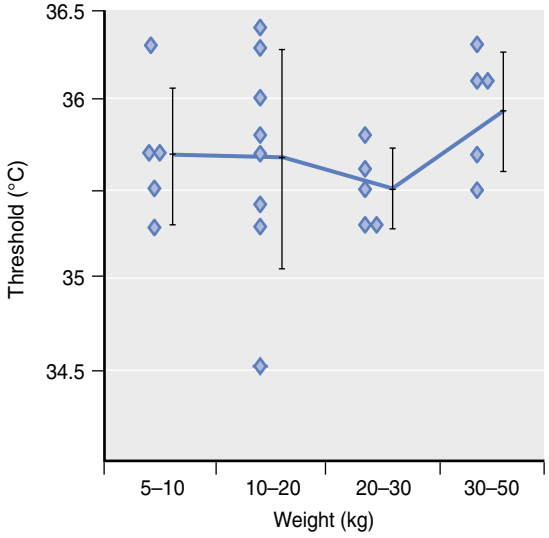

Figure 48-4 Core thermoregulatory threshold in 23 healthy children and infants undergoing abdominal surgery with halothane anesthesia. Differences among the groups are not statistically significant. Results are presented as means ± SD. *(From Bissonnette B, Sessler DI: Thermoregulatory thresholds for vasoconstriction in pediatric patients anesthetized with halothane or halothane and caudal bupivacaine. Anesthesiology 76:387-392, 1992.)*

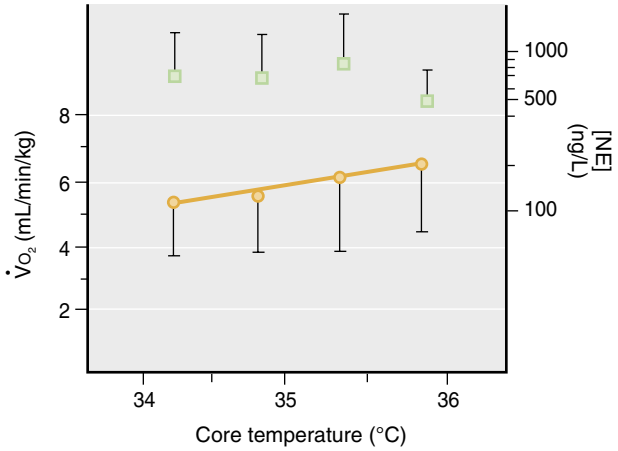

Figure 48-5 Progressive reduction in core temperature did not trigger an increase in oxygen consumption ($\dot{V}O_2$) that might indicate nonshivering thermogenesis. Instead, hypothermia decreased systemic oxygen consumption: $\dot{V}O_2 = 0.83$ (Core temperature) – 23.3 ; $r^2 = .92$. Intraoperative plasma norepinephrine concentrations ([NE]) were variable but did not change significantly as a function of core temperature. Data are presented as means ± SD. *(From Plattner O, Semsroth M, Sessler DI, et al: Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol. Anesthesiology 86:772-777, 1997.)*

threshold only slightly increased, but the gain and maximum intensity also remain normal. In contrast, the thresholds for vasoconstriction and shivering are markedly reduced, and furthermore, the efficacy of these responses is diminished even after being activated.

Development of Hypothermia During General Anesthesia

Inadvertent hypothermia is by far the most common perioperative thermal disturbance during anesthesia. Hypothermia results from a combination of anesthetic-impaired thermoregulation and exposure to a cold operating room environment. Of these two causes, impaired thermoregulation is much more important.

Heat Transfer

Heat can be transferred from a patient to the environment in four ways: radiation, conduction, convection, and evaporation. Among these mechanisms, radiation and convection contribute most to perioperative heat loss.

All surfaces with a temperature above absolute zero radiate heat; similarly, all surfaces absorb heat radiating from surrounding surfaces. Heat transfer via this mechanism is proportional to the difference of the fourth power of the absolute temperature difference between the surfaces. It is likely that radiation is the major type of heat loss in most surgical patients.[48]

Conductive heat loss is proportional to the temperature difference between two adjacent surfaces and the strength of the thermal insulation separating them. In general, conductive losses are negligible during surgery because patients usually only directly contact the foam pad (an excellent thermal insulator) covering most operating room tables.

Conductive loss of heat directly to air molecules is limited by the development of a layer of still air adjacent to the skin that serves as an insulator. When this layer is disturbed by air currents, the insulating properties diminish substantially, thereby increasing heat loss. This increase is termed convection and is proportional to the square root of the air speed; this is the basis of the familiar "wind chill" factor. Air speed in operating rooms—even those with high rates of air turnover—is typically only approximately 20 cm/sec, which only slightly increases loss when compared with still air. Nonetheless, convective loss is usually the second most important mechanism by which heat is transferred from patients to the environment. Presumably, convective loss increases substantially in operating rooms equipped to provide laminar flow. However, the actual augmentation has not been quantified and may be less than expected from the increase in air speed because surgical draping provides considerable thermal insulation.

Sweating increases cutaneous evaporative loss enormously but is rare during anesthesia. In the absence of sweating, evaporative loss from the skin surface is limited to less than 10% of metabolic heat production in adults. In contrast, infants lose a higher fraction of their metabolic heat from transpiration of water through thin skin. The problem becomes especially acute in

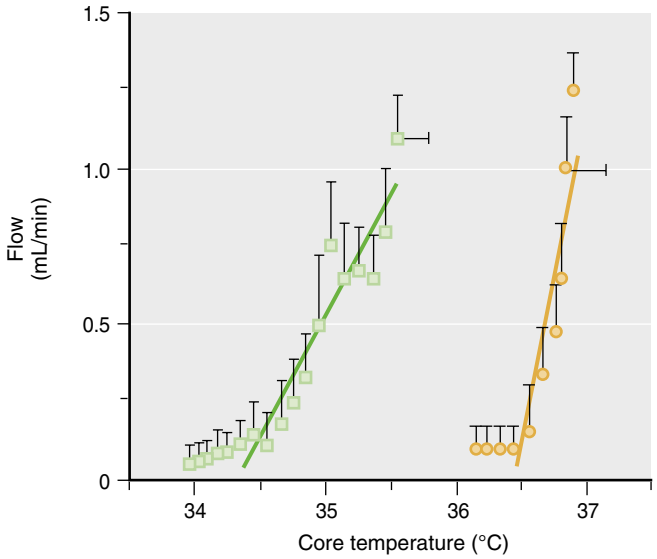

Figure 48-6 Finger blood flow without (*circles*) and with (*squares*) desflurane administration. Values were computed relative to the thresholds (finger flow = 1.0 mL/min) in each subject. Flows of exactly 1.0 mL/min are not shown because flows in each individual were averaged over 0.1°C or 0.05°C increments; each data point thus includes both higher and lower flows. The horizontal standard deviation bars indicate variability in the thresholds among the volunteers; although error bars are shown only at a flow near 1.0 mL/min, the same temperature variability applies to each data point. Slopes of the flow-versus–core temperature relationships (1.0 to ≈0.15 mL/min) were determined by linear regression. These slopes defined the gain of vasoconstriction with and without desflurane anesthesia. Gain was reduced by a factor of 3, from 2.4 to 0.8 mL/min/°C ($P < .01$). *(From Kurz A, Xiong J, Sessler DI, et al: Desflurane reduces the gain of thermoregulatory arterio-venous shunt vasoconstriction in humans. Anesthesiology 83:1212-1219, 1995.)*

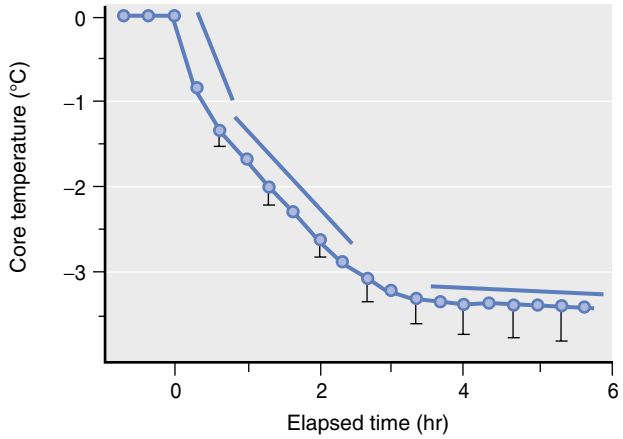

Figure 48-7 Hypothermia during general anesthesia develops with a characteristic pattern. An initial rapid decrease in core temperature results from a core-to-peripheral redistribution of body heat. This is followed by a slow, linear reduction in core temperature that results simply from heat loss exceeding heat production. Finally, core temperature stabilizes and subsequently remains virtually unchanged. This plateau phase may be a passive thermal steady state or result when sufficient hypothermia triggers thermoregulatory vasoconstriction. Results are presented as means ± SD.

premature infants, who may lose one fifth of their metabolic heat production via transcutaneous evaporation.[49] Simple thermodynamic calculations and clinical measurements indicate that only trivial amounts of heat are lost from the respiratory system.[50] Evaporation inside surgical wounds may contribute substantially to total heat loss[51] but has never been quantified in humans.

Patterns of Intraoperative Hypothermia

Hypothermia during general anesthesia develops with a characteristic pattern. An initial rapid decrease in core temperature is followed by a slow, linear reduction in core temperature. Finally, core temperature stabilizes and subsequently remains virtually unchanged (Fig. 48-7). Each component of this typical pattern has a different etiology.

Volatile anesthetics cause vasodilation via direct peripheral action.[52] More importantly, they also inhibit tonic thermoregulatory vasoconstriction, thereby resulting in arteriovenous shunt dilation.[20-24] Nonetheless, anesthetic-induced vasodilation increases cutaneous heat loss only slightly.[53] Anesthetics reduce the metabolic rate 20% to 30%.[54] However, even the combination of increased heat loss and reduced heat production is insufficient to explain the 0.5°C to 1.5°C decrease in core temperature generally observed during the first hour of anesthesia.

The key to understanding the initial decrease in core temperature is to appreciate that body heat is not normally distributed evenly. Core temperature represents only about half the body mass (mostly the trunk and head); the remaining mass is typically 2°C to 4°C cooler than the core. This core-to-peripheral tissue temperature gradient is normally maintained by tonic thermoregulatory vasoconstriction. Anesthetic-induced vasodilation, however, allows core heat to flow peripherally. This warms the arms and legs but does so at the expense of the core (Figs. 48-8 and 48-9).[55] The extent to which redistribution reduces core temperature depends on the core-to-peripheral tissue temperature gradient at the time of induction. This gradient, in turn, depends

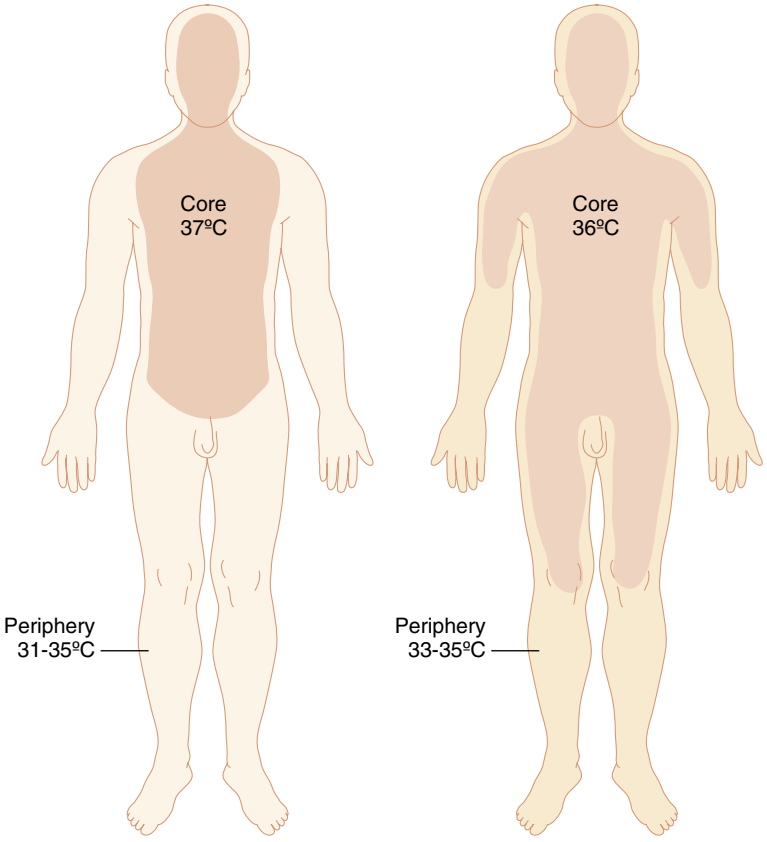

Figure 48-8 Drawing illustrating internal redistribution of body heat after induction of general anesthesia. Hypothermia after induction of spinal or epidural anesthesia results similarly, but redistribution is restricted to the legs.

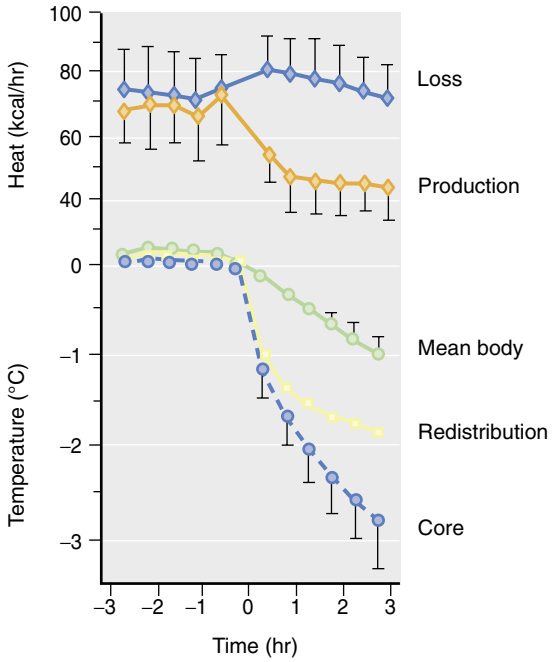

Figure 48-9 Changes in body heat content and distribution of heat within the body during induction of general anesthesia (at elapsed time zero). Subtraction of the change in mean body temperature from the change in core (tympanic membrane) temperature leaves the core hypothermia specifically resulting from redistribution. Redistribution hypothermia was thus not a measured value; instead, it is defined by the decrease in core temperature not explained by the relatively small decrease in systemic heat content. After 1 hour of anesthesia, core temperature had decreased 1.6 ± 0.3°C, with redistribution contributing 81% to the decrease. Even after 3 hours of anesthesia, redistribution contributed 65% to the entire 2.8 ± 0.5°C decrease in core temperature. Results are presented as means ± SD. *(Modified from Matsukawa T, Sessler DI, Sessler AM, et al: Heat flow and distribution during induction of general anesthesia. Anesthesiology 82:662-673, 1995.)*

on the patient's prior thermal environment and thermoregulatory status, both of which are difficult to determine clinically.

After initial redistribution hypothermia, core temperature usually decreases in a slow, linear fashion for 2 to 4 hours. This reduction results simply from heat loss exceeding metabolic heat production,[56] and the rate at which core temperature decreases depends on the difference and size of the patient. After 3 to 4 hours of anesthesia, core temperature usually reaches a plateau and remains virtually constant for the duration of surgery.[31] The core temperature plateau may simply represent a thermal steady state (heat production equaling heat loss) in patients remaining relatively warm. In others, however, the plateau phase is associated with peripheral thermoregulatory vasoconstriction triggered by core temperatures of 33°C to 35°C.

Thermoregulatory vasoconstriction during anesthesia decreases cutaneous heat loss,[44] but this decrease alone is usually insufficient to produce a thermal steady state. Furthermore, neither adults[40] nor infants[42] appear to be able to increase intraoperative heat production in response to hypothermia. An additional mechanism must therefore contribute to the core temperature plateau. Evidence suggests that a primary factor is constraint of metabolic heat to the core thermal compartment. In this scenario, distribution of metabolic heat (which is largely produced centrally) is restricted to the core compartment, thereby maintaining its temperature. Peripheral tissue temperature, in contrast, continues to decrease because it is no longer being supplied with sufficient heat from the core.[45] A core temperature plateau resulting from thermoregulatory vasoconstriction is thus not a thermal steady state, and body heat content continues to decrease even though core temperature remains nearly constant.

Neuraxial Anesthesia

Autonomic thermoregulation is impaired during regional anesthesia, and the result is typically intraoperative core hypothermia. Interestingly, this hypothermia is often not consciously perceived by patients but nonetheless triggers shivering. The result is frequently a potentially dangerous clinical paradox: a hypothermic patient who denies feeling cold (see Chapters 51, 52 and 87).

Thermoregulation

Epidural[57,58] and spinal[58,59] anesthesia each decrease the thresholds triggering vasoconstriction and shivering (above the level of the block) by about 0.6°C (Fig. 48-10). Presumably, this decrease does not result from recirculation of neuraxially administered local anesthetic because impairment is similar during epidural and spinal anesthesia,[57-59] although the amount and location of administered local anesthetic differ substantially. Furthermore, lidocaine administered intravenously in doses producing plasma concentrations similar to those occurring during epidural anesthesia has no thermoregulatory effect.[60] Finally, neuraxial administration of 2-choloprocaine, a local anesthetic with a plasma half-life of only about 20 seconds, also impairs thermoregulatory control.[61]

The vasoconstriction and shivering thresholds are comparably decreased during regional anesthesia,[59] suggesting an alteration in central, rather than peripheral control. The mechanism by

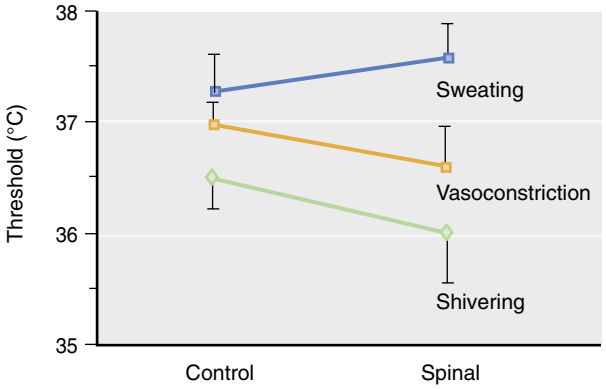

Figure 48-10 Spinal anesthesia increased the sweating threshold but reduced the thresholds for vasoconstriction and shivering. Consequently, the interthreshold range increased substantially. The vasoconstriction-to-shivering range, however, remained normal during spinal anesthesia. Results are presented as means ± SD. *(From Kurz A, Sessler DI, Schroeder M, Kurz M: Thermoregulatory response thresholds during spinal anesthesia. Anesth Analg 77:721-726, 1993.)*

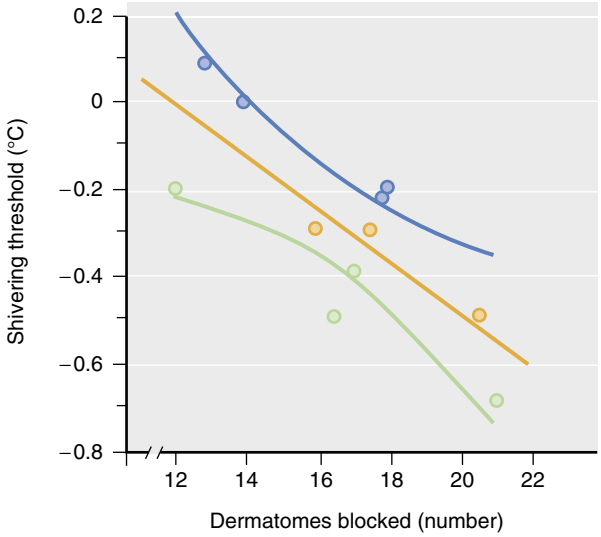

Figure 48-11 The number of dermatomes blocked (sacral segments = 5; lumbar segments = 5; thoracic segments = 12) versus reduction in the shivering threshold (difference between the control shivering threshold and the spinal shivering threshold). The shivering threshold was reduced more by extensive spinal blocks than by less extensive ones (Δ threshold = 0.74 – 0.06 [dermatomes blocked]; $r^2 = .58$, $P < .006$). The *curved lines* indicate 95% confidence intervals for the slope. *(From Leslie K, Sessler DI: Reduction in the shivering threshold is proportional to spinal block height. Anesthesiology 84:1327-1331, 1996.)*

which peripheral administration of local anesthesia impairs centrally mediated thermoregulation may involve alteration of afferent thermal input from the legs. The key factor here is that tonic cold signals dominate thermal input at leg skin temperatures in typical operating room environments.[2] Regional anesthesia blocks all thermal input from the blocked regions, which in the typical case is primarily cold information. The brain may then interpret decreased cold information as relative leg warming. This appears to be an unconscious process in that perceived temperature does not increase.[62] Because skin temperature is an important input to the thermoregulatory control system, leg warming proportionately reduces the vasoconstriction and shivering thresholds. Consistent with this theory, a leg skin temperature near 38°C is required to produce the same reduction in cold-response thresholds in an unanesthetized subject as produced by regional anesthesia.[63] Moreover, the reduction in thresholds is proportional to the number of spinal segments blocked (Fig. 48-11).[64] Major conduction anesthesia may thus reduce the vasoconstriction and shivering thresholds by producing an abnormal elevation in *apparent* (as opposed to actual) leg temperature. However, this explanation remains speculative.

Because neuraxial anesthesia prevents vasoconstriction and shivering in blocked regions, it is not surprising that epidural anesthesia decreases the maximum intensity of shivering. However, epidural anesthesia also reduces the gain of shivering, which suggests that the regulatory system is unable to compensate for lower body paralysis (Fig. 48-12).[26] Thermoregulatory defenses, once triggered, are thus less effective than usual during regional anesthesia.

Neuraxial anesthesia is frequently supplemented with sedative and analgesic medications that impair thermoregulatory control.[20,21,27] Such inhibition may be severe when combined with the intrinsic impairment produced by regional anesthesia and other factors, including advanced age and preexisting illness.

Interestingly, core hypothermia during regional anesthesia may not trigger a perception of cold.[57,65] The reason is that thermal perception (behavioral regulation) is largely determined by skin rather than core temperature. During regional anesthesia, core hypothermia is accompanied by a real increase in skin temperature. The result is typically a perception of continued or increased warmth accompanied by activation of autonomic thermoregulatory responses including shivering (Fig. 48-13).[57,65]

Taken together, these data indicate that neuraxial anesthesia inhibits numerous aspects of thermoregulatory control. The vasoconstriction and shivering thresholds are reduced by regional anesthesia[57-59,63,64] and further reduced by adjuvant drugs[21,36] and advanced age.[10] Even once triggered, the gain and maximum response intensity of shivering are about half-normal. Finally, behavioral thermoregulation is impaired.[65] The result is that cold defenses are triggered at a lower temperature than normal during regional anesthesia, defenses are less effective once triggered, and patients frequently do not recognize that they are hypothermic. Because core temperature monitoring remains rare during regional anesthesia, substantial hypothermia often goes undetected in these patients.[66]

Heat Balance

Hypothermia is common during regional anesthesia and may be nearly as severe as during general anesthesia.[67] Core temperature

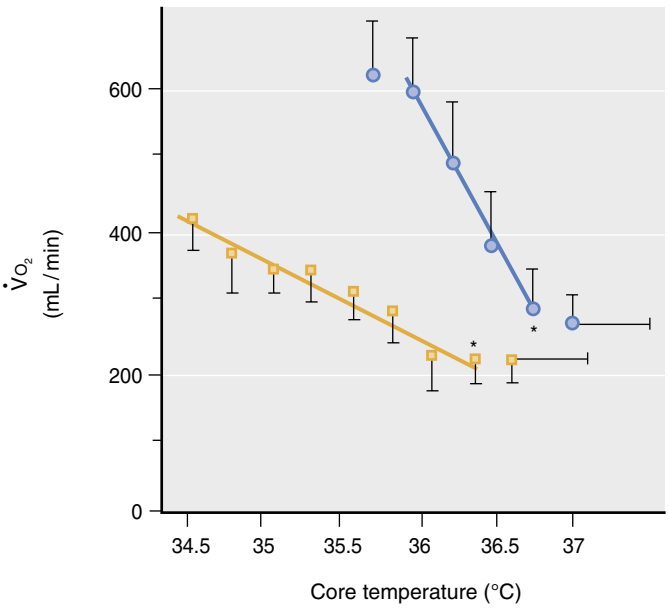

Figure 48-12 Systemic oxygen consumption without (*circles*) and with (*squares*) epidural anesthesia. The horizontal standard deviation bars indicate variability in the thresholds among the volunteers; although error bars are shown only once in each series, the same temperature variability applies to each data point. Slopes of the oxygen consumption–versus–core temperature relationships (*solid lines*) were determined by linear regression. These slopes defined the gain of shivering with and without epidural anesthesia. Gain was reduced 3.7-fold, from –412 mL/min/°C ($r^2 = .99$) to –112 mL/min/°C ($r^2 = .96$). *(From Kim J-S, Ikeda T, Sessler D, et al: Epidural anesthesia reduces the gain and maximum intensity of shivering. Anesthesiology 88:851-857, 1998.)*

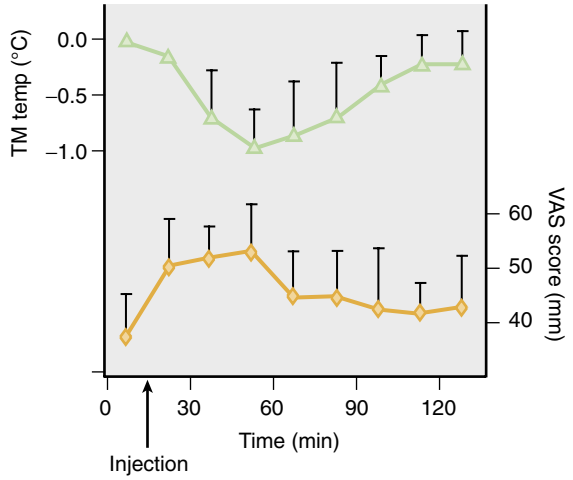

Figure 48-13 Induction of epidural anesthesia at an elapsed time of 15 minutes decreased core temperature and increased thermal comfort as determined by a 100-mm visual analog scale (VAS). Interesting, however, that maximal thermal comfort coincided with *minimum* core temperature. The results are presented as means ± SD. TM, tympanic membrane. *(Modified from Sessler DI, Ponte J: Shivering during epidural anesthesia. Anesthesiology 72:816-821, 1990.)*

typically decreases 0.5°C to 1.0°C shortly after induction of anesthesia. However, the vasodilation induced by regional anesthesia only slightly increases cutaneous heat loss. Furthermore, metabolic heat production remains constant or increases because of shivering thermogenesis. This rapid decrease in core temperature, similar to that seen after induction of general anesthesia, also results from an internal core-to-peripheral redistribution of body heat.[68] As during general anesthesia,[69,70] redistribution hypothermia during regional anesthesia can be minimized by cutaneous warming before induction.[71]

Subsequent hypothermia results simply from heat loss exceeding metabolic heat production. Unlike patients given general anesthesia, however, core temperature does not necessarily plateau after several hours of surgery. Not only is the vasoconstriction threshold centrally impaired by regional anesthesia,[58,59] but more importantly, vasoconstriction in the legs is also directly prevented by nerve block.[72] Because the legs constitute the bulk of the peripheral thermal compartment, an effective plateau cannot develop without vasoconstriction in the legs and the resulting decrease in cutaneous heat loss and constraint of metabolic heat to the core.

The importance of intraoperative leg vasoconstriction is illustrated during combined regional/general anesthesia. Consistent with the impairment of thermoregulatory responses with regional anesthesia alone,[58,59] vasoconstriction during combined regional/general anesthesia is triggered at a core temperature approximately 1°C lower than during general anesthesia alone. Moreover, once triggered, vasoconstriction produces a core temperature plateau during general anesthesia alone but not during combined regional/general anesthesia. The result is that core temperature during combined regional/general anesthesia continues to decrease throughout surgery.[73] Consequently, core temperature monitoring and thermal management are especially important in patients given simultaneous regional and general anesthesia.

Shivering

Shivering-like tremor in volunteers given neuraxial anesthesia is always preceded by core hypothermia and vasoconstriction (above the level of the block).[57] Furthermore, electromyographic analysis indicates that the tremor has the 4- to 8-cycle/min waxing-and-waning pattern that characterizes normal shivering.[61] The tremor is thus apparently normal thermoregulatory shivering, triggered when redistribution hypothermia decreases core temperature.

Spinal thermal receptors have been detected in every mammal and bird tested. Experimental stimulation of these receptors reliably produces shivering in animals. Stimulation of these putative receptors in humans by epidural anesthetic injection could theoretically initiate thermoregulatory responses, including shivering. However, epidural administration of large amounts of ice-cold saline does not trigger shivering in volunteers.[74] In addition, the incidence of shivering is comparable in volunteers[57] and patients[75] given warm or cold epidural anesthetic injections. These data indicate that the temperature of an injected local anesthetic does not influence the incidence of shivering during major conduction anesthesia.

The risk of shivering during neuraxial anesthesia is markedly diminished by maintaining strict normothermia.[57] However, there is a distinct incidence of low-intensity, shivering-like tremor that occurs in normothermic patients and is not thermoregulatory.[76] The cause of this muscular activity remains unknown, but it is associated with pain[77] and may thus result from activation of the sympathetic nervous system (Fig. 48-14).

Shivering during neuraxial anesthesia can sometimes be treated by warming sentient skin. This augments cutaneous

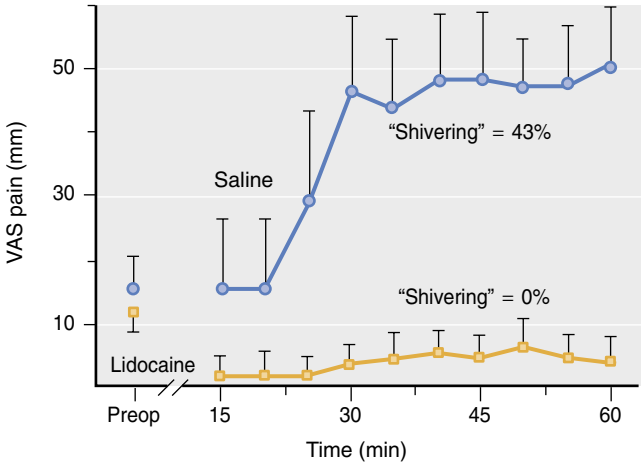

Figure 48-14 Visual analog pain scores (VAS) in normothermic patients given intra-articular lidocaine or saline after knee surgery. Pain was assessed postoperatively by an investigator blinded to the group assignment. Time zero indicates discontinuation of anesthesia. Data are presented as means ± SD. Patients receiving a local anesthetic block (lidocaine) had significantly less postoperative pain than those given saline; all values after 10 elapsed minutes differed significantly in the two groups. Shivering-like tremor was observed in 43% of the patients given saline versus 0% of those given lidocaine, thus indicating that the tremor is related to pain. *(From Horn E-P, Schroeder F, Wilhelm S, et al: Postoperative pain facilitates non-thermoregulatory tremor. Anesthesiology 91:979-984, 1999.)*

thermal input to the central regulatory system and thus increases the degree of core hypothermia tolerated. Because the entire skin surface contributes 20% to thermoregulatory control[5] and the lower body contributes about 10%,[63] sentient skin warming is likely to compensate for only small reductions in core temperature. The same drugs that are effective for postanesthetic tremor are also useful for shivering during regional anesthesia; such drugs include meperidine (25 mg intravenously [IV] or epidurally),[78] clonidine (75 μg IV),[79] dexmedetomine,[80] ketanserin (10 mg IV),[79] and magnesium sulfate (30 mg/kg IV).[81]

Consequences of Mild Intraoperative Hypothermia

Perianesthetic hypothermia produces potentially severe complications, as well as distinct benefits. Thermal management thus deserves the same thoughtful analysis of potential risks and benefits as other therapeutic decisions do.

Benefits

Substantial protection against cerebral ischemia and hypoxia is provided by hypothermia of just 1°C to 3°C in animals.[82,83] Protection was initially thought to result from the approximate 8%/°C linear reduction in tissue metabolic rate. However, the efficacy of mild hypothermia far exceeds that of treatments such as high-dose isoflurane or barbiturate coma, which comparably reduce the metabolic rate.[84] These data suggest that other actions (e.g., decreased release of excitatory amino acids) explain the protective action of hypothermia.[85] Accordingly, there is no reason to expect protection to augment linearly with temperature, and in animals it appears that much of the total benefit from moderate hypothermia takes place within the first couple of degrees.

Therapeutic hypothermia has twice been shown to improve outcomes after out-of-hospital cardiac arrest.[86,87] Rapid induction of hypothermia is thus becoming routine for patients after recovery from arrest and for asphyxiated neonates.[88-90]

The potential protection afforded by mild hypothermia is so great that reduced core temperature (i.e., ≈34°C) is increasingly being used during neurosurgery and other procedures in which tissue ischemia can be anticipated. The difficulty is that there are currently few outcome data substantiating an extrapolation from animal data to clinical practice. Furthermore, the appropriate target temperature for therapeutic hypothermia has yet to be established.

Hypothermia for brain trauma was initially claimed to be therapeutic based on a post hoc subgroup analysis of a study that overall showed no benefit.[91] A subsequent large randomized trial was unable to demonstrate any benefit overall or in subgroups—although interpretation of the study was limited by violations in the fluid administration protocol in some patients.[92] Most recently, hypothermia was shown to be beneficial in a nonrandomized study in which brain trauma patients with elevated intracranial pressure refractory to conventional treatment were assigned to therapeutic hypothermia. Despite being sicker than the comparison patients (who had low intracranial pressure), the hypothermic patients demonstrated improved outcomes.[93]

Small nonrandomized series suggested that mild hypothermia might improve the outcome after stroke.[94] A small feasibility trial for treatment of stroke with hypothermia has been published,[95] but no large trial is currently in progress.

Although the initial feasibility trials were encouraging,[95,96] a subsequent large outcome trial failed to demonstrate any improvement with therapeutic hypothermia in patients undergoing surgery for subarachnoid hemorrhage.[97] This result was especially disappointing because surgery is one of the few times in humans that hypothermia can be instituted before the onset of ischemia.

Hypothermic protection against ischemia may extend to other organs. For example, mild hypothermia markedly reduces infarct size in experimental acute myocardial infarction in human-sized pigs,[98] and a preliminary study in patients was encouraging.[99] However, a subsequent major outcome trial in humans failed to demonstrate convincing benefit (unpublished).

A limitation of most therapeutic hypothermia studies is that cooling began well after the ischemic insult and that patients typically took many hours to cool. It thus remains possible that benefit will yet be identified in future studies that initiate hypothermia earlier and use recently developed systems to cool patients faster. Table 48-1 lists selected major studies that have evaluated the potential benefits of mild perioperative hypothermia.

Complications

Coagulation is impaired by mild hypothermia. The most important factor is a cold-induced defect in platelet function.[107] Interestingly, the defect in platelet function is related to local temperature, not core temperature. Wound temperature, however, is largely determined by core temperature and will be distinctly higher in normothermic patients. Perhaps as important, hypothermia directly impairs enzymes of the coagulation cascade. This will not be apparent during routine coagulation screening because the tests are performed at 37°C. When these tests are performed at hypothermic temperatures, however, the defect becomes apparent.[108]

Consistent with these in vitro defects, nearly all randomized trials indicate that mild hypothermia increases blood loss during hip arthroplasty and increases allogeneic transfusion requirements.[109] Similarly, nearly all randomized trials report an increased transfusion requirement in hypothermic patients. Meta-analyses indicate that both blood loss and transfusion requirements are significantly increased by hypothermia.[106] The treatment effect is substantial, with just 1°C of core hypothermia increasing each by about 20%.

Wound infections are among the most common serious complications of anesthesia and surgery and probably cause more morbidity than all other anesthetic complications combined.[110] Hypothermia can contribute to wound infections both by directly impairing immune function[111] and by triggering thermoregulatory vasoconstriction, which in turn decreases oxygen delivery to wounds.[112] It is well established that fever is protective and that infections are aggravated when naturally occurring fever is prevented.[113] Similarly, mild hypothermia, maintained only during anesthesia, impairs subsequent resistance to both *Escherichia coli* and *Staphylococcus aureus* dermal infections in guinea pigs. As

Table 48-1 Major Complications of Mild Perioperative Hypothermia in Humans

Consequence	First Author	Year	*N*	ΔT_{core} (°C)	Normothermic	Hypothermic	*P*
Surgical wound infection	Kurz	1996	200	1.9	6%	19%	<.01
Duration of hospitalization	Kurz	1996	200	1.9	12.1 ± 4.4 days	14.7 ± 6.5 days	<.01
Duration of hospitalization	Frank	1997	300	1.3	8 (range, 5-13)	8 (5-11)	NS
Postoperative troponin I	Nesher[100]	2003	60	1.0	22 ± 9 ng/mL	8 ± 5 ng/mL	
Morbid cardiac events	Frank	1997	300	1.3	1%	6%	<.05
Myocardial damage	Nesher[100]	2003	60	1.0	8 ± 5 ng/ml	22 ± 9 ng/mL	<.01
Postoperative shivering	Just[101]	1992	14	2.3	141 ± 9 mL/min/m^2	269 ± 60 mL/min/m^2	<.001
Duration of postanesthetic recovery	Lenhardt[102]	1997	150	1.9	53 ± 36 min	94 ± 65 min	<.001
Adrenergic activation	Frank[103]	1995	74	1.5	330 ± 30 pg/mL	480 ± 70 pg/mL	<.05
Thermal discomfort	Kurz[104]	1995	74	2.6	50 ± 10 mm VAS	18 ± 9 mm VAS	<.001
Mortality after major trauma	Gentillo[105]	1997	57	≈1.5	2/29 (7%)	12/28 (43%)	<.05

Only prospective, randomized human trials are included; subjective responses were evaluated by observers blinded to the treatment group and core temperature. ***N*** = total number of subjects. ΔT_{core} = difference in core temperature between the treatment groups. Different outcomes of some studies are shown in separate rows. VAS is a 100-mm-long visual analog scale (0 mm = intense cold; 100 mm = intense heat). The study by Just and colleagues is but one of dozens of studies showing that hypothermia provokes shivering. The results are presented as means ± SD or median (interquartile range) unless otherwise specified. NS = not significant. For the effects of hypothermia on perioperative blood loss and transfusion requirement, see the meta-analysis by Rajagopalan and coworkers.[106]

might be expected from these in vitro and animal data, a prospective, randomized clinical trial indicated that mild intraoperative hypothermia triples the incidence of surgical wound infection in patients undergoing colon surgery. Furthermore, hypothermia delayed wound healing and prolonged the duration of hospitalization 20% even in patients without infection. Consistent with poor wound healing, urinary nitrogen excretion remains elevated for several postoperative days in patients allowed to become hypothermic during surgery.

Thermal comfort is markedly impaired by postoperative hypothermia, a feeling that persists for several hours in patients who are several degrees centigrade hypothermic at the beginning of recovery (Fig. 48-15).[104] Patients, asked years after surgery, often identify feeling cold in the immediate postoperative period as the worst part of their hospitalization—sometimes rating it worse than surgical pain. Postoperative thermal discomfort is also physiologically stressful in that it elevates blood pressure, heart rate, and plasma catecholamine concentrations.[103] These factors presumably contribute to what may be the most important consequence of mild perioperative hypothermia: a threefold increase in morbid myocardial outcomes. Given that myocardial ischemia is among the leading causes of unanticipated perioperative death, the results of this prospective, randomized trial must be taken extremely seriously. Drug metabolism is markedly decreased by perioperative hypothermia. For further information see Chapters 26 and 29. Table 48-2 lists the major studies that have evaluated complications caused by mild perioperative hypothermia.

Postanesthetic Shivering

The incidence of postoperative shivering-like tremor is reportedly about 40% but now appears to be less as more patients are kept normothermic and opioids are administered more frequently and in larger doses than in the past. It is a potentially serious complication that increases oxygen consumption roughly 100% in proportion to intraoperative heat loss.[116] Interestingly, though, myocardial ischemia is poorly correlated with shivering, suggesting that an increased metabolic rate is not the primary cause of this complication. In addition to increasing intraocular and

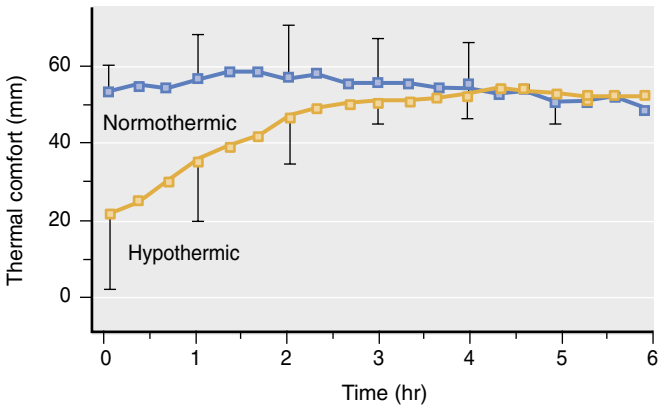

Figure 48-15 Patients who started recovery while about 2°C hypothermic reported feeling unpleasantly cold, and the sensation persisted longer than 2 hours. Only a few of the warmed patients shivered at any time during the recovery period. In contrast, most of the hypothermic patients demonstrated grade 2 or 3 tremor during the first postoperative hour. By the end of the first elapsed hour, however, shivering was rare, even in the hypothermic patients. Error bars indicate standard deviations. Thermal comfort is shown on a 100-mm visual analog scale, where 0 mm is the worst possible cold sensation, 50 mm is neutral, and 100 mm is extreme heat. *(From Kurz A, Sessler DI, Narzt E, et al: Postoperative hemodynamic and thermoregulatory consequences of intraoperative core hypothermia. J Clin Anesth 7:359-366, 1995.)*

Table 48-2 Potential Benefits of Mild Perioperative Hypothermia in Humans

Consequence	First author	Year	*N*	ΔT_{core} (°C)	Normothermic	Hypothermic	*P*
Mortality after brain trauma	Clifton[92]	2001	392	4.2	27%	28%	NS
Favorable Glasgow outcome score 3 months after brain trauma	Shiozaki[114]	2001	91	4	59%	47%	NS
Glasgow outcome score 12 months after brain trauma (1-3/4-5)	Marion[91]	1997	81	≈4	62%/38%	39%/61%	NS
Neurologic outcome after cardiac arrest (good)	Bernard[86]	2002	77	≈4	26%	49%	.01
Neurologic outcome 6 months after cardiac arrest (good recovery or moderate disability)	Hypothermia Group[87]	2002	273	≈4.5	55%	39%	.009
Mortality at 6 months	Hypothermia Group[87]	2002	273	≈4.5	55%	41%	.02
Neurologic outcome of neonatal hypoxia (death or moderate to severe disability)	Gluckman[88]	2005	218	≈2	66%	59%	.1
Neurologic outcome of neonatal hypoxia (death or moderate to severe disability)	Shankaran[89]	2005	208	3.8	62%	44%	.01
Good neurologic outcome after intracranial aneurysm surgery	Todd[97]	2005	1001	3.5	63	66	NS

Only prospective, randomized human trials are included; subjective responses were evaluated by observers blinded to the treatment group and core temperature. ***N*** = total number of subjects. ΔT_{core} = difference in core temperature between the treatment groups. Different outcomes of some studies are shown in separate rows. Results are presented as means ± SD or median (interquartile range) unless otherwise specified. NS = not significant. For the effects of mild hypothermia on neonatal asphyxia, see the Cochrane meta-analysis by Jacobs and coworkers.[115]

intracranial pressure, postoperative shivering possibly aggravates wound pain by stretching incisions. The most important determinants of shivering risk are young age and low core temperature.[117]

Unfortunately, the etiology of postanesthetic shivering-like tremor is unclear. Certainly, much postoperative tremor is simply normal shivering. As early as 1972, however, investigators recognized the existence of at least two distinct tremor patterns.[118] That perceptive observation was subsequently confirmed in a study that used electromyography to demonstrate that postoperative tremor has (1) a tonic pattern resembling normal shivering, typically with a 4- to 8-cycle/min waxing-and-waning component, and (2) a phasic, 5- to 7-Hz bursting pattern resembling pathologic clonus.[119] The clonic pattern was consistent with the previous observation that pathologic spinal cord responses, including clonus, nystagmus, and exaggerated deep tendon reflexes, were common during recovery from general anesthesia.[120] This combined tonic and clonic pattern is thermoregulatory; that is, it is always preceded by core hypothermia and arteriovenous shunt vasoconstriction.[121] The tonic pattern consistently demonstrated the 4- to 8-cycle/min waxing-and-waning pattern of normal shivering[16] and apparently is a simple thermoregulatory response to intraoperative hypothermia. In contrast, the clonic pattern is not a normal component of thermoregulatory shivering and appears to be specific to recovery from volatile anesthetics. Although the precise etiology of this tremor pattern remains unknown, it may result from anesthetic-induced disinhibition of normal descending control over spinal reflexes. Earlier data in surgical patients, however, belie the simple conclusion from a volunteer study[121] that all postanesthetic tremor is thermoregulatory. Instead, there appears to be a distinct incidence of non-thermoregulatory tremor in normothermic postoperative patients[122]; similar non-thermoregulatory tremor has been observed in women during labor.[76] The etiology of this tremor and why volunteers and patients should respond differently remain unknown, but surgical pain appears to be a key factor.[77]

Postanesthetic shivering can be treated by skin surface warming because the regulatory system tolerates more core hypothermia when cutaneous warm input is augmented. However, the skin surface contributes only 20% to control of shivering,[5] and available skin surface warmers increase mean skin temperature only a few degrees centigrade.[123] Consequently, cutaneous warming compensates for only small amounts of core hypothermia and will not usually prove effective in most patients with core temperatures much below 35°C.[124]

Postanesthetic shivering can also be treated with a variety of drugs, including clonidine (75 μg IV),[79] ketanserin (10 mg IV),[79] tramadol,[125] physostigmine (0.04 mg/kg IV),[126] nefopam (0.15 mg/kg),[127] dexmedetomidine, and magnesium sulfate (30 mg/kg IV).[81] The specific mechanisms by which ketanserin, tramadol, physostigmine, and magnesium sulfate stop shivering remain unknown. Similarly, how clonidine arrests shivering also remains unknown, but clonidine[32] and dexmedetomidine[22] comparably reduce the vasoconstriction and shivering thresholds, thus suggesting that they act on the central thermoregulatory system rather than preventing shivering peripherally. Postoperative shivering has been reviewed in detail[128] and treatment options have been subjected to a systematic review.[129]

Alfentanil, a pure μ-receptor agonist, significantly impairs thermoregulatory control.[21] However, meperidine is considerably more effective in treating shivering than equi-analgesic doses of other μ-agonists are.[130] Clinically, this efficacy is manifested as a shivering threshold that is reduced twice as much as the vasoconstriction threshold[27] without a decrease in the gain or maximum intensity of shivering.[46] The efficacy of meperidine is at least partially preserved during the administration of moderate doses of naloxone (0.5 μg/kg/min) but virtually obliterated by enormous doses (5.0 μg/kg/min).[131] These data suggest that the action of this

drug is in part mediated by non–μ-opioid receptors. Meperidine possesses considerable κ activity[132] and also has central anticholinergic activity. However, neither mechanism appears to mediate meperidine's special antishivering activity.

Perioperative Thermal Manipulations

Intraoperative thermoregulatory vasoconstriction, once triggered, is remarkably effective in preventing further core hypothermia.[39,45] Nonetheless, most patients are poikilothermic during surgery because they do not become sufficiently hypothermic to trigger thermoregulatory responses.[20,21,23,24] Therefore, intraoperative hypothermia can be minimized by any technique that limits cutaneous heat loss to the environment, such as loss caused by cold operating rooms, evaporation from surgical incisions, or conductive cooling produced by the administration of cold intravenous fluids. The efficacy of various approaches differs enormously, however.

Mean body temperature will decrease when heat loss to the environment exceeds metabolic heat production. Heat production during anesthesia is approximately 0.8 kcal/kg/hr. Because the specific heat of the human body is about 0.83 kcal/kg,[133] body temperature decreases approximately 1°C/hr when heat lost to the environment exceeds metabolic production by a factor of 2. Normally, about 90% of metabolic heat is lost through the skin surface. During anesthesia, additional heat is also lost directly from surgical incisions and by the administration of cold intravenous fluids.

Effects of Vasomotor Tone on Heat Transfer

Thermoregulatory vasodilation causes the initial core-to-peripheral redistribution of body heat[55]; similarly, re-emergence of vasoconstriction in patients becoming sufficiently hypothermic produces a core temperature plateau.[45] It is thus evident that vasomotor tone alters intercompartmental heat transfer. In addition to thermoregulatory arteriovenous shunt status, arteriolar tone is directly modulated by anesthetics per se.[52] Both factors potentially influence the speed with which peripherally applied heat reaches the core thermal compartment.

Thermoregulatory vasoconstriction slightly impairs induction of therapeutic hypothermia during neurosurgery.[134] However, arteriovenous shunt tone has little effect on intraoperative cooling[135] or heating.[136] Intraoperative vasoconstriction thus only slightly impedes peripheral-to-core transfer of cutaneous heating and cooling. Little clinical effect presumably results because intraoperative thermoregulatory vasoconstriction is opposed by direct anesthetic-induced peripheral vasodilation.

During postanesthetic recovery, however, the situation differs markedly. Here, dissipation of anesthetic-induced peripheral dilation[52,137] leaves thermoregulatory vasoconstriction unopposed. As might be expected, this vasoconstriction then becomes an important factor and significantly impairs transfer of peripherally applied heat to the core thermal compartment. Patients with residual spinal anesthetic block thus warm considerably faster than those recovering from general anesthesia alone

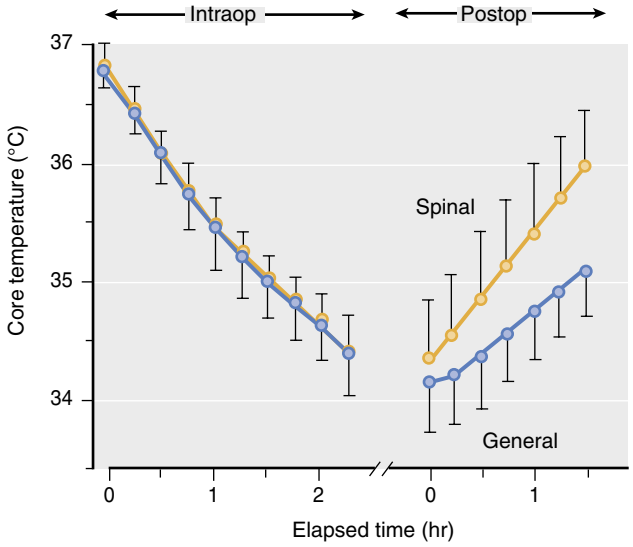

Figure 48-16 Intraoperative and postoperative core temperatures in patients assigned to general anesthesia ($n = 20$) and spinal anesthesia ($n = 20$). All patients were warmed with forced air during the postoperative period. Core temperature did not differ significantly during surgery but increased significantly faster postoperatively in patients given spinal anesthesia (1.2 ± 0.1°C/hr versus 0.7 ± 0.2°C/hr, means ± SD). *(From Szmuk P, Ezri T, Sessler DI, et al: Spinal anesthesia only minimally increases the efficacy of postoperative forced-air rewarming. Anesthesiology 87:1050-1054, 1997.)*

(Fig. 48-16).[138] Heat balance studies indicate that core warming is slowed because vasoconstriction constrains up to 30 kcal in peripheral tissues.[139]

Furthermore, it is easier to maintain intraoperative normothermia (when most patients are vasodilated) than rewarm patients postoperatively (when virtually all hypothermic patients are vasoconstricted). In addition to being more effective, intraoperative warming is more appropriate than postoperative treatment of hypothermia because it prevents the complications resulting from hypothermia.[109] Patients unavoidably becoming hypothermic during surgery should nonetheless be actively heated postoperatively to increase thermal comfort, decrease shivering, and hasten rewarming.

Preventing Redistribution Hypothermia

The initial 0.5°C to 1.5°C reduction in core temperature is difficult to prevent because it results from redistribution of heat from the central thermal compartment to cooler peripheral tissues.[55] Consequently, surface warming usually fails to prevent hypothermia during the first hour of anesthesia.[56] Lack of efficacy during this period results both because the central-to-peripheral flow of heat is massive and because transfer of applied cutaneous heat to the core requires nearly an hour, even in vasodilated patients.

Although redistribution is difficult to treat,[56] it can be prevented. Redistribution results when anesthetic-induced vasodilation allows heat to flow peripherally down the normal temperature gradient. Skin surface warming before induction of anesthesia does not significantly alter core temperature (which remains well regulated), but it does increase body heat content. Most of the increase is in the legs, the most important component of the

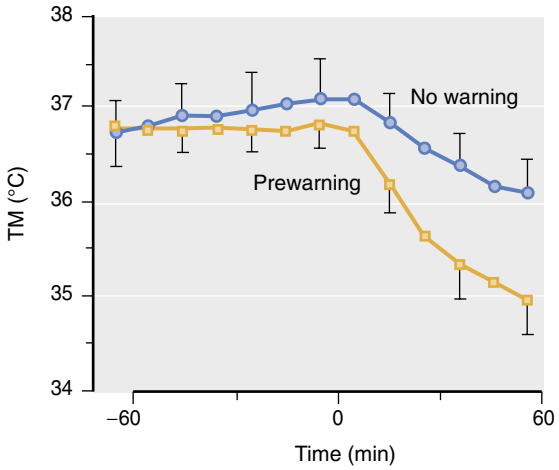

Figure 48-17 During the preinduction period (–120 to 0 minutes), volunteers were either actively warmed or passively cooled (no warming). At induction of anesthesia (time = 0 minutes), active warming was discontinued and volunteers were exposed to the ambient environment. Initial tympanic membrane (TM) temperatures were similar before each preinduction treatment. During the 60 minutes after induction of anesthesia, core temperature decreased less when volunteers were prewarmed. ($\Delta T = -1.1 \pm 0.3°C$) than when the same volunteers were not warmed ($\Delta T = -1.9 \pm 0.3°C$). Data are presented as means ± SD. *(From Hynson JM, Sessler DI, Moayeri A, et al: The effects of pre-induction warming on temperature and blood pressure during propofol/nitrous oxide anesthesia. Anesthesiology 79:219-228, 1993.)*

peripheral thermal compartment. When peripheral tissue temperature is sufficiently increased, subsequent inhibition of normal tonic thermoregulatory vasoconstriction produces little redistribution hypothermia because heat can flow only down a temperature gradient (Fig. 48-17).[69,70] Although substantial amounts of heat must be transferred across the skin surface, active prewarming for as little as 30 minutes probably prevents considerable redistribution.[140]

The "afterdrop" associated with discontinuation of cardiopulmonary bypass is a type of redistribution hypothermia that results from a substantial core-to-peripheral tissue temperature gradient. As might be expected, it is more impressive after bypass at 17°C[141] than at 27°C to 31°C.[142] Cutaneous warming during and after bypass reduces core temperature afterdrop by 60%. However, heat balance data indicate that this reduction results primarily because cutaneous warming prevents the typical decrease in body heat content after discontinuation of bypass rather than by reducing redistribution.[143]

Airway Heating and Humidification

Simple thermodynamic calculations indicate that less than 10% of metabolic heat production is lost via the respiratory tract. The loss results from both heating and humidifying inspiratory gases, but humidification requires two thirds of the heat.[50] Because little heat is lost via respiration, even active airway heating and humidification minimally influence core temperature.[56]

Because respiratory heat loss remains virtually constant during anesthesia, the fraction of total heat lost via the respiratory tract decreases dramatically during large operations in which substantial heat is lost from evaporation within surgical incisions.[51] Consequently, airway heating and humidification are even less effective than usual in patients most in need of effective warming.

Intravenous Fluids

Patients cannot be warmed by administering heated fluids because the fluids cannot (much) exceed body temperature. On the other hand, heat loss from cold intravenous fluids becomes substantial when large amounts of crystalloid solution or blood are administered. One unit of refrigerated blood or 1 L of crystalloid solution administered at room temperature each decreases mean body temperature approximately 0.25°C. (The blood is twice as cold, but only half the volume.) Fluid warmers minimize these losses and should be used when large amounts of intravenous fluid or blood are administered. In smaller cases, though, they contribute little.

For routine cases, there are no clinically important differences among the available fluid warmers. Although most warmers allow fluid to cool in the tubing between the heater and the patient, this cooling is of little consequence in adults: at high flow there is little cooling, and at low flow the amount of fluid given is trivial.[144] Special high-volume systems with powerful heaters and little resistance to flow facilitate care of trauma victims and are useful in other cases in which a large amount of fluid must be administered quickly.

Cutaneous Warming

Operating room temperature is the most critical factor influencing heat loss because it determines the rate at which metabolic heat is lost by radiation and convection from the skin and by evaporation from within surgical incisions. Consequently, increasing room temperature is one way to minimize heat loss. However, room temperatures exceeding 23°C are generally required to maintain normothermia in patients undergoing all but the smallest procedures[145]; most operating room personnel find such temperatures uncomfortably warm. Infants may require ambient temperatures exceeding 26°C to maintain normothermia. Such temperatures are sufficiently high to impair the performance of operating room personnel and decrease their vigilance.

The easiest method of decreasing cutaneous heat loss is to apply passive insulation to the skin surface. Insulators readily available in most operating rooms include cotton blankets, surgical drapes, plastic sheeting, and reflective composites ("space blankets"). A single layer of each reduces heat loss approximately 30%, and there are no clinically important differences among the types of insulation. The reduction in heat loss from all the commonly used passive insulators is similar because most of the insulation is provided by the layer of still air trapped beneath the covering. As a result, adding additional layers of insulation further reduces heat loss only slightly. For example, one cotton blanket reduces heat loss by about 30%, but three cotton blankets reduces heat loss only by 50%. Furthermore, warming the cotton blankets provides little benefit, and the benefit is short-lived.[146] These data indicate that simply adding additional layers of passive insulation or warming the insulation before application will usually be insufficient in patients becoming hypothermic while covered with a single layer of insulation.

Cutaneous heat loss is roughly proportional to surface area throughout the body.[147] (The popular perception that a large fraction of metabolic heat is lost from the head is false in adults. Loss from the head can be substantial in small infants,[148] but the loss is high mostly because the head represents a large fraction of the total surface area.) Consequently, the amount of skin covered is more important than which surfaces are insulated. It does not make sense, for example, to cover the head and leave the arms exposed because the arms have more surface area than the head and account for more heat loss.

Passive insulation alone is rarely sufficient to maintain normothermia in patients undergoing large operations; active warming will be required in such cases. Because about 90% of metabolic heat is lost via the skin surface, only cutaneous warming will transfer sufficient heat to prevent hypothermia. Consequently, for intraoperative use, circulating water and forced air are the two major systems requiring consideration.

Studies consistently report that circulating-water mattresses are nearly ineffective.[149] Presumably, they are unable to maintain normothermia because little heat is lost from the back into the 5 cm of foam insulation covering most operating room tables. Moreover, the combination of heat and decreased local perfusion (resulting when the patient's weight reduces capillary blood flow) increases the propensity for pressure/heat necrosis ("burns"). Such tissue injury can occur even when the water temperature does not exceed 40°C.[150] Circulating water is more effective—and safer—when placed *over* patients rather than *under* them and, in that position, can almost completely eliminate metabolic heat loss. Metabolic heat production will increase mean body temperature approximately 1°C/hr when cutaneous heat loss is eliminated. Recently developed circulating-water garments transfer large amounts of heat by increasing the warmed surface area or using materials that facilitate conduction.[151,152]

The most common perianesthetic warming system is forced air. The best forced-air systems completely eliminate heat loss from the skin surface.[123] Forced air usually maintains normothermia even during the largest operations[56] and is superior to circulating-water mattresses.[153] It is also remarkably safe, with few if any injuries reported with proper use.

Induction of Mild Therapeutic Hypothermia

There remains a paucity of evidence supporting the application of therapeutic hypothermia for indications other than out-of-hospital cardiac arrest and asphyxiated neonates. Nonetheless, hypothermia is occasionally used during neurosurgery or acute myocardial infarction. Typically, target core temperatures are 32°C to 34°C, and it is thought that reaching the target temperature quickly is important.

Passive cooling is far too slow for induction of therapeutic hypothermia. Immersion in cold water is the quickest noninvasive method of actively cooling patients. However, immersion is difficult under clinical conditions and poses a substantial electrical safety risk. Administration of refrigerated intravenous fluids is also effective and reduces mean body temperature 0.5°C/L.[154] However, this method may be impractical in neurosurgical patients, in whom fluids must be restricted.

Forced-air cooling is easy to implement but relatively slow in that it takes about 2.5 hours to cool neurosurgical patients to 33°C.[134] Conventional circulating-water mattresses are unlikely to be efficient because relatively little skin surface contacts the mattress and the patient's own body weight reduces blood-borne convection of heat to the back. Newer circulating-water systems include garment-like covers or "energy exchange pads" that cover far more skin surface and transfer large amounts of heat, and they are fairly effective.[155]

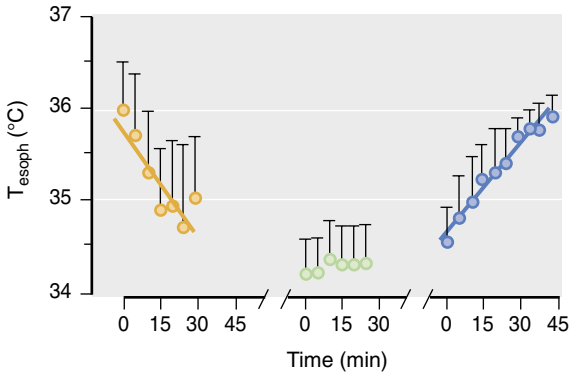

Figure 48-18 Average (±SD) intraoperative esophageal temperatures (T_{esoph}) during the cooling, temperature maintenance, and rewarming periods in eight neurosurgical patients who were cooled with endovascular heat-exchanging catheters in the vena cava. Time zero identified the beginning of each thermal management period; the duration of these periods differed in individual patients, depending on the duration of surgery and other factors. Regression lines are shown for the cooling and rewarming periods. *(From Doufas AG, Akça O, Barry A, et al: Initial experience with a novel heat-exchanging catheter in neurosurgical patients. Anesth Analg 95:1752-1756, 2002.)*

The best way to rapidly induce therapeutic hypothermia is probably endovascular cooling. These systems consist of a heat-exchanging catheter, usually inserted into the inferior vena cava via the femoral artery, and a servocontroller. They can decrease core temperatures at rates approaching 4°C/hr (Fig. 48-18).[156]

Inducing therapeutic hypothermia during surgery is relatively easy because anesthetics profoundly impair thermoregulatory responses. In contrast, unanesthetized patients—even those who have suffered a stroke—vigorously defend core temperature by vasoconstriction and shivering.[157] It is thus necessary to pharmacologically induce tolerance to hypothermia. The best method thus far identified is the combination of buspirone and meperidine, drugs that synergistically reduce the shivering threshold to around 34°C without provoking excessive sedation or respiratory toxicity.[158] The combination of dexmedetomidine and meperidine may also be helpful, although the interaction is simply additive in this case.[80] In contrast, ondansetron,[159] doxapram,[160] and magnesium sulfate[161] only slightly reduce the shivering threshold in humans. Although initially reported to be effective,[162] neither arm nor face warming reduces the shivering threshold by clinically important amounts.[163]

Deliberate Severe Intraoperative Hypothermia

Severe hypothermia may be induced deliberately to confer protection against tissue ischemia, specifically during cardiac surgery and, occasionally, neurosurgery. Drugs such as barbiturates and volatile anesthetics provide considerably less protection than

even mild hypothermia does.[84] Because many organs compensate poorly for hypothermia, temperatures as low as those deliberately induced are usually lethal when unintentional. Deliberate hypothermia is safe only because anesthesiologists understand and treat the physiologic changes caused by core temperatures 10°C to 15°C below normal.

Although deep hypothermia (i.e., 28°C) has been used to facilitate cardiopulmonary bypass for decades, recent evidence suggests that this degree of hypothermia is either unhelpful or simply harmful. For example, hypothermia may be associated with prolonged ventricular dysfunction[164] and does not limit cognitive impairment after bypass.[165] Consequently, cardiac surgery is increasingly being performed at either "tepid" temperatures (i.e., 33°C) or normothermia. There is increasing evidence that outcomes after bypass surgery, whether on- or off-pump, are improved by maintaining normothermia or near-normothermia.[166,167] Deep hypothermia (i.e., 18°C) remains routine for intentional circulatory arrest cases.[141]

Organ Function

Hypothermia decreases the whole-body metabolic rate by approximately 8%/°C[40] to approximately one half the normal rate at 28°C.[168] Whole-body oxygen demand diminishes, and oxygen consumption in tissues that have higher than normal metabolic rates, such as the brain, is especially reduced. Brain oxygenation is thus improved by hypothermia.[169] Low metabolic rates allow aerobic metabolism to continue during periods of compromised oxygen supply; toxic waste production declines in proportion to the metabolic rate. Although a decreased metabolic rate certainly contributes to the observed protection against tissue ischemia, other effects of hypothermia, including "membrane stabilization" and decreased release of toxic metabolites and excitatory amino acids, appear to be most important.[85]

Cerebral blood flow also decreases in proportion to the metabolic rate during hypothermia because of an autoregulatory increase in cerebrovascular resistance.[85] The arteriovenous Po_2 difference thus remains constant, and the venous lactate concentration does not increase. Cerebral function is well maintained until core temperatures reach approximately 33°C, but consciousness is lost at temperatures below 28°C. Primitive reflexes such as the gag, pupillary constriction, and monosynaptic spinal reflexes remain intact until approximately 25°C. Nerve conduction decreases, but peripheral muscle tone increases and results in rigidity and myoclonus at temperatures near 26°C. Somatosensory and audio evoked potentials are temperature dependent, but not significantly modified at core temperatures of 33°C or higher.

Hypothermic effects on the heart include a decrease in heart rate, increased contractility, and well-maintained stroke volume.[170] Cardiac output and blood pressure both decrease. At temperatures below 28°C, sinoatrial pacing becomes erratic and ventricular irritability increases. Fibrillation usually occurs between 25°C and 30°C, and electrical defibrillation is generally ineffective at these temperatures. Because coronary artery blood flow decreases in proportion to cardiac work, hypothermia per se does not cause myocardial ischemia. However, even mild hypothermia decreases tissue damage in response to experimental cardiac ischemia.[98]

Hypothermia decreases blood flow to the kidneys by increasing renovascular resistance. Inhibition of tubular absorption maintains normal urinary volume. As temperature decreases, reabsorption of sodium and potassium is progressively inhibited and thereby results in an antidiuretic hormone–mediated "cold diuresis." Despite increased excretion of these ions, plasma electrolyte concentrations usually remain normal. Kidney functions return to normal when patients are rewarmed. Respiratory strength is diminished at core temperatures lower than 33°C, but the ventilatory CO_2 response is minimally affected. Hepatic blood flow and function also decrease and thus significantly inhibit the metabolism of some drugs.

Acid-Base Changes

The pH of neutral water ($[OH^-] = [H^+]$) increases 0.017 unit for each 1°C reduction in temperature[171]; the pH of blood in a closed system (e.g., test tube or artery) changes similarly (see Chapter 49). Cold-blooded animals allow pH to vary with body temperature as it would in vitro (i.e., blood becomes more alkalotic as temperature decreases); in contrast, homeotherms, which decrease body temperature during hibernation, maintain an arterial pH near 7.4, a process known as pH-stat management. Interpretation of arterial pH in hypothermic humans is difficult because it is unclear which strategy is optimal.[172]

To mimic the compensatory mechanisms used by hibernating homeotherms, blood pH (which is measured by electrodes at 37°C) has traditionally been "corrected" to the patient's actual body temperature. Without correction, tissue oxygen availability decreases because hemoglobin's affinity for oxygen increases about 1.7%/°C. This effect is small in comparison to the 5.7%/°C increase in oxyhemoglobin affinity caused by hypothermia itself. Fortunately, the combined increases in affinity are offset by the 8%/°C reduction in metabolic rate caused by hypothermia. Tissue hypoxia is thus unlikely, with or without correction, and has not been demonstrated experimentally.

Ectothermic strategy is also known as "alpha-stat" because the dissociation constant of the α-imidazole group in histidine changes in parallel with that of water. Maintaining constant imidazole ionization results in optimal enzyme function as temperature changes. In contrast, homeothermic dynamics significantly decreases metabolic function, and animals are essentially anesthetized by cold. Constant relative alkalinity also maintains a stable intracellular-to-extracellular gradient that promotes the removal of acidic products of intracellular metabolism, which might be salutary.[173]

Both alpha- and pH-stat management seem to work well, and physiologic differences between them appear to be subtle. However, there is increasing evidence that pH-stat management better preserves neurons in the context of ischemic stress.[174-176] Furthermore, clinical outcomes seem to be improved by pH-stat management[177]—or at least not worsened.[178] Nonetheless, alpha-stat management remains common, and there is no consensus that either strategy markedly influences the outcome of cardiac surgery.

Hyperthermia and Fever

Hypothermia is by far the most common perianesthetic thermal perturbation. However, hyperthermia is probably more dangerous than a comparable degree of hypothermia, and hyperthermia

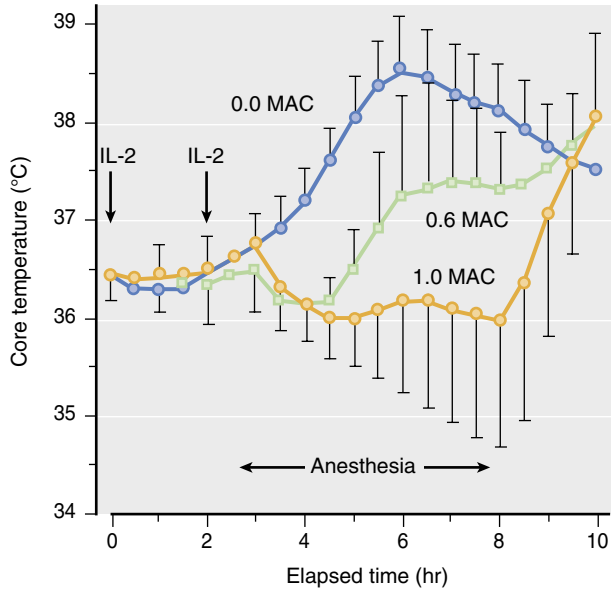

Figure 48-19 Change in core temperature after the administration of 50,000 IU/kg of interleukin-2 (IL-2), followed by a second dose of 100,000 IU/kg 2 hours later. The first dose of IL-2 defined elapsed time zero; anesthesia was started after 3 elapsed hours and continued for 5 hours. Data are presented as means ± SD. *(From Negishi C, Lenhardt R, Sessler DI, et al: Desflurane reduces the febrile response to interleukin-2 administration. Anesthesiology 88:1162-1169, 1998.)*

is certainly more dangerous when perturbations exceed a few degrees centigrade. Hyperthermia is a generic term simply indicating a core body temperature exceeding normal values. In contrast, fever is a regulated increase in the core temperature targeted by the thermoregulatory system. Hyperthermia can result from a variety of causes and usually indicates a problem of sufficient severity that physician intervention is required.

Passive Hyperthermia

Passive intraoperative hyperthermia results from excessive patient heating and is most common in infants and children. It is especially frequent when effective active warming is used without adequate core temperature monitoring. Passive hyperthermia, by definition, does not result from thermoregulatory intervention. Consequently, it can easily be treated by discontinuing active warming and removing excessive insulation.

For information on malignant hyperthermia, see Chapter 37.

Fever

Normal body temperature is neither set nor maintained by circulating factors. In contrast, fever results when endogenous pyrogens increase the thermoregulatory target temperature ("set point"). Endogenous pyrogens identified include interleukin-1, tumor necrosis factor, interferon-α, and macrophage inflammatory protein-1.[179] Although it was initially believed that these factors act directly on hypothalamic thermoregulatory centers,[180] there is increasing evidence of a more complicated system involving vagal afferents.[181] Most endogenous pyrogens have peripheral actions (e.g., activation of the immune system) in addition to their central generating capabilities.

Fever is relatively rare during general anesthesia even though febrile stimuli are frequently present. It is rare because volatile anesthetics per se inhibit expression of fever (Fig. 48-19),[182] as do opioids.[183] Infection is by far the most common cause of fever. However, perioperative fever also occurs in response to mismatched blood transfusions, blood in the fourth cerebral ventricle, and allergic reactions. Some degree of fever is also typical after surgery.[184] The causes of fever are sufficiently diverse—and potentially serious—that a search for a specific etiology is usually warranted.

Treatment of hyperthermia depends on the cause, with the critical distinction being between fever and other causes of hyperthermia. (In general, patients with fever and increasing core temperature will have constricted fingertips, whereas those with other types of hyperthermia will be vasodilated.) It is always appropriate to treat the underlying causes, but nonfebrile hyperthermia will also improve with cooling.

The first- and second-line treatments of fever are amelioration of the underlying cause and administration of antipyretic medications. The first treatment strategy often fails because the etiology of the fever remains unknown; alternatively, the source may be known but unresponsive. The second strategy also often fails or is only partially effective, perhaps because some fever is mediated by mechanisms that bypass conventional antipyretics.[179] It is in these patients that third-line treatment is most likely to be implemented: active cooling (Table 48-3). Active cooling of febrile

Table 48-3 Active Cutaneous Cooling as Treatment of Fever

	Control	Cooling	Warming
Integrated core temperature (°C/hr)	6.0 ± 1.6	5.7 ± 2.2	6.4 ± 1.2
Oxygen consumption (mL/min)	330 ± 50	430 ± 40*	310 ± 30
Duration of shivering (min)	33 ±11	229 ± 35	20 ± 0
Mean arterial pressure (mm Hg)	90 ± 4	98 ± 6*	86 ± 6†
Mean [norepinephrine] (nM)	1.0 ± 0.4	1.4 ± 0.7*	1.1 ± 0.5†
Baseline [epinephrine] (nM)	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
Mean [epinephrine] during treatment (nM)	0.3 ± 0.1	0.5 ± 0.1*	0.4 ± 0.1
Severe cold sensation (% of time)	27	89*	11

Volunteers were given 30,000 IU/kg of interleukin-2 (IL-2), followed 2 hours later by an additional dose of 70,000 IU/kg. The first dose of IL-2 defined elapsed time zero; thermal management started after 3 elapsed hours and continued for 5 hours. Each volunteer participated on 3 separate days: no warming or cooling, active cooling, and active warming. Mean and integrated values are presented over the treatment period, from 3 to 8 elapsed hours. Times are presented in terms of hours elapsed since the first injection of IL-2. Data are presented as means ± SD.
*Statistically significant differences from control.
†Statistically significant differences from the cooling day.
From Lenhardt R, Negishi C, Sessler DI, et al: The effects of physical treatment on induced fever in humans. Am J Med 106:550-555, 1999.

patients is intuitive. However, it frequently fails to reduce core temperature—while simultaneously worsening the situation by triggering thermoregulatory defenses, including intense discomfort, shivering, and activation of the autonomic nervous system.[185] Active cooling of febrile patients should thus be instituted with considerable care to be sure that the putative benefits outweigh the stress induced by the activation of thermoregulatory defenses.

Hyperthermia During Epidural Analgesia

Hyperthermia frequently complicates epidural analgesia for labor and delivery[186] and in nonpregnant postoperative patients.[187] It is more likely during prolonged labor (i.e., >8 hours). A clinical consequence of this hyperthermia is that women given epidural analgesia are more often administered antibiotics than those treated conventionally are, and their offspring are more commonly treated for sepsis.[188]

Because passive hyperthermia and excessive heat production are unlikely causes, elevated body temperature in laboring and postoperative patients is presumably true fever (i.e., a regulated increase in core temperature) resulting from infection or inflammation.[189] For example, Dashe and coworkers concluded that "Epidural analgesia is associated with intrapartum fever, but only in the presence of placental inflammation. This suggests that the fever reported with epidural analgesia is due to infection rather than the analgesia itself."[189]

The conventional assumption is that hyperthermia is *caused* by the technique, although no convincing mechanism has been proposed. It is worth remembering, though, that pain in "control" patients is usually treated with opioids—which themselves attenuate fever.[178] Fever associated with infection or tissue injury might then be suppressed by the low doses of opioids that are usually given to the "control" patients while being expressed normally in patients given epidural analgesia (Fig. 48-20).[190] The extent to which this mechanism contributes remains to be determined and has been disputed,[191] but no convincing alternative explanation has been advanced.

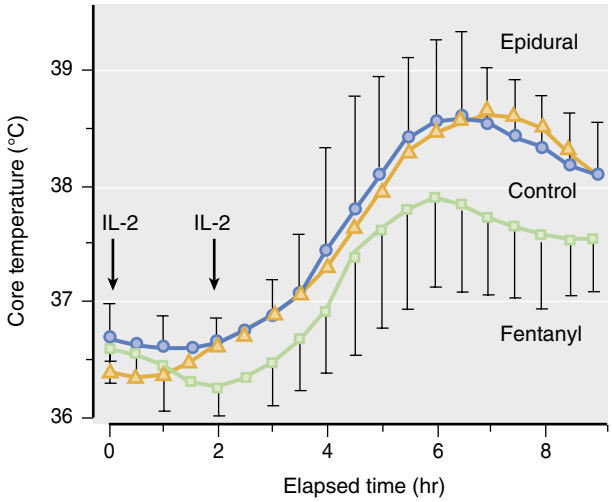

Figure 48-20 Core temperatures after the administration of 50 IU/g of interleukin-2 (IL-2), followed by a second dose of 100 IU/g 2 hours later. The first dose of IL-2 defined elapsed time zero. Data are presented as means ± SD. Error bars for the epidural days are omitted for clarity but were similar to those shown for control and intravenous fentanyl. *(From Negishi C, Lenhardt R, Ozaki M, et al: Opioids inhibit febrile responses in humans, whereas epidural analgesia does not: An explanation for hyperthermia during epidural analgesia. Anesthesiology 94:218-222, 2001.)*

Temperature Monitoring

Core temperature measurements (e.g., tympanic membrane measured with a thermocouple, pulmonary artery, distal part of the esophagus, and nasopharynx) are used to monitor intraoperative hypothermia, prevent overheating, and facilitate detection of malignant hyperthermia. Muscle or skin surface temperatures may be used to evaluate vasomotion[192] and ensure the validity of peripheral neuromuscular monitoring.[193]

Both core and skin surface temperature measurements are required to determine the thermoregulatory effects of different anesthetic drugs. The combination of core and mean skin temperature can be used to estimate mean body temperature—and therefore body heat content—with remarkable accuracy.[194] Temperatures are not uniform within the body; consequently, temperatures measured at each site have different physiologic and practical significance.

Thermometers

Mercury-in-glass thermometers are slow and cumbersome and thus have universally been replaced with electronic systems. The most common electronic thermometers are thermistors and thermocouples. Both devices are sufficiently accurate for clinical use and inexpensive enough to be disposable. Also sufficiently accurate for clinical use are "deep tissue" thermometers that are based on actively reducing the cutaneous heat flux to zero[195]; unfortunately, "deep tissue" thermometers are not currently available in Europe or the United States. Infrared monitors that extrapolate tympanic membrane temperature from outer ear temperature are unreliable,[196] as are infrared systems that scan forehead skin.[197]

Temperature-Monitoring Sites

The core thermal compartment is composed of highly perfused tissues whose temperature is uniform and high in comparison to the rest of the body. Temperature in this compartment can be evaluated in the pulmonary artery, distal part of the esophagus, tympanic membrane, or nasopharynx.[198,199] Temperature probes incorporated into esophageal stethoscopes must be positioned at the point of maximal heart sounds, or even more distally, to provide accurate readings. Even during rapid thermal perturbations such as cardiopulmonary bypass, these temperature-monitoring sites remain reliable. Core temperature can be estimated with reasonable accuracy by using oral, axillary, rectal, and bladder temperatures, except during extreme thermal perturbations.[198,199]

Skin surface temperatures are considerably lower than core temperature. Skin surface temperatures—when adjusted with an appropriate offset—nonetheless reflect core temperature reasonably well.[200] However, skin temperatures fail to reliably confirm

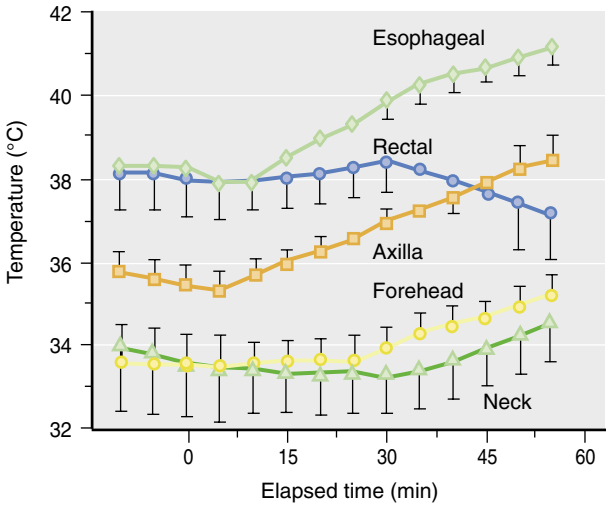

Figure 48-21 Axillary and esophageal temperatures correlated well during acute malignant hyperthermia in swine, but forehead and neck skin temperatures did not. Rectal temperature also failed to promptly identify the onset of malignant hyperthermia. Elapsed time zero indicates an end-tidal P_{CO_2} of 70 mm Hg. These data indicate that forehead and neck skin surface temperatures will not adequately confirm other clinical signs of malignant hyperthermia. Valid core temperature–monitoring sites include the distal part of the esophagus, pulmonary artery, nasopharynx, and tympanic membrane. Except during cardiopulmonary bypass, body temperature can also be measured in the mouth, axilla, and bladder. Data are presented as means ± SD. *(Modified from Iaizzo PA, Kehler CH, Zink RS, et al: Thermal response in acute porcine malignant hyperthermia. Anesth Analg 82:803-809, 1996.)*

the clinical signs of malignant hyperthermia (tachycardia and hypercapnia) in swine[201] and have not been evaluated for this purpose in humans (Fig. 48-21). Rectal temperature also normally correlates well with core temperature[198,199] but fails to increase appropriately during malignant hyperthermia crises[201] and under other documented situations.[202] Consequently, rectal and skin surface temperatures must be used with considerable caution.

Even during cardiopulmonary bypass, the core temperature–monitoring sites (e.g., tympanic membrane, nasopharynx, pulmonary artery, and esophagus) remain useful. In contrast, rectal temperatures lag behind those measured in core sites. Consequently, rectal temperature is considered an "intermediate" temperature in deliberately cooled patients. During cardiac surgery, bladder temperature is equal to rectal temperature (and therefore intermediate) when urine flow is low, but it is equal to pulmonary artery temperature (and thus core) when flow is high.[203] Because bladder temperature is strongly influenced by urine flow, it may be difficult to interpret in these patients. Adequacy of rewarming is best evaluated by considering both "core" and "intermediate" temperatures.

When Temperature Monitoring Is Required

Core hypothermia is as common during epidural and spinal anesthesia as during general anesthesia and can be nearly as severe.[66] Therefore, core temperature should be measured during regional anesthesia in patients likely to become hypothermic, which at the very least includes those undergoing body cavity surgery.

Core temperature monitoring is appropriate during most general anesthetics both to facilitate detection of malignant hyperthermia and to quantify hyperthermia and hypothermia. By far the most common perioperative thermal disturbance is inadvertent hypothermia. Core temperature usually decreases 0.5°C to 1.5°C in the first 30 minutes after induction of anesthesia. Hypothermia results from internal redistribution of heat and a variety of other factors whose importance in individual patients is hard to predict.[55,68] Core temperature perturbations during the first 30 minutes of anesthesia are thus difficult to interpret, and measurements are not usually required. Body temperature should, however, be monitored in patients undergoing general anesthesia exceeding 30 minutes in duration and in all patients whose surgery lasts longer than 1 hour.

Temperature-Monitoring and Thermal Management Guidelines

The objective of temperature monitoring and perioperative thermal management is to detect thermal disturbances and maintain appropriate body temperature during anesthesia. The data available suggest the following guidelines:

1. Core body temperature should be measured in most patients given general anesthesia for longer than 30 minutes.
2. Temperature should also be measured during regional anesthesia when changes in body temperature are intended, anticipated, or suspected.
3. Unless hypothermia is specifically indicated (e.g., for protection against ischemia), effort should be made to maintain intraoperative core temperature higher than 36°C.*

Various organizations have also proposed temperature-monitoring and thermal management strategies. The ASA standards requires only that "every patient receiving anesthesia shall have temperature monitored when clinically significant changes in body temperature are intended, anticipated or suspected." For office-based sedation, regional anesthesia, or general anesthesia, the ASA also requires that "the body temperature of pediatric patient shall be measured continuously."

The state of New Jersey has stronger requirements, specifically that the body temperature of each patient under general or regional anesthesia shall be continuously monitored. Italy probably has the strongest standards, which require, among other things, that (1) core temperature is measured in adults undergoing general anesthesia for longer than 30 minutes (and all children), (2) ambient operating room temperature exceeds 21°C, (3) patients are kept normothermic, and (4) patients who become hypothermic remain in the postanesthesia care unit until normothermia is restored.

In 2007, the American College of Cardiology and American Heart Association published guidelines for the care of patients undergoing noncardiac surgery. The guidelines include a class 1 recommendation that "maintenance of body temperature in a

*Opinions are the author's and not necessarily shared by the American Society of Anesthesiologists (ASA), but they should be.

normothermic range is recommended for most procedures other than during periods in which mild hypothermia is intended to provide organ protection (e.g., during high aortic cross-clamping)."[204] Based on overwhelming evidence of hypothermia-induced complications, maintaining perioperative normothermia is likely to be among the first anesthetic "pay-for-performance" measures.

Summary

Body temperature is normally controlled by a negative-feedback system in the hypothalamus that integrates thermal information from most tissues. Approximately 80% of this thermal input is derived from core body temperature, which can be measured with distal esophageal, nasopharyngeal, or tympanic membrane thermometer probes. The hypothalamus coordinates increases in heat production (nonshivering thermogenesis and shivering), increases in environmental heat loss (sweating), and decreases in heat loss (vasoconstriction) as needed to maintain normothermia.

Thermal steady state requires that heat loss to the environment equals metabolic heat production; hypothermia occurs when heat loss exceeds production. Mild core hypothermia is common during surgery and anesthesia and results initially from redistribution of body heat from the core to peripheral tissues and subsequently from heat loss exceeding metabolic heat production. Clinical doses of general anesthetics decrease the threshold for response to hypothermia from approximately 37°C (normal) to 33°C to 35°C. Anesthetized patients whose core temperatures exceed these values are usually poikilothermic and do not actively respond to thermal perturbations. Patients becoming sufficiently hypothermic do trigger thermoregulatory vasoconstriction, and the vasoconstriction is remarkably effective in minimizing further core hypothermia.

Mild intraoperative hypothermia provides significant protection against tissue ischemia and hypoxia in animals. Nonetheless, the only situations in which improved outcome has been demonstrated with therapeutic hypothermia in humans is out-of-hospital cardiac arrest and neonatal asphyxia. Hypothermia also decreases triggering of malignant hyperthermia and reduces the severity of the syndrome, once triggered. However, most consequences of inadvertent hypothermia are harmful. Major adverse effects include morbid myocardial outcomes, reduced resistance to surgical wound infections, increased blood loss and transfusion requirements, prolonged duration of drug action, shivering, and decreased postoperative thermal comfort.

Little metabolic heat is lost via the respiratory tract. Consequently, even active airway heating and humidification are of little benefit. Administration of sufficient volumes of cold intravenous fluid can produce substantial hypothermia. Fluids therefore should be warmed in patients requiring intravenous administration of more than several liters per hour; however, fluid warming should always be secondary to active cutaneous warming. Among the clinically available active systems, forced air offers the best combination of efficacy, safety, and price. Forced air can usually maintain normothermia even during the largest operations.

Regional anesthesia produces both peripheral and central inhibition of thermoregulatory control. Peripheral inhibition results when local anesthetics block nerves that are required for thermoregulatory defenses. Hypothermia during neuraxial anesthesia results initially from core-to-peripheral redistribution of body heat and subsequently from heat loss exceeding heat production. Hypothermia during major conduction anesthesia may be as severe as that during general anesthesia.

Increased core temperature can result from augmented thermogenesis (malignant hyperthermia), excessive heating (passive hyperthermia), or a specific increase in the thermoregulatory target temperature (fever). Because the causes of hyperthermia are varied and often serious, the etiology of observed increases in core temperature should be sought and appropriate treatments should be instituted.

A reasonable strategy for detecting and preventing thermal disturbances is to monitor core temperature in patients in whom general anesthesia will last longer than 30 minutes and in those undergoing major surgery with regional anesthesia. Unless hypothermia is specifically indicated (i.e., for protection against cerebral ischemia), core temperature should be maintained above 36°C.

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49 Perioperative Acid-Base Balance

Key Points

1. The presence of a significant acid-base abnormality often signals a serious underlying problem.
2. All acid-base abnormalities result from alterations in the dissociation of water.
3. Only three factors independently affect acid-base balance—the $Paco_2$, the strong ion difference (SID), and the total concentration of weak acids (A_{TOT}).
4. Respiratory acidosis is caused by hypercarbia, and respiratory alkalosis is caused by hypocarbia.
5. Metabolic acidosis is caused by decreased SID or increased A_{TOT}. Decreased SID results from accumulation of metabolic anions (shock, ketoacidosis, and renal failure), hyperchloremia, and free water excess. Increased A_{TOT} results from hyperphosphatemia.
6. Metabolic alkalosis is caused by increased SID or decreased A_{TOT}. SID increases as a result of sodium gain, chloride loss, or free water deficit. A_{TOT} decreases in hypoalbuminemia and hypophosphatemia. This is particularly common in critical illness.
7. Most acid-base disorders are treated by reversal of the cause.

The chemical composition of the extracellular and intracellular spaces is tightly controlled; this includes, but is not limited to, hydrogen and hydroxyl moieties. Alterations in the relative concentrations of these ions, widely described as disorders of acid-base chemistry, are associated with significant clinical problems. Consequently, the detection, interpretation, and treatment of acid-base abnormalities has become a core element of clinical care. Many clinicians struggle to understand acid-base chemistry because traditional educational approaches have focused on interpretation of laboratory data, rather than an understanding of underlying biophysical chemistry. The "modern" physical-chemical approach to acid-base balance has significantly enhanced understanding of these problems and simplified the clinical approach.[1-4]

A key to understanding acid-base chemistry is the realization that acid-base abnormalities are secondary phenomena; they result from other biochemical changes in the extracellular environment.[5] Alterations in the relative concentrations of hydronium and hydroxyl are less important than the chemical abnormalities causing them. Hydrogen (hydronium) and hydroxyl are the ion dissociation products of water and are modulated to maintain electric neutrality in response to changes in the local concentration of strong ions, weak acids, and carbon dioxide (CO_2). This chapter first explores the physical chemistry of water, then examines the evolution of acid-base medicine, and finally applies clinical approaches to acid-base conundrums.

Physical Chemistry of Water

The human body contains a large quantity of water. Consequently, the physical properties of water have enormous implications for maintenance of homeostasis. Water is a simple triatomic molecule. Its chemical formula is H_2O, and its structural formula is H—O—H. The charge distribution of each covalent bond is unequal. The molecule has a polar conformation and the H—O—H bond angle is 105 degrees. Water molecules attract and form hydrogen bonds with one another. These bonds are fundamental to the existence of life on Earth. Water molecules are in continuous motion. Occasionally, when molecules collide, enough energy is produced to transfer a proton from one water molecule to another. Water slightly dissociates into a negatively charged hydroxyl (OH^-) ion and a positively charged hydronium (H_3O^+) ion. Conventionally, this self-ionization of water is written as follows:

$$H_2O \leftrightarrow H^+ + OH^-$$

The symbol H^+ is convenient because, although protons dissociating from water have many aliases (e.g., H_3O^+ and $H_9O_4^+$), most physicians and chemists refer to them as hydrogen ions.

The extent to which water self-ionizes is minuscule. In pure water at 25°C, the $[H^+]$ and $[OH^-]$ are 1×10^{-7} mmol/L. The tendency for water to dissociate into its component parts is represented by the following:

$$K_{eq}H_2O = [H^+][OH^-]$$

The molarity of water is extremely high—55.5M ("there is a lot of water in water"). Because the concentration of water and the K_{eq} are constants, the ion-product dissociation constant for water can be expressed as follows:

$$K_{eq}H_2O = K_{eq}(55.5) = K_W{}' = [H^+][OH^-]$$

The implication is that the relative concentrations of hydroxyl and hydrogen are constant, so when there is an increase in the concentration of hydrogen ions, there is a concomitant decrease in the concentration of hydroxyl ions, and vice versa.

Pure water is considered neutral because the relative concentrations of hydrogen and hydroxyl are equal. A solution is considered acidic if the concentration of hydrogen ions exceeds that of hydroxyl ions ($[H^+] > 1.0 \times 10^{-7}$ mmol/L, $[OH^-] < 1.0 \times 10^{-7}$ mmol/L). A solution is considered alkaline if the hydroxyl ion concentration exceeds the hydrogen ion concentration.

Acids and Bases

The concept of acids and bases is relatively new. In the early part of the 20th century, it was known that in critical illness the CO_2 content of the blood decreased. In 1831, O'Shaughnessy identified loss of "carbonate of soda" from the blood as a fundamental disturbance in patients dying of cholera.[2] We now know that the loss of bicarbonate was related to hyperventilation and buffering of free hydrogen ions in dysoxic or dysmetabolic states. In 1909, Henderson[6] coined the term *acid-base balance*. He was able to define this process in terms of carbonic acid equilibrium, work that later was refined by Hasselbalch in 1916.[7] Essentially, their method described acid-base balance in terms of the hydration equation for CO_2,[4] the only clinical chemistry test available at that time:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

$$pH = pK_a + \log\left[[HCO_3^-]/[H_2CO_3]\right]$$

$$\text{Total } CO_2 = [HCO_3^-] + [\text{dissolved } CO_2] + [\text{carbamino } CO_2] + [H_2CO_3]$$
$$\approx P_{CO_2} \times 0.03 \text{ mmol } CO_2/\text{L/mm Hg}$$

so, substituting into the previous equation:

$pH = 6.1 + \log\left[[HCO_3^-]/P_{CO_2} \times 0.03\right]$: the Henderson-Hasselbalch equation

In 1903, the revolutionary theory of Arrhenius (1859-1927) established the foundations of acid-base chemistry. In an aqueous solution, an Arrhenius acid is any substance that delivers a hydrogen ion into the solution.[2] A base is any substance that delivers a hydroxyl ion into the solution. Because of its high dielectric constant, water is a highly ionizing solution. Substances with polar bonds dissociate into their component parts (dissolve) in water. Hydrogen chloride (HCl) is an acid, and potassium hydroxide (KOH) is a base.

The degree of dissociation of substances in water determines whether they are strong acids or strong bases. Lactic acid, which has an ion dissociation constant (pK_a) of 3.4, is completely dissociated at physiologic pH and is a strong acid. Conversely, carbonic acid, which has a pK_a of 6.4, is incompletely dissociated and is a weak acid. Similarly, ions such as sodium, potassium, and chloride that do not easily bind other molecules are considered strong ions—they exist free in solution. In any solution, the ion dissociation constant for water, K_W', dictates that the relative ratio of $[H^+]$ to $[OH^-]$ must always be constant, and electric neutrality must always hold. Consequently, strong cations—Na^+, K^+, Ca^{2+}, Mg^{2+}—act as Arrhenius bases (because they drive hydroxyl out of, and hydrogen into, solution, to maintain electric neutrality), and strong anions—Cl^-, LA^-, ketones, sulfate and formate—act as Arrhenius acids.

Aqueous solutions, such as ammonia (NH_3), sodium carbonate (Na_2CO_3), and sodium bicarbonate ($NaHCO_3$), are bases, but none are hydroxides. In 1923, Brønsted and Lowry proposed an expanded theory of acids and bases. They defined acids as proton donors and bases as proton acceptors. All Arrhenius acids and bases were also Brønsted-Lowry acids and bases. The Brønsted-Lowry approach accounts for the peculiar behavior of CO_2 and ammonia, as follows:

$$NH_3 + H_2O \leftrightarrow NH_4^+ + OH^-$$

In this situation, water is the proton donor, the Brønsted-Lowry acid, and ammonia is the proton acceptor, the Brønsted-Lowry base. Conversely, consider the following reaction:

$$HCl + H_2O \rightarrow H_3O^+ + Cl^-$$

In this reaction, hydrogen chloride acts as a Brønsted-Lowry acid, and water acts as a Brønsted-Lowry base:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

In this reaction, CO_2 is hydrated to carbonic acid, a Brønsted-Lowry acid, which subsequently dissociates to hydrogen and bicarbonate.

Stewart Approach

Determinants of Acidity or Alkalinity of a Solution

The extracellular fluid (ECF) is a solution containing many different molecules that directly influence the dissociation of water. It is inconvenient to use the molar concentration of hydrogen/hydroxide to reflect the relative acidity and alkalinity of a solution. The pH scale, developed by Sorenson in the 1920s, is a simple device for acid-case quantification. The pH scale was developed by using the negative logarithm of the hydrogen ion concentration. Neutral pH for pure water is 7.0 (1.0×10^{-7} mmol/L). Physiologic pH, for the ECF, is 7.4, which is alkaline. Conventionally, we refer to relative acidity and alkalinity from this starting point. If pH is greater than 7.4, the ECF is alkaline (relative to normal), and if pH is less than 7.4, the ECF is acidic (relative to normal). The pH of the intracellular space is 6.8 to 7.0, and remains constant despite dramatic changes in extracellular pH. The reason for the difference in acidity between the spaces is unclear.[8,9]

To determine the hydrogen ion concentration of ECF, the investigator must look at the dissociation equilibriums for all fully dissociated and partially dissociated ionic compounds and apply three simple rules, as follows:

1. Electric neutrality: in aqueous solutions, in any compartment, the sum of all of the positive charged ions must equal the sum of all of the negative charged ions.

2. Dissociation equilibriums: the dissociation equilibriums of all incompletely dissociated substances, as derived from the law of mass action, must be satisfied at all times.
3. Mass conservation: the amount of a substance remains constant unless it is added, removed, generated, or destroyed. The total concentration of an incompletely dissociated substance is the sum of concentrations of its dissociated and undissociated forms.

To determine the acid-base status of a fluid, all substances to which these rules might be applied must be accounted for. A discussion of key groups follows.

Strong Ions

The first group of ions, the strong ions, is simple to incorporate because they dissociate completely. The most abundant strong ions in the extracellular space are Na^+ and Cl^-. Other important strong ions include K^+, SO_4^{2-}, Mg^{2+}, and Ca^{2+}. In a solution containing strong ions created using specified concentrations of NaOH and HCl, the hydrogen ion concentration can calculated by solving for electric neutrality:

$$([Na^+]-[Cl^-])+([H^+]-[OH^-])=0$$

This creates two separate, simultaneous equations, as follows:

$$[H^+]=\sqrt{K_W{}'+([Na^+]-[Cl^-])^2/4}-([Na^+]-[Cl^-])/2$$

and

$$[OH^-]=\sqrt{K_W{}'+([Na^+]-[Cl^-])^2/4}-([Na^+]-[Cl^-])/2$$

These equations tell us that hydrogen and hydroxyl concentrations are determined by the $K_W{}'$ and the difference in charge between sodium and chloride. Because the former is constant, in this system, ($[Na^+] - [Cl^-]$) must determine $[H^+]$ and $[OH^-]$. Because the concentrations of sodium and chloride are known, the net positive charge minus net negative charge can be quantified. It is the strong ion difference (SID). Logically, in any solution, the sum total of the charges imparted by strong cations minus the charges from strong anions represents the SID. SID independently influences hydrogen ion concentration (Fig. 49-1). In human ECF, SID is positive:

$$\begin{aligned}SID&=([Na^+]+[K^+]+[Ca^{2+}]+[Mg^{2+}])-([Cl^-]+[A^-])\\&=40\text{-}44\ mEq\end{aligned}$$

Stewart's pioneering work revealed several facts regarding $[H^+]$ that had not previously been understood. SID is always positive in human ECF, and hydroxyl ions almost always exceed hydrogen ions quantitatively in solution. The relationship between SID and $[H^+]$ is nonlinear in these conditions. Any change in SID changes $[H^+]$ and $[OH^-]$ concentrations. Because of the water dissociation constant, this relationship is inverted: As $[H^+]$ increases, $[OH^-]$ decreases. SID is an independent variable; $[H^+]$ and $[OH^-]$ are dependent, meaning that the addition of hydrogen ions alone (without strong corresponding anions), cannot influence the pH of the solution.

Weak Acid "Buffer" Solutions

The degree of water dissociation—and the hydrogen ion concentration—also is influenced by charges derived from weak acids.

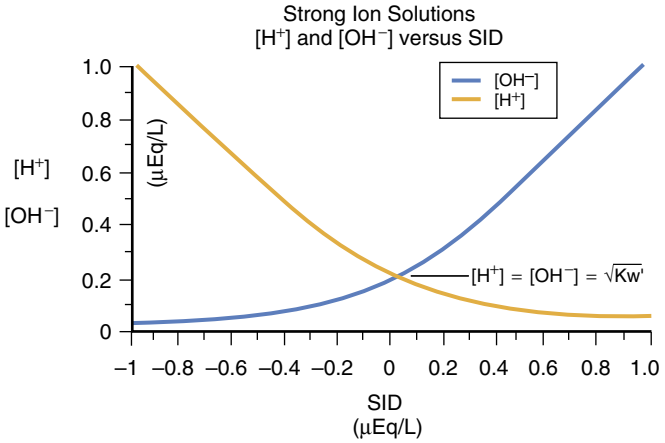

Figure 49-1 Effect of changes in the strong ion gap (strong ion difference [SID]) on hydrogen and hydroxyl ion concentration. *(Adapted from Stewart PA: Modern quantitative acid-based chemistry. Can J Physiol Pharmacol 61:1444-1461, 1983.)*

These weak acids are partially dissociated compounds whose degree of dissociation is determined by the prevailing temperature and pH. The predominant molecules in this group are albumin and phosphate. Stewart used the term A_{TOT} to represent the total concentration of weak ions that influenced acid-base balance.[10]

The acid HA only partly dissociates, represented by the following equilibrium:

$$[HA]=K_A[H^+][A^-]$$

K_A is the weak acid dissociation constant. If we assume that HA and A^- play no further part in this reaction (the law of mass conservation), the amount of A^- present in the solution must equal the amount initially present, so:

$$[HA][A^-]=[A_{TOT}]$$

where $[A_{TOT}]$ is the total weak acid concentration.

To calculate the effect of weak acid dissociation on $[H^+]$, we must take into account water dissociation and electric neutrality:

$$[H^+][OH^-]=K_W{}'\ (\text{water dissociation})$$
$$[SID]+[H^+]-[A^-]-[OH^-]=0\ (\text{electric neutrality})$$

These four simultaneous equations determine the $[H^+]$ in this solution containing strong ions and weak acids. SID and A_{TOT} are independent variables whose concentration was determined during the production of the system. $K_W{}'$ and K_A are constants. Consequently, the other variables [HA], $[H^+]$, $[OH^-]$, and $[A^-]$ must adjust to satisfy the equations. They are dependent variables.

Carbon Dioxide

Along with strong ions and weak bases, ECF contains CO_2. The concentration of CO_2 in ECF is determined by tissue production and alveolar ventilation. CO_2, when in solution, exists in four forms: CO_2 [denoted $CO_2(d)$], carbonic acid (H_2CO_3), bicarbonate ions (HCO_3^-), and carbonate ions (CO_3^{2-}).

The concentration of $CO_2(d)$ is determined by the solubility coefficient of CO_2 (S_{CO_2}), which depends on body temperature, P_{CO_2}, and other factors. Several equilibrium equations can be derived from the hydration of CO_2:

$$[CO_2(d)] = [S_{CO_2}] \times P_{CO_2}$$

The tendency for CO_2 to hydrate to H_2CO_3, and subsequently dissociate to H^+ and HCO_3^-, is reflected by the following equation:

$$[CO_2(d)] \times [OH^-] = K_1 \times [HCO_3^-]$$

These equations can be combined together and with water equilibrium as follows:

$$[H^+] \times [HCO_3^-] = K_c \times P_{CO_2}$$

Bicarbonate also dissociates to release hydrogen ions and carbonate, the equilibrium reaction for which is represented by:

$$[H^+] \times [CO_3^{2-}] = K_3 [HCO_3^-]$$

Factors Independently Influencing Water Dissociation

Now that we have looked at the different factors that may influence the concentration of hydrogen ions in a solution, strong ions, weak acids, and CO_2, we can combine the derived equations to solve for $[H^+]$:

Water dissociation equilibrium:	$[H^+] \times [OH^-] = K_W'$
Weak acid dissociation equilibrium:	$[H^+] \times [A^-] = K_A \times [HA]$
Conservation of mass for weak acids:	$[HA] + [A^-] = [A_{TOT}]$
Bicarbonate ion formation equilibrium:	$[H^+] \times [HCO_3^-] = K_C \times P_{CO_2}$
Carbonate ion formation equilibrium:	$[H^+] \times [CO_3^{2-}] = K_3 \times [HCO_3^-]$
Electric neutrality:	$[SID] + [H^+] - [HCO_3^-] - [A^-] - [CO_3^{2-}] - [OH^-] = 0$

There are six independent simultaneous equations, and just six unknown, dependent variables determined by them: $[HA]$, $[A^-]$, $[HCO_3^-]$, $[CO_3^{2-}]$, $[OH^-]$, and $[H^+]$. There are three known independent variables: SID, $[A_{TOT}]$, and P_{CO_2}

Although the above-listed equations look simple, they require fourth-order polynomials for solution. This is impossible without computer technology.

Solving the equations for $[H^+]$ is as follows:

$$[SID] + [H^+] - K_C \times P_C / [H^+] - K_A - [A_{TOT}] / (K_A + [H^+]) - K_3 \times K_C P_C / [H^+]^2 - K_W' / [H^+] = 0$$

In other words, $[H^+]$ is a function of SID, A_{TOT}, P_{CO_2}, and numerous constants. All other variables, most notably $[H^+]$, $[OH^-]$, and $[HCO_3^-]$, are dependent, and cannot independently influence acid-base balance.

Acid-Base Abnormalities

The value of the Stewart approach is that it allows us to use a simple model for explaining acid-base disturbances because all abnormalities can be explained in terms of SID, A_{TOT}, or P_{CO_2}. Traditionally, acid-base disturbances have been classified as being due to either alterations in arterial carbon dioxide ($Paco_2$) tension—respiratory acidosis or alkalosis—or alterations in blood chemistry—metabolic acidosis or alkalosis. This remains a useful classification, although respiratory or metabolic abnormalities rarely occur independently of one another.

Respiratory Acid-Base Abnormalities

Respiratory acidosis occurs when there is an acute increase in $Paco_2$ principally resulting from respiratory failure. Clinically, there are signs of CO_2 retention, including cyanosis, vasodilation, and narcosis. Respiratory alkalosis occurs when there is an acute decrease in $Paco_2$ as a result of hyperventilation. The patient presents with symptoms and signs of vasoconstriction, including lightheadedness, visual disturbances, dizziness, and perhaps hypocalcemia owing to increased binding of calcium to albumin. The last-mentioned is caused by an increase in the available negative charge on albumin in alkaline states. Acute hypocalcemia is associated with paresthesias and tetany.

Respiratory acidosis causes a rapid increase in $[H^+]$. Compensation for hypercarbia is slow, requiring increased urinary excretion of chloride.[8] There is a concomitant increase in the serum bicarbonate, reflecting higher total CO_2 load, rather than compensation. The acuity of respiratory failure can be deduced by looking at the relative ratio of CO_2 to HCO_3^- (Table 49-1). Many investigators have suggested that respiratory acidosis may not be harmful. There has been extensive clinical experience with "permissive hypercapnia" for acute respiratory failure, which seems to be well tolerated.[9,11,12]

Metabolic Acid-Base Disturbances

Metabolic acid-base abnormalities are caused by alterations in the SID or A_{TOT}, or both. An increase in the SID causes alkalemia; a decrease in the SID causes acidemia. The alteration may be caused by a change in the total or relative concentration of strong ions. A decrease in the SID (i.e., more anions relative to cations) causes acidosis; this may occur because of a net increase in anions (e.g., hyperchloremia, lactacidemia) or an increase in the volume of distribution of the same quantity of ions (e.g., dilutional acidosis) (Table 49-2).

Metabolic acidosis is of clinical significance for two reasons: (1) pathologies arising from the acidosis itself and (2) pathologies arising from the cause of the acidosis. Acidosis is associated with

Table 49-1 Changes in $Paco_2$ and $[HCO_3^-]$ in Response to Acute and Chronic Acid-Base Disturbances

Disturbances	$[HCO_3^-]$ versus $Paco_2$
Acute respiratory acidosis	$\Delta HCO_3^- = 0.2\ \Delta Paco_2$
Acute respiratory alkalosis	$\Delta HCO_3^- = 0.2\ \Delta Paco_2$
Chronic respiratory acidosis	$\Delta HCO_3^- = 0.5\ \Delta Paco_2$
Metabolic acidosis	$\Delta Paco_2 = 1.3\ \Delta HCO_3^-$
Metabolic alkalosis	$\Delta Paco_2 = 0.75\ \Delta HCO_3^-$

Δ, change in value; $[HCO_3^-]$, concentration of bicarbonate ion; P_{CO_2}, partial pressure of carbon dioxide.
Modified from Narins RB, Emmett M: Simple and mixed acid-base disorders: A practical approach. Medicine (Baltimore) 59:161-187, 1980.

Table 49-2 Classification of Primary Acid-Base Abnormalities

Abnormalities	Acidosis	Alkalosis
Respiratory	Increased P_{CO_2}	Decreased P_{CO_2}
Metabolic		
Abnormal SID		
Caused by water excess or deficit	Water excess = dilutional ↓ SID + ↓[Na^+]	Water deficit = contraction ↑ SID ↑[Na^+]
Caused by electrolytes	Chloride excess	Chloride deficit
Chloride (measured)	↓ SID ↑[Cl^-]	↑ SID + ↓[Cl^-]
Other (unmeasured) anions, such as lactate and keto acids	↓ SID ↑[UMA^-]	—
Abnormal A_{TOT}		
Albumin [Alb]	↑[Alb] (rare)	↓[Alb]
Phosphate [Pi]	↑[Pi]	

[Alb], concentration of serum albumin; A_{TOT}, total concentration of weak ions; [Cl^-], concentration of chloride ions; [Na^+], concentration of sodium ions; P_{CO_2}, partial pressure of carbon dioxide; [Pi], concentration of inorganic phosphate; SID, strong ion difference; [UMA^-], unmeasured anions.
Adapted from Fencl V, Jabor A, Kazda A, Figge J: Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 162:2246-2251, 2000.

alterations in transcellular ion pumps and increased ionized calcium. The result is vasodilation, diminished muscular performance (particularly myocardial), and arrhythmias. The oxyhemoglobin dissociation curve shifts rightward to increase oxygen offload into the tissues. Rapid-onset metabolic acidosis may be associated with profound hypotension, cardiac arrhythmias, and death. The malignancy of the acidosis is strongly related to the underlying disease process; lactic acidosis caused by circulatory shock is more malevolent than hyperchloremic acidosis caused by excessive administration of 0.9% saline solution.[13] The body is hyper-responsive to acidosis. Increasing hydrogen ion content in cerebrospinal fluid activates the respiratory center to stimulate respiration. Alveolar ventilation increases, reducing arterial CO_2 content, reducing the total body [H^+]. Bicarbonate concentration simultaneously decreases, owing to buffering activity, and owing to the reduction in total CO_2; this prevents abrupt reductions in plasma pH in acute metabolic acidosis.

Metabolic alkalosis rarely occurs as a result of acute illness. Symptoms and signs of metabolic alkalosis include widespread vasoconstriction, lightheadedness, tetany, and paresthesia. The main compensatory mechanism is hypoventilation, which may delay weaning from mechanical ventilation in critically ill patients.

An understanding of the mechanisms by which alterations in SID affect acid-base balance clarifies many of the abnormalities that have remained unexplained by traditional teaching. Of key importance is the ability to differentiate the change in the SID that results from altered free water balance from that arising from altered concentrations of measured and unmeasured electrolytes.

The following examples illustrate the theoretical basis of fluctuations in acid-base chemistry associated with alterations in the relative ratio of water and electrolytes in the extracellular space. An average man weighing 70 kg has a total body water of approximately 45 L, two thirds of which is in the intracellular space. Approximately 15 L is extracellular. The [Na^+] in this compartment is 140 mEq/L, [Cl^-] is 100 mEq/L, and [K^+] is 4 mEq/L. For simplicity, let us ignore magnesium, calcium, other strong ions, and CO_2. In this system, the SID is 44 mEq, this positive charge being balanced principally by weak acids. Anything that increases the SID increases the relative concentration of strong cations to strong anions, and alkalinizes the solution. Anything that decreases the SID decreases the relative concentration of cations to anions, and acidifies the solution.

If the volume of this compartment is expanded by 2 L, as would occur with rapid infusion of 5% dextrose, [Na^+] decreases to 123 mEq/L, [K^+] decreases to 3.5 mEq/L, and [Cl^-] decreases to 88 mEq/L. The relative ratio of cations to anions also decreases, and SID decreases to 38.5. The system becomes more acidic; this is the basis behind the concept of "dilutional acidosis."

Conversely, if 2 L of free water is removed from the system, the total amount of ions would remain unchanged (e.g., as would occur with profuse sweating or dehydration), and an opposite effect would occur. [Na^+] would increase to 161 mEq/L, [K^+] would increase to 4.6 mEq/L, and [Cl^-] would increase to 115 mEq/L. The relative ratio of cations to anions increases, and SID increases to 50.6. The system becomes more alkaline; this is the basis behind "contraction alkalosis."

In perioperative medicine, we commonly administer "normal saline" (NaCl 0.9%), containing 154 mEq of sodium and 154 mEq of chloride. The SID of this solution is 0. A patient who loses 5 L of ECF and is given 5 L of NaCl as replacement would be expected to have a net gain in sodium and chloride. In this scenario, [Na^+] increases to 144 mEq/L, [K^+] decreases to 2.6 mEq/L, and [Cl^-] increases to 118 mEq/L. The SID decreases to 29; this is the basis behind "hyperchloremic acidosis."[14]

Any process that leads to dilution of the total number of ions in the solution would be expected to cause acidosis. Consider the therapeutic use of mannitol (before the diuresis), hyperglycemia, or ethylene glycol or methanol poisoning. The presence of each of these osmotically active particles in the ECF results in an increase in the volume of extracellular water without changing the net charge; the consequence is a reduction in SID and a temporary dilutional acidosis.

Any process that removes chloride without sodium, such as aggressive nasogastric suctioning with loss of hydrogen chloride, causes metabolic alkalosis (hypochloremic alkalosis) as a result of an increase in SID. The alkalosis is caused by chloride loss and not hydrogen ions. There is a finite quantity of Cl^-, which is governed by the law of conservation of mass, whereas there is an effectively unlimited supply of hydrogen ions available from water, and conservation of mass does not apply. Severe diarrhea, which is associated with loss of potassium and sodium, reduces the SID, and is associated with metabolic acidosis. Aggressive use of diuretics causes a net loss of free water over sodium and chloride, and causes contraction alkalosis.

The most malignant form of metabolic acidosis is associated with a net gain of "unmeasured" (i.e., electrolytes not conventionally measured on serum chemistry analysis) anions, and, consequently, a decreased SID:

1. In dysoxia and states of severe stress, lactate is produced, reducing the SID and causing acidosis.
2. In uncontrolled diabetes, ketoacids—β-hydroxybutyrate and acetoacetate—are produced, reducing the SID and causing acidosis.

3. In severe renal failure, SO_4^{2-} and PO_4^{3-} ("fixed renal acids") are not excreted, causing acidosis.

The mechanism of acidosis is similar to before. If we add an additional anion (e.g., lactate) at a concentration of 10 mEq/L to the ECF of a patient with $[Na^+]$ of 140 mEq/L, $[Cl^-]$ of 100 mEq/L, and $[K^+]$ of 4 mEq/L, the SID decreases to 34 mEq/L, and the system becomes more acidemic.

The total weak acid pool, principally serum albumin and phosphate, also is an important determinant of acid-base status. Hyperphosphatemia has long been associated with the acidosis of renal failure. Hypoalbuminemia is common in clinical practice. There is a strong association between hypoalbuminemia and severity of critical illness. This association occurs as a result of hepatic reprioritization of visceral protein production toward acute-phase reactants, capillary leak, breakdown of preexisting albumin (so that its constituent amino acids can be used for protein synthesis), and hemodilution with isotonic fluids. Hypoalbuminemia decreases A_{TOT} and is associated with metabolic alkalosis.[15]

The impact of hypoalbuminemia on acid-base balance has been grossly underestimated. Stewart's original theory was subsequently modified by Figge and colleagues.[16] The serum albumin concentration is the core negative charge offsetting the net positive charge of the SID.[17] Consequently, the presence of hypoalbuminemia may mask the detection of acidosis[18] caused by unmeasured anions, when conventional tools of acid-base chemistry, pH, base deficit, and the anion gap are used.[19] The presence of hypoalbuminemia has significant implications, not least for its association with adverse outcomes.[18,20] Hyperalbuminemia is very unusual; nonetheless, in cholera, when associated with hemoconcentration, it is associated with acidosis.[21]

Fencl and colleagues[18] neatly categorized acid-base disturbances along respiratory and metabolic lines (see Table 49-2). This categorization elegantly explains all known acid-base disturbances.

There are significant differences between the mechanisms causing acid-base imbalances. It would be reasonable to predict significantly different outcomes for patients developing acidosis from dilution, poisoning, hyperchloremia, excessive use of normal saline infusions, or dysoxia owing to increased production of lactate. The acid-base abnormalities themselves may be of less clinical significance than previously thought.[9]

Regulation of Acid-Base Balance

Extracellular hydrogen ion concentration apparently is tightly controlled by the body. This control should be viewed in terms of volatile and metabolic acids. We have evolved various intracellular and extracellular weak acid buffering systems to prevent rapid changes in the extracellular electrochemical balance that may interfere with transcellular ion pumps. A buffer is a solution of two or more chemicals that minimizes changes in pH in response to the addition of an acid or base. Most buffers are weak acids. Ideally, a buffer has a pK_a that is equal to the pH, and an ideal body buffer has a pK_a between 6.8 and 7.2.

The major source of acid in the body is CO_2. CO_2 production from metabolism results in the generation of 12,500 mEq of H^+ daily; this is excreted by the lungs. By contrast, only 20 to 70 mEq of hydrogen ion–promoting anions are excreted through the kidney each day. Volatile acid is principally buffered by hemoglobin. Deoxygenated hemoglobin is a strong base, and there would be a huge increase in the pH of venous blood if hemoglobin did not bind hydrogen ions that are produced by metabolism.

CO_2 easily passes through cell membranes. Within the erythrocyte, CO_2 combines with H_2O, under the influence of carbonic anhydrase, to form H_2CO_3. This ionizes to hydrogen and bicarbonate. Hydrogen ions bind to histidine residues on deoxyhemoglobin (the "Haldane" effect), and bicarbonate is actively pumped from cells. Chloride moves inward to maintain electroneutrality (chloride shift) and to ensure the continued production of carbonic acid. CO_2 also is buffered directly by hemoglobin (carbaminohemoglobin) and by plasma proteins (carbamino proteins). Venous blood contains 1.68 mmol/L of extra CO_2 over arterial blood: 65% as HCO_3^- and H^+ bound to hemoglobin, 27% as carbaminohemoglobin (CO_2 bound to hemoglobin), and 8% dissolved.

When respiratory failure occurs, the principal CO_2 buffering system, hemoglobin, becomes overwhelmed. This leads to the rapid development of acidosis. In response, the kidney excretes an increased chloride load using NH_4^+, a weak cation, for electrochemical balance. ECF osmolality is maintained. This process is conventionally referred to as "metabolic compensation."[22] Chronic respiratory acidosis is associated with an increase in total body CO_2 content, reflected principally by an increase in serum bicarbonate. Mathematically, $\Delta HCO_3^- = 0.5\ \Delta Paco_2$.[23] $[HCO_3^-]$ is a dependent variable that increases or decreases with Pco_2. The rate of conversion of CO_2 to HCO_3^- depends on carbonic anhydrase activity and occurs slowly. It is possible to determine mathematically whether an increase in $Paco_2$ is acute or long-standing (see Table 49-1).

Hypercapnia is associated with a progressive increase in cerebrospinal fluid bicarbonate, reflecting an overall increase in total CO_2 load. Compensation of this hypercarbia is a reduction in cerebrospinal fluid chloride[24] and an increase in cerebrospinal fluid SID.[25-27] This is probably controlled by active transport mechanisms across the blood-brain barrier or at the level of the choroid plexus and can be blocked by furosemide and acetazolamide.[28-31]

Metabolic acid is buffered principally by increased alveolar ventilation producing respiratory alkalosis and extracellular weak acids. These weak acids include plasma proteins, phosphate, and bicarbonate. The bicarbonate buffering system (92% of plasma buffering and 13% overall) is probably the most important extracellular buffer. The pK_a of bicarbonate is low (6.1), but the system is extremely important because of the enormous quantity of CO_2 in the body. The coupling of bicarbonate and H_2O produces CO_2 that is excreted through the lungs via an increase in alveolar ventilation. Physicians must be aware of the importance of this compensatory mechanism. Anesthetized or critically ill patients on controlled mechanical ventilation lose the capacity to regulate their own Pco_2. Consequently, the combination of acute metabolic and respiratory acidosis can cause a devastating reduction in pH.

The major effect of the kidney on acid-base balance relates to renal handling of sodium and chloride ions. Because dietary intake of sodium and chloride is roughly equal, the kidney excretes a net chloride load using NH_4^+, a weak cation, to accompany chloride (electrochemically) in the urine.[22]

In metabolic acidosis, chloride is preferentially excreted by the kidney. In metabolic alkalosis, chloride is retained, while sodium and potassium are excreted. The presence of bicarbonate in the urine reflects the needs to maintain electric neutrality. Abnormalities in the renal handling of chloride may be responsible for several inherited acid-base disturbances. In renal tubular acidosis, there is inability to excrete Cl^- in proportion to Na^+.[32] The diagnosis can be made by observing a hyperchloremic metabolic acidosis with inappropriately low levels of Cl^- in the urine: The urinary SID is positive. If the urinary SID is negative, the process is nonrenal. Similarly, pseudohypoaldosteronism seems to be due to high reabsorption of chloride.[33] Bartter syndrome is caused by a mutation in the gene encoding the chloride channel—CLCNKB—that regulates the Na-K-2Cl cotransporter (NKCC2).[34] The other causes of hyperchloremic metabolic acidosis are gastrointestinal losses (diarrhea, small bowel or pancreatic drainage), parenteral nutrition, excessive administration of saline, and the use of carbonic anhydrase inhibitors.

Analytic Tools Used in Acid-Base Chemistry

Textbooks and clinical practice have tended to overestimate the importance of isolated changes in hydrogen or bicarbonate ion concentration. The clinical significance of acid-base perturbations is determined by the underlying cause, rather than the serum concentration of hydrogen and hydroxyl ions themselves. Nevertheless, acid-base chemistry remains a mainstay of clinical data interpretation because of ubiquitous availability, low cost, and universal acceptance. The accuracy of acid-base measurements is not determined, however, by the blood gas, which measures volatile acid and pH, alone. Measurement of all of the strong and weak ions that influence water dissociation, although cumbersome, is essential.

Acid-base abnormalities are best described by alterations in P_{CO_2}, SID, and A_{TOT}. Many approaches used to teach and describe the acid-base status of a patient fail to explain adequately many commonly seen perioperative acid-base abnormalities (e.g., dilutional or hyperchloremic acidosis) and are misleading with regard to the cause of the problem (e.g., dilutional acidosis is caused by reduced SID, not dilution of bicarbonate). Although it is important to consider historically used approaches, modern approaches to acid-base interrogation focus on physical chemistry either to calculate the magnitude of the disturbance in SID (strong ion gap [SIG]) or to recalculate the base deficit or excess using SID and A_{TOT} (see Fig. 49-4). In this section, we consider some of the tools that have evolved over the past 50 years to assist with interpretation of acid-base conundrums. None are entirely accurate, and each has a dedicated group of followers.[35]

Carbon Dioxide–Bicarbonate (Boston) Approach

Schwartz and colleagues, at Tufts University in Boston, developed an approach to acid-base chemistry using acid-base maps and the mathematical relationship between CO_2 tension and serum bicarbonate (or total CO_2), derived from the Henderson-Hasselbalch equation to predict the nature of acid-base disturbances (see Table 49-1). Patients with known acid-base disturbances, at steady states of compensation, were evaluated. The degree of compensation from what was considered normal was measured for each disease state. The investigators described six primary states of acid-base imbalance, using linear equations or maps, relating hydrogen ion concentration to P_{CO_2} for respiratory disturbances, and P_{CO_2} to HCO_3^- concentration for metabolic disturbances (Fig. 49-2). For any given acid-base disturbance, an expected HCO_3^- concentration was determined. For most simple disturbances, this is a reasonable approach.

Using these maps and equations, physicians have been able to determine the nature of most respiratory and metabolic acid-base disturbances. Although there is a mathematical relationship in place, alterations in H^+ and HCO_3^- do not reflect cause and effect. Chronic hypoventilation is associated with an increase in P_{CO_2} and HCO_3^-. Many physicians have incorrectly assigned the increase in HCO_3^- as compensation for increased P_{CO_2}. It is not. The increased HCO_3^- concentration reflects increased total CO_2 in the body. Alterations in HCO_3^- reflect its role as a buffer, CO_2 by-product, and weak acid.

Although the P_{CO_2}-HCO_3^- approach is accurate for most disturbances, there are several inherent pitfalls, particularly in relation to the metabolic component. First, the approach is not as simple as it seems. It requires the clinician to refer to confusing maps or to learn formulas and perform mental arithmetic. Second, the system neither explains nor accounts for many of the complex acid-base abnormalities seen in perioperative and critically ill patients. These include acute acidosis in the setting of hypoalbuminemia, hyperchloremic acidosis, and dilutional acidosis or lactic acidosis in the setting of chronic respiratory acidosis.

Base Deficit/Excess (Copenhagen) Approach

Singer and Hastings[36] pioneered an alternative approach to acid-base chemistry in 1948. Their method moved away from the Henderson-Hasselbalch equation and attempted to quantify the

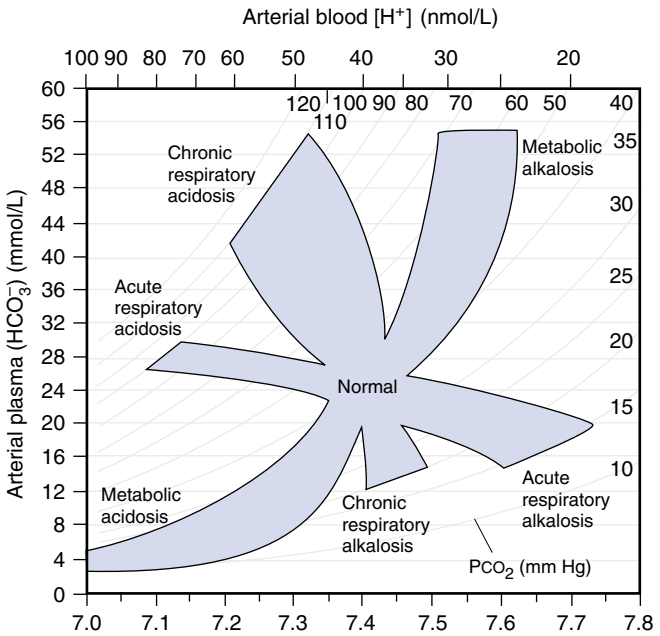

Figure 49-2 Acid-base nomogram using the Boston approach. Different acid-base disturbances can be distinguished based on the relative values of partial pressure of carbon dioxide (P_{aCO_2}) and concentration of bicarbonate ion ($[HCO_3^-]$). *(Adapted from Brenner BM, Rector FC: The Kidney, 3rd ed. Philadelphia, WB Saunders, 1986, p 473.)*

metabolic component. They proposed that the whole-blood buffer base could be used for this purpose. The buffer base represented the sum of the bicarbonate and the nonvolatile buffer ions (essentially serum albumin, phosphate, and hemoglobin). Applying the law of electric neutrality, the buffer base was forced to equal the electric charge difference between strong (fully dissociated) ions. Normally, buffer base = $[Na^+] + [K^+] - [Cl^-]$. Alterations in buffer base essentially represented changes in strong ion concentrations (these could not be easily measured in 1948). Buffer base increases in metabolic alkalosis and decreases in metabolic acidosis. The major drawback of the use of buffer base measurements is the potential for changes in buffering capacity associated with alterations in hemoglobin concentration.

In 1948, Siggard-Andersen* developed a simpler measure of metabolic acid-base activity, the base deficit/excess. This is defined as the amount of strong acid or base required to return pH to 7.4, assuming a P_{CO_2} of 40 mm Hg and temperature of 38°C. The initial use of whole-blood base excess was criticized because of the dynamic activity of red blood cells within the acid-base paradigm of gas and electrolyte exchange. This approach was modified in the 1960s to use only serum base excess, and the calculation became the *standardized* base excess. Similar to the Boston group, the Siggard-Andersen approach was based on data derived from a large population of patients that led to the development of nomograms (Fig. 49-3 and Table 49-3). Current algorithms for computing the standardized base excess are derived from the Van Slyke equation.[37] This base deficit excess (BDE) approach to acid-base chemistry has been successfully validated by Schlichtig et al.[38] The standardized base excess (SBE) is computed by blood gas analyzers as follows:

$$SBE = 0.9287\left[HCO_3^- - 24.4 + (pH - 7.4)\right]$$

Simple mathematical rules can be applied for using the BDE in each of the common acid-base disturbances. In acute respiratory acidosis or alkalosis, BDE does not change. Conversely, in acute metabolic acidosis, the magnitude of change of the P_{CO_2} (in mm Hg) is the same as that of the BDE (in mEq/L)

There has been considerable discussion over the past 30 years about the merits and demerits of the BDE compared with the CO_2-HCO_3^- system. In reality, there is little difference between the two; both equations and nomograms were derived from in vivo patient data and abstracted backward. Consequently, for most patients, either approach is relatively accurate but misleading. Using measures of buffer base as a means of quantifying acid-base disturbances does not allow the clinician to distinguish between acidosis caused by lactate or chloride or alkalosis caused by dehydration or hypoalbuminemia. These measures may miss the presence of an acid-base disturbance entirely; for example, a hypoalbuminemic (metabolic alkalosis), critically ill patient with a lactic acidosis may have a normal-range pH, bicarbonate, and base excess. This may lead to inappropriate or inadequate therapy.

Anion Gap Approach

The most widely used tool for investigating metabolic acidosis is the anion gap developed by Emmett and Narins.[39] The anion gap

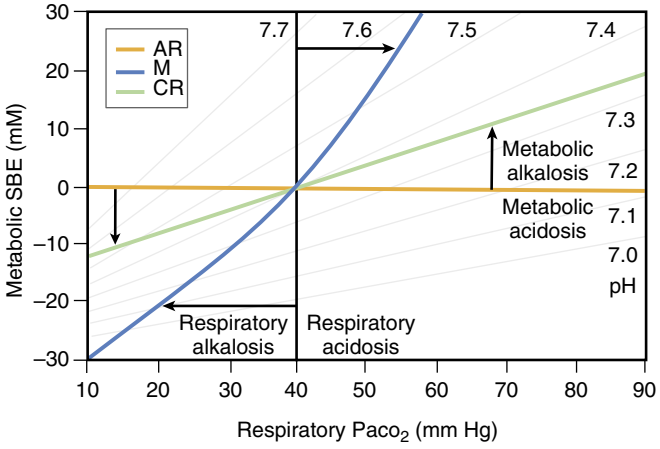

Figure 49-3 Acid-base nomogram using the Copenhagen approach as revised by Schlichtig. The various acid-base disturbances can be distinguished based on partial pressure of carbon dioxide (P_{aCO_2}) and base deficit or excess, here referred to as standard base excess (SBE). *Arrows* represent changes as the body compensates for acute acidosis or alkalosis. AR, acute respiratory acidosis or alkalosis; CR, chronic respiratory acidosis or alkalosis; M, metabolic acidosis or alkalosis. *(From Schlichtig R, Grogono AW, Severinghaus JW: Human P_{aCO_2} and standard base excess compensation for acid-base imbalance. Crit Care Med 26:1173-1179, 1998.)*

is based on the law of electric neutrality and is entirely consistent with the work of Stewart and Fencl. The system is based on data that were not easily available or known at the time of publication: the contribution to electric neutrality ascribed to weak acids (phosphate and albumin) and unmeasured anions. The sum of the difference in charge of the common extracellular ions reveals an unaccounted for "gap" of −10 to −12 mEq/L (anion gap = $(Na^+ + K^+ - (Cl^- + HCO_3^-))$ (Fig. 49-4). If the patient develops a metabolic acidosis, and the gap "widens" to −16 mEq/L, the acidosis is caused by unmeasured anions: lactate or ketones. If the gap does not widen, the anions are being measured, and the acidosis has been caused by hyperchloremia (bicarbonate cannot independently influence acid-base status).

Although the anion gap is a useful tool, it is weakened by the assumption of what is or is not a "normal gap."[40] Most critically ill patients are hypoalbuminemic, and many are also hypophosphatemic.[41] Consequently, the gap may be normal in the presence of unmeasured anions. This situation has been exten-

Table 49-3 Changes in Standardized Base Deficit or Excess in Response to Acute and Chronic Acid-Base Disturbances

Disturbance	BDE versus P_{aCO_2}
Acute respiratory acidosis	ΔBDE = 0
Acute respiratory alkalosis	ΔBDE = 0
Chronic respiratory acidosis	$\Delta BDE = 0.4\ \Delta P_{aCO_2}$
Metabolic acidosis	$\Delta P_{aCO_2} = \Delta BDE$
Metabolic alkalosis	$\Delta P_{aCO_2} = 0.6\ \Delta BDE$

BDE, base deficit or excess; Δ, change in value; P_{aCO_2}, partial pressure of arterial oxygen.
Modified from Narins RB, Emmett M: Simple and mixed acid-base disorders: A practical approach. Medicine (Baltimore) 59:161-187, 1980.

*Astrup P, Siggard-Andersen O: Micromethods for measuring acid-base values of blood. Adv Clin Chem 69:1-28, 1963.

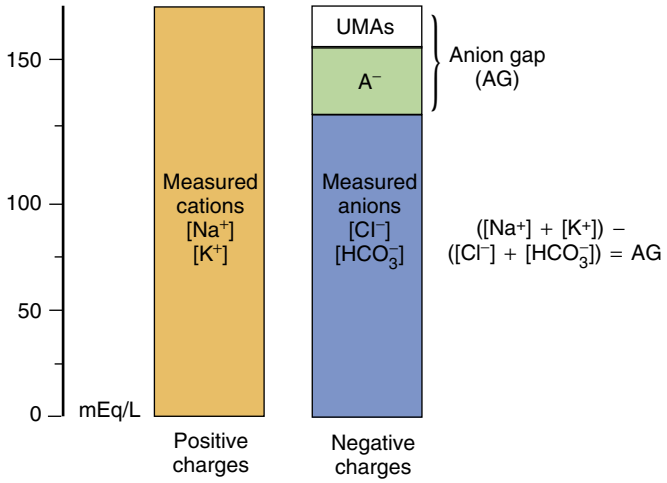

Figure 49-4 The anion gap represents the difference in charge between measured cations and measured anions. The missing negative charge is composed of weak acids (A^-), such as albumin and phosphate, and strong unmeasured anions (UMAs), such as lactate. The strong ion gap (SIG) approach is probably the most accurate method for evaluating acid-base anomalies and predicting outcomes.[42-45] The weakness of this system is that the SIG does not represent unmeasured strong anions, but rather all anions that are unmeasured. It is unclear whether this weakness is clinically significant because there is an emerging body of evidence that "stress acidosis" is associated with a medley of metabolic by-products, often in the absence of elevated serum lactate. The presence of a widened SIG is associated with worse outcomes.[46,47] This is important because many critical care practitioners continue to overestimate the importance of lactate in the evaluation and prognostication of major injury.[48]

sively studied by Figge and colleagues,[19] who have provided us with a variant known as the "corrected anion gap":

$$\text{Anion gap corrected (for albumin)} = \text{calculated anion gap} + 2.5\left(\text{normal albumin g/dL} - \text{observed albumin g/dL}\right)$$

The second weakness with this approach is the use of bicarbonate in the equation. An alteration in $[HCO_3^-]$ concentration can occur for reasons independent of metabolic disturbance (e.g., hyperventilation). The base deficit and anion gap frequently underestimate the extent of the metabolic disturbance.[18] The anion gap is nonetheless useful in discriminating acidosis from unmeasured anions from hyperchloremic acidosis in a previously healthy patient (e.g., in acute trauma).

Stewart-Fencl Approach

A more accurate reflection of true acid-base status can be derived using the Stewart-Fencl approach.[1,2] This approach is based on the concept of electric neutrality, a small advance from the anion gap. There exists, in plasma, a SID $[(Na^+ + Mg^{2+} + Ca^{2+} = K^+) - (Cl^- + A^-]$ of 40 to 44 mEq/L, balanced by the negative charge on bicarbonate and A_{TOT} (the buffer base). There is a small difference between apparent SID (apparent SID = $([Na^+]+ [K^+]+ [Mg^{2+}]+ [Ca^{2+}]) - [Cl^-]$) and buffer base. This effective SID = $[HCO_3^-]$ + [charge on albumin] + [charge on Pi] (in mmol/L). Because weak acids such as albumin and phosphate have known degrees of ionization, one can calculate the SIG, which quantifies the amount of unmeasured anion present (Fig. 49-5):

$$[\text{alb}^-] = [\text{alb g/L}] \times (0.123 \times \text{pH} - 0.631)$$

$$[\text{Pi}]\ (\text{in mg/dL}) = [\text{Pi}]/10 \times \text{pH} - 0.47$$

$$\text{SIG} = \text{apparent SID} - \text{effective SID}$$

SID changes quantitatively in absolute and relative terms when there are changes in plasma water concentration. Fencl and colleagues[18] addressed this by correcting the chloride concentration for free water (Cl^- *corr*) using the following equation:

$$[Cl^-]\ corr = [Cl^-]\ \text{observed} \times ([Na^+]\ \text{normal}/[Na^+]\ \text{observed}$$

This corrected chloride concentration may be inserted into the apparent SID equation. Likewise, the derived value for unmeasured anions should be corrected for free water using unmeasured anions instead of Cl^- in the previous equation.[18] In a series of nine normal subjects Fencl and colleagues[18] estimated the "normal" SIG as 8 ± 2 mEq/L.

Although accurate, the SIG is cumbersome and expensive, requiring measurement of multiple ions and albumin. An alternative approach, used by Gilfix and colleagues[49] and subsequently by Balasubramanyan and associates[45] and Story and associates,[50] is to calculate the base deficit-excess gap. This allows recalculation of BDE using strong ions, free water, and albumin. The resulting base deficit-excess gap should mirror the SIG and anion gap. We find the simplified calculation of Story and associates[50] to be most useful (Table 49-4). These investigators use two equations to calculate the BDE for sodium, chloride, and free water (BDE_{NaCl}) and for albumin.

It is probable that no single number will ever allow investigators to make sense of complex acid-base disturbances. Fencl and colleagues[18] suggested that, rather than focusing on anion gap or BDE, physicians should address each blood gas in terms of all alkalinizing and acidifying effects: respiratory acidosis or alkalosis, the presence or absence of abnormal SID (owing to water excess or deficit, measured electrolytes or unmeasured electrolytes), and abnormal A_{TOT}.

Although this approach may seem inelegant, it has the advantage of being comprehensive. Consider the following

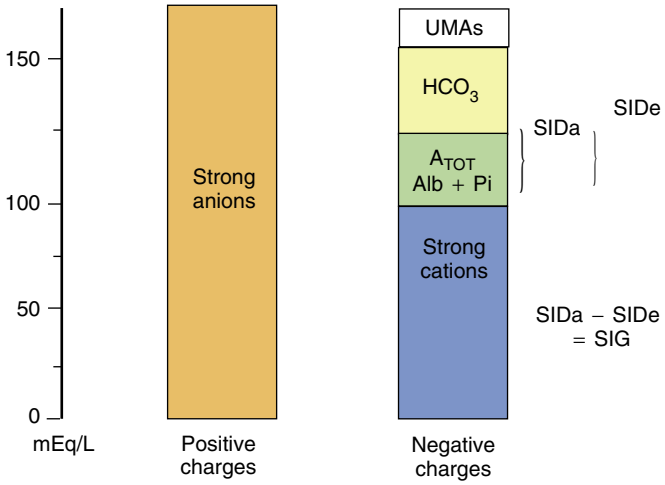

Figure 49-5 The strong ion gap. Apparent strong ion difference (SIDa) is the sum of the total concentration of weak ions (A_{TOT}) plus concentration of bicarbonate ion ($[HCO_3^-]$). Effective strong ion difference (SIDe) is the real SID. The difference between the two is composed of unmeasured anions (UMA).

Table 49-4 Calculation of Base Deficit or Excess of Sodium, Chloride, and Free Water, and Albumin

$BDE_{NaCl} = ([Na^+]–[Cl^-]) – 38$
$BDE_{Alb} = 0.25\ (42 – \text{albumin g/L})$
$BDE_{NaCl} – BDE_{Alb} = BDE_{calc}$
$BDE – BDE_{calc} = BDE\ gap = \text{the effect of unmeasured anions or cations}$
These calculations simplify the framework for "eyeballing" a chemistry series:
Normal Na = 140 mEq/L
For every 1 mEq/L increase in Na from 140, base excess increases by +1 (Na 150 = BDE +10 = contraction alkalosis)
For every 1 mEq/L decrease in Na from 140, base deficit increases by –1 (Na 130 = BDE –10 = dilutional acidosis)
Normal Cl = 102 mEq/L
For every 1 mEq/L increase in Cl from 102, base deficit increases by +1 (Cl 110 = BDE – 8 = hyperchloremic acidosis)
For every 1 mEq/L decrease in Cl from 102, base excess increases by +1 (Cl 90 = BDE +12 = hypochloremic, chloride sensitive, alkalosis)
Normal albumin = 42 g/L or 4.2 g/dL
For every 0.4 g/dL decrement in albumin from 4.0, there is a 1.0 mEq/L increase in base excess

Note: This approach involves calculating the base deficit or excess for sodium, chloride, and free water (BDE_{NaCl}), and that for albumin (BDE_{Alb}). The result is the calculated BDE (BDE_{calc}). This is subtracted from the measured BDE to find the BDE gap.

patient, described by Fencl and colleagues[18] (data in mEq/L unless otherwise stated):

> *Sodium 117, potassium 3.9, calcium 3, magnesium 1.4, chloride 92, inorganic phosphate 0.6 mmol/L, albumin 6 g/L, pH 7.33, P_{CO_2} 30 mm Hg, HCO_3 15, anion gap 13, corrected anion gap 23, base excess −10, SID 18, corrected chloride 112, corrected unmeasured anions 18.*

Using traditional methodology, one would describe this as a nongap metabolic acidosis, and look for causes of bicarbonate wasting, such as renal tubular acidosis or gastrointestinal losses. The degree of respiratory alkalosis is appropriate for the degree of acidosis ($\Delta BD = \Delta P_{CO_2}$). Fencl-Stewart methodology reveals a much more complex situation. SID is reduced to 18 mEq/L—caused by free water excess, unmeasured anions, and hyperchloremia (see the corrected chloride). The degree of acidosis does not mirror this metabolic disturbance, however, owing to the alkalizing force at play: hypoalbuminemia. The corrected anion gap mirrors the change in SID, but this is grossly underestimated by the base deficit. This patient has a dilutional acidosis, a hyperchloremic acidosis, and a lactic acidosis.

For most patients presenting to the emergency department or operating suite, who have been previously healthy, the use of tools such as the base deficit or anion gap to assess metabolic disturbances remains reasonable. For critically ill patients, the most effective method of interpreting acid-base conundrums involves unraveling synchronous acidifying and alkalinizing processes and using calculations or rules of thumb to distinguish between the various forces at play. A clinician's ability to interpret such information depends on the amount of available data. A simple blood gas alone may camouflage a significant acid-base disturbance. In the next section, we look at the causes of many commonly seen acid-base disturbances in different clinical settings.

Acid-Base Problems in Different Clinical Settings

Simple acid-base disturbances can be evaluated using the following strategy:

Step 1. Look at the pH (three possibilities):
- <7.35—acidosis
- 7.35-7.45—normal or compensated acidosis
- >7.45—alkalosis

Step 2. Look for respiratory component (volatile acid = CO_2):
- P_{CO_2} <35 mm Hg—respiratory alkalosis or compensation for metabolic acidosis (if so, BD* > −5)
- P_{CO_2} 35-45 mm Hg—normal range
- P_{CO_2} >45 mm Hg—respiratory acidosis (acute if pH <7.35, chronic if pH in normal range and BE† > +5)

Step 3. Look for a metabolic component (i.e., buffer base utilization):
- BD >−5—metabolic acidosis
- BE −5 to +5—normal range
- BE >5—alkalosis

Put this information together. Options:
1. Acidosis, CO_2 <35 mm Hg, ± BD >−5—acute metabolic acidosis
2. Normal range pH CO_2 <35, BD >−5—acute metabolic acidosis plus compensation
3. Acidosis, P_{CO_2} >45 mm Hg, normal range BE—acute respiratory acidosis
4. Normal range pH, P_{CO_2} >45 mm Hg, BE >+5—prolonged respiratory acidosis
5. Alkalosis, P_{CO_2} >45 mm Hg, BE >+5—metabolic alkalosis
6. Alkalosis, P_{CO_2} <35 mm Hg, BDE normal range—acute respiratory alkalosis
7. If the acid-base picture does not conform to any of these, a mixed picture is present.

Acid-Base Disturbances in the Emergency Setting

Acid-base disturbances are an important part of the laboratory investigation of acutely ill patients. Common disturbances are acute respiratory acidosis or alkalosis and acute metabolic acidosis. Acute metabolic alkalosis is unusual. Mixed respiratory acidosis/metabolic acidosis is seen in severely injured or infected patients.

Acute respiratory acidosis, as discussed earlier, results from hypoventilation. The hypoventilation may be due to loss of respiratory drive, neuromuscular or chest wall disorders, or rapid,

*Base deficit (BD) = amount of strong cation required to bring pH back to 7.4, with P_{CO_2} corrected at 40 mm Hg.

†Base excess (BE) = amount of strong anion required to bring pH back to 7.4, with P_{CO_2} corrected at 40 mm Hg.

shallow breathing that increases the fraction of dead space ventilation. Causes include neurologic injury (e.g., stroke, spinal cord injury, botulism, tetanus), toxic suppression of the respiratory center (e.g., opioids, barbiturates, benzodiazepines), neuromuscular disorders (e.g., Guillain-Barré syndrome, myasthenia gravis), abdominal hypertension, flail chest, hydrohemopneumothorax, pulmonary edema, and pneumonia.

Acute respiratory alkalosis is caused by hyperventilation. The hyperventilation most often results from anxiety, central respiratory stimulation (as occurs early in salicylate poisoning), or excessive artificial ventilation. Acute respiratory alkalosis often occurs in compensation for acute metabolic acidosis. In such cases, the reduction in P_{CO_2} from baseline (usually 40 mm Hg) is equal to the magnitude of the base deficit. In a patient with an acute lactic acidosis of 10 mEq/L, the base deficit should be −10, and the P_{CO_2} should be 30 mm Hg. If the P_{CO_2} is higher than expected, there is a problem with respiration. This situation is seen in a multitrauma patient, in whom there is massive blood loss causing lactic acidosis plus a flail chest causing respiratory acidosis.

Acute metabolic acidosis is caused by an alteration in the SID or A_{TOT}. An altered SID reflects a change in the relative ratio of strong anions to strong cations. This change can be caused by anion gain, as occurs with lactic acidosis, renal acidosis, ketoacidosis, or hyperchloremia. Alternatively, cations may be lost, as occurs with severe diarrhea or renal tubular acidosis. Acute acidosis also may reflect increased free water relative to strong ions—the so-called dilutional acidosis that may accompany excessive hypotonic fluid intake. Alcohols such as ethanol, methanol, isopropyl alcohol, and ethylene glycol are osmotically active molecules that expand extracellular water. Poisonings with these agents cause a dilutional acidosis. In addition, although hyperglycemia or administration of mannitol ultimately contracts ECF via an osmotic diuresis, the initial response is volume expansion.

To investigate acute metabolic acidosis in previously healthy patients, simple observational and mathematical tools, such as the anion gap and base deficit, are useful (Table 49-5). The base deficit shows the presence of an acid-base anomaly. The anion gap (anion gap = $[Na^+ + K^+ - (Cl^- + HCO_3^-)]$) distinguishes acidosis caused by hyperchloremia (renal tubular acidosis or excessive administration of "normal saline") from acidosis caused by "unmeasured" anions (many of which now are measurable) and dilution. When a patient presents with an acute metabolic upset (e.g., trauma, exsanguination, loss of consciousness, tachypnea), a blood gas, electrolyte panel, serum lactate, serum osmolality, and urinalysis are invaluable.

In acute metabolic acidosis, three diagnoses should be immediately investigated: (1) lactic acidosis (send a serum lactate—it should mirror the magnitude of base deficit); (2) ketoacidosis secondary to diabetes (the patient should be hyperglycemic and have positive urinary ketones); and, by exclusion, (3) acute renal failure, characterized by high serum urea and creatinine and low total CO_2.

Lactic acidosis in the presence of hypoxemia or hypoperfusion is termed type A lactic acidosis. When hypoxemia/hypoperfusion is absent, it is referred to as type B lactic acidosis, and is more often associated with inborn errors of metabolism and some drugs (e.g., biguanides and toxins). Another important source of lactate is administration of catecholamines, particularly epinephrine.

Table 49-5 Evaluation of a Patient with Metabolic Acidosis

1. Is acidosis being caused by measured or unmeasured anions (i.e., chloride)?
   - Look at blood chemistry
     - Calculate anion gap: Na + K − Cl = 10-12
     - If gap is normal, there is too much chloride present, owing to excessive administration, excess loss of sodium (diarrhea, ileostomy), or renal tubular acidosis
     - If gap is wide (>16), there are other unmeasured anions present, causing acidosis
   - Check serum lactate—if >2, probably lactic acidosis
     - If high lactate is explained by circulatory insufficiency (shock, hypovolemia, oliguria, under-resuscitation, anemia, carbon monoxide poisoning, seizures), then "type A" lactic acidosis
     - If not think about "type B (rare)" causes—biguanides, fructose, sorbitol, nitroprusside, ethylene glycol, cancer, liver disease
   - Look at creatinine and urine output
     - If patient is in acute renal failure, these may be renal acids
   - Look at blood glucose and urinary ketones
     - If patient is hyperglycemic and ketotic, this is diabetic ketoacidosis
     - If patient is ketotic (unmeasured anion) and normoglycemic, this is either alcoholic (check blood alcohol) or starvation ketosis
     - Check for presence of chronic alcohol abuse—high mean corpuscular volume, increased γ-glutamyl transferase on liver panel
2. If all of these tests are negative, think of intoxication
   - Send toxicology laboratory tests (particularly salicylates) and serum osmolality, and calculate osmolality using the formula: 2(Na + K) + Glucose/18 + BUN/2.8
   - Look for unmeasured source of osmoles: if gap between measured and calculated serum osmolality >12, think of alcohol, particularly ethylene glycol, isopropyl alcohol, and methanol

Diabetic ketoacidosis is characterized by ketosis and hyperglycemia. Ketone bodies are produced from β-hydroxylated fatty acids in states of starvation or insulin deficiency. They include acetate, acetoacetate, and β-hydroxybutyrate. These act as strong ions, causing metabolic acidosis. Patients with diabetic ketoacidosis have acidosis caused by ketones and lactate and hypoperfusion. They are characteristically dehydrated, owing to hyperglycemia induced diuresis.

Renal acidosis is caused by accumulation of strong ion products of metabolism, including sulfate and formate, excreted exclusively by the kidney. In addition, there is accumulation of a weak acid, phosphate; this is caused by relative deficiency of vitamin D. Lactic acidosis is treated with volume resuscitation and source control. Diabetic ketoacidosis is treated with volume resuscitation and insulin. Renal acidosis is treated with dialysis.

Finally, the presence of a low serum sodium (>135 mEq/L) should alert the clinician to the possibility of a dilutional acidosis, such as may be caused by alcohol poisoning. Alcohol poisoning is suspected by the presence of an osmolar gap, a difference between the measured and calculated serum osmolality of greater than 12 mOsm showing the presence of unmeasured osmoles. Toxicology laboratories can investigate for the presence of various toxic alcohols.

The use of sodium bicarbonate boluses or infusions is controversial in acute metabolic acidosis. There is little evidence of benefit using this agent in lactic acidosis or ketoacidosis.[9] The key to managing acid-base disturbances lies not in altering acid-base

balance, but rather in correcting the underlying defect. Sodium bicarbonate increases SID and can correct one cause of acidosis. Conversely, sodium bicarbonate is administered as an 8.4% hypertonic solution and has a plasma-expanding effect that can lead to a dilutional acidosis and increases $Paco_2$ as well. This expansion may provide a hemodynamic benefit in shock.[9] Sodium bicarbonate infusions, with the purpose of increasing SID, have been used in patients awaiting dialysis, to reduce patient symptoms and to prevent hyperkalemia.

Specific toxins require more specific treatment. Methanol is metabolized to formaldehyde and formate by alcohol dehydrogenase. These products are highly toxic, causing blindness, cardiovascular instability, and death. Treatment strategies include the use of ethanol, which competes for binding on alcohol dehydrogenase, and fomepizole, which inhibits the enzyme. Ethylene glycol poisoning causes central nervous system depression, lactic acidosis, formation of calcium oxalate urinary crystals leading to hypocalcemia and renal failure, cardiovascular depression, and death. Treatment is with fomepizole with or without hemodialysis.

Perioperative Acid-Base Disturbances

In addition to the acid-base disturbances seen in emergency situations, numerous acid-base conundrums are peculiar to perioperative and critically ill patients. These include respiratory acidosis and alkalosis associated with mechanical ventilation, acidosis secondary to hyperchloremia or contraction, and alkalosis owing to sodium gain or chloride loss. Perioperatively, respiratory acidosis likely is due to poorly chosen mechanical ventilation strategies, narcosis, or incomplete reversal of neuromuscular blockade. Respiratory alkalosis is caused by hyperventilation most often as a result of mechanical overventilation, or from pain or anxiety.

Metabolic acid-base disturbances are common perioperatively and often are iatrogenic. In particular, these disturbances reflect manipulation of SID by administration of electrolyte or osmotically imbalanced solutions.

Hyperchloremic acidosis is seen frequently in the operating suite. This usually follows administration of a large volume of 0.9% saline solution. This solution contains 154 mEq of Na^+ and Cl^- and has an SID of 0. Each liter of normal saline is associated with SID loss. Hyperchloremic acidosis also is associated with acute normovolemic hemodilution with 5% albumin solution or 6% hetastarch (both formulated in normal saline).[51] The key abnormality is chloride gain. Serum sodium may stay the same or increase. Dilutional acidosis refers to a condition in which there is an alteration in the relative quantity of sodium and chloride in free water such that serum sodium decreases. This condition most commonly reflects the perioperative administration of sodium-poor fluids. The perioperative stress response is associated with increased secretion of antidiuretic hormone and a reduced ability to excrete free water. Excessive administration of hypotonic fluids, such as dextrose 5% or 0.45% sodium chloride, leads to an expansion in free water, hyponatremia, and acidosis.

Case 1

A 45-year-old man is admitted after a motor vehicle crash. He is bleeding, and his pulse is thready. Blood pressure is 90/50 mm Hg, heart rate is 120 beats/min, respiratory rate is 36/min, and temperature is 35°C.

A serum chemistry and blood gas are taken. Does he have any acid-base disturbances?

Na^+ 144, K^+ 4, Cl^- 110, total CO_2 8, urea 10, creatinine 2, albumin 4, lactate 16, pH 7.28, Pco_2 24, HCO_3^- 8, BE –16

Anion gap = 26

Corrected anion gap = 27.25

Using traditional tools, the patient has a widened anion gap acidosis. This is a lactic acidosis, with appropriate respiratory compensation. The BDE and anion gap approach accurately detect the "unmeasured" anion, lactate.

The patient is aggressively volume resuscitated and brought to the operating room. A blood gas and serum chemistry are taken on the patient, now mechanically ventilated in the intensive care unit, 12 hours later.

Na^+ 148, K^+ 3, Cl^- 120, total CO_2 22, urea 10, creatinine 2, albumin 2, lactate 5, pH 7.33, Pco_2 35, HCO_3^- 18, BE –11

Is the patient still under-resuscitated? What intravenous fluid was used?

In this situation, traditional tools are unreliable. Using the Fencl-Gilfix[45,49] approach, correcting the base deficit excess for acidifying and alkalinizing processes reveals a complex situation.

Acidifying Process	Magnitude	BDC	Alkalinizing Process	Magnitude	BEC
Hyperchloremia	120 mEq/L	–17	Hypernatremia	148 mEq/L	+2.4
Lactacidemia	5 mEq/L	–5	Hypoalbuminemia	2 g/dL	+8.5
Total		–22	Total		+11.9

BDC – BEC = –10.1

(BDC = base deficit corrected; BEC = base excess corrected)

Using simple measures such as BDE to follow the resuscitation, one might assume, based on the base deficit, that serum lactate was significantly higher than it actually is, and that the patient is under-resuscitated. This is not so. The patient was resuscitated with "normal" saline.

The physiologic basis for dilutional acidosis is often misunderstood. It cannot truly be explained by dilution of bicarbonate because one would expect acids and bases to be equally effected.[52] Studies have failed to show reduced serum bicarbonate in "dilutional acidosis."[52,53] Bicarbonate concentration is determined by CO_2 equilibrium.[54] Alterations in pH reflect changes in the relative ratio of sodium and chloride. Morgan and coworkers[55] showed that in vitro hemodilution is associated with a simple linear relationship between diluent crystalloid SID and the rate and direction of change of plasma SID and whole-blood base excess.[55]

The presence of a hyperchloremia is associated with different outcomes than some other forms of acidosis. Brill and colleagues[13] found that hyperchloremic acidosis was associated with better outcomes than acidosis associated with lactic acidosis or ketoacidosis. This finding supports the contention that the underlying problem increases patient risk. Nonetheless, metabolic acidosis, regardless of origin, can depress myocardial contractility, reduce cardiac output, and impair tissue perfusion. Acidosis inactivates membrane calcium channels and inhibits the release of norepinephrine from sympathetic nerve fibers. This leads to vasodilation and maldistribution of blood flow. Additionally, metabolic acidosis is associated with an increased incidence of postoperative nausea and emesis.[56] Plasma chloride levels affect afferent arteriolar tone through calcium-activated chloride channels and modulate the release of renin.[57] Hyperchloremia can reduce renal and other splanchnic blood flow and glomerular filtration rate.[58,59] In a study of healthy volunteers, normal saline was associated with reduced urinary output compared with lactated Ringer solution.[60] Finally, in a study of fluid prehydration to prevent contrast nephropathy, the use of sodium bicarbonate was associated with a 11.9% absolute reduction in the risk of renal injury (defined as a 25% increase in creatinine).[61]

Hyperchloremic acidosis is treated by increasing the SID of infused fluids. This may be accomplished by infusing sodium without chloride. Although no such fluid is available commercially, isotonic sodium bicarbonate or sodium acetate solution can be administered.

Perioperative metabolic alkalosis most often is iatrogenic. Hyperventilation of patients with chronic respiratory failure results in acute metabolic alkalosis from chronic compensatory alkalosis associated with chloride loss in urine (Fig. 49-6).[8] More frequently, metabolic alkalosis is associated with increased SID owing to sodium gain. This results from administration of fluids in which sodium is "buffered" by weak ions, such as citrate (in blood products), acetate (in parenteral nutrition), and bicarbonate. Buffer ions such as citrate, acetate, gluconate, and lactate are rapidly cleared by the liver under normal conditions and do not contribute to acid-base balance. Sodium and chloride obey the law of conservation of mass. The so-called chloride-sensitive alkalosis really reflects sodium gain, treated by administration of net loads of chloride—0.9% sodium chloride or, perhaps more appropriately, potassium chloride, calcium chloride, and occasionally hydrogen chloride. It is important to correct chloride-sensitive alkalosis because the normal compensatory measure is hypoventilation, increasing $Paco_2$. This may lead to CO_2 narcosis, or failure to liberate from mechanical ventilation (Table 49-6).

Chloride loss can result in metabolic alkalosis in perioperative patients. Chloride most often is lost from the gastrointestinal tract as a result of continuous suctioning or vomiting. Gastric juice contains hydrochloric acid. The loss of chloride, not of H^+, causes the alkalosis, however, because chloride obeys the law of conservation of mass and alters the SID.

In maintaining perioperative patients, hypotonic and dextrose-containing fluids should be avoided. For patients receiving 1 or 2 L of perioperative fluid, the choice of fluids has little effect.

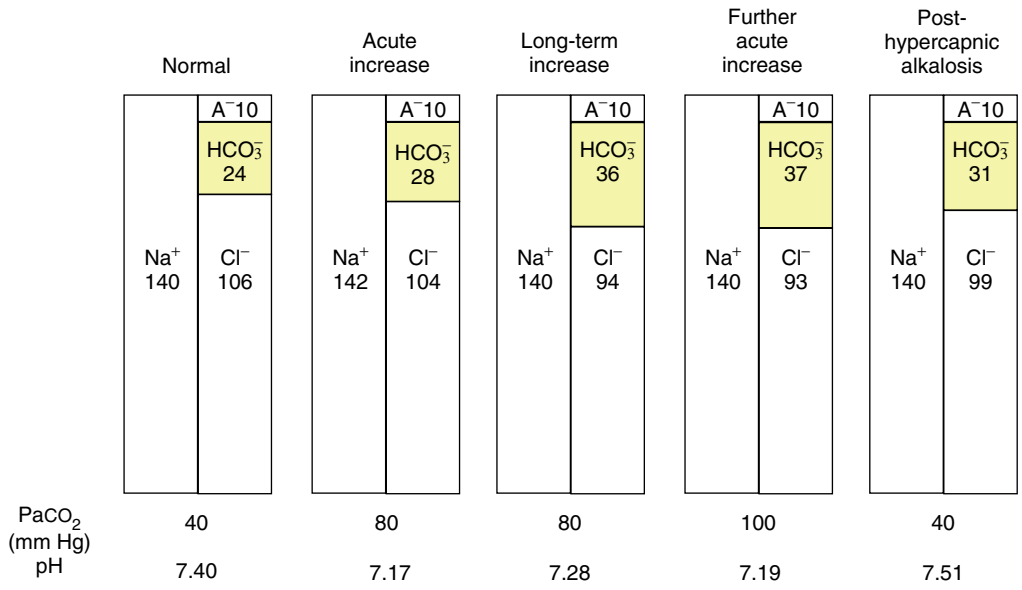

Figure 49-6 Changes in acid-base and electrolyte composition in patients with respiratory acidosis. *Left to right,* Normal acid-base status; adaptation to an acute increase in partial pressure of carbon dioxide ($Paco_2$) to 80 mm Hg; adaptation to a long-term increase in $Paco_2$ to 80 mm Hg; superimposition of an acute further increase in $Paco_2$ (to a level of 100 mm Hg) in the same patient; and post–hypercapnic alkalosis resulting from an abrupt reduction in $Paco_2$ to 40 mm Hg in the same patient. A^- denotes unmeasured plasma anions, and the numbers within the bars give ion concentrations in mmol/L. *(Adapted from Androgue H, Madias N: Management of life-threatening acid-base disorders: First of two parts. N Engl J Med 338:26-34, 1998.)*

Table 49-6 Acid-Base Disturbances Commonly Seen Perioperatively

Disorder	Cause
Respiratory acidosis	Hypoventilation—narcosis, incomplete reversal of neuromuscular blockade
Respiratory alkalosis	Hyperventilation—anxiety, pain
Metabolic acidosis secondary to unmeasured anions (widened gap acidosis)	Hypoperfusion—lactic acidosis; diabetic ketoacidosis; renal failure
Metabolic acidosis secondary to measured anions (non-gap hyperchloremic acidosis)	Hyperchloremia—"normal" saline, hetastarch, or albumin infusions; renal tubular acidosis; bladder reconstructions
Metabolic acidosis secondary to free water excess (hyponatremia, dilution acidosis)	Hypotonic fluid administration; sodium loss—diarrhea; administration of hyperosmolar fluids—mannitol, alcohol, hyperproteinemia
Metabolic alkalosis	Hyperventilation of patient with history of carbon dioxide retention (COPD); sodium gain (sodium bicarbonate, massive blood transfusion); chloride loss—nasogastric suctioning

COPD, chronic obstructive pulmonary disease.

If larger volumes of crystalloid are administered, it is important to use balanced buffered solutions that mirror the electrolyte content of ECF, such as lactated Ringer solution, Normosol, or Plasma-Lyte. Normal saline should be administered to a patient who has been on continuous nasogastric suctioning until the base deficit returns to zero. Likewise, normal saline should accompany large volumes of blood or frozen plasma. Care must be taken to avoid hypokalemia, hypocalcemia, hypomagnesemia, and hypophosphatemia. Patients who have received purgatives for bowel surgery should be treated with balanced buffer solutions. The same rules apply to colloid solutions. Human albumin solution, some hetastarches, and gelatins (available in Europe) are formulated in sodium chloride; large volumes cause hyperchloremic acidosis.

Acid-Base Disturbances in Critical Illness

Acid-base disturbances in critically ill patients may be complex and confounding (see Chapter 91). These may result in normal blood gases despite significant, off-setting perturbations of P_{CO_2}, SID, and A_{TOT}. Significant pathology may be overlooked.

The most important single disturbance in acid-base chemistry in critically ill patients is hypoalbuminemia.[15] This is ubiquitous and causes an unpredictable metabolic alkalosis that can mask significant alterations in SID, such as lactic acidemia. Although Figge and colleagues[19] have presented a mechanism for adjusting the anion gap for albumin, this implies that the physician is actually aware of an acid-base abnormality. Likewise, the use of base deficit to predict lactate is unreliable in critical illness.[18] Prolonged respiratory failure with associated hypercarbia leads to additional metabolic alkalosis as a result of chloride loss in urine.[8] Mechanical ventilation per se increases the circulating volume of atrial natriuretic hormone and antidiuretic hormone. The result is increased total body water and dilutional acidosis. This situation may be complicated further by renal insufficiency or renal failure, with concomitant accumulation of metabolic by-products, renal anions, and other unmeasured anions. Polyuric renal failure may be associated with significant contraction alkalosis, owing to loss of sodium, potassium, and free water.

Critically ill patients are vulnerable to significant changes in SID and free water. Nasogastric suctioning causes chloride loss, whereas diarrhea leads to sodium and potassium loss. Surgical drains placed in tissue beds may remove fluids with varying electrolyte concentrations (e.g., the pancreatic bed secretes fluid rich in sodium). Fever, sweating, oozing tissues, and inadequately humidified ventilator circuits lead to large-volume insensible loss and contraction alkalosis.

Infusions administered to patients may be responsible for unexpected alterations in serum chemistry. Many antibiotics, such as piperacillin-azobactam, are diluted in sodium-rich solutions. Others, such as vancomycin, are administered in large

Case 2

A 56-year-old man is chronically critically ill. A serum chemistry and blood gas are taken. Does he have any acid-base disturbances?

Na^+ 130, K^+ 4, Cl^- 100, total CO_2 24, urea 10, creatinine 1, albumin 1, lactate 6, pH 7.42, P_{CO_2} 40, HCO_3^- 24, BE +1

Using the Fencl-Gilfix approach,[45,49] correcting the BDE for acidifying and alkalinizing processes reveals a complex situation.

Acidifying Process	Magnitude	BDC	Alkalinizing Process	Magnitude	BEC
Hyponatremia	130 mEq/L	–3	Hypoalbuminemia	1 g/dL	+11.9
Hyperchloremia	100 mEq/L	–3			
Lactacidemia	5 mEq/L	–5			
Total		–11	Total		+11.9

BDC – BEC = 0.9

(BDC = base deficit corrected, BEC = base excess corrected)

In this example, the patient has three significant acidifying processes going on. The presence of lactic acidosis is sinister. However, using traditional approaches to this example would not reveal the abnormalities.

volumes of free water (5% dextrose). Lorazepam is diluted in propylene glycol, large volumes of which cause metabolic acidosis similar to that seen with ethylene glycol.[62]

Continuous renal replacement therapy is used to provide hemofiltration and hemodialysis to critically ill patients who are hemodynamically unstable. Rocktaschel and others[63,64] have shown that continuous renal replacement therapy resolves the acidosis of acute renal failure by removing strong ions and phosphate. This correction unmasked metabolic alkalosis owing to hypoalbuminemia, however.

Other seemingly innocuous therapies may cause significant disturbances to acid-base balance. Loop diuretics are often administered to critically ill patients in the mistaken view that they will liberate sequestered fluids. These agents cause hypochloremic and contraction alkalosis. Carbonic anhydrase inhibitors, such as acetazolamide, cause excretion of sodium and bicarbonate and retention of chloride. This results in hyperchloremic acidosis.

Contraction alkalosis is treated by correcting the free water deficit using the following formula:

$$\text{Free water deficit} = 0.6 \times \text{patient's weight in kg} \times \left(\text{patient's sodium}/140 - 1\right)$$

Hypochloremic alkalosis should be treated by correcting the chloride deficit, using normal saline.

Neurosurgical patients are vulnerable to various acid-base disturbances relating to osmotherapy and brain injury.[65] Mannitol administered to reduce intracranial pressure initially causes a mild dilutional acidosis. These patients are routinely treated with normal saline solution and frequently with hypertonic saline. Both can cause acidosis.[66] Diabetes insipidus frequently occurs as a complication of severe head injury. It is caused by disruption of the hypothalamic-pituitary axis. In the absence of antidiuretic hormone, the kidney is unable to concentrate the urine. This results in a massive diuresis. The disorder is characterized by an increase in plasma osmolality in the presence of a low urinary osmolality; this typically manifests as a contraction alkalosis. The treatment is hormonal replacement with either vasopressin or desmopressin.

Conclusion

Much of the confusion regarding acid-base chemistry relates to attempts to apply observational approaches, such as that of Henderson-Hasselbalch or Schwartz and Brackett, to the entire spectrum of pathophysiologic processes. The use of physical chemistry principles permits a better explanation of acid-base balance and provides tools to apply to a wide variety of clinical situations. This does not suggest that the "traditional" approach is incorrect, merely that it looks at a mirror image of that proposed by Stewart, Fencl, and others. All acid-base disorders can be explained in terms of SID, A_{TOT}, and P_{CO_2}. Anesthesiologists may have a significant impact on acid-base balance with choice of fluids and mechanical ventilation strategy.

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50 Airway Management in the Adult

Key Points

1. Three basic decisions needed before induction of anesthesia in every patient are whether to use awake intubation, use a percutaneous technique, or maintain spontaneous ventilation.
2. Conditions requiring particular caution include lesions at the base of the tongue, recent onset of hoarseness, upper airway obstruction, and obstructive sleep apnea.
3. The combination of mouth opening, jaw protrusion, and head extension is the core of airway assessment. The examination described by El-Ganzouri (mouth opening, prognathic ability, head extension, thyromental distance, and the Mallampati test) has been used with minor modification by others. It can be performed rapidly and is the most quantifiable (recording of actual values is recommended) of the tests included in the guidelines of the American Society of Anesthesiologists (ASA).
4. Radiology studies have shown that head extension is the most important single maneuver in maintaining space between the pharyngeal soft tissues. Head extension stretches the anterior neck structures and moves the hyoid bone and attached structures anteriorly.
5. Four principles are central to prevention of complications during tracheal intubation:
   - Maintenance of oxygenation must take priority over all other issues. Preoxygenation should be performed before induction of anesthesia. Mask ventilation should be used between attempts at tracheal intubation.
   - Trauma must be prevented. The first attempt at tracheal intubation should be performed under optimal conditions, including patient position, preoxygenation, and equipment preparation. The number of attempts with blind techniques should ideally be zero and certainly not more than four.
   - Anesthesiologists should have a sequence of backup plans in place before starting the primary technique. They should have the skills and the equipment needed to execute these plans. When unanticipated difficulty occurs in non-lifesaving surgery, the safest plan is to terminate attempts at tracheal intubation, awaken the patient, and postpone surgery.
   - Anesthesiologist should seek the best help available ("call for help") as soon as difficulty with tracheal intubation is experienced.
6. Immediate confirmation of correct tracheal tube placement is an essential and integral part of tracheal intubation. Several tests should be used because no single test is completely reliable. The most important safeguard is clinical suspicion. Visual confirmation of passage of the tracheal tube between the vocal cords is reliable, but not always possible, and experienced anesthesiologists are occasionally misled.
7. All anesthesiologists should be skilled in at least one alternative technique of tracheal intubation under vision. Strategies that include algorithms for the management of unanticipated difficult intubation have been devised by several organizations, including the ASA and the Difficult Airway Society, a U.K. organization. The ASA algorithm is the standard guide.
8. If noninvasive techniques do not restore oxygenation, cricothyrotomy is the percutaneous airway of choice because tracheotomy may take too long. It is not possible to define the Spo_2 at which cricothyrotomy should be performed—it depends on the degree of hypoxemia and how rapidly it is deteriorating.

Anesthesia was developed to enable the performance of therapeutic and diagnostic procedures that could not be performed in conscious or sedated patients. The reduction in consciousness produced by general anesthesia (or trauma or disease) is necessarily associated with depression of other physiologic systems. The depressant effects on airway, respiratory, and cardiovascular function can cause immediate threats to the patient. Airway management differs from management of other depressed function in that it requires a range of manual skills, as well as knowledge and judgment.

Some components of anesthesia respiratory care have become safer in the last 3 decades. American Society of Anesthesiologists (ASA) Closed Claims analyses show that nonspecific adverse respiratory system events decreased from about 37% of respiratory claims in the 1970s to 14% of claims in the 1990s. However, the proportions of claims attributable to difficult tracheal intubation has more than doubled.[1] The probable explanation is that monitoring has reduced the number of adverse outcomes from nonspecific events but prevention of adverse tracheal intubation outcomes is more difficult. Evidence of the limitations of "traditional" techniques has accrued and effective new techniques have been developed. However, many anesthesiologists continue to rely on multiple attempts with ineffective techniques.

Anatomy

The nose warms, filters, and humidifies incoming air and is the organ of smell. It consists of the external nose and the internal nasal cavity. The nasal cavities are divided by the nasal septum, which is frequently deviated with the consequence that the nasal cavities are narrowed or obstructed. The roof of the nasal cavity is the cribriform plate, a thin bone that is easily fractured, thereby resulting in communication between the nasal and intracranial cavities. The bony lateral wall of the nasal cavity is the origin of the three bony turbinates that project into the nasal cavity. They are easily damaged by force during the passage of nasotracheal tubes. Openings in the lateral wall communicate with the paranasal sinuses. Prolonged nasotracheal intubation impairs drainage through these openings, causing sinusitis. The lining of the nasal cavity is very vascular, and application of nasal vasoconstrictors to shrink the mucosa and dilate the airway reduces the risk of hemorrhage during the insertion of airway devices or tracheal tubes.

The roof of the mouth is bounded by the alveolar arch and teeth and consists of the hard palate anteriorly and the soft palate posteriorly. The tongue makes up most of the floor of the mouth, which is bounded by the mandible and teeth. Nonencapsulated lymphoid tissue on the posterior surface of the tongue (lingual tonsil) is part of the ring of Waldeyer. This tissue is important in that hypertrophy can cause serious difficulty in airway management.[2,3] The ability to achieve good mouth opening is important for many airway procedures. Initial mouth opening is achieved by rotation within the temporomandibular joint (TMJ) and subsequent opening by sliding (also known as protrusion, translocation, or subluxation) of the condyles of the mandible within the TMJ. The jaw-thrust maneuver uses the sliding component of the TMJ to move the mandible and attached structures anteriorly. The scissors maneuver (Fig. 50-1) achieves maximum mouth opening by the application of internal pressure on the teeth to achieve both TMJ movements. It can facilitate the insertion of oropharyngeal airways, supraglottic airway devices (SADs), and laryngoscopes. All movements of the TMJ should be firm but gentle to minimize the risk of joint damage.

The pharynx is a fibromuscular tube that extends from the base of the skull to the lower border of the cricoid cartilage. It joins the nasal and oral cavities above with the larynx and esophagus below. Both the pharynx and esophagus can be perforated by blind attempts at tracheal intubation. The nasopharynx is the part of the pharynx that lies posterior to the nose. Nasotracheal tubes

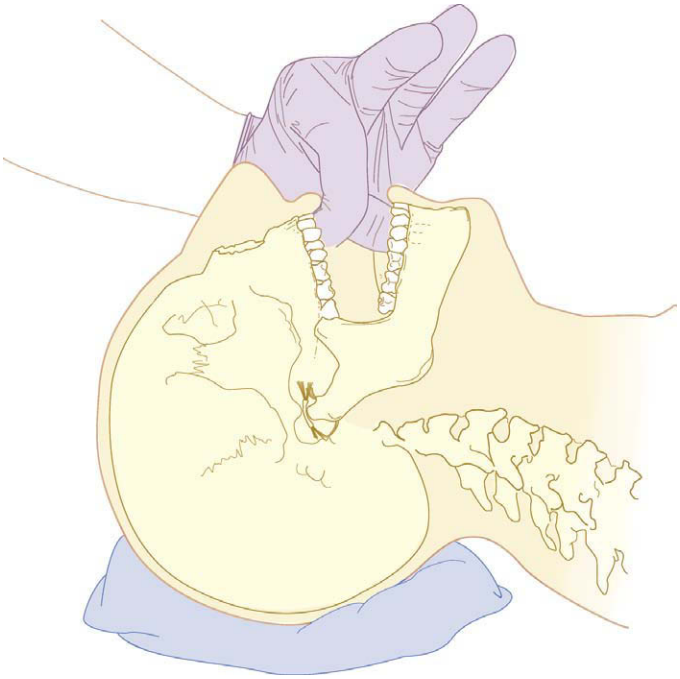


Figure 50-1 Scissors maneuver. The rotation and sliding components of the temporomandibular joint are used to achieve maximal mouth opening.

can impinge on the posterior wall of the nasopharynx, and application of increasing force when resistance is met can cause submucosal passage of the tube.

The larynx is situated at the upper end of the respiratory tract, where it extends from the epiglottis to the lower end of the cricoid cartilage. It evolved as a valve to protect the lower respiratory tract from alimentary contents and later developed into an organ of speech. The larynx bulges posteriorly into the laryngopharynx, with the piriform fossa lying on each side. The larynx consists of a framework of articulating cartilage connected by fascia, muscles, and ligaments. It is suspended from the hyoid bone by the thyrohyoid membrane. The principal cartilages are the thyroid, cricoid, and posterior (arytenoid, corniculate, and cuneiform) cartilage and the epiglottis. The cricoid cartilage is a complete ring that articulates with the thyroid and arytenoid cartilage. The arytenoid cartilage sits on the posterolateral border of the cricoid, from where it can be dislocated[4] during airway management. The laryngeal inlet is bounded by the epiglottis, aryepiglottic folds, posterior cartilage, and interarytenoid notch. The vocal cords run between the vocal processes of the arytenoid cartilage and the posterior surface of the thyroid cartilage. The lower end of the leaf-shaped epiglottis is attached to the middle of the posterior surface of the thyroid cartilage. The anterior surface is connected to the hyoid bone by the hyoepiglottic ligament and to the tongue by the median glossoepiglottic fold. The valleculae (often called vallecula) are depressions between the median and lateral glossoepiglottic folds that connect the lateral edges of the epiglottis to the base of the tongue. The Macintosh technique of laryngoscopy involves insertion of the tip of the laryngoscope into the vallecula, where it tensions the hyoepiglottic ligament to achieve indirect elevation of the epiglottis.

During swallowing the larynx is protected by several mechanisms. The larynx is tucked up behind the tongue, and the epiglottis diverts food away from the laryngeal inlet. The laryngeal

muscles can be grouped according to their actions on the vocal cords: abductors, adductors, and regulators of tension. Motor innervation to these muscles and the sensory innervation of the larynx are supplied by two branches of the vagus nerve: the superior and recurrent laryngeal nerves. The superior laryngeal nerve can be anesthetized at the point where it passes through the thyrohyoid membrane. The recurrent laryngeal nerve can be damaged during surgery on the thyroid gland or by pressure from a cuff that lies just below the vocal cords.[5]

The cricothyroid membrane joins the thyroid with the adjacent cricoid cartilage. It is close to the skin, relatively avascular, and the widest gap between the cartilage of the larynx and trachea, so it provides the best access for percutaneous airway rescue techniques. It is normally easy to palpate, but identification may not be possible in obese patients. In patients with fixed neck flexion, the cricothyroid membrane may lie behind the sternum.

The trachea extends from the lower edge of the cricoid cartilage to the carina. It consists of U-shaped cartilage joined by fibroelastic tissue and is closed posteriorly by the longitudinal trachealis muscle. The tracheal rings and trachealis muscle are responsible for the characteristic endoscopic appearance of the trachea.

Airway Assessment

Three basic decisions (Fig. 50-2) needed before induction of anesthesia in every patient[6] are whether

- To use awake endotracheal intubation
- To use a percutaneous technique
- To maintain spontaneous ventilation

These three strategies are safer than the use of an intravenous anesthetic with neuromuscular blocking drugs (NMBDs) in patients with potential airway difficulty, but they require more time and effort, and the anesthesiologist needs evidence on which to base these decisions. The purpose of airway assessment is to identify possible difficulty with direct laryngoscopy (and hence tracheal intubation), mask ventilation, or creation of a surgical (percutaneous) airway. This traditional approach may change with the introduction of sugammadex, an antagonist to replace neostigmine, into routine clinical practice (see Chapter 29). Rocuronium could be used to facilitate endotracheal intubation. If spontaneous ventilation is urgently needed, sugammadex can reverse profound neuromuscular blockade (i.e., no response to peripheral nerve stimulation) within 1.5 to 3.0 minutes.

Potential difficulty may be obvious in patients with anatomic or pathologic abnormalities, and further tests are not needed. Conditions requiring particular caution include lesions at the base of the tongue, recent onset of hoarseness, upper airway obstruction, and obstructive sleep apnea. However, the challenge is to detect potential difficulty in apparently normal patients. Airway assessment includes taking a history and performing a physical examination. Imaging is valuable in assessing a pathologic airway but is not practicable for routine assessment.

The *history* includes review of available previous anesthesia records, direct questioning of the patient, and in those with reduced consciousness, a search for communication about previous airway difficulty. A history of previous airway difficulty has a higher positive predictive value and lower negative predictive value than any tests.[7] However, a history of previous easy laryngoscopy does not guarantee straightforward intubation inasmuch as increased age or pathology may result in increased difficulty.

Airway tests to detect difficulty with direct laryngoscopy are based on anatomic features, and values have been selected as probable indicators of difficulty. The combination of mouth opening, jaw protrusion, and head extension is the core of airway assessment.[8] There is little interobserver variation in the assessment of mouth opening and jaw protrusion.[9] Mouth opening is measured as the interincisor distance, and a value of 4 cm (2 fingerbreadths) has been proposed as an indicator of probable difficult intubation.[10] The prognathic ability of the mandible depends on the size and shape of the mandible in relation to the maxilla and on TMJ function. Prognathic inability of the mandible (the mandibular incisors cannot be brought in line with the maxillary incisors) is associated with difficult intubation. Limited head (more accurately described as occipito-atlanto-axial) extension[10] impairs direct laryngoscopy. It can be measured as the angle between the occlusal surface of the maxillary teeth and the horizontal, with angles of less than 20 degrees suggesting difficult laryngoscopy. However, it is difficult to prevent extension of the midcervical vertebrae, so true head extension is frequently overestimated. The Mallampati test (visibility of pharyngeal structures) is of limited value on its own[11] but can be combined with an assessment of dentition.[12] The thyromental distance is of limited value as a predictor of difficult laryngoscopy,[13] but examination ensures that the laryngeal cartilage is palpated and submandibular compliance assessed. Evaluation of dentition is important in that caries or periodontitis increases the risk for dental damage. Some dental patterns, such as protruding or single or missing maxillary incisors,[14] increase the difficulty of direct laryngoscopy. The examination described by El-Ganzouri and colleagues[7] (assessment of mouth opening, prognathic ability, head extension, thyromental distance, and Mallampati test) has been used with minor modification by others.[3] It can be performed rapidly and contains the most quantifiable (recording of actual values is recommended) of the tests included in the ASA guidelines.[6]

Ventilation via mask requires the ability to achieve a seal between the mask and face and to overcome upper airway obstruction. Limited mandibular protrusion, abnormal neck anatomy, sleep apnea, snoring, and obesity are independent predictors of moderate or severe *difficulty with mask ventilation*. Snoring and a thyromental distance of less than 6 cm are independent predictors of severe difficulty.[15] No test can accurately predict complete failure of mask ventilation because its prevalence is as low as 0.07%.[7] Some pathologic causes of difficult mask ventilation cannot be predicted.[2]

Creation of a surgical airway (necessary for the management of a "cannot intubate, cannot ventilate" situation) depends on percutaneous access to the cricothyroid membrane. In some patients the cricothyroid membrane cannot be identified or lies behind the sternum, and creation of a percutaneous airway will not be possible. In such patients who have indications that laryngoscopy or mask ventilation will be difficult, the safest strategy is to secure the airway while the patient is conscious.

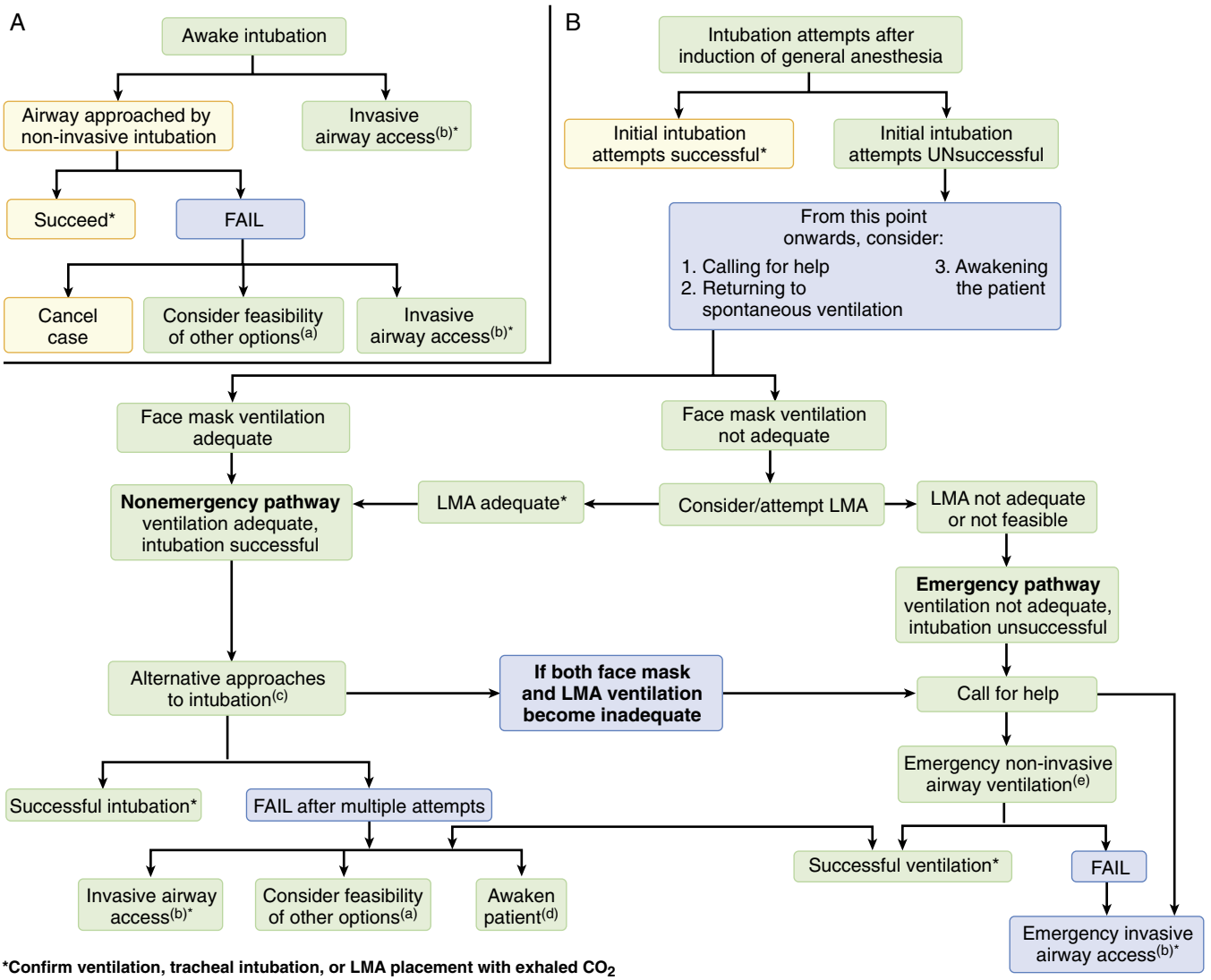
Integration of the evidence of difficulty with direct laryngoscopy, mask ventilation, and creation of a surgical airway has many limitations. The causes of difficult laryngoscopy are multifactorial, and single tests have limited value[11] as predictors. Prediction is improved by combining the results of different tests.[8]

Difficult Airway Algorithm

1. Assess the likelihood and clinical impact of basic management problems:
   - A. Difficult ventilation
   - B. Difficult intubation
   - C. Difficulty with patient cooperation or consent
   - D. Difficult tracheostomy
2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management:
3. Consider the relative merits and feasibility of basic management choices:

A	Awake intubation	vs.	Intubation attempts after induction of general anesthesia
B	Noninvasive technique for initial approach to intubation	vs.	Invasive technique for initial approach to intubation
C	Preservation of spontaneous ventilation	vs.	Ablation of spontaneous ventilation

4. Develop primary and alternative strategies:



***Confirm ventilation, tracheal intubation, or LMA placement with exhaled CO_2**

a. Other options include (but are not limited to) surgery utilizing face mask or LMA anesthesia, local anesthesia infiltration, and regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has beed reached via the Emergency Pathway.

b. Invasive airway access includes surgical or percutaneous tracheostomy or cricothyrotomy.

c. Alternative noninvasive approaches to difficult intubation include (but are not limited to) use of different larynoscope blades, LMA as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, retrograde intubation, and blind oral or nasal intubation.

d. Consider re-preparation of the patient for awake intubation or canceling surgery.

e. Options for emergency noninvasive airway ventilation include (but are not limited to): rigid bronchoscope, esophageal-tracheal Combitube ventilation, or transtracheal jet vantilation.

Figure 50-2 American Society of Anesthesiologists Difficult Airway Algorithm. *(From American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practice guidelines for management of the difficult airway. An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 98:1269-1277, 2003.)*

Scores[7,8] are formulas that combine the results of tests. These scores have been developed to improve prediction of difficulty but many omit at least one test of some value, and the indicators are not usually weighted for importance. It is more meaningful to describe the result of individual tests. Airway assessment cannot detect some serious problems, including asymptomatic lesions[2,3] in the vicinity of the larynx, skeletal factors, and some varieties of TMJ dysfunction.

The problem with airway assessment is that the risk of difficulty is overestimated and not all cases of difficult airway management can be predicted. However, serious airway morbidity, though infrequent, is a much worse outcome than performing an awake intubation that might not have been necessary. Airway evaluation gives some indication of potential difficulty and should always be performed.[6] The anesthesiologist must then make a judgment of whether direct laryngoscopy, mask ventilation, and percutaneous rescue are likely to be successful. The limitations of airway assessment mean that preparation of an airway strategy for the management of unanticipated difficulty is the ultimate key to safe practice. Strategies are discussed later in the section "Challenging Airway Management Scenarios."

Physiology and Pathophysiology of the Upper Airway

Upper Airway Obstruction

In an awake patient, airway patency is maintained by muscle tone in the head and neck, particularly the pharynx and tongue. As consciousness is lost and muscle tone is reduced, tissues fall backward under the influence of gravity in a supine patient and can obstruct the upper airway. The order of importance of these obstructing tissues is the soft palate (velopharynx), epiglottis, and tongue. Head extension (as a consequence of tensioning the strap muscles) and jaw thrust move the hyoid bone and attached structures anteriorly and relieve airway obstruction to a variable extent. Jaw thrust is also effective in reducing obstruction at the velopharynx in slim but not in obese patients. The lateral position can be used alternatively or in addition to the aforementioned techniques to allow the obstructing tissues to move downward so that obstruction is reduced.[16]

There is now evidence of an additional dynamic component of upper airway obstruction when consciousness is reduced. In the conscious state the tone of the pharyngeal muscles is increased by neural discharge just before phrenic nerve discharge. Loss of pharyngeal tone and collapse of the narrow velopharynx play an important role in upper airway obstruction during spontaneous ventilation in an anesthetized patient.[17] The airway in the nose and nasopharynx is held open by bone and cartilage and in the larynx and trachea by cartilage. Dynamic collapse of the intervening pharynx can occur when muscle tone is reduced. The structure of a collapsible segment between two rigid tubes corresponds to the basic elements of a Starling resistor in that flow can depend on the intraluminal pressure gradient or on transmural pressure in the collapsible area.[17] Flow through the collapsible segment depends on how the intraluminal pressure upstream and downstream relate to the tissue pressure around the pharynx. Factors that narrow the pharynx, increase pressure around it, reduce pressure within it, or make its walls more compliant will increase upper airway obstruction. The therapeutic consequence of dynamic collapse is that nasal continuous positive airway pressure (CPAP) reduces dynamic upper airway obstruction. Nasopharyngeal airways might reduce this dynamic airway obstruction.

Laryngospasm

Laryngospasm (reflex closure of the true vocal cords alone or with the false cords because of stimulation of the intrinsic laryngeal muscles) can result from the combination of reflex hyperactivity at an intermediate depth of anesthesia and noxious distant surgical or local stimuli. Laryngospasm is usually maintained well beyond the duration of the stimulus. It is responsible for a significant proportion of postoperative critical events. Morbidity and mortality may result from the immediate (hypoxemia and hypercapnia) and delayed ("negative-pressure pulmonary edema") consequences of laryngospasm, and thus every effort should be made to rapidly relieve the airway obstruction caused by laryngospasm.[18] Management is discussed later.

Negative-pressure pulmonary edema[18] is a consequence of forceful inspiratory effort in the presence of a closed glottis or other cause of upper airway obstruction. The subatmospheric alveolar pressure generated promotes transudation of fluid from pulmonary capillaries into the interstitial space and alveoli. Small vessel damage may be responsible for frank hemorrhage into alveoli. Management consists of relief of the obstruction, oxygen therapy, and standard management of pulmonary edema. Most cases resolve rapidly, but reintubation and positive-pressure ventilation are sometimes required.

Oxygenation and Preoxygenation

Hypoxemia can occur in the time between induction of anesthesia and attainment of airway security and is particularly likely if airway management proves difficult. It makes sense to maximize oxygen stores before induction to prolong the period before the onset of hypoxemia in the event of serious difficulty with airway management. The principal oxygen stores are in the lungs. These stores can be increased by using a maneuver called "preoxygenation" (also know as denitrogenation), which is achieved by having the patient breath 100% oxygen from a close-fitting facemask before induction of anesthesia. Several techniques of preoxygenation have been described, and the most effective technique should be used. Deep breathing with a high fresh gas flow for 1.5 minutes and tidal breathing for 3 minutes are equally effective. It is particularly important to avoid leaks in the circuit, which are indicated by a flaccid reservoir bag and absence of a normal capnograph waveform. Wherever possible, the end-tidal oxygen concentration should be used as a guide to the adequacy of preoxygenation, with a value of 90% being well accepted. Preoxygenation in the semi-sitting position prolongs the time to development of hypoxemia by increasing functional residual capacity in relation to the supine position, particularly in an obese patient.[19] Use of positive end-expiratory pressure (PEEP) during induction may further improve oxygenation.[20]

Pharmacology of Airway Management

The choice of pharmacologic technique is part of the essential planning of airway management and will be influenced by both airway and surgical requirements, particularly for surgical access and neuromuscular blockade. Satisfactory conditions for tracheal intubation are particularly demanding and may be facilitated by several pharmacologic techniques, each of which has advantages and disadvantages. Direct laryngoscopy is facilitated by a reduction in tone of the head and neck muscles. A high success rate and low risk for laryngeal trauma are facilitated when the vocal cords are open and nonreactive, at the cost of reduced protection against pulmonary aspiration.

Inhaled Induction of Anesthesia

Induction plus maintenance of anesthesia by the inhalation of gaseous and volatile anesthetics was the original pharmacologic technique for anesthesia. It remains an important technique in situations such as lack of venous access and anticipated airway difficulty in a patient who refuses awake techniques. A major advantage of inhaled induction of anesthesia is that spontaneous ventilation is maintained while changes in the depth of anesthesia and associated respiratory and cardiovascular effects occur gradually. Good facemask technical skills are essential to prevent airway obstruction and leaks around the mask.

Deep anesthesia is necessary for direct laryngoscopy and tracheal intubation with inhaled anesthetics alone. It can be complicated by hypotension, hypoventilation, and airway obstruction. A depth of anesthesia that allows controlled ventilation has been recommended when sevoflurane is used. Prior administration of topical anesthesia (e.g., 4% lidocaine, 3 to 5 mL) can facilitate tracheal intubation under lighter inhaled anesthesia.

Sevoflurane has advantages over other volatile anesthetics for inhaled induction of anesthesia. It has a low blood-gas partition coefficient and causes minimal airway irritation, which facilitates rapid smooth attainment of a depth of anesthesia sufficient for airway procedures. A rapid technique ("single breath") in which the patient breathes 8% sevoflurane from a prefilled anesthesia circuit has been advocated rarely but causes apnea more frequently than the traditional technique does. Furthermore, seizure activity with sevoflurane is more likely with rapid induction of anesthesia.[21]

Inhaled induction of anesthesia is very useful in a wide variety of difficult airway conditions. Its use has been advocated in patients with stridor but can result in sudden airway obstruction, which prevents rapid reduction of the depth of anesthesia. Relief of obstruction may be difficult or impossible, even when CPAP is used with mask ventilation, so emergency cricothyrotomy may be required. Propofol infusion, with topical anesthesia before endotracheal intubation, has been used successfully for the management of patients with a difficult airway.[22] Caution is required because apnea can occur when propofol is infused in patients with normal airways.

Intravenous Anesthesia with Neuromuscular Blocking Drugs

The combination of an intravenous anesthetic with an NMDB is the pharmacologic technique most frequently used for tracheal intubation in routine practice (see Chapter 29). It provides good conditions rapidly in most patients inasmuch as neuromuscular blockade facilitates laryngoscopy, opens the vocal cords, and prevents coughing. The high quality of intubating conditions produced by NMBDs reduces the risk for postintubation laryngeal damage.[23] However, the apnea caused by this pharmacologic approach has disadvantages. If tracheal intubation of an apneic patient proves impossible, oxygenation requires effective ventilation with a facemask or SAD, neither of which is completely reliable. Pharmacologic techniques that produce apnea should not be used when difficulty with tracheal intubation or mask ventilation is predicted. As indicated previously, the use of sugammadex may alter the approaches to difficult intubation.

In routine practice, nondepolarizing NMBDs are often preferable to succinylcholine to prevent its side effects (as described in Chapter 29). Succinylcholine is chosen when rapid onset and offset are important. Use of rocuronium as an alternative to succinylcholine has been suggested to avoid the side effects unique to succinylcholine. Although the duration of paralysis produced by rocuronium is very much longer, the use of sugammadex as a reversal agent makes recovery from an NMBD as quick as that from succinylcholine and more predictable. It is now clear that a combination of rocuronium and sugammadex can restore spontaneous ventilation more rapidly than waiting for succinylcholine to wear off. Possibly the need for succinylcholine may disappear completely.

Intravenous Anesthesia with Narcotics

The use of short-acting narcotics instead of NMBDs to facilitate tracheal intubation has been advocated as a means of avoiding the side effects of succinylcholine. This technique is effective in many patients who have no risk factors for difficult intubation. However, it has serious disadvantages.[24] Conditions for direct laryngoscopy and tracheal intubation are worse than when NMBDs are used, so there is a higher frequency of failed intubation and airway trauma. Arterial hypotension is more likely when large doses of intravenous anesthetics and narcotics are given.[24] A higher incidence of laryngeal trauma when intubation is performed without NMBDs has been reported.[23] Use of a large dose of narcotics when ventilation with a facemask or SAD is intended has other significant disadvantages. It may produce apnea and delay the return of spontaneous ventilation. More importantly, it can make ventilation of the lungs with a mask or SAD difficult or impossible as a consequence of vocal cord closure, a problem sometimes attributed to "chest wall rigidity."[25] The combination of intravenous anesthesia with topical anesthesia of the larynx produces good conditions[26] and may be a better alternative to the use of NMBDs.

Local Anesthetic and "Awake" Techniques of Airway Management

Tracheal intubation of a conscious patient can allow uninterrupted respiration and airway protection while avoiding the risk to airway maintenance and protection inherent with general anesthesia. It is indicated when there is a possibility of difficulty with airway management. Tracheal intubation of a conscious patient is often called "awake" intubation. Good topical airway anesthesia, rapport, and gentleness are the keys to success. Sedation is often used but cannot compensate for inadequate topical anesthesia and is dangerous in patients with a critical airway.[27]

Topical anesthesia of the airway can be used to facilitate the performance of many airway procedures (Box 50-1) in a conscious patient in whom reduced consciousness is likely to cause difficulty in airway management. Direct laryngoscopy has long been used for awake intubation but is often difficult and can be distressing for all involved. Use of a flexible fiberoptic laryngoscope (FFL) for tracheal intubation under topical anesthesia was a milestone in safe airway management because intubation of a conscious patient could now be achieved with minimal discomfort. This technique has become the standard for management of an anticipated difficult airway. Options are preserved if awake flexible fiberoptic intubation is not successful: surgery can be postponed and the patient awakened, an unhurried surgical airway can be performed, or tracheal intubation can be attempted in a breathing patient (awake or inhaled induction) with other visual techniques.

Topical anesthesia reduces the caliber of a normal airway. Use of topical anesthesia in a patient with a compromised airway can lead to loss of the airway and should be performed only by experts who have a team prepared for immediate creation of a surgical airway.

Lidocaine has a better safety profile than other agents used for airway anesthesia. However, excessive doses can cause fatal toxicity. Administration should be titrated and the mental state of the patient monitored. Blood concentrations are influenced by the technique chosen, and aerosol delivery to the lower respiratory tract should be minimized.

Several techniques of airway anesthesia are shown in Box 50-2. Each has advantages and disadvantages. Nebulizers have been used to deliver topical anesthesia to the airway. The optimum particle size is larger than that required for the treatment of asthma. Simple aerosol techniques, such as injection into oxygen flowing in a narrow tube, appear to work satisfactorily. Most of the inhaled solution is exhaled, and up to 20 minutes may be required to achieve satisfactory topical anesthesia. Inhalation of an aerosol of local anesthetic is usually well tolerated and can anesthetize the entire respiratory tract. The quality of topical anesthesia achieved with nebulizers is not as good as that achieved with other techniques, but it is a useful option when other techniques cannot be used or coughing is particularly undesirable.

Box 50-1 Airway Techniques That Can Be Performed Under Topical Anesthesia in an Awake Patient

"Supraglotti airway device insertion
Direct laryngoscopy and intubation
Blind nasal intubation
Retrograde intubation
Flexible fiberoptic laryngoscopy and intubation
Rigid indirect optical devices and intubation
Tracheotomy/Cricothyrotomy"

Box 50-2 Techniques of Airway Anesthesia

Nebulizers—entire airway
Topical sprays and gels—upper airway
Transtracheal injection—larynx and trachea
"Spray as you go"—larynx and trachea
Nerve blocks—distribution of the nerve supply
Combinations of the above

Local anesthetic sprays and gels achieve rapid topical anesthesia of the nose, mouth, and pharynx. Pressurized aerosol sprays contain preservatives that may cause a sore throat postoperatively, and they are less effective than gels. Lidocaine 4% administered by a spray attachment for syringes is popular. The first spray is pungent and patients should be warned. Lidocaine gel (2%) is very effective and well tolerated, but subsequent optical images through the gel may be slightly impaired. Most of the lidocaine applied with sprays or gels is swallowed and the absorbed drug metabolized in first-pass hepatic metabolism.

Topical anesthesia of the larynx and trachea may be achieved by transtracheal injection or a "spray as you go" (SAYGO) technique. SAYGO is an intermittent application technique that causes coughing and requires time for recovery after each application. Use of an epidural catheter within the working channel of the fiberscope is an effective means of administering SAYGO. Transtracheal injection through the cricothyroid membrane is more invasive but quickly produces good topical anesthesia. Coughing spreads the local anesthetic. A bolus of narcotic is frequently given before transtracheal injection to prevent excessive coughing. Narcotics themselves can cause coughing, which can be suppressed by the inhalation of salbutamol or beclomethasone or by intravenous lidocaine.[28] The quality of transtracheal anesthesia is preferred by patients and endoscopists over that produced by nebulizers or SAYGO.

Nerve blocks produce more profound and longer-lasting anesthesia than topical anesthesia does. A superior laryngeal nerve block created by injection through the thyrohyoid membrane is the least invasive of the airway nerve blocks and provides good anesthesia of the area between the vocal cords and the epiglottis.[29]

Facemask Airway

Facemask techniques are a core skill that often requires considerable expertise. Use of a facemask with spontaneous ventilation throughout induction and maintenance of anesthesia with inhaled agents is the simplest and least invasive anesthesia technique. It

is very suitable for short operations in all patients except those with an increased risk of vomiting or regurgitation. Facemasks are also used for controlled ventilation before and after the use of tracheal tubes.

Facemasks are designed to form a seal around the mouth and nose and to connect to a resuscitator or anesthesia circuit. The two key elements of the technique are maintenance of a good seal between the mask and the patient's face and an unobstructed airway. Clinical signs of air leak and airway obstruction must be sought constantly. The quality of the seal during spontaneous ventilation is monitored by observing the fullness and movement of the reservoir bag. Leaks occur most frequently around the nose and cheeks, the latter particularly in edentulous patients with concave cheeks. It is possible to compensate for a leak by using a high fresh gas flow, but use of the oxygen flush facility on the anesthesia machine will dilute the concentration of any inhaled agents being administered.

The pathophysiology of upper airway obstruction has been considered. The clinical features of airway obstruction depend on the site and degree of obstruction and whether spontaneous breathing or positive-pressure ventilation is being used. Laryngospasm may be a component of airway obstruction and is considered separately. The most important signs of airway obstruction are clinical. Noisy respiration ("snoring" with supraglottic obstruction and inspiratory stridor with glottic obstruction) is a classic sign of airway obstruction during spontaneous ventilation. However, noise depends on airflow, which is determined by the degree of obstruction and the respiratory drive. Powerful inspiration in the presence of airway obstruction produces the combination of inward movement of the upper chest region and outward movement of the lower chest and upper abdominal regions, thereby creating the classic "seesaw" movement sign. Powerful descent of the diaphragm in the presence of severe obstruction results in tracheal tug. Movement of the reservoir bag is a guide to tidal volume, which can be supplemented by electronic measurement. Reliance on the capnograph alone is dangerous. Serious hypercapnia caused by airway obstruction can exist despite a satisfactory Spo_2.

Radiology studies have shown that head extension is the most important single maneuver for maintaining space between the pharyngeal soft tissues. Head extension stretches the anterior neck structures and moves the hyoid bone and attached structures anteriorly. In patients with an unstable cervical spine, head extension should be used only if all other airway maneuvers fail to overcome the airway obstruction. Jaw thrust, achieved by exerting anterior pressure behind the angles of the mandible, uses the sliding component of the TMJ to move the mandible, hyoid bone, and attached structures anteriorly. Considerable strength is sometimes required to overcome airway obstruction with head extension and jaw thrust. Use of the lateral position can dramatically reduce airway obstruction.[16]

If head extension and jaw thrust fail to maintain an unobstructed airway, options include insertion of an oropharyngeal airway, nasopharyngeal airway, or SAD and tracheal intubation. An oropharyngeal airway (Fig. 50-3) is normally the first choice, provided that sufficient mouth opening is possible. The airway should be inserted only when the pharyngeal and laryngeal reflexes are depressed to minimize the risk of provoking coughing and laryngospasm. The risk of damage to the teeth during the insertion of oropharyngeal airways is increased in the presence of caries and gingivitis.

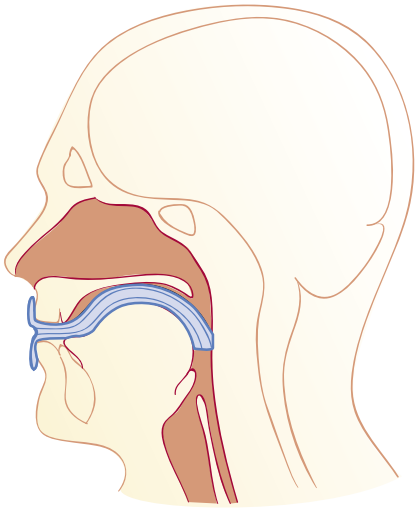


Figure 50-3 Oropharyngeal airway in place. The airway follows the curvature of the tongue. It pulls the tongue and the epiglottis away from the posterior pharyngeal wall and provides a channel for the passage of air. *(Adapted from Dorsch JA, Dorsch SE: Understanding Anesthesia Equipment, 4th ed. Baltimore, Williams & Wilkins, 1999.)*

If airway obstruction is not improved with the oropharyngeal airway, the next step has traditionally been insertion of a nasopharyngeal airway (Fig. 50-4), which often dramatically improves the airway. Nasopharyngeal airways may be preferable to oropharyngeal airways in the presence of limited mouth opening and dental caries or gingivitis. Once in place, a nasopharyngeal airway is less stimulating than an oral airway and better tolerated by lightly anesthetized patients. Insertion of a nasopharyngeal airway can cause epistaxis as a consequence of damage to the nasal mucosa, polyps, turbinates, or other tissues. This risk is minimized by gentle insertion of a well-lubricated small airway and termination if resistance is met. Unless other measures fail to maintain an adequate airway, nasopharyngeal airways should not

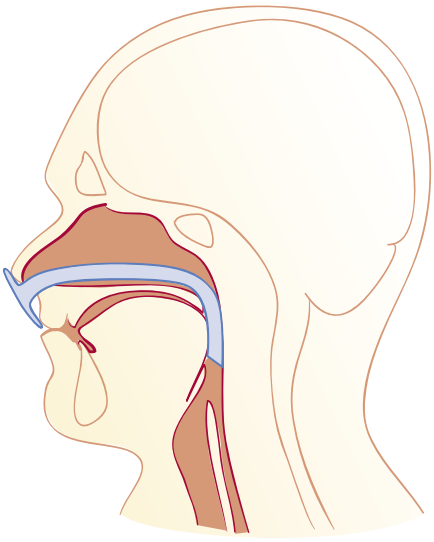


Figure 50-4 The nasopharyngeal airway in place. The airway passes through the nose and ends at a point just above the epiglottis. *(Adapted from Dorsch JA, Dorsch SE: Understanding Anesthesia Equipment, 4th ed. Baltimore, Williams & Wilkins, 1999.)*

be used in patients with basal skull fracture because of the risk of intracranial insertion. Ventilation through an SAD may be successful when facemask ventilation fails. A laryngeal mask airway (LMA) is now frequently inserted before trial of a nasopharyngeal airway if mouth opening is adequate and the depth of anesthesia is sufficient. Successful tracheal intubation will improve the airway when facemask ventilation is inadequate but may be hazardous because difficulty with facemask ventilation is associated with difficult tracheal intubation.

When airway obstruction makes facemask positive-pressure ventilation difficult, any of the aforementioned maneuvers may be used. Use of increased airway pressure has a good theoretical basis as a means of overcoming dynamic airway obstruction. Two-person techniques are of proven value. The more experienced person maintains head extension, bimanual jaw thrust, and mask seal while an assistant squeezes the reservoir bag under supervision. Excessive airway pressure should be avoided because it may insufflate gas into the stomach, thereby increasing the risk for regurgitation. Mask ventilation may be difficult or impossible,[2] particularly when cricoid pressure is applied.

Laryngospasm during Anesthesia

The pathophysiology of laryngospasm has been discussed. Laryngospasm during surgery can occur during use of a facemask or SAD. The clinical picture depends on the degree of obstruction and the respiratory drive. High-pitched inspiratory stridor is a classic sign, but complete airway obstruction is silent. Obstruction must be relieved rapidly to prevent hypoxemic damage and the development of negative-pressure pulmonary edema.[18] Mild laryngospasm should be managed initially with positive-pressure ventilation by facemask along with head extension and jaw thrust. The Larson maneuver of inward pressure in the "laryngospasm notch" (between the mandible and mastoid process) has no disadvantages and should be attempted.[30] When laryngospasm is severe with complete glottic closure, attempted facemask positive-pressure ventilation is ineffective because it distends the piriform fossae and presses the aryepiglottic folds more firmly against each other. The depth of anesthesia may be increased rapidly with intravenous anesthetics (preferably propofol). Stimulating surgery should be interrupted. If the obstruction or hypoxemia does not improve, a small dose (e.g., 0.1 mg/kg) of succinylcholine can relax the vocal cords for about 2 minutes and give time to increase the depth of anesthesia. This dose usually causes brief apnea, and laryngospasm may recur when neuromuscular transmission recovers. If the obstruction or hypoxemia is severe, an intubating dose of succinylcholine followed by tracheal intubation is indicated. If tracheal intubation fails, a percutaneous airway will be necessary.

Supraglottic Airway Devices

SADs have been used widely since the 1990s. They provide an airway intermediate between the facemask and tracheal tube in terms of anatomic position, invasiveness, and security. All are designed to form a seal in the pharynx between the respiratory and digestive tracts to protect the airway and facilitate gas exchange. All have a proximal tube that is connected to an anesthesia circuit or other device. All SADs are inserted blindly, and tests are then used to determine whether their function is satisfactory. Many classifications have been proposed; a simple differentiation is between esophageal obturator and periglottic devices.

Esophageal Obturator Devices

A tube with a closed distal end that is designed for passage into the esophagus is common to all esophageal obturator devices. A distal seal in the esophagus is provided by an inflatable cuff, and a proximal seal is achieved with a facemask or oropharyngeal cuff. Holes in the tube between the proximal seal and the distal cuff deliver gases to the laryngopharynx. The Combitube has been widely used in prehospital care. The proximal seal is provided by an oropharyngeal cuff. It has a second open-ended tube that can function as a tracheal tube if it is inadvertently inserted into the trachea. It gives protection against regurgitation similar to that provided by modern periglottic devices. The incidence of esophageal damage should be reduced when the SA (small adult) size is used. Its performance is inferior to that of the ProSeal LMA (PLMA) and the Laryngeal Tube Sonda (LT),[31] but it has been successful when other devices have failed. The LT is a single-lumen esophageal obturator device in which both cuffs are inflated from a single inflation line. Multiple- and single-use versions are available, and the size and number of holes between the two cuffs have been increased. Placement is rapid and the incidence of laryngospasm and coughing is low. The LT achieves a high leak pressure, thus facilitating higher airway pressure than with the LMA classic (LMAc) during positive-pressure ventilation. The LT has been used successfully in the "cannot intubate, cannot ventilate" situation and LMA failure. A gastric drainage tube was added in the "Sonda" models and perform well.[31] Other esophageal obturator devices are also available.

Periglottic Devices

Periglottic devices form a seal around the larynx, usually with an inflatable cuff. Most clinical experience has been with the LMA family of devices, and only these will be described in detail here. This does not imply that other devices are not of value.

The original LMA (now also known as the LMAc) was introduced into clinical practice in 1988 and has been used in more than 200 million patients. All LMAs have three main components: mask, airway tube, and inflation line. The mask has a bowl surrounded by an inflatable cuff, which is designed to form an airtight and fluid-tight seal round the larynx. The airway tube has a standard 15-mm connector.

Technique

Large LMAs may increase the risk for sore throat postoperatively but achieve a better seal.[32] An LMA is inserted blindly and thus gentleness is important.[33] Several insertion techniques will achieve an acceptable position and function in most patients. The technique developed over many years by Archie Brain (the inventor) (Fig. 50-5) is reliable but not always successful, and alternative techniques are sometimes needed. The "sniff" position is recommended for insertion of an LMA.

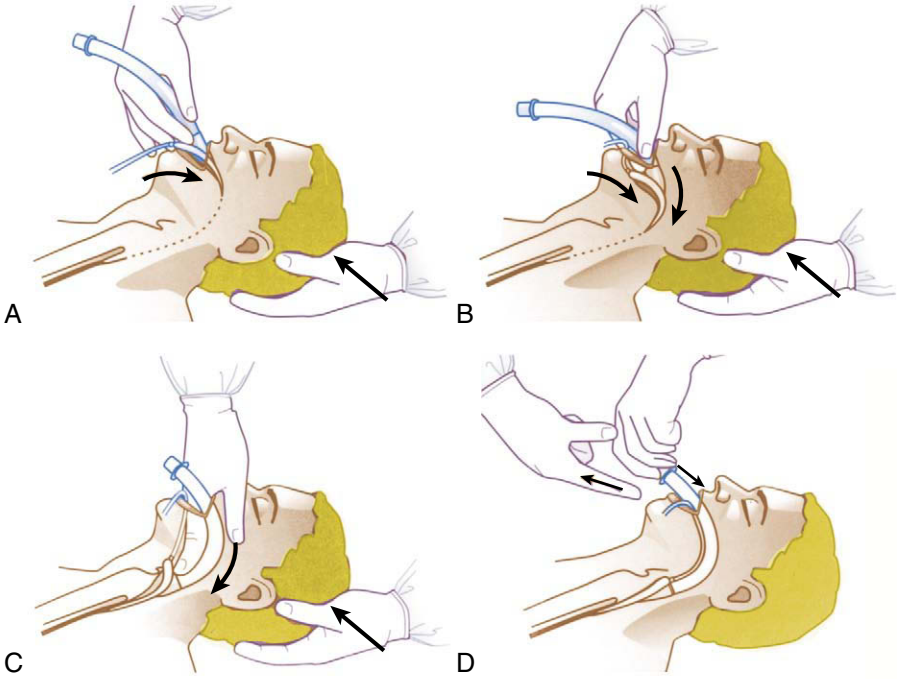


Figure 50-5 Insertion of a laryngeal mask airway (LMA). **A,** The tip of the cuff is pressed upward against the hard palate by the index finger while the middle finger opens the mouth. **B,** The LMA is pressed backward in a smooth movement. Notice that the nondominant hand is used to extend the head. **C,** The LMA is advanced until definite resistance is felt. **D,** Before the index finger is removed, the nondominant hand presses down on the LMA to prevent dislodgment during removal of the index finger. The cuff is subsequently inflated, and outward movement of the tube is often observed during this inflation. *(Courtesy of LMA North America, Inc., San Diego, CA.)*

Propofol or sevoflurane give good conditions for insertion of an LMA. The combination provides particularly good conditions with a low incidence of apnea and movement during insertion.[34] Short-acting narcotics improve the ease of insertion and airway patency.[35] Alfentanil (10 µg/kg) suppresses swallowing, coughing, gagging, and laryngospasm without unduly long apnea. Intravenous lidocaine facilitates LMA insertion and reduces the incidence of coughing and airway obstruction. Insertion should be performed only after an adequate depth of anesthesia has been achieved, best demonstrated by the ability to perform a "jaw thrust." The recommended technique involves passing the device along the palate and then the posterior pharyngeal wall until resistance increases, at which point the tip should be lie within the upper esophageal sphincter. This route should reduce the risk of posterior displacement of the epiglottis. Malposition of the LMA is less likely if jaw thrust or direct laryngoscopy is used to assist insertion. The laryngoscope-assisted technique has been successful when the standard technique has failed.

When resistance to insertion is detected, the tube is left free while air is inflated into the cuff. Inflation to the maximum recommended volume produces high cuff pressure and suboptimal function. Inflation to a cuff pressure not higher than 60 cm H_2O is recommended. The tube is connected to the anesthesia circuit and gentle manual ventilation begun. Initial checks of LMA function are now performed. Lung expansion is observed. Slow refill of the reservoir bag is a feature of airway obstruction. Auscultation over the neck may detect sounds of respiratory obstruction. When airway obstruction is detected, examination with an FFL is recommended because management of LMA impaction in the glottis is different from that of vocal cord closure.

LMA function is now assessed in more detail (Box 50-3). Two tests that correlate well with optimum position are the ability to generate an airway pressure of 20 cm H_2O and the ability to ventilate manually.[36] Gas exchange and the possibility of obstruction are assessed by capnography, expired tidal volume, and the flow-volume loop. Airway "leak" pressure may be used to quantify the efficacy of the seal between the mask and the larynx and indicates both the feasibility of positive-pressure ventilation and the degree of airway protection. The test is performed by determining the airway pressure at which gas escapes.

An effective seal depends on the size and position of the LMA, inflation of the cuff, low airway resistance, and high pulmonary compliance. Poor initial function may be caused by laryngospasm or bronchospasm. Withdrawal followed by readvancement (the up-down maneuver) may improve position and function of the LMA. The number of maneuvers should be limited because airway obstruction is occasionally caused by undiagnosed laryngeal lesions or laryngeal closure. If the airway remains unsatisfactory, the anesthesiologist may reinsert the same or a different size of LMA and accept some leakage, or use a facemask or tracheal intubation.

Box 50-3 Assessment of Function of the Laryngeal Mask Airway

- Observation of airway pressure and chest movement with a manual ventilation
- Reservoir bag refill during expiration
- Capnograph
- Auscultation over the neck
- Cuff leak pressure
- Expired tidal volume and flow-volume loop
- Examination with a flexible fiberoptic laryngoscope

The laryngeal mask is secured. A bite block should be inserted and remain in place until the LMA has been removed to reduce the possibility that biting will obstruct the airway or damage the tube.

Airway Obstruction

The final position of the LMA in relation to the vocal cords, epiglottis, and upper part of the esophagus varies greatly and has been investigated with the FFL. The average views obtained in 26 studies included an unobstructed view of the vocal cords in 40% and no view of the vocal cords in 6%.[37] Malposition occurs in 50% to 80% of patients, is usually associated with an undefined "clinically acceptable" airway,[37] but can adversely affect the quality of the airway.

There have been few scientific investigations of airway resistance as a measure of obstruction during the clinical use of SADs. An important study showed that although median airway resistance was similar in the LMA (plus larynx) and tracheal tube groups, airway resistance was greatly increased in 3 of 12 patients in the LMA group, indicative of significant airway obstruction.[38] Conversion to tracheal intubation has been required in 11.4% of patients in whom the LMA was used for tonsillectomy.[39] Head extension and jaw thrust have been required in 5% of patients. Failure to achieve a satisfactory airway occurred in 4.7% of LMA patients in one large study.[10] Variation in the incidence of "acceptable" or obstructed airways may be partly a consequence of differences in clinical criteria. Airway obstruction unresponsive to simple measures should be no more acceptable than with a facemask and should be relieved. Reversion to a facemask is often effective. Emergency intraoperative tracheal intubation is sometimes necessary and is likely to be more hazardous than elective intubation (Box 50-4).

Pulmonary Aspiration

The seal achieved by LMAs provides less protection against pulmonary aspiration than a properly inserted cuffed tracheal tube does. LMA malposition in which the upper end of the esophagus lies within the bowl of the LMA increases the risk that regurgitation or vomiting will result in pulmonary aspiration and has been reported in a third (or more) of patients. Massive pulmonary aspiration during LMA anesthesia is infrequent but can lead to death or serious morbidity.[40] The LMA should not be used in patients with an increased risk for regurgitation or vomiting.

Positive-pressure ventilation, with or without NMBDs, is frequently used with the LMA. Despite reports of safe use in large series, there is concern about the safety of this practice.[41] Positive-pressure ventilation increases the risk for gastric insufflation, which in turn increases the risk for regurgitation.

Box 50-4 Hazards of Intraoperative Tracheal Intubation

Surgery—Adverse Effects
Interruption
Sterility, integrity, and outcome threatened

Tracheal Intubation Problems
Patient position suboptimal
Hypoxemia and risk of increased hypoxemia
Risk of tissue trauma

Removal of the Laryngeal Mask Airway

Laryngeal function is depressed after LMA use.[42] Monitoring and oxygen administration should be continued during emergence from anesthesia. Removal of the LMA should always be carried out at locations where personnel and equipment are available to perform tracheal intubation. Most keep the LMA in place until consciousness recovers, airway reflexes return, and patients can open their mouth on command. Removal with the cuff inflated is associated with a higher incidence of hoarseness but not overall airway complications, and many recommend this technique.

Comparison of the Laryngeal Mask Airway with the Facemask and Tracheal Tube

Basic skill is mastered more readily with an LMA than with a facemask. A reasonable success rate is achieved more rapidly with an LMA than with the Macintosh technique of tracheal intubation. A greater degree of skill is required for tracheal intubation. An LMA is inserted blindly, whereas a tracheal tube is normally inserted under vision. Difficulty in LMA insertion occurs in at least 4.5% of patients, a incidence comparable to that of difficulty with the Macintosh technique. LMA insertion causes less hemodynamic stimulation than laryngoscopy and tracheal intubation do. The LMA has advantages over tracheal intubation at the time of "extubation." The incidence of minor laryngopharyngeal morbidity is similar with both devices. However, coughing is less frequent at LMA than at tracheal tube removal, and adverse hemodynamic effects occur less frequently. The glottic aperture is narrowed after tracheal intubation but not with use of an LMA.[42]

Complications and Contraindications

There are few published reports of serious complications as a consequence of LMA use, but there have been unreported deaths and cases of brain damage.[43] Less serious complications include nerve damage.

Role of the Laryngeal Mask Airway

The LMA is extremely useful when used conservatively and has proved valuable as a rescue device. The LMA is a key device at several places in the ASA algorithm for difficult airways.[6] There are many reports of successful use of an LMA as a rescue airway when tracheal intubation had failed, including the "cannot intubate, cannot ventilate" situation, and lives have been saved. However, the LMA does not always provide a satisfactory airway in the failed tracheal intubation situation.[2] Cricoid pressure can interfere with the insertion and function of SADs and should be reduced to a level that allows successful insertion and adequate function. An LMA may be used to allow completion of surgery if the latter cannot be postponed, although there is a risk of airway obstruction and pulmonary aspiration. The most prudent course is to postpone surgery and awaken the patient or to convert to tracheal intubation with a visual technique such as the Aintree intubating catheter (AIT).

Elective use of an LMA in a patient with a known or anticipated difficult airway has serious disadvantages. The difficult airway remains and the development of airway obstruction could produce a critical situation that requires immediate percutaneous

airway rescue. Asai states, "It is inadvisable to rely on the LMA when tracheal intubation is predicted to be difficult."[43a] Although the LMA has been inserted under topical anesthesia, gagging, coughing and a high incidence of sore throat have been reported.[44] The LMA has failed to provide a satisfactory airway in patients with micrognathia, previous oral or cervical radiotherapy, and laryngeal abnormalities and disease. Insertion of an LMA is frequently difficult in patients in whom tracheal intubation is difficult. Use of an LMA when the patient's position is other than "sniff" will delay conversion to tracheal intubation when necessary. The development of airway obstruction with such positions places the patient at risk, requires rapid repositioning of the patient by staff, and jeopardizes the surgical outcome. The risks associated with intraoperative tracheal intubation (see Box 50-4) will be increased.

The LMA has been used safely for major surgery, but the user must be very experienced with both the LMA and tracheal intubation, and that is the paradox. If future generations of anesthesiologists were to have less skill in tracheal intubation, use of an LMA instead of tracheal intubation for major surgery would become more risky. Skill in tracheal intubation is essential, and it is generally the safer option. Insertion of an LMA is regarded as less stressful for the anesthesiologist than the use of direct laryngoscopy for tracheal intubation. However, a tracheal tube is a more reliable airway that provides better protection against pulmonary aspiration. Most comparisons with tracheal intubation have used the Macintosh laryngoscope, the limitations of which are now better understood.[45] It is probable that problems and complications with tracheal intubation will become less frequent as alternative intubation techniques are used more regularly.[46,47] Expediency and some minor advantages of SADs must be offset against lower airway security and reliability. Patient safety must always be the prime concern.

Newer Supraglottic Airway Devices

Flexible, intubating, and ProSeal LMAs have been introduced. Several changes have been made to improve the performance of newer models. The LMA Flexible has a wire-reinforced, flexible airway tube designed to resist kinking during oral or other head and neck surgery. Some SADs introduced by other manufacturers perform well. The i-gel and LMA Supreme seem very promising, but there are still limited data and other new devices will certainly appear.

ProSeal Laryngeal Mask Airway

The PLMA was designed to facilitate positive-pressure ventilation with higher airway pressure than possible with the LMAc. A second posterior cuff and deeper bowl were designed to improve the seal around the larynx. The PLMA has a drainage tube to provide access to the esophagus. Other features of the PLMA include a reinforced airway tube that is narrower than that of the LMAc and an integrated bite block. The tip of the PLMA lacks the semirigid back plate of the LMAc.

Insertion Technique

A greater depth of inhaled and intravenous anesthesia is required for insertion of a PLMA than an LMAc. The technique of PLMA insertion is more demanding than that for an LMAc, but a high success rate can be achieved.[48] This effort is rewarded by a superior quality of airway. Airway seal pressure is increased by 50% in relation to the LMAc, thus facilitating positive-pressure ventilation and probably providing better airway protection. The device may be introduced digitally or with a special introducer. An alternative laryngoscope introducer technique has been developed to prevent folding of the mask tip during insertion. A lubricated introducer is passed through the PLMA drainage tube so that it protrudes beyond the tip. A Macintosh laryngoscope is used to facilitate insertion of the introducer into the esophagus. The laryngoscope is then removed and the PLMA inserted by using the introducer as a guide. This technique may be the most reliable but is most invasive method of PLMA insertion. After insertion, the PLMA cuff is inflated to a pressure not greater than 60 cm H_2O.

An incorrectly placed PLMA will result in unreliable or obstructed ventilation. The diagnosis of correct and incorrect PLMA position is considered in detail because it may be relevant to a new generation of SADs that incorporate a drainage tube. Correct placement of the PLMA should produce a leak-free seal around the glottis with the mask tip and drainage tube lying inside the upper esophageal sphincter. There are three important malpositions of the PLMA: (1) The PLMA may not be inserted sufficiently far, with the consequence that the tip of the drainage tube lies in the pharynx. Positive-pressure ventilation is ineffective because delivered gas passes out the drainage tube. (2) The tip of the PLMA may lie within the glottis, thereby obstructing ventilation and impairing function of the drainage tube. (3) The tip may be folded over and obstruct ventilation and the drainage tube. Malposition should be corrected by repositioning the PLMA, using a different insertion technique, or replacing it with an alternative airway device.

Initial checks of function are identical to those used with the LMAc. In particular, chest expansion should be good with reasonable airway pressure, and there should be no signs of obstruction of expiration, particularly slow refill of the reservoir bag. The capnograph should be square and the flow-volume loop closed without expiratory scalloping or other signs of obstruction. Airway leak pressure should be greater than 20 cm H_2O. Additional checks unique to devices with a drainage tube may then be performed. A thin layer of water-soluble gel or nontoxic soapy film is used to cover the proximal end of the drainage tube. The effect of changes in pressure in the lungs (sternal compression or positive-pressure ventilation) or esophagus (pressure on the suprasternal notch) are noted. Normal results are as follows:

- The drainage tube gel does not move with positive-pressure ventilation or brief firm pressure applied to the sternum.
- The drainage tube gel does not move when airway pressure is raised to 20 cm H_2O.
- The drainage tube gel moves slightly when brief "bobbing" pressure is applied to the suprasternal notch (the mechanism is pressure on the esophagus).

Protection against Pulmonary Aspiration

The PLMA provides greater protection against pulmonary aspiration than the LMAc does. In clinical practice, the PLMA has prevented aspiration in the presence of massive regurgitation. However, pulmonary aspiration has occurred when malposition of the PLMA was not corrected and function checks had been satisfactory. The PLMA provides good but incomplete protection against pulmonary aspiration.

Airway Obstruction

Significant airway obstruction has been reported with the PLMA. Intraoperative tracheal intubation was required in 13% of obese patients undergoing laparoscopic cholecystectomy.[49] Obstruction may be caused by malposition or obstruction of the bowl by folds of the inflated cuff, by narrowing of the glottis via direct pressure, or by laryngospasm during use of a properly positioned PLMA.

Use of the PLMA during major surgery such as laparoscopic cholecystectomy has been advocated[49] but is controversial.[41] Use of the PLMA for such surgery should be considered only in patients who have no extra risk factors (including obesity, symptomatic gastroesophageal reflux disease, reduced compliance, increased airway resistance) for SAD use. The anesthesiologist must be ready to convert to tracheal intubation at any time.[49] Tracheal intubation provides a more secure airway and should be the norm for major surgery.

Single-Use Supraglottic Airway Devices

The original LMAs were designed for use up to 40 times. Protein contamination occurs after the first use and increases with each subsequent use despite proper cleaning and autoclaving. Single-use SADs have been developed to prevent cross-infection. Ease and quality-of-use results from different studies have been conflicting.

Tracheal Tubes

Tracheal tubes are designed to provide a secure channel through the upper airway. The distal end lies in the mid to lower part of the trachea, whereas the proximal end lies outside the mouth or nose, where it is connected to an anesthesia circuit or other device. Tracheal tubes used in adult patients have a cuff near the distal end that is inflated to provide a seal against the tracheal wall to protect the lungs from pulmonary aspiration and to ensure that the tidal volume delivered ventilates the lungs rather than escapes into the upper airway. Cuffs are normally inflated with air and have an inflation tube with a pilot balloon that indicates cuff inflation.

The size of the tracheal tube is normally described as the internal diameter (ID) in millimeters, but the relationship of the ID to the external diameter varies between different designs and manufacturers. Use of the largest possible tracheal tube was once considered good practice. Very small tracheal tubes may allow insufficient time for completion of exhalation and produce air trapping ("auto-PEEP") with the risk of barotrauma and circulatory compromise. Others have found no evidence of obstruction to expiration with tube sizes as small as 6-mm ID, and the increased workload created is usually of little clinical significance during anesthesia. Use of small tracheal tubes reduces the incidence of sore throat and hoarseness. Small tracheal tubes are easier to insert than larger tubes and may cause less tissue pressure at the larynx. It is easier to pass small tracheal tubes over introducers or FFLs.[50] Restriction of gas flow through a tracheal tube is markedly increased by the presence of an FFL or suction catheter within the lumen of the tracheal tube. Tracheal tube sizes of 8 mm (ID) for males and 7.5 mm (ID) for females are often used.

Specialized tracheal tubes produced for anesthesia include preformed, adjustable shape, and reinforced. Specialized tubes are also used for ear, nose, and throat (ENT) surgery (laser and microlaryngeal surgery) and for thoracic anesthesia and critical care. Tracheal tubes can become kinked and hence obstructed when they are angulated. Armored (reinforced) tubes have an embedded coil (usually stainless steel) that minimizes kinking of the tube when it is subjected to angulation. Armored tracheal tubes are the tubes of choice in many head and neck procedures and patient positions other than supine. However, an armored tube that has been compressed remains pinched, so it is particularly important to prevent biting on such a tube.

The material and bevel shape of the tip of the tracheal tube can affect the ease and probably the trauma of tube passage. The tip of the earliest Magill tracheal tubes had a soft, simple bevel. The Murphy eye, a hole in the wall of a firm tip opposite the bevel, was designed to provide a patent airway if the tracheal tube became occluded at the bevel. Air leakage through the Murphy eye may facilitate early diagnosis of tracheal tube displacement before complete accidental extubation has occurred.

Cuff inflation achieves a seal between the tracheal tube and the wall of the trachea. There should be no air leak at airway pressures required for positive-pressure ventilation, and the lungs should be protected from aspiration. The cuffs of early tracheal tubes produced a high pressure that could cause mucosal ischemia. High-volume, low-pressure cuffs were developed to conform to the D-shaped cross section of the trachea and provide a seal at a lower cuff pressure, thereby reducing the risk of tracheal damage.

Inflation of the cuff with a volume that just prevents an air leak ("just-seal volume") is often recommended. However, this cuff pressure varies greatly. Prevention of excessive cuff pressure may reduce the incidence of tracheal damage, vocal cord dysfunction from recurrent laryngeal nerve palsy, and sore throat after surgery. Because palpation is not a good guide to cuff pressure, use of a monitor to maintain cuff pressure in the range of 25 to 30 cm H_2O is recommended.[51]

Cuff pressure can change after initial inflation. Inhaled N_2O diffuses into tracheal tube cuffs that have been inflated with air and increases the volume and pressure within the cuff enough to cause tracheal lesions and an increased incidence of sore throat. A leak in the cuff or valve or a reduction in trachealis muscle tone can lower cuff pressure and increase the risk for pulmonary aspiration. Early detection of both low and high pressure is important.

A properly inflated cuff protects against massive pulmonary aspiration, but silent aspiration (micro-aspiration) of pharyngeal contents occurs along channels between folds in the cuff and is a major contributor to ventilator-associated pneumonia in intensive care. New materials and cuff designs attempt to eliminate cuff channels and may help prevent micro-aspiration.

Tracheal Intubation

Tracheal intubation (insertion of the tracheal tube) is an essential skill in anesthetic practice. Indications for tracheal intubation are shown in Box 50-5. There are no absolute contraindications to tracheal intubation.

Box 50-5 Indications for tracheal intubation

Surgical and Anesthetic Indications

Surgical requirement for neuromuscular blocking drugs, e.g., abdominal surgery

Airway access shared with the surgeon, including ear, nose, and throat surgery

Patient position in which access to the airway is restricted or precludes rapid tracheal intubation, e.g., lateral, prone

Predicted difficult airway

Risk of aspiration of gastric contents or blood, e.g., upper gastrointestinal obstruction or sepsis, facial trauma, bleeding into the respiratory tract from any cause

Surgery that impairs gas exchange

Prolonged surgery

Other airway techniques ineffective

Critical Illness

Inability to protect the airway, e.g., coma from any cause

Impaired respiratory function (hypoxemia or hypercapnia) unresponsive to noninvasive management

Prevention of hypercapnia, e.g., raised intracranial pressure

Principles of Clinical Practice of Tracheal Intubation

The incidence of complications should be minimized by using best practice.[6] Adequate personnel, drugs, and equipment must be available. Four principles are central to prevention of complications[52]:

1. Maintenance of oxygenation must take priority over all other issues. Preoxygenation should be performed before induction of anesthesia.[6] Mask ventilation should be used between attempts at tracheal intubation.
2. Trauma must be prevented. The first attempt at tracheal intubation should be performed under optimal conditions (including patient position, preoxygenation, and equipment preparation).[53] The number of attempts with blind techniques should ideally be zero and certainly not more than four.
3. The anesthesiologist should have backup plans before starting the primary technique[6] and the skills and equipment needed to execute these plans. When unanticipated difficulty occurs in non-lifesaving surgery, the safest plan is to terminate attempts at tracheal intubation, awaken the patient, and postpone surgery.
4. The anesthesiologist should seek the best help available ("call for help") as soon as difficulty with tracheal intubation is experienced.

Intravenous access is secured (occasionally achieved only during inhaled induction of anesthesia) and standard monitoring is established. The patient should be in the optimal position. Time spent adjusting the position after induction of anesthesia may delay successful tracheal intubation, prolong the time at risk for pulmonary aspiration, and increase the risk for hypoxemia or airway trauma.

Nasotracheal Intubation

Nasotracheal intubation (NTI) is necessary when the oral route is not possible (e.g., limited mouth opening) or would impede surgical access. NTI was formerly considered the technique of choice for resuscitation, but orotracheal intubation using the rapid-sequence technique is now usually the first choice. NTI has been used in critical care as an alternative to tracheotomy because it is better tolerated than oral intubation. However the tube used must be longer and narrower than oral tracheal or tracheotomy tubes so that airway resistance is greater and therapeutic aspiration of pulmonary secretions is more difficult. Problems associated with prolonged duration of NTI include nasal damage, local abscesses, otitis media, and sinusitis. The nasal route is contraindicated in patients with a history (old or new) of basal skull fracture or surgery. Nevertheless, if there is no alternative, this infrequent complication may be less likely when a catheter is used as a guide.

The technique of NTI is influenced by the need to minimize the incidence of complications peculiar to this route, including cuff tears, damage to the nasal cavity (epistaxis, fractured turbinates, avulsed nasal polyps, septal abscess) and nasopharynx (avulsed adenoids). It is beneficial to use vasoconstrictors to shrink the mucosa of both nasal cavities before passage of the tube. Another complication is a consequence of the right angle through which the tube must turn when it passes from the nasal cavity into the oropharynx. The tube may impact on and tear the mucosa of the posterior nasopharynx and pass submucosally. This complication is less likely if a soft catheter is first passed into the oropharynx and then used as a guide. Tube factors that reduce the risk of trauma include diameter not larger than 7.5-mm ID for men and 7.0-mm ID for women, warming before insertion, and use of a soft tip. The tube is passed directly backward along the floor of the nose. Resistance to nasal passage may be overcome by gentle rotation or use of a narrower tube or the other nasal cavity. It is important to be gentle and stop if abnormal resistance is met. The risk of damage may be reduced by passage through the nasal cavity under vision with an FFL.

Blind nasal intubation was first used in patients breathing spontaneously under deep inhaled anesthesia but can also be performed in awake patients under topical anesthesia. Tube advancement is guided by changes in breath sounds at the proximal end of the tube (amplification by a whistle can be very helpful) and by external palpation of the larynx. Cessation of breath sounds indicates that the tip of the tube has entered the esophagus, piriform fossa, or vallecula. The tube is withdrawn until breath sounds are heard, the head and neck position is adjusted, and the tracheal tube is then readvanced. Temporary inflation of the cuff when in the oropharynx may improve success rates.[54] If the tube is held up at the larynx, head flexion can help the tracheal tube enter the trachea by improving alignment with the trachea. Blind nasal intubation during spontaneous ventilation may still be useful when an FFL is not available. Attempted blind NTI in an apneic patient risks trauma and failure.

NTI is often performed after the administration of intravenous anesthetics and NMBDs. A direct laryngoscope is used to facilitate NTI under vision and is inserted once the tip of the tube has reached the oropharynx. Magill forceps are frequently used to grasp the tracheal tube (avoiding the cuff) and guide it into the trachea. An assistant then advances the tube. Rigid indirect laryn-

goscopes (RILs) can facilitate NTI under vision in patients in whom this is not possible with direct laryngoscopes.

Direct Laryngoscopy: Theoretical Basis

Direct laryngoscopy is used to facilitate tracheal intubation under vision. Successful direct laryngoscopy depends on achieving a line of sight from the maxillary teeth to the larynx. The tongue and epiglottis are the anatomic structures that intrude into the line of sight. Management of the tongue and epiglottis is therefore central to successful direct laryngoscopy. Before the laryngoscope is inserted, the patient is normally placed in the "sniff" position (see later). The direct laryngoscope is then used to displace the tongue and epiglottis out of the line of sight. The tongue is displaced horizontally (normally to the left) from the line of sight, the hyoid bone and attached tissues are moved anteriorly, and the epiglottis is elevated directly or indirectly to reveal the larynx. The force applied to the laryngoscope handle should lift the hyoid bone and attached tissues parallel to the line of sight. Adequate lifting force, which may cause considerable tissue distortion,[7,55,56] is a key factor in successful direct laryngoscopy.[7,56] It is important to achieve the best possible view of the larynx without causing tissue trauma. It is not always possible to achieve line of sight with direct laryngoscopy.

The theoretical basis of the head and neck position used for direct laryngoscopy was attributed to the need to align the axes of the oral cavity, pharynx, and larynx on the basis of a radiology study. Magnetic resonance imaging in awake patients has been used to challenge this hypothesis, but the conclusions have been controversial. Understanding of management of the tongue and the epiglottis is more likely than the axis alignment hypothesis to improve direct laryngoscopy technique.

The "sniff" position (Fig. 50-6) is usually the best starting position for direct laryngoscopy. In the sniff position, the cervical spine below C5 is relatively straight, there is increasing flexion from C4 to C2, and the head is fully extended (occipito-atlanto-axial complex).[57] Neck flexion between C2 and C4 is achieved by elevation of the head. No statistical advantage of the sniff position over simple head extension was found in one study, except in the presence of obesity or limited head extension.[26] However, the sniff position facilitated a view of the larynx in 4% of patients in whom this was not possible with simple head extension. The sniff position also improves pharyngeal airway patency in patients with obstructive sleep apnea. Head extension facilitates insertion of the laryngoscope, reduces contact between the laryngoscope and the maxillary teeth, improves the view of the larynx, and facilitates full mouth opening. Head extension should be used unless there is a contraindication.



Figure 50-6 "Sniff" position. A volunteer positioned on the Popitz pillow (DermaCare, Louisville, KY) demonstrates cervical flexion and a small degree of atlanto-occipital extension. The flexion aligns the laryngeal and pharyngeal axes. Further extension of the head results in the true sniffing position.

Macintosh Laryngoscope and Technique of Orotracheal Intubation

The Macintosh curved laryngoscope is radically different from the preexisting straight laryngoscopes. In particular, the long axis of the blade is curved, the cross section is a right-angled "Z" section, the web and flange are bulky, the tip is atraumatic, and the light bulb is shielded by the web. However, Macintosh's key innovation was his novel technique of indirect elevation of the epiglottis, achieved by tensioning the hyoepiglottic ligament after the tip of the laryngoscope was positioned in the vallecula. This technique is the key to success of the Macintosh laryngoscope—and its fundamental flaw. When it works well, the epiglottis is elevated completely and lies behind and along the posterior surface of the laryngoscope blade. However, it is not possible to position the Macintosh laryngoscope correctly in some patients. Minor difficulty results in partial elevation of the epiglottis, erroneously described as a "floppy epiglottis," and major difficulty leads to complete failure to elevate the epiglottis with the consequence that the vocal cords cannot be seen.

Tracheal intubation is normally achieved with a rapid sequence of maneuvers in which all components of a complex technique merge into one another. The best technique will develop if all components are optimized. The three component steps of direct laryngoscopy are insertion of the laryngoscope, adjustment of its position and lifting force, and use of other maneuvers to optimize the view of the glottis.

The "sniff" position is used. Full mouth opening facilitates insertion of the laryngoscope. It is inserted from the right side of mouth and to the right of the tongue while taking care to not trap the lips between the laryngoscope blade and the teeth. The laryngoscope is advanced and simultaneously moved into the midline to displace the tongue to the left. Progressive visualization of anatomic structures minimizes the risk of trauma. The epiglottis is the first key anatomic landmark. The tip of the laryngoscope is advanced into the vallecula, and the epiglottis is elevated indirectly by applying a force that tensions the hyoepiglottic ligament. Elevation of the epiglottis is optimized and a further lifting force is applied to the laryngoscope to achieve the best view of the larynx (Fig. 50-7). It is very important not to lever on the maxillary teeth because this may cause dental damage[58] and reduce the view of the larynx. If visualization of the larynx cannot be achieved without pressure on the teeth, use of this laryngoscope should be abandoned and another technique of tracheal intubation used.

When a good view of the larynx is achieved, the vocal cords, aryepiglottic folds, posterior cartilage, and interarytenoid notch can be identified (Fig. 50-8). The view should be optimized

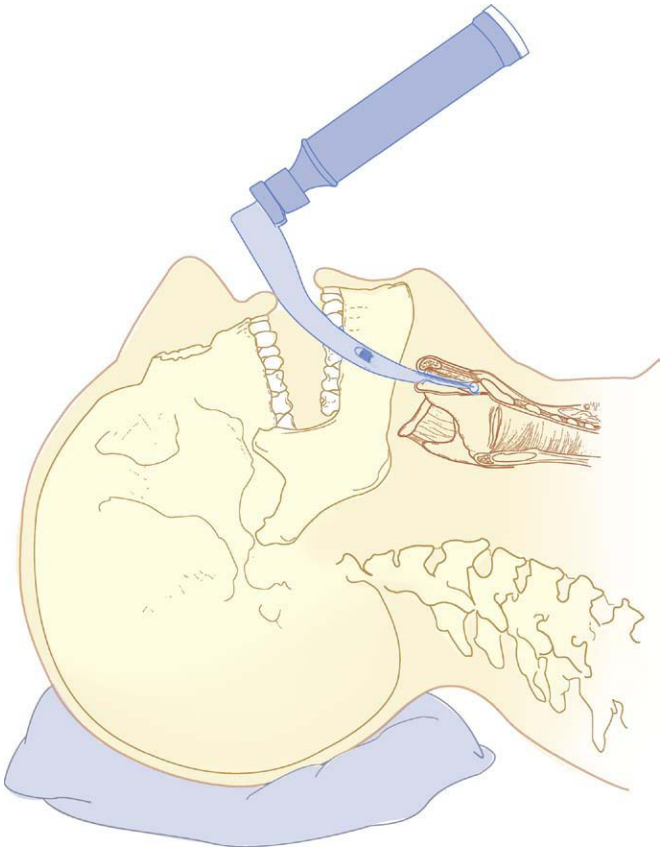


Figure 50-7 Macintosh laryngoscope in position. The laryngoscope tip is in the vallecula, the hyoepiglottic ligament is tensioned and the epiglottis has been elevated indirectly so that it lies along the posterior surface of the laryngoscope. *(From Key Topics in Airway Management, Cambridge University Press.)*

to facilitate passage of the tracheal tube. If the view of the larynx is poor, it is important to check that the basic technique has been performed optimally and other maneuvers used (Box 50-6). External laryngeal manipulation (better described as "bimanual laryngoscopy," which implies internal movement of the laryngoscope with external manipulation of the larynx), performed by the anesthesiologist who guides an assistant (Fig. 50-9), consistently improves the laryngeal view. It is a key maneuver.

Box 50-6 Maneuvers Used to Optimize the View at Direct Laryngoscopy

- Maximum head extension
- Tongue entirely to the left of the laryngoscope
- Optimal depth of insertion of the laryngoscope
- Strong lifting force applied in the correct direction to the laryngoscope
- External laryngeal manipulation—applied initially with the right hand of the anesthesiologist

Tracheal Tube Passage with Successful Macintosh Laryngoscopy

The view of the vocal cords is maintained while the anesthesiologist guides the tube under vision between the vocal cords. Passage of the tube from a position posterolateral to the larynx facilitates observation of progress of the tracheal tube toward and between the vocal cords. Steering of the tube and passage under vision are facilitated if the tube has the optimal "ice hockey stick" shape, normally created by the use of a stylet within the tube. The tracheal tube is advanced until the cuff is about 2 cm distal to the vocal cords. This position is important inasmuch as more proximal positions may cause cuff leaks and pressure on the recurrent laryngeal nerve.[5] The cuff is inflated to slightly higher than the "just-seal" pressure, and the correct position of the tube is confirmed. Cuff pressure is then adjusted to 25 to 30 cm H_2O.

If only the posterior portion of the vocal cords can be seen, including the interarytenoid notch, passage of the tracheal tube may be awkward but is not difficult. Either a styletted tracheal tube or passage of an introducer ("bougie") under vision, followed by passage of the tracheal tube over the introducer, may be used. Both are reliable visual techniques.

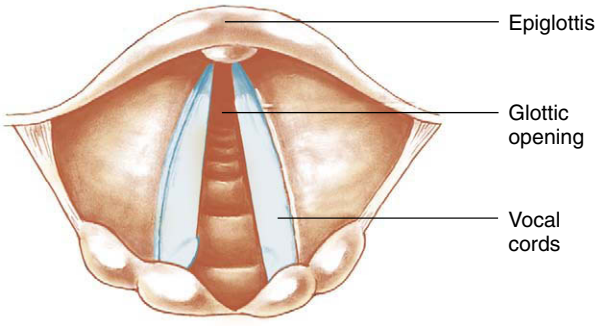


Figure 50-8 Schematic view of the glottic opening during direct laryngoscopy when the epiglottis is elevated with a curved or straight laryngoscope blade. The glottic opening is recognized by its triangular shape and the pale, white vocal cords. *(From Stoelting RK, Miller RD: Basics of Anesthesia, 3rd ed. New York, Churchill Livingstone, 1994.)*

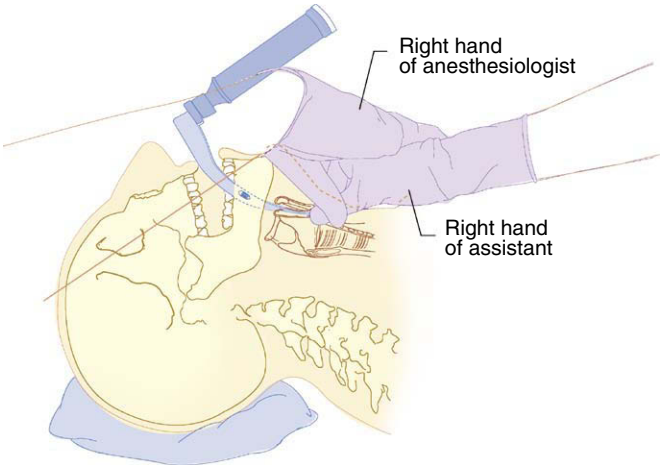


Figure 50-9 Bimanual laryngoscopy (external laryngeal manipulation). The anesthesiologist guides the position and pressure exerted by the assistant's hand on the larynx to maximize view of the vocal cords. The left hand of the anesthesiologist, which holds the laryngoscope handle, is omitted.

Difficulty with the Macintosh Technique

Difficulty with tracheal intubation is predominantly a consequence of failure to see the larynx.[53] The efficacy of direct laryngoscopy is measured in terms of the best view of the larynx achieved. The most widely used scale is that described by Cormack and Lehane (CL) (Fig. 50-10). The definitions used are grade 1, most of the glottis is visible; grade 2, only the posterior extremity of the glottis is visible; grade 3, no part of the glottis and only the epiglottis is visible; and grade 4, not even the epiglottis can be seen. The most useful modification is a subclassification of grade 3 into 3a when the epiglottis can be lifted from the posterior pharyngeal wall and 3b when it cannot be lifted.[59] This modification of grade 3 is important in clinical practice because the introducer technique does not work well in the grade 3b situation.[59] All the definitions apply to the best view that can be achieved, which implies the use of external laryngeal manipulation whenever the initial view is unsatisfactory.

The complexity of tracheal intubation may be recorded with the intubation difficulty scale (IDS),[60] a numerical score based on seven parameters—number of attempts, number of operators, number of alternative techniques, laryngeal view, lifting force required, application of laryngeal pressure, and vocal cord mobility—associated with difficult intubation. It does not include the duration of attempts. The IDS alone does not indicate the cause of the difficulty, and it is more important to communicate the scores for the individual elements of the IDS. A record of all these elements plus the duration of attempts is desirable after every tracheal intubation.

A 2% or lower incidence of CL grade 3 or 4 has been recorded. However, other large prospective studies, excluding patients with obvious[7] or anticipated[61] airway difficulty, have shown an incidence of CL grade 3 or 4 of 6.1%,[7] 10.1%,[61] or higher. External laryngeal manipulation was not used in most of these studies, so the clinically important incidence was probably half that reported. Difficulty with laryngoscopy has probably become more frequent as a consequence of patient factors such as increasing age, obesity, and modern dentistry. Anesthesiologists may also have become more reluctant to apply high lifting pressure to the laryngoscope as a result of awareness of airway trauma and the availability of alternative techniques.

Not all of the factors that contribute to difficulty with direct laryngoscopy have been identified. Factors that impair insertion of the laryngoscope, lateral displacement of the tongue, or elevation of the epiglottis will impair the efficacy of direct laryngoscopy. Anatomic causes include limited mouth opening, awkward dentition, hypoplastic mandible, impaired TMJ function, and limited head extension. A final common pathway of difficulty with the Macintosh laryngoscope was suggested by a soft tissue radiology study of laryngoscopy.[62] In patients with known difficult laryngoscopy the tongue could not be completely displaced and part was trapped between the tip of the laryngoscope and the hyoid bone. The tip of the laryngoscope could not enter the vallecula and advancement of the laryngoscope displaced the epiglottis further into the line of sight. Thus, indirect elevation of the epiglottis, the novel feature of the Macintosh technique, is also its fundamental flaw.

Blind Endotracheal Intubation with the Macintosh Laryngoscope

If the larynx cannot be seen, it is not possible to intubate the patient under vision with the Macintosh laryngoscope, and failure and soft tissue trauma are potential risks. The anesthesiologist must decide whether to use a blind technique with the Macintosh laryngoscope, abandon further attempts at tracheal intubation and awaken the patient, or use an alternative visual technique of laryngoscopy—provided that skills have been developed. Use of an SAD for elective surgery in these patients when tracheal intubation had been the first choice places them at risk if the airway becomes obstructed.

Blind techniques (styletted tracheal tube or introducer) have been the first alternative used when the larynx cannot be visualized with the Macintosh laryngoscope. Introducers, such as

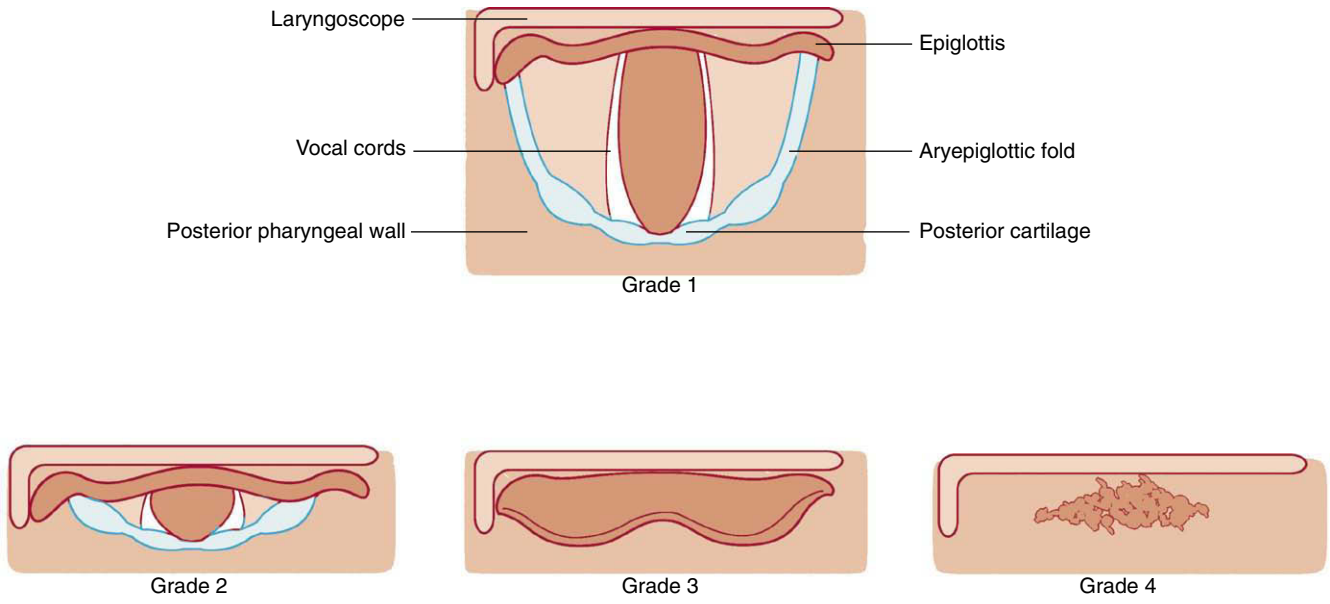


Figure 50-10 Laryngoscopy view grades.

"gum elastic bougies" with an angulated tip, are passed (introduced) into the trachea and then used as a guide for passage of the tube. The introducer technique is relatively simple and incorporates verification of its blind passage down the trachea.[52] It can be divided into three parts: passage of the introducer, confirmation of tracheal position, and passage of the tube over the introducer into the trachea. The laryngoscope is kept in the midline, and the anesthesiologist estimates the probable location of the larynx and attempts to pass the tip of the introducer behind the epiglottis and blindly between the vocal cords and into the trachea. Gentle technique should minimize trauma and facilitate verification of passage into the trachea. A sensation of clicks and distal holdup have been detected in at least 90% of correct intratracheal placements. Successful positioning of the introducer in the trachea is followed by passage of the tracheal tube over the introducer and into the trachea. This sometimes proves difficult.[52] The laryngoscope should be kept in place during passage of the tracheal tube, and 90-degree anticlockwise rotation of the tube is often effective. The use of small tracheal tubes facilitates passage of the tracheal tube. Other tracheal tube factors affecting the success of passage are considered in the section on use of the FFL. When the tube has been passed and the introducer removed, tracheal position must be confirmed. The blind introducer technique has a high success rate, such as 90% in a prospective study that permitted a maximum of two attempts.[63] However, there are many case reports of failure, and the technique does not work well when the epiglottis cannot be elevated from the posterior pharyngeal wall.[59]

The introducer technique was developed to overcome problems with the Macintosh technique before there was evidence of the efficacy of alternative techniques. There is now evidence of high success rates of tracheal intubation under vision with the straight laryngoscope,[45] FFL,[46] and RIL[47] when the Macintosh technique fails. Multiple blind attempts at tracheal intubation were often made in the past but are associated with morbidity and mortality.[43,64,65] Eventual tracheal intubation after several attempts with blind techniques should be regarded not as success but as a "near miss."

The role of blind techniques in modern practice should be questioned. The anesthesiologist should be aware that airway difficulty can be a consequence of friable lesions such as lingual tonsil hypertrophy.[3] Use of blind techniques in such unpredictable situations can cause airway obstruction. Some centers do not use blind techniques,[46,47] others limit the number of attempts to two,[63] and all should seek to emulate this enlightened practice. If a few attempts with alternative techniques are not successful, elective surgery should be postponed, the patient awakened, and subsequent awake flexible fiberoptic laryngoscopy scheduled.

Modifications of the Macintosh laryngoscope

Many variations have been described, most without data about their efficacy. A Macintosh-type laryngoscope with a hinged tip that flexes when a lever on the handle is depressed was introduced by McCoy. It works well in *simulated* difficult laryngoscopy, and there have been many clinical reports of success when the glottis could not be visualized with the Macintosh laryngoscope. However, an angulated straight laryngoscope performed much better than the McCoy in *clinical* unanticipated difficult intubation, and there have been many reports of failure of the McCoy laryngoscope to achieve a view of the glottis.

Straight Laryngoscope

Laryngoscopy for tracheal intubation was first performed with the straight laryngoscope, which remains the diagnostic and therapeutic laryngoscope used by ENT surgeons. Many studies[45] have reported successful tracheal intubation under vision with the straight laryngoscope in patients in whom intubation proved impossible with the Macintosh laryngoscope. Corroborative evidence of the value of this technique comes from many reports of successful use of the ENT straight laryngoscope and the rigid bronchoscope in such patients.

The mechanism of the greater efficacy of the straight laryngoscope is probably both improved control of the tongue and more reliable elevation of the epiglottis and is consistent with the reduced force and head extension needed with the straight laryngoscope.[55] The straight laryngoscope is of particular value with laryngeal lesions (including lingual tonsil hypertrophy) and in patients with a hypoplastic mandible. It is useful in some patients with awkward dentition, particularly the presence of a gap in the right upper dentition. Mastery of the straight laryngoscope is an asset to any anesthesiologist.

The technique described here, the paraglossal technique, affords optimum control of the tongue. Initial preparation for tracheal intubation is identical to that used with the Macintosh laryngoscope. Head extension is as important as in the Macintosh technique. It is essential to displace the entire tongue to the left of the laryngoscope. The laryngoscope is inserted lateral to the tongue and advanced carefully along the paraglossal gutter between the tongue and tonsil. Application of continued moderate lifting force to the laryngoscope handle helps maintain lateral displacement of the tongue and reduces contact with the maxillary teeth. As the laryngoscope is advanced, the epiglottis comes into view and the tip of the laryngoscope is passed posterior to it. The optimal position of the tip of the straight laryngoscope is in the midline of the posterior surface of the epiglottis, close to the anterior commissure of the vocal cords (Fig. 50-11). This position achieves good control of the epiglottis and facilitates passage of the tracheal tube. The direction of force applied to the handle of the straight laryngoscope is at right angles to the straight laryngoscope blade (and in line of sight of the larynx). Under no circumstances should levering action be applied to the teeth. Not only does this risk dental damage, but it also degrades the view. If a good view cannot be achieved, a different technique of laryngoscope or tracheal intubation should be used.

If the larynx is not visible, it is probable that the tip of the laryngoscope is located in the vallecula, piriform fossa (usually the right), posterior pharyngeal wall, or the esophagus. The basic checks and maneuvers for direct laryngoscopy techniques (see Box 50-6) are performed. Bimanual laryngoscopy, including lateral movement of the larynx (regularly used by ENT surgeons), is particularly important. Direct tracheal tube passage with the Miller laryngoscope can be awkward. The visual introducer technique is useful whenever it proves difficult to guide the tube to the larynx.

The Miller laryngoscope is popular because its low profile facilitates insertion and positioning, but there are some problems. The tip has a small point of contact with the posterior surface of the epiglottis, so there is a risk of trauma and unstable elevation of the epiglottis. Precise positioning is difficult because the tip is

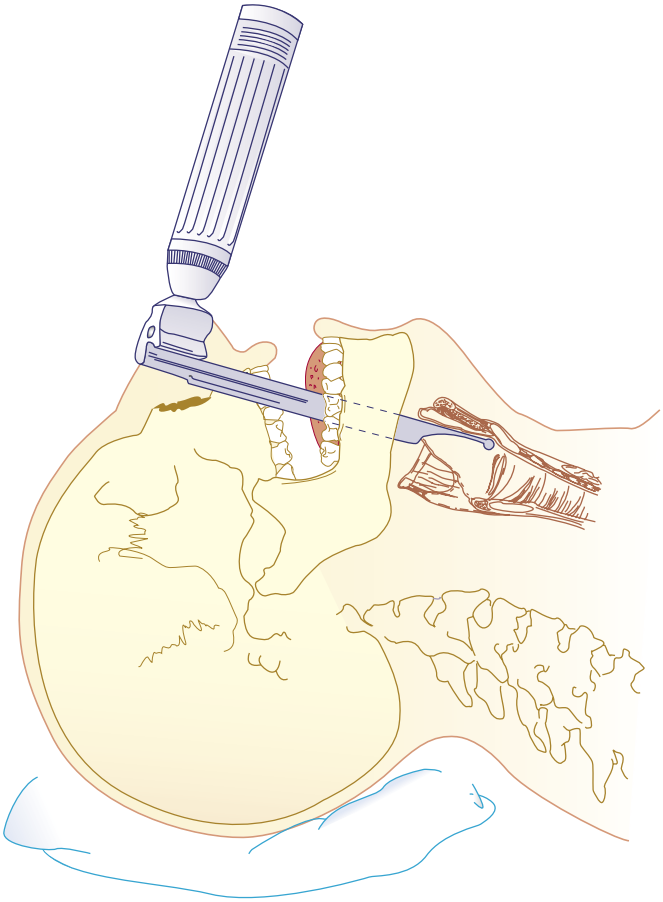


Figure 50-11 Straight laryngoscope in position. The laryngoscope tip is posterior to the epiglottis, which is elevated directly. The tip of the laryngoscope is close to the anterior commissure of the vocal cords. *(From Key Topics in Airway Management, Cambridge University Press.)*

not visible. The major problem with the Miller laryngoscope is that its cross section impedes passage of the tracheal tube. Straight laryngoscopes have been designed to overcome problems with the Miller laryngoscope. The Belscope is a narrow angulated straight laryngoscope with a low profile and an atraumatic tip that was designed to reduce contact with the maxillary teeth. The efficacy of the Belscope when the larynx cannot be seen with the Macintosh laryngoscope has been confirmed. The C-shaped cross section of the Henderson laryngoscope facilitates the passage of tracheal tubes.

Indirect Laryngoscopy: Theoretical Basis

In some patients, direct laryngoscopy cannot provide a view of the larynx. Optical devices have been developed to facilitate tracheal intubation under vision with technology that transmits the image from a distal lens to the proximal end of the device. Because the proximal end of the line of sight is transferred from above the maxillary teeth to the laryngopharynx, a view of the larynx is obtained from a position that cannot be achieved with direct laryngoscopy. Visualization of the larynx without the need to distort the tissues (displace the tongue to the left) or to use head extension becomes possible. Lower laryngoscope lifting force may be needed than is the case with direct laryngoscopy. Consequently, these techniques can be used readily with topical anesthesia in an awake patient. Indirect laryngoscopy allows tracheal intubation under vision in patients in whom this is not possible with direct laryngoscopy. Many devices have been designed, and features of the ideal technique are shown in Box 50-7. No single technique meets all these criteria.

Separation of anatomic structures beyond the distal lens is essential to provide adequate vision. Separation may be achieved by maneuvers such as jaw thrust (not normally necessary in an awake patient), displacement by the device itself (many RILs), or simultaneous use (frequently in the case of optical stylets [OSs]) of a laryngoscope. Problems with condensation, blood, and secretions are common to all these devices. Modern indirect laryngoscopes can be divided into flexible (FFLs) and rigid devices (RILs). Each group has advantages and disadvantages.

Flexible Fiberoptic Laryngoscope

The FFL uses flexible optical fibers to transmit images from a distal lens as it is steered under vision toward the larynx and into the trachea.[66] A typical FFL is shown in Figure 50-12. The insertion cord contains bundles of optical fibers that transmit the image, a different group of optical fibers that transmit light to the distal end, and cables from a control lever in the handpiece that flex and extend the distal section. The hollow channel can be used for aspiration of secretions or instillation of local anesthetic. The simplest FFLs have a proximal eyepiece. The image can be displayed on a monitor by attaching a camera to the eyepiece or by using an FFL with an integral camera. Some models have a distal video chip from which the image is transmitted electronically to a video display, so a more accurate term is "flexible video laryngoscope," but they function as FFLs and this term is used for simplicity. Use of video monitors incurs greater expense than

Box 50-7 Characteristics of the ideal laryngoscope technique for tracheal intubation

- Facilitates rapid tracheal intubation under vision
- Used with the patient in a neutral position
- Minimal tissue distortion required
- Tracheal tube passage integrated in design and technique
- Few steps involved in a technique that is intuitive
- Competence can be gained rapidly
- Equipment simple, robust, portable, and inexpensive
- High success rate in all clinical situations
- Preparation time should be minimal
- Sterilization easy and effective (or the device should be single-use type)
- Illumination good
- Optical device characteristics
  - Sufficient optical quality
  - Fogging of lens unlikely

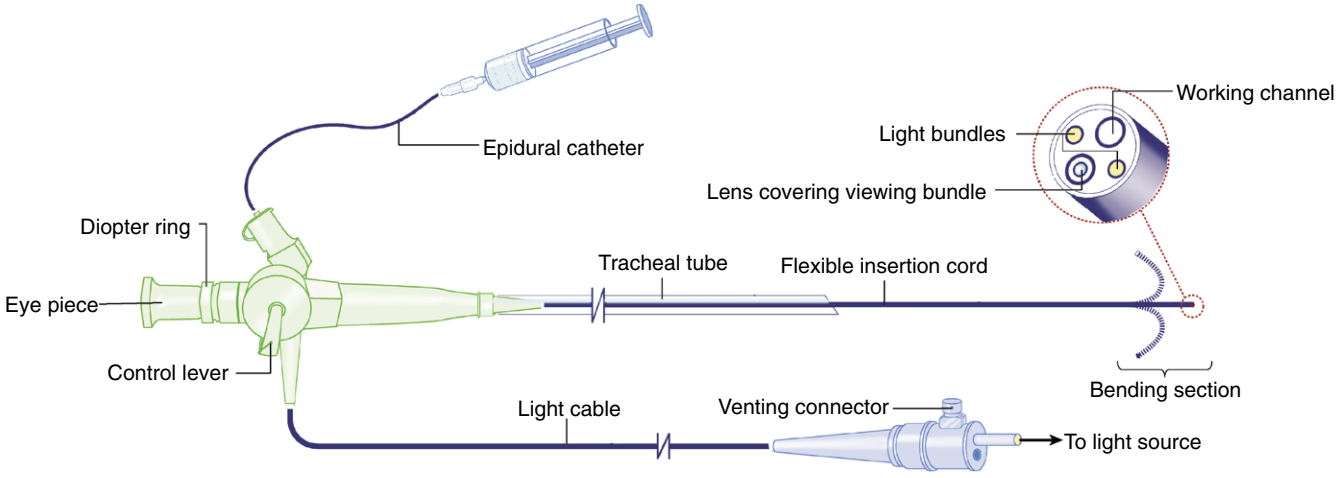


Figure 50-12 Flexible fiberoptic laryngoscope.

reliance on eyepieces, but they facilitate teaching and ease of use and may improve success rates.

The FFL is the most versatile laryngoscope (Box 50-8) for tracheal intubation and can facilitate intubation that could not be achieved with any other technique. Some advantages are shown in Box 50-9. A high success rate can be achieved.[67,68] Its use in patients with anticipated difficult intubation significantly reduces the number of complicated intubations and the incidence of intubation trauma and postoperative upper airway edema. The FFL in expert hands is well tolerated by an awake patient. Awake flexible fiberoptic laryngoscopy is the safest noninvasive means of securing a critical airway.[68] It is indicated in many situations, some of which are presented in Box 50-10. A low threshold for use of awake flexible fiberoptic intubation in emergency patients is particularly important inasmuch as the option of postponing surgery and awakening the patient is not available.

Neither deep sedation nor general anesthesia should be used when the airway is compromised.[27] When the patient is alert, ventilation, oxygenation, and airway protection are maintained. Normal pharyngeal tone is preserved, so there is sufficient space between structures to facilitate vision several centimeters beyond the distal lens. Phonation, which can help identify the larynx, is possible. Options are preserved. Because some patients will not tolerate awake flexible fiberoptic laryngoscopy, sedation or general anesthesia may be necessary, but there are risks of hypoventilation, upper airway obstruction, and hypoxemia. The ideal sedative would have little effect on spontaneous ventilation and allow patients to protect their airway. Dexmedetomidine may provide effective and safe sedation in apprehensive or combative patients. Remifentanil infusions have been used, but careful monitoring is essential to prevent hypoventilation and hypoxemia.

Box 50-8 Versatility of the Flexible Fiberoptic Laryngoscope

- Flexible and steerable
- Minimal tissue pressure and trauma
- Continuous visualization
- Oral or nasal route possible
- Other intubating devices may facilitate combination techniques
- Visual confirmation of the depth of intubation on withdrawal

Box 50-9 Advantages of Awake Patient State for Flexible Fiberoptic Laryngoscopy

- Spontaneous breathing continues
- Oxygenation and ventilation maintained
- Intubation easier
- Anatomy and muscle tone preserved
- Phonation as a guide
- Safety
- Airway protection preserved
- Options preserved

Technique

The technique is summarized in Box 50-11. The patient's position may be supine, semisupine, or sitting (Fig. 50-13), and the anesthesiologist may face or work from behind the patient. These choices are influenced by clinical requirements and personal preference. Use of the fully upright sitting position has been recommended when pulmonary aspiration is a consideration.

The FFL may be passed through the nose or mouth. The nasal cavity acts as a conduit that provides good alignment with the larynx as the FFL passes from the nasal cavity to the pharynx. Use of conduits such as tubular oropharyngeal airways[69] (e.g., Williams, Ovassapian, Bermann II), the intubating LMA (ILMA), or the AIT through other SADs may facilitate passage of the FFL through the mouth. These techniques keep the FFL in the midline and deliver its tip to the laryngopharynx. They also protect the FFL from biting. The gag reflex is more troublesome with the oral than with the nasal route. Experience in other fields of medicine and dentistry shows that gagging can be managed by hypnosis, control of hyperventilation, acupressure, or sedation with nitrous oxide or propofol.

Proper preparation contributes greatly to successful awake use of the FFL. Rapport with the patient and good topical anesthe-

Box 50-10 Indications for Flexible Fiberoptic Laryngoscopy

- Anticipated difficult tracheal *intubation*
- Anticipated difficult mask *ventilation*, including seep apnea
- Anticipated difficult *rescue* technique
- Confirmation of tracheal tube position
- Diagnosis of malfunction of a supraglottic airway device
- Cervical spine instability (the rigid indirect laryngoscope is an alternative)
- Positioning of a double-lumen tube and bronchial blocker
- Assessment of swelling or trauma after difficulty with airway management
- Tracheal tube change (between the nasal and oral routes)
- Intensive care use, including aspiration of secretions and confirmation of the dilatational tracheotomy site

Box 50-11 Flexible Fiberoptic Laryngoscopy Technique

- Drying agent
- Effective topical anesthetic
- Equipment check: lenses clean and focused, antifog agent applied
- Tracheal tube mounted
  - On the flexible fiberoptic laryngoscope for the nasal route
  - Within the oral airway for the oral route
- Patient position: supine, semisitting, or sitting
- Rapport: full explanation
- Flexible fiberoptic laryngoscope technique
  - Insertion cord kept straight and the scope maneuvered in three planes
  - Tip flexion-extension, rotation, and advance-withdrawal
  - Secretions aspirated
  - White-out, red-out, or loss of target—withdraw, indentify structures, readvance
  - Targets (epiglottis, vocal cords, tracheal cartilages, carina) kept in the center of view as the flexible fiberoptic laryngoscope is advanced
  - Advance to close to the carina
  - Tracheal tube passed over the flexible fiberoptic laryngoscope
  - Tube position confirmed and secured and anesthesia induced

sia of the airway are important. A drying agent (such as atropine or glycopyrrolate) may be given before the application of topical anesthesia to the airway to increase its efficacy and minimize problems with visualization caused by secretions. A vasoconstrictor is sprayed into the nose when the nasal route is planned. Equipment preparation includes checking the optics, cleaning and antifogging of the distal lens, passage of an epidural catheter through the working channel, and lubrication of the insertion cord. The tracheal tube is normally mounted on the FFL before NTI but may be positioned with the tip in the oropharynx before passage of the FFL.

General care of the patient during intubation is important, particularly maintenance of airway patency and oxygenation.[66] Insufflation of oxygen down the working channel of the FFL has been advocated to increase F_{IO_2} and keep the lens clear of secretions but has caused barotrauma and is not advisable. Oxygen should be administered nasally or via facemask, and the oximeter beep should be audible.

The principles of FFL manipulation are simple.[66] The basic maneuvers of flexion and extension of the tip combined with rotation of the insertion cord make it possible to steer the FFL under vision around tissues as it is moved toward the larynx and trachea. The external portion of the insertion cord must be kept

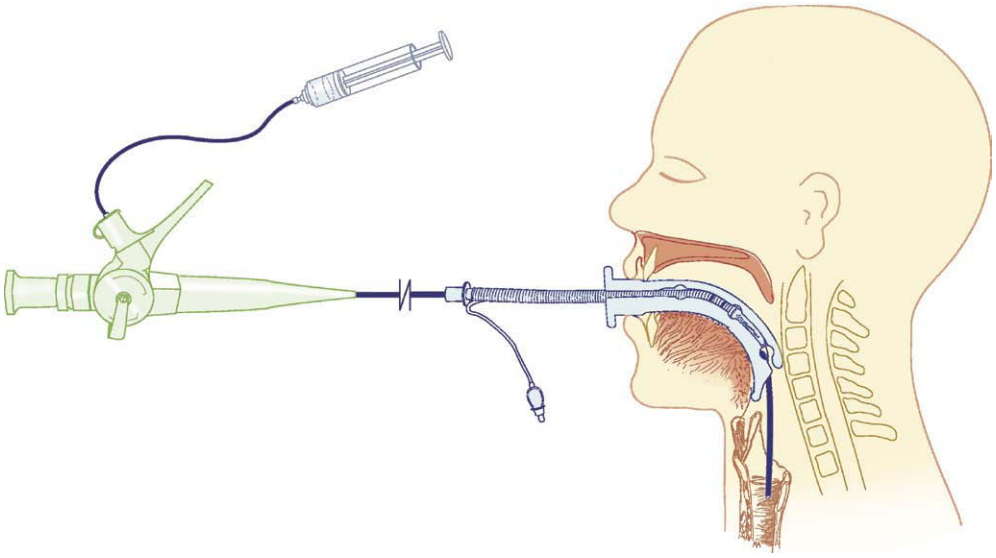


Figure 50-13 A flexible fiberoptic laryngoscope inserted through a Bermann airway in a patient in the sitting position. An epidural catheter attached to a syringe has been passed through the working channel. The tracheal tube has been placed within the airway and the fiberoptic laryngoscope is advanced under vision between the vocal cords and into the trachea.

straight during manipulation so that rotation of the handpiece is transmitted to the distal end. Movements should be gentle and fine. The FFL is advanced while keeping the target in the center of the image as the FFL moves toward the epiglottis, vocal cords, tracheal rings and muscle, and carina. The FFL is passed into the distal portion of the trachea and the tracheal tube then passed over it into the trachea as the patient is asked to inhale deeply. As soon as tracheal intubation is confirmed, the FFL should be withdrawn in an awake patient because respiration will be significantly obstructed while the FFL remains within the tracheal tube. However, premature removal of the FFL during passage of the tracheal tube can result in dislodgement of the tube and esophageal intubation. Tracheal intubation is confirmed by visualization of the carina close to the end of the tracheal tube, and this distance is adjusted to 3 to 4 cm. Additional confirmation of tracheal intubation with capnography is mandatory before anesthesia is induced.

The FFL technique is straightforward in most patients but may be difficult in those with distorted anatomy or very limited space. Jaw thrust may help in the latter situation. An opaque red view implies contact of mucosa or blood with the lens, and a white view is caused by secretions. If sight of the target is lost, the FFL should be withdrawn, the target identified, and the FFL advanced again.

In situations in which use of the FFL alone proves difficult, combination with other techniques may be successful. A retrograde guide can be threaded up the working channel of an FFL on which the tube had been mounted and the combined assembly then advanced to the cricothyroid membrane before the guide is removed. Alternatively, passing the FFL alongside a retrograde guide within a tracheal tube and then advancing the FFL to the carina to act as an introducer may be particularly reliable. Direct or indirect rigid laryngoscopy may be used with the FFL. Use of a capnograph as a guide has been described.[70] Use with SADs is described later.

Tracheal Tube Passage Issues

Difficulty passing tracheal tubes over a properly positioned FFL is common and can result in hypoxemia or airway trauma and be a threat to life.[50] The principal sites that obstruct passage of the tracheal tube are the interarytenoid notch and the right arytenoid cartilage and epiglottis, plus obstruction within the nasal cavity when that route is used.[50] A technique involving withdrawal of the tracheal tube 1 to 2 cm, 90-degree anticlockwise rotation, and readvancement often achieves tracheal intubation in these cases.[50] Jaw thrust may help steer the FFL into the trachea but can obstruct subsequent passage of the tracheal tube, so the thrust should be reduced after the tracheal tube has passed the larynx.[50] Force must not be used during attempts to pass the tracheal tube.

All measures should be taken to ensure that the first attempt at passage of the tracheal tube is likely to be successful.[50] Tracheal tube factors that can increase success of passage include a small gap between the tracheal tube and the FFL[50] and the type of tracheal tube.[50] Although use of a warmed standard tracheal tube has been recommended, it is not clear how long it retains increased softness, there is no evidence that it is better than an armored tracheal tube, and the risk of kinking may be increased. There is some disputed evidence that armored tubes pass more readily than standard tracheal tubes over the FFL into the trachea. Tracheal tubes with tips modified to facilitate passage into the trachea are of proven value and may be the current tracheal tubes of choice.

Limitations of the Flexible Fiberoptic Laryngoscope in Unanticipated Difficult Intubation

Use of the FFL in anesthetized patients immediately after failure of direct laryngoscopy can be difficult (Box 50-12). The flexibility that contributes to the versatility of the FFL in elective patients can be disadvantageous because rapid control of the tip's position is not possible. Use of the nasal route in an unprepared patient risks epistaxis, which is particularly hazardous in this situation. Oral fiberoptic intubation is preferable, but jaw thrust, tongue traction, or concomitant use of a direct laryngoscope may be required unless a conduit is used. Use of a tubular oral airway can be very successful when staff are well trained.[46] The airway must be kept in the midline and directed toward the larynx. Fiberoptic intubation through the ILMA or LMAc has been recommended in guidelines.[52] Use of the FFL through the ILMA is usually successful, but failures do occur.[71] Use of the Aintree or similar catheter with the LMAc is another good alternative.[72] Use of the FFL in a patient with an unanticipated difficult airway requires immediate availability of a sterile FFL.

Contraindications and Complications

There are no absolute contraindications to use of awake flexible fiberoptic laryngoscopy. It cannot be performed without patient cooperation. Awake intubation with the FFL is unlikely to work in the presence of massive airway bleeding, although the LMA can provide an effective conduit.

The arytenoid cartilage can be displaced, even when tube advancement seems atraumatic. Laryngeal damage is more likely when multiple efforts at passage of the tracheal tube are made, but such damage is less frequent and less serious than in patients managed with direct laryngoscopy. Morbidity and mortality associated with use of the FFL have been reported in closed claims.[43] Complete airway obstruction during "awake" fiberoptic intubation in patients with a critical airway has been reported, but heavy sedation and incomplete topicalization were blamed.[27] Awake flexible fiberoptic laryngoscopy is safe in a critical airway when expertly used.[68]

Box 50-12 Problems with the Flexible Fiberoptic Laryngoscope Technique in Unanticipated Difficult Intubation*

- High skill level needed for rapid control of the tip of the laryngoscope
- Two skilled practitioners needed
- Equipment often not ready (time)
- Secretions, edema, and hemorrhage
- Airway less open than when awake—jaw thrust and/or dedicated oral airway needed
- Cricoid pressure impeding entire procedure
- Tracheal tube passage difficult
- Patient risks: hypoxemia, hypoventilation, and pulmonary aspiration

*Patient anesthetized and paralyzed.

Rigid Indirect Optical Devices

The rigidity of rigid indirect optical devices allows rapid control of the position of the tip of the device at the expense of reduced versatility in comparison to flexible devices. They are also less expensive and more robust and portable than the FFL. They may be subdivided into RILs and OSs.

The blade of an RIL can retract tissues to achieve a line of sight from the distal lens, and this ability can be important when there is little space in the oropharynx and laryngopharynx. OSs are optical devices that fit inside the tracheal tube.

The term "video laryngoscope" has been used by manufacturers of devices that differ in many features. "Video laryngoscope" is not a good description for these devices because the display is not the key element in their success. However, video systems have advantages. They are of proven value for teaching flexible fiberoptic intubation and RIL technique[73] and may improve success rates. Ease of use is better because anesthesiologists do not need to follow the eyepiece with their head. Observation of structures throughout insertion and removal is facilitated. The video display facilitates help by assistants, who observe the effect of manipulations. Video tapes of the intubation can be reviewed later.

Rigid Indirect Laryngoscope

RILs vary greatly in features and technique. Most RILs have a distal curve that is designed to match the anatomic curve between the oral and pharyngeal portions of the tongue. Technologies used to transfer the image from the distal lens include lenses and prisms (e.g., Airtraq, TruView), fiberoptics (e.g., Bullard, Upsherscope, WuScope), and electronic transmission from a video chip to a monitor (e.g., Glidescope, McGrath, Pentax AWS). They may be used with the head and neck in a neutral or "sniff" position. The recommended technique of elevation of the epiglottis may be direct or indirect. Direct elevation is more likely to be successful in the presence of lingual tonsil hypertrophy or other laryngeal lesions. The technique of tracheal tube passage is integrated into the design of some RILs. NTI guided by RILs is a very useful technique that overcomes the problems of passage of the oral tracheal tube inherent in some RILs.

The Bullard laryngoscope, the first RIL, was introduced in the late 1980s. Very high success rates have been achieved in patients in whom the larynx cannot be seen with the Macintosh laryngoscope.[47] Techniques can be divided into different stages. The technique with the Bullard laryngoscope is illustrated in Figure 50-14. Most RILs are rotated over the dorsum of the tongue from the oropharynx into the laryngopharynx. Once the tip of the RIL is in the appropriate position in relation to the epiglottis, a lifting force is applied to elevate the epiglottis. Visualization of the larynx is optimized by adjustment of the lifting force and position of the RIL.

The technique of tracheal tube passage depends on the design of the RIL. Integrated tube passage may be accomplished with either a dedicated stylet attached to the RIL or a channel for the tube. Exit of the tube from such a stylet or channel is designed to converge with the line of sight a few centimeters distal to the lens. The tube is guided in a lateral or posterolateral direction to the RIL and is sometimes impeded by the right posterior cartilage or aryepiglottic fold. This problem can be overcome by manipulating the RIL so that the vocal cords are to the right of the center of the image and by leaving sufficient space between the tube and the aryepiglottic fold. An introducer with an angulated tip can be inserted within tubes passed through a dedicated channel to further facilitate passage into the trachea.

Some RILs do not have an integral tracheal tube passage system, so use of a detached stylet to create an optimal shape for delivery of the tracheal tube to the glottis is recommended. Both a "hockey stick" shape and a curvature that matches the RIL have been advocated, as have adjustable stylets. Passage of detached styletted tracheal tubes with RILs is likely to be inherently difficult, but performance improves with experience. The vector of advancement of oral tracheal tubes into the larynx is about 90 degrees from the direction of the force applied to the proximal end of the tube. Although good results have been reported, tracheal intubation can fail when the larynx is visible and multiple attempts at passage of the tracheal tube have been required.[74] Damage to the palatopharyngeal folds and palate by blind passage of detached styletted tracheal tubes through the mouth has been described. A technique that involves looking in the mouth when passing the Glidescope, at the monitor when optimizing its position, at the mouth again when passing the styletted tracheal tube into the pharynx, and then at the monitor when passing the tracheal tube into the trachea has been recommended[75] to reduce the risk of soft tissue damage.

There is good evidence of the efficacy of RILs in many situations. They should be accepted as a necessary alternative to direct laryngoscopy and should be included in plan A (initial tracheal intubation plan) for the management of unanticipated difficult intubation. They may also be useful in anticipated difficult direct laryngoscopy in an uncooperative patient, when an FFL is not available, and possibly when a minor degree of difficulty with direct laryngoscopy is anticipated. Their advantages of minimal neck movement and more reliable view of the larynx than with direct laryngoscopes are strong indications for use in patients with an unstable cervical spine if an FFL is not available.[57,76]

Optical Stylets

OSs are robust and portable stylets that incorporate a distal lens and optical system. They may be rigid or malleable or have a tip that can be flexed and extended. The tracheal tube is mounted on the stylet and advanced under vision for a variable distance into the larynx. The stylet is then held in place while the tracheal tube is advanced into the trachea. Midline or lateral routes may be used.[77] OSs cannot retract tissues, and failure to identify anatomic structures has been reported. Vision beyond the lens may be improved by separating the pharyngeal structure with the jaw-thrust maneuver,[76,77] displacing the tongue and opening the pharynx with a Macintosh or McCoy laryngoscope, or using anterior traction on the tongue.[77] Use of jaw thrust combined with a direct laryngoscope may be necessary in the most difficult patients. Recessed positioning of the tip within the tracheal tube may help keep secretions or blood off the tip. A high success rate in unanticipated difficult intubation has been reported,[78] but some find the technique difficult. It has been used successfully for passage of double-lumen tubes and in patients in whom use of the FFL proved difficult. In a patient with cervical spine injury, an OS may be better than the Macintosh but not as good as an RIL.[76] OSs have been used successfully in awake patients.

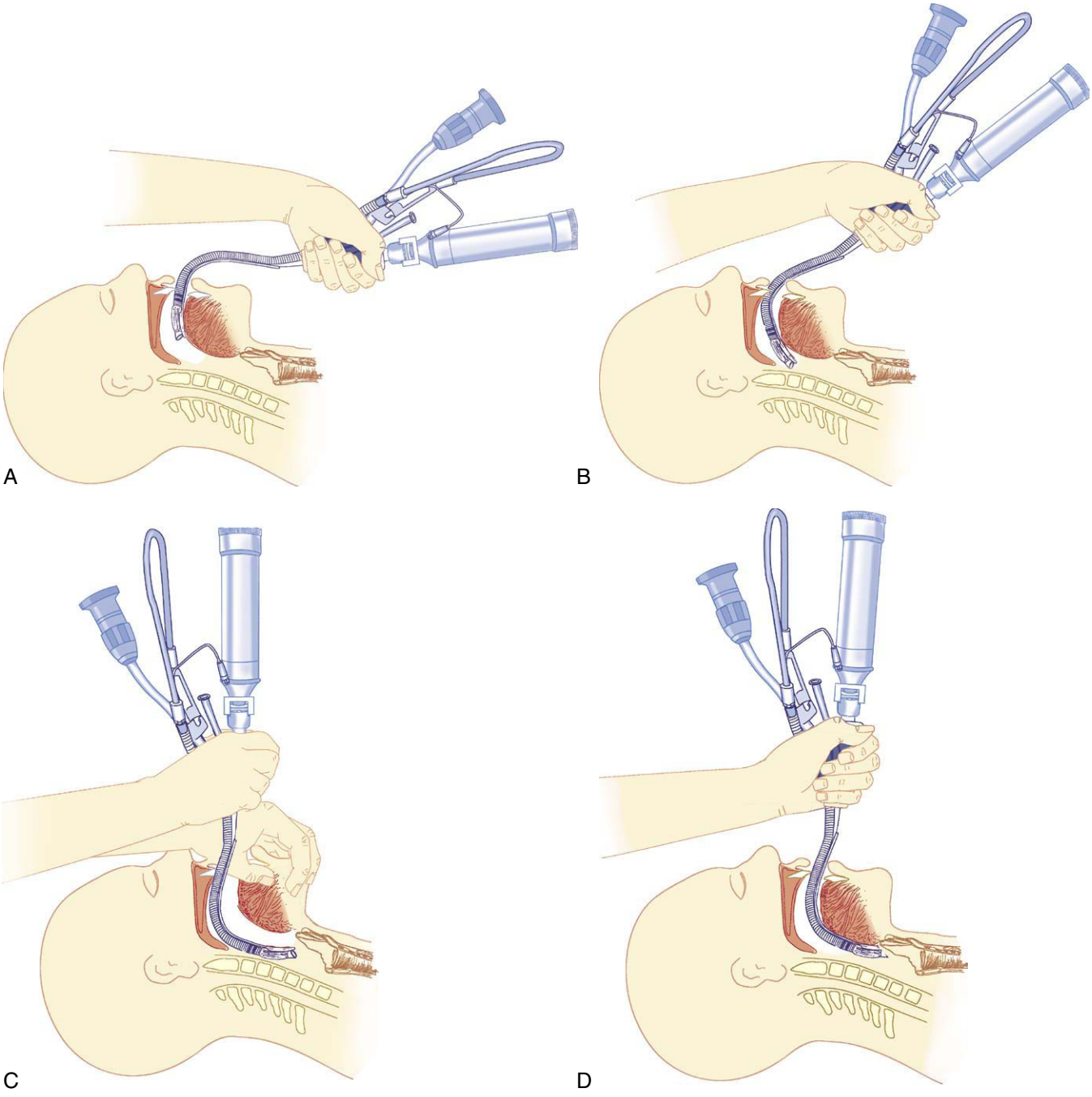


Figure 50-14 Insertion sequence for the Bullard laryngoscope. **A,** Start position with the Bullard handle close to the chest and the tip within the mouth. **B,** Midway through rotation of the Bullard laryngoscope. **C,** Rotation of the Bullard laryngoscope is complete, with the tip lying on the posterior pharyngeal wall and the handle vertical. The anesthesiologist has used a jaw thrust to increase space behind the tongue. **D,** The anesthesiologist seeks and optimizes the view of the larynx. The Bullard laryngoscope has been moved anteriorly so that the tip lies posterior to and elevates the epiglottis.

Tracheal Intubation through the Laryngeal Mask Airway

The LMAc has been used to facilitate tracheal intubation in both elective and rescue situations. Blind techniques have a low success rate and a significant risk of causing airway trauma. However, passage of a tracheal tube mounted on an FFL through the LMA can achieve a high tracheal intubation success rate with minimal risk of trauma,[79] but the widest tracheal tube that will pass down a size 3 or 4 LMA is 6 mm (ID). The tracheal tube must also be long enough for the cuff to lie 2 cm beyond the vocal cords when the proximal end is level with the LMA connector. A 6-mm (ID) microlaryngeal tube is particularly satisfactory because it is sufficiently long and the cuff diameter is suitable for adult patients. However positive-pressure ventilation during fiberoptic intubation through a size 3 or 4 LMA with a 6-mm tracheal tube is unsatisfactory because of the restricted air channel between the

tube and the LMA.[80] Techniques for subsequent LMA removal have been described, but they may fail and expose the patient to the danger of accidental extubation. The AIC (Fig. 50-15) is used in a two-stage fiberoptic technique that facilitates insertion of a wider tracheal tube and safe removal of the LMA.[72] This hollow guide is 56 cm long and fits snugly over a standard (narrower is recommended) FFL, apart from its controllable tip. The AIC is mounted on the FFL, and the combined unit is steered under vision through the LMA and into the trachea. When the tip of the AIC reaches the lower portion of the trachea, the LMA and FFL are withdrawn and a tracheal tube (7 mm or larger) is then passed over the AIC. The technique is mastered rapidly. The AIC has been used successfully with other SADs.

Intubating Laryngeal Mask Airway

The ILMA (Fastrach) was designed as a conduit for tracheal intubation to facilitate ventilation between attempts at tracheal intubation.[71] The rigid handle and airway tube enable rapid and precise control of mask position. The 13-mm ID allows passage of a tracheal tube as wide as 8 mm (ID). An epiglottic elevating bar is designed to elevate the epiglottis as the tube is advanced into the bowl. Single- and the original multiple-use versions of the ILMA are available. Dedicated reusable or single-use tracheal tubes are designed to facilitate atraumatic blind intubation through the ILMA. The tubes are straight, reinforced with wire, and have a soft molded tip with the leading edge close to the midline. The reusable tube has a low-volume, high-pressure cuff, whereas the single-use tube has a high-volume, low-pressure cuff. Standard polyvinyl chloride tracheal tubes should not be used for blind intubation through the ILMA because they exert much higher tissue pressure as they exit from the ILMA and repeated attempts at passage may cause serious damage to the esophagus.

The technique of insertion of the ILMA differs in many respects from insertion of the LMAc, and there is a significant learning curve. A "neutral" head position (nonextended head on a support) is recommended. The ILMA handle is used to rotate the mask into the pharynx. Oxygenation, ventilation, and anesthesia are stabilized after insertion. If resistance to ventilation is encountered, the position of the ILMA is adjusted. The "up-down maneuver" is recommended for management of a down-folded epiglottis, but prior jaw thrust may be needed. The "Chandy maneuver" consists of two separate maneuvers: The ILMA is rotated in the sagittal plane until resistance to bag ventilation is minimal. The ILMA is then lifted gently from the posterior pharyngeal wall just before passage of the tracheal tube. The value of the Chandy maneuver is disputed. Passage of the tracheal tube should be performed gently. The ILMA should be removed soon after tracheal intubation has been verified because its rigidity results in high pressure on adjacent tissues.

A high success rate can be achieved. However, the technique of tracheal tube passage is blind, several attempts may be required, and esophageal intubation can occur. Laryngeal and esophageal damage has been reported. The risk of failure is increased in the presence of laryngeal lesions and previous cervical radiotherapy. Intubation under vision with the FFL through the ILMA achieves higher first-attempt and overall success rates than blind techniques do.

The ILMA is the SAD of choice for blind tracheal intubation and is of proven value as a rescue device in cases of unanticipated difficult intubation. However visualization of the larynx through the ILMA is not as good as that achieved with the LMAc.[81] Use of the ILMA may be difficult if mouth opening is restricted or the glottis is displaced. Use of the ILMA in an "awake" patient when difficulty with tracheal intubation is anticipated has been reported. Awake intubation through the ILMA has few advantages and some disadvantages in comparison to awake FFL intubation through a tubular oropharyngeal airway.[69]

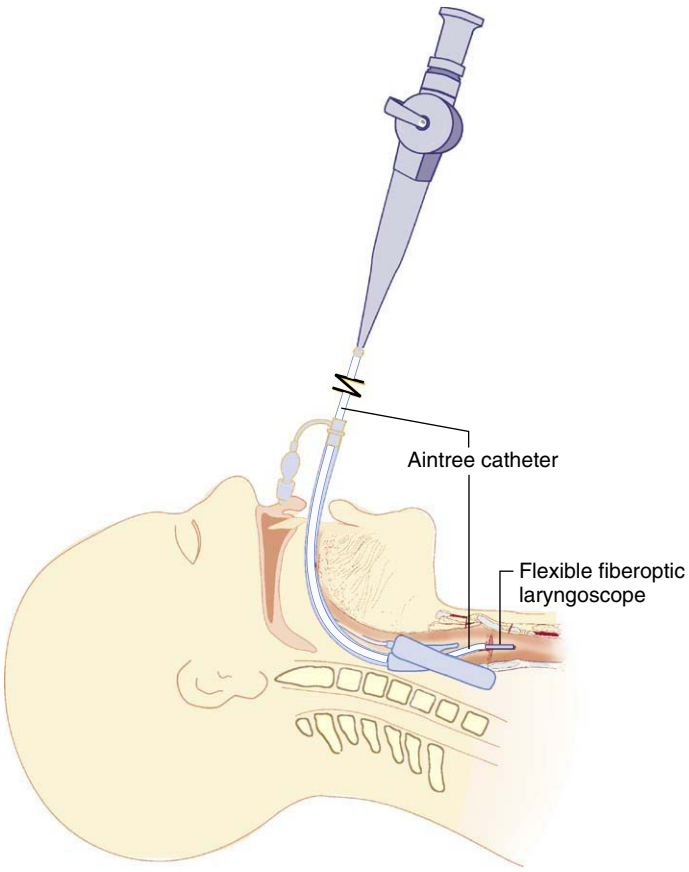


Figure 50-15 Aintree intubating catheter within a flexible fiberoptic laryngoscope, inserted through a laryngeal mask airway and advanced into the trachea.

C-Trach

The C-Trach is a variation of the ILMA that uses fiberoptic bundles to transmit an image from within the bowl of the mask and provides illumination through a light bundle. A separate unit that contains a camera, video display, and source of illumination is attached after insertion of the C-Trach. The display facilitates optimum positioning of the device, but the view remains poor in some patients.[82] Tracheal intubation under vision has been achieved with the C-Trach after failed intubation attempts with the FFL or ILMA,[82] including a case of undiagnosed lingual tonsil hypertrophy. The image is not as good as that produced by a conventional FFL,[82] with problems including secretions, inadequate light intensity, and obstruction of the view by the epiglottis.[83] However, the C-Trach is a relatively portable, inexpensive system that can be prepared rapidly and facilitates ventilation between attempts at passage of the tracheal tube.

Retrograde Intubation

The retrograde technique of intubation consists of percutaneously passing a narrow flexible guide into the trachea from a site below the vocal cords and advancing this guide through the larynx and out the mouth or nose. In the basic technique, the tracheal tube is then passed over the guide into the upper part of the trachea, the guide is removed, and the tube is advanced into the trachea (Fig. 50-16). Guides may emerge from the mouth or nose. If nasal intubation is planned and the guide comes out of the mouth, a soft catheter can be passed through the nose, retrieved from the mouth, and then used to bring the guide out through the nose. Guides used have included plastic introducers, epidural catheters, steel guidewires, and sutures. These guide materials have different properties, but their clinical efficacy has not been compared. Passage of an epidural catheter through the larynx has been successful after failure with a guidewire, and it is easier to retrieve a plastic guide than a steel guidewire from the mouth. Guidewires are a better choice for use with the FFL. The technique can be performed under topical anesthesia in a sedated patient.

Details of the technique are important. Neck extension facilitates access to the cricothyroid membrane. The guides are inserted through a needle or cannula that is inserted horizontally (so that the vocal cords are not damaged) with the bevel directed cephalad. The intratracheal position of the initial needle should be confirmed by aspiration of air. Jaw thrust and tongue traction can facilitate passage of the guide behind the tongue.

A number of problems with the retrograde technique have been reported and variations have been developed (Fig. 50-17) to improve reliability. The most frequent problem is that the tracheal tube springs into the esophagus after the guide is removed, which is a consequence of the location of the cricothyroid membrane (Fig. 50-18) only 1 cm below the vocal cords. Passage of a wider, stiffer plastic sheath over the guide to act as an introducer for the tracheal tube improves reliability. Excessive tension on the guide may pull the tracheal tube anteriorly, thereby causing misalignment and increasing the risk that the tube will be impeded by the epiglottis or other laryngeal structures. Retrograde intubation through the nose has succeeded when the oral route failed, probably because impingement on the anterior glottis is less likely. Use of the subcricoid (cricotracheal) instead of the cricothyroid space may improve reliability at the possible cost of a greater risk of bleeding. The guide may be threaded through the Murphy eye and then passed up through the proximal lumen of the tracheal tube. Pulling the tube after tying a knot inside the Murphy eye has succeeded when other techniques have failed.[84]

The retrograde technique has some disadvantages. It is invasive and advancement of the tracheal tube is blind. It involves several steps and can take some time. The most frequent complications are minor bleeding, subcutaneous emphysema, pneumomediastinum, and infection. Contraindications include coagulopathy, inability to identify landmarks, laryngeal disease, and local infection. Some have achieved high success rates with the retrograde technique,[84] but others have recorded low success and significant complication rates.[85]

The great merit of the technique is its simplicity. It has little place in elective practice in advanced hospitals. It may be the technique of choice when the patient has pharyngeal bleeding and intubation is anticipated to be impossible. It is useful when awake intubation is indicated but sophisticated equipment is not available.

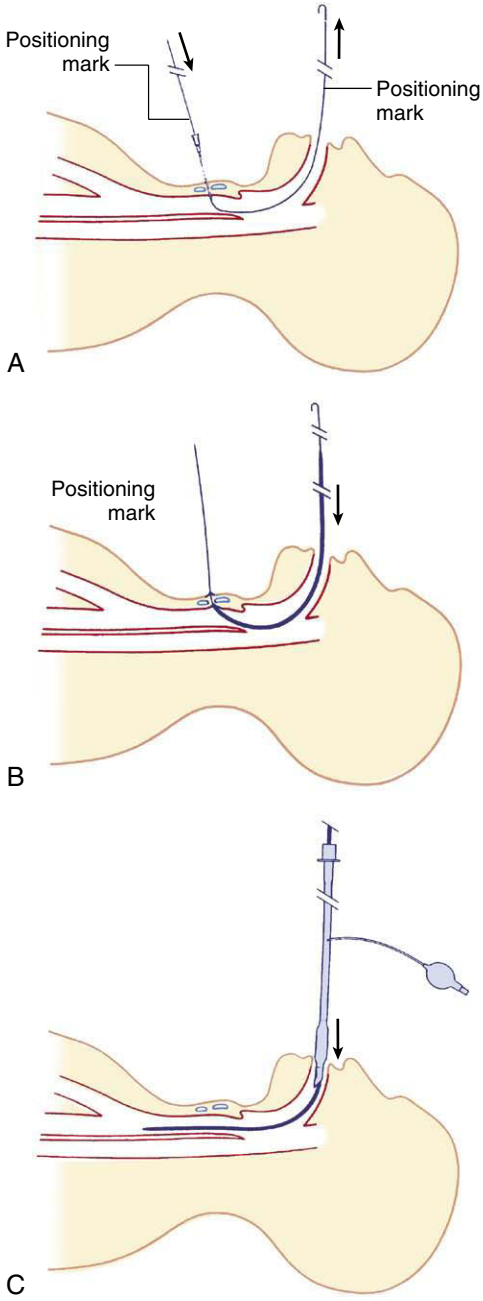


Figure 50-16 Retrograde intubation with the Cook Retrograde Intubation Set. **A,** After placement of an 18-gauge sheath needle into the larynx, the J end of the guidewire is inserted in a cephalad direction until it exits the mouth or nose. **B,** An 11.0 Fr Teflon catheter is threaded down over the guidewire until it contacts the laryngeal access site. The guidewire is removed from above. **C,** After advancing the Teflon catheter 2 to 3 cm, the endotracheal tube is advanced into the trachea while maintaining constant control of the catheter. *(Courtesy of Cook Critical Care, Bloomington, IN.)*

Lighted Stylet (Light-Guided Intubation)

The term "lighted stylet" may be used to describe any device that uses a bright light within the tip of a tracheal tube as a guide to

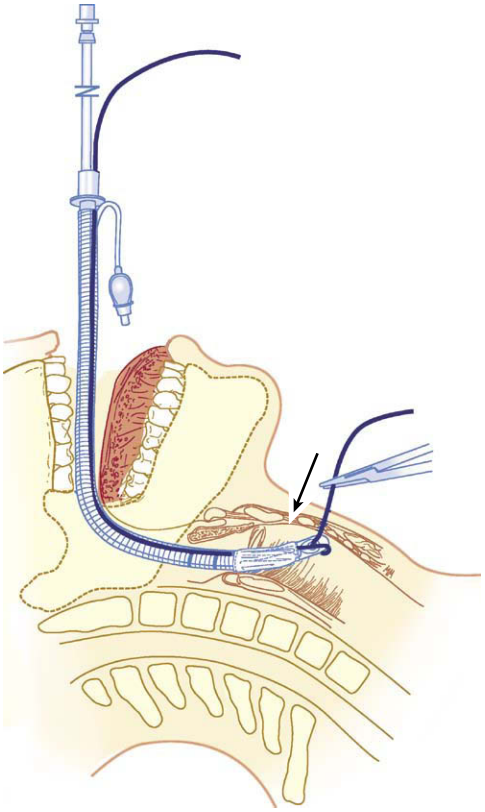


Figure 50-17 Variations on the retrograde technique. The cricothyroid membrane is indicated with an *arrow*. The guide has been inserted through the cricotracheal space, passed in a loop through the Murphy eye of the tracheal tube, and used to pull it toward the cricotracheal membrane. A hollow catheter has been passed through the tracheal tube for passage into the trachea to act as an introducer. These variations may not be used simultaneously in clinical practice.

facilitate tracheal intubation.[86] The technique depends on interpretation of the light transmitted through the skin of the neck to indicate the position of the tip of the tracheal tube. When the tip is at the larynx, the light should be in the midline, and its position in the longitudinal plane indicates its position in relation to the laryngeal cartilage. As the light passes more distally, a localized glow indicates a tracheal position and a diffuse glow indicates an esophageal position.

There is a significant learning curve, but high success rates with few complications can be achieved by those who use the technique regularly in routine practice.[87] It can be used with oral or nasal intubation, with double-lumen tubes, or in conjunction with other devices such as the LMA or ILMA. Successful use in many difficult airway conditions has been described,[87] including cervical spine disorders and intubation in the lateral position. Good success rates achieved after the use of NMBDs could not be repeated in nonparalyzed patients, in whom the incidence of adverse effects was not considered acceptable.[88] Causes of failure include poor illumination as a consequence of obesity[88] or skin pigmentation, resistance to advancement of the tracheal tube, and events such as coughing, hypoxemia, and esophageal intubation.[88] The technique is particularly difficult in the presence of cricoid pressure. It is a blind technique that can damage the larynx. Contraindications include airway tumors, infection, trauma, and foreign bodies.

Physiologic Response to Tracheal Intubation

Direct laryngoscopy and passage of a tracheal tube are noxious stimuli that can provoke adverse responses in the cardiovascular, respiratory, and other physiologic systems.

Significant hypertension and tachycardia are associated with tracheal intubation under light anesthesia. The magnitude of the response is greater with increasing force and duration[10] of laryngoscopy. The elevation in arterial pressure typically starts within 5 seconds of laryngoscopy, peaks in 1 to 2 minutes, and returns to control levels within 5 minutes. Such hemodynamic changes can result in myocardial ischemia but seem to cause little harm to most patients. However they are undesirable in patients with cardiac disease.

It is possible to separate the factors that contribute to the hemodynamic response. Hemodynamic changes start within seconds of direct laryngoscopy, and there is a further increase in heart rate and blood pressure with passage of the tracheal tube. Tracheal intubation through the ILMA causes a hemodynamic effect similar to that caused by direct laryngoscopy.[89] When orotracheal intubation or NTI is performed with the FFL under general anesthesia without topical anesthesia of the airway, hemodynamic changes are similar to those seen with the direct laryngoscope.

Many techniques have been tried in an effort to attenuate adverse hemodynamic responses to intubation, but none is ideal. Prevention by use of an increased depth of anesthesia is attractive in theory. However, changes in the concentration of anesthetic agents in blood and at effector sites occur slowly in relation to the onset and offset of airway stimuli and hemodynamic responses. Use of N_2O with a volatile agent may be beneficial. Large doses of narcotics (other than morphine), such as fentanyl, 6 µg/kg, suppress the hemodynamic response but risk prolonged respiratory depression. Aerosol or other application of topical anesthetics may be beneficial with a low risk of adverse effects. Application of such topical anesthesia may cause minor adverse hemody-

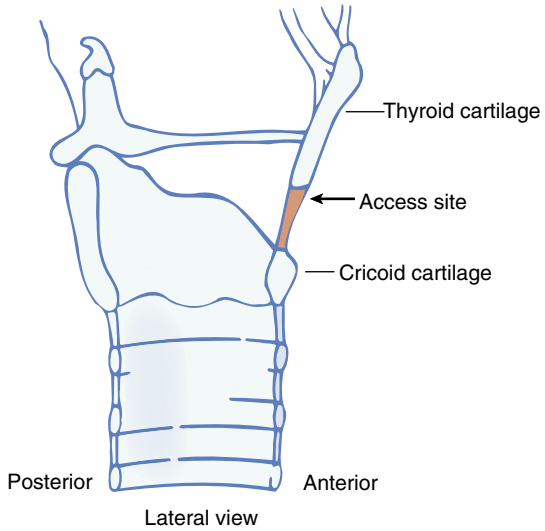


Figure 50-18 Anatomy of the cricothyroid membrane. *(Courtesy of Cook Critical Care, Bloomington, IN.)*

namic effects, much less[90] than those caused by tracheal intubation. Combinations of topical anesthetics with other drugs such as opioids may be useful.

Drugs that act primarily on the cardiovascular system have been studied. Many can reduce either the blood pressure or the heart rate response, but not both, and can cause hypotension or bradycardia. Labetalol and esmolol have been recommended, particularly in combination with narcotics. Use of such drugs is rarely indicated, however.

Another approach to reducing the cardiovascular response to tracheal intubation is to modify the technique of tracheal intubation. Awake flexible fiberoptic intubation with effective topical anesthesia almost eliminates the hemodynamic response to tracheal intubation.

Direct arterial pressure monitoring throughout induction of anesthesia is desirable in a high-risk patient so that the anesthesiologist can respond to accurate, continuous hemodynamic information. Moderate depression of arterial pressure and heart rate before laryngoscopy might limit the rise in arterial pressure at the expense of initial cardiorespiratory depression. Prolonged attempts at laryngoscopy should be avoided. Careful cardiovascular monitoring and willingness to interrupt direct laryngoscopy while anesthesia is deepened are keys to maintenance of reasonable homeostasis.

Respiratory System

Protection of the lungs from pulmonary aspiration is a core function of the upper airway. Laryngospasm is discussed elsewhere. It must be treated vigorously. Bronchospasm accounted for 2% of claims in the ASA Closed Claims Study, half in patients without a previous history of asthma.[64] An increase in airway resistance frequently occurs after tracheal intubation and can be reduced by prophylactic bronchodilator therapy. In patients with asthma, prophylactic steroids and bronchodilators[91] reduce the bronchoconstriction associated with tracheal intubation, as does topical lidocaine with flexible fiberoptic intubation.[92]

Confirmation of Tracheal Intubation

Misplacement of the tracheal tube in the esophagus or right main bronchus is still a major cause of avoidable anesthetic morbidity and mortality.[43] Immediate confirmation of correct tracheal tube placement is an essential and integral part of tracheal intubation. Several tests should be used because no single test is completely reliable.[93] The most important safeguard is clinical suspicion. Visual confirmation of passage of the tracheal tube between the vocal cords is reliable, but not always possible, and experienced anesthesiologists are occasionally misled. The esophageal detector (negative-pressure) test is simple and inexpensive and may be performed before initial ventilation. Air can readily be aspirated from the trachea, but attempted aspiration from the esophagus causes apposition of its walls around the tube so that aspiration of air is not possible. A syringe or self-inflating bulb may be used. It is particularly valuable in cardiac arrest and other emergency intubation situations, but misleading results occur, particularly after gastric insufflation and in the presence of pulmonary disease, obesity, and pregnancy. Airway obstruction has been caused by aspiration of mucus into the tracheal tube. It should be regarded as a device to augment other techniques, particularly when capnography is not available.

A gurgling sound with the first inflation suggests esophageal intubation. Auscultation over the epigastrium and axillae is usually reliable, but there are many sources of error[93] and other confirmation must be sought. Identification of CO_2 in the expired gas is the standard for verification of proper tracheal tube placement, and a characteristic waveform over several breaths is sought. However, there are many possible causes of false-negative and false-positive results.[93] Carbon dioxide concentrations are low or zero despite tracheal intubation in very low cardiac output states, severe respiratory disease, and capnograph or other equipment malfunction. A CO_2 waveform may be detected from the esophagus after gastric insufflation during facemask ventilation or ingestion of carbonated beverages, but these CO_2 concentrations decline rapidly with successive breaths. A glottic or pharyngeal position of the tracheal tube tip can give a normal capnograph and acceptable breath sounds but leave the patient exposed to the risk of accidental extubation and inadequate airway protection. Colorimetric devices sensitive to low concentrations of CO_2 may be misinterpreted as tracheal intubation when the tube is in the esophagus. Identification of the tracheal rings and carina through a standard or simplified[94] FFL passed down the tracheal tube provides reliable confirmation of proper position.

Early hypoxemia after tracheal intubation should be regarded as esophageal intubation until proved otherwise. If there is any suspicion of esophageal intubation, the traditional maxim is "*if in doubt, take it out*," but this strategy is not without risk in that a correctly placed tube may be removed from a hypoxemic patient.

Accidental bronchial intubation can occur during intubation or subsequently, especially if head flexion is increased after initial tracheal tube fixation, the diaphragm is elevated by increased intra-abdominal pressure, or a head-down position is used. It can cause serious morbidity. The most important sign is hypoxemia, usually combined with increased airway pressure. Bronchial intubation is suggested by asymmetric chest expansion. Auscultation over both axillae is usually, but not always diagnostic. Absence of breath sounds over one lung, generally the left, strongly suggests bronchial intubation, but pneumothorax and any causes of atelectasis can also produce this picture. The diagnosis can still be difficult in patients with lung disease, and use of the standard or simplified[95] FFL or chest radiography may be necessary.

Unplanned tracheal extubation is a significant cause of morbidity and mortality. The risk is high in patients with facial burns, in whom the tracheal tube should be left long to allow for facial swelling. The tracheal tube is secured after confirmation of satisfactory position so that it will neither come out nor advance into the right main bronchus. Adhesive or tie tape, or both, may be used. Venous congestion caused by tape tied around the neck should be prevented. Proprietary devices are available, and sutures have also been used.

Care During Surgery

When the airway has been secured, any immediate complications of intubation should be treated. TMJ function should be checked immediately after any procedure that involves maximum mouth opening to prevent undiagnosed dislocation.

Careful intraoperative monitoring of the airway is essential because problems during surgery are a cause of morbidity and mortality.[43] Intraoperative tracheal tube obstruction can be caused by biting, kinking, external compression, and secretions or other intraluminal material. The clinical picture of increased airway pressure and hypoxemia may also be caused by bronchospasm, pneumothorax, surgical manipulation, lung collapse, and raised intra-abdominal pressure. Resistance to passage of a gastric tube or suction catheter down the tracheal tube indicates obstruction but not the cause. Examination with the FFL may be needed to make a complete diagnosis.

Leaks in the anesthesia circuit may be caused by disconnection of the circuit, cuff leaks, or supraglottic position of the tube. Disconnection of anesthesia circuit components should be detected rapidly with the capnograph and respiratory volume monitoring. Leakage of air when the tracheal tube cuff is intact may be caused by insufficient depth of insertion of the tracheal tube so that the cuff lies between or proximal to the vocal cords. Cuff pressure is likely to be elevated, and the tube markings will indicate insufficient depth of insertion. The diagnosis can be confirmed by chest radiography or fiberoptic endoscopy. Low-pressure leaks may be due to damage to the cuff, inflation tube, or valve. Valve incompetence can often be managed by insertion of a three-way stopcock. If major leakage from the cuff cannot be managed by cuff inflation, the tracheal tube will need to be changed (preferably over an introducer or airway exchange catheter [AEC]) to prevent hypoventilation or pulmonary aspiration. If intraoperative tube replacement is judged too dangerous, pharyngeal packing may reduce the leak, but airway protection is limited and there is a risk of gastric insufflation. Inadvertent insertion of a nasogastric tube into the trachea is a rare cause of leakage.

Extubation

The tracheal tube (extubation) is removed when it is no longer needed for airway protection. Timing and technique are influenced by the balance between the residual effect of anesthetic drugs and recovery of airway and other reflexes. A significant number of complications (Box 50-13), including death, occur around the time of extubation.[43] The ASA recommends that the anesthesiologist have a preformulated strategy for extubation and management of postextubation problems.[6] Essential components of the strategy include continued administration of oxygen, continued ventilation, and a strategy to facilitate reintubation.

Box 50-13 Complications at Extubation

- Hypoventilation (residual effect of anesthetic drugs and neuromuscular blockade)
- Upper airway obstruction
- Laryngospasm and bronchospasm
- Coughing (wound disruption)
- Impaired laryngeal competence and pulmonary aspiration
- Hypertension, tachycardia, dysrhythmias, myocardial ischemia

Extubation may be performed at different depths of anesthesia, with the terms "awake," "light," and "deep" often being used. "Light" implies recovery of protective respiratory reflexes and "deep" implies their absence. "Awake" implies appropriate response to verbal stimuli. "Deep" extubation is performed to avoid adverse reflexes caused by the presence of the tracheal tube and its removal, at the price of a higher risk of hypoventilation and upper airway obstruction. Straining, which could disrupt the surgical repair, is less likely with "deep" extubation. Upper airway obstruction and hypoventilation are less likely during "light" extubation, at the price of adverse hemodynamic and respiratory reflexes. An alternative strategy of replacing a tracheal tube with an LMA during "deep" anesthesia has been described. However, there are risks of hypoventilation and malposition of the LMA.

Pathophysiology and Pharmacology of Extubation

Restart of respiration after positive-pressure ventilation can be erratic, with apnea occurring in the presence of hypercapnia. Respiratory complications at extubation include pulmonary aspiration, upper airway obstruction, or hypoventilation leading to hypoxemia and laryngospasm. Laryngeal function is impaired, even after use of an LMA,[42] and may be particularly severe after neck and thyroid surgery. The risk of impaired laryngeal function is increased in patients with neurologic or neuromuscular disease. Coughing may be particularly troublesome during "light anesthesia" extubation and cannot be entirely prevented. The frequency of cough may be reduced when the volatile used is sevoflurane. Intravenous alfentanil and lidocaine can also reduce the risk of coughing, as can local anesthetic in the tracheal tube cuff or applied to the airway.

Cardiovascular complications include arterial hypertension (with an associated increase in intracranial and ocular pressure), tachycardia, and dysrhythmias. Pulmonary edema may be caused by myocardial ischemia or by negative intrapulmonary pressure created by respiratory effort during airway obstruction. Marked increases in arterial blood pressure and heart rate occur frequently at the time of "light" extubation. These effects are alarming but normally transient, and there is little evidence of adverse consequences. However, they may cause detrimental increases in intracranial and intraocular pressure after neurologic and ophthalmic surgery. Many techniques can reduce the incidence of these adverse effects. Narcotics, β-adrenergic drugs, and calcium channel blocking drugs have been studied most extensively. The results are conflicting and there is a risk of adverse effects. On the rare occasions when these drugs are indicated, short-acting agents should be used and direct arterial pressure monitoring continued.

Rapid recovery of consciousness shortens the at-risk time during extubation and may reduce morbidity, particularly in obese patients. Avoidance of sedative premedication facilitates rapid recovery. Nitrous oxide, sevoflurane, and desflurane all contribute to rapid recovery, particularly after prolonged procedures. Remifentanil also facilitates rapid recovery, early extubation, and high Spo_2 values on admission to the postanesthesia care unit.

Position

The "sniff position" is the standard position for extubation. Its major advantage is that airway management, including reintubation, is optimized. The "recovery" (lateral) position may be a safer option when there is an increased risk for pulmonary aspiration.

Gravity causes soft tissues and any foreign material in the pharynx to move downward and away from the larynx and fluid to drain out of the mouth, so the risk of upper airway obstruction and pulmonary aspiration is reduced. Preemptive turning of at-risk patients into the recovery position is wise because emergency turning of a vomiting or regurgitating patient creates increased risk for the patient and staff. The combination of the recovery position with awake extubation is recommended for patients at high risk for pulmonary aspiration. If the recovery position cannot be used in such patients, awake extubation is mandatory. Use of the recovery position with minimal stimulation reduces the incidence of laryngospasm, coughing, and desaturation.[96]

Extubation after Uncomplicated Airway Management

Preparations for extubation are shown in Box 50-14. Recovery of neuromuscular function is essential, but confirmation can be difficult. Respiration should be well established and confirmed by capnography and measurement of ventilation. "Preoxygenation" before extubation delays the onset of hypoxemia if upper airway obstruction develops and is recommended. Throat packs must be removed before extubation. Complete airway obstruction caused by biting a tracheal tube as anesthesia lightens can lead to the rapid development of hypoxemia and may be followed by negative-pressure pulmonary edema. Bite blocks reduce but do not eliminate the risk of tracheal tube compression. Insertion of a bite block, if not in place, should be considered as the anesthesia lightens.

Suction of pharyngeal secretions or other material before extubation should reduce the risk of pulmonary aspiration or laryngospasm. Positive-pressure extubation may expel secretions lying above the cuff but should be performed carefully to prevent complications caused by raised airway pressure.

Inability to deflate the cuff may be due to occlusion of the pilot tube. Surgical fixation by sutures or other devices may cause resistance to withdrawal of the tube. Force should not be used. Fiberoptic examination may confirm the diagnosis, and surgical re-exploration may be necessary.

Laryngospasm at Extubation

Management of laryngospasm at extubation differs from intraoperative management of laryngospasm in that use of intravenous anesthetics will delay recovery. The Larson maneuver, pressure on the "laryngospasm notch" (between the angle of the mandible and the mastoid process), is noninvasive, safe, and often effective.[30] It is also a useful stimulant whenever there is respiratory depression after extubation. Helium is of proven value in the management of postextubation stridor. It does not resolve the underlying process but can increase tidal volume, improve oxygenation, and reduce anxiety. The ratio of oxygen to helium should be adjusted according to the clinical response.[97] If hypoxemia is severe or the laryngospasm does not respond to these noninvasive measures, succinylcholine should be given and the patient reintubated. The best help available should be sought whenever reintubation is performed in suboptimal conditions.

Box 50-14 Preparation for Extubation

Initial Plan

"Deep" extubation

"Awake" extubation

Deep replacement of the tracheal tube with a laryngeal mask airway

Other Preparations

Patient position plan

Bite block in place

Throat pack removed

Preoxygenation

Secretions aspirated from the pharynx (the trachea also if indicated)

Extubation of Patients with a Difficult Airway

Many surgical and anesthetic factors (including airway disease, surgery, and trauma; cervical spine and other head and neck surgery; and difficult tracheal intubation, especially multiple intubation attempts) can cause swelling of tissues in the upper airway and increase the risk for airway obstruction after extubation. Other risk factors include obesity and a history of obstructive sleep apnea.[43] Such patients have died at extubation as a consequence of airway obstruction and failure to reintubate.[98] Important management issues for extubation of these patients include airway risk assessment and location, time, and technique of extubation.

The principal extubation risk assessments tests are the leak test and visual inspection and imaging of airway swelling. Leak tests are used to determine whether gas can pass between the tracheal tube and wall of the trachea after cuff deflation. The hypothesis is that this information indicates the absence of swelling and predicts airway patency after removal of the tracheal tube. Leak tests have been performed in different ways. There is a risk that negative-pressure pulmonary edema will develop when the leak test is performed during spontaneous ventilation. Results are conflicting, and a leak does not guarantee airway patency after extubation. However, low leak volumes are associated with an increased risk for upper airway obstruction.[99] Whenever there is any doubt about risks, a flexible fiberoptic endoscope should be used to assess swelling and other causes of upper airway obstruction.

An extubation-risk patient should remain intubated in the intensive therapy unit until there is evidence that airway swelling has resolved. Other factors such as altered neurologic status may affect the time of extubation, and tracheotomy may be needed in such patients. Extubation should not be performed when there is an increased risk for vomiting or regurgitation. The intensive therapy unit and the operating room are the safest places for extubation. A full range of equipment and personnel should be available, and all preparations, including surgical, should be made for airway management. Extubation should be performed in an awake patient after breathing 100% oxygen to maximize oxygen stores. Helium, noninvasive ventilation, and CPAP may reduce the need for reintubation.

Airway Exchange Catheters

Solid introducers have been used as guides for reintubation. They are passed through the tracheal tube before extubation and kept in situ until the possible need for reintubation has passed. AECs have been introduced as hollow reintubation guides that have the additional potential capability of maintaining oxygenation or monitoring tracheal gas. They are normally supplied with 15-mm

and Luer connectors. The ideal depth of insertion of the tip of the AEC is midtracheal. AECs are generally well tolerated by awake patients, who can breath around them. Insufflation of oxygen at low pressure or positive-pressure ventilation by the intermittent application of high pressure is possible. If positive-pressure ventilation is used, it should be started with great caution. The lowest pressure that produces an acceptable tidal volume, judged by movement of the chest and upper part of the abdomen, should be used. The next inspiration should not start until the chest returns to its preinspiration position. Expiratory resistance should be minimized by jaw thrust and head extension, augmented by an oropharyngeal airway or LMA, if required. The concern about oxygenation through AECs is the significant risk for barotrauma.[100] Although insufflation through AECs without barotrauma has been reported, insufflation through the FFL and AEC has caused serious barotrauma. Insufflation through an AEC is of doubtful value when oxygen can be administered by facemask.[101] The need for AEC ventilation should be weighed against the risks. It should be considered only by users who have practiced the AEC technique in workshops.

Percutaneous Airway

A percutaneous (transcutaneous) airway connects the trachea and lower airway to the atmosphere, anesthesia circuit, or other device through a surgically created opening in the front of the neck that bypasses the larynx and upper airway. Rapid emergency creation of such an airway is necessary when noninvasive techniques fail to relieve the "cannot intubate, cannot ventilate" situation and severe increasing hypoxemia develops. Creation of a percutaneous airway involves significant hazards.

Tracheotomy

Tracheotomy requires incision of the skin and subcutaneous tissues, separation of the strap muscles, division of the isthmus of the thyroid gland, incision of the anterior wall of the trachea, and insertion of a cuffed tracheotomy tube. Access is improved by neck extension achieved by placing a bolster under the shoulders. Emergency tracheotomy can be very difficult and give rise serious complications.[102] A few surgeons may succeed in 3 minutes, but most take longer. Delay in completion of tracheostomy in this situation is likely to result in death of the patient. Elective tracheotomy for airway management is indicated when the risk of loss of the airway during attempted tracheal intubation is high, such as when respiration is compromised by laryngeal tumors or deep neck abscesses. Wherever possible, tracheotomy is performed in a patient who is already intubated because operating conditions are better for the surgeon. The anesthesiologist coordinates withdrawal of the tracheal tube with the surgical incision in the trachea. Sensible precautions include preoxygenation before incision of the trachea and insertion of an introducer or AEC as the tracheal tube is withdrawn so that reintubation is facilitated, if necessary. Tracheotomy is performed under local anesthesia in an awake patient if the risk of airway loss during tracheal intubation is high.

Tracheotomy is also used as a replacement for orotracheal intubation in a critically ill patient who requires prolonged airway support. Dilatational tracheotomy is used frequently. Discussion of the technique is beyond the scope of this chapter.

Cricothyrotomy

Cricothyrotomy creates a percutaneous airway through the cricothyroid membrane. Its advantages over tracheotomy are that the membrane is superficial and relatively avascular and cartilage incision is not necessary because the height of the membrane is greater than the distance between the tracheal rings. Cricothyrotomy can be performed with a surgical or cannula (needle) technique, and appropriate use can prevent anesthetic-related deaths. It is a core skill for the anesthesiologist.

Surgical Cricothyrotomy

Surgical cricothyrotomy uses surgical techniques to insert a cuffed tube in the trachea (successful low-pressure ventilation with an uncuffed tube is not guaranteed[103]). It facilitates rapid restoration of ventilation and oxygenation in the "cannot intubate, cannot ventilate" situation.[2] Emergency cricothyrotomy can cause serious complications,[102] although they are infrequent when staff is well trained.[104] The four-step simplified cricothyrotomy technique (Box 50-15) can be performed in 30 seconds.[105] A No. 20 scalpel is preferred because its width is sufficient for insertion of a narrow tube without the need for extension of the incision, and its length is such that damage to the posterior wall of the trachea is unlikely. In an obese patient in whom the laryngeal cartilage cannot be identified, step 1 is modified to include an initial vertical incision so that the cartilage can be identified. Insertion of the tube in an obese patient may be facilitated by passage of an introducer into the trachea. When oxygenation has been restored, hemostasis can be secured.

Seldinger Cricothyrotomy

Anesthesiologists are reluctant to perform emergency surgical techniques, and thus Seldinger guidewire cricothyrotomy techniques have been developed.[103] These techniques are preferred by

Box 50-15 Surgical Cricothyrotomy

Equipment

No. 20 scalpel

Cuffed tracheal or tracheostomy tube with a 6- or 7-mm internal diameter

Technique

Step 1: Extend the head and neck and identify and immobilize the cricothyroid membrane (initial vertical incision if identification is not possible)

Step 2: Horizontal stab incision through the skin and cricothyroid membrane. Leave the blade in place until the tracheal hook is in position (step 3)

Step 3: Caudal and outward traction on the cricoid cartilage with the tracheal hook; remove the scalpel

Step 4: Insert the tube and inflate the cuff

Step 5: Ventilate with a low-pressure source

Step 6: Confirm pulmonary ventilation

many anesthesiologists because they do not involve unfamiliar surgical techniques. Seldinger cricothyrotomy has taken longer than the surgical technique to restore the airway in most studies. Kinking of the guidewire can be a serious problem.

Cannula (Needle) Cricothyrotomy

Cannula cricothyrotomy requires the *combination* of a cannula through the cricothyroid membrane *with* high-pressure ventilation. It can provide effective ventilation,[46] although low success rates have been reported. Kink-resistant cannulas must be used because standard intravenous cannulas are easily kinked. The technique is summarized in Box 50-16 and described in detail elsewhere. Verification of correct cannula placement by aspiration of air into a large syringe before the use of high-pressure ventilation is essential. Subsequent dislodgement of the cannula must be prevented.

Effective ventilation through a cannula is possible only when a high-pressure (e.g., hospital pipeline) source is used, and an adjustable device with a Luer-Lok connection is recommended. Barotrauma is a serious complication. It is less likely if an initial inflation pressure of less than 4 kPa (55 psi) is used. Ventilation should be started cautiously. It is important to keep the upper airway as open as possible and to verify deflation of the lungs and exhalation through the upper airway. Cannula cricothyrotomy can be safe only if meticulous technique is practiced regularly and safety rules are observed. Elective cannula cricothyrotomy may have a role in ENT surgery and when a difficult airway is anticipated.[106]

Complications of Airway Management

Many complications are associated with airway management and some are considered elsewhere in this chapter. The most serious complications are hypoxemia and soft tissue damage to the pharynx and esophagus. Hypoxemia should be preventable when anesthesiologists avoid high-risk strategies and have a sufficient range of skills to manage a wide variety of scenarios. Soft tissue damage is responsible for 6% of closed claims.[65] Mediastinitis should be prevented by gentleness and avoiding repeated use of techniques, particularly blind ones, when they prove ineffective. Unfamiliar techniques should not be used for the first time in an emergency situation. The effects of any trauma should be mitigated by arranging good follow-up care.[65] Damage to the glossopharyngeal, hypoglossal, lingual, superior laryngeal, recurrent laryngeal, mental, and branches of the trigeminal nerve has been reported after airway management. This damage has been attributed to direct trauma or cuff pressure.

Less serious complications occur more frequently. Dental damage is the most frequent cause of complaints against anesthesiologists,[12] with an incidence of 1 in 4500 reported from one department.[58] Serious injuries include subluxation, fracture, and avulsion of teeth.[58] Diseased teeth are at particularly high risk, but healthy teeth can also be injured. Only the most serious injuries are likely to lead to complaint, so the incidence of minor dental injury is probably higher than realized. Use of dental guards during direct laryngoscopy has been advocated, but prevention of injury is not guaranteed, the efficacy of direct laryngoscopy may be reduced, and the risk of injury may be increased. Injury to healthy teeth in patients undergoing elective surgery should be prevented by using alternative airway techniques if pressure on teeth cannot be avoided with the first laryngoscopy technique chosen. Dental damage can also be caused by insertion and removal of or biting on several airway devices. An urgent dental consultation should be arranged after any dental damage. Any dislodged teeth or fragments should be located and, if in the respiratory tract, removed.

Laryngeal damage has been found in 84% of patients, 69% of whom were symptomatic, when computed tomography was performed 6 months or longer after tracheal intubation for elective surgery. Patients with hoarseness or other signs of laryngeal damage after airway management should be referred to an ENT surgeon. Laryngeal and tracheal damage after long-term intubation is beyond the scope of this chapter.

Although the number of claims for airway management complications remains substantial, results from single hospitals show that airway management can be accomplished with a very low incidence of serious complications.[10,46,47,63]

Box 50-16 Cannula Cricothyrotomy

Equipment

Kink-resistant cannula

High-pressure ventilation system

Technique

Insert the cannula through the cricothyroid membrane

Confirm tracheal position by aspiration of air with a 20-mL syringe

Maintain position of the cannula with a dedicated hand

Attach the ventilation system to the cannula

Ensure an open upper airway (including jaw thrust, head extension, and possibly a laryngeal mask airway)

Commence cautious ventilation

Confirm inflation and deflation of the lungs and exhalation through the upper airway

Convert to a surgical cricothyroidotomy if ventilation fails or any complications develop

Follow-up After Difficulty with Airway Management

The anesthesiologist has continuing responsibility for issues that may influence future safety of the patient. The ASA guidelines[6] recommend that the anesthesiologist document the presence and nature of any airway difficulty, inform the patient, and evaluate and arrange appropriate management of complications. Documentation is summarized in the ASA guidelines and should include a description of the airway difficulties, the management used, and the number and duration of attempts.[6] Possible notification systems include a written report or letter to the patient, a written report in the medical chart, and communication with the

patient's surgeon or primary caregiver. Because only a warning bracelet (e.g., www.medicalert.com) may be effective if the patient is admitted unconscious to hospital, additional use of this system is recommended.

Patients in whom laryngoscopy proves unexpectedly difficult are entitled to a diagnosis and appropriate management. Fiberoptic nasendoscopy[3,6] and appropriate imaging should be considered. Domino and coworkers stated that "patients in whom tracheal intubation has been difficult should be observed for and told to watch for the development of symptoms and signs of retropharyngeal abscess, mediastinitis, or both."[65] Death is less likely if the diagnosis is made and treatment started promptly.

Cleaning and Disinfection of Airway Equipment

Equipment used for invasive procedures, including airway management, should be sterile to prevent cross-infection. The risk of spreading prion disease with the use of contaminated medical equipment[107] is a particular problem because conventional cleaning and sterilization do not remove protein deposits from equipment. Furthermore, sterilization can cause deterioration in equipment performance, such as the effect of repeated autoclaving on the fiberoptic bundles of direct laryngoscopes.

Transfer of infected material can be prevented by using single-use equipment. However, single-use equipment (direct laryngoscopes, introducers, SADs) has frequently been introduced without evidence of efficacy. In the case of direct laryngoscopes, there has been great variation in rigidity in the longitudinal and torsional axes. The blades are often thicker and thus the view of the larynx is impaired, and there is less room for maneuvering the tracheal tube. The illumination provided by single-use blades varies in intensity, width of the beam, and direction. Plastic single-use blades perform less well than standard metal reusable blades, may result in a longer duration of laryngoscopy, and are not recommended for rapid-sequence induction (RSI).

Challenging Airway Management Scenarios

Risk of Pulmonary Aspiration

Foreign material may be aspirated into the lungs when the normal laryngeal protective mechanisms fail. Pulmonary aspiration was confirmed in 1 in 8600 anesthetic procedures in a recent review.[108] The clinical consequences depend on the quantity, nature, and distribution of the material aspirated; the relative impact of the acid, bacterial, and particle content; and patient factors. The range of effects varies from cough and laryngospasm caused by aspiration of a small volume of pharyngeal contents to drowning secondary to aspiration of liters of gastrointestinal contents. Pulmonary aspiration accounted for 4% of claims in the ASA Closed Claims Study.[1] Most cases occur during induction of anesthesia or, less frequently, at extubation and recovery.[108]

When the lower and upper esophageal sphincters are working optimally, they prevent passive regurgitation from the stomach to the esophagus and from the esophagus to the pharynx, respectively. Their tone is reduced as consciousness is lost. Tone may be increased or decreased as a secondary effect of a variety of procedures and drugs used by anesthesiologists.

Major risk factors for regurgitation and vomiting include pregnancy after the first trimester and acute gastrointestinal disease, particularly esophageal or gastric disease, small bowel obstruction, and ileus. Other risk factors for gastrointestinal stasis include trauma, diabetes, obesity, and the administration of drugs (such as narcotics) that inhibit gastrointestinal function. The head-down and lithotomy positions increase the risk for regurgitation. Parkinson's disease, bulbar palsy, myotonia dystrophica, and other neurologic diseases impair protective reflexes and increase the risk for pulmonary aspiration. Recent ingestion of food is a risk factor, but fasting from the midnight before surgery to any time in the following day is thought to be excessive.[109] Fasting for 6 hours after a light meal and 2 hours after clear fluids is widely accepted as safe practice for patients without risk factors[109]; however, regurgitation can occur in patients without risk factors and anesthesiologists should always be prepared.

Awake tracheal intubation is the technique of choice when there is a risk of pulmonary aspiration and difficulty with airway management is predicted. Concern that an increased risk for pulmonary aspiration may be produced by topical anesthesia of the larynx has proved unfounded in a large series of high-risk patients. Consciousness contributes significantly to airway protection.

RSI is used to reduce the risk of pulmonary aspiration in at-risk patients. The principle of RSI is that tracheal intubation is achieved as rapidly as possible to reduce the time at risk for pulmonary aspiration and the development of hypoxemia. Preoxygenation, intravenous anesthesia, rapid-onset neuromuscular blockade, and use of cricoid pressure (controversy discussed later) are the essential components of RSI.

Cricoid pressure has been used to prevent pulmonary aspiration since its description by Sellick. The hypothetical basis is that pressure on the front of the cricoid cartilage is transmitted to its posterior lamina, which occludes the esophagus by compression against the vertebral bodies. Radiology and cadaver studies have demonstrated occlusion of the esophagus with cricoid pressure. However, lateral displacement of the esophagus has been found in 91% of patients when cricoid pressure was applied.[110] Many recommendations about the technique of cricoid pressure have been made. It should be applied in such a way that it does not interfere with insertion of the laryngoscope. Cricoid pressure may be applied with an initial force of 10 N (a weight of about 1 kg, which is tolerable) when the patient is awake and then increasing to 30 N (about 3 kg), which minimizes the risk of airway obstruction, as consciousness is lost.[52] The force should be reduced, with suction at hand, if it impedes laryngoscopy or passage of the tracheal tube.

Cricoid pressure has disadvantages. It reduces the tone of the lower esophageal sphincter, so the risk of regurgitation from the stomach to the esophagus is increased. It can impair insertion of the laryngoscope, degrade the view of the larynx, impede passage of an introducer or tracheal tube, and cause airway obstruction.[111] Application of cricoid pressure by an assistant impedes external laryngeal manipulation by the anesthesiologist. Fracture of the cricoid cartilage has been attributed to cricoid pressure. Vomiting in the presence of cricoid pressure may gener-

ate enough pressure to rupture the esophagus, although low levels of cricoid pressure might be safe in the presence of vomiting.

The role of cricoid pressure has become controversial.[112] The lack of prospective studies has been criticized, but ethical issues make such studies impossible. Difficult laryngoscopy caused by cricoid pressure may have caused deaths. Pulmonary aspiration has occurred despite the use of cricoid pressure, possibly partly as a consequence of iatrogenic difficulty with tracheal intubation.[108] However, occasional complications do not mean that the technique is of no value. Pulmonary aspiration has occurred when cricoid pressure was not applied, and case reports of massive regurgitation after release of cricoid pressure provide evidence of its value. However, there must be a low threshold for reducing cricoid pressure when there are problems with mask ventilation, laryngoscopy, or passage of the tracheal tube.

Use of wide-bore gastric tubes to empty the stomach before RSI has been recommended even though pulmonary aspiration can occur despite the presence of a nasogastric tube. Suction on a nasogastric tube can reduce the volume of gastric contents, but there is no guarantee that the stomach will be emptied. The stomach regularly fills from below in patients with intestinal obstruction. The presence of a nasogastric tube may increase the risk associated with regurgitation, and removal of the tube while suctioning has been advised before the implementation of RSI. The opposite view is that gastric tubes may limit rises in gastric pressure. Insertion of a nasogastric tube before induction of anesthesia is rarely indicated except in patients with gastrointestinal obstruction or ileus.[113]

Drugs (antacids, histamine H_2 receptor antagonists, proton pump inhibitors) may be used to reduce the acidity or volume (or both) of gastric fluid. These drugs should be given on the day of surgery to patients for whom they are already prescribed. Their use for premedication of patients with symptoms of gastroesophageal reflux disease is prudent. Neutralization of gastric contents with nonparticulate antacid in obstetric or other patients at high risk for aspiration of acid is recommended.

Anticipated Difficult Intubation

The basic management decisions for all patients are described in the ASA guidelines (see Fig. 50-2),[6] specifically, awake versus anesthetized, noninvasive versus invasive, and preservation of spontaneous ventilation versus apnea. Although creation of a surgical airway in an awake patient is occasionally necessary, the safest plan for most cases of anticipated airway difficulty is to perform awake tracheal intubation under topical anesthesia.[67] The most versatile instrument for this technique is the FFL. The threshold for using awake flexible fiberoptic intubation should be particularly low if surgery is urgent (cancellation of surgery is not an option) or examination suggests that rescue techniques will be difficult or impossible.

Lack of patient cooperation precludes awake techniques. In these patients and if minor difficulty is anticipated before elective surgery, general anesthesia may be induced by experienced anesthesiologists, but muscle relaxants must be given until the airway has been secured. RILs may have a significant role in such patients.

Use of alternatives to tracheal intubation for patients with anticipated airway difficulty may be considered. Inhaled induction and maintenance of facemask anesthesia for minor surgery of short duration in a fasted patient is a good technique for a skilled user. The hazards of using SADs in such patients have been considered. Use of regional anesthesia in patients with an anticipated difficult airway does not remove the airway problem and carries the risk that failure of the regional technique (including increased duration or extension of surgery) could result in the need for difficult intraoperative tracheal intubation under suboptimal conditions (see Box 50-4).

Unanticipated Difficult Intubation

Unanticipated difficulty with direct laryngoscopy cannot be prevented, and a management strategy based on a sufficient range of skills should be in place. All anesthesiologists should be skilled in at least one alternative technique of tracheal intubation under vision.[47,114] Strategies that include algorithms for the management of unanticipated difficult intubation have been produced by several organizations, including the ASA and the Difficult Airway Society (DAS), a U.K. organization. The ASA algorithm is the standard guide (see Fig. 50-2). A great merit of the DAS algorithm[52] (Fig. 50-19) is its simplicity and emphasis on progression through a series of defined plans. Plan C, awakening the patient and postponing elective surgery, is an important means of maintaining oxygenation and preventing trauma. The choice of techniques within the plans is less important than the underling principles and strategy. Organizations and individuals should use evidence to select appropriate techniques within the strategy. However, guidelines cannot achieve their aims without good training. Some departments have produced their own guidelines, accompanied by a training program, and report excellent results.[46,63]

The most difficult situation is management of unanticipated airway difficulty in a patient requiring emergency surgery. The risks of delaying surgery must be balanced against the risk of proceeding with a suboptimal airway. If it is essential to proceed with surgery, a traditional technique has been to continue with a facemask and oral airway while maintaining cricoid pressure. Continuation of anesthesia with an LMAc is now an established technique, though not always effective. Insertion of SADs is impeded by cricoid pressure,[115,116] which should be reduced as necessary during insertion and then reapplied at a level that allows satisfactory function. The PLMA forms a better seal than the LMAc does and provides improved protection against aspiration. It may be preferred by users who have proven competence with the device. Early conversion to tracheal intubation with devices such as the AIC is desirable.

"Cannot Intubate, Cannot Ventilate" Situation

This situation may be defined as one in which ventilation with noninvasive techniques fails to maintain oxygenation and tracheal intubation proves impossible. This scenario may develop rapidly but often occurs after repeated unsuccessful attempts at intubation.[64]

Before resorting to invasive percutaneous airway techniques, maximum effort must be made to achieve ventilation and oxygenation with noninvasive techniques, such as optimum mask ventilation and use of SADs. Facemask ventilation may require

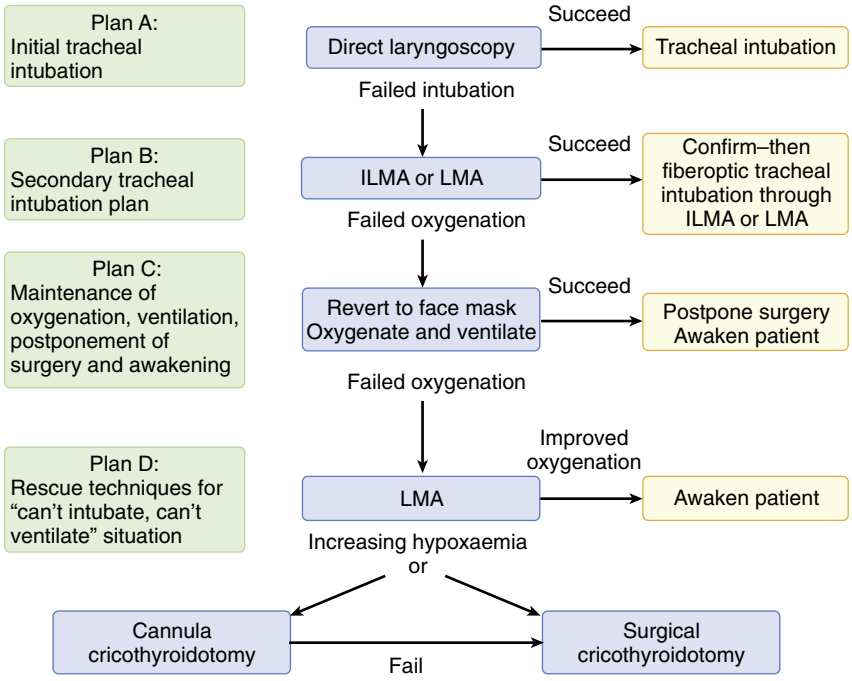


Figure 50-19 Basic algorithm of the Difficult Airway Society (DAS) guidelines for the management of unanticipated difficult tracheal intubation. *(From Henderson JJ, Popat MT, Latto IP, et al: Difficult Airway Society guidelines for management of the unanticipated difficult intubation. Anaesthesia 59:675-694, 2004.)*

the two-person technique and the use of an oral or nasal airway. It may be necessary to reduce cricoid pressure to achieve satisfactory ventilation. If satisfactory oxygenation cannot be achieved with a facemask, an SAD should be used instead. Insertion of an LMA in the "cannot intubate, cannot ventilate" situation has a significant failure rate.[43]

The risks associated with an invasive rescue technique must be constantly weighed against the risk of hypoxic brain damage or death. Rapid development of severe hypoxemia, particularly when associated with bradycardia, is an indication for imminent insertion of a percutaneous airway that can reliably deliver a large minute volume with an F_{IO_2} of 1.0. Many cricothyrotomy techniques have been criticized because they are not capable of providing effective ventilation.[117,118]

If noninvasive techniques do not restore oxygenation, cricothyrotomy is the percutaneous airway of choice[2] because tracheotomy may take too long. It is not possible to define the S_{PO_2} at which cricothyrotomy should be performed—it depends on the degree of hypoxemia and how rapidly it is deteriorating.[52] Cannula and surgical cricothyrotomy each have advantages and disadvantages. Cannula cricothyrotomy carries a lower risk of significant bleeding. It may be considered when dedicated equipment is immediately available and staff are fully trained in its use. However, it may fail or cause barotrauma.[2] If it cannot be performed rapidly, is ineffective,[2] or causes complications,[2] surgical cricothyrotomy should be performed immediately.[2] Surgical cricothyrotomy with insertion of a cuffed tube is more invasive but can be performed very rapidly and allows effective ventilation with low-pressure sources.

Emergency invasive airway access is a temporary measure to restore oxygenation and will be followed by definitive airway management. This may be a formal tracheotomy, but tracheal intubation is possible in some patients.

Summary

Airway management is at the core of care of anesthetized and unconscious patients. Though straightforward much of the time, it can be very difficult. Many new devices and techniques have become available, and their strengths and weaknesses have become apparent. Editorials have emphasized the need for skills in an increased range of techniques of tracheal intubation.[67,114] The range of equipment available, development and maintenance of skills, and organizational factors such as appropriate allocation of personnel are important safety issues.

Concern has been expressed about the airway skills of trainees, but experienced anesthesiologists have also been slow to develop and maintain airway skills in new techniques of proven value.[119] Popat stated that "most anaesthetists continue to use high-risk strategies as a consequence of a limited range of skills. Skills with the combination of the Macintosh laryngoscope, LMA and introducer are not sufficient core skills to allow safe airway management of all patients."[67] Crosby stated that "there is a population of patients for whom exclusive reliance on direct laryngoscopy is a high-risk strategy resulting in morbidity and occasional mortality … We should emphasise practitioners developing experience and a high comfort level with a limited number of alternatives."[114] However, there is hope. Departments that give sufficient time and resources to the development of airway skills have reported excellent results.[46,47,63] We should seek to emulate the safety culture of the airline industry, wherein regular practice is used to train staff to deal with infrequent emergencies—"There is no excuse for poorly designed procedures when human life is at risk."[120]

Caveats

Many airway devices have been introduced over the last few decades. Every effort has been made to include the most important devices, but it is possible that some have been omitted inadvertently. Omission of any such device does not imply that it might not be useful in clinical management. New devices are produced regularly and readers must research the market.

Statement of Interest

The author has received royalties from sales of the Henderson laryngoscope.

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David L. Brown

51 Spinal, Epidural, and Caudal Anesthesia*

Key Points

1. Low neuraxial anesthesia (i.e., T10 or lower sensory level) carries a physiologic impact different from that of a block performed to produce high (T5) neuraxial anesthesia.
2. Neuraxial anesthesia carries more risk with the perioperative introduction of low-molecular-weight heparin and potent (glycoprotein) platelet inhibitors.
3. Many spinal and epidural anesthetics fail because of inadequate intravenous sedation and anxiolysis rather than technically flawed blocks.
4. Bupivacaine, levobupivacaine, and ropivacaine provide excellent quality of anesthesia for neuraxial techniques.
5. It is estimated that cerebrospinal fluid volume accounts for 80% of the variability in peak block height and regression of sensory and motor block. Except for body weight, the volume of cerebrospinal fluid does not correlate with other anthropomorphic measurements available clinically.
6. The epidural space is more segmented and less uniform than previously believed, and the ligamentum flavum is not uniform from skull to sacrum or even within an intervertebral space.
7. During neuraxial anesthesia, venous and arterial vasodilation occurs, but because of the large amount of blood in the venous system (approximately 75% of the total blood volume), the venodilation effect predominates.
8. It has long been taught that the decrease in blood pressure after a neuraxial block can be minimized by the administration of crystalloids intravenously before the block; however, this logic needs rethinking.
9. Nausea and vomiting may be associated with neuraxial block in up to 20% of patients, and atropine is almost universally effective in treating the nausea associated with high (T5) neuraxial anesthesia.
10. As facility with spinal anesthesia increases, the use of smaller, similarly tipped needles will decrease the incidence of headache if the number of spinal punctures does not increase.
11. Transient neurologic symptoms after spinal anesthesia develop most frequently after ambulatory procedures, especially in patients placed in the lithotomy or knee arthroscopy positions.
12. The lower frequency of headache with cone-shaped needle tips may be the result of exposure of more inflammatory mediators around the opening rather than the often-quoted more gentle spreading of the meninges at the site of puncture.
13. Epidural blood patches are more than 90% effective in relieving post–spinal puncture headache.
14. One method of increasing the likelihood of correct caudal needle placement is to inject 5 mL of saline rapidly through the caudal needle while palpating the skin overlying the sacrum. If no midline bulge is detected, the needle is probably positioned correctly. If a midline bulge is detected during saline injection, the needle is positioned incorrectly.
15. Local anesthetic–induced systemic toxicity occurs primarily through unintentional administration of the drug into an epidural vein.

Spinal, epidural, and caudal neuraxial blocks result in sympathetic blockade, sensory analgesia, or anesthesia and motor blockade, depending on the dose, concentration, or volume of local anesthetic, after insertion of a needle in the plane of the neuraxis. Despite these similarities, there are significant physiologic and pharmacologic differences. Spinal anesthesia requires a small mass (i.e., volume) of drug, virtually devoid of systemic pharmacologic effect, to produce profound, reproducible sensory analgesia; in contrast, epidural anesthesia necessitates the use of a large mass of local anesthetic that produces pharmacologi-

*See American Society of Anesthesiologists Practice Guidelines for Acute Pain Management in the Perioperative Setting, Practice Guidelines for Chronic Pain Management, and Practice Guidelines for Obstetric Anesthesia.

cally active systemic blood levels, which may be associated with side effects and complications unknown with spinal anesthesia. The introduction of combined spinal and epidural techniques blurs some of these differences but also adds flexibility to clinical care.

The blurring of differences between spinal and epidural anesthesia began early, when Corning[1] reported on spinal anesthesia and local medications of the cord (see Chapter 1). Whether his injection of cocaine "between spinous processes" produced spinal or epidural anesthesia is not clear. Bier understood that he was producing spinal anesthesia in 1898, and through self-investigation of spinal anesthesia, he had personal knowledge of the symptoms of post–spinal puncture headache. These early years were principally involved with the advancement of spinal rather than epidural anesthesia for at least three reasons. First, the only practical local anesthetic available until 1904 (when procaine was synthesized) was cocaine, which was more suited to spinal than epidural anesthesia because of systemic side effects at doses required for each. Second, the equipment available for neuraxial blocks favored spinal anesthesia because the end point of cerebrospinal fluid (CSF) return was well defined and did not demand the sophisticated glass syringes and needles required for epidural anesthesia. Third, muscle relaxants had not been introduced, and spinal anesthesia produced superb skeletal muscle relaxation that facilitated surgical exposure.

These advantages of spinal anesthesia historically created many enthusiastic clinicians. Morton[2] promoted high spinal anesthesia for surgical procedures carried out on the head and neck, whereas Koster[3] used total spinal blockade for thoracic and intracranial procedures. Spinal anesthesia was not limited to surgical conditions but was also touted for the treatment of medical conditions (e.g., pulmonary edema) by taking advantage of its venodilatory effect. However, a number of impediments prevented more widespread use of spinal and epidural blocks.

Despite the many advantages and the safety of spinal anesthesia, Kennedy and colleagues[4] described "grave spinal cord paralysis" accompanying the use of spinal anesthesia in 1950; this report was followed by one in 1954 detailing the well-publicized Woolley and Roe trial in England.[5] In the latter instance, two patients, Woolley and Roe, suffered neurologic injury after receiving spinal anesthesia, which was administered in the same hospital, on the same day, and by the same anesthetist in 1947. The exact cause of their neurologic dysfunction remains cloudy. Was it contaminated ampules or a toxic substance administered into the subarachnoid space by mistake?[6]

Anesthesiologists continue to face confusion about balancing the risks and benefits of spinal anesthesia, specifically those involving continuous spinal anesthesia or the use of 5% lidocaine. The U.S. Food and Drug Administration (FDA) withdrew approval for some spinal catheters in 1992 because of concern about a perceived association between the small-bore catheters and the development of cauda equina syndrome.[7] This decision appears to have been made with as many political implications as scientific ones. Since that time, attention turned to questions about the appropriate use of intrathecal 5% lidocaine[8] and how to minimize the risks associated with neuraxial anesthesia and concomitant use of low-molecular-weight heparin (LMWH).[9] Small-bore spinal catheters are being used effectively in Europe and are beginning to reappear in the United States, although it has taken nearly a decade and a half to emerge from the regulatory cloud of the early 1990s.[10]

Other impediments to the effective use of neuraxial blocks are the predictable decreases in arterial blood pressure and heart rate through the accompanying sympathectomy with its attendant vasodilation and blockade of cardioaccelerator fibers. Maintaining arterial blood pressure and heart rate at normal values during these blocks often requires the administration of vasoactive drugs and intravenous fluids. The extent to which these steps are necessary is discussed later.

Another clinically important impediment to successful use of these blocks is the idea that the "blocks should do it all." It seems unreasonable to expect a single injection of local anesthetic into the subarachnoid or epidural space to provide ideal conditions for all patients undergoing various surgical procedures, even in the face of an adequate block. It seems likely that far more spinal and epidural anesthetics have failed because of inadequate intravenous sedation and anxiolysis rather than technically flawed blocks.

Evidence is accumulating that the use of neuraxial blocks, principally continuous epidural techniques to provide postoperative analgesia, may be able to decrease perioperative morbidity. These techniques may also decrease the length of hospital stay and allow more efficient use of our increasingly stretched health care money.[11,12] To gain maximum benefit and minimize complications from these blocks, attention to technique and anatomy is essential, and the blocks should be used when the risk-benefit equation for the block is favorable.[13-17]

Indications and Contraindications

At the most basic level, neuraxial blockade is indicated when the surgical procedure can be accomplished with a sensory level of anesthesia that does not produce adverse patient outcomes. The surgical procedure must include the amount and type of supplemental medications and even the capacity for administering "light general anesthesia" to ensure effective sedation and anxiolysis. The level of sensory analgesia required is of prime importance. It is clear that low spinal anesthesia (i.e., T10 or lower sensory level) carries a different physiologic impact than a block performed to produce high (T5) spinal anesthesia does.[18]

There are few strong contraindications to neuraxial blockade. Some of the most important include patient refusal; a patient's inability to maintain stillness during the needle puncture, which can expose the neural structures to an unacceptable risk of injury; and raised intracranial pressure, which may theoretically predispose to brainstem herniation. Relative contraindications that must be weighed against the potential benefits include intrinsic and idiopathic coagulopathy, such as that occurring with administration of warfarin (Coumadin) or heparin; skin or soft tissue infection at the proposed site of needle insertion; severe hypovolemia; and lack of anesthesiologist experience. The often-cited relative contraindication of preexisting neurologic disease (e.g., lower extremity peripheral neuropathy) is not usually based on medical criteria but rather on legal considerations.

When deciding between epidural and spinal anesthesia, a number of variables should be considered. Is the procedure (or surgeon's typical time) of predictable length, thus minimizing the need to consider a continuous catheter technique? Conversely, is the surgeon's estimate so unpredictable that a combined spinal

and epidural technique should be recommended? Is the surgical procedure so short that waiting for the epidural to take effect makes spinal anesthesia more practical? Is the patient a candidate for prolonged postoperative analgesia, thus making a continuous epidural technique preferred? Can the procedure be equally well handled with spinal or epidural anesthesia, thereby allowing consideration of patient variables affecting the incidence of headache (e.g., age and gender)? Are there concurrent patient diseases, such as hypertrophic cardiomyopathy, that may be of concern with either technique? Will the patient be traveling a significant distance immediately after the procedure, thus making epidural blood patch therapy for a post–spinal puncture headache problematic? These are some of the questions that should be considered when contemplating the risk and benefit of neuraxial blocks.

Anatomy

After a decision is made to use one of these blocks, the key feature of performing the block is combining appropriate technique with a three-dimensional understanding and tactile appreciation of anatomy.

Subarachnoid local anesthetics effect their sensory block at the spinal cord, which is continuous cephalad with the brainstem through the foramen magnum and terminates distally in the conus medullaris. This distal termination, because of differential growth rates between the bony vertebral canal and the central nervous system (CNS), varies from L3 in infants to the lower border of L1 in adults. Most of us develop the impression that the spinal nerve roots are uniform in size and structure, but Hogan and Toth[19] have shown that there is large interindividual variability in nerve root size. These differences may help explain the interpatient differences in neuraxial block quality when equivalent techniques are used on seemingly similar patients. Another anatomic relationship may affect neuraxial blocks; although the dorsal (sensory) roots are generally larger than the anterior (motor) roots, the dorsal roots are often blocked more easily. This seeming paradox is explained by organization of the dorsal roots into component bundles, which creates a much larger surface area on which the local anesthetics act, thus perhaps explaining why larger sensory nerves are blocked more easily than smaller motor nerves.[20] Lumbosacral CSF volume varies from patient to patient, in part because of differences in body habitus and weight.[21] It is estimated that CSF volume accounts for 80% of the variability in peak block height and regression of sensory and motor blockade. Nevertheless, except for body weight, the volume of CSF does not correlate with other anthropomorphic measurements available clinically.[22]

Surrounding the spinal cord in the bony vertebral column are three membranes (from within to the periphery): the pia mater, arachnoid mater, and dura mater (Fig. 51-1). The pia mater is a highly vascular membrane that closely invests the spinal cord and brain. The arachnoid mater is a delicate, nonvascular membrane closely attached to the outermost layer, the dura. Of these two membranes, it is thought that the arachnoid functions as the principal barrier to drugs crossing in and out of the CSF and is estimated to account for 90% of the resistance to drug migration.[23] As Lui and McDonald[20] and Bernards[24] emphasize, the functional proof of the arachnoid's role as the primary barrier to flow is the observation that spinal CSF resides in the subarachnoid and not the subdural space.

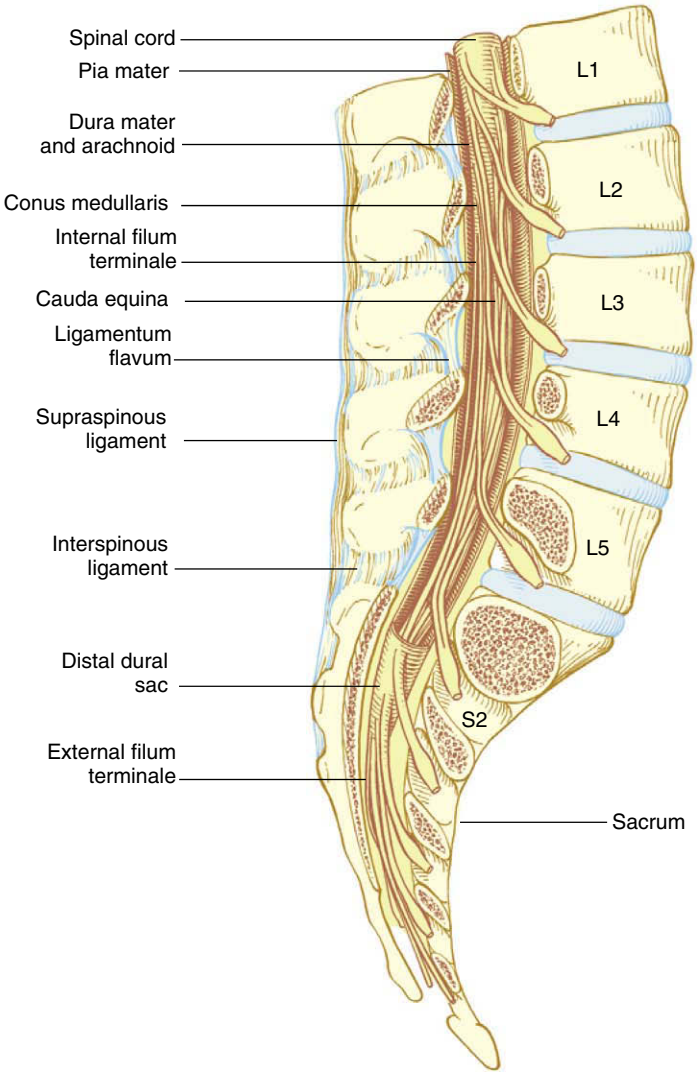

Figure 51-1 Spinal cord anatomy. Notice the termination of the spinal cord (i.e., conus medullaris) at L1-2 and termination of the dural sac at S2.

In the subarachnoid space are the CSF, spinal nerves, a trabecular network between the two membranes, and blood vessels that supply the spinal cord and lateral extensions of the pia mater and dentate ligaments, which provide lateral support from the spinal cord to the dura mater (Fig. 51-2).[25] Although the spinal cord ends at the lower border of L1 in adults, the subarachnoid space continues to S2.

The third and outermost membrane in the spinal canal is a randomly organized fibroelastic membrane, the dura mater (or theca).[26] This layer is a direct extension of the cranial dura mater and extends as the spinal dura mater from the foramen magnum to S2, where the filum terminale (an extension of the pia mater beginning at the conus medullaris) blends with the periosteum on the coccyx (see Fig. 51-1). There is a potential space between the dura mater and the arachnoid, the subdural space, that contains only small amounts of serous fluid and thus allows the dura and arachnoid to move over each other. This space is not

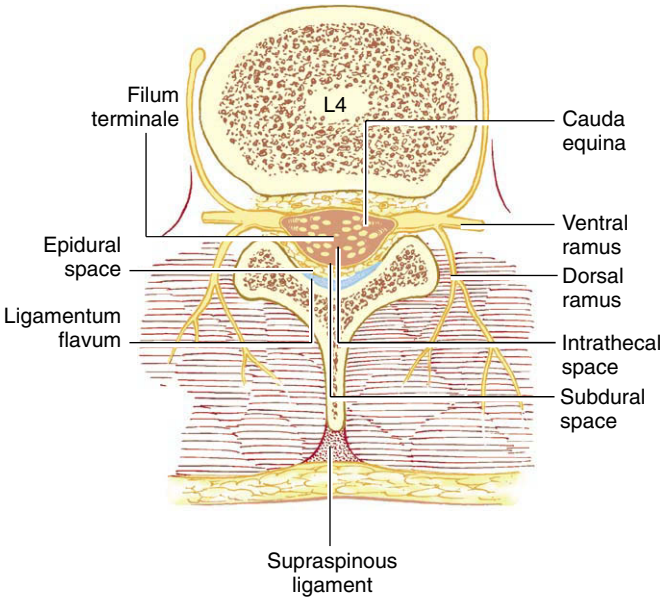

Figure 51-2 Contents of the dural sac at the level of L4. The cauda equina is contained within a dural sac filled with cerebrospinal fluid.

intentionally used by anesthesiologists, although injection into it during spinal anesthesia may explain the occasional failed spinal anesthetic and the rare "total spinal" after epidural anesthesia when there is no indication of errant injection of local anesthetic into CSF.

Surrounding the dura mater is another space that is often used by anesthesiologists, the epidural space. The spinal epidural space extends from the foramen magnum to the sacral hiatus and surrounds the dura mater anteriorly, laterally, and more usefully, posteriorly. The epidural space is bounded anteriorly by the posterior longitudinal ligaments, laterally by the pedicles and intervertebral foramina, and posteriorly by the ligamentum flavum. Contents of the epidural space include the nerve roots that traverse it from foramina to peripheral locations, as well as fat, areolar tissue, lymphatics, and blood vessels, including the well-organized Batson venous plexus. Hogan[27] suggests from his study of frozen cryomicrotome cadaver sections that the epidural space is more segmented and less uniform than previously believed from indirect anatomic analysis (Fig. 51-3). This lack of epidural space uniformity also extends to age-related differences. There is evidence that adipose tissue in the epidural space diminishes with age.[28] Another anatomic change in epidural space anatomy that has long been promoted is that the intervertebral foramina decrease in size with increasing age. This decrease has been linked conceptually to higher block levels for similar epidural doses of local anesthetic. Saitoh and coworkers[29] showed that this concept is probably wrong because they could find no correlation between leakage of radiocontrast material through the intervertebral foramina and age. When the data of Igarashi and associates[28] and Saitoh and colleagues[29] are considered together, it may be that the decrease in epidural space adipose tissue with age may dominate the age-related changes in epidural dose requirements. Unique insights into the epidural space are covered eloquently by Bernards.[24]

Posterior to the epidural space is the ligamentum flavum (the so-called yellow ligament), which also extends from the foramen magnum to the sacral hiatus. Although classically portrayed as a single ligament, it is really composed of two ligamenta flava, the right and the left, which join in the middle and form an acute angle with a ventral opening (Fig. 51-4).[27,30] The ligamentum flavum is not uniform from skull to sacrum, nor even within

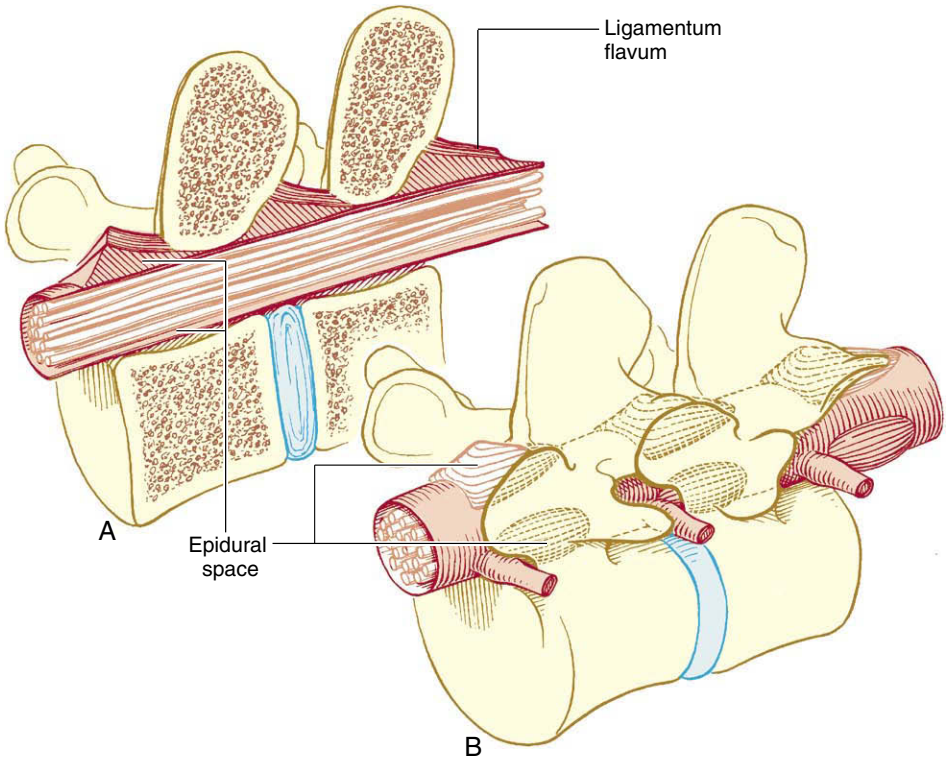

Figure 51-3 **A,** Sagittal section demonstrating that the contents of the epidural space depend on the level of the section. **B,** Three-dimensional drawing of the epidural space showing discontinuity of the epidural contents, but this potential space can be dilated by injection of fluid into the epidural space.

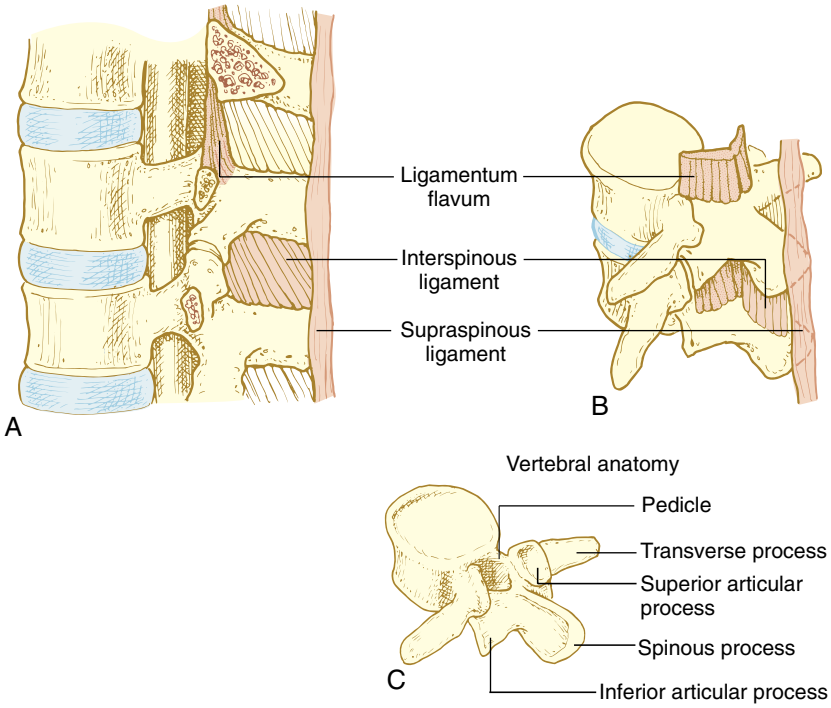

Figure 51-4 Vertebral anatomy. **A,** Sagittal view. **B,** Oblique view of the lumbar vertebrae showing the ligamentum flavum thickening in the caudad extent of the intervertebral space and in the midline. **C,** Oblique view of a single lumbar vertebra.

an intervertebral space. Ligament thickness, distance to the dura, and skin-to-dura distance vary with the area of the vertebral canal (Table 51-1). The two ligamenta flava are variably joined (fused) in the midline, and this fusion or lack of fusion of the ligamenta flava even occurs at different vertebral levels in individual patients.[27] Immediately posterior to the ligamentum flavum are the lamina and spinous processes of vertebral bodies or the interspinous ligaments. Extending from the external occipital protuberance to the coccyx posterior to these structures is the supraspinous ligament, which joins the vertebral spines (see Fig. 51-4).

Occasionally, clinically unilateral anesthesia may follow an apparently adequate epidural technique.[31,32] Hogan[33] has also shown in cadavers that spread of solution after epidural injection into tissues of the epidural space is nonuniform, and he postulated that this accounts for the clinical unpredictability of epidural drug spread.

Table 51-1 Characteristics of the Ligamentum Flavum at Different Vertebral Levels

Site	Distance from Skin to Ligament (cm)	Thickness of Ligament (mm)
Cervical	—	1.5-3.0
Thoracic	—	3.0-5.0
Lumbar	3.0-8.0*	5.0-6.0†
Caudal	Variable	2.0-6.0

*The distance is 4 cm for 50% of patients and 4 to 6 cm for 80% of patients.
†Within each interlaminar space, the ligamentum flavum varies in thickness from cephalad to caudad: near the rostral lamina, it is 1.3 to 1.6 mm, and near the caudad lamina, it is 6.9 to 9.1 mm.
Data from Cousins MJ, Bromage PR: Epidural neural blockade. *In* Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain. Philadelphia, JB Lippincott, 1988, p 255, and other sources.

Blomberg used a fiberoptic technique to demonstrate that the subdural extra-arachnoid space is easily entered in 66% of autopsy attempts in humans.[34] Despite this being an infrequent clinical problem with epidural anesthesia, it does allow a visual understanding of the subdural complications of epidural anesthesia.[35] Blomberg continued his endoscopic approach to understanding neuraxial anatomy with a subarachnoid study.[36] He identified in autopsy subjects that a distinct posterior midline structure was present in the lower thoracic and upper lumbar regions. He also found that fibrous attachments were present between nerve roots and other subarachnoid structures in many subjects. He postulated that these fibrous structures and attachments might help explain some variations in spinal anesthesia.

Performance of caudal anesthesia calls for an expanded understanding of epidural anatomy and especially the frequent variations in sacral anatomy.[37] The sacrum results from fusion of the five sacral vertebrae. The sacral hiatus, which is failure of the laminae of S5 and usually part of S4 to fuse in the midline, is the detail of interest. It results in a variably shaped and sized inverted V–shaped bony defect covered by the posterior sacrococcygeal ligament, a functional counterpart to the ligamenta flava. The sacral hiatus is identified by locating the sacral cornua, remnants of the S5 articular processes (Fig. 51-5). This bony defect allows access to the sacral canal, although needle insertion through this defect may be difficult because of the frequency of anatomic variation. For example, the shape of the space may vary from slitlike to a wide-based, inverted V, and in 1 in 20 patients, the bony defect may be absent, thereby precluding the caudal approach (Fig. 51-6).[38,39]

The sacral canal contains the terminal portion of the dural sac, which typically ends cephalad to a line joining the posterior superior iliac spines, or S2. Variation is found in this feature as well, with the termination of the dural sac being lower in children, although the ease of palpating the sacral hiatus in children may make the pediatric caudal technique easier overall. In addition to

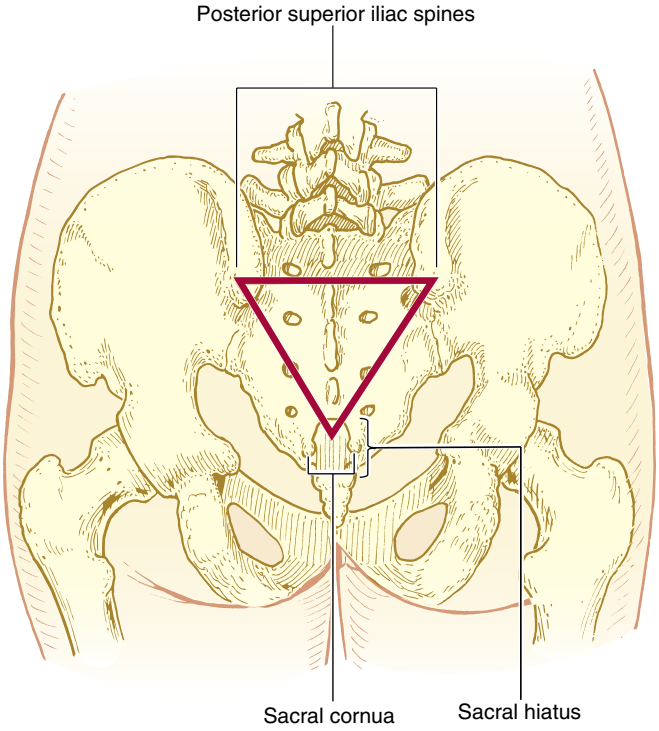

Figure 51-5 Sacral surface anatomy. An equilateral triangle can be drawn to connect the posterior superior iliac spines and the sacral hiatus. It can be useful in confirming palpation of the sacral hiatus.

the dural sac, the sacral canal contains a venous plexus, which is part of the valveless internal vertebral venous plexus. It is estimated from magnetic resonance imaging (MRI) studies that the volume of the caudal canal in adults, excluding the foramina and dural sac, is about 10 to 27 mL. Perhaps this wide variability in volume accounts for some of the variation in block height with caudal anesthesia.[37]

After the anatomy pertinent to neuraxial blocks is understood, it is tempting to administer the blocks immediately. Nevertheless, safe conduct of spinal, epidural, and caudal anesthesia requires an appreciation of the physiologic effects of these blocks if they are to be used appropriately.

Physiologic Effects

The physiologic effects of neuraxial blocks are often misinterpreted as complications, which is highlighted by observers listing hypotension under complications of the techniques. Clear distinction should be made between the physiologic effects of an anesthetic technique and complications, which imply some harm to the patient.[40] This distinction is important to determine the risk-benefit equation of the technique in question.

Cardiovascular Effects

The cardiovascular effects of neuraxial blocks are similar in some ways to the combined use of intravenous α_1- and β-adrenergic blockers: decreased heart rate and arterial blood pressure (see Chapter 16). The sympathectomy that accompanies the techniques depends on the height of the block, with the sympathectomy typically described as extending for two to six dermatomes above the sensory level with spinal anesthesia and at the same level with epidural anesthesia.[41] This sympathectomy causes venous and arterial vasodilation, but because of the large amount of blood in the venous system (approximately 75% of the total volume of blood), the venodilation effect predominates as a result of the limited amount of smooth muscle in venules; in contrast, the vascular smooth muscle on the arterial side of the circulation retains a considerable degree of autonomous tone. After neuraxial block–induced sympathectomy, if normal cardiac output is maintained, total peripheral resistance should decrease only 15% to 18% in normovolemic healthy patients, even with nearly total sympathectomy. In elderly patients with cardiac disease, systemic vascular resistance may decrease almost 25% after spinal anesthesia, whereas cardiac output decreases only 10%.[42] The heart rate during a high neuraxial block typically decreases as a result of blockade of the cardioaccelerator fibers arising from T1 to T4. The heart rate may decrease because of a fall in right atrial filling, which decreases outflow from intrinsic chronotropic stretch receptors located in the right atrium and great veins.[41]

The clinical question of what level of decrease in arterial blood pressure after a neuraxial block is acceptable remains to be answered. It will probably remain speculative because conducting ethical human investigations designed to define a dose-response curve of decreased arterial blood pressure accompanying neuraxial blockade would be difficult. That dilemma notwithstanding, it appears that total-body oxygen consumption in patients undergoing spinal anesthesia correlates with the extent of spinal anesthesia, thus providing a margin of safety for organ perfusion unavailable with non-neuraxial techniques.[43]

Some data are available to help determine the extent to which arterial blood pressure should be allowed to decrease. Despite methodologic problems with the study,* Kety and colleagues[44] demonstrated that producing spinal anesthesia to the midthoracic levels with procaine, even in patients with essential hypertension, results in a decrease in mean arterial pressure of 26% (155 to 115 mm Hg) accompanied by only a 12% (52 to 46 mL/100 g/min) decrease in CBF. When the level of spinal anesthesia was purposely increased to produce higher levels of block (T4) in normotensive and hypertensive patients, mean arterial pressure decreased by 32% (93 to 63 mm Hg) and 50% (158 to 79 mm Hg), respectively. Although CBF was unchanged in the normotensive group (45 to 46 mL/100 g/min), a 19% decrease occurred in the apparently untreated hypertensive patients (46.5 to 37.5 mL/100 g/min).[45] When coronary artery blood flow and myocardial metabolism were determined in humans during spinal anesthesia to T4 in hypertensive and normotensive patients, decreases in coronary blood flow (153 to 74 mL/100 g/min) paralleled the decrease in mean arterial blood pressure (119 to 62 mm Hg), and the percent extraction of myocardial oxygen was unchanged (75% to 72%). Extraction of oxygen was unchanged because myocardial work, as expressed by myocardial use of oxygen, paralleled the decrease in mean arterial pressure and coronary blood flow (16 to 7.5 mL/100 g/min).[46] These data

*Cerebral blood flow (CBF) was studied with nitrous oxide. Only global CBF was measured, and the patients studied were severely hypertensive (i.e., average mean arterial blood pressure of 155 mm Hg).

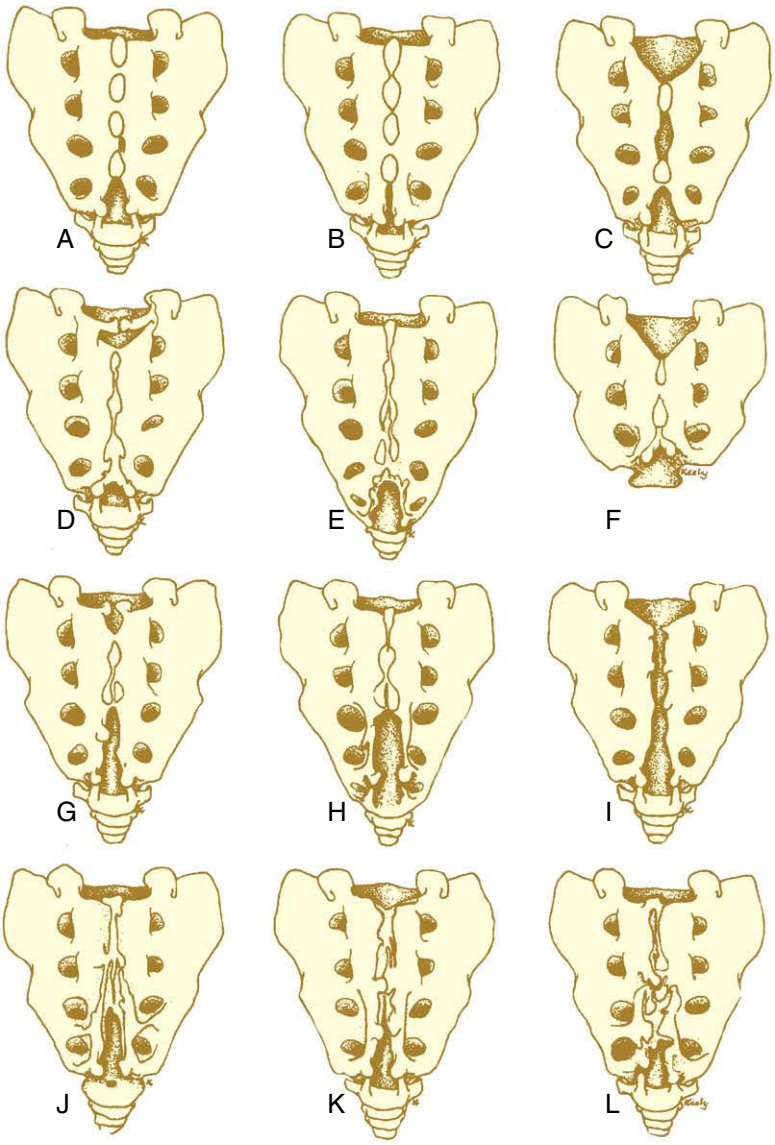

Figure 51-6 Anatomic variants of the sacrum and sacral hiatus. **A,** Normal. **B,** Longitudinal slitlike hiatus. **C,** Second midline hiatus. **D,** Transverse hiatus. **E,** Large hiatus with absent cornua. **F,** Transverse hiatus with absent coccyx, two prominent cornua, and two proximal "decoy hiatuses lateral to the cornua." **G-I,** Large midline defects contiguous with the sacral hiatus. **J-L,** Enlarged longitudinal hiatuses, each with an overlying decoy hiatus. *(From Willis RJ: Caudal epidural block.* In *Cousins MN, Bridenbaugh PO [eds]: Neural Blockade in Clinical Anesthesia and Management of Pain, 2nd ed. Philadelphia, JB Lippincott, 1988, p 365.)*

support the observations by Stanley and coworkers[43] but still do not provide a patient-by-patient indication of the organ most at risk for flow-related ischemia, suggesting that further research in this area is required.

Human investigations are limited by cerebral and myocardial blood flow methodologies that were not limiting factors when Sivarajan and associates[47] investigated organ blood flow by means of microspheres in rhesus monkeys during spinal anesthesia at the T10 and T1 levels. During the T10 block, there was no significant change in organ blood flow; during the T1 block, with a 22% decrease in mean arterial pressure, cerebral and myocardial blood flow was insignificantly altered. Prevention of decreases in mean arterial pressure of greater than 30% has some basis, but it is important to remember that these data were derived from severely hypertensive, presumably untreated patients. For normotensive and treated hypertensive patients, a wider undocumented margin of safety probably exists.

After arterial blood pressure decreases to a level at which treatment is believed to be necessary, ephedrine, a mixed adrenergic agonist, provides more appropriate therapy for the noncardiac circulatory sequelae of neuraxial block than a pure α-adrenergic agonist does (see Chapter 16), unless the patient has a specific and defined blood pressure requirement.[48] That the decrease in arterial blood pressure after neuraxial block can be minimized by the administration of crystalloids intravenously is probably not a valid concept. Specifically, 250- to 2000-mL preblock hydration regimens appear to temporarily increase preload and cardiac output without consistently increasing arterial blood pressure or preventing hypotension.[20]

Is there any indication that epidural and spinal anesthesia differ in their effect on arterial blood pressure? A common concept is that the decrease in arterial blood pressure is more gradual and of less magnitude with epidural than with spinal anesthesia of comparable levels. Despite this belief, it was shown that when tetracaine (10 mg) spinal anesthesia was compared with lidocaine (20 to 25 mL of a 1.5% solution) epidural anesthesia, there was a larger decrease in arterial blood pressure, approximately 10%, with the epidural technique than with the spinal

one.[49] The proposed advantage of a slower onset of epidural blockade is often mitigated by anesthesiologists administering a decreased volume of local anesthetic with the initial epidural therapeutic dose; when the block height does not rise as rapidly as desired, additional epidural local anesthetic is administered, and a higher block than necessary may result. The extent to which arterial blood pressure decreases with either technique depends on multiple factors, including patient age and intravascular volume status.

Respiratory Effects

Alterations in pulmonary variables in healthy patients during neuraxial block are usually of little clinical consequence. Tidal volume remains unchanged during high spinal anesthesia, and vital capacity decreases a small amount from 4.05 to 3.73 L.[50] This decrease in vital capacity is a result of a decrease in expiratory reserve volume related to paralysis of the abdominal muscles necessary for forced exhalation rather than a decrease in phrenic or diaphragmatic function.[18] This minimal impact on pulmonary function also holds for elderly patients undergoing lumbar and thoracic epidural anesthesia.[51] Pulmonary function testing in cesarean section patients undergoing epidural anesthesia shows that using lidocaine provides larger decrements in peak expiratory pressure (abdominal musculature–dependent maneuver) than using bupivacaine does.[52]

The rare respiratory arrest associated with spinal anesthesia is also unrelated to phrenic or inspiratory dysfunction but rather to hypoperfusion of the respiratory centers in the brainstem. Supportive evidence for this concept is observed after resuscitation, when apnea almost always disappears as soon as pharmacologic and fluid therapies have restored cardiac output and blood pressure. This would not be the case if phrenic paralysis induced by high levels of local anesthetic was the cause of the apnea.[18] There is experimental evidence from rabbits during epidural anesthesia that their response to hypoxia results in apnea, which is different from the response without neuraxial anesthesia.[53] This finding may have implications for understanding some episodes of cardiovascular depression during neuraxial blockade in humans, although confirmation is needed. Conversely, in a canine model of hypoxia, epidural anesthesia and hypoxic challenge result in the same outcome but with more normal acid-base function than in animals receiving general anesthesia alone.[54]

Neuraxial block should be used cautiously in respiratory cripples because of paralysis of the respiratory muscles. Except for severely compromised patients with respiratory failure, inspiratory muscle function during neuraxial blocks should be adequate to maintain ventilatory function. The physiologic consideration related to muscle paralysis with neuraxial block should focus on the expiratory muscles in these severely compromised patients because these muscles are important for effective coughing and clearing of intrapulmonary secretions.[42,50]

Gastrointestinal Function

Another organ system affected during neuraxial blockade is the gastrointestinal tract. Nausea and vomiting may be associated with neuraxial block in up to 20% of patients and are primarily related to gastrointestinal hyperperistalsis caused by unopposed parasympathetic (vagal) activity.[55] Atropine is effective in treating nausea associated with high (T5) subarachnoid anesthesia.[56,57] This gastrointestinal hyperperistalsis has the advantage of providing excellent surgical conditions because of a contracted gut. An often-cited advantage of regional anesthesia in patients with compromised gastrointestinal function (e.g., hepatic dysfunction) is that less physiologic impairment is possible than with general anesthesia. Nevertheless, it appears that if intra-abdominal surgery is performed, the magnitude of the decrease in hepatic blood flow parallels the site of surgery rather than the anesthetic technique chosen. The decrease in hepatic blood flow during spinal anesthesia parallels the decrease in mean arterial blood pressure.[58] When epidural analgesia is continued into the postoperative period, there may be a protective effect on the gastric mucosa because intramucosal pH is higher during postoperative epidural analgesia than during systemic analgesia.[59]

Renal Function

Renal function has a wide physiologic reserve. Despite predictable decreases in renal blood flow accompanying neuraxial blockade, the decrease is of little physiologic importance.[60] One aspect of genitourinary function that is of clinical importance is the belief that neuraxial blocks are a frequent cause of urinary retention, which delays discharge of outpatients and necessitates bladder catheterization in inpatients. Lower concentrations of local anesthetic are necessary for paralysis of bladder function than for paralysis of motor nerves to the lower extremities. However, some studies do not support this belief. For example, in orthopedic patients undergoing hip replacement, it was demonstrated that bladder catheterization was no more frequent after neuraxial (spinal or epidural) block than after general anesthesia and narcotic analgesics.[61] In any case, it is prudent to avoid administration of excessive volumes of crystalloid solutions intravenously to patients undergoing spinal anesthesia and to individualize the requirement for voiding before discharge in low-risk ambulatory surgery patients after short-acting spinal or epidural anesthetics are used.[62]

Effects Specific to Epidural Anesthesia

The physiologic effects of epidural anesthesia are similar to those of spinal anesthesia, with the exception that local anesthetic blood levels reach concentrations sufficient enough to produce systemic effects on their own. Even intravenously administered lidocaine (resulting in blood levels similar to those after continuous epidural analgesia) can decrease postoperative narcotic requirements (Fig. 51-7).[63] When blood levels are excessive, adverse CNS and cardiovascular effects occur (see Chapter 30).

Spinal Anesthesia

Technique

To perform spinal anesthesia, the pertinent anatomy must be constantly kept in mind while inserting the spinal needle. It is

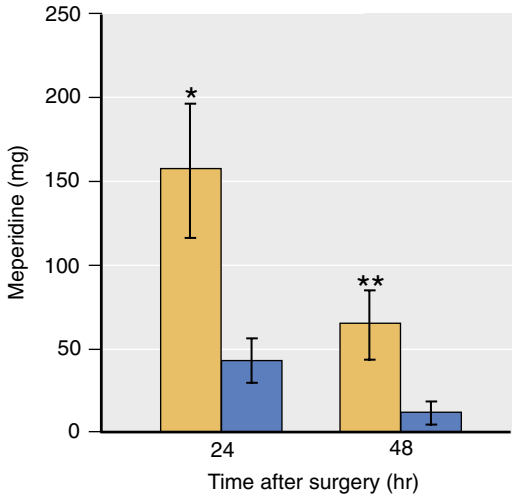

Figure 51-7 Meperidine requirements during the first and second postoperative days in patients receiving intravenous lidocaine (*blue bars*) and in control patients (*yellow bars*). Data are expressed as means ± SEM. **P* < .02; ***P* < .01 versus control data. *(Adapted from Cassuto J, Wallin G, Högström S, et al: Inhibition of postoperative pain by continuous low-dose intravenous infusion of lidocaine. Anesth Analg 64:971, 1985.)*

often helpful for the technique to be broken down into a series of steps (i.e., the four P's): preparation, position, projection, and puncture.

Preparation

Preparation of the equipment and drugs is essential for subarachnoid injection. When choosing a drug for subarachnoid injection, the duration of block should be matched to the surgical procedure and to patient variables (Table 51-2). It may be more time efficient to use a hypobaric solution in a patient in the prone jackknife position rather than turning the patient after a hyperbaric solution has been allowed time to take effect. Is the patient planning to go home after an outpatient procedure, thus dictating use of a shorter-acting drug? Will a prolonged period of lower extremity analgesia, such as that achieved by adding an opioid to the spinal drugs, be advantageous to a patient undergoing knee reconstruction and immediate postoperative use of a range-of-motion machine? These are only a few of the many clinical permutations that dictate familiarity with the combinations of drugs available for subarachnoid use.

When choosing equipment for spinal anesthesia, the initial choice involves reusable or disposable equipment. Most anesthesiologists are forced to accept disposable spinal trays, which may seem limiting, but suppliers are willing to customize trays to meet professional preferences. Despite the emphasis on disposable trays, there is no indication that these trays shift the spinal anesthesia risk-benefit equation in the patient's favor.[64]

Spinal needles fall into two main categories: those that cut the dura and those with a conical tip. The former include the Quincke-Babcock needle, the traditional disposable spinal needle, and the latter contain the Whitacre and Sprotte needles (Fig. 51-8). If a continuous spinal technique is chosen, use of a Tuohy or other thin-walled needle can facilitate passage of the catheter. The use of small needles reduces the incidence of post–spinal puncture headache, whereas the use of larger needles improves the tactile sense of needle placement. Multiple punctures probably increase the incidence of headaches. If use of a smaller needle increases the number of punctures, the difference between small and large needles in producing headaches may be reduced. There is also a decrease in the incidence of post–spinal puncture headache when a conical-tipped needle is used, even when needle sizes are comparable.[65] Nevertheless, as facility with spinal anesthesia increases, the use of a smaller, similarly tipped needle can decrease the incidence of headache if the number of dural punctures does not increase.

Position

Positioning (see Chapter 36) is frequently the most poorly managed part of the spinal technique for at least two reasons. First, the assistant often does not understand the rationale for positioning a patient, and second, patients are often inadequately or excessively sedated, thus making cooperation poor. The three

Table 51-2 Drug Selection for Hyperbaric Spinal Anesthesia

Local Anesthetic Mixture	Dose (mg)*		Duration (min)	
	To T10	To T4	Plain	Epinephrine, 0.2 mg
Lidocaine (5% in 7.5% dextrose)	50-60	75-100	60	75-100
Tetracaine (0.5% in 5% dextrose)	6-8	10-16	70-90	100-150
Bupivacaine (0.75% in 8.5% dextrose)	8-10	12-20	90-120	100-150
Ropivacaine (0.5% in dextrose)	12-18	18-25	80-110	—
Levobupivacaine	8-10	12-20	90-120	100-150

*Doses are for use in a 70-kg adult male of average height.

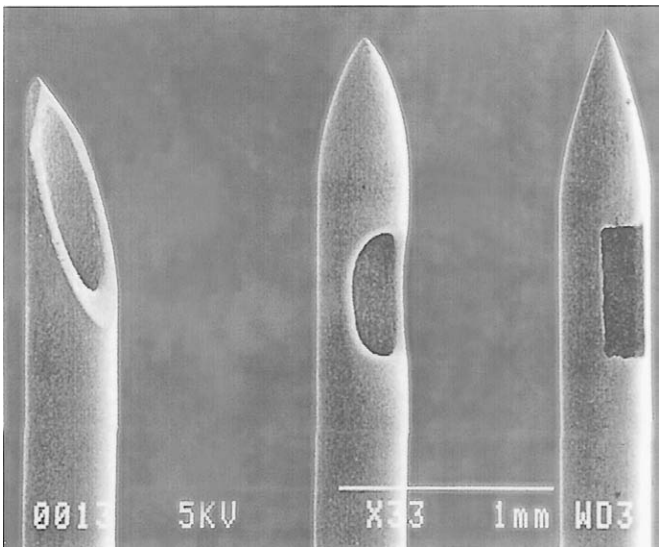

Figure 51-8 Scanning electron micrographs of spinal needle tip designs: Quincke (*left*), Sprotte (*middle*), and Whitacare (*right*). *(Adapted from Puolakka R, Andersson LC, Rosenberg PH: Microscopic analysis of three different spinal needle tips after experimental subarachnoid puncture. Reg Anesth Pain Med 25:163, 2000.)*



Figure 51-9 Lateral decubitus positioning for a neuraxial block. The assistant can help the patient assume the ideal position of "forehead to knees."

primary patient positions include the lateral decubitus, sitting, and prone positions, each with advantages in specific situations.

The lateral decubitus position is the most commonly used because it allows easier administration of more sedation and is less dependent on a well-trained assistant than the sitting position is. Patients are placed with their back parallel to the edge of the operating table nearest the anesthesiologist, their thighs flexed on their abdomen, and their neck flexed to allow the forehead to be as close as possible to the knees. The assistant may be invaluable during this positioning by encouraging and assisting a patient in assuming the ideal lateral decubitus position (Fig. 51-9). The patient should be positioned so that spread of hypobaric, isobaric, or hyperbaric solution to the operative site is optimized.

The sitting position should be chosen when low lumbar and sacral levels of sensory anesthesia are adequate for the surgical procedure, such as perineal and urologic operations, or when obesity or scoliosis makes identification of midline anatomy difficult in the lateral position. When placing patients in this position, a stool can be provided as a footrest and a pillow placed in the lap. The assistant then maintains the patient in a vertical plane while flexing the patient's neck and arms over the pillow to open up the lumbar vertebral space (Fig. 51-10). If the reason for choosing the sitting position is to keep the sensory level low, the patient should be maintained sitting for 5 minutes; if the choice was made because of obesity or scoliosis and a higher sensory level is needed, the patient should be placed supine immediately after subarachnoid injection, with the table manipulated appropriately. The most common error made in placing patients in this position is allowing the patient to slump, which loses the advantage of improved midline identification.

The prone position should be chosen when the patient is to be maintained in that position (often with the jackknife modification) during the surgical procedure. This position is often appropriate for rectal, perineal, or lumbar procedures. An advantage of the hypobaric technique is that patients can help position themselves, thus minimizing the opportunity for positioning injuries. After the patient is in position, lumbar lordosis should be minimized, and most often, the paramedian approach should be used. The anesthesiologist may have to aspirate for CSF because CSF pressure is minimized when insertion of the lumbar needle is carried out in this position.

Projection and Puncture

After the equipment, local anesthetics and additives, and the patient have been properly prepared, the midline or paramedian spinal puncture can be performed. The midline approach relies on the ability of patients and assistants to minimize lumbar lordosis and allow access to the subarachnoid space between adjacent spinous processes, usually at the L2-3, L3-4, or sometimes the L4-5 space. The palpating fingers (usually the index and third fingers) should identify the interspinous area by locating the caudad extent of the more cephalad spine and the midline by rolling the fingers in a medial-to-lateral direction (Fig. 51-11). A subcutaneous skin wheal is developed over this space, and the introducer is inserted into the substance of the interspinous ligament. The introducer is grasped with the palpating fingers and steadied while the other hand is used to hold the spinal needle like a dart, and the fifth finger is used as a tripod against the patient's back to prevent patient movement and unintentional insertion to a level deeper than intended. The needle, with its bevel parallel to the midline, is advanced slowly to heighten the sense of tissue planes traversed and to prevent skewing of nerve roots until the characteristic change in resistance is noted as the needle passes through ligamentum flavum and dura. The stylet is then removed, and CSF should appear at the needle hub. If it does not, the needle is rotated in 90-degree increments until CSF appears. If CSF does not appear in any quadrant, the needle should be advanced a few millimeters and rechecked in all four quadrants. If CSF still has not appeared and the needle is at a depth appropriate for the patient, the needle and introducer should be withdrawn and the insertion steps should be repeated

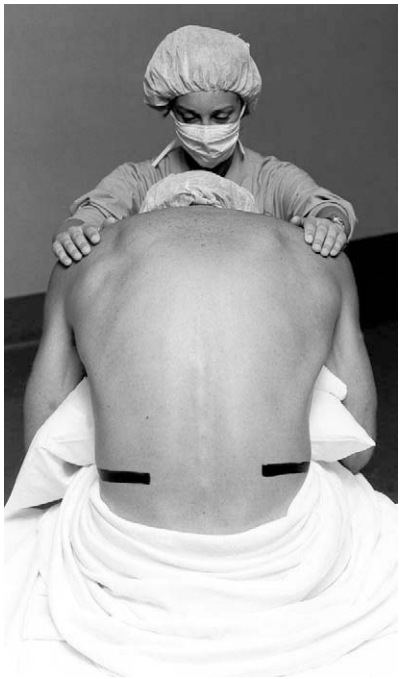

Figure 51-10 Sitting position for a neuraxial block. The assistant provides the patient with a foot rest (stool) and a pillow and prevents the patient from slumping to either side.

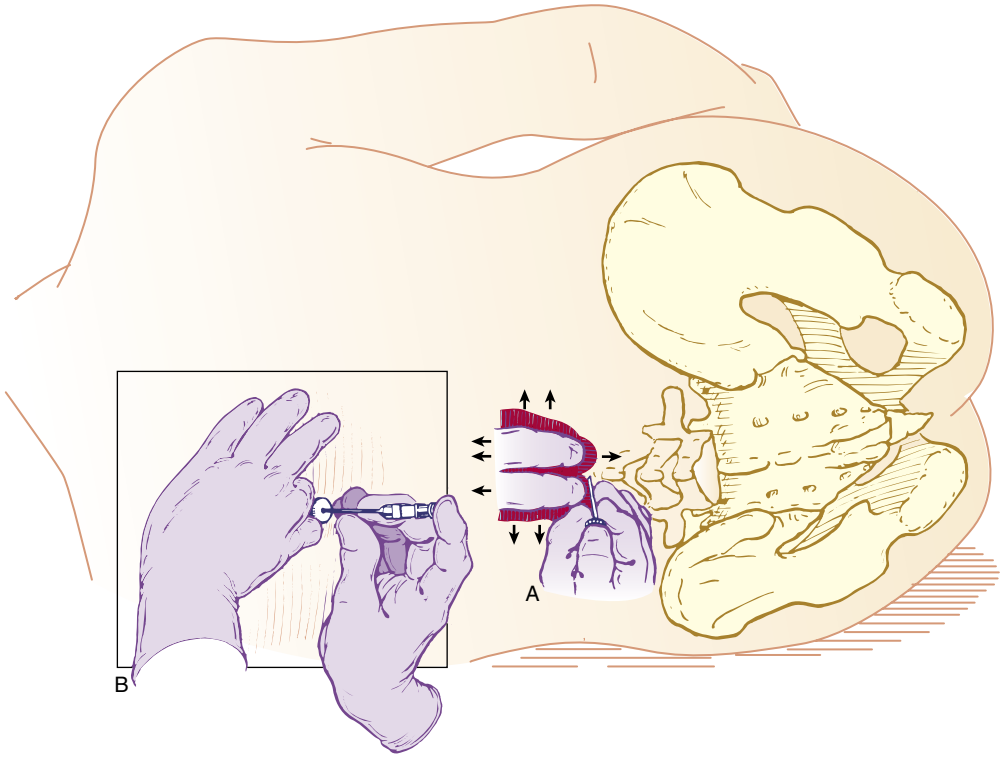

Figure 51-11 Insertion of the spinal needle. **A,** The palpating fingers are "rolled" in a side-to-side and a cephalad-to-caudad direction to identify the interspinous space. **B,** During needle insertion, the needle should be stabilized in a tripod fashion while placed in the hand, similar to a dart being thrown.

because the most common reason for lack of CSF return is that the needle is being inserted off the midline. Another common error preventing subarachnoid placement is excessive cephalad angulation on initial insertion of the needle.

After CSF is freely obtained, the dorsum of the anesthesiologist's nondominant hand steadies the spinal needle against the patient's back while the syringe containing the therapeutic dose is attached to the needle. CSF is again freely aspirated into the syringe, and the anesthetic dose is injected at a rate of approximately 0.2 mL/sec. After completion of the injection, 0.2 mL of CSF is aspirated into the syringe and reinjected into the subarachnoid space to reconfirm location and clear the needle of the remaining local anesthetic. The patient and operating table should then be placed in the position appropriate for the surgical procedure and drugs chosen.

The midline approach is the technique of first choice because it requires anatomic projection in only two planes (Fig. 51-12) and provides a relatively avascular plane. When difficulty in needle insertion is encountered with the midline approach, one option is to use the paramedian route, which does not require the same level of patient cooperation and reversal of lumbar lordosis for success.

The paramedian approach exploits the larger "subarachnoid target" that exists if a needle is inserted slightly lateral to the midline (see Fig. 51-12). The most common error when using the paramedian technique is that the needle entry site is placed too far off midline, which makes the vertebral lamina barriers to insertion of the needle. In the paramedian approach, the palpating fingers again identify the caudad edge of the cephalad spinous process, and a skin wheal is raised 1 cm lateral and 1 cm caudad to this point. A longer needle (e.g., 1.5 to 2 inches) is then used to infiltrate deeper tissues in a cephalomedial plane. The spinal introducer and needle are next inserted 10 to 15 degrees off the sagittal plane in a cephalomedial plane (see Fig. 51-12). Similar to the midline approach, the most common error is to angle the needle too far cephalad on initial insertion. Nevertheless, if the needle contacts bone, it is redirected slightly in a cephalad direction. If bone is again contacted, but at a deeper level, the slight cephalad angulation is continued because it is likely that the needle is being walked up the lamina. As in the midline approach, the characteristic feel of the ligaments and dura is possible, although needle angulation requires more of the needle to be inserted. After CSF is obtained, the block is carried out in a manner similar to that described for the midline approach.

A variation on the paramedian approach is the lumbosacral approach described by Taylor.[66] This technique is carried out at the L5-S1 interspace, the largest interlaminar interspace of the vertebral column. A 5-inch spinal needle is inserted in a cephalomedial direction through a skin wheal raised 1 cm medial and 1 cm caudad to the lowermost prominence of the posterior superior iliac spine. If bone is encountered on initial needle insertion, the needle is walked off the sacrum into the subarachnoid space. After CSF is obtained, the steps are similar to those outlined previously (Fig. 51-13).

If a continuous spinal anesthetic is prescribed, a needle with a laterally facing opening is typically used to perform the lumbar puncture (Fig. 51-14). A midline or paramedian approach may be used, with some authorities suggesting that use of the paramedian approach facilitates insertion of the catheter.[67] The catheter should be threaded 2 to 3 cm into the subarachnoid space and the needle withdrawn over the catheter. Care must be taken to ensure that the catheter is not inserted more deeply into

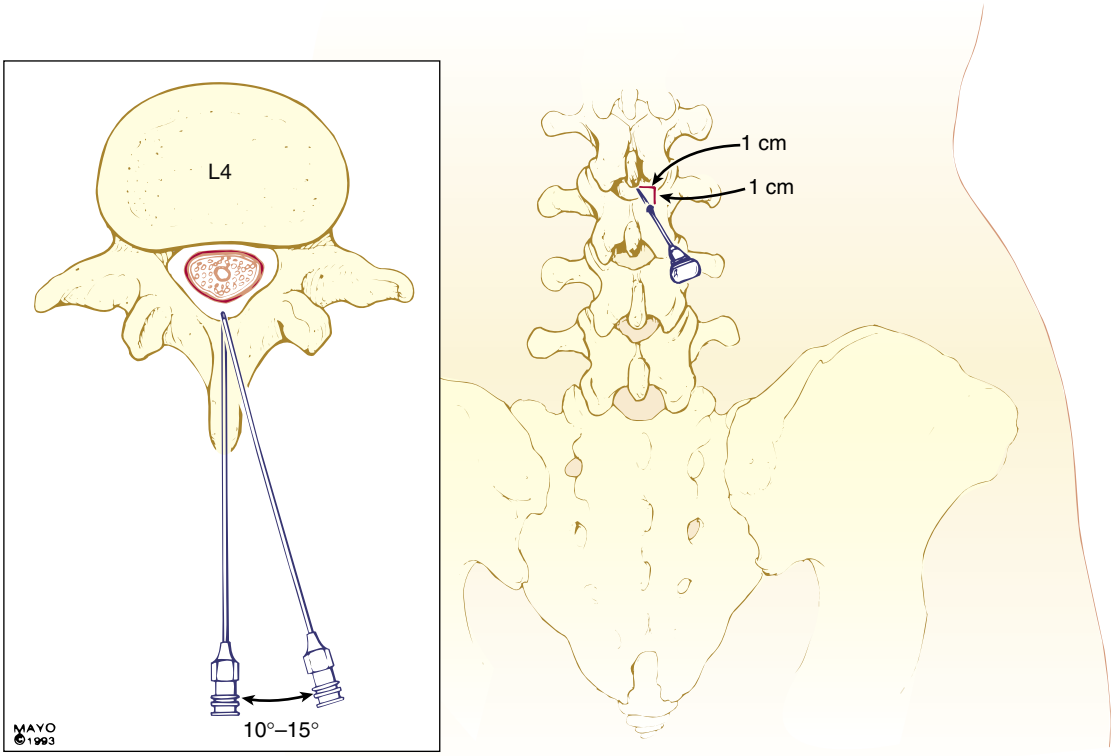

Figure 51-12 Vertebral anatomy of the midline and paramedian approaches to centroneuraxis blocks. The midline approach highlighted in the *inset* requires anatomic projection in only two planes: sagittal and horizontal. The paramedian approach shown in the *inset* and in the posterior view requires an additional oblique plane to be considered, although the technique may be easier in patients who are unable to cooperate in minimizing their lumbar lordosis. The paramedian needle is inserted 1 cm lateral and 1 cm caudad to the caudad edge of the more superior vertebral spinous process. The paramedian needle is inserted approximately 15 degrees off the sagittal plane, as shown in the *inset*. *(Courtesy of the Mayo Foundation, Rochester, MN.)*

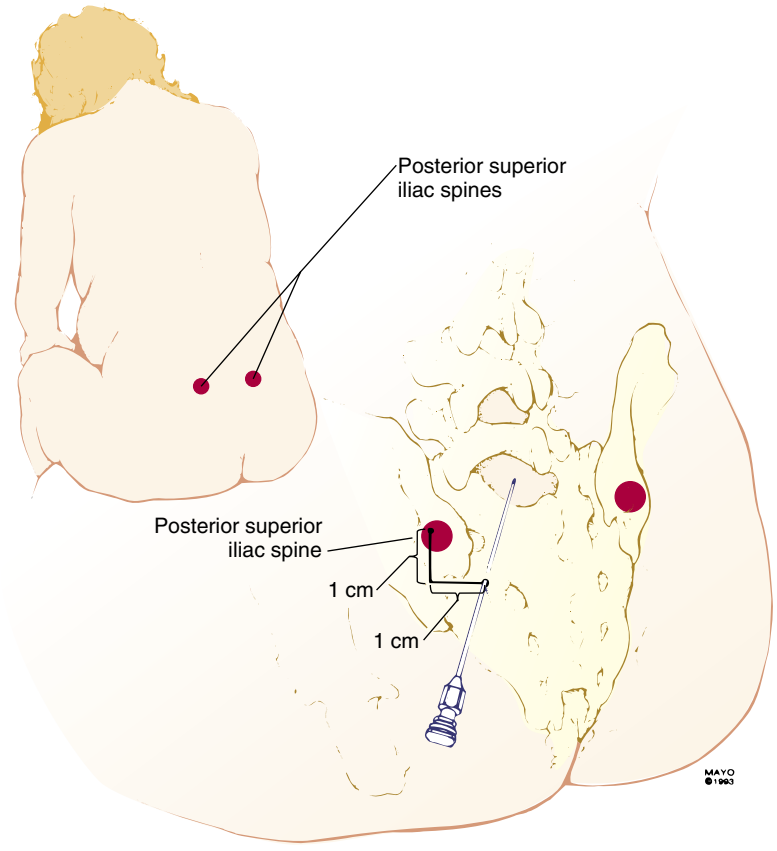

Figure 51-13 Neuraxial anatomy of the Taylor approach to spinal anesthesia. This is really a paramedian approach at the L5-S1 vertebral level. A skin mark is made 1 cm caudad and 1 cm medial to one of the posterior superior iliac spines. Through this skin mark, the needle is inserted in a cephalad and medial direction. The needle is walked off the sacrum and into the largest interspinous space, the L5-S1 intervertebral space. The posterior superior iliac spines are located immediately anterior to the "skin dimples" often found overlying the superior aspect of the sacrum. *(Courtesy of the Mayo Foundation, Rochester, MN.)*

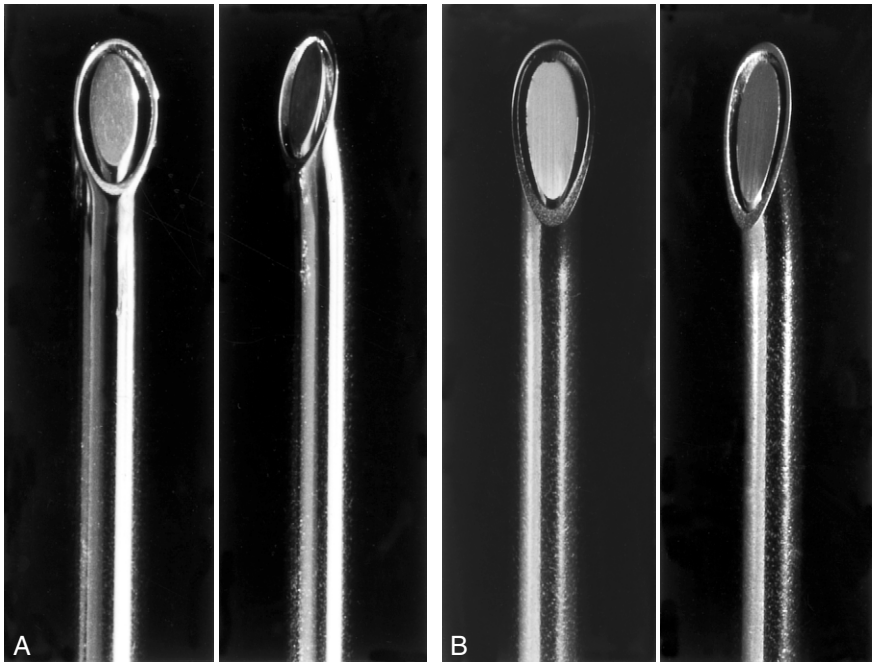

Figure 51-14 Examples of continuous spinal needles, including a disposable, 18-gauge Hustead (**A**) and a 17-gauge Tuohy (**B**) needle. Both have distal tips designed to direct the catheters inserted through the needles along the course of the bevel opening; 20-gauge epidural catheters are used with these particular needle sizes.

the subarachnoid space when the needle is withdrawn over the catheter. Catheter-over-the-needle devices are also available for use with continuous spinal anesthesia. They are promoted as minimizing leakage of CSF around the catheter.[68]

Pharmacology

Useful Drugs

There are many choices of drugs (see Chapter 30) in the United States to produce spinal anesthesia: procaine (Novocain), lidocaine (Xylocaine), mepivacaine (Carbocaine), tetracaine (Pontocaine), ropivacaine (Naropin), (*S*)-(−)-levobupivacaine (Chirocaine), and bupivacaine (Marcaine or Sensorcaine). These drugs provide a duration of spinal anesthesia ranging from 45 to 400 minutes and offer two clinical lengths of action: shorter (<90 minutes) and longer (>90 minutes).

Procaine is one of the oldest spinal anesthetics and originally replaced cocaine as the drug of choice for spinal anesthesia early in the 20th century. It is used for brief spinal anesthesia (<1 hour) but appears to be used less frequently than lidocaine for shorter spinal anesthesia because of three primary clinical differences. It is associated with a higher frequency of nausea (unexplained cause), a relatively high anesthetic failure rate, and a slower time to recovery.[69] It is often used as a hyperbaric drug in a dose ranging between 50 and 150 to 200 mg in a 10% concentration. The reason that some anesthesiologists continue in their use of procaine is the lower frequency of back and leg pain after its use than with lidocaine.[69]

Lidocaine is also often chosen for shorter procedures that can be completed in 1.5 hours or less. It has measurable effect in less than 5 minutes and is most commonly used as the 5% solution in 7.5% dextrose; however, many continue exploring reducing the concentration of the drug during spinal anesthesia.[70,71] It is not clear that reducing the concentration of lidocaine affects the incidence of the back and leg pain (called transient neurologic symptoms and formerly called transient radicular irritation) that follows its use for spinal anesthesia.[72] Transient neurologic symptoms develop most frequently after ambulatory procedures, especially in patients placed in the lithotomy or knee arthroscopy positions. Although many continue attempts to link these symptoms with subclinical neurologic injury, the evidence for such an association remains elusive.[73,74] A Cochrane review of transient neurologic symptoms strongly encourages discontinuation of the term to avoid linking the clinical symptoms of back pain and leg pain to neurologic change after the use of lidocaine, which remains unproven.[75] I further caution against abandoning the use of a useful, short-acting spinal anesthetic until the back pain associated with lidocaine spinal anesthesia is better defined. My use of lidocaine for spinal anesthesia is directed by the following suggestions. Limit the dose to 60 to 70 mg, inject the dose at a rate exceeding 0.2 mL/sec, keep the needle aperture directed cephalad, and limit use of the drug for continuous spinal techniques as much as practical.

Mepivacaine is another drug useful for spinal anesthesia and is being applied in settings in which lidocaine was used in the past. The drug-mass ratio for mepivacaine and lidocaine is approximately 1.3 : 1, suggesting that mepivacaine can be used for spinal anesthesia in a 30- to 60-mg dose and typically in the 2% concentration. In many aspects, mepivacaine is slightly longer-acting lidocaine, with variable reports of lower or equivalent rates of transient neurologic symptoms.[76-78]

When longer-acting agents for spinal anesthesia are desired, four drugs are available: tetracaine, bupivacaine, ropivacaine, and levobupivacaine. Tetracaine has been used in spinal anesthesia for years and is packaged as niphanoid crystals (20 mg) and as a 1% solution (20 mg). This drug has an onset of 5 to 10 minutes and is selected for procedures lasting up to 2 to 3 hours when epinephrine is added and up to 5 hours for lower extremity procedures when phenylephrine (0.5 mg) is added as a vasoconstrictor.[79,80] When niphanoid crystals are used, a 1% solution is obtained by adding 2 mL of sterile water (without preservatives) to the crys-

Table 51-3 Effect of Adding Epinephrine or Phenylephrine to Tetracaine Spinal Anesthesia

	Duration of Blockade*	
Group	**T10 (min)**	**L1 (min)**
I: Tetracaine (plain)	159 ± 41	230 ± 55
II: Tetracaine + epinephrine	234 ± 59†	327 ± 72† (0.5 mg)
III: Tetracaine + phenylephrine	273 ± 90†	406 ± 63†‡ (5 mg)

*The duration of blockade is defined as the time between administration of the spinal anesthetic and regression of the blockade to T10 or L1.
†Significant difference from group I ($P < .01$).
‡Significant difference from group II ($P < .025$).
Adapted from Caldwell C, Nielsen C, Baltz T, et al: Comparison of high-dose epinephrine and phenylephrine in spinal anesthesia with tetracaine. Anesthesiology 62:804, 1985.

tals. The appropriate milligram dose of the 1% solution is then mixed in equal volumes of 10% dextrose to produce a 0.5% tetracaine solution weighted with 5% dextrose. Subsequently, a vasoconstrictor may be added. Epinephrine and phenylephrine prolong spinal anesthesia with tetracaine (Table 51-3).[81,82]

Bupivacaine spinal anesthesia is commonly carried out with 0.75% and 0.5% solutions in dextrose, as well as with isobaric forms of the drug, the 0.5% and the 0.75% plain solutions. The clinical difference between 0.5% tetracaine and 0.75% bupivacaine as hyperbaric solutions is minimal, although more bupivacaine is used than tetracaine. It appears that when "isobaric" 0.5% and 0.75% bupivacaine are compared, the mass of drug (milligram dose) injected is more important in determining the eventual block height than the volume of isobaric drug administered.[83,84] Bupivacaine is appropriate for procedures lasting up to 2 to 2.5 hours.[85]

Ropivacaine is an amide local anesthetic that is frequently used for epidural anesthesia because of experimental evidence of less effect on the cardiac conduction system than occurs with bupivacaine. With spinal anesthesia, this difference is minimal because small doses are administered. When compared with bupivacaine, it is estimated to require 1.8 to 2 times the dose to produce a similar clinical effect.[86,87] Many believe that it is clinically indistinguishable from bupivacaine when the dose of drug administered is of a mass to produce an equal effect.[20]

Levobupivacaine is the isolated (*S*)-enantiomer of bupivacaine and is available for use as a spinal anesthetic. Clinical data suggest that this drug is converted to bupivacaine when used for spinal anesthesia, and for doses ranging from 4 to 12 mg, a volunteer study suggests little clinical difference between levobupivacaine and racemic bupivacaine.[88] In 80 patients undergoing elective hip replacement and receiving isobaric levobupivacaine (3.5 mL of a 0.5% solution) or isobaric bupivacaine (3.5 mL of a 0.5% solution), their clinical efficacy was judged equivalent.[89] In a clinical situation in which systemic toxicity is a minimal issue (or the typical spinal anesthetic), the advantage of levobupivacaine over bupivacaine appears to be more theoretical than real.

Spinal Anesthetic Additives

Some physicians are concerned that the use of additives, particularly vasoconstrictors, may be risky. The concept is that epinephrine and phenylephrine have such potent vasoconstrictive action that they place the blood supply of the spinal cord at risk. There are no human data supporting this theory. Kozody and colleagues[82,90,91] have shown that administering subarachnoid epinephrine (0.2 mg) or phenylephrine (5 mg) does not decrease spinal cord blood flow in dogs. These traditional vasoconstrictors are not the only adrenergomimetic agents being studied. Clonidine, an α_2-agonist, prolongs the motor block associated with tetracaine spinal anesthesia in dogs as much as epinephrine does while prolonging sensory blockade for an even longer interval.[92] The mechanism for this prolongation may involve vasoconstriction and antinociception from α-adrenergic stimulation.[93] Another drug investigated for spinal use as an additive is neostigmine.[94] This acetylcholinesterase inhibitor inhibits the breakdown of acetylcholine and thereby induces analgesia. It also prolongs and intensifies the analgesia through release of nitric oxide in the spinal cord. Despite the side effect of nausea and prolongation of motor block when combining it with local anesthetics, it is slowly gaining acceptance clinically.[95]

The interaction of various vasoconstrictors and local anesthetics is better understood. Traditionally, epinephrine was thought to prolong tetracaine spinal anesthesia but not bupivacaine or lidocaine spinal anesthesia.[96] This theory was postulated because of differences in the vasodilatory action of the local anesthetic drugs; plain lidocaine and bupivacaine cause vasodilation, whereas plain tetracaine does not. The original investigations of spinal anesthetic duration used two-dermatome regression in the thoracic dermatomes to establish duration.[97] Since that time it has become clearer that two-dermatome regression in the middle to high thoracic dermatomes may be misleading when measuring spinal anesthetic duration in the lower thoracic and lumbar dermatomes. Some data indicate that lidocaine spinal anesthesia is prolonged by epinephrine when measured by two-dermatome regression in the lower thoracic dermatomes and by occurrence of pain at the operative site for procedures carried out at the level of the lumbosacral dermatomes.[78,98]

When epinephrine has been compared with phenylephrine as a means of prolonging spinal anesthesia, conflicting information has resulted. Concepcion and coworkers[99] compared epinephrine (0.2 and 0.3 mg) and phenylephrine (1 and 2 mg) added to tetracaine and did not find a difference in increased duration with the two vasoconstrictors. Caldwell and associates[81] used larger doses of vasoconstrictors, epinephrine at 0.5 mg and phenylephrine at 5 mg, and showed that phenylephrine prolonged tetracaine spinal anesthesia significantly more than epinephrine did (see Table 51-3). Phenylephrine has been shown to prolong lidocaine spinal anesthesia, but it appears that the length of prolongation is more similar to that produced with epinephrine rather than significantly longer.[98,100] The duration of bupivacaine spinal anesthesia does not appear to be prolonged by phenylephrine.[97,101] Whichever local anesthetic solution and additives are selected for subarachnoid injection, special care should be taken to ensure that the clinician knows what substance is being injected and that all procedures have been carried out aseptically.

Hypobaric and Isobaric Spinal Anesthesia

The density of any solution is the weight in grams of 1 mL of the solution at a standard temperature. Specific gravity is the ratio of the density of a solution to the density of water. Baricity is a ratio comparing the density of one solution to another. If the other solution happens to be water, the baricity will be the same as the specific gravity. To make a drug hypobaric to CSF, it must be less dense than CSF, with a baricity appreciably less than 1.0000 or a

specific gravity appreciably less than 1.0069 (the mean value of the specific gravity of CSF).

In the United States, a common method of formulating a hypobaric solution is to mix tetracaine in a 0.1% to 0.33% solution with sterile water. This makes the baricity of the solution less than 0.9977 and allows clinically useful anesthesia to be induced. In the prone position for anorectal procedures or in the lateral position for hip repairs, 4 to 6 mg of a selected hypobaric dilution is often adequate. There is evidence that the rate of injection (0.02 versus 0.5 mL/sec) of hypobaric (0.2%) tetracaine influences spread of the drug.[102]

Another method of formulating a hypobaric-like solution is to use warmed 0.5% bupivacaine.[103] Data show that 0.5% bupivacaine warmed to 37°C as opposed to 4°C demonstrates hypobaric characteristics when the block is administered to sitting patients. The investigators suggest that warmed bupivacaine provides more predictable cephalad spread of the sensory level than a cold or room-temperature drug does. Another drug that has been investigated as a "clinically" hypobaric spinal drug is 2% lidocaine. Its physiochemical characteristics make it more similar to an isobaric than a hypobaric drug; however, some clinicians have found it useful in situations generally reserved for hypobaric techniques.[104]

When isobaric spinal anesthesia is planned, the drugs most often chosen across the globe are bupivacaine, ropivacaine, and levobupivacaine (in 0.5% or 0.75% concentrations). Another drug that can be used is tetracaine. It is formulated into an isobaric solution by diluting the niphanoid tetracaine crystals (20 mg) with CSF and then injecting the selected mass of drug in an isobaric fashion.

Box 51-1 Factors Postulated to Be Related to Spinal Anesthetic Block Height

- Patient characteristics
  - Age
  - Height
  - Weight
  - Gender
  - Intra-abdominal pressure
  - Anatomic configuration of the spinal column
  - Position
- Technique of injection
  - Site of injection
  - Direction of injection (needle)
  - Direction of bevel
  - Use of barbotage
  - Rate of injection
- Characteristics of spinal fluid
  - Volume
  - Pressure (cough, strain, Valsalva maneuver)
  - Density
- Characteristics of the anesthetic solution
  - Density
  - Amount (mass)
  - Concentration
  - Temperature
  - Volume
- Vasoconstrictors

Factors Affecting Block Height

More than 20 factors have been postulated to alter spinal anesthetic block height (Box 51-1).[105,106] Box 51-2 lists the most important documented factors known to influence block height. Age has a statistically significant effect on block height, but when examined, the difference in block height with isobaric bupivacaine in patients in the third to ninth decades is small (i.e., T9 for those 20 to 28 years old and T6 for those older than 80 years).[107,108] Unlike epidural dose requirements, weight is not related to block height during spinal anesthesia. Patient height is related, although the contribution is minor when compared with more important factors. Similarly, the injection rate and barbotage of isobaric and hyperbaric solutions have not been shown to affect block height, although injection rates in these studies have been greater than 0.1 to 0.2 mL/sec.[109] It is becoming clear that the direction of the laterally facing openings of spinal needles affects block height levels, even with isobaric spinal solutions.[110,111] Other maneuvers that do not appear to affect block height are coughing and straining after local anesthetic injection. This is related to the physics of injecting drugs into a closed column of CSF, which instantaneously transmits pressure changes throughout the CSF column, such as those that occur with coughing or straining (Box 51-3).[105]

When more global factors affecting block quality are examined, at least in some teaching programs, the spinal failure rate may be as high as one in six blocks.[112] To understand the failure rate fully, the definition must be examined. Investigators[113] considered the need to supplement the block with any inhaled anesthetic as failure. This is a key point because to provide comprehensive regional anesthesia, supplementation of the block must be considered appropriate rather than a de facto failure.[113] These data emphasize an important contributor to failed blocks, the lack of free flow of CSF after needle placement. Obviously, some level of experience is needed to carry out spinal anesthesia successfully, but even in a teaching program, this should not prohibit the successful use of spinal anesthesia because the failure rate can be as low as 1%.[55,85]

Box 51-2 Factors Influencing Block Height

Controllable Factors

- Dose (volume × concentration)
- Site of injection along the neuraxis
- Baricity of the local anesthetic solution
- Posture of the patient

Factors Not Controllable

- Volume of cerebrospinal fluid
- Density of cerebrospinal fluid

Adapted from Stienstra R, Veering BT: Intrathecal drug spread: Is it controllable? Reg Anesth Pain Med 23:347, 1998.

Box 51-3 Factors Probably Unrelated to Height of the Spinal Anesthetic Block

Added vasoconstrictor
Coughing, straining, or bearing down (labor)
Barbotage
Rate of injection (except hypobaric)
Needle bevel (except Whitacre needles)
Gender
Weight

Complications

Complications include neurologic changes; headache after spinal puncture; backache, which accompanies 25% of procedures performed with spinal anesthesia; and unexpected cardiac arrest.[114]

Neurologic injury after spinal anesthesia has received considerable media attention through the years, including the Wooley and Roe case in England, the investigation published by Kennedy and colleagues[4] in 1950 in the United States, and cases of cauda equina syndrome associated with small-bore continuous spinal anesthesia.[115] Overlooked by many is information from Marinacci,[116] whose investigation was performed after Kennedy and colleagues' publication. Marinacci, a neurologist, evaluated 542 patients who were thought to have neurologic complications related to previous spinal anesthesia. After neurologic evaluation, in only 4 of the 542 patients was there any indication that the prior spinal anesthetic was the cause of the postoperative neurologic change. The total number of patients undergoing spinal anesthesia that resulted in the four cases of neurologic symptoms related to spinal anesthesia is unknown.

Some reports outline the numerator and denominator of neurologic change after spinal anesthesia. Vandam and Dripps[117] documented 10,098 patients who underwent spinal anesthesia and reported no severe neurologic sequelae related to spinal anesthesia. A review of neurologic complications associated with neuraxial blocks, prompted by the chloroprocaine epidural controversy in the early 1980s, tabulated 304 patients undergoing spinal anesthesia with only one permanent lesion, a lumbar plexus injury, potentially related to spinal anesthesia.[118] Rigler and coworkers[115] reported cauda equina syndrome developing in four patients after continuous spinal anesthesia. The pool of patients from which the four patients were drawn is unknown. This research team has continued to highlight perceived difficulties with the spinal use of lidocaine and has added significant data to the question. Auroy and associates[119] reported on the regional anesthesia practice of more than 700 French anesthesiologists during a 5-month interval in the 1990s. These investigators highlighted that lidocaine appeared to be over-represented in their series of neurologic deficits after spinal anesthesia. The ultimate decision about using lidocaine for spinal anesthesia still requires consideration of the alternatives and suggestions outlined in the earlier section of this chapter on the pharmacology of spinal drugs.

The large series and case reports documenting infrequent neurologic lesions after spinal anesthesia should not provide a false sense of security.[120] Neurologic changes can occur; Reynolds has documented this in a group of predominately obstetric patients.[121] Fettes and Wildsmith addressed the findings of Reynolds in a thoughtful editorial and emphasized that we must always appreciate that another's nervous system is on the far end of the spinal needle.[122] The important point is that severe neurologic change can also occur after general anesthesia. The risk-benefit equation of anesthesia and neurologic injury must include the cases of neurologic injury (e.g., hypoxic CNS lesions) that are possible during general anesthesia if a logical and well-informed decision based on neurologic outcome is to be made.

A more common complication of spinal anesthesia is postoperative headache. This post–spinal puncture headache* is not exclusively related to spinal anesthesia; it also occurs after myelography and diagnostic lumbar puncture. Lybecker and coworkers[123] popularized a post–spinal puncture headache rating scale that may make comparison between future studies of postoperative headache more meaningful. Factors increasing the incidence of post–spinal puncture headache or unrelated to its development are listed in Table 51-4.[124]

Mihic's investigation of bevel direction during insertion of a spinal needle suggested that orienting a needle bevel parallel with the length of the neuraxis results in a lower incidence of post–spinal puncture headache.[125] Although needle type was unspecified in Mihic's report, it is likely that a Quincke-type needle was used. This clinical observation has been supported by a laboratory investigation by Ready and associates[65] showing that simulated spinal puncture with cone-shaped spinal needle tips produces slower transdural loss of fluid than a similar puncture

Table 51-4 Relationships Among Variables and Post–spinal Puncture Headache

Factors That May Increase the Incidence of Post–spinal Puncture Headache	
Age	Younger more frequent
Gender	Females > males
Needle size	Larger > smaller
Needle bevel	Less when the needle bevel is placed in the long axis of the neuraxis
Pregnancy	More when pregnant
Dural punctures (no.)	More with multiple punctures
Factors Not Increasing the Incidence of Post–spinal Puncture Headache	
Continuous spinals	
Timing of ambulation	

*Post–spinal puncture headache is used throughout chapter rather than post–dural puncture headache because it appears that arachnoid puncture is more linked to the resulting headache than the dural rent.[24]

with cutting-tipped needles does. Perhaps more important, a meta-analysis has shown that noncutting needle tip designs have a lower frequency of post–spinal puncture headache than cutting needle tip designs do.[126] Data from Reina and colleagues[26] have shown that the lower frequency of headache with cone-shaped needle tips may be the result of exposing more inflammatory mediators around the opening rather than the often-quoted more gentle spreading of the dura at the site of puncture. An arbitrary period of recumbency after spinal anesthesia has not been found to decrease the incidence of post–spinal puncture headache,[127] and some data indicate that early ambulation may actually decrease its incidence.[128,129]

Possibly more important than knowing all the variables resulting in an increased incidence of post–spinal puncture headache is understanding how and when to carry out the definitive therapy—epidural blood patch—for this complication.[130] Successful application of spinal anesthesia necessitates the early use of epidural blood patching when indicated. This therapy was introduced by Gormley[131]; its safety and efficacy (>90% effective in relieving headache per epidural patch) have been well documented, and contemporary practice has validated that epidural blood patch continues to have a greater than 90% improvement rate.[132]

A question that has been debated since its introduction concerns the volume of blood that is most effective in balancing blood patch efficacy and risks. By injecting radionucleotide-labeled red blood cells epidurally, Szeinfeld and coworkers[133] have shown that approximately 15 mL of blood provides efficacy and allows spread over a mean distance of nine spinal segments, thus providing some latitude for blood patch needle placement. They demonstrated that the blood was spread over more segments in the cephalad direction than in the caudad direction. As a result, they recommend inserting the blood patch needle in a more caudad site if it is impossible to insert the needle at the same level as that of the previous dural puncture. MRI of epidural blood patch spread has validated their data about primarily cephalad spread of an epidural blood patch.[134]

Data from Brown and Elman[135] demonstrate that approximately 25% of all surgical patients undergoing anesthesia, regardless of anesthetic technique, experience backache. Backache after neuraxial block should not immediately be attributed to "needling" of the back or to the use of 5% lidocaine.

When properly conducted, spinal anesthesia has proved to be extremely safe. Caplan and associates[114] identified 14 cases of sudden cardiac arrest in healthy patients receiving spinal anesthesia. Because these cases seemed to appear suddenly after stable hemodynamic status, they concluded that a poorly understood potential exists for sudden cardiac arrest in healthy patients. It can be debated whether this represented lack of vigilant monitoring and treatment as opposed to some mysterious physiologic explanation.[136] It is clear that hypoxemia and oversedation are not required for severe bradycardia and asystole to develop during well-conducted spinal anesthesia.[53,137] Likewise, it is clear that the development of severe bradycardia after spinal anesthesia is not a new phenomenon but has been recognized for many years.[138,139] In any case, it should be emphasized that cardiovascular changes can occur rather suddenly after spinal anesthesia, and as Auroy and colleagues[119] highlight, these events continue to occur.

Clinical Pearls

Frequently, the little things necessary to carry out effective spinal anesthesia are unstated because they somehow seem less important than the broader issues, such as the incidence of neurologic complications after spinal anesthesia. Nevertheless, the little things often spell the difference between successful use of the technique and failure.

Successful integration of neuraxial blocks into an anesthesia practice requires that anesthesiologists be willing to supplement their blocks with CNS depressants.[113] A concept has developed that a regional anesthetic should need no supplementation and that if it does, it should be considered a failed block. This reasoning needs rethinking. For example, an anesthesiologist would not be expected to pick an arbitrary concentration of an inhaled agent before general anesthesia and, on discovering that the concentration needs to be altered during the anesthesia, consider the technique a failure! Likewise, supplementation of a spinal or epidural anesthetic contributes to its comprehensive use and should not be a marker of failed blocks. After this concept is accepted, neuraxial blocks can be adapted to many more situations, thereby allowing an anesthesiologist's experience and confidence with the techniques to grow.

To prevent prolongation of a patient's recovery room stay and therefore unnecessarily introduce institutional inefficiency, inpatients should be allowed to leave the recovery room after spinal anesthesia as soon as it can be demonstrated that their block is receding appropriately (at least four dermatomes' regression or a spinal level of less than T10), they are hemodynamically stable, and they are comfortable. After spinal anesthesia, outpatients should be able to ambulate without orthostatic changes and void before discharge if they are in a high-risk group for urinary retention[62] (see Chapter 78).

Intraoperatively during high spinal anesthesia, patients occasionally complain excessively about dyspnea. This is not a result of significantly decreased inspiratory capacity but most often seems to be related to loss of chest wall sensation, which does not allow patients to experience the reassurance of a deep breath. This impediment to patient acceptance can often be overcome by instructing the patient to raise a hand near the mouth and exhale forcefully. The tactile appreciation of the deep breath seems to provide reassurance.

If a neurologic complication is identified after an operation performed with spinal anesthesia, it is useful to obtain neurologic consultation early so that an unbiased consultant can examine the patient and determine whether the "new" neurologic finding was preexistent, related to a peripheral neuropathy, or more rarely, potentially related to the spinal anesthetic. The latency in electromyographic alterations associated with denervation secondary to neurologic injury takes time (14 to 21 days) to develop in the lower extremities. The physician should obtain electromyographic studies early and serially after a potential spinal anesthetic–related lesion. In this manner, it is possible to document whether the lesion was preexisting or provide evidence that it is a peripheral rather than a central lesion.

Probably more important than any single factor for the success of spinal anesthesia in the day-to-day use of anesthesia is that it must be time efficient. It cannot add measurably to the surgical day if nurses and surgeons are to be coadvocates of the

technique. The physician should plan ahead to maximize time efficiency. Often overlooked is that patient preparation for surgery can begin almost as soon as the block is administered if sedation is at an appropriate level.

Epidural and Caudal Anesthesia

Epidural Technique

The technique of epidural anesthesia relies on the same four P's as spinal anesthesia, with minor modifications.

Preparation

In addition to patient preparation, selection of epidural equipment is essential. The physician must decide on a continuous or single-shot technique. This is the principal determinant of needle selection. If a single-shot epidural technique is chosen, a Crawford needle is appropriate; if a continuous catheter technique is indicated, a Tuohy or another needle with a laterally facing opening is chosen (Fig. 51-15). A method of identifying the epidural space must also be selected, with most using a loss-of-resistance technique. If a loss-of-resistance technique is used, an additional decision about the type of syringe (i.e., glass versus plastic and Luer-Lok versus friction hub) is required. The theoretical ideal is a Luer-Lok, finely ground glass syringe because it minimizes the chance of misidentification of the epidural space. Most disposable equipment can be customized to an individual's needs if the advantages of reusable equipment are not available.

Position

The patient positions necessary for epidural puncture are the same as those for spinal anesthesia, with the exception of the prone position for the caudal approach. Inadequate positioning

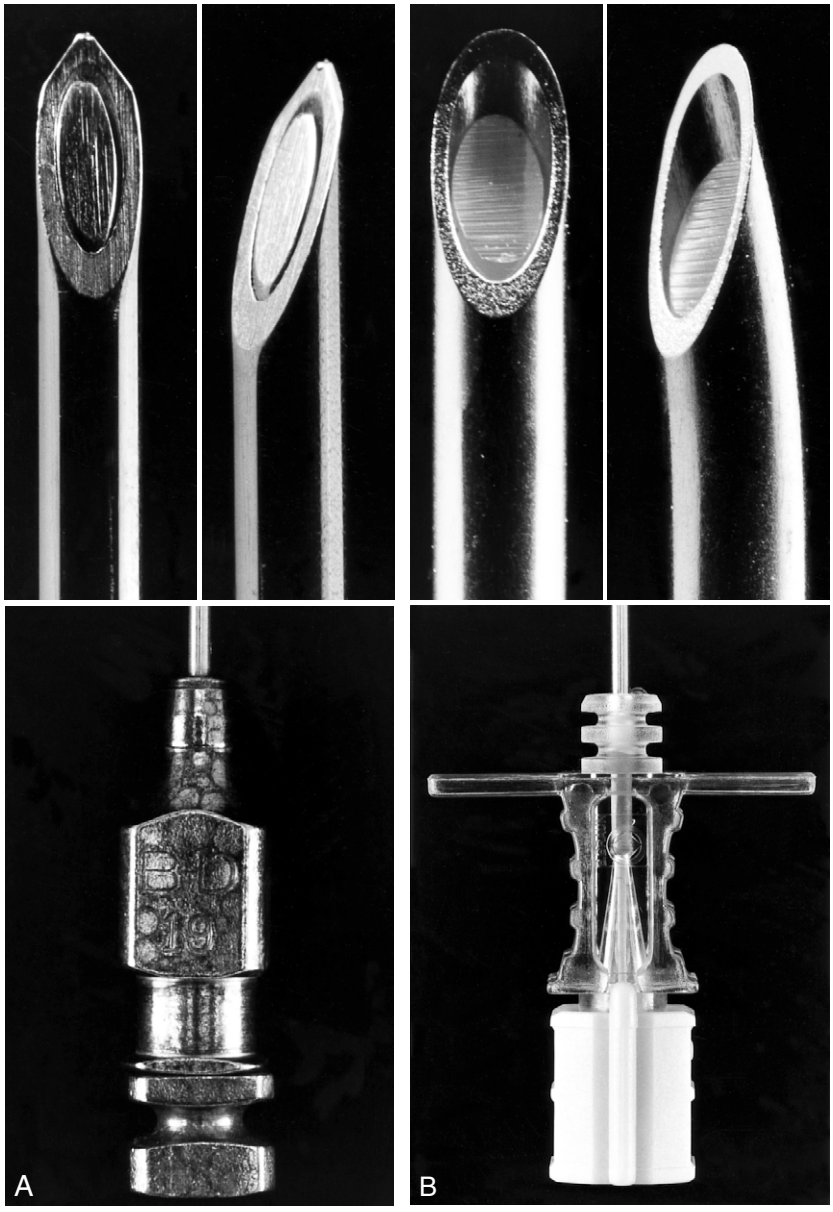

Figure 51-15 Epidural needles with catheter assortment. **A,** A 19-gauge, reusable Crawford epidural needle. **B,** A 19-gauge, disposable Tuohy needle.

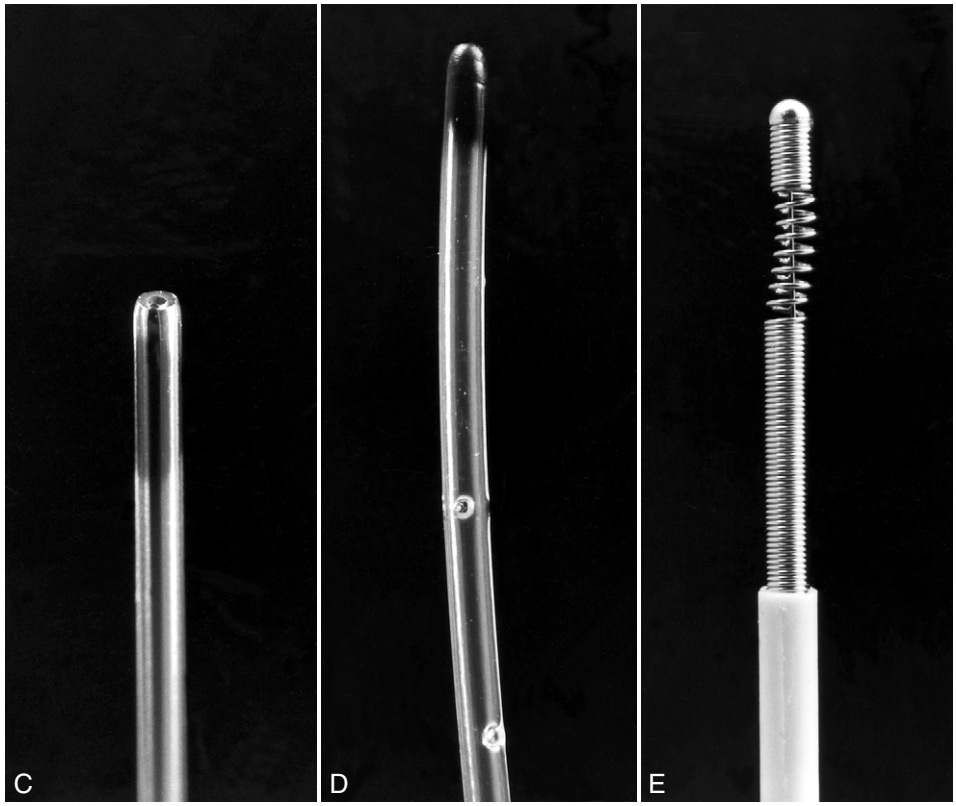

Figure 51-15, cont'd C, Single–end-hole epidural catheter. **D,** Closed-tip, multiple–side-hole catheter. **E,** Spring wire–reinforced, polymer-coated epidural catheter.

of the patient can negate otherwise meticulous technique and should be prevented. Limitation of block spread (i.e., height) is not clinically predictable with alterations in position during epidural anesthesia because gravity and solution baricity are not intimately related to block spread. Despite these facts, Seow and coworkers[140] have demonstrated slightly faster block onset times in patients' dependent body regions when the lateral decubitus position is used for epidural block.

Three positions are available for caudal anesthesia, with the prone position most often chosen in adults, the lateral decubitus position in children, and the knee-chest position infrequently used. The lateral decubitus position is used in children because it is easier to maintain a patent airway in this position than in the prone position, and the landmarks are more easily palpable than in adults (see Chapter 81). This consideration is valuable because caudal anesthesia is often combined with general anesthesia in pediatric patients to decrease the amount of volatile agent used intraoperatively or to provide postoperative analgesia. In contrast, a caudal block is often administered during preoperative sedation in adults and when the prone position is applicable. When placing a patient in the prone position, a pillow should be inserted beneath the iliac crests to rotate the pelvis and make cannulation of the caudal canal easier. An additional help is to spread the lower extremities about 20 degrees with the heels rotated laterally, which minimizes gluteal muscle contraction and eases needle insertion (Fig. 51-16).

Projection and Puncture

Epidural technique requires placement of the needle tip into the ligamentum flavum for the loss-of-resistance and hanging-drop methods. Placing the needle (with stylet) into the ligamentum flavum before attaching the syringe or placing solution into the needle hub allows an improved appreciation of epidural anatomy for the operator. If the needle is merely inserted into the supraspinous ligament and then loss-of-resistance or hanging-drop

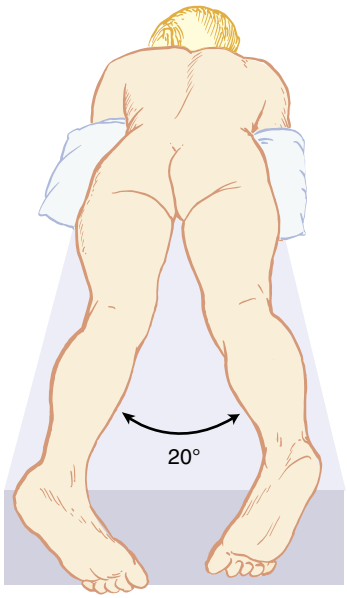

Figure 51-16 Prone position for the caudal technique. A pillow is used under the anterior iliac crests to rotate the pelvis, the legs are spread 20 degrees to ease identification of the sacral hiatus, and the heels are rotated laterally to relax the gluteal musculature.

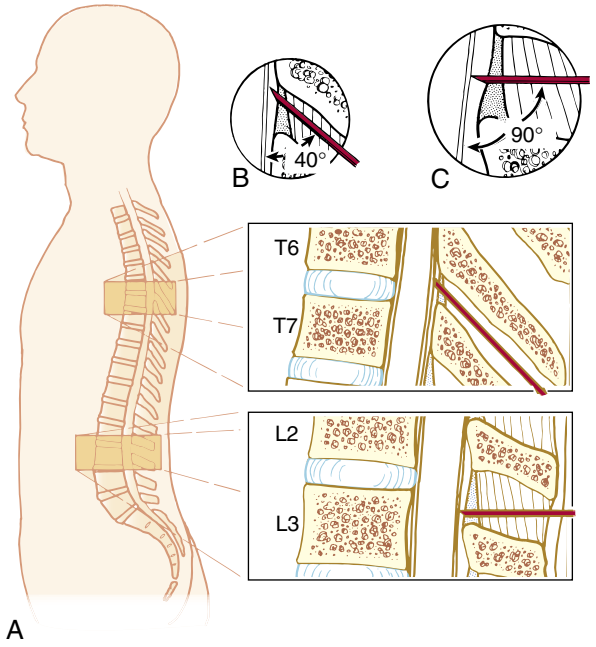

Figure 51-17 A, Lumbar and thoracic epidural technique. The increased angle of needle insertion during thoracic epidural cannulation may provide a slightly longer distance of "needle travel" before entering the subarachnoid space. In contrast to lumbar epidural cannulation (**B**), the distance traveled is modified by a more perpendicular angle of needle insertion (**C**).

insertion is begun, an increased chance of false release seems likely.

When a lumbar approach is used, the depth from skin to the ligamentum flavum commonly approaches 4 cm, with the depth in most (80%) patients being between 3.5 and 6 cm. In this region, the ligamentum flavum is 5 to 6 mm thick in the midline, which requires needle control if unintentional dural puncture is to be prevented. Some investigators are exploring the use of ultrasound to help minimize dural puncture by more accurately defining the distance between the skin and the epidural space.[141] When a thoracic approach is chosen, control is of equal or greater importance because injury to the spinal cord is possible if the needle is advanced too far. Theoretically, the increased angle of needle insertion in the thoracic region may provide an element of safety in that the more acute angle necessary to gain epidural cannulation provides some margin of safety (Fig. 51-17). Clinically, thoracic epidural anesthetics do not appear to be associated with an increased incidence of neurologic injury because those choosing to use the technique are most often anesthesiologists with considerable experience in lumbar epidural anesthesia.[142] In any event, significant caution about performing thoracic epidural techniques in adult patients receiving general anesthesia is warranted because these patients are unable to provide feedback to the operator about neural stimulation during needle insertion.

The preferred method of carrying out the loss-of-resistance technique involves inserting the needle to the ligamentum flavum and then attaching a 3- to 5-mL glass syringe filled with 2 mL of saline and a small (0.25-mL) air bubble. The needle is grasped with the nondominant hand and pulled toward the epidural space while the dominant hand (thumb) applies constant steady pressure on the syringe plunger to compress the air bubble. When the epidural space is entered, the pressure applied to the syringe plunger allows the solution to flow without resistance into the epidural space.

An alternative, although with a less precise end point, is the technique of hanging-drop identification of entry into the epidural space. After the needle is placed into the ligamentum flavum, a drop of solution is placed within the hub of the needle. When the needle is advanced into the epidural space, the solution should be "sucked in." The theory behind this maneuver has been attributed to subatmospheric pressure in the epidural space. The subatmospheric pressure has been related to expansion of the epidural space as the needle pushes the dura away from the ligamentum flavum.[143] The negative intrathoracic pressure may influence the pressure in the epidural space in the thoracic region.

Regardless of the method selected for needle insertion, when the anesthesiologist chooses to cannulate the epidural space with a catheter, success may be increased by advancing the needle 1 to 2 mm after the space is identified. The incidence of unintentional intravenous cannulation with an epidural catheter may be lessened by injecting air or solution before threading the catheter.[144,145] Unless radiographic guidance is used for some special reason, epidural catheters should be inserted only 2 to 3 cm into the epidural space for surgical or obstetric patients needing rapid onset of analgesia.[146] Threading more catheter may increase the likelihood of catheter malposition. If malposition does occur, data suggest that one of the more common sites of malposition is entry of the catheter into the anterior epidural space.[147] In obstetric patients, it appears that the catheter should be inserted between 4 and 6 cm to optimize efficacy and prevent unintentional movement of the catheter during prolonged labor analgesia.[148,149] Multiport (three lateral ports) or single–end-hole (uniport or distal port) catheters are available. The choice is up to individual clinicians, although it has been shown in laboring patients that the incidence of inadequate analgesia is less with multiport catheters than with uniport catheters.[150]

Despite an adequately positioned catheter during first use of a local anesthetic, each subsequent injection should be preceded by aspiration and an epidural test dose because catheter migration into vessels and the subarachnoid or subdural space does occur. In the past, many considered the catheter unusable in the event that the epidural catheter hub becomes disconnected from the epidural catheter. It appears that the catheter can be reused if strict reconnection criteria are followed.[151]

Caudal Technique

Caudal anesthesia requires identification of the sacral hiatus. The sacrococcygeal ligament (i.e., extension of ligamentum flavum) overlying the sacral hiatus lies between the sacral cornua. To facilitate locating the cornua, the posterior superior iliac spines should be located and, by using the line between them as one side of an equilateral triangle, the location of the sacral hiatus should be approximated (Fig. 51-18). After the sacral hiatus is identified, the index and middle fingers of the palpating hand are placed on the sacral cornua, and the caudal needle is inserted at an angle of approximately 45 degrees to the sacrum. While advancing the needle, a decrease in resistance to needle insertion should be appreciated as the needle enters the caudal canal. The needle is advanced until bone (i.e., dorsal aspect of the ventral plate of the sacrum) is contacted and then slightly withdrawn, and the needle

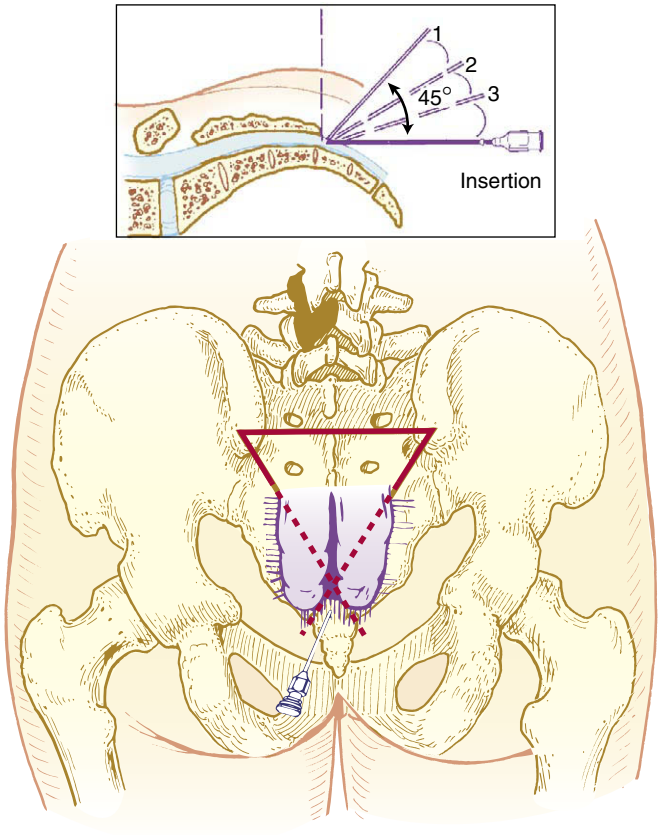

Figure 51-18 Caudal technique. Palpating fingers locate the sacral cornua by using the equilateral triangle (shown in Fig. 51-5). Needle insertion is carried out by insertion and withdrawal in stepwise fashion (*inset*; so-called 1-2-3 insertion) until the needle can be advanced into the caudal canal and the solution can be injected easily (without creation of a subcutaneous "lump" of fluid).

is redirected so that the angle of insertion relative to the skin surface is decreased. In male patients, this angle is almost parallel to the coronal plane; in female patients, a slightly steeper angle (15 degrees) is necessary. During redirection of the needle and after loss of resistance is again encountered, the needle is advanced approximately 1 to 2 cm into the caudal canal. Further advance is not attempted because dural puncture and unintentional intravascular cannulation become more likely. One method of increasing the likelihood of correct caudal needle placement is to inject 5 mL of saline rapidly through the caudal needle while palpating the skin overlying the sacrum. If no midline bulge is detected, the needle is probably positioned correctly. In contrast, if a midline bulge is detected during saline injection, the needle is positioned incorrectly.

After ensuring correct needle position and before injection of the therapeutic dose of caudal anesthetic, aspiration should be performed and a test dose administered because as in lumbar epidural anesthesia, a vein or the subarachnoid space can be entered unintentionally.

Pharmacology

Useful Drugs

Successful selection of drug for epidural anesthesia (see Chapter 30) requires an understanding of the local anesthetic's potency and duration, as well as estimation of the surgical requirements and duration and postoperative analgesia requirements. As with any regional anesthetic, the surgeon, anesthesiologist, procedure, and anesthetic technique must all be included in the drug choice equation.

Drugs available for epidural use can be categorized as short-, intermediate-, and long-acting local anesthetics, and with the addition of epinephrine to these agents, surgical anesthesia ranging from 45 to 240 minutes is possible (Table 51-5). Chloroprocaine, an ester local anesthetic, is a short-acting agent that was associated with neurotoxicity (i.e., adhesive arachnoiditis) when unintentionally injected in large volumes into the subarachnoid space before a change in formulation.[151,152] Since 1985, reduced bisulfate concentrations of the drug formulation have been available; since 1987, bisulfate-free 2-chloroprocaine has been available; and since 1996, preservative-free 2-chloroprocaine has been available. Since these formulation changes, there have been no reports of neurotoxicity attributable to 2-chloroprocaine until recently. Winnie and Nader[153] have highlighted that in this era of increasing drug costs, some hospitals are substituting generic formulations of anesthetic drugs, and in one situation, metabisulfite-containing 2-chloroprocaine was returned to anesthesia stock without knowledge of the physicians. We must all be aware of the solutions that we are using because this type of substitution is likely to increase.

In the era of ever-increasing numbers of surgical outpatients, combining 2-chloroprocaine and a catheter technique allows efficient matching of the surgical procedure and duration of epidural analgesia and enables patients to spend minimal recovery time in the facility. It is available in 2% and 3% concentrations, with the latter preferable for surgical anesthesia and the former for techniques not requiring muscle relaxation.

There is evidence that the back pain developing after larger volumes (>25 mL) of 2-chloroprocaine was related to the ethylenediaminetetraacetic acid used as a preservative in the chloroprocaine.[154] It appears that preservative-free chloroprocaine is not associated with back pain in larger doses at the same frequency.

Lidocaine is the prototypical amide local anesthetic and is used epidurally in 1.5% to 2% concentrations. Mepivacaine is

Table 51-5 Comparative Onset Times and Analgesic Durations of Local Anesthetics Administered Epidurally in 20- to 30-mL Volumes

			Duration (min)	
Drug	**Conc. (%)**	**Onset (min)**	**Plain**	**1:200,000 Epinephrine**
2-Chloroprocaine	3	10-15	45-60	60-90
Lidocaine	2	15	80-120	120-180
Mepivacaine	2	15	90-140	140-200
Bupivacaine	0.5-0.75	20	165-225	180-240
Etidocaine	1	15	120-200	150-225
Ropivacaine	0.75-1.0	15-20	140-180	150-200
Levobupivacaine	0.5-0.75	15-20	150-225	150-240

Data from Cousins MJ, Bromage PR: Epidural neural blockade. *In* Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain. Philadelphia, JB Lippincott, 1988, p 255, and other sources.

similar to lidocaine in the concentrations necessary for epidural anesthesia and lasts 15 to 30 minutes longer. Epinephrine prolongs the duration of surgical anesthesia by approximately 50% with lidocaine and mepivacaine.[116] Another additive to these drugs that may influence clinical use is fentanyl, an intermediate-acting amide drug for epidural use. When fentanyl was added to mepivacaine, it accelerated the onset of analgesia and enhanced the analgesic effect during epidural anesthesia.[155] One technique receiving more attention to minimize the length of an epidural motor block after surgery is completed is the use of saline in 15- to 30-mL volumes through the epidural catheter before it is removed.[156]

Bupivacaine remains the most widely used long-acting local anesthetic; it is used in 0.5% and 0.75% concentrations for surgical anesthesia. Analgesic techniques can be performed with concentrations from 0.125% to 0.25%. Its duration of action is less consistently prolonged by the addition of epinephrine, although up to 240 minutes of surgical anesthesia can be obtained when epinephrine is added. In 1983, the FDA stated that 0.75% bupivacaine was no longer recommended in obstetric anesthesia as a result of a perception that systemic toxicity at that concentration resulted in more difficult resuscitation than occurred with the lower concentrations. The evidence for this action remains controversial, although it does appear that bupivacaine and etidocaine are more likely than other local anesthetics to impair myocardial performance and conduction when systemic toxicity occurs.[157,158]

Ropivacaine is increasing in use as an epidural agent. It is used in 0.5% to 1.0% concentrations for surgical anesthesia and 0.1% to 0.3% concentrations for analgesia. Animal evidence supports the concept that ropivacaine has less impact on cardiac conduction and the frequency of arrhythmias than local anesthetics do at blood levels producing systemic toxicity.[159] In an individual patient, the clinical effect of ropivacaine is difficult to separate from a similar effect from bupivacaine, although it appears to produce less motor block and has a slightly shorter duration of action than bupivacaine does.[160] However, it is the only local anesthetic still in use that has a vasoconstrictive property at clinically used concentrations.

Levobupivacaine is also used as an epidural local anesthetic in 0.5% to 0.75% concentrations for surgical anesthesia, and analgesic techniques can be performed with concentrations of 0.125% to 0.25%. In an individual patient, the clinical anesthetic effect from the drug is indistinguishable from that of racemic bupivacaine.[161] Similar to ropivacaine, animal evidence supports the concept that levobupivacaine has less impact on cardiac conduction and the frequency of arrhythmias than local anesthetics do at blood levels producing systemic toxicity.

Etidocaine is an infrequently used epidural anesthetic, principally because of the perception and some data supporting that motor block is more profound than sensory block with the drug.[162] The reason may be that etidocaine is less effective than bupivacaine in producing small-fiber blockade.[163]

Additives

Some investigators advocate combining agents with local anesthetics to make epidural anesthesia last longer, to improve the quality of blockade, or to accelerate the onset of blockade. Epinephrine increases the duration of useful anesthesia with all the agents, although the proportional effect is greatest with lidocaine, mepivacaine, and 2-chloroprocaine; it shows a lesser effect with bupivacaine, levobupivacaine, and etidocaine and has a limited effect with ropivacaine (see Table 51-5). Phenylephrine has been used in epidural anesthesia less widely than in spinal anesthesia, perhaps because it does not reduce peak blood levels of local anesthetic as effectively as epinephrine does during epidural use.[164]

Carbonation of the local anesthetic solution has been suggested as a means of increasing the speed of onset and quality of the block by producing more rapid intraneural diffusion and more rapid penetration of connective tissue surrounding the nerve trunk.[165,166] Some data suggest that there are no clinical advantages for carbonated solutions,[167] and some disadvantages may occur more rapidly because peak blood levels of the drug are higher after carbonation of the local anesthetic and blood pressure decreases (see Chapter 30).[168,169]

The addition of bicarbonate has also been suggested as a means of increasing the pH of the local anesthetic solution and increasing the concentration of nonionized free base, which theoretically increases the rate of diffusion of the drug and the speed of onset of the block. Clinically, the addition of 1 mEq of sodium bicarbonate to each 10 mL of commercially prepared 1.5% lidocaine solution produces a significantly faster onset of anesthesia and more rapid spread of sensory block.[170] In addition to speeding onset of the block, there is evidence that a more complete block may be produced.[171] The clinical applicability of this modification should be considered individually on its merits by each institution's anesthesia group.

Another alteration of drugs for epidural use involves combining long- and short-acting drugs, theoretically to gain the benefits of each. This practice does not seem necessary or prudent because familiarity with the local anesthetics and additives available allows a spectrum of block lengths to be produced. Moreover, the purported advantage of faster onset with combinations of local anesthetics seems clinically inconsequential.

Complications

Intravascular Injection

Epidural anesthesia has the potential to produce local anesthetic–induced systemic toxicity (see Chapter 30), primarily through the unintentional administration of drug into an epidural vein. Considerable research has been undertaken to define the ideal test dose for continuous epidural catheter use. The use of test doses should minimize unintentional intravascular injections, although there are concepts in treating a local anesthetic–induced systemic toxicity reaction that all anesthesiologists should understand.

The toxic effects of local anesthetics primarily involve the CNS and cardiovascular system, with the CNS affected at lower blood levels. For example, four to seven times the dose of local anesthetic necessary to produce convulsions in dogs is required to produce cardiovascular collapse.[172] The CNS stimulation is a result of selective inhibition of inhibitory neurons in the cerebral cortex, which allows facilitatory neurons to discharge in unopposed fashion, producing CNS excitation.[173] After blood levels are high enough, inhibitory and facilitatory pathways are inhibited, thereby leading to CNS depression.

Initially, the potential for local anesthetic–induced toxicity (CNS and cardiovascular system) was thought to parallel anesthetic potency.[174,175] Information suggests that bupivacaine and

etidocaine may be proportionally more cardiotoxic than their anesthetic potency predicts.[176,177] This relative increase in cardiotoxicity appears to result from more potent electrophysiologic effects of the long-acting amides because of their fast-in–slow-out sodium channel blockade. Ropivacaine and (*S*)-(−)-levobupivacaine, other long-acting amide local anesthetics, have a CNS-to-cardiovascular toxicity ratio intermediate between that of lidocaine and bupivacaine.[178,179] The clinical importance of these observations about toxicity must be balanced against clinical studies showing limited cardiovascular depression in patients experiencing bupivacaine-induced seizures during regional anesthesia.[180]

If signs of CNS toxicity or frank convulsions occur, several steps must be followed if adverse outcomes are to be minimized (see Chapter 30). Early in local anesthetic–induced seizures, hypoxemia, hypercapnia, and acidosis develop rapidly, and symptomatic treatment of the toxicity must involve treatment of these factors. Oxygen should be given by bag and mask, and tracheal intubation is not mandated unless ventilation is ineffective.[181] The next step in therapy remains controversial, with administration of succinylcholine or an anticonvulsant. Succinylcholine is often recommended because the local anesthetic–induced seizures are usually short-lived and the muscle relaxation obtained facilitates ventilation and decreases the magnitude of the metabolic acidosis. Nevertheless, it does not decrease cerebral metabolism; CNS oxygen requirements remain increased. Others suggest that diazepam is effective in controlling local anesthetic–induced seizures, although 2 to 3 minutes is required to control seizures after administration.[182,183]

The most effective method of treating toxic reactions is prevention. Administration of excessive doses of local anesthetics should be prevented, and test doses of local anesthetics should be used before the injection of therapeutic doses. If a toxic reaction does occur, it is imperative that oxygen, a method of administering it, succinylcholine, and anticonvulsant drugs are immediately available.

Subarachnoid Injection

The adverse effects of unintentionally administering an epidural dose of local anesthetic into spinal fluid are highlighted by the neurologic changes that follow subarachnoid injection of 2-chloroprocaine. However, most subarachnoid injections of epidural local anesthetics are less dramatic; rather, the issue is how the physician should treat the cardiopulmonary effects resulting from such an injection. As in any neuraxial block that reaches high levels, arterial blood pressure and heart rate should be supported. The Trendelenburg position should be instituted to maximize venous return. Intravenous atropine and ephedrine are often effective and provide the time to administer a more potent catecholamine, if needed. Ventilation should be supported, and if the entire dose (20 to 25 mL) of local anesthetic has been administered into the CSF, tracheal intubation and mechanical ventilation are indicated because patients may require approximately 1 to 2 hours to maintain adequate spontaneous ventilation consistently. After a large dose of local anesthetic into the CSF, the pupils become dilated, which may seem to indicate CNS injury if this phenomenon is not recognized for what it is. The pupils return to the baseline state as the high block recedes. Fortunately, the necessity for sedation during the period of tracheal intubation and mechanical ventilation is minimal. These patients do not usually recall such events.[184]

When an epidural block is performed and a higher than expected block develops only after a delay of 15 to 30 minutes, subdural placement of local anesthetic must be considered. Treatment is symptomatic; the most difficult aspect is recognizing the possibility of a subdural injection.

Neurologic Injury

With the exception of the publicity surrounding 2-chloroprocaine–induced adhesive arachnoiditis, uncomplicated epidural anesthesia has not been linked to neurologic injury more frequently than with other anesthetics, regional or general.[117,120] No particular local anesthetic, needle versus catheter technique, addition or omission of epinephrine, or location of the epidural puncture seems to be associated with an increased incidence of neurologic injury. Despite this information, neurologic injury is often feared and epidural anesthesia is avoided in patients in whom antiplatelet drugs or other anticoagulants have been used preoperatively. Is this justified?

In patients taking the antiplatelet drug aspirin, there are no data showing an increased incidence of neurologic injury caused by epidural bleeding (hematoma) when epidural anesthesia is used.[185] It is doubtful that a perceived lack of data indicates that the problem has been overlooked because epidural anesthesia is frequently used in patients undergoing orthopedic procedures, in whom use of aspirin and nonsteroidal anti-inflammatory drugs is widespread. Nevertheless, there are isolated case reports of neurologic injury after epidural and spinal anesthesia in patients in whom antiplatelet drugs were used. It may be significant that in these case reports the initial neuraxial technique was abandoned after technical difficulties with needle placement.[186,187] The appropriate place of neuraxial techniques with the more potent antiplatelet drugs (e.g., abciximab, a glycoprotein IIb/IIIa receptor antagonist, and clopidogrel, a platelet aggregation inhibitor) remains undetermined, although significant caution is needed.

The use of epidural anesthesia for patients receiving anticoagulants is less clear because epidural anesthesia is often avoided in these patients. There are data from Odoom and Sih,[188] who used continuous epidural anesthesia without problem in 1000 vascular operations for patients receiving oral anticoagulants preoperatively. The acceptable magnitude of preoperative anticoagulation and the risk-benefit ratio of performing epidural anesthesia remain undetermined and should be focused on specific patients and their clinical setting. Despite lacking data, the use of epidural techniques in patients receiving subcutaneous heparin therapy is probably acceptable if the block can be performed atraumatically, although the risk-benefit ratio must be determined for each patient.[189] Some speculate that proof of minimal systemic effect from subcutaneous heparin (normal partial thromboplastin time) is necessary before neuraxial blockade.[188]

There is a consensus that when LMWH (e.g., enoxaparin) is used perioperatively, neuraxial block techniques need to be managed differently.[190] The risk of neuraxial bleeding is increased when LMWH and neuraxial techniques are combined if the following recommendations are not followed[9]:

1. Neuraxial block should be delayed for at least 10 to 12 hours after the last dose of LMWH in patients receiving the drug preoperatively.
2. Postoperative treatment with LMWH should be delayed at least 12 hours after completion of the surgical procedure.

3. Removal of the epidural and spinal catheters used for postoperative analgesia should take place 10 to 12 hours after the last dose, with subsequent dosing delayed for at least 2 hours.

It does seem that the issue of intraoperative anticoagulation after epidural catheter insertion is as settled as clinical data allow. Approximately 5000 patients have undergone epidural anesthesia for vascular surgery with intraoperative heparinization and without a neurologic injury attributable to epidural bleeding.[188,191,192] Despite minimal problems with epidural anesthesia and neurologic dysfunction related to anticoagulation, if a patient has neurologic symptoms consistent with a neuraxial mass after a regional block, immediate neurosurgical consultation is indicated because time is of the essence if permanent sequelae are to be prevented. If the patient appears to be at increased risk for neuraxial bleeding but the neuraxial technique remains indicated, it may be prudent to use a shorter-acting epidural local anesthetic, even if it means reinjecting more frequently, so that the block will resolve as rapidly as possible after the surgical procedure.

Clinical Pearls

"Success covers a multitude of blunders"* is an appropriate adage for the use of epidural anesthesia. To be successful, the anesthesiologist must perform the technique often enough to be technically facile. To increase use of the technique, several practical observations may be helpful.

If catheters can be avoided during epidural anesthesia (e.g., by selecting the appropriate local anesthetic), a potential source of difficulties with the technique can be avoided. It is important to allow the block enough "soak time" before the surgical procedure; this can be facilitated if the block is carried out in an induction room separate from the operating room. The anesthesiologist must recognize that there appears to be a plateau effect in dosing epidural local anesthetics. After some quantity of the local anesthetic has been injected, additional local anesthetic does not significantly increase block height but instead may make the block more dense (i.e., improve quality).[193] To be successful with the technique, the anesthesiologist should be prepared at all times to treat complications associated with epidural anesthesia; airway equipment, drugs, and especially oxygen and resuscitation must be immediately available.

Clinical Controversies and Neuraxial Blocks

Despite the many years that neuraxial blocks have been used, there remain controversies about the appropriate use of these blocks. Some continue to suggest that spinal anesthesia is inappropriate for outpatients because of the occurrence of post–spinal puncture headache, but there are data that the occasional headache can be successfully treated even in outpatients,[194] and considerable other data support use of the technique in outpatients (also see Chapter 78).[195] Similarly, spinal anesthesia seems to be well suited for use in patients undergoing cesarean section because of the short interval from injection to surgical anesthesia. If epidural blood patch therapy is used in timely fashion, the increased incidence of headache in this patient population should not necessarily limit use of the technique for cesarean section. An outgrowth of the management of post–spinal puncture headache was development of the "micro" or small-bore spinal catheter.[196] Appropriate reintroduction of this technique into anesthesia practice has not been established because there must be a point at which the risk-benefit ratio of a decreased incidence of spinal headache versus difficulties in technique with the microcatheter becomes unacceptable. These catheters (i.e., 27-gauge and smaller) are not available because the FDA withdrew the 510k approval in 1992 after concern over a possible association with the development of cauda equina syndrome.[7]

One reason that epidural anesthesia is not used as widely as may be indicated is that controversies surrounding its use create indecision. One of the most controversial adjuncts to epidural anesthesia has been the use of an epinephrine-containing test dose.[197] The original description used 15 μg of epinephrine in 3 mL of local anesthetic to indicate intravascular placement of an epidural catheter or needle. Most controversy surrounds the use of epinephrine in obstetric patients, in whom uterine blood flow may be decreased by the intravascular injection, thereby putting the fetus at risk. Some experimental data suggest that epinephrine may place the fetus at risk[198]; nevertheless, no clinical data suggest that any fetus has been harmed by use of a test dose, and many anesthesiologists believe that epinephrine-containing epidural test doses are useful in obstetric anesthesia.[199] Patients receiving β-adrenergic blockers also confound the use of a test dose. In these patients, heart rate may not change after the intravascular injection of 15 μg of epinephrine; rather, the heart rate may decrease as blood pressure increases.[200] The use of epidural anesthesia during general anesthesia may also confound interpretation of the epinephrine test dose.[201] Because there is no fail-safe method of guaranteeing an extravascular location of an epidural local anesthetic, prevention of systemic toxicity should also involve aspiration of the catheter and incremental dosing of the local anesthetic. It has been shown that onset of the block, quality of the block, and block height are unaffected by administration of the epidural drug in 5-mL fractions.[202]

Related to systemic toxicity with neuraxial blocks is information about benzodiazepines. Despite a widely held belief that benzodiazepines should be used with regional anesthesia to minimize systemic toxicity by elevating the seizure threshold, the data available indicate that this concept requires rethinking.[203] Resuscitation may be more difficult after cardiovascular collapse secondary to bupivacaine when diazepam is used as a premedication. It has also been demonstrated that animals premedicated with benzodiazepines may not show evidence of seizures before cardiovascular collapse.[204] The benzodiazepines may cover up one of the early signs of systemic toxicity, thereby potentially delaying definitive therapy.

The clinical arena has not been immune to controversy about epidural anesthesia. Yeager and colleagues[11] demonstrated a significant decrease in morbidity and mortality in high-risk patients undergoing epidural anesthesia and postoperative analgesia versus patients receiving high-dose narcotic anesthesia and parenteral narcotic analgesia. This information provided the impetus for many investigators to design studies to answer

*George Bernard Shaw (1856-1950).

whether the anesthetic technique, especially the postoperative analgesic technique, may be able to modify patient outcomes. In the case of Yeager and coworkers, it remains unclear whether their data support the benefits of the epidural techniques or condemn the use of high-dose narcotics and postoperative mechanical ventilation. Tuman and associates[12] addressed many of the criticisms directed at the work of Yeager and colleagues[11] and documented fewer complications in vascular surgery patients when epidural analgesia was used in an integrated perioperative regimen. Christopherson and coworkers[13] and Rosenfeld[14] and associates linked the analgesic regimens with possible mechanisms of improved patient outcomes. They found that continuing epidural anesthesia and analgesia into the postoperative period limited the adverse effects of surgery on the fibrinolytic system. Further investigations into the appropriate place of neuraxial blocks in anesthetic practice will have to be as concerned with the issue of cost in relation to outcome as with risk in relation to benefit to the patient.[16,17]

Another advance in neuraxial block technique that demands our attention is the development of effective methods of combining epidural and spinal anesthesia in a single-needle system.[204-207] These methods use epidural needle placement, followed by insertion of the spinal needle through a side lumen on the epidural needle or directly through the epidural needle lumen. The combined spinal-epidural technique allows flexibility in a number of clinical settings; some of the possible combinations and advantages are listed in Box 51-4. There is considerable evidence that combined spinal and epidural techniques can be used effectively in community practices and academic institutions.[208]

Box 51-4 Possible Clinical Advantages of Using Combined Spinal-Epidural Anesthesia

Initial epidural needle placement allows the spinal needle to be guided near the dura, thereby minimizing the number of times that the spinal needle tip touches bone and potentially becomes dulled.

Lower local anesthetic blood levels are possible when an initial spinal anesthetic is used for the operation and the epidural catheter is used for analgesia.

More rapid onset of spinal block allows the operative procedure to begin earlier, and the epidural catheter allows effective analgesia to be provided.

During labor, an opioid may be injected through a small spinal needle, and epidural analgesia can then be added if needed.

A lower initial mass of drug may be used during spinal anesthesia to minimize physiologic perturbations, whereas the epidural catheter is available to provide a higher level if needed.

The most common setting for combined spinal-epidural anesthesia is in obstetric anesthesia practice. When used for obstetric analgesia, typically a small amount of opioid is injected into the subarachnoid space via a spinal needle before insertion of the epidural catheter through the previously placed epidural needle. Infusion of a low-concentration combination of local anesthetic and opioid is then begun via the epidural catheter.

Simmons and colleagues completed a Cochrane database review focused on combined spinal and epidural anesthesia in labor. They found that overall there is little difference between combined spinal-epidural and other forms of low-dose epidural analgesia for relief of pain during labor.[209] This lack of difference is based on a similar effectiveness of labor analgesia with the techniques. There were limited differences in parturients' ability to ambulate or in obstetric and neonatal outcomes when comparing combined spinal-epidural and classic low-dose obstetric epidural analgesia. Despite these conclusions, many obstetric anesthesiologists continue to use a combined spinal-epidural technique for obstetric analgesia because of faster onset of analgesic action with the combined spinal-epidural technique and the ability to consistently and effectively use low-dose analgesic regimens with this method. Of interest, in the Cochrane database analysis, more mothers receiving the combined spinal-epidural technique itched than mothers administered the epidural-alone technique, probably because of the more rapid and profound analgesic action of the subarachnoid administered opioid. Overall, as a result of the significantly higher incidence of urinary retention and rescue interventions with the traditional standard-dose epidural-alone techniques, Simmons and colleagues suggested that the use of low-dose epidurals is preferred.[209] The most commonly used method for administering a low-dose epidural is as part of a combined spinal-epidural anesthesia technique.

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52 Nerve Blocks

Key Points

1. In performing peripheral nerve blocks, elicitation of a paresthesia is equivalent to electrical stimulation. The success rate and time of onset are further improved if multiple stimulations are performed.
2. Direct visualization of spread of local anesthetic by ultrasound produces similar success as a multistimulation technique.
3. Diaphragmatic paresis occurs in 100% of patients undergoing an interscalene block, even with dilute local anesthetic solutions.
4. A complete lumbar plexus block may be accomplished through a proximal (psoas compartment) approach, but rarely with the femoral 3-in-1 or fascia iliaca techniques.
5. Continuous peripheral blockade improves outcome and rehabilitation after major orthopedic surgery, including knee, hip, and shoulder replacement surgery.
6. The sciatic nerve divides into its tibial and peroneal components 7 to 10 cm above the knee; a popliteal fossa block should be performed at this level.
7. Regardless of the level of blockade, a tibial motor response elicited by neurostimulation techniques is more efficacious than a peroneal response during performance of a sciatic nerve block.
8. The total local anesthetic dosage should be determined and kept within acceptable limits. Accumulation with time may occur with continuous techniques.
9. The frequency of neurologic complications after peripheral blockade is less than that associated with neuraxial techniques. Neurotoxicity and direct needle trauma are the major causes of neurologic complications.

The techniques of peripheral neural blockade were developed early in the history of anesthesia (see Chapter 1). The American surgeons Halsted and Hall[1,2] described the injection of cocaine into peripheral sites, including the ulnar, musculocutaneous, supratrochlear, and infraorbital nerves, for minor surgical procedures in the 1880s. James Leonard Corning[3] recommended the use of an Esmarch bandage in 1885 to arrest the local circulation, prolong the cocaine-induced block, and decrease uptake of that local anesthetic from tissues. This concept was furthered by Heinrich F. W. Braun,[4] who substituted epinephrine, a "chemical tourniquet," in 1903. Braun[5] also introduced the term *conduction anesthesia* in his 1914 textbook on local anesthesia, which described techniques for every region of the body. In 1920, the French surgeon Gaston Labat was invited by Charles Mayo to teach innovative methods of regional anesthesia at the Mayo Clinic. During his appointment there, Labat authored *Regional Anesthesia: Its Technic and Application*.[6] The book was considered to be the definitive text on regional anesthesia for at least 30 years after its publication. Labat's textbook focused on the intraoperative management of patients undergoing intra-abdominal, head and neck, and extremity procedures under infiltration, peripheral, plexus, and splanchnic blockade; neuraxial techniques were not widely applied at the time.

Peripheral blockade remains a well-accepted component of comprehensive anesthetic care. Its role has expanded from the operating suite into the arena of postoperative and chronic pain management (see Chapters 58 and 87). With appropriate selection and sedation, these techniques can be used in all age groups. Skillful application of peripheral neural blockade broadens the anesthesiologist's range of options in providing optimal anesthetic care.

Techniques for Localizing Neural Structures

Several methods of needle localization have been described, including fascial "pops," elicitation of one or more paresthesias, perivascular or transarterial injection, electrical stimulation, and field infiltration. More recently, direct imaging by ultrasonography,

fluoroscopy, computed tomography (CT), and magnetic resonance imaging (MRI) has been used. Although no definitive study has identified the best method for needle placement, generalities are possible. For example, elicitation of a paresthesia appears to be equivalent to electrical stimulation. Success rates and onset times of paresthesia and nerve stimulation techniques are further improved if multiple injections are performed. Transarterial injection is variably successful; a two-injection transarterial technique is comparable to single-injection paresthesia or nerve stimulator approaches. The success rate with a fascial pop or click is variable, and it may be more reliable in pediatric patients than in adults.[7]

In recent years, the number of prospective randomized studies comparing ultrasound-guided and electrical stimulation techniques has steadily increased. In general, onset times and the number of needle passes required to obtain a motor response are reduced with the use of ultrasound guidance.[8-10] Ultrasound guidance increases the success rate provided that (1) the needle is redirected (as necessary) to achieve uniform spread around the neural structure and (2) blocks in the control group are performed with a single injection. At this time, peripheral techniques are performed under ultrasound guidance with *or* without confirmation of needle placement by electrical stimulation. Both approaches involve visualization of local anesthetic spread during injection.[11]

Ultrasound images of the distribution of local anesthetic have provided clinicians with visualization of successful blocks[8-10] and have documented *why* single-injection techniques are less reliable. Although it has been theorized that visualization of needle advancement would decrease the frequency (or severity) of needle misadventures, the small number of patients reported precludes determination of either the absolute or relative frequency of neurologic complications. Both intraneural needle placement and injection have been reported during ultrasound guidance.[12] However, the risk of large-volume intravascular injection of local anesthetic may be reduced in experienced ultrasonographers' hands.

Upper Extremity Blocks

Successful regional anesthesia of the upper extremity requires knowledge of brachial plexus anatomy from its origin, where the nerves emerge from the intervertebral foramina, to its termination in the peripheral nerves. Detailed anatomic knowledge enables the anesthesiologist to choose the appropriate technique for the intended surgical procedure and to salvage inadequate blocks by supplementation with local anesthetic. Without mastery of the anatomy, luck rather than skill becomes the primary determinant of successful neural blockade. Also important is an understanding of the side effects and complications of upper extremity regional techniques, as well as the clinical application of available local anesthetics for these blocks. The role of appropriate sedation during placement of the block and during the surgical procedure should not be underestimated. Many a "perfect" regional anesthetic technique has been undone by inadequate management of sedation.

Anatomy

The brachial plexus is derived from the anterior primary rami of the fifth, sixth, seventh, and eighth cervical nerves and the first thoracic nerve, with variable contributions from the fourth cervical and second thoracic nerves. After leaving their intervertebral foramina, these nerves course anterolaterally and inferiorly to lie between the anterior and middle scalene muscles, which arise from the anterior and posterior tubercles of the cervical vertebra, respectively. The anterior scalene muscle passes caudad and laterally and inserts into the scalene tubercle of the first rib; the middle scalene muscle inserts on the first rib posterior to the subclavian artery, which passes between these two scalene muscles along the subclavian groove. The prevertebral fascia invests the anterior and middle scalene muscles and fuses laterally to enclose the brachial plexus in a fascial sheath.

Between the scalene muscles, these nerve roots unite to form three trunks that emerge from the interscalene space to lie cephaloposterior to the subclavian artery as it courses along the upper surface of the first rib. The superior (C5 and C6), middle (C7), and inferior (C8 and T1) trunks are arranged accordingly and are not in a strict horizontal formation, as is often depicted. At the lateral edge of the first rib, each trunk forms anterior and posterior divisions that pass posterior to the midportion of the clavicle to enter the axilla. Within the axilla, these divisions form the lateral, posterior, and medial cords, named for their relationship with the second part of the axillary artery. The superior divisions from the superior and middle trunks form the lateral cord, the inferior divisions from all three trunks form the posterior cord, and the anterior division of the inferior trunk continues as the medial cord.

At the lateral border of the pectoralis minor, the three cords divide into the peripheral nerves of the upper extremity. The lateral cord gives rise to the lateral head of the median nerve and the musculocutaneous nerve; the medial cord gives rise to the medial head of the median nerve, as well as the ulnar, the medial antebrachial, and the medial brachial cutaneous nerves; and the posterior cord divides into the axillary and radial nerves (Fig. 52-1).

Aside from branches from the cords that form the peripheral nerves as described, several branches arising from roots of the brachial plexus provide motor innervation to the rhomboid muscles (C5), the subclavian muscles (C5 and C6), and the serratus anterior muscle (C5, C6, and C7). The suprascapular nerve arises from C5 and C6; it supplies the muscles of the dorsal aspect of the scapula and makes a significant contribution to the sensory supply of the shoulder joint.

Branches arising from the cervical roots are usually blocked only with the interscalene approach to the brachial plexus. The sensory distributions of the cervical roots and peripheral nerves are shown in Figure 52-2.

Interscalene Block

Clinical Applications

The principal indication for an interscalene block is surgery on or manipulation of the shoulder. Blockade occurs at the level of the upper and middle trunks. Although this approach can also be used for forearm and hand surgery, blockade of the inferior trunk (C8 through T1) is often incomplete and requires supplementation at the ulnar nerve for adequate surgical anesthesia in that distribution.[13]

Technique

The brachial plexus shares a close physical relationship with several structures that serve as important landmarks for perform-

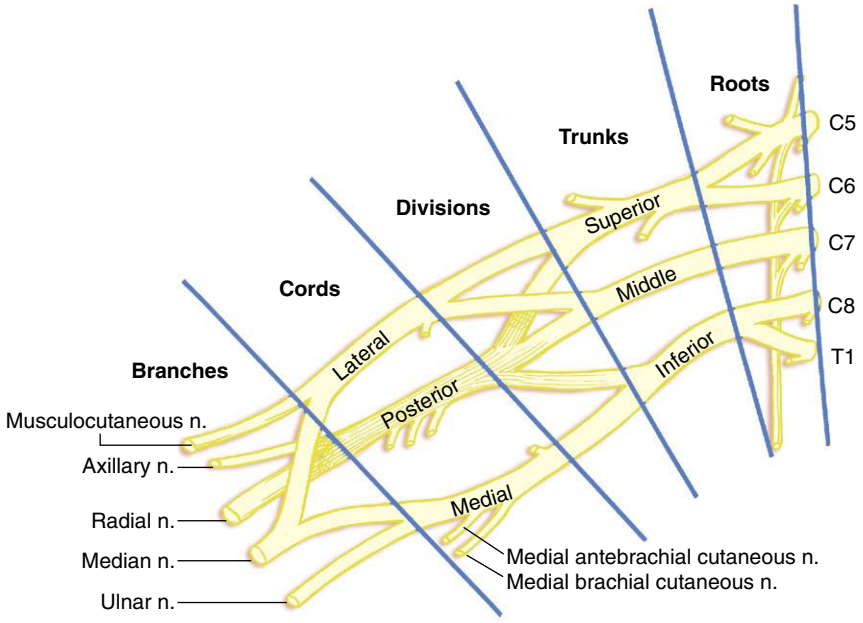

Figure 52-1 Roots, trunks, divisions, cords, and branches of the brachial plexus.

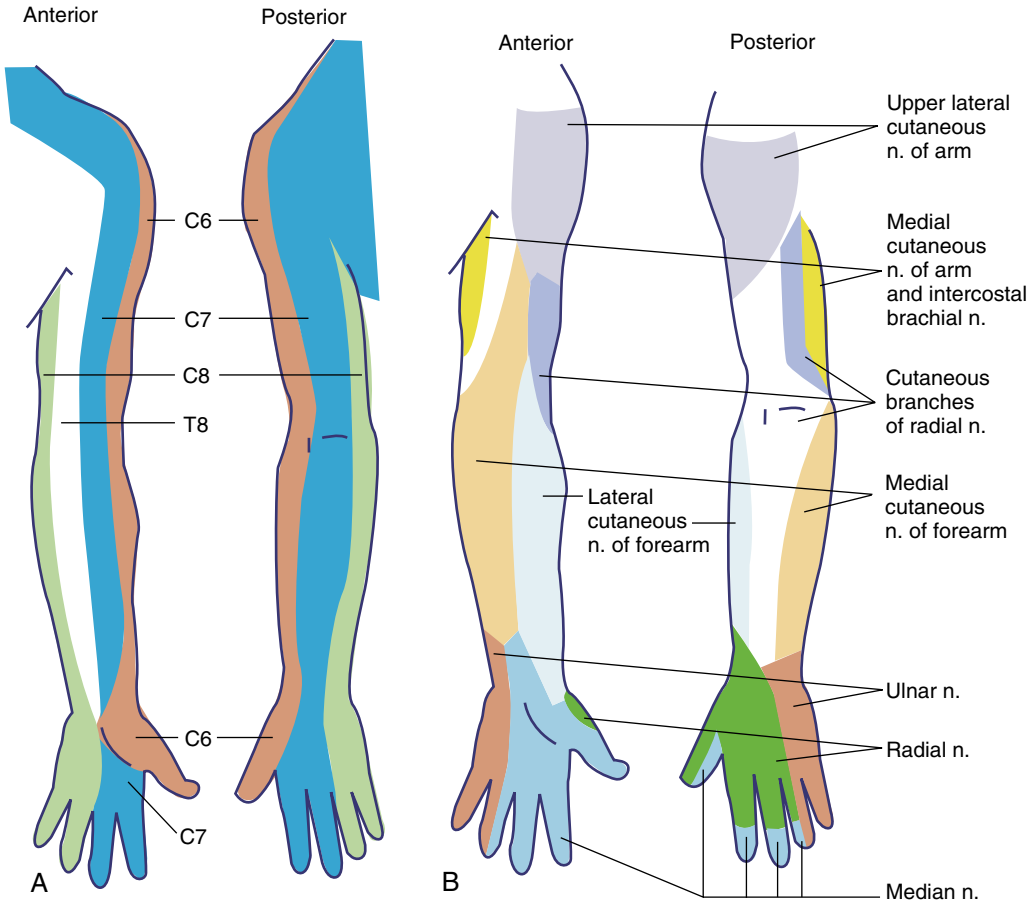

Figure 52-2 **A,** Cutaneous distribution of the cervical roots. **B,** Cutaneous distribution of the peripheral nerves.

ance of an interscalene block. In its course between the anterior and middle scalene muscles, the plexus is superior and posterior to the second and third parts of the subclavian artery. The dome of the pleura lies anteromedial to the inferior trunk.

This technique can be performed with the patient's arm in any position and is technically simple because of easy identification of the necessary landmarks.[14] The patient should be in the supine position with the head turned away from the side to be blocked. The posterior border of the sternocleidomastoid muscle is readily palpated by having the patient briefly lift the head. The interscalene groove may be palpated by rolling the fingers posterolaterally from this border over the belly of the anterior scalene muscle into the groove. A line extended laterally from the cricoid cartilage and intersecting the interscalene groove indicates the level of the transverse process of C6. Although the external jugular vein often overlies this point of intersection, it is not a constant or reliable landmark.

The use of a nerve stimulator or elicitation of paresthesias is recommended with this technique to accurately place the local anesthetic solution. After ordinary sterile precautions and development of a skin wheal, a 22- to 25-gauge, 4-cm needle is inserted perpendicular to the skin at a 45-degree caudad and slightly posterior angle (Fig. 52-3). The needle is then advanced until a paresthesia (usually the C5 and C6 dermatomes) or nerve stimulator response is elicited, which usually occurs at a very superficial level. Paresthesia and motor response of the arm or shoulder are equally efficacious.[15] If a blunt needle bevel is used, a "click" may be detected as the needle passes through the prevertebral fascia. If bone is encountered within 2 cm of the skin, it is likely to be a transverse process, and the needle may be "walked" across this structure to locate the nerve. Likewise, contraction of the diaphragm indicates phrenic nerve stimulation and anterior needle placement; the needle should be redirected posteriorly to locate the brachial plexus.

After the appropriate paresthesia or motor response is obtained, the needle is stabilized. The use of flexible extension tubing facilitates maintenance of the needle's position while aspiration and injection are taking place. After negative aspiration, 10 to 40 mL of solution is injected incrementally, depending on the desired extent of blockade. Radiographic studies suggest a volume-to-anesthesia relationship, with 40 mL of solution associated with complete cervical and brachial plexus blockade.[14] Clinical studies, however, indicate variable blockade of the lower trunk (i.e., ulnar nerve), even with large volumes of solution.[13] Digital pressure above the injection site and downward massage along with a 45-degree head-up position may facilitate caudad spread and blockade of the lower trunk.

Side Effects and Complications

Ipsilateral phrenic nerve block resulting in diaphragmatic paresis occurs in 100% of patients undergoing interscalene blockade,[16] even with dilute solutions of local anesthetics, and is associated with a 25% reduction in pulmonary function.[17,18] This effect probably results from anterior spread of solution over the anterior scalene muscle and may cause subjective symptoms of dyspnea. Although rare, respiratory compromise can occur in patients with severe respiratory disease. Involvement of the vagus, recurrent laryngeal, and cervical sympathetic nerves is rarely significant, but a patient experiencing symptoms related to these side effects may require reassurance. The incidence of pneumothorax is low when the needle is correctly placed at the C5 or C6 level because of the distance from the dome of the pleura.

Severe hypotension and bradycardia (i.e., the Bezold-Jarisch reflex) have been reported in awake, sitting patients undergoing shoulder surgery under an interscalene block. The cause is presumed to be stimulation of intracardiac mechanoreceptors by decreased venous return, which produces an abrupt withdrawal of sympathetic tone and enhanced parasympathetic output. This effect results in bradycardia, hypotension, and syncope. The frequency of this reflex is decreased when prophylactic β-blockers are administered.[19]

Nerve damage or neuritis can occur with any peripheral nerve block, but it is uncommon and is usually self-limited. Some surgical approaches to the shoulder, such as those for total-

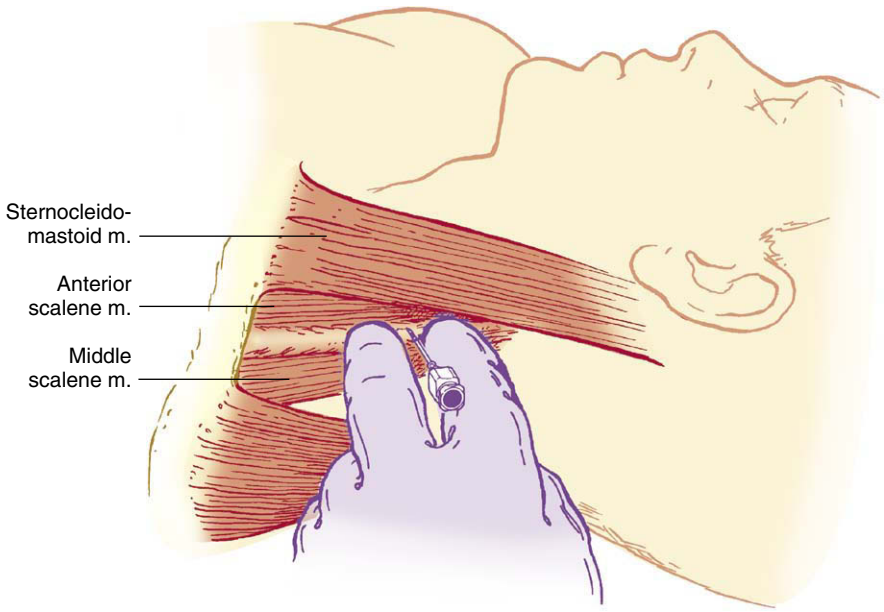

Figure 52-3 Interscalene block. The fingers palpate the interscalene groove, and the needle is inserted at a caudad and slightly posterior angle.

shoulder arthroplasty, are associated with neurologic risk to the brachial plexus.[20,21] In such cases an interscalene block may be placed postoperatively for pain relief after the surgical service has ascertained and documented that no neurologic damage has occurred. Epidural and intrathecal injections have been reported with this block, a finding emphasizing the importance of inserting the needle in a caudad direction.[22] The proximity of significant neurovascular structures may increase the risk for serious neurologic complications when an interscalene block is performed in heavily sedated or anesthetized patients.[23]

Several vascular structures are in proximity to a correctly placed needle. Local anesthetic toxicity as a result of intravascular injection should be guarded against by careful aspiration and incremental injection. Seizure activity from this complication is particularly undesirable after rotator cuff surgery because the repair can be compromised by the associated muscular activity.

Supraclavicular Block

Clinical Applications

Indications for a supraclavicular block are operations on the elbow, forearm, and hand. Blockade occurs at the distal trunk–proximal division level. At this point, the brachial plexus is compact and a small volume of solution produces rapid onset of reliable blockade of the brachial plexus. An additional advantage is that the block can also be performed with the patient's arm in any position.

Reliable supraclavicular blockade requires elicitation of a paresthesia or motor response. The classic block may be somewhat difficult to describe and to teach. A proposed modification of the technique, the so-called plumb-bob approach, may decrease complications and simplify the concept of this block.[24]

Technique

Several anatomic points are important in performance of the supraclavicular approach. The three trunks are clustered vertically over the first rib cephaloposterior to the subclavian artery, which can often be palpated in a slender, relaxed patient. The neurovascular bundle lies inferior to the clavicle at about its midpoint. The first rib acts as a medial barrier to the needle reaching the pleural dome and is short, broad, and flat, with an anteroposterior orientation at the site of the plexus.

The patient is placed in a supine position with the head turned away from the side to be blocked. The arm to be anesthetized should be adducted, and the hand should be extended along the side toward the ipsilateral knee as far as possible. In the classic technique, the midpoint of the clavicle should be identified and marked. The posterior border of the sternocleidomastoid can be palpated easily when the patient raises the head slightly. The palpating fingers can then roll over the belly of the anterior scalene muscle into the interscalene groove, where a mark should be made approximately 1.5 to 2.0 cm posterior to the midpoint of the clavicle. Palpation of the subclavian artery at this site confirms the landmark.

After appropriate preparation and development of a skin wheal, the anesthesiologist stands at the side of the patient facing the patient's head. A 22-gauge, 4-cm needle is directed in a caudad, slightly medial, and posterior direction until a paresthesia or motor response is elicited or the first rib is encountered. If a syringe is attached, this orientation causes the needle shaft and syringe to lie almost parallel to a line joining the skin entry site and the patient's ear. If the first rib is encountered without elicitation of a paresthesia, the needle can be systematically walked anteriorly and posteriorly along the rib until the plexus or the subclavian artery is located (Fig. 52-4). Location of the artery provides a useful landmark; the needle can be withdrawn and

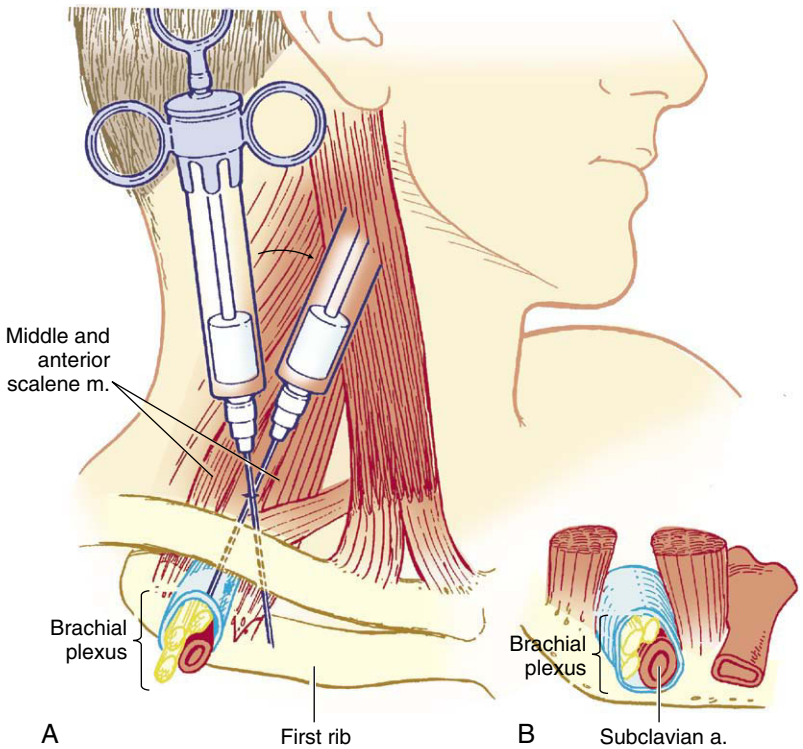

Figure 52-4 **A,** Supraclavicular block. The needle is systematically walked anteriorly and posteriorly along the rib until the plexus is located. **B,** The three trunks are compactly arranged at the level of the first rib.

reinserted in a more posterolateral direction, which generally results in a paresthesia or motor response. On localization of the brachial plexus, aspiration for blood should be performed before incremental injections of a total volume of 20 to 30 mL of solution.

The rib is usually contacted at a needle depth of 3 to 4 cm; however, in an obese patient or in the presence of tissue distortion from hematoma or injection of solution, the depth may exceed the length of the needle. Nonetheless, before the needle is advanced farther, gentle probing in the anterior and posterior directions should be done at the 2- to 3-cm depth if paresthesias are not obtained. Multiple injections may improve the quality or may shorten the onset of blockade.

The modified plumb-bob approach uses similar patient positioning, although the needle entry site is at the point where the lateral border of the sternocleidomastoid muscle inserts into the clavicle. After preparation and raising of a skin wheal, a 22-gauge, 4-cm needle is inserted while mimicking a plumb-bob suspended over the needle entry site (Fig. 52-5). Frequently, a paresthesia or motor response is elicited before contacting the first rib or artery. If no paresthesia or motor response is elicited, the needle is reinserted while angling the tip of the needle cephalad and then caudad in small steps until the first rib is contacted.

Side Effects and Complications

Although the block is more difficult in obese patients (also see Chapter 64), there does not appear to be an increased frequency of complications.[25] The prevalence of pneumothorax after a supraclavicular block is 0.5% to 6% and diminishes with experience. The onset of symptoms is usually delayed and may take up to 24 hours. Routine chest radiography after the block is not justified. The supraclavicular approach is best avoided when the patient is uncooperative or cannot tolerate any degree of respiratory compromise because of underlying disease. Other complications include frequent phrenic nerve block (40% to 60%), Horner's syndrome, and neuropathy. The presence of phrenic or cervical sympathetic nerve blockade normally requires only reassurance. Although nerve damage can occur, it is uncommon and usually self-limited.

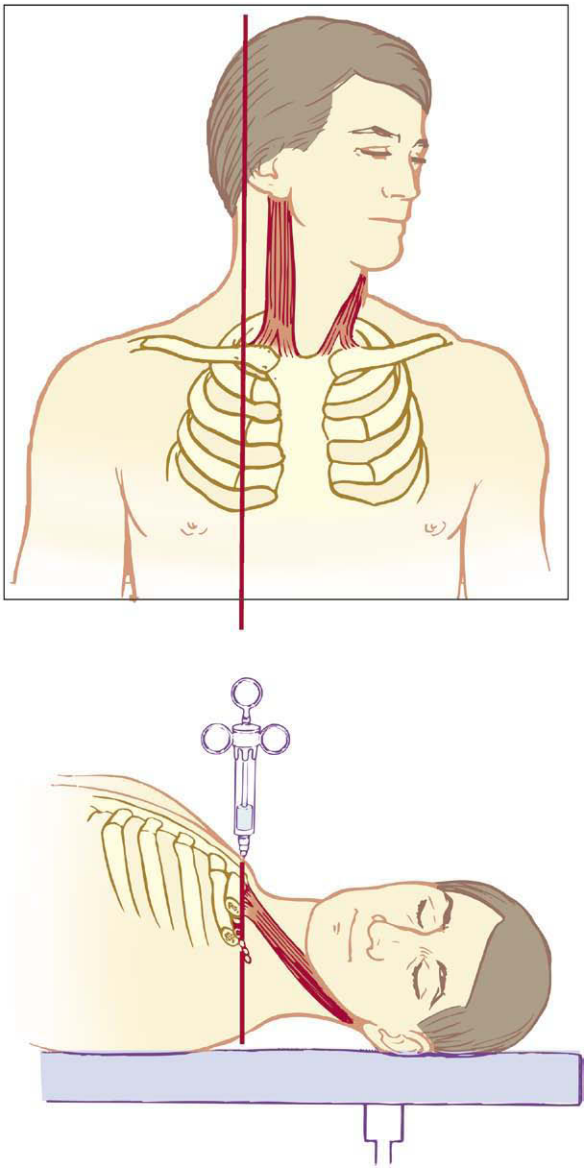

Figure 52-5 Supraclavicular block. The needle is inserted while mimicking a plumb-bob suspended over the needle entry site.

Infraclavicular Block

Clinical Applications

An infraclavicular block provides anesthesia to the arm and hand. Blockade occurs at the level of the cords and offers the theoretical advantages of avoiding pneumothorax while affording block of the musculocutaneous and axillary nerves. No special arm positioning is required. A nerve stimulator or ultrasound visualization is required because there are no palpable vascular landmarks to aid in directing the needle.

Technique

The needle is inserted 2 cm below the midpoint of the inferior clavicular border and advanced laterally, and a nerve stimulator is used to identify the plexus.[26] Marking a line between the C6 tubercle and the axillary artery with the arm abducted is helpful in visualizing the course of the plexus. Incremental injection of 20 to 30 mL of solution is sufficient after the needle is correctly placed. The success rate is improved with a distal motor response.[27] A coracoid technique consisting of insertion of the needle 2 cm medial and 2 cm caudal to the coracoid process has also been described.[28] However, the more lateral insertion site may result in the absence of blockade of the musculocutaneous nerve, thus removing the major advantage of this approach over the simpler axillary block.

Side Effects and Complications

Because of the necessarily blind approach to the plexus, the incidence of intravascular injection may be increased. Exaggerated medial needle direction may result in pneumothorax. Other rare complications such as infection and hematoma are theoretically possible.

Axillary Block

Clinical Applications

The axillary approach to the brachial plexus is the most popular because of its ease, reliability, and safety.[29] Blockade occurs at the level of the terminal nerves. Although blockade of the musculocutaneous nerve is not always produced with this approach, it can be supplemented at the level of the axilla or at the elbow. Indications for axillary block include surgery on the forearm and hand. Elbow procedures are also successfully performed with the axillary approach.[30] This block is ideally suited for outpatients and is easily adapted to the pediatric population.[31] However, an axillary block is unsuitable for surgical procedures on the upper part of the arm or the shoulder, and the patient must be able to abduct the arm to perform the block.

Technique

Anatomic concepts that should be considered before an axillary block include the following:

1. The neurovascular bundle is multicompartmental (Fig. 52-6).[32]
2. The axillary artery is the most important landmark; the nerves maintain a predictable orientation to the artery.
3. The median nerve is found superior to the artery, the ulnar nerve is inferior, and the radial nerve is posterior and somewhat lateral (Fig. 52-7).
4. At this level, the musculocutaneous nerve has already left the sheath and lies in the substance of the coracobrachialis muscle.
5. The intercostobrachial nerve, a branch of the T2 intercostal nerve, is usually blocked by the skin wheal overlying the artery; however, adequate anesthesia for the tourniquet can be ensured by extending the wheal 1 to 2 cm caudad and cephalad.



Figure 52-6 Computed tomogram after an axillary block with 0.5% bupivacaine combined with iodothalamate. Separate 10-mL injections of solution were performed after obtaining median and radial nerve paresthesias transarterially. The contrast medium appears to remain in three separate compartments.

The patient should be in the supine position with the arm to be blocked placed at a right angle to the body and the elbow flexed to 90 degrees. The dorsum of the hand rests on the bed or pillow; hyperabduction of the arm with placement of the hand beneath the patient's head is not recommended because this position frequently obliterates the pulse.

The axillary artery is palpated, and a line is drawn tracing its course from the lower axilla as far proximally as possible. The artery is then fixed against the patient's humerus by the index and middle fingers of the left hand, and a skin wheal is raised directly over the artery at a point in the axilla approximating the skin crease. Proximal needle placement and maintenance of distal pressure facilitate proximal spread of the solution.

Method of Needle Localization

Several methods of identifying the axillary sheath have been described, all with reportedly good results. Overall, paresthesias are unnecessary. However, multiple injections may shorten the onset and improve the reliability of blockade.

1. Paresthesias can be sought with a 25-gauge, 2-cm needle, beginning deeply (i.e., radial nerve) or with the nerves supplying the surgical site. Needles longer than 2 cm are rarely needed to reach the neurovascular bundle; smaller needles and a short needle bevel may be associated with a lower incidence of nerve damage.[33] Each paresthesia is injected with 10 mL of local anesthetic.
2. A nerve stimulator can also be used with an insulated needle to locate the nerves. This technique obviates the need for paresthesias.
3. A short-beveled needle can be advanced until the axillary sheath is entered, as evidenced by a fascial click, after which 40 to 50 mL of solution is injected after negative aspiration.
4. A transarterial technique can be used whereby the needle pierces the artery and 40 to 50 mL of solution is injected posterior to the artery; alternatively, half of the solution can be injected posterior and half injected anterior to the artery. Great care must be taken to avoid intravascular injection with this technique, particularly because the pressure of injection within the compartments of the axillary sheath may move anatomic structures in relation to the immobile needle. Some practitioners avoid intentional arterial puncture in the belief that it is unnecessarily traumatic.
5. Field block of the brachial plexus with a fanlike injection of 10 to 15 mL of local anesthetic solution on each side of the artery is a variation of the sheath technique. Paresthesias, though not sought, are often encountered with this technique and provide evidence of correct placement.
6. Ultrasound guidance with visualization of local anesthetic spread around the four nerves (with and without motor stimulation) decreases block onset time and may reduce the number of needle redirections. However, rates of

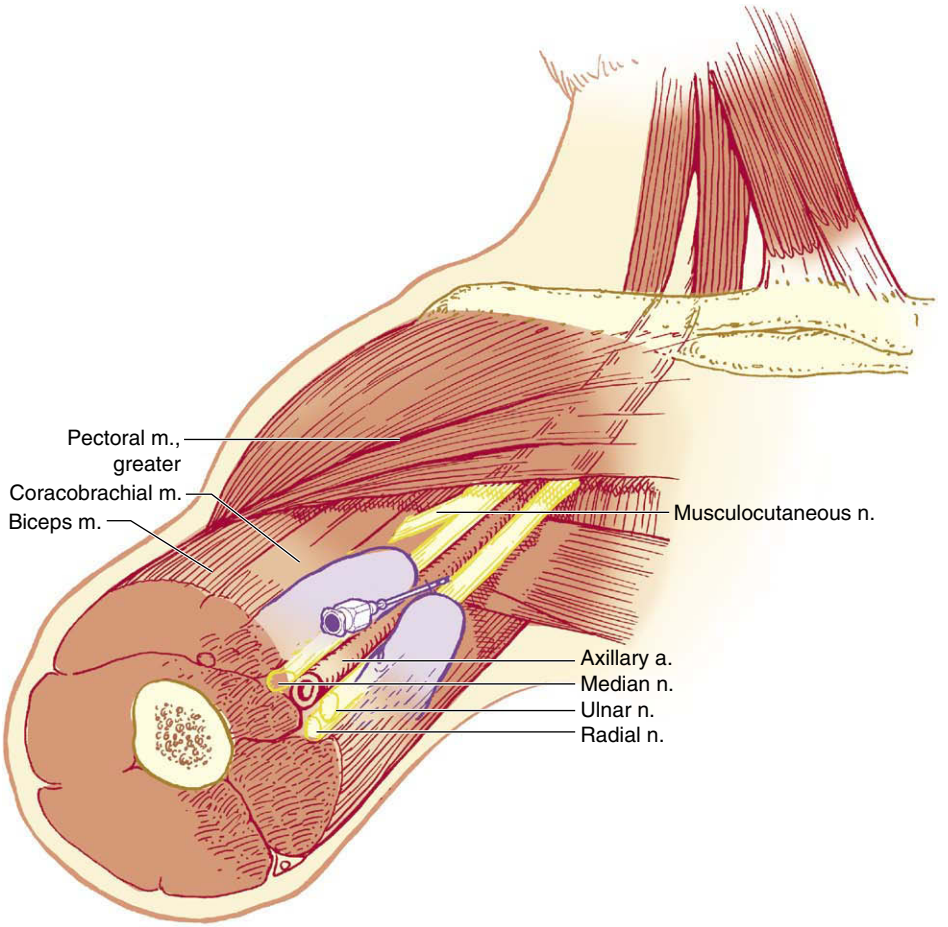

Figure 52-7 Axillary block. The arm is abducted at right angles to the body. Distal digital pressure is maintained during needle placement and injection of the local anesthetic.

success and complications are similar to those with other approaches.[34]

Classically, it was recommended that on completion of the injection, the arm should be adducted and returned to the patient's side to prevent the humeral head from obstructing proximal flow of the solution. However, a more recent study reported that maintaining the arm in abduction decreases onset time and prolongs both sensory and motor blockade.[35] If the musculocutaneous nerve is not blocked by the axillary approach, it can be blocked by injection within the body of the coracobrachialis muscle or at the elbow superficially at the lateral aspect of the antecubital fossa just above the interepicondylar line.

Success Rate with Axillary Block Techniques

The success rate of axillary blockade depends on the definition of a successful block (i.e., surgical anesthesia versus blockade of all four terminal nerves of the upper extremity), the technique used to localize the brachial plexus, and the number of injections. Success rates with single-injection techniques can vary.[36,37] Thompson and Rorie[32] concluded that the presence of multiple compartments limits diffusion of the solution (and the success of single-shot techniques). Although Partridge and coworkers[38] confirmed the presence of these compartments, they concluded that the "septa" dividing them were incomplete on the basis of injection of methylene blue and latex solutions into cadavers. The controversy surrounding single- versus multiple-injection techniques remains unresolved.

Eliciting a paresthesia is as efficacious as peripheral nerve stimulation (with a motor response of 0.5 to 0.8 mA). Most studies suggest that two-injection transarterial techniques are equivalent to single-paresthesia or single–nerve stimulation approaches. In general, the efficacy of paresthesia and peripheral nerve stimulator techniques increases when multiple injections are used. Conversely, success rates with the perivascular or fascial click approaches are variously reliable.[7] Familiarity with a variety of techniques for axillary block of the brachial plexus allows the anesthesiologist maximal flexibility in tailoring the anesthetic approach to the clinical situation.

Side Effects and Complications

Nerve injury and systemic toxicity are the most significant complications associated with the axillary approach. The assertion that neuropathies are more common with the paresthesia technique may be valid, but it is not supported by the data available. Even when paresthesias are not sought, they often occur unintentionally.[39] Injection of large volumes of local anesthetic, particularly via the transarterial approach, increases the risk for intravascular injection and systemic toxicity of local anesthetics. Hematoma and infection are rare complications. Central neural blockade and pneumothorax are not complications, as in other approaches to the brachial plexus.

Peripheral Blocks at the Midhumeral Level, Elbow, and Wrist

Clinical Applications

As techniques for brachial plexus blockade have gained popularity, indications for peripheral nerve blockade at the wrist and elbow have diminished. However, these techniques can be useful when limited anesthesia is required, when contraindications to a brachial plexus block (e.g., infection, bilateral surgery, coagulation abnormalities, bleeding diathesis, difficult anatomy) exist, or when brachial plexus blockade is incomplete. Only the midhumeral approach provides anesthesia for the use of a tourniquet. Most patients tolerate an inflated tourniquet for only a brief period.

Midhumeral Block

A midhumeral approach to the brachial plexus has been described. This novel approach involves blocking each of the four nerves of the brachial plexus separately in the humeral canal at the level of the proximal third and distal two thirds of the humerus. At this level, the median and ulnar nerves are located on the lateral and medial aspects of the brachial artery, respectively. The musculocutaneous nerve is identified within the body of the biceps muscle, and the radial nerve lies adjacent to the humerus. A volume of 8 to 10 mL of local anesthetic is injected after localization of each nerve with a nerve stimulator. Midhumeral block has been reported to have a higher success rate than traditional (defined as stimulation of two nerves) axillary brachial plexus block.[40] In this study, time to complete the block was not different between the two techniques; however, the onset of complete sensory block was shorter in the axillary approach, whereas the success rate of blockade of all four major nerves was higher in the midhumeral group. This technique may have applications when anatomic difficulties preclude a traditional approach or when the surgical procedure requires a dense block of all four major nerves. The safety and clinical practicality of the midhumeral approach remain to be proved.

Median Nerve Block

Blockade of the median nerve provides anesthesia of the palmar aspects of the thumb and index finger, the middle finger and radial half of the ring finger, and the nail beds of the same digits. Motor block includes the muscles of the thenar eminence, the lumbrical muscles of the first and second digits, and in the case of a block at the elbow, the median-innervated wrist flexor muscles of the forearm.

Technique at the Elbow

With the patient's arm placed in the anatomic position (i.e., palm up), a line is drawn connecting the medial and lateral epicondyles of the humerus. The major landmark for this technique is the brachial artery, which is found medial to the biceps tendon at the intercondylar line. The median nerve lies medial to the artery (Fig. 52-8) and can be blocked with 3 to 5 mL of solution after eliciting a paresthesia. If no paresthesia is obtained, the solution can be injected in a fanlike pattern medial to the palpated artery.

Technique at the Wrist

The median nerve is located between the flexor carpi radialis and palmaris longus tendons and can be blocked at a point 2 to 3 cm proximal to the wrist crease (Fig. 52-9). (The palmaris longus tendon is congenitally or postsurgically absent from some patients.) Loss of resistance is felt as the needle passes through the flexor retinaculum, at which point 2 to 4 mL of solution should be injected. A superficial palmar branch supplying the skin of the thenar eminence can be blocked by injecting 0.5 to 1 mL of solution subcutaneously above the retinaculum. Paresthesias should not be sought because of confinement of this nerve within the carpal tunnel.

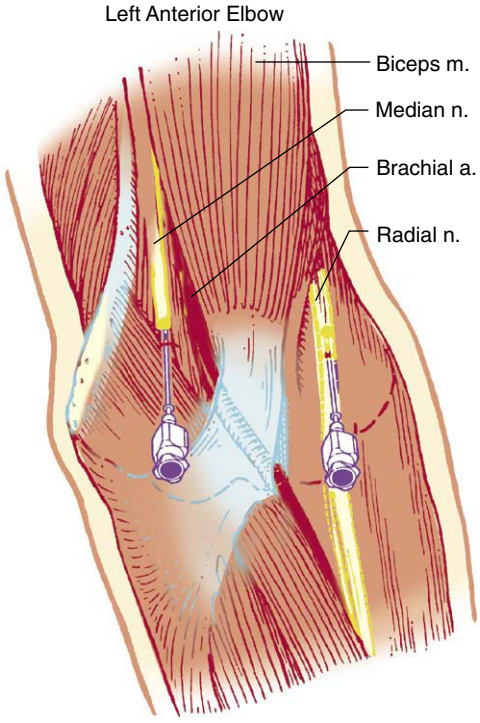

Figure 52-8 Anatomic landmarks for median and radial nerve blocks at the elbow.

Radial Nerve Block

Blockade of the radial nerve provides anesthesia to the lateral aspect of the dorsum of the hand (i.e., thumb side) and the proximal portion of the thumb, index, middle, and lateral half of the ring finger.

Technique at the Elbow

The radial nerve can be blocked at the elbow as it passes over the anterior aspect of the lateral epicondyle. The intercondylar line and lateral edge of the biceps tendon are marked. A 22-gauge, 3- to 4-cm needle is inserted at a point 2 cm lateral to the biceps tendon and advanced until bone is encountered (see Fig. 52-8). Three to 5 mL of solution is injected in a fanlike fashion.

Technique at the Wrist

The radial nerve block at the wrist is a field block of the multiple peripheral branches descending along the dorsum and radial side of the wrist. The extensor pollicis longus tendon can be identified when the patient extends the thumb. The needle insertion site is over this tendon at the base of the first metacarpal, and the solution is injected superficial to the tendon. A volume of 2 mL of local anesthetic is injected proximally along the tendon, and an

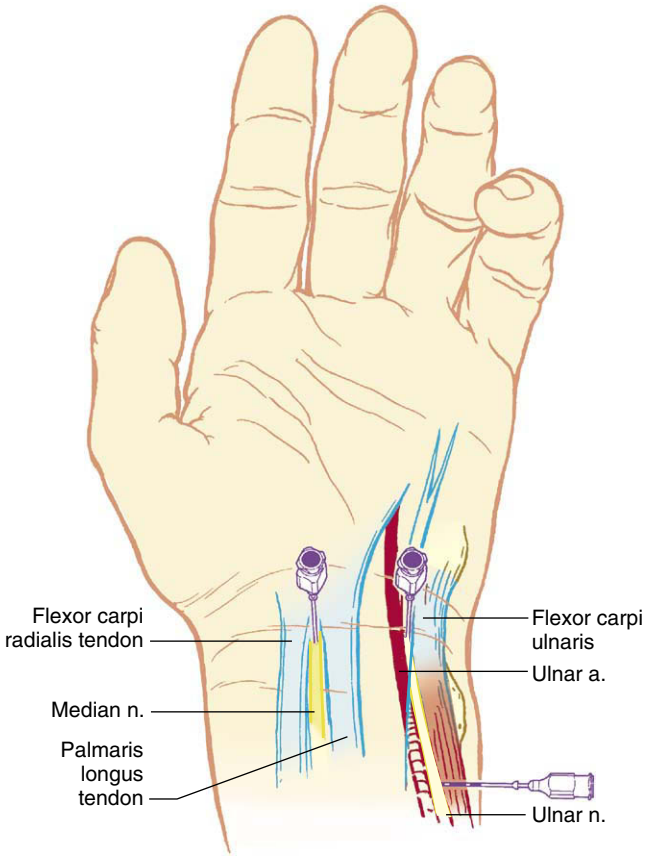

Figure 52-9 Anatomic landmarks for median and ulnar nerve blocks at the wrist. An alternative method for an ulnar nerve block, from the ulnar side of the wrist, is shown.

additional 1 mL is injected as the needle passes at a right angle across the anatomic snuffbox (Fig. 52-10).

Ulnar Nerve Block

Blockade of the ulnar nerve provides anesthesia to the ulnar side of the hand, the little finger, the ring finger, and all the small muscles of the hand, except those of the thenar eminence and the first and second lumbrical muscles.

Technique at the Elbow

Although the ulnar nerve is easily accessible at its subcutaneous position posterior to the medial epicondyle, blockade at this site is associated with a high incidence of neuritis. Because the nerve is surrounded by fibrous tissue at this point, intraneural injection is required for successful blockade. Use of a very fine needle along with a small volume of solution (1 mL) diminishes the risk; however, the nerve can be satisfactorily blocked with 5 to 10 mL of solution at a site 3 to 5 cm proximal to the elbow. The local anesthetic should be injected in a fanlike fashion without elicitation of a paresthesia.

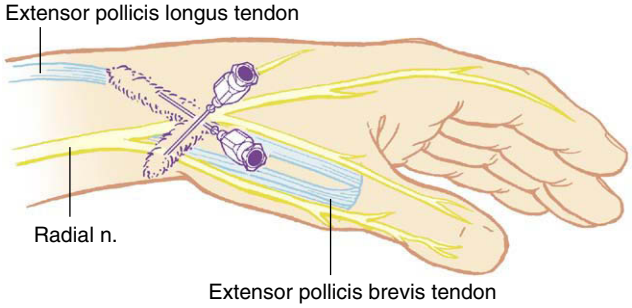

Figure 52-10 Anatomic landmarks and method of needle insertion for a radial nerve block at the wrist.

Technique at the Wrist

At the wrist, the ulnar nerve lies beneath the flexor carpi ulnaris tendon between the ulnar artery and the pisiform bone. At this point, it has already given off its palmar cutaneous and dorsal branches. The nerve can be approached by directing the needle medially from the radial side of the tendon or, alternatively, by directing the needle radially from the ulnar side of the tendon (see Fig. 52-9). After eliciting a paresthesia, 3 to 5 mL of anesthetic solution is injected or spread in a fanlike fashion.

Musculocutaneous Nerve Block

The musculocutaneous nerve terminates at the lateral cutaneous nerve of the forearm. This nerve provides sensory innervation to the skin on the radial side of the forearm up to the radiocarpal joint. This block is usually performed to supplement the axillary approach to brachial plexus anesthesia.

Technique at the Elbow

The lateral cutaneous nerve of the forearm can be blocked 1 cm proximal to the intercondylar line immediately lateral to the biceps tendon. Fanlike infiltration of 3 to 5 mL of solution subcutaneously at this site provides excellent anesthesia of this nerve.

Peripheral Blockade at the Elbow versus the Wrist

The forearm cutaneous nerves arise in the upper part of the arm and are not anesthetized by blockade of the peripheral nerves at the elbow. There is no relative advantage to blockade of the peripheral nerves of the upper extremity with either the elbow or the wrist technique; both provide sensory anesthesia of the hand.

Side Effects and Complications

In general, distal peripheral blocks are associated with a lower risk of complications. However, intravascular injection can occur, and the usual precautions of incremental injection after aspiration are recommended. The incidence of nerve injury is theorized to be greater when more distal peripheral blocks are performed, possibly because of superficial nerve placement between bony and ligamentous structures, which offers ready access to the probing needle point.

Intravenous Regional Blocks

Intravenous regional blocks were first described by a German surgeon, August Bier, in 1908.[41] Early methods involved two tourniquets and the first synthetic local anesthetic, procaine. The technique lost popularity as reliable methods of blocking the brachial plexus evolved.

Clinical Applications

The Bier block has multiple advantages, including ease of administration, rapidity of recovery, rapid onset, muscular relaxation, and controllable extent of anesthesia. It is an excellent technique for short (<90 minutes) open surgical procedures and for closed reduction of bony fractures.

Technique

An intravenous cannula is placed in the upper extremity to be blocked as far distally as possible; the patient should also have an intravenous cannula in the nonoperative upper extremity for administration of fluids and other drugs. Traditionally, a double tourniquet is placed on the operative side; both cuffs should have secure closure and reliable pressure gauges. After exsanguination of the arm, the proximal cuff is inflated to approximately 150 mm Hg more than systolic pressure, and absence of a radial pulse confirms adequate tourniquet pressure. The total dose of local anesthetic is based on the patient's weight, and it is injected slowly (3 mg/kg of 0.5% prilocaine or lidocaine, without epinephrine). The use of bupivacaine for intravenous regional anesthesia has been associated with local anesthetic toxicity and death[42] and therefore is not recommended. However, dilute solutions (0.125% levobupivacaine) of long-acting amides, as well as the addition of adjuvants (tramadol, ketorolac, clonidine), have been used to prolong sensory blockade and analgesia after deflation of the tourniquets.[43]

The onset of anesthesia usually occurs within 5 minutes. When the patient complains of tourniquet pain, the distal tourniquet, which overlies anesthetized skin, is inflated, and the proximal tourniquet is released. Use of a single wide cuff allows lower inflation pressures to be used during intravenous regional anesthesia. The postulated advantage is that the lower pressures will decrease the incidence of neurologic complications related to the high inflation pressures with the narrow double cuffs.[44] The tourniquet may be safely released after 25 minutes, but the patient should be closely observed for local anesthetic toxicity for several minutes after release of the tourniquet. Slow injection of local anesthetic solutions at a distal site has been shown to lower the risk for toxicity.[45]

Side Effects and Complications

Technical problems with this block include tourniquet discomfort, rapidity of recovery leading to postoperative pain, difficulty providing a bloodless field, and the necessity of exsanguination in the case of a painful injury. Accidental or early deflation of the tourniquet or use of excessive doses of local anesthetics can result in toxic reactions. Injection of the drug as far distally as possible at a slow rate has been shown to decrease blood levels and may theoretically increase safety.[45] Cyclic deflation of the tourniquet at 10-second intervals has been shown to increase the time to peak arterial lidocaine levels and may decrease any potential toxicity.[46] Other rare complications associated with this technique include phlebitis (with 2-chloroprocaine), the development of a compartment syndrome, and loss of a limb.

Lower Extremity Blocks

Knowledge of the anatomy of the lumbosacral plexus and peripheral nerves of the lower extremity enables anesthesiologists to provide more comprehensive anesthetic care. These blocks are safe and have certain advantages, such as postoperative pain relief and lack of complete sympathectomy, which make them ideal for selected patients.

Lower extremity blocks are less popular than those routinely used for surgical procedures on the upper extremity, in part because of the widespread acceptance and safety of spinal and epidural anesthesia. Unlike the brachial plexus, the nerves supplying the lower extremity are not anatomically clustered where they can easily be blocked with a relatively superficial injection of local anesthetic. Because of anatomic considerations, lower extremity blocks are technically more difficult and require more training and practice before expertise is acquired. Many of these blocks were classically performed with paresthesia, loss-of-resistance, or field block techniques, and success rates varied. Advances in needles, catheters, and nerve stimulator technology have facilitated localization of neural structures and improved success rates.[47] Recent applications have focused on prolonged postoperative analgesia to assist rehabilitation and hospital dismissal.

Anatomy

The nerve supply to the lower extremity is derived from the lumbar and sacral plexuses. The *lumbar plexus* is formed by the anterior rami of the first four lumbar nerves; it frequently includes a branch from T12 and occasionally from L5 (Fig. 52-11). The plexus lies between the psoas major and quadratus lumborum muscles in the so-called psoas compartment. The lower components of the plexus, L2, L3, and L4, primarily innervate the anterior and medial aspects of the thigh. The anterior divisions of L2, L3, and L4 form the obturator nerve; the posterior divisions of the same components form the femoral nerve; and the lateral femoral cutaneous nerve is formed from posterior divisions of L2 and L3.

The *sacral plexus* gives off two nerves important for lower extremity surgery: the posterior cutaneous nerve of the thigh and the sciatic nerve. The posterior cutaneous nerve of the thigh and the sciatic nerve are derived from the first, second, and third sacral nerves plus branches from the anterior rami of L4 and L5, respectively. These nerves pass together through the pelvis and the greater sciatic foramen and are blocked by the same technique. The sciatic nerve is a combination of two major nerve trunks, the tibial (i.e., ventral branches of the anterior rami of L4, L5, S1, S2, and S3) and the common peroneal (i.e., dorsal branches of the anterior rami of L4, L5, S1, S2, and S3). At or above the popliteal fossa, they separate, with the tibial nerve passing medially and the common peroneal passing laterally. Cutaneous distributions of the lumbosacral and peripheral nerves are shown in Figure 52-12.

Psoas Compartment Block (Posterior Approach to the Lumbar Plexus)

The psoas compartment block uses a technique in which a needle is placed into the space between the psoas major and quadratus lumborum muscles. It was initially performed with a loss-of-resistance technique and injection of a large volume of solution

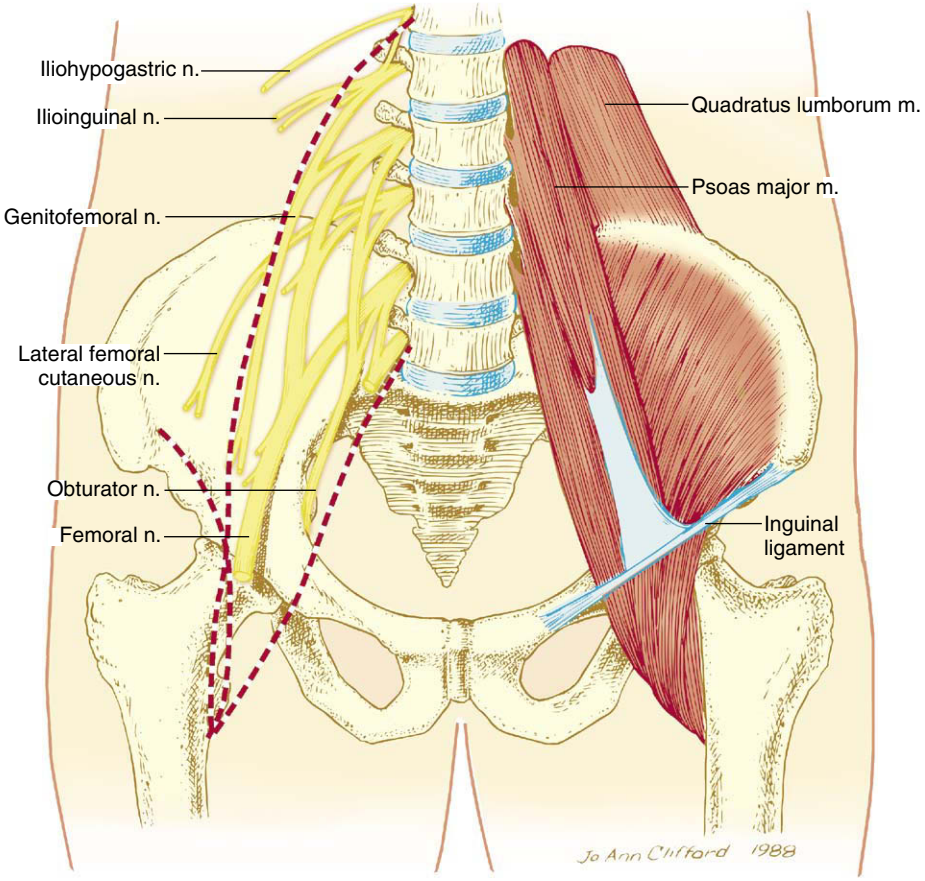

Figure 52-11 The lumbar plexus lies in the psoas compartment between the psoas major and quadratus lumborum muscles.

to provide anesthesia to the hip and anterolateral aspect of the thigh.[48]

Clinical Applications

A psoas compartment block offers a single injection rather than three separate needle insertions for anesthesia of the lumbar plexus.[49] The technique must be combined with a sciatic block for anesthesia of the entire lower extremity. A psoas compartment block is often used to provide postoperative analgesia for patients undergoing major knee and hip surgery.[50]

Technique

The patient is placed in the lateral position with the hips flexed and the operative extremity uppermost. A line is drawn to connect the iliac crests (i.e., intercristal line) and identify the fourth lumbar spine. After skin preparation, a skin wheal is raised 3 cm caudal and 5 cm lateral to the midline on the side to be blocked. A 21-gauge, 10-cm stimulating needle is then advanced perpendicular to the skin entry site until it contacts the fifth lumbar transverse process. The needle is redirected cephalad until it slides off the transverse process. The lumbar plexus is identified by elicitation of a quadriceps motor response. When the needle is in place, 30 mL of solution is injected.

Based on anatomic imaging studies, Capdevila and colleagues[51] modified the classic psoas technique (Fig. 52-13). The needle insertion site is the junction of the lateral third and medial two thirds of a line between the spinous process of L4 and a line parallel to the spinal column passing through the posterior superior iliac spine. (The spinous process of L4 was estimated to be approximately 1 cm cephalad to the upper edge of the iliac crests.) The needle is advanced perpendicular to the skin until it contacts the transverse process of L4 and is then advanced under the transverse process until quadriceps femoris muscle twitches are elicited. Despite a difference between men and women in the depth of the lumbar plexus (median values, 8.5 and 7.0 cm, respectively), the distance from the L4 transverse process to the lumbar plexus was comparable (median value, 2 cm) in both sexes (Fig. 51-14B). The investigators stressed the importance of achieving contact with the L4 transverse process to establish appropriate needle depth and position.

Side Effects and Complications

The deep needle placement with the posterior (psoas compartment) approach increases the risk for epidural, subarachnoid, or intravascular injection. Peripheral nerve damage is also a potential risk with this technique. A side effect of the paravertebral approach to the lumbar plexus is the development of a sympathetic block from extravasation of local anesthetic. This unilateral sympathectomy is usually of little consequence.

Epidural spread of local anesthetic is another common side effect of a psoas compartment block that occurs in 9% to 16% of adult patients.[47,49-51] This side effect is generally attributed to retrograde diffusion of the local anesthetic to the epidural space when large volumes of local anesthetic are used (>20 mL). In

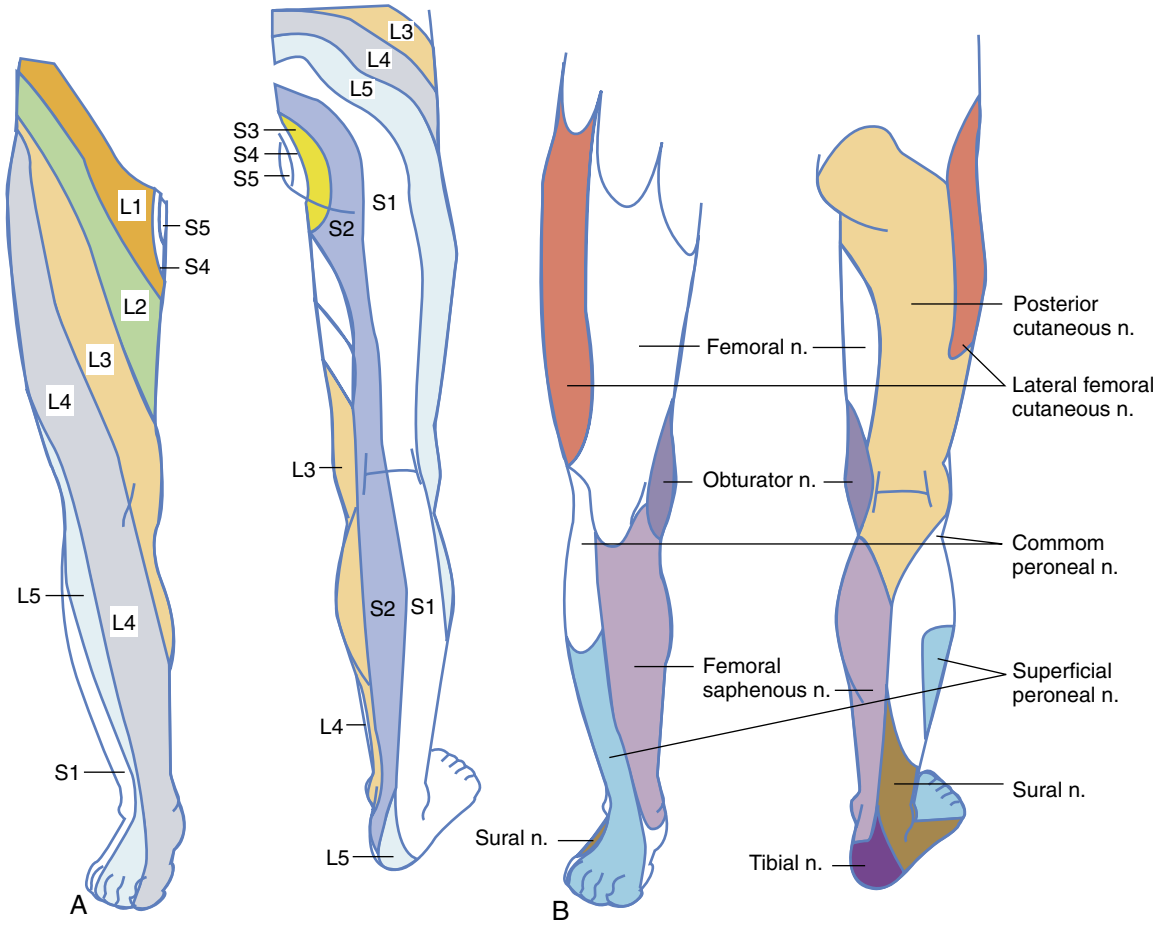

Figure 52-12 **A,** Cutaneous distribution of the lumbosacral nerves. **B,** Cutaneous distribution of the peripheral nerves of the lower extremity.

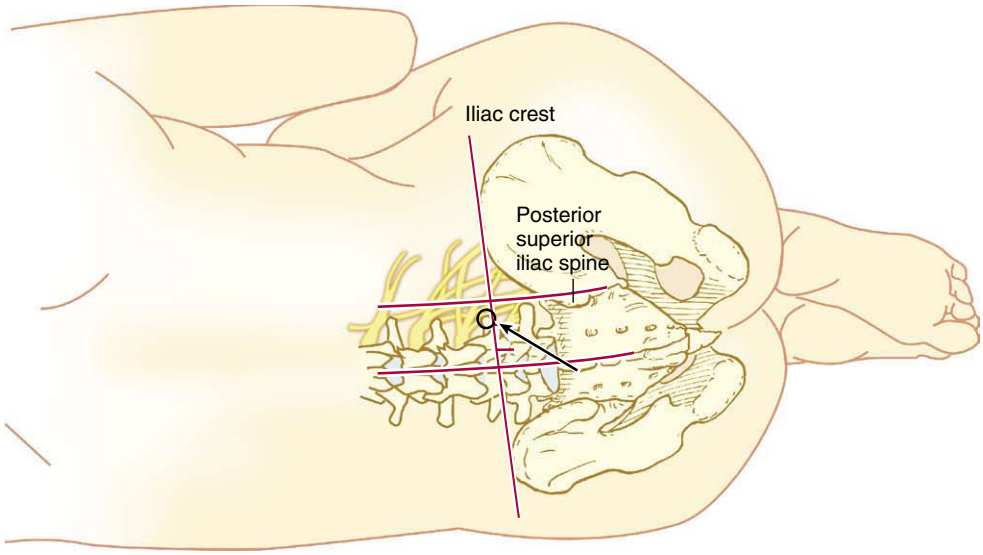

Figure 52-13 Psoas compartment block. The needle entry site is marked 1 cm cephalad to the intercristal line, two thirds of the distance from the midline to the posterior superior iliac spine line. The lumbar plexus is identified between the transverse processes of L4 and L5. Dural sleeves extend 3 to 5 cm laterally. The *circle* is the site of needle insertion. *(From Lennon RL, Horlocker TT: Mayo Clinic Analgesic Pathway, Peripheral Nerve Blockade for Major Orthopedic Surgery. Rochester, MN, Mayo Clinic Scientific Press, 2006.)*

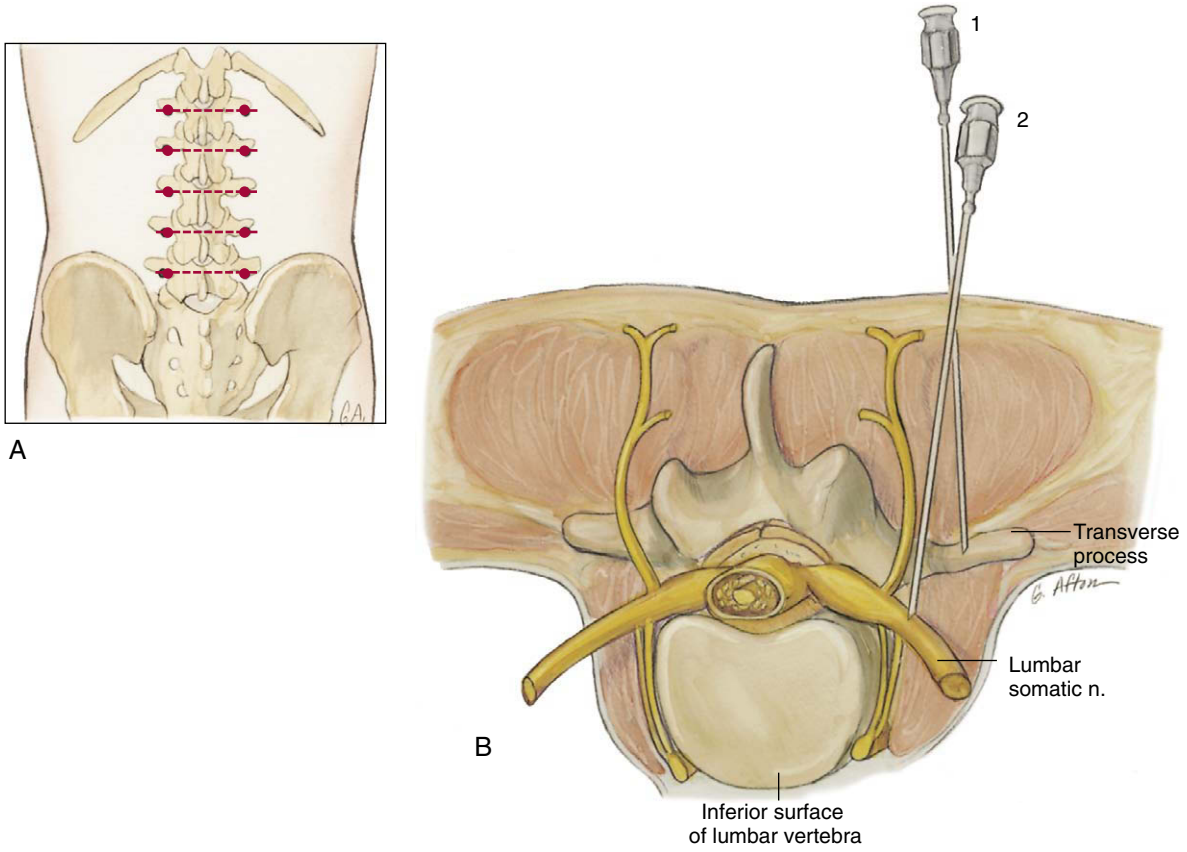

Figure 52-14 Paravertebral nerve block. **A,** Patient position and surface landmarks. **B,** The needle is advanced perpendicularly until it contacts the transverse process. It is redirected to walk off the caudad edge of the transverse process and advanced 1 to 2 cm.

most cases, residual lumbar plexus blockade is apparent after resolution of the contralateral block. However, because of case reports of total spinal anesthesia occurring during lumbar plexus blockade, vigilance must be maintained during management of this block.

Perivascular 3-in-1 (Femoral) Nerve Block

The femoral nerve is formed within the psoas major muscle by posterior divisions of the second, third, and fourth lumbar nerves. It emerges from the lateral border of the psoas muscle, descends in the groove between the psoas and iliacus muscles, and enters the thigh by passing beneath the inguinal ligament lateral to the femoral artery. At this point the nerve divides into multiple terminal branches, which have been classified as anterior and posterior. The anterior branches are primarily cutaneous, and the deep branches are chiefly motor. The femoral nerve supplies the anterior compartment muscles of the thigh (i.e., quadriceps, sartorius) and the skin of the anterior aspect of the thigh from the inguinal ligament to the knee. Its terminal branch is the *saphenous nerve*, which supplies an area of skin along the medial side of the leg from the knee to the big toe.

Clinical Applications

The perivascular approach (i.e., 3-in-1 block) to the lumbar plexus is based on the premise that injection of a large volume of local anesthetic within the femoral canal while maintaining distal pressure will result in proximal spread of solution into the psoas compartment and consequent lumbar plexus block.[52] However, recent imaging studies suggest that blockade occurs through lateral (lateral femoral cutaneous nerve) and medial (obturator nerve) spread of injected solution.[53]

Indications for femoral nerve block include anesthesia for knee arthroscopy in combination with intra-articular local anesthesia, as well as analgesia for femoral shaft fractures, anterior cruciate ligament reconstruction, and total-knee arthroplasty as a part of multimodal regimens. Their use in complex knee operations is associated with lower pain scores and fewer hospital admissions after same-day surgery.[47,50]

Technique

Femoral Block

The patient is placed in the supine position. A line is drawn between the anterior superior iliac spine and the pubic tubercle to identify the inguinal ligament. The femoral artery is marked. A 22-gauge, 4-cm needle is advanced lateral to this line (Fig. 52-15A). When the needle reaches the depth of the artery, a pulsation of the hub is visible. Elicitation of a paresthesia or motor response verifies correct needle position. Commonly, the anterior branch of the femoral nerve is identified first. Stimulation of this branch leads to contraction of the sartorius muscle on the medial aspect of the thigh and should not be accepted. The needle should be redirected slightly laterally and with a deeper direction to encounter the posterior branch of the femoral nerve. Stimulation of this branch is identified by patellar ascension as the quadriceps

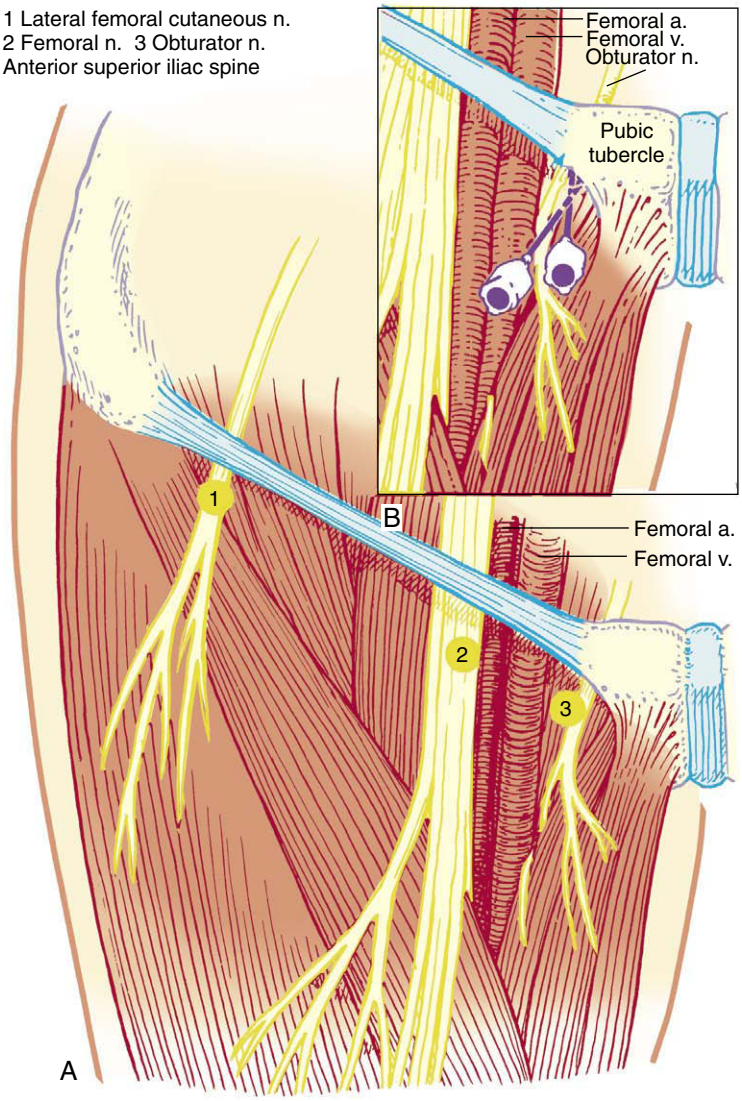

Figure 52-15 A, Anatomic landmarks for the lateral femoral cutaneous, femoral, and obturator nerve blocks. **B,** For an obturator nerve block, the needle is walked off the inferior pubic ramus in a medial and cephalad direction until it passes into the obturator canal.

contracts. A total of 20 to 40 mL of solution is injected incrementally after negative aspiration. Reliable anesthesia of the femoral and lateral femoral cutaneous nerves can be achieved with 20 mL. However, an obturator nerve block may not occur even with volumes greater than 30 mL.

Modified Femoral (Fascia Iliaca) Nerve Block

The fascia iliaca block was originally described in children. Clinical indications for its use are the same as those for a femoral nerve block.[50,54] Advocates believe that its utility lies in the double-pop technique for applying this block. The double pop refers to the sensation felt as the needle traverses the fascia lata and then the fascia iliaca. Penetration of both layers of fascia is important for successful fascia iliaca blockade (Fig. 52-16). To facilitate appreciation of the "clicks" or "pops," the use of a short-beveled or pencil-tipped needle has been advocated to provide more tactile feedback than can be obtained with cutting needles. This technique does not require a nerve stimulator; however, confirmatory motor responses may be sought. The needle entry site for the fascia iliaca block is determined by drawing a line between the pubic tubercle and the anterior superior iliac crest and dividing this line into thirds. The needle entry point is 1 cm caudal to the intersection of the medial two thirds and lateral third along this line. This site is well away from the femoral artery, thus making it useful for patients in whom femoral artery puncture is contraindicated.

Side Effects and Complications

Intravascular injection and hematoma are possible because of the proximity of the femoral artery. Anatomically, the nerve and artery are located in separate sheaths approximately 1 cm apart. In most patients with normal anatomy, the femoral artery can easily be palpated to allow correct, safe needle positioning lateral to the pulsation. The presence of femoral vascular grafts is a relative contraindication to these techniques. Nerve damage is rare.

Lateral Femoral Cutaneous Nerve Block

The lateral femoral cutaneous nerve (L2 and L3) emerges at the lateral border of the psoas muscle immediately caudad to the ilioinguinal nerve. It descends under the iliac fascia to enter the

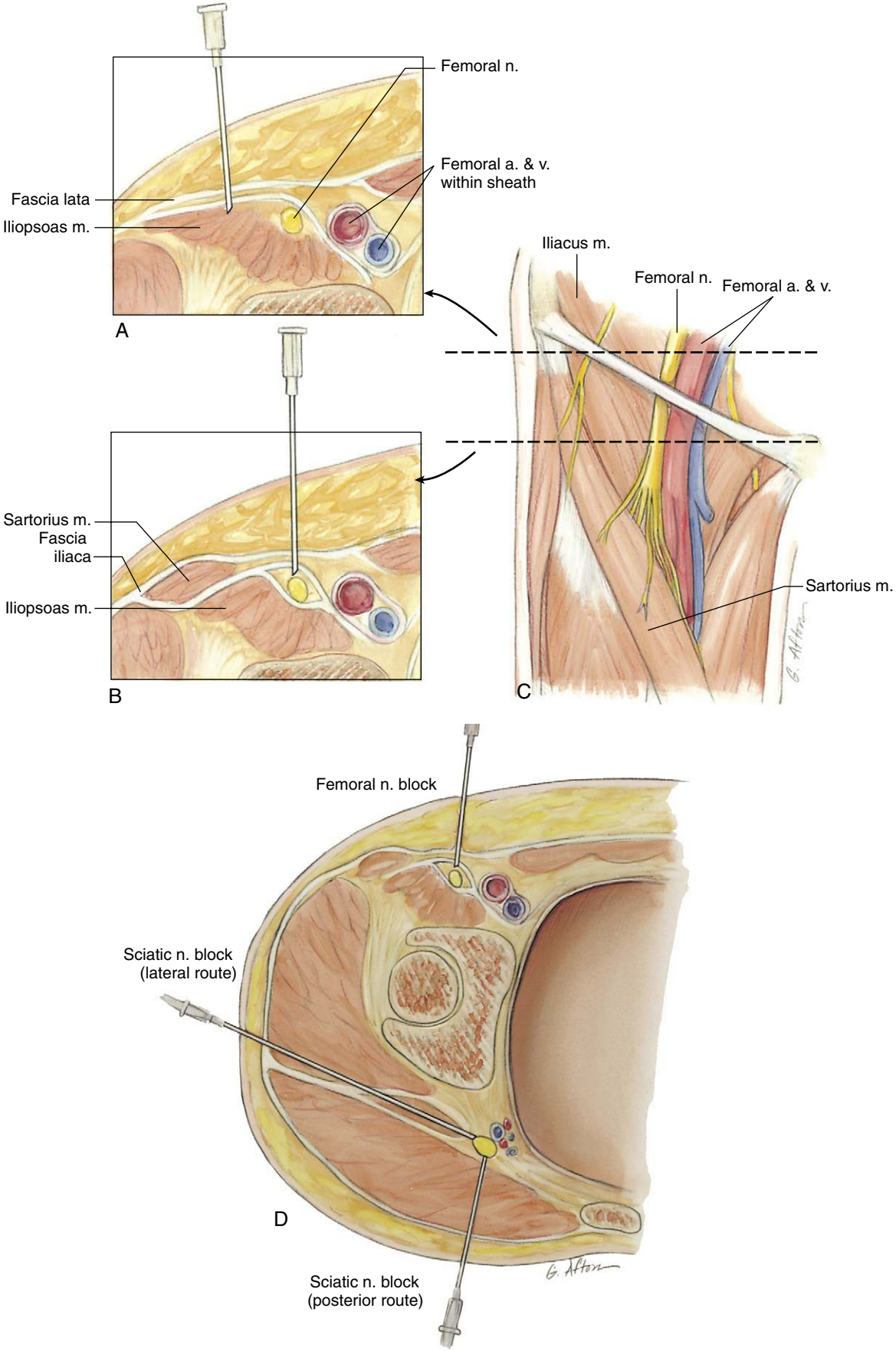

Figure 52-16 Proximal lower extremity blocks. **A,** Fascia iliaca compartment block. **B,** Classic femoral nerve block. **C,** Relationship of the femoral nerve in the groin. **D,** Insertion routes of the most common proximal blocks of the lower extremity (cross section of the thigh).

thigh deep to the inguinal ligament 1 to 2 cm medial to the anterior superior iliac spine. The nerve emerges from the fascia lata 7 to 10 cm below the spine and divides into anterior and posterior branches. The skin of the lateral portion of the thigh from the hip to the midthigh is supplied by the posterior branch; the anterior branch supplies the anterolateral aspect of the thigh to the knee.

Clinical Applications

This block is useful for skin graft harvesting and can be used in concert with other peripheral nerve blocks for complete anesthesia of the lower extremity.

Technique

A point is marked 2 cm medial and 2 cm caudad to the anterior superior iliac spine. A 22-gauge, 4-cm needle is advanced perpendicular to the skin entry site until sudden release indicates passage through the fascia lata. As the needle is moved in a fanlike pattern laterally and medially, 10 to 15 mL of solution is injected so that local anesthetic is deposited above and below the fascia (see Fig. 52-15A). Shannon and colleagues compared the traditional fan technique for lateral femoral cutaneous nerve block with the use of a nerve stimulator technique to seek tingling in the distribution of the nerve.[55]

Side Effects and Complications

The extent of anesthesia is quite limited with this block, but there is a low risk of associated complications. Neuritis of this nerve caused by needle trauma or drug toxicity is a potential but unlikely complication. There are no large blood vessels in the vicinity of this nerve, and the likelihood of rapid uptake or intravascular injection is very small.

Obturator Nerve Block

The obturator nerve is derived primarily from the third and fourth lumbar nerves with an occasional minor contribution from L2. The nerve lies deep in the obturator canal after having descended from the medial border of the psoas muscle. As the nerve leaves the obturator canal, it divides into anterior and posterior branches. The anterior branch supplies an articular branch to the hip and the anterior adductor muscles and a variable cutaneous branch to the lower medial portion of the thigh. The posterior branch innervates the deep adductor muscles and may send an articular branch to the knee.

Clinical Applications

The obturator nerve is usually blocked as part of regional anesthesia for knee surgery. Because it is primarily a motor nerve, it is rarely blocked on its own; however, an obturator nerve block can be useful in treating or diagnosing the extent of adductor spasm in patients with cerebral palsy and other muscle or neurologic diseases affecting the lower extremities before surgical intervention (e.g., adductor tenotomy).

Technique

The patient is placed in the supine position, and a mark is made 1 to 2 cm lateral and 1 to 2 cm caudad to the pubic tubercle. A skin wheal is raised, and a 22-gauge, 8- to 10-cm needle is advanced perpendicular to the skin entry site with a slight medial direction. The inferior pubic ramus is encountered at a depth of 2 to 4 cm, and the needle is walked in a lateral and caudad direction until it passes into the obturator canal. The obturator nerve is located 2 to 3 cm past the initial point of contact with the pubic ramus (see Fig. 52-15). After negative aspiration, 10 to 15 mL of local anesthetic is injected. A nerve stimulator is helpful in locating the obturator nerve, and correct needle position is evidenced by contraction of the adductor muscles of the medial aspect of the thigh.

The classic approach to an obturator nerve block involves painful periosteal contact and multiple needle redirections. An alternative interadductor approach was described by Wasseff.[44,56] In this technique, the needle is inserted behind the adductor tendon, near its pubic insertion, and directed laterally toward a mark on the skin 1 to 2 cm medial to the femoral artery and immediately below the inguinal ligament, which represents the obturator canal. The nerve is identified by a motor response to peripheral nerve stimulation in the adductor muscle. An inguinal approach consisting of insertion of the needle in the inguinal crease at the midpoint of a line drawn between the inner border of the adductor longus tendon and the femoral arterial pulse has been described recently.[57]

Side Effects and Complications

Complications are rare, but this block is technically more difficult than other lower extremity blocks. The obturator canal contains vascular and neural structures, and there is a theoretical risk of intravascular injection, hematoma, and nerve damage. Absence of anesthesia in the obturator nerve distribution can render an otherwise perfect lower extremity block inadequate for surgical procedures on the knee.

Parasacral Block

A parasacral block will consistently block both components of the sciatic nerve and the posterior cutaneous nerve of the thigh. Spread of local anesthetic may also anesthetize other branches of the sacral plexus, including the superior and inferior gluteal and pudendal nerves. The pelvic splanchnic nerves (S2-4), the terminal portion of the sympathetic trunk, the inferior hypogastric plexus, and the obturator nerve all lie in close proximity to elements of the sacral plexus and may be anesthetized with this approach.[58]

Clinical Applications

For procedures about the knee, a parasacral block may provide an advantage over more distal approaches to the sciatic nerve. For procedures below the knee, the adductor weakness from the obturator and superior gluteal nerve block may actually be disadvantageous for mobilization of the patient. This technique is also useful when immediate access to the individual nerves of the sacral plexus is not possible, for example, because of trauma or infection.

Technique

The parasacral approach is based on the bony relationship of the posterior superior iliac spine and the ischial tuberosity. The patient is positioned laterally with the side to be blocked uppermost. The most prominent aspects of the posterior superior iliac spine and the ischial tuberosity are identified, and a line is drawn joining these two points. Along the line a mark is made 6 cm

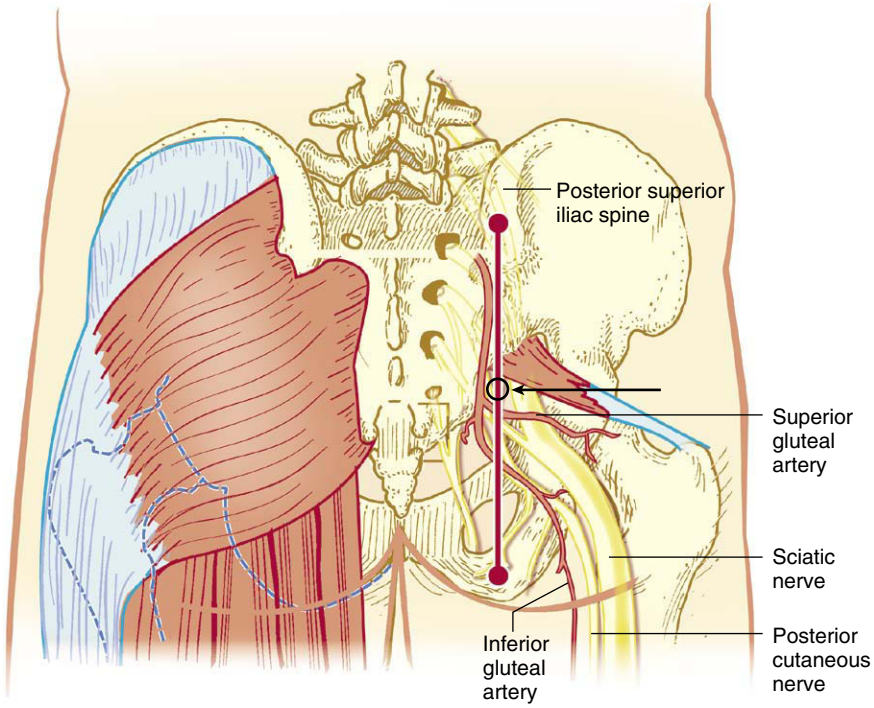

Figure 52-17 Parasacral block. This is the most proximal approach to the sciatic nerve and also results in block of the posterior femoral cutaneous nerve. The most prominent aspects of the posterior superior iliac spine and the ischial tuberosity are identified, and a line is drawn joining these two points. The needle insertion site is along the line, 6 cm inferior to the posterior superior iliac spine. *(From Lennon RL, Horlocker TT: Mayo Clinic Analgesic Pathway, Peripheral Nerve Blockade for Major Orthopedic Surgery. Rochester, MN, Mayo Clinic Scientific Press, 2006.)*

inferior to the posterior superior iliac spine to define the needle insertion site (Fig. 52-17). A 21-gauge, 10-cm insulated needle is advanced in a sagittal plane until an evoked motor response is elicited, typically at a depth of 5 to 7 cm from the skin. When the needle is properly placed, 20 to 30 mL of solution is slowly and incrementally injected. Plantar flexion of the foot (tibial nerve component) or dorsiflexion (common peroneal nerve) is an acceptable motor response. Because of the proximal nature of the block, a hamstring motor response is also acceptable.

Complications

Because the sacral nerves represent the parasympathetic portion of the autonomic nervous system, sympathetic blockade and its potential for hypotension are not seen with a transsacral block unless excessive volumes of solution spread proximally to the lumbar sympathetic fibers. Loss of parasympathetic innervation to the bowel, bladder, and sphincters may occur,[59] however. Injection of local anesthetic through misdirected needles into the subarachnoid or vascular compartments is a remote risk. Classically, the dural sac terminates at the lower border of S2; however, clinical reports of subarachnoid puncture with a 6- to 7-cm caudal needle suggest that there are individual variations below this "classic" location. Finally, an appreciation of the pelvic contents, especially the colon, rectum, and bladder, is important; should a deeply inserted needle enter the colon or rectum and not be noticed, it could result in seeding fecal material into the sacral canals.

Sciatic Nerve Block

The sciatic nerve (L4 and L5, S1 through S3) is the largest of the four peripheral nerves of the lower extremity, with a width of 2 cm as it leaves the pelvis along with the posterior cutaneous nerve of the thigh. The sciatic nerve is composed of two nerves bound by a common sheath of connective tissue; the tibial component is medial and anterior, and the common peroneal component is lateral and slightly posterior. After passing through the sacrosciatic foramen beneath the piriformis muscle, it lies between the greater trochanter of the femur and the ischial tuberosity. The nerve becomes superficial at the lower border of the gluteus maximus muscle, where it begins its descent down the posterior aspect of the thigh to the popliteal fossa. It supplies cutaneous innervation to the posterior of the thigh and all of the leg and foot below the knee, except for a thin medial strip supplied by the saphenous nerve.

Clinical Applications

Because of its wide sensory distribution, a sciatic nerve block can be used, together with a saphenous or femoral nerve block, for any surgical procedure below the knee that does not require a thigh tourniquet. It can also be combined with other peripheral nerve blocks to provide anesthesia for surgical procedures involving the thigh and knee. This form of anesthesia avoids the sympathectomy associated with neuraxial blocks and may therefore be advantageous when any shift in hemodynamics could be deleterious, such as in patients with significant aortic stenosis.

Technique

Classic (Posterior) Approach of Labat

For the classic (posterior) approach of Labat, the patient is positioned laterally, with the leg to be blocked rolled forward onto the flexed knee as the heel rests on the knee of the dependent (nonoperative) leg (Fig. 52-18).[6] A line is drawn to connect the posterior superior iliac spine to the greater trochanter of the femur. A perpendicular line bisecting this line is drawn and extended 5 cm caudad. A second line is drawn from the greater trochanter to the sacral hiatus. The intersection of this line with the perpendicular line indicates the point of needle entry, which falls 3 to 5 cm along

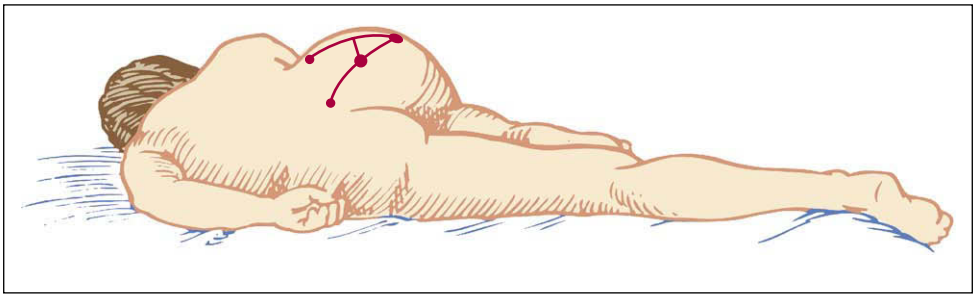

Figure 52-18 Patient positioning for the posterior approach to the sciatic nerve.

the line. A 22-gauge, 10- to 12-cm needle is advanced until a paresthesia or nerve stimulator response is elicited or bone is contacted (Fig. 52-19). If bone is encountered, the needle is redirected systematically in a lateral or medial direction. After the needle is properly placed, a total of 20 to 30 mL of solution is injected.

Subgluteal Approach

With this approach, the patient is positioned laterally in a modified Sims' position, and the leg to be blocked is rolled forward onto the flexed knee as the heel rests on the knee of the dependent (nonoperative) leg. This approach is based on the bony relationship to the greater trochanter and the ischial tuberosity. The most prominent aspects of the greater trochanter and the ischial tuberosity are identified by palpation, and a line is drawn joining these two points. A perpendicular line bisecting this line is drawn and extended 4 to 6 cm caudad. The second line approximates the location of the sciatic nerve. The site of needle insertion may be at the intersection of the two lines or as far as 6 cm distally along the second line. A 21-gauge, 10-cm insulated needle is inserted perpendicularly until a tibial or peroneal evoked motor response in the ankle or foot is elicited, and 20 to 30 mL of solution is injected incrementally (Fig. 52-20). The target response is an evoked response below the knee; stimulation of the tibial nerve component produces plantar flexion and inversion of the foot, and stimulation of the common peroneal nerve produces dorsiflexion and eversion. If no motor response is elicited, the needle may be redirected 1 to 2 cm medial or lateral to the original direction of the needle. It may be helpful to palpate or visualize the groove, which can be seen or palpated on the posterior aspect of the thigh. If bone contact is made, the needle is withdrawn and redirected medially.

Anterior Approach

The anterior approach is useful when the patient cannot be positioned for the classic posterior approach because of pain or lack

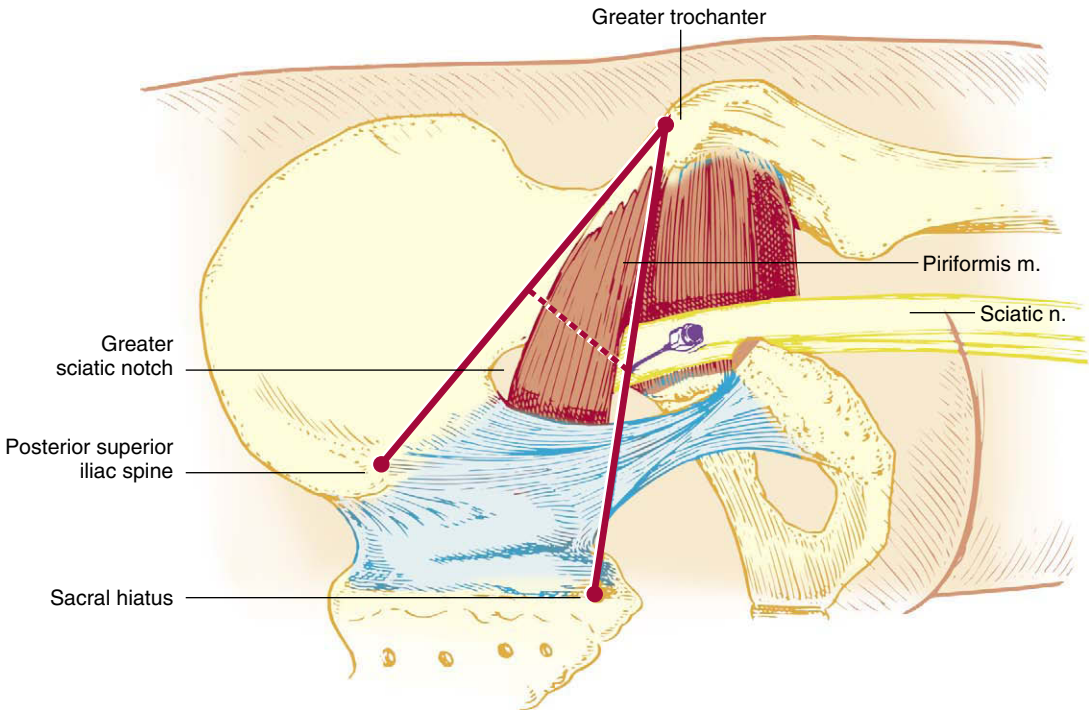

Figure 52-19 Anatomic landmarks for the posterior approach to a sciatic nerve block.

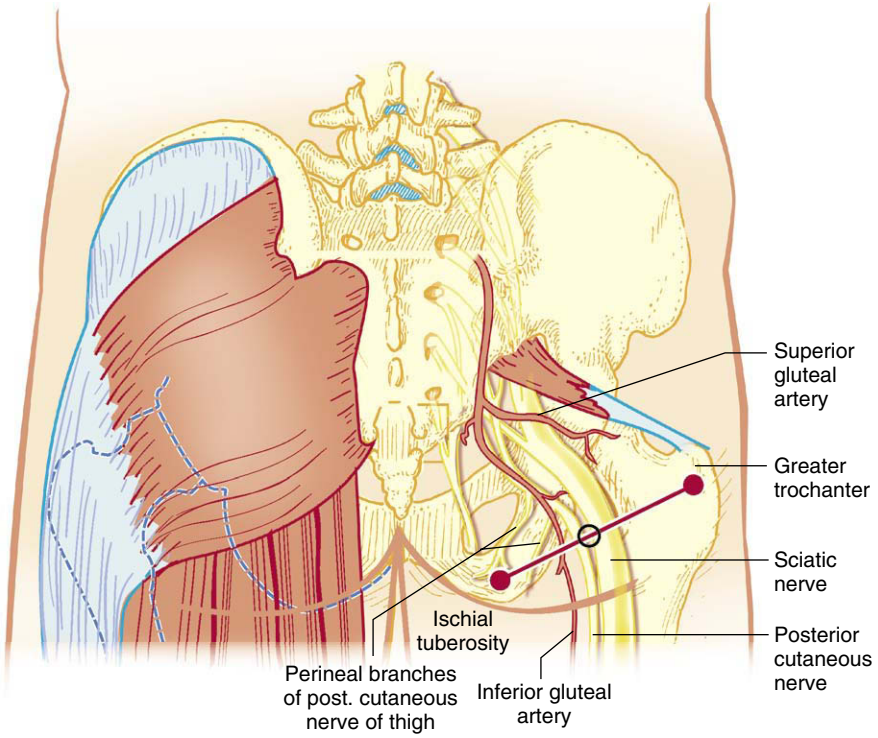

Figure 52-20 Sciatic nerve block (subgluteal approach). The sciatic nerve is relatively superficial at this level. Needle insertion is near the gluteal crease, between the hamstring muscles. *(From Lennon RL, Horlocker TT: Mayo Clinic Analgesic Pathway, Peripheral Nerve Blockade for Major Orthopedic Surgery. Rochester, MN, Mayo Clinic Scientific Press, 2006.)*

of cooperation.[60] Initial blockade of the femoral nerve decreases the pain associated with this approach.

With the patient in the supine position, a line drawn along the inguinal ligament from the anterior superior iliac crest to the pubic tubercle is trisected. A second line parallel to the inguinal ligament is drawn, beginning at the tuberosity of the greater trochanter. A 22-gauge, 10.5- to 12-cm needle is inserted perpendicularly with a slightly lateral angulation at the point where the line representing the juncture of the middle and medial thirds crosses the second line. The needle is advanced until it contacts bone, the lesser trochanter of the femur (Fig. 52-21). The needle is redirected medially past the femur, and a paresthesia or nerve stimulator response is sought at a depth of about 5 cm past the bone. A total of 20 to 25 mL of solution is injected incrementally after careful aspiration.

Other Approaches

The sciatic nerve can also be blocked with the patient in the lateral[61] and lithotomy positions,[62] although these are rarely used clinically.

Techniques to Improve Success Rates

Many methods have been tried in an attempt to improve success with sciatic nerve blockade. Attempts to place the needle in the middle of the sciatic nerve by identifying a specific motor end point (e.g., tibial response/foot inversion) may increase success rates.[63] Another method is the concept of multiple injections.[64] The two major components of the sciatic nerve are separately identified and blocked. Some experts recommend that sciatic nerve blocks be initiated well before the scheduled time of surgery to extend the dwell time and allow long latencies.

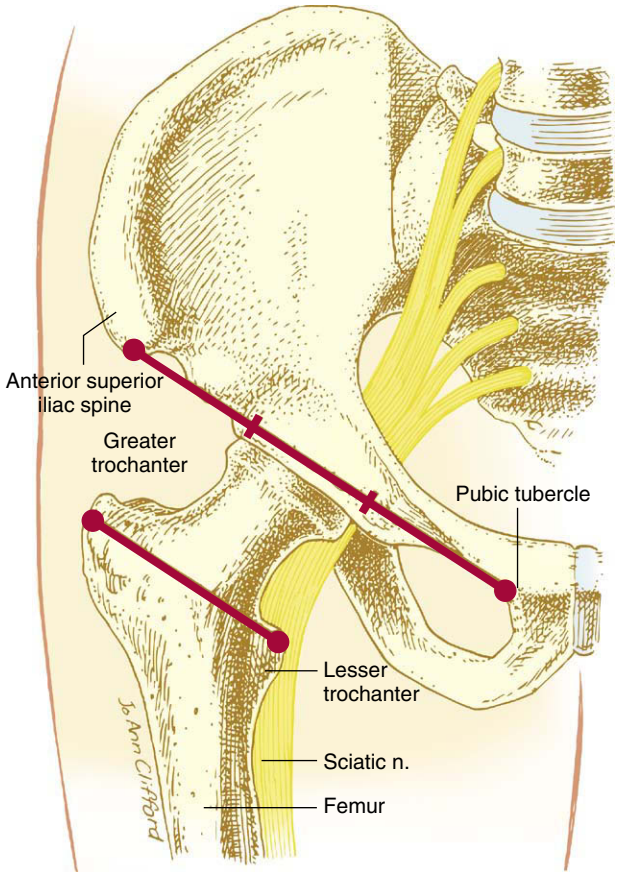

Figure 52-21 Anatomic landmarks for the anterior approach to a sciatic nerve block.

Side Effects and Complications

Serious complications of sciatic nerve block are rare. However, theoretical concerns regarding muscle trauma and puncture of a variety of vascular structures must be considered. A sciatic nerve block is primarily a somatic nerve block. It does carry some sympathetic fibers to the extremity, however, and may therefore allow pooling of small quantities of blood—usually insufficient to cause significant hypotension. In some situations, such as limb reimplantation and sympathetically mediated pain conditions, this sympathetic block may be advantageous. Residual dysesthesias for periods of 1 to 3 days are not uncommon but usually resolve within several months.[64,65] Importantly, many orthopedic surgical procedures (including total-hip and total-knee replacement) are associated with neurapraxia of one or both components of the sciatic nerve. Thus, thoughtful application of this technique is required to optimize neurologic outcome in patients considered to be at high risk for perioperative nerve injury from surgery or preexisting neurologic dysfunction.

Popliteal Fossa Block

The posterior muscles of the thigh are the biceps femoris, semimembranosus, semitendinosus, and posterior portion of the adductor magnus. As these muscles are traced distally from their origin on the ischial tuberosity, they separate into medial (semimembranosus, semitendinosus) and lateral (biceps) musculature, and they form the upper border of the popliteal fossa. The lower border of the popliteal fossa is defined by the two heads of the gastrocnemius. In the upper part of the popliteal fossa, the sciatic nerve lies posterolateral to the popliteal vessels. The popliteal vein is medial to the nerve, and the popliteal artery is most anterior, lying on the popliteal surface of the femur. Near the upper border of the popliteal fossa, the two components of the sciatic nerve separate. The peroneal nerve diverges laterally, and the larger tibial branch descends almost straight down through the fossa. The tibial nerve and popliteal vessels then disappear deep to the converging heads of the gastrocnemius muscle.

Clinical Applications

The popliteal fossa block is chiefly used for foot and ankle surgery. It has also been used in the pediatric population successfully. A popliteal fossa block is preferable to an ankle block for surgical procedures requiring the use of a calf tourniquet. The components of the sciatic nerve may be blocked at the level of the popliteal fossa through posterior or lateral approaches. Supplemental block of the saphenous nerve is required for surgical procedures on the medial aspect of the leg or when a calf tourniquet or Esmarch bandage is used.

Technique

Posterior Approach

The classic approach to the popliteal fossa is posterior with the patient positioned prone. However, access may also be achieved with the patient in the lateral position (i.e., operative side nondependent) or the supine position (i.e., with the leg flexed at the hip and knee).

The borders of the popliteal fossa are identified by flexing the knee joint. A triangle is constructed, with the base consisting of the skin crease behind the knee and the two sides composed of the semimembranosus (medially) and the biceps (laterally). A bisecting line is drawn from the apex to the base of the triangle, and a 5-cm needle is inserted at a site 5 to 10 cm above the skin fold and 0.5 to 1 cm lateral to the bisecting line (Fig. 52-22A). Classically, the 5-cm distance was described.[66] However, in an attempt to block the sciatic nerve before its division, a 7- to 10-cm distance has been recommended.[67] The needle is advanced at a 45-degree angle until a paresthesia or nerve stimulator response is elicited. With a nerve stimulator technique, inversion is the motor response that best predicts complete neural blockade of the foot.[68] Injection of approximately 30 mL of local anesthetic solution is sufficient.

The success rate is typically 90% to 95%.[66,68] No formal comparison between the paresthesia and nerve stimulator techniques has been made to assess efficacy and complications. It is believed that an incomplete block is the result of poor diffusion (because of the size of the sciatic nerve), the separate fascial coverings of the tibial and peroneal nerves, or blockade of only a single component of the sciatic nerve. Identification of the tibial and peroneal components decreases onset time and improves the success rate.[69]

Lateral Approach

A lateral approach to blockade of the sciatic nerve in the popliteal fossa has been described.[70] Although block time is somewhat longer, onset and quality of the block are similar to the posterior approach.[71] The lateral approach allows the patient to be positioned supine and eliminates the need for repositioning. The patient's leg is extended, with the long axis of the foot at a 90-degree angle to the table. The site of insertion is the intersection of a vertical line drawn from the upper edge of the patella and the groove between the lateral border of the biceps femoris and vastus lateralis. A 10-cm needle is advanced at a 30-degree angle posterior to the horizontal plane (see Fig. 52-22B). Because the common peroneal nerve is located lateral to the tibial nerve, the stimulating needle encounters the common peroneal nerve first with the lateral approach. As in the classic posterior approach, a tibial response is sought.[72] If a response associated with common peroneal nerve stimulation (e.g., eversion) is elicited, the needle is redirected more posteriorly.

Side Effects and Complications

As with other peripheral nerve blocks, neuropathy is the most common complication. Intravascular injection may occur as a result of the presence of vascular structures within the popliteal fossa. Performance of a popliteal fossa block in patients with previous total-knee arthroplasty or vascular bypass (femoral-popliteal) should be done with care. However, there have been no cases of graft disruption or joint infection related to needle placement in these patients.

Nerve Blocks at the Ankle

Four of the five individual nerves that can be blocked at the ankle to provide anesthesia of the foot are terminal branches of the sciatic nerve: the posterior tibial, sural, superficial peroneal, and deep peroneal branches. The sciatic nerve divides at or above the apex of the popliteal fossa to form the common peroneal and tibial nerves. The common peroneal nerve descends laterally around the head of the fibula, where it divides into the superficial and deep peroneal nerves.

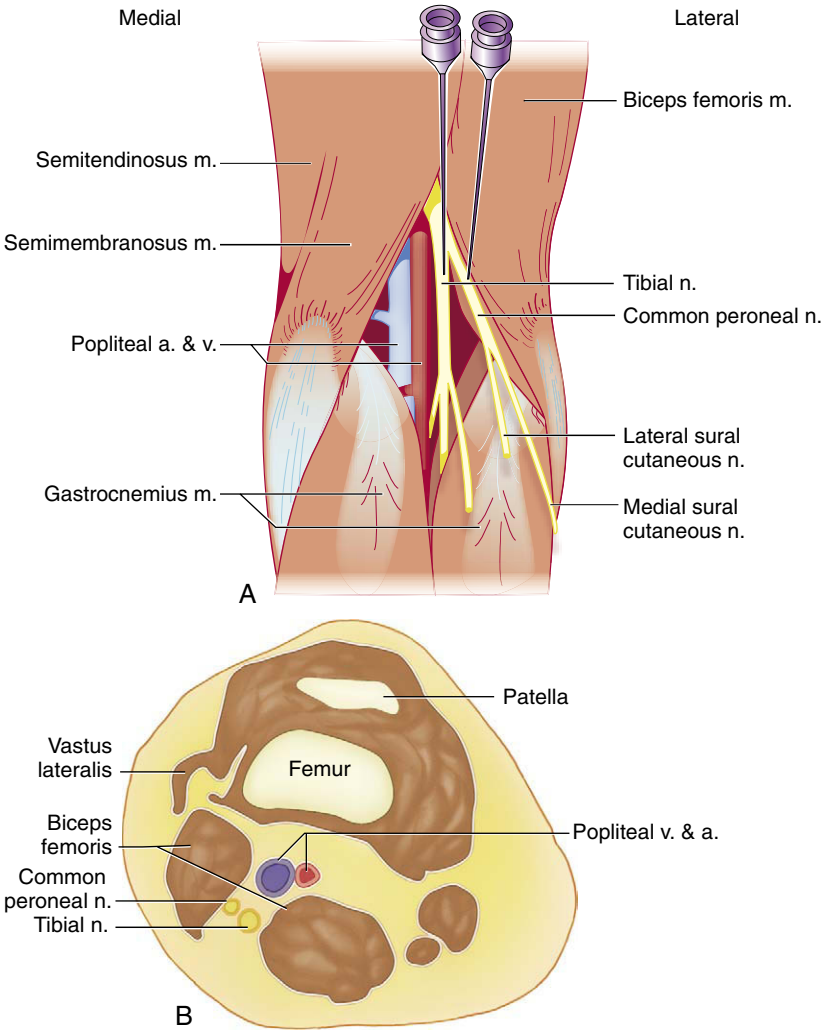

Figure 52-22 A, Anatomic landmarks for the posterior approach to the sciatic nerve in the popliteal fossa. **B,** Anatomic landmarks for the lateral approach to the sciatic nerve in the popliteal fossa.

The tibial nerve divides into the posterior tibial and sural nerves in the lower part of the leg. The posterior tibial nerve becomes superficial at the medial border of the Achilles tendon near the artery of the same name, and the sural nerve emerges lateral to the Achilles tendon.

Clinical Applications

Ankle blocks are simple to perform and offer adequate anesthesia for surgical procedures on the foot that do not require a tourniquet above the ankle.

Technique

Posterior Tibial Nerve

The posterior tibial nerve can be blocked with the patient in either the prone or the supine position. The posterior tibial artery is palpated, and a 25-gauge, 3-cm needle is inserted posterolateral to the artery at the level of the medial malleolus (Fig. 52-23A and B). A paresthesia is often elicited but is not necessary for a successful block. If a paresthesia occurs, 3 to 5 mL of local anesthetic should be injected. Otherwise, 7 to 10 mL of solution should be injected as the needle is slowly withdrawn from the posterior aspect of the tibia. Blockade of the posterior tibial nerve provides anesthesia to the heel, plantar portion of the toes, and the sole of the foot, as well as some motor branches in the same area.

Sural Nerve

The sural nerve is located superficially between the lateral malleolus and the Achilles tendon. A 25-gauge, 3-cm needle is inserted lateral to the tendon and directed toward the malleolus as 5 to 10 mL of solution is injected subcutaneously (see Fig. 52-23A and C). This block provides anesthesia to the lateral part of the foot and the lateral proximal aspect of the sole of the foot.

Deep Peroneal, Superficial Peroneal, and Saphenous Nerves

The deep peroneal, superficial peroneal, and saphenous nerves can be blocked through a single needle entry site (Fig. 52-24). A line is drawn across the dorsum of the foot connecting the malleoli. The extensor hallucis longus tendon is identified by having the patient dorsiflex the big toe. The anterior tibial artery lies between this structure and the tendon of the extensor digitorum longus muscle and is palpable at this level. A skin wheal is raised just lateral to the pulsation between the two tendons on the inter-

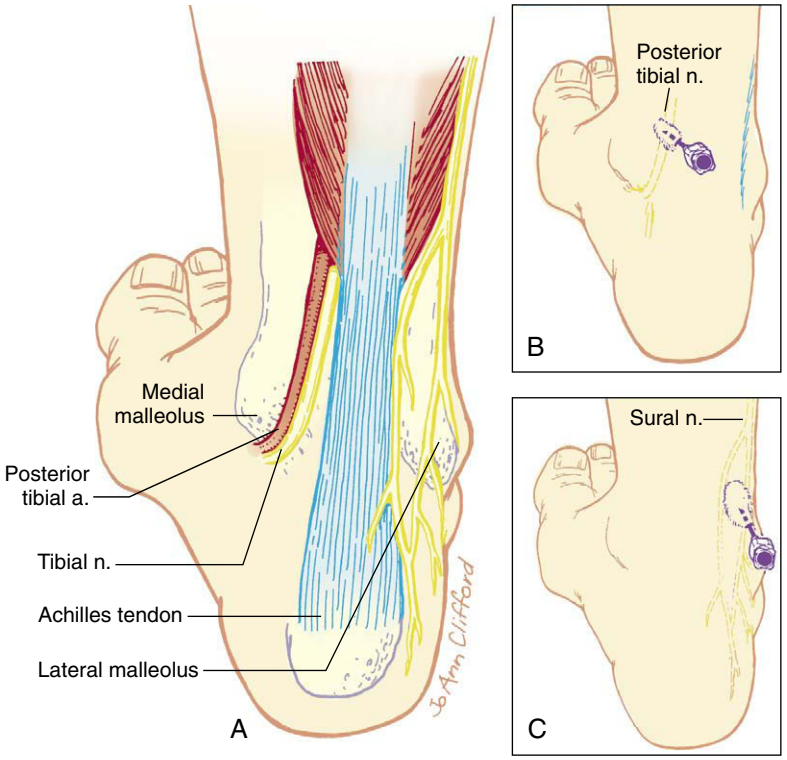

Figure 52-23 **A,** Anatomic landmarks for a block of the posterior tibial and sural nerves at the ankle. **B,** Posterior tibial nerve and method of needle placement for a block at the ankle. **C,** Sural nerve and method of needle placement for a block at the ankle.

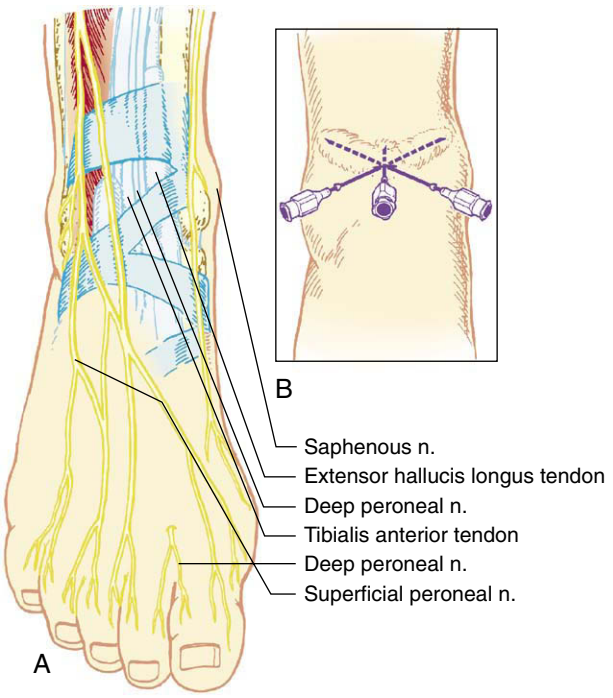

Figure 52-24 **A,** Anatomic landmarks for blockade of the deep peroneal, superficial peroneal, and saphenous nerves at the ankle. **B,** Method of needle placement for a block of the deep peroneal, superficial peroneal, and saphenous nerves through a single needle entry site.

malleolar line. A 25-gauge, 3-cm needle is advanced perpendicular to the skin entry site, and 3 to 5 mL of local anesthetic is injected deep to the extensor retinaculum to block the deep peroneal nerve. This technique anesthetizes the skin between the first and second toes and the short extensors of the toes.

The needle is directed laterally through the same skin wheal while injecting 3 to 5 mL of solution subcutaneously, which blocks the superficial peroneal nerve and results in anesthesia of the dorsum of the foot, excluding the first interdigital cleft. The same maneuver can be performed in the medial direction to anesthetize the saphenous nerve, a terminal branch of the femoral nerve that supplies a strip along the medial aspect of the foot.

Side Effects and Complications

The multiple injections required for some techniques result in discomfort for the patient. Persisting paresthesias may occur, but they are self-limited. The presence of edema or induration in the area of the ankle block can make palpation of landmarks difficult. Intravascular injection is possible but unlikely if aspiration for blood is negative. The volume of local anesthetic used is small, thereby decreasing the risk for local anesthetic toxicity.

Blocks of the Head and Neck

Regional anesthesia of the head and neck has become less popular as safer methods of general anesthesia have been developed. However, applications for these techniques still exist, especially in the postoperative and chronic pain settings. Airway anesthesia is often needed to facilitate endotracheal intubation.

The cutaneous innervation of the head and neck is provided by sensory fibers from the trigeminal nerve and the cervical plexus. Innervation of the airway is derived from the vagus and glossopharyngeal nerves. Sympathetic blockade of the face and upper extremity is achieved by anesthetizing the stellate ganglion.

Trigeminal Nerve Block

The trigeminal nerve divides into three main branches in the middle cranial fossa. These divisions—the ophthalmic, maxillary, and mandibular nerves—provide sensation to the eye and forehead, midface and upper jaw, and lower jaw, respectively (Fig. 52-25A). With the exception of motor fibers to the muscles of mastication, carried by the mandibular nerve, these nerves are wholly sensory.

A gasserian ganglion block, approached classically through the foramen ovale, is infrequently used for producing surgical anesthesia. In the past, it was primarily applied for the diagnosis and treatment of trigeminal neuralgia; however, the increasing popularity and safety of thermocoagulation for ablation of the ganglion have rendered neurolytic blocks obsolete.

Clinical Applications

Blockade of the second and third divisions of the trigeminal nerve, as well as blockade of the peripheral branches, is occasionally useful in the diagnosis and management of pain syndromes and for discrete surgical procedures in selected patients (see Fig. 52-25B).

Technique: Mandibular and Maxillary Nerves

The mandibular and maxillary nerves, two divisions of the trigeminal nerve, can be blocked through the same needle entry site (see Fig. 52-25B). The maxillary nerve (i.e., second division) is blocked as it exits the skull through the foramen rotundum and crosses the pterygopalatine or infratemporal fossa between the skull and the upper jaw. The nerve terminates as the infraorbital nerve as it exits through the infraorbital foramen, where it can also be anesthetized.

The coronoid notch of the mandible is located, and with the patient's mouth closed, a 22-gauge, 8-cm needle is inserted at the inferior edge of the coronoid notch perpendicular to the skin entry site. The needle contacts the lateral pterygoid plate at a depth of about 5 cm. It is then withdrawn and redirected anteriorly and superiorly to walk off the plate and is subsequently advanced approximately 0.5 cm into the pterygopalatine fossa (see Fig. 52-25C). Between 3 and 5 mL of local anesthetic solution produces anesthesia of the upper jaw and skin of the lower eyelid, cheek, and upper lip.

The mandibular nerve (i.e., third division) leaves the cranium through the foramen ovale and innervates the skin of the lower jaw and the skin anterior and superior to the ear by its posterior division. Peripheral sensory branches of cranial nerve V_3 include the buccal, auriculotemporal, lingual, and inferior alveolar (terminating in the mental nerve) nerves. The anterior division supplies motor innervation to the muscles of mastication.

The mandibular nerve is blocked through the same entry site as the maxillary nerve. The needle is advanced along the inferior margin of the coronoid notch until the bone of the lateral pterygoid plate is contacted (about 5 cm). The needle is withdrawn and redirected to walk off the posterior border of the pterygoid plate, and it is advanced in an attempt to elicit a paresthesia. The needle should not be inserted farther than 0.5 cm past the plate (see Fig. 52-25D). Injection of 3 to 5 mL of local anesthetic solution at this site is adequate.

Side Effects and Complications

Blockade of the maxillary nerve can be associated with hematoma formation and spread of the local anesthetic solution to the optic nerve, thereby causing temporary blindness. A mandibular nerve block is not associated with major complications. If the needle is advanced past the pterygoid plate more than the recommended 0.5 cm, the pharynx may be entered, which increases the risk of contaminating the infratemporal fossa. Rarely, subarachnoid spread of local anesthetic may occur and result in brainstem anesthesia.[73]

Terminal Sensory Branches of the Trigeminal Nerve

Clinical Applications

Blockade of the terminal branches of the three divisions of the trigeminal nerve is primarily used for the diagnosis of trigeminal neuralgia. Individual nerve blocks can also be used for minor surgical procedures.

Technique

Supraorbital and Supratrochlear Nerves

The supraorbital and supratrochlear nerves, branches of the ophthalmic nerve (i.e., cranial nerve V_1), are derived from the frontal nerve, which supplies the skin of the medial upper eyelid and forehead. The supraorbital notch can easily be palpated. This landmark lies on a vertical line with the pupil (when the eye is looking directly forward), the infraorbital foramen, and the mental foramen (Fig. 52-26).

A 25-gauge, 2-cm needle is inserted immediately superior to the supraorbital notch, and 2 to 4 mL of local anesthetic solution is injected. A paresthesia is sometimes elicited, but it is not essential. The supratrochlear nerve can be blocked by extending the supraorbital injection site medially with an additional 2 to 4 mL of solution.

Infraorbital Nerve

The infraorbital nerve can be blocked to provide anesthesia of the upper lip and skin of the cheek. The infraorbital notch lies on a line connecting the supraorbital and mental foramina and the pupil of the eye. The nerve can be blocked by advancing a 25-gauge, 3-cm needle laterally and cephalad toward the foramen from a point 1 cm inferior. A paresthesia is frequently elicited. When the needle tip is in the region of the foramen, 3 to 4 mL of solution is injected. It is not essential that the needle enter the foramen (see Fig. 52-26).

Mental Nerve

Blockade of the mental nerve as it exits the mental foramen provides anesthesia to the lower lip and chin. The mental foramen lies on a vertical line connecting the pupil of the eye with the

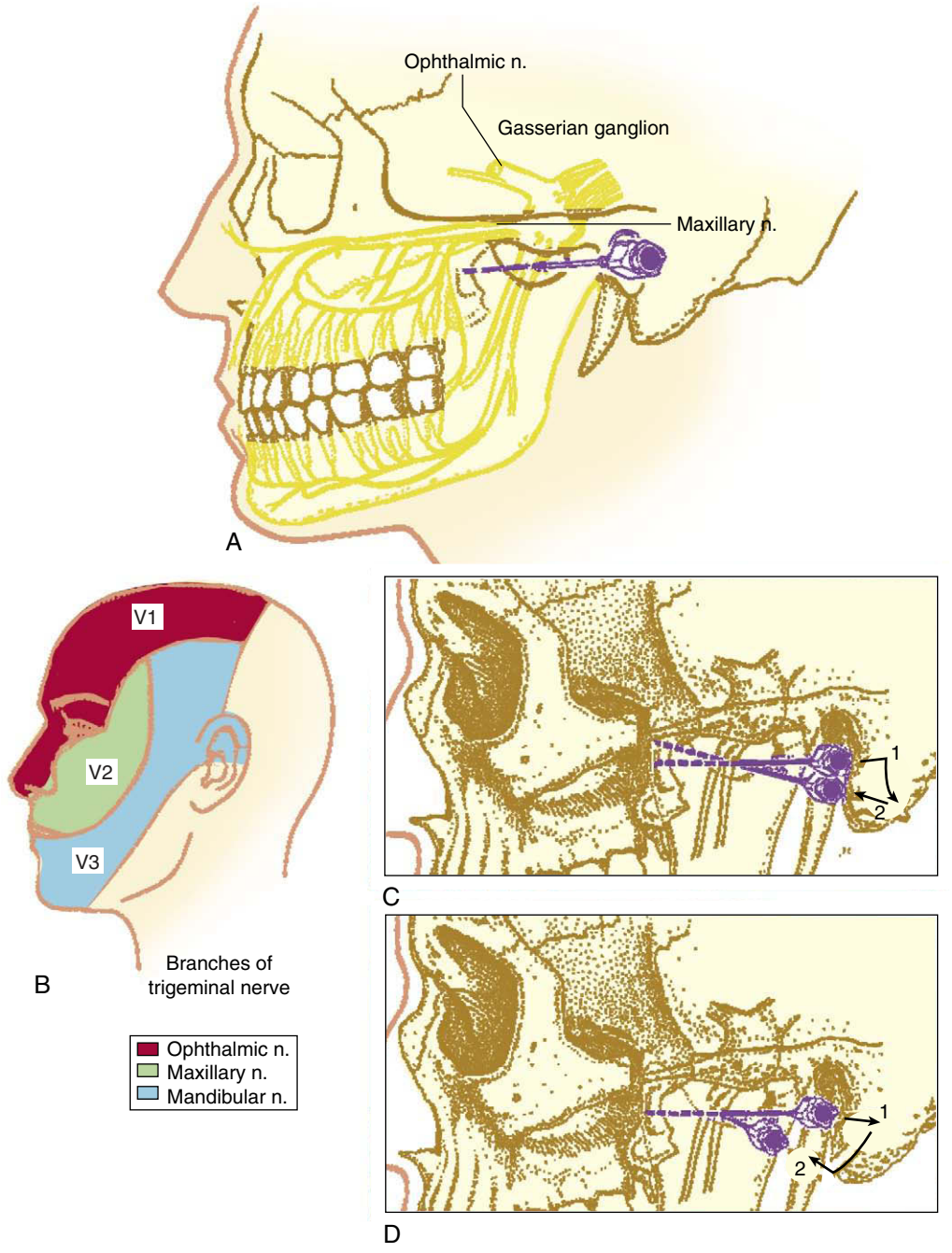

Figure 52-25 Anatomic landmarks and method of needle placement for maxillary and mandibular nerve blocks. **A,** The ophthalmic, maxillary, and mandibular nerves provide sensation to the eye and forehead, midface and upper jaw, and lower jaw, respectively. **B,** The mandibular and maxillary nerves can be blocked through the same needle entry site. **C,** A needle is inserted at the inferior edge of the coronoid notch perpendicular to the skin entry site, and after contacting the lateral pterygoid plate, it is withdrawn and redirected anteriorly and superiorly to walk off the plate (*arrows*). It is advanced approximately 0.5 cm into the pterygopalatine fossa. **D,** The mandibular nerve is blocked through the same entry site as the maxillary nerve and by the same method, except that the needle is withdrawn and redirected to walk off the posterior border of the pterygoid plate (*arrow*). When it is advanced to elicit paresthesia, the needle should not be inserted more than 0.5 cm past the plate.

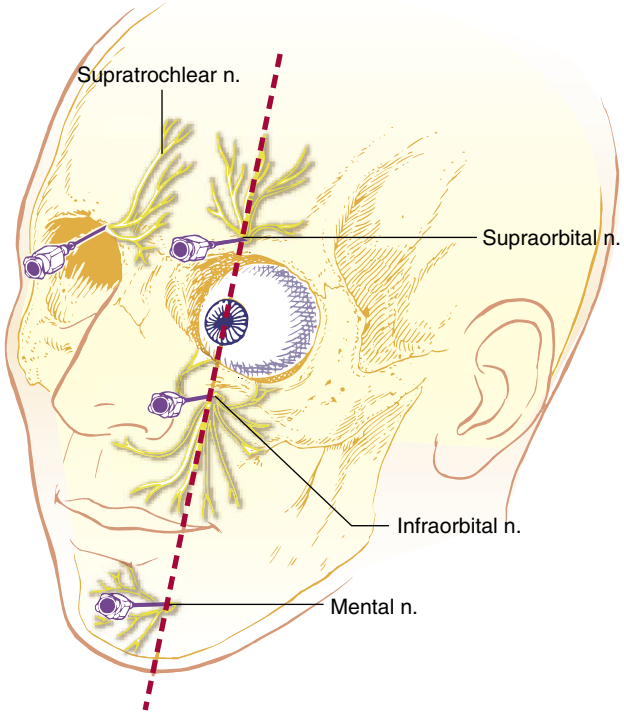

Figure 52-26 Blockade of the terminal sensory branches of the trigeminal nerve. A *vertical line* connects the supraorbital notch, infraorbital foramen, and mental foramen.

foramina of the peripheral nerves of V_1, V_2, and V_3. The foramen is palpated in the mandible, and a 25-gauge, 3-cm needle is inserted inferomedially. Infiltration of 2 to 4 mL of solution after elicitation of a paresthesia or in the region of the foramen results in anesthesia of the mental nerve (see Fig. 52-26).

Side Effects and Complications

Direct injection of the peripheral nerves within the bony foramina may result in nerve damage.

Cervical Plexus Blockade

The cervical plexus is derived from the C1, C2, C3, and C4 spinal nerves and supplies branches to the prevertebral muscles, strap muscles of the neck, and phrenic nerve. The deep cervical plexus supplies the musculature of the neck segmentally and the cutaneous sensation of the skin between the trigeminally innervated face and the T2 dermatome of the trunk. Blockade of the superficial cervical plexus results in anesthesia of only the cutaneous nerves.

Clinical Applications

Blockade of the cervical plexus is easy to perform and provides anesthesia for surgical procedures in the distribution of C2 to C4, including lymph node dissection, plastic repair, and carotid endarterectomy. The ability to monitor the awake patient's neurologic status continuously is an advantage of this anesthetic technique for the latter procedure and has resulted in an upsurge in popularity of this technique.[74] Bilateral blocks can be used for tracheostomy and thyroidectomy.

Technique

Superficial Cervical Plexus

The superficial cervical plexus is blocked at the midpoint of the posterior border of the sternocleidomastoid muscle. A skin wheal is raised at this point, and a 22-gauge, 4-cm needle is advanced while injecting 5 mL of solution along the posterior border and medial surface of the sternocleidomastoid muscle (Fig. 52-27). It is possible to block the accessory nerve with this injection, which results in temporary paralysis of the ipsilateral trapezius muscle.

Deep Cervical Plexus

The deep cervical plexus block is a paravertebral block of the C2 to C4 spinal nerves as they emerge from their foramina in the cervical vertebrae (Fig. 52-28). The traditional approach involves the use of three separate injections at C2, C3, and C4. The patient lies supine with the neck slightly extended and the head turned away from the side to be blocked. A line is drawn connecting the tip of the mastoid process and the Chassaignac tubercle (i.e., transverse process of C6); a second line is drawn 1 cm posterior to the first line. The C2 transverse process lies 1 to 2 cm caudad to the mastoid process, where it can usually be palpated. The C3 and C4 transverse processes lie at 1.5-cm intervals along the second line. After skin wheals are raised over the transverse processes of C2, C3, and C4, three 22-gauge, 5-cm needles are advanced perpendicular to the skin entry site at a slight caudad angulation. The transverse process is contacted at a depth of 1.5 to 3 cm. If a paresthesia is obtained, 3 to 4 mL of solution is injected after careful aspiration for blood and cerebrospinal fluid. If no paresthesia is elicited initially, the needle is walked along the transverse process in the anteroposterior plane until a paresthesia is obtained.

This block can also be performed with a single injection of 10 to 12 mL at the C4 transverse process.[75] Cephalad spread of the local anesthetic usually anesthetizes the C2 and C3 nerves. Cervical plexus anesthesia can also be observed after injection at the interscalene level for brachial plexus blockade. Maintenance

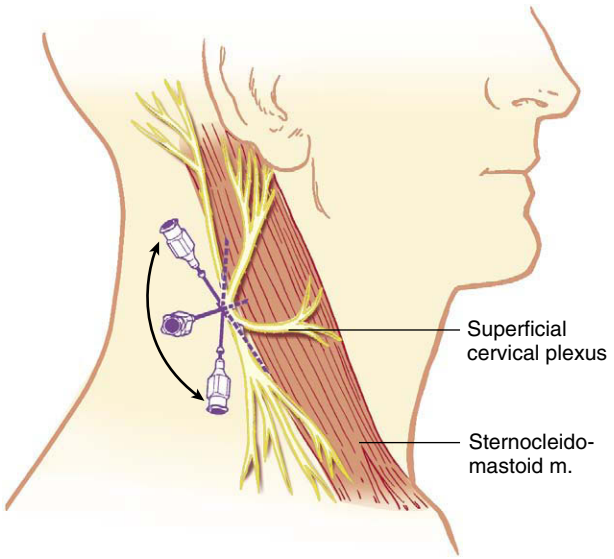

Figure 52-27 Anatomic landmarks and method of needle placement for a superficial cervical plexus block.

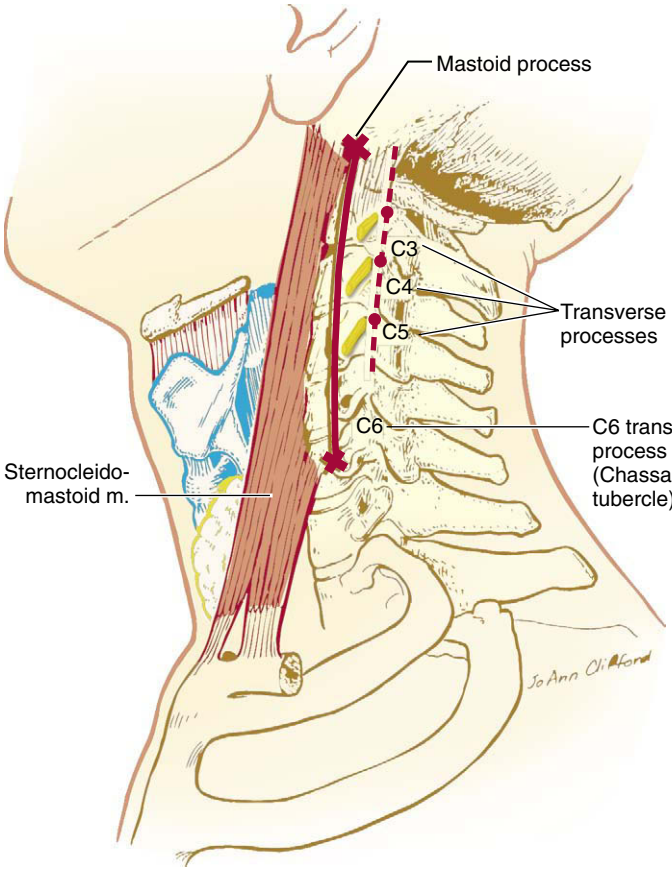

Figure 52-28 Anatomic landmarks and method of needle placement for deep cervical plexus blocks at C2, C3, and C4.

of distal pressure and a horizontal or slightly head-down position may facilitate the onset of cervical plexus blockade via the interscalene technique.

Side Effects and Complications

Although these blocks are technically straightforward, needle placement for a deep cervical block allows injection of local anesthetic in close proximity to a variety of neural and vascular structures. Reported complications and side effects include intravascular injection, blockade of the phrenic and superior laryngeal nerve, and spread of local anesthetic solution into the epidural and subarachnoid spaces.

Accessory Nerve Block

The accessory nerve (i.e., cranial nerve XI) is occasionally blocked to supplement the interscalene brachial plexus approach for shoulder procedures. Blockade of the accessory nerve results in motor paralysis of the trapezius muscle, thereby ensuring lack of patient movement during the surgical procedure. The nerve traverses the posterior triangle of the neck (bordered by the posterior border of the sternocleidomastoid muscle, middle third of the clavicle, and anterior border of the trapezius muscle) in a very superficial position after emerging from the substance of the sternocleidomastoid muscle at the junction of the superior and middle thirds of that muscle's posterior border. It can easily be blocked at that site by injecting 6 to 10 mL of local anesthetic. This nerve is often unintentionally anesthetized when a superficial cervical plexus block is performed.

Local Anesthesia of the Airway

Clinical Applications

Anesthesia of the airway can be used to facilitate diagnostic laryngoscopy and bronchoscopy and to allow comfortable placement of a tracheal tube in patients whose anatomy dictates an awake endotracheal intubation (also see Chapter 50). Block of the superior laryngeal nerves bilaterally, along with translaryngeal injection of local anesthetic, provides anesthesia of the airway from the infraglottic area to the epiglottis. Additional topical application of local anesthetic to the oral and nasal mucosa, along with appropriate sedation, provides satisfactory analgesia for endoscopic procedures.

Technique

Superior Laryngeal Nerve

The patient is placed supine with the neck extended. The hyoid bone is displaced laterally toward the side to be blocked, and a 25-gauge, 2.5-cm needle is walked off the greater cornu of the hyoid bone inferiorly and advanced 2 to 3 mm (Fig. 52-29). As the needle passes through the thyrohyoid membrane, a slight loss of resistance is felt, and 3 mL of local anesthetic solution is injected superficial and deep to this structure. The block is then repeated on the opposite side. This technique produces anesthesia from the inferior aspect of the epiglottis to the vocal cords.

Translaryngeal Block

A translaryngeal block is simple to perform and results in anesthesia of the trachea below the vocal cords. However, injection of local anesthetic usually stimulates the cough reflex, and this

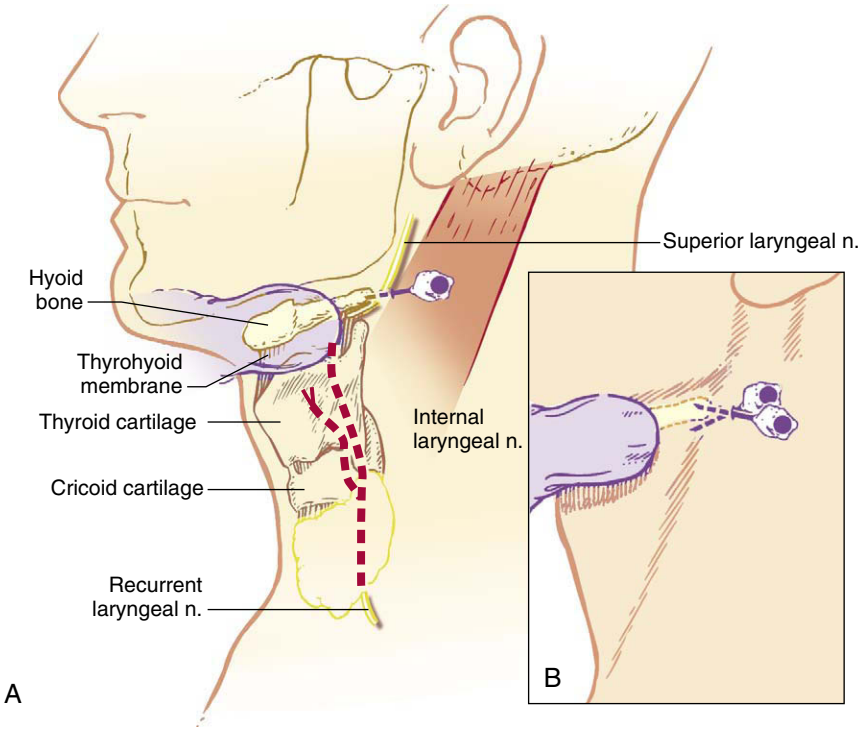

Figure 52-29 Needle placement for a translaryngeal nerve block.

block should be avoided in patients in whom coughing is undesirable.

With the patient in the supine position, the cricothyroid membrane is located, and a 20-gauge or smaller, 3- to 5-cm plastic catheter over a needle is introduced in the midline (Fig. 52-30). The inner steel cannula is withdrawn with the plastic catheter held firmly in place; aspiration of air confirms correct catheter placement. Between 3 and 5 mL of a 4% lidocaine solution is injected rapidly and usually results in a vigorous cough, which aids in spread of the solution within the trachea.

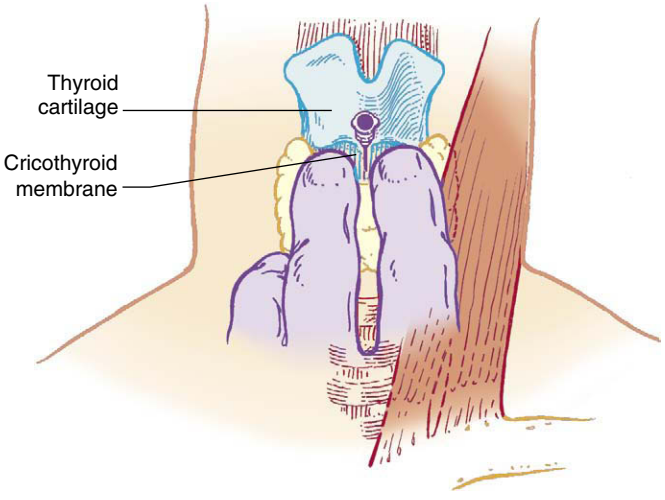

Figure 52-30 A, Anatomic landmarks and method of needle placement for a superior laryngeal nerve block. **B,** The needle is walked off the greater cornu of the hyoid bone inferiorly.

Intraoral Approach to a Glossopharyngeal Nerve Block

The glossopharyngeal nerve (i.e., cranial nerve IX) supplies sensation to the posterior third of the tongue, the pharynx, and the superior surface of the epiglottis. It can be blocked intraorally by injecting 5 mL of local anesthetic into the base of each posterior tonsillar pillar. An angled 22-gauge, 9-cm needle, which can be formed by bending the distal 1 cm of a spinal needle with its stylet removed, is used for this block. Visualization of the posterior pillar is facilitated by the gentle use of a no. 3 MacIntosh laryngoscope blade after topical anesthetic has been applied to the tongue. Careful aspiration before injection is mandatory because of proximity of the carotid artery.

Side Effects and Complications

The mucosa of the upper airway is well perfused, which results in rapid uptake of local anesthetics injected or applied topically in this area. Careful attention to total drug dosages, close observation of the patient, and compulsive aspiration before injection diminish the risk for local anesthetic toxicity. Other problems and complications are rare; however, caution should be used in a patient with a full stomach because these blocks abolish airway reflexes.

Retrobulbar and Peribulbar Blocks

Clinical Applications

Retrobulbar and peribulbar blocks and sub-Tenon blocks (see Chapter 75) provide anesthesia for corneal, anterior chamber, and lens procedures when combined with a block of the orbicularis oculi muscle. These blocks are often performed by the surgeon rather than the anesthesiologist, and they have gained increasing popularity for cataract surgery in the elderly outpatient population (also see Chapters 71 and 78). Retrobulbar and peribulbar

blocks provide equivalent akinesia and anesthesia.[76] The safety of these regional anesthetic techniques was documented by Backer and coworkers,[77] who demonstrated a zero incidence of reinfarction or death in 288 patients with a history of myocardial infarction undergoing local anesthesia or retrobulbar block, or both, for ophthalmologic procedures.

Technique

A *retrobulbar block* is performed with the patient supine and looking straight ahead. A 23-gauge, 3-cm blunted needle is inserted at the inferolateral border of the bony orbit and directed toward the apex of the orbit. A pop is often felt as the needle tip enters the orbital muscle cone, and 2 to 4 mL of solution is injected. With the *peribulbar approach*, the needle is inserted at the inferior orbital rim in the inferolateral quadrant and advanced along the floor of the globe to a depth of approximately 2.5 cm, and 5 mL of local anesthetic is injected. Many patients require a second injection to achieve complete akinesia and anesthesia. For the medial injection, the needle is inserted through the conjunctiva on the nasal side and directed straight back 2.5 cm, parallel to the orbital wall. An additional 5 mL of local anesthetic is injected. With both techniques, blockade of the facial nerve fibers that innervate the orbicularis oculi muscle is also performed to complete the anesthesia. Because these blocks may be uncomfortable for the patient, a small dose of a short-acting sedative, such as propofol, just before the injection prevents pain and patient movement.

Recently, a sub-Tenon (episcleral) block has been described.[78] The technique uses a blunt cannula inserted to contact the conjunctiva between the eyeball and the semilunaris fold. The needle is advanced in an anteroposterior direction, with the globe directed slightly medially by the needle until a "pop" is perceived, typically at a mean depth of 15 to 20 mm. This pop confirms the episcleral location of the needle tip. After an aspiration test, the local anesthetic is injected slowly.

Side Effects and Complications

Retrobulbar and peribulbar blocks are associated with several possible complications, including globe perforation, brainstem anesthesia, retrobulbar hemorrhage, optic nerve injury, local anesthetic toxicity, development of the oculocardiac reflex, and possible spinal anesthesia via the optic nerve sheath.[79] The risk of globe perforation is theoretically less with the peribulbar approach. The use of a blunt needle with the sub-Tenon block substantially decreases the incidence of complications when compared with the retrobulbar and peribulbar techniques.[78]

Stellate Ganglion Block

Clinical Applications

Blockade of the stellate ganglion is used primarily for the treatment of upper extremity sympathetic dystrophy and to increase blood flow to this area (Chapter 58).

Technique

The patient lies supine with the neck extended slightly. The most prominent cervical transverse process—the Chassaignac tubercle (C6)—is palpated between the sternocleidomastoid muscle and the trachea. The C6 tubercle is palpated between the index and middle fingers and the carotid artery is pushed laterally. A skin wheal is raised between the fingers over the tubercle, and a 22-gauge, 4-cm short-beveled needle with a 12-mL syringe attached is inserted in a perpendicular direction until the tip contacts the C6 transverse process (Fig. 52-31). The needle is then withdrawn 3 mm and fixed. After careful aspiration, 8 to 12 mL of local anesthetic solution is injected. Signs of a successful stellate ganglion block include Horner's syndrome, anhidrosis, injection of the conjunctiva, nasal stuffiness, vasodilation, and increased skin temperature.

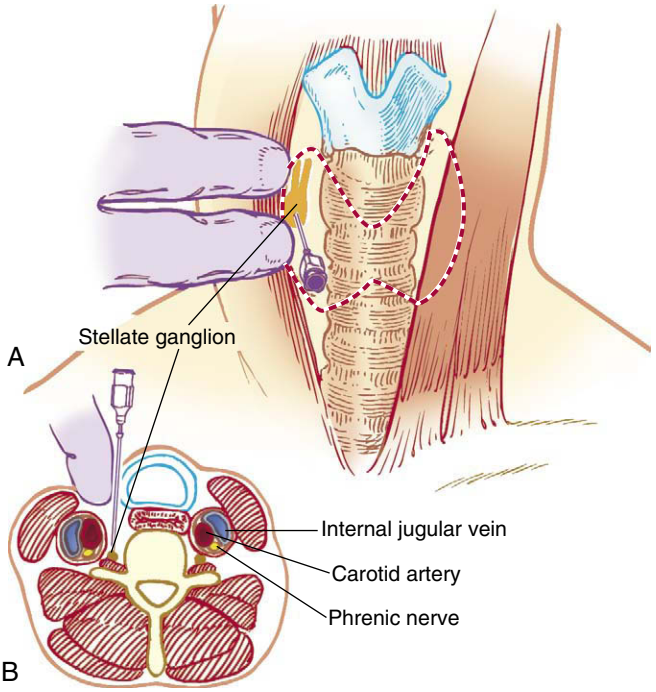

Figure 52-31 **A,** Anatomic landmarks and method of needle placement for a stellate ganglion block. **B,** Cross-sectional view of a stellate ganglion block.

Side Effects and Complications

Because of the proximity of several major neural and vascular structures to the site of needle insertion, side effects and complications can occur, including block of the brachial plexus and recurrent laryngeal nerves, hematoma formation, intravascular injection resulting in convulsions, and epidural and subarachnoid injection.[80]

Blocks of the Thorax and Abdomen

Intercostal Nerve Block and Interpleural Catheter Placement

The intercostal nerves are the primary rami of T1 through T11. T12 is technically a subcostal nerve and supplies branches to the ilioinguinal and iliohypogastric nerves. Fibers from T1 contribute to the brachial plexus; T2 and T3 provide a few fibers to formation of the intercostobrachial nerve, which supplies the skin of the

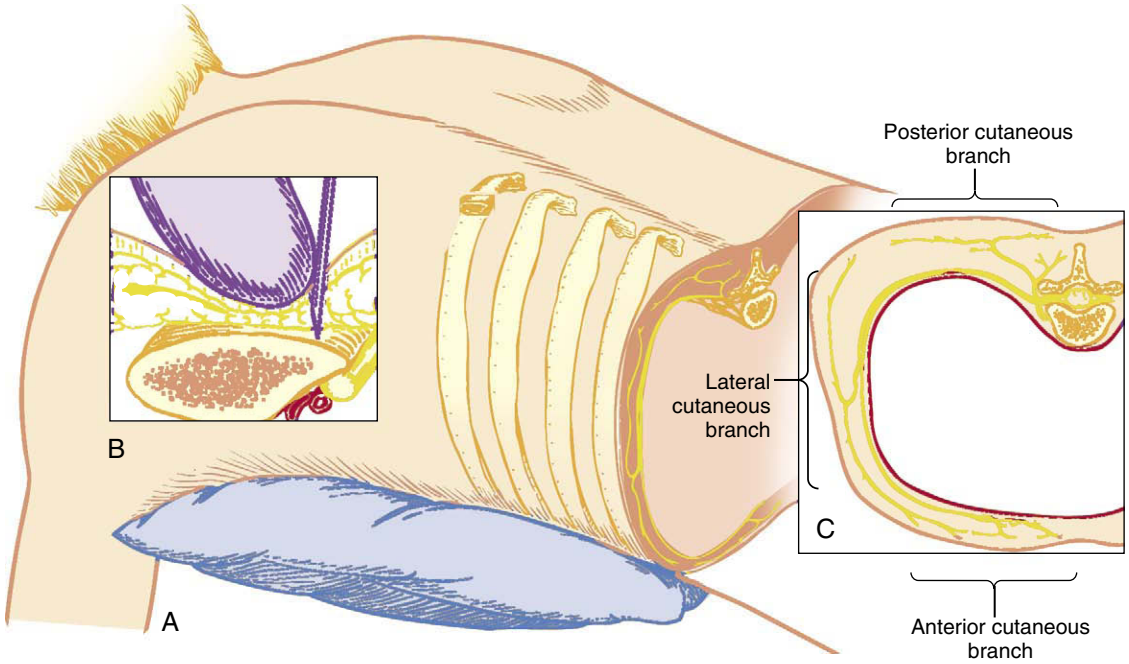

Figure 52-32 **A,** Patient positioning for an intercostal nerve block. **B,** The index finger displaces the skin up over the rib. The needle is inserted at the tip of the finger and rests on the rib. The needle is walked off the lower rib edge and inserted 3 to 5 mm. **C,** An intercostal nerve and its branches.

medial aspect of the upper part of the arm. Each intercostal nerve has four branches: the gray ramus communicans, which passes anterior to the sympathetic ganglion; the posterior cutaneous branch, which supplies the skin and muscle in the paravertebral area; the lateral cutaneous branch, which arises just anterior to the midaxillary line and sends subcutaneous branches anteriorly and posteriorly; and the anterior cutaneous branch, which is the termination of the nerve (Fig. 52-32C).

Medial to the posterior angles of the ribs, the intercostal nerves lie between the pleura and the internal intercostal fascia. At the posterior angle of the rib, the nerve lies in the costal groove accompanied by the intercostal vein and artery.

Clinical Applications

Few surgical procedures can be performed with an intercostal block alone, and application of these blocks in combination with other techniques has largely been supplanted by epidural blockade. However, in patients with contraindications to neuraxial blockade, these techniques can be used alone or combined with celiac plexus blocks and light general anesthesia to provide excellent surgical conditions for intra-abdominal procedures. In similar fashion, intrathoracic surgery can be accomplished with the use of intercostal and stellate ganglion blocks along with endotracheal sedation. Although surgical applications are possible, the majority of indications are for postoperative analgesia.

Interpleural catheter placement for management of postoperative pain was first described by Reiestad and Stromskag in 1986.[81] Enthusiasm for this technique has waxed and waned. Its mechanism of action is poorly understood, and reports of efficacy vary. Overall, the results with cholecystectomy have been most favorable.[82-85] The advantages of interpleural analgesia are more difficult to prove in patients undergoing thoracotomy, perhaps because of technical problems related to blood in the pleural space and chest tube drainage. More recent applications include analgesia after minimally invasive cardiopulmonary bypass surgery.[86]

Technique

Intercostal Block

The intercostal nerve can be readily blocked at the angle of the rib just lateral to the sacrospinalis muscle group. The patient is placed in the prone position with a pillow under the abdomen to reduce the lumbar curve (see Fig. 52-32A). A line is drawn along the posterior vertebral spines. Nearly parallel lines are drawn along the posterior angles of the rib, which can be palpated 6 to 8 cm from the midline. These lines angle medially at the upper levels to prevent overlying of the scapula. The inferior edge of each rib is palpated and marked on a line intersecting the posterior angle of the rib. After appropriate skin preparation, skin wheals are raised at each of these points. A 22-gauge, short-beveled 4-cm needle is attached to a 10-mL syringe. Beginning at the lowest rib, the index finger of the left hand displaces the skin up over the patient's rib. The needle is inserted at the tip of the finger until it rests on the rib. The fingers of the left hand are shifted to grasp the needle hub firmly. The left hand then walks the needle 3 to 5 mm off the lower rib edge, where 3 to 5 mL of local anesthetic is injected (see Fig. 52-32B). This process is repeated at each rib. Appropriate intravenous sedation to provide analgesia and some degree of amnesia is desirable for the patient's comfort.

Alternatively, an intercostal block can be performed in a supine patient at the midaxillary line. Theoretically, the lateral cutaneous branch of the nerve can be missed, but CT studies show that injected solutions spread several centimeters along the

costal groove.[68] Further injection of 1 to 2 mL of solution as the needle is withdrawn blocks the subcutaneous branches.

Interpleural Catheter

The technique for interpleural catheter placement is quite simple and can be performed with the patient in a lateral (and slightly oblique) or sitting position. The sixth or seventh intercostal space is identified. The needle is inserted about 10 cm lateral to the posterior midline, and an epidural needle tip is advanced until it rests on the cephalad edge of the rib below the intercostal space to be entered. A glass syringe filled with saline or air is then attached to the needle, and the unit is advanced slowly over the superior edge of the rib. When the tip of the needle enters the parietal pleura, the solution in the syringe is drawn into the chest cavity because of the negative intrathoracic pressure. This effect can be observed in mechanically and in spontaneously ventilating patients, but it is accentuated in the latter group.

The catheter is then inserted approximately 5 to 8 cm into the interpleural space and secured on the chest wall. During needle positioning and catheter placement, care must be taken to minimize entrainment of air through the needle. Lung parenchymal damage can occur with loss-of-resistance techniques or insertion of excessive lengths of catheter.

Side Effects and Complications

The major complication feared with intercostal blockade is pneumothorax. The actual incidence, however, was as low as 0.07% in a large series performed by anesthesiologists at all levels of training. Routine postoperative chest radiographs showed a 0.42% incidence of nonsymptomatic pneumothorax.[87] If this unusual complication occurs, treatment is usually limited to observation, administration of oxygen, or needle aspiration. Rarely, chest tube drainage is required when these treatments are unsuccessful.

A risk of systemic local anesthetic toxicity is present with multiple intercostal blocks because of the large volumes and rapid absorption of the solutions. Use of epinephrine has been shown to decrease blood levels. Patients should be monitored and observed carefully during the block and for at least 20 to 30 minutes afterward. An interpleural block should not be performed in patients with pleural fibrosis or inflammation, pleural effusion, lung parenchymal disease associated with pleural disease, or bleeding diatheses. Pleural disease can result in poor spread of local anesthetic solutions or rapid uptake in the case of inflammation. Patients with severe pulmonary disease who rely on their intercostal muscles may exhibit respiratory decompensation after bilateral intercostal blockade.[88]

Celiac Plexus Block

Clinical Applications

A celiac plexus block can be combined with an intercostal block to provide anesthesia for intra-abdominal surgery. Because it results in blockade of the autonomic nervous system, this block may help reduce stress and endocrine responses to surgery.

Anatomy and Technique

The celiac plexus contains visceral afferent and efferent fibers derived from T5 to T12 by means of the greater, lesser, and least splanchnic nerves. The plexus has no somatic fibers and is composed of a number of ganglia and nerve fibers. It innervates most of the abdominal viscera. Knowledge of the surrounding structures is important for correct needle placement. The plexus lies in close relation to the L1 vertebra. The vena cava lies anteriorly to the right, and on the left anteriorly is the aorta. The kidneys lie laterally, with the pancreas anterior. The number of ganglia varies from one to five, and each ganglion is 0.5 to 4.5 cm in diameter. Left-sided ganglia are usually lower than those on the right.

Bony surface landmarks can be used reliably for needle placement. With the patient in the prone position and a pillow beneath the abdomen, lines are drawn connecting the spine of T12 with points 7 to 8 cm laterally at the lower edges of the 12th ribs. These lines form a flattened isosceles triangle, the equal sides of which serve as directional guides for the needles (Fig. 52-33B). A 20-gauge, 10- to 15-cm needle is inserted on the left side through a skin wheal at a 45-degree angle toward the body of T12 or L1. Bone contact should be made at an average depth of 7 to 9 cm. The needle is then withdrawn and reinserted to allow the tip to slide off the vertebral body anterolaterally. The needle is advanced 1.5 to 2 cm past this point; aortic pulsations can be felt as they are transmitted along the needle when it is correctly placed (see Fig. 52-33). After this depth is ascertained, the right-sided needle is inserted in similar fashion to a depth of 1.0 to 1.5 cm farther (see Fig. 52-33A). When the needles are in position, observation for leakage of blood, urine, or cerebrospinal fluid is made before careful aspiration. A 3- to 5-mL test dose of local anesthetic is given before injection of 20 to 25 mL of solution through each needle.

Side Effects and Complications

Side effects associated with celiac plexus blockade include hypotension; spinal, epidural, or intravascular injection; pneumothorax; puncture of viscera, such as the kidney, ureter, or gut; and retroperitoneal hematoma.

Paravertebral Block

Clinical Applications

This block may be used to provide anesthesia or analgesia, or both, to patients undergoing thoracic, abdominal, or pelvic procedures, as well as surgery on the breast. Bilateral and continuous applications have been described.[89,90] In patients undergoing thoracotomy, a thoracic paravertebral block provides analgesia comparable to epidural techniques, but with fewer side effects.[91] A paravertebral block may be useful in the diagnosis and treatment of certain chronic pain disorders, including post-thoracotomy and postmastectomy pain.

Technique

Thoracic Paravertebral Block

Thoracic paravertebral blockade occurs at the point where the spinal nerves emerge from the vertebral foramina. This results in somatic and sympathetic blockade of multiple contiguous thoracic dermatomes above and below the injection site.

A thoracic paravertebral block can be performed with the patient in the sitting, lateral, or prone position; the sitting position

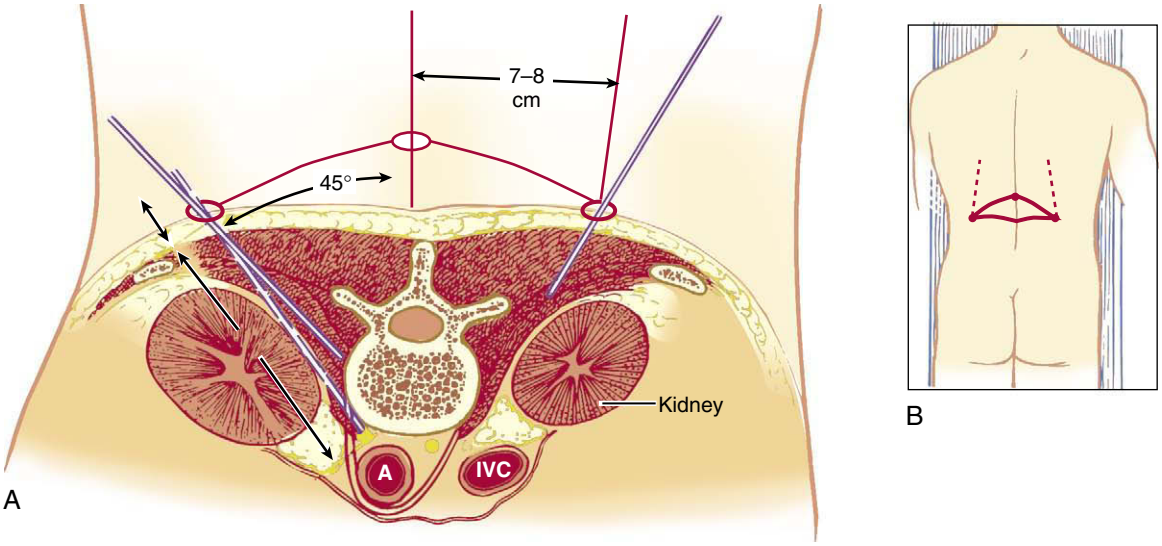

Figure 52-33 **A,** For a celiac plexus block, the needle is inserted at a 45-degree angle toward the body of L1. The tip slides off the vertebral body anterolaterally and is advanced 1.5 to 2 cm. **B,** Patient positioning and surface landmarks for a celiac plexus block. A, aorta; IVC, inferior vena cava.

allows easy identification of landmarks. The thoracic spinous processes are identified, and the needle is inserted 2.5 to 3 cm lateral to the most cephalad aspect of the spinous process and advanced perpendicular to the skin in all planes to contact the transverse process of the vertebra below, typically at a depth of 2 to 4 cm. After the transverse process is identified, traditionally the needle is redirected cephalad and gradually advanced until loss of resistance is felt 1 to 1.5 cm past the superior edge. However, walking the needle caudad may decrease the risk for pneumothorax.[90]

Although spread of local anesthetic is variable, a single injection of 15 mL produces unilateral somatic blockade over four or five dermatomes; there is a tendency for caudad (versus cephalad) spread.[90] To achieve greater spread, 3 to 4 mL of local anesthetic may be injected at each segment.[92]

Lumbar Paravertebral Block

Lumbar nerves exit the vertebral foramina inferior to the caudad edge of the transverse process. Each nerve divides into anterior and posterior branches; the anterior branches of L1 through L4 (with a contribution from T12) form the lumbar plexus.

The patient is placed in the prone position as described for intercostal blockade. Lines are drawn across the cephalad edges of the lumbar vertebral spinous processes. These lines lie opposite the caudad edges of the homologous transverse processes (see Fig. 52-14A). A skin wheal is raised 3 cm lateral to the midline, and a 20-gauge, 8-cm needle is advanced perpendicularly until it contacts the transverse process at a depth of 3 to 5 cm. The needle is then redirected to walk off the caudad edge of the transverse process. At 1 to 2 cm (the thickness of the transverse process) beyond this point, 6 to 10 mL of local anesthetic is injected (see Fig. 52-14B). Elicitation of a paresthesia or the use of a nerve stimulator is helpful in confirming correct needle placement.

Side Effects and Complications

Because of proximity of the neuraxis, epidural or subarachnoid injection of local anesthetic is a risk. Intravascular injection through the lumbar vessels, vena cava, or aorta is possible. Pleural puncture and pneumothorax have occurred at frequencies of 1.1% and 0.5%, respectively.[90]

Continuous Catheter Techniques

Advantages cited for continuous nerve blockade include prolongation of surgical anesthesia, decreased risk for toxicity because of lower incremental doses, and postoperative pain relief and sympathectomy. Catheter placement using over-the-needle and through-the-needle methods have been described. Advances in equipment technology, including the development of stimulating needles and catheters and portable pumps allowing infusion of local anesthetic after hospital dismissal, have increased the success rate and popularity of continuous peripheral blockade (Fig. 52-34).[93,94] Although concern regarding accurate catheter placement and maintenance still exists, the use of stimulating catheters and radiographic confirmation may further improve the functionality of this method.[95] Overall, continuous peripheral nerve blockade provides analgesia superior to that of conventional opioid therapy. Minor technical problems, such as catheter kinking, displacement, or leakage and bacterial colonization, are frequent, with no adverse clinical consequences in the large majority of cases. However, major neurologic and infectious adverse events are rare.[96]

Methods of providing continuous brachial plexus anesthesia have been described since at least the 1940s and frequently offer ingenious solutions for placement and securing of the needle or catheter. This technique is especially applicable to patients undergoing upper extremity or digit replantation or total-shoulder or total-elbow arthroplasty and in patients with reflex sympathetic dystrophies, in whom prolonged pain relief and sympathectomy are advantageous.[97]

Continuous lower extremity techniques were also described decades ago but remained underused in relation to continuous upper extremity and neuraxial approaches until recently. Reliable, improved success rates and the risk of spinal hematoma after

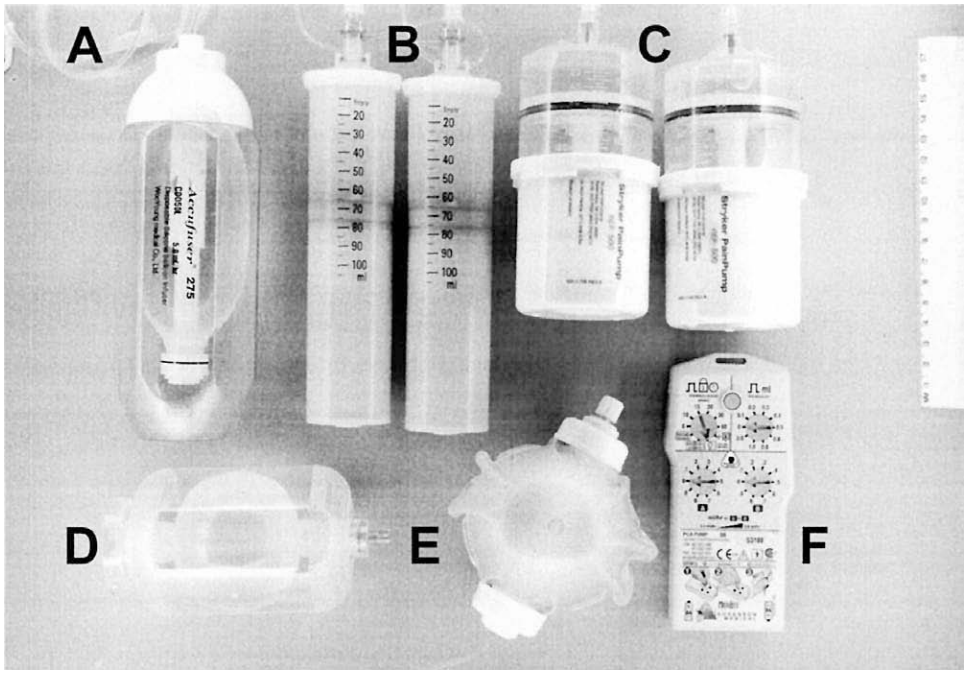

Figure 52-34 Portable infusion pumps. **A,** Accufuser (McKinley Medical, Wheat Ridge, CO). **B,** Sgarlato (Sgarlato Labs, Los Gatos, CA). **C,** Stryker PainPump (Stryker Instruments, Kalamazoo, MI). **D,** MedFlo II (MPS Acacia, Brea, CA). **E,** C-Bloc (I-Flow Corp., Lake Forest, CA). **F,** Microject PCA (Sorenson Medical, West Jordan, UT). *(From Ilfeld BM, Morey TE, Enneking FK: The delivery rate accuracy of portable infusion pumps used for continuous regional analgesia. Anesth Analg 95:1331, 2002.)*

neuraxial techniques led clinicians to again consider continuous lower extremity blocks. Contemporary applications for continuous psoas compartment and sciatic, femoral, and popliteal fossa blockade have been reported.[96] When compared with conventional systemic and neuraxial analgesic methods, continuous lower extremity blocks provide superior analgesia with fewer side effects, improve perioperative outcomes, and accelerate hospital dismissal after major joint replacement.[98,99]

Choice of Local Anesthetic

The choice of local anesthetic for a peripheral nerve block obviously depends to some degree on the duration of the surgical procedure, although other factors are also important (see Chapter 30). Prolonged blockade for up to 24 hours often occurs with long-acting agents such as bupivacaine or ropivacaine. Although such blockade results in superb postoperative pain relief for an inpatient, it may be undesirable for an ambulatory patient because of the possible risk of nerve or tissue injury in a partially blocked limb. A short- or medium-acting agent, such as lidocaine or mepivacaine, may be more appropriate in the outpatient setting. Whatever drug is chosen, the total dosage should be calculated for each patient and be kept within acceptable safe limits (see Chapter 30).

The highest concentrations of local anesthetic drugs are not appropriate for peripheral neural blockade; therefore, 0.75% bupivacaine or ropivacaine, 2% lidocaine, 2% mepivacaine, and 3% 2-chloroprocaine are not recommended. Conversely, the lowest concentrations of the same agents (i.e., 0.25% bupivacaine or ropivacaine and 0.5% mepivacaine or lidocaine) may not provide complete motor blockade.

Vasoconstrictors, usually epinephrine, can be added to the chosen local anesthetic to improve the onset of action, to decrease drug uptake, and to prolong action. A concentration of 1:200,000 epinephrine is usually recommended. Ideally, the epinephrine should be added to the local anesthetic at the time that the block is to be performed. Commercially prepared solutions with epinephrine have a lower pH than those in which it is freshly added, which results in a higher percentage of ionized drug molecules. These ionized molecules do not readily cross the neural membrane, thereby delaying the onset of drug action after injection. Epinephrine should not be added to the local anesthetic for blocks of the digits or penis because tissue ischemia may result. Various other additives, including clonidine, opioids, and ketamine, have been reported to enhance or prolong local anesthetic peripheral nerve blockade.[7]

Neurologic Complications

Nerve injury is a recognized complication of peripheral regional techniques. In a combined series involving more than 250,000 regional anesthetics, the frequency of neurologic complications after peripheral blockade was less than that seen with neuraxial techniques, and peripheral blockade was associated with pain on needle placement or injection of local anesthetic.[65,100] Risk factors contributing to neurologic deficit after regional anesthesia include neural ischemia, traumatic injury to nerves during needle or catheter placement, infection, and inappropriate selection of the local

anesthetic solution. However, postoperative neurologic injury as a result of pressure from improper patient positioning, tightly applied casts or surgical dressings, and surgical trauma is often attributed to the regional anesthetic. Patient factors such as body habitus or preexisting neurologic dysfunction may also contribute.

Although needle gauge, type (i.e., short versus long bevel), and bevel configuration may influence the degree of nerve injury after peripheral nerve blockade, the findings are conflicting and there are no confirmatory human studies. Theoretically, localization of neural structures with a nerve stimulator would allow a high success rate without increasing the risk for neurologic complications, but this has not been established. Serious neurologic injury has been reported after uneventful brachial plexus blockade with use of a nerve stimulator technique.[23] Likewise, prolonged exposure or high concentrations of local anesthetic solutions may also result in permanent neurologic deficits. In laboratory models, the addition of epinephrine increases the neurotoxicity of local anesthetic solutions and decreases nerve blood flow. However, the clinical relevance of these findings in humans remains unclear. Nerve damage caused by traumatic needle placement, local anesthetic neurotoxicity, and neural ischemia during performance of a regional block may worsen the neurologic outcome in the presence of an additional patient factor or surgical injury.[7,47]

Prevention of neurologic complications begins during the preoperative visit with a careful evaluation of the patient's medical history and appropriate preoperative discussion of the risks and benefits of the available anesthetic techniques. It is imperative that all preoperative neurologic deficits are documented to allow early diagnosis of new or worsening neurologic dysfunction postoperatively. Postoperative sensory or motor deficits must also be distinguished from residual (prolonged) local anesthetic effect. Imaging techniques such as CT and MRI are useful in identifying infectious processes and expanding hematomas. Although most neurologic complications resolve completely within several days or weeks, significant neural injuries necessitate neurologic consultation to document the degree of involvement and coordinate further workup. Neurophysiologic testing, such as nerve conduction studies, evoked potentials, and electromyography, are often useful in establishing a diagnosis and prognosis.

Summary

It is possible to perform all surgical procedures while the patient is under general anesthesia, but the addition of peripheral nerve block techniques to the anesthesiologist's armamentarium adds flexibility and skills that benefit the patient intraoperatively and postoperatively. Successfully mastering these techniques and applying them to the appropriate clinical situations add valuable options to anesthetic care. For the anesthesiologist, knowledge of regional anesthesia is essential for the diagnosis and treatment of acute and chronic pain syndromes (see Chapters 58 and 87).

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Andrew T. Gray

53 Ultrasound Guidance for Regional Anesthesia

Key Points

1. Ultrasound imaging elucidates the structure of peripheral nerves and adjacent anatomy for regional block.
2. Ultrasound also provides real-time imaging for needle tip placement and drug injection.
3. Peripheral nerves have a characteristic "honeycomb" echotexture formed by their connective tissue and nerve fibers. Sliding the ultrasound transducer along the known course of a nerve with it viewed in short axis is often the best way of visualizing fascicles to confirm nerve identity. With training, operators will learn to naturally tilt the transducer to enhance the received echoes from a nerve.
4. Successful local anesthetic injections clarify the border of the nerve and track along the nerve path and its branches. Anatomic variation in nerve location, which is a potential source of block failure, can be directly visualized.
5. Ultrasound imaging can prevent and detect critical events such as intravascular or intraneural injection, which may improve safety during regional anesthesia procedures.
6. The use of ultrasound imaging has become a common adjunct for regional block anesthetics techniques.

Ultrasound allows direct visualization of peripheral nerves, the block needle, and local anesthetic distribution.[1] This imaging modality has proven highly useful to guide targeted drug injections and catheter placement. The last several years have witnessed a tremendous increase in the use of ultrasound guidance for regional anesthesia. General principles of ultrasound imaging for regional block are presented in this chapter with specific examples of block procedures.

Principles of Ultrasound Imaging

Ultrasound is sound with frequency above the audible range (>20,000 cycles/sec). Frequencies used in clinical imaging are in the 1- to 20-MHz range. Ultrasound waves have velocity of 1540 msec in soft tissue (13 µsec/cm tissue back and forth for the total fly-back time of received echoes).

The velocity of sound is determined by the bulk modulus and density of the medium (Table 53-1). Therefore, the speed of sound in a given medium is essentially independent of frequency. The product of the frequency and wavelength of sound waves is the wave velocity (velocity = frequency × wavelength). For example, the wavelength of a 10-MHz sound wave in soft tissue is 0.154 mm. The attenuation of ultrasound in soft tissue is approximately 0.75 dB/(cm-MHz). This attenuation is primarily from absorption. Other tissues absorb sound waves less (e.g., fluids) or more (e.g., bone) than soft tissue. A reflective wave is generated at the interface of two media with different acoustic impedances. The acoustic impedance is the product of the density and velocity. The reflection coefficient $R = (Z1 - Z2)/(Z1 + Z2)$, where Z1 and Z2 are the acoustic impedances of the two media. If $Z1 = Z2$ there is no reflected wave.

The first imaging modality used with ultrasound was A-mode echo (Amplitude, displayed with an oscilloscope). Today, most imaging is performed with B-mode echo (Brightness). This modality uses postprocessing maps to assign gray-scale values to pixels from the received echo amplitudes. Frame rates for 2D imaging are approximately 30/sec. Ambient lighting has a large effect on visual discrimination, so dim lighting without glare is especially useful for imaging low-contrast targets such as nerves. Another useful imaging modality is M-mode echo (Motion). The sampling rates for M-mode are very high (around 1800/sec, with high resolution in time but only one spatial dimension).

There are no independently confirmed adverse biologic effects of diagnostic ultrasound. Although absorption of sound waves can contribute to heating, this effect is small in comparison to changes in body temperature in daily living (e.g., diurnal variation, exercise, sunbathing, fever). Bone has a high absorption coefficient; therefore, the largest thermal effects are seen at the bone–soft tissue interfaces. The propensity of ultrasound to cause heating is estimated by the thermal index. The bone thermal index (TIB) and soft tissue thermal index (TIS) track maximum temperature increases in those respective tissues. Cavitation is

Table 53-1 Acoustic Properties of Tissues and Materials

Substance	Attenuation (dB/[cm-MHz])	Impedance (Mrayls)	Speed of Sound (msec)	References
Water	0.002	1.48	1490	Ziskin, 1993[82] Martin, 2001[83]
Blood	0.18	1.61	1570	Ziskin, 1993[82] Pierce, 1982[84]
Soft tissue	0.75	1.65	1540	Ziskin, 1993[82] Goldstein, 2002[85]
Air	12	0.0001	330	Ziskin, 1993[82] Pierce, 1982[84]
Bone	20	8.00	4080	Ziskin, 1993[82] Pierce, 1982[84]
Metal	0.2	47	5850	Gawdzinska, 2005[86] Smith, 2002[87]

when dissolved gases become microbubbles. This can result in extravasation of blood cells in the lung. The mechanical index is probably the best index to indicate likelihood of this effect. Pulse-echo ultrasound does not produce cavitation because the pulses are very short (only sufficiently intense continuous-wave ultrasound will produce cavitation).

Limits of Ultrasound Resolution

Ultrasound imaging is limited in resolution because the acoustic pulse duration and beam width are finite.[2] Axial resolution along the beam depends on the spatial pulse length (SPL). The axial resolution is at best SPL/2, where SPL = nλ, with n the number of cycles per pulse and λ the wavelength. Axial resolution is essentially independent of depth. Lateral resolution depends on depth because the beam width changes with depth. The beam width also depends on the insonation frequency and focus. The effective beam cross section increases with transmission output or receiver gain. An increase in receiver gain causes the line widths to increase because the receiver now detects echoes at more lateral positions from the central ray.[3] The out-of-plane beam width (slice thickness or elevational resolution) can be estimated using a diagonally placed diffuse scattering plane.[4] These slice thickness estimates are not receiver gain dependent within a well-adjusted range because scattering plane echoes are substantially higher than background sound.

In clinical imaging the lateral and elevational resolution will be governed by local image contrast. In general, lateral and elevational resolution are worse than axial resolution.

Spatial Compound Imaging

Spatial compound imaging combines multiple lines of insonation within a planar scan to produce a single image (Fig. 53-1). The ultrasound beam in each frame of the scan sequence is steered by a different, predetermined angle (typically within 20 degrees from the perpendicular). This sonography reduces speckle (the granular appearance from scattering). Because the displayed image is acquired from multiple angles of insonation, anisotropic effects in musculoskeletal imaging will be reduced (see later).[5] Spatial compounding reduces acoustic shadows following a strong reflector (e.g., bone).[6] Another advantage for regional block is that definition of tissue planes and detection of nerve borders are improved.

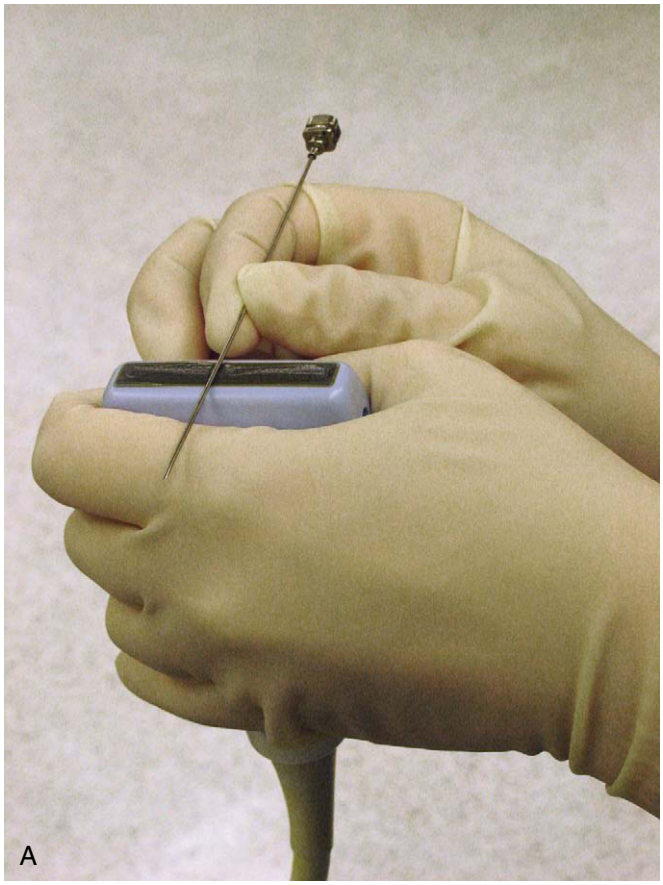
In the systems that have been tested, compound imaging improves needle tip visibility over a limited range of needle angles (<30 degrees).[7] Algorithms for beam steering are being developed to specifically enhance needle tip visibility.[8] Compounding imaging can result in lower frame rates and image blurring, which can be a disadvantage for some applications where temporal resolution related to tissue or transducer motion is important.

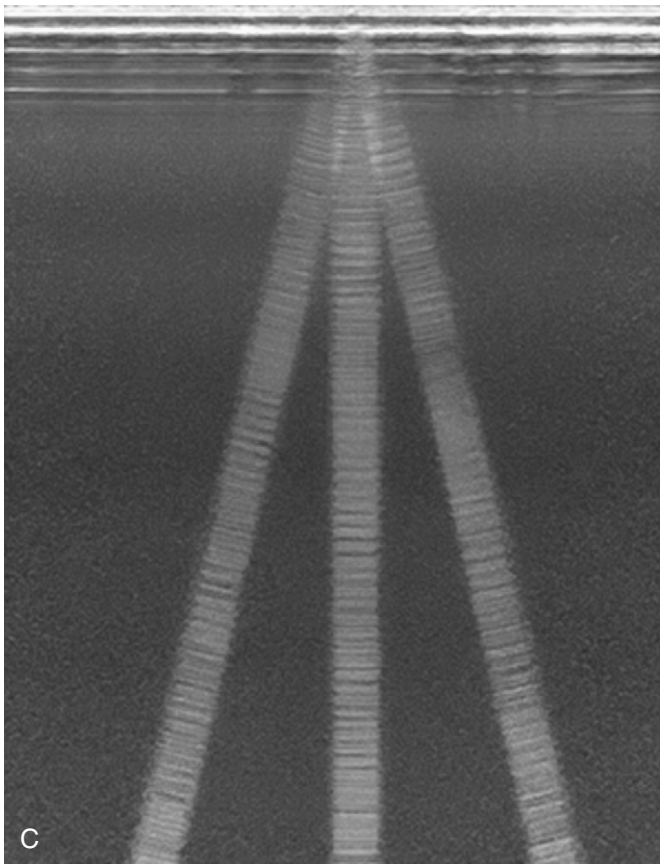
The linear array test tool is a metal rod (e.g., the solid metal stylet of a 17-gauge needle) that functions as a low-attenuating, reverberating structure in the path of the ultrasound beam.[9] A thin layer of gel is used so that only a single element acoustically couples to the rod (see Fig. 53-1). The size of contact between rod, transducer, and gel determines the extent of acoustic coupling. Actual test tool images will contain a broad line (or several lines with spatial compounding) whose width equals the transmit/receive aperture (typically several elements of a multi-element array). High overall receiver gain is necessary to obtain adequate images. Linear array test tools can be used to estimate the angles subtended by the ultrasound beam. Nonfunctioning elements of a linear or curvilinear array also can be detected. If the scanning surface is damaged, do not use it because of the potential for high-voltage injury.

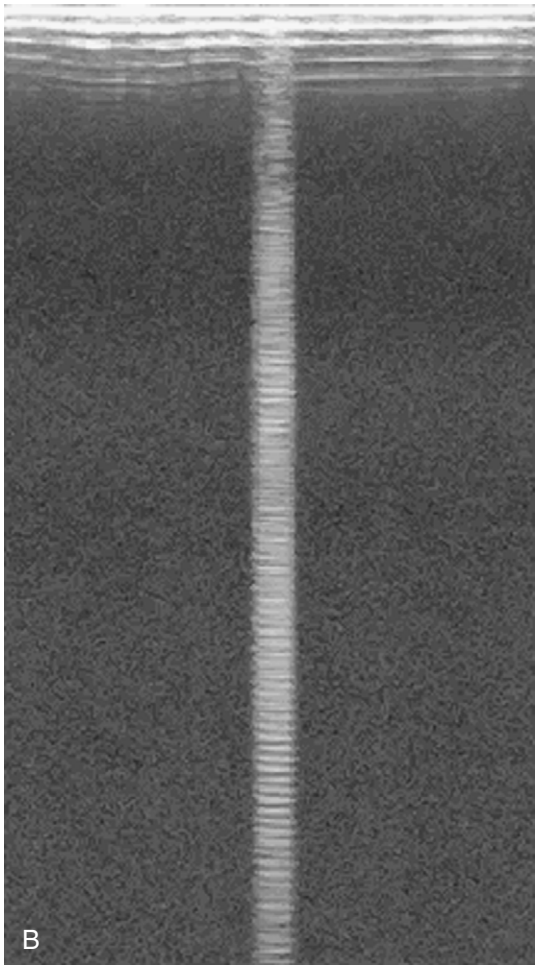
The Doppler Shift

The Doppler shift occurs when a wave source and receiver are moving relative to each other. This produces a change in frequency such that the frequencies of the transmitted and reflected sound waves are not the same. When a wave source and receiver are moving toward each other, the observed frequency is greater than the source frequency (and when moving away, the observed frequency is lower). The change in frequency is related to the velocity of moving reflectors and the angle of insonation. Red blood cells are the primary reflectors that produce Doppler shifts in clinical medicine.

There are different modes of Doppler ultrasound. Traditional color Doppler encodes pseudocolor based on mean-frequency shifts to provide directional velocity information (blue color indicates flow away from the transducer, whereas red color indicates flow toward the transducer by convention). More recently, a more sensitive Doppler technology has been developed that encodes color based on integration of the Doppler power spectrum.[10] Power Doppler is less angle dependent and not subject to aliasing. The disadvantages are that no directional information is provided and there is high motion sensitivity (flash artifact). Both Doppler modes are useful for detecting blood vessels. Small longitudinal vessels within the epineurium (lines) or microvasculature within nerves (spots) can occasionally be detected with color Doppler in normal subjects.[11]







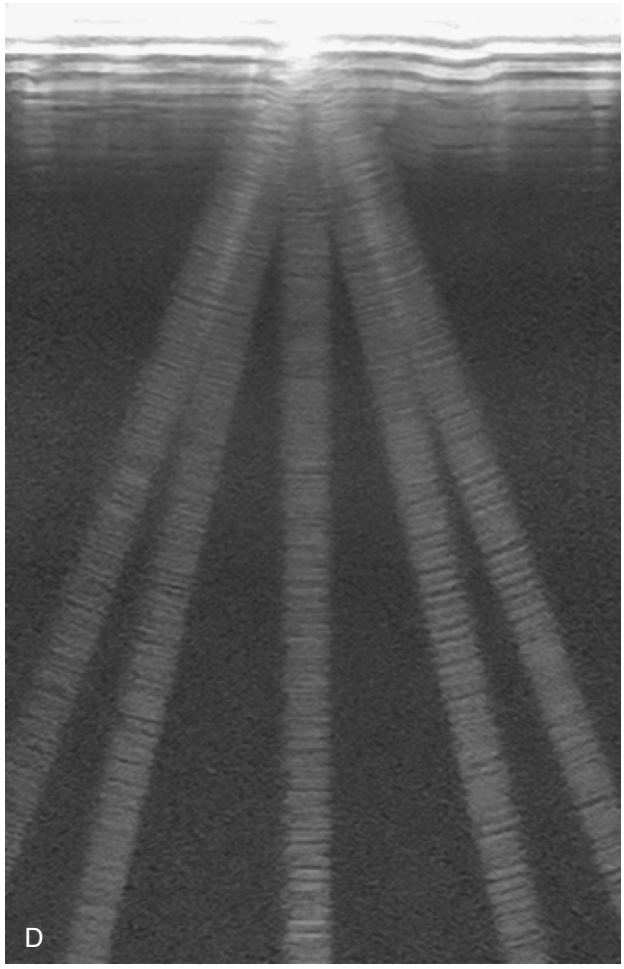


Figure 53-1 Spatial compound imaging. Some forms of ultrasound imaging utilize multiple lines of sight by electronically steering the beam to different angles. These sonograms were obtained by placing a linear array test tool (the solid metal stylet of a 17-gauge epidural needle) over the active face of the transducer to isolate a single element. **A,** External photograph of the linear array test tool applied to the active face of the ultrasound transducer. **B,** Single beam imaging. **C,** Three lines of sight are used to form a compound image (narrow range of angles). **D,** Five lines of sight are used to form a compound image (broad range of angles). Note that the test tool images do not display the beam itself but rather the transmit/receive apertures.

Ultrasound Transducers and Manipulation

Ultrasound transducers consist of piezoelectric crystals that emit and receive high-frequency sound waves by interconverting electrical and mechanical energy. Linear-array transducers have a high scan line density and therefore produce the best image quality. These transducers, in particular the high-frequency broad band linear probes, have proven the most useful for nerve imaging. Images from linear arrays are displayed in rectangular format. When a linear transducer is needed but the space at the block site is small, a compact linear ("hockey stick") transducer can be very useful. Peripheral nerves can be viewed in short axis or long axis (Fig. 53-2).

Curvilinear arrays produce images in sector format. These transducers are useful when the working room at the anatomic

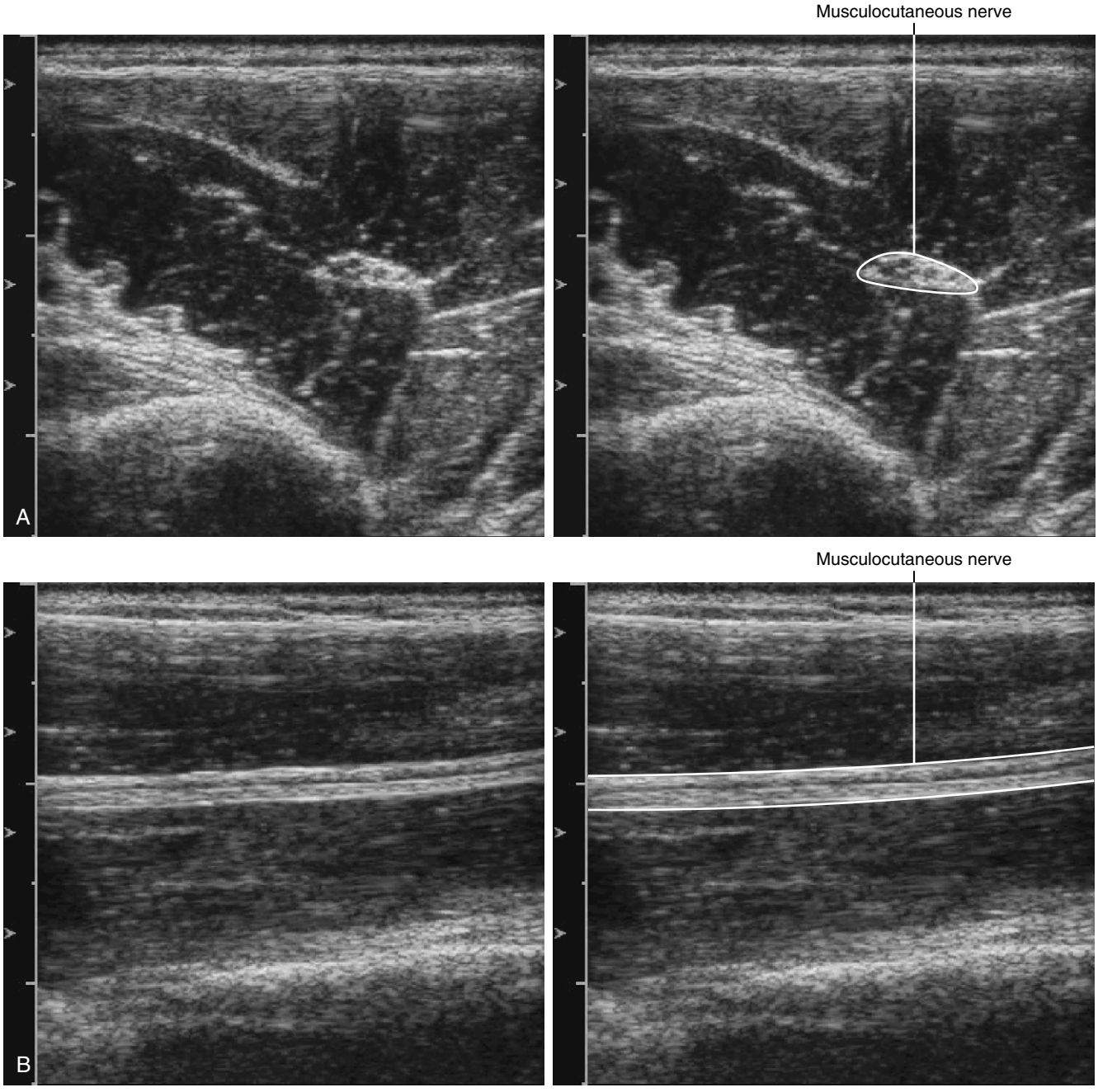


Figure 53-2 Imaging planes for regional block. Short-axis (**A**) and long-axis (**B**) views of the musculocutaneous nerve in the axilla. Short-axis views of peripheral nerves have dominated regional anesthesia practice. By musculoskeletal convention for long-axis views (**B**), proximal is shown on the left side of the image and distal on the right side.

site for the block is limited (e.g., the infraclavicular region). Curved probes are easier to rock (see later) and provide a broader view.

One of the essential skills to acquire for regional block with ultrasound is transducer manipulation. Standardized nomenclature has been established[12]:

- Sliding (moving contact). Sliding the transducer along the known course of the nerve using a short-axis view often helps with nerve identification.
- Tilting (cross-plane, side-to-side). The echobrightness of peripheral nerves will vary with the degree of tilt. Optimizing this angle is critical to promote nerve visibility.
- Compression. Compression is often used to confirm venous structures. To improve imaging, compression not only provides better contact but also brings the structures closer to the surface of the transducer. Soft tissue is subject to compression and therefore estimates of tissue distances will vary.
- Rocking (in-plane, toward/away from indicator). Rocking is often necessary to improve needle and anatomic structure visibility when the working room is limited.
- Rotation. Some rotation of the probe will produce true short-axis views rather than oblique or long-axis views.

Anisotropy is the change in echogenicity with inclination of the transducer. In general, when objects are imaged obliquely, they appear less echogenic (Figs. 53-3 and 53-4). This relationship is most pronounced for tendons but also occurs for muscle and nerves.[13,14] Although the term *anisotropy* was first used to describe changes in received echoes when rocking the transducer with structures viewed in long axis, it has also been used for short-axis views when tilting the transducer. With experience, operators will learn to naturally rock and tilt the transducer to fill in the received echoes.

Universal precautions should be used when handling dirty equipment. External surface probes require low-level disinfection between every use and after extended periods of nonuse. DO NOT soak or spray the probes with isopropyl alcohol (this will lead to lens delamination). DO NOT drop any ultrasound transducer (the active face of the transducer is especially sensitive to contact with hard surfaces).

Nerve Imaging with Ultrasound

Fascicles of peripheral nerves can be detected with high-resolution ultrasound imaging.[15] This fascicular echotexture is

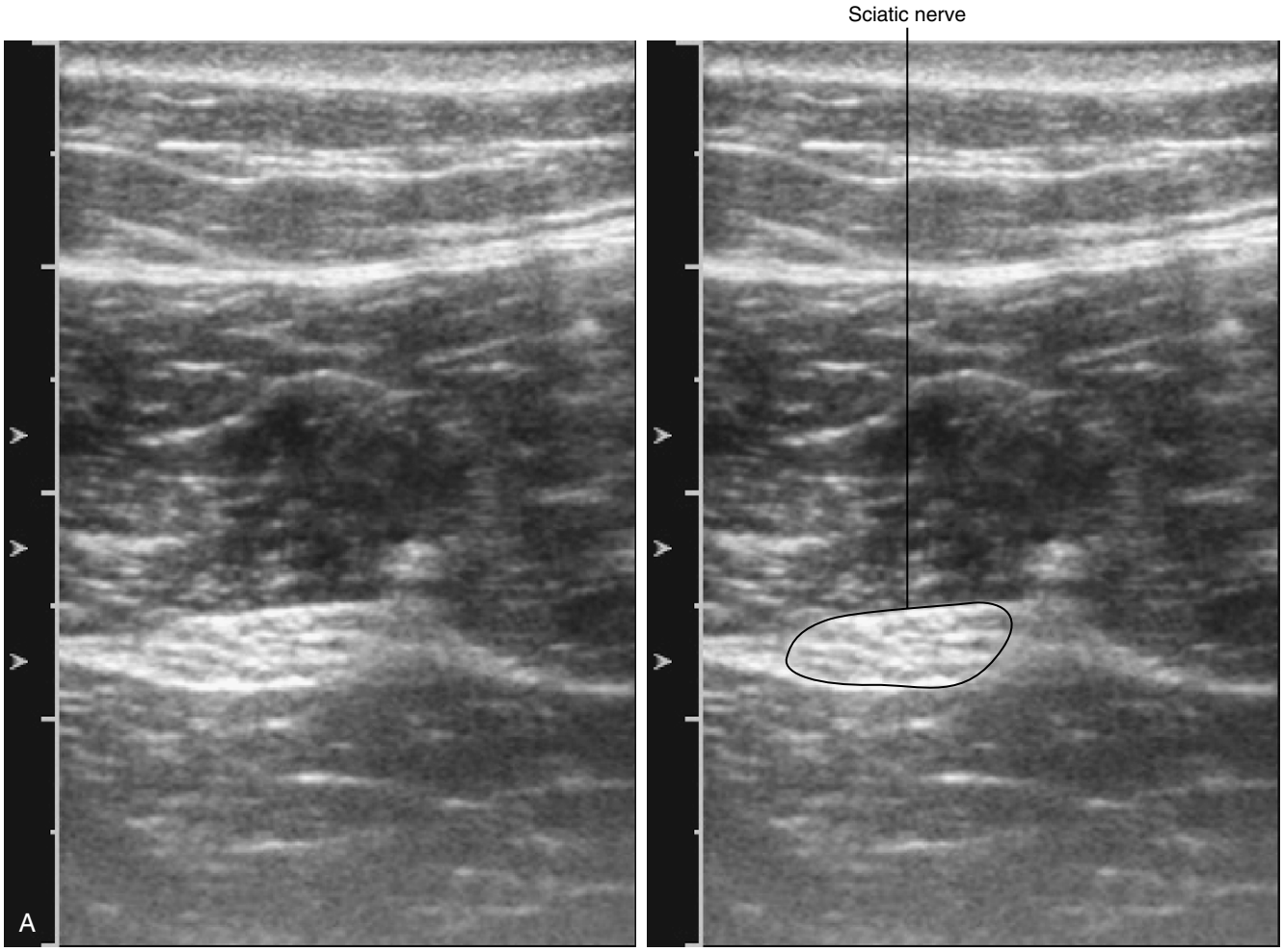


Figure 53-3 A, Sciatic nerve imaging in the subgluteal region.

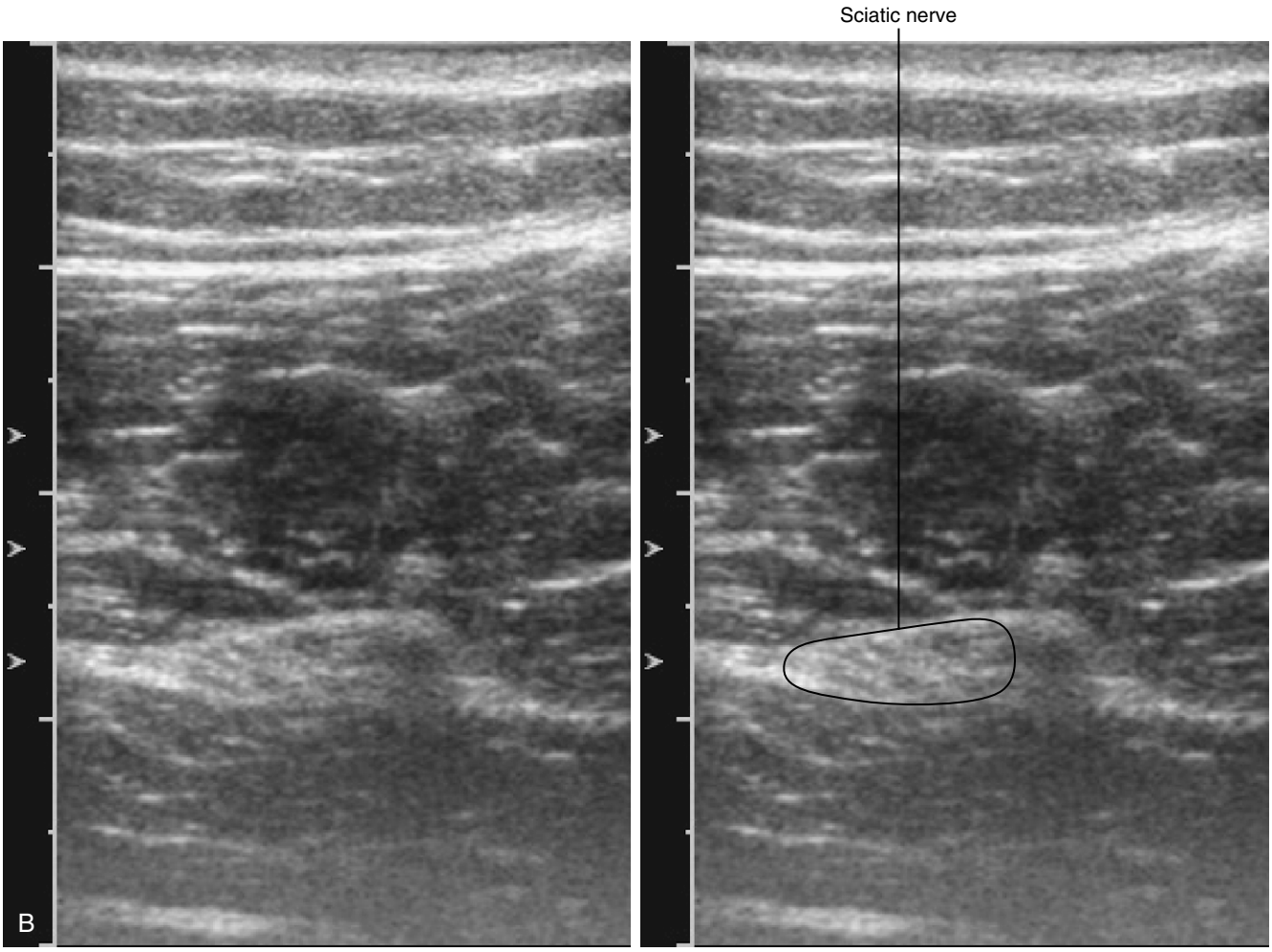


Figure 53-3, cont'd B, The amplitude of the received echoes diminishes when the angle of insonation is changed away from perpendicular to the nerve path, thereby demonstrating anisotropy.

the most distinguishing feature of nerves ("honeycomb" architecture) (Fig. 53-5). More central nerves, such as the cervical ventral rami, have fewer fascicles and therefore can appear monofascicular on ultrasound scans.[16,17] Ultrasound frequencies of 10 MHz or higher are required to distinguish tendons from nerves based on echotexture alone. One of the most powerful techniques to identify nerve fascicles is to slide a broad linear transducer over the known course of a peripheral nerve with the nerve viewed in short axis (transverse cross section).

Nerves can be round, oval, or triangular. Although nerve shape can change along the nerve path, the cross-sectional nerve area is constant in the absence of major branching (Fig. 53-6).[18] Peripheral nerves are pathologically enlarged by entrapment or in certain neuromuscular disorders such as Charcot-Marie-Tooth disease type IA (Fig. 53-7).[19] There is some evidence to suggest that patients with diabetic neuropathy also have enlarged peripheral nerves.[20]

Although direct nerve imaging has led to a phenomenal increase in ultrasound-guided regional anesthesia, the identification of other nearby structures (e.g., fascia and other connective tissues) also is critical in this endeavor. These structures permit favorable distribution of local anesthetic so that nerve contact with the block needle is not necessary. Successful drug injections should clarify the borders of the nerve (Fig. 53-8).

Block Needles for Ultrasound-Guided Procedures

Metal needles are hyperechoic and can cause reverberation artifact (see later). Needle tip visibility is best when the needle path is parallel to the active face of the transducer. Under this condition, the needle is perpendicular to the sound beam so strong specular reflections will be produced (mirror-like reflections from a smooth surface). As the angle of incidence is increased, the mean brightness will decrease.[21] In that same study, the bevel angles were ground from 10 to 70 degrees but were found to have no effect on the needle tip echo. However, bevel orientation does influence the needle tip echo, with best visibility with the bevel either directly facing or averting the transducer.[22] Because needle

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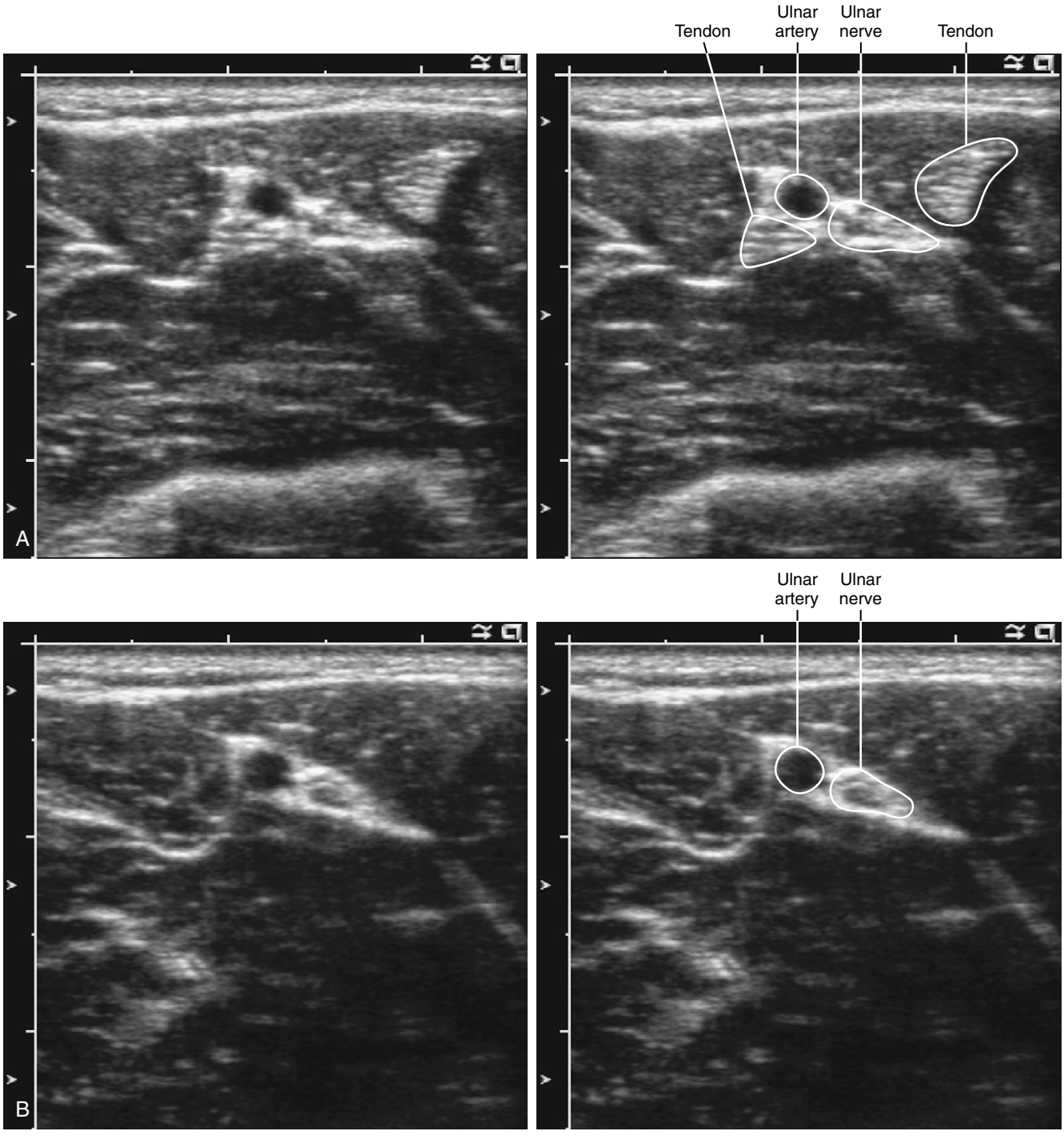


Figure 53-4 Ulnar nerve anisotropy in the forearm. **A** and **B,** These two sonograms were obtained by tilting the transducer just a few degrees with the ulnar nerve viewed in short axis. The received echoes from the adjacent tendons changes much more markedly than the ulnar nerve itself. Tendons are almost always more anisotropic than peripheral nerves.

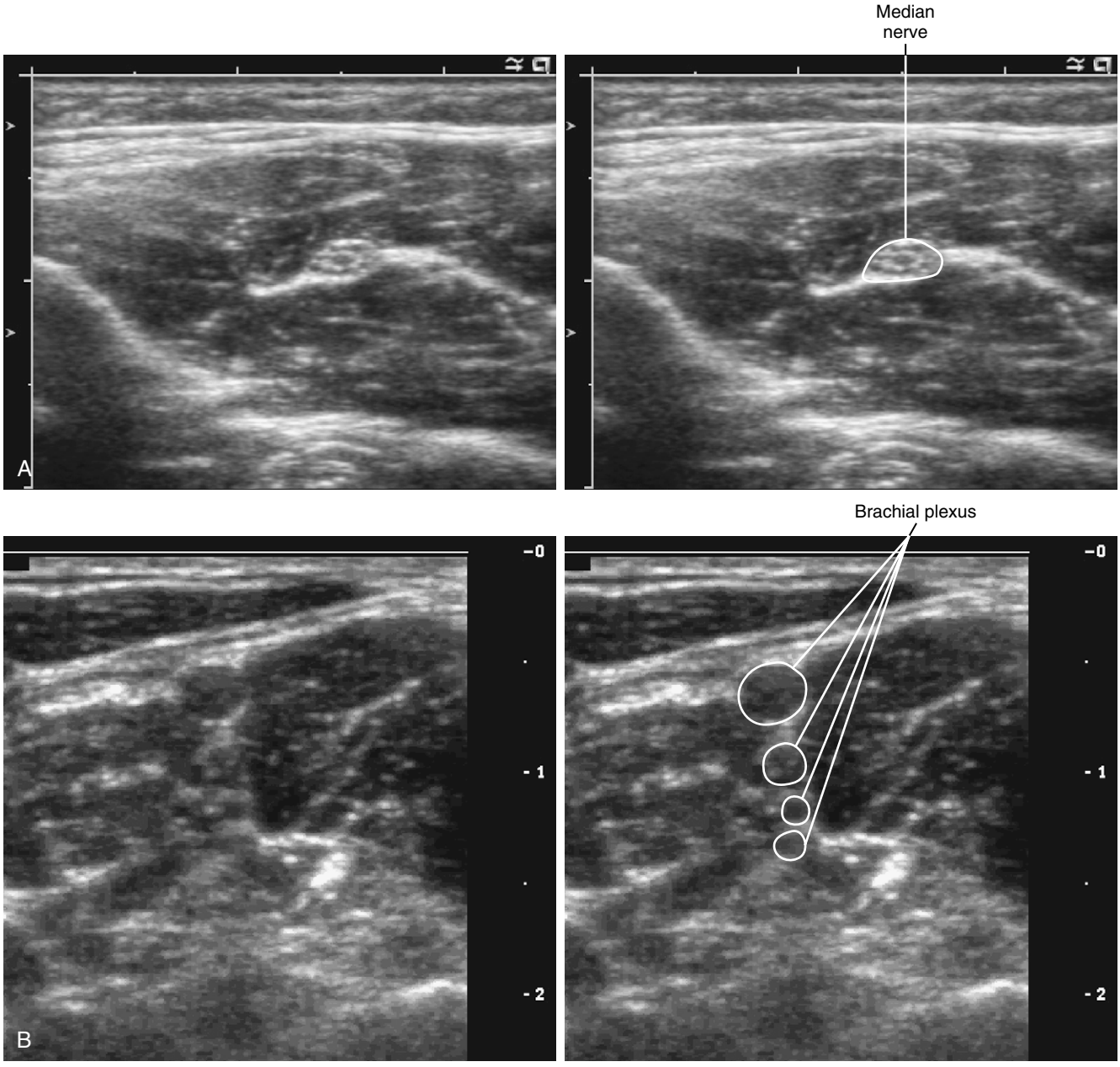


Figure 53-5 Nerve echotexture. **A,** Fascicles of the median nerve in the forearm. In this sonogram the "honeycomb" appearance of a polyfascicular peripheral nerve is observed. **B,** Monofascicular echotexture of the brachial plexus in the neck. This sonogram was obtained by scanning the interscalene region with the brachial plexus viewed in short axis. A large superficial nerve is identified, which probably is the superior trunk. In contrast to more peripheral nerves, cervical ventral rami and trunks often have monofascicular echotexture, consistent with the low number of fascicles observed in anatomic specimens from this region.

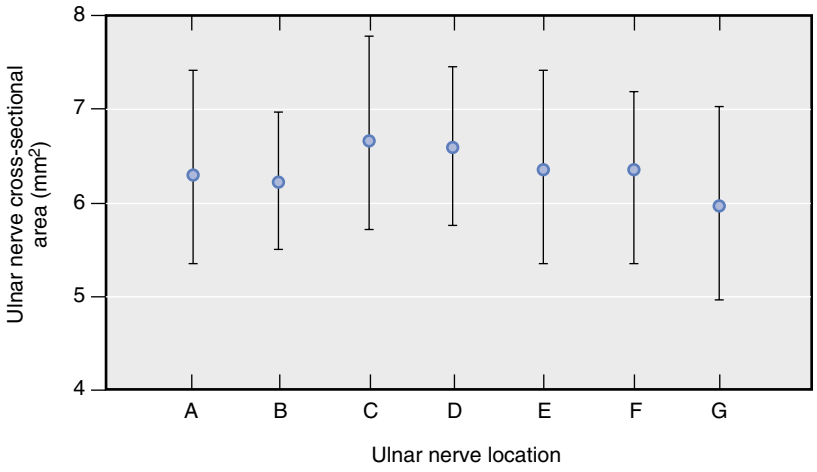


Figure 53-6 Cross-sectional area of a peripheral nerve as a function of nerve path length. In this figure the cross-sectional area of the ulnar nerve is shown at various points in the upper extremity. A = axilla, B = midhumerus, C = 2 cm proximal to medial epicondyle, D = medial epicondyle, E = 2 cm distal to medial epicondyle, F = arterial split, and G = wrist crease. Data are shown as mean values with standard deviations. Despite changes in shape that can occur, the cross-sectional area of nerves is relatively constant along the nerve path in the absence of major branching. (*Data from Cartwright MS, Shin HW, Passmore LV, Walker FO: Ultrasonographic findings of the normal ulnar nerve in adults. Arch Phys Med Rehabil 88:394-396, 2007.*)

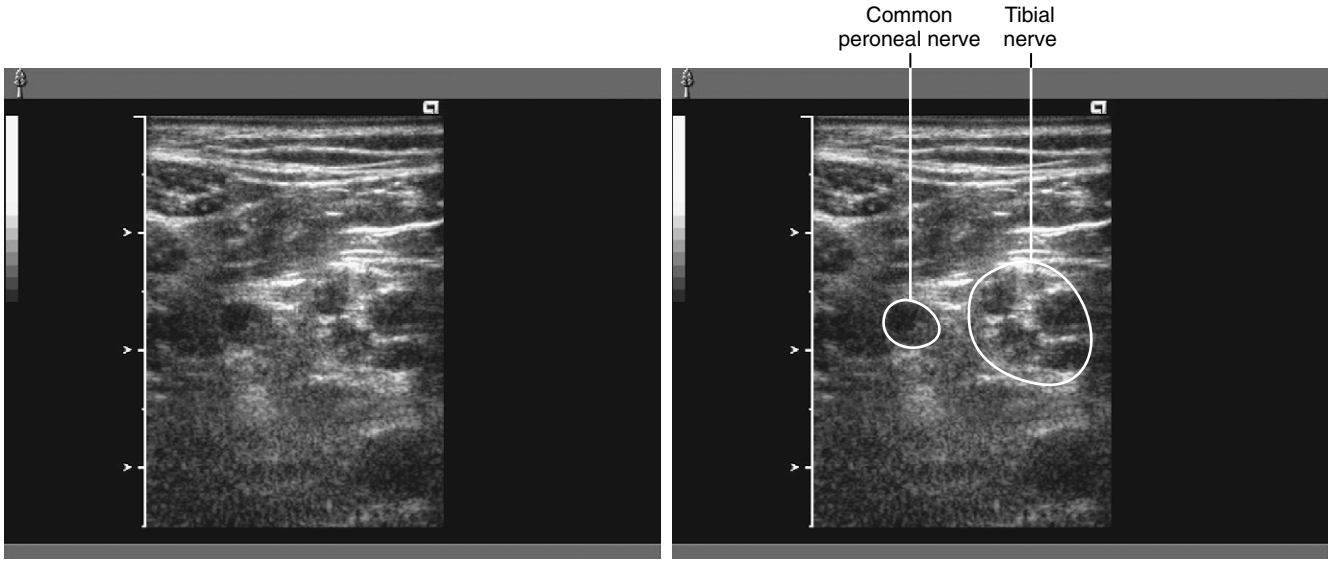


Figure 53-7 Sonogram of the popliteal fossa of a patient with Charcot-Marie-Tooth disease type 1A. The peripheral nerves are markedly enlarged because of the large fascicles. Nerves of the symptomatic and asymptomatic sides can appear similar in these patients. Large tick marks are 10 mm apart.

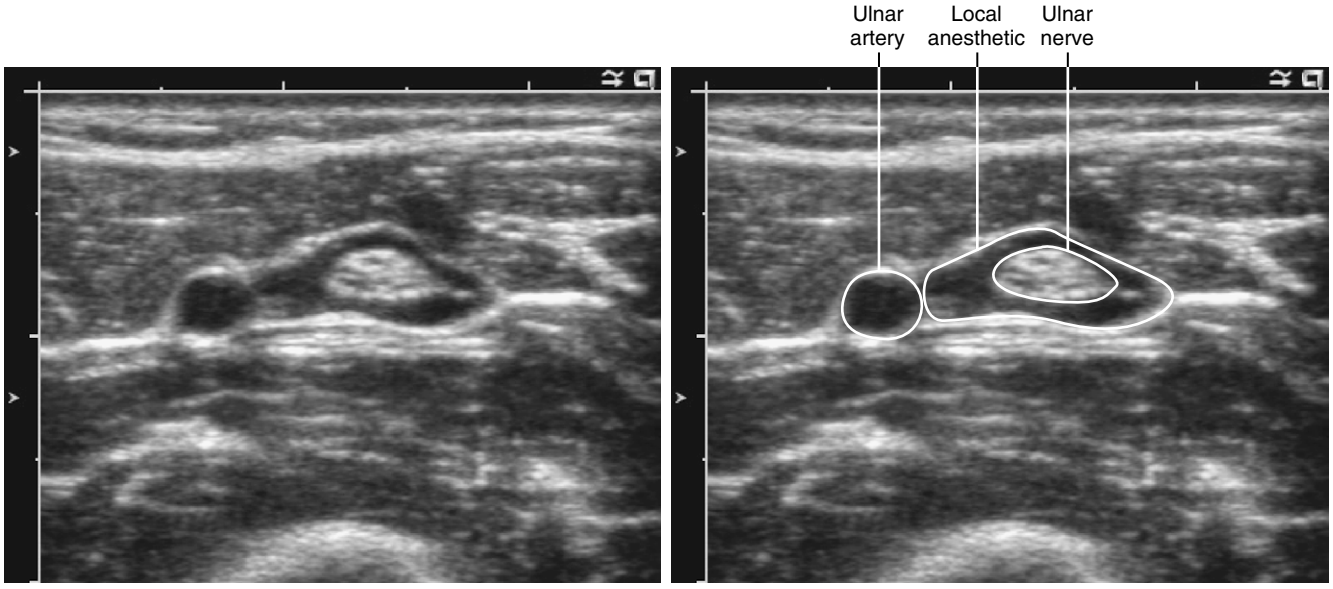


Figure 53-8 Local anesthetic injection for successful peripheral nerve block. In this sonogram, the ulnar nerve and ulnar artery are viewed in short axis in the forearm. The nerve is surrounded with anechoic local anesthetic.

diameters are smaller than the scan plane thickness, larger needles are more echogenic than finer ones.

Visualization of needles within echogenic tissue is difficult, particularly adipose tissue. A number of strategies have been proposed to improve needle tip visibility. A low receiver gain can improve detection of the needle tip echo. Spatial compound imaging can help identify the needle tip when the needle path is at an angle with respect to the transducer. Needles with echogenic modifications are now commercially marketed. Among needles developed for use in regional anesthesia, the Hustead needle has a bevel that tends to be more visible in contrast to side port needles, which lack cutting bevels.[23]

Ultrasound Artifacts in Regional Anesthesia

There are several common assumptions in ultrasound imaging.[24] First, the velocity of sound is assumed to be 1540 msec. This estimate was derived from measurements on soft tissue at body temperature. When local heterogeneities exist, artifactual bending of the block needle can be observed with sonography, the so-called bayonet artifact (Fig. 53-9).[25,26] Speed of sound artifacts relate to time-of-flight considerations and to refraction at the interface of tissues with different speeds of sound.

Second, sound waves are assumed to take a straight path to and from tissue. When this does not occur, reverberation artifacts occur from the multipath echoes. The comet tail artifact is a type of reverberation artifact. At low receiver gain, the comet tail is seen as a tapering series of discrete echo bands just deep to a strongly reflecting structure. The spacing between the bands represents the distance between the anterior and posterior walls of the object.[27] Internal reverberations (arising from within the object) cause the comet tail artifact, which is most intensely observed when the object is perpendicular to the beam. The pleura is a strong reflector that causes comet tail artifact. Reverberation echoes are seen when the block needle is near parallel to the active face of the transducer when strong specular reflections are received.

During supraclavicular block, mirror-image artifacts can be observed from reverberation. Where the pleura is adjacent to the subclavian artery, mirror-image artifacts can occur with gray-scale sonographic imaging and both spectral and color Doppler flow imaging.[28] The lung apex, which is located immediately posterior to the subclavian artery, acts as the highly reflective acoustic interface to form this artifact.

Third, all reflectors are assumed to be on the central ray of the transducer beam. When this is not true, out-of-plane artifacts are observed (slice thickness artifacts). Definitive proof of out-of-plane artifacts requires multiple views, which are recommended when ambiguities arise.

Unlike adjacent tissue, biologic fluids do not significantly attenuate the sound beam and therefore cause acoustic enhancement.[29] Acoustic enhancement artifacts deep to vessels can be erroneously interpreted as nerves. For example, acoustic enhancement deep to the axillary artery in the axilla can be mistaken for the radial nerve. In the infraclavicular region, acoustic enhancement deep to the axillary artery can be mistaken for the posterior cord of the brachial plexus.[30]

Anatomic Variation

Anatomic variation can be a source of frustration when nerve stimulation or surface landmarks are used for regional block. Even experienced clinicians cannot anticipate anatomic variation when these techniques are used. Ultrasound imaging not only

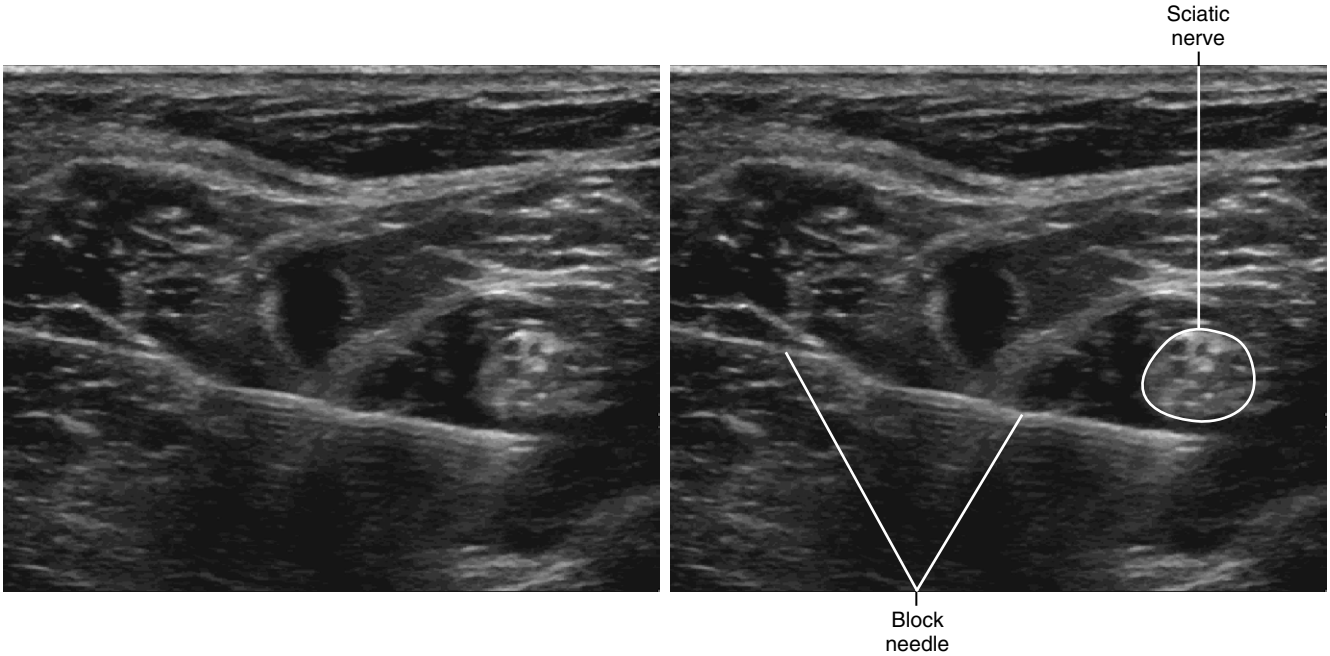


Figure 53-9 Bayonet artifact observed during popliteal block. In this sonogram, the block needle appears to bend as it approaches the sciatic nerve in the popliteal fossa.

Table 53-2 Anatomic Variation in Regional Block

Anatomic Variation	Location	Incidence	Implications and Significance	References
Passthrough/passover brachial plexus	Above clavicle	10-15%	Possible association with incomplete brachial plexus block	Kessler, 2007[36]
Cervical rib	Above clavicle	0.5-1.0%	Bony obstruction to brachial plexus block Preexisting nerve compression possible	Tubbs, 2006[37]
Duplicate axillary vein	Infraclavicular	10%	Duplicate vein lies adjacent to the lateral and posterior cords of the brachial plexus and therefore vascular puncture risked	Gusmao, 2002[88]
Duplicate axillary artery	Axilla	5-10%	Palpation of pulse for transarterial injection problematic	Bigeleisen, 2004[49]
Median-MCN fusion	Axilla	19%	If recognized will expedite MCN scanning and block	Orebaugh, 2006[50]
Passover MCN	Axilla	8-30%	Palpation of coracobrachialis muscle for MCN block problematic MCN usually more laterally positioned	Flatow, 1989[51] el-Naggar, 2001[52] Eglseder, 1997[53]
Superficial ulnar artery	Forearm and wrist	1-5%	Usual landmark for ulnar nerve now absent	Schafhalter-Zoppoth, 2004[89]
Persistent median artery	Forearm and wrist	25%	Associated with bifid median nerve	Gassner, 2002[90]
Sciatic nerve division by piriformis	Gluteal	1.5-21%	Incomplete block of divided nerve Possible association with piriformis syndrome	Benzon, 2003[73]

MCN, musculocutaneous nerve.

provides a means of recognizing anatomic variation but also modifies the approach to regional block based on the findings. It is important to develop the skill to accurately identify anomalies and understand their clinical implications (Table 53-2).

The overall incidence of anatomic variation is relatively low (usually in the 5% to 10% range). However, the reported rates of block failure are not substantially different. Studies examining an association between the two are in progress, and it is likely that anatomic variation is overrepresented among block failures for surface landmark–based techniques.

Although the spectrum of anatomic variation within the normal (asymptomatic) population is enormous, several themes recur. Venous anomalies are more common than arterial or nerve anomalies. Most visible nerve anomalies relate to abnormal nerve paths through or around muscles. Distal (peripheral) anomalies are more common than proximal (central) anomalies.

Supraclavicular and Interscalene Blocks

The first descriptions of ultrasound-guided blocks were in the supraclavicular region.[31,32] The advantages of the supraclavicular block are that the brachial plexus is compact, the nerve visibility is very good, and the structures are shallow (20-30 mm field). In the supraclavicular region, sonography will image the divisions of the brachial plexus.[33] Excellent block characteristics have been reported from ultrasound-guided supraclavicular blocks.[34] The principle concerns are the risk of vascular puncture in an area that is difficult to compress and the risk of pneumothorax.

An in-plane approach from medial to lateral so that the needle will pass over the subclavian artery can be used to reach the brachial plexus (Figs. 53-10 to 53-12). One current technique is to place the patient in a semi-sitting position with the head turned to the opposite side and the arms flush with the body. The operator will be standing at the head of the bed or at the patient's side depending on the side of the block and the handedness of the operator. Interscalene blocks can be performed in a similar fashion by sliding the transducer slightly more cephalad. In the interscalene view the brachial plexus is stacked between the scalene muscles. Proximity to the phrenic nerve will occur if the block location is too cephalad.

A compact linear transducer (20-30 mm footprint) is used for the procedure[35] to provide working room and allow rocking of the transducer. Some authors also have recommended a specialized compact linear "hockey stick" transducer for supraclavicular blocks.[30]

Anatomic Variation in the Supraclavicular and Interscalene Regions

Passover Brachial Plexus

The C5 ventral ramus (and other contributions to the brachial plexus) can pass over the anterior scalene muscle rather than between the scalenes. When this condition is identified, the block is usually performed at a more caudal position in the neck to avoid incomplete brachial plexus anesthesia.

Passthrough Brachial Plexus

C5 and C6 ventral rami can pass through the anterior scalene. Again, when this condition is identified, the brachial plexus block

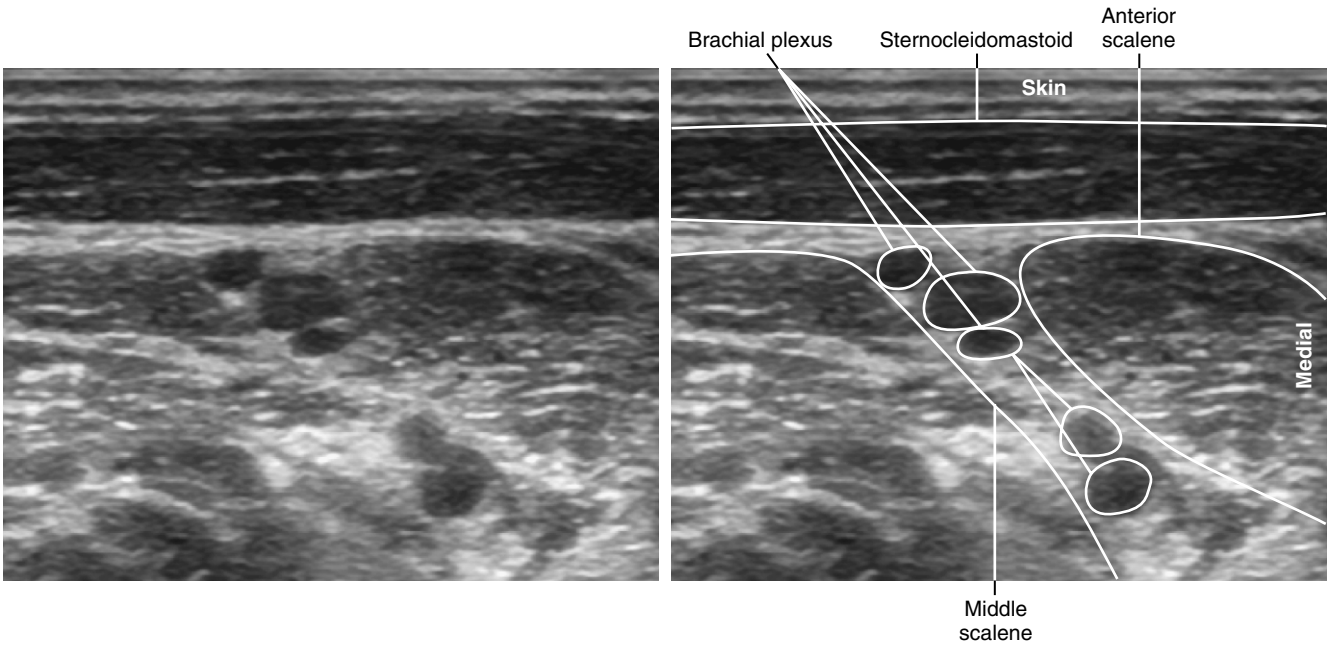


Figure 53-10 Interscalene view of the brachial plexus in the neck. In this sonogram the complexity of the brachial plexus is shown by identification of many components of the plexus in short-axis view. The cervical ventral rami have monofascicular echotexture as they lie between the anterior and middle scalene muscles.

is performed at a more caudal position in the neck to avoid incomplete brachial plexus anesthesia.

The incidence of scalene muscle anomalies is similar for sonography of volunteers and in cadaveric dissections, suggesting that ultrasound can accurately detect these anomalies.[36]

Cervical Ribs

Cervical ribs are relatively uncommon and occur in 0.5% to 1% of the population.[37] Partial cervical ribs usually present no difficulty for regional block. However, complete or large cervical ribs will make any approach to brachial plexus block

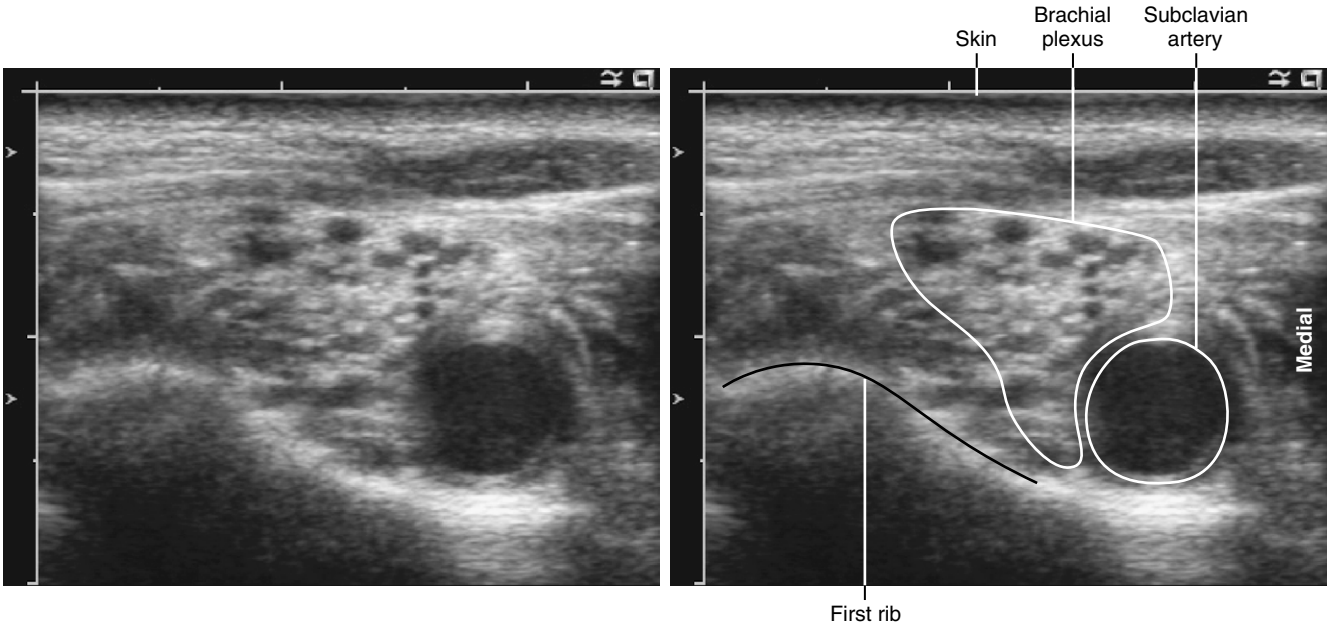


Figure 53-11 Ultrasound imaging for supraclavicular block. The compact brachial nerve plexus is seen superficial and lateral to the subclavian artery, pleura, and first rib.





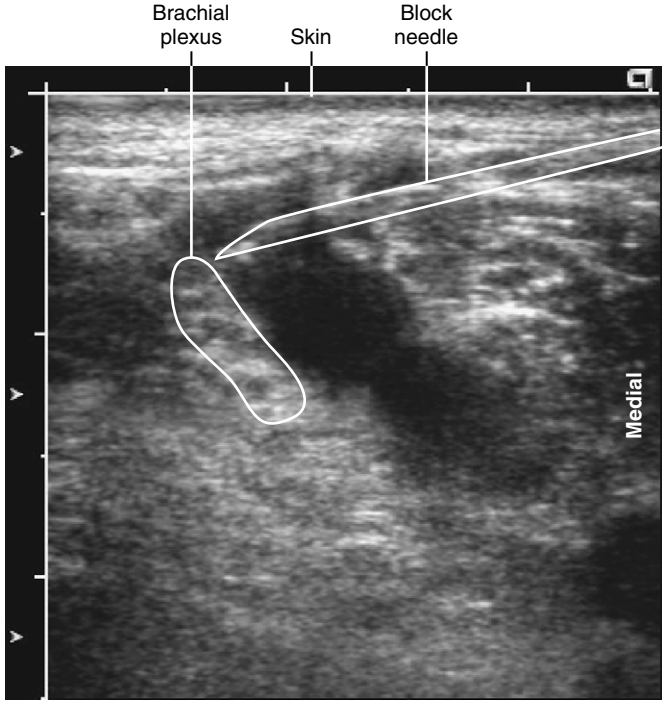


Figure 53-12 A, Ultrasound-guided supraclavicular block. In this clinical view, the needle approaches the brachial plexus from medial to lateral. **B,** Sonogram. For this procedure, the block needle approaches from medial to lateral within the plane of imaging. Local anesthetic is seen to distribute around the compact brachial plexus.

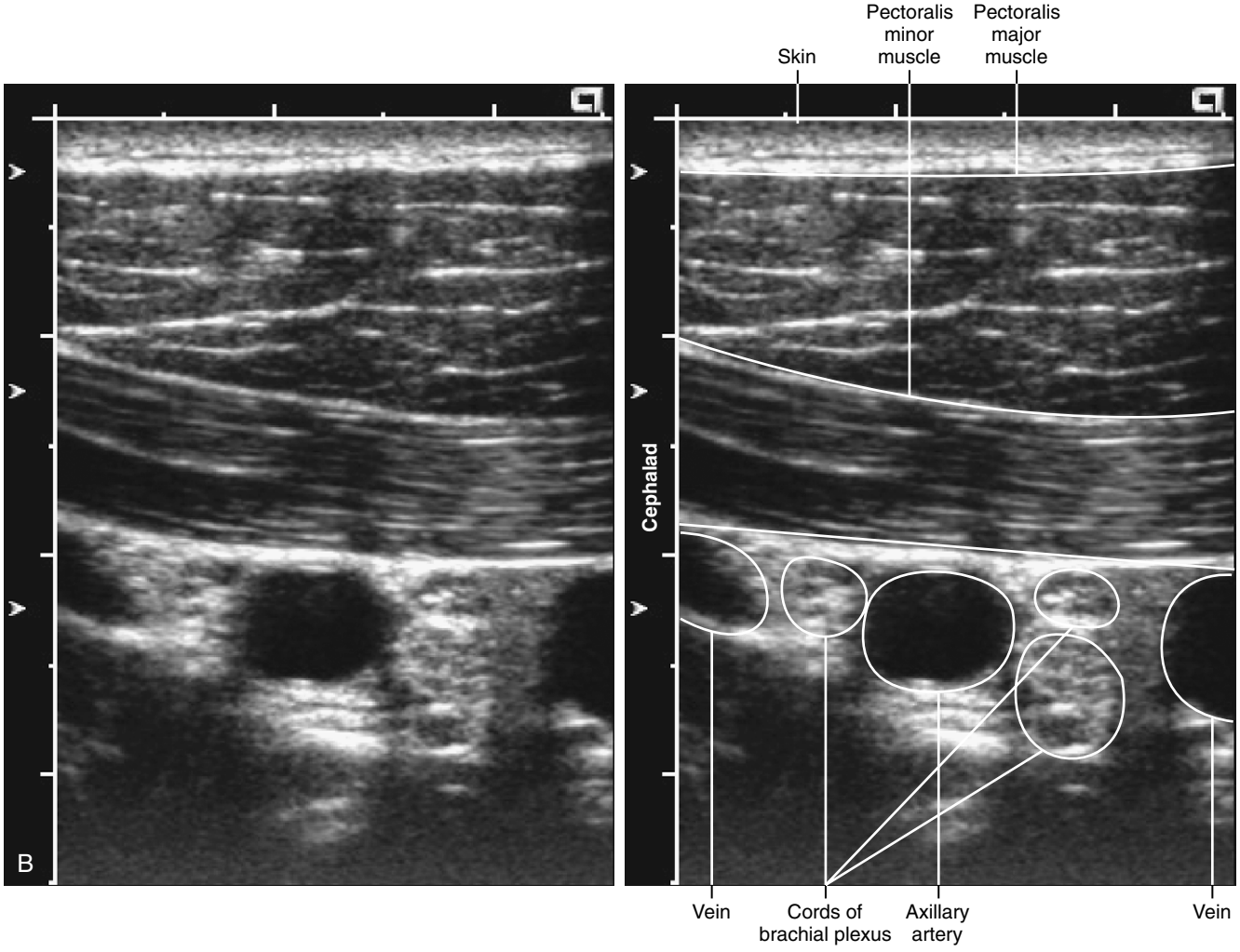
above the clavicle difficult (including an ultrasound-guided approach).

Infraclavicular Block

The advantages of the infraclavicular block are that it usually results in complete brachial plexus anesthesia, it is a stable place for a catheter, and no manipulation of the arm is necessary. The disadvantages are that it is a deeper block, and therefore needle/probe manipulation is necessary along with steep angles that result in needle tip visibility issues. Although the arm can remain at the side of the patient, the block is easier when the arm is abducted to straighten the neurovascular bundle.[38] The three arterial wall hugging cords are named with respect to the second part of the axillary artery so the expected positions are medial, lateral, and posterior. The artery is visualized in short-axis view deep to the pectoralis major and minor muscles (Fig. 53-13). Most practitioners use an in-plane approach from the head of the bed with the probe as lateral as possible. The ideal place for local anesthetic distribution to achieve complete infraclavicular block of the brachial plexus is posterior to the axillary artery for single-shot or catheter placement. There is substantial evidence that local anesthetic distribution posterior to the axillary artery produces complete brachial plexus block in the infraclavicular region.[39,40] The cords of the brachial plexus do not need to be directly visualized for successful block. A large retrospective clinical series supports



Figure 53-13 A, Clinical view of the setup for infraclavicular block. In this case, the arm has been abducted. **B,** Sonogram of the cords of the brachial nerve plexus are adjacent to the axillary artery. Anatomic variation in the infraclavicular region is rare, but in this patient, duplication of the axillary vein is seen deep to the pectoralis minor muscle.



the utility and safety of ultrasound-guided infraclavicular block.[41]

Anatomic Variation in the Infraclavicular Region

Duplicate Axillary Vein

Duplicate axillary vein is one of the few anatomic variations in the infraclavicular region. The clinical problem is that the accessory vein lies adjacent to the lateral cord of the brachial plexus and near the usual desired position of the needle tip. In the infraclavicular region, this vein will be difficult to compress with the ultrasound probe. When this anomaly is identified, caution and deliberate needle tip positioning are used to avoid intravenous injection.

Axillary Block

The axillary block is a versatile block for upper extremity anesthesia. Although relatively safe and commonly used with classic approaches, the one major limitation has been failure to block the musculocutaneous nerve. Now with the advent of ultrasound imaging, this sparing can be overcome by directly visualizing the musculocutaneous nerve itself.

The axillary block provides surgical anesthesia of the elbow and areas more distal, with adequate prevention of tourniquet pain.[42] The shallow depth of the neurovascular bundle (a 20-mm field is typical) and the large amount of working room make this a relatively easy block with ultrasound guidance. There are usually three arterial wall-hugging branches (median, ulnar, and radial) and one branch that has a characteristic medial to lateral course in the axilla (musculocutaneous). The musculocutaneous nerve also has a characteristic change in shape as it moves from adjacent to the artery (round), to within the coracobrachialis muscle (flat), to exit the muscle (triangular). Both out-of-plane (with needle approaching from distal to proximal) and in-plane (with needle approaching from the lateral side of the arm) techniques can be used. The neurovascular bundle is viewed in short axis with sufficient pressure to just coapt the walls of the axillary veins. Nerve location can be described with clock notation with respect to the axillary artery as viewed from the skin surface (with 3 o'clock indicating medial position). The usual locations are median (noon to 1 o'clock), ulnar (3 o'clock, between the artery and vein), radial (6 o'clock), and musculocutaneous (9 o'clock, with lateral takeoff expected).[43]

The block is performed in the proximal axilla, with the transducer gently pressed against the chest wall (Figs. 53-14 to 53-17). A high-frequency linear probe with a small footprint (25 to 30 mm) with sterile cover can be used for axillary block. The ideal location for local anesthetic injection is between the nerves and the artery so that separation between the two structures occurs, to ensure distribution within the neurovascular bundle. These injections result in excellent clinical blocks. The musculocutaneous nerve is usually blocked within the coracobrachialis, where its flat shape gives a large amount of surface area for rapid block of both sensory and motor fibers.[44]

Studies of the functional anatomy of the brachial plexus in the axilla suggest that multiple injections are required for complete brachial plexus anesthesia.[45,46] The approach described here is an ultrasound-guided modification of previously reported multiple injection techniques for axillary block. Ultrasound imaging has been shown to improve the success rate of axillary block compared with alternative approaches.[47,48] The low overall rates of axillary block success may reflect the strict clinical assessments in these carefully controlled trials.

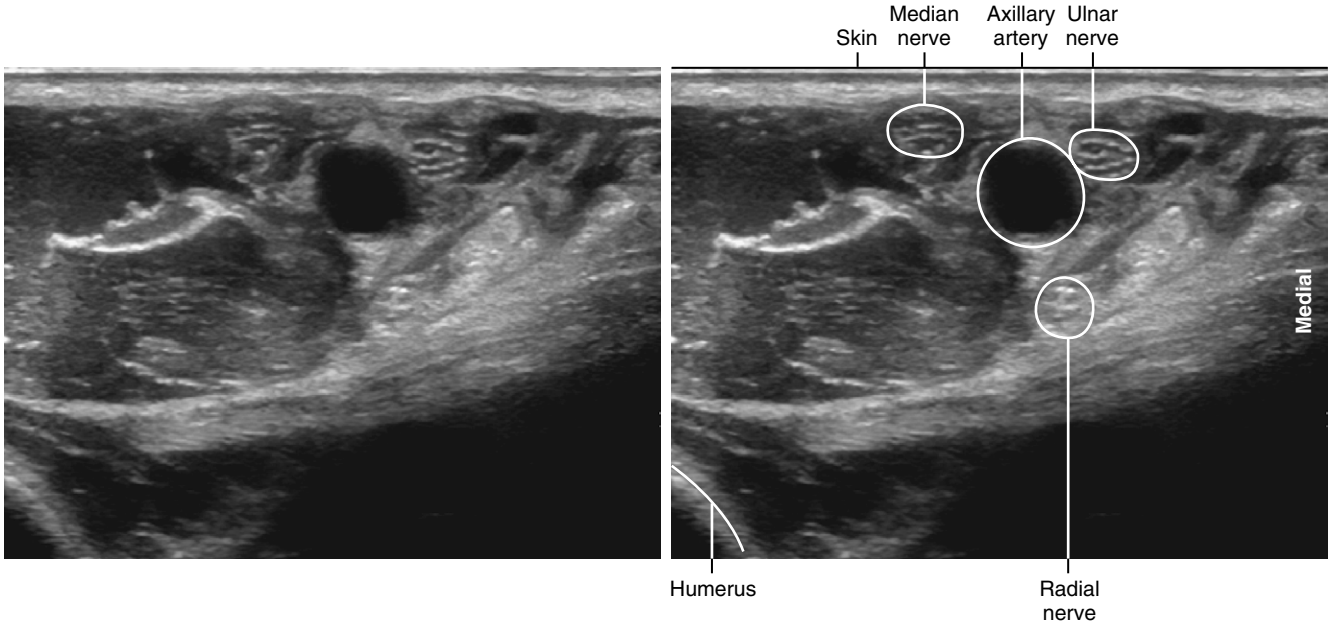
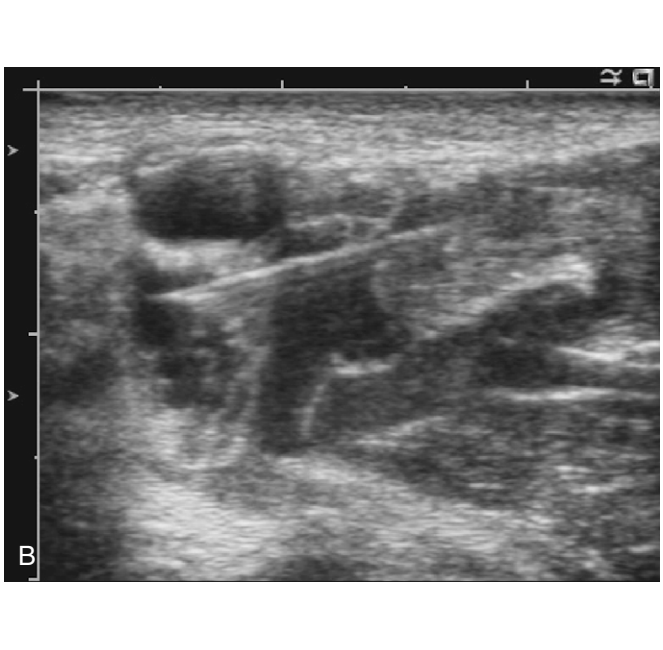


Figure 53-14 Ultrasound imaging in the axilla. In these sonograms, the median, ulnar, and musculocutaneous nerves are identified around the axillary artery. The radial nerve can be difficult to visualize.





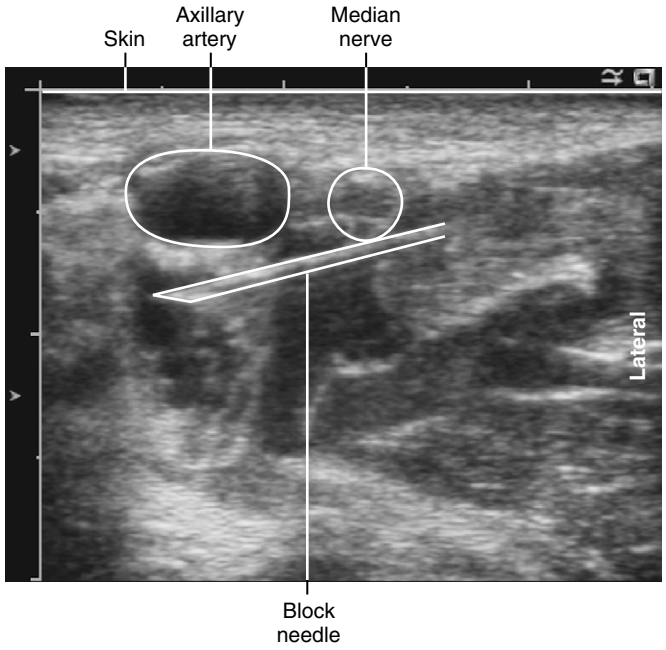


Figure 53-15 Axillary block with ultrasound guidance (in-plane approach). **A,** Clinical view of the approach. **B,** Sonogram of the neurovascular bundle in short-axis view with the needle tip in plane. The median nerve is identified adjacent to the axillary artery. The probe compression is just sufficient to coapt the walls of the satellite veins.

The disadvantages of the axillary block are that the patient must abduct the arm, catheter placement can be problematic due to incomplete blocks and catheter dislodgement, and in some individuals, the radial nerve takes off from the axillary artery proximally. The radial nerve exits the neurovascular bundle between the medial and lateral heads of the triceps muscle. In most subjects, the nerve travels with the profunda brachii artery (the deep branch of the axillary artery) to the spiral groove of the humerus. The radial nerve can be difficult to visualize and is often confused with acoustic enhancement deep to the back wall of the axillary artery.[30] When the radial nerve is not directly identified, the operator must be confident that there is local anesthetic distribution deep to the axillary artery proximal to the takeoff point of the profunda brachii artery to ensure block.

When first learning this technique with ultrasound, it will take 40 mL of local anesthetic for adequate block. With experience, volume reduction is possible to the 15- to 20-mL range. However, if the block is too targeted for the four nerves named previously, sparing of other smaller nerves (e.g., the medial antebrachial, medial brachial, and intercostobrachial nerves) can sometimes occur. Anatomic variation is relatively common in the axilla (see later).

Anatomic Variation in the Axilla

Duplicate Axillary Artery

One to 2% of adults have duplication of the axillary artery.[49] If direct nerve imaging is suboptimal, a more proximal approach to brachial plexus block can be indicated.

Musculocutaneous–Median Nerve Fusion (Low-Lying Lateral Cord in the Axillary Region)

Although the overall incidence is low,[50] this anomaly is probably the leading cause for failure to image the musculocutaneous nerve in the axilla. When identification of the musculocutaneous nerve is not possible, the operator should trace the course of the



Figure 53-16 Axillary block with ultrasound guidance (out-of-plane approach). **A,** External photograph of the approach. **B,** Sonogram of the neurovascular bundle in short-axis view with the needle tip crossing the plane of imaging. The probe compression is just sufficient to coapt the walls of the satellite veins.

median nerve down the arm. The median–musculocutaneous fusion bundle is larger than the normal median nerve and will give off branches laterally. It is important to recognize this anomaly so that time is not wasted (the nerve complex is usually already blocked by previous injections).

Passover Musculocutaneous Nerve

Rather than pass through the coracobrachialis muscle, the musculocutaneous nerve can pass over it.[51-53] The estimated incidence of passover musculocutaneous nerve ranges from 8% to 30%. This condition can be difficult to detect with ultrasound (not because the nerve is difficult to see but because the borders of the coracobrachialis are difficult to establish). Furthermore, in these cases the same shape changes occur, perhaps because the short head of the biceps muscle plays a similar mechanical role as the coracobrachialis. If the musculocutaneous nerve can be directly identified, this anatomic variation is easy to manage.

Ilioinguinal Block

The lower abdominal wall is primarily innervated by four peripheral nerves: the subcostal nerve, ilioinguinal nerve, iliohypogastric nerve, and genitofemoral nerve.[54] The first three nerves emerge between the transversus abdominis, internal oblique, and external oblique muscle layers. The extended course of these nerves through the abdominal wall within the layer between the transversus and internal oblique muscles makes this the desired anatomic location for regional block. The most common

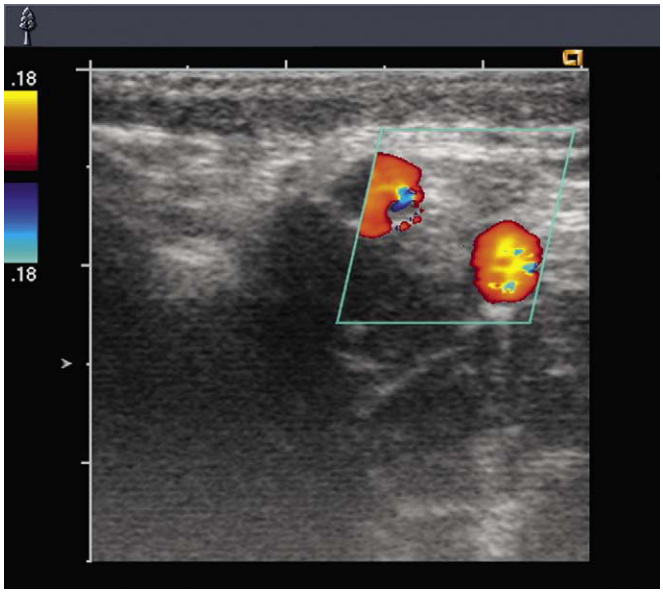


Figure 53-17 Duplication of the axillary artery. In this duplex sonogram, color Doppler reveals two axillary arteries in the axilla of this patient undergoing axillary block.

indication for ilioinguinal block is unilateral inguinal hernia repair.

For ultrasound-guided ilioinguinal block, the patient is placed supine (Figs. 53-18 to 53-20). The transducer is placed between iliac crest and costal margin (more cephalad than the usual location for ilioinguinal block). In this location, the muscle layers of the abdominal wall are well defined.[55] Of the three muscle layers (external oblique, internal oblique, and transversus), the internal oblique is usually the thickest.[56] In the more traditional location for ilioinguinal block, the muscles are often aponeurotic and therefore difficult to image.[57]

Injection must be within the fascial layer that separates the internal oblique muscle and the transversus muscle. Direct visualization and proximity to the nerves is not critical if 20 mL of local anesthetic is injected in the correct layer. The needle approach is in-plane from the anterior side, similar to transverse abdominal plane blocks.[58,59] Fine adjustments of the needle angle are not necessary because the probe can slide to find the crossing point of the tissue plane and the needle tip. The intent is to first visualize the needle tip in the external or internal oblique muscles before advancing deeper. The respiratory motion of the peritoneal cavity makes general anesthesia an appealing option for the block. The transversus muscle is thin, so the margin of safety between it and the peritoneal cavity is relatively small. For more complete blocks, local anesthetic can be injected into the other layers (between external oblique and internal oblique, and subcutaneous infiltration done between external oblique and skin) when pulling back the block needle.

For low-volume blocks, the needle tip is positioned between the ilioinguinal and iliohypogastric nerves within the fascial plane separating the internal oblique and transversus muscles. The iliohypogastric nerve runs superior and medial to the ilioinguinal nerve. The deep (medial) circumflex branch of the external iliac artery pierces the transversus muscle as it ascends the abdominal wall. Branches of the deep circumflex iliac artery often accompany the ilioinguinal nerves.

Clinical assessment of block is made difficult because of the anatomic variation in cutaneous innervation of the ilioinguinal and iliohypogastric nerves. The ilioinguinal and iliohypogastric nerves have small motor contributions to the transversus and internal oblique muscles. There is a tissue plane between the transversus abdominis muscle and the transversalis fascia that communicates with the femoral nerve,[60] so deep infiltration of sufficient volumes of local anesthetic can result in unintended femoral nerve block.

Femoral Block

Advantages of using ultrasound to guide femoral nerve block include more complete block, local anesthetic volume sparing, and fewer vascular punctures.[61,62] To be successful with this technique, detailed knowledge of the sonographic anatomy of the femoral nerve in the inguinal region is required.

The femoral nerve usually lies lateral to the femoral artery in the groove formed by the iliacus and psoas muscle. The nerve can be oval or triangular in cross-sectional shape with an anteroposterior diameter of approximately 3 mm and a mediolateral diameter of 10 mm.[63] Best depiction of the femoral nerve is from 10 cm proximal to 5 cm distal to the inguinal ligament. Some tilt of the ultrasound probe is necessary according to the pelvic inclination for the sound beam to meet the nerve perpendicularly for optimal scanning. In addition, the femoral nerve has a slight medial to lateral course so some rotation of the probe is also necessary to best view the nerve. Because the femoral nerve is covered by echobright adipose tissue and fascia, it can be difficult to establish the echogenic outer sheath of the nerve.[14]

In some subjects the psoas tendon can appear similar to the femoral nerve. However, the psoas tendon lies deep within the muscle. If the profunda femoris artery (the deep branch of the femoral artery) is visualized, then the transducer is too distal for complete femoral nerve block. The femoral nerve is often identified as a slight indentation of the iliacus and psoas muscles.

For femoral nerve block, a broad (35- to 50-mm footprint) linear transducer is used (Figs. 53-21 to 53-23). A short-axis view of the femoral nerve and vessels is obtained as described previously. Both out-of-plane (from distal to proximal) or in-plane (from lateral to medial) approaches have been used. The out-of-plane approach is often used for catheter placement.[64] The advantage of in-plane approach is visualization of the approaching needle. The disadvantages are the longer needle path and the fact that the needle has a tendency to skim over the fascia iliaca, thereby deforming it rather than puncturing it.

For either approach, the needle tip is positioned between the fascia iliaca and the iliopsoas muscle near the lateral corner of the femoral nerve to avoid the femoral vessels, similar to the method for fascia iliaca block.[65] The fascia iliaca has a characteristic mediolateral inclination, so lateral approaches are advantageous because they are more superficial and shallow than medial approaches. The desired distribution is local anesthetic layering under or completely around the femoral nerve. When layering of local anesthetic is observed over the nerve, the major concern is that the fascia iliaca is intact and block failure will result. For obese patients, femoral nerve imaging is challenging. In these patients, ultrasound can be combined with nerve stimulation for successful block. After successful injection of local anesthetic,

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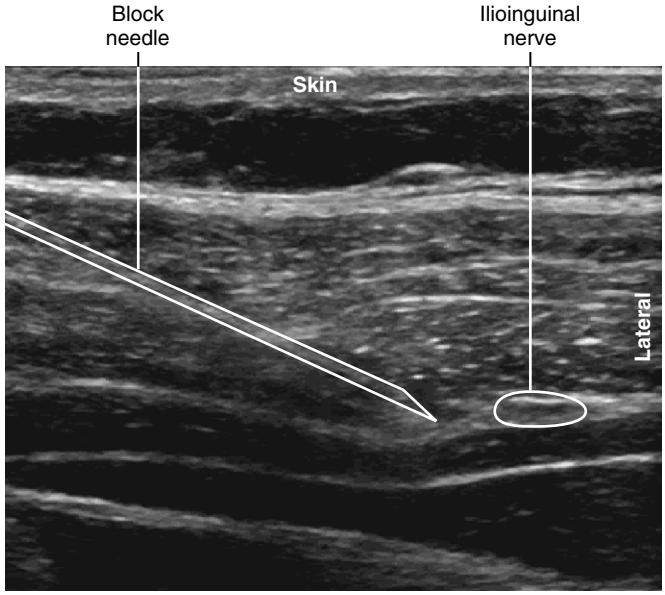

Figure 53-18 Ilioinguinal block with ultrasound guidance (in-plane approach). **A,** Clinical view. **B,** Sonogram of the block needle tip approaching the ilioinguinal nerve.

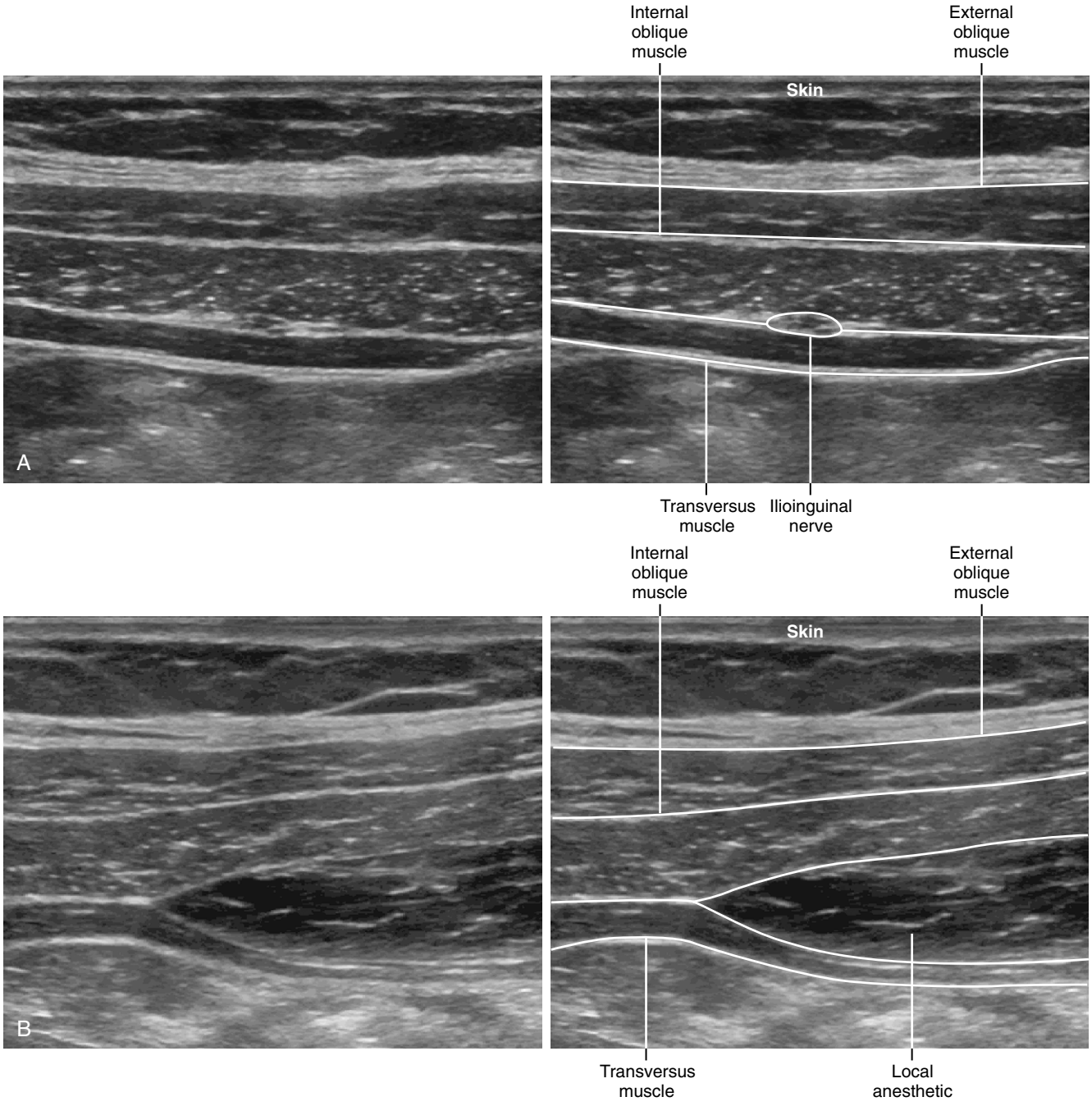

Figure 53-19 Abdominal wall imaging for ilioinguinal nerve block. **A,** In this sonogram, the external oblique, internal oblique, and transversus muscles are identified (the "three-layer cake" appearance). The ilioinguinal nerves are seen between the internal oblique and transversus muscles. **B,** The "kayak" sign of successful ilioinguinal injection. The fascia between the internal oblique and transversus muscles is split apart in the shape resembling a kayak.

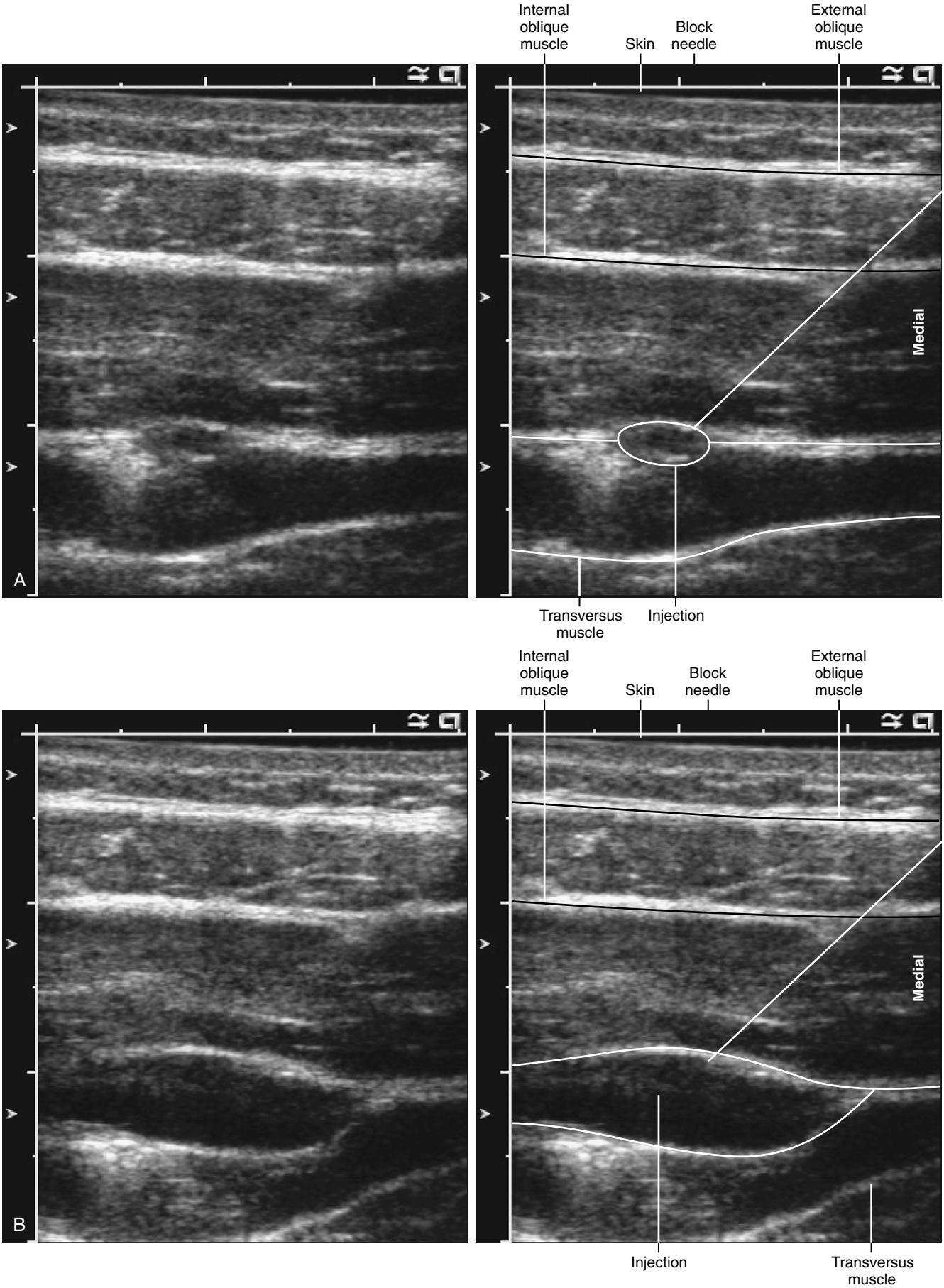

Figure 53-20 Ilioinguinal nerve block with ultrasound imaging. The needle approaches the fascia between the internal oblique and transversus muscles in the plane of imaging. **A,** At the start of injection. **B,** At the end of injection.

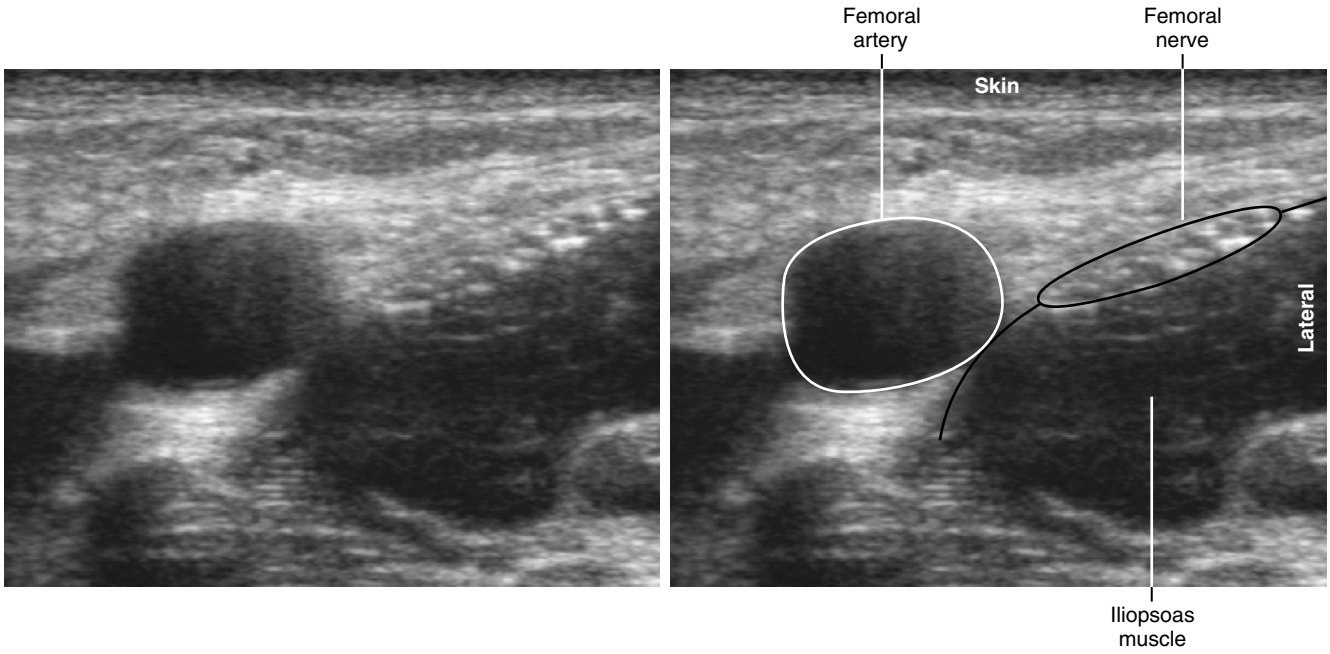

Figure 53-21 Femoral nerve sonography. The femoral nerve lies on the inclined surface of the iliopsoas muscle deep to the fascia iliaca and lateral to the femoral artery. This femoral nerve has the typical broad and flat shape in the inguinal region.

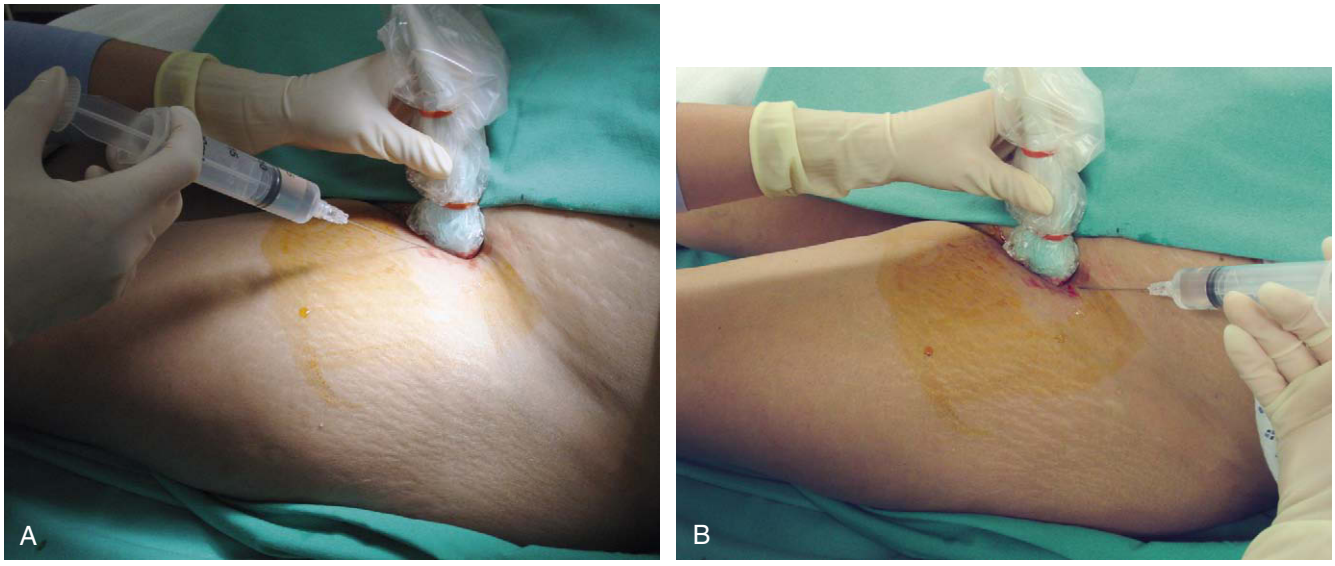

Figure 53-22 Femoral nerve block with ultrasound imaging. Clinical views of the setup for femoral nerve block (out-of-plane approach, **A**; in-plane approach, **B**).

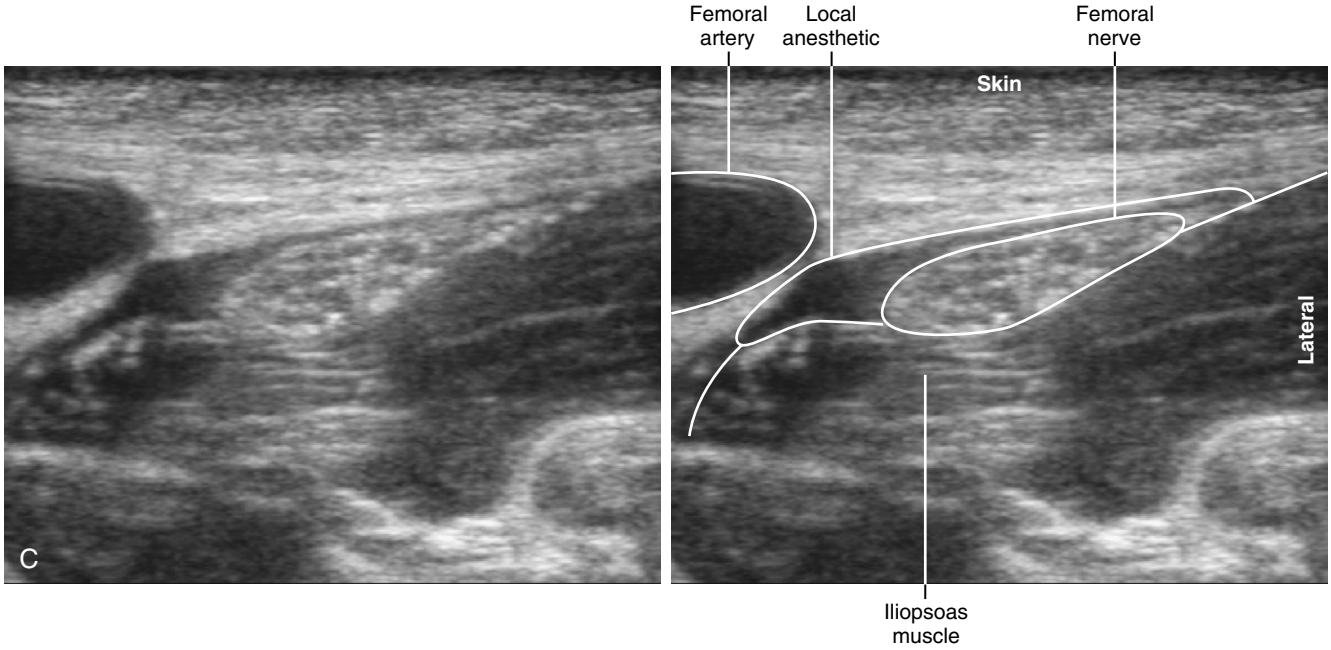

Figure 53-22, cont'd **C,** Local anesthetic surrounds the femoral nerve after injection.

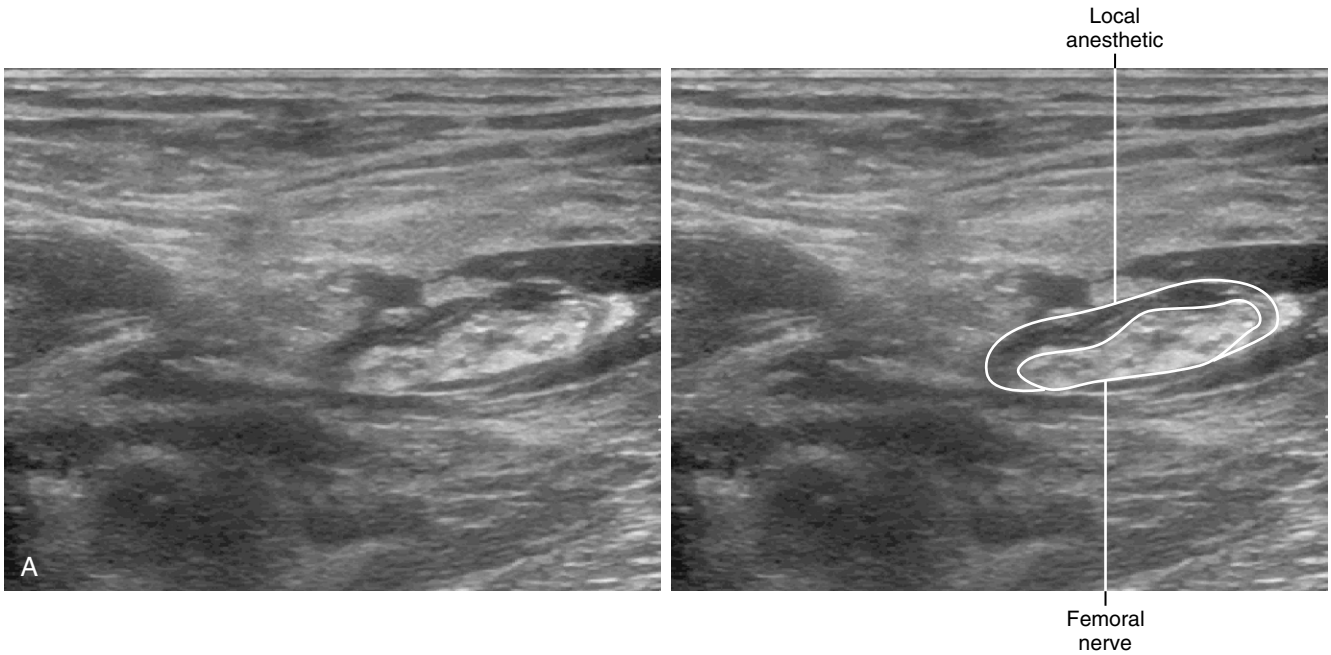

Figure 53-23 Femoral nerve imaging in the inguinal region after injection of local anesthetic. Local anesthetic tracks along branches of the femoral nerve, thereby confirming successful block (**A**, proximal; **B**, distal).

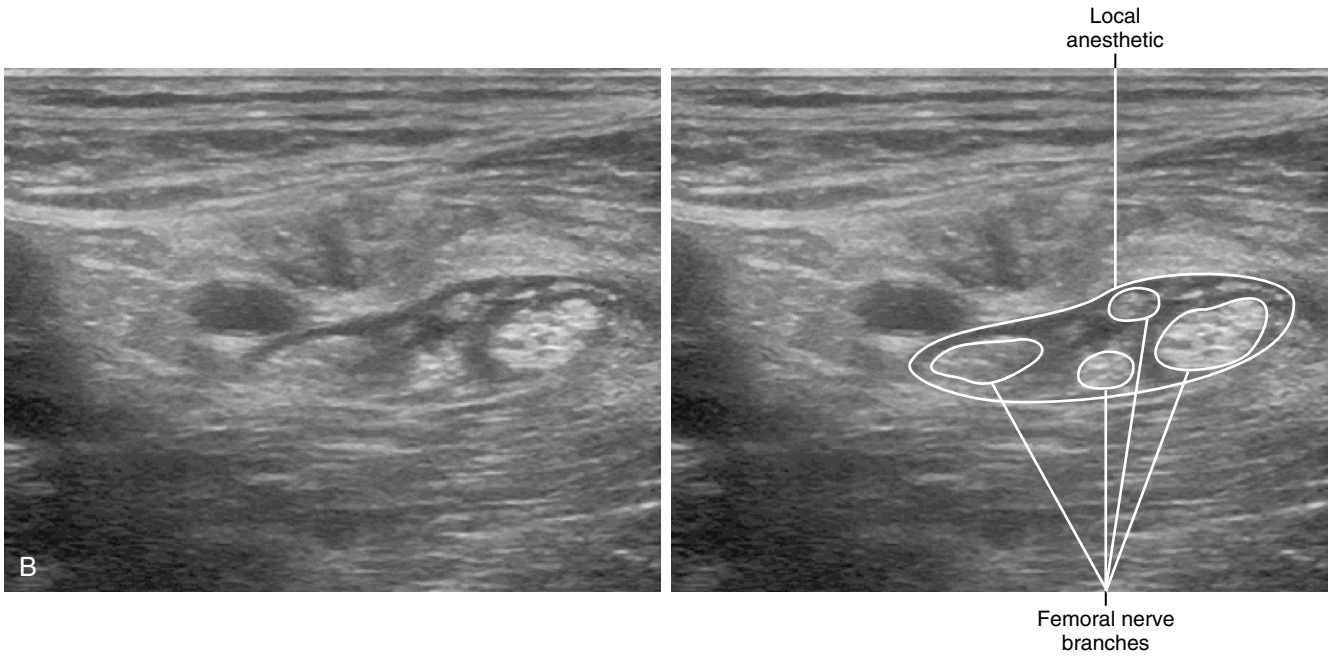

Figure 53-23, cont'd

branches of the femoral nerve can be appreciated by sliding the transducer along the known course of the nerve.

Sciatic Block

The sciatic nerve can be blocked anywhere along its course from the gluteal region to the popliteal fossa.[66] In this section, several common approaches to sciatic nerve block with ultrasound imaging are described (Figs. 53-24 and 53-25).

One of the first descriptions of sciatic nerve block used a short-axis view of the nerve(s) in the prone position with an out-of-plane approach in the popliteal fossa.[67] The advantage of a prone approach to popliteal sciatic nerve block is the stable imaging with the ultrasound transducer. In addition, the nerves can be blocked close to the surface. The division of the sciatic nerve provides a broad target with large surface area to promote block characteristics. This approach also allows a natural anatomic orientation of the field and monitor.

For this technique, the needle tip is positioned between the tibial and common peroneal components of the sciatic nerve near the division so that a single injection distributes to both nerves. By sliding the transducer along the known course of the sciatic nerve, its characteristic division in the popliteal fossa can be identified.[68] This method of sliding assessment is also important for verifying the local anesthetic distribution after injection. The tibial nerve has a more straight course than the common peroneal nerve and has about twice the cross-sectional area. The tibial nerve lies posterior to the popliteal artery and vein at the popliteal crease, and this can be a useful starting point when imaging is difficult. When the foot is moved, the nerves of the popliteal fossa have characteristic motions that can be helpful for nerve identification.[69]

The major disadvantage of the prone approach is that this position can be difficult for some patients. With the out-of-plane approach, inadvertent paresthesias and patient movement sometimes occur.

A similar approach to popliteal block can be used in supine position. For this the nerve(s) are viewed in short axis and the needle approach is in-plane from the lateral side of the thigh.[70] The leg must be elevated in a stable fashion to allow access for the ultrasound transducer. The advantages of this approach are the convenient position, the transducer position is remote from the site of needle entry, and the parallel in-plane approach of the block needle results in optimal needle tip visibility.

Analogous approaches to sciatic nerve block can be performed more proximally.[71] In some subjects the proximal biceps femoris tendon or semimembranosus tendon can appear similar to the subgluteal sciatic nerve. Some authors have suggested blocking the sciatic nerve deep to the gluteal muscles because the adjacent soft tissue permits favorable distributions of local anesthetic.[72]

Anatomic Variation in the Subgluteal Region

In some subjects, the sciatic nerve is divided by the piriformis muscle.[73] This can be detected in the subgluteal region by distinct common peroneal and tibial nerves. Multiple injections may be required for complete sciatic nerve anesthesia.

Phantom Training and Safety

Interventional sonography is not without risks.[74] Many recent studies have demonstrated efficacy of ultrasound-guided regional



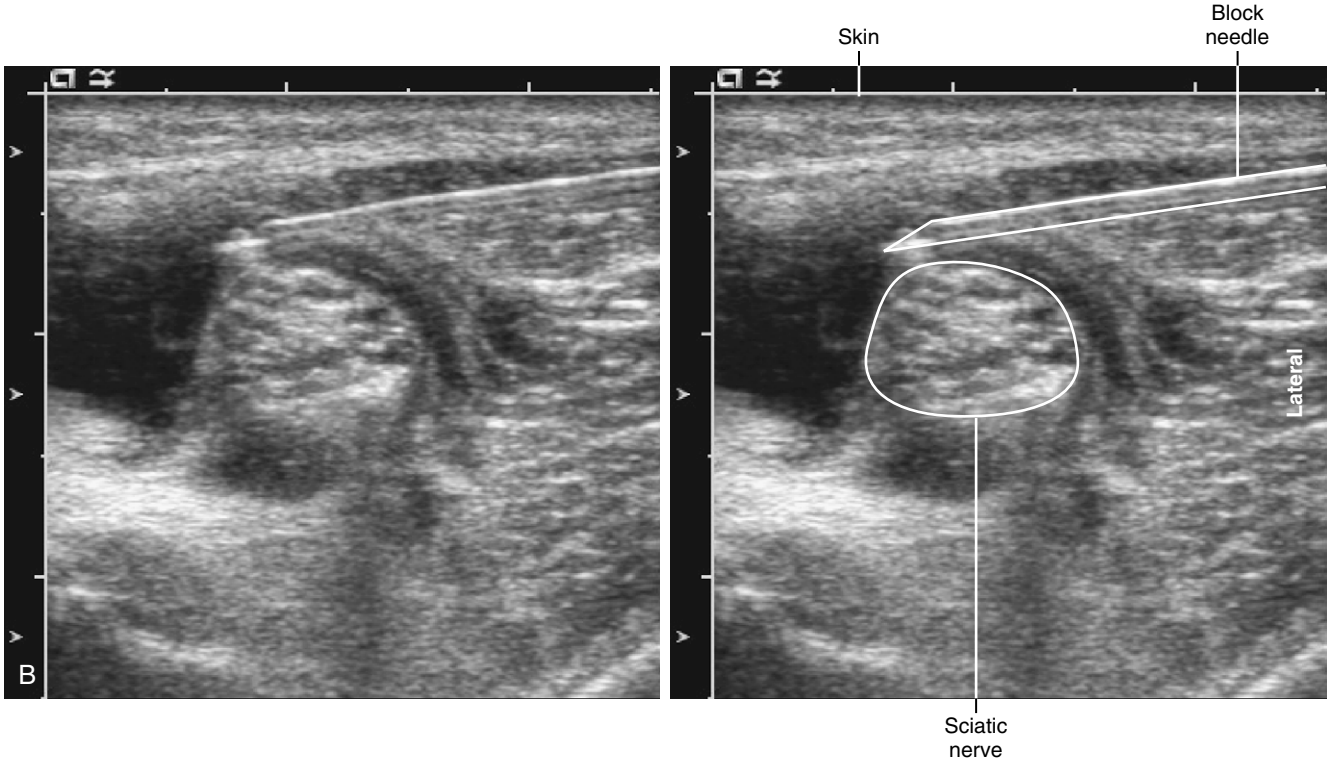

Figure 53-24 Popliteal block with ultrasound imaging (in-plane approach). **A,** Clinical view of the setup for popliteal nerve block in supine position. The leg is elevated and the transducer is applied to the posterior surface of the leg. **B,** The needle approaches the sciatic nerve in the plane of imaging from the lateral side of the leg.

blockade. Ultrasound has potential to prevent and detect two important adverse events during peripheral nerve blocks: intravascular injection and intraneural injection (Figs. 53-26 and 53-27).[75] Whereas ultrasound has tremendous promise in improving safety of regional blockade, this remains to be established in clinical practice.

One of the original techniques developed for training novices in ultrasound-guided interventions was use of a tissue-equivalent phantom.[76] The phantom consisted of simulated tissue for needle placement practice. To be realistic, the speed of sound must be the same as in soft tissue. In the first prototype, the phantom and container were clear so that visual confirmation was possible. Several phantoms are now marketed for regional anesthesia purposes, and biologic tissue models that simulate nerve blocks have been developed.[77]

Other teaching tools are being used. Cadavers have the advantage of realistic regional anatomy and can be used for simulated interventions. However, the cost and use of specialized embalming methods that preserve nerve imaging and flexibility have limited this approach to a few institutions.[78-80] We have yet to identify which tools are most effective at teaching ultrasound-guided regional blocks. Most training studies have concluded that

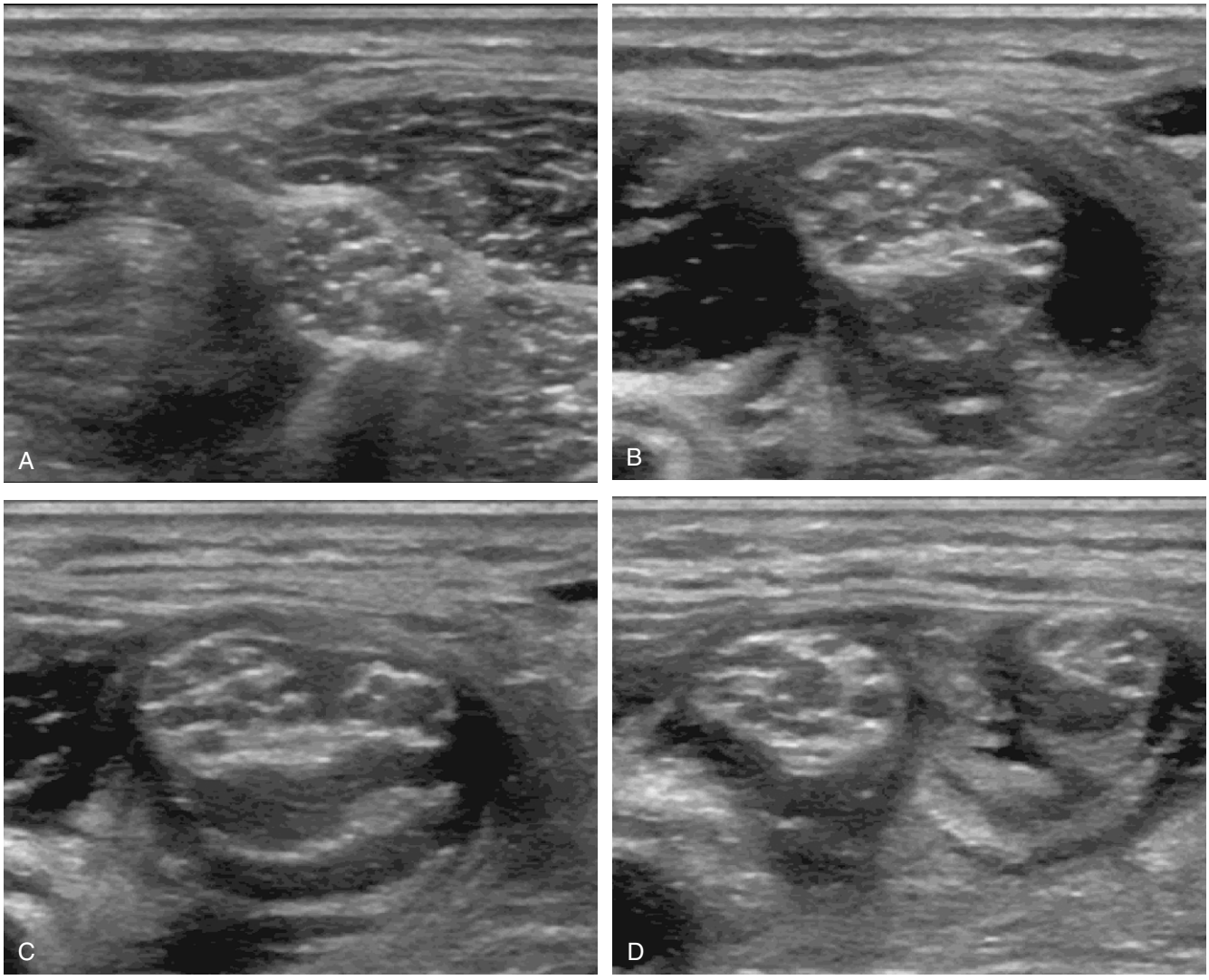

Figure 53-25 Sciatic nerve imaging in the popliteal fossa before (**A**), during (**B** and **C**), and after (**D**) division into the tibial and common peroneal nerves. Local anesthetic is seen to track with both individual nerves, thereby confirming successful block.

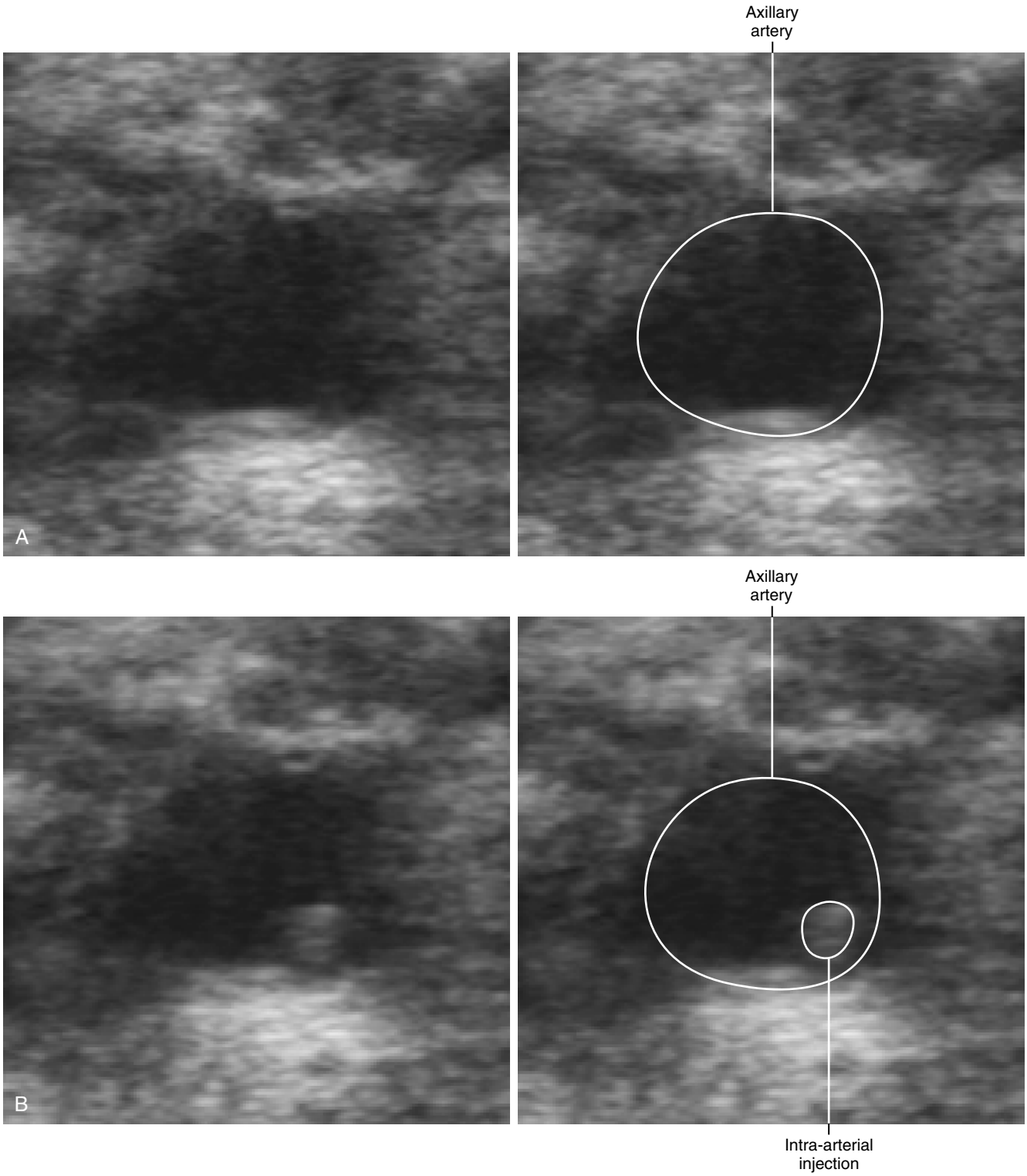

Figure 53-26 Intravascular injection detected by ultrasound imaging. These sonograms were obtained before (**A**) and during (**B**) a small local anesthetic injection within the axillary artery in the axilla.

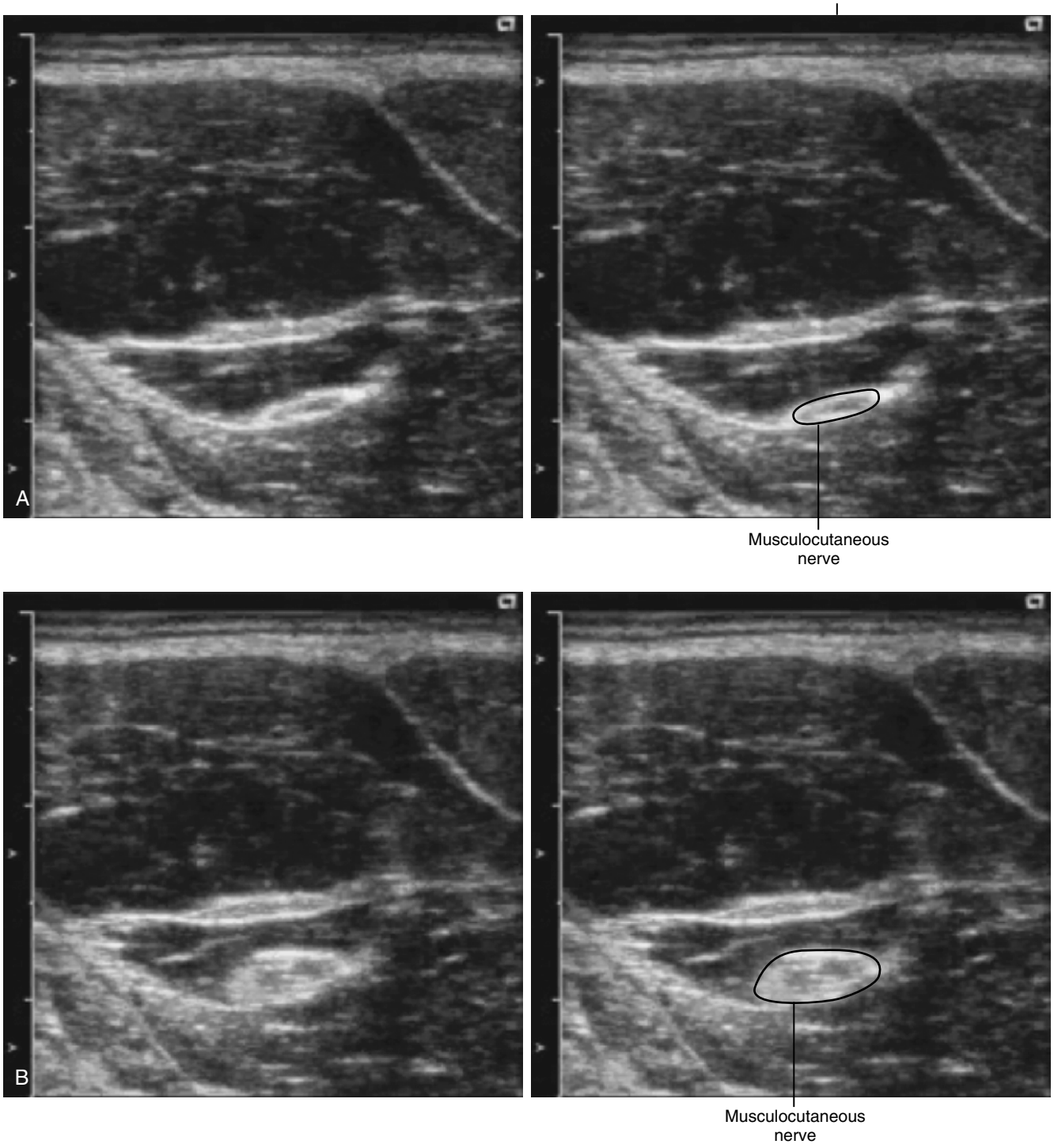

Figure 53-27 Intraneural injection revealed by ultrasound imaging. These sonograms were obtained in the axilla before (**A**) and after (**B**) injection within the musculocutaneous nerve. Nerve expansion is detected, but with preservation of the overall integrity of the nerve borders. No paresthesias were observed during or after the procedure. Neurologic outcome was favorable after this low-volume, low-pressure injection.

minimal training is necessary to acquire skills for ultrasound-guided procedures. Novices with 1 hour of training and supervised phantom work were proficient at ultrasound-guided nerve blocks (of the terminal branches of the brachial plexus) in the forearm.[81]

A recent training study identified common errors of novices while learning ultrasound-guided regional blocks.[64] These errors included advancing the needle when it was not visualized and unintentional probe movement. Novices often advance the needle even when it is not visualized, presumably because the natural inclination is to assume the needle has not reached the field of view. The potentially quality-compromising behaviors were largely eliminated by the end of the study period (which ranged from 66 to 114 blocks per training subject).

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54 Intravascular Fluid and Electrolyte Physiology

Key Points

1. Water is the major component of all fluid compartments within the body and represents approximately 60% of body weight.
2. Sodium is the most abundant positive ion of the extracellular fluid (ECF) compartment and is crucial in determining the extracellular and intracellular osmolality.
3. Potassium is the most abundant positive ion in the intracellular fluid and plays an important role in the membrane potential of cells.
4. Calcium is the key component that mediates muscle contraction; exocrine, endocrine, and neurocrine secretion; cell growth; and the transport and secretion of fluids and electrolytes.
5. Magnesium is essential for many biochemical reactions; its pharmacologic properties have only more recently been appreciated.
6. Phosphate stores and releases energy through high-energy phosphate bonds and is integral to the structure of proteins, lipids, and bone.
7. Chloride is the predominant anion in the ECF.
8. Glucose is a crucial fuel source, and insulin facilitates glucose movement into cells in a process that also requires potassium and phosphate.
9. Diabetes affects multiple organ systems, and the perioperative effect of diabetes can be profound.
10. The most common causes of metabolic alkalosis are antacid therapy, incidental administration of citrate with blood products, sodium bicarbonate administration, gastric drainage, and renal bicarbonate retention.
11. Metabolic acidosis is commonly caused by low cardiac output and end-stage liver disease.
12. Transfusion of blood products improves tissue oxygenation and decreases bleeding, but it also increases the risk of transmission of infectious diseases, transfusion reactions, immunosuppression, and alloimmunization.
13. Anesthetics may blunt the normal physiologic responses to hypovolemia and the stress response.
14. Shock is dysfunction of intracellular processes caused by the lack of energy.

Water Physiology

Water is the major component of all fluid compartments within the body (see Chapter 88). Total body water represents approximately 60% of the body's total weight in an average adult. In a 70-kg man, total-body water is about 600 mL/kg, or 40 L. The percentage of water varies significantly, however, with age, gender, and adiposity because muscle contains 75% water, whereas adipose tissue contains only 10% water. The percentage water content of a fetus is higher initially, but decreases progressively during late gestation and the first 3 to 5 years of life.

Total-body water may be divided into its two basic components, intracellular and extracellular. The compartments are separated by water-permeable cell membranes. In a 70-kg man, the intracellular fluid volume averages 400 to 450 mL/kg (about 30 L), and the extracellular fluid (ECF) volume averages 150 to 200 mL/kg (about 14 L). ECF volume is greater in young individuals and men than in elderly individuals and women (Table 54-1). The blood volume is 60 to 65 mL/kg, and is distributed as 15% in the arteries and 85% in the venous system.

The major components of the extracellular compartment are the plasma volume (30 to 35 mL/kg) and the interstitial fluid (120 to 165 mL/kg). Other constituents of the ECF include pleural fluid, peritoneal fluid, aqueous humor, sweat, urine, lymph, and cerebrospinal fluid. Plasma warrants special consideration because of its importance in clinical practice. Plasma is the noncellular component of blood and is continuously seeking equilibrium with the interstitial fluid. A major difference of plasma compared with interstitial fluid is the much higher concentration of proteins. This higher concentration of protein results in plasma having an osmotic pressure 20 mm Hg greater than the interstitial fluid and ECF. This gradient helps maintain the intravascular volume. The ECF compartment contains higher concentrations

Table 54-1 Electrolyte Composition in Body Fluids (Normal)

Electrolyte	Plasma (mEq/L)	Interstitial Fluid (mEq/L)	Intracellular Fluid (mEq/L)
Na^+	142	145	10
K^+	4	4	159
Mg^{2+}	2	2	40
Ca^{2+}	5	3	1
Cl^-	103	117	10
HCO_3^-	25	27	7

Adapted from Campbell I: Physiology of fluid balance. Anaesth Intensive Care Med 7:462-465 2006.

of sodium, chloride, and bicarbonate. Permeability to ions and proteins varies with each organ, with the brain having the lowest and the liver having the highest permeability.

Control of body water and its composition is multifactorial and involves many factors, including atrial natriuretic peptide (ANP), vasopressin (i.e., antidiuretic hormone [ADH]), aldosterone (e.g., renin, angiotensin), parathyroid hormone, calcitonin, prostaglandins, dopaminergic receptors, α-adrenergic receptors, the thirst mechanism, and intrinsic renal properties. Water balance describes the difference between water intake and water loss. The kidneys are the major regulators of water output.

Approximately 60% of the daily water loss is excreted in the urine. At high ambient temperatures or with significant exercise, the amount of water lost by sweating increases and may reflect most of the total daily water loss (Table 54-2). Heavy exercise can increase the loss of water through sweating 50 times the normal rate. Increased ventilation amplifies the insensible loss of water through the respiratory tract. Under these conditions, renal water loss decreases to compensate for the increased sweating and insensible water losses.[1]

Sodium Physiology

Sodium is the most abundant positive ion of the ECF and is crucial in determining the extracellular and intracellular osmolality. Serum osmolality is tightly regulated between 275 and 290 mOsm/kg, primarily through the influence of ADH, and is estimated by the following equation:

$$\text{Serum osmolality} = (2 \cdot \text{Na}) + (\text{glucose} \mid 18) + (\text{urea} \mid 2.8)$$

Osmoreceptors in the hypothalamus can detect changes of 1%. Most patients with hyponatremia have urine osmolality of more than 200 mOsm/kg, reflecting impairment in water excretion.[2] With regard to sodium physiology, the ratio of sodium between plasma and interstitial fluid is roughly 5:1 at equilibrium. The distribution equilibrium is usually complete within 15 to 20 minutes. Extracellular sodium balance is determined by sodium intake relative to sodium excretion. Most humans consume far more salt than they need. In normal, healthy individuals, the kidney's main function in sodium balance is excretion of excess sodium.

Sodium requirements vary with age. For infants born before 32 weeks' gestation, requirements are 3 mEq/kg/day, and at term, requirements are 2 to 3 mEq/kg/day (see Chapters 82 and 84).[3] Neonatal stool losses are about 1 mEq/kg/day, and the growth process uses 0.5 mEq/kg/day. Adult requirements decrease to about 1.5 mEq/kg/day. Urinary sodium excretion represents most of the sodium loss and approximately equals the daily intake of sodium. Extrarenal sodium loss by profuse sweating, burns, severe vomiting, or diarrhea is important.

Normally, 10 mL of urine can initially be formed for each 1 mOsm of solute excreted by the kidney. Normal kidneys respond to a free water challenge with diuresis and to a sodium load with natriuresis; if there is decreased sodium intake or volume depletion, the kidney responds with antinatriuresis and antidiuresis (e.g., a patient undergoing surgery may excrete only 1.2 to 1.6 mOsm/mL of solute). In various pathophysiologic processes, abnormally high or low urinary sodium excretion can occur.

Many of the factors that control tubular sodium reabsorption are affected during the perioperative period, including hemodynamic and physical factors (e.g., increased intra-abdominal pressure during laparoscopic procedures), hormonal factors, and renal sympathetic nerve activity. The balance of Starling forces (hydrostatic versus osmotic) is responsible for sodium and water transport across peritubular capillary walls. The net pressure in the peritubular capillaries is about 10 mm Hg in favor of uptake of reabsorbed fluid. Volume expansion with isotonic saline decreases plasma protein concentration and reduces colloidal osmotic pressure (COP) in peritubular capillaries.

The renin-angiotensin system (RAS) is involved in control of arterial blood pressure and blood volume along with the sympathetic nervous system, the kinin-kallikrein system, and arginine vasopressin. The RAS plays a role in sodium homeostasis and renal function, particularly under stress conditions. The RAS may be initiated by decreases in blood pressure in the renal artery, by decreases in sodium delivery to the macula densa, or by sympathetic nervous system activation. In response, renin is synthesized from its precursor, prorenin, and secreted by the juxtaglomerular cells of the kidney. Renin, an aspartyl-protease (similar to pepsin and cathepsin), cleaves its substrate, angiotensinogen, which is an α_2-globulin, to generate the decapeptide angiotensin I. Although renin is mostly produced by the kidney, renin isoenzymes have been found in many tissues, including brain, adrenals, vascular beds, uterus, and placenta.[4] The gene for human renin has been cloned. Angiotensinogen levels are increased after nephrectomy, by estrogens, by thyroid hormones, by glucocorticoids, and during angiotensin I–converting enzyme inhibition.[5,6]

Angiotensin I is rapidly converted to the octapeptide angiotensin II by angiotensin I–converting enzyme or by an endopepti-

Table 54-2 Daily Loss of Water

Source of Loss	Normal Activity and Temperature (mL)	Normal Activity High Temperature (mL)	Prolonged Exercise (mL)
Urine	1400	1200	500
Sweat	100	1400	5000
Feces	100	100	100
Insensible losses	700	600	1000
Total	***2300***	*3300*	***6600***

From Rhoades RA, Tanner GA: Medical Physiology. Boston, Little, Brown, 1995.

dase. The pulmonary circulation seems to be the major site of angiotensin-converting enzyme activity, although angiotensin-converting enzyme also is found in the vascular endothelium of the heart, kidney, adrenal cortex, testes, and brain.[7]

Angiotensin II is a potent vasopressor that stimulates aldosterone secretion through the adrenal cortex. Angiotensin II has a vagal inhibitory effect and causes ganglionic stimulation.[8-10] Angiotensin II partially suppresses renin secretion by a direct effect on the juxtaglomerular cells. Angiotensin II may stimulate a local increase of adenosine, a known inhibitor of renin release, and may participate in a negative feedback loop whereby angiotensin II limits its own biosynthesis.[11] Angiotensin II is degraded in the plasma to the carboxyl-terminal heptapeptide angiotensin III or the amino-terminal heptapeptide angiotensin (1-7), both of which seem to be biologically active.[12] A decline in arterial blood pressure, a decrease in sodium delivery to the macula densa, or sympathetic stimulation may activate the RAS, generating angiotensin II. This results in an increase in blood pressure and sodium retention caused by enhanced aldosterone secretion. The RAS does not have an active role in maintaining blood pressure in a normal, sodium-replete, intact individual. Hydrostatic forces act to maintain a stable glomerular filling pressure. This activity affects venous return, cardiac output, and blood pressure. Superimposed on this mechanism under stress conditions are various neurohumoral control systems, including the sympathetic nervous system, ADH, atrial natriuretic hormone, and prostaglandins (Table 54-3).

Nitroprusside-induced hypotension is associated with increases in renin activity and marked elevations in the plasma concentrations of ADH, which are not seen with the older agent trimethaphan used to induce blood pressure reductions.[13] Conversely, administration of the β-adrenergic blocker propranolol during nitroprusside-induced hypotension prevents increases in plasma renin activity.

Hyponatremia

Hyponatremia, typically defined as a plasma sodium concentration less than 135 mEq/L, can result from excessive loss of sodium from excessive sweating, vomiting, diarrhea, burns, and the administration of diuretics. The most common cause of hyponatremia is an excess of total-body water, not a deficiency of total-body sodium. Under normal conditions, water intake rarely exceeds the kidney's ability to excrete free water. Hyponatremia is usually associated with nonphysiologic vasopressin (i.e., ADH) release and impairment of the renal diluting capacity.

Table 54-3 Major Causes of Natriuresis and Antinatriuresis

Mechanism	Clinical Syndromes
Natriuresis	
Volume-expanded state	High sodium intake, inappropriate antidiuretic hormone secretion
Volume-depleted state	Addison's disease, renal salt wasting, diuretic excess/abuse
Antinatriuresis	
Edematous states	Heart failure, chronic liver disease, nephrotic syndrome, acute glomerulonephritis, idiopathic edema
Nonedematous states	Hemorrhage, low sodium intake, diuretic withdrawal, acute mineralocorticoid administration, nonrenal sodium loss by sweating or vomiting or both

Table 54-4 Causes of Hyponatremia as Related to Intravascular Volume Status

Hypovolemic	Hypervolemic	Euvolemic
Hemorrhage	Congestive heart failure	SIADH
Burn wound edema	Nephrotic syndrome	Pseudohyponatremia syndrome
Peritonitis	Cirrhosis	
Cerebral salt-wasting syndrome	TURP syndrome	

SIADH, syndrome of inappropriate secretion of antidiuretic hormone; TURP, transurethral resection of prostate.

Normal ADH secretion is mediated by an increase in plasma osmolality greater than 280 mOsm or a decrease in effective circulating volume. Other factors that result in release of ADH include pain, sympathetic stimulation, and nausea. After release, ADH binds to the V2 receptors in the medullary collecting ducts. ADH increases the water permeability of these segments by facilitating the fusion of water channels to the apical cell membrane.[14,15] When ascertaining the cause of hyponatremia, serum osmolality must be obtained to determine whether the hyponatremia reflects true hypotonicity; this gives insight into the underlying cause of low sodium levels. Hyponatremia can occur in patients who are hypotonic, normotonic, or hypertonic. Patients' intravascular volume status must be evaluated to understand further the underlying problem leading to abnormalities in sodium physiology (Table 54-4).

Factitious hyponatremia (normotonic hyponatremia) can be seen in hyperlipidemia (i.e., chylomicronemia) or hyperproteinemia. Hyperosmolality resulting from nonsodium molecules (e.g., hyperglycemia, mannitol overdose) draws water from the intracellular space to dilute the intravascular sodium concentration. Significant decreases in total-body sodium most commonly occur from diuretic administration.

Transurethral resection of prostate (TURP) syndrome is a recognized cause of hyponatremia (see Chapter 65). TURP syndrome is caused by intravascular absorption of irrigation solution, which typically contains glycine, but no other electrolytes.[16] The absorption of free water causes hyponatremia because of the dilution of serum sodium. TURP syndrome is a case of true hypotonic hyponatremia and is defined as a serum sodium level of less than or equal to 125 mmol/L with two or more associated clinical symptoms or signs, which can be masked under general anesthesia. A similar syndrome has been reported in 6% of women undergoing transcervical endometrial ablation and in patients undergoing neuroendoscopic ventriculostomy.[17]

The syndrome of inappropriate secretion of ADH (SIADH) is associated with numerous processes, including pulmonary and cranial disorders and several neoplasms, particularly oat cell carcinoma of the lung. Sympathetic activation (e.g., from postoperative pain) also can lead to significantly increased levels of ADH in the absence of volume constriction. SIADH may occur with administration of various drugs, including oral hypoglycemics, tricyclic antidepressants, and diuretics.[18] High levels of ADH are

secreted intermittently at an abnormally low threshold or continuously despite low osmolality. The presence of hyponatremia plus a urine osmolality higher than maximal dilution confirms the diagnosis. In patients with SIADH, the urinary sodium concentration usually exceeds 30 mEq/L, the fractional excretion of sodium is greater than 1%, and the serum uric acid is reduced. Patients with SIADH exhibit a characteristic response to water restriction; a 2- to 3-kg weight loss is accompanied by correction of hyponatremia and cessation of salt wasting over 2 to 3 days. This is another example of true hypotonic hyponatremia.

Hyponatremia also occurs in mixed disorders, in which nonosmotic ADH release and reductions in the rate of urinary sodium excretion blunt urinary diluting capacity. This can occur in advanced volume contraction, intractable heart failure, and advanced hepatic cirrhosis with ascites.

It is crucial for the anesthesiologist to recognize the signs and symptoms associated with hyponatremia, particularly for TURP syndrome managed with regional anesthesia. An awake patient permits detection of the signs of hyponatremia, including nausea, vomiting, visual disturbances, depressed level of consciousness, agitation, confusion, coma, seizures, muscle cramps, weakness, myoclonus, coma, and death. Cerebral edema occurs at or below a serum level of 123 mEq/L, and cardiac symptoms occur at 100 mEq/L. Hyponatremia associated with increased intravascular volume can result in pulmonary edema, hypertension, and heart failure.[19]

Initially, stopping the infusion of hypotonic glycine solution can resolve or at least improve the progression of hyponatremia. Because TURP syndrome is a case of water overload, the treatment should include water restriction. A loop diuretic may be added to facilitate free water excretion. Hypertonic saline should be used only in cases of severe hyponatremia with neurologic symptoms.[20]

In any patient whose hyponatremia warrants correction, the dose of sodium required to correct a deficit may be calculated using the following formula:

$$\text{Dose}\,[\text{mEq}] = \left(\text{weight}\,[\text{kg}] \times \left[140 - \left(\text{Na}^{+}\,[\text{mEq/L}]\right)\right]\right) \times 0.6$$

The optimal rate of correction seems to be 0.6 to 1 mmol/L/hr until the sodium concentration is 125 mEq/L; correction then proceeds at a slower rate. One half the deficit can be administered over the first 8 hours, and the next half can be administered over 1 to 3 days if symptoms remit. The appropriate treatment of hyponatremia, particularly in patients with neurologic symptoms, is, however, an area of controversy. Sodium concentration should be monitored every 1 to 2 hours during rapid correction.

Menstruant female patients are at greater risk for developing significant neurologic sequelae after hyponatremia. Ayus and colleagues[21] found that despite equal incidence of postoperative hyponatremia among men and women, 97% of patients with permanent brain damage were women, and 75% of those were of reproductive age. The mechanism of this gender difference is unknown; however, a potential explanation involves alterations in the brain's adaptive processes to hyponatremia. Estrogens seem to alter the function of Na^+/K^+-ATPase in the rat brain, which could alter the brain's compensatory mechanisms for hyponatremia.[22] Several agents that interfere with urine concentration at the collecting duct, including lithium and demeclocycline, have been used to manage chronic hyponatremia. ADH antagonists and the administration of urea as an osmotic diuretic are under investigation.

Table 54-5 Major Causes of Hyponatremia

Mechanism	Clinical Syndromes
Pseudohyponatremia (normal osmolality)	Hyperlipidemia, hyperproteinemia
Dilutional hyponatremia due to serum hyperosmolality	Hyperglycemia, mannitol administration
True hyponatremia with normal effective osmolality	γ-globulins, lithium, THAM
True hyponatremia with edema (sodium excess)—low effective osmolality	Congestive heart failure, nephrotic syndrome, cirrhosis of the liver, idiopathic edema, hypoalbuminemia (e.g., due to malnutrition)
True hyponatremia (sodium depletion)—low effective osmolality	Renal wasting (diuretics, renal tubular acidosis, cerebral salt-wasting syndrome); extrarenal wasting (vomiting, diarrhea, ostomy losses)
Hyponatremia with normal or expanded effective arterial volume	SIADH, water intoxication due to primary polydipsia, water overload due to advanced renal failure or vascular or inflammatory renal disease
Reduced sodium delivery to diluting segment	Starvation, myxedema (?)

SIADH, syndrome of inappropriate secretion of antidiuretic hormone; THAM, tris(hydroxymethyl)aminomethane.
Adapted from Oh M, Carrol H: Disorders of sodium metabolism: Hypernatremia and hyponatremia. Crit Care Med 20:94, 1992; and from Andreoli TE: Disorders of fluid volume, electrolyte, and acid-base balance. *In* Wyngaarden JB, Smith LH Jr (eds): Cecil Textbook of Medicine, 17th ed. Philadelphia, WB Saunders, 1985, p 525.

Rapid treatment of hyponatremia can lead to cerebral edema or central pontine myelinolysis. Management of hyponatremia involves elimination of the underlying condition when possible (e.g., stop TURP syndrome as soon as possible). The use of normal saline (308 mOsm/L) alone may worsen the hyponatremia, depending on the patient's serum and urine osmolality.[23] Severe coma or seizures can be managed with one or more approaches, including 3% hypertonic saline (513 mEq/L), fluid restriction, or furosemide.[24] The most likely cause of postoperative hyponatremia is SIADH (Table 54-5). SIADH and cerebral salt-wasting syndrome can best be differentiated by determination of total-body water by clinical measurements, including skin turgor, body weight, central venous pressure (CVP), and overall vital signs.

Hypernatremia

Hypernatremia is defined as an increase in extracellular sodium concentration, and may be accompanied by the presence of low, normal, or high total-body sodium content. The major causes of hypernatremia are excessive loss of water, inadequate intake of water, a lack of ADH, or excessive intake of sodium (e.g., with solutions containing a high sodium concentration, such as sodium bicarbonate or hypertonic saline).

Diabetes insipidus may result from a deficiency of ADH (vasopressin) or inability of the kidney to produce a hypertonic medullary interstitium. Diabetes insipidus is characterized by production of a large volume of dilute urine. Deficiency of vasopressin is known as central diabetes insipidus and is an endocrine disorder. Vasopressin deficiency is seen after pituitary surgery, basal skull fracture, and severe head injury. Conversely, nephrogenic diabetes insipidus results if the kidney cannot produce a hypertonic medullary interstitium and is unable to concentrate urine. Nephrogenic diabetes insipidus is defined as renal tubule cell insensitivity to the effects of vasopressin. Nephrogenic diabetes insipidus can result from any systemic or kidney disease that impairs tubular function. In central or nephrogenic diabetes insipidus, the patient loses a significant amount of body water in a short period, which can cause profound hypovolemia if the patient does not have adequate access to water.

Approximately 50% of patients with central diabetes insipidus are classified as having idiopathic disease. This condition is thought to be caused by an autoimmune process affecting the response of the hypothalamus to hypertonicity. Patients with nephrogenic diabetes insipidus have marked increases in the plasma levels of vasopressin because of significant hyperosmolality of the plasma. Renal tubular cells can become poorly responsive to the effects of vasopressin for a variety of reasons. Various insults to the collecting system, such as after ureteral obstruction or medullary cystic disease, lead to decreased sensitivity to vasopressin. Many pharmacologic agents impair the ability of vasopressin to affect tubular water transport and result in nephrogenic diabetes insipidus (Table 54-6).

Patients with continued urine output of more than 100 mL/hr who develop hypernatremia should be evaluated for diabetes insipidus by determining the osmolalities of urine and serum. If the urine osmolality is less than 300 mOsm/L, and serum sodium exceeds 150 mEq/L, the diagnosis of diabetes insipidus is likely. In patients with central diabetes insipidus, 1-deamino-8-D-arginine vasopressin (DDAVP), a vasopressin analog also known as desmopressin acetate, may be administered to correct the deficiency in vasopressin. The underlying cause of nephrogenic diabetes insipidus should be sought and treated if possible.

In the presence of an intact thirst mechanism, a slight increase in serum sodium concentration (e.g., 3 to 4 mmol/L) above baseline values elicits intense thirst. The lack of thirst in the presence of hypernatremia in a mentally alert patient indicates a defect in the osmoreceptor or in the cortical thirst center. The most common objective sign of hypernatremia is lethargy or mental status changes, which can proceed to coma and convulsions. Additional signs and symptoms of hypernatremia include thirst, shock, peripheral edema, myoclonus, ascites, muscular tremor, muscular rigidity, hyperactive reflexes, pleural effusion, and expanded intravascular fluid volume. With acute and severe hypernatremia, the osmotic shift of water from the cells can lead to shrinkage of the brain with tearing of the meningeal vessels and intracranial hemorrhage. Slowly developing hypernatremia is usually well tolerated because of the brain's ability to regulate its volume. Treatment involves restoring normal osmolality and volume and includes removal of excess sodium by the administration of diuretics and hypotonic crystalloid solutions. The speed of correction depends on the rate of development of hypernatremia and associated symptoms. Because chronic hypernatremia is well tolerated, rapid correction offers no advantage and may be extremely harmful or lethal because it may result in brain edema.[25,26] Typically, a maximum of 10% of the serum sodium concentration, or about 0.7 mmol/L/hr, should be the goal rate of correction. Hypernatremia increases the minimum alveolar concentration of inhaled anesthetic agents, possibly because of enhanced sodium conductance during depolarization of excitatory membranes (Table 54-7).

Table 54-6 Drugs Causing Nephrogenic Diabetes Insipidus

Lithium
Foscarnet
Glyburide
Demeclocycline
Methoxyflurane
Amphotericin B

Table 54-7 Major Causes of Hypernatremia

Mechanism	Clinical Syndrome(s)
Impaired thirst	Stupor/coma, essential hypernatremia
Solute (osmotic) diuresis	Diabetic ketoacidosis, hyperglycemic nonketotic coma, mannitol administration
Excessive water losses	
Renal	Pituitary diabetes insipidus, nephrogenic diabetes insipidus
Extrarenal	Sweating
Combined	Stupor/coma *plus* hypertonic enteric feeding

Note: Hyperglycemia or mannitol administration also can result in hyponatremia. Sweating also can result in hyponatremia.
Adapted from Andreoli TE: Disorders of fluid volume, electrolyte, and acid-base balance. *In* Wyngaarden JB, Smith LH Jr (eds): Cecil Textbook of Medicine, 17th ed. Philadelphia, WB Saunders, 1985, p 528.

Potassium Physiology

Potassium is the most abundant positive ion in the intracellular fluid, and nearly 98% of total-body potassium is intracellular. In the short-term (minutes), potassium balance is influenced by insulin, pH, β-adrenergic agonists, and bicarbonate concentration. Long-term regulation of potassium excretion and balance primarily involves the kidney and aldosterone. Potassium concentration to average 0.4 to 0.5 mEq/L lower when measured on heparinized arterial samples compared with clotted venous samples is due to several factors, including extrusion of potassium from erythrocytes during the clotting process.

Increases in potassium intake increase renal excretion of potassium through various cellular mechanisms. In response to increases in extracellular potassium levels, aldosterone is secreted from the zona glomerulosa of the adrenal gland and acts on cortical collecting ducts to increase potassium secretion into the tubular fluid and increase potassium excretion.

Many of the effects seen during alterations in normal potassium levels result from potassium's importance in the membrane potential of cells. Potassium is the principal intracellular cation, with more than 98% of the body's potassium found within the intracellular water. In the resting state, cell membrane conductance is higher for potassium than for sodium. This increased

conductance leads to transmembrane potential being closer to the transmembrane value of potassium (−90 mV). Alterations in extracellular potassium concentration alter the resting membrane potential, which may cause the cell to be unresponsive or overresponsive to sodium shifts into the cell. High or low potassium levels can result in potentially lethal problems in excitatory tissue, particularly cardiac tissue.

Multiple factors regulate the normal maintenance of the transmembrane potassium gradient. The most important transcellular enzyme involved in potassium regulation is Na^+/K^+-ATPase, which maintains the transcellular gradient. β_2-Adrenergic drugs increase the activity of Na^+/K^+-ATPase by binding to cell surface receptors, linking potassium transport to the sympathetic nervous system. Insulin causes more sodium to enter the cell through an Na^+/H^+-antiporter, which decreases intracellular proton concentration. To maintain electric neutrality, any increase in sodium must occur via exchange for potassium, decreasing extracellular potassium. Shock can have an adverse impact on the activity of Na^+/K^+-ATPase by limiting the amount of adenosine triphosphate (ATP) available for ion transport because of the shift to anaerobic metabolism.[27] Potassium transport is affected by pH. The body uses potassium to decrease excess extracellular hydrogen ions by moving potassium out of cells and hydrogen ions into cells. Acidemia potentiates hyperkalemia by moving potassium out of cells.

Potassium requirements vary with age and growth. A typical term infant requires 2 to 3 mEq/kg/day,[28] whereas adults use 1 to 1.5 mEq/kg/day (see Chapters 82 and 84). Potassium demands are related to metabolic rate (2 mEq/100 kcal). In this regard, the requirement increases dramatically during cell growth after establishment of nutrition in previously starved individuals. An extremely high or low level of potassium is life-threatening.

Hypokalemia

Hypokalemia (<3.5 mEq/L) may occur because of an absolute deficiency or redistribution into the intracellular space. A reduction in serum potassium of 1 mEq/L indicates a net loss of 100 to 200 mEq of potassium in a normal adult. Hypokalemia in the range of 2 to 2.5 mEq/L is likely to cause muscular weakness, arrhythmias, and electrocardiographic abnormalities, including sagging of the ST segment, depression of the T wave, and U wave elevation. These electrocardiographic changes do not correlate with the severity of potassium depletion. Cardiac dysrhythmias are more predictable, however, and most frequently involve atrial fibrillation and premature ventricular systoles.

The four most common causes of hypokalemia are reduced intake, gastrointestinal losses, excessive renal losses of potassium (e.g., with excess of mineralocorticoids or diuretics), and potassium shifts from the ECF to the intracellular fluid (e.g., owing to insulin administration). Such shifts can occur with acute alkalosis, insulin therapy, stress-related catecholamine activity, and hypokalemic periodic paralysis. Surgical stress may reduce the serum potassium concentration by 0.5 mEq/L. The administration of exogenous catecholamines, such as isoproterenol, terbutaline, epinephrine, and ritodrine, also decreases potassium levels[29,30]; clinically, this includes pregnant patients receiving tocolytic therapy or respiratory treatment with β_2-agonists and critically ill patients requiring pharmacologic cardiovascular support (see Chapters 69 and 92).

No studies show increased morbidity or mortality for patients undergoing anesthesia with a potassium level of at least 2.6 mEq/L. Anesthesiologists commonly administer supplemental potassium chloride, but studies show that in many instances therapy is ineffective, with most of the supplemental potassium being excreted in the urine despite continued hypokalemia.[31,32] If perioperative therapy is indicated, intravenous potassium chloride should be used. Because the rate of administration of potassium must be adjusted for the rate of distribution through the extracellular space before entry into the intracellular space, the rate of potassium administration is typically limited to approximately 0.5 mEq/kg/hr. The typical replacement rate is 10 to 20 mEq/hr for a normal adult with constant monitoring of the electrocardiogram.[33,34] Clinical anesthesiologists should be aware that safe administration of potassium is enhanced by the use of continuous electrocardiogram monitoring, bedside potassium measurement, and delivery with an infusion pump (Table 54-8).

Hyperkalemia

Hyperkalemia (>5.5 mEq/L) can occur in various disease states, in response to drugs that diminish renal potassium excretion (Table 54-9), or after sudden transcellular shifts of potassium from the intracellular fluid to the ECF. Potentially lethal hyperkalemia during anesthesia may occur with reperfusion of a large vascular bed after a period of ischemia (usually >4 hours). Ischemia results in significant acidosis in the affected area, which causes an outflow of intracellular potassium. When the area is reperfused, the body receives a large bolus of potassium that cannot be redistributed rapidly enough, resulting in potentially fatal hyperkalemia. Any condition or drug resulting in adrenal inhibition or decreasing aldosterone levels can cause potassium retention. Factitious (e.g., spurious) hyperkalemia also should be considered in the differential diagnosis and occurs in response to lysis of the cellular components of blood.

Table 54-8 Major Causes of Hypokalemia

Mechanism	Clinical Syndromes
Inadequate intake	Anorexia nervosa, starvation, alcoholism, mineralocorticoid excess (primary and secondary hyperaldosteronism)
Excess renal loss	Bartter's syndrome; diuresis (diuretics with a pre-late distal locus osmotic diuresis, chronic metabolic alkalosis); impermeant anion antibiotics (carbenicillin, penicillin, nafcillin, ticarcillin); renal tubular acidosis; hypomagnesemia; myelomonocytic leukemia
Gastrointestinal losses	Vomiting; diarrhea, particularly secretory diarrheas; villous adenoma
Shifts of extracellular fluid to intracellular fluid with altered internal potassium balance	β_2-agonists, acute alkalosis, hypokalemic periodic paralysis, insulin therapy, vitamin B_{12} therapy, lithium overdose

Adapted from Andreoli TE: Disorders of fluid volume, electrolyte, and acid-base balance. *In* Wyngaarden JB, Smith LH Jr (eds): Cecil Textbook of Medicine, 17th ed. Philadelphia, WB Saunders, 1985, p 532.

Table 54-9 Drugs Causing Hyperkalemia

Amiloride
Angiotensin II antagonists
Angiotensin-converting enzyme inhibitors
Mannitol
Pentamidine
Spironolactone
Succinylcholine
Triamterene
Trimethoprim

Hyperkalemia can be separated into acute and chronic processes. Acute hyperkalemia can occur in various circumstances and usually is more poorly tolerated than chronic hyperkalemia. The most common cause of chronic hyperkalemia occurring with anesthesia is renal failure. A patient undergoing anesthesia with even moderately elevated potassium concentration (>5.5 mEq/L) should have continuous electrocardiographic monitoring to help determine the severity of hyperkalemia.

Clinically, hyperkalemia can cause muscle weakness and paralysis. Alterations in cardiac conduction increase automaticity and enhance repolarization. Mild elevations in potassium levels (6 to 7 mEq/L) may manifest with peaked T waves; as levels approach 10 to 12 mEq/L, a prolonged P–R interval, widening of the QRS complex, ventricular fibrillation, or asystole can occur.

Conceptually, treatments are divided into (1) physiologic antagonists (calcium); (2) agents to shift potassium into cells (glucose, insulin, hyperventilation, bicarbonate, and β-adrenergic agonists); and (3) drugs and treatments to eliminate potassium from the body (sodium polystyrene sulfonate [Kayexalate], diuretics, aldosterone agonists, dialysis). Clinical treatment of hyperkalemia is determined by the setting and presence of electrocardiographic changes; it involves first stabilization of the heart from effects of the potassium with intravenous calcium (500 mg of calcium chloride or 1 g of calcium gluconate in an adult) and redistribution of potassium from the plasma into cells. As stated earlier, in addition to intravenous calcium, intravenous glucose, insulin, and bicarbonate (1 mEq/kg) and hyperventilation are the major therapies used in the operating room. Intravenous regular insulin, 5 to 10 U, administered with dextrose at a dose of 25 to 50 g (i.e., one to two 50-mL ampules of 50% dextrose solution), reduces serum potassium levels within 10 to 20 minutes, and the effects last 4 to 6 hours.[35] Resin exchange, dialysis, diuretics (e.g., furosemide, 20-40 mg intravenously), aldosterone agonists (e.g., fludrocortisone), and inhaled or intravenous β-adrenergic agonists are established additional therapies (Table 54-10).

Calcium Physiology

Calcium is the key component that mediates muscle contraction; exocrine, endocrine, and neurocrine secretion; cell growth; and the transport and secretion of fluids and electrolytes. A 70-kg adult contains approximately 1300 g of calcium, 99% of which is in the bones and teeth. The kidneys are the major organ responsible for regulating calcium between 4.5 and 5 mEq/L (8.5 to 10.5 mg/dL). Calcium is abundant in milk and milk products, is poorly absorbed by the intestine, and is excreted primarily in the feces and urine. Circulating calcium exists in three forms: bound to plasma proteins (primarily albumin) and not filtered by glomerular capillaries (40% to 50%); ionized, physiologically active, filtered at the glomerular membrane, and maintained at a concentration of 2 to 2.5 mEq/L (50%); and nonionized and chelated with phosphate, sulfate, and citrate (10%). Because changes in pH alter the fraction of calcium that is bound to albumin, the level of ionized calcium can change without alteration of total calcium. Total calcium varies with protein-binding capacity and results, under hyperaluminemia, in pseudohypercalcemia (most commonly associated with dehydration and multiple myeloma). Most filtered calcium is reabsorbed in the proximal tubule, the thick ascending limb of the loop of Henle, and the distal tubule.

Because of the importance of calcium in virtually all cellular functions, its intracellular and extracellular concentrations are tightly controlled. Energy is expended to pump intracellular calcium out of the cytosol into the sarcoplasmic reticulum or ECF. As with potassium, during shock and depletion of intracellular energy, calcium accumulates within cells and can facilitate cell death.

The concentration of serum proteins is an important determinant of calcium ion concentration. Ionized calcium can be measured directly with the use of calcium-specific electrodes. When ionized calcium cannot be measured, the approximate amount of calcium bound to protein is given by the following equation:

$$\text{Protein-bound calcium (\%)} = -0.8 \times \text{albumin}\,(\text{g/L}) + 0.2 \times \text{globulin}\,(\text{g/L}) + 3$$

Alternatively, a correction of 0.8 mg/dL is added to the serum calcium for every 1 g/dL that serum albumin is less than 4 g/dL.[36] If the serum calcium is 7.8 mg/dL (a subnormal value), and the serum albumin is only 3 mg/dL, the stated serum calcium is corrected by adding 0.8 mg/dL; the corrected value of 8.6 mg/dL is within the normal range. One advance in the management of perioperative calcium includes the ease of bedside serum ionized calcium measurement.

Within minutes of a slight decrease in extracellular calcium concentration, the parathyroid glands release parathy-

Table 54-10 Major Causes of Hyperkalemia

Mechanism	Clinical Syndromes
Pseudohyperkalemia	Sample lysis, technical problems
Altered internal potassium balance	Acidosis; insulin deficiency; hypoaldosteronism; malignant hyperthermia; periodic paralysis; cell necrosis; drugs (succinylcholine, digitalis, nonselective β-blockers)
Altered external potassium balance	Increased uptake by replacement therapy; transfusions; antibiotics containing potassium salts; decreased excretion by renal disease; hypoaldosteronism; drugs (heparin, amiloride, triamterene, spironolactone, nonsteroidal drugs, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists)

Adapted from Solomon RJ, Katz JD: Disorders of potassium homeostasis. *In* Stoelting RK (ed): Advances in Anesthesia. Chicago, Year Book Medical Publishers, 1986.

roid hormone, which increases calcium reabsorption in the thick ascending limb and distal tubule, decreasing calcium excretion. Excision of the parathyroid glands eliminates parathyroid hormone secretion, which can significantly disrupt calcium homeostasis.

Calcitonin, produced in the thyroid gland, decreases renal reabsorption of calcium acutely, but has little effect on long-term calcium homeostasis. Surgical removal of the thyroid gland eliminates calcitonin without changing extracellular calcium ion concentration.

Bone acts as the body's major reservoir of calcium. When the parathyroid gland releases parathyroid hormone in response to decreased calcium levels, bone reabsorption is favored, and calcium is released. Vitamin D increases absorption of calcium from the gastrointestinal tract, and its action is potentiated by parathyroid hormone.

Hypercalcemia

Hypercalcemia is associated with many disease processes and has many signs and symptoms. Mild to moderate hypercalcemia (11 to 14 mg/100 mL) often has no symptoms, but when levels reach 15 mg/100 mL, clinical changes become more common. Hypercalcemia produces changes primarily in the central nervous system (e.g., mental status changes), the gastrointestinal tract (e.g., vomiting), the kidneys (e.g., polyuria, renal calculi, oliguric renal failure), and the heart (e.g., cardiac conduction disturbances). Today, hypercalcemia is most commonly diagnosed in asymptomatic patients, whereas clinical features previously were the earliest manifestations. Potential causes of hypercalcemia include thiazide diuretic therapy, malignancy (now known as humoral hypercalcemia of malignancy), granulomatous disease (related to increased intestinal absorption of calcium induced by elevated calcitriol levels), vitamin D intoxication, or parathyroid hormone adenoma. Additional causes of hypercalcemia include lithium therapy, thyrotoxicosis, pheochromocytoma, immobilization, vitamin A intoxication, renal failure, and theophylline therapy.

Treatment of hypercalcemia essentially involves diuresis and administration of normal saline to dilute plasma calcium. These primary treatments also are useful because sodium inhibits the renal reabsorption of calcium. Additional therapies include bisphosphonates (pamidronate is the most commonly used), calcitonin, ambulation, hemodialysis, and treatment of the underlying condition. Certain conditions, including numerous cancer-related hypercalcemias, can be treated with calcium-lowering agents, such as mithramycin and glucocorticoids. The anesthetic management of a patient with hypercalcemia should involve avoidance of thiazide diuretics and maintenance of hydration and urine output with sodium-containing fluids. Monitoring the patient by means of electrocardiograms is useful to detect cardiac conduction abnormalities with shortened P–R or Q–T interval, with or without widening of the QRS complex. Patients who have muscle weakness should receive decreased doses of nondepolarizing muscle relaxants (Table 54-11).

Table 54-11 Major Causes of Hypercalcemia

Mechanism	Clinical Syndromes
Increased parathyroid hormone	Primary hyperparathyroidism (solitary or multiple adenoma, multiple endocrine neoplasia syndrome), lithium therapy, familial hypocalciuric hypercalcemia
Vitamin D related	Vitamin D intoxication; idiopathic hypercalcemia of infancy; increase in 1,25-dihydroxyvitamin D; sarcoidosis and other granulomatous diseases
Associated with high bone turnover	Hyperthyroidism, immobilization, thiazides, vitamin A intoxication
Malignancy related, including associated with renal failure	Solid tumors with metastases, solid tumors with humoral mediators of hypercalcemia, hematologic malignancies, severe secondary hyperparathyroidism (from chronic renal failure), aluminum intoxication, milk-alkali syndrome

Adapted from Potts JT: Diseases of the parathyroid gland and other hyper- and hypocalcemic disorders. *In* Isselbacher KJ, Braunwald E, Wilson JD, et al (eds): Harrison's Principles of Internal Medicine, 13th ed. New York, McGraw-Hill, 1995, p 2151.

Hypocalcemia

In the operating room, ionized hypocalcemia is most commonly caused by acute hyperventilation or the infusion of citrated blood greater than 1.5 mL/kg/min (see Chapter 55). The most common cause of hypocalcemia (plasma concentration <4.5 mEq/L) in hospitalized patients is a low albumin level, such as in critically ill patients with severe sepsis, burns, or acute renal failure, and in patients after extensive transfusions. Critically ill patients can have low plasma albumin and low plasma calcium levels with normal ionized calcium levels. There is no reason to correct the calcium deficiency, but overall nutrition should be improved. The major signs and symptoms of hypocalcemia include mental status changes, tetany, positive Chvostek and Trousseau signs, laryngospasm, hypotension, and dysrhythmias. Electrocardiographic evaluation may show prolongation of the Q–T interval or heart block in severe cases. Treatment, often prompted by hypotension, involves intravenous infusion of 10% calcium chloride (1.36 mEq/mL) or calcium gluconate (0.45 mEq/mL). When equivalent calcium doses are administered, both preparations are equally efficacious in restoring the calcium level to normal (Table 54-12). In this regard, calcium gluconate is especially advantageous in peripheral venous administration because extravasated calcium chloride solution can result in severe tissue destruction.

When hypocalcemia is caused by large-volume infusion of isotonic saline (as seen during resuscitation in shock), it may be accompanied by hypomagnesemia. Hypomagnesemia may impair the actions of vitamin D and delay correction of postresuscitation hypocalcemia. The magnesium level should be checked and corrected if necessary. In this regard, fluid resuscitation involving certain colloids can contribute to a hypocalcemic state.[37]

Magnesium Physiology

Magnesium sulfate has been used for many years on an empirical basis to control convulsions in patients with preeclamptic toxemia. Magnesium ions are essential for many biochemical reactions, and a deficiency may produce clinically important consequences. Many of the pharmacologic properties have only more recently been appreciated. Magnesium is excreted through the gastrointestinal tract and kidneys.

Table 54-12 Major Causes of Hypocalcemia Excluding Neonatal Conditions

Mechanism	Clinical Syndromes
Parathyroid hormone absent	Hereditary hypoparathyroidism, acquired hypoparathyroidism, hypomagnesemia
Parathyroid hormone ineffective	Lack of active vitamin D (decrease in intake or lack of sunlight), defective metabolism from anticonvulsant therapy, vitamin D–dependent rickets type I
Pseudohyperparathyroidism	Ineffective vitamin D (intestinal malabsorption), vitamin D–dependent rickets type II
Parathyroid hormone overwhelmed	Severe, acute hyperphosphatemia; tumor lysis; acute renal failure; rhabdomyolysis; osteitis fibrosa after parathyroidectomy

Adapted from Potts JT: Diseases of the parathyroid gland and other hyper- and hypocalcemic disorders. *In* Isselbacher KJ, Braunwald E, Wilson JD, et al (eds): Harrison's Principles of Internal Medicine, 13th ed. New York, McGraw-Hill, 1995, p 2165.

Total-body magnesium is approximately 2000 mEq. Magnesium is the fourth most prevalent cation in the body and activates approximately 300 enzyme systems, including many involved in energy metabolism.[40] It is essential for the production and functioning of ATP, which is fully functional only when chelated to magnesium. Other processes dependent on magnesium include the production of DNA, RNA, and protein synthesis.[40]

Magnesium is an essential regulator of calcium access into the cell and of the actions of calcium within the cell. Magnesium plays an essential role in the regulation of most cellular functions and may be regarded as a natural physiologic calcium antagonist.[40]

Hypomagnesemia

With an absence of magnesium in the diet, the kidneys are able to decrease excretion significantly; however, hypomagnesemia is common in hospitalized patients, especially patients in critical care areas, and it manifests with signs and symptoms similar to hypocalcemia. Slight hypomagnesemia occurs in athletes, in hypermetabolic states such as pregnancy, and during cold acclimatization. Magnesium stores can become depleted in patients undergoing prolonged diuretic therapy or patients with chronic diarrhea. Chronic alchohol ingestion leads to significant loss of magnesium, and most hospitalized alcoholics have low magnesium levels. Magnesium deficiency alone or in combination with diuretic-induced hypokalemia and digitalis-induced arrhythmia responds to magnesium therapy.[38]

Anesthetizing patients with magnesium deficiency is likely to increase the risk of perioperative arrhythmias. Respiratory muscle power is impaired by hypomagnesemia, which may have important clinical consequences for anesthesia and critical care. Additional manifestations include central nervous system irritability with seizures and hyperreflexia (e.g., Chvostek sign) and skeletal muscle spasm (e.g., Trousseau sign). Treatment in a 70-kg adult with normal renal function in whom intravenous therapy is warranted includes magnesium sulfate 1 to 2 g (8 to 16 mEq) over 15 minutes followed by 1 g/hr until serial serum magnesium levels indicate the deficiency has been corrected.[39] For acute arrhythmias, magnesium sulfate can be administrated in a dose of 1 to 2 g over approximately 5 minutes intravenously with close monitoring of blood pressure and heart rate. Arterial pressure, deep tendon reflexes, and magnesium concentration may aid the clinical anesthesiologist when overtreatment is suspected. In asymptomatic patients with mild hypomagnesemia, oral replacement is preferred. Beyond the theoretical risks of magnesium deficiency and neuromuscular blockade, the clinical importance of hypomagnesemia is related to the conditions and pathophysiologic processes associated with management of these conditions (Table 54-13).

Hypermagnesemia

Hypermagnesemia (>2.5 mEq/L) occurs most commonly from iatrogenic causes and excessive use of magnesium-containing antacids or laxatives. It is rare in clinical medicine because magnesium is relatively poorly absorbed from the gastrointestinal tract, and renal elimination of excess magnesium is extremely rapid (within 4 to 8 hours of a magnesium load). Because elimination is directly related to the glomerular filtration rate, patients with kidney failure are at increased risk of developing hypermagnesemia. Signs and symptoms are directly related to the blood level and include alterations in the nervous, cardiovascular, respiratory, and genitourinary systems.

Magnesium depresses the central nervous system. In the early 1900s, it was used effectively as a general anesthetic. Magnesium penetrates the blood-brain barrier poorly, however, and its level in the cerebrospinal fluid is well controlled by an active transport mechanism.[40]

In the peripheral nervous system, magnesium interferes with the release of neurotransmitters at all synaptic junctions and potentiates the action of local anesthetics.[40] At the neuromuscular junction, magnesium concentrations of 5 mmol/L cause signifi-

Table 54-13 Major Causes of Hypomagnesemia

Mechanism	Clinical Syndromes
Primary nutritional disturbances	Inadequate intake, total parenteral nutrition, refeeding syndrome
Gastrointestinal disorders	Specific absorptive defects, malabsorption syndromes, prolonged diarrhea, prolonged nasogastric suction, pancreatitis
Endocrine disorders	Hyperparathyroidism, hypoparathyroidism, hyperthyroidism, primary hyperaldosteronism, Bartter's syndrome, diabetic or alcoholic ketoacidosis, administration of epinephrine, SIADH, hungry bone syndrome after parathyroidectomy
Chronic alcoholism, alcoholic withdrawal, increased renal excretion	Ethanol ingestion; idiopathic; after renal transplantation; drugs (cisplatin, aminoglycoside, amphotericin B, diuretics, pentamidine, theophylline); recovery phase of acute tubular necrosis; colony-stimulating factor therapy

SIADH, syndrome of inappropriate secretion of antidiuretic hormone.
Adapted from Potts JT: Diseases of the parathyroid gland and other hyper- and hypocalcemic disorders. *In* Isselbacher KJ, Braunwald E, Wilson JD, et al (eds): Harrison's Principles of Internal Medicine, 13th ed. New York, McGraw-Hill, 1995, p 2188.

cant presynaptic neuromuscular blockade and enhance the action of the nondepolarizing muscle relaxants.[40] It can precipitate severe muscle weakness in patients with Eaton-Lambert syndrome, patients with myasthenia gravis, or patients pretreated with a small dose of a defasciculating agent.[40] Magnesium prolongs the action of depolarizing neuromuscular blocker drugs (e.g., succinylcholine); administration before the use of succinylcholine prevents the release of potassium provoked by the neuromuscular blocking drug (see Chapter 29).

In the cardiovascular system, magnesium produces vasodilation by direct action on blood vessels and by interfering with a wide range of vasoconstrictor substances. It also reduces peripheral vascular tone by sympathetic blockade and inhibition of catecholamine release.[40] In the isolated heart, increased concentrations of extracellular magnesium ion markedly depress contractile force. Decreased myocardial performance has been shown after a bolus of 2.5 g of magnesium sulfate. Severe myocardial depression can occur with combinations of magnesium and diltiazem. In the isolated heart, magnesium produces bradycardia, but in an intact subject, the inhibition of vagal acetylcholine release produced by magnesium overrides the intrinsic slowing, and a mild tachycardia occurs. Magnesium is effective in treating various arrhythmias, including ventricular arrhythmias, torsades de pointes, arrhythmias associated with epinephrine administration, and digitalis-associated arrhythmias. It also is efficacious in certain arrhythmias induced by hypokalemia, alcoholism, and myocardial infarction, and may offer partial protection against bupivacaine-induced arrhythmias.

In the respiratory system, magnesium has no effect on central respiratory drive, and its only respiratory depressant effect is caused by the neuromuscular blockade that it produces. It is an effective bronchodilator and has been used successfully in severe acute asthma, although no study to date has shown benefit in chronic asthma.

In obstetric practice, magnesium, at supraphysiologic concentrations, is a powerful tocolytic and has been used for many years in the management of premature labor. Magnesium also is used in obstetrics to prevent patients with preeclampsia from developing seizures. Animal studies have shown that magnesium suppresses electroencephalographic spike activity (see Chapter 69). Therapeutic magnesium levels are 5 to 7 mg/dL when administered for preeclampsia. When levels exceed 15 to 20 mg/dL, respiratory depression can become profound. In the kidney, magnesium is a renal vasodilator and a diuretic.

Symptoms and electrocardiographic changes of hypermagnesemia correspond to serum levels. Depressed cardiac conduction, widened QRS complexes, prolonged P–R intervals, and nausea appear with levels of 5 to 10 mg/dL. Sedation, hypoventilation, decreased deep tendon reflexes, and muscle weakness appear with levels of 20 to 34 mg/dL, with hypotension, bradycardia, and diffuse vasodilation occurring at levels of 24 to 48 mg/dL. Areflexia, coma, and respiratory paralysis occur at 48 to 72 mg/dL. For these reasons, all patients being treated with magnesium therapy are clinically observed for magnesium intoxication.

Elimination of magnesium involves fluid loading followed by or with concomitant diuresis. Definitive therapy involves dialysis. Temporary reversal of the effects of magnesium can be managed with calcium therapy. Because hypermagnesemia potentiates the effects of depolarizing and nondepolarizing muscle relaxants, these agents must be carefully titrated in conjunction with appropriate assessment of neuromuscular blockade.

The deleterious effects of magnesium deficiency are well recognized, and most critical care units monitor magnesium levels. In coronary care units, several studies have shown that the infusion of magnesium sulfate can reduce the incidence and severity of cardiac arrhythmias associated with myocardial infarction. Numerous reports in the literature describe the bronchodilator effect of magnesium and its successful use in the management of asthma. Magnesium may decrease the incidence of adrenergically mediated arrhythmias without interfering with the bronchodilating action of β-stimulants and contribute to smooth muscle relaxation of bronchioles.[40]

Magnesium has several important pharmacologic actions. Its route of elimination is renal, and any patient who is oliguric or in a reduced urine output state requires downward dosing adjustment of magnesium therapy. Magnesium should be regarded as a cardiovascular drug, first and foremost, with calcium antagonistic and antiadrenergic properties that may be accompanied by minimal myocardial depression.[40]

Phosphate Physiology

Phosphate is the most abundant intracellular anion, and is essential for membrane structure, cellular energy, and cell transport. Specifically, phosphate is required to produce ATP, DNA, RNA, and 2,3-diphosphoglycerate, which facilitates oxygen release from hemoglobin. About 1 g of phosphorus is ingested daily. Intake generally exceeds metabolic requirements. Approximately 70% (700 mg) is absorbed primarily from the small intestine, with the rest (300 mg) eliminated in the feces. In addition to 1,25-dihydroxyvitamin D_3 (vitamin D), parathyroid hormone facilitates absorption of phosphate from the gut lumen. The gut secretes phosphate into the lumen and then reabsorbs it, unless it is bound there by calcium or antacids or is lost by diarrhea or drainage through ostomies or fistulas. Under normal dietary conditions, absorption of phosphate occurs through paracellular diffusive pathways with little regulation. When luminal phosphate concentrations are low, an active sodium-dependent transport mechanism is activated, and additional phosphate is absorbed.[41] When dietary intake is normal, phosphate absorption is essentially an unregulated process. Cations such as calcium, magnesium, and aluminum decrease phosphate absorption, however, by directly binding with phosphate in the gut lumen. This is useful clinically in renal failure to limit the amount of phosphate reabsorbed by the gut. Because of the unregulated nature of phosphate absorption in the gut, the kidneys become the primary organ of excretion of excess phosphate. The kidneys normally excrete 700 mg/day by filtering 6 g and reabsorbing 5.3 g. Urinary phosphate elimination approximately equals intestinal absorption.

As mentioned, phosphate stores and releases energy through high-energy phosphate bonds and is integral to the structure of proteins, lipids, and bone (hydroxyapatite). Bone functions as the primary reservoir of phosphate and calcium in the body. When the body requires extra calcium, bone is broken down to release calcium for the body's use. In addition to calcium, significant amounts of phosphate also are liberated. This balance is controlled by the regulatory processes discussed in the previous section.

Factors favoring cellular uptake include ingestion of glucose or fructose, alkalosis, insulin level, β-adrenergic stimulation, and anabolism. Phosphate occurs in organic or inorganic forms. Most

intracellular phosphate is organic. Plasma contains lipid phosphates, organic ester phosphates, and inorganic phosphates, including divalent (HPO_4^{2-}) and monovalent ($H_2PO_4^-$) phosphate. At physiologic pH, 80% of the inorganic phosphate is divalent. Normally, plasma inorganic phosphate is maintained at 3 to 4.5 mg/100 mL in adults and 4 to 5 mg/100 mL in children. Parathyroid hormone inhibits proximal tubular inorganic phosphate reabsorption and increases inorganic phosphate excretion. In animals that are thyroparathyroidectomized, parathyroid hormone is absent, and reabsorption of inorganic phosphate increases significantly and ultimately increases plasma inorganic phosphate levels. In patients with primary hyperparathyroidism, parathyroid hormone secretion is elevated, and plasma levels of inorganic phosphate are low; however, steady-state urinary inorganic phosphate excretion is not markedly increased because it depends largely on intestinal inorganic phosphate absorption. Dietary restriction of inorganic phosphate leads to almost 100% reabsorption of filtered inorganic phosphate and to reduction of urinary phosphate to zero.[42]

Hyperphosphatemia

Severe hyperphosphatemia occurs after tissue damage or cell death. Moderate to severe hyperphosphatemia may be caused by an impaired ability to excrete phosphorus because of renal failure. As renal failure worsens, and the glomerular filtration rate declines to less than 25 mL/min, hyperphosphatemia may develop. Other causes include iatrogenic, hypothermia, massive liver failure, and certain hematologic malignancies associated with high cell turnover. The increased cell turnover can be part of the malignancy or may result from cell destruction when chemotherapy is instituted.

Hypoparathyroidism can cause hyperphosphatemia in the presence of normal renal function. Rapid increases in serum phosphate can lead to development of severe hypocalcemia. Hypocalcemia results from decreased calcitriol production, which causes significant decline in gastrointestinal tract absorption of calcium. There may be frank precipitation of calcium and phosphate, decreasing serum calcium levels further. When the calcium-phosphorus product exceeds 70 mg^2/dL^2, the risk of abnormal calcification is increased. An elevated calcium × phosphorus level represents poor phosphorus control and often is associated with metastatic tissue calcifications. Treatment involves administration of phosphate-binding antacids, such as aluminum antacids and sucralfate, calcium citrate, or calcium carbonate, and may include dialysis, especially in patients with renal failure (Table 54-14).

Table 54-14 Major Causes of Hyperphosphatemia

Mechanism	Clinical Syndromes
Binding to serum proteins	Including plasma cell dyscrasias
Decreased renal excretion	Renal insufficiency, hypoparathyroidism, pseudohypoparathyroidism types I and II, tumoral calcinosis, pseudoxanthoma elasticum, infantile hypophosphatasia, hyperostosis, hyperthyroidism, adrenal insufficiency, bisphosphonate therapy
Increased intestinal absorption	Phosphorus-containing cathartics; medication with vitamin D compounds; granulomatous disease producing vitamin D, including sarcoidosis and tuberculosis
Internal redistribution	Acute metabolic or respiratory acidosis, reduced insulin level, clonidine administration
Cellular release	Rhabdomyolysis; organ infarction; tumor lysis, as in Burkitt's or lymphoblastic lymphomas or metastatic small cell carcinoma
Parenteral administration	Intravenous phosphate salts, lipid (phospholipid) infusion

Adapted from Potts JT: Diseases of the parathyroid gland and other hyper- and hypocalcemic disorders. *In* Isselbacher KJ, Braunwald E, Wilson JD, et al (eds): Harrison's Principles of Internal Medicine, 13th ed. New York, McGraw-Hill, 1995, p 2186.

Hypophosphatemia

The typical normal range of phosphorus is 2.4 to 4.1 mg/dL. Hypophosphatemia has many causes and is severe when serum phosphorus levels decline to less than 1 mg/dL. Conditions causing such low phosphate levels include prolonged respiratory alkalosis and rapid cellular uptake. Severe hypophosphatemia with total-body deficiency usually reflects poor dietary intake or consumption of phosphate-binding antacids, or both.

Hypophosphatemia occurs in alcoholism (50% of hospitalized alcoholics), refeeding syndrome (commonly in the intensive care unit), malnutrition, sepsis, trauma, diuretic or steroid therapy, ketoacidosis, osmotic diuresis, acidosis, and catabolic states. Depressed intake or absorption and increased urinary losses are common causes. Starvation for 48 hours and poor nutritional status predispose to hypophosphatemia. In individuals with chronic alcoholism, reduction of the phosphorus content of skeletal muscle occurs as a result of renal phosphate loss. The hypophosphatemic syndrome includes phosphate trapping, rhabdomyolysis, cardiomyopathy, respiratory insufficiency from profound muscle weakness, erythrocyte and leukocyte dysfunction, skeletal demineralization, metabolic acidosis, and nervous system dysfunction (Table 54-15).

Before initiating treatment, the cause of hypophosphatemia should be clearly identified with measurement of arterial blood gases and the concentrations of ionized calcium, magnesium, potassium, and serum and urinary phosphorus. Phosphate salts, such as sodium and potassium phosphate, are available for oral or intravenous administration. Multiplying the volume of distribution (400 mL/kg) by the desired change in inorganic phosphate provides the total amount to be administered. The rate of intravenous administration should not exceed 0.25 mmol/kg over 4 to 6 hours to avoid hypocalcemia and tissue damage. Oral supplementation is often limited to 30 mmol/day (1 g/day) because of the induction of diarrhea. Hyperphosphatemia should be avoided because it can cause hypocalcemia and crystal deposition in the eyes, heart, lung, blood vessels, and kidneys. Most hypophosphatemic patients, such as patients with diabetic ketoacidosis or recovering from exercise, are not severely phosphorus-depleted, unless they have been sick for an extended time. They typically may be treated with a glass of milk (100 mg/dL or 33 mmol/L of phosphorus). After achieving normal serum phosphate levels, the concentrations of serum inorganic phosphate and ionized calcium and a 24-hour urine sample should be monitored to ensure that balance has been achieved.

Table 54-15 Major Causes of Hypophosphatemia

Chronic alcoholism and alcohol withdrawal
Dietary deficiency and phosphate-binding antacids
Severe thermal burns
Recovery from diabetic ketoacidosis
Hyperalimentation
Nutritional recovery syndrome
Respiratory alkalosis
Therapeutic hyperthermia
Neuroleptic malignant syndrome
Recovery from exhaustive exercise
Renal transplantation
Acute renal failure

Adapted from Potts JT: Diseases of the parathyroid gland and other hyper- and hypocalcemic disorders. *In* Isselbacher KJ, Braunwald E, Wilson JD, et al (eds): Harrison's Principles of Internal Medicine, 13th ed. New York, McGraw-Hill, 1995, p 2185.

Significant hypophosphatemia is common after surgery and can contribute to respiratory and cardiac failure. In one study of elective cardiac surgery, 34.3% of patients had significant hypophosphatemia. These patients were characterized by prolonged ventilation, had a larger cardioactive drug requirement, and had prolonged hospital stays.[43]

Chloride Physiology

Chloride is the predominant anion in the ECF volume. Hyperchloremic, metabolic acidosis results from excess intake or inadequate excretion because of renal dysfunction. When administering infusions to such patients, bicarbonate, acetate, citrate, or phosphate salts should be substituted for chloride salts.

Excess loss of chloride in gastric secretions or urine causes hypochloremic alkalosis. Chloride depletion tends to limit bicarbonate excretion, and this may be caused by reduced delivery of chloride to the collecting tubules, where chloride is needed for bicarbonate secretion by means of bicarbonate-chloride exchange. Sodium reabsorption is enhanced in chloride-depleted states because it is generally associated with ECF volume depletion. When less chloride is available for reabsorption, a greater fraction of the sodium must be reabsorbed with bicarbonate through increased proton secretion.[44] Sodium or potassium chloride should be administered if intravascular volume depletion or hypokalemia is present. If these are not a problem, 0.1N hydrochloric acid should be administered through a central catheter:

$$\text{Chloride dose} = \left(\text{Cl}_{\text{desired}} - \text{Cl}_{\text{measured}}\right) \times 0.2 \times \text{weight (kg)}$$

Glucose Physiology and Fluid Implications

Close Monitoring

Glucose is a crucial fuel source, and insulin facilitates glucose movement into cells in a process that also requires potassium and phosphate. Red blood cells, healing wounds, brain, and adrenal medulla require glucose for fuel, totaling approximately 2 mg/kg/min. When controlling blood glucose, close monitoring is crucial. Reagent strips containing glucose oxidase, used in conjunction with glucometers, provide rapid and reliable results. It is imperative to know the insulin regimen or oral hypoglycemic agent of each patient and then measure the blood glucose preoperatively, intraoperatively, and postoperatively. The degree of end-organ damage, coronary artery disease, and autonomic neuropathy can contribute to the risk of aspiration, myocardial infarction, and peripheral neuropathy.

Hyperglycemia

Hyperglycemia (>180 to 200 mg/dL) is most often caused by insulin deficiency, insulin receptor resistance, or glucose overadministration. Hyperglycemia produces osmotic diuresis; exacerbation of brain, spinal cord,[45] and renal damage[46] by ischemia; delayed gastric emptying[47]; hypophosphatemia[47]; delayed wound healing[47,48]; and impaired white blood cell function.[48] Maternal hyperglycemia increases the risk of neonatal jaundice, the risk of neonatal brain damage, and fetal acidosis if the fetus becomes hypoxic.

Even with supramaximal levels of insulin, adults can use glucose only at a rate of 3 to 5 mg/kg/min at rest (approximately 240 mL/hr of 5% solution). The maximal rate of metabolism is less in stress states and more with increased metabolic rates. Generally, the rate of administration should be limited to 2 to 3 mg/kg/min (120 to 180 mg/kg/hr), which is 100 g/hr for a 70-kg person (200 mL/hr of a 5% dextrose solution). Healthy infants and children become hyperglycemic if 5% dextrose is included in maintenance fluids.[49] The maximal rate of glucose disposition in young children is 4 to 8 mg/kg/min, and the optimal rate is less than 5 mg/kg/min.[50] It is unclear that glucose administration is necessary for intraoperative management of most patients.[51]

Diabetes Mellitus

Diabetes mellitus (see Chapter 35) is the most common endocrine disease and is characterized by long-term complications involving the eyes, kidneys, nerves, and blood vessels. Diabetes is a major risk factor for heart disease, stroke, kidney disease, blindness, and nontraumatic amputations. The cause of diabetic complications is multifactorial, including glycosylation of proteins and glucose reduction to sorbitol, which functions as a tissue toxin. This pathophysiologic process is associated with a decrease in *myo*-inositol content and metabolism and with a decrease in Na^+-K^+/ATPase activity. Hyperglycemia is recognized as a major factor in the development of complications associated with diabetes. The patient population is not homogeneous, and several diabetic syndromes have been delineated. There are almost 8 million diagnosed diabetics in the United States and another 8 million who are unaware of their diabetes. These numbers approach 10% of the overall U.S. population (Table 54-16).[52]

Pathology

Hyperglycemia of diabetes is the consequence of relative or absolute deficiency of insulin and a relative or absolute excess of glu-

Table 54-16 Classification of Diabetes

Class	Causes and Characteristics
Primary	IDDM, type 1—without insulin, the patient develops ketoacidosis and dies NIDDM, type 2—the patient does not always develop ketoacidosis without insulin Nonobese NIDDM (type 1 IDDM in evolution?) Obese NIDDM Maturity-onset diabetes of the young
Secondary	Pancreatic disease, hormonal abnormalities, drug or chemical induced, insulin receptor abnormalities, genetic syndrome, other

IDDM, insulin-dependent diabetes mellitus; NIDDM, non–insulin-dependent diabetes mellitus.
Adapted from Foster DW: Diabetes mellitus. *In* Isselbacher KJ, Braunwald E, Wilson JD, et al (eds): Harrison's Principles of Internal Medicine, 13th ed. New York, McGraw-Hill, 1995, p 1980.

cagon. In type 1 diabetes, there is an absolute deficiency in insulin production, and without insulin, patients die. These patients eventually become dependent on exogenous insulin to prevent lipolysis and eventually ketoacidosis. The onset of type 1 diabetes usually occurs by adolescence, although it may occur at any age and is thought to result from autoimmune destruction of islet cells in the pancreas.

Type 2 diabetes is characterized by a relative deficiency in insulin, typically caused by insulin resistance. The onset of this type of diabetes is usually in adulthood, although evidence suggests that the mean age of onset of type 2 diabetes is decreasing.[53] Type 2 diabetes almost certainly has a heterogeneous group of etiologic factors. Commonly associated findings in type 2 diabetes are obesity, abnormal insulin levels, and a strong genetic component (Table 54-17).[54]

A third type of diabetes mellitus is gestational diabetes (see Chapter 69). Gestational diabetes is defined as any degree of glucose intolerance with the onset first recognized during pregnancy. Gestational diabetes complicates approximately 4% of all pregnancies in the United States, resulting in about 135,000 cases annually.[55] Clinical recognition of gestational diabetes is important because therapy and antepartum fetal monitoring can reduce perinatal morbidity and mortality. Maternal complications related to gestational diabetes include an increased rate of cesarean delivery.

During the past decade, a new disorder known as syndrome X has been described. As the name implies, it is a syndrome rather than a specific disease state. The hallmark of syndrome X is insulin resistance with hyperinsulinemia. The underlying pathology is similar to type 2 diabetes; however, patients with syndrome X do not exhibit hyperglycemia. Patients with syndrome X may never develop type 2 diabetes. The clinical significance of this condition stems from its association with multiple metabolic abnormalities, including low levels of high-density lipoprotein, increased blood pressure, and increased plasminogen activator inhibitor-1 levels. All these abnormalities have a definite or possible association with coronary artery disease. Whether syndrome X and type 2 diabetes are on a spectrum of disease with insulin resistance as a common denominator or are totally separate entities has yet to be clarified.

Management and Evaluation of Diabetes Mellitus

Treatment and evaluation of diabetes (see Chapter 35) includes diet, oral hypoglycemic drugs, exercise, exogenous insulin, and weight reduction if warranted. Insulin preparations are produced from pork, beef, and human or recombinant sources. Most diabetics are prescribed a combination of rapid-acting and intermediate-acting insulin before breakfast and before bedtime. Rebound hyperglycemia may follow a hypoglycemic reaction (i.e., Somogyi effect). In the past decade, newer therapies for new-onset insulin-dependent diabetes mellitus (type 1 diabetes) have been introduced, including transplantation of pancreatic tissue and immunosuppression. Fifteen percent of patients with type 1 diabetes have other autoimmune processes, and the elevated glucose levels are probably caused by destruction of pancreatic β cells in these instances (Table 54-18).

Table 54-17 Characteristics of Type 1 and Type 2 Diabetes Mellitus

Characteristic	Type 1	Type 2
Genetic locus	Chromosome 5	Chromosome 11 (?)
Age at onset	≤40	>40
Body habitus	Normal to wasted	Obese
Plasma insulin	Low to absent	Normal to high
Plasma glucagons	High, suppressible	High, resistant
Acute complications	Ketoacidosis	Hyperosmolar coma
Insulin therapy	Responsive	Responsive to resistant
Sulfonylurea therapy	Unresponsive	Responsive

Foster DW: Endocrinology and metabolism. *In* Wilson JD, Braunwald E, Fauci AS, et al (eds): Harrison's Principles of Internal Medicine, 12th ed. New York, McGraw-Hill, 1991, p 1743.

Table 54-18 Classification of Insulin Preparations

Preparation	Type	Onset	Peak	Duration
Fast acting	Insulin lispro injection (Humalog)	15 min	30-90 min	3.5-4 hr
	Regular	30-60 min	2-4 hr	6-8 hr
	Semilente	1-3 hr	5-10 hr	16 hr
Intermediate acting	Isophane (NPH)	2-4 hr	6-12 hr	18-26 hr
	Lente (Humulin)	2-4 hr	6-12 hr	18-26 hr
Long acting	Protamine zinc	4-8 hr	14-24 hr	28-36 hr
	Ultralente	4-8 hr	14-24 hr	28-36 hr

Adapted from Stoelting RK, Dierdorf SF: Endocrine disease. *In*: Anesthesia and Co-Existing Disease, 3rd ed. New York, Churchill Livingstone, 1993, p 340.

Table 54-19 Insulin Analog Comparison

Analog	Brand Name	Manufacturer	Onset (min)	Peak (hr)	Duration (hr)
Lispro	Humalog	Eli Lilly	5-15	1-2	2-3
Glargine	Lantus	Hoechst-Marion Roussel for Aventis	1-3 hr	No true peak	24
Aspart	NovoRapid	NovoNordisk	5-15	1-2	2-3

Insulin therapy can result in anaphylactic and anaphylactoid reactions, especially when using protamine-containing insulin preparations. Protamine-derived insulin is made from fish sperm and can cause immunologic sensitization when protamine reversal is administered after cardiopulmonary bypass or heparin reversal.[56] The protamine reaction can be devastating and includes profound hypotension, pulmonary vasoconstriction, and noncardiogenic pulmonary edema. Insulin analogs have been developed with improved time-action profiles.

The first insulin analog was introduced in the mid-1990s. Several other insulin analogs subsequently have been formulated (Table 54-19). Insulin lispro (Humalog) is a genetically engineered protein identical to human insulin except for a reversal of the amino acids, proline and lysine, at positions 28 and 29 of the β chain.[57]

This reversal in the amino acid sequence allows for a more rapid absorption and faster onset of action compared with regular insulin.[58-61] Reversal of the proline-lysine sequence eliminates two crucial hydrophobic interactions responsible for the β-sheet conformational changes and dimerization. Decreased propensity for dimerization is the key to understanding the absorptive characteristics of insulin lispro.

Another insulin analog that has been released is insulin glargine (Lantus), which resembles the human insulin protein with addition of two arginine amino acids to the β chain and replaces asparagine with glycine at the α-21 position. The addition of the two arginine units causes a shift in the isoelectric point to 6.7 ± 0.2, which allows for precipitation of the insulin glargine in the neutral pH of human tissue. The substitution of glycine in the α chain and the addition of 30 μg/mL of zinc increase the hexamer stability of the precipitate.[62,63] This precipitate slowly dissolves and results in a constant time-action profile with no pronounced peak. This time-action profile allows for once-daily dosing and a duration of action of 18 to 24 hours. These new preparations are being encountered more often in patients being assessed for surgery, and understanding their time-action profiles is essential in clinical management.

Anesthetic Considerations

Because diabetes affects multiple organ systems, the perioperative impact can be profound. Several clinically relevant issues should be considered during perioperative anesthetic management, as follows:

1. Diabetes affects oxygen transport by causing glucose to bind covalently to the hemoglobin molecule, and alters the allosteric interactions between β chains. This alteration in normal hemoglobin has been shown to decrease oxygen saturation and red blood cell oxygen transport in pregnant diabetic patients.[64]
2. A common complication of diabetes is autonomic dysfunction. Patients in whom diabetes has been poorly controlled for many years often have damage to the autonomic nervous system. One study[65] showed that diabetic patients with previously diagnosed autonomic dysfunction are at increased risk for intraoperative hypothermia. The pathogenesis may be related to inappropriate regulation of peripheral vasoconstriction to conserve body heat.
3. Autonomic dysfunction also affects the body's ability to regulate arterial blood pressure, leading to significant orthostatic hypotension. This underlying defect is caused by a lack of appropriate vasoconstriction. This denervation also may involve vagal control of the heart rate. The changes in heart rate seen with atropine and β-blockers are blunted in patients with significant autonomic dysfunction.[66]
4. Damage to the autonomic nervous system can significantly affect the choice of anesthetic technique. Patients are at significantly increased risk of hypotension caused by induction agents, such as thiopental or propofol. For this reason, etomidate may be a better induction agent because of its considerably lower incidence of cardiovascular side effects.
5. Diabetes has well-defined adverse effects on the cardiovascular system. Men who have diabetes have twice the age-adjusted risk for coronary artery disease. The risk for women is tripled, indicating that they may be even more sensitive to the cardiovascular effects of diabetes.[67] Data show that patients with diabetes may be at even greater risk for coronary artery disease than was previously suspected. One study revealed that patients with type 2 diabetes had as great a risk for myocardial infarction as nondiabetic patients who already had a previous myocardial infarction.[68] This information reinforces the point that diabetic patients must be carefully evaluated preoperatively for coronary artery disease. Also, diabetic patients are more likely to have silent ischemia. They may not experience the classic chest pain and tightness associated with ischemic heart disease. Questions regarding exercise tolerance and shortness of breath with exertion may provide important information regarding underlying heart disease or the degree of compensation.
6. Diabetes affects the gastrointestinal tract in several ways. First, it damages the ganglion cells of the gastrointestinal tract, inhibiting motility, which delays gastric emptying and overall transit time through the gut. This increased transit time has a significant impact on the practice of anesthesia in that all diabetic patients should be treated as if they have a full stomach. Preoperative treatment with agents that inhibit acid secretion and neutralize stomach acid is essential. Rapid-sequence induction is commonly employed to try to minimize this risk of aspiration.

Perioperative and intraoperative glycemic-control regimens depend on several factors. First, differentiating type 1 from type 2 diabetes is crucial. Patients with type 1 diabetes are at risk for ketonemia if they are without insulin. The risk of ketosis is amplified when the patient undergoes the stress of surgery.

Second, the degree to which blood glucose levels are controlled long-term affects management. Glycosylated hemoglobin (hemoglobin A_{1c}) is the most accurate way to assess glucose control over the previous 2 to 3 months. As levels of hemoglobin A_{1c} increase, so does the complication rate of diabetes. The amount of exogenous insulin a patient normally requires is important in deciding how blood glucose should be treated intraoperatively. The magnitude of the surgery plays an important role in determining therapy. There are many different protocols for preoperative and intraoperative insulin management, but there are few prospective studies comparing regimens. Common protocols are discussed subsequently.

Successful perioperative glucose management depends on careful monitoring. Perioperative management of blood glucose during a brief surgical procedure in a patient with diet-controlled diabetes generally involves only monitoring of blood glucose immediately perioperatively and every 3 hours until oral intake is resumed.[69,70] The preoperative physical examination and history may reveal extensive diabetic neuropathy, which may be seen as orthostatic hypotension, syncopal episodes, mononeuropathies or polyneuropathies, erectile or bladder dysfunction, and an electrocardiogram showing a loss of R-to-R variability. Patients may present with numerous additional findings, including nonfamilial short stature, cerebrovascular disease, renal dysfunction, microalbuminemia, and tight, waxy skin. In an estimated 30% to 40% of diabetic patients, glycosylation of the atlanto-occipital joint may limit joint mobility and cause difficulty with airway management (i.e., stiff-neck syndrome).[71,72] Laboratory evaluation of hemoglobin A_{1c} is an accurate measure of the severity of hyperglycemia and has been shown to correlate directly with increasing rates of complications. Conversely, lower hemoglobin A_{1c} values are associated with decreased risk and can be considered a measure of the quality of the diabetic care. Hemoglobin A_{1c} provides the best evidence of overall blood glucose control over the past 1 to 2 months and should replace the oral glucose tolerance test as the gold standard for diagnosing diabetes.[73] Basic electrolyte and renal function tests should be evaluated, especially if the patient has frequent urinary tract infections or renal impairment.[74]

The preoperative hemoglobin A_{1c} level gives the anesthesiologist a reasonable idea about the patient's blood glucose level over the past several months, and this information can be used to evaluate the need for preoperative and intraoperative insulin requirements. The regimen selected to manage patients with diabetes undergoing surgery depends on the severity of the diabetes and the magnitude of the surgery. Frequent glucose monitoring and preparation for insulin administration are essential for a diabetic patient. Recommendations include discontinuation of long-acting insulin or oral hypoglycemic agents 1 to 2 days preoperatively. Short-acting insulin should be administered every 4 to 6 hours subcutaneously, with the dose adjusted according to glucose levels just before administration. Metformin, a biguanide oral hypoglycemic, also possesses a low risk of lactic acidosis (0.03 cases per 1000 patient-years). Despite these low figures, metformin should not be used in patients with mild renal dysfunction (serum creatinine >1.5 mg/dL in male patients or >1.4 mg/dL in female patients), congestive heart failure, recent myocardial infarction or any other condition producing a hypoxic state, current alcohol abuse, or impaired hepatic function. Metformin should be discontinued 24 hours before and for at least 48 hours after any procedure using intravenous contrast dye. It should be reinstituted only after renal function has been reevaluated and found to be normal.[75,76]

The typical "sliding scale" is destined to fail because it involves the administration of a fixed dose after documentation of hyperglycemia. A small modification improves control. The selected dose should be administered every 4 to 6 hours, based on response. If the glucose level is less than 60 mg/dL, the dose should be with held for at least 1 hour, and 50% dextrose should be given intravenously (0.01 to 0.02 mL/kg/min), with blood glucose monitored hourly. When the blood glucose is greater than 125 mg/dL without supplemental dextrose infusion, the next insulin dose should be 20% to 40% smaller. If the glucose is less than 100 mg/dL or is less than 125 mg/dL and decreasing, the scheduled dose should be maintained until the hourly measured glucose is greater than 125 mg/dL, followed by resumption with a 10% to 20% smaller dose. If the glucose level is 100 to 200 mg/dL and stable, the current dose and interval are continued. If the glucose level is 200 to 350 mg/dL, the scheduled dose is increased by 10% to 20%. If the glucose level is more than 350 mg/dL, the dose is increased by 20% to 40%.

On the day of surgery, a dextrose infusion (2 mg/kg/min) is started at the time a meal would have been ingested, and glucose is measured preoperatively. For patients currently receiving insulin, an insulin infusion is started at a rate of 0.5 to 1.25 U/hr, depending on the amount of insulin normally administered and the current glucose level. Blood glucose is monitored hourly, and the infusion rate is adjusted to maintain glucose concentration based on which glucose homeostasis protocol has been selected for use. Patients with obesity, liver disease, severe infections or on steroid therapy may require increased hourly insulin doses as may patients undergoing cardiopulmonary bypass.[77] After the blood glucose level is stable, urine glucose levels and ketone bodies are checked to ensure that glycosuria resulting from a low threshold does not confuse interpretation of urine output.

Oral intake may be stopped 12 hours before anesthesia because some element of gastroparesis exists in these patients. Typically, patients are administered a histamine blocker along with a gastric-emptying drug, such as metoclopramide, the night before and the morning of surgery. Because the gastrointestinal tract is a prime target for autonomic neuropathy, there may be esophageal dysfunction with difficulty swallowing, constipation, or diarrhea.

Diabetic ketoacidosis, dehydration, impaired wound healing, and electrolyte imbalance are minimized with the proper use of exogenous insulin. There is no clear consensus about the method of insulin therapy or the exact range of blood glucose that can affect morbidity or mortality.[78]

If a general anesthetic is used, clinical consideration should include a rapid-sequence induction because of the high rate of gastroparesis. Cerebrovascular accidents, peripheral vascular disease, and cardiovascular infarction are 2 to 10 times more common in diabetics. Strategies designed to reduce the risk of labile blood pressures and myocardial ischemia related to autonomic or vascular disease may include β-blockade to blunt the stress of induction, a narcotic-based anesthetic to minimize cardiopulmonary depression, and prophylactic nitroglycerin in these patients with their significant risk of coronary artery disease. Commonly associated conditions include obesity and stiff cervical joints, which may make airway management challenging. Associated cardiovascular conditions often result in the need for additional invasive monitoring.

Acute Hyperglycemia

The cellular effects of acute hyperglycemia are poorly understood, but reports have begun to shed some light on alterations in normal cell functions at the molecular level. One study[79] showed that acutely elevated glucose levels depress endothelin-induced calcium signaling in rat mesangial cells, depressing the contractile state of glomerular cells. Such information supports the hypothesis that acute hyperglycemia can affect cellular functions and may lead to clinically evident pathology.

National trends show a movement toward tighter control of glucose levels perioperatively. Acute consequences of elevated serum glucose levels include impaired wound healing, dehydration, impaired immune system response, and proteolysis. The dehydration seen during acute hyperglycemia results from the osmotic diuretic effect of high serum glucose levels. Patients with diabetes are well known for having poor wound healing, which is commonly believed to be caused by impaired blood flow to the wound. There is evidence, however, that acute hyperglycemia may impair fibroblast activity and impair vitamin C uptake by cells, inhibiting new collagen synthesis.[80]

In addition to delayed wound healing, elevated glucose levels inhibit immune function and increase the risk of postoperative infection. One study[81] suggested that continuous insulin infusions, used to control intraoperative and postoperative glucose levels, decrease the incidence of sternal wound infections after cardiac surgery. A second study[82] found that aggressive glucose control intraoperatively increased neutrophil activity in vitro significantly. Alveolar macrophages from normal hosts show impaired respiratory burst when exposed in vitro to elevated glucose concentrations.[83] Taken together, these data indicate that tight glucose control intraoperatively may significantly influence the ability of patients to recover more quickly from surgery and reduce morbidity.

Diabetic Ketoacidosis

Diabetic ketoacidosis is an emergent condition that often manifests in a diabetic patient with leukocytosis and an acute surgical abdominal emergency or with nausea, vomiting, lethargy, and signs of hypovolemia. The priorities are to restore intravascular volume (usually rapid intravenous administration of 1 L of saline), administer regular insulin (traditionally at a starting infusion rate of 0.1 U/kg/hr), eliminate the ketonemia, control blood glucose, and correct the underlying problem (e.g., antibiotics for urosepsis or pneumonia). Patients with ketoacidosis are dehydrated as a result of glucosuria; because the dehydration is caused by water and electrolyte loss, colloids are not indicated. If the patient's osmolality is elevated, 0.45% sodium chloride can be administered, and the volume administered should be guided by the hemodynamic response and urinary output. When the blood glucose declines to less than 250 mg/dL, dextrose should be added to the fluids. Urine or blood ketones are monitored every 2 hours after the blood glucose is within 100 to 200 mg/dL. If ketones are still present, the rates of glucose and insulin infusions should be increased.

Osmotic diuresis promotes loss of sodium, potassium, magnesium, and phosphate. Despite total-body deficiencies, however, their concentrations may be elevated at the time of presentation because of severe water loss. The best treatment for hyperkalemia in these patients is appropriate therapy for the diabetic ketoacidosis. Potassium levels decrease rapidly with appropriate volume replacement and insulin therapy. Most patients require electrolyte replacement after volume expansion has begun. Alternatively, severe hyperglycemia may extract water from the intracellular space and may dilute the electrolyte concentrations. If the initial potassium level is elevated, or the patient is anuric, potassium should not be administered. As hydration improves, and urinary output increases, potassium, magnesium, and phosphorus should be administered, and levels should be monitored frequently. Generally, acidosis should not be treated with buffers. Ketoacidosis is corrected as insulin and glucose levels improve, and lactic acidosis resulting from poor perfusion responds to intravascular fluid replacement. If the pH approaches 7.15, the bicarbonate ion concentration is less than 10 mEq/L, and hypotension fails to respond to intravascular fluid administration, sodium bicarbonate therapy may be required.

Hypoglycemia

Hypoglycemia (<50 mg/dL) is dangerous because glucose is the sole fuel source for much of the brain. Threshold levels depend on age. Signs of hypoglycemia include irritability, seizures, bradycardia, hypotension, and respiratory failure. Symptoms commonly occur in adults with blood glucose concentrations less than 57 mg/dL or in infants with levels of 30 to 50 mg/dL. Symptoms are seen at higher levels in diabetic patients than in nondiabetic patients and are obscured by general anesthesia. At about 70 mg/dL, a biochemical stress response occurs, including sympathetic nervous system stimulation and elevated levels of growth hormone or cortisol, or both. Neurologic and electroencephalographic depression appears at 50 to 55 mg/dL in nondiabetic patients and 70 to 85 mg/dL in diabetic patients.[84] Selective neuronal necrosis, not infarction, occurs in the caudate, putamen, and cortex. There is a compensatory increase in cerebral blood flow.

During labor, maternal starvation-induced ketosis has adverse fetal effects, including fetal ketonemia, hypoxia, and fetal lactic acidosis.[85] Neonates are at an increased risk for hypoglycemia because of limited glycogen stores and from large amounts of fetal insulin production in response to gestational hyperglycemic states. Adults also are at risk for hypoglycemia from inadequate gluconeogenesis coupled with inadequate nutritional intake or from excess insulin (e.g., from an insulinoma, pancreatic islet cell adenoma, or carcinoma; iatrogenic overadministration). Hypoglycemia also can follow too abrupt cessation of dextrose infusion during total parenteral nutrition (i.e., reactive hyperinsulinemic states). Inadequate gluconeogenesis occurs in liver failure, cortisol deficiency (primary or secondary), inadequate glucagon response, and growth hormone deficiency, and during β-adrenergic blockade. Fasting in women is likely to produce hypoglycemia in 24 hours, whereas men tolerate about 72 hours of fasting.[47] The incidence of hypoglycemia in healthy infants and children is low (2 of 446) with 4 to 8 hours of fasting.[50] Fetal hypoglycemia occurs if maternal glucose is greater than 150 mg/dL because glucose crosses the placenta, inducing fetal insulin secretion. Treatment consists of an intravenous bolus of

5 g of dextrose followed by increasing the rate of dextrose infusion by 1 to 2 mg/kg/min.

Acid-Base Factors

Metabolic Acidosis

The necessity for treating metabolic acidosis is judged largely on clinical grounds, with the metabolic acid level base excess (BE) used to determine the correct dose of bicarbonate (see Chapter 49). This prediction is based on the size of the treatable space and the magnitude of the problem:

$$\text{Dose}\,(\text{mEq}) = 0.3 \cdot \text{weight}\,(\text{kg}) \cdot \text{BE}\,(\text{mEq/L})$$

The dose calculated is sufficient to return the metabolic disturbance almost to zero. Bicarbonate therapy is reserved, however, for emergencies and situations in which indications for therapy are compelling. It is usual to give a reduced dose (about one half) for several reasons, as follows:

1. The bicarbonate is injected initially into the plasma volume (about 3 L) instead of into the calculated treatable space (21 L).
2. When bicarbonate is added to acid, it "fizzes." This does not occur literally in the blood. Nevertheless, most bicarbonate is converted to carbon dioxide and has to be eliminated. For each 100 mEq that is converted, about 2.24 L of carbon dioxide has to be exhaled, equivalent to 10 minutes of normal production.
3. The carbon dioxide that is produced enters the cells freely, in contrast to the bicarbonate ions that have been administered. The inside of the cell initially may become even more acid. Direct studies with nuclear magnetic resonance have not confirmed this, however (Severinghaus, personal communication, 1986).
4. The bicarbonate is accompanied by sodium ions that are responsible for a residual increase in the osmolality of the ECF. In combination with other therapy, such as intravenous glucose, the hyperosmolality may be critical and cause coma. In neonates, rapid infusion of bicarbonate may cause intracranial hemorrhage.
5. If the body deals with its metabolic acidosis, there is a residual metabolic alkalosis.

Anion Gap

Some causes of metabolic acidosis release anions into the ECF that are not normally measured. When this occurs, there is an unexpected discrepancy between the sums of the principal cations and anions. The usual sum is shown in the following equation:

$$Na^+ + K^+ = Cl^- + HCO_3^- + \text{gap}$$

$$140 + 5 = 105 + 25 + (-15)$$

When there are any additional, unmeasured anions, they become part of the gap, which is then correspondingly larger. A gap greater than 30 suggests that there is an increase in the concentration of the unmeasured anions. This method relies on the accuracy of the other measurements. Small errors in these large numbers cause a proportionately greater error in the result. If information is required about these anions, it is more appropriate to measure their concentration. In practice, it suffices to analyze lactate in cases of tissue hypoxia, 3-hydroxybutyrate in diabetic ketosis, and phosphate or sulfate in renal failure.

The common causes of perioperative metabolic alkalosis include antacid therapy, incidental administration of citrate with blood products, sodium bicarbonate administration, gastric drainage, or renal bicarbonate retention caused by diuresis or in compensation for respiratory acidosis. Sodium chloride or potassium chloride can be administered orally or through a peripheral intravenous catheter, or 0.1N hydrochloric acid may be administered slowly through a central venous catheter. The required dose is calculated as follows:

$$\text{Dose} = (Cl^-_{\text{desired}} - Cl^-_{\text{measured}}) \times 0.2\,(\text{L}) \times \text{weight}\,(\text{kg})$$

Clinical Acid-Base Balance Disturbances

This section provides practical clinical examples to assist in understanding acid-base balance.

Metabolic Acidosis from Low Cardiac Output

A patient with coronary artery disease and an ejection fraction of 15% experienced myocardial perforation while undergoing balloon angioplasty in the cardiac catheterization laboratory. After resuscitation, intubation, insertion of an arterial line, and initiation of dopamine by infusion, the patient was transferred to the operating room for emergency thoracotomy. Blood pressure was 80/50 mm Hg, and the heart rate was 120 beats/min. During preparation for central venous cannulation, the blood pressure decreased, followed by cardiac arrest. The patient underwent immediate thoracotomy. Blood gas determinations obtained at the time were as follows: pH_a 7.15, $Paco_2$ 35 mm Hg, BE −15 mEq/L, bicarbonate 12 mEq/L, and Pao_2 90 mm Hg. These values indicated a severe metabolic acidosis with mild respiratory alkalosis. After the administration of 4 U of packed red blood cells (PRBCs) and 88 mEq of sodium bicarbonate, repeat blood gas determinations were as follows: pH_a 7.14, $Paco_2$ 39 mm Hg, BE −14 mEq/L, bicarbonate 13 mEq/L, and Pao_2 95 mm Hg. These values still indicated a severe metabolic acidosis, but with no respiratory alkalosis.

The first blood gas determination revealed a metabolic acidosis attributable to the low cardiac output with tissue ischemia and with slight hyperventilation. The second blood gas determination showed almost no benefit from the bicarbonate, probably because of continuing low cardiac output. Bicarbonate is converted to carbon dioxide, which may explain the slightly higher level of $Paco_2$.

Metabolic Acidosis During Anhepatic Phase

A patient with end-stage liver disease caused by viral hepatitis underwent orthotopic liver transplantation. Blood gas analysis performed late in the anhepatic phase (see Chapter 67), after earlier administration of bicarbonate, revealed the following: pH_a 7.10, $Paco_2$ 28 mm Hg, BE −18 mEq/L, bicarbonate 8.6 mEq/L, Pao_2 260 mm Hg, and Na^+ 153 mEq/L. These values indicated a severe metabolic acidosis with a moderate respiratory alkalosis. The patient was treated with 500 mL (150 mEq, 18 g) of 0.3 M solution of tris(hydroxymethyl)aminomethane (THAM) by infusion over 20 minutes. Repeat blood gas analysis showed the following: pH_a 7.09, $Paco_2$ 30 mm Hg, BE −18 mEq/L, bicarbonate 9 mEq/L, Pao_2 251 mm Hg, and Na^+ 154 mEq/L. A second dose of THAM was administered by infusion. After transplantation, blood gas analysis showed the following: pH_a 7.30, $Paco_2$ 33 mm Hg, BE −9 mEq/L, bicarbonate 16 mEq/L, Pao_2 283 mm Hg, and Na^+ 149 mEq/L. These values indicated a marked metabolic acidosis with a mild respiratory alkalosis typical of a partially compensated metabolic disturbance.

The metabolic acidosis during the anhepatic phase showed the importance of the liver in metabolizing lactate to bicarbonate. The high sodium militated against repeat administration of sodium bicarbonate. In this case, THAM was used to minimize sodium administration while controlling the metabolic acidosis. On reperfusion (phase 3), the new liver started to function, and there was improvement in the metabolic acidosis.

Metabolic Alkalosis After Diuretics

A 3-month-old, 4-kg infant boy was presented for repair of an atrioventricular canal (see Chapter 83). The patient's congenital heart failure had been controlled with digitalis and furosemide. Before induction of anesthesia, blood gas analysis showed the following: pH_a 7.53, $Paco_2$ 44 mm Hg, BE 14 mEq/L, bicarbonate 35.9 mEq/L, and Pao_2 110 mm Hg. These values showed a severe metabolic alkalosis with a minimal respiratory acidosis typical of a partially compensated metabolic disturbance. After induction of anesthesia, blood gas analysis showed the following: pH_a 7.61, $Paco_2$ 35 mm Hg, BE 14 mEq/L, bicarbonate 34 mEq/L, and Pao_2 60 mm Hg. After completion of the procedure and cessation of cardiopulmonary bypass, the blood gas analysis showed the following: pH_a 7.40, $Paco_2$ 33 mm Hg, BE −4 mEq/L, and bicarbonate 20 mEq/L.

The hypochloremic alkalosis that accompanies prolonged administration of furosemide explains the first set of results. After induction of anesthesia, the hyperventilation decreased the $Paco_2$, but had no effect on the base excess. Two major factors explain the change during the procedure. Hemodilution tends to return the pH_a toward neutral (6.8 at body temperature), and low perfusion during bypass frequently produces a metabolic acidosis that, in this case, also helped to overcome the initial metabolic alkalosis.

Chronic Respiratory Failure in a Neonate

A 2.5-month-old, 3.5-kg infant boy with bronchopulmonary dysplasia was tracheally intubated and received supplemental oxygen (Fio_2 0.3). He presented for cryoablation for proliferative retinopathy (see Chapters 82 and 83). After the patient was transported to the operating room, blood gas analysis showed the following: pH_a 7.27, $Paco_2$ 65 mm Hg, BE 3 mEq/L, bicarbonate 29 mEq/L, and Pao_2 35 mm Hg. Anesthesia was induced, and ventilation was controlled, with a tidal volume of 60 mL, peak inspiratory pressure of 25 cm H_2O, positive end-expiratory pressure of 4 cm H_2O, respiratory rate of 40 breaths/min, no inspiratory pause, and Fio_2 of 0.3. Repeat analysis of blood gases showed the following: pH_a 7.36, $Paco_2$ 50 mm Hg, BE 3 mEq/L, bicarbonate 28 mEq/L, and Pao_2 48 mEq/L.

The mild metabolic alkalosis of the first analysis is compatible with compensation for chronic respiratory failure. The high $Paco_2$ value represented hypoventilation during transport. Appropriate selection of the ventilator settings returned the $Paco_2$ to a value more typical for a neonate with bronchopulmonary dysplasia with a pH_a about halfway between no compensation and complete compensation (see Chapters 82 and 83).

Preparation for Chronic Hyperventilation

A clinician was a member of a team providing plastic surgery at high altitude. For 2 days preceding the trip, he was advised to take a carbonic anhydrase inhibitor, acetazolamide, which would effectively slow the normal reversible reaction between carbonic acid and its dissociation products, carbonic acid and water. The drug alkalinizes the urine and produces a moderate metabolic acidosis, the typical response to hypoxic hyperventilation at altitude. A typical blood gas determination after acclimatization to altitude shows the following: pH_a 7.42, $Paco_2$ 31 mm Hg, BE 4 mEq/L, bicarbonate 19 mEq/L, and Pao_2 80 mm Hg.

The benefit of taking acetazolamide is debated by climbers, and the drug is not without side effects. During the initial experience of taking acetazolamide at sea level, a striking, if minor, side effect is the metallic taste associated with drinking any carbonated beverage, presumably attributable to the inability to convert the high carbon dioxide content in the beverages to carbonic acid.

Acute Hyperventilation and Hypotension

A 5-ft, 48-kg elderly woman had an arterial blood pressure of 115/75 mm Hg and heart rate of 70 beats/min (see Chapter 71). She was receiving no medications and was in otherwise normal health. She was scheduled for a laparotomy and hysterectomy. After induction of anesthesia and orotracheal intubation, controlled ventilation was initiated with a tidal volume of 900 mL and a respiratory rate of 12 breaths/min. Shortly before incision, the arterial blood pressure was 58/35 mm Hg, and the end-tidal Pco_2 was 22 mm Hg. (Blood gases were not tested, but typical values for a patient experiencing such acute hyperventilation are as follows: pH_a 7.53, $Paco_2$ 26 mm Hg, bicarbonate 21 mEq/L, and BE 0 mg/L.)

The ventilator was immediately reset to provide 4 breaths/min at a tidal volume of 500 mL. Arterial blood pressure about 2 minutes later was 85/55 mm Hg, and the next reading about 2 minutes later still was 95/65 mm Hg. The patient's end-tidal Pco_2 increased more slowly, and after about 8 minutes, it had returned to 36 mm Hg when the ventilatory rate was increased to 8 breaths/

min. (Typically, her blood gas values would be near-normal, such as pH_a 7.44, $Paco_2$ 38 mm Hg, bicarbonate 23.3 mEq/L, and BE 0 mg/L). Hyperventilation after induction is common and frequently contributes to hypotension by various methods, including increased intrathoracic pressure, diminished venous return, and depressed cardiac output.

Acute Hypoventilation

An obese, middle-aged woman was undergoing laparoscopic cholecystectomy. After a routine induction and orotracheal intubation, low-flow anesthesia was initiated, and the ventilator was set to provide a tidal volume of 700 mL at a rate of 10 breaths/min (measured exhaled tidal volume was 560 mL). Ten minutes after induction of anesthesia, the Pco_2 was 35 mm Hg, and the peak airway pressure was 28 mm Hg. Arterial blood gas determinations showed the following: pH_a 7.43, $Paco_2$ 35 mm Hg, bicarbonate 22.4 mEq/L, and BE −1 mEq/L. Thirty minutes into the procedure, the peak airway pressure was 48 mm Hg, the end-expired Pco_2 was 49 mm Hg, and the measured exhaled tidal volume was 380 mL. Repeat blood gas analysis showed the following: pH_a 7.27, $Paco_2$ 55 mm Hg, bicarbonate 24.9 mEq/L, and BE −1 mEq/L. The principal abnormality was a marked respiratory acidosis with no metabolic acidosis. It is characteristic of an acute respiratory disturbance.

The increase in $Paco_2$ can be attributed to two factors: uptake of the inflating gas (CO_2) in the abdomen and reduction of effective ventilation owing to increased airway pressure required to overcome abdominal distention. The discrepancy between end-tidal Pco_2 and arterial blood gas $Paco_2$ is typical and results from the patient's temperature being slightly less than that of the analyzer, lack of time between breaths to reach true end-tidal equilibration, normal pulmonary maldistribution, and the slight loss occurring on the length of the tubing.

Fluid Balance and Fluid Replacement Solutions

Transfusions of red blood cells, platelets, fresh frozen plasma, factor solutions, synthetic crystalloids and colloids, and cryoprecipitate have the potential for improving clinical outcomes in perioperative and peripartum settings. Potential benefits include improved tissue oxygenation and decreased bleeding; however, transfusions are not without risks or costs. Blood product transfusion can cause many complications. Although red blood cells and coagulation products have excellent volume-expanding capacity, they are not considered in this chapter (see Chapter 55).

The American Society of Anesthesiologists and the American Red Cross Blood Services have convened task forces and medical advisory boards on blood component therapy over the past decade to develop evidence-based guidelines on the proper indications for perioperative and peripartum administration of red blood cells, platelets, fresh frozen plasma, and cryoprecipitate. This section details only basic crystalloid, colloid, and hypertonic solution recommendations applicable to typical surgical and obstetric patients (Table 54-20). Information about infants, children, and special clinical settings can found elsewhere in this book (see Chapter 82).

Surgical Fluid Balance and Shock

Physiologic changes during surgery and anesthesia lead to shifts in fluid balance. Epidural, spinal, and caudal anesthesia all may cause variable amounts of sympathetic blockade (see Chapter 51). Although young, healthy, and well-hydrated patients may tolerate sympathectomy, patients who are older, severely dehydrated, or on antihypertensive drugs or diuretics may not be able to respond to the effects of sympathectomy. It is common to administer 1 L of fluid intravenously before placement of a spinal anesthetic, or to administer fluid concurrently when epidural anesthesia is being induced. Vasopressors, typically ephedrine or phenylephrine, are needed to overcome the hemodynamic effects of sympathetic block.

Although inhaled anesthetics do not directly alter fluid losses, all anesthetics may blunt the normal physiologic responses to hypovolemia and the stress response. The stress response to surgery involves an increase in ADH production, which can be blocked with anesthetics. Superimposed are the variable effects of intravenous and inhaled agents on the myocardium, venous return, blood pressure, and the vasculature. Mechanical ventilation can decrease the release of atrial natriuretic hormone and increase the release of ADH, resulting in retention of sodium and fluids.

Simple restoration of blood volume may not ensure survival. In addition to blood loss, significant third space loss may occur, which essentially involves fluid that is still in the body, but not contributing to intravascular volume, oxygen delivery, or waste removal; this is often difficult to measure. Patients undergoing major surgical procedures require fluid replacement beyond simple blood loss, and the anesthesiologist plays a vital role in assessing and ultimately administering appropriate fluid therapy in intraoperative and postoperative clinical settings. Even after normalization of cardiac output, cells in the liver and gut may remain ischemic after flow is reestablished in the macrocirculation because of occlusion of capillary networks caused by edema.[86]

The controversial issue of timing and volume of fluid resuscitation in uncontrolled hemorrhage has been reviewed. In 52 animal trials, fluid resuscitation seemed to decrease the risk of death in models of severe hemorrhage, but increased the risk of death in models with less severe hemorrhage. Hypotensive resuscitation, whenever tested, reduced the risk of death.[87]

Shock

Shock can be defined as dysfunction of intracellular processes as a result of lack of energy (see Chapter 72). This lack of energy is caused by deficient delivery of oxygen to tissue, resulting in an inability to maintain normal cellular respiration. Although shock is a cellular problem, therapy is directed at the systemic delivery of oxygen to the tissue.

Table 54-20 Composition of Replacement Fluids

Fluid	Sodium (mEq/L)	Potassium (mEq/L)	Glucose (g/L)	Osmolarity	pH	Other
Whole blood in CPD*	168-156	3.9-21	—	—	7.20-6.84	Hct = 35-40
PRBC,† AS-1	117	?-49	—	552	6.6	Hct = 59
PRBC,† CPD	—	?-95	—	—	6.6	Hct = 77
PRBC,† CPDA-1	169-111	5.1-78.5	—	—	7.55-6.71	Hct = 65-80
FFP	15.4	—	—	—	—	—
5% Albumin	145 ± 15	<2.5	0	330	7.4	COP = 32-35 mm Hg
2.5% Albumin	145 ± 15	<2	0	330	—	—
Plasmanate	145 ± 15	<2	—	—	7.4	COP = 20 mm Hg
10% Dextran 40	0	0	50	255	4.0	—
Hetastarch	154	0	0	310	5.9	—
0.9% Sodium chloride	154	0	0	308	6.0	—
Lactated Ringer's solution	130	4	0	273	6.5	Lactate = 28
5% Dextrose	0	0	50	252	4.5	—
D_5LR	130	4	50	525	5.0	—
$D_5$0.45% NaCl	77	0	50	406	4.0	—
Normosol	140	5	100	555	7.4	Mg = 3, acetate = 27, gluconate = 23
Normosol-M	40	13	50	363	5.0	Mg = 3, acetate = 16, gluconate = 27
Normosol-R	140	5	0	294	6.6	Mg = 3, acetate = 27, gluconate = 23
D_5 Normosol-R	140	5	0	547	5.2	Mg = 3, acetate = 27, gluconate = 23
Normosol-R pH 7.4	140	5	0	295	7.4	Mg = 3, acetate = 27, gluconate = 23

*The range of values refers to concentrations on day 1 and day 21 (CPD), 35 (CPDA-1), or 42 (AS-1) of storage.
†Fructose substituted for dextrose.
COP, colloid oncotic pressure; D_5LR, 5% dextrose in lactated Ringer solution; $D_5$0.45% NaCl, 5% dextrose in 0.45% sodium chloride; FFP, fresh frozen plasma; Hct, hematocrit; Mg, magnesium; PRBC, packed red blood cells.

In normal patients, the body maintains a balance between delivery of oxygen (Do_2) and global oxygen consumption (Vo_2). Global oxygen consumption is a measure of the total amount of oxygen consumed by all tissues per minute. The amount of oxygen consumed as a fraction of the amount delivered defines the oxygen extraction ratio (OER):

$$OER = Vo_2/Do_2$$

Vo_2 in a normal adult undertaking routine activities is approximately 250 mL/min with an extraction ratio of 25%. The OER can be increased to 75% during extreme exercise in a healthy adult. Oxygen not extracted from the blood returns to the lungs and can be measured as the mixed venous saturation ($S\bar{v}o_2$), which is a measure of global tissue oxygenation. $S\bar{v}o_2$ less than 60% to 70% usually indicates insufficient Do_2. A mixed venous blood sample is needed because the saturation of venous blood varies depending on the organ being measured. Venous blood returning from the liver has a saturation of 40% to 50%, and blood from the kidneys may have a saturation greater than 80%.

Oxygen consumption is directly related to cellular metabolic rate. Sympathetic activity, shivering, and physical activity all increase the cellular metabolic rate. As the delivery of oxygen decreases or the consumption increases, the OER increases to maintain aerobic metabolism. The OER can increase to approximately 60% to 70%, at which point further increase in consumption or decrease in delivery results in tissue hypoxia and anaerobic metabolism.

Tissue hypoxia and shock can result from inappropriate delivery of cellular oxygen or inappropriate cellular use of oxygen. There are two distinct types of shock. Type I involves patients who experience decreased delivery of oxygen, such as in hypovolemic or cardiogenic shock. Type II involves problems with inappropri-

ate distribution of oxygen delivery, such as in septic or neurogenic shock. Regardless of the underlying cause, appropriate fluid management is an absolute necessity.

Proper fluid management of shock can have a significant impact on the delivery of oxygen to tissues and prevention of anaerobic metabolism. Until more recently, vigorous fluid loading and inotropic agents were commonly used in what was called goal-directed therapy during the care of critically ill patients. Goal-directed therapy was based on the principle that critically ill patients had supranormal Vo_2 values. It was thought that by increasing Do_2 to supraphysiologic levels, cellular metabolism could be maintained in an aerobic state, and multisystem organ dysfunction could be avoided.[88] In the 1990s, two large, randomized trials showed this therapy to be ineffective and potentially dangerous, however.[89,90] Continuing research has shown that identifying and treating volume depletion and poor cardiac function early in shock is beneficial.[91-93]

The key to the different results between the early study by Shoemaker and colleagues[88] and later trials is recognizing the difference between early and late shock. Early shock involves acute tissue hypoxemia with end organs not yet sustaining irreversible damage. In type I shock (hypovolemic or cardiogenic), prompt treatment of the underlying cause of tissue hypoperfusion may prevent patients from progressing to late shock and multisystem organ failure. If tissue oxygenation is not restored soon enough, end-organ failure and endothelial cell dysfunction occur, signaling the onset of late shock. With end-organ failure and endothelial cell dysfunction, the body's normal control of regional blood flow is impaired, and further oxygen delivery to tissue is compromised. At this point, increasing the blood flow further with use of overaggressive volume loading and inotropic agents does not improve tissue oxygenation because blood is not being delivered to the tissue that needs it. During early shock, aggressive fluid resuscitation is appropriate to minimize end-organ hypoxemia as quickly as possible. After the patient has progressed to late shock, it is still important to maintain normal intravascular volumes, but overaggressive therapy with fluids and pressors has been shown to be detrimental.

Crystalloids

Crystalloids are fluids that contain water and electrolytes. They are grouped as isotonic, hypertonic, and hypotonic salt solutions. Crystalloid solutions are used to provide maintenance water and electrolytes and to expand intravascular fluid. The replacement requirement is threefold or fourfold the volume of blood lost because administered crystalloid is distributed in a ratio 1:4 similar to ECF, which is composed of about 3 L intravascularly (plasma) and about 12 L extravascularly (i.e., about 20% should remain in the intravascular space).

Balanced Salt Solutions

Balanced salt solutions have an electrolyte composition similar to ECF (e.g., lactated Ringer solution, Plasma-Lyte, Normosol). With respect to sodium, they are hypotonic. A buffer is included in place of bicarbonate, which hydrates to carbonic acid with the production of carbon dioxide, which diffuses from the solution. Compared with 0.9% NaCl, these solutions provide small quantities of other electrolytes, which are inadequate to meet daily maintenance requirements.

Normal Saline

Normal saline (0.9% NaCl) is isotonic and iso-osmotic, but contains more chloride than ECF. When used in large volumes, mild hyperchloremia (i.e., non–anion gap metabolic acidosis) results. Normal saline contains no buffer or other electrolytes. It is preferred to lactated Ringer's solution (which contains a hypotonic concentration of sodium) when brain injury, hypochloremic metabolic alkalosis, or hyponatremia occurs. Many patients with hyperkalemia, including patients with renal failure who are frequently in the operating room for vascular access bypass procedures, routinely receive normal saline because it contains no potassium.

Hypertonic Salt Solutions

Hypertonic salt solutions are less commonly used, and their sodium concentrations range from 250 to 1200 mEq/L. The greater the sodium concentration, the less the total volume is required for satisfactory resuscitation. This difference reflects the movement owing to osmotic forces of water from the intracellular space into the extracellular space. The reduced volume of water injected may reduce edema formation; this could be crucial in patients predisposed to tissue edema (e.g., prolonged bowel surgery, burns, brain injuries). Clinical studies have confirmed that a moderately hypertonic solution (250 mEq/L of sodium) can produce lower muscle interstitial pressure than lactated Ringer's solution. Bowel function returned earlier, although the pulmonary shunt fraction was no different.[94] Experimental studies have shown decreased intracranial pressures in animals receiving hypertonic solutions. The intravascular half-life of hypertonic solutions is no longer, however, than isotonic solutions of an equivalent sodium load. In most studies, sustained plasma volume expansion was achieved only when colloid was present in the resuscitation solution. The osmolality of these solutions can cause hemolysis at the point of injection.[95]

Hypertonic saline has been used for almost a century in clinical practice for a variety of reasons. Interest in its use in hemorrhagic shock was rekindled in 1980 in an experiment in dogs with severe hemorrhagic shock. These dogs were resuscitated solely with 7.5% NaCl or equal volumes of normal saline. All dogs in the hypertonic saline group survived; all dogs in the normal saline group died.[96] Many randomized trials have been conducted in the past 2 decades. Hypertonic saline increases mean arterial pressure, decreases systemic vascular resistance, decreases pulmonary vascular resistance, and reduces subsequent blood requirements.[97-99] Studies have shown no increase in complications, and there has been a trend toward decreased mortality.

There continues to be controversy regarding the use of hypertonic saline in hemorrhagic shock. During mass casualties as seen in natural or man-made disasters, hypertonic saline can be used during triage. It is particularly useful in this setting because of its ease of storage, low cost, and ability to expand

plasma volume rapidly. Results can be achieved with 250 mL of 7.5% saline that are comparable to resuscitation with 2 to 3 L of 0.9% saline.[87] Larger, randomized controlled studies are needed to evaluate thoroughly its use in standard practice. In this regard, to date, improved rates of survival with hypertonic saline were reported in seven of eight clinical trials, although statistically significant improvement in overall survival was seen in only one trial.[87]

Five Percent Dextrose

Five percent dextrose functions as free water because the dextrose is metabolized. It is iso-osmotic and does not cause the hemolysis that would occur if pure water were injected intravenously. Although it may be used to correct hypernatremia, 5% dextrose is most often used in the prevention of hypoglycemia in diabetic patients who have had insulin administered.

Crystalloids Versus Colloids

Much controversy exists about the role of crystalloids and colloids in fluid therapy (see Chapters 55 and 88). Proponents of colloid fluid point out that resuscitation with crystalloid solution dilutes the plasma proteins, with a subsequent reduction of plasma oncotic pressure resulting in fluid filtration from the intravascular to the interstitial compartment and the development of interstitial pulmonary edema. Proponents of crystalloid solutions have argued that albumin molecules normally enter the pulmonary interstitial compartment freely and then are cleared through the lymphatic system returning to the systemic circulation. Additional albumin should merely increase the albumin pool cleared by the lymphatics. A review of the literature by Moss and Gould[100] confirmed that all unflawed clinical and experimental studies showed that isotonic solutions are effective plasma volume expanders for resuscitation without the addition of a variety of colloid fluids. The additional cost and potential risks of colloids compared with crystalloids is another argument against colloid administration.

Colloids used in the United States include albumin, hydroxyethyl starch (hetastarch), and dextran. Because the molecules are large, colloids usually do not cross capillary membranes and remain intravascular. Distribution of fluid throughout the body is represented by the Starling-Landis equation:

$$J_v = K_h\ A\left(\left[P_{M\xi} - P_T\right] - \delta\left[COP_{M\xi} - COP_T\right]\right)$$

In this equation, J_v represents the net volume of fluid moving across the capillary wall per unit of time, expressed as $\mu m^3/min$; K_h is the hydraulic conductivity for water, which is the fluid permeability of the capillary wall, expressed as $\mu m^3/min$ per square micrometer of capillary surface area per 1 mm Hg pressure difference. The value of K_h increases up to fourfold from the arterial to the venous end of a typical capillary. $P_{M\xi}$ is the capillary hydrostatic pressure; P_T is the tissue hydrostatic pressure; *A* is the capillary surface area; and δ is the reflection coefficient for plasma proteins. This coefficient is necessary because the plasma proteins are slightly permeable to the microvascular wall, preventing full expression of the two COPs. When δ is 0, molecules cross the membrane freely; when δ is 1, molecules cannot cross the membrane. Typical δ values for plasma proteins in the microvasculature exceed 0.9 in most organs, and these values remain constant, but can be decreased significantly by pathophysiologic processes, including hypoxia, inflammation, and tissue injury. $COP_{M\xi}$ is the colloid oncotic pressure, and COP_T is the colloid oncotic pressure in the tissue.

The hydrostatic and colloid pressure differences across capillary walls (i.e., Starling forces) cause movement of water and dissolved solutes into the interstitial spaces. These movements play a minor role with regard to tissue nutrition relative to simple diffusion. The reflection coefficient that expresses the ability of the semipermeable membrane to prevent movement of a solute varies greatly among tissues. The lungs are moderately permeable relative to other organs, and during pathophysiologic processes such as surgical trauma, the reflection coefficient may change further to alter capillary permeability, resulting in increased capillary permeability or leak. In this setting, colloids move more easily into the interstitium and increase interstitial edema.

With leakage of colloid molecules into the interstitial space, further swelling of tissues occurs because of the unfavorable oncotic pressure gradient, and these molecules are removed by the lymphatic system. Removal of colloids requires longer periods than for crystalloids and can be a significant problem in burn patients and patients undergoing major surgery. A well-known meta-analysis by Velanovich[101] of mortality from eight studies published in 1989 concluded that trauma patients should be resuscitated with crystalloid solutions, whereas colloids were more effective in nonseptic, nontraumatic, elective surgical patients. Current data seem to support the concept that blood composition should be maintained as close to normal as possible in terms of directed transfusion of red blood cells and coagulation factors.[86]

Another factor that must be considered is the overall effect of resuscitation fluid on the coagulation cascade. It is a well-known phenomenon that after trauma, patients may have low levels of circulating coagulation factors. This deficiency may lead to transfusion of fresh frozen plasma to restore deficient factors. The clotting cascade is an extremely complex string of events, with many factors affecting the progression to clot. Studies using a thromboelastogram to measure trauma patients' clotting status have indicated that these patients may be hypercoagulable.[102] Another study using thromboelastographic profiles showed that patients undergoing major surgery who were given intraoperative lactated Ringer's solution also were hypercoagulable compared with baseline.[103] These studies suggest that the type of fluid used for volume resuscitation may play a role in the coagulopathy often seen in trauma patients (see Chapter 56). Definitive studies are still needed, however, to elucidate the true impact that resuscitation fluids play in the coagulation cascade.

Colloid Solutions and Blood Substitutes

Colloid solutions generally are administered in a volume equivalent to the volume of blood lost (see Chapter 55). The initial volume of distribution is equivalent to the plasma volume. The

half-life in circulation of albumin is normally 16 hours, but it can be only 2 to 3 hours in pathophysiologic conditions.[104] The synthetic colloids, processed albumin, and protein fractions have minimal or no risks of infection. Blood substitutes are useful to restore intravascular fluid volume temporarily until definitive treatment can be established. They are inexpensive, have a long storage life, and lack the risk of transmitting viral diseases.

Five Percent Albumin

Five percent albumin or plasma protein fractions (e.g., Plasmanate) have a COP of about 20 mm Hg (i.e., near-normal COP). Preparation methods eliminate infectious agents. These solutions are chosen when crystalloids fail to sustain plasma volume for more than a few minutes because of low COP. These solutions are most appropriate when there is an abnormal loss of protein from the vascular space, such as in cases of peritonitis or extensive burns.

Twenty-Five Percent Albumin

A colloid solution of 25% ("salt-poor") albumin contains purified albumin at five times the normal concentration. When administered, it has the potential to expand the plasma volume by up to five times the volume provided. It is selected when the current plasma volume is diminished, but blood pressure is acceptable, and the total ECF volume is expanded.

Six Percent Dextran 70

Dextran is available as dextran 40 or dextran 70. The numbers 40 and 70 refer to the average molecular mass of the molecules in the solution. The mean molecular weight of dextran 40 is about 40,000 daltons (40 kD), and the mean molecular mass of dextran 70 is about 70,000 daltons (70 kD). The dextran solutions are water-soluble glucose polymers synthesized by certain bacteria from sucrose. Both dextran solutions are ultimately degraded enzymatically to glucose. A colloid solution of 6% dextran 70 is administered for the same indications as 5% albumin. Dextran 40 is used in vascular surgery to prevent thrombosis and is rarely used as a volume expander.

Side effects include anaphylactic or anaphylactoid reactions in about 1 in every 3300 administrations, increased bleeding time caused by decreased platelet adhesiveness (at doses of 20 mL/kg/24 hr), rouleaux formation (i.e., interfering with crossmatching of blood), and rare cases of noncardiogenic pulmonary edema thought to be a direct toxic effect on pulmonary capillaries after intravascular absorption.[105]

Hydroxyethyl Starch

Hydroxyethyl starch (hetastarch) is a synthetic colloid solution in which the molecular mass of at least 80% of the polymers ranges from 10,000 to 2 million daltons. It is available in the United States as a 6% solution in 0.9% NaCl (Hespan). The pH of hetastarch is about 5.5, and the osmolarity is about 310 mOsm/L. The larger molecules are degraded enzymatically by amylase. It is stored in the reticuloendothelial system for several hours and is believed to be renally excreted. It produces dilutional effects similar to other volume expanders and reduces factor VIII:C and vWF levels by 50% to 80% in a dose of 1 to 1.5 L, with prolongation of the partial thromboplastin time.[106] Hetastarch also can interfere with platelet adhesion and clot formation by reduction in glycoprotein IIb/IIIa availability and direct movement of the hetastarch molecules into the fibrin clot.[106] In clinically recommended volumes (i.e., 20 mL/kg), there is minimal interference with subsequent crossmatching. Repeated doses can result in accumulation and side effects, which include allergic reactions and bleeding as described with higher doses (20 to 25 mL/kg). The combination of dextran with Hespan seems to blunt Hespan-induced neutrophil activation.[87]

A new form of hydroxyethyl cellulose has been approved for use in the United States. Hextend (Biotime, Berkeley, CA) contains 6% hetastarch in a solution that approaches physiologic concentrations of the major electrolytes. It also contains physiologic levels of glucose and lactate as a buffer. In contrast to Hespan, Hextend polymer units have an average molecular mass of 670 kd, with 80% within the range of 20 to 2500 kd, making these units significantly smaller than Hespan. Early studies have suggested that Hextend might not affect the coagulation process to the same degree as Hespan. In a study of 90 patients undergoing major surgery, the patients who were given Hextend had no significant change in their thromboelastogram profiles. Patients receiving lactated Ringer solution were found to be hypercoagulable, and patients receiving Hespan were found to be hypocoagulable compared with baseline.[103] In clinical practice, there is movement away from Hespan toward lower and medium molecular weight hetastarchs, which have less inhibitory effect on platelet function and coagulation factors, but a shorter intravascular half-life.

Pentastarch

Pentastarch is a lower molecular weight hetastarch with fewer hydroxyethyl groups per molecule. Pentastarch is undergoing clinical trials in the United States and has anticoagulant effects similar to those of hetastarch.

Perfluorochemical Emulsions and Hemoglobin-Based Oxygen Carriers

Perfluorochemical emulsions have linear oxygen-carrying capacity, but are insufficient to sustain human cellular function, and the first-generation emulsion, Fluosol-DA 20, was discontinued and is no longer available. The second-generation emulsion, Oxygent, discontinued clinical trials. Third-generation emulsions are currently in preclinical stages.

There are numerous classes of hemoglobin-based oxygen carrier solutions; these include cross-linked, polymerized, and conjugated hemoglobin solutions. Hemopure and PolyHeme have completed Food and Drug Administration phase II trials, and phase III trials are under way. Several newer generation hemoglobin-based oxygen carriers are in early preclinical evaluation (see Chapter 55).

Fluid Management of Specific Clinical Conditions

The following guidelines are intended to facilitate initiating therapy, but the choice of fluid and rate of administration must be adjusted to achieve physiologic goals. These guidelines are only a starting point for patients without other major comorbid diseases of vital organs. Careful observation of the patient's response forms the basis for ongoing modification in a continuous feedback loop.

Routine Maintenance Fluids

Routine maintenance fluids are described for a 70-kg postoperative patient. The patient requires 110 mL H_2O and 110 kcal/hr, or 2640 mL and 2640 kcal/day. This example is based on the 4-2-1 rule (Table 54-21), which provides a close approximation of water requirements. The sodium requirement (1.5 mEq/kg/day) is dissolved in the daily fluid requirement of 2.64 L; the 100 mEq/kg/day requirement for potassium is placed in the 2.64 L/day water requirement: 100 mEq K/2.64 L = 42 mEq/L. The potassium concentration needs to be limited, however, if the fluid is to be infused into a peripheral vein because of the chemical irritation induced by high concentrations of potassium.

The long-standing concept first presented in 1957 by Holliday and Seger of the 4-2-1 rule for crystalloid delivery has been challenged more recently. The focus of this challenge is on reduction of free water administration because of increased postoperative hyponatremia related to increased secretion of ADH. An alternative concept is for much lower glucose administration and isotonic sodium–containing solutions to avoid the rare problem of hyponatremic seizure and brain damage (seen mainly in children).[107]

The obligatory glucose needs of the brain and red blood cells are roughly 2 mg/kg/min. Because dextrose contains 3.41 kcal/g instead of 4 kcal/g of glucose, about 17% more dextrose than glucose is required. If carbohydrate is not provided, glycogenolysis and gluconeogenesis from amino acid pools provide the necessary glucose, but accelerate protein catabolism.

Carbohydrate is said to prevent catabolism (i.e., protein sparing), but the benefit of this dose of dextrose is unclear. Total starvation may be preferable because insulin concentrations decrease to very low levels, facilitating lipolysis as a caloric source.

Table 54-21 Calculations of Fluid Requirements by 4-2-1 Rule*

Body Weight (kg)	Fluid Rate (mL/kg)	Weight Category (kg)	Fluid (mL/hr)
0-10	4	10	40
11-20	2	10	20
>21	1	5	5
Total		*25*	***65***

*Assumes a patient weighing 25 kg, resulting in an estimated fluid requirement of 65 mL/hr.

Table 54-22 Volume and Composition of Gastrointestinal Fluids

Fluid Source	24-Hour Volume (mL)	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)
Saliva	500-2000	2-10	20-30	8-18	30
Stomach	1000-2000	60-100	10-20	100-130	0
Pancreas	300-800	135-145	5-10	70-90	95-120
Bile	300-600	135-145	5-10	90-130	30-40
Jejunum	2000-4000	120-140	5-10	90-140	30-40
Ileum	1000-2000	80-150	2-8	45-140	30
Colon	—	60	30	40	—

The osmolarity of 7.5% dextrose is 417 mOsm/L, to which is added 156 mOsm/kg H_2O, resulting in a highly hyperosmolar solution. A compromise between the need for glucose and hyperosmolality has been 5% dextrose.

If there are other losses (e.g., gastric drainage), additional sodium and water are required. Gastric drainage of 0.5 L/day loses 30 to 50 mEq of sodium and 50 to 65 mEq of chloride (Table 54-22). When these are added to the maintenance fluid, the concentration approximates 0.45% NaCl. This solution is commonly used as a maintenance intravenous fluid postoperatively in patients with nasogastric drainage.

Routine Intraoperative Fluid Administration

The goals of intraoperative fluid administration are to maintain adequate oxygen delivery, normal electrolyte concentrations, and normoglycemia. The total fluid requirement is composed of compensatory intravascular volume expansion (CVE), deficit replacement, maintenance fluids, restoration of losses, and substitution for fluid redistribution (i.e., third space fluids):

$$\text{Rate of fluid} = \text{CVE} + \text{deficit} + \text{maintenance administration} + \text{loss} + \text{third space}$$

Compensatory Intravascular Volume Expansion

Intravascular volume usually must be supplemented to compensate for the venodilation and cardiac depression caused by anesthesia. Sustaining adequate oxygen delivery in relation to oxygen consumption is an important goal of fluid therapy. Tissue oxygen delivery depends on hemoglobin concentration, oxygen tension, organ perfusion pressures, and organ vascular resistance. Organ perfusion pressures depend on systemic arterial pressure and the higher of organ venous pressure or tissue pressure. Arterial pressure depends on cardiac output and systemic vascular resistance. Cardiac output is related to stroke volume and heart rate, and stroke volume depends on preload, contractility, and afterload. Most general and regional anesthetics cause arteriolar and venous dilation, expanding the vascular capacity. The latter reduces peripheral venous pressure and venous return and cardiac

output. Fluid must be administered to expand the blood volume to compensate for venodilation.

General anesthetics produce myocardial depression (see Chapter 23). Increasing cardiac preload by infusing fluid intravascularly to take advantage of the Starling mechanism often returns stroke volume to an acceptable range. Postoperatively, venodilation and myocardial depression rapidly subside when administration of the anesthetic is stopped. Patients with impaired cardiac or renal responses may then become acutely hypervolemic. Compensatory intravascular volume expansion with 5 to 7 mL/kg of balanced salt solution must occur before or simultaneous with the onset of anesthesia.

Deficits

Characteristics of Fluid Deficits

The fluid deficit equals the maintenance fluid requirement multiplied by the hours since last intake plus unreplaced preoperative external and third space losses. When hypovolemia is present, sufficient fluid should be infused to restore mean arterial pressure, heart rate, and filling pressures to near-normal values before induction. If sufficient time is available, restoration of normal urine flow rate also is desirable. The fluid infusion rate for normal patients should be set to deliver three to four times the maintenance rate until the calculated deficit has been corrected.

Electrolyte abnormalities are common among hospitalized patients. Surgical urgency often forces us to evaluate and correct preexisting abnormalities that may be directly related to the surgical problem or to comorbid diseases or their therapy. The principles of management are outlined in other sections of this chapter. The induction of anesthesia and the onset of mechanical ventilation, fluid shifts, and stress responses induced by surgical trauma all lead to redistribution of water, protein, and electrolytes. The most common and most studied of these are abnormalities of potassium, calcium, and magnesium.

Maintenance Fluid

The maintenance fluid meets ongoing basal needs for water and electrolytes as described earlier. The onset of surgical stimulation and, to a smaller extent, onset of anesthesia elicit changes in catecholamines, cortisol, and growth hormone. These tend to reduce insulin secretion or impede its glucose-lowering effect, leading to hyperglycemia. If dextrose-containing solutions are infused at the usual 5% concentration at the rates often required during surgery, severe hyperglycemia results. The fluid used for volume maintenance should not contain dextrose.

Losses

External losses (e.g., blood, ascites) should be replaced to maintain normal blood volume and normal composition of the ECF volume. Blood loss is replaced initially with 3 mL of balanced salt solution or 0.9% NaCl for each 1 mL of blood loss. For each 1 mL of blood lost, 1 mL of colloid solution should be administered to provide improvement of filling pressures, arterial blood pressure, and heart rate. PRBC infusions are used at roughly 1 mL for each 2 mL of blood lost plus crystalloid or colloid, as previously described. Although the effect on volume is 1:1, the hematocrit of PRBCs (60% to 70%) is about twice the necessary hematocrit of the patient. In patients with reasonable cardiac reserve and without compromised regional circulations (e.g., coronary, cerebral, renal, intestinal), hemoglobin levels of 7.5 g/dL or greater are usually well tolerated.[108] If blood volume is normal, and cardiac failure is not a problem, signs of sympathetic activation, signs of mixed venous oxygen desaturation, or electrocardiogram signs of myocardial ischemia suggest the need for red blood cell administration. The following equation is used to calculate the necessary volume of red blood cells to be infused, and weight is measured in kilograms; because PRBCs have a hematocrit of 60%, the volume to be infused can be estimated:

$$\mathrm{PRBC_{infused}} = \left(\mathrm{Hct_{desired}} \times \mathrm{EBV} \times \mathrm{weight}\right) - \left(\mathrm{Hct_{observed}} \times \mathrm{EBV} \times \mathrm{weight}\right)/0.60$$

where EBV is estimated blood volume per kg: 55 mL/kg for women and 70 mL/kg for men. For a man with a hematocrit of 21% for whom the target hematocrit is 30%, the calculation would be $0.30 \times (70 \times 70) - 0.21 \times (70 \times 70)$ = PRBC infused, estimated at 735 mL, or about 3 U of PRBCs.

Ascites and pleural effusions drained during surgery reform at extremely variable rates. The electrolyte composition is the same as that at the ECF volume, but it also contains protein at concentrations 30% to 100% of the plasma value. Balanced salt solutions are most appropriate for replacement, but colloid should be added when dilution of the patient's COP becomes severe (<15 to 17 mm Hg), and the apparent volume of redistribution of crystalloid begins to increase.

The electrolyte composition of gastrointestinal tract losses depends on the site (see Table 54-22). Most gastrointestinal losses removed at the time of surgery entered the bowel lumen preoperatively and should be considered to be part of the deficit. Evaporation from exposed viscera is entirely water, but the electrolyte is left behind, leading to a need for free water. The amount evaporated is directly proportional to temperature and exposed surface area, and is inversely proportional to relative humidity. Excess urine caused by diuretics, glycosuria, or diabetes insipidus should be replaced with a solution based on urinary electrolyte measurements. The sodium concentration generally ranges from 50 to 100 mEq/L, and the potassium concentration ranges from 20 to 60 mEq/L.

Redistribution

Redistribution (so-called third space losses) results primarily from tissue edema and transcellular fluid displacement. Functionally, this fluid is not available to the vascular space.[109,110] The volume of edema formed is governed by the principles discussed earlier. Colloid enters the injured tissue at a more rapid rate than normal, but at a slower rate than electrolyte. Bowel wall edema may be lessened by using colloid-containing fluids compared with crystalloid.[111] The composition of third space losses is equivalent to the ECF volume electrolyte concentration plus a smaller amount of protein. Balanced salt solution is the most appropriate

Table 54-23 Fluid Calculations for a Simulated Case

Time	Compensatory (mL)	Deficit (mL)	Maintenance (mL)	Blood Loss (mL)*	Third Space (mL)	This Hour (mL)†	Cumulative‡
P-I§	350	220	110	0	0	680	680
I-S¶	—	220	110	0	0	330	1010
First hour¶	—	220	110	300	350	980	1990
Second hour¶	—	220	110	300	350	980	2970
Third hour¶	—	220	110	150	350	830	3800
Fourth hour¶	—	0	110	0	200	330	4130

*Reflects fluid replacement for blood loss. Preinduction phase lasts 15 to 20 minutes.
†Total fluid administered during the hour.
‡Grand total since beginning of the case.
§Preinduction phase lasts 15 to 20 minutes.
¶Induction until intra-abdominal surgical entry (assumed to be 1 hour).
¶Operative time.

replacement fluid. The volume redistributed correlates roughly with the degree of tissue manipulation. Intra-abdominal procedures with small incisions (e.g., hysterectomy) may require an additional 2 mL/kg/hr, whereas a major bowel resection requires an additional 4 to 6 mL/kg/hr.

Table 54-23 describes the fluid management, starting with a hemoglobin level of 15 g/dL, for a 70-kg patient undergoing gastrectomy who has been fasting for 10 hours. The maintenance rate is 110 mL/hr, producing a deficit of 1100 mL.

During the first and second hours of intra-abdominal activity, 100 mL of blood was lost and replaced at a 3:1 rate with a balanced salt solution. By the fourth hour, the deficit had been replaced, and because the abdomen was being closed during part of that hour, the estimate of third space losses was likewise reduced, and no further blood loss occurred. The assumption is made that urine flow was 50 to 80 mL/hr, and that heart rate and arterial blood pressure were in an acceptable range, and the CVP remained 6 to 9 mm Hg. Had the CVP or urine output begun to increase, the rate of fluid administration would have been slowed. If oliguria and tachycardia had occurred, a fluid bolus would have been administered.

Pediatric Patient

There are few special considerations relevant to pediatric fluid management in addition to those for adults (see Chapter 82). Neonates have limited ability to dilute or concentrate urine and have a high fluid requirement. Neonates should not be without fluid for more than 3 to 4 hours; otherwise, significant dehydration may result. Food should be offered until 6 to 8 hours before anesthesia induction, and glucose-containing clear liquids should be given about 4 hours before induction. Clear liquids are defined as transparent liquids that do not contain particulate material or protein, which coagulate in the acid medium of the stomach. Using the same principles as outlined for adults, a neonate requires maintenance fluids of 0.3% NaCl with potassium. Dextrose administration should not exceed 5 mg/kg/min. This requirement generally can be met by using 2.5% dextrose–containing fluids. During extensive, prolonged procedures, blood glucose should be monitored, and the rate of dextrose administration should be modified accordingly. Otherwise, the choice and volumes of fluid are as described for an adult.

Postoperative Patient with Bowel Obstruction

Patients with bowel obstruction are often older and have limited reserves in several organ systems. Estimating the degree of loss of fluids is difficult because fluid is retained in the bowel lumen, where it cannot be measured. The slowly developing volume depletion allows time for full expression of compensatory mechanisms that mask the degree of the deficit. Patients have often ingested no fluids for many hours before entering the hospital and are often vomiting. The patient may have ischemic bowel injury with severe bowel wall edema and continued sequestration of luminal fluid and formation of ascites. Perioperative fluid intake is much larger than measured output, leading consultants to suggest diuresis for fluid overload. Nutrition is impaired preoperatively, and protein losses into the bowel are increased, leading to hypoalbuminemia and exacerbating the loss of fluid from the vascular space. The clinical picture is one of ongoing fluid requirement in the absence of external fluid loss, commonly referred to as third spacing.

The goals of fluid management in this group are similar to the goals for other patients and include restoration of the vascular volume and interstitial volume, correction of electrolyte depletion, correction of acidosis, reduction of systemic vascular resistance into the normal range, and optimization of oxygen delivery and use. Initial fluid infusion can restore intravascular volume sufficiently for blood pressure and heart rate to improve. Intravascular volume still may be depleted, however, with a low cardiac output and severe arterial and venous vasoconstriction. The ECF volume (except for the bowel) remains dehydrated and continues to accept fluids from the vascular space. A patient with vasoconstriction fails to perfuse all tissues, limiting the rate at which the ECF volume can be replenished. If fluids are infused more rapidly than the rate at which they can enter the ECF volume, increased filling pressures may result in pulmonary edema. It is crucial to estimate filling pressures, cardiac output, and systemic vascular

resistance while aggressive intravascular fluid with balanced salt solution and colloid is pursued. It may be necessary to administer arterial vasodilators, such as nitroprusside, to facilitate correction.

Management of a typical patient includes frequent monitoring of arterial blood pressure, heart rate, CVP, pulse pressure, respiratory variation, urine output, and electrolytes. If these parameters are stable, the hemoglobin level and COP should be monitored every 2 to 4 hours until stable. An increasing hemoglobin level indicates ongoing loss of plasma water, with or without protein loss. An increasing COP indicates continued loss of plasma water greater than protein loss. Because maintenance fluid requirements persist, dextrose 5% is infused in 0.45% NaCl with 20 to 40 mEq/L of potassium chloride at maintenance rate.

The fluid lost to the bowel and ECF volume is similar to plasma water in electrolyte composition, and a balanced salt solution is a reasonable first choice for the fluid boluses required to sustain plasma volume. Because the fluid lost also contains protein, albumin or COP should be monitored, and colloid should be infused. If a low COP (approximately 15 to 18 mm Hg) coexists with hemodynamic instability, replacement should be started at 3 mL/kg/hr if the CVP (and pulmonary artery occlusion pressure [PAOP] if a pulmonary artery catheter has been placed) is within the patient's usual range. If COP is high, replacement should start at 1 to 2 mL/kg/hr. If the urine output increases to greater than 1.5 mL/kg/hr, the physician should check for glucosuria. If glucosuria is absent, the fluid infusion rate is reduced by 0.5 mL/kg/hr. If the CVP or PAOP value increases to greater than the patient's usual values, and urine output is 0.5 to 1.5 mL/kg/hr, the fluid infusion rate is reduced by 0.5 mL/kg/hr. If the values for CVP or PAOP or both decrease below the patient's baseline, and the urine flow rate is low, balanced salt or colloid solution is administered rapidly (0.5 to 2 mL/kg/min) with close monitoring of filling pressures.

Patient with Liver Failure

Fluid management in a patient with liver failure (see Chapters 66 and 67) is complicated by several interacting problems. These patients seem to be simultaneously hypervolemic and hypovolemic. Most infused fluid is retained, but renal function deteriorates, along with avid sodium retention and arterial underfilling. Neither sodium retention nor arterial underfilling explains all the clinical findings or leads to consistently successful therapy.

According to the arterial underfilling (primary vasodilation) hypothesis,[112] some factor produced by or not catabolized by the failing liver causes inappropriate arterial dilation. The relative hypotension leads to activation of the systematic nervous system and the RAS and vasopressin release. Subsequent sodium and water retention results in ascites and tissue edema.

Cirrhotic patients have a low systemic vascular resistance, high cardiac output, and relative hypotension. Persistent endotoxemia (shunting through portosystemic anastomoses and enhanced endotoxin absorption from the intestine as a result of bile salt deficiency) may contribute to the vasodilation by activation of a cascade of secondary mediators, beginning with tumor necrosis factor and interleukins. Other vasodilator neurotransmitters may be produced or may not be cleared by the damaged liver.

The primary sodium retention hypothesis explains the avid sodium retention on the basis of hormonal (aldosterone) hyperactivity because of failure of the liver to metabolize aldosterone. Given the ECF volume expansion, the distribution into ascites and tissue edema is explained by the abnormally high portal venous pressures and hypoalbuminemia. Abnormalities of ANP have been investigated. ANP levels are normal or low in cirrhotic patients; this contrasts with the increase usually found in volume-expanded patients.[113] ANP increased with water immersion or fluid administration, but natriuresis was not closely correlated with ANP levels. Water immersion of the lower body compresses the venous capacitance system, resulting in centralization of blood volume. This centralization of blood volume simulates a volume infusion without adding any sodium or water to the body and should cause ANP release. Water immersion did not increase ANP levels in patients with ascites, who have blunted responses. Impaired ANP release failed to explain sodium retention.[113] Patients with tense ascites had increased ANP, renin, and aldosterone concentrations. After paracentesis, ANP increased, but renin and aldosterone levels decreased.[114] The reasons for these findings were not clarified, but a reduction in intra-abdominal pressure could have decreased inferior caval pressure, facilitated venous return, and increased ANP levels. Decreased intra-abdominal pressures also would improve renal perfusion pressure, causing a reduction in renin release and subsequent aldosterone generation.

The role of increased intra-abdominal pressure may be important in sustaining sodium retention after ascites develops. Increased intra-abdominal pressure increases caval pressure; this decreases renal blood flow and glomerular filtration rate because the renal perfusion pressure gradient (i.e., mean arterial pressure minus renal venous pressure) is decreased by systemic hypotension and increased caval pressure. The hypotension and reduction in renal blood flow can lead to renin activation, with aldosterone production. Hypotension, increased aldosterone, and a decreased glomerular filtration rate lead to enhanced sodium reabsorption and low fractional excretion of sodium.

Hypoalbuminemia results from impaired synthesis by the liver, transudation into ascitic fluid owing to portal hypertension, and malnutrition. Low COP favors loss of fluid from the vascular space into the interstitial space, producing intravascular hypovolemia. Ascites results from high portal venous pressure and hypoalbuminemia, markedly increasing the volume of transcellular fluid, which is functionally excluded from rapid exchange in the ECF volume.

Splanchnic blood pooling resulting from increased portal venous resistance plus lower body pooling resulting from elevated caval pressures from ascites tend to decrease net systemic venous return. Patients are functionally hypovolemic despite normal or elevated total blood volume. Heart failure from alcoholic cardiomyopathy may complicate the clinical picture further.

The goals in these patients are to avoid increasing interstitial fluid overload, maintain normal potassium concentration, and maintain intravascular volume. If cardiac failure is present, treatment must include administration of inotropic drugs and diuretics when filling pressures are increased. Intravascular COP should be restored by infusion of 25% albumin when possible. If the patient is acutely hypovolemic, 5% albumin solutions should be preferred to crystalloid, which tend to expand further the already overexpanded ECF volume (i.e., produce more edema and ascites). Intra-abdominal pressure should be estimated from urinary bladder pressure, and paracentesis should be performed whenever it increases to greater than 20 to 25 mm Hg. Trials of

dopamine, norepinephrine, phenylephrine, or vasopressin may be performed in hypotensive patients with low vascular resistance and hypotension to increase renal perfusion pressure and renal blood flow.

Patient with Heart Failure

Fluid management of heart failure is directed to optimize cardiac preload, avoid overadministration of sodium, diminish edema, and correct common electrolyte abnormalities (see Chapter 60). Maintaining ideal cardiac preload during rapid fluid shifts that occur perioperatively is facilitated with direct or indirect measures of preload and cardiac contractile function. Measures of preload include CVP, thermodilution cardiac output, end-diastolic volume, echocardiography, PAOP, and left atrial pressure. Measures of cardiac contractile function include stroke volume, ejection fraction, and stroke work.

Patients with a history of cardiac failure scheduled for major or prolonged surgery should have monitoring instituted preoperatively, and an intravascular fluid challenge (i.e., 500 to 1000 mL/70 kg of crystalloid) should be performed to identify the optimal preload level. Tissue edema is avoided by frequent monitoring of preload and arterial blood pressure coupled with support of contractility and control of vascular resistance. These patients have impaired ability to excrete fluids during the fluid mobilization, which occurs postoperatively. Because the ECF volume is usually already expanded in these patients, the initial rates of fluid infusion intraoperatively should be at the lower ranges of estimates. Similarly, maintenance of intravascular volume without expansion of the interstitial space favors the use of colloid during the immediate perioperative period.

Postoperatively, hemodynamic monitoring is continued until fluid mobilization is complete. The goal postoperatively is to give as little crystalloid as required to maintain adequate overall cardiovascular performance. Perioperative patients commonly receive more than 200 mEq of sodium per day, including maintenance fluids, saline used to measure cardiac output, sodium from antibiotics administration, and sodium infused with vasoactive medications and inotropic agents. Fluid should be maintained at a low maintenance level, and flush fluids and sodium dosage should be measured. As soon as urine output begins to increase, or filling pressures or diastolic volume begins to increase, maintenance fluids should be stopped completely. If preload becomes excessive, diuretics should be administered.

Patients with heart failure have primary electrolyte problems because of compensatory physiologic mechanisms activated by the impaired cardiac performance. These are complicated by therapy with diuretics, digitalis, vasodilators, and angiotensin-converting enzyme inhibitors. Hyponatremia is common because of excess activation of the vasopressin system despite sodium retention. Treatment is directed at excreting the excess water load with diuretics, which should increase free water excretion more than sodium excretion. Sodium administration is not indicated, unless volume depletion is documented. Aldosterone activation and diuretics lead to loss of potassium and magnesium. These ions are crucial for maintaining the stability of cardiac electrophysiology and the effectiveness of digitalis and catecholamine. Ionized calcium is crucial for cardiac contractility, and hypocalcemia is extremely common during the perioperative period. Ionized calcium must be measured and corrected routinely. Severe hypophosphatemia often coexists with abnormalities of calcium, potassium, and magnesium, and leads to depressed contractility.

Patient with Cerebral Edema

Fluid management in patients with cerebral edema (see Chapters 13 and 63) is directed at maintaining cerebral perfusion pressure, avoiding elevations of cerebral venous pressure and hypertension, preventing large changes in plasma osmolality (particularly depression of plasma osmolality), and avoiding hyperglycemia. Cerebral perfusion pressure should be maintained in the high-normal range (see Chapter 63) because autoregulation is impaired in the damaged brain, with a baseline increase in cerebrovascular resistance. Avoidance of intracranial hypertension, the other determinant of cerebral perfusion pressure, is crucial to preserve blood flow to compromised but viable brain tissue. Cerebral edema formation is related to capillary pressure, COP, and permeability. The capillary pressure is between the arterial and venous pressures. Systemic arterial or venous hypertension should be prevented. The normal brain capillary bed is essentially impermeable to sodium, mannitol, and protein, although water crosses freely. The damaged capillary bed becomes excessively permeable, with conductivity being greatest for the smallest molecules, but less for colloids.

Free water restriction without hypovolemia is desired to maintain the plasma sodium level between 142 mEq/L and 148 mEq/L. It is common to provide 75% to 90% of maintenance fluids with 0.9% NaCl or lactated Ringer's solution and to minimize water volume required for other medications. Isotonic crystalloids or colloids do not cause edema in normal brain and can be used to sustain intravascular volume.[115] Hyponatremia is often caused by hypovolemia with inappropriate sodium loss[116] and subsequent water retention. Hyponatremia should be treated with intravascular volume expansion with isotonic or hypertonic sodium chloride. Parenteral nutrition can be prepared with 15% amino acid solutions, 20% lipid, and 70% dextrose to give full protein and caloric support in a minimal volume. Similarly, tube-feeding formulations with 2 cal/mL should be prescribed. Hypovolemia must be carefully avoided. Colloid infusion to sustain intravascular volume, guided by hemodynamic monitoring, tends to provide better long-term control of the intravascular volume than crystalloid. If diuretics or diabetes insipidus causes loss of greater than 2 mL/kg/hr for more than 2 to 4 hours, a pulmonary artery catheter may be indicated for closer monitoring. Blood glucose should be maintained at 80 to 175 mg/dL by close monitoring, initially hourly, with decreasing frequency as stability is exhibited. During acute resuscitation, dextrose administration is limited to no more than 2 mg/kg/min. Indications for steroid use have become fewer in recent years, lessening the problems of hyperglycemia.

Patient with Anuric Renal Failure Undergoing Nontransplantation Surgery

Fluid management in a patient with anuric renal failure for nontransplantation surgery should avoid excessive intravascular fluid

administration and ECF volume expansion, and should maintain or correct electrolyte and acid-base status (see Chapter 96). The anesthesiologist also should attempt to prevent precipitating conditions that would require dialysis during the immediate postoperative period (e.g., hyperkalemia, pulmonary edema, metabolic acidosis). Dialysis is difficult or impossible in a hemodynamically unstable patient, and anticoagulation may be strongly contraindicated for several hours postoperatively. Patients with chronic renal failure often present with hypertension, diabetes, and vascular disease. Avoidance of hypotension may be indicated to maintain coronary or cerebral perfusion pressure. In patients with acute renal failure, hypotension may worsen ischemic renal injury. In contrast, there is a lack of concern for an adverse effect on renal function in a patient with chronic renal failure. Recent dialysis often induces acute electrolyte shifts, hypovolemia, and acidosis. The best compromise seems to be dialysis 12 to 24 hours preoperatively. If dialysis is performed close to the time of surgery, volume removal should be minimal. Patients with renal failure are often malnourished, have hypoproteinemia, are anemic, and have poor glucose tolerance.

Hemodynamics should be closely monitored. If hypovolemia develops, colloid should be used early, but the physician should avoid producing vascular overexpansion. Likewise, interstitial fluid overload should be avoided because it would require acute postoperative dialysis. Crystalloid replacement of third space losses should be limited to 1 to 2 mL/kg/hr, whereas blood loss should be replaced with colloid or RBCs. Correction of sodium, potassium, and acidosis can be achieved by the use of isotonic fluid without potassium (to correct sodium), with reduced amounts of chloride (to correct potassium), and with increased amount of buffer (to correct acidosis). Initially, an infusion of 30% of calculated maintenance fluid rate is important because approximately 70% of normal fluid requirements are used in excreting solute through the kidney, a route no longer available. The pH and levels of sodium, potassium, bicarbonate, and glucose should be monitored at regular intervals.

Patient with Adult Respiratory Distress Syndrome

Fluid management in a patient with adult respiratory distress syndrome (ARDS) (see Chapters 91 and 92) involves maintaining COP and requires a CVP and PAOP value as low as possible that is consistent with good ventricular function. Oxygen delivery should be sustained, ideally greater than 600 mL/min/m^2, by increasing cardiac index and hemoglobin concentration. Compensation for hemodynamic effects of increased airway pressure is achieved by maintaining adequate right and left ventricular filling volumes. When airway pressure increases, the lung expands in proportion to its compliance. The intrapleural pressure increases in direct proportion to lung expansion and inversely with chest-diaphragm compliance. The increased intrapleural pressure increases CVP, which reduces the gradient between the periphery and the CVP. This reduces venous return, unless peripheral venous tone increases, or fluids are administered. The increased venous pressure increases fluid filtration out of the capillary bed, tending to produce hypovolemia. The increased pleural pressure is transmitted through the pericardium to reduce the filling pressure gradient for all cardiac chambers. The consequent reduction in end-diastolic volume diminishes preload to all chambers. The elevation of intrapulmonary pressure increases pulmonary artery pressure, which leads to augmented right ventricular afterload. The reduced venous return, decreased right ventricular preload, and increased afterload may severely compromise right ventricular stroke volume, cause stiffening of the interventricular septum, and reduce preload for the left ventricle.

All these consequences can be improved by intravascular volume expansion except for the increased afterload on the right ventricle. CVP and right ventricular end-diastolic volume are monitored to aid in the decision to institute inotropic therapy. An increase in CVP also compromises lymphatic return from the lung and periphery. Sepsis, the most common coexisting condition with ARDS, causes increased vascular capacity and vasodilation, decreases COP, and results in tissue edema. The net clinical outcome of these factors is that fluid intake usually exceeds output until ARDS and sepsis begin to subside. Studies comparing crystalloid and colloid management over the entire time course of ARDS are being evaluated. After 48 hours, pulmonary function may be better, however, in patients managed in part with colloid than with crystalloids alone.

Acutely Burned Patient

Fluid management in an acutely burned patient focuses on restoration of plasma volume and a shift of the ECF volume into the burned but viable tissue, accompanied by increased losses caused by loss of the normal barrier function of the skin. The tissue injury produced by the burn leads to an abrupt disruption of the capillary bed, manifested by local vasodilation, increased permeability, and, presumably, decreased reflection coefficient to proteins. Vasodilation increases the surface area for filtration and tends to increase capillary pressure. The lowered reflection coefficient diminishes the ability of colloids to retain fluid in the capillaries. Water, electrolytes, and protein enter the burned tissue at the expense of the intravascular volume. Fluid is mobilized from uninjured tissues by various processes, with a net result of transfer of fluid from normal tissue into the injured tissue and intravascular hypovolemia. Capillary permeability was formerly thought to increase in all tissues after a serious burn injury, but this is not the currently held view.[117] In addition to the tissue edema, there is a marked increase in loss of water by evaporation from the wound surface, and the metabolic rate increases dramatically, leading to proportionate increases in fluid requirements.

Several formulas have been developed to aid in writing the initial fluid prescription. The key to success is close hemodynamic monitoring with titration of therapy to the individual patient's physiology. If urine output increases progressively, or if filling pressures increase, fluid administration must be decreased. The Parkland formula[118] prescribes fluids based on the percentage of the body surface area (BSA) burned (% BSA-burned): 2 mL/kg/% BSA-burned during the first 8 hours and 2 mL/kg/% BSA-burned during the next 16 hours. The formula prescribes the following regimen of fluids:

Lactated Ringer's solution at $\left(\left[0.25\,\text{mL/kg}\right]/[\%\ \text{BSA-burned}]\right)/$ hr for 8 hours

Lactated Ringer's solution at $\left(\left[0.125\,\text{mL/kg}\right]/[\%\ \text{BSA-burned}]\right)/$ hr for 16 hours

5% dextrose in water at $\left(\left[0.8\,\text{mL/kg}\right]/[\%\ \text{BSA-burned}]\right)/$ hr plus 5% albumin at $\left(\left[0.015\,\text{mL/kg}\right]/[\%\ \text{BSA-burned}]\right)/$ hr for 24 hours

A 50-kg person with 50% BSA burn should receive fluids equal to (50 kg) × (0.25 mL/kg) × (50% BSA-burned), or 625 mL/hr for 8 hours. This is followed by fluids equal to (50 kg) × (0.125 mL/kg) × (50% BSA-burned), or 310 mL/hr for 16 hours. During the second 24 hours, fluids administered equal (50 kg) × (0.08 mL/kg) × (50% BSA-burned), or 200 mL/hr of 5% dextrose in water, plus (50 kg) × (0.015 mL/kg) × (50% BSA-burned), or 37.5 mL/hr of 5% albumin. Colloids are not contraindicated, even during the acute phase of fluid resuscitation. Although they pass into the injured tissue at an accelerated rate, they have a more sustained effect on plasma volume than crystalloid alone.

Pregnant Patient with Preeclampsia

Goals of fluid management in a pregnant patient with preeclampsia (see Chapter 69) are to restore the contracted intravascular volume,[119] avoid excessive intravascular fluid administration because of normal postpartum fluid mobilization, replace increased sensible (sweat) and insensible (respiratory) losses resulting from labor, be prepared to replace rapid blood loss, avoid hypotension resulting from anesthetic-induced vasodilation to preserve uteroplacental flow, maintain normoglycemia, avoid decreasing the COP further, and prevent pulmonary and cerebral edema. Restoration of depleted plasma volume to normal is crucial for control of hypertension and for administration of anesthesia. Plasma volume is decreased in preeclamptic patients because of elevated lower body venous pressure from uterine compression, pressure-induced natriuresis as seen in hypertension, severe vasoconstriction, and hypoproteinemia owing to proteinuria. After parturition, the fluid retained during pregnancy is usually quickly mobilized and excreted. The preeclamptic patient may have compromised hepatic, renal, or cardiac function, however, impeding the timely excretion of this fluid. These patients are at risk for pulmonary edema because of cardiac failure secondary to severe hypertension and lowered COP. Cardiac filling pressures should be monitored, and a PAOP of less than 12 to 15 mm Hg should be maintained. Plasma tonicity must be maintained by administration of isotonic fluid because these patients are at risk for cerebral edema.

Patient Undergoing Liposuction

Patients undergoing liposuction pose unique challenges in regard to intraoperative fluid management (see Chapter 64). A major factor determining the amount of intravascular volume changes during surgery is the type of liposuction being performed. Liposuction can be an office-based procedure using minimal sedation and subcutaneous infiltration of large volumes of dilute lidocaine and epinephrine solution. This is referred to as the tumescent technique and tends to be used to remove smaller volumes of fat (<3000 mL). Infiltration of large fluid volumes is used to make the tissue firm and to facilitate removal of adipose tissue. Because of the smaller volumes of fat removed and less damage to subcutaneous tissue, the tumescent technique has less risk of large fluid shifts. Semitumescent liposuction tends to involve removal of larger volumes of fat, larger volumes of lidocaine plus epinephrine solution, and more sedation. When a volume of more than 2000 to 3000 mL of fat is removed, the patient may require general anesthesia. These cases may lead to life-threatening complications involving fluid management. Ideally, the epinephrine in the tumescent solution decreases systemic absorption of the extremely large volumes of fluid administered subcutaneously. If the fluid is not removed before the effect of the epinephrine has worn off, however, the patient can absorb a significant amount of the administered fluid. Case reports[120-122] have described the development of pulmonary edema after liposuction.

Complicating the management of liposuction patients further are the large doses of lidocaine administered. During this procedure, patients receive 70 to 80 mg/kg of lidocaine. Vasoconstriction and removal of most of the infused solution is thought to prevent lidocaine toxicity.[123] One report[124] suggested, however, that lidocaine might impair alveolar epithelial fluid clearance. This impaired clearance of pulmonary fluid in conjunction with increased intravascular volume from the absorbed solution may explain some of the adverse occurrences, including death, reported after liposuction. There are significant data to support the increase in the maximum dose of lidocaine from the standard 7 mg/kg, but the maximum safe dosage of lidocaine for tumescent liposuction is still controversial.

The American Academy of Dermatology has published guidelines for liposuction.[125,126] The use of significant amounts of intravenous sedation or analgesic administration was considered to be potentially dangerous, particularly when conducted in an office-based setting. The recommended maximum dose of lidocaine was 55 mg/kg. This increased dosage mandates proper preoperative evaluation of patients' medications to determine whether they are using any drugs that inhibit the cytochrome 3A4 or 1A2 system. These are the major pathways by which lidocaine is metabolized, and even mild inhibition of these enzyme systems can lead to potentially lethal serum lidocaine levels.

Controlled trials regarding the best method for performing liposuction are lacking. A large body of practical knowledge suggests, however, that liposuction can be performed safely using large doses of lidocaine and large volumes of infused solution. Vigilance regarding potential volume overload and pulmonary edema is required to perform this procedure safely.

Intravascular Volume Resuscitation of Patient in Hemorrhagic Shock

The urgent priorities for the resuscitation of a seriously bleeding patient are (1) ensuring an adequate airway, (2) ensuring adequate respiration, and (3) supporting the circulation. Stopping blood loss is most often achieved through manual pressure on the bleeding site or operative intervention (rarely arterial tourniquet application), or both. Formerly, intravenous crystalloid (United States) or colloid (Europe) solution was administered to normalize blood

pressure. More recently, such intravenous fluids have been administered at rates just sufficient to maintain arterial systolic blood pressure between 80 and 100 mm Hg (with some centers limiting total infused volume during emergency medical services transport to 1 to 2 L of balanced salt solution [permissive hypotension]).[86] Benefits of this approach (achieved at the expense of non–vital organ hypoperfusion and lactic acidosis) include minimizing (1) the rate of additional blood loss, (2) hypothermia from the rapid intravenous administration of room temperature fluids, and (3) the dilution of blood hemoglobin and plasma coagulation factors.

When the patient is on the operating table, blood volume expansion is best achieved with fresh whole blood (now rarely available except at forward military trauma centers using a "walking blood bank" of pretyped soldiers) or the next best thing: combined infusion of warmed PRBCs, fresh frozen plasma, cryoprecipitate, and platelets in ratios sufficient to maintain normal coagulation status (e.g., PRBC-to-fresh frozen plasma ratio = 1 : 1 after the one blood volume exchange; 10 U of cryoprecipitate and platelets per 10 U of PRBCs for coagulopathic bleeding). More recently, there have been case reports of the administration of recombinant activated factor VII (NovoSeven) arresting exsanguinating hemorrhage owing to dilutional coagulopathy, but the precise use and dosing of this agent in trauma resuscitation have yet to be fully elucidated (see Chapter 72).

During massive transfusion of a severely hemorrhaging patient undergoing operative intervention, circulating volume can repeatedly alternate between hypovolemia and normovolemia, depending on the progress of surgery and the speed at which the hospital blood bank can provide blood components to the anesthesia team. Especially if balanced salt solutions are given in large quantities, overhydration (especially with mildly hypotonic Ringer's lactate solution) should be avoided in patients with head injury because this increases cerebral edema, increases intracranial pressure, and reduces cerebral perfusion pressure and brain oxygenation.

The patient's acid-base status should be corrected primarily through ensuring adequate ventilation and normalizing blood volume and composition. Metabolic acidosis usually can be rapidly reversed by intravenous administration of sodium bicarbonate, but at the expense of temporary elevation in sodium (which may be beneficial in head-injured patients). Ten percent calcium gluconate or calcium chloride solution (the latter being the more histotoxic of the two in the event of extravasation) should be administered to counteract the calcium-binding effects of the citrate in blood products if (1) laboratory or bedside monitoring reveals a low ionized calcium level, (2) the patient receives blood products at a rate of 10 combined units of PRBCs and fresh frozen plasma per hour, (3) hepatic function (cirrhosis) or hepatic blood flow (high aortic cross-clamp) is compromised, or (4) hypotension remains unresponsive to apparently adequate volume administration.

In addition to ensuring that all crystalloid, colloid, and blood product infusions are warmed (preferably to 40°C [104°F]), surface heating should be implemented (though use of forced-air heating blankets and, if necessary, warming the operating room to 26.6°C [80°F]). Hypotensive patients also should be evaluated for nonhemorrhagic mechanisms of shock, including cardiac/obstructive (tamponade, tension pneumothorax, air embolism) and distributive (head and spinal cord injury, anaphylaxis, transfusion reaction).

In addition to providing life support, the anesthesia team should administer central nervous system depressant medications as tolerated to provide unconsciousness (e.g., administer scopolamine for systolic blood pressure <60 mm Hg; administer ketamine or midazolam, or both, for systolic blood pressure 60 to 90 mm Hg; add fentanyl for systolic blood pressure 80 to 100 mm Hg; and add an inhaled agent when systolic blood pressure is sustained >100 mm Hg, with normal urine flow and minimal arterial pressure variation with mechanical ventilation). Complete muscle relaxation often must be achieved whether or not fully anesthetizing drug doses are tolerated, and brain wave monitors can be helpful beyond standard monitors, an arterial line, and a central venous catheter.

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Ronald D. Miller

55 Transfusion Therapy

Key Points

1. The most common causes of transfusion-induced death are bacterial contamination transfusion-related acute lung injury, transfusion reactions (i.e., ABO mismatch), and bacterial contamination.
2. Although the overall condition of the patient is of prime importance, a transfusion trigger of a hemoglobin level of 8 g/dL or less can be tolerated by relatively healthy, younger patients. Those who are not critically ill or have severe cardiorespiratory disease may require a transfusion trigger of 9 to 11 g/dL.
3. Because of storage at room temperature, platelets are the blood component most frequently contaminated with bacteria, which is the cause of platelet-induced sepsis.
4. Transfusion-transmitted hepatitis and human immunodeficiency virus (HIV) infection are rare. West Nile virus infection was a rapidly emerging problem but now can be tested for and is now rare.
5. Like in many countries in Europe and also Canada, leukoreduction of blood products is becoming universal in the United States.
6. Human and bovine modified hemoglobin products are undergoing clinical trials as synthetic blood or oxygen carriers, similar to allogeneic blood. Whether they will ever be used routinely is very questionable.

Blood Therapy

Eighty percent of the world's population has access to only 20% of the world's "safe" blood, that is blood that is properly collected and tested. Only 30% of the world's countries have a nationwide transfusion service.[1] The conclusions presented in this chapter assume the use of contemporary concepts and technology via organized transfusion services. According to a survey conducted by the Committee on Blood and Blood Products of the American Society of Anesthesiologists,[2] much of all blood given to patients is during the perioperative period. The anesthesiologist should be an expert on the implications and the complications associated with blood transfusions and should be a leader of acute transfusion medicine in the hospital setting.

Indications for Transfusion

Allogeneic (Homologous) Blood

Blood transfusions are given to increase oxygen-carrying capacity and intravascular volume. Theoretically, increasing vascular volume is not an indication for blood transfusions because volume can be augmented with administration of fluids that do not transmit infections (e.g., crystalloids or some colloids). On the practical side, when a patient is hemorrhaging, blood is given to increase oxygen-carrying capacity and intravascular volume. The goals should be to restore intravascular volume, cardiac output, and organ perfusion to normal levels. By using crystalloids and/or colloids to treat hypovolemia, normovolemic dilutional anemia will be created. Increasing cardiac output will enhance oxygen delivery to the tissues to a limited extent. In fact, using normovolemic anemia clinically, Mathru and colleagues found inadequate splanchnic and preportal oxygen delivery and consumption when the hemoglobin level was 5.9 g/dL.[3] Additional oxygen delivery to organs and tissues can only be enhanced by red blood cells via whole blood or packed red blood cells, Thus, increasing oxygen-carrying capacity is the only real indication for blood transfusions.

What are the specific indications for blood transfusions? With a specific indication (i.e., increase oxygen-carrying capacity), this question, at first glance, should be easy to answer. Unfortunately, there is little or no way, except in severe life-and-death situations, to determine whether oxygen-carrying capacity is inadequate. The controversy revolves around how much emphasis should be placed on hemoglobin or hematocrit values. The limitation of such values is based on a potential extreme variability from one patient to another regarding the need for increased oxygen-carrying capacity. For example, young healthy patients with normal cardiorespiratory function may easily compensate

Table 55-1 American College of Surgeons' Classes of Acute Hemorrhage

Factors	Class I	Class II	Class III	Class IV
Blood loss (mL)	750	750-1500	1500-2000	2000 or more
Blood loss (% blood volume)	15	15-30	30-40	40 or more
Pulse (beats/min)	100	100	120	140 or higher
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respirations per minute	14-20	20-30	30-40	35
Urine output (mL/hr)	30	20-30	5-10	Negligible
Central nervous system: mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement (3-1 rule)	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

for anemia (i.e., chronic or acutely induced by hemorrhage), whereas at an identical hematocrit value, elderly patients with cardiac disease may have serious problems with surgery and anesthesia. An individual patient's hemoglobin level may vary markedly in the perioperative period independent of and in addition to transfusions of red blood cells (RBCs). This concern has led many medical organizations to place emphasis on overall medical judgment rather than a specific laboratory value,[4] with some debate.[5] Conversely, other organizations have chosen to make far more complex directions, such as those in Table 55-1 from the American College of Surgeons. Despite the intellectual appeal of the latter approach, most of the American College of Surgeons' criteria cannot distinguish inadequate intravascular volume from diminished oxygen-carrying capacity.

The foundation for using the hemoglobin or hematocrit value as the initial consideration for defining transfusion requirements followed a 1988 National Institutes of Health Consensus Conference[6] that concluded that otherwise healthy patients with a hematocrit value more than 30% rarely require perioperative blood transfusions, whereas patients with acute anemia (as in intraoperative blood loss) of less than 21% frequently require blood transfusions. They also recognized that patients with chronic anemia (as in renal failure) might tolerate a hemoglobin concentration of less than 7 g/dL. Amazingly and despite many studies, publications, and debates, the fundamental guidelines have not changed substantially in the 20 years after this conference.

The ultimate determination of the hematocrit or hemoglobin value at which blood should be given will have to be a clinical judgment based on many factors, such as cardiovascular status, age, anticipated additional blood loss, arterial oxygenation, mixed venous oxygen tension, cardiac output, and blood volume. Oxygen extraction ratio has been recommended as an indicator for transfusions,[7] but this technique requires invasive monitoring. Even so, the results by this indicator were not dramatic between groups who were or were not transfused.

Several groups have attempted to define, usually in patients in intensive care units, the point at which blood transfusions should be given by measures of tissue oxygenation and hemodynamics (e.g., increase in oxygen consumption in response to added oxygen content).[8-10] No specific measure could consistently predict when a patient would benefit from a blood transfusion. However, evidence suggests that the quality (e.g., age) of the blood and its increased oxygen capacity (e.g., hemoglobin level > 10 g/dL) may benefit very sick patients. Purdy and colleagues,[11] found that patients who received 17-day-old blood (range, 5 to 35 days) versus 25-day-old blood (range, 9 to 36 days) had a higher survival rate. In 1999, the length of storage of banked blood was associated with the development of postoperative pneumonia after cardiac surgery.[12] However, in 2003, prolonged storage of blood was not associated with increased morbidity after cardiac surgery.[13]

Yet the saga continues. In 2006, Weiskopf and coworkers performed studies in healthy volunteers who were evaluated by a standard computerized neuropsychological test 2 days and 1 week after acute isovolemic anemia was induced.[14] When correcting the anemia, they concluded that erythrocytes stored for 3 weeks are as efficacious as those stored for 3.5 hours. Spahn[15] wrote an accompanying editorial agreeing with Weiskopf and coworkers[2] and, furthermore, postulated that 2,3-diphosphoglycerate (2,3-DPG) levels may not be the key factor in determining the oxygen-delivery of oxygen (i.e., 2,3-DPG levels are reduced in older blood, but the blood still delivers oxygen).

Two years later, different conclusions were published. Koch and colleagues[16] concluded that giving erythrocytes (packed red cells) older than 14 days was associated with an increased risk of postoperative complications along with reduced short-term and long-term survival in patients undergoing coronary artery bypass surgery. This article also had an accompanying editorial that concluded that "to the extent possible, newer blood might be used in clinical situations that seem to call for it."[17] Rather than continuing the ongoing saga and debate regarding the influence of the age of blood transfused, all of the available studies need to be analyzed together that probably relate to the underlying health of the patient and the condition that requires blood transfusions. This debate is not close to being resolved. Because the quality of blood decreases with length of storage, an association with morbidity would not be surprising. The influence of the age of blood infused is discussed later in this chapter.

Perhaps the development of more sensitive indicators of tissue oxygenation (e.g., intramucosal pH) will provide indicators for transfusion. In the 1990s, several efforts could not relate postoperative hemoglobin levels to specific outcomes. Furthermore, Weiskopf and coworkers[18] found that decreases in hemoglobin concentration to 5.0 g/dL did not produce any evidence of inade-

quate oxygenation in healthy patients. However, these patients were not subjected to the stresses of recovery from surgery and anesthesia. Still, Weiskopf and coworkers[18] found that these patients compensated for their low hemoglobin levels by increasing heart rate and stroke volume. It is tempting to argue that patients who have a more rapid than expected heart rate or who cannot increase their cardiac output should receive a transfusion to a higher hemoglobin level than 10 g/dL. Unfortunately, precise conclusions cannot be derived from these helpful and suggestive data.

To arrive at some conclusions in the presence of incomplete data, two complementary recommendations are given. In 2006, the American Society of Anesthesiologists Practice Guidelines[4] offered these recommendations:

1. Transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute.
2. The determination of whether intermediate hemoglobin concentrations (6 to 10 g/dL) justify or require RBC transfusion should be based on the patient's risk for complications of inadequate oxygenation.
3. The use of a single hemoglobin "trigger" for all patients and other approaches that fail to consider all important physiologic and surgical factors affecting oxygenation is not recommended.
4. When appropriate, preoperative autologous blood donation, intraoperative and postoperative blood recovery, acute normovolemic hemodilution, and measures to decrease blood loss (i.e., deliberate hypotension and pharmacologic agents) may be beneficial.
5. The indications for transfusion of autologous RBCs may be more liberal than those for allogeneic RBCs because of less frequent (but still significant) risks associated with the former.

The following indications were recommended in the 6th edition of *Anesthesia* with the rule of thumb that administration of 1 unit of packed RBCs will increase hematocrit value by 3% to 5%:

1. Blood loss greater than 20% of blood volume when more than 100 mL
2. Hemoglobin level less than 8 g/dL
3. Hemoglobin level less than 10 g/dL with major disease (e.g., emphysema, ischemic heart disease)
4. Hemoglobin level of less than 10 g/dL with autologous blood
5. Hemoglobin level less than 12 g/dL and ventilator dependent

Although these recommendations are current, the elusive "transfusion trigger" remains in a prominent part of the debates in anesthesia specifically and in medicine in general. Both recommendation lists[4] agree that a transfusion trigger of 8.0 g/dL or less can be tolerated by patients who are not critically ill or do not have severe cardiorespiratory disease. That conclusion is still valid.

In the past 5 years, research has been directed toward how liberal the transfusion trigger should be in critically ill patients. Unfortunately, there are almost no data regarding intraoperative transfusion triggers. Still, critical care physicians have suggested that administration of blood transfusions is related to the incidence of ventilator-assisted pneumonia[19] and nosocomial infections[20]; while this possibility cannot be excluded, these are complicated problems with many variables. Despite the problem with identifying a specific transfusion trigger, Ely and Bernard[21] have generally confirmed the conclusions listed above in the sixth edition of *Miller's Anesthesia*. Subsequent efforts and editorials have leaned toward a lower transfusion trigger for even critically ill patients.[22,23] Ensuing studies have found no apparent benefit or a trend toward better outcomes with transfusion-induced hemoglobin levels more than 8.0 g/dL (i.e., 9.0 to 10.0 g/dL).[24,25] Yet most recently, Vincent and associates, using a multicenter observational study, found that "blood transfusions may no longer be associated with increased mortality rates and may be associated with improved survival."[26] Although these multicenter studies have statistical challenges,[27] a more liberal transfusion trigger is suggested. Perhaps the margin of safety should be increased by increasing the hemoglobin in critically ill patients, including those with cardiorespiratory disease. There is increasing concern about the underuse of blood transfusion therapy.[28] However, blood is a valuable resource that sometimes is in short supply. Perhaps with the availability of erythropoietin and synthetic RBCs, a more liberal hemoglobin concentration can be used. As concluded by Weiskopf,[29] "We merely await advances in technology that will enable us to measure directly the value of concern and thereby free us from arguments over which surrogate (e.g., hemoglobin) to measure and what value indicates the need for augmented oxygen delivery."

Autologous Blood

Autologous blood (see also Chapter 57) is assumed to be much safer than allogeneic blood, mainly because of the decreased risk of infection. Because of a marked decrease in infectivity from allogeneic blood (see "Infectivity of Blood"), the difference in safety compared with autologous blood is much less. Not surprisingly, the proportion of autologous blood collected has significantly decreased since the peak in 1992. In fact, autologous blood may not be safer than allogeneic blood. Furthermore, autologous blood does have risks. One of every 16,000 autologous blood donations results in a reaction severe enough to require hospitalization.[30] Complications associated with autologous blood transfusions include the following:

- Anemia
- Preoperative myocardial ischemia from anemia induced by preoperative donation
- Autologous units given to wrong patient (1 per 13,000 to 62,000)[31]
- Need for more frequent blood transfusions

In fact, transfusion-related bacterial sepsis may be more frequent with use of autologous blood because of the underlying medical condition of the donor and less stringent donor selection. Also, autologous blood must be tested the same as allogeneic blood.

The testing and screening of blood donors is by no means perfect. Ask yourself a question: If given a choice, would you want your own blood or allogeneic blood?[32]

Compatibility Testing

The ABO-Rh type, crossmatch, and antibody screen are frequently referred to as compatibility tests (see Chapter 57). These tests were designed to demonstrate harmful antigen-antibody interactions in vitro so that harmful in-vivo antigen-antibody interactions could be prevented. Donor blood used for emergency transfusion of group-specific blood must be screened for hemolytic anti-A or anti-B antibodies or both. All donor blood must be tested for the correct ABO and Rh type and screened for unexpected antibodies. Similarly, recipient blood must also undergo ABO-Rh typing, as well as testing for unexpected antibodies. Once this has been completed, proper selection of donor blood requires a test for compatibility between recipient blood and donor blood; this test is known as a crossmatch (Fig. 55-1).

ABO-Rh Typing

Determination of the patient's correct blood type is exceedingly important because the most serious and tragic reactions are usually caused by accidental transfusion of ABO-incompatible blood. These reactions result from naturally occurring antibodies (i.e., anti-A and anti-B), which activate complement and lead to rapid intravenous hemolysis. Anti-A or anti-B antibodies, or both, are formed whenever the individual lacks either or both of the A and B antigens. In essence, antibodies are directed against those antigens that are lacking in the individual's own cells. ABO typing is performed by testing RBCs for the A and B antigens and the serum for the A and B antibodies before transfusion (Table 55-2).

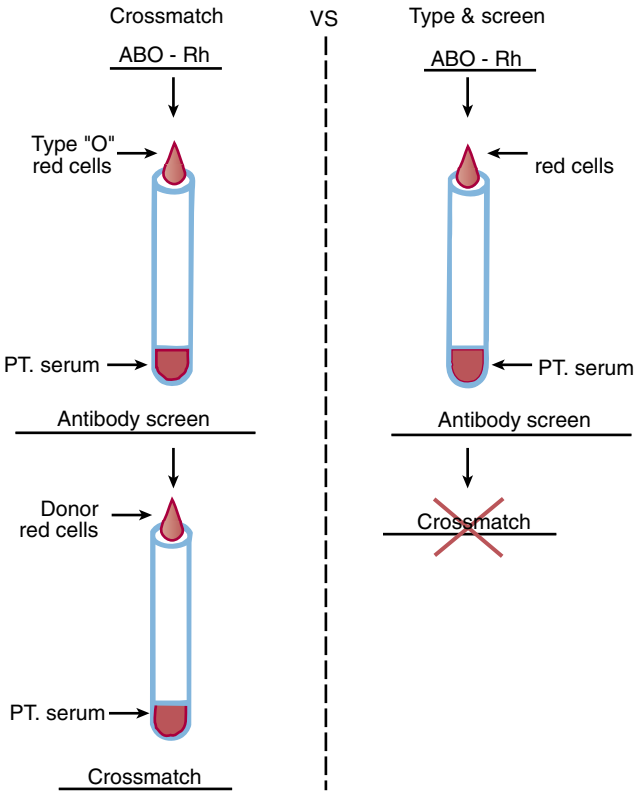

Figure 55-1 Outline of the tests used for a crossmatch. The X over the word crossmatch means that the crossmatch is not included in the type and screen.

Table 55-2 ABO Compatibility Testing

	Red Cells Tested With		Serum Tested With	
Blood Group	**Anti-A**	**Anti-B**	**A Cells**	**B Cells**
A	+	–	–	+
B	–	+	+	–
AB	+	+	–	–
O	–	–	+	+

The only additional required testing is that for the Rh(D) antigen. Antigen D is a very common one and, except for the A and B antigens, the one most likely to produce immunization. Sixty to 70 percent of Rh(D)-negative recipients are immunized (produce anti-D) if they are given blood transfusions with Rh(D)-positive blood. About 85% of individuals possess the D antigen and are classified as Rh(D) positive; the remaining 15%, who lack the D antigen, are classified as Rh(D) negative. Because anesthesiologists and surgeons often have difficulty understanding the blood grouping system, Table 55-3 is included to facilitate identification of donor blood groups whose blood patients can receive.

Crossmatching

A crossmatch is essentially a trial transfusion within a test tube in which donor RBCs are mixed with recipient serum to detect a potential for serious transfusion reaction. The crossmatch can be completed in 45 to 60 minutes and is carried out in three phrases: an immediate phase, an incubation phase, and an antiglobulin phase.

The first phase is conducted at room temperature and is a check against errors in ABO typing. It detects ABO incompatibilities and those caused by naturally occurring antibodies in the MN, P, and Lewis systems. This takes 1 to 5 minutes to complete.

The second phase involves incubation of the first-phase reactions at 37°C in albumin or low-ionic strength salt solution. The addition of albumin and low-ionic-strength salt solution aids in the detection of incomplete antibodies or those antibodies that are able to attach to a specific antigen (i.e., sensitization) but are unable to cause agglutination in a saline suspension of RBCs. This phase primarily detects antibodies in the Rh system. The incubation of 30 to 45 minutes in albumin and of 10 to 20 minutes in

Table 55-3 Donor Blood Groups that Patients Can Receive

Donor	Recipient
O	O, A, B, AB
A	A, AB
B	B, AB
AB	AB

low-ionic-strength salt solution in this phase is of sufficient duration to allow antibody uptake sensitization by cells so that incomplete antibodies missed in this phase can be detected in the subsequent antiglobulin phase.

The third phase of the crossmatch, the indirect antiglobulin test, involves the addition of antiglobulin sera to the incubated test tubes. With this addition, antihuman antibodies present in the sera become attached to the antibody globulin on the RBCs, causing agglutination. This antiglobulin phase detects most incomplete antibodies in the blood group systems, including the Rh, Kell, Kidd, and Duffy blood group systems.

Although all three phases of the crossmatch are important, the first two stages are of prime importance in preventing serious hemolytic transfusion reactions (see "Type and Screen"). The incubation and antiglobulin phases are especially important because the antibodies appearing in these phases are capable of causing serious hemolytic reactions. Except for hemolytic reactions involving anti-A and anti-B, reactions caused by antibodies appearing in the immediate phase (RT) are frequently less severe. This is because many of the antibodies appearing in this phase are naturally occurring antibodies present in a low titer and are not reactive at physiologic temperatures.

Antibody Screening

The antibody screen is also carried out in three phases and is similar in length to the crossmatch. The screen, however, is a trial transfusion between the recipient's serum and commercially supplied RBCs that are specifically selected to contain optimal numbers of RBC antigens or those antigens that will react with antibodies that are commonly implicated in hemolytic transfusion reactions.

The screen for unexpected antibodies is also used on donor serum and is performed shortly after withdrawal of blood from the donor. It is necessary to screen donor serum for unexpected antibodies to prevent their introduction into the recipient serum. This screen is performed primarily to prevent reactions between transfused donor units.

Approaches Requiring Less Than a Complete Crossmatch

Type and Screen

The term *type and screen* refers to elimination of the crossmatch in which blood is set aside with only the ABO-Rh type having been determined and antibody screening having been performed. The type and screen without crossmatch determines the ABO-Rh of the patient and the presence of the most commonly found unexpected antibodies. Specifically, the patient's serum is screened for the presence of unexpected antibiotics by incubating it with selected reagent RBCs (i.e., screen cells).[33] These cells contain all antigens capable of inducing clinically significant RBC antibody reactions.

Complete transfusion testing for compatibility between donor and recipient blood ensures optimal safety and therapeutic effect of transfused blood. In some cases, however, the crossmatch is eliminated and blood can be set aside in which only the ABO-Rh type and antibody screen are performed (i.e., type and screen). For those few patients in whom the antibody screen reveals the presence of unexpected antibody, the antibody is subsequently identified in the blood bank and units of blood lacking the corresponding antigen are set aside for surgery. If an emergency transfusion is required after type and screen alone, an immediate-phase crossmatch is performed before transfusion to eliminate reactions that may result from human errors in ABO-Rh typing. Blood given in this manner is more than 99% effective in preventing incompatible transfusion reactions due to unexpected antibodies.[34] The type and screen without the complete crossmatch does not protect against reactions due to antibodies reactive against lower-incidence antigens, those not represented on the screening cells but present on the donor RBCs. Generally, antibodies that are not detected in the type and screen are weakly reactive antibodies that do not result in serious hemolytic transfusion reactions. In a study of 13,950 patients, Oberman and associates[35] discovered only eight "clinically significant" antibodies after complete crossmatch that were not detected during the antibody screening. The antibodies were all in lower titer and were believed by Oberman and coworkers to be unlikely to cause serious hemolytic reactions.

Type and screen should not be confused with the term *type and hold*. This term refers to a sample of blood from a potential blood recipient received by the blood bank in which the blood type but no crossmatch has been ordered. This term is misleading because it does not denote how long the blood should be held, nor does it indicate that an antibody screen has been performed on the sample. However, in most cases in which a type and hold has been ordered, an antibody screen is performed on that sample. Because of the confusion that has arisen with type and screen, the type and hold terminology and method of ordering blood have been abandoned by most blood banks.

Maximal Surgical Blood Order Schedule

Routine preoperative crossmatching of blood for surgical cases means that crossmatched blood is unavailable for others for 24 to 48 hours. During this time, 1 to 2 days is lost and the chance for outdating increases. A second aspect relates to the growing realization that, for certain elective surgical procedures, the number of crossmatched units that are ordered frequently far exceeds the number actually transfused. To quantify this problem better, the crossmatch-to-transfusion (C/T) ratio has been used. If the C/T ratio is high, the blood bank is burdened with keeping a large blood inventory, using excessive personnel time, and having a high incidence of outdated units. Sarma[36] recommended that for surgical procedures in which the average number of units transfused per case is less than 0.5, determination of the ABO-Rh type and a screen of the patient serum for unexpected antibodies (type and screen) should be used. This would be in lieu of a complete type and crossmatch for patients with negative antibody screens. For those with a positive antibody screen, the blood bank must provide compatible units that lack the corresponding antigen. Blood banks attempt to maintain C/T ratios of 2.1 to 2.7.[36] To increase the rate of use and lower the C/T ratio, blood banks attempt to decrease the emphasis on crossmatching of blood through such means as the type and screen and such programs as the maximal surgical blood order schedule.[37] This schedule consists of a list of surgical procedures and the maximal number

of units of blood that the blood bank will crossmatch for each procedure. This schedule is based on the blood transfusion experience for surgical cases in hospitals in which the schedule is employed. Each hospital's maximal surgical blood order schedule is developed by the suppliers and the users of blood in that hospital, such as blood bankers, anesthesiologists, and surgeons.

Is the Crossmatch Really Needed?

In previously transfused or pregnant patients, only about 1 patient in 100 may have an irregular antibody other than the anti-A and anti-B antibodies. However, some of these irregular antibodies are reactive only at temperatures below 30°C and therefore are insignificant in most transfusions. Others that are reactive at about 30°C can produce serious reactions if the transfused cells contain appropriate antigen. In order of probable significance, anti-Rh(D), Kell, C, E, and Kidd are the most common of clinically significant antibodies. After anti-A and anti-B, anti-Rh(D) is the most common significant antibody. If the correct ABO and Rh blood type is given, the possibility of transfusing incompatible blood is less than 1 chance in 1000. Put in other terms, ABO-Rh typing alone results in a 99.8% chance of a compatible transfusion, the addition of an antibody screen increases the safety to 99.94%, and a crossmatch increases this to 99.95%.[38]

The blood bank can reduce the chance of incompatibility by performing an antibody screen. The chance of this screening test missing an antibody that is potentially dangerous has been estimated to be no more than 1 in 10,000.

Emergency Transfusion

In many situations, there is urgent need for blood before completion of compatibility testing (ABO-Rh, antibody screen, and crossmatch) (see Chapter 72). For those situations that do not allow time for complete testing, an abbreviated format for testing can be used. The preferred order for the selection of partially crossmatched blood is as follows.

Type-Specific, Partially Crossmatched Blood

When using uncrossmatched blood, it is best to obtain at least an ABO-Rh typing and an immediate-phase crossmatch. This incomplete crossmatch is accomplished by adding the patient's serum to donor RBCs at room temperature, centrifuging it, and then reading it for macroscopic agglutination. This takes 1 to 5 minutes and eliminates serious hemolytic reactions resulting from errors that may occur in ABO typing. Only a few unexpected antibodies outside the ABO systems are detected, such as those directed against antigens in the MN, P, and Lewis systems, most of which are not clinically significant.

Type-Specific, Uncrossmatched Blood

For proper use of type-specific blood, the ABO-Rh type must be determined during the patient's hospitalization. Blood types from historical records, relatives, ambulance drivers, and other hospitals are frequently inaccurate. For those who have never been exposed to foreign RBCs, most ABO type-specific transfusions are successful. Caution should be used for patients who have previously received transfusions or have had pregnancies. In my experience in the military, type-specific uncrossmatched blood was frequently used in emergencies with no serious consequence. In the civilian setting, using 1 year's experience with 56 patients, uncrossmatched, type-specific blood for emergency transfusion produced no adverse effects, even though complete serologic testing had not been performed.[39] These investigators concluded that although the use of uncrossmatched blood is usually safe, the potential for serious reaction still exists, and they cautioned against its indiscriminate use. About 1 in 1000 patients has an unexpected antibody detected in crossmatch. For those who have previously been exposed to RBC antigens, transfusion of the ABO-Rh type-specific, uncrossmatched blood may be more hazardous. For every 100 of these individuals, 1 has an antibody detected by the crossmatch.

Type O Rh-Negative (Universal Donor), Uncrossmatched Blood

Type O blood lacks the A and B antigens and consequently cannot be hemolyzed by anti-A or anti-B antibodies in the recipient's blood (see Tables 55-2 and 55-3). Because of this, people with type O blood have been called universal donors and their blood can be used in emergency transfusions when typing or crossmatching is not available. However, some type O donors produce high titers of hemolytic IgG, IgM, anti-A, and anti-B antibodies. High titers of these hemolysins in donor units are capable of causing destruction of A or B RBCs of a non–type O recipient. Type O Rh-negative, uncrossmatched packed RBCs should be used in preference to type O Rh-negative whole blood because packed erythrocytes have smaller volumes of plasma and are almost free of hemolytic anti-A and anti-B antibodies. If type O Rh-negative whole blood is to be used, the blood bank must supply type O blood that is free of hemolytic anti-A and anti-B antibodies.

During emergency transfusion of more than two units of type O Rh-negative, uncrossmatched whole blood, the patient probably cannot be switched to his or her blood type (A, B, or AB) as soon as the blood bank determines the correct blood type. Switching could cause major intravascular hemolysis of donor RBCs by increasing titers of transfused anti-A and anti-B. Continued use of O Rh-negative whole blood results only in minor hemolysis of recipient RBCs, with hyperbilirubinemia as the only complication. The patient must not be transfused with his or her correct blood type until the blood bank determines that the transfused anti-A and anti-B has decreased to levels that permit safe transfusion of type-specific blood.

Specific Recommended Protocol

In view of the aforementioned considerations, the following steps are recommended for patients who are hypovolemic and require blood transfusion:

1. Infuse crystalloids or colloids.
2. Draw a blood sample for typing and crossmatching.

3. If crossmatched blood is not ready to give, use type-specific or type O Rh-negative cells or type O Rh-positive cells for males or postmenopausal females without a history of transfusions; type-specific, partially crossmatched blood; or type-specific, crossmatched blood.

Storage of Blood

Citrate phosphate dextrose adenine (CPDA-1) is an anticoagulant preservative in which blood is stored at 1°C to 6°C. Citrate is an anticoagulant, phosphate serves as a buffer, and dextrose is a red cell energy source. The addition of adenine to CPD solution allows RBCs to resynthesize adenosine triphosphate (ATP), which extends the storage time from 21 to 35 days. As a result, RBCs or whole blood can be stored for 35 days when stored in CPDA-1.[40] The shelf life can be extended to 42 days when AS-1 (Adsol), AS-3 (Nutricel), or AS-5 (Optisol) is used.[41,42] Adsol contains adenine, glucose, mannitol, and sodium chloride; Nutricel contains glucose, adenine, citrate, phosphate, and sodium chloride. Optisol contains only dextrose, adenine, sodium chloride, and mannitol. On a local level, 90% of our RBCs are mostly stored in AS-1 at the University of California, San Francisco. On a national level, 85% of the RBCs are collected in AS-1. The hematocrit of packed red cells stored in AS-1 is approximately 60%. This duration of storage has been set by U.S. federal regulation and is determined by the requirement that at least 70% of the transfused RBCs remain in circulation for 24 hours after infusion. RBCs that survive 24 hours after transfusion disappear from the circulation at a normal rate. Those that do not survive are subsequently removed from the circulation by the blood recipient.

That blood can be stored for 42 days is a mixed blessing. The obvious advantage is the increased availability of blood. However, there are increasing numbers of articles whose authors believe that blood stored for long periods is less effective than fresher blood in critically ill patients, probably because of a leftward shift in the oxygen-dissociation curve (see "Changes in Oxygen Transport").[13] An increased incidence of postoperative pneumonia in cardiac patients has been associated with the use of older blood.[12]

The citrate ion prevents clotting by binding calcium; dextrose allows the RBCs to continue glycolysis and maintain sufficient concentrations of high-energy nucleotides (ATP) to ensure continued RBC metabolism and subsequent viability during storage. The storage at 1°C to 6°C assists preservation by slowing the rate of glycolysis approximately 40 times the rate at body temperature. The addition of adenine prolongs storage time by increasing RBC survival by allowing RBCs to resynthesize the ATP needed to fuel metabolic reactions. Without adenine, RBCs gradually lose their ATP and their ability to survive after transfusion.

During storage of whole blood and packed RBCs, a series of biochemical reactions occur that alter the biochemical makeup of blood and account for some of the complications that are discussed later. During storage, RBCs metabolize glucose to lactate, hydrogen ions accumulate, and plasma pH decreases. The storage temperatures of 1°C to 6°C stimulate the sodium-potassium pump, and RBCs lose potassium and gain sodium. The osmotic fragility of RBCs increases during storage, and some cells undergo lysis, resulting in elevated plasma hemoglobin levels. Storage is associated with progressive decreases in RBC concentrations of ATP and 2,3-DPG.

Packed RBCs have a slightly lower survival than whole blood (Table 55-4), although values for hemoglobin and potassium concentrations may appear somewhat high in 35-day stored RBC concentrates. However, the total plasma volume in the concentrates is only 70 mL.

Innovative methods of storing blood are being developed. For example, storing blood in an electrostatic field of 500 to 3000 V decreases hemolysis and attenuates the decrease in pH associated with prolonged storage.[43]

Complications

Changes in Oxygen Transport

RBCs are transfused primarily to increase transport of oxygen to tissues. An increase in the circulating red cell mass produces an increase in oxygen uptake in the lungs and a corresponding probable increase in oxygen delivery to tissues. The respiratory function of red cells may be impaired during preservation, making it difficult for them to release oxygen to the tissues immediately after transfusion.

Table 55-4 Properties of Whole Blood and Packed Red Cell Concentrates Stored in CPDA-1

	Days of Storage		
Parameter	**0**	**35 (Whole Blood)**	**35 (Packed Cells)**
pH	7.55	6.73	6.71
Plasma hemoglobin (mg/dL)	0.50	46.00	246.00
Plasma potassium (mEq/L)	4.20	17.20	76.00
Plasma sodium (mEq/L)	169.0	153.00	122.00
Blood dextrose (mg/dL)	440.0	282.00	84.00
2,3-Diphosphoglycerate (μM/mL)	13.20	1.00	1.00
Percent survival*	—	79.00	71.00

*Percent recovery of O_R-tagged red blood cells at 24 hours.
CPDA-1, citrate phosphate dextrose adenine-1.

Review of the Oxygen Dissociation Curve

The oxygen dissociation curve is determined by plotting the partial pressure of oxygen (Po_2) in blood against the percentage of hemoglobin saturated with oxygen (Fig. 55-2). As hemoglobin becomes more saturated, the affinity of hemoglobin for oxygen also increases. This is reflected in the sigmoid shape of the curve, which indicates that a decrease in Pao_2 makes considerably more oxygen available to the tissues. The sigmoid shape of the curve implies greater efficiency of blood transportation of oxygen from the lungs to tissues.

Shifts in the oxygen dissociation curve are quantitated by the P_{50}, which is the partial pressure of oxygen at which hemoglobin is half saturated with oxygen at 37°C and pH 7.4. A low P_{50} indicates a left shift in the oxygen-dissociation curve and an increased affinity of hemoglobin for oxygen; in other words, the left shift of the curve indicates that a lower-than-normal oxygen tension saturates hemoglobin in the lung and the subsequent release of oxygen to the tissues occurs at a lower-than-normal capillary oxygen tension. An increased affinity may be enough to ensure that oxygen is released to the tissues unless the tissue Po_2 is in the hypoxic range. The clinical evidence supporting the accuracy of this hypothesis during infusion is discussed in the following section.

Clinical Evidence

The clinical evidence is not consistent, reflecting the difficulty of conducting a systematic study of seriously ill patients in varied clinical settings. For 40 years, various clinicians in a variety of clinical settings have tried to establish a firm relationship between the 2,3-DPG levels associated with stored blood and patient welfare (e.g., organ function). In 1993, Marik and Sibbard[8] found that the administration of blood that had been stored for more than 15 days actually decreased intramucosal pH, suggesting that splanchnic ischemia had occurred. In the past 10 years, numerous studies have tried to prove that older blood (and therefore decreased oxygen delivery) is not as beneficial as fresher blood in critically ill patients. Although a definitive conclusion cannot be made, I believe that blood with less than 15 days of storage should be used in very ill patients.

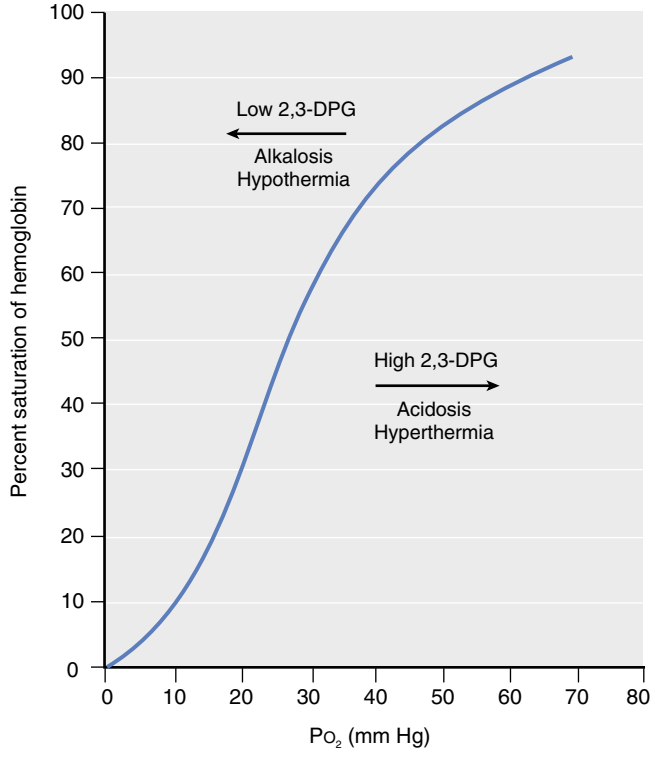

Figure 55-2 Factors that shift the oxygen dissociation curve. 2,3-DPG, 2,3-diphosphoglycerate. *(From Miller RD: The oxygen dissociation curve and multiple transfusions of ACD blood.* In *Howland WS, Schweizer O [eds]: Management of Patients for Radical Cancer Surgery. Clinical Anesthesia Series, vol 9. Philadelphia, FA Davis, 1972, p 43.)*

Coagulation

Unless a patient has a preoperative coagulopathy (e.g., aspirin, antiplatelet drugs, hemophilia), major trauma and/or blood loss in itself will initiate a cascade of coagulation abnormalities, including a consumptive coagulopathy from tissue hypoperfusion as manifested by increased protein C levels.[44] The addition of a large amount of blood (e.g., 6 to 10 units of packed RBCs) only augments this coagulopathy. Various protocols have been developed for approaches to massive blood transfusion administration (Fig. 55-3). This coagulopathy is caused by a combination of factors, of which the most important are the volume of blood given and the duration of hypotension or hypoperfusion. Patients who are well perfused and are not hypotensive for a long period (e.g., 1 hour) can tolerate multiple units of blood without developing a coagulopathy. The patient who is hypotensive and has received many units of blood probably has a coagulopathy from a condition that resembles disseminated intravascular coagulation (DIC) and dilution of coagulation factors from stored bank blood. When such bleeding occurs, the differential diagnosis for a patient who did not have a pretransfusion coagulopathy (e.g., hemophilia) is dilutional thrombocytopenia, low factors V and VIII, a DIC-like syndrome, or hemolytic transfusion reaction. Clinical manifestations include oozing into the surgical field, hematuria, gingival bleeding, petechial bleeding from venipuncture sites, and ecchymoses.

Dilutional Thrombocytopenia

Dilutional thrombocytopenia is a cause of a hemorrhagic diathesis in a patient who has received multiple units of bank blood. Independent of whether whole blood or packed RBCs are given, few viable platelets exist when storage has been for more than 24 hours. For whole blood at a storage temperature of 4°C, platelets in stored blood are damaged sufficiently to be readily trapped and absorbed by the reticuloendothelial system soon after infusion. Even those platelets that are not immediately stored have a reduced survival time. Considering survival time and viability, total platelet activity is only 50% to 70% of the original in vivo activity after 6 hours of storage in bank blood at 4°C. After 24 or 48 hours of storage, platelet activity is only about 10% or 5% of normal, respectively. Infusion of bank blood stored for longer than 24 hours dilutes the available platelet pool. In my colleagues and my study during the U.S.-Vietnam conflict, platelet counts decreased to less than 100,000/mm^3 when 10 to 15 units of blood had been given to acutely wounded, previously healthy soldiers.[45] The platelet count in smaller, older patients may decrease to 100,000/mm^3 after being given fewer units of blood because these patients have a

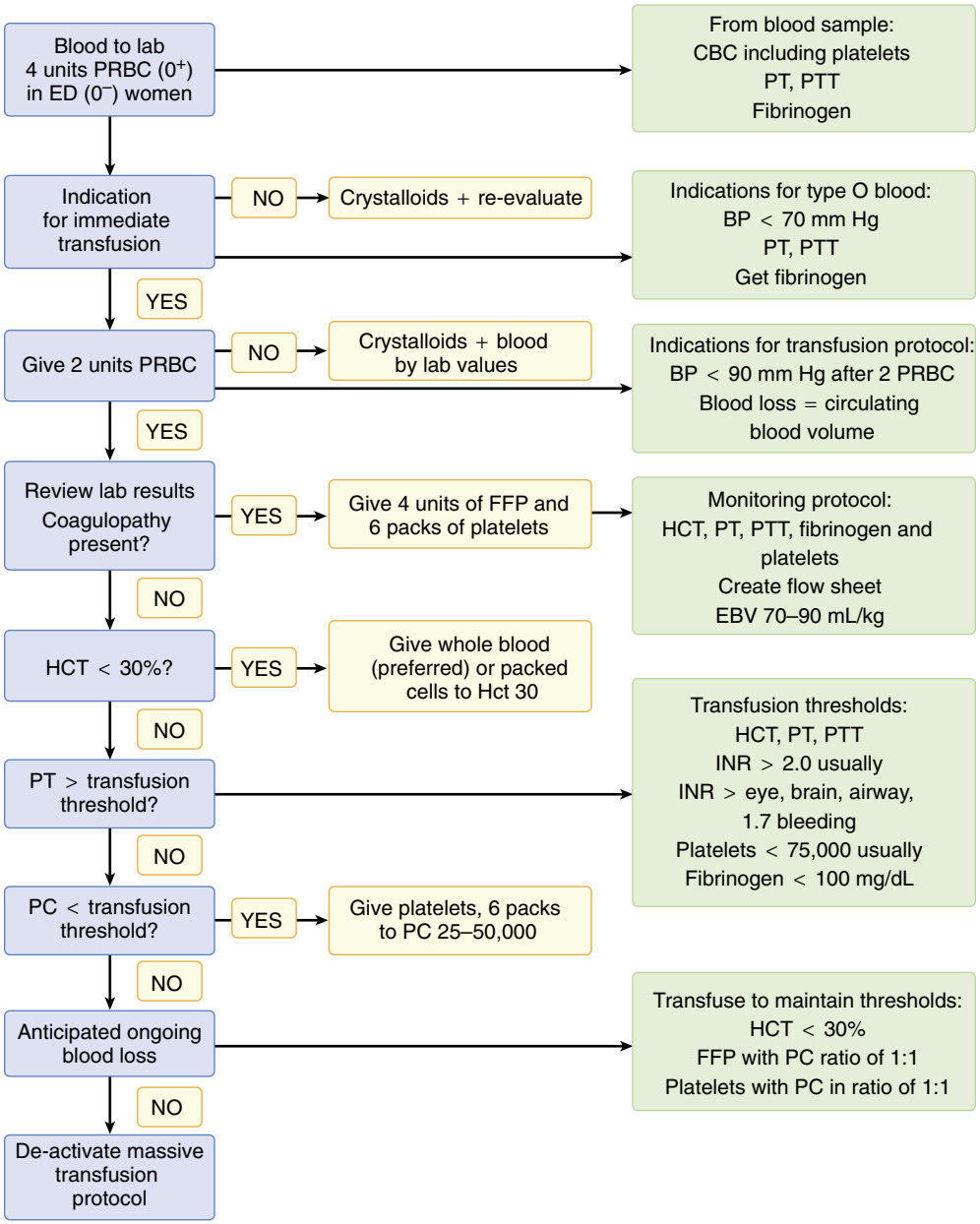

Figure 55-3 This algorithm for diagnosing and treating a massive transfusion was modified from the massive transfusion protocol used at the San Francisco General Hospital. There are many other similar approaches (e.g., Figure 55-7 provides an algorithm for a pure coagulation). This protocol suggests how to approach a patient with major blood loss but does not include the use of recombinant activated factor VII, which may be possible in the future.[76] BP, blood pressure; CBC, complete blood cell count; EBV, effective blood volume; ED, emergency department; FFP, fresh frozen plasma; Hct, hematocrit; INR, international normalized ratio; PC, platelet count; PRBCs, packed red blood cells; PT, prothrombin time; PTT, partial thromboplastin time.

smaller blood volume and possibly a lower preoperative platelet count than soldiers do. We[45] defined the importance of the platelet count because when it is approximately 75,000/mm^3 or less, a hemorrhagic diathesis is likely to occur (Table 55-5).

Although major emphasis had been placed on monitoring the platelet count, several investigators[46,47] have questioned the role of dilutional thrombocytopenia in the coagulopathy of massively transfused patients. They correctly point out that the platelet count rarely decreases to as low a level as would be predicted from dilution alone (Fig. 55-4). This is probably because platelets are released into the circulation from the spleen and bone marrow and because of the presence of nonfunctional platelets. Reed and associates[47] found no benefit to prophylactic platelet administration during massive transfusion. Platelets should not be given to treat laboratory evidence of thrombocytopenia unless clinical coagulopathy is also present. Treating laboratory numbers without correlation with the clinical status is fundamentally contrary to good medical practice; transfusion medicine is no exception. When the platelet count is less than 50,000 to 75,000/mm^3, a bleeding problem is likely and is probably a combination of dilutional thrombocytopenia and DIC. Platelet therapy would be appropriate in this situation (see "Platelet Concentrates" later).

To place such emphasis on the platelet count as a guide is appropriate, as defended previously, with some exceptions. For example, patients with chronic thrombocytopenia or leukemia are commonly known to survive and not have a hemorrhagic

Table 55-5 Correlation between Platelet Count and Incidence of Bleeding

Platelet Count (cells/mm^3)	Total No. of Patients	No. of Patients with Bleeding
>100,000	21	0
75,000-100,000	14	3
50,000-75,000	11	7
<50,000	5	5

Data from Miller RD, Robbins TO, Tong MJ, et al: Coagulation defects associated with massive blood transfusions. Ann Surg 174:794, 1971.

diathesis with a platelet count lower than 15,000 cells/mm^3. However, this does not negate the general guideline that patients with a platelet count of less than 75,000 cells/mm^3 are likely to bleed. For unexplained reasons, patients with an acutely induced thrombocytopenia (e.g., from blood transfusions) develop a hemorrhagic diathesis at a much higher platelet count than do patients with a chronically induced thrombocytopenia (e.g., idiopathic thrombocytopeniac purpura). A higher platelet count is required to maintain adequate hemostasis with a surgical incision or trauma because damaged capillaries require platelets to plug the holes. The platelet count is a reasonably accurate guide as to when patients will develop a bleeding problem from dilutional thrombocytopenia (see Table 55-5).

Low Levels of Factors V and VIII

Most of the factors are stable in stored blood, with two exceptions: factors V and VIII.[48] These factors gradually decrease to 15% and 50% of normal, respectively, in whole blood after 21 days of storage. Packed RBCs even have fewer coagulation factors. Consequently, administration of fresh frozen plasma (FFP), which contains all the factors except platelets, has been recommended on a therapeutic or a prophylactic basis. However, this practice is of questionable benefit because only 5% to 20% of factor V and 30% of factor VIII are needed for adequate hemostasis during surgery. In other words, in spite of a patient's receiving massive blood transfusion, factors V and VIII rarely decrease below those levels required for hemostasis. My colleagues and I[45] examined this problem by giving 500 to 1000 mL of FFP to 5 patients who had received more than 15 units of bank blood and who had a clinically significant hemorrhagic diathesis. Despite the partial thromboplastin times (which measure all factors except VII and XIII) and platelets' having returned to normal, bleeding persisted in every patient. Only when platelets in the form of fresh blood were administered did bleeding cease.[45] Although low factors V and VIII appear to be an unlikely primary cause of bleeding during massive blood transfusion, such deficiencies may intensify bleeding from other causes, usually dilutional thrombocytopenia in the case of blood transfusion.

In 1985, the National Institutes of Health conducted a consensus conference on this issue.[49] The conference concluded that there was little or no scientific evidence for the administration of FFP as part of the therapy for coagulopathy induced by multiple blood transfusions. The following criteria should be used:

1. Generalized bleeding that cannot be controlled with surgical sutures or cautery
2. Partial thromboplastin time at least 1.5 times normal
3. Platelet count greater than 70,000/mm^3 (to ensure that thrombocytopenia is not the cause of bleeding)

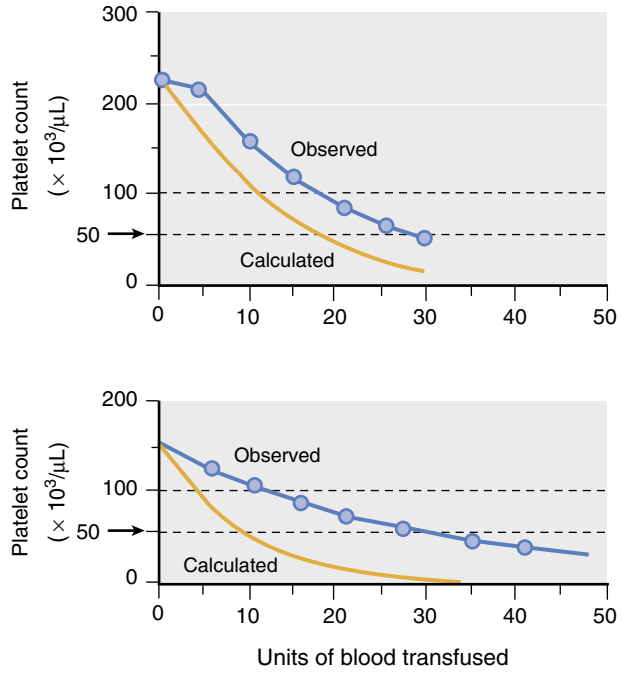

Figure 55-4 Mean platelet counts after massive transfusions in relation to number of units of blood transfused. Observed versus predicted values calculated on the basis of blood exchange model. *(From Myllylä G: New transfusion practice and haemostasis. Acta Anaesthesiol Scand Suppl 89:76, 1988.)*

Disseminated Intravascular Coagulation-like Syndrome (DIC)

The coagulation system consists of clotting and fibrinolytic mechanisms. The function of the former is to prevent excessive blood loss, and that of the latter is to ensure circulation within the vasculature. With this DIC-like syndrome, the clotting system is deranged and this leads to disseminated fibrin deposition, which renders the fluid blood unclottable. The deposited fibrin may severely alter the microcirculation and lead to ischemic necrosis in various organs, particularly the kidney. The unclottable blood or circulating serum may induce a severe hemorrhagic diathesis.

The specific reasons for the development of DIC syndrome are usually not apparent. However, hypoxic acidotic tissues with stagnant blood flow probably release tissue thromboplastin

directly or through liberation of some toxin as possibly modulated through the protein C pathway.[44] The release of tissue plasminogen activator from damaged tissue may cause fibrinolysis. In sepsis and eventual organ failure, the pathogenesis of this DIC syndrome is more apparent. The extrinsic route of coagulation is activated by tumor necrosis factor and endotoxins. Presumably, tumor necrosis factor induces tissue factor expression on the surface of activated monocytes and possibly by exposure to subendothelially localized tissue factor in blood[50] (see Chapter 56 for more details). Although the intrinsic system does not induce DIC, it may contribute to hypotension. This triggers the coagulation process, resulting in consumption of factors I, II, V, and VIII and platelets. Supposedly, thrombi and fibrin are deposited in the microcirculation of vital organs, interrupting their blood flow.

In an attempt to counteract the hypercoagulable state, the fibrinolytic system is activated to lyse the excessive fibrin almost simultaneously; this is called secondary fibrinolysis (see Chapter 56). DIC should not be considered a distinct disease entity but rather a sign of another disease. DIC has been associated with almost all life-threatening diseases. Any condition in which tissue damage is sufficient to release tissue products or toxins into the circulation can be associated with DIC. If enough thromboplastin lodges in the circulating blood, the result is massive focal necrosis or more generalized activation of the coagulation system.

Hemolytic Transfusion Reaction

The appearance of a hemorrhagic diathesis after blood transfusion should signal the possibility of a hemolytic transfusion. This entity is discussed later in this chapter.

Diagnosis and Treatment of a Hemorrhagic Diathesis after Whole Blood Transfusions

Although treatment is more likely to be successful when the cause of the bleeding problem has been identified, precise diagnosis is often difficult. One approach is to obtain a blood specimen on which the following tests can be performed: platelet count, partial thromboplastin time, plasma fibrinogen level, and observation of a clot for size, stability, and lysis and of the plasma for evidence of hemolysis. Provided that the partial thromboplastin time is 1.5 times normal or more and other tests are normal, the bleeding is probably a result of very low levels of factors V and VIII. This can be treated with FFP, which contains all the coagulation factors except platelets, or with cryoprecipitate. Although the preceding situation is a nice textbook description, I have never observed a clinical situation involving blood transfusions in which the partial thromboplastin time was increased without the presence of thrombocytopenia.

Dilutional thrombocytopenia in association with DIC and hypoperfusion is the most likely cause of bleeding from blood transfusion.[45,48] When the platelet count is less than 100,000/mm^3, a bleeding problem is likely to develop (see Table 55-4); therefore, platelets are ordered. The rule of thumb is based on the fact that a bleeding diathesis probably will develop after infusion of 20 units of stored blood in healthy patients and after lesser amounts in debilitated or small patients (Fig. 55-5).

Whether platelets are administered in the form of fresh blood, platelet-rich plasma, or platelet concentrates depends on

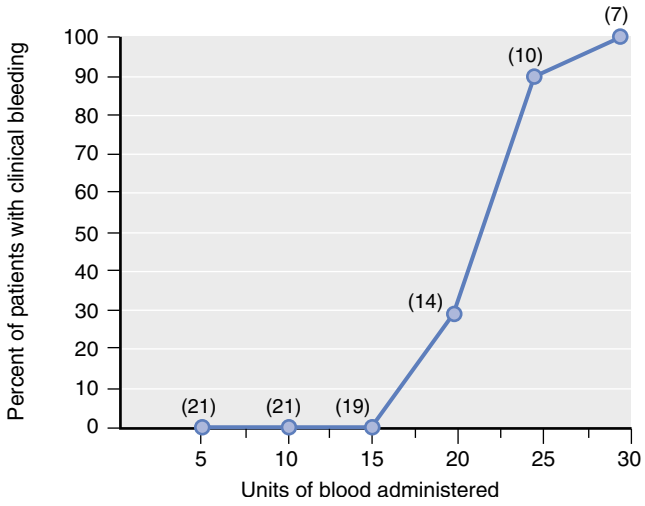

Figure 55-5 Correlation between units of blood administered and percent of patients who had a hemorrhagic diathesis. The numbers in parentheses represent the number of patients at each data point. *(From Miller RD: Transfusion therapy and associated problems. Reg Refresher Course Anesthesiol 1:101, 1973.)*

intravascular volume replacement requirements, personal preference, and availability of laboratory personnel. Fresh blood (≤6 hours old) supplies the largest number of platelets per donation. More than 80% of the platelets can be given by platelet-rich plasma, which has one half of the volume of a unit of blood. However, because most blood banks advocate giving patients only those components that are necessary, platelet concentrates are frequently recommended. The remainder of the unit of blood, such as RBCs, plasma, and albumin, can be saved for other patients. Platelet concentrates are contained in a 50-mL unit and provide about 70% of the platelets in a unit of blood. In a 70-kg person, about 10 units of platelet concentrates are required to increase the platelet count by 100,000/mm^3.

Although logistically difficult to obtain, fresh blood is extremely effective in treating transfusion-induced coagulopathies. My personal and subjective observations in Vietnam indicated that fresh blood (i.e., 6 hours or less and unrefrigerated blood) had a dramatic effect in patients with extensive hemorrhage.[45] About 20 years later, Lavee and associates[51] found that 1 unit of fresh whole blood was as effective as, if not superior to, 8 to 10 platelet units. In 1996, Erber and colleagues,[52] used fresh unrefrigerated whole blood in surgical patients with ongoing extensive bleeding despite adequate component replacement therapy and adequate surgical hemostasis. An accompanying editorial expressed caution and described the unfortunate problems with conducting a larger trial with fresh blood.[53] I believe that fresh blood also contains unidentified factors that make it far more effective than blood components.

Determining the plasma fibrinogen level is useful because this coagulation factor does not decrease in bank blood. If the in vivo plasma fibrinogen level is low (<150 mg/dL), it is not a result of a dilutional coagulopathy and strongly suggests DIC or a DIC-like syndrome. DIC is likely with thrombocytopenia, hypofibrinogenemia, and lysis of a clot within 2 hours.[48] Unfortunately, fibrinogen levels in packed RBCs decrease with increasing storage time. As a result, hypofibrinogenemia occurs on a dilutional basis when multiple units of packed RBCs are given.[54]

ε-Aminocaproic acid (EACA) inhibits the formation of plasmin and attenuates fibrinolysis. EACA should not be used in the treatment of DIC. Blocking the fibrinolytic system and having the coagulation system activated have resulted in disseminated thrombosis. Because primary fibrinolysis is rare other than in prostatectomy and liver transplantation[55] (see Chapter 56), EACA should probably not be given unless the preceding diagnosis is clearly established after expert consultation. Despite all of the previous recommendations, bleeding from a transfusion-associated coagulopathy occasionally persists. A new approach has been described. Administration of recombinant activated coagulation factor VII (rfVIIa, Novo Nordisk Pharmaceuticals, Plantation, FL) has produced successful treatment of such coagulopathies intraoperatively. Most of these patients also had other conditions, such as necrotizing pancreatitis, cirrhosis, or severe trauma. This exciting product is extremely expensive and should be viewed as a rescue therapy until approval by the U.S. Food and Drug Administration (FDA) is more broadly based[56] (see Chapter 56 for details).

Drugs Used to Improve Hemostasis

In addition to EACA, three other drugs have been recommended for perioperative coagulation problems.[57] Two of those drugs have received special attention. The first is desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]), a synthetic analog of the antidiuretic hormone vasopressin. It increases the levels of factor VIII and von Willebrand factor and is a well-established therapy for hemophilia and von Willebrand disease. It also reduces blood loss and transfusion requirement in patients with normal preoperative coagulation status who are undergoing spinal or cardiac surgery. However, the ultimate role of desmopressin remains to be determined.[57] It can cause hypotension, hyponatremia, and increased platelet adhesion.

Another drug is aprotinin, a serine protease inhibitor that inhibits fibrinolysis and improves platelet function. It has been used to decrease blood loss in multiple surgical procedures, including cardiopulmonary bypass. However, its ultimate place in the treatment of coagulopathies has not been established.

The third drug is tranexamic acid, which is also an antifibrinolytic drug. Two studies found a decreased blood loss from total-knee arthroplasty. Presumably, release of the pneumatic tourniquet releases fibrinolytic material, which is inhibited by tranexamic acid.

A large meta-analysis using perioperative blood transfusion as the outcome in cardiac surgery concluded that aprotinin and tranexamic acid, but not desmopressin, decreased the exposure of patients to allogeneic blood transfusion perioperatively.[58] The ultimate use of these drugs is evolving.

Diagnosis and Treatment of Hemorrhagic Diathesis after Packed Red Blood Cell Transfusions

With much less plasma, dilution of certain coagulation values may be more profound with the use of packed RBCs rather than whole blood. Murray and coworkers[54] specifically examined the question of using packed RBCs for major blood loss. In general, the direction of coagulation changes was similar to that seen with whole blood, with one major exception. With use of packed RBCs, fibrinogen levels decreased significantly in contrast to use of whole blood, in which fibrinogen levels remained unchanged unless DIC was present (see Fig. 55-6). Although all the coagulation factors decreased, the decrease was less than expected from dilution. The researchers believed that factors such as factor VIII are probably stored in endothelial cells and released from the endothelium during surgical stress. When packed RBCs are used to replace major blood loss, the clinician may be tempted to give FFP prophylactically. However, Murray and associates[54] specifically recommended not following the policy; they stated that FFP was needed only when prothrombin time and partial thromboplastin time were at least 1.5 times normal and fibrinogen levels were less than 75 mg/dL. These recommendations are similar to those stated in the section "Fresh Frozen Plasma." Leslie and Toy[59] provided more specific guidelines when packed RBCs are used for massive transfusions. They believed that when 12 or more units of packed RBCs or cell-saver blood had been given, coagulation factors (i.e., FFP) were necessary. Patients who received 20 or more units often required platelet therapy, a finding identical to that of patients given whole blood.

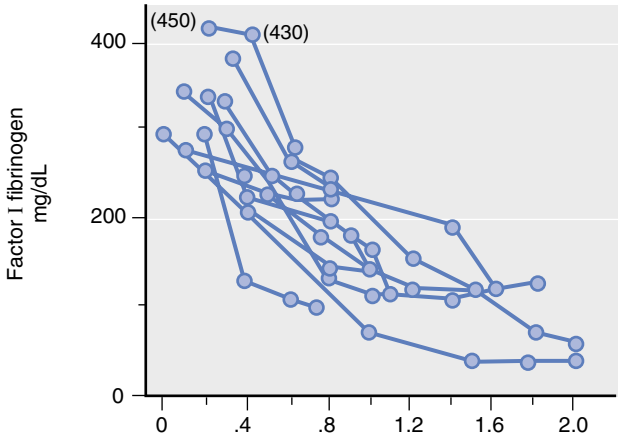

Figure 55-6 Decreases in fibrinogen level as blood volume is replaced with Adsol-packed red blood cells and crystalloid solutions. Each patient is represented by a *solid line. (From Murray DJ, Olson J, Strauss R, Tinker JH: Coagulation changes during packed red cell replacement of major blood loss. Anesthesiology 69:839, 1988.)*

An algorithm for the evaluation and initial therapy of a patient with a suspected coagulopathy is given in Figure 55-7.

Citrate Intoxication and Hyperkalemia

Citrate intoxication is not caused by the citrate ion per se; it occurs because citrate binds calcium. The signs of citrate intoxication are those of hypocalcemia: hypotension, narrow pulse pressure, and increased intraventricular end-diastolic pressure and central venous pressure. However, citrate intoxication is very rare. Having hypothermia, liver disease, liver transplantation, or hyperventilation or being a pediatric patient[60] increases the possibility of citrate intoxication. The appearance of severe hypocalcemia during liver transplantation is well documented (see Chapter 67). The combination of infusion of large amounts of citrate (i.e., through blood transfusions) and of reduced

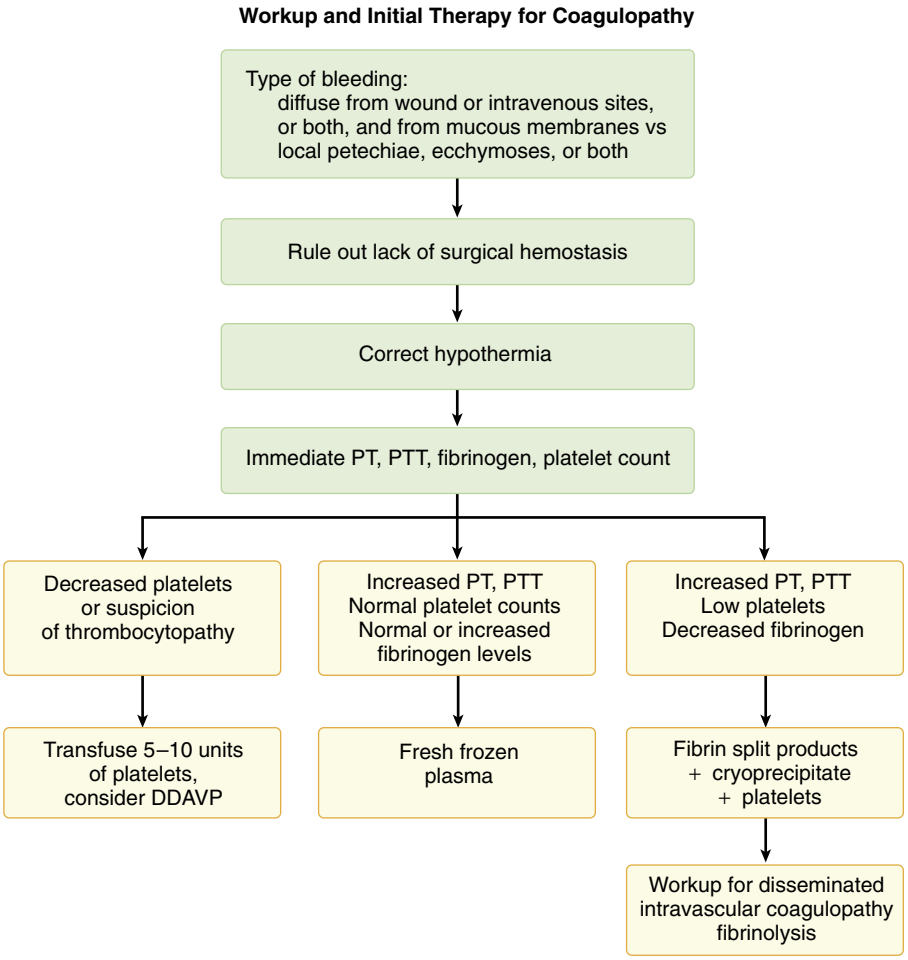

Figure 55-7 Algorithm of the evaluation and initial therapy of a patient with suspected perioperative coagulopathy. The evaluation is based on the clinical scenario and is affected by the type and location of injury, the amount of fluid administered, and the age and body temperature of the patient. DDAVP, 1-deamino-8-D-arginine vasopressin, a vasopressin analog also known as desmopressin acetate; PT, prothrombin time; PTT, partial thromboplastin time. *(Adapted from Habibi S, Corrsin DB, McDermott JC, et al: Trauma and massive hemorrhage. In Muravchick S, Miller RD [eds]: Atlas of Anesthesia: Subspecialty Care. New York, Churchill Livingstone, 1998, pp 6.2-6.17.)*

metabolism from absent or reduced liver blood flow (i.e., in the anhepatic phases of liver transplantation) leads to citrate intoxication. As a result, calcium infusions are common during liver transplantation. The rate of citrate metabolism is decreased by 50% when body temperature is decreased from 37° to 31°C. Excluding these conditions, infusion of more than 1 unit of blood every 10 minutes is necessary for ionized calcium levels to begin to decrease. Even at these rates of infusion, ionized calcium levels do not decrease enough to cause bleeding. As indicated previously, if a hemorrhagic diathesis starts after administration of blood, low calcium levels are not part of the differential diagnosis.

As evidenced from the preceding discussion, citrate intoxication is rare. Serum potassium levels may be as high as 19 to 30 mEq/L in blood stored for 21 days. Although hyperkalemia is occasionally reported,[60,61] large amounts of blood must be given. For significant hyperkalemia to occur clinically, bank blood must be given at a rate of 120 mL/min or more. The fact that such rapid infusion rates of blood are required for the production of hyperkalemia suggests that the potassium ion must leave the intravascular spaces by diffusion into extravascular spaces, by reuptake into RBCs, or through the kidneys. As with citrate intoxication, hyperkalemia is rare and this also rules against the routine administration of calcium. Calcium may cause cardiac arrhythmias, particularly in patients anesthetized with halothane. Calcium administration should be based on diagnostic signs of hyperkalemia (i.e., peak T wave). Although irritating to veins, 10% calcium chloride provides three times more calcium than an equal volume of 10% calcium gluconate because chloride has a molecular mass of 147 and gluconate has a molecular mass of 448.

Temperature

Administration of unwarmed blood that has been stored at 4°C can decrease the recipient's temperature. If the temperature decreases to less than 30°C, ventricular irritability and even cardiac arrest may occur. This can be prevented by warming the blood to body temperature before transfusion. There are more subtle reasons for warming all blood, even in patients receiving only 1 to 2 units intraoperatively. Because of the cool temperature of the operating room, body temperature often decreases, particularly in patients undergoing extensive abdominal surgery; administration of cold blood further decreases temperature. Maintaining a patient's normal temperature is considered to be increasingly important (see Chapter 48).

Perhaps the safest and most common method of warming blood is to pass it through plastic coils or plastic cassettes in a warm water (37° to 38°C) bath or warming plates. These heat exchangers should have upper (e.g., 43°C) and lower (e.g., 33°C) temperature limits (see Chapter 48).

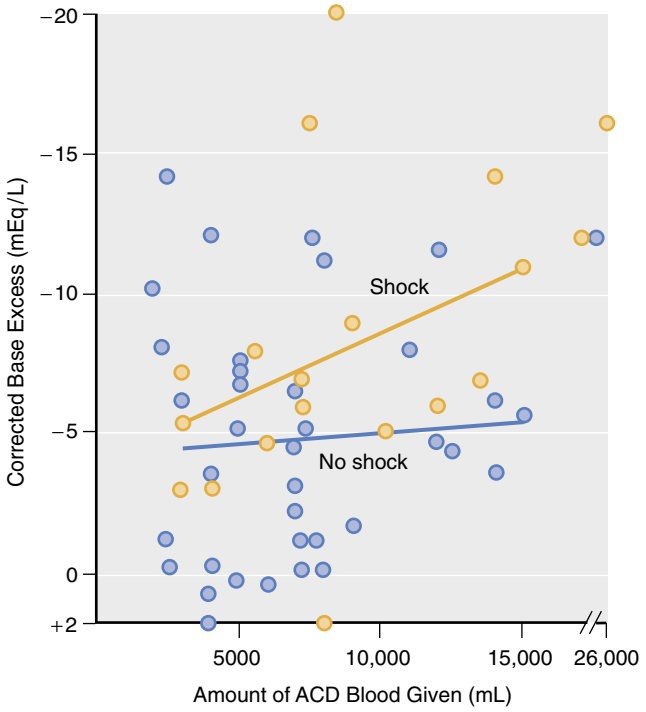

Figure 55-8 Correlation between the amount of blood administered (mL) and corrected base excess intraoperatively. *(From Miller RD, Tong MJ, Robbins TO: Effects of massive transfusion of blood on acid-base balance. JAMA 216:1762, 1971.)*

Acid-Base Abnormalities

The pH of most storage media is very acidotic (e.g., 5.5 for CPD). When this solution is added to a unit of freshly drawn blood, the pH of the blood immediately decreases from 7.0 to 7.1. As a result of accumulation of lactic and pyruvic acids by RBC metabolism and glycolysis, the pH of bank blood continues to decrease to about 6.9 after 21 days of storage. A large portion of the acidosis can be accounted for by the P_{CO_2} of 150 to 220 mm Hg. The P_{CO_2} is high mainly because the plastic container of blood does not provide an escape mechanism for carbon dioxide. With adequate ventilation in the recipient, the high P_{CO_2} should be of little consequence. Even when the P_{CO_2} is returned to 40 mm Hg, metabolic acidosis is still present in blood (see Table 55-4). Other reasonably well-controlled clinical studies have indicated that not only is empirical administration of sodium bicarbonate not indicated but it actually may also be unwise without concomitant analysis of arterial blood for P_{CO_2} and pH.[62] Miller and colleagues[63] found that the metabolic acid-base response to blood transfusion was variable (Fig. 55-8). Blood transfusions provide a substrate, namely, citrate, in large quantities for the endogenous generation of bicarbonate, and this accounts for the significant incidence of metabolic alkalosis after blood transfusions.[62] There is little logic in the empirical administration of bicarbonate for prophylactic treatment of an unpredictable acid-base abnormality.

Transfusion Reactions

Hemolytic Transfusion Reaction

From 2004 to 2006, three of the four most common causes of transfusion-related deaths were hemolytic transfusion reactions, septic transfusions (e.g., bacterial contamination), and transfusion-related acute lung injury (TRALI) (Table 55-6).[64] Since 1975, the FDA has required that all fatal reactions occurring in blood recipients or donors must be reported within 24 hours by telephone or within 7 days in writing by all FDA-registered transfusion services. In the 10-year period from 1976 to 1985, 328 deaths have been reported and analyzed.[65] Of these deaths, 159 were acute from hemolytic reactions and 23 from delayed reactions. Of the 159 deaths due to acute hemolytic reaction, 137 were caused by errors involving ABO incompatibility. More than one half of these mistakes occurred after the blood had been issued by the blood bank and were committed by nurses and physicians in the operating room, emergency department, or ward. The incidence of hemolytic transfusion reaction is sufficient enough that the Joint Accreditation of Healthcare Organizations (JCAHO)[66] requires peer-review programs to reduce transfusion errors and complications. Specifically, two patient identifiers are required before a blood product can be given. New technologies (e.g., radiofrequency identification bar coding) are being used to facilitate a decreased incidence of transfusion-related errors. However, when delayed hemolytic reactions (discussed later) are included, the incidence of ABO-incompatible RBC transfusions is higher.[67] One of the most catastrophic transfusion reactions is that arising from intravascular hemolysis. Intravascular hemolysis occurs when there is a direct attack on transfused donor cells by recipient antibody and complement. Such a reaction can occur from infusion of as little as 10 mL of blood.[68] If properly treated, death is

Table 55-6 Transfusion-Related Fatalities in the United States, 2004-2006

Cause of Fatality	2004-06	Average per Year
TRALI	86	29
Other reactions (non-ABO hemolytic therapy; anaphylaxis)	67	22
Bacterial contamination	20	7
ABO hemolytic transfusion therapy	15	5
Transfusion not ruled out	31	10

TRALI, Transfusion-related acute lung injury.
Data from Leslie Holness, Office of Blood Research and Review, FDA personal communication, January 24, 2007; American Blood Center Newsletter, April 13, 2007.

rare.[66] However, prevention of kidney failure and a coagulopathy (DIC) is crucial. Hemolytic transfusion reactions involving extravascular RBC destruction are generally less serious than those of the intravascular variety. In these cases, recipient antibody coats but does not immediately hemolyze the transfused RBCs. Destruction occurs primarily in the reticuloendothelial system.

Signs and Symptoms

The clinical consequences of incompatible blood transfusions are very serious but quite variable. Factors include volume of transfused blood, number of antigenic sites on the red cell membrane, and activity of the reticuloendothelial system. The properties of the antibody, including concentration and ability to activate complement, are also important.

The classic signs and symptoms (Table 55-7) of a hemolytic transfusion reaction—chills, fever, chest and flank pain, and nausea—are masked by anesthesia. Under general anesthesia, the only signs may be hemoglobinuria, bleeding diathesis, or hypotension. The presenting sign is usually hemoglobinuria. As little as 50 mL of incompatible blood may exceed the binding capacity of haptoglobin, which is a protein that can bind about 100 mg of hemoglobin per 100 mL of plasma. When hemoglobin not exceeding this amount is injected or liberated into the bloodstream, the hemoglobin circulates as a complex with haptoglobin, which is cleared by the reticuloendothelial system (Fig. 55-9). A sample of plasma that contains 2 mg/dL of hemoglobin is faintly pink or light brown. When the level of hemoglobin reaches 100 mg/dL, the plasma is red. When the level of plasma hemoglobin reaches 150 mg/dL, hemoglobinuria occurs. In general, the quantity of the free hemoglobin in the plasma correlates with the volume of incompatible blood transfused. Also, complement activation causes release of all sorts of substances including histamines and vasoactive amines. The symptoms can be so alarming that cessation of blood is indicated, even if hemoglobin is not seen in plasma. Laboratory tests that should be performed if hemolytic transfusion reaction is suspected include serum haptoglobin, plasma and urine hemoglobin, bilirubin, and direct antiglobulin determinations. The direct antiglobulin test can confirm the presence of hemolytic transfusion reaction because it shows that there is antibody attached to transfused donor RBCs.

Table 55-7 Frequency and Signs and Symptoms of Hemolytic Transfusion Reactions in 40 Patients

Sign or Symptom	No. of Patients
Fever	19
Fever and chills	16
Chest pain	6
Hypotension	6
Nausea	2
Flushing	2
Dyspnea	2
Hemoglobinuria	1

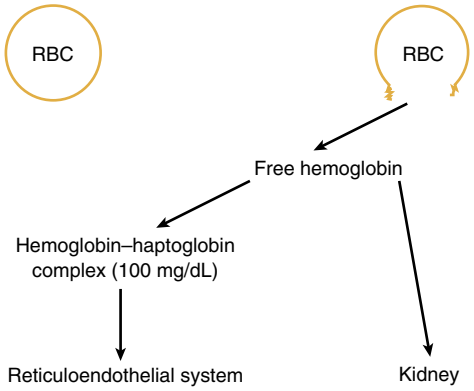

Figure 55-9 Schematic representation of what happens to hemolyzed erythrocytes (RBC) as a result of the administration of incompatible blood.

Treatment

If a hemolytic reaction is suspected, blood and urine samples should be sent to the laboratory for examination. The blood bank should check all paperwork to ensure that the correct blood component was transfused to the patient. Laboratory tests should be performed to determine the presence of hemoglobinemia: a direct antiglobulin test, repeat compatibility testing, repeat other serologic tests (i.e., ABO and Rh), and analysis of urine for hemoglobinuria.

Although there are several consequences of intravascular hemolysis, mainly the renal and coagulation systems are affected. The exact cause of acute renal failure from intravascular hemolysis is controversial, but the most common hypothesis is that hemoglobin in the form of acid hematin precipitates in the distal tubule and causes mechanical tubular blockage. The magnitude of the precipitation probably is inversely related to the volume of urine flow and its pH. The primary emphasis of therapy should be directed toward maintaining urinary output in excess of 75 mL/hr by generous administration of intravenous fluids and diuretics. One approach is summarized in Table 55-8 and includes the administration of lactated Ringer's solution to maintain the central venous pressure between 10 and 15 cm H_2O while initially administering 12.5 to 50 g of mannitol. If this is ineffective, the dose of mannitol may be increased or the use of more potent diuretics, such as furosemide, which increases blood flow to the renal cortex, may be required to maintain adequate urinary output. Alkalinization of the urine to prevent precipitation of acid hematin in the distal tubules is of questionable value but is easy and therefore recommended. DIC commonly occurs with hemolytic transfusion reactions, probably because RBC stroma is severed, releasing erythrocytin, which activates the intrinsic system of coagulation. This activated coagulation leads to fibrin formation. Subsequently, platelets and factors I, II, V, and VII are consumed. As soon as a hemolytic transfusion reaction is recognized, platelet count, prothrombin time, and partial thromboplastin time should be determined to provide baseline values with which subsequent laboratory values can be compared. Hypotension during a hemolytic transfusion reaction may result from activation of the kallikrein system.[69] After a series of reactions, plasma kininogen is converted to bradykinin, a potent vasodilator that can cause hypotension.

Table 55-8 Steps in the Treatment of a Hemolytic Transfusion Reaction

1. STOP THE TRANSFUSION.
2. Maintain the urine output at a minimum of 75 to 100 mL/hr by the following methods:
   a. Generously administer fluids intravenously and possibly mannitol (12.5 to 50 g, given over 5 to 15 minutes).
   b. If intravenously administered fluids and mannitol are ineffective, administer furosemide (20 to 40 mg) intravenously.
3. Alkalinize the urine; because bicarbonate is preferentially excreted in the urine, only 40 to 70 mEq of sodium bicarbonate per 70 kg of body weight is usually required to raise the urine pH to 8, whereupon repeat urine pH determinations indicate the need for additional bicarbonate.
4. Assay urine and plasma hemoglobin concentrations.
5. Determine platelet count, partial thromboplastin time, and serum fibrinogen level.
6. Return unused blood to blood bank for repeat crossmatch.
7. Send patient's blood and urine sample to blood bank for examination.
8. Prevent hypotension to ensure adequate renal blood flow.

Another approach to treatment of a severe hemolytic transfusion reaction has been proposed by Seager and coworkers,[70] who postulated that the kidneys might be spared from exposure to massive amounts of hemolyzed red cells by removing all blood from a patient and replacing it with compatible blood. This was accomplished in a patient who had received 3000 mL of incompatible blood by hemodilution by use of an extracorporeal circuit. Because the patient had rapid recovery of urinary function, this method shows much promise.

In summary, hemoglobinuria or hemolysis should be assumed to be a hemolytic transfusion reaction until proved otherwise. The steps outlined in Table 55-8 should be taken when the diagnosis is suspected or confirmed.

Delayed Hemolytic Transfusion Reaction (Immune Extravascular Reaction)

An immediate hemolytic transfusion reaction often is a dramatic event because the concentration of the antibody is high enough to cause immediate and appreciable RBC destruction. In many cases of hemolytic transfusion reaction, the transfused donor cells may survive well initially, but after a variable delay (2 to 21 days) they are hemolyzed.[71] This type of reaction occurs mainly in recipients sensitized to RBC antigens by previous blood transfusions or pregnancy. As a result, this type of delayed reaction is more common in females who have a known disposition of alloimmunization. These reactions are delayed hemolytic transfusion reactions and are those in which the level of antibody at the time of transfusion is too low to be detected or too low to cause RBC destruction. RBC destruction occurs only when the level of antibody is increased after a secondary stimulus (i.e., anamnestic response). These delayed reactions are often manifested only by a decrease in the post-transfusion hematocrit value. However, jaundice and hemoglobinuria can occur in these patients and can cause some impairment in renal function but only rarely do they lead to death. Unlike immediate reactions, antibodies most commonly involved in delayed hemolytic reactions are those in the Rh and Kidd systems rather than the ABO system. Although improved blood-banking procedures have decreased the incidence of immediate hemolytic transfusion reactions, the delayed hemolytic reaction may not be preventable, because pretransfusion testing is unable to detect very low levels of antibody present in potential blood recipients.

Although impairment of renal function is uncommon, the surgical team should include in their differential diagnosis a delayed hemolytic transfusion reaction in any patient who has an unexplained decrease in hematocrit 2 to 21 days after a transfusion, even without obvious manifestation of hemolysis. This is especially important in a postoperative patient when the decrease in hematocrit value is thought to be from blood loss and may be an important criterion as to whether additional surgery is necessary.

Nonhemolytic Transfusion Reactions

Nonhemolytic reactions to blood transfusions usually are not serious and are febrile or allergic in nature. Specific infectious causes of febrile reactions are discussed in "Infectivity of Blood." Occasionally, fever may be the first sign of a hemolytic reaction or of bacterial contamination.

The most common adverse reactions to blood transfusions are the less serious febrile reactions. The symptoms consist of chills, fever, headache, myalgia, nausea, and nonproductive cough occurring shortly after blood transfusion caused by pyrogenic cytokines and intracellular contents released by donor leukocytes. Use of leukoreduced blood will reduce the incidence of febrile reactions.[72] Less frequently, the patient may have hypotension, chest pain, vomiting, and dyspnea. Even pulmonary infiltrations with x-ray evidence of prehilar nodule formation and lower lung infiltrates along with overt pulmonary edema have been reported.[72] Because febrile reactions obviously involve fever, they can be easily confused with a hemolytic transfusion reaction. A direct antiglobulin test readily differentiates a hemolytic reaction from a febrile reaction because this test rules out the attachment of an RBC antibody to transfused donor RBCs. More serious complications need to be ruled out (hemolytic and septic reactions), which may also be associated with fever and chills. There is no clear consensus on whether the transfusion should be terminated when a febrile reaction occurs.[73,74]

Allergic reactions can be minor, anaphylactoid, or anaphylactic. Anaphylactoid is similar to anaphylaxis clinically but are not mediated by IgE. Most allergic transfusion reactions are minor and are thought to be caused by the presence of foreign protein in the transfused blood. The most common symptom is urticaria associated with itching. Occasionally, the patient has facial swelling. When these reactions are clearly not a serious hemolytic reaction, the transfusion does not need to be discontinued. Antihistamines are used to relieve the symptoms of the allergic reaction. Infrequently, a more severe form of allergic reaction involving anaphylaxis occurs in which the patient has dyspnea, hypotension, laryngeal edema, chest pain, and shock. These are anaphylactic reactions caused by the transfusion of IgA to patients who are IgA deficient and have formed anti-IgA. This type of reaction does not involve red cell destruction and it occurs very rapidly, usually after the transfusion of only a few milliliters of blood or plasma. The patients who experience these anaphylactic reactions can be given transfusions with washed RBCs from which all traces of donor IgA have been removed or with blood lacking the IgA protein. Several investigators have reviewed many other rare transfusion reactions.[65,68,75,76]

Infectivity of Blood

For the past 25 years, transfusion-induced hepatitis and AIDS were dominant concerns regarding allogeneic blood administration. Intensified blood donor evaluation, deferral of high-risk donors, and the use of more sensitive screening tests have made these infectious risks quite rare (Table 55-9).

Non–donor-transmitted issues have become dominant concerns (see "Transfusion Reactions") (see Table 55-6). The summary of Fiebig and Busch[77] provides definitive information on this topic.

Several blood-safety changes made from 1982 to 2008 have made the risk of disease transmission by allogenic blood so small, that even the demand for autologous blood has decreased because of the safety of allogeneic blood. Perhaps the West Nile virus story illustrates how rapidly our blood banks can respond. In 2002, West Nile virus caused the largest outbreak of arboviral encephalitis ever recorded in the United States (i.e., about 4200 patients). Twenty-three cases of transfusion-transmitted infections resulted in seven deaths. In 2003, we had testing that now makes that infection very rare (see Table 55-9).

Yet many questions arise. What about variant Creutzfeldt-Jakob disease? There are three probable transfusion-transmitted cases in Great Britain. How strict should testing be? As described recently,[78] "the sheer number of potential pathogens that have threatened the blood supply[79,80] since 1995 renders it impractical to keep adding expensive safety measures" for each new agent. Surveillance needs to be added to all these tests as a safety measure.

Hepatitis B

Testing for hepatitis B is an example of a practical decision. Hepatitis B virus (HBV) is hepatotropic DNA virus that has an incubation period of 4 to 10 weeks but may be as long as 6 months. Prevention of blood-transfusion–induced hepatitis B is dependent on exclusion of high-risk donors and detection of antibodies to HBcAg. It is controversial whether HBV nucleic acid technology testing should be used. Quantitation of risk is more complicated with hepatitis B virus than for human immunodeficiency virus (HIV) and hepatitis C virus because the accurate measurement of HBV donor incidence is uncertain as described by Kleinman and Busch.[79] The possible gain in safety versus cost is too small.

As indicated earlier, one of the major reasons for the decrease in blood-borne infections has been the use of nucleic acid technology. The changes in blood transfusion testing can be appreciated when comparing tests used in 1998 (Table 55-10) with those used in 2008 (Table 55-11). The use of nucleic acid technology testing has decreased the window of infectivity (i.e., time from being infected to a positive test result), which is a major reason for the decrease in infectivity with hepatitis, HIV, and West Nile virus.[81] Better donor screening and restrictive donor eligibility also have helped. The near-elimination of transfusion-transmitted hepatitis, HIV, and West Nile virus has made the exact incidence difficult to determine. However, emerging infectious risks, including Chagas' disease, malaria, and even variant Creutzfeldt-Jakob disease are of increasing concern (Table 55-12). Because hepatitis and AIDS have been dominant concerns for years, their history is discussed in the following sections.

Hepatitis C

When blood transfusions became a reality in the 1940s, viral hepatitis was recognized as a major complication. The concern is mainly with hepatitis B, C, and rarely D, which are parenterally transmitted viruses. Before 1985, the overall incidence of post-transfusion hepatitis ranged from a low of 3% to a high of 19%, depending on the institution and the location (e.g., donors from large cities have a more frequent incidence of the hepatitis virus). In most areas, the incidence of hepatitis has ranged from 3% to 10%. Ninety percent of post-transfusion hepatitis is caused by the hepatitis C virus. Less than one third of these patients develop jaundice.[82] To determine their ultimate fate, Tong and colleagues[82] monitored 131 patients with chronic post-transfusion hepatitis C for several years and found the following incidence of signs, symptoms, and conditions:

- Fatigue (67%)
- Hepatomegaly (67%)
- Chronic hepatitis (23%)
- Chronic active hepatitis (51%)
- Hepatocellular carcinoma (11%)

It was found that 20 patients had died of the following:

Table 55-9 Percentage Risk of Transfusion-Transmitted Infection with a Unit of Screened Blood in the United States

Infection	Risk	Window Period (days)
Human immunodeficiency virus-1	1/2,135,000	11
Human T-lymphotropic virus (HTLV-II)	1/2,993,000	51
Cytomegalovirus (CMV)	Infrequent with leukocyte-reduced components	
Hepatitis C virus (HCV)	1/1,935,000	40
Hepatitis B virus (HBV)	1/205,000	
West Nile virus (WNV)	1/1,100,000	?

From Fiebig ER, Busch MP: Infectious risks of transfusions. In Spiess BD, et al (eds): Perioperative Transfusion Medicine. Philadelphia, Lippincott Williams & Wilkins, 2006, pp 131-152.

Table 55-10 Infectious Disease Testing for Blood Transfusions, 1998

1. Discontinue serum alanine aminotransferase testing
2. Hepatitis C antibody testing
3. Antibody to hepatitis B core antigen
4. Human immunodeficiency virus (HIV) type 1
5. HIV-2
6. HIV Ag (p24 antigen)
7. Human T-cell lymphotropic virus (HTLV) types 1 and 2
8. Serologic test for syphilis

Adapted from Infectious disease testing for blood transfusions. NIH Consensus Development Panel on Infectious Disease Testing for Blood transfusions. JAMA 274:1374-1379, 1995.

- Complications of cirrhosis (8 patients)
- Hepatocellular carcinoma (11 patients)
- Chronic active hepatitis-pneumonia (1 patient)

Since 1985, the incidence of post-transfusion hepatitis has decreased, probably for three reasons. The first is improved donor screening. In 1984, donors who were in a high-risk category for AIDS were requested not to donate blood on a volunteer basis. Second, in 1985, all donor blood was tested for antibodies to HIV (see "Acquired Immunodeficiency Syndrome"). Third, a specific test for hepatitis C was developed. Specifically, molecular techniques were used to derive clones from the genome of hepatitis C. The derived proteins from these clones were used to develop an enzyme-linked immunosorbent assay to detect antibodies to hepatitis C. Nucleic acid technology testing is now being used, which makes post-transfusion hepatitis so uncommon that its actual incidence is difficult to determine (see Tables 55-9 and 55-11). Despite the effectiveness of this test, donor infectivity is important as a screening device. The demographics of infectivity among donors are variable, and HIV infection is especially common in intravenous drug users. Many blood components, such as FFP and platelet concentrates, also transmit hepatitis at an incidence equal to that of whole blood and packed RBCs. Certainly the HCV nucleic acid technology testing represents a dramatic increase in blood safety, although HCV RNA can be below detection by this process, which probably represents the occasional ongoing transmission risk.[78]

Acquired Immunodeficiency Syndrome

AIDS is characterized by severe depression of cellular immunity. Several measures have been recommended to decrease the chances that donor blood will be infected with HIV. Blood banks have instituted procedures to discourage members of high-risk groups from donating blood. Designated donors and surrogate testing were recommended.[83] Despite these measures, there were hundreds of cases of transfusion-transmitted HIV. In March 1985, all donor blood was tested for the presence of antibodies to HIV-1. It is a major health care advance or even a miracle that HIV is only rarely transmitted by blood transfusions except in some developing countries[2] (see Table 55-9).

Human T-Cell Lymphotropic Virus Type 1

Human T-cell lymphotropic virus type 1 (HTLV-1) can be transmitted by blood transfusions and has been causally associated with adult T-cell leukemia and progressive myelopathy. Cohen and coworkers[83] found that there is a very small risk of HTLV-1 infection from transfused blood and blood products that have been screened for antibodies to HIV but that risk is nearly 10-fold higher than risk of HIV infections. The estimated risk is about 1 in 641,000 (see Table 55-9). Even though there is no firm association between transfusion and leukemia or myelopathy, the decision was made to test all donor blood for antibodies to HTLV-1 (see Table 55-11).

Cytomegalovirus

Asymptomatic chronic infection with cytomegalovirus (CMV) is so common in healthy adults that this agent can almost be viewed as normal flora. CMV survives best within cells and is thought to exist in latent form in the monocytes of many people with antibodies indicative of earlier infection. Fortunately, the primary concern is recipients who are at risk because of pregnancy (multiple), immaturity, or immunosuppression. CMV seroconversion usually occurs in subsets of patients receiving multiple transfusions. CMV causes a heterophil antibody-negative response that closely resembles infectious mononucleosis in many respects. An infectious mononucleosis–like syndrome that can occur 1 to 2 months after open-heart surgery is known as the postperfusion syndrome or post-transfusion mononucleosis.[84] The evidence for transmission of CMV is most convincing when the recipient changes from a seronegative state before transfusion to a seropositive state accompanied by the mononucleosis-like illness several weeks after transfusion.

Transfusion-transmitted CMV can cause significant clinical problems in certain patient populations, such as premature neonates, allograft recipients, and patients who have had their spleens removed.[85] To prevent infection in high-risk populations, use of leukocyte-depleted blood, use of frozen deglycerolized RBCs, and screening of donors for the absence of antibody to CMV have been sometimes recommended (see "Leukoreduction

Table 55-11 Tests Used for Detecting Infectious Agents in All Units of Blood, 2008

Virus	RNA Minipool	Antibody To
Human immunodeficiency virus (HIV)	Nucleic acid technology	HIV-1, HIV-2
Hepatitis C virus (HCV)	Nucleic acid technology	HCV
Hepatitis B virus (HBV)		HCV
Human T-cell lymphotropic, virus (HTLV)		HTLV-1, HTLV-2
West Nile virus	Nucleic acid technology	

Table 55-12 Infectious Diseases Theoretically Transmissible by Blood Transfusion for Which No Test Is Available, 2004

Disease	Risk
Malaria	<1 : 1 million in the United States
Chagas' disease	<1 : 1 million
Severe acute respiratory syndrome (SARS)	?
Variant Creutzfeldt-Jakob	3 cases (?) in the United Kingdom

of Red Blood Cell Transfusions" and "Acquired Immunodeficiency Syndrome"). The risk of seroconversion is about 0.14% overall, or 0.38% per unit of seropositive donor blood. Wilhelm and associates[86] concluded that it is not necessary to provide blood products from CMV-seronegative donors for most patients who receive blood transfusions. They continue to use CMV-seronegative blood to prevent CMV infection in preterm and newborn infants.

Plasma components, such as fresh frozen plasma and cryoprecipitate, components from seronegative donors, and leukoreduced components are considered to be CMV safe.

Other Transfusion-Associated Infectious Diseases

Although many other infectious diseases can theoretically be transmitted by blood transfusion, only a few are of real concern. They include *Yersinia enterocolitica* infection, syphilis, malaria, Chagas' disease, variant Creutzfeldt-Jakob disease, parvovirus B19, and severe adult respiratory syndrome (SARS) (see Table 55-12).

During the late 1980s, Tripple and colleagues[87] described seven cases of fatal transfusion-associated *Y. enterocolitica* sepsis. These investigators also reviewed the literature and found 26 cases of gram-negative bacterial sepsis with whole blood or packed RBCs. *Y. enterocolitica* is a bacterium that can cause mostly mild gastrointestinal problems. However, in severe cases, sepsis and death can occur. Unfortunately, storage of blood at 4°C in phosphate buffer enhances its growth.

Post-transfusion syphilis is unlikely because the infective agent cannot survive during storage at 1°C to 6°C. The only blood products that have the potential to transmit syphilis are those stored at room temperature. Platelet concentrates are the blood component most likely to be implicated because they commonly are stored at room temperature.

Post-transfusion malaria has never been a significant cause of blood recipient morbidity. Nevertheless, malaria can occur, especially if blood donors at risk of harboring parasites are not excluded. Consequently, blood banks thoroughly question donors for history of travel or migration from areas where malaria is endemic.

Several other diseases have been reported to be transmitted by blood transfusion, including herpesvirus infections, infectious mononucleosis (i.e., Epstein-Barr virus), toxoplasmosis, trypanosomiasis, leishmaniasis, brucellosis, typhus, filariasis, measles, salmonellosis, and Colorado tick fever.

Like malaria, several infectious agents are feared as possibly transmitting disease to patients through blood transfusions for which there are no blood testing methods (Table 55-13). Without a specific test, donor screening with increasingly restrictive criteria are used. For example, in 2003 in the United States, donors with suspected SARS or who traveled to certain countries in Southeast Asia would not be accepted. Even though there are no cases of variant Creutzfeldt-Jakob disease from blood transfusions, the virus can be transmitted by blood in animal models, and stringent donor policies based on travel and residence in England or other countries in Europe are in place. Do these increasingly restrictive donor policies increase the risk of an inadequate blood supply[88] (see "Synthetic Oxygen-Carrying Substances")?

Other Adverse Effects of Blood Transfusion

Transfusion-Associated Graft-versus-Host Disease

Transfusion-associated graft-versus-host disease is caused by engraftment of donor lymphocytes from transfused blood products, initiating an immune reaction against recipient tissues. Severely immunocompromised patients are at risk. Also, directed donations from first- or second-degree relatives are at risk because transfused lymphocytes with shared HLA haplotypes cannot be recognized and eliminated.[89] A generalized rash, leukopenia, and thrombocytopenia occur. Sepsis and death usually result. Irradiation of blood can prevent transfusion-associated graft-versus-host disease from occurring, although there is a report of one case occurring despite leukocyte filtering.[90]

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is now the leading cause of transfusion-related mortality (see Table 55-6), although it probably is underdiagnosed and underreported.[91-93] This injury manifests as noncardiogenic pulmonary edema. Clinically, symptoms and signs appear 1 to 2 hours after transfusion and are in force within 6 hours. Fever, dyspnea, fluid in the endotracheal tube, and severe hypoxia are typical. During anesthesia, a persistent decrease in blood oxygen saturation can be the presenting sign. Although the chest radiograph is characteristic of pulmonary edema, circulatory overload (i.e., left atrial hypertension) is not present. All blood components, especially FFP, are implicated as caustic factors. There is no specific therapy other than stopping the transfusion and instituting critical care supportive measures. However, the transfusion should be immediately stopped and the blood bank notified for a different donor and quarantining all units from that donor. All records should be re-examined and the results of the patient's HLA testing should be evaluated if possible. Most patients recover in 96 hours, although TRALI remains the leading cause of transfusion-related death.

Adverse Ocular Reaction

In 1997, 112 cases of bilateral conjunctival erythema were reported to have occurred within 24 hours of transfusion. The Centers for Disease Control and Prevention studied 49 other cases in 1997 and 1998 and concluded that they were toxic reactions to a chemical or material used in the blood collection filtration system, most likely a leukocyte-reducing filter system.[94]

Transfusion-Related Immunomodulation

Homologous (allogeneic) blood transfusion exerts a nonspecific immunosuppressive action on the recipient. More than 150 clinical studies have tried to relate allogeneic blood transfusions

Table 55-13 Comparison of Whole Blood and Packed Red Blood Cells

Value	Whole Blood	Packed Red Blood Cells
Volume (mL)	517	300
Erythrocyte mass (mL)	200	200
Hematocrit (%)	40	70
Albumin (g)	12.5	4
Globulin (g)	6.25	2
Total protein (g)	48.8	36
Plasma sodium (mEq)	45	15
Plasma potassium (mEq)	15	4
Plasma acid (citric-lactic)	80	25 (mEq)
Donor-to-recipient ratio	1 unit per patient	1 unit per 4-6 patients

From Landers DF, Hill GE, Wong KC, et al: Blood transfusion-induced immunomodulation. Anesth Analg 82:187, 1996.

to recurrence of resected cancers, postoperative infections, and virus activation, with the conclusion that adverse effects may be caused by transfusion-related immunomodulation. Although the conclusions of these studies are contradictory and inconclusive, universal leukocyte reduction of RBCs is moving forward (see "Leukoreduction of Red Blood Cell Transfusions").[95]

Leukoreduction of Red Blood Cell Transfusions

One of the most dramatic changes in transfusion medicine in the past 10 years has been the universal use of leukoreduced packed RBCs internationally, which includes Western Europe, the United Kingdom, and Canada. In the United States as of 2004, more than 50% of the packed RBCs given are leukoreduced. What is the logic on which the increased use of leukoreduced blood is based?

There are some clear indications for leukoreduced blood. The chances of a febrile reaction can be reduced, especially in patients who are already alloimmunized from pregnancy. The risk of HLA alloimmunization from blood transfusions can be reduced, which would be especially helpful in minimizing refractoriness to platelet transfusions, and the risk of CMV can be reduced by using leukoreduced blood.

Universal leukoreduction has been seriously considered or implemented because of some anticipated benefits, including decreased transmission of variant Creutzfeldt-Jakob disease, leukocyte-induced immunomodulation, and even decreased postoperative mortality. In 2001, the case for and against universal leukoreduction was debated.[96,97] As of 2004, these anticipated benefits were not confirmed, despite numerous studies attempting to do so.[98] As nicely summarized by Corwin and AuBuchon,[96] a "may help, won't hurt" approach has been used to justify universal leukoreduction. However, this approach can be expensive. Bacterial contamination of platelets, TRALI, and acute hemolytic reactions cause more morbidity and mortality that would not be significantly helped by leukoreduction (see Table 55-6). Nevertheless, universal leukoreduction is the direction in which transfusion medicine is going.

Blood Component Therapy

A major advance in the field of blood banking has been the development of blood component therapy. It is beyond the scope of this chapter to describe the various separation steps in detail, but a superficial outline of the scheme by which various blood components are derived is shown in Figure 55-10. The basic philosophy is based on the concept that patients are best treated by administration of the specific fraction of blood that they lack. This concept has presented problems to the surgical team, who often desire whole blood.

Packed Red Blood Cells

Packed RBCs contain the same amount of hemoglobin as whole blood, but much of the plasma has been removed. The hematocrit value is 40% in whole blood and 70% in packed erythrocytes (see Table 55-13). Philosophically, whole blood provides oxygen-carrying capacity and intravascular blood volume expansion. Other than severe hemorrhage, most indications for red blood cells can be effectively treated with packed RBCs, retaining the plasma and the components thereof for other patients (see Fig. 55-10). Many blood banks have conscientiously followed this principle, and whole blood cannot be obtained in the operating rooms except by special request. In essence, blood bankers are saying that except for a rare situation (e.g., hypovolemic shock), whole blood is not necessary.

Because of this trend, some hospitals do not have whole blood readily available.

The administration of packed RBCs is facilitated by reconstituting them with a crystalloid or colloid; however, not all crystalloids are suitable. If the solution contains calcium, clotting occurs. Lactated Ringer's solution is not recommended for use as a diluent for packed RBCs (Table 55-14). Conversely, using flow rates and clot formation, Cull and colleagues[99] found lactated Ringer's solution and normal saline to be equally acceptable. A more important factor may be whether the diluent is hypotonic with respect to plasma. If so, the RBCs will swell and eventually lyse. Solutions that cause hemolysis are listed in Table 55-14. Clinicians who fear that the crystalloid-reconstituted RBCs may cause low serum concentrations may be tempted to use a plasma derivative, such as Plasmanate. However, these solutions also can cause hemolysis. The osmolality of Plasmanate is only 180 mOsm/kg. Solutions recommended for reconstituted packed erythrocytes are 5% dextrose in 0.4% saline, 5% dextrose in 0.9% saline, 0.9% saline, and Normosol-R with a pH of 7.4.

Platelet Concentrates

Platelet concentrates are prepared by differential centrifugation from freshly drawn units of blood or from donors who specifically donate large amounts of platelets by plateletpheresis techniques. If platelets are stored at room temperature, they are satisfactory to use 7 days after collection with constant and gentle agitation. Platelet concentrates present unique "conflicts" in medicine. First, bacterial contamination, mainly from platelet

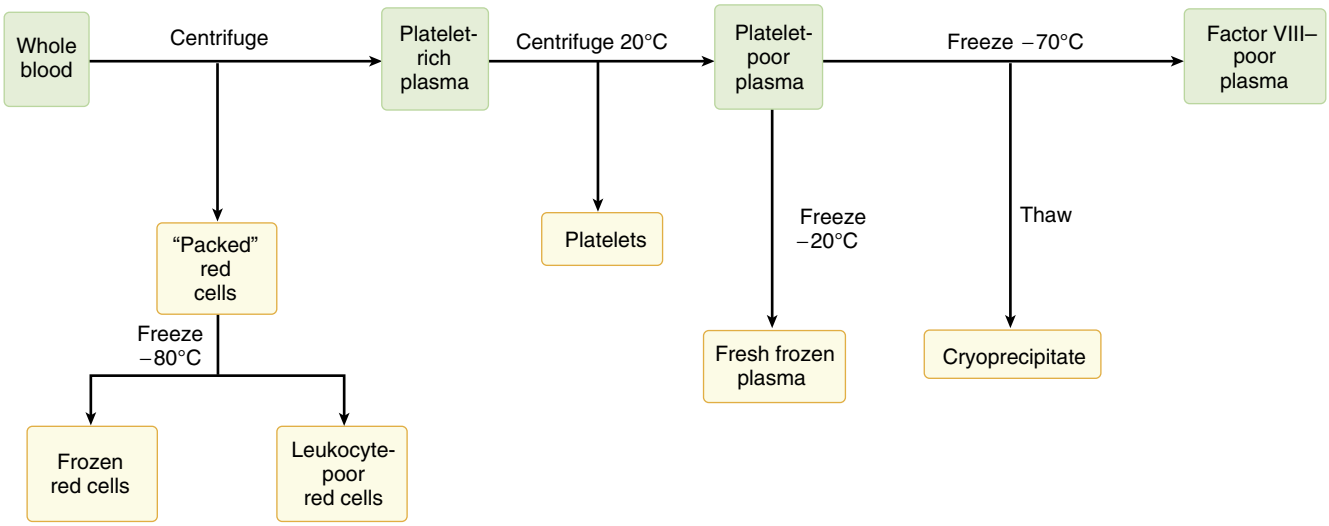

Figure 55-10 Scheme for separation of whole blood for component therapy.

concentrates, is the third leading cause of transfusion-related deaths (see Table 55-6). They are primarily effective at room temperature, which enhances bacterial growth. Furthermore, this has been a problem for more than 20 years. In the report of 10 septic platelet transfusions between 1982 and 1985, one half were platelets stored for 5 days or more. A prospective analysis from 1987 to 1990 resulted in seven cases of sepsis in patients receiving platelets for thrombocytopenia secondary to bone marrow failure.[100] Because use of multidonor platelet products stored for 5 days results in an incidence of sepsis five times higher than use of those stored for 4 days, shorter storage times are being emphasized. The incidence of platelet-related sepsis was about 1 case in 12,000 people.[101] The estimated incidence of bacterial contamination of platelets was about 1 case in 2,000.[102]

The increased risk of bacterial overgrowth is related to the storage temperature of 20°C to 24°C. For any patient who develops a fever within 6 hours after receiving platelets, sepsis from platelets should be considered. The evaluation of storing platelets for increased efficacy, but yet needing additional testing, actually makes the platelets available to the clinician for only about 3 days (Table 55-15). More recently, allowing platelets to be stored for 7 days minus 2 days for testing makes them available for 5 days, which enhances overall use of a valuable product and improved platelet inventory management. Presently, platelet concentrates are routinely tested for bacteria and are the only blood product that is stored at room temperature.[103] The rate of bacteria in platelets was 1/5000 before and 1/50,000 after routine bacteria culturing.[103] Data in 2007 indicated 186 positive cultures in 1,004,206 units, out of which 20 were septic reactions. Thirteen of these occurred 5 days after collection and resulted in three fatalities.[104]

Indications for the use of platelets are somewhat difficult to define. In the July 1989 *FDA Drug Bulletin* it was stated that platelets should not be given to patients with immune thrombocytopenic purpura (unless there is life-threatening bleeding), prophylactically with massive blood transfusion, or prophylactically after cardiopulmonary bypass. The American Society of Anesthesiologists (ASA) Task Force[4] provided the following recommendations:

Table 55-14 Compatibility of Blood with Intravenous Solutions

	Hemolysis at 30 Minutes	
Blood to Intravenous Solution (1 : 1 Ratio)	**Room Temperature**	**37°C**
5% Dextrose in water	1+	4+
Plasmanate*	1+	3+
5% Dextrose in 0.2% saline	0	3+
5% Dextrose in 0.4% saline	0	0
5% Dextrose in 0.9% saline	0	0
0.9% Saline	0	0
Normosol-R, pH 7.4†	0	0
Lactated Ringer's solution	0 (clotted)	0 (clotted)

*Cutter Laboratories, Berkeley, CA.
†Abbott Laboratories, Chicago, IL.

Table 55-15 History of Platelet Concentrates Shelf-Life in Relationship to Key Events

Year	Shelf-Life	Practical Shelf-Life*
1984-1986	7 days	6-7 days†
1986-1999	5 days	3 days‡
1999-2004	5 days	3 days§
2004-present	5 days	2.5 to 3 days

*Days that platelet concentrates are actually available to clinicians.
†Reports of bacterial contamination.
‡Nucleic acid technology testing, centralized blood donor testing.
§Bacterial detection implemented.

1. Prophylactic platelet transfusion is ineffective and rarely indicated when thrombocytopenia is due to increased platelet destruction (e.g., idiopathic thrombocytic purpura).
2. Prophylactic platelet transfusion is rarely indicated in surgical patients with thrombocytopenia due to decreased platelet production when the platelet count is greater than 100×10^9/L and is usually indicated when the platelet count is less than 50×10^9/L. The determination of whether patients with intermediate platelet counts (50 to 100×10^9/L) require therapy should be based on the patient's risk of bleeding.
3. Surgical and obstetric patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than 50×10^9/L and rarely require therapy if it is greater than 100×10^9/L. With intermediate platelet counts (50 to 100×10^9/L), the determination should be based on the patient's risk for more significant bleeding.
4. Vaginal deliveries or operative procedures ordinarily associated with insignificant blood loss may be undertaken in patients with platelet counts less than 50×10^9/L.
5. Platelet transfusion may be indicated despite an apparently adequate platelet count if there is known platelet dysfunction and microvascular bleeding.

Patients with severe thrombocytopenia (<20,000 cells/mm^3) and clinical signs of bleeding usually require platelet transfusion. However, patients may have very low platelet counts (much less than 20,000 cells/mm^3) and not have any clinical bleeding. Patients such as these probably do not need platelet transfusions. Individuals who have undergone trauma or require surgery need higher platelet counts, probably 100,000 cells/mm^3, to maintain adequate hemostasis (see Table 55-5). Laboratory determinations and clinical evaluations must be taken into account before a decision to transfuse platelets is made.

When possible, ABO-compatible platelets should be used. The need to use them, however, is not well documented. Specific testing is difficult. Aggregation, the end point of RBC crossmatch, cannot be used because platelets cause clumping. The platelet membrane has immunoglobulins. Any additional deposit of recipient antibodies is difficult to detect. Despite the fact that platelets can be destroyed by antibodies directed against class I human leukocyte antigen proteins on their membranes and, to a lesser extent, by antibodies against ABO, platelets chosen for transfusion probably will continue to be chosen without regard to antigen systems.[102] ABO-incompatible platelets produce very adequate hemostasis.

The effectiveness of platelet transfusions is difficult to monitor. Under ideal circumstances, one platelet concentrate usually produces an increase of about 7000 to 10,000 platelets/mm^3 at 1 hour after transfusion to the 70-kg adult. Ten units of platelet concentrates are required to increase the platelet count by 100,000 cells/mm^3. However, many factors, including splenomegaly, previous sensitization, fever, sepsis, and active bleeding, may lead to decreased survivals and decreased recovery of transfused platelets.

Various different types of platelet concentrates have been proposed, including apheresis (i.e., collecting more platelets from one donor to avoid pooling of platelets from multiple donors), leukocyte-depleted platelets, and ultraviolet B–irradiated platelets. The use of these products is reviewed by Kruskall.[102]

Fresh Frozen Plasma

FFP is prepared at the time that blood is obtained from a donor. It contains all the plasma proteins, particularly factors V and VIII, which gradually decline during the storage of blood. The use of FFP carries with it certain inherent risks that are observed with the use of essentially any blood product. The major risk is transmission of infectious diseases, such as hepatitis B, hepatitis C, and AIDS. Other risks include sensitization to foreign proteins. To increase overall utilization of blood products, many variations on the production of FFP exist. For example, there is variation in how long FFP is viable after thawing from 24 hours to 5 days. Also, plasma frozen 24 hours after phlebotomy (FP24) is comparable to FFP except for an approximate 25% decrease in factor VIII.[105]

Despite all the problems associated with FFP, its use increased 10-fold between 1974 and 1984, when consumption had reached almost 2 million units annually. This alarming increase caused the National Institutes of Health to conduct a Consensus Development Conference on Fresh Frozen Plasma in September 1984, of which I was a member.[49] More recently, the ASA Task Force[4] recommended the administration of FFP with the following guidelines:

1. For urgent reversal of warfarin therapy
2. For correction of known coagulation factor deficiencies for which specific correlates are unavailable
3. For correction of microvascular bleeding in the presence of increased (>1.5 times normal) prothrombin time or partial thromboplastin time
4. For correction of microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than 1 blood volume and when prothrombin time and partial thromboplastin time cannot be obtained in a timely fashion
5. FFP should be given in doses calculated to achieve a minimum of 30% of plasma factor concentration (usually achieved with administration of 10 to 15 mL/kg of FFP), except for urgent reversal of warfarin anticoagulation, for which 5 to 8 mL/kg of FFP usually suffice. Four to five platelet concentrates, 1 unit of single-donor apheresis platelets, or 1 unit of whole blood provides a quantity of coagulation factors similar to that contained on 1 unit of

FFP (except for decreased, but still hemostatic, concentrations of factors V and VIII in whole blood).
6. FFP is contraindicated for augmentation of plasma volume or albumin concentration.

The ASA Task Force[4] concluded that there was little scientific evidence to support the increasing use of FFP in clinical medicine. Although FFP is a reliable solution for intravascular volume replacement in cases of acute blood loss, alternative therapies are equally satisfactory and considerably safer. There is no documentation that FFP has a beneficial effect when used as part of transfusion management of patients with massive hemorrhage.

The practice of administering packed RBCs and FFP to the same patient should be discouraged because this adds to the cost and doubles the infection exposure. When conditions are appropriate, whole blood should be given.

The only indications for FFP administration the ASA Task Force[3] agreed on were the following:

1. Replacement of isolated factor deficiencies (as documented by laboratory evidence)
2. Reversal of warfarin effect
3. In cases of antithrombin III deficiency
4. Treatment of immunodeficiencies
5. Treatment of thrombotic thrombocytopenia purpura
6. Massive blood transfusion (rarely and only when factors V and VIII are less than 25% of normal)
7. Requirements for indications 1 and 6 are prothrombin and partial thromboplastin times at least 1.5 times longer than normal.

As of 2004, our policy at the University of California, San Francisco, is that in patients with clinical bleeding or oozing or those with an invasive procedure (e.g., percutaneous liver biopsy), the use of FFP is appropriate with a prothrombin time of 17 seconds or longer if the platelet count is more than 50,000 cells/mm^3 and the blood fibrinogen concentration is more than 100 mg/dL. FFP may be indicated for dilutional coagulopathy in patients with a prothrombin time more than 17 seconds and in whom administration of more crystalloids is anticipated.

Cryoprecipitate

Cryoprecipitate is prepared in such a way that it contains significant levels of factor VIII and fibrinogen. It also contains von Willebrand factor and fibronectin. All other plasma proteins are present in only trace amounts in cryoprecipitate. The use of cryoprecipitate in the treatment of factor VIII deficiency or hemophilia A has been outlined by Brown and coworkers.[106] Cryoprecipitate contains factor VIII:C (i.e., procoagulant activity), factor VIII:vWF (i.e., von Willebrand factor), fibrinogen, factor XIII, and fibronectin, which is a glycoprotein that may play a role in reticuloendothelial clearance of foreign particles and bacteria from the blood. Cryoprecipitate can also be used in the treatment of fibrinogen deficiencies and is preferable to commercially prepared fibrinogen preparations, which have a very high incidence of hepatitis, whereas the risk of hepatitis in cryoprecipitate is no more frequent than that from a single unit of blood.

Cryoprecipitate is frequently administered as ABO compatible; however, this probably is not very important because the concentration of antibodies in cryoprecipitate is extremely low. Cryoprecipitate may contain RBC fragments, and cryoprecipitate prepared from Rh-positive individuals can possibly sensitize Rh-negative individuals to the Rh O antigen.

Cryoprecipitate should be administered through a filter and as rapidly as possible. The rate of administration should be at least 200 mL/hr, and infusion should be completed within 6 hours of thawing.

Commercial concentrates of factor VIII have been the standard therapy for hemophilia. Although heat inactivation of factor VIII concentrate reduces infectivity, such a risk is still present. Recombinant DNA techniques have been used to develop factor VIII, which is free of disease transmission.[107] Mild cases of hemophilia may be treated without blood products by administration of desmopressin. Appropriate therapy is difficult to ascertain for patients who have inhibitors (i.e., alloantibodies) to factor VIII.

Fibrin glue is used occasionally by surgeons to create local hemostasis. It is prepared in a manner similar to that of cryoprecipitate. When FFP is thawed, the precipitate contains large amounts of fibrinogen. When centrifuged, about 4 mL of concentrated precipitate results. With added thrombin, it is applied locally, the efficacy of which is difficult to determine.

Prothrombin Complex

Factor IX can be recovered from plasma or plasma fractions by absorption with ion exchanges or inorganic chemicals. These products are all complexes of factors II, VII, IX, and X. Two commercial preparations are Konyne (Cutter Laboratories, Berkeley, CA) and Proplex (Hyland Division of Travenol Laboratories, Costa Mesa, CA). Other products include Alpha Nine SD, BeneFix, Mononine, and Profilnine SD. Bebulin VH is a vapor-heated concentrate of vitamin K–dependent factors in a much smaller volume than is achievable with FFP.

The main indication for these products is treatment of factor IX deficiency, or hemophilia B (i.e., Christmas disease). This is a hemorrhagic disorder that is distinguishable from hemophilia A only by laboratory tests. Factor IX or prothrombin complex has also been used for the treatment of acquired hypoprothrombinemic bleeding disorders, principally sodium warfarin overdose; however, its use is limited because of the risk of hepatitis.

Single-Donor Plasma

Single-donor plasma is plasma that has been removed from stored blood without any effort being made to preserve coagulation factors. Single-donor plasma is very effective as a volume expander. All the precautions outlined for the administration of FFP should be followed when single-donor plasma is administered. It obviously cannot be used to correct deficiencies in coagulation factors.

Other Options to Reduce Infectivity

Solvent-Detergent

Plasma from multiple donors is pooled and subjected to a lipid-destroying mixture of a solvent (tri-n-butyl phosphate) and a detergent (Triton X-100) to inactivate lipid-enveloped infectious agents, including HIV, HTLV, hepatitis C virus, and hepatitis B virus.[108] It has several disadvantages, including the risk of contamination of nonenveloped agents. Recalls can occur after any fraction of a lot has been released. It can be much more expensive than other preparations.

Single-Donor Plasma, Donor Retested

A donation is made, and FFP is prepared. The unit (the first donation) is kept if all history and infectious diseases markers are negative. That unit is not released for use until the same donor donates a second unit at least 3 months after the first donation and again passes all donor-intake and serologic testing. At that time, the first unit is released. The second unit is not released until the donor returns more than 3 months later for a third donation and again passes all the testing. At that time, the second unit can be released for use. This approach has obvious advantages but is administratively complex.

Frequent-Donor Plasma

An inverse relationship exists between the number of donations a person has given and the chance that he or she will become seropositive for a disease. The relationship is independent of the time over which the donations were given. A maximum reduction of the incidence of seropositivity is reached at four or more donations. Predictions are that reduction in seropositivity (and therefore transmission) to one third to one half of the current figures is possible.

These options were presented at the University of California, San Francisco, Transfusion Committee meeting and indicate that clinicians will have many ways of ensuring safer plasma for patients. With the newer tests of infectivity, the previously described FFP approaches may not be necessary.

Albumin and Plasma Protein Preparations

Several commercial products containing albumin are available for use to increase intravascular volume. Albumin is available as a 5% or a 25% solution in isotonic saline. Plasma protein fractions containing albumin and α and β globulins are available. These solutions are prepared commercially from albumin fractions from large pools of plasma reconstituted in isotonic electrolyte solutions. Such solutions can be given without regard to ABO blood type and without crossmatch and should be used primarily as volume expanders. They are very expensive and in short supply. Bacterial sepsis has been associated with albumin administration.[109] For much of 1997, there was a shortage of 5% albumin because of the concern about contamination with variant Creutzfeldt-Jakob disease. If available, albumin should be administered within 4 hours of initiation of the infusion because of the potential for contamination after opening the bottle. In 2003, Vincent and associates[110] analyzed all adverse reports on the 10 major suppliers of human albumin worldwide from 1998 to 2000. Although cases were possibly underreported, the investigators concluded that adverse events were rare with human albumin administration. It appears to be quite safe, but the indications for its use are controversial.

Administration of the plasma protein fraction of 5% serum albumin solutions should be restricted for the treatment of documented hypoproteinemia or conditions such as burns and peritonitis, in which hypoproteinemia is likely. These solutions expand the vascular space for a longer period than balanced electrolyte solutions do. However, albumin's osmotic ability draws fluid into the vascular space from other extracellular fluid compartments. In most states of hypovolemia and dehydration, the entire extracellular fluid space already is depleted. Fluids such as 0.9% saline or lactated Ringer's solution, which expand the entire extracellular fluid space, should be given.

Synthetic Colloid Solution Therapy

The crystalloid versus colloid conflict has been debated for many years. The University Hospital Consortium developed guidelines for the use of albumin, nonprotein colloid, and colloid solutions.[111] Unfortunately, no anesthesiologists were represented in the Consensus exercise. Since 2000, Boldt's[112] analysis of the literature, including a Cochrane Group review in 2002, found no consistent difference between crystalloids (i.e., isotonic and hypertonic) and different types of colloids as a basis for intravascular volume replacement. There is no doubt that colloids expand intravascular volume more than crystalloids (i.e., a smaller amount of colloid is required for adequate intravascular resuscitation).[113] However, outcomes (e.g., mortality) do not provide convincing evidence that one fluid replacement strategy is better than others.

Synthetic Hydroxyethyl Starch

Between 2000 and 2003, Boldt[112] found 40 original studies with a total of 2454 subjects. The most commonly used preparation was 6% hydroxyethyl starch (HES, Hespan). Although an effective intravascular expander, it has not gained widespread popularity probably because of its effects on coagulation, particularly with regard to increased bleeding and platelet function. The molecular mass plays some role in the adverse coagulation effects (i.e., smaller molecular mass has less effect on coagulation). Two new HES preparations have been developed to decrease coagulation effects. Hextend has been studied extensively. It is 6% HES but also contains a physiologically balanced medium of electrolytes, glucose, and lactate. It has a similar pharmacokinetic and dynamic profile to other starch preparations with fewer effects on

coagulation.[114] Gelatin has also been used, but it has not been as widely studied as HES.[115]

Dextrans

Dextran 70 (Macrodex), with a molecular mass of about 70,000 daltons, is an effective volume expander. However, after infusion of more than 20 mL/kg in 24 hours, dextran 70 may interfere with normal blood clotting, causing a deficiency with crossmatching procedures and possibly a bleeding diathesis. These clotting defects reflect reduced platelet adhesiveness resulting from an antithrombin effect. The incidence of severe anaphylactoid or anaphylactic reactions is a concern. These reactions are mediated by dextran-reactive antibodies that are IgG immunoglobulins. Dextran-reactive antibodies are formed in response to dextran polysaccharides. This process can be prevented if the potentially reactive sites on the dextran-reactive antibody are blocked before the antibody is given. By prior administration of a hapten, a substance capable of combining with immunoglobulins but not producing a reaction, the reactive sites are occupied and unable to react to the antigen. Prior administration of dextran I (Promit, molecular mass of 1000 daltons) has proved effective as a hapten and decreases, but does not eliminate, the incidence of severe reactions.[116] Dextran 70 exerts a higher colloid osmotic pressure than blood. Dextran 70 and albumin may deplete the extracellular fluid space of water, as does albumin.

Dextran 40 (Rheomacrodex), with a molecular mass of 40,000 daltons, has been used primarily to reduce blood viscosity and cellular aggregation and to improve microcirculation during low-flow states. It is often given prophylactically to decrease the incidence of postoperative thromboembolism. Blood viscosity may be increased by trauma, blood loss, burns, and endotoxin shock. Although viscosity can be decreased by dextran 40, the presumed improvement in flow through the microcirculation has not been well documented.

Hypertonic Saline, Possibly with Dextran

The sodium concentration of hypertonic saline solutions is 250 to 1200 mEq/L. The theoretical advantage is that the greater the sodium concentration, the less total volume is required for adequate resuscitation. The lower infusion volume probably reflects the osmotically related movement of intracellular water into the extracellular space. Other mechanisms include a direct inotropic effect on the myocardium and a direct peripheral vasodilator effect. The main problem is severe hypernatremia, which can cause brain dehydration and can be fatal.

Various hyperosmotic-hyperoncotic solutions have been used for resuscitation of hypovolemic patients. The most common combination is hypertonic saline and 6% dextran 70. In animals, these fluids restore gut and kidney microcirculation more effectively than normal saline.[117,118] The addition of dextran increases the intravascular volume effect of hypertonic saline but does not extend the duration of effect in a clinically significant manner.[117] Clinical practice will be required to ascertain the ultimate role, if any, of these fluids.

Synthetic Oxygen-Carrying Substances

Other Than Human Red Blood Cells (Blood)

Other various substances that carry or facilitate the transport of oxygen have been made. Two concepts of synthetic blood have been attempted. The first approach uses linear binding kinetics, unlike the nonlinear binding of hemoglobin. The most notable is the perfluorochemical emulsion called Fluosol-DA. However, it had little use because it carries oxygen (i.e., a small amount) only when the Pao_2 is more than 300 mm Hg.[118] A newer perfluoro compound, perfluorooctyl bromide, carries three to four times more oxygen and has a longer half-life and presumably fewer problems than are associated with Fluosol-DA. Other related products are Oxygent (Alliance), Oxycyte (synthetic blood), and several other perfluorocarbon emulsions.

The remaining synthetic blood (a term this author uses but not one officially accepted by industry and the FDA) or oxygen therapeutics are labeled as hemoglobin-based oxygen carriers (HBOCs). These products modify the hemoglobin molecule from humans, animals, or recombinant technology. Original efforts required hemoglobin to be stroma free to prevent nephrotoxicity. The stroma-free hemoglobin needed to be modified to have a favorable oxygen affinity and to extend its relatively short intravascular half-life. Only three products have been undergoing clinical trials. Two products are from outdated human RBCs and the third from bovine RBCs. However, these solutions are not without complications. The most serious are kidney toxicity, an increase in affinity for oxygen (i.e., left shift in the oxygen dissociation curve), and arteriolar vasoconstriction from nitric oxide scavenged by the infused hemoglobin. As described at the end of this section, this vasoconstriction may prove to be their ultimate downfall. A variety of approaches are being used, including crosslinking, pyridoxylation and polymerization, and conjugation and encapsulation, to decrease oxygen affinity, to increase deposition in the reticuloendothelial system, and to increase half-life.

Genetic engineering has provided hope for blood products. Initially, recombinant erythropoietin was developed for treatment of anemias and facilitation of autologous blood donation (see Chapter 57). In 1992, a human recombinant hemoglobin (rHb 1.1) was designed as a blood substitute.[119] With the use of genetic engineering techniques, it was made from *Escherichia coli*. It functions as normal hemoglobin in terms of oxygen-carrying capacity, but it does not require crossmatching, nor does it transmit disease or become rapidly outdated. How much recombinant material can be tolerated by humans remains to be determined. Unfortunately, this caused arteriolar vasoconstriction from nitric oxide scavenging. While arterial blood pressure was sustained, it was at the expense of severe vasoconstriction of microvascular structures, which is not beneficial for organ perfusion. Recently, rHbg 2.0, which minimizes nitric oxide scavenging, caused little arteriolar vasoconstriction when compared with rHbg 1.1 and diaspirin crosslinked hemoglobin.[120,121] It is hoped that studies of these newer hemoglobin solutions will lead to new synthetic blood products in humans.

An example of a product that appears to be the initial one possibly approved for routine clinical practice is Hemopure.[122] It is from ultrapurified bovine RBCs that have been glutaraldehyde polymerized. It has a higher P_{50} (i.e., 43 instead of 26 mm Hg), which means that it should deliver oxygen to the tissues at least as well, if not better, than human RBCs.[122] It has the added advantage of not requiring type and crossmatch and not transmitting infectious agents such as HIV and hepatitis virus.[121,122] These, of course, are typical characteristics of most synthetic blood products (Table 55-16). Many clinical trials have been safely conducted with a few possibly minor complications, the significance of which are not clear. Complications include a slight increase in mean arterial blood pressure and a decrease in cardiac index, which presumably may be from nitric oxide. Hemopure has been approved for routine clinical use in South Africa. Its indication will probably be treatment of acute anemia in some type of surgery. Most of the clinical trials have shown a decreased use of allogeneic blood transfusions.[123]

However, the most recent information regarding HBOCs is not encouraging. Natanson and associates[124] performed a cumulative meta-analysis on 16 trials involving five different products and 3711 patients. They concluded that there was a significant increased risk of myocardial infarction and death when HBOCs were given. An accompanying editorial by Fergusson and McIntyre[125] concluded that a 30% increased risk of death and a 3-fold increase in the risk of myocardial infarction should preclude any additional studies. Furthermore, there was a consistency of harm among all of the technologies (e.g., cross-linked, polymerized, or conjugated). In essence, investigators must demonstrate that HBOCs are at least as effective in reducing mortality or serious morbidity as the current standards of care. I have reluctantly concluded that use of synthetic blood (HBOCs) is not likely with the current technologic approaches.

Table 55-16 Comparison of Synthetic Blood in General with Allogeneic Blood

Parameter	Synthetic	Allogeneic
Oxygen delivery	Rapid and consistent	Dependent on 2,3-DPG
Risk of disease transmission	None	See Table 55-9
Storage	Room temperature Stable efficacy	Refrigeration Loss of efficacy
Shelf life	1-3 years	42 days
Preparation	Ready to use	Crossmatch
Compatibility	Universal	Type specific
Duration of action	1-3 days	60-90 days

Informed Consent

Before any transfusion is given, informed consent should be obtained from the patient or guardian (see Chapter 10). What constitutes consent varies across the United States and is still changing. If a patient is damaged by a transfusion administered without a valid consent, damages may be recovered even though the defendant did everything properly.[124] During the past decade, the public has demanded to know more about transfusions. A dramatic example was the passage of the Paul Gann Blood Safety Act in California. This law mandates that patients be informed of the risks of blood transfusions and of any alternatives. This law has apparently already had a restrictive impact on transfusion practice in California.[126] The rapid changes in transfusion medicine probably dictate an intense, ongoing educational process for clinicians who administer blood products to ensure that they are compliant with current laws and regulations.

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56 Coagulation

Key Points

1. Under normal physiologic conditions, clot formation requires participation of vascular endothelium, platelets, and plasma-mediated hemostasis.
2. Tissue factor (extrinsic pathway) initiates plasma-mediated hemostasis, whereas factor XI (intrinsic pathway) amplifies the response.
3. Thrombin generation proves the key regulatory enzymatic step in hemostasis.
4. Platelets participate in clot formation as (1) anchoring sites for coagulation factor activation complexes; (2) delivery "vehicles" releasing hemostatically active proteins; and (3) major structural components of the clot.
5. A carefully performed history of bleeding remains the most effective means for identifying bleeding and thrombotic tendencies.
6. Thrombosis is potentiated by stasis, vascular endothelial injury, and underlying hypercoagulable conditions.
7. Heparin-induced thrombocytopenia (HIT) comprises a heparin-mediated autoimmune response potentiating platelet activation as well as venous and arterial thromboses.

Normal Hemostasis

Hemostasis comprises cellular and biochemical processes that limit blood loss resulting from injury, maintain intravascular blood fluidity, and promote revascularization of thrombosed vessels after injury. Normal physiologic hemostasis necessitates a delicate balance between procoagulant pathways responsible for generation of a stable localized hemostatic "plug" and counterregulatory mechanisms inhibiting thrombus formation beyond the injury site. Vascular endothelium, platelets, and plasma coagulation proteins play equally important roles in this process. Failure to maintain balance commonly leads to excessive bleeding or pathologic thrombus formation.

Vascular endothelial injury, mechanical or biochemical, leads to platelet deposition at the injury site, a process often referred to as primary hemostasis. Although primary hemostasis may prove adequate for a minor injury, control of more significant bleeding necessitates stable clot formation incorporating cross-linked fibrin—a process mediated by activation of plasma clotting factors and often referred to as secondary hemostasis. Although the terms *primary* and *secondary hemostasis* remain relevant for descriptive and diagnostic purposes, advances in understanding cellular and molecular processes underlying hemostasis suggest a far more complex interplay between vascular endothelium, platelets, and plasma-mediated hemostasis than is reflected in this model.

Vascular Endothelial Role in Hemostasis

Under normal conditions, vascular endothelium provides a nonthrombogenic surface to promote blood fluidity. Healthy endothelial cells possess antiplatelet, anticoagulant, and profibrinolytic effects to inhibit clot formation.[1] Negatively charged vascular endothelium repels platelets and produces prostacyclin (PGI_2) and nitric oxide (NO), which are potent platelet inhibitors.[2] Adenosine diphosphatase (ADPase) synthesized by vascular endothelial cells degrades adenosine diphosphate (ADP), another potent platelet activator. Given these endogenous antiplatelet effects, nonactivated platelets do not adhere to healthy vascular endothelial cells. Vascular endothelium further expresses several inhibitors of plasma-mediated hemostasis, including thrombomodulin (an indirect thrombin inhibitor), heparin-like glycosaminoglycans, and tissue factor pathway inhibitor (TFPI).[3] Finally, vascular endothelium synthesizes tissue plasminogen activator (t-PA), which is responsible for activating fibrinolysis—a primary counterregulatory mechanism limiting clot propagation.

Despite these natural defense mechanisms to inhibit thrombus generation, a variety of mechanical and chemical stimuli may shift the balance such that the endothelium promotes clot formation. Damage to vascular endothelial cells exposes the underlying extracellular matrix (ECM) including collagen, von Willebrand factor (vWF), and other platelet-adhesive glycoproteins.[4,5] Platelets bind to and are activated by exposure to ECM

components. Exposure of tissue factor, constitutively expressed by fibroblasts in the ECM, activates plasma-mediated coagulation pathways to generate thrombin and, ultimately, fibrin clot. Certain cytokines (i.e., interleukin-1, tumor necrosis factor, and γ-interferon) and hormones (i.e., desmopressin acetate or endotoxin) induce prothrombotic changes in vascular endothelial cells, including synthesis and expression of vWF, tissue factor, plasminogen activator inhibitor (PAI-1, an inhibitor of fibrinolysis), as well as downregulate normal antithrombotic cellular and biochemical pathways.[6,7] Thrombin, hypoxia, and high fluid shear stress induce prothrombotic vascular endothelial changes. Increased vascular endothelial synthesis of PAI-1 and associated inhibition of fibrinolysis have been implicated in the prothrombotic state and high incidence of venous thrombosis after surgery.[8,9]

Platelets and Hemostasis

Platelets contribute a critical role in hemostasis. Derived from bone marrow megakaryocytes, nonactivated platelets circulate as discoid anuclear cells.[10] The platelet membrane is characterized by numerous receptors and a surface-connected open canalicular system serving to increase platelet membrane surface area as well as to provide rapid communication between the platelet interior and external environment.[11] Under normal circumstances, platelets do not bind vascular endothelium; however, when injury exposes ECM, platelets undergo a series of biochemical and physical alterations characterized by three major phases: adhesion, activation, and aggregation.

Exposure of subendothelial matrix proteins (i.e., collagen, vWF, fibronectin) allows for platelet adhesion to the vascular wall. vWF proves particularly important as a bridging molecule between ECM and platelet glycoprotein Ib/factor IX/factor V receptor complexes.[12] Absence of either vWF (von Willebrand disease) or glycoprotein Ib/factor IX/factor V receptors (Bernard-Soulier syndrome) results in a clinically significant bleeding disorder.

As platelets adhere along the ECM, a series of physical and biochemical changes occur termed *platelet activation.* Platelets contain two specific types of storage granules: alpha granules and dense bodies.[11] Alpha granules contain numerous proteins essential to hemostasis and wound repair, including fibrinogen, coagulation factors V and VIII, vWF, platelet-derived growth factor, and others. Dense bodies contain the adenine nucleotides ADP and adenosine triphosphate (ATP) as well as calcium, serotonin, histamine, and epinephrine. During the activation phase, platelets release granular contents, resulting in recruitment and activation of additional platelets as well as propagation of plasma-mediated coagulation.[13] During activation, platelets undergo structural changes to develop pseudopod-like membrane extensions and to release physiologically active microparticles, with both mechanisms serving to increase dramatically platelet membrane surface area. Redistribution of platelet membrane phospholipids during activation exposes newly activated glycoprotein platelet surface receptors and phospholipid binding sites for calcium and coagulation factor activation complexes, which is critical to propagation of plasma-mediated hemostasis.[14]

During the final phase of platelet aggregation, activators released during the activation phase serve to recruit additional platelets to the site of injury. Newly active glycoprotein IIb/IIIa receptors on the platelet surface bind fibrinogen to provide for cross-linking with adjacent platelets (platelet aggregation).[15] The importance of these receptors is reflected by the bleeding disorder associated with their hereditary deficiency: Glanzmann thrombasthenia.

Plasma-Mediated Hemostasis

Plasma-mediated hemostasis, the coagulation cascade, might best be summarized as an amplification system to accelerate thrombin generation from an inactive precursor (i.e., prothrombin). Trace plasma proteins, activated by exposure to tissue factor or exposure to foreign surfaces, initiate a cascading series of reactions culminating in conversion of soluble fibrinogen to insoluble fibrin clot.[16] Thrombin generation, the "thrombin burst," represents the key regulatory step in this hemostatic process. Thrombin not only generates fibrin but also activates platelets and mediates a host of additional processes affecting inflammation, mitogenesis, and even downregulation of hemostasis.[17]

Traditionally, the "coagulation cascade" describing plasma-mediated hemostasis has been depicted as intrinsic and extrinsic pathways, both of which culminate in a common pathway where fibrin generation occurs.[18] Although this cascade model has proved an oversimplification, it remains a useful descriptive tool for organizing discussions of plasma-mediated hemostasis (Fig. 56-1). Coagulation factors are, for the most part, synthesized hepatically and circulate as inactive proteins termed *zymogens.* The somewhat confusing nomenclature of the classic coagulation cascade derives from the fact that inactive zymogens were identified using Roman numerals assigned in order of discovery. As the zymogen is converted to an active enzyme, a lower-case letter "a" is added to the Roman numeral identifier. For example, inactive prothrombin is referred to as factor II, whereas active thrombin is identified as factor IIa. Some numerals were subsequently withdrawn or renamed as our understanding of the biochemistry underlying hemostasis evolved.

The coagulation cascade characterizes a series of enzymatic reactions in which inactive precursors—zymogens—undergo activation to amplify the overall reaction. Each stage of the cascade requires assembly of membrane-bound activation complexes, each composed of an enzyme (activated coagulation factor), substrate (inactive precursor zymogen), cofactor (accelerator/ catalyst), and calcium.[19] Assembly of these activation complexes occurs on phospholipid membranes (most often platelet or microparticle membranes) that serve to localize and concentrate reactants. In the absence of phospholipid membrane anchoring sites, activation of coagulation factors slows dramatically, further serving to localize clot generation to injury sites.

Extrinsic Pathway of Coagulation

The extrinsic pathway of coagulation, widely recognized as the initiating step in plasma-mediated hemostasis, begins with exposure of blood plasma to tissue factor.[20] Tissue factor is prevalent in subendothelial tissues surrounding vasculature; however, under normal conditions the vascular endothelium minimizes contact between tissue factor and plasma coagulation factors. After vascular injury, small concentrations of factor VIIa circulating in

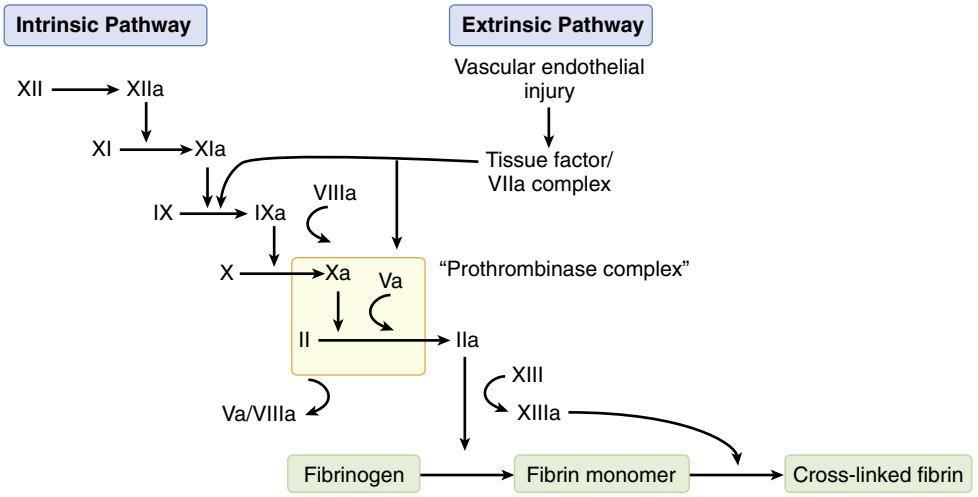

Figure 56-1 Depiction of the classic coagulation cascade incorporating extrinsic and intrinsic pathways of coagulation. *(From Slaughter TF: The coagulation system and cardiac surgery. In Estafanous FG, Barash PG, Reves JG [eds]: Cardiac Anesthesia: Principles and Clinical Practice, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2001, p 320, with permission.)*

plasma form phospholipid-bound activation complexes with tissue factor, factor X, and calcium to promote conversion of factor X to Xa.[21] Recently, the tissue factor/factor VIIa complex has been demonstrated to activate factor IX of the intrinsic pathway, further demonstrating the key role of tissue factor in initiating hemostasis.[22]

Intrinsic Pathway of Coagulation

Classically, the intrinsic or contact activation system was described as a parallel pathway for thrombin generation by way of factor XII. However, the rarity of bleeding disorders resulting from contact activation factor deficiencies led to our current understanding of the intrinsic pathway as an amplification system to propagate thrombin generation initiated by the extrinsic pathway.[22] Recent cell-based models of coagulation suggest that thrombin generation by way of the extrinsic pathway is limited by a natural inhibitor, tissue factor pathway inhibitor (TFPI).[23] However, small quantities of thrombin generated before neutralization of the extrinsic pathway activate factor XI and the intrinsic pathway. The intrinsic pathway subsequently amplifies and propagates the hemostatic response to maximize thrombin generation (Fig. 56-2). Although factor XII may be activated by foreign surfaces (i.e., cardiopulmonary bypass circuits or glass vials), the intrinsic pathway appears to play a minor role in initiation of hemostasis. Proteins of the intrinsic pathway may, however, contribute to inflammatory processes, complement activation, fibrinolysis, kinin generation, and angiogenesis.[22,24]

Common Pathway of Coagulation

The final pathway, common to both extrinsic and intrinsic coagulation cascades, depicts thrombin generation and subsequent fibrin formation. Signal amplification through both extrinsic and intrinsic pathways culminates in formation of prothrombinase complexes (phospholipid membrane bound activation complexes)

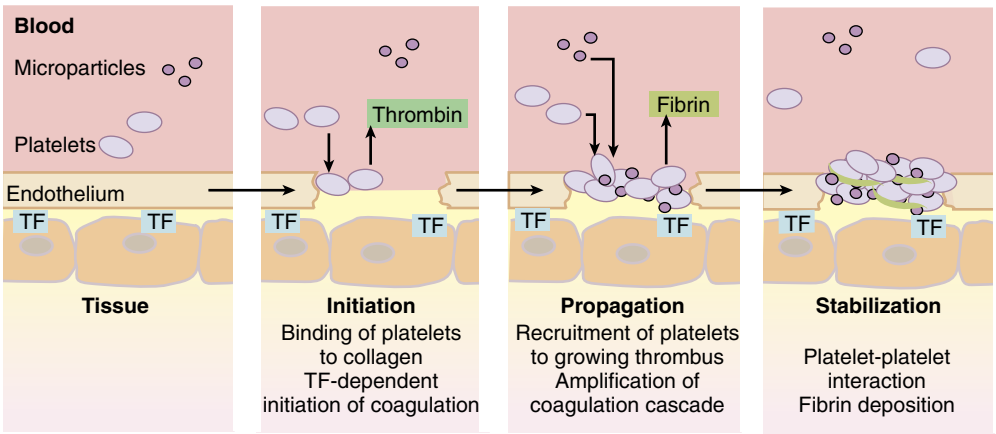

Figure 56-2 Clot formation at vascular injury site. Vascular injury exposes subendothelial tissue factor initiating plasma-mediated hemostasis via the extrinsic pathway. The intrinsic pathway further amplifies thrombin and fibrin generation. Platelets adhere to exposed collagen to undergo activation, resulting in recruitment and aggregation of additional platelets. *(From Mackman N, Tilley RE, Key NS: Role of extrinsic pathway of blood coagulation in hemostasis and thrombosis. Arterioscleros Thromb Vasc Biol 27:1688, 2007, with permission.)*

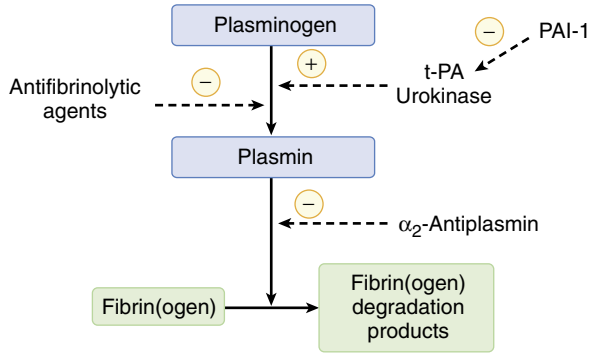

Figure 56-3 Principal mediators of fibrinolysis. *Dashed lines* depict sites of action for promoters and inhibitors of fibrinolysis. *(From Slaughter TF: The coagulation system and cardiac surgery. In Estafanous FG, Barash PG, Reves JG [eds]: Cardiac Anesthesia: Principles and Clinical Practice, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2001, p 320, with permission.)*

comprised of factor Xa, factor II (prothrombin), factor Va (cofactor), and calcium ions.[25] Prothrombinase complexes mediate the thrombin burst—a surge in thrombin generation from the inactive precursor prothrombin. Thrombin proteolytically cleaves fibrinopeptides A and B from fibrinogen molecules to generate fibrin monomers, which polymerize into fibrin strands (i.e., fibrin clot).[25] Finally, factor XIIIa, a transglutaminase activated by thrombin, covalently crosslinks fibrin strands to produce an insoluble fibrin clot resistant to fibrinolytic degradation.[26] Again, thrombin generation is the key enzymatic step regulating hemostasis.[27] Not only does thrombin activity mediate conversion of fibrinogen to fibrin, but it also activates platelets, converts inactive cofactors V and VIII to active conformations, activates factor XI and the intrinsic pathway of coagulation, upregulates cellular expression of tissue factor, and stimulates vascular endothelial expression of PAI-1 to downregulate fibrinolytic activity.[17,27]

Intrinsic Anticoagulant Mechanisms

Once activated, regulation of hemostasis proves essential to limit clot propagation beyond the injury site. One simple, yet important, anticoagulant mechanism derives from flowing blood and hemodilution. The early platelet/fibrin clot proves highly susceptible to disruption by shear forces within flowing blood. Blood flow further limits localization and concentration of both platelets and coagulation factors such that a critical mass of hemostatic components may fail to coalesce.[25,28] However, later in the clotting process more robust counterregulatory mechanisms are necessary to limit clot propagation. Four major counterregulatory pathways have been identified that appear particularly crucial for downregulating hemostasis: fibrinolysis, TFPI, the protein C system, and serine protease inhibitors.

The fibrinolytic system comprises a cascade of amplifying reactions culminating in plasmin generation and proteolytic degradation of fibrin and fibrinogen. As with the plasma-mediated coagulation cascade, inactive precursor proteins are converted to active enzymes, necessitating a balanced system of regulatory controls to prevent excessive bleeding or thrombosis (Fig. 56-3). The principal enzymatic mediator of fibrinolysis, plasmin, is generated from an inactive precursor, plasminogen.[29] *In vivo*, plasmin generation most often is initiated by release of t-PA or urokinase from vascular endothelium. Thrombin provides a potent stimulus for t-PA synthesis.[27] Factor XIIa and kallikrein of the intrinsic pathway activate fibrinolysis after exposure to foreign surfaces. The presence of fibrin accelerates plasmin generation.[30] Rapid inhibition of free plasmin also limits spread of fibrinolytic activity. In addition to enzymatic degradation of fibrin and fibrinogen, plasmin inhibits hemostasis by degrading essential cofactors V and VIII as well as reducing platelet glycoprotein surface receptors essential to adhesion and aggregation.[31] Fibrin degradation products possess mild anticoagulant properties as well.

TFPI inhibits the tissue factor/factor VIIa complex and thereby the extrinsic coagulation pathway, which is responsible for initiation of hemostasis. TFPI and factor Xa form phospholipid membrane-bound complexes that incorporate and inhibit tissue factor/factor VIIa complexes.[3] Most TFPI is bound to vascular endothelium but may be released into circulation by heparin administration. Heparin further catalyzes TFPI inhibitory activity.[32] As TFPI rapidly extinguishes tissue factor/VIIa activity, the critical role of the intrinsic pathway to continued thrombin and fibrin generation becomes apparent.[22]

The protein C system proves particularly important in downregulating hemostasis because it inhibits thrombin as well as the essential cofactors Va and VIIIa. Thrombin initiates this inhibitory pathway by binding a membrane-associated protein, thrombomodulin, to activate protein C.[33] Protein C, complexed with the cofactor protein S degrades both cofactors Va and VIIIa. Loss of these critical cofactors limits formation of "tenase" and "prothrombinase" activation complexes essential to formation of factor X and thrombin, respectively. Thrombin, once bound to thrombomodulin, is inactivated and removed from circulation, providing another mechanism by which protein C downregulates hemostasis.[33]

The most significant serine protease inhibitors regulating hemostasis include antithrombin (AT) and heparin cofactor II. Antithrombin binds to and inhibits thrombin as well as factors IXa, Xa, XIa, and XIIa. Heparin cofactor II inhibits thrombin alone. Although the precise physiologic role for heparin cofactor II remains uncertain, antithrombin plays a major role in downregulating hemostasis.[34] Heparin, a catalyst accelerator, binds antithrombin to promote inhibition of targeted enzymes.[35] Heparin-like glycosaminoglycans, located on vascular endothelial cells, provide inhibitory sites for thrombin and factor Xa *in vivo*.

Disorders of Hemostasis

Evaluation of Bleeding Disorders

Few would argue the importance of assessing bleeding risk preoperatively; however, appropriate methods for ascertaining this risk remain subject to debate. Although routine coagulation testing of all surgical patients preoperatively intuitively may be appealing, this approach lacks predictive value for bleeding disorders and certainly lacks cost effectiveness.[36] A carefully performed history of bleeding remains the single most effective predictor for perioperative bleeding.

A well-conducted history should focus on prior bleeding episodes experienced by the patient.[37] Does the patient have a history of "excessive" bleeding in association with trauma or prior surgery? Were blood transfusions or reoperation required to control the bleeding? A history suggestive of a bleeding disorder might include frequent epistaxis of a severity necessitating

"packing the nasal passage" or surgical intervention. Oral surgery and dental extractions prove a particularly good test of hemostasis due to high concentrations of fibrinolytic activity in the oral cavity. Von Willebrand's disease not infrequently manifests as menorrhagia, and postpartum hemorrhage commonly occurs in women with underlying disorders of hemostasis.[38] A history of spontaneous hemorrhage (nontraumatic) proves particularly concerning when associated with joints (hemarthroses) or deep muscles. Identification of a bleeding disorder at an early age or in family members suggests an inherited, as opposed to acquired, condition.[39] A careful medication history including direct questions relating to consumption of aspirin-containing nonprescription drugs, herbs, and fish oil may prove noteworthy. Finally, inquiries regarding coexisting diseases should be included (i.e., renal, hepatic, thyroid, bone marrow disorders, and malignancy).

For most patients, a thoughtfully conducted bleeding history will eliminate need for preoperative laboratory-based coagulation testing. Regardless, there remain several valid reasons for preoperative coagulation testing. Should the preoperative history or physical examination reveal signs or symptoms suggestive of a bleeding disorder further laboratory-based assessment of coagulation would be indicated. Preoperative screening tests of coagulation may be indicated, despite a negative history, in cases in which major surgery commonly associated with significant bleeding is planned (i.e., cardiopulmonary bypass). Finally, preoperative testing may prove justified in settings in which the patient is unable to provide a bleeding history preoperatively. Should evidence of a bleeding disorder be detected preoperatively, underlying mechanisms must be ascertained if possible before proceeding with surgery.

Inherited Bleeding Disorders

Although inherited disorders of hemostasis may involve platelet function, plasma-mediated hemostasis, or fibrinolytic pathways, von Willebrand's disease characterized by quantitative or qualitative deficiencies of vWF proves the most common of inherited bleeding disorders.[38] Variants include types I and III with varying quantitative vWF deficiencies and type II comprising a collection of qualitative defects affecting vWF function. Under normal conditions, vWF plays a critical role in platelet adhesion to ECM. vWF further acts as a carrier molecule preventing proteolytic degradation of factor VIII in free plasma.[40] Classically, patients with von Willebrand's disease describe a history of easy bruising, recurrent epistaxis, and menorrhagia, all characteristic of defects in primary (i.e., platelet mediated) hemostasis. In more severe cases (i.e., type III vWD), concomitant reductions in factor VIII may lead to serious spontaneous hemorrhage, including hemarthroses, which is common in hemophilia. Laboratory testing often demonstrates mild to moderate prolongation of the activated partial thromboplastin time (aPTT), prolonged bleeding time, decreased immunoreactive vWF concentrations, and reduced platelet aggregation in response to ristocetin.[38,41] Increasingly, the PFA-100 and similar *ex-vivo* platelet function tests have replaced bleeding times in assessing for vWD.[42] Measurable reductions in factor VIII activity may occur in severe cases. Mild cases of vWD often respond to desmopressin acetate (DDAVP); however, given a significant bleeding history, specific replacement of vWF and factor VIII with select factor VIII concentrates (i.e., Humate-P: Armour Pharmaceuticals, Kankakee, IL) may be indicated.[43,44]

Although relatively uncommon, the hemophilias merit consideration given their diverse clinical presentation. Hemophilia A, characterized by variable degrees of factor VIII deficiency, is an X-linked inherited bleeding disorder most frequently presenting in childhood as spontaneous hemorrhage involving joints or deep muscles or both. Hemophilia A occurs with an incidence of 1:5000 males; however, nearly one third of cases represent new mutations with no family history.[45] In mild cases, patients with hemophilia may not be identified until later in life, often after unexplained bleeding with surgery or trauma. Classically, laboratory testing in patients with hemophilia reveals prolongation of the aPTT, whereas the prothrombin time (PT) and bleeding time remain within normal limits. Specific measurement of factor VIII:C is required to confirm the diagnosis and to clarify the severity of factor VIII deficiency. Mild cases of hemophilia A may be treated with desmopressin; however, in most cases perioperative management of these patients necessitates consultation with a hematologist and administration of recombinant or purified factor VIII concentrates.[43,46] An increasingly common complication of hemophilia, particularly in the case of hemophilia A, has been development of alloantibodies directed against the factor VIII protein. In cases of high titer antibodies, administration of factor VIII concentrates may fail to control bleeding. Several approaches have reduced bleeding in these patients, including substitution of porcine factor VIII, administration of "activated" or "nonactivated" prothrombin complex concentrates, or treatment with recombinant factor VIIa (NovoSeven, Novo Nordisk, Copenhagen, Denmark) (see Chapter 57).[44,47] Also inherited as an X-linked disorder, hemophilia B (i.e., Christmas disease) occurs in approximately 1:40,000 and necessitates blood component replacement with factor IX concentrates.

Acquired Bleeding Disorders

A detailed account of acquired hemostatic disorders is beyond the scope of this discussion; however, given that a limited number of drugs and coexisting medical conditions account for the majority of acquired bleeding disorders, these conditions merit consideration. Heparin, warfarin, and fibrinolytic drugs historically accounted for most serious drug-induced bleeding complications (Table 56-1).[48,49] More recently, antiplatelet drug therapy further has complicated perioperative management (Table 56-2).[49-52] Unfractionated heparin comprises a heterogeneous mixture of membrane-associated glycosaminoglycans derived from either bovine or porcine mucosal tissues. Specificity and potency of unfractionated heparin varies by molecular weight, which ranges between 5,000 and 30,000 daltons.[35] Heparin derives its anticoagulant effect by interacting with plasma antithrombin, which in turn inhibits serine proteases participating in plasma-mediated hemostasis.[34] The half-life of heparin is 1 to 2 hours and varies directly with total dose. Heparin is cleared from the circulation both renally and hepatically. Most often, heparin's anticoagulant effect is monitored using the aPTT with a target prolongation of one and one-half to two times control, commonly used for treatment of venous thrombosis.[53] At heparin concentrations exceeding measurement limits of the aPTT, such as during cardiopulmonary bypass or interventional cardiovascular procedures, the activated clotting time (ACT) provides an alternative,

Table 56-1 Anticoagulant Agents

Drug	Site of Action	Route	Plasma Half-life	Excretion	Antidote	Stop before Procedure	Prolongation of PT/aPTT
Unfractionated heparin	IIa/Xa	IV/SC	1.5 hr	Hepatic	Protamine	6 hr	No/Yes
LMWH	Xa	SC	4.5 hr	Renal	Protamine (partial reversal)	12-24 hr	No/No
Streptokinase	Plg	IV	23 min	Hepatic	Antifibrinolytics	3 hr	Yes/Yes
t-PA	Plg	IV	<5 min	Hepatic	Antifibrinolytics	1 hr	Yes/Yes
Warfarin	Vitamin K–dependent factors	Oral	2-4 days	Hepatic	Vitamin K rfVIIa PCCs Plasma	2-4 days	Yes/No
Pentasaccharide	Xa	SC	14-17 hr	Renal	rfVIIa	4 days	No/No
Bivalirudin	IIa	IV	25 min	Hepatic	None	2-3 hr	Yes/Yes
Argatroban	IIa	IV	45 min	Hepatic	None	4-6 hr	*Yes/Yes
Hirudin	IIa	IV	1.5 hr	Renal	PMMA, dialysis	8 hr	*Yes/Yes
APC	Va/VIIIa	IV	2 hr	Hepatic	None	12 hr	No/Yes
Ximelagatran	IIa	Oral	3 hr	Renal	None	24 hr	Yes/Yes

*Argatroban and lepirudin may increase the normal PT 4 to 5 seconds.

APC, activated protein C; HIT, heparin-induced thrombocytopenia; IV, intravenous; LMWH, low molecular weight heparin; PCCs, prothrombin complex concentrates; Plg, plasminogen; PMMA, polymethyl methylacrylate; rFVIIa, recombinant factor VIIa; SC, subcutaneous; IIa, thrombin; t-PA, tissue plasminogen activator.
From Roberts HR, Monroe DM, Escobar MA: Current concepts of hemostasis: Implications for therapy. Anesthesiology 100:722-730, 2004, with permission.

albeit less sensitive, measure of heparin anticoagulation.[54] Heparin's anticoagulant effect is rapidly reversible by protamine administration.[55]

More recently, low-molecular-weight heparins (LMWHs) have gained favor as a result of reduced dosing frequency and the lack of need for monitoring. Owing to shorter saccharide chain lengths, LMWHs exhibit reduced inhibitory activity toward thrombin while retaining factor Xa inhibitory activity.[56] Theoretically, LMWHs should be associated with reduced bleeding tendencies. Regardless, LMWHs have a more predictable pharmacokinetic response, fewer effects on platelet function, and a reduced risk for heparin-induced thrombocytopenia (HIT). Although monitoring of LMWHs is not performed routinely, the PT and aPTT most often are unaffected, necessitating measurement of anti–factor Xa activity. Furthermore, should rapid reversal of LMWH prove necessary, protamine proves only partially effective.[57]

Oral anticoagulant therapy in the form of coumarin derivatives, interferes with hepatic synthesis of vitamin K–dependent coagulation factors: factors II, VII, IX, X, protein C, and protein S.[58] Specifically, coumarin inhibits carboxylation of glutamic acid residues essential for anchoring coagulation factor activation complexes to phospholipid membranes. Coumarin therapy is monitored using the INR (International Normalized Ratio) system derived from the PT. Generally, an INR of 2 to 3 is considered reflective of adequate anticoagulation.[53] In most cases, excessive coumarin anticoagulation is managed by withholding drug administration. However, given a half-life of 2 to 4 days,

Table 56-2 Antiplatelet Agents

Drug	Site of Action	Route	Plasma Half-life	Metabolism	Antidote	Stop before Procedure	Prolongation of PT/aPTT
Aspirin	COX 1-2	Oral	20 min	Hepatic	None	7 days	No/No
Dipyridamole	Adenosine	Oral	40 min	Hepatic	None	24 hr	No/No
Clopidogrel	ADP	Oral	7 hr	Hepatic	None	5 days	No/No
Ticlopidine	ADP	Oral	4 days	Hepatic	None	10 days	No/No
Abciximab	GPIIb-IIIa	IV	30 min	Renal	None	72 hr	No/No
Eptifibatide	GPIIb-IIIa	IV	2.5 hr	Renal	None	24 hr	No/No
Tirofiban	GPIIb-IIIa	IV	2 hr	Renal	Hemodialysis	24 hr	No/No

ADP, adenosine diphosphate; COX, cyclooxygenase diphosphate; IV, intravenous; GP, glycoprotein.
From Roberts HR, Monroe DM, Escobar MA: Current concepts of hemostasis: Implications for therapy. Anesthesiology 100:722-730, 2004, with permission.

more rapid reversal in perioperative settings may be needed. Vitamin K administered orally or parentally in doses of 1 to 2 mg reverses coumarin anticoagulation.[58] More rapid reversal may be achieved by administration of plasma or prothrombin complex concentrates.[59] Recombinant factor VIIa also has proved effective at reversing coumarin-associated bleeding.

Despite relatively short half-lives and increasing fibrin specificity, fibrinolytic drug administration continues to be associated with significant bleeding potential. Bleeding after fibrinolytic drugs proves multifactorial in origin, resulting from proteolytic degradation of fibrin and fibrinogen, proteolysis of cofactors V and VIII, and digestion of platelet glycoprotein surface receptors.[29] In addition, both fibrin and fibrinogen degradation fragments impair platelet function and inhibit assembly of fibrin monomers into strands. Once the fibrinolytic agent is cleared from plasma, antifibrinolytic drugs prove of limited benefit. Therapy must rely on selective repletion of platelet and plasma protein constituents. In many cases, cryoprecipitate will be administered to replace fibrinogen and platelet infusions will be needed to compensate for qualitative platelet dysfunction. Plasma infusions may be required to replete plasma coagulation factors, particularly cofactors V and VIII.

Liver Disease

Hemostatic defects associated with hepatic failure prove complex and multifactorial. Severe liver disease impairs synthesis of coagulation factors, impedes clearance of activated clotting and fibrinolytic proteins, and produces quantitative and qualitative platelet dysfunction. Laboratory findings commonly associated with liver disease include a prolonged PT, possible prolongation of the aPTT, and thrombocytopenia.[60] Prolongation of bleeding time reflects qualitative defects in platelet adhesion and aggregation. Treatment of bleeding in the setting of liver disease most often is based on laboratory abnormalities. Plasma and platelets frequently are administered for acute bleeding. Low fibrinogen concentrations may necessitate cryoprecipitate administration. In addition, low-grade fibrinolysis may benefit from antifibrinolytic drug administration in select settings.

Renal Disease

Platelet dysfunction commonly occurs in association with chronic renal failure, as reflected by a prolonged bleeding time and propensity for bleeding associated with surgery or trauma. Underlying mechanisms appear multifactorial and may include accumulation of guanidinosuccinic acid and nitric oxide in uremic plasma.[61] In addition, red blood cell concentration has been speculated to play a role as correction of anemia results in shortened bleeding times, presumably related to the role of red blood cells in causing platelet margination along the vessel wall under laminar flow conditions.[28] Both dialysis and correction of anemia have been reported to shorten bleeding times in patients with chronic renal failure. Traditionally, cryoprecipitate administration occurs in this setting; however, desmopressin (0.3 μg/kg) and conjugated estrogens similarly may shorten bleeding times.[43] Risks associated with these therapies, and the predictive value of bleeding time for subsequent hemorrhage, remain unclear.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) comprises a pathophysiologic hemostatic response to tissue factor/factor VIIa complex exposure and activation of the extrinsic pathway of coagulation. Numerous underlying disorders may precipitate DIC, including trauma, amniotic fluid embolus, malignancy, sepsis, or incompatible blood transfusions.[62] Most often, DIC presents clinically as a diffuse bleeding disorder associated with consumption of coagulation factors and platelets during widespread microvascular thrombotic activity. Underlying fibrinolysis, providing a counterregulatory mechanism to maintain vascular integrity, proves common as well. Laboratory findings typical of DIC include reductions in platelet count, prolongation of the PT, aPTT, and thrombin time (TT), and elevated concentrations of soluble fibrin and fibrin(ogen) degradation products. Chronic DIC states have been identified with relatively normal screening tests of coagulation accompanied by elevated concentrations of soluble fibrin and fibrin(ogen) degradation products.[63] Management of DIC requires alleviating the underlying condition precipitating hemostatic activation. Otherwise, treatment includes selective blood component transfusions to replete coagulation factors and platelets consumed in the process. Antifibrinolytic therapy generally is contraindicated in DIC owing to potential for catastrophic thrombotic complications.

Prothrombotic States

Thrombophilia, a propensity for thrombotic events, most often manifests clinically in the form of venous thrombosis (frequently deep venous thrombosis of the lower extremity).[64] As with bleeding disorders, thrombophilia may result from inherited or acquired conditions (Table 56-3). In the majority of cases, a precipitating event may be identified.[65] For example, thrombotic complications often occur after surgery, during pregnancy, and in association with obesity or underlying malignancy.[66] Random screening of asymptomatic patients for thrombotic risk has not proved cost effective or clinically efficacious.[67,68] As with bleeding disorders, a careful history focusing on prior thrombotic events, family history of thrombosis, and concurrent drug therapy offers greater predictive value than random screening.

Common Inherited Thrombotic Disorders

Although understanding of thrombotic disorders from a biochemical and molecular level remains limited at present, careful testing may identify an underlying heritable thrombotic

Table 56-3 Hypercoagulable States and Risk for Perioperative Thrombosis

High Risk
Heparin-induced thrombocytopenia (HIT)
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Antiphospholipid antibody syndrome
Moderate Risk
Factor V Leiden genetic polymorphism
Prothrombin G20210A genetic polymorphism
Hyperhomocysteinemia
Dysfibrinogenemia
Postoperative prothrombotic state
Malignancy
Immobilization

predisposition in as many as 50% of patients with venous thromboembolism.[69] Relatively common inherited conditions underlying prothrombotic tendencies include single point mutations in genes for factor V (factor V Leiden) or prothrombin (prothrombin G20210A). In the case of the factor V Leiden mutation, the essential cofactor Va acquires resistance to degradation by protein C.[70] This simple alteration in balance between hemostasis and the protein C counterregulatory system induces a prothrombotic tendency present in approximately 5% of the population. In the case of the prothrombin gene mutation, increased prothrombin concentrations in plasma again generate a hypercoagulable state. Less common inherited forms of thrombophilia include deficiencies of antithrombin, protein C, and protein S.[34] Inherited forms of thrombophilia are characterized by highly variable penetrance affected by blood type, sex, and other confounding variables. In the absence of coexisting precipitating conditions, absolute thrombotic risk secondary to a heritable thrombophilia proves limited.[71] In the presence of a family history or test abnormality suggesting thrombophilia with no history of thrombosis, risks associated with long-term preventive anticoagulation may outweigh potential benefits. After a thrombotic complication, however, these patients most often are managed with life-long anticoagulation.

Common Acquired Thrombotic Disorders

Antiphospholipid Syndrome

Antiphospholipid syndrome describes an acquired autoimmune disorder characterized by venous and/or arterial thromboses as well as recurrent pregnancy loss. This syndrome may occur secondarily to autoimmune disorders such as systemic lupus erythematosus or rheumatoid arthritis, or it may occur in isolation. Characteristically, antiphospholipid syndrome results in mild prolongation of the aPTT and positive testing for lupus anticoagulant or anticardiolipin antibodies.[72] Despite the prolonged aPTT, antiphospholipid syndrome poses no increased bleeding risk but rather increases the potential for thrombosis. Antibodies associated with antiphospholipid syndrome interfere with phospholipids common to many laboratory-based tests of coagulation. Isolated prolongation of an aPTT in a preoperative patient merits consideration of the diagnosis of antiphospholipid syndrome. Patients with this syndrome who have experienced a thrombotic complication are at increased risk for recurrent thrombosis and most often are managed by life-long anticoagulation.[73]

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia describes an autoimmune-mediated drug reaction occurring in as many as 5% of patients receiving heparin therapy. As opposed to other drug-induced thrombocytopenias, HIT results in platelet activation and potential for venous and arterial thromboses.[74,75] Evidence suggests that HIT is mediated by immune complexes (composed of IgG antibody, platelet factor 4 [PF4], and heparin) that bind platelet Fcγ receptors to activate platelets. Anti-PF4/heparin antibodies may "activate" vascular endothelium, monocytes, and macrophages by upregulating tissue factor expression (Fig. 56-4). Patients developing HIT during heparin therapy experience substantially increased risk for thrombosis (odds ratio 20-40, absolute risk 30%-75%).[74,75]

In most cases, HIT manifests clinically as thrombocytopenia occurring 5 to 14 days after initiating heparin therapy. However, with prior heparin exposure, thrombocytopenia or thrombosis may occur within 1 day. In some reported cases, thrombosis occurred simultaneously with thrombocytopenia, providing no warning. Although HIT remains a clinical diagnosis, laboratory testing provides confirmatory evidence. Both functional (i.e., serotonin platelet release assays or heparin-induced platelet aggregation) and quantitative (i.e., solid-phase enzyme-linked immunosorbent assays [ELISA]) tests for PF4/heparin

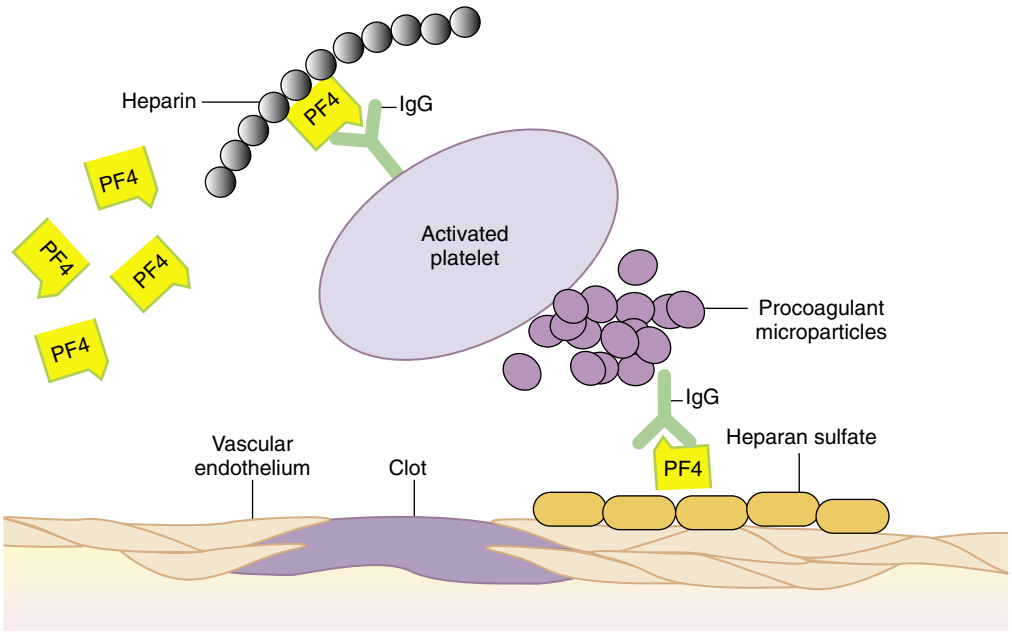

Figure 56-4 Mechanisms underlying thrombosis in heparin-induced thrombocytopenia (HIT). Immune complexes composed of heparin, platelet factor 4 (PF4), and antibodies bind to platelet surface Fcγ receptors to activate platelets. PF4/heparin immune complexes further activate vascular endothelium, monocytes, and macrophages to increase tissue factor expression. *(From Slaughter TF, Greenberg CS: Heparin-associated thrombocytopenia and thrombosis: Implications for perioperative management. Anesthesiology 87:669, 1997, with permission.)*

immune complexes prove beneficial.[75] Recent evidence suggests that PF4/heparin antibodies alone, in the absence of thrombocytopenia or thrombosis, may predict adverse outcomes.[76,77]

A diagnosis of HIT should be entertained for any patient experiencing thrombosis or thrombocytopenia (absolute or relative [≥ 50% reduction in platelet count]) during or after heparin administration. In cases in which HIT is suspected, heparin must be discontinued immediately (i.e., including unfractionated heparin, heparin-bonded catheters, heparin flushes, LMWH). Alternative non-heparin anticoagulation must be administered concurrently. In most cases, a direct thrombin inhibitor (i.e., bivalirudin, lepirudin, argatroban) is substituted for heparin until adequate prolongation of the INR may be achieved with warfarin.[78,79] Typically, PF4/heparin immune complexes clear from the circulation within 3 months. If possible, patients experiencing HIT should avoid future exposure to unfractionated heparin; however, several reports describe subsequent limited perioperative reexposure to unfractionated heparin after laboratory testing to ensure absence of PF4/heparin immune complexes.

Monitoring Coagulation

Traditionally, perioperative coagulation monitoring has focused on (1) preoperative testing to identify patients at increased risk for perioperative bleeding and (2) intraoperative monitoring of heparin therapy during cardiac and vascular surgery. As discussed previously, routine preoperative coagulation testing lacks either predictive value or cost efficacy.[80] However, in patients with a history suggestive of a bleeding disorder or whose surgery may be associated with a high incidence of bleeding or coagulopathy, baseline preoperative coagulation testing may be advisable.

Given the widely acknowledged pharmacokinetic and pharmacodynamic response to heparin, monitoring anticoagulation during cardiac and vascular surgery remains common. Patient-specific factors affecting response to heparin include age, weight, intravascular volume, and plasma/membrane concentrations of antithrombin, heparin cofactor II, platelet factor 4, and other heparin binding proteins. Therefore, patients experience widely divergent anticoagulant responses to identical weight-based doses of heparin. Regardless, monitoring of heparin anticoagulation must be performed if only to prevent the rare, but potentially lethal, complication resulting from inadvertent failure to administer heparin before cardiopulmonary bypass or vascular surgery.

The ideal test of perioperative coagulation would prove simple to perform, accurate, reproducible, diagnostically specific, and cost effective. No current coagulation monitor meets these expectations; however, integrating results from multiple forms of monitoring may provide valuable diagnostic insight into perioperative coagulopathies.

Common Laboratory-Based Measures of Coagulation

Activated Partial Thromboplastin Time

The aPTT assesses integrity of the intrinsic and common pathways of plasma-mediated hemostasis. It measures the time required in seconds for clot formation to occur after mixing a sample of patient plasma with phospholipid, calcium, and an activator of the intrinsic pathway of coagulation (i.e., celite, kaolin, silica, or ellagic acid). In most cases, coagulation factor deficiencies are detectable at factor concentrations below 30% to 40% of normal; however, aPTT reagents vary in sensitivity to factor concentrations, necessitating institutional specific determination of "normal" ranges.[81] Prolongation of the aPTT is evaluated further with mixing studies to determine whether delayed clot formation is attributable to a coagulation factor deficiency or an inhibitor (i.e., heparin, antiphospholipid antibody, fibrin split products). The mixing study is performed by mixing the patient's plasma sample with "normal" donor plasma. In the case of a coagulation factor deficiency, time to clot formation will correct and sequential assays for specific coagulation factor concentrations allow for identification of the deficiency. A common means of confirming heparin prolongation of the aPTT is to perform a thrombin clotting time (TCT). In this test, the patient's citrate-containing plasma sample is mixed with thrombin and time to clot formation is measured in seconds.[39] The most common mechanism underlying prolongation of the TCT is presence of heparin or a direct thrombin inhibitor anticoagulant; however, dysfibrinogenemia or fibrin(ogen) degradation products also may impair clot formation in this setting.

Prothrombin Time

The PT assesses integrity of the extrinsic and common pathways of plasma-mediated hemostasis. It measures time required in seconds for clot formation to occur after mixing a sample of patient plasma with tissue factor (thromboplastin) and calcium. As with the aPTT, thromboplastin test reagents vary in sensitivity, limiting the ability to compare results between laboratories. Given the importance of monitoring PT results for patients on long-term warfarin therapy, the INR was introduced as a means of normalizing PT results among different laboratories.[81] Thromboplastin reagents are tested against an international recombinant standard and assigned an international sensitivity index (ISI) based on results. The INR subsequently is calculated as INR = (patient PT/standard PT)^{ISI} in which the "standard PT" represents the geometric mean of multiple normal samples from the testing laboratory. Institution of the INR substantially reduced interlaboratory variations in the PT. As with the aPTT, prolongation of the PT is assessed further with mixing studies.

Platelet Count and Bleeding Time

The platelet count remains a standard component in screening for coagulation abnormalities. Automated platelet counts are performed in bulk using either optical- or impedance-based measurements. Recommendations regarding optimal platelet counts prove somewhat arbitrary; however, platelet counts exceeding 100,000/μL usually are associated with normal hemostasis. Abnormally low platelet counts merit further assessment, including a visual platelet count using a blood smear. Sample hemodilution and platelet clumping are common causes for false low platelet counts. EDTA-induced platelet clumping, a common artifact explaining thrombocytopenia, may be identified by manually counting platelets or by substituting a citrate anticoagulant, as opposed to EDTA common to platelet collection vacutainers.

Although the bleeding time, as a test of platelet dysfunction, has lost much of its popularity in the past 10 years, many clinicians continue to rely on bleeding time assessment as a measure of platelet function and primary hemostasis. With the use of a commercial template cutting device and a sphygmoma-

nometer adjusted to 40 mm Hg venous pressure, bleeding times of 2 to 10 minutes on the anterior forearm are considered normal. Limitations of the bleeding time include poor reproducibility, time needed to perform the test, and potential for scarring. Furthermore, the bleeding time is affected by numerous confounding variables, including skin temperature, skin thickness, age, ethnicity, anatomic test location, and a host of other factors.[82] In general, the bleeding time has not proved predictive of bleeding and for that reason its use as a preoperative screening test to assess bleeding risk is not recommended.

Common Point-of-Care Measures of Coagulation

Although laboratory-based measures of coagulation remain the mainstay of preoperative coagulation testing, increasing availability of sensitive and specific point-of-care coagulation monitoring may soon offer opportunities to direct blood component and hemostatic drug therapy more specifically without delays inherent to standard laboratory testing. Commercially available point-of-care monitors applicable in the perioperative setting may be considered in four broad categories: (1) functional measures of coagulation or assays that measure the intrinsic ability of blood to generate clot; (2) heparin concentration monitors; (3) viscoelastic measures of coagulation; and (4) platelet function monitors.

Functional Measures of Coagulation

The activated coagulation time (ACT), described by Hattersley in 1966 as a variation of the Lee-White whole blood clotting time, employs a contact activation initiator, typically celite (diatomaceous earth) or kaolin, to accelerate clot formation and reduce time for assay completion. Kaolin is recommended for use in patients receiving the antifibrinolytic drug aprotinin because celite ACTs in this setting are subject to artifactual prolongation.[83] Failure to appreciate this drug-mediated effect may result in inadequate heparin administration if using celite ACT measurements with aprotinin. Whether high plasma concentrations of aprotinin may affect the kaolin ACT remains unclear.

Current commercial ACT monitors automate clot detection. One of the more widely available ACT monitors uses a glass test tube containing a small magnet (Hemochron; International Technidyne, Inc., Edison, NJ). After adding sample blood, the tube is placed into the analyzer and the tube is rotated slowly at 37°C, allowing the magnet to maintain contact with a proximity detection switch. As fibrin clot forms, the magnet becomes entrapped and dislodged from the detection switch, thereby triggering an alarm to signal completion of the ACT. Another ACT device uses a "plumb bob" flag assembly that is raised and released repeatedly to settle in the sample vial containing blood and contact activator (Hepcon and ACT II; Medtronic Blood Management, Parker, CO). With clot formation, the descent rate of the flag through the blood sample slows, triggers an optical detector, and sets off an alarm to signal completion of the ACT.

The ACT in normal individuals is 107 ± 13 seconds (mean ± SD). However, the time at which a patient's "baseline" ACT is measured influences the result.[83] After surgical incision, baseline ACT may decrease. Because the ACT measures clot formation by way of intrinsic and common pathways, heparin and other anticoagulants prolong time to clot formation; however, the ACT proves somewhat resistant to platelet dysfunction and thrombocytopenia.

ACT testing remains a popular perioperative coagulation monitor because of its simplicity, low cost, and linear operating response at high heparin concentrations. Limitations of ACT monitoring include lack of sensitivity at low heparin concentrations and poor reproducibility.[83] ACT tubes containing heparinase improve sensitivity for detecting low heparin concentrations. Further limitations of the ACT include artifactual prolongation of results with hemodilution or hypothermia and the fact that ACT values beyond 600 seconds exceed the linear response range for the assay. Duplicate measurements improve results; however, newer electrochemically based ACT analyzers (ISTAT; Abbott Laboratories, Chicago, IL) improve reproducibility such that single ACT determinations may prove adequate.

The high-dose thrombin time (HiTT) (International Technidyne, Edison, NJ) provides an alternative functional measure of heparin anticoagulation. Primarily employed in cardiac surgical settings, the HiTT assay contains high thrombin concentrations to cleave fibrinogen directly and generate fibrin clot.[84] Given excess thrombin concentrations, clot formation occurs independently of plasma coagulation factors other than fibrinogen. As a result, HiTT is prolonged by heparin (or other thrombin inhibitors), extreme degrees of hypofibrinogenemia or dysfibrinogenemia, and high concentrations of fibrin split products (as occur with fibrinolysis). During most surgical procedures requiring heparin administration, HiTT prolongation will correlate with heparin anticoagulant effect.

Heparin Concentration Measurement

Protamine titration remains the most popular point-of-care method for determining heparin concentration in perioperative settings. Protamine, a strongly basic polycationic protein, directly inhibits heparin in a stoichiometric manner. In other words, 1 mg of protamine will inhibit 1 mg (approximately 100 U) of heparin, thereby forming the basis for protamine titration as a measure of heparin concentration. As increasing concentrations of protamine are added to a sample of heparin-containing blood, time to clot formation decreases until the point at which the protamine concentration exceeds heparin concentration to delay clot formation. If a series of blood samples with incremental doses of protamine are analyzed, the sample in which the protamine and heparin concentrations are most closely matched will clot first. In this manner, protamine titration methodology allows for heparin concentration estimation. Assuming that the heparin-protamine titration curve for an individual patient remains constant throughout the operative period, protamine titration methods may estimate heparin doses required to achieve a desired plasma heparin concentration or the protamine dose needed to reverse a given heparin concentration in blood.[54] Current point-of-care heparin concentration monitors employ automated measurement techniques (Hepcon HMS; Medtronic Blood Management, Parker, CO). Advantages of heparin concentration measurement include sensitivity for low heparin concentrations as well as relative insensitivity to hemodilution and hypothermia. In addition, heparin concentration measures are unaffected by aprotinin.

A major limitation of heparin concentration monitoring is failure to assess directly for an anticoagulant effect. To use an extreme example, consider a patient with a homozygous deficiency of antithrombin; in this setting, heparin concentration

determination alone would fail to identify the lack of anticoagulant effect after heparin administration.

Viscoelastic Measures of Coagulation

Initially developed in the 1940s, viscoelastic measures of coagulation have undergone a resurgence in popularity. The unique aspect of viscoelastic monitors lies in their ability to measure the entire spectrum of clot formation from early fibrin strand generation through clot retraction and eventual fibrinolysis. The thromboelastograph (TEG) (Haemoscope, Niles, IL), developed by Hartert in 1948, uses a small 0.35-mL blood sample placed into a disposable cuvette within the instrument. The cuvette is maintained at a temperature of 37°C and continuously rotates around an axis of approximately 5 degrees. A metal piston attached by a torsion wire to an electronic recorder is lowered into the blood within the cuvette. As clot formation occurs, the piston becomes enmeshed within the clot and rotation of the cuvette is transferred to the piston, torsion wire, and electronic recorder.[85]

Although variables derived from the TEG tracing do not coincide directly with laboratory-based tests of coagulation, the TEG depicts characteristic abnormalities in clot formation and fibrinolysis. Various parameters describing clot formation and lysis are identified and measured by the TEG. For example, the R value (reaction time) measures time to initial clot formation (normal, 7.5 to 15 minutes). Comparable to the whole blood clotting time, addition of a contact activator such as celite or kaolin to the sample cuvette reduces time to results. The R value may be prolonged by a deficiency of one or more plasma coagulation factors or inhibitors such as heparin. Maximum amplitude (MA) provides a measure of clot strength and may be decreased by either qualitative or quantitative platelet dysfunction or decreased fibrinogen concentration. Normal MA is 50 to 60 mm. The alpha angle and K (BiKoatugulierung or coagulation) values measure rate of clot formation and may be prolonged by any variable slowing clot generation such as a plasma coagulation factor deficiency or heparin anticoagulation.[86]

The Sonoclot (Sienco, Inc., Wheat Ridge, CO) provides an alternative viscoelastic measure of coagulation. In contrast to the TEG, Sonoclot immerses a rapidly vibrating probe into a 0.4-mL sample of blood. As clot formation occurs, impedance to probe movement through the blood increases and generates an electrical signal and characteristic clot "signature." The Sonoclot may be used to derive the ACT, as well as to provide information regarding clot strength and fibrinolysis.

Both the TEG and Sonoclot generate characteristic diagrams by translating mechanical resistance to sensor movement in a blood sample to a waveform. One of the more common applications for the TEG has been real-time detection of excess fibrinolysis during liver transplantation. The TEG also may prove beneficial in differentiating surgically related bleeding from that of a coagulopathy. More widespread application of viscoelastic coagulation monitoring has been hindered by lack of specificity associated with abnormal findings and qualitative assay interpretation.[86] Digital automation of these instruments has simplified and improved reproducibility.

Platelet Function Monitors

Assessment of platelet function has proved challenging for a number of reasons. Historically, tests of platelet function have proved costly, time consuming, and technically demanding. Platelet dysfunction may occur as a result of diverse inherited or acquired disorders affecting surface receptors involved in adhesion or aggregation, storage granules, internal activation pathways, phospholipid membranes, or other mechanisms.[51] Lack of standardized quality controls necessitates use of local donors' blood to establish normal control ranges. Furthermore, even established tests such as platelet aggregation lack performance standardization resulting in widely varying results among laboratories. Complicating assessment further is the fact that platelets are highly susceptible to activation or desensitization during sample collection, transport, storage, and processing.

Although viscoelastic measures of coagulation (i.e., TEG/Sonoclot) may detect severe platelet dysfunction, sensitivity and specificity are limited. The standard laboratory-based method for identifying qualitative platelet dysfunction remains optical aggregometry performed using specific platelet agonists and samples of platelet-rich plasma. Flow cytometry employing fluorescent-labeled antibodies provides another sensitive method for quantitating platelet activation, responsiveness, and surface receptor availability.[87] Despite representing standards of care, these measures remain technically challenging, costly, and time-consuming laboratory-based assays.

Fortunately, an increasing array of platelet function assays specifically designed as point-of-care instruments are available.[88,89] As a measure of primary hemostasis, the PFA-100 (Platelet Function Analyzer; Dade International Inc, Miami, FL) increasingly has replaced the bleeding time in assessment of primary hemostasis. Unique among both laboratory-based and point-of-care platelet function monitors, the PFA-100 incorporates high-shear conditions to simulate small vessel injury in the presence of either ADP or epinephrine, both potent platelet activators.[90] Time to clot–mediated aperture occlusion is reported as "closure time." The PFA-100 has proved effective in detecting von Willebrand's disease as well as aspirin-mediated platelet dysfunction. This instrument, as a component of a standardized screening protocol, reduces time to identify and classify platelet dysfunction. Limitations of the PFA-100 include interference by thrombocytopenia and hemodilution.

The HemoSTATUS (Medtronic Blood Systems, Parker, CO) platelet function test exploits the ability of platelet activating factor (PAF) to accelerate clot formation of the kaolin-activated ACT. HemoSTATUS testing is performed on the Medtronic HMS coagulation analyzer employing a 6-channel kaolin ACT cartridge preloaded with serially increasing concentrations of PAF. A clot ratio is determined for each individual patient assay based on the ratio of the PAF-accelerated ACT to the standard ACT. An individual patient's clot ratio is compared with a maximal clot ratio derived from normal volunteers to provide a relative measure of platelet function. In the presence of platelet dysfunction, higher concentrations of PAF are required to achieve a comparable PAF-activated ACT. In cardiac surgery, investigators demonstrated a relationship between platelet dysfunction and postoperative bleeding.[83] Furthermore, the maximal clot ratio as determined by HemoSTATUS improved after desmopressin or platelet administration. Other investigators, however, failed to identify a relationship between platelet dysfunction as measured by HemoSTATUS and postoperative bleeding.

The Rapid Platelet Function Analyzer (RPFA; Accumetrix, San Diego, CA) is an automated turbidimetric whole blood platelet function assay that assesses ability of activated platelets to bind

fibrinogen-coated polystyrene beads. On addition of the whole blood test sample, thrombin receptor activating peptide (TRAP) directly activates platelets within the sample to stimulate glycoprotein IIb/IIIa platelet surface receptor expression. As activated platelets bind and aggregate fibrinogen-coated beads, light transmission through the sample increases to generate a signal. Although the RPFA is simple to operate and provides a rapid bedside measure of platelet function, a baseline reference measurement is required for each patient to calculate the extent of subsequent changes in platelet function.[88] Potential applications of this methodology in the perioperative setting remain unclear.

Plateletworks (Helena Laboratories, Beaumont, TX) employs a hemocytometer to perform automated platelet counts on whole blood samples collected in the presence and absence of platelet-stimulating agonists such as collagen or ADP. The difference in platelet counts before and after agonist addition provides a direct measure of platelet aggregation (i.e., platelet responsiveness) and is reported as "% aggregation." Preliminary investigations demonstrated reasonable correlations between platelet counts performed with the Ichor hematology analyzer and laboratory-based instruments.[88] In addition, the Plateletworks assay proved effective in identifying platelet dysfunction in the setting of glycoprotein IIb/IIIa antagonists and appears to correlate relatively well with laboratory-based measures of platelet aggregation.

Employing a sample of whole blood, the Hemodyne Hemostasis Analyzer (Hemodyne, Richmond, VA) measures platelet contractile force, the force produced by platelets during clot retraction, and clot elastic modulus, a measure of clot rigidity. In preliminary investigations, platelet contractile force was reduced after cardiopulmonary bypass and modestly correlated with perioperative blood loss.

Advances in our understanding of hemostasis and thrombosis at the molecular level have contributed directly to recent biotechnologic innovations in point-of-care testing. Further advances in point-of-care coagulation monitoring offer the opportunity for clinicians to make informed decisions about transfusion therapy and hemostatic drug administration to minimize perioperative bleeding. In considering any point-of-care coagulation testing, one must recognize that results will not necessarily mirror those reported from laboratory-based testing. Reagent sensitivities vary from manufacturer to manufacturer and even one lot of reagent to another. In addition, point-of-care testing typically relies on whole blood samples for testing as opposed to laboratory-based testing using plasma or processed platelets. A final consideration for which point-of-care platelet function testing provides a particularly relevant example is that monitors from different manufacturers measure differing aspects of platelet- or plasma-mediated hemostasis. In the case of platelet function monitors, a dozen instruments purport to measure "platelet function." However, using different instruments one may obtain results varying from "severe" platelet dysfunction to "no platelet dysfunction" in a single sample of blood. Before adopting any point-of-care monitoring, an understanding of the quality assurance requirements, test methodology, and concomitant strengths and weaknesses will be essential to benefit patient care.

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Lawrence T. Goodnough and Terri G. Monk

57 Autologous Transfusion, Recombinant Factor VIIa, and Bloodless Medicine

Key Points

1. Reinfusion of shed blood was employed as early as 1818. Preoperative donation of autologous blood was advocated in the 1930s when the first blood banks were established. Autologous transfusion has grown in popularity in response to the increase in complex operative procedures and new technologic advances that allow its safe use.
2. The two primary reasons for employing autologous transfusion are avoidance of complications associated with allogeneic transfusion and conservation of blood resources.
3. The three types of autologous blood transfusion are preoperative autologous donation (PAD), acute normovolemic hemodilution (ANH), and intraoperative and postoperative blood recovery (salvage).
4. PAD became accepted as a standard practice in certain elective surgical settings such as total joint replacement surgery, so that by 1992 more than 6% of the blood transfused in the United States was autologous. Subsequently, substantial improvements in blood safety have been accompanied by a decline in PAD as well as an interest in ANH as an alternative, lower cost strategy.
5. The criteria for autologous donors are not as stringent as those for allogeneic donors. Transfusion service policies, implemented under the auspices of hospital transfusion committees, differ regarding collection and use of autologous blood with positive viral markers. It is common practice to preclude the blood reactive for hepatitis B surface antigen and human immunodeficiency virus because of concerns for the safety of both patients and personnel. Contraindications include evidence of infection and risk of bacteremia, scheduled surgery for correction of aortic stenosis, and unstable angina.
6. Although autologous blood collections have become popular, the costs associated with their collection are higher than those associated with the collection of allogeneic blood.
7. ANH is the removal of whole blood from a patient while restoring the circulating blood volume with an acellular fluid shortly before an anticipated significant surgical blood loss. The chief benefit of ANH is the reduction of red blood cell losses when whole blood is shed perioperatively at lower hematocrit levels after ANH is completed.
8. Because there is no good evidence that either PAD or ANH is effective at eliminating allogeneic blood transfusions, these autologous blood collection techniques cannot be considered cost-effective alternatives to allogeneic blood.
9. The term *intraoperative blood collection* or *recovery* describes the technique of collecting and reinfusing blood lost by a patient during surgery. The oxygen-transport properties of recovered red blood cells are equivalent to stored allogeneic red blood cells. The survival of recovered blood cells appears to be at least comparable to that of transfused allogeneic red blood cells.
10. Postoperative blood collection denotes the recovery of blood from surgical drains followed by reinfusion, with or without processing. Postoperative autologous blood transfusion is practiced widely but not uniformly.
11. Fibrin glue is derived from a source of fibrinogen and factor XIII (fibrin-stabilizing factor), in which a solution of fibrinogen is mixed with a solution of thrombin and applied to a surgical field. These preparations represent additional allogeneic blood donor exposure. Patients should be made aware of the potential complications as well as the potential benefits.
12. Recombinant factor VIIa (rfVIIa) has been approved for treatment of bleeding in hemophilia patients with inhibitors. It has also been successful in patients without hemophilia with acquired antibodies against factor VIII (acquired hemophilia). Pharmacologic doses of rfVIIa enhance the thrombin generation on already activated

platelets and, therefore, may also be of benefit in providing hemostasis in other situations, such as those characterized by profuse bleeding and impaired thrombin generation.

13. Bloodless medicine and surgery is defined using a team approach that reduces blood loss and employs the best available alternatives to allogeneic transfusion therapy while focusing on the provision of the best possible medical care to all patients. Some patients, however, object to receiving blood or blood products as part of their medical treatment on religious grounds or because of concern about the safety of blood transfusions, regardless of their religious background.

There are three types of autologous blood transfusion: preoperative autologous donation (PAD), acute normovolemic hemodilution (ANH), and intraoperative and postoperative blood recovery (blood salvage). The advantages, disadvantages, applications, and complications vary with the techniques being used.

The two primary reasons for employing autologous transfusion are avoidance of complications associated with allogeneic transfusion and conservation of blood resources. Patients with rare blood phenotypes or alloantibodies can benefit from autologous transfusion because compatible allogeneic blood may not always be available.[1] Potential complications of allogeneic transfusion that can be eliminated or minimized when autologous blood is administered include acute and delayed hemolytic reactions, alloimmunization, allergic and febrile reactions, and transfusion-transmitted infectious diseases. Intraoperative blood recovery may be the only option for providing a sufficient volume of compatible blood when severe, rapid blood loss occurs. ANH provides the only practical source of fresh whole blood.

The role of autologous blood procurement in surgery remains in evolution, based on improved blood safety, increased blood costs, and emerging pharmacologic alternatives to blood transfusion.[2-4] PAD became accepted as a standard practice in certain elective surgical settings such as total joint replacement surgery, so that by 1992 more than 6% of the blood transfused in the United States was autologous.[5] Subsequently, substantial improvements in blood safety have been accompanied by a decline in PAD (Table 57-1) as well as an interest in ANH as an alternative, lower cost strategy.[6] Nevertheless, public perception of blood safety and the reluctance to accept allogeneic blood transfusion in the elective transfusion setting,[7] along with emerging blood inventory shortages, continue to give autologous blood procurement strategies an important role in the surgical arena.

Preoperative Blood Donation

Patient Selection

The criteria for autologous donors are not as stringent as those for allogeneic donors. The American Association of Blood Banks (AABB) Standards for Blood Banks and Transfusion Services requires that the donor-patient's hemoglobin (Hb) be no less than 11 g/dL or the hematocrit (Hct) be less than 33% before each donation.[8] There are no age or weight limits. Patients may donate 10.5 mL/kg, in addition to testing samples. Donations may be scheduled more than once a week, but the last should occur no less than 72 hours before surgery to allow time for restoration of intravascular volume and for transport and testing of the donated blood.

Transfusion service policies, implemented under the auspices of hospital transfusion committees, differ regarding collection and use of autologous blood with positive viral markers. It is common practice to preclude use of blood reactive for hepatitis B surface antigen and the human immunodeficiency virus because of concerns for the safety of both patients and personnel. Some hospitals accept and transfuse autologous blood with any positive viral markers, and denying patients infected with human immunodeficiency virus the opportunity to receive their own blood could be a violation of the Americans with Disabilities Act.[9] Candidates for preoperative collection are stable patients scheduled for surgical procedures in which blood transfusion is likely. For procedures that are unlikely to require transfusion (i.e., a maximal surgical blood ordering schedule [MSBOS] does not suggest that crossmatched blood must be available),[10] the use of preoperative blood collection is not recommended.

Table 57-1 Collection and Transfusion of Autologous Blood* in the United States

Source	1980	1986	1989	1992	1994	1997	1999	2001
Transfused autologous (% of all blood units)	N/A	N/A	369 (3.1%)	566 (5.0%)	482 (4.3%)	421 (3.7%)	367 (3.0%)	359 (2.6%)
Total transfused	9934	12,159	12,059	11,307	11,107	11,476	12,389	13,361
Collected autologous (% of all blood units)	28 (0.25%)	206 (1.5%)	655 (4.8%)	1,117 (8.5%)	1,013 (7.8%)	611 (4.9%)	651 (4.7%)	619 (4.0%)
Total collected	11,174	13,807	13,554	13,169	12,908	12,550	13,649	14,259

*Thousands of units.
N/A, not available.
Modified from Goodnough LT, Brecher ME, Kanter MH, et al: Medial progress: Transfusion medicine. Part I. Blood transfusion. N Engl J Med 340:439-447, 1999.

In selected patient subgroups, preoperative collection of autologous blood can significantly reduce exposure to allogeneic blood. Preoperative autologous collections should be considered for patients scheduled for procedures in which they are likely to receive transfusion, such as major orthopedic procedures, vascular surgery, cardiac or thoracic surgery, and radical prostatectomy.[11] The most common surgical procedures for which autologous blood is predonated are total joint replacements.[12] Autologous blood should not be collected for procedures that seldom (<10% of cases) require transfusion, such as cholecystectomy, herniorrhaphy, vaginal hysterectomy, and uncomplicated obstetric delivery.[13]

In special circumstances, preoperative autologous blood collection can be performed for patients who would not ordinarily be considered for autologous donation. Availability of medical support is important in assessing patient suitability. With suitable volume modification, parental cooperation, and attention to preparation and reassurance, pediatric patients can participate in preoperative collection programs.[14] Patients with significant cardiac disease are considered poor risks for autologous blood donation. Despite reports of safety in small numbers of such patients who underwent autologous blood donation,[15] the risks that are associated with autologous blood donation[16] in these patients are greater than estimated current risks of allogeneic transfusion.[4,5] Table 57-2 summarizes the medical contraindications to a patient's participation in an autologous blood donation program.[17] The collection of autologous blood from women during routine pregnancy is unwarranted,[18] because blood is so seldom needed. PAD can be considered for women with alloantibodies to multiple or high-incidence antigens or with placenta previa or other conditions placing them at high risk for antepartum or intrapartum hemorrhage.[13] AABB Standards no longer permit allogeneic transfusion of unused autologous units ("crossover") because autologous donors are not, in the strictest sense, volunteer donors.[8]

Attempts to stratify patients into groups at high and low risk for needing transfusion based on the baseline level of hemoglobin and on the type of procedure show some promise. In a Canadian study using a point score system, 80% of patients undergoing orthopedic procedures were identified to be at low risk (<10%) for transfusion, and therefore autologous blood procurement for these patients would not be recommended.[19] However, one problem with algorithms that consider the estimated blood loss and preoperative hematocrit is that blood losses are difficult to measure[20] or predict because specific surgical procedures performed even by the same surgeon can be accompanied by a wide range of blood loss.

Table 57-2 Contraindications to Participation in Autologous Blood Donation Programs

1. Evidence of infection and risk of bacteremia
2. Scheduled surgery to correct aortic stenosis
3. Unstable angina
4. Active seizure disorder
5. Myocardial infarction or cerebrovascular accident within 6 months of donation
6. Patients with significant cardiac or pulmonary disease who have not yet been cleared for surgery by their treating physician
7. High-grade left main coronary artery disease
8. Cyanotic heart disease
9. Uncontrolled hypertension

The Role of Aggressive Phlebotomy and the Use of Erythropoietin

The efficacy of PAD is dependent on the degree to which the patient's erythropoiesis increases the production of red blood cells (RBCs).[21] The endogenous erythropoietin response and compensatory erythropoiesis are suboptimal under "standard" conditions of 1 blood unit donated weekly. As shown in Table 57-3, weekly PAD is accompanied by an expansion in RBC volume of 11% (with no oral iron supplementation) to 19% (with oral iron supplementation), which is not sufficient to prevent increasing anemia in patients undergoing PAD. If the erythropoietic response to autologous blood phlebotomy does not maintain the patient's hematocrit level during the donation interval, the donation of autologous blood actually may be harmful[22,23] by causing perioperative anemia and an increased likelihood of allogeneic blood transfusion. A mathematical model[22] has been published to demonstrate the relationship between anticipated surgical blood losses, the desired hematocrit, and the need for autologous blood donation.

In contrast to autologous blood donation under "standard" conditions, studies of "aggressive" autologous blood phlebotomy (twice weekly for 3 weeks, beginning 25 to 35 days before surgery) have demonstrated that endogenous erythropoietin levels do increase, along with enhanced erythropoiesis representing RBC volume expansion of 19% to 26% (see Table 57-3). Exogenous (pharmacologic) erythropoietin therapy to further stimulate erythropoiesis (up to 50% RBC volume expansion[24-26]) during autologous phlebotomy has been approved in Canada and Japan but not in the United States.[27] Perisurgical erythropoietin therapy is approved worldwide for anemic (Hct < 39%) patients scheduled for noncardiac, nonvascular surgeries.

Transfusion Trigger

Disagreement exists about the proper hemoglobin/hematocrit level ("transfusion trigger") at which autologous blood should be given (see Chapter 55).[28] Autologous blood transfusion recipient risks are given in Table 57-4. Perhaps autologous and allogeneic blood transfusion triggers should be similar, because the mortality risks related to allogeneic blood are less than risks of mortality from administrative errors that are associated with both autologous and allogeneic blood.[29]

Preoperative Collection of Components

Preoperative or intraoperative collection of platelet-rich plasma during cardiopulmonary bypass surgery may improve hemostasis and decrease allogeneic exposures.[28] Preoperative collection of autologous platelets, especially in cardiac surgery, is often impractical because patients may be taking antiplatelet drugs; surgery is often scheduled on an emergency basis; and relatively low numbers of platelets are harvested.

Table 57-3 Endogenous Erythropoietin-Mediated Erythropoiesis*

		RBC (mL)		Net RBC		
	Patients (*n*)	Removed (Donated)	Produced	Expansion (%)	Iron Therapy	Reference
Standard Phlebotomy	108	522	351	19	PO	36
	22	590	220	11	None	33
	45	621	331	17	PO	33
	41	603	315	16	PO, IV	33
Aggressive Phlebotomy	30	540	397	19	None	34
	30	558	473	23	PO	34
	30	522	436	21	IV	34
	24	683	568	26	PO	37, 38
	23	757	440	19	PO	39

*Data are expressed as means.
PO, oral; IV, intravenous.
From Goodnough LT, Skikne B, Brugnara C: Erythropoietin, iron, and erythropoiesis. Blood 96:823-833, 2000.

Cost-Effectiveness

Although autologous blood collections have become popular, the costs associated with their collection are higher than those associated with the collection of allogeneic blood. The continued need for autologous blood programs has been questioned because the reduced risk of allogeneic blood transfusions has made PAD poorly cost effective.[30,31]

Acute Normovolemic Hemodilution (ANH)

ANH is the removal of whole blood from a patient while restoring the circulating blood volume with an acellular fluid shortly before an anticipated significant surgical blood loss. To minimize the manual labor associated with hemodilution, the blood should be collected in standard blood bags containing anticoagulant on a tilt-rocker with automatic cutoff via volume sensors. The blood is then stored at room temperature and reinfused during surgery after major blood loss has ceased, or sooner if indicated. Simultaneous infusions of crystalloid (3 mL crystalloid for each 1 mL of blood withdrawn) and colloid (dextrans, starches, gelatin, albumin [1 mL for each 1 mL of blood withdrawn]) have been recommended.[32] Blood units are reinfused in the reverse order of collection since the first unit collected; therefore, the last unit transfused has the highest hematocrit and concentration of coagulation factors and platelets. While this technique has been primarily developed and utilized in Europe, increasing interest in the United States has led to data[3] that show promise in the use of ANH as an alternative method of autologous blood procurement. Augmented hemodilution (replacement of ANH collected in part by synthetic oxygen carriers) is an integral part of many phase III studies designed to obtain U.S. Food and Drug Administration (FDA) approval for artificial oxygen carriers.

Physiologic Considerations

Conserved Red Blood Cell Mass

The chief benefit of ANH is the reduction of RBC losses when whole blood is shed perioperatively at lower hematocrit levels after ANH is completed.[33] Mathematical modeling has suggested that severe ANH to preoperative hematocrit levels of less than 20%, accompanied by substantial blood losses, would be required before the red cell volume "saved" by ANH would become clinically important.[34] A clinical analysis of patients who had undergone "minimal" ANH (representing 15% or less of patients' blood volume) estimated that only 100 mL of RBCs (the equivalent of ½ unit of blood) was "saved" under these conditions.[35] With moderate hemodilution (target hematocrit levels of 28%), the "savings" becomes more substantial. The removal of 3 blood units in a patient who subsequently underwent a blood loss of 2600 mL resulted in surgical RBC losses "saved" by hemodilution of 215 mL, or the equivalent of 1 allogeneic blood unit (Fig. 57-1).[36] This RBC

Table 57-4 Advantages and Disadvantages of Autologous Blood Donation

Advantages	Disadvantages
Prevents transfusion-transmitted disease	Does not affect risk of bacterial contamination
Prevents red cell alloimmunization	Does not affect risk of ABO incompatibility error
Supplements the blood supply	Is more costly than allogeneic blood
Provides compatible blood for patients	Results in wastage of blood not transfused with alloantibodies
Prevents some adverse transfusion reactions	Increased incidence of adverse reactions to autologous donation
Provides reassurance to patients concerned about blood risks	Subjects patient to perioperative anemia and increased likelihood of transfusion

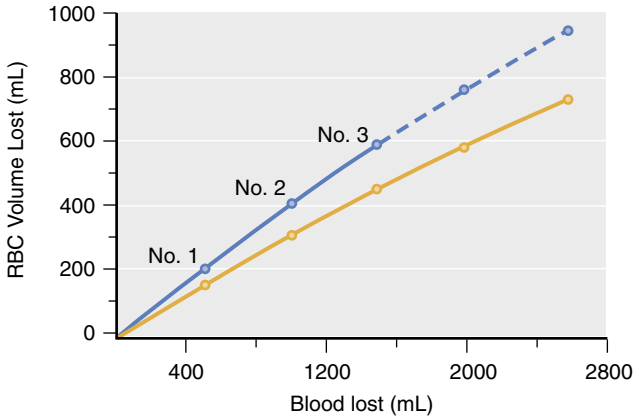

Figure 57-1 The relationship between whole blood volume (mL) lost (*abscissa*) and red blood cell (RBC) volume lost (*ordinate*) in a 100-kg patient undergoing hemodilution: RBC volume lost with 2800 mL whole blood lost intraoperatively after hemodilution of 1500 mL whole blood (*solid blue line*); RBC volume lost with 2800 mL whole blood lost during hemodilution at each of three 500 mL volumes (*solid orange line*); cumulative RBC volume lost intraoperatively, derived for 2800 mL whole blood lost if hemodilution had not been performed (*blue dashed line*). A net of 215 mL reduction in RBC volume lost with hemodilution is illustrated by the divergence of the two curves. (*From Goodnough LT, Grishaber JE, Monk TG, et al: Acute normovolemic hemodilution in patients undergoing radical suprapubic prostatectomy: A case study analysis. Anesth Analg 78:932-937, 1994, with permission.*)

volume approaches the RBC volume expansion generated by autologous blood predonation under standard phlebotomy conditions.

The benefit of ANH as determined in a mathematical model[32] is illustrated in Figure 57-2. An adult with an estimated 5-L blood volume and an initial hematocrit of 40%, with surgical blood losses of up to 3000 mL would result in a hematocrit level that would remain 25% postoperatively without an autologous blood intervention. This level is generally considered safe for patients without known risk factors. In this model, the performance of ANH with initial hematocrit levels of 40% to 45% would allow up to 2500 to 3500 mL of surgical blood loss; yet the nadir level of hematocrit could be maintained at 28%.

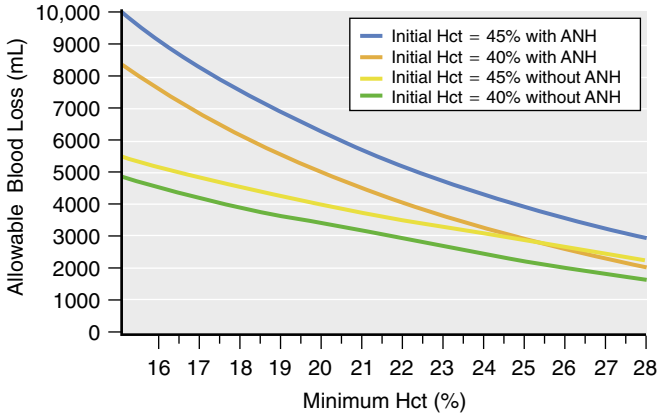

Figure 57-2 The maximum allowable blood loss in a patient with a blood volume of 5000 mL and an initial hematocrit level of 45% (*blue and yellow lines*) or 40% (*green and orange lines*), with and without acute normovolemic hemodilution (ANH). (*From Goodnough LT, Brecher ME, Monk TG: Acute normovolemic hemodilution in surgery. Hematology 2:413-420, 1992, with permission.*)

Improved Oxygenation

Withdrawal of whole blood and replacement with crystalloid or colloid solution decreases arterial oxygen content, but compensatory hemodynamic mechanisms and the existence of surplus oxygen-delivery capacity make ANH safe. A sudden decrease in RBC concentration decreases blood viscosity, thereby decreasing peripheral resistance and increasing cardiac output. If cardiac output can effectively compensate, oxygen delivery to the tissues at a hematocrit of 25% to 30% is as good as, but no better than, oxygen delivery at a hematocrit of 30% to 35%.[37]

Preservation of Hemostasis

Because blood collected by ANH is stored at room temperature and is usually returned to the patient within 8 hours of collection, there is little deterioration of platelets or coagulation factors. The hemostatic value of blood collected by ANH is of questionable benefit for orthopedic or urologic surgery because plasma and platelets are rarely indicated in this setting. Its value in protecting plasma and platelets from the acquired coagulopathy of extracorporeal circulation in cardiac surgery (known as "blood pooling") is better established.[38]

Clinical Studies

Prospective, randomized studies in radical prostatectomy,[39] knee replacement,[40] and hip replacement[41] suggest that ANH can be considered equivalent to PAD as a method of autologous blood procurement. Additional, selected clinical trials of ANH are summarized in Table 57-5.[42-48] Reviews[49] and commentaries[50] on the merits of ANH have been published. When ANH and reinfusion are accomplished in the operating room by on-site personnel, the procurement and administration costs are minimized. Blood obtained during ANH does not require the commitment of the patient's time, transportation, costs, and loss of work time that can be associated with PAD. The wastage of PAD units (approximately 50% of units collected)[13] also is eliminated with ANH. Additionally, autologous blood units procured by ANH require no inventory or testing costs. Because the blood never leaves the patient's room, ANH minimizes the possibility of an administrative or clerical error that could lead to an ABO-incompatible blood transfusion and death, as well as bacterial contamination associated with prolonged storage at 4°C.

Some practical considerations are important regarding an ANH program. Decisions about ANH should be based on the surgical procedure and on the patient's preoperative blood volume and hematocrit, target hemodilution hematocrit, and other physiologic variables. The institution's policy and procedures and the mechanisms for educating staff should be established and periodically reviewed.

There should be careful monitoring of the patient's circulating volume and perfusion status during the procedure. Blood must be collected in an aseptic manner, ordinarily into standard blood collection bags with citrate anticoagulant. Units must be properly labeled and stored. The label must contain, at a minimum, the patient's full name, medical record number, date and time of

Table 57-5 Selected Clinical Trials of Acute Normovolemic Hemodilution (ANH)

	Estimated Blood Loss (mL)			Postoperative Hematocrit (%)			Allogeneic RBC-Containing Units or Liters ( ) Transfused			
Type of Surgery	**Control**	**ANH**	***P* Value**	**Control**	**ANH**	***P* Value**	**Control**	**ANH**	***P* Value**	**Reference**
Vascular	2250	2458	NS	NR	33.0	NR	6.0	2.6	<0.01	60
Liver resection	1479	1284	NS	37.9	33.8	< .01	3.8	0.4	<0.001	61
Hip arthroplasty	1800	2000	NS	38.4	32.4	NS	(2.1)	(0.9)	NR	62
Spinal fusion	5490	1700	< .005	NR	28.7	NR	8.6	<1	<0.001	63
Colectomy	NR	NR	NR	37.0	35.0	NR	2.4	0	NR	64
Prostate	1246	1106	NS	35.5	31.8	< .001	0.16	0	NS	65
Prostate	1717	1710	NS	29.5	27.9	< .5	0.30	0.13	NS	66

NR, not reported; NS, not significant.
Modified from Brecher ME, Rosenfeld M: Mathematical and computer modeling of acute normovolemic hemodilution. Transfusion 34:176-179, 1994.

collection, and the statement "For Autologous Use Only." Room temperature storage should not exceed 8 hours. If more time elapses between collection and transfusion, the blood should be stored in a monitored refrigerator. Suggested criteria for patient selection are listed in Table 57-6.

Cost-Effective Analysis of ANH versus PAD

Because there is no good evidence that either PAD or ANH is effective at eliminating allogeneic blood transfusions, autologous blood collection techniques cannot be considered cost-effective alternatives to the use of allogeneic blood. The majority of the trials evaluating the efficacy of ANH compare this blood conservation technique to PAD because autologous blood donation is considered to be a "standard of care" for many elective surgical procedures in the United States and many patients request its use. Medicolegal concerns may also prevent the inclusion of a treatment arm consisting of only allogeneic blood transfusion because blood safety acts in several states mandate that physicians discuss autologous blood options before elective surgical procedures.[3] All of these studies found ANH to be equivalent to PAD in eliminating the need for allogeneic blood transfusions and suggest that ANH and PAD are equivalent for avoiding allogeneic blood transfusions during elective surgery.[51] Long-term outcomes including anesthesia and surgery times, intraoperative hemodynamic values, and length of hospital stays were also equivalent in PAD and ANH.

Because ANH and PAD appear to have equivalent efficacy, it is not possible to do a cost-effectiveness evaluation comparing these autologous transfusion modalities. However, if two interventions have equivalent outcomes but different costs, medical economists often perform a cost minimization analysis to determine the least-cost alternative.[52] Despite the fact that only a few studies include economic evaluations comparing the cost of autologous blood techniques, all of these studies demonstrate that ANH is much less costly than PAD.[51] ANH can, therefore, be considered a cost-minimizing technique for procuring autologous blood before elective surgery.

Table 57-6 Criteria for Selection of Patients for Acute Normovolemic Hemodilution

1. Likelihood of transfusion exceeds 10% (i.e., blood requested for crossmatch according to a maximum surgical blood order schedule)
2. Preoperative hemoglobin level of at least 12 g/dL
3. Absence of clinically significant coronary, pulmonary, renal, or liver disease
4. Absence of severe hypertension
5. Absence of infection and risk of bacteremia

Intraoperative Blood Collection

The term *intraoperative blood collection* or *recovery* describes the technique of collecting and reinfusing blood lost by a patient during surgery. The oxygen-transport properties of recovered RBCs are equivalent to those of stored allogeneic RBCs. The survival of recovered RBCs appears to be at least comparable to that of transfused allogeneic RBCs.[53] Intraoperative collection is contraindicated when certain procoagulant materials (e.g., topical collagen) are applied to the surgical field, because systemic activation of coagulation may result. Microaggregate filters (40 ∝m) are most often used, because recovered blood may contain tissue debris, small blood clots, or bone fragments.

Cell washing devices can provide the equivalent of 12 units of banked blood per hour to a massively bleeding patient.[53] Data regarding adverse events of reinfusion of recovered blood have been published.[54] Air embolus is a potentially serious problem. Three fatalities from air embolus were reported over a 5-year interval to the New York State Department of Public Health, for an overall fatality risk of 1 in 30,000.[30] Hemolysis of recovered blood can occur during suctioning from the surface instead of from deep pools of shed blood. For this reason, manufacturers' guidelines recommend a maximum vacuum setting of no more than 150 mm Hg: one study found that vacuum settings as high as 300 mm Hg could be used, when necessary, without causing excessive hemolysis.[55] Patients exhibit a level of plasma-free hemoglobin that is usually higher than after allogeneic transfusion. The clinical importance of free hemoglobin in the concentrations usually seen has not been established, although excessive free hemoglobin may indicate inadequate washing. Positive bacterial cultures from recovered blood are sometimes observed;

however, clinical infection is rare.[56] Most programs use machines that collect shed blood, wash it, and concentrate the RBCs. This process typically results in 225-mL units of saline-suspended RBCs with a hematocrit of 50% to 60%.

Clinical Studies

As with PAD and ANH, collection and recovery of intraoperative autologous blood should undergo scrutiny with regard to both safety and efficacy. A controlled study in cardiothoracic surgery demonstrated a lack of efficacy when transfusion requirements and clinical outcomes were followed.[56] A second study found that only a minority of patients undergoing major orthopedic and cardiac surgery achieved cost equivalence with intraoperative blood recovery using semi-automated instruments compared with banked blood.[57] Although the collection of a minimum of one blood unit equivalent is possible for less expensive (with unwashed blood) methods, at least two blood unit equivalents need to be recovered using a cell-recovery instrument (with washed blood) to achieve cost-effectiveness.[58] The value of intraoperative blood collection is apparent for vascular surgeries with large blood losses, such as aortic aneurysm repair and liver transplantation.[59] However, a prospective, randomized trial[58] of intraoperative recovery and reinfusion in patients undergoing aortic aneurysm repair showed no benefit in a reduction of allogeneic blood exposure. The value of this technology may be in cost savings and blood inventory considerations in patients with substantial blood losses.

Medical Controversies

Collection devices that neither concentrate nor wash shed blood before reinfusion increase the risk of adverse effects. Shed blood has undergone varying degrees of coagulation/fibrinolysis and hemolysis, and infusion of large volumes of washed or unwashed blood has been described in association with disseminated intravascular coagulation.[59] In general, blood collected at low flow rates or during slow bleeding from patients who are not systemically anticoagulated will have undergone coagulation and fibrinolysis and will not contribute to hemostasis on reinfusion. The high suction pressure and surface skimming during aspiration and the turbulence or mechanical compression that occurs in roller pumps and plastic tubing make some degree of hemolysis inevitable. High concentrations of free hemoglobin may be nephrotoxic to patients with impaired renal function. Many programs limit the quantity of recovered blood that may be reinfused without processing. To minimize hemolysis, the vacuum level should ordinarily not exceed 150 mm Hg, although higher levels of suction may occasionally be needed during periods of rapid bleeding.

An alternative approach is to collect blood in a canister system designed for direct reinfusion and then to concentrate and wash the recovered RBCs in a blood bank cell washer. Intraoperatively collected and recovered blood must be handled in the transfusion service laboratory like any other autologous unit. The unit should be reinfused through a filter.

Some practical considerations for cell recovery programs are listed in Table 57-7. If collected under aseptic conditions with a saline-wash device and if properly labeled, blood may be stored at room temperature for up to 4 hours or at 1° to 6°C for up to 24 hours, provided that storage at 1° to 6°C is begun within 4 hours of ending the collection.[8] Note that the allowable interval of room temperature storage is shorter for recovered blood (4 hours) than for ANH blood (8 hours). Storage times are the same for recovered blood whether unwashed or washed.

Table 57-7 Practical Considerations for Intraoperative Cell Recovery, Storage, and Reinfusion

1. If not transfused immediately, units collected from a sterile operating field and processed with a device for intraoperative blood collection that washes with 0.9% saline, USP, shall be stored under one of the following conditions prior to initiation of transfusion:
   a. At room temperature for up to 4 hours after terminating collection
   b. At 1-6°C for up to 24 hours, provided that storage at 1-6°C is begun within 4 hours of ending the collection.
2. Transfusion of blood collected intraoperatively by other means shall begin within 6 hours of initiating the collection.
3. Each unit collected intraoperatively shall be labeled with the patient's first name, last name, and hospital identification number; the date and time of initiation of collection and of expiration; and the statement "For Autologous Use Only."
4. If stored in the blood bank, the unit shall be handled like any other autologous unit.
5. The transfusion of shed blood collected under postoperative or post-traumatic conditions shall begin within 6 hours of initiating the collection.

Postoperative Blood Collection

Postoperative blood collection denotes the recovery of blood from surgical drains followed by reinfusion, with or without processing.[60] In some programs, postoperative shed blood is collected into sterile canisters and reinfused, without processing, through a microaggregate filter. Recovered blood is dilute, is partially hemolyzed and defibrinated, and may contain high concentrations of cytokines. For these reasons, most programs set an upper limit on the volume (e.g., 1400 mL) of unprocessed blood that can be reinfused. If transfusion of blood has not begun within 6 hours of initiating the collection, the blood must be discarded.

Clinical Studies

The evolution of cardiac surgery has been accompanied by broad experience in postoperative conservation of blood. Postoperative autologous blood transfusion is practiced widely but not uniformly. Prospective and controlled trials have disagreed over the efficacy of postoperative blood recovery in cardiac surgery patients; at least three such studies have demonstrated lack of efficacy,[61,62] whereas at least two studies have shown benefit.[63] The disparity of results in these studies may be explained, in part, by differences in transfusion practices. Modification of physician transfusion practices may have been an uncredited intervention in these blood conservation studies.

In the postoperative orthopedic surgical setting, a number of reports have similarly described the successful recovery and reinfusion of washed[64] and unwashed[65] wound drainage blood from patients undergoing arthroplasty. The volume of reinfused

drainage blood has been reported to be as much as 3000 mL and averages more than 1100 mL in patients undergoing cementless knee replacement.[65] Because the RBC content of the fluid collected is low (hematocrit levels of 20%) the volume of RBCs reinfused is often small.[66] A prospective, randomized study of postoperative salvage and reinfusion in patients undergoing total knee or hip replacement found no differences in perioperative hemoglobin levels or allogeneic blood transfusions between patients who did or did not have joint drainage devices.[67]

The safety of reinfused unwashed orthopedic wound drainage has been controversial. Theoretical concerns have been expressed regarding infusion of potentially harmful materials in recovered blood, including free hemoglobin, RBC stroma, marrow fat, toxic irritants, tissue or methacrylate debris, fibrin degradation products, activated coagulation factors, and complement. Although two small studies have reported complications,[68,69] several larger studies have reported no serious adverse effects when the drainage was passed through a standard 40-∝m blood filter.[64,65,70]

The potential for decreasing exposure to allogeneic blood among orthopedic patients undergoing postoperative blood collection, whether washed or unwashed, is greatest for cementless bilateral total knee replacement, revision hip or knee replacement, and long-segment spinal fusion. As in the case of intraoperative recovery, blood loss must be sufficient to warrant the additional cost of processing technology.[71] As in selection of patients who can benefit from PAD and ANH, prospective identification of patients who can benefit from intraoperative and postoperative autologous blood recovery is possible if patients' preoperative hemoglobin level, anticipated surgical blood losses, and the perioperative "transfusion trigger" are taken into account.

Fibrin Glue

Fibrin glue and fibrin gel are blood derivatives rather than pharmacologic agents, but their increasing use as an intervention in surgical hemostasis and blood conservation deserves mention. Fibrin glue is derived from a source of fibrinogen and factor XIII (fibrin-stabilizing factor), in which a solution of fibrinogen is mixed with a solution of thrombin and applied to a surgical field.[72] These agents can be applied directly to wounds that display diffuse microvascular bleeding or can be used to seal vascular grafts. It is important to note that these preparations represent additional allogeneic blood donor exposure. Alternatively, the source of fibrinogen and factor XIII can be derived from as little as 40 mL of the patient's autologous blood.[73]

Patients should be made aware of the potential complications as well as the potential benefits of its use.[74] One case of anaphylactic reaction after a total of only 8 mL of fibrin glue administration[75] and one case of human immunodeficiency virus transmission[76] have been described. A solvent-detergent–treated fibrin glue preparation is now available.[77] Reports of two cardiac surgery patients who presented with acquired thrombin or factor V inhibitors, each of whom had been previously exposed to bovine thrombin,[78] cause concern over the potential toxicities associated with the use of either allogeneic or autologous fibrin sealants. Issues of informed consent for administration of these blood products and criteria for their use need to be addressed.

Recombinant Factor VIIA

Recombinant factor VIIa (rfVIIa) has been approved for treatment of bleeding in hemophilia patients with inhibitors. Pharmacologic doses of rfVIIa have been found to enhance the thrombin generation on activated platelets and, therefore, may also likely be of benefit in providing hemostasis in other (nonapproved) situations characterized by profuse bleeding and impaired thrombin generation,[79] such as in patients with thrombocytopenia and in those with functional platelet defects.[80,81] Additionally, it has been used successfully in a variety of less well-characterized surgical bleeding situations with dilutional or consumptive coagulopathies and in patients with impaired liver function.[82-84] Policies for the approval of rfVIIa therapy in nonapproved settings should therefore undergo periodic review and revision as relevant new information and data are generated.[85] Because of the recent trends in rfVIIa usage in nonapproved settings, significant concerns about its safety, efficacy, and costs have arisen. Additionally, dosing of rfVIIa for these potentially broad clinical applications is not standardized.

Complex Surgery and Traumas Resulting in Profuse Bleeding

A hemostatic effect has been demonstrated after the administration of rfVIIa in a limited number of patients after trauma and bleeding.[82,83] Seven trauma patients treated with rfVIIa after failure of conventional measures to achieve hemostasis[83] reported cessation of diffuse bleeding and correction of abnormal coagulation assays; three of the seven patients died of reasons other than bleeding or of thromboembolism.

Anecdotal case reports have been published that describe the successful use of rfVIIa in patients with substantial perisurgical bleeding. The experience of rfVIIa use in trauma with excessive bleeding as well as in profuse postoperative bleeding, based largely on case reports, has indicated a hemostatic effect of rfVIIa given in doses ranging from 20 to 120 ∝g/kg. The issue of preemptive, preoperative rfVIIa (40-90 ∝g/kg) was studied in nine patients with coagulopathy and urgent neurosurgical intervention.[86] Post-rfVIIa coagulation parameters normalized as early as 20 minutes after infusion, with no noted procedural or operative complications. No associated thromboembolic complications were observed. Subsequently, a prospective, randomized study of rfVIIa (20 ∝g/kg or 40 ∝g/kg) versus placebo perioperatively in 36 patients undergoing radical retropubic prostatectomy found that the cohorts receiving rfVIIa had substantially less median operative blood loss compared with placebo (1235 mL, 1089 mL, and 2688 mL, respectively).[87] This study was not powered to demonstrate reductions in blood transfusions.

In single center series, 51 patients undergoing rfVIIa therapy for intractable blood loss after cardiac surgery were compared with 51 matched controls.[88] The authors found that bleeding 1 hour after therapy was reduced in the treated cohort, compared with the control cohort. No differences in serious adverse events were noted. A subsequent review from the same institution of 114 cardiac surgery patients who received rfVIIa compared with 541 concurrent patients who did not receive rfVIIa concluded that rfVIIa is not associated with increased risk

of adverse events and early treatment may be associated with better outcomes.[89] A second series of rfVIIa in 53 patients during cardiac surgery found a significant decrease in doses of all blood products.[90] However, a third series of 24 patients treated with rfVIIa for refractory bleeding after cardiac surgery, compared with 24 matched controls, found no differences in red blood cells or plasma units transfused over a 24-hour period.[91]

Recently, a pilot study of 20 patients undergoing complex noncoronary cardiac surgery who were randomized to receive either placebo or rfVIIa (90 ∝g/kg) prophylactically after completion of cardiopulmonary bypass and reversal of heparin found a significantly reduced need for allogenic transfusion in the cohort who received rfVIIa.[92] However, a pediatric study of 76 pediatric patients undergoing surgery for congenital heart disease found no benefit of rfVIIa (40 ∝g/kg) prophylaxis as determined by chest closure time after cardiopulmonary bypass.[93]

Two randomized placebo-controlled trials of rfVIIa as adjunctive therapy for control of bleeding in trauma patients were published.[94] In an analysis of 143 patients with blunt trauma, the percentage of patients alive at 48 hours receiving more than 20 units of RBCs was reduced from 33% to 14% ($P = .03$). For 143 patients with penetrating trauma, the reduction from 19% to 7% was not significant ($P = .08$). No differences in serious adverse events between the rfVIIa-treated and placebo cohorts were observed.

Dose

A retrospective review of 40 patients with coagulopathic bleeding in a variety of medical and surgical settings from 13 hospitals in an Internet-based database (excluding history of coagulopathy and trauma patients) who received rfVIIa (15 to 180 ∝g/kg, with 38 patients receiving fewer than five doses) found that 32 (80%) achieved complete ($n = 18$) or partial ($n = 14$) cessation of bleeding.[95] Responses occurred in all dose ranges, without any evidence of a dose-response effect; the percentages of complete, partial, or no response were not different at doses of less than 70 ∝g/kg, 70 to 90 ∝g/kg, or more than 90 ∝g/kg (Fig. 57-1). Significantly fewer blood products were administered after rfVIIa therapy. Twenty-three (58%) patients died, reflecting the unstable clinical status of the patients at the decision point for considering rfVIIa therapy. On the basis of this study, we have recommended a nonweight dosage strategy in which a 4.8-mg vial administered to an adult patient weighing 50 to 100 kg represents a 100-∝g/kg to 50-∝g/kg dose.[85]

Patients Receiving Oral Anticoagulant Therapy

One report describes the use of rfVIIa in seven adult patients with prolonged international normalized ratio (INR), three of whom required surgery. The doses administered ranged from 20 to 90 ∝g/kg, and all patients were reported to have a positive outcome.[96] These observations indicate that rfVIIa may be used to reverse the effect of warfarin (Coumadin) or other vitamin K–antagonist therapy in cases in which the administration of vitamin K alone has been found to be insufficient. Two published reports of 15 total patients treated with rfVIIa for reversal of excessive anticoagulation with warfarin support a dosage of 20 ∝g/kg, or 1.2 mg for an adult patient.[97,98] A recent review of 12 patients with acute warfarin-associated intracranial hemorrhage over this same time period at one institution, all of whom received rfVIIa (30 to 135 ∝g/kg) as well as vitamin K (10 mg/day · 3) and fresh frozen plasma (1307 ± 652 mL) for treatment, found that treatment was associated with rapid correction of the INR and that single doses appeared safe in this high-risk population.[99]

Patients with Impaired Liver Function

A multicenter trial studied 71 patients with advanced liver disease who were undergoing laparoscopic liver biopsy.[100] The patients were randomized to receive one of four doses of rfVIIa (5, 20, 80, or 120 ∝g/kg); 48 (74%) of 65 patients achieved hemostasis within 10 minutes. One thrombotic event and one case of disseminated intravascular coagulation were reported, not believed by the authors to be related to rfVIIa therapy. Despite these complications, the authors concluded that laparoscopic liver biopsy can be performed safely and reliably by using rfVIIa in patients in whom the standard procedure might be contraindicated because of coagulopathy.

The safety and efficacy of rfVIIa in patients with cirrhosis with upper gastrointestinal hemorrhage was studied in a randomized study of 245 patients with a composite primary endpoint, including failure to control bleeding within 24 hours after first dose, failure to prevent rebleeding within 24 hours to 5 deaths, or death within 5 days.[101] There were no significant differences found between the placebo compared with the rfVIIa (8 doses at 100 mg/kg over 30 hours) cohorts: failures on composite endpoint were 16% and 14%, respectively ($P = .72$). Similarly, a randomized, controlled study of patients with cirrhosis who underwent partial hepatectomy found no benefit to rfVIIa compared with placebo when the volume of blood products administered, or percentage of patients transfused, was analyzed.[102] Finally, no value for peri-adjuvant rfVIIa was found in patients undergoing liver transplantation, when compared with placebo.[103]

Patients with Normal Hepatic Function

A prospective, randomized, double-blind multicenter study evaluated the efficacy of two different doses of rfVIIa compared with placebo on RBC transfusions for adult patients without cirrhosis undergoing partial hepatectomy.[104] Mean RBC volume transfused was 1024, 1354, and 1036 mL for placebo, 20 ∝g/kg rfVIIa, and 80 ∝g/kg rfVIIa, respectively ($P > .05$). Similarly, there were no differences in percentage of patients transfused and in intraoperative blood losses. Serious adverse events were not different.

Patients with Hemorrhagic Stroke

A recent prospective, randomized, double-blind placebo-controlled trial of three doses of rfVIIa compared with placebo was reported in patients presenting with acute (<4 hr) hemorrhagic stroke.[105] At 24 hours after treatment, the percentage of patients showing expansion was 28%, 16%, 14%, and 11% for the placebo, 40 ∝g/kg, 80 ∝g/kg, and 160 ∝g/kg, respectively ($P < .05$

treatment cohorts versus placebo). Percentage of patients with mortality was 29%, 18%, 18%, and 19%, respectively ($P < .05$, treatment cohorts versus placebo). Impairment scored at 90 days was also improved in the treatment cohorts compared with placebo. A follow-up, clinical trial (placebo, 40 ∝g/kg, and 80 ∝g/kg) failed to show any benefit for rfVIIa compared with placebo.[106]

Safety

Of the more than 170,000 standard doses of rfVIIa given after its approval (almost all to patients with hemophilia and inhibitors), only rare (<1:11,300) thrombotic events have been reported.[79] Thrombotic complications have also been reported with rfVIIa therapy in patients without inhibitors to factor VIII or IX. An acute cerebrovascular accident and death occurred in a clinical trial of rfVIIa (90 ∝g/kg) before and after minor surgery or dental procedures in patients with factor XII deficiency.[107] The last of 10 patients enrolled in an open label trial, dose-escalation trial to prevent rebleeding after subarachnoid hemorrhage developed middle cerebral artery thrombosis after receiving rFVIIa.[108] In a high-risk trauma population, 3 of 40 (7.5%) patients who were deemed at high risk for thrombosis developed thrombotic complications after receiving rfVIIa.[109]

Although SAE and thrombotic events have been distributed evenly among treatment and placebo cohorts in several large randomized clinical trials of patients undergoing radical prostatectomy,[87] trauma,[96] upper gastrointestinal bleeding,[101] or partial hepatectomy,[107] there was an uneven distribution of thromboembolic events in the clinical trial of patients with hemorrhagic stroke[107]; total events were 2 (2%), 7 (6%), 4 (5%), and 10 (10%) for the placebo, 40, 80, and 160 ∝g/kg cohorts, respectively. Most of these events were arterial, including thrombotic stroke and myocardial infarction. Whether these serious adverse events are attributed to rfVIIa or to a population at risk for these events will need to be determined in a follow-up clinical trial.

A summary of thromboembolic events reported to the FDA from March 1999 to December 2004 indicated a total of 151 events in settings with unlabeled indications.[110] These included deep venous thrombosis (42), cerebrovascular accidents (39), acute myocardial infarctions (34), pulmonary thromboembolus (32), arterial thrombosis (26), and clotted devices (10). Thirty-eight percent of cases had concomitant use of other hemostatic agents. In 36 (72%) of 50 reported deaths, rfVIIa was listed as the probable cause. The authors concluded that randomized clinical trials are necessary to demonstrate safety and efficacy of rfVIIa in nonapproved settings. A subsequent report analyzed safety data from 13 clinical trials in patients treated with rfVIIa for cirrhosis, trauma, or reversal of anticoagulant therapy.[111] The authors reported thrombotic adverse events in 5.3% of patients who received placebo, compared with 6.0% in patients who received rfVIIa ($P = .57$).

In cardiac surgery patients, cohort-matched studies[87,88] and a systematic review[112] found no differences in serious adverse events in patients treated with rfVIIa. We reported a patient who had a fatal thrombosis after administration of activated prothrombin complex concentrate who had also received two doses of rfVIIa more than 6 hours earlier, while supported by extracorporeal membrane oxygenation.[113] Because of this experience, we recommend that patients should not receive combination therapy with both activated prothrombin complex concentrate and rfVIIa.

On the basis of these reports, use of activated factor concentrates should be used with caution in patients with known hypercoagulability (e.g., history of thrombotic complications, established thrombotic disorders such as factor V Leiden, antiphospholipid syndrome) or who have excessive bleeding in the setting of disseminated intravascular coagulation or other states of generalized activation of the hemostatic system (e.g., after cardiac surgery, patients on extracorporeal membrane oxygenation or ventricular assist devices) based on the potential for development of localized or systemic intravascular thrombosis.

In summary, dose, timing, and safety of rfVIIa have yet to be defined in this diverse patient population and formal prospective trials are needed. Consensus-based recommendations on the use of rfVIIa in nonapproved settings have been developed.[114] The decision on when and where to use rfVIIa for patients with uncontrolled bleeding continues to be one that must be made by individual physicians, assisted by their hospital pharmacotherapeutic or transfusion committees.[115]

Bloodless Medicine

Some patients object to receiving blood or blood products as part of their medical treatment. Many of these individuals are Jehovah's Witnesses and refuse the transfusion of another person's blood based on strict interpretations of both Old and New Testament texts that refer to the sanctity of blood.[116] This religious group currently has over 6 million active and 14 million associated followers worldwide, and its publications are translated into over 200 different languages. In the 1980s, bloodless medicine programs were started at the request of Jehovah's Witness patients who wanted hospitals where they could receive the best medical care and have their desire to avoid allogeneic blood transfusions respected.[116]

Recently, a substantial proportion of the population in the United States, regardless of their religious background, has voiced concern about the safety of blood transfusions. A telephone survey found that only 61% of the respondents believed the blood supply in the United States was safe, and 33% said that they would refuse blood transfusions if hospitalized.[7] In the past decade, public concern about problems with the blood supply and shortages in the availability of volunteer blood donors have also led to the development of bloodless medicine centers.

Bloodless medicine and surgery is defined as a team approach "that reduces blood loss and uses the best available alternatives to allogeneic transfusion therapy while focusing on the provision of the best possible medical care to all patients."[1] The objectives of a bloodless medicine program should include "providing leadership within an institution for bloodless medicine and being the advocate for patients not accepting transfusion."[117] All clinicians should realize that a philosophy of blood management that incorporates the avoidance of unnecessary blood transfusions in all patients is appropriate even if a bloodless medicine center does not exist at their institutions.[1] The general principles of surgical and anesthetic bloodless management are detailed in Table 57-8.[118]

Table 57-8 Surgical and Anesthetic Principles of Bloodless Medicine Management

Preoperative Assessment and Planning
Management of anemia
Management of anticoagulation and congenital and drug-induced coagulopathies
Prophylactic interventional radiology and embolization
Prescribing and scheduling of cell salvage apparatus
Restricted diagnostic phlebotomy
Intraoperative Blood Conservation
Meticulous surgical hemostasis
Blood salvage
Hemodilution
Pharmaceutical enhancement of hemostasis
Maintenance of normothermia
Surgical positioning to minimize blood loss and hypertension
Postoperative Blood Conservation
Blood salvage
Tolerance of anemia
Optimum fluid and volume management
Restricted diagnostic phlebotomy
Adequate analgesia, maintenance of normothermia
Maintain appropriate fluid resuscitation. Significant normovolemic anemia is well tolerated in hemodynamically stable patients.
In actively bleeding patients, the first management priority must be to stop the bleeding. Avoid attempts to normalize blood pressure until bleeding is stopped.
Prevent or treat coagulation disorders promptly.
Oral or parenteral iron may be used to improve iron stores. Exogenous erythropoietin therapy effectively increases RBC mass.
Hematology and Oncology
Aggressive exogenous erythropoietin therapy and iron therapy for the prophylaxis of anemia
Individualized chemotherapy protocols to minimize hematologic toxicity
Pharmacologic prophylaxis and treatment of bleeding
Tolerance of anemia
Restricted diagnostic phlebotomy

RBC, red blood cell.
From Goodnough LT, Shander A, Spence RK: Bloodless medicine: Clinical care without allogeneic blood transfusion. Transfusion 43:668-676, 2003.

Summary

A substantial proportion of patients in the United States consider the administration of an allogeneic blood transfusion to have a bad outcome. Autologous transfusion regimens are reported to decrease allogeneic transfusion requirements in surgical patients, but the cost-effectiveness of all of these techniques remains in question. Further research to define the indications for, and limitations of, each autologous technique is needed. Clinical trials that evaluate combinations of several blood conservation techniques may be necessary if the goal is to eliminate the need for allogeneic blood transfusions in the future.

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Christoph Stein and Andreas Kopf

58 Anesthesia and Treatment of Chronic Pain

Key Points

1. The normal physiology of neuronal function, receptors, ion channels, and plasticity is altered by persistent pain.
2. Because of the large number of sources and manifestation of chronic pain, classification needs to include cancer-related, non–cancer-related, neuropathic, inflammatory, arthritis, and musculoskeletal pain.
3. Interdisciplinary management of chronic pain must include specialists in psychology, physical therapy, occupational therapy, and anesthesiology.
4. Drugs used for chronic pain are multiple and include opioids, nonsteroidal anti-inflammatory drugs and antipyretic analgesics, serotonin receptor ligands, antiepileptics, antidepressants, topical analgesics (e.g., nonsteroidal anti-inflammatory drugs, capsaicin, local anesthetics, opioids), other analgesics, and adjuvants such as local anesthetics, α_2-agonists, baclofen, botulinum toxin, antiemetics, laxatives, novel drugs such as cannabinoids, and ion channel blockers.
5. Interventional management of chronic pain includes the use of diagnostic blocks, therapeutic blocks, continuous catheter techniques, and stimulation techniques such as acupuncture, transcutaneous electrical nerve stimulation, and spinal cord stimulation.
6. Perioperative management of patients with chronic pain involves the use of opioid and nonopioid analgesics; evaluation for dependence, addiction, and pseudo-addiction; and practical considerations.

Physiologic Changes in Patients with Persistent Pain

Excitatory Mechanisms

Pain may be roughly divided into two broad categories: physiologic and pathologic pain. Physiologic (acute, nociceptive) pain is an essential early warning sign that usually elicits reflex withdrawal and thereby promotes survival by protecting the organism from further injury. In contrast, pathologic (e.g., neuropathic) pain is an expression of the maladaptive operation of the nervous system; it is pain as a disease.[1] Physiologic pain is mediated by a sensory system consisting of primary afferent neurons, spinal interneurons and ascending tracts, and several supraspinal areas. Trigeminal and dorsal root ganglia give rise to high-threshold Aδ and C fibers innervating peripheral tissues (skin, muscles, joints, viscera). These specialized primary afferent neurons, also called nociceptors, transduce noxious stimuli into action potentials and conduct them to the dorsal horn of the spinal cord (Fig. 58-1). When peripheral tissue is damaged, primary afferent neurons are sensitized or directly activated (or both) by a variety of thermal, mechanical, and chemical stimuli. Examples are protons, sympathetic amines, adenosine triphosphate (ATP), glutamate, neuropeptides (calcitonin gene–related peptide, substance P), nerve growth factor, prostaglandins, bradykinin, proinflammatory cytokines, and chemokines.[2,3] These agents lead to opening (gating) of cation channels in the neuronal membrane. Such channels include the capsaicin-, proton-, and heat-sensitive transient receptor potential vanilloid 1 (TRPV1) or the ATP-gated $P2X_3$ receptor. Gating produces an inward current of Na^+ and Ca^{2+} ions into the nociceptor terminal. If this depolarizing current is sufficient to activate voltage-gated Na^+ channels (e.g., $Na_V1.8$), they too will open, thus further depolarizing the membrane and initiating a burst of action potentials that are then conducted along the sensory axon to the dorsal horn of the spinal cord.[3,4] Thereafter, these impulses are transmitted to spinal neurons, the brainstem, the thalamus, and the cortex.[5,6]

Transmission of input from nociceptors to spinal neurons that project to the brain is mediated by direct monosynaptic contact or by multiple excitatory or inhibitory interneurons. The central terminals of nociceptors contain excitatory transmitters such as glutamate, substance P, and neurotrophic factors that activate postsynaptic *N*-methyl-D-aspartate (NMDA), neurokinin,

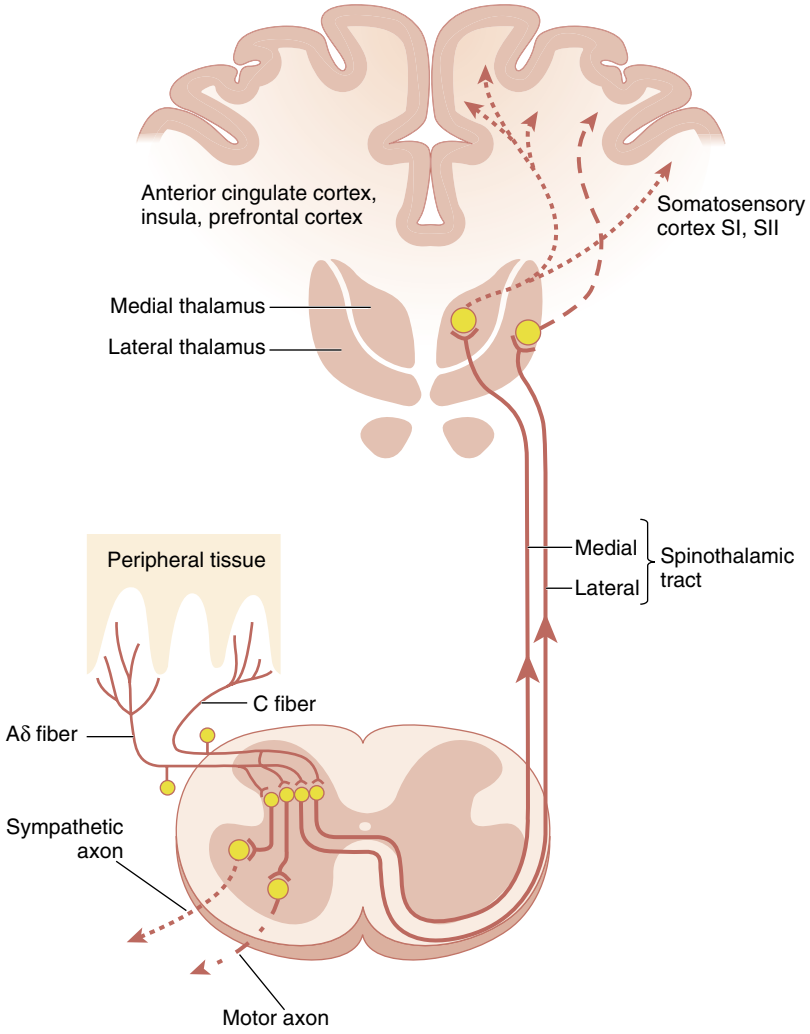

Figure 58-1 Nociceptive pathways. For details see text. *(Adapted from Brack A, Stein C, Schaible HG: Periphere und zentrale Mechanismen des Entzündungsschmerzes.* In *Straub RH [ed]: Lehrbuch der klinischen Pathophysiologie komplexer chronischer Erkrankungen, vol 1. Göttingen, Germany, Vandenhoeck & Ruprecht, 2006, pp 183-192.)*

and tyrosine kinase receptors, respectively. Repeated nociceptor stimulation can sensitize both peripheral and central neurons (activity-dependent plasticity). In spinal neurons such a progressive increase in output in response to persistent nociceptor excitation has been termed "wind-up." Later, sensitization can be sustained by transcriptional changes in the expression of genes coding for various neuropeptides, transmitters, ion channels, receptors, and signaling molecules (transcription-dependent plasticity) in both nociceptors and spinal neurons. Important examples include the NMDA receptor, cyclooxygenase-2 (COX-2), Ca^{2+} and Na^{+} channels, and cytokines and chemokines expressed by neurons and glial cells.[7,8] In addition, physical rearrangement of neuronal circuits by apoptosis, nerve growth, and sprouting occurs in the peripheral and central nervous systems.[1,5] For ethical reasons, animal studies are limited to several days or weeks, but human chronic pain usually lasts for months or years. Therefore, animal models do not mirror the truly chronic clinical situation and are more cautiously termed "persistent pain." Human brain-imaging studies have begun to investigate changes in patients with neuropathic pain, phantom pain, postherpetic neuralgia, back pain, and other chronic pain syndromes. However, with the exception of primary headaches, functional imaging has not yet provided reproducible findings specific for the disease or a pathophysiologic basis for these syndromes.[9]

Inhibitory Mechanisms

Concurrent with the events just described, powerful endogenous mechanisms counteracting pain unfold both in the periphery and in the central nervous system. In injured tissue this occurs by interactions between leukocyte-derived opioid peptides and peripheral nociceptor terminals carrying opioid receptors[10,11] and by the action of anti-inflammatory cytokines.[2] Inflammation of peripheral tissue leads to increased expression, axonal transport, and enhanced G protein coupling of opioid receptors in neurons of the dorsal root ganglia. These phenomena are dependent on sensory neuron electrical activity, production of proinflammatory cytokines, and the presence of nerve growth factor within the inflamed tissue.[12] In parallel, opioid peptide–containing immune cells extravasate and accumulate in the inflamed tissue.[13,14] These cells upregulate the gene expression of opioid peptide precursors[15] and the enzymatic machinery for their processing into functionally active peptides.[16] In response to stress, corticotropin-

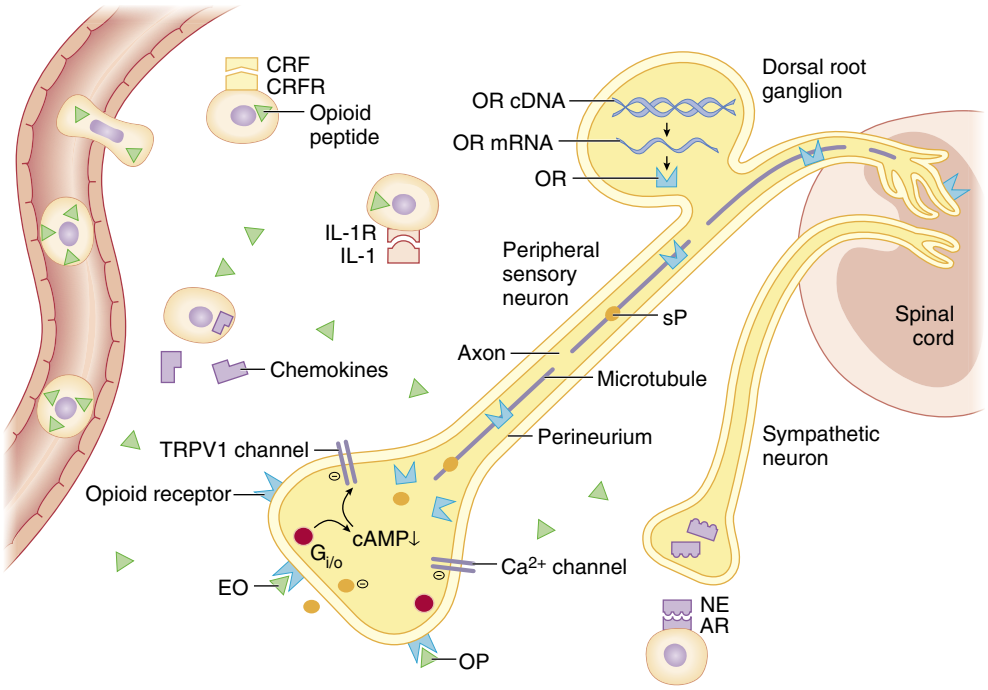

Figure 58-2 Endogenous antinociceptive mechanisms within peripheral injured tissue. Opioid peptide–containing circulating leukocytes extravasate on activation of adhesion molecules and chemotaxis by chemokines. Subsequently, these leukocytes are stimulated by stress or releasing agents to secrete opioid peptides. For example, corticotropin-releasing factor (CRF), interleukin-1β (IL-1), and norepinephrine (NE, released from sympathetic neurons) can elicit release of opioid by activating their respective CRF receptors (CRFR), IL-1 receptors (IL-1R), and adrenergic receptors (AR) on leukocytes. Exogenous opioids (EO) or endogenous opioid peptides (OP) (*green triangles*) bind to opioid receptors (OR), which are synthesized in dorsal root ganglia and transported along intra-axonal microtubules to the peripheral (and central) terminals of sensory neurons. The subsequent inhibition of ion channels (e.g., TRPV1, Ca^{2+}) (see Fig. 58-3 and text) and release of substance P (sP) result in antinociceptive effects. cAMP, cyclic adenosine monophosphate. *(Adapted from Rittner HL, Machelska H, Stein C: Leukocytes in the regulation of pain and analgesia. J Leukoc Biol 78:1215-1222, 2005.)*

releasing factor, cytokines, chemokines, or catecholamines, leukocytes secrete opioids, which then activate peripheral opioid receptors and produce analgesia by inhibiting the excitability of nociceptors or the release of excitatory neuropeptides, or both (Fig. 58-2).[17,18] The clinical relevance of these mechanisms has been shown in studies demonstrating that patients with knee joint inflammation express opioid peptides in immune cells and opioid receptors on sensory nerve terminals within synovial tissue. After knee surgery, such patients exhibited significantly enhanced postoperative pain and analgesic consumption when the interaction between opioid peptides and receptors was blocked by intraarticular application of the antagonist naloxone.[19,20]

In the spinal cord, inhibition is mediated by the release of opioids, γ-aminobutyric acid (GABA), or glycine from interneurons, which then activate presynaptic opioid or GABA receptors (or both) on central nociceptor terminals to reduce the release of excitatory transmitters. In addition, opening of postsynaptic K^+ or Cl^- channels by opioids or GABA, respectively, evokes hyperpolarizing inhibitory potentials in the dorsal horn neurons. During ongoing nociceptive stimulation, spinal interneurons upregulate gene expression and the production of opioid peptides.[21,22] Powerful descending inhibitory pathways from the brainstem also become active by operating mostly through the noradrenergic, serotonergic, and opioid systems. A key region is the periaqueductal gray matter. It projects to the rostral ventromedial medulla, which then projects along the dorsolateral funiculus to the dorsal horn.[23] Integration of signals from excitatory and inhibitory neurotransmitters with cognitive, emotional, and environmental factors (see later) eventually results in the central perception of pain. When the intricate balance among biologic, psychological, and social factors becomes disturbed, chronic pain can develop.

Clinical Definitions, Prevalence, and Classification of Chronic Pain

Definitions

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[24] This classification further states that pain is always subjective and that it is a sensation in part of the body. At the same time it is unpleasant and therefore also has an emotional component. Many people report pain in the absence of tissue damage or any probable pathophysiologic cause. There is usually no way to distinguish their experience from that attributable to tissue damage. If patients regard their experience as pain or if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to a

stimulus. Nociception alone, or activity induced in peripheral sensory neurons (nociceptors) and higher nociceptive pathways by a noxious stimulus, is not pain. Pain is always a psychological state, even though it often has a proximate physical cause.[24] Chronic pain is defined as "pain of a duration or intensity that adversely affects the function or well-being of the patient" by the American Society of Anesthesiologists.[25] The IASP defines it as "pain without apparent biological value that has persisted beyond the normal tissue healing time usually taken to be 3 months."[26] The presence or extent of chronic pain often does not correlate with the documented tissue pathology.

Prevalence

Beyond these general definitions, there is no common understanding of the characteristics of a chronic pain patient, which may be one reason why estimates of pain prevalence differ greatly from one publication to another. Heterogeneous populations, the occurrence of undetected comorbidity, different definitions of chronic pain, and different approaches to data collection result in estimates of prevalence ranging from 20% to 60%. The data available indicate a higher prevalence in women and the elderly (usually musculoskeletal pain).[27,28] Chronic pain has enormous socioeconomic cost. In the United States alone, annual expenditures amount to $150 billion for health care, disability compensation, lost workdays, and related expenses. Similar figures have been reported by other countries.[29,30]

Classification

It is traditional to distinguish between malignant (related to cancer and its treatment) and nonmalignant (e.g. neuropathic, musculoskeletal, inflammatory) chronic pain. However, little evidence suggests that different somatic or psychological mechanisms warrant such a distinction.[31] Cancer patients tend to have more serious health restrictions and are prescribed more opioids and other medications than patients with chronic nonmalignant pain. Some studies suggest that patients with nonmalignant pain report higher pain scores, expect more pain relief than cancer patients, and believe that higher pain scores would result in increases in medication.[32] Nonmalignant chronic pain is frequently classified into inflammatory (e.g., arthritic), musculoskeletal (e.g., low back pain), headaches, and neuropathic pain (e.g., postherpetic neuralgia, phantom pain, complex regional pain syndrome [CRPS], diabetic neuropathy, human immunodeficiency virus–associated neuropathy). The chief symptoms of neuropathic pain include spontaneous lancinating, shooting, or burning pain; hyperalgesia; and allodynia; or any combination of such pain.[33] Cancer pain can originate from invasion of the tumor into tissues densely innervated by primary afferent neurons (e.g., pleura, peritoneum) or directly into a peripheral nerve plexus. In the latter, neuropathic symptoms may be predominant. A problem in the treatment of cancer pain is a lack of correlation between the patient's self-reporting and assessment of the clinical staff. In some studies the patient's pain may have been underestimated by medical staff and family members, which may have resulted in poor pain control.[34] Many therapies for cancer are associated with severe pain. For example, cytoreductive radiotherapy or chemotherapy frequently causes painful oral mucositis, especially after bone marrow transplantation.[35]

Biopsychosocial Concept of Chronic Pain

Cancer and noncancer patients with chronic pain have in common the complex influences of biologic (tissue damage), cognitive (memory, expectations), emotional (anxiety, depression), and environmental factors (reinforcement, conditioning). Many patients have limited mobility, lack of motivation, depression, anger, anxiety, and fear of reinjury, characteristics that hamper return to normal work or recreational activities. Such patients may become preoccupied with pain and somatic processes, which may disrupt sleep and cause irritability and social withdrawal. Other cognitive factors such as patients' expectations or beliefs (e.g., perceived inability to control the pain) influence psychosocial and physical functioning. Pain behavior such as limping, medication intake, or avoidance of activity is subject to operant conditioning; that is, it responds to reward and punishment. For example, pain behavior may be positively reinforced by attention from a spouse or health care provider (e.g., by inadequate use of nerve blocks or medications). Conversely, such behavior can be extinguished when it is disregarded and incremental activity is reinforced by social attention and praise.[36,37] Respondent learning mechanisms (i.e., classic conditioning) may also contribute to chronicity.[38] Other issues often coexist, such as substance abuse problems, family dysfunction, and conflicts with legal or insurance systems. Consequently, care seeking is an integral feature of the pain experience, and excessive use of the health care system ensues. The interplay between these biologic, psychological, and social factors results in the persistence of pain and illness behavior.[37,38] Treating only one aspect of this complex syndrome is obviously insufficient. Therefore, a biopsychosocial concept of pain has been adopted. This concept was first described by Engel in 1959 but was implemented into daily practice only recently, especially with regard to chronic pain patients.[39,40] With the help of this concept it is possible to understand why chronic pain may exist without obvious physical cause or why pathologic somatic findings may remain unnoticed by the patient. Interestingly, recent studies have shown that the experience and regulation of social and physical pain may share a common neuroanatomic basis.[41] In a multimodal approach, management of pain addresses physical, psychological, and social skills and underscores patients' active responsibility to regain control over life by improving function and well-being.[38,42]

Interdisciplinary Management of Chronic Pain

The anesthesiologist John J. Bonica was the first to appreciate the need for a multidisciplinary approach to chronic pain. Bonica's early experiences in and after World War II convinced him that complex pain problems could be treated more effectively when different disciplines contribute their specialized knowledge and skills to the common goal of making a correct diagnosis and developing the most effective therapeutic strategy. The first multidisciplinary facility was put into practice at the Tacoma General

Hospital, followed by the University of Washington in 1960. From 1970 through 1990, the number of pain management facilities continued to increase, mostly directed by anesthesiologists in North America and Europe. Such comprehensive pain centers should have personnel and facilities to evaluate and treat the biomedical, psychosocial, and occupational aspects of chronic pain and to educate and teach medical students, residents, and fellows. Guidelines for desirable characteristics of pain treatment facilities have been published by the IASP.[43] Multidisciplinary and multimodal management results in increased physical and psychosocial function, reduced health care use, and vocational rehabilitation.[40,44] Meta-analyses have shown that such programs offer the most efficacious and cost-effective evidence-based treatment of chronic nonmalignant pain.[30,45,46] Treatment of chronic pain without an interdisciplinary approach is inadequate and may lead to misdiagnosis (e.g., overlooking psychological processes in presumed diskogenic back pain or overlooking a somatic etiology in a presumed "psychogenic" pain disorder).[47] Moreover, conventional monomodal approaches such as pharmacotherapy alone only perpetuate the expensive, futile, and endless search for medical solutions.[30,42]

The core team consists of a pain management physician (anesthesiologist with subspecialty training), a psychologist, a physical therapist, and an occupational therapist. Depending on local circumstances, this team may be supplemented by administrators, nurse specialists, and pharmacists. The initial screening of the patient by members of the core team determines what other specialists will be needed for complete assessment. After this evaluation, the patient is presented to the entire core team and a comprehensive treatment plan is developed. This plan is tailored to the patient's needs, abilities, and expectations, with a focus on establishing measurable treatment goals for the patient. For some patients, education and medical management may suffice, whereas for others, an intensive full-day rehabilitation program conducted over a period of several weeks may be needed. To foster patient compliance, open discussion of treatment goals with regard to the patient's anticipations is essential. Many patients expect complete resolution of the pain and return to full function, a goal that may not be achievable. In many cases, realistic options are a reduction in pain; improved physical function, mood, and sleep; development of active coping skills; and return to work. Thus, rehabilitation rather than cure is the most appropriate therapeutic option.[30,48]

Psychology

The role of the psychologist includes initial assessment and treatment approaches such as education, cognitive-behavioral therapy, and relaxation training. Assessment of the patient addresses the sensory, affective, cognitive, behavioral, and occupational dimensions of the pain problem. An extensive (biographic) history, behavioral analysis, and the use of questionnaires are obligatory. Most questionnaires include scoring systems for pain intensity (e.g., numerical or visual analog scales), pain behavior (e.g., West Haven–Yale Multidimensional Pain Inventory), multidimensional pain quality, cognitive coping, fear (e.g., State Trait Anxiety Inventory), depression, and other associated symptoms. Indications for psychological pain management are relevant somatization, depressive disorders, inadequate coping, drug abuse, and high levels of pain behavior reinforced by the environment (e.g., family members). The type of therapy depends on the pain syndrome. For instance, chronic headache, inflammatory rheumatic pain, and unspecific back pain specifically benefit from behavioral therapy,[38,49] which usually means a complete change of view for the patient from a purely passive recipient of curative treatment to an active, self-reliant approach to functional restoration, vocational rehabilitation, and reduced health care use despite pain. Thus, pain reduction alone is no longer the focus of therapy.[42]

Physical Therapy

The role of the physical therapist includes initial evaluation of the musculoskeletal system, assessment of the patient's workplace and home, education in active physical coping skills, and management of the physical rehabilitation process. An intensive exercise program with emphasis on responsibility of the patient for self-management is an integral part of comprehensive programs for chronic nonmalignant pain.[30,40,44] Improving fitness, mobility, and posture counteracts the effects of disuse and complements behavioral treatment. The physical therapist encourages the adoption of regular exercise into daily life, facilitates repeated exposure to movement as much as possible despite pain, and reinforces education on the biopsychosocial model of pain management. Different techniques of exercise such as muscle conditioning, aerobics, and others are efficacious in improving endurance and reducing pain, disability, and fear avoidance behavior.[50-53] On the other hand, passive treatments such as massage or chiropractic interventions are not beneficial.[54,55] The regimen of graded exercise follows the original concept of Fordyce and colleagues.[36] Patients are instructed to find a baseline tolerance level for each exercise. Next, a program of improvement is negotiated and agreed upon. Patients note improvement on a daily basis and are required to complete the exercise plan regardless of how they feel. Thus, control over exercise behavior is contingent on the plan rather than pain because exercise and pain are disconnected. Individual motivation is an important factor in determining how well patients learn to manage pain.[56]

Occupational Therapy

The occupational therapist teaches the patient to achieve life goals despite pain and to overcome the limitations imposed by pain. Initial assessment includes a history of working life and place, family life, and daily activities, as well as physical examination to determine range of motion and the presence of movement disorders or deformities that might hinder performance. The primary therapeutic objectives are reduction of pain and associated disability, promotion of optimal function in everyday life, and encouragement of meaningful family, social, and work relationships.[57] An important target is supporting return to work by the patient, including specific work conditioning.[58] The chance of returning to work after a period of sick leave from low back pain, for example, apparently decreases over time, thereby generating enormous cost to society through wage compensation, social support, and loss of production.[29,59] Barriers to return to work

include job dissatisfaction and perceptions of the impact of work on the cause of the pain.[60] Together with the patient, the occupational therapist should develop a program to increase self-esteem, restore self-efficacy, and promote optimal occupational and recreational function despite pain.

Anesthesiology

The role of the anesthesiologist in the treatment of chronic pain has changed considerably over the last decades. "Nerve block practices" have been replaced by interdisciplinary pain management centers. In this context the anesthesiologist acts as a physician-educator, not only as a technical expert. The challenge is to optimally combine regional anesthesia skills and pharmacologic knowledge with the psychosocial components of chronic pain to render more comprehensive pain management services. Anesthesiologists need to use their expertise in pharmacotherapy, nerve blocks, and skilled techniques within the broad-based biopsychosocial approach. The focus is not only on reducing pain but also on decreasing disability, improving quality of life, and enhancing function. It is of crucial importance to recognize that the conventional way of administering medication "as needed" or to use nerve blocks for short-term pain relief may reinforce pain behavior and the patient's belief in an underlying physical abnormality that is best managed by biomedical procedures.[42] Moreover, false expectations are maintained, such as the notion that the patient should be the passive recipient rather than an active participant in the process, and false assumptions are promoted, such as the belief that pain is the primary problem in the patient's life. This approach neglects psychosocial factors, perpetuates the expensive and futile search for unidimensional biomedical solutions, and promotes iatrogenic somatization, medicalization, and high health care use by chronic pain patients.[42] The role of the anesthesiologist within the interdisciplinary team differs depending on the type of patient being treated. Cancer and acute pain management demand the full range of the anesthesiologist's technical skills and pharmacologic knowledge. In chronic nonmalignant pain, the anesthesiologist's abilities as an educator, coach, and motivator are far more important. As a member of the interdisciplinary team, the anesthesiologist has to reinforce and maintain the biopsychosocial focus, respond appropriately to somatic concerns, and manage medications. In concert with other members of the team, the anesthesiologist uses motivational strategies to encourage the patient to attain self-managed reactivation goals in the physical, psychosocial, recreational, and vocational domains. At the same time, the anesthesiologist's presence provides "white coat credibility" and is essential to avoid the patient's pejorative conclusion that the pain is "all in my head." The anesthesiologist monitors the patient's physical status, potential development of new medical problems, and medications. In addition, the anesthesiologist provides real-time reassurance and education regarding the absence of any relevant abnormality and the minimal role of surgery and conveys medical information to make informed choices. The anesthesiologist plays a crucial role within the multidisciplinary team in directing the patient toward a multimodal pain treatment plan. This is reflected by the fact that the majority of pain therapists worldwide are anesthesiologists. In the described clinical setting, anesthesiologists work closely with other health care professionals, thereby gaining added recognition outside the operating room.[42]

Drugs Used for Chronic Pain

Analgesic drugs interfere with the generation or transmission (or both) of impulses after noxious stimulation of the nervous system (nociception). This can occur at both the peripheral and central levels of the neuraxis. The therapeutic goal is to diminish the perception of pain. Analgesics are used to modulate either the generation of noxious chemicals (e.g., prostaglandins) or the activation of neuronal receptors or ion channels transducing or transmitting noxious stimuli (e.g., peptide, kinin, monoamine receptors, Na^+ channels). Drugs currently used for chronic pain include opioids, nonsteroidal antiinflammatory drugs (NSAIDs), serotonergic compounds, antiepileptics, and antidepressants (Table 58-1). Other classes, such as adrenergic receptor agonists, excitatory amino acid receptor (e.g., NMDA) antagonists, neurotrophin antagonists, neuropeptide (e.g., calcitonin gene–related peptide) receptor antagonists, kinin receptor antagonists, prostaglandin E receptor (EP) antagonists, cannabinoids, and ion channel (e.g., TRP, P2X) blockers, are currently under investigation but are not yet used routinely. Local anesthetics are used for local and regional anesthetic techniques. Mixed drugs combine different mechanisms, such as inhibition of noradrenaline reuptake and opioid agonist effects (tramadol) or opioid agonist and NMDA antagonist effects (ketamine). Various routes of drug administration (e.g., oral, intravenous, subcutaneous, intrathecal, epidural, topical, intra-articular, transnasal) can be used, depending on the clinical circumstances. Chronic pain requires a multidisciplinary approach that encompasses various pharmacologic and nonpharmacologic (psychological, physiotherapeutic) treatment strategies (see the earlier section "Interdisciplinary Management of Chronic Pain").

Opioids

Opioids act on heptahelical G protein–coupled receptors. Three types of opioid receptors (μ, δ, κ) have been cloned. Additional subtypes (e.g., μ_1, μ_2, δ_1, δ_2), possibly resulting from gene polymorphisms, splice variants, or alternative processing, have been proposed. Opioid receptors are localized and can be activated at all levels of the neuraxis, including the peripheral and central processes of primary sensory neurons (nociceptors), spinal cord (interneurons, projection neurons), brainstem, midbrain, and cortex. All opioid receptors couple to G proteins (mainly G_i/G_o) and subsequently inhibit adenylyl cyclase, decrease the conductance of voltage-gated Ca^{2+} channels, or open rectifying K^+ channels, or any combination of these effects (Fig. 58-3, upper panel). These effects ultimately result in decreased neuronal activity. Prevention of Ca^{2+} influx inhibits the release of excitatory (pronociceptive) neurotransmitters. A prominent example is suppression of release of substance P from primary sensory neurons both within the spinal cord and from their peripheral terminals within injured tissue. At the postsynaptic membrane, opioids produce hyperpolarization by opening K^+ channels, thereby preventing excitation or propagation of action potentials in second-order projection neurons. In addition, opioids inhibit sensory neuron–specific tetrodotoxin-resistant Na^+ channels, TRPV1 channels, and excitatory postsynaptic currents evoked by glutamate receptors (e.g., NMDA) in the spinal cord. The result is decreased transmission of nociceptive stimuli at all levels of the neuraxis

Table 58-1 Analgesic Drugs, Targets, Mechanisms, and Side Effects

Drugs	Targets	Mechanisms	Functional Consequences	Side Effects
Opioids	G protein–coupled μ-, δ-, κ-receptors	↓ cAMP ↓ Ca^{2+} currents ↑ K^+ currents	↓ Excitability of peripheral and central neurons ↓ Release of excitatory neurotransmitters	μ, δ: sedation, nausea, euphoria/reward, respiratory depression, constipation κ: dysphoria/aversion, diuresis, sedation
NSAIDs	Cyclooxygenases (COX-1, COX-2)	↓ Prostaglandins ↓ Thromboxanes	↓ Sensitization of sensory neurons ↑ Inhibition of spinal neurons	Nonselective: gastrointestinal ulcers, perforation, bleeding, renal impairment COX-2: thrombosis, myocardial infarction, stroke
Serotonin agonists	G protein–coupled 5-HT receptors 5-HT_3: ion channels	↓ cAMP (5-HT_1) ↑ cAMP ($5\text{-HT}_{4\text{-}7}$) ↑ PLC (5-HT_2)	↓ Release of excitatory neuropeptides ↓ Neurogenic inflammation ↑ Vasoconstriction	Myocardial infarction, stroke, peripheral vascular occlusion
Antiepileptics	Na^+, Ca^{2+} channels GABA receptors	↓ Na^+ currents ↓ Ca^{2+} currents ↑ GABA receptor activity	↓ Excitability of peripheral and central neurons ↓ Release of excitatory neurotransmitters	Sedation, dizziness, cognitive impairment, ataxia, hepatotoxicity, thrombocytopenia
Antidepressants	Norepinephrine/5-HT transporters Na^+, K^+ channels	↓ Norepinephrine/5-HT reuptake ↓ Na^+ currents ↑ K^+ currents	↓ Excitability of peripheral and central neurons	Cardiac arrhythmia, myocardial infarction, sedation, nausea, dry mouth, constipation, dizziness, sleep disturbance, blurred vision

cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine; NSAIDs, nonsteroidal anti-inflammatory drugs; PLC, phospholipase C.

and profoundly reduced perception of pain. Endogenous opioid receptor ligands are derived from the precursors proopiomelanocortin (encoding β-endorphin), proenkephalin (encoding met-enkephalin and leu-enkephalin), and prodynorphin (encoding dynorphins). These peptides contain the common Tyr-Gly-Gly-Phe-Met/Leu sequence at their amino terminals, known as the opioid motif. β-Endorphin and the enkephalins are potent antinociceptive agents acting at μ- and δ-receptors. Dynorphins can elicit both pronociceptive and antinociceptive effects via NMDA receptors and κ-opioid receptors, respectively. A fourth group of tetrapeptides (endomorphins) with yet unknown precursors do not contain the pan-opioid motif but bind to μ-receptors with high selectivity. Opioid peptides and receptors are expressed throughout the central and peripheral nervous systems, in neuroendocrine tissues, and in immune cells.[61]

The opioids commonly available (morphine, codeine, methadone, fentanyl and its derivatives) are μ-agonists. Naloxone is a nonselective antagonist at all three receptors. Partial agonists must occupy a greater fraction of the available pool of functional receptors than full agonists to induce a response of equivalent magnitude. Mixed agonist/antagonists (buprenorphine, butorphanol, nalbuphine, pentazocine) may act as agonists at low doses and as antagonists (at the same or a different receptor type) at higher doses. Such compounds typically exhibit ceiling effects for analgesia, and they may elicit an acute withdrawal syndrome when administered together with a pure agonist. All three receptors (μ, δ, κ) mediate analgesia, but with differing side effects. μ-Receptors mediate respiratory depression, sedation, reward/euphoria, nausea, urinary retention, biliary spasm, and constipation. κ-Receptors mediate dysphoric, aversive, sedative, and diuretic effects but do not mediate constipation. δ-Receptors mediate reward/euphoria and, to a lesser degree, respiratory depression and constipation. Tolerance and physical dependence may occur with prolonged administration of pure agonists, and abrupt discontinuation or administration of an antagonist can result in a withdrawal syndrome (see also the later section "Perioperative Management of Patients with Chronic Pain").

Tolerance describes the phenomenon that the magnitude of a given drug effect decreases with repeated administration of the same dose or that increasing doses are needed to produce the same effect. Tolerance is not synonymous with dependence (see "Perioperative Management of Patients with Chronic Pain"). All effects of opioids (e.g., analgesia, nausea, respiratory depression, sedation, constipation) can be subject to the development of tolerance, albeit to different degrees. For example, tolerance to respiratory depression, sedation, and nausea often develops faster than tolerance to constipation or miosis[62,63] (see also the later section "Other Analgesics and Adjuvants"). Incomplete cross-tolerance between opioids or genetic differences may explain the clinical observation that switching drugs ("opioid rotation") is occasionally useful in patients with inadequate pain relief or intolerable side effects.[64] Opioid-induced adaptations occur at multiple levels in the nervous and other organ systems, beginning with direct modulation of opioid receptor signaling and extending to complex neuronal networks, including learned behavior. Proposed mechanisms involved in pharmacodynamic tolerance include opioid receptor–G protein uncoupling, decreased receptor internalization/recycling, and increased sensitivity of the NMDA receptor (see Fig. 58-3, lower panel).[61,65] In addition, pharmacokinetic (e.g., altered distribution or metabolism of the opioid) and learned tolerance (e.g., compensatory skills developed during mild intoxication) and increased nociceptive stimulation by tumor growth, inflammation, or neuroma formation are possible reasons for increased dose requirements.[62,66] There is a

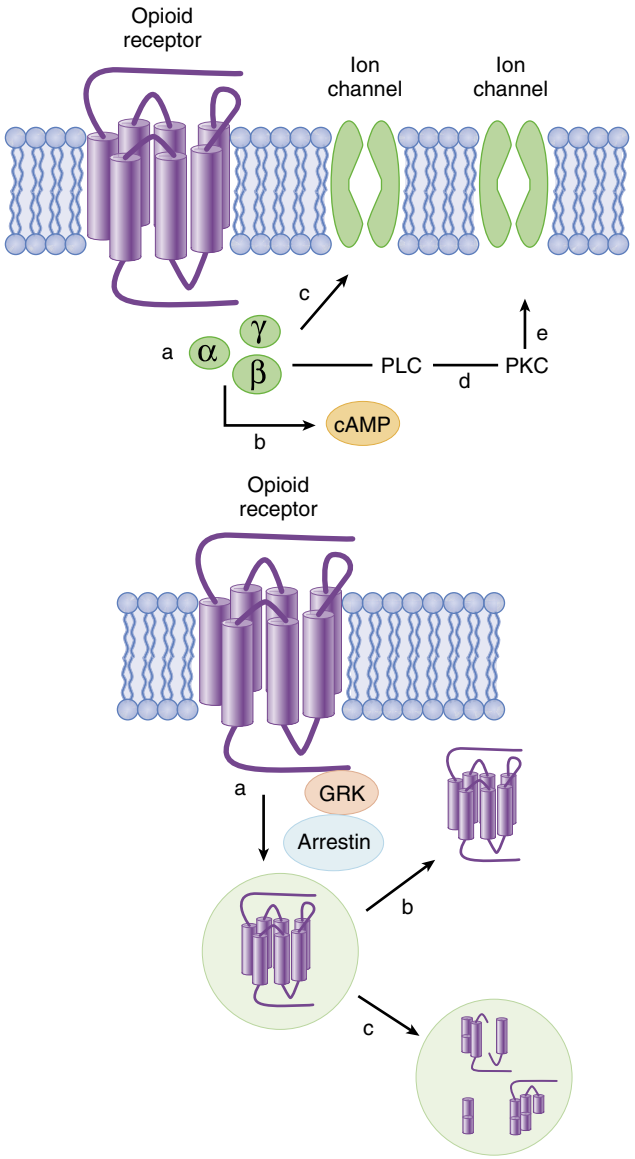

Figure 58-3 Opioid receptor signaling and recycling. **Upper panel,** Opioid ligands induce a conformational change at the receptor that allows coupling of G proteins to the receptor. The heterotrimeric G protein dissociates into active Gα and Gβγ subunits (a) that can inhibit adenylyl cyclase and reduce cyclic adenosine monophosphate (cAMP) (b), decrease the conductance of voltage-gated Ca^{2+} channels, or open rectifying K^+ channels (c). In addition, the phospholipase C (PLC)/phosphokinase C (PKC) pathways can be activated (d) to modulate Ca^{2+} channel activity in the plasma membrane (e). **Lower panel,** Opioid receptor desensitization and trafficking are activated by G protein–coupled receptor kinases (GRK). After binding of arrestin, the receptor is in a desensitized state at the plasma membrane (a). Arrestin-bound receptors can then be internalized via a clathrin-dependent pathway and either be recycled to the cell surface (b) or degraded in lysosomes (c). *(Adapted from Zöllner C, Stein C: Opioids. Handb Exp Pharmacol 177:31-63, 2007.)*

lack of carefully controlled clinical studies that unequivocally demonstrate pharmacodynamic tolerance to opioid analgesia in patients.[67]

There is ongoing debate whether opioids may paradoxically induce hyperalgesia.[68] However, on closer scrutiny of the data available it appears that most of these studies have in fact shown withdrawal-induced hyperalgesia, a well-known phenomenon after abrupt cessation of opioids (see also the later section "Perioperative Management of Patients with Chronic Pain"). At ultrahigh doses, occasionally encountered in patients with extreme cancer pain, singular cases of allodynia have been observed and attributed to the neuroexcitatory effects of opioid metabolites.[69] There is no conclusive evidence that hyperalgesia occurs during the perioperative or chronic administration of regular opioid doses in patients.[68]

Opioids are effective in the periphery (e.g., topical or intraarticular administration, particularly in inflamed tissue), at the neuraxis (intrathecal, epidural, or intracerebroventricular administration), and systemically (intravenous, oral, subcutaneous, sublingual, or transdermal administration).[61,70] The clinical choice of a particular compound or its formulation is based on pharmacokinetic considerations (route of administration, desired onset or duration, lipophilicity) and on side effects associated with the respective route of drug delivery.[71,72] Dosages are dependent on patient characteristics, the type of pain, and the route of administration. Systemically and spinally administered opioids can produce similar side effects, depending on the dosage and rostral/systemic redistribution. For intrathecal application, lipophilic drugs are preferred because they are trapped in the spinal cord and less likely to migrate to the brain within cerebrospinal fluid. Adverse side effects can be minimized by careful dose titration and close patient monitoring, or they can be treated by comedication (antiemetics, laxatives) or naloxone. No significant side effects have been reported with the peripheral (e.g., topical) application of small, systemically inactive doses of opioids. Current research aims at the development of systemically applicable opioids with restricted access to the brain.[11,73]

Opioids are the most effective drugs for severe acute and cancer-related chronic pain. The use of opioids in chronic non–cancer-related pain (e.g., neuropathic, musculoskeletal) is not unequivocally supported by adequately powered, blinded, randomized controlled trials (RCTs), and epidemiologic data suggest that opioids do not improve quality of life or functional capacity.[74] Thus far, double-blind placebo-controlled studies have investigated a maximum treatment duration of 8 weeks.[75,76] Only a few RCTs have required strict discontinuation of prestudy nonopioid analgesics to test the effects of a sole opioid medication,[75,77-80] and several others have examined an unspecified mixture of opioid and nonopioid drugs. The maximum reduction in pain scores was 17% in comparison to placebo, a clinically nonsignificant effect. More important outcome parameters such as psychosocial factors, quality of life, and functional status have been investigated in just a few trials.[75-79,81,82] Only one study using opioids alone[78] and two using mixed drugs[82,83] showed modest improvement. The well-known adverse side effects of opioid medication (nausea, sedation, constipation, dizziness, etc.) were reported in all these studies and led to the dropout of significant numbers (up to 58%) of subjects. Thus, consistent with the multifactorial nature of chronic pain, it is highly questionable whether opioids alone can produce an analgesic response if, for example, there is a major affective component of the pain or if learned pain behavior is the main problem. In addition, the prevalence of addiction is as high as 50% in patients treated with opioids for chronic nonmalignant pain.[84,85] The central point to keep in mind is that the entire patient must be evaluated, not just the pain.[86] The target of intervention is not only the source of nociception (if at all identifiable) but also suffering, dysfunction, psychosocial factors, and dependence on the health care system (see earlier). Thus, the use of opioids as a sole treatment modality in chronic nonmalignant pain is not recommended.

Nonsteroidal Anti-inflammatory Drugs and Antipyretic Analgesics

The acidic NSAIDs and the nonacidic antipyretic analgesics (e.g., acetaminophen, phenazones) inhibit COXs, enzymes that catalyze the transformation of arachidonic acid (a ubiquitous cell component generated from phospholipids) to prostaglandins and thromboxanes.[87] Two isoforms, COX-1 and COX-2, are constitutively expressed in peripheral tissues and in the central nervous system. In response to injury and inflammatory mediators (e.g., cytokines, growth factors), both isoforms can be upregulated, which results in increased concentrations of prostaglandins. In the periphery, prostaglandins (mainly PGE_2) sensitize nociceptors by phosphorylation of ion channels (e.g., Na^+, TRPV1) via EP receptor activation. As a result, nociceptors become more responsive to noxious mechanical (e.g., pressure, hollow organ distention), chemical (e.g., acidosis, bradykinin, neurotrophic factors), or thermal stimuli. In the spinal cord, PGE_2 blocks glycinergic neuronal inhibition, enhances excitatory amino acid release, and depolarizes ascending neurons. These mechanisms facilitate the generation of impulses within nociceptors and their transmission through the spinal cord to higher brain areas. By blocking one (selective COX-2 inhibitors) or both enzymes (nonselective NSAIDs), prostaglandin formation diminishes. Subsequently, nociceptors become less responsive to noxious stimuli and spinal neurotransmission is attenuated.

Less severe pain states (e.g., early arthritis, headache) are commonly treated with nonselective NSAIDs (e.g., aspirin, ibuprofen, indomethacin, diclofenac) or antipyretic analgesics (e.g., acetaminophen), mostly used orally. Some agents are available for parenteral, rectal, or topical application. Over-the-counter availability and self-medication have led to frequent abuse and toxicity. Side effects have been attributed to COX-1–induced blockade of thromboxane production and impairment of platelet function (gastrointestinal and other bleeding disorders), decrease in tissue-protective prostaglandins (gastrointestinal ulcers, perforation), decrease in renal vasodilatory prostaglandins (nephrotoxicity), and the formation of highly reactive metabolites (acetaminophen hepatotoxicity). The development of selective COX-2 inhibitors was driven by the assumption that COX-2 expression is selectively induced in inflamed tissue and that the constitutive tissue-protective COX-1 would be spared. It has now become clear that COX-2 expression is constitutive in many tissues (e.g., gastrointestinal epithelium, vascular endothelium, spinal cord) and that inhibition of COX-2 may exacerbate inflammation, impair ulcer healing, and decrease the formation of vasoprotective prostacyclin. Selective COX-2 inhibitors confer an increased risk for thrombosis, myocardial infarction, renal impairment, hypertension, stroke, and liver toxicity. Both classes of COX inhibitors can cause rare anaphylactic reactions. Acetaminophen (paracetamol) has relatively weak anti-inflammatory and antiplatelet activity. It is used for osteoarthritis, headache, and fever.[87]

Serotonergic Drugs

Serotonin (5-hydroxytryptamine [5-HT]) is a monoamine neurotransmitter found in the sympathetic nervous system, in the gastrointestinal tract, and in platelets. It acts on 5-HT receptors expressed at all levels of the neuraxis and on blood vessels. Within the dorsal horn of the spinal cord, serotoninergic neurons contribute to endogenous pain inhibition. With the exception of 5-HT_3 (a ligand-gated ion channel), 5-HT receptors are G protein–coupled receptors. 5-$HT_{1B/1D}$ agonists (triptans) have been studied extensively and are effective against neurovascular (migraine, cluster) headaches. Migraine is thought to be related to the release of neuropeptides (e.g., calcitonin gene–related peptide) from trigeminal sensory neurons innervating meningeal and intracranial blood vessels. This leads to vasodilation, an inflammatory reaction, and subsequent pain. Triptans inhibit neurogenic inflammation via 5-HT_{1D} receptors on trigeminal afferents, with possible additional sites of action on thalamic neurons and in the periaqueductal gray matter. Activation of vascular 5-HT_{1B} receptors constricts meningeal (and coronary) vessels. The latter effects have stimulated a search for nonvasoconstrictor approaches, such as highly selective 5-HT_{1D} and 5-HT_{1F} agonists. However, none of them have demonstrated clinical antimigraine effects thus far.

Triptans can be applied orally, subcutaneously, or transnasally and have been used for the treatment of migraine. All triptans narrow coronary arteries via 5-HT_{1B} receptors by up to 20% at clinical doses and should not be administered to patients with risk factors or coronary, cerebrovascular, or peripheral vascular disease. Some triptans have the potential for significant drug-drug interactions (e.g., with monoamine oxidase inhibitors, propranolol, cimetidine, hepatic P450-metabolized medications, P-glycoprotein pump inhibitors). Rational use of triptans should be restricted to patients with disability associated with migraine.[88]

Antiepileptic Drugs

Antiepileptics are used for the treatment of neuropathic pain resulting from lesions to the peripheral (e.g., diabetes, herpes) or central nervous system (e.g., stroke). Such syndromes have been attributed to ectopic activity in sensitized nociceptors from regenerating nerve sprouts, recruitment of previously "silent" nociceptors, or spontaneous neuronal activity (or any combination of these processes). These events may result in sensitization of primary afferents and subsequent sensitization of second- and third-order ascending neurons. Among the best-studied mechanisms are the increased expression and trafficking of ion channels (e.g., Na^+, Ca^{2+}, TRP) and increased activity at glutamate (NMDA) receptor sites. Mechanisms of action of antiepileptics include stabilization of the neuronal membrane by blockage of pathologically active voltage-sensitive Na^+ channels (carbamazepine, phenytoin, lamotrigine, topiramate), blockage of voltage-dependent Ca^{2+} channels (gabapentin, pregabalin), inhibition of presynaptic release of excitatory neurotransmitters (gabapentin, lamotrigine), and enhancement of the activity of GABA receptors (topiramate).

Antiepileptics have been used for neuropathic pain and for migraine prophylaxis. They are frequently coadministered with antidepressants. Their most common adverse effects are impaired mental (somnolence, dizziness, cognitive impairment, fatigue) and motor function (ataxia), which limit their clinical use, particularly in elderly patients. Serious side effects have been reported, including hepatotoxicity, thrombocytopenia, and life-threatening dermatologic and hematologic reactions. Plasma drug concentrations should be monitored.[88]

Antidepressants

Antidepressants are used for the treatment of neuropathic pain and headache. They include the classic tricyclic compounds, which are divided into nonselective norepinephrine/5-HT reuptake inhibitors (amitriptyline, imipramine, clomipramine, venlafaxine), preferential norepinephrine reuptake inhibitors (desipramine, nortriptyline), and selective 5-HT reuptake inhibitors (citalopram, paroxetine, fluoxetine). The reuptake blockade leads to stimulation of endogenous monoaminergic pain inhibition in the spinal cord and brain. In addition, tricyclic antidepressants have NMDA receptor antagonist, endogenous opioid–enhancing, Na^+ channel–blocking, and K^+ channel–opening effects that can suppress peripheral and central sensitization. Block of cardiac ion channels by tricyclic antidepressants can lead to arrhythmias. The selective 5-HT transporter inhibitors have a different side effect profile and are safer in cases of overdose.

Tricyclic antidepressants require monitoring of plasma drug concentrations to achieve optimal effect and avoid toxicity, unless sufficient pain relief is obtained with low doses (up to 75 mg/day of imipramine or amitriptyline). Patients with ischemic heart disease may have an increased risk for sudden arrhythmia, and patients with recent myocardial infarction, arrhythmia, or cardiac decompensation should not take tricyclic antidepressants at all. Tricyclic antidepressants also block histamine, cholinergic, and adrenergic receptor sites. Adverse events include sedation, nausea, dry mouth, constipation, dizziness, sleep disturbance, and blurred vision.[88]

Topical Analgesics

The topical application of various analgesics is an area of considerable interest because many chronic pain syndromes depend to some degree on the peripheral activation of primary afferent neurons. Localized administration can potentially optimize drug concentrations at the site of pain generation while avoiding high plasma levels, systemic side effects, drug interactions, and the need to titrate doses into a therapeutic range. RCTs have demonstrated the effectiveness of topical NSAIDs, tricyclic antidepressants, capsaicin, local anesthetics, and opioids.[11,73,88]

Topical NSAIDs are typical over-the-counter medications, widely advertised and used for acute and chronic pain. A large number of formulations (cream, gel, ointment) are commercially available, with varying drug delivery to the skin and subcutaneous tissue.[89] Two meta-analyses concluded that topical NSAIDs are effective for a limited period (2 weeks) for chronic musculoskeletal pain[90] but not for osteoarthritis.[91] Local adverse effects included rash and pruritus. A topical tricyclic antidepressant (doxepin) has shown efficacy in a mixed group of patients with neuropathic pain and, as a mouthwash, in patients with chemotherapy-induced oral mucositis. Side effects included burning discomfort.[73]

Capsaicin is the active pungent ingredient in chili peppers. Topically applied capsaicin interacts with nociceptive neurons via the vanilloid receptor (TRPV1). It causes initial activation of these neurons with release of substance P. This is perceived as a burning or itching sensation with a flare response and occurs in a high number (up to 80%) of patients. Desensitization develops after repeated application, probably because of depletion of substance P in sensory neurons. Another potential mechanism is a direct neurotoxic effect that results in the degeneration of small-diameter sensory nerve fibers.[73] Capsaicin is available as 0.025% and 0.075% cream. It was shown to achieve pain relief in patients with postherpetic neuralgia, postmastectomy syndrome, osteoarthritis, and a variety of neuropathic syndromes. A systematic review revealed moderate to poor effectiveness with a number needed to treat of 5.7.[92] One approach to minimizing side effects and enhancing analgesia has been the application of high concentrations (5% to 10%) under regional anesthesia,[93] but the concomitant application of local anesthetics did not prevent capsaicin-induced burning pain.[94] Thus, topical capsaicin may be a supplement for the treatment of neuropathic pain in a small number of patients unresponsive to or intolerant of other therapeutic approaches.

Topical formulations of local anesthetics block Na^+ channels in primary afferent neurons. Blockade of Na^+ channels reduces impulse generation in both normal and damaged sensory neurons. Such neurons exhibit spontaneous and ectopic firing, which possibly contributes to certain conditions of chronic neuropathic pain. Under these conditions, the altered expression, distribution, and function of ion channels along axons are associated with increased sensitivity to local anesthetics. Thus, pain relief can be achieved with local anesthetic concentrations below those that totally block conduction of impulses.[95,96] Controlled studies using lidocaine patches and gels showed pain reduction in patients with postherpetic neuralgia and allodynia.[88,97] In addition, patients with painful diabetic polyneuropathy, CRPS, postmastectomy syndrome, or post-thoracotomy syndrome can achieve relief of pain. Except for skin irritation, there have been no reports of serious side effects. Gel formulations of 5% lidocaine may be useful for the treatment of postherpetic neuralgia or oral mucositis.[98,99]

Topically applied or locally injected opioids produce analgesia by activating opioid receptors on primary afferent neurons. This leads to inhibition of Ca^{2+}, Na^+, and TRPV1 currents, which are activated by inflammatory agents.[61,100] Subsequently, the excitability of nociceptors, propagation of action potentials, and release of proinflammatory neuropeptides (substance P) from sensory nerve endings are inhibited. All these mechanisms result in analgesia or anti-inflammatory effects (or both).[11,61] Other mechanisms accounting for the particular efficacy of peripheral opioids in relieving pain associated with inflammation include upregulation[101] and accelerated centrifugal transport of opioid receptors in sensory neurons,[102] enhanced G protein coupling of peripheral opioid receptors,[103] and facilitation of access of opioid agonists to their receptors by disruption of the perineural barrier.[104] Consistently, clinical studies indicate that perineural application of opioids along uninjured nerves (e.g., axillary plexus) does not reliably produce analgesic effects.[105] In addition, the production and secretion of endogenous opioid peptides from immune cells within inflamed tissue[2,20] appear to produce additive/synergistic interactions[106] rather than cross-tolerance at peripheral opioid receptors.[107] Peripheral opioid administration is regularly used and well documented in the case of perioperative intra-articular morphine[108-111] (www.guideline.gov). Intra-articular morphine also produces analgesia in chronic rheumatoid and osteoarthritis, where its potency was shown to be similar to standard intra-articular steroids and long lasting (up to 7 days), possibly because of morphine's anti-inflammatory activity.[112,113] In observational studies, opioids have been applied locally (e.g., in gels) to treat pain from skin ulcers, cystitis, cancer-related oral mucositis,

corneal abrasion, and bone injury. No significant adverse effects have been reported thus far.[73,99]

Other Analgesics and Adjuvants

Local anesthetics have been used topically, orally, intravenously, in trigger point injections, and in regional anesthetic techniques for selected chronic pain syndromes (see later in the section "Interventional Methods Used for Chronic Pain" and Chapters 30, 51, and 52). Their systemic application (e.g., oral mexiletine) exhibited mixed success in various neuropathies. The evidence to date supports mexiletine as a third-line drug in selected patients with diabetic neuropathy.[88] Meta-analyses indicate that intravenous infusion of local anesthetics is not effective for postherpetic neuralgia but may have short-lasting effects (30 minutes) on other types of neuropathic pain.[114,115] Severe side effects, including arrhythmias, dizziness, nausea, and fatigue, limit the systemic application of local anesthetics.

α_2-Adrenergic receptors are G protein–coupled receptors. Similar to opioids, α_2-agonists (clonidine) lead to opening of K^+ channels, inhibition of presynaptic Ca^{2+} channels, and inhibition of adenylyl cyclase. Thus, like opioids, α_2-agonists reduce release of neurotransmitters and decrease postsynaptic transmission, thereby resulting in an overall inhibitory effect.[116] The evidence available indicates that epidural or systemic clonidine is analgesic in patients with CRPS and neuropathic and cancer pain but that its use is limited by a high incidence of sedation, hypotension, and bradycardia.[88]

Baclofen activates $GABA_B$ receptors presynaptically and postsynaptically, which leads to a decrease in excitatory and an increase in inhibitory neurotransmission. In some reports baclofen was found to exhibit analgesic effects in trigeminal neuralgia and central neuropathic pain. The most common side effects are drowsiness, dizziness, and gastrointestinal distress.[88] Botulinum toxin is assumed to inhibit release of acetylcholine at the neuromuscular junction and to thereby alleviate muscle spasticity. The (unlabeled) use of botulinum toxin injections has produced inconsistent results in relieving headaches[117] and was not effective for myofascial trigger points and orofacial or neck pain.[118-120] Side effects include pain and erythema at the injection site and unintended paralysis of adjacent muscles.[121] Under the assumption of anti-inflammatory activity, steroid injections are frequently used epidurally or perineurally, albeit without convincing evidence of effectiveness (see the later section "Therapeutic Nerve Blocks").

Antiemetics are used to treat nausea, a frequent side effect of analgesics (particularly opioids) and a frequent complaint in cancer patients (also see Chapter 86).[122] Recommendations for the treatment of postoperative nausea and vomiting cannot readily be extrapolated to chronic pain patients. For example, in cancer patients causes other than opioids have to be considered, such as radiotherapy and chemotherapy, uremia, hypercalcemia, bowel obstruction, and increased intracranial pressure. In addition, pain itself, as well as anxiety, can cause nausea. Opioid-related nausea usually diminishes by tolerance within a few weeks. Management guidelines for the treatment of nausea and vomiting are available, and selection of antiemetics should be based on mechanism of action, if possible, although few controlled studies exist.[123-125] The medullary chemoreceptor trigger zone, gastrointestinal stimulation or failure, and vestibular and cortical mechanisms, as well as alterations in taste and smell, may contribute to nausea and vomiting, particularly in cancer patients. Most recommendations for the choice of antiemetic medication include gastrointestinal prokinetics (metoclopramide), phenothiazines (e.g., levomepromazine), dopamine receptor antagonists (e.g., haloperidol), serotonin antagonists (e.g., ondansetron), and antihistamines (e.g., cyclizine). In addition, the use of methylnaltrexone (an exclusively peripherally acting opioid antagonist), dexamethasone (unknown mechanism), the anticholinergic scopolamine, and the neurokinin-1 receptor antagonist aprepitant has been reported. Combinations of antiemetics with different modes of action can be used.[123,124,126] Many of these drugs cause undesirable side effects by themselves. For example, dimenhydrinate and cyclizine produce drowsiness but are especially effective if bowel obstruction, pharyngeal stimulation, or increased intracranial pressure coexists. Cannabinoids and benzodiazepines may be considered for nausea unresponsive to conventional antiemetics, although their efficacy is thought to be comparatively low.[124,127]

Laxatives are indicated when bowel movements are less frequent than three per week and associated with difficulty or discomfort. Risk factors for constipation include opioid medication, older age, advanced cancer, hypokalemia, immobilization, and therapy with tricyclic antidepressants, phenothiazines, anticonvulsants, diuretics, and iron supplements. Opioid-related is not associated with is mediated through intestinal and (partially) through central μ-receptors.[61] It is the most commonly occurring side effect of opioid medications in cancer patients and frequently does not exhibit tolerance. Ample fluid intake, fiber-rich nutrition, and mobilization are nonpharmacologic approaches to prophylaxis. Laxatives include bulk-forming, osmotic, and hyperosmolar agents; substances for colonic lavage; prokinetic drugs; and opioid antagonists. Recommendations usually include lactulose, senna, or polyethylene glycol as a first choice.[123,128] However, lactulose should be avoided in patients with impaired fluid intake, such as the elderly and those with advanced cancer. If insufficient, the agents of first choice may be combined with paraffin or anthraglycosides (bisacodyl). Rectal sorbitol or contrast medium is the choice for the next more intensified step. Prokinetic agents, such as metoclopramide, are sometimes added for refractory constipation. An interesting alternative for opioid-related constipation is opioid antagonists. To avoid central effects antagonizing analgesia or producing withdrawal, oral naloxone and the peripherally restricted antagonists methylnaltrexone and alvimopan were tested. Both demonstrated dose-dependent reversal of constipation.[123,129,130] In patients with malignant bowel obstruction, however, different algorithms have to be followed.[131]

Development of Novel Analgesics

Cannabinoids are currently under intense investigation. Animal and in vitro models have shown that derivatives of tetrahydrocannabinol produce antinociceptive effects and that cannabinoid receptors and their endogenous ligands are expressed in pain-processing areas of the brain, spinal cord, and periphery.[132] Animal studies have shown that peripheral cannabinoid receptors play a particularly prominent role in pain inhibition.[133,134] A meta-analysis of clinical studies concluded that the analgesic effects of cannabinoids are not superior to those of oral opioids such as codeine.[135] Psychotropic side effects, sedation, dizziness, cognitive

impairment, motor deficits, and other adverse effects are major limiting factors in clinical practice.[88,135] Ion channel blockers are also an area of intense research. Examples emerging as potential drug targets include $Na_V1.8$, a Na^+ channel expressed mainly in peripheral nociceptive neurons; $Ca_V2.2$, a voltage-gated Ca^{2+} channel blocked by the conotoxin ziconotide; TRPV1, the capsaicin receptor; and the $P2X_3$ receptor, a ligand-gated cation channel located on peripheral nociceptive neurons.[4,136,137]

Interventional Methods Used for Chronic Pain

The popularity of interventional methods has decreased over time. Although early pain therapists (e.g., Leriche) generally used "blocks" to treat pain,[138] the biopsychosocial concept of chronic pain has led to a much more cautious and judicial use of such techniques (see earlier in the section "Interdisciplinary Management of Chronic Pain"), particularly since most of these techniques are not evidence based. Block therapy alone is not usually curative, but it can facilitate participation in rehabilitation and therefore does have a role in the management of chronic pain. Regardless of which procedure is considered, a consensus on its use has to be reached within the interdisciplinary team.

Diagnostic Nerve Blocks

Neural blockade is thought to be a useful tool to better understand the mechanisms underlying pain in an individual patient and to provide a prognosis for planned neuroablative procedures (particularly in cancer pain) (also see Chapters 52 and 53). Differential blockade aims to selectively block either single peripheral nerves to identify an anatomic pain source or to selectively block only one type of nerve fiber (autonomic versus somatic).[139] Frequently, active and nonactive compounds are injected sequentially to differentiate drug-related from placebo responses. Differential neural blockade can be performed at the peripheral and central (neuraxial) levels. A popular protocol is the sequential intrathecal application of short- and long-acting local anesthetics (or opioids) or increasing concentrations of a local anesthetic, as originally described by Cherry and revised many times since then. Diagnostic neural blockade is used for low back pain, headache, neuropathic pain, and CRPS. Examples include zygapophyseal (facet) joint injections and medial branch blocks,[140] sacroiliac joint injections,[141] trigger point injections, spinal nerve blocks, occipital nerve blocks, and sympathetic blocks.[139] The last may be achieved by injection of local anesthetic at the sympathetic chain (e.g., stellate ganglion) or by intravenous regional infusion of sympatholytic drugs (e.g., phentolamine). However, an extensive review of the experimental and clinical literature concluded that none of these procedures has unequivocally proved to be clinically useful in controlled studies.[139] This was confirmed in recent systematic reviews.[140,141] In particular, the validity of diagnostic nerve blocks is limited by the complexity of factors determining pain perception (see earlier under "Biopsychosocial Concept of Pain" and "Interdisciplinary Management of Chronic Pain"). Furthermore, the assumption that local anesthetics can selectively produce conduction block of only one fiber type in a nerve is probably false.[139,142] Nevertheless, experienced and observant clinicians have found that such procedures may occasionally provide information that is helpful in guiding subsequent therapy. Nerve blockade may still play a role in the comprehensive workup of chronic pain patients, provided that the clinician takes great care in carrying out the technique, interpreting the results, and integrating them into interdisciplinary decisions.[139]

Therapeutic Nerve Blocks

Cancer Pain

Therapeutic nerve blocks are used mostly for the management of cancer-related pain (also see Chapter 52). Here, interventional treatment may represent the fourth step in the World Health Organization analgesic ladder.[143] Ninety percent to 95% of patients with cancer pain usually obtain adequate pain relief from pharmacologic management, and only a small fraction need interventions such as nerve blocks.[144-146] A comprehensive biopsychosocial approach to pain management that carefully balances risks against benefits in individual patients is a prerequisite for successful use of interventional techniques.[147] Therapeutic nerve blocks extend the treatment range when conservative methods fail to achieve tolerable levels of pain or side effects. For example, neuropathic and incidental (breakthrough) pain is sometimes poorly controlled by systemic analgesics and may be an indication for invasive therapy.

In patients with unresectable pancreatic cancer, neurolysis of the celiac plexus is frequently used for treatment of pain (Fig. 58-4). Patients with other upper abdominal malignancies, such as

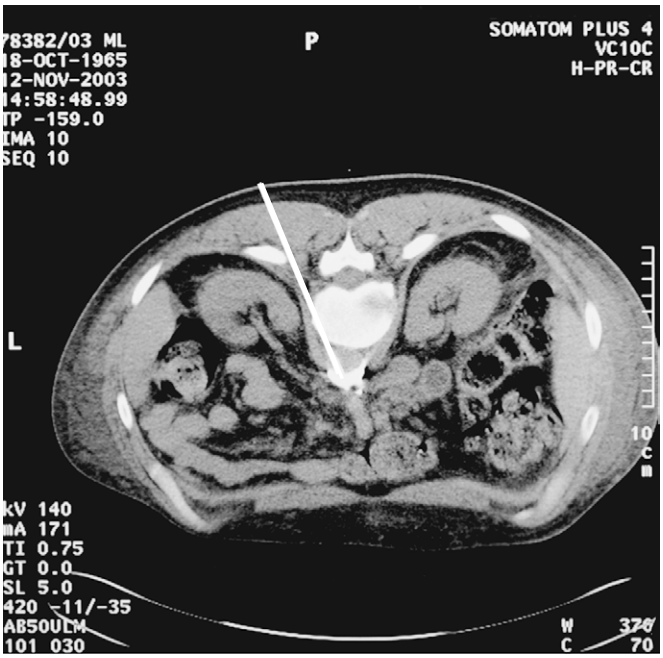

Figure 58-4 Transaortic approach to neurolysis of the celiac plexus with typical dye distribution ventral to the aorta. For details, see text. *(From the authors' archives.)*

hepatic or gastric cancer, may also benefit from this intervention. This technique is based on the assumption that nociceptive stimulation is transmitted along primary afferent fibers that travel with the sympathetic fibers of the splanchnic nerves arising from T5-T12 and with the parasympathetic efferent fibers that together form the celiac plexus. The ganglia are situated in the retroperitoneal space adjacent to the L1 vertebral body. Anatomic landmarks can be identified with the help of computed tomography, fluoroscopy, and ultrasound.[148] The most common techniques include the bilateral transcrural[149] and the unilateral transaortic approaches[150] with the use of alcohol (50% to 100%) or phenol (7% to 12%). In patients undergoing laparotomy, intraoperative neurolysis of the celiac plexus can also be performed.[151] Most centers advocate a diagnostic local anesthetic block to predict the analgesic and side effects (mostly diarrhea and hypotension).[152] A recent systematic review of RCTs comparing neurolytic celiac plexus blockade with standard treatment (oral NSAIDs and morphine) plus sham blockade or sham blockade alone concluded that celiac plexus neurolysis was associated with lower pain scores, decreased morphine use, and reduced constipation, albeit with minimal clinical significance.[153]

Less common sites for neurolysis are the intercostal nerves (e.g., in rib metastasis), the superior hypogastric ganglion, the ganglion impar, and the lumbar sympathetic ganglia (e.g., for pelvic tumors). In perineal pain caused by local infiltration of rectal cancer, intrathecal neurolysis may be considered if bladder and sphincter function is not of concern.[154] An indication for thoracic intrathecal or epidural neurolysis might be advanced lung cancer.[155] As a neurolytic agent, alcohol may be preferred because of its perceived higher success rate and longer duration of pain relief (3 to 6 months) than achieved with phenol (2 to 3 months), although no studies directly comparing these two agents are available. A diagnostic local anesthetic block to predict analgesic and side effects is advocated. Because alcohol is hypobaric and phenol is hyperbaric, the patient needs to be positioned accordingly during intrathecal neurolysis. In many cases pain relief is incomplete, but intake and side effects of opioids decrease. The limited period of pain reduction and the limited possibility of repeat injections are reasons why neurolysis is used mostly in patients with a short life expectancy.[156]

Non–Cancer-Associated Pain

Both the complexity of factors contributing to pain perception and perpetuation (see earlier in the sections "Biopsychosocial Concept of Pain" and "Interdisciplinary Management of Chronic Pain") and the detrimental long-term effects of nerve destruction (neuropathic pain caused by spontaneous ectopic neuronal discharge, upregulation of neuronal ion channels and excitatory amino acid receptors; see earlier in the sections "Physiologic Changes in Persistent Pain" and "Antiepileptic Drugs") caution against neuroablative procedures in patients with non–cancer-related pain. Nonetheless, many practitioners perform radiofrequency ablation or cryoneurolysis at the facet joints and sacroiliac joints, as well as several other destructive procedures.[157] However, such interventions have never been shown to provide long-term pain relief in RCTs.[157,158]

Nondestructive procedures include trigger point, epidural, perineural, and intra-articular injections of local anesthetics or steroids (or both). Steroids are used under the assumption of anti-inflammatory activity. For example, in chronic back or neck pain, injections into facet (or zygapophyseal) joints or along the medial branch from the posterior ramus of the spinal nerve root are frequently performed, but without convincing long-term results.[157] Similarly, injections into the sacroiliac joints or trigger points or occipital nerve blocks show no consistent long-lasting effects.[159-161] Epidural steroids are also used extensively for low back and neck pain but have not been shown to provide long-term pain relief in RCTs.[157] There is no evidence that the addition of other agents such as hyaluronic acid produces better results.[157] Neither preoperative nor postoperative nerve blocks have shown consistent improvement of phantom limb pain.[162] Some evidence from RCTs indicates that epidural or intrathecal steroids combined with local anesthetics can be effective in patients with herpes zoster and postherpetic neuralgia.[163]

Sympathetic nerve blocks with local anesthetics, often carried out as a series, are commonly used for herpes zoster–associated pain and CRPS, but evidence from RCTs is lacking. Some studies were able to demonstrate short-term effects but no clear reduction of the risk for postherpetic neuralgia.[163,164] Similarly, the long-term effectiveness of sympathetic blockade in CRPS has not been demonstrated in RCTs.[165,166] Anecdotal reports have described sympathetic blocks for ischemic pain, such as in peripheral vascular disease or Raynaud's disease.

In contrast with the lack of evidence of long-term effects, interventional techniques can produce short-term pain relief. In the context of interdisciplinary management, such techniques may be used to facilitate initial physical therapy sessions in patients with chronic nonmalignant pain.[157,159,167]

Continuous Catheter Techniques

Continuous drug delivery to the intrathecal or epidural space can be accomplished with programmable implanted pumps, implanted accessible reservoir systems, and tunneled exteriorized catheters. The principal benefit appears to be a reduction in systemic side effects. As with nerve blocks, evidence of effectiveness of these approaches is stronger for cancer pain than for chronic nonmalignant pain.

Cancer Pain

Only a small minority of cancer patients require neuraxial drug delivery because of intolerable side effects and refractory pain with systemic analgesics. The preponderance of evidence supporting this mode of drug delivery is derived from nonrandomized, uncontrolled studies.[148,168] The advantage of the epidural technique is its ubiquitous availability in most anesthesia departments, but disadvantages are the chance of inhomogeneous distribution of the analgesics, high drug volume requirements and possible systemic absorption, and limited duration of therapy as a result of local granuloma formation and technical failure.[148] The intrathecal approach allows homogeneous distribution of analgesics, low-volume injections, control of catheter positioning with aspiration of fluids, and long-term therapy with a minimal infection rate, although case reports on catheter tip inflammatory granulomas have occurred. Usually, morphine (1 to 15 mg dependent on preceding systemic dosage) or hydromorphone is recommended as the drug of first choice. For refractory pain, combinations with bupivacaine, clonidine, ziconotide, and other compounds have been used.[168] This technique should be used

only if the treatment center has the capacity for emergency in-house treatment, 24-hour emergency calls, and adequate home care service with stringent protocols to avoid infections. To transfer the patient from high-dose systemic to intraspinal analgesia, 24-hour monitoring is required. The initial intrathecal morphine dose is about 1% of the oral morphine equivalent. Thereafter, the systemic opioid dose is reduced by 50% and then slowly tapered by 10% daily to avoid withdrawal while at the same time allowing the usual systemic opioid doses as rescue medication.

Non–Cancer-Associated Pain

No RCTs are available, but a number of observational reports describe continuous catheter techniques for chronic nonmalignant pain.[148,169] Most of these studies used intrathecal morphine and some used hydromorphone, baclofen, or ziconotide in patients with chronic low back pain. On average, these patients exhibited increasing daily morphine doses over time and a high incidence (up to 25%) of complications such as catheter obstruction, catheter tip granuloma formation, pruritus, urinary retention, and infection. Effectiveness of these techniques in relieving pain or improving function in comparison with placebo, natural history, or other treatments has not been shown.[148,169]

Stimulation Techniques

Stimulation techniques frequently used in pain management include acupuncture, spinal cord (or dorsal column) stimulation (SCS), and transcutaneous electrical nerve stimulation (TENS). Acupuncture has been popular among patients for a long time and lately also within the medical community. Systematic reviews of sham-controlled studies of migraine prophylaxis and arthritic pain have shown that using traditional Chinese concepts of meridians and specified classic points is as effective as selection of acupuncture points at random.[170,171] The conclusion was that there is no specific effect of acupuncture when compared with standard medical migraine prophylaxis.[170] In osteoarthritis, adequately blinded studies have yielded inconclusive results.[171,172] In rheumatoid arthritis, acupuncture was not recommended.[173] In chronic low back pain, several reviews concluded that in the long term, acupuncture is not more effective than other treatments.[174-176] With respect to pain relief in cancer patients, the data available do not support its effectiveness either.[177]

The idea of modulating neural transmission by electrical stimulation dates back to ancient Rome with the observation that gout pain was alleviated by accidental contact with a torpedo fish. The gate theory of pain in the 1960s proposed that pain perception was influenced by the balance of firing between large and small nerve fibers and that retrograde nonpainful stimulation of large fibers would "close the gate" by adjusting the level of voltage.[148] This prompted the development of TENS, SCS, and various techniques of brain stimulation that have been applied in patients with refractory CRPS or neuropathic, low back, and ischemic pain. None of these methods have been validated by adequately powered and blinded RCTs for chronic pain.[178,179] Unblinded studies suggest that selected patients with CRPS or back pain might benefit from SCS, but controlled trials are needed. Complications include electrode displacement, infection, and battery failure.[179,180] Because it is noninvasive and easy to administer, TENS is used widely. However, systematic reviews of its application for chronic low back pain[181] and painful rheumatoid arthritis or osteoarthritis[182,183] have not yielded conclusive evidence of its effectiveness.

Perioperative Management of Patients with Chronic Pain

Characteristics of Chronic Pain Patients in the Perioperative Period

A chronic pain patient has certain distinctive features important for perioperative management (also see Chapter 87). Altered opioid sensitivity and behavior are the major points to be considered. The preanesthetic visit should therefore include questions regarding chronic pain and regular use of analgesics and adjuvant medication. Although a number of characteristics, including increased opioid demand, underreporting of pain, and noncompliance are known, only a few specific recommendations are available, such as an adequate increase in the opioid dose for analgesia, continuation of preoperative analgesics to prevent withdrawal, and intensive education to strengthen the patient's coping potential. No differences between specific techniques for postoperative analgesia (e.g., systemic, patient-controlled, or regional analgesia) have been shown thus far.

Some unique personality features are possibly relevant in the perioperative period. In the Minnesota Multiphasic Personality Inventory, chronic pain patients scored high on the hypochondria and hysteria scales.[184] The hypochondria scale tests preoccupation with physical discomfort, and the hysteria scale reveals information concerning coping with stress. Both are important parameters indicating a need for the patient to master the perioperative situation and have consequences on patient cooperation. Thus, studies have shown that rates of noncompliance with the patient-controlled analgesia (PCA) technique are increased and the duration of PCA treatment is prolonged.[32] Furthermore, the preoperative intensity of pain alone—independent of the use of analgesics—correlates positively with postoperative pain.[185] Anxiety is another factor that can complicate postoperative recovery. In clinical practice it may be difficult to distinguish normal from maladaptive anxiety, but in general, patients with cancer pain are more likely to be anxious than, for example, cancer patients without pain.[186] In addition, a chronic pain patient, especially one with cancer, is not as confident of recovery as other patients with chronic diseases.[32]

Chronic pain patients are often pretreated with opioids, COX inhibitors, antidepressants, anticonvulsants, or any combination of these treatments. They suffer from prolonged inactivity or neurologic deficits (or both), which increases the risk for adverse events during the perioperative period. Tolerance, drug interactions, and side effects may occur. In addition, inappropriate or excessive medication is commonly observed.[187] Chronic pain patients tend to underestimate and underreport their medication use. Studies suggest that this tendency is more pronounced for opioid analgesics than for other medications and is greater in women than in men.[188] Thus, undertreatment in the perioperative period may be unnoticed and might induce withdrawal, which can result in serious cardiopulmonary strain associated with the neuroexcitatory withdrawal syndrome. Some key issues are summarized in Box 58-1.

Box 58-1 Risk Factors in the Perioperative Management of Chronic Pain Patients

Conventional perioperative analgesia regimens do not meet the needs of chronic pain patients.

Unrelieved postoperative pain because of undermedication may provoke withdrawal.

Patients tend to underreport their medication.

With uncontrolled anxiety or fear of pain, patients tend to overestimate the effect of painful stimuli.

Epidural and intravenous opioid (including patient-controlled analgesia) requirements can be two to four times higher in opioid-consuming than in opioid-naive patients.

Prolonged recovery and need for postoperative analgesia should be expected.

Anxiety and insufficient coping result in poor compliance with analgesic strategies.

Individual variations in response to opioids may necessitate selection of the optimal drug and dosing by sequential trials.

Individual titration of doses to find the optimal balance between analgesia and adverse effects is required.

Adjuvant medication may interfere with anesthesia and postoperative analgesia.

Adapted from Kopf A, Banzhaf A, Stein C: Perioperative management of the chronic pain patient. Best Pract Res Clin Anaesthesiol 19:59-76, 2005.

Chronic Use of Analgesics and Adjuvant Drugs

During the past decade, chronic opioid medication has been discussed thoroughly in the literature (see earlier in the section "Opioids"). Together with aggressive marketing, this has gradually led to decreasing reservations by practitioners regarding the use of these drugs. As a result, opioids are used more frequently in patients with both cancer-related and non–cancer-related pain. Although this seems justified in cancer pain and certain chronic destructive diseases, indications for the use of opioids in patients with chronic non–cancer-related pain are less convincing (see "Opioids"). Nevertheless, the anesthesiologist is increasingly confronted with patients receiving long-term opioid treatment. Such pretreatment can result in a several-fold increased and prolonged requirement for systemic and epidural analgesics in the perioperative period when compared with opioid-naïve patients.[63,67,189] Chronic pain patients with prior opioid consumption also exhibit higher postoperative pain scores.[32] The increased postoperative analgesic demands may be due to lower pain thresholds or a need for higher drug concentrations. In addition, opioid requirements can be influenced by gender, genetic predisposition, age, type of surgery, and preoperative pain levels.[64,185] In contrast, opioid-related side effects (e.g., nausea, pruritus) may be less dominant.[32,190] Physicians and nurses may overestimate tolerance, addiction, and sedation but underestimate dependence.[67,191] A paramount concern is maintenance of adequate perioperative opioid dosing to prevent withdrawal.[67]

COX inhibitors are the most commonly used nonopioid analgesics. Unlike opioids, they are not associated with tolerance and physical dependence but produce serious side effects mainly in the gastrointestinal tract, coagulation system, and kidneys (see earlier in the section "Drugs Used for Chronic Pain"). A major concern for the anesthesiologist is coagulation disturbances and the increased risk of hematoma formation associated with spinal and epidural anesthesia. Practice guidelines do not differentiate between selective COX-2 and nonselective COX inhibitors. European and American societies disagree in their recommendations. Before neuraxial anesthesia, a 24- to 72-hour (in case of aspirin) drug-free interval is recommended by the German Society of Anesthesiology and Intensive Care Medicine and by the Spanish Consensus Forum, whereas the American Society of Regional Anesthesia and Pain Medicine does not believe that there is any added significant risk with these drugs. This discrepancy probably arises from the fact that development of a spinal or epidural hematoma is a rare event (about 1 in 220,000 spinal and 1 in 150,000 epidural anesthetics) and that none of the studies to date have a large enough patient population to predict that there is no risk of hematoma formation when COX inhibitors are continued before surgery.[192]

Antiepileptic drugs can interfere with anesthesia in different ways. The sedation produced by anticonvulsant drugs may have additive effects with anesthetics, whereas drug-induced enzyme induction could alter responses to or contribute to the organ toxicity of anesthetics. Gabapentin has a favorable side effect profile, and its relative absence of drug interactions allows continuation and rapid titration in the perioperative period.[193] Phenytoin and carbamazepine accelerate recovery from nondepolarizing muscle relaxants, but the mechanism is unclear. A kinetic rather than a pharmacodynamic cause is suggested.[194] Preoperative exclusion of toxic serum levels of phenytoin is recommended to reduce the risk for atrioventricular conduction block. States of disorientation, nystagmus, ataxia, and diplopia may be manifestations of excessive plasma concentrations. Carbamazepine may produce sedation, ataxia, nausea, and (rarely) bone marrow depression or hepatorenal dysfunction. Plasma sodium levels have to be monitored perioperatively to avoid hyponatremia. Oral valproic acid is commonly used for the prophylaxis of migraine, and intravenous valproic acid may be used to control episodic headaches.[195] It may inhibit the activity of hepatic microsomal enzymes and interfere with platelet aggregation.[196] Antiepileptics should never be discontinued abruptly to avoid central nervous system hyperexcitability. Stable dosages need to be maintained throughout the perioperative period.

Antidepressants are frequently used for neuropathic pain and for associated depression. Adverse effects are numerous and include sedation, anticholinergic effects, and cardiovascular changes. Electrocardiographic changes, such as prolongation of the PR interval and widening of the QRS complex, can occur, but previous suggestions of an increased risk for perioperative cardiac dysrhythmias have not been substantiated in the absence of drug overdose.[197] Therefore, antidepressants need not be discontinued before anesthesia, but increased anesthetic requirements may be expected because of enzyme induction. Postoperatively, the likelihood of delirium and confusion may potentially be increased as a result of additive anticholinergic effects. Selective serotonin reuptake inhibitors and atypical antidepressants such as mirtazapine or venlafaxine are less likely to interfere with anesthesia.

Ketamine is a mixed opioid agonist/NMDA antagonist that can produce analgesia at subanesthetic doses in selected patients with neuropathic pain.[198,199] Very rarely, patients taking oral

ketamine on a chronic basis will be encountered. In these cases, perioperative administration of ketamine should be discontinued because correct conversion from oral to intravenous ketamine is difficult.[200] Within analgesic dose ranges, the risk of a withdrawal syndrome is low.[199,201]

Benzodiazepines are not analgesic and rarely used for chronic pain with the exception of palliative care situations.[202] Nevertheless, chronic pain is a predictor of increased benzodiazepine use.[203] Side effects relevant to anesthesia include sedation and skeletal muscle weakness. Because of their long half-life, delayed withdrawal has to be anticipated and must be avoided by maintaining a stable perioperative dosage. Neuroleptics are also inappropriate but sometimes are used for chronic pain.[88] In the perioperative period it has to be kept in mind that neuroleptic malignant syndrome can develop in patients treated with antipsychotic drugs. Hyperthermia, hypertonicity of skeletal muscles, fluctuating levels of consciousness, and autonomic nervous system instability are typical symptoms.

Dependence, Addiction, and Pseudo-addiction

Physical dependence is defined as a state of adaptation manifested by a drug class–specific withdrawal syndrome that can be elicited by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, or administration of an antagonist (also see Chapter 101).[204] Dependence is not synonymous with tolerance (see earlier in the section "Opioids"). All opioids, benzodiazepines, and anticonvulsants produce clinically relevant physical dependence when administered for a prolonged period, but sometimes physical dependence can develop within hours of agonist exposure.[205,206] Thus, all patients with continuous preoperative opioid intake should be considered at risk for a withdrawal syndrome if adequate substitution of opioids in the perioperative period is withheld. Opioid and benzodiazepine withdrawal syndromes, especially tachycardia and hypertension, may be detrimental in high-risk cardiac patients. Rapid withdrawal from an anticonvulsant drug may trigger seizures, anxiety, and depression.[207]

Addiction is defined as a behavioral syndrome characterized by evidence of psychological dependence (craving), uncontrolled/compulsive drug use despite harmful side effects, and other drug-related aberrant behavior (e.g., altering prescriptions, manipulating health care providers, drug hoarding or sales, unsanctioned dose escalation).[84,204] Reviews indicate that the prevalence of opioid addiction is as high as 50% in patients with chronic nonmalignant pain and up to 7.7% in patients with cancer-related pain.[84,85] Many comments regarding opioid-consuming chronic pain patients also apply to those who abuse or are addicted to opioids. The daily dose of opioids in abusing or addicted patients is typically larger, such patients often have coexisting psychiatric diseases (depression, anxiety, psychosis), and the known history of abuse may lead to tempered use of opioids by health care providers, which makes these patients particularly vulnerable to inadequate postoperative pain control.[67] Additional special considerations in the management of drug-addicted patients are discussed elsewhere (e.g., see Carroll and colleagues and Peng and coworkers[67,208]).

Pseudo-addiction describes a situation in which medical personnel do not provide a sufficient dosage of medication. This provokes repetitive demands from the patient for analgesics and may be interpreted to be an indication of "drug-seeking behavior." Pseudo-addiction can be avoided with adequate algorithms and regular education of health care providers.[62]

Management and Practical Recommendations

Preoperative Evaluation

Preanesthesia evaluation is necessary to educate patients, to organize resources for preoperative improvement of the patient's physical function, to choose optimal anesthetic techniques, and to formulate plans for postoperative recovery, including perioperative pain management.[67] Misconceptions about the surgical procedure, the role of the anesthesiologist in perioperative care, and postoperative pain treatment are common in patients.[209] A thorough history must be obtained to identify all preoperative medications, including opioids, other analgesics, and adjuvants, as well as signs of psychiatric comorbidity and aberrant drug-related behavior. Consultation with a pain specialist should always be considered. Pertinent issues and practical recommendations are summarized in Boxes 58-1 and 58-2.

Perioperative Management

To avoid opioid withdrawal, the preoperative systemic dosage has to be continued throughout the perioperative period, and mixed agonist/antagonists (buprenorphine, nalbuphine) must be avoided. For minor surgery, oral slow-release opioid medication may be continued at its regular intervals. For medium and major surgery, oral opioids should be discontinued and replaced with equivalent doses of intravenous opioids, which have to be maintained for the entire perioperative period. This applies to general as well as regional anesthesia. The anesthesia technique should be selected on an individual basis because no data are available in favor of general, regional, or combined anesthesia for this patient population. The frequency and extent of monitoring techniques should be adapted to the risk of patient instability. Pain should be periodically assessed during emergence and recovery.[210] For thorough evaluation of pain relief, functional criteria (ability to cough, breathe deeply, perform physical therapy, ambulate) should be used in conjunction with patient-generated pain ratings to determine the end points for analgesic therapy.[32] One has to keep in mind that pain acts as an antagonist to central nervous system depressants and in particular to the respiratory depressant effects of opioids. Thus, any surgical procedure that removes a major nociceptive stimulus (e.g., a tumor) may lead to unopposed opioid-mediated respiratory depression or somnolence in the postoperative period. For patients without chronic pain, randomized trials suggest that a multimodal approach to ensuring adequate postoperative analgesia may facilitate return of gastrointestinal function, be cardioprotective, reduce pulmonary complications, and shorten length of stay in the intensive care unit and hospital.[211] Whether these findings are applicable to chronic pain patients is unknown. Individually adapted regimens are usually superior to "conventional" analgesia, regardless of the specific analgesia technique used.[212] In minor and medium-complexity surgery, an opioid/NSAID combination should always be considered to enhance the effects of the opioid. If pain is not sufficiently controlled with opioids and NSAIDs, adjuvant anal-

Box 58-2 Preoperative Considerations and Recommendations for Patients with Chronic Pain

Take a thorough history to identify all analgesic and adjuvant medications, risk factors, and comorbidity.

Educate the patient about the perioperative procedures, the potential for aggravated pain, and increased opioid requirements.

Communicate plans to the designated anesthesiologist in the operating room, the postanesthesia care unit, and the surgical and nursing personnel on the ward.

Differentiate among addiction, pseudo-addiction, and physical dependence in patients maintained on long-term opioid medication.

Expect physical dependence in patients receiving long-term opioid medication.

Continue previous long-acting opioid analgesics for short procedures.

For major surgery, calculate and order a background infusion of an equianalgesic opioid dose for patients held without oral intake for longer than 8 hours to be started in the operating room.

Order regular opioid medication on the morning of surgery.

Maintain anticonvulsant drugs and benzodiazepines at preoperative doses.

Discontinue all other adjuvants if kept without oral intake for longer than 24 hours.

Identify untreated depressive disorders with screening questions for disturbed sleep, depressed mood, reduced concentration, self-confidence, and motivation.

Identify untreated anxiety disorders with screening questions for restlessness, irritability, difficult-to-control anxiousness, and worrying.

Consider referral to a pain specialist for evaluation.

Choose regional or general anesthesia based on individual considerations.

Adapted from Kopf A, Banzhaf A, Stein C: Perioperative management of the chronic pain patient. Best Pract Res Clin Anaesthesiol 19:59-76, 2005.

gesics such as anticonvulsants or alternative routes of opioid administration may be required.[67] Support from a multimodal pain treatment facility should be requested. Apart from the choice of analgesia techniques and exploitation of opioids, optimization of organizational structures is a key factor for improving perioperative analgesia.[213] If addiction is suspected, the patient should be re-evaluated after the acute postoperative pain has resolved.[214] Specific risk factors in chronic pain patients are summarized in Box 58-1.

Postoperative Regional Anesthesia

Despite the lack of strong evidence indicating superiority of particular anesthetic techniques for postoperative analgesia in chronic pain patients, individual considerations may favor regional anesthesia, particularly since these patients are prone to intensified postoperative pain experiences. Chronically opioid-consuming patients need their daily systemic dosage by the intravenous or oral route to prevent withdrawal.[67] In addition, postoperative analgesia via an epidural or plexus catheter may be accomplished with a combination of local anesthetics and opioids, as in patients without chronic pain (see Chapters 51 and 87). However, higher doses of epidural opioids are recommended because cross-tolerance between orally and epidurally administered opioids has been described.[190] Epidural lipophilic opioids (fentanyl, sufentanil) appear to provide better postoperative pain relief than epidural morphine does in chronically opioid-consuming patients,[215,216] an observation that has been attributed to the need for lower receptor occupancy or incomplete cross-tolerance between morphine and sufentanil.[217]

Postoperative Intravenous Opioids

The total opioid dose required consists of the daily dose taken before and the dose made necessary by surgical stimulation. A continuous perioperative intravenous opioid infusion equivalent to the regular daily dosage is recommended if the oral route is unavailable.[67,212] Additional bolus doses of opioid or nonopioid analgesics (or both) have to be titrated to individual needs to achieve adequate pain control in the postanesthesia care unit. Depending on local circumstances, this may be patient, nurse, or physician controlled. The size of the bolus should be equal to the hourly dose of the background infusion. Once the patient demands less than four extra bolus doses per day, the background infusion may be reduced in daily steps of about 20% to 30%. For calculation of opioid dose equivalents, the relative potency, half-life, bioavailability, and route of administration have to be considered.[218] As soon as possible, oral medication should be resumed. Intravenous doses during the first 24 to 48 hours after surgery should be converted to oral dose equivalents. Half the total dosage may be delivered as long-acting and half as short-acting breakthrough medication.[67]

Perioperative Transdermal Opioids

Transdermal fentanyl patches are relatively reliable in administering controlled amounts of the drug to the circulation over long periods. However, during surgery the amount of drug delivered to the patient may shift significantly. Changes in intravascular volume, body temperature, and volatile anesthetics alter skin permeability and perfusion and thereby result in relatively large fluctuations in transdermal fentanyl passage. In addition, forced-air warming blankets and heat packs applied onto the patch itself can lead to several-fold increases in permeation of fentanyl through the skin.[63] Thus, in major surgery, removal of transdermal systems is advisable to avoid unforeseen decreases and increases in systemic opioid uptake. The transdermal opioid dose should be converted to intravenous morphine administered as a continuous background infusion.[218] Pertinent issues and practical recommendations are summarized in Box 58-3.

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Box 58-3 Intraoperative and Postoperative Management Issues and Practical Recommendations

Start a background opioid infusion immediately when the patient arrives in the operating room.

Remove the opioid patch when major surgery is planned; with minor surgery, the patch may be continued without a background infusion.

Every chronic pain patient should be seen postoperatively three times daily to evaluate pain at rest, pain with exercise (e.g. coughing), nausea, sedation, mobilization, and sleep quality.

Monitor closely for signs of respiratory depression and withdrawal (e.g., unexplained tachycardia, restlessness, sweating, confusion, hypertension).

Integrate the patient in the acute pain service protocol if available.

Titrate a short-acting opioid for acute pain at two to four times the usual starting dose needed for an opioid-naive patient.

Add cyclooxygenase inhibitors, anticonvulsants, and other adjuvants as needed.

Evaluate the demand-delivery ratio of patient-controlled analgesia frequently; adapt the demand dose to the background infusion (the demand dose equals the hourly dose of the background infusion).

Increase the background infusion in patient-controlled analgesia in proportion to the cumulative daily opioid demand dose (add 50% to 75% of the daily demand dose to the background infusion).

Change the technique of postoperative analgesia if inadequate use persists despite repeated patient education.

If insufficient epidural analgesia is achieved with morphine, use epidural fentanyl or sufentanil.

In the event of escalation of the intravenous opioid dose, consider spinal/epidural opioid application or switch the intravenous agonist.

Reduce daily opioid doses after the second postoperative day stepwise to the preexisting dose.

Switch back to oral or transdermal medication as early as possible; use 50% to 75% of the last daily intravenous opioid dose as slow-release oral or transdermal delivery plus the rest as a demand dose.

When switching back to the transdermal route, consider 12- to 16-hour delayed effects and supply the patient for this period with sufficient on-demand analgesia.

Do not attempt to solve a chronic pain problem in the immediate postoperative period.

Use nonpharmacologic techniques (distraction, relaxation) when appropriate and offer counseling in the pain unit after postoperative recovery.

Adapted from Kopf A, Banzhaf A, Stein C: Perioperative management of the chronic pain patient. Best Pract Res Clin Anaesthesiol 19:59-76, 2005.

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Peter D. Slinger and Javier H. Campos

59 Anesthesia for Thoracic Surgery

Key Points

1. Patients undergoing pulmonary resection should have a preoperative assessment of their respiratory function in three areas: lung mechanical function, pulmonary parenchymal function, and cardiopulmonary reserve (the "three-legged stool" of respiratory assessment).
2. After lung resection surgery, it is usually possible to wean and extubate patients with adequate predicted postoperative respiratory function in the operating room provided they are "AWaC" (alert, warm, and comfortable).
3. Interventions that have been shown to decrease the incidence of respiratory complications in high-risk patients undergoing thoracic surgery include cessation of smoking, physiotherapy, and thoracic epidural analgesia.
4. Geriatric patients are at a high risk for cardiac complications, particularly arrhythmias, after large pulmonary resections. Preoperative exercise capacity is the best predictor of post-thoracotomy outcome in the elderly.
5. The ability to perform fiberoptic bronchoscopy and a detailed knowledge of bronchial anatomy are necessary for anesthesiologists to provide reliable lung isolation.
6. Use of double-lumen endobronchial tubes (DLTs) is the standard method of providing lung isolation in adults. Bronchial blockers are a reasonable alternative for lung isolation in patients with abnormal upper or lower airways.
7. With the use of intravenous anesthetic techniques or volatile anesthetics at less than or equal to 1-MAC doses, hypoxemia during one-lung ventilation (OLV) occurs infrequently. The use of continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) as treatment for hypoxemia during OLV should be guided by the individual patient's lung mechanics.
8. The use of large tidal volumes during OLV (e.g., 10 mL/kg) can contribute to acute lung injury, particularly in patients at increased respiratory risk, such as after pneumonectomies.
9. Anesthetic management of a patient with an anterior or superior mediastinal mass should be guided by the patient's symptoms and the preoperative CT scan and echocardiography. The fundamental principle of anesthetic management for these patients is *noli ponti ignii consumere* ("don't burn your bridges").
10. Continuous paravertebral local anesthetic blockade combined with multimodal analgesia is a reasonable alternative to epidural analgesia for thoracic surgery with fewer side effects.

Thoracic anesthesia encompasses a wide variety of diagnostic and therapeutic procedures involving the lungs, airways, and other intrathoracic structures. As the patient population presenting for noncardiac thoracic surgery has evolved so have the anesthetic techniques to manage these patients. Thoracic surgery at the beginning of the past century was primarily for infectious indications (e.g., lung abscess, bronchiectasis, empyema). Although these cases still present for surgery in the postantibiotic era, now the most common indications are related to malignancies (pulmonary, esophageal, and mediastinal). In addition, in the past 2 decades we have seen the beginnings of surgical therapy for end-stage lung diseases with procedures such as lung transplantation and lung volume reduction. Fundamental to anesthetic management for the majority of thoracic procedures are two techniques: lung isolation to facilitate surgical access within the thorax and management of one-lung anesthesia. In this chapter we initially discuss preanesthetic assessment for thoracic surgery, then outline intraoperative management principles common to most thoracic surgical procedures, then discuss specific anesthetic considerations in common and less-common surgical operations, and finish with a description of postoperative management issues in thoracic surgical patients.

Preoperative Evaluation of the Thoracic Surgery Patient

Preoperative anesthetic assessment before chest surgery is a continually evolving science and art. Recent advances in anesthetic management, surgical techniques, and perioperative care have expanded the group of patients now considered to be "operable."[1] This discussion focuses primarily on preanesthetic assessment for pulmonary resection surgery in cancer patients. However, the basic principles described will apply to all other types of nonmalignant pulmonary resections and to other chest surgery. The major difference is that in patients with malignancy the risk-benefit ratio of canceling or delaying surgery pending other investigation/therapy is always complicated by the risk of further spread of cancer during any extended interval prior to resection. This is never completely "elective" surgery.

Although 87% of patients with lung cancer will die of their disease, the 13% cure rate represents approximately 26,000 survivors per year in North America. Surgical resection is responsible for essentially all of these cures. A patient with a "resectable" lung cancer has a disease that is still local or locoregional in scope and can be encompassed in a plausible surgical procedure. An "operable" patient is someone who can tolerate the proposed resection with acceptable risk. Several general points should be appreciated in the assessment of pulmonary resection patients.

Currently, the reality of practice patterns in anesthesia has changed such that a patient is commonly assessed initially in an outpatient clinic and often not by the member of the anesthesia staff who will actually administer the anesthesia. The actual contact with the responsible anesthesiologist may be only 10 to 15 minutes before induction. It is necessary to organize and standardize the approach to preoperative evaluation for these patients into two temporally disjoint phases: the initial (clinic) assessment and the final (day-of-admission) assessment. There are elements vital to each assessment that will be described.

There has been a comparatively small volume of research on the short-term (<6 weeks) outcome of these patients. However, this research area is currently very active and there are several studies that can be used to guide anesthetic management in the immediate perioperative period where it has an influence on outcome.

An increasing number of thoracic surgeons are now being trained to perform "lung-sparing" resections such as sleeve-lobectomies or segmentectomies and to perform resections with minimally invasive techniques such as video-assisted thoracoscopic surgery (VATS). The postoperative preservation of respiratory function has been shown to be proportional to the amount of functioning lung parenchyma preserved. To assess patients with limited pulmonary function the anesthesiologist must appreciate these newer surgical options in addition to the conventional open lobectomy or pneumonectomy.

Most commonly it is not the anesthesiologist's function to assess these patients to decide who is or is not an operative candidate. In the majority of situations, the anesthesiologist will be seeing the patient at the end of a referral chain from chest or family physician to surgeon. At each stage there should have been a discussion of the risks and benefits of operation. It is the anesthesiologist's responsibility to use the preoperative assessment to identify those patients at elevated risk and then to use that risk assessment to stratify perioperative management and focus resources on the high-risk patients to improve their outcome. This is the primary function of the preanesthetic assessment. However, there are occasions when the anesthesiologist is asked to contribute an opinion whether a specific high-risk patient will tolerate a specific surgical procedure. This may occur preoperatively but also occurs intraoperatively when the surgical findings suggest that a planned procedure, such as a lobectomy, may require a larger resection, such as a pneumonectomy. For these reasons it is imperative that the anesthesiologist have a complete preoperative knowledge of the patient's medical status and also an appreciation of the pathophysiology of lung resection surgery.

Prethoracotomy assessment naturally involves all of the factors of a complete anesthetic assessment: past history, allergies, medications, upper airway, and so on. This section will concentrate on the additional information, beyond a standard anesthetic assessment, that the anesthesiologist needs to manage a pulmonary resection patient.

Perioperative Complications

The major causes of perioperative morbidity and mortality in the thoracic surgical population are respiratory complications. Major respiratory complications include atelectasis, pneumonia, and respiratory failure, occur in 15% to 20% of patients, and account for the majority of the expected 3% to 4% mortality.[2] For other types of surgery, cardiac and vascular complications are the leading causes of early perioperative morbidity and mortality. Cardiac complications such as arrhythmia and ischemia occur in 10% to 15% of the thoracic population.

Assessment of Respiratory Function

The best assessment of respiratory function comes from a detailed history of the patient's quality of life. All pulmonary resection patients should have baseline simple spirometry preoperatively.[3]

Objective measures of pulmonary function are required to guide anesthetic management and to have this information in a format that can be easily transmitted between members of the health care team. It is useful to think of the respiratory function in three related but somewhat independent areas: respiratory mechanics, gas exchange, and cardiorespiratory interaction (see Chapter 15). These can be remembered as the basic functional units of extracellular respiration that are to get the oxygen: (1) into the alveoli, (2) into the blood, and (3) to the tissues (the process is reversed for carbon dioxide removal).

Respiratory Mechanics

Many tests of respiratory mechanics and volumes show correlation with post-thoracotomy outcome: forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), maximal voluntary ventilation (MVV), residual volume/total lung capacity ratio (RV/TLC), and so on (see Chapter 15 on pulmonary function testing). It is useful to express these as a percent of predicted volumes corrected for age, sex, and height (e.g., FEV_1%). Of these the most valid single test for post-thoracotomy respiratory complications is the predicted postoperative FEV_1 ($ppoFEV_1$%),[4] which is calculated as follows:

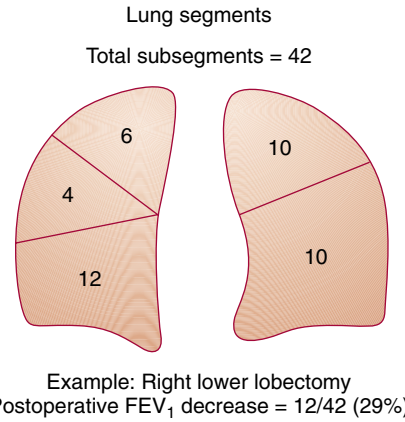

Figure 59-1 The number of subsegments of each lobe is used to calculate the predicted postoperative pulmonary function. For example, after a right lower lobectomy a patient with a preoperative FEV_1 (or DLco) 70% of normal would be expected to have a postoperative $FEV_1 = 70\% \times (1 - 29/100) = 50\%$. (*Reproduced with permission from Slinger PD, Johnston MR: Preoperative assessment: an anesthesiologist's perspective. Thorac Surg Clin 15:11, 2005.*)

$$\text{ppoFEV}_1\% = \text{preoperative FEV}_1\% \times \left(1 - \%\ \text{functional lung tissue removed}/100\right)$$

One method of estimating the percent of functional lung tissue is based on a calculation of the number of functioning subsegments of the lung removed (Fig. 59-1). Patients with a $ppoFEV_1$ greater than 40% are at low risk for postresection respiratory complications. The risk of major respiratory complications is increased in the subgroup with a $ppoFEV_1$ less than 40% (although not all patients in this subgroup develop respiratory complications), and patients with a $ppoFEV_1$ less than 30% are at high risk.

Lung Parenchymal Function

As important to the process of respiration as the mechanical delivery of air to the distal airways is the subsequent ability of the lung to exchange oxygen and carbon dioxide between the pulmonary vascular bed and the alveoli. Traditionally, arterial blood gas data such as Pao_2 less than 60 mm Hg or $Paco_2$ greater than 45 mm Hg have been used as cutoff values for pulmonary resection. Cancer resections have now been successfully done or even combined with volume reduction in patients who do not meet these criteria, although they remain useful as warning indicators of increased risk. The most useful test of the gas exchange capacity of the lung is the diffusing capacity for carbon monoxide (DLco). The DLco correlates with the total functioning surface area of the alveolar-capillary interface. This simple noninvasive test, which is included with spirometry and plethysmography by most pulmonary function laboratories, is a useful predictor of perioperative mortality but not long-term survival.[5] The corrected DLco can be used to calculate a postresection (ppo) value using the same calculation as for the FEV_1 (see Fig. 59-1). A ppoDLco less than 40% predicted correlates with both increased respiratory and cardiac complications and is, to a large degree, independent of the FEV_1. The National Emphysema Treatment Trial has shown that patients with a preoperative FEV_1 or DLco less than 20% had an unacceptably high perioperative mortality rate.[6] These can be considered as the absolute minimal values compatible with successful outcome.

Cardiopulmonary Interaction

The final and perhaps most important assessment of respiratory function is an assessment of the cardiopulmonary interaction. Formal laboratory exercise testing is currently the "gold standard" for assessment of cardiopulmonary function,[7] and the maximal oxygen consumption (Vo_{2max}) is the most useful predictor of postthoracotomy outcome. The risk of morbidity and mortality is unacceptably high if the preoperative Vo_{2max} is less than 15 mL/kg/min.[8] Few patients with a Vo_{2max} greater than 20 mL/kg/min have respiratory complications (for comparison, the highest Vo_{2max} recorded is 85 mL/kg/min by the American cyclist Lance Armstrong in 2005[8]). Complete laboratory exercise testing is expensive. Several alternatives have been demonstrated to be valid surrogate tests for prethoracotomy assessment. The traditional, and still extremely useful, test in ambulatory patients is stair climbing.[9] Stair climbing is done at the patient's own pace but without stopping and is usually documented as a certain number of flights. There is no exact definition for a "flight," but 20 steps at 6 in/step is a frequent value. The ability to climb five flights correlates with a Vo_{2max} greater than 20 mL/kg/min, and climbing two flights corresponds to a Vo_{2max} of 12 mL/kg/min. A patient unable to climb two flights is at extremely high risk.[10]

The distance that a patient can walk during a 6-minute test (6MWT) also shows an excellent correlation with Vo_{2max} and requires little or no laboratory equipment. A 6MWT distance of less than 2000 ft (610 m) correlates to a Vo_{2max} less than 15 mL/kg/min and also correlates with a fall in oximetry (Spo_2) during exercise. Patients with a decrease of Spo_2 greater than 4% during exercise (stair climbing two or three flights or equivalent)[11] are at increased risk for morbidity and mortality. Postresection exercise capacity can be estimated based on the amount of functioning lung tissue removed (see Fig. 59-1). An estimated $ppoVo_{2max}$ less than 10 mL/kg/min may be an absolute contraindication to pulmonary resection. In a small series,[12] the mortality rate was 100% (3/3) patients with a $ppoVo_{2max}$ less than 10 mL/kg/min.

After pulmonary resection there is a degree of right ventricular dysfunction that seems to be in proportion to the amount of functioning pulmonary vascular bed removed. The exact etiology and duration of this dysfunction remains unknown. Clinical evidence of this hemodynamic problem is minimal when the patient is at rest but is dramatic when the patient exercises, leading to elevation of pulmonary vascular pressures, limitation of cardiac output, and absence of the normal decrease in pulmonary vascular resistance usually seen with exertion.[13]

Ventilation-Perfusion Scintigraphy

Prediction of postresection pulmonary function can be further refined by assessment of the preoperative contribution of the lung or lobe to be resected using ventilation-perfusion $\left(\dot{V}/\dot{Q}\right)$ lung scanning. If the lung region to be resected is nonfunctioning or minimally functioning, the prediction of postoperative function can be modified accordingly. This is particularly useful in pneumonectomy patients,[14] and $\dot{V}/\dot{Q}$ scanning should be considered for any pneumonectomy patient who has a preoperative FEV_1 and/or DLco less than 80%. Because the $\dot{V}/\dot{Q}$ scanning is performed at rest while the FEV_1 is a forced maneuver, there is always some error in estimating the true eventual lung mechanics after a pulmonary resection.

Split-Lung Function Studies

A variety of methods have been described to try and simulate the postoperative respiratory situation by unilateral exclusion of a lung or lobe with an endobronchial tube/blocker or by pulmonary artery balloon occlusion of a lung or lobe artery, or by both. These tests have not shown sufficient predictive validity for universal adoption in lung resection patients. Lewis and colleagues[15] have shown that in a group of patients with chronic obstructive pulmonary disease (COPD) (ppoFEV_1 < 40%) undergoing pneumonectomy there were no significant changes in the pulmonary vascular pressures intraoperatively when the pulmonary artery was clamped but the right ventricular ejection fraction and cardiac output decreased. Echocardiography may offer more useful information than vascular pressure monitoring in these patients.[16] For the present, split-lung function studies have been replaced in most centers by a combination assessment involving, spirometry, DLco, exercise tolerance, and $\dot{V}/\dot{Q}$ scanning.

Combination of Tests

No single test of respiratory function has shown adequate validity as a sole preoperative assessment. Before surgery, an estimate of respiratory function in all three areas—lung mechanics, parenchymal function, and cardiopulmonary interaction—should be made for each patient. These three aspects of pulmonary function form the "three-legged stool" that is the foundation of prethoracotomy respiratory assessment (Fig. 59-2). These data can then be used to plan intraoperative and postoperative management (Fig. 59-3) and also to alter these plans when intraoperative surgical factors necessitate that a resection becomes more extensive than foreseen. If a patient has a ppoFEV_1 less than 40%, it should be possible for that patient to be extubated in the operating room at the conclusion of surgery, assuming the patient is alert, warm, and comfortable ("AWaC"). Patients with a ppoFEV_1 less than 40% will usually comprise about a fourth of an average thoracic surgical population. If the ppoFEV_1 is more than 30% and exercise tolerance and lung parenchymal function exceed the increased risk thresholds, then extubation in the operating room should be possible, depending on the status of associated medical conditions. Those patients in this subgroup who do not meet the minimal criteria for cardiopulmonary and parenchymal function should be considered for staged weaning from mechanical ventilation postoperatively so that the effect of the increased oxygen consumption of spontaneous ventilation can be assessed. Patients with a ppoFEV_1 of 20% to 30% and favorable predicted cardiorespiratory and parenchymal function can be considered for early extubation if thoracic epidural analgesia if used or if the resection is performed with VATS. Otherwise, these patients should have a postoperative staged weaning from mechanical ventilation. In the borderline group (ppoFEV_1 30%-40%) the presence of several associated factors and diseases that should be documented during the preoperative assessment will enter into the considerations for postoperative management (see later).

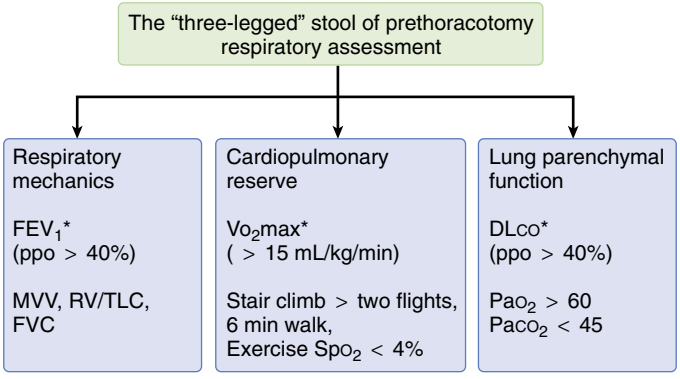

Figure 59-2 The "three-legged" stool of prethoracotomy respiratory assessment. ppo, predicted postoperative. (*Reproduced with permission from Slinger PD, Johnston MR: Preoperative assessment: An anesthesiologist's perspective. Thorac Surg Clin 15:11, 2005.*)

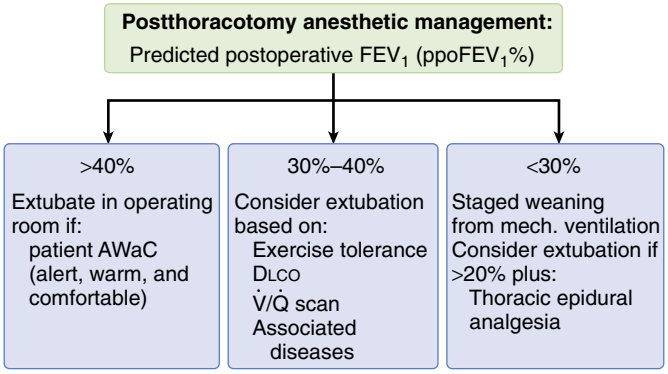

Figure 59-3 Anesthetic management guided by preoperative assessment and the amount of functioning lung tissue removed during surgery. ppo, predicted postoperative. (*Reproduced with permission from Slinger PD, Johnston MR: Preoperative assessment: An anesthesiologist's perspective. Thorac Surg Clin 15:11, 2005.*)

Concomitant Medical Conditions

Cardiovascular Disease

Cardiac complications represent the second most common cause of perioperative morbidity and mortality in the thoracic surgical population.

Ischemia

Because the majority of pulmonary resection patients have a smoking history, they already have one risk factor for coronary artery disease. Elective pulmonary resection surgery is regarded as an "intermediate risk" procedure in terms of perioperative cardiac ischemia.[17] The overall documented incidence of postthoracotomy ischemia is 5% and peaks on days 2 to 3 postoperatively. Beyond the standard history, physical examination, and electrocardiogram, routine screening testing for cardiac disease does not appear to be cost effective for all prethoracotomy patients. Noninvasive testing is indicated in patients with major (unstable ischemia, recent infarction, severe valvular disease, significant arrhythmia) or intermediate (stable angina, remote infarction, previous congestive failure, or diabetes) clinical predictors of myocardial risk (see Chapter 35). Therapeutic options to be considered in patients with significant coronary artery disease are optimization of medical therapy, coronary angioplasty, or coronary artery bypass, either before or at the time of lung resection. Timing of lung resection surgery after a myocardial infarction is always a difficult decision. Limiting the delay to 4 to 6 weeks in a medically stable and fully investigated and optimized patient seems acceptable after myocardial infarction. The appropriate

delay after coronary stenting is controversial. Surgery needs to be delayed until it is safe to temporarily discontinue major antiplatelet drugs (except aspirin). This represents a delay of 3 months for bare metal stents and of more than 6 months for drug-eluting stents.[18] The use of prophylactic β-blockers to reduce the risk of perioperative ischemia in thoracic surgical patients with known or suspected coronary artery disease in the absence of contraindications seems justified based on the recent literature.[17]

Arrhythmia

Dysrhythmias (see Chapter 42) are a common complication of pulmonary resection surgery, and the incidence is 30% to 50% of patients in the first week postoperatively when Holter monitoring is used.[19] Of these arrhythmias, 60% to 70% are atrial fibrillation. Several factors correlate with an increased incidence of arrhythmias: extent of lung resection (pneumonectomy, 60%, versus lobectomy, 40%, versus nonresection thoracotomy, 30%) intrapericardial dissection, intraoperative blood loss, and age of the patient. Extrapleural pneumonectomy patients are a particularly high-risk group.[20]

Two factors in the early post-thoracotomy period interact to produce atrial arrhythmias: (1) increased flow resistance through the pulmonary vascular bed due to permanent (lung resection) or transient (atelectasis, hypoxemia) causes, with attendant strain on the right side of the heart; and (2) increased sympathetic stimuli and oxygen requirements, which are maximal on the second postoperative day as patients become more mobile.

In pneumonectomy patients, versus lobectomy patients, followed for 24 hours with right ventricular ejection fraction (RVEF) catheters there was a significant fall of RVEF on the first postoperative day. This was accompanied by an increase in right ventricular size and in pulmonary artery pressures. Pneumonectomy patients did not demonstrate the early postoperative increase in oxygen delivery, oxygen consumption, or cardiac index seen in lobectomy patients.[21] This suggests that in some pneumonectomy patients the right side of the heart may not be able to increase its output adequately to meet the usual postoperative stress. Transthoracic echocardiographic studies have shown that pneumonectomy patients develop an increase in right ventricular systolic pressure as measured by the tricuspid regurgitation jet on postoperative day 2 but not on day 1. An increase in tricuspid regurgitation jet velocity has been associated with post-thoracotomy supraventricular tachyarrhythmias.[20] Preoperative exercise testing, which assesses the cardiopulmonary interaction, can predict post-thoracotomy arrhythmias. Patients with COPD are more resistant to pharmacologic rate control when they develop post-thoracotomy atrial fibrillation and often require multiple drugs.[22]

Many antiarrhythmic agents have been tried to decrease the incidence of atrial arrhythmias after lung surgery, especially digoxin preparations. Yet, digoxin does not prevent arrhythmias after pneumonectomy or other intrathoracic procedures. Other antiarrhythmics that have been tried to prevent post-thoracotomy arrhythmias, include β-blockers, verapamil, and amiodarone. All of these drugs decrease arrhythmias in thoracic patients. However, they are all associated with side effects that preclude their widespread application in this surgical population. At present, diltiazem is the most useful drug for post-thoracotomy arrhythmia prophylaxis.[1] It seems that atrial arrhythmias are only a symptom of the dysfunctional right side of the heart and preventing the symptom does not solve the underlying problem. In one study,[23] patients who subsequently developed atrial tachyarrhythmias could be identified in the early postoperative period by their right ventricular response to the withdrawal of supplemental oxygen. On the first postoperative day, a decrease of F_{IO_2} from 0.35 to 0.21 caused a significant rise of right ventricular end-diastolic pressure (RVEDP) in the patients who subsequently developed arrhythmias. Thoracic epidural analgesia with local anesthetics may decrease the incidence and severity of arrhythmias. This effect is due to increasing myocardial refractory period, decreasing ventricular diastolic pressures, and improving endocardial/epicardial blood flow ratios.[24]

Age

There is no maximum age that is a cutoff for pulmonary resection.[4] The operative mortality in a group of patients 80 to 92 years of age was 3%, a very respectable figure, in one series.[25] However, the rate of respiratory complications (40%) was double that expected in a younger population and the rate of cardiac complications (40%), particularly arrhythmias, was nearly triple that which would be seen in younger patients. In the elderly, thoracotomy should be considered a high-risk procedure for cardiac complications and cardiopulmonary function is the most important part of the preoperative assessment. An algorithm for the cardiac assessment of the elderly for thoracic surgery is presented in Figure 59-4. Although the mortality resulting from lobectomy among the elderly is acceptable, the mortality from pneumonectomy, particularly right pneumonectomy, is excessive.[26] Exercise tolerance seems to the primary determinant of outcome in the elderly.[27] The American College of Cardiology/American Heart Association guidelines[17] suggest that with "adequate functional capacity" (i.e., 4 Mets or one-flight stair climbing) patients with "intermediate" predictors of coronary artery disease do not need further cardiac assessment. However, this recommendation should not be extrapolated to elderly patients. The elderly should also have, as a minimum cardiac investigation, a transthoracic echocardiogram, to rule out pulmonary hypertension.

Renal Dysfunction

Renal dysfunction after pulmonary resection surgery is associated with a high mortality. Golledge and Goldstraw[28] reported a perioperative mortality of 19% (6/31) in patients who developed a significant elevation of serum creatinine concentration in the post-thoracotomy period, compared with 0% (0/99) in those who did not show any renal dysfunction. The factors, which were associated with an increased risk of renal impairment, were history of previous renal impairment, diuretic therapy, pneumonectomy, postoperative infection, and blood transfusion. Nonsteroidal anti-inflammatory drugs (NSAIDs) were not associated with renal impairment in this series but are clearly a concern in any thoracotomy patient with an increased risk of renal dysfunction. The high mortality in pneumonectomy patients from either renal failure or postoperative pulmonary edema emphasizes the importance of fluid management in these patients[29] and the need for close and intensive perioperative monitoring, particularly in those patients on diuretics or with a history of renal dysfunction.

Chronic Obstructive Pulmonary Disease

The most common concurrent illness in the thoracic surgical population is COPD, which incorporates three disorders: emphy-

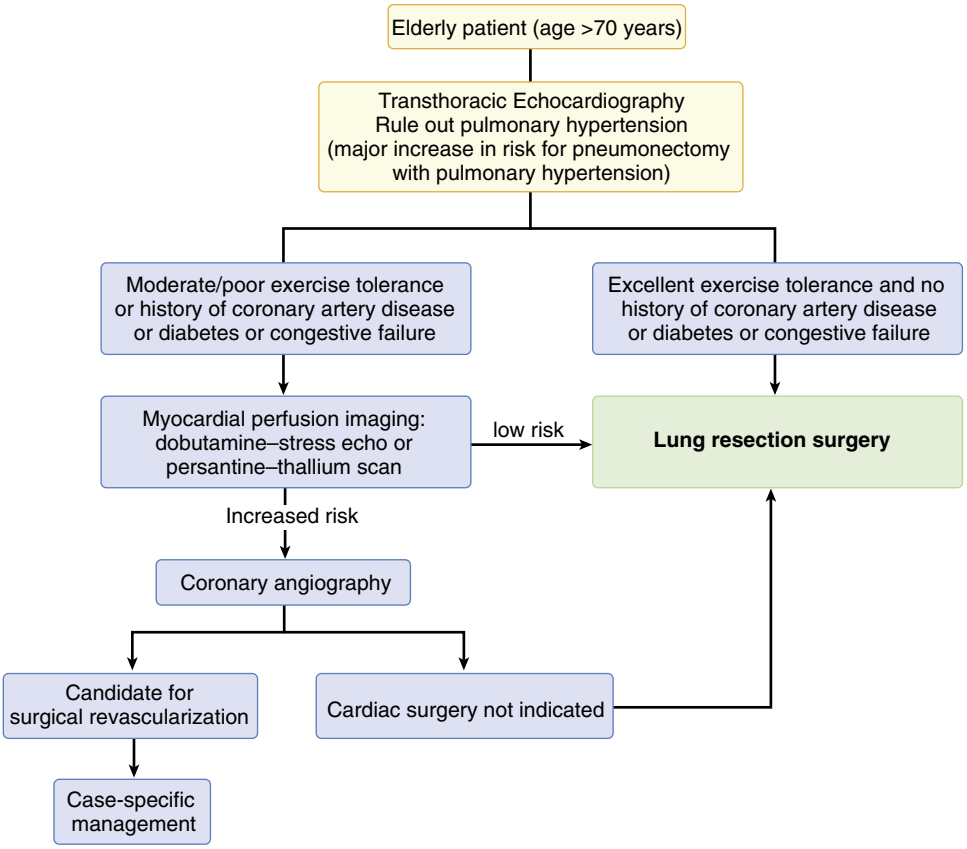

Figure 59-4 Algorithm for the preoperative cardiac assessment of elderly patients for thoracic (noncardiac) surgery.

sema, peripheral airways disease, and chronic bronchitis (see Chapter 35). Any individual patient may have one or all of these conditions, but the dominant clinical feature is impairment of expiratory airflow.[30] Assessment of the severity of COPD has traditionally been on the basis of the FEV_1% of predicted values. The American Thoracic Society currently categorizes stage I as greater than 50% predicted (this category previously included both "mild" and "moderate" COPD), stage II as 35% 50%, and stage III as less than 35%. Life expectancy may be less than 3 years in stage III patients older than age 60 years. Stage I patients should not have significant dyspnea, hypoxemia, or hypercarbia, and other causes should be considered if these are present. Recent advances in the understanding of COPD that are relevant to anesthetic management are discussed next.

Respiratory Drive

Many stage II or III COPD patients have an elevated P_{ACO_2} at rest. It is not possible to differentiate these "CO_2 retainers" from nonretainers on the basis of history, physical examination, or spirometric pulmonary function testing. This CO_2 retention seems to be more related to an inability to maintain the increased work of respiration (W_{Resp}) required to keep the P_{ACO_2} normal in patients with mechanically inefficient pulmonary function and not primarily due to an alteration of respiratory control mechanisms. It was previously thought that chronically hypoxemic/hypercapnic patients relied on a hypoxic stimulus for ventilatory drive and became insensitive to P_{ACO_2}. This explained the clinical observation that COPD patients in incipient respiratory failure could be put into a hypercapnic coma by the administration of a high concentration of oxygen (F_{IO_2}). Actually, only a minor fraction of the increase in P_{ACO_2} in such patients is due to a diminished respiratory drive, because minute ventilation is basically unchanged. The P_{ACO_2} rises because a high F_{IO_2} causes a relative decrease in alveolar ventilation and an increase in alveolar dead space and shunt by the redistribution of perfusion away from lung areas of relatively normal $\dot{V}/\dot{Q}$ matching to areas of very low $\dot{V}/\dot{Q}$ ratio because regional hypoxic pulmonary vasoconstriction (HPV) is decreased[31] and also due to the Haldane effect.[32] However, supplemental oxygen must be administered to these patients postoperatively to prevent the hypoxemia associated with the unavoidable fall in functional residual capacity (FRC). The attendant rise in P_{ACO_2} should be anticipated and monitored. To identify these patients preoperatively, all stage II or III COPD patients need arterial blood gas analysis.

Nocturnal Hypoxemia

COPD patients desaturate more frequently and severely than normal patients during sleep. This is due to the rapid/shallow breathing pattern that occurs in all patients during rapid-eye-movement (REM) sleep. In COPD patients breathing air, this causes a significant increase in the respiratory dead space/tidal volume (V_{DS}/V_T) ratio and a fall in alveolar oxygen tension (P_{AO_2}) and P_{aO_2}. This is not the sleep apnea/hypoventilation syndrome (SAHS). There is no increased incidence of SAHS in COPD. In 8 of 10 COPD patients studied, the oxygen saturation fell to less than 50% at some time during normal sleep, and this

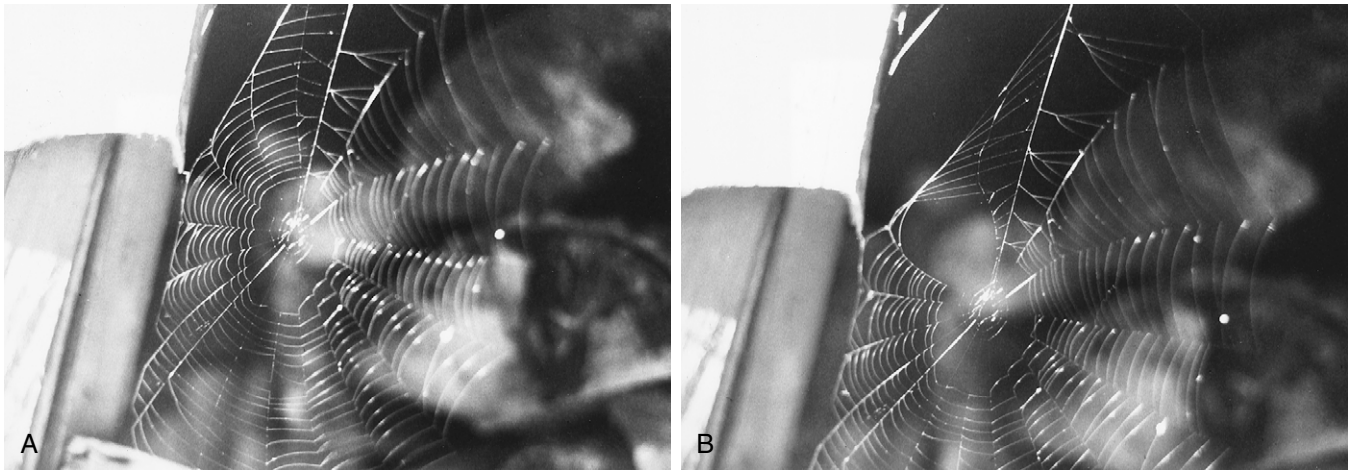

Figure 59-5 A, A spider's web as a lung model to demonstrate the pathophysiology of bullae. **B,** Breaking one septum of the spider's web causes a bulla to appear as elastic recoil pulls the web away from the area where structural support has been lost. Although the cells surrounding the bulla appear compressed, this is due only to redistribution of elastic forces. It is not positive pressure inside the bulla that causes this appearance of surrounding compression. (*Reproduced with permission from Slinger P: Anesthesia for lung resection surgery. In Thys D [ed]: Textbook of Cardiothoracic Anesthesia. New York, McGraw-Hill, 2001.*)

was associated with an increase in pulmonary artery pressure. This tendency to desaturate, combined with the postoperative fall in FRC and opioid analgesia, places these patients at high risk for severe hypoxemia postoperatively during sleep.

Right Ventricular Dysfunction

Right ventricular (RV) dysfunction occurs in up to 50% of COPD patients. The dysfunctional right ventricle is poorly tolerant of sudden increases in afterload,[33] such as the change from spontaneous to controlled ventilation.[34] RV function becomes critical in maintaining cardiac output as the pulmonary artery pressure rises. The RV ejection fraction does not increase with exercise in COPD patients as it does in normal patients. Chronic recurrent hypoxemia is the cause of the RV dysfunction and the subsequent progression to cor pulmonale. Patients who have episodic hypoxemia in spite of normal lungs (e.g., central alveolar hypoventilation, SAHS)[35] develop the same secondary cardiac problems as in COPD patients. Cor pulmonale occurs in 40% of adult COPD patients with an FEV_1 less than 1 L and in 70% with an FEV_1 less than 0.6 L. Mortality in COPD patients is primarily related to chronic hypoxemia. The only therapy that has been shown to improve long-term survival and decrease right-sided heart strain in COPD is oxygen. COPD patients who have resting Pao_2 less than 55 mm Hg should receive supplemental home oxygen; this includes those who desaturate to less than 44 mm Hg with usual exercise. The goal of supplemental oxygen is to maintain a Pao_2 of 60 to 65 mm Hg. Compared with patients with chronic bronchitis, emphysematous COPD patients tend to have a decreased cardiac output and mixed venous oxygen tension while maintaining lower pulmonary artery pressures. Pneumonectomy candidates with a $ppoFEV_1$ less than 40% should have transthoracic echocardiography to assess right-sided heart function. Elevation of right-sided heart pressures places these patients in a very high-risk group.

Bullae

Many patients with moderate or severe COPD will develop cystic air spaces in the lung parenchyma known as bullae. These bullae will often be asymptomatic unless they occupy more than 50% of the hemithorax, in which case the patient will present with findings of restrictive respiratory disease in addition to their obstructive disease. Previously, it was thought that bullae represented positive-pressure areas with in the lung that compressed surrounding lung tissue. It is now appreciated that a bulla is actually a localized area of loss of structural support tissue in the lung with elastic recoil of surrounding parenchyma (Fig. 59-5). The pressure in a bulla is actually the mean pressure in the surrounding alveoli averaged over the respiratory cycle. This means that during normal spontaneous ventilation the intra-bulla pressure is actually slightly negative in comparison with the surrounding parenchyma.[36] However, whenever positive-pressure ventilation is used the pressure in a bulla will become positive in relation to the adjacent lung tissue and the bulla will expand with the attendant risk of rupture, tension pneumothorax, and bronchopleural fistula. Positive-pressure ventilation can be used safely in patients with bullae provided the airway pressures are kept low and there is adequate expertise and equipment immediately available to insert a chest drain and obtain lung isolation if necessary. Management of patients for bullectomy is discussed later in this chapter.

Flow Limitation

Severe COPD patients are often "flow limited" even during tidal volume expiration at rest.[37] Flow limitation is present in normal patients only during a forced expiratory maneuver. Flow limitation occurs when an equal pressure point develops in the intrathoracic airways during expiration. During quiet expiration in the normal patient the pressure in the lumen of the airways always exceeds the intrapleural pressure because of the upstream elastic recoil pressure that is transmitted from the alveoli. The effect of this elastic recoil pressure diminishes as air flows downstream in the airway. With a forced expiration the intrapleural pressure may equal the intraluminal pressure at a certain point, the equal pressure point, which then limits the expiratory flow. Then, any increase in expiratory effort will not produce an increase in flow at that given lung volume.[38]

Flow limitation occurs particularly in emphysematous patients, who primarily have a problem with loss of lung elastic recoil and have marked dyspnea on exertion. Flow limitation causes dyspnea because of stimulation of mechanoreceptors in the muscles of respiration, thoracic cage, and airway distal to the equal pressure point. Any increase in the work of respiration will lead to increased dyspnea. This variable mechanical compression of airways by overinflated alveoli is the primary cause of the airflow obstruction in emphysema.

Severely flow-limited patients are at risk for hemodynamic collapse with the application of positive-pressure ventilation owing to dynamic hyperinflation of the lungs.[34] Even the modest positive airway pressures associated with manual ventilation with a bag/mask at induction can lead to hypotension because these patients have no increased resistance to inspiration but a marked obstruction of expiration. In some of these patients this has contributed to the "Lazarus" syndrome, in which patients have recovered from a cardiac arrest only after resuscitation and positive-pressure ventilation were discontinued.[39]

Auto-PEEP

Patients with severe COPD often breathe in a pattern that interrupts expiration before the alveolar pressure has fallen to atmospheric pressure. This incomplete expiration is due to a combination of factors, which include flow limitation, increased work of respiration, and increased airway resistance. This interruption leads to an elevation of the end-expiratory lung volume above the FRC. This positive end-expiratory pressure (PEEP) in the alveoli at rest has been termed *auto-PEEP* or *intrinsic-PEEP.* During spontaneous respiration the intrapleural pressure will have to be decreased to a level that counteracts auto-PEEP before inspiratory flow can begin. Thus, COPD patients can have an increased inspiratory load added to their already increased expiratory load.

Auto-PEEP becomes even more important during mechanical ventilation. It is directly proportional to tidal volume and inversely proportional to expiratory time. The presence of auto-PEEP is not detected by the manometer of standard anesthesia ventilators. It can be measured by end-expiratory flow interruption, a feature available on the newer generation of intensive care ventilators. Auto-PEEP has been found to develop in most COPD patients during one-lung anesthesia.[40]

Combined Cancer and Emphysema Surgery

Although the predicted values for $ppoFEV_1$ are very useful for the anesthesiologist to stratify a patient's perioperative risk, the actual postoperative FEV_1 that the patient will reach by 3 months after recovery from surgery will usually exceed the $ppoFEV_1$ owing to compensatory hyperinflation of the residual lung. For lobectomies the eventual FEV_1 will usually exceed the $ppoFEV_1$ by approximately 250 mL and for pneumonectomies by 500 mL.[41] This improvement can be particularly noticed in some emphysema patients who experience a "volume reduction" effect from their pulmonary resection for cancer. The combination of volume reduction surgery and/or bullectomy in addition to lung cancer surgery has been reported in emphysematous patients who would previously not have met minimal criteria for pulmonary resection due to their concurrent lung disease.[42]

Preoperative Therapy for COPD

There are four treatable complications of COPD that must be actively sought and therapy begun at the time of the initial preoperative assessment. These are atelectasis, bronchospasm, respiratory tract infections, and pulmonary edema (Table 59-1). Atelectasis impairs local lung lymphocyte and macrophage function, predisposing to infection. Pulmonary edema can be very difficult to diagnose by auscultation in the presence of COPD and may present in very abnormal radiologic distributions (e.g., unilateral, upper lobes). Bronchial hyperreactivity may be a symptom of congestive failure or may represent an exacerbation of reversible airways obstruction. All COPD patients should receive maximal bronchodilator therapy as guided by their symptoms. Only 20% to 25% of COPD patients will respond to corticosteroids. In a patient who is poorly controlled on sympathomimetic and anticholinergic bronchodilators, a trial of corticosteroids may be beneficial.

Table 59-1 Concurrent Problems That Should Be Treated before Anesthesia in COPD Patients

Problem	Method of Diagnosis
Bronchospasm	Auscultation
Atelectasis	Chest radiography
Infection	History, sputum analysis
Pulmonary edema	Auscultation, chest radiography

Physiotherapy

Patients with COPD have fewer postoperative pulmonary complications when a perioperative program of intensive chest physiotherapy is initiated preoperatively (see Chapter 93).[43] Among the different modalities available (e.g., cough and deep breathing, incentive spirometry, PEEP, continuous positive airway pressure [CPAP]), there is no clearly proven superior method. The important variable is the quantity of time spent with the patient and devoted to chest physiotherapy. Family members or nonphysiotherapy hospital staff can easily be trained to perform effective preoperative chest physiotherapy, and this should be arranged at the time of the initial preoperative assessment. Even in the most severe COPD patient, it is possible to improve exercise tolerance with a physiotherapy program. Little improvement is seen before 1 month. Among COPD patients, those with excessive sputum benefit the most from chest physiotherapy.

A comprehensive program of pulmonary rehabilitation involving physiotherapy, exercise, nutrition, and education can improve functional capacity for patients with severe COPD.[44] These programs are usually of several months' duration and are generally not an option in resections for malignancy, although rehabilitation should be considered for nonmalignant resections in patients with severe COPD. The benefits of short-duration rehabilitation programs before malignancy resection have not been fully assessed.

Smoking

Pulmonary complications are decreased in thoracic surgical patients who cease smoking for more than 4 weeks before surgery.[45] Carboxyhemoglobin concentrations decrease if smoking is stopped more than 12 hours.[46] It is extremely important for patients to avoid smoking postoperatively. Smoking leads to a prolonged period of tissue hypoxemia. Wound tissue oxygen tension correlates with wound healing and resistance to infection.

There is no rebound increase in pulmonary complications if patients stop for shorter (<8 wk) periods before surgery.[47] The balance of evidence suggests that thoracic surgical patients should be counseled to stop smoking and advised that the longer the period of cessation the greater the risk reduction for postoperative pulmonary complications.

Primary Thoracic Tumors

The majority of patients presenting for major pulmonary surgery will have some type of malignancy. Because the different types of thoracic malignancies have varying implications for both surgery and anesthesia, it is important for the anesthesiologist to have some knowledge of the presentation and biology of these cancers. By far the most common tumor is lung cancer. There are over 200,000 new cases of lung cancer diagnosed per year in North America and more than 1.2 million in the world. Lung cancer is currently the leading cause of cancer deaths in both sexes in North America subsequent to the peak incidence of smoking in the period 1940 to 1970.[48]

Lung cancer is broadly divided into small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC), with 75% to 80% of these tumors being NSCLC. Other less common and less aggressive tumors of the lung include the carcinoid tumors (typical and atypical) and adenoid cystic carcinoma. In comparison to lung cancer, primary pleural tumors are rare. They include the localized fibrous tumors of pleura (previously referred to as benign mesotheliomas) and malignant pleural mesothelioma. Asbestos exposure is implicated as a causative effect in up to 80% of malignant pleural mesotheliomas. A dose-response relationship is not always apparent, and even brief exposures can lead to the disease. An exposure history is often difficult to obtain because the latent period before clinical manifestation of the tumor may be as long as 40 to 50 years.

Tobacco smoke is responsible for approximately 90% of all lung cancers, and the epidemiology of lung cancer follows the epidemiology of cigarette smoking, with approximately a 3-decade lag time.[49] Other environmental causes include asbestos and radon gas (a decay product of naturally occurring uranium), which act as co-carcinogens with tobacco smoke. For a pack-a-day cigarette smoker the lifetime risk of lung cancer is approximately 1 in 14. Assuming current mortality patterns continue, cancer will pass heart disease as the leading cause of death in North America in this decade.

Non–Small Cell Lung Cancer

This pathologically heterogeneous group of tumors includes squamous cell, adenocarcinoma, and large-cell carcinoma. Overall 5-year survival with surgery approaches 40%. This seemingly low figure must be viewed in the light of an estimated 5-year survival without surgery of less than 10%. Although it is not always possible to be certain of the pathology of a given lung tumor preoperatively, many patients will have a known tissue diagnosis at the time of preanesthetic assessment on the basis of prior cytology, bronchoscopy, mediastinoscopy, or transthoracic needle aspiration. This is useful information for the anesthesiologist to obtain preoperatively. Specific anesthetic implications of the different types of lung cancer are listed in Table 59-2.

Table 59-2 Anesthetic Considerations for Different Types of Lung Cancer

Type	Considerations
Squamous cell	Central lesions (predominantly) Often with endobronchial tumor Mass effects: obstruction, cavitation Hypercalcemia
Adenocarcinoma	Peripheral lesions Extrapulmonary invasion common Most Pancoast tumors Growth hormone, corticotropin Hypertrophic osteoarthropathy
Large cell	Large, cavitating peripheral tumors Similar to adenocarcinoma
Small cell	Central lesions (predominantly) Surgery usually not indicated Paraneoplastic syndromes Lambert-Eaton syndrome Fast growth rate Early metastases
Carcinoid	Proximal, endobronchial Bronchial obstruction with distal pneumonia Highly vascular Benign (predominantly) No association with smoking 5 year survival > 90% Carcinoid syndrome (rarely)

Squamous Cell Carcinoma. This subgroup of NSCLC is strongly linked to cigarette smoking. The tumors tend to grow to a large size and metastasize later than others. They tend to cause symptoms and signs related to local effects of a large tumor mass with a dominant endobronchial component, such as cavitation, hemoptysis, obstructive pneumonia, superior vena cava syndrome, and involvement of mainstem bronchus, trachea, carina, and main pulmonary arteries. Hypercalcemia is specifically associated with this cell type due to elaboration of a parathyroid-like factor and not due to bone metastases.

Adenocarcinoma. Adenocarcinoma is currently the most common NSCLC in both sexes. These tumors tend to be peripheral and often metastasize early in their course, particularly to brain, bone, liver, and adrenal. They often invade extrapulmonary structures, including chest wall, diaphragm, and pericardium. Almost all Pancoast tumors are adenocarcinomas. A variety of paraneoplastic metabolic factors can be secreted by adenocarcinomas, such as growth hormone and corticotropin. Hypertrophic pulmonary osteoarthropathy (HPOE) is particularly associated with adenocarcinoma.

Bronchioloalveolar carcinoma (BAC) is a subtype of adenocarcinoma that is not related to cigarette smoking. In its early stages it lines the alveolar membrane with a thin layer of tumor cells without destroying the alveolar architecture. Because of its low potential to spread outside of the lungs, multifocal BAC can be treated by lung transplantation.[50]

Large Cell Undifferentiated Carcinoma. This is the least common of the NSCLCs. It tends to present as a large, often cavitating peripheral tumor. The rapid growth rate may lead to widespread metastases, similar to adenocarcinoma.

Small Cell Lung Cancer

This tumor of neuroendocrine origin is considered metastatic on presentation and is usually regarded as a medical, not a surgical,

disease. The staging system differs from NSCLC and is divided simply into limited stage and extensive stage. Treatment of limited-stage SCLC with combination chemotherapy (etoposide/cisplatin or cyclophosphamide/doxorubicin/vincristine) gives objective response rates in over 80% of patients. In addition, these patients typically receive aggressive radiotherapy to the primary lung tumor and prophylactic cranial irradiation. Despite this initial response, the tumor invariably recurs and is quite resistant to further treatment. The overall survival rate is no better than 10%. Extensive-stage disease is treated with chemotherapy and palliative radiation as needed.

There are two situations in which surgery for SCLC might be considered. The rare instance in which a solitary pulmonary nodule is diagnosed as SCLC should be treated with surgical resection followed by chemotherapy. Salvage resection of a residual mass after chemotherapy for limited-stage disease may offer some long-term survival in selected cases. Many of these patients will have mixed SCLC/NSCLC in which the small cell component has responded to chemotherapy and the non–small cell component is then resected.

SCLC causes a variety of paraneoplastic syndromes owing to the production of peptide hormones and antibodies. The most common of these is hyponatremia usually due to an inappropriate production of antidiuretic hormone (SIADH). Cushing's syndrome and hypercortisolism through ectopic production of adrenocorticotropic hormone (ACTH) are also commonly seen.

A well-known but rare neurologic paraneoplastic syndrome associated with small cell lung tumors is the Lambert-Eaton (also called Eaton-Lambert) myasthenic syndrome due to impaired release of acetylcholine from nerve terminals. This typically presents as proximal lower limb weakness and fatigability that may temporarily improve with exercise. The diagnosis is confirmed by electromyography (EMG) showing increasing amplitude of unusual action potentials with high-frequency stimulation. Similar to patients with true myasthenia gravis, patients with myasthenic syndrome are extremely sensitive to nondepolarizing muscle relaxants (see Chapter 29). However, they respond poorly to anticholinesterase reversal agents.[51] Subclinical involvement of the diaphragm and muscles of respiration may be involved. Thoracic epidural analgesia has been used after thoracotomy in these patients without complication. Also, neuromuscular function may improve after resection of the lung cancer.

Carcinoid Tumors

Carcinoid tumors are part of a continuum of neuroendocrine tumors that form a spectrum of diseases from SCLC as the most malignant to a typical carcinoid as the most benign. Five-year survival after resection for a typical carcinoid tumor exceeds 90%. Lymph node metastasis is not uncommon and does not impact survival. Systemic metastasis is rare, as is the carcinoid syndrome, which is caused by the ectopic synthesis of vasoactive mediators and is usually seen with carcinoid tumors of gut origin that have metastasized to the liver. Atypical carcinoid tumors are more aggressive. They often metastasize both regionally and systemically.

Carcinoid tumors can precipitate an intraoperative hemodynamic crisis or coronary artery spasm even during bronchoscopic resection.[52] The anesthesiologist should be prepared to deal with severe hypotension that may not respond to the usual vasoconstrictors and will require the use of the specific antagonists octreotide or somatostatin.[53]

Pleural Tumors

Localized fibrous tumors of pleura are usually large, space-occupying masses that are attached to visceral or parietal pleura. They can be either benign or malignant, but most are easily resected with good results.

Malignant pleural mesotheliomas are strongly associated with exposure to asbestos fibers. Their incidence in Canada has almost doubled in the past 15 years. With the phasing out of asbestos-containing products and the long latent period between exposure and diagnosis, the peak incidence is not predicted for another 10 to 20 years. The tumor initially proliferates within the visceral and parietal pleura, typically forming a bloody effusion. Most patients present with shortness of breath or dyspnea on exertion from this pleural effusion. Thoracentesis often relieves the symptoms but rarely provides a diagnosis. Pleural biopsy by VATS is most efficient to secure a diagnosis, and talc poudrage is performed under the same anesthetic to treat the effusion.

Malignant pleural mesotheliomas respond poorly to therapy, and the median survival is less than 1 year. In patients with very early disease extrapleural pneumonectomy may be considered but it is difficult to know whether survival is improved. Recently, several groups have reported improved results with combinations of radiation therapy, chemotherapy, and surgery. Extrapleural pneumonectomy is an extensive procedure that is rife with potential complications, both intraoperative and postoperative.[54] Blood loss from the denuded chest wall or major vascular structures is always a risk. Complications related to resection of diaphragm and pericardium are additional risks to that of pneumonectomy.

Assessment of the Patient with Lung Cancer

At the time of initial assessment cancer patients should be assessed for the "4 Ms" associated with malignancy (Table 59-3): *m*ass effects, *m*etabolic abnormalities, *m*etastases, and *m*edications. The prior use of medications that can exacerbate oxygen-induced pulmonary toxicity such as bleomycin should be considered.[55] Bleomycin is not used to treat primary lung cancers, but patients presenting for excision of lung metastases from germ cell tumors will often have received prior bleomycin therapy. Although the association between previous bleomycin therapy and pulmonary toxicity from high-inspired oxygen concentrations is well documented, none of the details of the association are understood (i.e., safe doses of oxygen or safe period after bleomycin exposure). The safest anesthetic management is to use the lowest F_{IO_2} consistent with patient safety and closely monitor oximetry in any patient who has received bleomycin. We have seen lung cancer patients who received preoperative chemotherapy with cisplatin and then developed an elevation of serum creatinine when they

Table 59-3 Anesthetic Considerations in Lung Cancer Patients (the "4 Ms")

Mass effects: Obstructive pneumonia, lung abscess, superior vena cava syndrome, tracheobronchial distortion, Pancoast's syndrome, recurrent laryngeal nerve or phrenic nerve paresis, chest wall or mediastinal extension
Metabolic effects: Lambert-Eaton syndrome, hypercalcemia, hyponatremia, Cushing's syndrome
Metastases: particularly to brain, bone, liver, and adrenal
Medications: chemotherapy agents, pulmonary toxicity (bleomycin, mitomycin C), cardiac toxicity (doxorubicin), renal toxicity (cisplatin)

received nonsteroidal anti-inflammatory analgesics (NSAIDs) postoperatively. For this reason, we do not routinely administer NSAIDs to patients who have been treated recently with cisplatin.

Postoperative Analgesia

The strategy for postoperative analgesia (see Chapter 87) should be developed and discussed with the patient during the initial preoperative assessment. A discussion of postoperative analgesia is presented at the end of this chapter. Many techniques have been shown to be superior to the use of on-demand parenteral (intramuscular or intravenous) opioids alone in terms of pain control. These include the addition of neuraxial blockade, paravertebral blocks, and anti-inflammatory agents to narcotic-based analgesia. Only epidural techniques have been shown to consistently have the capability to decrease post-thoracotomy respiratory complications in high-risk patients.[2] However, continuous paravertebral blockade may offer comparable analgesia with a lower rate of block failure and fewer side effects.[56]

At the time of initial preanesthetic assessment the risks and benefits of the various forms of post-thoracotomy analgesia should be explained to the patient. Potential contraindications to specific methods of analgesia should be determined, such as coagulation problems, sepsis, or neurologic disorders. If the patient is to receive prophylactic anticoagulants and it is elected to use epidural analgesia, appropriate timing of anticoagulant administration and neuraxial catheter placement needs to be arranged. American Society of Regional Anesthesia (ASRA) guidelines suggest an interval of 2 to 4 hours before or 1 hour after catheter placement for prophylactic heparin administration.[57] Low-molecular-weight heparin (LMWH) precautions are less clear: an interval of 12 to 24 hours before and 24 hours after catheter placement is recommended.

Premedication

Premedication should be discussed and ordered at the time of the initial preoperative visit (see Chapter 34). The most important aspect of preoperative medication is to avoid inadvertent withdrawal of those drugs that are taken for concurrent medical conditions (e.g., bronchodilators, antihypertensives, β-blockers). For some types of thoracic surgery, such as esophageal reflux surgery, oral antacid and H_2-blockers or proton-pump inhibitors are routinely ordered preoperatively. We do not routinely order preoperative sedation or analgesia for pulmonary resection patients. Mild sedation such as an intravenous short-acting benzodiazepine is often given immediately before placement of invasive monitoring lines and catheters. In patients with copious secretions, an antisialagogue (e.g., glycopyrrolate) is useful to facilitate fiberoptic bronchoscopy for positioning of a double-lumen tube (DLT) or bronchial blocker. It is a common practice to use short-term intravenous antibacterial prophylaxis such as a cephalosporin in thoracic surgical patients. If it is the local practice to administer these drugs before admission to the operating room they will have to be ordered preoperatively. Consideration for those patients allergic to cephalosporins or penicillin will have to be made at the time of the initial preoperative visit.

Summary of the Initial Preoperative Assessment

The anesthetic considerations that should be addressed at the time of the initial preoperative assessment are summarized in Table 59-4. Patients need to be specifically assessed for risk factors associated with respiratory complications, which are the major cause of morbidity and mortality after thoracic surgery.

Table 59-4 Initial Preanesthetic Assessment for Thoracic Surgery

1. All patients: Assess exercise tolerance, estimate predicted postoperative FEV_1%, discuss postoperative analgesia, discontinue smoking
2. Patients with predicted postoperative FEV_1< 40%: DLco, $\dot{V}/\dot{Q}$ scan, Vo_2 max
3. Cancer patients: consider the "4 Ms": mass effects, metabolic effects, metastases, medications
4. COPD patients: Arterial blood gas analysis, physiotherapy, bronchodilators
5. Increased renal risk: Measure creatinine and blood urea nitrogen

Final Preoperative Assessment

The final preoperative anesthetic assessment for the majority of thoracic surgical patients is carried out immediately before admission of the patient to the operating room (see Chapter 34). At this time it is important to review the data from the initial prethoracotomy assessment and the results of tests ordered at that time. In addition, two other specific areas affecting thoracic anesthesia need to be assessed: the potential for difficult lung isolation and the risk of desaturation during one-lung ventilation (OLV) (Table 59-5).

Difficult Endobronchial Intubation

Anesthesiologists are familiar with the clinical assessment of the upper airway for ease of endotracheal intubation. In a similar fashion, each thoracic surgical patient must be assessed for the ease of endobronchial intubation. At the time of the preoperative visit, there may be historical factors or physical findings that lead to suspicion of difficult endobronchial intubation (previous radiotherapy, infection, prior pulmonary or airway surgery) (see Chapter 50). In addition, there may be a written bronchoscopy report with detailed description of anatomic features. The most useful predictor of difficult endobronchial intubation is the plain chest radiograph (Fig. 59-6).

The anesthesiologist should personally view the chest radiograph before induction of anesthesia because neither the radiologist's nor the surgeon's report of the radiograph is made with the specific consideration of lung isolation in mind. A large portion of thoracic surgical patients will also have had a chest CT scan done preoperatively. As anesthesiologists have learned to assess x-rays for potential lung-isolation difficulties, it is also worthwhile to learn to examine the CT scan. Distal airway problems not detectable on the plain chest film can sometimes be visualized on the CT scan: a side-to-side compression of the distal trachea, the so-called saber-sheath trachea, can cause obstruction of the tracheal lumen of a left-sided DLT during ventilation of the dependent lung for a left thoracotomy.[58] Similarly, extrinsic

Table 59-5 Final Preanesthetic Assessment for Thoracic Surgery

1. Review initial assessment and test results.
2. Assess difficulty of lung isolation: examine chest radiograph and computed tornography scan.
3. Assess risk of hypoxemia during one-lung ventilation.

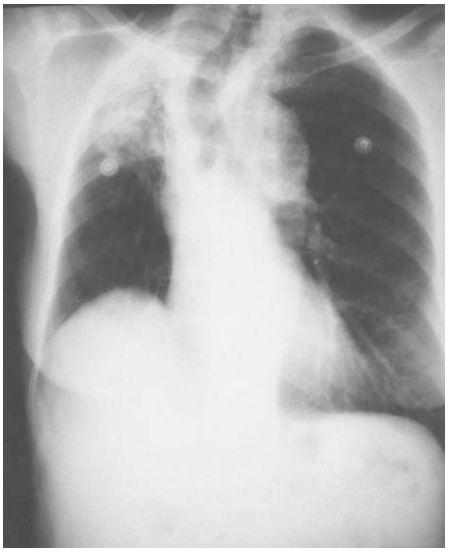

Figure 59-6 Preoperative chest radiograph of a 50-year-old woman with a history of previous tuberculosis, right upper lobectomy, and recent hemoptysis presenting for right thoracotomy for a possible complete pneumonectomy. The potential problems of positioning a left-sided double-lumen tube in this patient are easily appreciated by viewing the radiograph but are not mentioned in the radiologist's report. The anesthesiologist must examine the chest images preoperatively to anticipate problems in lung isolation. (*Reproduced with permission from Slinger PD, Johnston MR: Preoperative assessment: An anesthesiologist's perspective. Thorac Surg Clin 15:11, 2005.*)

compression or intraluminal obstruction of a mainstem bronchus that can interfere with endobronchial tube placement may be evident only on CT (Fig. 59-7). The major factors in successful lower airway management are anticipation and preparation based on the preoperative assessment. Management of lung isolation in patients with difficult upper and lower airways is discussed later in this chapter.

Prediction of Desaturation during One-Lung Ventilation

In the vast majority of cases it is possible to determine those patients who are most at risk of desaturation during OLV for thoracic surgery. The factors that correlate with desaturation during OLV are listed in Table 59-6. In patients at high risk of desaturation, prophylactic measures can be used during OLV to decrease this risk. The most useful prophylactic measures are the use of CPAP of 2 to 5 cm H_2O of oxygen to the nonventilated lung or PEEP to the dependent lung or both (see Chapter 15).

Table 59-6 Factors That Correlate with an Increased Risk of Desaturation during One-Lung Ventilation

- High percentage of ventilation or perfusion to the operative lung on preoperative $\dot{V}/\dot{Q}$ scan
- Poor Pao_2 during two-lung ventilation, particularly in the lateral position intraoperatively
- Right-sided thoracotomy
- Normal preoperative spirometry (FEV_1 or FVC) or restrictive lung disease
- Supine position during one-lung ventilation

The most important predictor of Pao_2 during OLV is the Pao_2 during two-lung ventilation, specifically the intraoperative Pao_2 during two-lung ventilation in the lateral position before OLV.[59] The proportion of perfusion or ventilation to the nonoperated lung on preoperative $\dot{V}/\dot{Q}$ scans also correlates with the Pao_2 during OLV.[60] If the operative lung has little perfusion preoperatively due to unilateral disease, the patient is unlikely to desaturate during OLV. The side of the thoracotomy has an effect on Pao_2 during OLV. Because the left lung is 10% smaller than the right there is less shunt when the left lung is collapsed. In a series of patients the mean Pao_2 during left thoracotomy was approximately 70 mm Hg higher than during right thoracotomy.[61] Finally, the degree of obstructive lung disease correlates in an inverse fashion with Pao_2 during OLV. Other factors being equal, patients with more severe airflow limitation on their preoperative spirometry will tend to have a better Pao_2 during OLV than patients with normal spirometry (this will be discussed below under "Anesthetic Management"; see Chapter 15).

Assessment for Repeat Thoracic Surgery

Patients who survive lung cancer surgery form a high-risk cohort to have a recurrence of the original tumor or to develop a second primary tumor. The incidence of developing a second primary

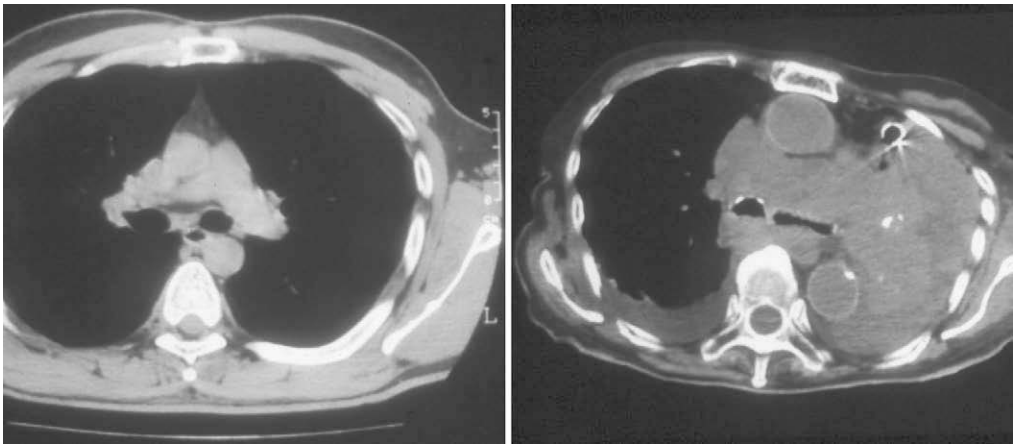

Figure 59-7 CT scans from just below the level of the carinal bifurcation. A normal scan is shown on the left. On the right is a scan from a 70-year-old woman scheduled for thoracoscopic left lung biopsy. The patient has a left-sided lung tumor and effusion that compresses the left mainstem bronchus. This bronchial compression was not evident on the chest radiograph. It may be difficult to place a left-sided double-lumen tube in this patient. (*Reproduced with permission from Slinger P: Anesthesia for lung resection surgery. In Thys D [ed]: Textbook of Cardiothoracic Anesthesia. New York, McGraw-Hill, 2001.*)

lung tumors is estimated at 2% per year. The use of routine screening low-dose spiral CT scans will probably increase the rate of early detection.[62] Patients who present for repeat thoracotomy should be assessed using the same framework as those who present for surgery the first time. Predicted values for postoperative respiratory function based on the preoperative lung mechanics, parenchymal function, exercise tolerance, and the amount of functioning lung tissue resected should be calculated and used to identify patients at increased risk.

Intraoperative Monitoring

General principles of monitoring are discussed in Chapters 38 and 44. A few points specific to intraoperative monitoring of the thoracic surgical patient need to be emphasized.

A majority of these operations are major procedures of moderate duration (2-4 hours) and performed in the lateral position with the hemithorax open. Thus, consideration for monitoring and maintenance of body temperature and fluid volume should be given to all of these cases. Because surgery is usually performed in the lateral position, monitors will initially be placed with the patient in the supine position and have to be rechecked and often repositioned after the patient is turned. It is often difficult to add additional monitoring, particularly invasive vascular monitoring, after the case is started if complications arise. Thus, the risk-benefit ratio often tends to favor being overly invasive at the outset. Several intraoperative complications that can occur during all types of surgery are more prone to occur during thoracotomy. Choice of monitoring should be guided by a knowledge of which complications are likely to occur (Table 59-7).

There are also complications that are more prone to occur with certain procedures, for example, hemorrhage from an extrapleural pneumonectomy, contralateral lung soiling with resection of an abscess or bronchiectasis, and air leak, hypoventilation, or tension pneumothorax with a bronchopleural fistula. Monitoring for these specific types of surgery will be directed in part by the intraoperative complications associated with the underlying disease.

Table 59-7 Intraoperative Complications That Occur with Increased Frequency during Thoracotomy

Complication	Etiology
Hypoxemia	Intrapulmonary shunt during one-lung ventilation
Sudden severe hypotension	Surgical compression of the heart or great vessels
Sudden changes in ventilating pressure or volume	Movement of endobronchial tube/blocker, air leak
Arrhythmias	Direct mechanical irritation of the heart
Bronchospasm	Direct airway stimulation, increased frequency of reactive airways disease
Massive hemorrhage	Surgical blood loss from great vessels or inflamed pleura
Hypothermia	Heat loss from the open hemithorax

Oxygenation

Significant desaturation (Spo_2 < 90%) during OLV occurs in 1% to 10% of the surgical population in spite of a high Fio_2 (1.0) (see "Management of One-lung Ventilation" later). For several reasons, pulse oximetry (Spo_2) has not negated the need for direct measurement of Pao_2 via intermittent blood gas analysis in the majority of thoracotomy patients. First, the Pao_2 value offers a more useful estimate of the margin of safety above desaturation than the SpO_2. A patient with a two-lung ventilation Pao_2 greater than 400 mm Hg with an Fio_2 of 1.0 (or an equivalent Pao_2/Fio_2 ratio) is unlikely to desaturate during OLV whereas a patient with a Pao_2 of 200 mm Hg is prone to desaturate during OLV, although both may have SpO_2 values of 99% to 100%. Second, the rapidity of the fall in Pao_2 after the onset of OLV is an indicator of the risk of subsequent desaturation. For this reason it is useful to measure Pao_2 by arterial blood gas analysis before OLV and 20 minutes after the start of OLV. Third, there are significant intermanufacturer differences in the accuracy of SpO_2 monitors. Although the trends are reliable, to use a specific cutoff of SpO_2 value as a guideline for treatment of hypoxemia the accuracy of the oximeter should be verified intraoperatively with arterial blood gas measurement. Also, during hypoxemia, SpO_2 sensor malpositioning can cause significant underestimation of saturation.

Capnometry

The end-tidal CO_2 ($Petco_2$) is a less reliable indicator of the $Paco_2$ during OLV than during two-lung ventilation, and the $Paco_2$- $Petco_2$ gradient tends to increase during OLV. Although the $Petco_2$ is less directly correlated with alveolar minute ventilation during OLV, because the $Petco_2$ also reflects lung perfusion and cardiac output it gives an indication of the relative changes in perfusion of the two lungs independently during position changes and during OLV.[63] As the patient is turned to the lateral position the $Petco_2$ of the nondependent lung will fall relative to the dependent lung, reflecting increased perfusion of the dependent lung and increased dead space of the nondependent lung. However, the fractional excretion of CO_2 will be higher from the nondependent lung in most patients owing to the increased fractional ventilation of this lung. Patients with higher fractional excretion of CO_2 from the dependent lung (i.e., better perfusion) during two-lung ventilation tend to have better Pao_2 values during OLV.[64]

At the onset of OLV the $Petco_2$ of the dependent lung will usually fall transiently as all the minute ventilation is transferred to this lung. The $Petco_2$ will then rise as the fractional perfusion is increased to this dependent lung by collapse and pulmonary vasoconstriction of the nonventilated lung. If there is no correction of minute ventilation, the net result will be both an increased baseline $Paco_2$ and $Petco_2$ with an increased gradient. However, severe (>5 mm Hg) or prolonged falls in $Petco_2$ can indicate an maldistribution of perfusion between ventilated and nonventilated lungs and may be an early warning of a patient who will subsequently experience desaturation during OLV (see Chapter 15).

Invasive Hemodynamic Monitoring

Arterial Line

There is a significant incidence of transient severe hypotension from surgical compression of the heart or great vessels during intrathoracic procedures. For this reason, plus the utility of intermittent arterial blood gas sampling, it is useful to have beat-to-beat assessment of systemic blood pressure during a majority of thoracic surgery cases. Naturally, exceptions occur during limited procedures such as thoracoscopic resections in younger and healthier patients. For most thoracotomies placement of a radial artery catheter can be in either the dependent or the nondependent arm.

Central Venous Pressures

Central venous pressure (CVP) monitoring and access is a routine for thoracic surgery in some centers. However, it is a common impression that CVP readings in the lateral position with the chest open are not reliable. The CVP is a useful monitor postoperatively, particularly for cases in which fluid management is critical (e.g., pneumonectomies). It is our practice to routinely place CVP lines in pneumonectomy patients but not for lesser resections unless there is significant other concurrent illness. For lobectomies that unforeseeably become pneumonectomies during the course of the surgery, a CVP catheter is placed at the end of the operation. Our choice is to use the right internal jugular vein to minimize the risk of pneumothorax for CVP access unless there is a contraindication. Internal jugular CVP data are not reliable in patients with superior vena cava obstruction.

Pulmonary Artery Catheters

Similar to CVP data, intraoperative pulmonary artery pressure may be a less accurate indicator of true left heart preload in the lateral position with the chest open than in other clinical situations. This is partly because it is often initially not known if the catheter tip lies in the dependent or nondependent lung. Also, it is possible that thermodilution cardiac output data may be unreliable if there are significant transient unilateral differences in perfusion between the lungs, as can occur during OLV and positive pressure. There is no consensus on the reliability of thermodilution cardiac output data during OLV.

When left-sided pulmonary artery catheter placement is required it can be achieved in 50% of patients (versus the usual 10%) by floating the catheter into the pulmonary artery when the patient is in the right lateral position.[65] It is usually possible for the surgeon to confirm the placement of the pulmonary artery catheter once the chest is open. It is extremely important to remember that a pulmonary artery catheter ipsilateral to the side of surgery must be withdrawn before vascular clamping or it could be transected. Complications from the use of pulmonary artery catheters including arrhythmias, hemorrhage, pulmonary infarction, and so on are well documented.[66] Also, if a pulmonary artery catheter is in the nonventilated lung it frequently becomes accidentally wedged without balloon inflation as the lung collapses. The risk-benefit ratio for the routine use of pulmonary artery catheters for pulmonary resection surgery favors their use only in certain specific cases, such as patients with major coexisting disease (e.g., cardiac, renal) or having particularly extensive procedures (e.g., extrapleural pneumonectomy).

Fiberoptic Bronchoscopy

Placement of DLTs and bronchial blockers is discussed later in the section on "Lung Isolation." Significant malpositions of DLTs and blockers that can lead to desaturation during OLV are often not detected by auscultation or other traditional methods of confirming placement.[67] Placement of DLTs or blockers should be performed with fiberoptic bronchoscopic guidance and should be reconfirmed after placing the patient in the surgical position because a large number of these tubes/blockers migrate during repositioning of the patient.[68]

Continuous Spirometry

The development of side-stream spirometry has made it possible to continuously monitor inspiratory and expiratory volumes, pressures, and flow interactions during one-lung anesthesia. This monitoring is particularly useful during pulmonary resection surgery. The breath-by-breath monitoring of inspired and expired tidal volumes gives early warning of accidental changes in the intraoperative position of a DLT, with loss of lung isolation if the expired volume suddenly decreases (there is normally a 20- to 30-mL/breath difference owing in part to the uptake of inspired oxygen). The development of a persistent end-expiratory flow during OLV, which correlates with the development of auto-PEEP, can be seen on the flow-volume loop. Also, the ability to accurately measure differences in inspiratory and expiratory tidal volumes is extremely useful to aid the surgeon in assessing and managing pulmonary air leaks during pulmonary resections.

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) allows the anesthesiologist to have a continuous real-time monitor of myocardial function and cardiac preload (see Chapter 41). This information is difficult to estimate intraoperatively in the lateral position from other hemodynamic monitors. However, there are also disincentives to the routine use of TEE in thoracic surgery. The equipment is cumbersome and expensive, and there is a specific expertise required to obtain and interpret the images.[69] Also, many thoracic surgical patients have esophageal pathology precluding TEE and there is the potential for laryngopharyngeal trauma when both a DLT and a TEE probe are placed in smaller patients. The American Society of Anesthesiologists and Society of Cardiovascular Anesthesiologists have published indications for the use of perioperative TEE.[70] Potential indications for the intraoperative TEE that apply to thoracic surgery include hemodynamic instability (Fig. 59-8), pericardial effusions, cardiac involvement by tumor, air emboli, pulmonary thromboendarterectomy, thoracic trauma, lung transplantation, and pleuropulmonary disease (Table 59-8).

Assessment of right ventricular function is a very appealing potential use for TEE, particularly in patients with limited cardiac reserves who are having major pulmonary resections. Right ventricular ejection fraction catheters have been tried for this purpose but have not gained wide acceptance, probably owing to the errors in the measurements. Quantitative assessment of right ventricular function is a valid procedure when performed by transthoracic echocardiography.[71] However, owing to imaging difficulties, at present TEE is commonly used only for qualitative assessment of the right ventricle.

A rare cause of hypoxemia associated with thoracic surgery is reversal of shunt flow through an undiagnosed patient foramen

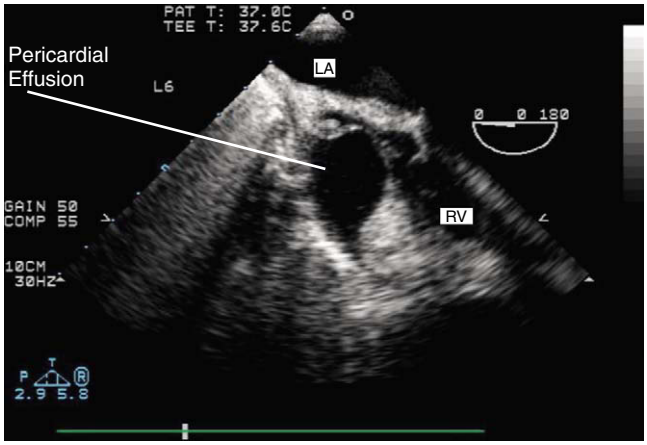

Figure 59-8 Transesophageal echocardiography (TEE), midesophageal view, in patient with metastatic breast cancer who had a hemodynamic collapse after induction of general anesthesia for a VATS drainage of a left pleural effusion. TEE was performed for diagnosis of hemodynamic instability. TEE revealed a previously undiagnosed large pericardial effusion. The "Pericardial Effusion" label shows complete collapse of the right atrium during systole due to the effusion, consistent with tamponade. The VATS procedure was modified to include creation of a pericardial window. LA, left atrium; RV, right ventricle. VATS, video-assisted thoracoscopic surgery.

ovale. When PEEP (to 15 cm H_2O) was applied during controlled ventilation for nonthoracic surgery 9% of patients developed a right-to-left intracardiac shunt.[72] TEE should be capable of detecting patients who might intraoperatively develop a right-to-left interatrial shunt during or after thoracic surgery.

Lung-Isolation Techniques

Lung-isolation techniques are primarily designed to facilitate OLV in patients undergoing cardiac, thoracic, mediastinal, vascular, esophageal, or orthopedic procedures involving the chest cavity.[73] Lung isolation is also used to protect the lung from soiling by the contralateral lung in such cases as bronchopleural fistula, pulmonary hemorrhage, and whole-lung lavage. And, lung isolation can be used to provide differential patterns of ventilation in cases of unilateral reperfusion injury (after lung transplantation or pulmonary thromboendarterectomy) or in unilateral lung trauma.

Lung isolation can be achieved by three different methods: DLTs, bronchial blockers, or single-lumen endobronchial tubes (SLTs) (Table 59-9). The most common technique is with a DLT. The DLT is a bifurcated tube with both an endotracheal and an endobronchial lumen and can be used to achieve isolation of either the right or the left lung. The second method involves blockade of a mainstem bronchus to allow lung collapse distal to the occlusion. These bronchial blockers can be used with an standard endotracheal tube or contained within a separate channel inside a modified SLT such as the Univent tube. The final option for lung isolation is to use either an SLT or endobronchial tube that is advanced into the contralateral mainstem bronchus, protecting this lung while allowing collapse of the lung on the side of surgery (Fig. 59-9). This technique is rarely used today in adult practice (except in some cases of difficult airways, emergencies, or after a pneumonectomy), owing to the limited access to the nonventilated lung and the difficulty in positioning a standard SLT in the bronchus. This technique is still used when needed in infants and small children: an uncuffed uncut pediatric size endotracheal is advanced into the mainstem bronchus under direct guidance with an infant bronchoscope.

Double-Lumen Endotracheal Tubes

The use of the Carlens design of DLT (Fig. 59-10) for lung surgery in 1950 was a landmark in the development of thoracic anesthesia because it allowed anesthesiologists to obtain reliable lung isolation in a majority of patients using only laryngoscopy and auscultation. However, the Carlens tube had a high flow resistance owing to the narrow lumens and also the carinal hook was difficult to pass through the glottis in some patients. In the 1960s, Robertshaw introduced design modifications for separate left- and right-sided DLTs, removing the carinal hook and using larger lumens. In the 1980s, manufacturers introduced disposable DLTs made of polyvinyl chloride based on the design of the Robertshaw DLT. Among other subsequent improvements is the inclusion of radiographic markers near the endotracheal and endobronchial cuffs and a radiographic marker surrounding the ventilation slot for the right upper lobe bronchus for the right-sided DLT version. Bright blue, low-volume, low-pressure endobronchial cuffs are incorporated for easier visualization during fiberoptic bronchoscopy. Table 59-10 lists the different sizes of DLT, the appropriate fiberoptic bronchoscope sizes to be used, and the comparable diameters of SLTs.

Size Selection

A properly sized, left-sided DLT should have a bronchial tip 1 to 2 mm smaller than the patient's left bronchus diameter to allow

Table 59-8 Indications for Transesophageal Echocardiography in Thoracic Surgery

Category 1*	Category 2†	Category 3‡
Hemodynamic instability Assessment of pericardial effusion or tamponade	Cardiac and/or great vessel involvement by intrathoracic tumors Pulmonary thromboendarterectomy Air emboli Lung transplantation Thoracic trauma	Right ventricular function in pulmonary resection

*Supported by the strongest evidence or expert opinion.
†Supported by weaker evidence or expert opinion.
‡Little current scientific or expert support.

Table 59-9 Options for Lung Isolation

Options	Advantages	Disadvantages
Double-lumen tube 1. Direct laryngoscopy 2. Via tube exchanger 3. Fiberoptically	Quickest to place successfully Repositioning rarely required Bronchoscopy to isolated lung Suction to isolated lung CPAP easily added Can alternate OLV to either lung easily Placement still possible if bronchoscopy not available	Size selection more difficult Difficult to place in patients with difficult airways or abnormal tracheas Not optimal for postoperative ventilation Potential laryngeal trauma Potential bronchial trauma
Bronchial blockers (BB) Arndt Cohen Fuji	Size selection rarely an issue Easily added to regular ETT Allows ventilation during placement Easier placement in patients with difficult airways and in children Postoperative two-lung ventilation by withdrawing blocker Selective lobar lung isolation possible CPAP to isolated lung possible	More time needed for positioning Repositioning needed more often Bronchoscope essential for positioning Nonoptimal right lung isolation due to RUL anatomy Bronchoscopy to isolated lung impossible Minimal suction to isolated lung Difficult to alternate OLV to either lung
Univent tube	Same as BBs Less repositioning compared with BBs	Same as for BBs ETT portion has higher air flow resistance than regular ETT ETT portion has larger diameter than regular ETT
Endobronchial tube	Like regular ETTs, easier placement in patients with difficult airways Longer than regular ETT Short cuff designed for lung isolation	Bronchoscopy necessary for placement Does not allow for bronchoscopy, suctioning or CPAP to isolated lung Difficult right lung OLV
Endotracheal tube (ETT) advanced into bronchus	Easier placement in patients with difficult airways	Does not allow for bronchoscopy, suctioning or CPAP to isolated lung Cuff not designed for lung isolation Extremely difficult right OLV

CPAP, continuous positive airway pressure; ETT, endotracheal tube; OLV, one-lung ventilation; RUL, right upper lobe.

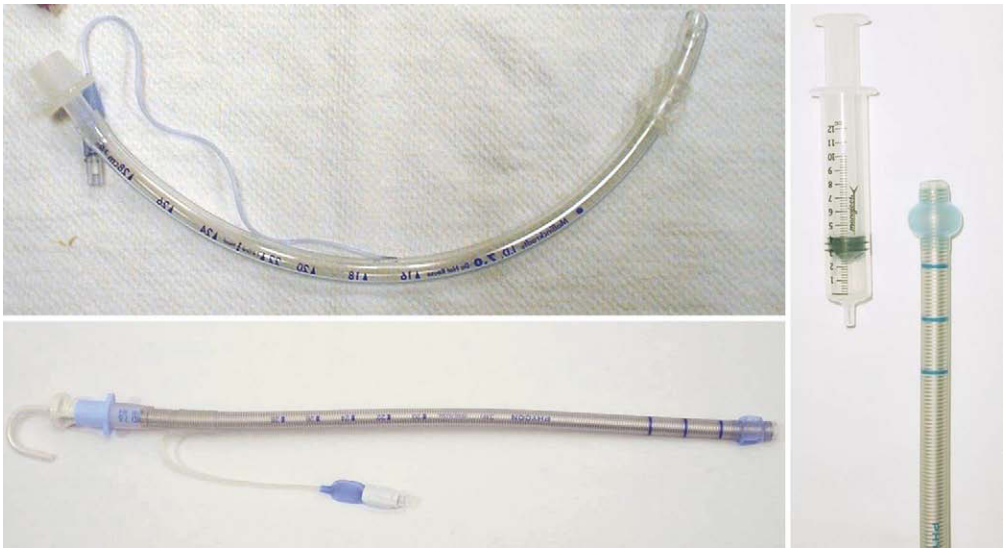

Figure 59-9 Photographs of a standard single-lumen endotracheal tube (*upper left*) and a specifically designed single-lumen endobronchial tube (*lower left and right*). The endobronchial tube is longer and has a shorter cuff. It can be used as an endotracheal tube and advanced into a mainstem bronchus with fiberoptic guidance when needed for lung isolation. (*Courtesy of Phycon, Fuji Systems Corp., Tokyo, Japan.*)

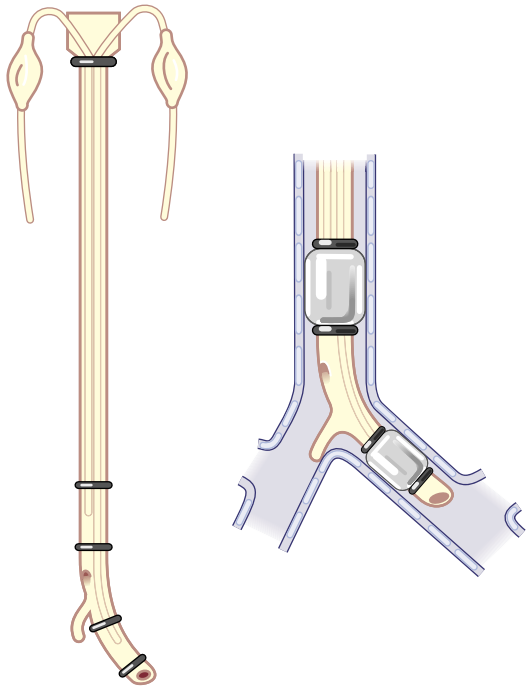

Figure 59-10 **A,** Diagram of the original Carlens red rubber double-lumen tube. **B,** Close-up of placement of the Carlens tube at the tracheal carina. Note that the left endobronchial lumen and the carinal hook straddle the carina. (*From Benumof JL: Anesthesia for Thoracic Surgery. Philadelphia, WB Saunders, 1987.*)

for the space occupied by the deflated bronchial cuff. A study by Eberle and associates[74] used a three-dimensional image reconstruction of tracheobronchial anatomy from the spiral CT scans combined with superimposed transparencies of DLTs to predict proper size for a right- or left-sided DLT. Chest radiographs and CT scans are valuable tools for selection of proper DLT size in addition to their proven value in assessment of abnormal tracheobronchial anatomy and should be reviewed before the placement of the DLT. A simplified method of selection of DLT size is given in Table 59-11. It is important to appreciate that, compared with

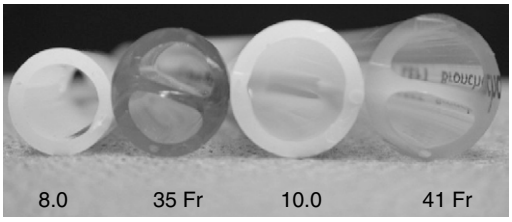

Figure 59-11 Photograph of the cut cross-sections of several single- and double-lumen tubes (DLTs). Note that the external diameter of a 35-Fr DLT is larger than that of an 8.0 mm (ID) single-lumen tube and a 41-Fr DLT is larger than a 10-mm single-lumen tube. (*Photograph courtesy of Dr. J. Klafta.*)

SLTs, DLTs have a large external diameter (Fig. 59-11) and they should not be advanced against significant resistance.

Methods of Insertion

Two techniques are used commonly when inserting and placing a DLT. One is the blind technique: the DLT is passed with direct laryngoscopy and then turned 90 degrees counterclockwise (for a left-sided DLT placement) after the endobronchial cuff has passed beyond the vocal cords. The DLT should pass the glottis without any resistance. Seymour[75] showed that the mean diameter of the cricoid ring is approximately the same as that of the left mainstem bronchus. The optimal depth of insertion for a left-sided DLT is strongly correlated with the patient's height in average-sized adults. In adults, depth, measured at the teeth, for a properly positioned DLT will be approximately 12 + (patient

Table 59-11 Selection of Double-Lumen Tube Size Based on Adult Patients' Sex and Height

Sex	Height (cm)	Size (Fr)
Female	<160 (63 in.)*	35
Female	>160	37
Male	<170 (67 in.)†	39
Male	>170	41

*For females of short stature (< 152 cm or 60 in.), examine bronchial diameter on CT scan and consider 32 Fr.
†For males of short stature (<160 cm or 63 in.), consider 37 Fr.

Table 59-10 Comparative Diameters of Single- and Double-Lumen Tubes

Single-Lumen Tubes		Double-Lumen Tubes			
Internal Diameter (mm)	External Diameter (mm)	French Size (Fr)	External Diameter (mm)*	Bronchial Internal Diameter (mm)	FOB Size (mm)†
6.5	8.9	26	8.7	3.2	2.4
7.0	9.5	28	9.3	3.4	2.4
8.0	10.8	32	10.7	3.5	2.4
8.5	11.4	35	11.7	4.3	≥3.5
9.0	12.1	37	12.3	4.5	≥3.5
9.5	12.8	39	13.0	4.9	≥3.5
10.0	13.5	41	13.7	5.4	≥3.5

*The approximate external diameter of the double-lumen portion of the tube.
†FOB, fiberoptic bronchoscope. The maximal diameter of FOB that will pass through both lumens of a given size of double-lumen tube.

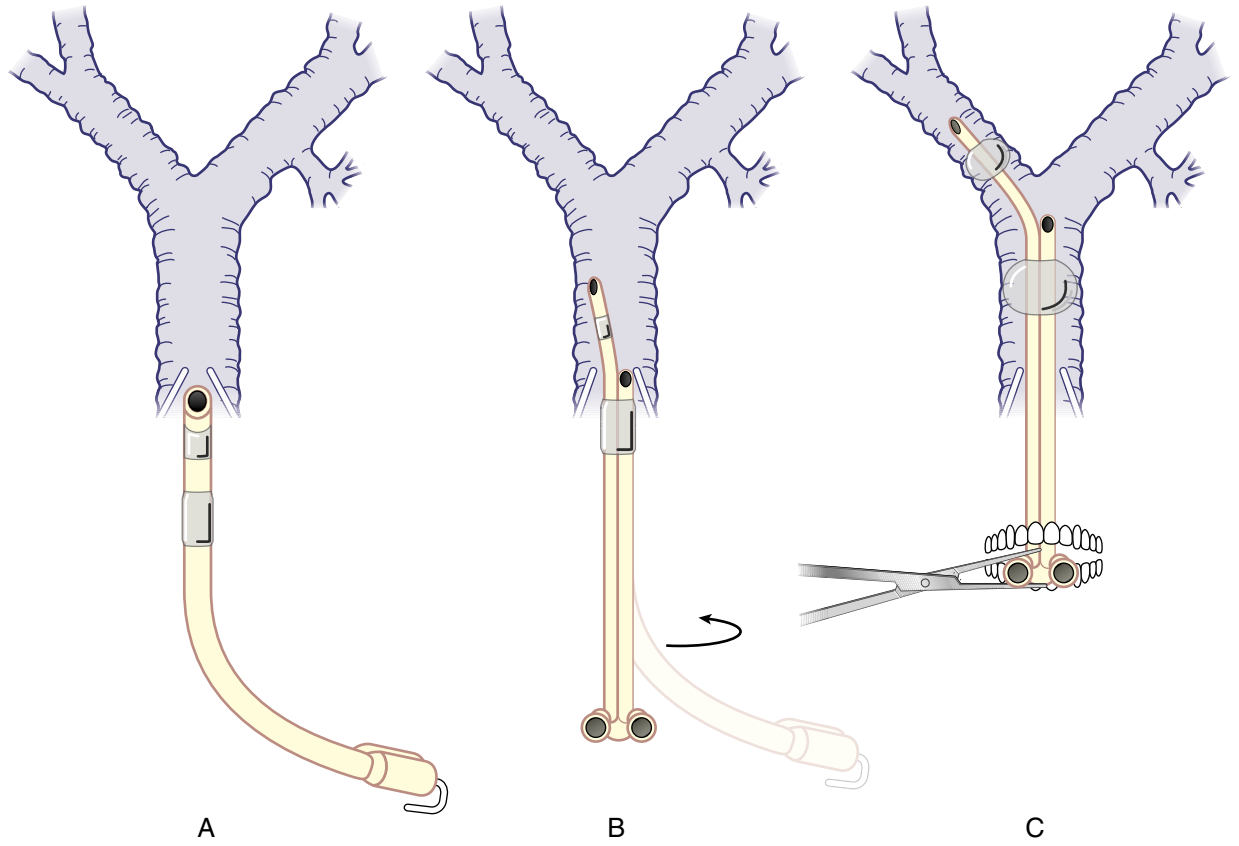

Figure 59-12 Blind method for placement of a left-sided double-lumen endotracheal tube (DLT). **A,** The DLT is passed with direct laryngoscopy beyond the vocal cords. **B,** The DLT is rotated 90 degrees to the left (counterclockwise). **C,** The DLT is advanced to an appropriate depth (in general, to the 27 to 29 cm marking at the level of the teeth).

height/10) cm.[76] In patients of Asian descent, which comprises many individuals of shorter stature (<155 cm), patient height is not a good predictor of depth of insertion of a DLT.[77] An inadvertently deep insertion of a DLT can lead to serious complications, including rupture of the left mainstem bronchus. Figure 59-12 depicts the blind method technique for insertion of a left-sided DLT.

The direct vision technique uses bronchoscopic guidance, in which the tip of the endobronchial lumen is guided into the correct bronchus after the DLT passes the vocal cords using direct vision with a flexible fiberoptic bronchoscope. A study by Boucek and associates[78] comparing the blind technique versus fiberoptic bronchoscopy-guided technique showed that of the 32 patients who underwent the blind technique approach, primary success occurred in 27 patients and eventual success occurred in 30 patients. In contrast, in the 27 patients using the bronchoscopy-guided technique, primary success was achieved only in 21 patients and eventual success in 25 patients. Although both methods resulted in successful left mainstem bronchus placement in all patients, more time was required when fiberoptic bronchoscopy guidance technique was used (88 versus 181 seconds).

Right-Sided Double-Lumen Endobronchial Tubes

Although a left-sided DLT is used more commonly for most elective thoracic procedures,[79] there are specific clinical situations in which the use of a right-sided DLT is indicated (Table 59-12). The anatomic differences between the right and the left mainstem bronchus are reflected in the fundamentally different designs of the right-sided and left-sided DLTs. Because the right mainstem bronchus is shorter than the left bronchus and because the right upper lobe bronchus originates at a distance of 1.5 to 2 cm from the carina, techniques using right endobronchial intubation must take into account the location and potential for obstruction of the orifice of the right upper lobe bronchus. The right-sided DLT incorporates a modified cuff, or slot, on the endobronchial side that allows ventilation for the right upper lobe (Fig. 59-13).[80]

Table 59-12 Indications for a Right-Sided Double-Lumen Tube*

Distorted Anatomy of the Entrance of Left Mainstem Bronchus
External or intraluminal tumor compression
Descending thoracic aortic aneurysm
Site of Surgery Involving the Left Mainstem Bronchus
Left lung transplantation
Left-sided tracheobronchial disruption
Left-sided pneumonectomy†
Left-sided sleeve resection

*This is a common clinical practice pattern for using right-sided DLTs and assumes normal tracheobronchial anatomy—specifically, a normal position of the orifice of the right upper lobe. However, some clinicians prefer to use right DLTs for all left-sided surgery.

†It is possible to manage a left pneumonectomy with a left-sided DLT or bronchial blocker. However, the tube or blocker will have to be withdrawn before stapling the left mainstem bronchus.

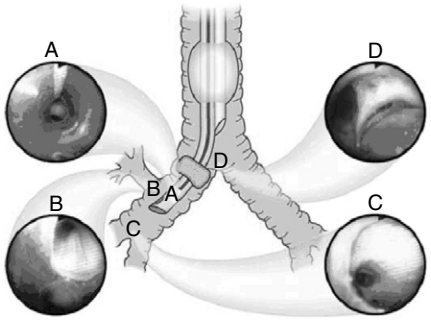

Figure 59-13 Fiberoptic bronchoscopic examination of a Rusch right-sided double-lumen tube. **A,** The white line marker when the bronchoscope is passed through the bronchial lumen. **B,** Slot of the bronchial lumen properly aligned within the entrance of the right upper lobe bronchus. **C,** Part of the bronchus intermedius when the bronchoscope is advanced through the distal portion of the bronchial lumen. **D,** Edge of the bronchial cuff at the entrance of the right mainstem bronchus when the bronchoscope is passed through the tracheal lumen. (*Reproduced with permission from Campos JH: Current techniques for perioperative lung isolation in adults. Anesthesiology 97:1295, 2002.*)

Positioning of Double-Lumen Tubes

Auscultation alone is unreliable for confirmation of proper DLT placement. Auscultation (Fig. 59-14) and bronchoscopy should both be used each time a DLT is placed and again when the patient is repositioned. Fiberoptic bronchoscopy is performed first through the tracheal lumen to ensure that the endobronchial portion of the DLT is in the left bronchus and that there is no bronchial cuff herniation over the carina after inflation. Through the tracheal view, the blue endobronchial cuff ideally should be seen approximately 5 mm below the tracheal carina in the left bronchus. It is crucial to identify the takeoff of the right upper lobe bronchus through the tracheal view. Going inside this right upper lobe with the bronchoscope should reveal three orifices (apical, anterior, and posterior). This is the only structure in the tracheobronchial tree that has three orifices. In the supine patient the takeoff of the right upper lobe is normally on the lateral wall of the right mainstem bronchus at the 3- to 4-o'clock position in relation to the main carina (Fig. 59-15). Broncho-Cath tubes from Mallinckrodt have a radiopaque line encircling the tube. This line is proximal to the bronchial cuff and can be useful while positioning a left-sided DLT. The radiopaque marker is 4 cm from the distal tip of the endobronchial lumen. This marker reflects white during fiberoptic visualization and, when positioned slightly above the tracheal carina, should provide the necessary margin of safety for positioning into the left mainstem bronchus.[81] The next observation with the fiberoptic bronchoscope is made through the endobronchial lumen to check for patency of the tube and determination of margin of safety. The orifices of both the left upper and lower lobes must be identified to avoid distal impaction in the left lower lobe and occlusion of the left-upper lobe (Fig. 59-16). Figure 59-17 displays the

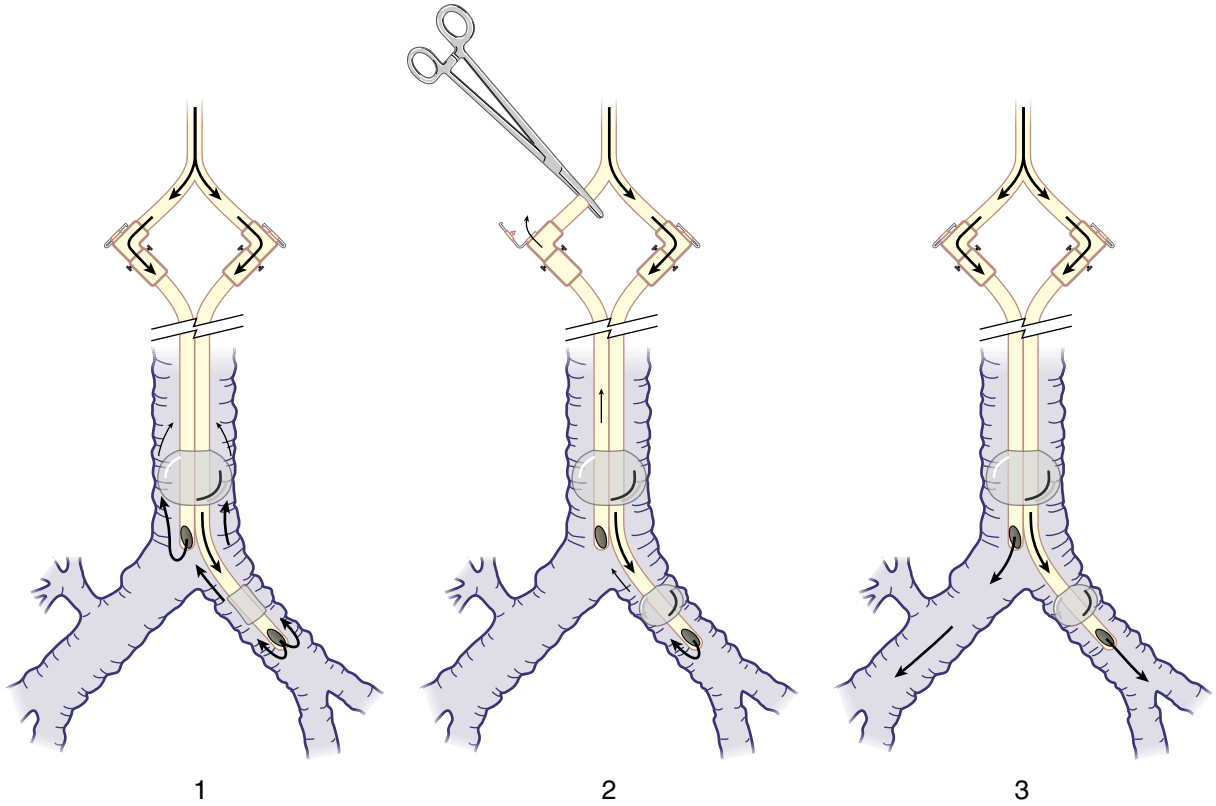

Figure 59-14 A "three-step" method to confirm position of a left DLT by auscultation: *Step 1.* During bilateral ventilation, the tracheal cuff is inflated to the minimal volume that seals the air leak at the glottis. Auscultate to confirm bilateral ventilation. *Step 2.* The tracheal lumen of the DLT is clamped proximally ("clamp the short side short") and the port distal to the clamp opened. During ventilation via the bronchial lumen the bronchial cuff is inflated to the minimal volume that seals the air leak from the open tracheal lumen port. Auscultate to confirm correct unilateral ventilation. *Step 3.* The tracheal lumen clamp is released and the port closed. Auscultate to confirm resumption of bilateral breath sounds. (*From Youngberg JA: Cardiac, Vascular and Thoracic Anesthesia. Philadelphia, Churchill Livingstone, 2000.*)

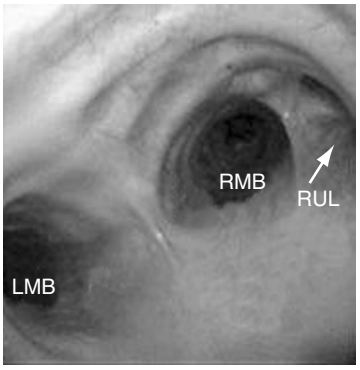

Figure 59-15 Abnormally high takeoff of the right upper lobe bronchus (RUL, *arrow*) at the level of the main carina. A right double-lumen tube in this patient would block the RUL orifice. LMB, left main bronchus; RMB, right main bronchus.

tracheobronchial anatomy along with fiberoptic bronchoscopy findings from the endotracheal or endobronchial lumen for a left-sided DLT.

Problems Related to Double-Lumen Tubes

The most common problems and complications associated with the use of a DLT are malposition and airway trauma. A malpositioned DLT will fail to allow collapse of the lung, causing gas trapping during positive-pressure ventilation, or it may partially collapse the ventilated or dependent lung, producing hypoxemia. A common cause of malposition is dislodgment of the endobronchial cuff because of overinflation, surgical manipulation of the bronchus, or extension of the head and neck during or after patient positioning. Fiberoptic bronchoscopy is the recommended method to diagnose and correct intraoperative malposition of DLTs. If a DLT is malpositioned in the supine or lateral decubitus position, there is a greater likelihood of hypoxemia during OLV.[82] If a DLT is in the optimal position, but lung deflation is not completely achieved, a suction catheter should be passed to the side where lung collapse is supposed to occur. This suction will expedite lung deflation. The suction catheter must then be removed to avoid including it in a suture line.

Airway trauma and rupture of the membranous part of the trachea or the bronchus is a potential complication with the use

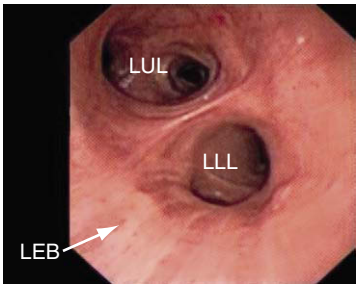

Figure 59-16 The view from the distal bronchial lumen of a well-positioned left-sided double-lumen tube. Both the orifices of the left upper lobe (LUL) and left lower lobe (LLL) can be identified. Note the longitudinal elastic bundles (LEB, *arrow*). These extend down the posterior membranous walls of the trachea and mainstem bronchi. They are useful landmarks to orient the bronchoscopist to anteroposterior directions. In the left mainstem bronchus they extend into the left lower lobe and are a useful landmark to distinguish the lower from the upper lobe.

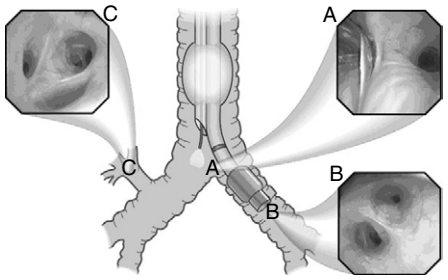

Figure 59-17 Fiberoptic bronchoscopic examination of a Mallinckrodt left-sided double-lumen tube. **A,** The edge of the endobronchial cuff around the entrance of the left mainstem bronchus when the bronchoscope is passed through the tracheal lumen. A white line marker is seen above the tracheal carina. **B,** Clear view of the bronchial bifurcation (left upper and left lower bronchi) when the left-sided DLT is in the optimal position and the fiberoptic bronchoscope is being advanced through the endobronchial lumen. **C,** Clear view of the right upper lobe bronchus and its three orifices: apical, anterior, and posterior segments. (*Reproduced with permission from Campos JH: Progress in lung separation. Thorac Surg Clin 15:71, 2005.*)

of DLTs.[83] Airway trauma can occur from an oversized DLT or when an undersized DLT migrates distally into the bronchus and the main (i.e., tracheal) body of the DLT comes into the bronchus, producing lacerations or rupture of the airway. Airway damage during the use of DLTs can present an unexpected air leak, subcutaneous emphysema, massive airway bleeding into the lumen of the DLT, or protrusion of the endotracheal or endobronchial cuffs into the surgical field, with visualization of this by the surgeon. If any of the above-mentioned problems occur, a bronchoscopic examination and surgical repair should be performed. Another potential problem is the development of a tension pneumothorax in the dependent, ventilated, lung during OLV.[84]

Bronchial Blockers

An alternative method to achieve lung separation involves blockade of a mainstem bronchus to allow lung collapse distal to the occlusion. Bronchial blockers also can be used selectively to achieve lobar collapse if necessary.[73] Currently, there are several different bronchial blockers available to facilitate lung separation. These devices are either within a modified SLT as an enclosed bronchial blocker (Torque Control Blocker Univent; Vitaid, Lewinston, NY) or are used independently with a conventional SLT, the Arndt wire-guided endobronchial blocker (Cook Critical Care, Bloomington, IN), the Cohen tip-deflecting endobronchial blocker (Cook Critical Care, Bloomington, IN), and the Fuji Uniblocker (Vitaid, Lewinston, NY).

There are specific conditions in which a bronchial blocker may be preferred to a DLT, such as patients with previous oral or neck surgery who present with a challenging airway and require lung separation for intrathoracic surgery. In these cases the use of an SLT during an awake nasotracheal, or orotracheal, intubation or via tracheostomy secures the airway and thereafter an independent bronchial blocker can be placed to achieve lung separation. Another group of patients who may benefit from the use of bronchial blockers are those cancer patients who have undergone a previous contralateral pulmonary resection. In such cases selective lobar blockade with a bronchial blocker in the ipsilateral side improves oxygenation and facilitates surgical

Table 59-13 Characteristics of the Cohen, Arndt, and Fuji Bronchial Blockers

	Cohen Blocker	Arndt Blocker	Fuji Uniblocker
Size	9 Fr	5 Fr, 7 Fr, and 9 Fr	5 Fr, 9 Fr
Balloon shape	Spherical	Spherical or elliptical	Spherical
Guidance mechanism	Wheel device to deflect the tip	Nylon wire loop that is coupled with the fiberoptic bronchoscope	None, preshaped tip
Smallest recommended ETT for coaxial use	9 Fr (8.0 ETT)	5 Fr (4.5 ETT), 7 Fr (7.0 ETT), 9 Fr (8.0 ETT)	9 Fr (8.0 ETT)
Murphy eye	Present	Present in 9 Fr	Not present
Center channel	1.6 mm ID	1.4 mm ID	2.0 mm ID

ETT, single endotracheal tube; ID, internal diameter.
From Campos JH: Which device should be considered the best for lung isolation: Double-lumen endotracheal tube versus bronchial blockers. Curr Opin Anaesthesiol 20: 30, 2007, with permission.

exposure. Bronchial blockers are most commonly used intraluminal (coaxial) with an SLT. They can also be placed separately thorough the glottis or tracheostomy exterior to an SLT. This allows the use of a smaller SLT and is often an option in pediatrics. Another advantage of the bronchial blockers is when postoperative mechanical ventilation is being considered after prolonged thoracic or esophageal surgery. In many instances these patients have an edematous upper airway at the end of the procedure. If a bronchial blocker is used there is no need to change the SLT and there is no compromise of the airway if mechanical ventilation is needed in the postoperative period. Table 59-13 describes the characteristics of current bronchial blockers. The smallest internal diameter (ID) of an endotracheal tube that will allow passage of both a bronchial blocker and a fiberoptic bronchoscope depends on the diameters of the bronchoscope and blocker. For standard adult 9-Fr blockers, an endotracheal tube greater than or equal to 7.0 mm ID can be used with a bronchoscope less than 4.0 mm in diameter. Larger bronchoscopes will require an endotracheal tube greater than 7.5 mm ID. All blockers need to be well lubricated before placement.

Torque Control Blocker (Univent)

Placement of the Univent is straightforward (Fig. 59-18). The enclosed bronchial blocker is fully retracted into the standard lumen of the tube. Conventional endotracheal tube intubation technique is used. Then a fiberoptic bronchoscope is passed into the main lumen through a bronchoscopy adaptor. Under direct vision the enclosed bronchial blocker is advanced into the targeted bronchus of the surgical side, where lung collapse is to occur.

The Wire-Guided Endobronchial Blocker (Arndt Blocker)

Figure 59-19 displays the placement of the Arndt blocker by placing the endobronchial blocker through the endotracheal tube and using the fiberoptic bronchoscope and wire-guided loop to direct the blocker into a mainstem bronchus. The fiberoptic bronchoscope has to be advanced distally enough so that the Arndt blocker enters the bronchus while it is being advanced. When the deflated cuff is beyond the entrance of the bronchus approximately 2 cm inside the bronchus, then the fiberoptic bronchoscope is withdrawn. Once the patient is turned into a lateral decubitus position then the cuff of the endobronchial blocker is fully inflated with fiberoptic visualization with 4 to 6 mL of air to obtain total bronchial blockade. For a right mainstem bronchus blockade, the Arndt blocker can be advanced independently of the wire loop by observing its entrance into the right mainstem bronchus under fiberoptic visualization. The optimal position of the Arndt blocker in the left or in the right bronchus is achieved when the blocker balloon's outer surface is seen with the fiberop-

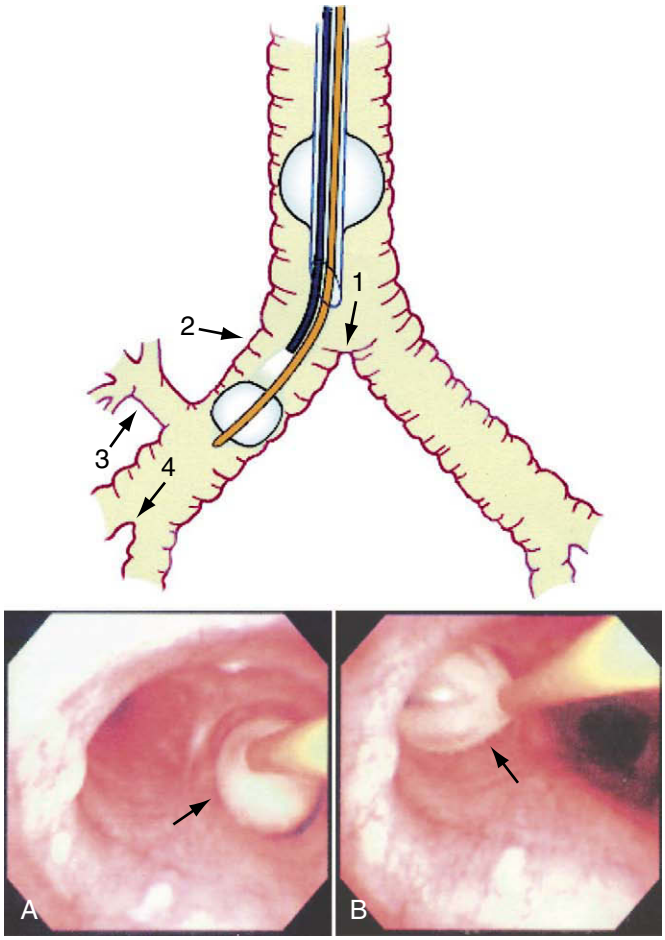

Figure 59-18 Univent torque control blocker. The optimal position of the Univent torque control blocker in the right (**A**) and left (**B**) mainstem bronchus. (*Reproduced with permission from Campos JH: An update on bronchial blockers during lung separation techniques in adults. Anesth Analg 97:1269, 2003.*)

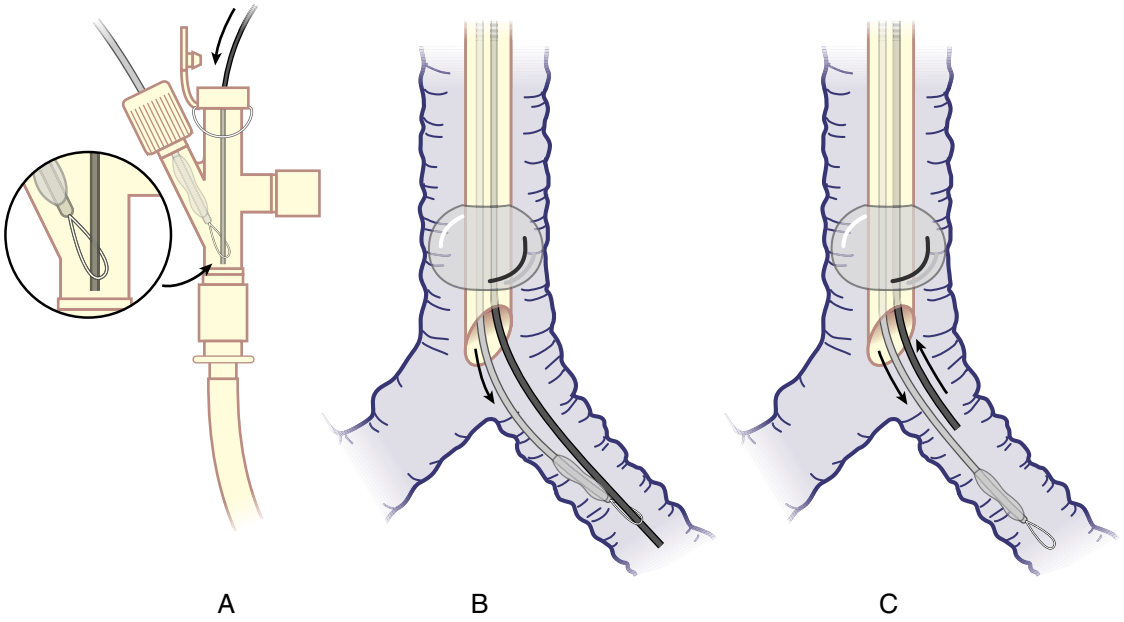

Figure 59-19 Placement of the Arndt wire-guided endobronchial blocker. **A,** Coupling of the nylon wire loop and the fiberoptic bronchoscope through a single-lumen endotracheal tube. **B,** The Arndt blocker along with the fiberoptic bronchoscope is advanced together inside the left mainstem bronchus. **C,** Disengagement of the blocker by withdrawing the fiberoptic bronchoscope.

tic bronchoscope at least 5 mm below the tracheal carina in the target bronchus and the proper seal is obtained.

Cohen Endobronchial Blocker

The Cohen blocker uses a wheel located in the most proximal part of the unit that deflects the tip of the distal part of the blocker into the desired bronchus. This blocker has been pre-angled at the distal tip to facilitate insertion into a target bronchus. On the distal shaft above the balloon, there is an arrow that, when seen with the fiberoptic bronchoscope, indicates in which direction the tip deflects. To position the Cohen blocker, the arrow is aligned with the bronchus to be intubated, the proximal wheel is turned to deflect the tip toward the desired side and then the blocker is advanced with fiberoptic guidance.

Fuji Uniblocker

The Fuji Uniblocker is an independent blocker that is made of silicone material and has a fixed distal angulation to facilitate insertion. Methods of placement and insertion are similar to the ones described for the Cohen blocker but without the wheel device. The optimal position of this device is achieved after the patient is turned into the lateral decubitus position. The characteristics of the independent bronchial blockers are presented in Table 59-13.

Complications Related to the Bronchial Blockers

A complication seen with early versions of the Univent occurred when a fracture of the blocker cap connector was found.[73] Failure to achieve lung separation because of abnormal anatomy or lack of a seal within the bronchus also has been reported.[85] Inclusion of the bronchial blocker or the distal wire loop of an Arndt blocker into the stapling line has been reported during a right upper lobectomy[86] and required surgical reexploration after unsuccessful removal of the bronchial blocker after extubation. To avoid these mishaps communication with the surgical team regarding the presence of a bronchial blocker in the surgical side is crucial and if the blocker is near the staple line. Clearly, the bronchial blocker needs to be withdrawn a few centimeters before stapling.

Another potentially dangerous complication with all bronchial blockers is that the inflated balloon may move and lodge above the carina or be accidentally inflated in the trachea. This leads to inability to ventilate, hypoxia, and potentially cardiorespiratory arrest unless quickly recognized and the blocker deflated.[87] There is a report of a sheared balloon of the Arndt blocker that occurred when the blocker was removed through the multiport blocker side port.[88] It is advised that when an independent bronchial blocker is not in use it needs to be removed with the multiport connector in place rather than through the connector.

Difficult Airways and One-Lung Ventilation

A number of patients requiring OLV are identified during preoperative evaluation to have a potentially difficult airway. Others present with unexpected difficulty to intubate after induction of anesthesia. Between 5% and 8% of patients with primary lung carcinoma also have a carcinoma of the pharynx, usually in the epiglottic area.[89] Many of these patients have had previous radiation therapy on the neck or previous airway surgery, such as hemi-mandibulectomy or hemiglossectomy, making intubation and achievement of OLV difficult due to distorted upper airway anatomy. Also, a patient who requires OLV might have distorted anatomy at or beyond the tracheal carina, such as descending thoracic aortic aneurysm compressing the entrance of the left mainstem bronchus or an intraluminal or extraluminal tumor near the tracheobronchial bifurcation that makes the insertion of

a left-sided DLT relatively difficult or impossible. Such anomalies can be detected by reviewing the chest radiographs and CT scans of the chest (see Fig. 59-7). A flexible fiberoptic bronchoscopic examination is necessary to assess a distorted area of the airway before selection of a specific tube or blocker to achieve OLV.

In patients who require OLV and present with a difficult airway, the primary goal is to establish an airway with an SLT placed orally with the aid of a flexible fiberoptic bronchoscope, after appropriate airway anesthesia is achieved. In selected patients who seem easy to ventilate, this may be performed after induction of anesthesia with a bronchoscope or with a videolaryngoscope.[90] Once the SLT is in place, an independent bronchial blocker can be passed. If the patient requires OLV and cannot be intubated orally, an awake nasotracheal intubation can be performed with an SLT and, once the airway is established, then a bronchial blocker can be passed.

An alternative to achieve OLV in a patient with a difficult airway is to intubate the patient's trachea with an SLT; then a tube-exchange technique can be used to replace the existing SLT for a DLT after general anesthesia is induced. A tube-exchange catheter should have a hollow center channel and universal adapters to insufflate oxygen or be connected to a jet ventilator if necessary. The exchange catheter must be flexible, be long, and have markings on the outer surface to control the depth of insertion while in use. For a DLT the exchange catheter should be at least 83 cm. A 14-Fr exchange catheter can be used for 41-Fr and 39-Fr DLTs; for 37-Fr or 35-Fr DLTs an 11-Fr exchange catheter is used. Specially designed exchange catheters for DLTs are available with a softer distal tip to try to decrease the risk of distal airway trauma (e.g., Cook Exchange Catheter, Cook Critical Care, Bloomington, IN).

The exchange catheter, SLT, and the DLT combination should be tested in vitro before the exchange. A sniffing position facilitates tube exchange. After the exchange catheter is lubricated, it is advanced through an SLT. The catheter should not be inserted deeper than 24 cm at the lips to avoid accidental rupture or laceration of the trachea or bronchi. After cuff deflation, the SLT is withdrawn. Then the endobronchial lumen of the DLT is advanced over the exchange catheter. It is optimal to use a videolaryngoscope during the tube exchange to guide the DLT thorough the glottis under direct vision. If a videolaryngoscope is not available, having an assistant perform standard laryngoscopy during tube exchange partially straightens out the alignment of the oropharynx and glottis and facilitates the exchange. Proper final position of the DLT is then achieved with auscultation and bronchoscopy.

Lung-Isolation Techniques in Patients with a Tracheostomy in Place

Placement of a DLT through a tracheostomy stoma may be prone to malposition because the upper airway has been shortened and the conventional DLT may be too long. Before placing any lung-isolation devices through a tracheostomy stoma it is important to consider whether it is a fresh stoma (i.e., a few days old, when the airway can be lost immediately on decannulation) versus a chronic tracheostomy. The alternatives to achieve OLV in a tracheostomized patients include (1) insertion of an SLT followed by an independent bronchial blocker[91]; (2) the use of a disposable cuffed tracheostomy cannula with an independent bronchial blocker passed coaxially; (3) replacement of the tracheostomy cannula with a specially designed short DLT such as the Naruke DLT, which is made for use in tracheostomized patients[92]; (4) placement of a small DLT through the tracheostomy stoma; or (5) if possible, oral access to the airway for standard placement of a DLT or blocker (this is occasionally an option in patients on prolonged mechanical ventilation for respiratory failure or postoperative complications).

In summary, the optimal method of lung isolation will depend on a number of factors, including the patient's airway anatomy, the indication for lung isolation, the available equipment, and the training of the anesthesiologist. Suggested methods for lung isolation in specific clinical situations are listed in Table 59-14. Whatever method of lung isolation is used, the "ABCs" of lung isolation are:

*A*natomy. Know the tracheobronchial anatomy. One of the major problems that many anesthesiologists have in achieving satisfactory lung isolation is due to lack of familiarity with distal airway anatomy (Fig. 59-20).

*B*ronchoscopy. Whenever possible use a fiberoptic bronchoscope to position endobronchial tubes and blockers. The ability to perform fiberoptic bronchoscopy is now a fundamental skill needed by all anesthesiologists providing anesthesia for thoracic surgery. An online bronchoscopy simulator has been developed to help train anesthesiologists in positioning DLTs and blockers. This simulator, which uses real-time video, is available without cost at www.thoracicanesthesia.com.

*C*hest imaging. The anesthesiologist should always look at the chest imaging before placement of a DLT or blocker. Abnormalities of the lower airway can often be identified in advance, and this will have an impact on the selection of the optimal method of lung isolation for a specific case (see Figs. 59-6 and 59-7).

Positioning

The majority of thoracic procedures are performed with the patient in the lateral position, most often the lateral decubitus position, but, depending on the surgical technique, a supine, semisupine, or semiprone lateral position may be used (see Chapter 36). These lateral positions have specific implications for the anesthesiologist.

Position Change

It is awkward to induce anesthesia with the patient in the lateral position. Thus, monitors will be placed and anesthesia will usually be induced with the patient in the supine position and the anesthetized patient will then be repositioned for surgery. It is possible to induce anesthesia in the lateral position, and this may rarely be indicated with unilateral lung diseases such as bronchiectasis or hemoptysis until lung isolation can be achieved. However, even these patients will then have to be repositioned and the diseased lung turned to the nondependent side.

Because of the loss of venous vascular tone in the anesthetized patient it is not uncommon to see hypotension on turning the patient to or from the lateral position. All lines and monitors will have to be secured during position change and their function

Table 59-14 Suggested Methods of Lung Isolation for Specific Indications

Indication for Lung Isolation	Preferred Method(s)	Possible Alternative(s)
Pulmonary resection right side	Left DLT	BB/Left EBT
Pulmonary resection left side:		
Pneumonectomy unlikely	Left DLT	BB/Right DLT
Pneumonectomy	Right DLT	Left DLT/BB
Thoracoscopy (either side)	Left DLT	BB/Right DLT
Pulmonary hemorrhage	Left DLT	BB/contra-lateral EBT
Bronchopleural fistula		
Left mainstem bronchus	Right DLT	EBT
All other sites	Left DLT	Right DLT/BB/EBT
Purulent secretions (e.g., abscess, cyst, etc.)	Left DLT	Right DLT/BB/EBT
Bullae, blebs	Left DLT	Right DLT/BB
Nonpulmonary surgery (e.g., thoracic aorta, esophagus)	Left DLT/BB	Right DLT/EBT
Bronchial surgery (tumor, trauma)		
Left side	Right DLT	EBT
Right side	Left DLT	EBT
Upper airway abnormalities	BB	Left DLT/EBT
Lung transplantation:		
Bilateral	Left DLT	BB/EBT
Single right lung	Left DLT	BB/EBT
Single left lung	Right DLT	BB/Left DLT/EBT
Whole lung lavage	Left DLT	
Independent lung ventilation	Left DLT	Right DLT

BB, ipsilateral bronchial blocker; DLT, Double-lumen tube; EBT, contralateral single-lumen endobronchial tube.

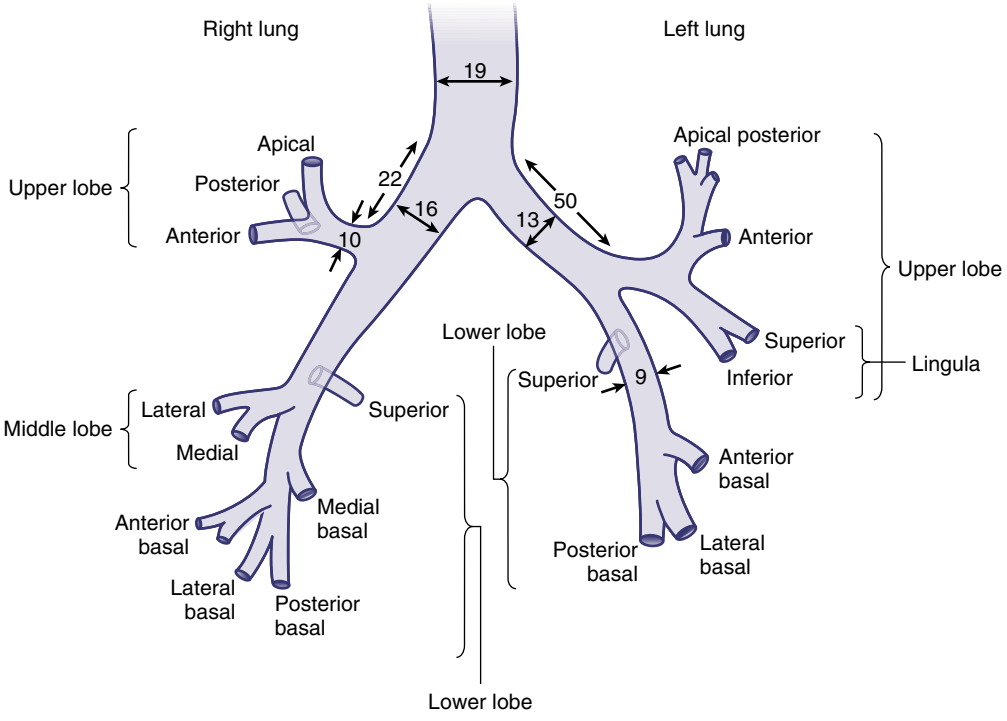

Figure 59-20 Diagram of the tracheobronchial tree. Mean lengths and diameters are shown in millimeters. Note that the right middle lobe bronchus exits directly anteriorly while the superior segments (some authors refer to these as the "apical" segments) of the lower lobes exit directly posteriorly. Using the apical designation on the right side the segmental bronchi in a rostral to caudal sequence give the mnemonic "A PALM A MAPL." (*From Youngberg JA: Cardiac, Vascular and Thoracic Anesthesia. Philadelphia, Churchill Livingstone, 2000.*)

reassessed after repositioning. The anesthesiologist should take responsibility for the head, neck, and airway during position change and must be in charge of the operating team to direct repositioning. It is useful to make an initial "head-to-toe" survey of the patient after induction and intubation, checking oxygenation, ventilation, hemodynamics, lines, monitors, and potential nerve injuries. This survey then must be repeated after repositioning. It is nearly impossible to avoid some movement of a DLT or bronchial blocker during repositioning.[68] Certainly the patient's head, neck, and endobronchial tube should be turned "en bloc" with the patient's thoracolumbar spine. However, the margin of error in positioning endobronchial tubes or blockers is often so narrow that even very small movements can have significant clinical implications.[81] The carina and mediastinum may shift independently with repositioning, and this can lead to proximal misplacement of a previously well-positioned tube. Endobronchial tube/blocker position and the adequacy of ventilation must be rechecked by auscultation and fiberoptic bronchoscopy after patient repositioning.

Neurovascular Complications

There are a specific set of nerve and vascular injuries related to the lateral position that must be appreciated. The brachial plexus is the site of a majority of intraoperative nerve injuries related to the lateral position. These are basically of two varieties: the majority are compression injuries of the brachial plexus of the dependent arm, but there is also significant risk of stretch injuries to the brachial plexus of the nondependent arm. The brachial plexus is fixed at two points: proximally by the transverse process of the cervical vertebrae and distally by the axillary fascia. This two-point fixation plus the extreme mobility of neighboring skeletal and muscular structures makes the brachial plexus extremely liable to injury (Table 59-15). The patient should be positioned with padding under the dependent thorax (Fig. 59-21) to keep the weight of the upper body off the dependent arm brachial plexus. However, this padding will exacerbate the pressure on the brachial plexus if it migrates superiorly into the axilla.

The brachial plexus of the nondependent arm is most at risk if it is suspended from an independently fixed arm support or "ether screen." Traction on the brachial plexus in these situations is particularly likely to occur if the patient's trunk accidentally slips toward a semiprone or semisupine position after fixation of the nondependent arm. Vascular compression of the nondependent arm in this situation is also possible, and it is useful to monitor pulse oximetry in the nondependent hand to observe

Table 59-15 Factors Contributing to Brachial Plexus Injury in the Lateral Position

Dependent Arm (Compression Injuries)
Arm directly under thorax
Pressure on clavicle into retroclavicular space
Cervical rib
Caudal migration of thorax padding into the axilla*
Nondependent Arm (Stretch Injuries)
Lateral flexion of cervical spine
Excessive abduction of arm (>90%)
Semiprone or semisupine repositioning after arm fixed to a support

*Unfortunately this padding under the thorax is misnamed an "axillary roll" in some institutions. This padding absolutely should NOT be placed in the axilla.

this. The arm should not be abducted beyond 90 degrees and should not be extended posteriorly beyond the neutral position nor flexed anteriorly greater than 90 degrees. Fortunately, the majority of these nerve injuries resolve spontaneously over a period of months.

Anterior flexion of the arm at the shoulder (circumduction) across the chest or lateral flexion of the neck toward the opposite side can cause a traction injury of the suprascapular nerve. This causes a deep, poorly circumscribed pain of posterior and lateral aspects of the shoulder and may be responsible for some cases of post-thoracotomy shoulder pain.

Repositioning the patient in the lateral decubitus position can easily cause excessive lateral flexion of the cervical spine because of improper positioning of the patient's head. This malpositioning that exacerbates brachial plexus traction can cause a "whiplash" syndrome and can be difficult to appreciate from the head of the operating table, particularly after the surgical drapes have been placed. It is useful for the anesthesiologist to survey the patient from the side of the table immediately after turning to ensure that the entire vertebral column is aligned properly.

The dependent leg should be slightly flexed with padding under the knee to protect the peroneal nerve lateral to the proximal head of the fibula. The nondependent leg is placed in a neutral extended position and padding placed between it and the dependent leg. The dependent leg must be observed for vascular compression. Excessively tight strapping at the hip level can compress the sciatic nerve of the nondependent leg. Other sites particularly liable for neurovascular injury in the lateral position are the dependent ear pinna and eye. A "head-to-toe" protocol to monitor for possible neurovascular injuries related to the lateral decubitus position is presented in Table 59-16.

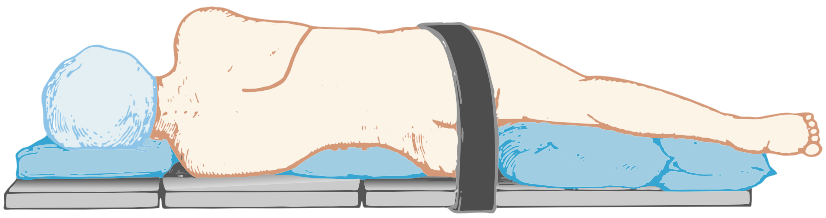

Figure 59-21 Typical positioning of a patient in the lateral decubitus position for thoracotomy seen from behind. It is useful for the anesthesiologist to survey the anesthetized patient from this perspective before draping to ensure that there is no lateral flexion of the cervical spine, which can be very difficult to appreciate from the head of the operating table. Note also padding of the dependent thorax and the nondependent leg. (*From Kaplan J, Slinger P [eds]: Thoracic Anesthesia, 3rd ed. Philadelphia, Churchill Livingstone, 2003.*)

Table 59-16 Neurovascular Injuries Specific to the Lateral Position: Routine "Head-to-Toe" Survey

1. Dependent eye
2. Dependent ear pinna
3. Cervical spine in line with thoracic spine
4. Dependent arm:
   a. Brachial plexus
   b. Circulation
5. Nondependent arm*:
   a. Brachial plexus
   b. Circulation
6. Dependent and nondependent suprascapular nerves
7. Nondependent leg: sciatic nerve
8. Dependent leg:
   a. Peroneal nerve
   b. Circulation

*Neurovascular injuries of the nondependent arm are more likely to occur if the arm is suspended or held in an independently positioned armrest.

Physiologic Changes in the Lateral Position

Ventilation

Significant changes in ventilation develop between the lungs when the patient is placed in the lateral position. Originally this was explained by the theory that the lungs move up and down a common compliance curve with the dependent lung becoming less compliant and the nondependent lung more compliant. However, subsequent studies suggest that the reality is more complex.[93] The compliance curves of the two lungs are different because of their difference in sizes. The lateral position, anesthesia, paralysis, and opening of the thorax all combine to magnify these differences between the lungs (Fig. 59-22). The compliance curve (change in volume versus change in pressure) of a lung depends on the balance of two "springs": the chest wall (normally distending the lung) and the elastic recoil of the lung itself. Any factor that changes the mechanics of either of these springs places the lung on a different compliance curve.[94]

In a healthy, conscious, spontaneously breathing patient, the ventilation of the dependent lung will increase approximately 10% when the patient is turned to the lateral position. Once the patient is anesthetized and paralyzed, the ventilation of the dependent lung will then decrease 15%. Although the ventilation will not change significantly once the nondependent hemithorax is open, the FRC of this nondependent lung will tend to increase approximately 10%. These changes will depend on the method used for ventilation in the individual patient. When the chest is open, due to disruption of the chest wall, both lungs will tend to collapse to a minimal lung volume if expiration is prolonged. Thus the end-expiratory volume of each lung is directly a function of the time allowed for expiration. The compliance of the entire respiratory system will increase significantly once the nondependent hemithorax is open (see Chapter 15).

Because of the fall in FRC and compliance of the nondependent lung in the lateral position, application of PEEP selectively to this lung only (using a DLT and two anesthetic circuits) will improve gas exchange.[95] This is different than the effect of nonselectively applying PEEP to both lungs in the lateral position where PEEP tends to preferentially distribute to the most compliant lung regions and will tend to hyperinflate the nondependent lung without causing any improvement in gas exchange.

Atelectasis will develop in an average of 6% of the lung parenchyma after induction of anesthesia in the supine position. This atelectasis will be evenly distributed in the dependent portions of both lungs.[96] After turning the patient to the lateral position there will be a slight decrease of total atelectasis to 5% of lung volume, but this will now be concentrated totally in the dependent lung (Fig. 59-23). Further complicating our understanding of this physiology in clinical thoracic anesthesia is the fact that most studies of the effects of position on ventilation were done in healthy subjects and the majority of thoracic surgery patients have underlying lung disease with altered respiratory resistance and compliance, so the intraoperative distribution of ventilation becomes even less predictable.

Perfusion

Traditional teaching has been that turning the patient from the supine to the lateral position will decrease the blood flow of the nondependent lung due to gravity. This decrease has been assumed to be approximately 10% of the total pulmonary blood flow. Subsequent animal research has led to some question about the effects of gravity on pulmonary blood flow distribution.[97] The distribution of pulmonary blood flow in various positions may be more related to inherent pulmonary vascular anatomic factors than to gravity (see Chapter 15). The matching of ventilation and perfusion will usually be decreased in the lateral position compared with the supine position during anesthesia. Pulmonary arteriovenous shunt during general anesthesia will usually increase from approximately 5% in the supine position to 10% to 15% in the lateral position.[98]

Anesthetic Management

The development of thoracic anesthesia and thoracic surgery was delayed more than 50 years after the introduction of ether because anesthesiologists could not manage patients during mask anesthesia with spontaneous ventilation and an open chest. These patients developed what was originally called the "pneumothorax syndrome." The respiratory systems of mammals do not function

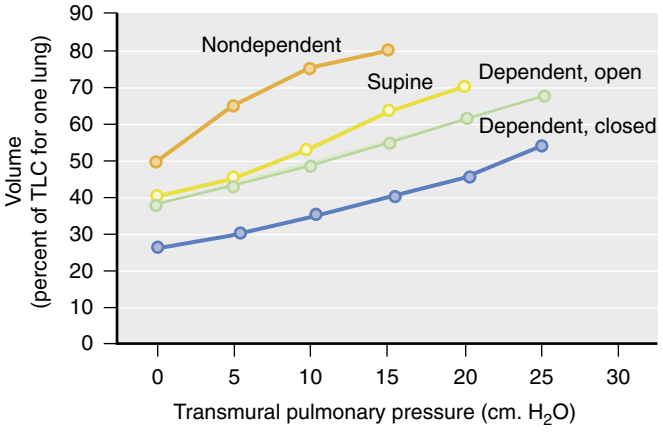

Figure 59-22 Changes in the compliance of a single lung during position changes in an anesthetized, paralyzed patient during controlled mechanical ventilation. These compliance changes are responsible for the resulting differences in ventilation between the lungs that occur in the lateral position. TLC, total lung capacity.

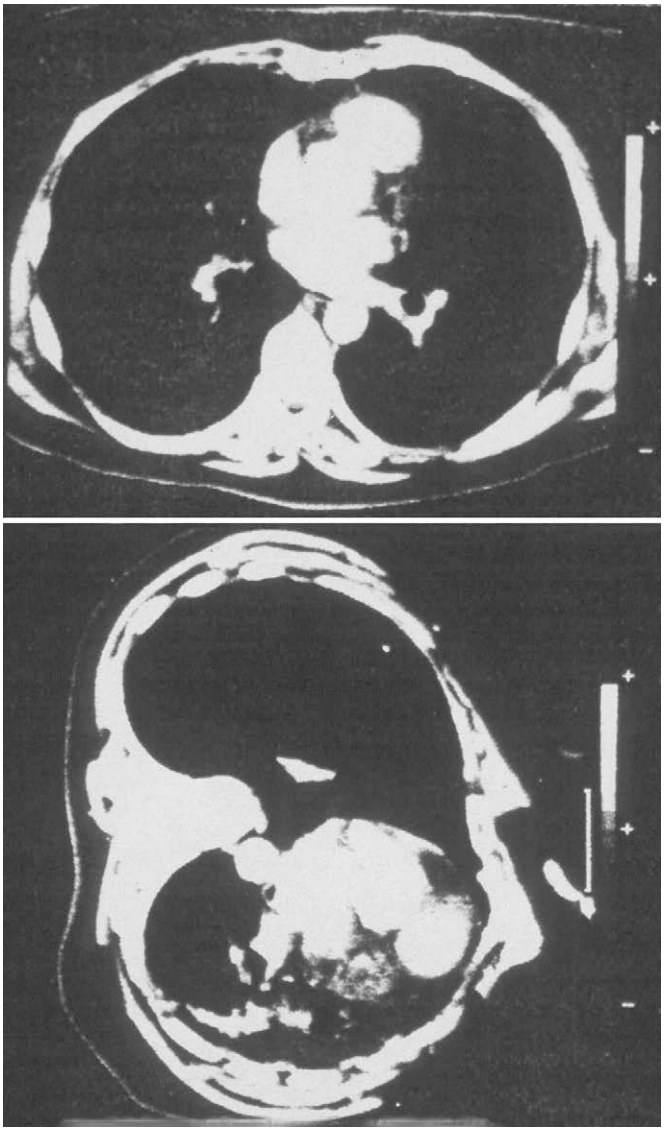

Figure 59-23 Atelectasis develops in the dependent portions of both lungs after induction of anesthesia, as seen in this chest CT scan (*top*). This atelectasis disappears in the nondependent lung after turning the patient to the lateral position but increases in the dependent lung (*bottom*). This is the lung that will subsequently be used for gas exchange during one-lung ventilation. (*From Kaplan J, Slinger P [eds]: Thoracic Anesthesia, 3rd ed. Philadelphia, Churchill Livingstone, 2003.*)

adequately with open hemithoraces because of two physiologic problems. First, paradoxical ventilation (also called "pendelluft") occurs in which gas moves into the lung in the open hemithorax from the lung in the closed hemithorax during expiration. Flow reverses during inspiration. This leads to hypercapnia and hypoxemia. Second, there is swinging motion of the mediastinum between the hemithoraces during the respiratory cycle that interferes with cardiac preload and causes hemodynamic instability. In the early 1900s, several pioneers, such as the New Orleans surgeon Matas, advocated positive-pressure ventilation and a primitive form of endotracheal ventilation, which had been demonstrated to be safe in animal experiments, for thoracic anesthesia. Modern methods, incorporating OLV, have evolved from these experiments. Essentially, any anesthetic technique that provides safe and stable general anesthesia for major surgery can and has been used for lung resection. There is currently a major trend to the use of combined thoracic epidural and general anesthesia for thoracic surgery.

Fluid Management

Because of hydrostatic effects, excessive administration of intravenous fluids can cause increased shunting and subsequently lead to pulmonary edema of the dependent lung, particularly during prolonged surgery. Because the dependent lung is the lung that must carry on gas exchange during OLV it is best to be as judicious as possible with fluid administration. Intravenous fluids are administered to replace volume deficits and for maintenance only during lung resection anesthesia. No volume is given for theoretical "third space" losses during thoracotomy; there is no good evidence that such third space losses occur during lung resection as they do during abdominal or other types of surgery (Table 59-17). The commonly accepted dictum is "don't drown the down lung."

Nitrous Oxide

Nitrous oxide/oxygen (N_2O/O_2) mixtures are more prone to cause atelectasis in poorly ventilated lung regions than oxygen by itself. Although N_2O is relatively insoluble compared with other volatile anesthetics, it is more soluble than atmospheric gases (nitrogen, oxygen, argon). The rate of uptake of an N_2O/O_2 mixture from an unventilated lung exceeds that of pure oxygen. The maximal uptake is with a mixture of N_2O/O_2 with an F_{IO_2} of 0.4 to 0.5.[99] The use of N_2O/O_2 mixtures is associated with a higher incidence of post-thoracotomy radiographic atelectasis (51%) in the dependent lung than when air/oxygen mixtures are used (24%). Nitrous oxide also tends to increase pulmonary artery pressures in patients who have pulmonary hypertension,[100] N_2O inhibits HPV,[101] and N_2O is contraindicated in patients with blebs or bullae. For these reasons N_2O is usually avoided during thoracic anesthesia.

Temperature

Maintenance of body temperature can be a problem during thoracic surgery because of heat loss from the open hemithorax. This is particularly a problem at the extremes of the age spectrum. Most of the body's physiologic functions, including HPV, are inhibited during hypothermia. Increasing the ambient room tem-

Table 59-17 Fluid Management for Pulmonary Resection Surgery

1. Total positive fluid balance in the first 24-hour perioperative period should not exceed 20 mL/kg.
2. For an average adult patient, crystalloid administration should be limited to < 3 L in the first 24 hours.
3. There should be no fluid administration for third space fluid losses during pulmonary resection.
4. Urine output > 0.5 mL/kg/hr is unnecessary.
5. If increased tissue perfusion is needed postoperatively, it is preferable to use invasive monitoring and inotropes rather than to cause fluid overload.

perature, fluid warmers, and the use of lower- or upper-body forced-air patient warmers (or both) are the best methods to prevent inadvertent intraoperative hypothermia.

Prevention of Bronchospasm

Because of the high incidence of coexisting reactive airways disease in the thoracic surgical population it is generally advisable to use an anesthetic technique that decreases bronchial irritability. This is particularly important because the added airway manipulation caused by placement of a DLT or bronchial blocker is a potent trigger for bronchoconstriction. The principles of anesthetic management are the same as for any asthmatic patient: avoid manipulation of the airway in a lightly anesthetized patient, use bronchodilating anesthetics, and avoid drugs that release histamine. For intravenous induction of anesthesia either propofol or ketamine can be expected to diminish bronchospasm. This benefit will not be seen with barbiturate, opioid, benzodiazepine, or etomidate intravenous induction. For maintenance of anesthesia, propofol and/or any of the volatile anesthetics will diminish bronchial reactivity. Sevoflurane may be the most potent bronchodilator of the volatile anesthetics.[102]

Coronary Artery Disease

Because the lung resection population is largely elderly and smokers there is a high coincidence of coronary artery disease. This consideration will be a major factor in the choice of the anesthetic technique for most thoracic patients. The anesthetic technique should optimize the myocardial oxygen supply/demand ratio by maintaining arterial oxygenation and diastolic blood pressure while avoiding unnecessary increases in cardiac output and heart rate. Thoracic epidural anesthesia/analgesia may aid in this (see "Postoperative Analgesia" later).

The ability to provide effective regional anesthesia with thoracic epidural blockade has opened the possibility of performing some thoracic surgical procedures in awake patients. A wide variety of thoracic operations have been reported using this technique, including thoracoscopy, thoracotomy, and sternotomy.[103] Epidural block is often combined with ipsilateral stellate ganglion block to decrease the cough reflex from stimulation of the hilum. The specific indications to use these techniques do not arise commonly but may occur in severely compromised patients with airway management issues.[104] Obviously the original concerns with the "pneumothorax syndrome" apply to prolonged surgery with these techniques. However, during VATS the operative hemithorax is effectively closed, and gas exchange is usually adequate during spontaneous ventilation with supplemental oxygen.

Management of One-Lung Ventilation

During OLV the anesthesiologist has the unique and often conflicting goals of trying to maximize atelectasis in the nonventilated lung to improve surgical access while trying to avoid atelectasis in the ventilated lung (usually the dependent lung) to optimize gas exchange. The gas mixture in the nonventilated lung immediately before OLV has a significant effect of the speed of collapse of this lung. Because of its low blood gas solubility, nitrogen (or an air-oxygen mixture) will delay collapse of this lung (Fig. 59-24).[105] This is particularly a problem at the start of VATS surgery, when surgical visualization in the operative hemithorax is limited and in patients with emphysema who have delayed collapse of the nonventilated lung due to decreased lung elastic recoil. It is important to thoroughly de-nitrogenate the operative lung, by ventilating with oxygen, immediately before it is allowed to collapse. Although nitrous oxide is even more effective than oxygen in speeding lung collapse, for the reasons cited earlier it is not commonly used in thoracic anesthesia.

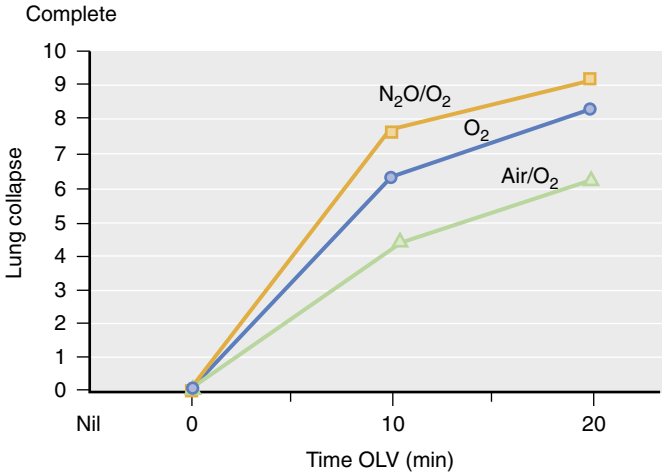

Figure 59-24 The effects of the gas mixture used during two-lung ventilation, immediately before one-lung ventilation (OLV), on the speed of collapse of the nonventilated lung during OLV. O_2 = F_{IO_2} 1.0; N_2O/O_2 = nitrous oxide/oxygen 60/40; Air/O_2 = air/oxygen F_{IO_2} 0.4. All patients were ventilated with an F_{IO_2} of 1.0 during OLV. The poorly soluble nitrogen in the air/oxygen mixture delays collapse of the nonventilated lung. (*Based on data from Ko R, Kruger M, McRae K, et al: Impact of inspired gas mixtures on oxygenation and surgical conditions during one-lung ventilation. Can J Anesth 50:A13, 2003.*)

Also during the period of two-lung anesthesia before the start of OLV, atelectasis will develop in the dependent lung (see Fig. 59-23). It is useful to perform a recruitment maneuver (similar to a Valsalva maneuver, holding the lung at an end-inspiratory pressure of 20 cm H_2O for 15 to 20 sec) immediately after the start of OLV to decrease this atelectasis. This recruitment has been shown to increase the mean Pao_2 levels during subsequent OLV (see Chapter 15).[106]

Hypoxemia

A major concern that influences anesthetic management for thoracic surgery is the occurrence of hypoxemia during OLV. There is no universally acceptable figure for the safest lower limit of oxygen saturation during OLV. A saturation greater than or equal to 90% (Pao_2 > 60 mm Hg) is commonly accepted, and for brief periods a saturation in the high 80s may be acceptable in patients without significant comorbidity. However, the lowest acceptable saturation will be higher in patients with organs at risk of hypoxia

due to limited regional blood flow (e.g., coronary or cerebrovascular disease) and in patients with limited oxygen transport (e.g., anemia or decreased cardiopulmonary reserve). It has been shown that during OLV patients with COPD desaturate more quickly during isovolemic hemodilution than normal patients.[107]

Previously, hypoxemia occurred frequently during OLV. Reports for the period 1950-1980 describe an incidence of hypoxemia (arterial saturation < 90%) of 20% to 25%. During the 1990s reports described an incidence of less than 10%,[108] and more recently the incidence of hypoxemia during OLV for thoracic surgery has been reported at less than 1%.[109] This improvement is most likely due to several factors: improved lung-isolation techniques such as routine fiberoscopy to prevent lobar obstruction from DLTs, improved anesthetic techniques that cause less inhibition of HPV, and better understanding of the pathophysiology of OLV. The pathophysiology of OLV involves the body's ability to redistribute pulmonary blood flow to the ventilated lung. Several factors aid and impede this redistribution, and these are under the control of the anesthesiologist to a variable degree. These factors are illustrated in Figure 59-25. The anesthesiologist's goal during OLV is to maximize pulmonary vascular resistance (PVR) in the nonventilated lung while minimizing PVR in the ventilated lung. Key to understanding this physiology is the appreciation that PVR is correlated with lung volume in a hyperbolic fashion (Fig. 59-26). PVR is lowest at FRC and increases as lung volume rises or falls above or below FRC (see Chapter 15).[110] The anesthesiologist's aim, to optimize pulmonary blood flow redistribution during OLV, is to maintain the ventilated lung as close as possible to its FRC while facilitating collapse of the nonventilated lung to increase its PVR.

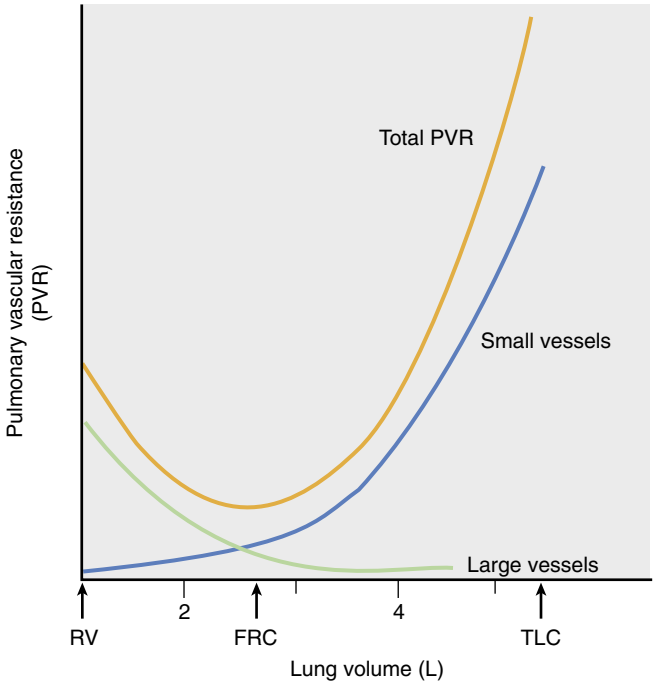

Figure 59-26 The relationship between pulmonary vascular resistance (PVR) and lung volume. PVR is lowest at functional residual capacity (FRC) and increases as the lung volume decreases toward residual volume (RV), owing primarily to increase in resistance of large pulmonary vessels. PVR also increases as lung volume increases above FRC toward total lung capacity (TLC) because of an increase in the resistance of small interalveolar lung vessels.

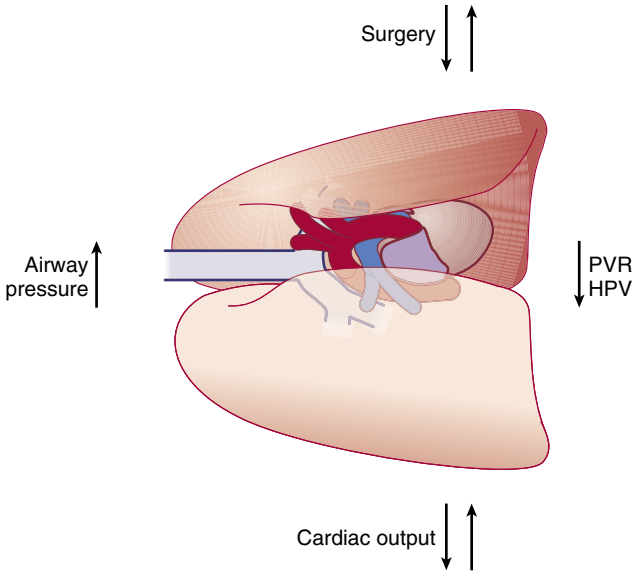

Figure 59-25 Factors affecting the distribution of pulmonary blood flow during one-lung ventilation. Hypoxic pulmonary vasoconstriction (HPV) and the collapse of the nonventilated lung, which increases pulmonary vascular resistance (PVR), tend to distribute blood flow toward the ventilated lung. The airway pressure gradient between the ventilated and nonventilated thoraces tends to encourage blood flow to the nonventilated lung. Surgery and cardiac output can have variable effects, either increasing or decreasing the proportional flow to the ventilated lung (see text).

Intraoperative Position

Most thoracic surgery is performed in the lateral position. Patients having OLV in the lateral position have significantly better Pa_{O_2} levels than patients during OLV in the supine position.[111] This applies both to patients with normal lung function and to those with COPD (Fig. 59-27).[112]

Hypoxic Pulmonary Vasoconstriction

HPV is generally considered to be a factor governing the redistribution of blood flow during OLV. It is thought to be able to decrease the blood flow to the nonventilated lung by 50%. The stimulus for HPV is primarily the alveolar oxygen tension ($P_{A_{O_2}}$), which stimulates precapillary vasoconstriction redistributing pulmonary blood flow away from hypoxemic lung regions via a pathway involving NO and/or cyclooxygenase synthesis inhibition.[113] The mixed venous P_{O_2} ($P\bar{v}_{O_2}$) is also a stimulus, although considerably weaker than $P_{A_{O_2}}$, and the Pa_{O_2} has a biphasic effect on HPV. HPV in humans has a rapid onset over the first 30 minutes and then a slower increase to a maximal response at approximately 2 hours. HPV is a reflex that has a preconditioning effect, and the response to a second hypoxic challenge will be greater than to the first challenge.[114]

The surgical trauma to the lung can affect pulmonary blood flow redistribution. Surgery may oppose HPV by release of vasoactive metabolites locally in the lung or may cause autonomic effects by trauma to the perihilar plexus. Conversely, surgery can

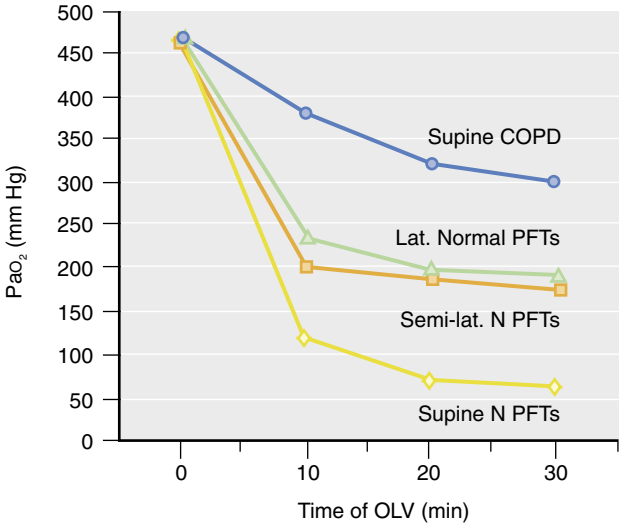

Figure 59-27 Mean Pao_2 in groups of patients vs. time of one-lung ventilation (OLV). Supine COPD, patients with COPD having OLV in the supine position; Lat. PFTs, patients with normal pulmonary function having OLV in the lateral position; Semi-lat. N PFTs, patients with normal pulmonary function having OLV in the semi-lateral position; Supine N PFTs, patients with normal pulmonary function having OLV in the supine position. Patients with normal pulmonary function having OLV in the supine position are the most likely to desaturate. (*Based on data from Watanabe S, Noguchi E, Yamada S, et al: Sequential changes in arterial oxygen tension in the supine position during one-lung ventilation. Anesth Analg 90:28, 2000; and Bardoczky GI, Szegedi LL, d'Hollander AA, et al: Two-lung and one-lung ventilation in patients with chronic lung disease: The effects of position and Fio_2. Anesth Analg 90:35, 2000.*)

dramatically decrease blood flow to the nonventilated lung by deliberately or accidentally mechanically interfering with either the unilateral pulmonary arterial or venous blood flow.[115] Ventilation increases blood flow through a hypoxic lung more than in a normoxic lung, which is generally not of clinical relevance but does complicate studies of HPV. HPV is decreased by vasodilators such as nitroglycerin and nitroprusside. In general, vasodilators can be expected to cause a deterioration in Pao_2 during OLV. Thoracic epidural sympathetic blockade probably has little or no direct effect on HPV, which is a localized chemical response in the lung.[116] However, thoracic epidural anesthesia can have an indirect effect on oxygenation during OLV if it is allowed to cause hypotension and a fall in cardiac output (see "Cardiac Output" later).

Choice of Anesthetic

All of the volatile anesthetics inhibit HPV in a dose-dependent fashion. Animal studies suggest that this inhibition is dependent on the agent: halothane > enflurane > isoflurane. The older agents were potent inhibitors of HPV, and this may have contributed to the high incidence of hypoxemia reported during OLV in the 1960s and 1970s (see earlier); many of these studies used 2- to 3-MAC doses of halothane.

In doses less than or equal to 1 MAC, the modern volatile anesthetics (isoflurane, sevoflurane,[117] and desflurane[118]) are weak, and equipotent, inhibitors of HPV. The inhibition of the HPV response by 1 MAC of a volatile agent such as isoflurane is approximately 20% of the total HPV response, and this could account for only a net 4% increase in total arteriovenous shunt during OLV, which is a difference too small to be detected in most clinical studies.[119] In addition, volatile anesthetics cause less inhibition of HPV when delivered to the active site of vasoconstriction via the pulmonary arterial blood than via the alveolus. This pattern is similar to the HPV stimulus characteristics of oxygen. During established OLV, the volatile agent only reaches the hypoxic lung pulmonary capillaries via the mixed venous blood. No clinical benefit in oxygenation during OLV has been shown for total intravenous anesthesia above that seen with 1 MAC of the modern volatile anesthetics.[120]

Cardiac Output

The effects of alterations of cardiac output during OLV are complex (Fig. 59-28). Increasing cardiac output tends to cause increased pulmonary artery pressures and passive dilation of the pulmonary vascular bed, which in turn opposes HPV and has been shown to be associated with increased arteriovenous shunt $\left(\dot{Q}s/\dot{Q}t\right)$ during OLV.[121] However, in patients with a relatively fixed oxygen consumption, as is seen during stable anesthesia, the effect of an increase in cardiac output is to increase the mixed venous oxygen saturation $(S\bar{v}O_2)$. Thus, increasing cardiac output during OLV tends to increase both shunt and $S\bar{v}O_2$, which have opposing effects on Pao_2. There is a ceiling effect to the amount that $S\bar{v}O_2$ can be increased. Increasing the cardiac output to supranormal levels by administering inotropes such as dopamine tends to have an overall negative effect on Pao_2.[122] Conversely, allowing the cardiac output to fall will lead to falls in both shunt and $S\bar{v}O_2$ with a net effect of decreasing Pao_2. Because even with optimal anesthetic management there is usually a shunt of 20% to 30% during OLV, it is very important to maintain cardiac output.

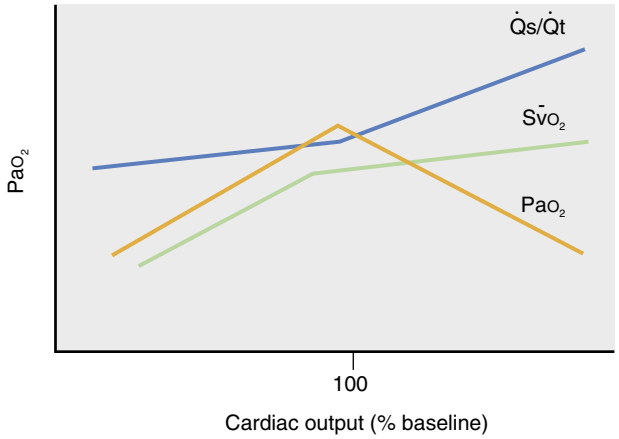

Figure 59-28 The relationship between Pao_2 and cardiac output during one-lung ventilation (OLV). As cardiac output falls below baseline, arteriovenous shunt $\left(\dot{Q}s/\dot{Q}t\right)$ falls but the mixed venous oxygen saturation ($S\bar{v}O_2$) also decreases, resulting in a net fall in Pao_2. Conversely, raising cardiac output above baseline tends to increase $S\bar{v}O_2$ but also to increase $\dot{Q}s/\dot{Q}t$, and the net result again is a decrease in Pao_2. (*Based on data from Slinger P, Scott WAC: Arterial oxygenation during one-lung anesthesia: A comparison of enflurane and isoflurane. Anesthesiology 82:940, 1995; and Russell WJ, James MF: The effects on arterial haemoglobin oxygen saturation and on shunt of increasing cardiac output with dopamine or dobutamine during one-lung ventilation. Anaesth Intens Care 32:644, 2004.*)

Ventilation Strategies

The strategy used to manage the ventilated lung during OLV plays an important part in the distribution of pulmonary blood flow between the lungs. It has been the practice of many anesthesiologists to use the same large tidal volume (e.g., 10 mL/kg ideal body weight) during OLV as during two-lung ventilation. This strategy decreases hypoxemia probably by recurrently recruiting atelectatic regions in the dependent lung. There is a trend to use smaller tidal volumes with PEEP during OLV for several reasons. First, the incidence of hypoxemia during OLV is much lower than 20 to 30 years ago. Second, there is a risk of causing acute injury to the ventilated lung with prolonged use of large tidal volumes. And third, a ventilation pattern that allows recurrent atelectasis followed by recruitment of lung parenchyma seems to be injurious.[29] The ventilation technique needs to be individualized depending on the patient's underlying lung mechanics.

Respiratory Acid-Base Status

The efficacy of HPV in a hypoxic lung region is increased in the presence of respiratory acidosis and is inhibited by respiratory alkalosis. However, there is no net benefit to gas exchange during OLV from hypoventilation because the respiratory acidosis preferentially increases the pulmonary vascular tone of the well-oxygenated lung and this opposes any clinically useful pulmonary blood flow redistribution.[123] Overall, the effects of hyperventilation will usually tend to decrease pulmonary vascular pressures.

Positive End-expiratory Pressure

Resistance to blood flow through the lung is related to lung volume in a biphasic pattern and is lowest when the lung is at its FRC (see Fig. 59-26 and Chapter 15). Keeping the ventilated lung as close as possible to its normal FRC favorably encourages pulmonary blood flow to this lung. Several intraoperative factors that are known to alter FRC tend to cause the FRC of the ventilated lung to fall below its normal level; these include lateral position, paralysis, and opening the nondependent hemithorax, which allows the weight of the mediastinum to compress the dependent lung. Attempts to measure FRC in human patients during OLV have been complicated by the presence of a persistent end-expiratory airflow in COPD patients.[124] Many patients do not actually reach their end-expiratory equilibrium FRC lung volume as they try to exhale a relatively large tidal volume through one lumen of a DLT. These patients develop dynamic hyperinflation and an occult positive end-expiratory pressure (auto-PEEP).[40]

Auto-PEEP

Auto-PEEP is most prone to occur in patients with decreased lung elastic recoil such as the elderly or those with emphysema.[125] Auto-PEEP increases as the inspiratory/expiratory (I:E) ratio increases (i.e., as the time of expiration decreases). This auto-PEEP, which averages 4 to 6 cm H_2O in most series of lung cancer patients studied, opposes the previously mentioned factors, which tend to diminish dependent-lung FRC during OLV. The effects of applying external PEEP through the ventilator circuit to the lung in the presence of auto-PEEP are complex (Fig. 59-29). Patients with a very low auto-PEEP (<2 cm H_2O) will experience a greater increase in total PEEP from a moderate (5 cm H_2O) external PEEP than those with a high level of auto-PEEP (>10 cm H_2O). Whether the application of PEEP during OLV will improve a patient's gas exchange depends on the individual's lung mechanics. If the application of PEEP tends to shift the expiratory equilibration position on the compliance curve toward the lower inflection point (LIP) of the curve (i.e., toward the FRC), then external PEEP is of benefit (Fig. 59-30). However, if the application of PEEP raises the equilibration point such that it is farther from the LIP, then gas exchange deteriorates.

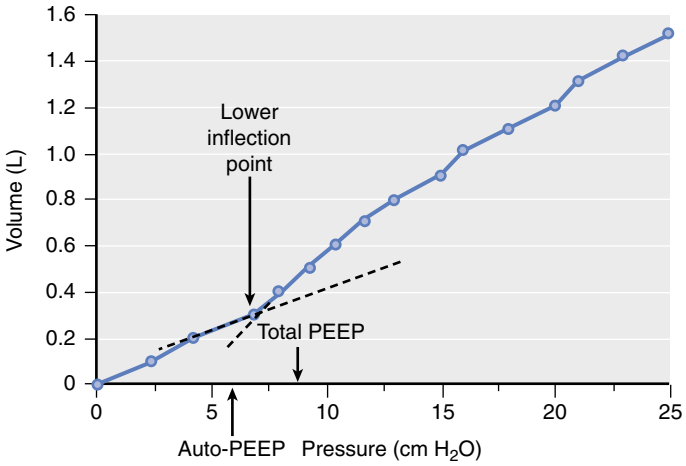

Figure 59-29 The static compliance curve of the ventilated (dependent) lung in a typical lung cancer patient with mild chronic obstructive pulmonary disease. The lower inflection point is thought to represent functional residual capacity (FRC). This patient had 6 cm H_2O of auto-PEEP during OLV. Adding 5 cm H_2O PEEP to the ventilator resulted in a total-PEEP in the circuit of 9 cm H_2O. This patient had a decrease in Pao_2 with the addition of PEEP (positive end-expiratory pressure). (*Based on data from Slinger P, et al: Relation of the static compliance curve and positive end-expiratory pressure to oxygenation during one-lung ventilation. Anesthesiology 95:1096, 2001.*)

Auto-PEEP is difficult to detect and measure using currently available anesthetic ventilators. To detect auto-PEEP the respiratory circuit must be held closed at the end of a normal expiration until an equilibrium appears in the airway pressure. Most current intensive-care unit ventilators can be used to measure auto-PEEP.

Tidal Volume

There will be an optimal combination of tidal volume, respiratory rate, I:E ratio, and pressure- or volume-control ventilation for each individual patient during OLV. However, to try to assess each of these parameters while still providing anesthesia with the available anesthetic ventilators is not practical and the clinician must initially rely on a simplified strategy (Table 59-18). The results of alterations in tidal volume are unpredictable. This may be due in part to the interaction of tidal volume with auto-PEEP. The use of 5 to 6 mL/kg ideal body weight tidal volumes plus 5 cm H_2O PEEP initially for most patients (except those with COPD) seems a logical starting point during OLV. Tidal volume should be managed so that peak airway pressures do not exceed 35 cm H_2O. This will correspond to a plateau airway pressure of approximately 25 cm H_2O.[126] Peak airway pressures exceeding 40 cm H_2O may contribute to hyperinflation injury of the ventilated lung during OLV.[127]

Turning the patient to the lateral position will increase respiratory dead space and the arterial to end-tidal CO_2 tension gradient (Pa-$ETco_2$). This will usually require a 20% increase in minute ventilation to maintain the same $Paco_2$. Individual

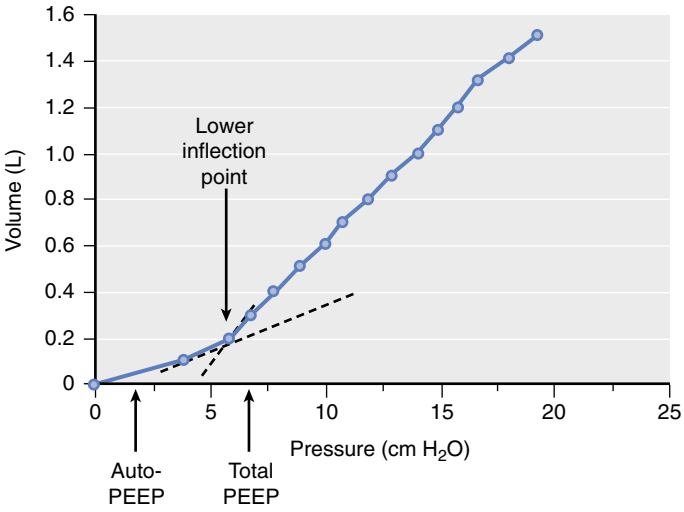

Figure 59-30 Static compliance curve of a young patient with normal pulmonary function during one-lung ventilation (OLV) (in this case, for removal of a mediastinal tumor). The lower inflection point of the curve (FRC) was at 6 cm H_2O. The patient had 2 cm H_2O auto-PEEP during OLV. Adding 5 cm H_2O PEEP to the ventilator raised the total PEEP to 7 cm H_2O and improved Pa_{O_2}. Young patients, and patients with increased lung elastic recoil (such as due to restrictive lung diseases), have an increase in Pa_{O_2} from PEEP during OLV. (*Based on data from Slinger P, et al: Relation of the static compliance curve and positive end-expiratory pressure to oxygenation during one-lung ventilation. Anesthesiology 95:1096, 2001.*)

variations in Pa-ET_{CO_2} gradient become much larger and P_{ETCO_2} is less reliable as a monitor of Pa_{CO_2} during OLV. This effect is possibly because there are individual differences in the excretion of CO_2 between the dependent and nondependent lungs.

Volume-Controlled Versus Pressure-Controlled Ventilation

Traditionally, volume-controlled ventilation has been used in the operating room for all types of surgery. The recent availability of anesthesia ventilators with pressure-control modes has made it possible to study and use this form of ventilation during thoracic surgery. Pressure-controlled ventilation has not been shown to improve oxygenation versus volume-controlled ventilation for most patients, although the peak airway pressures are lower.[128] There is a report suggesting that pressure-controlled ventilation may lead to improved oxygenation in COPD patients.[129] Pressure-controlled ventilation will avoid sudden increases in peak airway pressures that may result from surgical manipulation in the chest. This will be of benefit in patients at increased risk for lung injury from high volumes or pressures such as after lung transplantation or during a pneumonectomy.[130] Because of the rapid changes of lung compliance that occur during pulmonary surgery when pressure-controlled ventilation is used, the delivered tidal volume needs to be closely monitored because this may change suddenly.

Prediction of Hypoxemia

The problem of hypoxemia during OLV has prompted much research in thoracic anesthesia. Hypoxemia during OLV is predictable (see Table 59-6), preventable, and treatable in the vast majority of cases.[131]

Preoperative Ventilation-Perfusion Scan

The shunt and Pa_{O_2} during intraoperative OLV are highly correlated with the fractional perfusion of the ventilated lung, as determined by a preoperative $\dot{V}/\dot{Q}$ scan.[132] Patients with long-standing unilateral disease on the operative side develop a unilateral decrease of ventilation and perfusion and tolerate OLV very well. Similarly, patients who intraoperatively have a higher proportion of gas exchange in the dependent lung during OLV tend to have better oxygenation during OLV.

Side of Operation

Patients having right-sided thoracotomies tend to have a larger shunt and lower Pa_{O_2} during OLV because the right lung is larger and normally 10% better perused than the left. The overall mean Pa_{O_2} difference between left and right thoracotomies during stable OLV is approximately 100 mm Hg.[133]

Two-Lung Oxygenation

Patients who have better Pa_{O_2} levels during two-lung ventilation in the lateral position tend to have better oxygenation during OLV. These patients may have better abilities to match ventilation and perfusion (individual variability of HPV response) and/or they may have less atelectasis in the dependent lung. This is a particularly relevant consideration in trauma patients who may require a thoracotomy but have a contusion of the dependent lung.

Preoperative Spirometry

Studies consistently show that when the previous factors are controlled, patients with better spirometric lung function preoperatively are more likely to desaturate and have lower Pa_{O_2} values

Table 59-18 Suggested Ventilation Parameters for One-Lung Ventilation

Parameter	Suggested	Guidelines/ Exceptions
Tidal volume	5-6 mL/kg	Maintain: Peak airway pressure < 35 cm H_2O Plateau airway pressure < 25 cm H_2O
Positive end-expiratory pressure	5 cm H_2O	Patients with COPD: no added PEEP
Respiratory rate	12 breaths/min	Maintain normal Pa_{CO_2}; Pa-ET_{CO_2} will usually increase 1-3 mm Hg during OLV
Mode	Volume or pressure controlled	Pressure control for patients at risk of lung injury (e.g., bullae, pneumonectomy, post lung transplantation)

Table 59-19 Therapies for Desaturation during One-Lung Ventilation

Severe or precipitous desaturation: Resume two-lung ventilation (if possible).

Gradual desaturation:

1. Ensure that delivered F_{IO_2} is 1.0.
2. Check position of double-lumen tube or blocker with fiberoptic bronchoscopy.
3. Ensure that cardiac output is optimal; decrease volatile anesthetics to < 1 MAC.
4. Apply a recruitment maneuver to the ventilated lung (this will transiently make the hypoxemia worse).
5. Apply PEEP 5 cm H_2O to the ventilated lung (except in patients with emphysema).
6. Apply CPAP 1-2 cm H_2O to the nonventilated lung (apply a recruitment maneuver to this lung immediately before CPAP).
7. Intermittent reinflation of the nonventilated lung
8. Partial ventilation techniques of the nonventilated lung:
   a. Oxygen insufflation
   b. High-frequency ventilation
   c. Lobar collapse (using a bronchial blocker)
9. Mechanical restriction of the blood flow to the nonventilated lung

during OLV. Clinically this is evident because emphysematous lung volume reduction patients generally tolerate OLV very well. The explanation is not clear but may be related to maintenance of a more favorable FRC in patients with obstructive airways disease during OLV with an open hemithorax due to the development of auto-PEEP.[40]

Treatment of Hypoxemia

During OLV there will be a fall in arterial oxygenation that usually reaches its nadir 20 to 30 minutes after the initiation of OLV; then the saturation will stabilize or may rise slightly as HPV increases over the next 2 hours. A majority of patients who desaturate do so quickly and within the first 10 minutes of OLV. Hypoxemia during OLV responds readily to treatment in the vast majority of cases. Potential therapies are outlined in Table 59-19.

1. Resume two-lung ventilation. Reinflate the nonventilated lung and deflate the bronchial cuff of the double lumen tube or the bronchial blocker. This will necessitate interruption of surgery but is necessary in case of severe or precipitate desaturation. After an adequate level of oxygenation is obtained, the diagnosis of the cause of desaturation can be made and prophylactic measures instituted (see later) before another trial of OLV is attempted.
2. Increase F_{IO_2}. Ensure that the delivered F_{IO_2} is 1.0. This is an option in essentially all patients except those who have received bleomycin or similar therapies that potentiate pulmonary oxygen toxicity.
3. Recheck the position of the DLT or bronchial blocker. Ensure that there is no lobar obstruction in the ventilated lung.
4. Check the patient's hemodynamics to ensure that there has been no decrease in cardiac output. It is very common for the surgeon to accidentally compress the inferior vena cava during pulmonary resections, and the fall in blood pressure and cardiac output that this causes leads to rapid desaturation during OLV. Treat the fall in cardiac output as indicated (e.g., inotropes/vasopressors if due to thoracic epidural sympathetic blockade). Stop administration of vasodilators, and decrease MAC of volatile anesthetics to less than or equal to 1 MAC.
5. Perform a recruitment maneuver of the ventilated lung. To eliminate any atelectasis, inflate the lung to 20 cm H_2O or more for 15 to 20 seconds. This may cause transient hypotension and will also cause a transient further fall in the Pao_2 as the blood flow is temporarily redistributed to the nonventilated lung.
6. Apply PEEP to the ventilated lung. It is necessary to perform a recruitment maneuver before applying PEEP to get the maximal benefit (see Chapter 15). PEEP will raise the end-expiratory volume of the ventilated lung toward the FRC in patients with normal lung mechanics and in those with increased elastic recoil due to restrictive disease. It is not possible to predict the optimal PEEP for individual patients; a level of 5 cm H_2O is a useful starting point. PEEP will increase the end-expiratory lung volume of patients with significant levels of auto-PEEP (e.g., emphysema patients). Unlike CPAP, application of PEEP does not require reinflation of the nonventilated lung and interruption of surgery. PEEP has been shown to be as effective for increasing Pao_2 levels during OLV in patients with normal lung function as CPAP (Fig. 59-31).[134] For patients with normal pulmonary function it is logical to routinely apply a recruitment maneuver and PEEP from the start of OLV.

CPAP with oxygen to the nonventilated lung is a most useful ventilatory manipulation in patients with COPD and the next line of therapy after application of PEEP in patients with normal pulmonary function. There is an important caveat to be observed when CPAP is applied to the nonventilated lung, and

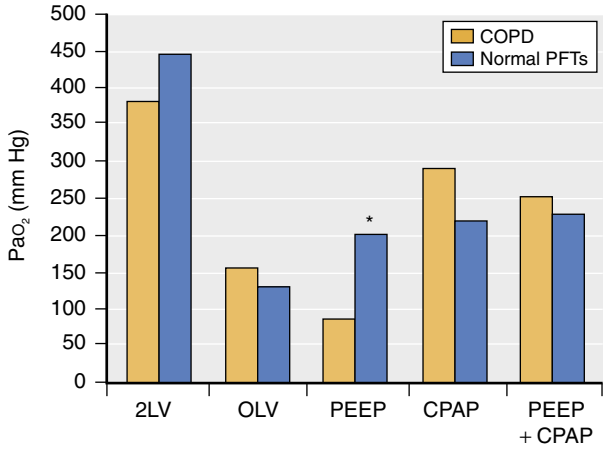

Figure 59-31 A comparison of the effects of positive end-expiratory pressure (PEEP) to the ventilated lung and continuous positive airway pressure (CPAP) to the nonventilated lung on mean Pao_2 levels during one-lung ventilation (OLV). 2LV, two-lung ventilation; COPD, a group of lung cancer surgery patients; Normal PFTs, a group of esophageal surgery patients with normal preoperative pulmonary function tests. Asterisk indicates significant $P < .05$ vs. OLV. (*Based on data from Fujiwara M, Abe K, Mashimo T: The effect of positive end-expiratory pressure and continuous positive airway pressure on the oxygenation and shunt fraction during one-lung ventilation with propofol anesthesia. J Clin Anesth 13:473, 2001; and Capan LM, Turndorf H, Patel C, et al: Optimization of arterial oxygenation during one-lung anesthesia. Anesth Analg 59:847, 1980.*)



Figure 59-32 Photograph of a commercial disposable CPAP circuit applied to the nonventilated lung during a left thoracotomy (in this case applied to the tracheal lumen of a right-sided double-lumen tube). This circuit has an adjustable exhaust valve that allows titration of CPAP between 1 and 10 cm H_2O. (*Courtesy of Mallinckrodt, St. Louis, MO.*)

that is that CPAP must be applied to a fully inflated (recruited) lung to be effective. The opening pressure of atelectatic lung regions is greater than 20 cm H_2O,[135] and these units will not be recruited by simple application of CPAP levels of 5 to 10 cm H_2O. Even a period as short as 5 minutes of collapse before CPAP application can have deleterious effects on oxygenation during OLV.[136] When CPAP is applied to a fully inflated lung, levels of CPAP as low as 1 to 2 cm H_2O can be used.[137] Because the normal transpulmonary pressure of the lung at FRC is approximately 5 cm H_2O, levels of 5 to 10 cm H_2O CPAP applied to a fully recruited lung result in a large-volume lung that impedes surgery. Because surgical exposure is the most common indication for OLV, it is preferable to use lower levels of CPAP that, owing to lung elastic recoil, result in a nonventilated lung that is one third to one half of its resting FRC volume and during open thoracotomy does not interfere with surgical access into the operative hemithorax.

CPAP levels less than 10 cm H_2O do not interfere with hemodynamics. The beneficial effects of low levels of CPAP are primarily due to oxygen uptake from the nonventilated lung and not due to blood flow diversion to the ventilated lung. CPAP is most effective when oxygen (F_{IO_2} 1.0) is applied to the nonventilated lung. Lower F_{IO_2} levels of CPAP are of clinical benefit and can be used along with decreased F_{IO_2} to the ventilated lung in patients at risk of oxygen toxicity.

Numerous anesthetic systems to apply CPAP to the nonventilated lung have been described. Essentially all that is required is a CPAP (or PEEP) valve and an oxygen source. Ideally, the circuit should permit variation of the CPAP level and include a reservoir bag to allow easy reinflation of the nonventilated lung and a manometer to measure the actual CPAP supplied. Such circuits are commercially available (Fig. 59-32) or can be readily constructed from standard anesthetic equipment.[138] CPAP can be applied with either a DLT or through the suction channel of a bronchial blocker.

CPAP, even when properly administered, is not completely reliable to improve oxygenation during OLV. When the bronchus of the operative lung is obstructed, or open to atmosphere (as in a bronchopleural fistula or during endobronchial surgery), CPAP will not improve oxygenation. Also in certain situations, particularly during thoracoscopic surgery where access to the operative hemithorax is limited, CPAP can significantly interfere with surgery.[139]

Pharmacologic Manipulations

Eliminating known potent vasodilators such as nitroglycerin, halothane, and large doses of other volatile anesthetics will improve oxygenation during OLV.[140] The selective administration of the vasodilator prostaglandin E_1 to the ventilated lung[141] or a nitric oxide synthase inhibitor (L-NAME)[142] to a hypoxic lobe results in improved redistribution of pulmonary blood flow in animal models. This is not applicable in humans at present. Selective administration of nitric oxide (NO) alone to the ventilated lung was not shown to be of benefit in humans.[143] The combination of NO (20 ppm) to the nonventilated lung and an intravenous infusion of almitrene, which enhances HPV, restores Pa_{O_2} values during OLV in humans to essentially the same levels as during two-lung ventilation. However, this may have been due primarily to the augmentation of HPV by almitrene.[144] It is unlikely that almitrene, which was previously available in North America as a respiratory stimulant, will be reintroduced to this market owing to side effects such as hepatic enzyme changes and lactic acidosis. However, the combination of nitric oxide and other pulmonary vasoconstrictors such as phenylephrine has been shown to improve oxygenation in ventilated intensive care unit patients with adult respiratory distress syndrome,[145] and this may have applications in OLV (see Chapter 31).

Intermittent Reinflation of the Nonventilated Lung

HPV becomes more effective during repeated hypoxic exposure.[118] Often after reinflation, the oxygen saturation will be more acceptable during a second period of lung collapse. Re-expansion can be performed by regular re-expansion of the operative lung via an attached CPAP circuit.

Partial Ventilation Methods

Several alternative methods of OLV, all involving partial ventilation of the nonventilated lung, have been described and improve oxygenation during OLV. These techniques are useful in patients who are particularly at risk of desaturation, such as those who have had previous pulmonary resections of the contralateral lung. These alternatives include the following:

1. Selective lobar collapse of only the operative lobe in the open hemithorax.[146] This is accomplished by placement of a blocker in the appropriate lobar bronchus of the ipsilateral operative lung.
2. Differential lung ventilation can be done by only partially occluding the lumen of the DLT to the operative lung or by insufflating oxygen with a cannula in the lumen of the DLT to the nonventilated lung.
3. High-frequency positive-pressure ventilation (HFPPV)[147] of the nonoperative lung tends to increase the diameters of the central airways in the operative lung and make pulmonary resections surgically more difficult. These methods are most useful to improve oxygenation for intrathoracic nonpulmonary surgery, such as thoracic esophageal or aortic surgery. High-frequency ventilation techniques are also useful because they can be delivered through a catheter in

cases involving surgery on the main bronchi, such as sleeve resection.

Mechanical Restriction of Pulmonary Blood Flow

It is possible for the surgeon to directly compress or clamp the blood flow to the nonventilated lung.[148] This can be done temporarily in emergency desaturation situations or definitively in cases of pneumonectomy or lung transplantation. Another technique of mechanical limitation of blood flow to the nonventilated lung is the inflation of a pulmonary artery catheter balloon in the main pulmonary artery of the operative lung. The pulmonary artery catheter can be positioned at induction with fluoroscopic guidance and inflated as needed intraoperatively. This has been shown to be a useful technique for resection of large pulmonary arteriovenous fistulas.[149]

Prophylaxis for Hypoxemia

The majority of the treatments outlined as therapies for hypoxemia can be used prophylactically to prevent hypoxemia in patients who are at high risk of desaturation during OLV. The advantage of prophylactic therapy of hypoxemia, in addition to the obvious patient safety benefit, is that maneuvers involving CPAP or alternative ventilation patterns of the operative lung can be instituted at the onset of OLV in a controlled fashion and will not require interruption of surgery and emergent reinflation of the nonventilated lung at a time that may be extremely disadvantageous.

Bilateral Pulmonary Surgery

Because of mechanical trauma to the operative lung, the gas exchange in this lung will always be temporarily impaired after OLV. Desaturation during bilateral lung procedures is particularly a problem during the second period of OLV (i.e., during OLV of the lung that has already had surgery).[150] Thus, for bilateral procedures it is advisable to operate first on the lung that has better gas exchange and less propensity to desaturate during OLV. For the majority of patients this means operating on the right side first.

Anesthetic Management for Common Surgical Procedures

Flexible Fiberoptic Bronchoscopy

Flexible fiberoptic bronchoscopy is a diagnostic and therapeutic procedure of great value in the clinical practice of thoracic surgery and anesthesia. In many centers, it is common practice to perform flexible fiberoptic bronchoscopy before lung resections, to reconfirm the diagnosis (if a tumor compresses the airway), or to determine the invasion and obstruction of the distal airway (in relation to the extension of the bronchial resection).

There are multiple techniques for flexible fiberoptic bronchoscopy. Options include awake versus general anesthesia and oral versus nasal approaches. Options for local anesthesia include topical anesthesia via a nebulizer, handheld aerosol, or soaked pledgets; nerve blocks (laryngeal and/or glossopharyngeal nerves); direct administration of local anesthetic through the bronchoscope (spray-as-you-go technique),[151] with/without sedation/opioid or antisialagogues. Options during general anesthesia include spontaneous versus positive-pressure ventilation with/without muscle relaxation. Airway management during general anesthesia can be with an endotracheal tube or a laryngeal mask airway (LMA). The most common method is with the use of a large SLT (e.g., 8.0 mm ID) placed under direct laryngoscopy. Once the tube is advanced, the tip of the endotracheal tube should come to rest 3 to 4 cm above the tracheal carina. A Portex swivel connector with a self-sealing valve is used to facilitate the ventilation and manipulation of the bronchoscope at the same time (Fig. 59-33). Inhalation and/or intravenous anesthetics can be used for anesthesia. Patients who have copious secretions in the preoperative period should receive anticholinergic medication to ensure a dry field, which provides optimal visualization with the flexible bronchoscope. When using a large SLT, an adult fiberoptic bronchoscope should be used (5.2 mm ID). For smaller tubes (i.e., 7.0-7.5 mm ID), a 3.2- or 4.2-mm ID flexible fiberoptic bronchoscope is used.

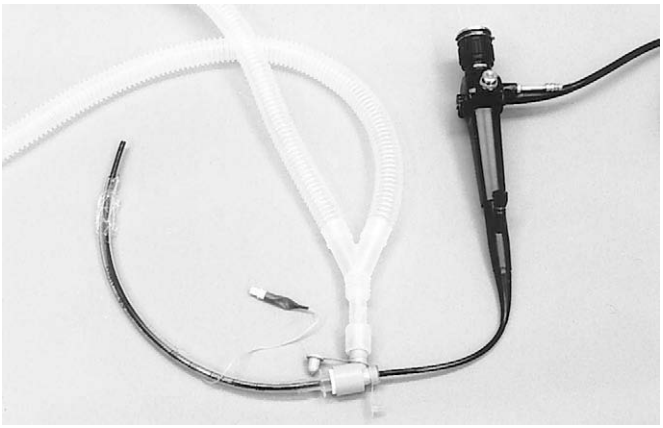

Figure 59-33 Photograph of a fiberoptic bronchoscope inserted through a bronchoscopy adapter on the proximal end of an endotracheal tube with the anesthetic circuit attached. With this technique, when the endotracheal tube cuff is inflated in the trachea, the airway is reasonably protected from aspiration during bronchoscopy and expired CO_2 and anesthetic gases can be monitored. (*From Kaplan J, Slinger P [eds]: Thoracic Anesthesia, 3rd ed. Philadelphia, Churchill Livingstone, 2003.*)

The advantages of an LMA technique include that it allows visualization of the vocal cords and subglottic structures and there is a lower airway resistance versus an endotracheal tube when the bronchoscope is inserted (Fig. 59-34). This is particularly useful in the patient with a difficult airway when maintaining spontaneous respiration may be the safest method of anesthetic management.[152]

Rigid Bronchoscopy

Rigid bronchoscopy has traditionally been considered the technique of choice for the preoperative diagnostic assessment of an airway obstruction involving the trachea and in the therapy of massive hemoptysis and foreign bodies in the airway. The role of interventional bronchoscopy with laser, bronchial dilation, or stent insertion is well established for the palliative treatment of malignant endobronchial lesions as well as for the management of benign central airway lesions (Fig. 59-35).[153] Because rigid

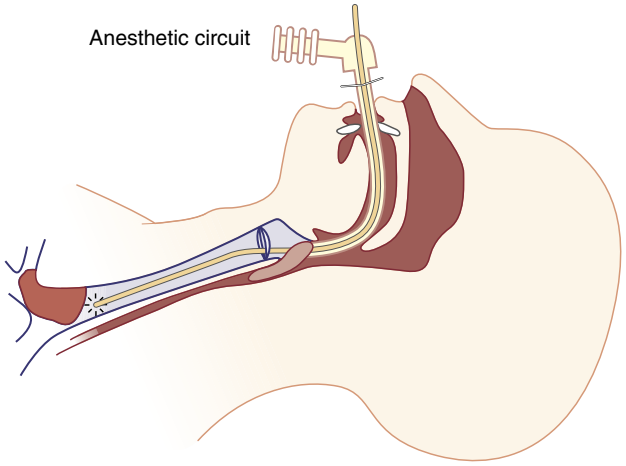

Figure 59-34 Diagram of fiberoptic bronchoscopy performed via a laryngeal mask airway (LMA) during general anesthesia in a spontaneously breathing patient with a carinal tumor, in this case for diagnosis and Nd:YAG laser tumor excision. The LMA permits visualization of the vocal cords and subglottic structures with the bronchoscope, which is not possible when fiberoptic bronchoscopy is performed via an endotracheal tube.

bronchoscopy is performed with ventilating instrumentation, it is the procedure of choice for operative procedures such as dilation of tracheal stenosis.

Central airway obstruction produces symptoms of dyspnea, stridor, or obstructive pneumonia and is often misdiagnosed as asthma. In most cases, resection and surgical reconstruction provides the best opportunity for definitive management. Bronchoscopic management is the first step in providing a diagnosis, stabilizing the obstructed airway, and evaluating the resection. Interventions commonly used for these patients include dilatation, laser ablation, stenting, and palliative creation of an air passage through an obstructing tumor.

Patients undergoing rigid bronchoscopy should have a complete preoperative evaluation, including radiologic studies. Chest radiographs and chest CT scans should be reviewed in the preoperative evaluation. If time permits, it is recommended that patients with severe stridor receive pharmacologic interventions for temporary stabilization of the condition. Treatments may include inspired cool saline mist, nebulized racemic epinephrine, and the use of systemic corticosteroids.[154]

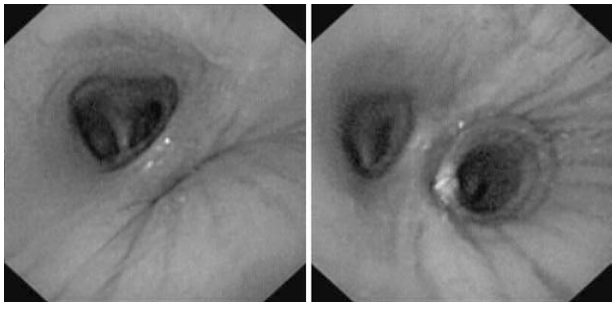

Figure 59-35 Left, Photograph of the airways in a patient with a collapse of the left lower lobe bronchus after lung transplantation. **Right,** A Silastic stent has been placed in the left lower lobe bronchus with rigid bronchoscopy.

There are four basic methods of ventilation management for rigid bronchoscopy:

1. Spontaneous ventilation. The addition of topical anesthesia or nerve blocks to the airway decreases the tendency to breath hold and cough when volatile anesthetics are used.
2. Apneic oxygenation (with/without insufflation of oxygen). This requires thorough preoxygenation, and the anesthesiologist will have to interrupt surgery to ventilate the patient before desaturation occurs. This should allow the surgeon working intervals of 3 minutes or longer depending on the underlying condition of the patient.
3. Positive-pressure ventilation via a ventilating bronchoscope (Fig. 59-36). This allows the use of a standard anesthetic circuit but may cause significant air leaks if there is a discrepancy between the size of a smaller bronchoscope and a larger airway.
4. Jet ventilation. This can be performed with a handheld injector such as the Sanders injector or with a high-frequency ventilator. These techniques are most useful with intravenous anesthesia because they entrain gas from either the room air or an attached anesthetic circuit and the dose of any volatile agent delivered will be very uncertain.

The use of anticholinergic agents (e.g., glycopyrrolate 0.2 mg IV) before manipulation of the airway will decrease secretions during the bronchoscopic examination. For a patient undergoing rigid bronchoscopy, the surgeon must be at the bedside for the induction of anesthesia and be prepared to establish airway control with the rigid bronchoscope. Anesthetic induction, maintained by spontaneous ventilation, with the use of a combined inhalation anesthetic such as sevoflurane, with/without a short-acting intravenous agent (e.g., propofol), may be used until the airway is secured. This is the ideal management in children but may not be tolerated in the elderly owing to the cardiovascular depression associated with high doses of volatile anesthetics.

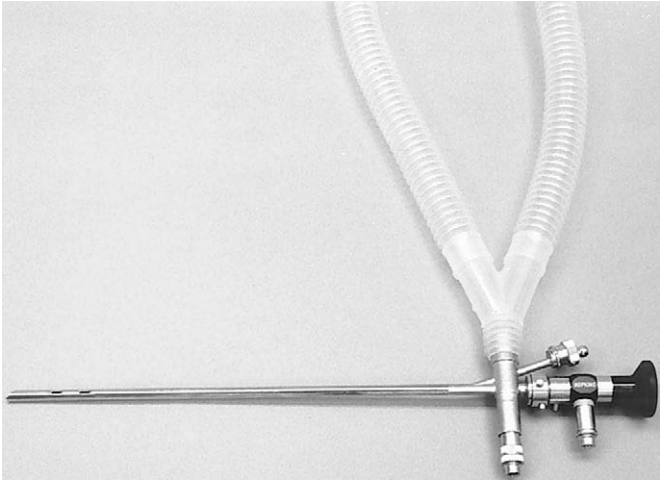

Figure 59-36 Photograph of a ventilating rigid bronchoscope with an anesthetic circuit attached to the side arm. In this photograph there is a telescopic lens sealing the proximal end of the bronchoscope. (*From Kaplan J, Slinger P [eds]: Thoracic Anesthesia, 3rd ed. Philadelphia, Churchill Livingstone, 2003.*)

In cases, for which the use of muscle relaxants is not contraindicated, a short-acting agent (succinylcholine) can be used initially to facilitate intubation with either a small SLT or the rigid bronchoscope. Nondepolarizing relaxants may be needed for prolonged procedures such as stent placement or tumor resection. Mouthguards should be used to protect the upper and lower teeth and gums from the pressure of the bronchoscope. Remifentanil and propofol infusions can be administered if an intravenous regimen is the planned anesthetic.[155] This is a useful technique if the surgeon needs repeated access (for suction or instrumentation) to the open airway because it maintains the level of anesthesia and avoids contaminating the operating room with exhaled anesthetic vapors.

In cases in which a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser is used, the inspired fraction of oxygen should be maintained in the lowest acceptable range (i.e., < 40% if possible) according to patient oxygen saturation, to avoid the potential for fire in the airway (see Chapter 77). Because any common material (including porcelain and metal) can be perforated by the Nd:YAG laser it is best to avoid any potentially combustible substance in the airway when the Nd:YAG laser is used.[156] Because of its high energy and short wavelength the Nd:YAG laser has several advantages for distal airway surgery over the CO_2 laser, which is used in upper airway surgery: the Nd:YAG laser penetrates tissue more deeply so it causes more coagulation in vascular tumors, and it can be refracted and passed in fibers through a flexible or rigid bronchoscope. However, there is a higher potential for accidental reflected laser strikes and there is more delayed airway edema.

Rigid bronchoscopes have different sizes, with diameters commonly ranging from 3.5- to 9-mm diameters, with a ventilating side port to facilitate ventilation when the bronchoscope is placed into the airway. If excessive leak of tidal volume occurs around the bronchoscope with positive-pressure ventilation, it may be necessary to place throat packs to facilitate ventilation. Continuous communication with the surgeon or pulmonologist is necessary in case desaturation occurs. If desaturation does occur it must be corrected by stopping surgery and allowing the anesthesiologist to ventilate and oxygenate the patient, either via the rigid bronchoscope or by removing the bronchoscope and ventilating with a mask or endotracheal tube.

Pulse oximetry is vital during rigid bronchoscopy because there is a high risk of desaturation. There is no simple way to monitor $ETCO_2$ or volatile anesthetics because the airway remains essentially open to atmosphere. For prolonged procedures, it is useful to perform repeated arterial blood gas analysis to confirm the adequacy of ventilation. An alternative is to interrupt surgery and ventilate the patient with a standard circuit and a mask or endotracheal tube to assess the $ETCO_2$.

Unlike during fiberoptic bronchoscopy via an endotracheal tube, with rigid bronchoscopy the airway is never completely secure and there is always the potential for aspiration in patients at increased risk, such as those with a full stomach, hiatal hernia, or morbid obesity. It is always best to defer rigid bronchoscopy to decrease the aspiration risk if possible in these patients. When there is no benefit to be gained by deferring and/or the airway risk is acute (e.g., aspiration of an obstructing foreign body) there is no simple solution and each case will need to managed on an individual basis depending on the context and weighing the competing risks.

Other uses of the rigid bronchoscope that require anesthesia include dilation for benign airway stenosis, core out of malignant lesions in the trachea, laser ablation of endobronchial and carinal tumors, and therapeutic bronchoscopic interventions before surgical resection of lung cancer. Additionally, interventional bronchoscopy is often used for the management of airway complications after lung transplantation.

Complications of rigid bronchoscopy include airway perforation, mucosal damage, hemorrhage, postmanipulation airway edema, and potential airway loss at the end of the procedure. In some situations, it may be necessary to keep the patient intubated with a small (i.e., 6.0 mm ID) SLT after a rigid bronchoscopy if an edematous airway is suspected or the patient is not able to be extubated. These patients may require the use of corticosteroids and racemic epinephrine via nebulization in the postoperative period.

Mediastinoscopy

Mediastinoscopy is the standard method for the evaluation of mediastinal lymph nodes in the staging of NSCLC. In addition, mediastinoscopy is used to aid in the diagnosis of anterior/superior mediastinal masses.[157] The most common mediastinal diagnostic procedure is a cervical mediastinoscopy in which a small transverse incision (2 to 3 cm) is made in the midline of the lower neck in the suprasternal notch. The pretracheal fascial plane is dissected bluntly and the mediastinoscope inserted toward the carina (Fig. 59-37). An alternative procedure is a parasternal (or anterior) mediastinoscopy with a small incision made through the interchondral space or the space of the excised second costal cartilage. Left parasternal mediastinoscopy may be used for staging some left upper lobe lesions because of the lymphatic drainage of the left upper lobe. Cervical mediastinoscopy and anterior mediastinotomy have been advocated as the most reliable techniques for establishing histologic diagnosis in patients with superior vena cava obstruction.[158]

Morbidity related to mediastinoscopy ranges from 2% to 8%. The most severe complication of mediastinoscopy is major hemorrhage, which may require emergent thoracotomy. Central airway obstruction due to compression of the trachea may occur during induction of anesthesia or during the manipulation of the mediastinoscope near the trachea. Other potential complications include compression of the innominate artery, pneumothorax, paresis of the recurrent laryngeal nerve, phrenic nerve injury, esophageal injury, chylothorax, and air embolism.[159]

For patients undergoing cervical mediastinoscopy, it is important to review the chest radiograph and CT scan or the magnetic resonance (MR) image of the chest for the presence of a mass that might obstruct the airway during the preoperative evaluation. It is possible to perform mediastinoscopy with local anesthesia. This may be an option (most commonly using anterior mediastinoscopy) with an anterior mediastinal mass in a cooperative adult with a compromised airway. However, patient coughing or movement could result in surgical complications. The majority of these patients require general anesthesia with placement of an SLT. In some centers, the operating room table is rotated 90 degrees; thus, extension of the anesthesia breathing circuit may be necessary. After a shoulder roll pack is placed, the SLT should be stabilized and secured because the potential for dislodgment of the tube exists. An arterial line is not necessarily used in these cases. However, it is mandatory to monitor the pulse in the right arm (pulse oximeter on the right hand, arterial line,

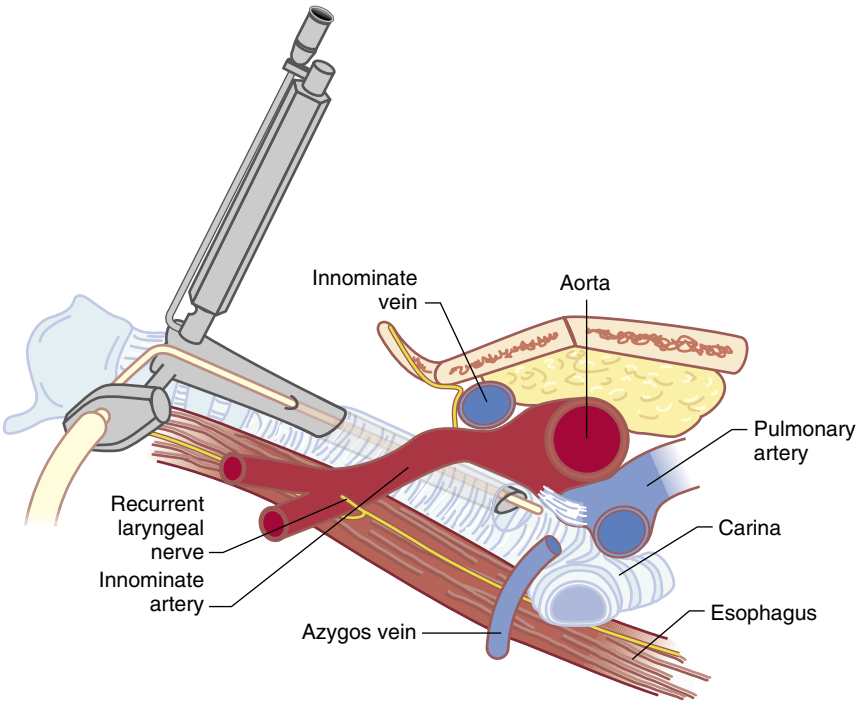

Figure 59-37 Diagram of a mediastinoscope in the pretracheal fascia along with relevant surrounding structures. Note the innominate artery immediately anterior to the mediastinoscope. The azygos vein drains into the superior vena cava, which has been omitted from the drawing because it would cover the location of the mediastinoscope. (*From Kaplan J, Slinger P [eds]: Thoracic Anesthesia, 3rd ed. Philadelphia, Churchill Livingstone, 2003.*)

or the anesthesiologist's finger) because compression of the innominate artery by the mediastinoscope may occur and the surgeon usually is not aware that this is happening. The innominate artery supplies not only the right arm but also the right common carotid. Patients who do not have good cerebral collateral circulation (it is generally not possible to predict which patients these are) are at risk for cerebrovascular ischemia with innominate compression. A noninvasive blood pressure cuff is placed on the left arm to confirm the correct systolic pressure in case of suspected innominate compression.

Mild mediastinal hemorrhage may respond to conservative measures: the patient can be placed in the head-up position, the systolic pressure kept in the 90s, and the wound tamponaded with surgical sponges. However, massive hemorrhage requires an emergent thoracotomy to stop the bleeding (Table 59-20). A bronchial blocker can be passed through the lumen of the existing lung-isolation device if lung isolation is required because it is often difficult to change to a DLT while the surgeon is tamponading the wound. An arterial line should be placed (if not placed previously) to measure arterial blood pressure. If hemorrhage originates from a tear in the superior vena cava, volume replacement and drug treatment may be lost into the surgical field unless they are administered through a peripheral intravenous line placed in the lower extremity.

Table 59-20 Anesthetic Management of Mediastinoscopy Hemorrhage

1. Stop surgery and pack the wound. There is a serious risk that the patient will get too close to the point of hemodynamic collapse if the surgery-anesthesia team does not admit soon enough that there is a problem.
2. Begin the resuscitation and call for help, both anesthetic and surgical.
3. Obtain large-bore vascular access in the lower limbs.
4. Place an arterial line (if not placed at induction).
5. Prepare for massive hemorrhage with blood warmers and rapid infusers.
6. Obtain cross-matched blood in the operating room.
7. Place a double-lumen tube or bronchial blocker if the surgeon believes thoracotomy is a possibility.
8. Once the patient's condition is stabilized and all preparations are made, the surgeon can re-explore the cervical incision.
9. Convert to sternotomy or thoracotomy if indicated.

Pneumothorax is an infrequent complication of mediastinoscopy. Pneumothorax that occurs intraoperatively (as evidenced by increased peak inspiratory pressure, tracheal shift, distant breath sounds, hypotension, and cyanosis) requires immediate treatment by chest tube decompression. All patients must have a chest radiograph taken in the postanesthesia care unit after mediastinoscopy to rule out pneumothorax.

When mediastinoscopy causes injury to the recurrent laryngeal nerve, it can be permanent in approximately 50% of the cases. If injury to the recurrent laryngeal nerve is suspected, the vocal cords should be visualized while the patient is spontaneously breathing. If the vocal cords do not move or are in a midline position, consideration has to be given to the problem of postoperative laryngeal obstruction.

During mediastinoscopy, the tip of the mediastinoscope is intrathoracic and therefore it is directly exposed to pleural pressure. A venous air embolus can occur if patients are breathing spontaneously because of the development of negative intrathoracic pressure during inspiration if venous bleeding occurs. The use of controlled positive-pressure ventilation during this procedure minimizes the risk of air embolism. Autonomic reflexes may result from compression or stretching of the trachea, vagus nerve, or great vessels. With an uncomplicated mediastinoscopy, the patient can be extubated in the operating room and discharged home the same day.

Endobronchial Ultrasound–Guided Biopsy

Various alternative techniques are available for obtaining pathology specimens from the mediastinal lymph nodes. These include CT-guided percutaneous needle aspiration, conventional bronchoscopy with transbronchial needle aspiration, and endobronchial ultrasound–guided biopsy. Endobronchial ultrasonography (EBUS) employing a radial probe through a working channel of the flexible fiberoptic bronchoscope can be used to identify mediastinal and hilar lymph nodes.[160] Under direct endobronchial ultrasonography guidance with fine-needle aspiration for mediastinal staging, an ultrasound puncture bronchoscope can be used to assist with the safe and accurate diagnostic interventional bronchoscopy of the mediastinal and hilar lymph nodes.

Management of these patients is often done at a satellite location, either in the bronchoscopy facility or CT suite. In general, these patients are managed with topical anesthesia (aerosolized lidocaine) and conscious sedation (e.g., fentanyl and/or midazolam). EBUS may replace mediastinoscopy as the standard method of staging lung cancer before resection.

Pulmonary Surgery

Any given pulmonary resection can be accomplished by a variety of different surgical approaches. The approach used in an individual case will depend on the interaction of several factors, which include the site and pathology of the lesion(s) and the training and experience of the surgical team. Common thoracic surgical approaches and their generally accepted advantages and disadvantages are listed in Table 59-21.

Video-assisted Thoracoscopic Surgery

Video-assisted thoracoscopic surgery is the procedure of choice for the diagnosis and management of diseases of the pleura, nondiagnosed peripheral pulmonary nodules, and interstitial lung disease. Since the start of the modern era of thoracoscopic surgery in the early 1990s, VATS has been proposed as a less invasive approach than open procedures. Today it is a well-accepted and established procedure and has become the first choice technique for lung biopsies, pleurectomies, sympathectomies, and other various pulmonary disorders.[161]

In addition, VATS may be used in a variety of other surgical procedures. Specific centers routinely perform lobectomies under VATS, and some centers perform VATS with the aid of a robotic system. Other surgeries, such as spinal fusion and scoliosis, have been performed with VATS. The advantage of VATS, when compared with open thoracotomy, include (1) reduced hospital length of stay, (2) less blood loss if no mishaps occur, (3) less pain, (4) improvement in pulmonary function when compared with open thoracotomy,[162] (5) early patient mobilization with early recovery and rapid return to work and daily activities, and (6) less inflammatory reaction, as measured by cytokine response in patients undergoing VATS lobectomy compared with open thoracotomy.[163]

VATS lobectomy has been demonstrated to be a safe and effective procedure to treat early-stage NSCLC.[164] Thoracoscopic lobectomy is performed with a limited number of ports (one to three) and an access incision of approximately 5 cm in length.[165] The advantage of the VATS technique is that the ribs are not spread. VATS procedures are commonly performed in the lateral decubitus position; however, bilateral VATS procedures, such as bilateral wedge resections or lung volume reduction, can be performed in the supine position.

Thoracoscopic surgery can be performed under local, regional, or general anesthesia with two-lung ventilation or OLV.[166] For minor diagnostic procedures VATS can be done in the awake patient. Intercostal nerve blocks performed at the level of the incision and two interspaces above and below provide adequate analgesia. Partial collapse of the lung on the side of surgery occurs when air enters the pleural cavity. When using local anesthesia with the patient awake, it is hazardous to insufflate gases under pressure into the hemithorax in an attempt to increase visualization of the pleural space. Although many patients suffer from advanced pulmonary disease, changes in Pao_2, $Paco_2$, and cardiac rhythm are usually minimal during the procedure when it is performed under local anesthesia and the patient is

Table 59-21 Comparison of Surgical Approaches for Pulmonary Resections

Incision	Pro	Con
Posterolateral thoracotomy	Excellent exposure to entire operative hemithorax	Postoperative pain ± respiratory dysfunction (short and long term)
Lateral muscle-sparing thoracotomy	Decreased postoperative pain	Increased incidence wound seromas
Anterolateral thoracotomy	Better access for laparotomy, resuscitation, or contralateral thoracotomy especially in trauma	Limited access to posterior thorax
Axillary thoracotomy	Decreased pain Adequate access for first rib resection, sympathectomy, apical blebs or bullae	Limited exposure
Sternotomy	Decreased pain Bilateral access	Decreased exposure of left lower lobe and posterior thoracic structures
Trans-sternal bilateral thoracotomy ("clam shell")	Good exposure for bilateral lung transplantation	Postoperative pain and chest wall dysfunction
Video-assisted thoracoscopic surgery (VATS)	Less postoperative pain and respiratory dysfunction	Technically difficult with central tumors and chest wall adhesions

breathing spontaneously.[167] However, it is recommended that a high F_{IO_2} is delivered via a facemask to overcome the shunt due to the loss in lung volume caused by the unavoidable pneumothorax.

For most invasive procedures VATS is performed under general anesthesia with a DLT or a bronchial blocker to achieve OLV. Lung collapse will take longer when a bronchial blocker is used; if rapid lung collapse is needed, a DLT may be the preferred choice. If the procedure is short in duration and the lung needs to be deflated for only a brief period, blood gases are not routinely monitored during the procedure. However, for patients undergoing prolonged VATS procedures such as lobectomy or for patients with marginal pulmonary status, an arterial line and measurement of arterial blood gases is required. Paravertebral blocks have been used with a single dose of local anesthetics and have been shown to reduce pain after thoracoscopic surgery for 6 hours.[168]

Anesthetic complications are rare during this procedure, although it is possible that any structure that the surgeon has to manipulate may be damaged. The anesthesiologist needs to be aware of the potential for conversion to open thoracotomy if massive bleeding ensues or the surgeon is unable to localize the lung nodule to be sampled. The majority of thoracoscopic surgery requires placement of a chest tube postoperatively. It is important to have a functional chest tube with underwater seal drainage so that extubation can be performed safely.

Lobectomy

Lobectomy is the standard operation for the management of lung cancer because local recurrence of the tumor is reduced compared with lesser resections. Lobectomy is commonly performed via open thoracotomy or VATS. Occasionally, if the clinical staging of the lung cancer is advanced, an elective lobectomy is converted to a bilobectomy (right lung) or pneumonectomy during the operation. Although a posterolateral thoracotomy is the classic incision for lobectomies, anterolateral and muscle-sparing lateral incisions have also been used.

Postoperative analgesia is commonly performed with thoracic epidural analgesia (TEA) or paravertebral analgesia (see "Postoperative Analgesia" later). An arterial line for management of arterial blood gases and measurement of systemic blood pressure is used in all patients requiring an open thoracotomy or major VATS surgery. In addition, a large-bore intravenous catheter should be placed to facilitate rapid transfusion if necessary. Patients undergoing a lobectomy must be kept normothermic, normotensive, and with an acceptable Pa_{O_2} and oxygen saturation, particularly during OLV. Patients should have a thermal blanket on the lower extremities to prevent hypothermia and its deleterious effects during HPV. Potential intraoperative problems include damage to the airway while using lung-isolation devices and the potential for bleeding or hypoxemia during OLV. After the lobe and blood vessels have been dissected, a test maneuver is performed with the surgeon clamping the surgical bronchus to confirm that the specific lobe is extirpated. This maneuver is accomplished by unclamping the limb of the DLT connector of the respective side or, in the case of a bronchial blocker, by deflating the blocker balloon and re-expanding the lung with manual ventilation. During VATS lobectomy, owing to the interference to the surgical field caused by reinflating the residual lobe, the anesthesiologist may be asked to fiberoptically inspect the bronchial tree to confirm patency of the bronchus of the noninvolved lobe. Once the lobectomy has been performed, the bronchial stump is usually tested with 30 cm H_2O positive pressure in the anesthetic circuit to detect the presence of air leaks. A patient undergoing an uncomplicated lobectomy can be usually extubated in the operating room provided preoperative respiratory function is adequate (see "Preoperative Assessment" earlier) and the patient is alert, warm, and comfortable ("AWaC").

Pancoast tumors are carcinomas of the superior sulcus of the lung and can invade/compress local structures, including the lower brachial plexus, subclavian blood vessels, stellate ganglion (causing Horner's syndrome), and vertebrae. Lobectomy may require a two-stage procedure with an initial operation for posterior instrumentation/stabilization of the spine. During lobectomy, extensive chest wall resection may be required and massive transfusion is a possibility. Peripheral lines and monitoring should be in the contralateral arm due to frequent compression of the ipsilateral vessels during surgery.

Sleeve Lobectomy

Bronchial sleeve resections are performed for neoplasms or benign strictures. Bronchogenic carcinoma is the most frequent indication for a sleeve lobectomy, followed by carcinoid tumors, endobronchial metastases, primary airway tumors, and bronchial adenomas. Sleeve resections have been associated with shorter intensive care unit stays and periods of postoperative mechanical ventilation. Sleeve lobectomy involving parenchyma-sparing techniques in patients with limited pulmonary reserve is an alternative surgery for patients who cannot tolerate a pneumonectomy. Overall survival is higher and with fewer locoregional recurrences after sleeve lobectomy. The sleeve technique involves mainstem bronchial resection without parenchymal involvement and possibly resection of pulmonary arteries to avoid pneumonectomy (Fig. 59-38).

Patients undergoing sleeve lobectomy require lung isolation with a contralateral DLT or endobronchial tube (i.e., use of a right-sided DLT for a left sleeve lobectomy). High-frequency jet ventilation (HFJV) can be used for resections close to the tracheal carina. For a sleeve lobectomy involving transplantation of vessels, heparinization is necessary. In these cases, thoracic epidural catheters should not be manipulated for 24 hours after heparin administration. During pulmonary arterioplasty uncontrollable bleeding may occur. For this reason, large-bore intravenous catheters should be used. Patients undergoing sleeve lobectomy are usually extubated in the operating room before transfer to the postanesthesia care unit. Immediate- and long-term survival is better after sleeve lobectomy compared with right pneumonectomy for comparable stages of right upper lobe cancer.[169]

Pneumonectomy

Complete removal of the lung is required when a lobectomy or its modifications is not adequate to remove the local disease and/or ipsilateral lymph node metastases. Atelectasis and pneumonia occur after pneumonectomy as they do after lobectomy but may in fact be less of a problem per se due to the absence of residual parenchymal dysfunction on the operative side. However, the mortality rate after pneumonectomy exceeds that for lobectomy because of postoperative cardiac complications and acute lung injury. The overall operative mortality for the first 30 days after pneumonectomy ranges from 5% to 13%. Mortality correlates inversely with the surgical case-volume.[170]

Thoracotomy for pneumonectomy is usually performed through a standard posterolateral incision. The mediastinal pleura

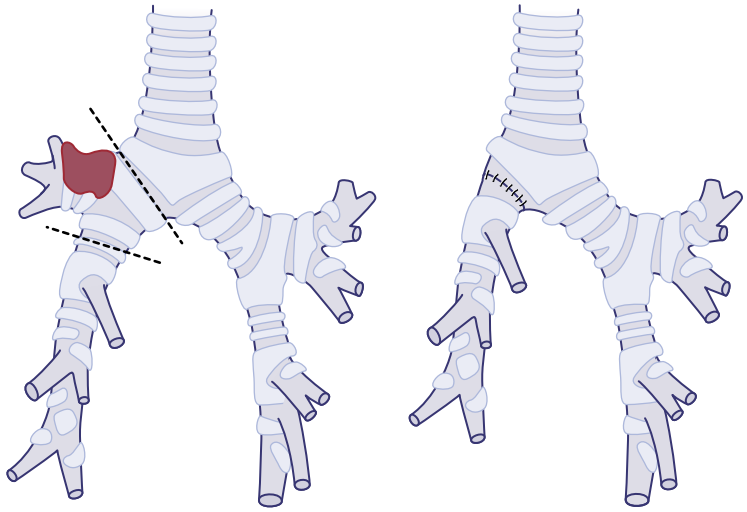

Figure 59-38 Diagram of the surgical procedure for a right upper sleeve lobectomy. Note that it will not be possible to position an endobronchial tube or bronchial blocker in the ipsilateral right mainstem bronchus during this procedure. (*From Shields TW: Surgical therapy for carcinoma of the lung. Clin Chest Med 14:121, 1993.*)

are incised, and the pulmonary artery, the superior and inferior pulmonary veins, and the mainstem bronchus are evaluated for resectability. After all vessels are stapled, stapling of the bronchus occurs and the entire lung is taken from the chest. A test for air leaks is generally performed at this point, and reconstruction of the bronchial stump is completed. The bronchial stump should be as short as possible to prevent a pocket for the collection of secretions.

There is no consensus among thoracic surgeons on the best method of management of the postpneumonectomy space. If suction is applied to an empty hemithorax or a chest drain is connected to a standard underwater-seal system it may cause a mediastinal shift with hemodynamic collapse. Some thoracic surgeons do not place a chest drain after a pneumonectomy. Some thoracic surgeons prefer to use a temporary drainage catheter to add or remove air. The removal of air, ranging from 0.75 up to 1.5 L, is necessary to empty the chest and to keep the mediastinum ("balanced") and the trachea in the midline. Some surgeons place a specifically designed postpneumonectomy chest drainage system with both high- and low-pressure underwater relief valves to balance the mediastinum.[171] A chest radiograph is mandatory after the patient arrives in the postanesthesia care unit or in the surgical intensive care unit to assess the mediastinal shift.

The patient scheduled to undergo a pneumonectomy is considered at high risk for perioperative morbidity and mortality. Patients undergoing a pneumonectomy commonly receive a thoracic epidural catheter for postoperative analgesia, unless there is a contradiction. The placement of large-bore intravenous lines is necessary in case blood products need to be administered. An invasive arterial line is placed for measurement of beat-to-beat blood pressure and to monitor arterial blood gases. A central venous pressure catheter is recommended to help guide intravascular fluid management, specifically in the postoperative period.

A major lung resection, such as pneumonectomy, decreases ventilatory function and has significant effects on the right ventricular function.[172] Immediately after pneumonectomy, the right ventricle may dilate and the right ventricular function decreases. Increased right ventricular afterload is due to an increase in pulmonary artery pressure and pulmonary vascular resistance. This is considered to be one of the main causes of right ventricular dysfunction after a major lung resection.

Management of lung isolation in a pneumonectomy patient can be achieved with a DLT, bronchial blocker, or SLT. When using a DLT for a pneumonectomy patient, it is optimal to use a device that does not interfere with the ipsilateral airway (i.e., for a right pneumonectomy, a left-sided DLT). If a left-sided DLT or bronchial blocker is used for a left pneumonectomy, it must be withdrawn before stapling the bronchus to avoid accidental inclusion into the suture line.

Specific areas of concern in the management of the patient undergoing pneumonectomy include (1) fluid management, (2) intraoperative tidal volume, and (3) acute lung injury post surgery. Fluid administration after major lung resection continues to be an issue. In a retrospective report by Zeldin and associates, the risk factors that were identified for the development of acute lung injury ("postpneumonectomy pulmonary edema") were a right-sided pneumonectomy, increased perioperative intravenous fluid administration, and increased urine output in the postoperative period.[172a] A more recent study by Licker and colleagues has shown that the excessive administration of intravenous fluids in thoracic surgical patients (more than 3 L in the first 24 hours) is an independent risk related to an acute lung injury.[173] There is reasonable clinical evidence that excessive fluid administration is associated with the development of an acute lung injury, which has a high mortality rate after pneumonectomy.[29] Consequently, pneumonectomy patients should have restricted intraoperative fluid administration while preserving renal function. Some cases may require the use of inotropes/vasopressors to maintain hemodynamic stability while restricting fluids (see Table 59-17).

Respiratory failure is a leading cause of postoperative morbidity and mortality in patients undergoing pneumonectomy. A retrospective report involving 170 pneumonectomy patients showed that patients that received median tidal volumes greater than 8 mL/kg had a greater risk of respiratory failure in the postoperative period after pneumonectomy.[174] In contrast, patients who received tidal volumes less than 6 mL/kg were at lower risk of respiratory failure. Schilling and coworkers[175] have shown that a tidal volume of 5 mL/kg during OLV significantly reduces the inflammatory response to alveolar cytokines. Considering these factors, it is prudent to use lower tidal volumes (i.e., 5 to 6 mL/kg, ideal body weight) in the pneumonectomy patient and limit peak and plateau inspiratory pressures (i.e., <35 and 25 cm H_2O, respectively) during OLV.

The incidence of acute lung injury (postpneumonectomy pulmonary edema) after pneumonectomy is only 4%. However, the mortality rate is 30% to 50%. The etiology seems multifactorial. One study[173] has identified four independent risk factors for acute lung injury after pulmonary resection; these include (1) pneumonectomy, (2) excessive administration of fluids in the intraoperative period, (3) high intraoperative ventilatory pressure index (combined airway pressure and time), and (4) preoperative alcohol abuse. The incidence of an acute lung injury is greater for a right- versus left-sided pneumonectomy. The presentation is biphasic. The primary form has a clinical onset during the first 72 hours. The secondary, or late form, appears after 72 hours and is usually related to other complications such as aspiration, bronchopleural fistula, or surgical complications. At the present time only symptomatic management is appropriate. This includes fluid restrictions, diuretic administration, low ventilatory pressures, and tidal volumes (if mechanical ventilation is used) and measures to decrease the pulmonary artery pressure. Although pneumonectomy is associated with mild postoperative pulmonary hypertension during exercise, right ventricular systolic function is usually minimally affected.[13]

Extrapleural Pneumonectomy

Extrapleural pneumonectomy is a therapeutic option for selected patients with malignant pleural mesothelioma.[176] Significant improvement in survival has been achieved in patients who have an advanced malignant pleural mesothelioma with extrapleural pneumonectomy and high-dose radiotherapy in the postoperative period. Extrapleural pneumonectomy involves an extensive resection that may include lymph nodes, pericardium, diaphragm, parietal pleura, and the chest wall. The anesthetic management of the extrapleural pneumonectomy patient is characterized by significant loss of blood due to chest wall vessel involvement. In these patients, it is recommended that a central venous pressure catheter be used to guide intravascular fluid administration and ensure large-bore intravenous access. During tumor dissection, venous return to the heart may be compromised because of multiple factors, including blood loss, compression effect by the tumor in superior vena cava, or surgical causes. If excessive bleeding ensues, it must be replaced to maintain an acceptable hematocrit and the coagulation profile kept within normal limits. Because of extensive tumor resection and the potential for a pericardial resection in right-sided surgery, cardiac herniation or hemodynamic instability can appear postoperatively after the patient is turned from lateral decubitus to supine position. It is common to ventilate these patients for a short period postoperatively owing to the extended duration of the surgery and the large fluid shifts. If a DLT is used intraoperatively, the DLT is usually replaced at the end of the case with an SLT (see "Lung Isolation" earlier).

Sleeve Pneumonectomy

Tumors involving the most proximal portions of the mainstem bronchus and the carina may require a sleeve pneumonectomy. These are most commonly performed for right-sided tumors and can usually be performed without cardiopulmonary bypass (CPB) via a right thoracotomy. A long SLT can be advanced across into the left mainstem bronchus during the period of tracheobronchial anastomosis. HFPPV has also been used for this procedure, and the combined use of HFPPV and a DLT has been described.[177] Because the carina is surgically more accessible from the right side, left sleeve pneumonectomies are commonly performed as a two-stage operation: first a left thoracotomy and pneumonectomy, then a right thoracotomy for the carinal excision. The complication rate and mortality are higher and the 5-year survival (20%) significantly lower than for other pulmonary resections. Postpneumonectomy pulmonary edema is particularly a problem after right sleeve pneumonectomy.

Limited Pulmonary Resections: Segmentectomy and Wedge Resection

A limited pulmonary resection is one in which less than a complete lobe is removed. The two procedures fitting this definition are segmentectomy and wedge resection. Segmentectomy is an anatomic pulmonary resection of the pulmonary artery, vein, bronchus, and parenchyma of a particular segment of the lung. Segmentectomy is usually performed as surgical therapy for patients with primary lung cancer and limited cardiorespiratory reserves. In contrast, a wedge resection is a nonanatomic removal of a portion of the lung parenchyma with a 1.5- to 2.0-cm margin and can be accomplished by open thoracotomy or VATS. Wedge resections are most commonly performed for diagnosis of lung lesions with unknown histology or as palliation in patients with metastatic lesions in the lungs from distant primary tumors. Lung cancers that are considered for limited resection are usually less than 3 cm and are located in the periphery of the lung with regional lymph nodes free of metastatic cancer.

A group of patients considered for limited pulmonary resection are those who develop a new primary lesion after a previous lobectomy or pneumonectomy. The patient with compromised lung function presents a greater risk in the intraoperative period (hypoxemia during OLV or prolonged intubation after surgery). Cerfolio and colleagues[178] reported that lung cancer patients with compromised pulmonary function can safely undergo limited pulmonary resection if selected appropriately. Segmentectomies and wedge resections can be performed with any of the standard thoracotomy or VATS incisions. Segments that are most commonly resected are in the upper lobes or the superior segments of the lower lobes.

Anesthetic technique and monitoring are essentially the same as for larger pulmonary resections. To facilitate surgical exposure and achieve OLV, it is necessary to use either a DLT or a bronchial blocker. If the patient had a previous contralateral lobectomy or a pneumonectomy, selective lobar collapse with the use of a bronchial blocker will facilitate surgical exposure while maintaining oxygenation. In selected cases the combined use of a DLT and a bronchial blocker will allow selective lobar collapse/ventilation in the ipsilateral lung.[179] It is very important to use low tidal volumes (i.e., 3 to 5 mL/kg) during selective lobar ventilation, particularly in patients with previous pneumonectomy to prevent overinflation in the remaining lobes.

Segmentectomy plays a significant role in the management of patients with a second primary lung cancer. Many of these patients have previously undergone thoracic surgery that includes previous lobectomy or pneumonectomy; therefore, the potential for increased intraoperative bleeding is always a risk. In addition, because many of these patients have compromised lung function, early extubation may not be feasible. A common complication after surgery is an air leak. Chest tubes are placed to maximize postoperative expansion and minimize space complications. Suction and underwater seal chest drainage is used in the postoperative period.

Anesthetic Management for Specific Surgical Procedures

Esophageal Surgery

Esophageal surgery is performed for both malignant and benign disease and may be curative or palliative. General considerations that apply to almost all esophageal surgery patients include an increased risk of aspiration due to esophageal dysfunction and the possibility of malnutrition.

Esophagectomy

Esophagectomy is a palliative and potentially curative treatment for esophageal cancer and may occasionally be required for some benign obstructive lesions that do not respond to conservative therapy. It is a major surgical procedure and is associated with high morbidity and mortality rates (10%-15%). There is an inverse correlation between perioperative mortality and surgical volume, and the cure rate of esophageal cancer with esophagectomy is between 10% and 50%. There are multiple surgical procedures for esophageal cancer (Table 59-22) that combine some or all of three fundamental approaches: (1) transthoracic approach, (2) transhiatal approach, and (3) minimally invasive surgery (laparoscopic/thoracoscopic or robotic esophagectomy).[180] The incidence of respiratory complications has been reported to be between 18% and 26% for both the transthoracic and transhiatal esophagectomy approaches.[181] One study showed that the development of acute respiratory distress syndrome (ARDS) occurred in 14.5% of patients and acute lung injury in 24%.[182] Complications associated with the gastroesophageal anastomosis are anastomotic leakage/dehiscence (5% to 26%) and stenosis (12% to 40%).

Transthoracic Approach

Transthoracic esophagectomy is commonly a two-phase procedure. The first phase involves a laparotomy performed with the patient in the supine position and the creation of a neoesophagus tube using the stomach. The second phase involves a right-sided thoracotomy in the left lateral position and esophageal reconstruction through the thoracic route. Some surgeons may perform this procedure through a single extended left thoracoabdominal incision.

The anesthetic management for these patients includes the use of standard monitors and an invasive arterial line and a central venous pressure catheter due to the large fluid shifts. Access to the right internal jugular is not a problem, but there is always a possibility of a surgical esophageal anastomosis in the left neck contraindicating access to the left internal jugular. A thoracic epidural catheter is usually placed to provide postoperative analgesia. Because of the wide number of dermatomes that must be covered for both incisions by the epidural infusion, it is best to use hydrophilic opioids (e.g., hydromorphone) in combination with local anesthetics in preference to lipophilic opioids. Most patients with an esophageal carcinoma have gastric reflux; for this reason, precautions (including a rapid-sequence induction with cricoid pressure) should be taken to protect the airway against aspiration.

During the second phase (right thoracotomy), a left-sided DLT or a right-sided bronchial blocker is required to facilitate lung collapse. Because esophagectomy requires a prolonged period of OLV, this procedure is marked by an important inflammatory response. Michelet and associates[183] have shown that the use of protective ventilatory strategies during OLV decrease the proinflammatory systemic response. This decreased response can be achieved by delivering 5 mL/kg of tidal volume and a PEEP of 5 cm H_2O to the dependent lung, instead of the 9 mL/kg of tidal volume that is conventionally used during esophagectomy.

Manipulation of the esophagus during thoracotomy may compromise venous return, which can cause hypotensive episodes. Early extubation in the operating room is encouraged if the patient meets standard criteria for extubation. If extubation is not possible, the DLT should be replaced for an SLT and mechanical ventilation used in the postoperative period.

Table 59-22 Surgical Approaches for Esophagectomy and Esophagogastrectomy

Surgery	Incisions	Anesthetic Considerations
Laparotomy and right thoracotomy "Ivor Lewis"	Two incisions: upper abdominal midline, then right thoracotomy at 5th to 6th intercostal spaces	One-lung ventilation necessary. Repositioning supine to right-lateral intraoperatively.
Transhiatal "Orringer" (lower third lesions; may be used for mid third in some centers)	Two incisions: upper abdominal midline then left neck	Hemodynamic instability from cardiac compression during blunt intrathoracic dissection. Possibility of occult perforation of tracheobronchial tree during blunt dissection (leave endotracheal tube uncut in case of need to advance into bronchus) No vascular access in left neck
Left thoracoabdominal (lower esophageal lesions only)	One incision: left lateral thoracotomy extended to left upper lateral abdominal	One-lung ventilation desirable
Combined chest, abdominal, and neck ("three hole") (upper/midesophageal lesions)	Three incisions: right thoracotomy, then laparotomy, then left neck	One-lung ventilation necessary Repositioning lateral to supine intraoperatively No vascular access in left neck
Thoracoscopy plus laparotomy or laparoscopy	One or two incisions, plus video port access Thoracoscopy to avoid blunt dissection in chest Neck incision at end	One-lung ventilation necessary Potentially prolonged surgery

Transhiatal Approach

Airway management is with an SLT. Apart from this, anesthetic management is essentially the same as for a transthoracic approach. Of special concern is that the blunt/blind manual dissection of the thoracic esophagus by the surgeon through the hiatus during this approach is often associated with cardiac compression and sudden severe hypotension. Also, this blind dissection can cause vascular or distal airway injuries if the tumor is adherent. It is a good practice not to cut the endotracheal tube for this procedure in case of surgical perforation of the trachea or bronchus, necessitating advancement of the endotracheal tube into a mainstem bronchus for emergent OLV.

Minimally Invasive Approach

Minimally invasive esophagectomy involves the use of laparoscopic, thoracoscopic, or robotic surgical approaches. For a laparoscopic approach, distention of the peritoneum may produce hemodynamic changes due to the intragastric pressure generated by carbon dioxide insufflation. In these cases, it is important to adjust ventilatory parameters to achieve an optimal $Paco_2$. For the thoracoscopic approach, a left-sided DLT or a bronchial blocker is required. During robotic surgery, the use of a lung-isolation device is required to achieve OLV. Special considerations for robotic surgery include protecting the patients against any injury related to the robot and not moving the operating room table while the robot is being used. The thoracoscopic-assisted esophagectomy has several advantages, including less blood loss, less pain, and a shorter length of hospitalization. This method does, however, require a prolonged duration of surgery.

Patients undergoing esophagectomy require third-space fluid administration and periodically inotropic support. In addition, all patients undergoing esophagectomy require a nasogastric tube, which must be well-secured at the end of the operation. Respiratory complications, including the development of an acute lung injury, may be present after an esophagectomy. Intrathoracic anastomotic leakage is a feared major complication after esophageal surgery and carries a high mortality rate of 4% to 30%.[184] To treat this potential complication, nasogastric decompression and nutritional support should be used. Severe leakage usually occurs in the early postoperative period as a consequence of gastric necrosis, and it may present as respiratory symptoms and signs of shock. Even though there is a very high mortality rate, prompt surgical intervention is recommended. Patients older than 80 years of age have an increased risk of mortality after esophagectomy, independent of comorbidity.[185]

Esophageal Surgery for Benign Disease

Hiatal Hernia

Although most patients with gastroesophageal reflux have a hiatal hernia, most patients with a hiatal hernia do not have significant reflux.[186] Patients with heartburn have a lowered barrier pressure and may be at increased risk for regurgitation of gastric contents. Two types of hiatal hernia have been described. Type I hernias, also called sliding hernias, make up approximately 90% of esophageal hiatal hernias. In this type, the esophagogastric junction and fundus of the stomach have herniated axially through the esophageal hiatus into the thorax (Fig. 59-39). The term *sliding* refers to the presence of a sac of parietal peritoneum. The lower esophageal sphincter is cephalad to the diaphragm and may not respond appropriately to increased abdominal pressure. Thus, a reduced barrier pressure during coughing or breathing leads to regurgitation. The type II, or paraesophageal, hiatal hernia, is characterized by portions of the stomach herniating into the thorax next to the esophagus. In the presence of a type II hernia, the esophagogastric junction is still located in the abdomen. The most common complications from type II hernias are blood loss, anemia, and gastric volvulus.



Figure 59-39 Chest radiograph of a patient with a hiatal hernia and a dilated intrathoracic stomach who was scheduled for hiatal hernia repair via a left thoracotomy. An air-fluid level can be seen in the stomach behind the heart. These patients are at high risk for aspiration on induction of anesthesia.

The goal of surgical repair of a sliding hernia is to obtain competence of the gastroesophageal junction. Because restoration of the normal anatomy is not always successful in preventing subsequent reflux, several antireflux operations have been developed, such as the Nissen fundoplication. Repair of hiatal hernia can be performed via a thoracotomy, laparotomy, or minimally invasively.

Benign Esophageal Stricture

Chronic reflux of acidic gastric contents can lead to ulceration, inflammation, and eventually stricture of the esophagus. The pathologic changes are reversible if the acidic gastric contents cease their contact with the esophageal mucosa. Surgery may be necessary if medical treatment and dilatations are inadequate. There are two types of surgical repair, both of which are usually approached via a left thoracoabdominal incision. Gastroplasty after esophageal dilatation interposes the fundus of the stomach between esophageal mucosa and the acidic milieu of the stomach. The remaining fundus may be sewn to the lower esophagus to create a valve-like effect. The second type of repair is resection of the stricture and the creation of a thoracic end-to-side esophagogastrostomy. Vagotomy and antrectomy are performed to

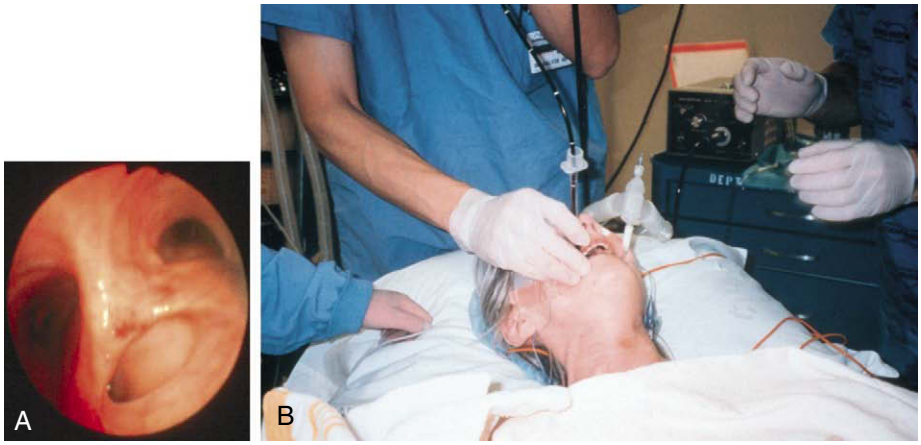

Figure 59-40 A, Fiberoptic bronchoscopic photograph of a tracheoesophageal fistula due to esophageal cancer. The fistula is seen posteriorly at the level of carina at 5 o'clock. The left mainstem bronchus is at 9 o'clock and the right mainstem bronchus at 2 o'clock. **B,** Photograph of the fiberoptic-guided placement of bilateral endobronchial tubes (5-mm ID microlaryngoscopy tubes) for repair of tracheoesophageal fistula in the same patient. (*Photographs courtesy of Dr. R. Grant.*)

eliminate stomach acidity, and a Roux-en-Y gastric drainage procedure is performed to prevent alkaline intestinal reflux.

Esophageal Perforation and Rupture

There are multiple causes of esophageal perforation, including foreign bodies, endoscopy, bougienage, traumatic tracheal intubation, gastric tubes, and oropharyngeal suctioning. Iatrogenic causes are the most common, with upper gastrointestinal endoscopy being the most frequent cause. A rupture is a burst injury often due to uncoordinated vomiting, straining associated with weight lifting, childbirth, defecation, and crush injuries to the chest and abdomen. The rupture is usually located within 2 cm of the gastroesophageal junction on the left side. Rupture is due to a sudden increase in abdominal pressure with a relaxed lower esophageal sphincter and an obstructed esophageal inlet. In contrast to a perforation, in the presence of a rupture, the stomach contents enter the mediastinum under high pressure and the patient becomes symptomatic much more abruptly.

In addition to chest and/or back pain, patients with intrathoracic esophageal perforation or rupture may develop hypotension, diaphoresis, tachypnea, cyanosis, emphysema, and hydrothorax or hydropneumothorax.[187] Radiologic studies may reveal subcutaneous emphysema, pneumomediastinum, widening of the mediastinum, pleural effusion, and pneumoperitoneum. These patients will rapidly develop mediastinitis and sepsis if not treated surgically, so repair and drainage is an emergency procedure usually performed via a left or right thoracotomy.

Achalasia

Achalasia is a disorder in which there is a lack of peristalsis of the esophagus and a failure of the lower esophageal sphincter to relax in response to swallowing. Clinically, the patients have esophageal distention that may lead to chronic regurgitation and aspiration. The goal of treatment is to alleviate the distal obstruction. This can be done by either esophageal dilatation or surgery. Dilatation, which carries with it the risk of perforation, can be achieved by mechanical, hydrostatic, or pneumatic means. The surgical repair consists of a Heller myotomy, which is an incision through the circular muscle of the esophagogastric junction. The myotomy is often combined with a hiatal hernia repair to prevent subsequent reflux. This can be performed via thoracotomy, laparotomy, or laparoscopy.[188] The Dor operation is a modification of the procedure in which a stent is inserted into the muscular defect created by the myotomy to prevent muscular reapposition and, thus, recurrent dysphagia.[189]

Esophagorespiratory Tract Fistula

Esophagorespiratory tract fistula in an adult is most often due to malignancy. Occasionally, the fistula is benign and may be due to injury by a tracheal tube, trauma, or inflammation. Of the malignant fistulas, approximately 85% are secondary to esophageal cancer. In contrast to the pediatric patient with esophagorespiratory tract fistulas, which usually connect the distal esophagus to the posterior tracheal wall, these fistulas may connect to any part of the respiratory tract.[190] In most cases, the fistula can be seen on esophagoscopy or bronchoscopy. In malignant cases, the goal of surgery is usually palliation. The technique of lung isolation will depend on the location of the fistula. One option in adults with a distal tracheal fistula is the use of bilateral small (5-6 mm ID) endobronchial tubes (Fig. 59-40).[191]

Zenker's Diverticulum

Zenker's diverticulum is actually a diverticulum of the lower pharynx. It arises from a weakness at the junction of the thyropharyngeus and cricopharyngeus muscles just proximal to the esophagus. It is commonly considered as an esophageal lesion because of its proximity to the upper esophagus and because the underlying cause may be a failure of relaxation of the upper esophageal sphincter during swallowing. Early symptoms may be nonspecific, with dysphagia and complaints of food sticking in the throat. As the diverticulum enlarges, patients describe noisy swallowing, regurgitation of undigested food, and supine coughing spells. Recurrent aspiration and pneumonia may develop.

The major concern for anesthesia is the possibility of aspiration on induction of general anesthesia for excision of the diverticulum.[192] Even prolonged fasting does not ensure that the diverticulum will be empty. The best method to empty the diverticulum is to have the patient express and regurgitate the contents

immediately before induction. Many of these patients will be used to doing this on a regular basis at home. Because the diverticulum orifice is almost always above the level of the cricoid cartilage, cricoid pressure during a rapid-sequence induction does not prevent aspiration and may contribute to aspiration by causing the sac to empty into the pharynx. Surgical excision is usually done through a lower left neck incision.

The safest method of managing the airway for these patients may be awake fiberoptic intubation. However, these have been managed without incident using a modified rapid-sequence induction without cricoid pressure and with the patient supine and head up 20 to 30 degrees. Other considerations in these patients include the possibility of perforation of the diverticulum when passing an orogastric or nasogastric tube or an esophageal bougie.

Tracheal Resection

Tracheal resection and reconstruction is indicated in patients who have a tracheal obstruction as a result of a tracheal tumor, previous tracheal trauma (most commonly due to postintubation stenosis), congenital anomalies, and vascular lesions. For patients who have operable tumors, approximately 80% undergo segmental resection with primary anastomosis, 10% undergo segmental resection with prosthetic reconstruction, and the remaining 10% undergo placement of a T-tube stent.

Diagnostic studies are reviewed as part of the preoperative evaluation. Linear tomography of the trachea is considered the most accurate tool to define the degree, level, and length of the lesion. The CT scan is a useful diagnostic tool to evaluate extratracheal or extrabronchial involvement by a tumor. Bronchoscopy is one of the definitive diagnostic tests for tracheal obstruction. In cases of moderate to severe obstruction, fiberoptic bronchoscopic examination is usually deferred until the time of definitive treatment, such as surgical intervention. Bronchoscopy for a patient with tracheal stenosis should be carried out in the operating room where the surgical and anesthesia teams are present and ready to intervene should loss of airway occur. An advantage of rigid bronchoscopy over flexible bronchoscopy is that it can bypass the obstruction and provide a ventilation pathway if complete obstruction occurs. During surgery, all patients should have an invasive arterial catheter placed to facilitate measurement of arterial blood gases, as well as measure arterial blood pressure. Central venous pressure or pulmonary artery catheters are only used if the patient requires CPB.

A variety of methods for providing adequate oxygenation and elimination of CO_2 have been used during tracheal resection. The different alternatives include (1) standard orotracheal intubation, (2) insertion of a sterile SLT into the opened trachea or bronchus distal to the area of resection, (3) HFJV through the stenotic area, (4) HFPPV, and (5) the use of CPB.

Induction of anesthesia in patients with a compromised airway requires good communication between the surgical team and the anesthesiologist. The surgeon should always be in the operating room during induction and available to manage a surgical airway if this becomes necessary.[193] A rigid bronchoscope must be immediately available. The patient should be thoroughly preoxygenated with 100% O_2 prior to the initiation of inhalation induction. The safest and most commonly recommended method of induction is with spontaneous ventilation. The use of sevoflurane is recommended because, of all the inhaled anesthetics, it has the least irritant effects in the airway. When adequate depth of anesthesia is achieved, topicalization of the airway with local anesthetics is done with 4% lidocaine and mask ventilation is reconfirmed. Bronchoscopy can then be performed to assess the airway and location of the stenosis or lesion. The airway should be secured before using muscle relaxants. Short-acting muscle relaxants, such as succinylcholine, are preferable initially.

One airway management technique is with an SLT that is placed above the tracheal lesion, under direct flexible fiberoptic bronchoscopy guidance after induction of general anesthesia. The tube is then manipulated by the surgeon distal to the mass or the area of stenosis. This technique is limited to patients with relatively mild stenosis, and the presence of an SLT in the surgical field makes completion of the tracheal anastomosis more difficult.

Another technique is to insert an endotracheal or endobronchial tube into the opened trachea distal to the site of resection. Initially, either a small SLT is passed distal to the obstruction or a standard SLT is placed proximal to it. All further tracheal and endobronchial intubations are performed preferably with an armored sterile tube passed into the airway, which is surgically opened distal to the lesion.

With a low tracheal lesion, a right thoracotomy provides the optimal surgical exposure. A sterile SLT is used to provide ventilation to the lung distal to the resection. After the posterior anastomosis is completed, the endobronchial tube is removed and the original SLT is advanced past the site of resection (Fig. 59-41). This technique can also be used for carinal resection.

A third technique for airway management during tracheal resection includes HFJV through a small-bore endotracheal tube or catheter.[194] With this technique, a small-bore uncuffed catheter is placed through the stenotic area and ventilation is accomplished by intermittently exposing the lung to a high flow of fresh gas through the catheter. Oxygen jets entrain ambient air, which in turn provides the volume necessary for adequate ventilation. Disadvantages of this technique include (1) possible inadequate escape of air around the jet catheter during exhalation when the catheter is passed through a tight stenotic area causing barotrauma, (2) plugging of the catheter with blood, (3) displacement of the catheter, (4) aspiration of blood, and (5) technical difficulties with high-pressure injectors. The catheters used for HFJV have an internal diameter ranging from 2 to 5 mm, with a length of either 45 or 50 cm. In these patients, the trachea is intubated orally and the lungs ventilated with intermittent positive-pressure ventilation until the trachea is transected. Then HFJV is initiated through a fine catheter inserted in the SLT and positioned either in the distal trachea or left mainstem bronchus. Other techniques that have been used for oxygenation during distal airway resections include HFPPV, helium-oxygen mixtures, and CPB.

After the tracheal resection is completed, most patients are kept in a position of neck flexion to reduce tension on the suture line. A thick chin-sternum suture may be placed for several days to maintain neck flexion or a cervical splint may be used.[195] A small SLT or tracheostomy tube (preferably uncuffed) or a T-tube with upper limb 0.5 to 1 cm above the vocal cords may be inserted at the end of surgery in cases when glottic edema is a concern or for patients requiring ventilatory support. If a tracheostomy is performed, it will be done distal to the anastomosis. Early extubation is highly desirable. If a patient requires reintubation, it should

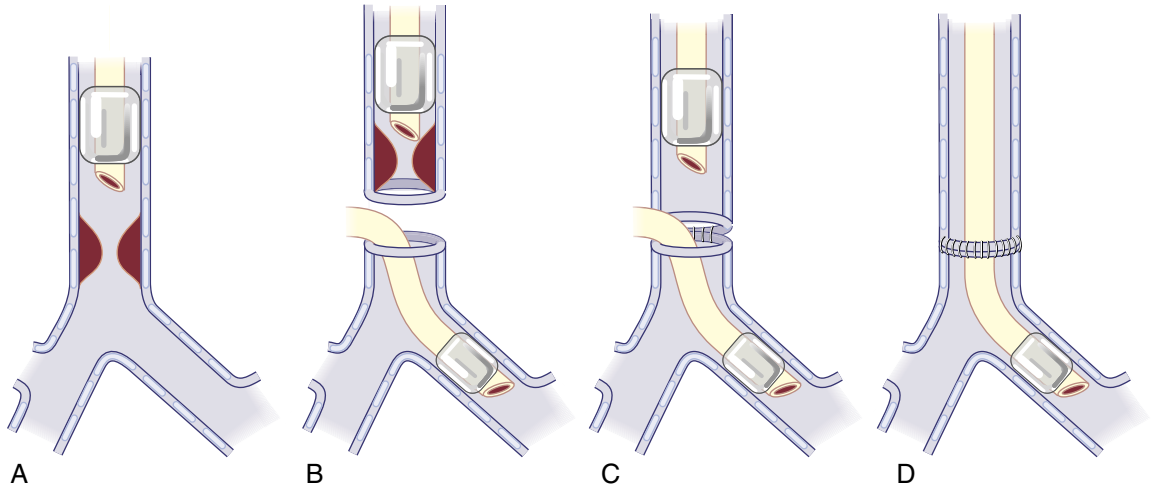

Figure 59-41 Airway management and surgical procedure for resection of a low tracheal lesion. **A,** Initial intubation above the lesion. **B,** Left endobronchial intubation distal to the lesion after the trachea has been opened. **C,** Placement of sutures for the posterior anastomosis. **D,** The endobronchial tube has been removed, and the original endotracheal tube has been advanced distal to the anterior anastomosis into an endobronchial position. (*Modified from Geffin B, Bland J, Grillo HC: Anesthetic management of tracheal resection and reconstruction. Anesth Analg 48:884, 1969.*)

be performed with a flexible fiberoptic bronchoscope by advancing an SLT under direct vision over the bronchoscope and then placing it in the patient's trachea. The patient is kept in a head-up position to diminish swelling. Racemic epinephrine, corticosteroids, diuretics, and fluid restriction may be useful in these cases to decrease airway edema.

One of the complications in the postoperative period is tetraplegia, with hyperflexion of the neck having been implicated as a potential cause. In these cases, it is necessary to cut the chin stitch. Tracheal extubation can be challenging. An infusion of propofol and remifentanil, with fiberoptic bronchoscopy guidance and full patient cooperation, can aid extubation.[196]

Bronchiectasis/Lung Abscess/Empyema

Bronchiectasis is a disease that causes localized, irreversible dilatation of part of the bronchial tree. Involved bronchi are inflamed and easily collapsible, resulting in airflow obstruction and impaired clearance of secretions. Bronchiectasis is associated with a wide range of disorders, but it usually results from necrotizing bacterial infections. It may require surgery if it causes hemoptysis or recurrent pneumonia. An abscess is a nonanatomic area of liquefactive necrosis of the lung often distal to an obstruction or following pneumonia (Fig. 59-42). An empyema

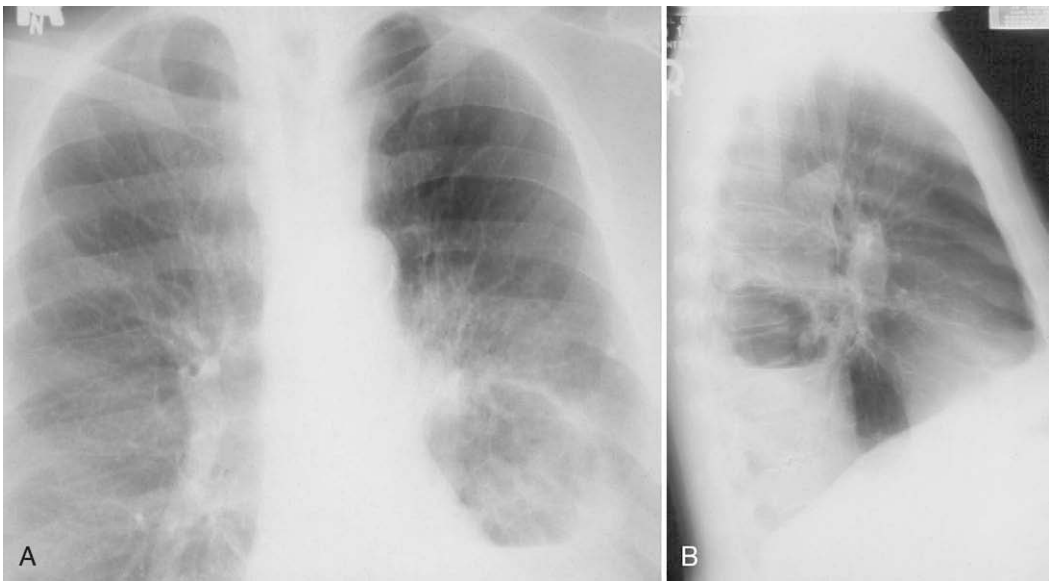

Figure 59-42 Posteroanterior (**A**) and lateral (**B**) chest radiographs of a patient with a lung abscess distal to an obstructing carcinoma of the left lower lobe. The diagnostic thick wall of the abscess and the air-fluid level can be appreciated in the left lower thorax. These patients are at risk for soiling of uncontaminated lung regions during surgery from pus in the abscess. The optimal method of lung isolation is with a double-lumen tube.



Figure 59-43 **A,** Chest radiograph of a patient immediately postoperatively after a right pneumonectomy. **B,** The same patient on postoperative day 6. This is a normal postpneumonectomy film. The right hemithorax is gradually filling with serous fluid. **C,** The same patient on postoperative day 7. The patient had the sudden onset of severe dyspnea, desaturation, and coughing. The chest radiograph reveals a decrease in the fluid level in the right hemithorax. This is diagnostic of a bronchopleural fistula caused by dehiscence of the bronchial stump.

is a collection of pus between the visceral and parietal pleural layers that is often a complication of pneumonia or surgery. Empyema complicating lung resections occurs in 2% to 16% of cases and with a 40% increase in the associated perioperative mortality rate. Mortality further increases when the empyema is associated with a bronchopleural fistula. Surgical interventions for patients with empyema include decortication (the method of choice when the underlying lung is unable to expand due to a thick inflammatory coat) or open window thoracostomy (the ideal method for drainage of the pleural cavity to control septic symptoms in patients with postpulmonary resection empyema).[197] In less severe cases, tube drainage, antibiotic irrigation, and débridement may be sufficient.

All of these infective indications for thoracic surgery are less common in the developed world since the introduction of antibiotics. Anesthetic considerations during surgery for these infective indications include the need for lung isolation to protect uninvolved lung regions from soiling by pus in the infected areas. Also, owing to the inflammation, surgery is technically more difficult and there is a greater risk of massive hemorrhage.

Some of these patients may present with sepsis at the time of surgery. In these patients the placement of a thoracic epidural catheter is not recommended. These patients require lung isolation, preferably with a DLT. The DLT facilitates suctioning of debris and copious secretions that are present in the tracheobronchial tree. Patients undergoing a decortication may have massive blood loss. If the lung has been chronically collapsed, expansion should be done gradually to avoid the development of pulmonary edema on re-expansion. Extubation in the operating room is encouraged if the patient meets standard criteria for extubation.

Bronchopleural Fistula

A bronchopleural fistula may be caused by (1) rupture of a lung abscess, bronchus, bulla, cyst, or parenchymal tissue into the pleural space; (2) the erosion of a bronchus by carcinoma or chronic inflammatory disease; or (3) stump dehiscence of a bronchial suture line after pulmonary resection. Pneumonectomy patients have an incidence of bronchopleural fistula, ranging from 2% to 11%,[198] with a mortality ranging from 5% to 70%.

The diagnosis of bronchopleural fistula is usually made clinically. After pneumonectomy, the diagnosis is based on the sudden onset of dyspnea, subcutaneous emphysema, contralateral deviation of the trachea, and a decrease of fluid level on serial radiographs of the chest (Fig. 59-43). In lobectomy patients, persistent air leak, purulent drainage, and expectoration of purulent material are usually diagnostic indicators of a bronchopleural fistula. When the fistula appears after removal of a chest tube, the diagnosis of bronchopleural fistula is made on the basis of fever, purulent sputum, and a new air-fluid level in the pleural cavity on the chest radiograph.

The diagnosis is confirmed by bronchoscopic examination. Additionally, bronchography and sinograms of the fistula may be used to confirm the diagnosis. Other diagnostic methods include the injection of an indicator, such as methylene blue, into the pleural space and subsequent recovery of the indicator from sputum. Accumulation of radionuclide in the pleural space after inhalation of xenon or a mixture of O_2 and N_2O to detect the presence of a bronchopleural fistula can also be used as indicators.[199]

If the disruption occurs early in postpneumonectomy patients, it is possible to resuture the stump. Late or chronic postpneumonectomy bronchial disruption is managed with drainage or with the Clagett procedure, which includes open pleural drainage and the use of a muscle flap to reinforce the bronchial stump. In nonpneumonectomy cases, if the lung expands to fill the thoracic cavity, the air leak can usually be controlled with chest tube drainage alone. However, if the fistula is large and a significant leak through a large persistent pleural space occurs, it is unlikely that the fistula will close, and surgical resection is necessary

The patient with a bronchopleural fistula presents several intraoperative challenges for the anesthesiologist; these include (1) the need for lung isolation to protect healthy lung regions, (2) the possibility of tension pneumothorax with positive-pressure ventilation, and (3) the possibility of inadequate ventilation due to air leak from the fistula. Preoperatively, it is useful to estimate the loss of tidal volume through the bronchopleural fistula, which may be done in two ways. First, one should determine whether air bubbles flow intermittently or continuously through the chest tube. If air bubbles flow intermittently, then the fistula is small. In contrast, when a patient has a large bronchopleural fistula or bronchial rupture, air will bubble continuously through the water-seal chamber of the chest tube drainage system. Second, the size of the bronchopleural fistula may be quantified by the difference between inhaled and exhaled tidal volumes. In a nonintubated patient, this may be determined with a tight-fitting mask and a

fast-responding spirometer. In an intubated patient, it is determined by direct attachment of the spirometer to the endotracheal tube. The larger the air leak, the greater the need to isolate the bronchopleural fistula with the use of a lung-isolation device (a DLT or an independent bronchial blocker).

Several nonsurgical approaches (i.e., the use of various mechanical ventilation/chest tube drainage systems) have been used for the treatment of patients with a bronchopleural fistula. These approaches consist of OLV and differential lung ventilation, including high-frequency ventilation, PEEP to the pleural cavity equal to intrathoracic PEEP, and unidirectional chest tube valves.

For patients undergoing operative repair, the ability to adequately deliver positive-pressure ventilation intraoperatively must be carefully considered before surgery. A chest drain should be placed before induction to avoid the possibility of tension pneumothorax with positive-pressure ventilation. If a fistula is small, chronic, and uninfected, an SLT can be used safely. If the air leak is significant, then a DLT is the best choice for delivering positive-pressure ventilation. The DLT can provide positive-pressure ventilation to the normal lung without loss of minute ventilation through the fistula and prevent the hazard of contamination of the uninfected lung with infected material when the patient is turned to the lateral decubitus position.

The safest method of obtaining lung isolation is awake fiberoptic intubation with a DLT.[200] However, this requires a cooperative patient and excellent topical anesthesia and is often not an option. Another option is to maintain spontaneous ventilation during induction and intubation until lung isolation is secured. This avoids the possibility of inadequate positive-pressure ventilation due to air leak but is not well tolerated in older patients with significant comorbidity. If the patient has a post-pneumonectomy fistula, the DLT or SLT must be guided under direct vision with the assistance fiberoptic bronchoscopy and the tip of the endobronchial lumen should be placed in the existing lung (e.g., for right-sided fistula a left-sided tube). After the chest is opened, if an excessive leak is encountered when using an SLT, ventilation can be improved by lung packing and manual control of the air leak.

One option to avoid instrumentation of the airway in patients with bronchopleural fistula after pneumonectomy is the use of thoracic epidural anesthesia with intravenous sedation during minimally invasive surgery.[201] An alternative method of ventilating patients with multiple bronchopleural fistulas is the use of high-frequency oscillatory ventilation with permissive hypercapnia. This avoids barotrauma to the nonoperative lung, decreases bronchopleural fistula air leak, and optimizes the operative outcome.[202] The advantage of high-frequency oscillatory ventilation over conventional mechanical ventilation is that it uses lower peak airway pressure and may decrease the air leak across the fistula. Early extubation in the operating room should be attempted in all patients undergoing fistula repair to avoid barotrauma to the surgical stump from positive-pressure ventilation in the postoperative period.

Blebs, Bullae, Cysts, and Pneumatoceles

Blebs

A bleb is a subpleural collection air under the visceral pleura caused by a ruptured alveolus. The air dissects through the pulmonary parenchyma and enlarges to form a bubble on the surface of the lung. Blebs most commonly occur at the apices of the lung and can rupture into the interpleural space, causing a pneumothorax. A single episode of spontaneous pneumothorax is usually treated conservatively with chest tube drainage until the air leak has stopped. Resection of blebs is commonly indicated for recurrent pneumthoraces, bilateral pneumothoraces, or prolonged chest tube drainage. Resection of blebs after a single pneumothorax may be indicated if the patient's occupation exposes him or her to significant rapid fluctuations in atmospheric pressure (e.g., flight crews or scuba divers). Resection is most commonly combined with a procedure to obliterate the pleural space by partial pleurectomy or pleural abrasion. Resection of blebs is most often performed by VATS. Although VATS procedures per se are generally associated with limited need for postoperative analgesia, pleurectomy or abrasion is very painful.

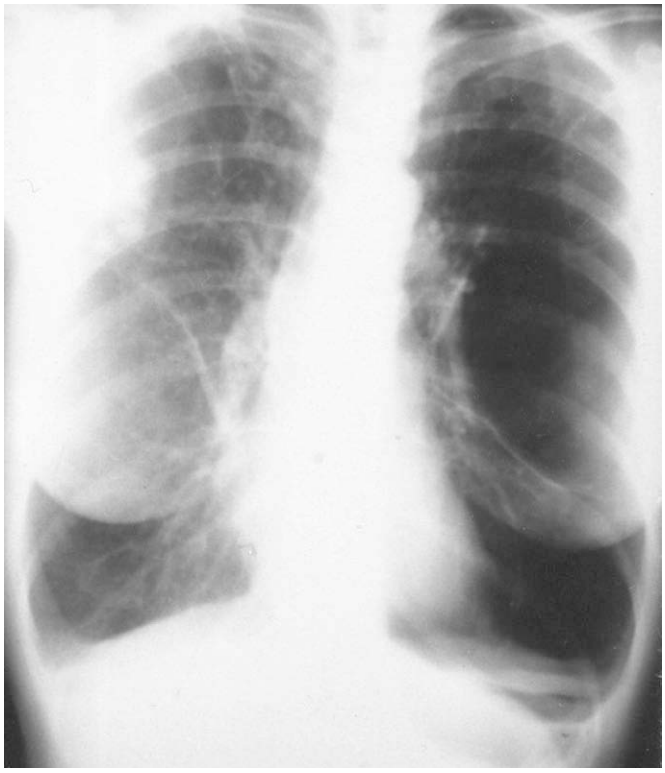

Figure 59-44 Chest radiograph of a patient with severe emphysema and multiple bullae, including giant bullae of the left upper land lower lobes.

Bullae

Bullae are thin-walled air-filled intraparenchymal lung spaces caused by the loss of alveolar structural tissue (Fig. 59-44). These are usually associated with emphysema, but their exact cause is unclear. Although there is some confusion over terminology in this area, bullous-like lesions of the lung associated with congenital malformations or secondary to trauma or infection are more correctly termed pneumatoceles or cysts. There are no universally accepted surgical indications for resection of lung bullae. A patient with symptomatic dyspnea and a giant bulla (or bullae) that occupies more than 30% of a hemithorax, and in whom a radiograph and CT scan suggest that reasonably functional lung tissue can be restored to a more anatomically favorable position, should be considered for bullectomy. Factors that support the

effect of the bullae as a cause of a patient's dyspnea are a restrictive pattern of spirometry (proportional decrease of both FEV_1, and FVC) and a discrepancy in lung volume studies in which the FRC measured by plethysmography exceeds the FRC measured by helium dilution by more than 2 L.

In the usual tidal volume range, bullae are more compliant than normal lung and fill preferentially during spontaneous ventilation. However, beyond the normal tidal volume range, bullae become much less compliant and the intrabulla pressure rises acutely as airway pressure increases. Measurement of in vivo intrabullae pressures in patients using fine needles both before and during anesthesia showed no evidence of a valve mechanism.[36] All bullae studied communicated with the central airways, although some very slowly. The typical compression pattern seen on radiography or CT is most likely due to secondary elastic recoil of normal lung regions (see Fig. 59-5). Intrabulla pressure at FRC corresponds with the mean airway pressure averaged over the respiratory cycle. Thus, during spontaneous ventilation, the intra-bulla pressure will be negative with respect to surrounding lung tissue. However, whenever positive pressure is used, the intra-bulla pressure will rise in relation to surrounding lung regions. There is a risk of hyperinflation and rupture whenever positive pressure is used. The complications of bulla rupture can be life threatening due to hemodynamic collapse from tension pneumothorax or inadequate ventilation due to a resultant bronchopleural fistula.

Relief of dyspnea symptoms and improved pulmonary function are well documented in patients after resection of giant bullae with most patients showing an increase in FEV_1 of more than 0.3 L and excellent short-term improvement in quality of life, but with a decrease in improvement by 3 years.[203] Hypercapnia is not a contraindication to bullae resection. Lung infection must be meticulously treated preoperatively. Outcome depends on patient age, smoking history, and cardiac status. In the postoperative period lung air leaks are the major complication.

The surgical approach can be by traditional or modified thoracotomy, sternotomy, or VATS. Laser resection may decrease the incidence of air leaks. Various nonsurgical thoracoscopic and bronchoscopic procedures such as the subsegmental injections of fibrin glue have been used to deal with these air leaks.

The anesthetic considerations for bullectomy are similar to those for a patient with a bronchopleural fistula with the exceptions that it is best not to place a chest drain prophylactically because this may enter the bulla and create a fistula and there is not the risk of soiling healthy lung regions from extrapleural fluid that exists with fistulas. For induction of anesthesia it is optimal to maintain spontaneous ventilation until the lung or lobe with the bulla or bleb is isolated.[204] When there is a risk of aspiration or it is believed that the patient's gas exchange or hemodynamics may not permit spontaneous ventilation for induction, the anesthesiologist will have to use small tidal volumes and low airway pressures during positive-pressure ventilation until the airway is isolated.

Cysts

Congenital bronchogenic cysts are products of abnormalities in the tracheobronchial budding process of lung organogenesis. They may occur peripherally within the lung parenchyma (70%) or centrally attached to the mediastinum or hilum. Bronchogenic cysts become problematic if they become enlarged, exerting a mass effect on functional lung or mediastinal structures or if they rupture and create a pneumothorax, or if they become infected. Small cysts without communications to a bronchus are asymptomatic and may be incidentally noted as round, clearly demarcated lesions on chest radiographs. Communicating cysts often produce air-fluid levels, are prone to recurrent infection, and may trap air by a ball-valve mechanism risking rapid expansion or rupture. Infected cysts may be obscured by surrounding pneumonia or may be difficult to differentiate from an empyema. CT scans help differentiate cystic from solid lesions. Conservative surgical excision of bronchogenic cysts is generally recommended whether or not a bronchial communication is evident.

Pulmonary hydatid cysts are watery, parasitic cysts containing larvae of the dog tapeworm *Echinococcus granulosus*.[205] Echinococcosis is a relatively common cause of pulmonary cysts in endemic areas (Australia, New Zealand, South America, and some third world regions). Hydatid cysts may grow in diameter by as much as 5 cm per year and become medically problematic in several ways. By mass effect they may exert pressure on adjacent structures (e.g., bronchus, great vessels, esophagus). Spontaneous or traumatic rupture may occur, sending fluid, parasites, or laminated debris into adjacent tissue, bronchus, pleura, or the circulation (systemic emboli). Hypersensitivity reactions, bronchospasm, and anaphylaxis can result. Drainage into the bronchi may cause dramatic expulsion of fluid with respiratory distress or asphyxiation, depending on the amount of fluid involved. Rupture into the pleural space may result in a large hydropneumothorax, severe dyspnea, shock, suffocation, or anaphylaxis. Rupture becomes more dangerous and more likely as cysts become larger. It is recommended that any cyst larger than 7 cm be removed.

Small, intact, peripheral cysts are often easily enucleated without loss of lung parenchyma. Segmentectomy or lobectomy is indicated when single or multiple cysts occupy most of the segment or lobe. Patients with suppurative cysts should be prepared for surgery with postural drainage and antibiotics. Lung isolation and/or reduced airway pressure during dissection may be helpful in preventing herniation of the cyst. Increased airway pressure at the time of delivery may aid removal of the cyst. The multiple bronchial openings in the residual cavity must then be identified and closed. Multiple "leak tests" with saline in the residual opening may be required to locate all bronchial openings. An alternative surgical strategy is to inject hypertonic saline into the cyst to sterilize it, followed by aspiration of the contents and removal of the evacuated cyst.

Pneumatoceles

Pneumatoceles are thin-walled, air-filled spaces generated by pulmonary infections or trauma. They usually appear in the first week of a pneumonia and resolve spontaneously within 6 weeks. As with other lung cysts, potential complications of pneumatoceles include secondary infection and enlargement as a result of air entrapment, with possible rupture or displacement and compression of normal lung. Adverse hemodynamic consequences may result either from a tension pneumothorax or a tension pneumatocele. The latter is unusual and is presumed to result from a one-way valve mechanism, usually in the setting of positive-pressure mechanical ventilation.[206] Occasionally, surgical decompression is required and has been performed by percutaneous needle aspiration, catheter drainage, or chest tube drainage under CT or fluoroscopic guidance. Rarely is thoracoscopic or open surgical drainage or excision required.

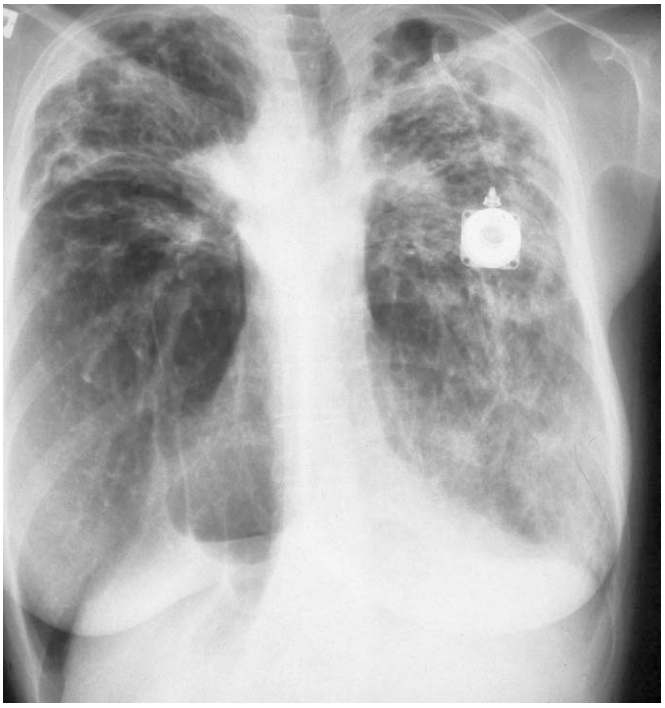

Figure 59-45 Chest radiograph of a patient with cystic fibrosis as indication for bilateral lung transplantation. The chest image shows a typical pattern of bronchiectasis. A subcutaneous intravenous injection reservoir is seen over the upper left chest.

Lung Transplantation

End-stage pulmonary disease is one of the most common causes of death. Lung transplantation is a definitive treatment for these patients (see Chapter 67). Indications and contraindications to lung transplantation are summarized in Table 59-23. Approximately 1500 lung transplantations are performed annually worldwide; the number is limited by the supply of donor organs. Recipients fall into four major categories (by frequency of indication):

1. COPD
2. Cystic fibrosis (CF) (Fig. 59-45) and other congenital forms of bronchiectasis
3. Pulmonary fibrosis: idiopathic, associated with connective tissues disorders, etc.
4. Primary pulmonary hypertension

There are also several other, rarer indications such as primary bronchoalveolar lung cancer, lymphangioleiomyomatosis, and so on.[207] Depending on the patient's pathophysiology, there are several surgical options: single-lung transplantation, bilateral sequential lung transplantation, en-bloc double-lung transplantation, heart-lung transplantation, and living-related lobar transplantation. An overall 5-year survival rate of 50% is the benchmark, but depends on recipient age and diagnosis. Survival is generally better with double- than single-lung transplants with the exception of elderly pulmonary fibrotic patients, where there is no outcome difference between the two procedures.

Anesthetic airway management is most commonly with a DLT. The advantage of a DLT in transplantation is that it allows direct continuous access to both lungs for suctioning, oxygenation, and examination of the bronchial anastomoses. Several advances have allowed the use of DLTs for transplantation. The use of segmental bronchial lavage at induction via an SLT, before placement of the DLT facilitates suctioning via the DLT in patients with copious secretions. Improved DLT designs with shorter endobronchial segments and increased familiarity of anesthesiologists with fiberoscopic lobar anatomy has aided positioning of DLTs.

Monitoring includes invasive arterial and pulmonary catheters and TEE in most centers. Anesthetic maintenance is based mainly on intravenous infusions owing to the frequent need for airway access (e.g., suctioning, bronchoscopy),

Table 59-23 Indications and Contraindications for Lung Transplantation

Indications
Untreatable end-stage pulmonary, parenchymal, and/or vascular disease
Absence of other major medical illnesses
Substantial limitation of daily activities
Projected life expectancy < 50% with 2- to 3-year predicted survival
NYHA class III or IV functional level
Rehabilitation potential
Satisfactory psychosocial profile and emotional support system
Acceptable nutritional status
Disease-specific mortality exceeding transplant-specific mortality over 1 to 2 years
Relative Contraindications
Age > 65 years
Critical or unstable clinical conditions (e.g., shock, mechanical ventilation or ECMO)
Severely limited functional status with poor rehabilitation potential
Colonization with highly resistant or virulent bacteria, fungi, or mycobacteria
Severe obesity defined as a body mass index > 30 kg/m^2
Severe or symptomatic osteoporosis
Other medical conditions resulting in end-organ damage (e.g., diabetes mellitus, systemic hypertension, peripheral vascular disease, patients with coronary artery disease status post coronary artery stenting or PTCA)
Absolute Contraindications
Untreatable advanced dysfunction of another major organ system (e.g., heart, liver, or kidney)
Active malignancy within the previous 2 years
Noncurable chronic extrapulmonary infection
Chronic active viral hepatitis B, hepatitis C, or HIV
Significant chest wall/spinal deformity
Documented nonadherence or inability to follow through with medical therapy, office follow-up, or both
Untreatable psychiatric or psychologic condition associated with inability to cooperate or comply with medical therapy
Absence of a consistent or reliable social support system
Substance addiction (e.g., alcohol, tobacco or narcotics) that is either active or within the previous 6 months

NYHA, New York Heart Association; ECMO, extracorporeal membrane oxygenation; PTCA, percutaneous transluminal coronary angioplasty; HIV, human immunodeficiency virus.

Based on Orens JB, Estenne M, Arcasoy S, et al: International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 25:145, 2006.

which causes problems maintaining a stable level of inspired anesthetic vapor. In spite of advances in lung preservation techniques, it is optimal to limit the donor lung ischemic period to 4 hours.

There are wide variations in the frequency of use of CPB during lung transplantation: some centers always use CPB and some centers almost never use it. CPB temporarily decreases postoperative gas exchange, increases intraoperative blood loss, and increases the duration of postoperative mechanical ventilation. There is no net decrease in short- or long-term mortality attributable to CPB. Extracorporeal membrane oxygenation (ECMO) is used in some centers in place of CPB intraoperatively[208] and is also used increasingly for postoperative respiratory support.

The intraoperative anesthetic complications depend, in large part, on the underlying lung disease. Emphysema patients are prone to hypotension on induction from positive-pressure ventilation (see earlier). Problems in cystic fibrosis patients include the inability to deal with thick bronchial secretions and to adequately ventilate these patients. These patients, because they have both increased inspiratory and expiratory flow resistances, may benefit from slow inspiratory phase ventilation with a high airway pressure.[209] Because of the severely decreased lung compliance this method of ventilation causes little hemodynamic compromise in this subgroup of patients, if air trapping is avoided. Other recipient disease-specific problems include hemodynamic collapse on induction due to right-sided heart dysfunction in primary pulmonary hypertensives, the poor tolerance of pulmonary fibrotic patients for OLV, and the risk of pneumothoraces in patients with lymphangiomyomatosis.

Subsequent Anesthesia for the Pulmonary Transplant Recipient

Many lung transplant recipients subsequently require anesthesia for related, or unrelated, surgical problems.[210] The frequency with which they present for surgery may be due to complications of immunosuppression (e.g., infection, tumor, renal failure) or of the transplantation (e.g., bronchial stenosis, bronchiolitis obliterans). Most transplant recipients can be managed according to routine anesthetic practice, including optimal perioperative respiratory care, antibiotic prophylaxis, and maintenance of immune suppression. Results of recent blood gas analysis, chest radiographs, and CT scans are vital in managing these patients. Most adults will have bronchial anastomoses, and there will be no problem with endotracheal intubation. If endobronchial intubation or a DLT is used, a bronchoscopy should be performed first to assess the bronchial anastomoses and the intubation should be with fiberoptic guidance.

Single-lung transplant recipients with native lung emphysema are a specific concern. They have a marked imbalance in pulmonary compliance, with the native lung highly compliant and the donor lung of normal or reduced (if there is rejection) compliance. However, the major proportion of the pulmonary blood flow is usually to the allograft. With standard methods of positive-pressure ventilation they may develop dynamic hyperinflation of the emphysematous lung with hemodynamic instability and problems with gas exchange. These patients may require the use of a DLT and independent lung ventilation techniques to reduce the airway pressure and minute ventilation in the native lung if positive-pressure ventilation is required.

Lung Volume Reduction

Although resection of bullae is a well-established thoracic surgical procedure, the use of multiple wedge resections to reduce lung volume and improve symptoms in severe emphysema (lung volume reduction) is a procedure in evolution. First proposed in the 1950s, this operation had a worldwide resurgence of interest in the 1990s[211] as a bridge or alternative to lung transplantation. The exact indications and the suitable patient population are still being clarified. The medical advances that have permitted the rebirth of this operation are multidisciplinary and include surgery (bovine pericardial reinforced lung stapling), anesthesia (thoracic epidural analgesia, lung-isolation techniques), and radiology (CT, lung scintigraphy). Depending on the patient and center this procedure may be unilateral or bilateral and performed by thoracotomy, sternotomy, or VATS. The surgery is more effective in patients with heterogeneous lung disease in which the most severely affected areas (often apical) can be resected than in patients with homogeneous types of emphysema (e.g., α_1-antitrypsin deficiency). Patients with extremely severe disease (FEV_1 or DLco < 20% predicted) have poor survival after surgery.[212]

Immediate postoperative improvements in symptoms and pulmonary function are often remarkable; many patients are able to discontinue or reduce home oxygen therapy. These changes are due to a decompression of the airways and a reduction of airflow resistance and work of breathing,[213] which results in a dramatic fall in auto-PEEP (intrinsic PEEP) with a corresponding increase in dynamic compliance. In spite of the encouraging changes in early postoperative pulmonary function, the improvement in respiratory function due to this surgery is transient.[214] However, this must be viewed in the context of the short life expectancy of patients with this degree of emphysema and the potential for improvement in their quality of life from the operation.

Anesthetic management is similar to that for other patients with severe COPD having thoracic surgery (see earlier) with the risk of hypotension on induction due to auto-PEEP and the need for excellent analgesia to avoid postoperative mechanical ventilation.[215] This procedure is now performed in some centers using one-way valves placed bronchoscopically in the most involved segments to cause collapse of severely emphysematous distal lung regions,[216] thus avoiding surgery.

Pulmonary Hemorrhage

Massive hemoptysis is defined as expectoration of more than 200 mL of blood in 24 to 48 hours. The most common causes are carcinoma, bronchiectasis, and trauma (blunt, penetrating, or secondary to a pulmonary artery catheter). Death can occur quickly due to asphyxia. Management requires four sequential steps: lung isolation, resuscitation, diagnosis, and definitive treatment. The anesthesiologist is often called to deal with these cases outside the operating room. There is no consensus on the best method of lung isolation for these cases. The initial method for lung isolation will depend on the availability of appropriate equipment and an assessment of the patient's airway. All three basic methods of lung isolation have been used: DLTs, SLTs, and bronchial blockers. Fiberoptic bronchoscopy is usually not helpful to position endobronchial tubes or blockers in the presence of torrential pulmonary hemorrhage, and lung isolation must be guided by clinical

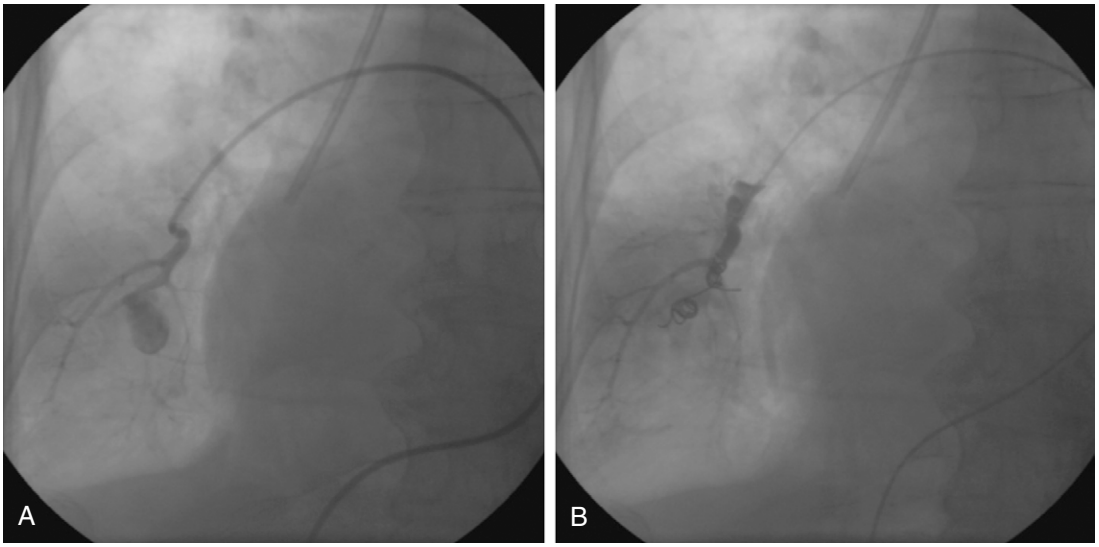

Figure 59-46 **A,** Radiographic dye injection showing a false aneurysm of the pulmonary artery of the right lower lobe after massive hemoptysis induced by pulmonary artery catheter rupture. **B,** A coil has been placed by interventional radiology in the false aneurysm of the right lower pulmonary artery in the same patient. Dye injection shows that the aneurysm has embolized with no further leakage.

signs (primarily auscultation). DLTs will achieve rapid and secure lung isolation. Even if a left-sided tube enters the right mainstem bronchus only the right upper lobe will be obstructed. However, suctioning large amounts of blood or clots is difficult through the narrow lumens of a DLT. An option is initial placement of an SLT for oxygenation and suctioning and then replacement with a DLT either by laryngoscopy or with an appropriate tube exchanger. An uncut SLT can be advanced directly into the right mainstem bronchus or rotated 90 degrees counterclockwise for advancement into the left mainstem bronchus. A bronchial blocker will normally pass easily into the right mainstem bronchus and is useful for right-sided hemorrhage (90% of pulmonary artery catheter–induced hemorrhages are right sided). Except for cases with blunt or penetrating trauma, after lung isolation and resuscitation have been achieved, diagnosis and definitive therapy for massive hemoptysis are now most commonly performed by radiology (Fig. 59-46).[217]

Pulmonary Artery Catheter–Induced Hemorrhage

Hemoptysis in a patient with a pulmonary artery catheter must be assumed to be caused by perforation of a pulmonary vessel by the catheter until proven otherwise. The mortality rate may exceed 50%. This complication seems to be occurring less than previously, possibly related to stricter indications for the use of pulmonary artery catheters and more appropriate management of pulmonary artery catheters with less reliance on wedge measurements. Therapy for pulmonary artery catheter–induced hemorrhage should follow an organized protocol with some variation depending on the severity of the hemorrhage (Table 59-24).

During Weaning from Cardiopulmonary Bypass

Weaning from CPB is one of the times when pulmonary artery catheter–induced hemorrhage is most likely to occur. Management of the pulmonary artery catheter during CPB by withdrawal from a potential wedge depth and observing the pulmonary artery pressure waveform to avoid wedging during CPB may decrease the risk of this complication. When hemoptysis does occur in this situation there are several management options available (Fig. 59-47). The anesthesiologist should resist the temptation to rapidly reverse the anticoagulation in order to quickly discontinue CPB because this can lead to fatal asphyxiation from hemorrhage. Resumption of full CPB ensures oxygenation while the tracheobronchial tree is suctioned and then visualized with fiberoptic bronchoscopy. The use of a pulmonary artery vent may be required to decrease the pulmonary blood flow sufficiently to define the bleeding site (usually the right lower lobe). The pleural cavity should be opened to assess the lung parenchymal damage. Conservative management with lung isolation, avoiding lung resection, is optimal therapy if possible. In patients with persistent hemorrhage who are not candidates for lung resection, temporary lobar pulmonary artery occlusion with a vascular loop during and after weaning from CPB may be an option.

Post-tracheostomy Hemorrhage

Hemorrhage in the immediate postoperative period after a tracheostomy is usually from local vessels in the incision such as the anterior jugular or inferior thyroid veins. Massive hemorrhage 1 to 6 weeks postoperatively is most commonly caused by tracheoinnominate artery fistula.[218] A small sentinel hemorrhage occurs in most patients before a massive hemorrhage. The man-

Table 59-24 Management of the Patient with a Pulmonary Artery Catheter–Induced Pulmonary Hemorrhage

1. Initially position the patient with the bleeding lung dependent.
2. Perform endotracheal intubation, oxygenation, airway toilet.
3. Obtain lung isolation with endobronchial double- or single-lumen tube or bronchial blocker.
4. Withdraw the catheter several centimeters, leaving it in the main pulmonary artery. Do not inflate the balloon (except with fluoroscopic guidance).
5. Position the patient with the isolated bleeding lung nondependent. Provide positive end-expiratory pressure to the bleeding lung if possible.
6. Transport patient to medical imaging for diagnosis and embolization if feasible.

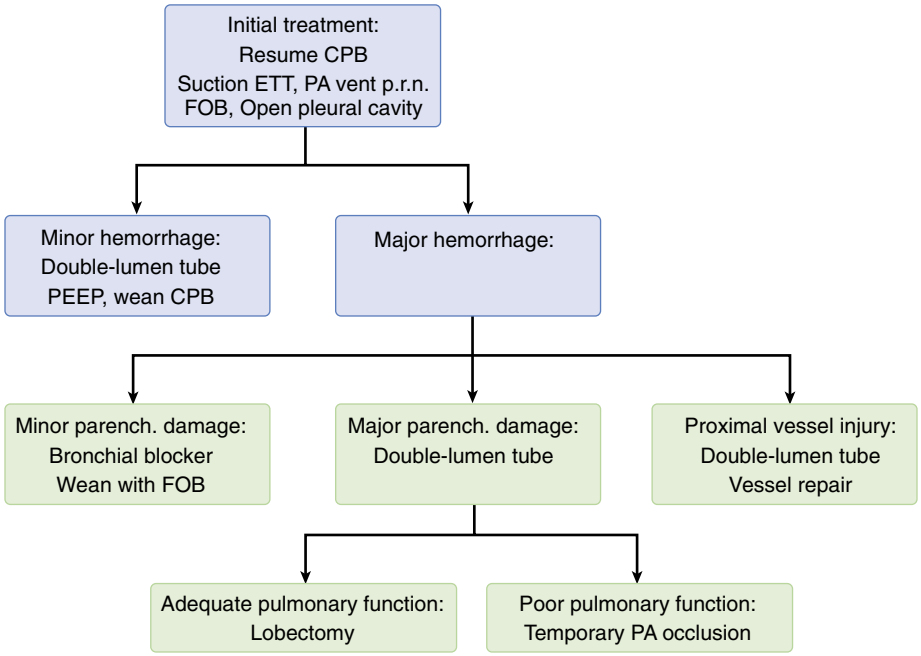

Figure 59-47 Flow diagram of management of massive hemoptysis during weaning from cardiopulmonary bypass (CPB). ETT, endotracheal tube; PA, pulmonary artery; FOB, fiberoptic bronchoscopy; Parenc., lung parenchyma.

agement protocol for tracheoinnominate artery fistula is outlined in Table 59-25.

Pulmonary Thromboendarterectomy

Pulmonary thromboendarterectomy is a potentially curative procedure for chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is a progressive disorder that responds poorly to conservative therapy, and PTE is the most appropriate treatment with a perioperative mortality of approximately 4%, which is less than lung transplantation. A majority of patients with CTEPH present for medical evaluation late in the disease because many have not had an obvious episode of deep venous thrombosis or pulmonary embolus and the progression of the disease is insidious. Patients present with severe dyspnea on exertion and signs of right-sided heart failure. Surgical candidates have hemodynamically significant pulmonary vascular obstruction (pulmonary vascular resistance > 300 dynes•sec•cm^{-5}) with potentially accessible proximal areas of thromboembolus.

An inferior vena cava filter is often placed prophylactically before surgery. Surgery is performed via a midline sternotomy with CPB with or without periods of deep hypothermic circulatory arrest (DHCA). Anesthetic management is essentially the same as for a patient with primary pulmonary hypertension for lung transplantation with the exception that there is no need for lung isolation so airway management is with a standard endotracheal tube. Monitoring includes femoral and pulmonary artery catheters, TEE, processed electroencephalography, and rectal/bladder temperatures.[219]

These patients are at risk for hemodynamic collapse from right ventricular failure from hypotension during induction of general anesthesia. Induction may be performed with etomidate or ketamine to avoid hypotension. Support of systemic vascular resistance with norepinephrine or phenylephrine is usually required. If DHCA is used, it is preceded by mannitol, methylprednisolone, and pentothal to try to decrease cerebral cellular edema and to improve free-radical scavenging. The speed of warming and cooling is controlled on CPB to maintain a temperature gradient less than 10°C between blood and bladder/rectal temperatures. Periods of DHCA are usually limited to 20 minutes. Massive pulmonary hemorrhage occurs rarely during CPB in these cases. Management of pulmonary hemorrhage is according to the algorithm outlined in Figure 59-47. The instillation of phenylephrine, 10 mg, and vasopressin, 20 units, diluted in 10-mL saline via the endotracheal tube may be beneficial. Postoperatively, the patients are kept sedated, intubated, and ventilated for at least 24 hours to decrease the risk of reperfusion pulmonary edema. Norepinephrine or vasopressin infusions may be used to elevate the systemic vascular resistance and decrease cardiac output to decrease pulmonary blood flow.

Table 59-25 Management of Tracheoinnominate Artery Fistula Hemorrhage

1. Overinflate the tracheostomy cuff to tamponade the hemorrhage.

If this fails:

2. Replace the tracheostomy tube with an oral endotracheal tube. Position the cuff with fiberoptic bronchoscopic guidance just above the carina.
3. Use digital compression of the innominate artery against the posterior sternum using a finger passed through the tracheostomy stoma.

If this fails:

4. Slowly withdraw the endotracheal tube and overinflate the cuff to tamponade.
5. Then proceed with definitive therapy: sternotomy and ligation of the innominate artery.

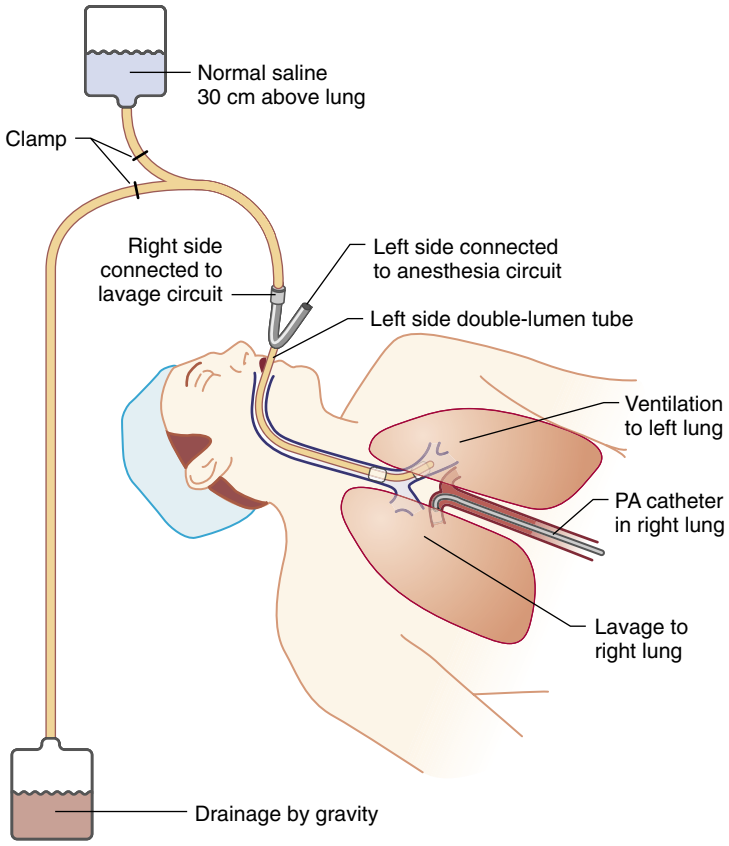

Figure 59-48 Technique for bronchopulmonary lavage. A double-lumen tube allows ventilation to the left lung during lavage of the right lung (and vice versa). Normal saline is infused and drained by gravity; clamps on the connection tubes determine the direction of fluid flow. (*From Benumof JL: Anesthesia for Thoracic Surgery. Philadelphia, WB Saunders, 1987.*)

Bronchopulmonary Lavage

Bronchopulmonary lavage is a treatment during which up to 10 to 20 L of normal saline is instilled then drained in 500 to 1000-mL aliquots through one side of a DLT into one lung under general anesthesia.[220] It may then be performed on the contralateral lung during the same anesthetic or during a subsequent anesthetic after a period of several days for recovery. It is the most effective treatment modality for symptomatic pulmonary alveolar proteinosis. This lung disease results from accumulation in the alveoli of a lipoproteinic material similar to surfactant. Since the introduction of bronchopulmonary lavage by Ramirez-Rivera in 1965, the prognosis of pulmonary alveolar proteinosis has greatly improved. Other pathologic states that have been treated by bronchopulmonary lavage include cystic fibrosis, asthma, radioactive dust inhalation, lipoid pneumonitis, and silicosis, all without convincing success.

Radiologic imaging, CT, and ventilation-perfusion scans help to determine the most impaired lung, which will be lavaged first. Monitoring is essentially the same as for a standard pulmonary resection. Some centers also monitor central venous or pulmonary artery pressures or TEE.[221] General anesthesia is induced and maintained with intravenous infusions as for lung transplantation. Airway management is with a left-sided DLT. Precise placement of the tube is confirmed by fiberoptic bronchoscopy, and air-tight isolation is determined by monitoring inspired and expired tidal volumes with side-stream spirometry. Tube dislodgment and flooding of the nonlavaged lung is a major complication of this procedure. Specifically during lavage of the left lung, the pressure of saline in the lung will tend to push the bronchial cuff of the DLT proximally. To prevent this it is recommended that the anesthesiologist maintain his or her hand on the DLT, securing it firmly at the patient's mouth, throughout the entire procedure. The pulmonary compliance of the ventilated lung needs to be continuously monitored to diagnose any liquid spillage from the lavage lung.

The patient is kept in the supine position during the procedure. To improve the effectiveness of the lavage, ventilation with F_{IO_2} 100% for a few minutes is initiated after induction to denitrogenate both lungs. OLV is instituted with the nonlavage lung. A disposable irrigation and drainage system is used to instill approximately 1 L of warm normal saline (37°C) into the lavage lung (Fig. 59-48). The irrigating liquid is suspended 30 cm above the patient's mid-chest level to the lavage lung. Thereafter, the saline is rapidly drained by gravity into a container positioned 60 cm below or with the assistance of a small level of suction (<20 cm H_2O). This process is repeated as needed until the effluent fluid is clear. Chest physiotherapy—mainly percussion, vibration, and pressure—is applied during the filling and the drainage phases. The use of flannel protects the patient's chest wall from trauma due to physiotherapy during the percussion. If the cumulative total of the instilled fluid volume exceeds the drainage volume by more than 1000 mL a hydrothorax should be suspected and the procedure should be interrupted while an intraoperative chest radiograph is obtained to rule this out.

Because of transmitted hydrostatic pressure from the lavage lung to the pulmonary circulation, oxygenation increases during the filling phase and decreases during the emptying phase in

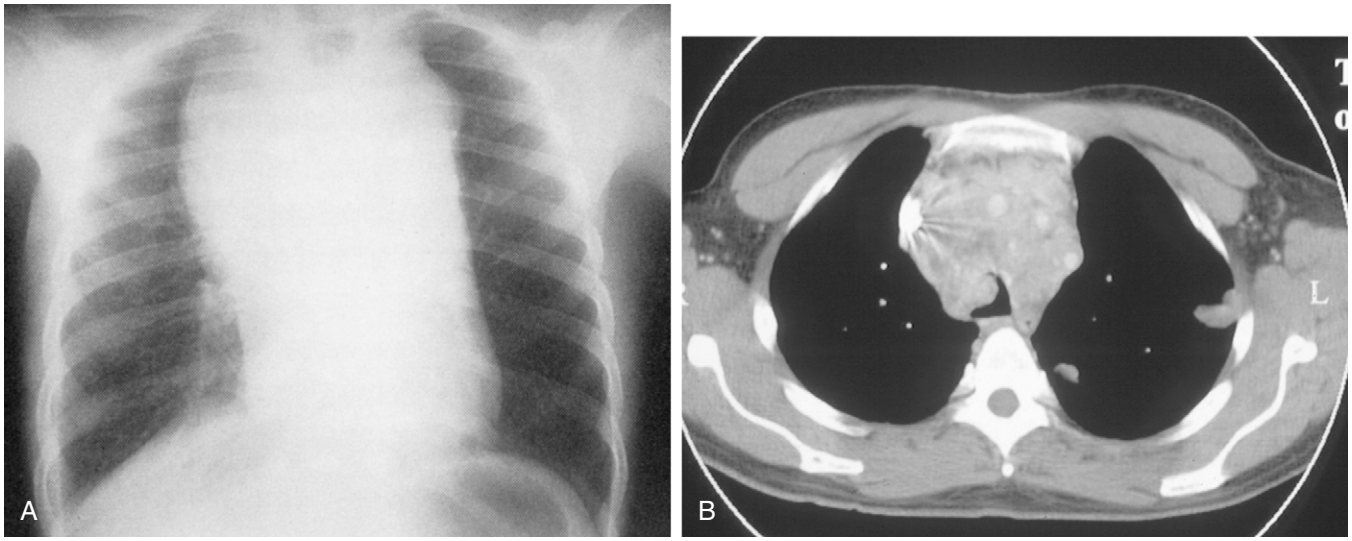

Figure 59-49 A, Chest radiograph of an adult patient with an anterosuperior mediastinal mass. This mass was a lymphoma. **B,** A thoracic contrast-enhanced CT scan just above the level of the carina shows partial compression of the carina and right mainstem bronchus. This patient has an "uncertain" airway (see text).

synchrony with changes in the pulmonary blood flow distribution. These changes are usually transient and well tolerated. In severely hypoxemic patients presenting for bronchopulmonary lavage a variety of maneuvers have been used (e.g., inflation of a pulmonary artery catheter balloon in the pulmonary artery of the lavage lung while adding nitric oxide to the ventilated lung[222] or the use of ECMO) to maintain oxygenation.

Usually 10 to 15 L is instilled and more than 90% is recovered, leaving a deficit of less than 10%. At the end of the procedure the lavaged lung is thoroughly suctioned. A dose of furosemide (10 mg) is administered to increase diuresis of absorbed saline. If the plan is to proceed to a lavage of the contralateral lung there is a period of at least 1 hour of two-lung ventilation to allow recovery of the lavaged lung, during which arterial blood gases are monitored. If there is a persistent large alveolar-arterial oxygen gradient the procedure is terminated at this stage. After the procedure, after re-intubation with a single-lumen tracheal tube, inspection with fiberoptic bronchoscopy is performed for suctioning. Conventional ventilation with PEEP is continued, usually for less than 2 hours. Alveolar infiltrates seen on the chest radiography immediately after lavage normally clear within 24 hours. Observation in the intensive care unit for 24 hours is part of the routine procedure. Before the contralateral lavage, compliance and oxygenation should have recovered, at least to their initial values as measured before the first lavage. At that time, oxygenation is usually not a problem because the treated lung will be used to support gas exchange during the procedure. Some patients require lavage every few months, whereas others remain in remission for years.

Mediastinal Masses

Patients with mediastinal masses, particularly masses in the anterior or superior mediastinum, or both, present unique problems for the anesthesiologist. Patients may require anesthesia for biopsy of these masses by mediastinoscopy or VATS, or they may require definitive resection via sternotomy or thoracotomy. Tumors of the mediastinum include thymoma, teratoma, lymphoma, cystic hygroma, bronchogenic cyst, and thyroid tumors. Mediastinal masses may cause obstruction of major airways, main pulmonary arteries, atria, and the superior vena cava. During induction of general anesthesia in patients with an anterior or superior mediastinal mass, airway obstruction is the most common and feared complication. It is important to note that the point of tracheobronchial compression usually occurs distal to an endotracheal tube (Fig. 59-49) and it is not possible to forcibly pass a tube through the airway once it has collapsed. A history of supine dyspnea or cough should alert the clinician to the possibility of airway obstruction on induction of anesthesia. Life-threatening complications may occur in the absence of symptoms in children. The other major complication is cardiovascular collapse secondary to compression of the heart or major vessels (Fig. 59-50). Symptoms of supine presyncope suggest vascular compression.

Anesthetic deaths have mainly been reported in children. These deaths may be the result of the more compressible cartilaginous structure of the airway in children or because of the difficulty in obtaining a history of positional symptoms in children. The most important diagnostic test in the patient with a mediastinal mass is CT of the trachea and chest. Children with tracheobronchial compression greater than 50% on a CT scan cannot safely be given general anesthesia.[223] Flow-volume loops, specifically the exacerbation of a variable intrathoracic obstructive pattern (expiratory plateau) when supine, are unreliable[224] for predicting which patients will have intraoperative airway complications.[225] Transthoracic echocardiography is indicated for patients with vascular compression symptoms.

General anesthesia will exacerbate extrinsic intrathoracic airway compression in three ways. First, reduced lung volume occurs during general anesthesia and tracheobronchial diameters decrease according to lung volume. Second, bronchial smooth muscle relaxes during general anesthesia, allowing greater compressibility of large airways. And, third, paralysis eliminates the caudal movement of the diaphragm seen during spontaneous ventilation. This eliminates the normal transpleural pressure

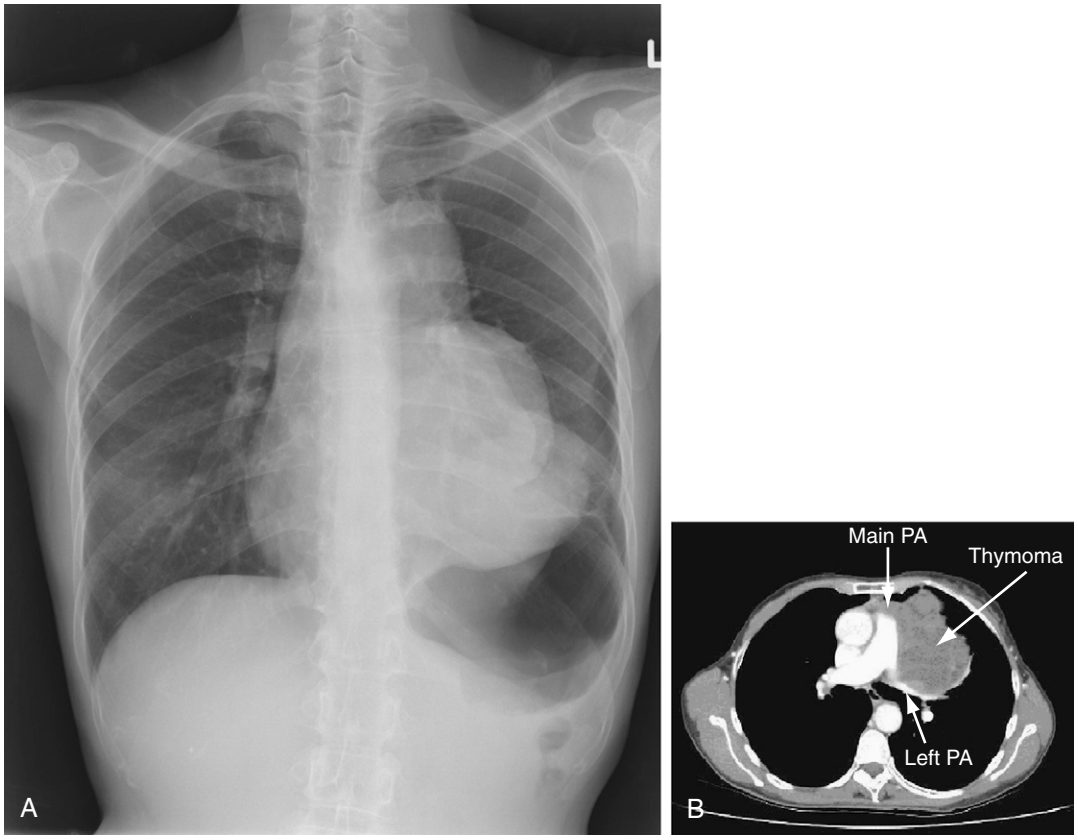

Figure 59-50 **A,** Chest radiograph of an adult patient with a thymoma who presented with symptoms of supine presyncope. **B,** Contrast CT scan shows the thymoma and partial compression of the main pulmonary artery (Main PA) with almost complete occlusion of the left pulmonary artery (Left PA).

gradient that dilates the airways during inspiration and minimizes the effects of extrinsic intrathoracic airway compression.

Management of these patients is guided by their symptoms and the CT scan (Tables 59-26 and 59-27). Patients with "uncertain" airways should have diagnostic procedures performed under local or regional anesthesia whenever possible. Patients with "uncertain" airways requiring general anesthesia need a step-by-step induction of anesthesia with continuous monitoring of gas exchange and hemodynamics. This "NPIC" (*noli pontes ignii consumere,* i.e., "don't burn your bridges") anesthetic induction can be an inhalation induction with a volatile agent such as sevoflurane or intravenous titration of propofol with or without ketamine, maintaining spontaneous ventilation until either the airway is definitively secured or the procedure is completed.[226] Awake intubation of the trachea before induction is a possibility in some adult patients if the CT scan shows an area of noncompressed distal trachea to which the endotracheal tube can be advanced before induction. If muscle relaxants are required, ventilation should first be gradually taken over manually to ensure that positive-pressure ventilation is possible and only then can a short-acting muscle relaxant be administered (Table 59-28).

Development of airway or vascular compression requires that the patient be awakened as rapidly as possible and then other options for the procedure be explored. Intraoperative life-threatening airway compression usually has responded to one of two therapies: either repositioning of the patient (it must be deter-

Table 59-26 Grading Scale for Symptoms in Patients with an Anterior or Superior Mediastinal Mass

Asymptomatic
Mild: Can lie supine with some cough/pressure sensation
Moderate: Can lie supine for short periods but not indefinitely
Severe: Cannot tolerate supine position

Table 59-27 Stratification of Patients with Mediastinal Masses Regarding Safety for General Anesthesia

A	**Safe**	(I)	Asymptomatic adult, CT minimum tracheobronchial diameter > 50% of normal
B	**Unsafe**	(I)	Severely symptomatic adult or child
		(II)	Children with CT tracheobronchial diameter < 50% of normal, regardless of symptoms
C	**Uncertain**	(I)	Mild/moderate symptomatic child with CT tracheobronchial diameter > 50% of normal
		(II)	Mild/moderate symptomatic adult with CT tracheobronchial diameter < 50% of normal
		(III)	Adult or child unable to give history

CT, computed tomographic scan.

Table 59-28 Management for All Patients with a Mediastinal Mass and an "Uncertain" Airway for General Anesthesia

1. Determine optimal positioning of patient preoperatively.
2. Secure airway beyond stenosis while awake if feasible.
3. Have rigid bronchoscope and surgeon available at induction.
4. Maintain spontaneous ventilation if possible ("NPIC": see text).
5. Monitor for airway compromise postoperatively.

mined before induction if there is a position that causes less compression and fewer symptoms) or rigid bronchoscopy and ventilation distal to the obstruction (this means that an experienced bronchoscopist and equipment must always be immediately available in the operating room for these cases). The rigid bronchoscope, even if passed into only one mainstem bronchus, can be used for oxygenation during resuscitation (see "Rigid Bronchoscopy," earlier).[227] Once adequate oxygenation has been restored, the rigid bronchoscope can be used to position an airway exchange catheter over which an endotracheal tube is passed after the bronchoscope is withdrawn. An alternative technique to secure the airway with rigid bronchoscopy is to first mount an endotracheal tube over a small rigid bronchoscope (e.g., 6 mm) and then perform rigid bronchoscopy using the bronchoscope to deliver the tube distal to the obstruction.[228]

Institution of femorofemoral CPB before induction of anesthesia is a possibility for some adult patients who are "unsafe" for NPIC general anesthesia. The concept of CPB "standby" during attempted induction of anesthesia is fraught with danger[229] because there is not enough time after a sudden airway collapse to establish CPB before hypoxic cerebral injury occurs.[230] Other options for "unsafe" patients include local anesthetic biopsy of the mediastinal mass or biopsy of another node (e.g., supraclavicular), preoperative radiotherapy with a nonirradiated "window" for subsequent biopsy, preoperative chemotherapy or short-course corticosteroids, and CT-guided biopsy of mass or drainage of a cyst. The salient points in managing a patient with an anterior or superior mediastinal mass include the following[231]:

1. In virtually all children and adults with a mediastinal mass diagnostic procedures and imaging and can be performed, if necessary, without subjecting the patient to the risks of general anesthesia.[232]
2. An extrathoracic source of tissue for diagnostic biopsy (pleural effusion or extrathoracic lymph node) should be sought as an initial measure in every patient.
3. Regardless of the proposed diagnostic or therapeutic procedure, the flat, supine position is never mandatory.
4. In the high-risk child (Table 59-29) without extrathoracic lymphadenopathy or a pleural effusion, prebiopsy corticosteroid therapy is justifiable.[233] In this case, coordination with oncologist, surgeon, and anesthesiologist is essential to organize timing of the biopsy. An alternative to preoperative corticosteroids in the cooperative high-risk patient includes irradiating the tumor while leaving a small area covered with lead for subsequent biopsy.

Table 59-29 Predictors of Airway Compromise in Children with a Mediastinal Mass

Anterior location
Histologic diagnosis of lymphoma
Superior vena cava syndrome
Radiologic evidence of major vessel compression or displacement
Pericardial or pleural effusion

Based on Lam JC, Chui CH, Jacobsen AS, et al. When is a mediastinal mass critical in a child? An analysis of 29 patients. Pediatr Surg Int 20:180, 2004.

With improved awareness of the risk of acute intraoperative airway obstruction in these patients, life-threatening events are now less likely to occur in the operating room. In children, these events now tend to occur preoperatively if the patient is forced to assume a supine position for imaging. In adults, acute airway obstruction is now more likely to occur postoperatively, in the recovery room.[234] Vigilance must be maintained throughout the entire perioperative period.

Thymectomy for Myasthenia Gravis

Myasthenia gravis is a disease of the neuromuscular junction; affected patients have weakness due to a decreased number of acetylcholine receptors at the motor end plate.[235] Patients may or may not have an associated thymoma. Thymectomy is frequently performed to induce clinical remission, even in the absence of a thymoma. The effects of muscle relaxants are modified by this disease; myasthenic patients are resistant to succinylcholine and extremely sensitive to nondepolarizing blockers (see Chapter 29). Thymectomy may be performed via full or partial sternotomy or a minimally invasive approach via a transcervical incision or VATS. For thymectomy with a thymoma, a sternotomy is used. In the absence of an identifiable tumor, minimally invasive techniques are commonly used. Ideally, the use of neuromuscular relaxation is avoided. Induction of anesthesia with propofol, remifentanil, and topical anesthesia of the airway facilitates intubation without the use of muscle relaxants. Alternatively, inhalational induction with a halogenated agent such as sevoflurane may be performed.[236] For sternotomy, combined general and thoracic epidural anesthesia is a useful technique.

Most patients take pyridostigmine, an oral anticholinesterase, and many patients are on immunosuppressive medication (e.g., corticosteroids). On the day of surgery, pyridostigmine dosing should ensure that the patient's usual regimen is provided during the immediate perioperative period. A few patients require intravenous dosing with neostigmine until they are able to resume oral intake of pyridostigmine. A scoring system was devised for prediction of the need for prolonged mechanical ventilation after thymectomy via sternotomy. Among the criteria that contributed to the predicted need for support were disease duration longer than 6 years, chronic respiratory illness, pyridostigmine dosage greater than 750 mg/day, and vital capacity less than 2.9 L. The relevance of this score has diminished with better preoperative preparation and minimally invasive surgery.[237] Referral for surgery early in the course of the disease and stabilization of symptoms with medication and plasmapheresis, combined with increased use of minimally invasive approaches, have made the need for postoperative ventilation infrequent. In optimized patients, mean hospital length of stay can be reduced to 1 day after minimally invasive, and 3 days after trans-sternal, thymectomy.[238] Patients should remain on their full medical regimen postoperatively. The remission from myasthenia gravis after thymectomy occurs slowly over a period of months to years.

Postoperative Management

Early Major Complications

There are multiple potential major complications that can occur in the immediate postoperative period after thoracic surgery, such as torsion of a remaining lobe after lobectomy, dehiscence of a bronchial stump, or hemorrhage from a major vessel. Fortunately these are infrequent, and when they do occur, the principles of management are as outlined earlier for common and specific procedures. Among these possible complications, two will be discussed in more detail: respiratory failure, because it is the most common cause of major morbidity after thoracic surgery, and cardiac herniation, because although it is rare, it is usually fatal if not quickly diagnosed and appropriately treated.

Respiratory Failure

Respiratory failure is a leading cause of postoperative morbidity and mortality in patients undergoing major lung resection. Acute respiratory failure after lung resection is defined as the acute onset of hypoxemia ($Pao_2 < 60$ mm Hg) or hypercapnia ($Paco_2 >$ 45 mm Hg) or the use of postoperative mechanical ventilation for more than 24 hours or reintubation for controlled ventilation after extubation. The incidence of respiratory failure after lung resection is between 2% and 18%. Patients with decreased respiratory function preoperatively are at increased risk of postoperative respiratory complications. In addition, age, presence of coronary artery disease, and the extent of lung resection play major roles in predicting postoperative mortality and morbidity. Crossover contamination, owing to failure of lung isolation intraoperatively during lung resection in patients with contaminated secretions, can result in contralateral pneumonia and postoperative respiratory failure.[239] Mechanical ventilation during the postoperative period after lung resection is associated with the risk of acquired nosocomial pneumonia and bronchopleural fistula.

Decreased pulmonary complications in high-risk patients are associated with the use of thoracic epidural analgesia during the perioperative period.[2] The prevention of atelectasis and secondary infections has been attributed to better preservation of the functional residual volume, efficient mucociliary clearance, and alleviation of the inhibiting reflexes acting on the diaphragm in patients receiving epidural analgesia.[240] Chest physiotherapy, incentive spirometry, and early ambulation are crucial to minimize pulmonary complications after lung resection. For an uncomplicated lung resection, early extubation is desirable to avoid potential complications that can arise due to prolonged intubation and mechanical ventilation. Current therapy to treat acute respiratory failure is supportive therapy that attempts to provide better oxygenation, treat infection, and provide vital organ support without further damaging the lungs.

Cardiac Herniation

Acute cardiac herniation is an infrequent, but well-described complication of pneumonectomy when the pericardium is incompletely closed or the closure breaks down.[241] It usually occurs immediately or within 24 hours after chest surgery and is associated with a greater than 50% mortality. Cardiac herniation may also occur after a lobar resection with pericardial opening or in other chest tumor resections involving the pericardium or in trauma.[242] When cardiac herniation occurs after a right pneumonectomy the clinical presentation is due to impairment of the venous return to the heart with a concomitant increase in central venous pressure, tachycardia, profound hypotension, and shock. An acute superior vena cava syndrome ensues due to the torsion of the heart.[243] In contrast, when the cardiac herniation occurs after a left-sided pneumonectomy there is less cardiac rotation but the edge of the pericardium compresses the myocardium. This may lead to myocardial ischemia, the development of arrhythmias, and ventricular outflow tract obstruction. Cardiac herniation occurs after chest closure due to the pressure differences between the two hemithoraces. This pressure difference may result in the heart being extruded through a pericardial defect.

Management for a patient with a cardiac herniation should be considered as dire emergent surgery. The differential diagnosis should include massive intrathoracic hemorrhage, pulmonary embolism, or mediastinal shift from improper chest drain management. Early diagnosis and immediate surgical treatment by relocation of the heart to its anatomic position with repair of the pericardial defect or by the use of analogous or prosthetic patch material is key to patient survival. Because these patients have undergone a previous thoracotomy, all precautions should be taken for a "redo" exploration. This includes the use of large-bore intravenous catheters and an arterial line. Maneuvers to minimize the cardiovascular effects include positioning the patient in the full lateral position with the operated side up. Because time is crucial, an SLT is used. Vasopressors or inotropes or both are required to support the circulation while exploration takes place. The use of TEE intraoperatively, after resuscitation and relocation of the heart, can be considered during pericardial patch repair to prevent excessive compression of the heart by the repair.[244] In general, patients undergoing an emergency thoracic re-exploration remain intubated and are transferred to the intensive care unit postoperatively.

Postoperative Analgesia (See Chapter 87)

Studies before 1990 consistently report a 15% to 20% rate of major respiratory complications (atelectasis, pneumonia, respiratory failure) within the first 3 days after thoracic surgery.[1] This time of onset may relate to the unique pattern of recovery of pulmonary function after thoracotomy, which shows a delay in the initial 72-hour postoperative period that is not seen with other major surgical incisions. The incidence of post-thoracotomy respiratory complications has shown an overall decline to less than 10% while the cardiac complication rate has not changed.[2] Improvements in postoperative care, specifically pain management, are the major cause of this decline.

There are multiple sensory afferents that transmit nociceptive stimuli after thoracotomy (Fig. 59-51). These include the incision (intercostal nerves T4-T6), chest drains (intercostal nerves T7-T8), mediastinal pleura (vagus nerve, CN X), central diaphragmatic pleura (phrenic nerve, C3-C5),[245] and ipsilateral shoulder (brachial plexus). There is no one analgesic technique that can block all these various pain afferents, so analgesia should be multimodal. The optimal choice for an individual patient will depend on patient factors (contraindications, preferences), surgical factors (type of incision), and system factors (available equipment, monitoring, nursing support). The ideal post-thoracotomy

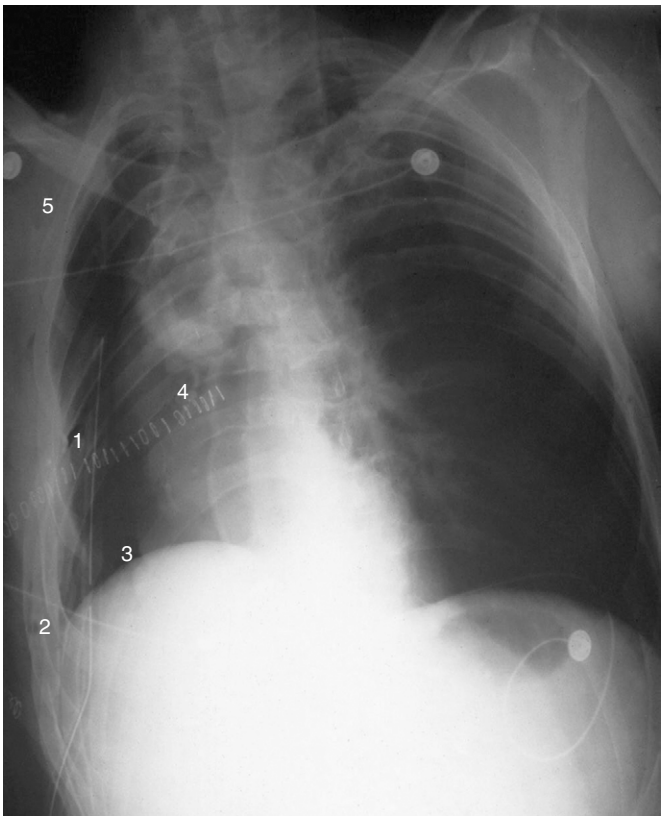

Figure 59-51 Multiple sources of afferent transmission of pain sensations after thoracotomy. 1, Intercostal nerves at the site of the incision (usually T4-6); 2, intercostal nerves at the site of chest drains (usually T7-8); 3, phrenic nerve afferents from the dome of the diaphragm; 4, vagal nerve innervation of the mediastinal pleura; 5, brachial plexus.

analgesic technique will include three classes of drugs: opioids, anti-inflammatory agents, and local anesthetics.

Systemic Analgesia

Opioids

Systemic opioids alone are effective in controlling background pain, but the acute pain component associated with cough or movement requires plasma levels that produce sedation and hypoventilation in most patients. Even when administered by patient-controlled devices, pain control is generally poor[246] and patients have interrupted sleep patterns when serum opioid levels fall below the therapeutic range.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs can reduce opioid consumption more than 30% after thoracotomy and are particularly useful treating the ipsilateral shoulder pain that is often present postoperatively and is poorly controlled with epidural analgesia. NSAIDS act through reversible inhibition of cyclooxygenase, which has anti-inflammatory and analgesic effects but can also be associated with decreased platelet function, gastric erosions, increased bronchial reactivity, and decreased renal function. Acetaminophen is an antipyretic/analgesic with weak cyclooxygenase inhibition and can be administered orally or rectally in doses up to 4 g/day. It is effective against shoulder pain and has a low toxicity compared with more potent cyclooxygenase-inhibiting NSAIDs.[247]

Ketamine

Low-dose intramuscular ketamine (1 mg/kg) is equivalent to the same dose of meperidine and causes less respiratory depression. Ketamine can also be administered as a low-dose intravenous infusion and may be useful in patients whose condition is refractory to other therapies or when there is a contraindication to more common techniques.[248] The possibility of psychomimetic effects with ketamine is always a concern but is rarely seen with analgesic, subanesthetic doses.

Dexmedetomidine

Dexmedetomidine, a selective adrenergic α_2-receptor agonist, has been reported as a useful adjunct for post-thoracotomy analgesia and can significantly decrease the requirement for opioids when used in combination with epidural local anesthetics. Maintenance infusion doses for analgesia in children and adults are in the range of 0.3 to 0.4 µg/kg/hr.[249] It is associated with some hypotension, but it seems to preserve renal function.

Local Anesthetics/Nerve Blocks

Intercostal Nerve Blocks

Regional blocks of the intercostal nerves supplying the dermatomes of the surgical incision can be an effective adjunct to methods of post-thoracotomy analgesia (see Chapter 52). These can be done percutaneously or under direct vision when the chest is open. The duration of analgesia is limited to the duration of action of the local anesthetic used and the blocks will need to be repeated to have any useful effect on postoperative lung function. Indwelling intercostal catheters are an option, but they can be difficult to position reliably percutaneously. Nerve blocks are useful supplements for the pain associated with the multiple small port incisions and chest drains following VATS. It is important to avoid injection into the intercostal vessels, which are adjacent to the nerve in the intercostal groove. It is also important to place the block near the posterior axillary line to be certain to block the lateral cutaneous branch of the intercostal nerve. Total bupivacaine dose for a single session of blocks should not exceed 1 mg/kg (e.g., for a 75-kg patient: 3 mL bupivacaine 0.5% with epinephrine 1:200,000 at each of five levels).

Intrapleural Analgesia

Intrapleural local anesthetics produce a multilevel intercostal block. The analgesia is extremely dependent on patient position, infusion volume, chest drains, and the type of surgery. In spite of occasional successes, most clinicians have not found the reliability of intrapleural techniques adequate to justify their use on a routine basis.[250]

Other Techniques

Application of a −60°C probe to the exposed intercostal nerves intraoperatively produces an intercostal block that can persist for up to 6 months. This can be moderately efficient to decrease postoperative pain but is associated with an incidence of chronic neuralgia that has led many centers to abandon the technique. Transcutaneous electrical nerve stimulation (TENS) may be useful in mild to moderate pain but is ineffective when pain is severe.[251]

Epidural Analgesia

The routine use of neuraxial analgesia for post-thoracotomy patients is a relatively recent concept. Spinal injection of opioids can have a duration of analgesia that approaches 24 hours after thoracotomy. Because of the concerns of possible infection with subarachnoid catheters and the need to repeat spinal injections, investigation and therapy have focused on epidural techniques. A meta-analysis of respiratory complications after various types of surgery has shown that epidural techniques reduce the incidence of respiratory complications.[252] Lumbar epidural analgesia has gradually been replaced by thoracic epidural analgesia for thoracic surgery in the 1990s. In a survey of U.S. teaching hospitals,[253] the majority of thoracotomies received a thoracic epidural between T3 and T8, with infusions of bupivacaine plus either fentanyl or hydromorphone. The evolution of routine thoracic epidural infusion analgesia has been delayed pending advances in technology and knowledge. The technology required was the development of portable, safe, and reliable infusion pumps, which did not delay postoperative ambulation. The knowledge required was in several areas: First, the importance of the synergy between local anesthetics and opioids for segmental thoracic analgesia was not appreciated originally. Combinations of local anesthetic and opioids provide better epidural analgesia at lower doses than either drug alone.[254] Second, the concern for patient risks due to postoperative neuraxial analgesia delayed widespread acceptance. The risks of respiratory depression and hemodynamic instability are largely due to the use of bolus injection techniques. The use of epidural infusions has an excellent record for patient safety when used on routine postoperative surgical wards.[255] The risk of accidental direct spinal cord trauma from thoracic epidural needles and catheters slowed the adoption of this technique by many anesthesiologists. A study of more than 4000 thoracic epidural analgesic placements in a German teaching hospital[256] documented no permanent neurologic sequelae and a 1% incidence of accidental dural puncture that was less than the expected risk of dural puncture for lumbar epidurals. Third, many anesthesiologists believe that thoracic epidural catheter placement is a difficult technique. The use of a paramedian approach to the epidural space in the midthoracic levels (Fig. 59-52) has improved the success rate for many clinicians.

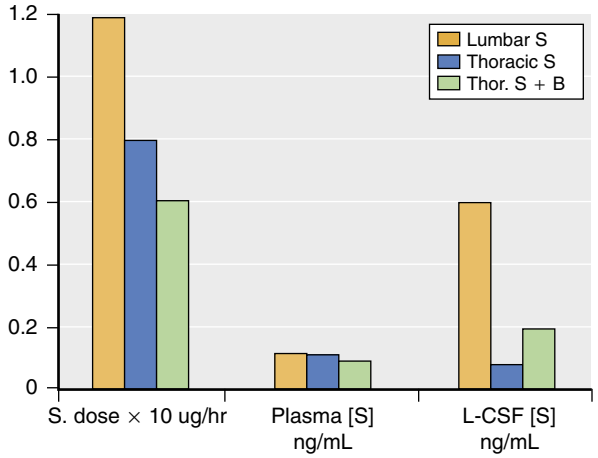

Figure 59-53 Differences in the pharmacology of post-thoracotomy epidural infusions of lumbar sufentanil (Lumbar S), thoracic sufentanil (Thoracic S), and thoracic sufentanil plus bupivacaine (Thor. S + B). Thoracic S + B produced significantly superior analgesia with movement with lower total sufentanil dosage (S. dose) and lower plasma levels (Plasma [S]) than the other two techniques. Note that, in spite of lower dosage, Thoracic S + B patients had higher mean lumbar cerebrospinal fluid (CSF) sufentanil levels than the thoracic sufentanil group measured by separate lumbar punctures at 24 and 48 hours postoperatively. This suggests a pharmacokinetic mechanism with local anesthetics that facilitates transfer of epidural opioid into the CSF. (*Based on data from Hansdottir V, Wostenborghs R, Nordberg G: The pharmacokinetics of continuous epidural sufentanil and bupivacaine infusion after thoracotomy. Anesth Analg 83:394, 1996.*)

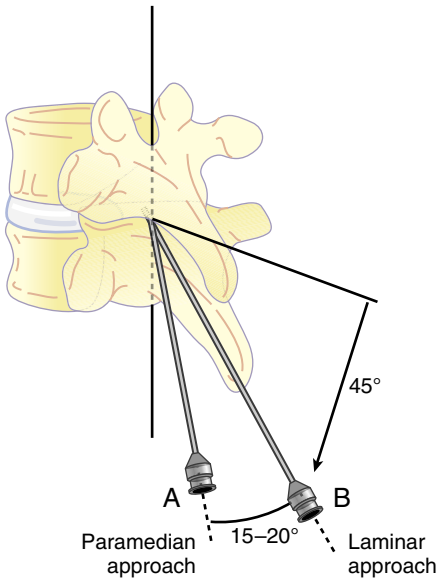

Figure 59-52 The paramedian approach (A) to the epidural space is now favored by most anesthesiologists at the midthoracic levels. The needle is inserted 1 cm lateral to the superior tip of the spinous process and then advanced perpendicular to all planes to contact the lamina of the vertebral body immediately below. The needle is "walked" up the lamina at an angle rostrally (45 degrees) and medially (20 degrees) until the rostral edge of the lamina is felt. The needle is advanced over the edge of the lamina, seeking a loss of resistance on entering the epidural space after transversing the ligamentum flavum. The laminar approach (B) is favored by some practitioners. The needle is inserted next to the rostral edge of the spinous process and advanced straight without any angle from the midline. (*Reprinted with permission from Ramamurthy S: Thoracic epidural nerve block. In Waldman SD, Winnie AP [eds]: Interventional Pain Management. Philadelphia, WB Saunders, 1996.*)

Research has shed light on the pharmacology that underlies the synergy between local anesthetics and opioids to produce segmental epidural analgesia. In a double-blind randomized study, Hansdottir and coworkers[257] compared epidural infusions of lumbar sufentanil, thoracic sufentanil, and thoracic sufentanil plus bupivacaine for post-thoracotomy analgesia. Infusions were titrated for equianalgesia at rest. Thoracic sufentanil plus bupivacaine provided significantly better analgesia with movement and less sedation than the other infusions. Although sufentanil dosages and serum levels were significantly lower in the combined sufentanil plus bupivacaine group than in the other two groups, lumbar cerebrospinal fluid levels of sufentanil at 24 and 48 hours were higher in the combined group than in the thoracic sufentanil group (Fig. 59-53). This suggests that the local anesthetic facilitates entry of the opioid from the epidural space into the cerebrospinal fluid.

In patients with severe emphysema, thoracic epidural analgesic doses of bupivacaine do not cause any significant reduction in lung mechanics or increase in airway resistance.[258] In volunteers, a thoracic level of epidural blockade increases FRC.[259] This increase is largely due to an increase in thoracic gas volume caused by a fall in the resting level of the diaphragm without a fall in tidal volume. Although it is possible to deliver an opioid to the spinal cord receptors via a lumbar epidural catheter in adequate amounts for thoracic analgesia, the beneficial and synergistic effects of local anesthetics on respiratory mechanics require a thoracic epidural catheter.

Differences in lipid solubility that create relatively minor clinical differences in the effects of opioids when used systemically cause major differences in the effects of these same opioids when used neuraxially (Fig. 59-54). The highly lipid-soluble agents (e.g., fentanyl, sufentanil) are associated with narrow dermatomal spread, rapid onset, and low incidence of pruritus/nausea and can be potentiated by epinephrine. However, these lipid-soluble agents have significant absorption and systemic effects when used as epidural infusions.[260] For incisions that cover many dermatomes (e.g., sternotomy) or for procedures that have combined abdominal and thoracic incisions (e.g., esophagectomy) the hydrophilic opioids (e.g., morphine, hydromorphone) are preferable.

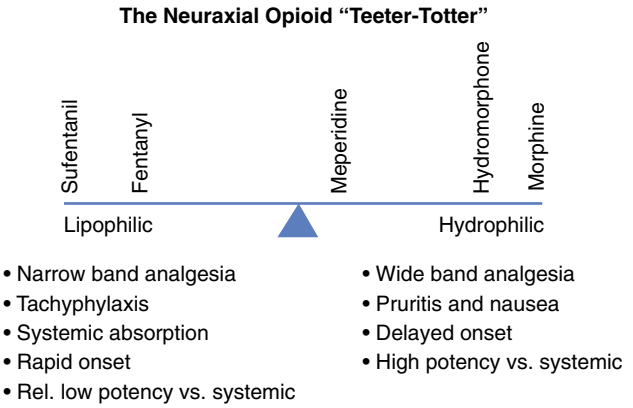

Figure 59-54 The neuraxial opioid "teeter-totter." When choosing an opioid to use for epidural analgesia the anesthesiologist needs to balance the pros and cons of each agent in the clinical context. A major pharmacokinetic factor that determines the effects and side effects of the neuraxial opioids is their lipid solubility. Low-lipid-solubility agents (i.e., hydrophilic, e.g., morphine) tend to produce a wider band of analgesia with slower onset and offset and more minor side effects. Highly lipid-soluble (lipophilic) agents can cause central nervous system effects from systemic absorption when used for prolonged periods, and patients develop tachyphylaxis. Meperidine has a lipid solubility toward the middle of the range, but the accumulation of active metabolites is a concern. Patient factors to be weighed in choosing a neuraxial opioid include the rostral-caudal width of the analgesia band required (thoracotomy versus sternotomy versus thoracoabdominal incision) and the anticipated duration of the epidural infusion. (*From Conacher ID, Slinger PD: Pain management. In Kaplan J, Slinger P [eds]: Thoracic Anesthesia, 3rd ed. Philadelphia, Churchill Livingstone, 2003.*)

Paravertebral Block

The paravertebral space is a potential space deep to the endothoracic fascia that the intercostal nerve traverses as it passes form the intervertebral foramen en route to the intercostal space (see Fig. 59-55). A catheter can be placed in the thoracic paravertebral space either percutaneously or by approaching the space anteriorly and directly when the chest is open intraoperatively (see Chapter 52).

For the open direct-vision technique, an epidural catheter is first passed into the open hemithorax via a Tuohy needle through an intercostal space in the lateral chest wall. To site the catheter, the surgeon then makes a small incision in the parietal pleura and fascia covering the paravertebral gutter and, with blunt dissection, threads the tip of the catheter close to the neurovascular bundle of the next cephalad space (Fig. 59-56).[261] An absorb-

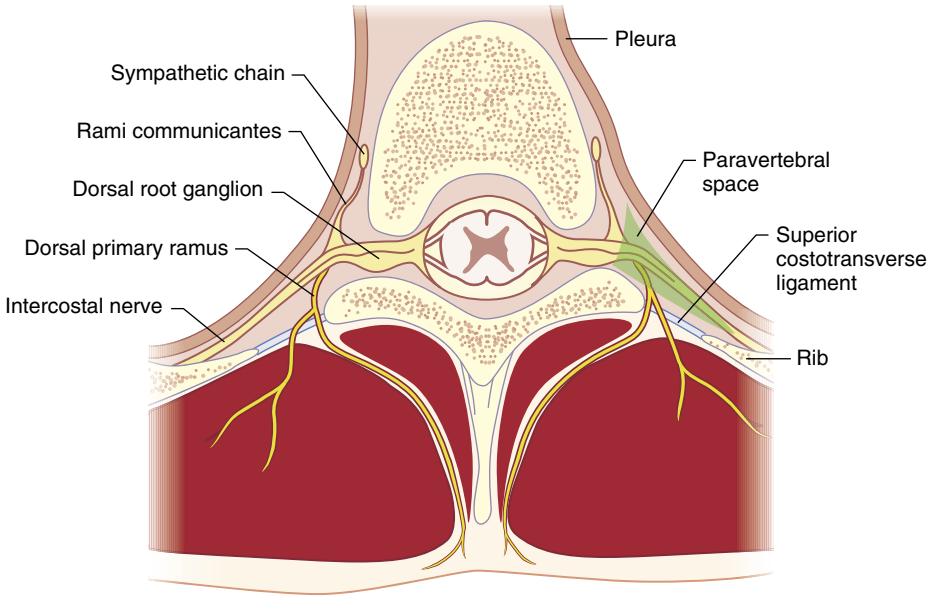

Figure 59-55 Diagram of the paravertebral space. The space is bounded medially by the vertebral body, posteriorly by the costotransverse ligaments and the heads of the ribs, and anteriorly by the endothoracic fascia and parietal pleura. (*From Conacher ID, Slinger PD: In Kaplan J, Slinger P [eds]: Thoracic Anesthesia, 3rd ed. Philadelphia, Churchill Livingstone, 2003.*)

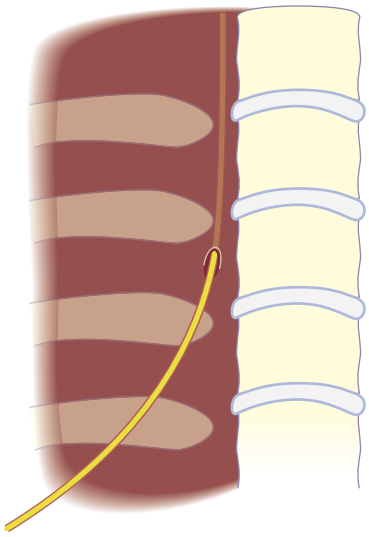

Figure 59-56 A method of open direct-vision placement of a paravertebral catheter intraoperatively. The epidural catheter is passed into the paravertebral space through a small defect created in the extrapleural (endothoracic) fascia. The proximal end of the catheter is then brought out of the chest through a separate needle puncture in an intercostal space near the chest drains. (*From Conacher ID, Slinger PD: In Kaplan J, Slinger P [eds]: Thoracic Anesthesia, 3rd ed. Philadelphia, Churchill Livingstone, 2003.*)

able suture is often used to reseal the wound and limit the leakage of local anesthetic.

There is also a combined percutaneous/direct-vision method in which the tip of the Tuohy needle is advanced percutaneously into the paravertebral space under direct vision either during open thoracotomy or VATS. The tip of the needle is seen to enter the paravertebral space and the pleura is not punctured. Saline is injected via the Tuohy needle to hydrodissect the paravertebral space, and an epidural catheter is passed into the pocket that has been created in the paravertebral space and then secured at the skin.

Paravertebral local anesthetics provide a reliable multilevel intercostal blockade that tends to be unilateral with a low tendency to spread to the epidural space. Clinically, the analgesia is comparable to that from epidural local anesthetics.[262] Studies comparing paravertebral versus thoracic epidural analgesia for thoracotomies have suggested the following advantages for paravertebral blockade[263]: comparable analgesia, fewer failed blocks, decreased risk of neuraxial hematoma, and less hypotension, nausea, or urinary retention. Because there is the option to place the paravertebral catheter under direct vision, this may contribute to the lower incidence of failed blocks versus thoracic epidural analgesia.

Paravertebral infusions in combination with NSAIDs and systemic opioids are a reasonable alternative to epidural techniques in children or patients with contraindications to neuraxial blockade.[56] When common therapeutic doses are used (e.g., 0.1 mL/kg/hr of bupivacaine 0.5%), serum bupivacaine levels can approach toxic levels by 4 days.[264] An alternative regimen for paravertebral infusions is lidocaine 1%, 1 mL/10 kg/hr, maximum 7 mL/hr. It has not yet been demonstrated if paravertebral analgesia can contribute to a decrease in respiratory morbidity in high-risk cases, which has been shown for thoracic epidural analgesia.[265]

Postoperative Pain Management Problems

Shoulder Pain

After thoracotomy up to 80% of patients with a functioning epidural block describe ipsilateral shoulder pain. Shoulder pain occurs after both thoracotomy and VATS and is thought to be primarily referred pain of diaphragmatic irritation transmitted by phrenic nerve afferents.[246] Other factors, including position during operation and major bronchus transection, have been incriminated, although the mechanisms are not clear. Several other causes of shoulder pain should be considered when evaluating a patient with shoulder pain postoperatively:

1. A chest drain placed too far into the apex of the hemithorax will irritate the parietal pleura and cause shoulder pain (Fig. 59-57). The postoperative chest radiograph should be checked and the chest drain partially withdrawn if this is suspected as the cause.
2. The posterior end of a large posterolateral thoracotomy incision may not be well blocked by a functioning thoracic epidural block, and this may be described as shoulder pain. The extent of the sensory block should be determined on the skin. If inadequate block is a possibility, the thoracic epidural analgesia can be "topped up."
3. Patients with chronic arthralgia of the shoulder may experience an exacerbation from the intraoperative positioning of the ipsilateral arm. It is important to ask about shoulder problems preoperatively and to position the arms in a manner that does not exacerbate shoulder problems.

Shoulder pain is refractory to thoracic epidural analgesia and requires anti-inflammatory agents with or without opioids.

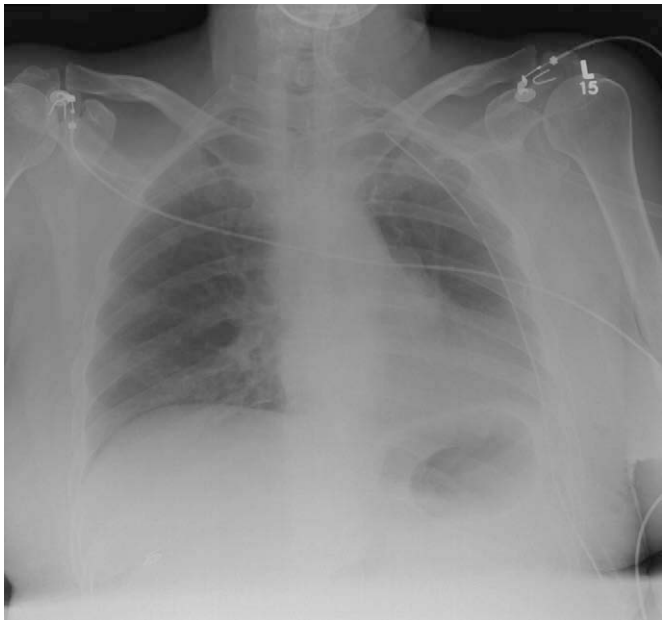

Figure 59-57 Postoperative chest radiograph of a patient who complained of left shoulder pain after a left VATS lobectomy. This pain was due to irritation of the apical parietal pleura by a chest drain that was inserted too far into the hemithorax. The pain resolved when the chest drain was partially withdrawn

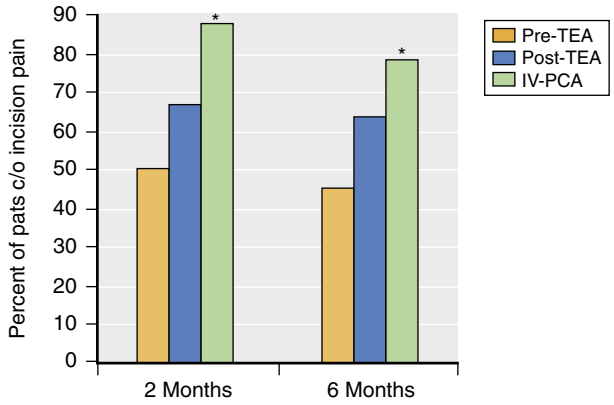

Figure 59-58 A comparison of the effects of three different analgesia regimens on the percentage of patients complaining of incisional pain (%pats c/o incis. pain) 2 and 6 months after thoracotomy. Pre-TEA, patients treated with a thoracic epidural infusion of local anesthetic and opioid before, during,and after surgery; Post-TEA, a group of patients in whom the TEA was only used postoperatively; IV-PCA, a group of patients who received postoperative intravenous patient-controlled opioid analgesia. The use of TEA, started before the surgical incision, was associated with less short- and long-term pain than IV-PCA (* = $P < .05$). (*Based on data from Sentürk M, Ozcan PE, Talu GK, et al: The effects of three different analgesia techniques on long-term postthoracotomy pain. Anesth Analg 94:11, 2002.*)

Shoulder pain is usually transient and often is resolved completely by the second postoperative day. There are several reports of the use of nerve blocks to treat post-thoracotomy shoulder pain. Phrenic nerve infiltration and interscalene brachial plexus block[266] have had some success but carry a risk of causing diaphragm dysfunction.

Post-thoracotomy Neuralgia and Chronic Incisional Pain

The transition of acute pain syndromes, associated with thoracic surgery, to chronic ones such as post-thoracotomy neuralgia may be partially preventable with analgesic regimens that prophylactically block nerves and desensitize peripheral nerve endings and dorsal horn cells of nerves that are damaged by surgery (Fig. 59-58).

Management of Opioid-Tolerant Patients

The opioid-tolerant patient requiring thoracic surgery presents a significant challenge. Patients may be using physician-prescribed opioids for pain related to their thoracic pathologic process or other chronic pain syndromes. Active abusers of narcotics or those in a rehabilitation program, receiving daily methadone, also are included in this group. Whenever possible, patients should take their regular analgesia or methadone preoperatively; otherwise, substitute opioids must be provided. The opioid doses required to produce adequate postoperative analgesia are increased.

A multimodal analgesic regimen is optimal. A choice must be made regarding the method of increased opioid delivery, either systemically or through an epidural solution. Increased narcotic may be provided in the epidural solution, or standard narcotic concentrations may be used in the epidural solution with additional systemic narcotic. De Leon-Casasola[267] reports that higher epidural doses of opioid are able to curtail the appearance of narcotic withdrawal in most patients. More frequently, the patient receives a standard or slightly increased concentration of opioid in the epidural infusion and additional systemic opioid to minimize the occurrence of withdrawal. A convenient way to provide drug delivery in patients not immediately able to take oral medication is in the form of a transdermal fentanyl patch. Systemic opioids can be provided as a continuous intravenous infusion or in oral format.

Patient-controlled analgesic techniques are often difficult to manage in these patients, and they may be best managed with fixed dosage regimens that are modified as needed. Ultimately, after dose titration, the patient may be receiving both increased epidural opioid and greater than preoperative doses of systemic opioid, without significant side effects. Patients in whom epidural bupivacaine-morphine analgesia is inadequate may respond to a switch to bupivacaine-sufentanil.[268] Patients in drug rehabilitation programs with methadone may be reluctant to modify their methadone dose perioperatively, having struggled to establish a stable dose in the past. They frequently can take their full methadone dose throughout the perioperative period.

Supplemental therapies to be considered for these patients include adding epinephrine, 5 µg/mL, to the epidural infusion solution and the addition of low-dose continuous intravenous ketamine infusions.[269] All opioid-tolerant patients require frequent adjustment of analgesic doses. Despite this, pain scores of 4 to 5/10 with movement are often the lowest achievable. The increased analgesic requirements of opioid-tolerant patients are for a longer duration postoperatively than the usual need for analgesia in opioid-naive patients.

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60 Anesthesia for Cardiac Surgical Procedures

Key Points

1. The most common causes of central nervous system injury or dysfunction in cardiac surgical patients are thought to be microemboli and macroemboli.
2. After coronary revascularization, mortality was far lower in patients with normal renal function (0.9%) than in patients with acute renal failure (63%).
3. In addition to activating the extrinsic and intrinsic hemostatic pathways, cardiopulmonary bypass (CPB) directly affects platelet function through the effects of hemodilution, hypothermia, and contact activation by bypass circuit materials.
4. When choosing anesthetic agents and doses during induction and maintenance, one should consider any pharmacodynamic properties that might affect blood pressure, heart rate, or cardiac output, as well as the desirability of "early" extubation (i.e., within a few hours after the operation is completed).
5. Patients undergoing "redo" cardiac surgery (i.e., those who have had a previous median sternotomy) warrant special concern about the possibility of sudden massive hemorrhage.
6. Right ventricular dysfunction or failure may also occur after CPB because of inadequate myocardial protection, inadequate revascularization with resultant right ventricular ischemia or infarction, preexisting pulmonary hypertension, intracoronary or pulmonary air embolism, chronic mitral valve disease, or tricuspid regurgitation.
7. Numerous clinical approaches have been shown to measurably reduce the inflammatory response in cardiac surgical patients: modification of surgical and perfusion techniques, modification of circuit components, and pharmacologic strategies.
8. No single anesthetic "recipe" is suitable for all patients undergoing coronary artery bypass graft (CABG) procedures.
9. Randomized trials comparing off-pump CABG with on-pump CABG have not found convincing or consistent evidence to support one approach over another.
10. Types of procedures that are performed in the cardiac catheterization laboratory include (1) electrophysiologic assessment of rhythm disorders and management by ablation or by implantation of devices, (2) biventricular pacing for heart failure, (3) stenting of abdominal or thoracic aortic aneurysms, (4) balloon dilation and stenting for valvular and subvalvular lesions, and (5) the use of occlusion or umbrella devices to close an atrial or ventricular septal defect or a patent ductus arteriosus. Sedation or anesthesia improves the efficacy and safety of many procedures.
11. Even after uncomplicated cardiac surgery, a midline sternotomy (or thoracotomy) causes a significant reduction in total lung capacity, vital capacity, forced expiratory volume in 1 second, and functional residual capacity.
12. In 2007, the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists published a joint statement on practice guidelines for transfusion and blood conservation in cardiac surgery.

Cardiovascular Disease in the 21st Century

The "Graying" of America

An estimated 79,400,000 American adults (1 in 3) have one or more types of cardiovascular disease (CVD), and of those, 37,500,000 are estimated to be 65 years or older.[1] Data from the Framingham Heart Study of the National Heart, Lung, and Blood Institute (NHLBI), which collected follow-up data from participants for 44 years and from their offspring for 20 years, indicate that the average annual rate of first major cardiovascular events rises from 7 per 1000 for men aged 35 to 44 years to 68 per 1000 for men aged 85 to 94.[2] For women, the rates are comparable but occur approximately 10 years later in life, although this gender gap narrows with advancing age. In 2007, the estimated direct and

indirect cost of CVD in the United States was $431.8 billion.[1] Data for 2004, the most recent available, estimate that 6,363,000 inpatient cardiovascular operations and procedures were performed in the United States.[3] Mortality data show that CVD is the underlying cause of death in 36.3% of the 2,398,000 deaths that occurred in 2004 (1 in every 2.8 deaths) in the United States.[1] In fact, CVD claims more lives each year than cancer, chronic lower respiratory diseases, diabetes mellitus, and accidents combined do.[4] As the U.S. population ages, these proportions will only increase.

Gender and Cardiac Disease

Data indicate that the lifetime risk for CVD is 2 in 3 for men and 1 in 2 for women after 40 years of age.[1] The fact that CVD kills twice as many women as breast cancer does (more than half a million women each year) has led to campaigns such as the NHLBI's *The Heart Truth* campaign and the American Heart Association's *Go Red for Women* campaign.[5-8]

Whether female gender is a risk factor for short- or long-term mortality after cardiac surgery is a subject of ongoing debate. Many studies of in-hospital mortality after coronary artery bypass grafting (CABG) surgery in men versus women have revealed a significantly higher unadjusted in-hospital mortality for women.[9-11] In a study of 15,440 patients, female gender independently predicted higher in-hospital mortality even when all comorbid conditions were taken into account.[11]

Other studies, however, do not show any survival handicap for female cardiac surgical patients. A large study by Koch and colleagues[12] used propensity-matching techniques to show that female gender was not associated with increased in-hospital mortality. Similarly, in other studies that showed a significant unadjusted increase in perioperative mortality in women versus men, this difference was no longer significant when the data were adjusted for age, cardiovascular risk factors, and body size.[13,14]

Several studies of the effects of gender on CABG outcomes have shown that women are more likely than men to need CABG surgery urgently or on an emergency basis.[9,10,14] Urgent or emergency performance of CABG surgery is generally a result of intractable myocardial ischemia or infarction. Therefore, the results of a study by Vaccarino and coworkers,[15] which showed increased in-hospital mortality in women versus men admitted for acute myocardial infarction (MI), are cause for concern. The reason for this difference in mortality is unclear; in some cases, women with significant coronary artery disease may not be appropriately identified and referred for more invasive studies.

In cardiac surgical patients, technical factors undoubtedly play a critical role in determining short- and long-term mortality in patients undergoing CABG.[16] Some studies have noted lower in-hospital mortality in women who undergo off-pump surgical revascularization than in women treated with on-pump surgery.[17-19] However, data on the long-term results of off-pump versus on-pump surgery are not yet available for either gender.

Regarding long-term survival, several studies have found that 5-year post-CABG survival is actually better in women than in men,[13,14,20] even though other studies have shown that women's short-term survival is poorer than men's after CABG.[9-11] Part of the difference in long-term survival may be attributable to preexisting gender differences in longevity: in the United States, women live an average of 5.2 years longer than men.[4] Therefore, it may be that a woman who undergoes CABG surgery is at greatest risk for mortality during the perioperative period. If she can survive this period, however, she should live as long as, if not longer, than a man. Nevertheless, once discharged from the hospital, women apparently have more difficult recovery than men do in terms of their rate of persistent symptoms and hospital readmission.[21]

As further knowledge about gender-specific risk factors accumulates, means may be devised to mitigate these factors and thus improve outcomes.

Genetic Influences on Cardiac Disease

Although mortality from coronary artery disease has decreased in the past 35 years, such mortality has consistently been higher in black patients than white patients. Furthermore, there are racial disparities in outcomes after CABG; both unadjusted mortality and mortality adjusted for patient characteristics are higher in black than in white patients.[22] There is also racial disparity in the use of cardiovascular procedures to address chest pain.[23] In fact, as an unfortunate consequence of the public release of quality information through CABG "report cards" in certain states, institutions and individual surgeons may use "racial profiling" in selecting patients for CABG.[24] For example, in New York State, physician avoidance of racial and ethnic minorities, who may be at higher risk for poor outcomes, may have temporarily widened the disparity in CABG use between white versus black and Hispanic patients.[24] At least one study, however, suggests that racial differences in the frequency of cardiovascular procedures reflect "overuse" among whites rather than "underuse" among blacks.[25]

Patients with complex comorbid conditions are exposed to "controlled trauma" in the cardiac surgical operating room. Genome-wide linkage analysis has been used to identify genetic determinants of patients' responses to this sort of trauma and thus to complex cardiovascular outcomes such as MI and stroke (Fig. 60-1). For example, functional genetic variants in cytokine and leukocyte-endothelial interaction pathways have been shown to be independently associated with the severity of myonecrosis

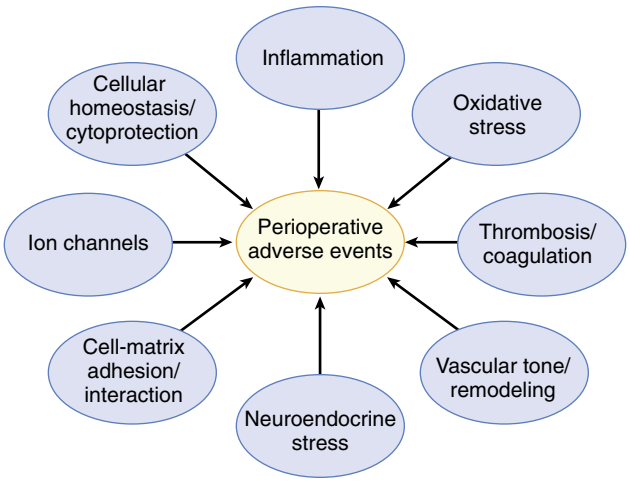

Figure 60-1 Biologic systems and mechanistic pathways genetically associated with perioperative adverse events. *(Redrawn from Podgoreanu MV, Schwinn DA: New paradigms in cardiovascular medicine: Emerging technologies and practices: Perioperative genomics. J Am Coll Cardiol 46:1965-1977, 2005.)*

after cardiac surgery.[26] Additionally, common genetic variants of C-reactive protein and interleukin-6 are significantly associated with risk for stroke after cardiac surgery.[27] C-reactive protein and P-selectin genes may also modulate susceptibility to cognitive decline after cardiac surgery.[28] These findings suggest a pivotal role of inflammation in cardiac surgery–related myocardial and neurologic injury.

Postoperative renal dysfunction, another common complication of cardiac surgery, is not easily predicted from preoperative factors. To address this problem, one study assessed 12 candidate genetic variants and found several alleles that had a strong association with renal injury.[29] When added to the clinical risk factors typically used to predict postoperative renal dysfunction, this genetic information increased predictive accuracy fourfold, but only in whites; there was only a twofold improvement in blacks, suggesting that genetic risk factors may differ among racial groups.

Genetic factors have been associated with other postoperative complications of cardiac surgery as well, including bleeding and coagulopathy[30,31] and respiratory complications that necessitate prolonged mechanical ventilation[32] after cardiac surgery. Additionally, responses to medications commonly used in the perioperative period exhibit genetic variance that can affect morbidity and mortality.[33,34]

Approach to Anesthesia for Adult Cardiac Patients

Preoperative Evaluation, Preparation, and Monitoring

Heart and Vascular System

Electrocardiography

Standard monitoring of cardiac surgical patients via the electrocardiogram (ECG) often involves using the five-lead electrode system (see Chapter 42).

Despite appropriate lead selection and the use of automated ST-segment monitoring, perioperative ECG monitoring has important limitations. Visual inspection of the ECG on the monitor has low sensitivity in diagnosing ischemic changes, and automated ST-segment analysis depends on the computer's ability to accurately set the isoelectric and J-point reference points. During cardiac surgery, the set points should be checked before and after bypass and when there have been any significant persistent changes in the patient's heart rate because the reference points chosen at the beginning of the procedure may not be accurate for conditions that may exist later.

Arterial and Central Venous Pressure Monitoring

Invasive arterial cannulation and monitoring are considered to be a standard of care for cardiac surgical patients. Patient risk factors and comorbid conditions often necessitate real-time, beat-to-beat assessment of arterial perfusion pressure, changes in volume associated with surgery, and arterial blood gases. Furthermore, during nonpulsatile cardiopulmonary bypass (CPB), noninvasive blood pressure recordings are not accurate.

Although the radial artery is the most commonly accessed site, the femoral, brachial, ulnar, dorsalis pedis, posterior tibial, and axillary arteries can be also used. When cannulating a radial artery, one should consider the native state of the collateral circulation in the hand and possible surgical use of a radial artery free graft as an arterial conduit. If a radial arterial graft is to be harvested, it is usually taken from the nondominant hand or arm; thus, the arterial line should be placed on the dominant side.

Central venous pressure (CVP) monitoring and central venous access are essential during cardiac surgery. Central venous catheters, in addition to monitoring CVP, provide portals for volume replacement, pharmacologic therapy, and insertion of other invasive monitors such as pulmonary artery (PA) catheters. An internal jugular vein is most commonly selected because it provides ease of approach and optimal distance from the operative field. A femoral or subclavian vein can be considered as well, but groin access can be challenging in obese patients and may be inappropriate if placement of a femoral bypass cannula or harvesting of a vein graft is necessary. The subclavian approach is also imperfect because it is associated with a greater propensity for catheter obstruction during sternal retraction.

Ultrasound is increasingly being used to guide the placement of central venous catheters and to reduce complications associated with them. In many patients, use of a central venous catheter may offer a better risk-benefit ratio than use of a PA catheter.[35]

Pulmonary Artery Catheterization

The PA catheter is a flow-directed catheter typically placed through a catheter "introducer" in the central venous compartment via the internal jugular, subclavian, or femoral vein (see Chapter 40). Pulmonary capillary wedge pressure (PCWP) can both overestimate and underestimate left ventricular (LV) filling pressure. A summary of these variables is included in Box 60-1. There is some evidence that in certain clinical situations, right

Box 60-1 Conditions Resulting in Discrepancies between Pulmonary Capillary Wedge Pressure and Left Ventricular End-Diastolic Pressure

PCWP > LVEDP

Positive-pressure ventilation

PEEP

Increased intrathoracic pressure

Non-West lung zone III PAC placement

Chronic obstructive pulmonary disease

Increased pulmonary vascular resistance

Left atrial myxoma

Mitral valve disease (e.g., stenosis, regurgitation)

PCWP < LVEDP

Noncompliant left ventricle (e.g., ischemia, hypertrophy)

Aortic regurgitation (premature closure of the mitral valve)

LVEDP > 25 mm Hg

LVEDP, left ventricular end-diastolic pressure; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure; PEEP, positive end-expiratory pressure.

Adapted from Tuman KJ, Carroll CC, Ivankovich AD: Pitfalls in interpretation of pulmonary artery catheter data. Cardiothorac Vasc Anesth Update 2:1, 1991.

ventricular (RV) end-diastolic volume and index correlate better with LV preload and cardiac index (CI) than PCWP does.[36-40]

The risk-benefit ratio involved in use of PA catheter data, including pressures, derived indices, and waveforms, has been a subject of controversy for 3 decades.[41,42] In a review of the literature, Murphy and coauthors[42] reported that since 1970, more than 1500 articles and abstracts have been published that have variously found PA catheters to be beneficial, neutral, or detrimental with respect to patient morbidity and outcome. Large clinical trials have not shown any clear outcome benefits in critically ill patients monitored with PA catheters.[43-46] However, the limitations of trials and studies that have examined the efficacy of PA catheter monitoring include inadequate sample size, lack of randomization, lack of standardized therapeutic intervention guided by PA catheter findings, medically uncertain (unvalidated) treatment goals and therapies, inappropriate use of PA catheters in low-risk patients, and inadequate user knowledge and skill.[42] With the recent, better-constructed clinical trials of PA catheters, the debate will probably continue.

It is acknowledged that there have been only a few randomized trials of goal-directed therapy in cardiac surgical patients.[47,48] Standardization of PA catheter measurements and therapeutic interventions guided by these measurements is needed to fully assess the value of the PA catheter—or any monitor—in improving patient outcome.[41,49] American Society of Anesthesiologists (ASA) practice guidelines for PA catheter use, created by a task force after a review of the literature and expert opinion, concluded that there is incomplete evidence to support the use of PA catheters, primarily because of deficiencies in "study design and performance," and that monitoring with a PA catheter is "both appropriate and necessary in selected surgical patients" based on preexisting patient risk factors (which would increase perioperative risk), procedural factors (major surgical procedures that in and of themselves significantly increase perioperative risk), and practice setting (because the PA catheter is useful only if the physicians and nurses have knowledge of and skill competence with it).[50] Expert opinion does not support routine use of the PA catheter in low-risk patients[35,42] unless it can be justified by clinical judgment and the factors noted by the ASA task force.[50] An optimal risk-benefit ratio may be achieved only by pairing use of the PA catheter in appropriate patients with treatment protocols that have been proved to be effective.[41]

Echocardiography

Since its introduction to operating rooms in the early 1980s, transesophageal echocardiography (TEE) has established itself as extremely helpful both as a monitoring system and as a tool for the hemodynamic management of patients under general anesthesia. The use of TEE to make intraoperative diagnoses is now well established (see Chapter 41).[51]

Intraoperative evaluation of valvular function with the use of TEE has proved to be of immense importance, not only because TEE can directly visualize the cardiac structures but also because it can measure blood flow velocity.[52] Also, TEE is routinely used to monitor for the presence of retained intracardiac air after open chamber procedures such as valvular surgery. Additionally, TEE's ability to image the thoracic aorta in real time is an invaluable aid in correctly positioning intra-aortic balloon pumps (IABPs).[53] Similarly, TEE plays a central role in the insertion of ventricular assist devices (VADs) (please see the later section "Heart Failure").[54]

Evaluation for diastolic dysfunction should be part of the routine echocardiographic examination of cardiac surgical patients. Patients with preexisting diastolic dysfunction are prone to post-CPB complications, including difficulty separating from CPB and the need for more vasoactive support in the intensive care unit (ICU).[55] Figure 60-2 illustrates a practical approach to evaluating diastolic dysfunction.

Contraindications to the placement of a TEE probe may necessitate the use of an alternative imaging modality in certain patients. Intraoperative epicardial echocardiography is an alternative to TEE for assessing the ascending aorta and the aortic arch, as well as for diagnosing intracardiac disease.[52]

Central Nervous System

Many patients undergoing cardiac surgery are at risk for central nervous system (CNS) injury as a result of advanced age and comorbid diseases, in addition to the surgical risk of embolization and hypoperfusion and the inflammatory response associated with CPB. Type I CNS complications (fatal or nonfatal stroke or transient ischemic attack) occur in 3.1% of CABG patients.[56]

To predict stroke after CABG surgery, a risk index has been developed (Fig. 60-3) that uses weighted factors, including age and history of neurologic disease, vascular disease, diabetes, previous CABG, unstable angina, and pulmonary disease.[57] Subsequent research has also identified gender as a risk factor for stroke in cardiac surgical patients.[58,59]

The elevated risk for type I CNS injury in patients undergoing CABG combined with another open cardiac surgical procedure, such as valve repair or replacement, is higher than the risk after CABG alone. Wolman and coworkers[60] reported an 8.4% incidence of type I CNS complications in 273 patients undergoing these combined procedures. Similarly, a large retrospective analysis of more than 16,000 patients in Germany revealed a risk of stroke approaching 10% in patients undergoing double or triple valve replacement without CABG.[61]

The types of CNS injury that cardiac surgical patients may incur are not limited to frank ischemic or embolic stroke but also include more subtle neurocognitive dysfunction, which has a variety of causes (Table 60-1). Newman and associates[62] found that 53% of CABG patients in their study showed evidence of new neurocognitive dysfunction at the time of discharge from the hospital. In fact, after initial improvement in many patients, 42% had persistent neurocognitive deficits 5 years after surgery. Data are inconsistent regarding whether the risk of neurocognitive decline is higher after open versus closed cardiac procedures.[63,64] Furthermore, in a study of CABG versus percutaneous transcoronary angioplasty, new neurocognitive deficits were present with equal incidence after either procedure (at 6 weeks and 1 year).[65]

CNS Monitoring

The most common causes of CNS injury or dysfunction in cardiac surgical patients are thought to be microemboli and macroemboli. Additional causes of and contributors to CNS injury include cerebral hypoperfusion, inflammatory effects, cerebral edema, pharmacologic effects, dysfunction of the blood-brain barrier, and genetic risk factors (see Table 60-1). Increasing understanding of the etiology of injury and dysfunction in the CNS has prompted the development of methods to monitor intraoperative brain function and guide interventions to ameliorate postoperative focal deficits and cognitive dysfunction. However, widespread application of intraoperative CNS monitoring has lagged because

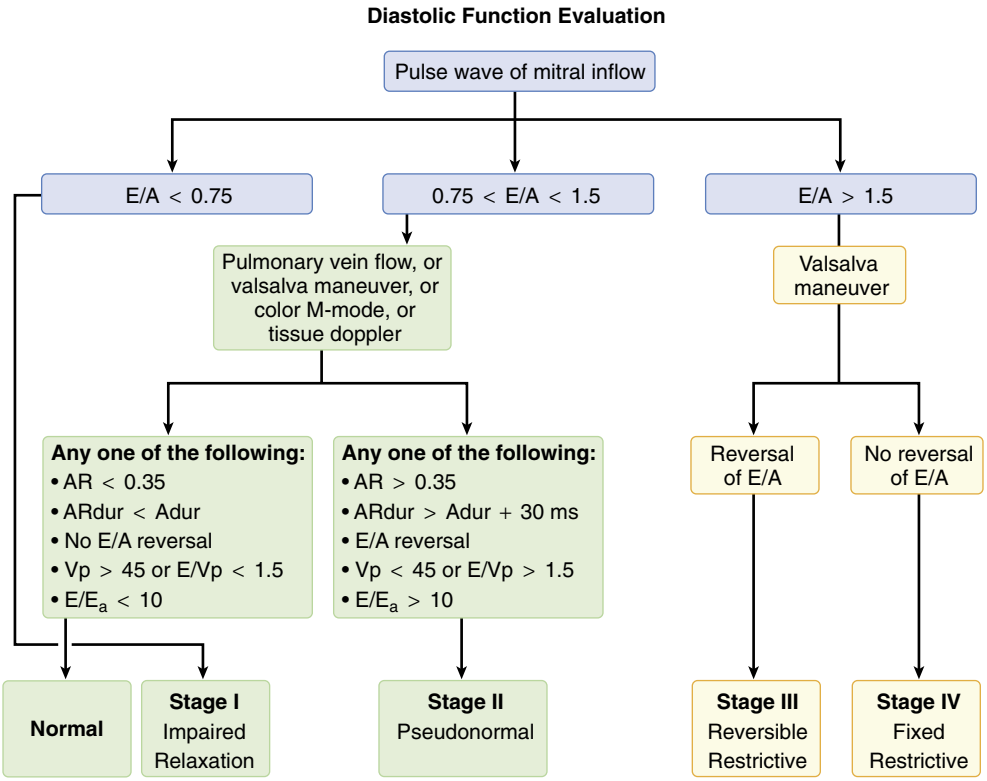

Figure 60-2 Evaluation of diastolic dysfunction based on echocardiographic parameters. A, peak late diastolic transmitral flow velocity; Adur, duration of A wave; AR, peak pulmonary venous atrial reversal flow velocity; ARdur, AR duration; E, peak early diastolic transmitral flow velocity; E_a, peak early diastolic myocardial velocity; V_p, flow propagation velocity. *(Redrawn from Khouri SJ, Maly GT, Suh DD, et al: A practical approach to the echocardiographic evaluation of diastolic function. J Am Soc Echocardiogr 17:290-297, 2004.)*

Risk factor	Score
Age	(age–25) × 1.43
Unstable angina	14
Diabetes mellitus	17
Neurological disease	18
Prior CABG	15
Vascular disease	18
Pulmonary disease	15

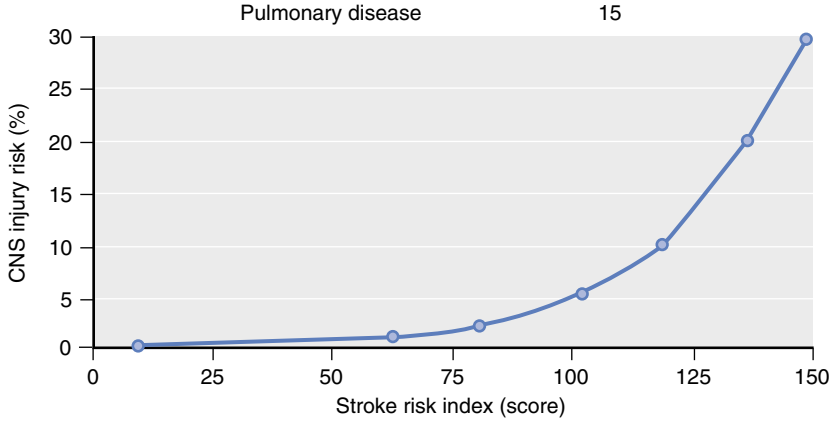

Figure 60-3 Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery. Definitions: Diabetes mellitus—history of either type 1 or type 2 diabetes or insulin use on admission or before surgery; neurologic disease—previous stroke or transient ischemic attack; vascular disease—peripheral vascular disease, known carotid vascular disease, claudication, or vascular surgery; pulmonary diseases—emphysema, chronic bronchitis, asthma, restrictive lung disease. CABG, coronary artery bypass grafting surgery; CNS, central nervous system. *(Adapted with permission from Newman MF, Wolman R, Kanchuger M: Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery. Multicenter Study of Perioperative Ischemia [McSPI] Research Group. Circulation 94[9 Suppl]:II74-II80, 1996.)*

Table 60-1 Causes of Cognitive Dysfunction after Cardiac Surgery

Cause	Possible Settings
Cerebral microemboli	Generated during CPB (mobilization of atheromatous material or entrainment of air from the operative field; injection of gas into the venous reservoir of the CPB apparatus)
Global cerebral hypoperfusion	Hypotension; occlusion by an atheromatous embolus leading to stroke
Inflammation (systemic and cerebral)	Injurious effects of CPB as a result of blood interacting with the foreign surfaces of the pump oxygenator; upregulation of proinflammatory cyclooxygenase mRNA
Cerebral hyperthermia	Hypothermia during CPB; hyperthermia during and after cardiac surgery, e.g., during aggressive rewarming
Cerebral edema	Edema from global cerebral hypoperfusion or hyponatremia; increased cerebral venous pressure from cannula misplacement
Blood-brain barrier dysfunction	Diffuse cerebral inflammation; ischemia from cerebral microembolization or increased intracranial pressure
Pharmacologic influences	Anesthetic-related cognitive damage; necrosis of neonatal brains; proteomic changes
Genetic influences	Effects of single-nucleotide polymorphisms on risk for Alzheimer's disease or for acute coronary syndromes and other thrombotic disorders

CPB, cardiopulmonary bypass; mRNA, messenger ribonucleic acid.
From Kaplan JA, Reich DL, Lake CL, et al (eds): Kaplan's Cardiac Anesthesia, 5th ed. Philadelphia, Elsevier Saunders, 2006, p 671.

no adequately powered, randomized, prospective clinical studies have been conducted to demonstrate the efficacy of any particular monitoring method.[66] The scope of this chapter does not allow an in-depth discussion of each available monitoring technique and does not include monitoring used in aortic surgery, such as somatosensory or motor evoked potentials. However, a brief review of monitors that are commonly used for CNS assessment and protection is appropriate.

Transesophageal and Epiaortic Echocardiography TEE allows direct visualization of the first segment of the ascending aorta, the mid-distal segment of the aortic arch, and a good portion of the descending thoracic aorta. However, the distal segment of the ascending aorta and the proximal midportion of the aortic arch cannot be visualized well because of the interposition of the trachea and bronchi between the TEE probe and these aortic structures. Instead, epiaortic imaging with a hand-held, high-frequency probe placed on the ascending aorta or aortic arch can be used to visualize aortic segments that are in the TEE probe's "blind spot."

Katz and coworkers[67] were among the first investigators to link the echocardiographic finding of protruding atheromas with elevated stroke risk in cardiac surgical patients. The grading system developed for their study is still commonly used to assess the overall atheroma burden of the aorta (Table 60-2). The severity of atheromatous disease of the aorta is a strong predictor of death and stroke after CABG.[68] Patients with atheromatous disease of the ascending aorta tend to be older, have a higher incidence of smoking in their history, have symptoms or a diagnosis of peripheral vascular disease, and have an increased risk for preoperative neurologic events.[69] Using TEE to guide cannula placement or treatment selection when indicated significantly reduced the stroke rate in a series of 500 consecutive patients versus controls in a state-wide database.[70] The addition of epiaortic scanning of the ascending aorta increases the sensitivity of intraoperative echocardiography in identifying significant atheromatous disease in this segment of the aorta. Certainly, this combination of techniques is superior to surgical palpation in detecting such disease.[71,72]

Transcranial Doppler Transcranial Doppler (TCD) involves ultrasonic interrogation of blood flow through the middle cerebral or common carotid arteries. Red blood cells (RBCs) reflect ultrasound energy back to the transducer; the exact frequency of the reflected sound varies with the velocity of each RBC. These velocities can be processed and displayed by pulsed-wave spectral analysis or nonspectral M-mode.

Classically, TCD has been used to detect emboli moving through the middle cerebral artery. Emboli, whether solid or gaseous, have higher acoustic impedance than RBCs do and show up as high-intensity "blips" on the spectral or nonspectral display. One early study using TCD showed increased embolic load in patients without arterial line filtration and a trend toward poorer function on postoperative tests of neurocognition in these patients.[73]

One of the primary limitations of TCD technology has been its inability to discern gaseous from solid emboli. Newer TCD monitors are capable of simultaneously generating Doppler frequencies of 2.0 and 2.5 MHz. Recent studies are inconclusive regarding the sensitivity and specificity of the technology.

Another application of TCD technology is measurement of cerebral blood flow velocity and documentation of changes from baseline during cardiac surgery with various techniques: traditional CPB, off-pump coronary revascularization, minimally invasive CABG, valve procedures involving nontraditional cannula placement or intra-aortic "endoclamp" occlusive balloon catheters, or deep hypothermic circulatory arrest with selective antegrade or retrograde cerebral perfusion.[74] In one study of patients undergoing operations on the great vessels requiring circulatory arrest and retrograde cerebral perfusion, TCD-guided cannula placement and retrograde cerebral perfusion reduced postoperative confusion, delirium, and agitation.[75]

Table 60-2 Grading Aortic Atherosclerosis

Aortic Atheromatous Disease	Echocardiographic Findings
Grade 1	Normal or mild intimal thickening
Grade 2	Severe intimal thickening No protruding atheromas
Grade 3	Atheroma protruding less than 5 mm into the lumen
Grade 4	Atheroma protruding 5 mm or more into the lumen
Grade 5	Atheroma of any size with a mobile component

From Béïque FA, Joffe D, Tousignant G, Konstadt S: Echocardiography-based assessment and management of atherosclerotic disease of the thoracic aorta. J Cardiothorac Vasc Anesth 12:206-220, 1998.

The general limitations of TCD technology include the following: (1) the quality of information is heavily user dependent, (2) accuracy requires stable and precise probe placement, (3) information is affected by patient characteristics such as skin thickness, and (4) signal acquisition is dependent on probe design and thus varies among probe models.

CNS Monitoring Summary The difficulties involved in using neuromonitoring in cardiac surgery include the fact that monitors are global in nature and cannot monitor focal areas of injury. Furthermore, there is a paucity of adequately powered prospective studies that would allow evidence-based recommendations about CNS monitoring. Despite these limitations, neuromonitoring will undoubtedly continue to receive significant research effort.

Renal System

In a healthy individual, about 20% of the total cardiac output (about 1 L/min) is received by the kidneys. The percentage of oxygen consumption versus total-body oxygen utilization does not usually exceed about 10%. Despite such a low oxygen extraction ratio, the kidneys are extremely sensitive to hypoperfusion occurring as a result of hypotension.

A number of control mechanisms maintain a strict balance of medullary oxygenation. In the event of failure of these control mechanisms, the outer medullary region is at risk for hypoxic injury, which can lead to acute tubular necrosis.

Perioperative monitoring of renal function is reviewed in Chapter 45.

In addition to fluid loss, the myocardial depression and peripheral vasodilation caused by most anesthetics can also compromise organ perfusion. In the kidneys, arteriolar glomerular filtration pressure is maintained by vasoconstriction of the efferent arterioles. Efferent arteriolar vasoconstriction and, ultimately, maintenance of glomerular filtration pressure are dependent on angiotensin II. Long-term treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers can enhance the decline in perfusion pressure caused by anesthetic medications. Fluid replacement or use of a vasoconstrictor should be considered as a means of maintaining adequate organ perfusion.

For patients undergoing cardiac surgery, factors related to CPB add further complexity. The systemic inflammatory response and loss of pulsatile flow during CPB and hypoperfusion may contribute to the development of renal failure after cardiac surgery.[77-79] The best available evidence of the role that fluid balance plays in the development of nephropathy comes from studies performed with radiocontrast dye. The intrarenal hemodynamic disturbances caused by such dye seem to produce ischemic injury comparable to that associated with cardiac and aortic surgery.[76] Hydration of patients before administration of contrast material appears to have a protective effect on the kidneys.[80]

Some studies suggest that increases in creatinine are smaller after CABG surgery performed off-pump than after CABG surgery with CPB, but the evidence for this finding is mixed.[81,82] Regardless, conventional wisdom holds that urine flow greater than 0.5 mL/kg/hr should be maintained during the perioperative period, although randomized studies are lacking at this time to confirm this statement.[77]

Renal impairment after cardiovascular surgery remains a major cause of perioperative mortality and morbidity. Mangano and colleagues[83] found that after coronary revascularization, mortality was far lower in patients with normal renal function (0.9%) than in patients with acute renal failure (ARF) (63%). Unfortunately, no strategy, other than maintaining normovolemia, appears to be uniformly effective in preventing postoperative renal impairment.[76]

Endocrine System: Glucose, Thyroid Hormone, and Hormone Replacement Therapy

Glucose Control

Hyperglycemia in surgical patients is a consequence of the inflammatory or "stress" response to the trauma of surgery. Components of this response include an endocrine response (i.e., increased production of "counter-regulatory" hormones such as cortisol, growth hormone, glucagon, and catecholamines) (Fig. 60-4), an immune response resulting in increased cytokine production, an autonomic response resulting in increased sympathetic stimulation, and altered insulin signaling. These changes increase glucose production, decrease glucose elimination during CPB, and induce insulin resistance, thereby causing hyperglycemia.[84]

Although cardiac surgery without CPB initiates a stress response, CPB increases this response manyfold.[84] The degree of hyperglycemia depends on several variables associated with the use of CPB, such as the pump prime fluid selected, the degree of hypothermia induced, and the medications administered.

Older patients, diabetic patients, and patients with coronary artery disease are particularly prone to perioperative hyperglycemia, the deleterious effects of which include reduced vasodilation in response to ischemia, decreased response to vasodilator therapy, decreased collateral coronary circulation, increased levels of reactive oxygen species, reduced constitutive nitric oxide synthesis, reduced adenosine triphosphate–regulated activation of potassium channels, and reduced responses to ischemic or anesthetic preconditioning.[85]

Hyperglycemia may increase operative risk in patients undergoing cardiovascular procedures; it has been associated with increased mortality and morbidity, including a higher incidence of deep sternal wound infections and longer hospital stay.[85] Evidence suggests that in critically ill patients who receive insulin therapy to keep blood glucose levels between 4.4 and 6.1 mmol/L (80 to 110 mg/dL) for a few days after complicated, high-risk, or extensive surgery or trauma, survival improves and morbidity decreases.[86] However, in a recent randomized trial,[87] cardiac surgical patients whose glucose levels were maintained at 80 to 100 mg/dL during the intraoperative and postoperative periods by means of intensive insulin therapy did not have less mortality or morbidity than those who received conventional glucose management (i.e., treatment of glucose levels >200 mg/dL). In fact, the investigators noted a statistically nonsignificant increase in the incidence of death and stroke (Table 60-3) in the intensive insulin treatment group. Although various limitations of the study were noted by the investigators, these findings raise concern about the routine implementation of intensive insulin therapy during cardiac surgery.

In diabetic patients undergoing cardiac surgery, hyperglycemia may only partly explain an increased risk for adverse outcomes. Immunologic abnormalities common to diabetic patients, such as decreased chemotaxis, phagocytosis, opsonization, bacterial killing, and antioxidant defense, also promote adverse outcomes by increasing diabetic patients' risk of infection.[88]

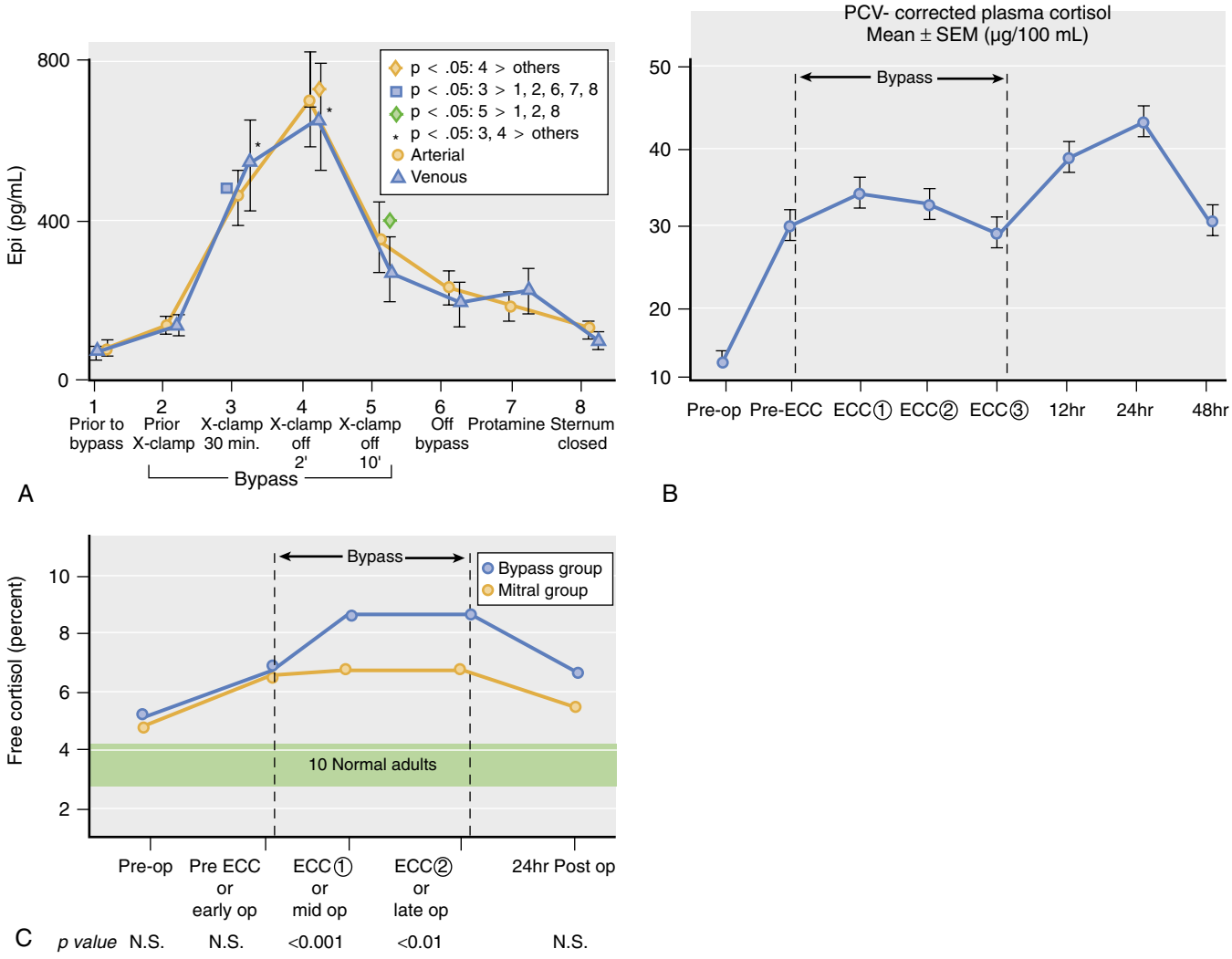

Figure 60-4 **A,** Plasma levels of epinephrine (Epi) during cardiac surgery. *Bars* indicate SEM; X-clamp, cross-clamp. **B** and **C,** Levels of cortisol during cardiac surgery. Preop, preoperatively; ECC, extracorporeal circulation; PCV, packed cell volume; SEM, scanning electron microscope. *(**A** Redrawn from Reves JG, Karp RB, Buttner EE, et al: Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. Circulation 66:49-55, 1982; **B** and **C,** from Taylor KM, Jones JV, Walker MS, et al: The cortisol response during heart-lung bypass. Circulation 54:20-25, 1976.)*

Thyroid Hormone

Abnormal thyroid function ultimately affects cardiac function in many ways (Table 60-4). During cardiac surgery, the effect of CPB on thyroid hormone production is uncertain. Results of studies vary and have shown both increased and decreased levels of thyroid hormone during or immediately after CPB. Factors that might contribute to low levels of thyroid hormone include hypothermia, nonpulsatile blood flow, and reduced conversion of thyroxin (T_4) to triiodothyronine (T_3). However, initial reports that intravenous T_3 hormone administration improves cardiac function were contradicted in subsequent investigations.[89]

On the other hand, preexisting thyroid dysfunction can occasionally be severely aggravated by CPB. For example, hypothyroidism is more common in female than in male CABG patients.[90] Zindrou and associates[91] noted a 17% higher mortality rate in women who underwent CABG while receiving thyroxine replacement therapy for hypothyroidism than in women who did not require hormone replacement. In the same study, no difference was noted among men with and without thyroid hormone replacement therapy (HRT).

Hypothyroidism is associated with impaired contractility and an enhanced risk for MI. A review of the literature by Edwards and colleagues concluded that ensuring a perioperative euthyroid state in women with hypothyroidism who were undergoing CABG might be helpful in reducing the perioperative mortality of these patients.[16]

Hormone Replacement Therapy

According to the database of the Society of Thoracic Surgeons (STS), women account for 29% of CABG patients. Female sex may be an independent risk factor for operative mortality, low-output syndrome, and MI in CABG surgery.[16,92]

Although HRT has been a focus of investigation in postmenopausal women for possible protection from CVD, prospective randomized studies have not demonstrated that HRT is beneficial in either primary or secondary prevention of coronary

Table 60-3 Comparison of Primary and Secondary Outcomes of Diabetic Patients*

Outcome	Intensive Treatment Group (n = 37) (%)	Conventional Treatment Group (n = 36) (%)	P Value†
Any event‡	19 (51)	22 (61)	.40
In hospital	19 (51)	21 (58)	
After discharge (up to 30 days after surgery)	2 (5)	2 (6)	
Death	2 (5)	0 (0)	.49
In hospital	2 (5)	0 (0)	
After discharge (up to 30 days after surgery)	0 (0)	0 (0)	
Stroke	2 (5)	0 (0)	.49
In hospital	1 (3)	0 (0)	
After discharge (up to 30 days after surgery)	1 (3)	0 (0)	
Deep sternal infection	3 (8)	1 (3)	.61
In hospital	2 (5)	1 (3)	
After discharge (up to 30 days after surgery)	1 (3)	0 (0)	
Cardiac arrest	0 (0)	0 (0)	1.00
In hospital	0 (0)	0 (0)	
After discharge (up to 30 days after surgery)	0 (0)	0 (0)	
Heart block requiring a pacemaker	2 (5)	0 (0)	.49
In hospital	2 (5)	0 (0)	
After discharge (up to 30 days after surgery)	0 (0)	0 (0)	
New-onset atrial fibrillation	13 (35)	16 (44)	.42
In hospital	13 (35)	15 (42)	
After discharge (up to 30 days after surgery)	0 (0)	1 (3)	
Acute renal failure	3 (8)	2 (6)	1.00
In hospital	3 (8)	1 (3)	
After discharge (up to 30 days after surgery)	0 (0)	1 (3)	
Prolonged (>24 hr) intubation	7 (19)	9 (25)	.53
In hospital	7 (19)	9 (25)	
After discharge (up to 30 days after surgery)	0 (0)	0 (0)	

*Variables are compared across treatment groups by using the chi-square or Fisher exact test.
†*P* values are unadjusted.
‡Numbers for "any event" correspond to the number of patients who experienced one or more individual events.
From Gandhi GY, Nuttall GA, Abel MD, et al: Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: A randomized trial. Ann Intern Med 146:233-243, 2007.

artery disease.[93-95] In fact, taking HRT may increase women's risk for adverse cardiovascular events.

Single-center, retrospective studies of female CABG patients have noted lower mortality in those taking HRT at the time of admission.[96-98] A multicenter study found a trend toward lower mortality in women receiving HRT but no statistically significant effect of HRT on mortality or morbidity.[99] The investigators concluded that women taking HRT should not discontinue it before or after surgery. However, a recent task force report on gender guidelines for CABG published by the STS concluded that

Table 60-4 Effects of Thyroid Dysfunction on Hemodynamics and Cardiac Function

Parameter	Normal Values	Hyperthyroidism	Hypothyroidism
Blood volume (% of normal value)	100	105.5	84.5
Heart rate (beats/min)	72-84	88-130	60-80
Cardiac output (L/min)	4.0-6.0	>7.0	<4.5
Systemic vascular resistance (dyne•sec•cm^{-5})	1500-1700	700-1200	2100-2700
Left ventricular ejection fraction (%)	>50	>65	≤60
Isovolumic relaxation time (msec)	60-80	25-40	>80

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given the potential risk for thromboembolic events posed by HRT, the wisdom of continuing HRT in patients undergoing CABG is uncertain.[16]

Hematologic System

The impact of CPB on the human hematologic system is well known. Bleeding is the primary complication of cardiac surgery requiring CPB. In fact, 15% to 20% of the blood product use in the United States is associated with cardiac surgery.[100-102] The global cost is also impressive; it is reported that worldwide, 1 to 1.25 million adult cardiac operations are performed annually, with a price tag of 50 billon U.S. dollars per year.[102] Beyond the economic burden of blood product transfusion in cardiac surgery is evidence that there are important clinical ramifications as well: transfusion has been associated with increased rates of hospital mortality,[103] perioperative infection and sepsis,[104] pulmonary dysfunction, prolonged mechanical ventilation,[105] and renal dysfunction,[106] as well as a persistent reduction in quality of life after surgery.[107]

Anticoagulation in Cardiopulmonary Bypass

Heparin Since its discovery by Jay McLean, MD, in 1915, heparin has stood the test of time and remains the primary anticoagulant used in cardiac surgery requiring CPB. The mechanism underlying heparin's anticoagulant effect revolves around the heparin molecule's ability to bind simultaneously to antithrombin III (AT III) and thrombin. The binding process is mediated by a unique pentasaccharide sequence that binds to AT III. The proximity of AT III and thrombin, mediated by the heparin molecule, allows AT III to inhibit the procoagulant effect of thrombin by binding to the active-site serine residue of the thrombin molecule. The inhibitory effect of AT III is increased 1000-fold in the presence of heparin. The heparin–AT III complex can affect several coagulation factors, but factor Xa and thrombin are most sensitive to inhibition by heparin, and thrombin is 10 times more sensitive to the inhibitory effects of heparin than factor Xa is.[108]

Only about a third of heparin molecules in a dose of heparin contain the critical pentasaccharide segment that is needed for high-affinity binding to AT III.[109] Thus, relatively large doses are required to produce the anticoagulant effect necessary for CPB. In fact, dosing of heparin for CPB is somewhat empirical. After a baseline activated clotting time (ACT) is measured (the normal range is 80 to 120 seconds), a dose of 300 to 400 U/kg is given in intravenous bolus form. Subsequent heparin dosing for extracorporeal circulation is targeted at maintaining ACT values greater than 480 seconds.

The dose of heparin used in patients undergoing CPB is based on early landmark work published by Bull and coauthors in 1975.[109a] A small study that sought evidence of thrombin activity during CPB in primates and pediatric patients found results supporting a safe lower limit for ACT of at least 400 seconds.[110] In 1979, Doty and colleagues[111] proposed a simplified dosing regimen guided by ACT values without dose-response curves. The data and recommendations that these few studies produced are the primary references for current heparin dosing protocols.

Despite heparin's historic and continued role in anticoagulation for patients maintained on CPB, it is not a perfect anticoagulant. Intrinsic and extrinsic pathway coagulation occurs despite heparin administration, and platelets can still be activated by contact with the bypass circuitry and by heparin directly.[112,113]

Table 60-5 Clinical Factors Affecting the Activated Clotting Time

Hemodilution	Prolongs the ACT in the presence of heparin
Hypothermia	Prolongs the ACT
Thrombocytopenia	Prolongs the ACT
Platelet inhibitors	Prolongs the ACT
Platelet lysis	Shortens the ACT
Aprotinin	Prolongs the ACT with celite activator
Surgical stress	Shortens the ACT

ACT, activated clotting time.

Alternative anticoagulants are discussed briefly in the section "Heparin-Induced Thrombocytopenia."

Using ACT to monitor the efficacy of heparin is not an exact science. There is tremendous variability in patients' anticoagulation response to a given dose of heparin. Hence, ACT values correlate poorly with actual heparin concentrations.[114] A brief review of anticoagulation monitoring in CPB follows.

Monitoring of Anticoagulation Since the publication of Bull and colleagues' early work, ACT has been the mainstay of anticoagulation monitoring in cardiac surgery requiring CPB. Whole blood is added to a tube containing a contact-phase activator, celite or kaolin, and a small iron cylinder. The sample is warmed to 37°C, and the tube is rotated. Clot formation is detected by retracting the iron cylinder, which disrupts a magnetic field.[115]

Several clinical variables can affect the ACT (Table 60-5). Additionally, ACT values can vary with the manufacturer of the machine and between adult and pediatric populations. Some authors argue that because of these interfering factors, the ACT alone is not an adequate monitor of heparin efficacy and that simultaneous or adjunctive monitoring of the heparin concentration should also be used during CPB.[114] Prolongation of the ACT by non–heparin-related clinical factors, such as hypothermia, hemodilution, or quantitative or qualitative platelet abnormalities, requires the anesthesiologist to reduce heparin doses to keep the ACT at a set, arbitrary level. Because the ACT correlates poorly with the measured heparin concentration, it is possible that this dose reduction can render the heparin concentration inadequate, even when the ACT remains within an acceptable range. There are point-of-care (POC) monitors, such as the Hepcon HMS system, that use a protamine titration assay to calculate the heparin concentration. Despotis and colleagues[116] argue that monitoring the heparin concentration and giving larger doses of heparin actually protect the hemostatic system and may decrease transfusion requirements. However, other investigators have not been able to confirm better hemostatic protection with higher doses of heparin because markers of ongoing coagulation are essentially the same whether traditional ACT monitoring or monitoring of the heparin concentration is used.[117]

The high-dose thrombin time (HiTT) correlates well with the heparin concentration, both before and during CPB.[118] Unlike the ACT, HiTT is not affected by hemodilution and hyperthermia; in addition, it is a more specific test of heparin's effect on thrombin, and it appears to possess less artifactual variability.[112] Aprotinin and preoperative heparin infusions do not affect HiTT values.[119,120]

Protamine and Reversal of Anticoagulation Protamine, which has been in clinical use about as long as heparin, remains the heparin reversal agent of choice in cardiac surgery. The protamine dose required to reverse heparin is somewhat controversial. The amount quoted in most cardiac anesthesia texts is 1 to 1.3 mg of protamine for every 100 units of heparin. The question to be answered revolves around which end point one uses in the protamine calculation: the total amount of heparin used for the procedure or the amount present in the patient at the time of reversal. In current practice, dosing usually follows one of the following protocols:

1. Protamine is administered according to the total amount of heparin given for the procedure, specifically, 1 to 1.3 mg protamine per 100 units of heparin. This method may result in luxuriant protamine doses, which reduces any theoretical or real risks of heparin rebound but may put the patient at higher risk for the anticoagulant effect of protamine.[115]
2. Another practice involves the use of calculated heparin concentrations obtained automatically from a heparin concentration monitoring system, such as the Hepcon HMS system, or graphically derived by plotting ACT values throughout the procedure and creating heparin dose-response curves. The amount of protamine used in this method is based on the circulating concentration of heparin in the patient at the time of reversal. Because theoretically there is no excess protamine, these patients might be at risk for heparin rebound and could require additional protamine.[117,121]

Hemostatic Effects of Cardiopulmonary Bypass The hemostatic effects of CPB are myriad. Exposure of blood to the surfaces of the bypass circuitry is a profound stimulus for inflammatory upregulation, and activation of the hemostatic system is a component of the normal inflammatory response. According to traditional models of hemostasis, CPB is thought to activate the intrinsic and extrinsic hemostatic pathways and to directly affect platelet functionality. Current concepts in vascular biology and hemostasis implicate tissue factor–bearing leukocytes and endothelial cells activated by the inflammatory stimulus of bypass and circulating tissue thromboplastin generated from the surgical field.[122-124] Activation of the intrinsic pathway can occur by activation of factor XII to factor XIIa on the various surfaces of the bypass circuit.[122,125] Generation of thrombin by the tissue factor pathway assumes a primary role in CPB-associated hemostatic abnormalities (Fig. 60-5).[124,126]

In addition to activating the extrinsic and intrinsic hemostatic pathways, CPB directly affects platelet function through the effects of hemodilution, hypothermia, and contact activation by bypass circuit materials. Platelets express numerous glycoproteins on their surface that serve as receptors for several circulating ligands, such as fibrinogen, thrombin, and collagen (Fig. 60-6).[122] The components of the bypass circuit adsorb circulating proteins that can serve as foci for platelet attraction and adherence. These surface-bound platelets activate and release the contents of their cytoplasmic granules, which can then serve as localized sources of thrombin generation or embolize to initiate microvascular thrombosis.[127] The resulting functional platelet disorder can complicate hemostasis after CPB is terminated and heparin is reversed by protamine.

Fibrinolytic activity is also increased by CPB. Contact activation of factor XII, prekallikrein, and high-molecular-weight kininogen leads to fibrinolytic activation through activation of endothelial cells to produce tissue plasminogen activator (t-PA) and lysis of fibrin strands and the fibrin precursor fibrinogen (Fig. 60-7).[122,128]

Endothelial cells themselves are vulnerable to inflammatory activation by the effects of CPB. Vascular endothelium is an active substrate that expresses and releases anticoagulant and procoagulant factors.[123] Endothelial cells, when exposed to hypoxia or inflammatory mediators during bypass, can induce a relatively prothrombotic state that leads to upregulation of tissue factor, accelerated platelet adhesion, and increased expression of leukocyte adhesion molecules (Fig. 60-8).[122,123]

Unique Clinical Considerations in Cardiac Surgery

Antithrombin III Deficiency/Heparin Resistance Heparin resistance has been defined as an ACT of less than 480 seconds after 500 U/kg of heparin is administered intravenously. Others have defined heparin resistance as an ACT of less than 400 seconds at any time during the course of CPB and heparin administration. A more accurate term to describe the clinical findings is "altered heparin responsiveness."[129] In a recent, small study of cardiac surgery patients stratified by their history of preoperative heparin use, altered heparin responsiveness was found in approximately 40% of the patients who had received preoperative heparin therapy.[130] Reported risk factors for altered heparin responsiveness include AT III levels less than 60% of normal, preoperative heparin therapy, a platelet count less than 300,000/mm^3, and age younger than 65 years.[131] In a second, larger study, Ranucci and coworkers[132] found heparin resistance in 20% of the patients studied and confirmed that AT III activity levels, platelet counts greater than 300,000/mm^3, and heparin pretreatment—but not age—were risk factors for heparin resistance. Ranucci and colleagues also found a small group of patients in their cohort with normal or supranormal AT III activity who had altered heparin responsiveness that did not respond to the administration of AT III. The precise mechanism of action of an altered response to heparin is unclear. The usual treatment is supplemental doses of heparin. In refractory cases, treatment with fresh frozen plasma (FFP), AT III concentrate, or recombinant AT III usually restores heparin responsiveness.[133,134]

Heparin Rebound Heparin rebound is clinical bleeding that occurs within approximately 1 hour of protamine neutralization. It is accompanied by coagulation test results indicating residual heparinization, such as a prolonged partial thromboplastin time or thrombin time and increased anti–factor Xa activity. Mechanisms of heparin rebound include slow dissociation of protein-bound heparin after protamine clearance, more rapid clearance of protamine than heparin, lymphatic return of extracellular sequestered heparin, or clearance of an unknown heparin antagonist. Heparin rebound is treated with supplemental protamine.

Heparin-Induced Thrombocytopenia Heparin-induced thrombocytopenia (HIT) is an immune-mediated prothombotic disorder that occurs in patients exposed to heparin. Antibodies form against the protein platelet factor 4 (PF4) when PF4 has formed a complex with heparin. Although PF4 is found in only trace amounts in human plasma and is stored in platelet granules, the presence of heparin increases plasma concentrations of PF4 15- to 30-fold by displacing bound PF4 on endothelial cell sur-

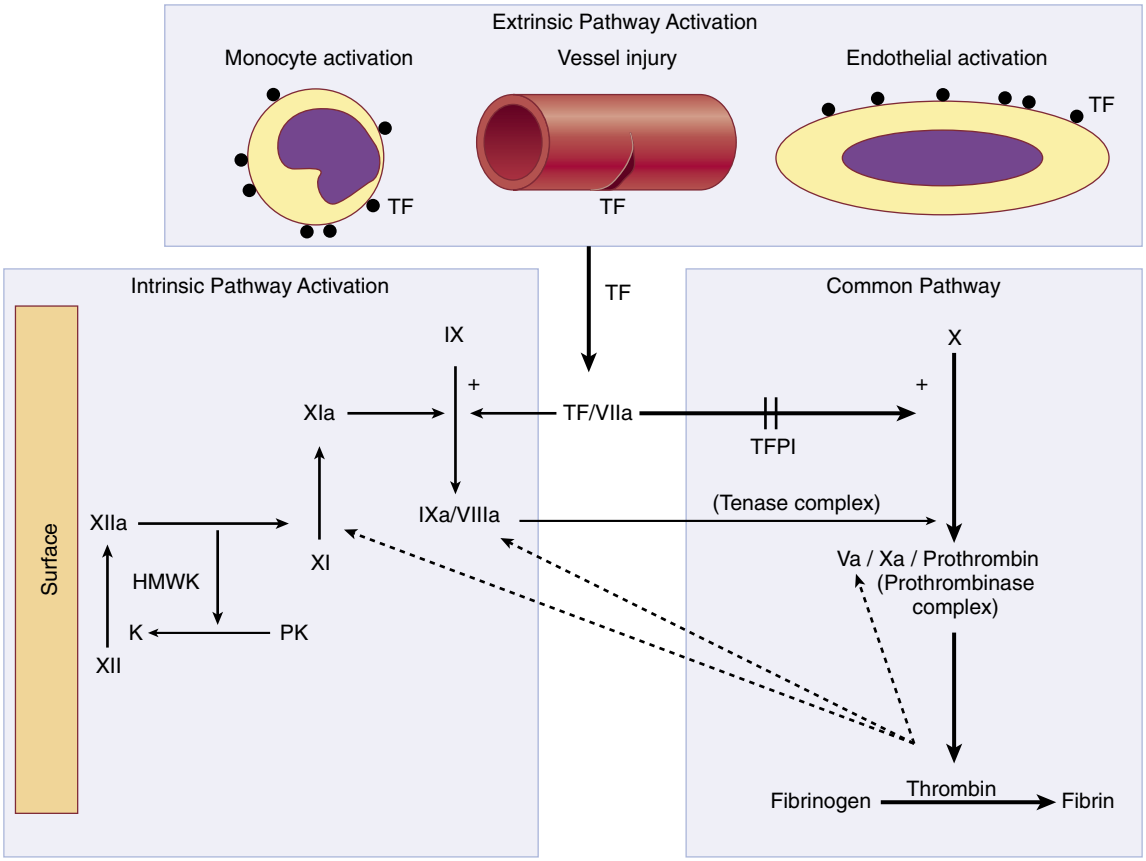

Figure 60-5 Coagulation can be activated during cardiopulmonary bypass (CPB) by the intrinsic pathway, with surface adsorption and activation of factor XII, high-molecular-weight kininogen (HMWK), and prekallikrein (PK). Activation of the extrinsic pathway during CPB occurs with tissue injury, as well as with systemic inflammation, and leads to monocyte and endothelial expression of tissue factor (TF). TF, in combination with factor VIIa, starts the common pathway with the activation of factor X to factor Xa. Assembly of the prothrombinase complex on phospholipid surfaces leads to the production of thrombin and conversion of fibrinogen to fibrin. Tissue factor pathway inhibitor (TFPI) inhibits TF/VIIa. Thrombin can overcome this TFPI blockade by activating factors XI, VIII, and V and initiating activation of factor X by the tenase complex. K, kallikrein. *(From Kottke-Marchant K, Sapatnekar S: Hemostatic abnormalities in cardiopulmonary bypass: Pathophysiologic and transfusion considerations. Semin Cardiothorac Vasc Anesth 5:187-206, 2001.)*

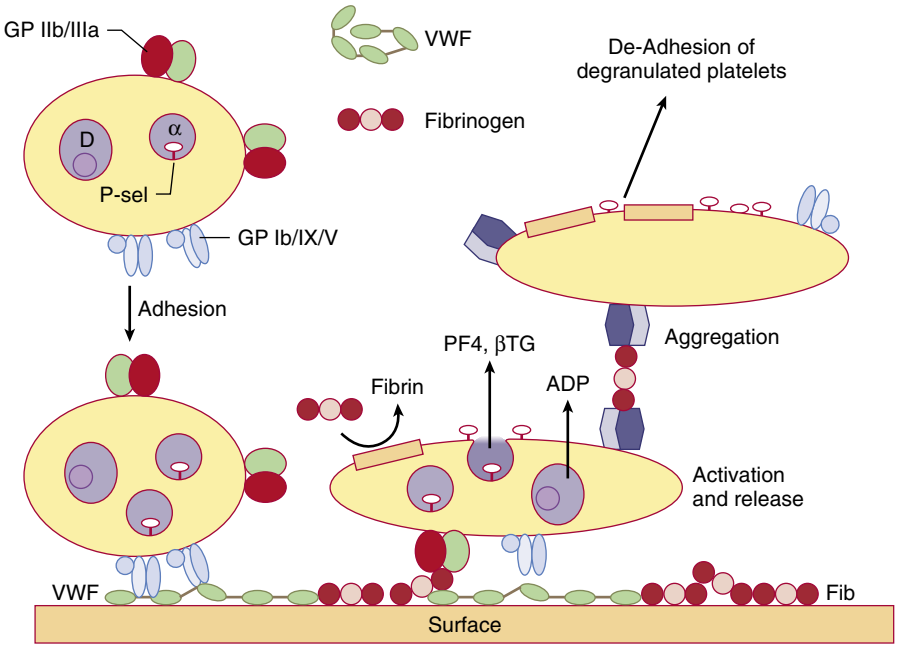

Figure 60-6 Platelet activation by cardiopulmonary bypass materials is facilitated by rapid adhesion and conformational alteration of plasma proteins, including von Willebrand factor (VWF) and fibrinogen. Platelets adhere to VWF through the glycoprotein (GP) Ib/IX/V surface glycoprotein and to fibrinogen through the GP IIb/IIIa receptor. Platelet adhesion stimulates intracellular signaling, which leads to degranulation of alpha granules (platelet factor 4 [PF4] and β-thromboglobulin [βTG]) and phospholipid reorganization with the formation of coagulation complexes and fibrin formation. Release of adenosine diphosphate (ADP) from dense granules and activation of the GP IIb/IIIa receptor also occur and lead to the aggregation of platelets to the adherent layer. Because of shear forces, adherent and aggregated platelets can detach from the membrane and circulate in a degranulated state or form small microaggregates that lodge in the distal vasculature. *(From Kottke-Marchant K, Sapatnekar S: Hemostatic abnormalities in cardiopulmonary bypass: Pathophysiologic and transfusion considerations. Semin Cardiothorac Vasc Anesth 5:187-206, 2001.)*

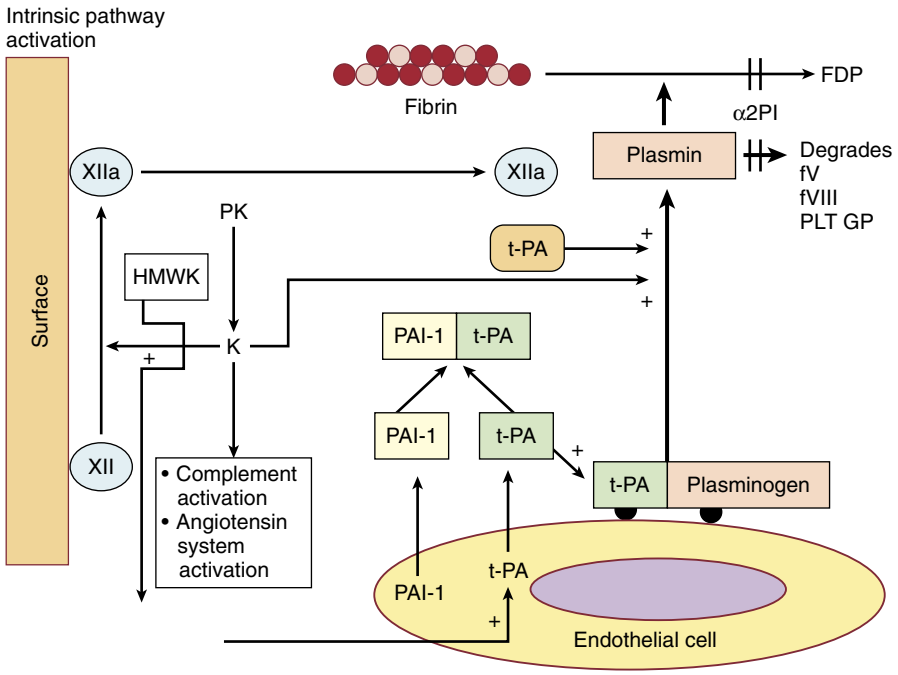

Figure 60-7 The fibrinolytic system results in the degradation of fibrin by plasmin. The intrinsic factors participate in the fibrinolytic system. Adsorption and activation of factor XII, high-molecular-weight kininogen (HMWK), and prekallikrein (PK) occurs on the cardiopulmonary bypass material surfaces. Kallikrein (K) and factor XIIa participate in the conversion of plasminogen to plasmin. Plasminogen is also activated by tissue plasminogen activator (t-PA), which is released from endothelial cells, along with its inhibitor PAI-1. Plasmin not only degrades fibrin but also degrades coagulation factors V and VIII and platelet surface glycoproteins (PLT GP). Kallikrein plays additional roles in the activation of complement and the angiotensin system, and HMWK accelerates fibrinolysis by stimulating endothelial production of t-PA. FDP, fibrin degradation product. *(From Kottke-Marchant K, Sapatnekar S: Hemostatic abnormalities in cardiopulmonary bypass: Pathophysiologic and transfusion considerations. Semin Cardiothorac Vasc Anesth 5:187-206, 2001.)*

faces making it available to bind with heparin. Binding of the resulting PF4-heparin complex to platelets leads to immunologically mediated platelet activation.

The hallmark of findings in patients with HIT is a decrease in the platelet count to less than 100,000 or to less than 50% of the baseline count.[135] The incidence of seroconversion after bypass and heparin exposure is quite high (20% to 50%).[135-137] However, the reported prevalence of HIT after CPB is only 1% to 3%.[137] Thus, the risk of HIT in cardiac surgery patients with postoperative seroconversion is less than 10%. The strength of the immunologic response, not the mere presence of PF4/heparin antibodies, may determine which patients are prone to HIT and are at risk for thromboembolic complications.[135,137]

Clinically, HIT is categorized into type I (platelet counts >100,000) and type II (platelet counts <100,000), and it is sometimes accompanied by clinical thrombosis.[129] Regardless of the clinical manifestation, it is challenging to anticoagulate patients with preoperative type I or type II HIT who need to be exposed

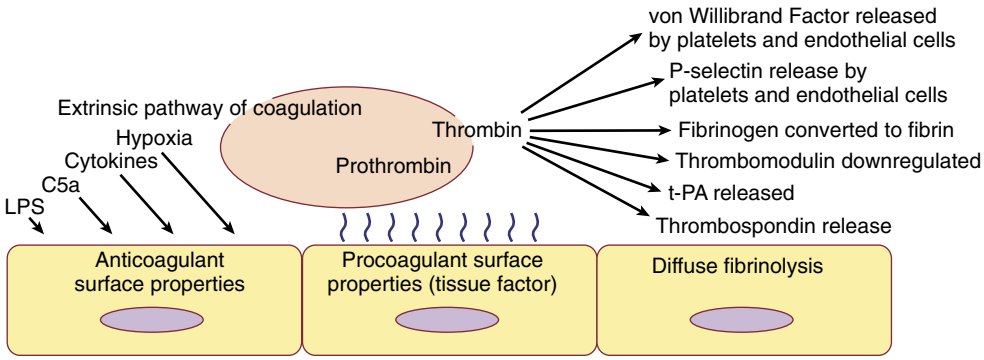

Figure 60-8 Procoagulant endothelial cell activation. When endothelial cells are activated, they express tissue factor, which converts prothrombin to thrombin. Thrombin has multiple biologic actions: (1) stimulation of the release of von Willebrand factor and P-selectin, which cause platelet clumping and platelet/neutrophil/endothelial cell adhesion; (2) conversion of fibrinogen to fibrin, the solid component of clot; (3) downregulation of the thrombomodulin/protein C and S systems; (4) release of tissue plasminogen activator (t-PA), which catalyzes the formation of plasmin; and (5) release of thrombospondin, which binds to t-PA, prevents its breakdown by plasminogen activator inhibitor-1 (PAI-1), and accelerates the formation of plasmin. LPS, lipopolysaccharide. *(From Boyle EM Jr, Verrier ED, Spiess BD: Endothelial cell injury in cardiovascular surgery: The procoagulant response. Ann Thorac Surg 62:1549-1557, 1996.)*

to CPB. In this situation, the use of nonheparin anticoagulation must be considered.

It is preferred, when possible, to defer surgery until antibody titers have become undetectable or only weakly positive. If surgical postponement is not practical, other therapeutic options must be considered. Lepirudin and argatroban are approved by the Food and Drug Administration (FDA) for use in patients with HIT-related thrombosis. Bivalirudin has been approved by the FDA for use in percutaneous interventions. To date, four clinical trials have tested bivalirudin as an anticoagulant for CPB in patients with HIT.[138-141] However, no drug other than heparin has FDA approval for specific use as an anticoagulant in patients during CPB.[129] Table 60-6 and Box 60-2 summarize the therapeutic options and alternative anticoagulant strategies for the patient with HIT whose operation cannot be deferred until seronegativity is documented.

Protamine Reactions Protamine is associated with several hemodynamic effects that can be categorized by their manifestations and mechanism.[142] Adverse reactions to protamine range from seemingly innocuous hypotension to more profound and hemodynamically significant reactions that have been linked to increased in-hospital mortality.[143,144] The clinical expression of these reactions serves as a starting point for understanding the mechanistic relationships. Commonly, what is seen is either (1) isolated hypotension, with normal to low filling pressure and normal airway pressure, or (2) hypotension accompanied by elevated PA pressure, evidence of bronchoconstriction with elevated airway pressure, evidence of acute RV failure on visual inspection or intraoperative echocardiography, or any combination of these findings. The first manifestation is usually mild and responds to volume infusion, slowing of protamine infusion, and gentle titration of vasoactive medications. The second can be profound and could result in global cardiovascular collapse or necessitate a return to CPB because of intractable RV failure. Fortunately, catastrophic hypotension and intractable RV failure are relatively rare events on the spectrum of protamine reactions.[145,146]

Table 60-6 Alternative Anticoagulants for the Treatment of Heparin-Induced Thrombocytopenia

Anticoagulant	Dosing (Therapeutic Range)	Pharmacokinetics ($t_{1/2}$)	Comment
Agents Approved for the Treatment of HIT			
Danaparoid sodium (Orgaran)	Bolus: 2250 U* Infusion: 400 U/hr × 4 hr then 300 U/hr × 4 hr then 200 U/hr, with monitoring by anti–factor Xa levels (0.5-0.8 anti-Xa U/mL†)	Renal metabolism (25 hr [anti–factor Xa activity], 2-4 hr [anti–factor IIa activity])	Approved for the treatment and prevention of HIT-associated thrombosis in the European Union, Canada, New Zealand, and Australia Withdrawn from U.S. market in April 2002 because of the potential for in vivo cross-reactivity (rare), which is not predictable by in vitro testing. Thus, cross-reactivity testing is not recommended before use
Lepirudin (Refludan)	Bolus: 0.4 mg/kg‡ Infusion: 0.15 mg/kg/hr (target aPTT range, 1.5-2.5 × baseline‡§)	Renal excretion (80 min)	Approved in the United States, Canada, and the European Union for the treatment of HIT-associated thrombosis; $t_{1/2}$ rises considerably in patients with renal failure; high rate of antihirudin antibodies (40% -60%) that are not usually clinically significant; anaphylaxis reported after lepirudin bolus (rare), especially with a repeat treatment course
Argatroban (Novastan in some non-U.S. jurisdictions)	2 µg/kg/min without an initial bolus (target aPTT range, 1.5-3.0 × baseline§)	Hepatobiliary excretion (40-50 min)	Approved in the United States and Canada for prevention and treatment of HIT-associated thrombosis (identical therapeutic dose regimens used for both indications); argatroban increases the INR, so a higher therapeutic range is required during overlapping argatroban/warfarin
Investigational Agents for the Treatment of HIT			
Bivalirudin (Angliomax)	0.15-0.20 mg/kg/hr without an initial bolus (target aPTT range, 1.5-2.5 × baseline§¶)	Enzymic > renal (25 min)	Approved in the United States for anticoagulation during percutaneous coronary interventions (non-HIT); low $t_{1/2}$ and enzymic metabolism are theoretical advantages over lepirudin for cardiac surgery in patients with HIT (under current investigation)
Fondaparinux (Arixtra)	Uncertain	Renal (17-20 hr)	Approved for DVT prophylaxis after orthopedic surgery; theoretically, lack of in vitro cross-reactivity with HIT antibodies suggests that it may be efficacious in patients with HIT (not yet studied for this indication)

*Adjust the intravenous danaparoid bolus for body weight: less than 60 kg, 1500 U; 60 to 75 kg, 2250 U; 75 to 90 kg, 3000 U; greater than 90 kg, 3750 U.
†Anticoagulant monitoring by anti–factor Xa levels is not always necessary but is preferred (when available) for very small or large patients, patients with renal failure, or those with life- or limb-threatening thrombosis.
‡In the absence of life-threatening thrombosis or when treating isolated HIT, it may be prudent to omit the initial bolus and to aim for an aPTT of 1.5 to 2.0 times baseline.
§The patient's baseline aPTT (when available) is generally preferred for calculating the target aPTT range.
¶Anecdotal experience in HIT.
aPTT, activated prothrombin time; DVT, deep venous thrombosis; INR, international normalized ratio; $t_{1/2}$, half-time.
From Warkentin TE: Heparin-induced thrombocytopenia: Pathogenesis and management. Br J Haematol 121:535-555, 2003.

Box 60-2 Anticoagulation Options for Cardiac Surgery

A. Acute HIT (documented thrombocytopenia, detectable HIT antibodies, with or without thrombosis)
   Defer surgery if possible. Follow antibody titers. Go to C.
   Surgery not deferrable; choose an alternative anticoagulation strategy
   1. Bivalirudin
   2. Lepirudin
   3. Epoprostenol plus heparin
   4. Tirofiban plus heparin
   5. Danaparoid (requires anti-Xa monitoring)

B. Subacute HIT (diagnosed recent HIT, resolution of thrombocytopenia, HIT antibody titers still positive)
   Defer surgery if possible. Follow antibody titers. Go to C
   If surgery is not deferrable, use
   1. An off-pump technique, with bivalirudin or alternative nonheparin anticoagulant used if needed
   2. Heparin if the antibody test is only weakly positive
   3. Acute HIT options above

C. Previous HIT (prior diagnosis of HIT, antibodies no longer detectable)
   Use heparin (ensuring no long-term exposure to heparin from invasive lines in the intensive care unit). Reverse completely with protamine

HIT, heparin-induced thrombocytopenia.
From Warkentin TE, Greinacher A: Heparin-induced thrombocytopenia and cardiac surgery. Ann Thorac Surg 76:2121-2131, 2003.

Mechanistic explanations for protamine reactions include mast cell degranulation, endothelial release of nitric oxide, and hypotension associated with rapid infusion.[129,146] Both immunologic and nonimmunologic anaphylactoid reactions may cause the more hemodynamically significant manifestations. Anaphylactoid reactions include protamine sensitivity reactions, which are classically immunologic or allergic in nature in that they are mediated by IgE antibody, and nonimmunologic mechanisms, which may involve IgG antibodies or complement activation.[129,147-149]

A study by Kimmel and associates[150] found that neutral protamine Hagedorn (NPH) insulin use, documented fish allergy, and a history of nonprotamine medical allergies were independent risk factors for protamine hypersensitivity reactions. In this study, 39% of patients about to undergo cardiac surgery had one or more of these risk factors. Other possible, but unconfirmed risk factors include previous exposure to protamine, a history of vasectomy, decreased LV function, and hemodynamic instability.[129,150] The site of injection does not influence the incidence of protamine reactions.[151] Interestingly, thromboxane receptor inhibition prevents heparin-protamine–induced pulmonary hypertension in sheep,[152] whereas in humans, preoperative aspirin use may be protective.[151] Pretreatment with histamine blockade is not preventive.[153]

The following principles summarize the treatment options for patients at risk for intraoperative protamine reactions:

1. Protamine should be administered slowly, over a period of 5 minutes or longer.[129]
2. In patients with documented protamine allergy, consideration might be given to using non–heparin-based CPB (as used in patients with HIT), performing off-pump coronary artery bypass (OPCAB) without using heparin, using nonprotamine heparin reversal agents such as PF4, administering heparinase, or even foregoing heparin reversal.[129]
3. The hypotension associated with protamine reversal of heparin is often ameliorated by simply slowing or pausing the protamine infusion while volume is infused through intravenous lines or the aortic cannula. Vasoactive medications, such as phenylephrine or ephedrine, or increased inotropic support may be necessary.
4. Severe or intractable hypotension, with or without evidence of pulmonary circulatory involvement, bronchospasm, or overt RV failure, demands immediate aggressive attention, intervention, and planning for a potential return to CPB. Steps to consider include the following:
   a. Reheparinization can be carried out to prepare the patient for return to CPB and to reduce heparin-protamine complex size. If hemodynamics permits, a low dose of heparin (70 U/kg) might be tried first while treatment continues, followed by a full CPB dose of heparin (300 U/kg) if it becomes necessary to return the patient to CPB.[129]
   b. Inotropic support, either by infusion or by intermittent boluses, is warranted. Epinephrine and milrinone are acceptable options, and isoproterenol may be considered as well.
   c. If hemodynamics allows, nebulized albuterol is helpful in the management of bronchospasm and elevated airway pressure.
   d. Hypotension accompanied by direct or echocardiographic evidence of acute RV distention and failure should prompt immediate consideration of return to CPB. Hypotension accompanied by pulmonary hypertension and acute severe RV failure can become a vicious cycle leading to RV ischemia and further dysfunction because of high RV intracavitary pressure and decreased coronary perfusion of the right ventricle.
   e. Consideration should be given to not rechallenge a patient who has had a significant adverse event related to protamine. Pharmacologic alternatives to protamine could be considered, or a decision can be made to not reverse heparin.

Hypercoagulable States Over the past decade, the use of antifibrinolytics has become common in cardiac surgery requiring CPB. Recently, as it relates to perioperative risk in cardiac surgery and noncardiac surgery, the role of congenital thrombophilic states has been considered.[154] These states may be important in light of current practices that involve pharmacologically inhibiting fibrinolytic pathways in cardiac surgical patients. The factor V Leiden (FVL) deficiency mutation is the most common inherited thrombophilic disorder, with a prevalence of 3% to 7% in white populations. Mechanistically and clinically, FVL deficiency has been implicated in thrombotic complications in cardiac operations, most often those involving a period of circulatory arrest and the use of antifibrinolytics.[155-158] In a review of FVL deficiency, Donahue[154] gives the following summation and recommendations:

- Cardiac surgery patients who carry the FVL deficiency mutation bleed less than noncarriers do.
- Early graft thrombosis may be increased in patients with FVL deficiency.
- Increased thrombotic risk in FVL deficiency with the use of antifibrinolytics (ε-aminocaproic acid [EACA], aprotinin, tranexamic acid [TA]) is a pharmacologically theoretical risk.
- Anecdotal evidence suggests that in patients with FVL deficiency who are exposed to deep hypothermic cardiac arrest (DHCA), antifibrinolytics increase the risk for thrombosis.

For further information on congenital thrombophilic states, the reader is referred to a review article by Crowther and Kelton.[159]

Anticoagulated Patients Undergoing Cardiac Surgery Antithrombotic therapy in cardiac surgery patients has many roles and applications. Patients with ischemic heart disease can be managed acutely or chronically with pharmacologic agents that may include aspirin, AT III inhibitors (heparins), direct thrombin inhibitors, or an array of platelet inhibitors (adenosine diphosphate [ADP] receptor inhibitors and glycoprotein IIb/IIIa [GP IIb/IIIa] receptor inhibitors). Patients with a history of peripheral or central vascular disease, valvular heart disease, or low–ventricular ejection states may likewise be managed with some form of antithrombotic therapy that may also include warfarin. Frequently, patients arrive for surgery while taking multiple antithrombotic medications. Thus, postoperative bleeding is a common but challenging complication of cardiac surgery, especially when it involves CPB.

The advancement of percutaneous interventions such as angioplasty and intracoronary stent deployment for ischemic heart disease has led to the use of antithrombotic medications, especially antiplatelet drugs, to maintain stent patency and prevent stent occlusion. The most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines for percutaneous coronary intervention (PCI) give both aspirin and clopidogrel a class I recommendation (based on evidence and a consensus agreement that the therapy is beneficial) for use in the pericatheterization period and in the long term (e.g., up to a year after placement of a drug-eluting stent).[160] In addition, GP IIb/IIIa receptor inhibitors and low-molecular-weight heparin (LMWH) have received either class I or class IIa recommendations for use in the postintervention period.[160] Because these recommendations have led to the widespread use of heparin in patients who undergo PCI, it can be challenging to treat these patients if they require urgent or emergency conversion to surgical revascularization.

Consensus has not been reached regarding whether aspirin and newer antiplatelet agents, if recently administered, increase the risk for bleeding after cardiac surgery. There is evidence for and against the ability of aspirin to increase mediastinal chest tube output and transfusion requirements.[161-164] In the European and U.S. literature, the ADP receptor antagonist clopidogrel (Plavix) has been associated with increased perioperative blood loss, an elevated risk for reoperation, increased mortality, and increased packed RBC and clotting factor use.[165-171] This trend has even been purported to occur in the OPCAB population.[172] However, one study did not show an association between the preoperative use of clopidogrel and increased bleeding and reoperation rates.[173]

Patients with a history of GP IIb/IIIa receptor blockade as a part of management of their acute coronary syndrome are at risk for increased bleeding and blood component use when given abciximab, especially within 12 hours of surgery.[174-177] Shorter-acting GP IIb/IIIa receptor antagonists have not been associated with increased bleeding or adverse outcomes. In fact, a study of dogs undergoing CPB found less platelet consumption, better platelet function, and less postoperative bleeding when the dogs were treated with eptifibatide.[178] Additionally, the PURSUIT (Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial showed that eptifibatide reduced death and MI at 7 days to 6 months after surgery.[179]

Enoxaparin, an LMWH, has been associated with increased transfusion rates and an increased risk for surgical re-exploration.[180,181] LMWH may also decrease heparin responsiveness.[182] Although LMWH is a weaker anticoagulant overall than heparin is, it has greater antithrombotic activity.[183]

Finally, patients with active, uncorrected use of warfarin who undergo surgery always have undesirable bleeding. The long-acting effects of warfarin usually require factor replacement, especially after surgery involving CPB.

In summary, patients who undergo cardiac surgery with preexisting, pharmacologically induced inhibition of the hemostatic system may have undesirable post-CPB bleeding. Diagnosis and treatment of this complication should be consistent, regardless of whether the derangement is a function of CPB itself, coexisting pharmacologic inhibition, or both. Management and treatment guidelines are discussed in the section addressing post-bypass bleeding and coagulopathy.

Induction of Anesthesia and the Prebypass Period

Premedication

The anesthesiologist should ensure that appropriate medications are administered with a sip of water on the morning of surgery. With a few exceptions, patients should receive their usual long-term medications on the day of surgery, particularly β-adrenergic blocking agents. The clinician should be aware that ACEIs, if administered on the day of surgery, may increase the patient's propensity for hypotension.[184] With respect to aspirin, it is well recognized that aspirin administration in the early postoperative period reduces the risk of ischemic complications after CABG surgery.[185] However, patients receiving aspirin immediately before surgery may have more mediastinal bleeding and greater transfusion requirements. A consensus statement published by the American College of Chest Physicians recommends starting aspirin administration within 6 hours after CABG surgery, regardless of whether preoperative aspirin therapy is discontinued.[186] A consensus statement published by the STS recommends that aspirin be continued until the time of surgery in patients at high risk for coronary thrombosis (i.e., those with unstable angina or recent MI). On the other hand, in patients undergoing unquestionably elective cardiac surgery, the STS recommends that aspirin be discontinued for 3 to 5 days beforehand because active platelet aggregation is less of a risk factor for ischemia in these patients.[187] Likewise, clopidogrel is usually discontinued 5 to 7 days before elective cardiac surgery.[187] Decisions about stopping administration of antiplatelet drugs and about surgical timing with respect

to bleeding risk are facilitated by platelet function testing, particularly with newer testing systems.[188]

The prospect of undergoing cardiac surgery provokes anxiety in most patients. Furthermore, insertion of intravenous and arterial catheters is painful and occurs before anesthesia is induced. The resultant anxiety and pain can lead to undesirable sympathetic stimulation resulting in tachycardia and hypertension. The first step in preventing this cycle is thoroughly explaining the anticipated anesthetic techniques and procedures to the patient. Premedication with a narcotic or anxiolytic agent (or both) to mitigate pain and anxiety is usually indicated before the patient is transported to the operating suite. Supplemental intravenous drugs—commonly midazolam and fentanyl—are often necessary during radial artery cannulation before induction of anesthesia. However, in patients with low cardiac output secondary to congestive heart failure (HF), sedation should be performed judiciously to avoid myocardial depression and resultant hypotension. Moreover, in patients with significant pulmonary hypertension, oversedation and respiratory depression leading to hypercapnia or hypoxia must be avoided.

Induction of Anesthesia

Anesthetics and techniques for induction of anesthesia should be selected with consideration of the patient's cardiac pathophysiology and other comorbid conditions. No single "recipe" can guarantee hemodynamic stability during anesthetic induction. Hypotension may result from a relatively hypovolemic state and vasodilation secondary to a reduction in sympathetic tone induced by anesthetics. Hypotension is particularly common in patients with poor LV function. Conversely, in patients with good myocardial function, hypertension may occur during induction because of preinduction anxiety or sympathetic stimulation caused by laryngoscopy and endotracheal intubation.

It is obviously important to cannulate the radial artery or an alternative site before induction of anesthesia to monitor arterial pressure on a beat-to-beat basis. If the radial artery is being harvested as a vascular conduit, the contralateral radial or brachial artery or a femoral artery may be used. Noninvasive blood pressure measurement can be used to check the accuracy of pressure readings if the arterial catheter is "positional" or "dampened." Of course, basic monitors, including the ECG and pulse oximeter, should also be used during induction of anesthesia. During any cardiac surgical procedure, central venous access is necessary to facilitate volume infusion, possibly including transfusion therapy, and to ensure that vasoactive agents are administered directly into the central circulation. A central venous catheter, a PA catheter, or both can be placed either before or after anesthesia is induced, although an increasing number of anesthesiologists defer central line placement until after anesthetic induction. The urinary bladder catheter, nasogastric tube, TEE probe, and any additional temperature monitors (e.g., a nasopharyngeal probe) are positioned after induction of anesthesia.

When choosing anesthetic agents and doses during induction and maintenance, one should consider any pharmacodynamic properties that might affect blood pressure, heart rate, or cardiac output, as well as the desirability of "early" extubation (i.e., within a few hours after the operation is completed). Anesthesia is most commonly induced with an opioid and a sedative-hypnotic (etomidate, thiopental, or propofol). It should be remembered that all anesthetics decrease blood pressure by decreasing sympathetic tone, decreasing systemic vascular resistance (SVR), inducing bradycardia, or directly depressing myocardial function. The only exception is ketamine, which has sympathomimetic effects; however, in patients with catecholamine depletion, ketamine's sympathomimetic effects may not counterbalance its direct negative inotropic effects. Because of their pharmacologic complexities, all anesthetics should be administered judiciously in patients who are critically ill or who have poor LV function.

Muscle relaxants are usually given early in the sequence of induction, particularly if relatively high doses of opioids are administered, to minimize chest wall rigidity. In addition, the vagolytic effects of pancuronium nicely counteract the vagotonic effects of high doses of opioids. Another muscle relaxant may be selected if maintaining a relatively slow heart rate is a primary consideration.

With the routine use of "fast-track" anesthesia techniques, including a trend toward earlier extubation, volatile agents are often chosen as the primary maintenance anesthetic. The predominant effect of isoflurane, desflurane, and sevoflurane is dose-dependent vasodilation with resultant decreases in SVR and blood pressure. These volatile agents may have an advantage in inducing preconditioning, which is particularly important in patients undergoing either CABG with CPB or OPCAB, in which myocardial ischemic insults are likely. Multiple cardioprotective effects of the volatile anesthetics have been studied, including triggering of the preconditioning cascade and mitigation of reperfusion injury.[189-192] However, nitrous oxide is avoided by most cardiac anesthesiologists because of its ability to increase gaseous bubble size and its undesirable effect on pulmonary vascular resistance (PVR).

The Pre–Cardiopulmonary Bypass Period

After induction of anesthesia, several important details must be remembered. Methods for positioning the arms vary according to institutional practice but must avoid causing brachial plexus injury by hyperextending the arms, ulnar nerve injury by improperly padding the olecranon, radial nerve injury by compressing the upper part of the arm against the sternal retractor support posts, or finger injury by entrapping the finger against the metal edge of the surgical table. Proper positioning also ensures that arterial catheters previously placed in the radial, ulnar, or brachial arteries are not "dampened." The head should be padded and occasionally repositioned during the procedure to prevent occipital alopecia, which can occur several days postoperatively. The eyes should be taped, possibly lubricated, and definitely free from pressure. Pressure-related injury to any soft tissue will potentially be exacerbated by hypothermia and decreased perfusion during CPB. All monitors and tubing should be checked after final positioning to ensure that none are kinked, entrapped, tangled, or inaccessible. Additionally, antibiotics must be administered (with documentation) within 1 hour of incision (vancomycin within 2 hours). Arterial blood gases and blood chemistry (electrolytes, glucose, and calcium) should be measured shortly after anesthesia is induced.

During the prebypass period, the anesthesiologist's major goal is to maintain hemodynamic and metabolic stability of the patient while making preparations for CPB. The degree of surgical stimulation varies markedly during this period. Patient positioning, preparation of the skin, and harvesting of the saphenous vein or veins cause only minimal sympathetic stimulation. Therefore, hypovolemic patients and those with poor ventricular function may be susceptible to hypotension during these periods. On the

other hand, chest incision, sternal splitting, and harvesting of the internal mammary artery (IMA) involve more intense surgical stimulation. These events may cause hypertension, tachycardia, and dysrhythmias, even in previously hypotensive patients. Just before initiation of CPB, during cannulation of the great vessels, surgical stimulation is again minimal, and manipulation of the heart and great vessels may transiently decrease venous return and cause a precipitous decline in blood pressure.

The anesthesiologist must be ready to treat hemodynamic aberrations. Specific cardiovascular medications to have immediately available include phenylephrine, ephedrine, calcium chloride, epinephrine, atropine, lidocaine, esmolol, and nitroglycerin. Other drugs that should be readily available include norepinephrine, vasopressin, nitroprusside, nicardipine, magnesium, potassium, and amiodarone. Of course, heparin (systemic dose plus supplemental doses) must also be immediately available. Although protamine should be accessible during the postbypass period, many institutions require that protamine be stored in unique packaging or in a separate, nearby location to prevent inadvertent inappropriate or premature administration.

In preparation for CPB, anticoagulation must be achieved. Heparin is still the standard agent used and is administered through a central venous catheter at an initial dose of 300 U/kg. Onset is almost immediate, but generally, the drug is allowed to circulate for 3 to 5 minutes before its effect is measured. The ACT must increase to at least 300 seconds before CPB is initiated, although most institutions use at least 400 seconds as their standard. Additional heparin is administered, if necessary, to increase the ACT to the desired level.

After heparinization, the next major step in the prebypass phase is vascular cannulation (Figs. 60-9 and 60-10).[193] One or more large veins or the right atrium (RA) is cannulated so that all systemic venous blood is diverted to the pump oxygenator; additionally, a large artery, usually the ascending aorta, is cannulated so that oxygenated blood is delivered back to the arterial

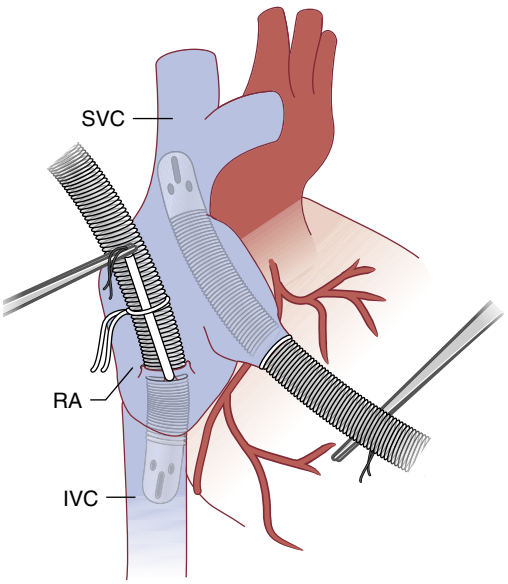

Figure 60-9 Position for two-vessel cannulation of the right atrium (RA) with placement of drainage holes into the superior vena cava (SVC) and inferior vena cava (IVC). The aortic cannula is not shown. *(From Connolly MW: Cardiopulmonary Bypass. New York, Springer-Verlag, 1995, p 59.)*

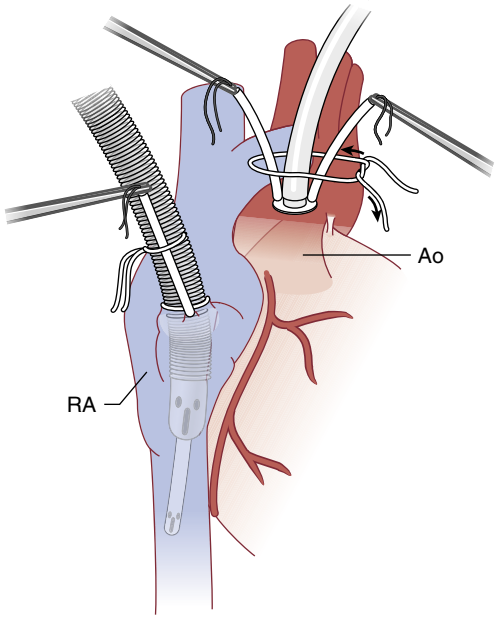

Figure 60-10 Aortic (Ao) and single, double-staged, right atrial (RA) cannulation. Notice the drainage holes of the venous cannula in the right atrium and inferior vena cava. *(From Connolly MW: Cardiopulmonary Bypass. New York, Springer-Verlag, 1995, p 59.)*

circulation. Heparin is always administered before cannulation. Usually, arterial cannulation is established before venous cannulation to allow rapid volume or blood resuscitation if necessary. Complications of aortic cannulation include arterial dissection, hemorrhage and resultant hypotension, inadvertent cannulation of the aortic arch vessels, and embolic phenomena caused by dislodged atherosclerotic plaque or by air introduced into or entrained around the aortic cannula. Complications of venous cannulation include hypotension from blood loss, dysrhythmias, and surgical mechanical compression of the heart or great vessels. When arterial cannulation is successful and the cannula has been inspected to ensure that no air is present, volume can be administered in 100-mL increments to treat bleeding and hypovolemia. If necessary, dysrhythmias are treated by cardioversion, medications, or rapid initiation of CPB.

Patients undergoing "redo" cardiac surgery (i.e., those who have previously had a median sternotomy) warrant special concern about the possibility of sudden massive hemorrhage. Frequently, the surgeon will elect to use an oscillating saw in these patients, but mediastinal structures adherent to the underside of the sternum may nevertheless be injured. If the RA, right ventricle, great vessels, or an existing coronary graft is cut, the surgeon may elect to initiate CPB on an emergency basis. Therefore, the anesthesiologist should have a systemic dose of heparin prepared. As soon as the patient is heparinized, the femoral or aortic arterial cannula is inserted, and the cardiotomy suckers may be used to create venous return (the so-called sucker bypass). At least 2 units of blood should also be immediately available for all redo cases.

Onset of Cardiopulmonary Bypass

With the onset of CPB, to guard against malposition of the aortic or venous cannula, the perfusionist checks the aortic inflow line pressure and for signs of inadequate venous return, while the anesthesiologist checks for persistently low arterial pressure, uni-

lateral blanching of the face, or any swelling in the neck veins, face, or conjunctiva. Once full bypass is established and aortic ejection by the heart has ceased, ventilation and inhaled drugs can be discontinued. If a PA catheter is present, it is pulled back 3 to 5 cm to minimize the risk of pulmonary perforation as the pulmonary arteries collapse. Prebypass urine output is recorded and emptied so that urine output during CPB can be monitored separately. The TEE probe may be used to watch for LV distention with the onset of CPB, which may indicate aortic valve regurgitation or other hemodynamic problems. Once CPB is established, the probe is left in the unlocked (neutral) position until the cardiac chambers are de-aired and the patient is weaned from CPB.

To ensure adequate anesthetic depth, supplemental intravenous sedative-hypnotics are administered, or a volatile agent is administered via a vaporizer connected to the oxygenator gas inlet of the CPB circuit. Administration of muscle relaxant is continued to prevent spontaneous ventilation, movement, or shivering during hypothermia and rewarming.

Weaning from Cardiopulmonary Bypass

Preparations for Weaning from Cardiopulmonary Bypass: The "CVP" Mnemonic

Fortunately, for most patients, separation from CPB is a relatively uneventful process. Several criteria should be met in all cardiac surgical cases before attempting weaning from CPB. Romanoff and Royster[194] suggest a mnemonic, "CVP," to help the clinician remember the main tasks necessary for successful termination of CPB (Table 60-7).

The first "C" stands for "cold" and refers to the patient's temperature at the time of weaning from CPB, which should be 36°C to 37°C. Neither the temperature of the venous blood returning to the CPB circuit nor nasopharyngeal temperature should ever exceed 37°C because hyperthermia may increase the risk for postoperative neurologic complications (please see the section on temperature).

The second "C" stands for "conduction" and refers to cardiac rate and rhythm. A heart rate of 80 to 100 beats/min is usually desirable. Bradycardia is treated with epicardial pacing wires and with β-adrenergic agents that have chronotropic and dromotropic, as well as inotropic properties. Tachycardia (i.e., heart rate >120 beats/min) is also undesirable. Sinus tachycardia may be due to anemia, hypovolemia, "light" anesthesia, or the administration of chronotropic agents; treatment is tailored to the presumed cause. Rhythm is also an important factor in optimizing cardiac output. Third-degree atrioventricular (AV) block requires pacing, ideally AV pacing. Sinus rhythm is preferable, particularly in patients with poor LV compliance, who are especially dependent on an "atrial kick" to achieve adequate filling. If supraventricular tachycardia is present, direct synchronized cardioversion is often warranted. In addition, pharmacologic therapy with amiodarone, esmolol, verapamil, or adenosine may be used in the initial treatment of or to prevent the reoccurrence of supraventricular tachycardia.

The third "C" stands for "cardiac output" or "contractility." Contractility may be estimated from TEE and cardiac output can be measured with a PA catheter, if available.

The fourth "C" refers to "cells" (i.e., RBCs). The patient's hemoglobin concentration should be 7 to 8 g/dL or slightly higher before weaning from CPB. If the hemoglobin concentration is less than 6.5 g/dL when rewarming commences, the perfusionist and anesthesiologist can consider hemoconcentration or transfusion of a unit of packed RBCs.

The fifth "C" stands for "coagulation," which means that in patients at risk for coagulation abnormalities, the prothrombin time, partial thromboplastin time, and platelet count should be measured a few minutes after protamine is administered. Examples of patients at risk for coagulation abnormalities include those with long CPB times; those with extreme hypothermia, elective circulatory arrest, or both during CPB; and those with chronic renal failure. Platelet function tests may be useful in patients taking platelet inhibitors such as clopidogrel or aspirin.

The first "V" is for "ventilation" of the lungs. As CPB is discontinued, the venous outflow line is gradually occluded, and PA blood flow is gradually restored. Pulmonary ventilation and oxygenation must be reestablished to allow the lungs to again become the site of gas exchange. Ideally, the lungs are initially reinflated "by hand" with a few sustained inflations to a peak pressure of about 30 cm H_2O. If an IMA has been grafted to a coronary artery, the anesthesiologist must examine the surgical field during these inflations to ascertain that the grafted artery is not overstretched, which could disrupt the distal anastomosis. Additionally, the compliance of the lungs is judged by these initial inflations, and bronchodilators can be administered if necessary. The surgeon should remove any fluid or blood from the pleural spaces and ensure that any pneumothorax is treated with a chest tube.

The second "V" is for "visualization" of the heart, both directly in the surgical field (where the right-sided chambers are visible) and on TEE, to estimate global and regional contractility. Furthermore, the degree of chamber filling (hypovolemic, euvolemic, or distended) can be estimated. In addition, one can perform a final check for air within the cardiac chambers with TEE.

The third "V" is for "vaporizer," which means that if volatile agents were used to ensure lack of awareness or to control blood pressure during CPB, the clinician should consider reinstituting a low dose immediately after weaning. However, because all of the volatile agents decrease contractility and blood pressure, these effects can confuse the differential diagnosis of hypotension and myocardial dysfunction during weaning.

The final "V" is for "volume expanders." When all products from the pump have been exhausted and if blood transfusion is

Table 60-7 Elements of Romanoff and Royster's "CVP" Mnemonic for Weaning Patients from Cardiopulmonary Bypass

C	V	P
Cold	Ventilation	Predictors
Conduction	Visualization	Pressure
Cardiac output	Vaporizer	Pressors
Cells	Volume expanders	Pacer
Calcium		Potassium
Coagulation		Protamine

From Romanoff ME, Royster RL: The postcardiopulmonary bypass period: Weaning to ICU transport. *In* Hensley FA, Martin DE, Gravlee GP (eds): A Practical Approach to Cardiac Anesthesia, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2008, pp 230-260.

not indicated, crystalloid and albumin or hetastarch should be readily available to rapidly increase preload if necessary.

As for the letter "P in the "CVP" mnemonic, Romanoff and Royster explain that the first "P" represents the need to be aware of "predictors" of adverse cardiovascular outcome. For example, a preoperative low ejection fraction (EF) and prolonged duration of CPB often predict difficulty in weaning the patient from CPB and the need for inotropic support. In addition, emergency surgery in patients with an acute coronary syndrome may lead to myocardial stunning. Furthermore, inadequate surgical repair (e.g., incomplete coronary revascularization) may result in ongoing ischemia.

The second "P" is for "pressure." Calibration and rezeroing are accomplished shortly before starting to wean the patient from CPB. Any discrepancy between distal (usually radial) arterial pressure and central aortic pressure should be recognized. Occasionally, the surgeon may need to insert a temporary aortic root cannula or a longer-lasting femoral arterial cannula to accurately monitor systemic blood pressure during and after termination of CPB.

The third "P" is for "pressors" (i.e., vasopressors and inotropic agents), which should be immediately available. Likewise, a vasodilator (e.g., nitroglycerin, nicardipine, or nitroprusside) should be immediately available.

The fourth "P" is for "pacer" because an external pacemaker should be readily available for all patients. Pacing is often needed to treat bradycardia. In patients with heart block, ideally an AV sequential pacemaker is used to maintain the atrial "kick."

The fifth "P" is for "potassium" because hypokalemia may contribute to dysrhythmias and hyperkalemia may result in conduction abnormalities. In addition, the patient's ionized Ca^{2+} level is usually checked; most clinicians have a low threshold for administering additional calcium chloride. Furthermore, magnesium (2 to 4 g) is generally administered before CPB is terminated. Although magnesium's efficacy in preventing postoperative atrial or ventricular dysrhythmias has not been clearly demonstrated,[195] hypomagnesemia is common after CPB, and the risk-benefit ratio for administering a 2- to 4-g dose is low.

The final "P" is for "protamine."

Termination from Cardiopulmonary Bypass

After ventilation has been reestablished, venous return to the pump is reduced by gradually clamping the venous line. The patient's intravascular volume is carefully increased by continued inflow via the aortic or other arterial cannula. Ventricular distention should be avoided because it increases wall tension and myocardial oxygen consumption. Pump flow into the aorta is lowered, in effect moving into a "partial bypass" phase wherein some of the venous blood is still going into the pump and some passes through the right ventricle and lungs to be ejected into the aorta by the left ventricle. When loading conditions are optimal and contractility appears adequate, the aortic inflow line may be clamped to separate the patient from CPB.

If CPB has been successfully terminated but cardiac performance is not optimal, preload can be increased by infusing additional blood from the pump into the aortic cannula, usually in 100-mL increments in adult patients. Monitoring left intraventricular volume in a qualitative fashion by observing the right ventricle directly and with TEE, as well as monitoring filling pressures, gives a good estimate of the adequacy of preload. At this point the anesthesiologist and surgeon jointly determine whether myocardial performance is adequate, which can best be accomplished by using TEE to observe the global and regional function of both ventricles. Supplemental information can be obtained by measuring cardiac output, if possible. Afterload can also be optimized at this point. Elevated systolic blood pressure should be avoided to prevent excessive stress on suture lines in the heart and aorta. Usually, 95 to 125 mm Hg is a desirable systolic pressure in adult patients in the postbypass period. If the patient is hemodynamically unstable and additional time is needed to administer initial or additional inotropes or vasoconstrictors, CPB can be reinstituted by unclamping the venous outflow line and directing all flow to the oxygenator again.

When protamine is administered, reinstitution of CPB becomes a more complicated process because the patient must first be reheparinized. Therefore, final checks of cardiac function, heart rate and rhythm, preload, afterload, and perfusion should be made jointly by the anesthesiologist and surgeon. The venous cannula or cannulas are usually removed after the initial test dose of protamine is given. Many surgeons remove the aortic cannula only after at least half of the protamine dose has been administered. The rate and mode of protamine administration (incremental small boluses versus continuous infusion) vary according to institutional and individual clinicians' practices, but a large dose of protamine should never be administered as a rapid bolus.

The Postbypass Period

Common Problems after Cardiopulmonary Bypass

Awareness

The potential for patient awareness must be assessed during and after CPB. Although patients may sweat during the rewarming period, usually because of perfusion of the thermoregulatory site in the hypothalamus with warm blood, sweating may also be due to awareness as the brain becomes normothermic during rewarming. Awareness may be more likely if considerable time has elapsed since any sedative-hypnotic or narcotic has been administered, if small doses of anesthetic agents were administered during CPB, or if the patient is young. Use of the bispectral index (BIS) monitor to guide isoflurane administration during and after CPB has been suggested.[196] However, falsely high BIS values during cardiac surgery have been attributed to interference from pump head rotation, pacemakers, and hypothermia itself.[197,198] Consideration should be given to continuing to administer a volatile agent once pulmonary ventilation is reestablished and to administering additional sedative/hypnotic doses, a narcotic agent, or both. Some clinicians begin infusing an agent such as propofol or dexmedetomidine shortly after weaning the patient from CPB and plan to continue it during and after transport to the ICU or cardiac recovery area.

Another important decision to be made is whether additional muscle relaxant is needed during and after weaning from CPB. Although patient movement may serve as an indication of patient awareness, such movement can be extremely dangerous if it results in dislodgement of the aortic or venous cannulas. Furthermore, shivering can occur because of the "afterdrop" in temperature after a period of hypothermic CPB and should be prevented by administering a muscle relaxant.

Cardiovascular Decompensation

Failure of the left or right ventricle is one of the common causes of cardiovascular decompensation during or shortly after weaning from CPB. Such failure may result in part from preexisting chronic ventricular dysfunction exacerbated by the ischemia-reperfusion injury that occurs during CPB with cardioplegia-induced cardiac arrest. In operations involving revascularization for coronary artery disease, myocardial injury resulting in postbypass ischemia or infarction is particularly likely. Causes include thrombosis or particulate or air emboli in a coronary graft or a native coronary artery, kinking of the graft, a distal suture causing constriction, coronary spasm, incomplete myocardial preservation during CPB, and incomplete revascularization secondary to distal disease or inoperable vessels. When valvular heart disease is present, there may be native valve gradients, a prosthetic valve may be malpositioned or malfunctioning, or ventricular dysfunction may be unmasked after mitral valve replacement or repair for mitral regurgitation (MR).

Usually, LV dysfunction is amenable to inotropic therapy or combination therapy with positive inotropic and vasodilator agents to optimize cardiac output. Sympathomimetic amines (i.e., catecholamines such as epinephrine, norepinephrine, dopamine, and dobutamine) and phosphodiesterase inhibitors (e.g., milrinone) are commonly used as first-line therapy. (Please refer to Chapters 16 and 23 for specific drug pharmacology and doses.) Small boluses of ephedrine (5 to 20 mg) or diluted epinephrine (2 to 10 μg) may be administered initially to temporarily treat ventricular dysfunction and hypotension while infusions are being prepared. Milrinone, an inodilator, improves cardiac output but significantly reduces SVR; concomitant use of an arterial vasoconstrictor is often necessary. Nitroglycerin is usually administered if ischemia is suspected. Occasionally, a mechanical assist device, such as an IABP or VAD, is necessary.

RV dysfunction or failure may also occur after CPB because of inadequate myocardial protection, inadequate revascularization with resultant RV ischemia or infarction, preexisting pulmonary hypertension, intracoronary or pulmonary air embolism, chronic mitral valve disease, or tricuspid regurgitation (TR). RV failure may be evidenced by RV distention and hypokinesis on TEE, as well as by elevations in CVP and pulmonary artery pressure (PAP). Therapy for RV failure includes inotropic support; milrinone, dobutamine, and isoproterenol are first-line agents. Other pharmacologic agents occasionally used to achieve pulmonary vasodilation include nitroglycerin, nitroprusside, prostaglandin E_1 (PGE_1), B-type natriuretic peptide (e.g., nesiritide), sildenafil, or inhaled agents such as nitric oxide and prostacyclin (prostaglandin I_2 [PGI_2, epoprostenol]). In addition, levosimendan, a new drug that is a myofilament Ca^{2+} sensitizer with inotropic and vasodilatory effects, is available clinically in Europe and undergoing evaluation in the United States.[199] It has been used in cardiac surgical patients with difficulty weaning from CPB or with severe LV or RV failure after mitral valve replacement.[200,201] Of course, hypoxemia should be avoided and hyperventilation should be instituted to decrease $Paco_2$ and PVR. Rarely, patients may require support with a right VAD.

Vasodilation with low SVR is another common cause of immediate post-CPB cardiovascular decompensation that may cause unacceptable hypotension. Predisposing factors include chronic administration of medications such as ACEIs, severe anemia with decreased viscosity, acid-base disturbances, and sepsis. Treatment with infusion of a vasoconstrictor agent such as phenylephrine, norepinephrine, or vasopressin is usually successful.

Dysrhythmias

Either supraventricular or ventricular arrhythmias may occur in the immediate postbypass period. Atrial fibrillation (AF) is the most common dysrhythmia after cardiac surgery, although it usually develops 2 to 5 days postoperatively. AF or atrial flutter occurring in the immediate postbypass period can often be converted to normal sinus rhythm with synchronized cardioversion, especially if sinus rhythm was present before CPB. Hypokalemia should be corrected. Magnesium is thought to have a low risk-benefit ratio and may modify the ventricular response rate and promote conversion to sinus rhythm.[195,202] Pharmacologic agents are available as well. Frequently, amiodarone is used both initially and as a continuous infusion.[202] Other agents that are occasionally used for initial treatment include esmolol, verapamil, and adenosine.

Ventricular flutter or fibrillation must be treated immediately with defibrillation. Internal paddles are applied directly to the heart to deliver 10 to 20 J of electricity. If ventricular arrhythmias persist or recur, an antiarrhythmic drug, usually lidocaine or amiodarone, is infused.

Usually, if bradycardia, complete heart block, or asystole develops after CPB, temporary epicardial pacing wires are used to provide electrical pacing, preferably AV sequential pacing. If an organized atrial rhythm is absent (e.g., patients with AF) and the ventricular response rate is slow, ventricular pacing is the only option. However, with this mode of pacing there is no atrial "kick," which would otherwise promote adequate filling of the LV chamber. Loss of the atrial kick is particularly detrimental in patients with poor LV compliance.

Bleeding and Coagulopathy

Although inadequate surgical hemostasis is the most common reason for blood loss after CPB, coagulation abnormalities certainly do occur and can contribute to unacceptable microvascular bleeding. Historically, the most common causes of excessive bleeding in cardiac surgical patients have been related to fibrinolysis and platelet activation induced by CPB, especially in elderly patients.[203]

Platelet dysfunction is frequently implicated in postbypass bleeding.[204] Exposure of blood to the oxygenator and CPB circuitry causes platelet activation, degranulation, and aggregation. Furthermore, relative thrombocytopenia commonly occurs after CPB as a result of hemodilution and platelet sequestration, adhesion, and destruction. Usually, these CPB-related platelet abnormalities are not clinically important because coagulopathies requiring platelet therapy do not develop in most patients who undergo cardiac surgery.[188] Nevertheless, bleeding difficulties develop in a subset of patients. Chen and colleagues[166] found that preheparinization testing of platelet function with ADP-mediated aggregometry can identify patients at highest risk for perioperative bleeding and transfusions and may further reduce perioperative transfusion requirements (Fig. 60-11).

Another cause of coagulopathy is thrombin production and fibrinolysis. Thrombin is produced by the extrinsic and intrinsic coagulation pathways and by activated platelets and is only partially suppressed by heparin during CPB. Ongoing

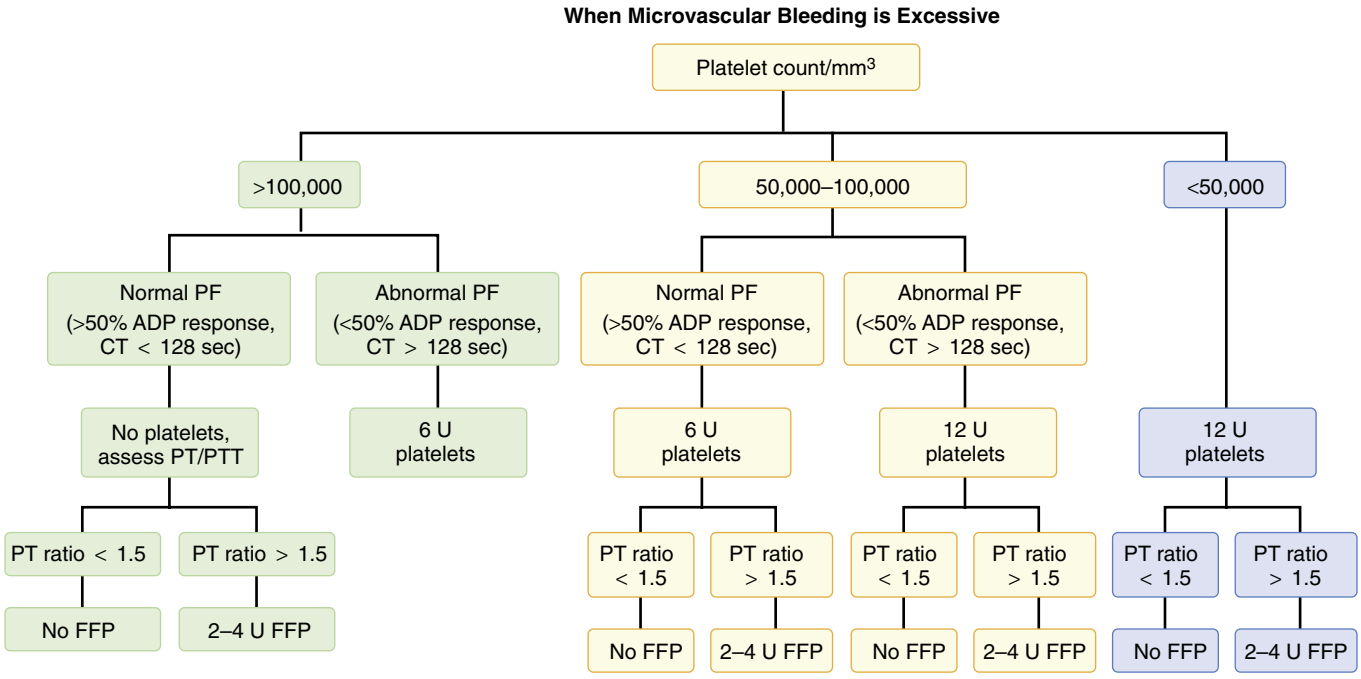

Figure 60-11 Bleeding management algorithm used for the treatment of excessive microvascular bleeding. ADP, adenosine diphosphate; CT, closure time; FFP, fresh frozen plasma; PF, platelet function; PT, prothrombin time; PTT, partial thromboplastin time. U, units. *(Reprinted with permission from Chen L, Bracey AW, Radovancevie R, et al: Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting. J Thorac Cardiovasc Surg 128:425-431, 2004.)*

thrombin generation during CPB results in low-grade consumption of multiple factors in the coagulation cascade. If CPB is prolonged, these factors may be depleted. Fibrinolysis, an intrinsic response to coagulation, is activated by the t-PA that is released by injured endothelial cells. With excessive fibrinolysis, depletion of fibrinogen can result in consumptive coagulopathy. In addition, fibrinolysis exerts important deleterious effects because fibrin degradation products and plasmin inhibit platelet function.

An evidence-based approach to the diagnosis and treatment of residual, unacceptable post-CPB microvascular bleeding and to thorough surgical hemostasis dictates timely detection and treatment of specific causes of coagulopathy. Patients with this complication benefit from point-of-care (POC) testing and incorporation of this testing into a transfusion algorithm. Algorithms are designed to minimize unnecessary and indiscriminate blood product transfusions.[166,205-208]

Pulmonary Complications

Pulmonary complications immediately after CPB vary from mild to severe and include atelectasis, bronchospasm, hemothorax, pneumothorax, endobronchial intubation, mucous plugs or blood clots in the endotracheal tube, pulmonary edema, and pulmonary dysfunction that varies from a mild increase in the alveolar-arterial O_2 gradient to a form of adult respiratory distress syndrome (ARDS) known as "postperfusion lung syndrome."

Atelectasis is a common cause of decreased arterial oxygenation in the postbypass period because during CPB, either the lungs are not ventilated or very small tidal volumes are used. Ideally, the lungs are fully reinflated "by hand" before machine ventilation is reestablished during weaning from CPB. Patients with chronic obstructive pulmonary disease (COPD) or any preexisting tendency toward bronchospasm may experience an exacerbation during CPB. Treatment includes inhaled β_2-agonists (e.g., albuterol), inhaled anticholinergic agents (e.g., ipratropium), epinephrine, and corticosteroids.

Hemothorax is caused by the accumulation of blood and clot in the pleural cavity, which should be surgically removed before chest closure. Pneumothorax may result from entry of the pleural cavity during dissection of the IMA or from excessive positive-pressure ventilation of the lungs. Pneumothorax may not be manifested until after chest closure; it is treated by insertion of a chest tube.

Endobronchial intubation may occur when the head is partially hidden from the anesthesiologist's view. Expansion of both lungs should be checked during initial full ventilation before weaning from CPB, when the chest is open, so that a good view of both lungs may be obtained. If there is any blood or mucus in the endotracheal tube, it should be suctioned during and after weaning from CPB.

Pulmonary edema may be cardiogenic because of preexisting HF exacerbated by the additional fluid load in the pump prime. Ultrafiltration during CPB and diuresis during and after CPB may minimize such pulmonary edema. Noncardiogenic pulmonary edema (i.e., ARDS) may occur after prolonged CPB with sequestration of neutrophils in the pulmonary capillaries and elevation of lysosomal enzyme activity resulting in a localized "inflammatory response" and increased capillary permeability. Other causes of ARDS include multiple pulmonary emboli and transfusion reactions.

Metabolic Disturbances

Hypokalemia is relatively common after CPB and may contribute to the development of dysrhythmias. Causes include diuresis secondary to preoperative diuretics, mannitol administration during CPB, alkalemia, and hyperglycemia treated with insulin administration. Hypokalemia may be corrected by carefully monitored

administration of potassium via an infusion pump at a rate of 10 to 20 mEq/hr, with frequent measurement of potassium, as well as glucose and arterial blood gases.

Hyperkalemia also occurs occasionally after CPB and is usually caused by large doses of cardioplegia or, occasionally, large amounts of blood products. Hyperkalemia is more likely to occur if renal function is impaired. Occasionally, hyperkalemia is severe enough to interfere with conduction. It can be treated with moderate hyperventilation or the administration of calcium or glucose and insulin, or both.

Hypocalcemia can occur after CPB, particularly in bleeding patients who are receiving multiple blood transfusions with large amounts of citrate. This phenomenon is exacerbated by hypothermia and low-output states. Hypocalcemia is corrected by the administration of 10% calcium chloride in 5- to 10-mg/kg doses.

Hypomagnesemia is common in the postbypass period and is due to hemodilution with magnesium-free fluids during CPB. Many centers routinely administer 2 to 4 g of magnesium during weaning or after CPB in an attempt to minimize the incidence of ventricular and atrial arrhythmias.[195,202]

Hyperglycemia is extremely common after CPB (please see the earlier section "Endocrine System: Glucose, Thyroid Hormone, and Hormone Replacement Therapy"). A few centers wait until the postoperative period to begin insulin therapy.[209] Most centers treat glucose levels greater than 200 mg/dL with intermittent doses of insulin or with an insulin infusion, although some centers treat cardiac surgical patients more aggressively in an attempt to keep glucose levels below 150 mg/dL.[84,85,88] In a recent study, patients were randomized to intensive intraoperative insulin treatment (to maintain glucose levels at 80 to 100 mg/dL) or to standard insulin treatment (to keep glucose levels below 200 mg/dL).[87] Surprisingly, the investigators reported a statistically nonsignificant increase in the incidence of death and stroke in the intensive insulin treatment group. Further study is needed to determine how aggressively hyperglycemia should be treated during surgery.[86]

Chest Closure

Hemodynamic deterioration may occur during chest closure because of cardiac tamponade in patients with ongoing bleeding. Other reasons for severe hypotension during chest closure include hypovolemia, ischemia secondary to kinking of an arterial or venous coronary graft, and impairment of RV contractility and venous return in patients with significant myocardial edema. TEE is often particularly useful in determining the cause of hypotension during chest closure because tamponade, hypovolemia, RV or LV global dysfunction, and severe new wall motion abnormalities can be quickly recognized with this monitor. Reopening the chest may be necessary while treatment is instituted. Occasionally, the patient's sternum cannot be closed because of hemodynamic instability; in such cases, only skin closure is attempted, and plans are made to return to the operating room for sternal wiring after a period of myocardial recovery in the ICU.

Transport to the Intensive Care Unit

After all incisions are closed and dressings are applied, provided that the patient is hemodynamically stable, the next step is transport to the ICU. Monitoring should not be completely interrupted even for a few moments—the ideal transport monitoring system has a "brick" that can be ejected from the operating room monitor and is compatible with the transport monitor. If such equipment is not available, sequential disconnection of monitoring devices is advised so that an "on-line" monitor is always visible.

On arrival at the ICU or cardiac recovery area, monitoring devices should be transferred in the same careful way. Changes in patient status necessitating changes in volume infusion, vasoactive drugs or doses, pacemaker settings, or ventilator settings and concerns about bleeding potential should be reviewed with ICU personnel. The anesthesiologist should remain with the patient until hemodynamic and overall stability is ensured.

Cardiopulmonary Bypass

CPB is a form of extracorporeal (*extra* = "outside of," *corporeal* = "the body") circulation (ECC) in which the patient's blood is rerouted outside the vascular system and the function of the heart, the lungs, and to a lesser extent the kidneys is temporarily assumed by surrogate technology. The circuitry and equipment used to facilitate this substitution are topics of the next section of this chapter.

Circuitry and Equipment

The goal of ECC is to provide a motionless and bloodless field for the surgeon by rerouting blood away from the area of surgical interest. The most common and most complicated ECC procedure is CPB, which involves rerouting the patient's entire cardiac output around both the heart and lungs. Other ECC techniques include left heart bypass (LHB), cardiopulmonary support (CPS), and extracorporeal membrane oxygenation (ECMO).

The pumps, tubing, artificial organs, and monitoring systems used in CPB are diagrammed in Figure 60-12. Simply stated, venous blood is intercepted as it returns to the RA and diverted through the *venous line* of the CPB circuit to a *venous reservoir*. The *arterial pump* functions as an artificial heart by withdrawing blood from the reservoir and propelling it through a *heat exchanger*, an artificial lung (the *oxygenator*), and an *arterial line filter* before returning it through the *arterial line* to the patient's arterial system. Additional pumps and components are used to assist in the operation to manage shed blood (the *pump sucker*), decompress the heart (*vent*), and deliver *cardioplegia solution*.

Blood Tubing

The tubing used to connect the various components and conduct blood into and out of the patient's vascular system is medical-grade polyvinyl chloride (PVC). For decades, the blood-tubing interface was untreated PVC. However, the newer generation of PVC tubing has surface coatings and other modifications that significantly alter the bioactivity of the surface. Collectively, these coatings have been shown to reduce markers of subclinical coagulation, attenuate the elevation of cytokines and other inflammatory markers, and shorten intubation times.[210-213]

Venous Reservoirs

Blood reservoirs perform an important function in the conduct of CPB by facilitating the displacement of a large volume of blood out of the circulation at strategic times during the operation.

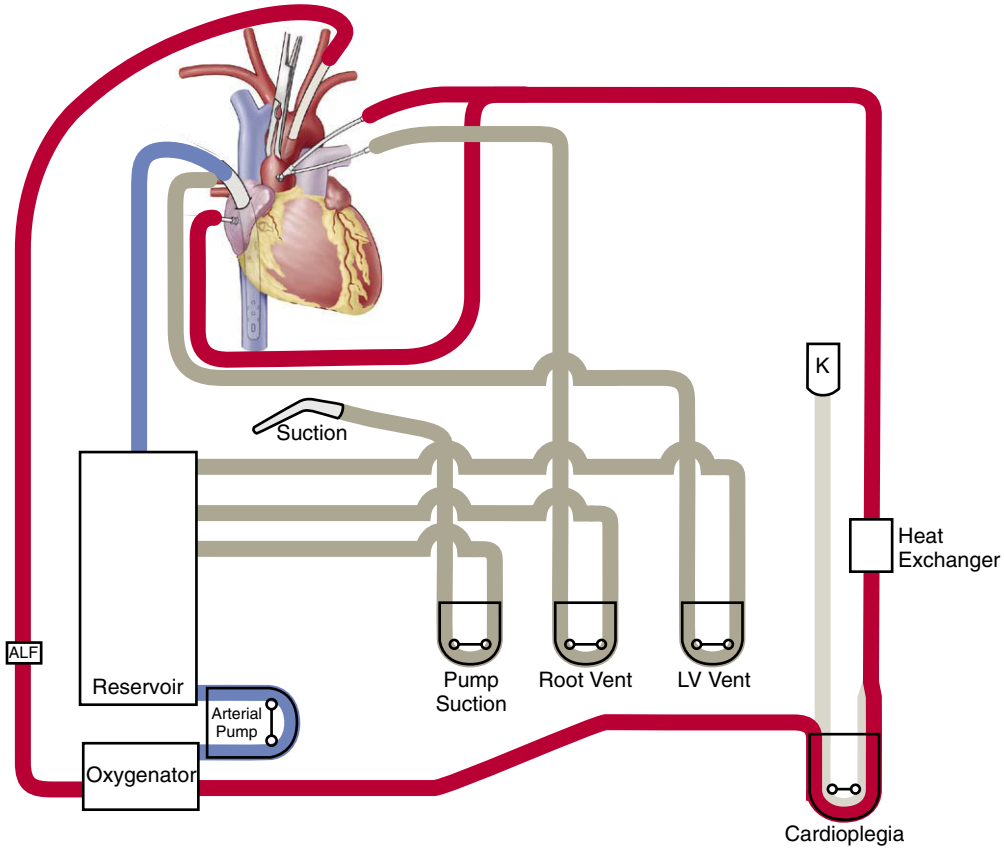

Figure 60-12 A typical cardiopulmonary bypass circuit interfaced with a patient.

Positioned between the venous line and the arterial pump, blood reservoirs may be collapsible plastic bags or clear plastic hard-shelled containers. Hard-shelled reservoirs include an integral filtration mechanism with a screen and depth filters through which blood must pass before leaving the outlet of the vessel. Almost universally, hard-shelled reservoirs have integrated positive and negative pressure release valves, which are necessary for the application of suction to the reservoir to augment venous drainage.

Arterial Pumps

The pumping device used to replace the function of the heart generally uses one of two primary technologies: a roller pump or a centrifugal pump. Roller pumps are positive-displacement pumps that function by occluding a point in a piece of tubing and then rolling the occlusive point of contact along a length of the tubing. This forces the fluid in the tubing to move forward in front of the occlusive point while simultaneously drawing in fluid behind the occlusive point. Centrifugal pumps, in contrast, are nonocclusive kinetic pumps that generate flow by magnetically coupling the high-speed revolution of a reusable motor to the plastic plates, fins, or channels inside a disposable cone. This produces a constrained vortex that propels fluid through the opening on the side of the cone while drawing fluid into the point of the cone. Both pump technologies are traumatic to the formed elements in blood; however, centrifugal pumps are thought to be less traumatic than roller pumps.[214,215]

Each type of pump poses unique risks that must be appreciated. Roller pumps, by virtue of their occlusive nature, are capable of generating extremely high positive and negative pressure and are also able to pump massive quantities of air. Consequently, the national standard of care requires that these pumps be servoregulated to automatically reduce their speed when high pressure or air is detected in the path of the blood. In contrast, centrifugal pumps, being nonocclusive, are unable to generate extremely high or low pressure. Additionally, if a large bolus of air is introduced into the disposable cone, the pump will deprime, rendering it unable to pump large volumes of air. However, the lack of a point of tubing occlusion inside the pump allows retrograde flow from the patient's high-pressure arterial system backward through the arterial line, filter, and oxygenator and ultimately into the low-pressure venous reservoir. This may occur whenever the pump's revolutions per minute are reduced below a critical threshold. A large-bore one-way valve can be positioned in the arterial line to eliminate the possibility of retrograde arterial flow and inadvertent patient exsanguination.

Heat Exchanger

Heat exchangers are essential to CPB because they facilitate management of the patient's blood temperature. Throughout the period of CPB, 20% to 35% of the patient's circulating blood volume is outside the body and is exposed to the ambient temperature of the operating suite, which can cause hypothermia. Therefore, in all CPB procedures there is an inherent need to warm the blood before CPB is terminated. Additionally, for many surgical procedures, some amount of hypothermia, from mild (35°C) to profound (18°C), is desirable to reduce the patient's metabolic rate. In these cases, the heat exchangers may be used

to reduce the temperature of the blood on initiation of CPB and then to warm the blood before the termination of CPB.

Oxygenator

The oxygenator substitutes for the patient's native lungs and performs the essential function of gas exchange. There are several similarities between the native lung and the oxygenator. Both have a gas phase and a blood phase, both are driven by passive diffusion gradients, and both use a membrane to separate the blood from the gas. In the oxygenator, the membrane is usually made from microporous polypropylene. This material is extruded into thin straws with an outer diameter of 200 to 400 µm, a wall thickness of 20 to 50 µm, and a total surface area of 2 to 4 m^2. Typically, oxygenators have a static priming volume of 135 to 340 mL and are capable of arterializing up to 7 L/min of typical venous blood.[216]

The native lung uses the conductive airways for both inspiration and expiration and is dependent on a certain tidal volume and respiratory rate to regularly refresh the gas in the alveolar space. The oxygenator, however, has separate gas inlet and outlet ports and can refresh the gas inside its gas space (the internal lumen of the straws) with a continuous flow or "*sweep*" of gas through the oxygenator. The blood space of an oxygenator is the space around the outside of the straws. Venous blood entering the oxygenator is directed across the outside of the fibers while gas is concurrently circulated through the inside of the fibers. Pressure gradients between the blood space and the gas space drive oxygen across the membrane and into the blood, whereas carbon dioxide is driven out of the blood and into the gas phase. Unlike the membrane in the native lung, however, the oxygenator's membrane is not a true membrane because the microscopic pores on the sides of the fibers (0.5 to 1.0 µm) are small enough to prevent plasma and the formed elements of blood from leaking through but are still large enough to allow gas to pass through. Therefore, care must be taken to ensure that the pressure in the gas space never exceeds the pressure in the blood space or gaseous emboli will form in the blood. In appreciation of the risks inherent in using a pressurized gas phase, most oxygenators are designed with multiple gas outlet ports. In any case, caution should be exercised to ensure that the outlet of the gas phase cannot become occluded.

Arterial Line Filter

In adult practice in the United States, arterial line filters are used in more than 95% of CPB procedures. These filters are placed in the arterial line as the last component through which blood passes before it returns to the patient. With pore sizes of 20 to 40 µm, arterial line filters increase patient safety by removing particulate and gaseous microemboli. To effectively remove bubbles from the blood path, arterial line filters must be continuously "purged" by allowing a small amount of blood to recirculate from the top of the filter back into the venous reservoir.

Sequence of Events

Although the approach to surgical procedures requiring CPB varies among institutions, all procedures loosely follow a predictable *sequence of events*. CPB at any institution requires circuit selection and priming, anticoagulation, cannulation, initiation and maintenance of CPB, myocardial protection, and finally, weaning and termination from CPB.

Circuit Selection and Priming

When selecting the components for an extracorporeal circuit, the perfusionist first calculates the highest blood flow that may be necessary during the procedure. Typically, the highest blood flow is approximately 2.4 to 3.0 L/min/m^2 or 60 to 70 mL/kg/min. The calculated flow is then compared with the "rated flow" for the components of the ECC circuit. This flow rating represents the highest blood flow at which the component can perform its function within the acceptable range of hydraulic forces (pressure and sheer stress) without causing an unacceptable amount of blood trauma.

The combination of components included in the ECC determines the "prime volume" of the circuit, or the volume of balanced electrolyte solution necessary to completely de-air the circuit. This prime volume is the main cause of the hemodilution associated with CPB. Therefore, the perfusionist must calculate the patient's resultant hematocrit (HCTr), which is the patient's predicted hematocrit after the patient's preoperative blood volume is mixed with the asanguineous prime volume of the ECC. The HCTr is computed by dividing the patient's calculated volume of RBCs into the calculated total volume of distribution represented by the addition of the ECC prime volume to the patient's blood volume (Box 60-3). An adult patient's intravascular volume of distribution will increase by 20% to 35% when CPB is initiated. This increased volume of distribution dilutes not only all of the proteins and formed elements of the blood but also plasma levels of drugs. If this dilution is not anticipated, the patient's depth of anesthesia and circulating concentrations of many pharmacologic agents may be reduced when CPB is initiated.

The solution used to prime the CPB circuit is generally a balanced electrolyte solution containing normal plasma concentrations of many of the standard blood ions. Various drugs may be added to the solution to attenuate the dilutional effect of CPB on those agents (e.g., albumin, heparin, bicarbonate) or to discourage edema formation or encourage diuresis of the prime fluid by the patient (e.g., mannitol).

Anticoagulation

With the circuit primed and the vessels exposed, standard procedure requires that the patient be fully anticoagulated before can-

Box 60-3 Resultant Hematocrit (HCT) Formula

HCTr = Patient's preoperative red blood cell volume/Total volume of distribution at the start of CPB

$$HCTr = (BVp \cdot HCT)/(BVp + PVc)$$

$$HCTr = (kg \cdot 75 \cdot HCT)/(kg \cdot 75) + PVc$$

where

HCTr = resultant hematocrit

BVp = patient's blood volume

kg = patient's weight in kg

PVc = prime volume of the ECC

CPB, cardiopulmonary bypass; ECC, extracorporeal circuit.

nulation. Dosing of heparin and monitoring of the ACT have been discussed earlier in the chapter. Importantly, there are many commercial devices designed to monitor the ACT, and although the ACT is used as if it were a standardized test, the results produced by different instruments are far from standardized. We have shown that these devices, when used on the same pool of heparinized blood, can produce ACT results that vary by as much as 40% (Fig. 60-13).

The ACT test is not used to monitor heparin levels but to monitor the anticoagulant effects of heparin and other anticoagulants. Thus, elevated ACT measurements taken before, during, or after CPB may be influenced by variables other than heparin (e.g., hypothermia, hemodilution, and aprotinin).

POC heparin level tests are commercially available and may be used to monitor circulating heparin levels in CPB-supported patients. Indeed, some centers monitor both the circulating level of heparin and its anticoagulant effects and administer heparin intermittently throughout the procedure to maintain a predetermined therapeutic heparin level and a minimally acceptable ACT.

Heparin dosing may be based on the patient's weight (300 to 400 U/kg) or determined by a dose-response curve. Heparin dose-response curves are determined in vitro by measuring the ACT of the patient's blood at baseline (without heparin) and after a known concentration of heparin (2.5 U/mL) is added. By graphing the ACT in seconds against the blood concentration of heparin, one can extrapolate the blood concentration of heparin needed to achieve a target ACT acceptable for CPB. Most patients need 1.5 to 3.0 U/mL heparin to achieve an ACT of 480 seconds. A commercial device designed to automate this process is available, and from the patient's height, weight, sex, and heparin dose-response test results, the machine calculates the appropriate heparin dose to administer during CPB.

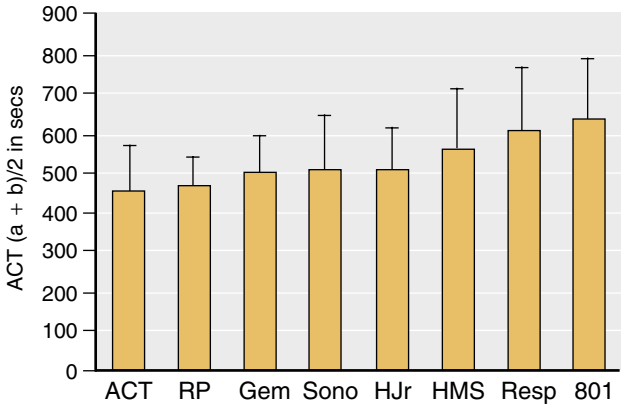

Figure 60-13 Results from eight different activated clotting time (ACT) tests from a group of heparinized patients undergoing cardiopulmonary bypass. Results may vary as much at 40% between different manufacturers' tests.

Cannulation

Every CPB procedure requires a high-flow cannula in a large vein and another in a large artery for withdrawing blood from and returning blood to the patient (Table 60-8). Most procedures include additional cannulas for administering cardioplegia solutions to the heart and removing (venting) blood and air from the chambers of the heart. Different surgical procedures require different cannulation techniques, the most common of which will be described here.

The target for venous cannulation is generally the RA. The RA is the central repository for all venous blood, and the right atrial appendage is conveniently accessible through a sternotomy. Although RA cannulation is optimal for most cardiac surgical cases, the cannula may not perform well when the heart is being

Table 60-8 Common Approaches to Venous and Arterial Cannulation for Cardiopulmonary Bypass

Procedure	Venous	Arterial	Cardioplegia	Vent	Comments
CABG	2-stage approach in the RA	Ascending aorta	Root and/or CS	Aortic root	Patients with low EF or failure to wean from CPB may benefit from LV venting
AVR	2-stage approach in the RA	Ascending aorta	Root and/or CS, plus hand-held selective once the root is open	LV and aortic root	None
MVR	Bicaval	Ascending aorta	Root and/or CS	LV and aortic root	None
Aortic root replacement, not including the arch	2-stage approach in the RA	Ascending aorta	Root and/or CS	LV and aortic root	The closer the repair gets to the head vessels, the more difficult aortic cannulation becomes
Aortic arch	2-stage approach in the RA	Axillary or femoral artery	Root and/or CS	LV and aortic root	CS cardioplegia unlikely if the coronaries are unobstructed
Redo procedures	Femoral vein	Femoral artery	Root and/or CS	Aortic root and/or LV	Only in extreme cases, i.e., when the heart is tightly adhered to the back of the sternum, or any time that the heart is lacerated during sternotomy
Other intracardiac procedures	Bicaval	Ascending aorta	Root and/or CS	LV and aortic root	Any procedure that requires opening the RA or excessive surgical retraction

AVR, aortic valve repair/replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; CS, coronary sinus; EF, ejection fraction; LV, left ventricle; MVR, mitral valve repair/replacement; RA, right atrium.

retracted. Significant retraction of the heart is necessary to access some posterior coronary arteries for bypass or to access the mitral valve through a left atriotomy. Because of surgical retraction involving the RA, the venous cannulation site for mitral valve repair or replacement procedures is generally moved away from the RA to the superior and inferior venae cavae. If a single cannula is placed in each vena cava, venous blood can be intercepted just before it enters the RA so that the cannula can provide acceptable drainage throughout the procedure. The RA may also be approached through the femoral vein. A femoral venous cannula extends the entire length of the inferior vena cava and rests with its openings in the RA.

An improperly sized or positioned venous cannula will obstruct the flow of blood into the ECC circuit. This may elevate CVP and encourage extravasation of blood volume from the vascular compartment into the extracellular compartment (third spacing). Therefore, it is important to evaluate the performance of the venous cannula or cannulas on initiation of CPB. Properly placed venous cannulas will allow complete decompression of the right side of the heart, as indicated by a CVP and PAP of zero.

The ECC returns oxygenated blood to the patient through the arterial cannula. For CABG and valve procedures, the standard target for the arterial cannula is the portion of the ascending aorta below the aortic arch but still 3 to 4 cm above the aortic valve. The alternative approaches of axillary or femoral artery cannulation are used in procedures that require manipulation of much of the aortic root, arch, or both. Axillary artery cannulation is generally facilitated by the anastomosis of a tube graft to the side of the axillary artery to provide access for the arterial cannula without interrupting blood flow to the right arm. An added benefit of axillary cannulation for aortic arch procedures is that clamping the innominate artery allows antegrade cerebral perfusion to be performed during a period of circulatory arrest. Femoral arterial cannulation involves inserting the cannula through the femoral artery and into the abdominal aorta. Blood flow to the thorax is directed retrogradely up the aorta. Ischemia of the cannulated limb is a risk commonly associated with femoral arterial cannulation, and dissection of the cannulated artery is a risk associated with all arterial cannulation sites. Proper cannula placement should be confirmed before CBP is initiated.

With venous and arterial cannulas in place, the heart and the lungs can be bypassed. However, additional cannulas are needed to facilitate aortic cross-clamping and cardiac arrest. For example, cardioplegia cannulas can be placed in the ascending aorta, and then the aorta can be occluded by placing a large vascular clamp (i.e., a cross-clamp) across it. Occluding the aorta between the arterial cannula and the antegrade cardioplegia cannula interrupts blood flow from the arterial line of the ECC to the coronary arteries, thereby initiating a period of global myocardial ischemia. Intermittent or continuous administration of cardioplegia through the antegrade and retrograde cardioplegia cannulas serves to attenuate the ischemic insult (via a mechanism discussed later).

Bronchial pulmonary vascular connections deliver approximately 1% of the cardiac output to the lungs, where it is subsequently returned to the left side of the heart. In patients with chronic pulmonary disease, this recirculation may increase to more than 10% of cardiac output.[217] During the period when the aorta is cross-clamped, this blood volume will distend the left side of the heart and the pulmonary vasculature if the blood is not actively removed. Additionally, intracardiac procedures inherently introduce air into the left-sided chambers, and this air must be removed before the patient is weaned from CPB.

Vent cannulas facilitate decompression and de-airing of the heart. The heart is most commonly vented at the aortic root or directly from the left ventricle. Aortic root vents use the same cannula that is used to deliver antegrade cardioplegia and draw blood and air from the left ventricle across the aortic valve and into the reservoir of the ECC circuit. Because the antegrade cardioplegia needle has a small gauge and is positioned above the aortic valve, root vents have several significant limitations: they cannot be used when antegrade cardioplegia is being administered, and they are ineffective in decompressing the left ventricle when the cross-clamp has been removed. These limitations are not generally significant for an uncomplicated CABG procedure, but for CABG in patients with severely compromised ventricular function and for all intracardiac procedures, direct LV venting becomes essential. LV vents are typically introduced through the right superior pulmonary vein and advanced through the left atrium (LA), across the mitral valve, and into the left ventricle. The 10- to 14-Fr cannula used for this purpose offers significantly better venting capacity than the root vent does. Flows in the range of several liters per minute can be drawn through these cannulas when necessary, and because they are inserted directly inside the left ventricle, they are very effective in removing air bubbles that remain after an intracardiac procedure has been completed. Additionally, because the LV vent is separate from the cardioplegia cannula, it can be used to decompress the heart during antegrade cardioplegia administration, which may be necessary for patients with aortic insufficiency. Unfortunately, there are numerous case reports of patient injuries that resulted from air being pumped into the heart through malfunctioning vent lines.

Initiation and Maintenance of CPB

With the patient anticoagulated and cannulated, CPB may be initiated. Before initiating CPB, it is good practice to verify the patency of the arterial cannula. After proper position of the arterial cannula is confirmed, CPB may be initiated by removing the clamps on the venous line between the venous cannula and the reservoir. The patient's blood then passively drains into the ECC. Simultaneously, the arterial pump on the CPB machine begins to infuse the mixture of prime solution and autologous blood into the patient through the arterial cannula. It is very important to evaluate the performance of the venous and arterial cannulas during the initial seconds of CPB. The pressure in the arterial line of the ECC should be maintained below 300 mm Hg to prevent excessive trauma to the formed elements of the blood. Cannula position is evaluated mainly by examining the patient's hemodynamics. Provided that the venous cannula is adequately draining the venous return to the heart, right-sided heart pressure (CVP and PAP) should decrease to 0 mm Hg and become nonpulsatile, and arterial blood pressure should reach a normal mean pressure (60 to 90 mm Hg) while also becoming nonpulsatile.

The arterial trace usually becomes nonpulsatile as the heart is emptied and the pumping force is changed from the ventricle to the nonpulsatile arterial pump of the heart and lung machine. However, patients with aortic insufficiency will continue to have a pulsatile arterial trace despite complete venous drainage (CVP and PAP = 0 mm Hg) because of regurgitation of blood from the arterial cannula across the incompetent aortic valve and back into the left ventricle. If right heart pressure does not reduce to zero, the arterial trace remains pulsatile, and arterial pump flow cannot

be increased to full flow, the position of the cannulas must be re-evaluated. Once full flow has been achieved, the function of the heart and lungs will have completely made transition to the CPB machine, and the anesthesiologist may turn off the ventilator.

Initiation of CPB is often associated with a period of hypotension, which can be managed with the administration of an α-agonist (e.g., phenylephrine) into the venous reservoir of the ECC circuit (Fig. 60-14). While CPB is maintained, the adequacy of perfusion is continuously evaluated by monitoring hemodynamic variables. Blood flow from the arterial pump can be manipulated across a range of 1.6 to 3.0 L/min/m^2 to deliver an arterial blood pressure of 50 to 90 mm Hg and a mixed venous saturation ($S\bar{v}O_2$) greater than 65%. Any hypotension and hypertension that occur despite adequate flow and $S\bar{v}O_2$ can be treated by adjusting the patient's SVR with vasoconstrictors or vasodilators.

Arterial blood gas samples should be taken at least every 30 minutes to assess the performance of the oxygenator and to monitor the patient for the development of acidosis and proper anticoagulation status. Base deficit values of −5 or less can be corrected with sodium bicarbonate, but the underlying cause of the acid production should ultimately be addressed. Increased perfusion flow and pressure may be indicated. ACT values below the institutional parameter acceptable for CPB (usually ≥400 sec) should be treated with a heparin bolus administered into the ECC.

Urine output is also monitored during CPB as an indicator of perfusion flow and pressure. Poor urine production during CPB has not been shown to predict postoperative renal deficiency. Rather, age, preoperative renal function, the duration of CPB, and EF have been correlated with postoperative renal dysfunction.[81]

Myocardial Protection

To provide a motionless field for the surgeon, the heart is arrested in diastole by the administration of a potassium-enriched cardioplegia solution to the heart.

Interrupting myocardial electromechanical activity is the single most important step in reducing the heart's metabolism. Potassium-induced arrest alone reduces the heart's myocardial oxygen consumption by 90%. It is common to augment this reduction with hypothermia by administering cold cardioplegia solution. The combined influence of potassium arrest and myocardial temperatures lower than 22°C reduces myocardial oxygen consumption by 97% and enables the tissue to withstand complete interruption of blood flow for periods of 20 to 40 minutes. At the completion of surgery, myocardial arrest can be reversed by reperfusing the heart with warm normokalemic blood.

With regard to cardioplegia solutions, their ingredients vary considerably from institution to institution, the exception being potassium used as the arrest agent. Whereas some centers may use a very simple solution of potassium-enriched whole blood, others may choose a more complex solution with a variety of chemical additives. The trend in clinical practice has been to not use purely crystalloid cardioplegia solutions, and most centers now use some form of blood cardioplegia. The ratio of blood to crystalloid is generally 4:1 or 8:1. The crystalloid solution is often mixed with arterialized whole blood from the ECC circuit in an exact ratio by placing two different-sized tubes (the larger drawing from the arterial line of the ECC and the smaller drawing from the bag of cardioplegia) through a single roller pump and splicing the two tubes together downstream from the outlet of the pump. Generically, the chemicals added to the cardioplegia solutions are designed to make the solution slightly hypertonic to reduce edema, and these chemicals include a buffer to counter the heart's production of acidic metabolites and a substrate for energy or catalysts to assist the heart in production of adenosine triphosphate. Typically, solutions with two different potassium concentrations are used during the procedure. For induction of cardioplegic arrest, a "high-K" solution with a potassium concentration of approximately 20 to 30 mEq is used. After isoelectric arrest is induced, the solution is changed to a "low-K" mixture with a potassium concentration of about 10 mEq.

These solutions can be administered *antegradely* into the coronary arteries via the aortic root, through a needle placed between the aortic cannula and the aortic valve, or *retrogradely* into the coronary veins, via a balloon-tipped cannula placed in the coronary sinus. Antegrade cardioplegic delivery is the most physiologic approach. However, when the patient has pronounced coronary artery disease or aortic valve insufficiency, antegrade administration may not uniformly deliver cardioplegia to the myocardium. Retrograde cardioplegia administration also has limitations. For example, the free wall of the right ventricle and the posterior third of the septum (the distribution territory of the right coronary artery [RCA]) are poorly perfused by retrograde delivery.[218] Additionally, the microvascular areas of the heart that are perfused by retrograde cardioplegia are less able to sustain normal myocardial energy metabolism.[219] Thus, the most complete technique for myocardial protection involves both antegrade and retrograde delivery. In fact, it is not uncommon for cardioplegia to be delivered both antegradely and retrogradely simultaneously.

It is common for cardioplegia to be administered intermittently in a volume-dosing regimen. After an initial arrest dose of

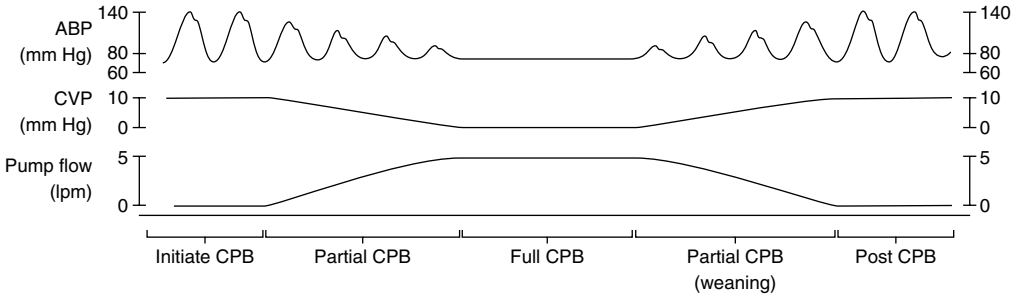

Figure 60-14 Illustration of a patient's hemodynamics before cardiopulmonary bypass (CPB), during the initiation of CPB, during full CPB, while weaning from CPB, and after CPB. ABP, arterial blood pressure; CPB, cardiopulmonary bypass; CVP, central venous pressure; lpm, liters per minute.

approximately 1000 to 1500 mL of "high-K" solution is administered, perfusion of the heart is suspended for a period of 10 to 40 minutes while the surgeon works on the heart. Then, periodically throughout the procedure, 200- to 500-mL doses of low-K solution are administered to deliver nutrients to the cells and maintain the potassium concentration. Intraoperative evaluation of the adequacy of myocardial protection is empirical and based on the quiescence of the ECG, the time since the last dose was administered, and the temperature of the heart. The filling state of the ventricular chambers should also be evaluated. If the vent lines are not keeping the heart empty, it will warm more quickly and the heart muscle will be under tension. This state increases myocardial oxygen consumption and reduces the adequacy of myocardial protection. To reinstitute electromechanical activity of the heart, warm normokalemic blood is infused into the coronaries. This may be done by administering a "hot shot" through the cardioplegia cannulas or by simply removing the cross-clamp.

Weaning and Termination of CPB

The process of weaning the patient from the heart and lung machine requires an increased level of communication and awareness between the anesthesiologist, perfusionist, and surgeon. Before weaning and termination, the patient should be rewarmed and the heart de-aired. Regular cardiac electrical activity should be confirmed and supported with a pacemaker if necessary. Ventilation of the lungs must be resumed and laboratory values confirmed and corrected if needed. By slowly reducing venous drainage to the ECC and transfusing volume from the reservoir to the patient, normal filling volume can be returned to the heart. As the cardiac output of the heart is returned to normal, flow from the arterial pump of the heart and lung machine is decreased and eventually terminated. Immediately after termination of CPB, the patient is often hemodynamically supported by volume replacement with the blood remaining in the ECC, frequently supplemented with vasopressors or inotropic agents (please see the earlier section "Weaning from Cardiopulmonary Bypass").

When the patient is hemodynamically stable, protamine can be administered to reverse the anticoagulatory effect of heparin. Administration of protamine to the patient is a sentinel event that must be communicated clearly between the anesthesiologist, perfusionist, and surgeon. In the event of inadvertent return of blood containing protamine to the ECC through the pump sucker, the blood remaining in the circuit may coagulate and render the circuit unusable for urgent reinstitution of CPB. Therefore, all cannulas should be removed before the action of heparin is fully reversed, and the blood remaining in the ECC should be salvaged by centrifugation or hemofiltration for return to the patient by the anesthesiologist.

Protamine inactivates heparin by irreversibly binding with the strongly acidic heparin molecule to form a stable salt with no anticoagulant effects. A commercial device such as the HMS machine can produce a protamine dose-response curve to calculate the dose of protamine necessary to neutralize the active heparin in circulation. In the absence of a protamine dose-response curve, many institutions calculate the protamine dose needed based on the total dose of heparin delivered to the patient, which usually results in the administration of 1 to 1.3 mg of protamine for every 100 units of heparin given. Protamine should be administered slowly over a period of 5 to 10 minutes to reduce the risk for hypotension. ACTs after protamine administration should return to baseline. An elevated ACT value may indicate residual heparin or may be the result of a coagulation deficiency requiring additional laboratory testing such as coagulation panel tests, heparin assays, platelet function analysis, thromboelastography, or any combination of such testing.

Other Issues

Temperature

Deliberate hypothermia is a reliable method of neuroprotection and is often used during routine CPB. Deep hypothermia unquestionably confers cerebral protection when the circulation must be arrested during cardiac surgery. Even mild hypothermia (as little as 1°C to 2°C) minimizes the severity of cerebral ischemia in animal models.[220]

Various suggested mechanisms for the neuroprotective effects of hypothermia have been tested in animal models (Table 60-9).[221] Hypothermia may attenuate the effects of cerebral ischemia by creating a favorable balance between oxygen supply and demand and by decreasing the cerebral metabolic rate of oxygen ($CMRO_2$). Hypothermia not only reduces the metabolic rate but also delays the release of excitatory amino acids, neurotransmitters that play an important role in the process of neuronal death.[222] Additionally, hypothermia reduces the permeability of brain arterioles and prevents blood-brain barrier dysfunction.[223] Hypothermia may also interfere with the inflammatory response by suppressing adhesion of polymorphonuclear leukocytes in the damaged region.[224]

However, after performing a meta-analysis, Rees and colleagues[225] concluded that there is no definitive evidence for a neuroprotective effect of hypothermia during routine CPB, although the studies examined in that analysis have some important limitations. For example, the timing of hypothermia may have limited its protective value. Hypothermia is always initiated after aortic cannulation and the onset of bypass, but macroembolization to the brain is unlikely during this period because the heart is excluded from the circulation by the aortic cross-clamp. Instead, evidence suggests that the periods of highest risk for microembolization and macroembolization are during and shortly after aortic manipulation, cross-clamping, and unclamp-

Table 60-9 Protective Effects of Hypothermia and Deleterious Effects of Hyperthermia during Cerebral Ischemia

Hypothermia	Hyperthermia
Favorable balance between O_2 supply and demand	Imbalance between O_2 supply and demand
↓ Excitotoxic neurotransmitter release	↑ Excitotoxic neurotransmitter release
↓ Blood-brain barrier permeability	↑ Blood-brain barrier permeability
↓ Inflammatory response	↑ Inflammatory response ↑ Free radical production ↑ Intracellular acidosis Destabilized cytoskeleton

From Hindler K, Nussmeier NA: Central nervous system risk assessment. *In* Newman M, Fleisher L, Fink M (eds): Perioperative Medicine: Managing for Outcome. Philadelphia, Elsevier, 2008, pp 69-88.

ing[226,227] because aortic cannulation and cross-clamping are performed near the start of CPB, when the brain is not yet cold. Likewise, the aortic cross-clamp is removed near the end of CPB, usually after the patient has been rewarmed.

In contrast, hyperthermia is known to be deleterious. Elevation of body temperature by as little as 2°C decreases cerebral tolerance to ischemia. Hyperthermia delays neuronal metabolic recovery and increases excitotoxic neurotransmitter release, oxygen free radical production, intracellular acidosis, and blood-brain barrier permeability, with subsequent multifocal breakdown at sites in the thalamus, hippocampus, and striatum (see Table 60-9).[228,229] Hyperthermia also affects protein kinase activity and destabilizes the cytoskeleton. Clinically, fever and hyperthermia worsen the prognosis of hospitalized stroke patients.[230,231]

In the 1990s, some centers began using normothermic cardioplegia to improve cardiac outcomes while avoiding deliberate hypothermia.[232] This practice of "warm heart surgery" was debated because of concern that the neuroprotective effects of hypothermia would be lost. Subsequent studies produced inconsistent results with respect to the incidence of stroke and postoperative neurocognitive decline.[233] Such differences in neurologic outcome may have resulted from variations in the temperature management strategies used in different "warm heart surgery" studies; these variations ranged from allowing a downward "drift" that results in actual mild hypothermia to active rewarming that may have led to inadvertent cerebral hyperthermia.[234]

In patients undergoing CPB, cerebral hyperthermia during the rewarming period may aggravate any cerebral injury that has occurred.[235] Aggressive rewarming was once commonly practiced to prevent the "afterdrop" in temperature that usually occurs after CPB is discontinued, but this practice can cause cerebral hyperthermia at the exact moment when cerebral embolization is most likely. Therefore, rewarming should be gradual and should start early enough to achieve stability of the desired temperature before CPB is terminated.[236]

It is also important to be aware of the limitations of any temperature monitoring site used during CPB. Brain parenchymal temperature cannot be measured directly during cardiac surgery; rather, it must be estimated from tympanic, nasopharyngeal, esophageal, rectal, bladder, skin surface, pulmonary arterial, or jugular venous bulb temperature. However, there is poor concordance between cerebral temperature and temperatures measured at most of these sites.[237,238] Jugular bulb temperature is generally considered to be the "gold standard" because the proximity of the jugular bulb to the carotid origins and the aortic cannula makes jugular bulb temperature more similar to brain temperature than temperatures measured at other commonly used sites.[237,239] Temperatures measured at the nasopharyngeal, esophageal, bladder, rectal, or skin surface sites underestimate jugular bulb temperature during rewarming.[237,238] Because monitoring jugular bulb temperature is not usually feasible, monitoring the temperature of the blood in the arterial line that exits the oxygenator[237] or in the PA[238] may be the best ways to estimate global brain temperature.

Some clinicians advocate weaning high-risk patients from CPB at a temperature that is slightly lower than normal (approximately 35°C to 36°C). In a randomized, controlled study, Nathan and colleagues[240,241] showed that patients rewarmed to a lower than normal temperature (34°C) were significantly less likely to have postoperative cognitive deficits than were patients rewarmed to 37°C. Although this approach has advantages, postoperative hypothermia may increase a patient's risk for coagulopathy, hemodynamic instability, and shivering, which increases myocardial oxygen consumption.[242,243] All these factors must be considered if one is to select the best rewarming approach for an individual patient.

Hyperthermia that develops after surgery may be just as hazardous as intraoperative hyperthermia. Temperatures exceeding 38.5°C are common during the first 48 hours after cardiac surgery and occur in nearly 40% of patients.[244] This postoperative hyperthermia is known to be correlated with increased cognitive dysfunction 6 weeks after cardiac surgery.[245] Therefore, hyperthermia in the postoperative period should be treated with antipyretics and, if necessary, active body surface cooling.

In summary, patients maintained on CPB should be rewarmed early and slowly. No monitored temperature should be allowed to exceed 36.5°C to 37.0°C. This practice prevents cerebral overheating. In patients at high risk for adverse neurologic outcomes, limited rewarming (up to 36.0°C) followed by gradual (i.e., 4-hour) surface warming to 37.0°C may be considered as a means of preventing cerebral hyperthermia while minimizing the risk for postoperative hypothermia.[246]

Blood Gas Management (see also Chapter 49)

Temperature has a significant effect on the solubility of gases in solution. Specifically, in blood gas analysis, the CO_2 concentration (and consequently the pH) is profoundly altered by changes in temperature. As temperature decreases, $Paco_2$ decreases as CO_2 becomes more soluble in plasma. Therefore, inducing hypothermia during CPB poses a dilemma in terms of how best to approach acid-base management at lower temperatures, that is, whether *temperature-corrected* or *temperature-uncorrected* blood gas values should be used to manage the patient's care. This question has been the basis for a decades-old debate: α-stat versus pH-stat blood gas management (Table 60-10).

The α-Stat Hypothesis

In aqueous systems, neutrality (pN) is said to occur when $[H^+] = [OH^-]$. The dissociation of water is dependent on temperature; therefore, the pH value at which pN occurs varies with the temperature. Acid-base comparative physiologic studies of animals whose blood temperature varies (i.e., ectotherms and poikilotherms) suggest that blood and intracellular pH values parallel the temperature-related changes seen in the neutrality of water.[247] From these findings has emerged the α-stat strategy, which endeavors to maintain intracellular electrochemical neutrality across all temperatures.

Maintaining this neutrality requires an appropriate buffering system. It is thought that protein buffering is largely responsible for maintaining this temperature-pH relationship. Specifically, the imidazole group of the amino acid histidine has a p*K* value similar to that of blood. Therefore, if CO_2 stores are held constant during cooling, the ionization state (termed "alpha" [α]) will remain constant. This may be important because the ionization state affects both the structure and the function of proteins. Keeping the charge state constant (α-stat) by allowing blood pH to change with the neutrality of water is thought to be essential for maintenance of the most physiologically beneficial structure and function of enzymes during hypothermia. Research suggests that when the α-stat strategy is used, cerebral autoregulation remains largely intact until deep hypothermic temperatures are reached.[248]

Table 60-10 Summary of Blood Gas Management Strategies

Strategy	Goal	Implementation	Total CO_2 Content	Theoretical Benefits
Alpha-stat	Achieve electrochemical neutrality by maintaining a constant OH^-/H^+ ratio	Use normal *temperature-uncorrected* blood gas values	Constant	Preserves enzyme function and cerebral autoregulation
pH-stat	Maintain constant pH	Use normal *temperature-corrected* blood gas values	Increases	Produces more homogeneous brain cooling; decreases brain O_2 consumption
Combination	Maintain constant pH during cooling, then restore electrochemical neutrality before circulatory arrest	During the cooling phase, use *temperature-corrected* values, then switch to *temperature-uncorrected* values before interrupting flow. Use *temperature-corrected* values during the rewarming period	Initially increases during cooling, then returns to baseline	Produces homogeneous brain cooling, then restores neutrality; improves $CRMO_2$

To manage acid-base balance during hypothermic CPB by using the α-stat approach, one must maintain temperature-*un*corrected blood gas values. The term "*un*corrected" is often confusing because it refers to the values that are typically reported by the blood gas machine without programming the machine to correct the values to the actual temperature of the patient. For example, blood drawn from a patient undergoing CPB at 18°C is measured in a blood gas machine, which anaerobically warms the sample to 37°C and reports values at normothermia. With α-stat management, one would strive for normal temperature-uncorrected results, which would theoretically maintain intracellular electrochemical neutrality.

The pH-Stat Hypothesis

An alternative strategy is the pH-stat approach to acid-base management. The pH-stat strategy endeavors to maintain a constant pH despite changes in temperature. Hibernating animals tend to follow this strategy. To counter the tendency of cooling blood to follow the neutrality of the water curve and become more alkalotic as temperature decreases, these animals increase their blood CO_2 content and maintain normal pH at hypothermic body temperatures.[249]

Carbon dioxide is a potent cerebral vasodilator; therefore, the increase in CO_2 content during pH-stat management uncouples cerebral autoregulation; cerebral blood flow increases independent of cerebral metabolic demand.[250] These effects are thought to be neuroprotective for infants maintained on CPB who may have aortopulmonary collaterals and also to promote deep homogeneous cooling of the brain before circulatory arrest.[251,252] However, during rewarming, the higher cerebral blood flow that results from using pH-stat management may increase the embolic load sent to the brain.[253]

Using the pH-stat strategy with CPB involves managing blood gas parameters with temperature-*corrected* values by programming the blood gas machine to correct the values to the patient's body temperature. During bypass, decreasing blood temperature increases the solubility of CO_2 and, consequently, results in decreased $Paco_2$ values. Therefore, the perfusionist must either decrease the "sweep speed" of the air-oxygen mixture or, less commonly, add CO_2 to the oxygenator ventilation system to increase the CO_2 content and maintain a $Paco_2$ of 40 mm Hg (and normal pH) as the temperature of the blood decreases. It is important that the extracorporeal circuitry is equipped with an in-line blood gas analyzer so that $Paco_2$ levels can be continually monitored during CPB.

Which Strategy Is Best?

Currently, the debate about which acid-base strategy provides the best outcomes in patients is unsettled. In the adult patient population, several independent, prospective randomized trials have shown that using α-stat management during moderate hypothermia produces better neurologic outcomes than using pH-stat management does.[253-255] These and other data have led to an evidence-based recommendation (ACC/AHA class I, level A) that α-stat management be used in adults undergoing moderate hypothermic CPB.[256] It is unclear which strategy is superior in adults when deep hypothermia is used with or without circulatory arrest.

In pediatric CPB, a single prospective randomized trial showed no significant neurologic outcome benefit of the pH-stat strategy.[257] Other human and animal studies, however, suggest that pH-stat management may be more beneficial than α-stat management for infants.[251,258-262] These studies showed that pH-stat management produced more homogeneous cooling, less oxygen consumption, and better cerebral metabolic recovery than α-stat management did. The clear trend in pediatric CPB is to use pH-stat alone or in combination with α-stat (i.e., to use pH-stat during cooling and α-stat during rewarming) when deep hypothermia is used.[263]

Inflammatory Response to Cardiopulmonary Bypass

During the past 20 years, much has been written about the rapid and profound inflammatory response that CPB elicits. Surgical stress itself causes an inflammatory response, which CPB aggravates by subjecting the patient's blood to contact with foreign surfaces, ischemia-reperfusion, and gaseous and particulate microembolization, which initiate and amplify multiple redundant and interconnected immune cascades. With the onset of CPB, the increased expression of *initiator* substances (including endotoxin, tumor necrosis factor, and nuclear factor κB, as well as anaphylatoxins and cytokines) stimulates *effector* cells (including polymorphonuclear neutrophils, platelets, and endothelial cells) to upregulate adhesion molecules and release cytotoxic oxygen radicals and proteases. This response can produce tissue injury of varying degree in a variety of organ systems.[264,265]

Numerous clinical approaches have been shown to measurably reduce the inflammatory response in cardiac surgical patients (Fig. 60-15). These approaches can be loosely grouped into three primary categories: modification of surgical and perfusion techniques, modification of circuit components, and pharmacologic strategies.

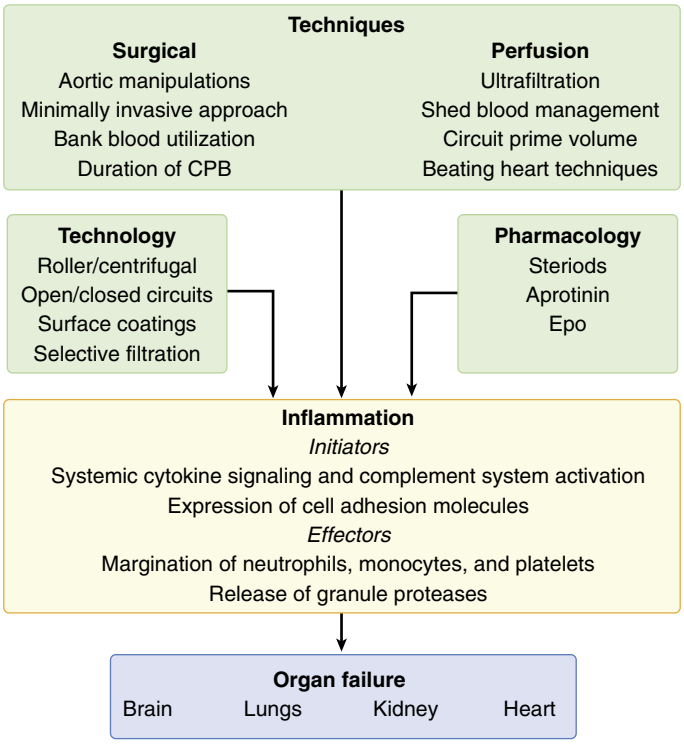

Figure 60-15 Brief review of the current understanding of the many variables that influence the inflammatory response in cardiopulmonary bypass patients. CPB, cardiopulmonary bypass.

Modification of Surgical and Perfusion Techniques

The movement toward minimally invasive cardiac surgery is at least partly motivated by the goal of reducing inflammation in the patient. The term *minimally invasive* may refer to procedures that use modified surgical techniques, including miniature incisions with or without robotic assistance, and to procedures that use classic surgical approaches but that minimize or eliminate the use of CPB and thus exposure to the ECC (e.g., OPCAB). Although OPCAB does not eliminate the patient's inflammatory response, it may produce less expression of inflammatory cytokines than CABG with CPB does.[266] However, it may be that the OPCAB-related reduction in inflammation is minimal in the days after surgery.[267]

Reasons for the lack of consensus about the exact contribution of CPB to the inflammatory process include the fact that perfusion practice is far from standardized.[256] A variety of perfusion techniques and technologies have been shown to reduce inflammation, including ultrafiltration,[268,269] shed blood management,[270] temperature management,[271] circuit miniaturization,[272,273] prime volume reduction,[274] and on-pump beating-heart techniques.[275]

Moreover, any improvements in outcomes that may be attributable to the use of OPCAB instead of standard CABG are probably not exclusively due to elimination of the ECC. Rather, minimizing or eliminating aortic manipulation, particularly in patients with severe atherosclerosis, may independently reduce the incidence of stroke.[276] Furthermore, a meta-analysis of randomized controlled trials comparing OPCAB and CABG with CPB confirmed that OPCAB was associated with a reduced risk for stroke and AF.[277]

Perfusion Technology

In addition to the ways in which perfusion technology is used, the type of technology used can moderate the inflammatory response to CPB. Evidence suggests that roller pumps may be less inflammatory than centrifugal pumps.[278,279] Some investigators have shown that using modified surface materials in the CPB circuit, such as heparin coatings, may reduce inflammation.[280-283] Additionally, selective filtration of leukocytes from the arterial circulation, the blood cardioplegia solution, or both may reduce inflammation,[284-286] although the efficacy of leukocyte-depleting filters in improving outcomes is controversial.[287,288]

Pharmacologic Strategies

Several pharmacologic agents have been shown to attenuate the inflammatory response to CPB. At the time of this writing, the serine protease inhibitor aprotinin is no longer being marketed; however, there is little question that it is effective in quelling hemostatic and inflammatory processes.[289]

In summary, several perioperative interventions may reduce the inflammatory response.[290,291] However, it is difficult to demonstrate the benefits of any one intervention in the clinical setting, where many other variables can also influence the inflammatory response and the clinical outcomes being measured.

Deep Hypothermic Circulatory Arrest

DHCA involves reducing the patient's core temperature to profoundly hypothermic levels (15°C to 22°C) before globally interrupting blood flow to the body, draining all the blood out of the patient, and collecting it in the ECC reservoir. In adults, this procedure is primarily used during surgical repair of the aorta, especially in cases of dissection or aneurysm involving the transverse arch.

Deliberate hypothermia with systemic cooling is the only reliable method of neuroprotection during complete global ischemia.[292] Some clinicians also put ice bags on the patient's head to augment or maintain cerebral cooling. Pharmacologic approaches to neuroprotection, such as steroids to reduce inflammation or barbiturates or propofol to induce burst suppression, are used in some centers, although there is scant evidence to support their efficacy in the setting of complete global ischemia.[293] Furthermore, if the electroencephalogram (EEG) is monitored, it is important to induce EEG isoelectricity with hypothermia before commencing the period of circulatory arrest rather than relying on supplemental barbiturates or propofol to provide neuroprotection.[294]

The equipment and circuitry of the heart and lung machine used for DHCA procedures are not generally different from that used for standard CPB procedures. Blood gas management during cooling and rewarming for DHCA procedures typically follows the α-stat management scheme in adult patients and the pH-stat management scheme in pediatric patients (see the earlier section "Blood Gas Management"). Systemic cooling is begun when CPB is initiated and is continued until the temperature of the patient is low enough to provide adequate protection for the anticipated duration of circulatory arrest. When deciding what temperature is "adequate," one must give top priority to protecting the brain. Because there is no clinically feasible method for measuring brain temperature, surrogate temperatures must be used to estimate

core temperature (see the earlier section "Temperature"). There is a time lag between the time that arterial blood reaches a target temperature and the time that the brain's parenchymal tissue equilibrates with the blood temperature. Consequently, when aggressive cooling is used, arterial blood temperature underestimates brain temperature. For an average-sized adult, cold arterial perfusion at full cardiac output flow should be continued for 20 to 30 minutes after the "goal" arterial blood temperature is reached to ensure that the brain has had sufficient time to cool. For an anticipated circulatory arrest period of 30 to 40 minutes, a temperature of 18°C to 20°C is probably adequate; however, slightly warmer temperatures may be acceptable if a shorter period of arrest is used or if cerebral perfusion is maintained.[295] It is also good practice to monitor multiple patient temperature sites, in addition to blood temperature, to observe their relative change over time during cooling and rewarming. Furthermore, the EEG provides a good pharmacodynamic end point for the cerebral effects of cooling; hypothermia-induced EEG isoelectricity should be present before elective circulatory arrest commences.[294]

As the patient cools, the viscosity of blood will increase. At temperatures of 18°C, the viscosity of blood with a hematocrit of 30% to 35% will increase to three to four times its normal level. Cardiac surgical textbooks suggest that hemodilution is important in minimizing any microcirculatory disturbances that may occur because of increased blood viscosity.[221] Consequently, some clinicians may target a hematocrit value that is appropriate to the patient's temperature during DHCA, approximately 18% to 20%. However, Duebener and colleagues[296] performed a study in piglets in which it was suggested that a hematocrit of 30% is preferable if DHCA is used.

When the patient has reached an appropriate core temperature as determined by temperatures measured at multiple sites and after there has been adequate time for equilibration, the arterial blood flow from the pump is stopped and the patient's blood is drained into the ECC reservoir. During the period of circulatory arrest, the blood in the ECC reservoir should be recirculated to prevent stasis and maintain the desired temperature. Gas flow to the oxygenator should be discontinued to prevent profound hypocapnia. Reperfusion should be initiated with cold blood. An initial period (5 to 10 minutes) of cold reperfusion is believed to enhance cerebral protection by removing accumulated metabolic products from the cerebral capillary beds while maintaining a low $CMRO_2$.[297]

The risk of neurologic injury after cardiac surgery involving DHCA extends into the postoperative period because cerebral vascular resistance is increased and cerebral blood flow is decreased for several hours after the procedure.[297] In addition, hyperthermia, possibly secondary to a systemic inflammatory response, is common in the postoperative period and should be treated aggressively.

In an effort to reduce the period of cerebral ischemia during the circulatory arrest period, selective cerebral perfusion techniques have been developed. Selective retrograde cerebral perfusion is delivered via a snared cannula introduced into the RA and advanced into the superior vena cava (SVC), and this type of perfusion can be initiated after the patient's systemic perfusion is discontinued. Cold oxygenated blood from the ECC can be administered at a flow rate (approximately 5 mL/kg/min) high enough to maintain SVC pressure between 35 and 40 mm Hg.[298] Selective antegrade cerebral perfusion can be accomplished by directly cannulating the left common carotid artery or can easily be delivered through the right common carotid when the aortic cannulation approach for CPB involves cannulation of the axillary or innominate artery.[295,299] This technique facilitates delivery of arterial return from the ECC to the entire circulatory system during cooling and rewarming or, with the addition of a clamp to the proximal innominate artery, selectively into the right common carotid and radial arteries. Because of the proximity of the arterial cannula to the right radial artery, arterial blood pressure monitored in the right radial artery may be significantly higher than pressure monitored in the left radial or femoral artery. Consequently, right radial arterial pressure should not be used to control perfusion during cooling and rewarming. Although there is still some debate about whether selective cerebral perfusion of any kind is necessary to achieve optimal neurologic outcome after DHCA procedures,[300] it is generally agreed that antegrade cerebral perfusion, when used properly, is superior to retrograde perfusion.[301]

Left Heart Bypass

If a descending aortic aneurysm or aortic dissection is to be surgically replaced with a tube graft, blood flow through the patient's thoracic aorta must be interrupted. The application of vascular clamps to this major vessel acutely increases the afterload of the heart and produces global ischemia in all parts of the body distal to the clamp. Patients with compromised cardiac function or those undergoing a surgical procedure in which the duration of ischemia will be unacceptably long require some method of circulatory support. Temporary interposition of a shunt (e.g., a Gott shunt) around the area of repair is the simplest approach but it does not offer the level of support that can be achieved with LHB or CPB.

For these procedures, the approach is usually through a left thoracotomy incision, which provides excellent access to the LA. The simplest approach to LHB is to withdraw blood from the LA with a centrifugal pump and return the blood to the patient's femoral artery. This *simple* LHB circuit gives the clinician excellent control of blood flow distal to the clamps and therefore the ability to manipulate the afterload that the heart must work against. However, the complexity of some surgical procedures requires that full CPB is used.

Complications of surgery are not uncommon in these patients and include hypoxia, hypothermia, and exsanguination. A double-lumen endotracheal tube or bronchial blocker is often used to isolate the left lung from the right. After left thoracotomy and exposure of the aneurysm, ventilation of the left lung is discontinued. Patients with preexisting lung dysfunction or traumatic lung injury associated with aortic dissection may have difficulty maintaining oxygenation with a single lung. Because of the large surgical exposure required and the sometimes extended duration of the procedure, it is not unusual for the patient to become hypothermic. Furthermore, these procedures carry an elevated risk of blood loss and the consequent need for rapid replacement of fluids and blood products. It is often advisable to use *complete* LHB to reduce these risks.

Figure 60-16 illustrates the simple- and complete-circuit approaches to LHB. The major difference between a complete LHB circuit and the standard CPB circuit is the position of the

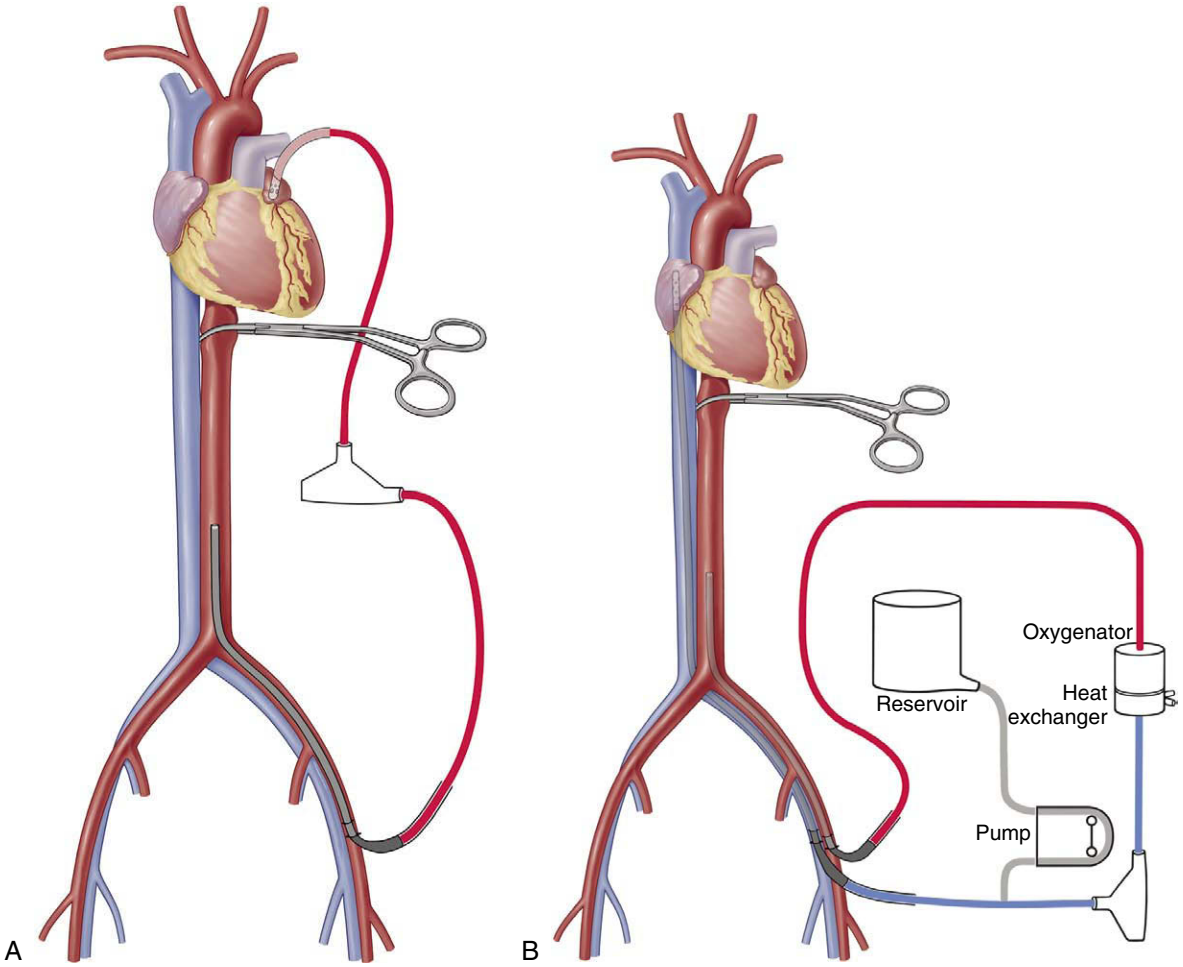

Figure 60-16 Left heart bypass (LHB) diagram. **A**, Simple LHB (left atrium [LA] – cone – femoral arery [FA]). **B**, Complex LHB (including an oxygenator, heart exchanger, and reservoir for fluid administration).

reservoir in the circuit and the position of the venous cannula in the patient. In a complete LHB circuit, the reservoir does not receive the blood returning from the patient as the CPB circuit does. With the reservoir out of the pathway of the blood, the effective surface area of the ECC is reduced, which attenuates contact activation of the blood and minimizes the need for high-dose heparinization.

In both circuits the management goal is the same—to keep arterial blood pressure above 60 mm Hg both proximal and distal to the aortic cross-clamp throughout the procedure. However, the complete LHB circuit gives the clinician the ability to manage hypoxia, hypothermia, and blood loss. The addition of an oxygenator to the circuit makes it possible to augment the patient's ventilation and oxygenation. The heat exchanger is used to maintain normothermia. The reservoir facilitates the addition of large volumes of fluid or blood products in the event of hemorrhage, hypovolemia, or both.

Cardiopulmonary Support and Extracorporeal Membrane Oxygenation Circuits

For all practical purposes, there is no difference between a CPS circuit and an ECMO circuit. Both consist of a CPB circuit without a reservoir, an arterial line filter, or any of the ancillary pumps that are used during cardiac surgery (i.e., pump suction, vent, and cardioplegia). Because the reservoir is removed from the circuit, these systems are considered to be "closed," which means that there is very little opportunity to remove emboli that enter the circuit from the venous line. Traditionally, an ECMO circuit has longer lengths of tubing, an arterial roller pump, and a silicone membrane oxygenator. The CPS circuit emphasizes minimalism in its design and has shorter lengths of tubing, a centrifugal arterial pump, and a hollow-fiber oxygenator.

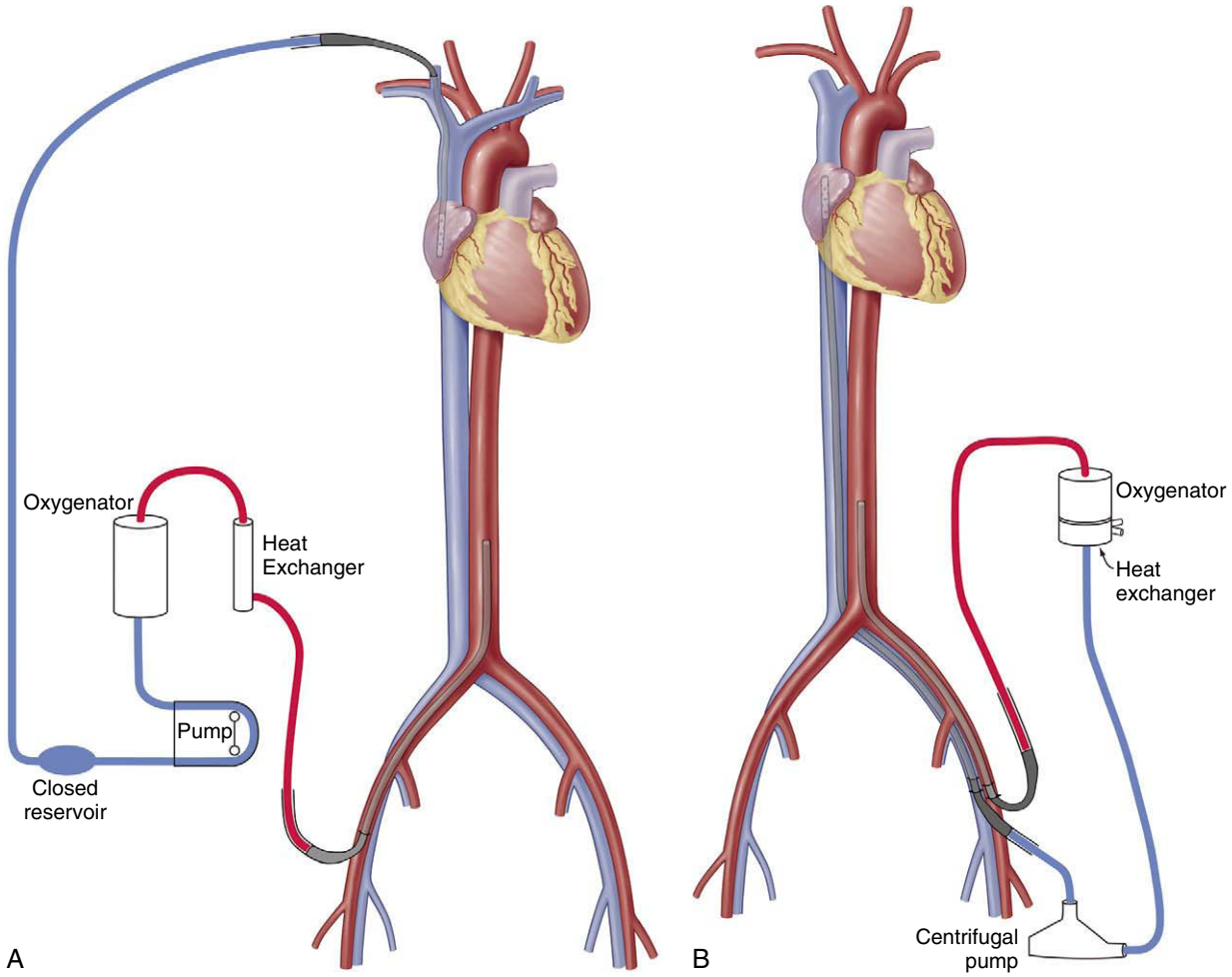

Figure 60-17 **A,** Patient cannulated via the internal jugular vein and femoral artery, with a traditional extracorporeal membrane oxygenation (ECMO) circuit. **B,** Patient cannulated via the femoral vein and femoral artery, with a simple cardiopulmonary support (CPS) circuit.

In intensive care settings, ECMO or CPS is used to support the heart, lungs, or both for days or weeks. The newer generation of centrifugal pumps and hollow-fiber oxygenators that have been developed over the past decade perform acceptably well during these long-term applications and are becoming more commonly used in desperate situations (Fig. 60-17).

Specific Cardiovascular Disease States

Coronary Artery Disease

On-Pump Coronary Artery Bypass Graft Surgery

Anesthetic management of patients undergoing CABG surgery with CPB or OPCAB surgery without CPB requires a basic understanding of coronary anatomy, the balance between myocardial oxygen supply and demand, and the determinants of myocardial ischemia.

Coronary Anatomy

Coronary arterial blood flows from the aorta through the left and right main coronary arteries. The left main coronary artery (LMCA) divides into the left anterior descending (LAD) and the left circumflex (LCx) arteries. The LAD artery courses anteriorly in the interventricular groove and gives rise to one, two, or three diagonal, and several septal, branches. The LAD itself terminates at the apex of the left ventricle. The diagonal branches of the LAD distribute blood to the anterolateral aspect of the heart. The septal branches of the LAD supply the interventricular septum, the bundle branches, and the Purkinje system. The other branch of the LMCA is the LCx artery, which courses along the left AV groove and gives rise to one to four obtuse marginal branches that supply the lateral wall of the left ventricle.

The RCA traverses the right AV groove and gives rise to acute marginal branches that supply the right anterior wall of the right ventricle. In 85% of the population, the RCA gives rise to the posterior descending artery (PDA), which supplies the posterior inferior aspect of the left ventricle ("right-dominant" system). In the other 15% of the population, this aspect of the left ventricle is supplied by a PDA arising from the LCx ("left-dominant"

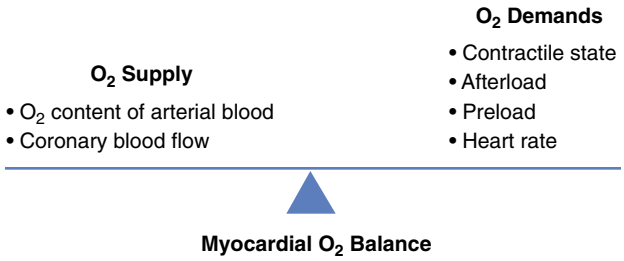

Figure 60-18 Factors determining myocardial oxygen supply and demand. *(From London M, Mittnacht A, Kaplan JA: Anesthesia for myocardial revascularization.* In *Kaplan's Cardiac Anesthesia, 5th ed. Philadelphia, Elsevier, 2006, p 594.)*

system) or both the RCA and the LCx systems ("codominant" system). The sinus node artery arises from the RCA distribution in 55% of the population and from the LCx arterial distribution in the other 45%.

Myocardial Oxygen Supply and Demand

The balance of oxygen supply versus demand is somewhat complex (Fig. 60-18). Extraction of O_2 from arterial blood is maximal at rest. As demand increases (with exercise or hemodynamic stress), the oxygen supply to the myocardium must also increase. Oxygen supply is determined by the oxygen content of arterial blood and by coronary blood flow.

The oxygen content of blood is dependent on hemoglobin-bound oxygen and, to a lesser extent, dissolved oxygen. Although a high hemoglobin level gives the blood high oxygen-carrying capacity, the minimum level of hemoglobin necessary to avoid ischemia has not been well defined in clinical studies. Factors that affect this limit include the severity of coronary artery disease, the heart rate, perfusion pressure, and myocardial wall thickness and tension. Furthermore, actual delivery of oxygen to myocardial tissue is dependent on release of oxygen from hemoglobin according to the oxyhemoglobin dissociation curve. A leftward shift of this curve caused by alkalosis, hypothermia, or low levels of 2,3,-diphosphoglycerate (which may be observed after the transfusion of a large volume of stored autologous blood) will decrease the release of oxygen.

The duration of diastole is another important factor affecting oxygen supply to the myocardium because 70% to 80% of coronary arterial blood flow occurs during the diastolic phase of the cardiac cycle. During the systolic phase, cardiac contraction increases intraventricular cavitary pressure and coronary vascular resistance, thus impeding myocardial perfusion. There is a nonlinear relationship between heart rate and the duration of diastole.[302] The total time per minute spent in diastole is a function of the heart rate. This is a major reason for the use of β-blockers as anti-ischemic agents both for long-term therapy and for preventing even small increases in heart rate during the perioperative period.

Determinants of blood flow in normal coronary arteries include the pressure differential across the coronary bed (coronary perfusion pressure) and coronary vascular resistance. The coronary perfusion pressure for the left ventricle is the aortic blood pressure during diastole minus left ventricular end-diastolic pressure (LVEDP); thus, elevations in LVEDP impede subendocardial blood flow. Because coronary stenosis causes vessels to dilate maximally distal to the stenosis, manipulation of coronary perfusion pressure becomes an important factor determining coronary blood flow (and preventing or treating myocardial ischemia). However, because the determinants of myocardial oxygen balance are complex, altering any one of them can produce multiple effects. For example, an increase in blood pressure increases coronary blood flow but also increases afterload, thereby increasing wall tension and oxygen demand.

In anesthetized patients undergoing anesthesia for coronary revascularization, vigilant monitoring for myocardial ischemia is necessary throughout the perioperative period.

Preoperative Evaluation and Management

Typically, patients undergoing cardiac surgery with CABG have had extensive preoperative assessment of their cardiac disease (see Chapter 34). Coronary artery anatomy should be noted, particularly a high-grade lesion in the left main or proximal LAD or triple-vessel disease. Ventricular function, assessed by angiography or echocardiography, is usually recorded as an estimated EF. Patients with an EF that is "normal" or greater than 50% have a low risk, whereas those having an EF of 25% to 50% have an intermediate risk for the development of postoperative low cardiac output syndrome (LCOS). Patients with an EF of less than 25% are at high risk. Patients with acute unstable angina, acute MI, or overt congestive HF are at very high risk. Those in cardiogenic shock, often with an IABP in situ, are at highest risk for LCOS and mortality.

Other cardiac pathophysiology discovered in the preoperative workup should be noted and understood, including valvular abnormalities such as concurrent MR, aortic stenosis (AS), aortic insufficiency, atrial or ventricular septal defect, or ventricular aneurysm. The anesthesiologist should be aware of any abnormal cardiac rhythm on the ECG or noted in the history, such as AF or other supraventricular tachycardia (which may lead to hemodynamic instability or increase the risk for an embolic neurologic complication), left bundle branch block or a prolonged PR interval (which may progress to a more advanced heart block), or a complete heart block, which may be underlying a paced rhythm. Antiarrhythmic therapy, either pharmacologic agents or devices such as a pacemaker or automatic implantable pacemaker/cardioverter-defibrillator (AICD), should be noted. Finally, the presence of pericardial effusion on the preoperative chest radiograph or echocardiogram has implications for hemodynamic compromise.

Surgical Considerations

Conventional (on-pump) CABG surgery is the most commonly performed procedure in cardiac surgery. A full median sternotomy performed with a sternal saw is standard. Ventilation of the lungs is halted briefly during sawing of the sternum to avoid a pleural tear. An oscillating saw may be used in patients with a previous sternotomy (redo). The risks of redo sternotomy include perforation of the right ventricle, damage to existing vein grafts, and ventricular fibrillation from transmission of electrocautery energy via preexisting sternal wires. Therefore, packed RBCs (2 units) should be immediately available and external defibrillation pads should be positioned before preparation and draping. Furthermore, surgical manipulation of previous vein grafts may result in embolization of atheroma and resultant ischemia. If a complication does occur during sternotomy or exposure of the heart and cannulation sites, emergency bypass may be established via cannulation of a femoral artery and vein.

If an IMA is to be used, the surgical table is elevated and often rotated somewhat to the left to facilitate surgical comfort in performing the dissection. Tidal volumes are also reduced to facilitate exposure. Administration of heparin usually occurs before clamping of the IMA pedicle, and papaverine may be injected into this vessel. The prebypass period for on-pump CABG may be relatively short (<1 hour) or may require several hours for dissection of the left IMA, right IMA, radial arteries, or any combination of these vessels. Harvesting of adequate venous conduits must also be accomplished for most CABG cases.

Before aortic cannulation, TEE or epiaortic echocardiography (or both) provides critical information regarding the presence and precise location of calcification or mobile atheromas in the aortic arch. TEE guidance for placement of the retrograde catheter into the coronary sinus may be requested by the surgeon. Insertion of the retrograde cannula may be difficult, and hemodynamic compromise or arrhythmias may necessitate rapid institution of CPB. After initiation of CPB, TEE may also be used to ensure correct placement of the LV vent, as well as to verify the absence of LV thrombus in patients with a recent anterior wall MI or aneurysm.[303]

Surgical and technical ischemic complications of CABG surgery include (1) poor-quality proximal or distal anastomoses of the grafts, (2) inadvertent incision of the coronary back wall leading to coronary dissection, (3) suturing the coronary artery closed, (4) inadequate vein graft length with stretching of the vein when the heart is filled, (5) excessive vein graft length leading to kinking of the vein, and (6) vein graft thrombosis.[304] Other causes of ischemia include (1) coronary embolization of air or atheromatous debris, (2) coronary spasm, and (3) vein graft stretching or occlusion of IMA flow secondary to overinflation of the lungs. Residual effects of cardioplegia, a ventricular aneurysm, or pericarditis may cause ST-segment elevation without actual ischemia.

Anesthetic Considerations

Monitoring for Ischemia Electrocardiography remains the standard to monitor for ischemia (see Chapter 42). For cardiac surgical patients, a display monitor that allows viewing of two ECG leads simultaneously, usually leads II and V_5, along with automated ST-segment analysis is preferred (see Chapter 42). PA catheters are used less commonly now than in the recent past because several recent observational and randomized studies have noted that such catheters do not improve outcome.[41,43,45] Certainly, the absolute PAP is not diagnostic of ischemia, although waveform changes may be more predictive; for example, the appearance of a new V wave on the PCWP tracing indicates ischemic papillary muscle dysfunction (see Chapter 40).

However, ECG changes and PA catheter waveform and pressure changes are less sensitive to ischemia than TEE-detected regional wall motion abnormalities are. Therefore, TEE is commonly used during revascularization procedures to assess regional wall motion by qualitative inspection of radial shortening and wall thickening (see Chapter 41). TEE usually provides better information than other modalities and is particularly valuable in assessing the patient after separation from CPB.

Selection of Anesthetic Agents No single anesthetic "recipe" is suitable for all patients undergoing CABG procedures. Most opioids, hypnotics, and volatile anesthetics have been used successfully in different combinations for induction and maintenance of anesthesia. Anesthetic drugs and doses are selected according to two main considerations, the first being LV function.[303] Patients with good LV function often have a strong sympathetic response to intense surgical stimulation such as sternotomy. If not adequately treated, tachycardia, hypertension, and ischemia result. Relatively large doses of anesthetics, often combined with β-blockers, vasodilators, or both, are required. On the other hand, in patients with poor LV function, hypotension may develop with the administration of anesthetics because of a reduction in cardiac output or vasodilation (or both). Such patients may require vasopressor or inotropic pharmacologic support, or both.

The second consideration for selection of anesthetic agents and doses is the probability of early extubation (within 4 to 6 hours of arrival in the ICU).[303] So-called fast-track management is becoming the standard, particularly for primary (first-time) isolated CABG (CABG without additional procedures such as valve replacement or ventricular aneurysmectomy). In making the decision to wean from ventilator support, clinicians (surgeons, anesthesiologists, and intensivists) assess whether the surgery was uneventful and whether the patient has normalized physiologic parameters. Such assessment includes observation for normothermia, absence of excessive bleeding or documented coagulopathy, and acceptable urine output, blood gases, and hematocrit. After weaning from sedation and assessment of neurologic status, patients must meet institutional criteria for extubation. Please see the earlier section "The Postbypass Period" and the later section "Problems in the Postoperative Period" for further details.

Off-Pump Coronary Artery Bypass Surgery

Surgical Considerations

The OPCAB grafting technique is performed through a full median sternotomy but avoids exposure to CPB. Currently, OPCAB revascularization accounts for 20% to 30% of all CAB operations.[305,306]

Potential sources of bypass grafts include the right and left mammary arteries, the saphenous veins, and the radial arteries. The pericardium is incised, reflected, and secured to the edges of the mediastinum. Special sternal retractors allow the placement of adjustable and flexible fixation devices that work by direct surface pressure on the myocardium, by suction, or by both methods. These devices stabilize the target vessel and allow the surgeon to "verticalize" the cardiac apex out of the pericardial well to access the posteriorly and laterally located vessels (Fig. 60-19).

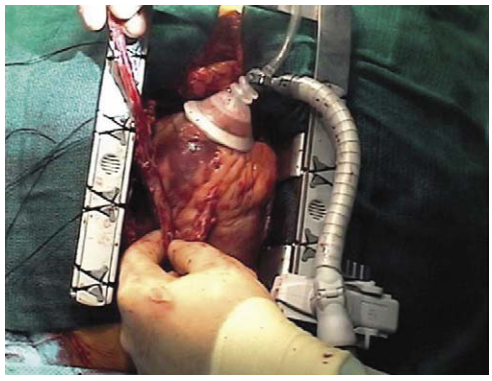

Figure 60-19 Verticalization of the cardiac apex in an off-pump coronary artery bypass (OPCAB) operation.

When the target vessel and surrounding myocardium are stabilized, an elastic ligature is placed circumferentially around the coronary artery to minimize bleeding as an arteriotomy is performed. Surgical visualization is also optimized by the application of a blower/mister, held by a surgical assistant, that releases sterile irrigation fluid aerosolized in carbon dioxide gas. Under these conditions, one or more distal coronary anastomoses are performed. The proximal connections of saphenous vein grafts or free arterial conduits are anastomosed directly to the aorta with a side-biting clamp. Alternatively, an indirect proximal connection is made via creation of a T-graft (end-to-side anastomosis) to a mammary artery that is still connected to a vascular pedicle on the subclavian artery.

Anesthetic Considerations

Anesthetic considerations for OPCAB revolve around hemodynamic perturbations. These are due to the compressive effects of myocardial stabilizers, altered ventricular filling secondary to verticalization of the cardiac ventricular apex, and the effects of myocardial ischemia in native coronary arteries or induced by temporary elastic suture ligation of a target vessel or decreased coronary perfusion caused by hemodynamic changes. Application of a surface stabilizer and an apical displacement device was associated with significant reductions in stroke volume, cardiac output, coronary blood flow, and mean arterial pressure in a porcine OPCAB model.[307,308] Biventricular filling is compromised, particularly in the thin-walled, easily compressed right ventricle.[308] Apical displacement and external compression can also distort the mitral valve annulus and lead to elevated atrial filling pressure, restricted diastolic filling, and MR.[309] Clinical studies have associated hemodynamic deterioration with the apical displacement that is necessary for grafting the RCA and circumflex artery distributions.[310-312] Furthermore, ischemia of distal myocardial segments occurs during the anastomosis of bypass grafts, and the degree of functional deterioration depends on the severity of the stenosis and the extent of collateralization.[313]

Patient monitoring includes a five-lead ECG and an invasive arterial pressure catheter. PAP and cardiac output measurements or continuous pulse contour cardiac output can be considered.[313] TEE is beneficial, but only to a limited degree, because verticalization of the heart and the application of external compression footplates cause suboptimal imaging. The mid-esophageal imaging view rather than the transgastric view may be best for continuous TEE monitoring while distal coronary anastomoses are being performed.

Because these patients are not on bypass, "rewarming" from hypothermia with the pump is not an option. Surface convective warming is somewhat limited because of the need for intrathoracic surgical exposure and access to the patient. Therefore, patient heating blankets and a warm operating room environment are essential to prevent unacceptable reductions in body temperature.

Hemodynamic changes in OPCAB surgery are initially treated by volume expansion with crystalloid, colloid, or both. Blood transfusion is considered in high-risk patients who arrive at the operating suite with preoperative anemia, which may be exacerbated by non–cell-containing fluid expansion and surgical blood loss during harvest of the mammary artery and anastomotic intervals. When intravascular fluid augmentation is inadequate, Trendelenburg positioning has been shown to be effective in restoring stroke volume, CI, and mean arterial pressure in animal models.[307,308] When increased mitral insufficiency further exacerbates the hemodynamic changes, repositioning the heart is a simple maneuver that may increase ventricular filling and normalize ventriculo-annular geometry.

Patients with abnormal LV function may tolerate poorly verticalization of the heart. Persistent hypotension can be treated by administering vasoactive medications, such as phenylephrine or vasopressin, or inotropic agents, especially when there is evidence of impaired tissue perfusion (CI <1.5, $S\bar{v}O_2$ < 60%, or poor urine output). Norepinephrine is a reasonable choice given that its adrenergic properties include α- and β-agonist effects at low doses. Ischemic changes manifested as ST-segment changes or new wall motion abnormalities on TEE can be treated by raising perfusion pressure through volume expansion, pharmacologic vasoconstriction, or inotropic support. Nitroglycerin should be used cautiously because preload reserves are usually compromised by changes in cardiac position in OPCAB surgery.

Persistent or worsening ECG changes or impending cardiovascular collapse warrants quick action on the part of the anesthesiologist and surgeon. One option is to have a low threshold for the insertion of small, flexible intracoronary stents into the open coronary anastomosis to allow some distal segment flow. Instituting full or partial CPB and placing an IABP are other therapeutic options. Emergency conversion from OPCAB to CABG with CPB, which occurs in approximately 3% of these cases,[314,315] is not an innocuous event. Such unplanned conversions are reportedly associated with an elevated risk for death, stroke, renal failure, wound infections, and respiratory failure.[315]

Outcomes

Short-term outcomes and the long-term efficacy of OPCAB surgery continue to be investigated and debated in the literature. The largest observational study, constructed from the New York State Cardiac Surgery Database, showed similar inpatient mortality rates in the on-pump CAB and OPCAB groups but lower rates of stroke and bleeding requiring reoperation and shortened length of stay in the OPCAB group.[316] However, the on-pump cohort had better 3-year survival and freedom from revascularization.[316] Randomized trials comparing OPCAB with on-pump CABG have not found convincing or consistent evidence to support one approach over another.[317,318]

A meta-analysis of randomized trials revealed that OPCAB produces a statistically significant reduction in the incidence of postoperative AF, but not in other adverse clinical outcomes, when compared with on-pump CABG.[319] However, there were trends suggesting that OPCAB reduced 30-day mortality, MI, and stroke.[319] In another meta-analysis, Lim and coworkers[320] used graft patency as an end point and concluded that OPCAB patients have worse patency rates and a statistically significant reduction in the number of grafts performed when compared with on-pump patients. These findings suggest that myocardial revascularization is more complete in CABG with CPB. Notably, however, recent large, retrospective reviews of traditional CABG versus OPCAB procedures have found a gender-specific benefit for women undergoing OPCAB surgery, with statistically significant reductions in mortality, stroke, and major adverse cardiac events.[305,321]

Minimally Invasive Surgery

Surgical Considerations

A minimally invasive direct coronary artery bypass (MIDCAB) grafting technique is accomplished through a limited anterior thoracotomy, usually a left-sided one, for revascularization of a

LAD arterial atherosclerotic lesion (Fig. 60-20). Patients selected for this operation may be relatively healthy and considered to be "low-risk" but have a complicated LAD lesion that is not ideally treated by PCI. Occasionally, MIDCAB is attempted in patients with a severely atherosclerotic aorta, in whom standard CPB is thought to incur an excessive risk for stroke because instrumentation and manipulation of the ascending aorta are necessary.

Although MIDCAB can involve surgical approaches to the RCA or PDA through a right anterior thoracotomy or subxiphoid laparotomy, a surgical approach through a left anterior thoracotomy to address LAD or circumflex arterial atherosclerotic disease is more common. The procedural details are similar; thus, only the left-sided approach is discussed here.

The left internal mammary artery (LIMA) is harvested under direct vision through the thoracotomy incision or by using thoracoscopic instruments or robotic technology through small port incisions. Single-lung ventilation is often requested for port-access harvesting of the LIMA in order to optimize surgical exposure and visualization. The pericardium is incised and reflected, and the target vessel or vessels are exposed. As in OPCAB performed through a median sternotomy, special myocardial stabilizers are used to isolate and transfix the site for coronary arteriotomy and the immediately adjacent myocardium, and elastic ligatures are placed around the vessel. Coronary flow is then interrupted while the LIMA is surgically anastomosed to the LAD. A vein graft or radial artery graft can also be connected to the LIMA pedicle graft (T-graft) if it is necessary to revascularize secondary lesions in the LAD or circumflex artery distributions.

Anesthetic Considerations

Management of anesthesia and hemodynamics for MIDCAB is similar to that for OPCAB surgery. Additionally, single-lung ventilation may be requested for harvesting of the LIMA graft, the coronary anastomosis, or both. Single-lung ventilation can be accomplished with a standard double-lumen tube, a bronchial blocker catheter placed through a standard endotracheal tube, or specialized endotracheal tubes (Univent).

Patients may have significant postoperative thoracotomy incisional pain, which must be managed to allow "fast-track" extubation, ambulation, and recovery. Pain management options include epidural narcotic analgesia delivered via a thoracic epidural catheter, intrathecal narcotic analgesia, local anesthetic nerve blocks extending a few levels above and below the thoracotomy, an intercostal analgesia catheter, and intercostal nerve cryoablation.

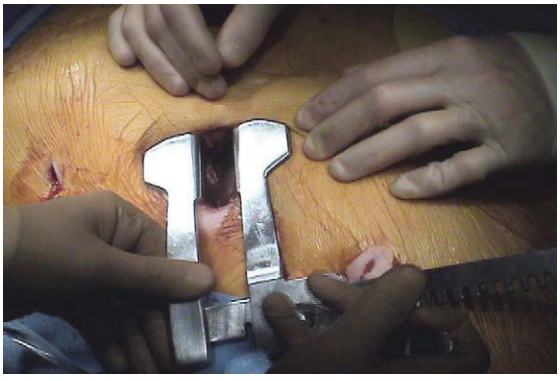

Figure 60-20 Left anterior thoracotomy for minimally invasive direct coronary artery bypass (MIDCAB).

Outcomes

Outcomes with MIDCAB are favorable. A large European retrospective study of more than 1300 MIDCAB patients reported 89.5% freedom from adverse events and angina at 5 years and 83.3% freedom at 7 years after surgery.[322] Studies comparing bare-metal stent PCI with MIDCAB surgical revascularization report similar or slightly lower rates of adverse cardiac or cerebrovascular events with MIDCAB and higher restenosis rates with PCI.[323-326] Finally, it is possible to combine MIDCAB surgical revascularization of the LAD with PCI in patients with complex multivessel disease, thereby creating a hybrid approach to coronary revascularization.[327,328]

Cardiac Valve Lesions

Mitral Valvular Disease

In the United States and other industrialized nations, mitral valve disease is usually caused by primary degenerative (i.e., age-associated) or inherited mitral valvular abnormalities or, increasingly, by ischemic heart disease resulting in functional mitral incompetence rather than by rheumatic heart disease. Primary or "organic" mitral valve disease involves abnormalities in the valve itself or in its subvalvar structural components. Mitral valve prolapse, myxomatous degeneration of the mitral valve, rheumatic mitral insufficiency, cleft mitral valve associated with an AV septal defect, and any infiltrative/fibrotic processes caused by systemic diseases are all associated with inherent structural abnormalities of the mitral valve. The most common indication for surgical repair or replacement of the regurgitant mitral valve is myxomatous degeneration, which includes mitral valve prolapse syndromes.[329] Chronic ischemic or functional MR is present in 10% to 20% of patients with coronary artery disease, and unlike primary valvular causes of MR, the morphology of the mitral valve is normal. Nonetheless, the long-term morbidity and mortality associated with this type of MR are significant.[330]

Anatomy of the Mitral Valve

The mitral valve leaflets are composed of segments, more easily discernible in the posterior leaflet, that are sometimes referred to as "scallops." In the Carpentier classification scheme,[331] the segments of the posterior leaflet are labeled P1, P2, and P3, with P1 being laterally oriented and P3 medial. The segments of the anterior leaflet are labeled A1, A2, and A3 and have the same medial/lateral orientation as the segments of the posterior leaflet (Fig. 60-21). This terminology is used to ensure accurate communication between the surgeon and the echocardiographer, who is often an anesthesiologist, as they attempt to localize valve abnormalities.

Mitral Stenosis

Pathophysiology The disease process of rheumatic mitral stenosis (MS) includes thickening and commissural fusion of the mitral valve leaflets and increased rigidity of the valve leaflets, as well as thickening, fusion, and contracture of the chordae and papillary heads. Furthermore, with long-standing rheumatic disease, some degree of calcification of the valve apparatus inevitably occurs. Physiologically, these changes result in obstruction at the level of the mitral valve.

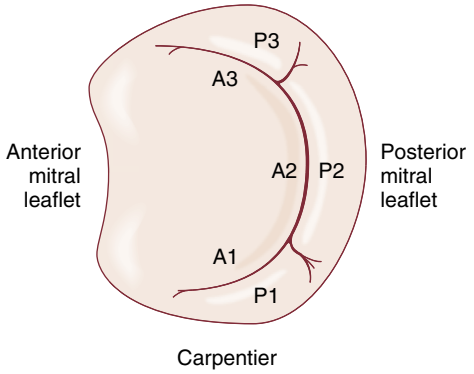

Figure 60-21 Standard terminology as applied to the mitral valve leaflets is illustrated in this image. The anterior and posterior mitral valve leaflets are each divided into three segmental regions. *(From Savage RM, Aronson S, Thomas JD, et al [eds]: Comprehensive Textbook of Intraoperative Transesophageal Echocardiography. Baltimore, Lippincott Williams & Wilkins, 2005, Figure 14.2.)*

The normal mitral valve orifice area is approximately 4 to 5 cm^2.[332] Symptoms can occur with a valve area of less than 2.5 cm^2 and can be precipitated by clinical events associated with increased cardiac output and consequent increased flow across the valve. Symptoms do not usually occur at rest unless the mitral valve area (MVA) has become less than 1.5 cm^2. Obstructed flow across the mitral valve is associated with a pressure differential or "gradient" across the valve. The more severe the MS, the greater the gradient, as long as flow across the valve is held constant.

Transmitral pressure gradients through the mitral valve are dependent on the volume flow rate. Severe MS may be present with a low measured or calculated gradient across the valve, such as in patients with right HF and pulmonary hypertension. An MVA estimate is a more independent measure of the severity of MS. Currently, MS is primarily diagnosed and monitored with echocardiography, although MVA can be calculated during catheterization by using the Gorlin equation. Assessment of severity by echocardiography includes two-dimensional planimetry of the valve orifice and Doppler-derived measurements of the gradient, pressure half-time, and deceleration time.

Management considerations in MS emphasize the pathophysiologic changes that occur in the LA, the pulmonary vasculature, the right heart, and the left ventricle. Obstructed mitral inflow with secondary increases in left atrial pressure (LAP) gradually produces enlargement of the LA, which can lead to the onset of AF, thromboembolic complications, or both, if low-velocity blood flow causes clot formation in the atrium or appendage.

Patients with MS and chronic AF are at increased risk for embolic stroke, at a rate of 7% to 15% per year.[333] Treatment may include anticoagulation with intravenous heparin or oral warfarin, pharmacologic rate control, and pharmacologic or electrical cardioversion for hemodynamically significant or acute-onset AF. In patients scheduled for cardioversion, TEE may need to be performed first to rule out the presence of a left atrial thrombus.[332]

Elevated LAP leads to passive increases in pulmonary venous and arterial pressure. Most patients with MS have pulmonary pressures greater than would be expected if they were estimated solely from elevations in LAP. These exaggerated pressures are secondary to reactive pulmonary vasoconstriction or histologic changes in the medial and intimal layers of pulmonary arteries and arterioles. Pulmonary pressures do exhibit a trend with the severity of MS, but pressures range widely with varying degrees of MS severity. In a study of 744 patients with severe MS, Otto and associates[334] found that multivariate predictors of elevated PVR and gradients across the pulmonary vascular bed included the transmitral pressure gradient, LVEDP, the MVA, and a history of chronic pulmonary disease.

The chronic elevation in pulmonary pressure caused by MS leads to compensatory and decompensatory changes in the right ventricle. Exposure to elevated pressure leads to compensatory RV hypertrophy; however, the response in the right ventricle is less efficient than in the left ventricle because of the right ventricle's shape, wall thickness, and smaller muscle mass. Because of the right ventricle's relative vulnerability, chronic pulmonary hypertension invariably leads to progressive RV dilation and eventual RV failure.

The effect of MS on the left ventricle is primarily due to obstruction of diastolic inflow. The narrowed mitral valve orifice leads to prolonged early diastolic mitral inflow and delayed filling of the left ventricle. Late diastolic filling, which occurs during atrial systole, is obviously compromised in patients who have AF secondary to MS. In cases of MS, pressure-volume loops are shifted to the left, so LVEDP and LV end-diastolic volume (LVEDV) are lower. Stroke volume is diminished, especially in clinical situations that result in an elevated heart rate and shortened diastolic filling intervals (Fig. 60-22).

LV function or contractility is assumed to be normal in most patients with MS. However, in a review of the literature, Klein and Carroll[335] showed that the assumption of preserved LV contractility in patients with MS is debatable. Instead, LV dysfunction may occur in as many as 30% of patients with MS. Proposed mechanisms include reduced filling of the left ventricle, muscle atrophy, inflammatory myocardial fibrosis leading to wall motion abnormalities, scarring of the subvalvular apparatus, abnormal patterns of LV contraction, reduced LV compliance with diastolic dysfunction, increased LV afterload leading to ventricular remodeling, right-to-left septal shift secondary to the effect of pulmonary hypertension on the right ventricle, and coex-

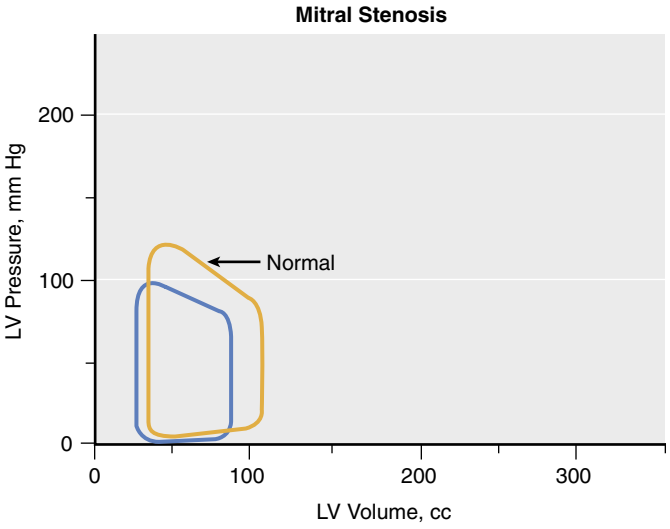

Figure 60-22 Pressure-volume loop in mitral stenosis. *(From Jackson JM, Thomas SJ, Lowenstein E: Anesthetic management of patients with valvular heart disease. Semin Anesth 1:239, 1982.)*

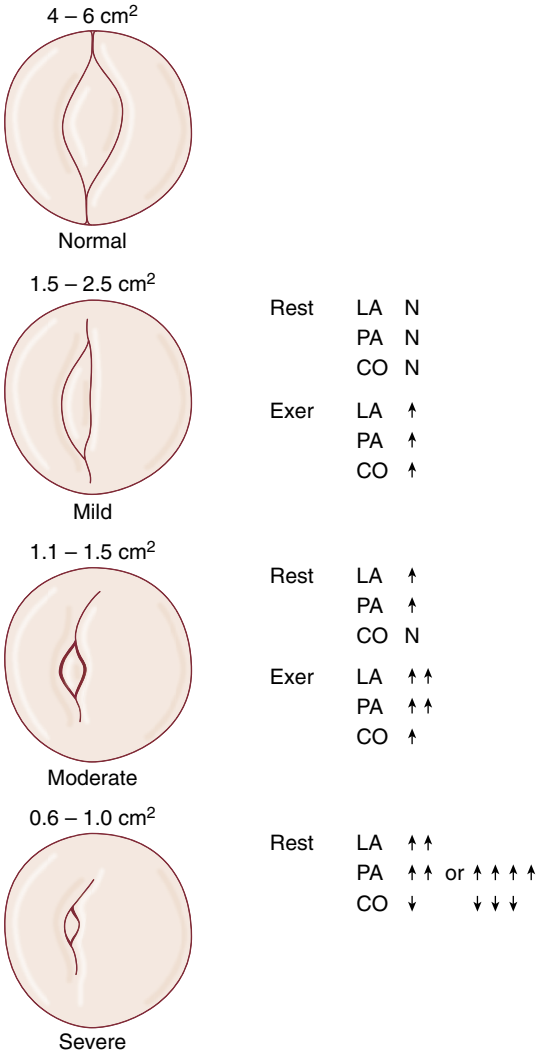

Figure 60-23 Diagrammatic representation of the hemodynamic changes that occur at various stages of severity of mitral stenosis. The valve area is listed above each stage. ↑, increased; ↓ decreased; CO, cardiac output; Exer, exercise; LA, left atrial pressure; N, normal; PA, pulmonary arterial pressure. *(From Rappaport E: Natural history of aortic and mitral valve disease. Am J Cardiol 35:221-227, 1975.)*

istent diseases such as systemic hypertension and coronary artery disease.[335] The hemodynamic changes associated with MS are summarized in Figure 60-23.

Anesthetic Management An understanding and appreciation of the pathophysiologic changes associated with MS form the foundation of anesthetic management in these patients. Primary concerns in patients with MS include management of ventricular preload, heart rate, coexisting pulmonary hypertension, and potentially diminished RV and LV contractile function. Most patients with valvular heart disease have an increased dependency on and sensitivity to ventricular preload. Flow through a stenotic mitral valve requires a higher than normal pressure gradient between the LA and the left ventricle. Thus, a reduction in preload, either from blood loss or from the venodilatory effects of anesthesia, can markedly affect stroke volume, cardiac output, and tissue perfusion. However, in higher grades of MS, LAP may be very high, and the difference between adequate filling pressure and an LAP that leads to congestive failure may be small. Thus, judicious fluid management is required.

In patients with MS, the heart rate should be kept within its normal range. Tachycardia may be poorly tolerated because of the decreased time for diastolic filling. Moreover, pressure gradients are somewhat flow dependent in MS. Elevated flow states, such as pregnancy and increased sympathetic activity from any source, can dramatically increase the pressure gradient across the valve and are reflected in elevated LAP or pulmonary venous pressure. Echocardiographically, the concept of valve gradients is derived through the use of a modified form of Bernoulli's equation, $\Delta P = 4v^2$, where "v" is the measured velocity of blood flow through the valve. Thus, any increase in the transvalvular flow rate caused by an increase in the heart rate has a significant impact on transvalvular flow dynamics and on LAP.

Atrial contributions to stroke volume may be elevated in MS patients who are in the early stages of the disease and not in AF. When AF has occurred, the atrial kick is lost. However, the most important factor in deterioration of the patient's clinical condition is tachycardia itself rather than loss of the atrial kick.

Contractility and SVR are usually preserved in MS. If anything, the left ventricle is chronically underloaded, but wall motion abnormalities or global systolic dysfunction may develop in a small percentage of MS patients. Usually, SVR is not a factor in augmenting forward flow because stroke volume is determined by the mitral valve orifice area and the diastolic filling interval. It may be appropriate to lower SVR for a left ventricle that has marked systolic dysfunction, but care must be exercised because a reduction in afterload is inevitably accompanied by a reduction in preload, which may not be desirable in patients with significant MS.

RV dysfunction probably poses a greater challenge in treating patients with MS than LV dysfunction does. The chronic elevations in LAP lead to pulmonary venous congestion, elevated pulmonary venous pressure, and eventually, elevated PAP. The right ventricle becomes hypertrophic and dilates in response to chronically elevated PAP. Long-standing elevations in pressure eventually cause RV contractile dysfunction. Although valve replacement may reduce pulmonary pressure, thereby unloading a dysfunctional right ventricle, the elevated PAP associated with long-standing MS may have a permanent component, especially in patients with comorbid pulmonary disease. Therefore, RV dysfunction can be persistent. In a patient with residual pulmonary vascular disease and RV dysfunction, supporting a failing or marginally functional right ventricle becomes the top clinical priority.

Monitoring for these patients includes standard noninvasive modalities and invasive monitoring of blood pressure, CVP, and intraoperative echocardiography. Monitoring PAP and cardiac output with a PA catheter may be very helpful, but care and judgment must be exercised given the propensity for PA rupture in patients with long-standing pulmonary hypertension. Inotropic support may be needed for patients with secondary RV dysfunction or failure. Epinephrine and milrinone are good therapeutic options. Management of RV dysfunction includes optimizing acid-base balance and using hypocapnia, hyperoxia, and possibly vasodilators to decrease PVR.

Mitral Regurgitation

MR can be classified as either organic (intrinsic valvular disease) or functional (i.e., related to nonvalvular components of the

mitral apparatus). It is common for MR to have a functional and an organic component, as in rheumatic valve disease resulting in annular or LV dilation with superimposed abnormalities of leaflet coaptation. In developed countries, the most common causes of MR are (1) myxomatous degeneration of the mitral valve resulting in annular dilation, chordal elongation and rupture, and redundant, prolapsing, or flail mitral valve leaflets and (2) mitral insufficiency caused by ischemic heart disease.

The severity of MR is assessed in the context of whether the MR is acute or chronic. Symptoms, physical examination, hemodynamics, and echocardiography all provide useful information for ascribing a severity grade (Table 60-11). Echocardiographic assessment is particularly important for guiding intraoperative decisions about the need for intervention and the adequacy of repair or replacement of the mitral valve. As with MS, several echocardiographic parameters, both two-dimensional and Doppler derived, can be used to grade the severity of MR (Table 60-12).

Pathophysiology The incompetent mitral valve allows retrograde passage of blood from the left ventricle into the LA during systole. The magnitude of the regurgitant volume is a function of the size of the regurgitant orifice, the pressure differential between the LA and the left ventricle, and the duration of the regurgitant cycle. Thus, higher systolic driving pressures, as in hypertension, can increase the regurgitant volume. Loading conditions are important as well, especially whenever functional changes in annular and LV geometry are important components of the mechanism of MR. These conditions should be considered during intraoperative evaluation of MR because anesthetic effects on afterload and preload can drastically alter the severity of MR from its baseline level, as seen during preoperative echocardiographic or catheterization assessment.

LV function and pressure tend to be normal in patients with chronic MR. The EF is often normal or supranormal unless the ventricle has decompensated with chronic MR or is acutely ischemic. A normal EF can be misleading, and masked ventricular dysfunction may be revealed after valve repair or replacement.

Table 60-11 Acute and Chronic Mitral Regurgitation

Characteristic	Chronic Compensated	Chronic Decompensated	Acute
Symptom onset	None	Gradual DOE	Abrupt CHF
Physical examination			
Blood pressure	Normal	Normal	↓
Pulmonary congestion	None	Variable	↑↑↑↑
Hemodynamics			
LA pressure	Normal	↑	↑↑
v wave	Absent	Variable	↑
Echocardiography			
LV size	↑	↑↑	Normal
LA size	↑	↑	Normal
MR jet v wave	Absent	Variable	↑

DOE, dyspnea on exertion; CHF, congestive heart failure; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; arrows indicate relative increase (↑) or decrease (↓) in comparison to normal.
From Otto CM: Valvular heart disease: Prevalence and clinical outcomes. *In* Otto CM (ed): Valvular Heart Disease, 2nd ed. Philadelphia, WB Saunders, 2004, pp 1-17.

Table 60-12 Estimation of Severity of Mitral Valve Regurgitation

Method	Mild	Moderate	Severe
Secondary two-dimensional changes	Mild LAE	Moderate LAE	Severe LAE
Spatial area mapping with color Doppler	<4.0 cm^2	4.0-8.0 cm^2	>8.0 cm^2
Pulmonary venous flow profiles	Normal pattern, S waveform ≥ D waveform	Blunted pattern, S waveform < D waveform	Systolic flow reversal, S waveform < 0
Regurgitant volume	30-40 mL	40-60 mL	>60 mL
Regurgitant fraction	10%-30%	30%-50%	>55%
Regurgitant orifice area	<0.2 cm^2	0.3-0.4 cm^2	>0.4 cm^2
Vena contracta	≤0.3 cm		≥0.5 cm

LAE, left atrial enlargement; S, systolic; D, diastolic.
From Savage RM, Aronson S, Thomas JD, et al (eds): Comprehensive Textbook of Intraoperative Transesophageal Echocardiography. Baltimore, Lippincott Williams & Wilkins, 2005, pp 399-419.

The LA serves as a low-pressure pathway during systolic ejection, so EF overestimates ventricular function.

With acute onset of MR, LAP is elevated because there has been no time for left atrial compensatory changes to occur. A "v" wave may be present on the LAP, PAP, or PCWP recordings. In contrast, in chronic MR, the increases in LAP are less dramatic because of compliance changes in the LA as a function of chamber dilation.

The long-term sequelae of MR are related to chronic pressure and volume effects on the LA and left ventricle. The left ventricle is exposed to a chronic, isolated volume-overload state. Eccentric LV hypertrophy develops and causes chamber enlargement without significant increases in wall thickness. Forward cardiac output is preserved because of eccentric hypertrophy and the low impedance of the LA—a physiologic equivalent of afterload reduction. The larger stroke volume ejected by the left ventricle is composed of normal venous return into the LA plus the regurgitant volume from the previous cardiac cycle. In the early stages of MR, LVEDP is relatively normal because of compliance changes in the left ventricle. With time, however, compensatory eccentric hypertrophy fails to preserve LV systolic function, and gradual systolic failure ensues, as noted on pressure-volume loops (Fig. 60-24).

The LA is exposed to increases in volume and pressure. The LA dilates to compensate for the regurgitant volume during systole, and in the early stages of MR, preservation of nearly normal LAP and protection of the pulmonary vasculature is likely. Progressive left atrial enlargement commonly leads to AF, which occurs in about 50% of patients who are to undergo surgical correction of MR.[336] However, patients with MR appear to be at lower risk for thromboembolic complications than patients with MS are.[337] When LAP compliance thresholds are reached, LAP and PAP become elevated. Eventually, if chronically exposed to elevated PAP, the right ventricle progressively enlarges and RV dysfunction develops.

Anesthetic Management In anesthetic management of MR, the primary goal is maintaining forward systemic flow. In chronic, compensated MR, maintaining preload, judiciously

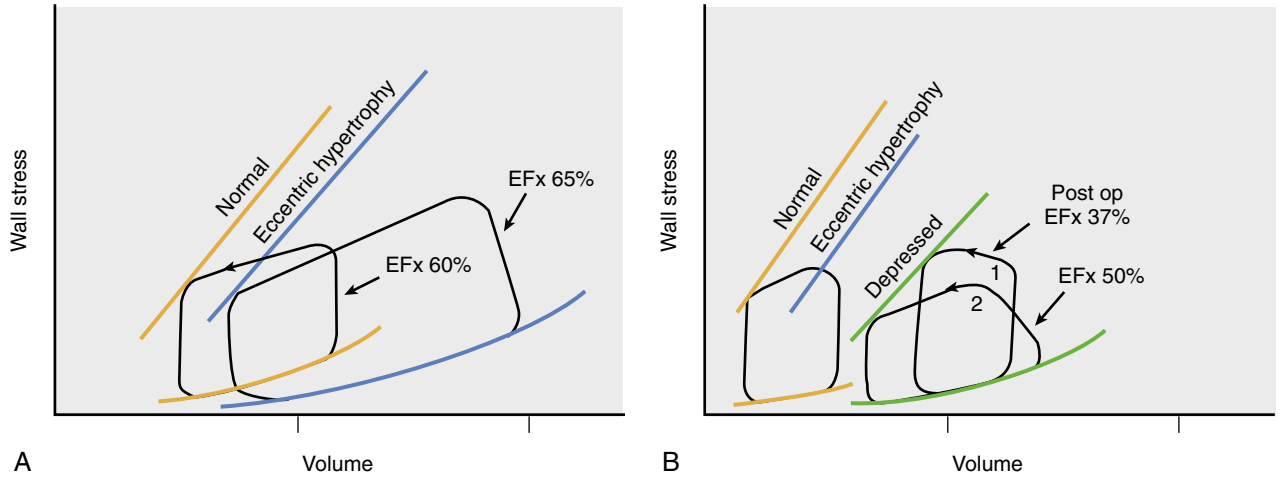

Figure 60-24 Diagram of wall stress-volume loops and end-systolic volume–wall stress relationships in severe mitral regurgitation. **A,** As in aortic regurgitation, the shift to the right of the diastolic and end-systolic relationships allows the volume-overloaded left ventricle to maintain a high stroke volume. Mean wall stress during ejection is somewhat reduced, and in mitral regurgitation the ejection fraction (EF) is high normal when contractility is normal. **B,** With the development of depressed contractility, the end-systolic wall stress–volume relationship is shifted to the right before surgery. Despite severely depressed contractility, the ventricle is able to deliver a nearly normal EF because of the very large ventricular volume and the relatively low mean wall stress during ejection (beat 2, ejection fraction = 50%). Contractility remains depressed after mitral valve replacement, and with correction of the low-impedance leak, the ventricle must now deliver the total stroke volume into the aorta against higher wall stress; the EF therefore falls to 37% (beat 1).

reducing afterload, and keeping the heart rate in the high-normal range may be adequate. General management goals can be summarized as follows:

PRELOAD As with most compensated forms of valvular heart disease, patients with hemodynamically significant MR are sensitive to ventricular loading conditions. Augmenting preload may be prudent in the interval before anesthetic induction. However, one must remember that MR is dynamic; ventricular distention can lead to expansion of an already dilated mitral annulus and thus worsen MR.

HEART RATE AND RHYTHM The heart rate should be maintained in the high-normal range (i.e., 80 to 100 beats/min). Bradycardia has dual detrimental effects on MR: it increases the duration of the systolic period, thereby prolonging regurgitation, and it increases the diastolic filling interval, which can lead to LV distention. A sinus rhythm is preferred, but there is less dependency on atrial kick than in stenotic valvular heart disease.

CONTRACTILITY In early compensated MR, LV contractility may be preserved. It is important to remember that EF indices are poorly correlated with LV systolic function in patients with moderate to severe MR and that underlying systolic dysfunction may be woefully underestimated. Hypotension in patients with significant MR can be managed to a certain degree by manipulating the heart rate and volume, but persistent hemodynamic instability may best be treated with inotropic support. Dobutamine, low-dose epinephrine, and milrinone are all acceptable inotropic choices, depending on the clinician's interpretation of the monitor data.

AFTERLOAD The general rule of thumb for patients with MR is to lower SVR so that forward cardiac output is maximized. Adequate anesthetic depth, systemic vasodilators, inodilators, and at times, mechanical reduction of afterload with an IABP may be clinical options, depending on the situation. Direct-acting α_1-agonists increase SVR and blood pressure, lower the heart rate, and may worsen the MR. Temporary use of small doses of ephedrine may be a better choice, after which inotropic support should be considered if there is a persistent need to augment pressure.

PULMONARY HYPERTENSION PAP and PVR may be elevated in patients with acute or long-standing MR. Secondary changes in RV size and function may be important clinical considerations. Factors that may increase PVR and unfavorably load an already dysfunctional right ventricle, such as hypoxia, hypercapnia, and acidosis, should be tested for and corrected whenever possible.

Finally, in the patient with acute severe MR and cardiogenic shock from ischemic rupture of a papillary muscle, pharmacologic support of the left ventricle, often accompanied by mechanical support with IABP counterpulsation, may be necessary.

Hypertrophic Obstructive Cardiomyopathy and the Mitral Valve

Classically, hypertrophic obstructive cardiomyopathy (HOCM) is a familial disease transmitted with autosomal dominant inheritance. Inheritance and phenotypic expression are heterogeneous and vary in manifestations. Some mutations in genes that code for cardiac sarcomere proteins can cause hypertrophy of segments of the ventricle. Septal involvement is common, but HOCM can involve other areas of the left ventricle as well. This disease is the most common cause of sudden cardiac death in young people, but it can also cause death and morbidity in older patients.

When the basal septum of the left ventricle is affected, the left ventricular outflow tract (LVOT) can narrow. Depending on the shape of the ventricle and the mitral valve, dynamic outflow tract obstruction can occur, paired with mitral valve insufficiency. As the outflow tract is narrowed by hypertrophy, the basal septum and the anterior leaflet of the mitral valve come into close proximity. The hypertrophy and the reduced septal-anterior leaflet distance can create a channel that narrows to the point of creating a pressure gradient across the outflow tract. This obstructed flow and its pressure gradient lead to progressive compensatory hyper-

trophy, which in turn further narrows the outflow tract and worsens the gradient. As blood is ejected through this narrowed outflow channel during systole, the velocity of blood increases through the narrowed orifice. This increased blood velocity creates a Venturi effect that pulls the anterior leaflet of the mitral valve or the chordal structures into the outflow tract, which results in mechanical and dynamic obstruction of the LVOT and MR because of a coaptation defect of the mitral valve. Echocardiographically, this is termed systolic anterior motion (SAM) of the mitral valve. Such dysfunctional mitral valve motion is seen in cardiac surgical patients who come for surgical management of known HOCM (i.e., for surgical myomectomy, mitral valve repair, or both).

Sometimes, SAM is noted preoperatively or as an incidental finding at the time of surgery in patients undergoing surgical revascularization or mitral valvular surgery. Furthermore, SAM may be created iatrogenically as a result of surgical mitral valve repair. In patients with MR who are to undergo mitral valve repair, echocardiographic assessment and surgical inspection are performed to elucidate the mechanism of the mitral insufficiency. There may be ruptured or elongated chordal attachments, redundant or prolapsing leaflet tissue, or annular dilation that reduces effective leaflet coaptation. Frequently, multiple contributing factors are present. Surgical treatment can involve just a simple annuloplasty ring in the case of isolated annular dilation, but it more commonly involves resection of diseased segments of the mitral valve, possibly chordal reassignment or reconstruction, and a ring valvuloplasty. Depending on LV geometry and size and the physical characteristics of the mitral valve, surgical repair may bring the anterior leaflet and the coaptation point of the valve into close approximation with the interventricular septum and the LVOT. That septal coaptation point can narrow enough to create a gradient in the outflow tract so that the anterior leaflet is pulled into the LVOT by the Venturi effect, thereby leading to obstruction and secondary mitral insufficiency. Discovery of this anterior displacement of the mitral coaptation point has led to the development of techniques for identifying patients at risk for this complication, as well as to the development of alternative surgical strategies, such as the sliding annuloplasty repair[338] and the Alfieri double-orifice repair technique,[339] to minimize its occurrence in patients with at-risk anatomy. Risk factors for postrepair SAM and outflow tract obstruction have been delineated in studies by Lee,[340] Maslow,[341] and their colleagues.

Anesthetic management of obstructive cardiomyopathy centers on fluid and pharmacologic interventions to decrease the magnitude of the obstruction and, at the same time, lessen the severity of the mitral insufficiency. Most patients with outflow tract abnormalities have normal to supranormal contractility. Generally, inotropic agents should not be used. The thick, hypertrophied ventricle usually has reduced compliance and is very load sensitive, so outflow tract obstruction increases in hypovolemic conditions. Optimizing preload and ventricular filling is appropriate in managing a patient with outflow tract obstruction and in assessing the need for surgical reconstruction of the LVOT, repair of the mitral valve, or both. Afterload reduction should be avoided because it worsens the obstruction. Conversely, increasing afterload decreases the trans–outflow tract gradient, which leads to a reduction in SAM and outflow tract obstruction. Hence, vasoconstrictors such as phenylephrine and vasopressin should be considered. In both congenital and iatrogenic LVOT obstruction, the degree of obstruction is dynamic. Obstruction is exacerbated by hypercontractile states and elevations in heart rate; therefore, reducing the heart rate with β-adrenergic blockade should be considered.

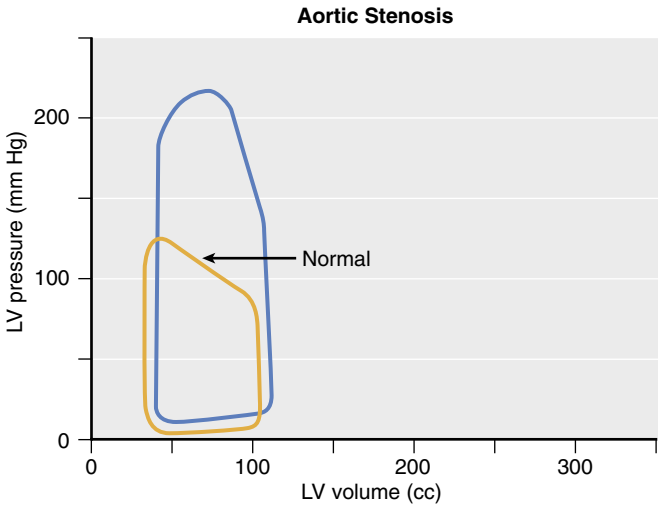

Figure 60-25 Pressure-volume loop in aortic stenosis. *(Adapted from Jackson JM, Thomas SJ, Lowenstein E: Anesthetic management of patients with valvular heart disease. Semin Anesth 1:239, 1982.)*

Continuous, skilled echocardiographic assessment and interpretation are important for optimal intraoperative management of these patients. Assessing the severity and mechanism of outflow tract obstruction and possibly the need to return to bypass to revise the repair or replace the valve are not innocuous decisions and they must be carefully made jointly by the anesthesiologist and the surgeon, ideally with input from the appropriate cardiologist.

Aortic Valvular Disease

Aortic Stenosis

PATHOPHYSIOLOGY Aortic stenosis (AS) is the most common cardiac valve lesion found in the United States. Figure 60-25 shows a typical pressure-volume loop for a patient with AS. The peak pressure generated by the left ventricle during systole is much higher because of the high transvalvular pressure gradient. Concentric LV hypertrophy develops as a result of the increase in pressure load (Fig. 60-26).

Aortic stenosis is usually caused by congenital defects in the valve because 1% to 2% of the population are born with a bicuspid aortic valve. Inheritance has been found to play a role, with an autosomal dominant pattern and variable penetrance.[342,343] A bicuspid aortic valve that does not yet show any signs of damage nevertheless tends to open and close with abnormal folding and creasing, thereby leading to scarring and calcification and ultimately culminating in AS with or without aortic regurgitation (AR). Although patients with a bicuspid aortic valve are asymptomatic until late in the disease process, severe, symptomatic AS or AR may develop in midlife. In addition, the abnormal motion of these bicuspid leaflets causes some turbulent flow into the aorta, which can eventually lead to dilatation and subsequent rupture or dissection.

Acquired AS is usually due to senile degeneration with sclerosis and calcification of the valve. There is a clear association between clinical risk factors for atherosclerotic disease and the

development of AS, including the process of chronic inflammation. The prevalence of AS increases with age; it is now seen in 2% to 4% of adults older than 65 years, and this prevalence is expected to increase.[344] In developed countries, rheumatic disease is a less common cause of AS, and it is usually associated with concomitant AR.

Anesthetic Management Premedication may alleviate a patient's anxiety regarding cardiac surgery, and it helps prevent perioperative tachycardia in patients with AS. Monitoring for these patients includes standard noninvasive modalities and invasive monitoring of blood pressure and CVP. Depending on the severity of the AS, the arterial line tracing can show some typical changes. Pulse pressure may be as low as 50 mm Hg or less. The upslope of the trace is delayed and has a prominent anacrotic notch, which occurs at a lower level as the severity of AS increases, whereas the dicrotic notch reduces in size or even disappears with progression of the disease. Insertion of a PA catheter may be considered for monitoring PAP and cardiac output during surgery and particularly in the postoperative period. A TEE probe is nearly always desirable if there are no contraindications to its placement.

Anesthetic management of patients with AS revolves around avoiding fluctuations in the patient's hemodynamics while achieving adequate anesthetic depth. Induction of anesthesia should not involve any medication that might have negative inotropic or vasodilatory effects. Any agents that might cause tachycardia should also be avoided. Furthermore, every effort should be made to ensure that the patient stays in sinus rhythm. In patients with AS, the "atrial kick" may contribute as much as 40% of the total cardiac output.[345] Therefore, to treat any possible arrhythmia, external cardioversion pads should be considered, preferably before induction of anesthesia.

Finally, it is important to realize that the presence of severe AS reduces the usefulness of cardiopulmonary resuscitation (CPR) for maintaining a cardiac output sufficient to meet the patient's physiologic needs. Table 60-13 summarizes the goals of anesthetic care of a patient with AS.

Aortic Regurgitation

Pathophysiology AR is flow of blood from the aorta backward into the left ventricle during the diastolic phase of the cardiac cycle. The overall prevalence of AR was noted to be 13% in men and 8.5% in women in the Framingham Offspring Study.[346] Chronic AR is more prevalent and carries a much better prognosis than acute AR does. However, the precise prevalence of AR—acute and chronic—remains unknown.[347]

Chronic and acute AR each have their own etiology. Causes of chronic AR include congenital lesions, degenerative processes, and rheumatic disease, but idiopathic causes seem to be the most common.[347] These processes cause malcoaptation of the aortic valve leaflets by causing abnormalities in the leaflets themselves or dilation of the aortic valve annulus, the aortic root, or both.[347]

Abnormalities of the aortic valve leaflets include congenital conditions (e.g., bicuspid aortic valve), endocarditis, rheumatic disease, inflammatory diseases, certain connective tissue diseases, and chest wall trauma causing injury to an aortic valve leaflet. Dilation of the proximal aortic root may be caused by annuloaortic ectasia resulting from long-term chronic hypertension or simply from the normal aging process. Other aortic valve annular or aortic root causes of AR include Marfan's syndrome, syphilis, connective tissue diseases, congenital diseases such as osteogenesis imperfecta and Ehlers-Danlos syndrome, and idiopathic causes.

Chronic Aortic Regurgitation Patients with chronic AR may remain asymptomatic for years or even decades. The left ventricle undergoes a process of remodeling caused by series replication of sarcomeres and the development of eccentric ventricular hypertrophy and chamber enlargement in the face of a chronically increasing volume of regurgitation (Fig. 60-26).[348] Although the pressure-volume loop is shifted far to the right in patients with chronic AR, LVEDP remains relatively normal because LDEDV increases slowly (Fig. 60-27). Forward flow is improved by peripheral vasodilation. Typically, a normal EF is maintained by a large stroke volume. However, over time, increases in LV wall stress and afterload result. Eventually, as LV dilation and hypertrophy progress, irreversible LV dysfunction develops, and patients become symptomatic. As a compensatory mechanism for poor cardiac output, sympathetic constriction of the peripheral vasculature occurs to maintain blood pressure, but this adaptation results in worsening of regurgitation and cardiac output.

Although patients with chronic AR can remain asymptomatic for decades, afterload reduction may become necessary as the disease progresses. A critical question that remains unanswered is at what point in the course of the disease should surgery be performed to prevent the development of irreversible LV dysfunction, especially in patients with severe chronic AR.[347]

Acute Aortic Regurgitation Acute AR is less common than chronic AR but carries a more ominous prognosis. Common causes of acute AR include trauma, bacterial endocarditis, and aortic dissection. Rarely, acute AR occurs as an idiopathic complication, such as after aortic valvuloplasty.[347] The pathophysiology of acute AR centers around the fact that it causes an acute increase in the volume coming into the left ventricle. Because the left ventricle has not had time to undergo the process of eccentric hypertrophy as it does in chronic AR, it is unprepared to accommodate this sudden increase in volume. As shown in Figure 60-27, this sudden increase in LVEDP causes a rightward shift in the pressure-volume loop.[348] A sympathetic response is activated; tachycardia and an increased contractile state are the chief compensatory mechanisms for maintaining adequate cardiac output.

Table 60-13 Goals for Anesthetic Care of Patients with Aortic Stenosis and Aortic Regurgitation

	Left Ventricular Preload	Heart Rate	Contractile State	Systemic Vascular Resistance	Pulmonary Vascular Regurgitation
Aortic stenosis	↑	↓ (sinus)	Maintain	↑	Maintain
Aortic regurgitation	↑	↑	Maintain	↓	Maintain

From Sukernik MR, Martin DE: Anesthetic management for the surgical treatment of valvular heart diseases. *In* Hensley FA, Martin DE, Gravlee GP (eds): A Practical Approach to Cardiac Anesthesia, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2008, pp 316-347.

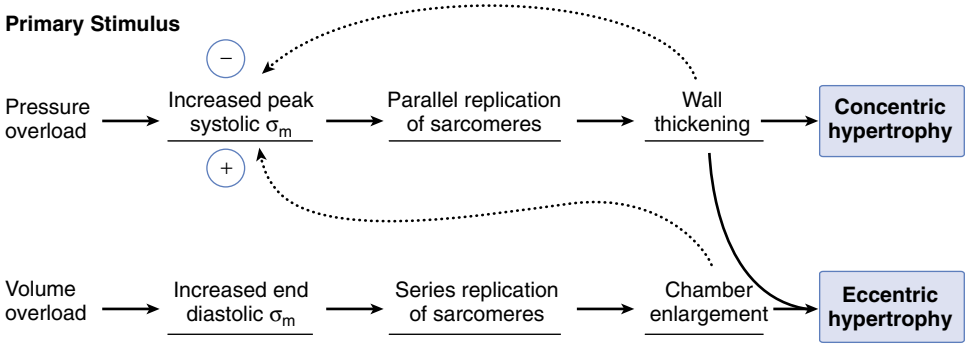

Figure 60-26 The increased peak systolic wall stress resulting from chronic pressure overload directly stimulates concentric ventricular hypertrophy, which tends to counteract or "normalize" the elevated ventricular wall stress. *(From Grossman W, Jones D, Mclaurin LP: Wall stress and pattern of hypertrophy in the human left ventricle. J Clin Invest 56:56, 1975.)*

Unless the AR is managed appropriately, these compensatory mechanisms rapidly fail. Furthermore, the sympathetic response also causes sympathetic constriction of the peripheral vasculature, thereby increasing SVR and further worsening the AR. LV function can deteriorate rapidly and necessitate emergency surgery. Vasodilator therapy may temporarily stabilize the patient during transport to the operating room.[347,349]

Anesthetic Management Anesthetic management of patients with AR should include maintenance of a relatively fast heart rate (approximately 90 beats/min) and a relatively low SVR while maintaining preload and contractility. Light premedication is recommended. Table 60-13 shows the anesthetic goals for inducing and maintaining anesthesia in patients with AR. In considering the choice of drugs for general anesthesia in these patients, medications that cause bradycardia or high blood pressure should be avoided because these changes worsen the degree of AR and can precipitate LV failure.

Preoperative placement of an arterial line is standard. During surgery and in the postoperative period, "high" arterial blood pressure is avoided in patients who undergo aortic valve replacement because the aortic incision creates the possibility of bleeding or aortic dissection. A central line is standard, and a PA catheter may be considered for monitoring cardiac function during and after the operation. In the prebypass period, TEE allows the anesthesiologist to ascertain the cause of the AR, assess the severity of the AR, and determine LV size and function. Furthermore, TEE assessment in the immediate postbypass period confirms proper positioning and function of the new valve.

Weaning from CPB may be complicated by preexisting LV dysfunction. Furthermore, mechanical aortic valve replacement results in a mild transvalvular pressure gradient. Therefore, inotropic agents may be needed to improve LV function. Preload augmentation must be continued to maintain filling of the dilated left ventricle.

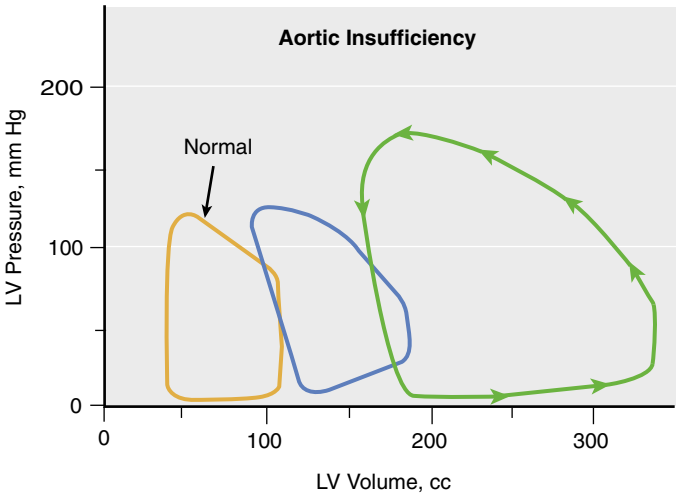

Figure 60-27 Pressure-volume loop in aortic regurgitation (AR). Acute AR, middle loop; chronic AR, right loop. *(Adapted from Jackson JM, Thomas SJ, Lowenstein E: Anesthetic management of patients with valvular heart disease. Semin Anesth 1:239, 1982.)*

Other Valvular Disease

Tricuspid Valve Disease

Tricuspid Regurgitation Right-sided valvular disease in adults is most often a manifestation of pulmonary hypertension secondary to intrinsic lung disease, pulmonary vascular disease, or left-sided cardiac disease. Primary TR can be rheumatic, traumatic, or infectious. Secondary or functional TR can be a manifestation of cor pulmonale, primary pulmonary hypertension, or left-sided cardiac disease that results in elevated pulmonary vascular pressure.

Tricuspid valvular disease is predominately regurgitant in nature. Patients with significant TR may have symptoms of dyspnea and evidence of elevated RA pressure (e.g., hepatomegaly, peripheral edema). Compensatory changes with long-standing TR involve RV and RA chamber dilation. Because of RA enlargement, many patients exhibit AF. Long-standing TR and RV enlargement can result in RV systolic dysfunction, which leads to further chamber enlargement, tricuspid annular dilation, and worsening of TR severity. If the tricuspid insufficiency is secondary to RV pressure overload states, as with pulmonary hypertension, RV hypertrophy ensues. This hypertrophy and increased RV pressure can lead to leftward displacement of the interventricular septum and impaired LV systolic and diastolic performance.

Anesthetic management concerns include preload preservation and appropriate inotropic support as dictated by the clinical situation. If the TR is secondary to elevations in pulmonary vascular pressure or resistance, efforts to reduce PVR will be beneficial. Forward flow can be maximized by high-normal heart rates. Surgical annuloplasty, although usually successful, can leave

residual TR or may create an elevated pressure gradient across the tricuspid valve.[350]

Tricuspid Stenosis Tricuspid stenosis (TS) is a relatively rare clinical finding in adults. Patients with TS may have significant RA enlargement and possibly AF. Chronic elevation of RA pressure leads to inferior vena cava dilation, jugular venous distention, and hepatic congestion. Clinical symptoms and signs can include hepatomegaly (with or without hepatic dysfunction), ascites, peripheral edema, fatigue, and dyspnea.[350,351]

TS results in reduced RV filling. The normal tricuspid valve area is 7 cm^2, and ventricular filling is compromised once the valve area falls below 1.5 cm^2. The severity of TS is usually assessed echocardiographically by measuring the Doppler-derived transvalvular gradient. Mild TS is associated with a gradient of 2 mm Hg or less; moderate TS, 2 to 6 mm Hg; and severe TS, greater than 6 mm Hg.

Anesthetic management centers on maintaining preload and controlling the heart rate. Overt tachycardia should be avoided because it significantly shortens the interval for diastolic filling, which needs to be prolonged in these patients. The target heart rate is not frank bradycardia because cardiac output may not be optimal, but the heart rate should be in the low-normal range. When AF is not part of the clinical picture, preserving atrioventricular synchrony is important to maintain RV output. Although RV inotropic failure is not usually a major concern in isolated TS, it may be when TS is a part of multivalvular heart disease or ischemic heart disease, thus warranting consideration of inotropic support. SVR should be maintained because the obstruction at the level of the tricuspid valve prevents a compensatory increase in preload if afterload declines.

Pulmonic Valve Disease

Pulmonic Stenosis Pulmonic valvular disease can be congenital or acquired. Pulmonic stenosis (PS) is caused by congenital valve abnormalities in 95% of cases.[350] Elevated transvalvular pressure gradients lead to RV hypertrophy, dilation, and eventual failure. Treatments include balloon valvuloplasty, surgical valvotomy, and valve replacement. Subvalvar muscular infundibular obstruction can result from long-standing PS. Tachycardia and hypovolemia can precipitate a dynamic clinical scenario in which outflow tract obstruction is accentuated. Management strategies include judicious heart rate control, preload maintenance, and inotropic support if RV systolic failure occurs.

Pulmonic Insufficiency Pulmonic insufficiency (PI) can result from the pulmonic valves being rendered incompetent during childhood balloon valvuloplasty for congenital PS or surgical valvotomy for the tetralogy of Fallot or its variants. PI may also be associated with rheumatic heart disease, pulmonary embolism, carcinoid, trauma, Marfan's syndrome, idiopathic dilation of the pulmonary trunk, and endocarditis.[350] Most patients are asymptomatic, but long-standing severe PI can lead to symptomatic RV dilation and failure, thus warranting replacement of the pulmonary valve.

Anesthetic management concerns include consideration of the primary cardiac or pulmonary disease that led to the pulmonic valvular insufficiency (e.g., endocarditis, emboli, and multifactorial causes of pulmonary hypertension). In primary PI, anesthetic management goals may include maintaining preload, supporting contractility, and reducing PVR by lowering $Paco_2$ and increasing Fio_2.

Minimally Invasive Procedures

Minimally invasive valve surgery was first reported by Cosgrove and Sabik[352] in 1996. In 1998, these investigators followed up with a summary report of 100 patients who underwent minimally invasive valve surgery through a right parasternal approach.[353] This report included 72 aortic and 28 mitral valve operations, and it described minimally invasive valve surgery as safe and "effective in reducing surgical trauma and cost." Reported benefits included improved cosmetic appearance, reduced pain, improved respiratory function, earlier extubation, less bleeding, fewer transfusions, and a safer approach for reoperative sugery.[353] Mihaljevic and colleagues,[354] who published a series of 1000 minimally invasive valve operations performed between 1996 and 2003, noted similar benefits, including reduced bypass and cross-clamp times, reduced stroke and MI rates, reduced length of hospital stay, and a higher rate of discharges home rather than to another facility. Other authors agree that minimally invasive valve surgery has evolved into a safe and efficacious option for many patients.[355]

Minimally Invasive Aortic Valve Surgery

The surgical approach to the aortic valve can be made through several different incisions, including a right parasternal incision, upper hemisternotomy, or lower hemisternotomy. A surgical decision may be made to perform femoral arterial cannulation. Alternatively, aortic cannulation may best be accomplished through an incision directly into the aorta or the axillary artery, particularly if aortic atheromatous disease precludes retrograde aortic arterial flow or direct cannulation of the ascending aorta. Venous bypass drainage can be accomplished by cannulating the RA (if surgical exposure is not compromised) or the femoral vein. Positioning of the distal drainage portion of the femoral vein cannulas into the inferior vena cava, RA, or distal segment of the superior vena cava is guided and confirmed by TEE (Fig. 60-28).

To reduce the incidence and magnitude of retained intracavitary LV air, CO_2 gas can be insufflated into the surgical field. Because surgical exposure is limited, sterile transcutaneous defibrillator pads should be placed, should the need to defibrillate arise. Other surgical and anesthetic concerns about the conduct of CPB and care of the patient are similar to those discussed in the sections on aortic valve surgery and CPB.

In general, anesthetic monitoring considerations are similar to those for standard approaches to valvular heart surgery.

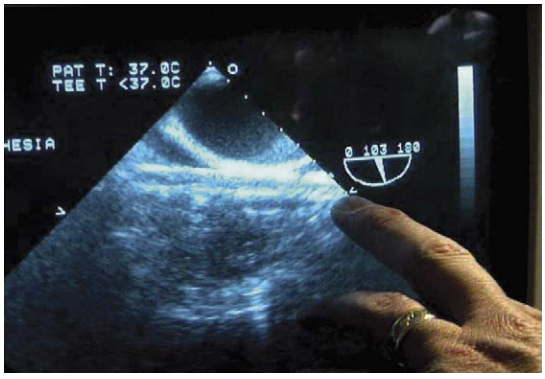

Figure 60-28 Venous cannula placement through inferior vena cava (IVC)–right atrium into the superior vena cava (SVC).

However, in the absence of direct visualization, TEE is even more valuable in these procedures because of the importance of assessing bypass cannula placement and ensuring adequate ventricular de-airing. If retrograde cardioplegia is required, TEE may be used to guide a transjugular retrograde catheter into the coronary sinus.

A recent report of a large series of minimally invasive aortic valve procedures included more than 900 patients.[356] The authors reported lower mortality rates than the national average, decreased blood product use (with 53% of first-time aortic valve surgery patients receiving no blood products), an average length of hospital stay of 6.9 days, and higher rates of discharge home (including 40% of their octogenarian patients).[356]

Minimally Invasive Mitral Valve Surgery

The mitral valve can be accessed through a lower hemisternotomy, a right parasternal incision excising the cartilaginous portions of the third and fourth ribs, or a right thoracotomy. The mitral valve is then exposed through the LA or via a "transseptal" approach through the RA. Visualization of the valve for repair or replacement can be done by direct inspection and instrumentation; by "port access" under thoracoscopic guidance and video assistance, which can involve voice-activated, robotic movement of the thoracoscopic instruments; or by a more complete endoscopic technique using the DaVinci robotic system (Intuitive Surgical, Inc., Sunnyvale, CA). The DaVinci system uses robotic arms and instrumentation controlled by the surgeon sitting at a remote computer-enhanced three-dimensional imaging console to assist in completion of the surgery.

Endoscopic or minimally invasive mitral procedures usually involve CPB with aortic and venous cannulas placed via the femoral artery and vein. In addition, the surgeon may choose to use novel aortic occlusion devices that allow a bloodless operative field and delivery of cardioplegia. However, the Heartport endoaortic occlusion and cardioplegia delivery catheter is challenging to position in the aortic root and requires intraoperative fluoroscopy or echocardiography to regularly confirm the catheter's position. Known concerns and risks include migration of the catheter into the heart across the aortic valve and distal migration with occlusion of the brachiocephalic trunk. Alternatively, aortic occlusion can be applied directly with flexible cross-clamps introduced through small chest wall incisions. Cardioplegia needles may be inserted via direct visualization or under thoracoscopic guidance. Retrograde cardioplegia, although not necessarily used in all patients, can be accomplished by direct cannulation of the coronary sinus with a retrograde catheter in the operative site (right atrial approach) or through the use of a percutaneous coronary sinus catheter placed in the internal jugular vein and positioned under echocardiographic guidance.

Secondary operative considerations include the unique space/positioning required for the use of robotic instrumentation. Most minimally invasive approaches require a 30-degree "right side up" position.

In general, monitoring considerations are similar to those for standard approaches to valvular heart surgery, including a five-lead ECG, an invasive arterial catheter, and central venous access. Adequate surgical visualization often necessitates offering selective lung ventilation using a double-lumen tube or bronchial blocker. As noted with minimally invasive aortic valve surgery, the surgeon and anesthesiologist must rely heavily on TEE imaging.

Outcomes of minimally invasive mitral valve surgery have been encouraging. Reports of the Brigham experience describe mortality and morbidity rates comparable to those of full-sternotomy approaches and trends toward a reduced length of hospital stay and a higher rate of discharge home.[354,355] Although prospective trials comparing minimally invasive mitral valve surgery and standard approaches are limited, a phase II randomized multicenter trial of the DaVinci robotic system has shown the technology to be efficacious and safe while acknowledging that it entails a "learning curve."[355,357]

Other Uses of the Minimally Invasive Approach

Minimally invasive approaches can also be used to surgically treat tricuspid valve disease and atrial septal defects. Newer developments in operative treatment of ischemic heart disease have led to the consideration of "hybrid" operative and percutaneous therapies in patients with multivessel coronary artery disease. Additionally, some clinicians have attempted to combine minimally invasive valvular surgery with percutaneous catheter intervention for coexisting ischemic heart disease.[358]

Notably, early trials of Heartport technology with endoaortic occlusion catheters showed an elevated risk for intraluminal aortic injury and aortic dissection.[359,360] These reports were confirmed by the Port-Access International Registry, which showed initial trends toward higher dissection rates.[361] However, later series showed no increase in complication rates, perhaps because of increasing surgical experience.[362] At this time, the Heartport technology is still in use in some centers for port-access mitral valve surgery, and the endoaortic occlusion technology may offer an alternative when standard aortic cross-clamping is contraindicated.[363]

Heart Failure

HF has been defined as a complex clinical syndrome caused by any structural or functional cardiac disorder that impairs the ability of the ventricle or ventricles to maintain adequate cardiac output and thereby results in hemodynamic changes that perturb many neuroendocrine, humoral, and inflammatory feedback loops (Box 60-4). In the United States, more than 5 million people have HF, and its prevalence is estimated at 6.8% in people older than 65 years.

The ACC/AHA guidelines for the evaluation and management of chronic HF place patients in four classes based on the stages of the syndrome (Table 60-14).[364] Early in the course of the disease, ventricular contractility is maintained by adrenergic stimulation and activation of the renin-angiotensin-aldosterone and other neurohormonal and cytokine systems[365,366]; patients in this stage would be considered to be in ACC/AHA class B. However, these compensatory mechanisms become less effective over time, and ventricular dilation and fibrosis occur and cardiac function deteriorates. This produces a chronic state of low perfusion and refractory end-stage HF, labeled class D in the ACC/AHA classification scheme. The New York Heart Association (NYHA) functional classification system is also used to assess the severity of functional limitations and correlates fairly well with prognosis (Table 60-15).

Strategies for treating end-stage HF aim to limit disease progression, prolong life, and improve quality of life. Medical therapies, such as ACEIs, β-blockers, diuretics, inotropic agents,

Box 60-4 Pathophysiology of Heart Failure—From Injury to Clinical Syndrome

1. Causes
   a. Myocardial injury
      i. Ischemia
      ii. Toxins
      iii. Volume overload
      iv. Pressure overload
   b. Genetic perturbation
2. Cardiac remodeling
   a. Myocyte growth
      i. Concentric hypertrophy
      ii. Eccentric hypertrophy
   b. Interstitial fibrosis
   c. Apoptosis
   d. Sarcomere slippage
   e. Chamber enlargement
3. Clinical heart failure milieu
   a. Pump performance
   b. Circulatory dynamics
   c. Metabolic abnormalities

and antiarrhythmics, represent the usual standard of care for HF patients. However, even multidrug regimens may not prevent progression toward class D HF. A patient who has reached this category has a 2-year mortality risk greater than 75%; surgical intervention is the only effective treatment in these patients.

Heart Transplantation

According to the ACC/AHA guidelines, the only established surgical treatment option for advanced HF is cardiac transplantation,[364] which is associated with excellent 1-year survival rates (>85%), 5-year survival rates (70%), and functional capacity.[367] Discovery of the immunosuppressive agent cyclosporine in the early 1980s made cardiac transplantation an accepted surgical option for end-stage HF.[368] Since then, techniques for detecting and grading the extent of rejection have been refined, and immunosuppressive protocols have been further improved. Furthermore, newer immunosuppressants are being evaluated.[369] Early graft failure as a result of acute rejection is now rare, but late graft failure secondary to transplant coronary artery disease remains problematic. Repeat cardiac transplantation is not rare, and even third-time transplantation may be justified.

Table 60-14 ACC/AHA Classification of Chronic Heart Failure

Stage	Description
A—High risk for heart failure	Hypertension, diabetes mellitus, CAD, family history of cardiomyopathy
B—Asymptomatic heart failure	Previous MI, LV dysfunction, valvular heart disease
C—Symptomatic heart failure	Structural heart disease, dyspnea and fatigue, impaired exercise tolerance
D—Refractory end-stage heart failure	Marked symptoms at rest despite maximal medical therapy

ACC/AHA, American College of Cardiology/American Heart Association; CAD, coronary artery disease; LV, left ventricular; MI, myocardial infarction.
From Hunt SA, Baker DW, Chin MH, et al: ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration with the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. Circulation 104:2996-3007, 2001.

Table 60-15 New York Heart Association Heart Failure Symptom Classification System

NYHA Class	Level of Impairment
I	Ordinary physical activity not limited by symptoms
II	Ordinary physical activity somewhat limited by dyspnea
III	Exercise limited by dyspnea during a mild workload
IV	Dyspnea at rest or with very little exertion

Most candidates for cardiac transplantation have idiopathic or ischemic cardiomyopathy; less common diagnoses include viral cardiomyopathy, postpartum cardiomyopathy, refractory valvular disease, primary myocardial diseases (e.g., sarcoidosis, amyloidosis), drug-induced myocardial disease, and complex congenital heart disease (CHD) in adults. All patients on the transplant waiting list have had a recent multidisciplinary evaluation, including history taking and physical examination, routine hematologic testing, serum chemistry panels, viral serologic testing, electrocardiography, echocardiography, chest radiography, right- and left-heart catheterization, and pulmonary function tests. The goal of the evaluation is to confirm a diagnosis of class D HF that has been maximally treated but will result in death in less than 1 year.

In the United States, cardiac transplantation is performed in member centers of the United Network for Organ Sharing (UNOS), an umbrella organization responsible for coordinating organ procurement, organ allocation, and statistical information. The UNOS selection guidelines for cardiac transplantation give priority to patients with end-stage HF and a life expectancy of less than 1 year, such as patients in cardiogenic shock or a low-output state requiring mechanical or inotropic support, patients with advanced symptomatic HF and peak oxygen uptake less than 10 mL/kg/min (with achievement of an anaerobic threshold), patients with NYHA class IV HF because of advanced hypertrophic or restrictive cardiomyopathy, patients with refractory angina pectoris caused by inoperable coronary artery disease, and patients with life-threatening ventricular arrhythmias that are refractory to all appropriate medical and surgical treatment.[370] Usually, the patient's EF is less than 20%. However, patients with NYHA class III HF who are at risk for sudden death related to malignant arrhythmias are sometimes placed on the waiting list.

Assessing PVR and "reversibility" is also important. Patients with ischemic or idiopathic cardiomyopathy and increased LAP often have reversible elevated PVR, a condition that usually normalizes during the first week after heart transplantation. A pressure gradient across the vascular bed (also known as a transpulmonary gradient and calculated as the difference between mean PAP and mean PCWP) that is higher than 14 mm Hg indicates significant elevation of PVR. A reduction in PCWP to 20 mm Hg that occurs during treatment with pulmonary vasodilatory medication and is associated with persistent high PAP sug-

gests elevated PVR. A PVR that is higher than 5 dyne·sec·cm^{-5} and is unresponsive to pulmonary vasodilators indicates a major "fixed" component of vascular resistance, a condition associated with an increased risk for early mortality after orthotopic heart transplantation.[371]

The UNOS allocates donor hearts according to each patient's priority status, ABO group compatibility, body size match, and distance from the donor center. The highest priority is given to inpatients supported by mechanical circulatory assist devices for acute hemodynamic decompensation, patients maintained on assist devices who have significant device-related complications, patients requiring continuous infusion of single or multiple high-dose intravenous inotropic medications, and those with a life expectancy of less than 7 days without transplantation.

In recent years, the selection criteria have been broadened for both heart recipients and heart donors.[372] For example, HF patients in two previously excluded categories—those with diabetes and those older than 65 years—are now considered transplantation candidates in many centers.[369] In addition, although centers generally prefer donors to be younger than 35 years, these criteria have been expanded to include suitable donors (e.g., those without cardiac risk factors or evidence of coronary artery disease) who are 60 years or older.

Once a prospective donor has been identified, the accepting center must ensure that the heart is further evaluated by echocardiography and possibly by coronary angiography. Cardiac donors are accepted after careful determination of the extent of hypotension, hypoxia, and tissue trauma and after confirmation of brain death and organ viability. Echocardiography is an essential tool for donor evaluation, particularly after the patient is weaned from inotropic support. Echocardiography can be used to assess global and segmental wall motion abnormalities, RV function, valve function, the presence of a patent foramen ovale, and the presence of intracardiac air. Mild LV hypertrophy is usually acceptable. Mitral valve prolapse is common and does not contraindicate donation unless it causes severe MR.

Ideally, the donor does not have major hemodynamic or metabolic derangements requiring continuous high-dose inotropic support.[373] Frequently, the donor has been selected for multiorgan donation, and the heart procurement team must potentially coordinate with the kidney, liver, and lung procurement teams. The anesthesiologist's main concerns are to maintain hemodynamic stability and euvolemia, ideally with systemic blood pressure greater than 100 mm Hg and CVP of 8 to 12 mm Hg, and to maintain arterial blood gases within normal limits, with Pa_{O_2} greater than 100 mm Hg.

In the donor, after a median sternotomy, myocardial function is carefully evaluated, and the heart is inspected for abnormalities. The other teams are then allowed to dissect the remaining organs to be harvested. Systemic heparinization is achieved (300 U/kg), the superior vena cava is ligated, and the inferior vena cava is transected. The aorta is cross-clamped, the heart is decompressed, and cold (4°C) cardioplegia solution is infused. The heart is then removed and prepared for transport: it is placed in a sterile plastic bag that is placed inside another bag filled with ice-cold saline. This package is then carried in an ice chest. The upper time limit between harvesting and reimplantation of the heart is thought to be approximately 6 hours.[373]

Therefore, from the anesthesiologist's perspective, the preoperative period is often limited by important time constraints because induction should be timed so that CPB can commence immediately on arrival of the donor heart. Nevertheless, the preoperative evaluation should include all aspects of a routine urgent preanesthetic evaluation, including a quick inspection of the results of the most recent cardiology workup and collection of information about any recent cardiac decompensation, history of previous surgical procedures, the presence of an implantable cardioverter-defibrillator (ICD) that must be deactivated in the operating room just before or after anesthetic induction, current laboratory values, and last oral intake.

Orthotopic heart transplantation is performed via a median sternotomy. Because many recipients have had one or more previous cardiac surgical procedures, repeat sternotomy is carefully performed with an oscillating saw. The groin is prepared and draped to provide a rapid route for CPB cannulation, should it become necessary. After the pericardial incision, heparin (300 U/kg) is administered. Cannulas for CPB are placed in the ascending aorta and in the venae cavae via the RA.[369] After CPB is initiated, systemic hypothermia (28°C to 30°C) is instituted. The native heart is excised at the midlevel of the atria. The donor and recipient left atria are anastomosed first, followed by the right atria. Commonly, the superior and inferior venae cavae are anastomosed directly, and the LA is excised down to the entry of the pulmonary veins (Fig. 60-29). While systemic rewarming is begun, the PA and ascending aorta are anastomosed. Air is then aspirated from the heart, and TEE is used to ensure that the cardiac chambers are adequately de-aired before the patient is weaned from CPB. A dose of steroid (methylprednisolone) is administered as the last anastomosis is completed, before release of the aortic cross-clamp, to attenuate the immune response.[373] Lymphocyte depletion may be achieved with an infusion of polyclonal antithymocyte globulin, a preparation containing various amounts of specific antibodies directed against T-cell molecules, B-cell molecules, monocytes, macrophages, neutrophils, platelets, and endothelial cells.

If the donor heart fails to resume normal sinus rhythm, electrical cardioversion should be performed. Many patients need an infusion of an inotropic and chronotropic agent during reperfusion and weaning from bypass. If the heart rate is slow, isoproterenol or dobutamine is infused, and a temporary pacing wire is routinely placed on the right ventricle; pacing is usually set at 100 beats/min.[369] Weaning from CPB begins after ventilation is resumed and the cannula is removed from the superior vena cava. When the patient is separated from CPB, the PA catheter can be advanced into position.

Several complications can occur during the process of weaning a patient from CPB. RV failure is by far the most common cause of inability to wean from CPB and it carries a significant risk of mortality and morbidity. The donor heart is not conditioned to face such an acutely elevated RV afterload. Early signs of RV failure (RV distention and hypokinesis) may be detected with TEE, and by elevation in CVP and PAP. RV failure is thought to be caused by preexisting pulmonary hypertension, transient pulmonary vasospasm, tricuspid or pulmonary valve insufficiency, donor-recipient size mismatch, intracoronary air emboli, prolonged donor heart ischemia, or inadequate myocardial protection. Therapy for RV failure includes inotropic support, starting with isoproterenol or dobutamine. Other pharmacologic agents commonly used for pulmonary vasodilation include phosphodiesterase inhibitors (e.g., milrinone), PGE_1, B-type natriuretic peptide (i.e., nesiritide), and inhaled PGI_2 (epoprostenol) or

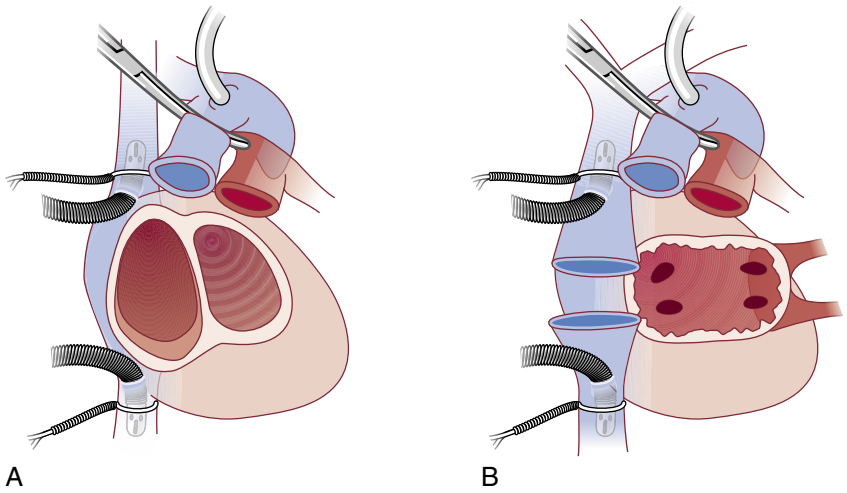

Figure 60-29 Surgical techniques for cardiac transplantation. **A,** Biatrial technique. The donor heart is anastomosed to the main bulk of the recipient's native right and left atria. **B,** Bicaval technique. The donor left atrium is anastomosed to a single left atrial cuff, including the pulmonary veins, in the recipient.

inhaled nitric oxide (Boxes 60-5 to 60-7). Vasopressin preserves SVR without causing significant changes in PVR and is often used to maintain RV perfusion pressure (Box 60-8). Rarely, patients may require support with an RV assist device.

LV dysfunction can occur as the result of prolonged donor heart ischemia, inadequate myocardial protection, coronary air embolization, or inadequate myocardial perfusion during the early post-CPB period. High-dose inotropic and vasoactive support with epinephrine, milrinone, and vasopressin may be required.

Protamine is administered after satisfactory weaning from CPB. In the postbypass period, TEE can provide additional useful information about right and left heart function and volume and can document a normal flow pattern through each anastomotic site.[373]

Box 60-5 Goals of Perioperative Management of Right-Sided Heart Failure

1. Preserving coronary perfusion by maintaining systemic blood pressure
2. Optimizing RV preload
3. Reducing RV afterload by decreasing pulmonary vascular resistance
4. Limiting pulmonary vasoconstriction through optimal ventilation
   a. High inspired oxygen concentration (100% Fio_2)
   b. Hyperventilation to a $Paco_2$ of 25 to 30 mm Hg
   c. Optimal tidal volumes
   d. Correction of acid-base abnormalities
5. Supporting RV function
   a. Pharmacologic agents
   b. Intra-aortic balloon pump
   c. RV assist devices

Fio_2, fraction of inspired oxygen; $Paco_2$, partial pressure of CO_2; RV, right ventricular.

Coagulopathy is a common complication of cardiac transplantation and is probably related to chronic hepatic congestion, preoperative anticoagulation, CPB-induced platelet dysfunction, hypothermia, and hemodilution of clotting factors. When coagulopathy occurs, it requires meticulous attention to surgical hemostasis and, possibly, administration of platelets, FFP, and cryoprecipitate or factor VII, as indicated by coagulation studies. Blood product administration should be guided by close monitoring of coagulation status. Adequate hemostasis should be achieved before the sternotomy is closed and the patient is transported to the ICU.

Even though a well-preserved transplanted heart maintains its normal contractility, it lacks the autonomic control of chronotropy and inotropy as a result of autonomic denervation. Thus, the transplanted heart responds only to direct-acting medication. Isoproterenol is often used for its chronotropic and inotropic effects. Dobutamine is routinely administered to patients with elevated PVR to increase the inotropy and chronotropy of the right ventricle. Occasionally, pacing is required to achieve faster heart rates and to reduce ventricular distention. Renal dysfunction, pulmonary dysfunction, and hyperacute allograft rejection are other possible early postoperative complications of cardiac transplantation.

Certainly, cardiac transplantation represents the definitive therapy for terminal HF. However, cardiac transplantation is not a solution for most patients with end-stage HF. More than 10,000 patients are on the heart transplant waiting list, but fewer than 2200 donor hearts are available each year.[374] In addition, these organs are usually reserved for patients younger than 65 years, even though older patients have the highest prevalence of HF. Furthermore, patients with comorbid diseases are often ineligible for transplantation. It is this mismatch between the increasing number of potential candidates for cardiac transplantation and the relatively fixed number of donors, as well as the large number of acute HF deaths, that continues to stimulate the search for alternative surgical therapies.

Ventricular Assist Devices

Mechanical circulatory support includes the use of a wide variety of devices designed to connect to the heart or to be placed within

Box 60-6 Pulmonary Vasodilator Agents

1. **Phosphodiesterase III Inhibitors**
   - Inhibition of myocardial type III phosphodiesterase leads to an increase in myocardial cAMP, which increases the influx of intracellular Ca^{2+} and has a positive inotropic effect
   - Unique mechanism of inotropic effects independent of β-receptor stimulation
   - Bypass β-adrenergic receptors in patients with preexisting heart failure
   - Additive effect with catecholamines
   - Pulmonary vasodilation
   - Coronary vasodilation
2. **B-Type Natriuretic Peptide**
   - Recombinant human B-type natriuretic peptide
   - Site of action: guanylate cyclase receptor of vascular smooth muscle and endothelial cells
   - Effect: increased intracellular cGMP and smooth muscle cell relaxation, dose-dependent reduction in PCWP and systemic arterial pressure in patients with heart failure, increased permeability of vascular endothelium, inhibition of the renin-angiotensin-aldosterone axis
   - Dose: 2-μg/kg bolus followed by a 0.01- to 0.03-μg/kg/min infusion
   - Plasma half-life: 18 minutes
3. **Prostaglandin I_2 (PGI_2)**
   - Endogenous prostaglandin
   - Synthesized by the cyclooxygenase arm of the arachidonic acid metabolic pathway
   - Potent vasodilator
   - Inhibits neutrophil activation
   - Stabilizes cell membranes
   - Enhances myocardial inotropy by activating adenylate cyclase and increasing intracellular cAMP
4. **Nitric Oxide**
   - Selective pulmonary dilator; less potent than inhaled prostacyclin
   - Activates guanylate cyclase
   - Improves ventilation-perfusion distribution
   - No effect on the cardiac or stroke index
   - Complex and expensive technology necessary for safe and effective use
   - Prolonged use can cause rebound pulmonary vasoconstriction
   - Toxic metabolites: nitrogen dioxide and methemoglobin
5. **Prostaglandin E_1 (PGE_1)**
   - Endogenous prostaglandin
   - Synthesized by the cyclooxygenase arm of the arachidonic acid metabolic pathway
   - Potent pulmonary and systemic vasodilator
   - Cleared from the circulation during its first pass through the lung

cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; PCWP, pulmonary capillary wedge pressure.

Box 60-7 Pharmacologic Agents for Inotropic Support of the RV

1. **Isoproterenol**
   - Nonselective β-adrenergic agonist
   - Positive chronotropic and inotropic agent
   - Pulmonary and systemic vasodilator
2. **Dobutamine**
   - β-Adrenergic receptor agonist with minimal α-adrenergic receptor agonist activity
   - Positive chronotropic and inotropic agent
   - Pulmonary and systemic vasodilator
3. **Epinephrine**
   - α- and β-adrenergic receptor agonist
   - β-Adrenergic receptor predominance at lower doses
   - Potent right ventricular inotrope
   - Has significant arrhythmogenic potential

the heart to assume some of its workload and permit the ventricle to rest, thereby potentially allowing reverse remodeling and recovery of some contractile function. The latest applications of mechanical circulatory support include reversing ventricular dysfunction after cardiac surgery, bridging patients to heart transplantation, and serving as destination therapy for patients who are not transplant candidates.

Studies have shown that the myocardium can repair itself during a period of unloading, after which some patients experience an improvement in quality of life.[375-381] Therefore, VADs can be used for short- or long-term support of the ventricle. The use of VADs as bridges to cardiac transplantation improves the survival rates and outcomes of patients with decompensated HF.[375-383] In addition, evidence suggests that long-term support of the left ventricle with a VAD (i.e., an LVAD) is superior to optimal medical treatment in patients with end-stage HF who are not candidates for heart transplantation.[383] Thus, mechanical circulatory support has become an important tool in the surgical management of patients with failing hearts.

Most VADs can be classified as either nonpulsatile or pulsatile (Tables 60-16 and 60-17), depending on the type of blood flow that they promote. Alternatively, when the site of the pump is taken into account, VADs can be categorized as extracorporeal

Box 60-8 Arginine Vasopressin

Endogenous peptide with osmoregulatory and vasomotor properties

End-organ effect mediated by

V_1 receptor present in vascular smooth muscle

Promotes vasoconstriction by activating G protein and phospholipase C, thereby releasing calcium from the sarcoplasmic reticulum

V_2 receptor present in the distal and collecting tubules

Promotes water resorption by increasing intracellular levels of cAMP and activating protein kinase A

cAMP, cyclic adenosine monophosphate.

Table 60-16 Pulsatile Ventricular Assist Devices

Device	Length of Support	Position	Ventricular Support	Drive Mechanism
Abiomed BVS 5000	Short term	Extracorporeal	LV, RV, BV	Pneumatically driven atrial and ventricular chambers
Thoratec VAD	Short to medium term	Extracorporeal	LV, RV, BV	Pneumatically driven sac
HeartMate IP and VE	Long term as a bridge to transplantation or recovery or as destination therapy (HeartMate VE)	Intracorporeal, abdominal (preperitoneal or intraperitoneal)	LV	Pneumatically or electrically driven, flexible, textured polyurethane diaphragm
Novacor	Long term as a bridge to transplantation or recovery	Intracorporeal, abdominal (preperitoneal or intraperitoneal)	LV	Polyurethane pump sac compressed by electrically driven pusher plates

BV, biventricular; BVS, biventricular support; IP, implantable pneumatic; LV, left ventricular; RV, right ventricular; VAD, ventricular assist device; VE, vented electric.

or intracorporeal. Most extracorporeal VADs, whether pulsatile or nonpulsatile, are used for short- or medium-term support.

Pulsatile assist devices provide a pulsatile flow and can generate a cardiac output of 6 to 9 L/min, given an adequate venous return. Currently, U.S. FDA–approved pulsatile VADs include the Abiomed BVS 5000, the Thoratec VAD System, the Novaco, and the HeartMate. The HeartMate VE (vented electric) is the only mechanical device currently approved by the FDA for destination therapy.

Nonpulsatile devices are designed with either centrifugal or axial flow patterns. These pumps generate continuous flow and have the advantage of being small, silent, valveless, and fully implantable. By working in concert with the heart, they improve the position of the left ventricle on the Frank-Starling curve. The Jarvik 2000 and the HeartMate II VADs can produce high flow rates and generate virtually all of the cardiac output. They can also operate at lower speeds, which allows the left ventricle to assume some of the workload. The Jarvik 2000 is an intraventricular device that is implanted at the LV apex, with the outflow cannula placed in the descending thoracic aorta (Fig. 60-30). The HeartMate II operates at 6000 to 15,000 rpm and provides up to 10 L/min of continuous cardiac output. An inflow graft delivers blood from the left ventricle to the pump, and an outflow graft delivers blood from the pump to the ascending aorta (Fig. 60-31). A driveline connects the pump to the external system driver. The Jarvik 2000 and the HeartMate II are used for long-term ventricular support as a bridge to heart transplantation.

Not all patients with advanced HF are good candidates for LVAD support. Contraindications to LVAD placement include active infection, irreversible renal dysfunction, severe liver impairment, stroke, severe pulmonary hypertension, incurable malignancy, and for the larger LVADs, a small body surface area (<1.5 m^2).[384] Nonetheless, the smaller size and ease of implantation of the newer axial flow LVADs make this technology potentially lifesaving for a wide range of patients, including those with a small body surface area, such as women and children.[369,385]

Because decompensated HF refractory to medical management is the principal feature of candidates for LVAD insertion, these patients may have different degrees of end-organ dysfunction caused by decreased cardiac output and perfusion pressure. Sepsis, pneumonia, ischemia, arrhythmias, and uremia secondary to renal insufficiency are common. Patients also often have reactive pulmonary hypertension caused by chronic elevation of LAP. Heart catheterization should be performed in these patients to obtain information about PVR, the pulmonary vascular response to vasodilators, cardiac output, and LV filling pressure.

Coagulopathy is common in HF patients receiving VAD support. Chronic, passive hepatic congestion may coincide with RV failure and can interfere with coagulation factor–dependent synthetic function. In addition, because prolonged or intermittent use of heparin is common in this patient population, VAD-supported patients have a higher incidence of HIT than other patients undergoing cardiac surgery do.[386,387] Testing for HIT antibodies in VAD patients, as well as implementing an alternative anticoagulation regimen, may lead to desirable outcomes.[388] In addition, VAD systems are known to activate the coagulation, thrombolytic, and inflammatory systems,[389] and platelet morphology and function are significantly altered by VAD-induced surface activation.[390]

Table 60-17 Nonpulsatile Ventricular Assist Devices

Device	Flow Type	Length of Support	Position	Ventricular Support	Drive Mechanism
Levitronix CentriMag	Centrifugal	Short term	Extracorporeal	LV, RV, BV	Electric
Tandem Heart	Centrifugal	Short term	Extracorporeal	LV	Electric
Impella	Axial	Short term	Extracorporeal	LV	Electric
Jarvik 2000	Axial	Long term	Intracorporeal	LV	Impeller electrically driven
DeBakey LVAD	Axial	Long term	Intracorporeal	LV	Electric
HeartMate II	Axial	Short term	Intracorporeal	LV	Electric

BV, biventricular; LV, left ventricular; LVAD, left ventricular assist device; RV, right ventricular.

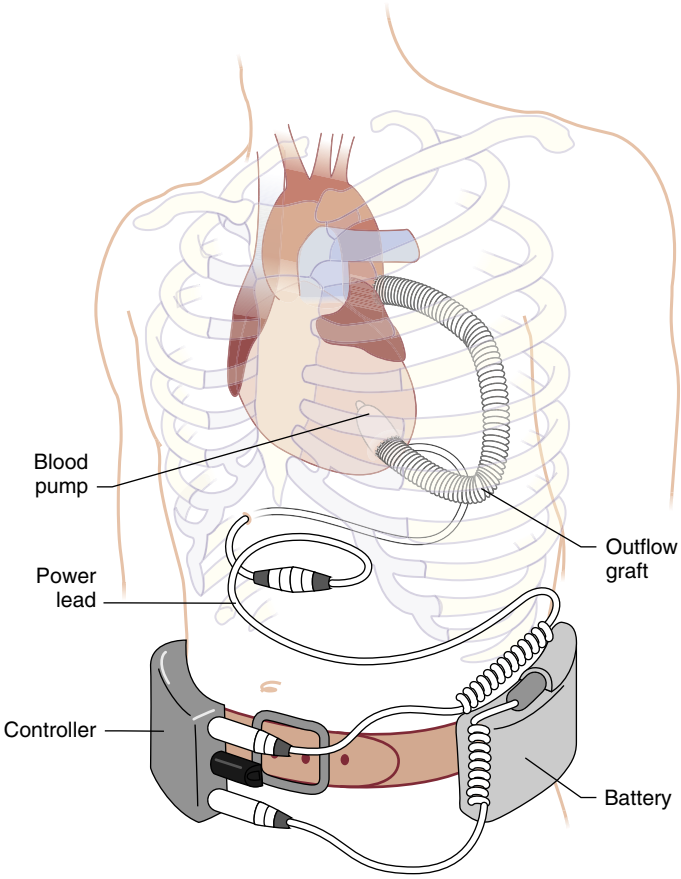

Figure 60-30 The Jarvik 2000.

Therefore, before surgery a rapid transfusion system should be prepared. Large-bore intravenous access is secured via an internal jugular or femoral vein for rapid administration of blood products. A reserve of blood and other products (e.g., FFP and platelets) is ensured. The use of antifibrinolytic agents (e.g., EACA) to minimize blood loss may be considered, although cases of fatal pulmonary embolization by microthrombi have been associated with the use of these agents.[391] In addition, the CPB circuit may be primed with FFP instead of crystalloid. Many patients have excess intravascular volume. Administering diuretics and using hemoconcentration during CPB are common methods of increasing the hemoglobin concentration in these patients.

In addition to standard monitors, a continuous cardiac output PA catheter is often inserted before or after anesthetic induction in LVAD recipients to continuously assess PAP, cardiac output, and trends in $S\bar{v}O_2$. TEE is performed before the start of CPB to identify any specific anatomic problems that could prevent the device from functioning as intended or that could cause predictable complications once LVAD support is engaged.[392] Such structural abnormalities can be categorized into those that will (1) impair effective LVAD filling (e.g., MS, poor RV function, and significant TR), (2) impair forward LVAD outflow and reduce effective decompression of the left ventricle by the device (e.g., aortic insufficiency), or (3) cause introduction problems or complications related to anatomic placement or to the physiologic changes introduced by the device (e.g., patent foramen ovale, other atrial septal defects, ventricular septal defects, ascending aortic plaques, and ventricular thrombi).

Before an LVAD is implanted, LV and RV function must be carefully evaluated, and the LA and left ventricle must be examined for thrombus, particularly at the apex of the left ventricle and in the left atrial appendage. Baseline TR should be evaluated because once the left ventricle is decompressed, the subvalvular apparatus of the tricuspid valve will be distracted to the left, which often results in failure of apposition of the tricuspid leaflets and increased TR. Thus, anything more than mild TR generally necessitates tricuspid annuloplasty. Significantly decreased RV function should prompt consideration of biventricular support because the risk of RV failure is increased when the left side of the heart is decompressed (as a result of altered RV geometry, increased preload, potential stunning during CPB, and potentially increased TR).

Aortic valve function is assessed because moderate to severe aortic valvular insufficiency will result in regurgitation of blood into the left ventricle when the LVAD is activated. This regurgitation will prevent effective decompression of the left ventricle by the LVAD; consequently, although LVAD flow will increase, effective forward systemic perfusion will be compromised. The atrial septum is inspected for a patent foramen ovale because when LVAD support is engaged, left atrial pressures will become less than right atrial pressures; this pressure differential will cause right-to-left shunting through the defect, thereby impairing systemic oxygenation. The thoracic aorta is assessed for calcification, plaques, and dilation.

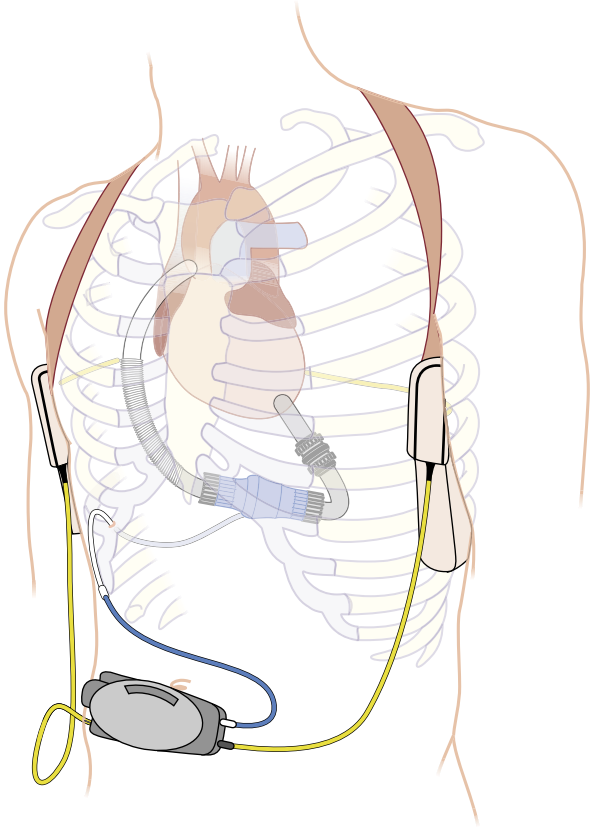

Figure 60-31 The HeartMate II continuous-flow ventricular assist device.

During CPB, TEE is used to ensure that the inflow cannula to the LVAD is centered in the left ventricle and is appropriately directed away from the LV septum or free wall (to avoid inlet occlusion) and toward the mitral valve to ensure optimal, unobstructed filling. When the LVAD is activated and the de-airing protocol is initiated near the end of CPB, TEE is used to assess the adequacy of air removal.

To function properly, LVADs must have adequate preload. The faster the LVAD fills, the faster the LVAD ejects, thereby increasing the effective LVAD output. Adequate preload depends on the ability of the right ventricle to pump a sufficient volume of blood across the pulmonary circuit and on the degree to which the pulmonary circuit permits blood flow. Therefore, successful weaning from CPB usually requires adequate RV function and reasonably low PAP.[393] Monitoring with TEE can detect early signs of RV failure (i.e., RV distention and hypokinesis), in conjunction with elevations in CVP and PAP. RV failure carries a significant risk of mortality and morbidity. Therapy for RV failure after VAD insertion is similar to therapy after heart transplantation (see the earlier section and Boxes 60-5 to 60-7), including the possible need for vasopressin (see Box 60-8). Rarely, patients may require support with an RV assist device.

After CPB is discontinued, TEE is also important for assessing the adequacy of intravascular volume, possible right-to-left shunting, the appearance (or worsening) of aortic or tricuspid valve incompetence, decompression of the left ventricle, the adequacy of inflow to the LVAD, and the absence of any residual air. If LVAD flows are less than expected, TEE is useful to rule out hypovolemia or tamponade. Moreover, TEE can be used to reassess the positions of the inflow and outflow cannulas because partial obstruction of LVAD inflow or outflow can cause hemolysis through shear stress as flow accelerates around the mouth of one or both cannulas. Such hemodynamic problems are best detected with Doppler color flow mapping.

In the postbypass period, reversing anticoagulation and achieving adequate hemostasis are the clinician's chief goals. The required volume of blood products may be high, and devices for rapid infusion of blood components are needed. Because LVAD flow is volume dependent, decreased flow usually results from a volume deficit, although RV dysfunction may also cause decreased flow. Also, even if volume loading and LVAD output are adequate, systemic perfusion pressure may be too low in the early stages after pump insertion. This problem can be caused by vasodilatory shock related to the patient's decompensated preoperative state, altered metabolism of ACEIs or amiodarone, side effects of milrinone, or deficiency of arginine vasopressin.[394] Therefore, administration of vasopressin may be necessary to maintain systemic pressure.

After LVAD implantation, primary chest closure may not be possible for 24 to 48 hours, until cardiac function has stabilized and the risk of hemorrhage has been controlled. Once sternal closure is possible, patients can be weaned from the ventilator. For successful extubation, it is often necessary to promote diuresis to alleviate residual pulmonary interstitial volume overload.

Recovery

Even though bridging to heart transplantation and destination therapy with LVADs is well studied, long-term bridging to recovery is less developed and understood. Reverse remodeling has been reported with prolonged LV unloading by an LVAD, in conjunction with the administration of clenbuterol, a β_2-adrenergic receptor agonist, to prevent myocardial atrophy.[395] Further research is needed to determine the duration of VAD support necessary for myocardial recovery, define the optimal level of ventricular unloading, and establish the sustainability of this recovery.[381,396]

Other Procedures

Surgical Ventricular Remodeling

Posterior Ventricular Excision Procedure In patients with HF, the left ventricle dilates and causes increased ventricular wall stress, myocardial cell death, and fibrosis. It has been thought that reversing ventricular dilation may prevent further myocardial cell death.[369] Therefore, procedures meant to "remodel" the left ventricle have been investigated.

Partial left ventriculectomy (LV reduction surgery) was introduced by Batista and colleagues[397] in Brazil. This procedure involves resecting a segment of the enlarged myocardium to restore normal size and function. The mitral valve is also repaired or replaced, and CABG may be performed, if necessary. Results have been variable: HF has worsened in some patients but shown stable improvement in others.[369,398]

Dor Procedure Another ventricular remodeling technique, the Dor procedure, involves placing an endoventricular patch through a ventriculotomy.[399] The procedure is meant to reduce the volume of the dilated left ventricle, thereby lessening stress on the remodeled ventricle, as well as reducing MR.[400] Restoration of a more normal elliptical shape may also improve systolic performance. One multicenter study of 1198 patients noted that the average EF improved from 30% to 40% after the Dor procedure.[401]

Extrinsic Ventricular Constraint Techniques

Cardiomyoplasty Another option that has been investigated for the surgical treatment of end-stage HF is dynamic cardiomyoplasty, in which an electrically stimulated flap of skeletal muscle, usually from the latissimus dorsi, is wrapped around the heart in an attempt to augment systolic function.[369] Dynamic cardiomyoplasty is used mainly to treat ischemic and dilated cardiomyopathy involving isolated LV failure. The main benefit of the procedure may be the mechanical "girdling" effect of wrapping the heart to prevent further LV dilation. At present, the clinical application of cardiomyoplasty remains limited.

Acorn CorCap The Acorn CorCap (for external splinting; Acorn Cardiovascular, Inc., St. Paul, MN) is a polyester-mesh cardiac support device that is surgically implanted to fit over the heart to produce passive ventricular reshaping (Fig. 60-32). It has been shown to slow the progression of HF, promote reverse remodeling, and improve functional status.[402,403] Clinical trials are being conducted to further address the safety and efficacy of the device.

Passive Ventricular Reshaping

Another innovative technique aims to preempt ventricular remodeling and address the MR that coexists with advanced HF. A novel device, the Coapsys (Myocor, Inc., Maple Grove, MN), is used to draw the mitral valve leaflets together by means of two epicardial pads connected by a flexible cord that runs beneath the valve. Early clinical results with the Coapsys have been promising in patients with moderate to severe functional mitral valve regurgitation.[404] Similarly, the use of polyester tension rods (Myosplint; Myocor, Inc., Maple Grove, MN; Fig 60-33) to draw the walls of

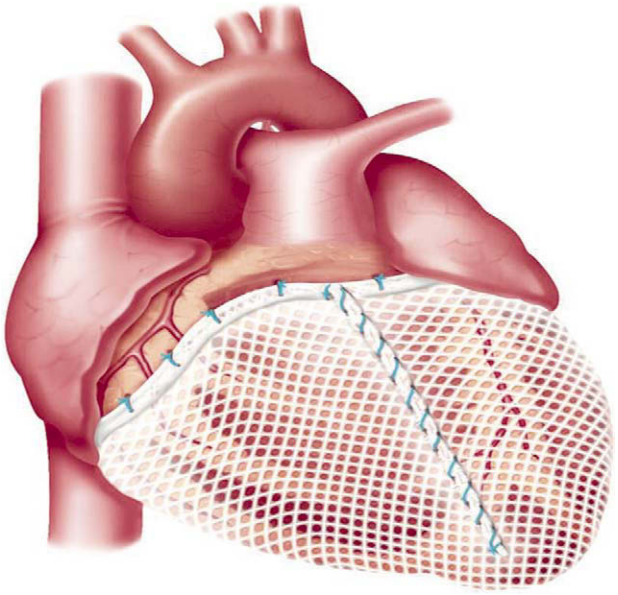

Figure 60-32 CorCap device.

the failing left ventricle together and thus alter its geometry has shown promise in patients with HF.[405]

Total Artificial Heart

The SynCardia CardioWest Total Artificial Heart (TAH) is a biventricular, orthotopic, pneumatically driven pulsatile pump. The TAH has two Medtronic-Hall inflow (27 mm) and outflow (25 mm) valves that are mounted on the housing. The ventricles fill fully and eject 70 mL per beat. Currently, the CardioWest pump is the only TAH used to bridge patients to heart transplantation.[406] In a study of this device in transplant candidates, 68% of the patients survived long term.[407] Recently, the CardioWest TAH was successfully used in a selected group of patients with irreversible cardiogenic shock. Patients recovered from all organ dysfunction and underwent successful heart transplantation.[408]

Congenital Heart Disease in Adults

Background and Current Perspective

Whereas in the 1950s only 25% of children born with CHD could be expected to reach adulthood, medical and surgical advances made since then have enabled a new and expanding clinical cohort of patients with CHD to survive to adulthood. Currently, 85% to 95% of babies born with such disease reach their adult years, and the number of adults with CHD now equals the number of children with congenital anomalies.[409,410] In fact, it is estimated that at least 800,000 adults in the United States have CHD and that 400,000 of them have moderate or complex disease.[411] Attendant adult issues, such as the long-standing effects of "corrected" or palliated CHD, acquired noncardiac disease or injury, and reproductive issues such as pregnancy, must be addressed. In addition, both females and males with CHD who reach reproductive age appear to have a greater risk for having offspring with CHD than the general population does.[412]

Given the size of the population of adults with CHD and the complexity of their original pathophysiology—complicated further by surgical repairs, palliation, or both—it seems prudent to consider this group of patients as separate and distinct within the adult surgical population. There is a misperception held by many patients and their families—and possibly by many health care professionals—that surgical treatment results in a cure. The reality is that most CHD patients face a lifetime of significant medical challenges[409] ranging from the implications of long-term antibiotic prophylaxis to the long-term sequelae of cardiac arrhythmias and ventricular dysfunction. Unlike the onset and progression of acquired adult heart disease, the progression of CHD may be slow and insidious, so CHD is often not addressed until the patient has reached adulthood, by which time the disease has caused severe, irreversible cardiac valvular and ventricular dysfunction.[409]

Preoperative Anesthetic Considerations

An appreciation of both cardiac and noncardiac pathophysiology is useful in planning an anesthetic approach to adult patients with CHD. A number of noncardiac organ systems can be involved, either as physiologic sequelae of the specific congenital heart defect or as part of a genetic/chromosomal syndrome whose manifestation includes cardiac anomalies.

Treatment of adults with CHD is conceptually facilitated by recent recommendations. The approach suggested by Perloff and Warnes[412] is based on understanding and differentiating between "residua" (anatomic or physiologic abnormalities left behind at the time of reparative surgery) and "sequelae" (new disorders or physiologic changes that are intentionally created or incurred and viewed as acceptable and necessary consequences of surgical treatment). This conceptual foundation provides a basic and much-needed framework on which anesthetic care providers may base their understanding of an adult patient with CHD.

Residua of surgery for CHD can be electrophysiologic, valvular, ventricular, vascular, or noncardiovascular.[412] Electrophysiologic residua include axis deviation on the ECG, AV block, ectopic atrial foci, and atrial tachyarrhythmias.

Valvular residua are structural and functional abnormalities of the cardiac valves. They result immediately from surgery or develop gradually as a consequence of long-standing primary pathophysiologic stress and secondary failing compensatory mechanisms.

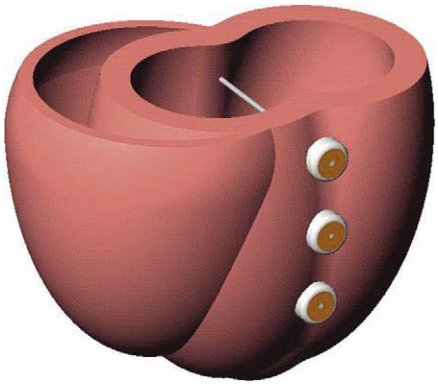

Figure 60-33 Myosplint concept.

Ventricular residua are among the most important perioperative considerations. The ventricular effects of CHD and its surgical repair or palliation include permanent structural abnormalities or dysfunction of the ventricle or ventricles and changes in ventricular function or mass that occur over time, such as the ventricular hypertrophy that develops in patients with a congenital bicuspid aortic valve that is inherently stenotic or that becomes so over a lifetime.

Vascular residua include structural abnormalities of the cerebral, coronary, and great arteries. Patients with a history of coarctation of the aorta or supravalvular AS have a diffuse inherited angiopathy that predisposes them to cerebral aneurysm formation, aortic aneurysm development, and even aortic rupture.[409] These medial aortic wall abnormalities appear to be part of a number of congenital cardiac anomalies and can involve the systemic and pulmonary arterial walls.[413] Elevated vascular pressure and resistance in the systemic or pulmonary vascular beds are other vascular residua that occur in adults with CHD. For example, postoperative residual systemic hypertension can complicate the long-term course of older patients with coarctation and is one of several syndromes that include supravalvular AS. In the pulmonary vasculature, long-standing luxuriant pulmonary blood flow can result in proliferation of pulmonary medial smooth muscle cells, which can cause elevations in PVR and possibly fixed pulmonary hypertension.

Noncardiac residua seen in adult patients with CHD are myriad. Mental retardation and somatic growth disorders complicate many congenital syndromes. Skeletal, facial, and airway abnormalities are common expressions of genetic dysmorphisms. Neurologic residua can persist as a consequence of primary cardiac disease. For example, paradoxical emboli can occur in a patient with atrial-level shunting. Furthermore, common age-associated medical problems, such as essential systemic hypertension, diabetes, and acquired coronary artery disease, may develop in adult patients with CHD.

Sequelae—new disorders or physiologic changes that develop as a consequence of correction or palliation—can be classified in a similar way. Electrophysiologic sequelae include the effects of surgical violation of atrial or ventricular muscle during intracardiac surgery and later exposure of cardiac chambers to elevated pressure and wall stress. Atrial arrhythmias, heart block, and tachyarrhythmic sudden death after ventriculotomy are known sequelae of surgical repair of CHD. Valvular sequelae can also be significant.

Furthermore, surgical repair of RV outflow tract obstruction, as performed in correction of the tetralogy of Fallot, can produce obligatory pulmonary insufficiency whereby the resultant volume overload affects the right ventricle. Sequelae of repair of inflow (mitral or tricuspid) valves are even more prevalent because of the complex nature of the inflow valvular apparatus and the functional dependence of the valve on LV or RV geometry and function.[412]

In addition, uniquely significant sequelae occur with the use of prosthetic material in the form of patches, conduits, or valves. Such material includes autografts (same individual), homografts (same species), xenografts (different species), and synthetic substances. Graft-related sequelae include accelerated fibrocalcific degeneration, thromboembolic complications, and elevated long-term risk for endocarditis.

Neurologic sequelae can include focal deficits, impaired higher cortical function, or CNS injury occurring as a consequence of brain or spinal cord malperfusion during complicated cardiac or aortic operations, especially those requiring circulatory arrest. Fortunately, advances in surgical and bypass techniques have minimized such sequelae. More subtle evidence of neurologic dysfunction includes lower than normal academic performance levels in Fontan patients or decreased motor performance and behavioral dysfunction in patients who have undergone circulatory arrest or low-flow CPB, had a prolonged stay in the ICU, or had disease involving single-ventricle pathophysiology.[414-418]

The initial assessment, history taking, and physical examination of an adult patient with CHD must be broadly systemic in nature to capture any noncardiac organ involvement. A full review of each organ system is beyond the scope of this chapter, but readers are referred to two excellent review articles by Chassot and Bettex and by Lovell.[419,420] Appropriate consultation with the patient's cardiologist (pediatric or adult), as well as access to old medical records, is optimal, especially for patients who have complex CHD or have undergone complex surgical procedures. Preoperative echocardiography is extremely helpful in understanding CHD patients' anatomy and cardiac function, both primary and compensatory.

One of the early clinical decisions to be made for an individual patient involves determining the appropriateness of surgical care in a given institution. Obviously, emergency procedures give very little latitude, but elective procedures should warrant careful assessment, especially of the abilities and experience of the anesthesiologist who will be caring for a patient with complex corrected or palliated CHD. In 2001, the 32nd Bethesda Conference on CHD advocated the creation of regional centers for the care of adults with CHD (ACHD centers), whose personnel would include a cardiac anesthesiologist with expertise in the management of patients with CHD.[411,421] The conference recommended that all adult patients with complex CHD (Boxes 60-9 and 60-10) be referred to such ACHD centers.

Intraoperative Anesthetic Considerations

In-depth discussion of the anesthetic management of particular congenital heart defects in adult patients is not the purpose of this section. However, a few basic principles are essential for all anesthesiologists to know, especially those who do not have specialized training in cardiac anesthesia or CHD but who may be faced with an older patient with CHD who needs urgent noncardiac surgery.

Principle 1: The Presence or Absence of Cyanosis

Cyanosis is usually a marker for complex CHD. Chronic cyanosis can lead to the development of abnormalities of RBC production and hemostasis. Elevated levels of erythropoietin in cyanotic patients can lead to a hyperviscosity syndrome and elevated neurologic risk. Risk factors include coexistent systemic hypertension, AF, and a history of phlebotomy and microcytosis.[422]

In any patient with cyanotic CHD, the anesthesiologist should establish intravenous fluid therapy and monitor urine output to minimize the circulatory effects of perioperative fasting, dehydration, and intraoperative hypovolemia. These conditions cause hyperviscosity, which can be associated with hemostatic abnormalities. Long-term administration of antiplatelet medications to ensure conduit patency can also cause such abnormalities.

The decision whether to measure CVP should be approached with caution and should involve consultation with a cardiologist

Box 60-9 Types of Adult Patients with Congenital Heart Diseases of Great Complexity*

Conduits, valved or nonvalved
Cyanotic congenital heart disease (all forms)
Double-outlet ventricle
Eisenmenger's syndrome
Fontan procedure
Mitral atresia
Single ventricle (also called double inlet or outlet, common or primitive)
Pulmonary atresia (all forms)
Pulmonary vascular obstructive diseases
Transposition of the great arteries
Tricuspid atresia
Truncus arteriosus/hemitruncus
Other abnormalities of atrioventricular or ventriculoarterial connection not included above (i.e., crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)

*These patients should be seen regularly at adult congenital heart disease centers.
Modified from Connelly MS, Webb GD, Somerville J, et al: Canadian Consensus Conference on Adult Congenital Heart Disease, 1996. Can J Cardiol 14:395-452, 1998.

familiar with CHD and with the patient's diagnosis. This decision also requires complete understanding of the patient's anatomy and underlying cardiac function, as well as the proposed surgical intervention. Caval-pulmonary connections, such as the bidirectional Glenn or Fontan procedures, elevate the patient's risk for thrombosis from indwelling venous catheters.

Principle 2: The Presence or Absence of Intracardiac or Extracardiac Shunts

Intracardiac shunts are classically located at the level of the atria or ventricles. The magnitude of the shunt is often expressed in terms of the ratio of pulmonary blood flow (Qp) to systemic blood flow (Qs): Qp/Qs. Balanced flow is the hallmark of normal physiology. A Qp/Qs ratio greater than 1 is generally consistent with acyanotic heart disease and luxuriant pulmonary blood flow. A Qp/Qs ratio less than 1 would be consistent with the clinical manifestation of cyanotic heart disease. Chassot and Bettex[419] remind us in their review article that there are important subcharacteristics of intracardiac shunts:

1. The direction of shunt flow is important. Shunts can be right, left, or bidirectional. Shunt flow can be influenced by changes in driving pressure across a shunt or pressure in the receiving chamber. The high intrathoracic pressure that can occur with mechanical ventilation, coughing, the Valsalva maneuver, bronchospasm, or positive end-expiratory pressure can actually reverse the direction of a left-to-right shunt or at least make it bidirectional. Therefore, paradoxical embolization by clot or air is a real risk in patients with intracardiac shunts and warrants fastidious attention to de-airing intravenous lines and careful administration of drugs via syringes through ports in intravenous lines.
2. The size of the intracardiac defect is important. Shunts are commonly labeled as restrictive or nonrestrictive according to their blood velocity or pressure characteristics measured at catheterization or by echocardiography. Large defects with associated low pressure or gradients across them have nonrestrictive flow. In addition, larger defects can be expected to have a greater effect on downstream structures and pressures. Small defects with high pressure or gradients restrict the amount of blood flow. The mainstay of anesthetic management of shunt lesions is to understand and control factors that may influence the direction and magnitude of the shunt. Shunt flow and direction are directly influenced by both PVR and SVR. Elevated SVR and decreased PVR will generally increase the magnitude and propensity for left-to-right shunting. Conversely, decreased SVR will decrease the magnitude of left-to right shunting, as will elevations in PVR. Mechanical ventilation, the inspired oxygen concentration, carbon dioxide levels, and the hemodynamic effects of anesthetic drugs are all used to accomplish certain therapeutic goals in relation to shunt management. Oxygen is a potent pulmonary vasodilator, as is a lower $Paco_2$. If the clinical problem is luxuriant pulmonary blood flow, a high Fio_2 is not optimal and

Box 60-10 Types of Adult Patients with Congenital Heart Disease of Moderate Severity*

Aortic–left ventricular fistulas
Anomalous pulmonary venous drainage, partial or total
Atrioventricular canal defects (partial or complete)
Coarctation of the aorta
Ebstein's anomaly
Infundibular right ventricular outflow obstruction of significance
Ostium primum atrial septal defect
Patent ductus arteriosus (not closed)
Pulmonary valve regurgitation (moderate to severe)
Pulmonic valve stenosis (moderate to severe)
Sinus of Valsalva fistula/aneurysm
Sinus venosus atrial septal defect
Subvalvar or supravalvar aortic stenosis (except hypertrophic obstructive cardiomyopathy)
Tetralogy of Fallot
Ventricular septal defect with
  Absent valve or valves
  Aortic regurgitation
  Coarctation of the aorta
  Mitral disease
  Right ventricular outflow tract obstruction
  Straddling tricuspid/mitral valve
  Subaortic stenosis

*These patients should be seen periodically at regional adult congenital heart disease centers.
Modified from Connelly MS, Webb GD, Somerville J, et al: Canadian Consensus Conference on Adult Congenital Heart Disease, 1996. Can J Cardiol 14:395-452, 1998.

should be avoided. Similarly, the direction and magnitude of the shunt flow determine whether one should hyperventilate a patient to achieve a low $Paco_2$ or tolerate a high-normal $Paco_2$.

3. In the presence of a shunt, the potential enlargement of receiving chambers and high downstream pressure are important. A shunt above the level of the AV valves, such as a left-to-right shunt at the atrial level, will usually cause right-sided chamber enlargement. Defects or shunts below the AV valves, such as a ventricular septal defect or patent ductus arteriosus, will initially result in left-sided chamber enlargement. Shunts at both locations increase pulmonary blood flow and, with time, can lead to potentially irreversible elevations in PVR and pulmonary pressure. Furthermore, exposure to elevated pulmonary pressure and afterload leads to RV enlargement, RV failure, bidirectional shunting, and in the most extreme cases, reversal of shunt direction and cyanosis, as in patients with Eisenmenger's syndrome.

Extracardiac shunts can be native to CHD (aberrant pulmonary venous return), surgically created (Blalock-Taussig shunt placement in some cases of cyanotic heart disease), or compensatory (aortopulmonary collateral formation with long-standing cyanotic heart disease). Special mention of aortopulmonary shunts, such as the Blalock-Taussig, Pott, and Waterson shunts, is warranted. These systemic-to-pulmonary shunts are used to palliate some forms of cyanotic heart disease. The proximal connection may be to the ascending aorta, brachiocephalic trunk, or subclavian artery. Because blood flow through this type of shunt is dependent on systemic blood pressure, systemic hypotension may lead to worsening hypoxemia. Long-term exposure to these extracardiac shunts can result in left-sided chamber enlargement and dysfunction secondary to chronic volume overload.

Principle 3: The Presence of Pulmonary Hypertension

Pulmonary arterial hypertension is defined as a mean PAP greater than 25 mm Hg or greater than 30 mm Hg with exercise. Some degree of pulmonary hypertension develops in 5% to 10% of adult patients with CHD, and the presence of pulmonary hypertension, as well as the associated exercise intolerance and decrease in functional capacity, appears to have important prognostic implications.[423] In a study of gravid patients with the tetralogy of Fallot, maternal complications were associated with pulmonary hypertension.[424]

Anesthetic management of patients with pulmonary hypertension can be problematic. Invasive monitoring and careful anesthetic titration may be required. Regional anesthesia may be used for appropriate procedures, but neuraxial blocks should be administered with caution. Patients with significant pulmonary hypertension are very sensitive to preload; therefore, hypovolemia, whether primary (blood loss) or secondary (vasodilation), should be treated immediately and aggressively. Pulmonary hypertension can be managed pharmacologically and mechanically. Factors associated with decreasing PVR and, subsequently, reductions in PAP are listed in Box 60-11.[420]

Box 60-11 Factors Associated with Decreasing Pulmonary Vascular Resistance and Reductions in Pulmonary Artery Pressure

Decrease in Pulmonary Vascular Resistance
Increasing Pao_2
Hypocapnia
Alkalemia
Minimizing intrathoracic pressure
- Spontaneous ventilation
- Normal lung volumes
- High-frequency and jet ventilation
- Avoidance of sympathetic stimulation
- Deep anesthesia

Pharmacologic methods
- Isoprenaline
- Phosphodiesterase III inhibitors
- Prostaglandin infusion (PGE_1 and PGI_2)
- Inhaled nitric oxide

Increase in Pulmonary Vascular Resistance
Sympathetic stimulation
- Light anesthesia
- Pain

Acidemia
Hypoxia
Hypercapnia
Hypothermia
Increased intrathoracic pressure
- Controlled ventilation
- Positive end-expiratory pressure
- Atelectasis

From Lovell AT: Anaesthetic implications of grown-up congenital heart disease. Br J Anaesth 93:129-139, 2004.

Principle 4: The Presence of Ventricular Dysfunction

As in adult patients with heart disease that is not congenital, the presence of ventricular dysfunction is an important risk factor for morbidity and mortality, both in the perioperative period and in the long term. Regarding RV dysfunction, pulmonary hypertension, pulmonic valve incompetence, and consequent dysfunction of the subpulmonic ventricle appear to be predictors of a poor outcome.[424,425] In a study by Khairy and associates,[425] pulmonary edema complicating pregnancy was associated with subpulmonic ventricular dysfunction, severe pulmonary insufficiency, or both, independent of LV systolic function. Nevertheless, dysfunction of the systemic ventricle (the ventricle below the aortic valve) is also associated with an increased risk for morbidity and mortality.[424]

Other Cardiac Procedures

Cox-Maze Procedure

The classic Maze procedure is currently the most effective curative therapy for AF.[426] To simplify the procedure and improve its results, Cox and colleagues modified the operation twice, thus its current name, the Cox-Maze III procedure.[426,427] This procedure apparently cures AF in 99% of cases. Indications for the Cox-Maze III operation include drug intolerance, arrhythmia intolerance, and recurrent embolic events.[428]

Ablative treatments of AF involve making right and left atrial incisions and cryolesions to interrupt the multiple reentrant circuits that cause AF. Isolating the pulmonary veins and excising

Table 60-18 Energy Sources for Surgical Ablation of Atrial Fibrillation

Energy Type	Endocardial Application	Epicardial Application	Flexible Probe	Assess Transmural	No Char	Rapid
Radiofrequency*	+	+	+	+	–	+
Microwave	+	+	+	–	+	+
Cryothermy	+	+	–	–	+	–

*Radiofrequency energy may be delivered in unipolar or bipolar fashion. A commercially available bipolar instrument allows the operator to assess transmurality.
From Gillinov AM, Blackstone EH, McCarthy PM: Atrial fibrillation: Current surgical options and their assessment. Ann Thorac Surg 74:2210-2217, 2002.

the left atrial appendage are integral parts of the Maze procedure, which requires CPB (for 45 to 60 minutes if the operation is performed by an experienced surgeon)[429-431] and cardiac arrest. This procedure can be performed through a minimally invasive chest incision, as an alternative to sternotomy, while the patient is maintained on CPB and is in cardiac arrest with cardioplegia.

A study done by Prasad and colleagues[428] found that the Cox-Maze III procedure effectively cured AF when performed alone or concomitantly with coronary or valve procedures. In patients undergoing such concomitant operations, the Cox-Maze III procedure did not significantly add to the mortality or morbidity associated with the revascularization or valve repair procedure.

New Developments in the Surgical Ablation of Atrial Fibrillation

Currently, newer technologies enable rapid creation of lines of conduction blockade, which surgeons use to ablate AF in patients undergoing concomitant cardiac surgical procedures. Such technologies include alternative energy sources such as radiofrequency (RF) and microwave energy, ultrasound, cryotherapy, and laser (Table 60-18). These technologies are also used in minimally invasive surgical ablation procedures to cure isolated AF.[426] Furthermore, the development of epicardial probes has facilitated "off-pump" ablation of AF in the beating heart.[432]

Because cardiac structures can be visualized directly during open surgery, ablation lines can be created safely, thus avoiding the complication of pulmonary vein stenosis. An epicardial approach to ablation eliminates the risk of esophageal injury.[426,433] The advantage of a surgical approach is the ease of excising the left atrial appendage, which virtually eliminates the risk of stroke. However, isolation of the pulmonary vein and excision of the left atrial appendage can now be done through the minimally invasive "keyhole approach" (Fig. 60-34) or a thoracoscopic approach.[433] Both approaches can be used without the need for CPB.[426]

Pericardial Tamponade and Constrictive Pericarditis

Pericardial Tamponade

The pericardial sac has two layers: the outer parietal pericardium and the inner visceral pericardium (epicardium), which is directly adherent to the surface of the heart. The normal amount of fluid between the two layers is 15 to 30 mL, which generates a pressure that is 5 mm Hg less than CVP and approximates pleural pressure.

Cardiac tamponade occurs when the volume of fluid trapped in the pericardial sac increases and compresses the heart, thereby compromising cardiac output.[434] In a classic tamponade scenario, the circulation adapts by increasing systemic venous and pulmonary venous pressure to equalize with pericardial pressure so that total collapse of the cardiac chambers is prevented.[435] PCWP and LV, RV, and RA diastolic pressure increase to equalize with pressure in the pericardium. As a result, atrial and ventricular diastolic transmural pressures are essentially zero, a hallmark of pericardial tamponade. Although this virtual loss of pressure

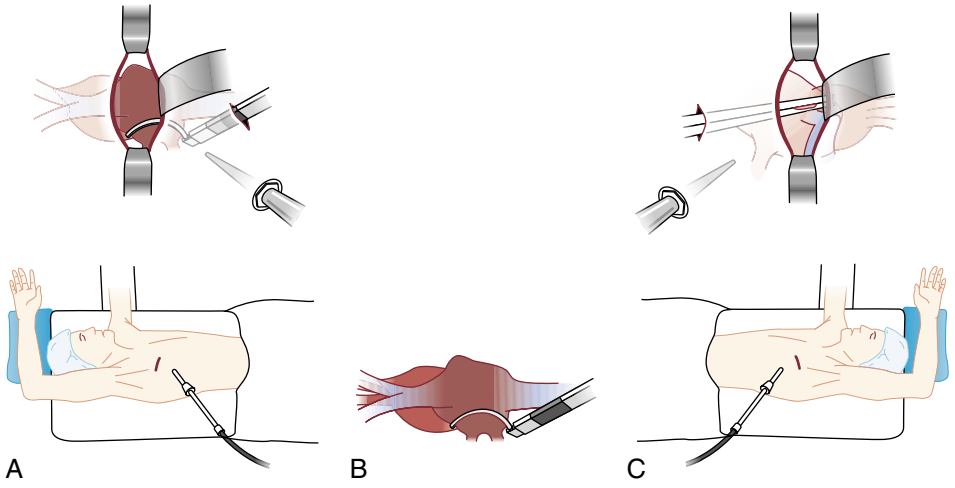

Figure 60-34 "Keyhole" approach for minimally invasive epicardial pulmonary vein isolation with excision of the left atrial appendage. **A,** Access to the right pulmonary veins is gained through a keyhole incision under endoscopic guidance. **B,** A bipolar radiofrequency clamp is used to isolate the left atrial cuff adjacent to the right pulmonary veins. **C,** Stapled excision of the left atrial appendage after the left pulmonary veins are isolated with a technique similar to that shown for the right pulmonary veins. *(From Gillinov AM, Wolf RK: Surgical ablation of atrial fibrillation. Prog Cardiovasc Dis 48:169-177, 2005.)*

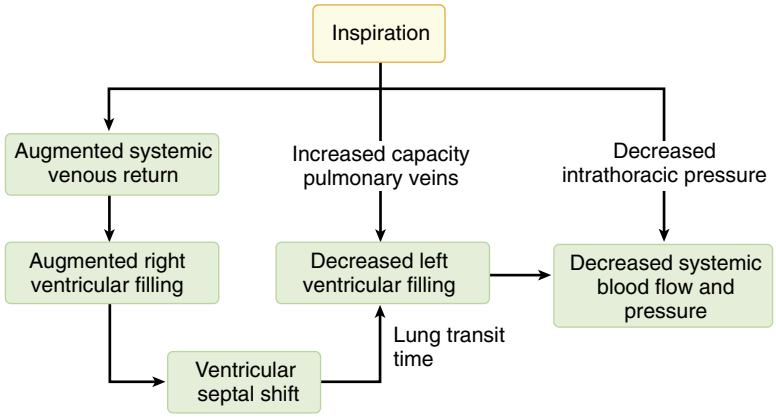

Figure 60-35 Physiology of paradoxical pulses in cardiac tamponade. *(Reproduced with permission from Fowler NO: Diseases of the pericardium.* In *Harvey WP, de Leon AC Jr, Leonard JJ, et al* [*eds*]*: Curr Probl Cardiol 2:6-38, 1978. Copyright © 1978 by Year Book Medical Publisher, Inc., Chicago.)*

reduces stroke volume, high adrenergic tone helps partially preserve cardiac output by increasing the heart rate.

If enough fluid accumulates, the pericardium reaches a stage at which it can no longer distend; therefore, the total pericardial volume no longer changes throughout the respiratory cycle.[435] This results in a phenomenon referred to as ventricular interdependence, wherein any change in the volume of one side of the heart causes the opposite change in the volume of the other side. During inspiration, increased venous return and filling of the right heart cause the interatrial and interventricular septa to bulge to the left, and opposite changes occur during expiration. Such ventricular interdependence is evident on echocardiography.

Ventricular interdependence is manifested clinically as pulsus paradoxus,[436] an exaggeration of the normal diminution of the radial pulse on inspiration (Fig. 60-35). Pulsus paradoxus is defined as a drop in systolic blood pressure exceeding 10 mm Hg during inspiration.[437] In particularly severe cases, there may be no palpable brachial or radial pulse on inspiration.[438]

Cardiac tamponade is not necessary to cause pulsus paradoxus. Wide swings in intrathoracic pressure and conditions such as pulmonary embolism or hypovolemic shock can also give rise to the phenomenon. Additionally, patients with cardiac tamponade may not have pulsus paradoxus if they have coexisting aortic insufficiency, an atrial septal defect, or preexisting elevated LVEDP secondary to LV hypertrophy or dilatation.

Figure 60-36 illustrates the pressure-volume relationship as fluid accumulates in the pericardial sac. This J-shaped curve suggests that a sudden increase in pericardial fluid volume of 100 to 200 mL can increase pericardial pressure to 30 mm Hg or more and cause severe cardiac tamponade.[435] The faster the fluid accumulation, the more severe the hemodynamic compromise. Causes of this type of acute tamponade include rupture of a thoracic aortic aneurysm, traumatic mediastinal injury, and accidental puncture of a cardiac chamber or blood vessel in the cardiac catheterization laboratory.[435]

In cases in which accumulation of pericardial fluid is slower, the compliance of the parietal pericardium is greater, and changes in volume produce smaller rises in pressure than they would if fluid accumulated more rapidly. As pericardial volume increases, so does intrapericardial pressure, with a compensatory increase in CVP to maintain a gradient to allow cardiac filling.[434] When pericardial compliance cannot increase any more, intrapericardial pressure gradually equalizes with pressure in the cardiac chambers. Cardiac output gradually declines, accompanied by a compensatory tachycardia, peripheral vasoconstriction, and increased contractility.[439]

Symptoms and Signs of Pericardial Tamponade

Patients with pericardial tamponade may have pain or feelings of fullness in the chest, dyspnea, lethargy, fever, cough, weakness, fatigue, anorexia, or palpitations.[434] The Beck triad may appear as a combination of three signs of severe tamponade: low blood pressure, increased jugular venous pressure, and distant heart sounds. However, patients whose tamponade develops secondary to a chronic medical condition (malignancy, end-stage renal disease, collagen vascular disease, etc.) may not exhibit the classic findings of the Beck triad.

Echocardiographic Features of Pericardial Tamponade Of the various echocardiographic signs of cardiac tamponade (Box 60-12), one of the most well established is diastolic

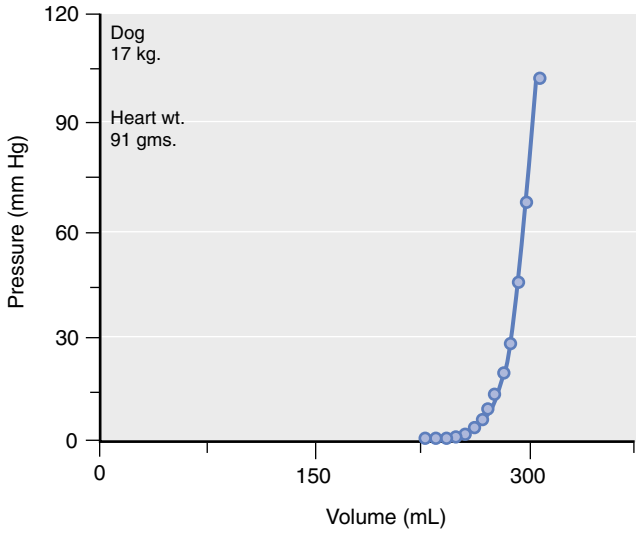

Figure 60-36 Pericardial pressure-volume curve demonstrating that a slight increase in volume can cause a significant increase in pressure. *(From Holt JP, Rhode EA, Kines H: Pericardial and ventricular pressure. Circ Res 8:1171-1181, 1960. Copyright © 1960 American Heart Association.)*

Box 60-12 Doppler Echocardiographic Signs of Cardiac Tamponade

Exaggerated inspiratory variation of the two ventricles (inspiratory expansion of the right ventricle and simultaneous compression of the left ventricle; reciprocal changes in the expiratory phase)
Right atrial collapse
Right ventricular collapse
Left atrial collapse
Left ventricular collapse
Inferior vena cava plethora

Abnormal increased respiratory variation in transvalvular blood flow velocities (mitral and aortic flow reduction in the inspiratory phase)

From Pepi M, Muratori M: Echocardiography in the diagnosis and management of pericardial disease. J Cardiovasc Med (Hagerstown) 7:533-544, 2006.

Box 60-13 Indications for Pericardiocentesis/Surgical Drainage

- Pericardiocentesis is indicated in patients with overt clinical tamponade, in those with suspicion of purulent pericarditis, and in patients with idiopathic chronic large pericardial effusion.
- Indications for surgical drainage are tamponade, either unresolved or relapsing after pericardiocentesis, and persistent active illness 3 weeks after hospital admission.
- Pericardial drainage does not seem to be warranted in the initial management of patients with large pericardial effusions without clinical tamponade because of its low diagnostic yield and poor influence on the evolution of pericardial effusion. Even the presence of echocardiographic right chamber collapse (suggesting raised intrapericardial pressure) does not by itself warrant pericardial drainage because most of these patients do not evolve to overt tamponade.

From Soler-Soler J, Sagrista-Sauleda J, Permanyer-Miralda G: Management of pericardial effusion. Heart 86:235-240, 2001.

collapse of the RA or right ventricle. Collapse of the right ventricle, seen in early diastole, appears as an invagination of the RV free wall. In contrast, right atrial collapse is seen in late diastole and early systole and appears as an invagination of the right atrial wall. The timing of collapse of the two chambers is related to the lowest intracavitary pressure in these chambers (i.e., early diastole for the right ventricle and late diastole for the RA). The presence of both RV and right atrial collapse indicates hemodynamically significant pericardial effusion (Fig. 60-37). Left heart collapse is rarely seen, because the thickness and stiffness of the left ventricle enables it to resist collapse and because the LA is located posteriorly. However, in patients with very large effusions, fluid does accumulate behind the LA and eventually collapses this chamber.[440]

Anesthetic Management of Pericardial Tamponade

Indications for pericardiocentesis (surgical drainage of pericardial effusion) are summarized by Soler-Soler and coworkers (Box 60-13).[441] Surgical intervention for pericardial disease warrants invasive monitoring, which should involve an intra-arterial catheter and possibly a central venous catheter.

In patients who are severely hemodynamically compromised, one surgical option is to perform pericardiocentesis or subxiphoid exploration under local anesthesia[442] and induce general anesthesia after the tamponade has been partially relieved. If general anesthesia is planned, watchwords in the management of cardiac tamponade are *fast*, *full*, and *strong*. It is important to administer intravenous fluids before induction to optimize preload. Increasing intravascular volume helps increase the effective filling pressure of the heart, restore the gradient between the chambers, and increase arterial pressure.

Any manipulation that can decrease venous return to the heart should be avoided, including controlled positive-pressure ventilation with large tidal volumes, which may significantly

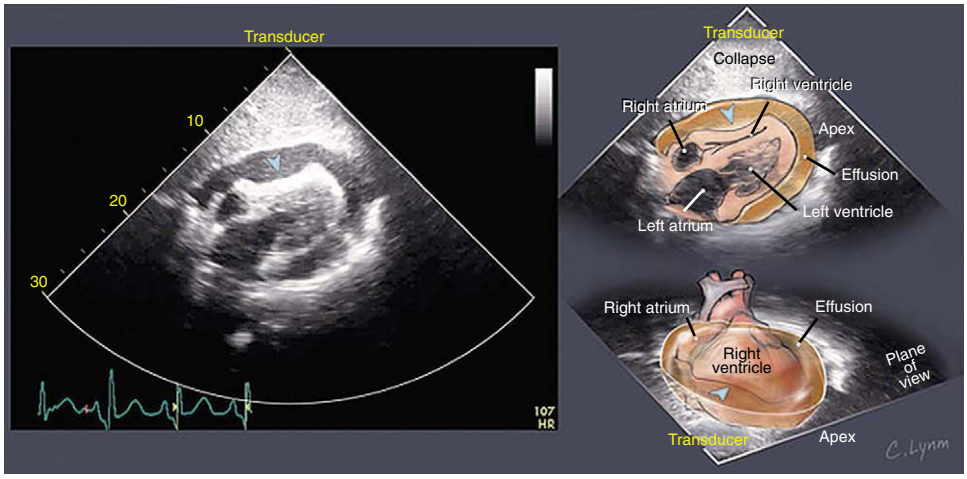

Figure 60-37 Echocardiogram showing pericardial effusion causing cardiac tamponade. A subcostal view in early diastole shows a large circumferential pericardial effusion compressing the heart, with the right ventricle completely collapsed. *(From Roy CL, Minor MA, Brookhart MA, et al: Does this patient with a pericardial effusion have cardiac tamponade? JAMA 297:1810-1818, 2007.)*

decrease preload and cardiac output.[442] Instead, if general anesthesia is required, one option is to allow the patient to breathe spontaneously until the pericardial sac is opened.[442] Alternatively, a ventilation pattern of high rate and low tidal volume can be used to minimize mean airway pressure.

Drugs that may cause myocardial depression should be avoided. Additionally, bradycardia should be avoided because tachycardia is the most important compensatory mechanism for preserving cardiac output. The use of ketamine to induce general anesthesia for creation of a pericardial window has been described.[443]

When cardiac tamponade is relieved, endogenously generated and exogenously administered catecholamines may cause sudden, severe increases in blood pressure and heart rate. This phenomenon should be anticipated and treated.

Constrictive Pericarditis

Constrictive pericarditis is said to be present when diastolic filling of the heart is restricted by a thickened and adherent pericardium. Several causes of constrictive pericarditis have been identified, including infectious processes and complications of cardiovascular surgery, and it may occur as part of Dressler's syndrome weeks or months after an MI.[444,445] However, constrictive pericarditis is most commonly idiopathic.[446]

Pathophysiology In cases of constrictive pericarditis, the thickened pericardium does not allow the heart to expand fully as it fills with blood during diastole. Instead, blood flows rapidly into the cardiac chambers during the first third of diastole and then suddenly stops as the thickened pericardium reaches its expansion limit.

Signs and Symptoms of Constrictive Pericarditis Typically, patients with constrictive pericarditis have elevated systemic venous pressure and low cardiac output.[447] Another feature of constrictive pericarditis is the diastolic equalization of pressures.[444] Because the heart is encased in a stiff pericardium, similar increases in diastolic pressure, usually within 5 mm Hg of one another, are noted in all four chambers.

Another sign seen in constrictive pericarditis is Kussmaul's sign, (an exaggeration of the x and y descent on the CVP tracing), which is elicited in response to increased blood return to the right heart on inspiration. Because the thickened pericardium no longer allows the heart to expand to accommodate all the blood flowing into it, the pressure generated by this returning volume is transmitted to the central venous system.[444]

As in pericardial tamponade, pulsus paradoxus is also usually seen in constrictive pericarditis. However, in some cases, thickening of the pericardium can shield the myocardium from the effects of the respiratory cycle, and therefore pulsus paradoxus might not be that obvious. Dyspnea and orthopnea are common in patients with constrictive pericarditis[446] because the low cardiac output caused by constrictive pericarditis severely reduces the patient's exercise tolerance and, in extremely advanced cases, causes cardiac cachexia and muscle wasting.[445] Ascites and peripheral edema may also be seen.

Anesthetic Considerations for Pericardiectomy Pericardiectomy is the treatment of choice for curing constrictive pericarditis.[444] This procedure is usually performed through a sternotomy, but it can also be performed through a left thoracotomy incision.[444,446] In patients with severe cases of the disease, pericardiectomy may involve stripping the pericardium off the heart, which may necessitate the use of CPB.

Anesthetic management of a patient undergoing pericardiectomy for constrictive pericarditis is similar to that of a patient undergoing a surgical intervention for pericardial effusion and tamponade. However, because the pericardium may need to be "peeled" from the surface of the heart, pericardiectomy carries an additional risk of arrhythmia and injury to the myocardium itself, including rupture of one of the chambers. Measures should be taken to avoid and treat arrhythmias and massive intraoperative bleeding.

Cardiac and Aortic Trauma

Penetrating Cardiac Injury

With the increase in violent crime over the last few decades, the number of cases of gunshot and stab wounds to the heart has risen.[448] Patients with penetrating cardiac injury may be critically unstable because of hemorrhage or cardiac tamponade, or they may have a benign injury to the heart.[449] An echocardiogram can detect the presence of blood around the heart[448] and can aid in making the surgical decision of whether to perform a sternotomy or to use an alternative approach.[450]

Anesthetic management of patients with penetrating cardiac injury is similar to that of other trauma patients. Unstable patients require emergency surgical intervention. The anesthesiologist must ascertain that blood is available on first knowledge of impending surgery for penetrating cardiac injury. With critically unstable patients, the anesthesiologist must secure the airway, establish intravenous access, and place the monitoring lines while the surgical incision is being made. An assistant can be very helpful in efficiently caring for such a patient. In planning induction of anesthesia and securing of the airway, the anesthesiologist should consider that the patient probably has a full stomach and volume depletion. Monitoring lines should include an arterial line and a central venous catheter. Barring any contraindications on the basis of the scant history that may be available at that time, TEE should be considered as an additional monitor. Anesthesia management involves attempting to maintain stable hemodynamics and prevent recall.

As in any trauma case, if the patient is unstable when first seen, controlled postoperative ventilation is usually preferred. The patient should be transported to the ICU with full monitoring and ventilatory support.

Traumatic Aortic Injury

Blunt aortic injury, which can result in either traumatic aortic transection (TAT) or acute rupture, is one of the most common causes of death from blunt trauma, second only to head injury. On arrival at the hospital, only 25% of patients with blunt thoracic trauma and resultant aortic injury (TAT or acute rupture) are alive.[451] Furthermore, the prognosis of patients who survive the initial injury and remain untreated is poor: 30% die within the first 6 hours, 50% die in the first 24 hours, and 90% die within the first 4 months.[452]

In blunt trauma to the chest, the mechanism of injury to the thoracic aorta is sudden traction on the relatively immobile portion of the aorta, the isthmus, as a result of sudden deceleration.[451] The isthmus is distal to the left subclavian artery, proximal to the third intercostal artery, and fixed to the left pulmonary artery by the ligamentum arteriosum.[453] This area of attachment of the ligamentum arteriosum acts as a hinge for movement of the aortic arch; thus, it receives the brunt of the shearing force during violent injury to the chest area. Hence, it is the most

common location for rupture of the aorta (50% to 70%), followed by the ascending aorta or the aortic arch in 18% and the distal thoracic aorta in 14% of cases.[451,453] The spectrum of injuries to the thoracic aorta in blunt thoracic trauma ranges from simple subintimal hemorrhage to complete aortic transection.[453]

The diagnosis of aortic injury may be made on the basis of a plain chest radiograph, computed tomography, angiography, or TEE. Smith and coworkers,[454] in a study of 93 trauma patients, concluded that TEE was a very sensitive and specific method of detecting aortic injuries in patients with blunt thoracic trauma and compared favorably with aortography. Diagnosing TAT with TEE requires recognition of a mediastinal hematoma[453]; a gap of more than 7 mm between the probe and the aorta at the level of the proximal descending thoracic aorta, plus blood between the aortic wall and the pleura, strongly suggests disruption of the aorta.[453,455] TEE can also be useful in monitoring the progression of a small intimal tear or as a screening tool for patients who have a normal mediastinum after blunt thoracic trauma.

Management of TAT focuses on the high risk of rupture that this injury entails; in-hospital rupture rates are as high as 13% in some series of TAT cases.[453,456-458] The unpredictable timing of this event adds to the concern for these patients. Aggressive management of blood pressure in the preoperative period is necessary to minimize the risk of rupture.[459] Systolic blood pressure should not exceed 100 mm Hg, and heart rate should not exceed 100 beats/min. The use of β-blockers and nitroglycerin or sodium nitroprusside infusions is recommended.

Monitoring during surgery should include an arterial catheter and central venous access. The keys to anesthetic management of patients with TAT are avoiding wide swings in systolic blood pressure and continuously monitoring the patient for end-organ ischemia. Because many operations on patients with TAT are performed on an emergency basis, aspiration precautions may be required. Additionally, some experts recommend using a modified rapid-sequence induction. Despite all precautions, marked swings in blood pressure are often seen during induction and laryngoscopy. Agents such as nitroglycerin and esmolol should be immediately available to treat any undesirable hypertension while the airway is being secured.

Intraoperatively, one major concern is the preservation of vital organs, most of all the spinal cord. In open procedures, using partial CPB (LHB) can facilitate the operation and, at the same time, preserve visceral organ perfusion and the spinal cord. This technique also prevents the aggravation of any other injuries that the patient might have sustained because this type of bypass does not require heparin.[452]

Aggressive management of blood pressure (i.e., keeping systolic blood pressure ≤100 mm Hg) and the heart rate[459] remains the cornerstone of the postoperative management of patients with traumatic thoracic aortic injuries. Another priority is maintenance of adequate perfusion of the vital organs and spinal cord.

Endovascular Aortic Repair

Endovascular repair of the aorta is a less invasive alternative to conventional open operations for aortic disease. With the endovascular technique, there is less blood loss, a reduction in the extent of hemodynamic fluctuations, and less metabolic stress on the patient. In addition, endovascular repair is often more acceptable to patients.[460] Because of the possibility of aortic rupture, preparations for emergency conversion to an open procedure should always be made in advance.[461]

General anesthesia is used during endovascular repair of TAT. As with open repair, anesthetic care of a patient undergoing endovascular repair should include an arterial catheter and central venous access.[460] TEE is valuable for locating the lesion in the thoracic aorta, positioning the guidewires, and deploying endografts.[461,462] Orihashi and associates[462] state that the sensitivity and specificity of TEE for detecting endoleaks are 100%. However, one's ability to visualize the distal ascending aorta and the proximal aortic arch with TEE is limited by the presence of the trachea and the right bronchus between the esophagus and the aorta.[463,464] Additionally, TEE can be used only when the fluoroscope is not in active use.

Ischemic Emergencies

With rapid advances in interventional cardiology, the number of patients undergoing interventional therapy in catheterization laboratories in the United States and Europe is increasing. Morris and colleagues[465] studied 5614 coronary interventions performed over a 3-year period at a single institution, 81 of which involved angiography-related accidents necessitating emergency cardiac surgery. Such emergencies included coronary artery dissection, free rupture, tamponade, foreign body embolism, and wire entrapment.

Patients may be at high risk for complications in the catheterization laboratory if they have unfavorable coronary anatomy or severe ventricular dysfunction. In some cases, cardiac surgery and cardiac anesthesia services should be consulted and placed on standby for possible emergency intervention. The rapidity of surgical intervention (e.g., revascularization or temporary mechanical support) plays a crucial role in reducing the mortality and morbidity of patients who suffer angiography-related accidents.

When ischemic complications occur during cardiac catheterization with percutaneous transcoronary angioplasty and stenting, pharmacologic intervention and possibly a device such as an IABP or VAD may be used to stabilize the patient's hemodynamic condition before being urgently or emergently transferred to the operating room for open coronary revascularization. Patients may be intubated on an emergency basis in the catheterization laboratory. In patients with coronary dissection or severe ischemia, it may be necessary to perform CPR during transport to the operating room.[466] Although the anesthesiologist, cardiologist, or both may lead these resuscitative efforts, all members of the catheterization team—physicians, nurses, and technologists—should complete a course in basic CPR; additionally, certification in advanced cardiac life support, with annual recertification, is strongly urged.[467]

If the patient is not already intubated, the choice of induction agents should be tailored to the patient's hemodynamic condition, with avoidance of hypotension and tachycardia while keeping in mind the patient's oral intake status. Perioperative monitoring of these patients should include an arterial line and central intravenous access, which should be established as soon as possible. TEE can be of immense importance in diagnosing the cardiac problem and in monitoring the patient intraoperatively.

Other procedures performed in the catheterization laboratory, notably aortic aneurysm stenting, may also require operating room backup. A dedicated surgical team should be available in the event of a life-threatening complication. Planning for the possibility of conversion to an "open" procedure is imperative, such

as when an aneurysm is leaking or a catheter has perforated a major blood vessel or cardiac chamber. If hemodynamic stability can be achieved, the patient can be urgently transported to the general operating suite. However, bringing a surgical team into the catheterization laboratory may be the most efficient strategy when circumstances are more dire, such as when a patient's aneurysm ruptures and the team is needed to directly cross-clamp the aorta.

Optimal care also depends on the ready availability of a stat laboratory. Blood gas analysis, as well as assessment of electrolytes and hemoglobin or hematocrit, is important in urgent situations. Patients undergoing procedures for coronary revascularization may be receiving platelet inhibitor drugs. Conventional coagulation tests may not be sufficient for diagnosing clinical bleeding in these patients, and tests that evaluate platelet function might be necessary.[188]

When compared with elective cardiac surgical procedures, emergency cardiac surgery carries a higher risk for mortality and morbidity, especially if the patient is in cardiogenic shock.[468] Identification of high-risk patients going to the catheterization laboratory for interventional procedures and communication among the interventional cardiologists, cardiac surgeons, and cardiac anesthesiologists about these high-risk patients are of prime importance in improving the outcome of these emergency procedures.

Procedures in the Cardiac Catheterization Laboratory and the Hybrid Operating Room

In the last 3 decades, the scope of activity in the cardiac catheterization laboratory (CCL) has greatly increased and has diverged considerably from the simple diagnosis and evaluation of valvular heart disease, coronary artery disease, and CHD.[469] In an increasing number of cases, anesthesia for patients with cardiac disease is being administered outside the standard operating suite, with the CCL being a primary site. Cardiac anesthesiologists may thus find themselves in a relatively isolated environment with bulky equipment, subdued lighting, and limited access to the patient.[469] Assistance from surgical colleagues, if required, may not be readily available. Furthermore, the services of anesthesia support personnel, the pharmacy, and the stat laboratory may not be immediately available. Finally, a recovery area suitable for patients with moderate or severe cardiac disease who have undergone heavy sedation or general anesthesia may be in a distant location.

To address some of these issues, so-called hybrid operating rooms with complete dual capability for procedures that require fluoroscopy, open surgery, or both have been designed and built within or adjacent to the regular surgical suite in some institutions. The physical location of such hybrid rooms may represent an advance in care in that key personnel are more readily available to handle unanticipated complications and emergencies.

The types of procedures that are done in the CCL or the hybrid operating room vary according to institutional preferences but may include (1) electrophysiologic assessment of rhythm disorders and management by ablation or by implantation of devices, (2) biventricular pacing for heart failure, (3) stenting of abdominal or thoracic aortic aneurysms, (4) balloon dilation and stenting for valvular and subvalvular lesions, and (5) the use of occlusion or umbrella devices to close an atrial or ventricular septal defect or a patent ductus arteriosus.

Although requirements vary depending on the nature of the procedure, sedation or anesthesia improves the efficacy and safety of many procedures.[469] Providing stable hemodynamics for organ perfusion and preservation during anesthesia is an important goal. Many CCL procedures can be performed with the aid of "monitored anesthesia care" (MAC) or regional blocks, provided that a certain patient comfort level can be achieved.[470] However, during difficult and lengthy procedures, patients may have trouble staying still. In many cases, a general anesthetic may be the best option. If indicated, general anesthesia with endotracheal intubation provides a controlled situation: patient comfort is maximized, and the airway is secured.[466] Use of a laryngeal mask or a standard mask airway is also possible, but the constant diaphragmatic movements that occur during spontaneous ventilation may interfere with fluoroscopic visualization of cardiac and vascular structures.

Radiation Safety

Because fluoroscopy is frequently used during interventional procedures in the CCL and hybrid operating rooms, it can present a significant risk of radiation exposure to patients and health care workers. Potential hazards of ionizing radiation include skin injuries and cellular mutation, which can lead to leukemia, bone cancer, and birth defects.

The radiation safety program at the Centers for Disease Control and Prevention (CDC) has developed the concept that radiation doses should be "as low as reasonably achievable" (ALARA). Exposure to radiation can be minimized by three means: distance, time, and barriers.[467] The distance between the person and the source should be maximized because the dose rate varies with the inverse square of that distance. In addition, the person's exposure time should be minimized because the dose rate and time are directly related. Finally, personal shielding and shielding of the radiation source should be maximized.

The roentgen equivalent man (rem) is the unit used to quantify radiation exposure.[466] It represents a unit of absorbed dose equal to the radiation absorbed dose (rad) multiplied by a factor weighted according to the type of radiation used. For radiographs, 1 rem is equal to 1 rad. A chest radiograph delivers a dose of 40 mrem, whereas a nuclear medicine study delivers about 14 mrem.

It is imperative that health care personnel in a radiation environment wear a dosimeter badge to track cumulative radiation exposure. The dosimeter should be worn on areas at highest risk for frequent exposure and outside any shielding garments (e.g., on the thyroid collar). Corrective action is recommended if an individual (patient or provider) receives more than 5 rem/yr to the whole body. In the case of pregnant individuals, the total radiation exposure to the fetus throughout gestation should be no more than 0.05 rem/mo or 0.5 rem total.[467]

Radiocontrast Media

Preventing allergic reactions to contrast agents is another consideration unique to procedures performed in the CCL or hybrid

suite. A complete description of any previous exposure to radiographic contrast material and whether any reaction occurred should be obtained. In many CCLs, an intravenous steroid is administered a few hours before the procedure, although there are no data to support or refute the advantages of this practice.[467] In addition, H_1 and H_2 blockers are often used to further reduce the possibility of an allergic reaction.

In patients with renal insufficiency, radiocontrast media–induced nephropathy is a concern, and diabetic patients are at particularly high risk for ARF after exposure to contrast agents.[466,467] These effects can be minimized through careful administration of contrast agents and limitation of the total dose.[466] Preprocedural and postprocedural hydration is recommended. However, in patients with severe HF, near–end-stage renal disease, or both, one must be careful to avoid volume overload.[466,467] Elevated serum creatinine levels are common after the administration of radiocontrast media, and these levels should be monitored for 72 or more hours in patients at risk. Fortunately, renal dysfunction is usually transient and rarely progresses to ARF.

Anesthesia for Electrophysiologic Procedures

Invasive cardiac electrophysiology studies are now common procedures in the CCL. Examples include electrophysiologic mapping with RF ablation or implantation and testing of an AICD. Electrophysiologic studies involve placing diagnostic catheters within various cardiac chambers to determine the origin and pathway of arrhythmias.[469] Arrhythmias are actually reproduced under controlled conditions by applying timed electrical impulses. Such arrhythmia induction, as well as any subsequently delivered "shock," is unpleasant and necessitates sedation or brief anesthesia in most patients. However, a relatively small proportion of adult patients require general anesthesia throughout the duration of the procedure. Many sedative and anesthetic agents have potential effects on cardiac rate, rhythm, or both. These effects need to be considered because the electrophysiologist must be able to induce a pathologic tachycardia to locate the pathway and successfully ablate it (or test the ability of an AICD device to terminate the arrhythmia).

Electrophysiologic Studies and Ablation

RF catheter ablation has, in many cases, replaced pharmacologic antiarrhythmic therapy for the treatment of recurrent or persistent tachyarrhythmias. Tachyarrhythmias appropriate for this treatment include those with a focal origin and, more commonly, those with a reentrant circuit. Electrophysiologic studies in the CCL usually involve inducing the tachycardia, mapping it, and performing transcatheter RF ablation.[471] Three to five electrode catheters are inserted percutaneously via venous access or via retrograde aortic catheter insertion and a transseptal approach. The catheters are positioned within the heart to allow induction of the arrhythmia and recording at key sites. Induction of the arrhythmia may be performed with pacing maneuvers that introduce critically timed ectopic beats to establish reentrant excitation. Heightened adrenergic tone, usually achieved by the administration of isoproterenol, may be necessary.

Induction of arrhythmia is unpleasant and requires some sedation. General anesthesia may be required in adults who are unable to cooperate. Many agents commonly used as part of the anesthetic technique may affect cardiac rhythm (e.g., lidocaine), and the use of such agents should be discussed with the electrophysiologist. It should be remembered that all inhaled agents affect the conduction system of the heart, whereas most intravenous induction agents have little effect on this system.[469] Once the arrhythmia's site of origin has been identified, the electrode catheter is positioned in direct contact with this site, and RF energy is delivered through the catheter. Any patient movement during ablation can result in catheter dislodgement and potential damage to normal conduction tissue.[469]

If catheter RF ablation fails, isolation of pulmonary vein foci and catheter ablation or a surgical approach may be required.[426] Further details are provided in the section "Cox-Maze Procedure."

Pacemaker/AICD Insertion, Generator Change, and Laser Lead Extraction

An AICD is a device capable of arrhythmia detection and automatic defibrillation. Such devices are often indicated for patients with advanced HF to decrease their risk of sudden death.[472] Patients require close monitoring, often including an arterial catheter, because of the potential for rapid blood pressure changes during the testing process. Central venous catheter placement should be considered in patients with poor peripheral venous access. If a technique is chosen that involves local anesthesia supplemented with sedation, administration of a small dose of propofol (in 0.25-mg/kg increments) or etomidate (0.05 to 0.1 mg/kg) in patients with preexisting hypotension may be necessary before inducing ventricular fibrillation and subsequently delivering an uncomfortable shock. It may take some time for hemodynamic variables to return to baseline after tests involving purposeful fibrillation followed by defibrillation.

Laser extraction of an AICD lead that is infected or damaged is another procedure that may be of long duration and require general anesthesia. The lead may be attached firmly to the endocardium and necessitate the use of a special coaxial laser device that slides over the lead to help burn it free. Myocardial perforation with ensuing cardiac tamponade is a rare but potentially lethal complication of this procedure.[469]

Patients with an AICD who undergo surgery (cardiac or noncardiac) should have the defibrillator disabled before anesthesia is induced and the surgical procedure begins, particularly if the use of electrocautery is planned. Preparation of an alternative method of defibrillating a potentially lethal arrhythmia, such as placement of an external defibrillator pad, must be done before the AICD is disabled. It is also important to ensure that the AICD is re-enabled immediately after the procedure is completed.

Biventricular Pacing

In many patients with advanced HF, defects in sinus or AV node function, intraventricular conduction defects (commonly left bundle branch block), or both delay the onset of LV or RV systole.[473] This lack of coordination of the left and right ventricles further reduces cardiac output and may increase the risk for mortality in these patients.[474] Cardiac resynchronization therapy is a variant of traditional AV pacing that involves placing additional pacing leads on the lateral wall of the left ventricle in a coronary

vein (accessed via the coronary sinus). Both ventricles can then be paced in a carefully timed manner to "resynchronize" RV and LV contraction, improving mechanical efficiency and cardiac output. Anesthesiologists are sometimes asked to provide sedation for these procedures, which may be somewhat lengthy. All the usual considerations for a patient with advanced HF are applicable, even if a "lighter" plane of sedation is chosen.

Problems in the Postoperative Period

Low Cardiac Output Syndrome

A combination of ischemia and reperfusion injury after cardiac surgery contributes to an energy deficit state in the myocardium that limits uptake of exogenous energy substrates from blood. Myocardial dependence on endogenous energy substrates results. Patients with preexisting cardiac failure experience a delay in myocardial recovery after cardiac surgery and require measures to relieve the workload of the heart.[475]

Criteria used to define LCOS include a CI of less than 2.4 L/min/m^2, elevated lactate levels, and urine output of less than 0.5 mL/hr for more than 1 hour.[476] $S\bar{v}O_2$ is also a good indicator of LCOS in that it reflects the balance between cardiac output and systemic oxygen demand.

Studies of patients undergoing CPB for cardiac surgery have found several preoperative risk factors for postoperative LCOS, including poor LV function, reoperation, urgency of the operation, female gender, diabetes mellitus, advanced age, left main coronary artery disease, MI within the previous 30 days, triple-vessel disease, hypertension, peripheral vascular disease, and renal dysfunction.[477,478] Furthermore, in patients undergoing cardiac surgery, preexisting diastolic dysfunction is associated with an increased risk of difficulty in separating the patient from CPB and need for vasoactive support in the ICU.[55] Therefore, evaluation of diastolic function should be part of the routine echocardiographic assessment of patients undergoing cardiac surgery. Intraoperative risk factors include myocardial ischemia during cross-clamping, reperfusion injury, cardioplegia-induced myocardial dysfunction, and activation of the inflammatory and coagulation cascades.[476]

Postoperative management of patients at high risk for LCOS requires a physiologic approach. Reducing afterload and optimizing preload help maximize cardiac function. Tachycardia should be avoided because it increases the risk for ischemia and postoperative MI. In addition, shivering should be prevented because it raises the heart rate by increasing oxygen demand.[477] Postoperative deep sedation and muscle relaxation are often used to reduce myocardial workload by reducing the body's overall metabolic demand by 25% to 30%.[475]

Pharmacologic support is sometimes needed to improve contractility as the patient is weaned from CPB and, eventually, recovering in the ICU.[476] Catecholamines and phosphodiesterase inhibitors are the main classes of pharmacologic agents used for this purpose. Table 60-19 lists the significant findings of studies of these inotropes completed by 2004. Although not yet available in the United States, a new class of drugs—calcium sensitizers, such as levosimendan—exhibit potent inodilatory properties.[199] In a study of patients with LCOS after cardiac surgery, levosimendan was found to enhance calcium sensitivity in cardiac

Table 60-19 Summary of Literature Search Findings on Therapy after Cardiac Surgery

Agent	Total Number of Studies	"Level I" Studies	"Level II" Studies	Significant Findings
Epinephrine	15	0	10	Increases CI with a biphasic effect on the SVR index. Produces a rise in serum lactate
Dopamine	22	0	14	Increased the SVR index at doses above 5.0 μg/kg/min. Less clinical efficacy than with dobutamine, dopexamine, amrinone, or enoximone. Higher incidence of adverse cardiac events than with dopexamine
Dobutamine	23	0	18	Better efficacy than dopamine and epinephrine. Decreased SVR index. Tachycardia and tachyarrythmia (especially AF) associated with its use. More ischemic complications than with amrinone
Dopexamine	20	0	12	Greater tachycardia than with dobutamine. More efficacious and fewer adverse events than with dopamine
Amrinone	27	1	13	Improved weaning from CPB. Improves CI and decreases the SVR index with minimal effects on HR. Fewer ischemic complications than with dobutamine. Reports of thrombocytopenia associated with use
Enoximone	24	0	15	Significant increase in CI without tachycardia. Decreases the SVR index. As effective as dobutamine
Milrinone	27	0	17	Significant increase in CI without tachycardia. Decreases the SVR index. As effective as dobutamine but less AF. Lusitropic. Improves IMA graft flow. As effective as 20 ppm NO in pulmonary hypertension

AF, atrial fibrillation; CI, cardiac index; CPB, cardiopulmonary bypass; HR, heart rate; IMA, internal mammary artery; NO, nitric oxide; SVR, systemic vascular resistance.
From Gillies M, Bellomo R, Doolan L, et al: Bench-to-bedside review: Inotropic drug therapy after adult cardiac surgery—a systematic literature review. Crit Care 9:266-279, 2005.

myocytes, thereby increasing stroke volume and CI while decreasing PA occlusion pressure.[479]

Arrhythmias

Cardiac arrhythmias are a common and well-recognized complication of cardiac surgery. Postoperative arrhythmias are seen in 10% to 40% of patients who undergo cardiac surgery.[480-482]

Atrial Arrhythmias

Atrial arrhythmias occur in up to 50% of patients who have undergone valve surgery[483-486] and in 17% to 33% of patients who have undergone CABG.[481,487] The most common arrhythmia after cardiac surgery is AF. Patients are at highest risk for new-onset AF in the first few days after cardiac surgery. New-onset AF can cause hemodynamic compromise, and it increases the risk for thromboembolic complications, thereby potentially prolonging a patient's hospital stay.[483-486,488]

Many potential risk factors have been studied in an effort to predict the occurrence of postoperative AF. One known preoperative risk factor is age. Age-related atrial dilatation with hypertrophy and fibrosis provides a substrate for reentrant arrhythmias.[489] This dilatation interrupts cell-to-cell electrical coupling between atrial muscle fibers.[490] Other preoperative risk factors for postoperative AF include COPD, use of digoxin within 2 weeks before surgery, low resting pulse rate, high resting systolic blood pressure, ischemia or infarction, withdrawal of β-blockers, RCA stenosis, and sinus or AV nodal artery disease.[488,491] Intraoperative risk factors for AF include cardiac venting via the right superior pulmonary vein, mitral valve repair and replacement, use of inotropic agents for more than 30 minutes after the termination of CPB, trauma from cannulation, hypomagnesemia, inflammation caused by CPB, prolonged cross-clamp times, and the type of cardioplegia used.[488,491] Pericarditis and low levels of magnesium have been proposed as possible causes of supraventricular arrhythmias in the postoperative period, but studies have not confirmed this relationship.[488]

Treatment of AF has been achieved by pharmacologic agents and electrical means. Studies have shown that β-blockers and amiodarone may be effective prophylaxis against postoperative AF.[488] In most patients, AF is self-limited, and patients usually spontaneously convert to sinus rhythm.[489] Synchronized cardioversion is reserved for patients who show signs of hemodynamic instability in the presence of AF.[488] Patients with persistent AF who do not urgently need cardioversion should be managed with the goal of controlling the ventricular rate.[488]

Ventricular Arrhythmias

Although ventricular arrhythmias occur after cardiac surgery, sustained ventricular arrhythmias are relatively uncommon. Associated factors may include hemodynamic instability, electrolyte abnormalities, hypoxia, hypovolemia, ischemia or infarction, acute graft closure reperfusion, and inotropic agents.[488]

Ventricular arrhythmias can range from simple premature ventricular complexes (PVCs) to ventricular tachycardia (VT). Simple PVCs do not pose a significant risk of life-threatening ventricular arrhythmia. On the other hand, complex ventricular arrhythmias, including both frequent PVCs (>30/hr) and nonsustained VT, may make patients prone to sudden death, especially in the long term. Sudden death is even more likely if ventricular function is also compromised. A study of 126 patients with postoperative complex ventricular ectopy reported a mortality rate of 75%.[488] During an average follow-up period of 15 months, sudden death occurred in 33% of the patients whose left ventricular ejection fraction (LVEF) was 40% or less, whereas none of the patients with a normal LVEF had sudden death.[493] Patients with sustained ventricular arrhythmias have a poor prognosis in both the short and long term.

Patients who are asymptomatic and hemodynamically stable do not usually require acute treatment of PVCs or even short runs of nonsustained VT, although any reversible causes should be corrected. On the other hand, patients with VT accompanied by hemodynamic instability need immediate synchronized cardioversion.[494] Amiodarone is reserved for hemodynamically stable patients with VT or an uncertain rhythm.[494] Ventricular fibrillation should be treated promptly with electrical defibrillation.[488] For long-term management of ventricular arrhythmias, in addition to antiarrhythmic agents, electrophysiologic studies or placement of an ICD should be considered.[488]

Bradyarrhythmias

Bradyarrhythmias are not uncommon in the immediate postoperative period. In most cases, a temporary epicardial pacemaker is sufficient. In a small percentage of patients, a permanent pacemaker may be necessary, especially in those with sinus node dysfunction or AV conduction disturbances after either CABG or valve surgery.[488]

Patients who need a permanent pacemaker may receive either a single-chamber or a dual-chamber pacemaker. Factors that influence the selection of a permanent pacemaker range from the patient's particular cardiac disease to access to technical support.[495] Both the single- and dual-chamber pacemakers have specific timing designs.

Hypertension

Immediately after cardiac surgery, the patient remains prone to hemodynamic instability, including hypertension.[496] Causes of postoperative hypertension are often multifactorial and may include withdrawal from preoperative antihypertensive medications (e.g., β-blockers and centrally acting α_2-agonists), pain, hypoxemia, hypercapnia, and hypothermia. However, arterial vasoconstriction usually plays a central role in acute postoperative hypertension.[497] Hazards of untreated postoperative hypertension include increased myocardial work and oxygen consumption, MI, rhythm disturbances, increased bleeding, and even suture line disruption. In the postoperative period, deepening sedation to control a hypertensive episode may not be the best or the only approach, particularly if "early" extubation (fast-tracking) is desirable.[496,497]

Several pharmacologic agents are available for use as antihypertensives; the ones most commonly used in clinical practice are the nitrovasodilators and the dihydropyridine-type calcium channel blockers (Box 60-14). Because of its anti-ischemic effects and familiarity, nitroglycerin is often the first agent used to treat hypertension in patients who have undergone coronary revascularization. However, nitroglycerin is not always effective in this setting because it primarily causes venodilation rather than arterial dilation. Moreover, patients tend to develop tolerance to nitroglycerin.[497]

Box 60-14 Vasodilators Available for the Treatment of Perioperative Hypertension

Adenosine
α_1-Adrenergic antagonists
α_2-Adrenergic agonists
Angiotensin-converting enzyme inhibitors (enalaprilat)
Angiotensin II antagonists
Atrial natriuretic peptide (nesiritide)
β_2-Adrenergic agonists
Dihydropyridine-type calcium channel blockers*
Dopamine agonists
Hydralazine
Nitrovasodilators*
Phosphodiesterase enzyme inhibitors
Prostaglandins

*Intravenous vasoactive therapies in widespread use to treat perioperative hypertension.
From Levy JH: Management of systemic and pulmonary hypertension. Tex Heart Inst J 32:467-471, 2005.

Because arterial vasoconstriction plays an important role in the development of hypertension after cardiac surgery, the therapeutic agent chosen should usually be one that effectively reduces hypertension. Sodium nitroprusside, a nonspecific venous and arterial vasodilator, is a common choice. However, theoretically, nitroprusside can cause coronary steal.[497] Furthermore, in patients with renal failure, elimination of sodium nitroprusside is reduced, thus making the patient vulnerable to the toxic effects of this drug's metabolites (cyanide and thiocyanate).

Fenoldopam is a short-acting dopamine agonist that causes arterial-specific vasodilation by stimulating D_1 receptors. Unlike sodium nitroprusside, fenoldopam increases renal blood flow to produce diuresis and natriuresis. Nevertheless, most clinical trials on the renal protective effects of fenoldopam are, at best, equivocal.[498] However, in one trial in cardiac surgical patients, the investigators concluded that fenoldopam did prevent acute kidney injury in a high-risk population of patients undergoing cardiac surgery.[499] Higher doses of fenoldopam may be needed for severe hypertension but may be associated with undesirable increases in heart rate.

Dihydropyridine-type calcium channel blockers, such as nicardipine and clevidipine, selectively relax arterial resistance vessels without negative inotropic or dromotropic (conduction) effects; they result in generalized vasodilation of the renal, cerebral, intestinal, and coronary vascular beds. Although cost is higher than that for the older agents (nitroglycerin or nitroprusside), nicardipine and clevidipine are recommended by some experts as first-line treatment for cardiac surgical patients with acute hypertension requiring immediate control.[497]

It is important to ensure that the patient's intra-arterial pressure is monitored adequately when any vasoactive agent is administered. Vasoconstriction or poor perfusion of the extremities may create a discrepancy between central aortic and peripheral arterial pressure. In addition, a radial arterial catheter may be "positional" if hand positioning is suboptimal, or "dampening" of the tracing may occur as a result of poor perfusion of the distal extremities. Occasionally during the perioperative period, the cardiac anesthesiologist or surgeon must replace a peripheral catheter (e.g., insert a femoral arterial catheter) to ensure that the effects of vasoactive therapy are monitored accurately.

Renal Insufficiency

Perioperative renal dysfunction, when it occurs, can have serious consequences. In a multicenter study of more than 2000 patients who underwent coronary revascularization with or without valvular surgery, Mangano and coworkers[83] found postoperative renal dysfunction in 7.7%, including 30 (1.4%) patients in whom dialysis was needed. In that study, mortality was higher in patients with ARF requiring dialysis (63%) and those with renal dysfunction (19%) than in patients who had neither (0.9%). Additionally, patients with postoperative renal failure had significantly longer hospital and ICU stays than did patients who had no renal failure or dysfunction in the postoperative period. Bove and associates,[81] in a study of more than 5000 patients who underwent cardiac surgery with CPB, found that 1.9% required postoperative dialysis and had an in-hospital mortality of 64%.

Preoperative risk factors that are commonly associated with postoperative renal dysfunction after cardiac surgery include preexisting renal insufficiency,[500,501] type 1 diabetes mellitus, age older than 65 years, major vascular surgery, arteriopathy, genetic predisposition, and recent exposure to nephrotoxic agents, such as radiocontrast dyes, bile pigments, aminoglycoside antibiotics, and nonsteroidal anti-inflammatory drugs. Also, several intraoperative factors may predispose a patient to renal dysfunction, including the need for emergency surgery,[81] CPB time exceeding 3 hours,[76] and poor cardiac function.[501] Other perioperative risk factors for renal dysfunction after cardiac surgery are hypovolemia, hypotension secondary to either hypovolemia or LCOS, and embolic phenomena.[76] Furthermore, damage to nephrons in the medullary region of the kidney is the most common cause of acute tubular necrosis, with hypoxia being a common cause of damage to nephrons in this region.[76]

Based on studies performed in patients with radiocontrast nephropathy, it has been concluded that hydration before the administration of radiocontrast media may protect the kidneys against the occurrence of postoperative renal dysfunction.[76] Because the mechanism of renal injury after CPB appears to be similar to that after the administration of radiocontrast dyes, it is thought that adequate hydration and maintenance of normovolemia can help in the prevention of postoperative renal dysfunction in cardiac surgical patients.[76] Furthermore, in patients at high risk for ARF, perioperative care should optimize cardiac output and, if possible, reduce the duration of CPB.[81]

Although the definition of ARF varies between studies, three useful criteria include (1) a serum creatinine level greater than 44 mmol/L (>0.5 mg/dL) above its preoperative value, (2) a serum creatinine level greater than 50% above its preoperative value, and (3) a serum creatinine level higher than 177 mmol/L (>2.0 mg/dL).[76] Another definition of ARF involves a classification scheme (Table 60-20) that uses the acronym "RIFLE."[502] A study performed by Kuitunen and colleagues[502] concluded that 90-day mortality is high in patients with a severe RIFLE classification.

Certainly, postoperative ARF in cardiac surgical patients is associated with longer ICU stay, longer overall hospital stay, and

Table 60-20 The RIFLE* Classification Scheme for Acute Renal Failure

	GFR Criteria	Urine Output Criteria
Risk	Plasma creatinine increased 1.5× or GFR decrease >25%	<0.5 mL/ kg/h × 6 hr
Injury	Plasma creatinine increased 2× or GFR decrease >50%	<0.5 mL/kg/hr × 12 hr
Failure	Plasma creatinine increased 3×, acute plasma creatinine ≥350 µmol/L, or acute rise ≥44 µmol/L	<0.3 mL/kg/hr × 24 hr or anuria × 12 hr
Loss	Persistent acute renal failure = complete loss of kidney function >4 wk	
ESKD	End-stage kidney disease (>3 mo)	

*Acronym for risk, injury, failure, loss, and end-stage kidney disease (ESKD).
GFR, glomerular filtration rate.
From Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettilä V: Acute renal failure after cardiac surgery: Evaluation of the RIFLE classification. Ann Thorac Surg 81:542-546, 2006.

increased mortality[76,83]; thus, it should be prevented whenever possible. Several treatment modalities have been suggested to prevent or ameliorate postoperative renal dysfunction (Box 60-15).[76] Unproven pharmacologic therapies include dopamine, dopexamine, the loop diuretics, mannitol, calcium channel entry blockers, ACEIs, and atrial natriuretic peptide.

Central Nervous System Dysfunction

CNS dysfunction is a common and potentially catastrophic complication of cardiac surgery and CPB. Rates of CNS injury vary between studies, but a large multicenter study found an overall 6.1% incidence of adverse cerebral outcomes.[56] Other studies, examining only neurocognitive dysfunction, have reported incidences approaching 60%.[62] A large European study involving more than 16,000 patients reported the following injury rates: OPCAB, 1.9%; CABG, 3.8%; aortic valve operations, 4.8%; CABG combined with valve procedures, 7.4%; mitral valve operations, 8.8%; and multiple-valve procedures, 9.7%.[61]

The impact of surgery-related CNS injury is profound. In a single-institution database study of 10,860 cardiac surgical patients, those who had overt perioperative strokes had survival rates of 64% at 1 year and 44% at 5 years, whereas patients who did not have perioperative strokes had survival rates of 94% at 1 year and 81% at 5 years.[503] The impact of stroke on health care resource utilization is also a cause for concern. Roach and colleagues[56] found that 47% of patients who had a type I neurologic event (stroke or transient ischemic attack) were discharged from the hospital to a skilled nursing facility or rehabilitation center. Furthermore, 30% of patients with more subtle neurocognitive dysfunction (type II event) after cardiac surgery were discharged to such facilities versus 8% without type I or type II events. Given that the clinical manifestation of cerebral injury is primarily a postoperative diagnosis, often with potentially irreversible neurologic sequelae and significant consequences for resource utilization, preoperative risk stratification and intraoperative management are important focal points for efforts to ameliorate and reduce CNS dysfunction and injury within the cardiac surgical population.

Neuroprotection Strategies

Numerous strategies have been tried in an attempt to decrease the incidence and severity of neurologic injury in cardiac surgical patients. A recent review of the literature by Hogue and associates,[234] using methods promoted by the AHA for making evidence-based recommendations, yielded only four management strategies with current evidence, albeit of a low to intermediate level, to support their use: epiaortic scanning leading to alterations in bypass or surgical technique, maintaining higher mean arterial pressure during CPB, using pulsatile perfusion, and using α-stat pH management during CPB. Each strategy received only a class IIb rating, which Hogue and colleagues define as follows:

> "*Class IIb: interventions are acceptable, safe, and useful. Considered 'within' the standard of care: reasonable prudent physicians can choose. Considered optional or alternative intervention by a majority of experts.*"

Many therapies and strategies received an indeterminate classification in Hogue and colleagues' review because there is not yet adequate evidence that they produce any improvement in neurologic outcome. Most pharmacologic strategies, such as the use of thiopental, propofol, nimodipine, and other drugs, received a class III rating, which means that the existing literature did not provide evidence of their efficacy. Table 60-21 lists the evidence-based ratings for various neuroprotective strategies.

Postoperative Management of Central Nervous System Injury or Dysfunction

Stroke after surgery may be indicated by the patient's inability to follow commands or move all extremities shortly after surgery. Neurologic consultation should be obtained, including diagnostic imaging. Diffusion-weighted magnetic resonance imaging is the most sensitive and accurate imaging technique for postoperative cardiac surgical patients.[504] It detects more microembolic lesions than conventional magnetic resonance imaging does and is better able to find multiple, "watershed" lesions.[505]

Box 60-15 Aims of and Treatment Modalities to Reduce or Prevent the Development of Postoperative Renal Dysfunction

1. Maintain adequate oxygen delivery—by ensuring adequate cardiac output, adequate oxygen-carrying capacity, and proper hemoglobin saturation
2. Suppression of renovascular constriction—by ensuring adequate volume preload and use of infusions of mannitol, calcium entry blockers, and angiotensin-converting enzyme inhibitors
3. Renal vasodilation—by dopaminergic agents, prostaglandins, and atrial natriuretic peptide
4. Maintain renal tubular flow—by loop diuretics and mannitol (which may act to prevent tubular obstruction, which can cause cellular swelling, ischemia, and death)
5. Decrease oxygen demand—by the use of loop diuretics and mild cooling
6. Attenuate ischemic reperfusion injury—as a result of the release of oxygen free radicals and calcium ions

From Sear JW: Kidney dysfunction in the postoperative period. Br J Anaesth 95:20-32, 2005.

Table 60-21 Evidence-Based Ratings for Pharmacologic and Nonpharmacologic Neuroprotection during Cardiopulmonary Bypass

Intervention	Rating
Heparin-bonded CPB circuits	Class indeterminate
Epiaortic ultrasound–guided changes in the surgical approach	Class IIb
Modified aortic cannula	Class indeterminate
Leukocyte-depleting filters	Class indeterminate
Cell-saver processing of pericardial aspirate	Class indeterminate
CO_2 wound insufflation	Class indeterminate
Maintaining "higher" MAP targets (i.e., greater than than the lower target of 50 mm Hg)	Class IIb for patients at high risk for neurologic injury
Nonpulsatile (versus pulsatile) perfusion	Class IIb (class indeterminate for patients at high risk for neurologic injury)
α-stat (versus pH-stat) acid base management	Class IIb (class indeterminate for patients at high risk for neurologic injury)
Minimal hematocrit target during CPB of >27%*	Class indeterminate
Thiopental, propofol, nimodipine, prostacylin, GM_1 ganglioside, pegorgotein, clomethiazole	Class III
Remacemide, lidocaine, aprotinin, pexelizumab	Class indeterminate
"Tight" intraoperative glucose control	Class indeterminate
Hypothermia	Class indeterminate

*The optimal hematocrit during CPB is not defined by available data. A hematocrit of greater than 27% is chosen as being indicative of "high" hematocrit based on its use in available randomized trials.
CPB, cardiopulmonary bypass; MAP, mean arterial blood pressure.
From Hogue CW Jr, Palin CA, Arrowsmith JE: Cardiopulmonary bypass management and neurologic outcomes: An evidence-based appraisal of current practices. Anesth Analg 103:21-37, 2006.

Management of CNS injury or dysfunction after cardiac surgery consists of general supportive measures. Hypotension should be avoided, and consideration should be given to using volume expansion, inotropic augmentation (pharmacologic or mechanical), or vasoactive medications (vasopressin or phenylephrine) to support blood pressure and brain perfusion. The brain oxygen supply-demand balance should be optimized through adequate oxygenation, sedation, and temperature control (because fever increases oxygen extraction). As mentioned in the section on glucose control, hyperglycemia should be avoided. Lytic therapy is of little use in cardiac surgery because it poses a risk for postoperative surgical bleeding.

Encephalopathic neurologic dysfunction can include neurocognitive decline, delirium, and seizure activity. Neurocognitive dysfunction, as mentioned previously,[62] has been reported to occur frequently after cardiac surgery requiring bypass. Neurocognitive decline can be manifested subtly, diagnosable only with complicated psychometric testing, or at the other extreme, it can be manifested as postoperative delirium. Delirium is characterized by disturbed consciousness and altered cognition that develops acutely. In one series of more than 16,000 cardiac surgical patients, delirium was reported to occur in 8.4% of cases.[506] Independent predictors of postoperative delirium included a history of cerebrovascular disease, peripheral vascular disease, AF, diabetes, LV dysfunction, preoperative cardiogenic shock, hemofiltration, elevated transfusion load, and operative times longer than 3 hours.

Recognition is a key element in the management of delirium, which is often multifactorial. Medications are a common cause. Clinical factors that may be important but cannot be mitigated in the postoperative period include advanced age, exposure to extended periods of CPB, the effects of microemboli, inflammatory mediators, preexisting dementia, and a history of CNS disease. Treatment revolves around delineating any treatable medical conditions that may be the precipitating cause of the delirium, such as drug or chemical toxicity or withdrawal, metabolic disorders such as hypoglycemia/hyperglycemia and uremia, fluid and electrolyte disturbances, inadequate cerebral perfusion because of a low–cardiac output or low-perfusion state, and infection or sepsis.

Peripheral Neuropathy

Peripheral nerve injury frequently follows cardiac surgery. In a review article, Sharma and coauthors[507] reported injury rates of 1.5% to 24% for the brachial plexus and 10% to 60% for the phrenic nerve. Phrenic nerve injury can occur as a result of the use of slushed ice in the pericardial well to provide surface cooling for the heart. Numbness, weakness, pain, decreased reflexes, and diminished coordination in an extremity are suggestive of peripheral nerve injury. Sensory findings in the fourth and fifth fingers, consistent with ulnar neuropathy, are most common.[508,509] The mechanisms of injury are most often related to the use of a sternal retractor and compression of the brachial plexus, although upper extremity neuropathy can occur as a consequence of arm positioning as well. Symptoms are usually self-limited and improve with time and, if needed, with physical therapy.

Respiratory Insufficiency

Even after uncomplicated cardiac surgery, a midline sternotomy (or thoracotomy) causes significant reductions in total lung capacity, vital capacity (VC), forced expiratory volume in 1 second (FEV_1), and functional residual capacity.[510] These changes may result in postoperative atelectasis and, frequently, at least mild hypoxemia. More severe postoperative respiratory insufficiency causing difficulty weaning may be due to intrinsic pulmonary problems (e.g., COPD, atelectasis, pneumonia, or surgical trauma to the lungs), ARDS related to CPB or transfusion (transfusion-related acute lung injury [TRALI]), pulmonary embolism, or cardiogenic pulmonary edema secondary to low cardiac output.

Preoperative efforts to minimize pulmonary complications after cardiac surgery include optimizing pulmonary function for patients undergoing elective surgery. With regard to the surgical approach, it has been theorized that off-pump surgery causes fewer changes in pulmonary mechanics than on-pump surgery does, but studies have shown little difference between the techniques.[511-513] Likewise, ministernotomy techniques have not been shown to improve pulmonary mechanics or arterial blood gases.[514,515] However, in some studies, off-pump MIDCAB per-

formed through an anterior thoracotomy resulted in less impairment of VC and FEV_1 than on-pump[516] or off-pump[517] CABG performed through a median sternotomy did.

Pain management should be included in postoperative efforts to minimize pulmonary complications. Sternotomy pain may limit the patient's ability to cough and perform deep-breathing exercises, and incisional leg pain from harvesting of saphenous veins may prevent early ambulation, thereby increasing the risk for pulmonary complications. Gust and colleagues[518] noted less atelectasis when patient-controlled analgesia rather than nurse-controlled analgesia was used after CABG. However, it is unclear whether the reduced atelectasis translates into less pulmonary morbidity.[519] The reader is referred to the section on pain at the end of this chapter for other options for improving postoperative pain control and thereby minimizing "splinting" and complications such as lobar collapse, pneumonia, and increased duration of hospitalization.

After cardiac surgery, traditional management has included overnight mechanical ventilation. Certainly, it is clinically important to have a period of controlled ventilation to allow rewarming and emergence from anesthesia, optimize cardiac function, and ensure hemodynamic stability and the absence of unacceptable bleeding. However, currently many patients are extubated within 3 to 6 hours of arriving in the postoperative care unit (so-called "fast-tracking"). In planning for fast-tracking, one should avoid using high-dose narcotic anesthetic techniques, and postoperative doses and the timing of analgesic and sedative administration must be appropriate.[520]

Fortunately, only a small percentage of patients require prolonged mechanical ventilation after cardiac surgery. Data from the STS National Adult Cardiac Surgery Database[521] and the Cardiothoracic Centre–Liverpool[522] show that 5.5% of patients who undergo CABG require mechanical ventilation for more than 48 hours afterward. Independent risk factors for prolonged ventilation include advanced age, preoperative ventilation, elevated serum creatinine, EF less than 30%, valve surgery, previous cardiac surgery, urgent or emergency surgery, recent MI, peripheral vascular disease, use of CPB, current smoking, and an FEV_1 less than 70% of the predicted value.[522]

Prolonged ventilation is most commonly due to cardiac dysfunction and cardiogenic pulmonary edema. Patients with marginal cardiac function may require diuresis, afterload reduction, or inotropy. Pulmonary-related reasons for inability to wean from mechanical ventilation include noncardiogenic pulmonary edema, pneumonia, severe COPD, ARDS, and pulmonary embolism. Finally, nonpulmonary complications such as persistent postoperative bleeding, neurologic complications (including stroke and delirium), renal insufficiency/failure, gastrointestinal complications, and sepsis may also result in a need for prolonged mechanical ventilation. Not surprisingly, poor in-hospital survival and poor long-term outcome have been associated with nonpulmonary complications that result in prolonged mechanical ventilation.[523]

Bleeding/Coagulopathy

Definition, Incidence, and Mechanisms

In cases of documented coagulopathy, transfusion often seems inevitable, but it carries a cost in terms of health care resources and patient outcomes. A study of more than 1900 cardiac surgical patients found that those receiving transfusions had a 70% increased risk for death and a doubling of their 5-year mortality rate, after adjustment for comorbid conditions, when compared with patients not receiving transfusion.[524] In addition, in a retrospective database study of more than 8000 patients who underwent cardiac operations at New England institutions, RBC transfusion was an independent predictor of LCOS requiring IABP counterpulsation, return to CPB, and persistent inotropic support.[525] Long-term reductions in quality of life have also been associated with a high RBC transfusion load in cardiac patients.[107] Furthermore, a multinational observational study found that differences between countries in perioperative outcome of patients undergoing CABG were related to intraoperative transfusion of FFP or platelets, among other hematologic factors.[526]

Efforts to Attenuate Perioperative Bleeding in Cardiac Surgery

In 2007, the STS and the Society of Cardiovascular Anesthesiologists (SCA) published a joint statement on practice guidelines for transfusion and blood conservation in cardiac surgery.[527] They reviewed all the available literature on blood conservation and transfusion practices in cardiac surgery and found six factors that appear to be important predictors of blood product transfusion in cardiac surgery.

- Advanced age
- Low preoperative red cell volume (i.e., preoperative anemia or low body surface area)
- Preoperative antiplatelet or antithrombotic medications
- Complex or redo operation
- Emergency operation
- Noncardiac comorbidity

Having identified a population of patients (as just listed) who are most likely to require blood products during cardiac procedures, this task force gave specific recommendations on blood conservation that include the following five points[527]:

- Consideration should be given to the use of drugs that either increase preoperative blood volume (e.g., erythropoietin) or decrease postoperative bleeding (e.g., antifibrinolytics).
- Techniques of conserving blood, including cell-saver sequestration and retrograde priming of the pump, should be included in the operative plan.
- To spare the patient's blood from the insult of CPB, autologous predonation and normovolemic hemodilution should be considered.
- Institutions should implement transfusion algorithms supported with POC testing.
- Multimodal application of all the aforementioned guidelines is the best way to conserve blood.

Correcting Existing Coagulopathies

Preoperative coagulopathy can result from congenital or acquired abnormalities. Hereditary coagulopathies include clotting factor deficiencies and platelet defect diseases such as von Willebrand's, Hermansky-Pudlak, Bernard-Soulier, Scott's, Werlhof's, and Glanzmann's syndromes.[527]

Acquired coagulopathy is usually drug induced. Patients receiving warfarin will require 2 to 5 days without warfarin for

normalization of the prothrombin time and the international normalized ratio.[109] Patients whose operations cannot be deferred until laboratory normalization will need treatment with FFP. Patients receiving aspirin have irreversible thromboxane receptor inhibition; 7 to 10 days without aspirin is necessary for new, uninhibited platelets to regenerate. Treatment of bleeding thought to be associated with aspirin has traditionally included platelet transfusion, desmopressin (DDAVP), or both. However, DDAVP may not be effective for managing bleeding in CABG patients treated with aspirin.[528]

New antithrombotic medications have added to the breadth and complexity of coagulopathic manifestations of patients undergoing cardiac surgery. Such agents include LMWH, platelet receptor antagonists, direct thrombin inhibitors, t-PA, and streptokinase. The STS/SCA blood conservation and transfusion guidelines recommend that clopidogrel and related thienopyridine antiplatelet medications be discontinued 5 to 7 days before surgery to limit blood loss.[527] Patients requiring platelet inhibition to manage their acute coronary syndromes can be changed to shorter-acting GP IIb/IIIa receptor inhibitors, such as tirofiban or eptifibatide.[527] Because clopidogrel's binding to platelets is irreversible, platelet transfusion is the only therapeutic option for patients who are taking clopidogrel, although routine platelet transfusion is not advocated.[527] Because of individual variability in the degree of platelet inhibition with clopidogrel,[529,530] POC monitoring is recommended to assess platelet function and the need for platelet transfusion.[527]

The GP IIb/IIIa receptor inhibitors have similar considerations. Bleeding associated with noncompetitive inhibition of abciximab must be reversed with platelet transfusion. Although short-acting inhibitors may be associated with bleeding,[527] some studies show that they provide a measure of platelet protection and better patient outcomes.[178,179] Like clopidogrel, drugs that inhibit the GP IIb/IIIa receptor exhibit individual variability,[531] thus supporting recommendations for POC, data-driven transfusion guidelines.

LMWH has little association with an increased bleeding risk.[527] There is no effective antidote for the anti–factor Xa inhibition caused by LMWH. Bleeding caused by t-PA or streptokinase is treated with antifibrinolytic therapy (EACA or TA).[129]

Pharmacologic Attenuation of Bleeding

Pharmacologic attenuation of cardiac surgical bleeding revolves around the use of a few specific medications: synthetic antifibrinolytics, aprotinin, DDAVP, and recombinant factor VII. The STS/SCA guidelines provide the strongest support for their evidence-based recommendations regarding the efficacy of synthetic antifibrinolytics and aprotinin in reducing perioperative bleeding in cardiac operations.[527] However, aprotinin marketing has been suspended because of ongoing concerns regarding patient outcomes.[532]

In structural terms, the synthetic antifibrinolytics are lysine analogs. They bind to plasminogen and plasmin, which inhibits their ability to bind to lysine residues on fibrin and thereby impedes fibrinolysis. The two synthetic antifibrinolytics that are used clinically are EACA (Amicar) and TA. They differ primarily in potency and elimination half-life: TA is 6 to 10 times more potent and has a longer half-life than EACA does.[533]

Standard dosing of EACA consists of a 50-mg/kg load followed by an infusion of 25 mg/kg/hr; standard dosing of TA consists of a 10-mg/kg load followed by an infusion of 1 mg/kg/hr. However, many other dosing strategies are described in the literature.[534-539] Interested readers might consider examining the work of Dowd and coworkers[540] on the pharmacokinetics of TA and their recommendations for higher continuous infusions of TA on-pump to maintain stable blood concentrations.

A recent meta-analysis of the literature on antifibrinolytics came to the following conclusions[541]:

- Both TA and EACA significantly reduce blood loss when compared with placebo.
- EACA reduces packed RBC transfusion rates by approximately 37%, and TA reduces these rates by approximately 25%.
- Both drugs may reduce rates of surgical re-exploration; in the meta-analysis, these reductions were not statistically significant, but there was a trend that seemed to indicate that these reductions did occur.
- Neither TA nor EACA seems to produce any adverse outcomes.

Both drugs are renally excreted, so they should not be given to patients with upper urinary tract bleeding because the concentration of the drug in the renal collection system could cause thrombosis and obstructive nephropathy.[129]

Antifibrinolytic therapy—specifically, the use of aprotinin—became controversial in 2006.[542] Aprotinin is a powerful serine protease inhibitor that is extracted from bovine lung tissue. Other serine proteases include plasmin, kallikrein, and factor XIIa. Royston and coauthors[543] originally published findings of reduced bleeding in cardiac surgical patients in 1987. Numerous subsequent studies have demonstrated a reduction in bleeding associated with cardiac surgery and CPB.[527] Traditional dosing of aprotinin is based on its ascribed kallikrein inhibitory potential and consists of a loading dose of 2 million KIU (kallikrein inhibitory units) intravenously and in the pump prime, followed by an infusion of 500,000 KIU/hr. Monitoring of ACT must use a kaolin-based activator because aprotinin prolongs celite-based ACTs, thereby potentially leading to heparin underdosing.

Aprotinin is a bovine source protein, and anaphylaxis has been reported.[544-546] The risk of anaphylaxis with re-exposure is reported to be approximately 2.8%.[547] The risk appears greatest for those re-exposed to aprotinin within a 6-month window. To minimize this risk, dosing recommendations include delaying the bolus injection until the surgeon is prepared to initiate bypass, administering a 1-mL (10,000 KIU) test dose to all patients, considering the use of H_1/H_2 receptor blockade before re-exposure, and avoiding re-exposure to aprotinin within 6 months of a previous exposure.[548]

Controversy surrounding aprotinin has existed for some time. Given aprotinin's powerful antifibrinolytic activity, there has been clinical concern regarding increased risk for perioperative MI and early graft closure, stroke, and renal dysfunction.[549] An initial clinical report from the Cleveland Clinic noted a statistical trend toward increased MI and graft closure; this trend was eventually explained by heparin underdosing related to the use of celite ACTs.[550] Subsequently, more liberal trends in the use of aprotinin in cardiac surgery developed, and some clinicians advocated its use in both first-time and redo operations.[551] Furthermore, Mora Mangano and colleagues[552] reported no association between aprotinin use and postoperative renal dysfunction in 853 patients undergoing deep hypothermia and circulatory arrest.

Royston and coauthors[553] reported that aprotinin was associated with a lower overall risk of adverse outcomes. However, in 2006, Mangano and associates,[554] in an observational study of 4374 patients undergoing cardiac surgery, reported that aprotinin use was associated with a doubling of the risk of dialysis-dependent renal failure, as well as a 55% increase in the risk for MI or HF and a 181% increase in the risk for stroke or encephalopathy. Subsequently, in 2007, Mangano and colleagues[542] reported that aprotinin use was an independent predictor of 5-year mortality. Furthermore, a meta-analysis of 138 trials comparing aprotinin, TA, and EACA showed that all three agents were efficacious in reducing blood loss and transfusion rates but that high-dose aprotinin was associated with an increased risk for renal dysfunction.[541] Finally, in November 2007, the FDA announced that at the agency's request, Bayer Pharmaceuticals had agreed to a marketing suspension of aprotinin based on preliminary results from a randomized, double-blind Canadian study comparing the safety and efficacy of EACA, TA, and aprotinin. Findings from this study suggested that when compared with EACA and TA, aprotinin increased the risk for death.[532]

The STS/SCA task force gave its weakest categorical support to the use of desmopressin and recombinant factor VIIa (rVIIa) to treat bleeding associated with cardiac surgery.[527] Use of desmopressin was classified as "not unreasonable" in patients with characteristics known to be responsive to desmopressin (von Willebrand factor or factor VIII deficiencies, cirrhosis, aspirin use, and uremic platelet dysfunction).[527] Desmopressin is administered in doses of 0.3 to 0.4 μg/kg, which are usually given slowly over a period of 20 to 30 minutes to reduce the drug's propensity to cause hypotension. Use of rVIIa is classified as "not unreasonable" for treating intractable life-threatening hemorrhage unresponsive to traditional therapies.[527]

rVIIa increases the amount of thrombin needed to promote hemostasis. It was initially developed as therapy for patients with hemophilia and has since been used "off-label" to treat cardiac surgical patients with intractable bleeding after surgery and bypass. Factor VII may serve as an activator of factors IX and X and may also bind directly to platelets, thereby leading to localized activation of factor X and subsequent generation of thrombin on the surface of platelets.[555]

A few observational studies have associated rVIIa administration with reductions in bleeding in patients with significant perioperative hemorrhage during cardiac surgery.[102,556-558] A recent literature review[559] identified six comparative studies[560-565] and concluded that rVIIa at doses of 40 to 100 μg/kg is recommended to treat intractable hemorrhage in cardiac surgical patients when standard hemostatic therapies have failed.[527,559] Redosing may be considered if hemorrhage is refractory 30 to 60 minutes after the initial dose. Prophylactic use of rVIIa is not currently indicated in cardiac surgery. Questions about the risk of thromboembolic complications remain unanswered and will require larger, adequately powered prospective and randomized studies.

Transfusion Triggers

An impediment to the development of uniform guidelines in transfusion medicine for cardiac surgical patients has been the lack of scientific and clinical consensus on what level of anemia requires intervention. The increasing surgical complexity, patient age, and number of comorbid conditions seen in current cardiac surgical practice have promoted the idea that raising hemoglobin levels may be warranted. However, blood products should be used cautiously in cardiac operations.[107,524-526] Although the transfusion of blood products is associated with well-known clinical complications, such as pathogen transmission and TRALI, as well as system issues, such as supply/demand issues and cost,[566] absolute indicator values for transfusion remain elusive. Randomized, double-blind, and placebo-controlled studies designed to answer transfusion outcome questions are ethically challenging and are not found in the literature.[566] Furthermore, clinical data that indicate a need to transfuse based on tissue or organ oxygen debt are often unavailable.[567]

Data-Driven Transfusion Guidelines

In summary, the clinical practice guidelines published by the STS/SCA task force in 2007 strongly encourage multimodal efforts to reduce transfusion rates and conserve blood products. Studies using transfusion algorithms paired with POC data to guide therapy have found these measures to be both efficacious and cost-effective.[527] An example of a standard laboratory test–based algorithm is shown in Figure 60-38. Algorithms can be constructed to incorporate any particular dynamic POC monitor or monitors.[205-208,568-570] In one prospective study with three treatment arms using three different POC monitors, all treatments were equally efficacious in reducing transfusion rates and amounts when compared with the control condition, in which transfusions were performed according to the surgeon's judgment.[205] Another study of 100 consecutive CABG operations in which strict transfusion guidelines and an algorithmic approach were used reported no transfusions in any patient.[568] For a clinical initiative regarding blood product utilization and blood salvage to be effective, it must involve all care providers at each level of clinical intervention and care. Data-driven management of coagulopathies conserves a somewhat limited resource (blood products), and it produces better clinical outcomes.

Pain

Pain after cardiac surgery can have many sources, including the sternotomy incision, chest tubes, and leg incisions. Some of the deleterious effects of postoperative pain after cardiac surgery are due to the stress response and enhanced sympathetic tone,[571,572] which can increase the heart rate, PVR, myocardial work, and myocardial oxygen consumption. In addition, α-receptors in the coronary vasculature may respond to sympathetic stimulation by producing coronary vasoconstriction, which may further aggravate postoperative myocardial ischemia. Thus, pain can contribute significantly to postoperative cardiac morbidity after cardiac surgery.

Post-cardiac surgical pain can also negatively affect the respiratory system. Typically, a restrictive defect occurs that is characterized by loss of lung volumes, with 30% to 35% reductions in tidal volume, VC, and functional residual capacity, thereby potentially contributing to atelectasis.[518,519,573] Moreover, the patient's pain may cause voluntary reduction of muscular movement in the thorax and abdomen, a phenomenon often described as "splinting." Such splinting interferes with the patient's ability to cough effectively and clear secretions. Ultimately, this problem can lead to lobar collapse, pneumonia, and increased duration of hospitalization.[518,519,573]

Unrelieved pain also has psychological effects. Pain-related anxiety, depression, and sleep deprivation may contribute to delirium in patients in the intensive care setting.

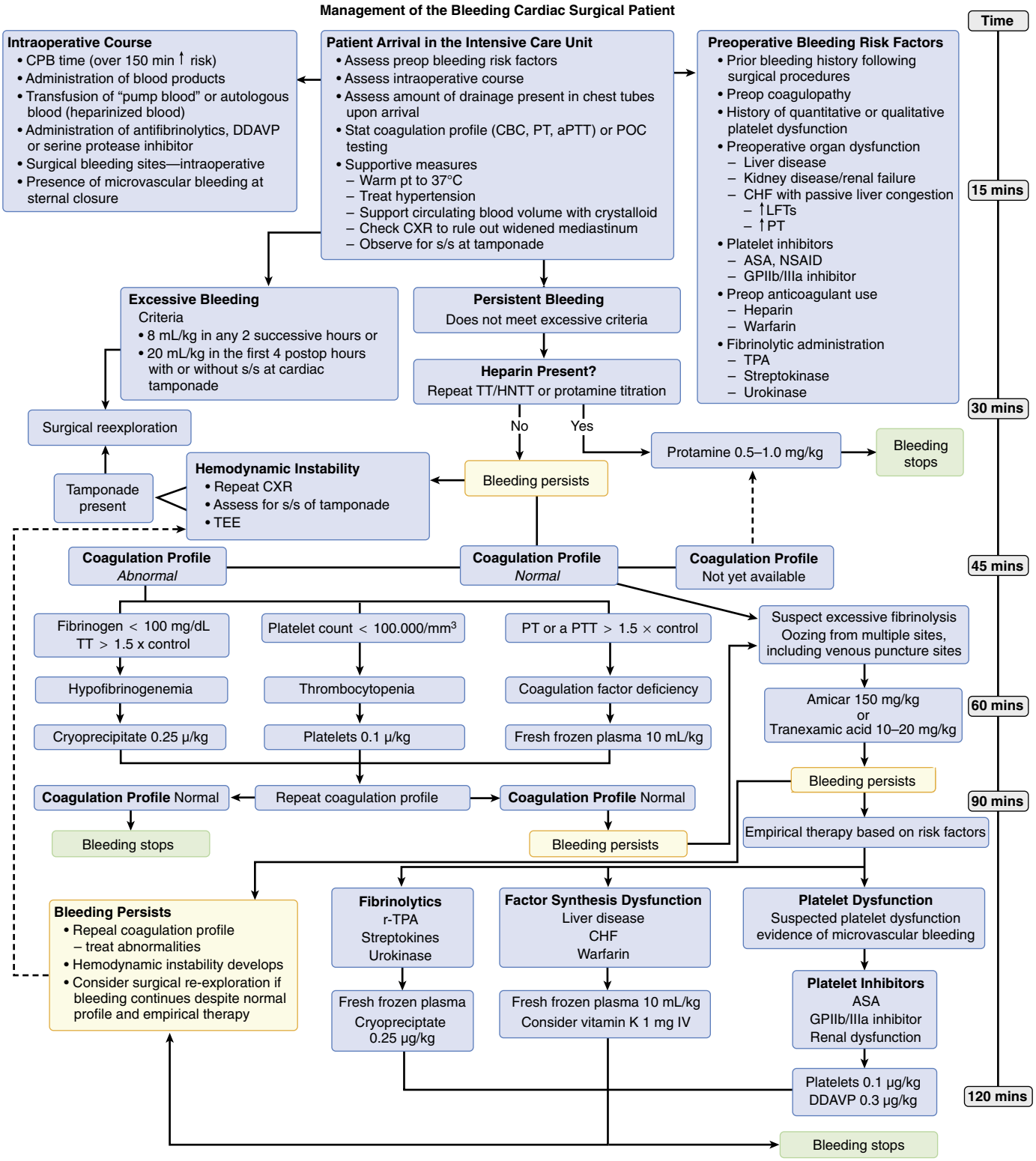

Figure 60-38 Example of a scheme for treating excessive bleeding. *(From Milas B, Johes D, Gorman R: Management of bleeding and coagulopathy after heart surgery. Semin Thorac Cardiovasc Surg 12:326, 2000.)*

In recent years, so-called fast-track anesthesia, entailing earlier extubation, a relatively brief stay in the ICU, faster discharge from the hospital, and lower overall cost, has become a standard of care for the cardiac anesthesiologist. Effective pain control helps achieve these goals.

Opioids remain the "gold standard" for pain control but they have side effects that include nausea, vomiting, urinary retention, decreased gastric motility, pruritus, sedation, and respiratory depression. Interest has emerged in the use of intrathecal and epidural local anesthetics and narcotics to improve analgesia

in patients undergoing cardiac surgery. Two meta-analyses of anesthetic techniques used in cardiac surgical patients have found that neither thoracic epidural analgesia nor intrathecal analgesia had a significant effect on MI or mortality, nor did they shorten patients' hospital stays.[574,575] However, in many studies, thoracic epidural analgesia did significantly reduce pain and the risk for dysrhythmias, pulmonary complications, and time to tracheal extubation, and it reduced analog pain scores at rest and with activity. Intrathecal analgesia modestly decreased systemic morphine use and pain scores but significantly increased the incidence of itching. Although a major concern surrounding the use of intrathecal and particularly epidural analgesia in cardiac surgery is the use of anticoagulation during the operation and consequent fear of spinal cord damage from a possible epidural hematoma, this complication is rare.[575]

Other techniques include the use of bilateral single-shot paravertebral blocks[576] or intercostal nerve blocks followed by a subcutaneous continuous infusion of local anesthetics.[577] Additionally, because all analgesics have side effects, some authors have suggested that it is better to use combinations of drugs or techniques, or so-called multimodal analgesia. Theoretically, multimodal analgesia may allow the use of lower doses of all agents and thus reduce the severity of the dose-related side effects of any single agent used.[578] Despite the appeal of the idea of multimodal analgesic techniques, cyclooxygenase-2–selective inhibitors and probably all nonsteroidal anti-inflammatory drugs are contraindicated after cardiac surgery with CPB.[579,580]

Additional studies will be required to solidify the link between pain relief and decreased morbidity, shorter hospital stay, and reduced cost.[581]

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61 Anesthesia for Correction of Cardiac Arrhythmias

Key Points

1. Cardiac arrhythmias are caused by disorders of impulse formation or disorders of impulse conduction, or both. Cardiac arrhythmia may be life-threatening because of a reduction in cardiac output, reduction in myocardial blood flow, or precipitation of a more serious arrhythmia.
2. Radiofrequency ablation is the therapy of choice for many types of cardiac arrhythmias.
3. Electrophysiologic studies are used to map out normal and abnormal intracardiac structures. In this process, the mechanism of arrhythmia is delineated, and ablation can be performed at the same time.
4. Pacing technologies have been developed to treat heart failure resulting in increases in pulse pressure, left ventricular stroke volume, cardiac index, and wedge pressure.
5. Implantable pacemakers are placed for treatment of symptomatic bradycardia with the ability to respond to changing hemodynamic demands.
6. The development of implantable cardioverter-defibrillators (ICDs) to terminate ventricular tachyarrhythmias by delivering high-voltage shocks to the ventricle has revolutionized therapy for cardiac arrhythmias.
7. The main purpose of ICD placement is to prevent sudden cardiac death resulting from hemodynamically unstable ventricular arrhythmias.
8. An ICD also can be placed for cardiac resynchronization. Cardiac resynchronization therapy has been shown to improve heart failure symptoms, quality of life, exercise capacity, and electrocardiographic variables.
9. Anesthetic management of patients for correction of cardiac arrhythmias depends on associated comorbid illness and the procedure that is planned.

Cardiac arrhythmias are caused by disorders of impulse formation or disorders of impulse conduction, or both. Disorders of impulse formation include enhancement or depression of automaticity, parasystolic activity, and triggered activity. Disorders of conduction include decremental conduction, re-entry, entry block, exit block, concealed conduction, and supernormal conduction.[1]

At the present time, radiofrequency catheter ablation has replaced antiarrhythmic drug therapy as the treatment of choice for many types of cardiac arrhythmias. Before the 1980s, cardiac electrophysiology was primarily used to confirm mechanisms of arrhythmias, with management mainly by pharmacologic means. As a result of shortcomings in antiarrhythmic drug therapy (including the results of randomized trials), radiofrequency ablation and implantable cardioverter-defibrillators (ICDs) were developed.[2,3]

Historical Perspectives

The treatment of cardiac arrhythmias with device-based therapy may have begun in 1899, when Prevost and Batteli[4] noted almost as an afterthought that direct electric shock could terminate ventricular fibrillation in dogs. Hooker and colleagues[5] showed 3 decades later that the passage of electric current across the heart can initiate and terminate ventricular fibrillation. In 1947, Beck saved the first human life by the successful use of cardiac defibrillation in a 14-year-old boy, who developed ventricular fibrillation during a thoracic procedure and went on to achieve full recovery.[6] These early achievements provided the foundation for the landmark work of Mirowski and Mower,[6a] which ultimately led to the development of ICDs in humans in 1980.

Scope of Cardiac Arrhythmias

Cardiac arrhythmias are common (see Chapters 42 and 43). Some cardiac arrhythmias are life-threatening, and others are merely a nuisance. Cardiac arrhythmias are caused by abnormalities in impulse formation or conduction that lead to slow or fast, regular or irregular heart rhythms. At the present time, it is not difficult to treat slow rhythms because available pacemakers are able to adapt slow function to the needs of the body.[7] The situation is different, however, for patients with rapid rhythms. Rapid rhythms may originate anywhere in the heart and result from various mechanisms. These mechanisms may be focal, meaning that the abnormal impulse formation is confined to a small area, or they may be the result of an impulse running in a circuit composed of several interconnected cardiac cells. Such a circuit may be small or large, as in atrial flutter and in arrhythmias in which the normal atrioventricular conduction system and an extra connection between the atrium and the ventricle are incorporated into the circuit of the arrhythmia.[8]

Pharmacologic interventions originally were used in attempts to terminate and prevent rapid rhythms. It has become clear in the past several decades, however, that antiarrhythmic drugs may have serious side effects and sometimes may even facilitate the occurrence of life-threatening arrhythmias and sudden death.[9] As a result of these effects, techniques were developed for localizing the site of origin or pathway of an arrhythmia and then isolating or destroying the tissue that is responsible. By employing an intracardiac catheter, it is now possible to determine the site of origin or pathway of an arrhythmia and cure the rhythm disturbance by applying through the catheter radiofrequency, laser, ultrasound, or microwave energy or freezing temperatures to the tissue causing the arrhythmia.

Heart failure is a major problem in elderly patients (see Chapter 71). Although pharmacologic treatment of heart failure has improved, outcome generally remains poor. New pacing technologies may now be used to treat selected patients with heart failure. For many years, permanent pacing has been used to treat symptomatic bradycardia, and pacing may alleviate heart failure when associated with heart block. Several studies have examined the use of conventional dual-chamber atrioventricular–right ventricular pacing for treatment of heart failure in the absence of symptomatic bradycardia or heart block.[3,10] Biventricular pacing aims to restore synchronous cardiac contraction. Studies have shown that when ventricular desynchrony is reduced, the heart is able to contract more efficiently and increase left ventricular ejection fraction and cardiac output, while working less and consuming less oxygen.[11] In addition, re-establishment of left ventricular synchrony can increase left ventricular filling times, decrease pulmonary capillary wedge pressure, and reduce mitral regurgitation.

Normal Cardiac Rhythm

In the normal heart, the dominant impulse arises in the sinus node with a rate of 60 to 100 beats/min. During sleep, the rate may decrease to 30 to 50 beats/min.[12] Episodes of sinus pauses up to 3 seconds, sinoatrial block, junctional rhythms, and first-degree and second-degree atrioventricular nodal block that occur often enough (especially in trained athletes) are considered to be normal variants.[7]

The impulses generated from the sinoatrial node propagate along three intra-atrial conduction pathways: the anterior, middle, and posterior internodal tracts. These tracts are not discrete pathways, but groups of cells that conduct slightly faster than the atrial myocardium.[13] The internodal tracts give rise to interatrial fibers. The electric impulse, whether propagated in the atrial myocardium or along the internodal tracts, converges on the atrioventricular junction. The atrioventricular node located in the atrioventricular junction ultimately receives the impulses generated from the sinoatrial node. The impulses are delayed in the atrioventricular node before they are finally distributed to the ventricular myocardium via the His-Purkinje system.

Normally, the heart rate increases with exercise to at least 85% of the age-predicted maximum of 220 minus age in years; failure to do so is termed *chronotropic incompetence*. Sinus arrhythmia is defined as sinus rhythm with P-to-P variations of more than 10%. Sinus arrhythmia is due to cyclic variations in vagal tone commonly related to respiration (the rate is faster with inspiration and slower with expiration).[14] Sinus arrhythmia disappears with exercise, breath-holding, and atropine, and is more likely to be seen in individuals who do not have heart disease.[15]

Cardiac Arrhythmias

Cardiac arrhythmia is caused by a disorder of impulse generation, impulse conduction, or a combination of both. Cardiac arrhythmia may be life-threatening because of a reduction in cardiac output, reduction in myocardial blood flow, or precipitation of a more serious arrhythmia.[16] Arrhythmias may be described based on (1) rate (bradycardia or tachycardia); (2) rhythm (regular or irregular); (3) origin of impulse (supraventricular, ventricular, or artificial pacemaker); (4) impulse conduction (atrioventricular, ventriculoatrial, or block); (5) ventricular rate; or (6) special phenomena (e.g., pre-excitation).

Re-entry is a common electrophysiologic mechanism that predisposes to most ventricular arrhythmias and to most supraventricular tachyarrhythmias. The most common mechanism of re-entry is based on the model originally proposed by Erlanger and Schmitt and later modified by Wit.[1] This model postulates the presence of a ring or loop of cardiac tissue that is functionally separate from neighboring tissue and the presence of transient or permanent unidirectional block in a portion of the loop. Unidirectional block may be anatomic in origin (e.g., bundle branches, fibrosis, dual pathways, atrioventricular node plus accessory pathway) or functional (e.g., ischemia, drug effect).

Atrial flutter is a macro-re-entrant arrhythmia identified by flutter waves, often best seen in the inferior leads at 250 to 350 beats/min. Patients often present with a 2:1 atrioventricular conduction with a ventricular rate of 150 beats/min, although the atrioventricular conduction ratio can change abruptly.

Atrial fibrillation is a narrow-complex tachyarrhythmia and is the most common in the general population. The prevalence of atrial fibrillation in the general population increases exponentially with age, from 0.9% in individuals age 40 to 5.9% in individuals older than age 65. The most important risk factors for development of atrial fibrillation in the general population are

structural heart disease, valvular heart disease, and left ventricular hypertrophy.[17]

Ventricular tachyarrhythmia is defined as three or more consecutive ectopic beats at a rate greater than 100 beats/min.[18] Ventricular tachyarrhythmia is traditionally classified as nonsustained or sustained. Sustained ventricular tachyarrhythmia is defined as ventricular tachyarrhythmia lasting more than 30 seconds. Nonsustained ventricular tachyarrhythmia is defined as ventricular tachyarrhythmia that terminates spontaneously within 30 seconds. Sustained ventricular tachyarrhythmia also is traditionally classified as monomorphic (one site of origin) or polymorphic (two or more sites of origin).[18] Monomorphic ventricular tachyarrhythmia usually results from re-entry, and the site of re-entry depends in part on the type of heart disease. In patients with coronary artery disease, the re-entry circuit is usually located in ventricular myocardium, whereas in dilated cardiomyopathy with left bundle branch block, bundle branch re-entry is common.[19] Monomorphic ventricular tachyarrhythmia may occur in individuals with an otherwise normal heart, whereas polymorphic ventricular tachyarrhythmia may occur in acquired states that produce a marked prolongation of the Q–T interval. Nonsustained ventricular tachyarrhythmia is frequently asymptomatic, but may produce palpitations, weakness, and presyncope.[19]

Torsades de pointes is a French term translated as "twisting of the points." It is a syndrome composed of polymorphic ventricular tachyarrhythmia. It may be due to various medications or electrolyte imbalances. Torsades de pointes is usually paroxysmal, but is frequently symptomatic and often produces loss of consciousness. It occasionally degenerates to ventricular fibrillation.

Ventricular fibrillation accounts for 80% to 85% of sudden cardiac deaths.[19] Ventricular fibrillation is usually preceded by ventricular tachyarrhythmia, but also may occur as a primary arrhythmia. More recent studies suggest that ventricular fibrillation results from multiple wavelengths that disperse randomly, using the leading circle form of re-entry.[19] The most common cause of ventricular fibrillation is acute myocardial infarction. It also is observed in patients with chronic ischemic heart disease, hypoxia resulting from any cause, acidosis, hypokalemia, and massive hemorrhage.

Indications for Correction of Cardiac Arrhythmias

Intracardiac electrophysiologic studies can give valuable information about normal and abnormal electrophysiology of intracardiac structures (see Chapters 42, 43, and 97). These studies are used to confirm the mechanism of an arrhythmia, to delineate its anatomic substrate, and to ablate it. The electric stability of the ventricles also can be assessed, as can the effects of an antiarrhythmic regimen.

In addition, pacing technologies have been developed to treat heart failure with promising results, leading to improvement in morbidity and mortality in these patients. Hemodynamic responses to biventricular pacing include an increase in the rate of elevation of left ventricular pressure and increases in pulse pressure, left ventricular stroke work, cardiac index, and wedge pressure.[20] Cardiac resynchronization therapy improves ventricular function without increasing myocardial energy consumption, in contrast to the effect of inotropic agents, such as dobutamine.[11] In addition, cardiac resynchronization therapy may reverse left ventricular remodeling over time.[21]

Permanent Pacing

Indications for pacemaker therapy have increased in recent years and now include the treatment of bradyarrhythmias and heart failure according to the American College of Cardiology and American Heart Association guidelines.[22] These guidelines discuss indications for pacing in patients with sinus node dysfunction, acquired atrioventricular block, chronic bifascicular and trifascicular block, hypersensitive carotid sinus, and neurally mediated syndromes. The guidelines serve to direct the treating physician in selecting which patients would benefit from device therapy.

A Swedish team led by Sennings and Elmqvist implanted the first pacemaker in 1958.[23] A thoracotomy was required, and pacing was done through electrodes sutured to the epicardium. In these early systems, significant problems with changes in pacing threshold, lead infection, and lead breakage were common. Transvenous lead implantation subsequently developed by Furman would resolve many of these issues.[24] In 1958, Furman successfully paced an elderly patient with a catheter electrode inserted transvenously. Other investigators took on the challenge of solving various technical problems, such as device miniaturization, longer life batteries, and stable, reliable lead material.[25]

As the indication for implantation expanded from atrioventricular conduction disturbances to management of sinus node dysfunction, the need for implantable pacemakers grew in proportion.[25] Technology evolved rapidly with the development of lithium-iodide batteries that had greater longevity. Electronic advances then led to major miniaturization using integrated circuits as opposed to discrete components. Lead materials used in today's pacemaker rely on silicone and polyurethane, which are more biocompatible and reliable than earlier materials. With all these technical refinements, present-day pacemakers are small and can pace reliably for 8 to 10 years before generator replacement is needed.

The primary functional challenge for contemporary pacemakers is to maintain the heart rate based on circulatory needs, pacing in a manner that mimics the natural physiology of excitation and conduction. In a healthy heart, the sinus node is modulated by the autonomic nervous system, and its rate is determined by a multiplicity of factors, such as physical activity, emotion, and blood pressure. Not only the rate, but also the activation sequence and atrioventricular conduction time vary with demand; these requirements also must be considered. Rate is controlled by pacemaker discharge, and the excitation and conduction sequence depend on the placement of pacing electrodes.

Approximately 120,000 pacemakers are implanted each year in the United States. Indication for implantation for most of these cases is sick sinus syndrome. Other indications include atrioventricular block, carotid sinus hypersensitivity, malignant vasodepressor syndrome, and hypertrophic cardiomyopathy.[26]

The primary purpose of implantable pacemakers is to treat symptomatic bradycardia. With the extraordinary developments that have occurred in pacemaker therapy for the traditional indi-

cation, bradycardia, new uses are now beginning to be explored. Pacemakers have progressed from large, fixed-rate, single-chamber devices to multiprogrammable, multichamber devices with the ability to respond to changing hemodynamic demands. As technology advances, other possible uses are likely to be conceived.

Resynchronization Therapy

Cardiac resynchronization therapy has been shown to improve heart failure symptoms, quality of life, exercise capacity, hospitalization, and echocardiographic variables.[27] Based on the available data, cardiac resynchronization therapy is indicated in patients with drug-refractory, symptomatic New York Heart Association functional class III and IV heart failure of either ischemic or nonischemic origin.[28] In addition, these patients are protected from associated risk of sudden cardiac death when combined with an ICD system.[29]

The development of an automatic internal defibrillator or ICD began in the 1960s. External cardiac defibrillation was increasingly being used in coronary care units for the treatment of ventricular fibrillation and sudden cardiac death. Although the idea of automatic external defibrillation had been discussed initially by Zycoto, Mirowski and colleagues[30] were the first to champion and begin practical development of an automatic internal device. In 1969, Mirowski and Mower developed the prototype of today's automatic internal defibrillator.[31]

The primary goal of all defibrillators is to terminate ventricular tachyarrhythmias by delivering high-voltage shocks to the ventricle. As with implantable pacemakers, defibrillating devices need to be small and reliable, and to have adequate longevity. ICDs have evolved not only to perform this function, but also to take on additional tasks, such as antitachycardia pacing of the ventricle, dual-chamber pacing, and termination of atrial tachyarrhythmias.

A key difference between pacing and defibrillation of the heart is that for pacing; only a very small mass of myocardium needs to be stimulated, whereas for defibrillation, most, if not all, of the myocardium must be stimulated. Because the myocardium is easily excitable throughout diastole, a small wave of depolarization during pacing can readily propagate throughout the whole heart. In contrast, during ventricular fibrillation, there are usually multiple re-entrant wave fronts that are continuously changing in location and size that must be quelled. To defibrillate successfully, most of these wavefronts have to be interrupted simultaneously; to achieve this, one needs to capture most of the tissue that is in a state of relative refractoriness.[32] One unique property of defibrillation success is that it is probabilistic.[33] The same energy that can defibrillate the heart on one occasion may be unsuccessful at another time.

The main purpose of ICD placement is to prevent death from hemodynamically unstable ventricular tachyarrhythmias. Although advances in technology have made these devices much more flexible in terms of arrhythmia detection and electric therapy potions, their main purpose is to reduce sudden cardiac death, which claims approximately 300,000 lives in the United States annually. Secondary prevention of sudden cardiac death in patients who have survived cardiac arrest is another major indication for ICD placement. In such patients and especially in patients of this group for whom no reversible or curable cause can be found, ICD implantation has been repeatedly documented to provide a major mortality benefit.[34] Interest in managing atrial tachyarrhythmias also has grown significantly in recent years. It is now recognized that about 30% of patients with ventricular tachyarrhythmia also have atrial tachyarrhythmias.[35] Such atrially initiated tachyarrhythmias can worsen patient symptoms, can result in inappropriate ventricular shocks, and may be responsible for initiating ventricular tachyarrhythmias that can exacerbate other pathologies, such as heart failure. New strategies for treatment and prevention of atrial tachyarrhythmias are incorporated into devices that are capable of defibrillation and antitachycardia pacing in the atrium and the ventricle, in addition to combined dual-chamber pacing.[36]

The relative ease of ICD implantation and longevity of current defibrillators have made them a valuable tool in primary prevention. Patients no longer must survive a cardiac arrest to justify the risk of ICD implantation.

Preoperative Evaluation

Most patients who require pacemaker or ICD placement have significant cardiovascular disease. In addition, correction of cardiac arrhythmia may require radiofrequency catheter ablation. Radiofrequency catheter ablation has proved highly effective in the treatment of atrioventricular nodal re-entrant and accessory pathway tachycardias. Indications for pacemaker and ICD placement continue to evolve as the utility of these devices continues to increase. Although most pacemaker placement is done with local anesthetic infiltration, ICD placement may require monitored anesthesia care or in some cases general anesthesia. The modern ICD unit is capable of delivering the full spectrum of therapy for ventricular tachyarrhythmias and for bradycardia therapy with dual-chamber pacing/sensing, rate modulation, and mode-switching features.

As mentioned earlier, there are two common indications for ICD placement. One is continued ventricular tachyarrhythmias despite adequate drug therapy. Another indication is history of sudden cardiac arrest that is not associated with myocardial infarction.

Preoperative evaluation processes necessary for placement of an ICD should be complete by the time the decision is made to place the device (see Chapters 34 and 35). These patients need a thorough preoperative evaluation. This evaluation includes electrophysiologic testing to determine the inducibility of ventricular tachycardia and electrophysiologically guided drug therapy. Preoperative pulmonary function tests may be necessary in patients on amiodarone to evaluate possible toxicity of this drug, which can result in chronic obstructive pulmonary disease or interstitial lung disease. In some instances, the underlying pathophysiology of malignant ventricular arrhythmias is related to ischemic or idiopathic cardiomyopathy.[37] These patients often present with poor left ventricular function and higher incidence of congestive heart failure. Patients with a history of congestive heart failure should be in optimal condition before surgery.

Generally, all patients who present for correction of cardiac arrhythmia require preoperative evaluations including electrocardiogram, chest radiograph, hemoglobin, and electrolytes. Patients should be NPO (have nothing by mouth) at least 8 hours before the procedure. In addition, patients who require device and lead extractions because of malfunction or infection may require blood product transfusions during the procedure. Consequently,

type and crossmatch of blood products is frequently necessary for these procedures.

Anesthetic Considerations

Pacemakers

Permanent implantable pacemakers have been the standard modality of treatment for patients with all types of bradyarrhythmias. A significant number of these patients present with sick sinus syndrome and are older. Consequently, devices are placed under general anesthesia in these patients. As a result of more recent advances in pacemaker technology, these devices now can be placed as a therapeutic modality to alter hemodynamic states. Surgeons used to be primarily responsible for device insertion. Now the task falls under the services of cardiologists. Device placement is commonly performed in the cardiac catheterization suite under local anesthesia on an outpatient basis. Complicated high-risk patients now present for pacemaker insertion, however, in addition to more recent indications by the American College of Cardiology/American Heart Association for these devices. In light of these increased indications, the expertise of anesthesiologists is needed for monitoring and perioperative care of these patients.

Monitored Anesthesia Care

Currently, most pacemaker insertions are performed by cardiologists. Most of these cases are performed under local anesthesia with sedation. Depending on the level of training, administration of sedatives and analgesics can be provided by nurses.

In instances that require deeper sedation for a patient's comfort or for critically ill patients with hemodynamic instability, monitored anesthesia care by an anesthesiologist may be required (see Chapter 78). Adequate monitoring and resuscitation equipment is required in such situations. The goal of monitored anesthesia care is to provide analgesia, sedation, and anxiolysis, while ensuring rapid recovery with minimal or no side effects. Any sedative-hypnotic medication may be used during monitored anesthesia care with a wide variety of delivery systems.[38] Subanesthetic concentrations of inhaled agents also have been used to supplement local anesthetics. Newer drugs, such as centrally mediated α_2-agonists, have been shown to produce anxiolysis, sedation, and reduced requirements for supplemental analgesic medications during monitored anesthesia care.

General Anesthesia

Patients requiring pacemaker placement rarely require general anesthesia for placement. If general anesthesia is required, it should be directed toward underlying cardiac pathophysiology, indications, complications, and hemodynamic goals. Immediate access to life-support equipment, such as a cardiac defibrillator and a transcutaneous pacemaker, is necessary if the device is being placed under general anesthesia.

Implantable Cardioverter-Defibrillator

Since the 1980s, indications for use and implantation of ICDs have steadily increased. Over the past 2 decades, ICDs have undergone a significant evolution. In the 1970s and 1980s, ICD placement usually required thoracotomy for placement of epicardial patches.

Preoperative Evaluation

As mentioned earlier, common indications for ICD implantation include continued ventricular tachyarrhythmias unresponsive to adequate pharmacotherapy and history of sudden cardiac arrest unassociated with myocardial infarction. Newer indications include patients with various forms of the congenital long QT syndrome.[39] Patients with long QT syndrome who have already survived an episode of cardiac arrest or documented polymorphic ventricular tachyarrhythmia, especially if on pharmacotherapy at the time, are increasingly being evaluated as ICD candidates. In addition, patients with hypertrophic cardiomyopathies and without a history of sudden death are usually evaluated for ICD placement.[40] In these patients, sustained ventricular arrhythmias, nonexertional syncope, or a strong family history of sudden death with early age of presentation strongly indicates ICD implantation.

In all instances, the evaluation that is necessary for ICD implantation is completed by the time the decision is made to place the device (see Chapters 34 and 35). Electrophysiologic studies may have been done to determine the forms of arrhythmias present. When the pathophysiology of ventricular arrhythmias is related to idiopathic or ischemic cardiomyopathy,[41] these patients may present with poor left ventricular function and a high incidence of congestive heart failure. Consequently, they should be optimized as much as possible preoperatively.

Anesthetic Considerations

In the 1980s, ICD implantation was done with epicardial leads via thoracotomy under general anesthesia with one-lung ventilation. The technologic development of implantable ICDs with transvenous lead systems has simplified their implantation. Consequently, it was reasoned that ICDs can be placed under deep sedation with little or no intervention by the anesthesiologist analogous to what is needed for pacemaker placement.[42] Placement of an ICD under general anesthesia may be safer and more comfortable for the patient, however. Patients who present for ICD placement are often critically ill with cardiopulmonary comorbidity. It is not unusual for these patients to present with ejection fractions less than 30% and to require vasopressors to support hemodynamics during the procedure. In addition, some form of general anesthesia is necessary for intraoperative testing of defibrillating thresholds.

Monitored Anesthesia Care

Small, new-generation devices and transvenous lead systems lend themselves to the use of local anesthesia and intravenous sedation for ICD implantation. Midazolam and fentanyl are usually the drugs of choice when an ICD is placed under monitored anesthesia care (see Chapter 78). Monitoring includes pulse oximetry, five-lead electrocardiogram, and noninvasive blood pressure. Depth of anesthesia is monitored clinically. One of the major aspects of ICD placement is testing the device. Testing the device may require deep sedation or general anesthesia because the shocks that are associated with this procedure can be very painful.

The presence of an anesthesiology team may be necessary for ICD placement under monitored anesthesia care.

General Anesthesia

Most patients who present for ICD placement typically have comorbidities such as ventricular tachycardia, congestive heart failure with ejection fraction less than 30%, coronary artery disease, pulmonary hypertension, chronic renal insufficiency, or valvular heart disease. These patients may be unable to lie flat for the prolonged period necessary for placement of the ICD. In addition, they may require close hemodynamic monitoring during the testing of the device. General anesthesia should be considered in these patients. When general anesthesia is chosen, in addition to standard monitoring, an arterial line may be added. External cardioverter-defibrillator pads are required for all ICD placements. These are employed in cases where an implanted defibrillator fails. General anesthesia also may be requested for anxious and extremely nervous patients. Because pacemakers and ICDs are placed percutaneously, anesthesiologists must be vigilant to possible complications, such as myocardial infarction, stroke, possible cardiac injury (perforation/tamponade), and pneumothorax from subclavian vascular access.

Extraction of Devices

As a result of continued growth and expanding indications for pacemakers and ICD placement, leads may require extraction because of mechanical dysfunction, the need to upgrade to more complex devices, or local or systemic infection. Lead extractions are probably one of the most challenging procedures that a cardiac electrophysiologist has to face today.

Indications for lead extractions can be divided into two categories—patient-related and lead-related. Patient-related indications include infection, ineffective therapy (high defibrillation threshold), perforation, migration, embolization, induction of arrhythmias, venous thrombosis, unrelenting pain, device interactions, and device upgrades.[43] Lead-related indications include lead recalls, lead failure, and lead interactions.[44]

Lead extraction is performed via powered sheaths through which energy is delivered to the tip in the form of excimer laser light or electrocautery. These systems burn through scar tissue adherent to the wall of the lead throughout its course. The potential for life-threatening complications, such as lead fracture, venous or myocardial rupture, and tamponade, makes general anesthesia with invasive monitors a prudent choice for lead extractions.

Postoperative Care

Postoperative care of patients with pacemaker or ICD implantation depends on various factors surrounding the implantation of the device (see Chapter 85). As mentioned earlier, most of these patients are quite ill with significant comorbidities. It is not unusual for patients to have congestive hart failure with an ejection fraction less than 30% as a result of poor left ventricular function. Consequently, it is imperative to have these patients monitored in the postanesthesia care unit, especially if the device is placed or extracted under general anesthesia. The spectrum of recovery sites after these procedures may vary from postprocedure units to a coronary intensive care unit. Most of these procedures are done on an outpatient basis; anesthesia is tailored to ensure rapid recovery after implantation.

Correction of Cardiac Arrhythmias with Ablation Therapy

Catheter ablation is a safe and curative option for most cardiac arrhythmias, with 85% to 98% cure rates among the arrhythmias treated most frequently.[45] The rate of major complications is less than 3%.[45] Cardiac ablation therapy involves the delivery of energy through a catheter that is usually placed in the endocardial position in the heart, destroying myocardial tissue that is responsible for the tachyarrhythmia. Multiple electrodes are inserted to locate the arrhythmia and ablate it. Usually the diagnostic portions of the ablation study are done during the same procedure.[46] The efficacy of catheter ablation depends on the accurate identification of the site of origin of the arrhythmia. When the site is identified, the electrode catheter is positioned in direct contact with the site of the arrhythmia, and radiofrequency energy is delivered through the catheter to destroy it.

The current that is generated by radiofrequency is alternating current, and is delivered at cycle lengths of 300 to 750 kHz when used for catheter ablation.[47] It causes resistive heating of the tissue in contact with the electrode. The degree of tissue heating is inversely proportional to the radius to the fourth power.[48] Consequently, the lesions created by radiofrequency energy are small. Although electric injury may be a contributing factor, the primary mechanism of tissue destruction by radiofrequency current is thermal injury. Acute lesions created by a radiofrequency current consist of a central zone of coagulation necrosis surrounded by a zone of hemorrhage and inflammation.[49]

Cardiac arrhythmias that can be treated with radiofrequency ablation include paroxysmal supraventricular tachycardia, Wolff-Parkinson-White syndrome, atrial flutter, atrial fibrillation, and idiopathic ventricular tachycardia. Most cardiac arrhythmias that are treated with radiofrequency ablation are not life-threatening, but have a significant impact on a patient's quality of life.[50] Advantages of radiofrequency ablation of cardiac arrhythmias include relief of symptoms, improvement in functional capacity and quality of life, and elimination of the need for lifelong antiarrhythmic drug therapy. The principal disadvantage is the risk of complications, which varies depending on the type of ablation procedure and skill of the operator.

Anesthetic Considerations

Catheter ablation was introduced into clinical practice in 1982. Initially, ablation was performed with direct electric shocks.[51] As a result of several advantages over direct current, radiofrequency ablation has replaced direct current ablation. These advantages include the absence of skeletal and cardiac muscle stimulation, minimal discomfort during delivery of energy, the possibility of performing the procedure in conscious patients, and the discrete nature of resulting lesions.[49]

Most cardiac ablation therapy for correction of arrhythmias can be performed under moderate sedation or monitored

anesthesia care. In some of these cases, deep sedation may be required as the case progresses. In a few cases, general anesthesia may be required if the patient is anxious or cannot tolerate lying in the supine position for an extended period. General anesthesia may be implemented for these patients with standard American Society of Anesthesiologists monitors with adequate vascular access. Catheter ablation is the first-choice treatment for most cardiac arrhythmias. It is a safe treatment and is usually effective as a single procedure. Because it is curative in many patients, it is offered to all patients who would otherwise be committed to long-term drug therapy.

Future Trends

Correction of cardiac tachyarrhythmias has improved dramatically in the past 2 decades. Emphasis has shifted from pharmacologic therapy to nonpharmacologic therapy of tachyarrhythmias; this has led to a significant increase in the numbers of radiofrequency catheter ablations and defibrillator implantations. These developments were triggered by technologic advances that showed superiority of these procedures over the use of antiarrhythmic drugs.[52] As a result, treatment of supraventricular tachycardias and tachycardias involving accessory atrioventricular pathways will probably remain the domain of catheter ablation. The cure rates of patients treated with catheter ablation is very high. In addition, treatment of life-threatening ventricular tachyarrhythmia will remain in the domain of ICDs for the foreseeable future. The role of ICD therapy has been clearly defined with respect to prolongation of life and has been expanded to include primary prophylaxis of sudden death in high-risk populations.[53]

As a result of these developments, the presence of an anesthesiology team will continue to grow in cardiology suites. Patients who are being cared for in these areas are sicker with significant comorbidities. The role of conscious sedation will continue to diminish in the performance of these procedures. These patients will require full monitoring and care under the direction of an anesthesiologist.

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Edward J. Norris

62 Anesthesia for Vascular Surgery

Key Points

1. Recent advances in our understanding of the biology of atherogenesis suggest that endothelial dysfunction is a critical element in the pathogenesis of atherosclerotic cardiovascular disease and its complications. Inflammation in the artery wall probably plays a fundamental role as well.
2. Major vascular surgery is particularly challenging to the anesthesiologist because these are high-risk operations in a patient population with a high prevalence of either overt or occult coronary artery disease, which is the leading cause of perioperative and long-term mortality after vascular surgery.
3. Accurate clinical assessment of the pretest probability of significant coronary artery disease is necessary for prudent use and rational interpretation of preoperative cardiac testing.
4. Guidelines on perioperative cardiovascular evaluation and care suggest that coronary intervention is rarely necessary to simply lower the risk of surgery unless such intervention is indicated irrespective of the preoperative context. Current evidence does not support the role of prophylactic coronary revascularization as a means to reduce perioperative or long-term morbidity after major vascular surgery.
5. Perioperative management of patients undergoing vascular surgery requires an understanding of the underlying pathophysiology of the specific vascular lesion.
6. Patients should be maintained on their usual cardiovascular medications throughout the perioperative period. Antiplatelet therapy requires special consideration and must be individualized to each patient.
7. Prevention and treatment of perioperative myocardial ischemia require careful control of the determinants of myocardial oxygen supply and demand. ST-segment monitoring, particularly with computerized ST-segment analysis, should be used to detect myocardial ischemia during the perioperative period.
8. Clinical trial data suggest that initiation of perioperative β-blocker therapy has potential benefits and risks.
9. The clinical usefulness of any intraoperative monitoring technique ultimately depends on patient selection, accurate interpretation of data, and appropriate therapeutic intervention.
10. Evidence suggests that maintenance of vital organ perfusion and function by the provision of stable perioperative hemodynamics is more important to overall outcome after aortic surgery than is the choice of anesthetic agent or technique.
11. The pathophysiology of aortic cross-clamping and unclamping is complex and depends on many factors, including the level of the cross-clamp, the extent of coronary artery disease and myocardial dysfunction, blood volume and distribution, activation of the sympathetic nervous system, and the anesthetic agents and techniques.
12. The degree of preoperative renal insufficiency is the strongest predictor of postoperative renal dysfunction.
13. Endovascular aortic surgery has recently emerged as a less invasive alternative to conventional open aortic repair. Endoleak, or the inability to obtain or maintain complete exclusion of the aneurysm sac from arterial blood flow, is a complication specific to endovascular aortic repair.
14. The primary clinical utility of cerebral monitoring during carotid endarterectomy is to identify patients in need of carotid artery shunting; secondarily, such monitoring is used to identify patients who may benefit from blood pressure augmentation or change in surgical technique.
15. Postoperative hypothermia is associated with many undesirable physiologic effects and may contribute to adverse cardiac outcome.

Perioperative management of patients undergoing vascular surgery is challenging because of the frequent occurrence of coexisting disease in elderly patients, the hemodynamic and metabolic stress associated with arterial cross-clamping and unclamping, and the ischemic insults to vital organs, including the brain, heart, kidneys, and spinal cord. As a result, perioperative morbidity and mortality are more frequent with vascular surgery than with most other surgical procedures. Anesthesia care must focus on preservation of vital organ function, with a strong emphasis on the heart, which is the single most important cause of morbidity after vascular surgery. The clinical controversies associated with vascular surgery are diverse and involve aspects of preoperative, surgical, anesthetic, and postoperative management. The controversy associated with routine preoperative screening for coronary artery disease (CAD), as well as appropriate treatment if detected, has particular importance (see Chapters 34 and 35). Ongoing debate continues over anesthetic technique and outcome because vascular procedures often lend themselves to local, regional, general, or combined regional and general anesthesia.

In the 1970s, vascular surgery was recognized as a risk factor for perioperative cardiac morbidity. In the 1980s, the focus shifted to risk stratification in an effort to identify patients who were at greatest risk for morbid outcomes. In the 1990s, intensive clinical investigation involving anesthetic technique, sympatholytic drugs, hemodynamic control, and analgesic technique was undertaken and provided important insight into the prevention, treatment, and mechanisms of cardiac and other morbidity. During this time, a guideline-based approach to health care was initiated, primarily in the United States (see Chapter 92). More recently, there has been a paradigm shift away from routine preoperative screening for CAD with a focus on risk stratification and treatment of CAD to an intensive strategy of perioperative cardiac risk reduction using medications and risk factor modification (see Chapters 34 and 35). Additionally, over the last decade the multidisciplinary field of endovascular surgery has provided less invasive approaches or alternatives to conventional vascular reconstruction. These less invasive procedures, initially offered to patients traditionally considered unfit for open surgery, are being widely applied to the larger cohort of patients undergoing vascular surgery.

The goal of this chapter is to review issues related to the perioperative care of vascular surgery patients and to address the underlying controversies. For simplicity, the five major categories of vascular surgical procedures are discussed separately: abdominal aortic surgery, thoracoabdominal aortic surgery, endovascular aortic surgery, lower extremity vascular surgery, and carotid surgery.

Atherosclerosis

Atherosclerosis is a progressive disease process that compromises the arterial blood supply to any or all of the vital organs or the extremities. Atherosclerotic cardiovascular diseases are the leading cause of death and disability in the United States. Established risk factors are male gender, age, family history of premature cardiovascular disease, high levels of low-density lipoprotein (LDL) cholesterol, low levels of high-density lipoprotein (HDL) cholesterol, diabetes, obesity, hypertension, and smoking. More recently identified risk factors include homocysteine, fibrinogen, lipoprotein(a), apolipoproteins B and A-I, and C-reactive protein (CRP). Because atherosclerosis usually has no early warning signs, prevention is difficult and risk modification is often delayed until the patient has progressed to an advanced stage of disease. The lesions of atherosclerosis occur primarily in large- and medium-sized arteries and may be present throughout one's lifetime. Although atherosclerotic lesions result from a variety of pathogenetic processes, progression of atherosclerosis occurs in three general stages. The initial lesion of atherosclerosis, the fatty streak, starts in early childhood and forms beneath the normal endothelium. These lesions consist of lipid-laden macrophages (i.e., foam cells), smooth muscle cells, and elastic and collagen fibers. The fatty streak progresses to a fibrous plaque consisting of degenerated foam cells covered by a layer of proliferated smooth muscle cells. Unlike the fatty streak, these lesions may compromise blood flow through a vascular bed and cause ischemia or thrombosis to the vital organs or extremities and subsequent infarction. The advanced lesions of atherosclerosis represent a progression of the fibrous plaque, with an expanded lipid-rich core, accumulation of calcium, and disruption of endothelial integrity. Physical disruption of the plaque's protective cap permits contact between flowing blood and the highly thrombogenic material located in the lesion's lipid core (e.g., tissue factor), which results in thrombus formation (i.e., atherothrombosis). Thrombosis may lead to complete occlusion and clinically important complications (e.g., acute myocardial infarction [MI]) or, in the case of intraplaque hemorrhage, to plaque progression.

The American Heart Association Committee on Vascular Lesions has provided a numerical classification of histologically defined atherosclerotic lesion types.[1] Figure 62-1 outlines the most updated classification.[2] Lesion types I, II, and III are always small and clinically silent. With the development of type IV lesions, the pathways to clinical disease vary (see Fig. 62-1). Although lesions IV through VI may progress such that they obstruct the lumen of a medium- or large-size artery and produce a clinical event (i.e., MI, stroke, or extremity ischemia), the clinical manifestations of atherosclerotic disease are most often associated with type VI lesions. The criteria for type VI histology are often interrelated and include one or more of the following: surface defect, hematoma, and thrombosis. Regression of lipid from lesion types IV, V, and VI may result in lesion morphology similar to that of type VII and VIII lesions.

Inflammation in the artery wall plays a fundamental role in the initiation and progression of atherosclerosis.[3,4] As a result of this new understanding, inflammation has become a therapeutic target in the prevention and treatment of atherosclerosis and its complications. Established pharmacologic strategies, such as those for preventing recurrent MI and death, may have unexpected anti-inflammatory effects. For example, inhibitors of hydroxymethylglutaryl coenzyme A (i.e., statins) reduce LDL cholesterol levels but also have anti-inflammatory actions such as a reduction in leukocyte adhesion and macrophage activation.[5] Serum markers of inflammation are now being used as markers of atherosclerosis risk. Elevated plasma levels of CRP, an acute-phase reactant produced in response to inflammatory cytokines (primarily interleukin-6), are being used in cardiovascular risk stratification.[6,7] CRP levels are correlated with risk of death and MI[8] and with the development of peripheral vascular disease.[9] Aspirin's ability to reduce MI probably relates to both its antiplatelet and anti-inflammatory (i.e., reduces CRP levels) actions.[10]

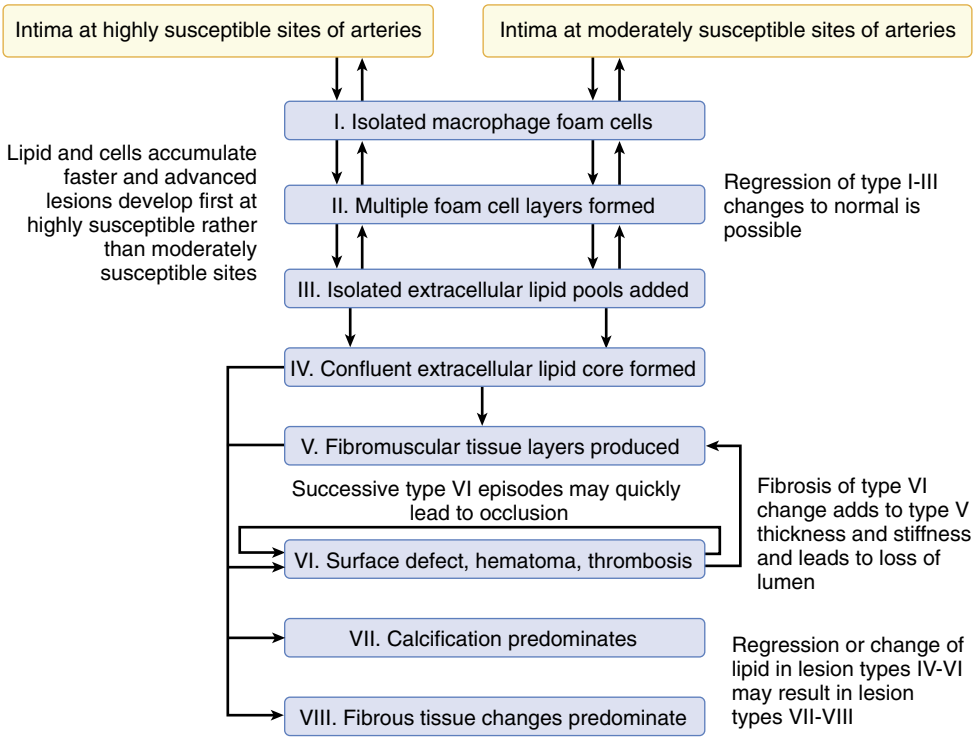


Figure 62-1 Outline of the sequence in the evolution of atherosclerotic lesions from type I to type IV and of the various possible subsequent pathways of progression to lesion types beyond type IV. The diagram lists the main histologic characteristics of each sequential step (lesion type). *Thick* or *thin arrows* differentiate between the relative ease with which lesions develop at specific sites, or they indicate the relative frequency and importance of a pathway section. *(From Stary HC: Natural history and histological classification of atherosclerotic lesions: An update. Arterioscler Thromb Vasc Biol 20:1177-1178, 2000.)*

The anatomic distribution of atherosclerotic lesions is shown in Fig. 62-2. The most common sites are the coronary arteries, the carotid bifurcation, the abdominal aorta, and the iliac and femoral arteries. Atherosclerotic lesions tend to develop near arterial branch points and along the outer surfaces of arterial curves. Their development may be related to increased shear stress and injury to the endothelial surface. Increased cholesterol blood levels are related to atherosclerosis.[11] Statins are the lipid-modifying drugs of choice for the treatment and prevention of atherosclerosis. The efficacy of statins in reducing cholesterol levels and cardiovascular events is well established in large outcome-based clinical trials.[12-14] When the cholesterol level is less than 150 mg/dL, lipids are mobilized from atherosclerotic lesions.[15] Estrogens protect against atherosclerosis in part by increasing HDL and decreasing LDL. Some evidence supports the role of antioxidants in preventing atherosclerotic lesions.[16] Vitamins C and E, carotenoids, and folic acid may be beneficial in this regard. Aspirin, by means of its anti-inflammatory and antiplatelet effects, is effective in preventing stroke and MI.

Preoperative Evaluation

Coexisting Disease

Patients undergoing vascular surgery have a high incidence of coexisting disease, including diabetes mellitus, hypertension, renal impairment, and pulmonary disease, all of which should be assessed and, if possible, optimized before surgery (see Chapters 34 and 35). Because of the systemic nature of atherosclerotic disease, vascular patients frequently have arterial disease affecting multiple vascular territories. CAD is the leading cause of perioperative mortality at the time of vascular surgery, and long-term survival after vascular procedures is significantly limited by the frequent occurrence of morbid cardiac events.[17] Less than 10% of patients who undergo vascular surgery have normal coronary arteries, and more than 50% have advanced or severe CAD. Unrecognized MI (determined by wall motion abnormalities at rest in the absence of a history of MI) and silent myocardial ischemia (determined by stress-induced wall motion abnormalities in the absence of angina) often occur in vascular surgery patients (23% and 28%, respectively) and are associated with increased long-term mortality and adverse cardiac events.[18] Left ventricular systolic dysfunction is five times more common in patients with vascular disease than in matched controls.[19] It is not clear whether any specific category of vascular disease is associated with a greater likelihood of coexisting CAD. Some investigators have shown a similar incidence and severity of CAD in patients with aortic, lower extremity, and carotid disease.[20] Others have shown that patients with lower extremity vascular disease are more likely to have significant CAD and to experience perioperative morbidity.[21-23] Medical therapy is the cornerstone of the management of CAD.

Perioperative and Long-Term Cardiac Outcomes

Preoperatively, the potential for MI and death in patients undergoing vascular surgery must be considered (Table 62-1). Nonfatal

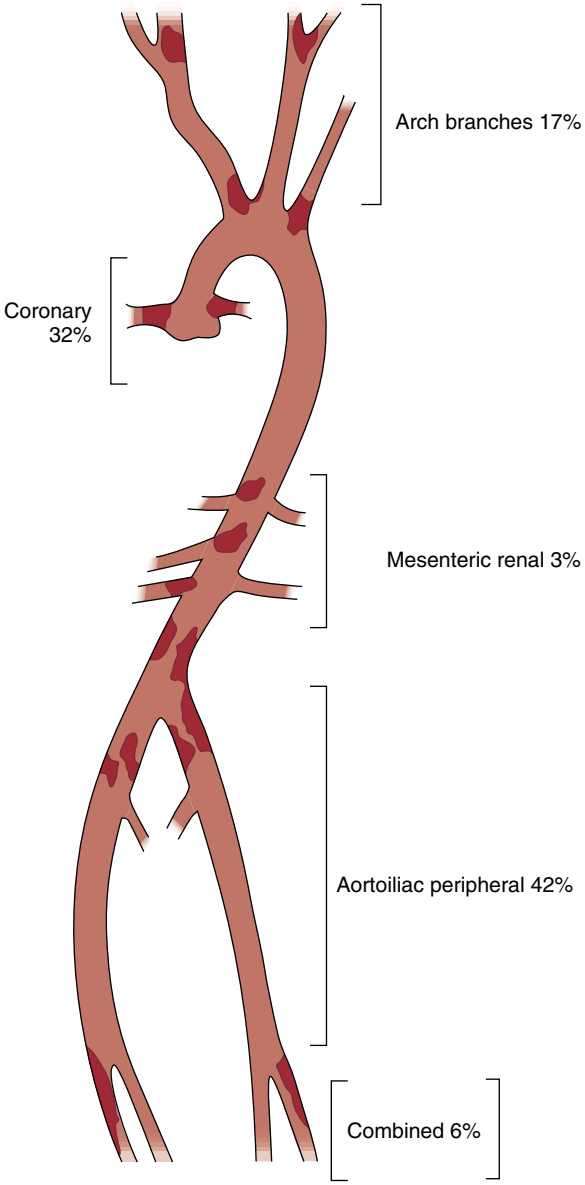


Figure 62-2 Distribution of atherosclerotic lesions. Plaques occur at the origins of large vessels and at bifurcations. Distribution and relative severity differ according to risk factors. *(From Zwolak RM, Cronenwett JL: Pathophysiology of vascular disease.* In *Yeager MP, Glass DD* [*eds*]*: Anesthesiology and Vascular Surgery. East Norwalk, CT, Appleton & Lange, 1990, pp 3-29.)*

and fatal MIs are the most important and specific outcomes that determine perioperative cardiac morbidity. When multiple recent studies are pooled, the overall prevalence of perioperative MI and death is 4.9% and 2.4%, respectively. When outcomes are assessed over the long term (2 to 3 years), the prevalence of MI and death is 8.9% and 11.2%, respectively. This perioperative and long-term morbidity and mortality persist despite aggressive medical and surgical therapy.[35]

Guideline-Based Approach

A guideline-based approach to health care is relatively new and originated primarily in the United States. The American College of Cardiology (ACC) Foundation and the American Heart Association (AHA) have jointly produced guidelines in the area of cardiovascular disease for more than 2 decades. The ACC/AHA Task Force on Practice Guidelines published "Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery" in 1996.[38] This evidence-based approach to perioperative evaluation and management was updated in 2002[39] and most recently in 2007.[40,41] A stepwise approach (simplified from the 2007 guidelines) to perioperative cardiac evaluation and care for noncardiac surgery is provided in Chapter 34. The authors emphasize that the purpose of the preoperative evaluation is not to give medical clearance but rather to perform an evaluation of the patient's current medical status; make recommendations concerning the evaluation, management, and risk of cardiac problems; and provide a clinical risk profile that the patient and caregivers can use in making treatment decisions that may influence perioperative and longer-term cardiac outcomes. The overriding theme of the perioperative guidelines is that intervention is rarely neces-

Table 62-1 Rates of Myocardial Infarction and Death in Patients Undergoing Vascular Surgery

Study	MI (%)	Death (%)	Comments
Short-Term Follow-up (in Hospital or 30 Day)*			
Ouyang et al.[24]	8	0	Small study
Raby et al.[25]	2.3	0.06	Aortic, lower extremity, carotid
Mangano et al.[26]	4.1	2.3	Vascular patients only reported
Bode et al.[27]	4.5	3.1	All lower extremity vascular
Christopherson et al.[28]	4.0	2.0	All lower extremity vascular
Mangano et al.[29]	5.0	0	Vascular patients only reported
Fleisher et al.[30]	6.0	3.0	Vascular patients only reported
Pasternack et al.[31]	4.5	1.0	Aortic, lower extremity, carotid
Krupski et al.[21]	2.1	2.9	Aortic, lower extremity
Baron et al.[32]	5.9	4.0	All aortic
Norris et al.[33]	3.3	5.4	All aortic
Fleron et al.[34]	5.5	4.1	All aortic
McFalls et al.[35]	8.4	3.2	Aortic, lower extremity
Average	4.9	2.4	
Long-Term Follow-up (in Hospital and after Discharge)*			
Raby et al.[25]	7.4	5.1	20-month follow-up
Mangano et al.[26]	4.7	3.5	15-month follow-up
Mangano et al.[36]	19.4	13.5	24-month follow-up
Hertzer et al.[37]		12	5-year follow-up
Krupski et al.[22]	3.9	11.2	24-month follow-up
McFalls et al.[24]	NA	22	2.7-year follow-up
Average	8.9	11.2	2.5-year average follow-up

*For short-term follow-up, outcomes are reported for the duration of the hospital stay or 30 days, and death from MI was classified as both MI and Death. For long-term follow-up, MI was not included as a subset of Death because the cause of death was often unknown. The incidence of MI is underestimated in the long-term part of the table.

sary to simply lower the risk associated with surgery unless such intervention is indicated irrespective of the preoperative context. Thus, preoperative testing should not be performed unless it is likely to influence patient care. The particular challenge that the vascular surgery patient presents is emphasized throughout the document. Aspects of the updated guidelines and its evidence-based approach will be discussed throughout this chapter.

Cardiac Risk Assessment

The preoperative cardiac assessment presents an opportunity to initiate and optimize pharmacologic management, perform appropriate diagnostic and therapeutic interventions, and adjust overall care to decrease not only perioperative risk but also long-term risks from cardiovascular events. The ACC/AHA stepwise approach considers vascular surgery distinct from other noncardiac surgical procedures and is reviewed in detail in Chapter 34. Only issues specific to vascular surgery are reviewed in this chapter.

After assessment of cardiac risk, there is the additional challenge of modifying perioperative management to reduce risk by adjusting or adding cardiac medications (e.g., β-adrenergic blocker), direct coronary intervention (e.g., percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), modifying or intensifying perioperative management (e.g., invasive hemodynamic monitoring), or changing preoperative plans (e.g., performing endovascular aortic repair rather than open aortic repair). Coordination is essential between surgeons, anesthesiologists, and cardiologists, each of whom may have different criteria for risk assessment and different objectives for risk modification.

Clinical Risk Indices

Assessing cardiac risk in patients before vascular surgery is a controversial and difficult task (see Chapters 33 and 34). Although risk indices are a cost-effective screening method for determining which patients require further cardiac evaluation (i.e., additional risk stratification with noninvasive technologies), the high pretest probability of CAD in vascular surgery patients makes the risk index somewhat less useful. Risk indices do not provide specific risk prediction for individuals, but rather place patients in general risk categories, most commonly designated as low (cardiac risk generally <1%), intermediate (cardiac risk of 1% to 5%), or high (cardiac risk often >5%). As discussed later, clinical risk variables identified by logistic regression in vascular surgery cohorts can be used along with noninvasive cardiac testing to optimize preoperative assessment of cardiac risk before vascular surgery.[42,43] From the registry of the Coronary Artery Revascularization Prophylaxis (CARP) trial, the absence of multiple preoperative cardiac risk variables identifies patients with the best long-term surival after elective vascular surgery.[44]

Previous Coronary Artery Bypass Surgery

Previous coronary revascularization may not provide the same level of protection against MI and death after major vascular surgery.[45] Results from the randomized, prospective CARP trial demonstrated that an aggressive strategy of prophylactic coronary artery revascularization before vascular surgery in patients with stable cardiac symptoms does not improve short-term outcome or long-term survival.[35] At 2.7 years after randomization, mortality was 22% and 23% in patients with and without revascularization, respectively. Postoperative MI, defined by elevated troponin levels, occurred in 12% and 14% of patients with and without revascularization, respectively. Among those randomized to revascularization, patients undergoing CABG had fewer perioperative (6.6% versus 16.8%) and late postoperative (9.9% versus 23.7%) MIs than did patients undergoing PCI despite more diseased vessels in the CABG group (3.0 versus 2.2).[46] Completeness of the revascularization procedure (CABG > PCI) was the predominant variable accounting for this difference. The DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo)-V pilot study investigated in a randomized fashion the role of prophylactic coronary revascularization in high-risk (three or more clinical risk variables and extensive stress-induced ischemia on noninvasive cardiac testing) patients undergoing major vascular surgery.[47] Preoperative coronary revascularization was not associated with improved short- or long-term outcome. There was no significant difference in the composite end point of all-cause death or nonfatal MI at 30 days

(43% versus 33%) or during 1-year follow-up (49% versus 44%) between patients randomized to revascularization or no revascularization. No difference was observed in the incidence of perioperative cardiac events between patients treated with CABG or PCI. The results of these two randomized trials are congruent with the current ACC/AHA guidelines on perioperative management[40] and CABG,[48] in which preoperative revascularization is reserved for patients with unstable cardiac conditions or advanced coronary disease, for whom a survival benefit with CABG has been proved. Of note, periprocedural complications after CABG are substantially higher in patients with peripheral arterial disease than in those without such disease.[49] These complications may preclude or alter the timing of subsequent vascular surgery.

Previous Percutaneous Coronary Intervention

The role of prophylactic percutaneous coronary revascularization in the preoperative management of vascular surgery patients is controversial.[35,47] Current evidence appears to limit PCI to patients with unstable active CAD.[41] Patients with peripheral vascular disease are often not ideal candidates for PCI. These interventions require placement of a large-diameter introducer sheath in the femoral artery, which predisposes to pseudoaneurysm and compromised blood flow to the lower extremities.[50] PCI can be performed through the brachial artery, but it is technically difficult. PCI in patients with peripheral arterial disease, as opposed to those without peripheral arterial disease, is associated with lower procedural success, higher in-hospital cardiovascular complications, and higher mortality on follow-up.[51] Thus, current guidelines indicate that PCI before noncardiac surgery, including vascular surgery, is of no value in preventing perioperative cardiac events, except in patients in whom PCI is independently indicated for unstable active cardiac conditions.[41]

Noninvasive Diagnostic Cardiac Testing

Accurate clinical assessment of the pretest probability of significant CAD is necessary for the prudent use and rational interpretation of preoperative cardiac testing. In general, noninvasive cardiac testing prior to vascular surgery is best directed at patients considered to be at intermediate clinical risk. Such testing should not be undertaken if it is unlikely to alter patient management and should not be considered as a preliminary step leading to coronary revascularization, as it is rarely necessary to perform a revascularization procedure solely for the purpose of getting a patient through the perioperative period. Extensive cardiac evaluation prior to vascular operations can result in morbidity, delays, and patient refusal to undergo vascular surgery. A complete review of this subject is found in Chapters 34 and 42.

Cardiac Catheterization and Prophylactic Revascularization

The largest series on outcome in vascular surgery patients is that of Hertzer and colleagues[20] from the Cleveland Clinic. These investigators performed cardiac catheterization in 1000 consecutive patients scheduled to undergo peripheral vascular surgery (aortic aneurysm resection, carotid endarterectomy, and lower extremity revascularization). The incidence and severity of CAD were assessed according to the following classification: normal coronary arteries; mild to moderate CAD with no lesion exceeding 70% stenosis; advanced, compensated CAD with one or more lesions exceeding 70% stenosis but with adequate collateral circulation; severe, correctable CAD with greater than 70% stenosis in one or more coronary arteries; and severe inoperable CAD with greater than 70% stenosis in one or more coronary arteries and severe distal disease or poor ventricular function. The most remarkable findings were that only 8.5% of patients had normal coronary arteries and 60% had advanced or severe coronary lesions (>70% stenosis).[20] Even when CAD was not suspected by the clinical history, more than a third of patients had advanced or severe coronary lesions. The results are shown in Table 62-2.

Combined mortality rates over the immediate- and long-term (4.6-year follow-up) postoperative period are shown in Table 62-3. Of the 216 patients who underwent coronary revascularization (CABG), 12 (5.5%) died after this surgery. This mortality rate is greater than that reported for patients undergoing CABG surgery without peripheral vascular disease (1% to 2%), which suggests that the risks associated with CABG should be seriously considered as part of the preoperative evaluation of these patients. When overall early and late mortality (>5 years) is considered, death occurred in 12% versus 26% of patients who did or did not undergo CABG, respectively. Although these data appear to support the beneficial effect of CABG on outcome, the mortality from CABG itself (5.5%) reduces its apparent benefits.

Two randomized clinical trials have been performed to determine the impact of prophylactic coronary artery revascularization on outcome after vascular surgery.[35,47] Of the 5859 patients screened in the CARP trial,[35] 1190 underwent coronary angiography based on a combination of clinical risk factors and noninvasive stress imaging data.[42] The incidence and severity of CAD on these angiograms were reported as follows: 43% of patients had one or more major coronary arteries with at least a 70% stenosis suitable for revascularization (and were randomized to either revascularization or no revascularization before vascular surgery), 31% had nonobstructed coronary arteries, 18% had coronary stenosis considered unsuitable for revascularization, and 5% had left main coronary artery stenosis of 50% or greater. The CARP trial showed that prophylactic revascularization (by CABG or PCI) was generally safe but did not improve long-term outcome after vascular surgery. Long-term mortality (2.7 years) was 22% in the revascularization group and 23% in the no-revascularization group (Fig. 62-3). Although the trial was not designed to test the short-term benefit of prophylactic revascularization, there was no reduction in perioperative outcomes,

Table 62-2 Results of Coronary Angiography in 1000 Patients with Peripheral Vascular Disease

	Clinical CAD					
	None		Suspected		Total	
Angiographic Classification	No.	%	No.	%	No.	%
Normal coronary arteries	64	14	21	4	85	8.5
Mild to moderate CAD	218	49	99	18	317	32
Advanced, compensated CAD	97	22	192	34	289	29
Severe, correctable CAD	63	14	188	34	251	25
Severe, inoperable CAD	4	1	54	10	58	5.8

CAD, coronary artery disease.
Data from Hertzer NR, Beven EG, Young JR, et al: Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 199:223-233, 1984.

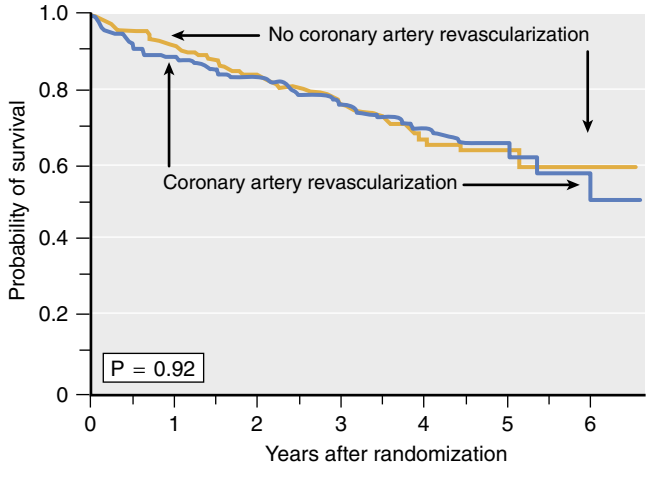
Table 62-3 Perioperative and Late Cardiac Deaths after Peripheral Vascular Reconstruction in 846 Patients Monitored over a 5-year Period According to Coronary Angiographic Classification

Clinical Features	Total No. of Patients	Normal or Mild to Moderate CAD		Advanced, Compensated CAD		Severe, Correctable CAD				Severe, Inoperable CAD		Total Cardiac Deaths	
						With CABG		No CABG					
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Men	685	10/242	4.1	33/204	16	13/174	7.5	6/24	25	14/41	34	76	11
Women	315	5/160	3.1	12/85	14	12/42	29	3/11	27	8/17	47	40	13
Age <70 yr	722	10/328	3.0	29/198	15	19/148	13	3/20	15	13/28	46	74	10
Age ≥70 yr	278	5/74	6.8	16/91	18	6/68	8.8	6/15	40	9/30	30	42	15
Normotensive	403	7/185	3.8	15/102	15	8/82	9.8	2/15	13	8/19	42	40	9.9
Hypertensive	597	8/217	3.7	30/187	16	17/134	13	7/20	35	14/39	36	76	13
Nondiabetic	830	12/348	3.4	28/232	12	17/183	9.3	8/30	27	13/37	35	78	9.4
Diabetic	170	3/54	5.6	17/57	30	8/33	24	1/5	20	9/21	43	38	22
Total	1000	15/402	3.7	45/289	16	25/216	12	9/35	26	22/58	38	116	12

CABG, coronary artery bypass grafting; CAD, coronary artery disease.
From Hertzer NR, Young JR, Beven EG, et al: Late results of coronary bypass in patients with peripheral vascular disease. II. Five-year survival according to sex, hypertension, and diabetes. Cleve Clin J Med 54:15-23, 1987.

including death (3.1% versus 3.4%) and MI (12% versus 14%). The CARP trial results can be applied to a large percentage of the vascular surgery population; however, they cannot be extrapolated to patients with unstable cardiac symptoms, left main coronary artery disease, aortic stenosis, or severe left ventricular dysfunction because these conditions excluded patients from study participation. The DECREASE-V trial[47] screened 1880 vascular surgery patients, 430 of whom with three or more clinical risk factors underwent noninvasive stress testing using stress-echo or perfusion imaging. Patients with extensive stress-induced ischemia (26%) were randomly assigned to revascularization or no revascularization. Coronary angiography showed two-vessel disease in 24%, three-vessel disease in 67%, and left main coronary artery disease in 8%. Prophylactic coronary revascularization (CABG or PCI) did not improve perioperative or long-term outcome (Table 62-4). The incidence of all-cause death or nonfatal MI at 30 days in patients who underwent revascularization or did not was 43% versus 33%, respectively. The incidence of the composite end point at 1 year was similar, 49% versus 44%, respectively.

The lack of benefit of prophylactic coronary revascularization in the CARP and DECREASE-V trials is difficult to reconcile



No. at Risk

Revascularization	226	175	113	65	18	7
No revascularization	229	172	108	55	17	12

Figure 62-3 Long-term survival in patients randomized to undergo coronary artery revascularization or no coronary artery revascularization before elective major vascular surgery (Coronary Artery Revascularization Prophylaxis trial). Kaplan-Meier estimates were used to generate survival curves from the time of randomization for all patients. *(From McFalls EO, Ward HB, Moritz TE, et al: Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 351:2796-2804, 2004.)*

Table 62-4 Perioperative and Long-Term Patient Outcomes from the DECREASE-V Trial

	Revascularization, No. (%)	No Revascularization, No. (%)	HR (95% CI)	*P* Value
Number of patients	49	52		
Events before surgery				
All-cause mortality	2 (4.1)	0		.23
Myocardial infarction	1 (2.1)	0		
Composite	3 (6.1)	0		.11
Events up to 30 days after surgery				
All-cause mortality	11(22.5)	6 (11.5)	2.2 (0.74-6.6)	.14
Myocardial infarction	17 (34.7)	16 (30.8)		
Composite	21 (42.9)	17 (32.7)	1.4 (0.73-2.8)	.30
Events up to 365 days after surgery				
All-cause mortality	13 (26.5)	12 (23.1)	1.3 (0.55-2.9)	.58
Myocardial infarction	18 (36.7)	19 (36.5)		
Composite	24 (49.0)	23 (44.2)	1.2 (0.68-2.3)	.48

CI, confidence interval; HR, hazard ratio.
From Poldermans D, Schouten O, Vidakovic R, et al: A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery. The DECREASE-V Pilot Study. J Am Coll Cardiol 49:1763-1769, 2007.

with the more favorable data from Hertzer and coworkers[20] and other studies (Coronary Artery Surgery Study [CASS][52] and Bypass Angioplasty Revascularization Investigation [BARI][53]), but it is consistent with current guideline recommendations.[40] Clearly, issues are at play that go beyond critical coronary lesions, which suggests that current understanding of the coronary anatomy predisposing to cardiac risk is lacking. There is emerging evidence that perioperative MI may be caused by culprit lesions (i.e., vulnerable plaques) often located in coronary vessels without critical stenosis.[54] Strategies aimed at reducing the perioperative stress response and potential triggers of coronary plaque rupture may be more appropriate than those leading to coronary revascularization.

Assessment of Pulmonary Function

Postoperative pulmonary complications are potentially serious in patients undergoing vascular surgery, with the most significant morbidity seen in patients undergoing open aortic procedures (see Chapter 93). The most important pulmonary complications are atelectasis, pneumonia, respiratory failure, and exacerbation of underlying chronic disease. Given the prevalence of cigarette smoking in this population, chronic obstructive pulmonary disease and chronic bronchitis are common and, when present, place the patient at increased risk for postoperative pulmonary complications. When clinical assessment suggests severe pulmonary compromise, pulmonary function tests may be useful in evaluating and optimizing respiratory function (see Chapter 44). Preoperative blood gas determination can be used to establish a baseline for postoperative comparison. Baseline hypercapnia (partial pressure of arterial carbon dioxide >45 mm Hg) indicates a higher risk for postoperative morbidity. Bronchodilator therapy may be indicated on the basis of results of pulmonary function tests, although the risk of β-agonist–induced arrhythmia or myocardial ischemia must also be considered. Preoperative treatment with a short course of glucocorticoids (prednisone, 40 mg/day for 2 days) may be helpful for patients with significant chronic obstructive pulmonary disease or asthma.[55] Evidence of pulmonary infection requires treatment with appropriate antibiotics. Although there is limited evidence for improved pulmonary outcome with regional anesthesia,[56] patients with significant pulmonary disease may benefit from epidural techniques that are maintained into the postoperative period because the use of local anesthetics helps avoid respiratory depression from systemic opiates. Effective strategies to prevent pulmonary complications in the postoperative period are limited. Incentive spirometry and continuous positive airway pressure are the only modalities of proven benefit.[57] Given proper pulmonary care, even patients with severe pulmonary insufficiency, however, may undergo aortic surgery with acceptable morbidity and mortality.[58]

Assessment of Renal Function

Chronic renal disease is common in vascular surgery patients and is associated with an increased risk for death and cardiovascular disease (see Chapters 33 and 45).[59] Chronic renal disease strongly predicts long-term mortality in patients with symptomatic lower extremity arterial occlusive disease irrespective of disease severity, cardiovascular risk, and concomitant treatment.[60] Cardiovascular disease, itself, is independently associated with a decline in renal function and the development of kidney disease.[61] Serum creatinine and creatinine clearance are commonly used to assess renal function perioperatively. A preoperative serum creatinine level higher than 2 mg/dL is an independent risk factor for cardiac complications after major noncardiac surgery.[62] Preoperative creatinine clearance less than 60 mL/min is an independent predictor of both short- and long-term mortality after elective vascular surgery.[63] Perioperative β-blocker[63] use and perioperative statin[63] use are associated with a lower risk of death in vascular surgery patients with renal impairment. Atherosclerotic disease in the abdominal aorta or renal arteries may compromise renal blood flow and renal function. Conversely, renal artery stenosis causes hypertension through renin- and angiotensin-induced vasoconstriction. Hypertension itself may cause renal insufficiency or

failure. Diabetic nephropathy is also common. Superimposed on baseline abnormalities in renal function are the preoperatively and intraoperatively administered angiographic dyes, which are directly nephrotoxic. Renal ischemia occurs with interruption of renal blood flow from aortic cross-clamping. Even with infrarenal aortic cross-clamps, there can be a significant reduction in renal blood flow despite normal systemic arterial blood pressure and cardiac output. Embolic plaque can be showered into the renal arteries, especially when suprarenal aortic cross-clamps are applied and released. Fluctuations in intravascular volume and cardiac output can compromise renal perfusion during the intraoperative and postoperative periods. In one series of more than 500 patients, the prevalence of acute renal failure was 7% after abdominal aortic reconstruction.

Perioperative Myocardial Ischemia

Etiology and Prevention

Ischemic cardiac morbidity is the most common cause of perioperative (and overall) death in the United States.[17] Table 62-5 summarizes eight studies showing the relative incidence of preoperative, intraoperative, and postoperative myocardial ischemia. The two studies[28,33] with the lowest rates of intraoperative myocardial ischemia both rigorously controlled intraoperative heart rate and blood pressure by protocol. Norris and associates[33] continued this "tight" hemodynamic control into the postoperative period and reported the lowest rate (15%) of postoperative myocardial ischemia. These studies suggest that good control of perioperative hemodynamics, with an emphasis on heart rate control (<85 beats/min), probably plays an important role in reducing myocardial ischemia. Despite evidence supporting the potential benefit of even tighter heart rate control (<70 beats/min) in reducing myocardial ischemia after vascular surgery,[67] there is strong evidence, suggesting potential harm.[68] There is little information available regarding the importance of blood pressure control. A rational approach that appropriately addresses patients with hypertension or hypotension is described in Figure 62-4.

Several clinical studies have increased our understanding of the clinical variables that may precipitate myocardial ischemia, such as heart rate. After vascular surgery, unlike CABG, patients leave the operating room with the same coronary disease that they came in with, only to experience the stress of the postoperative period. Some vascular patients exhibit heart rate–related myocardial ischemia at "subtachycardic" heart rates.[69] In certain high-risk patients, heart rates of about 85 beats/min consistently trigger ischemic ST-segment changes. The primary role of the anesthesiologist is not merely to control the heart rate but also to diagnose and treat the underlying cause of heart rate changes.

The optimal hematocrit value for vascular surgery patients is unknown. An increased incidence of myocardial ischemia and cardiac morbidity appears to occur if hemoglobin concentrations are less than 9.0 g/dL in the early postoperative period.[70] Therefore, the practice of maintaining hemoglobin concentrations above 9.0 g/dL in vascular patients, especially those at significant risk for ischemic cardiac morbidity, makes sense (see Chapter 55).

Monitoring for Myocardial Ischemia

Three methods are used to detect myocardial ischemia during the perioperative period: surface ECG, transesophageal echocardiography (TEE), and pulmonary artery catheterization (see Chapters 40 to 42). The sensitivity and specificity for detection of ischemia, the level of training required, and the cost of these methods differ and are important considerations. Monitoring for ischemia is important during and after vascular surgery. Ischemia may lead to infarction,[26,71] especially when the ischemia is sustained over time (>2 hours).[72,73] Although no controlled clinical trials have demonstrated a reduction in perioperative morbidity with ischemia monitoring and treatment, the clinical determinants of myocardial oxygen supply and demand should be optimized in an attempt to resolve the ischemic condition.

Table 62-5 Incidence of Myocardial Ischemia* during the Preoperative, Intraoperative, and Postoperative Periods in Vascular Surgery Patients

Study	Preoperative	Intraoperative	Postoperative	Overall
Pasternack et al.[31]				
Aortic/lower extremity	40	38	48	61
Carotid	38	41	54	68
Ouyang et al.[24]	13	21	63	
McCann and Clements[64]	14	38		
Mangano et al.[26]	20	25	41	
Raby et al.[65]	18	30		
Christopherson et al.[28]	8	11	40	40
Boylan et al.[66]	35			
Norris et al.[22]	3†	4†	15†	16
Average	19	23	42	43

*Percentage of patients with myocardial ischemia as detected by continuous Holter monitoring and ST-segment analysis.
†Unpublished data.

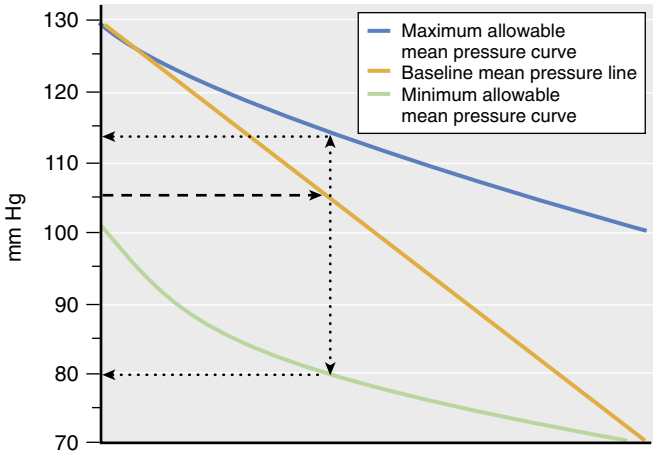


Figure 62-4 Nomogram used to determine minimum and maximum mean blood pressure limits. The nomogram is used by reading the baseline mean arterial pressure (MAP) from the left-hand axis horizontally onto the diagonal baseline mean pressure line. The point of intersection on this line is then extended vertically to intersect with the minimum and maximum allowable mean pressure curves. A patient with a baseline MAP of 105 mm Hg, shown in the figure, would have an allowable MAP range of 80 to 114 mm Hg. *(From Norris EJ, Beattie C, Perler BA, et al: Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery. Anesthesiology 95:1054-1067, 2001.)*

Perioperative β-Blocker Therapy

Perioperative β-blocker therapy is an important and controversial topic, particularly in patients undergoing vascular surgery, and is reviewed more fully in Chapters 34 and 35. Patients maintained on chronic β-blocker therapy should continue taking β-blockers throughout the perioperative period. β-Blockers should not be used as the initial or primary treatment of tachycardia caused by perioperative events, such as hypovolemia, anemia, pain, or infection, because these conditions require prompt treatment of the underlying cause. Treatment of tachycardia caused by the sympathetic stimulation associated with surgical stress should be considered in high-risk patients, particularly those with known ischemic potential (i.e., ischemia on preoperative testing). Caution must be taken to avoid hypotension and bradycardia. Acute initiation of high-dose β-blockade in the perioperative period should be avoided. If a decision is made to initiate β-blocker treatment in the perioperative period in an effort to reduce cardiac risk, the safest approach may be to initiate therapy with a low dose and titrate to effect over a 7- to 10-day period before the planned surgery. Although perioperative β-blocker therapy may decrease the number of patients referred for preoperative cardiac testing, such testing will not probably be eliminated, and careful consideration must be given to this approach in terms of its risk-to-benefit ratio.

Hemodynamic Monitoring

The appropriate level of invasive hemodynamic monitoring (see Chapter 40) in patients undergoing vascular surgery is a controversial issue. Multiple considerations determine the need for monitoring, and it is difficult to generalize for all vascular patients. Given the frequency of coexisting disease, the potential for fluid shifts and blood loss, and the physiologic changes associated with cross-clamping and unclamping, virtually all patients undergoing major vascular surgery should be monitored with an intra-arterial catheter. This allows beat-to-beat blood pressure monitoring, accurate determination of diastolic pressure, and sampling of arterial blood for diagnostic purposes. The radial artery is most commonly selected for cannulation because of its superficial location and the presence of collateral circulation. The need to verify collateral blood flow is questionable. The Allen test[74] can be used to assess collateral flow in the palmar arch, but there is evidence that ischemic injury can occur in patients with a normal Allen test result and that no injury occurs in patients with an abnormal Allen test result when the radial artery is cannulated.[75] When the radial artery is difficult to cannulate, the ulnar or axillary arteries are alternative sites. The axillary artery can be cannulated by use of the Seldinger technique, but extreme care should be taken to avoid injecting air when flushing an axillary catheter because the tip may lie close to or inside the aortic arch and thus allow air to enter the cerebral circulation. Whenever possible, the femoral arteries should be avoided in patients with peripheral vascular disease.

Vascular surgery patients often have a large discrepancy in arterial blood pressure between the right and left arms as a result of atherosclerotic lesions in the subclavian or axillary arteries; such discrepancy results in a falsely low pressure in the ipsilateral arm.[76] Patients scheduled for carotid surgery have the highest incidence of right/left arm blood pressure differences.[76] To avoid "pseudohypotension," arterial blood pressure should be verified in both arms, and the arm with the higher pressure should be monitored during surgery. Both arms may have falsely low blood pressure as a result of bilateral disease. In this case, the femoral artery may be the best option for monitoring.

There is significant controversy over the utility of central venous and pulmonary artery catheters for hemodynamic monitoring of patients during vascular surgery. The surgical procedure often determines the degree of fluid shifting and blood loss and thus the usefulness of invasive monitoring. The patient's underlying cardiac, pulmonary, and renal status also needs to be considered. Although cardiovascular function is highly dependent on adequate ventricular filling (i.e., the heart cannot pump out more

blood than it receives), values of central venous pressure and pulmonary artery occlusion pressure do not correlate with values of measured circulating blood volume.[77] Additional information, such as stroke volume and cardiac output, are often important when extreme stress is placed on an already impaired heart. The indications for central venous pressure and pulmonary artery catheter monitoring are discussed in further detail in the subsequent sections.

The role of TEE (see Chapter 41) in the perioperative period has expanded rapidly over the last decade. TEE is useful in identifying anatomic and functional cardiac abnormalities and is a sensitive monitor for detection of myocardial ischemia. During complex aortic reconstruction, TEE provides important real-time information on cardiac filling and function and is particularly useful when unexplained hemodynamic instability is encountered.

Abdominal Aortic Reconstruction

Anesthesia for conventional abdominal aortic reconstruction requires an understanding of the pathophysiology, extensive knowledge of the surgical procedure, the ability to interpret sophisticated hemodynamic data, and skillful pharmacologic control and manipulation of hemodynamics. Preoperative and intraoperative communication with the surgical team is essential. All open operative procedures on the abdominal aorta and its major branches require large incisions and extensive dissection, clamping and unclamping of the aorta or its major branches, varying duration of organ ischemia-reperfusion, significant fluid shifts and temperature fluctuations, and activation of neurohumoral and inflammatory responses. The major objectives of surgical treatment of the aorta are to relieve symptoms, reduce the frequency of associated complications, and in the case of aortic aneurysm, prevent rupture. Over the last decade, the growth and development of catheter-based technology for the treatment of peripheral arterial disease have generated tremendous interest for less invasive methods to treat aortic disease. Endovascular aortic surgery (discussed later) has emerged as a less invasive alternative to conventional surgical repair. The endovascular field is evolving rapidly with new devices, innovations, and indications for aortic disease.

Natural History and Surgical Mortality

Abdominal Aortic Aneurysm

Abdominal aortic aneurysms occur frequently in elderly men, with an incidence approaching 8%. Age, smoking, family history of abdominal aortic aneurysm, and atherosclerotic disease are risk factors for abdominal aortic aneurysm. Although the prevalence is much lower in women, the risk factors for abdominal aortic aneurysm are similar to those in men. More than 8000 deaths result from rupture of abdominal aortic aneurysms each year in the United States.[78] The number of hospital discharges each year with the first diagnosis of aortic aneurysm is nearly 70,000.[78] Approximately 40,000 patients undergo open repair of abdominal aortic aneurysm each year in the United States, at a cost likely to exceed a billion dollars. The incidence of abdominal aortic aneurysm appears to be rising and is age and sex dependent.

Abdominal aortic aneurysm is a multifactorial disease associated with aortic aging and atherosclerosis. Although no unified concept of pathogenesis exists, there are genetic, biochemical, metabolic, infectious, mechanical, and hemodynamic factors that may contribute to the development of abdominal aortic aneurysmal disease.[79,80] Adventitial elastin degradation (elastolysis), a hallmark of abdominal aortic aneurysm formation, may be the primary event.[81] Chronic inflammation is a prominent feature of abdominal aortic aneurysms and probably plays a fundamental role in the destruction of connective tissue in the aortic wall.[82] Concomitant aortoiliac occlusive disease is present in approximately 20% to 25% of patients with abdominal aortic aneurysms. Approximately 5% of patients undergoing abdominal aortic resection have inflammatory aneurysms. Rare causes of abdominal aortic aneurysm disease include trauma, mycotic infection, syphilis, and Marfan's syndrome.

The natural history of abdominal aortic aneurysmal disease is one of progressive enlargement and ultimate rupture and death. Perioperative mortality from elective resection of infrarenal aortic aneurysms has progressively declined from 18% to 20% during the 1950s, to 6% to 8% in the mid-1960s, to 5% to 6% in the early 1970s, to 2% to 4% in the 1980s, at which time it plateaued. A publication of 1000 consecutive elective infrarenal aneurysm repairs over a 15-year period reported a perioperative mortality rate of 2.4%.[83] Hertzer and coworkers[84] reported a mortality rate of 1.2% for 1135 consecutive elective abdominal aortic repairs at the Cleveland Clinic. This single-center mortality rate is considerably lower than the mortality rates of 5.6% to 8.4% reported from large national data sets.[85,86] These higher mortality rates on the national level have prompted some to suggest that all of the technologic and treatment advances over the last 2 decades have not had an impact on outcomes of patients with abdominal aortic aneurysms.[86] Regionalization of care and endovascular treatments currently hold the most promise for improvement in operative mortality.

For ruptured abdominal aortic aneurysms, perioperative mortality has not changed significantly over the last 4 decades and remains nearly 50%, with few exceptions. If one takes into consideration patients with rupture who die before reaching a hospital, the overall mortality rate after rupture may very well exceed 90%.[87]

The diameter and rate of expansion of abdominal aortic aneurysms are currently the best predictors of the risk for rupture. The Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery have published guidelines for the treatment of abdominal aortic aneurysms.[88] These guidelines emphasize that it is not possible or appropriate to recommend a single threshold diameter for operative intervention that can be generalized to all patients. There is nearly uniform agreement that elective repair should be undertaken in all patients with abdominal aortic aneurysms 6 cm or greater in diameter. Although some controversy exists regarding elective abdominal aortic aneurysm repair when its diameter is in the 5.5- to 5.9-cm range,[89] it is currently accepted that the risk for rupture of a 5.5-cm aneurysm (per year) is equal to or greater than the risk for perioperative mortality, and thus surgical repair is indicated. The 1-year incidence of probable rupture in patients refusing or unfit for elective repair has recently been reported as 9.4%, 10.2%, and

32.5% for aneurysms 5.5 to 5.9 cm, 6.0 to 6.9 cm, and 7.0 cm or greater, respectively.[90]

The natural history of abdominal aortic aneurysms 4.0 to 5.5 cm in diameter is not well defined, and significant controversy exists regarding surgical repair.[91-93] Two prospective randomized clinical trials conducted in the United Kingdom (United Kingdom Small Aneurysm Trial[94]) and the United States (Aneurysm Detection and Management Study[95]) concluded that surveillance of abdominal aortic aneurysms 4.0 to 5.5 cm in diameter is a safe management option and that early surgical repair did not result in any long-term survival advantage. However, surgical repair is often recommended if such aneurysms become symptomatic or expand more than 0.5 cm in a 6-month period. Aneurysms less than 4 cm in diameter are thought to be relatively benign in terms of rupture and expansion.

The long-term durability of open infrarenal abdominal aortic aneurysm repair is excellent and well established. The incidence of late graft complications is very low (0.4% to 2.3%).[84] Late survival rates after repair of nonruptured abdominal aortic aneurysms are 92% at 1 year and 67% at 5 years.[87]

Aortoiliac Occlusive Disease

As noted earlier, the infrarenal aorta and the iliac arteries are two of the most common sites of chronic atherosclerosis. Because of the diffuse and progressive nature of aortoiliac atherosclerosis, plaque enlargement may reduce blood flow to the lower extremities below a critical level and result in symptoms of ischemia. Unlike patients with aortic aneurysmal disease, patients undergo surgery for aortoiliac occlusive disease only if they are symptomatic. Surgical intervention is indicated for disabling intermittent claudication and limb-threatening ischemia. Intervention is directed toward restoring peripheral pulsatile circulation to relieve claudication and toward preventing amputation. Patients with localized aortoiliac occlusive disease typically have claudication because collateral circulation adequate to prevent critical lower extremity ischemia usually exists. Perioperative mortality is lower in patients undergoing aortoiliac reconstruction than in those undergoing abdominal aortic surgery.[96]

Therapeutic options for managing aortoiliac occlusive disease include anatomic or direct reconstruction (i.e., aortobifemoral bypass), extra-anatomic or indirect bypass grafts (i.e., axillofemoral bypass), and catheter-based endoluminal techniques (i.e., percutaneous transluminal angioplasty with or without stent insertion). Aortobifemoral bypass is viewed as the "gold standard" in treating aortoiliac occlusive disease.[96] Extra-anatomic bypass grafts are generally reserved for specific indications, usually patients with infection, failure of previous reconstruction, or prohibitive risk. Reduced long-term patency and inferior functional results are frequently the trade-off for lower perioperative morbidity and mortality. Catheter-based endoluminal techniques, such as percutaneous transluminal angioplasty, are used for relatively localized disease and may be reasonable alternatives to aortobifemoral bypass in 10% to 15% of patients with aortoiliac occlusive disease.[96]

Renal and Visceral Arterial Insufficiency

Atherosclerosis is the most common cause of renal artery stenosis. Occlusive lesions are located almost exclusively in the proximal segment and orifice of the renal artery and are usually an extension of aortic atherosclerosis. Fibromuscular dysplasia is an important, but less common cause of renal artery stenosis and most frequently involves the distal two thirds of the renal arteries. Hemodynamically significant renal artery stenosis may cause hypertension by activation of the renin-angiotensin-aldosterone system, and bilateral involvement may result in renal failure. Patients with renovascular hypertension frequently have poorly controlled hypertension despite maximal medical therapy. These patients often have severe bilateral renal artery stenosis and may have recurrent congestive heart failure or flash pulmonary edema. Indications for intervention include control of hypertension and salvage of renal function. Operative interventions include aorto-renal bypass, extra-anatomic bypass (hepatorenal or splenorenal bypass), or transaortic endarterectomy. Suprarenal or supraceliac aortic cross-clamping is frequently required for open operative interventions. Percutaneous transluminal angioplasty with stenting of the renal artery is used as the first-line treatment in selected patients.

Stenosis at the origin of the celiac and mesenteric arteries occurs as a result of extension of aortic atherosclerosis. The inferior mesenteric artery is by far the most commonly involved, followed by the superior mesenteric artery and the celiac artery. Occlusion of a single vessel rarely causes ischemic symptoms because of the extensive nature of visceral collateralization. However, occlusion or significant stenosis of any two vessels may compromise collateral flow sufficiently to give rise to chronic visceral ischemia. Operative repair of visceral artery stenosis is reserved for symptomatic patients. Operative interventions include transaortic endarterectomy and bypass grafts, which frequently require supraceliac aortic cross-clamping. Mortality rates for such procedures range from 7% to 18%. To avoid the high mortality associated with open repair, percutaneous transluminal angioplasty with stenting has increasingly been applied in patients with chronic visceral ischemia. Acute visceral artery occlusion can be caused by an embolus or, less commonly, by thrombosis. To avoid the extremely high mortality associated with acute visceral ischemia, diagnosis and surgical intervention must occur before gangrene of the bowel develops.

Aortic Cross-Clamping

The pathophysiology of aortic cross-clamping is complex and depends on many factors, including level of the cross-clamp, status of the left ventricle, degree of periaortic collateralization, blood volume and distribution, activation of the sympathetic nervous system, and anesthetic agents and techniques. Most abdominal aortic reconstructions require clamping at the infrarenal level. However, clamping at the suprarenal and supraceliac levels is required for suprarenal aneurysms and renal or visceral reconstructions and is frequently necessary for juxtarenal aneurysms, inflammatory aneurysms, and aortoiliac occlusive disease with proximal extension. These higher levels of aortic occlusion have a significant impact on the cardiovascular system, as well as on other vital organs rendered ischemic or hypoperfused. Ischemic complications may result in renal failure, hepatic ischemia and coagulopathy, bowel infarction, and paraplegia. As endovascular repair becomes more common, an increasing proportion of patients undergoing open repair will have anatomically complex aneurysms, many of which will require suprarenal cross-clamping.

Hemodynamic and Metabolic Changes

The hemodynamic and metabolic changes associated with aortic cross-clamping are summarized in Box 62-1. It is critically impor-

tant to understand that the magnitude as well as direction of these changes is complex and dynamic, not consistent across experimental and clinical studies, and highly dependent on a number of important factors (Box 62-2). The systemic cardiovascular consequences of aortic cross-clamping can be dramatic, depending primarily on the level at which the cross-clamp is applied. Arterial hypertension above the clamp and arterial hypotension below the clamp are the most consistent components of the hemodynamic response to aortic cross-clamping at any level. The increase in arterial blood pressure above the clamp is primarily due to the sudden increase in impedance to aortic blood flow and the resultant increase in systolic ventricular wall tension or afterload. However, factors such as myocardial contractility, preload, blood volume, and activation of the sympathetic nervous system may also be important.[97] Cross-clamping of the aorta at or above the diaphragm results in the most profound increases in arterial blood pressure unless diverting circulatory support or intravenous vasodilators are used.

Changes in cardiac output and filling pressure with aortic cross-clamping are not consistent and require an *integrated approach* in an attempt to understand the direction and magnitude of such changes (Fig. 62-5). Cross-clamping of the proximal descending thoracic aorta increases mean arterial, central venous, mean pulmonary arterial, and pulmonary capillary wedge pressure by 35%, 56%, 43%, and 90%, respectively, and decreases the cardiac index by 29%. Heart rate and left ventricular stroke work are not significantly changed. Supraceliac aortic cross-clamping increases mean arterial pressure by 54% and pulmonary capillary wedge pressure by 38%.[98] Ejection fraction, as determined by two-dimensional echocardiography, decreases by 38%. Despite normalization of systemic and pulmonary capillary wedge pressure with anesthetic agents and vasodilator therapy, supraceliac aortic cross-clamping causes significant increases in left ventricular end-systolic and end-diastolic area (69% and 28%, respectively), as well as wall motion abnormalities indicative of ischemia in 11 of 12 patients (Table 62-6). Aortic cross-clamping at the suprarenal level causes similar but smaller cardiovascular changes, and clamping at the infrarenal level is associated with only minimal changes and no wall motion abnormalities.

The marked increases in ventricular filling pressure (preload) reported with high aortic cross-clamping have been attributed to blood volume redistribution and increased afterload. The most substantial body of evidence supports the hypothesis of *blood volume redistribution* during thoracic aortic cross-clamping. The splanchnic circulation, an important source of functional blood volume reserve, is central to this hypothesis. The splanchnic organs contain nearly 25% of the total blood volume, nearly two thirds (>800 mL) of which can be autotransfused from the

Box 62-1 Physiologic Changes with Aortic Cross-Clamping* and Therapeutic Interventions

Hemodynamic Changes
↑ Arterial blood pressure above the clamp
↓ Arterial blood pressure below the clamp
↑ Segmental wall motion abnormalities
↑ Left ventricular wall tension
↓ Ejection fraction
↓ Cardiac output†
↓ Renal blood flow
↑ Pulmonary occlusion pressure
↑ Central venous pressure
↑ Coronary blood flow

Metabolic Changes
↓ Total-body oxygen consumption
↓ Total-body carbon dioxide production
↑ Mixed venous oxygen saturation
↓ Total-body oxygen extraction
↑ Epinephrine and norepinephrine
Respiratory alkalosis‡
Metabolic acidosis

Therapeutic Interventions
Afterload reduction
- Sodium nitroprusside
- Inhaled anesthetics
- Amrinone
- Shunts and aorta-to-femoral bypass

Preload reduction
- Nitroglycerin
- Controlled phlebotomy
- Atrial-to-femoral bypass

Renal protection
- Fluid administration
- Distal aortic perfusion techniques
- Selective renal artery perfusion
- Mannitol
- Drugs to augment renal perfusion

Other
- Hypothermia
- ↓ Minute ventilation
- Sodium bicarbonate

*These changes are of greater significance with longer duration of cross-clamping and with more proximal cross-clamping.
†Cardiac output may increase with thoracic cross-clamping.
‡When ventilatory settings are unchanged from preclamp levels.

Box 62-2 Factors That May Influence the Magnitude and Direction of Physiologic Changes Occurring with Aortic Cross-Clamping

Level of aortic cross-clamp
Species differences
Anesthetic agents and techniques
Use of vasodilator therapy
Use of diverting circulatory support
Degree of periaortic collateralization
Left ventricular function
Status of the coronary circulation
Volume status
Neuroendocrine activation
Duration of aortic cross-clamping
Body temperature

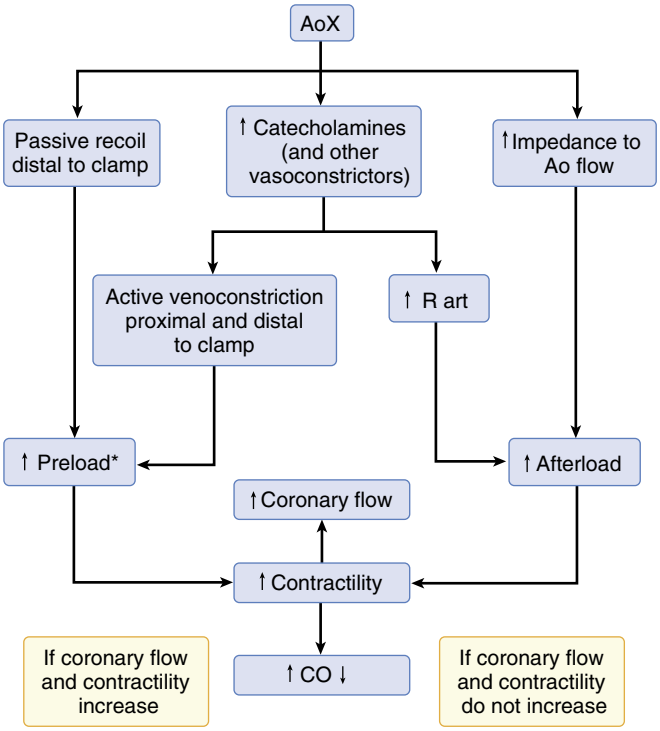


Figure 62-5 Systemic hemodynamic response to aortic cross-clamping. Preload (*asterisk*) does not necessarily increase with infrarenal clamping. Depending on splanchnic vascular tone, blood volume can be shifted into the splanchnic circulation, and preload will not increase. Ao, aortic; AoX, aortic cross-clamping; R art, arterial resistance. *(Adapted from Gelman S: The pathophysiology of aortic cross-clamping. Anesthesiology 82:1026-1060, 1995.)*

highly compliant venous vasculature into the systemic circulation within seconds.[99] Primarily because of lower splanchnic venous capacitance, blood volume is redistributed from vascular beds distal to the clamp to the relatively noncompliant vascular beds proximal to the clamp (Fig. 62-5). Both passive and active mechanisms lower splanchnic venous capacitance with thoracic aortic cross-clamping. Cross-clamping the aorta above the splanchnic system dramatically reduces splanchnic arterial flow, which produces a significant reduction in pressure within the splanchnic capacitance vessels.[77] This reduction in pressure allows the splanchnic veins to *passively* recoil and increase venous return to the heart and blood volume proximal to the clamp. Thoracic aortic cross-clamping also results in significant increases in plasma epinephrine and norepinephrine, which may enhance venomotor tone both above and below the clamp. The splanchnic veins are highly sensitive to adrenergic stimulation. The major effect of catecholamines on the splanchnic capacitance vessels is venoconstriction, which *actively* forces out splanchnic blood, reduces splanchnic venous capacitance, and increases venous return to the heart.[77]

Several animal studies that support the blood volume redistribution hypothesis merit mention. Cross-clamping the thoracic aorta in dogs results in marked increases in mean arterial pressure and end-diastolic left ventricular pressure (84% and

Table 62-6 Percent Change in Cardiovascular Variables on Initiation of Aortic Occlusion

	Percent Change Occlusion		
Cardiovascular Variable	*Supraceliac*	*Suprarenal-Infraceliac*	*Infrarenal*
Mean arterial blood pressure	54	5*	2*
Pulmonary capillary wedge pressure	38	10*	0*
End-diastolic area	28	2*	9*
End-systolic area	69	10*	11*
Ejection fraction	–38	–10*	–3*
Patients with wall motion abnormalities	92	33	0

*Statistically different ($p < 0.05$) from group undergoing supraceliac aortic occlusion.
From Roizen MF, Beaupre PN, Alpert RA, et al: Monitoring with two-dimensional transesophageal echocardiography. Comparison of myocardial function in patients undergoing supraceliac, suprarenal-infraceliac, or infrarenal aortic occlusion. J Vasc Surg 1:300-305, 1984.

188%, respectively) and no significant change in stroke volume. In this same experimental model, simultaneous cross-clamping of the thoracic aorta and the inferior vena cava resulted in no significant change in mean arterial pressure or preload (Fig. 62-6). Stroke volume was reduced by 74%. By transfusing blood (above the clamps) during this period of simultaneous clamping, the authors reproduced the hemodynamic effect of thoracic aortic cross-clamping alone. This study also demonstrated that thoracic aortic cross-clamping is associated with a significant and dramatic increase (155%) in blood flow above the level of the clamp whereas no change in blood flow occurred with simultaneous aortic and inferior vena cava clamping. In other animal models, the proximal aortic hypertension and increased central venous pressure occurring after thoracic aortic cross-clamping were completely reversed by phlebotomy.[100] Aortic cross-clamping at the thoracic and suprarenal levels in dogs both resulted in proximal aortic hypertension, but only occlusion at the thoracic level increased central venous pressure.[101] In this study, thoracic aortic occlusion increased blood volume in organs and tissues proximal to the clamp, whereas no such increase occurred with suprarenal aortic cross-clamping. These experimental data strongly support the hypothesis of blood volume redistribution during aortic cross-clamping and help explain the marked differences in hemodynamic responses observed after aortic cross-clamping at different levels.[98]

Afterload-dependent increases in preload also occur with aortic cross-clamping, usually in the setting of impaired myocardial contractility and reduced coronary reserve. The impaired left ventricle may respond to increased afterload with an increase in end-systolic volume and a concomitant reduction in stroke volume (afterload mismatch). The reduction in stroke volume may be due to limited preload reserve, myocardial ischemia, or inability of the heart to generate a pressure-induced increase in contractility (the Anrep effect). If right ventricular function remains normal, the preclamp right ventricular stroke volume added to the elevated left ventricular end-systolic volume results in left ventricular dilation and elevated end-diastolic volume. If corrective measures are not undertaken, overt left ventricular overload may result, with severe peripheral organ dysfunction and pulmonary edema.

Most clinical studies indicate that cardiac output decreases with thoracic aortic cross-clamping (without vasodilator therapy or diverting circulatory support), whereas most animal studies show no significant change or an increase in cardiac output. Although this inconsistency is complex and not easily reconciled, the status of the left ventricle probably plays a major role. Whereas a normal intact heart can withstand large increases in loading conditions without significant ventricular distention or dysfunction, an impaired heart with reduced myocardial contractility and coronary reserve may respond to such loading conditions with marked ventricular distention as a result of acute left ventricular dysfunction and myocardial ischemia. Although impaired myocardial contractility and reduced coronary reserve are rare in animal experiments, such disorders are frequent in the elderly population undergoing aortic reconstruction. The increase in ventricular loading conditions seen with thoracic and supraceliac cross-clamping in the clinical setting[98] may increase left ventricular wall stress (afterload), with resultant acute deterioration of left ventricular function and myocardial ischemia. Impaired subendocardial perfusion caused by high intramyocardial pressure may be the cause of wall motion abnormalities and changes in ejection fraction. Reflex mechanisms causing immediate feedback inhibition may also explain the reduction in cardiac output with aortic cross-clamping. For example, baroreceptor activation resulting from increased aortic pressure should depress the heart rate, contractility, and vascular tone. Thoracic aortic cross-clamping with

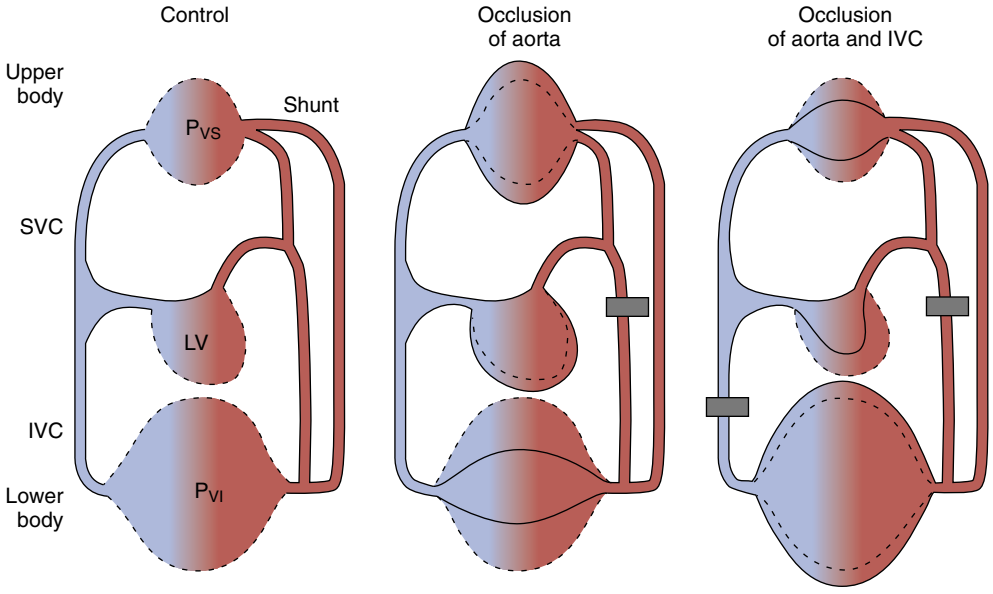


Figure 62-6 Schematic drawing of the circulation. Compliant regions (*dashed lines*) of the upper and lower part of the body and end-diastolic volumes of the left ventricle in the control state (*left panel*) are shown after occlusion of the aorta alone (*middle panel*) and combined occlusion of the aorta and inferior vena cava (*right panel*). IVC, inferior vena cava; LV, left ventricle; P_{VS} and P_{VI}, pressure in compliant regions of the upper and lower parts of the body, respectively; Shunt, physiologic shunt; SVC, superior vena cava. *(From Stokland O, Miller MM, Ilebekk A, Kiil F: Mechanism of hemodynamic responses to occlusion of the descending thoracic aorta. Am J Physiol 238:H423-H429, 1980.)*

the use of vasodilator therapy to normalize ventricular loading conditions maintains or increases cardiac output.[102,103]

The metabolic effects of aortic cross-clamping are summarized in Box 62-1. Cross-clamping of the thoracic aorta decreases total-body oxygen consumption by approximately 50%.[102,104] For reasons that are unclear, oxygen consumption decreases in tissues above the clamp.[104] In clinical studies, increased mixed venous oxygen saturation occurs with aortic cross-clamping above the celiac axis.[105,106] This increase in mixed venous oxygen saturation may be explained by a reduction in oxygen consumption that exceeds the reduction in cardiac output, thus decreasing total-body oxygen extraction.[106] Central hypervolemia and increased arteriovenous shunting in tissues proximal to the aortic clamp may play a role in reducing total-body oxygen extraction.

Arterial blood pressure, blood flow, and oxygen consumption distal to a thoracic aortic cross-clamp decrease by 78% to 88%,[107] 79% to 88%,[104] and 62%,[104] respectively, from baseline values before clamping. Blood flow through tissues and organs below the level of aortic occlusion is dependent on perfusion pressure and is independent of cardiac output. Administration of sodium nitroprusside to maintain proximal aortic pressure above the cross-clamp at preclamp levels has been shown to further reduce arterial pressure distal to the clamp by 53%. As discussed later, these data have significant implications regarding vital organ protection during aortic cross-clamping.

The cardiovascular response to infrarenal aortic cross-clamping is less significant than with high aortic cross-clamping (see Table 62-6). Although several clinical reports have noted no significant hemodynamic response to infrarenal cross-clamping,[108] the hemodynamic response generally consists of increases in arterial pressure (7% to 10%) and systemic vascular resistance (20% to 32%) with no significant change in heart rate. Cardiac output is most consistently decreased by 9% to 33%.[108,109] Reported changes in ventricular filling pressure have been inconsistent.[98,108,109] Blood volume redistribution may affect preload with infrarenal aortic cross-clamping (see Fig. 62-5). In this situation, blood volume below the clamp shifts to the compliant venous segments of the splanchnic circulation above the clamp, thereby dampening the expected increase in preload. The preload changes with infrarenal aortic cross-clamping may also be dependent on the status of the coronary circulation. An early report found that patients with severe ischemic heart disease responded to infrarenal aortic cross-clamping with significantly increased central venous (35%) and pulmonary capillary (50%) pressure whereas patients without CAD had decreased filling pressure. Echocardiographically detected segmental wall motion abnormalities occur in up to 30% of patients during infrarenal aortic reconstruction,[110] with 66% occurring at the time of aortic cross-clamping.[110,111] Clinical studies imply that patients with aortoiliac occlusive disease have less hemodynamic response to infrarenal aortic cross-clamping than do patients with abdominal aortic aneurysmal disease,[112] perhaps as a result of more extensive periaortic collateral vascularization.[113]

Renal Function and Protection

Preservation of renal function is of significant importance during aortic reconstructive surgery. Acute renal failure occurs in approximately 3% of patients undergoing elective infrarenal aortic reconstruction, and mortality resulting from postoperative acute renal failure is greater than 40%.[97] Despite significant improvements in the perioperative care of patients undergoing aortic reconstruction, the high morbidity and mortality resulting from acute renal failure are largely unchanged over the last several decades. Much of the morbidity associated with significant postoperative renal dysfunction is *nonrenal* in nature.

Although urine output is closely monitored and often augmented during aortic surgery, intraoperative urine output does not predict postoperative renal function.[114,115] Thus, adequacy of renal perfusion cannot be assumed by urine output. Procedures requiring aortic cross-clamping above the renal arteries dramatically reduce renal blood flow. Experimental studies report an 83% to 90% reduction in renal blood flow during thoracic aortic cross-clamping. Infrarenal aortic cross-clamping in humans is associated with a 75% increase in renal vascular resistance, a 38% decrease in renal blood flow, and a redistribution of intrarenal blood flow toward the renal cortex.[108] These rather profound alterations in renal hemodynamics occurred despite no significant change in systemic hemodynamics, and they persisted after unclamping. The sustained deterioration in renal perfusion and function during and after infrarenal aortic cross-clamping has been attributed to renal vasoconstriction, but the specific pathophysiology remains unknown.[108] Renal sympathetic blockade with epidural anesthesia to a T6 level does not prevent or modify the severe impairment in renal perfusion and function that occurs during and after infrarenal aortic cross-clamping. Although plasma renin activity is increased during aortic cross-clamping,[116] pretreatment with converting enzyme inhibitors before infrarenal aortic cross-clamping does not attenuate the decreased renal blood flow and glomerular filtration rate. Other mediators, such as plasma endothelin, myoglobin, and prostaglandins, may contribute to the decreased renal perfusion and function after aortic cross-clamping.

Acute tubular necrosis accounts for nearly all the renal dysfunction and failure after aortic reconstruction. The degree of preoperative renal insufficiency remains the strongest predictor of postoperative renal dysfunction. In addition to aortic cross-clamping–induced reductions in renal blood flow, ischemic reperfusion injury, intravascular volume depletion, embolization of atherosclerotic debris to the kidneys, and surgical trauma to the renal arteries all contribute to renal dysfunction.

Mannitol, loop diuretics, and dopamine are used clinically in an attempt to preserve renal function during aortic surgery. Significant controversy exists regarding the use of these agents, as well as the mechanisms by which they may offer a protective effect. Despite studies demonstrating little or no benefit,[117-119] it is widely believed that renal protection before aortic cross-clamping is beneficial, and therefore many clinicians administer these drugs. The use of mannitol to induce osmotic diuresis before aortic cross-clamping is ubiquitous in clinical practice. Mannitol improves renal cortical blood flow during infrarenal aortic cross-clamping and reduces ischemia-induced renal vascular endothelial cell edema and vascular congestion. Other mechanisms by which mannitol may be beneficial include acting as a scavenger of free radicals, decreasing renin secretion, and increasing renal prostaglandin synthesis.[120]

Loop diuretics and low-dose dopamine (1 to 3 μg/kg/min) have been advocated to protect the kidneys from aortic cross-clamp–induced injury by increasing renal blood flow and urine output intraoperatively. Some clinicians advocate the routine use of these agents for patients with preoperative renal insufficiency and for procedures requiring suprarenal aortic cross-clamping. Intraoperative use of these agents requires increased surveillance of intravascular volume and electrolytes during the postoperative period. Therapy with these agents could actually be harmful

because of hypovolemia and resultant renal hypoperfusion. In addition, dopamine's positive inotropic and chronotropic activity may cause tachycardia and increase myocardial oxygen consumption in patients with limited coronary reserve. Although I have virtually abandoned the prophylactic use of dopamine, I often administer diuretics to patients with low urine output after aortic unclamping, particularly those maintained on chronic diuretic therapy.

Fenoldopam mesylate, a selective dopamine type 1 agonist that preferentially dilates the renal and splanchnic vascular beds, has shown some early promise as a renoprotective drug.[121,122] However, its role in the prevention of renal dysfunction after aortic surgery is not known.[123] Statin use is associated with preserved renal function after aortic surgery requiring suprarenal aortic cross-clamping.[124] Remote ischemic preconditioning reduces the incidence of renal impairment after open aortic surgery.[125]

Optimal systemic hemodynamics, including maintenance of intravascular volume, is the most effective means of renal protection during and after aortic cross-clamping.[126,127] The goal is to achieve a preload adequate to allow the left ventricle to cope with cross-clamping–induced changes in contractility and afterload while maintaining cardiac output. However, in providing such therapy, excessive intravascular volume should be avoided, which may lead to inappropriate increases in preload or pulmonary edema in patients with decreased myocardial reserve.

Therapeutic Strategies

Patients with preexisting impaired ventricular function and reduced coronary reserve are most vulnerable to the stress imposed on the cardiovascular system by aortic cross-clamping. Rational therapeutic strategies to prevent the deleterious effect of aortic cross-clamping primarily include measures to reduce afterload, normalize preload, and maintain cardiac output. Vasodilators, positive and negative inotropes, and controlled volume depletion (i.e., phlebotomy) may be used selectively.

Patients with impaired ventricular function requiring supraceliac aortic cross-clamping are the most challenging. Myocardial ischemia, reflecting an unfavorable balance between myocardial oxygen supply and demand, may result from the hemodynamic consequences of aortic cross-clamping. Controlled (i.e., slow clamp application) supraceliac aortic cross-clamping is important to avoid abrupt and extreme stress on the heart. Both afterload and preload reduction is often required. Afterload reduction, most commonly accomplished with the use of sodium nitroprusside (predominantly an arteriolar dilator), is necessary to "unload" the heart and reduce ventricular wall tension. In a large series of patients requiring cross-clamping of the descending thoracic aorta, stable left ventricular function was maintained with sodium nitroprusside during cross-clamping. Sodium nitroprusside allowed adequate intravascular volume before unclamping, which resulted in stable unclamping hemodynamics, although isoflurane can provide hemodynamics comparable to that provided by sodium nitroprusside during thoracic aortic cross-clamping,[102] Though not widely used, amrinone provides hemodynamic control equivalent to that of sodium nitroprusside during abdominal aortic surgery.[128] A normal preload is equally important and involves careful fluid titration and vasodilator administration. Nitroglycerin is commonly used in this setting because it increases venous capacity to a greater extent than sodium nitroprusside does. Infusion of nitroglycerin during abdominal aortic surgery maintains ventricular function during the cross-clamp period.

In patients without evidence of left ventricular decompensation or myocardial ischemia during supraceliac aortic cross-clamping, a proximal aortic mean arterial pressure of up to 120 mm Hg may be acceptable. The surgeon may request lower proximal arterial pressure if friable aortic tissue is encountered. Blood flow below the aortic clamp is dependent on pressure and decreases further during therapy with vasodilators.[104] In this setting, vital organs and tissues distal to the clamp are exposed to reduced perfusion pressure and blood flow. Though infrequent, maintenance of adequate cardiac output may require active intervention with inotropic agents. In general, anesthetic agents that significantly depress myocardial function are avoided during aortic procedures.

Aortic Unclamping

The hemodynamic and metabolic effects of aortic unclamping are listed in Box 62-3. The hemodynamic response to unclamping depends on a number of factors, including the level of aortic occlusion, total occlusion time, the use of diverting support, and intravascular volume. Hypotension, the most consistent hemodynamic response to aortic unclamping, can be profound, particularly after removal of a supraceliac cross-clamp (Fig. 62-7). Reactive hyperemia in tissues and organs distal to the clamp and

Box 62-3 Physiologic Changes with Aortic Unclamping* and Therapeutic Interventions

Hemodynamic Changes
↓ Myocardial contractility
↓ Arterial blood pressure
↑ Pulmonary artery pressure
↓ Central venous pressure
↓ Venous return
↓ Cardiac output

Metabolic Changes
↑ Total-body oxygen consumption
↑ Lactate
↓ Mixed venous oxygen saturation
↑ Prostaglandins
↑ Activated complement
↑ Myocardial depressant factor(s)
↓ Temperature
Metabolic acidosis

Therapeutic Interventions
↓ Inhaled anesthetics
↓ Vasodilators
↑ Fluid administration
↑ Vasoconstrictor drugs
Reapply cross-clamp for severe hypotension
Consider mannitol
Consider sodium bicarbonate

*These changes are of greater significance with longer duration of cross-clamping and with more proximal cross-clamping.

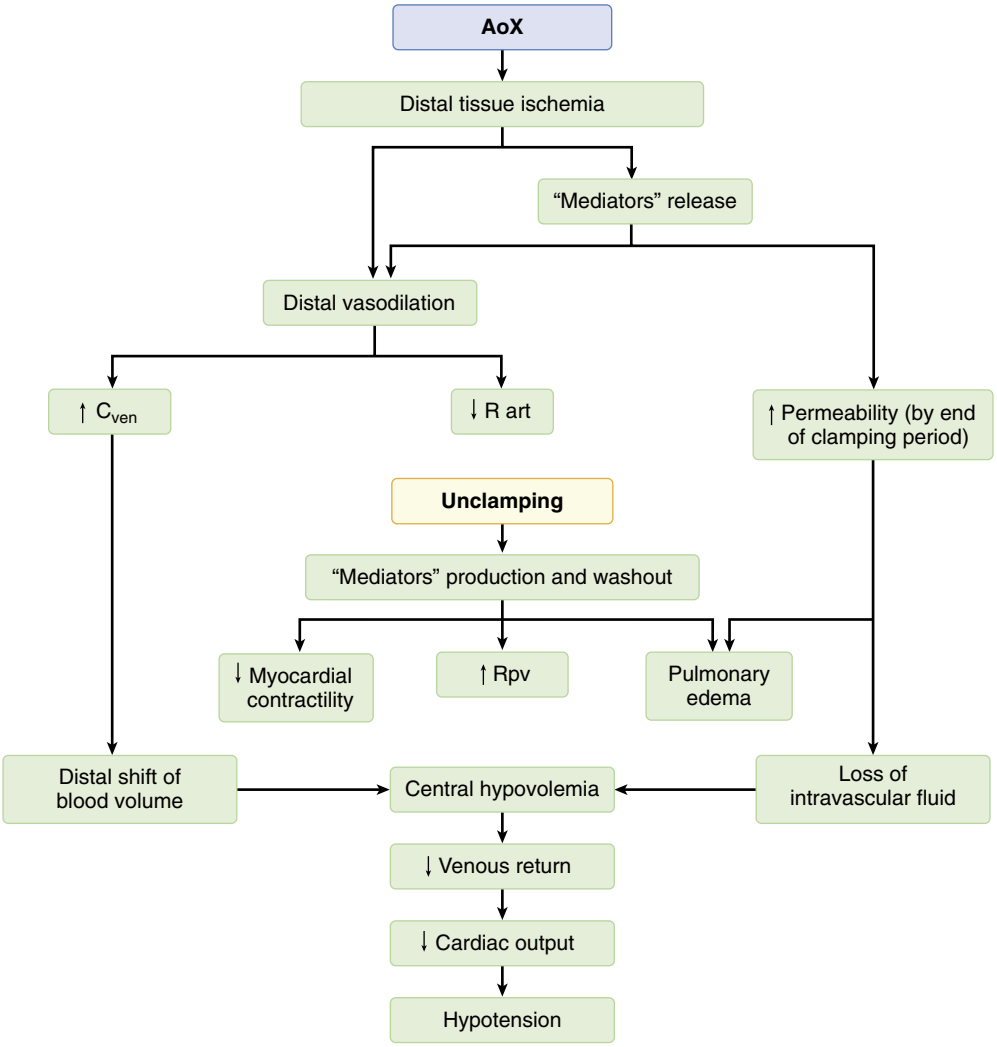


Figure 62-7 Systemic hemodynamic response to aortic unclamping. AoX, aortic cross-clamping; C_{ven}, venous capacitance; R art, arterial resistance; Rpv, pulmonary vascular resistance. *(From Gelman S: The pathophysiology of aortic cross-clamping and unclamping. Anesthesiology 82:1026-1060, 1995.)*

the resultant relative central hypovolemia are the dominant mechanisms of the hypotension. Washout of vasoactive and cardiodepressant mediators from ischemic tissues, as well as humoral factors, may also contribute to the hemodynamic responses after unclamping the aorta. These humoral factors and mediators, which may also play a role in organ dysfunction after aortic occlusion, include lactic acid, renin-angiotensin, oxygen free radicals, prostaglandins, neutrophils, activated complement, cytokines, and myocardial-depressant factors.[97]

Avoidance of significant hypotension with unclamping requires close communication with the surgical team, awareness of the technical aspect of the surgical procedure, and appropriate administration of fluids and vasoactive agents. It is essential that preoperative fluid deficits, intraoperative maintenance requirements, and replacement of blood loss be accomplished before unclamping. Vasodilators, if used, should be gradually reduced and discontinued before unclamping. Potent inhaled agents should be decreased. Moderate intravascular volume loading (approximately 500 mL) during the immediate prerelease period is indicated for infrarenal unclamping. More aggressive intravascular fluid administration is required in the period immediately preceding supraceliac unclamping. Maintaining increased central venous or pulmonary capillary wedge pressure *during* the cross-clamp period is not indicated and may result in significant overtransfusion of fluids and blood products. Gradual release of the aortic clamp and reapplication or digital compression if significant hypotension results are important measures in maintaining hemodynamic stability during unclamping. Although vasopressor requirements are minimal after release of the infrarenal clamp, significant support is often needed after the removal of supraceliac clamps. Caution must be observed when vasopressor support is used in this setting because profound proximal hypertension may occur if reapplication of the cross-clamp is required above the celiac axis. In addition, hypertension should be avoided to prevent damage to or bleeding from the vascular anastomoses.

Anesthetic Management

Intraoperative Monitoring

The potential for significant and rapid blood loss cannot be underestimated. I most commonly use one 8.5 Fr internal jugular

catheter and one or two large-bore peripheral catheters. A hemostatic valve with a side port is placed on the 8.5-Fr catheter to accept either a central venous or a pulmonary artery catheter. Placement of an arterial catheter should be routine in all patients undergoing aortic reconstruction. As with other vascular procedures, the radial artery is most commonly selected for cannulation because of its superficial location, easy accessibility, and low complication rate. A noninvasive blood pressure cuff should be placed on the arm contralateral to the arterial catheter in the event of catheter malfunction.

A central venous catheter should be used for all open aortic procedures. It allows monitoring of central venous pressure and administration of drugs directly into the central circulation. The routine, nonselective use of pulmonary artery catheter monitoring is not recommended for patients undergoing infrarenal abdominal aortic reconstruction.[129,130] For these procedures, pulmonary artery catheters should be considered for patients with significant left ventricular dysfunction (ejection fraction <30%), a history of congestive heart failure, significant renal impairment (preoperative creatinine >2.0 mg/dL), or cor pulmonale. In patients with good left ventricular and pulmonary function, central venous pressure correlates well with left ventricular filling pressure.[131] I routinely insert a pulmonary artery catheter for all patients requiring supraceliac aortic cross-clamping. The invasive monitoring catheters can be placed before or after induction of general anesthesia. The advantage of preinduction catheter placement is assessment of the patient's awake (i.e., baseline) cardiovascular status, which allows correction of severe abnormalities in cardiac filling and function before induction.

With selective use, accurate interpretation of data, and rational treatment strategies, pulmonary artery catheter monitoring may be beneficial in high-risk patients undergoing complex aortic reconstruction. However, the clinical value of pulmonary artery catheter monitoring in high-risk patients has not been established. Clinical studies over the last 2 decades have yielded quite conflicting results. Some studies have reported a decrease in mortality, some no effect,[132,133] and others an increase in mortality.[134] Consensus statements have been published,[135,136] most recently by the National Heart, Lung and Blood Institute and the Food and Drug Administration (FDA).[136] A large prospective, randomized trial compared goal-directed therapy guided by a pulmonary artery catheter with standard care without the use of a pulmonary artery catheter in high-risk surgical patients and reported no benefit of treatment guided by a pulmonary artery catheter.[137] This study did not find an increase in mortality with insertion and use of a pulmonary artery catheter.

Two-dimensional TEE has been used intraoperatively to assess global ventricular function, guide fluid therapy, and monitor for myocardial ischemia. Continuous monitoring of ventricular function is commonly obtained with a single short-axis view at the level of the midpapillary muscle. Using this same view, visualization of the left ventricle at end-diastole allows rapid assessment of ventricular filling (preload). Ejection fraction area can be calculated by use of the left ventricular end-diastolic and end-systolic area. In patients undergoing abdominal aortic reconstruction, echocardiographic short-axis left ventricular end-diastolic area, end-systolic area, and ejection fraction area correlate closely with changes in corresponding left ventricular volume and ejection fraction obtained by radionuclide angiography.[138,139] Patients requiring supraceliac aortic cross-clamping have significant increases in end-diastolic area and significant decreases in ejection fraction on echocardiography that are not completely normalized with vasodilators and frequently are not detected by pulmonary artery catheter monitoring.[98]

TEE can also reveal abnormalities in left ventricular wall motion and wall thickening. The relationship between these abnormalities and coronary perfusion has been established experimentally and clinically,[140] and such abnormalities may precede ECG evidence of ischemia.[141] The short-axis view at the level of the midpapillary muscles allows assessment of all three major coronary distributions. TEE-detected segmental wall motion abnormalities may occur in up to 37% of patients during infrarenal aortic reconstruction[142] and in more than 90% of patients requiring supraceliac aortic cross-clamping.[98,110] The natural history of echocardiographic segmental wall motion abnormalities was studied in 156 patients undergoing noncardiac surgery who were at risk for cardiac morbidity.[142] The 24 patients undergoing aortic surgery had the highest incidence of new segmental wall motion abnormalities (38%). Surprisingly, the incidence of new segmental wall motion abnormalities did not differ in patients with known CAD and those with cardiac risk factors only. Ischemic episodes detected by TEE correlated poorly with postoperative cardiac complications. The authors also reported a discordant relationship between new segmental wall motion abnormalities and ischemic changes on the ECG. In a subsequent report, a subset of 285 patients who were at high risk for cardiac complications and were undergoing noncardiac surgery were studied with continuous intraoperative use of a two-lead ECG, 12-lead ECG, and TEE for the detection of ischemia.[143] A lack of concordance was found between the three different ischemia monitors. When compared with preoperative clinical data and intraoperative monitoring in which a two-lead ECG was used, routine monitoring for myocardial ischemia with TEE or a 12-lead ECG during noncardiac surgery had little incremental clinical value in identifying patients at high risk for perioperative ischemic outcomes. Thus, the sensitivity and specificity of segmental wall motion abnormalities cannot be used as a marker for myocardial ischemia or as a predictor of perioperative ischemic outcomes.

The optimal intraoperative monitoring techniques for patients undergoing abdominal aortic reconstruction have not been established. Existing clinical studies offer insufficient data to conclusively answer the question of whether pulmonary artery catheter or TEE monitoring improves outcome. The clinical usefulness of any monitoring technique ultimately depends on patient selection, accurate interpretation of data, and appropriate therapeutic intervention.

Autologous Blood Procurement

Elective abdominal aortic reconstruction may result in substantial blood loss and warrants the routine crossmatching of 4 to 6 units of packed red blood cells. Suprarenal aneurysms and other more complex aortic reconstructions often demand even greater allogeneic blood availability. Over the last 2 decades, concerns regarding the safety, availability, and acceptability of allogeneic blood have led to greater use of autologous blood procurement (see Chapters 55 and 57). Preoperative autologous donation, intraoperative cell salvage, and acute normovolemic hemodilution have all been used during aortic surgery to reduce or eliminate exposure to allogeneic blood and the associated risks of transfusion-related complications.

Intraoperative cell salvage is the most widely used technique and in some centers is considered routine. The equipment is expensive and requires significant training and expertise. An early, nonrandomized study reported a 75% reduction in the number of allogeneic red cell units transfused during elective aortic surgery with the use of cell salvage.[144] Later randomized studies have reported conflicting results.[145,146] The routine use of cell salvage during aortic surgery may not be cost-effective ($250 to $350 per case), and thus it may best be reserved for a select group of patients with high expected blood loss.[147] The equivalent of at least 2 units of washed blood needs to be recovered for this technique to be cost-effective.[148] A cost-effective option is to use the cell salvage reservoir for blood collection and activate the full salvage process only if large blood loss occurs.

Acute normovolemic hemodilution is often used in conjunction with intraoperative cell salvage during aortic surgery. Two randomized studies reported that the combined use of hemodilution and cell salvage reduced the allogeneic blood requirement in patients undergoing aortic surgery.[149,150] As with cell salvage alone, this benefit is probably greater with procedures involving higher blood loss. Another randomized study found that the combined use of the two techniques during aortic surgery was cost neutral in comparison to standard allogeneic transfusion.[151] Hemodilution does not worsen myocardial ischemia and may improve hemodynamic tolerance to aortic cross-clamping in patient with CAD.[152]

Anesthetic Drugs and Techniques

A variety of anesthetic techniques, including general anesthesia, regional (epidural) anesthesia, and combined techniques, have been used successfully for abdominal aortic reconstruction. Combined techniques most commonly use a lumbar or low thoracic epidural catheter in addition to a "light" general anesthetic. Local anesthetics, opioids, or more commonly, a combination of the two may be administered by bolus or continuous epidural infusion. Evidence suggests that maintenance of vital organ perfusion and function by the provision of stable perioperative hemodynamics is more important to overall outcome than the choice of anesthetic agent or technique is.[33] Therefore, the specific anesthetic technique for patients undergoing abdominal aortic reconstruction is important insofar as it allows rapid and precise control of hemodynamic parameters. Given the high incidence of cardiac morbidity and mortality in patients undergoing aortic reconstruction, special emphasis must be placed on factors that influence ventricular work and myocardial perfusion.

Induction of general anesthesia should proceed in a controlled fashion such that stable hemodynamics is maintained during loss of consciousness, laryngoscopy and intubation, and the immediate postinduction period. A variety of intravenous anesthetics (thiopental, etomidate, propofol) are suitable. The addition of a short-acting, potent opioid such as fentanyl (3 to 5 μg/kg) usually provides stable hemodynamics during and after induction. Volatile anesthetics may be administered in low concentration before intubation during assisted ventilation as an adjunct to blunt the hyperdynamic response to laryngoscopy and endotracheal intubation. Esmolol (10 to 25 mg), sodium nitroprusside (5 to 25 μg), nitroglycerin (50 to 100 μg), and phenylephrine (50 to 100 μg) should be available for bolus administration during induction if needed to maintain appropriate hemodynamics.

Maintenance of anesthesia may be accomplished with a combination of a potent opioid (fentanyl or sufentanil) and an inhaled anesthetic (sevoflurane, desflurane, or isoflurane) (i.e., balanced anesthesia). Patients with severe left ventricular dysfunction may benefit from a pure opioid technique, but a balanced anesthetic technique allows the clinician to take advantage of the most desirable characteristics of potent opioids and inhaled agents while minimizing their undesirable side effects.

Nitrous oxide can be used to supplement either an opioid or an inhaled anesthetic. In general, nitrous oxide decreases cardiac output and arterial pressure while increasing systemic vascular resistance.

Various regional anesthetic and analgesic techniques have been used effectively during and after aortic reconstruction. Does the use of regional anesthetic and analgesic techniques reduce the incidence of perioperative morbidity in patients undergoing aortic reconstruction? The benefits of combined general-epidural anesthesia intraoperatively, with or without epidural analgesia continued into the postoperative period, remain controversial.[32,33,153-156] Moreover, if outcome is improved, are the benefits from the intraoperative anesthetic technique or the postoperative pain regimen, or both, contributors? In a randomized trial using epidural morphine in patients undergoing aortic surgery, Breslow and associates[157] found attenuation of the adrenergic response and a lower incidence of hypertension in the postoperative period. A large randomized trial reported no reduction in nonsurgical complications with the use of intrathecal opioid.[34] The effects of the anesthetic or analgesic technique on the incidence of perioperative myocardial ischemia have received considerable attention. Four randomized trials, with nearly 450 combined patients undergoing aortic reconstruction, failed to demonstrate a reduction in the incidence of perioperative,[33,158] intraoperative,[111] or postoperative[155] myocardial ischemia when epidural techniques were used. Additionally, randomized trials have not demonstrated a reduction in the incidence of cardiovascular, pulmonary, or renal complications after aortic surgery with the use of epidural techniques.[32,33,66,154,155]

The duration and intensity of postoperative care after aortic surgery are critically dependent on the physiologic derangements incurred during the perioperative period (i.e., depression of consciousness, hypothermia, fluid overload, incisional pain, ileus, and respiratory depression), as well as on the development of certain less common, but more severe postoperative complications (i.e., MI, pneumonia, sepsis, renal failure, and decreased tissue perfusion). Length of hospital stay may therefore be considered the outcome variable most directly proportional to an integrated final negative effect of all significant perioperative morbidity (excluding in-hospital death) and the variable most likely to be altered by the anesthetic or analgesic technique. Randomized trials have not demonstrated any reduction in length of hospital stay after aortic surgery with the use of regional techniques.[32-34,66,154,155] Norris and colleagues reported the results of a randomized clinical trial comparing alternative combinations of intraoperative anesthesia (i.e., general or combined epidural-general) and postoperative analgesia (i.e., intravenous patient-controlled analgesia or epidural patient-controlled analgesia) with respect to length of stay after abdominal aortic surgery.[33] Two unique features of the trial included a factorial design (Fig. 62-8), which allowed the inclusion of all four combinations of intraoperative anesthesia and postoperative analgesia and the ability to separate the influence of time period and technique, and a double-blind design, which helped eliminate investigator and treating physician bias. The study rigorously protocolized perioperative management, standardized postoperative surgical care,

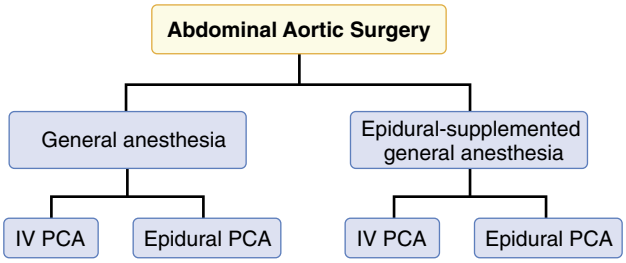


Figure 62-8 Outline of factorial study design. This design allows the inclusion of all four possible combinations of intraoperative anesthesia and postoperative analgesia and the ability to separate the influences of time period and technique. Data analysis by treatment group, intraoperative treatment, postoperative treatment, and any epidural activation, as well as simultaneous consideration of both intraoperative and postoperative treatment in the same model (factorial analysis), is possible and allows improvement in outcome to be attributed to intraoperative anesthesia, postoperative analgesia, the combination of the two, or unrelated factors. PCA, patient-controlled analgesia. *(From Norris EJ, Beattie C, Perler B, et al: Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery. Anesthesiology 95:1054-1067, 2001.)*

and optimized postoperative pain management. Although the overall length of stay was much shorter (median, 7.0 days) than that reported in other studies,[32,66,154,155] we were not able to demonstrate a reduction in length of stay or direct medical costs based on anesthetic or analgesic technique (Table 62-7). The overall incidence of postoperative complications in the trial was low and not different based on anesthetic or analgesic technique. Postoperative pain was well controlled overall, with similar pain scores in both analgesic treatment groups. Thus, if perioperative care and pain relief are optimized, epidural anesthetic and analgesic techniques for aortic surgery offer no major advantage or disadvantage over general anesthesia and intravenous patient-controlled analgesia.

Clinical studies have identified several disadvantages in the use of epidural local anesthetics in combination with general anesthesia during aortic reconstruction, including hypotension at the time of aortic unclamping and increased intravascular fluid and vasopressor requirements. Supraceliac aortic cross-clamping may significantly exaggerate these disadvantages, and as a result, some clinicians avoid epidural local anesthetics for such procedures. Epidural opioids without local anesthetics can be used for procedures requiring supraceliac aortic cross-clamping. Epidural local anesthetic can be given later, after aortic unclamping, when hemodynamics and intravascular volume have stabilized. For low thoracic or high lumbar epidural catheters, the initial bolus should be limited to 6 to 8 mL of local anesthetic. Additional local anesthetic is administered by continuous infusion at 4 to 6 mL/hr with adjustments based on hemodynamics and inhaled anesthetic requirements during surgery. Although elective aortic reconstruction via the retroperitoneal approach using straight epidural anesthesia (no general anesthetic) has been reported,[159,160] this technique is not recommended for routine use.

Emergence from anesthesia should be conducted after restoration of circulation and establishment of adequate organ perfusion. Hemodynamic, metabolic, and temperature homeostasis must be achieved before skin closure; otherwise, patients are transported to the intensive care unit (ICU) with their trachea intubated and their ventilation controlled. Extubation of the trachea is not generally attempted in patients with supraceliac aortic cross-clamp times longer than 30 minutes, patients with poor baseline pulmonary function, or patients requiring large volumes of blood or crystalloid during surgery. At the start of skin closure, inhaled anesthetics are discontinued, nitrous oxide is increased to 70%, and any residual neuromuscular blockade is reversed. A large nasal airway can be inserted after induction but before systemic heparinization in all patients for whom extubation is planned in the operating room. Hypertension and tachycardia are aggressively controlled during emergence by the use of short-acting agents such as esmolol, nitroglycerin, and sodium nitroprusside. Patients are placed in a recumbent, head-up posi-

Table 62-7 Duration of Hospital Stay and Direct Medical Costs by Randomized Treatment Assignment for Patients Surviving to Discharge after Abdominal Aortic Surgery

	GA-IVPCA	RSGA-IVPCA	GA-EPCA	RSGA-EPCA	Total	*P* Value
No. of patients	35	36	36	44	151	
Duration of hospital stay (days)*	7.0 (2.2)	8.0 (2.8)	7.0 (2.0)	7.0 (2.8)	7.0 (2.2)	0.833†
Range	4-43	5-28	5-20	5-18	4-43	
95% CI	7.0-13.3	7.4-10.2	6.9-8.8	7.6-9.6	7.9-9.7	
Direct medical costs (1997 dollars)*						
Inpatient	12,413 (2867)	13,786 (4413)	12,492 (3111)	13,767 (3900)	12,793 (3777)	0.242
Physician	10,394 (5993)	10,288 (4538)	9,609 (3866)	9,790 (3567)	9,934 (4072)	0.459
Total	22,674 (8783)	23,001 (6079)	22,182 (3914)	22,727 (3961)	22,674 (4903)	0.851

*Values are medians ($SD_{resistant}$).
†No significant difference in length of stay was observed between intraoperative treatment groups (GA versus RSGA; $P = .416$), postoperative treatment groups (IVPCA versus EPCA; $P = .673$), epidural activation (GA-IVPCA versus RSGA-IVPCA, RSGA-EPCA, and GA-EPCA; $P = .854$), or factorial analysis ($P = .648$).
CI, confidence interval; GA-IVPCA, general anesthesia and intravenous patient-controlled analgesia; RSGA-IVPCA, regional-supplemented general anesthesia and intravenous patient-controlled analgesia; GA-EPCA, general anesthesia and epidural patient-controlled analgesia; RSGA-EPCA, regional-supplemented general anesthesia and epidural patient-controlled analgesia.
From Norris EJ, Beattie C, Perler B, et al: Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery. Anesthesiology 95:1054-1067, 2001.

tion, and nitrous oxide is discontinued. If spontaneous ventilation is adequate, the trachea is extubated. Some centers advocate extubation of all patients in the ICU after a period of stability has been established. In these cases, mild sedation with a benzodiazepine such as midazolam is appropriate.

Temperature Control

Postoperative hypothermia is associated with many undesirable physiologic effects[161-163] and may contribute to adverse outcomes (see Chapter 48).[164-167] Normothermia should be maintained before skin incision by increasing ambient temperature in the operating room, applying warm cotton blankets, and warming intravenous fluids. If significant hypothermia occurs early in the procedure, normothermia is extremely difficult to achieve, and emergence and tracheal extubation may be delayed. During surgery, all fluids and blood products should be warmed before administration. A forced-air warming blanket should be applied over the upper part of the body. The lower part of the body should not be warmed because doing so can increase injury to ischemic tissue distal to the cross-clamp by increasing metabolic demands.

Thoracoabdominal Aortic Surgery

Open repair of the thoracoabdominal aorta is widely regarded as the most challenging surgical procedure in terms of overall anesthetic and perioperative management. Surgical repair is required for a spectrum of disease, including degenerative aneurysm, acute and chronic dissection, intramural hematoma, mycotic aneurysm, pseudoaneurysm, penetrating aortic ulcer, coarctation, and traumatic aortic tear. Since the first thoracoabdominal aortic aneurysm (TAA) repair in 1955, tremendous advances have been made in the field. These advances have led to significant reductions in operative mortality and perioperative complications. However, even in centers where numerous procedures are performed, morbidity and mortality are high, especially in patients with dissecting or ruptured aneurysms. To successfully care for these patients, the anesthesiologist must be knowledgeable in the areas of one-lung ventilation; extracorporeal circulatory support, including circulatory arrest; renal and spinal cord protection; induced hypothermia; invasive hemodynamic monitoring, including TEE; massive transfusion; and management of coagulopathy. Intraoperative management requires a team effort with intimate cooperation between surgeons, anesthesiologists, perfusionists, nurses, and electrophysiologic monitoring staff. Endovascular stent-graft repair of lesions that affect the descending thoracic and thoracoabdominal aorta is evolving rapidly. As discussed later, accumulating experience with stent-graft repair of thoracic aortic aneurysm, dissection, and traumatic tear has demonstrated this modality to be an effective alternative to open repair for select patients.

Etiology and Classification

Aneurysms of the thoracoabdominal aorta occur primarily because of atherosclerotic degenerative disease (80%) and chronic aortic dissection (17%).[168] The remainder are caused by either trauma or connective tissue diseases involving the aortic wall from conditions such as Marfan's syndrome, cystic medial degeneration, Takayasu's arteritis, or syphilitic aortitis.[169] The true incidence of TAA is unknown, but population studies suggest a prevalence much less than that of infrarenal abdominal aortic aneurysm. Degenerative and dissecting TAAs differ in their associated risk factors, extent of aortic involvement, and natural history.[170,171] Thus, complete characterization of each TAA is required to formulate a comprehensive treatment plan. Development of both degenerative and dissecting TAAs is ultimately related to weakening of the aortic wall. Although the natural history of TAA without surgery is uncertain, enlargement tends to be progressive and nonoperative management is generally associated with a poor prognosis. With progressive enlargement, nutritional blood flow to the aorta is compromised. The increasing diameter is associated with increased wall tension, even when arterial pressure is constant (law of Laplace). The high incidence of associated systemic hypertension enhances aneurysm enlargement.

Degenerative and dissecting TAAs are symptomatic at initial evaluation in 57% and 85% of patients, respectively.[170,171] The most common initial complaint is back pain. Additional symptoms can be caused by compression of organs or structures adjacent to the aneurysm. Aortic rupture, as a manifestation of TAA, occurs with equal frequency (9%) in both degenerative and dissecting aneurysms.[170,171] Rupture of the thoracic and abdominal segments occurs with equal frequency and primarily in patients with aneurysms larger than 5 cm. Surgical repair is usually recommended when aneurysm diameter exceeds 6 cm,[172] but earlier repair may be offered to patients with Marfan's syndrome and those with a strong family history of an aortic aneurysm.

In addition to cause, aneurysms of the thoracoabdominal aorta may be classified according to their anatomic location. In 1986, Crawford and colleagues,[168] recognizing the correlation between aneurysm extent and clinical outcome, proposed a classification based on the extent of aortic involvement (Fig. 62-9). The Crawford classification defines aneurysms as types I, II, III, and IV and is appropriately applied to aneurysms of all causes (degenerative and dissecting). Type I aneurysms involve all or most of the descending thoracic aorta and the upper abdominal aorta. Type II aneurysms involve all or most of the descending thoracic aorta and all or most of the abdominal aorta. Type III aneurysms involve the lower portion of the descending thoracic aorta and most of the abdominal aorta. Type IV aneurysms involve all or most of the abdominal aorta, including the visceral segment. Types II and III are most difficult to repair because they involve both the thoracic and the abdominal segments of the aorta. Patients with Crawford type II aneurysms are at greatest risk for paraplegia and renal failure from spinal cord and kidney ischemia during cross-clamping. Even with extracorporeal circulatory support, there is an obligatory period when blood flow to these organs is interrupted because the origin of the blood flow is between the cross-clamps. For this reason, protective measures to prevent ischemic injury are important in reducing morbidity.

Aortic dissection, with or without aneurysm formation, has likewise been classified according to the extent of aortic involvement. The most widely used classification, proposed by DeBakey and colleagues, defines aortic dissection as types I, II, and III (Fig. 62-10). Type I aneurysms begin in the ascending aorta and extend throughout the entire aorta. These lesions are usually repaired via a two-stage approach, with the first procedure

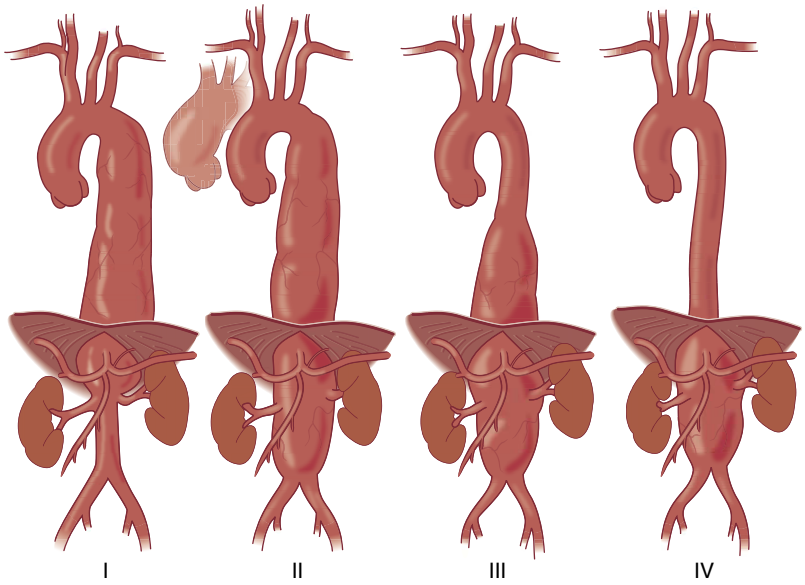


Figure 62-9 The Crawford classification of thoracoabdominal aortic aneurysms is defined by anatomic location and extent of involvement. Type I aneurysms involve all or most of the descending thoracic aorta and the upper abdominal aorta; type II aneurysms involve all or most of the descending thoracic aorta and all or most of the abdominal aorta; type III aneurysms involve the lower portion of the descending thoracic aorta and most of the abdominal aorta; and type IV aneurysms involve all or most of the abdominal aorta, including the visceral segment. *(Adapted from Crawford ES: Thoracoabdominal and supra-renal abdominal aortic aneurysm.* In *Ernst CB, Stanley JC* [*eds*]*: Current Therapy in Vascular Surgery. Philadelphia, BC Decker, 1987, pp 96-98.)*

on the ascending aorta and aortic arch and the second procedure on the descending thoracic aorta. Type II aneurysms are confined to the ascending aorta. Both types I and II often involve the aortic valve and cause aortic regurgitation, and sometimes they involve the ostia of the coronary arteries. Type III aneurysms begin just distal to the left subclavian artery and extend either to the diaphragm (type IIIA) or to the aortoiliac bifurcation (type IIIb). Another commonly used classification of aortic dissection is the Stanford classification. This more simplified classification divides aortic dissection into those that involve the ascending aorta (Stanford type A) and those that do not involve the ascending aorta (Stanford type B). Aortic dissection is also classified by duration, with those less than 2 weeks classified as acute and those greater than 2 weeks classified as chronic. This classification has

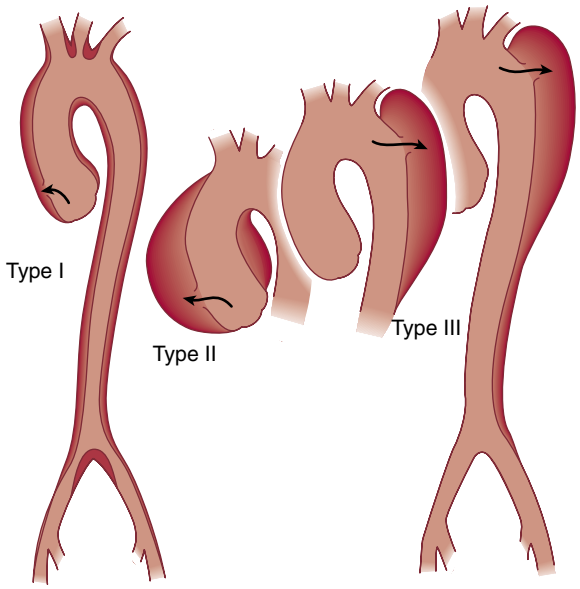


Figure 62-10 The DeBakey classification of dissecting aneurysms of the aorta. Type I has an intimal tear in the ascending aorta with dissection extending down the entire aorta. Type II has an intimal tear in the ascending aorta with dissection limited to the ascending aorta. Type III has an intimal tear in the proximal descending thoracic aorta with dissection either limited to the thoracic aorta (type IIIA) or extending distally to the abdominal aorta or aortoiliac bifurcation (type IIIB). *(Adapted from DeBakey ME, Beall AC Jr, Cooley DA, et al: Dissecting aneurysms of the aorta. Surg Clin North Am 46:1045-1055, 1966.)*

very significant mortality implications, with much higher mortality in the acute phase.

Acute aortic dissection involving the ascending aorta (DeBakey types I and II, Stanford type A) is a surgical emergency that requires immediate cardiac surgical repair (see Chapter 60).[173] Acute dissections involving the descending aorta (DeBakey type III, Stanford type B) are most often treated conservatively (i.e., blood pressure, heart rate, and pain control) because surgical repair has no proven benefit over medical or interventional treatment in stable patients.[174] Early surgical intervention may be required for a variety of reasons, including aneurysmal formation, impending rupture, organ or leg ischemia, and inadequate response to medical therapy. In approximately 20% to 40% of patients with chronic aortic dissection, significant aneurysmal dilatation of the descending thoracic or thoracoabdominal aorta will develop.[175]

Morbidity and Mortality

Despite tremendous development in surgical and anesthetic technique, mortality and complication rates remain high for open surgical repair of TAA. Patients who undergo replacement of the entire thoracoabdominal aorta (Crawford extent type II) have the highest perioperative risk.[176] Contemporary mortality rates reported from large institutional series range from 5% to 14%.[176-179] Statewide and nationwide mortality rates may be considerably higher (approximately 20%).[180,181] The perioperative mortality rate may significantly underestimate the risk associated with TAA repair. In a large statewide series, the mortality with elective TAA repair was 19% at 30 days and 31% at 365 days.[181]

The incidence of paraplegia or paraparesis in patients undergoing surgical repair of TAA is reported to be 3.8% to 40%, depending on factors such as anatomic location, the duration of cross-clamping, the use of protective measures, the degree of dissection, and whether the aneurysm has ruptured.[168,176-179,182] Extensive dissecting TAA repair carries the highest risk of neurologic deficit. A contemporary report of 210 consecutive open TAA repairs reported three patients with paraplegia and two with temporary paraparesis for an overall rate of neurologic deficit of 2.4% (1.4% permanent).[183] Renal failure occurs in 3% to 30% of patients, depending on similar factors noted earlier.[176,184,185] Overall, approximately 6% of patients need postoperative dialysis after TAA repair, which is associated with high mortality (30% to 60%).[185,186] Gastrointestinal complications occur in approximately 7% of patients[187,188] and are associated with a mortality approaching 40%.[178] Not surprisingly, pulmonary complications are the most common problem associated with TAA repair. The incidence of postoperative pulmonary insufficiency approaches 50%,[183,189] with 8% to 14% of patient requiring tracheostomy.[179,189] As with all other vascular surgical procedures, cardiac complications are common and a leading cause of perioperative mortality. In general, perioperative mortality and major complication rates after open isolated descending thoracic aortic replacement are lower than those described for TAA repair.[190]

Preoperative Preparation and Monitoring

Open surgical TAA repair requires extensive preoperative evaluation and planning. The evaluation and management of coexisting cardiac and pulmonary disease are discussed earlier in this chapter. Before the day of surgery, the anesthesiologist and vascular surgeon should discuss, at a minimum, the following issues: extent of the aneurysm and technique of surgical repair, plans for distal aortic perfusion, monitoring for spinal cord ischemia, renal and spinal cord protection, hemodynamic monitoring, and ventilation strategy.

Blood loss during TAA repair can be profound, and the need for massive transfusion must not be underestimated. I routinely have 15 units of packed red blood cells and 15 units of thawed fresh frozen plasma immediately available in the operating room, and additional units must be readily obtainable. I use a large cooler to store blood products on ice in the operating room so that they can be returned to the blood bank if not used. Platelets should be readily available as well. A dedicated critical care technician is helpful in assisting with laboratory testing and retrieving products from the blood bank.

Large-bore intravenous access is obviously important, especially if partial bypass (in contrast to full bypass) is planned because it is difficult or impossible for the perfusionist to administer fluid or blood products into the closed partial bypass circuit. Three 8.5-Fr catheters can be inserted into the internal jugular and antecubital veins. One of these accepts a pulmonary artery catheter, and the other two are connected to a rapid infuser system (RIS, Haemonetics, Braintree, MA). This system allows the delivery of up to 1500 mL/min of blood products at a temperature of 37°C to 38°C. A right radial arterial catheter is used for aneurysms involving the proximal descending thoracic aorta because occasionally the cross-clamp is placed proximal to the left subclavian artery, thus occluding flow to the left upper extremity. When distal aortic perfusion techniques are used, I monitor arterial blood pressure distal to the cross-clamps. This can be accomplished with the placement of a right femoral arterial catheter, or the surgical team can place a catheter directly into the femoral artery or distal aorta. This catheter monitors perfusion pressure to the kidneys, spinal cord, and mesenteric circulation during the time when the cross-clamps are high on the descending aorta and the lower body region is perfused by a shunt or bypass circuit. Radial and femoral arterial pressure should be simultaneously displayed on the anesthesiologist's monitor and a monitor visible to the surgeons and the perfusionists. TEE is used routinely during TAA repair (see Chapter 41). When used by a properly trained individual, assessment of left ventricular end-diastolic volume, myocardial ischemia, and valvular function is possible. It is also possible to determine the size and the extent of the aneurysm.

A double-lumen endobronchial tube should be inserted for the purpose of one-lung ventilation (see Chapter 59). One-lung ventilation provides optimal visualization of the surgical field and reduces retraction related trauma to the left lung. A left-sided endobronchial tube is optimal because it is more easily positioned and less likely to become malpositioned. Additionally, there is risk of occluding the right upper lobe bronchus with a right-sided tube. I position all double-lumen tubes under direct vision using a fiberoptic bronchoscope because it facilitates quick and definitive placement and allows direct visualization of the distal trachea and mainstem bronchi. Occasionally, when the left mainstem bronchus is compressed by a large aneurysm,[191] the lumen does not accommodate an endobronchial tube. In this situation, a right-sided endobronchial tube might be necessary. Rarely, the right mainstem bronchus may be compressed by a large aneurysm.[192] The double-lumen tube is usually changed, if possible, to a single-lumen tube at the completion of surgery. This facilitates

ICU management of pulmonary hygiene and reduces resistance to breathing during weaning in the postoperative period. The airway is often edematous after surgery, and it may be difficult or impossible to change the double-lumen tube without tube-changing catheters.

Many centers use electrophysiologic monitoring with somatosensory evoked potentials (SSEPs) or motor evoked potentials (MEPs) to monitor for spinal cord ischemia (see Chapter 46). These monitoring techniques may be helpful in both identifying the important intercostal arteries that perfuse the spinal cord and confirming successful reimplantation into the aortic graft.[193] If spinal cord ischemia is identified, cross-clamps can often be repositioned, upper or lower body blood pressure can be increased to augment perfusion through collateral channels, or other measures may be taken to protect the spinal cord (i.e., cerebrospinal fluid [CSF] drainage, induced hypothermia, or intrathecal pharmacologic agents). These techniques are discussed later. There are three general problems with SSEP monitoring when used during TAA repair. First, sensory monitoring is more likely to detect lateral and posterior sensory column ischemia and is a poor monitor for the anterior motor column. As a result, paraplegia can occur despite normal SSEP signals.[194] Second, inhaled anesthetics and hypothermia can significantly interfere with SSEP signals. Third, ischemia affects peripheral nerves, and ischemia in the lower extremities delays conduction from the usual stimulation sites (e.g., posterior tibial nerve).[195] To eliminate the peripheral nerves as a confounding factor, spinal stimulation via a lumbar epidural electrode can be used, which may be more specific for ischemic injury than peripheral monitoring is.[195] Lower extremity and peripheral nerve ischemia can be avoided with the use of distal aortic perfusion techniques. To avoid lower extremity ischemia from occlusion of the left femoral artery at the insertion site of the retrograde perfusion cannula, some surgeons suture a small-caliber graft onto the femoral artery (end to side) for insertion of the cannula, which allows both antegrade and retrograde perfusion. These limitations of SSEP monitoring just outlined probably accounted for the lack of improvement in neurologic outcome in a large prospective series of TAA repairs.[196] In this same series, the incidence of false-negative responses was 13% and that of false-positive responses was 67%, thus making identification of critical spinal arteries impossible.

The transcranial MEP technique has been used successfully to monitor the anterior columns of the spinal cord. The technique is relatively simple and can be viewed as a "train-of-four" for the brain and spinal cord. Electrical stimulation over the motor cortex activates α-motor neurons, and evoked electromyographic responses are obtained in lower extremity muscle. Only electromyogenic responses are specific for the status of the motor neurons in the anterior horn gray matter. Bilateral recording needles should be placed in the popliteal fossae (i.e., popliteal nerve) and bilateral surface electrodes over the gastrocnemius and tibialis anterior muscles. Bilateral stimulating needles are routinely placed in the popliteal fossae to monitor direct muscle responses and the level of neuromuscular blockade. During aortic cross-clamping, MEPs are monitored every minute. A reduction in MEP amplitude to less than 25% of baseline is considered an indication of spinal cord ischemia and requires corrective measures. Because signal averaging is not required and the anterior horn cells react with an almost immediate functional loss after the onset of ischemia, the technique can be used to rapidly identify intercostal arteries supplying the spinal cord. Additionally, the technique can be used to evaluate the adequacy of distal aortic perfusion and the patency of reimplanted critical intercostal arteries. Careful titration of a short-acting neuromuscular blocker is required to maintain a stable level of neuromuscular blockade. Complete neuromuscular blockade makes MEP monitoring impossible. A continuous infusion technique should be used to maintain electrical muscle amplitude at approximately 50% of baseline. Isoflurane, desflurane, sevoflurane, and nitrous oxide all depress synaptic conduction and significantly decrease the amplitude of myogenic MEPs. Although modifications of the stimulating technique have improved monitoring with inhaled anesthetics somewhat, a total intravenous anesthetic technique may be optimal. Fentanyl and ketamine have little effect on myogeneic MEPs and have been used successfully as a combined anesthetic in a large series of patients undergoing TAA repair with MEP monitoring.[183] This series of 210 consecutive patients had the lowest rate of neurologic deficit (2.4%) and permanent paraplegia (1.4%) reported.[183]

Body temperature should be monitored at two sites (core and peripheral) to assess cooling and warming when bypass techniques are used. There is an important difference, however, between full and partial bypass with regard to temperature monitoring. With full bypass, perfusion is usually into the ascending aorta, and typically the upper body core temperature (i.e., nasopharynx or esophagus) cools and warms fastest, whereas the lower body temperature changes more slowly. With partial bypass, the opposite is true. The blood from bypass is returned into the femoral artery, and the lower part of the body (i.e., rectum or bladder) changes before the upper part changes. This difference is important to recognize in order to achieve complete cooling and warming because the lagging temperature should be the end point for cooling and warming.

Anesthetic Management

Simple Aortic Cross-Clamping

Descending thoracic and thoracoabdominal aortic surgery can be performed without extracorporeal support (i.e., left heart bypass or cardiopulmonary bypass). Large series of the "clamp-and-sew" technique have been published with relatively favorable outcomes, but these cases are from institutions with the greatest clinical experience and the shortest cross-clamp times. Advocates of this technique favor its surgical simplicity. However, the benefits of avoiding the complexity and complications of bypass must be weighed against the risk of vital organ ischemia and complications such as renal failure and paraplegia.

Other than the location and extent of the aneurysm, the duration of cross-clamping on the aorta is the single most important determinant of paraplegia and renal failure with the clamp-and-sew technique. Clamp times of less than 20 to 30 minutes are associated with almost no paraplegia.[168,197] When clamp times are between 30 and 60 minutes (the vulnerable interval), the incidence of paraplegia increases from approximately 10% to 90% as time progresses. Because clamp times are typically in this range or longer, specific adjuncts directed against end-organ ischemic complications are often used.[198] Such adjuncts include epidural cooling for spinal cord protection, regional hypothermia for renal protection, and in-line mesenteric shunting to reduce visceral ischemia.[178]

When the simple clamp-and-sew technique is used, application of the aortic cross-clamp results in significant proximal hypertension, which requires active pharmacologic intervention.

Management strategies have been discussed previously in the section on abdominal aortic reconstruction. Briefly, both sodium nitroprusside and isoflurane[102] have been used successfully to control the proximal hypertension associated with high aortic cross-clamping. Isoflurane is best reserved for patients with good myocardial function. Vasodilators, such as sodium nitroprusside, must be used with caution because they can result in significant overperfusion of the body proximal to the clamp and very low pressures distally. Nitroglycerin can be used to normalize preload and cardiac filling and thus reduce ventricular wall tension. Although nitroglycerin does not control proximal hypertension well as a single agent, it is very helpful when used in combination with sodium nitroprusside. Management of aortic unclamping has been discussed earlier.

Left Heart Bypass

Maintaining lower body perfusion with the use of retrograde distal aortic perfusion reduces ischemic injury and improves outcome, provided that the pressure is high enough to perfuse the organs. The simplest method of providing distal aortic perfusion is a passive conduit or shunt. The heparin-bonded Gott shunt was developed to avoid the need for systemic heparinization and is used to divert flow passively from the left ventricle or proximal descending thoracic aorta to the distal aorta. Some centers place a temporary axillary-to-femoral artery graft to function as a shunt during aortic cross-clamping.

Partial bypass, also referred to as left heart bypass or left atrial-to-femoral bypass, is the most commonly used distal aortic perfusion technique (Fig. 62-11). This technique allows adjustment of blood flow and usually draws blood from the left atrium and returns blood to the left femoral artery. A centrifugal pump is used (Biomedicus, Eden Prarie, MN), and there is no need for full-dose systemic heparin because the circuit is coated with heparin. The typical heparin dose for partial bypass is 100 U/kg. With this technique, an oxygenator is unnecessary because only the left side of the heart is bypassed. Insertion of a heat exchanger into the circuit allows cooling and warming, which is beneficial but not absolutely essential. Variations of left heart bypass include cannulating the aortic arch or proximal descending thoracic aorta instead of the left atrium. With this circuit, the left ventricle is relieved of the increased afterload during aortic cross-clamping. With left atrial cannulation, the left ventricle is relieved of preload and cardiac output is reduced. Either way, proximal hypertension is controlled, the work of the ventricle is decreased, and perfusion is provided to the distal aorta. My colleagues and I have had even greater success with cannulation of a pulmonary vein instead of the left atrium. This method accomplishes the same effect as with atrial cannulation but is associated with less atrial irritability. When hypothermia (30°C) is combined with atrial cannulation, approximately 15% of patients experience new atrial fibrillation.[199] Although most patients revert to sinus rhythm on rewarming, direct cardioversion may be required.

During left heart bypass, it is essential that arterial blood pressure be monitored above and below the aortic cross-clamps. I simultaneously display radial and femoral artery pressure and aim for a mean arterial pressure of 80 to 100 mm Hg above the cross-clamp and at least 60 mm Hg below the cross-clamp. Careful control of intravascular volume, bypass pump flow, and vasoactive drugs is required to achieve the target blood pressures. Management of left heart bypass requires continuous communication and cooperation between the surgeon, anesthesiologist, and perfusionist. We typically set the initial pump flow to approximately

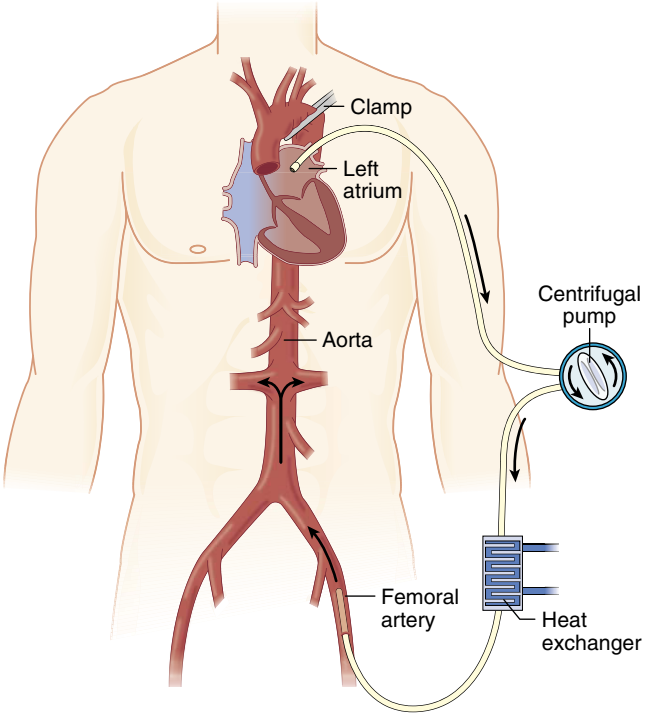


Figure 62-11 Diagram of left atrial-femoral bypass. The left atrium and the left femoral artery are cannulated, and a centrifugal pump is used with heparin-coated tubing. A heat exchanger may be added to the circuit for cooling and rewarming.

50% of the patient's cardiac output with application of the proximal aortic clamp. Flow is then adjusted to maintain target proximal and distal pressures. Administration of vasodilators is very infrequently required at this stage. With no vital organ ischemia, the surgeon can complete the proximal anastomoses in an unhurried fashion. With sequential aortic clamping, intercostal arteries can be reimplanted with minimal adjustments of pump flow. Pump flow is eventually reduced significantly during reimplantation of the visceral and renal arteries. At this time, distal perfusion is only to the lower extremities. We routinely use moderate hypothermia (32°C) during bypass to protect the vital organs during obligate periods of ischemia. After completion of the distal anastomoses, pump flow is increased and the patient is actively warmed to 37°C.

Deep Hypothermic Circulatory Arrest

Complex aneurysms involving the aortic arch often require elective cardiopulmonary bypass with an interval of deep hypothermic (15°C) circulatory arrest (DHCA) because cerebral blood flow is transiently interrupted during surgery (see Chapter 60). Bypass can be accomplished by cannulation of the femoral artery and the femoral vein (i.e., femoral-femoral bypass). During the interval of DHCA, some centers also use anterograde (i.e., innominate artery) or retrograde (i.e., internal jugular vein) selective cerebral perfusion with cold oxygenated blood to extend the safe maximum duration of circulatory arrest.[200] Without this technique, 45 to 60 minutes is thought to be the safe limit of DHCA, but 90 minutes has been reported with selective cerebral perfusion.[201]

DHCA may also be necessary whenever the location, extent, or severity of aortic disease precludes placement of a proximal aortic clamp during thoracic or thoracoabdominal aortic repair.[202] This is often the case in patients with previous aortic arch repair, where adhesions and scarring make application of the proximal aortic cross-clamp difficult or impossible during TAA repair.[203] DHCA eliminates the need for proximal aortic clamping and allows a bloodless field for the proximal aortic anastomosis. Some centers advocate the use of DHCA during complex aortic reconstruction because deep hypothermia may provide better end-organ and spinal cord function.[204,205] This potential benefit must be carefully weighed against the risks associated with prolonged cardiopulmonary bypass and circulatory arrest. After completion of the proximal anastomosis and intercostal artery–to-graft anastomoses under DHCA, the aortic graft is cannulated and bypass flow is reestablished to the upper part of the body. During a period of hypothermic low bypass flow, the distal anastomoses are completed and then rewarming is initiated.

Anesthetic Technique

There is no single best anesthetic technique for TAA repair. Usually, balanced anesthesia is provided with a combination of an opioid, a low-dose potent volatile anesthetic, a benzodiazepine, and a long-acting muscle relaxant. A total intravenous technique may be optimal if transcranial MEP monitoring is used. Induction of general anesthesia should be slow and controlled. Hypertension should be avoided because acute stress on the aneurysm can cause rupture. The heart rate should be maintained at or below baseline because myocardial ischemia is often related to the heart rate. Extubation should always take place in the ICU and only after a significant period of hemodynamic and metabolic stability. The postoperative analgesic regimen should focus on pain control and stable hemodynamics.

Spinal Cord Ischemia and Protection

Paraplegia is a devastating complication of aortic surgery. The incidence of paraplegia is reported to be 0.5% to 1.5% for coarctation repair, 0% to 10% for thoracic aneurysm repair, 10% to 20% for thoracoabdominal repair, and as high as 40% for extensive dissecting TAA repair.[206-210]

The spinal cord receives its blood supply from two posterior arteries (≈25%) and one anterior spinal artery (≈75%) (Fig. 62-12). The posterior spinal arteries, which supply the sensory tracts in the spinal cord, receive flow from the posterior and inferior cerebellar arteries, the vertebral arteries, and the posterior radicular arteries. The anterior spinal artery, which supplies the motor tracts in the spinal cord, is formed by two branches of the intracranial portion of the vertebral arteries. The upper cervical segment of the spinal cord receives most of its blood flow from the vertebrals. The thoracic portion of the anterior spinal artery is supplied by the anterior radicular arteries (one or two cervical, two or three thoracic, and one or two lumbar). The largest of the radicular arteries is called the great radicular artery (GRA) or the artery of Adamkiewicz. The GRA is the major blood supply to the lower two thirds of the spinal cord. The segmental supplier of the GRA is variable (T5-L5) but is located between T9 and T12 in approximately 75% of cases. The variation in origin of the GRA explains why even infrarenal aortic aneurysm repair is associated with a 0.25% incidence of paraplegia. The specific impact of extensive segmental artery sacrifice on spinal cord perfusion during TAA repair is poorly understood.

Various methods have been used to prevent ischemic injury to the spinal cord. Distal aortic perfusion with extracorporeal support has been shown to reduce the incidence of paraplegia.[211] Any of the various methods of distal bypass are likely to be beneficial when the anticipated cross-clamp time is longer than 30 minutes, but they are probably not beneficial when cross-clamp time is less than 20 minutes. CSF drainage is frequently used to improve spinal cord perfusion during TAA repair and is often used in combination with distal aortic perfusion.[177,212] Spinal cord perfusion pressure is defined as distal mean aortic pressure minus CSF pressure or central venous pressure, whichever is greatest. Autoregulation of spinal cord blood flow is similar to cerebral autoregulation, and blood flow is relatively constant over the range of 50 to 125 mm Hg. During hypoxia or hypercapnia, autoregulation is lost, and flow becomes linearly related to perfusion pressure. Thus, significant flow may remain even at very low perfusion pressure. Drainage of CSF is thought to be important because CSF pressure often increases (by 10 to 15 mm Hg) with cross-clamping of the descending thoracic aorta. The increase in CSF pressure reduces spinal cord perfusion pressure and increases the likelihood of ischemic spinal cord injury.

Despite evidence from animal studies that CSF drainage protects the spinal cord, clinical use of this technique is controversial. One randomized trial reported a reduced incidence of paraplegia,[213] but another reported no benefit.[214] The majority of the evidence in support of CSF drainage comes from nonrandomized historical cohort studies in which the technique is used in combination with other adjuncts, such as intrathecal papaverine[213,215] and hypothermic partial bypass.[177,182,199,212] Coselli and colleagues[216] offered the strongest evidence supporting the efficacy of CSF drainage. They conducted a prospective, randomized

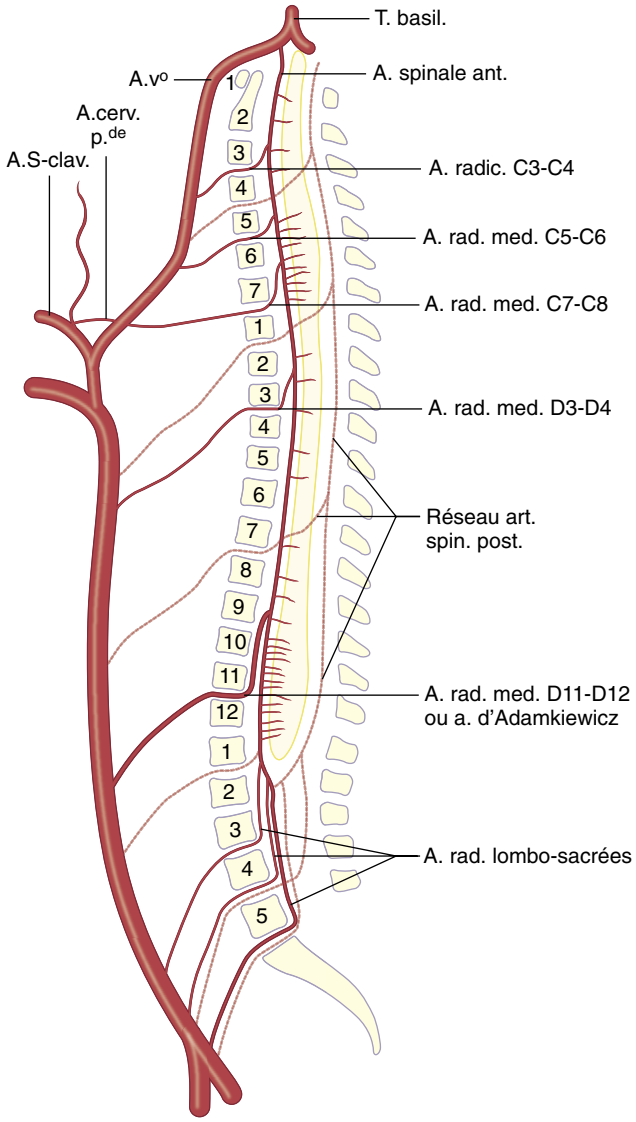


Figure 62-12 Diagram of the blood supply to the spinal cord showing the anterior and posterior radiculomedullary branches seen in a lateral view. The primary blood supply to the thoracolumbar portion of the spinal cord is derived from the artery of Adamkiewicz; its origin varies but it usually branches off the aorta in the T9 to T12 region. *(From Djindjian R: Arteriography of the spinal cord. Am J Roentgenol Radium Ther Nucl Med 107:461-478, 1969.)*

clinical trial to evaluate the impact of CSF drainage on the incidence of spinal cord injury after Crawford type I and II TAA repair. CSF drainage resulted in an 80% reduction in the relative risk for a postoperative deficit. Nine patients in the control group (13%) had paraplegia or paraparesis versus only two patients in the CSF drainage group (2.6%). Left heart bypass, moderate heparinization, permissive mild hypothermia, and reimplantation of patent intercostal and lumbar arteries were performed in both treatment groups. The target CSF pressure was 10 mm Hg. CSF drainage has also been shown (in case reports) to reverse delayed-onset neurologic deficit after open[217] and endovascular[218] TAA repair.

Although CSF drainage is widely used during TAA repair, the technique is not without risks. Potential complications include headache, meningitis, chronic CSF leakage, spinal or epidural hematoma, and subdural hematoma. The possibility of intraspinal pathology should be considered in any patient with a postoperative lower extremity neurologic deficit.[219] A recent retrospective review of 230 patients who underwent TAA repair with CSF drainage at the Johns Hopkins Hospital reported eight subdural hematomas (3.5%).[220] High-volume CSF drainage was identified as a risk factor for its occurrence. Six patients had subdural hematomas detected during hospitalization, with an associated mortality of 67%. Two patients were seen in a delayed fashion, and both required an epidural blood patch to control chronic CSF leakage.

Hypothermia is probably the most reliable method of neuroprotection from ischemic injury. By reducing oxygen requirements by approximately 5% for each degree centigrade, a twofold prolongation of tolerated cross-clamp time is achieved by cooling even to mild hypothermia (34°C). Because the reduction in metabolic rate is linearly related to temperature, moderate or profound hypothermia provides even greater protection. Both systemic and regional spinal cord cooling is beneficial. Systemic hypothermia can been achieved with either full cardiopulmonary bypass (with or without DHCA)[221] or partial bypass.[199,222] Cooling to 30°C to

32°C with left atrial-to-femoral bypass in conjunction with CSF drainage was associated with no permanent neurologic sequelae in a series of 20 patients despite a relatively long average cross-clamp time (≈70 minutes).[199] My colleagues and I have since used this technique in more than 250 patients cooled to 32°C, with a 5% incidence of paraplegia. Although some risk is incurred when a beating heart is subjected to moderate hypothermia, the benefits appear to outweigh the risks. Supraventricular and ventricular dysrhythmias respond well to cardioversion or mild warming to 33°C to 34°C. Regional cooling of the spinal cord by cold perfusion of the GRA with blood[223] or crystalloid provides significant protection during spinal ischemia in animal models. Regional cooling is beneficial in humans who received epidural infusions of 4°C saline.[224] Even if active cooling is not used, it is advantageous to allow patients to passively cool to 33°C to 34°C during TAA repair. With passive cooling, the challenge is rewarming after the surgical repair. This is most easily accomplished with the use of a forced-air blanket over the upper part of the body. The lower body region should not be actively warmed because warming ischemic tissue increases metabolic requirements, acidosis, and ischemic injury.

A variety of drugs have been studied in an attempt to reduce the incidence of ischemic spinal cord injury. Barbiturates have been shown to provide significant protection.[225] Corticosteroids provide protection in dogs[226] but were beneficial in humans only when they were combined with CSF drainage.[227] Calcium channel blockers were protective against spinal cord ischemia in some studies[228,229] but not in others.[230,231] *N*-methyl-D-aspartate receptor antagonists have been investigated because ischemic injury appears to be related to increased levels of excitatory amino acids (particularly glutamate), which allow increased permeability to calcium ions and high intracellular calcium concentrations. Dextrorphan (a noncompetitive *N*-methyl-D-aspartate receptor antagonist) shows promise during spinal cord ischemia.[232] Magnesium, another *N*-methyl-D-aspartate receptor antagonist, improves recovery from spinal cord ischemia in rat and dog models when administered intrathecally.[233,234] Naloxone is protective in patients with traumatic spinal cord injuries and in a rabbit model of spinal ischemia. Naloxone also shows promise when combined with CSF drainage in patients undergoing TAA repair.[235] Intrathecal papaverine appears to be protective,[215] especially when combined with CSF drainage.[213,236] Other agents under investigation include levosimendan, allopurinol, adenosine, ziconotide, activated protein C, and desferrioxamine. Other than the use of corticosteroids and naloxone at a few centers, most of these agents are considered investigational.

Preoperative spinal cord angiography in patients with TAA has been reported by several groups. The rationale for this highly invasive angiographic procedure is that precise identification of intercostal arteries giving rise to the GRA will allow focused reimplantation of these vessels during surgical repair and help prevent spinal cord injury. Selective intercostal angiography identifies the GRA when an intercostal branch is found making a cephalad hairpin turn to enter the spinal canal and supply a midline longitudinal artery (i.e., the anterior spinal artery) (Fig. 62-13). The GRA can be identified in 43% to 86% of patients studied with traditional angiography.[237,238] Higher detection rates for GRA localization have been reported with computed tomographic angiography and magnetic resonance angiography, with the latter achieving rates of nearly 100%.[239]

The importance of reimplanting the intercostal arteries identified as supplying the GRA is not universally accepted. Clinical reports have demonstrated that even in patients with an identified and reimplanted GRA, spinal cord injury could not always be prevented.[240] Some investigators have concluded that preoperative localization of the GRA has little impact on neurologic outcome after TAA repair. A report from my institution[237] found no improvement in overall neurologic outcome with preoperative spinal cord angiography, but it offered important insight regarding the type of aneurysm, identification of the GRA, and neurologic outcome. In patients undergoing TAA repair for extensive degenerative aneurysms, spinal cord injury occurred in 0 of 45 patients versus 10 (12%) of 81 patients with and without an identified GRA, respectively. In contrast, identification of the GRA was not helpful in the case of chronic expanding aortic dissection, with 3 (15%) of 20 patients versus 3 (6%) of 49 patients suffering spinal cord injury with and without an identified GRA, respectively. The investigators hypothesized that mural thrombus in degenerative aneurysms results in the occlusion of many intercostal arteries and favors the development of extensive paravertebral collateral channels (see Fig. 62-13). Identification of a GRA allows focused reimplantation with uniform success. In patients with chronic dissection, most intercostal arteries are patent, collateralization is minimal, and reimplantation of one or two intercostal arteries may be insufficient to supply blood flow to the spinal cord. This collateral blood supply concept is further supported by clinical studies demonstrating that clamping the segmental supplier to the GRA during TAA repair does not produce critical spinal cord ischemia in the majority of patients.[241] Sufficient collateral blood supply, independent of the GRA, must therefore exist to maintain spinal cord integrity.

Delayed-onset neurologic deficits are common after TAA repair.[242] In a large series of 2368 TAA repairs, 93 (3.9%) patients had postoperative paraplegia or paraparesis, 34 (37%) of whom initially had intact spinal cord function but a deficit developed later.[243] Preoperative renal dysfunction, acute dissection, and extent type II TAA are significant predictors of delayed neurologic deficit.[244] Postoperative hypotension and CSF drain malfunction may play an important role in the development of these deficits.[245] In one report, 57% of patients recovered neurologic function with optimization of blood pressure and CSF drainage.[244]

Renal Ischemia and Protection

Renal failure after TAA repair results from preexisting renal dysfunction, ischemia during cross-clamping, thrombotic or embolic interruption of renal blood flow, and hypovolemia and hypotension. Approximately 6% of patients require postoperative dialysis, even in centers with the most clinical experience.[185,186] The associated mortality can be high.[185] The primary predictor of postoperative renal failure is preoperative renal dysfunction.[246] The duration of cross-clamp time is very important with the clamp-and-sew technique.

Retrograde distal aortic perfusion techniques are widely used to preserve renal function during the cross-clamp period. Adequate bypass flow and arterial blood pressure are essential for maintaining renal function. Systemic and regional hypothermia, by reducing oxygen requirements, protects the kidneys during ischemia. Some centers advocate the use of DHCA in the treatment of distal TAAs (i.e., extent type III and IV) to preserve renal function.[247]

The role of pharmacologic protection is somewhat controversial. Mannitol (12.5 to 25.0 g/70 kg) is often given before cross-clamping. Mannitol improves renal cortical blood flow and the

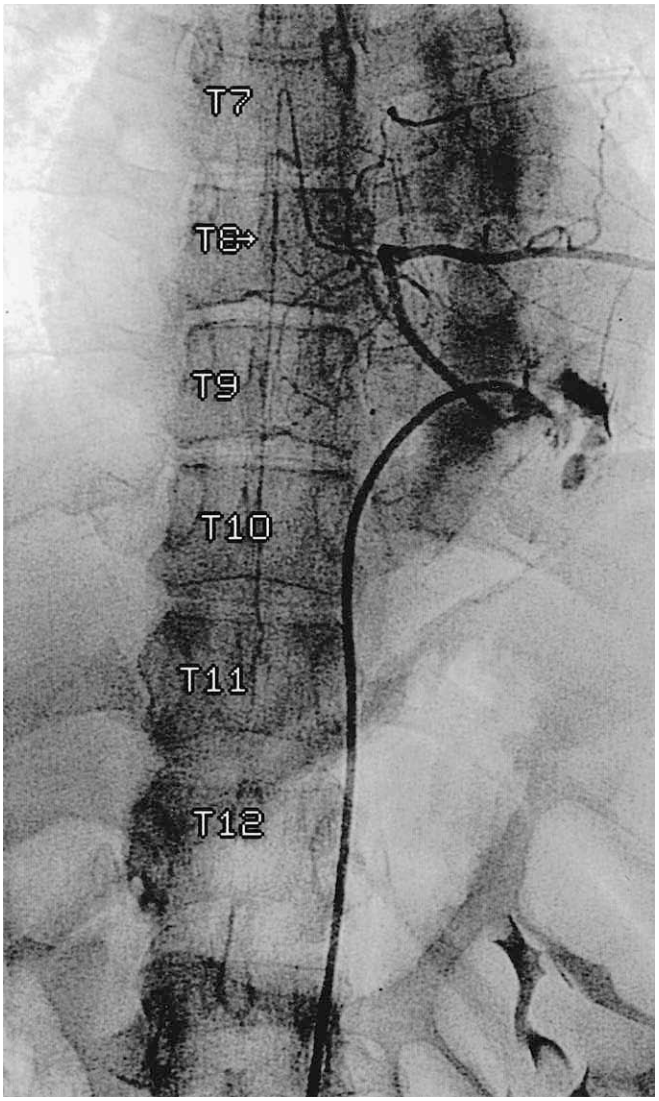


Figure 62-13 Spinal cord angiogram of an extensive degenerative thoracoabdominal aortic aneurysm. Selective injection of the intercostal artery at T8 (*arrow*) demonstrates the great radicular artery and the extensive paravertebral collateralization.

glomerular filtration rate in animal models of ischemia. Endothelial cell swelling is decreased, and an osmotic diuresis occurs. There is evidence of free radical scavenging with mannitol and subsequent protection from ischemia in animals.[120] Loop diuretics are sometimes given, but these drugs have been less effective than mannitol in experimental models. In clinical studies, the prophylactic use of loop diuretics has not been shown to improve outcome or to reduce the need for dialysis for patients with acute renal failure. Dopamine given in low doses (3 μg/kg/min) dilates renal blood vessels and increases renal blood flow and urine output. Despite these beneficial effects, there is no clear evidence from clinical trials that dopamine provides renal protection during ischemia. Fenoldopam mesylate, a selective dopamine type 1 agonist that preferentially dilates the renal and splanchnic vascular beds, has shown some early promise as a renoprotective agent.[121,122]

At the present time, optimal renal protection during TAA surgery should rely on hypothermia, mannitol, and prevention of hypotension and hypoperfusion of the kidneys.

Coagulation and Metabolic Management

Coagulopathy is a frequent complication during TAA repair. A dilutional coagulopathy in which platelets become deficient after approximately one blood volume of replacement develops during massive transfusion (see Chapter 55). At somewhere between one and two blood volumes of replacement, coagulation factors are diluted to levels low enough to increase bleeding. Other contributing factors are residual heparin; ischemia of the liver, where most coagulations factors are produced; and persistent hypothermia after weaning from bypass. With the early use of fresh frozen plasma and platelets, severe coagulopathy can often be avoided. The prothrombin time, partial thromboplastin time, fibrinogen level, and platelet count should be measured frequently. Cryoprecipitate may be necessary to correct coagulopathy, especially when the prothrombin time and partial thromboplastin time are prolonged and hypervolemia prevents the administration of significant volumes of fresh frozen plasma. When coagulopathy persists despite these efforts, ε-aminocaproic acid is beneficial as antifibrinolytic therapy, and desmopressin can be given to increase

circulating levels of von Willebrand factor and factor VIII. Normothermia should be achieved by complete rewarming before separation from bypass, by increasing ambient temperature after separation from bypass, and by forced-air warming over the upper body skin surface.

Arterial blood gases and electrolyte levels should be measured frequently. Sodium bicarbonate should be given to treat the metabolic acidosis that occurs during and after cross-clamping. Hyperkalemia should be treated aggressively, especially in oliguric or anuric patients. Calcium chloride and sodium bicarbonate are the primary acute treatments of hyperkalemia.

Endovascular Aortic Repair

Endovascular surgery is one of the most exciting developments in the treatment of vascular disease and is revolutionizing current treatment modalities for aortic disease, including aneurysm, dissection, rupture, and traumatic injury. The endovascular approach was developed as a less invasive alternative to open abdominal aortic aneurysm repair and to provide a treatment option for patients considered to be poor surgical candidates. The use of endoluminal grafts to treat peripheral arterial disease began experimentally in the late 1960s. The feasibility of this technique for the treatment of abdominal aortic aneurysm was established experimentally some 2 decades later. In 1991, Parodi and colleagues[248] reported the first clinical use of the technique in five patients with abdominal aortic aneurysms. They described the placement of an endoluminal, stent-anchored, Dacron tube graft via retrograde cannulation of the common femoral artery under local or regional anesthesia. Balloon expansion of the stents fixed the ends of the graft to the aortic wall and excluded the aneurysm from the systemic circulation. The technique was satisfactory in three of the five patients. Since these early reports, there has been an explosive increase in the use of endoluminal devices to treat aortic disease. These devices accounted for nearly 50% (29,542 of 61,598) of elective repairs of abdominal aortic aneurysm in Medicare beneficiaries during the period 2001 to 2004.[249]

Interest in endoluminal aortic grafting has expanded to include disease of the thoracic and thoracoabdominal aorta. Endovascular grafting has also emerged as a viable alternative to open repair of aortic rupture and complex aortoiliac occlusive disease. As experience with endoluminal stent-graft systems and endoluminal techniques increases, along with continued refinement of devices, the endovascular approach will be applied to more patients with increasingly complex aortic disease.[250]

Stent-Graft Devices and Approval

The FDA approved the use of two endovascular stent-graft devices for repair of infrarenal abdominal aortic aneurysms in the United States in 1999, with a 5-year surveillance requirement. This surveillance requirement has been extended to lifelong because of reported cases of aneurysm rupture and death. FDA approval of these devices was granted without the usual requirement for a randomized controlled trial. Instead, the FDA allowed a concurrent "matched" group of patients treated by open repair to serve as a control group. One of the two devices approved for use in 1991 was withdrawn from clinical use because of difficulty in delivery and deployment. Three additional stent-graft devices have received regulatory approval in the United States, and more will probably be approved in the near future. Several other stent-grafts are approved for use by other governments around the world. Stent-grafts are often used "off-label" or under physician Investigation Device Exemption studies for indications other than infrarenal abdominal aortic aneurysm repair. Since regulatory device approval, a rapid increase in endovascular abdominal aortic aneurysm repair has occurred nationwide. The stent-grafts used for infrarenal abdominal aortic aneurysm repair are Y-shaped devices. The stent-graft is often modular in design and made of synthetic fabric with reinforcing stent struts. The larger main trunk is designed for the distal aorta and the two smaller branches are for the iliac arteries.

Since the initial report by Dake and coworkers in 1994,[251] tremendous progress has been made in the endovascular treatment of thoracic aortic disease. In 2005, the FDA approved the use of a thoracic stent-graft device for the treatment of descending thoracic aortic aneurysms.[252] Two additional devices are awaiting FDA approval. Several thoracic stent-grafts are commercially available around the world and have been used extensively for a spectrum of aortic disease, including dissection, penetrating ulcer, rupture, and traumatic transection.

Procedures on the thoracoabdominal aorta require novel (i.e., multibranched or fenestrated) endovascular grafting systems or staged hybrid approachs. Tubular aortic stent-graft devices can be modified to incorporate a combination of fenestrations and branches based on the anatomy of the visceral aortic segment. These complex devices are currently in use in Europe and await FDA approval in the United States pending completion of ongoing clinical trials. Hybrid approachs often require open visceral and renal bypass followed by stent-graft implantation over the "debranched" visceral segment. Similar approaches are being used to treat complex aneurysms that encroach on the distal aortic arch. In patients with aneurysmal disease of the entire aortic arch, the traditional "elephant trunk" procedure has been combined with a second-stage stent-graft procedure of the descending thoracic aorta. The distal end of the elephant trunk serves as the proximal attachment site for the stent graft.

Endovascular Technique

The endovascular approach can be undertaken without the large incisions, extensive dissections, prolonged aortic cross-clamp times, and significant blood loss and fluid shifts associated with open repair. The arterial access site for endovascular stent-graft placement is selected on the basis of vessel size and degree of obstructing atherosclerotic disease. The technique most commonly requires bilateral transverse groin incisions to expose the common femoral arteries. In patients with severely diseased femoral or iliac arteries, balloon angioplasty or local endarterectomy can be performed to allow passage of the delivery system. Adjunctive retroperitoneal procedures may be necessary in up to 20% of patients during endovascular abdominal aortic aneurysm repair.[253] Indications include small external iliac arteries that limit femoral access and a concomitant iliac artery aneurysm that precludes distal fixation of the stent-graft in the common iliac artery. In these cases, a transverse lower abdominal incision with retroperitoneal dissection exposes the iliac artery, and a synthetic conduit is sutured (end to side or end to end) onto the common

iliac artery. The delivery system is endoluminally placed into the aorta through this iliac conduit. At the termination of the procedure, the conduit can be ligated, attached to the external iliac artery (interposition graft), or attached to the common femoral artery (iliofemoral bypass graft). Although adjunctive retroperitoneal procedures may allow a larger number of patients to undergo endovascular aortic repair, such procedures are associated with an increased risk for complications, greater blood loss, longer procedure time, and longer hospital length of stay than endovascular repair with standard femoral access is.[253] Obviously, the advantage of endovascular techniques being less invasive than open repair is reduced when adjunctive procedures are required. Adjunctive procedures may also be needed with endovascular repair of the thoracic aorta. One series involving patients with a spectrum of aortic disease reported that 25% of patients needed open surgical access to the aorta and 21% needed left subclavian–carotid transposition to provide an adequate proximal fixation site.[254]

Although adjunctive surgical procedures may be needed, the technical skill required for endovascular aortic surgery is primarily catheter based. Thus, appropriately trained cardiologists, radiologists, and vascular surgeons can all deliver endovascular treatment of aortic disease. A multispecialty approach is commonly used and offers patients the expertise of both surgical and catheter-based specialists. Even though no standard has been set, the requirements for endovascular aortic surgery are the same wherever it is performed. The standard operating room environment is ideal from the surgical and anesthesia standpoint, particularly when conversion to an open repair is required. The operating room must be equipped with endovascular supplies, portable radiologic imaging tools, and an angiographic table. Angiographic suites often have superior radiographic imaging tools and angiographic tables and are better equipped to deal with ionizing radiation. The superior imaging may reduce radiation exposure and decrease contrast dye loads. In an effort to provide an optimized environment for multispecialty endovascular intervention, many centers are constructing sophisticated operative angiographic suites in or adjacent to the operating room.

Endovascular stent-grafting of the aorta requires preoperative diagnostic imaging to precisely evaluate and delineate the aortic anatomy. For abdominal aortic aneurysms, length and diameter of the proximal neck, location of important aortic and iliac side branches (accessory renal arteries, inferior mesenteric artery, and hypogastric arteries), and distal fixation site characteristics must be determined. Significant aneurysm neck angulation, short neck length, large neck diameter, and severe aortic calcification currently exclude many patients from endovascular repair. TEE and intravascular ultrasonography are often used to locate the entry and exit sites of dissections and to confirm precise stent-graft placement.

Endovascular stent-grafts are often custom-made for each patient based on aortic anatomy. Each endovascular stent-graft delivery device has a unique method of deployment, and many individual variations in technique are possible. First-generation endografts were not fully stented and required balloon expansion of the proximal portion at the time of deployment. Metal hooks in the proximal portion were embedded into the aortic wall with balloon inflation, which resulted in complete aortic occlusion, not unlike aortic cross-clamping. These unsupported endografts were prone to complications such as migration and kinking. Distal migration during proximal endograft deployment was particularly troublesome with intrathoracic endograft placement. Induced hypotension,[255] adenosine-induced asystole,[256] and induced ventricular fibrillation[257] have all been used successfully to reduce endograft migration during deployment. Current-generation endografts are fully stented (i.e., stent-grafts) and self-expanding. Balloon expansion is not required at the time of deployment. Stent-graft migration at the time of deployment is largely prevented and associated complications are reduced. A unique trilobed aortic balloon can be used to expand the stent-graft for aortic apposition after deployment without complete aortic occlusion.[258] Though no longer a requirement, mild induced hypotension (with nitroglycerin or sodium nitroprusside) can be used selectively during stent-graft deployment.

Anesthetic Management

Local,[259] regional,[260] and general anesthesia[261] techniques have all been described for endovascular aortic repair shortly after its introduction. A variety of regional techniques have been used, including paravertebral, spinal, continuous spinal, epidural, and combined spinal/epidural. General anesthesia was commonly used with early-generation devices because procedure times were often long. As centers have gained experience with newer-generation devices, procedure times have been reduced and local and regional techniques are used more often, most commonly with intravenous sedation. A sedation technique using dexmedetomidine with local anesthesia has been reported.[262] Despite procedural advances and the established feasibility of local and regional anesthesia, these techniques have not become accepted on a large scale. An analysis of anesthesia type based on data from the EUROSTAR registry (5557 endovascular repairs of infrarenal aortic aneurysm) reported the use of local, regional, and general anesthesia in 6%, 25%, and 69% of patients, respectively.[263] The influence of anesthesia type on outcome based on the EUROSTAR data indicates that the use of local or regional anesthesia may reduce ICU admission, hospital length of stay, and early complications.[263] Further analysis of high-risk patients from this registry suggests that a mortality benefit may exist when local or regional anesthesia is used.[264] A retrospective analysis of 229 endovascular abdominal aortic aneurysm repairs using local anesthesia with intravenous sedation or general anesthesia reported similar rates of cardiac and pulmonary morbidity.[261] Reduced intraoperative fluid requirements[261,265] and less vasopressor support[265] have been reported with the use of local anesthesia. Given the retrospective nature of these reports and the significant selection bias regarding assignment of anesthetic technique, specific recommendations regarding the use of local, regional, and general anesthesia are premature. As with open aortic repair, maintenance of vital organ perfusion and function by the provision of stable perioperative hemodynamics is probably more important to overall outcome than the choice of anesthetic technique is.

I commonly use a general anesthetic technique for endovascular aortic repair in patients requiring extensive groin dissection or any retroperitoneal dissection and those requiring complex repairs, where conversion to open repair may be more likely. A balanced technique using relatively short-acting agents maximizes management flexibility. Opioid requirements are usually minimal (2 to 4 μg/kg fentanyl), and postoperative pain is easily managed. Esmolol, sodium nitroprusside, nitroglycerin, and phe-

nylephrine should be available and used to maintain appropriate hemodynamics. Epidural and spinal anesthesia is used selectively based primarily on patient and surgeon preference.

Placement of a radial artery catheter should be routine for all endovascular aortic repairs. It should be placed on the right side because a catheter may be placed percutaneously in the left brachial artery for aortic angiography. Central venous and pulmonary artery catheter monitoring is not routine. Two large-bore peripheral intravenous catheters are recommended. Although blood loss and fluid requirements are not usually excessive, the potential for rapid blood loss is real. The possibility of acute aortic rupture necessitates the availability of fluids, blood, and a rapid infusion device. Catheterization of the bladder is required for most procedures. Monitoring of urine output can help guide fluid management, particularly when high volumes of heparinized flush solution and radiographic contrast material are used and when diuretics (i.e., mannitol or furosemide) are administered. Fluid management is directed primarily at maintaining normovolemia. Isotonic bicarbonate infusion is often used in patients with renal dysfunction to reduce the incidence of contrast-induced nephropathy.[266] Active patient warming is frequently necessary to prevent hypothermia, particularly with longer procedures.

Endovascular repairs involving the descending thoracic aorta require additional preparation and monitoring. These procedures are often performed in the operating room under general anesthesia. Although current-generation devices are much less prone to graft migration during deployment, pharmacologically (i.e., sodium nitroprusside or nitroglycerin) induced hypotension (i.e., systolic blood pressure <100 mm Hg) is commonly used during deployment. TEE monitoring is frequently used and can be extremely helpful in identifying proximal and distal stent-graft landing zones, entry and exit points of dissections, true and false lumens, and aneurysm exclusion. Although published reports of endovascular repairs involving the descending thoracic aorta are limited, neurologic deficits consistent with spinal cord ischemia have been reported.[267,268] Concomitant or previous abdominal aortic repair and long-segment thoracic aortic exclusion appear to be important risk factors.[267-269] Postoperative hypotension may play a role as well.[268] Delayed paraplegia 10 months after endovascular repair of thoracic aortic aneurysms has been reported.[270] CSF drainage has been shown to reverse delayed-onset neurologic deficit after endovascular TAA repair,[217,218,268] thus prompting some centers to use perioperative CSF drainage in all high-risk patients.[268] Intraoperative spinal evoked potential monitoring plus temporary (15 minutes) balloon occlusion of the thoracic aorta before stent-graft deployment has been reported as a means to evaluate the patient's risk for spinal cord ischemia.[271]

Endoleak

The inability to obtain or maintain complete exclusion of the aneurysm sac from arterial blood flow, termed *endoleak*, is a complication specific to endovascular aortic repair. The concern is that any pressurization of the aneurysm sac (i.e., endotension) can lead to aneurysm enlargement and rupture. Endoleaks can be detected by arteriography, computed tomographic scanning, magnetic resonance imaging, and duplex ultrasound scanning. A classification system developed for endoleak describes four distinct types.[272] Type I endoleak occurs when there is an inadequate seal between the stent-graft and the aortic wall at the proximal or distal attachment sites. Type II endoleak occurs when there is retrograde filling of the aneurysm sac from patent intercostal, lumbar, inferior mesenteric, or testicular arteries. Type III endoleak is due to structural failure of the stent-graft that allows blood to flow directly into the aneurysm sac. The structural failure may be due to tears in the graft fabric or separation of individual components of a modular endograft. Type IV endoleak relates directly to the porosity of the graft material. Endoleaks are also classified as primary (after deployment) or secondary (after initial seal). A "type V" endoleak has appeared in the literature and refers to persistent pressurization of the aneurysm sac after endovascular repair *without* an identified leak on imaging studies.

The rate of occurrence of endoleak depends on many factors, including the endograft device, the method of deployment, vascular anatomy, and progression of disease. Management of endoleak after endograft placement is quite controversial and ranges from observation with periodic imaging surveillance to immediate endovascular or surgical correction. Type I and III endoleaks are associated with an increased risk of rupture[273] and are almost uniformly treated aggressively. Although type II endoleaks do not often require urgent treatment and many spontaneously thrombose, they are associated with aneurysm enlargement.[273] Type IV endoleaks are usually self-limited and rarely require specific treatment. Type V endoleaks require intervention if aneurysm growth is detected.

Endovascular extension grafts, coil embolization, and conversion to open repair have been used successfully to repair endoleaks.[274]

Morbidity and Mortality

A meta-analysis of 39 studies reported on perioperative (30-day, 2387 patients) and postoperative (>30-day, 1645 patients) complications after endovascular abdominal aortic repair.[275] Mean follow-up was 13.9 months. The perioperative mortality rate was 3.7%, and the annual mortality rate was 5.0% per year. Rates of both endoleak (13.1%) and conversion to open repair (5.0%) were higher in the perioperative period than postoperatively (5.4% and 1.4% per year, respectively). The EUROSTAR registry was established in 1996 to collect data on the outcome of endovascular repair of abdominal aortic aneurysms in Europe. In a publication from the EUROSTAR database involving 3222 patients who received a variety of endografts, operative mortality was 2.0%.[276] Mean follow-up was 13.7 months. Early conversion to open repair occurred in 1.5% of patients, and secondary interventions occurred at a rate of 10% per year (1% per year conversion to open repair and 9% per year revision). The risk of rupture was 0.46% per year with an associated mortality rate of 56%. This database has confirmed the importance of endoleak, stent-graft failure, and stent-graft migration in the causation of aneurysm rupture.[277]

The Cleveland Clinic group reported their experience involving 703 patients who underwent endovascular repair of abdominal aortic aneurysms with several devices.[278] As with other reports, the average follow-up was just over 12 months. Overall, secondary procedures were required in 15% of patients, with a cumulative risk of 12% at 1 year, 24% at 2 years, and 35% at 3 years. The mortality associated with these secondary proce-

dures was 8% overall and 18% in patients who required conversion to open repair. In another report from this same group, outcome after endovascular repair was significantly worse with larger (>5.5 cm) aneurysms. At 24 months, patients with larger aneurysm had more type I endoleaks, device migration, and conversion to open repair. Of even greater importance, survival was diminished (71% versus 86%), and risk for aneurysm-related death was increased (6.1% versus 1.5%) at 24 months in patients with large aneurysms. The midterm (4 years) outcome results from the EUROSTAR database (4392 patients) also found large aneurysms to be associated with increased rates of aneurysm-related death, non–aneurysm-related death, and rupture.[279]

Limited information is available regarding endovascular repair involving the descending thoracic aorta. Although short-term results from small to moderate-sized retrospective series are encouraging,[258,280,281] severe complications, including paraplegia, aortic rupture, stroke, renal failure, and respiratory failure, have been reported.[282] Additionally, major procedure- or device-related complications occur in up to 38% of patients.[283] A mortality rate of 6.2% has been reported for 642 patients treated worldwide.[284] The long-term durability of endovascular repair of the descending thoracic aorta is unknown. Long-term endograft surveillance is required to detect device failure.

Randomized Clinical Trials

Endovascular repair of abdominal aortic aneurysms was originally developed to provide a treatment option for patients considered to be poor surgical candidates. Early controlled clinical trials reported greater hemodynamic stability,[285] reduced stress response,[286] shorter postoperative length of stay,[287] and better analgesic control[288] than with open aortic repair. These nonrandomized trials demonstrated that endovascular aortic aneurysm repair is feasible and safe and may reduce perioperative morbidity when compared with open repair.[289-291] Based on these early reports and without the benefit of long-term outcome data or randomized clinical trials, endovascular aneurysm repair has been applied to a large proportion of patients with abdominal aortic aneurysms. Randomized clinical trials have been conducted in Europe and are currently in progress in the United States to answer several critical questions related to the broad application of endovascular technology in patients fit and unfit for open repair.

Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial

The DREAM trial randomized 351 patients (from the Netherlands and Belgium) with abdominal aortic aneurysms greater than 4.9 cm who were considered suitable candidates for both open and endovascular options to either open repair or endovascular repair. Operative mortality (30 day) was 1.2% in the endovascular repair group and 4.6% in the open repair group.[292] The combined rate of operative mortality and severe complications was 4.7% in the endovascular repair group and 9.8% in the open repair group.[292] However, 2 years after randomization, the cumulative survival rates did not differ between treatment groups (90%).[293] Cumulative rates of aneurysm-related death were 2.1% for endovascular repair and 5.7% for open repair.[293] The rates of survival free of complications were also similar in the two groups (66%).[293] The authors concluded that the perioperative survival advantage with endovascular repair versus open repair is not sustained after the first postoperative year.[293] Quality of life in the first postoperative year was evaluated in a subset of DREAM trial participants. Although endovascular repair had a quality-of-life advantage in the early postoperative period, at 6 months and beyond, patients reported better quality of life after open repair.[294] In a follow-up report on cost-effectiveness, endovascular repair (in patients fit for open repair) did not result in a quality-adjusted life-year gain at 1 year after surgery, provided only marginal survival benefit, and was associated with a substantial increase in cost.[295] The outcome results of endovascular repair in the DREAM trial are comparable to observations from a large common practice–derived database (EUROSTAR registry) and appear to be generalizable to common clinical practice.[296]

EVAR-1 Trial

The EVAR-1 trial randomized 1082 patients (United Kingdom) with abdominal aortic aneurysms greater than 5.5 cm, older than 60 years, and judged fit for open repair to either endovascular repair or open repair. The primary end point was all-cause mortality. Secondary end points were aneurysm-related mortality, postoperative complications, health-related quality of life, and hospital costs. Operative mortality (30 day) was 1.7% in the endovascular repair group and 4.7% in the open repair group,[297] closely matching the DREAM trial results.[292] Secondary interventions (30 day) were more common in patients undergoing endovascular repair (9.8% versus 5.8%).[297] After a follow-up of 4 years, all-cause mortality did not differ between groups (26% for endovascular versus 29% for open)[298] despite an initial postoperative benefit of endovascular repair.[297] Aneurysm-related mortality at 4 years was lower in the endovascular repair group (4% versus 7%)[298] and in accord with the operative mortality benefit. Overall rates of complications (41% versus 9%) and reinterventions (20% versus 6%) were lower in the open repair group. Of patients undergoing endovascular repair, 2.7% required conversion to open repair during the follow-up period. There were no clinically significant differences in health-related quality of life. Hospital costs were approximately a third higher for endovascular repair.

EVAR-2 Trial

The EVAR-2 trial was designed to compare endovascular repair versus no intervention in patients deemed unfit for open abdominal aortic aneurysm repair. A total of 338 patients (from the United Kingdom) with abdominal aortic aneurysms greater than 5.5 cm, older than 60 years, and deemed unfit for open repair because of comorbid conditions were randomized to undergo endovascular repair or no intervention. All patients received best medical treatment for their comorbid conditions. Primary and secondary end points were the same as for the EVAR-1 trial. Operative mortality (30 day) for the endovascular group was 9%,[299] considerably higher than that reported in EVAR-1. The overall mortality rate at 4 years was 64%, and there was no difference between the endovascular group and the no-intervention group in aneurysm-related mortality or all-cause mortality.[299] Although there were more deaths from aneurysm rupture in the no-intervention group, the initial high mortality in the endovascular group resulted in no late differences in mortality. The authors concluded that endovascular repair did not improve survival over no intervention, had little effect on health-related

quality of life, and was associated with a need for continued monitoring and reintervention, at substantially increased cost.[299] In-hospital mortality for the highest-risk patients undergoing endovascular aortic aneurysm repair in the United States may be lower than that reported in EVAR-2, suggesting that these high-risk patients should not be denied endovascular repair.[300]

These completed European trials, as well as those currently under way in the United States, will aid understanding and improve the application of both endovascular and open repair for abdominal aortic aneurysm.

Lower Extremity Revascularization

Lower extremity arterial insufficiency, or peripheral arterial disease, is a common condition that affects as many as 10 million people in the United States, and its incidence is increasing annually.[301] Because individuals with lower extremity peripheral arterial disease are most often asymptomatic or have symptoms other than classic intermittent claudication, the true prevalence of the disease is unknown. In a population-based study of individuals 55 years and older, the prevalence of peripheral arterial disease was 19.1% (16.9% in men and 20.5% in women).[302] The prevalence of peripheral arterial disease in primary care practices in the United States is high (29%), and the condition is often unrecognized (44%).[303] Arterial disease of the upper extremity does occur but is much less common than lower extremity involvement.

Atherosclerosis is the most common cause of peripheral arterial disease. Risk factors for atherosclerosis of the lower extremity are the same as for other vascular areas and include advanced age, male sex, hypertension, smoking, hyperlipidemia, and diabetes. Infrainguinal atherosclerosis may involve the femoral artery, popliteal artery, and any of the infrapopliteal arteries. The superficial femoral artery is the most common site of major atherosclerotic involvement below the inguinal ligament. Nonatherosclerotic causes of peripheral arterial disease include embolism, thromboangiitis obliterans (Buerger's disease), immune arteritis, radiation arteritis, giant cell arteritis, adventitial cystic disease, fibromuscular dysplasia, and homocysteinemia.

As previously noted, peripheral arterial disease is a very strong indicator of generalized atherosclerosis and is a risk marker for other vascular conditions, including CAD, cerebrovascular disease, and aneurysmal disease. For example, patients with concomitant CAD and peripheral arterial disease have a higher prevalence of triple-vessel coronary disease than patients with CAD alone do.[304] Additionally, over 20% of patients with peripheral arterial disease have a 70% or greater carotid artery stenosis.[305] It is well documented that patients with peripheral arterial disease are at higher risk for cardiovascular morbidity and mortality than individuals without peripheral arterial disease are.[306-310] The increased cardiovascular risk may not be entirely due to atherosclerosis because these patients may have an enhanced prothrombotic state secondary to platelet activation[311] and a high prevalence of diverse hypercoagulable states.[312] The natural history of atherosclerotic lower extremity peripheral arterial disease is illustrated in Figure 62-14.

Acute Arterial Occlusion

Acute peripheral arterial occlusion occurs primarily as a result of embolism and thrombosis. Pseudoaneurysm after invasive procedures in which the femoral artery is cannulated is a much less common cause of acute ischemia. The vast majority of emboli to the lower extremity originate in the heart, with intermittent atrial fibrillation and myocardial infarction being the most common causes of emboli. Although rheumatic heart disease is now a rare cause of embolic occlusion, prosthetic heart valves may be a source of emboli. Other causes of embolization include bacterial endocarditis, atrial myxoma, paradoxical venous emboli, and atheromatous debris from proximal aneurysms. Arterial emboli often lodge at vessel bifurcations. Common sites in the lower extremity include the femoral artery bifurcation, iliac artery bifurcation, and popliteal artery.

Thrombotic occlusions probably outnumber embolic occlusions by a ratio as high as 6:1.[313] Acute arterial thrombosis of native vessels almost always occurs in the setting of severe and long-standing atherosclerosis. It can be viewed as the terminal event in the progression of atherosclerosis. Thrombosis of vascular bypass grafts is common and may result in acute ischemia. The high prevalence of diverse hypercoagulable states in patients with peripheral arterial disease may predispose such patients to thrombosis.[312]

The clinical manifestation of acute arterial occlusion will vary depending on the location of the obstruction and the extent of collateral circulation. In patients with a sudden onset of acute extremity ischemia, the occlusion often occurs abruptly and without the preexisting development of collateral pathways. Although ischemic symptoms are often more severe in patients with embolic occlusion than in patients with thrombotic occlusion, differentiation between embolic and thrombotic occlusion may be difficult. Acute occlusion of a previously patent extremity artery is a dramatic event characterized by pulselessness, pain, pallor, paresthesia, and paralysis (the "five P's"). Absence of pulses and pallor are early manifestations. The sudden onset of pain is very common, and it may be intense. Motor weakness and paresthesia are usually late manifestations of severe ischemia.

Acute ischemia needs to be evaluated rapidly because irreversible tissue injury can occur within 4 to 6 hours.[314] Initial management usually involves immediate anticoagulation to prevent propagation of thrombus, stabilization and control of coexisting medical conditions, and arteriography. Immediate surgical revascularization is generally indicated in the profoundly ischemic extremity. Patients with embolization to a nonatherosclerotic extremity are frequently managed with femoral thromboembolectomy under local anesthesia. Management of patients with peripheral arterial disease who are suspected of having thrombotic occlusion requires arteriography to determine the severity and anatomic location of the occlusion. Angioplasty or thrombolytic therapy may be performed in conjunction with arteriography. Intra-arterial thrombolysis is often used as an initial intervention in an effort to unmask the culprit lesion responsible for the occlusive event. Patients are frequently scheduled for lower extremity bypass surgery the following day, pending evaluation of lower extremity blood flow. The frequent use of heparin anticoagulation and thrombolytics has significant implications for the anesthesiologist because regional anesthesia is not

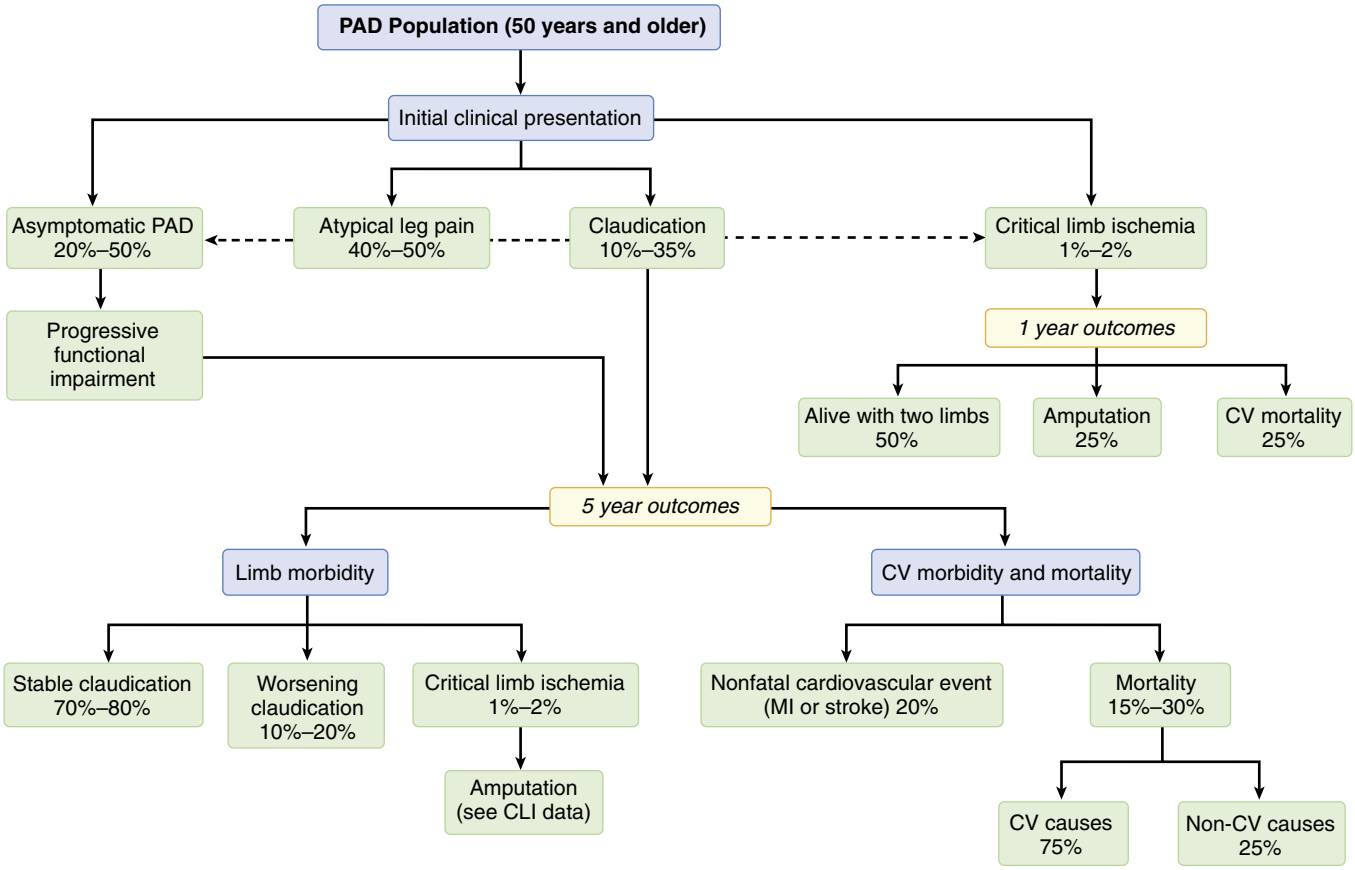


Figure 62-14 Natural history of atherosclerotic lower extremity peripheral arterial disease (PAD). Individuals with atherosclerotic lower extremity PAD may be asymptomatic (without identified ischemic leg symptoms, albeit with a functional impairment) or have leg symptoms (classic claudication or typical leg symptoms) or critical limb ischemia (CLI). All individuals with PAD face a risk of progressive limb ischemic symptoms, as well as a high short-term cardiovascular ischemic event rate and increased mortality. These event rates are most clearly defined for individuals with claudication or CLI and less well defined for individuals with asymptomatic PAD. CV, cardiovascular; MI, myocardial infarction. *(From Hirsch AT, Haskal ZJ, Hertzer NR, et al: ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease [lower extremity, renal, mesenteric, and abdominal aortic]: Executive summary. A collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines [Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease] endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol 47:1239-1312, 2006.)*

an option in an anticoagulated patient. Morbidity and mortality rates in this patient population are high, particularly in patients requiring significant operative intervention.[315-317]

Chronic Arterial Occlusion

Chronic arterial insufficiency is most often secondary to long-standing atherosclerosis in which the arterial lumen of the lower extremity becomes progressively stenosed by atherosclerotic plaque. When the stenosis approaches total occlusion, the marked reduction in blood flow leads to thrombotic occlusion. Hemodynamically significant stenosis and total-vessel occlusion commonly exist in the lower extremity with no or very minimal symptoms. The development of collateral vessels around a stenosed or occluded arterial segment often prevents clinical symptoms until multiple occlusions exist in major vessels. Thus, the majority of patients with peripheral arterial disease are asymptomatic. Patients with symptoms most commonly have mild intermittent claudication—pain or fatigue in the muscles of the lower extremity caused by exertion and relieved with rest. The pain usually occurs in the muscle group distal to the site of arterial insufficiency. With disease progression, severe disabling intermittent claudication or rest pain, so-called critical limb ischemia, can develop.

Noninvasive testing with the ankle-brachial index (ABI) is the clinical standard for documenting the presence and severity of peripheral arterial disease. The ABI is determined by dividing ankle systolic pressure by brachial systolic pressure. Normally, the ABI is between 1.0 and 1.1; a value less than 0.9 indicates arterial disease proximal to the point of measurement. The ABI approximates the degree of arterial insufficiency; claudication occurs with indexes ranging from 0.3 to 0.9, disabling claudication or rest pain with indexes less than 0.5, and gangrenous extremities with indexes less than 0.2.[318]

One of the most important aspects of peripheral arterial disease is that it is a very strong marker for early mortality. In patients with peripheral arterial disease the risk of amputation is much less than the risk of death.[319] A low ABI is a strong predictor for disease progression,[320,321] but it is also one of the strongest risk

factors for all-cause mortality.[310] Claudication is associated with a high rate of mortality[309] but is relatively benign in terms of lower extremity outcome.[310,320]

Surgical Management

Accepted treatments of lower extremity arterial disease include both nonoperative and operative modalities. Nonoperative options include lifestyle and risk factor modification, exercise programs, and pharmacologic therapy. Operative options include percutaneous endovascular modalities and surgical reconstruction. Endovascular techniques include more established therapies such as intra-arterial thrombolytic therapy, balloon catheter embolectomy, transluminal balloon angioplasty, and angioplasty and stent placement, as well as new technologies such as novel angioplasty balloons, atherectomy and laser angioplasty systems, cryotherapy, and placement of nitinol and drug-eluting stents.[322] Surgical procedures include endarterectomy, bypass grafting (primary or revision), and amputation.

Lower extremity arterial reconstruction is performed both for severe disabling claudication and for critical limb ischemia (limb salvage). The choice of operative approach depends primarily on the location and distribution of arterial occlusions. There are several surgical approaches to patients with lower extremity arterial insufficiency. For occlusion distal to the inguinal ligament, a femoral-popliteal bypass with an autologous great saphenous vein (reversed) graft is most often the procedure of choice. Graft patency rates with this approach are reported to be 59% at 5 years and 38% at 10 years. The saphenous vein may be used in situ (not reversed), but this technique is more demanding and requires excision of the valves to allow adequate flow. Human umbilical vein and polytetrafluoroethylene grafts can be used when an autologous saphenous vein is unavailable, which is often the case when patients have previously undergone coronary artery bypass or lower extremity bypass. The cephalic and basilic veins from the upper extremities are sometimes used as a graft. Harvesting vein from the upper extremities has obvious implications with regard to intravenous catheter placement and the use of regional anesthesia.

In patients with aortoiliac disease who are not candidates for aortobifemoral bypass because of coexisting medical diseases, an extra-anatomic procedure (axillofemoral or femorofemoral bypass) is an alternative approach that is thought to be a less stressful procedure. Distal arterial reconstruction with a bypass to the tibial, peroneal, or pedal vessels is almost exclusively performed for limb salvage. Prosthetic grafts have very high failure rates, and every attempt is made to harvest adequate autologous vein.

Preoperative Preparation and Monitoring

Preoperative assessment and optimization of cardiac risk were discussed previously (also see Chapters 34 and 35). It is extremely important that long-term cardiac and respiratory medications be given the morning of surgery. Continuing chronic β-blocker therapy is particularly important because acute withdrawal can be associated with significant morbidity. Current, recent, and anticipated use of hemostasis-altering drugs should be established and discussed with the surgical team. In most instances, antiplatelet therapy with aspirin should be continued. Preoperative termination of other antiplatelet therapy, such as thienopyridine derivatives, should be made on an individual basis.

Monitoring for lower extremity arterial revascularization should include an intra-arterial catheter that permits continuous blood pressure monitoring to optimize coronary artery and lower extremity graft perfusion, as well as blood sampling for diagnostic laboratory testing. A urinary bladder catheter is usually indicated because the duration of the procedure may be long and urine output may be useful for assessing intravascular volume and cardiac output. Although central venous catheters are not necessarily helpful in routine cases, central venous pressure monitoring should be considered for patients with significant renal dysfunction, in whom intravascular volume should be carefully monitored, and for patients with significantly impaired ventricular dysfunction or congestive heart failure. In these patients, pulmonary artery catheter monitoring may be helpful, but given the relatively low potential for blood loss and third-space fluid loss with lower extremity vascular procedures, the pulmonary artery catheter is usually reserved for patients with active congestive heart failure or unstable angina. Our criteria for using invasive hemodynamic monitoring have been described previously.[28] As discussed earlier, computerized ST-segment monitoring is helpful in monitoring for myocardial ischemia.

Regional versus General Anesthesia

The most appropriate regimen of intraoperative anesthesia and postoperative analgesia for high-risk patients undergoing vascular surgery remains controversial. Competing concerns regarding both the quality and escalating costs of perioperative care have challenged clinicians to establish practice standards that are both safe and efficient. Postoperative complications after vascular surgery are common and have an adverse impact on both clinical outcome and resource use. Improvement in clinical outcome and reduced use of medical resources in patients undergoing vascular surgery may result from the use of one particular regimen of anesthesia and analgesia over another.[56,323] If such improvement can be achieved, selection of the most appropriate anesthetic and analgesic regimen would then be of great benefit to patients, providers, payers, and society.

The question of whether regional or general anesthesia is preferable for vascular surgery has been debated for years, but only in the past decade have well-designed prospective randomized trials been completed. Earlier nonrandomized trials were prone to significant bias because many clinicians had the unfounded belief that regional anesthesia was safer for patients with advanced cardiac or pulmonary disease. Even the prospective studies must be interpreted cautiously because many suffer from deficiencies in design and methodology, including nonuniform patient populations,[56,156,323] lack of standardization or control of perioperative treatments,[27,32,56,66,154,156,158,323] use of nonequivalent modalities for postoperative pain relief,[27,32,56,156,158,323] and possible investigator bias.[27,28,32,56,66,154-156,158,323] It should be recognized that many clinical trials have attempted to optimize the delivery and management of anesthetic techniques, which may mask the true risks associated with the anesthetic. An example is the strict hemodynamic control, transfusion thresholds, and postoperative analgesia regimens that have been used in clinical trials.[28,33] The physician must also appreciate that the overall complication rates

reported in clinical trials may seem high, but this may be explained by the aggressive surveillance commonly used in clinical trials. In general, it is often best to choose the anesthetic and analgesic techniques that are most familiar to a particular institution because, for example, unfamiliarity and mismanagement of epidural catheters can cause serious complications. It is my personal hypothesis that overall optimization of perioperative care, rather than anesthetic or analgesic selection, is the most important factor in improving outcome after vascular surgery.

Occasionally, surgical procedures such as embolectomy and femoral pseudoaneurysm repair can be completed with the patient under local anesthesia with intravenous sedation. Because these procedures may progress to more invasive arterial reconstruction, a regional or general anesthetic should be considered before the procedure begins to avoid an unplanned conversion to general anesthesia.

In some situations, one anesthetic technique (regional or general) is preferable to the other. The patient may have a preference for one technique over another based on a number of factors. Regional techniques should be avoided in patients who are uncooperative, demented, or unable to lie flat. Needle or catheter placement can be difficult in patients with severe spine deformity or previous spinal instrumentation. Local infection, neurologic disease affecting the lower part of the body, and hemostasis-altering drugs are all considered, to varying degree, a contraindication to regional anesthesia. Anticoagulant and antiplatelet therapy is common in the vascular surgery population and often precludes the use of spinal or epidural techniques.[324] Symptomatic bleeding within the neuraxis (spinal or epidural hematoma) is a potentially devastating complication of neuraxial anesthesia that can lead to permanent neurologic injury. I view preoperative anticoagulation with heparin or warfarin and any active thrombolytic therapy as a contraindication to the use of spinal and epidural anesthesia. In patients in whom such agents have recently been discontinued, very careful consideration should be given on an individual basis before performing neuraxial techniques. The anesthesiologist must take into consideration the agent used, the duration of discontinuance, current coagulation status, and concomitant administration of medications affecting hemostasis. The use of regional techniques during intraoperative systemic heparinization does not appear to represent a significant risk.[325] Although it has been recommended that surgery be canceled when blood is obtained through the neuraxial needle, support for this recommendation is lacking.[326] Much more importantly, it has also been recommended that epidural catheters not be removed until anticoagulants have been discontinued in the postoperative period.[324] The use of and indications for low-molecular-weight heparin continue to increase, and there is evidence to suggest a significant risk of spinal/epidural hematoma when regional techniques are used in conjunction with these drugs.[327] Current recommendations suggest that regional techniques be delayed at least 12 to 24 hours after the last dose of low-molecular-weight heparin.[324] The use of antiplatelet agents is a complex topic, and it is important to note the pharmacologic differences among the drugs when regional techniques are desired.[324,328] Although some centers routinely check a bleeding time in patients who have taken aspirin in the 7 days before a planned regional anesthetic technique, there is no evidence that a bleeding time is useful in this setting.[329,330] In general, when a regional technique is desired for a patient with any question of a coagulation abnormality, spinal anesthesia with the smallest-diameter needle is preferable to epidural anesthesia.[327] A comprehensive consensus report on neuraxial anesthesia and anticoagulation is available and should be read by all clinicians.[324]

Given the relative risks associated with neuraxial anesthesia in patients receiving anticoagulant or antithrombolytic therapy, some clinicians advocate the broader use of peripheral nerve blocks, such as sciatic, femoral, popliteal, and ankle (see Chapter 52). Continuous catheter techniques can be used to provide both anesthesia and postoperative analgesia. High-resolution ultrasound imaging of neural structures, percutaneous electrode guidance, and the use of stimulating catheters have recently been introduced into clinical practice. Peripheral nerve blocks are probably associated with fewer systemic and neuraxial side effects, but little clinical information is available in the vascular surgical population. Because of the high volume of local anesthetics frequently used for peripheral nerve blocks, the issue of systemic toxicity must be considered. Caution should be considered with the use of peripheral nerve block in an anticoagulated patient, particularly when the neural structures are deep or located in close proximity to vascular structures.

Because regional anesthesia does not require airway instrumentation, neuromuscular blocking agents, or volatile agents, it has traditionally been a prevailing belief that regional anesthesia is preferable in patients with significant pulmonary disease. Although it is true that instrumentation of the airway may precipitate bronchospasm or increase the risk for nosocomial infection, general anesthesia with endotracheal intubation does allow complete airway and ventilation control, the ability to effectively administer inhaled bronchodilators, and the ability to easily suction airway secretions. A reduction in time to extubation after aortic surgery is a fairly consistent theme with regional anesthesia and analgesia, but this does not appear to have any impact on clinically relevant pulmonary outcomes.[32,23,66,156]

Epidural analgesia has been championed over parenteral opioid analgesia as a means of optimizing postoperative pulmonary function by improving pain control and respiratory muscle function. Although epidural analgesia can provide excellent postoperative pain control and may improve postoperative lung function (i.e., increased tidal volume and vital capacity), clinical studies do not support a consistent finding of improved pulmonary outcomes.[331] Overall, there is little evidence from well-designed clinical studies to demonstrate improved pulmonary outcome with regional anesthesia and analgesia.[332] Because postoperative maneuvers to increase mean lung volumes are of proven benefit in preventing postoperative pulmonary complications, it has been recommended that maneuvers to encourage deep breathing, such as deep-breathing exercises, incentive spirometry, and chest physiotherapy, should be the focus of preventive efforts.[332]

Cardiac morbidity is the most common cause of death in patients undergoing surgery, and the incidence of perioperative cardiac morbidity is 10 times greater in vascular surgery patients than in nonvascular surgery patients.[17] Eleven prospective randomized trials evaluating the effects of regional versus nonregional anesthesia or analgesia in vascular surgical patients have reported on cardiac outcomes and death. Three studies (Cook and colleagues,[333] Christopherson and coworkers,[28] and Bode and associates[27]) compared pure regional (spinal or epidural) versus general anesthetic techniques in lower extremity vascular patients. Tuman and colleagues[323] compared combined epidural/general versus general anesthetics in aortic and lower extremity surgical patients. Six studies (Baron and coworkers,[32] Davies and associates,[154] Garnett and colleagues,[158] Bois and coworkers,[155] Boylan and

Table 62-8 Cardiac and Vascular Outcomes in Studies of Regional versus General Anesthesia in Vascular Surgery Patients

Study	No. of Patients	Death		MI		Myocardial Ischemia		CHF		Graft Occlusion		Comments
		RA	GA	RA	GA	RA	GA	RA	GA	RA	GA	
Cook et al.[333]	101	2%	6%	4%	2%							Spinal anesthesia, lower extremity surgery
Tuman et al.[323]	80	0%	0%	0%	8%			5%	10%	3%	20%	Aortic and lower extremity surgery
Baron et al.[32]	167	4%	5%	6%	6%	20%	19%	6%	8%			Aortic surgery
Christopherson et al.[28]	100	2%	2%	4%	4%	35%	45%			4%	22%	Lower extremity surgery
Davies et al.[154]	50	8%	4%	8%	4%		12%	8%				Aortic surgery
Garnett et al.[158]	99	0%	4%	6%	10%	58%	51%	6%	10%			Aortic surgery
Bode et al.[27,334]	423	3%	3%	5%	4%			10%	9%	6%	4%	Spinal and epidural anesthesia, lower extremity surgery
Bois et al.[155]	114	2%	2%	4%	8%	18%	19%	5%	0%			Aortic surgery
Boylan et al.[66]	40	0%	0%	5%	5%	32%	38%	11%	5%			Aortic surgery
Norris et al.[33]*	168	5%	5%	4%	0%	16%	17%	1%	0%			Aortic surgery, double-blinded study

*Any epidural use included in the regional anesthesia group.
CHF, congestive heart failure; GA, general anesthesia; MI, myocardial infarction; RA, regional anesthesia.

associates,[66] and Norris and colleagues[33]) compared epidural and nonepidural anesthetic or analgesic techniques (or both) in aortic surgical patients. Fleron and coworkers[34] compared intrathecal opioid versus intravenous analgesia in aortic surgical patients. Of note, only the report by Norris and associates[33] had a double-blinded design. The results of these studies, involving more than 1500 patients, are shown in Table 62-8.

In summary, no study demonstrated any difference in outcome with regard to mortality, MI, myocardial ischemia, or congestive heart failure. Only the study by Tuman and colleagues[323] reported a difference in cardiac outcome. Outcome was significantly improved by epidural anesthesia and analgesia, but only when more subtle outcomes (i.e., dysrhythmias) were included. Christopherson and coworkers[28] (i.e., the Perioperative Ischemia Randomized Anesthesia Trial [PIRAT]) and Norris and associates[33] (i.e., PIRAT II) found no difference in cardiac events or myocardial ischemia as detected by continuous Holter monitoring over a 3-day postoperative period. In these studies from my institution, strict intraoperative and postoperative protocols were used to guide and optimize perioperative management and postoperative analgesia. Bode and colleagues[27] reported on the largest randomized trial, which included a spinal anesthesia group in addition to general and epidural groups. There were no differences in cardiac events in any of the three groups. Of note, a failed spinal or epidural technique in this trial was associated with 9% mortality, as opposed to 2% for all successful general and regional anesthetics.[27]

One of the most interesting and clinically significant finding in these randomized trials is the beneficial effect of regional anesthesia on lower extremity graft patency in the postoperative period. Two of the studies (Tuman and colleagues[323] and Christopherson and coworkers[28]) reported a fivefold greater incidence of graft occlusion after general (relative to regional) anesthesia. Most graft occlusions occurred in the first 1 to 3 days after surgery, after which the established difference in the incidence of graft occlusion between anesthetic techniques was maintained over time (6 weeks and beyond) (Fig. 62-15). This time course suggests that anesthetic technique may have played a role in graft occlusion. Bode's group[334] reported an overall very low incidence of graft occlusion, but differences in hemodynamic management, surgical technique, and the patient population may explain these findings. For example, intraoperative intravascular angioscopy was used to inspect the grafts to confirm patency before completion of surgery, and all patients were cared for in an intensive care setting for 48 hours after surgery. Thus, optimization of care with respect to graft patency may negate any beneficial effect of regional techniques. It is also important to keep in mind that none of these studies were specifically designed to evaluate surgical outcome (i.e., graft patency) in a prospective manner. A retrospective review of more than 300 primary femoropopliteal-tibial bypass procedures reported no differences in graft thrombosis rates for epidural (14%) or general anesthesia (9.4%).[335]

The proposed mechanism for the benefit of regional anesthesia is the effect of the anesthetic technique on coagulation. General anesthesia is associated with a hypercoagulable state in the early postoperative period, whereas regional anesthesia attenuates this effect.[336] Tuman and colleagues[323] demonstrated this by thromboelastography and Rosenfeld and coworkers[336] by increased plasminogen activator inhibitor (Fig. 62-16) and fibrinogen levels. It appears that fibrinolysis is decreased after general anesthesia and is normal after regional anesthesia. These findings may be related to attenuation of the surgical stress response with regional anesthesia because there appears to be a link between stress, catecholamines, and acute-phase reactants, such as plasminogen activator inhibitor and fibrinogen.[337,338] Platelet reactivity is also enhanced in the presence of a stress response.[338] Another important mechanism for the increased lower extremity graft patency with regional anesthesia may be the increased lower extremity blood flow associated with sympathectomy.

In the postoperative period, Breslow and associates[339] demonstrated differences in the adrenergic response with general versus regional anesthesia (Fig. 62-17). Epinephrine and norepinephrine are increased after general anesthesia relative to regional anesthesia. The cortisol response after general anesthesia is also greater than that after regional anesthesia.[339] This "stress response" is associated with increased blood pressure and hemo-

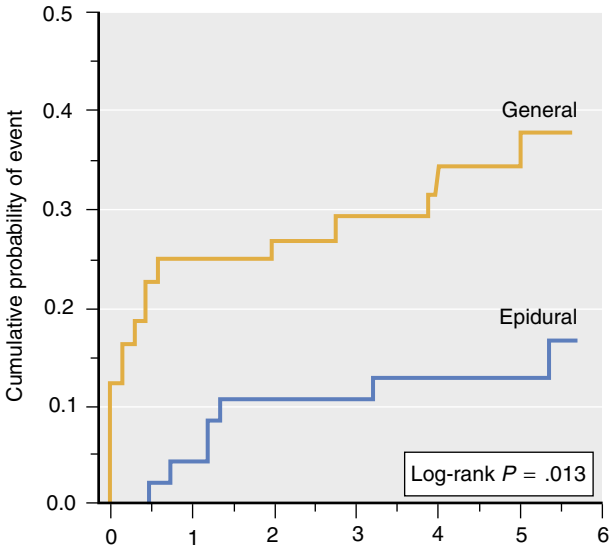


Figure 62-15 Cumulative probability of reoperation for regrafting, thrombectomy, or amputation over a 6-week follow-up period. Reoperation was significantly more frequent after general than after epidural anesthesia. *(From Christopherson R, Beattie C, Norris EJ, et al: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 79:422-434, 1993.)*

dynamic liability during the intraoperative and early postoperative periods after general anesthesia as compared with regional anesthesia.[28,340] When the hemodynamic parameters are controlled pharmacologically, however, there is no difference related to anesthetic technique in myocardial ischemia or cardiac morbidity.[27,28,33]

Postoperative pain is recognized as one of the many factors contributing to the surgical stress response. In studies comparing epidural analgesia with parenteral opioid analgesia for control of postoperative pain after major surgery, improved pain control with epidural techniques is often reported. A recent meta-analysis review supports the view that epidural analgesia provides better postoperative analgesia than parenteral opioids do.[341] However, the historical studies that form the basis of the meta-analysis review have often neglected to control, specify, and, most importantly, optimize treatment in the nonepidural arms of their studies. Unfortunately, this issue remains a significant limitation in more recent trials.[156,342] Epidural analgesic techniques will probably continue to outperform "suboptimal" nonepidural analgesic techniques. I believe that intravenous patient-controlled analgesia is the optimal mode of delivery for opioid analgesia and should be used as the nonepidural arm of all postoperative pain studies. Postoperative epidural analgesia does not consistently outperform intravenous patient-controlled opioid analgesia.[343] Of particular note, patient-controlled epidural analgesia outperforms both intermittent-bolus and continuous-infusion epidural

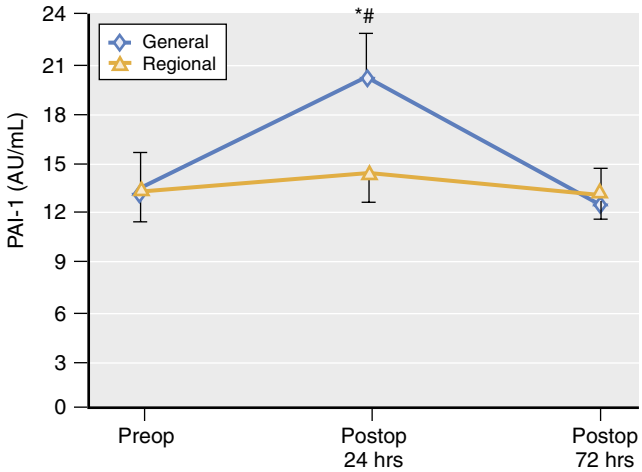


Figure 62-16 Plasminogen activator inhibitor-1 (PAI-1) levels in activity units (AU) per milliliter measured preoperatively and at 24 and 72 hours postoperatively after lower extremity revascularization. PAI-1 levels in the general anesthesia group increased from 13.6 ± 2.1 AU/mL to 20.2 ± 2.6 AU/mL at 24 hours and returned to baseline at 72 hours. In contrast, PAI-1 levels in the regional anesthesia group remained unchanged over time. *(Adapted from Rosenfeld BA, Beattie C, Christopherson R, et al: The effects of different anesthetics regimens on fibrinolysis and the development of postoperative arterial thrombosis. Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 79:435-443, 1993.)*

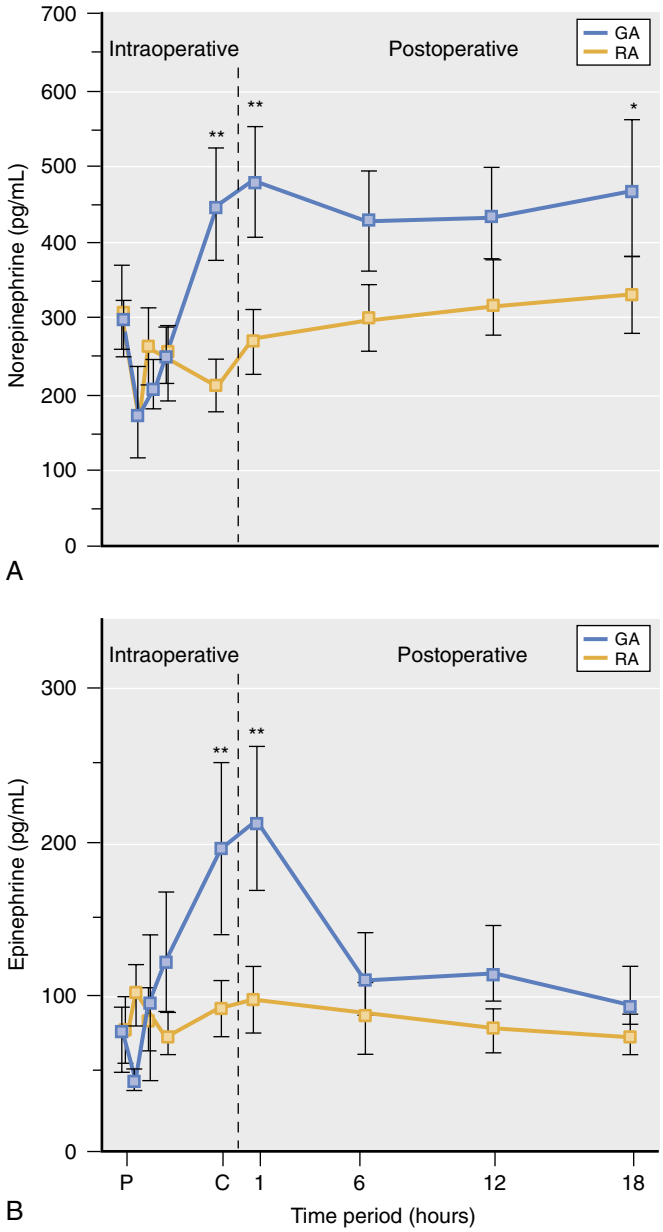


Figure 62-17 Plasma norepinephrine (**A**) and epinephrine (**B**) concentrations before induction of anesthesia (P), at skin closure (C), and at 1, 6, 12, and 18 hours after lower extremity revascularization. GA, general anesthesia with postoperative parenteral morphine by patient-controlled analgesia; RA, regional (epidural) anesthesia with postoperative epidural analgesia by patient-controlled analgesia. *(Adapted from Breslow MJ, Parker SD, Frank SM, et al: Determinants of catecholamine and cortisol responses to lower extremity revascularization. The PIRAT Study Group. Anesthesiology 79:1202-1209, 1993.)*

analgesia. Thus, the mode of delivery is an important factor with both epidural and parenteral opioid analgesia. The clinician also needs to keep in mind that the superior pain control reported with epidural techniques is relative, with adequate pain control consistently reported for parenteral analgesia.[344] In the only double-blinded trial in vascular surgery patients, Norris and colleagues[33] reported no difference in postoperative pain scores in patients randomized to either patient-controlled epidural analgesia or patient-controlled intravenous analgesia after aortic surgery. In this trial, postoperative pain management (i.e., epidural and intravenous) was optimized, continued for 72 hours, and managed by an acute pain service. Postoperative epidural catheter failure may occur in up to 6.3% of patients.[345]

Anesthetic Management

A variety of anesthesia techniques, including general anesthesia, regional (i.e., epidural or spinal) anesthesia, and combined techniques, have been used successfully for lower extremity reconstruction. General anesthesia is usually delivered with use of a balanced technique consisting of opioids, potent inhaled anesthetics, nitrous oxide, and neuromuscular blockade. Induction of anesthesia should proceed in a controlled fashion such that a stable hemodynamic profile is maintained. Maintenance of anesthesia may be accomplished with a low-dose inhaled anesthetic (i.e., isoflurane, desflurane, or sevoflurane) in 50% nitrous

oxide and opioid (3 to 5 μg/kg of fentanyl). Because virtually all patients are extubated in the operating room, high doses of opioid are generally avoided. The goal is to maintain stable hemodynamics and to prevent myocardial ischemia during the intraoperative and postoperative periods. Judicious use of β-blockers and vasoactive drugs is often necessary.

Regional anesthesia can be accomplished with spinal or epidural techniques. Disadvantages of spinal anesthesia include the limited duration of action in the setting of a surgical procedure that is somewhat unpredictable in length and complexity. The level of sympathetic block is somewhat less controllable than with the epidural technique. Hypotension can occur with either technique and should be treated promptly with judicious use of fluids and vasopressors. An advantage of an epidural technique is the ability to continue drug delivery into the postoperative period for analgesia and attenuation of the stress response. A lumbar epidural catheter is ideal for lower extremity vascular procedures. The dermatomes that need to be anesthetized are innervated at the same level where the catheter is inserted because the incision is usually in the L1 to L4 region. Small volumes of local anesthetic are recommended because a T10 block is generally sufficient. Usually, 9 to 12 mL (including the test dose) is sufficient for the initial dose, and more drug is given as needed. Because vascular surgery patients are generally advanced in age and thus prone to higher block levels, larger doses may result in high sympathetic blockade with significant hypotension.[346] A high sympathetic block is problematic because of decreased coronary perfusion and excessive fluid and vasopressor requirements. Congestive heart failure may result in the postoperative period when the sympathectomy resolves and the intravascular space contracts. When administering an epidural test dose, careful attention should be directed to both the heart rate and blood pressure. Blood pressure may be a more reliable indicator of an intravascular injection because vascular surgery patients may have little or no increase in heart rate as a result of β-blocker therapy and decreased β-adrenergic responsiveness secondary to aging.[347] When hypotension results from sympathectomy, a low-dose phenylephrine infusion is helpful in reducing intravenous fluid requirements. I believe that this approach is more physiologic than administration of large fluid volumes.

Postoperative Considerations

Pain and anxiety should be carefully controlled in the postoperative period because the stress response and myocardial ischemia are of greatest concern at this time. Intravascular volume should be optimized, significant anemia avoided (hemoglobin maintained at >9.0 g/dL), and heart rate and blood pressure carefully controlled. Computerized ST-segment analysis is helpful in identifying ischemic changes. Peripheral pulses should be checked frequently to verify lower extremity graft patency. Blood pressure augmentation and anticoagulants may be necessary when peripheral perfusion is limited. Urgent surgery may be required to reopen clotted or stenotic grafts.

Postoperative analgesia can be provided by intravenous or epidural opioids delivered by patient-controlled analgesia or epidural opioids with local anesthetics delivered by continuous infusion or patient-controlled analgesia. For epidural patient-controlled analgesia, a dilute concentration of local anesthetic should be used to allow neurologic evaluation of the lower extremities to rule out spinal/epidural hematoma. Bupivacaine (0.0625%) is ideal in this regard. Fentanyl (5 μg/mL) can be added and the solution infused at 2 mL/hr, with an on-demand (patient-controlled analgesia) bolus of 2 to 4 mL and a lockout interval of 10 minutes.

Carotid Endarterectomy

The strong association between stroke and carotid artery occlusive disease is well known. The principal cause of carotid artery occlusive disease is atherosclerosis, which most commonly involves the bifurcation of the common carotid artery with frequent extension into both the internal and external carotid arteries. The clinical manifestations of carotid artery disease represent a spectrum of conditions, with fatal or debilitating stroke secondary to cerebral infarction at one end of the spectrum and ranging successively through nondebilitating stroke, transient ischemic attack, and amaurosis fugax (transient attack of monocular blindness) to an asymptomatic bruit. Cerebrovascular sequelae of carotid atherosclerosis may result either from embolization of thrombus or atheromatous debris or from a reduction in flow (hypoperfusion) secondary to stenosis. The latter probably accounts for less than 10% of the cerebrovascular sequelae of carotid atherosclerosis. Although much is known about the genesis and evolution of atherosclerosis, significantly less is known about the circumstances that lead to plaque instability and rupture. Regardless of the mechanism, the degree of cerebral injury depends on such factors as plaque morphology, characteristics of the embolus, duration of hypoperfusion, cerebrovascular vasoreactivity, integrity of the circle of Willis, and cerebral collateral circulation.

Stroke is a major public health burden worldwide. It is the third leading cause of death and the leading cause of serious, long-term disability in the United States. Stroke is also a major contributor to health care costs. The direct and indirect costs of stroke in the United States in 2008 are estimated at $65.5 billion.[348] Approximately 780,000 people experience a new (≈600,000) or recurrent (≈180,000) stroke each year in the United States.[348] Annually, there are more than 950,000 hospitalizations and 165,000 deaths from stroke. There are well-defined risk factors in patients with stroke, the most important of which is hypertension. Approximately 83% of strokes are ischemic (i.e., cerebral thrombosis or embolism) in nature, and 7.6% of ischemic strokes result in death within 30 days of initial evaluation.[349] Less than 20% of strokes are preceded by a transient ischemic attack. Despite a well-documented decline in stroke mortality, the annual incidence rate of stroke may be increasing.[350] This increase is probably due to growth in high-risk populations. Indeed, if recent trends continue, increases in stroke death will outpace the overall population growth, with a doubling in deaths over the next 30 years.[351] The incidence of perioperative stroke in unselected patients,[352] patients with asymptomatic carotid bruit, and patients with at least 50% carotid stenosis[353] undergoing general anesthesia and surgery is approximately 0.1%, 1.0%, and 3.6%, respectively.

Although treatment options to reverse the effect of acute ischemic stroke are limited, outcomes may be improved with appropriate therapy.[354] The only approved therapy is intravenous recombinant tissue plasminogen activator.[355] Given the narrow 3-hour treatment window from the onset of symptoms, prompt

evaluation and diagnosis of ischemic stroke are critical. With the exception of acute stroke after carotid endarterectomy, surgical treatment of patients with acute ischemic stroke is controversial and not generally recommended because of limited data and perceived high risk. Endovascular treatment of patients with acute ischemic stroke is undergoing intense investigation. Emergency angioplasty and stenting, mechanical disruption of arterial clot, and mechanical extraction of thrombi are interventions currently being evaluated.[356] The AHA/American Stroke Association has recently published revised guidelines for the early management of patients with ischemic stroke.[357]

Indications

Endarterectomy of the carotid bifurcation reduces symptoms and prevents stroke for more than 40 years. The efficacy of carotid endarterectomy for prevention of ipsilateral stroke in patients with and without symptoms has been demonstrated in large-scale randomized clinical trials.[358,359] In centers of excellence, it is a low-risk procedure with excellent long-term durability.[360] The first successful carotid endarterectomy was performed by DeBakey in 1953 and later reported with a 19-year follow-up.[361] Carotid endarterectomy is the most common peripheral vascular surgical procedure performed in the United States, with an estimated 130,000 procedures performed annually.[362] The AHA[363] and others[364] have published guidelines for carotid endarterectomy. The rate and number of carotid endarterectomies have fluctuated significantly since the early 1970s. With marked growth in the specialty of vascular surgery and an expanding list of surgical indications, the number of carotid endarterectomies performed in nonfederal hospitals increased from 15,000 in 1971 to 107,000 in 1985[365] and then declined substantially over the next 5 to 6 years.[366] The decline was probably due to publications questioning the indications for the procedures and isolated reports citing excessively high rates of operative morbidity and mortality.[367]

In 1992, a marked increase in the number of carotid endarterectomies occurred after the results of two large-scale, prospective randomized trials were published.[366] The North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial both reported definitive results for symptomatic patients with high-grade carotid stenosis (70% to 99%).[358,368] In the North American Symptomatic Carotid Endarterectomy Trial, at 2 years' follow-up the stroke rate for surgical patients was 9% versus 26% for medical patients.[358] This benefit of carotid endarterectomy has persisted at 8 years of follow-up.[369] In the European Carotid Surgery Trial, the long-term stroke rate was 2.8% for surgical patients, excluding a perioperative stroke and death rate of 7.5%, and 16.8% for medically managed patients.[368]

The efficacy of carotid endarterectomy in asymptomatic patients with carotid stenosis has been evaluated in five randomized trials.[359,370-373] The Carotid Artery Surgery Asymptomatic Narrowing Operation Versus Aspirin trial, the first to publish its results, concluded that carotid endarterectomy was not indicated for asymptomatic patients with 50% to 90% carotid stenosis.[370] Unfortunately, this study was seriously flawed and the results questioned. The Mayo Asymptomatic Carotid Endarterectomy Study was terminated early because of a significantly increased number of MIs and transient cerebral ischemic events in the surgical group.[371] Most of these events were not related to the surgery itself but rather to the absence of aspirin in the surgical group. The Department of Veterans Affairs trial was designed to compare the effects of carotid endarterectomy plus aspirin versus medical treatment (i.e., aspirin) in asymptomatic male patients with 50% or greater carotid stenosis.[372] This trial demonstrated a significant reduction in ipsilateral neurologic events in the surgical group (8%) versus the medical group (20.6%). However, the combined incidence of stroke and death was not different between study groups. The Asymptomatic Carotid Atherosclerosis Study demonstrated that patients with asymptomatic carotid stenosis (≥60%) who were treated with carotid endarterectomy and aspirin have a reduced 5-year risk of ipsilateral stroke when compared with patients treated with aspirin alone (5.1% versus 11.0%).[359] These results reflect only a 5.9% absolute risk reduction in 5 years, which is just above 1% per year. Of note, improvement in outcome for patients randomized to undergo endarterectomy in this trial did not reach significance until 3 years after surgery. The European Asymptomatic Carotid Surgery Trial, the largest trial to date, largely replicated the results of the Asymptomatic Carotid Atherosclerosis Study, but in a somewhat more pragmatic setting.[373] This trial demonstrated that patients with asymptomatic carotid stenosis (≈70%) on ultrasound who were treated by immediate carotid endarterectomy plus medical treatment have a reduced 5-year risk of stroke when compared with patients treated with medical therapy alone (6.4% versus 11.8%). Of note, half of this 5-year benefit involved disabling or fatal strokes.

Although landmark randomized clinical trials have clearly defined individuals who are likely to benefit from carotid endarterectomy (and set the standard for developing evidence-based practice guidelines throughout the world), it has been suggested that the significant increase in the number of carotid endarterectomies performed over the last decade may be due in part to the extrapolation of trial results to patients and settings not directly supported by the trials.[362,374] For example, both the North American Symptomatic Carotid Endarterectomy Trial and the Asymptomatic Carotid Atherosclerosis Study restricted enrollment to patients younger than 80 years, and both trials carefully selected institutions and surgeons to optimize the results of surgery. Additionally, the Asymptomatic Carotid Atherosclerosis Study, in subgroup analysis, could not demonstrate a significant benefit for women.[359] With the advent of a second interventional treatment modality, percutaneous carotid angioplasty and stenting (discussed later), this issue has become more complex.

Perioperative Morbidity and Mortality

Although the randomized trials just noted have demonstrated a protective effect of carotid endarterectomy on ipsilateral stroke, the critical determinants of benefit for any given patient must include the perioperative event rate and expected long-term survival. The perioperative complication rate for carotid endarterectomy needs to be very low (≈3% or less) to maintain the beneficial effects of surgery over medical therapy.[363] A systematic review of 51 studies (1980 to 1995) reported an overall mortality of 1.6% and a risk of stroke or death of 5.6% after carotid endarterectomy for symptomatic carotid stenosis.[375] Another systematic review of 25 studies (1980 to 1995) reported a 30-day mortality of 1.3% for asymptomatic stenosis and 1.8% for symptomatic stenosis.[376] The overall risk of stroke or death was 3.4% for asymptomatic stenosis and 5.2% for symptomatic stenosis.[376] The incidence of periopera-

tive stroke is highest in patients in whom stroke is diagnosed, lower in patients with transient ischemic attack, and lowest in asymptomatic patients. Neurologic deficits occur most commonly in patients with poorly controlled preoperative hypertension or in those with hypertension or hypotension postoperatively. More than half of these deficits occur more than 4 hours postoperatively. The incidence of perioperative MI in patients undergoing carotid endarterectomy ranges from 0% to 4%.[377,378] MI is the leading cause of both perioperative and late mortality after carotid endarterectomy. Recent reports suggest that carotid endarterectomy can be performed safely in the very elderly and those deemed high risk, with combined stroke or death rates being comparable to those found in randomized trials (North American Symptomatic Carotid Endarterectomy Trial and Asymptomatic Carotid Artery Study).[379-381]

Preoperative Evaluation

As discussed previously, successful evaluation of patients with arterial occlusive disease must address the systemic and progressive nature of atherosclerosis. CAD is common in patients undergoing carotid endarterectomy and is the leading cause of both early and late mortality.[382-384] Hertzer and coworkers performed coronary angiograms in 506 patients scheduled for carotid endarterectomy and found severe correctable CAD in 28%. Despite the known high incidence of CAD in patients undergoing carotid endarterectomy, preoperative studies are rarely needed for the evaluation of myocardial function or ischemic potential. Exceptions to this practice are patients with unstable angina, recent MI with evidence of ongoing ischemia, decompensated congestive heart failure, and significant valvular disease. Unless the surgical plan can be altered, perioperative management improved, or mortality reduced, specialized studies are not appropriate in most patients scheduled for carotid endarterectomy. This approach is based on the following rationale. First, randomized trials have definitively established that carotid endarterectomy can prevent stroke in appropriately selected patients.[278,283,358,359] Second, although percutaneous angioplasty plus stenting of the carotid artery is evolving into an appropriate alternative for some high-risk patients,[385] at the present time carotid endarterectomy remains the gold standard.[386,387] Third, based on the previous two reasons, it would be unlikely that the results of specialized testing would cause the procedure to be canceled. Fourth, because careful intraoperative and postoperative monitoring and medical management are standard for all patients undergoing carotid endarterectomy, specialized testing has little potential to alter perioperative management. Finally, there is no good evidence to suggest that preoperative strategies leading to coronary angiography and ultimately coronary revascularization are appropriate in patients undergoing carotid endarterectomy given the low overall rates of perioperative cardiac morbidity and mortality. Reduction in short-term mortality has not been shown with prophylactic coronary revascularization before aortic or lower extremity vascular surgery.[35,47] Thus, in patients with asymptomatic or stable CAD, I believe that the best strategy is to proceed with carotid endarterectomy without additional studies. This approach does not take into consideration the potential long-term benefits from aggressive preoperative cardiac assessment and ultimate coronary revascularization. However, there is no convincing evidence that such benefit exists.

Patients with both severe CAD and severe carotid artery occlusive disease represent somewhat of a management dilemma[388] because it is often unclear which disease should be treated first.[389] The severity of cerebrovascular and coronary disease must be evaluated in terms of clinical symptoms and anatomic lesions, and a decision must be made to perform either a combined or a staged procedure. A meta-analysis of 16 studies with 844 combined patients and 920 staged patients reported that the combined approach may be associated with a higher risk for stroke or death.[390] A staged approach with carotid endarterectomy as the first procedure may result in significant morbidity from cardiac causes. Conversely, performing coronary revascularization first may result in a high incidence of stroke. For patients with both unstable CAD and symptomatic carotid artery disease, a combined procedure has been advocated.[391] Numerous reports from centers of excellence support a combined approach, which has demonstrated both low morbidity and low mortality.[388,392-394] However, these reports may not reflect community-wide outcomes of the combined approach.[395] To date, no randomized trials have been performed to assess the benefit of combined versus staged procedures. Given this lack of objective data, management of an individual patient should be guided by careful assessment of the relative severity of the coronary and carotid disease with particular emphasis on both surgeon- and institution-specific results in these patient populations. Carotid artery angioplasty plus stenting has recently been introduced as an alternative revascularization modality before staged CABG. However, data are limited, and the role of carotid artery angioplasty and stenting in this setting is unproven.[396]

Anesthetic Management

Anesthetic management goals for carotid endarterectomy include protection of the heart and brain from ischemic injury, control of the heart rate and blood pressure, and ablation of the surgical pain and stress responses. These goals must be achieved with another important goal in mind—to have an awake patient at the end of surgery for the purpose of neurologic examination.

The preoperative visit is particularly important in patients undergoing carotid surgery. During this visit, a series of blood pressure and heart rate measurements are obtained from which acceptable ranges for perioperative management can be determined. Patients are instructed to continue all long-term cardiac medications up to and including the morning of surgery. Unless contraindications exist, aspirin therapy should be continued throughout the perioperative period. As noted earlier, discontinuation of aspirin therapy may be related to an increased rate of MI and transient ischemic events in patients undergoing carotid endarterectomy.[281] When patients arrive at the hospital on the day of surgery, they are queried regarding any new cardiovascular or cerebrovascular symptoms. Long-term cardiovascular medications not taken at home should be administered in the preoperative holding area whenever possible. Patient reassurance is particularly important at this time because anxiety is associated with increases in heart rate, systemic vascular resistance, and myocardial oxygen consumption, which in this patient population could precipitate significant cardiac morbidity.[397]

I routinely monitor leads II and V_5 for detection of rhythm disturbances and ST-segment changes. On-line ST-segment analysis is particularly helpful and is used routinely. An intra-arterial catheter for beat-to-beat blood pressure monitoring is placed in

all patients. Central venous and pulmonary artery catheters are usually unnecessary for carotid surgery. If such monitors are used, the subclavian or femoral insertion sites are most practical because inadvertent carotid puncture could compromise blood flow as a result of hematoma. In my experience, the most common reason for central access is difficult or inadequate peripheral access. Intravenous access for fluid and drug administration can be accomplished with a single, secure, medium-bore (16-gauge) catheter. Because both arms will be tucked to the patient's sides, the intravenous catheter must run well after patient positioning.

General Anesthesia

Any of the commonly used induction agents, maintenance anesthetics, and short- to intermediate-acting nondepolarizing muscle relaxants can be used safely during carotid endarterectomy, given that stable hemodynamics are maintained and the patient is awake at the end of the procedure. My induction technique with sufentanil is as follows. After placement of routine monitors and administration of oxygen by facemask, a sufentanil infusion (0.5 to 1.0 μg/kg) is initiated. If the patient becomes at all sedated during the planned 10- to 15-minute infusion period, as evidenced by slowed speech or delayed response to questioning, the infusion is discontinued. No additional opioids are administered intraoperatively. Induction of anesthesia is accomplished with incremental doses of thiopental (≤8 mg/kg) followed by succinylcholine, unless contraindications exist. Etomidate or propofol may also be used. Esmolol is particularly effective in blunting the increases in heart rate and blood pressure during laryngoscopy and intubation and is used liberally during the induction period.[398] Blood pressure responses during and after endotracheal intubation are unpredictable in this patient population, and the clinician must be prepared for immediate treatment of extremes in blood pressure. My preference is to use short-acting drugs, such as phenylephrine (50 to 100 μg) for hypotension and sodium nitroprusside (5 to 25 μg) for hypertension. Patients with poorly controlled hypertension (diastolic blood pressure >100 mm Hg) require special care. These patients are often intravascularly volume depleted and may have significant hypotension with induction. Administration of fluids intravenously (5 mL/kg), careful titration of anesthetics, and immediate treatment of hypotension are especially important.

Anesthesia is maintained with 50% nitrous oxide in oxygen and low-dose (i.e., less than half the minimum alveolar concentration) potent inhaled anesthetics. Isoflurane is preferred because fewer ischemic electroencephalographic (EEG) changes occur during carotid occlusion than with halothane[399,400] or enflurane.[399-401] In addition, studies using EEG and regional cerebral blood flow (rCBF) measurements suggest that the critical rCBF (the rCBF below which EEG changes of cerebral ischemia occur) is lower for isoflurane than for halothane or enflurane.[399,400] Sevoflurane may be a good alternative because its critical rCBF in patients undergoing endarterectomy is similar to that determined with isoflurane[402] and it may facilitate more rapid emergence.[403] I typically use vecuronium for muscle relaxation because the procedure rarely lasts longer than 90 minutes. I do not use a cervical plexus block or request local anesthetic infiltration for skin incisions because the surgical stimulation is minimal and it is frequently necessary to support blood pressure. A combined remifentanil and propofol anesthetic technique has been reported but offered little advantage over inhaled anesthetics.[404]

Despite only modest surgical stimulation, hemodynamic fluctuations are common during carotid endarterectomy. Blood pressure and heart rate are controlled within predetermined and individualized ranges during the surgical procedure with short-acting agents whenever possible (esmolol, phenylephrine, nitroglycerin, and sodium nitroprusside). Arterial blood pressure should be maintained in the high-normal range throughout the procedure and particularly during the period of carotid clamping in an attempt to increase collateral flow and prevent cerebral ischemia. In patients with contralateral internal carotid artery occlusion or severe stenosis, induced hypertension to approximately 10% to 20% above baseline is advocated during the period of carotid clamping when neurophysiologic monitoring is not used. Blood pressure preservation or augmentation can be accomplished by maintaining light levels of general anesthesia or by administering sympathomimetic drugs such as phenylephrine and ephedrine. Some caution must be exercised when using vasopressors to augment blood pressure during carotid endarterectomy because the increases in blood pressure and heart rate may increase myocardial oxygen requirements, as well as the risk for myocardial ischemia[405] or infarction. The restrictive use of vasopressors for specific instances of cerebral ischemia has been advocated.[406] In one report, induced hypertension during the period of carotid occlusion was not associated with myocardial ischemia.[407]

Surgical manipulation of the carotid sinus with activation of the baroreceptor reflexes can cause abrupt bradycardia and hypotension. Cessation of surgical manipulation promptly restores the hemodynamics, and infiltration of the carotid bifurcation with 1% lidocaine usually prevents further episodes. Infiltration may, however, increase the incidence of both intraoperative and postoperative[408] hypertension. I do not advocate routine infiltration of the carotid bifurcation.[409]

With closure of the deep fascial layers in the neck, isoflurane is discontinued, nitrous oxide is increased to 70%, and ventilation is controlled manually. On application of the surgical dressings, neuromuscular reversal agents are administered, and oxygen is increased to 100%. At this time I decrease external stimuli to the patient by quieting the room, turning off the overhead surgical lights, and placing the patient in a head-up recumbent position. Ventilation is gently assisted until the patient exhibits spontaneous eye opening or movement. With rare exceptions, all patients are extubated after neurologic integrity is established. Neurologic deficits on emergence require immediate discussion with the surgeon about the need for angiography, reoperation, or both. The period of emergence and extubation may be associated with marked hypertension and tachycardia, which may require aggressive pharmacologic intervention. Tight hemodynamic control during this period is likely to be more demanding than during induction.[407] Greater hemodynamic stability and decreased pharmacologic intervention during emergence have been reported in patients undergoing carotid endarterectomy with propofol versus isoflurane.[407] In addition, a significantly lower incidence of myocardial ischemia on emergence was found in the propofol group than in the isoflurane group (1 of 14 versus 6 of 13). Of particular note, all patients with myocardial ischemia on emergence had systolic blood pressure higher than 200 mm Hg.

Regional and Local Anesthesia

Regional and local anesthetic techniques for carotid endarterectomy have been in use for more than 40 years, and many centers consider them to be the techniques of choice.[410,411] Regional anesthesia is accomplished by blocking the C2 to C4 dermatomes

by use of a superficial and deep cervical plexus block (see Chapter 52). Adequate anesthesia can be obtained with an isolated superficial cervical plexus block, possibly as a result of spread of local anesthetic to the cervical nerve roots.[412] Local infiltration of the surgical field can also provide the necessary sensory blockade. Regional anesthesia allows continuous neurologic assessment of awake patients, which is believed to be the most sensitive method for detecting inadequate cerebral perfusion and function.[413] Other advantages that have been reported include avoidance of expensive cerebral monitoring, reduced need for shunting,[414-416] greater stability of blood pressure and decreased vasopressor requirements,[415,417] and reduced hospital costs.[414,417,418]

Local or regional anesthesia requires significant patient cooperation throughout the procedure and is best maintained with constant communication and gentle handling of tissues. Supplemental infiltration of local anesthetic by the surgeon, especially at the lower border and ramus of the mandible, is frequently helpful. Sedation, if used at all, must be kept to a minimum to allow continuous neurologic assessment. Levels of consciousness, speech, and contralateral handgrip are assessed throughout the procedure. Handgrip can be assessed with the use of a squeaky toy. Blood pressure is augmented with phenylephrine when patients exhibit neurologic changes during carotid artery test clamping or after shunt placement. A 2- to 3-minute test clamp in awake patients allows prompt identification of those who would benefit from shunt placement.[419] Patient acceptance of regional anesthesia is high,[420] as evidenced by a 92% preference for repeat cervical plexus block for future carotid endarterectomy.[421] The surgical drapes are "tented" over the head and face area to minimize claustrophobic anxiety. It has been suggested that no absolute contradiction to regional anesthesia for carotid endarterectomy exists.[320] In my practice, I avoid regional anesthesia under the following circumstances: strong preference for general anesthesia expressed by the patient (i.e., claustrophobia), language barriers that make communication difficult, and difficult vascular anatomy. Difficult anatomy is usually manifested by a patient with a short neck and a high (more cephalad) bifurcation and may require vigorous submandibular retraction.

Regional versus General Anesthesia

Most reports comparing local or regional anesthesia with general anesthesia indicate no differences in the perioperative stroke or death rate on the basis of anesthetic technique.[27,320,321,326,418,422-424] Three reports have found an increased incidence of perioperative stroke in patients under general anesthesia.[325,425] An increased incidence of cardiopulmonary complications in patients under general anesthesia has been reported in five studies.[27,326,422,424] Potential disadvantages of local or regional anesthesia include an inability to use pharmacologic cerebral protection with anesthetics, patient panic or loss of cooperation, seizure or loss of consciousness with carotid clamping, and inadequate access to the airway should conversion to general anesthesia be necessary. The incidence of serious complications from a cervical plexus block is low; however, near-toxic levels of local anesthetic have been reported in almost half of patients after superficial and deep cervical plexus block.[426] Although no major complications related to local anesthetic toxicity occurred, some caution should be exercised when requesting the surgeon to supplement with additional local anesthetic. Phrenic nerve paresis is common after cervical plexus block[427] and is of little clinical consequence except in patients with severe chronic obstructive pulmonary disease or contralateral diaphragmatic dysfunction. Rates of conversion from regional anesthesia to general anesthesia of approximately 2% to 6% have been reported.[320,323,428] In patients undergoing carotid endarterectomy under cervical plexus blockade, ST-segment depression occurring during clamping or shortly after declamping was highly predictive of adverse cardiac complications.[429]

Intraoperative neurologic changes during carotid endarterectomy under local or regional anesthesia occur in 2.4% to 24% of patients.[428,430,431] Patients undergoing carotid endarterectomy under cervical plexus blockade who experience intraoperative neurologic changes are six times more likely (6.6% versus 1.1%) to have a postoperative stroke.[428] When compared with general anesthesia, regional anesthesia for carotid endarterectomy may be associated with increased levels of blood catecholamines.[432] A high incidence of tachycardia has been reported in patients undergoing regional anesthesia for carotid endarterectomy.[421] To date, no large-scale, prospective randomized trials have evaluated whether neurologic or cardiac outcomes differ with regional versus general anesthesia. The ultimate decision to use one technique over the other must be based on the surgeon's and the anesthesiologist's experience and the patient's preference.

Carbon Dioxide and Glucose Management

Cerebrovascular carbon dioxide reactivity is part of the complex autoregulatory system to control cerebral blood flow. Normal cerebral autoregulation responds to acute changes in $Paco_2$ by decreasing cerebral blood flow (i.e., vasoconstriction) with hypocapnia and increasing cerebral blood flow (i.e., vasodilatation) with hypercapnia. In patients with carotid artery stenosis or occlusion, ipsilateral cerebral blood flow may be impaired because of poor intracerebral collateral blood flow. In the setting of poor collateralization and resultant cerebral hypoperfusion, cerebral resistance vessels in the hypoperfused territories will dilate in an effort to maintain cerebral blood flow. These chronically dilated resistance vessels may demonstrate a diminished or absent (i.e., vasomotor paralysis) cerebral blood flow response to carbon dioxide. Impaired cerebrovascular reactivity to hypercapnia may play a significant role in the development of stroke ipsilateral to carotid stenosis or occlusion.[433,434] Although one might expect that impaired carbon dioxide reactivity would increase the risk for cerebral ischemia after carotid artery clamping, the results of intraoperative cerebral monitoring suggest that no such relationship exists.[435] Impaired cerebrovascular reactivity to carbon dioxide will significantly improve after carotid endarterectomy.[435]

Control of ventilation and carbon dioxide during general anesthesia is a matter of some controversy. Hypercapnia may cause a "steal" phenomenon (i.e., shunting of blood away from hypoperfused territories with dilated vasculature) and is generally avoided. Hypocapnia, with its associated cerebral vasoconstriction, has been advocated to promote a reversal of this steal phenomenon. However, there is little clinical evidence for this "reverse" steal effect.[436] Additionally, experimental data do not support the use of hypocapnia as a therapeutic maneuver to produce a favorable redistribution of blood flow during focal cerebral ischemia.[437] Indeed, in this animal model of focal cerebral ischemia, hypocapnia ($Paco_2$ of 23 mm Hg) actually increased the size of the region at risk for ischemia.[437] It is therefore common

practice to maintain normocapnia or mild hypocapnia during carotid endarterectomy.

There is evidence of increased ischemic injury to neural tissue when ischemia occurs in the presence of hyperglycemia. Recent data from The Johns Hopkins Hospital found that operative-day glucose greater than 200 mg/dL at the time of carotid endarterectomy was associated with an increased risk for perioperative stroke or transient ischemic attack, MI, and death.[438] Thus, until additional data become available, it may be beneficial to maintain a blood glucose level below 200 mg/dL in patients undergoing carotid endarterectomy. If hyperglycemia is treated with insulin preoperatively or intraoperatively, the blood glucose level should be carefully monitored, especially during general anesthesia, to avoid the dangers of hypoglycemia.

Neurologic Monitoring and Cerebral Perfusion

Intraoperative monitoring for cerebral ischemia or hypoperfusion and, more recently, for cerebral emboli during carotid endarterectomy is controversial (see Chapter 46). Monitoring techniques includes internal carotid artery stump pressure determinations, rCBF measurements, EEG and SSEP monitoring, and transcranial Doppler ultrasonography (TCD). Other modalities, such as cerebral oximetry and jugular bulb venous monitoring, are being evaluated as well. The rationale for the use of such monitoring is based on the need to prevent intraoperative strokes. The primary clinical utility of cerebral monitoring is to identify patients in need of carotid artery shunting. Secondarily, cerebral monitoring is used to identify patients who may benefit from blood pressure augmentation or change in surgical technique. Despite a tremendous amount of investigative effort, there are only limited data to support the assumption that cerebral monitoring actually improves patient outcome after carotid endarterectomy.

Stump Pressure

The internal carotid artery stump pressure represents the backpressure resulting from collateral flow through the circle of Willis via the contralateral carotid artery and the vertebrobasilar system. The advantages of monitoring carotid stump pressure are that it is inexpensive, relatively easy to obtain, and continuously available during carotid clamping (dynamic stump pressure). Despite these advantages, few centers use stump pressure monitoring because its accuracy in determining the adequacy of collateral flow and the need for selective shunting have been questioned.[431,439-441] Although the critical stump pressure is unknown, pressures below 50 mm Hg are associated with hypoperfusion.

Regional Cerebral Blood Flow

rCBF measurements during carotid endarterectomy are obtained by intravenous or ipsilateral carotid artery injection of radioactive xenon and analysis of decay curves obtained from detectors placed over the area of the ipsilateral cortex supplied by the middle cerebral artery. Measurements are typically obtained before, during, and immediately after carotid clamping. This technology, combined with the EEG monitoring, has provided important insight into the relationship between rCBF and EEG evidence of cerebral ischemia and the critical rCBF associated with various anesthetics.[310,311] The critical rCBF varies depending on the volatile anesthetic used. In patients receiving nitrous oxide plus a volatile anesthetic, rCBF is approximately 20, 15, 10, and 10 mL/100 g of brain tissue per minute for halothane, enflurane, isoflurane, and sevoflurane, respectively.[310-312] The expense and the expertise required to make and interpret these blood flow measurements have limited the use of this technology to only a few centers.

Electroencephalography

Many centers advocate intraoperative use of EEG monitoring for the detection of cerebral ischemia and subsequent selective shunting (see Chapter 46).[442-444] The full 16-channel strip-chart EEG and the processed (compressed spectral array) EEG monitor are used for this purpose. Although the processed EEG monitor is more easily interpreted, it is less sensitive than the raw EEG monitor. Significant ischemic EEG changes occur in 7.5% to 20% of monitored patients during carotid clamping under general anesthesia.[316,443,445-450] Significant EEG changes occur more frequently in patient with contralateral carotid disease than in those without (14.3% versus 5.1%).[449] The presence of a contralateral carotid occlusion may increase the rate of significant ischemic EEG changes to nearly 50% during carotid clamping.[447] Because contralateral occlusion is highly predictive of ischemic EEG changes with carotid clamping, it has been recommended that EEG monitoring be eliminated in this circumstance.[450] Ischemic EEG changes may also be seen with shunt malfunction, hypotension, or cerebral emboli.

When the electroencephalogram is used for cerebral ischemia monitoring during carotid endarterectomy, a stable physiologic and anesthetic milieu is mandatory. Isoflurane, desflurane, and sevoflurane produce similar ECG changes at equipotent levels and, when used at 0.5 MAC, allow for more reliable ECG cerebral ischemia monitoring.

The clinical usefulness of intraoperative EEG monitoring for ischemia during carotid endarterectomy is limited by several factors.[446] First, it may not detect subcortical or small cortical infarcts. Second, false-negative results (i.e., neurologic deficit with no ischemic EEG changes intraoperatively) are not uncommon. Patients with preexisting stroke or reversible neurologic deficits may have a particularly high incidence of such results. Third, EEG monitoring is not specific for ischemia and may be affected by changes in temperature, blood pressure, and anesthetic depth. Fourth, false-positive results (i.e., no perioperative neurologic deficit with significant ischemic EEG changes intraoperatively) occur because not all cerebral ischemia uniformly proceeds to infarction. Finally, intraoperative EEG monitoring is inherently limited because most intraoperative strokes are thought to be thromboembolic and most perioperative strokes occur postoperatively. At present, no consistent data demonstrate that EEG monitoring is clearly superior to other methods of intraoperative cerebral monitoring or that the use of EEG monitoring improves outcome.

Somatosensory Evoked Potentials

SSEP monitoring is based on the response of the sensory cortex to electrical impulses from peripheral sensory nerve stimulation. The sensory cortex, being primarily supplied by the middle cerebral artery, is at risk during carotid artery clamping. SSEP monitoring, unlike EEG monitoring, is able to detect subcortical sensory pathway ischemia. Characteristic SSEP tracings (i.e., decrease in amplitude, increase in latency, or both) occur with decreased rCBF and are abolished in primates when flow decreases

to less than 12 mL/100 g of brain tissue per minute. No specific reduction in amplitude or increase in latency has been established as a physiologic marker of impaired rCBF under operative conditions in humans. Anesthetics, hypothermia, and blood pressure may affect SSEPs significantly, and false-negative results have been reported.[451] The validity of SSEPs as an intraoperative monitor of cerebral ischemia during carotid endarterectomy has not been definitively established.

Transcranial Doppler Ultrasonography

TCD allows continuous measurement of mean blood flow velocity and detection of microembolic events in the middle cerebral artery (see Chapter 46). These parameters have important clinical implications because most perioperative neurologic deficits are thought to be thromboembolic in origin.[452] With TCD, intraoperative embolization has been detected in more than 90% of patients undergoing carotid endarterectomy.[453,454] Most intraoperative emboli are characteristic of air and are not associated with adverse neurologic outcomes. TCD may provide useful information regarding shunt function, malfunction, and the incidence of emboli during shunt insertion. Embolization during carotid artery dissection may indicate plaque instability and the need for early carotid artery clamping.[454] Embolization during dissection and wound closure is associated with operative stroke.[455] One center has reported that combined TCD monitoring and completion angiography resulted in a reduction in the intraoperative stroke rate from 4% to 0%.[456] Early postoperative embolization has been detected in more than 70% of patients after carotid endarterectomy[445] and is exclusively particulate in nature.[457] Most TCD-detected emboli occur in the first 2 to 3 hours after surgery.[458] Persistent particulate embolization in the early postoperative period has been shown to predict thrombosis and the development of a major neurologic deficit.[453] Frequent early postoperative TCD embolic signals have been demonstrated to be highly predictive of early postoperative ipsilateral focal cerebral ischemia.[454] Intervention with dextran has been shown to reduce and ultimately stop sustained embolization after carotid endarterectomy.[458] Perioperative microembolization is more common in women and patients with symptomatic carotid disease.[459,460] TCD monitoring has been reported to detect early asymptomatic carotid artery occlusion and hyperperfusion syndrome after carotid endarterectomy.[461,462] Although TCD monitoring holds some promise, conclusive evidence demonstrating improved outcome has not been reported. Additionally, the high rate of technical failures significantly limits the clinical utility of this monitoring modality.[463]

Cerebral Oxygenation

Direct monitoring of cerebral oxygenation can be obtained with jugular bulb venous monitoring. Such monitoring allows determination of the arterial—jugular venous oxygen content difference and jugular venous oxygen saturation and therefore provides information on global cerebral oxygen metabolism. Jugular venous samples are obtained from a catheter inserted into the jugular bulb ipsilateral to the surgical site. Continuous fiberoptic jugular venous oximetry catheters are available as well. Significant technical and methodologic shortcomings have limited the clinical application of this monitoring during carotid endarterectomy.

Near-infrared spectrophotometry is a noninvasive technique that allows continuous monitoring of regional cerebral oxygen saturation through the scalp and skull. Similar to pulse oximetry, cerebral oximetry is based on the different absorption characteristics of the near-infrared spectrum of oxygenated and deoxygenated hemoglobin. However, unlike pulse oximeters, cerebral oximeters measure the oxygen saturation of hemoglobin in the entire tissue bed (i.e., brain tissue and arterial and venous blood), which is predominately venous blood, and therefore approximates venous blood oxygen saturation. A commercially available cerebral oximetry sensor is applied to the forehead skin ipsilateral to the surgical site, and regional cerebral oxygen saturation from a small sample of the frontal cortex below the sensor is provided. To date, wide patient-to-patient variability in baseline cerebral oxygen saturation and the lack of a clinical threshold of a decrease in cerebral oxygen saturation predictive of the need for shunt placement have impeded the widespread use of this novel monitoring modality.

Postoperative Considerations

Most neurologic complications (transient and permanent) after carotid endarterectomy are explained by intraoperative embolization, hypoperfusion during carotid clamping, and embolization or thrombosis from the endarterectomy site. Other important, but less common factors include intracerebral hemorrhage and cerebral hyperperfusion. It is generally accepted that most neurologic complications are related to surgical technique. Thromboembolic rather than hemodynamic factors appear to be the major mechanism of perioperative neurologic complications,[452] and most perioperative neurologic deficits occur in the postoperative period.[464-466] Hemodynamic factors may account for up to 21% of perioperative strokes.[452] Neurologic complications attributable to carotid artery thrombosis may occur with an incidence as high as 3.3% and are associated with a high rate of major stroke or death despite immediate operative intervention.[337,453,467-469] The reported incidence of intracerebral hemorrhage after carotid endarterectomy ranges from 0.4% to 2.0%.[466] Most intracerebral hemorrhages occur 1 to 5 days after the operation and are associated with significant morbidity and mortality.[470,471]

Hypertension is common in the postoperative period after carotid endarterectomy. Not surprisingly, patients with poorly controlled preoperative hypertension often have severe hypertension postoperatively. The causes are not well understood, but surgical denervation of the carotid sinus baroreceptors is probably contributory. Regional anesthesia is associated with less hypertension. Other causes of postoperative hypertension, such as hypoxemia, hypercapnia, bladder distention, and pain, should be excluded or treated. Because neurologic and cardiac complications may be associated with postoperative hypertension,[472,473] blood pressure should be aggressively controlled to near preoperative values after surgery. Short-acting drugs are the safest and most effective. Patients with persistent hypertension are ultimately converted to longer-acting intravenous or oral agents before discharge from the ICU.

Postoperative cerebral hyperperfusion syndrome is an abrupt increase in blood flow with loss of autoregulation in the surgically reperfused brain and is manifested as headache, seizure, focal neurologic signs, brain edema, and possibly intracerebral hemorrhage.[473] Unfortunately, little is actually known about the etiology and management of this syndrome. Typically, this syn-

drome does not occur until several days after carotid endarterectomy. Patients with severe postoperative hypertension and severe preoperative internal carotid artery stenosis are believed to be at increased risk for this syndrome.[473,474] However, more recent data do not corroborate this common belief and suggest that recent contralateral carotid endarterectomy may be predictive of cerebral hyperperfusion.[475]

Postoperative hypotension occurs almost as frequently as hypertension after carotid endarterectomy.[476,477] Carotid sinus baroreceptor hypersensitivity or reactivation probably plays an important role. Postoperative hypotension may be more common after regional anesthesia.[338,472,476-478] To avoid cerebral and myocardial ischemia, hypotension should be corrected promptly. Cardiac output is frequently normal or elevated and systemic vascular resistance reduced in hypotensive patients after carotid endarterectomy.[476] Intensive surveillance for evidence of myocardial and cerebral ischemia and judicious use of fluids and vasopressors are recommended for postoperative hypotension. In most cases the hypotension resolves over a period of 12 to 24 hours.

Cranial and cervical nerve dysfunction after carotid endarterectomy is well documented in the literature.[479-482] Although most injuries are transient, permanent injuries can lead to significant disability.[479] Patients should be examined for injury to the recurrent laryngeal, superior laryngeal, hypoglossal, and marginal mandibular nerves shortly after extubation. Unilateral recurrent laryngeal nerve injury may result in ipsilateral true vocal cord paralysis in the paramedian position. Although most patients have hoarseness and an impaired cough mechanism, the injury is usually well tolerated. However, bilateral recurrent laryngeal nerve injury and resultant bilateral vocal cord paralysis can result in life-threatening upper airway obstruction. This situation must be anticipated in patients who have previously undergone contralateral carotid endarterectomy or neck surgery.

Carotid body denervation may occur after carotid endarterectomy as a result of surgical manipulation. Though rarely of clinical significance, unilateral loss of carotid body function may result in an impaired ventilatory response to mild hypoxemia.[483] Bilateral carotid endarterectomy is associated with loss of the normal ventilatory and arterial pressure responses to acute hypoxia and an increased resting partial pressure of arterial carbon dioxide. In this situation, the central chemoreceptors are the primary sensors for maintaining ventilation, and serious respiratory depression may result from opioid administration. Fortunately, most patients require little more than acetaminophen or ketorolac for postoperative pain.

Wound hematoma probably occurs more frequently than reported in the literature. In the North American Symptomatic Carotic Endarterectomy Trial,[358] 5.5% of patients had wound hematomas. Most cases are the result of venous oozing and require little more than external compression for 5 to 10 minutes. Expanding hematomas require prompt evaluation at the bedside and immediate evacuation if airway compromise is evident. Aggressive postoperative blood pressure control may help reduce the incidence of hematoma.

I believe that all patients should be monitored in an intensive care setting for at least 8 to 12 hours after carotid endarterectomy because most events requiring intervention occur within this timeframe.[484-486] Although some clinicians believe that intensive care monitoring is not routinely required, a significant number of patients do require intensive monitoring and active intervention.[484,487]

Endovascular Treatment of Carotid Disease: Carotid Artery Stenting

Endovascular therapy can be defined as the treatment of vascular pathology accomplished with the percutaneous transvascular passage of a therapeutic device, such as a catheter, guidewire, or stent. Over the past 2 decades, percutaneous revascularization techniques have become accepted alternatives to surgical revascularization of aortoiliac, renal, subclavian, and femoropopliteal lesions. Endovascular treatment of carotid artery disease is an innovation in evolution for stroke prevention and currently involves percutaneous transluminal angioplasty and stenting. Although the use of carotid artery stenting is increasing rapidly, the safety and efficacy of this approach have not been established.[488] A major concern is the potential for carotid artery stenting to produce embolic particles that may result in neurologic deficit.[489] Increasing attention is currently being focused on embolic protection devices to prevent embolization during catheter manipulation and balloon or stent deployment.[489,490] These devices are deployed distal to the lesion in the internal carotid artery and are designed to capture atheromatous debris released during the procedure.

Proponents of carotid stenting have recommended the procedure as an alternative to endarterectomy, particularly in specific patient subsets considered to be at high risk for open surgery.[491,492] A published consensus statement supports the use of carotid artery stenting in high-risk patients.[493] However, the concept of the high-risk endarterectomy patient has been questioned[290,291] because no data exist that clearly define any such large group of patients. Early randomized trial reports[494] have documented combined stroke and death rates of 10% to 12% with carotid artery stenting without embolic protection, thus raising significant safety concerns. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial reported that carotid artery stenting with embolic protection was not inferior to endarterectomy.[495] This trial led to FDA approval of carotid artery stenting for the treatment of patients with symptomatic carotid stenosis. Two recently completed randomized trials reported much less favorable results for carotid artery stenting, which has refueled the debate between stenting and endarterectomy.[496,497] Additional large, multicenter randomized trials of carotid artery stenting versus endarterectomy are ongoing.[498]

Most carotid artery stenting procedures are performed under local anesthesia with light or no sedation in specialized endovascular suites. General anesthesia is used at some centers, particularly in the early phase of program development. Some degree of bradycardia and hypotension has been reported in 68% of patients undergoing carotid artery stenting.[499] A large percentage of these procedures are performed by cardiologists (57%) and radiologists (30%).[500]

Postoperative Management of Vascular Surgery Patients

Vascular surgery patients require special attention during the postoperative period because most cardiac complications occur postoperatively and other problems may arise that require imme-

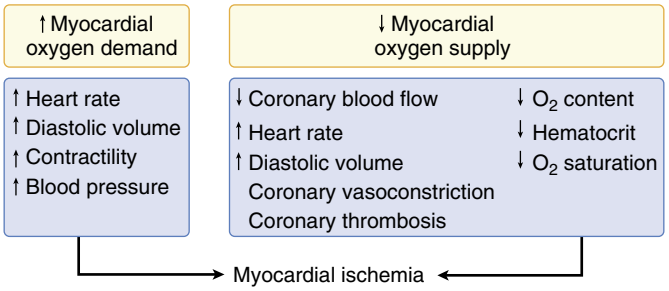


Figure 62-18 Determinants of myocardial oxygen supply and demand that lead to myocardial ischemia. During the perioperative period, virtually every determinant is altered by factors such as fluid shifts, blood loss, pain, catecholamines, altered coagulability, and ventilatory insufficiency. *(Adapted from Beattie C, Fleisher LA: Periopeative myocardial ischemia and infarction. Int Anesthesiol Clin 30:1-17, 1992.)*

diate attention. Conventional practice is to monitor all vascular surgery patients in an ICU setting after surgery. Some centers have set up specialized vascular step-down units in which lower-risk patients can be evaluated frequently by specialized nursing staff. There are, however, no clinical trials to support this practice, and most centers admit all vascular surgery patients to the ICU postoperatively.

Myocardial ischemia and cardiac morbidity occur most frequently in the postoperative period. Patients should be carefully monitored for signs and symptoms of ischemia, but up to 90% of these episodes are asymptomatic.[501-505] The determinants of myocardial oxygen supply and demand should be optimized for all patients (Fig. 62-18) to prevent ischemia before it develops. β-Blocker and statin therapy should be continued throughout the postoperative period. Dysrhythmias may be secondary to ischemia or to sympathectomy associated with regional anesthesia.

Besides myocardial ischemia and cardiac morbidity, other problems include coagulopathy, either from residual heparin or from dilutional coagulopathy after massive transfusion. Even in the absence of coagulopathy, bleeding through fresh vascular anastomoses may occur when significant postoperative hypertension is untreated. Hypovolemia occurs after aortic surgery as a result of significant third-space fluid loss and bleeding. Hypovolemia may lead to hypotension and hypoperfusion of the coronary arteries or lower extremity vascular grafts. Graft occlusion in the lower extremities occurs in 3% to 10% of patients[27,28,323] after lower extremity or aortic surgery and should be recognized immediately and surgically corrected. Lower extremity pulses should be checked at hourly intervals. Some patients require the administration of heparin or dextran to prevent thrombosis when the surgical repair is questionable or when patients have diffuse atherosclerotic disease.

Residual hypothermia in the early postoperative period is associated with an increased incidence of myocardial ischemia and cardiac morbidity; therefore, body temperature should be carefully monitored and controlled in all vascular surgery patients. In a prospective randomized trial, the relative risk for early postoperative cardiac morbidity was reduced by 55% when normothermia was maintained by use of a forced-air warming system.[165] In the early postoperative period, vascular surgery patients have a twofold to threefold greater incidence of myocardial ischemia when core temperature is less than 35°C.[166] Even mild hypothermia of approximately 35°C is associated with a 200% to 700% increase in norepinephrine levels,[163,506] generalized vasoconstriction,[507] and increased blood pressure in postoperative patients.[163] Shivering occurs and increases total-body oxygen consumption, but only by about 40% in the typical elderly vascular patient.[152]

It is important to control the stress response in the postoperative period. This includes preventing the potential triggers for myocardial ischemia (pain, anemia, hypothermia, hemodynamic extremes, and ventilatory insufficiency). In mechanically ventilated patients, the weaning period is especially stressful, and myocardial ischemia occurs frequently during this time.[508] Careful sedation and expeditious weaning are desirable. When possible, extubation in the operating room is less stressful and is preferable for carotid and lower extremity vascular surgery patients. For more invasive surgical procedures (TAA and abdominal aortic aneurysm), postoperative mechanical ventilation is usually necessary.

Vascular surgery continues to challenge the anesthesiologist, given the significant physiologic stress superimposed on a relatively elderly patient population with a high incidence of coexisting disease. Clinical studies provide insight into the preoperative assessment and optimization of cardiac risk, the implications of anesthetic technique, and the diagnosis, prevention, and treatment of myocardial ischemia in vascular surgery patients. These studies have improved our ability to care for vascular surgery patients with reduced morbidity and better overall outcome.

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John C. Drummond and Piyush M. Patel

63 Neurosurgical Anesthesia

Key Points

1. For the purposes of planning a control strategy for intracranial pressure (ICP), the clinician should consider the four subcompartments of the intracranial space: cells, interstitial and intracellular fluid, cerebrospinal fluid, and blood.
2. The venous side of the cerebral circulation is a largely passive compartment that is often the cause of increased ICP or "tightness" of the surgical field, but that is commonly overlooked by clinicians.
3. Cerebral perfusion pressure (CPP) should be supported at or near waking normal levels in patients with recent cerebral injuries (e.g., traumatic brain injury [TBI], subarachnoid hemorrhage [SAH]) because of low resting cerebral blood flow and impaired autoregulation.
4. When patients are managed in the sitting position, blood pressure should be corrected to the level of the external auditory meatus, and mean arterial pressure (MAP) should be maintained at 60 mm Hg in normotensive adults.
5. The minimal standard of care for monitoring to detect venous air embolism in at-risk situations includes the precordial Doppler and end-tidal carbon dioxide analysis.
6. Despite encouraging preclinical data, therapeutic mild hypothermia cannot currently be advocated in the care of head-injured patients in the intensive care unit or during the operative management of patients with intracranial aneurysms because of negative human trials in those patient groups.
7. The most important consideration in the anesthetic management of patients undergoing clipping or coiling after acute SAH is the prevention of paroxysmal hypertension with its attendant risk of aneurysm rerupture. Nonetheless, adequate perfusion pressure is needed if temporary clips are used or during management of cerebral vasospasm.
8. Although induced hypotension is very rarely employed electively in aneurysm surgery, the clinician must be ready to reduce blood pressure immediately and accurately in the event of aneurysm rupture.
9. Tracheal intubation of a head-injured patient with an undefined cervical spine injury can be accomplished using a rapid-sequence induction with manual in-line stabilization (occiput held rigidly to the backboard) with only a very small risk of injury to the spinal cord.
10. CPP (CPP = MAP – ICP) should be supported at 60 mm Hg in the first 48 hours after TBI in adults.
11. Hypocapnia has the potential to cause cerebral ischemia, particularly in recently injured brain and in brain beneath retractors; it should be used only when absolutely necessary for the control of critically increased or uncertain ICP.

This chapter provides guidelines for the management of common situations in neurosurgical anesthesia. First, issues that arise in connection with a variety of neurosurgical procedures are reviewed. These issues constitute a checklist that the practitioner should review before undertaking anesthesia for any neurosurgical procedure. Procedure-specific discussions follow. This chapter assumes familiarity with the cerebral physiology and effects of anesthetics as described in Chapter 13. Neurologic monitoring is described in Chapter 46, and carotid endarterectomy is discussed in Chapter 62.

Recurrent Issues in Neuroanesthesia

Several basic elements of neurosurgical/neuroanesthetic management are recurrent and, in the absence of an established understanding between the surgeon and anesthesiologist, should be discussed and agreed on at the outset of every neurosurgical procedure. The list varies with the procedure and may include the

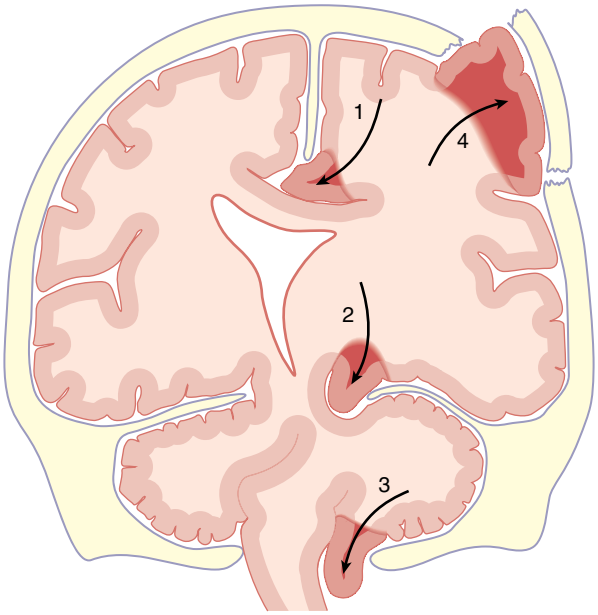

Figure 63-1 Schematic representation of various herniation pathways: (1) subfalcine, (2) uncal (transtentorial), (3) cerebellar, and (4) transcalvarial. *(From Fishman RA: Brain edema. N Engl J Med 293:706-711, 1975.)*

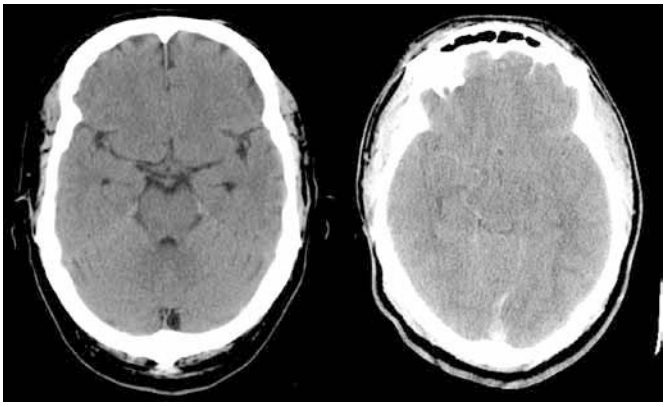

Figure 63-2 CT scan depicting normal (*left*) and compressed (*right*) basal cisterns. The basal, or perimesencephalic, cerebrospinal fluid space consists of the interpeduncular cistern (anterior), the ambient cisterns (lateral), and the quadrigeminal cisterns (posterior). In the *right panel,* in a patient with diffuse cerebral swelling (owing to sagittal sinus thrombosis), the cisterns have been obliterated. *(Image provided by Ivan Petrovitch, MD.)*

intended surgical position and requisite positioning aids; intentions with respect to the use of steroids, diuretics, anticonvulsants, and antibiotics; the surgeon's perception of the "tightness" of the intracranial space and the remaining intracranial compliance reserve; appropriate objectives for the management of blood pressure, $Paco_2$, and body temperature; anticipated blood loss; the intended use of neurophysiologic monitoring (which may impose constraints on the use of anesthetics or muscle relaxants, or both); and, occasionally, the perceived risk of air embolization. The considerations driving the decisions made about these issues are presented in this section. One additional recurrent issue, brain protection, is discussed briefly in the section on aneurysms and arteriovenous malformations and in detail in Chapter 13.

Control of Intracranial Pressure and Brain Relaxation

The necessity of preventing increases in intracranial pressure (ICP) or reducing an ICP that is already elevated is recurrent in neuroanesthesia. When the cranium is closed, the objective is to maintain adequate cerebral perfusion pressure (CPP) (CPP = mean arterial pressure [MAP] – ICP), and prevent the herniation of brain tissue between intracranial compartments or through the foramen magnum (Fig. 63-1). When the cranium is open, the issue may be one of providing relaxation of the intracranial contents to facilitate surgical access or, in extreme circumstances, reverse the process of brain herniation through a craniotomy. The principles that apply are similar whether the cranium is open or closed.

The various clinical indicators of increased ICP include headache (particularly headache that awakens the patient at night), nausea and vomiting, blurred vision, somnolence, and papilledema. Suggestive findings on computed tomography (CT) include midline shift, obliteration of the basal cisterns, loss of sulci, ventricular effacement (or enlarged ventricles in the event of hydrocephalus), and edema. Edema appears on a CT scan as a region of hypodensity. The basal cisterns appear on CT as a black (fluid) halo around the upper end of the brainstem (Fig. 63-2). They include the interpeduncular cistern, which lies between the two cerebral peduncles; the quadrigeminal cistern, which overlies the four colliculi; and the ambient cisterns, which lie lateral to the cerebral peduncles.

Figure 63-3 shows the pressure-volume relationship of the intracranial space. The plateau phase occurring at low volumes reveals that the intracranial space is not a completely closed one, and that there is some compensatory latitude. Compensation is accomplished principally by the translocation of cerebrospinal

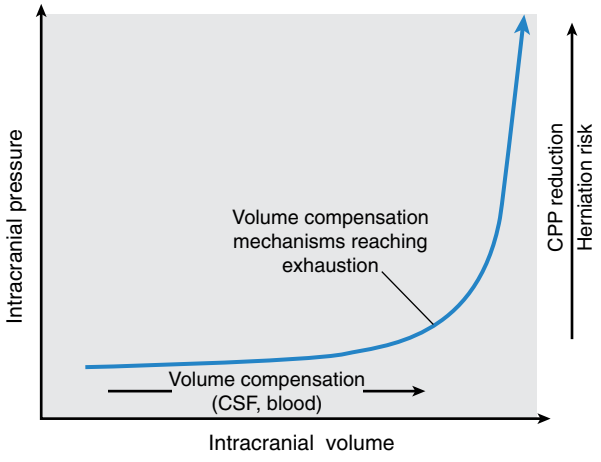

Figure 63-3 The intracranial pressure-volume relationship. The horizontal portion of the curve indicates that there is initially some latitude for compensation in the face of an expanding intracranial lesion. That compensation is accomplished largely by displacement of cerebrospinal fluid (CSF) and venous blood from intracranial to extracranial spaces. When the compensatory latitudes are exhausted, small volume increments result in large increases in intracranial pressure with the associated hazards of herniation or of decreased cerebral perfusion pressure (CPP) resulting in ischemia.

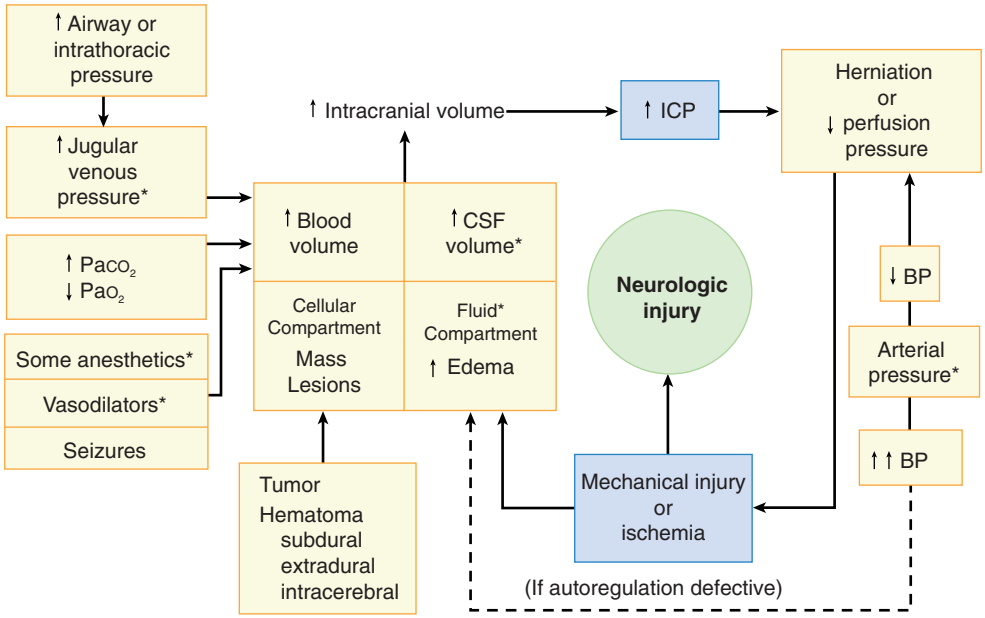

Figure 63-4 The pathophysiology of intracranial hypertension. The figure depicts the manner in which increases in the volumes of any or all of the four intracranial compartments—blood, cerebrospinal fluid (CSF), fluid (interstitial or intracellular) and cells—result in intracranial pressure (ICP) increases and eventual neurologic damage. The elements that are potentially under the control of the anesthesiologist are indicated by asterisks (*). (Control of CSF volume requires the presence of a ventriculostomy catheter.) BP, blood pressure.

fluid (CSF) to the spinal CSF space and venous blood to the extracranial veins. Ultimately, when the compensatory potential is exhausted, even tiny increments in volume of the intracranial contents can result in substantial increases in ICP. These increases have the potential to result in either herniation of brain tissue from one compartment to another (or into the surgical field) (see Fig. 63-1), with resultant mechanical injury to brain tissue, or reduction in perfusion pressure, leading to ischemic injury.

Several variables can interact to cause or aggravate intracranial hypertension (Fig. 63-4). For clinicians faced with the problem of managing increased ICP, the objective is, broadly speaking, to reduce the volume of the intracranial contents. For mnemonic purposes, the clinician can divide the intracranial space into four subcompartments (Table 63-1): cells (including neurons, glia, tumors, and extravasated collections of blood), fluid (intracellular and extracellular), CSF, and blood.

Table 63-1 Intracranial Compartments and Techniques for Manipulation of Their Volume

Compartment	Volume Control Methods
Cells (including neurons, glia, tumors, and extravasated blood)	Surgical removal
Fluid (intracellular and extracellular)	Diuretics Steroids (principally tumors)
CSF	Drainage
Arterial blood	Decrease CBF
Venous blood	Improve cerebral venous drainage

CBF, cerebral blood flow; CSF, cerebrospinal fluid.

1. *The cellular compartment*: This compartment is largely the province of the surgeon. It may be the anesthesiologist's responsibility, however, to pose a well-placed diagnostic question. When the brain is bulging into the surgical field at the conclusion of evacuation of an extradural hematoma, the clinician should ask whether a subdural or extradural hematoma is present on the contralateral side that warrants either immediate bur holes or immediate postprocedure radiologic evaluation.
2. *The CSF compartment*: There is no pharmacologic manipulation of the CSF space, the time course and magnitude of which are relevant to the neurosurgical operating room. The only relevant means for manipulating the size of this compartment is by drainage. A tight surgical field sometimes can be improved by passage of a brain needle by the surgeon into a lateral ventricle to drain CSF. Lumbar CSF drainage can be used to improve surgical exposure in situations with no substantial hazard of uncal or transforamen magnum herniation.
3. *The fluid compartment*: This compartment can be addressed with steroids and diuretics. The use of these agents is discussed subsequently.
4. *The blood compartment*: This is the compartment that receives the anesthesiologist's greatest attention because it is the most amenable to rapid alteration. The blood compartment should be considered as two separate components: venous and arterial.

We suggest giving first consideration to the venous side of the circulation. It is largely a passive compartment that is frequently overlooked. Passive though it is, engorgement of this compartment is a common cause of increased ICP or poor conditions in the surgical field (Fig. 63-5). A head-up posture to ensure

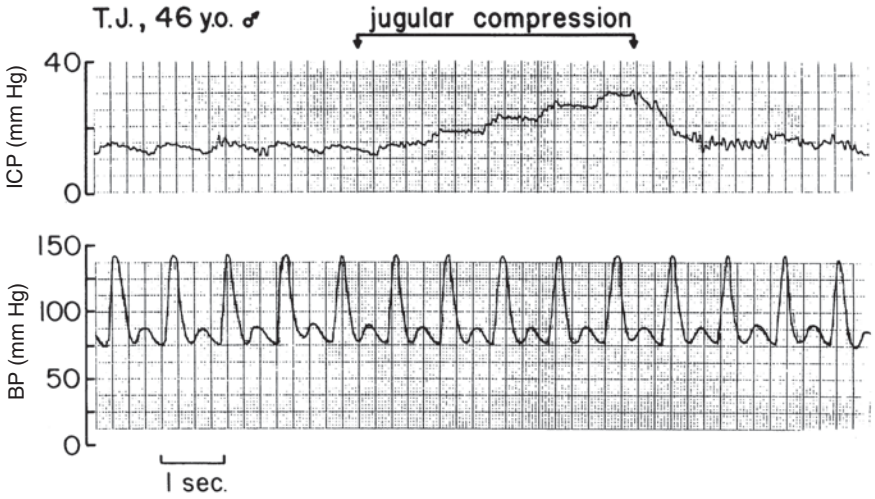

Figure 63-5 The effect of cerebral venous outflow obstruction on intracranial pressure (ICP) in a patient with an intracerebral hematoma. Bilateral jugular compression was applied briefly to verify the function of a newly placed ventriculostomy. The ICP response illustrates the importance of maintaining unobstructed cerebral venous drainage. BP, blood pressure.

good venous drainage is the norm in neurosurgical anesthesia and critical care. Obstruction of cerebral venous drainage by extremes of head position or circumferential pressure (e.g., Philadelphia collars, endotracheal tube ties) should be avoided. Phenomena occurring downstream from the venous structures of the neck also may be relevant, including any condition that can increase central venous pressure, such as positive end-expiratory pressure (PEEP) or cardiac failure. Anything that causes increased intrathoracic pressure can result in obstruction of cerebral venous drainage. Various commonplace events can lead to obstruction, including kinked or partially obstructed endotracheal tubes, tension pneumothorax, coughing or straining against the endotracheal tube, or gas trapping as a result of bronchospasm. These events also should be sought and remedied. Most practitioners carefully maintain paralysis during craniotomies, unless a contraindication is present, because a sudden cough can result in dramatic herniation of cerebral structures through the craniotomy.

Thereafter, the anesthesiologist should consider the arterial side of the circulation. Attention to the effect of anesthetic drugs and techniques on cerebral blood flow (CBF) (see Chapter 13) is an established part of neuroanesthesia. Such attention is relevant because increases in CBF generally are associated with increases in cerebral blood volume (CBV).[1-3] The notable exception to this rule occurs in the context of cerebral ischemia caused by hypotension or vessel occlusion, at which times CBV may increase as the cerebral vasculature dilates in response to a sudden reduction in CBF. The relationship generally applies, however, and attention to the control of CBF is relevant in situations in which volume compensation mechanisms are exhausted, or ICP is already increased. The general approach is to select anesthetics and control the physiologic parameters in a manner that avoids unnecessary increases in CBF. The parameters that influence CBF are listed in Table 63-2 and are discussed in Chapter 13.

Selection of Anesthetics

The question of which anesthetics are appropriate, especially in the context of unstable ICP, arises often. Chapter 13 provides relevant information in detail, and only broad generalizations are offered here. Generally, intravenous anesthetic, analgesic, and sedative drugs are associated with parallel reductions in CBF and cerebral metabolic rate (CMR) and do not have adverse effects on ICP. Ketamine, given in large doses to patients with a generally normal level of consciousness before anesthesia, may be the exception. Autoregulation and carbon dioxide (CO_2) responsiveness are generally preserved during the administration of intravenous drugs (see Chapter 13).

By contrast, all of the volatile anesthetics can be, depending on physiologic and pharmacologic circumstances, dose-dependent cerebral vasodilators. The order of vasodilating potency is approximately halothane >> enflurane > desflurane > isoflurane > sevoflurane. As noted in Chapter 13, the CBF differences among isoflurane, desflurane, and sevoflurane are probably not significant to the clinician. The net CBF effect of introducing a volatile anesthetic depends on the interaction of several factors, including the concentration of the anesthetic, the extent of previous CMR depression, simultaneous blood pressure changes acting in conjunction with previous or anesthetic-induced autoregulation abnormalities, and simultaneous changes in $Paco_2$ in conjunction with any disease-related impairment in CO_2 responsiveness.

Nitrous oxide (N_2O) is also a cerebral vasodilator, the CBF effect of which is the most profound when it is administered as a sole anesthetic, and least when it is administered against a back-

Table 63-2 Factors That Influence Cerebral Blood Flow*

Pao_2
$Paco_2$
Cerebral metabolic rate
Arousal/pain
Seizures
Temperature
Anesthetics
Blood pressure/status of autoregulation
Vasoactive agents
Anesthetics
Pressors
Inotropes
Vasodilators
Blood viscosity
Neurogenic pathways (intra-axial and extra-axial)

*See Chapter 13 for detailed discussion.

ground of narcotics, propofol, or benzodiazepines, and to a lesser extent when administered with volatile anesthetics (see Chapter 13). Nonetheless, experience dictates that N_2O and volatile anesthetics, the latter usually in concentrations less than the minimum alveolar concentration (MAC), when administered as components of a balanced anesthetic technique in combination with narcotics, can be used in most elective and many emergency neurosurgical procedures. Exceptions are rare, but when they occur (e.g., a somnolent, vomiting patient with papilledema, a large mass, and compressed basal cisterns, or a head injury victim with an expanding mass lesion or obliterated cisterns and sulci on CT scan), the clinician may be well advised to use a predominantly intravenous technique until the cranium and dura are open, and the effect of the anesthetic technique can be assessed by direct observation of the surgical field. Inhaled anesthetics are entirely acceptable components of most anesthetics for neurosurgery. In circumstances in which ICP is persistently elevated (in a closed-cranium procedure), or the surgical field is persistently "tight," N_2O and volatile anesthetics should be viewed as potential contributing factors,[4] however, and should be eliminated from the anesthetic in favor of intravenous anesthetics.

Muscle relaxants (see Chapter 29) that have the potential to release histamine (mivacurium, atracurium) should be given in small, divided doses. Although succinylcholine increases in ICP, these increases are small and transient. The increases can be blocked by a preceding dose of metocurine, 0.03 mg/kg[5] (and probably other nondepolarizers), and, in at least some instances, are not evident in patients with common emergency neurosurgical conditions (i.e., head injury, subarachnoid hemorrhage [SAH]).[6] In a clinical situation that calls for rapid relaxation for the purpose of controlling or protecting the airway, succinylcholine in conjunction with proper management of the airway and MAP is reasonable.

From the material just presented and the discussion of cerebral physiology in Chapter 13, a systematic clinical approach should follow readily. A schema for approaching the problem of an acute increase in ICP or acute deterioration in conditions in the surgical field is presented in Table 63-3. If the problem has not resolved satisfactorily after following the approach in Table 63-3, Table 63-4 presents other options.

Table 63-3 High Intracranial Pressure/"Tight Brain" Checklist

1. Are the relevant pressures controlled?
   - Jugular venous pressure
     - Extreme head rotation or neck flexion?
     - Direct jugular compression?
     - Head-up posture?
   - Airway pressure
     - Airway obstruction?
     - Bronchospasm?
     - Straining, coughing, adequately relaxed?
     - Pneumothorax?
   - $Paco_2$ and Pao_2
   - Arterial pressure
2. Is metabolic rate controlled?
   - Pain/arousal?
   - Seizures?
3. Are any potential vasodilators in use?
   - N_2O, volatile agents, nitroprusside, calcium channel blockers
4. Are there any unrecognized mass lesions?
   - Blood, air with or without N_2O

Table 63-4 Methods for Rapid Reduction of Intracranial Pressure and Brain Volume*

- Further titration of $Paco_2$ (≥25 mm Hg)
- CSF drainage (ventriculostomy, brain needle)
- Diuresis (usually mannitol)
- CMR suppression (barbiturates, propofol)
- MAP reduction (if dysautoregulation)
- Surgical control (i.e., removal of bone flap or lobectomy)

*After review of the checklist in Table 63-3.
CMR, cerebral metabolic rate; CSF, cerebrospinal fluid; MAP, mean arterial pressure.

CSF drainage was discussed earlier. The use of additional osmotic diuretics is theoretically limited by an upper acceptable osmolarity limit of approximately 320 mOsm/L. In extremis, the use is frequently empirical, however, and repeated doses (e.g., 12.5 g) are administered until a clinical response is no longer observed. Barbiturates have long been the most widely used drugs for inducing a reduction in CMR, with the objective of causing a coupled reduction in CBF and CBV. Propofol is gaining popularity for this application. Although the use of barbiturates is supported by intensive care unit (ICU) experience showing efficacy in ICP control[7] (if not outcome), no such experience has been accumulated for propofol. A frequently fatal syndrome of metabolic acidosis and rhabdomyolysis has been recognized in patients who have received prolonged propofol infusions in the ICU.[8,9] MAP reduction occasionally reduces vascular engorgement and reduces total brain bulk, but should be applied with extreme caution if patients have compromised intracranial collateral circulation. This approach is most likely to be relevant in the event of dysautoregulation occurring in the context of resection of arteriovenous malformations (AVMs) (see the later section on aneurysms and arteriovenous malformations).

Management of $Paco_2$

At the outset, the anesthesiologist and the surgeon should agree on the objectives with respect to $Paco_2$. Induction of hypocapnia is a time-honored part of the management of intracranial neurosurgical procedures. The rationale is principally that the concomitant reduction in CBF (see Fig. 13-4) and CBV results in a reduction in ICP, or "brain relaxation." The rationale is valid.[10] Two considerations should influence the clinician's use of hyperventilation, however. First, the vasoconstrictive effect of hypocapnia has the potential to cause ischemia in certain situations. Second, the CBF-lowering and ICP-lowering effect is not sustained.[11]

Hypocapnia-Induced Cerebral Ischemia

At first, clinicians were skeptical that hyperventilation could result in ischemia, and normal brain seems unlikely to be damaged by the typical clinical use of hyperventilation. This may not be the case, however, in certain pathologic conditions.

Normal Brain. Available data[12-16] indicate that in normal subjects, ischemia does not occur at a $Paco_2$ greater than 20 mm Hg. This generalization seems also to apply during induced hypotension.[17-19] Physiologic alterations, as evidenced by metabolic and electroencephalogram (EEG) abnormalities, have been observed,

however, in human volunteers[13,15,20] with severe hypocapnia. In one of these studies,[15] EEG abnormalities and paresthesias occurred in volunteers hyperventilating to $Paco_2$ values less than 20 mm Hg, and these effects were reversed by hyperbaric oxygenation, suggesting that they may truly have been caused by ischemia. Given that a $Paco_2$ of less than 20 to 25 mm Hg offers very little additional benefit in terms of improvement in intracranial compliance, it seems prudent to limit acute $Paco_2$ reduction to 25 mm Hg in previously normocapnic individuals. Normal brain should not be injured by this degree of hypocapnia.

Injured Brain. Although preventing herniation, maintaining ICP less than 20 mm Hg, minimizing retractor pressure, and facilitating surgical access remain priorities that may justify hypocapnia, evidence also is accumulating that hyperventilation is potentially deleterious and should not be overused. Available evidence indicates that hyperventilation can result in ischemia,[21-31] especially when baseline CBF is low,[32] as is commonly the case in the first 24 hours after injury.[33-39] An increased frequency of brain regions with very low CBF has been shown in head-injured patients who were acutely hyperventilated.[21,30,31] In addition, from centers that monitor jugular venous oxygen saturation ($Sjvo_2$), there have been numerous observations that low $Sjvo_2$ values can be increased, and that lactate levels in the jugular venous effluent can be decreased by reducing the degree of hyperventilation,[23,32,40] although the inability of $Sjvo_2$ monitoring to detect ischemia consistently also has been reported.[29-31]

At present, there is little information to confirm a deleterious effect of hyperventilation. The closest thing to "proof" resides in a subset analysis from a study of patients with moderate head injuries by Muizelaar and colleagues.[24] The study included a near-normocapnic group, in which $Paco_2$ was maintained at approximately 35 mm Hg, and a hypocapnic group, in which $Paco_2$ was maintained at approximately 25 mm Hg. Outcomes 3 and 6 months after injury revealed a poorer status in a subpopulation of the hyperventilation group. That subpopulation included patients with the best initial motor scores, a subgroup in which the severity of injury was such that they merited intubation by conventional criteria, but whose clinical condition may have been such that hyperventilation was not required for control of ICP and who had little to gain from hyperventilation.

Hyperventilation should not be an automatic component of every "neuroanesthetic." It should be treated in a manner any other therapeutic intervention. There should be an indication for instituting it (usually elevated or uncertain ICP or the need to improve conditions in the surgical field, or both). Hyperventilation should be used with the knowledge that it has the potential for causing an adverse effect, and as is the case with any other therapeutic intervention, it should be withdrawn as the indication for it subsides. The concern regarding the hazards of hypocapnia, which evolved in the context of head injury, has influenced all of neurosurgery. In particular, hyperventilation is now widely avoided in the management of SAH because of the low-CBF state that is known to occur.[41] In addition, brain tissue beneath retractors can have a similarly reduced CBF.[26,42]

Duration of Hypocapnia-Induced Reduction in Cerebral Blood Flow

The effect of hypocapnia on CBF is not sustained. Figure 63-6 is a nonquantitative representation of changes in CBF and CSF pH occurring in association with a sustained period of hyperventilation. With the onset of hyperventilation, the pH of CSF and the brain's extracellular fluid space increases, and CBF decreases abruptly. The cerebral alkalosis is not sustained, however. By alterations in the function of the enzyme carbonic anhydrase, the concentration of bicarbonate in CSF and the brain's extracellular fluid space is reduced, and in a time course of 6 to 18 hours, the pH of these compartments returns to normal.[43] Simultaneously, CBF returns toward normal levels.[43,44]

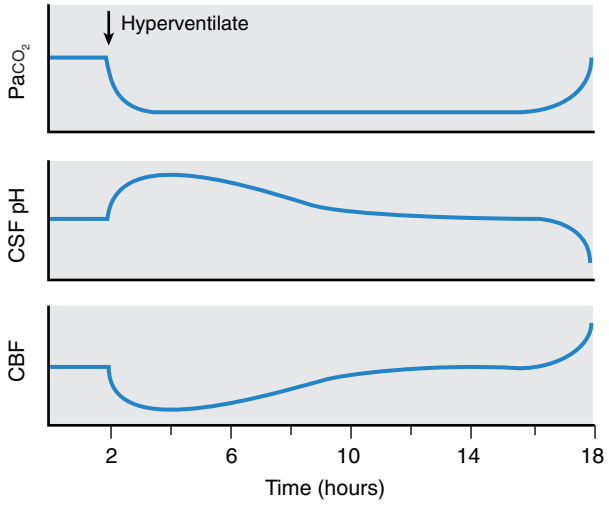

Figure 63-6 $Paco_2$, cerebral blood flow (CBF), and cerebrospinal fluid (CSF) pH changes with prolonged hyperventilation. Although the decreased arterial $Paco_2$ (and the systemic alkalosis) persist for the duration of hyperventilation, the pH of the brain and CBF return toward normal over 8 to 12 hours.

The implications are twofold. First, the clinician ideally should hyperventilate patients for only as long as a reduction in brain volume is required. Prolonged, but unnecessary, hyperventilation may lead to a circumstance wherein subsequent clinical events call for additional maneuvers to reduce the volume of the intracranial contents. However, if carbon dioxide tension is already in the 23 to 25 mm Hg range, it would be difficult to impose sufficient additional hyperventilation to once again accomplish the original reduction in CBF without the hazard of pulmonary barotrauma. Second, in a patient who has been hyperventilated for a sustained period (e.g., 2 days in the ICU), rapid restoration of $Paco_2$ from values in the vicinity of 25 mm Hg to typical normal values (e.g., 40 mm Hg) ideally should be accomplished slowly. A sudden increase in $Paco_2$ from 25 to 40 mm Hg in an individual who has been chronically hyperventilated would have the same physiologic effect that a rapid change from 40 to 55 mm Hg would have in a previously normocapnic subject. If hypocapnia has been required as an adjunct to brain relaxation during craniotomy, $Paco_2$ also should be allowed to increase when the retractors are removed (if dural closure requirements permit) to minimize the residual intracranial pneumatocele (see later section on pneumocephalus).

Management of Arterial Blood Pressure

Acceptable blood pressure limits should be agreed on at the beginning of a neurosurgical procedure. A prominent theme of contemporary neurosurgery is that CPP should be maintained at normal or even high-normal levels after acute central nervous

system insults and during most intracranial neurosurgical procedures. This concept has evolved from the growing understanding that CBF is frequently very low in some brain regions after acute neurologic insults, in particular, head injury (see discussion in the later section on head injury) and SAH. Two additional factors should be considered. The first is that the autoregulatory response to decreasing blood pressure may not be intact throughout the brain. Figure 63-7 depicts the ischemic hazard that attends the circumstance of a low resting CBF and absent autoregulation even at blood pressure levels considered safe when autoregulation is intact. Second, there is the understanding that maintenance of arterial pressure also is relevant to brain compressed under retractors[26] because the effective perfusion pressure there is reduced by increased local tissue pressure.

Although little other than anecdotal data support the notion, we believe that an aggressive attitude toward blood pressure support should be extrapolated to patients who have sustained a recent spinal cord injury, to patients whose spinal cord is under compression or at risk for compression or vascular compromise because of a disease process (most commonly cervical spinal stenosis with or without ossification of the posterior longitudinal ligament) or an intended surgical procedure, and to patients undergoing surgery involving retraction of the spinal cord. Were we empowered to "legislate" the standard of care, we would mandate that blood pressure during anesthesia in these patients be maintained as close as possible to, and certainly within 10% of, average awake values.

Steroids

The administration of steroids for the purpose of reducing or limiting the formation of edema is another time-honored practice in neurosurgery. The efficacy of steroids in reducing the edema and increasing blood-brain barrier permeability associated with tumors is well confirmed.[45-47] The time course of this effect is rapid, although not so rapid that it is relevant to the management of acute intraoperative events. Administration beginning 48 hours before an elective surgical procedure has the potential, however, to reduce edema formation and improve the clinical condition by the time of craniotomy.[45,48,49]

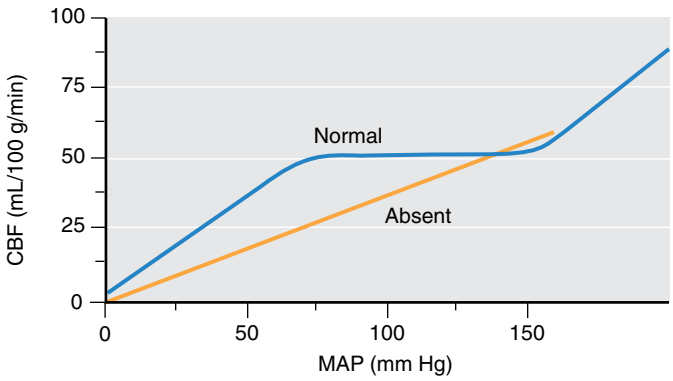

Figure 63-7 Normal and absent autoregulation curves. The "absent" curve indicates a pressure-passive condition in which cerebral blood flow (CBF) varies in proportion to cerebral perfusion pressure. This curve is drawn to indicate subnormal CBF values during normotension, as have been shown to occur immediately after head injury[23] and subarachnoid hemorrhage.[41] The potential for modest hypotension to cause ischemia is apparent. MAP, mean arterial pressure.

Although clinical improvement—specifically, a decreased frequency of ICP plateau waves and an improvement in the pressure-volume response (the increment in ICP in response to a standardized intracranial volume challenge)—occurs within 24 hours,[48] a reduction in ICP may not occur for 48 to 72 hours after the initiation of therapy.[48] This finding has been interpreted to indicate that steroids in some way improve the "viscoelastic properties" of the intracranial space before a reduction in edema occurs, although the mechanism is undefined.[49] Steroids are often given intraoperatively and postoperatively to maintain the effects achieved by preoperative treatment. The practice of administering steroids to adult head injury patients has been abandoned as a result of controlled trials that showed either no benefit or deleterious effects.[50]

Diuretics

Diuretics are used widely in neurosurgery to reduce the volume of the brain's intracellular and extracellular fluid compartment. It is probably largely the extracellular compartment that is influenced because neurons and glia have quick and efficient cell volume regulation mechanisms. Osmotic and loop diuretics have been employed. Although data suggest that loop diuretics can be effective,[51] osmotic diuretics, principally mannitol, are preferred clinically because of their speed and efficacy. The only U.S. Food and Drug Administration approved osmotic diuretic available on most formularies is mannitol. Hypertonic saline is an understudied alternative for which there is a small favorable experience and some enthusiasm in the neurosurgical community.[52,53] There is no confirmation of superiority to mannitol, however.

Data indicate that mannitol enters brain and, over a short time course, appears in the CSF space.[54] The possibility that the mannitol that gains access to the parenchyma aggravates swelling has resulted in varying degrees of reluctance among clinicians to administer mannitol.[55] Nonetheless, most clinicians find it a mainstay of ICP management. There is the concern that mannitol is effective only when some degree of blood-brain barrier integrity is preserved in a significant portion of the brain. Most clinicians respond to this concern by making empirical use of this agent (i.e., if it is effective in reducing ICP or improving conditions in the surgical field, repeated doses can be administered). If it is ineffective (or if serum osmolarity reaches the traditional limit of 320 mOsm/L), its administration is withheld.

The doses of mannitol employed vary from 0.25 g/kg to 100 g "for all comers"; 1.0 g/kg seems to be the most common dose. A systematic study in head-injured patients showed, however, that an equivalent initial ICP-reducing effect can be achieved with 0.25 g/kg, although that effect may not be as well sustained as with greater doses.[56] Mannitol should be administered by infusion (e.g., over 10 to 15 minutes). Sudden exposure of the cerebral circulation to extreme hyperosmolarity can have a vasodilatory effect, which can produce brain engorgement and increased ICP that does not occur with slower infusions.

Some clinicians advocate the combined administration of a loop diuretic (usually furosemide) and an osmotic diuretic. The superficial rationale is that mannitol establishes an osmotic gradient that draws fluid out of brain parenchyma, and that the furosemide, by hastening excretion of water from the intravascular

space, facilitates the maintenance of that gradient. A second mechanism may add additional justification for the practice of combining the two agents. Neurons and glia, as mentioned earlier, seem to have powerful homeostatic mechanisms to ensure regulation of cell volume. Neurons and glia that shrink in response to an increased osmolarity in the external environment recover their volume rapidly as a consequence of the accumulation of so-called idiogenic osmoles that serve to minimize the gradient between the internal and external environment. One of those idiogenic osmoles is chloride. The loop diuretics inhibit the chloride channel through which this ion must pass and retard the normal volume-restoring mechanism.[57,58]

The normal volume regulatory mechanisms of neurons and glia also may be relevant to the phenomenon of rebound swelling. Rebound is commonly attributed to the prior use of mannitol and assumed to be a function of the accumulation of mannitol in cerebral tissue. Although this may be part of the story, the rebound may be "hypertonic rebound," rather than "mannitol rebound." After a sustained period of hyperosmolarity of any etiology, rebound swelling of neurons and glia (which have accumulated idiogenic osmoles) may occur in the event that systemic osmolarity decreases rapidly toward normal levels. It is well known that rebound cerebral swelling can occur after an episode of extreme increases in blood glucose concentration. Hypertonic saline rather than mannitol may not obviate this phenomenon.

Anticonvulsants

The general principle is that any acute irritation of the cortical surface has the potential to result in seizures; this includes acute neurologic events such as head injury and SAH.[59,60] Cortical incisions and brain surface irritation by retractors may similarly be potential foci. Given the benign nature of diphenylhydantoin, routine administration in patients undergoing most supratentorial craniotomies and in patients who have sustained a significant recent head injury[59] or SAH seems appropriate in the absence of a contraindication. Diphenylhydantoin should be administered at rates not more rapid than 50 mg/min. There is no need for rapid administration to prevent *postoperative* seizures, and it should be administered at a significantly slower rate.

Positioning

The intended surgical position and the necessary position aids should be agreed on at the outset. Table 63-5 lists the commonly used positions and positioning aids and supports (see also Chapter 36).

General Considerations

The prolonged duration of many neurosurgical procedures should be taken into account in all positions. Pressure points should be identified and padded carefully. Pressure and traction on nerves must be avoided. Given the high risk of thromboembolic complications in neurosurgical patients, precautions including support hose and sequential compression devices are indicated. For cranial procedures, almost invariably some component of head-up posturing (e.g., 15 to 20 degrees) is appropriate to ensure optimal venous drainage. The conspicuous exception occurs with evacuation of a chronic subdural hemorrhage, after which patients are usually nursed flat to discourage reaccumulation. Patients also are often maintained flat after CSF shunting to avoid too-rapid collapse of the ventricles.

Table 63-5 Common Neurosurgical Positions and Positioning Aids

Positions
Supine
Lateral (park bench)
Semilateral (Janetta)
Prone
Sitting
Positioning Aids and Supports
Pin (Mayfield) head holder
Radiolucent pin head holder
Horseshoe head rest
Foam head support (e.g., Voss, O.S.I., Prone-View)
Vacuum mattress ("bean bag")
Wilson-type frame
Andrews ("hinder binder")-type frame
Relton-Hall (four-poster) frame

Supine

The supine position is used with the head neutral or rotated for frontal, temporal, or parietal access. Extremes of head rotation can obstruct the jugular venous drainage, and a shoulder roll can attenuate this problem. The head is usually in a neutral position for bifrontal craniotomies and transsphenoidal approaches to the pituitary. The head-up posture is best accomplished by adjusting the operating table to a chaise lounge (lawn chair) position (flexion, pillows under the knees, slight reverse Trendelenburg). This orientation, in addition to promoting cerebral venous drainage, decreases back strain.

Semilateral

The semilateral position, also known as the Janetta position after the neurosurgeon who popularized its use for microvascular decompression of the fifth cranial nerve, is used for retromastoid access. It is achieved by lateral tilting of the table 10 to 20 degrees combined with a generous shoulder roll. Extreme head rotation, sufficient to cause compression of the contralateral jugular by the chin, should be avoided.

Lateral

The lateral position can be used for access to the posterior parietal and occipital lobes and the lateral posterior fossa, including tumors at the cerebellopontine angle and aneurysms of the vertebral and basilar arteries. An axillary roll is important for preventing brachial plexus injury.

Prone

The prone position is used for spinal cord, occipital lobe, craniosynostosis, and posterior fossa procedures. The prone position also has been referred to, aptly, as the Concorde position because, for cervical spine and posterior fossa procedures, the final position commonly entails neck flexion, reverse Trendelenburg, and elevation of the legs. This orientation brings the surgical field to a horizontal position.

The anesthesiologist should have a plan for detaching and reattaching monitors in an orderly manner to prevent an excessive monitoring "window." Awake tracheal intubation and prone positioning can be employed in patients with an unstable cervical

spine, in whom an unchanged neurologic status should be confirmed before induction of anesthesia in the final surgical position. It also is occasionally done in very obese patients.

The head can be positioned in a pin head holder (applied before the turn), a horseshoe head rest, or a disposable foam head rest. A complication of the prone position is retinal ischemia and blindness owing to orbital compression causing central retinal vessel occlusion; constant attention must be directed toward avoiding this complication. It must be intermittently confirmed (e.g., every 15 minutes), and confirmed after any surgery-related head or neck movement that pressure has not come to bear on the eye.

Not all postoperative visual loss is a result of direct orbital compression, however. Ischemic optic neuropathy (ION) seems to be a more frequent cause of postoperative visual loss than pressure causing occlusion of central retinal vessels. The cause-and-effect relationships associated with ION are uncertain, but low arterial pressure, low hematocrit, and lengthy surgical procedures are statistically associated with the phenomenon.[61] Ophthalmologists have long recognized the phenomenon of anterior ION in nonanesthetized patients, and have identified as risk factors many causes of vascular disease (e.g., hypertension, diabetes, smoking, hyperlipidemia) and hypotension, especially when it occurs in hypertensives.[62,63] It also is suspected that certain normal anatomic and physiologic variations, including poor collateralization or absence of autoregulation of the vasculature of the optic nerve head,[62] a small and anatomically "crowded" optic nerve head (the "disk at risk"[64]), an increase in intraocular pressure that has been observed to occur during prolonged prone spine surgery,[65] and impaired cerebral venous drainage,[66] may contribute to the intraoperative occurrence of ION. The notion that ION is merely a function of arterial hypotension is probably an inaccurate oversimplification of a phenomenon that almost certainly involves the interplay of numerous preoperative and intraoperative factors.[67,68]

Direct pressure also can result in various degrees of pressure necrosis of the forehead, maxillae, and chin, especially with prolonged spinal procedures. The clinician should ensure that pressure is as evenly distributed as possible over facial structures. Other pressure points to be checked include the axillae, breasts, iliac crests, femoral canals, genitalia, knees, and heels. When the arms are placed in the "stick-em up" position, traction on the brachial plexus must be avoided. That can usually be accomplished by not exceeding a "90-90" position (arms abducted not greater than 90 degrees; elbows extended not greater than 90 degrees) with care taken to ensure that the elbow is anterior to the shoulder to prevent wrapping of the brachial plexus around the head of the humerus. An antisialogogue (e.g., glycopyrrolate) and adhesive (e.g., benzoin) may help reduce loosening of tape used to secure the endotracheal tube.

An objective during prone positioning, especially for lumbar spine surgery, is the avoidance of compression of the inferior vena cava. Impairment of vena caval return diverts blood to the epidural plexus and increases the potential for bleeding during spinal surgery. Optimizing venous return is an objective of all of the spinal surgery frames and is accomplished very effectively by the Relton-Hall, Wilson, and Andrews variants. Use of these frames introduces a risk of air embolism,[69,70] although clinical occurrences have been very rare.[71]

Attention should be directed toward preventing injury to the tongue in the prone position. With cervical and posterior fossa procedures, it is frequently necessary to flex the neck substantially to facilitate surgical access. This flexion reduces the anterior-posterior dimension of the hypopharynx, and compression ischemia of the base of the tongue (and the soft palate and posterior wall of the pharynx) can occur in the presence of foreign bodies (i.e., endotracheal tube, esophageal stethoscope, oral airway). The consequence can be macroglossia, caused by accumulation of edema after reperfusion of the ischemic tissue causing postextubation airway obstruction of rapid onset (see later). Unnecessary paraphernalia in the oral cavity and pharynx should be avoided. Omitting the oral airway entirely is unwise because the tongue may then protrude between and be trapped by the teeth as progressive swelling of facial structures occurs during a prolonged prone procedure. A rolled gauze bite block prevents this problem without adding bulk to the hypopharynx.

Sitting

There have been several reviews of large experiences with the sitting position.[72-76] All concluded that the sitting position can be employed with acceptable rates of morbidity and mortality. These reports were prepared by groups that perform 50 to 100 or more of these procedures per year, however, and the hazards of the sitting position may be greater for teams who have less frequent occasion to use it. With increasing frequency, the sitting position is being avoided through the use of one of its alternatives (i.e., prone, semilateral, lateral). We are likely to continue encountering it, however, because even surgeons who are inclined to use alternative positions may opt for the sitting position when access to midline structures (i.e., the floor of the fourth ventricle, the pontomedullary junction, and the vermis) is required. Nonetheless, alternative positions for posterior fossa surgery exist and should be considered when there are contraindications to the sitting position.

Achieving the Sitting Position. A properly positioned patient is more commonly in a modified recumbent position as shown in Figure 63-8, rather than truly sitting. The legs should be kept as high as possible (usually with pillows under the knees) to promote venous return. Ideally, the head holder should be attached to the back portion of the table (see Fig. 63-8A), rather than to the portions under thighs or legs (see Fig. 63-8B). This permits lowering of the head, and closed chest massage if necessary, without the necessity of first taking the patient out of the head holder.

When procedures are performed in the sitting position, the clinician should think in terms of measuring and maintaining perfusion pressure at the level of the surgical field. This is best accomplished by referencing transducers to the interaural plane. If a manual blood pressure cuff on the arm is employed, a correction* to allow for the hydrostatic difference between the arm and the operative field should be applied.

A series of hazards are associated with the sitting position. Circulatory instability, macroglossia, and quadriplegia are discussed in this section. Pneumocephalus is discussed in the section on pneumocephalus. Venous air embolism (VAE) and paradoxical air embolism (PAE) are discussed in the section on venous air embolism. Several of these hazards also are relevant when cervical spine and posterior fossa procedures are done in nonsitting positions, but occur with greater frequency in the sitting position.

*A column of water 32 cm high exerts a pressure of 25 mm Hg.

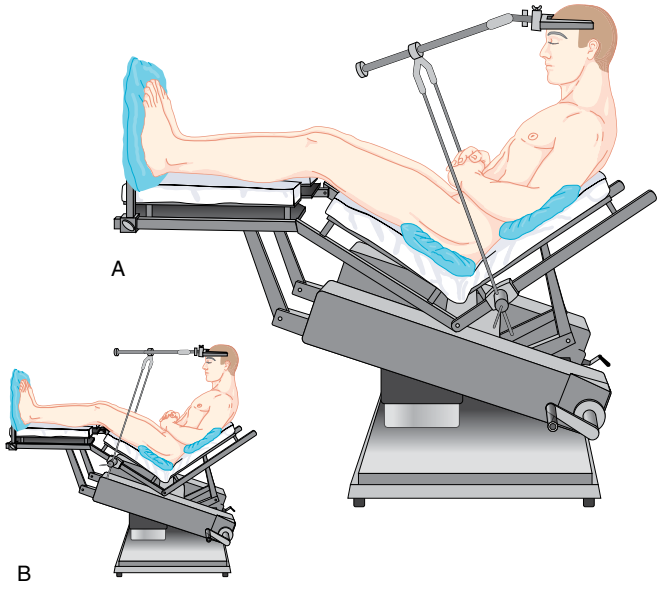

Figure 63-8 **A** and **B,** The sitting position. The patient is typically semirecumbent rather than sitting. In **A,** the head holder support is correctly positioned such that the head can be lowered without the need to detach the head holder first. The configuration in **B,** with the support attached to the thigh portion of the table, should be avoided. *(From Martin JT: Positioning in Anesthesia and Surgery. Philadelphia, WB Saunders, 1988.)*

Cardiovascular Effects of the Sitting Position. Placing the anesthetized patient in the sitting position conveys some risk of impaired cardiovascular function, in particular, hypotension. Pressor administration is required in some patients. Measures to avoid hypotension include prepositioning hydration, wrapping of the legs with elastic bandages to counteract gravitational shifts of blood, and slow, incremental adjustment of table position. Aggressive volume loading and the G suit (also known as pneumatic antishock trousers or military antishock trousers) attenuate the effects of assuming the sitting position.[77-79] Neither of these measures has been widely applied, however.

In most healthy subjects, the hemodynamic changes are of a nonthreatening magnitude. In a study of healthy anesthetized adult subjects, 22 to 64 years old, Marshall and colleagues[80] observed modest changes. MAP was relatively unaffected, whereas wedge pressure, stroke volume, and cardiac index decreased—the last-mentioned by approximately 15%—although there was some variation with the anesthetic drugs employed. The combination of an unchanged MAP (which generally requires the use of a "light," high sympathetic tone anesthetic) and a reduced cardiac index implies that systematic vascular resistance increased. Their calculations and the observations of other investigators[81] reveal significant elevation of systematic vascular resistance. For patients in whom an abrupt increase in systematic vascular resistance may be poorly tolerated, the sitting position may represent a physiologic threat, and alternative positions should be considered. A pulmonary arterial catheter may be warranted when there is clinical or historical evidence of antecedent coronary artery or valvular heart disease and arbitrarily in patients older than 60 to 65 years.

During procedures performed in the sitting position, MAP should be corrected to head level to obtain a meaningful index of CPP. Specifically, CPP (MAP − estimated ICP) should be maintained at a minimum value of 60 mm Hg in healthy patients in whom it is reasonable to assume a normal cerebral vasculature. The safe lower limit should be increased for elderly patients, for patients with hypertension or known cerebrovascular disease, and for patients with degenerative disease of the cervical spine or cervical spinal stenosis who may be at risk for decreased spinal cord perfusion, and in the event that substantial or sustained retractor pressure must be applied to brain or spinal cord tissue.

Macroglossia. There have been sporadic reports of upper airway obstruction after posterior fossa procedures in which swelling of pharyngeal structures, including the soft palate, posterior wall, pharynx, and base of the tongue, has been observed.[82] These episodes have been attributed to edema formation at the time of reperfusion after trauma or prolonged ischemia occurring as the result of foreign bodies (usually oral airways) causing pressure on these structures in the circumstances of lengthy procedures with sustained neck flexion (which is usually required to improve access to posterior structures). It is customary (and we think ideal, although there is no science to support the practice) to maintain at least two fingerbreadth's distance between the chin/mandible and the sternum/clavicle to prevent excessive reduction of the anterior-posterior diameter of the oropharynx. In addition, we position patients with the oral airway in place and then, after the final head position is achieved, withdraw it until its tip functions as a bite block between the teeth. The macroglossia phenomenon also may be relevant as clinicians contemplate the use of transesophageal echocardiography (TEE) in the neurosurgery suite. The centers that routinely employ TEE in neurosurgery, for the most part, use either pediatric or custom-made small-diameter probes to avoid trauma to pharyngeal and perilaryngeal structures.

Quadriplegia. The sitting position per se has been implicated as a cause of rare instances of unexplained postoperative paraplegia. It has been hypothesized[83] that the neck flexion that is a common concomitant of the seated position may result in stretching or compression of the cervical spinal cord. This possibility may represent a relative contraindication to the use of this position in patients with significant degenerative disease of the cervical spine, especially when there is evidence of associated cerebrovascular disease. The implications for blood pressure management are mentioned in the preceding section on cardiovascular effects. It also may represent a justification for somatosensory evoked response monitoring during the positioning phase of a sitting procedure for patients perceived to be at high risk.

Pneumocephalus

The issue of pneumocephalus arises most often in connection with posterior fossa craniotomies performed with a head-up posture.[84,85] During these procedures, air may enter the supratentorial space, much as air enters an inverted bottle. Depending on the relationship of the brainstem and temporal lobes to the incisura, the pressure in the air collection may or may not be able to equilibrate with atmospheric pressure. This phenomenon has relevance to the use of N_2O because any N_2O that enters a trapped gas space would augment the volume of that space. In (probably

uncommon) intraoperative circumstances in which there is a completely closed intracranial gas space, the use of N_2O may result in an effect comparable to that of an expanding mass lesion. We do not view N_2O as absolutely contraindicated because, before dural closure, intracranial gas is probably only rarely trapped. Nonetheless, attention to this possibility is important when one is presented with the problem of an increasingly "tight" brain during a posterior fossa craniotomy.[86,87]

During a posterior fossa procedure done in a head-up posture, when surgical closure has reached a stage such that the intracranial space has been completely sealed from the atmosphere, N_2O should not be given because of the possibility of contributing to a tension pneumocephalus. The use of N_2O up to the point of dural closure may represent a clinical advantage[88] because the gas pocket can be expected to shrink more rapidly owing to the presence of N_2O (because N_2O diffuses out much more quickly than nitrogen does). Tension pneumocephalus is often naively viewed as exclusively a function of the use of N_2O. Tension pneumocephalus can occur, however, as a complication of intracranial neurosurgery entirely *un*related to the use of N_2O.[89]

Tension pneumocephalus is one of the causes of delayed awakening or nonawakening after posterior fossa and supratentorial procedures (Fig. 63-9).[89,90] It occurs because air enters the cranium while the patient is in a head-up position at a time when the volume of the intracranial contents has been reduced as a result of some combination of hypocapnia, good venous drainage, osmotic diuresis, and CSF loss from the operative field. When the cranium is closed, and the patient is returned to the near-supine position, CSF, venous blood volume, and extracellular fluid return or reaccumulate, and the air pocket becomes an unyielding mass lesion (because of the very slow diffusion of nitrogen). This mass may cause delayed recovery of consciousness or severe headache. Among supratentorial craniotomies, the largest residual airspaces occur after frontal skull base procedures in which energetic brain relaxation measures are used to facilitate subfrontal access (see Fig. 63-9). At the end of these procedures, typically done in a supine/brow-up position, it is not feasible to fill the intracranial dead space with normal saline as is commonly done with smaller craniotomy defects, and there may be a large residual pneumatocele. We doubt that the possible occurrence of this phenomenon represents a contraindication to N_2O. Withdrawal of N_2O may be appropriate at the time of cranial closure, however. The diagnosis of pneumocephalus is confirmed by a brow-up lateral x-ray or CT scan. The treatment is a twist-drill hole followed by needle puncture of the dura.

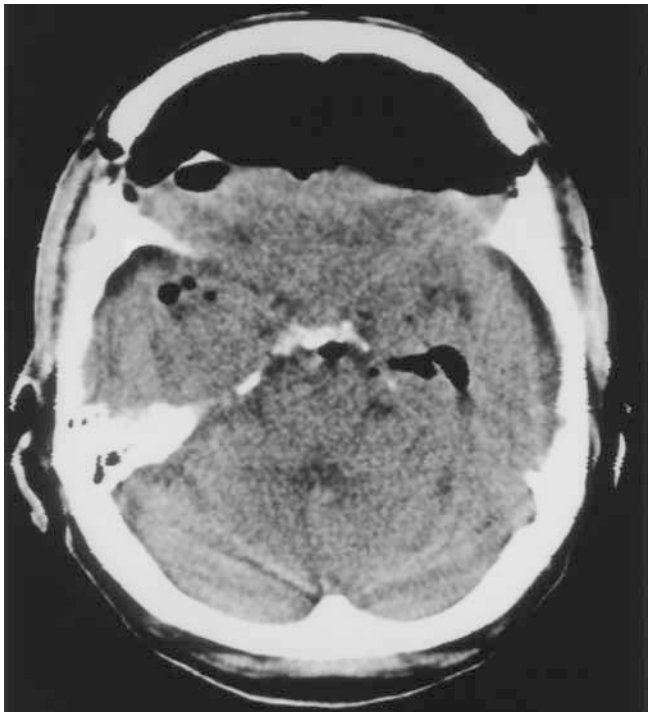

Figure 63-9 Postoperative CT scan shows a large pneumocephalus after a subfrontal approach to a suprasellar glioma. Immediately postoperatively, the patient was confused and agitated and complained of severe headache.

Residual intracranial air should be considered at the time of repeat anesthesia, neurosurgical or non-neurosurgical. Air frequently remains evident on CT scan for more than 7 days after a craniotomy.[91] Pneumocephalus also can develop de novo in the postoperative period in patients who have a residual dural defect and a communication between the nasal sinuses and the intracranial space.[92]

Venous Air Embolism

The rate of occurrence of VAE varies according to the procedure, the intraoperative position, and the detection method used. During posterior fossa procedures done in the sitting position, VAE is detectable by precordial Doppler in approximately 40% of patients and by TEE in 76%.[93-96] The incidence of VAE during posterior fossa procedures performed in nonsitting positions is much less (12% using precordial Doppler in the report of Black and colleagues[74]), and it is probable, but unproven, that the average volume of air entrained per event also is smaller. The rate of VAE is apparently lower with cervical laminectomy (25% using TEE in the sitting position versus 76% for posterior fossa procedures[95]). Although VAE is principally a hazard of posterior fossa and upper cervical spine procedures, especially when they are performed in the sitting position, it can occur with supratentorial procedures. The most common situations involve tumors, most often parasagittal or falcine meningiomas, that encroach on the posterior half of the sagittal sinus (Fig. 63-10) and craniosynostosis procedures, typically performed in children.[97,98] Pin sites and trapped gas under pressure also can lead to VAE, although clinically relevant events have been very rare.

The common sources of critical VAE are the major cerebral venous sinuses, in particular, the transverse, the sigmoid, and the posterior half of the sagittal sinus, all of which may be noncollapsible because of their dural attachments. Air entry also may occur via emissary veins, particularly from suboccipital musculature, the diploic space of the skull (which can be violated by the craniotomy and pin fixation), and the cervical epidural veins. We believe, although this has not been confirmed by systematic study, that the VAE risk associated with cervical laminectomy is greatest when the exposure requires dissection of suboccipital muscle with the potential to open emissary veins to the atmosphere at their point of entry into occipital bone. There also is anecdotal evidence[99] that air under pressure in the ventricles or subdural space occasionally can enter the venous system, perhaps following the normal egress route of the CSF.

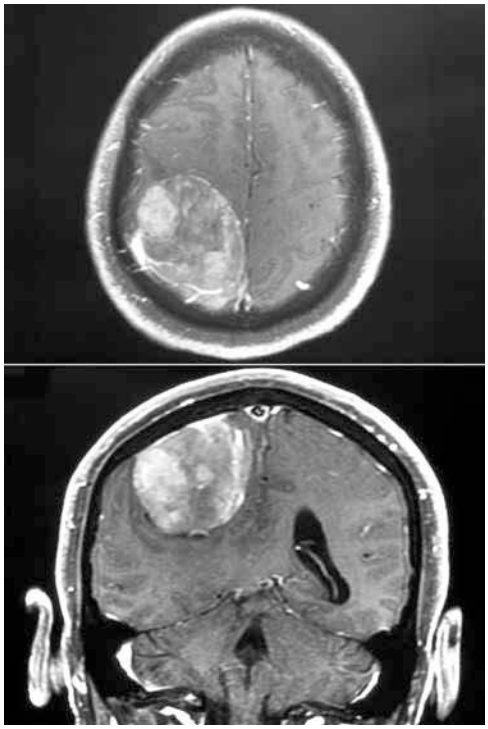

Figure 63-10 Horizontal (*top*) and coronal (*bottom*) MR images of a parasagittal meningioma. Resection of meningiomas arising from the dural reflection overlying the sagittal sinus or from the dura of the adjacent convexity or falx entails a risk of venous air embolism because of the proximity of the sagittal sinus (the triangular structure at the superior end of the interhemispheric fissure in the *bottom panel*).

Detection of Venous Air Embolism

The monitors employed for the detection of VAE should provide (1) a high level of sensitivity, (2) a high level of specificity, (3) a rapid response, (4) a quantitative measure of the VAE event, and (5) an indication of the course of recovery from the VAE event. The combination of a precordial Doppler and expired CO_2 monitoring meet these criteria and are the current standard of care. Doppler placement in a left or right parasternal location between the second and third or third and fourth ribs has a very high detection rate for gas embolization,[100] and when good heart tones are obtained, maneuvers to confirm adequate placement seem to be unnecessary. TEE is more sensitive than precordial Doppler to VAE (Fig. 63-11),[101] and offers the advantage of identifying right-to-left shunting of air.[95,102-104] Its safety during prolonged use (especially with pronounced neck flexion) is not well established, however. Expired nitrogen analysis is theoretically attractive. The expired nitrogen concentrations involved in anything less than catastrophic VAE are very small, however, and push the available instrumentation to the limits of its sensitivity (see Fig. 63-11).[105]

Figure 63-12 shows the physiologic and monitor response to an air embolic event. Table 63-6 presents an appropriate management response to such an event.

Right Heart Catheter

Essentially all patients who undergo sitting posterior fossa procedures should have a right heart catheter. Although catastrophic, life-threatening VAE is relatively uncommon, a catheter that permits immediate evacuation of an air-filled heart occasionally is the sine qua non for resuscitation. The latitudes are much wider

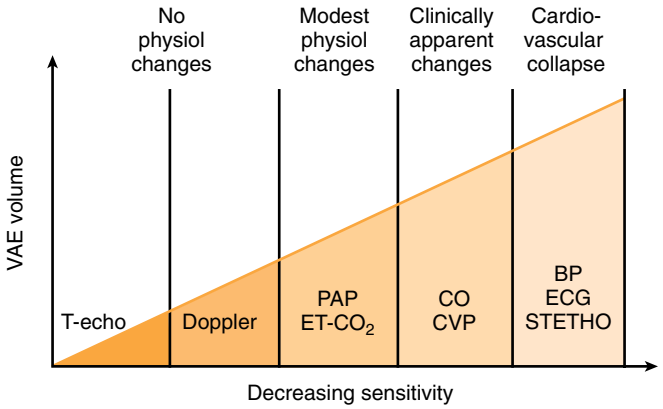

Figure 63-11 The relative sensitivity of various monitoring techniques to the occurrence of venous air embolism (VAE). BP, blood pressure; CO, cardiac output; CVP, central venous pressure; ECG, electrocardiogram, ET-CO_2, end-tidal carbon dioxide; PAP, pulmonary arterial pressure; physiol, physiological; T-echo, transesophageal echo.

with the nonsitting positions, and it is frequently appropriate, after a documented discussion with the surgeon, to omit the right heart catheter. The variables that contribute to this decision are the perceived risks of VAE associated with the intended procedure and the patient's physiologic reserve.

An example of a procedure for which the right heart catheter is usually omitted is microvascular decompression of the fifth cranial nerve for tic douloureux or the seventh cranial nerve for hemifacial spasm. The essentially horizontal semilateral position and the very limited retromastoid craniectomy these procedures require have resulted (at our institution) in a very low incidence of Doppler-detectable VAE. One should come to know the local surgical practices, however, particularly with respect to the degree of head-up posture, before becoming casual about omitting the right atrial catheter. With regard to the Janetta procedure, the necessary retromastoid craniectomy is performed in the angle between the transverse and sigmoid sinuses, and venous sinusoids and emissary veins in the suboccipital bone are common. If this procedure is performed with any degree of head-up posturing, the risk of VAE may still be substantial.

Which Vein Should Be Used for Right Heart Access. Although some surgeons may ask that neck veins not be used, a skillfully placed jugular catheter is usually acceptable. In a very few patients, high ICP may make the head-down posture undesirable. In others, unfavorable anatomy with an increased likelihood of a difficult cannulation and hematoma formation also may encourage the use of alternative access sites. Access to the brachial

Table 63-6 Management of an Acute Air Embolic Event

Prevent further air entry
Notify surgeon (flood or pack surgical field)
Jugular compression
Lower the head
Treat intravascular Air
Aspirate right heart catheter
Discontinue N_2O
Fio_2: 1.0
Pressors/inotropes
Chest compression

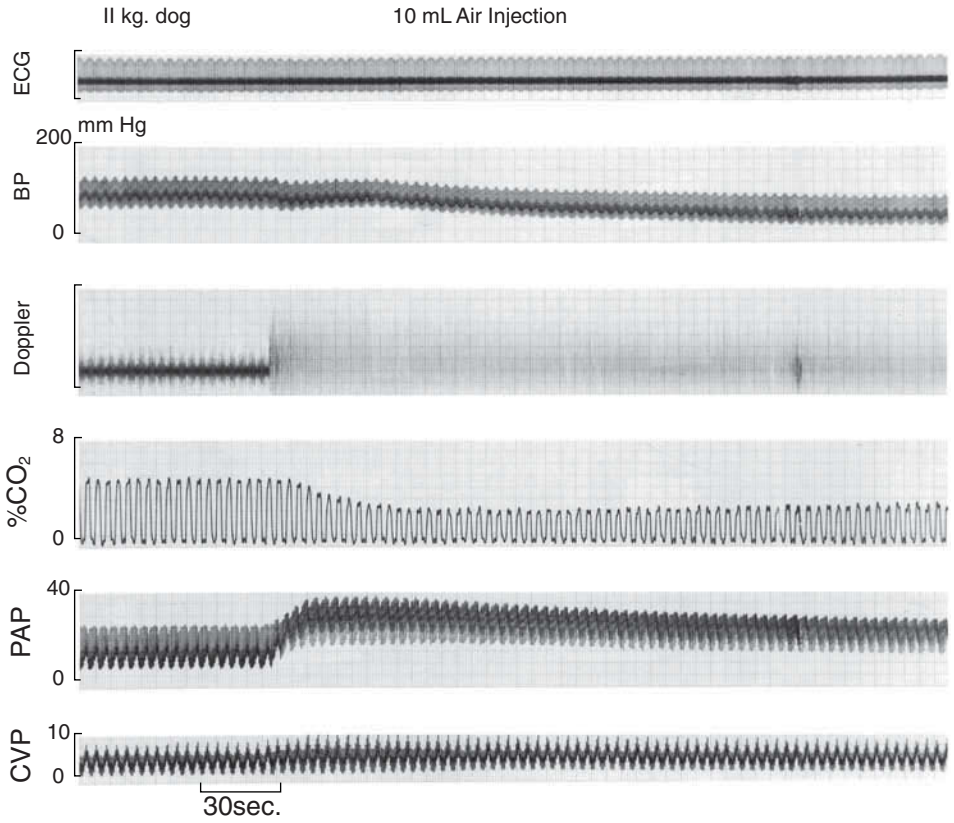

Figure 63-12 The responses of electrocardiogram (ECG), arterial pressure (blood pressure [BP]), pulmonary arterial pressure (PAP), pan-tidal carbon dioxide (CO_2) concentration, precordial Doppler, and central venous pressure (CVP) to the intravenous administration of 10 mL of air over 30 seconds to an 11-kg dog.

veins has been greatly facilitated by the commercial availability of multiorificed catheters that use a Seldinger cannulation technique and a lengthy J-tipped guidewire to negotiate the axilla or deltopectoral groove.

Positioning the Right Heart Catheter. Bunegin and colleagues[106] suggested that a multi-orificed catheter should be located with the tip 2 cm *below* the superior vena caval–atrial junction, and a single-orificed catheter should be located with the tip 3 cm *above* the superior vena caval–atrial junction. Although these small distinctions in location may be relevant for optimal recovery of small volumes of air when cardiac output is well maintained, for the recovery of massive volumes of air in the face of cardiovascular collapse, anywhere in the right atrium should suffice. Right heart placement can be confirmed by (1) x-ray, (2) pull back from the right ventricle while monitoring intravascular pressure, or (3) intravascular electrocardiogram (ECG).[107] Although there is no literature to support the practice, with catheter access via the right internal jugular vein, a measured placement to the level of the second or third right intercostal space should suffice when the catheter passes readily.

The intravascular ECG technique makes use of the fact that an ECG "electrode" placed in the middle of the right atrium initially "sees" an increasing positivity as the developing P-wave vector approaches it (Fig. 63-13), and then an increasing negativity as the wave of atrial depolarization passes and moves away from it. The resultant biphasic P wave is characteristic of an intra-atrial "electrode" position. The technique requires that the CVP catheter becomes an exploring ECG electrode. This is accomplished by filling the catheter with an electrolyte solution (bicarbonate is best) and attaching an ECG lead (the leg lead if lead II is selected) to the hub of the CVP catheter. Commercial CVP kits with an ECG adapter are available. The ECG configurations that are observed at various intravascular locations are shown in Figure 63-13. To minimize the microshock hazard, a battery-operated ECG unit is preferable, and unnecessary electric apparatus should be detached from the patient during catheter placement (see Table 63-6).

Paradoxical Air Embolism

There has been much concern about the possibility of the passage of air across the interatrial septum via a patent foramen ovale (known to be present in approximately 25% of adults).[108] The concern is that this phenomenon carries the risk of major cerebral or coronary morbidity, although there has been no precise definition of the morbidity that can realistically be attributed to PAE. Although the minimal pressure required to open a probe patent foramen ovale is not known with certainty, it is thought that the necessary gradient may be 5 mm Hg. In a clinical investigation, Mammoto and colleagues[104] observed that PAE occurred only in the context of major air embolic events, suggesting that significant increases in right heart pressures are an important predisposing factor of the occurrence of PAE.

Several clinical investigations have examined factors that influence the right atrial pressure (RAP) to left atrial pressure (LAP) gradient. The use of PEEP was shown to increase the inci-

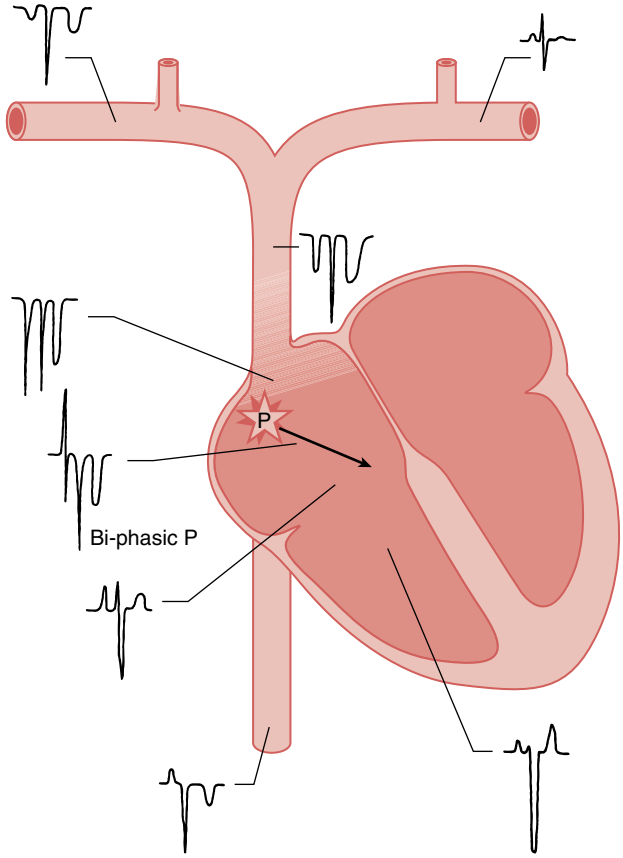

Figure 63-13 Electrocardiogram (ECG) configurations observed at various locations when a central venous catheter is used as an intravascular ECG electrode. The configurations in the figure are observed when "lead II" is monitored and the positive electrode (the leg electrode) is connected to the catheter. P indicates the sinoatrial node. The *heavy black arrow* indicates the P wave vector. Note the equi-biphasic P wave when the catheter tip is in the mid right atrial position.[107]

dence of a positive RAP to pulmonary wedge pressure gradient,[109] and generous fluid administration (e.g., 2800 mL/patient versus 1220 mL/control patient[110]) was shown to reduce it. As a result, the use of PEEP, which was previously advocated as a means of preventing air entrainment, diminished, and the practice of more generous fluid administration for patients undergoing posterior fossa procedures evolved. Subsequent data indicated, however, that even when *mean* LAP exceeds mean RAP, PAE can still occur because transient reversal of the interatrial pressure gradient can occur during each cardiac cycle.[111]

Some centers have advocated performing bubble studies preoperatively with either precordial echocardiography[96] or transcranial Doppler (TCD)[112] or prepositioning TEE[113] to identify patients with a patent foramen ovale with a view to using alternatives to the sitting position in this subpopulation.[95,114] Some centers thereafter advocate the use of TEE to identify PAE intraoperatively.[95,103] This practice is not universal,[76] however, and at the time of writing (2009) it is not a community-wide standard of care. Because the morbid events attributable to PAE have been infrequent, surgeons who are convinced that the sitting position is optimal for a given procedure[76] are loath to be dissuaded from using it on the basis of what may seem like the very minor possibility of an injury to the patient occurring by this mechanism.

Transpulmonary Passage of Air

Air apparently can occasionally traverse the pulmonary vascular bed to reach the systemic circulation.[115,116] Transpulmonary passage is more likely to occur when large volumes of air are presented to the pulmonary vascular "filter."[117,118] There is also evidence suggesting that pulmonary vasodilators, including volatile anesthetics, may decrease the threshold for transpulmonary passage.[117-119] Differences among anesthetics are negligible. N_2O should be discontinued promptly after even apparently minor VAE events, however, because of the possibility that air may reach the left-sided circulation via a patent foramen ovale or the pulmonary vascular bed.

Techniques for Reducing the Incidence of Venous Air Embolism

As noted previously, PEEP has been advocated in the past as a means of reducing the incidence of VAE or of responding to an acute VAE event to prevent further air entry. Perkins and Bedford[109] suggest that PEEP increases the risk of PAE, however, and argue against the use of PEEP in seated neurosurgical procedures. As these authors point out, even 10 cm of PEEP would be unlikely to result in positive venous pressures in cerebral venous structures, which may be 25 cm above the heart. The ineffectiveness of PEEP[120] and the relative superiority of jugular venous compression[121,122] in increasing cerebral venous pressures have been confirmed by several investigations. An inflatable neck tourniquet available for rapid inflation in the event of VAE has been studied in animals and used in humans by Pfitzner and McLean.[123] There are additional arguments against the acute use of increased positive airway pressure in the event of VAE. The release of a Valsalva maneuver promotes paradoxical embolism. In addition, the impairment of systemic venous return caused by the sudden application of substantial PEEP may be undesirable in the face of the cardiovascular dysfunction already caused by the VAE event.

It has been associated that a patient who has sustained a hemodynamically significant VAE should be placed in a lateral position with the right side up. The rationale is that air would remain in the right atrium, where it would not contribute to an air lock in the right ventricle, and where it would remain amenable to recovery via a right atrial catheter. The first difficulty is that this repositioning is all but impossible with a patient in a pin head holder. In addition, the only systematic attempt to examine the efficacy of this maneuver, albeit performed in dogs, failed to identify any hemodynamic benefit.[124]

Nitrous Oxide. N_2O diffuses into air bubbles trapped in the vascular tree; N_2O should be eliminated after a clinical VAE event to avoid aggravating the cardiovascular impact. As noted earlier, the PAE phenomenon adds an additional reason for eliminating N_2O *after* the occurrence VAE. When major VAE occurs, no matter how the RAP-LAP gradient was manipulated before the event, RAP increases abruptly with respect to LAP,[125] and major VAE results in an acutely increased risk of PAE in patients with a patent foramen ovale.[104] Should N_2O be used at all in patients at risk for VAE? Some clinicians may decide that it is the "path of least resistance" simply to avoid it, and to avoid having to worry

about the considerations it creates. N_2O can be used, however, with the knowledge that it neither increases the incidence of VAE[126] nor aggravates the hemodynamic response to VAE, provided that it is eliminated when VAE occurs.[127]

Monitoring

Neurologic monitoring techniques are discussed in Chapter 46. Invasive monitoring is frequently appropriate in neurosurgery Table 63-7 lists indications for an arterial catheter.

Patients with increased ICP may be intolerant of the vascular engorgement associated with sudden hypertension occurring as a consequence of light anesthesia. Surgical relief of increased ICP may be associated with sudden hypotension as brainstem compression is relieved. Beat-by-beat arterial pressure monitoring also serves as an important monitor of depth of anesthesia and as an early warning system for neurologic injury. Much of the brain is insensate. Consequently, the intracranial portion of many neurosurgical procedures is not very stimulating, and to achieve circulatory stability, light anesthesia is often necessary. The anesthesiologist should be constantly aware of the possibility of sudden arousal (most often associated with cranial nerve traction or irritation). This is especially important when paralysis is precluded by the use of electromyographic recording from facial muscles to monitor cranial nerve integrity. Blood pressure responses may reveal imminent arousal. Blood pressure responses also may serve to warn a surgeon of excessive or unrecognized irritation, traction, or compression of neurologic tissue.

Table 63-7 Relative Indications for Intra-arterial Pressure Monitoring

Elevated ICP
Ischemia or incipient ischemia of neurologic tissue
Recent SAH
Recent head injury
Recent spinal cord injury
Intended or potential temporary vessel occlusion
Circulatory instability
Trauma
Spinal cord injury (spinal shock)
Sitting position
Possible barbiturate coma
Possibility of induced hypotension
Possibility of induced hypertension
Anticipated/potential major blood loss
Aneurysm clipping
Arteriovenous malformations
Vascular tumors
Tumors involving major venous sinuses
Craniofacial reconstruction
Extensive craniosynostosis procedures
Anticipated light anesthesia without paralysis
Brainstem manipulation/compression/dissection
Anticipated cranial nerve manipulation (especially CN V)
Advantageous for postoperative intensive care
Hypervolemic therapy
Head injury
Diabetes insipidus
Incidental cardiac disease

CN, cranial nerve; ICP, intracranial pressure; SAH, subarachnoid hemorrhage.

These occur most often with posterior fossa procedures involving brainstem or cranial nerves, and abrupt changes should be reported to the surgeon immediately.

The use of right heart catheters for air retrieval is discussed in the section on venous air embolism. Thereafter, anticipated blood loss and fluid flux (including aggressive mannitol use) and an evaluation of the patient's physiologic reserve should determine the necessity for CVP or pulmonary arterial catheters. The use of the precordial Doppler also is described in the section on venous air embolism.

Intravenous Fluid Management

The general principles of fluid management (see Chapter 54) for neurosurgical anesthesia are (1) maintain normovolemia, and (2) avoid reduction of serum osmolarity. The first principle is a derivative of the concept presented in the section on management of blood pressure that it is generally ideal to maintain a normal MAP in patients undergoing most neurosurgical procedures and neurosurgical critical care. Maintaining normovolemia is simply one element of maintaining a normal MAP. The second principle is a derivative of the often repeated observation that reducing serum osmolarity results in edema of normal and abnormal brain.[128] Administering fluids that provide free water (i.e., fluids that do not have sufficient nonglucose solutes to render them iso-osmolar with respect to blood) reduces serum osmolarity if the amount of free water administered is greater than that required to maintain ongoing free water loss.

Normal saline and lactated Ringer's solution are the fluids most often used intraoperatively. At 308 mOsm/L, normal saline is slightly hyperosmolar with respect to plasma (295 mOsm/L). It has the disadvantage that in large volumes it can cause a hyperchloremic metabolic acidosis.[129] The physiologic significance of this acidosis, which involves the extracellular, but not the intracellular, fluid space, is unclear. At a minimum, it has the potential to confuse the diagnostic picture when acidosis is present. As a result, many clinicians use predominately lactated Ringer's solution. Although lactated Ringer's solution (273 mOsm/L) theoretically is not ideal for individual replacement of blood and third space loss or insensible losses, it serves as a reasonable compromise for meeting both needs simultaneously and is very suitable in most instances. It is a hypo-osmolar fluid, however, and in a healthy experimental animal, it is possible to reduce serum osmolarity and produce cerebral edema with a large volume of lactated Ringer's solution.[128] In the setting of large-volume fluid administration (e.g., significant blood loss, multiple trauma), we alternate, liter by liter, lactated Ringer's solution and normal saline.

The crystalloid versus colloid discussion is a recurrent one. This discussion usually arises in the context of a head injury victim. Although there are numerous fervent beliefs regarding this issue, there has been only a single demonstration that the reduction of colloid oncotic pressure in the absence of a change of osmolarity can contribute to an augmentation of cerebral edema in the setting of experimental head injury.[130] The transcapillary membrane pressure gradients that can be produced by reduction of colloid oncotic pressure are very small compared with those created by changes in serum osmolarity. Nonetheless, it seems that those small gradients have the potential—probably in the setting of a blood-brain barrier injury of intermediate severity—to augment edema. It seems reasonable then to select a

fluid administration pattern that, in addition to maintaining normal serum osmolarity, would prevent substantial reductions in colloid oncotic pressure. For most elective craniotomies, this would *not* require the administration of colloid solutions. In situations requiring substantial volume administration (e.g., multiple trauma, aneurysm rupture, cerebral venous sinus laceration, fluid administration to support filling pressure during barbiturate coma), a combination of isotonic crystalloid and colloid may be appropriate.

Which Colloid Solutions Should Be Employed

On the basis of empirical local experience, we view albumin to be a reasonable choice as a colloid solution. There are conflicting opinions and cross-currents in the literature, however. A more recent analysis of the subset of patients in the Saline versus Albumin Fluid Evaluation (SAFE) trial with severe head injury (Glasgow Coma Scale [GCS] score 3 to 8) revealed increased mortality in patients who received saline.[131] There is no accepted explanation. The formation of cerebral edema, which is more difficult to clear, is an inevitable suspicion. By contrast, a nonconcurrent, retrospective (i.e., less than scientifically ideal) comparison of outcome after volume support in patients with vasospasm after SAH revealed deterioration in outcomes when albumin was abandoned in favor of saline.[132] Finally, an evolving literature, containing preclinical and clinical data, suggests an improvement in neurologic outcome when albumin is administered after stroke.[133] These data have been sufficient to justify a phase III trial in human stroke, which began in 2006.[134] At most, the existing literature might justify consideration of limiting albumin volumes in patients with severe head injury, although the driving observations should be replicated before any firm principle is established.

The dextran-containing solutions are generally avoided because of their effects on platelet function. The various starch-containing solutions should be used cautiously in neurosurgery because, in addition to a dilutional reduction of coagulation factors, they interfere directly with platelets and the factor VIII complex.[135] The literature addressing the coagulation effects of starches should be read with the understanding that the effects on coagulation are proportional to the average molecular weight of the starch preparation. In North America, preparations with the greatest molecular weights are used. When hetastarch solutions are used in neuroanesthesia, the clinician should respect the manufacturers' recommended dose restrictions, and should use additional restraint in situations where there are other reasons for impairment of the coagulation mechanism. Several reported instances of bleeding in neurosurgical patients have been attributed to hetastarch administration. All of those instances have involved circumstances in which the manufacturer's recommended limit of 20 mL/kg/day was exceeded,[136] or in which hetastarch was administered up to the recommended limit on successive days, probably resulting in an accumulation effect.[137] The decision to use or not use these products frequently is a matter of local bias. If the products are used, the manufacturers' recommended limit (20 mL/kg/24 hr) should be observed.

There is substantial current interest in the use of hypertonic fluids for the resuscitation of multiple trauma victims in general[138] and of patients with neurologic injuries in particular.[52,139] Improvement in outcome has yet to be shown in the latter group in association with hypertonic solutions, however.[139] It seems unlikely that the initial ICP effect of these fluids on the brain is substantially different from an equiosmolar exposure to mannitol[140,141] (although that notion should be qualified that there are reports of patients who had become refractory to mannitol who then responded to hypertonic saline).[53,142] For the time being, when decisions about the appropriateness and relevance of these fluids in the resuscitation process are eventually made, it seems unlikely that those decisions should be made on the basis of specific cerebral effects. It seems more likely that the final judgment regarding this class of fluids would be made on the basis of their effects on the systemic circulation. Generally, an intervention that has the advantage of more effectively restoring systemic hemodynamics is likely to be advantageous to the injured brain. That assertion is made with the proviso that sustained hyperosmolarity (e.g., >320 mOsm/L) caused by any fluid has the potential to result in rebound swelling of the brain.

Hypothermia

The effects of hypothermia on cerebral physiology and its potential cerebral protective mechanisms are presented in Chapter 13. The efficacy of mild hypothermia (32°C to 34°C) in reducing the neurologic injury occurring after standardized cerebral and spinal cord ischemic insults has been shown in numerous laboratories. On that basis, the use of induced hypothermia in the management of cerebrovascular procedures, in particular, aneurysms and occasionally AVMs, became widespread. An international, multicenter trial of mild hypothermia in 1001 relatively good-grade patients undergoing aneurysm surgery revealed no improvement, however, in neurologic outcome.[143] The routine use of intraoperative hypothermia is likely to diminish.

Although mild hypothermia is perceived to increase the risk of coagulation dysfunction and dysrhythmias, neither of those problems has been evident in the temperature ranges typically used (32°C to 34°C). The issue of where body temperature should be recorded to reflect best brain temperature during craniotomy has been addressed.[144] Esophageal, tympanic membrane, pulmonary artery, and jugular bulb temperature all are similar and provide a reasonable reflection of deep brain temperature, whereas bladder temperature does not. Superficial layers of cortex may be substantially cooler than deep brain and central temperatures.

Because ischemia is recognized to make a post insult contribution to neuronal injury after head injury,[23,145] hypothermia was also studied in the laboratory in the context of traumatic brain injury.[146] It was effective and this resulted in at least four single institution trials of 24 to 48 hours of mild hypothermia after head injury.[147-150] These investigations revealed some physiologic dysfunction associated with more prolonged mild hypothermia, all of which was reversible with restoration of normal temperature. This included decreased creatinine clearance, elevation of pancreatic enzymes, and a suggestion of an increased infection rate. A decreased incidence of seizures was an apparent adjunctive benefit in one study. As a result, a multicenter, prospective trial of hypothermia was performed but did not show a benefit of hypothermia (33°C) induced within 8 hours of injury and maintained for 48 hours.[151] Post hoc subgroup analysis indicated that patients younger than age 45 years who arrived at the tertiary care facility with a temperature less than 35°C who were randomly assigned to the cooling limb of the trial did have an improved outcome. A follow-up trial in which the protocol seeks to achieve cooling more rapidly is under way.

On the basis of lack of demonstrated efficacy in humans, routine use of hypothermia in neurosurgery cannot be advocated in a standard text. The decision to employ it, usually in the context of aneurysm surgery, will be a local one. We continue to use mild hypothermia selectively, most commonly in patients perceived to be at especially high risk of intraoperative ischemia. If hypothermia is employed, it should be done so with attention to the possibility of cardiac dysrhythmias and coagulation dysfunction if temperatures become too low and with attention to the necessity to rewarm adequately before emergence to avoid shivering and hypertension.

Yet another application of mild hypothermia is evolving. Two multicenter trials have shown improved neurologic outcome among survivors of witnessed cardiac arrest cooled to 32°C to 34°C within 4 hours and maintained at that temperature for 12 to 24 hours.[152,153] Widespread clinical application has been advocated by an international task force.[154] Systematic clinical application is evolving slowly, however, probably because of the time necessary for technical and ICU protocol developments.

Emergence from Anesthesia

Most practitioners of neuroanesthesia believe that there is a premium on a "smooth" emergence—one free of coughing and straining and arterial hypertension. The avoidance of arterial hypertension is considered desirable because of the belief that arterial hypertension can contribute to intracranial bleeding and increased edema formation.[155-158] In the face of a poorly autoregulating cerebral vasculature, hypertension also has the potential, through vascular engorgement, to contribute to elevation of ICP. Much of the concern with coughing and straining has a similar basis. The sudden increases in intrathoracic pressure are transmitted to arteries and veins, producing transient increases in cerebral arterial and venous pressure with the same potential consequences: edema formation, bleeding, and elevation of intracranial pressure.

Coughing is a specific concern with certain individual procedures. In transsphenoidal pituitary surgery in which a surgeon has opened, and subsequently taken pains to close, the arachnoid membrane to prevent CSF leakage, coughing has the potential to disrupt this closure because of the sudden and substantial increases in CSF pressure. Opening a pathway from the intracranial space to the nasal cavity conveys a substantial risk of postoperative meningitis. In other procedures, notably operations that have violated the floor of the anterior fossa, there is also the theoretical potential for air to be driven into the cranium and, in the event of a flap-valve mechanism, to cause a tension pneumocephalus. This latter event can occur only when coughing occurs after the endotracheal tube has been removed.

There is a paucity of systematically obtained clinical data to give a perspective to the actual magnitude of the risks associated with emergences that are not "smooth." A retrospective study revealed that elevated postoperative arterial blood pressure was a correlate of intracerebral bleeding after craniotomy.[159] Hypertension occurring at emergence is not correlated with postoperative intracerebral bleeding, however. Although one clinical investigation reported an association of increased CBF velocity with hypertension occurring during emergence,[160] a second study observed that 60% increases in CBF velocity occurred even in the absence of hypertension, and concluded that hyperemia may be a normal concomitant of arousal at the end of an anesthetic.[161] A relationship between hypertensive transients at emergence and edema formation also is unconfirmed. Sudden, substantial increases in arterial pressure in anesthetized animals can result in a breach of the blood-brain barrier with extravasation of tracers such as Evans blue.[156] There are no data, however, to confirm that the pressure transients associated with the typical coughing episode or typical emergence hypertensive transient are associated with increased edema formation. Nonetheless, it seems reasonable to take measures, to the extent that these measures do not themselves add potential patient morbidity, to prevent these occurrences.

A common method for managing systemic hypertension during the last stages of a craniotomy is the expectant or reactive (or both) administration of vasoactive agents, most commonly labetalol and esmolol.[162] Other agents, including enalapril, nicardipine, and diltiazem, have been used to good effect. Administration of dexmedetomidine during the procedure also has been reported to reduce the hypertensive response to emergence.[163]

There are also many approaches to the prevention of coughing and straining. We have several biases. We encourage trainees to include in their anesthetic technique "as much narcotic as is consistent with spontaneous ventilation at the conclusion of the procedure." This practice is based on the same physiologic effect that justifies the administration of codeine and related compounds as antitussive medication (i.e., the depression of airway reflexes by narcotics). We also have the bias that patients emerge more rapidly and smoothly when the last inhaled agent to be withdrawn is N_2O, and that clinicians should seek to avoid the "neither here nor there" phase of anesthesia that occurs in patients who are stimulated in the face of residual exhaled concentrations of volatile agent on the order of 0.2 to 0.3 MAC. A common practice among neuroanesthesiologists near the conclusion of a craniotomy is the relatively early discontinuation of the volatile agent with supplementation of residual N_2O with propofol by either bolus increments or infusion at rates of 25 to 100 μg/kg/min.

An additional principle relevant to the emergence from neurosurgical procedures that practitioners may learn from a book or by bad experience is that emergence should be timed to coincide not with the final suture, but rather with the conclusion of the application of the head dressing. Good anesthetics for neurosurgery have been spoiled by severe coughing and straining occurring in association with endotracheal tube motion during the application of the head dressing. Another nuance of our practice has been to withhold administration of neuromuscular antagonists as long as possible as a "hedge" against misjudgment while lightening a patient in the later stages of the procedure. The administration of lidocaine is another apparently effective technique for reducing airway responsiveness and the likelihood of coughing and straining as depth of anesthesia is reduced in anticipation of emergence. Bolus doses of approximately 1.5 mg/kg, usually given as the application of the head dressing begins, are appropriate for this purpose.

The premium placed on minimizing coughing and straining and hypertension results, in most instances, in patients being extubated expediently when extubation is appropriate. In some instances, anesthesiologists may be tempted to extubate patients before complete recovery of consciousness. This early extubation may be acceptable in some circumstances. It should be undertaken with caution, however, when the circumstances of the surgical

procedure make it possible that neurologic events have occurred that would delay recovery of consciousness, or when there may be lower cranial nerve dysfunction. In these circumstances, it generally is best to wait until the likelihood of the patient's recovery of consciousness is confirmed or wait until patient cooperation and airway reflexes are likely to have recovered.

Specific Procedures

Many of the considerations relevant to individual neurosurgical procedures are generic ones that have been presented in the preceding section on recurrent issues. The descriptions that follow highlight only procedure-specific issues.

Supratentorial Tumors

Craniotomies for excision or biopsy, or both, of supratentorial tumors are common neurosurgical procedures. Gliomas and meningiomas are among the most frequent tumors. Relevant preoperative considerations include the patient's ICP status and the location and size of the tumor. Location and size give the anesthesiologist an indication of the surgical position and the potential for blood loss, and occasionally reveal a risk of air embolism. Risk of VAE is quite low for most supratentorial tumors. However, lesions (usually convexity meningiomas) that encroach on the sagittal sinus may convey a substantial risk of VAE. Full VAE precautions, including a right atrial catheter, are usually reserved for only supratentorial tumors that lie near the posterior half of the superior sagittal sinus.

Excision of craniopharyngiomas and pituitary tumors with suprasellar extension may entail dissection in and around the hypothalamus. Irritation of the hypothalamus can elicit sympathetic responses, including hypertension. Damage to the hypothalamus can result in a spectrum of physiologic disturbances, notably in water balance. Diabetes insipidus is the most likely disturbance, although cerebral salt-wasting syndrome can potentially occur. The latter has been very rare. The various disturbances of water balance typically have a delayed onset, beginning 12 to 24 hours postoperatively, rather than in the operating room. Postoperative temperature homeostasis also may be disturbed.

Patients who undergo a craniotomy involving a subfrontal approach occasionally may manifest a disturbance of consciousness in the immediate postoperative period. Retraction and irritation of the inferior surfaces of the frontal lobes can result in a patient who is lethargic and does not awaken "cleanly," and who may exhibit delayed emergence or some degree of disinhibition, or both. Patients exhibiting this phenomenon are sometimes referred to as "frontal lobey." The phenomenon is more likely to be evident when there has been bilateral subfrontal retraction than when it occurs only unilaterally. The anesthetic implication is that the clinician should be more inclined to confirm return of consciousness before extubating the patient than to extubate expectantly. We also believe (although this has not been confirmed by any systematic study) that a less liberal use of intravenous anesthetics (e.g., narcotics, benzodiazepines) may be appropriate when there is to be bilateral, subfrontal retraction. This is based on the rationale that low residual concentrations of these agents that would be compatible with reasonable recovery of consciousness in the majority of patients, may be less well tolerated in this population. Subfrontal approaches are most commonly employed in patients with olfactory groove meningiomas and patients with suprasellar tumors (craniopharyngiomas and pituitary tumors with suprasellar extension).

Preoperative Preparation

Patients with a significant tumor-related mass effect, especially if there is tumor-related edema, should receive preoperative steroids. A 48-hour course is ideal (see previous discussion of steroids), although 24 hours is sufficient for a clinical effect to be evident. Dexamethasone is the most commonly used agent; a regimen such as 10 mg intravenously or orally followed by 10 mg every 6 hours is typical. Because of the concern about producing CO_2 retention in a patient whose intracranial compliance is already abnormal, patients with any substantial mass effect are usually not premedicated outside of the operating room.

Monitoring

Frequently, the nature of the procedure does not require anything more than routine monitoring (see Chapter 46). Some situations may warrant invasive monitors (see Table 63-7). Preinduction placement of an arterial catheter may be appropriate in patients with severe mass effect and little residual compensatory latitude. It is the period of induction during which hypertension, with its attendant risks in a patient with impaired compliance and autoregulation, is most likely to occur. Procedures with a substantial blood loss potential (e.g., tumors encroaching on the sagittal sinus, large vascular tumors) also may justify arterial or CVP catheters. If not already present for other indications, is ICP monitoring ever warranted for intraoperative management? In our opinion, the answer is generally "no." Anesthesiologists have a sufficient understanding of the potential impact of anesthetic agents and techniques that they should be able to manage induction of anesthesia "blind." When the cranium is open, observation of conditions in the surgical field provides equivalent information.

Management of Anesthesia

The principles governing the choice of anesthetic agents were presented earlier in the section on control of intracranial pressure and brain relaxation.

Aneurysms and Arteriovenous Malformations

Contemporary management of intracranial aneurysms calls for early intervention after SAH, ideally within 24 hours and definitely within 48 hours. Intervention may entail either operative clipping or an endovascular approach. The latter is discussed in the subsequent section on interventional neuroradiology.

Early intervention was originally undertaken only in patients in the better neurologic grades—grades I through III and perhaps IV of the World Federation of Neurosurgeons classification (Table 63-8) or grades I through III of the Hunt-Hess classification (Table 63-9)—but more recently has been extended to patients of higher grades.[164] If early intervention is not feasible, and a surgical approach is intended, surgery is usually delayed for

Table 63-8 World Federation of Neurosurgeons (WFNS) Subarachnoid Hemorrhage Scale

WFNS Grade	GCS Score	Motor Deficit
I	15	Absent
II	14-13	Absent
III	14-13	Present
IV	12-7	Present or absent
V	6-3	Present or absent

GCS, Glasgow Coma Scale.

10 to 14 days to be safely beyond the period of maximal vasospasm risk (i.e., days 4 to 10 post-SAH).

The rationale for early intervention is severalfold. First, the sooner the aneurysm is clipped or obliterated, the less likelihood of rebleeding (and rebleeding is the principal cause of death for patients hospitalized after SAH[165]). Second, the management of the ischemia caused by vasospasm involves volume loading and induced hypertension. Early occlusion of the aneurysm eliminates the risk of rebleeding associated with this therapy. Vasospasm seems to be related to the presence of blood in the basal cisterns in the vicinity of the circle of Willis. Some of this blood can be removed at the time of the aneurysm clipping, and intracisternal fibrinolytics (for which there is limited proof of efficacy[166]) can be administered. Early operative clipping not only makes the therapy of vasospasm safer, but also may reduce the incidence and severity of the problem. Prior surgical practices entailed maintaining the patient at bed rest until approximately day 14, when the period of spasm risk had passed. Early aneurysm clipping reduces the period of hospitalization and reduces the incidence of the medical complications (e.g., deep vein thrombosis, atelectasis, pneumonia) associated with a lengthy period of enforced bed rest.

Early intervention can make the surgeon's task more difficult. The brain in the early post-SAH period is likely to be more edematous than after a 2-week delay. A mild degree of hydrocephalus is common after blood contaminates the subarachnoid space. Ten percent to 20% of SAH patients may require CSF diversion at some point in their course.[167] Early intervention also may enhance the risk of intraoperative aneurysmal rupture because of the shorter period of time for clot to organize over the site of the initial bleed. All of this places a substantial premium on techniques designed to reduce the volume of the intracranial contents (see the section on control of intracranial pressure and brain relaxation) to facilitate exposure and minimize retraction pressures.

Preoperative Evaluation

Many patients scheduled for intracranial aneurysm clipping come directly from the ICU, and elements of their management in the ICU may influence their immediate preoperative status.

Fluid Management. Some patients develop the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) after SAH and are appropriately managed with fluid restriction. However, hyponatremia after SAH is more likely to be the result of the cerebral salt-wasting syndrome, which probably occurs as a result of the release of a natriuretic peptide by the brain (similar to that which occurs in the heart).[168] Cerebral salt-wasting syndrome is characterized by the triad of hyponatremia, volume contraction, and high urine sodium concentrations (>50 mmol/L). The distinction between this syndrome and SIADH is important. SIADH, which is characterized by normovolemia or mild hypervolemia, is treated by volume restriction. Cerebral salt wasting is associated with a *contracted* intravascular volume. Fluid restriction and further volume contraction may be especially deleterious in a patient after SAH[169,170] and should be avoided. Although the clinical distinction between these two causes of hyponatremia (SIADH and cerebral salt-wasting syndrome) may be difficult, management of both is simple: administration of isotonic fluids using intravascular normovolemia as the end point.

Vasospasm. The anesthesiologist should determine whether vasospasm has occurred, and what, if any, therapies for it have been undertaken. Vasospasm is thought to be caused by the breakdown products of hemoglobin from the blood that has accumulated around the vessels of the circle of Willis after SAH. A specific mechanism/mediator has not been identified, but the current focus is on endothelin.[171,172] A phase II trial of the endothelin A receptor antagonist clazosentan indicated effective reversal of established vasospasm and a substantial reduction in the incidence of new infarctions.[173] A phase III trial is under way, and a preliminary report of drug-related reductions in vasospasm-related hypoperfusion in those patients has appeared.[174]

When there is a clinical suspicion of vasospasm (typically because of a change in sensorium or new neurologic deficit), surgery is deferred, and TCD, angiography, or other imaging is performed.[175-177] Confirmed vasospasm is commonly treated with the "triple H" therapy described in the next paragraph and sometimes by balloon angioplasty or intra-arterial vasodilators.

For patients proceeding to surgery, CPP should be maintained intraoperatively in a high-normal range. Despite the former popularity of induced hypotension, the potential for induced hypotension to cause or aggravate cerebral ischemia in a patient with some degree of vasospasm is now recognized.[178,179] This concern extends even to a patient classified as World Federation of Neurosurgeons grade I who may have regions of cerebral ischemia[41] that are subclinical when the patient is normotensive.

In the ICU, the regimens employed to treat vasospasm usually involve some combination of hypervolemia, hemodilution, and hypertension. The science behind hypervolemic-

Table 63-9 Hunt-Hess Classification of Neurologic Status after Subarachnoid Hemorrhage

Grade	Criteria*
I	Asymptomatic, or minimal headache and slight nuchal rigidity
II	Moderate to severe headache, nuchal rigidity, no deficit other than cranial nerve palsy
III	Drowsiness, confusion, or mild focal deficit
IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances
V	Deep coma, decerebrate rigidity, moribund appearance

*Serious systemic diseases, such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and severe vasospasm seen on arteriography, result in placement of the patient in the next less favorable category.

hypertensive therapy is "soft," and the efficacy of neither "triple H" therapy nor volume expansion in isolation has been proved by prospective study.[180,181] The importance of the rheologic and the pressure effects is undefined, although there is evidence for the relevance of blood pressure elevation in isolation.[182,183] Phenylephrine and dopamine are the most commonly employed pressors; the specific pressor choice should be governed primarily by systemic cardiovascular considerations. The end point for pressor administration varies. Most commonly, the objective is an increase in MAP of approximately 20 to 30 mm Hg above "baseline" systolic pressure. It has been reported, however, that augmentation of cardiac output with dobutamine, without simultaneous MAP increase, augments CBF in vasospastic territories.[184] Some authors believe that the hematocrit should be reduced to the low 30s. Commonly, hematocrit reduction occurs secondarily as a result of attempts to produce hypervolemia (usually with colloid solutions) as a part of the effort to increase blood pressure.

Calcium Channel Blockers. Calcium channel blockers are now an established part of the management of SAH. Administration of nimodipine has been shown to decrease the incidence of morbidity from cerebral ischemia occurring after SAH.[185-187] These studies failed to show any reduction in the incidence of vasospasm, however, as detected by angiography.[186] The beneficial effect of these agents may be the result of effects on neurons, rather than vascular smooth muscle. Patients coming to the operating room after SAH should be receiving nimodipine. Nimodipine must be administered orally; nicardipine has been evaluated as an intravenous alternative. The multicenter nicardipine trial[188,189] revealed a reduced incidence of symptomatic vasospasm, but no improvement in outcome. Consequently, nimodipine is more commonly employed. Because papaverine may be neurotoxic, intra-arterial calcium entry blockers, including verapamil and nicardipine, are being increasingly used as a primary treatment for medically refractory vasospasm.

Magnesium, Statins, and Endothelin Antagonists. More recent clinical trials have identified several agents that may soon become part of the routine management of patients with SAH. The endothelin antagonist clazosentan was mentioned earlier in this section. A randomized, blinded, placebo-controlled trial reported fewer new ischemic deficits and improved outcome among patients who received magnesium sulfate starting within 4 days of SAH. Two phase II trials have examined the post-SAH administration of statins. Together, these trials showed reductions in vasospasm, delayed ischemic deficits, and improvement in outcome.[190,191] Although some centers have already implemented some of these therapies as part of the local routine, widespread adoption is not likely until the completion of larger trials that confirm these initial results.

Antifibrinolytics. Antifibrinolytics have been administered in an attempt to reduce the incidence of rebleeding. Meta-analysis suggests, however, that although they accomplish the latter, they do so at the cost of an increased incidence of ischemic symptoms and hydrocephalus with the result being no net improvement in outcome.[192]

Subarachnoid Hemorrhage–Associated Myocardial Dysfunction. SAH can result in a reversible, "stunning"-like myocardial injury. The severity of the dysfunction correlates best with the severity of the neurologic injury,[193] and occasionally is sufficient to require pressor support.[194] The mechanism is uncertain, but it is thought to be catecholamine mediated.[195] This suspicion is supported by the observation that more severe dysfunction occurs in SAH patients with genetic polymorphisms associated with greater catecholamine receptor sensitivity. Troponin elevation occurs commonly, although typically reaching levels less than the diagnostic threshold for myocardial infarction.[196] Peak troponin levels correlate with the severity of neurologic injury and echocardiographic myocardial dysfunction.[194]

ECG abnormalities are common after SAH.[193] In addition to the classic "canyon T waves" (Fig. 63-14), nonspecific T-wave changes, Q-T prolongation, ST-segment depression, and U waves have been described. There is typically no relationship between the ECG changes and echocardiographic myocardial dysfunction.[196] ECG abnormalities do not herald evolving or impending cardiac disease.[197] When ECG patterns other than those that are typical of myocardial ischemia are observed, no specific interventions or modifications of patient management are warranted, other than attention to the possibility of dysrhythmias. In particular, an increased Q-T interval (>550 msec) occurs frequently after SAH, especially in patients with more severe SAH,[198] and has been associated with an increased incidence of malignant ventricular rhythms, including torsades de pointes.[199,200]

Anesthetic Technique

The important considerations in anesthetic technique include the following:

1. Absolute avoidance of acute hypertension with its attendant risk of rerupture
2. Provision of intraoperative brain relaxation to facilitate surgical access to the aneurysm
3. Maintenance of a high-normal mean arterial (perfusion) pressure to prevent critical reduction of CBF in recently insulted and now marginally perfused areas of brain, or regions critically dependent on collateral pathways
4. Preparedness to perform precise manipulations of MAP as the surgeon attempts to clip the aneurysm or to control bleeding from a ruptured aneurysm, including management of temporary vascular occlusion

Monitoring. An arterial line is invariably appropriate. CVP may be relevant if the institutional practices involve large doses of mannitol to promote brain relaxation and may be used in older patients to guide volume replacement in the event of bleeding.

Anesthetic Selection. Any technique that permits proper control of MAP is acceptable. In the face of increased ICP or a tight surgical field, an inhaled agent technique may be less suitable. The prevention of paroxysmal hypertension is the only absolute requirement in patients undergoing aneurysm clipping. Rebleeding kills,[165] and a poorly organized clot over the aneurysms of patients undergoing early post-SAH clipping makes them particularly prone to rebleeding. A rebleed at induction is frequently fatal. The escaping arterial blood is more likely to penetrate brain substance because it cannot dissect through the CSF space (filled with clot), and the ICP increase is extreme because of the poor compliance of the intracranial space (swollen brain, hydrocephalus).

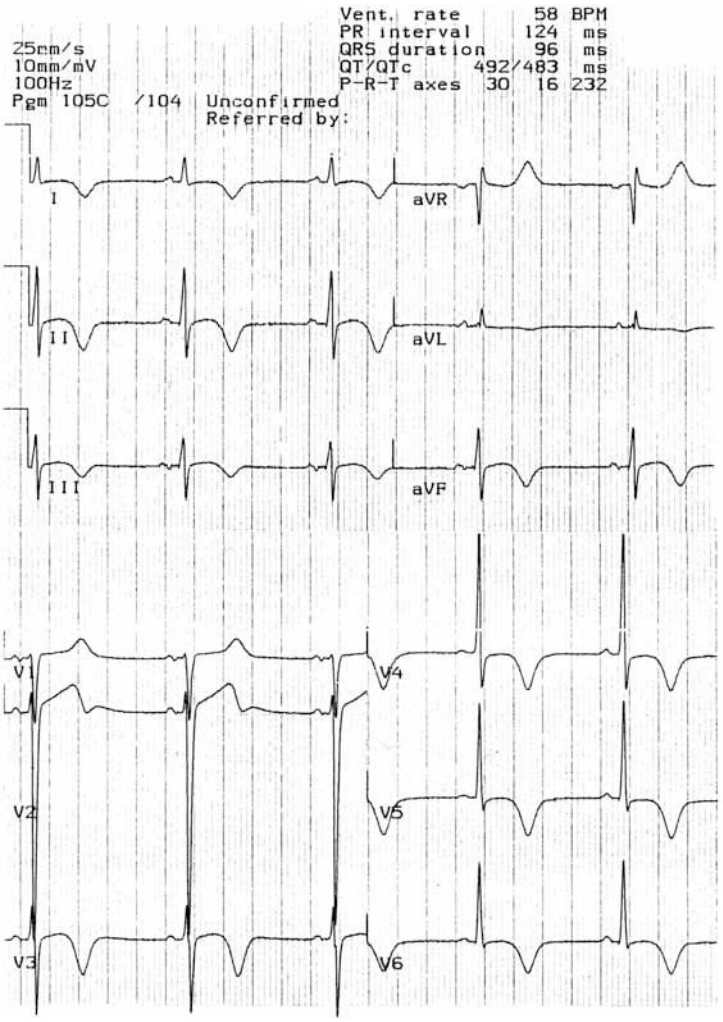

Figure 63-14 Electrocardiogram abnormalities associated with subarachnoid hemorrhage (SAH). The "canyon" T waves that may be seen after SAH are evident.

Induced Hypotension. The routine use of induced hypotension is diminishing (see previous section on management of arterial blood pressure). Nonetheless, the anesthesiologist should be prepared to reduce blood pressure immediately and precisely if called on to do so. Preparation must occur before the episode of bleeding. We prepare a sodium nitroprusside infusion before induction. It is placed in line at a Y-injection port at the hub of the CVP or intravenous catheter. A carrier drip flows steadily such that any change in nitroprusside infusion rate is reflected as rapidly as possible in the central compartment. There are theoretical pros and cons for various hypotensive agents. The data indicate that regimens that entail the use of an agent that is also a cerebral vasodilator (e.g., isoflurane, nitroprusside) are preferable in terms of brain oxygen delivery to approaches that do not involve cerebral vasodilation (e.g., trimethaphan, controlled hypovolemia).[201] The choice should ultimately be made on the basis of which regimen, in the hands of the individual practitioner, results in the most precise control of MAP. Occasionally, the anesthesiologist may be asked to control MAP in the range of 40 to 50 mm Hg, in the face of the active arterial bleeding. This can be extremely difficult in a patient who is hypovolemic at the beginning of the bleeding episode. It is our practice to maintain normovolemia.

Induced Hypertension. Hypertension may be requested during periods of temporary arterial occlusion (see the later section on trapping) to augment collateral CBF. In addition, after clipping of the aneurysm, some surgeons puncture the dome of the aneurysm to confirm adequate clip placement, and may request transient elevation of the systolic pressure to 150 mm Hg. Phenylephrine is suitable in either instance.

Hypocapnia. Hypocapnia traditionally has been employed as an adjunct to brain relaxation. The practice has been questioned, however, because of the concern that it would aggravate ischemia (see the earlier section on management of $Paco_2$). The circumstances regarding ICP and brain relaxation should probably dictate its use or avoidance.

Lumbar Cerebrospinal Fluid Drainage. Some surgeons employ elective CSF drainage to facilitate exposure. Its use seems to be diminishing, however, because surgeons have appreciated that the same brain-relaxing effect can be achieved by release of CSF from the basal cisterns. It is appropriate, when placing a lumbar CSF drain, to avoid excessive loss of CSF. Sudden reduction of the transmural pressure gradient across the dome of the aneurysm (by sudden reduction of ICP consequent on substantial

CSF drainage) should be avoided because of the theoretical concern that this decompression might encourage rebleeding. The common practice is, having verified the patency of the lumbar drainage system, to leave it closed until such time as the surgeon is opening the dura. The drain may be opened at that time and allowed to drain freely with the bag at floor level. Drainage should be discontinued promptly after final withdrawal of the retractors to allow CSF to reaccumulate and to reduce the size of the potential pneumocephalus. The drain is usually removed immediately postoperatively.

Mannitol. Some surgeons make relatively aggressive use of mannitol (e.g., 2 g/kg). It is used, in part, to shrink the brain and to facilitate exposure and reduce retractor pressures. There is evidence that mannitol may have additional benefits. Specifically, data derived in animals and humans indicate that mannitol may have a CBF-enhancing effect in regions of moderate CBF reduction.[202-205] The mechanism is not defined. Reduction of interstitial tissue pressure around capillaries or an alteration of blood rheology, or both, have been proposed to contribute. Typically, mannitol is administered in a dose of 1 mg/kg just before dural opening. Surgeons who believe in the flow-enhancing effect may request a second 1 mg/kg dose approximately 15 minutes before an anticipated temporary occlusion.

Trapping

It is occasionally necessary for the surgeon to "trap" the aneurysm (i.e., to occlude the vessel on either side of the aneurysm temporarily) to complete dissection of the neck and apply the clip. The need for trapping is more common with larger aneurysms. With giant aneurysms in the vicinity of the carotid siphon, the inferior occlusion may be performed at the level of the internal carotid artery via a separate incision in the neck. A clinical survey by Samson and coworkers[206] of the neurologic outcome after temporary occlusion in normothermic, normotensive adults revealed that occlusion times of less than 14 minutes were invariably tolerated. The likelihood of an ischemic injury increased with longer occlusions and reached 100% with occlusions longer than 31 minutes.[206] In another institution, the threshold for ischemic injury was 20 minutes of occlusion.[207] Typically, it is appropriate to support MAP at high normal levels during periods of occlusion to facilitate collateral CBF.

Brain Protection

Important brain protection techniques include maintenance of MAP to ensure collateral flow and perfusion under retractors, efficient brain relaxation to facilitate surgical access and reduce retractor pressures, limitation of the duration of episodes of temporary occlusion, and perhaps mild hypothermia. Specific anesthetic agents also have been used to protect the brain (see the discussion in Chapter 13). Propofol and etomidate are currently used. However, no convincing laboratory studies have shown that propofol provides any greater tolerance to a standardized ischemic insult than anesthesia with a volatile agent. Attempts to show protection by etomidate in an animal model of focal ischemia showed an adverse effect of etomidate.[208] A clinical investigation during aneurysm clipping revealed decreases in brain tissue Po_2 in association with administration of etomidate, which contrasted with the brain Po_2 increases that occurred with the introduction of desflurane. During subsequent temporary vessel occlusion, tissue pH decreased alarmingly in patients receiving etomidate and was unchanged with desflurane.[209]

Although the available data collectively do not support an assertion that etomidate is harmful in the setting of aneurysm surgery, we think that they should dissuade any anesthesiologist from advocating the administration of etomidate as a uniquely protective substance in the context of aneurysm surgery. With respect to the volatile agents, attempts in the laboratory to confirm the once proclaimed protective efficacy of isoflurane have shown that there are no differences among the various volatile agents in terms of their influence on outcome after focal or global ischemia.[208,210-212] In addition, there has been no demonstration of greater protective efficacy with concentrations of volatile agents sufficient to cause EEG suppression as opposed to more modest (e.g., 1.0 MAC) levels.[212,213] Nonetheless, these animal investigations suggest that a standardized experimental ischemic insult is better tolerated, relative to the awake state, by animals receiving a volatile anesthetic.[211,212,214] Data derived in animals also suggest that there may be a relative protective advantage to an anesthetic that includes a volatile agent compared with a strict N_2O-narcotic technique.[212,214]

The magnitude of the differences among anesthetics and the absence of proof of relevance in patients precludes advocacy of a particular anesthetic regimen in a standard text. The important anesthetic objectives are precise hemodynamic control and timely wake-up, and these two constraints should dictate the choice of the anesthetic regimen for most aneurysm procedures. Among anesthetic agents, only for the barbiturates has additional protective efficacy been shown convincingly (see Chapter 13). Because of their potentially adverse effects on hemodynamics and wake-up, barbiturates are not ideal for routine administration. They probably should be reserved for situations in which a prolonged vessel occlusion is unavoidable, and in that circumstance it would be ideal that the ischemic hazard be first confirmed by observation of the EEG response to a temporary occlusion.[215]

Hypothermia

As noted in the earlier section on hypothermia, a prospective trial of mild hypothermia in patients undergoing aneurysm surgery revealed no improvement in neurologic outcome. Nonetheless, many neurosurgical teams that were already employing mild hypothermia (32°C to 34°C) are continuing its use for procedures in which temporary vessel occlusion may occur. Institutions that use the lower temperatures are those in which the team is willing to accept a delay in emergence from anesthesia to achieve sufficient rewarming to avoid the extreme hypertension that can occur when a patient is awakened during hypothermia.

Neurophysiologic Monitoring

Evoked responses and EEG (see Chapter 46) have been employed for monitoring,[215,216] although neither technique has been used widely. EEG monitoring can be used as a guide to management during the period of flow interruption or to guide the administration of CMR-reducing anesthetic agents given before occlusion.[215] An electrode strip can be placed over the region of cortex at risk during the intended occlusion. However, the more commonly used skin surface frontal-mastoid derivation is probably sufficient to reveal a major ischemic event. The EEG can be either the conventional "raw" polygraph or a processed derivative. In most circumstances, if occlusion is deemed necessary, a temporary

occlusion is done, and the EEG is observed. If the EEG shows significant slowing, the clip can be repositioned, or MAP can be increased by some combination of phenylephrine and lightening of anesthesia to find a way of temporary clipping without a major EEG disturbance. If this cannot be accomplished, and a sustained period of occlusion seems likely, barbiturates (see earlier) should be given to produce burst suppression.

Intraoperative Angiography

Intraoperative angiography is an increasingly common component of the management of intracranial aneurysms. It does not have substantial implications for the anesthesiologist. Apparatus around the patient's head must be organized, however, so as to allow C-arm access without snagging of airway and monitoring equipment. In addition, the radiologist must have access to groin vessels. The vascular access sheath, for a patient who will ultimately be in the lateral position, is easiest to use when the nondependent femoral artery is chosen. The rate of administration of heparin "flush" via the vascular access sheath should be monitored.

Special Considerations for Specific Aneurysms

The most common procedures are done for aneurysms arising in or close to the circle of Willis. The vessel of origin may be the anterior communicating artery, the middle cerebral artery, the anterior cerebral artery, the ophthalmic artery, the tip of the basilar artery, the posterior communicating artery, or, less frequently, the posterior cerebral artery. These procedures all are similar for the anesthesiologist and typically require a supine position with the head turned slightly away from the operative side.

Ophthalmic Artery Aneurysms. Access to the origin of the ophthalmic artery, which is the first intradural branch of the carotid artery, is made difficult by the anterior clinoid process and the optic nerve. As a result, these aneurysms frequently require temporary vascular occlusion. The surgeon commonly first exposes the carotid artery in the neck. When the surgeon reaches the stage of seeking definitive access to the neck of the aneurysm, he or she will occlude first the carotid artery in the neck and then the intracranial portion of the carotid artery immediately proximal to the origin of the posterior communicating artery.

Vertebrobasilar Aneurysms. These procedures are typically performed in the lateral position. The exposure may involve a combined middle and posterior fossa approach, with some attendant, although minor, risk of venous air embolism. Cortical or skin surface EEG monitoring is of less relevance with vertebrobasilar aneurysms. Auditory or somatosensory evoked responses, or both, have been employed.[217] As in any other procedure involving the potential for mechanical or vascular injury to the brainstem, cardiovascular responses should be monitored, and sudden changes in response to surgical manipulation should prompt immediate notification to the surgeon. Spontaneous ventilation may be appropriate for procedures involving surgical manipulation of the vertebral arteries, the vertebrobasilar junction, and the middle portion of the basilar artery. Apnea, gasping, or other sudden changes in ventilatory pattern during manipulation of the vasculature provide important, although nonspecific, warning of compromise of the vascular supply of the brainstem.[218]

Now largely supplanted by endovascular approaches, management of these aneurysms occasionally requires cardiopulmonary bypass and deep hypothermic circulatory arrest.[219]

Vein of Galen Aneurysms. Vein of Galen "aneurysms" are congenital dural arteriovenous fistulas, usually treated in neonates using endovascular methods, and share considerations relevant to AVMs. These include anticipation of the possibility of the cerebral dysautoregulation phenomenon and are considered subsequently.

Arteriovenous Malformations

For most intracranial AVMs, the general considerations are similar to the considerations appropriate to aneurysm surgery: avoidance of acute hypertension and the capability to manipulate blood pressure accurately in the event of bleeding. A problem that is specific to AVMs is the phenomenon known as "perfusion pressure breakthrough," or cerebral dysautoregulation.[220,221] It is characterized by an often sudden engorgement and swelling of the brain, sometimes with a relentless cauliflower-like protrusion from the cranium. This phenomenon tends to occur in the advanced stages of lengthy procedures on large AVMs, or accounts for otherwise unexplained postoperative swelling and hemorrhage. The phenomenon is not entirely understood and is almost certainly related to the "hyperemic" complications seen after carotid endarterectomy or angioplasty.

In textbooks, this syndrome has been described as relating to the acute obliteration of a high-volume, low-resistance pathway (the AVM) that has chronically diverted blood from adjacent, marginally perfused vascular territories. It has been theorized that these tissues have long been maximally vasodilated without the need ever to vasoconstrict and have become incapable of doing so. Experimental data are not generally consistent with this mechanism, however.[221-223] The observed "hyperemic" complications are probably not passive. One might speculate that the vasodilation is neurogenic in origin, or involves some kind of paracrine signaling. Such events might lead to vascular wall protease activation and vasogenic edema or vascular rupture. Supranormal flow rates also can activate protease activity. The area is in need of further study.

Anesthetic Technique

The management constraints are essentially the same as those relevant to aneurysm surgery, although the risk of intraoperative rupture is much less. Institutional practices vary. We do not employ induced hypotension unless required to by bleeding. We reason that the effects on the surrounding brain of devascularizing the AVM would be best appreciated if the devascularization occurs at normal pressures. If refractory brain swelling occurs, tight blood control is essential; decreasing MAP may be useful to control swelling. The hyperemic complications with carotid surgery seem to be related, but not uniquely determined, by poor post-treatment blood pressure control. The speculation is that blood flow through the involved area is pressure-passive and decreases as MAP is reduced.

With severe episodes of swelling, we have employed (in addition to hypotension, which we use cautiously because of the associated ischemia risk) hypocapnia, hypothermia, and barbitu-

rates. These three techniques probably reduce the bulk of only normal brain tissue—hypocapnia via a direct effect on CBF, and barbiturates and hypothermia via the coupled effects of reduction of CMR on CBF. Induced hypothermia also is an adjunct to minimizing the barbiturate doses. In all of neurosurgery, we seek to prevent postoperative hypertension; however, in AVM surgery, this should be accomplished with greatest care because of the concern that the "dysautoregulating" brain adjacent to the resected AVM will develop edema or hemorrhage if hypertension occurs.

Head Injury

Intubating a Head-Injured Patient

The anesthesiologist's first encounter with a patient who has sustained a traumatic brain injury (TBI) may come as a result of a request for assistance with airway management. Patients with GCS scores of 7 or 8 or less (Table 63-10) require intubation and controlled ventilation for ICP or airway control or both. Patients with less severe head injuries also may require intubation because of trauma-related cardiopulmonary dysfunction or, when uncooperative, to facilitate diagnostic procedures.

In choosing the intubation technique, the anesthesiologist may encounter numerous conflicting constraints (Table 63-11), including (1) elevated ICP, (2) a full stomach, (3) uncertain cervical spine status, (4) uncertain airway status (e.g., presence of blood, possible laryngotracheal injury, possible skull base fracture), (5) uncertain volume status, (6) an uncooperative or combative patient, and (7) hypoxemia. There is no "correct" way, and the "best" approach is determined by the relative weight of these various factors along with the degree of urgency. The anesthesiologist must not become distracted by placing an excessive initial emphasis on ICP. The anesthesiologist needs to keep sight of the ABCs of resuscitation: Securing the airway, guaranteeing gas exchange, and stabilizing the circulation are higher initial priorities than ICP. One must not risk losing the airway or causing severe hypotension for the sake of preventing coughing on the tube or brief hypertension with intubation.

Table 63-10 Glasgow Coma Scale

Eyes open	Never	1
	To pain	2
	To speech	3
	Spontaneously	4
Best verbal responses	None	1
	Garbled/incomprehensible sounds	2
	Inappropriate words	3
	Confused but converses	4
	Oriented	5
Best motor responses	None	1
	Extension (decerebrate rigidity)	2
	Abnormal flexion (decorticate rigidity)	3
	Withdrawal	4
	Localizes pain	5
	Obeys commands	6
Total		*3-15*

Table 63-11 Factors That May Be Relevant during Intubation of a Head-Injured Patient

- Full stomach
- Uncertain cervical spine
- Uncertain airway
  - Blood
  - Airway injury (larynx, cricoarytenoid cartilage)
  - Skull base fracture
- Uncertain volume status
- Uncooperative/combative
- Hypoxemia
- Increased ICP

ICP, intracranial pressure.

Cervical Spine

The possibility of causing or aggravating an injury to the cervical spine is a relevant concern. Approximately 2% of blunt trauma victims who survive to reach a hospital and 8% to 10% of TBI victims with GCS less than 8 have a fracture of the cervical spine.[224,225] This incidence suggests that a "hypnotic-relaxant-direct laryngoscopy" approach for all patients with a closed-head injury might convey a measurable risk of injuring the cervical cord. Nonetheless, although the literature contains contradictions, several published series have concluded that a rapid-sequence induction does not convey significant risk of neurologic injury.[226-230] It is possible, however, that the incidence of intubation-related neurologic injury is underreported. An informal survey reported by Criswell and colleagues[226] indicated that there have been more such events than one can infer from the published literature.[231,232]

Nonetheless, the literature argues that we will "get away with it" most of the time, and most TBI patients requiring airway control are intubated using a hypnotic-relaxant-direct laryngoscopy sequence. It is our (probably minority) opinion, however, that the possibility of devastating spinal cord injury exists, probably most so with injuries in the atlanto-occipital region, which are also difficult to identify radiologically,[233] and that the anesthesiologist should identify circumstances in which time latitudes allow more detailed examination or radiologic evaluation. When there is any uncertainty regarding the airway or the cervical spine, direct laryngoscopy (with vigorous atlanto-occipital extension) should probably be avoided, unless the exigencies of airway control demand it (which often is the case). The nasal route can be considered if the clinical context warrants, bearing in mind that risk of infection may be increased with skull base fracture and CSF leak. The anesthesiologist needs to use discretion (e.g., in the presence of an obvious facial smash, the nasal route should be avoided because of the possibility of entering the cranium) and be sensitive to unusual resistance in passing the endotracheal tube.

When a hypnotic muscle-relaxant sequence is used, the standard approach includes the use of cricoid pressure and in-line axial stabilization. In-line traction previously was favored, but has been supplanted by stabilization because of the perceived risk of overdistraction and cord injury in the event of gross instability. The largest of the clinical series that concluded that oral intubation with anesthesia and relaxation is reasonable[227] used in-line stabilization with the patient's occiput held firmly on the backboard, limiting the amount of "sniff" that was feasible (Fig. 63-15). There is no question that in-line stabilization, properly performed, makes laryngoscopy more difficult, but it decreases the amount

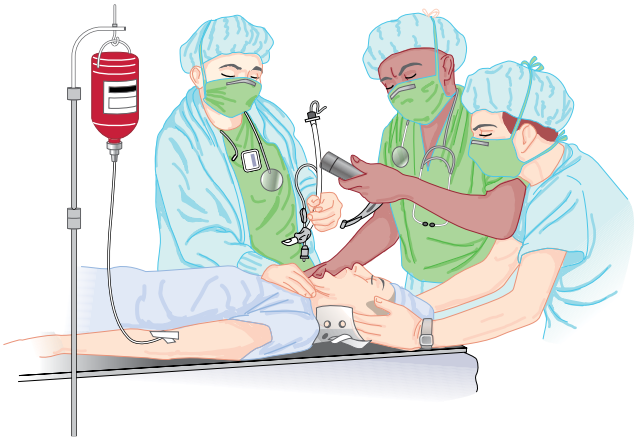

Figure 63-15 Intubating an acute trauma patient with an uncertain cervical spine injury . A hypnotic and a relaxant have been administered. One assistant maintains in-line axial stabilization with the occiput held firmly to the back-board; a second applies cricoid pressure. The posterior portion of the cervical collar remains in place to "discourage" atlantoaxial extension. *(From Stene JD: Anesthesia for the critically ill trauma patient.* In *Siegel JH [ed]: Trauma: Emergency Surgery and Critical Care. Melbourne, Churchill Livingstone, 1987, pp 843-862.)*

of atlanto-occipital extension necessary to achieve visualization of the glottis.[234] This is probably because performing the laryngoscopy against the assistant's counter pressure results in greater compression of the soft tissue structures of the tongue and floor of the mouth. Some recommend leaving the back half of the Philadelphia collar in place during laryngoscopy (see Fig. 63-15) because it functions as a strut between the shoulder and the occiput limits atlanto-occipital extension.

In the resuscitation situation, before initiating a hypnotic-relaxant sequence, the anesthesiologist should confirm the availability of cricothyrotomy equipment and of someone to make immediate, skilled use of it if necessary. The recently injured brain is very intolerant of hypoxia and hypotension.[235] The occasional failed intubation is inevitable. In the extensive experience of the Cowley Shock-Trauma Center in Baltimore, the cricothyrotomy/tracheostomy rate is 0.3%.[236] As is the case in many other situations, the laryngeal mask may be a useful device for temporizing in the face of a failed intubation, and may provide access for intubation as an alternative to cricothyrotomy.

As noted Chapter 13, although succinylcholine can cause ICP increases, these increments are small; they probably do not occur at all in patients with serious cerebral injuries.[6] Succinylcholine should not be contraindicated in a patient with TBI. If there is an urgent need to secure the airway (to guarantee oxygenation and control $Paco_2$), and if succinylcholine is in other respects the appropriate drug to achieve that end, it should be used.

The situation of a patient whose cervical spine has not been "cleared" should arise with decreasing frequency in unconscious patients because of the proliferation of multidetector CT scanners, which allow rapid, thin-slice evaluation, with sagittal reconstruction, of the cervical spine. The combination of a three-view plain film series and CT scanning (and most of these patients require CT evaluation for other reasons) is reported by one reviewer to have a false-negative rate for serious injury of less than 0.1%.[237] Another survey reported, however, that CT may miss a significant number of ligamentous injuries.[238] With respect to a conscious patient who has not yet undergone complete radiologic evaluation, several clinical surveys have confirmed that patients who are alert, nonintoxicated, and free of significant distracting injuries invariably have pain, midline tenderness, limitation of voluntary movement, or neurologic signs[239-241] if they have a cervical spine fracture.

Despite the frequency with which an anesthesiologist may encounter a patient still wearing a Philadelphia collar because his or her neck has not yet been "cleared," no special precautions seem warranted in an asymptomatic, alert patient. If the clinical situation or examination is suspicious for a cervical spine injury, a normal lateral x-ray (the anteroposterior and through-the-mouth odontoid views are frequently not taken during initial evaluation) cannot provide complete reassurance. The lateral view has been reported to miss 15%[242] to 26%[239] of fractures.

Anesthetic Technique

Choice of Anesthetic Drugs. Craniotomies most commonly are performed for the evacuation of subdural, epidural, or intracerebral hematomas. The anesthetic approach is similar for all three. The guiding principles have been discussed in the section on control of intracranial pressure and brain relaxation. Generally, anesthetics that are cerebral vasoconstrictors are preferable to anesthetics that have the potential to dilate the cerebral circulation. All of the intravenous anesthetics except perhaps ketamine cause some cerebral vasoconstriction and are reasonable choices, provided that they are consistent with hemodynamic stability. All of the inhaled anesthetics (N_2O and all of the vapors) have some cerebral vasodilatory effect. Although their administration frequently is consistent with acceptable ICP levels and appropriate conditions in the surgical field, when the ICP is out of control (or unknown), or the surgical field is "tight," eliminating the inhaled agents in favor of fixed agents is appropriate.

For patients who are likely to remain intubated postoperatively, an anesthetic based primarily on a narcotic (e.g., fentanyl) and a muscle relaxant usually serves well. Any muscle relaxant is acceptable with the proviso that agents that can release histamine should be titrated in careful increments. When immediate tracheal extubation is a possibility (e.g., a patient with an acute epidural hematoma who had a lucid interval before witnessed deterioration), the technique should be modified after the opening of the cranium. Introduction of inhaled anesthetics or the use of shorter acting intravenous anesthetics, or both, can be undertaken as guided by observation of the surgical field. If N_2O is contemplated at any time, the anesthesiologist must remember the possibility, in the setting of missile injury or compound skull fracture, of intracranial air.

Monitoring. The anesthesiologist should appreciate that the priority is to open the cranium as rapidly as possible. After achieving intravenous access, the risks and benefits of delaying craniotomy for line placement should be carefully considered. An arterial line, often placed after induction in urgent situations, is appropriate for essentially all acute trauma craniotomies. The decision to achieve central venous access can be made on the basis of the patient's hemodynamic status. Cardiovascular collapse after dural opening with high ICP may occur[243]; adequate volume resuscitation may mitigate this complication. Infrequently, the management of a depressed skull fracture over the sagittal sinus justifies

a precordial Doppler and, subject to the surgeon's assessment of VAE risk, a right heart catheter.

Blood Pressure Management. The concept that the injured brain is extremely vulnerable to what would otherwise be a minor insult (e.g., modest hypotension, moderate hypoxia) has been well confirmed in the laboratory.[244,245] Although there are as yet no completely conclusive data derived in humans, several clinical surveys confirm the association of otherwise minor degrees of hypotension and hypoxia and poor outcome in TBI patients.[235,246-250] The explanation for this vulnerability to hypotension probably relates partly to the observation that some patients in the postinjury period have regions of brain with precariously low CBF,[23,33,38,251] in which autoregulation also may be defective.[37,252] Although it has been argued that reduced CBF is partly a normal concomitant of the reduced CMR that commonly occurs after TBI, there is nonetheless ample reason to worry about the occurrence of ischemia. First, a large percentage of patients who die after TBI have pathologic changes consistent with ischemia.[145] Second, there is considerable evidence that the low postinsult CBF values correlate with a poor eventual outcome.[23,36,247,253,254] These observations have resulted in a much greater emphasis among neurosurgeons, neurointensivists, and anesthesiologists on aggressive support of blood pressure in the TBI patient.

What constitutes an appropriate blood pressure? Systematic studies, in particular the studies conducted at the University of Edinburgh, revealed that indices of the adequacy of cerebral perfusion derived from $SjvO_2$ and TCD data begin to deteriorate below a mean CPP (CPP = MAP − ICP) of 70 mm Hg,[247,255,256] and many centers adopted 70 mm Hg as the target CPP. A clinical investigation by Robertson and colleagues[257] comparing the ICU management of TBI patients at CPPs of 70 mm Hg and 50 mm Hg showed that although indices of cerebral well-being were improved by the former, there was no outcome advantage, apparently because of the cardiopulmonary morbidity associated with achieving a sustained CPP of 70 mm Hg. As a result, many groups and authorities have adopted 60 mm Hg as the minimum CPP management objective.[258-261] The most recent recommendations of the Brain Trauma Foundation give clinicians wide latitude in recommending CPP target values "within the range of 50-70 mm Hg."[59]

There are at least two alternative opinions regarding blood pressure management (Fig. 63-16). The first, promoted by the neurosurgery group at the University of Alabama, Birmingham, is that induced hypertension can be employed as an adjunct to ICP control.[23,262] This idea is based on the belief that autoregulation is at least partially preserved after head injury, and that an increased CPP results in autoregulation-mediated vasoconstriction with a concomitant reduction in CBV and ICP. These investigators reported a very satisfactory local experience[262] with this approach, but it has not been applied widely, and others have reported that induced hypertension was either ineffective or deleterious as a means of reducing increased ICP.[10,263] The second alternative is the so-called Lund concept, which is based on the premise that high blood volume and hydrostatically driven edema accumulation make a substantial contribution to increased ICP.[264-266]

As originally described, the Lund approach entailed dehydration; hyperosmolarity; and the administration of metoprolol, clonidine, and dihydroergotamine to reduce blood pressure to a

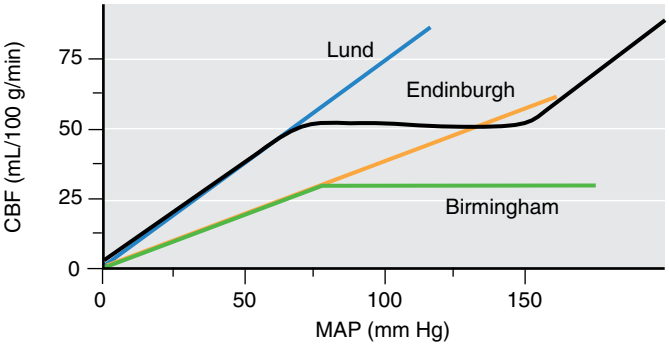

Figure 63-16 The relationship of cerebral blood flow (CBF) to blood pressure after head injury. There are three cerebral perfusion pressure (CPP) management strategies (see text) driven by differing beliefs about common pathophysiologic derangements. The most commonly used strategy, "Edinburgh" (named for the institution of the original proponents), emphasizes low postinjury CBF, impaired autoregulation, and the necessity to support CPP (mean arterial pressure [MAP] – intracranial pressure [ICP]) to 70 mm Hg. The "Lund" concept emphasizes the contribution of hyperemia to the occurrence of elevated ICP. This approach uses antihypertensive agents to reduce blood pressure, while maintaining CPP greater than 50 mm Hg.[264] That CPP target has increased, in the most recent iteration, to 60 to 70 mm Hg with allowance for occasional reduction to 50 mm Hg.[266] An approach from the University of Alabama, identified as "Birmingham," entails pharmacologically induced hypertension. This approach is based on the belief that autoregulation is largely intact, and that hypertension would result in cerebral vasoconstriction with concomitantly reduced cerebral blood volume and ICP.[262,331]

CPP target of 50 to 55 mm Hg. At its inception, the approach was controversial because it ran counter to the perceptions of many clinicians of the importance of maintaining a CPP of 70 mm Hg, and because of the later demonstration that a negative fluid balance in patients with TBI is deleterious.[249] Over time (and in parallel with a relaxation the CPP targets by others[59,258-260]), the Lund proponents have modified their approach, and now "a CPP of 60-70 is considered optimal," and normovolemia is the clinical objective.[266]

The essence of the previously controversial Lund approach is no longer the aggressive CPP reduction that was the originally proclaimed cornerstone, although sedatives, clonidine, and metoprolol are administered to prevent hypertension. The Lund concept's distinguishing features are now (1) the routine infusion of low-dose thiopental (to reduce the "stress response" and to decrease CMR and CBV); (2) the maintenance of colloid osmotic pressure at unspecified levels by the generous administration of albumin; and (3) the cautious administration of dihydroergotamine, also to reduce CBV (by a putative selective cerebral venoconstrictive effect).[266] Although there is a theoretical basis for each of the components, the existing literature provides no compelling support. Although the proponents of the Lund approach assert improvements in outcome, those reports invariably entail either no control group or comparisons with nonconcurrent controls.[267-269] The approach has not been adopted in North America.

What should an anesthesiologist managing a TBI patient do in the face of these various approaches? The approaches have in common perfusion pressure support of varying degrees. The characteristic behavior of CBF after head injury is an initially low CBF followed by a gradual increase over 48 to 72 hours to normal or sometimes even slightly hyperemic levels.[23,33,37,38,251,258,270] Aggressive support of CPP in the 60 to 70 mm Hg range during

that period would be the most reasonable general approach. In patients with subarachnoid blood, a second period of low CBF may occur from days 2 to 13 postinjury, apparently on a vasospasm-related basis.[35,271] Phenylephrine, norepinephrine, and dopamine all have been employed to increase blood pressure. Norepinephrine has been reported to accomplish CBF augmentation more consistently than dopamine.[272]

There are exceptions to the foregoing generalizations about CBF after TBI. Although an initially low postinjury CBF is probably the most common clinical occurrence, hyperemia does occur.[35,39,270,271,273] It tends to occur in patients with mass lesions rather than contusions, although patients with contusions have an immediate postinjury period of low CBF, with delayed hyperemia peaking at 24 hours or later.[34,35,253,270,273] Hyperemia also may be common in children.[274] In the ideal situation, CPP management should be "targeted" to the pathophysiology that prevails in the individual patient.[275] There is substantial evidence that not all TBI patients benefit from increases in perfusion pressure. Patients with impaired autoregulation, low baseline flows, and increased ICP are most likely to benefit.[276-278] Techniques to discriminate the various flow states (CBF measurement, TCD, $Sjvo_2$, brain tissue Po_2—see later) are not universally available or applied, however, and in their absence, the common practice is to maintain CPP 60 to 70 mm Hg in the first 72 hours after TBI.[256,258,261,279-281] A CPP target of 45 mm Hg has been recommended for children.[282] With these firm recommendations offered, it must be acknowledged that convictions vary, and anesthesiologists should come to an understanding with the local traumatologists and neurosurgeons regarding blood pressure targets.

Hyperventilation. The use of hypocapnia has been reviewed in detail in the section on management of $Paco_2$. Hyperventilation has long been a component of the management of TBI patients, and the effectiveness of acute hypocapnia in reducing ICP is well confirmed.[10] There is substantial evidence, however, that hyperventilation is potentially deleterious[23,24,29-31,283] and should not be overused. The evidence suggests that hyperventilation and the concomitant vasoconstriction can result in ischemia,[21,29-32] especially when baseline CBF is low,[32] as is likely to be the case in the first 48 to 72 hours after head injury.[23,33,38,39] The expert panel convened by the Brain Trauma Foundation specified that prophylactic hyperventilation is "not recommended," and that "hyperventilation should be avoided during the first 24 hours after injury when CBF is often critically reduced."[59] The available information argues that hyperventilation should be used selectively rather than routinely in the management of TBI patients. Maintaining ICP less than 20 mm Hg, preventing or reversing herniation, minimizing retractor pressure, and facilitating surgical access are still important objectives in the management of TBI patients and to the extent that hyperventilation contributes to these objectives, it is still appropriate. The anesthesiologist should agree on management parameters with the surgical team at the outset of a procedure.

Fluid Management. Fluid management of head-injured patients was addressed in the earlier section on intravenous fluid management. The important principles are that fluids should be chosen invariably to prevent reduction of serum osmolarity and should probably be chosen to prevent profound reduction of colloid oncotic pressure; in the circumstances of a large-volume resuscitation (arbitrarily, greater than half a circulating volume), a mix of colloids and crystalloids is probably appropriate. The clinical objective should be to maintain intravascular normovolemia, in part as an adjunct to MAP and CPP support. A chronic negative fluid balance, as can occur with the combination of modest fluid restriction and liberal use of osmotic diuretics, has been shown to be deleterious and should be avoided.[249] The severely injured brain can liberate sufficient thromboplastin into the circulation to result in a consumptive coagulopathy.[284] Appropriate laboratory tests and replacement should be performed. The clinician also may find a serum osmolarity determination early in the course of anesthetic management useful in appreciating the cumulative effects of prior mannitol administration. The use of hypertonic solutions and the relevant attributes of colloid solutions were discussed in the section on intravenous fluid management.

Jugular Venous Oxygen Saturation

Numerous centers have studied or made use of $Sjvo_2$ monitoring as a guide to the clinical management of head-injured patients.[29-32,40,247,256,257,281,285] The underlying concept is that a marginal or inadequate CBF results in an increasing oxygen extraction, a widening arteriovenous content difference, and reduction of $Sjvo_2$. Normal subjects at rest may have $Sjvo_2$ values between 55% and 75%. $Sjvo_2$ less than 50% for 5 minutes is commonly accepted as constituting "jugular desaturation." There have been numerous reports of low $Sjvo_2$ values improving with interventions including reducing hyperventilation, increasing MAP, or inducing hypervolemia. $Sjvo_2$ measurement makes an assessment of *global* oxygen extraction. It might be expected to have limited sensitivity to highly *focal* events, and instances in which focal inadequacy of perfusion was not reflected by low $Sjvo_2$ have been reported.[29-31,39] One of those investigations offers a possible explanation for normal $Sjvo_2$ in the face of significant focal ischemia. Coles and colleagues[39] showed the coexistence of areas of hyperemia and hypoperfusion in individual TBI patients. The former would tend to mask the $Sjvo_2$ reduction that would occur if the latter (hypoperfusion) were to occur in isolation. An additional limitation inherent to the unilateral placement of the catheter was found by Stocchetti and associates,[286] who observed that there was an average side-to-side difference between simultaneous jugular bulb saturations of 5.3 ± 5%, and that side-to-side differences in hemoglobin saturation of 15% were common.

Despite the reported successes with $Sjvo_2$ monitoring,[40,287,288] we do not believe that the method is sufficiently well defined to justify advocating widespread intraoperative application. In the ICU, it seems potentially useful as a trend monitor that may serve to identify the level of CPP or hyperventilation below which cerebral perfusion *begins* to be compromised, with the proviso that there is a significant potential for false-negative results.[29-31,39] The technique also has a potential use beyond using $Sjvo_2$ values to warn of inadequate perfusion. High $Sjvo_2$ values may serve to identify a patient with elevated ICP in whom hyperemia is an important contributing factor, and in whom aggressive attempts to decrease CBF (e.g., hyperventilation, barbiturates) may be beneficial.

Brain Tissue Po_2 Monitoring

There are small-diameter intraparenchymal electrodes that allow measurement of brain tissue Pbo_2 (and sometimes pH and $Pbco_2$). They have been used to monitor cerebral well-being during the ICU management of TBI and SAH patients, and to

assess the effect of operative interventions.[289] A Pbo_2 of 20 mm Hg or greater is viewed as normal, and values of 10 mm Hg or less are assumed to convey a substantial risk of hypoxic injury. Pbo_2 monitors have the inverse of the problem that prevails with $Sjvo_2$ monitoring—they provide very focal information about the oxygenation status of only small regions of brain surrounding the tip. If they are placed remote from focal injuries to provide a "global" measure of oxygenation, they may not "see" adverse events in at-risk but salvageable perilesional tissue. They may similarly fail to be a useful therapeutic guide if they are within irredeemably injured brain.

So far, the use of Pbo_2 monitoring is neither standardized nor widespread. One center has reported, however, on the basis of a comparison with a historic control group, a reduction in mortality when established management guided by CPP and ICP was supplemented with Pbo_2-directed care, with the probe placed in white matter adjacent to, but not within, areas of severe injury.[290] The same group has reported that 29% of TBI patients with a GCS score of 8 or less have brain regions with Pbo_2 of 10 mm Hg or less despite meeting CPP and ICP targets of 60 mm Hg and greater (CPP) or less than 25 mm Hg (ICP).[261]

Hypothermia

There is clearly an ischemic component to the pathophysiology of TBI, and mild induced hypothermia was shown to be highly protective in experimental cerebral ischemia (see also the preceding section on hypothermia). On that basis, study of hypothermia after experimental head injury was undertaken, and improvements in outcome were shown.[146] Hypothermia in the management of TBI patients was the subject of at least four small, prospective controlled trials.[147-150] Because those trials seemed to indicate good patient tolerance of sustained mild hypothermia (32°C to 34°C) and improvement in ICP, cerebral oxygen supply and demand, and outcome, a multicenter trial was performed. This trial revealed no overall benefit of hypothermia.[151] As a result, there is no established role for hypothermia in head injury management as of this writing.

Post hoc analysis showed that patients younger than age 45 who were already hypothermic (≤35°C) at the time of admission to the hospital did have an improved outcome. This finding led to the concern that the protocol, which required induction of hypothermia within 8 hours of injury, was not achieving hypothermia rapidly enough to achieve the potential benefits. A follow-up trial is under way. Patients 16 to 45 years old, with a GCS score less than 8, who arrive at the hospital with a bladder temperature of 35°C or less are to be randomly assigned to cooling to 32.5°C to 33.5°C (within 4 hours of injury) for 48 hours or passive rewarming to normothermia. Outcome is to be assessed at 6 months.

Intracranial Pressure Monitoring for Non-neurologic Surgery in a Head-Injured Patient

In the ideal situation, neurosurgical consultation will be readily available, and, appropriately, the anesthesiologist will rarely have to make the decision regarding ICP monitoring. It may be necessary, however, for the anesthesiologist to participate in this decision. The relevant variables are as follows:

1. *The level of consciousness*. If there has been a loss of consciousness at any time, or if the GCS score is less than 15, a CT scan should be obtained. If the CT scan reveals compressed basal cisterns (indicative of an exhaustion of supratentorial compensatory latitudes), midline shift, or effaced ventricles, and probably any intracranial lesion (e.g., contusion, small subdural), an ICP monitor should be placed. Excessive comfort should not be taken from a good GCS score. Patients with good GCS scores can "talk and deteriorate" or "talk and die" after a head injury associated with loss of consciousness. Delayed deterioration has been observed 48 hours after the initial injury (average 17 hours).[291] Patients with lesions, usually contusions, in the frontotemporal region and especially patients with medial temporal lesions are most at risk for this phenomenon. Modest expansion of lesions in this location (i.e., close to the uncus and the incisura where herniation occurs) can result in herniation even at relatively low ICPs (e.g., approximately 20 mm Hg). At our institution, neurosurgeons would recommend avoiding an anesthetic in these patients and would advise ICP monitoring if general anesthesia were unavoidable.
2. *Time since injury*. The longer the patient has had to declare his or her clinical course, the less pressing is the need for ICP monitoring. Delayed deterioration, as noted previously, has been observed for up to 48 hours,[291] however, and a patient with a demonstrable CT lesion is a candidate for a monitor for at least this period of time.
3. *Intended aortic occlusion* (i.e., repair of ruptured aorta). Dramatic increases in ICP have been associated with aortic occlusion. This may in large part be the result of the abrupt increase in blood pressure or the agents used to control it, or both. In addition, the increased airway and venous pressures associated with the lateral position and one-lung ventilation plus occasional difficulties in maintaining hypocapnia during one-lung ventilation should result in a low threshold for ICP monitoring in this situation. The intent to heparinize systemically essentially precludes the placement of a monitor, although lumbar drains have been used with cardiopulmonary bypass.[219]
4. *Nature and duration of the intended procedure*. The risks of an untoward ICP event are inevitably greater in a 6-hour spine instrumentation in the prone position than for a 20-minute débridement and suturing of an arm laceration.

Posterior Fossa Procedures

Most of the topics relevant to posterior fossa procedures (Table 63-12) have been discussed in the section on recurrent issues. These include the sitting position and its cardiovascular effects and complications (e.g., quadriplegia, macroglossia), pneumocephalus, and VAE and PAE. The use of the sitting position to facilitate surgery in the posterior fossa increases the likelihood of all of these phenomena, although they are relevant to nonsitting positions as well. This section reviews the cardiovascular events associated with direct stimulation of the brainstem and their possible implications for postoperative management.

Brainstem Stimulation

Irritation of the lower portion of the pons and of the upper medulla and of the extra-axial portion of the fifth cranial nerve can result in numerous cardiovascular responses. The former two areas are most often stimulated during procedures on the floor of

Table 63-12 Considerations Relevant to Posterior Fossa Procedures and the Location (Section, Subsection) of the Related Discussion in Chapter

Consideration	Section, Subsection
Hemodynamic effects of sitting position	Positioning, Sitting
Venous air embolism	Venous Air Embolism
Paradoxical air embolism	Venous Air Embolism
Hemodynamic effects of brainstem and cranial nerve manipulation	Posterior Fossa Procedures
Macroglossia	Positioning, Sitting
Pneumocephalus	Pneumocephalus
Quadriplegia	Positioning, Sitting

the fourth ventricle and the last during surgery at or near the cerebellopontine angle (e.g., acoustic neuromas, microvascular decompression of fifth [tic douloureux], seventh [hemifacial spasm], or ninth [glossopharyngeal neuralgia] cranial nerves). The cardiovascular responses may include bradycardia and hypotension, tachycardia and hypertension, bradycardia and hypertension, and ventricular dysrhythmias.[292] Meticulous attention to the ECG and a directly transduced arterial pressure during manipulation in this region are necessary to provide the surgeon with immediate warning of the risk of damage to the adjacent cranial nerve nuclei and respiratory centers. Pharmacologic treatment of the dysrhythmias that occur may attenuate the very warning signs that should be sought.

Balloon compression of the trigeminal ganglion is another situation in which a dysrhythmia may occur. The procedure attempts to produce a neurapraxia of the fifth cranial nerve by the rapid inflation of a Fogarty-type balloon within Meckel's cave.[293,294] The balloon is introduced percutaneously through the cheek and beneath the maxilla. The procedure is best accomplished with a general anesthetic because the entry of the needle into Meckel's cave and the balloon compression (lasting several minutes) are intensely stimulating. A relatively profound, although transient, bradycardia occurs and is sought as confirmation of adequate compression. External pacemaker pads have been advocated, but in our experience are unnecessary.

Irritation and injury of posterior fossa structures that may have occurred during surgery should be taken into account in planning extubation and postoperative care. In particular, procedures involving dissection on the floor of the fourth ventricle entail the possibility of injury to cranial nerve nuclei or postoperative swelling in that region, or both. Cranial nerve dysfunction, particularly of cranial nerves IX, X, and XII, can result in loss of control and patency of the upper airway, and swelling of the brainstem can result in impairment of cranial nerve function and respiratory drive. The posterior fossa is a small space, and its compensatory latitudes are even more limited than those of the supratentorial space. Relatively little swelling can result in disorders of consciousness, respiratory drive, and cardiomotor function. A meeting should occur between the anesthesiologist and the surgeon to make decisions as to whether extubation is appropriate, and where postoperative observation should occur (i.e., ICU or non-ICU).

Spontaneous ventilation was previously advocated for procedures that entailed a risk of damage to the respiratory centers. Spontaneous ventilation is now rarely used because the proximity of the cardiomotor areas to the respiratory centers should permit cardiovascular signs to serve as an indicator of impending injury to the latter. In our opinion, respiratory pattern is more likely to be a relevant monitor when the "threat" to the brainstem is the result of vessel occlusion (as might occur with accidental interruption of perforating vessels during vertebrobasilar aneurysm surgery[295]) than when it is because of direct mechanical damage caused by retraction of or dissection in the brainstem.

Various electrophysiologic monitoring techniques may be used during posterior fossa surgery, including somatosensory evoked responses, brainstem auditory evoked responses, and electromyographic monitoring of the facial nerve. Electromyography requires that the patient not be paralyzed or have a constant state of incomplete paralysis. Somatosensory evoked response monitoring imposes some constraints with respect to the selection of anesthetic agents. These are discussed in Chapter 46.

Transsphenoidal Surgery

The transsphenoidal approach to the sella turcica is used for the excision of tumors that lie within the sella or that have extended to or originated in the immediate suprasellar area. The most common lesions are prolactin-secreting microadenomas and nonsecreting macroadenomas. Patients with the former are usually women who present with secondary amenorrhea. Nonsecreting adenomas tend to manifest with mass effects (i.e., headache, visual disturbance, hypopituitarism) and are typically larger at the time of diagnosis. There are three other, less common pituitary tumors: Growth hormone–secreting lesions result in acromegaly, adrenocorticotropic hormone (ACTH)–secreting tumors cause Cushing's disease, and a very rare thyroid-stimulating hormone–secreting lesion results in hyperthyroidism. A detailed review of the perioperative management of this group of patients is available.[296]

Preoperative Evaluation

The important preoperative considerations relate to the patient's endocrine status. Generally, as a pituitary lesion expands and compresses the pituitary tissue, the sequence in which hormonal function is lost is first gonadotropins; second, growth hormone; third, ACTH; and fourth and last, thyroid-stimulating hormone. The precise definition of the adrenal status of these patients is often not critical because the patients commonly receive adrenal hormone supplementation at least temporarily. Profound hypocortisolism, with associated hyponatremia, should be corrected preoperatively. It is uncommon for thyroid deficiency to occur. Hypothyroidism should be sought and corrected preoperatively, however, because hypothyroid patients have a diminished tolerance to the cardiovascular depressant effects of anesthetic agents. Hypertension, diabetes, and central obesity are common concomitants of ACTH-secreting adenomas (Cushing's disease). Patients with advanced acromegaly can develop an enlarged tongue and a narrowed glottis, and the airway should be evaluated accordingly (Table 63-13).

Monitoring

Many practitioners place an arterial catheter, but it is not absolutely necessary. Access for blood sampling is a valuable adjunct to postoperative care if diabetes insipidus develops. Blood loss is

Table 63-13 Tumors of the Pituitary Region

Location	Hormone Secreted	Clinical Presentation	Comment
Anterior pituitary	Prolactin	Galactorrhea, amenorrhea, hypogonadism, infertility	Bromocriptine sensitive
	Adrenocorticotropin	Cushing's disease (hypercortisolism)	Basophilic adenoma; centripetal obesity; diabetes mellitus; friable tissues
	Growth hormone	Acromegaly/gigantism, glucose intolerance	Eosinophilic adenoma; difficult airway; thick skin (difficult cannulation); hypertension/cardiomyopathy
	Nonsecretory	Mass effect, panhypopituitarism	Chromophobic adenoma; consider preoperative hormone replacement
Suprasellar	Nonsecretory	Panhypopituitarism, SIADH, visual symptoms, hydrocephalus	Craniopharyngioma, Rathke cleft cyst, or suprasellar extension of pituitary lesion

SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

usually modest. The cavernous sinus is in immediate lateral relation of the pituitary, however, and may be entered during the resection of large tumors. The carotid arteries pass through the cavernous sinuses and are similarly at risk. In addition, in some patients, there is a venous sinusoid that lies in front of the pituitary gland and connects the two cavernous sinuses. This can be the origin of substantial blood loss. It has occasionally precluded this approach to the pituitary gland.

Anesthetic Technique

The latitudes are broad with respect to choice of agent, although tumors with suprasellar extension can cause hydrocephalus and add increased ICP constraints to the anesthetic technique. The procedure is performed in a supine position usually with some degree of head-up posture to avoid venous engorgement. A pharyngeal pack prevents an accumulation of blood in the stomach (which causes vomiting) or in the glottis (which contributes to coughing at extubation). A RAE-type tube secured to the lower jaw at the corner of the mouth opposite the surgeon's dominant hand (e.g., left corner of mouth for a right-handed surgeon) is suitable. A small esophageal stethoscope and temperature probe can lie with the endotracheal tube. Covering the entire bundle with a towel drape (a plastic sheet with an adhesive edge) placed just below the lower lip so that it hangs from the lower jaw like a veil protects it from the preparation solutions.

The procedure is commonly performed with a C-arm image intensifier (lateral views), and the head and arms are relatively inaccessible when the patient is draped. It is appropriate to establish the nerve stimulator at a lower extremity site. The surgical approach is via the nasal cavity, usually through an incision made under the upper lip. During the approach, the mucosal surfaces within the nose are infiltrated with a local anesthetic and epinephrine solution, and the patient should be observed for the occurrence of dysrhythmias.

Surgical preferences for CO_2 management vary. In some instances, hypocapnia is requested to reduce brain volume and minimize the degree to which the arachnoid bulges into the sella. An important surgical consideration is the avoidance, where possible, of opening the arachnoid membrane. Postoperative CSF leaks can be persistent and are associated with a considerable risk of meningitis. By contrast, when there is suprasellar extension of a tumor, normal or increased CO_2 helps to deliver the lesion into the sella for excision.[297] As an alternative way to accomplish this, some surgeons have resorted to "pumping" of saline or air into the lumbar CSF space.[298,299]

Diabetes insipidus is a potential complication of this procedure. Antidiuretic hormone is synthesized in the supraoptic nuclei of the hypothalamus and is transported down the supraoptic-hypophyseal tract to the posterior lobe of the pituitary. This portion of the pituitary gland is frequently spared. Even when it is excised, water homeostasis commonly normalizes, presumably because antidiuretic hormone is released from the cut-end of the tract. When the pituitary stalk is transected, and occasionally even when the posterior lobe of the pituitary is left intact, transient diabetes insipidus may occur. Diabetes insipidus very rarely arises intraoperatively. It usually occurs 4 to 12 hours postoperatively and is typically transient. The clinical picture is one of polyuria in association with an increasing serum osmolality. The diagnosis is made by comparison of the osmolalities of urine and serum. Hypo-osmolar urine in the face of an increased and increasing serum osmolality strongly supports the diagnosis. Urine specific gravity is a useful bedside test. In the presence of bona fide diabetes insipidus, specific gravity is low (i.e., ≤1.002).

When the diagnosis of diabetes insipidus is established, an appropriate fluid management regimen is hourly maintenance fluids plus two thirds of the previous hour's urine output. (An acceptable alternative is previous hour's urine output minus 50 mL plus maintenance.) The choice of fluid is dictated by the patient's electrolyte picture. Generally, the patient is losing fluid that is hypo-osmolar and relatively low in sodium. Half-normal saline and 5% dextrose in water are commonly used as replacement fluids. Hyperglycemia is a risk when large volumes of 5% dextrose in water are employed. An *un*acceptable fluid regimen that has been employed calls for maintenance fluids plus previous hour's urine output. This has the potential to put the anesthesiologist and the patient in a "chase your tail" situation. Should the patient become iatrogenically fluid overloaded, this regimen precludes his or her returning to isovolemia, and when the maintenance fluid allowance is generous, it guarantees that the patient will become increasingly hypervolemic. If the hourly requirement exceeds 350 to 400 mL, desmopressin (DDAVP) is usually administered.

A smooth emergence (see the section on emergence from anesthesia) is desirable especially if the CSF space has been opened (and resealed with fibrin glue or by packing the sphenoid sinus with fat or muscle). Repeated, intense Valsalva maneuvers,

as with coughing or vomiting, may contribute to the reopening of a CSF leak and worsen the risk of a subsequent meningitis. The airway should be cleared of debris, including formed clot. In situations in which there is concern that a persistent CSF leak may occur, the surgeon may place a lumbar CSF drain to maintain CSF decompression in the early postoperative period.

Awake Craniotomy and Seizure Surgery

Awake craniotomies are performed when tumors or epileptic foci lie close to cortical areas required for either speech or motor function or to mesiotemporal structures critical to short-term memory. Many patients have so-called temporal lobe epilepsy. There is commonly a structural lesion visible on magnetic resonance imaging (MRI). Sometimes there is a history of trauma. More commonly, the etiology is presumed to be an asphyxial birth injury.

Presurgical Evaluation

Before the resection, most patients have undergone a Wada test or video-telemetry or both. More recently, functional testing employing MRI or positron emission tomography, or both, has been introduced to the presurgical evaluation. The Wada test involves selectively anesthetizing the cerebral hemispheres, usually by injection of sodium amytal into the carotid artery to localize the hemisphere that controls speech or to confirm that there is bilateral representation for short-term memory, or both. Speech is an issue when the posterolateral portions of the temporal lobe are involved, and memory is the concern when the involvement is medial.

Anesthesia for Electroencephalogram Electrode Placement

Video-telemetry is performed to permit localization of the seizure focus that is responsible for the clinically problematic events. This evaluation usually requires prior placement of either subdural strip electrodes (via bur holes) or a subdural electrode grid (requiring a craniotomy). Occasionally, electrodes are placed deep into parenchyma, usually within the temporal lobe (placed stereotactically via bur holes), or are positioned so as to "look at" the inferior surfaces of the temporal lobe. The latter is commonly accomplished with so-called foramen ovale electrodes. These are placed using a needle similar to an epidural needle. The point of entry is about 2 cm lateral to the angle of the mouth. The needle is passed through soft tissue, under the temporal process of the zygomatic bone and medial to the ramus of the mandible, up to the base of the skull in the vicinity of the foramen ovale. Typically, this procedure is performed as a "MAC," although small doses of anesthetics, most often propofol, are usually required at the time of stimulation by the needle of the periosteum at the base of the skull. After placement of the relevant electrodes, the patient's seizure medication is discontinued, and the patient remains in an observation unit with EEG and patient behavior recorded continuously. In this manner, the EEG events associated with the clinically significant seizure events and their anatomic origin can be identified.

Preanesthetic Evaluation and Preparation

At the preoperative interview, the patient should be educated about the nature and duration of the procedure and the limitations on patient movement. One should obtain a description of the aura and the seizures to facilitate recognition of them. One should ascertain whether the patient is subject to grand mal convulsions. If intraoperative electrocorticography to identify seizure foci is intended, it is common to discontinue or reduce by half the anticonvulsants according to the perceived risk of uncontrolled seizures. Premedicants with an anticonvulsant effect (e.g., benzodiazepines) should not be used because they may interfere with intraoperative EEG localization.

Anesthetic Technique

The objectives of the anesthetic technique are as follows:

1. To minimize patient discomfort associated with the potentially painful portions of the procedure and with the prolonged restriction of movement
2. To ensure patient responsiveness and compliance during the phases of the procedure that require assessment of either speech or motor/sensory responses to cortical stimulation
3. To select anesthetic techniques that produce minimal inhibition of spontaneous seizure activity.

There are probably many ways of providing sedation that are consistent with the above-listed objectives. The techniques employed range from minimal sedation approaches, to deep sedation during which intermittent unresponsiveness is achieved with spontaneous ventilation and an unprotected airway, to asleep-awake-asleep techniques with intermittent airway management with a laryngeal mask airway (LMA), sometimes with positive-pressure ventilation.

At the outset, the anesthesiologist should appreciate that the essential element of an "anesthetic" for an awake craniotomy is the surgeon's local anesthetic technique. "Sedation" cannot compensate for inadequate anesthesia of the scalp, as accomplished by nerve blocks (Fig. 63-17), and pin site infiltration. Although the anesthesiologist can contribute enormously to the patient's comfort and tolerance of the painful components of the procedure and the prolonged immobilization, the anesthesiologist must not get trapped into thinking that it is his or her responsibility to provide a general anesthetic-equivalent in a spontaneously breathing patient with an unprotected and all but inaccessible airway.

For sedation, some clinicians use principally propofol by either physician-controlled or patient-controlled infusion.[300,301] The combination of propofol with either fentanyl or remifentanil in low dose (e.g., remifentanil, 0.02 to 0.05 μg/kg/min) also is reasonable.[302,303] Great care should be taken in administering additional sedative agents, especially narcotics, whose respiratory depressant effects would be synergistic with propofol. This is especially relevant with the use of pin fixation, which severely restricts the anesthesiologist's capacity to intervene quickly in the event of excessive respiratory depression or loss of patency of the airway.

Propofol should be discontinued at least 15 minutes before EEG recording. Despite prompt awakening, propofol leaves a residual EEG "footprint" characterized by high-frequency, high-amplitude beta activity, which can obscure the abnormal activity that is being sought in the cortical surface EEG.[300] The use of dexmedetomidine, which in addition to sedation and anxiolysis provides some analgesia with minimal respiratory depression, is

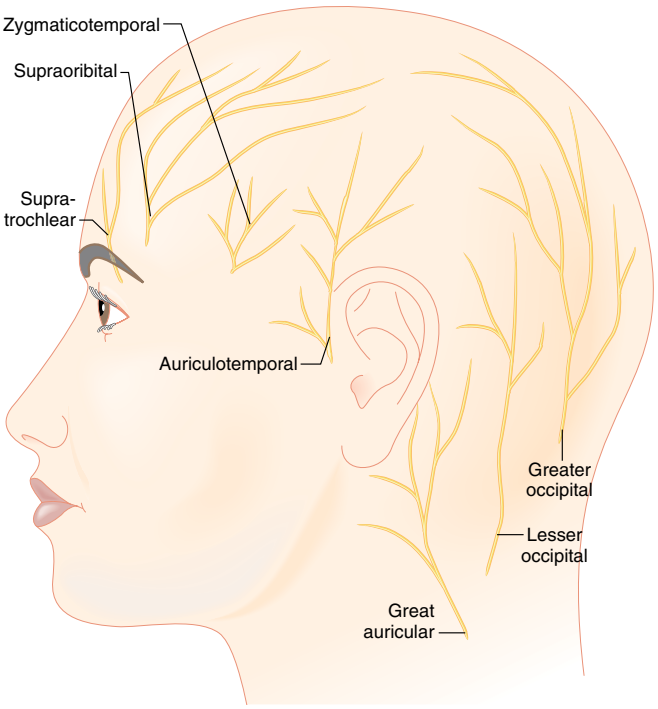

Figure 63-17 Cutaneous nerves to the scalp.

increasing.[304-306] The authors of those series report satisfactory conditions for functional testing, including brain stimulation for speech mapping and electrocorticography with the dexmedetomidine infusion ongoing at 0.1 to 0.5 µg/kg/hr during the testing.[305,307,308] The occurrence of delays in achieving satisfactory patient responsiveness has been reported,[306,309] however, and employing modest infusion rates (i.e., 0.1 to 0.3 µg/kg/hr) during neurocognitive testing seems advisable.[307] Administration of antiemetics (i.e., ondansetron, dexamethasone, or both) probably should be routine, especially if narcotics are administered.

Various groups have reported the use of the LMA, commonly with narcotic-propofol sedation and spontaneous ventilation during the craniotomy, with cessation of sedative administration and LMA removal after the brain surface is exposed.[304-307,310] Many approaches can be effective, but, to our knowledge, the LMA techniques have not been reported in patients in pin fixation.

Routine, noninvasive monitors are almost always sufficient. Reliable capnography, to provide breath-by-breath confirmation of airway patency and respiratory drive, is an essential component of the technique if deep sedation is intended for any portion of the procedure. These procedures are often lengthy, and attention to the details of patient comfort (e.g., warming blankets, a sheepskin, room temperature) improves patient tolerance.

The uncomfortable phases of the procedure are pin head holder placement (not all groups use a pin head holder) and the craniotomy. Many patients also find manipulation of the dura, in particular traction on subtemporal dura, painful. The actual manipulation of supratentorial brain parenchyma is painless. The volume of local anesthetic used to infiltrate pin sites and perform the scalp nerve blocks can be substantial. It is appropriate for the anesthesiologist to keep track of the doses of local anesthetic agents used.

The anesthesiologist should participate actively at the time of head positioning. The more "sniff" that can be achieved before the final lock-down of the head holder, the wider the latitudes will be for sedating the patient, while maintaining spontaneous ventilation and a patent airway. During positioning of the patient, the clinician also should pay attention to the need to maintain visual access to the face. A clear line of sight to the face is necessary to present the patient with images to name as part of speech testing and to identify the occurrence of facial motor responses during mapping of the motor strip.

Generally, after the dural opening is complete, cortical surface EEG recording is performed to locate the seizure focus. If no seizure activity is observed, provocative maneuvers may be requested.[311] Methohexital in a dose of approximately 0.3 mg/kg is generally safe and effective. Etomidate, approximately 0.05 to 0.1 mg/kg, also has been used. Localization of seizure focus also can be accomplished during light general anesthesia (e.g., N_2O/fentanyl/low-dose isoflurane). During general anesthesia, alfentanil in a bolus dose of 30 to 50 µg/kg,[312,313] etomidate in doses of 0.2 to 0.3 mg/kg,[314,315] and remifentanil in a bolus dose of 2.5 µg/kg[316] have been reported to be effective in activating seizure foci.

After localization by EEG, functional testing may be performed by stimulating the cortical surface electrically and observing for motor, sensory, or speech interruption effects. During stimulation, the anesthesiologist should be prepared to treat grand mal convulsions when they are not self-limited (e.g., with propofol in 0.5 to 1 mg/kg increments). Propofol should be withheld, however, until it is clear that the seizure is not going to terminate spontaneously because propofol may interfere with subsequent EEG localization of the seizure focus for some time.[300]

Stereotactic Procedures

Stereotactically guided procedures are done for numerous indications, including biopsy of small, deep-seated lesions; placement of deep brain stimulation electrodes, the latter; occasionally for seizure control and, more commonly, for the treatment of movement disorders (e.g., Parkinson's disease, essential tremor, dystonias).[317] Procedures related to movement disorders most often target the subthalamic nucleus, the internal segment of the globus pallidus, or the ventral intermediate nucleus of the thalamus (Fig. 63-18).[317] The mechanism of the beneficial effect is not well understood. A prominent theory is that the abnormal motor patterns are caused by abnormally synchronized oscillations in neural circuits involving several basal ganglia nuclei and the cortex, and that high-frequency stimulation of any of several points along the pathway can interfere with the oscillation.[318]

The issues with which the anesthesiologist must contend include restriction of airway access by the frame, restriction regarding choice of sedative when electrophysiologic recordings are to be performed as a guide to device placement, and the detection and management of complications (principally, seizures and intracerebral hematomas). Preoperative evaluation should include attention to ensuring that the coagulation process is intact, and that the patient has not been taking platelet-inhibiting agents (including herbal medications). There should be careful explana-

tion of the procedure, its likely duration, and the necessary restraints on patient movement.

Commonly, the stereotactic frame, of which there are many variations, is placed using local anesthetic, and the patient undergoes an imaging study before being brought to the operating room. In some instances, the frame prevents mask application and ventilation, laryngoscopy, and neck extension. If a general anesthetic is to be employed, an awake intubation occasionally may be required. If sedation is to be employed, the anesthesiologist should have certain knowledge as to how to remove the device rapidly in an urgent situation (including knowledge of the whereabouts of the requisite "key" or spanner device).

When electrophysiologic recordings are not intended, sedative regimens similar to those used for awake craniotomy (see earlier) may be appropriate. For thalamic and subthalamic nucleus stimulator placements, part of the localization process entails identifying the typical electrophysiologic "footprint" of specific nuclei. Because the nature and duration of the effects of anesthetic agents on these signals have not been systematically defined, some surgeons and electrophysiologists may request that no sedative agent whatsoever be given. The patient's tremor is an important end point for determining the adequacy of stimulator position and current and must not be suppressed by the sedative agents. Such suppression may occur with propofol. However, Rozet and colleagues[319] reported satisfactory electrophysiologic recordings and preservation of tremor when dexmedetomidine was used for deep brain stimulator placement in patients with Parkinson's disease. They administered dexmedetomidine in a dose sufficient to maintain a lethargic response to normal speech.

An additional issue that arises in some patients with movement disorders is the problem of obtaining high-quality radiologic images in the presence of a persistent tremor. Sedation immediately preceding the stereotactic placement may be inevitable. Propofol has been employed, but the window between propofol administration and subsequent recording should be as long as possible. If sedatives are administered, they must be given in a manner that ensures the ability to perform precise intermittent neurologic examinations of the patient.

During the subsequent procedure, among the anesthesiologist's objectives is the prevention or treatment of hypertension. The concern is that, in the face of multiple needle passes through the brain, hypertension would precipitate development of an intracerebral hematoma. Dexmedetomidine has the added advantage that it may reduce hypertension. In the event of a substantial hematoma, an urgent craniotomy may be required, and the anesthesiologist should be prepared from the outset for this eventuality.

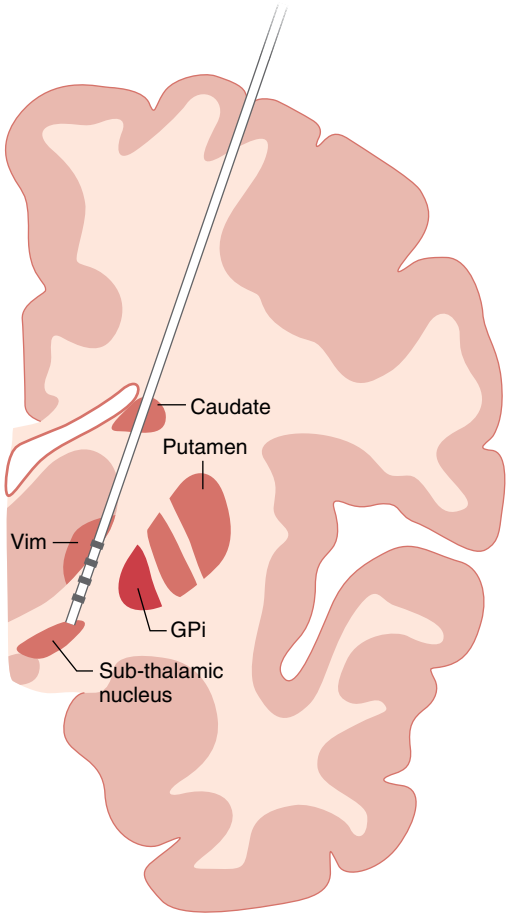

Figure 63-18 Deep brain stimulation electrode target sites. The most commonly targeted nuclei for the treatment of movement disorders are the subthalamic nucleus, the ventral intermediate nucleus of thalamus (Vim), and the internal segment of globus pallidus (GPi).

Neuroradiologic Procedures

Magnetic Resonance Imaging

The major constraints of MRI are created by the powerful magnetic field employed. It creates at least two conditions that have an impact on anesthetic technique. First, any ferromagnetic object that approaches the magnet has the potential to become a dangerous projectile. Second, many of the monitoring devices used in the operating room do not function properly in the vicinity of the magnet. The equipment limitations have largely been circumvented, however. MRI-compatible ECG machines, oximeters, capnographs, noninvasive blood pressure monitors, and gas machines are now widely available. Only temperature monitoring cannot be readily accomplished, and with that exception, there is no longer any justification for incomplete monitoring of patients undergoing MRI.

Most frequently, it is children, claustrophobic adults, and patients with painful conditions who require anesthesia to undergo MRI. Sedation with propofol and an unprotected airway, and general anesthesia with either an LMA or an endotracheal tube have been employed successfully.

Interventional Neuroradiology

A wide variety of procedures are available to evaluate and treat intracranial and extracranial disease. These include, principally, attempts to obliterate aneurysms or devascularize tumors and AVMs. An extensive review is available.[320]

Tumors and Arteriovenous Malformations. Hyperventilation may be appropriate in an attempt to divert flow away from normal brain and toward a lesion that is intended to receive the occlusive device or material. The anesthesiologist may be asked

to reduce systemic blood pressure, which reduces flow through fistulous lesions. Hypotension is usually requested to obtain greater precision for delivery of cyanoacrylate glues and to prevent glue passage into the draining veins or systemic venous system. The choice of hypotensive agent depends on the anesthesiologist's experience and systemic cardiovascular considerations. Adenosine is occasionally effective.[321]

Intracranial Aneurysms. A discussion of the relative merits of open clipping and endovascular management (usually coiling) for intracranial aneurysms is beyond the scope of this chapter. The International Subarachnoid Aneurysm Trial (ISAT) has confirmed the broad applicability of endovascular treatment,[322] and most aneurysms are currently managed by endovascular approaches. Nonetheless, numerous patients continue to undergo operative clipping[323]—primarily patients with wide-necked aneurysms or otherwise complex anatomies. At present, the durability of coil therapy is inferior to direct clipping[324]; a small but significant number of patients treated with coils need additional treatment, usually determined during routine follow-up angiography. Attempts to define the characteristics of patients best managed by operative clipping are ongoing.

Many of these procedures—in particular, procedures involving the treatment of vasospasm by selective intra-arterial installation of papaverine or more commonly by balloon dilation—can be accomplished without the involvement of an anesthesiologist. The duration of a procedure, individual patient factors, and, occasionally, the necessity for precise physiologic control may result in requests for monitored anesthesia care or general anesthesia. A chin-tucked position (to remove the bones of the face from the line of the anteroposterior x-ray source) and absolute immobility are commonly needed by the radiologist, and, consequently, when the anesthesiologist's assistance is requested, a general anesthetic often is necessary. In addition, anesthesiologists may become involved during the resuscitation stage in the event of vascular rupture or of the migration of an intravascular device to an incorrect location. In the event of rupture, the interventionist may request blood pressure reduction while the coil packing of the aneurysm is completed hastily. Immediate reversal of heparinization also would be required. When detachable devices (i.e., coils, balloons) are misplaced, and ischemia ensues, fluid loading and pressor administration may be requested to improve collateral CBF while the device is retrieved.

Carotid Angioplasty and Stenting. The role of carotid angioplasty is undefined. Carotid angioplasty and stenting (CAS) was originally proposed as an alternative for patients deemed to be of the highest medical risk. An early prospective comparison of CAS and carotid endarterectomy (CEA) among moderately high-risk patients revealed similar outcomes for the two procedures.[325] Reports have subsequently appeared of two additional trials, one of which was halted when an interim data analysis revealed a greater "any stroke or death" rate among CAS patients.[326] The second trial reported similar rates of any stroke or death for CAS and CEA.[327] There was a nonsignificant trend, however, toward an increase in the rate of occurrence of "disabling stroke or death" in the CAS group.

Finally, an interim report on patients enrolled in the ongoing Carotid Revascularization versus Stent Trial (CREST) revealed an unexpectedly high rate of stroke and death among patients older than 75 years of age, which was not explained by adjustment for comorbidities.[328] The suspicion is that the increased stroke incidence may be related to embolism from the arch of the aorta or the carotid, and it has been reported unofficially that some centers have discontinued enrollment of patients older than 75 years. It may evolve that some of the patients who were originally viewed as part of the target population (the very elderly) for this procedure may be among the patients for whom the procedure is relatively contraindicated.

It seems probable that the future holds a place for CAS and CEA, in part, because there are numerous relative contraindications to both procedures. The relative contraindications to CAS include antiplatelet agent intolerance, other pending surgery that precludes antiplatelet agents, aortic arch disease (age), and various elements of carotid morphology, including carotid tortuosity, concentric calcification (which entails a risk of vessel rupture), heavy thrombus burden, and unstable plaque (the latter two entail increased embolization risk). The relative contraindications to CEA include prior irradiation, prior radical neck surgery, tracheostomy, restenosis after CEA, high carotid bifurcation, contralateral recurrent laryngeal nerve palsy, and (perhaps) severe coronary or pulmonary disease (or both).

The procedure is almost always accomplished using monitored anesthesia care. Vascular access is most often achieved via the femoral artery. The anesthesiologist is usually asked to titrate heparin by bolus and infusion to achieve an activated clotting time of 250 to 300 seconds. Thereafter, the principal concern is the occurrence of what may be a profound bradycardia first with balloon dilation of the stenotic region and subsequently with expansion of the stent across the same region. Our practice is to titrate glycopyrrolate from the beginning of the procedure to achieve a heart rate of about 70 beats/min before the dilation and to have atropine at the ready and an external pacemaker in the room. We have never had to use the latter. In our institution, the presence of an anesthesia provider for this procedure is typically requested for only the most physiologically compromised patients. In this population, we have found it advantageous to have an independent (i.e., radial) arterial line.

Cerebrospinal Fluid Shunting Procedures

CSF shunts are inserted for the relief of various hydrocephalic states and pseudotumor cerebri. Hydrocephalus can be communicating or noncommunicating. In a noncommunicating hydrocephalus, CSF egress from the ventricular system is obstructed. This can occur as a result of blood or infection in the ventricular system or tumors in or adjacent to the ventricular system. In communicating hydrocephalus, the CSF escapes from the ventricular system, but is not absorbed by the arachnoid villi; this occurs most commonly secondary to infection or blood in the CSF space. Some degree of communicating hydrocephalus is particularly common after SAH.

The ventriculoperitoneal shunt is the most commonly employed device. Usually, a catheter is inserted via a bur hole into

the frontal horn of the lateral ventricle on the nondominant (usually the right) side. A reservoir is placed subcutaneously adjacent to the bur hole, and the drainage limb passes via a subcutaneous tunnel to a point near the epigastrium, where it is inserted into the peritoneal space via a very small laparotomy. A moderate degree of muscle relaxation may be helpful. A distended stomach can result in an inadvertent "gastrostomy." Occasionally, most commonly in pediatric patients, there may be an obstruction at more than one level in the ventricular system, and a so-called double-barreled shunt becomes appropriate. In this instance, there are two proximal ends—usually one in the lateral ventricle and one in the fourth ventricle. This latter procedure is usually performed in the prone position, whereas most ventriculoperitoneal shunts are done supine.

Occasionally, when there is a communicating hydrocephalus, a lumboperitoneal shunt is inserted. The patient is placed in a lateral position, and a catheter is put in the lumbar CSF space via a Tuohy-type needle. The catheter is tunneled subcutaneously around to the anterior abdominal wall and inserted into the peritoneal space via a small laparotomy.

Anesthetic Management

Invasive monitoring is generally not required. The anesthetic technique should be chosen to avoid further increases in ICP. Moderate hyperventilation ($Paco_2$ 25 to 30 mm Hg) is customary. The procedure is usually performed in the supine position, with the table turned 90 degrees and the head turned toward the anesthesiologist. Blood pressure may decrease abruptly (as brainstem pressure is relieved) when the ventricle is first cannulated. Infrequently, brief pressor support is required. Burrowing the subcutaneous tunnel can produce a sudden painful stimulus. There is only minor postoperative discomfort.

In contrast to most neurosurgical patients, shunt patients are often nursed flat after their procedures in an attempt to prevent an excessively rapid collapse of the ventricular system. Empirically, there is a small incidence of subdural hematoma after shunting, and the tearing of bridging veins at the time of rapid brain shrinkage is a suspected cause.

Pediatric Ventriculoperitoneal Shunts

Shunts are probably more commonly performed in children than in adults. Common indications are hydrocephalus occurring in association with meningomyelocele, neonatal intraventricular hemorrhage, and posterior fossa tumors. Although one can never be casual about the management of these patients, open fontanelles seem to provide some margin for error in younger patients, and palpation of the fontanelles provides online trend monitoring of "ICP." Despite the theoretical considerations, inhaled inductions using volatile agents are empirically well tolerated, even in children with closed fontanelles. We would avoid inhaled induction in a child who was already stuporous, however. When an intravenous line is available, we usually employ a propofol-relaxant induction sequence. For children in whom cannulation of a peripheral vein cannot be accomplished readily, an inhalation induction with sevoflurane is a common approach, with initiation of controlled ventilation, by bag and mask, as rapidly as possible. After establishing controlled ventilation, an ideal course at this point is to establish an intravenous line and administer a muscle relaxant and perhaps an intravenous anesthetic, and to intubate the trachea in these optimal circumstances.

Anesthesia is most commonly maintained thereafter with 60% to 70% N_2O, mechanical hyperventilation, and isoflurane or sevoflurane as required. For children older than 6 months who were not stuporous at the outset, we commonly administer 2 to 3 µg/kg of fentanyl in the belief that this procedure is not entirely pain-free postoperatively, and that a smoother emergence can be accomplished with a narcotic background.

Pediatric Neurosurgery

Table 63-14 lists common pediatric procedures and their anesthetic considerations (see Chapter 82). The most frequent procedures are probably the placement and revision of CSF shunts. These are discussed in the preceding section. Most pediatric tumors occur in the posterior fossa. Most are near the midline, and many are associated with hydrocephalus. For pediatric posterior fossa procedures, VAE risk, monitoring, and treatment are similar for adults and children and have been discussed previously. A Doppler is invariably indicated, and right heart catheters are generally placed when procedures are done in the sitting position. Craniosynostosis procedures have the potential for substantial blood loss that is roughly proportional to the number of sutures involved. There is a significant VAE risk that justifies the use of a precordial Doppler.[97]

Spinal Surgery

Table 63-15 summarizes the many issues that may arise in the context of spinal cord or spinal column procedures undertaken by neurosurgeons. The physiology of the spinal cord is generally similar to that of the brain: CO_2 responsiveness, blood-brain barrier, autoregulation, high metabolic rate and blood flow (although less than the brain), and substantial ischemic vulnerability of gray matter. Measures to reduce spinal cord swelling, analogous to ICP reduction maneuvers, are, however, rarely used. The relevant electrophysiologic monitoring techniques are described in Chapter 46. Prone positioning considerations and the phenomenon of postoperative visual loss are addressed in the discussion of the prone position.

Acknowledgment

The authors gratefully acknowledge the contribution of Harvey M. Shapiro to the origins of this chapter.

Table 63-14 Common Pediatric Neurosurgical Disorders and Anesthetic Considerations

Age Group	Lesion	Pathogenesis	Anesthetic Considerations
Neonates	Intraventricular hemorrhage	Subependymal vascular rupture	Associated problems of prematurity
	Depressed skull fracture	Forceps injury	Associated cerebral edema
Infants	Hydrocephalus	Varied	Increased ICP, especially dangerous in shunt-dependent revisions
	Meningocele	Outpouching of meninges through skull defect	Large size creates airway management problems Prone or lateral position Substantial blood loss Repair may increase ICP
	Encephalocele	Outpouching of meninges through skull defect with brain tissue enclosed	
	Myelomeningocele	Protrusion of spinal meninges and roots through spina bifida	Prone or lateral position Substantial blood loss Respiratory restriction after covering large defects
	Arnold-Chiari malformation	Impaction of posterior fossa contents into foramen magnum	Brainstem compression with head flexion
		With or without hydrocephalus	Increased ICP Latex allergy
		With or without myelomeningocele	Postoperative respiratory depression
	Craniosynostosis	Premature cranial suture fusion	Substantial blood loss Air embolism Supine or prone position
	Craniofacial dysostosis	Developmental abnormality	Lengthy procedures Substantial blood loss Brain retraction Air embolism Endotracheal tube damage
	Vascular malformations	Varied	Congestive heart failure Large blood loss Elective hypotension
	Subdural hematoma/effusion	Trauma	Associated injuries
Older children	Posterior fossa tumors	Ependymoma Astrocytoma	Malnutrition/dehydration Hydrocephalus Increased ICP Prone or sitting position Air embolism Brainstem compression Postoperative cranial nerve dysfunction or brainstem swelling or compression

ICP, intracranial pressure.

Table 63-15 Anesthetic Considerations and Position Requirements Associated with Various Spinal Surgical Procedures

Spinal Segment and Surgical Condition	Problems/Considerations	Positions Used and Comments
Thoracolumbar region: degenerative disease, spinal stenosis, trauma	Major position change	Prone, lateral, or knee-chest position
	Awake intubation and position	If unstable after trauma and major position change required
	Blood loss	Especially with redos, instrumentation, and spinal stenosis; risk of occult aortoiliac or major venous injury
	Air embolism	Infrequent; perhaps increased with knee-chest position and Relton-Hall frame
	Postoperative visual loss	Etiology unclear; associated with long prone procedures, low hematocrit, large estimated blood loss, and hypotension. Patient variables may contribute
		See Section on Positioning, Prone

Table 63-15 Anesthetic Considerations and Position Requirements Associated with Various Spinal Surgical Procedures—cont'd

Spinal Segment and Surgical Condition	Problems/Considerations	Positions Used and Comments
Cervical region: degenerative disk disease, stenosis, trauma, rheumatoid arthritis	Maintain neutral neck position to avoid cord compression	Supine/anterior approach for most diskectomies. Posterior approach (prone or sitting) for laminectomy and occasional diskectomy
	Maintain perfusion pressure at waking normal levels	If existing cord compression or recent cord injury or if cord retraction required
	Hypotension (spinal shock)	Occurs with complete cervical cord injury
	Postoperative respiratory insufficiency	Occurs with cervical cord injury
	Methylprednisolone[329,330]	30 mg/kg over 1 hr period, then 5.4 mg/kg for 23 hr
	Air embolism	With sitting laminectomies
Anterior cervical diskectomy	Traction required for anterior graft insertion	
	Retractor compression of airway	
	Postoperative swelling/airway compression	
	Postoperative cranial nerve dysfunction	
Cervical instability	Awake intubation	
	Awake positioning	Prone or supine
	Axial stabilization for intubation	If awake intubation not feasible
Vertebral metastasis	Large blood loss	Prone or anterolateral/retroperitoneal
		Double-lumen tube for lesions above L1
Spinal cord tumors	Maintain perfusion pressure during retraction	Prone
	Methylprednisolone	
Procedures with major neurologic risk	Wake-up test	Prone. Rehearse with patient
	Somatosensory evoked responses	Anesthetic restrictions
	Motor evoked responses	Anesthetic/relaxant restrictions
	Pedicle screw electromyogram	Relaxant restriction

EMG, electromyogram.

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64 Anesthesia for Bariatric Surgery

Key Points

1. In the United States, 200 million people are overweight or obese. Across the globe, more people are obese than malnourished. Obesity may become the largest single preventable cause of death, and it results in major morbidity and mortality.
2. Metabolic syndrome includes abdominal obesity, decreased high-density lipoprotein, increased insulin, glucose tolerance, and hypertension and is present in nearly 50 million people in the United States alone.
3. The biggest single risk factor for sleep apnea is obesity; a majority of patients affected have increased oral and pharyngeal tissue, which makes ventilation, intubation, and extubation more challenging.
4. Choices for medical management of obesity are limited, and success with just medical management is uncommon. Changes in behavior are important for success.
5. Surgery for obesity is recommended at a body mass index (BMI) of 40 kg/m^2 or at a BMI greater than 30 kg/m^2 with comorbid conditions expected to respond to weight loss secondary to surgical therapy, such as hypertension, diabetes, and hypercholesterolemia. In clinical trials, long- term survival is better in the surgically treated group than in those managed medically.
6. Preoperative evaluation should focus on cardiopulmonary issues and securing an airway, along with the problems of diabetes, hypertension, sleep apnea, and other conditions.
7. Anesthetic drugs should be tailored according to their lipid solubility and knowledge of their lingering depressive effects on respiration.
8. Preparation and positioning are key to successful airway management. Preoperative pressure-support ventilation should be used adjunctively if possible.
9. Intraoperative ventilation is assisted by complete paralysis, moderate positive end-expiratory pressure, tidal volumes based on ideal body weight, and recruitment maneuvers as needed.
10. Common serious postoperative complications are deep venous thrombosis and staple line issues.
11. Obese patients undergoing non–weight loss surgery would benefit from an approach similar to that for bariatric surgery.

Obesity As a Disease

Globally obesity was considered a rarity until the middle of the 20th century.[1] Today, a significant proportion of the adult population in the United States and throughout the developed world suffers from obesity.[2-4] It is currently estimated that more than 200 million Americans, or 65% of the U.S. adult population, are overweight or obese. Obesity and its associated health concerns now represent major causes of morbidity and mortality and have an enormous impact on health care spending. More than 300,000 deaths per annum in the United States and more than $100 billion in annual health care spending are attributable to obesity. It is second only to smoking as a preventable cause of death.[5]

Obesity can be defined as a "disease" because it is a physiologic dysfunction of the human organism with environmental, genetic, and endocrinologic causes.[5]

Obesity most frequently develops when food calorie intake exceeds energy expenditure over a long period. Factors influencing obesity involve energy intake or expenditure (or both) and are influenced by genetic, behavioral, cultural, and socioeconomic factors. For example, syndromes associated with obesity include leptin deficiency, Prader-Willi syndrome, and Lawrence-Moon-Biedl syndrome.[3] Metabolic factors, including hormones, peptides, nutrients, uncoupling proteins, and neural regulatory substances emanating from gut, liver, brain, and fat cells, can influence energy regulation, but most of them are not well understood.

The body mass index (BMI) has become the most widely applied classification tool used to assess individual weight status.[6] BMI is defined as the patient's weight, measured in kilograms, divided by the square of the patient's height, measured in meters, which yields a measurement bearing the unit kg/m^2. Figure 64-1

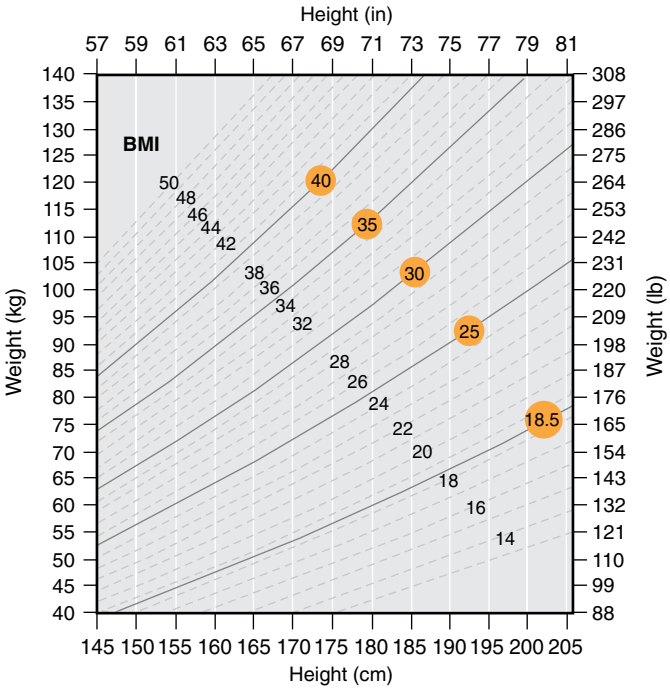

Figure 64-1 A family of iso-BMI curves for BMI ranging from 13 to 50 and mapped on axes for height (in both centimeters and inches) and weight (in both kilograms and pounds). BMI, body mass index.

shows a family of iso-BMI curves for BMI ranging from 13 to 50 and mapped on axes for height (in both centimeters and inches) and weight (in both kilograms and pounds). Using this system, patients are classified according to BMI, and the associated risk of health problems developing is shown in Table 64-1. Patients are considered to be overweight with a BMI between 25 and 29.9 kg/m^2 and obese with a BMI between 30 and 49.9 kg/m.^{2} The obese classification is further subdivided into class 1 (BMI range of 30 to 34.9 kg/m^2), class 2 (35 to 39.9 kg/m^2), and class 3 (40 to 49.9 kg/m^2). Patients with a BMI of 50 kg/m^2 or greater are considered superobese. As BMI increases beyond normal weight, the risk of serious health problems developing rises greatly (Table 64-2). Malnourishment and malnutrition are commonly offered as explanations for the fact that underweight patients are also at increased risk for contracting illnesses.

Table 64-1 Levels of Risk Associated with Increasing Body Mass Index

Classification	BMI (kg/m^2)	Risk of Health Problems Developing
Underweight	<18.5	Increased
Normal weight	18.5-24.9	Least
Overweight	25.0-29.9	Increased
Obese		
Class 1	30.0-34.9	High
Class 2	35.0-39.9	Very high
Class 3	40.0-49.9	Extremely high
Superobese	≥50	Exceedingly high

Table 64-2 Waist Circumference and Risk

Waist Circumference	Body Mass Index (kg/m^2)		
	Normal Weight	Overweight	Obese Class 1
<102 cm (♂) <88 cm (♀)	Least risk	Increased risk	High risk
≥102 cm (♂) ≥88 cm (♀)	Increased risk	High risk	Very high risk

Specific diseases are commonly associated with obesity, and obesity is often accompanied by multiple comorbid states.[7] Such states frequently include insulin resistance, type 2 diabetes mellitus, obstructive sleep apnea (OSA), hypoventilation, cardiovascular disease, hypertension, certain malignancies, and osteoarthritis.[7-14] Virtually all organ systems can be included in the extended list of health risks associated with having an increased BMI. A listing of the most common specific disease states along with their obesity-associated risk is detailed in Table 64-3. As a result of these concomitant conditions, obesity is also associated with early death.[6] Of the health risks listed in Table 64-3, metabolic syndrome and OSA merit additional attention because they pose special concerns for the anesthetic care of the obese population.

Metabolic Syndrome

The clustering of a group of defined metabolic and physical abnormalities is now referred to as "metabolic syndrome."[15] Patients with metabolic syndrome commonly have abdominal obesity, reduced levels of high-density lipoprotein (HDL), hyperinsulinemia, glucose intolerance, hypertension, and other characteristic features (Box 64-1).[15] Clinical criteria for diagnosing metabolic syndrome require at least three of the following: abdominal obesity, elevated fasting glucose, hypertension, low HDL levels, and hypertriglyceridemia. Specific diagnostic criteria are presented in Table 64-4. Weight gain with visceral obesity is a major predictor of metabolic syndrome. The clinical approach uses waist circumference rather than BMI to define the adipose mass component contributing to metabolic syndrome because BMI has been shown to be a relatively insensitive indicator of the risk for obesity-associated metabolic and cardiovascular disease. Waist circumference, but not BMI, reflects abdominal subcutaneous adipose tissue, as well as abdominal visceral adipose tissue, and is therefore a better index of central, or truncal, fat mass.

In the United States, nearly 50 million people have metabolic syndrome, for an age-adjusted prevalence of almost 24%. Of such people, more than 83% meet the criterion of abdominal obesity. The incidence of metabolic syndrome increases with age, with more than 40% of the U.S. population affected by the age of 60 years.[15] Men are affected more commonly than women, and Hispanics and south Asians appear to be particularly susceptible. Its frequency is lower in African American than in white men. Metabolic syndrome may result from the use of some commonly prescribed drugs, including corticosteroids, antidepressants, and antipsychotic agents. The protease inhibitors used to treat human immunodeficiency virus infection can induce metabolic syndrome secondary to insulin resistance.

Table 64-3 Health Risks Associated with Increasing Body Mass Index

Metabolic syndrome	30% of middle-aged people in developed countries have features of metabolic syndrome
Type 2 diabetes	90% of type 2 diabetics have a BMI > 23 kg/m^2
Hypertension	5× the risk with obesity 66% of hypertension is linked to excess weight 85% of hypertension is associated with a BMI >25 kg/m^2
Coronary artery disease and stroke	3.6× the risk for coronary artery disease for each unit change in BMI Dyslipidemia progressively develops as BMI increases from 21 kg/m^2 with a rise in small-particle low-density lipoprotein 70% of obese women with hypertension have left ventricular hypertrophy Obesity is a contributing factor to cardiac failure in >10% of patients Overweight/obesity plus hypertension is associated with an increased risk for ischemic stroke
Respiratory effects	Neck circumference >43 cm in men and >40.5 cm in women is associated with obstructive sleep apnea, daytime somnolence, and development of pulmonary hypertension
Cancer	10% of all cancer deaths among nonsmokers are related to obesity (30% of endometrial cancers)
Reproductive function	6% of primary infertility in women is attributable to obesity Impotency and infertility are frequently associated with obesity in men
Osteoarthritis	Frequent association in the elderly with increasing body weight—the risk of disability attributable to osteoarthritis is equal to that for heart disease and greater than that for any other medical disorder of the elderly
Liver and gallbladder disease	Overweight and obesity are associated with nonalcoholic fatty liver disease and NASH; 40% of NASH patients are obese and 20% have dyslipidemia 3× the risk for gallbladder disease in women with a BMI >32 kg/m^2; 7× the risk if the BMI >45 kg/m^2

BMI, body mass index; NASH, nonalcoholic steatohepatitis.

Patients with metabolic syndrome have a higher risk for cardiovascular disease and are at increased risk for all-cause mortality. Metabolic syndrome increases the risk for type 2 diabetes, which itself is an important risk factor for atherosclerotic disease and may be considered a coronary heart disease equivalent.[9,15] Metabolic syndrome is also associated with a variety of other conditions, such as polycystic ovary syndrome, nonalcoholic fatty liver disease, gallstones, sleep disturbances, sexual impotence, and some forms of cancer, thus giving it considerable overlap with obesity for the comorbid states detailed in Table 64-3.

Inflammatory processes appear to play an important role in the metabolic syndrome.[12] Adipose tissue has two major functions: storage and release of energy-rich fatty acids and secretion of proteins required for endocrine and autocrine regulation of energy metabolism. Adipocytes exert their metabolic effects by release of free fatty acids, which is enhanced by the presence of catecholamines, release of glucocorticoids, increased β-agonist receptor activity, and reduction of lipid storage mediated by insulin. Visceral adipose tissue has been identified as an important source of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), as well as anti-inflammatory cytokines such as adiponectin. Increased levels of proinflammatory cytokines probably contribute to the cause of insulin resistance. This works primarily by obstructing insulin signaling and contributing to downregulation of peroxisomal proliferator–activated receptor-γ—fundamentally important regulators of adipocyte differentiation and control. Additionally, insulin resistance may promote inflammation through diminution of insulin's anti-inflammatory effects. Finally, oxidative stress is increased with obesity, largely as a result of excessive intake of macronutrients and a concomitant increase in metabolic rate. These factors may also contribute to the inflammatory response noted with obesity.[12]

Cytokines (primarily IL-6 and TNF-α) and adipokines (leptin, adiponectin, adipose-derived resistin) are the two major groups of inflammatory proteins produced and released by adipose and adipose-associated tissue.[12] Serum and adipose tissue obtained from obese subjects consistently have elevated levels of IL-6 and TNF-α, and circulating levels of IL-6 are consistently increased in individuals with type 2 diabetes or impaired glucose tolerance. Proteins such as leptin and adiponectin, which are produced mainly by adipocytes, are classified as adipokines.

Box 64-1 Features Associated with Metabolic Syndrome

Abdominal obesity

Atherogenic dyslipidemia (TGs, ↓ HDL-C, ApoB, small LDL particles)

Elevated blood pressure

Insulin resistance with or without glucose intolerance

Proinflammatory state (hsCRP)

Prothrombotic state (PAI-1, ↓ FIB)

Other (endothelial dysfunction, microabuminuria, polycystic ovary syndrome, hypoandrogenism, nonalcoholic fatty liver disease, hyperuricemia)

ApoB, apolipoprotein B; FIB, fibrinogen; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PAI, plasminogen activator inhibitor; TGs, triglycerides.

Table 64-4 Clinical Criteria for Diagnosing Metabolic Syndrome*

Criteria	Defining Value
Abdominal obesity	Waist circumference >102 cm in men and >88 cm in women
Triglycerides	≥150 mg/dL
High-density lipoprotein cholesterol	<40 mg/dL in men and <50 mg/dL in women
Blood pressure	≥130/85 mm Hg
Fasting glucose	≥110 mg/dL

*Three of five criteria must be met.

Although leptin is primarily involved in appetite control, its immunologic effects include protection of T lymphocytes from apoptosis and regulation of T-cell activation and proliferation. Reduced leptin levels may increase appetite and slow metabolism, but it may also increase susceptibility to the toxicity of proinflammatory stimuli such as endotoxin and TNF-α. High levels of leptin are proinflammatory, which probably plays an important role in the progression of heart disease and diabetes, especially in obese patients. Serum levels of adiponectin, another adipokine, correlate with insulin sensitivity and do not rise in obesity. Significantly reduced adiponectin levels are found in patients with type 2 diabetes. Adiponectin reduces both TNF-α production and activity. It also inhibits IL-6 production. Resistin, an adipokine that causes insulin resistance, is induced by endotoxin and cytokines. Resistin acts at the cellular level to upregulate the production of pro-inflammatory cytokines, most likely through the nuclear factor κB (NFκB) pathway. Resistin appears to represent a molecular link between metabolic signaling, inflammatory processes, and the development of cardiovascular disease. Increased resistin levels have been associated with inflammatory markers in humans, apparently independent of BMI.[12]

An understanding of the role of NFκB in insulin resistance is required to fully appreciate the link between obesity and inflammation. Free fatty acids and TNF-α act via intracellular inflammatory cascade pathways to arrest insulin signaling. This process is mediated by activation of transcription factors present within the cell cytoplasm. After translocation to the nucleus, they eventually bind to transcription factors regulating the inflammatory process. The cytoplasm also contains NFκB, another transcription factor whose activation is implicated in a number of diseases, including diabetes. NFκB is also induced by hypoxia, and it increases production of the proinflammatory cytokines TNF-α and IL-6, both of which are frequently increased in patients with OSA syndrome.[12] Hence, inflammation provides the common linkage underlying the association between obesity, metabolic syndrome, and OSA.[16]

Obstructive Sleep Apnea/Hypopnea Syndrome

OSA and obstructive sleep hypopnea are related conditions characterized by recurrent episodes of upper airway obstruction occurring during sleep (see Chapter 34).[17] OSA is defined as complete cessation of airflow during breathing lasting 10 seconds or longer despite maintenance of neuromuscular ventilatory effort and occurring five or more times per hour of sleep, accompanied by a decrease of at least 4% in Sao_2. Obstructive sleep hypopnea is defined as partial reduction of airflow of greater than 50% lasting at least 10 seconds, occurring 15 or more times per hour of sleep, and accompanied by a decrease of at least 4% in Sao_2. The diagnosis can be made only in patients who undergo polysomnography, or a sleep study, during which the patient's electroencephalogram, electrocardiogram, electro-oculogram, capnogram, nasal or oral airflow, esophageal pressure, blood pressure, pharyngeal and extremity electromyelograms, pulse oximetry, and room noise are typically monitored and recorded.[17] The results of polysomnography are reported as the apnea/hypopnea index (AHI), which is derived from the total number of episodes of apnea and hypopnea divided by the total sleep time. A normal lower limit for AHI has not yet been defined in an epidemiologic study of healthy subjects. Most sleep centers commonly use an AHI of between 5 and 10 events per hour as a normal limit. The severity of obstructive sleep apnea/hypopnea syndrome (OSAHS) is defined arbitrarily, but a recent recommendation for classification of the disease is as follows[17]:

Mild disease—AHI of 5 to 15 events per hour
Moderate disease—AHI of 15 to 30 events per hour
Severe disease—AHI of greater than 30 events per hour

Because of risk for the development of systemic and pulmonary hypertension, left ventricular hypertrophy, cardiac arrhythmias, cognitive impairment, persistent daytime somnolence, and other conditions, treatment is recommended for patients with moderate or severe disease. Treatment depends partly on the severity of the sleep-disordered breathing, but the consensus is that patients with moderate or severe apnea should be treated with continuous positive airway pressure (CPAP) during sleep. Other conservative measures may include weight loss, avoidance of alcohol before bedtime, and sleeping on one's side.

Numerous studies have confirmed that obesity is the greatest risk factor for OSAHS, and about 70% of patients (up to 80% of males and 50% of females) with OSAHS are obese. Severe sleep apnea is more common in men, and a strong negative correlation between AHI and the minimum Sao_2 has been observed. Importantly, the diagnosis of OSAHS may be missed until the patient undergoes surgery. In a study of 170 patients about to undergo surgery, in which only 15% had sleep apnea previously been diagnosed, preoperative testing demonstrated that 76% were found to have OSAHS.[18] We believe that it is important that obese patients scheduled for bariatric surgery undergo preoperative polysomnographic testing for OSAHS. Preoperative diagnosis and appropriate interventional management can have the following benefits: less postoperative sleep deprivation, improved response to analgesic and anesthetic drugs, and normalization of cardiovascular disturbances.[19]

Anatomically, obese patients with OSAHS typically have increased amounts of adipose tissue in their oral and pharyngeal tissues, including the uvula, tonsils, tonsillar pillars, tongue, aryepiglottic folds, and lateral pharyngeal walls. An inverse relationship exists between the degree of obesity and pharyngeal area. Deposition of fat in the lateral walls decreases the size of the airway and changes the shape of the oropharynx into an ellipse with a short transverse and long anteroposterior axis.[20-22] This can contribute to the development and severity of airway obstruction and also increase the probability that it will be more difficult to maintain airway patency during mask ventilation and perform direct laryngoscopy for endotracheal intubation with general anesthesia.[23,24] Additionally, airway obstruction after extubation is likely to be complicated by the use of opiate and sedative drugs needed for postoperative pain management because such medications tend to decrease pharyngeal dilator tone and increase the likelihood of upper airway collapse.[23]

OSA also plays an important role in inflammation and the metabolic syndrome.[12,16] The hypopneic and apneic events that occur in OSAHS are part of a cycle of events that involves arousal from random eye movement (REM) sleep and oxyhemoglobin desaturation. The sympathetic nervous system is activated as patients with untreated OSA undergo cyclic episodes of hypoxia

and reoxygenation; such activation leads to elevated levels of proinflammatory cytokines and potentially oxidative stress of vascular endothelium, which induces an even more heightened state of systemic inflammation in obese patients with OSA.[16] Levels of many different inflammatory mediators, including IL-6, C-reactive protein, leptin, TNF-α, IL-1, reactive oxygen species, and adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), are increased in patients with OSAHS.[12] Thus, obesity, metabolic syndrome, and OSAHS are interrelated diseases that significantly alter a patient's inflammatory disease profile and result in multiple health risks, particularly those of cardiovascular- and airway-related origin.

Nonsurgical Management of Obesity

The primary goals of nonsurgical management of obesity involve weight loss, treatment of the abnormalities associated with metabolic syndrome, and prevention of events related to type 2 diabetes and cardiovascular disease. Treatment of metabolic syndrome needs to follow an aggressive, multifaceted approach to simultaneously address multiple underlying metabolic abnormalities and coexistent risk factors.[15] An appropriate initial treatment of obesity and metabolic syndrome is therapeutic lifestyle change, including dietary modification, weight loss, physical activity, and potentially discontinuation of smoking. The goal of treatment is improved health, which is the primary reason for advocating weight loss. It is therefore important to monitor the effects of treatment on risk factors and comorbid conditions. Success of treatment should be reflected in a decreased need to treat other coexisting diseases.

The goal of weight loss in therapeutic lifestyle change is not to achieve normal or ideal body weight (IBW). Even modest weight loss, in the range of 5% to 10%, can result in significant initial improvement in the comorbid conditions of diabetes, dyslipidemia, and hypertension by lowering total cholesterol and triglyceride levels, raising HDL cholesterol (HDL-C), lowering blood pressure and blood glucose, and reducing insulin resistance.[15,25] Guidelines for the management of obesity stress the need for weight reduction via behavioral change to reduce caloric intake and increase physical activity. Reduced-energy diets are more effective and more healthful for achieving long-term weight loss. Long-term maintenance of any weight loss achieved is best accomplished with the inclusion of regular exercise as a staple of the weight reduction regimen. Regular physical exercise improves several risk factors associated with obesity and metabolic syndrome.[26] The standard recommendation for exercise is a daily minimum of 30 minutes of moderate-intensity physical activity that is practical to perform. Larger weight loss goals are more appropriate for the more profoundly obese individuals who are contemplating surgical interventions. Even with surgery, IBW is hardly ever achieved, and after a number of years at a plateau, weight gain often recurs. In some patients, especially in the presence of severe comorbid conditions, simple prevention of additional weight gain may be the most reasonable goal.

Beyond the beneficial effects of therapeutic lifestyle change, specific intervention may be required to treat the dyslipidemia and hypertension associated with obesity and metabolic syndrome.[27] Most commonly, patients with metabolic syndrome have elevated triglyceride levels and low HDL-C levels. Many patients receive statin therapy as the treatment of choice when low-density lipoprotein cholesterol (LDL-C) levels are excessive. Statins have been shown to reduce the risk for cardiovascular disease in patients with type 2 diabetes and metabolic syndrome. Ezetimibe, which selectively inhibits intestinal absorption of cholesterol, can be combined with statin therapy to further reduce LDL-C by 15% to 20%. Fibrates effectively decrease triglyceride levels while increasing HDL-C. Fibrates lower LDL-C levels mildly, but when combined with statin therapy, fibrates may increase the risk for myopathy. Omega-3 fatty acids decrease triglyceride levels and improve insulin resistance in patients with metabolic syndrome. They are often used in combination therapy with other classes of hypolipidemic drugs. Nicotinic acid is highly effective in raising HDL-C levels in patients with metabolic syndrome. Nicotinic acid decreases the concentration of small, dense LDL particles and also lowers serum levels of lipoprotein(a).[27]

Dietary salt restriction and therapeutic lifestyle changes are the primary means of addressing hypertension in obesity and metabolic syndrome. Patients with blood pressure higher than 140/90 mm Hg require antihypertensive drug therapy. There is no specific antihypertensive agent that is recommended as a first-line treatment in these patients, and generally, achievement of the goal of antihypertensive therapy requires the use of polypharmacy. A considerable amount of the reduction in risk with antihypertensive therapy results solely from lowering of blood pressure.

Treatment of insulin resistance and hyperglycemia in patients with metabolic syndrome, type 2 diabetes, and obesity is usually achieved with oral hypoglycemic agents.[27] A number of different drug groups (and drugs within each group) that work through various mechanisms of action are available to treat hyperglycemia. Such drugs include α-glucosidase inhibitors, sulfonylureas, meglitinides, D-phenylalanine derivatives, diguanides, and thiazolidinediones.[27] Anesthetic implications include the need to assess and treat abnormal blood glucose levels in the perioperative period while being especially careful in the use of insulin in patients who are insulin resistant and temporarily unable to continue oral medication. Presently, there is considerable uncertainty regarding the anesthetic management of patients who are taking metformin because of the potential for the postoperative development of lactic acidosis. This has led some physicians to routinely cancel or delay surgical procedures if metformin has been ingested within 48 hours of scheduled surgery. Some physicians, however, continue metformin administration, before and after surgery, without interruption if possible. Recent evidence indicates that patients taking metformin have a reduced risk for complications. It thus appears that metformin may be used safely in the perioperative period.[28]

Patients with metabolic syndrome and obesity may also be prescribed antiplatelet therapy. The American Heart Association presently recommends that low-dose aspirin be used as a form of primary prevention in patients with metabolic syndrome whose 10-year risk for cardiovascular disease is 10% or greater as determined by Framingham risk scoring.

Behavioral Modification and Interventions

Behavioral interventions and behavioral modification are essential for obese patients to change their learned habits regarding

eating and physical activity so that they can achieve weight loss and maintain long-term weight reduction.[27] The key features of typical behavioral programs include self-monitoring, goal setting, nutrition and exercise education, stimulus control, problem solving, cognitive restructuring, and prevention of relapse. Patients often benefit from referral to multidisciplinary weight loss programs that incorporate diet, physical activity, and behavioral interventions to achieve their weight loss goals because these combined interventions provide the best weight loss and weight maintenance results without pharmacologic or surgical intervention. However, it is essential to identify patients with eating disorders or major psychiatric disorders so that they can receive the specialized psychiatric and psychological treatment that they require to achieve meaningful weight loss.

Pharmacotherapy for Weight Loss

Recommendations for pharmacotherapy as a treatment of obesity first and foremost stress lifestyle and behavioral modifications as the initial approach to a weight loss program.[27] Patients who do not achieve reasonable weight loss goals through a combination of diet and exercise may be given pharmacotherapy to increase weight loss. Several weight loss drugs have been approved by the Food and Drug Administration (FDA) and are currently prescribed for long-term use. They are typically used as an adjunct to diet and exercise for patients with a BMI of 30 or greater (≥27 for patients with obesity-related risk factors or comorbid diseases). In current practice, there are only two categories of weight loss drugs—appetite suppressants and lipase inhibitors—and only three drugs are approved for the specific indication of weight loss—phentermine, sibutramine, and orlistat.[27] Phentermine, an adrenergic reuptake inhibitor, augments adrenergic signaling within the central nervous system and peripheral tissues. Phentermine decreases appetite and food intake and increases the resting metabolic rate to promote weight loss. Its side effects include tachycardia and hypertension. Sibutramine is an adrenergic and serotoninergic agent that suppresses appetite and increases thermogenesis. Common side effects include hypertension, tachycardia, insomnia, and dry mouth. Sibutramine is relatively contraindicated in patients taking serotonin-selective reuptake inhibitors because of the potentially increased risk for serotonin syndrome. Orlistat, a lipase inhibitor, reversibly binds to lipase and prevents both absorption and digestion of certain dietary fats. Because orlistat also interferes with the absorption of fat-soluble vitamins, patients taking this drug need to be supplemented with the fat-soluble vitamins A, D, E, and K. It has significant gastrointestinal side effects, including diarrhea, steatorrhea, flatulence, fecal incontinence, and oily rectal discharge.

Dietary and Herbal Medications

In 2001, Allison and colleagues[29] reviewed the literature on dietary and herbal medications for weight loss. These agents are marketed as "food supplements" and thus escape the purview of the FDA. Even though these supplements cannot legally claim to treat a disease, they can claim to reduce the risk of contracting a disease.

According to the review, claims for weight loss have been made for multiple products, including chitosan, chromium picolinate, conjugated linoleic acid, ephedra alkaloids (ma huang),[30] and *Garcinia cambogia*.[29] Most of the reports involving these compounds come from poor-quality studies without any randomization, control groups, or blinding, thereby placing in question the efficacy and safety of these compounds. The only studies involving herbals that have consistently demonstrated weight loss involve combinations of ephedrine and caffeine.[31-33] Pharmacologically, this is expected because ephedrine, an adrenergic agonist, is known to be an appetite suppressant and a thermogenic agent. For this reason, ma huang, a natural source of the ephedra alkaloid, is added to most, if not all, dietary supplements marketed for weight loss. Ephedrine's success as a weight loss agent, in combination with caffeine or aspirin (or both), is well established. Unfortunately, multiple cases of cardiac and neurologic sequelae, including hypertension, stroke, seizure, and even death, have been reported,[34] possibly related to the inconsistent doses in the preparations and lack of medical supervision in people consuming these products for weight loss. Consequently, the National Institutes of Health has banned these products from any recommended weight loss regimen.

Implanted Electrical Stimulators

Implantable gastric stimulators are subcutaneously placed, cardiac pacemaker–like devices that stimulate regions along the lesser curvature of the stomach. They have been tried in the last decade and found to have modest weight loss with few side effects.[35,36] These studies have been performed in Europe and trials are ongoing in the United States. One study documented a 25% excess weight loss, improved response to the oral glucose tolerance test, decreases in blood pressure, and an improvement in symptoms of gastroesophageal reflux disease, along with increased parasympathetic drive. No serious side effects were noted in the first 65 patients reported in this study[35] or in the 20 patients in the other.[36] Modification of Ghrelin levels may play a role in the success of these devices.

Surgical Management of Obesity

Adult obesity has the bulk of its roots in childhood obesity. One of the principal predictors of adult obesity is childhood obesity. Large children grow up to be large adults. Unfortunately, pediatric obesity is the most common childhood nutritional disorder in the United States. The significant and increasing prevalence of obesity in the young is one of the tragedies of the current obesity epidemic. The diagnosis of pediatric obesity, however, is commonly made by using BMI, age, and sex-specific clinical growth charts according to a definition promulgated by the Centers for Disease Control and Prevention (CDC).[37] These percentile curves apply to the ages of 2 to 20 years, and because BMI exhibits nonlinear variation during growth, percentile ranges are used. The CDC defines children with a BMI in the 5th to 85th percentile as having "healthy weight." BMI values in the 85th to 95th percentile are "at risk for overweight," whereas those greater than the 95th percentile are classified as "overweight," previously regarded as "overweight" and "obese," respectively. This switch in terminology continues to be a source of confusion. Exceeding the 99th percentile is referred to as extreme pediatric obesity.

Data from the National Health and Nutrition Examination Survey (2003-2004) show that the prevalence of overweight children 2 to 5, 6 to 11, and 12 to 19 years of age is 13.9%, 18.8%, and 17.4%, respectively. There does not appear to be an influence of gender on the prevalence of overweight children older than 6 years. However, in a cohort of children aged 2 to 5 years, girls exhibited a doubling in prevalence during the past 20 years, whereas boys exhibited an increase of only 25%. Developing countries such as Egypt, Algeria, Peru, South Africa, and Jamaica have childhood prevalence rates higher than those in the United States,[38] indicating that adolescent obesity is no longer simply a problem of the "developed world."

Treatment of pediatric obesity is based on the balance of caloric intake and expenditure. Adoption of lifestyle changes is most successful with family intervention and support. The three pillars of success in such treatment are better eating habits, increased physical activity, and decreased sedentary activity.[39] Success involves more than education of the child and family; it also incorporates goal setting, self-monitoring, incentives, and stimulus control. Drugs approved for the treatment of pediatric obesity include orlistat and sibutramine (see the earlier section "Pharmacotherapy for Weight Loss").

Even though less than 1% of all bariatric surgery patients in the United States in 2003 were younger than 20 years,[40] the total number continues to increase. Unfortunately, more and more teenagers are now undergoing weight loss surgery, usually gastric banding, after failing to reduce weight or comorbid conditions in medically supervised and pharmacologically assisted weight loss programs. Although many adult bariatric surgery programs are well qualified to provide safe and effective perioperative care for these patients, they may not be as well equipped to handle the unique metabolic and psychological needs of teenagers. Because of the shorter duration of obesity and fewer age-related comorbid diseases, adolescent patients have a shorter length of hospital stay and lower immediate postoperative mortality than adults do.[40]

Consent is an important issue in this population. Is parental consent for a semi-elective, relatively high-risk procedure appropriate? Does the child really understand the concept of a high risk of death in the month after surgery? These and other such questions need to be addressed in the future but are beyond the scope of this chapter.

The rapid increase in the prevalence of morbid obesity and superobesity, together with the increased risk for early demise within the obese population, has significantly increased the number of bariatric surgical procedures performed annually. The term *bariatric surgery* refers to surgical alteration of the small intestine or stomach with a view toward producing weight loss. It is estimated that more than 175,000 bariatric surgeries were performed in 2006 and that more than 200,000 will be performed in 2008 and beyond. Care of obese patients is not limited to obesity surgery, however, because these patients undergo all types of operations. Nonetheless, the benefits of surgical treatment of obesity now appear to have clear endocrinologic and cardiovascular value for reversing the pathophysiologic effects of metabolic syndrome, type 2 diabetes, and other comorbid diseases of obesity, in addition to providing a mechanical means of enhancing weight loss.[41-47] There are several alternative procedures in bariatric surgery, but the operations all fall into one of two groups: gastric-restrictive procedures and procedures that combine gastric restriction with induction of nutrient malabsorption.[48-57]

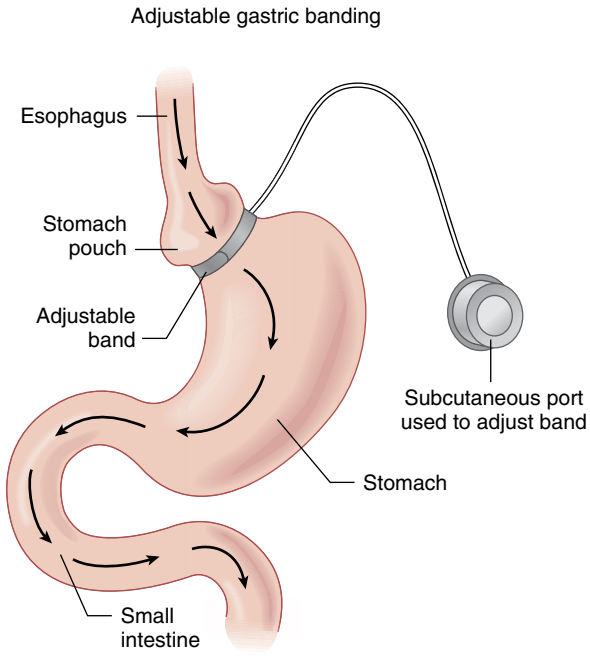

Figure 64-2 Gastric banding. An adjustable band is placed on the stomach. Connected to the band is a piece of tubing with a port at the other end. The port is placed just under the skin. To adjust the tightness of the band, a special needle is inserted in the port. Fluid can be added to the band to make the passageway smaller or remove fluid from the band to make the passageway larger.

Restrictive Procedures

The surgical goal of restrictive operative procedures is to reduce and limit the patient's capacity for intake of food.[54] This goal is most commonly achieved by creating a small pouch from the proximal part of the stomach just distal to the gastroesophageal junction. Construction of the newly created pouch allows it to drain through only a narrow opening. This increases mechanical resistance to gastric emptying of ingested solids, whereas emptying of liquids proceeds normally. Vertical band gastroplasty (VBG) was a widely practiced restrictive procedure in the previous 2 decades, but it has largely been replaced by the minimally invasive laparoscopic gastric band (LGB) procedure (Fig. 64-2). A specific advantage of the LGB procedure is avoidance of permanent alteration of gastric anatomy by tissue stapling. The LGB procedure has an exceptional safety record with exceedingly low operative mortality, although reoperation rates for minor problems are not trivial.[57]

Malabsorptive Procedures

The surgical goal of malabsorptive procedures is to cause weight loss by gastric restriction and malabsorption of nutrients. Historically, early surgical procedures involved the creation of a long jejunoileal bypass. Patients achieved significant weight reduction, but this was commonly accompanied by an unacceptable incidence of serious vitamin and protein malabsorption, osteoporosis, and hepatic failure.

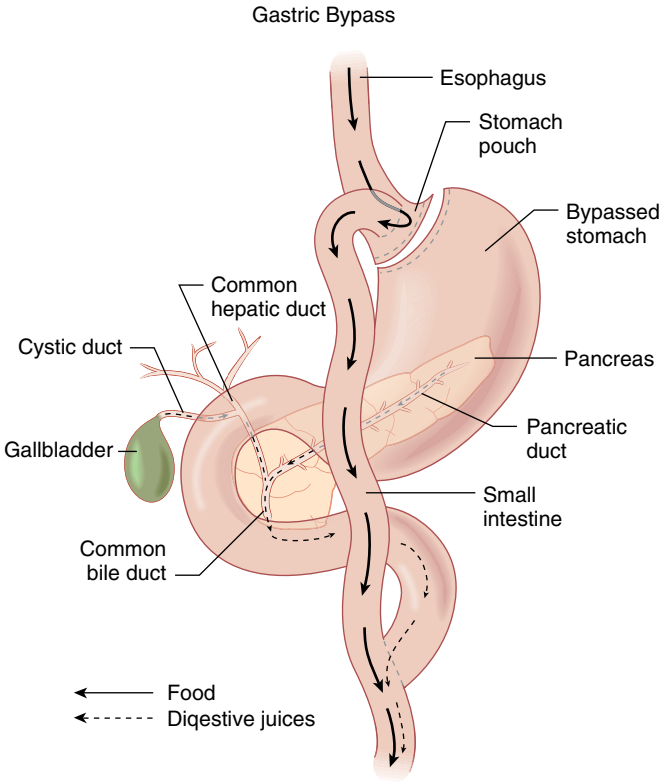

Figure 64-3 Roux-en-Y gastric bypass. Part of the stomach is detached from the rest to create a small pouch. The pouch is connected to a lower part of the small intestine by a piece of small intestine, resembling a Y. As a result, parts of the stomach and small intestine are bypassed. However, digestive juices (bile acids and pancreatic enzymes) can still mix with the food to enable the body to absorb vitamins and minerals, thereby reducing the risk for nutritional deficiencies.

Presently, gastric bypass (GBP) (Fig. 64-3) and biliary pancreatic diversion (BPD) are the two commonly performed malabsorptive operations, and both have been shown to be safe and effective.[54] GBP is performed more commonly than BPD and it is considered the safer of the two malabsorptive procedures. GBP surgery involves the creation of a small gastric pouch by stapling or banding the stomach, which results in an element of gastric restriction. GBP also involves the creation of a Roux-en-Y anastomosis in which the small gastric pouch is directly connected to the middle portion of the jejunum.[58] The path of food through the gastrointestinal tract subsequently bypasses the gastric remnant and the upper portion of the duodenum. This procedure can be performed with a laparotomy incision or by using laparoscopic techniques.[59] Although GBP is considered to be a safe operation, the associated perioperative mortality is higher than that of LGB.[51] Additionally, there are some important long-term complications such as vitamin B_{12} deficiency, anemia, incisional hernia, cholelithiasis, and staple line failure, which occur at significant frequency. Often, a cholecystectomy is performed concurrently to prevent future cholelithiasis.[60] BPD is also a form of Roux-en-Y GBP for reconstructing the alimentary anatomy in which the bypassed intestinal segment includes the portion of duodenum at the point of entry of biliary and pancreatic secretions. This procedure allows the bypassed intestine to be exposed to bile and pancreatic juice. The antrum is removed to avoid peptic ulceration, and food intake is affected to only a limited degree. The essential element of this operation is division of the small intestine about its midlength, with the distal end of the alimentary limb being anastomosed to a generous gastric remnant. The more proximal biliopancreatic limb is anastomosed to the alimentary limb about 50 cm from the ileocecal valve. After either the GBP or BPD form of weight loss surgery, patients require lifelong follow-up and may need long-term micronutrient replacement.

Health Benefits of Bariatric Surgery

The two most significant outcome measures of the success of bariatric surgery are weight loss and resolution of comorbid conditions. The major effects of bariatric operations have been well summarized in two published meta-analyses.[43,61] Absolute weight loss averaged 46.4 kg for BPD, 43.5 kg for GBP, 39.8 kg for VBG, and 28.6 kg for gastric banding. This magnitude of weight loss is far greater than that commonly achievable by nonsurgical methods, and it is considerably closer to patients' desired and expected weight loss. Long-term maintenance of weight loss of this magnitude can also be sustained for well over a decade.

Improvement in the comorbid diseases associated with obesity and metabolic syndrome has also been evaluated.[43,61] Diabetes improved in more than 85% of patients and resolved in more than 75% overall (98.9% for BPD, 87.3% for GBP, 71.6% for VBG, and 47.9% for gastric banding). Resolution of diabetes after surgery is inversely related to the preoperative duration of the disease and occurs more in patients whose diabetes is controlled with oral hypoglycemic agents. This clearly distinguishes surgical treatment of obesity as an important endocrinologic intervention, especially because the modest improvement in diabetes management that is produced by nonsurgical weight loss is accompanied by relapsing disease in nearly 100% of patients within 5 years. Surgical effects on hyperlipidemia are similarly impressive. Approximately 70% of the entire population experienced improvement, with greatest, intermediate, and least change occurring after BPD, GBP, and gastric banding, respectively. Hypertension resolved in more than 60% of patients and improved in more than 18%. Postsurgical effects on hypertension were greatest after BPD (83%), intermediate after GBP (67.5%) and VBG (69%), and least after gastric banding (43%). Resolution of OSAHS seems to be independent of the specific bariatric surgical procedure used, with resolution occurring in 85.7% of patients overall. Postsurgical improvement in other comorbid diseases has also been demonstrated, with improvement in fatty infiltration of the liver, improvement in respiratory function and asthmatic symptoms, reversal of the cardiomyopathy of obesity, and improvement in joint pain and mobility all having been reported.[47,62-66]

Anesthetic Management of Bariatric Surgical Patients

Preoperative Evaluation

The preoperative assessment for anesthesia should include consideration of hypertension, diabetes, heart failure, and obesity-

hypoventilation syndrome. The results of the sleep study that the patient underwent are important. An AHI score greater than 30, implying severe sleep apnea, is a warning sign and a predictor for rapid and severe desaturation at induction. CPAP levels greater than 10 imply a patient with the potential for difficult mask ventilation.

Another useful piece of information in the preoperative evaluation is gleaned by examining the history of previous surgeries, their anesthetic challenges (i.e., ease or difficulty in securing the airway, intravenous access), need for ICU admission, surgical outcomes, and the weight of the patient at that time. This information may help ease some concerns or allow us to better prepare for the upcoming anesthetic care. Recommended preoperative laboratory evaluations include fasting blood glucose, lipid profile, serum chemistries (to evaluate renal and hepatic function), complete blood count, ferritin, vitamin B_{12}, thyrotropin, and 25-hydroxyvitamin D.

If appropriately evaluated, ideally prepared, and optimally managed perioperatively, even patients with known coronary artery disease (CAD) have comparable morbidity and mortality to those without CAD.[67] The effect of OSA on perioperative risk remains controversial,[68] but most patients are screened for OSA by means of overnight oximetry or polysomnography, or both, if appropriate. If identified with OSA and CPAP is recommended, patients are encouraged to initiate therapy at home, and it should be continued throughout the perioperative period.

Liver function abnormalities are common in this patient population, especially nonalcoholic fatty liver disease, with the extent of disease being a determining factor for perioperative risk and postoperative outcomes. Cirrhotic liver disease with portal hypertension may be considered a contraindication to bariatric surgery.[68] Gastrointestinal symptoms of dyspepsia may indicate the presence of *Helicobacter pylori*, which requires treatment by the standard medical regimen.

Factors that may be considered contraindications to bariatric surgery include unstable CAD, uncontrolled severe OSA, uncontrolled psychiatric disorder, mental retardation (IQ < 60), inability to understand the surgery, perceived inability to adhere to postoperative restrictions, continued drug abuse, and malignancy with a poor 5-year survival prognosis. In most situations, preoperative management of any medical morbidity can help optimize risk and convert high-risk patients to ones with acceptable risk.

The anesthetic care of patients with OSA is complicated by the side effects of anesthetic drugs on an already compromised respiratory system. The commonly present comorbid conditions in this patient population accentuate the problem.[69,70] The change in perioperative risk based on the anesthetic agent used has been deduced only from anecdotal reports of different cases. There has been a paucity of trials to definitively answer that question. The question that commonly arises and cannot yet be answered on the basis of scientific evidence involves the safety of outpatient procedures in patients with sleep apnea. What procedures pose sufficient risk to the patient to recommend an overnight hospital stay? Does narcotic use affect this decision? Would the increased role of nonsteroidal anti-inflammatory drugs change these recommendations? Factors such as neck size and open versus laparoscopic surgery are being studied regarding their impact on outcomes. Further research on these questions is ongoing.

Intraoperative Care

Obese patients present special challenges for the anesthesiologist in airway management, positioning, monitoring, choice of anesthetic technique and anesthetic agents, pain control, and fluid management. Many of these issues are equally important in their postoperative care. The most significant and best studied are airway management, including endotracheal intubation, pulmonary physiology, and techniques of maintaining adequate blood oxygenation and lung volume. Specific interventions, techniques, and approaches used by the anesthesia care team providing anesthesia for obese patients are important determinants of outcome.

Patient Positioning (also see Chapter 36)

Despite the lack of evidence-based studies demonstrating that obese patients have more frequent complications from positioning, it seems fairly intuitive that morbidly obese patients do require extra care in positioning. Even in the supine position, rhabdomyolysis from pressure on the gluteal muscles leading to renal failure[71] and death[72] has been reported. For obese patients placed in the prone position, cushioning gel pads or other weight-bearing rolls may have excessive weight placed on them. Pressure points must be checked carefully, and even though pressure sites may be carefully padded, skin breakdown can still occur. This may cause tissue necrosis and infections, especially with lengthy surgery.[73] It is difficult to protect the dependent hip from pressure effects when patients are placed in the lateral decubitus position. Obese patients have excess axillary tissue, which may make it impossible or unnecessary to place a traditional axillary roll in this position. In the lithotomy position, the challenge may be in supporting the weight of the patient's legs with regular, not oversized stirrups. To minimize the risk of tissue compression injury or the development of compartment syndrome, the duration during which the legs are held in stirrups should be kept as short as possible.[74]

Airway Management (also see Chapter 50)

A critical issue is positioning of an obese individual for laryngoscopy and endotracheal intubation. These procedures are often considered to be much more difficult to perform in obese patients than in patients with a normal BMI. Difficulty with laryngoscopy and intubation is usually thought to result from the obese patient having a short, thick neck, large tongue, and significant redundant pharyngeal soft tissue. However, the correlation between morbid obesity and difficult laryngoscopy and intubation is not universally observed in clinical practice. It is possible that no difference exists between laryngoscopy and intubation in thin and obese patients if one follows the simple, but important, approach to clinical care of paying careful attention to patient positioning before induction of general anesthesia. Appropriate positioning plays an important role in providing optimal conditions for successful placement of the endotracheal tube under direct vision.

A number of studies have been conducted to determine the incidence of difficult laryngoscopy or intubation in the obese

population, with mixed findings. One study found an association between oropharyngeal Mallampati classification and BMI as a predictor of difficult laryngoscopy.[75] During laryngoscopy, patients' heads were placed in the optimum sniffing position, regardless of BMI. In a study conducted exclusively with obese patients, BMI was not found to be associated with intubation difficulties.[24] A high Mallampati score was identified as a predictor of "potential intubation problems," but intubation by direct laryngoscopy was successful in 99 of 100 patients studied. All patients were positioned with pillows or towels under their shoulders, the head elevated, and the neck extended. Another group studied both lean and obese patients and found a Mallampati score of III or IV to be the only independent risk factor for difficult intubation in the obese group.[76] The authors demonstrated that the Mallampati score had low specificity and low positive predictive value (62% and 29%, respectively) for difficult intubation. They concluded that intubation was more difficult in obese patients. During intubation, patients were placed in a semirecumbent position (30-degree elevation) with the head in the sniffing position. In another study, ultrasound was used to quantify the amount of soft tissue between the skin and the anterior aspect of the trachea at the level of the vocal cords.[77] The authors also assessed the airway by measurement of the thyromental distance, mouth opening, degree of neck mobility, Mallampati score, neck circumference, and the presence of OSA. Only an abundance of pretracheal soft tissue measured ultrasonically and neck circumferences were found to be positive predictors of difficult intubation with laryngoscopy performed with patients in the sniffing position. A meta-analysis of 35 studies was conducted to determine the diagnostic accuracy of preinduction tests for predicting difficult intubation in patients with no airway pathology.[78] The incidence of difficult intubation in obese patients was three times the incidence in the nonobese population. This may have resulted from suboptimal patient positioning, which was not clearly described in any of the preceding studies, including ramped positioning or elevating the upper body and head of morbidly obese patients to align the ear with the sternum horizontally, as has been shown to improve the laryngoscopic view.[79] Collins and colleagues studied morbidly obese patients who were assigned to be placed in a sniffing position or in a ramped position for airway management. The study demonstrated a statistically significant difference in laryngeal view, with the ramped position providing the superior view.

Based on the evidence from randomized controlled trials and other literature on the airway management of obese patients, patients should be readily intubated by direct laryngoscopy if placed carefully in the ramped position. Obese patients must be examined for the common objective signs of potential difficult intubation, which include small mouth opening, large protuberant teeth, limited neck mobility, and retrognathia. Alternative airway management techniques such as awake, topicalized direct laryngoscopy with modest sedation can be used to assess the laryngoscopic view when deciding whether to proceed with induction of general anesthesia or awake, sedated fiberoptic intubation. Of course, the equipment for emergency airway management, including laryngeal masks and a fiberoptic bronchoscope, should be immediately available.

Another area that requires specific attention during the perioperative period is the obese patient's pulmonary physiology. It is especially important to appreciate techniques to maintain oxygenation and lung volume when caring for an obese patient. First, obese patients have multiple pulmonary abnormalities, including decreased vital capacity, inspiratory capacity, expiratory reserve volume, and functional residual capacity. Second, closing capacity in obese individuals is close to or may fall within tidal breathing, particularly in the supine or recumbent position. As a result of the underlying physiology, an obese patient is likely to undergo rapid oxygen desaturation, especially during periods of apnea such as occurs during induction of general anesthesia. Patients may also continue to derecruit gas exchange units throughout the anesthetic course.[80] A variety of maneuvers have been studied in an attempt to preserve oxygenation and maintain lung volume specifically in the obese population.

In one study of the rate of development of hypoxemia in patients during apnea, patients received 100% oxygen by facemask to achieve denitrogenation before induction of general anesthesia.[80] The apneic period was continued after induction until Spo_2 fell to 90%. Obese patients reached the end point in less than 3 minutes, whereas it took 6 minutes in patients with a normal BMI. Efforts to prevent the formation of atelectasis and desaturation during induction of general anesthesia in obese individuals include application of CPAP during preoxygenation[81-83] and mask application of positive end-expiratory pressure (PEEP) and mechanical ventilation after induction.[83] Use of 10 cm H_2O CPAP during preoxygenation in the supine position resulted in a higher Pao_2 after intubation and decreased the amount of atelectasis that developed.[81] The combination of CPAP during preoxygenation and PEEP/mechanical ventilation after induction significantly increased the duration of nonhypoxemic apnea from 2 minutes, found in controls not receiving CPAP or PEEP, to 3 minutes. Use of 7.5 cm H_2O CPAP during 3 minutes of preoxygenation while supine, however, did not change the time required for obese patients to desaturate to an Spo_2 of 90%.[82] Preoxygenation using 25-degree head-up (back inclined) as opposed to supine positioning without positive airway pressure did increase the time needed for anesthetized, apneic obese individuals to desaturate to an Spo_2 of 92%.[84] Patients in the head-up position had a significantly higher Pao_2 after preoxygenation, just before induction. The obesity-associated gas exchange defect depended on the waist-to-hip ratio, an index of the distribution of adipose tissue surrounding the thorax.[85] This study further demonstrated that morbidly obese men are more likely than morbidly obese women to have poorer pulmonary gas exchange. In a study conducted to assess the relationship between patient positioning and the development of hypoxemia in obese patients during apnea after induction of anesthesia and intubation, patients were ventilated with a 50% oxygen/50% air mixture for 5 minutes before the ventilator circuit was disconnected.[86] Apnea was continued until the Spo_2 fell to 92%, at which time ventilation was resumed. Patients in the supine position reached the end point in 2 minutes, but it took 30 seconds longer if the supine position with the back elevated 30 degrees was used and 1 minute longer if the 30-degree reverse Trendelenburg position was used. Use of the 30-degree reverse Trendelenburg position in obese patients undergoing bariatric surgery was also shown to reduce the alveolar-to-arterial oxygen difference, as well as to increase total ventilatory compliance and reduce peak and plateau airway pressure when compared with the supine position.[87] Vital capacity has also been shown to decrease to a greater extent under general anesthesia in obese patients than in normal-weight patients.[88]

A variety of intraoperative maneuvers to maintain lung volume and oxygenation have also been studied. Increasing tidal

volume incrementally from 13 to 22 mL/kg in obese patients ventilated under general anesthesia did not improve the gas exchange defect but did increase airway pressure.[89] Use of 10 cm H_2O PEEP has been demonstrated to have a greater effect in obese patients than in normal subjects on improving ventilatory mechanics, increasing Pao_2, and decreasing the alveolar-to-arterial oxygen difference during general anesthesia with neuromuscular blockade.[90] Pneumoperitoneum during laparoscopic procedures increases pulmonary resistance and decreases dynamic lung compliance.[91] During pneumoperitoneum, alterations in body position, tidal volume and respiratory rate had no effect on the alveolar-to-arterial oxygen difference in obese patients.[92] During pneumoperitoneum for laparoscopic bariatric surgery, alveolar recruitment by repeated sustained lung inflation to 50 cm H_2O followed by mechanical ventilation with 12 cm H_2O PEEP has been shown to increase Pao_2 intraoperatively, but at the expense of causing hypotension that required the use of vasopressors.[93] In an attempt to optimize PEEP in obese patients undergoing LGB surgery, a normal functional residual capacity was maintained with 15 ± 1 cm H_2O PEEP. Infusion of intravascular volume expanders was required to prevent PEEP-induced hemodynamic compromise.[94]

In summary, the most favorable patient position or optimal amount of PEEP during preoxygenation, induction of anesthesia, or intraoperatively has not been clearly established for obese patients. Furthermore, the application of noninvasive modes of ventilation, including pressure support and bilevel support delivered by mask for preoxygenation, induction, and maintenance of anesthesia to maintain oxygenation and ventilatory mechanics in obese patients, has not been sufficiently studied. The ideal patient positioning, use of PEEP, and special modes of ventilation just before emergence and extubation to maintain pulmonary function and gas exchange after extubation have not been identified. Currently, there are no published guidelines to address the issues of maintenance of oxygenation and ventilatory mechanics in obese patients undergoing general anesthesia. Accordingly, in view of the airway management issues detailed previously, as well as the oxygenation, lung volume, and ventilatory mechanics issues just described for obese individuals, anesthesia care providers should position patients to achieve the combined goals of providing a superior laryngoscopic view for ease of endotracheal intubation while establishing optimal conditions for oxygenation and preservation of pulmonary mechanical function.

It is the practice at our institution that obese patients initially be placed in a ramped position and then in the reverse Trendelenburg position, if needed, to achieve a 25- to 30-degree incline of the thorax before preoxygenation. Patients are then preoxygenated for 3 to 5 minutes with 100% oxygen delivered under positive pressure. For patients receiving CPAP at home for OSA, we use CPAP or pressure-support ventilation by facemask at a pressure level identical to the patient's home CPAP setting. Otherwise, CPAP of 8 to 10 cm H_2O is appropriate. After induction, it is reasonable to maintain 10 to 12 cm H_2O PEEP intraoperatively, but care must be taken to treat any hypotension that may occur. Finally, if the patient's position must be changed intraoperatively, one must return the patient to the head-up position before emergence and extubation.

In preparation for emergence from anesthesia, the neuromuscular blockade must be fully reversed before the patient is extubated. Given the advent of a pressure-support ventilation mode on many newer models of anesthesia machines, a bariatric patient can be maintained on pressure support during emergence as soon as spontaneous ventilation has resumed. When adequate muscle strength has returned, as demonstrated by sustained tetanus with the nerve stimulator and performance of a 5-second head lift, an awake patient who is following commands can be safely extubated. Pressure support or CPAP can be delivered immediately by mask applied to the face as is done during preoxygenation before induction of anesthesia. A variety of devices are available to provide CPAP during transport of the patient from the operating room. We use CPAP during recovery, especially in patients who are already prescribed CPAP for their OSA.

Anesthetic Drugs and Dosing

Anesthetic drugs such as opioids, propofol, and benzodiazepines are all well known to have exaggerated responses in patients with OSA. They may decrease pharyngeal musculature tone, which is essential in maintaining airway patency.[95,96] Volatile agents are known to diminish the ventilatory response to carbon dioxide in the setting of OSA, at least in children with tonsillar hypertrophy. Another pediatric study showed that spontaneously breathing, intubated children with a history of OSA have depressed ventilation and half have apnea with 0.5 μg/kg of intravenous fentanyl. Although these data are from the pediatric literature, it would be prudent to apply these same principles to obese adult patients until proved otherwise. It therefore becomes attractive to use short-acting drugs and nondepressors of ventilation such as the α_2-agonist dexmedetomidine. This should, at least in theory, speed up the return to baseline respiratory function.[73]

Commonly used anesthetic drugs can be dosed according to total-body weight (TBW) or IBW based on lipid solubility. In the past, IBW was interpreted to mean fat-free weight, thus implying that it could be used as a substitute for lean body weight or more correctly, lean body mass, usually approximated as 120% of IBW. Lean body mass is a good weight approximation to use when dosing hydrophilic medications. As expected, the volume of distribution is changed in obese patients with regard to lipophilic drugs. This is especially true of benzodiazepines and barbiturates, among the commonly used anesthetic drugs. Three exceptions to this rule are digoxin,[97] procainamide,[98] and remifentanil,[99] which even though highly lipophilic, have no relationship between properties of the drug and their volume of distribution.[100] Consequently, dosing of commonly used anesthetic drugs such as propofol, vecuronium, rocuronium, and remifentanil is based on IBW. In contrast, thiopental, midazolam, succinylcholine, atracurium, cisatracurium, fentanyl, and sufentanil should be dosed on the basis of TBW. Another caveat to this recommendation is that maintenance doses of propofol should be based on TBW and, conversely, on IBW for sufentanil.[100] This implies that one can use, based on patient weight, larger amounts of benzodiazepines, fentanyl, or sufentanil, although these drugs are best titrated to the desired clinical effect. Conversely, based on real body weight, smaller amounts of propofol are needed to anesthetize the patient.

With vecuronium or rocuronium, the initial dose should be based on IBW and redoses based on the closely followed state of neuromuscular blockade. Complete blockade in the morbidly obese is necessary not just for surgeons' convenience but also to facilitate mechanical ventilation. The drug chosen is not as important as the state of paralysis.

The choice of volatile agents is based on the physical characteristics of tissue solubility, expressed as blood-gas partition coefficients and fat-blood partition coefficients. Some evidence suggests that desflurane may be the anesthetic of choice because of a more consistent and rapid recovery profile than is seen with sevoflurane and propofol.[101,102] However, a more recent study has suggested that the difference in immediate recovery between sevoflurane and desflurane is not clinically significant.[103]

Even though nitrous oxide provides some analgesic effect and is eliminated rapidly, we prefer to avoid it because of the high oxygen demand in the obese. Its entry into air spaces during short intra-abdominal surgery may not be a significant factor, but in bariatric surgery, especially when done laparoscopically, any increase in bowel gas volume could make a challenging surgical procedure even more difficult for the surgeon.

Induction of Anesthesia

There has been considerable debate regarding obesity, the risk for aspiration of gastric contents, and the need to provide prophylaxis for aspiration.[104] Abdominal bloating or fullness and female sex are associated with delayed gastric emptying of solids and liquids in diabetic patients.[105] Although many obese patients have type 2 diabetes, separate studies of gastroesophageal reflux during anesthesia have not demonstrated body habitus to be a predictor of reflux rates.[106] Gastric fluid volume and pH have been shown to be the same in obese patients who are fasting and in those who have oral intake of up to 300 mL of clear liquid 2 hours before being anesthetized.[107] Obesity itself does not increase the risk for aspiration. However, acid aspiration prophylaxis, including H_2 receptor agonists or proton pump inhibitors, must be considered in patients with identifiable risk for aspiration. Awake fiberoptic intubation may also be considered in such patients.[23]

Based on experience from obstetric practice, there is a body of evidence showing that regional anesthesia, especially epidural and spinal, is safe and feasible in patients with large body habitus.[73] However, regional anesthesia is technically more difficult because of the physical challenge of placing the catheters and the tendency of these catheters to migrate out of the epidural space. Special equipment, in terms of longer needles or special ultrasound probes, may be needed for correct placement of catheters in these patients. Care should be exercised in dosing these catheters because of the increased cephalad spread of the drug and the block as a result of a smaller epidural space than in normal-weight patients.[108,109] The degree of respiratory compromise suffered by obese patients will also be of a larger magnitude than that of normal-weight patients with a high regional block.

There is little evidence suggesting that epidural pain management improves overall outcomes. Because the trend of laparoscopic surgery is increasing at the expense of open laparotomy, this becomes less of an issue. In the morbidly obese who undergo open laparotomy, use of epidural catheters to control pain via a thoracic epidural has the most important benefit of reducing the attenuation in vital capacity postoperatively.[110]

Obesity per se does not require invasive monitoring, so GPB surgery can be performed safely with routine monitoring. Indications for invasive monitoring stem from the comorbid conditions noted in these patients. Because such conditions tend to be present in obese patients needing surgery, the incidence of invasive monitoring in these patients thereby increases.[111] The morbidly obese with serious comorbid diseases such as obesity-hypoventilation syndrome with pulmonary hypertension and cor pulmonale may require a pulmonary artery catheter or intraoperative use of transesophageal echocardiography. The rationale for central venous access may stem from difficulties in peripheral access rather than any other indication. Access should probably be achieved under ultrasound guidance to decrease complications, as well as to increase ease of placement. Similarly, difficulty in noninvasive blood pressure measurements because of body habitus–related difficulty in appropriate cuff placement may be an indication for placement of an arterial catheter. Arterial blood gas analysis may help guide intraoperative ventilation and extubation.

Postoperative pain management in weight loss surgery patients can involve intravenous analgesia via patient-controlled analgesia (PCA) or thoracic epidural analgesia. There are no clear data proving the superiority of one technique over the other, so in many instances, surgical technique, open versus laparoscopic, may help guide that decision. In our practice we tend to reserve epidural analgesia for patients undergoing open GBP. Even with these drawbacks, we have approximately an 80% success rate in supermorbidly obese patients.

Opioid-based PCA with local anesthetic infiltration of the wound and adjunctive non-narcotic medication is a reasonable approach for most patients. Injection of local anesthetic into the incision site before making the incision may result in preemptive analgesia. Adjunctive analgesia with non-narcotic medications, unless contraindicated, will decrease opioid requirements and thereby opioid-induced side effects as well.

Intraoperatively, using the appropriate table for the patient's weight is critical inasmuch as the consequences of having a table not rated for the patient's weight can have serious consequences for the patient and the operating room personnel. It may be useful to keep the patient strapped throughout the period of sedation and sleep. Along with a safety strap, it might also be helpful to apply a bean bag under the patient to keep the patient from sliding off the operating room table.

Thermal management in the operating room is best accomplished with forced-air warmers. Armboards may need extra padding to keep the patient from having the arm and shoulder out of an anatomic position. If the arms are to be tucked by the side of the patient, a wide, well-padded sled may be useful.

Fluid requirements may be greater than predicted, and in even a relatively short, 2- to 3-hour case, 4 to 5 L of crystalloid fluid may be needed to prevent acute tubular necrosis in the kidneys. Hypovolemia, which can cause a protracted prerenal state, can be prevented by appropriate hydration. Retrospective data from the University of Pittsburgh Medical Center suggest that primary acute renal failure after weight loss surgery occurs on the order of 2%. Other predisposing factors are BMI greater than 50 kg/m^2, prolonged surgical time, previous history of renal disease, and intraoperative hypotension.[112]

Postoperative Management

In our practice, we prefer to have bariatric patients stay at the same location consistently after surgery. This practice allows skilled nursing and ancillary care to be provided to patients on a consistent basis. These patients are maintained on their CPAP or

biphasic positive airway pressure machines as much as possible, with monitoring of Spo_2 by pulse oximetry recommended.

If and when patients are found to have a difficult airway, they are labeled at the Hospital of the University of Pennsylvania with an armband for the remainder of their hospital stay. A note by the attending anesthesiologist explaining the difficulty in intubation, as well as the means used to secure the airway in the operating room, is available in the room. In case of an unexpected emergency intubation, for whatever reason, we believe that this extra information is extremely useful to the resuscitation team.

Management of Complications

Bariatric surgery is considered to be very safe, but not without potential complications. In-hospital mortality rates for LGB and open GBP surgery are 0.27% and 0.81%, respectively, a statistically significant difference.[113] Mortality is associated with a need for reoperation during the same hospitalization,[114] with intestinal leakage being a serious complication accounting for a large number of patient deaths.[115] Risk factors also include the comorbid conditions of congestive heart failure and renal failure.

Morbidity occurring during the immediate postoperative in-hospital period typically falls into one of four categories: wound, gastrointestinal, pulmonary, and cardiovascular complications. Complication rates are significantly lower in each category for patients undergoing laparoscopic rather than open procedures and range from 1.35% (wound complications) to 4.52% (gastrointestinal complications) after LGB and from 1.98% (wound complications) to 5.33% (gastrointestinal complications) after open GBP.[113]

The most common complications requiring reoperation include postoperative intra-abdominal bleeding, anastomotic leakage, suture line dehiscence, small bowel obstruction, and deep wound infection (Table 64-5),[115-120] all of which may require a general anesthetic for repeat laparotomy. Despite prophylaxis therapy, deep vein thrombosis or pulmonary embolism can also develop and require an anesthetic for placement of an inferior vena cava filter device.

Table 64-5 Specific and Nonspecific Complications

	All Surgeries	Gastric Banding	Roux-en-Y
Early	Bleeding Infection Dehydration Peritonitis Bowel obstruction Perforation Pneumonia DVT/PE Death	Band slippage Band malfunction Infection at band site	Leak from anastomotic site
Late	Cholelithiasis Cholecystitis Pouch dilation GERD/dysphagia Herniation at the surgical site Nutritional issues Fat-soluble vitamin deficiencies, especially vitamin B_{12}	Anorexia Band slippage Band malfunction Infection at the band site	Small bowel obstruction Marginal ulcers Pancreatitis Stricture

DVT, deep venous thrombosis; GERD, gastroesophageal reflux disease; PE, pulmonary embolism.

In all cases requiring reoperation shortly after the original bariatric procedure, it is prudent to review the anesthesia record. Specific attention should be paid to documentation of the patient's position and the technique used for airway management during the previous anesthesia. Patients may be hypovolemic from blood loss, inadequate hydration, vasodilatation, and insensitive fluid losses associated with fever and infection. It is especially important to consider additional or new risks for aspiration of gastric contents. Aspiration may be due to the presence of postoperative ileus, small bowel obstruction, and surgical creation of a Roux-en-Y gastric bypass limb that excludes the pylorus as an element of protection from reflux of intestinal contents. Decompression of the gastric pouch in patients undergoing surgery to relieve a small bowel obstruction can be achieved with careful introduction of a nasogastric or orogastric tube placed in the OR just before induction of general anesthesia. Since this may increase the risk of violating a fresh, competent anastomotic suture line, communication between the anesthesiologist and surgeon can be pursued to determine the risks/benefits of this maneuver. During laparotomy, any perforation resulting from the attempt to decompress the gastrointestinal tract can be repaired and the nasogastric or orogastric tube can be left in place for continued postoperative drainage.

Depending on the extent of the reoperation, requirement for volume resuscitation or blood transfusion, the degree of peritonitis with an anastomotic leak, and the presence of sepsis or other significant continued risks to health, patients undergoing a reoperation may require prolonged postoperative ventilation. Requirements for postoperative pain management may also be considerably different from those associated with the initial bariatric procedure. In patients who are sufficiently hemodynamically stable immediately before reoperation, an epidural catheter can be placed before induction for pain management as part of the postoperative care. This is especially valuable in obese patients undergoing laparotomy as described elsewhere in this chapter.

A number of potential major complications can also occur and require surgical intervention weeks, months, or even years after a bariatric surgical operation has been performed. Anastomotic strictures or ulcers, ventral hernias, gastrogastric fistulas, and severe reflux disorders requiring additional surgery may develop.[60] Small bowel obstruction may appear weeks after surgery.[119] Patients may desire cosmetic operations to remove excess skin or liposuction procedures to sculpt dysmorphic body areas after significant weight loss. Patients may also require adjustment of a gastric band or pursue band removal. Anesthetic considerations for such patients should include a review of the previous anesthetic record to glean information regarding airway and pain management. The degree of weight loss achieved and the resolution of comorbid diseases, including diabetes, hypertension, and OSA, may significantly alter the approach used in the bariatric operation.

Significant neurologic complications develop in a fraction of patients after GBP surgery,[121-123] including polyneuropathy, polyradiculoneuropathy, myelopathy, encephalopathy, and optic neuropathy. Myelopathy occurs most frequently but is not manifested until about 10 years after surgery.[121] These patients have demonstrable nutritional deficiencies, but except for the vitamin B_{12} and copper deficiencies found in patients with myelopathy, no

specific nutritional profile has been found to correlate with neurologic complications. Although the neurologic symptoms accompanying weight loss surgery are not likely to result in additional surgery, they represent new or additional comorbid conditions that should be fully considered by the anesthesiologist caring for patients who have previously undergone bariatric surgery.

The nutritional and metabolic complications of bariatric surgery also include protein and protein-calorie malnutrition. Patients may have excessive weight loss occurring either too rapidly or beyond the predetermined goals, steatorrhea or severe diarrhea, hypoalbuminemia, marasmus, edema, and hyperphagia.[60,124-126] In cases of severe malnutrition, patients may require enteral or parenteral nutrition therapy. Surgical revision may be required to correct the excessive weight loss and hypoalbuminemia. Under such circumstances, an anesthetic regimen accounting for the decreased drug-binding effects of a low serum albumin level must be considered.

Considerations for Management of Obese Patients Undergoing Nonbariatric Surgery

Few studies have evaluated the importance of morbidity when performing common surgical procedures. A study by Dindo and coworkers[127] evaluated 6336 patients and did not find any difference in the incidence or severity of complications after elective general surgery, except for surgical site infections. Other studies have assessed the effect of obesity on wound infections and have shown that they are increased.[128,129]

Multiple studies had demonstrated that obese patients are at higher risk after gynecologic, orthopedic, cardiovascular, urologic, and transplantation surgery, whereas other studies have not.[130,131]

From the data of Dindo and associates[127] regarding complications and the type of surgical procedure, operative severity and open laparoscopic surgery were independent risk factors for postoperative complications. They found no differences in the type of postoperative complications in obese and nonobese groups. This study provides data to decrease the prejudice that patients with obesity are implied to have a higher incidence of postoperative complications. This preconception may pertain more to the perception of the medical team as a result of technical difficulties on the anesthetic and surgical end. Surgeries may last longer, about 25% more time for laparoscopic than for open cholecystectomy in the morbidly obese. Significantly, the wound infection rate was much better after laparoscopic than after open surgery, which supports the practice of performing laparoscopic surgery in obese patients rather than the alternative.

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65 Anesthesia and the Renal and Genitourinary Systems

Key Points

1. Innervation of the intra-abdominal components of the genitourinary system—the kidney and the ureter—is primarily thoracolumbar (T8-L2). The nerve supply of the pelvic organs—the bladder, the prostate, the seminal vesicles, and the urethra—is primarily lumbosacral with some lower thoracic input.
2. The spinal level of pain conduction for the external genitourinary organs is S2-4 except for the testes (T10-L1).
3. The kidneys receive 15% to 25% of the total cardiac output, with most of this blood directed to the renal cortex. Renal medullary papillae are more vulnerable to ischemic insults. Kidneys successfully autoregulate their blood flow between 60 mm Hg and 160 mm Hg mean arterial pressures.
4. The glomerular filtration rate (GFR) is the best measure of glomerular function. Creatinine clearance is a good measure of the GFR; urine output is not.
5. Hypervolemia, acidemia, hyperkalemia, cardiorespiratory dysfunction, anemia, and bleeding disturbances are manifestations of chronic renal failure.
6. Although renal transplantation reverses most of the abnormalities in end-stage renal disease, dialysis improves only some, and introduces additional complications of its own.
7. Newer techniques, such as laser prostatectomy, are making transurethral resection of the prostate (TURP) syndrome a rare event. TURP syndrome is a constellation of symptoms caused by the absorption of hypotonic bladder irrigants. Cardiovascular and neurologic changes are due to hypo-osmolality, hyponatremia, hyperglycinemia, hyperammonemia, and hypervolemia.
8. Regional anesthesia offers several advantages over general anesthesia for standard, but not laser, TURP, although 30-day mortality rates remain unchanged at 0.2% to 0.8%.
9. Laparoscopic surgery in urology frequently requires insufflation of carbon dioxide into the retroperitoneal space. In lengthy procedures, pneumomediastinum and subcutaneous emphysema of the head and neck may occur.
10. Extracorporeal shock wave lithotripsy (ESWL) is associated with significant physiologic changes related to immersion if a water bath is used. Shock waves can cause arrhythmias and injury to the lungs. Pregnancy and untreated bleeding disorders are contraindications to ESWL.
11. Of renal tumors, 5% to 10% extend into the renal vein, inferior vena cava, and right atrium. Complications ranging from circulatory failure to embolization of tumor during surgery may occur. Cardiopulmonary bypass may be necessary for surgery.
12. Radical prostatectomy is accompanied by significant blood loss. Intraoperative venous air embolism has been reported. Regional anesthesia with spontaneous ventilation is associated with less blood loss than general anesthesia and intermittent positive-pressure ventilation. Other advantages of epidural anesthesia include decreased deep vein thrombosis and preemptive analgesia. Although some studies report better outcomes with epidural anesthesia, others do not.
13. Robotic radical prostatectomy is associated with reduced blood loss and postoperative pain compared with open radical prostatectomy. Anesthetic concerns are related to steep head-down tilt and pneumoperitoneum and include hypercarbia, hypoxemia, increased intraocular and intracranial pressures, decreased perfusion pressure to lower extremity, and positional injuries.

Table 65-1 Pain Conduction Pathways and Spinal Segment Projection of Pain of the Genitourinary System

Organ	Sympathetics, Spinal Segments	Parasympathetics	Spinal Levels of Pain Conduction
Kidney	T8-L1	CN X (vagus)	T10-L1
Ureter	T10-L2	S2-4	T10-L2
Bladder	T11-L2	S2-4	T11-L2 (dome), S2-4 (neck)
Prostate	T11-L2	S2-4	T11-L2, S2-4
Penis	L1 and L2	S2-4	S2-4
Scrotum	NS	NS	S2-4
Testes	T10-L2	NS	T10-L1

NS, not significant for nociceptive function.

Patients requiring anesthesia for renal and genitourinary surgery are frequently at the extremes of age. In addition to the physiologic changes of aging in elderly patients, concomitant cardiovascular and respiratory comorbidity is common. A medical history, physical examination, and appropriate laboratory tests are necessary to evaluate concomitant disease. In pediatric urologic patients, a careful history should exclude other nonurologic congenital lesions.

Urologic procedures are performed mostly on the kidneys, adrenals, ureters, urinary bladder, prostate, urethra, penis, scrotum, testis, and spermatic cord. Because their sensory nerve supply is primarily thoracolumbar and sacral outflow (Table 65-1), these structures are well adapted for regional anesthesia.

Innervation of the Genitourinary System

The parts of the genitourinary system that are in the abdomen receive their nerve supply from the autonomic nervous system by means of sympathetic and parasympathetic pathways. The pelvic urinary organs and genitalia are supplied by somatic and autonomic nerves. Table 65-1 summarizes the pain conduction pathways and spinal levels of the genitourinary system.

Kidney and Abdominal Ureter

Sympathetic nerves to the kidney originate as preganglionic fibers from the eighth thoracic through the first lumbar segments and converge at the celiac plexus and aorticorenal ganglia (Fig. 65-1). Postganglionic fibers to the kidney arise mainly from the celiac and aorticorenal ganglia. Some sympathetic fibers may reach the kidney via the splanchnic nerves. Parasympathetic input is from the vagus nerve.[1] Sympathetic fibers to the ureter originate from the 10th thoracic through the 2nd lumbar segments and synapse with postganglionic fibers in the aorticorenal and superior and inferior hypogastric plexuses. Parasympathetic input is from the second through fourth sacral spinal segments.[1] Nociceptive fibers travel along the sympathetics to the same spinal segments. Pain from the kidney and ureter is referred mainly to the somatic

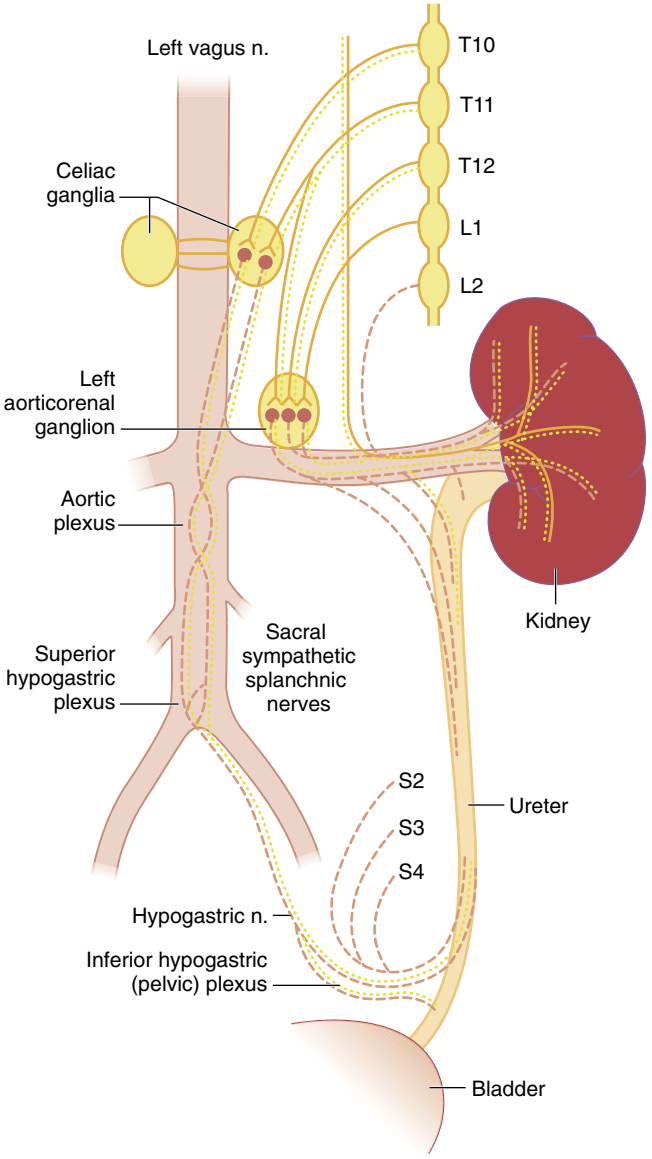

Figure 65-1 Autonomic and sensory innervation of the kidney and ureters. *Solid line* indicates preganglionic fibers; *dashed line* indicates postganglionic fibers; and *dotted line* indicates sensory fibers. *(From Gee WF, Ansell JF: Pelvic and perineal pain of urologic origin.* In *Bonica JJ [ed]: The Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, pp 1368-1378.)*

distribution of the 10th thoracic through the 2nd lumbar segments—the lower part of the back, flank, ilioinguinal region, and scrotum or labia. Effective neural block of these segments is necessary to provide adequate analgesia or anesthesia.

Bladder and Urethra

Sympathetic nerves to the bladder and urethra originate from the 11th thoracic to the 2nd lumbar segments, travel through the superior hypogastric plexus, and supply the bladder through the right and the left hypogastric nerves.[2] Parasympathetic nerves arise from the second through the fourth sacral segments and form the pelvic parasympathetic plexus, which is joined by the hypogastric plexus. Vesical branches proceed toward the bladder base, where they provide the nerve supply to the bladder and proximal part of the urethra (Fig. 65-2). Parasympathetic fibers are the main motor supply to the bladder (with the exception of the trigone) and far outnumber sympathetic fibers in the bladder.[2]

The afferents carrying sensations of stretch and fullness of the bladder are parasympathetic, whereas pain, touch, and temperature sensations are carried by sympathetic nerves. Sympathetic fibers are predominantly α-adrenergic in the bladder base and urethra, and β-adrenergic in the bladder dome and lateral wall. Knowledge of these aspects of neuroanatomy is important to appreciate the pharmacologic effects on the urologic system of neural ablation or regional block and drugs with adrenergic or cholinergic effects.[2]

Prostate and Prostatic Urethra

The prostate and prostatic urethra receive sympathetic and parasympathetic supply from the prostatic plexus arising from the pelvic parasympathetic plexus, which is joined by the hypogastric plexus. The spinal origin of the nerve supply is primarily lumbosacral (see Fig. 65-2).[2]

Penis and Scrotum

The autonomic supply to the penile urethra and the cavernous tissue comes from the prostatic plexus. Somatic fibers from the pudendal nerve (S2-4) supply the external sphincter. The dorsal nerve of the penis, the first branch of the pudendal

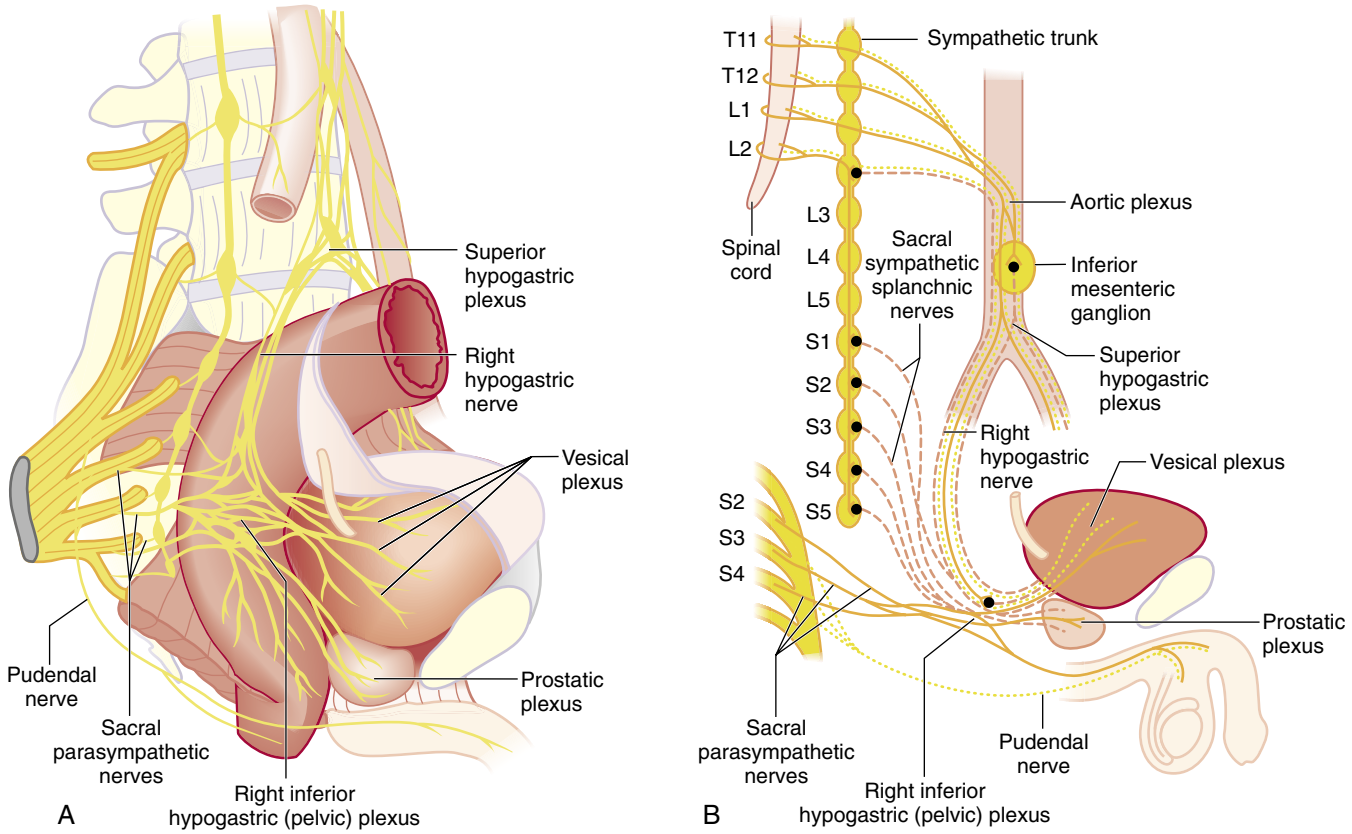

Figure 65-2 **A,** Nerve supply of the urinary bladder and prostate showing the relationship of the various nerve structures to the large intestine and their distribution in the bladder and prostate. **B,** Schematic illustration showing the segmental nerve supply to the bladder, penis, and scrotum. *Solid lines* indicate preganglionic fibers; *dashed lines* indicate postganglionic fibers; and *dotted lines* indicate sensory fibers. *(From Gee WF, Ansell JF: Pelvic and perineal pain of urologic origin.* In *Bonica JJ [ed]: The Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, pp 1368-1378.)*

nerve, is its main sensory supply. The scrotum is innervated anteriorly by the ilioinguinal and genitofemoral nerves (L1 and L2) and posteriorly by perineal branches of the pudendal nerve (S2 and S4).[2]

Testes

The testes descend from their intra-abdominal location to the scrotum during fetal development. Because they share their embryologic origin with the kidney, their nerve supply is similar to that of the kidney and upper part of the ureter and extends up to the T10 spinal segment.[2]

Renal Blood Flow

The kidneys receive approximately 15% to 25% of total cardiac output, or 1 to 1.25 L of blood per minute through the renal arteries, depending on the state of the body. Most of the blood is received by the renal cortex, with only 5% of cardiac output flowing through the renal medulla, which makes the renal papillae vulnerable to ischemic insults. Renal blood flow is regulated by various mechanisms that control the activity of vascular smooth muscle and alter vascular resistance. Sympathetic tone of renal vessels increases during exercise to shunt renal blood flow to exercising skeletal muscle; similarly, renal blood vessels relax during the resting condition of the body. Sympathetic stimulation as a result of surgery can increase vascular resistance and reduce renal blood flow, whereas anesthetics may reduce renal blood flow by decreasing cardiac output.

Glomerular capillaries separate afferent arterioles from efferent arterioles. Glomerular capillaries are high-pressure systems, whereas peritubular capillaries are low-pressure systems. Consequently, the glomerular capillaries are a fluid-filtering system, whereas the peritubular capillaries are a fluid-absorbing system. The vasa recta, a specialized portion of peritubular capillaries formed from efferent arterioles, are important in the formation of concentrated urine by a countercurrent mechanism. An intrinsic mechanism that causes vasodilation and vasoconstriction of renal afferent arterioles regulates the autoregulation of renal blood flow. A decrease in mean arterial pressure also decreases renal blood flow and eventually affects the glomerular filtration rate (GFR) when the pressure decreases to less than 60 mm Hg. A persistently low mean arterial pressure greater than 60 mm Hg affects renal blood flow, but does not affect the GFR because of the intrinsic mechanism of autoregulation (Fig. 65-3). Autoregulation maintains mean arterial pressure between 60 mm Hg and 160 mm Hg in intact and denervated kidneys.[3]

Although knowledge of neuroanatomy and renal blood flow is essential to provide adequate anesthesia, a thorough understanding of renal physiology and pharmacology is equally important. Genitourinary surgical patients frequently have mechanical or functional renal disease. Anesthetics and surgery can significantly alter renal function. Conversely, renal dysfunction significantly affects the pharmacokinetics and pharmacodynamics of anesthetics and adjuvant drugs. Evaluation of a patient with renal disease is discussed later.

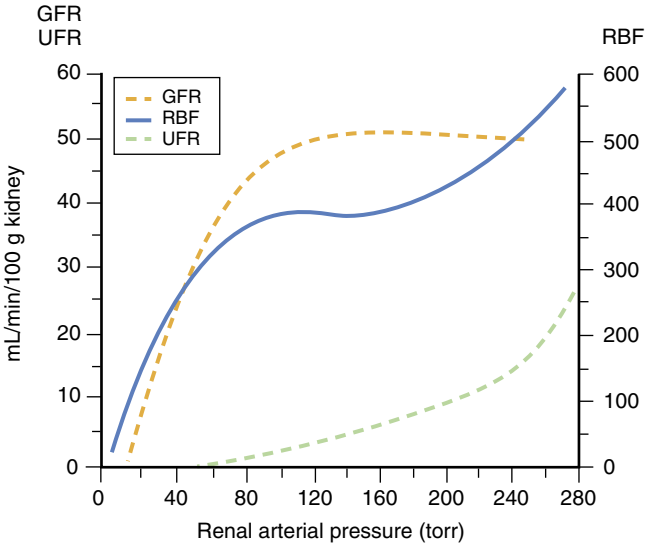

Figure 65-3 Autoregulation of renal blood flow (RBF) and the glomerular filtration rate (GFR). The relationships between RBF, GFR, and urine flow rate (UFR) and mean renal arterial pressure in dogs are shown as renal arterial pressure is varied from 20 to 280 mm Hg. Autoregulation of RBF and GFR is observed between about 80 mm Hg and 180 mm Hg. *(Redrawn from Hemmings HC: Anesthetics, adjuvants and drugs and the kidney.* In *Malhotra V [ed]: Anesthesia for Renal and Genitourinary Surgery. New York, McGraw-Hill, 1996, p 18.)*

Anesthesia for Patients with Renal Disease

Evaluation of Renal Function

Renal disease may be discovered incidentally during a routine medical evaluation, or patients may present with evidence of renal dysfunction, such as hypertension, edema, nausea, and hematuria (see Chapter 18). The initial approach in both situations should be to assess the cause and severity of renal abnormalities. In all cases, this evaluation includes (1) an estimation of disease duration, (2) a careful urinalysis, and (3) an assessment of the GFR. The history and physical examination, although equally important, are variable among renal syndromes; specific symptoms and signs are discussed in sections on each disease entity. Further diagnostic categorization is according to anatomic distribution: prerenal disease, postrenal disease, and intrinsic renal disease. Intrinsic renal disease can be divided further into glomerular, tubular, interstitial, and vascular abnormalities. Laboratory tests useful in evaluating renal function are described next (Table 65-2).

Glomerular Function

Glomerular Filtration Rate

The GFR is the best measure of glomerular function. Normal GFR is approximately 125 mL/min. Manifestations of reduced GFR are not seen, however, until the GFR has decreased to 50% of normal.

Table 65-2 Commonly Ordered Renal Function Tests

Test Name	Reference Range	Units
Urea nitrogen	5-25	mg/dL
Creatinine	0.5-1.5	mg/dL
Sodium	133-147	mmol/L
Potassium	3.2-5.2	mmol/L
Chloride	94-110	mmol/L
CO_2	22-32	mmol/L
Uric acid	2.5-7.5	mg/dL
Calcium	8.5-10.5	mg/dL
Phosphorus	2.2-4.2	mg/dL
Urinalysis, routine		
Color	Straw-amber	
Appearance	Clear-hazy	
Protein	0	mg/dL
Blood	Negative	
Glucose	0	mg/dL
Ketones	0	mg/dL
pH	4.5-8.0	
Specific gravity	1.002-1.030	
Bilirubin	Negative	
Urinalysis, microscopic		
Red blood cells	0-3	per high-power field
White blood cells	0-5	per high-power field
Casts	0-2	per low-power field

From Miller ED Jr: Understanding renal function and its preoperative evaluation. *In* Malhotra V (ed): Anesthesia for Renal and Genitourinary Surgery. New York, McGraw-Hill, 1996, p 9.

When GFR decreases to 30% of normal, a stage of moderate renal insufficiency sets in. Patients remain asymptomatic with only biochemical evidence of a decline in GFR (i.e., an increase in serum concentrations of urea and creatinine). Further workup usually reveals other abnormalities, such as nocturia, anemia, loss of energy, decreasing appetite, and abnormalities in calcium and phosphorus metabolism.

As the GFR decreases further, a stage of severe renal insufficiency begins. This stage is characterized by profound clinical manifestations of uremia and biochemical abnormalities, such as acidemia; volume overload; and neurologic, cardiac, and respiratory manifestations. At the stages of mild and moderate renal insufficiency, intercurrent clinical stress may compromise renal function further and induce signs and symptoms of overt uremia. When the GFR is 5% to 10% of normal, it is called end-stage renal disease (ESRD), and continued survival without renal replacement therapy becomes impossible. Although most clinical abnormalities of corticotropin-releasing factor (CRF) are reversed by renal transplantation, the response to dialysis is quite variable (Table 65-3).

Blood Urea Nitrogen

The blood urea nitrogen (BUN) concentration is not a direct correlate of reduced GFR. BUN is influenced by nonrenal variables, such as exercise, bleeding, steroids, and massive tissue breakdown. The more important factor is that BUN is not elevated in kidney disease until the GFR is reduced to almost 75% of normal.[4]

Creatinine and Creatinine Clearance

Measurements of creatinine provide valuable information regarding general kidney function. Creatinine in serum results from turnover of muscle tissue and depends on daily dietary intake of protein. Normal values are 0.5 to 1.5 mg/100 mL; values of 0.5 to 1 mg/100 mL are present during pregnancy. Creatinine is freely filtered at the glomerulus, and apart from an almost negligible increase in content because of secretion in the distal nephron, it is neither reabsorbed nor secreted. Serum creatinine measurements reflect glomerular function (Fig. 65-4),[4] and creatinine clearance is a specific measure of GFR. Creatinine clearance can be calculated by the following formula derived by Cockcroft-Gault that accounts for age-related decreases in GFR, body weight, and sex:

$$\text{Creatinine clearance}\left(\text{mL/min}\right) = \frac{\left(140-\text{age}\right)\times\text{lean body weight}\left(\text{kg}\right)}{\text{plasma creatinine}\left(\text{mg/dL}\right)\times 72}$$

This value should be multiplied by 0.85 for women because a lower fraction of body weight is composed of muscle.

Because there is such a wide range in normal values, a 50% increase in serum creatinine concentration, indicative of a 50% reduction in GFR, may go undetected unless baseline values are known. Also, excretion of drugs dependent on glomerular filtration may be significantly decreased despite what might seem to be only slightly elevated serum creatinine values (1.5 to

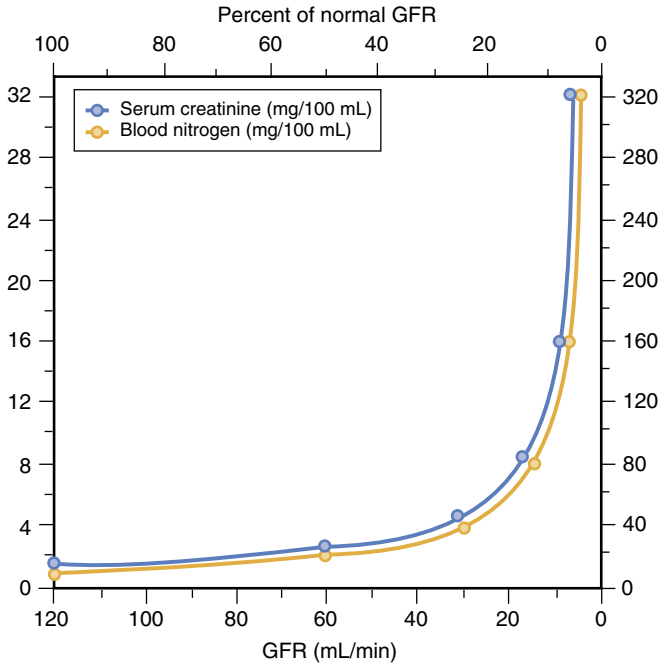

Figure 65-4 Theoretical relationship between blood urea nitrogen and creatinine versus glomerular filtration rate (GFR). *(Redrawn from Kassirer JP: Clinical evaluation of kidney function-glomerular function. N Engl J Med 285:385, 1971.)*

Table 65-3 Clinical Abnormalities in Chronic Renal Failure and Their Response to Dialysis and Erythropoietin Treatment

Improved by Dialysis	Improved by Adding Erythropoietin	Variable Response	Not Improved	Develop after Dialysis Therapy
Volume expansion and contraction	Fatigue Impaired mentation	Secondary hyperparathyroidism	Increased lipoprotein level	Adynamic osteomalacia β_2-Microglobulinemia
Hypernatremia and hyponatremia	Lethargy Pallor	Hyperuricemia Hypertriglyceridemia	Decreased high-density lipoprotein level	Muscle cramps Dialysis dysequilibrium syndrome
Hyperkalemia and hypokalemia	Anemia Bleeding diathesis	Protein-calorie malnutrition	Impaired growth and development	Hypotension and arrhythmias
Metabolic acidosis Hyperphosphatemia Hypocalcemia		Headache Peripheral neuropathy Restless legs syndrome	Infertility and sexual dysfunction	Hepatitis Idiopathic ascites
Vitamin D–deficient osteomalacia		Paralysis Seizures	Amenorrhea Amenorrhea	Peritonitis Leukopenia
Carbohydrate intolerance		Myopathy	Sleep disorders	Hypocomplementemia
Hypothermia		Arterial hypertension	Pruritus	
Asterixis		Cardiomyopathy	Lymphocytopenia	
Muscular irritability Myoclonus		Accelerated atherosclerosis	Splenomegaly and hypersplenism	
Coma		Vascular calcification		
Congestive heart failure or pulmonary edema		Hyperpigmentation Peptic ulcer		
Pericarditis		Gastrointestinal bleeding		
Uremic lung		Increased susceptibility to infection		
Ecchymoses				
Uremic frost				
Anorexia				
Nausea and vomiting				
Uremic fetor				
Gastroenteritis				

2.5 mg/100 mL). The serum creatinine concentration and clearance are better indicators of general kidney function and GFR than similar measurements of urea nitrogen (Table 65-4). There are disease states, however, in which even the serum creatinine may be affected independent of the GFR (Table 65-5).

Table 65-4 Conditions Affecting Blood Urea Nitrogen (BUN) Independently of Glomerular Filtration Rate

Increased BUN
Reduced effective circulating blood volume (prerenal azotemia)
Catabolic states (gastrointestinal bleeding, corticosteroid use)
High-protein diets
Tetracycline
Decreased BUN
Liver disease
Malnutrition
Sickle cell anemia
SIADH

SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Tubular Function

Concentration

Urinary specific gravity is an index of the kidney's concentrating ability, specifically, renal tubular function. Determination of urinary osmolality (i.e., measurement of the number of moles of solute [osmoles] per kilogram of solvent) is a similar, more specific test. Excretion of concentrated urine (specific gravity 1.030; 1050 mOsm/kg) is indicative of excellent tubular function, whereas a urinary osmolality fixed at that of plasma (specific gravity 1.010; 290 mOsm/kg) indicates renal disease. The urinary dilution mechanism persists after concentrating defects are present, so a urinary osmolality of 50 to 100 mOsm/kg still may be consistent with advanced renal disease.

Protein

Patients without renal disease may excrete 150 mg of protein per day; greater amounts may be present after strenuous exercise or after standing for several hours. Massive proteinuria (i.e.,

Table 65-5 Conditions Affecting Serum Creatinine Independently of Glomerular Filtration Rate

Condition	Mechanism
Conditions Causing Elevation	
Ketoacidosis	Noncreatinine chromogen
Cephalothin, cefoxitin	Noncreatinine chromogen
Flucytosine	Noncreatinine chromogen
Other drugs—aspirin, cimetidine, probenecid, trimethoprim	Inhibition of tubular creatinine secretion
Conditions Causing Decrease	
Advanced age	Physiologic decrease in muscle mass
Cachexia	Pathologic decrease in muscle mass
Liver disease	Decreased hepatic creatine synthesis and cachexia

>750 mg/day) is always abnormal and usually indicates severe glomerular damage.

Glucose

Glucose is freely filtered at the glomerulus and is subsequently reabsorbed in the proximal tubule. Glycosuria signifies that the ability of the renal tubules to reabsorb glucose has been exceeded by an abnormally heavy glucose load and is usually indicative of diabetes mellitus. Glycosuria also may be present in hospitalized patients without diabetes who are receiving intravenous glucose infusions.

Additional Diagnostic Tests

Urinalysis and Appearance

Gross and microscopic observation of urine and its sediment, along with determination of urinary pH, specific gravity, protein content, and glucose content, is one of the most readily available, inexpensive, and informative laboratory tests. The gross appearance of urine may indicate the presence of bleeding or infection in the genitourinary tract. Microscopic examination of urinary sediment may reveal casts, bacteria, and various cell forms, supplying diagnostic information in patients with renal disease.

Serum and Urine Electrolytes

pH and Blood Gases. Sodium, potassium, chloride, and bicarbonate concentrations should be determined if impairment in renal function is suspected. The results of these tests usually remain normal until frank renal failure is present, however, and hyperkalemia does not occur until patients are uremic.[5] Measuring urinary sodium or chloride excretion is especially useful when attempting to differentiate between causes of hyponatremia, as seen in volume contraction (whether a decrease in total circulatory volume or a decrease in effective arterial blood volume), versus conditions associated with increased salt loss, such as the syndrome of inappropriate secretion of antidiuretic hormone, salt-losing nephropathy, or adrenal insufficiency.[6] If significant renal disease is present, patients consuming a diet high in animal protein may have metabolic acidosis.

Electrocardiogram. The electrocardiogram (see Chapter 34) reflects the toxic effects of potassium excess more closely than determination of the serum potassium concentration.

Imaging Studies

Computed Tomography Scan of Kidneys. A stone protocol computed tomography (CT) scan of the kidneys, ureter, and bladder has become the study of choice for the detection of kidney stones because of its ability to detect stones of all kinds, including uric acid stones and nonobstructing stones in the ureter. Masses in the kidney can be evaluated using either contrast-enhanced CT or renal ultrasound.[6]

Computed Tomography Angiography. CT angiography is used for the evaluation of renal artery stenosis and is emerging rapidly as a useful study. Although it is comparable to magnetic resonance angiography as a noninvasive tool, it requires the use of iodinated contrast material, which may cause renal dysfunction in patients with chronic kidney disease.[7]

Magnetic Resonance Imaging with Magnetic Resonance Angiography The use of magnetic resonance imaging (MRI) with magnetic resonance angiography has revolutionized the evaluation of renovascular disease. The test is highly sensitive, but tends to overestimate the degree of stenosis. Its accuracy in detecting fibromuscular dysplasia causing renal artery stenosis has not been well validated. MRI also can be used to evaluate renal masses. Its main advantages of MRI are that it is a noninvasive test and does not require iodinated contrast material.

Important Pathophysiologic Manifestations of Chronic Renal Failure (see also Chapter 96)

Hypervolemia

Total-body contents of Na^{++} and H_2O are increased in chronic renal failure (CRF),[4] although this increase may not be clinically apparent until the GFR is reduced to very low levels. Weight gain is usually associated with volume expansion and is offset by the concomitant loss of lean body mass. The combination of loop diuretics with metolazone, which acts by inhibiting the Na-Cl cotransporter of the distal convoluted tubule, can overcome diuretic resistance.

Acidemia

Although urine can be acidified normally in most patients with CRF, these patients have a reduced ability to produce ammonia. In the early stages, the accompanying organic anions are excreted in urine, and the metabolic acidosis is of the non–anion gap variety. With advanced renal failure, a fairly large "anion gap" may develop (to approximately 20 mmol/L), however, with a reciprocal decrease in plasma HCO_3^- concentration. This acidemia is usually corrected by hemodialysis. Although acidemia is well compensated in moderate CRF, patients can become acidemic and hyperkalemic[8] in the postoperative period (Table 65-6).

Table 65-6 Metabolic Acidosis in Chronic Renal Failure

	$Paco_2$ (mm Hg)	pH	HCO_3^- (mEq/L)	K^+ (mEq/L)
Preoperative	32	7.32	17	5
Intraoperative	40	7.25	18	5.3
Postoperative	44	7.21	19	5.6
	48	7.18	19	5.9

The patient is a 36-year-old man with severe diabetic nephropathy and end-stage renal failure undergoing cadaver renal transplantation. Preoperatively, the patient has a chronic metabolic acidosis (HCO_3^- 17 mEq/L) with partial respiratory compensation ($Paco_2$ 32 mm Hg; pH 7.32). Potassium is high normal at 5 mEq/L. Intraoperatively, he is given "standard" mechanical minute ventilation, and with "normal" $Paco_2$ (40 mm Hg), the metabolic acidosis is unmasked (pH 7.25), and potassium increases to 5.3 mEq/L. His trachea is extubated at the end of the procedure, but graft function is sluggish, and the metabolic acidosis remains unchanged. With residual opioid-induced narcosis, moderate CO_2 retention occurs ($Paco_2$ 44 mm Hg and 48 mm Hg), pH decreases further to 7.18, and a dangerous degree of hyperkalemia develops (K^+ 5.9 mEq/L).

Hyperkalemia

The approximate daily filtered load of K^+ is 700 mmol. Most of this filtered load is reabsorbed in tubule segments, and most of the K^+ excreted in the final urine reflects events governing K^+ handling at the level of the cortical collecting tubule and beyond. K^+ excretion in the gastrointestinal tract is augmented in patients with CRF. Hyperkalemia may be precipitated, however, in numerous clinical situations, including protein catabolism, hemolysis, hemorrhage, transfusion of stored red blood cells, metabolic acidosis, and exposure to various medications that inhibit K^+ entry into cells or K^+ secretion in the distal nephron.

Cardiac and Pulmonary Manifestations

Hypertension is a common complication of CRF and ESRD. Because hypervolemia is the major cause of hypertension in uremia, normotension is usually restored by the use of diuretics in predialysis patients or by dialysis in ESRD patients. Despite therapy, patients continue to be hypertensive because of the vasodilators required for the management of overwhelming hyperreninemia. Patients generally have left ventricular hypertrophy and accelerated atherosclerosis (disordered glucose and fat metabolism). Pericarditis can be observed in underdialyzed patients versus patients with CRF who undergo regular dialysis.

A unique form of pulmonary congestion and edema may occur even in the absence of volume overload and is associated with normal or mildly elevated intracardiac and pulmonary capillary wedge pressure. This entity, characterized radiologically by peripheral vascular congestion giving rise to a "butterfly wing" distribution, is due to increased permeability of alveolar capillary membranes. This "low-pressure" pulmonary edema and the cardiopulmonary abnormalities associated with circulatory overload usually respond promptly to vigorous dialysis.[9]

Hematologic Manifestations

CRF usually causes a normochromic, normocytic anemia. Anemia is generally observed when the GFR decreases to less than 30 mL/min and is due to insufficient production of erythropoietin by the diseased kidneys. Other factors are iron deficiency, either related to or independent of blood loss from repeated laboratory testing, blood retention in the dialyzer, or gastrointestinal bleeding.[10] Treatment of anemia with iron, darbepoetin alfa, and human recombinant erythropoietin (Table 65-7) normalizes the hematocrit, avoids repetitive red blood cell transfusion, reduces the requirement for hospitalization, and decreases cardiovascular mortality by about 30%.[11]

Prolongation of the bleeding time because of decreased activity of platelet factor 3, abnormal platelet aggregation and adhesiveness, and impaired prothrombin consumption contributes to the clotting defects. The abnormality in platelet factor 3 correlates can be corrected by dialysis, although prolongation of the bleeding time can be observed in well-dialyzed patients. Abnormal bleeding times and coagulopathy in patients with renal failure may be managed with desmopressin, cryoprecipitate, conjugated estrogens, blood transfusions, and erythropoietin use.[10]

Effects of Drugs in Patients with Reduced Renal Function

Most anesthetic drugs are weak electrolytes and are lipid soluble in the un-ionized state; they are extensively reabsorbed by renal tubular cells (see Chapters 26 and 29). Termination of their action does not depend on renal excretion; redistribution and metabolism produce this effect. After biotransformation, these drugs are excreted in urine as water-soluble, polar forms of the parent compound. They are usually pharmacologically inactive, and their retention is harmless.[10] Most drugs with prominent central and peripheral nervous system activity fall into this category, including most narcotics, barbiturates, phenothiazines, butyrophenone derivatives, benzodiazepines, ketamine, and local anesthetics.[12] Several drugs are lipid insoluble or are highly ionized in the

Table 65-7 Management Guidelines for Correction of Anemia of Chronic Renal Disease

Erythropoietin	
Starting dosage	50-150 U/kg/wk IV or SC (once, twice, or three times per week)
Target hemoglobin	11-12 g/dL
Optimal rate of correction	Increase hemoglobin by 1-2 g/dL over 4 wk
Darbepoetin alfa	
Starting dosage	0.45 μg/kg administered as single IV or SC injection once weekly 0.75 μg/kg administered as a single IV or SC injection once every 2 wk
Target hemoglobin	12 g/dL
Optimal rate of correction	Increase hemoglobin by 1-2 g/dL over 4-wk period
Iron	
Monitor iron stores by TSat and serum ferritin	
If patient is iron-deficient (TSat <20%; serum ferritin <100 g/L), administer iron, 50-100 mg IV twice per week for 5 wk; if iron indices are still low, repeat the same course	
If iron indices are normal but hemoglobin is still inadequate, administer IV iron as outlined above; monitor hemoglobin, TSat, and ferritin.	
Withhold iron therapy when TSat >50% or ferritin >800 ng/mL (>800 g/L)	

IV, intravenously; SC, subcutaneously; TSat, percent transferrin saturation.

physiologic pH range, however, and are eliminated unchanged in urine. Their duration of action may be extended in patients with impaired renal function. Drugs in this category include muscle relaxants, cholinesterase inhibitors, thiazide diuretics, digoxin, and many antibiotics (Table 65-8).[13]

Opioids

Renal failure has implications of major clinical importance with respect to morphine and meperidine (see Chapter 27). For the fentanyl congeners, the clinical importance of renal failure is less marked.[14]

Morphine is an opioid with active metabolites that depend on renal clearance mechanisms for elimination. Morphine is principally metabolized by conjugation in the liver, and the water-soluble glucuronides (morphine-3-glucuronide and morphine-6-glucuronide) are excreted via the kidney. The kidney also plays a role in the conjugation of morphine, accounting for nearly 40% of its metabolism.[15] Patients with renal failure can develop very high levels of morphine-6-glucuronide and life-threatening respiratory depression.[14] In view of these changes induced by renal failure, morphine may not be a good choice in patients with severely altered renal clearance mechanisms.

The clinical pharmacology of meperidine also is significantly altered by renal failure. Normeperidine, the chief metabolite, has analgesic and central nervous system (CNS) excitatory effects.[16] Because the active metabolites are subject to renal excretion, this potential CNS toxicity secondary to normeperidine accumulation is especially a concern in patients in renal failure.

The clinical pharmacology of the fentanyl congeners is not grossly altered by renal failure, although a decrease in plasma protein binding potentially may alter the free fraction of the fentanyl class of opioids.[14] Fentanyl clearance is not altered by renal failure. As with fentanyl, sufentanil pharmacokinetics are not altered in any consistent fashion by renal disease, although greater variability exists in the clearance and elimination half-life of sufentanil when patients have impaired renal function.[17] An increased clinical effect is likely with alfentanil in renal failure because of a decreased initial volume of distribution and an increased free fraction of alfentanil.[18] No delay in recovery after alfentanil administration should be expected, however. Neither the pharmacokinetics nor the pharmacodynamics of remifentanil are altered by impaired renal function.[18]

Hydromorphone,[19] as the parent drug, does not substantially accumulate in hemodialysis patients. Conversely, an active metabolite, hydromorphone-3-glucuronide, quickly accumulates between dialysis treatments, but seems to be effectively removed during hemodialysis. With careful monitoring, hydromorphone may be used safely in dialysis patients. It should be used with caution, however, in patients with a GFR less than 30 mL/min who have yet to start dialysis or who have withdrawn from dialysis.

Table 65-8 Drugs Used or Encountered in Anesthesia Practice That Significantly Depend on Renal Elimination

Completely Dependent	Partially Dependent
Digoxin, inotropes (used frequently; monitoring of blood levels indicated in chronic renal failure)	IV anesthetics—barbiturates
Others—aminoglycosides, vancomycin, cephalosporins, and penicillins	Muscle relaxants—pancuronium
	Anticholinergics—atropine, glycopyrrolate
	Cholinesterase inhibitors—neostigmine, edrophonium
	Others—milrinone, hydralazine, cycloserine, sulfonamides, and chlorpropamide

Inhaled Anesthetics

All inhaled anesthetics (see Chapters 20, 21, and 24) are biotransformed to some extent, with the nonvolatile products of metabolism eliminated almost entirely by the kidney.[20] Reversal of the CNS effects of inhaled anesthetics depends on pulmonary excretion, however, so impaired kidney function would not alter the response to these anesthetics. From the viewpoint of selecting an anesthetic that would not be harmful to patients with mild or moderate impairment of renal function, all the modern potent anesthetics are suitable. Enflurane is biotransformed to inorganic fluoride, but levels after 2 to 4 hours of anesthesia average only 19 μM in patients with mild to moderate kidney disease, significantly lower than the nephrotoxic threshold of 50 μM, which is frequently reported after the administration of methoxyflurane.[21,22] This level of fluoride should not cause further renal impairment. Fluoride levels after isoflurane increase by only 3 to 5 μM,[23] and by only 1 to 2 μM after halothane,[22] so these anesthetics have no nephrotoxic potential.

Desflurane and sevoflurane, two newer inhaled anesthetics, are remarkably different in their molecular stability and biotransformation. Desflurane is highly stable and resists degradation by soda lime[24] and the liver. The mean inorganic fluoride concentration after 1 minimum alveolar concentration (MAC)–hour exposure to desflurane was less than 1 μmol/L.[25] The safety of desflurane in renal failure patients has been confirmed.[26] In addition, more sensitive indices of renal function—urine retinol-binding protein and β-*N*-acetylglucosaminidase—showed no evidence of renal damage. Prolonged exposure to desflurane (7 MAC-hours) has been associated with normal renal function.[26]

Sevoflurane is not very stable. Soda lime causes it to decompose,[27] and it is biotransformed by the liver. Plasma inorganic fluoride concentrations approaching nephrotoxic levels (50 μmol/L)[28] have been reported after prolonged inhalation of sevoflurane. No evidence of gross changes in renal function was found in humans, however.[29] In one study, sevoflurane was used at low flow (1 L/min), and there was no relationship to compound A and renal function.

Inhaled anesthetics cause a transient reversible depression in renal function. GFR, renal blood flow, urine output, and urinary excretion of sodium are decreased (Table 65-9). Probable mechanisms include reduced renal blood flow, loss of renal autoregulation, neurohumoral factors (e.g., antidiuretic hormone, vasopressin, renin), and neuroendocrine responses. Although most inhaled anesthetics have been shown to reduce GFR and urinary excretion of sodium, their effects on renal blood flow have yielded conflicting results, which can be explained by differences in experimental methodology. Data suggest that renal blood flow is maintained with halothane, isoflurane, and desflurane,[30,31] but it is decreased with enflurane and sevoflurane.[32,33]

Table 65-9 Effects of Various Anesthetics on Renal Function

	RBF	GFR	Urine Output	Urine Solutes
General anesthesia	↓	↓	↓	↓
Intravenous anesthetics				
Thiopental	↔	↓	↓	↓
Midazolam	↔	↔	↓	↔
Fentanyl/droperidol	↔	↔	↓	↓
Fentanyl (high dose)	↔	↔	↔	↔
Inhaled anesthetics				
Halothane	↔	↓	↓	↓
Enflurane	↓	↓	↓	↓
Isoflurane	↔	↓	↓	↓
PEEP	↓	↓	↓	o
Regional anesthesia				
Epidural (with epinephrine)	↓	↓	↓	o
Epidural (without epinephrine)	↔	↔	↔	o
Spinal	↔	↔	↔	o

Note: Although conflicting reports of anesthetic effects on RBF have been reported because of different investigative methods, the current literature seems to support these data.
Key: ↔, no significant change; o, significant data; ↓, decrease.
GFR, glomerular filtration rate; PEEP, positive end-expiratory pressure; RBF, renal blood flow.
From Hemmings HC Jr: Anesthetics, adjuvant drugs and the kidney. *In* Malhotra V (ed): Anesthesia for Renal and Genitourinary Surgery. New York, McGraw-Hill, 1996, p 20.

Intravenous Anesthetics

Reversal of CNS effects after the administration of ultrashort-acting barbiturates such as thiopental and methohexital occurs as a result of redistribution, and hepatic metabolism is the sole route of elimination of these drugs (see Chapter 26). Thiopental is 75% to 85% bound to albumin,[34] the concentration of which may be markedly reduced in uremia. Because it is a highly bound drug, reduced binding permits a greater proportion of an administered dose of thiopental to reach receptor sites. In addition, thiopental is a weak acid, with its pK_a in the physiologic range; acidosis results in more un-ionized, nonbound, active thiopental. In combination, these changes produce an increase in the free fraction of thiopental from 15% in normal patients to 28% in patients with CRF.[35] With thiopental metabolism essentially unchanged in renal disease, the dose to produce and maintain anesthesia should be reduced.[35] The same considerations are true for methohexital, although metabolism plays a slightly greater part in termination of its therapeutic effect.[36]

Propofol does not adversely affect renal function as reflected by measurements of creatinine concentration. Prolonged infusions of propofol may result in the excretion of green urine because of the presence of phenols in the urine. This discoloration does not affect renal function. Urate excretion is increased after the administration of propofol and is usually manifested as cloudy urine when urate crystallizes under conditions of low pH and temperature.[37]

There are no reports of the disposition of narcotics and tranquilizers when used in large dosage for anesthesia in uremic patients. These drugs are extensively metabolized before excretion, so when combined with 30% to 50% nitrous oxide, they should not have a particularly prolonged effect. The benzodiazepines, especially diazepam,[13] have a long half-life, so they tend to accumulate in any case. Because of the greater ease of reversibility of the potent inhaled anesthetics versus intravenous drugs, inhaled anesthetics may offer some advantages for the induction of general anesthesia in uremic patients.

Muscle Relaxants and Their Antagonists

Succinylcholine has been used without difficulty in patients with decreased or absent renal function (see Chapter 29). Its metabolism is catalyzed by pseudocholinesterase to yield the nontoxic end products succinic acid and choline. The metabolic precursor of these two compounds, succinylmonocholine, is excreted by the kidney. Large doses of succinylcholine, which might result from prolonged infusion, should be avoided in patients with renal failure. Although pseudocholinesterase levels are reduced in uremia,[38] these reductions are insufficient and they cause a prolonged block. Hemodialysis has been reported to have no effect on cholinesterase levels.[39]

Administration of succinylcholine causes a rapid, transient increase of 0.5 mEq/L in the serum potassium concentration. In traumatized, burned, or neurologically injured patients, the increase may be 5 to 7 mEq/L, probably as a consequence of denervation supersensitivity of the muscle membrane to succinylcholine and to acetylcholine,[40] which can result in cardiovascular collapse. An exaggerated increase in serum potassium could be particularly dangerous in uremic patients with hyperkalemia, so the use of succinylcholine is inadvisable, unless the patient has undergone dialysis within 24 hours before surgery. If the patient has recently undergone dialysis or has normal serum potassium, the use of succinylcholine is reportedly safe.

The disposition of nondepolarizing muscle relaxants has been well studied. Renal failure influences the pharmacology of nondepolarizing muscle relaxants by producing either decreased elimination of the drug or its metabolites by the kidney or decreased activity of enzymes that metabolize the drug, such as in the case of mivacurium (see Table 65-12). Consequently, the duration of action of muscle relaxants may be prolonged in patients with renal failure.

As can be appreciated from examination of the pharmacokinetics data in Table 65-10, excretion of tubocurarine is delayed in patients with renal failure.[41] Although tubocurarine is no longer used, studies with this drug served as a standard for the current drugs. Clearance is reduced, and the volume of distribution is unchanged—hence an increase in the terminal elimination half-life. With protein binding sensitivity of the neuromuscular junction to tubocurarine unchanged in patients with renal failure, the consequence of delayed excretion would be a prolonged duration of action. This would not be apparent after the administration of a single small dose because redistribution, rather than excretion, is responsible for termination of action.[42] Recovery after a single large dose or several small doses of tubocurarine is directly related to the terminal elimination half-life. Maintenance doses for patients with decreased renal function should be smaller than for patients with normal renal function, the interval between doses should be increased,[43] and administration should be monitored with a nerve stimulator.

Approximately 40% to 50% of pancuronium is excreted in urine. A portion of this excretion occurs after biotransformation to the less active metabolite 3-hydroxypancuronium.[43] Pancuronium has a prolonged terminal elimination half-life in patients

Table 65-10 Pharmacokinetics Data for Nondepolarizing Muscle Relaxants in Normal and Anephric Patients

Drug	Patients Studied	Elimination Half-Life (hr)	Clearance (mL/kg/min)	Volume of Distribution (L/kg)
Vecuronium	Normal	0.9	5.3	0.20
	Anephric	1.4	3.1	0.24
Atracurium	Normal	0.3	6.1	0.18
	Anephric	0.4	6.7	0.22
Tubocurarine	Normal	1.4	2.4	0.25
	Anephric	2.2	1.5	0.25
Pancuronium	Normal	1.7	1	0.14
	Anephric	8.2	0.3	0.14
Metocurine	Normal	6	1.2	0.57
	Anephric	11.4	0.4	0.48
Rocuronium	Normal	0.71	2.9	0.207
	Anephric	0.97	2.9	0.264
Cisatracurium	Normal	—	5.2	0.031
	Anephric	—	—	—
Mivacurium	Normal	0.03	106	0.278
	Anephric	0.06	80	0.475

with reduced renal function (see Table 65-10),[44] so it should be administered cautiously, particularly when several doses are required.

Two nondepolarizing muscle relaxants, atracurium and vecuronium, were introduced into clinical practice during the early 1980s. Atracurium is degradated by enzymatic ester hydrolysis and nonenzymatic alkaline degradation (Hofmann elimination) to inactive products that are not dependent on renal excretion for termination of action.[45] Predictably, their terminal elimination half-life and indices of neuromuscular blockade (onset, duration, and recovery) are the same in patients with normal and absent renal function.[46]

About 30% of a dose of vecuronium is eliminated by the kidneys. Lynam and colleagues[47] found that the duration of neuromuscular blockade after the administration of vecuronium was longer in patients with renal failure than in patients with normal renal function (99 minutes versus 54 minutes) because of a longer elimination half-life (83 minutes versus 52 minutes) and lower plasma clearance (3.1 mL/kg/min versus 5.3 mL/kg/min). In a related area, an interaction between the solvent of cyclosporine (Cremophor) with atracurium and vecuronium has been reported, with the action of these muscle relaxants potentiated in cats,[48] but it is unknown whether such potentiation also occurs in human renal transplant recipients.

Cisatracurium is the single *cis* isomer of atracurium. Organ-independent mechanisms (Hofmann elimination) account for 77% of the total clearance of cisatracurium. Because renal excretion accounts for only 16% of the elimination of cisatracurium, renal failure should have little impact on its duration of action.[46]

The short-acting drug mivacurium is metabolized by plasma pseudocholinesterase. Its effect has been shown to be lengthened by 10 to 15 minutes in patients with ESRD, most likely because of a decrease in plasma cholinesterase activity in these patients associated with uremia or hemodialysis,[49,50] and a decrease in the mivacurium requirement by infusion in anephric patients.[50]

The elimination half-life of rocuronium is increased in renal failure because of an increase in the volume of distribution with no change in clearance. This explanation may account for a longer duration of action in anephric patients, although its clinical significance is uncertain.[51]

Pharmacokinetics data for the cholinesterase inhibitors neostigmine, pyridostigmine, and edrophonium for normal, anephric, and renal transplant patients are presented in Table 65-11; there are no major differences among the three drugs.[52-54] Renal excretion is of major importance for the elimination of all three agents, with approximately 50% of neostigmine and 70% of pyridostigmine and edrophonium excreted in urine. Excretion of all the cholinesterase inhibitors is delayed in patients with impaired renal function to the same or perhaps to a slightly greater extent than is elimination of muscle relaxants. "Recurarization" after reversal of neuromuscular blockade in a patient with renal failure is, in most cases, due to some other cause, such as an interaction of the residual muscle relaxant with an antibiotic or a diuretic. Table 65-11 contains data indicating that the pharmacokinetics of all the cholinesterase inhibitors is similar in normal patients and patients with well-functioning newly transplanted kidneys.

Comparable findings have been reported for tubocurarine pharmacokinetics, and they probably hold for the disposition of pancuronium. As a category, transplant recipients with well-functioning kidneys can be considered normal in the way that they eliminate renally excreted drugs. There is sufficient interindividual variability in these data, however, to indicate that treatment with muscle relaxants and their antagonists should be individualized, as determined by clinical signs and the results of tests with a nerve stimulator.

Table 65-11 Pharmacokinetics Data for Cholinesterase Inhibitors in Normal, Anephric, and Renal Transplant Patients

Drug	Patients Studied	Elimination Half-Life (hr)	Clearance (mL/kg/min)	Volume of Distribution (L/kg)
Neostigmine	Normal	1.3	8.4	0.7
	Anephric	3*	3.9*	0.8
	Renal transplant	1.7	9.4	1.1
Pyridostigmine	Normal	1.9	8.6	1.1
	Anephric	6.3*	2.1*	1
	Renal transplant	1.4	10.8	1
Edrophonium	Normal	1.9	8.2	0.9
	Anephric	3.6*	2.7*	0.7
	Renal transplant	1.4	9.9	0.9

*$P < .05$ versus normal.

Vasopressors and Antihypertensive Drugs

Patients with severe renal disease are frequently given antihypertensive and other cardiovascular medications (see Chapter 12). More than 90% of the thiazides[55] and 70% of furosemide[56] are excreted by the kidney and have prolonged durations of action in patients with abnormal or absent renal function. Propranolol is almost completely metabolized in the liver, and esmolol is biodegraded by esterases in the cytosol of red blood cells, so their effects are not prolonged in patients with abnormal or absent renal function.[57] The calcium channel–blocking agents nifedipine, verapamil, and diltiazem are extensively metabolized in the liver to pharmacologically inert products; they may be administered in usual doses to patients with renal insufficiency.[58] Nitroglycerin is useful because it is metabolized rapidly, with less than 1% excreted unchanged in urine.[59]

Sodium nitroprusside has had a resurgence in use since its initial introduction as a hypotensive drug in the 1920s. Cyanide is an intermediate in the metabolism of sodium nitroprusside, with thiocyanate being the final metabolic product. Although cyanide toxicity as a complication of sodium nitroprusside therapy is well described,[60] it is less well appreciated that thiocyanate is also potentially toxic. The half-life of thiocyanate is normally more than 4 days, and it is prolonged in patients with renal failure.[60] Hypoxia, nausea, tinnitus, muscle spasm, disorientation, and psychosis have been reported when thiocyanate levels are greater than 10 mg/100 mL. Sodium nitroprusside is less desirable for prolonged administration than either trimethaphan or nitroglycerin.

Hydralazine is slower acting than the other three drugs discussed previously. Its action is terminated by hydroxylation and subsequent glucuronidation in the liver, with approximately 15% excreted unchanged in urine.[61] The elimination half-life of hydralazine is prolonged in uremic patients, so caution is required when it is administered.[62] After a single intravenous dose of 0.5 mg/kg of labetalol, the volume of distribution, clearance, and elimination half-life were similar in patients with ESRD and normal volunteers.[63] Esmolol is independent of renal function because it is metabolized by red blood cell cytosol esterases.[64]

If administration of a vasopressor is necessary, a direct α-adrenergic-stimulating drug such as phenylephrine would be effective. This type of vasopressor causes the greatest interference with renal circulation. Although β-adrenergic-stimulating drugs such as isoproterenol maintain heart and brain perfusion without renal vasoconstriction, they also increase myocardial irritability. When possible, it is best to substitute simple measures such as blood volume expansion for drug therapy. If these measures are inadequate, β-adrenergic-stimulating drugs or dopamine should be used.

Acute Renal Failure and Hemodialysis

Acute Renal Failure

Acute renal failure (ARF) is defined as the sudden inability of the kidneys to vary urine volume and content appropriately in response to homeostatic needs. Synonymous terms are *acute tubular necrosis* and *lower nephron nephrosis*. The three major types of ARF when classified according to their predominant etiologic antecedents are prerenal (caused by acute circulatory problems that impair renal perfusion), renal (caused by primary or secondary renal disease, toxins, and pigments), and postrenal (caused by obstruction of the urinary tract).[65] Table 65-12 lists common prerenal, renal, and postrenal causes of perioperative oliguria. Prerenal failure is usually reversible if the circulatory status is promptly improved; postrenal failure is reversible when the obstruction is removed. ARF secondary to primary renal disease is the most serious of the three types and most often requires hemodialysis.

Renal failure also is classified according to urine flow rates, so the terms *oliguric, nonoliguric,* and *polyuric renal failure* are often encountered. The diagnosis of acute oliguric renal failure is made when creatinine and BUN concentrations progressively increase while urine flow remains less than 20 mL/hr in an adequately hydrated patient who has stable blood pressure and a patent urinary outflow tract. Urine chemistry values are as indicated in Table 65-13. In some cases, patients with ARF may have normal or high (>2.5 L/day) urine flow rates, but they have biochemical abnormalities that are similar to the abnormalities occurring in patients with low urine output. Their management is less complex than that of oliguric patients because adequate drug therapy and proper nutrition are easier to maintain, given the less stringent limitations on daily fluid intake.

The major problem arising from ARF is an inability to maintain dynamic balance between dietary intake of essential substances and production of waste products. This imbalance results in a progressive increase in serum urea, creatinine, uric acid, magnesium, sulfate, phosphate, some amino and organic acids, and polypeptides; a daily increase in serum potassium of 0.3 to 3 mEq/L except when there is concomitant potassium loss from diarrhea or vomiting (greater increases may occur in trau-

Table 65-12 Perioperative Causes of Oliguria

Prerenal
Hypovolemia
Dehydration
Low cardiac output states
Aortic/renal artery clamping
Thromboembolic phenomena
Hemorrhage
Transfusion reaction
Renal
Ischemic injury from shock (cardiogenic, septic, hemorrhagic)
Nephrotoxins
Antibiotics
Chemotherapeutic agents
Radiocontrast dyes
Free hemoglobin and myoglobin
Cellular debris
Acute interstitial nephritis
Hypersensitivity reactions
Acute glomerulonephritis
Postrenal
Calculi
Tumors
Clot retention
Surgical ligation
Edema

From Patafio O: Acute renal failure and perioperative oliguria. *In* Malhotra V (ed): Anesthesia for Renal and Genitourinary Surgery. New York, McGraw-Hill, 1996, p 38.

matized or postsurgical patients); a decrease in serum sodium and calcium; a decrease in serum proteins, particularly albumin; a consistent increase in total reducing substance in serum, frequently occurring with true hyperglycemia, which may be either sensitive or resistant to insulin; elevation of total lipids, cholesterol, phosphorus, and neutral fats; and metabolic acidosis.[65,66] The kidney functions as an endocrine and as an excretory organ. Disorders of renin-angiotensin and aldosterone secretion occur and contribute to the hypertension that develops in patients with severe renal disease. Reduced erythropoietin production leads to anemia. Heart failure and abnormalities in liver function and blood coagulation also may occur in patients with renal shutdown. Infection is common and difficult to treat because the altered excretion of antibiotics leads to the rapid development of toxic levels of these drugs.

When established, oliguria is usually present for 10 to 18 days, but may persist for 30 to 45 days. During this period, hemodialysis is required every 2 to 4 days. When diuresis occurs, the beginning of the recovery phase is signaled. During the diuretic phase, urine volume gradually increases until 5 to 6 L of urine is produced daily. Management of the patient is directed at maintaining fluid and electrolyte balance in the face of these large losses. Finally, concentrating ability gradually returns toward normal. Complete return of all measurable parameters of renal function occurs in approximately two thirds of patients who survive. Fifty percent to 60% of patients with ARF do not survive long enough for recovery or the development of CRF, however.[67] Arrhythmias, bleeding, and infection are the most frequent causes of death.

Outcome analysis indicates that the overall mortality rate from ARF has not been significantly reduced in recent years despite earlier and more frequent dialysis. It is likely that there has been an increase in the survival rate of some categories of patients without any change in the overall rate because of an increase in the proportion of seriously ill patients who are now treated in dialysis units. This conclusion is suggested by the steady improvement in mortality data of obstetric patients with renal failure. The low (15%) mortality rate for this group emphasizes that the most significant feature determining survival is the physical status of the patient before the onset of renal failure.

As noted earlier, many patients with ARF have normal or high urinary flow rates. In these patients, the antecedent cause of renal failure may be the same as that in patients with classic oliguric renal failure, but an oliguric or anuric phase is not identifiable. Patients are unable to alter urinary volume and content appropriately, with an average daily output often greater than 2.5 L/day. The more frequent incidence of nonoliguric and polyuric renal failure in recent years compared with the 1940s and 1950s is thought to be due, in part, to more vigorous early treatment of patients with incipient oliguric renal failure.

Hemodialysis

The steady improvement in hemodialysis techniques (see Chapter 67) from the first artificial kidney developed in 1944 by Kolf and Berk[68] to the current practice of home dialysis has resulted in additional years of productive life for patients with CRF. This improvement, coupled with the 1976 federal legislation extending Medicare coverage to renal failure patients, has resulted in a large increase in the number of hemodialysis patients. Dialysis improves most of the signs and symptoms of uremia (e.g., volume overload, acid-base and electrolyte imbalance, abnormal mental function, peripheral neuropathy, muscle weakness, and defective coagulation). Hypertension is improved except in patients with high renin levels. Some patients have been undergoing hemodialysis for more than 10 years. The 3-year survival rate for U.S. patients 20 to 25 years old treated by hemodialysis is 85%; for patients 60 to 65 years old, 3-year survival is 60%.

Presently, two basic dialysis techniques are used: peritoneal dialysis and hemodialysis. Peritoneal dialysis can be either

Table 65-13 Urinary Composition of Oliguria

	Physiologic Oliguria	Prerenal Failure	Acute Tubular Necrosis
Urinary sodium	<10 mEq/L	<25 mEq/L	>35 mEq/L
Urinary specific gravity	>1.024	>1.015	1.010-1.015
Urinary osmolality	>700 mOsm/kg	>500 mOsm/kg	<350 mOsm/kg
Urinary/plasma osmolality	>2.5:1	>1.8:1	≤1.1:1
Urinary/plasma urea	>100:1	>20:1	3:1, rarely >10:1
Urinary/plasma creatinine	>60:1	>30:1, rarely <10:1	<10:1
Fractional sodium excretion	<1	>1	>0.5

long-term intermittent or continuous ambulatory; both are performed at home dialysis centers. In most circumstances, hemodialysis is used, and it is generally the method of choice. Peritoneal dialysis is preferred for patients who have had (1) recent cerebral surgery, a cerebrovascular accident, or trauma because the risk of fluid shifts or bleeding after heparinization is greater with hemodialysis; (2) recent cardiac surgery or a myocardial infarction because the risk of hypotension and arrhythmias is greater with hemodialysis; (3) a recent acute hemorrhage; or (4) a severe coagulopathy. Peritoneal dialysis also is frequently used in children.

The dialysis principle involves equilibration of waste products in the patient's blood across a semipermeable membrane to the dialysis bath. Peritoneal dialysis relies on the patient's peritoneum as the exchange membrane, avoiding the need for vascular cannulas and expensive equipment. Exchange volume rates during peritoneal dialysis are 1 to 3 L/hr. Clearance of small molecules is less than with hemodialysis (e.g., urea, 25 versus 150 mL/min), but clearance of large molecules is greater. The ionic content of the dialysate may be altered to suit the patient's needs, and the fluid may be made hypertonic or hypotonic to plasma to remove or add fluid to the patient's extracellular fluid volume. Peritoneal dialysis is less efficient than hemodialysis, so dialysis times are longer. In addition, peritonitis is a danger, and pain during dialysis may be severe.

Hemodialysis is the most commonly used dialysis technique today. Originally, polytetrafluoroethylene (Teflon) shunts were inserted between the radial artery and a forearm vein with a connector between them to allow access to the circulation. Today, vascular access is usually obtained by the creation of an end-to-side arteriovenous fistula in the forearm or by insertion of a prosthetic arteriovenous graft when the vessels are inadequate. During hemodialysis, which is performed two or three times weekly, the patient and the external circuit are heparinized to prevent clotting. Flow rates are usually 500 mL/min, so the patient's blood is exposed to 120 L of fluid during a standard 4-hour dialysis. Variation in ionic content and osmolarity of the dialysate permit correction of abnormalities in fluid and electrolyte balance. If fluid and electrolyte shifts are too rapid, dialysis dysequilibrium may occur. This syndrome is characterized by weakness, nausea, and vomiting, and occasionally convulsions and coma. In the interval between treatments, clotting does not occur because the shunted circuit is short, and blood flow is rapid (150 to 300 mL/min).

Local infiltration, axillary block, and general anesthesia have been used successfully for creation of arteriovenous fistulas (see Chapters 52 and 53). Several anesthetic precautions are appropriate. Uremic patients may be debilitated, in which case smaller doses of all drugs, including local anesthetics, should be administered. Hyperkalemia, acidosis, and overhydration can combine to cause myocardial irritability; local anesthetic solutions that contain epinephrine should be used with caution. If epinephrine is used, concentrations greater than 1:200,000 are not necessary, and solutions as dilute as 1:400,000 are probably adequate. Brachial plexus block may facilitate greatly the introduction of cannulas by producing analgesia combined with peripheral vasodilation. Bromage and Gertel[68a] reported that brachial plexus block had a 38% shorter duration in renal failure patients than in patients with normal renal function. This finding could not be confirmed, however, in a subsequent study of renal failure patients.[68b]

Preservation of Renal Function

Conducting renal preservation therapy studies is difficult because ARF has multiple etiologies, occurs in multiple clinical settings, affects patients with normal versus preexisting renal disease, and has therapy initiation before onset or after newly diagnosed renal insufficiency (see Chapter 96). It is estimated that 5% of hospitalized patients experience renal failure, resulting in greater than 50% mortality. Optimizing patients with renal insufficiency and perioperative renal preservation remain important goals. It is crucial to renal preservation strategies to maintain adequate renal oxygen delivery by maintaining circulating blood volume and oxygen carrying capacity.

Dopamine has been used for decades to prevent or ameliorate renal insufficiency. Use of dopamine is criticized because of the lack of prospective, large, randomized clinical trials revealing a permanent, positive outcome. An adequately powered study of septic patients in critical care revealed that dopamine at 2 μg/kg/min for nearly 4 days failed to protect from renal dysfunction.[69] A large dopamine meta-analysis by Friedrich and colleagues[70] involved 3359 patients in 61 trials using dopamine at 5 μg/kg/min or less. Analysis revealed a significant increase in urine output of 24% on day 1, but improved serum creatinine and creatinine clearance observed on day 1 were clinically insignificant. Overall, dopamine therapy had no effect on mortality, need for renal replacement therapy, or incidence of adverse events. Off-label use of the dopamine-1 receptor agonist fenoldopam has generated interest in renal preservation. A meta-analysis involving 1290 patients in 16 randomized controlled trials by Landoni and coworkers,[71] including critical care unit patients and patients undergoing major surgery, suggested that fenoldopam reduced the need for renal replacement therapy and mortality during episodes of acute renal injury. The authors cautioned that a large, multicenter, adequately powered trial is needed to confirm these results.

Mannitol has been described to have a protective renal effect if administrated in the setting of a preischemic renal insult therapy. This benefit is postulated to occur by renal vasodilation via prostaglandin effect, from free radical scavenging to reduce the effects of hydroxyl-type free radical injury, and by maintaining or improving urine production as an osmotic diuretic to diminish tubular obstruction. Loop diuretics continue to be administered in the clinical setting without reproducible evidence of a renoprotective perioperative benefit. A meta-analysis by Ho and Sheridan[72] analyzing 849 patients in 23 randomized controlled trials evaluated the need for renal placement therapy and mortality. The findings revealed a lack of support for any significant clinical benefit using furosemide. The antioxidant *N*-acetyl cysteine and intravenous $NaHCO_3$ therapy have been used and evaluated mainly in the setting of contrast-induced nephropathy with inconsistent conclusions regarding revealing a renal preservation benefit. In analysis of 12 meta-analyses evaluating *N*-acetyl cysteine during intravenous contrast dye exposure, 9 suggested improved renal outcomes.[73] Significant study heterogenicity was cited as the primary reason by this review to prevent a conclusion regarding a positive benefit of *N*-acetyl cysteine therapy.

Several additional renal preservation therapy studies, including the use of atrial natriuretic peptide, theophylline, dopexamine (β_2-agonist), calcium channel blockers, prostaglan-

din E_1, growth factors, hemodialysis, and hemofiltration, have been published. Results from these clinical trials are often inconsistent across similar studies and cannot yet be recommended as standard therapy for clinical use as part of a standard renal preservation strategy.

Renal and Genitourinary Procedures

Transurethral Resection of the Prostate

Pathophysiology of Prostate Hypertrophy

The prostatic gland consists of four closely integrated zones—the anterior, peripheral, central, and preprostatic zones. Each zone consists of secretory, smooth muscle, and fibrotic tissue. All four zones are enclosed in one capsule. The gland is rich in blood supply. Arteries and veins penetrate the prostatic capsule and branch inside the gland. The venous sinuses adjacent to the capsule are particularly large. Nodules begin to develop by the fourth decade of life in the preprostatic zone and form middle, lateral, and posterior lobes. The middle and posterior lobes are most often associated with symptoms of urinary tract obstruction.[74]

Surgical Procedures

Transurethral resection of the prostate (TURP) is performed by inserting a resectoscope through the urethra and resecting prostatic tissue with an electrically powered cutting-coagulating metal loop. As much prostatic tissue as possible is resected, but the prostatic capsule is usually preserved. If the capsule is violated, large amounts of irrigation solution are absorbed into the circulation and the periprostatic and retroperitoneal spaces.

Bleeding during TURP is common, but usually controllable; however, when large venous sinuses are opened, hemostasis becomes difficult. If bleeding becomes uncontrollable, the procedure should be terminated as quickly as possible, and a Foley catheter should be passed into the bladder and traction applied to it. The catheter's inflated balloon exerts lateral pressure on the prostatic bed and reduces bleeding. Bleeding requiring transfusion occurs in about 2.5% of TURP procedures.[75]

Irrigation Solutions

Ideally, an irrigation solution for TURP should be isotonic, electrically inert, nontoxic, transparent, easy to sterilize, and inexpensive. Such a solution does not exist. Distilled water is electrically inert and inexpensive and has excellent optical properties, but it is extremely hypotonic. When absorbed into the circulation in large amounts, plain water causes hemolysis, shock, and renal failure.

Numerous nearly isotonic irrigation solutions are available. Commonly used solutions are glycine 1.2% and 1.5%, mannitol 3% to 5%, glucose 2.5% to 4%, sorbitol 3.5%, Cytal (a mixture of sorbitol 2.7%, and mannitol 0.54%), and urea 1% (Table 65-14). These solutions are purposely moderately hypotonic to preserve their transparency.

Although they cause no significant hemolysis, excessive absorption of these irrigation solutions might lead to other complications, such as pulmonary edema and hyponatremia. In addition, the solutes may have adverse effects. Glycine may cause cardiac and retinal toxic effects, mannitol rapidly expands the blood volume and might cause pulmonary edema in cardiac patients, and glucose might cause severe hyperglycemia in diabetic patients. These complications are discussed in detail later.

Table 65-14 Osmolality of Irrigation Solutions Used for Transurethral Resection of the Prostate

Solution	Osmolality (mOsm/kg)
Glycine, 1.2%	175
Glycine, 1.5%	220
Sorbitol, 3.5%	165
Mannitol, 5%	275
Cytal (see text)	178
Glucose, 2.5%	139
Urea, 1%	167

Replacement of distilled water with nearly isosmotic solutions has eliminated hemolysis and its sequelae as a complication of TURP. The incidence of severe CNS problems associated with extreme hyponatremia, such as convulsions and coma, has been reduced. The other major problem associated with the absorption of large volumes of irrigating solution, overhydration, still remains, however.

Anesthetic Techniques

Spinal anesthesia is the most frequently used anesthetic for TURP in the United States and is believed to be the technique of choice by many anesthesiologists. A spinal anesthetic provides adequate anesthesia for the patient and good relaxation of the pelvic floor and the perineum for the surgeon. The signs and symptoms of water intoxication and fluid overload can be recognized early because the patient is awake. Accidental bladder perforation also is recognized easily if the spinal level is limited to T10 because the patient would experience abdominal or shoulder pain. Satisfactory regional anesthesia for TURP involves achieving an anesthetic block level that interrupts sensory transmission from the prostate and bladder neck. In addition, the uncomfortable sensation of bladder distention must be considered.[76,77]

As explained earlier, the visceral pain sensation from the prostate and bladder neck is transmitted by afferent parasympathetic nerve fibers derived mostly from the second and third sacral roots traveling with the pelvic splanchnic nerves. Bladder sensation is supplied by sympathetic nerves of the hypogastric plexus, derived from nerve roots extending inferiorly from T11 to L2. Regional anesthesia resulting in a sensory level to T10 is required to eliminate the discomfort caused by bladder distention and other aspects of this procedure; however, slightly lower sensory levels often suffice for smaller lesions. In one study in which bladder pressure was monitored and kept low, anesthetic levels to T12 or L1 were adequate, but midlumbar blocks to L3 were not.[78] Sensory levels above T9 should not be sought because the capsular sign (i.e., pain on perforation of the prostatic capsule) would not be present should perforation occur.

Subarachnoid anesthesia is generally preferred over continuous epidural anesthesia for the following reasons. It is technically easier to perform in elderly patients, and the duration of surgery is generally not very long. The incomplete block of sacral nerve roots that occasionally occurs with the extradural technique is usually avoided with subarachnoid anesthesia.

Caudal and sacral blockade also has been used effectively for prostate surgery, and bladder distention is avoided with the use of continuous irrigation. Caudal anesthesia has been used effectively in high-risk patients undergoing laser prostatectomy.[79] Hemodynamic stability is the main advantage with this technique. Local infiltration of the perineum and the prostatic fossa also has been advocated by some anesthesiologists for limited TURP procedures, although the operative analgesia afforded by local infiltration is not comparable in quality to spinal anesthesia. General anesthesia may be necessary in patients who require ventilatory or hemodynamic support, have a contraindication to regional anesthesia, or refuse regional anesthesia.

Advantages of Regional Anesthesia over General Anesthesia

Regional anesthesia offers several advantages over general anesthesia for TURP (see Chapter 51). The incidence of deep vein thrombosis is decreased, and the amount of operative blood loss is reduced with regional anesthesia compared with general anesthesia. The reduction in operative blood loss when regional rather than general anesthesia is used has been shown to be the case in other pelvic procedures in addition to TURP, such as cystectomy and major vaginal surgery.[80] The decrease in systemic blood pressure secondary to the sympathetic blockade produced by the regional technique was determined not to be the only factor in reducing blood loss. Good evidence indicates that peripheral venous pressure and central venous pressure decrease during regional anesthesia and spontaneous ventilation. It is postulated that this decrease in peripheral venous pressure might result in reduced blood loss during prostatic and other surgery.

Additional factors influencing blood loss during TURP are the vascularity and size of the gland and the duration of surgery. An increase in fibrinolysis during prostate resection as a result of the release of urokinase from prostate tissue also factors into the blood loss that occurs. Other factors that affect blood loss during TURP include the size of the gland, the duration of the procedure, the number of sinuses opened during resection, the presence of infection, and prostate inflammation from repeated or recent catheterizations. These factors make it quite difficult to compare studies evaluating blood loss during TURP or to arrive at conclusive findings based on meta-analysis.[75,77]

Patients undergoing prostatectomy are prone to deep vein thrombosis for many reasons, including advanced age and the presence of malignancy, cardiac disease, varicose veins, and obesity. In this case, the increased blood flow resulting from the sympathetic blockade of regional anesthesia may play a role in reducing deep vein thrombosis formation.[81] More recent data also confirm the earlier belief that regional anesthesia decreases the hypercoagulable tendency in the postoperative period and helps maintain normal coagulation and platelet function; these benefits are believed to be due to modulation of the neuroendocrine response to tissue injury. There is evidence that homeostasis of the neuroendocrine system and the immune response are better preserved after regional anesthesia than after general anesthesia.[81]

TURP is associated with a particular set of complications with anesthetic implications. These problems must be considered, along with the usual considerations, such as the general health of the patient, the length of the procedure, and patient and surgeon preferences, when choosing an anesthetic technique.

The use of regional anesthesia for TURP can allow the anesthesiologist the advantage of monitoring the patient's mental status intraoperatively. Excessive absorption of irrigating fluid during the procedure produces numerous problems with cardiovascular and neurologic implications. A change in the patient's mental status provides an early indication that excessive absorption of irrigating fluid has occurred. These changes are described more fully in the next section.

Visual disturbances, such as blurred vision and transient blindness, have been reported in association with TURP (see Chapter 90). The biotransformation of absorbed glycine to ammonia has been implicated in these and other CNS abnormalities. Another potential complication during TURP is bladder perforation secondary to overdistention with irrigation fluid or contact of the bladder wall with the surgeon's resectoscope. Conscious patients may experience symptoms related to perforation well before it becomes apparent to the surgeon, alerting the operating team early on. Signs and symptoms of bladder perforation include bradycardia, hypotension, restlessness, diaphoresis, nausea, abdominal pain, dyspnea, shoulder pain, and hiccups. Extraperitoneal perforation may be manifested as pain in the periumbilical, inguinal, or suprapubic area. Intraperitoneal bladder perforation, a less frequent event, may cause symptoms related to diaphragmatic irritation (i.e., pain referred to the upper part of the abdomen, precordial area, shoulder region, or neck).[81]

Regional anesthesia for TURP offers some advantages over general anesthesia. Although laboratory monitoring of electrolytes is useful intraoperatively, a change in mental status in a conscious patient provides an early indication of electrolyte disturbances. Bladder perforation is recognized earlier in a conscious or lightly sedated patient, as noted previously.

Sensory levels above T9 are undesirable because pain caused by perforation of the prostatic capsule (capsular sign) would not be apparent to the patient if this complication occurs. Another benefit of regional anesthesia for TURP is a decreased requirement for analgesics in the immediate postoperative period compared with general anesthesia.[82]

Morbidity and Mortality after Transurethral Resection of the Prostate

Although spinal anesthesia offers certain distinct advantages over general anesthesia for TURP surgery, mortality and many markers of patient outcome have been similar for both groups. What constitutes the safest anesthetic for prostatectomies was debated in 1924, with proponents of regional anesthesia gaining ground quickly thereafter.[83] Currently, the 30-day mortality rate associated with TURP is 0.2% to 0.8%.[77] Mortality rates are similar in patients receiving regional anesthesia or general anesthesia.[84] With mortality rates as low as 0.2%, however, many more patients need to be studied than previously examined in any of the studies to draw a meaningful and statistically significant conclusion.[76] The postoperative morbidity rate in one study was 18%.[77] Increased morbidity was found in patients with resections exceeding 90 minutes, gland size larger than 45 g, acute urinary retention, and age older than 80 years.[77] Ashton and coworkers[85]

studied 250 men undergoing TURP and observed one postoperative myocardial infarction (0.4%) resulting in one death. The incidence of postoperative complications, including myocardial infarction, pulmonary embolism, cerebrovascular accidents, transient ischemic attacks, renal failure, hepatic insufficiency, and the need for prolonged ventilation, is similar when comparing patients receiving regional anesthesia with patients receiving general anesthesia.[75,77]

Many investigators have studied postoperative cognitive function after TURP performed under general versus regional anesthesia. Most studies have failed to show any significant difference in cognitive function in patients receiving regional anesthesia and patients receiving general anesthesia.[86] Postoperative behavioral changes in TURP patients are believed to be related to fluid absorption and increased cerebral fluid; cerebral oximetry studies have confirmed this relationship.[87] Preoperative mental impairment in elderly patients also influences postoperative mental function, which makes another case against the use of heavy sedation in these patients.

Complications of Transurethral Resection of the Prostate

Absorption of Irrigating Solution

Because the prostate gland contains large venous sinuses, it is inevitable that irrigating solution would be absorbed. Simple principles govern the amount of absorption: (1) The height of the container of irrigating solution above the surgical table determines the hydrostatic pressure driving fluid into prostatic veins and sinuses, and (2) the time of resection is proportional to the quantity of fluid that is absorbed. On average, 10 to 30 mL of fluid is absorbed per minute of resection time, with 6 to 8 L absorbed in some procedures lasting up to 2 hours. Whether patients experience complications as a consequence of the absorption of irrigating fluid depends on the amount and type of fluid absorbed.[88,89]

Excessive Circulatory Volume, Hyponatremia, and Hypo-osmolality

Solutions such as normal saline and lactated Ringer's solution would be well tolerated when absorbed intravascularly, but these electrolyte solutions are highly ionized and facilitate the dispersion of high-frequency current from a monopolar resectoscope. Solutions of nonelectrolytes, such as glucose, urea, glycine, mannitol, sorbitol, or Cytal, have replaced distilled water. Of all the irrigating solutions available today (see Table 65-14), glycine and Cytal are the two most commonly used.[88]

Replacement of distilled water with nearly isosmotic solutions has eliminated hemolysis and its sequelae as a complication of TURP. The incidence of severe CNS problems associated with extreme hyponatremia, such as convulsions and coma, has been reduced[89]; however, the other major problem associated with the absorption of large volumes of irrigating solution, overhydration, remains. Under usual conditions, only 20% to 30% of a load of crystalloid solution remains in the intravascular space; the remainder enters the interstitial space. When intravascular pressure is increased, movement of fluid into the interstitial space and the development of pulmonary edema are favored. Whether symptoms of circulatory overload develop in a given patient depends on the patient's cardiovascular status, the amount and rapidity of absorption of irrigating fluid, and the extent of surgical blood loss.[89]

The situation is dynamic, and patients must be monitored carefully. In this regard, spinal or epidural anesthesia, supplemented with only light intravenous sedation, has the advantage of allowing the patient's subjective judgment to contribute to assessment of his or her condition during surgery. In addition, the cardiovascular depression associated with the administration of potent inhaled anesthetics is avoided. Another advantage of regional anesthesia is that the sympathetic block that it produces increases venous capacitance and tends to mitigate intraoperative fluid overload. When the block dissipates, venous capacity acutely decreases, and circulatory overload can occur.

Concomitant with the circulatory overload caused by significant absorption of irrigating fluid are usually hyponatremia and hypo-osmolality. TURP syndrome has been typically described as being caused by hyponatremia and subsequent water intoxication. It is now recognized that the classic CNS signs of TURP are not caused by hyponatremia per se, but are due to the accompanying acute serum hypo-osmolality that allows movement of water into cells and causes cerebral edema.[88,89]

The use of nonelectrolyte isosmotic irrigating solutions has reduced the incidence of severe CNS complications because extreme extracellular fluid hypo-osmolality does not occur, and the subsequent development of cerebral edema is avoided.[88,89] That CNS symptoms occur at all is probably due to the fact that the incidence and extent of hyponatremia are unchanged. The concentration of extracellular sodium must be in the physiologic range for depolarization of excitable cells and production of the action potential. CNS symptoms, which include irritability, apprehension, confusion, and headache, provide early warning signs of rapidly developing hyponatremia. Further progression of hyponatremia (sodium ≤102 mEq/L) and decreased serum osmolality lead to the development of seizures and coma. The CNS effects become apparent at sodium levels less than 120 mEq/L. The cardiovascular effects of severe hyponatremia include negative inotropy, hypotension, and dysrhythmias. At sodium levels less than 115 mEq/L, electrocardiogram changes are made manifest by QRS widening and ST-segment elevation.[81]

When extracellular sodium levels are less than 100 mEq/L, consciousness is lost, and convulsions may ensue.[89] Signs and symptoms of cardiovascular dysfunction secondary to hyponatremia also may occur, including arrhythmias, hypotension, and pulmonary edema.[90] It is often impossible, however, to separate the latter events from events attributable to fluid overload.

Glycine Toxicity

Since the early 1980s, attention has turned to the absorption of glycine (HO_2—CCH_2—NH_2), a nonessential amino acid, as a possible cause of some CNS symptoms associated with TURP. In one publication, five cases of transient blindness were attributed to glycine toxicity.[91] Glycine has a distribution similar to that of aminobutyric acid, the latter being an inhibitory transmitter in the brain; it has been suggested that glycine is a major inhibitory transmitter acting in the spinal cord and brainstem.[91] Normal plasma glycine levels are 13 to 17 mg/L, whereas levels of 1029 mg/L were measured during one episode of blindness. Twelve hours later, the glycine level in this case had declined to 143 mg/L, by

which time vision had returned; however, an overall correlation between plasma glycine levels and CNS toxicity has not been established, so the relationship, although interesting, still must be considered speculative. Glycine also has been implicated in the myocardial depression and hemodynamic changes associated with TURP syndrome.[92]

Ammonia Toxicity

Absorption of glycine may result in CNS toxicity as a result of oxidative biotransformation of glycine to ammonia.[93,94] In a report of delayed awakening after TURP in three patients,[93] an association with elevated blood ammonia concentrations was noted. Blood ammonia levels of 500 M were noted in this and another case report.[94] Deterioration of CNS function is said to occur when ammonia levels are greater than 150 M. In a prospective study examining glycine metabolism, blood ammonia levels were increased postoperatively in 12 of 26 patients in whom 1.5% glycine was used as the irrigating solution for TURP.[93] Blood glycine levels also were measured. Glycine and ammonia levels did not correlate; the opposite relationship was prevalent. High ammonia levels were not associated with CNS symptoms of toxicity. Although the investigators postulated that delayed awakening and other CNS symptoms were due to ammonia toxicity, it is unclear whether this hypothesis is correct.

Perforation

Another common complication of TURP is perforation of the bladder.[95] Perforations usually occur during difficult resections and are most often made by the cutting loop or knife electrode. Some are made by the tip of the resectoscope, whereas others may result from overdistention of the bladder with irrigation fluid. Most perforations are extraperitoneal, and in a conscious patient they result in pain in the periumbilical, inguinal, or suprapubic regions; additionally, the urologist may note the irregular return of irrigating fluid. Less often, the perforation is through the wall of the bladder and is intraperitoneal, or a large extraperitoneal perforation may extend into the peritoneum. In such cases, pain may be generalized in the upper part of the abdomen or be referred from the diaphragm to the precordial region or the shoulder. Other signs and symptoms, such as pallor, sweating, abdominal rigidity, nausea, vomiting, and hypotension, have been reported; the number and severity depend on the location and size of the perforation and the type of irrigating fluid. In an early series of 2015 cases in which the incidence of complications of TURP was examined, perforation occurred in 25 patients (1.2%).[96] Four deaths and five additional major complications occurred in 12 patients in whom suprapubic cystostomy was delayed more than 2 hours after perforation. Distilled water was the bladder irrigant in most of these cases, so it is unclear whether these morbidity and mortality data are still relevant.

Transient Bacteremia and Septicemia

The prostate harbors many bacteria, which can be a source of intraoperative and postoperative bacteremia through the prostatic venous sinuses. This risk is increased further by the presence of an indwelling urinary catheter. Bacteremia is usually asymptomatic and easily treated with commonly used antibiotic combinations that are effective against gram-positive and gram-negative bacteria. In 6% to 7% of patients, septicemia may occur, however.[77] Common manifestations include chills, fever, and tachycardia. In severe cases, bradycardia, hypotension, and cardiovascular collapse may occur, with mortality rates of 25% to 75%. Aggressive treatment with antibiotics and cardiovascular support is warranted.

Hypothermia

Irrigating fluids stored at room temperature are frequently used during TURP. Heat loss as a result of irrigation and significant absorption of this fluid may lead to a decrease in the patient's body temperature and cause shivering. The use of warmed irrigating solutions has been shown to be efficacious in reducing heat loss and the resultant shivering.[97] Although one may believe that warming of fluids might cause increased bleeding because of vasodilation, such is not the case, as shown by the study of Heathcote and Dyer.[98] The use of systemic and intrathecal opioids decreases postoperative shivering from cold.[99]

Bleeding and Coagulopathy

A hypertrophied prostate is highly vascular, and operative bleeding can be significant. The blood is washed into the draining bucket and mixed with ample quantities of irrigant fluid. Estimation of blood loss is inaccurate and extremely difficult. Efforts have been made to quantify blood loss based on resection time (2 to 5 mL/min of resection time) and size of the prostate in grams (20 to 50 mL/g); however, these guidelines are rough estimates at best, and the patient's vital signs and serial hematocrit values should be monitored to assess better the blood loss and need for transfusion. Because adrenergic receptors are abundant in prostate tissue, the use of adrenergic agonists would cause vasoconstriction of prostatic blood vessels and a decrease in blood loss.

Abnormal bleeding after TURP occurs in less than 1% of cases; it is believed by some clinicians to be due to systemic fibrinolysis secondary to plasmin. The prostate releases plasminogen activator, which converts plasminogen to plasmin. Other clinicians believe that the fibrinolysis is secondary to disseminated intravascular coagulation triggered by the systemic absorption of resected prostate tissue, which is rich in thromboplastin.[75] If primary fibrinolysis is suspected, aminocaproic acid may be effective when given intravenously in a dose of 4 to 5 g during the first hour, followed by 1 g/hr.[75]

Treatment of Transurethral Resection of the Prostate Syndrome

Treatment of TURP syndrome (Table 65-15) consists of fluid restriction and a loop diuretic such as furosemide. Hypertonic saline (3% sodium chloride) is rarely, if ever, necessary and should be considered only in patients with severe hyponatremia. CNS complications of hypertonic saline include cerebral edema and pontine myelinolysis.[76,89] Cardiovascular support should be provided as necessary.

Anesthetic considerations for TURP should include positioning. TURP is usually performed in the lithotomy position with a slight Trendelenburg tilt. This positioning results in changes in pulmonary blood volume; a decrease in pulmonary compliance; a cephalad shift of the diaphragm; and a decrease in lung volume parameters such as residual volume, functional residual volume, tidal volume, and vital capacity. Cardiac preload may increase. Nerve injuries to the common peroneal, sciatic, and femoral nerves are likely.[76]

Table 65-15 Signs and Symptoms of Transurethral Resection of the Prostate Syndrome

Cardiovascular and Respiratory	Central Nervous System	Metabolic	Other
Hypertension	Agitation/confusion	Hyponatremia	Hypo-osmolality
Bradyarrhythmias/tachyarrhythmias	Seizures	Hyperglycinemia	Hemolysis
Congestive heart failure	Coma	Hyperammonemia	
Pulmonary edema and hypoxemia	Visual disturbances (blindness)		
Myocardial infarction			
Hypertension			

Laser Prostatectomy, Cryosurgery, and Microwave Ablation

Laser prostatectomy has found renewed interest among urologists and is being conducted in several centers. Based on initial experience, it promises to replace conventional TURP in the near future. The neodymium: yttrium-aluminum-garnet (Nd-YAG) laser has been replaced by holmium and potassium-titanyl-phosphate (KTP) lasers. These lasers produce varying degrees of coagulation and vaporization of prostate tissue. The main advantages over conventional TURP include minimal blood loss (50 to 70 mL) and minimal fluid absorption, which should nearly eliminate these two major complications of TURP; however, other potential complications are introduced, including coagulation through the prostatic fossa and sloughing of prostatic debris in the postoperative period, with subsequent urinary obstruction and urinary retention.[100-104] Protective eyewear and a means to evacuate the smoke plume are needed.[105] In critically ill patients, caudal anesthesia has been successfully used for laser prostatectomy because the use of continuous irrigation combined with minimal bleeding obviates the need for copious irrigation and minimizes bladder distention.[79]

In a systematic review of randomized, controlled trials evaluating the efficacy and safety of laser prostatectomy techniques versus TURP for symptomatic benign prostatic obstruction, the authors observed that TURP provided slightly greater improvement in urinary symptoms and flow. Laser procedures resulted in fewer transfusions and strictures and shorter hospitalizations. Reoperation was required more often after laser procedures.[106]

Cryosurgery has proved to be technically complex and has not attained much popularity. Microwave ablation of the prostate is another promising technique that can be performed on an outpatient basis under local or sacral block.

New Therapies for Transurethral Resection of the Prostate

Traditional monopolar electrode and previously described laser TURP therapies are currently being challenged with new urethral prostate resection techniques. Bipolar electrode resection and next-generation prostate lasers are proving to be alternative surgical therapies for benign prostatic hyperplasia resection. An advantage of bipolar electrode resection is that normal saline can be used to avoid morbidity associated with hypo-osmolar bladder irrigants such as glycine. Laser therapy delivers vaporization energy creating a thin resecting coagulation treatment zone that also can be created using normal saline bladder irrigation. Both treatments are promoted to prevent excessive prostatic bleeding, extend rather than limit resection time, and reduce hospital stay. Hanson and associates[107] reviewed the anesthetic implications of the newer prostate laser resection therapies. The described advantages included minimal bladder irrigating fluid absorption, a minimized risk of TURP syndrome, potential to perform the procedure on anticoagulated patients, delivery in an outpatient setting, and less emphasis on describing regional as the preferred anesthetic technique.

Laser Lithotripsy

Laser lithotripsy is used for ureteral stones that are low in the ureter and not amenable to extracorporeal shock wave lithotripsy (ESWL). A pulsed dye laser is generated with a laser beam of 504-nm wavelength passing through an organic green dye.[108] This laser beam is easily absorbed by the stones, and pulsatile energy is released that causes disintegration of the stones. The beam is carried over a bare wire passed through a rigid ureteroscope, which is longer and more pointed than a cystoscope, so the risk of ureteral perforation exists. Ideally, general anesthesia with paralysis should be maintained to avoid patient movement. If regional anesthesia is chosen, a spinal level of T8 to T10 is required. The bare laser wire is sharp and can cause mucosal injury to the ureter. These lasers are not well absorbed by red blood cells or other tissues, however, which provides safety against tissue coagulation or thermal injury. Because the laser beam is reflective, the user, other personnel, and the patient should wear protective eyeglasses. Some hematuria always occurs; good intravenous hydration is recommended.[108]

Laparoscopic Surgery in Urology

Urologic laparoscopic surgery continues to pioneer new surgical approaches for treatment of diseases previously performed by an open surgery. Advances in this area now routinely include laparoscopic varicocelectomy, hernia repair, adrenalectomy, partial adrenalectomy, renal pelvis or ureter percutaneous stone retrieval, nephrectomy, radical prostatectomy, extra-adrenal pheochromocytoma, nephropexy, pyeloplasty, nephrectomy, partial nephrectomy, and cystectomy. Many of these surgeries are robot assisted for tumor resection and reconstruction. During robotic laparoscopic surgery, the surgeon is stationed in the operating room away from the operating room table while working at a computer

console with a three-dimensional view of the operating field and manual controls at the console for robotic instruments placed in the abdomen via laparoscopy trocars.

For radical prostatectomy, the objectives of laparoscopic surgery are to reduce perioperative morbidity compared with conventional surgery and allow a more precise operative procedure. The quality of surgery can be improved by better visualization of the operative site as a result of optical magnification and the maneuverability of the laparoscope, which provides a hitherto unobtainable anatomic view. The laparoscopic approach not only improves the postoperative course, but also allows better preservation of periprostatic vascular, muscular, and neurovascular structures.[109]

A unique challenge in nephron-sparing laparoscopic surgery is achieving successful renal hypothermia for renal preservation during renal artery occlusion. Techniques described for renal hypothermia include laparoscopic deployed ice slush kidney surface cooling (preferred option), endoscopic retrograde cold saline infusion, and transarterial renal hypothermia via femoral artery catheter approach.

Although all the conventional complications and concerns associated with laparoscopy are applicable to urologic procedures (see Chapter 68), two unique problems also are identified. First, because the urogenital system is mainly retroperitoneal, the large retroperitoneal space and its communications with the thorax and subcutaneous tissue are exposed to the insufflated carbon dioxide. Subcutaneous emphysema occurs frequently in these patients and may extend all the way up to the head and neck.[110] The upper airway is at risk for compromise in the most severe cases because of pharyngeal swelling secondary to submucous carbon dioxide. This complication should be kept in mind before extubation of these patients. Second, the procedures tend to be lengthy, allowing for sufficient absorption of carbon dioxide to result in acidemia and marked acidosis.[110] Because of significant increases in intra-abdominal and intrathoracic pressure as a result of insufflated carbon dioxide, a steep Trendelenburg position, and lengthy procedures, general anesthesia with controlled ventilation is the method of choice. Despite adequate hydration, intraoperative oliguria may occur and be followed by diuresis in the immediate postoperative period. Although the exact mechanism is unclear, it is believed to be due to increased perirenal pressure exerted by the insufflated gas in the retroperitoneal space.

Extracorporeal Shock Wave Lithotripsy

ESWL has become the treatment of choice for disintegration of urinary stones in the kidney and upper part of the ureter. The first clinical model of the lithotripter introduced into common practice (Dornier HM-3) used a water bath in a steel tub and a metal gantry chair to support the patient suspended in a sitting position. This first-generation lithotripter is still used in some institutions and presents complex challenges of immersion physiology and monitoring difficulties. Second-generation and third-generation lithotripters (e.g., Siemens, Lithostar, Wolf Piezolith, Dornier HM-4, MFL 5000, MPL 9000) have evolved mainly in the direction of multipurpose use, eliminating the water bath and producing a pain-free lithotripter. All lithotripters share similar technologic principles in having three main components: (1) an energy source, most commonly a spark plug (alternatively, an electromagnetic membrane or piezoelectric elements); (2) a system to focus the shock wave, such as ellipsoid or reflecting mirrors; and (3) fluoroscopy or ultrasound to visualize and localize the stone in focus.[111]

Technical Aspects

The patient is immersed in water up to the clavicles (see Chapter 100). An electrode (or spark plug) is placed in the water at the base of the tub in an ellipse and is connected to a generator that supplies 16 to 24 kV of electricity. The electric energy creates a spark across the gap in the electrode with the generation of a loud noise, intense heat, and explosive vaporization of water. The sudden expansion of air bubbles created sets up a pressure wave (shock wave) with distinct mechanical and acoustic properties. The shock wave is focused by the ellipse to a focal point called the F2 focus (the tip of the electrode is the first focus). The shock wave travels through water and body tissues without significant localized dissipation of energy because the acoustic impedance of the two media is similar. When the shock wave arrives at the entry surface of the stone, however, it encounters a sudden change in impedance that causes it to release compressive energy on the magnitude of several atmospheres. Similarly, when the wave exits on the opposite surface of the stone, an interface is encountered again, and shock wave energy is released in a blast. Repeat applications cause the stone to disintegrate. Shock wave energy is most concentrated in the F2 focal zone and rapidly decreases beyond it.[112]

Biomechanical Effects of Shock Wave Therapy

For shock waves to be most effective, the stone should remain in the F2 focus during treatment.[79] Pressure energy measurements show an exponential decrease beyond this small focal zone. The kidneys and the kidney stone follow the up-and-down movements of the diaphragm during respiration. The stone is likely to move in and out of focus during respiration. This issue has been studied, and ventilatory techniques such as decreased tidal volumes with increased respiratory rates and high-frequency jet ventilation have been used to increase the efficacy of the treatment.[113] Other data[114] and wide clinical experience with success rates of lithotripsy do not support or justify the routine use of these techniques, which add their own complexity and complications to the procedure.[115] Regional anesthesia and analgesia-sedation are frequently used for lithotripsy, in which case spontaneous ventilation is the only option. Studies in sedated patients with intercostal blocks and local infiltration anesthesia have documented that stone movement with spontaneous respiration is mainly restricted to the F2 focal zone during ESWL.[116]

Conventional ventilation during general anesthesia or spontaneous respiration during regional anesthesia is generally acceptable for lithotripsy. Occasionally in an awake patient, one may have to titrate sedation carefully, or if the patient is under general anesthesia, one may need to manipulate respiratory parameters to decrease abnormally large stone movement.

For effective stone disintegration, shock waves should reach the stone unimpeded. The flank area should be kept free of any medium that would provide an interface for the dissipation of shock wave energy. Nephrostomy dressings should be removed, and the nephrostomy catheter should be taped clear of the blast path. Similarly, epidural catheters and dressings should be taped well clear of the blast path. Pandit and associates[117] noted an unusually high rate of failure of lithotripsy in their patients receiving epidural fentanyl analgesia. They discovered that the

foam tape placed to secure the epidural catheter was frequently in the blast path of the shock waves and could absorb 80% of the shock wave energy.

Except when piezoelectric lithotripters or lithotripters with very low shock wave energy are used, the procedure is painful and requires some form of anesthesia. Shock waves produce sharp stinging pain at the entry site in the flank along with a sensation of deep visceral pressure discomfort.

Although shock waves pass through most tissues relatively unimpeded, they do cause tissue injury, the extent of which depends on the tissue exposed and the shock wave energy at the tissue level. Skin bruising and flank ecchymoses are common at the entry site. Painful hematoma in the flank muscles may occur. Hematuria is almost always present at the end of the procedure and results from shock wave–induced endothelial injury to the kidney and ureter. Adequate hydration is necessary to prevent clot retention. A decrease in postoperative hematocrit should arouse suspicion of a large perinephric hematoma. Punctate hemorrhages have been observed in the stomach and bowel, and this injury might be responsible for abdominal distention, nausea, and vomiting in some patients.

Lung tissue is especially susceptible to injury by shock waves. Air trapped in alveoli presents the classic water (tissue)-air interface to the shock wave and causes dissipation of energy with alveolar rupture and hemoptysis. Massive hemoptysis and death from pulmonary damage have been reported in laboratory animals after a single exposure of the thorax to a shock wave.[118] Shock wave–induced hemoptysis in a child and a pulmonary contusion with life-threatening hypoxemia in an adult have been reported.[119,120] Children are more likely to sustain pulmonary damage from shock waves because of the shorter distance of the lung bases from the kidneys than in adults. It is recommended that a Styrofoam sheet or Styrofoam board be placed under the back in children to shield the lung bases from shock waves during ESWL.[119,120]

Shock wave–induced cardiac arrhythmias previously reported in 10% to 14% of patients undergoing lithotripsy are extremely rare nowadays.[121,122] These arrhythmias are believed to be due to mechanical stress on the conduction system exerted by the shock waves. The intricate grounding system of the lithotripter ensures that any current-induced arrhythmias are unlikely. Atrial and ventricular premature complexes, atrial fibrillation, and supraventricular and ventricular tachycardia have been reported.[121,122] Artifacts on electrocardiogram also are common. Artifacts and arrhythmias usually disappear when the lithotripsy is stopped. Arrhythmias occasionally may persist and require treatment, however.

Physiologic Changes During Immersion Lithotripsy

Water immersion with the Dornier HM-3 lithotripter produces significant changes in the cardiovascular and respiratory systems (Table 65-16). Cardiovascular changes include an increase in central blood volume with an increase in central venous and pulmonary artery pressure.[123,124] Weber and colleagues[123] observed that increases in central venous pressure and pulmonary arterial pressure were directly correlated with the depth of immersion. The sitting position, together with general or epidural anesthesia, would tend to cause peripheral pooling and decreased venous return. A decrease in cardiac output and an increase in systemic vascular resistance during immersion lithotripsy under general anesthesia has been documented.[124] Respiratory changes with immersion up to the clavicles are significant; functional residual capacity and vital capacity are reduced by 20% to 30%, pulmonary blood flow has been shown to increase,[125,126] and tight abdominal straps and the hydrostatic pressure of water on the thorax impart a characteristic shallow, rapid breathing pattern.[126] Ventilation-perfusion mismatch and hypoxemia are more likely. The renal effects of immersion include diuresis, natriuresis, and kaliuresis. A decrease in antidiuretic hormone and renal prostaglandins occurs. The temperature of the bath water can cause profound changes in the patient's temperature. This heat transfer is augmented further by the vasodilation produced by general or epidural anesthesia. Hypothermia and hyperthermia have been reported.[127]

Table 65-16 Changes on Immersion during Lithotripsy

Cardiovascular	Increased	Central blood volume
	Increased	Central venous pressure
	Increased	Pulmonary artery pressure
Respiratory	Increased	Pulmonary blood flow
	Decreased	Vital capacity
	Decreased	Functional residual capacity
	Decreased	Tidal volume
	Increased	Respiratory rate

Anesthetic Choices for Lithotripsy

Anesthetic regimens used successfully for lithotripsy include general anesthesia, epidural anesthesia, spinal anesthesia, flank infiltration with or without intercostal blocks, and analgesia-sedation, including patient-controlled analgesia.[128-136] General anesthesia offers the advantages of rapid onset and control of patient movement. Ventilatory parameters can be controlled to decrease stone movement with respiration. Disadvantages include a likelihood of positional injury and difficulty in transporting an anesthetized patient to other locations if adjunctive procedures become necessary.

Epidural anesthesia offers the advantage that an awake patient can help with transfers, reducing the likelihood of injury. With epidural anesthesia using loss of resistance to air to identify the epidural space, only the smallest amount of air necessary should be injected. Air in the epidural space provides an interface and causes dissipation of shock wave energy and local tissue injury. Korbon and associates[137] found a decrease in epidural compliance and pain on injection with repeat epidurals for subsequent lithotripsies in their patients. In animal experiments, they were able to show epidural tissue damage after injection of air and exposure to shock waves.[138] It is reassuring, however, that in most lithotripsies performed under epidural anesthesia worldwide, neurologic injury has not been a problem.[139]

The main disadvantage of epidural anesthesia is its slow onset. Spinal anesthesia offers a reasonable alternative with its rapid onset. The incidence of hypotension (the patient is in a sitting position for treatment) is higher, however. In one series, the incidence of hypotension with general, epidural, and spinal anesthesia was 13%, 18%, and 27%.[140] Local anesthetic infiltration of the flank with or without intercostal blocks provides adequate anesthesia when combined with intravenous sedation and avoids hypotension.[128] Intravenous analgesia-sedation in various combinations has been used successfully by many anesthesiologists.[130,131]

Newer Lithotripters

Newer lithotripters have no water bath, and they tend to use multifunctional tables that allow other procedures, such as cystoscopy and stent placement, to be accomplished without moving the patient off the table. The shock waves are tightly focused, so they cause less pain at the entry site, and intravenous analgesia-sedation is the mainstay of anesthesia with these newer lithotripters. Other incidental interventions, such as cystoscopy, stone manipulation, or stent placement, alter anesthetic requirements. Many of these newer lithotripters have a much smaller focal zone for the shock waves. It is even more imperative that adequate analgesia and sedation be provided, so that stone excursion with respiration is limited to the focal zone. Most analgesia-sedation combinations are adequate. Even patient-controlled analgesia with alfentanil and a combination of propofol and alfentanil has been used.[141,142] Many centers routinely use general anesthesia with short-acting inhaled or intravenous anesthetics and employ laryngeal mask airway for ventilation.

Contraindications

Pregnancy and untreated bleeding disorders are the only contraindications to lithotripsy. Women of childbearing age must have a pregnancy test that is documented to be negative before lithotripsy. Standard tests of coagulation, such as the platelet count, prothrombin time, and partial thromboplastin time, should be obtained. Pacemakers, automatic implanted cardioverter-defibrillators (AICDs), abdominal aortic aneurysm, orthopedic prostheses, and obesity are no longer considered contraindications.

Patients with pacemakers can be treated safely if the pacemaker is pectorally placed and the following precautions are observed (see Chapter 43).[143-145] Pacemaker programmability should be established before the treatment, and the pacemaker should be switched to a nondemand mode in case the shock waves interfere with pacemaker function. Alternative means of pacing should be available. Although most pacemakers located pectorally are at a safe distance from the blast path, some may be damaged. Weber and coworkers[143] examined 43 different pacemakers and found that 3 were affected. Dual-chamber pacemakers tend to be more sensitive to interference. Treatment must be started at a low energy level and gradually increased while observing pacemaker function.

Manufacturers of AICDs and lithotripters generally consider an AICD a contraindication for lithotripsy. Patients with AICDs have been treated successfully with lithotripsy, however.[144] Transvenous AICDs are less of a concern than the older abdominally implanted defibrillators. AICD devices should be shut off immediately before lithotripsy and then reactivated immediately after treatment.[146]

Patients with small aortic aneurysms have been treated safely, provided that the stone is not close to the aneurysm. Orthopedic prostheses, such as hip prostheses and even Harrington rods, are not a problem if they are not in the blast path, which is usually the case. Positioning of obese patients may be problematic at times. Not only do extremely obese patients present anesthetic challenges related to obesity, but also focusing of the stone may be extremely difficult in the very obese, and it is common for the procedure to be abandoned in these patients because of an inability to bring the kidney stone into the F2 focal zone. It is prudent for focusing of the stone to be attempted before administering any anesthetic in this high-risk population. With the newer lithotripters, some of these patients may have to be placed prone, a position that they may not be able to tolerate safely.

Radical Surgery in Urology

Radical surgery is becoming common in the urologic suite with the introduction of radical nephrectomy, radical cystectomy, and radical retropubic prostatectomy. Common features include lengthy procedures, associated sudden and significant blood loss, and attention to renal function preservation. With radical nephrectomy, significant cardiorespiratory changes attendant to the flank position are a concern. Respiratory changes include decreases in thoracic compliance, tidal volume, vital capacity, and functional residual capacity. Dependent atelectasis is common and may lead to hypoxemia. Pneumothorax may occur and can have significant respiratory and hemodynamic consequences intraoperatively. It is common to see a decrease in blood pressure when the kidney rest is raised. This decrease is usually due to compression of the inferior vena cava. In addition, hepatic encroachment on the vena cava and mediastinal shift may reduce venous return and stroke volume further. Cervical plexus, brachial plexus, and common peroneal neuropathies may occur as a result of stretch or compression of nerves in the lateral position.

Radical Nephrectomy for Renal Cell Carcinoma

The most common malignancy of the kidney is renal cell carcinoma; 85% to 90% of all solid renal masses are renal cell carcinoma.[147] Because renal cell carcinoma is refractory to chemotherapy and radiation therapy, surgical resection or ablation can offer curative treatment of localized disease (Table 65-17). More recently, resection of the ipsilateral adrenal gland has been reserved for patients with large upper pole lesions or when the adrenal gland is enlarged or appears abnormal.[148] Partial nephrectomy (nephron-sparing surgery) is considered for patients with small lesions or bilateral tumors or for patients at risk because of other diseases, such as diabetes or hypertension.[147-150]

In 5% to 10% of patients, the tumor extends into the renal vein and the inferior vena cava and right atrium. Tumor extension into the inferior vena cava and atrium occurs more frequently with right-sided renal cell carcinoma. Several problems can occur

Table 65-17 Anesthetic Implications of Radical Nephrectomy for Tumors

85%-90% are for renal cell cancer
5%-10% extension to the IVC and right atrium
Large-bore IV access, A-line, IJV line (preferably on left side if IVC is involved)
Paraneoplastic syndrome
Hypercalcemia, eosinophilia; increased prolactin, erythropoietin, and glucocorticoids
Men > women
Chronic smoking history usually associated
CAD, COPD
Renal failure

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IJV, internal jugular vein; IVC, inferior vena cava.

in these patients, ranging from circulatory failure as a result of complete occlusion of the vena cava by tumor to acute pulmonary embolization of tumor fragments during surgery. To operate on these patients safely, the extent of the lesion must be defined preoperatively. Cardiopulmonary bypass is often required in these cases to prevent tumor embolization, and necessary with tumor thrombus extension into the upper portion of the hepatic vena cava or when venous return is significantly compromised. Right heart catheterization is potentially hazardous because of the danger that a part of the tumor may be dislodged and embolize. Some anesthesiologists use a central venous pressure catheter inserted through left internal jugular or external jugular vein so as not to place it beyond the superior vena cava. Central venous pressure in such cases may not reflect intravascular volume accurately because venous return through the inferior vena cava is impaired by the thrombus, and transesophageal echocardiography may be of value.[151] This decrease in venous return also predisposes the patient to hypotension during induction of anesthesia. Venous obstruction leads to dilation of the epidural veins and the development of abdominal wall and retroperitoneal collaterals. The emphasis is on appropriate preoperative preparation, which is possible only when the full extent of the lesion has been defined.[150]

Radical Prostatectomy

Localized prostate cancer is treated by either radiation therapy or radical prostatectomy (Table 65-18). Radical prostatectomy has become more commonly performed because of routine prostate-specific antigen testing in men older than 50 years and popularization of the nerve-sparing surgery to reduce the risk of impotence. Although originally described in 1905 via the transperineal approach, the retropubic approach is mostly used now. The prostate, the ejaculatory ducts, the seminal vesicles, and part of the bladder neck are removed along with the pelvic lymph nodes.

Generally, the procedure is performed by open laparotomy, but laparoscopic and robotic surgery are being used more frequently. The most common intraoperative problem is hemorrhage and massive blood loss requiring blood transfusion. Autologous predonation, preoperative recombinant erythropoietin therapy, intraoperative isovolemic hemodilution, and cell salvage are commonly practiced to reduce the patient's exposure to allogeneic blood. The routine use of these practices, their indications, and the need for transfusion in these patients have been questioned by some. Early postoperative complications, including deep vein thrombosis, pulmonary embolism, hematoma, seroma, and wound infection, occur in 0.5% to 2% of cases.[152] Death within 30 days has been reported by several centers to occur in approximately 0.2%.[152] Late complications include incontinence, impotence, and bladder neck contracture.[153] Patients undergoing radical prostatectomy are placed supine in the Trendelenburg position with the back extended, which places the pubis above the head. Air embolism from the prostatic fossa as a result of a gravitational gradient between the prostatic veins and the heart has been reported.[154]

Table 65-18 Anesthetic Implications of Radical Prostatectomy

Disease of the elderly
CAD, COPD, and renal dysfunction
Significant blood loss
Wide-bore IV access and invasive monitoring
Acute normovolemic hemodilution versus autologous blood donation
Hyperextended position
Nerve injuries, soft tissue injury, joint dislocations
Venous air embolism
Anesthesia
Benefits of regional anesthesia versus general anesthesia debated
Not known to influence mortality
Epidural anesthesia with spontaneous ventilation decreases blood loss
General or combined anesthesia with IPPV increases blood loss

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IPPV, intermittent positive-pressure ventilation.

Comparison of Anesthetic Techniques for Radical Prostatectomy

Epidural anesthesia, spinal anesthesia, general anesthesia, and combined epidural and general anesthesia have been used for this surgery. For the epidural component of combined techniques, a thoracic or a lumbar approach to anesthesia or analgesia has been used, and spontaneous ventilation or intermittent positive-pressure ventilation (IPPV) has been used for the general anesthesia component. Many investigators have reported their findings in comparing the three anesthetic techniques for radical retropubic prostatectomy,[155-158] and certain trends emerge.

Intraoperative blood loss is significantly less if epidural anesthesia or a combined epidural and general anesthetic with spontaneous ventilation is used. In one study, blood loss in the general anesthesia and the combined anesthesia group with IPPV was significantly more than in the epidural anesthesia group despite little difference in arterial pressure among the three groups.[155] It was postulated that the increased venous pressure as a result of IPPV was the most likely cause of increased bleeding in the general and the combined anesthesia groups during radical prostatectomy. Previous studies had shown that central and peripheral venous pressure was lower in patients during spontaneous ventilation under epidural anesthesia or combined epidural-general anesthesia than in patients receiving IPPV during general anesthesia.[159] Epidural anesthesia alone or when added to a general anesthetic decreases postoperative hypercoagulability, decreasing the risk of thromboembolism.[160] The preemptive analgesia provided by the epidural block decreases postoperative pain and analgesic requirements.[161] Homeostasis of neuroendocrine responses may be better maintained with regional block than with general anesthesia. Recovery of bowel function occurs faster with epidural anesthesia than with general anesthesia, although it does not result in earlier hospital discharge of the patient.[162]

The length of stay and the cost of hospitalization can be decreased with the judicial use of epidural anesthesia and established clinical pathways.[163,164] In one study, 80% of patients were satisfactorily discharged after 1 day, and the mean length of stay was 1.34 days.[165]

Although some studies report better outcomes with epidural anesthesia than with general anesthesia, others fail to support such results. The divergent findings in these studies com-

paring three anesthetic techniques may be a consequence of small numbers of subjects in many studies, difference in design (e.g., retrospective, prospective, controlled, randomized), the use of different techniques (e.g., thoracic versus lumbar epidural block), the use of spontaneous ventilation versus IPPV, and the use of local anesthetics with or without opiates. Local practices are based on the preferences of the urologist, the anesthesiologist, and the patient, and these preferences assume precedence over almost everything else.

Robotic Assisted Radical Prostatectomy

Many surgical advantages of robotic assisted radical prostatectomy (RARP) are described, including better visualization, more controlled finer movements of robotic arms allowing better dissection, decreased blood loss, less scarring and pain, shorter recovery time, faster return to daily activity, and possibly improved continence and potency rates (although these last outcomes have been suggested only given the short-term follow-up at this time). Anesthetic concerns are primarily related to steep head down tilt and pneumoperitoneum required for surgery.

Ventilatory and respiratory changes resulting from pneumoperitoneum include decreased compliance, increased airway pressures, increased ventilation-perfusion mismatch. Application of positive end-expiratory pressure improves oxygenation in these patients.[166] Hypercapnia develops within 15 to 30 minutes of carbon dioxide insufflation with resultant hypercarbia, acidosis, tachycardia, arrhythmias, and other deleterious hemodynamic and CNS effects.[167] Increase in mechanical ventilation can obviate these changes in most patients, and most healthy patients tolerate the changes even though they are clinically significant. Extraperitoneal insufflation of carbon dioxide is associated with larger increases in arterial P_{CO_2} than intraperitoneal insufflation.[168] Hemodynamic changes include decreased venous return with decreased cardiac output despite an increase in filling pressures indicative of increased intrathoracic pressures.

Physiologic changes resulting from steep head down tilt include hemodynamic effects such as decreased perfusion pressure of lower extremities, increased mean arterial pressure at the circle of Willis, increased central blood volume, decreased cardiac output, and a decreased perfusion of vital organs in a normovolemic patient. Increased myocardial oxygen consumption, ischemia, arrhythmias, and decreased oxygen delivery are potential risks in patients with cardiac disease. Respiratory effects of steep head down tilt—decreased compliance, reduced vital capacity and functional residual capacity, 20% decrease in lung volumes, and ventilation-perfusion mismatch—compound the effects of pneumoperitoneum. Pulmonary congestion and edema have been reported in susceptible patients.

Other significant effects of steep head down tilt include increased intracranial pressure and increased intraocular pressure, venous air embolism, brachial plexopathy, arthralgias, and finger injuries. Regurgitation in this position in patients with history of reflux increases their risk of aspiration. Maintaining normothermia may be a problem in some cases because of prolonged pneumoperitoneum with dry cold gases.

Compared with retropubic radical prostatectomy, robotic assisted radical prostatectomy is associated with much less blood loss, although in one study transfusion rate was not much different despite this finding.[169] Mild to moderate pain is expected postoperatively, and low pain scores of 0 to 4 have been reported after retropubic radical prostatectomy and robotic assisted radical prostatectomy using preemptive analgesia with ketorolac given intraoperatively combined with rescue opiate or nonopiate analgesia.[170] Most patients are discharged home the day after surgery. Use of robots in urologic surgery has been extended to include radical cystectomy, pyeloplasty, and renal and adrenal surgery in adults and children, and newer indications are developing.

Urogenital Pain Syndromes

Pain syndromes of the urogenital system result from inflammatory disease, anatomic anomalies, obstructive uropathy, and malignancies (see Chapter 58). The visceral type of renal pain is frequently caused by pyelonephritis or ischemic events secondary to an embolus or a thrombus. The hematuria in sickle cell disease or sickle cell trait is typically painless. The site of pain, the characteristics of referred pain, and the quality of pain help the clinician identify the source of pain.

Benign Renal Neoplasms

Flank pain is a common symptom in adults with angiomyolipoma (more common in women than in men) and in children with mesoblastic nephroma and Wilms' tumor or nephroblastoma. Nephroblastomas may be combined with several congenital malformations, such as sporadic anhidrosis (lack of sweating), microcephaly, mental retardation, and spina bifida. Treatment consists of surgical resection of the tumor supplemented by chemotherapy and adequate pain management. Opiates are the mainstay of pain management.

Renal Cell Carcinoma

Renal cell carcinoma, also known as hypernephroma, is characterized by the classic triad of hematuria, flank pain, and a renal mass. The development of pain may be a warning sign for metastatic disease. Pain control becomes an important issue with metastatic disease, and an intrathecal implantable pump or permanent placement of an epidural catheter for continuous delivery of pain medications may be indicated. Less than 5% of tumors of renal origin are sarcomas; most are leiomyosarcomas. The peak age is the fourth and fifth decades of life. Flank pain is usually the initial symptom, and this pain is mainly due to stretching of Gerota's fascia or compression and invasion of intercostal nerves, or both.

Inflammatory Renal Diseases

Inflammatory renal diseases commonly producing flank pain include acute pyelonephritis, pyelitis, renal carbuncle, and perinephritic abscess. Spiking fever is an important associated finding that suggests the presence of infection. The most prominent sign is tenderness in the flank. Because the kidneys are retroperitoneal organs, peritoneal signs develop very late. The differential diagnosis must include pneumonitis, pancreatitis, appendicitis, and cholecystitis. Oral or parenteral narcotics are very effective for pain control. Systemic antibiotics and fluid resuscitation are important for the management of renal infections.

Perinephritic fasciitis is an inflammation of the renal capsule and fascia of Gerota, and it may follow a perinephritic abscess. Depression of the immune system (e.g., owing to human immunodeficiency virus infection, chemotherapy, radiotherapy) and sickle cell disease are the major risk factors. Perinephritic abscesses need to be drained. Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in treating the associated reflex skeletal muscle spasm.

Idiopathic nephralgia is a rare condition that mimics renal pain and other urologic symptoms. The pain is thought to originate from uncoordinated hyperactivity and spasms of calyces and the renal pelvis. A comprehensive psychological evaluation may be required to eliminate psychological factors as a source of pain. Diagnostic and therapeutic paravertebral blocks may help diagnose and treat this disabling pain condition.

Pseudorenal pain syndromes are caused by genital nerve entrapment and ilioinguinal neuropathy after inguinal surgery, and they may mimic renal pain. Referred pain in the dermatomal distribution is characteristic of these conditions. Diagnostic and therapeutic ilioinguinal or genitofemoral nerve blocks help establish the diagnosis and treat this pain. In congenital polycystic kidney disease, renal pain is caused by distention of the cysts and stretching of Gerota's fascia. Hemorrhage in the cysts, rupture of the cysts, or infection produces exacerbation of pain. Surgical intervention, including percutaneous drainage of solitary renal cysts, may relieve the symptoms. Renal vein thrombosis and renal infarctions cause acute or acute-on-chronic pain syndromes. Along with treatment of shock and embolectomy, narcotics are used to control pain.

Obstructive Uropathy

Obstruction of the urinary tract causes severe pain in the flank. Chronic conditions cause a constant dull ache, in contrast to the spasmodic episodic pain with acute obstruction. Surgery may be indicated. Generally, pain from the upper third of the ureter is referred to the loin, pain from the middle third is referred to the iliac fossa, and pain from the lower third is referred to the suprapubic and groin area. The pain caused by ureteric calculi is often felt in the upper inner aspect of the thigh and the ipsilateral testicle in males and the labia majora in females. NSAIDs are helpful in relieving pain, an effect believed to be due to the antiprostaglandin action of NSAIDs. Ketorolac is the only NSAID available in injectable form and is a drug of choice for renal colic. Calcium channel blockers (verapamil, diltiazem, and nifedipine) have been effective in treating ureteric colic. Although it is believed by some clinicians that morphine and meperidine may have a spasmogenic effect on the ureter, opiates remain the mainstay of treatment of ureteric colic.

Bladder Pain

Bladder pain is mostly a dull ache and is usually localized to the suprapubic region. The most common causes of pain are bladder distention by obstruction and cystitis. Bladder distention accompanied by acute or chronic inflammation is manifested as severe suprapubic spasmodic pain, urinary frequency, and dysuria. Treatment of the cause of inflammation (e.g., obstruction, stone, enlarged prostate, vesicoureteral reflux) is the treatment of choice for pain. Untreated cystitis may result in upper urinary tract infection. Pregnancy, diabetes mellitus, and immunodeficiency are additional risk factors.

Interstitial cystitis is a condition with unknown cause that frequently poses a challenge to physicians. The pathologic features of interstitial cystitis are nonspecific chronic inflammatory infiltrates, edema, and vasodilation. Suprapubic pain is due to bladder spasm or uncoordinated detrusor muscle contraction. Suprapubic pain and the frequency of micturition may become so incapacitating that cystectomy may be required in extreme cases. Options for pain control include bladder denervation (rhizotomy), transurethral electrocautery, cystolysis, presacral nerve blocks, and neurolytic blocks. Medical management includes antihistamines, corticosteroids, anticholinergics, and calcium channel blockers.[171]

Urothelial Tumors

The most common urothelial tumor is transitional cell carcinoma of the urinary bladder. Painless hematuria is the most common manifestation. Thirty percent of patients initially may complain of bladder irritability, which is thought to be due to muscular involvement. Surgical treatment includes fulguration, transurethral resection, or more extensive radical cystectomy with urinary diversion. Pain control is an integral part of treatment in metastatic disease of the bladder.

Testicular Pain

The most common testicular congenital anomaly producing pain is cryptorchidism. Pain in an undescended testis without trauma usually indicates infection or torsion. Emergency surgical exploration is the treatment of choice. The incidence of malignancy is 20 times higher in an undescended testis than in a descended testis. Bacterial or viral orchitis or epididymo-orchitis is a painful condition that needs urgent attention.

Tumors of the testis are generally malignant; however, extratesticular tumors within the scrotum are usually benign. The earliest sign of the tumor is a painless testicular mass. Pain is a late sign and is usually described as a dull ache, testicular heaviness, or dragging. Treatment of testicular tumor depends on the cell type and disease stage. Seminoma is generally radiosensitive.

Prostatic Pain

Acute or chronic prostatitis is very painful. Acute prostatitis is usually caused by a bacterial infection and responds to antibiotic therapy. Chronic prostatitis is due to inadequate treatment of acute infection, recurrent infection, or prostatic uroliths. Treatment includes prostatic massage, NSAIDs, antibiotics, and surgical drainage.

Adenocarcinoma of the prostate is the most common male cancer and is usually painless. Rectal or sacral pain with prostatic cancer may be a sign of metastatic disease. Patients with sacral or pelvic pain should be investigated for bone metastasis. Oral or parenteral high-dose opiates are the mainstay of treatment initially. Permanent placement of an epidural catheter or intrathecal

implantable pump for continuous delivery of medications and radiation therapy should be considered for metastatic disease.

Priapism

Priapism is a prolonged pathologic and painful erection caused by engorgement and thrombosis of the pelvic veins. It is seen in patients with metastatic malignant diseases such as pancreatic cancer and leukemia, pelvic trauma, sickle cell disease, or spinal trauma. Pathology of the corpora and local neurovascular abnormality also can cause priapism. Prompt therapy should be instituted to control pain and prevent subsequent impotence from fibrosis of the corpora cavernosa. The cause of priapism may be important in defining the treatment. Sickle cell priapism is treated with hydration, alkalinization, and blood transfusion to increase hemoglobin to more than 10 mg/dL. The priapism associated with leukemia responds to radiation therapy. Intracorporeal injection of phenylephrine is recommended for selected cases of priapism. Stepwise institution of pain medications from NSAIDs to opiates is recommended. Severe pain warrants parenteral administration of morphine or hydromorphone.

Peyronie's disease is a sexually crippling condition that causes severe penile pain during sexual intercourse because of curvature. The treatment of choice is surgery and NSAIDs for pain.

Female Genital Pain

Vulvodynia is a chronic pain condition of unknown cause that is associated with sexual inactivity or dysfunction, depression, anxiety, and obsessive behavior. Vestibulitis is characterized by painful penetration during coitus. It is more common in white women and is resistant to most medical treatment. Some success with tricyclic antidepressants and antihistamines has been reported. Heat treatment (sitz bath) also is helpful.

Chronic dysmenorrhea is a severe pain-producing condition caused by the hypercontractility of uterine muscles during menstruation. Ovulation suppression and the use of NSAIDs are effective because of the antiprostaglandin effect. Presacral neurectomy can be considered as a last resort after other options have been tried and failed.

Uncoordinated contraction of the muscles of the pelvic floor (levator ani, pubococcygeus, and deep transverse perineal) causes vaginismus. It produces extreme spasms and painful sexual dysfunction. Psychological factors, such as rigid sexual upbringing and traumatic sexual experience, inadvertently reinforce the vaginal spasm. Treatment involves correction of any physical conditions and then behavior modification that includes desensitization techniques.

Dyspareunia is defined as recurrent and persistent genital pain before or after intercourse; it may be due to infection, trauma, or lack of lubrication. Treatment includes psychotherapy and systemic desensitization.

Chronic pelvic pain also is known as pelvic congestion, pelvic fibrosis, pelvic neurodynia, and pelvic sympathetic syndrome. The pain is often multifactorial and requires multidisciplinary pain management involving psychotherapy, medications, and trigger point injections. In selected cases, nerve root blocks and neuraxial opioid therapy are promising. Metastatic disease of the cervix and uterus can cause severe vulvovaginal pain syndrome and requires aggressive opioids and adjuvant pain treatment.[172]

Role of Sympathetic Blocks

The pelvic viscera in men and women—the urogenital organs, the colon, and the rectum—are supplied by afferent fibers from the lumbar sympathetic chain. The pelvic pain caused by either inflammatory diseases or cancer can be relieved by interruption of bilateral sympathetic pathways,[173,174] which can be achieved with a superior hypogastric plexus block (see Chapter 58). The superior hypogastric plexus is a retroperitoneal structure that is formed by confluence of the bilateral lumbar sympathetic chains; it is situated between the body of the L5 and S1 vertebrae. Interruption of the ganglion impar is targeted to mixed somatic and sympathetic pain arising from the distal end of the urethra, the vulva, the perineum, and the distal third of the vagina.

General Considerations

General considerations for genitourinary pain management follow the same principles of pain management elsewhere. For nonmalignant acute pain, medical management is the first choice. Narcotics and non-narcotic medications, such as acetaminophen, aspirin, and NSAIDs, are indicated for the control of acute pain. Tricyclic antidepressants (amitriptyline and nortriptyline) are often the first choice for neuropathic pain. Difficult neuropathic pain may respond well to the combination of tricyclic antidepressants and anticonvulsant agents (gabapentin and pregabalin). When oral administration is not feasible, parenteral administration of narcotics should be used. Patient-controlled epidural analgesia or continuous epidural infusion produces segmental dose-related analgesia and prevents atelectasis. The use of lipophilic versus hydrophilic narcotics depends on the segmental level of epidural catheter placement. Intravenous patient-controlled analgesia should be the next option. Meperidine and morphine should be avoided in patients with compromised renal function because of the long half-life of metabolites. Normeperidine, a metabolite of meperidine that lowers the seizure threshold and induces CNS excitability, and morphine-6-glucuronide and morphine-3-glucuronide metabolites of morphine may accumulate and enhance sedation and respiratory depression in patients with renal failure. Hydromorphone, a semisynthetic opioid, is recommended for patients with renal failure because of the lack of identifiable metabolites. The antiprostaglandin effect of NSAIDs affects the regulation of renal blood flow in susceptible patients. Patients requiring long-term NSAIDs should be appropriately monitored for renal function.

A pain management algorithm based on a World Health Organization–recommended stepladder approach to management of malignant pain syndromes is shown in Figure 65-5. Interventional techniques are an integral part of pain control in chronic nonmalignant and malignant pain syndromes. Continuous epidural infusion of opioids causes minimal fluctuation of drug levels in cerebrospinal fluid. Before consideration of a tunneled epidural catheter, pain should be treated aggressively with sustained-release morphine preparations, methadone, and fentanyl transdermal patches to optimize the medication requirement. If

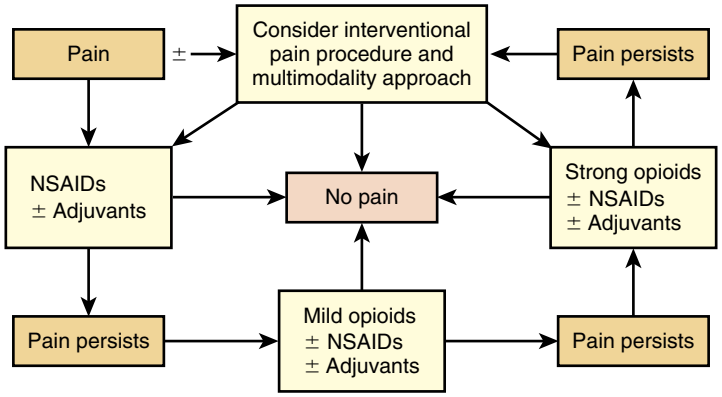

Figure 65-5 Cancer pain management algorithm based on World Health Organization stepladder approach to pain management. NSAIDs, nonsteroidal anti-inflammatory drugs.

intractable pain persists despite aggressive systemic opioids and adjuvant drug therapy, treatment with an implantable drug delivery system should be considered. Methadone is often an alternative to opioid-tolerant patients with neuropathic pain owing to its mu receptor agonistic and *N*-methyl-D-aspartate receptor antagonistic effect. Because of the safety, efficacy, and relative ease of intraspinal administration of opioids for the control of intractable pain resulting from metastatic disease, implantable intrathecal and epidural drug administration systems are being used increasingly.

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66 Anesthesia and the Hepatobiliary System

Key Points

1. All volatile anesthetics decrease hepatic blood flow, but desflurane and sevoflurane have the least significant effect on total hepatic blood flow and hepatic oxygen delivery, whereas halothane induces the most profound reductions in hepatic blood flow.
2. Advanced liver disease may impair the elimination, prolong the half-life, and potentiate the clinical effects of several drugs, including morphine, meperidine, alfentanil, vecuronium, rocuronium, mivacurium, benzodiazepines, and dexmedetomidine. These drugs should be used cautiously in patients with cirrhosis or end-stage liver disease from any cause and their dosage and administration should be adjusted accordingly.
3. Abnormal liver enzyme test results may be seen in up to 4% of normal individuals and up to 36% of psychiatric patients, although the prevalence of clinically significant hepatic dysfunction in these individuals is less than 1%, thus suggesting that further costly preoperative testing is unnecessary in asymptomatic patients.
4. Patients with asymptomatic elevations in serum transaminase levels (less than two times normal values) may undergo surgery with minimal impact on perioperative outcome.
5. Retrospective data suggest that patients with acute hepatitis from any cause are at increased risk for hepatic failure and death after elective surgery. Thus, elective surgery should be delayed in these individuals until resolution of acute hepatocellular dysfunction can be confirmed.
6. Asymptomatic patients with any form of chronic hepatitis should be carefully assessed before elective surgery and meticulous care should be taken to maintain hepatic perfusion in the perioperative period and to avoid any hepatotoxic drugs or significant hypotension that might precipitate liver failure or hepatic encephalopathy.
7. Based on large retrospective studies, patients with cirrhosis who are undergoing abdominal surgery, especially those in CPT class C, appear to have an increased risk of perioperative death. Elective surgery in these individuals should be avoided, if possible, in favor of less invasive procedures.
8. Postoperative jaundice may occur as a result of intraoperative hepatobiliary injury, anesthetic-induced hepatotoxicity, severe hepatic hypoperfusion (e.g., cardiogenic or hypovolemic shock), and a variety of medications.
9. Patients with the most advanced forms of liver disease (e.g., CPT class B or C cirrhosis) should receive management designed to maximize hepatic perfusion and hepatic oxygen delivery and to prevent and treat the complications of hepatic encephalopathy, cerebral edema, coagulopathy, hemorrhage, and portal hypertension.

The liver is the largest internal organ in the body and it plays a critical role in the homeostasis of many physiologic systems, including nutrient and drug metabolism, synthesis of plasma proteins and critical hemostatic factors, and detoxification and elimination of many endogenous and exogenous substances.[1] Acute or chronic liver dysfunction can impair the response to anesthesia and surgery in several critical ways, whereas certain anesthetics and hemodynamic disturbances can induce unique and serious alterations in postoperative hepatic function.

In this chapter we will review the anesthetic implications of acute and chronic liver disease, discuss the impact of anesthetics on hepatic function, evaluate perioperative changes in liver function test results and hepatobiliary function, and provide periprocedural considerations for some selected surgical procedures involving the liver and gallbladder.

Effect of Anesthetics on Hepatic Function

This section will focus on the impact of volatile and intravenous anesthetics on liver blood flow and hepatic function. Halothane

hepatitis and related volatile anesthetic-induced hepatotoxicity are discussed in Chapter 24.

Volatile Anesthetics

Volatile anesthetics variably affect blood flow to the liver, whereas intravenous anesthetics and opioids have a less significant impact, although their propensity to alter hepatic blood flow has been less extensively investigated than that of volatile agents. Interpretation of clinical and experimental results is further limited by numerous potential confounding variables that may influence hepatic blood flow and liver function, including the animal species studied, subject age, intravascular volume status, type of mechanical ventilation used, body position at the time of physiologic measurements, simultaneous surgical procedures, changes in blood pressure, concomitant use of vasopressor drugs and local anesthetics, and alterations in hemoglobin and arterial oxygen concentrations. Despite these variables, reasonably firm conclusions can be reached regarding the impact and probable clinical significance of anesthetic agents on hepatic function in normal and cirrhotic patients.

The impact of volatile anesthetics on hepatic blood flow (including hepatic arterial and portal venous blood flow), oxygen delivery, and hepatic oxygen supply-demand ratios has been extensively evaluated for all the major volatile anesthetics, primarily in rat and pig experimental models. Available data from human studies also support the findings of these early experimental investigations.[2,3] A variety of measurement techniques have been used to assess hepatic and portal venous blood flow, but plasma clearance of indocyanine green is most commonly used to assess hepatic blood flow. Transesophageal echocardiography is a new investigative tool that has been used to evaluate hepatic vein flow, but it can be considered only an indirect measurement of hepatic perfusion and oxygenation. A novel technique involving pulsed Doppler probes implanted in animals and in humans undergoing cholecystectomy has allowed accurate measurement of hepatic arterial and portal vein blood flow.[4] Most anesthetics decrease portal blood flow (PBF) because of decreased cardiac output; however, hepatic arterial blood flow (HABF) may increase, although often not sufficiently to restore total hepatic blood flow (THBF) to normal values.[5] THBF is equal to the sum of PBF and HABF. A consistent finding from most studies has been a reduction in mean arterial pressure (MAP) and a modest decrease in cardiac output with all volatile anesthetics but a more pronounced reduction in PBF, HABF, and THBF with halothane and enflurane than with isoflurane and sevoflurane (Fig. 66-1).[2-4,6-10] These changes generally apply across a range of minimum alveolar concentrations (MACs). Volatile anesthetics also alter portal venous and hepatic arterial vascular resistance to variable degrees, which in conjunction with decreases in cardiac output, MAP, and mesenteric sympathetic activity modifies hepatic vascular supply.[11]

Although all current volatile anesthetics decrease MAP and PBF, halothane has a more consistently dramatic impact on HABF. Halothane appears to cause vasoconstriction in the hepatic arterial vascular bed, as reflected by an increase in hepatic arterial resistance.[4,12] In vivo videomicroscopy after halothane exposure in rats has demonstrated reduced sinusoidal blood flow as a result of decreased sinusoidal diameter, thus providing direct evidence of vasoconstriction at the microvascular level.[12] In contrast, isoflurane increased flow velocity in hepatic sinusoids and in this way preserved microvascular blood flow more than halothane or enflurane.[12] Interestingly, Benumof and colleagues[13] demonstrated markedly reduced HABF after halothane administration in two patients during hepatic arteriography; hepatic blood flow returned to normal 20 minutes after discontinuation of halothane anesthesia.

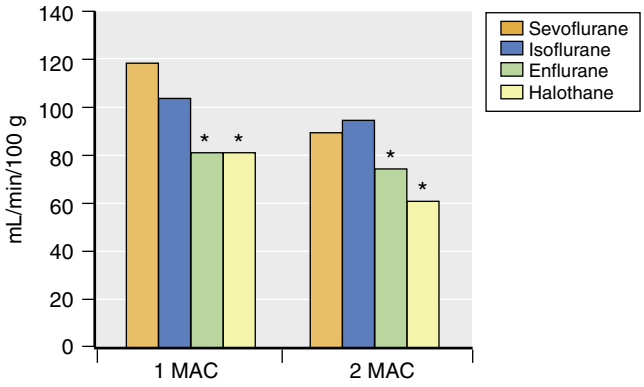

Figure 66-1 Impact of halothane, enflurane, isoflurane, and sevoflurane at 1.0 and 2.0 minimum alveolar concentration (MAC) on total hepatic blood flow (THBF) in dogs. THBF decreased with increasing anesthetic concentrations of each volatile agent. Sevoflurane and isoflurane were similar in their modest effect on THBF, whereas halothane caused a dramatic decrease in THBF, especially at 2-MAC exposure. *Differs from sevoflurane and isoflurane at comparable MAC values ($P < .05$). (*Data from Frink EJ, Morgan SE, Coetzee A, et al: The effects of sevoflurane, halothane, enflurane, and isoflurane on hepatic blood flow and oxygenation in chronically instrumented greyhound dogs. Anesthesiology 76:85-90, 1992.*)

Halothane also reduces hepatic oxygen delivery and hepatic venous oxygen saturation (Fig. 66-2).[14] These changes are related to decreased MAP and more dramatic reductions in cardiac

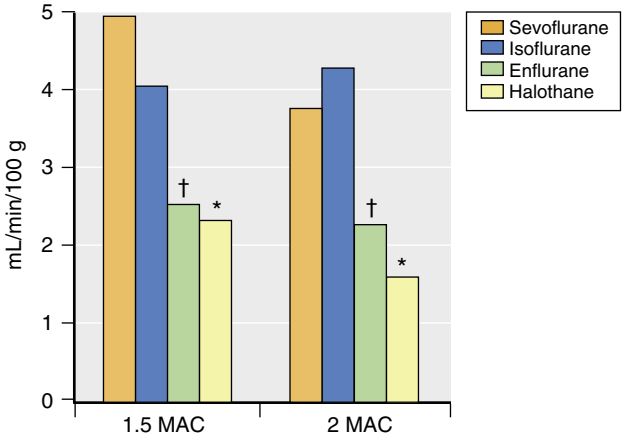

Figure 66-2 Impact of halothane, enflurane, isoflurane, and sevoflurane at 1.5 and 2.0 minimum alveolar concentration (MAC) on hepatic arterial oxygen delivery in chronically instrumented dogs. Halothane produced the greatest reduction in hepatic arterial oxygen delivery, whereas sevoflurane and isoflurane had insignificant effects on oxygen delivery at any MAC level. *Differs from isoflurane and sevoflurane at comparable MAC values ($P < .05$). †Differs from sevoflurane at comparable MAC values ($P < .05$). (*Data from Frink EJ, Morgan SE, Coetzee A, et al: The effects of sevoflurane, halothane, enflurane, and isoflurane on hepatic blood flow and oxygenation in chronically instrumented greyhound dogs. Anesthesiology 76:85-90, 1992.*)

output with halothane than with any other volatile anesthetics.[5] Gelman and associates[9] demonstrated that during surgical stress in pigs, fentanyl or isoflurane anesthesia, which decreases blood pressure by less than 30%, provides adequate oxygen supply whereas halothane anesthesia, which produces decreases in blood pressure greater than 30%, provides inadequate hepatic oxygen supply. This finding also applied to episodes of hepatic ischemia, where fentanyl or isoflurane provided better protection than halothane or enflurane. In addition to vascular changes, hepatic function, as measured by serum transaminase levels, also suggests an unfavorable impact of halothane versus isoflurane.[3]

Volatile anesthetic-induced alterations in hepatic blood flow are, in part, mediated by an autoregulatory mechanism that maintains constant THBF. This physiologic adaptation is termed the *hepatic arterial buffer response* (HABR), which matches reductions in PBF with increases in HABF to maintain total blood flow to the liver constant in the presence of profound hypovolemia, indirect effects of major abdominal surgery, or severe hemorrhage.[15] Halothane appears to disrupt this compensatory response, whereas sevoflurane and isoflurane maintain HABR.[15,16] Sevoflurane further suppresses hepatic arterial vasoconstriction and thus maintains HABF more effectively than halothane does.[17] Sevoflurane is also consistently equivalent or superior to isoflurane in maintaining HABF, hepatic O_2 delivery, and O_2 delivery-to-consumption ratios.[10,18,19] In addition, laboratory studies demonstrate insignificant changes in conventional liver function test results after exposure to isoflurane or desflurane.[3,20-22]

The encouraging results obtained with sevoflurane versus older volatile anesthetics are further supported by the observation that compound A produced by prolonged, low-flow sevoflurane anesthesia does not adversely affect hepatic function in adult surgical patients as determined by liver function testing or measurement of arterial ketone body ratios, a putative measure of hepatocyte function.[23-27] In the largest clinical study of sevoflurane, Bito and colleagues[27] noted mild postoperative increases in bilirubin and transaminase values in 100 surgical patients receiving low- and high-flow sevoflurane or isoflurane anesthesia but no evidence of clinical hepatotoxicity. It is notable that routine liver function test results are often mildly elevated after surgery and anesthesia using a variety of different volatile anesthetics, although the specific contribution of the anesthetic itself is debatable.[3,23,24,28]

Administration of either sevoflurane[25,26,29] or desflurane[30,31] to human volunteers not undergoing surgery produced no significant abnormalities in liver function test results, thus suggesting that other perioperative surgical factors may induce mild, transient alterations in plasma transaminase levels. In fact, early human investigations found steep declines in estimated hepatic blood flow immediately after the induction of anesthesia that correlated with the decrease in blood pressure[32]; hepatic blood flow rapidly returned to normal soon after the start of surgery, suggesting global reductions in cardiac output and blood pressure as mechanisms responsible for the reduced hepatic blood flow rather than a sustained adverse influence of specific volatile or intravenous anesthetics on hepatic blood flow.

Desflurane has effects similar to those of isoflurane on hepatic blood flow and function when assessed in animal and human investigations. In chronically instrumented dogs, Merin and associates[33] demonstrated slight, but significant decreases in THBF at 1.75 MAC as a result of decreased PBF but no significant differences between desflurane and isoflurane in any measure of hepatic blood flow over a range of MAC values. Armbruster and coworkers[21] observed decreased THBF at 1 MAC desflurane in pigs, but only at levels of hypotension unlikely to be encountered clinically and without alterations in liver function test results. Other canine data suggest better preservation of THBF with desflurane than with halothane or isoflurane (Fig. 66-3).[34] Subsequent studies in human volunteers examining hepatic function rather than hepatic blood flow failed to demonstrate any hepatotoxic effects of desflurane.[29-31]

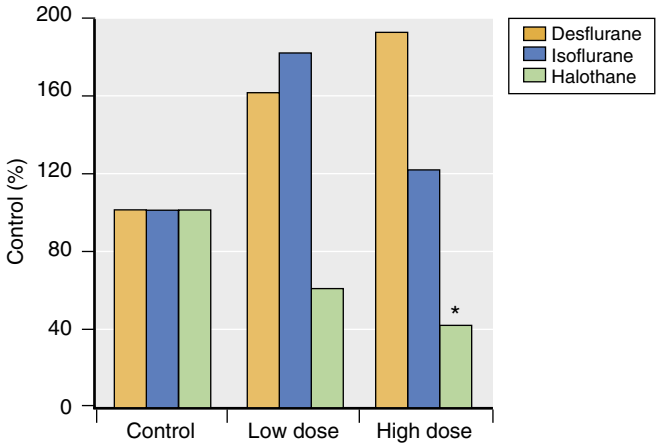

Figure 66-3 Influence of low- and high-dose desflurane, halothane, and isoflurane on total hepatic blood flow (THBF) as measured with radioactive microspheres in chronically instrumented dogs. In contrast to desflurane and isoflurane, which increased THBF, halothane caused a significant decrease in THBF at high doses. *Significantly different from conscious control ($P < .05$). (*Data from Hartman JC, Pagel PS, Proctor LT, et al: Influence of desflurane, isoflurane and halothane on regional tissue perfusion in dogs. Can J Anaesth 39:877-887, 1992.*)

In contrast to healthy volunteers and surgical patients, substantially less information is available describing the impact of anesthetics on hepatic function in patients with advanced liver disease. Limited data suggest that desflurane and isoflurane do not change perioperative liver function test results in adult surgical patients with chronic liver disease.[35] Isoflurane seems to be more efficient at preserving hepatic blood flow in cirrhotic animals than ketamine or halothane,[36] although other studies show no difference in hepatic function in cirrhotic rats exposed to fentanyl, halothane, enflurane, or isoflurane.[37] However, based on the less favorable effects of halothane on both hepatic blood flow and hepatic function, its use should be avoided in patients with advanced liver disease. Given the current availability of suitable alternative volatile anesthetics and the overall declining use of halothane, this issue has become primarily of historical interest. Moreover, as a consequence of the hepatotoxic potential of halothane, many authorities currently consider it unjustifiable to use halothane in healthy adults or any patient with significant hepatic dysfunction.

In this regard, consideration for newer inhaled anesthetics devoid of hepatotoxicity bear mentioning. Xenon, an inert gas, first described as having anesthetic properties in 1951,[38] has been considered to be an ideal inhaled anesthetic because it is nonexplosive and nonflammable, exhibits low toxicity, has no known teratogenic effects, and has rapid induction and recovery profiles owing to its extremely low blood-gas coefficient of 0.115, the lowest of all known anesthetics.[39,40] It has no significant effect on

left ventricular function, systemic vascular resistance, or systemic blood pressure.[40-42] Its hemodynamic profile is similar to propofol anesthesia in humans[41] and was associated with less hypotension and no effect on left ventricular function when compared with isoflurane in human studies.[42,43] Whereas animal investigations suggest a substantial increase in cerebral perfusion with xenon when compared with intravenous anesthetics, it appears to have no effect on other regional organ perfusion, including liver perfusion. It does not alter HABF; and given the absent effect on cardiac output, it should, in theory, have no impact on THBF (unlike all other volatile anesthetic agents). It also does not alter the results of liver function tests. In an experimental model, Reinelt and associates noted higher hepatic venous oxygen content levels in pigs exposed to 73% to 78% xenon versus intravenous anesthesia with pentobarbital and buprenorphine.[44] Their observations were considered to be secondary to a possible reduction of plasma catecholamine levels and subsequent reduced hepatic metabolism and increased hepatic venous oxygen content. Xenon may therefore prove to be an ideal anesthetic relative to hepatic perfusion. Larger clinical trials in patients with both normal and abnormal hepatic function are necessary before definitive conclusions can be reached relative to its safety in patients with acute and chronic liver disease. Unfortunately such a trial with xenon is unlikely.

In summary, the influence of volatile anesthetics on hepatic blood flow and function is complex and related not only to features unique to the anesthetic itself but also to other patient-related variables such as the severity of underlying liver dysfunction, the presence of advanced age, and the impact of surgical stress and intra-abdominal surgical manipulation. However, sevoflurane, desflurane, and isoflurane have been consistently shown to better preserve hepatic blood flow and function than halothane or enflurane. Large-scale prospective studies will be necessary to better define the impact of newer volatile anesthetics on hepatic blood flow in patients with advanced liver disease.

Intravenous Anesthetics

When compared with volatile anesthetics, less information is available regarding the impact of intravenous anesthetics on hepatic function (see Chapters 26 and 27). Early investigations suggested that etomidate and thiopental decreased hepatic blood flow, either from increased hepatic arterial vascular resistance or from reduced cardiac output and blood pressure,[45] whereas ketamine has little impact on hepatic blood flow, even with large doses.[46] With the use of sensitive radiolabeled microsphere determinations of organ blood flow in animals, propofol increased THBF in both the hepatic arterial and portal venous circulation, suggesting a significant splanchnic vasodilator effect of propofol.[47,48] THBF was maintained in some animal models even with significant reductions in MAP,[49] whereas others showed decreased mean hepatic blood flow despite increased MAP, a finding attributed to species-specific effects of propofol.[50] Propofol probably has a more favorable splanchnic and hepatic oxygen delivery balance than halothane.[51] Based on limited clinical and experimental data, intravenous anesthetics have only a modest impact on hepatic blood flow and no meaningful adverse influence on postoperative liver function when arterial blood pressure is adequately maintained.

Central Neuraxial Blockade

The effect of spinal or epidural anesthesia on liver blood flow and hepatic function is not clearly an anesthetic drug-induced alteration in hepatic function (see Chapter 51). Early human investigations by Kennedy and colleagues[52,53] showed that hepatic blood flow decreased during high spinal and epidural anesthesia and appeared to mirror simultaneous reductions in systemic arterial blood pressure. Other animal data have suggested reduced PBF and unchanged HABF with high epidural blockade, thus causing a decrease in THBF.[54] These adverse changes may be reversed and hepatic blood flow may be maintained with the administration of vasopressor drugs (e.g., dopamine or ephedrine) to restore PBF[55-57] or fluid administration to maintain normal arterial blood pressure.[58] Presumably, hypotension-induced reductions in hepatic blood flow are secondary to decreased splanchnic blood flow and, thus, reduced PBF. More recently, Vagts and coworkers noted no change in hepatic oxygen delivery and uptake in anesthetized pigs undergoing thoracic epidural anesthesia with bupivacaine, despite a decrease in HABF. In this study, administration of fluids intravenously before thoracic epidural anesthesia had no effect on THBF.[59]

Effect of Hepatic Dysfunction and Hepatobiliary Disease on Anesthetic Drug Pharmacokinetics

Liver disease may have a significant impact on drug metabolism and pharmacokinetics as a result of alterations in protein binding, reduced levels of serum albumin and other drug-binding proteins, altered volume of distribution because of ascites and increased total-body water compartments, and reduced metabolism secondary to abnormal hepatocyte function (see Chapter 19). In addition, sedatives and opioids may have exaggerated effects in patients with advanced liver disease and may either induce or worsen hepatic encephalopathy.[60] The impact of chronic alcohol ingestion on hepatic enzyme induction may also influence the ultimate effect of drugs in patients with cirrhosis.

The impact of liver disease on drug disposition depends not only on the elimination pathways for a given drug but also on the severity of the underlying hepatic dysfunction. The efficiency of drug removal by the liver is determined by several factors, including hepatic blood flow, hepatic enzyme activity and efficiency, the extent of plasma protein binding, cholestasis-induced alterations in the enterohepatic circulation and metabolism of enteral drugs, and the presence of portosystemic shunts that exclude certain drugs from elimination by the diseased liver.[61] In addition, the influence of liver disease on drug elimination differs for enteral and parenteral drugs.[60] In general, severe liver disease predictably alters the metabolism of drugs with large extraction ratios, such as lidocaine and meperidine, where clearance is primarily dependent on hepatic blood flow or portosystemic shunting. Conversely, the metabolism of low-extraction drugs, such as the benzodiazepines, is influenced mainly by protein binding, where unbound drug is available for elimination,

and by intrinsic hepatic clearance and metabolism, which is reduced in accordance with the severity of hepatocellular dysfunction.[60,61] However, an increased free fraction of a drug because of reduced levels of plasma proteins may counter the impact of reduced hepatic metabolism and lead to modest changes in the ultimate effect of the drug.[61] Finally, greater free fractions of available drug as a result of reduced protein binding may lead to greater drug deposition in tissues (and a potentially increased volume of distribution), which in conjunction with reduced hepatic metabolism may increase drug half-life.[61] It is evident that drug pharmacokinetics in the presence of advanced liver disease is complex. The impact on different classes of drugs is discussed separately.

Opioids

The significantly reduced metabolism of morphine in patients with advanced cirrhosis leads to a prolonged elimination half-life, markedly increased bioavailability of orally administered morphine, decreased plasma protein binding, and potentially exaggerated sedative and respiratory-depressant effects (see Chapter 27).[61] Although extrahepatic metabolism may contribute to morphine clearance in patients with cirrhosis, the administration interval probably should be increased 1.5- to 2-fold in these patients and the oral dose of the drug should be reduced because of increased bioavailability.[61] Similar changes occur with meperidine, for which there is a 50% reduction in clearance and a doubling of the half-life. In addition, clearance of normeperidine is reduced and patients with severe liver disease may experience neurotoxicity from accumulation of normeperidine.[61]

In contrast to these drugs, fentanyl is a highly lipid-soluble synthetic opioid that has a short duration of action after a single intravenous bolus dose because of rapid redistribution into storage sites. With repeated administration or continuous infusions, accumulation may occur and lead to prolonged effects.[61] Because fentanyl is almost completely metabolized in the liver, its elimination should be predictably prolonged in patients with advanced liver disease. However, fentanyl elimination is not appreciably altered in patients with cirrhosis.[61,62] Whether the limited extent of liver disease in the study patients affected the pharmacokinetic data or whether continuous infusions or repeated dosing in cirrhotic patients will produce more exaggerated and pronounced effects is unknown.

Sufentanil, a more potent but similar synthetic lipophilic opioid, is also extensively metabolized by the liver and is highly protein bound. A single-dose pharmacokinetic is not significantly altered in patients with cirrhosis, although the impact of continuous infusions and reduced protein binding is as ill defined for sufentanil as for fentanyl.[63] Alfentanil, a short-acting opioid less potent than fentanyl, is also exclusively metabolized by the liver and is highly protein bound.[61] However, unlike fentanyl or sufentanil, the half-life of alfentanil is almost doubled in patients with cirrhosis and higher free fractions of the drug are observed, which can potentially lead to a prolonged duration of action and enhanced effects.[64,65] Remifentanil is a synthetic opioid with an ester linkage that allows for rapid hydrolysis by blood and tissue esterases; such hydrolysis leads to high clearance, rapid elimination, and recovery that is almost independent of the dose or duration of infusions.[61] Predictably, its clearance should be unaffected by hepatic dysfunction, and available data indicate that remifentanil elimination is indeed unaltered in patients with severe liver disease or in those undergoing liver transplantation.[61,66-68] (See Chapter 67.)

Sedative/Hypnotic Drugs

Thiopental has a small hepatic extraction ratio, and therefore its metabolism and clearance should be adversely affected in patients with liver disease. However, the elimination half-life of thiopental is unchanged in cirrhotic patients, possibly because of a large volume of distribution.[69,70] A prolonged effect from standard doses of thiopental thus seems unlikely in this patient population. In contrast, other intravenous anesthetics, including methohexital, ketamine, etomidate, and propofol, are highly lipid soluble, are metabolized by the liver, have a large hepatic extraction ratio, and would be expected to have diminished clearance in the presence of advanced liver disease.[71] Despite this pharmacokinetic profile, etomidate clearance is unchanged in cirrhotic patients, although increased volumes of distribution may prolong the elimination half-life and result in unpredictable recovery times.[72] Methohexital and propofol also have an elimination kinetic profile in cirrhotic individuals that is similar to that in normal patients,[71] both after single-bolus administration of propofol[73] and after propofol infusion.[74] However, mean clinical recovery times may be longer after discontinuation of propofol infusions in cirrhotic patients.[74] The reduced clearance of midazolam in patients with end-stage liver disease produces prolonged elimination half-lives.[75,76] In conjunction with reduced protein binding and increased free fractions of midazolam, a prolonged duration of action and an enhanced sedative effect should be anticipated in patients with severe liver disease, especially after multiple doses or prolonged infusions. Similar changes have also been observed with diazepam.[76]

Dexmedetomidine, an α_2-adrenergic agonist with sedative and analgesic properties, is primarily metabolized in the liver with minimal renal clearance. Generally, patients with hepatic failure of varying severity have decreased clearance, prolonged half-lives, and lower bispectral index values than in patients with normal liver function.[77] Dosage adjustments are therefore indicated when dexmedetomidine is used in patients with significant hepatic dysfunction. This evidence mirrors, in part, findings from dexmedetomidine use in individuals with renal dysfunction, where prolonged sedation despite unchanged pharmacokinetics has been attributed to altered protein binding, a factor that also applies to patients with hepatic dysfunction.[78,79]

In summary, despite substantial hepatic metabolism of most intravenous anesthetics, cirrhosis has minimal impact on the pharmacokinetic profile of sedative/hypnotic drugs. Given that the clinical effect and duration of action of benzodiazepines are more pronounced in the presence of severe liver disease, these drugs should be given cautiously when using repeated dosing or prolonged infusions, either in the operating room or in the intensive care unit, where drug accumulation, prolongation of effects, and increased risk of hepatic encephalopathy can be anticipated.

Neuromuscular Blocking Drugs

In contrast to the scant pharmacokinetic data described earlier for opioids and intravenous anesthetics, more comprehensive

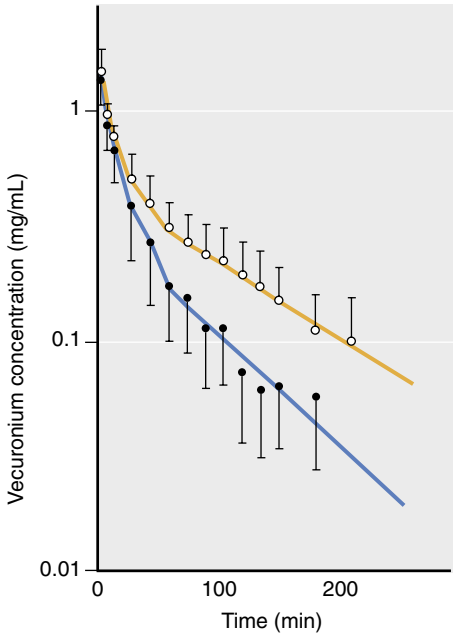

Figure 66-4 Disappearance of vecuronium from plasma after a single bolus dose of 0.2 mg/kg. A semi-logarithmic plot of plasma concentration versus time shows that the vecuronium concentration remained at a much higher level during the elimination phase in patients with cirrhosis (*open circles*) than in normal control patients (*black circles*). This difference reflects the markedly decreased plasma clearance of vecuronium, increased elimination half-life, and increased duration of neuromuscular blockade in patients with cirrhosis versus normal individuals. (*From Lebrault C, Berger JL, D'Hollander AA, et al: Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) in patients with cirrhosis. Anesthesiology 62:601-605, 1985.*)

information is available regarding the impact of cirrhosis on the pharmacokinetics and pharmacodynamics of muscle relaxants (see Chapter 29). Vecuronium is a steroidal muscle relaxant that undergoes hepatic elimination[80,81] and has decreased clearance, a prolonged elimination half-life, and prolonged neuromuscular blockade in patients with cirrhosis (Fig. 66-4).[82,83] The impact of alcoholic liver disease is less definite, with clearance and elimination half-lives typically unchanged.[84] Rocuronium, another steroidal muscle relaxant with a faster onset of action than vecuronium, also undergoes hepatic metabolism and elimination.[85] Hepatic dysfunction can increase the volume of distribution of rocuronium, thereby prolonging its elimination half-life[85] and producing a longer clinical recovery profile and return of normal twitch tension.[85,86] Gao and associates observed a 24% decrease in rocuronium infusion requirement in 17 patients during the anhepatic phase of liver transplantation.[87] (See Chapter 67.) Although the initial clinical recovery of neuromuscular function is not affected by liver disease, larger initial doses or repeated administration will typically prolong the effect of rocuronium in the presence of significant hepatic dysfunction.[85]

The increased volume of distribution for some drugs observed in cirrhotic patients can also prolong the elimination half-life of pancuronium.[88] In patients with end-stage liver disease, muscle relaxants that undergo organ-independent elimination, such as atracurium (nonspecific ester hydrolysis) and cisatracurium (Hofmann elimination), have elimination half-lives and clinical durations of action similar to those in normal patients.[89-92] Laudanosine, a metabolite of both atracurium and cisatracurium, is eliminated primarily by the liver; and although its concentration may increase in patients undergoing liver transplantation, clinically relevant neurotoxicity has not been reported.[93] The unique elimination of mivacurium by plasma cholinesterase is, however, altered by cirrhosis.

Mivacurium will be discussed even though it is not available in some countries and is associated with significantly longer recovery of twitch tension and has a longer elimination half-life (18 versus 34 minutes in normal versus cirrhotic patients, respectively) and a longer residence time in patients with hepatic failure than in normal patients, a finding closely correlated to reduced plasma cholinesterase activity in cirrhotic patients.[94-96] This reduced activity appears to be related to reduced clearance by plasma cholinesterase of the two active isomers of mivacurium, *cis-trans* and *trans-trans*.[96] Infusion rates of mivacurium should be adjusted accordingly in patients with advanced liver disease. The changes observed with mivacurium are predictably expected with succinylcholine if decreased plasma cholinesterase levels are present because of advanced liver disease. Lowered cholinesterase levels have been observed in these individuals[97] and may prolong the effect of succinylcholine.

In summary, cirrhosis and other forms of advanced liver disease will predictably reduce the elimination of vecuronium, rocuronium, and mivacurium and prolong the duration of neuromuscular blockade, especially after repeated doses or the use of prolonged infusions. Atracurium and cisatracurium are not dependent on hepatic elimination and can be used without modification of dosing in patients with end-stage liver disease.

Risk Factors for Postoperative Hepatobiliary Complications

The anesthesia literature is replete with detailed descriptions regarding the preoperative assessment of cardiac risk for noncardiac surgery.[98] In addition, preoperative renal risk factors have been delineated.[99] Defining preoperative risk factors for the development of postoperative hepatic dysfunction or failure after nonhepatic surgery, however, has not been clearly elucidated, and, as such, anesthesiologists have based decisions regarding the care of patients with preoperative hepatic dysfunction on data derived 4 to 5 decades ago. Unfortunately, prospective studies addressing these issues in the current era of newer anesthetic and surgical techniques are lacking. Assessment of risk factors for postoperative hepatic insufficiency requires consideration of (1) asymptomatic elevations in preoperative liver enzyme test results; (2) acute hepatitis (viral, drug, toxin), steatosis, chronic hepatitis, and cirrhosis; and (3) the types of surgery that potentially predispose to postoperative liver dysfunction.

Asymptomatic Preoperative Liver Enzyme Test Abnormalities

Indiscriminate laboratory test screening may reveal abnormally elevated liver enzyme test results in otherwise healthy patients. Abnormalities in standard liver enzyme tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and

alkaline phosphatase, occur in 0.1% to 4% of the general population[100,101] and in as many as 36% of psychiatric patients in whom alcohol and illicit drug abuse is prominent.[102] However, the overall prevalence of clinically significant hepatic dysfunction in asymptomatic patients is less than 1%. Thus, pursuing more extensive evaluation with costly tests such as ultrasonography, radionuclide imaging, or liver biopsy is rarely indicated.

In general, the most appropriate initial approach to a surgical patient with abnormal liver enzyme test results is a detailed history and physical examination. Symptoms of fatigue, anorexia, nausea, vomiting, biliary colic, pruritus, fever, or dark-colored urine warrant further evaluation because they may suggest clinically active hepatobiliary disease and thus potentially preclude elective surgery. If, however, the patient is asymptomatic, the significance of abnormal enzyme test results can be questioned. The patient should be further queried about a history of associated diseases such as chronic hepatitis, a family history of Wilson's disease, hemochromatosis, α_1-antitrypsin deficiency, diabetes mellitus, hyperthyroidism or hypothyroidism, and previous transfusion history. All medications, including vitamins and herbal or other homeopathic remedies, should be reviewed for potential hepatotoxic side effects. The patient should be further questioned regarding alcohol or other illicit drug use, the presence of tattoos, sexual promiscuity, and consumption of raw seafood because they are potential risk factors for infectious hepatitis.

Physical examination may reveal findings consistent with active liver disease, such as icterus, palmar erythema, spider angiomas, gynecomastia, hepatosplenomegaly, ascites, or peripheral edema. Although these findings invariably suggest a diagnosis of cirrhosis, it is reasonable to repeat the test if a complete history and physical examination fail to suggest an etiology of the biochemical abnormality. Minor elevations in liver enzyme test results are considered to be less than twice the normal value[103] and, given a negative history and physical examination, do not warrant additional testing before anesthesia and surgery. Assessment of larger elevations in liver enzyme test results requires an analysis of the specific abnormality.

AST and ALT are sensitive indicators of hepatocyte integrity. AST is present in hepatocyte cytoplasm and mitochondria, but it is also ubiquitous in cardiac and skeletal muscle; kidney, brain, pancreas, and lung tissue; and red and white blood cells. AST is therefore a less specific index of cellular injury than ALT is, which is primarily found in the cytoplasm of hepatocytes. Both enzymes are released when the hepatic cell membrane is injured, although there appears to be a correlation between the degree of injury and serum aminotransferase levels. The AST/ALT ratio may also be helpful in distinguishing between alcohol-induced hepatitis and viral hepatitis. Alcohol tends to preferentially damage hepatocyte mitochondria, thereby causing an elevation in AST usually greater than twice the ALT.[104] In addition, ALT activity is diminished in patients with alcohol-induced liver disease because these individuals tend to have deficiencies of pyridoxal 5-phosphate, a vitamin necessary for ALT function. In contrast, a decrease in the AST/ALT ratio is more consistent with a diagnosis of viral hepatitis. Aminotransferases also increase in choledocholithiasis, cholangitis, and ischemic hepatitis. Ischemic hepatitis may not uncommonly produce levels greater than 10,000 IU/L.

Similar to AST, alkaline phosphatase is present in many tissues, including bone, intestine, kidney, and placenta, as well as in leukocytes. The enzyme catalyzes the hydrolysis of orthophosphate from ester substrates at an alkaline pH. In hepatocytes, alkaline phosphatase is synthesized by biliary epithelial cells and is released in relation to the degree of bile duct obstruction. Measuring serum γ-glutamyltransferase (GGT), an enzyme found predominantly in hepatocytes and biliary epithelial cells, may aid in distinguishing between hepatic and bone etiologies of increased alkaline phosphatase. Although GGT is a very sensitive indicator of the presence or absence of hepatobiliary disease, by itself it lacks specificity because it is also increased in patients with myocardial infarction, renal disease, diabetes mellitus, and chronic obstructive pulmonary disease. If alkaline phosphatase and GGT are elevated, the abnormality probably reflects hepatobiliary disease. Increased levels of alkaline phosphatase and GGT usually occur with extrahepatic bile duct obstruction and intrahepatic cholestasis from infiltrative diseases such as sarcoidosis, from mass lesions such as primary or metastatic carcinoma, or from drug-induced cholestasis.

Although liver enzyme elevation is an indication of active disease, synthetic hepatic function is best measured by serum bilirubin, albumin, and the prothrombin time. The bilirubin concentration in plasma varies in accordance with its production and inversely with hepatic clearance. Hepatic microsomal enzymes convert unconjugated bilirubin to the more water-soluble form, thereby permitting excretion in bile and preventing central nervous system toxicity. Total bilirubin levels represent conjugated (direct bilirubin) and unconjugated (indirect bilirubin) forms. Unconjugated hyperbilirubinemia suggests hemolysis or an inherited disorder of bilirubin metabolism such as Gilbert's syndrome. If more than 50% of the total serum bilirubin is conjugated, cholestasis or hepatocellular dysfunction is implied. Albumin is synthesized solely in the liver and, in healthy adults, has a half-life of approximately 21 days. The normal level of 3.5 g/dL usually decreases in long-standing and severe liver disease but is also influenced by overall nutritional status.

Finally, hepatobiliary dysfunction can cause an abnormal prothrombin time by impairing synthesis of the essential clotting factors II (prothrombin), VII, IX, and X. Hepatic synthesis of these factors is dependent on vitamin K, a fat-soluble vitamin found in certain foods and produced by intestinal bacteria, so abnormalities in prothrombin activity (as expressed by the international normalized ratio [INR]) may also occur in patients with malnutrition or malabsorption syndromes. The plasma half-time of these vitamin K–dependent factors is very short (less than 24 hours) and hence the INR responds rapidly to changes in synthetic function, which makes this test a more sensitive index of hepatic function than serum albumin.

Although no prospective, randomized, controlled studies have been designed to assess the perioperative risk of anesthesia or surgery in asymptomatic patients with elevated liver enzyme test results, a suggested approach to these patients is outlined in Figure 66-5. Abnormal liver enzyme test results in an otherwise healthy patient reflect either a subclinical acute process such as viral or toxin-mediated hepatitis or a chronic disorder such as chronic hepatitis.

Acute Hepatitis

The diverse role of the liver in drug metabolism, hemostasis, and coagulation function, in association with surgery and anesthesia-related alterations in hepatic perfusion, make it an organ extremely susceptible to clinically important viral-, alcohol-, or other

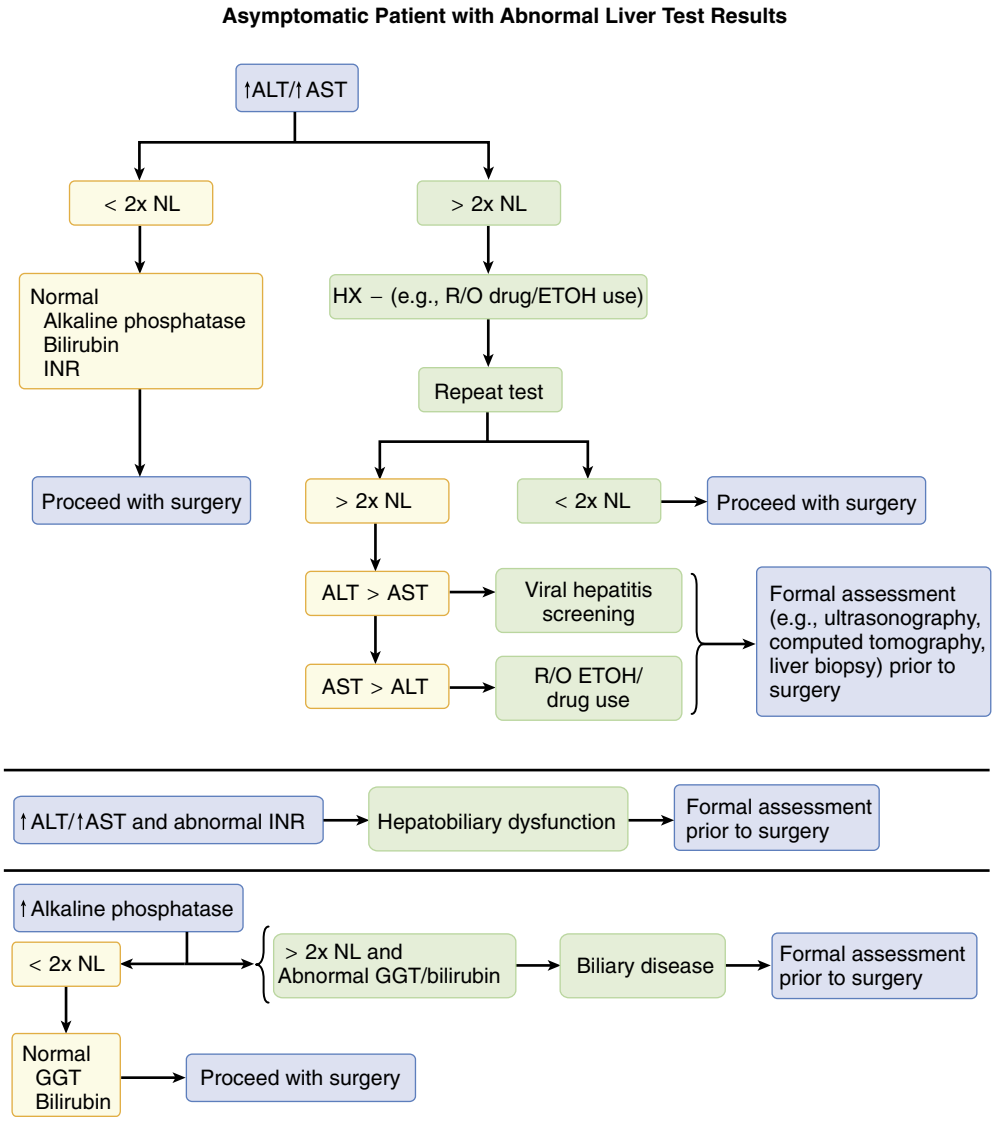

Figure 66-5 Approach to asymptomatic patients with abnormal liver test results presenting for surgery. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ETOH, ethyl alcohol; GGT, γ-glutamyl transferase; HX, history; INR, international normalized ratio; NL, normal limit; R/O, rule out.

drug-induced hepatocellular injury. Consensus opinion, based largely on data derived from older, predominantly retrospective studies, is that acute hepatitis, whether viral, alcohol, or drug induced, is a risk for the development of hepatic failure or death after elective surgery. In 1982, Powell-Jackson and coauthors[105] described 36 patients who underwent exploratory laparotomy for either suspected extrahepatic biliary tract obstruction or intra-abdominal malignancy, all of whom were ultimately found to have viral or alcoholic hepatitis, cirrhosis, or Budd-Chiari syndrome. Of these patients, 61% suffered significant morbidity, including postoperative liver failure, and 31% died within 1 month of surgery. All of the patients with histologically proven hepatitis died. Greenwood and associates[106] also reported high mortality rates in patients with alcoholic hepatitis undergoing open liver biopsy. Bell and colleagues,[107] however, noted that survival rates were not influenced by the presence of biopsy-proven hepatitis in 164 patients with alcoholic cirrhosis requiring emergency portocaval shunts for esophageal variceal bleeding.

In the current era of advanced diagnostic testing and imaging where nonoperative management of extrahepatic biliary tract obstruction can be performed with endoscopic retrograde cholangiopancreatography (ERCP), invasive procedures such as open liver biopsy or exploratory laparotomy can often be avoided. Elective surgery should be delayed in patients with acute hepatitis of any etiology until resolution of hepatocellular dysfunction can be confirmed.[60] The influence of the type of surgery on patients with hepatitis is described later.

Steatosis and Steatohepatitis

Patients with chronic, asymptomatic elevations in serum aminotransferase levels are often found by liver biopsy to have steatosis (fatty liver) or steatohepatitis.[108] Hultcrantz and coworkers[109] studied 149 asymptomatic patients with at least a 6-month history of elevated aminotransferase levels found incidentally during

routine laboratory screening.[109] Liver biopsy confirmed the diagnosis of steatosis in 64% of these patients, most of whom were obese or diabetic or had a history of excessive alcohol use. In a subsequent study, Hay and colleagues[108] demonstrated a 21% incidence of steatohepatitis in a similar patient population. Both studies concluded that chronic hepatitis or cirrhosis cannot be differentiated from steatosis or steatohepatitis based solely on clinical laboratory or noninvasive radiologic or ultrasonographic criteria. In a retrospective analysis of 135 patients who underwent hepatic resection, Behrns[110] noted an increased incidence of postoperative liver failure and mortality when the histopathology revealed hepatocytes with greater than 30% fatty infiltration. Brolin and associates[111] noted a 6% incidence of biopsy-proven nonalcoholic steatohepatitis and subclinical cirrhosis in patients undergoing gastric bypass surgery; postoperative mortality was higher in affected patients than in those with normal hepatic histology. Despite recommendations to the contrary,[112] steatosis and steatohepatitis should probably be considered significant risk factors for postoperative complications, especially after abdominal procedures. For this reason, patients with asymptomatic, chronic (>6 months) elevations in hepatic enzyme levels should be thoroughly evaluated before elective surgery.

Chronic Hepatitis

The extent of anesthetic or surgical risk imposed by chronic forms of hepatitis primarily relates to the severity of associated hepatic synthetic dysfunction. Runyon[113] retrospectively studied 20 asymptomatic patients who had chronic hepatitis B or C and were undergoing general or spinal anesthesia for a total of 34 surgical procedures, most of which were at operative sites distant from the liver. Liver enzyme test results did not worsen postoperatively, nor did any patient experience postoperative liver failure or death. Subsequently, Higashi and colleagues[114] assessed the postoperative outcomes of 119 patients with chronic hepatitis who were undergoing liver resection for primary hepatocellular carcinoma (HCC). Patients with the most impaired liver enzyme test results had a higher incidence of hepatic failure, recurrent HHC, and death.[115]

These observations suggest that asymptomatic patients with any form of chronic hepatitis should be screened before elective surgery for evidence of hepatic dysfunction, with the INR being the most sensitive indicator of the severity of hepatocellular dysfunction. When surgery cannot be avoided, meticulous care should be taken perioperatively to maintain hepatic perfusion and avoid factors that might precipitate liver failure, hepatic encephalopathy, or both (see later).

Cirrhosis as a Perioperative Risk Factor

Cirrhosis is a syndrome of end-stage liver disease pathologically characterized by severe fibrosis and nodular regeneration of the liver parenchyma (see Chapter 67). Alcohol abuse remains the most common cause of cirrhosis. Other causes include chronic hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson's disease, and idiopathic cirrhosis. In the past, the Child-Turcotte-Pugh (CTP) scoring system was the most frequently used tool to predict perioperative risk in cirrhosis patients undergoing abdominal surgery, exclusive of portosystemic shunt procedures (Table 66-1).[116] This scoring system assigned points based on levels of serum albumin and bilirubin, the INR, the degree of ascites, and the presence and grade of encephalopathy and stratified risk in order of severity as class A, B, or C. A number of studies have used this system to predict perioperative outcome in cirrhosis patients undergoing a variety of surgeries.

Table 66-1 Modified Child-Turcotte-Pugh Scoring System

Parameters	Modified Child-Turcotte-Pugh Score*		
	1	2	3
Albumin (g/dL)	>3.5	1.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
Bilirubin (mg/dL)†	<2	2-3	>3
Ascites	Absent	Slight-moderate	Tense
Encephalopathy	None	Grade I-II	Grade III-IV

*Class A = 5.6 points, B = 7 to 9 points, and C = 10 to 15 points.
†For cholestatic diseases (e.g., primarily biliary cirrhosis), the bilirubin level is disproportionate to the impairment in hepatic function and an allowance should be made. For these conditions, assign 1 point for a bilirubin level less than 4 mg/dL, 2 points for a bilirubin level of 4 to 10 mg/dL, and 3 points for a bilirubin level over 10 mg/dL.
From Pugh RNH, Murray-Lyon IM, Dawson JL, et al: Transection of oesophagus for bleeding of oesophageal varices. Br J Surg 60:646-649, 1973.

Garrison and coworkers[117] retrospectively evaluated outcomes in 100 patients with histologically proven cirrhosis who were undergoing surgery predominantly for biliary tract procedures (cholecystectomy, choledochotomy), as well as for gastroduodenal repair, colon and small bowel resection, and open liver biopsy. An overall operative mortality of 30% and an additional perioperative morbidity of 30% were noted, with sepsis-mediated multiorgan system failure being the major cause of death (87%). When stratified to CTP classes A, B, or C, mortality was 10%, 31%, and 76%, respectively. Excluding the CTP classification, the authors also performed a multivariate analysis of other perioperative variables and concluded that preoperative prolongation of the prothrombin time, decreased serum albumin, and a total leukocyte count greater than 10,000/cm^3 predicted increased mortality. Finally, operative mortality was considerably more frequent in patients requiring urgent versus elective surgery (57% versus 10%). Over a decade later, Mansour and associates[118] retrospectively analyzed 92 cirrhotic patients undergoing abdominal procedures and described nearly identical results, with mortality rates of 10%, 30%, and 82% in patients with CTP classes A, B, and C, respectively. Other retrospective studies have also shown that perioperative risk is exceedingly high when performing major abdominal surgery, especially under emergency circumstances and in CTP class C cirrhotic patients.[119-122]

In contrast, Rice and colleagues,[123] described the lack of predictability of the CTP classification in patients with chronic liver failure undergoing not only abdominal surgery but also coronary bypass grafting, orthopedic procedures, as well as other peripheral surgeries. In this retrospective analysis of 40 patients, perioperative prolongation of the INR and clinical evidence of encephalopathy were the only variables most associated with

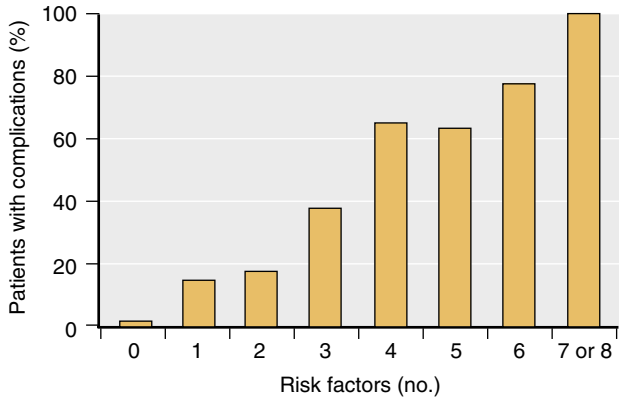

Figure 66-6 Effect of the number of risk factors on the perioperative complication rate in cirrhotic patients undergoing surgery. Risk factors included the CPT score, the presence of ascites, a diagnosis of cirrhosis other than primary biliary cirrhosis, serum creatinine concentration, a diagnosis of chronic obstructive pulmonary disease, preoperative infection, preoperative upper gastrointestinal bleeding, higher American Society of Anesthesiologists physical status score, intraoperative hypotension, and higher surgical severity score. (*From Ziser A, Plevak DJ, Wiesner RH, et al: Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. Anesthesiology 90:42-53, 1999.*)

increased mortality (10 and 35 times that of normal individuals, respectively).

Ziser and coworkers,[124] in the largest of all these retrospective studies, established an 11.6% 30-day mortality rate in 773 patients with cirrhosis who were undergoing a variety of surgical procedures involving local, regional, or general anesthesia. Multivariate analysis identified male gender, CTP class C, ascites, azotemia, perioperative infection, higher American Society of Anesthesiologists (ASA) physical classification, a diagnosis of cryptogenic cirrhosis, and surgery on the respiratory system as risk factors independently associated with mortality. Further analysis identified additional risk factors for perioperative complications (Fig. 66-6).

Predicting perioperative risk of cirrhosis and other forms of acute and chronic liver disease may be further enhanced by the incorporation of the Model for End-stage Liver Disease (MELD) score.[125] Although the MELD score was introduced as a tool to better prioritize organ allocation for orthotopic liver transplantation (see Chapter 67), retrospective and prospective studies suggest the superiority of MELD to CPT in predicting both intermediate and long-term survival for patients with cirrhosis, acute alcoholic hepatitis, and other forms of chronic liver disease.[126-128] Refinements to the predictive value of this scoring system include the MELD score over time[129] and the incorporation of the serum sodium level.[130] Relative to surgical risk, Salerno and associates noted improved accuracy of MELD over CPT scores in predicting survival of patients undergoing transjugular intrahepatic portosystemic shunting (TIPS).[131] However, large prospective studies comparing MELD to CPT in cirrhotic patients undergoing other nonhepatic surgeries are lacking, and, as such, CPT continues to be employed as a measure of assessing perioperative risk.

Despite the lack of prospective studies, cirrhosis is still considered a major risk factor for patients undergoing nonhepatic surgery, with elective surgery considered contraindicated in CTP class C patients.[132] In addition, it is probably prudent to avoid elective surgery in cirrhotic patients with a prolonged INR, hypoalbuminemia, and evidence of preoperative infection or encephalopathy. Alternatives to extensive abdominal procedures, such as cholecystostomy or laparoscopic cholecystectomy versus open cholecystectomy, should be considered for the treatment of cholelithiasis.[133,134] Preoperative decompression of portal hypertension by TIPS may also improve postoperative outcomes in certain patients.[135] Finally, elective abdominal surgery should probably be avoided if a diagnosis of cirrhosis is made fortuitously at the time of surgery.[111]

Surgical Procedures That Increase the Risk of Postoperative Liver Failure

In addition to the severity of preoperative hepatic dysfunction, the actual surgical procedure performed may be the most important risk factor for postoperative liver failure.[136] Under normal circumstances, the liver is able to adapt to changes in perfusion pressure by altering either HABF or PBF. In a diseased state, pathologic changes may diminish the adaptive capacity of this dual blood supply and predispose the liver to the deleterious effects of surgery. Abdominal surgery per se appears to significantly reduce THBF. Surgical manipulation of the splanchnic bed may reduce both PBF and HABF, in part because of resultant systemic arterial hypotension mediated by prostacyclin-induced dilation of the venous capacitance vessels.[137] The effect of pneumoperitoneum on hepatic blood flow remains controversial; however, Meierhenrich and colleagues, utilizing transesophageal echocardiography, noted an increase in hepatic perfusion with carbon dioxide insufflation in healthy patients undergoing laparoscopic hernia repair.[138]

In addition to surgery on the biliary tract, stomach, and colon, hepatic resection for HCC is a known risk factor for the development of liver failure in patients with preoperative hepatic dysfunction. Most patients with HCC have liver dysfunction associated with either chronic hepatitis or cirrhosis.[115,139] The diminished functional hepatic reserve of these patients may decrease the amount of tissue that can be resected without compromising viable parenchyma and causing liver failure, the most common cause of death after this surgery. Wu and coworkers[140] retrospectively analyzed cirrhotic patients undergoing hepatic resection for HCC based on degree of hepatic dysfunction. By limiting the amount of tissue resection in patients with significant hepatic dysfunction (i.e., poorer CPT class), the authors noted 5-year survival rates comparable to those in patients with less severe forms of cirrhosis who underwent more extensive resections. Perioperative hemorrhage is a common occurrence in cirrhotic patients undergoing resection for HCC because of contributing factors such as portal hypertension, coagulation abnormalities, and highly vascular adhesions in those with previous abdominal surgery. Preoperative evaluation of patients with HCC by indocyanine green 15-minute retention[140,141] or direct measurement of the hepatic venous pressure gradient[142] can be beneficial in predicting postoperative outcomes in cirrhotic patients undergoing hepatic resection for HCC.

Cardiothoracic surgery is associated with a high mortality rate in patients with preexisting liver disease.[124,143-145] Hepatic dysfunction is often exacerbated by cardiopulmonary bypass (CPB), although the precise mechanism of this dysfunction has not been clearly elucidated. In a canine model of hypothermic nonpulsatile

CPB, Koizumi and colleagues[146] noted a decrease in PBF and HABF without a concomitant change in hepatic oxygen metabolism. Normothermic CPB was associated with a similar decline in PBF, but HABF was maintained. Increasing the dose of fentanyl from 10 to 50 µg/kg/hr significantly suppressed HABF and impaired hepatic oxygen metabolism in normothermic and hypothermic CPB, suggesting the possibility of fentanyl-mediated peripheral venous pooling and subsequent lowering of cardiac output. More recently, Okano and coworkers[147] assessed hepatosplanchnic oxygenation in 25 patients with no history of hepatic dysfunction who were undergoing elective coronary artery bypass grafting with either normothermic (>35°C) or hypothermic (<32°C) CPB. Hepatic venous desaturation and functional impairment of hepatic sinusoidal endothelial cells occurred in both groups, but hepatocellular dysfunction was not observed.

In addition to the possible effects of hepatic artery and portal venous perfusion, other potential determinants of hepatic dysfunction after CPB include hypotension, low cardiac output syndrome, hypoxemia, microembolism or macroembolism, cytokine and oxygen-free radical formation, and the influence of vasoactive and anesthetic drugs. Small retrospective studies have shown 11% to 30% mortality rates in CTP class A and B patients undergoing nonemergency cardiac surgery.[143-145] Although more deaths occurred in the CTP class B group, significant morbidity, particularly in the form of postoperative hemorrhage and infection, was seen in the CTP class A patients. Finally, noncardiac, thoracic surgery may be a risk factor for postoperative mortality in patients with cirrhosis, although the basis for this association remains speculative.[124]

Postoperative Jaundice

Postoperative jaundice occurs as a result of overproduction and underexcretion of bilirubin, direct hepatocellular injury, or extrahepatic obstruction.[148] Most causes of postoperative jaundice manifest within 3 weeks of surgery and can be classified as either mild (<4 mg/dL) or severe (>4 mg/dL). Table 66-2 lists the most common causes of postoperative jaundice based on the nature of the pathophysiology.[148] If jaundice is secondary to hemolysis, the liver's capacity to conjugate bilirubin (normal rate of production, 250 to 300 mg/day) has been exceeded. Hemolysis-induced anemia is therefore associated with unconjugated (indirect) hyperbilirubinemia and, in the perioperative period, can usually be attributed to either drug-induced or mechanically induced erythrocyte destruction. The primary mechanisms by which certain drugs cause hemolysis and subsequent jaundice are (1) the drug adsorption type, whereby an antibody (IgG) reacts with a drug bound to the red blood cell membrane; (2) the neoantigen type (so-called innocent bystander), whereby the drug combines with the erythrocyte membrane and an antibody reacts with the newly formed antigenic site to activate the complement cascade; and (3) the autoimmune type caused by an autoantibody (IgG) to erythrocytes. Medications commonly used perioperatively and associated with one or more forms of hemolytic anemia are listed in Table 66-3.[149]

The degree of associated jaundice is related to the rate of hemolysis and excess production of bilirubin, with the neoantigen mechanism most likely to cause acute anemia, hemoglobinuria, and renal failure. The diagnosis is made by the laboratory constellation of anemia, indirect hyperbilirubinemia, positive direct antiglobulin test, low serum haptoglobin, and the presence of fragmented erythrocytes and reticulocytosis on the peripheral blood smear. Mechanical destruction of erythrocytes can also occur from surgically implanted prosthetic heart valves or from intrinsically diseased valves.[150]

Multiple blood transfusions can increase levels of unconjugated bilirubin because approximately 10% of stored whole blood undergoes hemolysis within 24 hours of transfusion (see Chapter 55). Each 0.5-L unit of blood stored in citrate-phosphate-dextrose-adenine (CPDA-1) yields 7.5 g of hemoglobin, which is then converted to approximately 250 mg of bilirubin.[151] Multiple units of blood may therefore overwhelm the liver's ability to conjugate and excrete bilirubin. Finally, reabsorption of extravasated blood, as occurs with retroperitoneal or intra-abdominal hematomas, may increase the bilirubin load and cause postoperative jaundice. This etiology is not uncommon after major trauma or repair of ruptured aortic aneurysms.

Hepatocellular injury can cause postoperative jaundice (as previously discussed) by drug, ischemia, or virally mediated mechanisms. In addition to potential anesthetic-induced hepatotoxicity, a number of commonly prescribed drugs can cause hepatocellular injury that mimics either hepatitis or cholestasis based on liver test abnormalities (Tables 66-4 and 66-5[152-199]). With the

Table 66-2 Etiology of Postoperative Jaundice by Time Course

Immediate Postoperative Jaundice (<3 wk)
Hemolysis
Anesthesia
Hypotension/hypovolemia
Drugs
Infection/sepsis
Bleeding/resorption of hematoma
Bile duct ligation/stricture/surgical injury
Hepatic artery ligation
Retained common duct stone
Postoperative pancreatitis/cholecystitis
Acute viral hepatitis
Gilbert's syndrome/Dubin-Johnson syndrome
Inflammatory bowel syndrome
Heart failure
Pulmonary postoperative jaundice
Blood transfusion
Delayed Postoperative Jaundice (>3 wk)
Drugs
Blood transfusion
Post–intestinal bypass status
Total parenteral nutrition

Table 66-3 Medications Associated with Hemolysis

Acetaminophen
Cephalosporins
Hydralazine
Ibuprofen and other NSAIDs (e.g., diclofenac, tolmetin)
Insulin
Intravenous contrast media
Penicillin and all derivatives (e.g., ampicillin, methicillin)
Procainamide
Ranitidine
Sodium thiopental

Table 66-4 Drug-Induced Hepatotoxicity

Agent	Hepatocellular Cytotoxicity	Steatosis	Cholestasis
Acetaminophen[152]	✓		
Alcohol[153]		✓	
Allopurinol[154]	✓		
Amiodarone[155]		✓	
Amoxicillin/clavulanic acid[156]			✓
Aspirin[157]	✓	✓	
Azathioprine[156]	✓		✓
Bleomycin[158]		✓	
Bosentan[159]	✓		
Calcium channel blockers[156]	✓		
Captopril[160]			✓
Carbamazepine[156]	✓		✓
Chlorpromazine[161]			✓
Cisplatin[162]		✓	
Cyclosporine[156]			✓
Danazol[163]	✓		
Dantrolene[164]	✓		
Dapsone[165]	✓		✓
Disulfiram[166]	✓		
Enalapril[156]	✓		
Erythromycin[167]			✓
$FeSO_4$[168]	✓		
Floxuridine[169]	✓		
Gold[153]	✓		
Isoniazid[170]	✓		
Ketoconazole[160]	✓		✓
Methimazole[171]			✓
Methotrexate[172]	✓	✓	
Methyldopa[173]	✓		
Nafcillin[153]			✓
Nevirapine[160]	✓		
Niacin[174]	✓		
Nitrofurantoin[159]	✓		
NSAIDs[175-177](diclofenac, naproxen, indomethacin, piroxicam, etodolac, oxaprozin)	✓		✓ (sulindac)
Pemoline[178]	✓		
Penicillins (oxacillin)[167]			✓
Phenytoin[164]	✓		
Propafenone[160]			
Propylthiouracil[177]	✓		✓
Quinidine[176]			
Rifampin[179]	✓		✓
Riluzole[180]	✓		✓
Steroids, anabolic[181]	✓		
Steroids, oral contraceptives[182]			✓
Sulfonamides[177]	✓		
Tacrine[183]	✓		
Tamoxifen[160]	✓	✓	✓
Tetracycline IV[184]	✓	✓	
Ticlopidine[176]			✓
Tolcapone[185]	✓		
Total parenteral nutrition[186]			✓
Trazodone[164]	✓		✓
Valproic acid[187]		✓	
Vitamin A[188]	✓	✓	
Zafirlukast[189]	✓		

exception of acetaminophen, which can directly cause hepatocyte necrosis, drug-induced hepatotoxicity is primarily the result of either idiosyncratic reactions or alterations in bile flow resulting in cholestasis.

Postoperative jaundice may also occur as a result of hepatic hypoperfusion. Cardiogenic and noncardiogenic shock can decrease HABF and PBF and cause hepatocellular necrosis. Marked increases in aminotransferase levels are common, with hyperbilirubinemia usually a late finding. In addition to hemodynamic alterations in hepatic blood flow, sepsis or the systemic inflammatory response syndrome is associated with cholestasis and jaundice, presumably because of the effects of circulating endotoxins or other inflammatory mediators on bile formation and flow.[200] Finally, it is important to exclude viral hepatitis as the cause of postoperative jaundice because viral exposure may have occurred before surgery.

Obstruction of the common bile duct from a gallstone, stricture, or tumor can result in failure to excrete conjugated bilirubin (obstructive jaundice) and has been associated with significant perioperative morbidity and mortality. Factors associated

Table 66-5 Herbal Products and Hepatotoxicity

Herbal	Hepatocellular	Cholestasis
Black cohosh[190]	✓	
Celandine[191]		✓
Chaparral[192]	✓	
Comfrey[193]	✓	
Echinacea[194]		
Germander[195]	✓	
Jin bu huan (levotetra-hydropalmatine)[196]	✓	
Kava[197]	✓	
Margosa oil[156]	✓	
Mu huang[198]	✓	
Sassafras[156]		✓
Skullcap[199]	✓	
Yerba[156]	✓	

with a poor outcome after surgery in patients with obstructive jaundice include extrahepatic obstruction as a result of malignancy, malnutrition, hypoalbuminemia, low hematocrit (<30%), azotemia, and the level and duration of hyperbilirubinemia.[201,202] Dixon and coauthors[203] cited an overall mortality rate of 9.1% in a retrospective analysis of 373 patients requiring surgery for obstructive jaundice, but a 60% mortality rate for patients with anemia, malignancy, and marked hyperbilirubinemia (>11 mg/dL). Of paramount significance is the association of acute renal failure with obstructive jaundice.[204,205] The incidence of postoperative acute renal failure is 8% to 10% and correlates directly with the degree of hyperbilirubinemia, with mortality rates as high as 70% to 80% reported. Neither bilirubin nor bile acids themselves are directly nephrotoxic, but experimental evidence suggests a negative chronotropic, vasodilatory, and diuretic effect of bile salts, resulting in systemic and thus renal hypoperfusion. The changes appear to be related to enhanced absorption of endotoxin from the gastrointestinal tract because of low intestinal levels and high serum levels of bile acids. This stimulates a release of inflammatory mediators, in particular endothelin, a potent renal vasoconstrictor that leads to a further decline in renal perfusion.[206,207] Other experimental data have implicated endotoxemia-induced nitric oxide release as a further mediator of renal hypoperfusion.[208] These patients clearly pose a challenge to the anesthesiologist, who is often forced to rely on the limitations of urine output as a method of monitoring renal perfusion. It is probably more reliable to monitor effective blood volume and cardiac function with either a central venous or pulmonary artery catheter or perform transesophageal echocardiography, with the goal of maintaining renal perfusion by augmenting cardiac output.[99] No data have documented the clinical benefit of mannitol, furosemide, or dopamine in perioperative renal protection,[99,209] and the potential benefit of endothelin receptor blockers has yet to be thoroughly assessed in clinical studies.[206]

Perioperative Management of Patients with Asymptomatic or Chronic Liver Dysfunction

The goal of perioperative management of patients with asymptomatic elevations in aminotransaminase, alkaline phosphatase, or bilirubin levels or those with preexisting chronic liver disease is prevention of acute liver failure or further hepatic deterioration. Acute liver failure, defined by encephalopathy in the setting of acute liver injury (e.g., viral hepatitis, toxin ingestion, idiosyncratic drug reaction, sepsis, or shock), is further categorized into hyperacute, acute, or subacute forms based on the time interval between the onset of jaundice and encephalopathy (0 to 7 days, 8 to 28 days, >28 days, respectively).[210] Patients with the hyperacute form of acute liver failure tend to have a more favorable survival rate (35%), whereas those with the acute and subacute forms have poorer prognoses, with mortality rates of 93% and 86%, respectively.[210] It is therefore imperative to identify perioperative risks and direct therapy to minimize hepatotoxicity and maximize hepatic oxygen delivery. For example, drugs such as acetaminophen or combined drugs such as acetaminophen/hydrocodone probably should not be administered to patients with asymptomatic elevation of liver enzyme test results or chronic liver dysfunction. In patients with cholelithiasis and biliary tract obstruction, it may be prudent to limit the use of opiates preoperatively because they have been reported to cause spasm of the choledochoduodenal sphincter (sphincter of Oddi) and a subsequent increase in intrabiliary tract pressure.[211,212] These effects appear to be more pronounced for fentanyl, morphine, and meperidine and less severe for opiate agonist-antagonists.[211,212] Intraoperatively, opiates may be used with the recognition that the possible development of sphincter of Oddi spasm can be treated directly with naloxone or by relaxing smooth muscle tone with either glucagon or nitroglycerin[212,213] (which induces release of nitric oxide).[214,215] (See Chapter 31.)

Remifentanil appears to have a similar effect as other opiates on the sphincter of Oddi. Fragen and colleagues[216] studied remifentanil given to six healthy adult volunteers who underwent radionuclide imaging of the gallbladder before and after remifentanil infusion. The recovery time for dye to appear in the duodenum after discontinuation of the infusion was significantly greater than in the control phase of the study. The authors noted, however, that this delay in recovery of gallbladder function was shorter than in studies using morphine or meperidine. Finally, no data support the benefit or detriment of regional versus general anesthesia, nor do data suggest particular anesthetic drugs that should be administered or avoided with preexisting hepatic dysfunction, with the exception of halothane, as previously discussed.

Patients with more advanced liver disease (e.g., CTP class B or C cirrhosis) require an anesthetic plan designed to maximize hepatic oxygen delivery and prevent and treat the complications of encephalopathy, cerebral edema, coagulopathy, hemorrhage, and portal hypertension. Hepatic encephalopathy commonly occurs in patients with chronic liver disease because of the accumulation of circulating neurotoxins such as unmetabolized ammonia, gut-derived false neurotransmitters, γ-aminobutyric acid (GABA), and endogenous GABA receptor agonists; altered

neurotransmission by the excitatory neurotransmitter glutamate; or altered cerebral energy homeostasis.[217] Clinically, hepatic encephalopathy is manifested by neuropsychiatric abnormalities ranging from subtle personality changes and cognitive dysfunction to more advanced depression of consciousness, delirium, and coma. Clinical signs include abnormalities in psychometric testing and apraxia, as well as the more severe findings of asterixis, hyperreflexia, and decerebration. When hepatic encephalopathy occurs with acute liver failure, it often has a rapid onset and is invariably complicated by cerebral edema. Cerebral edema develops as a result of the osmotic effect of accumulated glutamine producing astrocyte cell swelling or as a result of cerebral vasodilation caused by loss of autoregulation, or because of both mechanisms.[218] These patients invariably require urgent liver transplantation. (See Chapter 67.)

A multitude of factors may precipitate hepatic encephalopathy in patients with chronic liver disease. Potassium levels should be monitored and hypokalemia should be treated to decrease the effect of decreased potassium levels on renal production of ammonia. Arterial pH should be maintained near normal because systemic alkalemia is also noted to increase the diffusion of ammonia across the blood-brain barrier, which can potentially worsen the degree of encephalopathy.[217] Effective circulating blood volume should be maintained and anemia should be corrected to maintain hepatic oxygenation and promote the metabolism of circulating toxins. Benzodiazepines should be used judiciously because they may activate the central GABA-benzodiazepine receptor ligand and worsen hepatic encephalopathy. In this regard, it should be noted that all psychoactive drugs will have potential deleterious effects on hepatic encephalopathy by further suppressing a vulnerable central nervous system. Hepatic encephalopathy is also a recognized complication of the TIPS procedure.[219]

When patients remain obtunded or comatose after anesthesia and surgery, therapy is often directed toward decreasing ammonia production. Lactulose is administered either by nasogastric tube or by enema to create an osmotic, cathartic effect and to lower intestinal pH, thereby decreasing the survival of ammonia-producing bacteria.[169] Flumazenil, a specific antagonist of central benzodiazepine receptors, can improve the level of consciousness in selected cirrhotic patients with severe hepatic encephalopathy.[220]

Perioperative hemorrhage in patients with significant liver dysfunction may occur because of bleeding diatheses or the complications of portal hypertension (or both). Synthetic hepatic function, as measured by the INR, is useful to assess the severity of the coagulopathy and to gauge therapy, including the subcutaneous administration of vitamin K, transfusion of fresh frozen plasma, use of recombinant factor VII or other factors, and plasmapheresis.[210] (See Chapter 55.) In patients with acute liver failure, plasmapheresis may have potential benefit because it promotes rapid correction of coagulopathy while minimizing volume overload, but no large prospective controlled studies have yet validated this practice.[221]

Hemorrhage may also occur as a result of gastrointestinal bleeding from rupture of esophageal or gastric varices as a complication of portal hypertension. Intraoperatively, it is advisable to avoid the placement of a transesophageal echocardiography probe to avoid initiation of bleeding in patients with esophageal varices. Pharmacologic therapy for acute esophageal variceal bleeding includes use of the combination of vasopressin and nitroglycerin, somatostatin, or octreotide, a synthetic analog of somatostatin.[222,223]

Portal hypertension may also lead to the development of ascites. Ascites occurs with advanced liver disease secondary to renal retention of sodium and water and localization of this excess fluid in the peritoneal cavity because of portal hypertension. In addition to the general measures of sodium and water restriction and diuretic therapy, therapeutic paracentesis may be indicated if a patient presents for surgery with tense ascites.[224] Relief of tense ascites may improve pulmonary gas exchange and reduce the risk of gastric aspiration. Care should be taken, however, to prevent circulatory collapse by the concomitant administration of intravenous colloid solutions because intravascular volume re-equilibration occurs 6 to 8 hours after the removal of a larger volume of ascitic fluid.[222] Finally, patients with end-stage liver disease are at risk for the development of either hepatorenal or hepatopulmonary syndrome. Hepatorenal syndrome is a state of functional renal failure characterized by azotemia, hyperosmolar urine, and urinary sodium excretion less than 10 mEq/L.[225] Although the pathogenesis of this syndrome has not been clearly elucidated, there appears to be a decrease in renal perfusion pressure related to systemic vasodilation in combination with a loss of renal autoregulation because of increased sympathetic activity.[224] The diagnosis of hepatorenal syndrome in patients with end-stage liver disease usually signals the need for orthotopic liver transplantation. In the event that transplantation is not possible, management is supportive and consists of the use of intravenous volume challenges and large-volume paracentesis to relieve tense ascites.

The hepatopulmonary syndrome, which is defined by the triad of end-stage liver disease, increased alveolar-arterial gradient, and intrapulmonary vascular dilation, is characterized by the clinical features of digital clubbing, cyanosis, dyspnea, platypnea, and orthodeoxia, in addition to the other clinical characteristics of portal hypertension. Orthodeoxia, defined as arterial oxygen desaturation that is more pronounced in the upright position and relieved by recumbency, is a common phenomenon of hepatopulmonary syndrome.[226] The pathogenesis of hepatopulmonary syndrome is considered to be primarily related to intrapulmonary vascular dilation diagnosed by contrast-enhanced echocardiography, perfusion lung scanning, or pulmonary arteriography. Current pharmacologic therapy for this disorder is limited; however, orthotopic liver transplantation may lead to a reversal of these pulmonary changes (see Chapter 67).

Anesthetic Considerations for Procedures Involving the Liver and Biliary System

Transjugular Intrahepatic Portosystemic Shunt Procedure

TIPS is a percutaneously created intrahepatic connection of the portal and systemic circulations. This procedure is typically used in patients with end-stage liver disease to decrease portal pressure and attenuate the complications related to portal hypertension, such as variceal bleeding or refractory ascites. Diversion of PBF into the hepatic vein is achieved by placement of an expandable intraparenchymal tract (Fig. 66-7).

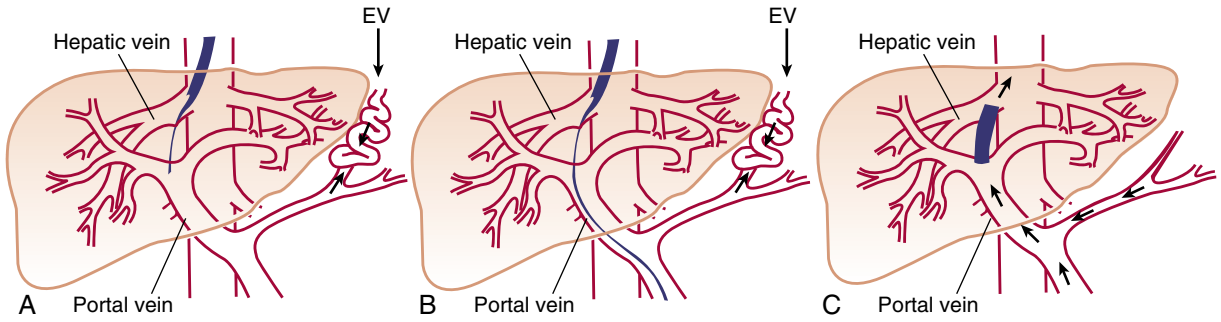

Figure 66-7 Transjugular intrahepatic portal-systemic shunt (TIPS) procedure. A stent (or stents) is passed through the internal jugular vein over a wire into the hepatic vein (**A**); dilated esophageal varices (EV) are apparent. The wire and stent or stents are then advanced into the portal vein (**B**), after which blood can pass through the portal vein into the hepatic vein and bypass and decompress dilated esophageal veins (**C**). (*Reproduced with permission from www.med.umich.edu/1libr/topics/liver09.htm.*)

Although most patients can undergo TIPS placement with sedation, some clinicians prefer to use general anesthesia in selected patients because of the prolonged nature of the procedure, the potential respiratory-depressant effects of sedatives in cirrhotic patients with underlying pulmonary dysfunction as a result of ascites and/or hypoxemia from the hepatopulmonary syndrome, and concern regarding possible gastric aspiration. Regardless of the anesthesia chosen, appropriate intravascular volume resuscitation is necessary before the procedure, especially in patients who have had variceal bleeding. In addition, patients with cirrhosis undergoing a TIPS procedure frequently have a severe coagulopathy that requires preprocedural procoagulant therapy.

Several complications can occur during placement of TIPS that may require intervention by the anesthesiologist. Pneumothorax or neck vessel injury can occur during vessel puncture. These complications may be reduced by ultrasonographic guidance during jugular vein puncture. Additionally, cardiac dysrhythmias can be mechanically induced during intracardiac catheter passage. Finally, the anesthesiologist should be prepared to manage acute, life-threatening hemorrhage caused by hepatic artery puncture in conjunction with a hepatic capsular tear or by extrahepatic portal venous puncture. Hemodynamic status can deteriorate with the development of pulmonary edema and congestive heart failure in patients with borderline cardiac reserve.[227]

Hepatic Resection

Preoperative considerations before hepatic resection involve risk assessment primarily utilizing the CTP or MELD classification. Upper endoscopy, CT scan, and/or MRI are often performed to rule out significant esophageal varices. Severe thrombocytopenia or large varices represent major perioperative risk and should preclude surgery until treated.[228] Significant anemia and coagulopathy, if present, should be corrected preoperatively. Decisions regarding the choice and dosing of anesthetic drugs should account for any baseline hepatic parenchymal dysfunction as well as the potential postoperative dysfunction resulting from resection of a major portion of the liver parenchyma.

Although the risk of significant intraoperative blood loss is well known and the need for appropriate monitoring and sufficient vascular access to permit rapid transfusion is widely accepted, overall fluid management during major hepatic resection is controversial. At some centers, fluid and blood administration is used liberally beginning early in the course of resection with the goal of increasing intravascular volume as a buffer against sudden blood loss. Other centers favor maintenance of a low central venous pressure during resection to minimize blood loss from hepatic venous radicals, major hepatic veins, or the vena cava. These sites typically contribute to most bleeding during hepatic resection. Notably, reduction of intrahepatic venous pressure can also be achieved by using a modest degree of the Trendelenburg position, an approach that will potentially maintain or even increase cardiac preload and cardiac output, as well as reduce the risk of air embolism from disrupted hepatic veins. In patients without preexisting renal dysfunction, the latter approach does not appear to have a significant impact on postoperative renal function.[229]

Although basic postoperative management concerns are similar to those of other major abdominal procedures, several aspects of care are notable. Intravenous fluids should be supplemented with either sodium or potassium phosphate, which is often needed to prevent severe hypophosphatemia and also to facilitate liver regeneration. Decreased clearance of hepatically metabolized drugs is important in selecting and titrating methods of postoperative analgesia.

Hepatic Cryotherapy

Hepatic cryotherapy involves the application of material at subzero temperature by multiple-lumen probes positioned intraoperatively under sonographic guidance. This procedure is used to treat nonresectable malignant hepatic tumors. Preanesthetic considerations for hepatic cryotherapy are similar to those for hepatic resection. Heat conservation measures should be instituted during the procedure, with continual monitoring of core temperature. Intraoperative bleeding is rarely significant enough to cause hemodynamic instability. Postoperative pulmonary, renal, and coagulation problems may be manifested as sequelae of the "cryoshock syndrome," even after a procedure with unequivocal intraoperative stability.[230]

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67 Anesthesia for Abdominal Organ Transplantation

Key Points

Solid Organ Transplantation

1. Solid organ transplantation is an accepted treatment of end-stage organ disease.
2. The discrepancy between the number of organ donors and organ recipients is increasing.
3. To increase the donor pool, living organ donors and extended criteria donors are being used.
4. Preoperative evaluation of organ systems should consider interval changes.

Kidney Transplantation

1. Patients with end-stage renal disease are subject to accelerated atherosclerosis and should be considered to have a significant perioperative cardiac risk.
2. Maintenance of adequate perfusion pressure to the newly transplanted kidney is crucial for initial graft function.
3. Anesthetic drugs that are dependent on renal excretion, especially muscle relaxants or their metabolites, should be used with caution.

Pancreas Transplantation

1. Patients may undergo pancreas transplantation alone, in combination with kidney transplantation, or after kidney transplantation.
2. Close glucose monitoring is required throughout the procedure.
3. Administration of colloids is preferred intraoperatively.
4. The immunosuppressive drug OKT3 can cause significant hemodynamic instability and noncardiogenic pulmonary edema.

Liver Transplantation

1. The model of end-stage liver disease calculates the severity of liver disease.
2. Preparation for massive transfusion and significant hemodynamic instability is essential.
3. Extubation in the operating room can be safely performed in selected patients.

Improvement in the success of solid organ transplantation over the past decades is remarkable and well documented. Refinement of perioperative care and improved post-transplant patient management over recent years have resulted in dramatic improvements in 1-year and 5-year graft survivals. These changes have led to a significant increase in the number of medical centers performing solid organ transplantation and increased public awareness. In addition, the indications for solid organ transplantation have been broadened. Some perceived contraindications, such as concomitant human immunodeficiency virus (HIV) infection and advanced age, are being overlooked in selected cases.[1,2] Similarly, patients receiving methadone maintenance therapy are considered for transplantation.[3,4]

As of the end of 2004, 153,245 people were living with a functioning organ transplant in the United States. The number of patients wait-listed for solid organ transplantation is steadily increasing and is currently around 90,000. The organs most frequently transplanted are the kidney and liver, which together accounted for more than 70% of all transplanted organs.

Only 54% of all donated organs from deceased donors were actually recovered in 2001. This fact, in conjunction with public perception about organ donation and brain death and limited awareness of health care professionals, has contributed to a severe shortage of cadaver donor organs. Different strategies have been adopted to increase the donor pool, including extension of donor criteria and the use of living related and unrelated donors, particularly for kidney and liver transplantation. These attempts alone are unlikely, however, to ameliorate the donor organ shortage in the long run. To help address the issue of maximizing the number of organs available for transplant, the Health Resources and Services Administration launched the Organ Donation Breakthrough Collaborative in 2005. As outlined in the mission statement, the collaborative intends to identify and promote the best practices in organ donation for adoption by hospitals and

organ procurement organizations, ultimately with the goal to increase transplantable organs from deceased donors. One recognized need is the identification of beneficial interventions in donors after determination of neurologic death.

The success of organ transplantation is based on a highly specialized team approach, including the cooperation of procurement organizations, transplant coordinators, and nurses, and physicians from many specialties. Except for kidney transplantation, most solid organ transplantations are performed at tertiary medical centers, which can provide all the needed medical, logistic, and technical expertise necessary to support a successful transplant program. Increasingly, medical subspecialties are providing physicians dedicated to the field of transplantation. In addition to transplant surgeons, most major centers rely on dedicated transplant hepatologists and nephrologists.

Anesthesia for kidney and pancreas transplantation is performed by most anesthesiologists, whereas most major centers have a dedicated liver transplant anesthesia team. Smaller centers may not have enough transplant volume or personnel, however, to staff a separate liver transplant anesthesia team. As a result, anesthesiologists who have experience in major hepatic surgery or cardiothoracic surgery are frequently called on to provide anesthesia for these complex and challenging cases. New guidelines regarding perioperative anesthesia coverage are currently being considered by the American Society of Anesthesiologists and United Network for Organ Sharing (UNOS).

This chapter reviews anesthetic considerations for kidney, liver, pancreas, and intestinal transplantation in adult recipients. Solid organ transplantation in pediatric patients is not addressed in this chapter (see Chapter 82).

Care of Organ Donors after Neurologic Determination of Death

Most potential deceased donors are previously healthy or relatively healthy individuals who have experienced brain death and do not have an extracranial malignancy or untreatable infection. Less than 5% of deaths satisfy these criteria, and only 10% to 20% of these eligible subjects actually become organ donors. In addition, a significant proportion of potential organ donors are lost because of medical exclusion (e.g., sepsis, malignancy, incurable infection) or inability to obtain consent for donation.[6,7] Historically, organs from older donors (>60 years old) have inferior survival rates than grafts from younger donors, but if proper selection criteria are applied, long-term graft survival reaches those of younger donors.[8]

In an attempt to fulfill the need for more organs, organs are being transplanted from extended criteria donors—donors who are considered not ideal because of underlying demographics or medical conditions (e.g., age, hypertension) or subsequent prolonged ischemia times. Outcomes data for all solid organs are not consistent with studies performed in kidney transplantation, reporting either similar or inferior post-transplant graft quality.

Nonetheless, significant ethical conflicts surrounding the definition of brain death in different social and cultural settings have been an obstacle in transplantation.[9] In the United States and Western Europe, a consensus has been reached among the scientific community with regard to the definition of brain death. There is, and will continue to be, considerable discussion, however, about concepts and definitions of death and the legal definition of death.[10] These issues are colored by the effects of cultural differences; concepts and definitions of death are not equally accepted from one culture to another. Many Western cultures have committed to deceased organ donation, and the emphasis of discussion is quite different from that in Japan or Taiwan, for example.

Determination and Declaration of Brain (Neurologic) Death

There is uniform agreement on the neurologic examination of adult brain-dead subjects, also called donors after determination of neurologic death, with the exception of the apnea test (see Chapter 98). Standardization of the procedures for diagnosing brain death is quite different among countries, however.[11] Criteria promulgated by the American Academy of Neurology in 1995 are generally applied in North, Central, and South America.[11,12] These standards grew out of the landmark Harvard Criteria published in 1968.[12] In Europe, criteria for the clinical evaluation of brain death also are fairly uniform, with the principal difference being the number of physicians needed to confirm the diagnosis.

Several requirements need to be met to declare brain death. At the time of examination, the patient must be comatose with neither spontaneous movement nor response to painful stimuli. A lack of brainstem activity should be confirmed by assessment of brainstem reflexes (Table 67-1) and the apnea test. Possible causes of reversible cerebral dysfunction should be excluded (e.g., hypothermia, residual drug effects). For the apnea test, the patient breathes 100% oxygen for 10 minutes, during which time the P_{CO_2} is confirmed to be in the normal range (35 to 45 mm Hg). Subsequently, mechanical ventilation is terminated, and blow-by oxygen is administered with a T-piece. After 7 to 10 minutes, an analysis of arterial blood gases is performed. A P_{CO_2} value greater than 60 mm Hg confirms lack of brainstem control of ventilation and represents a positive apnea test. No signs of spontaneous respiratory effort should be observed during this procedure. Confirmatory tests, such as transcranial Doppler, electroencephalography, and auditory evoked potentials, also may be used.

Intraoperative Management

Organ retrieval is not performed solely at major medical centers. Most organ retrievals are performed at community hospitals

Table 67-1 Brainstem Reflexes That Should Be Absent in Brain Death

Pupillary response to light
Corneal reflex
Oculocephalic reflex (doll's eye response)
Oculovestibular reflex (caloric response)
Gag and cough reflex
Facial motor response

without academic affiliation. Any anesthesiologist may be confronted with a brain-dead patient and the attendant pathophysiologic perturbations. The logistics of harvesting organs, the social circumstances (i.e., interaction with relatives of the potential organ donor), and the unusual sequence of intraoperative events may seem intimidating to the anesthesiologist.

Cessation of cerebral function invariably results in a sequence of pathophysiologic changes leading to death of the potential organ donor within a few days, unless appropriate intervention is undertaken. At the same time, it may take several days for identification of a possible organ donor, declaration of brain death, consent, and eventual organ recovery. Perioperative hemodynamic stabilization is crucial for prevention of donor organ damage or loss.

After an initial hyperdynamic response consisting of hypertension with or without tachycardia, brain-dead patients brought to the operating room for organ recovery experience hypotension, reduced cardiac output, myocardial dysfunction,[14] and vasodilation (decreased systemic vascular resistance). In addition, diminished oxygenation as a result of neurogenic pulmonary edema and diabetes insipidus secondary to decreased circulating levels of antidiuretic hormone may be observed. The latter also may lead to hypernatremia and hypokalemia. Hyperglycemia, coagulopathy, and hypothermia may be encountered and must be corrected when severe. The aggressiveness of treatment is determined by which organs are being recovered because the quality of resuscitation may have an impact on organ viability.

Certain guidelines[15] can be summarized as follows:

- Systolic blood pressure greater than 100 mm Hg (mean 70 to 110 mm Hg)
- Po_2 greater than 100 mm Hg
- Urine output greater than 100 mL/hr (1 to 1.5 mL/kg/hr)
- Hemoglobin concentration greater than 100 g/L
- Central venous pressure (CVP) 5 to 10 mm Hg
- Fio_2 less than 40% (if tolerated) for lung retrieval
- Glucose concentrations less than 200 mg/dL (or even <150 mg/dL)

To achieve these goals, the anesthesiologist should use standard monitors, measure urine output, and use invasive measurements of arterial pressure and CVP (frequently with a pulmonary artery catheter).

Hypotension should be treated initially by intravenous administration of fluids. A mixture of crystalloid and colloid solutions, and occasional administration of blood, most rapidly corrects hypovolemia with the goal of increasing urine output. For lung and pancreas transplant retrieval, colloids are preferred over crystalloids. Frequent communication with the surgical team regarding intravascular volume replacement is essential. Excessive fluid administration may result in swelling and even loss of the organ. To decontaminate the intestines for retrieval of the pancreas, a mixture of povidone-iodine (Betadine), amphotericin, and normal saline is administered through an orogastric/nasogastric tube. If pharmacologic support of the circulation is necessary, the inotrope of choice is usually dopamine; however, other cardiovascular drugs, such as norepinephrine, epinephrine, vasopressin, and dobutamine, may be added to maintain hemodynamic stability during the later stages of organ dissection and harvest.

Surgical techniques may vary depending on whether the procedure is for recovery of a single organ or multiple organs.[13] Generally, wide exposure of the surgical field is established, cannulas are placed for in situ perfusion, and the organs to be removed are isolated with preservation of their central vascular structures. Heparin is administered (approximately 20,000 to 30,000 IU) when requested by the recovery team. If recovery of the heart or lung is anticipated, pulmonary artery catheters or central venous catheters need to be withdrawn before cross-clamping. If lung recovery is anticipated, the lungs are ventilated well beyond cross-clamping and initiation of organ recovery other than the lung. Removal of the organs is performed under cold protection by applying ice to the surgical field. Organs are removed according to their susceptibility to ischemia, with the heart first and the kidney last in a multiorgan donor. Excellent communication between the often different surgical teams (e.g., abdominal organ team versus thoracic organ team) and the anesthesiologist is crucial to ensure optimal organ quality.[13] In the United States, several donor management initiatives critically review current standard-of-care practices and develop new and uniform management algorithms. In several Western European countries, uniform treatment algorithms are already successfully used.

Vasodilators such as phentolamine or alprostadil (lung recovery) may be administered during cross-clamping with the goal of decreasing systemic vascular resistance and allowing even distribution of the preservation solution. Long-acting nondepolarizing muscle relaxants should be used for optimal intra-abdominal and intrathoracic exposure. Clinically significant bradycardia in brain-dead patients does not respond to atropine, so a direct-acting chronotrope such as isoproterenol must be readily available. Patients declared brain-dead do not have pain perception, so analgesia is not required. Volatile anesthetics or narcotics may facilitate hemodynamic stability, however. The changes in heart rate and arterial blood pressure that may occur with surgical stimulation are the result of intact spinal reflexes. Although these hemodynamic changes can often be easily controlled with vasoactive agents alone, the anesthesiologist probably would be most comfortable responding to these changes by increasing the amount of volatile anesthetics.

Finally, the anesthesiologist may be asked to draw blood for several pretransplant tests. The volume may vary in different organ procurement organizations, but is generally 60 to 200 mL in adults.

Donation after Cardiac Death

A more recent development to increase the organ supply is the use of donation after cardiac death, formerly known as non–heart-beating organ donors. Originally introduced in the 1960s, it was subsequently abandoned and has been reintroduced only more recently. Medical centers re-explored this source of potential donors for abdominal organs (mainly kidneys).[16] In the United States, the use of organs from donations after cardiac death has steadily increased over the past decade, and these donors now represent about 7% of kidney transplants.[17] In 1993, the number of non–heart-beating organ donors in the United States was 42; it increased to 167 by 2001 and increased further to 561 by 2005.[18]

Policies were developed by organ procurement officials and hospitals to allow organ donation as an option to be considered for relatives of patients who potentially qualify as donors after cardiac death. In contrast to deceased donors, whose heart function, circulation, and tissue oxygenation are preserved until the organs are retrieved, organs from donors after cardiac death can be removed only after cardiac arrest. The difference invariably introduces a longer warm ischemia time that can potentially result in suboptimal donor organs. Donation after cardiac death can be categorized as controlled or uncontrolled, and these categories determine the extent of warm ischemia experienced by the organ donors. Controlled donations after cardiac death are from patients for whom the transplant team is awaiting the cardiac arrest, and all necessary preparations for rapid organ recovery are in place. In contrast, uncontrolled donations after cardiac death are from patients who have experienced unanticipated cardiac arrest; resuscitation has been unsuccessful, and consideration is being given to possible organ donation.

In addition to a prolonged warm ischemia time, legal, ethical, and logistic concerns prevent many centers from adopting this form of organ donation.[19] More recent studies from Switzerland and the United States have shown favorable long-term results, however, with regard to graft function in recipients of organs donated after cardiac death.[20-22] It remains to be seen whether this form of organ procurement from donation after cardiac death will achieve wider acceptance in the transplant community and provide a means to augment the donor organ pool significantly.

Organ Preservation

Solid organ harvesting and transplantation invariably cause injury to the donor organ. Three main distinct periods have been identified that contribute to injury: (1) storage of recovered organs ex vivo during transport (generally under hypothermic conditions) from the donor to the recipient, (2) the implantation phase (rewarming phase) without reperfusion, and (3) the initial reperfusion phase with the reintroduction of oxygen. Each period contributes to deterioration of the organ through a different pathway. Ex vivo storage involves immediate cooling and flushing of the organ after recovery with several available preservation solutions. Currently, most organs are stored at 4°C without continuous perfusion after initial flushing. At some centers and organ procurement organizations, organs are continuously perfused, in some cases with normothermic preservation.

Various cold storage solutions used worldwide include Collins, Euro-Collins (Fresenius, Germany), Bretschneider/Histidin-Tryptophan-Ketogluterat (HTK) (Franz Koehler Chemie, Germany), Celsior (Sangstat Medical Corporation, United States), Perfadex (Vitrolife, Sweden), and University of Wisconsin (UW) (Du Pont, United States).[23,24] Although the UW solution is probably the most frequently used solution, especially for intra-abdominal organs, the significantly cheaper HTK solution has been increasingly used with good results.[25] Most solutions are modified with additives (e.g., oxygen radical scavengers) that are believed to improve organ storage conditions. The content of the various organ preservation solutions varies widely, as does the amount used. UW solution contains 120 mmol/L of potassium versus only 10 mmol/L in the HTK solution. These differences may have clinical implications, such as a greater potential for hyperkalemia after reperfusion of organs (mainly liver) preserved in UW solution. Hyperkalemia is seen mainly, however, in cases in which the preservation solution is not adequately flushed with colloids before implantation. Organ-specific flush solution is commonly used with Euro-Collins solution, and more recently, Perfadex solution especially for lung storage. The heart is frequently stored in Celsior preservation solution, but medical centers occasionally may have center-specific cardioplegia solutions. Sometimes perfluorocarbons are used as a component of the two-layer method for preservation of the pancreas.[26] Organ preservation solutions are under constant review and undergo frequent modifications.

The maximum cold preservation time varies among organs and solutions used. Typically, kidneys can be stored in cold preservation solution for up to 24 to 30 hours before transplantation, although the ischemia time does have an impact on outcome. In contrast, hearts must be transplanted within hours of retrieval. Continuous machine perfusion (as opposed to cold storage) of the organ has attracted some attention.[27] This method is not widely adopted currently, however, and large randomized trials are necessary to show its feasibility.[28]

Care of Living Organ Donors

The first living donor transplantation was performed in 1954, when a kidney was transplanted from one man to his twin brother.[29] The lack of effective immunosuppressive treatment at that time prohibited the use of deceased organs. With the introduction of immunosuppressive drugs, improved long-term graft survival was achieved, and the use of deceased donors rapidly accelerated in most Western countries. In Japan, transplantation from deceased donors has not been well accepted, mainly because of cultural and ethical norms. In 1997, legislation was passed in Japan that allowed organ donation from selected brain-dead donors.[30] Organ transplantation from living donors has become an important, well-developed alternative for patients with end-stage organ disease in Japan and other Asian countries.[31] The benefits to donor and recipient must outweigh the risk associated with the recovering of a living donor organ.[32]

Living donors generally are very healthy and almost exclusively classified as American Society of Anesthesiologists grade I or II patients. In the past, donors were usually relatives of the prospective recipient. More recently, candidates unrelated to the recipient are increasingly being accepted as donors. By the time that they are determined to be eligible for donation, donors have undergone an extensive medical, psychological, and social evaluation.[33,34] Many living donor and recipient pairs are turned down during the screening process for medical and nonmedical reasons (e.g., social or psychological concerns) that may affect the donor or recipient. A major concern surrounding living organ donation is the potential for great harm to be inflicted on entirely healthy individuals who undergo major surgery for purely altruistic reasons. The ethical and psychological aspects (e.g., coercion of the donor) of living organ donation, particularly liver donation, continue to be widely examined and discussed.[32,35-39] In addition, the quality of life after organ donation and the financial impact on the donor are of great concern.[40,41]

Organ donation from living donors has significant advantages over deceased organ donation. In contrast to deceased

donors, living donors are always hemodynamically stable, and the procedure can be planned on an elective basis. In addition, the cold ischemia time of the organ can be minimized compared with that associated with deceased donors. Perhaps the most important advantage of living donor transplantation is the significant reduction in time spent on the waiting list to receive an organ from a deceased donor.

Living Kidney Donor

Renal transplantation with organs from living donors has rapidly been increasing in recent years. In the past, donor nephrectomy was done by the traditional approach through a subcostal lateral incision, by minimal incision nephrectomy, or by the laparoscopic approach. Laparoscopic live donor nephrectomy now has almost completely replaced the traditional open approach via subcostal lateral flank incision. Melcher and colleagues[42] reported 500 consecutive laparoscopic donor nephrectomies without the need to open or reoperate for technical difficulties. The laparoscopic approach has been shown to be advantageous with regard to decreased postoperative pain, time of hospitalization, recovery, and improved cosmetic results.[43,44]

Morbidity after living kidney donation is low, and the type of complication (e.g., reoperation, ileus, readmission to the hospital) depends on the surgical technique. Matas and coworkers[45] reported two donor deaths and one donor who has remained in a persistent vegetative state in a series of 10,828 living kidney donations between 1999 and 2001. Shokeir[46] performed a meta-analysis of 69 studies comparing open versus laparoscopic donor nephrectomy and discovered eight perioperative deaths after laparoscopic nephrectomy. More recent studies confirmed that laparoscopic donation results in a safer procedure, a more rapid convalescence, and a lower opioid consumption compared with open donation. Placement of an epidural catheter is not indicated.[46-48] Nevertheless, Ellison and colleagues[49] caution that the long-term risks may not yet be apparent, and that long-term follow-up data are needed.

Either kidney can be used for donation; however, the left kidney is usually preferred because of easier surgical exposure and a longer vascular supply. The patient is placed in either a right or a left lateral position with the table flexed and the kidney rest elevated. Invasive monitoring is not required, and one or two large peripheral intravenous lines suffice. Some centers have 2 U of blood (frequently autologous) available in the operating room in case of injury to major vascular structures, which would require emergency exploratory laparotomy. To maintain good diuresis and to optimize graft function, fluid administration is generous (10 to 20 mL/kg/hr), even though blood loss is minimal in most cases. The preferred type of fluid in this setting is unknown because no human trial has yet addressed this issue. In the absence of scientific data, most centers use isotonic crystalloids. The anesthetic technique in these healthy patients is not different from that used for other laparoscopic procedures. Nitrous oxide is contraindicated because it causes bowel distention and worsens surgical exposure.[50] Similarly, the potential complications seen during any laparoscopic procedure (e.g., pneumothorax, subcutaneous emphysema) can be encountered during this procedure.

The first phase of the procedure consists of mobilization of the colon followed by the upper portion of the kidney, with subsequent identification and dissection of the ureter, renal vein, and artery. Division of the adrenal vein also is performed.[51] The surgeon may request administration of furosemide or mannitol (or both) during the operation to maintain adequate urine output. Shortly before the renal vessels are clamped, intravenous heparin (3000 to 5000 IU) is administered. Protocols may vary among institutions, and close communication with the transplant surgeon is essential. After complete mobilization of the kidney and clamping of the vascular structures, the kidney is retrieved by either a hand-assisted or non–hand-assisted[52] technique through a small periumbilical or infraumbilical incision under direct laparoscopic vision. If heparin has been given, protamine may be administered to normalize coagulation. After the kidney is removed, the surgical field is inspected again for bleeding. Closure, as in all laparoscopic cases, is rapid, and care should be taken to maintain reversibility of neuromuscular blocking agents at the conclusion of the procedure. Postoperative pain is usually mild to moderate and can be managed easily in most cases with supplemental intravenous opioids in the immediate postoperative period.

Living Liver Donor

Living donor liver transplantation began in the early 1990s and quickly became a widely accepted technique in children.[37,53] The regenerative capability of the liver has long been recognized and exploited, and complete recovery of liver function in the donor and the recipient can be expected after donation of a portion of the liver. The primary presurgical consideration is determination of the mass of transplanted liver that is needed to support a given patient and to leave enough liver mass with the donor. Several formulas, including the graft-recipient body weight ratio and graft weight as percentage of standard liver mass, are used to ensure adequate liver mass in the donor and recipient.[33,54]

Pediatric living donor liver transplantations generally require resection of only the left lateral segment (segments II and III) or a total left hepatic lobectomy (segments II, III, and IV) to provide sufficient liver mass. These types of grafts are expected to grow along with the patients as they mature. From a surgical point of view, a left hepatectomy is less complex, and the duration of surgery is shorter.[55,56]

This technique has been extended to adult patients as well. The number of living donor liver transplantations performed annually in the United States grew slowly through most of the 1990s (representing about 1% of liver transplants), but increased dramatically beginning in 1998 (from 56 in 1996 to 515 in 2001). The number has now plateaued between 200 and 300. This rapid increase is primarily due to increased numbers of right hepatic lobectomy for adult-to-adult living donor liver transplantation. The surgical technique for right hepatectomy involves separation of the right hepatic lobes (segments V, VI, VII, and VIII) from the left (Fig. 67-1). This technique results in a graft weighing 500 to 1000 g, which leaves the donor with about one third of the original liver mass. In select cases, the left lobe of a large donor may suffice for a small recipient, either with or without a portal shunt.

Volumetric studies have shown that the donor's liver regains its original size in a short time, often within weeks to months.[57,58] Functional recovery may take much longer, however.[59,60]

Most living donor liver transplantations are done in patients with chronic liver failure and are done on an elective basis.

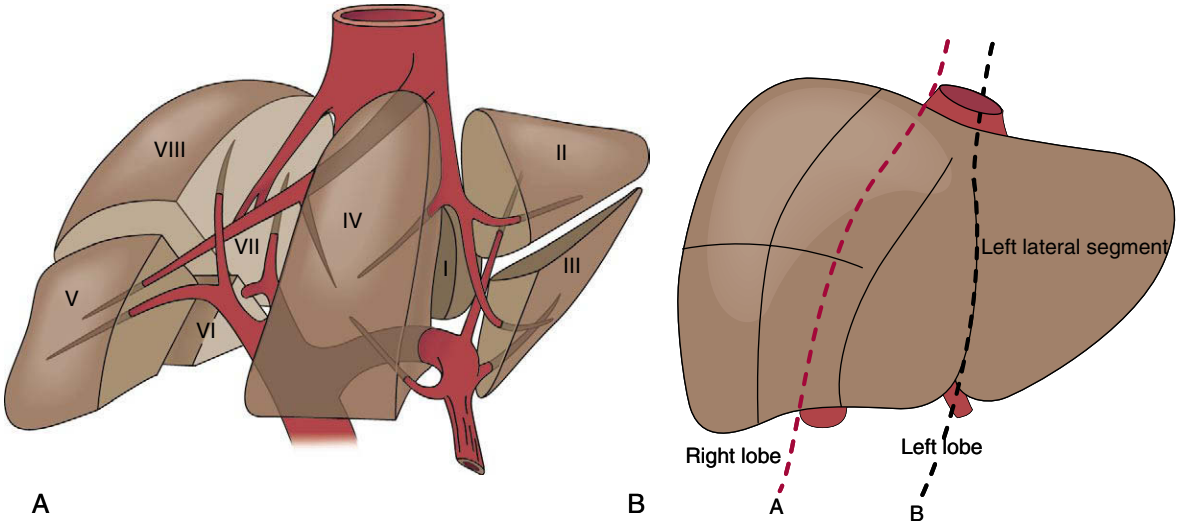

Figure 67-1 **A,** Segmental liver anatomy. Each segment is supplied by a portal pedicle consisting of the hepatic artery, portal vein branch, and bile duct. **B,** Segments V to VIII are frequently used for adult-to-adult living donor transplantation. *(Redrawn from Renz JF, Yersiz H, Farmer DG, et al: Changing faces of liver transplantation: Partial-liver grafts for adults. J Hepatobil Pancreat Surg 10:31-44, 2003.)*

Although it is controversial, living donor transplantation may be performed in rare cases in patients with very advanced disease or decompensated end-stage liver disease.[61,62] In contrast, in children with subacute or acute liver failure, living donation, mostly from parents, is commonly accepted. The ethical issues, such as coercion of the donor, involved in these cases are even more pronounced.[63,64] In addition, relative inexperience with the procedure may lead to an unacceptably high complication rate. Worldwide, several donor deaths related to the surgical procedure have occurred. The overall complication rate is variable[35] and ranges from 0% to 67%, with a crude morbidity rate of 31%. This large variation can be attributed to differing definitions of morbidity and study design.[66] Editorials have raised significant concern about donor safety, the lack of adequate outcome data, and the need for regulation and oversight.[39,67,68]

The intraoperative care of patients undergoing right hepatectomy for liver donation is similar to care of other patients having hepatic surgery. Preoperative placement of a thoracic epidural catheter is done in some transplant centers; however, other centers use only patient-controlled analgesia for postoperative pain control. The choice of postoperative pain control seems to depend partly on the postoperative monitoring capabilities and the familiarity of the nursing staff on the floor with each technique. Avoidance of epidural catheter placement based on concerns of postoperative coagulopathy from extensive hepatectomy does not seem to be justified. The prothrombin time usually peaks on postoperative day 2 to 3 and returns to baseline by day 5. Several studies have failed to show any adverse effect of epidural catheters in this patient population.[60,69] The largest study was reported from Japan and involved 755 donors who received an epidural catheter for postoperative pain management.[70] No complications associated with the epidural catheter were reported. A study from South Korea including 242 living liver donors also showed that epidural analgesia seems to be a safe option when used carefully.[71] Because of the very low incidence of epidural hematomas overall, however, these studies lack the power to assess the risk of epidural hematoma developing in this patient population. General anesthesia is standard and may consist of a balanced technique or be combined with intraoperative supplementation of epidural analgesia.

Intraoperatively, the patient is placed in a supine position, frequently with one arm tucked (right or left) at the side and the other abducted. An orogastric/nasogastric tube is placed for decompression of the stomach and improved surgical exposure, particularly when a left hepatectomy is performed. Two large-bore intravenous catheters and invasive arterial blood pressure monitoring are used in most centers.[60,70] Continuous monitoring of CVP has been advocated by some authors to ensure a low CVP because an elevated CVP is considered to be a prime determinant of bleeding from liver parenchyma during transection.[72] Fluid is administered sparingly until the donor liver lobes are removed. In a retrospective study, CVP monitoring did not seem to reduce blood loss compared with patients without CVP monitoring. In centers with extensive experience, CVP monitoring may be unnecessary.[73] As an alternative to conventional CVP measurements, Choi and colleagues[74] suggested peripheral venous pressure measurements in the arm. An autotransfusion system is used at most centers, and patients frequently donate 1 to 2 U of whole blood preoperatively. At centers where this procedure is done on a routine basis, blood loss is generally less than 1 L.[60,75] Because of the nature of the procedure, however, preparation and vigilance for sudden extensive blood loss are always warranted.

Frequently and especially for right lobe donation, an L-shaped (hockey stick) or standard bilateral subcostal incision with a midline extension is used. The procedure can be divided into three stages: (1) mobilization of the liver and identification of vascular structures, (2) transection of the liver, and (3) hemostasis and closure. During the first stage of the operation, manipulation of the liver occasionally can result in decreased venous return to the heart with consequent brief episodes of hypotension. It is important to be aware of this possibility before initiating any therapy. The parenchymal division is completed with several

different devices, such as the CUSA ultrasonic surgical aspirator (Valley Lab, Boulder, CO) or the Harmonic Scalpel (Ethicon Endo-Surgery, Somerville, NJ).[59,60] After the vasculature of the donor lobe is clamped and divided, the graft is removed, and the vasculature and bile duct are oversewn. Subsequently, hemostasis is achieved, and the abdomen is closed.

In uncomplicated cases, the patient can be extubated in the operating room and transferred to the postoperative care unit. Admission to the intensive care unit (ICU) is generally unnecessary. Nevertheless, standard practice in some institutions has been to manage living liver donors in the ICU in the early postoperative period.

Contraindications to Solid Organ Transplantation

For all transplant candidates, the number of absolute and relative contraindications has diminished in recent years. Overall, candidates for kidney transplantation are increasingly older and have more complex medical problems. Active infection is an absolute contraindication until it has been treated, and the infection has resolved. Evidence of malignancy is not a contraindication per se. Hepatocellular carcinoma with underlying cirrhosis is considered an indication for liver transplantation as long as the tumor burden does not exceed established guidelines, such as the Milan[76] or the University of California San Francisco criteria.[77] Similarly, select patients are reconsidered for renal transplantation after successful treatment of malignancy and no evidence of recurrence. Relative contraindications, such as noncompliance or a history of drug abuse, exist, but vary among centers. Contraindications to specific transplant procedures are outlined as necessary in each section.

Kidney Transplantation

The first description of anesthesia for kidney transplantation appeared in the early 1960s. It detailed the pioneering efforts in Boston with living donor kidney transplantation between identical twins.[78] The only monitors used then were a blood pressure cuff and electrocardiogram (ECG), and the recipient received spinal anesthesia. Much has changed in the anesthetic management of these cases. What was previously seen as heroic and exceptional is now commonplace. These patients are challenging to anesthetize because end-stage renal disease (ESRD) often causes dysfunction of other organ systems, which may produce less predictable responses to anesthetic drugs and techniques. In addition, these patients are at high risk for cardiac and other perioperative complications because of their underlying disease.

Kidney transplantation is indicated for patients with ESRD caused by glomerular disease, diabetes mellitus, hypertensive kidney disease, polycystic kidney disease, other familial or congenital diseases, and tubulointerstitial disease. Kidney transplantations are the most commonly performed transplantations in each of three major regions of the world—the United States, Europe, and Asia.[79] This number represents a steady increase throughout the 1990s. Considerable variation in the proportion of organs that come from deceased versus living donors occurs worldwide, with some countries relying almost entirely on deceased donors (e.g., China) and some relying largely on living donors (e.g., Japan, Taiwan). In the United States, transplantation of kidneys from deceased donors were 8849, down from 10,659 in 2006, whereas the number of living donors also decreased from 6432 in 2006 to 5094 in 2007.

In early 2008, approximately 78,700 patients were awaiting kidney transplantation in the United States, with an average waiting time of longer than 3 years.[5] This fact implies that recipients as a group are older and sicker than previously. Nonetheless, kidney transplantation is one of the most important, cost-effective methods of treating ESRD; it confers a 40% to 60% decrease in the death rate compared with patients remaining on dialysis. The overall graft survival rate among cadaver kidney transplant recipients at 3 years is greater than 88%, and it is approximately 93% in recipients who receive a kidney from a living donor.[80]

Organ Matching and Allocation

Initial testing is done to determine major blood group (ABO) compatibility. A second test determines the HLA profile of the recipient. Finally, a crossmatch is done by mixing recipient blood with donor blood cells to determine the presence of preformed reactive antibodies against donor antigens.[81]

Pathophysiology of End-Stage Renal Disease

The kidneys are essential for adjusting body fluid volumes, electrolyte composition, acid-base balance, and hemoglobin concentration. The kidneys receive about 25% of cardiac output and function as filters for toxins and drugs in the circulation. When kidney function declines, these functions are impaired. Chronic renal failure results in a steady decline in glomerular filtration and urine production, which has deleterious effects on multiple organ systems throughout the body. Patients with glomerular filtration rates less than 30 mL/min/1.72 m^2 (normal 120 mL/min) show an increase in blood nitrogenous wastes, mainly urea, and begin to retain fluid and electrolytes. When urine production declines to less than 400 mL/day, the patient becomes oliguric and is unable to excrete dietary fluid and electrolyte loads. Abnormalities in Na^+, K^+, Ca^{++}, Mg^{++}, and phosphate levels can develop, with the most life-threatening being hyperkalemia.

Cardiovascular disease is the predominant cause of death in patients with ESRD, and even after renal transplantation it is a major cause of death.[82] Acute myocardial infarction, cardiac arrest of unknown etiology, cardiac arrhythmia, and cardiomyopathy account for greater than 50% of deaths in patients maintained on dialysis.[83] The death rate from cardiac causes in dialysis patients increases with age; it is approximately twofold higher for patients 45 to 64 years old and four times higher in patients older than 65 compared with patients 20 to 44 years old. When echocardiography is done as a screening tool, a high incidence of abnormalities is found. Furtermore, left ventricular or right ventricular hyper-

trophy or pericarditis was detected in 60% of autopsies performed on dialysis patients.[84]

Dilated cardiomyopathy and concentric hypertrophy can develop in response to increases in intravascular volume and afterload. Fluid overload and congestive heart failure occur when the kidneys cannot excrete the daily fluid intake, and hypervolemia ensues. The accumulation of uremic toxins and metabolic acids contributes to poor myocardial performance. Cho and coworkers[85] documented that some patients with a low ejection fraction secondary to uremic cardiomyopathy completely normalized their cardiac function after successful renal transplantation. ESRD with significantly depressed ventricular function is not a contraindication to renal transplantation, but it may complicate the anesthetic management.

Hypertension produced by renal disease is the result of (1) deranged renal handling of Na^+ and fluids leading to volume expansion and (2) alterations in levels of vasoactive substances resulting in systemic and local changes in arterial tone. Hyperreninemia may lead to increased systemic vascular resistance and elevated systemic blood pressure, but it is not always present. If untreated, the elevated systemic pressure within the kidney causes damaging sclerotic changes in the renal vasculature. A vicious cycle ensues in which hypertension damages the kidney and creates the conditions for escalating hypertension. Hypertension also can be a manifestation of fluid overload when oliguria has developed, causing increased myocardial afterload and wall stress, which, in conjunction with uremia, produce changes in the heart consistent with cardiomyopathy. Chronically elevated systemic pressure lead to left ventricular hypertrophy and increased myocardial oxygen requirements.

Renal failure also accelerates the progression of atherosclerosis, especially in the coronary circulation. Uremia causes changes in lipid metabolism, leading to increased concentrations of serum triglycerides and reduced levels of protective high-density lipoproteins.

Other cardiac conditions, such as pericardial disease and arrhythmia, may be encountered in patients with ESRD. Pericarditis, which may coexist with hemorrhagic pericardial effusion, is reversible with dialysis. Generally, patients who are adequately dialyzed have resolution of their pericardial effusion. The occurrence of arrhythmias may be the consequence of electrolyte abnormalities, or may represent episodes of myocardial ischemia.

Diabetes mellitus is the cause of ESRD in nearly 30% to 40% of cases, and these patients represent more than 30% of individuals on the waiting list for a kidney transplant. Nephropathy develops in nearly 60% of insulin-dependent diabetics. Patients with ESRD and diabetes mellitus have higher cardiovascular risk than patients with uremia alone because of the associated acceleration of small-vessel atherosclerosis.

Chronic uremia also causes delayed gastric emptying. The mechanism for this is unknown, but gastric dysrhythmia with discoordinated myoelectric activity has been found in uremic patients on maintenance hemodialysis.[86] There seems to be no difference in delayed gastric emptying whether patients are undergoing peritoneal dialysis or hemodialysis. All patients presenting for kidney transplantation should be considered to have full stomachs, regardless of the period of preoperative fasting. Rapid-sequence induction should be considered, especially in patients with diabetes. This recommendation is underscored by the finding that gastric volumes greater than 0.4 mL/kg were found in 50% of diabetic uremic patients, but in only 4 of 24 nondiabetic uremic patients.

Patients in renal failure generally have normochromic, normocytic anemia because of decreased erythropoiesis and retained toxins secondary to kidney failure. Treatment with recombinant erythropoietin frequently can increase hemoglobin levels to 10 to 14 g/dL, which reduces symptoms of fatigue and improves cerebral and cardiac function.[87-89] In some patients, preexisting hypertension can worsen with erythropoietin therapy.[87]

An association between renal failure and bleeding tendency has long been recognized. A qualitative defect in platelet function produced by uremia itself seems to be central. The defect results from accumulation of the compound guanidinosuccinic acid in uremic blood, which inhibits adenosine diphosphate–induced platelet aggregation.

Although a qualitative platelet defect can be identified in uremic patients, more recent studies have pointed out that a prothrombotic state also may coexist with uremia. A thromboelastographic study of whole-blood clotting found increased coagulability and decreased fibrinolysis in uremic patients versus controls.[90] Platelet-derived microparticles (small vesicles with procoagulant activity that are released from activated platelets) may be involved in clinical thrombogenesis.[91]

Uremia may cause central nervous system disturbances ranging from drowsiness, memory loss, and decreased concentration to myoclonus, seizure, stupor, and coma. Signs of peripheral or autonomic neuropathy are considered strong indications for dialysis.

Surgical Procedure

Donor kidneys, whether from a living or a deceased source, are usually implanted in the iliac fossa. Either side of the abdomen can be used. An incision approximately 8 to 10 inches (20 to 25 cm) provides sufficient exposure. Usually, the incision extends from the midline of the pubic symphysis to a point 2 to 3 cm superomedial to the anterior superior iliac spine. Anatomic variations are common and often require repair or reconstruction of vessels or the ureter. Two or more renal arteries can supply the donor kidney, with both originating from the aorta. Although vascular anastomoses can be done with different recipient vessels, the external iliac artery and vein are frequently used for the vascular anastomoses (Fig. 67-2). Distal and proximal clamps are placed on the external iliac artery and vein, and the donor renal artery (occasionally two) and vein are connected by end-to-side anastomosis. The period of warm ischemia generally lasts 15 to 30 minutes.

After completion of the anastomoses, the clamps are released in staged fashion. The bladder is subsequently filled through a Foley catheter to facilitate implantation of the ureter directly into the bladder. The wound is closed in layers with special attention paid to urine output to identify vascular or ureteral compromise during closure.

Preoperative Considerations

Fifty percent of patients with ESRD have one or more of the comorbid conditions described previously. The presence of these

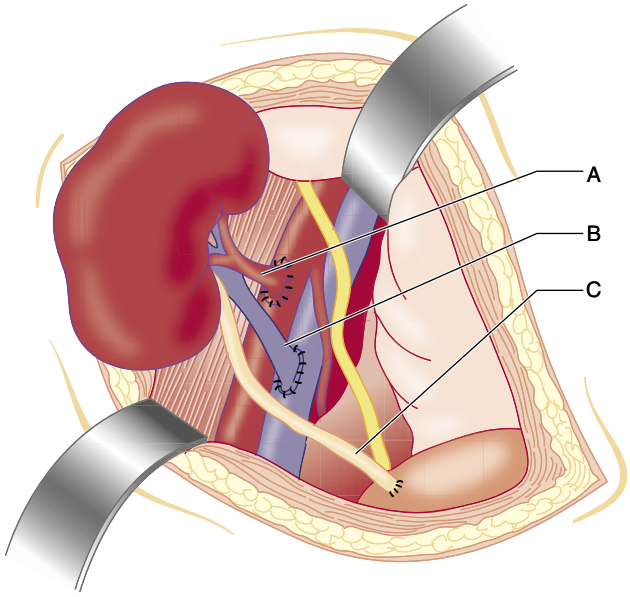

Figure 67-2 **A,** Renal artery anastomosis performed end-to-side to the external iliac artery. **B,** Renal vein anastomosis performed end-to-side to the external vein. **C,** Ureteral anastomosis to the bladder mucosa. *(From Hardy JD: Hardy's Textbook of Surgery, 2nd ed. Philadelphia, JB Lippincott, 1988.)*

comorbidities greatly influences the approach to anesthesia chosen for these patients. Although transplants involving deceased donor organs are often scheduled as urgent or emergency cases, prolonged cold preservation of the kidney is well tolerated and should provide enough time to allow transplant candidates to be reasonably well prepared for surgery. If possible, recipients should be dialyzed to correct electrolyte imbalances and volume status before surgery. Patients not maintained on dialysis generally produce sufficient urine volume to prevent fluid overload. Electrolyte concentrations, particularly K^+ and HCO_3^-, still may be grossly abnormal, however, and suggest a worsened homeostatic condition.

One method to estimate volume status is to compare patients' weight with their "dry weight," which hemodialysis patients usually know. Occasionally, continuous ambulatory peritoneal dialysis is used as an alternative to hemodialysis. Patients undergoing hemodialysis may have fluid removed just before surgery to facilitate perioperative fluid management. Such removal of fluid may render patients hypovolemic and put them at risk for significant hypotension on induction of anesthesia. Potassium levels should be reviewed immediately before surgery, especially in patients who may have missed a regular dialysis appointment. Although unlikely after immediate preoperative completion of dialysis, potassium levels greater than 6 mEq/L may require a delay in surgery and correction of potassium levels.

Preoperative evaluation of cardiac function is of central importance and is dictated by the underlying renal disease, its duration, and attendant comorbidities. A preoperative ECG and stress test may be sufficient for a patient who is young with newly diagnosed ESRD unrelated to diabetes, whereas a stress echocardiogram or a cardiac catheter may be indicated for symptomatic patients or patients with long-standing ESRD associated with diabetes. Many older and diabetic patients are unable to undergo exercise ECG testing and may have "silent" cardiac ischemia.[92] There is not absolute consensus at this point on the optimal cardiac workup for ESRD patients coming for kidney transplant.

Several noninvasive screening tests have been studied to determine their ability to identify coronary artery disease (CAD) in this patient population. In a prospective study, Herzog and coworkers[93] performed dobutamine stress echocardiography before quantitative coronary angiography in a mixed population of ESRD patients who were candidates for transplantation. More than 50% of patients had some degree of CAD (coronary stenosis >50%). Dobutamine stress echocardiography displayed a sensitivity of only 52% to 75% and a specificity of 74% to 76%, however, in identifying patients with CAD. These patients were monitored for 2 years. During this time, 20% of patients with negative dobutamine stress echocardiography experienced cardiac death or myocardial infarction or underwent coronary revascularization. Herzog and coworkers[93] concluded that dobutamine stress echocardiography was a useful, but imperfect tool for identifying patients needing further workup. Dobutamine stress echocardiography detects functionally significant stenosis; however, most sudden cardiac deaths occur in functionally insignificant lesions (e.g., acute thrombosis in patients with coronary stenosis of 20% to 30%). Other noninvasive tests also have been found to have limited usefulness in identifying ESRD patients with CAD. In one study, dipyridamole thallium scintigraphy showed adequate sensitivity (80%), but poor specificity (37%).

Other studies suggest that determination of cardiac risk should begin with the analysis of easily obtainable clinical variables, rather than widely pursuing expensive tests with limited sensitivity and specificity.[94] A history of chest pain is a helpful starting point in detecting CAD in these patients because it has a sensitivity and specificity of 65% for CAD.[92] A more comprehensive system, such as the revised cardiac risk index, was originally derived from retrospective data and shown in a prospective population to be a good predictor of the cardiac risk for patients without renal failure undergoing noncardiac surgery. It focuses on the presence or absence of six variables: high-risk surgical procedure, history of ischemic heart disease (excluding previous coronary revascularization), history of heart failure, history of stroke or transient ischemic attacks, preoperative insulin therapy, and preoperative creatinine levels greater than 2 mg/dL (>152.5 µmol/L).

These risk factors appear with high frequency in patients presenting for kidney transplantation. With zero or one risk factor, the rate of a major perioperative cardiac event is quite low; however, the rate increases rapidly to 6.6% and 11% when two and three or more of these risk factors are present. In addition, it is now widely understood that patients awaiting kidney transplantation require repeated cardiovascular surveillance. In the case of an initial negative cardiovascular evaluation, patients are risk-stratified (e.g., diabetic ESRD, nondiabetic risk factors) and assessed annually, biannually, or less frequently. Patients with a positive initial cardiovascular workup (with or without a previous medical intervention) are mostly evaluated annually.[65]

Patients can be initially stratified into basic risk groups (low, medium, or high) based on history, symptoms, and basic examination (see Chapter 34). Low-risk patients may proceed to

transplantation without additional workup, and high-risk patients should probably undergo invasive studies (e.g., cardiac catheterization). For intermediate-risk patients, it may be useful to perform a screening stress test, such as dobutamine stress echocardiography or radionuclide scintigraphy.

The use of perioperative β-blockade is suggested as a means of decreasing perioperative risk in these high-risk patients undergoing kidney transplantation. Several studies throughout the late 1990s established that perioperative β-blockade provides significant risk protection from major cardiac events in high-risk, nontransplant patients, although the POISE trial has questioned this contention. No prospective, randomized trials have been conducted with perioperative β-blockade in kidney transplant patients. It is unknown at present whether such treatment can be applied safely to these patients, especially patients with diabetes mellitus (see Chapter 35).

Diabetic patients have a higher incidence of autonomic neuropathy, which can be manifested as a higher heart rate and blood pressure than in nondiabetic ESRD patients.[95] Type 2 diabetics often have a combination of visceral obesity, atherogenic dyslipidemia (low levels of high-density lipoprotein and elevated levels of triglycerides), hypertension, and insulin resistance. This combination leads to a heightened risk of CAD and cardiovascular disease.

It should be determined when antiglycemic agents were last taken. Oral agents should not be taken the day of surgery because of the potential for unrecognized hypoglycemia under anesthesia. Insulin-dependent patients who are extremely brittle and have declining insulin levels are at risk for the development of ketosis and intraoperative acidemia.

Coagulation status, as reflected by prothrombin time, international normalized ratio, partial thromboplastin time, fibrinogen, and platelet count, is routinely assessed before surgery. Although ESRD patients may be consuming protein-restricted diets, it is rare for such diets to cause a significant clotting factor deficiency. A helpful preoperative screen to predict bleeding is a carefully conducted history that includes family, dental, obstetric, surgical, transfusion, and drug histories; the bleeding time is not a useful screening test to predict intraoperative bleeding.[96]

Intraoperative Management

Although spinal anesthesia was used exclusively for the first reported anesthetics,[78] and other centers have more recently reported successful use of regional anesthesia for these cases,[97] most centers now use general endotracheal anesthesia to provide stable hemodynamics, excellent muscle relaxation, and predictable depth of anesthesia. A balanced technique combining volatile anesthetics with opioids has been compared with total intravenous anesthesia using opioids and propofol, with no differences found.[98] Standard American Society of Anesthesiologists monitors may be all that are needed for these cases. Patients with more advanced stages of comorbid conditions may require more extensive monitoring, such as continuous arterial pressure or CVP monitoring, or both. Major swings in blood pressure may occur, with hypotension (49.6%) being more likely than hypertension (26.8%) in one large series. Patients with the most severe comorbid conditions, such as symptomatic CAD or a history of congestive heart failure, should be monitored for the development of ischemia or severe hemodynamic impairment intraoperatively with a pulmonary artery catheter or transesophageal echocardiography (TEE). The status of hemodialysis shunts or fistulas should be monitored during positioning and intraoperatively to confirm the presence of a thrill and to document patency.

With CVP monitoring, the goal is to keep CVP 10 to 15 mm Hg to optimize cardiac output and renal blood flow. Immediate graft function has been associated with a blood volume greater than 70 mL/kg and a plasma volume greater than 45 mL/kg.[99] Another study showed that pulmonary arterial pressure correlated with graft function. Higher filling pressure (pulmonary arterial pressure >20 mm Hg/diastolic pulmonary arterial pressure >15 mm Hg) resulted in better graft function than lower filling pressure. Recently, there has been some discussion of whether a particular crystalloid is better than others in terms of postoperative renal function. A national survey of fluid choice at 49 hospitals in the United States found that greater than 90% of patients receive normal saline or normal saline–based solutions during their transplant.[100] However, a single prospective randomized, double-blind study comparing normal saline with lactated Ringer solution for intraoperative intravenous fluid therapy for kidney transplantation showed significantly higher rates of severe hyperkalemia and metabolic acidosis in the normal saline group.[101] Although the recipient's blood should be typed and screened, transfusion is unlikely to be necessary because blood loss is usually minimal.

Patients with uremia and other comorbid conditions (e.g., diabetes) should be considered at risk for aspiration during induction of anesthesia. Pretreatment with a clear, nonparticulate antacid, such as 30 mL of sodium citrate, increases gastric pH. To prevent reflux and aspiration, rapid-sequence induction while maintaining cricoid pressure should be considered.

Several studies have shown that the induction dose of propofol needed to achieve clinical hypnosis and reduction of the bispectral index to 50 was 40% to 60% higher than needed for normal patients.[102,103] In the study of Goyal and colleagues,[103] 0.2 mg/kg of propofol was titrated every 15 seconds to predefined end points. The authors found a negative correlation between the propofol dose and preoperative hemoglobin levels. The exact mechanism is not understood, and administering an increased bolus induction dose based on these findings is strongly discouraged.

Patients with preexisting hypertension are at risk for large fluctuations in arterial blood pressure and heart rate during induction of anesthesia and endotracheal intubation. Because these patients have a high prevalence of CAD and myocardial ischemia, goals at induction should include careful control of the heart rate and blood pressure to minimize the possibility of myocardial ischemia. Several methods have been used to achieve adequate heart rate and blood pressure control during induction. Moderate to large doses of opioids such as fentanyl can blunt the response to laryngoscopy; however, blood pressure frequently may be more difficult to maintain without the use of vasoconstrictors after induction. In recent years, the short-acting opioid remifentanil, metabolism of which occurs in plasma, has been an effective drug for good heart rate control. The rate of remifentanil administration can be titrated to allow for rapid adjustment of anesthetic depth. The short-acting β-adrenergic blocker esmolol (0.5 to 1 mg/kg) is used to blunt the hemodynamic response to intubation and is ideally suited in this patient population with adequate ventricular function.

The use of succinylcholine is not absolutely contraindicated in patients with ESRD (see Chapter 29).[104] Plasma cholinesterase activity is less than normal in more than 20% of ESRD patients

regardless of whether they were receiving any form of dialysis. Whether receiving peritoneal dialysis, hemodialysis, or no dialysis, the patients did not experience prolonged paralysis after an intubating dose of succinylcholine, unless they also had an atypical form of serum cholinesterase. The increase in serum potassium after an intubating dose of succinylcholine is the same, approximately 0.6 mEq/L, for patients with and without ESRD. This increase can be tolerated without significant cardiac risk even with an initial serum K^+ concentration greater than 5 mEq/L.

Long-acting muscle relaxants (e.g., pancuronium) depend on the kidney for elimination and have a prolonged duration of action in patients with ESRD. Atracurium and cisatracurium are metabolized by spontaneous Hofmann degradation and plasma cholinesterase, which makes their duration of action independent of either liver or kidney function. Patients with ESRD have an increased sensitivity to vecuronium with a prolonged duration of action.[105] Rocuronium at a bolus dose of 0.6 mg/kg also has a prolonged duration of action (25% T1 recovery: 49 minutes versus 32 minutes with normal renal function).[106]

Inhaled anesthetic include desflurane, isoflurane, and sevoflurane. The metabolism of sevoflurane has been implicated in renal toxicity, but no controlled studies are available to indicate clearly either safety concerns or danger when using sevoflurane in the setting of a newly transplanted kidney. There are two concerns with regard to toxicity: (1) production of fluoride ion from the metabolism of sevoflurane and (2) generation of "compound A" by the breakdown of sevoflurane by sodium or barium hydroxide lime. However, sevoflurane seems to have a very good safety record. It has been administered to tens of millions of patients worldwide with no conclusive evidence of renal toxicity. Two volunteer studies have found biochemical evidence of renal injury during sevoflurane anesthesia, whereas five other volunteer studies have not.[107-110] Kidney transplantation represents a situation of increased renal risk, however, as defined more recently by Artru.[111] Two studies have shown that sevoflurane, at fresh gas flow rates greater than 4 L/min, did not change renal function indices or biochemical markers in patients with mildly impaired renal function (baseline creatinine >1.5 mg/dL).[112] In addition, no significant effect on renal function parameters such as serum creatinine or creatine clearance were found in patients with baseline renal insufficiency (creatinine >1.5 mg/dL) after exposure to low-flow sevoflurane or low-flow isoflurane.[113]

With regard to perioperative pain control, drugs such as morphine, meperidine (Demerol), or oxycodone should be used with caution in patients with renal failure because these agents or their active metabolites depend on renal excretion and may accumulate.[114-116] Fentanyl, sufentanil, alfentanil, and remifentanil are safe alternatives. The pharmacokinetic parameters of sufentanil are very similar in patients with ESRD and healthy control patients.[114,117] The duration of action of remifentanil is short, even in patients with ESRD.[118] The principal metabolite of remifentanil, GR90291, is eliminated primarily by the kidneys. The fact that it is only $\frac{1}{4000}$ as potent as the parent compound makes remifentanil safe to use in these patients.[119]

Hypotension may occur after unclamping the iliac vessels and reperfusion of the graft. Because renal graft function depends on adequate perfusion, every effort should be made to avoid episodes of marked hypotension. It is generally thought that vasoconstrictors with strong α-adrenergic effects, such as phenylephrine, should be drugs of last resort. Several animal models have shown that vessels in the transplanted organ seem to be more sensitive to sympathomimetics, which are thus more likely to compromise renal blood flow to the transplanted kidney.[120,121]

Immediate urine production is seen in more than 90% of living donor kidney transplants and 40% to 70% of deceased transplants. During the latter stages of closure of the surgical wound, a decrease in urine output strongly suggests mechanical impingement of the graft, vessel, or ureter. The Foley catheter should be irrigated to ensure that clot or tissue has not affected its patency. If intraoperative ultrasound is immediately available, it can be used to examine flow in the arterial and venous anastomoses. In addition to maintaining adequate intraoperative perfusion pressure, urine production is frequently enhanced intraoperatively by mannitol, loop diuretics, and occasionally dopamine, albeit the evidence is controversial.

Mannitol is freely filtered and not reabsorbed by the nephron, which causes osmotic expansion of urine volume. It also may have a protective effect on the cells lining the renal tubule. Mannitol is usually administered to donors before recovery and to recipients just before unclamping the arterial blood flow. In this way, mannitol may protect from ischemic injury and induce osmotic diuresis in the newly transplanted kidney. In most centers, low doses of mannitol are administered, 0.25 to 0.5 mg/kg, and reports of large changes in electrolyte concentrations are unwarranted. Delayed graft function of deceased kidneys can be prevented by the intraoperative administration of mannitol.[122]

Loop diuretics work by blocking the action of Na^+/K^+ pumps present in the thin ascending limb of Henle, preventing reabsorption of electrolytes in this segment of the nephron. The high-osmolar fluid that is carried along to the distal tubule prevents the reabsorption of water, and causes the excretion of large volumes of urine with high electrolyte content. Although the main effect of loop diuretics is increased urine output, the ability to prevent oliguria (<400 mL/day) can be a significant achievement.

"Renal-dose" or low-dose dopamine (2 to 3 μg/kg/min) is commonly used to stimulate DA_1 dopaminergic receptors in the kidney vasculature to induce vasodilation and increased urine output. Some small trials have shown improved urine output and creatinine clearance[123] with low-dose dopamine during kidney transplantation, whereas other larger studies have shown no significant improvement.[124,125] The utility of this approach has been questioned because a newly transplanted, denervated kidney may not respond to low-dose dopamine the way normal kidneys do. Doppler ultrasound examination of newly transplanted kidneys found no significant change in blood flow at dopamine infusion rates of 1 to 5 μg/kg/min.[126]

Another dopamine agonist, fenoldopam, maintains renal blood flow during cardiopulmonary bypass and during surgery involving aortic cross-clamping and in critically ill patients. The effects of fenoldopam on the function of newly transplanted kidneys have not been systematically studied.

Postoperative Care

All renal transplant patients should have muscle relaxants fully reversed, be extubated if possible, and be taken to the postoperative recovery area. Renal transplant patients generally have a low incidence of postoperative ICU admission—around 1% in one large series. If ICU admission is required, it is usually for sepsis or fluid overload.[127]

Urine output is closely monitored, and any significant decline should raise suspicion of a possibly correctable mechanical problem with the newly transplanted kidney. Re-exploration of the wound should not be delayed if kinking of the vascular attachments or obstruction of the ureter along its course or at the site of bladder reimplantation is suspected.

Postoperative pain is usually mild to moderate after kidney transplantation. One study showed that the choice of intraoperative anesthetic influenced postoperative pain control—patients who received propofol as a component of anesthesia had better recovery of psychomotor function and used patient-controlled analgesia more effectively than patients receiving halothane or isoflurane.[128] Placement of intercostal nerve blocks did not change the use of patient-controlled analgesia or pain scores after surgery.[129]

Anesthesia for Patients after Kidney Transplantation

Patients with good graft function as determined by laboratory values (e.g., blood urea nitrogen, creatinine) and with sufficient urine volume should be considered to have adequate renal function. The average glomerular filtration rate 6 months after deceased renal transplantation is almost 50 mL/min.[130] About 50% of patients show a slow decline in glomerular filtration rate over the course of years, but 30% have a stable glomerular filtration rate.

Given the improvement in patient survival after renal transplantation, it is likely that the rapid progression of cardiovascular disease is slowed, but not halted. These patients are still at higher cardiac risk than individuals who did not have ESRD; this is mainly due to persistent risk factors, such as hypertension, diabetes, dyslipidemia, and secondary hyperparathyroidism. Considerable progression of coronary artery calcification was found in renal transplant patients at least 1 year after surgery. Findings were related to ethnicity of patients, blood pressure, body mass index, renal function, and baseline coronary artery calcification.[131] Patients who do require cardiac surgery after successful kidney transplantation showed no difference in the 30-day complication rate, however, compared with a nontransplant control population, except for a significantly increased likelihood of postoperative renal dysfunction and need for hemodialysis.[132] Aside from cardiac risk, graft rejection, viral infection, anemia,[83,133] and treatment with immunosuppressive drugs such as cyclosporine may cause significant cardiovascular morbidity (e.g., hypertension), but newer immunosuppressants seem to be better tolerated.[134] Congestive heart failure (e.g., cardiomyopathy), left ventricular hypertrophy, and ischemic heart disease remain important complications in renal transplant recipients.[83]

Pancreas and Kidney-Pancreas Transplantation

Pancreas transplantation is a primary cure for diabetes mellitus because it provides nearly physiologic insulin replacement. Nephropathy develops in about 50% to 60% of insulin-dependent diabetic patients, so it is common also to transplant a kidney at the time of pancreas transplantation. The appearance of new immunosuppressants, such as tacrolimus and mycophenolate mofetil, has dramatically increased pancreas graft survival.[135] The best results in terms of graft survival are obtained with simultaneous pancreas-kidney transplantation (SPK), but good results also are achieved with a pancreas transplant alone (PTA) or a pancreas transplant after successful kidney transplantation (PAK). Diabetic patients who undergo SPK have greater long-term survival than diabetics who receive a deceased kidney alone.[136]

In 2005, 540 pancreas transplants and more than 900 SPKs were performed in the United States. More than 23,000 pancreas transplants have been performed worldwide according to the International Pancreas Transplant Registry through 2004. The 3-year graft survival rate is around 65%. In early 2008, approximately 1600 patients were waiting for a pancreas transplantation and 2350 patients were waiting for a kidney and pancreas transplantation.

Organ Matching and Allocation

Solid organ pancreas transplantation is indicated for the treatment and cure of patients with type 1 diabetes mellitus and select patients with type 2 diabetes mellitus (<5%). Pancreas transplantation also can be considered in patients with diabetes mellitus secondary to chronic pancreatitis or cystic fibrosis.

The initial testing determines the major blood group (ABO) compatibility and HLA profile of the recipient. These data are used for the initial matching of donor to recipient. A final check is made at crossmatch when recipient blood is mixed with donor blood cells to determine whether the recipient has preformed reactive antibodies against donor antigens.

Pathophysiology of Pancreatic Insufficiency

The primary defect in diabetes mellitus is a relative deficiency of insulin for regulation of blood and tissue glucose levels. Two forms of the disease are recognized. Type 1 diabetes mellitus is characterized by a significant deficiency in insulin production by the islet cells of the pancreas, possibly from autoimmune destruction. In type 2 diabetes mellitus, insulin levels may be normal, but patients have a relative resistance to the action of the hormone. Patients with type 1 diabetes mellitus are more likely to require daily administration of exogenous insulin, to be prone to ketosis, and to have wide fluctuations in blood glucose levels. The symptoms can be completely relieved by successful pancreas transplantation, but it is still uncertain whether the progression of comorbidities in all organ systems is abated.

Diabetes mellitus severely affects the cardiovascular system by accelerating atherosclerotic vascular disease. Accelerated atherosclerosis and autonomic nervous system dysfunction are the major cardiovascular changes present in diabetic patients. If ESRD also is present, the cardiovascular risk increases dramatically. Diabetic patients with severe CAD may not recognize anginal symptoms due to impairment of the autonomic nervous system. Autonomic dysfunction also can limit control of the car-

diovascular reflexes and result in increased lability of blood pressure and heart rate. One index of autonomic dysfunction that has been studied is a decrease in heart rate variability, which reflects a defect in the autonomic nervous system. These defects may give rise to dysrhythmias and put patients at increased risk for sudden death during pancreas transplantation.[137]

Patients with ESRD superimposed on diabetes mellitus are subject to the same hemodynamic, fluid, volume, and electrolyte problems as patients with ESRD alone. They probably are maintained on some form of dialysis to manage fluid overload and accumulation of electrolytes. They may also have significant systemic hypertension for the reasons discussed in the section on kidney transplant. Finally, they may have the same problems of chronic anemia and uremic coagulopathy as patients with renal failure alone.

After successful SPK, pathologic cardiac changes, such as diastolic dysfunction and left ventricular hypertrophy, can improve or stabilize.[138] It has not been proved whether other manifestations of diabetes mellitus, such as accelerated atherosclerosis, neuropathy, or vascular insufficiency, improve or stabilize.

Surgical Procedure

The usual exposure for pancreatic transplantation requires a generous midline incision extending from the epigastrium to the symphysis pubis (Fig. 67-3). The pancreas is placed in the abdomen with an arterial blood supply from the aorta via a vessel graft. Several options are available for venous drainage and implantation of the exocrine duct. Venous outflow from the pancreas, which is the source of insulin, may go into the inferior vena cava directly into the systemic circulation, or it may be directed in a more physiologically correct manner into the portal vein draining the splanchnic circulation. The exocrine pancreatic flow may be connected to the small bowel or, less often, through a cuff of donor intestine into the bladder. The latter method allows for monitoring of urine amylase as a marker of rejection or injury to the transplanted pancreas. Enteric drainage is preferred for SPK because it is more physiologic and avoids bladder complications. Bladder drainage may be a better option for PTA and PAK, however, because of the greater likelihood of rejection with these types of transplantation. Surveillance of urine amylase allows for early detection of rejection.

Preoperative Considerations

Diabetic patients have a more frequent incidence of autonomic neuropathy, which can be manifested as a higher heart rate and higher blood pressure than in nondiabetic ESRD patients (see Chapter 35).[95] Patients with type 2 diabetes often have metabolic syndrome, a combination of visceral obesity, atherogenic dyslipidemia (low levels of high-density lipoprotein and elevated levels of triglycerides), hypertension, and insulin resistance. This combination leads to a heightened risk for CAD and cardiovascular disease. Orally administered drugs should not be taken the day of surgery to avoid the potential for unrecognized hypoglycemia under anesthesia. Insulin-dependent patients who are extremely brittle and have declining insulin levels are at risk for ketosis and intraoperative acidemia.

Historically, the principal candidates for pancreas transplantation have been younger than individuals receiving kidney transplants, with most being in the age range of 18 to 35 years. Younger patients tended to have fewer of the long-term manifes-

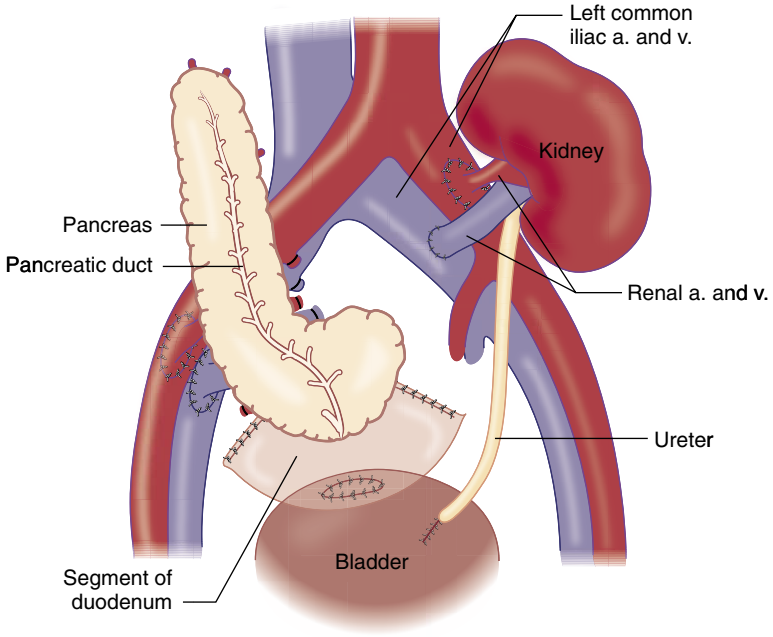

Figure 67-3 Transplantation of the pancreas with drainage of the bladder through a pancreaticoduodenocystostomy. A renal transplant also is shown with the common iliac vessels used for vascular anastomoses. *(Modified from Moody FG [ed]: Surgical Treatment of Digestive Disease, 2nd ed. St Louis, Mosby-Year Book, 1990.)*

tations of diabetes mellitus, such as atherosclerotic vascular disease and severe autonomic dysfunction. More recently, increasing numbers of older diabetic patients are being considered for pancreas transplantation. These patients are at higher risk for a major cardiovascular event perioperatively. An extensive cardiac workup is indicated before surgery to rule out severe CAD. Preoperative evaluation by history and physical examination, ECG, treadmill testing, echocardiography with or without dobutamine stress, radionuclide scintigraphy, and cardiac angiography represents the full spectrum of workup that may be applicable.

It was suggested in the early 1990s that tracheal intubation should be considered more difficult in diabetic patients as a group because of changes in their upper airway tissues from exposure to high serum glucose levels. One study found a 31% incidence of difficult intubation conditions in this patient population. Subsequently, a large study by the Mayo Clinic reviewed the anesthetic records of 150 patients with diabetes who underwent general anesthesia and tracheal intubation, and found only a slightly increased incidence of "more difficulty visualizing" airway structures.[139] Halpern and associates[140] reported only one difficult intubation in a series of 130 patients presenting for pancreas transplantation. It seems that long-standing diabetes mellitus alone does not predispose to airway difficulties, but may be considered a contributing factor in a patient with other potentially problematic airway features.

Intraoperative Management

Because pancreas transplantation procedures can be long and surgically tedious, and involve extensive abdominal exposure, general endotracheal anesthesia with muscle relaxation is the best choice. Patients may have significant postoperative pain from the extensive abdominal dissection, so placement of an epidural catheter for postoperative pain control may be warranted. Splanchnic perfusion to the transplanted organs is a major concern, however, and some centers opt to defer placement of an epidural catheter.

Because the pancreas seems to be a highly immunogenic organ, intensive immunosuppression is needed to prevent graft loss. The anesthesia team administers the initial dose of immunosuppressant, so it is essential that the desired drugs be present and administered correctly in the operating room.

Standard monitors (e.g., five-lead ECG, noninvasive blood pressure measurement, pulse oximetry, end-tidal gas concentrations) plus arterial and central venous lines are usually required. The arterial line enables careful tracking of blood pressure and the ability to draw samples for blood gas, glucose, and electrolyte determinations. Insertion of a central venous catheter permits monitoring of cardiac filling pressure and central administration of drugs.

Diabetic patients, by virtue of their high incidence of autonomic dysfunction, are likely to have gastroparesis and large residual gastric volumes. This risk is even greater if the patient has ESRD and uremia. Administration of a nonparticulate antacid along with maintenance of cricoid pressure during rapid-sequence induction should be considered.

Patients with autonomic neuropathy apparently are not at greater risk for severe cardiovascular depression during induction of anesthesia. A study of uremic patients undergoing kidney transplantation found, that diabetic patients with known preexisting autonomic neuropathy had hemodynamic responses to induction that were similar to the responses of nondiabetic uremic patients.[141] Hemodynamic stability for long periods is probably best achieved by using a balanced anesthetic technique. As with kidney transplantation alone, adequate arterial blood pressure is desired to provide good perfusion pressure for a newly anastomosed pancreas.

One of the most challenging aspects of these cases is determining the amount and type of fluids to administer. If fluid is given, it is probably best from a surgical standpoint to use colloid-based fluid, rather than a large volume of crystalloid solutions alone. Although no controlled studies have been conducted, swelling of the pancreas graft seems to be less with colloids than with crystalloids.

Abdominal muscle relaxation is essential for these procedures. The same issues outlined previously for patients undergoing kidney transplantation apply to the choice of muscle relaxant to be used in patients undergoing SPK. Because of the duration of these cases, a continuous infusion of cisatracurium allows for titration of the level of block with reliable reversibility. Alternatively, the intermittent administration of vecuronium, if titrated by train-of-four monitoring,[105] can produce excellent relaxation conditions. For patients who are undergoing PTA or PAK and have adequate renal function, the use of any intermediate-acting nondepolarizing muscle relaxant should not cause problems.

Control of blood glucose intraoperatively is important to prevent the development of ketoacidosis in patients with unopposed counter-regulatory hormone secretion and to allow assessment of the function of the transplanted pancreas. Before unclamping the pancreas, glucose should be checked hourly. Hyperglycemia may cause depressed immune function and decreased wound healing and put patients at an increased risk for worsened neurologic injury if brain ischemia occurs.[142] After the pancreas is unclamped, glucose should be monitored every 30 minutes. Typically, glucose concentrations decrease approximately 50 mg/dL/hr after unclamping the pancreas.

A randomized trial of insulin administration to patients with insulin-dependent type 2 diabetes compared a continuous glucose-insulin infusion with intermittent intravenous insulin injection in major and minor surgery. Very little difference was found in the ability to control intraoperative and postoperative glucose levels and metabolism.[143] The manner of reducing glucose does not seem to be as important as the glucose level itself.

Postoperative Care

Successful transplantation usually results in rapidly declining insulin requirements. Blood glucose levels should be monitored closely in the recovery room or ICU to avoid hypoglycemia (see Chapter 92). If simultaneous kidney transplantation is performed, close monitoring of urine output to detect reversible graft impingement is necessary.

Anesthesia for Patients after Pancreas Transplantation

Surgical complications after these complex operations are frequent and often require one or more re-explorations during the perioperative period. If pancreas graft function is good, blood glucose levels are corrected within days of transplantation. During

the perioperative period, the same cardiac concerns that were present before transplantation apply.

Liver Transplantation

In 2007, the number of liver transplantations performed in the United States decreased slightly to 6494 from 6650 in 2006. In 2007, 1559 liver transplantations were reported by Eurotransplant, which covers seven central European states.* As of early 2008, approximately 17,200 patients were on the waiting list for liver transplantation in the United States; approximately 1600 to 1800 patients die each year while awaiting liver transplantation. Nationwide, the 3-year patient survival rate after transplantation is greater than 75%.[144] This rate underscores the fact that liver transplantation should not be considered experimental and is the treatment of choice for eligible patients with end-stage liver disease.

The growing discrepancy between organ supply and recipients on the waiting list has made finding alternatives to deceased liver transplantation of paramount importance. This discrepancy may become greater in view of the fact that cirrhosis is likely to develop in 25% to 30% of the more than 4 million Americans with hepatitis C.[145,146] Recurrent disease, especially with hepatitis C, necessitates retransplantation in future years, which aggravates the acute organ shortage problem further.[147] Based on UNOS data, there has been no improvement in long-term liver transplant graft survival in the last decade. This finding could be explained by an increase in patients with hepatitis C virus and an increase in patients with hepatitis C virus antibody.[148] The challenge of meeting organ shortages may be overcome if donor liver allocation is optimized, and the donor pool can be increased with new approaches, such as the use of living liver donors or extended criteria donors.

Combined liver-kidney transplantation is done infrequently and constitutes only a very small fraction of abdominal transplant volume. Renal disease in the setting of cirrhosis can be due to primary renal disease, hepatorenal syndrome, and acute tubular necrosis.[149] Considerable controversy exists with regard to patient selection for this procedure because of the organ shortage and the possibility of inferior patient and graft survival compared with single-organ transplantation. It is advocated that patients be highly selected, and that hemodynamically stable patients with primary disease in both organs be preferred.[149]

Organ Matching and Allocation

The ABO blood group system is the primary immunologic barrier to transplantation,[150] and this classification system is the most important for liver transplantation. The four ABO groups are not proportionally distributed among cadaver donors and possible recipient candidates. The matching strategy between donor and possible recipient is crucial in liver allocation. Donor and recipient ABO blood type matching can be classified as follows: identical (e.g., A to A), compatible (e.g., O to A), and incompatible (e.g., A to O).[151] Identical matching generally is preferred because patient and graft survival is superior with compatible organs. In select cases, such as acute hepatic failure or acute deterioration of chronic liver disease, incompatible organs are transplanted. Graft survival is poorer in patients receiving incompatible organs compared with patients receiving identical matching. Acceptable patient survival may be achieved by retransplantation, however.

The organ allocation policy varies among countries. In the United States, deceased donor livers are allocated to patients who are registered with a national registry. In contrast, several European countries allocate donor livers primarily to transplant centers. These centers subsequently identify a suitable recipient candidate. Regardless of the respective organ allocation policy, recipient candidates have to be well screened regarding their eligibility for liver transplantation.

The number of diseases amenable to treatment with liver transplantation has steadily increased in recent years. Although there is regional variation, the most important cause of end-stage liver disease is chronic hepatitis C, which is responsible for almost 40% of all liver transplantations, especially in the United States. Causes of chronic disease in adults can be classified as follows: (1) noncholestatic (e.g., alcohol, hepatitis A, hepatitis B, hepatitis C), (2) cholestatic (e.g., primary biliary cirrhosis, primary sclerosing cholangitis), (3) metabolic disease (e.g., Wilson's disease), and (4) selected cases of hepatocellular carcinoma often associated with hepatitis B or C. Fulminant hepatic failure can be drug induced (e.g., acetaminophen overdose, idiosyncratic), caused by the ingestion of poisonous mushrooms or herbs, and secondary to acute viral hepatitis.[152,153]

Reasons to deny transplantation may vary among centers. Liver transplantation is an extremely stressful procedure for patients. Significant CAD, cardiac dysfunction, and moderate to severe pulmonary hypertension are considered contraindications to liver transplantation. Uncontrolled infection or sepsis also excludes a patient from transplantation. A positive HIV test, without evidence of acquired immunodeficiency syndrome, is no longer a contraindication. Recent case series have reported good results in HIV-infected patients undergoing liver or kidney transplantation.[1] Advanced malignant hepatic disease or metastatic disease generally is considered to be a contraindication, as is uncontrolled and markedly documented elevated intracerebral pressure in the setting of fulminant hepatic failure. Psychosocial factors, such as active alcohol abuse or the lack of a good social support system, may prevent a patient from being a candidate for transplantation. Advanced age per se is not a reason to deny liver transplantation. Patients older than 65 years are increasingly undergoing transplantation.

In the past, the Child-Turcotte-Pugh (CTP) classification had been used widely as an index of disease severity for patients with end-stage liver disease. This classification, in conjunction with UNOS status, was the determining factor for organ allocation in the United States until early 2002. Because of shortcomings of CTP scores and subsequent limitations in organ allocation, the model for end-stage liver disease (MELD) has been introduced for adults in the United States.[154,155] This model resulted from a growing realization that the previous UNOS scoring system, which was based on the CTP score of liver disease severity plus the amount of time on a waiting list, did not always ensure that organs were allocated to the sickest patients with the greatest risk of mortality.

*Austria, Belgium, Croatia, Germany, Luxembourg, the Netherlands, Slovenia.

The MELD risk score is a mathematical formula based on the following factors:

1. Creatinine (for adult patients undergoing dialysis twice a week within the last week, the creatinine value would be automatically set to 4 mg/dL)
2. Bilirubin (mg/dL)
3. International normalized ratio

MELD calculates a single numerical value from a formula that gives each value particular weighting. Most patients on the liver transplant waiting list have a MELD score between 11 and 20.[144] The MELD system was originally devised as a means for predicting the risk of death in patients with liver failure after transjugular intrahepatic portosystemic shunting (TIPS).[156] TIPS patients with scores greater than 18 had a median survival of 3 months or less after a TIPS procedure. MELD scoring proved superior to the CTP score in predicting survival.[156]

Several adjustments in the new system have been introduced to make it as equitable as possible. Hepatocellular carcinoma confined to the liver can progress to inoperable lesions before manifesting changes in MELD criteria. UNOS has adopted the rule that patients with hepatocellular carcinoma be assigned a MELD score equivalent to the risk of death based on rapid disease progression.[157,158] Some studies have suggested that sodium should be added to MELD to improve accuracy of survival prediction. Finally, a peer review mechanism has been instituted, and the current classification is under constant review and adjustment. Nevertheless, reports indicate that use of the MELD criteria has been shown to be better associated with 1-year patient survival in liver transplant recipients than the former UNOS status.[159]

Pathophysiology of End-Stage Liver Disease

Although the reasons for end-stage liver disease may vary significantly, similar organ pathophysiology tends to develop in patients with advanced liver disease. Virtually all organ systems can be affected by end-stage liver disease. Consequently, a global assessment that includes consideration of all organ systems is of great importance. A significant number of the complications in patients with end-stage liver disease are the result of portal hypertension, which can be defined as portal venous pressure greater than 10 to 12 mm Hg.[160] The pathogenesis of portal hypertension is increased hepatic resistance to flow as a result of cirrhotic changes in the liver and a hyperdynamic circulatory state secondary to systemic vasodilation and presumably volume expansion.[161]

There is some controversy whether patients with end-stage liver disease have an excessively large or depleted intravascular volume. In advanced disease, abnormalities in fluid, such as altered extracellular fluid regulation and electrolyte balance, are frequently manifested as ascites, pleural effusion, and edema.[162] Subsequent changes in the splanchnic and renal circulation may lead to sodium and water retention. Abnormalities in sodium electrolyte levels are frequently observed and are often related to volume status and sodium retention; these abnormalities can result in either hyponatremia or hypernatremia.[163] Similarly, renal dysfunction and diuretic use can cause either hyperkalemia or hypokalemia along with hypomagnesemia.

Central nervous system changes in chronic liver disease are often manifested as hepatic encephalopathy, but the degree of encephalopathy may vary significantly among patients.[164,165] Ammonia levels are frequently monitored, but do not seem to correlate well with the degree of hepatic encephalopathy. Increased intracranial pressure (ICP) may develop in patients with acute hepatic failure, primarily because of cerebral edema. Accurate assessment of the severity of ICP and remaining neurologic function is of paramount importance because intractable elevated ICP is a significant reason to exclude a patient from transplantation. There is considerable controversy, however, whether the potential benefits of invasive monitoring for elevated ICP (e.g., bolt placements) outweigh the potential risk of devastating bleeding during placement.[166] The U.S. Acute Liver Failure Study Group recommends (beyond generally accepted supportive measures for elevated ICP) a stepwise approach to management of elevated ICP. When ICP is greater than 25 mm Hg, osmotic therapy should be started, and sodium should be kept within normal limits. Hypertonic saline may be considered as an alternative to mannitol. Additional treatment that may be considered is moderate hypothermia, broad-spectrum antibiotics, and barbiturate coma. Supporting scientific evidence for these interventions is insufficient, however.[167]

In addition to the standard treatment of elevated ICP, early studies have shown that the molecular adsorbents recirculating system (MARS) may be able to decrease ICP and improve cerebral perfusion pressure.[168] Designed as a liver support device for patients in fulminant hepatic failure or the acute decompensation of chronic failure,[169] MARS has been able to improve systemic vascular resistance and mean arterial blood pressure.[170] Presumably, these improvements in organ function may account for a reduction in mortality.[171,172] A clear survival benefit for patients treated with MARS has not been shown, however. MARS is based on dialysis across an albumin-impregnated membrane that removes plasma albumin-bound toxins. The dialysate is subsequently cleaned by activated charcoal and anion exchange resin.[173]

The cardiovascular system undergoes profound changes in patients with advanced liver disease that result in a hyperdynamic state. Generally, systemic vascular resistance is low, the heart rate is elevated, and arterial blood pressure is normal or slightly decreased.[174] These hemodynamic changes result in supranormal cardiac output in patients with end-stage liver disease, unless the patient is taking a β-blocker for the prevention of upper gastrointestinal bleeding. Occasionally, relatively depressed cardiac function can be associated with cirrhotic cardiomyopathy, alcoholic cardiomyopathy, or infiltrative cardiac involvement in unrecognized hemochromatosis, and these conditions should be kept in mind.[175,176] Left ventricular diastolic dysfunction seems to be more common than previously assumed. A more recent study in transplant candidates showed a high prevalence of atherosclerotic risk factors and a 26% prevalence of moderate to severe coronary artery disease. Severe CAD was found in older men with risk factors such as hypertension and diabetes.[177] The results mirror current practice of accepting older candidates with comorbidities for liver transplantation. Overall, more patients with cardiac disease and a history of interventions such as coronary artery stent placement are expected to be undergoing liver transplanta-

tion. In select cases, liver transplantation is combined with simultaneous cardiac surgery.

The pulmonary system in patients with end-stage liver disease can undergo changes, and two distinct pathophysiologic syndromes that can be recognized are hepatopulmonary syndrome and portopulmonary syndrome. The principal finding in hepatopulmonary syndrome is decreased oxygenation (Pao_2 <70 mm Hg or a $PAO_2 - Pao_2$ gradient >20 mm Hg on room air) associated with intrapulmonary vascular dilation. A hallmark of this syndrome is intrapulmonary shunting.[178,179] Patients with hepatopulmonary syndrome may show changes in oxygen saturation when changing from the supine to erect positions. The presence of orthodeoxia is a significant clue for the examining physician that the patient has hepatopulmonary syndrome.

The hepatopulmonary syndrome is an independent risk factor for mortality and an indication for liver transplantation. Frequently, but not always, hepatopulmonary syndrome resolves spontaneously months after liver transplantation.[180] After transplantation, long-term survival of patients with hepatopulmonary syndrome is favorable, albeit a small study suggested that postoperative mortality may be higher.[181]

Such resolution is not the case with portopulmonary hypertension, a fairly uncommon complication of portal hypertension,[182] which may worsen after liver transplantation. Patients with liver disease experience an increased prevalence of pulmonary vascular diseases compared with the normal population.[183] Although cirrhosis was thought to be the etiology, portal hypertension seems to be the only consistent factor predisposing patients to the development of pulmonary hypertension. Patients are considered to have portopulmonary hypertension if they meet the following three criteria: (1) mean pulmonary arterial pressure greater than 25 mm Hg, (2) pulmonary vascular resistance greater than 240 • sec • cm^{-5}, and (3) pulmonary capillary wedge pressure less than 15 mm Hg in the setting of portal hypertension.[184] Although these criteria are reasonable, diagnostic caution should be exercised because interpretation of measured hemodynamic values may be obscured by the hyperdynamic circulation that occurs in patients with liver disease.[178] Portopulmonary hypertension may progress rapidly and carries high perioperative morbidity and mortality when significant. Therapeutic agents used to treat primary pulmonary hypertension not associated with liver disease also have been administered to patients with this condition, with mixed results.[185-188]

Renal dysfunction also develops in many patients with end-stage liver disease. Calculated glomerular filtration rate tends to overestimate actual glomerular filtration rate in patients with end-stage liver disease. Renal dysfunction is usually the result of primary renal disease, acute tubular necrosis, or hepatorenal syndrome. Hepatorenal syndrome develops in the setting of severe liver disease and in the absence of other causes, such as hypovolemia, drug toxicity, or underlying intrinsic renal disease. There are two types of hepatorenal syndrome. Type I develops rapidly over weeks and is progressive and associated with high mortality.[189,190] Renal function may recover spontaneously when liver function improves, or the patient receives a liver transplant. It is most frequently seen in patients with acute liver failure, alcoholic hepatitis, or acute decompensation of chronic liver disease. Type II follows a less acute course and is seen mainly in patients who become resistant to diuretic therapy.

Patients who experience spontaneous bacterial peritonitis are at risk to develop renal failure. Spontaneous bacterial peritonitis is considered the most frequent cause of renal failure in patients with cirrhosis.[190] The mechanism of hepatorenal syndrome is thought to be a combination of reversible renal vasoconstriction in structurally normal kidneys and changes in vasoconstrictor and vasodilator factors.[190] The degree of preoperative renal dysfunction correlates with increased patient mortality postoperatively.[149,191] This correlation is mainly observed in patients undergoing only liver transplantation from a deceased donor, but not in patients undergoing combined kidney and liver transplantation.[192]

Various hemostatic abnormalities are found in patients with end-stage liver disease who present for liver transplantation. These changes can be caused by preoperative coagulation disorders or may be related to the procedure itself. Levels of procoagulant factors (II, V, VII, IX, X) and anticoagulant factors (protein C and S, antithrombin III) are frequently decreased in patients with end-stage liver disease.[193-195] Thrombocytopenia as a result of hypersplenism, qualitative platelet dysfunction, and disorders of the fibrinolytic system (reduced levels of plasminogen, α_2-antiplasmin, and factor XIII, and increased plasma tissue-type plasminogen activator levels) are often encountered during the perioperative period.[196] Although end-stage liver disease often increases the risk of bleeding, thrombotic complications such as portal vein thrombosis also are seen in this patient population. Several case reports and case series have shown intraoperative thrombus formation in the cardiopulmonary system.[197-201] Frequently, thrombus formation was associated with the coadministration of antifibrinolytics, such as aprotinin or aminocaproic acid. A conclusive statement with regard to antifibrinolytics and thrombus formation cannot be made because of the lack of sufficient data and the absence of large controlled studies.

Surgical Procedure

Liver transplantation generally can be divided into three stages: (1) the dissection phase, which includes lysis of adhesion and mobilization of the liver; (2) the anhepatic phase, which consists of removal of the native liver and implantation of the donor liver; and (3) the reperfusion (neohepatic) phase, which involves the completion of several anastomoses, hemostasis, and closure. Each phase is described in more detail.

Preoperative Considerations

Patients who are candidates for liver transplantation will have undergone a rigorous preoperative evaluation by multiple medical specialists (see Chapters 34 and 35). Patient evaluation is usually conducted in different phases and may take weeks to months to complete. Pathophysiologic changes as described previously should be identified and addressed. An increasing proportion of patients are now admitted for liver transplantation from home, which often results in a significant interval between the last evaluation or diagnostic test and admission for liver transplantation. All cases should be considered emergency cases (with the exception of living donor recipients).

It is important to perform a detailed medical and physical examination with a strong emphasis on changes that have

occurred since the last evaluation. Of great importance is the time span between performance of the diagnostic test and the anticipated liver transplantation. Patients may wait several years for liver transplantation, and tests performed early in the evaluation process may not reflect the progression or new onset of organ-specific disease. Simultaneously, all diagnostic tests (i.e., echocardiogram, cardiac catheterization, pulmonary function tests, renal function tests) performed during the workup for liver transplantation and any recent notes from the primary team should be evaluated. In the case of pulmonary hypertension, two-dimensional echocardiography has been shown to be a sensitive tool for detecting portopulmonary hypertension. Because echocardiography has a poor positive predictive value, however, catheterization of the right side of the heart is recommended to confirm portopulmonary hypertension.[202]

Most tests are likely to show that either the patient is fit for surgery without any further medical therapy, or medical management is needed before liver transplantation (e.g., treatment of moderate pulmonary hypertension before transplantation). Knowledge and documentation of preoperative testing are essential because the results of such testing dictate the perioperative management of the patient. Evidence of moderate pulmonary hypertension on echocardiography in a patient without cardiac catheterization may warrant perioperative placement of a pulmonary artery catheter with pressure measurements before incision. Ideally, placement of the pulmonary artery catheter should be done in the ICU before taking the patient to the operating room. Conversely, immediate preoperative right cardiac catheterization with no evidence of pulmonary hypertension may render placement of a perioperative pulmonary artery catheter for monitoring purposes unnecessary.

Preoperative renal dysfunction has been shown to be an independent risk factor for postoperative morbidity and mortality in patients undergoing liver transplantation.[191] Longitudinal assessment is crucial because previously diagnosed borderline renal function may have progressed to renal failure requiring intraoperative interventions such as continuous venovenous hemofiltration or dialysis,[203] or even a combined liver-kidney transplant. Screening for any new infections on the day of surgery also is crucial because new-onset or uncontrolled ongoing infections may require postponement of surgery.[204]

Intraoperative Management

The intensity of intraoperative resource and personnel usage varies widely among liver transplant centers and is influenced by institutional practice, caseload, and personal experience. Standardization of clinical practice has not been fully established for liver transplantation as it has for other procedures. Hemodynamic monitoring may include a pulmonary artery catheter, TEE, or simple CVP monitoring. The type of high-volume infusion equipment differs among transplant centers, as does the use of venovenous bypass (VVBP) during the anhepatic phase. In a survey of 62 transplant centers in the United States done by Schumann, a pulmonary artery catheter was used in approximately 30%, TEE was in 11.3%, and VVBP was used in roughly half of adult transplants. A tendency toward decreased use of pulmonary artery catheters and VVBP was shown with increasing case volume.[205] Binding recommendations with regard to resource use are difficult to make and depend on various factors. More recently, TEE has been increasingly used for management of fluid therapy, monitoring of cardiac function, and identification of intraoperative complications (e.g., pulmonary embolus).

Close communication with the blood bank before surgery is crucial. Standard protocols should be instituted with a recommended setup for blood products. Blood products may include 10 U of red blood cells and 10 U of fresh frozen plasma to be brought to the operating room, with 4 U of single-donor platelets available on request. Because of the magnitude of fluids that may be administered, separate laboratory and fluid flow sheets can facilitate more accurate record keeping and aid in identification of trends. The frequency of blood sampling for laboratory analysis is dictated by the medical condition of the patient, progress of the procedure, and experience of the transplant team.

Most patients already have intravenous access on arrival at the operating room that can be used during induction. The use of epidural catheters is discouraged in this procedure because a significantly prolonged perioperative coagulopathy can persist. Placement of an arterial line to monitor blood pressure or a central line/pulmonary artery catheter before induction is not essential. Many patients presenting for liver transplantation may receive nonspecific β-blockade for secondary prophylaxis of upper gastrointestinal bleeding (e.g., esophageal varices). These patients tend to be stable during the induction.

Most patients have well-preserved cardiac function and no significant arterial or pulmonary hypertension. Induction can be achieved with an intravenous anesthetic, such as propofol, thiopental, or etomidate, with or without opioids and short-acting or intermediate-acting neuromuscular blocking agents.

End-stage liver disease results in changes in hepatic blood flow, decreased ability to biotransform certain drugs, hypoalbuminemia, and altered volume of distribution.[174] Several studies in patients with end-stage liver disease have shown changes in the pharmacokinetics and pharmacodynamics of drugs commonly used in anesthesia, including nondepolarizing muscle relaxants and benzodiazepines. Extrapolation of this information to intraoperative management is difficult, however, in view of the dynamic nature of the procedure (i.e., anhepatic phase, major blood loss, hypothermia). Most importantly, a functioning liver is implanted at a given point, which makes longitudinal pharmacokinetics and pharmacodynamics studies very difficult to interpret. Most studies have focused on one particular aspect of liver transplantation, such as the impact of the anhepatic phase or hypothermic preservation on drug metabolism. Such studies have suggested that drugs such as sufentanil and propofol exhibit some degree of extrahepatic metabolism.[206]

Based on existing knowledge, it is reasonable to choose cisatracurium or atracurium over vecuronium as the muscle relaxant of choice for liver transplantation. The pharmacokinetics and pharmacodynamics of vecuronium have been shown to be substantially altered by liver disease, whereas cisatracurium and atracurium are cleared independently of liver function.[207] Muscle relaxants have been used as a probe to evaluate the function of the newly implanted liver.[208-211] Nonetheless, all nondepolarizing agents have been used successfully in liver transplantation as long as appropriate neuromuscular monitoring is performed.

Similarly, different opioids, such as fentanyl, sufentanil, alfentanil, and remifentanil, have been used during liver transplantation. A rapid-sequence or modified rapid-sequence induction is often warranted because patients frequently have significant ascites or experience delayed gastric emptying. Postinduction hypotension may occur as a result of the very low systemic vas-

cular resistance and relative hypovolemia of these patients. It usually can be treated with small amounts of vasoconstrictors (e.g., phenylephrine). With the exception of halothane, all volatile anesthetics are suitable for liver transplantation. Isoflurane and desflurane are the most frequently used.

Correction of severe coagulopathy before line placement may be considered, and the use of ultrasound may facilitate central venous cannulation, but there are no generally accepted guidelines. Line placement should include a radial arterial line for invasive blood pressure monitoring and two to three large-bore intravenous catheters, ideally including a rapid-infusion catheter. The choice of hemodynamic monitoring is determined by institutional practice. When pulmonary hypertension is suspected or known, a pulmonary artery catheter should be placed, and pulmonary arterial pressure should be determined before induction or incision. Newly diagnosed moderate to severe pulmonary hypertension should be considered a reason to abort the procedure. These patients can be relisted for transplantation after successful medical therapy has been initiated. The diagnosis alone does not imply that the patient is denied a necessary transplant.

An orogastric/nasogastric tube is placed to decompress the stomach and improve surgical exposure. This is important during the dissection phase, and even more so during the anhepatic phase when the vascular anastomoses are performed. Patients are frequently severely coagulopathic, and the placement of a nasogastric tube may result in significant bleeding. Rarely, patients undergoing liver transplantation experience uncontrolled upper gastrointestinal bleeding during surgery that may require placement of a Minnesota or Sengstaken-Blakemore tube.

Before the incision is made, appropriate antibiotic and immunosuppressive (e.g., steroid administration) coverage should be ensured. Immunosuppressive protocols vary among medical centers, and clear communication is crucial.

The patient should be kept normothermic throughout the operation. A large surgical field combined with prolonged exposure, major fluid shifts, and the implantation of a cold organ renders the patient susceptible to significant hypothermia, which may worsen coagulopathy and drug metabolism. It also may prevent extubation of the patient at the end of the procedure. All administered fluids should be delivered through a fluid warmer, and forced-air heating blankets should be applied to all patients.

No optimal anesthetic technique has been established for maintenance of anesthesia. A balanced technique using volatile anesthetics in an oxygen/air mixture and opioids results in stable intraoperative hemodynamics. A combination of opioids and benzodiazepines and total intravenous anesthesia with propofol also have been used for liver transplantation. Nitrous oxide should not be used to avoid intestinal distention, and because in selected cases (not always predictable) a Roux-en-Y choledochojejunostomy is done at the end of the procedure.

Significant coagulopathy, blood loss, and electrolyte and metabolic derangements require frequent intraoperative laboratory tests. Measurement of arterial blood gases, blood glucose, electrolytes (sodium, potassium, and ionized calcium), and hematocrit is routine in most transplant centers. Monitoring of arterial blood gases allows one to assess oxygenation and base deficits and possibly lactate levels. Correction of the base deficit and reduction in lactate levels may be indirect indicators that the donor liver is functioning adequately.

The glucose-insulin pathway is frequently impaired in patients with end-stage liver disease. In contrast to patients with acute liver failure who may have hypoglycemia, patients with chronic end-stage liver disease experience impaired insulin-mediated glucose uptake. Glucose metabolism may worsen during liver transplantation, and progressive hyperglycemia may ensue, especially in the reperfusion phase. Several mechanisms have been implicated, including enhanced glycogenolysis by the donor liver, decreased glucose use, and insulin resistance.[163,212]

Close observation of electrolytes is essential. Hyperkalemia/hypokalemia may be present as a result of either renal dysfunction and massive transfusion or aggressive diuresis.[213] Hyponatremia frequently is encountered in end-stage liver disease, but overzealous correction during the perioperative phase should be avoided because of the associated risk of central pontine myelinolysis. Ionized calcium levels are often significantly decreased during liver transplantation, particularly during the dissection and anhepatic phases.[163] An exogenous citrate load from transfused blood products and the decreased ability of the diseased liver to metabolize citrate are thought to be responsible for the severely depressed ionized calcium levels, and calcium infusions are frequently required. Treatment of ionic hypocalcemia can be similarly accomplished with calcium chloride or calcium gluconate.[214] After reperfusion, and with the onset of function of the grafted liver, calcium hemostasis is often corrected, and calcium supplementation generally is unnecessary.

Less consistency is found among centers regarding the monitoring of coagulation parameters. The prothrombin time, international normalized ratio, partial thromboplastin time, fibrinogen, and platelets are measured by most programs. Thromboelastography is used in approximately 33% of liver transplant centers, and the activated clotting time is used in approximately 18%.[205] Severe coagulopathy and intraoperative blood loss remain the most significant problems encountered in patients undergoing liver transplantation. Impaired hemostasis, especially after receiving an extended criteria liver, is usually multifactorial and includes hyperfibrinolysis, depletion of coagulation factors, thrombocytopenia, and platelet dysfunction.[215] Approaches to correct hemostasis vary significantly among institutions and depend partly on institutional transfusion preferences and the coagulation monitoring method.[216,217]

The administration of fresh frozen plasma, red blood cells, platelets, and cryoprecipitate remains the mainstay of therapy for blood loss and coagulopathy during liver transplantation. Overall use of blood products during liver transplantation has been significantly reduced in recent years because of improved surgical technique, intraoperative management, and patient selection. This is an important accomplishment because blood transfusion results in immunomodulation and seems to affect long-term outcome adversely.[218] Pharmacologic agents known to alter hemostasis also have been investigated as adjunctive therapies. Aprotinin, aminocaproic acid, tranexamic acid, and conjugated estrogen all have been studied in this context[219-225]; one study showed improved hemodynamics with the administration of aprotinin.[227] These studies have produced conflicting results, however, partly because of study designs. In a meta-analysis including 1043 patients, Warnaar and colleagues[228] showed that aprotinin apparently is safe and results only in transient renal dysfunction. Aprotinin was withdrawn from the market in late 2007, however, based on complication rates in the cardiac surgery population.

The true efficacy of a drug can be determined only when the optimal treatment dosage (established through rigorous

dose-finding studies) is used.[229] To compare the efficacy of different drugs, knowledge of the optimal dosage of each is necessary. Similarly, the safety profile of a drug has to be taken into account. A dosage that maximally reduces blood loss and transfusion requirements during liver transplantation also may increase the risk of hepatic artery or portal vein thrombosis. It is not surprising that there is no consensus on the use of any of these hemostatic agents at liver transplant centers worldwide, despite promising studies.[229]

Another drug, recombinant factor VIIa, has attracted significant attention for improving coagulopathy and reducing intraoperative blood loss.[230] Recombinant factor VIIa was initially developed for patients with hemophilia and particularly for patients unable to receive conventional therapy because of antibodies against factors VIII and IX. Recombinant factor VIIa increases thrombin generation in conjunction with activated platelets.[231] Several case reports, case series, and noncontrolled studies have shown the potential usefulness of recombinant factor VIIa in the setting of liver transplantation.[226,232,233] In 2005, two prospective randomized trials in liver transplant patients resulted in disappointing results, in part because of poor patient selection.[234-235] A small retrospective study showed that in a select group of patients with prolonged prothrombin time and high MELD score, the prophylactic application of recombinant factor VIIa at the start of orthotopic liver transplantation may reduce perioperative transfusion requirements.[236] In view of the very high cost of the drug and the lack of scientific data, it can be recommended only for compassionate use in extreme situations.

As outlined earlier, liver transplantation can be divided into three stages: dissection, anhepatic, and reperfusion (neohepatic) phases. The surgical goals of the dissection phase are to mobilize the vascular structures around the liver (suprahepatic vena cava, infrahepatic vena cava, portal vein, and hepatic artery) and isolate the common bile duct. Frequently, adhesions between the liver, diaphragm, and retroperitoneal areas must be dissected to allow full mobilization of the liver within the right upper quadrant. Manipulation of the liver can impede venous return and result in hypotension. Similarly, acute decompression of ascites early during the dissection phase can result in hypotension. During this phase, adequate fluid replacement is crucial, and colloids frequently are used.

Diuresis should be established early during the procedure to facilitate fluid management, and it may produce some renal protection in anticipation of relative renal ischemia during the anhepatic period. Commonly used drugs to maintain good urine output are loop diuretics, dopamine, mannitol, and, more recently, fenoldopam. It has not yet been established which regimen, if any, is the most protective during liver transplantation. As for dopamine, sound scientific data on the beneficial effect of fenoldopam are lacking in the liver transplant population. In a review article on fenoldopam, only two small studies were referenced that showed potential renal protective properties during liver transplantation under defined study conditions.[237,238] The comparably high cost probably excludes fenoldopam as a first-line drug for renal protection in routine liver transplantation. However, interventions frequently used for perioperative renal protection either are without beneficial effect[239] or are possibly harmful in the noncardiac patient population.[240]

During the end of the dissection stage, the donor organ, which is stored in preservation solution, is flushed with crystalloid or colloid solution on a separate table (back table). During the anhepatic stage, the new liver is primarily implanted by either infracaval interposition or piggyback technique. The choice of surgical technique has important anesthetic implications.

During infracaval interposition, complete vascular occlusion is established by clamping the hepatic artery, portal vein, infrahepatic vena cava, and suprahepatic vena cava (Fig. 67-4A). Because the inferior vena cava is occluded, cardiac preload becomes dependent on collateral flow, and severe hypotension can occur. Cardiac output often decreases significantly with an accompanying increased heart rate. If VVBP is not used, volume loading with a target CVP of 10 to 20 mm Hg and occasionally small infusions of vasopressors (e.g., phenylephrine) are needed before the infrahepatic and suprahepatic caval clamps are placed to prepare for the anhepatic phase. In a retrospective study, Schroeder and colleagues[241] suggested that a low CVP during liver transplantation may decrease the rate of blood transfusion, but it increases postoperative renal failure and 30-day mortality. The results have to be interpreted with caution, however, because of significant shortcomings in the study design. Massicotte and associates[242] showed in a prospective study that reducing CVP (e.g., phlebotomy) reduces blood loss, but does not result in increased adverse outcomes.

Because the response to caval occlusion may differ among patients, a temporary "test clamp" on the inferior vena cava may help guide management before vascular clamps are permanently placed for the anhepatic phase. Alternatively, VVBP can be instituted before vascular exclusion of the liver is established. Bypass is usually accomplished by cannulation of the femoral and portal veins with diversion to the suprahepatic vena cava through the axillary, subclavian, or jugular vein.[243,244]

Extensive research was conducted in the 1980s and 1990s to understand the advantages and disadvantages of VVBP, particularly after one group reported a 10% intraoperative mortality without VVBP that was attributed to hemodynamic instability during the anhepatic phase. Advantages of VVBP include improved hemodynamic stability, improved perfusion of organs during the anhepatic phase, decreased red blood cell and fluid requirements, splanchnic decompression, reduced renal impairment, limited metabolic impairment, and a reduced incidence of pulmonary edema.[243] Several disadvantages also were reported, with complications related to cannula placement being the most significant. Lymphocele, hematoma, major vascular injury, nerve injury, pulmonary air embolism, and death have been associated with VVBP; in one study, the complication rate was reported to be 10% to 30%. A more recent retrospective study noted that VVBP can be initiated during liver transplantation with acceptable risks.[245] More recent North American studies have reported, however, that most centers rarely use VVBP, if at all.[205,246,247]

Even centers not routinely using VVBP may consider it for selected patients, such as patients with significant preexisting cardiac disease, severe pulmonary hypertension, significant hemodynamic instability, or when the anesthesiologist is unfamiliar with caval clamping.[247,248] In the past, a greater than 50% reduction in cardiac output after vena cava clamping was considered an indication for VVBP. This indication has been challenged in a study in which it was shown that a reduction in cardiac output of more than 50% after vena cava clamping was not associated with increased perioperative morbidity and mortality com-

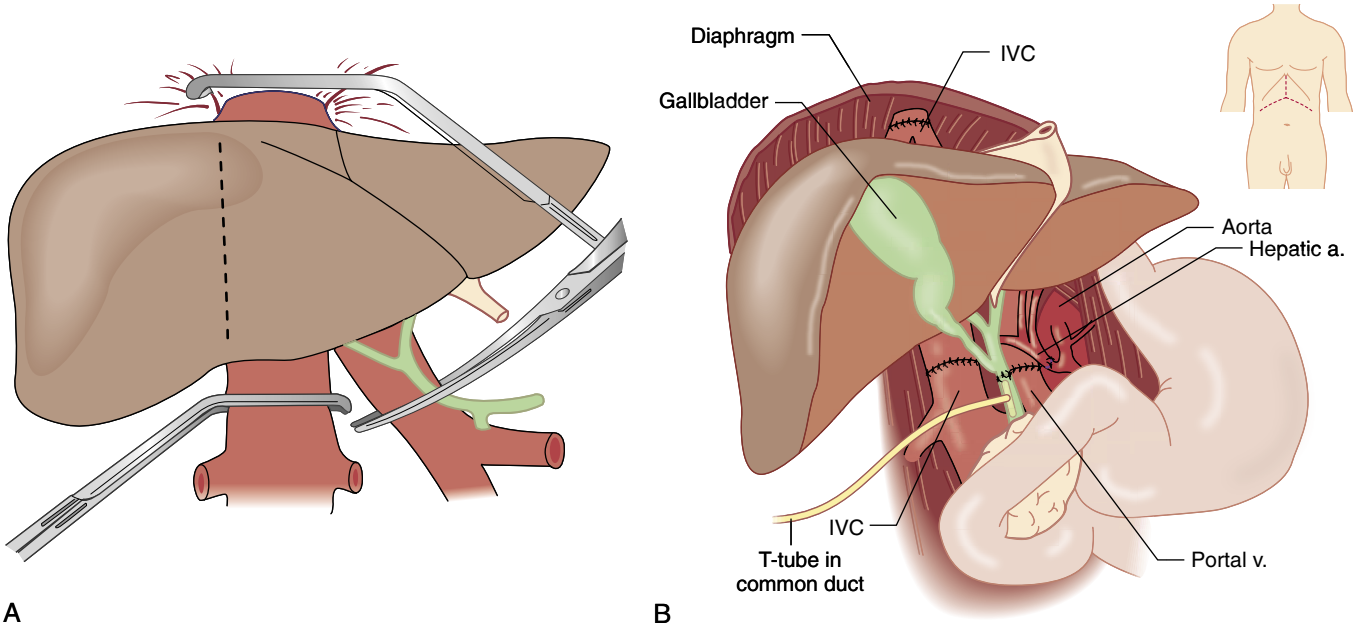

Figure 67-4 A, With the use of a caval interpositional technique immediately before the anhepatic phase, the suprahepatic vena cava, the infrahepatic vena cava, and the portal vein are clamped. The hepatic artery is frequently clamped late in the dissection phase. **B,** Anastomoses during liver transplantation. The donor's suprahepatic vena cava and infrahepatic vena cava are anastomosed to the recipient, followed by the portal vein. Frequently, the hepatic artery and bile duct are anastomosed in the reperfusion phase. A Roux-en-Y loop of the small intestine is an alternative biliary drainage conduit. Reconstruction of the hepatic artery, portal vein, or bile duct is occasionally necessary. Placement of a T-tube for drainage of the bile duct is not mandatory and is increasingly not being done. IVC, inferior vena cava. *(From Hardy JD: Hardy's Textbook of Surgery, 2nd ed. Philadelphia, JB Lippincott, 1988.)*

pared with patients with a less pronounced reduction in cardiac output.[249]

Alternatively, a piggyback technique can be used. During this approach, the vena cava is either partially or entirely occluded during the anhepatic phase. Although improved hemodynamics has been shown (with partial occlusion) with this technique, it is considered surgically more difficult than caval interposition, and may lead to greater technical complications.[250]

The anhepatic stage begins with excision of the native liver and control of bleeding. The ice-cold liver donor graft is placed into the surgical field. The suprahepatic, infrahepatic, and portal vein anastomoses are completed in that order. The hepatic artery anastomosis can be performed before reperfusion or after restoration of blood flow (Fig. 67-4B). Profound acidosis and hypocalcemia frequently develop during the anhepatic stage, so laboratory parameters should be monitored closely. Fluid management can be challenging during this phase, and the return of significant volume when the clamps are released at completion of the vascular anastomoses must be anticipated. Overly aggressive fluid management to maintain adequate blood pressure during the anhepatic phase may result in fluid overload with possible cardiopulmonary compromise and considerable liver and intestinal swelling. An engorged liver and intestines may pose a significant technical challenge for the surgeon during the reperfusion phase, especially when performing a Roux-en-Y choledochojejunostomy.

At the end of the anhepatic phase, the vascular clamps are removed in staged fashion, and each anastomosis is inspected for leakage. The return of preload by establishment of continuous caval flow results in normal or supranormal filling pressure. Removal of the portal vein clamp allows blood flow from the splanchnic circulation into the donor liver and constitutes the beginning of the reperfusion phase. The most critical part of the reperfusion phase is the period immediately after the vascular clamps are removed from the liver graft. Significant hemodynamic instability and cardiac arrest can occur within seconds to minutes of unclamping, particularly after unclamping the portal vein. Reduced cardiac contractility,[251] arrhythmias, severe bradycardia, profound hypotension, and hyperkalemic arrest all have been reported, and anesthetic management is directed at maintaining or recovering cardiovascular stability. This goal may require immediate pharmacologic intervention, such as the administration of epinephrine, atropine, calcium, or occasionally sodium bicarbonate. Methylene blue has been shown in one small study to attenuate hemodynamic changes of the reperfusion syndrome.[252] Preoperative placement of external pads may be helpful for immediate postreperfusion cardiac arrest.

The physiologic perturbations seen in the immediate reperfusion phase are often described as reperfusion syndrome. The exact mechanism is unknown and remains elusive.[253] Several factors alone or in combination are postulated to produce this hemodynamic instability, including high potassium concentrations[254] in the preservative solution (UW solution), donor demographics,[255] the surgical technique,[256] and decreased systemic vascular resistance.[257] Less well established, and in part controversial, factors, such as hypothermia, metabolic acidosis, endogenous vasoactive peptides from the intestine, and sudden atrial stretching in response to unclamping and reperfusion, are some mechanisms that have been postulated to cause the observed hemodynamic changes.

After the initial reperfusion phase, the hepatic artery anastomosis is completed, the gallbladder (in liver grafts from deceased donors) is removed, and the bile duct is reconstructed. Hepatic artery reconstruction is mostly done by end-to-end anastomosis and, in select cases (with unfavorable anatomy), by a jump graft from the aorta. Bile drainage is usually accomplished by choledochocholedochostomy and occasionally by Roux-en-Y choledochojejunostomy. Attention should be paid to the diagnosis and management of significant coagulopathy (e.g., dilution and consumption of clotting factors, platelet entrapment, endogenous heparinoid-like substances, primary fibrinolysis) and resultant bleeding in the reperfusion phase. Laboratory analysis (with consideration of its limitations) and clinical evidence of surgical bleeding should guide management of the coagulopathy.

The immediate function of the newly transplanted liver can be assessed by monitoring obtainable parameters in the operating room. Intraoperative parameters associated with prediction of the outcome of liver transplantation include transfusion requirements, intraoperative bile and urine production, technical complications, and total operating time. The lack of bile production, the need for platelet transfusion, and decreased urine output seem to be associated with a significant increase in ICU and hospital stay.[258]

When adequate hemostasis is established, the abdomen is closed. Hypertension may develop toward the end of the procedure in some patients, and treatment should be initiated before leaving the operating room.

Postoperative Care

Postoperative tracheal intubation is no longer mandatory as long as significant respiratory compromise or concern for airway protection is absent, and established criteria for extubation are fulfilled. Immediate postoperative extubation of liver transplant patients while still in the operating room was reported in 1997 in a cooperative study between the University of Colorado and the University of California at San Francisco.[259] A small group of patients with characteristics associated with few postoperative complications were studied. The successful outcome of this study was followed by reports of immediate or early extubation from institutions in the United States and Europe.[260-264] More recent studies have reported that 75% of first-time deceased liver transplant patients without fulminant failure could be extubated in the operating room by physicians who had experience with early extubation protocols.[263,265] A prospective multicenter study confirmed that early extubation in liver transplantation patients is safe when strict guidelines are followed.[266]

Fluid shifts or blood loss per se should not be considered an indication for postoperative intubation. The standard criteria for extubation in addition to some patient-specific considerations (e.g., significant preoperative hepatic encephalopathy, fulminant hepatic failure) suffice to assist in determining whether a patient should be considered for extubation. Nevertheless, regardless of whether the patient is extubated in the operating room, most centers admit patients to the ICU for close monitoring purposes. There have been more recent reports of uncomplicated cases with patient disposition to the postoperative anesthesia care unit and subsequent floor admission.

Postsurgical pain control is not generally a problem. Several studies have shown that analgesic requirements in patients with end-stage liver disease undergoing liver transplantation appear to be significantly decreased compared with other major abdominal surgery.[267-269] In one study, the neuropeptide metenkephalin, which is involved in pain modulation, was shown to be significantly elevated in liver transplant patients compared with the control population. The exact mechanism of this clinical observation is unknown, and preoperative administration of large doses of steroids may play some role. Whether this applies to transplant patients with hepatocellular carcinoma and preserved synthetic liver function is unknown. The postoperative course of patients who have undergone liver transplantation is primarily dictated by the degree of immediate liver function and recovery of organs that were compromised before transplantation (e.g., hepatorenal syndrome, hepatopulmonary syndrome).

Recovery can range from uncomplicated to extremely complex. Frequent assessment of cardiac and pulmonary function, serum glucose and electrolytes, renal and liver function, and coagulation and the blood count is crucial. In most cases, therapy is supportive and follows the guidelines established for all ICU patients. Certain aspects require special attention, however. Patients occasionally need fresh frozen plasma therapy postoperatively to offset an initially low graft liver function. Fresh frozen plasma requirements also are considered an indirect measure of postoperative liver function. The need for administering platelets or cryoprecipitate postoperatively is low, and such administration is reserved for selected cases. One should have a low threshold for re-exploration. Leakage from vascular anastomosis sites, or "bleeders," and diminished flow or thrombosis in the hepatic artery or portal vein should always be considered. Patients who have adequate postoperative liver function and have received steroids tend to be hyperglycemic, which may warrant an infusion of insulin.

Anesthesia for Patients after Liver Transplantation

Liver transplant recipients occasionally return to the operating room shortly after the procedure for exploratory laparotomy. Reasons for exploration include bleeding, biliary leak, bowel obstruction, and abscess formation. Liver function may not have returned to baseline in the immediate post-transplant period, and additional surgical stress may result in significant worsening of hepatic function. Coagulation studies should be monitored carefully throughout the case, and fresh frozen plasma should be made readily available.

The most common reason to operate after liver transplantation is for biliary reconstruction. At this point, liver function is generally normal, and anesthetic considerations (including regional techniques such as epidural catheters) are similar to those for any abdominal procedure. These patients have been receiving powerful immunosuppressive therapy, however, which leads to an increased risk for infectious complications, drug toxicity, and adverse drug interaction. Placement of any intravenous or epidural catheters should be done under strict sterile conditions with maximum barrier protection. The patient's drug regimen should be reviewed and screened for known interactions with drugs used during the perioperative period. The medical history and physical examination done at this point should include screening for these adverse immunosuppressive drug effects, including, but not limited to, neurotoxicity and renal toxicity.

Intestine Transplantation

Intestinal transplantation is done much less frequently than transplantation of other solid organs. In 2007, 198 intestinal transplants were done in the United States, and there were approximately 222 patients on the waiting list. Short-gut syndrome accounted for more than 60% of these transplants, and half the recipients were younger than 6 years.[144]

The overall graft survival rate at 1 year was 66% and at 5 years was 20%. These outcomes are markedly improved compared with earlier years, when early universal graft failure was very common. Changes in immunosuppressive therapy are thought to be responsible for the improved graft survival.[270] Only a few centers perform this procedure as either an isolated intestinal transplantation or a combined liver-intestinal transplantation. Dependence on total parenteral nutrition can lead to steatotic liver disease with hepatic failure requiring combined liver-intestinal transplantation. Optimization of hepatosplanchnic blood flow is essential for these cases. Fluid loading and inotropic support may be beneficial.[271] No studies have investigated the perioperative anesthetic management and graft and patient outcome.

Infection after Abdominal Solid Organ Transplantation

After transplantation, organ recipients are at significant risk for various complications, including bacterial, fungal, and viral infections. Infections in this patient population are associated with increased morbidity and mortality because transplant recipients have unique infectious risks compared with immunocompetent ICU patients. Studies of patients receiving different transplanted abdominal organs show the importance of postoperative infection in transplant recipients. In the first month after transplantation, the sources of infection are primarily nosocomial secondary to the surgical technique or technical complications. After transplantation of any abdominal organ, there is a risk of surgical site infections, intra-abdominal abscesses, and infected hematomas. Multidrug-resistant microorganisms are increasingly seen in this population and are likely to represent a significant challenge in the future.

In liver transplantation, surgical complications such as biliary leaks can lead to subsequent infections, including peritonitis, cholangitis, and hepatic abscesses.[272] The risk of fungal infections after orthotopic liver transplantation increases with renal failure, transfusions, retransplantation, repeat laparotomy, and creation of a Roux-en-Y biliary duct anastomosis.

Surgical site infections of the soft tissue are usually diagnosed clinically by the presence of erythema, tenderness, purulence, and crepitus around the wound.[9] Often, superficial surgical site infections can be treated with antibiotics only; however, any rapidly progressing soft tissue infection requires prompt surgical treatment. Gram-positive organisms usually cause superficial surgical site infections, but necrotizing infections are often polymicrobial. Surgical site infection involving deeper tissue structures may be more difficult to recognize. Diagnostic procedures include culturing and Gram staining of any fluid from the wound or drains, ultrasound or CT scanning to localize possible fluid collections, and possible repeat laparotomy. Laparotomies are associated with an increased mortality, but are often necessary in critically ill transplant patients, especially patients with sepsis and multiorgan failure.[273] CT-guided drains successfully treat 80% of abdominal abscesses in general surgical patients.[274] Intra-abdominal abscesses in orthotopic liver transplantation are often near the biliary tract, especially if a Roux-en-Y choledochojejunostomy was used for the biliary reconstruction.

Renal allograft recipients with high serum creatinine, urinary fistulas or leaks, and prolonged urinary bladder catheterization have a higher risk for wound infections.[275] After simultaneous pancreas and kidney transplant, the risk of an intra-abdominal surgical site infection may be increased slightly if pancreatic exocrine secretions are drained enterically, rather than drained via pancreatic duct anastomosis to the bladder.[276] Additionally, kidney transplant recipients with a peritoneal dialysis catheter present before transplantation may have increased risk for intra-abdominal, bloodstream, and wound infections.[275]

Frequently, transplant patients require extensive postoperative critical care with prolonged intubation and indwelling central venous and urinary catheters. These devices are significant risk factors for ventilator-associated pneumonia, urinary tract infections, and catheter-related bloodstream infections in a significantly immunocompromised patient population.

Comorbidities, such as diabetes and persistent renal dysfunction, can contribute to increased susceptibility to infections. Renal failure incurs a 15-fold to 21-fold increased risk of invasive fungal infection. Pneumonia accounts for 41% of febrile episodes in the ICU in the first 7 days postoperatively; the risk of catheter-related bloodstream infections increases threefold after the first week. Patients are often taking multiple immunosuppressants that act through multiple inhibitory mechanisms and may facilitate infection.

Immunosuppression

Recognition of a foreign alloantigen after organ transplantation triggers an immune response in the host. An immediate goal of immunosuppressive therapy is to prevent the rejection of grafts from genetically nonidentical donors. Various immunosuppressive drugs have been developed to diminish the immunologic attack on grafts and target T-cell activation, which triggers the predominant form of acute rejection. Individual immunosuppressants inhibit different steps in T-cell activation, which is a very complex process that can be divided into two stages—a sensitization phase and an effector stage. The first stage of T-cell activation involves interaction between antigen-presenting cells of the graft and host T cells, such as CD3. The second stage involves participation of costimulatory receptors such as B7, CD28, and CD40, which also activate the T-cell response, and subsequent secretion of cytokines by activated T cells. An interaction of intracellular adhesion molecules and cytokines (e.g., interleukin-2, interferon-γ, and tumor necrosis factor-β) activates the transcription cascade, which further amplifies T-cell activation through DNA synthesis and T-cell proliferation, and plays a central role in graft rejection. Graft rejection reactions have various time courses: hyperacute rejection occurs within the first 24 hours after transplantation, acute rejection reactions usually

begin in the first few weeks after transplantation, and chronic rejection can occur months to years after transplantation.[277,278]

Immunosuppressive drugs are used for the prevention or treatment of acute and chronic rejection of a transplanted organ. The growing success of organ transplantation is closely linked to the evolution of immunosuppressive therapy. The first immunosuppressive drug, azathioprine, was introduced in 1962 and increased the possibilities for successful human transplants, earning a Nobel Prize for innovative pharmacologic progress. In the last 20 years, important medical breakthroughs, such as tissue typing and the introduction of calcineurin inhibitor–based immunosuppression, have dramatically improved the survival rate of transplant recipients. In 1983, the "calcineurin inhibitors era" was ushered in after the discovery of cyclosporine (1979). Transplantation of extrarenal organs became routine, with excellent outcomes for liver, pancreas, heart, and lung transplants.[279]

Immunosuppressive therapy is increasingly being tailored to the specific organs transplanted and their individual risk factors. Patients who are presensitized or who receive a blood group–incompatible organ are, from an immunologic point of view, considered to be high-risk patients. They are likely to require more potent, aggressive immunosuppressive therapy than needed for other transplant patients.[280] Frequently, the type of immunosuppressive drug (e.g., calcineurin inhibitors) or increased doses of immunosuppressive drugs are linked, however, to increased end-organ toxicity, such as neurotoxicity or nephrotoxicity. In patients with delayed renal graft function after transplantation, initial omission of calcineurin inhibitors is crucial to avoid further renal damage. Immunosuppressive drugs are frequently combined to take advantage of additive or synergistic immunosuppressive interaction and to limit drug-specific toxicity (Table 67-2).[281]

Therapy must be maintained lifelong, although isolated cases without graft loss after complete withdrawal of all immunosuppressive drugs have been reported. A typical regimen consists of different phases, starting with the induction phase, therapy during hospitalization, the maintenance phase, and, if necessary, antirejection treatment. Each phase may consist of different drugs or doses and is constantly adjusted as dictated by the medical condition of the patient. The major limitation of current immunosuppressive drugs is that no currently available therapy is entirely effective in preventing rejection.[280] The use of multiple immunosuppressive drugs predisposes patients to a host of infectious and malignant complications. Long-term survival of patients after solid organ transplantation has improved with adequate immunosuppressive therapy. Modification of the immune system also has increased the risk of malignancy, however, especially types of malignancy involving viruses.[282] Azathioprine has been associated with a significant increase in skin cancer, and prolonged cyclosporine administration has been associated with Kaposi's sarcoma. Malignancy is now responsible for substantial morbidity and mortality in this patient population.

With many different available immunosuppressant combinations, acute rejection rates are acceptable, and the focus of interest in transplantation has significantly shifted and expanded toward tolerability and long-term graft and patient survival. The goals of therapy for new immunosuppressants drugs should include (1) prevention of the immune response (i.e., acute and chronic rejection and vascular remodeling); (2) prevention of the complications of immunodeficiency, such as opportunistic infections and malignancies; and (3) minimization of drug-induced toxicity. Many new trials are under way to identify the best immunosuppressant regimen.

Table 67-2 Immunosuppressive Drugs Used in Solid Organ Transplantation and Their Side Effects

Mechanism of Action	Side Effects
Inhibition of T-cell interaction	
Prednisolone	As with all steroids: osteoporosis, diabetes mellitus, glaucoma, infections
Muromonab-CD3 (Orthoclone OKT3)	Fever, lymphoproliferative disease, pulmonary edema, anaphylactic reaction, neoplasia
15-Deoxyspergualin	Bone marrow suppression, gastrointestinal syndromes, paresthesia
Inhibition of adhesion molecules	
Rabbit/horse antithymocyte globulin	Fever, nausea, anaphylactic reaction, higher incidence of cytomegalovirus and Epstein-Barr virus infection
Antilymphocyte globulin	Fever
Enlimomab	Fever, hypertension, chills, nausea, vomiting
OKT4A	Unknown
Inhibition of cytokine synthesis	
Cyclosporine	Nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension, hyperlipidemia, hirsutism, tremor, gingival hyperplasia, diabetes
Tacrolimus (FK506)	Nephrotoxicity, neurotoxicity, hypertension, hyperlipidemia, hyperglycemia
Sirolimus (rapamycin)	Hyperlipidemia, myelosuppression, infections
SDZ-RAD (everolimus)	Hyperlipidemia, myelosuppression, infections
Inolimomab	Headache, leukopenia, thrombocytopenia
Basiliximab	No major adverse effects
Daclizumab	No major adverse effects
Inhibition of DNA synthesis	
Azathioprine	Myelosuppression, hepatotoxicity, development of malignancy
Mycophenolate mofetil	Leukopenia, gastrointestinal syndromes

Because the therapeutic range of most immunosuppressive drugs is narrow, perioperative monitoring of drug levels is important. Several immunosuppressives (e.g., cyclosporine, tacrolimus, and sirolimus) are substrates or modulators (or both) of cytochrome P4503A and P-glycoprotein.[283,284] P-glycoprotein is a member of the ABC (adenosine triphosphate [ATP]–binding cassette) transport protein family. It is found in various tissues, including the blood-brain barrier, gastrointestinal tract, kidneys, adrenal cortex, and several more. One of the functions of P-glycoprotein is the energy-dependent transport of drug acquired from the cytoplasm or plasma membrane into the extracellular space.[285] Several other drug classes (e.g., antifungals, calcium channel blockers, HIV protease inhibitors) administered to transplant

patients also are substrates or modulators (or both) of cytochrome P4503A and P-glycoprotein. These drugs themselves may interact with drugs commonly administered during the perioperative period.[286,287]

Although interactions between immunosuppressive and anesthetic drugs are likely to occur, few studies have examined in a prospective randomized fashion the impact of immunosuppressive drugs on selected anesthetics. In animal studies, cyclosporine was shown to alter barbiturate, fentanyl, and isoflurane requirements.[288-291] However, the clinical relevance of these interactions remains to be investigated, however. Similarly, cyclosporine seems to enhance the effects of neuromuscular blockade, as shown in several animal studies and case reports.[292-295] Despite the lack of adequate trials in humans, it seems to be reasonable to anticipate reduced requirements of nondepolarizing muscle relaxants in patients taking cyclosporine. Azathioprine, in contrast, produced a small and transient antagonism to nondepolarizing muscle blockade in patients with renal failure that was considered clinically insignificant. An animal study also showed no effect of azathioprine on atracurium requirements.

The complexity of the immunosuppressive regimen in conjunction with adjunct therapies makes clinically relevant drug-drug interactions likely. A detailed preoperative review of the patient's medication should focus on possible side effects, drug-drug interactions, and potential implications for the anesthetic plan.[296]

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Jean L. Joris

68 Anesthesia for Laparoscopic Surgery

Key Points

1. CO_2 pneumoperitoneum results in ventilatory and respiratory changes. Pneumoperitoneum decreases thoracopulmonary compliance. $Paco_2$ increases (15% to 25%) due to CO_2 absorption from the peritoneal cavity. Capnography reliably reflects this increase, which plateaus after 20 to 30 minutes.
2. In compromised patients, cardiorespiratory disturbances aggravate the increase in $Paco_2$ and enlarge the gradient between $Paco_2$ and $Petco_2$.
3. Any increase in $Petco_2$ larger than 25% or occurring later than 30 minutes after the beginning of peritoneal CO_2 insufflation should suggest CO_2 subcutaneous emphysema, the most frequent respiratory complication during laparoscopy.
4. Peritoneal insufflation induces alterations of hemodynamics, characterized by decreases of cardiac output, elevations of arterial pressure, and increases of systemic and pulmonary vascular resistances. Hemodynamic changes are accentuated in high-risk cardiac patients.
5. The pathophysiologic hemodynamic changes can be attenuated or prevented by optimizing preload before pneumoperitoneum and by vasodilating agents, α_2-adrenergic receptors agonists, high doses of opioids, and β-blocking agents.
6. Similar pathophysiologic changes occur during pregnancy and in children. Laparoscopy can be safely managed in pregnant women before the 23rd week of pregnancy provided that hypercarbia is prevented. The open laparoscopy approach should be considered to avoid damaging the uterus.
7. Gasless laparoscopy may be helpful to reduce pathophysiologic changes induced by CO_2 pneumoperitoneum but unfortunately increases technical difficulty.
8. Laparoscopy results in multiple postoperative benefits, allowing for quicker recovery and shorter hospital stay. These advantages explain the increasing success of laparoscopy, which is proposed for many surgical procedures.
9. Although no anesthetic technique has proved to be clinically superior to any other, general anesthesia with controlled ventilation seems to be the safest technique for operative laparoscopy.
10. Improved knowledge of the intraoperative repercussions of laparoscopy permits safe management of patients with more and more severe cardiorespiratory disease, who may subsequently benefit from the multiple postoperative advantages offered by this technique.

Surgical procedures have been improved to reduce trauma to the patient, morbidity, mortality, and hospital stay, with consequent reductions in health care costs. The provision of better equipment and facilities, along with increased knowledge and understanding of anatomy and pathology, has allowed the development of endoscopy for diagnostic and operative procedures. Starting in the early 1970s, various pathologic gynecologic conditions were diagnosed and treated using laparoscopy. This endoscopic approach was extended to cholecystectomy in the late 1980s. Since the introduction of the first laparoscopic cholecystectomy procedures,[1] laparoscopy has expanded impressively both in scope and volume. It quickly became apparent that laparoscopy results in multiple benefits compared with open procedures[2,3] and was characterized by better maintenance of homeostasis. Overenthusiasm ensued, which explains the effort to use the laparoscopic approach for gastrointestinal (e.g., colonic, gastric, splenic, hepatic surgery), gynecologic (e.g., hysterectomy), urologic (e.g., nephrectomy, prostatectomy), and vascular (e.g., aortic) procedures.

The pneumoperitoneum and the patient positions required for laparoscopy induce pathophysiologic changes that complicate anesthetic management. An understanding of the pathophysiologic consequences of increased intra-abdominal pressure (IAP) is important for the anesthesiologist who must ideally prevent or, when prevention is not possible, adequately respond to these

changes and who must evaluate and prepare the patient preoperatively in light of these disturbances. The pathophysiologic changes and the complications of laparoscopy are reviewed first. The postoperative period is considered next, with examination of the benefits of laparoscopy and certain specific postoperative problems (e.g., pain, nausea). Practical consequences for the anesthetic management of laparoscopy are presented. Many animal and human studies of the consequences of laparoscopy have been published since the early 1970s. Because much higher IAPs (>20 mm Hg) were previously used and because of potential species differences, we have focused on the human literature published after 1990 using low IAP (<15 mm Hg) and modern anesthesia techniques.

Ventilatory and Respiratory Changes During Laparoscopy

Intraperitoneal insufflation of carbon dioxide (CO_2), the currently routine technique to create pneumoperitoneum for laparoscopy, results in ventilatory and respiratory changes and can cause four principal respiratory complications: CO_2 subcutaneous emphysema, pneumothorax, endobronchial intubation, and gas embolism.[4]

Ventilatory Changes

Pneumoperitoneum decreases thoracopulmonary compliance by 30% to 50% in healthy[5-7] and obese patients.[8,9] Reduction in functional residual capacity[10] and development of atelectasis due to elevation of the diaphragm[11] and changes in the distribution of pulmonary ventilation and perfusion from increased airway pressure can be expected.[11] However, increasing IAP to 14 mm Hg with the patient in a 10- to 20-degree head-up or head-down position does not significantly modify either physiologic dead space or shunt in patients without cardiovascular problems.[12,13]

Increase in the Partial Pressure of Arterial Carbon Dioxide

During uneventful CO_2 pneumoperitoneum, the partial pressure of arterial carbon dioxide ($Paco_2$) progressively increases to reach a plateau 15 to 30 minutes after the beginning of CO_2 insufflation in patients under controlled mechanical ventilation during gynecologic laparoscopy in the Trendelenburg position[14] or during laparoscopic cholecystectomy in the head-up position (Fig. 68-1).[15,16] Any significant increase in $Paco_2$ after this period requires a search for a cause independent of or related to CO_2 insufflation, such as CO_2 subcutaneous emphysema. The increase in $Paco_2$ depends on the IAP.[17] During laparoscopy with local anesthesia, $Paco_2$ remains unchanged but minute ventilation significantly increases.[18]

Capnography and pulse oximetry provide reliable monitoring of $Paco_2$ and arterial oxygen saturation in healthy patients and in the absence of acute intraoperative disturbances (see Figure 68-1).[15,16] Although mean gradients (Δa-$ETCO_2$) between $Paco_2$ and the end-tidal carbon dioxide tension ($Petco_2$) do not change significantly during peritoneal insufflation of CO_2, individual patient data regularly show variations of this difference during pneumoperitoneum.[19,20] $Paco_2$ and Δa-$ETCO_2$ increase more in ASA class II and III patients than in ASA class I patients (Fig. 68-2).[21,22] These findings have been documented in patients with chronic obstructive pulmonary disease (COPD)[23] and in children with cyanotic congenital heart disease.[24] These data therefore highlight the lack of correlation between $Paco_2$ and $Petco_2$ in sick patients, particularly those with impaired CO_2 excretion capacity, and in otherwise healthy patients with acute cardiopulmonary disturbances. Consequently, hypercapnia can develop, even in the absence of abnormal $Petco_2$. Postoperative intra-abdominal CO_2 retention results in increased respiratory rate and $Petco_2$ of patients breathing spontaneously after laparoscopic cholecystectomy as compared with open cholecystectomy.[25]

During CO_2 pneumoperitoneum, the increase of $Paco_2$ may be multifactorial: absorption of CO_2 from the peritoneal cavity, impairment of pulmonary ventilation and perfusion by mechanical factors such as abdominal distention, patient posi-

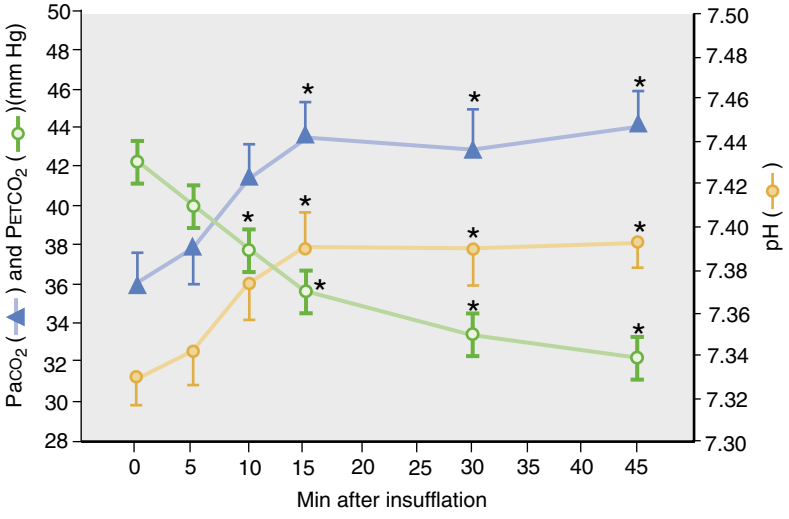

Figure 68-1 Ventilatory changes (pH, $Paco_2$, and $Petco_2$) during CO_2 pneumoperitoneum for laparoscopic cholecystectomy. For 13 American Society of Anesthesiologists (ASA) class I and II patients, minute ventilation was kept constant at 100 mL/kg/min with a respiratory rate of 12 breaths/min during the study. Intra-abdominal pressure was 14 mm Hg. Data are given as the mean ± SEM.*, P < .05 compared with time 0.

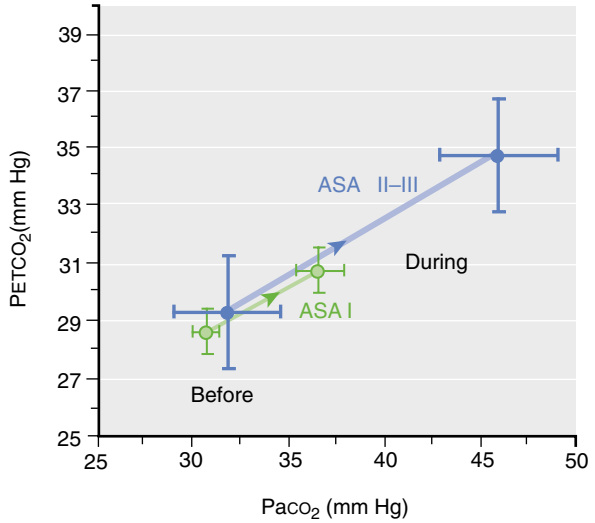

Figure 68-2 Ventilatory changes as a function of patient physical status. The $Paco_2$ and $Petco_2$ were measured before and during CO_2 insufflation. Patients were grouped according to ASA classification: group 1 (*green circles*), ASA I ($n = 20$); group 2 (*blue circles*), ASA II-III ($n = 10$). *(Data from Wittgen CM, Andrus CH, Fitzgerald SD, et al: Analysis of the hemodynamic and ventilatory effects of laparoscopic cholecystectomy. Arch Surg 126:997, 1991.)*

tion, and volume-controlled mechanical ventilation. The observation of an increase in $Paco_2$ when CO_2, but not nitrous oxide (N_2O) or helium, was used as the insufflating gas suggests that the main mechanism of the increased $Paco_2$ during CO_2 pneumoperitoneum is absorption of CO_2 rather than the mechanical ventilatory repercussions of increased IAP.[26,27] Accordingly, direct measurement of CO_2 elimination $(\dot{V}co_2)$ using a metabolic monitor combined with investigation of gas exchange showed a 20% to 30% increase of $\dot{V}co_2$ without significant changes in physiologic dead space in healthy patients undergoing pelvic laparoscopy (IAP of 12 to 14 mm Hg) in the head-down position[14,28] or laparoscopic cholecystectomy in the head-up position.[14,29] The time courses of the increase in $\dot{V}co_2$ and $Paco_2$ are similar. The absorption of a gas from the peritoneal cavity depends on its diffusibility, the absorption area, and the perfusion of the walls of that cavity. Because CO_2 diffusibility is high, absorption of large quantities of CO_2 into the blood and the subsequent marked increases in $Paco_2$ would be expected to occur. The limited rise of $Paco_2$ actually observed can be explained by the capacity of the body to store CO_2[30] and by impaired local perfusion due to increased IAP.[17] During deflation, CO_2 that accumulated in collapsed peritoneal capillary vessels reaches the systemic circulation, leading to transient increases in $Paco_2$ and $\dot{V}co_2$.[31]

Respiratory changes during the laparoscopic procedure may contribute to increasing CO_2 tension. Mismatched ventilation and pulmonary perfusion can result from the position of the patient and from the increased airway pressures associated with abdominal distention.[18,32] Lister and colleagues[17] investigated the relationship between $\dot{V}co_2$ and intraperitoneal CO_2 insufflation pressure in pigs. For an IAP up to 10 mm Hg, increased $\dot{V}co_2$ accounts for the increased $Paco_2$. At higher IAPs, the continued rise of $Paco_2$ without a corresponding increase in $\dot{V}co_2$ results from an increase in respiratory dead space, as reflected by a widening of the $\Delta a\text{-}ETCO_2$ gradient.[17] If controlled ventilation is not adjusted in response to the increased dead space, alveolar ventilation will decrease and $Paco_2$ will rise. In healthy patients, absorption of CO_2 from the abdominal cavity represents the main (or the only) mechanism responsible for increased $Paco_2$,[13] but in patients with cardiorespiratory problems, ventilatory changes also significantly contribute to increasing $Paco_2$.[21] Pao_2 values and intrapulmonary shunt do not significantly change during laparoscopy.[12,13]

It is wise to maintain $Paco_2$ within a physiologic range by adjusting the mechanical ventilation. Except in special circumstances, such as when CO_2 subcutaneous emphysema occurs (see later), correction of increased $Paco_2$ can be easily achieved by a 10% to 25% increase in alveolar ventilation.

Respiratory Complications

CO_2 Subcutaneous Emphysema

CO_2 subcutaneous emphysema can develop as a complication of accidental extraperitoneal insufflation[33] but can also be considered as an unavoidable side effect of certain laparoscopic surgical procedures that require intentional extraperitoneal insufflation, such as inguinal hernia repair, renal surgery, and pelvic lymphadenectomy (Fig. 68-3).[14,34,35] During laparoscopic fundoplication for hiatal hernia repair, the opening of the peritoneum overlying the diaphragmatic hiatus allows passage of CO_2 under pressure through the mediastinum to the cervicocephalic region. In these circumstances, $\dot{V}co_2$, $Paco_2$, and $Petco_2$ increase.[14] Any increase in $Petco_2$ occurring after $Petco_2$ has plateaued should suggest this complication. The increase in $\dot{V}co_2$ may be such that prevention of hypercapnia by adjustment of ventilation becomes almost impossible. In this case, laparoscopy must be temporarily interrupted to allow CO_2 elimination and can be resumed after correction of hypercapnia using a lower insufflation pressure. Indeed, CO_2 pressure determines the extent of the emphysema and the magnitude of CO_2 absorption. CO_2 subcutaneous emphysema readily resolves once insufflation has ceased. CO_2 subcutaneous emphysema, even cervical, does not counterindicate tracheal extubation at the end of surgery.[36] We recommend keeping the patient mechanically ventilated until hypercapnia is corrected, particularly in COPD patients, to avoid an excessive increase in the work of breathing.

Pneumothorax, Pneumomediastinum, Pneumopericardium

Movement of gas during the creation of a pneumoperitoneum can produce pneumomediastinum,[37] unilateral and bilateral pneumothoraces,[38] and pneumopericardium.[39] Embryonic remnants constitute potential channels of communication between the peritoneal cavity and the pleural and pericardial sacs, which can open when intraperitoneal pressure increases. Defects in the diaphragm or weak points in the aortic and esophageal hiatus may allow gas passage into the thorax. Pneumothoraces may also develop secondary to pleural tears during laparoscopic surgical procedures at the level of the gastroesophageal junction (e.g., fundoplication for hiatal hernia). Although opening of peritoneopleural ducts is associated with mainly right-sided pneumothoraces (in the same way that ascites or peritoneal dialysis may be associated with right-sided pleural effusions[40]), the pneumothorax associated with fundoplication is more frequently in the left side of the chest.

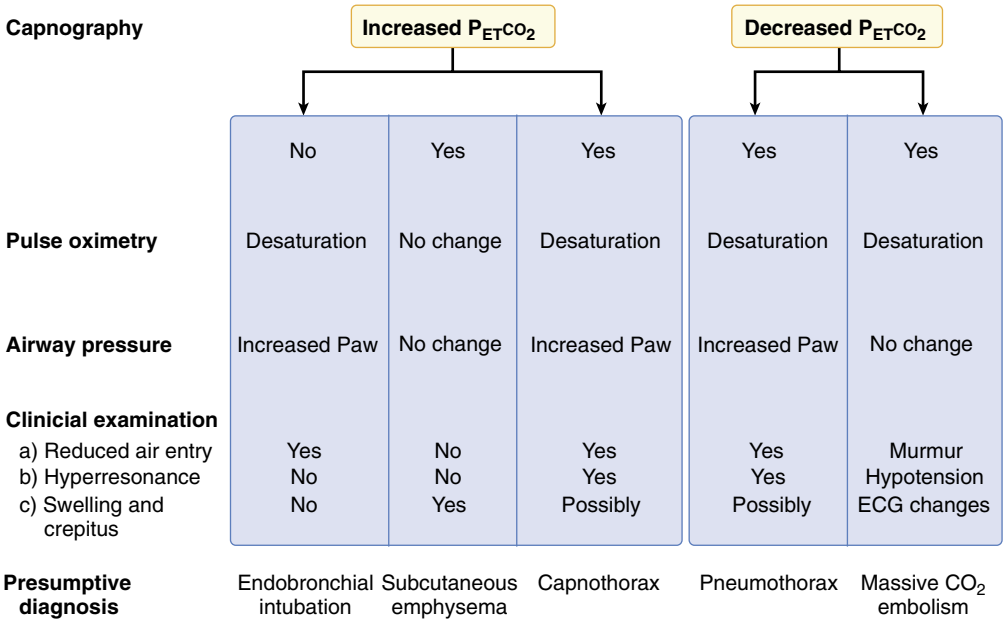

Figure 68-3 Diagnosis of respiratory complications during laparoscopy. ECG, electrocardiographic; Paw, airway pressure; P_{ETCO_2}, end-tidal carbon dioxide tension. (*Data from Wahba RW, Tessler MJ, Kleiman SJ: Acute ventilatory complications during laparoscopic upper abdominal surgery. Can J Anaesth 43:77, 1996.*)

These complications are potentially serious and may lead to respiratory and hemodynamic disturbances. Capnothorax (CO_2 causing a pneumothorax) reduces thoracopulmonary compliance and increases airway pressures. $\dot{V}_{CO_2}$, Pa_{CO_2}, and P_{ETCO_2} also increase.[41] In effect, the absorption surface of CO_2 is increased and the absorption from the pleural cavity is greater than from the peritoneal cavity. When a pneumothorax occurs secondary to alveolar rupture, the P_{ETCO_2} decreases because of decreased cardiac output. Hemodynamic changes and oxygen desaturation should suggest the presence of a tension pneumothorax. The laparoscopist may observe abnormal motion of one hemidiaphragm when a tension pneumothorax has occurred. It should be noted that cervical and upper thoracic subcutaneous emphysema can develop without the presence of a pneumothorax.

When a pneumothorax is caused by highly diffusible gas such as N_2O or CO_2 without associated pulmonary trauma, spontaneous resolution of the pneumothorax occurs within 30 to 60 minutes without thoracocentesis.[42] When capnothorax develops during laparoscopy, treatment with positive end-expiratory pressure (PEEP) is an alternative to chest tube placement.[41] In contrast, if the pneumothorax is secondary to rupture of preexisting bullae, PEEP must not be applied and thoracocentesis is mandatory.

Endobronchial Intubation

Cephalad displacement of the diaphragm during pneumoperitoneum results in cephalad movement of the carina in children[43] and adults,[44] potentially leading to an endobronchial intubation. Cases of endobronchial intubation associated with laparoscopy are reported during procedures in the head-down position[45] and in the head-up position.[44,46] This complication results in a decrease in the oxygen saturation as measured by pulse oximetry (Spo_2) associated with an increase in plateau airway pressure (see Fig. 68-3).

Gas Embolism

Although rare, gas embolism is the most feared and dangerous complication of laparoscopy. Intravascular injection of gas may follow direct needle or trocar placement into a vessel, or it may occur as a consequence of gas insufflation into an abdominal organ. This complication develops principally during the induction of pneumoperitoneum,[47,48] particularly in patients with previous abdominal surgery.[49] Gas embolism may also occur later during surgery.[50,51] CO_2 is used most frequently for laparoscopy because it is more soluble in blood than either air, oxygen, or N_2O.[30] Rapid elimination also increases the margin of safety in case of intravenous injection of CO_2. All these characteristics explain the rapid reversal of the clinical signs of CO_2 embolism with treatment. Consequently, the lethal dose of embolized CO_2 is approximately five times greater than that of air.

The pathophysiology of gas embolism is also determined by the size of the bubbles and the rate of intravenous entry of the gas.[52,53] During laparoscopy, the rapid insufflation of gas under high pressure probably causes a "gas lock" in the vena cava and right atrium; obstruction to venous return with a fall in cardiac output or even circulatory collapse can result. Acute right ventricular hypertension may open the foramen ovale, allowing paradoxical gas embolization.[50,54] Paradoxical embolism, however, may occur without patent foramen ovale.[55] Volume preload diminishes the risk of gas embolism[56] and of paradoxical embolism.[57] Ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatching develops with increases in physiologic dead space and hypoxemia.

The diagnosis of gas embolism depends on the detection of gas emboli in the right side of the heart or on recognition of the physiologic changes from embolization. Early events, occurring with 0.5 mL/kg of air or less, include changes in Doppler sounds and increased mean pulmonary artery pressure. The low incidence of gas embolism during laparoscopy precludes the routine use of invasive or expensive monitors to detect embolization of small quantities of gas. When the size of the embolus

increases (2 mL/kg of air), tachycardia, cardiac arrhythmias, hypotension, increased central venous pressure, alteration in heart tones (i.e., millwheel murmur), cyanosis, and electrocardiographic changes of right-sided heart strain can develop; all these changes are rarely consistently positive.[58] Pulmonary edema can also be an early sign of gas embolism.[54] Although pulse oximetry is helpful in recognizing hypoxemia, capnometry and capnography are more valuable in providing early diagnosis of gas embolism and determining the extent of the embolism. P_{ETCO_2} decreases in the case of embolism owing to the fall in cardiac output and the enlargement of the physiologic dead space. Consequently, $\Delta a\text{-}ET CO_2$ increases. The decrease in P_{ETCO_2} may be preceded by an initial increase secondary to pulmonary excretion of the CO_2, which has been absorbed into the blood.[53] Aspiration of gas or foamy blood from a central venous line establishes the diagnosis. Routine preoperative insertion of a central venous line, however, does not appear justified for these procedures.

Treatment of CO_2 embolism consists of immediate cessation of insufflation and release of the pneumoperitoneum. The patient is placed in steep head-down and left lateral decubitus (Durant) position. The amount of gas that advances through the right side of the heart to the pulmonary circulation is less if the patient is in this position because the buoyant foam is displaced laterally and caudally away from the right ventricular outflow tract. Discontinuing N_2O will allow ventilation with 100% O_2 to correct hypoxemia and reduce the size of the gas embolus and its consequences.[53] Hyperventilation increases CO_2 excretion and is made necessary by the increase in the physiologic dead space. If these simple measures are not effective, a central venous or pulmonary artery catheter may be introduced for aspiration of the gas. Cardiopulmonary resuscitation must be initiated if necessary. External cardiac massage may be helpful in fragmenting CO_2 emboli into small bubbles. The high solubility of CO_2 in blood, resulting in rapid absorption from the bloodstream, accounts for the rapid reversal of the clinical signs of CO_2 embolism with treatment.[48] CO_2 embolism, however, may be fatal. Cardiopulmonary bypass has been used successfully to treat massive CO_2 embolism.[50] Hyperbaric oxygen treatment should be strongly considered if cerebral gas embolism is suspected.[54]

Risk of Aspiration of Gastric Contents

Patients undergoing laparoscopy might be considered to be at risk for acid aspiration syndrome (see also Chapter 50). However, the increased IAP results in changes of the lower esophageal sphincter that allow maintenance of the pressure gradient across the gastroesophageal junction and that may therefore reduce the risk of regurgitation.[59,60] Furthermore, the head-down position should help to prevent any regurgitated fluid from entering the airway.

Hemodynamic Problems During Laparoscopy

Hemodynamic changes observed during laparoscopy result from the combined effects of pneumoperitoneum, patient position, anesthesia, and hypercapnia from the absorbed CO_2. In addition to these pathophysiologic changes, reflex increases of vagal tone and arrhythmias can also develop.

Hemodynamic Repercussions of Pneumoperitoneum in Healthy Patients

Peritoneal insufflation to IAPs higher than 10 mm Hg induces significant alterations of hemodynamics.[61,62] These disturbances are characterized by decreases in cardiac output, increased arterial pressures, and elevation of systemic and pulmonary vascular resistances. Heart rates remain unchanged or increased only slightly. The decrease in cardiac output is proportional to the increase in IAP.[63] Cardiac output has also been reported to be increased[64] or unchanged during pneumoperitoneum.[65,66] These discrepancies might be caused by differences in rates of CO_2 insufflation, IAP,[67] steepness of patient tilt, time intervals between insufflation and collection of data, techniques used to assess hemodynamics, and anesthetic techniques. However, most studies have shown a fall of cardiac output (10% to 30%) during peritoneal insufflation whether the patient was placed in the head-down[68,69] or head-up position.[70,71] These adverse hemodynamic effects of pneumoperitoneum have been confirmed by studies using pulmonary artery catheterization,[69,71] thoracic electrical bioimpedance,[68,70] esophageal echo-Doppler,[72] and transesophageal echocardiography.[73-75] Normal intraoperative values of venous oxygen saturation ($S\bar{v}O_2$) and lactate concentrations suggest that changes in cardiac output occurring during pneumoperitoneum are well tolerated by healthy patients.[71,76] Cardiac outputs, which decrease shortly after the beginning of the peritoneal insufflation, subsequently increase, probably as a result of surgical stress.[70,71] Hemodynamic perturbations occur mainly at the beginning of peritoneal insufflation.

The mechanism of the decrease of cardiac output is multifactorial (Fig. 68-4). A decrease in venous return is observed after a transient increase in venous return at low IAPs (<10 mm Hg).[77,78] Increased IAP results in caval compression,[79] pooling of blood in the legs,[80] and an increase in venous resistance.[77,78] The decline in venous return, which parallels the decrease in cardiac output,[63] is confirmed by a reduction in left ventricular end-diastolic volume measured using transesophageal echocardiography.[74] Cardiac filling pressures, however, rise during peritoneal insufflation.[69,71] The paradoxical increase of these pressures can be explained by the increased intrathoracic pressure associated with pneumoperitoneum.[70,81,82] Right atrial pressure and pulmonary artery occlusion pressure can no longer be considered reliable indices of cardiac filling pressures during pneumoperitoneum. The fact that atrial natriuretic peptide concentrations remain low despite increased pulmonary capillary occlusion pressure during pneumoperitoneum further suggests that abdominal insufflation interferes with venous return.[83] The reduction in venous return and cardiac output can be attenuated by increasing circulating volume before the pneumoperitoneum is produced (Fig. 68-5).[77,84] Increased filling pressures can be achieved by fluid loading or tilting the patient to a slight head-down position before peritoneal insufflation, by preventing the pooling of blood with intermittent sequential pneumatic compression device,[85] or by wrapping the legs with elastic bandages.[86]

The ejection fraction of the left ventricle, assessed by echocardiography, does not appear to decrease significantly when IAP increases to 15 mm Hg.[73,74] However, all studies describe an increase in systemic vascular resistance during the existence of the pneumoperitoneum. This increase in afterload is not a reflex sympathetic response to the decreased cardiac output.[73,82]

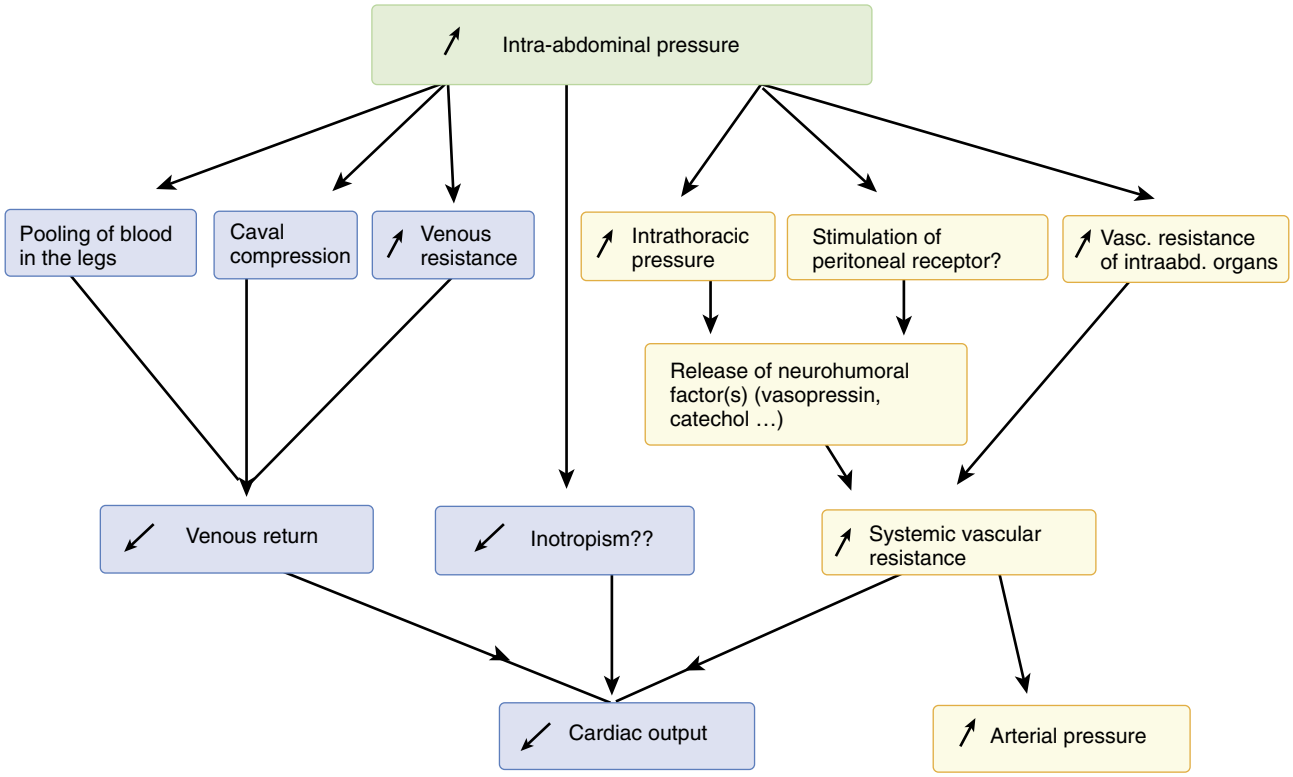

Figure 68-4 Schematic representation of the different mechanisms leading to decreased cardiac output during pneumoperitoneum for laparoscopy.

Systemic vascular resistance was reported to be increased in studies where no decrease in cardiac output was found.[73,76] Although the normal heart tolerates increases in afterload under physiologic conditions, the increases in afterload produced by the presence of a pneumoperitoneum can be deleterious to patients with cardiac disease.[87]

The increase in systemic vascular resistance is affected by patient position. The Trendelenburg position attenuates this increase; the head-up position aggravates it.[65,69,76,83] The increase in systemic vascular resistance can be corrected by the administration of vasodilating anesthetic agents, such as isoflurane,[82] or direct vasodilating drugs, such as nitroglycerin[88] or nicardipine.[89]

The increase in systemic vascular resistance is thought to be mediated by mechanical and neurohumoral factors.[90] The return of hemodynamic parameters to baseline values is gradual, taking several minutes, suggesting the involvement of neurohumoral factor(s).[68,82,87] Catecholamines, the renin-angiotensin system, and especially vasopressin are all released during the presence of the pneumoperitoneum and may contribute to increasing the afterload.[70,71,81,83,91,92] However, only the time course of vasopressin release parallels that of the increase in systemic vascular resistance.[70,71,92] Increases in plasma vasopressin concentrations correlate with changes in intrathoracic pressure and transmural right atrial pressure.[81] Mechanical stimulation of peritoneal receptors also results in increased vasopressin release,[93] systemic vas-

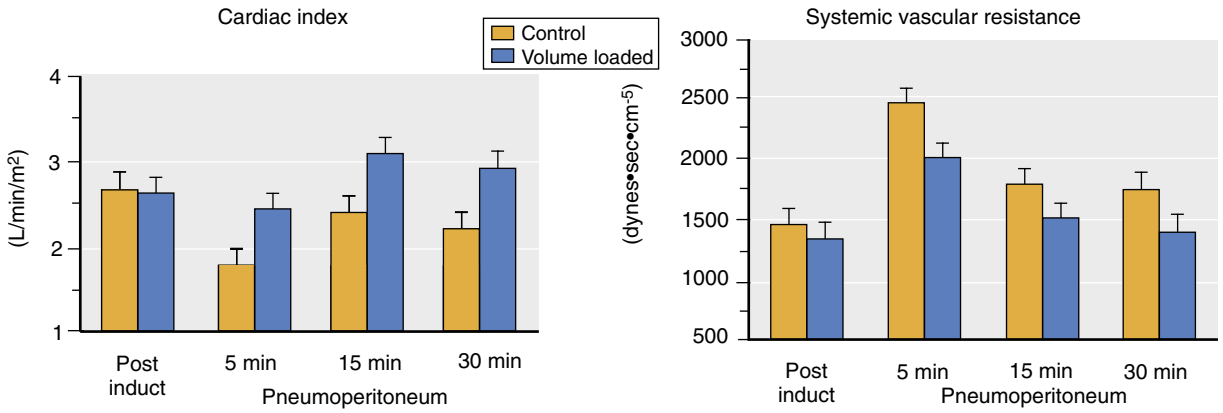

Figure 68-5 Changes in the cardiac index and systemic vascular resistance during laparoscopy in two groups of patients. For group 1 (controls, $n = 10$, *yellow bars*), pneumoperitoneum was induced with patients in a 10-degree head-up position. Group 2 (volume loaded, $n = 10$, *blue bars*) patients received 500 mL of lactated Ringer's solution before anesthesia induction and were insufflated in the supine position. Data are presented as the mean ± SEM.

cular resistance, and arterial pressure.[94] However, whether increasing IAP to 14 mm Hg is sufficient to stimulate these receptors is unknown. The increase in systemic vascular resistance also explains why the arterial pressure increases but the cardiac output falls.[62,90] Use of α_2-adrenergic agonists such as clonidine[71,95] or dexmedetomidine[96,97] and of β-blocking agents[98] significantly reduces hemodynamic changes and anesthetic requirements. Use of high doses of remifentanil almost completely prevents the hemodynamic changes.[66]

Effect of Pneumoperitoneum on Regional Hemodynamics

Increased IAP and the head-up position result in lower limb venous stasis.[80,85,99] Femoral vein blood flow decreases progressively with increasing IAP, and no adaptation to the reduced femoral venous outflow occurs, even during prolonged procedures.[100] These changes may predispose to the development of thromboembolic complications. Although cases of thromboembolism have been reported in the literature, their actual incidence does not seem to be increased by laparoscopy.[101-103]

The effect of CO_2 pneumoperitoneum on renal function has also been investigated.[104-106] Urine output, renal plasma flow, and glomerular filtration rate decrease to less than 50% of baseline values during laparoscopic cholecystectomy and are significantly lower than those during open cholecystectomy.[104] Urine output significantly increases after deflation.

Controversy exists regarding the effect of the CO_2 pneumoperitoneum on splanchnic and hepatic blood flow. A significant reduction was reported in animals[107] and humans.[108-110] However, others have not observed any significant changes.[111-114] Blobner and coworkers,[112] comparing CO_2 pneumoperitoneum and air pneumoperitoneum in pigs, observed a reduction in splanchnic blood flow during air pneumoperitoneum but not during CO_2 pneumoperitoneum. They suggest that the direct splanchnic vasodilating effect of CO_2 may counteract the mechanical effect of increased IAP.

Cerebral blood flow velocity increases during CO_2 pneumoperitoneum in response to the increased $Paco_2$.[115,116] When normocarbia is maintained, pneumoperitoneum combined with the head-down position does not induce harmful changes in intracranial dynamics.[117] Intracranial pressure nevertheless rises during CO_2 pneumoperitoneum, independently of changes in $Paco_2$, in pigs with preoperative induced intracranial hypertension or normal intracranial pressure[118,119] and in children with ventriculoperitoneal shunts.[120] Intraocular pressure is not affected by pneumoperitoneum in women with no preexisting eye disease.[121] In an animal model of glaucoma, pneumoperitoneum only slightly increases intraocular pressure.[122]

Hemodynamic Repercussions of Pneumoperitoneum in High-Risk Cardiac Patients

The demonstration of significant hemodynamic changes during pneumoperitoneum raises the question of tolerance of these changes in cardiac patients (see Chapters 35 and 60). In patients with mild to severe cardiac disease, the pattern of change in mean arterial pressure, cardiac output, and systemic vascular resistance is qualitatively similar to that in healthy patients.[87,88,123-126] Quantitatively, these changes appear to be more marked. In a initial study including ASA class III or IV patients, $S\bar{v}o_2$ decreased in 50% of patients despite preoperative hemodynamic optimization using a pulmonary artery catheter.[124] Patients who experienced the most severe hemodynamic changes with inadequate oxygen delivery were patients with low preoperative cardiac outputs and central venous pressures and high mean arterial pressures and systemic vascular resistances—a profile suggesting depleted intravascular volume. The investigators suggest preoperative preload augmentation to offset the hemodynamic effect of pneumoperitoneum. Intravenous nitroglycerin, nicardipine, or dobutamine has been used to manage the hemodynamic changes induced by increased IAP in selected patients with heart disease.[88,126] Nitroglycerin was chosen to correct the reduction in cardiac output associated with increased pulmonary capillary occlusion pressures and systemic vascular resistance. The administration of nicardipine may be more appropriate than that of nitroglycerin. Right atrial and pulmonary capillary occlusion pressures are not reliable indices of cardiac filling pressure during pneumoperitoneum. Increased afterload is a major contributor to the altered hemodynamics seen during pneumoperitoneum in cardiac patients. Nicardipine acts selectively on arterial resistance vessels and does not compromise venous return.[127] This drug is beneficial in case of congestive heart failure.[128] Because normalization of hemodynamic variables does not occur for at least 1 hour postoperatively in certain patients,[87,125] congestive heart failure can develop in the early postoperative period. Dhoste and associates[129] did not observe impaired hemodynamics in elderly ASA class III patients, but they used low IAP (10 mm Hg) and slow insufflation rates (1 L/min). The hemodynamic consequences of pneumoperitoneum are minor in heart transplant recipients who have good ventricular function.[130,131] Laparoscopic adrenalectomy in patients with pheochromocytoma can be successfully managed using a continuous infusion of nicardipine.[89,132] Several studies suggest that hemodynamic changes during pneumoperitoneum are well tolerated by morbidly obese patients.[8,133,134]

Cardiac Arrhythmias During Laparoscopy

Arrhythmias during laparoscopy have several causes. The increased $Paco_2$ may not be the cause of the arrhythmias occurring during laparoscopy. Arrhythmias do not correlate with the level of the $Paco_2$ and may develop early during insufflation, when high $Paco_2$ is not present.

Reflex increases of vagal tone may result from sudden stretching of the peritoneum and during electrocoagulation of the fallopian tubes.[135] Bradycardia, cardiac arrhythmias, and asystole can develop. Vagal stimulation is accentuated if the level of anesthesia is too superficial or if the patient is taking β-blocking drugs. These events are easily and quickly reversible. Treatment consists of interruption of insufflation, atropine administration, and deepening of anesthesia after recovery of the heart rate.

Cardiac irregularities occur most often early, during insufflation, when pathophysiologic hemodynamic changes are the most intense. For this reason, arrhythmias may also reflect intolerance of these hemodynamic disturbances in patients with

known or latent cardiac disease. Gas embolism can also result in cardiac arrhythmias.

Problems Related to Patient Position

Patient positioning (see Chapter 36) depends on the site of surgery; whereas head-down tilt is used for pelvic and lower abdominal surgery, the head-up position is preferred for upper abdominal surgery. The patient is often placed in the lithotomy position. These positions may be responsible for, or contribute to, the development of pathophysiologic changes or injury during laparoscopy. The steepness of the tilt also affects the magnitude of these changes.

Cardiovascular Effects

In normotensive subjects, the head-down position results in an increase in central venous pressure and cardiac output. The baroreceptor reflex response to increased hydrostatic pressure consists of systemic vasodilation and bradycardia. Although these different reflexes may be impaired during general anesthesia, the hemodynamic changes induced by this position during laparoscopy remain insignificant.[69,76] However, central blood volume and pressure changes are greater in patients with coronary artery disease, particularly with poor ventricular function, leading to potentially deleterious increased myocardial oxygen demand.[32] The Trendelenburg position may also affect the cerebral circulation, particularly in case of low intracranial compliance,[136] and result in elevation of the intraocular venous pressure (which can worsen acute glaucoma).[121] Although the intravascular pressure increases in the upper torso, the head-down position decreases transmural pressures in the pelvic viscera, reducing blood loss but increasing the risk of gas embolism.[32,56]

With the head-up position, a decrease in cardiac output and mean arterial pressure results from the reduction in venous return.[69,76,82] This decrease in cardiac output compounds the hemodynamic changes induced by pneumoperitoneum. The steeper the tilt, the greater the fall in cardiac output.

Venous stasis in the legs occurs during the head-up position and may be aggravated by the lithotomy position with knees flexed.[32] Because pneumoperitoneum further increases blood pooling in the legs,[80,99] any additional factor contributing to circulatory dysfunction should be avoided. The legs must be freely supported and not tightly strapped, and pressure on the popliteal space must be prevented.

Respiratory Changes

The head-down position facilitates the development of atelectasis. Steep head-down tilt results in decreases in the functional residual capacity, the total lung volume, and the pulmonary compliance. These changes are more marked in obese, elderly, and debilitated patients. In healthy patients no major changes are seen.[32] The head-up position is usually considered to be more favorable to respiration.[30,32]

Nerve Injury

Nerve compression is a potential complication during the head-down position. Overextension of the arm must be avoided. Shoulder braces should be used with great caution and must not impinge on the brachial plexus. Lower extremity neuropathies (e.g., peroneal neuropathy, meralgia paresthetica, femoral neuropathy) have been reported after laparoscopy.[137,138] The common peroneal nerve is particularly vulnerable and must be protected when the patient is placed in the lithotomy position. Prolonged lithotomy position, such as required for some operative laparoscopies, can result in lower extremity compartment syndrome.

Postoperative Benefits and Consequences of Laparoscopy

Implicit in the decision to use the laparoscopic approach is the assumption that the intraoperative consequences of pneumoperitoneum described in the previous sections are counterbalanced by multiple postoperative benefits. In contrast to laparotomy, improved and more rapid recovery, reduced postoperative fatigue,[139,140] and a heightened feeling of well-being are commonly reported and reflect better maintenance of homeostasis.[3,139]

Stress Response

In patients undergoing cholecystectomy, the laparoscopic approach allows for a reduction of the acute phase reaction seen after open cholecystectomy. Plasma concentrations of C-reactive protein and interleukin-6, which reflect the extent of tissue damage, are significantly lower after laparoscopy as compared with laparotomy.[3,139,141-143] The metabolic response (e.g., hyperglycemia, leukocytosis) is also reduced after laparoscopy. As a consequence, nitrogen balance and immune function might be better preserved.[144-147] Laparoscopy avoids prolonged exposure and manipulation of the intestines and decreases the need for peritoneal incision and trauma. Consequently, postoperative ileus and fasting, duration of intravenous infusion, and hospital stay are significantly reduced after laparoscopy.[2,3,141,147-149] The duration of postoperative ileus is less shortened when compared with laparotomy than previously reported.[150] The economic implications of these factors are self-evident and beneficial.[151-153]

Surprisingly, whereas laparoscopy allows for a reduction of surgical trauma, the endocrine response to laparoscopic and open cholecystectomy does not differ significantly; plasma concentrations of cortisol and catecholamines,[3,139,154,155] urinary concentrations of cortisol and catecholamine metabolites,[141] and anesthetic requirements[3] are similar after both procedures. Combined general and epidural anesthesia for laparoscopic cholecystectomy does not result in a decreased stress response compared with general anesthesia alone.[154] Several hypotheses can be invoked to explain these observations. Pain and discomfort from peritoneal stretching, hemodynamic disturbances, and ventilatory changes induced by pneumoperitoneum may contribute to the stress response of laparoscopy. Although parietal afference, which is markedly reduced by laparoscopy, appears to be an important stimulus for postoperative hyperglycemia, visceral nociception, which is less

affected by laparoscopy, may contribute more to adrenocortical stimulation.[139] The intraoperative stress response, however, can be reduced by preoperative administration of α_2-agonists.[71,96,97]

Postoperative Pain

Surgical trauma contributes to pain and pulmonary dysfunction. Laparoscopy allows a significant reduction in postoperative pain and analgesic consumption (see Chapter 87).[3,141,154,156-160] Nevertheless, pain intensity may be significant.[161-163] The nature of pain varies depending on the surgical technique; after laparotomy, patients complain more of parietal pain (e.g., abdominal wall), whereas after laparoscopic cholecystectomy, patients report also visceral pain (e.g., biliary colic [cholecystectomy], pelvic spasm [tubal ligation]), and shoulder-tip pain resulting from diaphragmatic irritation.[162,163] Pain after laparoscopy is multifactorial, and different treatments have been proposed to provide pain relief.[164,165] Local anesthetic infiltration (e.g., intraperitoneal, port-site infiltration) for postoperative pain relief after laparoscopic cholecystectomy produces contradictory results.[166-170] Benefits of intraperitoneal local anesthetic are greater after gynecologic laparoscopy.[166,171] Mesosalpinx block decreases postoperative pain and analgesic consumption after laparoscopic sterilization.[166] Residual CO_2 pneumoperitoneum contributes to postoperative pain. Careful evacuation of residual CO_2 after desufflation was shown to be effective.[164,172,173] Preoperative administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and of cyclooxygenase-2 inhibitors decreases pain, as does opiate consumption after gynecologic laparoscopy[174-177] and laparoscopic cholecystectomy.[178-182] However, others have failed to demonstrate any significant effect of preoperative NSAID on pain after laparoscopic sterilization more severe than after diagnostic gynecologic laparoscopy.[183-186] Dexamethasone is also effective in reducing postoperative pain.[187] Multimodal analgesia is now recommended to prevent and treat post-laparoscopy pain.[188-190]

Pulmonary Dysfunction

Upper abdominal surgery results in postoperative changes in pulmonary function (see also Chapter 93). Respiratory dysfunction is less severe and recovery is quicker after laparoscopy.[3,90,141,154,156,157,191-193] Nevertheless, diaphragmatic function remains significantly impaired after laparoscopy.[194-196] Thoracic epidural analgesia does not improve lung function after laparoscopic cholecystectomy.[154] Greater reductions in expiratory volumes and slower recovery of pulmonary function after laparoscopy are reported in older patients,[197] obese patients,[159,198] smokers, and patients with COPD[198] than in healthy patients. Postoperative pulmonary function of these patients, however, is improved after laparoscopy as compared with laparotomy.[159,160,198] Postoperative pulmonary function is less impaired after gynecologic laparoscopy than after upper abdominal laparoscopic surgery.[199]

Postoperative Nausea and Vomiting

Laparoscopy is frequently associated with minor postoperative sequelae that can persist more than 48 hours and that can significantly delay discharge of outpatients.[200] In addition to postoperative pain of various types, one of the main complaints is postoperative nausea and vomiting (PONV) (40% to 75% of patients).[201-203] Whereas perioperative opioids increase the incidence of PONV,[204-206] propofol anesthesia can markedly reduce the high incidence of these side effects.[206,207] The effect of N_2O on the incidence of nausea is still controversial.[206,208,209] Intraoperative drainage of gastric contents also reduces PONV.[210] Intraoperative administration of droperidol and a 5-hydroxytryptamine type 3 antagonist appears to be helpful in the prevention and treatment of these side effects.[206,211-215] Transdermal scopolamine reduces nausea and vomiting after outpatient laparoscopy.[201] Perioperative liberal intravenous fluid therapy can contribute to decreasing these symptoms and to improve postoperative recovery.[216-218]

Alternatives to CO_2 Pneumoperitoneum

New approaches have been investigated to reduce pathophysiologic consequences of CO_2 pneumoperitoneum.

Inert Gases

Insufflation of inert gas (e.g., helium, argon) instead of CO_2 avoids the increase in $Paco_2$ from absorption.[219,220] Consequently, hyperventilation is not required.[27,221-223] Also, the ventilatory consequences of the increased IAP persist. The hemodynamic changes produced by pneumoperitoneum using inert gas are similar to those observed with CO_2. However, the use of these gases accentuates the decrease in cardiac output, whereas the increase in arterial pressure is attenuated.[27,90,223,224] Unfortunately, the low blood solubility of the inert gases raises the issue of safety in the event of gas embolism.[225,226]

Gasless Laparoscopy

Another alternative is gasless laparoscopy. The peritoneal cavity is expanded using abdominal wall lift obtained with a fan retractor. This technique avoids the hemodynamic and respiratory repercussions of increased IAP and the consequences of the use of CO_2.[227-231] Renal and splanchnic perfusion is not altered.[108,232] Port-site metastases after laparoscopic surgery for cancer are reduced after gasless laparoscopy.[233,234] This technique, therefore, is appealing for patients with severe cardiac or pulmonary disease. However, gasless laparoscopy compromises surgical exposure and increases technical difficulty.[229,233,234] Combining abdominal wall lifting with low pressure CO_2 pneumoperitoneum (5 mm Hg) may improve surgical conditions.

Laparoscopy During Pregnancy and in Children

The most common nonobstetric surgical procedures during pregnancy are adnexal surgery, appendectomy, and cholecystectomy,

and they are amenable to laparoscopic surgery (see Chapter 69).[235] Laparoscopy during pregnancy raises several concerns. Abdominal surgery increases the risk of miscarriage or premature labor. However, all the reports in the literature of laparoscopy carried out between 4 and 32 weeks of estimated gestational age have resulted in uncomplicated pregnancies.[236-240] Another concern is the risk of damaging the gravid uterus. This can be avoided by alternative entry sites for the Veress needle and trocars. CO_2 pneumoperitoneum induces significant fetal acidosis. Fetal heart rate and arterial pressure increase, but these changes are minimal.[241] Provided maternal $Paco_2$ is maintained at normal levels, fetal placental perfusion pressure and blood flow, pH, and blood gas tensions are unaffected by insufflation or desufflation.[242] Capnography is adequate to guide ventilation during laparoscopy in pregnant patients.[243] Hemodynamic changes induced by pneumoperitoneum are similar in pregnant and nonpregnant women.[244] The following recommendations are for safe laparoscopy in pregnant patients[236]:

1. The operation should occur during the second trimester, ideally before the 23rd week of pregnancy, to minimize the risk of preterm labor and to maintain adequate intra-abdominal working room.
2. Tocolytics are beneficial to arrest preterm labor, but their prophylactic use is debatable.
3. Open laparoscopy should be used for abdominal access to avoid damaging the uterus.
4. Fetal monitoring may be performed using transvaginal ultrasonography.
5. Mechanical ventilation must be adjusted to maintain a physiologic maternal alkalosis.

Gasless laparoscopy is an alternative to avoid the potential side effects of CO_2 pneumoperitoneum and can sometimes be managed using epidural anesthesia.[245,246]

Laparoscopy is frequently performed in infants and children (see Chapter 82). Knowledge of the pathophysiologic changes induced by laparoscopy in children is necessary to adapt their monitoring and anesthetic technique.[247] CO_2 pneumoperitoneum induces the same changes in respiratory mechanics to those reported in adults.[248-250] $Paco_2$ and $Petco_2$ increase during pneumoperitoneum, but $Petco_2$ may sometimes overestimate $Paco_2$.[251] The profile of CO_2 absorption and the magnitude of CO_2 absorption compared with metabolic $\dot{V}co_2$ are similar in infants and children to those recorded in adults.[252] The hemodynamic changes observed in children are similar to those reported in adults.[253-257] Pneumoperitoneum results in oliguria or anuria in children, reversible after desufflation.[258] Controversy concerning the benefits (improved analgesia and postoperative recovery) of laparoscopy for appendectomy, the most frequent indication for laparoscopy in children, persists.[259-261]

Complications of Laparoscopy

With the development of more sophisticated endoscopic operations, it is important to consider the risks and benefits of laparoscopy. Although the benefits of the laparoscopic approach are well documented, knowledge of the incidence of complications is more imprecise and is frequently based on retrospective studies.

The experience of gynecologic laparoscopists extends over a relatively long time and, as a result, large surveys are available.[262,263] Mortality rates have varied from 1 per 10,000 to 1 per 100,000 cases. The number of serious complications requiring laparotomy was 2 to 10 per 1000 cases. Intestinal injuries accounted for 30% to 50% of these and remained undiagnosed during laparoscopy in one half of the cases. Vascular complications also accounted for 30% to 50%. Burns were responsible for 15% to 20% of the reported complications. Although the death rate decreased, the complication rate was slightly higher in the most recent surveys, probably because of the increased complexity of the laparoscopies performed over the past few years.

Large surveys of complications after laparoscopic cholecystectomy are available.[152,264-268] The overall mortality rate is 0.1 to 1 per 1000 cases.[268] Conversion to laparotomy was necessary in approximately 1% of patients. Bowel perforation occurred in about 2 per 1000 cases, common bile duct injury in 2 to 6 per 1000 cases, and significant hemorrhage in 2 to 9 per 1000 cases. Laparoscopic cholecystectomy was accompanied by a greater frequency of minor operative complications, whereas open cholecystectomy had a more frequent rate of minor general complications. A learning curve was demonstrated for laparoscopic cholecystectomy; experience was associated with decreased operative times and rates of minor or moderate complications. Some of these complications might be prevented by open laparoscopy.[269]

Although large vessel injury (e.g., aorta, inferior vena cava, iliac vessels) caused emergency situations, retroperitoneal hematoma can develop insidiously and result in significant blood loss without major intraperitoneal effusion, leading to delayed diagnosis. During gynecologic laparoscopy, complications occur more frequently during the creation of pneumoperitoneum and the introduction of trocars, whereas during gastrointestinal surgery they are more closely related to the surgical procedure itself.[152,270,271] Injuries provoked by the Veress needle are usually less severe than those by trocars and may even remain undiagnosed. Unrecognized gastrointestinal tract injury and subhepatic abscess formation can lead to potentially lethal septic complications.[272] The rate of postoperative infections (e.g., surgical site, respiratory) seems to be significantly lower after laparoscopy than after laparotomy.[273] Although all these events are surgery related, the anesthesiologist must be aware of the complications and timing of their occurrence. He or she must be ready to respond promptly and adequately to these mishaps and to help the surgeon diagnose a complication.

Anesthesia for Laparoscopy

Preoperative Evaluation of the Patient and Premedication

Without regard to surgical contraindications, absolute contraindications to laparoscopy and pneumoperitoneum are rare, and some still require characterization (see Chapter 34). Pneumoperitoneum is undesirable in patients with increased intracranial pressure (e.g., tumor, hydrocephalus, head trauma) and hypovolemia. Laparoscopy can be performed safely in patients with ventricular peritoneal shunt and peritoneojugular shunt that are

provided with unidirectional valve resistant to IAPs used during pneumoperitoneum. In case of glaucoma, the effects on intraocular pressure do not seem to be clinically significant but deserve further confirmation.[122]

In patients with heart disease, cardiac function should be evaluated in light of the hemodynamic changes induced by pneumoperitoneum and patient position, particularly in case of compromised ventricular function (Table 68-1). Patients with severe congestive heart failure and terminal valvular insufficiency are more prone to develop cardiac complications than patients with ischemic cardiac disease during laparoscopy. Whether laparoscopy is more dangerous than laparotomy in these patients has not yet been explored directly but deserves careful consideration. For these patients, the postoperative benefits of laparoscopy must be balanced against the intraoperative risks when the choice of laparoscopy versus laparotomy is discussed. Gasless laparoscopy may represent an alternative for these patients.

Because of the side effects of increased IAP on renal function, patients with renal failure deserve special care to optimize hemodynamics during pneumoperitoneum, and the concomitant use of nephrotoxic drugs should be avoided.

In patients with respiratory disease, laparoscopy appears preferable to laparotomy because of reduced postoperative respiratory dysfunction. This positive effect counterbalances the risk of pneumothorax during pneumoperitoneum and the risk of inadequate gas exchange from $\dot{V}/\dot{Q}$ mismatching.

Because of venous stasis in the legs during laparoscopy, prophylaxis of deep vein thrombosis should be the same as for laparotomy.

Premedication should be adapted to the duration of the laparoscopy and to the necessity for quick recovery in the outpatient setting. Preoperative administration of NSAIDs may be helpful in reducing postoperative pain and opiate requirements. Preoperative clonidine and dexmedetomidine decrease the intraoperative stress response and improve hemodynamic stability.[71,95-97]

Table 68-1 Management of Patients with Cardiac Disease for Laparoscopy

Preoperative Evaluation: Echocardiography
If left ventricular ejection fraction < 30%:
Intraoperative monitoring
Intra-arterial line
Pulmonary artery catheter?
Transesophageal echocardiography
Continuous ST-segment analysis?
Gasless laparoscopy?
Laparotomy?
Intraoperative Management
Slow insufflation
Low intra-abdominal pressure
Hemodynamic optimization before pneumoperitoneum (preload augmentation)
Patient tilt after insufflation
Anesthesia: remifentanil, vasodilating anesthetic and drugs (nicardipine, nitroglycerin), cardiotonic agents
Experienced surgeon
Postoperative Care
Slow recovery from anesthesia (benefit of clonidine)

Patient Positioning and Monitoring

Patients must be positioned (see Chapter 36) with great care to prevent nerve injuries; padding should protect from nerve compression, and shoulder braces, if needed, should be placed overlying the coracoid process. Patient tilt should be reduced as much as possible and should not exceed 15 to 20 degrees. Tilting must be slow and progressive to avoid sudden hemodynamic and respiratory changes. The position of the endotracheal tube must be checked after any change in patient position. Induction and release of the pneumoperitoneum must be smooth and progressive. Mask ventilation before intubation can inflate the stomach with gas, which must be aspirated before trocar placement to avoid gastric perforation, particularly for supramesocolic laparoscopy. The bladder should be emptied before pelvic laparoscopy or prolonged procedures.

During laparoscopy, arterial blood pressure, heart rate, electrocardiography, capnometry, and pulse oximetry must be continuously monitored. Although this level of monitoring is valuable for detection of cardiac arrhythmias, gas embolism, CO_2 subcutaneous emphysema, and pneumothorax, it provides only indirect evidence of the hemodynamic changes induced by the pneumoperitoneum. Although more invasive hemodynamic monitoring may be necessary in patients with cardiac diseases, increased intrathoracic pressure complicates the interpretation of measured central venous and pulmonary artery pressures. Transesophageal echocardiography may be more helpful in patients with severe cardiac disease (see Table 68-1). P_{ETCO_2} and Spo_2 reliably reflect $Paco_2$ and arterial oxygen saturation (Sao_2). However, the $\Delta a\text{-}ETCO_2$ may vary from patient to patient and during the course of laparoscopy in the same patient. P_{ETCO_2} must be monitored carefully to avoid hypercapnia and to detect gas embolism. Because $\Delta a\text{-}ETCO_2$ may increase more in patients with cardiac and pulmonary diseases, cannulation of a radial artery may be helpful to allow direct measurement of $Paco_2$ from an arterial blood sample.

Anesthetic Techniques

General, local, and regional anesthesia have all been used successfully and safely for laparoscopy.

General Anesthesia

General anesthesia with endotracheal intubation and controlled ventilation is certainly the safest and most commonly used technique and therefore is recommended for inpatients and for long laparoscopic procedures. During pneumoperitoneum, controlled ventilation must be adjusted to maintain P_{ETCO_2} between 35 and 40 mm Hg. In our experience, this requires no more than a 15% to 25% increase of minute ventilation, except when CO_2 subcutaneous emphysema develops. Increase of respiratory rate rather than of tidal volume may be preferable in patients with COPD and in patients with a history of spontaneous pneumothorax or bullous emphysema to avoid increased alveolar inflation and reduce the risk of pneumothorax. Infusion of vasodilating drugs, such as nicardipine,[89,132] α_2-adrenergic

receptor agonists,[71,95-97] and remifentanil[66] reduces the hemodynamic repercussions of pneumoperitoneum and may facilitate management of cardiac patients (see Table 68-1). The actual contribution of N_2O to PONV is probably less than previously considered.[206] Although N_2O does not seem to be contraindicated for laparoscopic cholecystectomy,[208] omission of N_2O improves surgical conditions for intestinal and colonic surgery.[274] The choice of anesthetic technique does not seem to play a major role in patient outcome.[275-277] Propofol, nevertheless, results in fewer postoperative side effects.[278-280] Propofol anesthesia for laparoscopic fertility procedures involving genetic material transfers, however, is associated with lower clinical and ongoing pregnancy rates compared with isoflurane.[281] IAP should be monitored, kept as low as possible to reduce hemodynamic and respiratory changes, and not allowed to exceed 20 mm Hg. Increases in IAP can be avoided by ensuring a deep plane of anesthesia. Whether profound muscle relaxation is necessary for laparoscopy is not clear.[282] Liberal perioperative intravenous fluid therapy decreases hemodynamic changes from pneumoperitoneum[77,84] and PONV and improves postoperative recovery.[216-218] Because of the potential for reflex increases of vagal tone during laparoscopy, atropine should be available if necessary.

The laryngeal mask airway results in fewer cases of sore throat and may be proposed as an alternative to endotracheal intubation[283-287] (also see Chapter 50) even if this device does not protect the airway from aspiration of gastric contents.[288,289] It allows controlled ventilation and accurate monitoring of P_{ETCO_2}. However, decreased thoracopulmonary compliance during pneumoperitoneum frequently results in airway pressures exceeding 20 cm H_2O. The ProSeal laryngeal mask airway may be an alternative to guarantee an airway seal up to 30 cm H_2O.[290,291]

General anesthesia in patients breathing spontaneously without intubation can be performed safely and avoids tracheal irritation as well as administration of muscle relaxant. This anesthetic technique must be restricted to short procedures performed using low IAP and small degrees of tilt.[292] In these conditions, the laryngeal mask airway might improve the safety of anesthesia[283,286,293] and is therefore recommended.

Local and Regional Anesthesia

Local anesthesia offers several advantages: quicker recovery, decreased PONV, early diagnosis of complications, and fewer hemodynamic changes (see Chapters 30, 51, and 52).[294,295] However, this anesthetic approach requires precise and gentle surgical technique and may result in increased patient anxiety, pain, and discomfort during the manipulation of pelvic and abdominal organs. For these reasons, local anesthesia is routinely supplemented with intravenous sedation. The combined effect of pneumoperitoneum and sedation can lead to hypoventilation and arterial oxygen desaturation.[296] Complex laparoscopic procedure must not be managed with local anesthesia.

Regional anesthesia, including epidural and spinal techniques, combined with the head-down position can be used for gynecologic laparoscopy without major impairment of ventilation.[18,297,298] Laparoscopic cholecystectomy has been successfully performed using epidural anesthesia in COPD patients.[299,300] The metabolic response is reduced by regional anesthesia.[301] Globally, epidural and local anesthesia share the same benefits and disadvantages. Regional anesthesia reduces the need for sedatives and narcotics, produces better muscle relaxation, and can be proposed for laparoscopic procedures other than sterilization. Shoulder-tip pain from diaphragmatic irritation and discomfort from abdominal distention are incompletely alleviated using epidural anesthesia alone.[302] Extensive sensory block (T4-L5) is necessary for surgical laparoscopy and may also lead to discomfort. The epidural administration of opiates or clonidine, or both, may help to provide adequate analgesia.[302] The hemodynamic effects of pneumoperitoneum under epidural anesthesia have not been studied. Regional anesthesia can provide adequate relief of pain and discomfort in case of gasless laparoscopy, thus avoiding most of the side effects of CO_2 pneumoperitoneum.[246,303]

Recovery and Postoperative Monitoring

Hemodynamic monitoring should be continued in the PACU (see Chapter 85). Hemodynamic changes induced by the pneumoperitoneum, and more particularly the increased systemic vascular resistance, outlast the release of the pneumoperitoneum. The hyperdynamic state developing after laparoscopy could conceivably lead to a precarious hemodynamic situation in patients with cardiac disease.[87,125]

Despite the reduction in postoperative pulmonary dysfunction, Pao_2 still decreases after laparoscopic cholecystectomy.[3,156,192] Increased oxygen demand is observed after laparoscopy. Although laparoscopy tends to be considered a minor surgical procedure, oxygen should be administered postoperatively, even to healthy patients.[304]

Finally, prevention and treatment of nausea, vomiting, and pain are important, particularly after outpatient laparoscopic procedures.

Summary

Laparoscopy results in multiple postoperative benefits including less trauma, less pain, less pulmonary dysfunction, quicker recovery, and shorter hospital stay. These advantages are regularly emphasized and explain the increasing success of laparoscopy, which is now proposed for many surgical procedures. Intraoperative cardiorespiratory changes occur during pneumoperitoneum. $Paco_2$ increases because of CO_2 absorption from the peritoneal cavity. In compromised patients, cardiorespiratory disturbances aggravate this increase in $Paco_2$. Hemodynamic changes are accentuated in high-risk cardiac patients. Improved knowledge of the pathophysiologic hemodynamic changes in healthy patients allows for successful anesthetic management of cardiac patients, by optimizing preload before pneumoperitoneum and through judicious use of vasodilating agents. Alternative insufflating gases (e.g., He, Ar, N_2O) do not seem to reduce the hemodynamic changes. Gasless laparoscopy may be more helpful but unfortunately increases technical difficulty. The incidence of complications has now been reported in several large surveys and compares favorably with that of open surgery. The death rate during operative laparoscopy is 0.1 to 1 per 1000 cases; the incidence of hemorrhagic complications and visceral injury is 2 to 5 per 1000 cases. Whereas no anesthetic technique has proved to be clinically superior to any other, general anesthesia with controlled ventilation

seems to be the safest technique for operative laparoscopy. Improved knowledge of the intraoperative repercussions of laparoscopy permits safe management of patients with more and more severe cardiorespiratory disease, who may subsequently benefit from the multiple postoperative advantages offered by this approach.

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69 Anesthesia for Obstetrics

Key Points

1. Functional residual capacity (FRC) begins to decrease in the second trimester of pregnancy and is decreased to 80% of the nonpregnant value at full term. This decrease in FRC causes maternal hypoxemia to develop very quickly after apnea associated with the induction of general anesthesia. Although general anesthesia is no longer routinely used for elective cesarean deliveries, it continues to have a place in current practice.
2. The presence of fetal heart rate (FHR) variability is predictive of fetal well-being and early neonatal health. FHR accelerations signal fetal well-being, whereas late decelerations are suggestive of fetal hypoxia.
3. Animal studies have suggested that vasopressors with predominantly α-adrenergic activity cause a reduction in uterine blood flow that can adversely affect the fetus. Studies in women undergoing elective cesarean section have not confirmed these animal data and have suggested that small doses of phenylephrine may improve the mother's hemodynamics without adversely affecting the fetus.
4. No epidural test dose will exclude all instances of intravenous or intrathecal placement of catheters; however, aspiration of a multiorificed catheter will detect many of them. The combination of aspiration, test dose, and fractionation of doses increases the safety of epidural anesthesia.
5. If an accidental dural puncture occurs during placement of an epidural block, threading the epidural catheter into the spinal space to provide continuous spinal anesthesia offers many advantages. If the epidural block is relocated to another interspace, however, the loss of resistance to air technique should not be used because of the risk of pneumocephalus and severe headache.
6. Many cases of failed intubation occur when a "difficult airway" is not recognized before induction of general anesthesia. Airways change during pregnancy and may worsen during labor, especially in a preeclamptic patient. Careful airway evaluation, although imperfect, must be performed before initiation of general anesthesia.
7. Uterine rupture is a rare event that can cause maternal and fetal mortality. Its incidence during vaginal birth after cesarean section is greater than previously thought. A sudden increase in baseline uterine tone or the sudden absence of uterine pressure coupled with evidence of acute fetal bradycardia may indicate uterine rupture.
8. Magnesium sulfate is the agent of choice for seizure control in preeclamptic patients and is a first-line tocolytic therapy for preterm labor. Treatment with magnesium can produce hypotension and may later potentiate the maternal hemodynamic response to pressors. Magnesium also potentiates the action of both depolarizing and nondepolarizing muscle relaxants.

The challenges presented by a parturient requiring anesthesia or analgesia, or both, make the role of the obstetric anesthesiologist both challenging and rewarding. Those providing anesthetic services to the labor and delivery suite must be familiar with the unique physiology of the parturient and the effects of numerous drugs and techniques on the parturient and fetus.

Continuous improvements in drugs and techniques have led to a significant decrease in anesthetic-related deaths in the delivery suite. The maternal mortality rate in the United States is estimated at 7.5 per 100,000 live births[1]; however, many suggest that this statistic is misleading because of underreporting of maternal deaths.[2] A retrospective analysis of maternal mortality during hospitalization by Panchal and colleagues suggested that anesthesia-related complications accounted for 5.2% of maternal deaths.[3]

In 1992, the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics made recommendations concerning anesthetic coverage in the labor and delivery suite. These recommendations included the availability of 24-hour coverage in larger facilities for complicated patients, the ability to perform an emergency cesarean section in all facilities with delivery suites, and the availability of properly trained personnel to manage anesthetic complications.[4]

Appreciation of the roles of the obstetrician, anesthesiologist, pediatrician, and other personnel who care for the mother and child will facilitate the highest level of care. Communication between the various members of the labor and delivery team is paramount. This chapter provides an overview of the principles and techniques that can be used by the anesthesiologist in the labor and delivery suite.

Physiologic Changes of Pregnancy

Maternal physiologic changes in pregnancy occur as a result of hormonal alterations, mechanical effects of the gravid uterus, increased metabolic and oxygen requirements, metabolic demands of the fetoplacental unit, and hemodynamic alterations associated with the placental circulation. Such changes become more significant as pregnancy progresses, and they have major implications for anesthetic management, especially in high-risk parturients.

Cardiovascular System

The cardiovascular system adjusts throughout pregnancy to meet the changes that occur. Hemodynamic and maternal cardiovascular changes in pregnancy are outlined in Table 69-1. Although the physiologic changes in the cardiovascular system appear to begin in the first trimester, these changes continue into the second and third trimesters, when cardiac output increases by approximately 40% of nonpregnant values. Cardiac output increases from the fifth week of pregnancy and reaches its maximum levels at approximately 32 weeks, after which there is only a slight increase until labor, delivery, and the postpartum period.[5] Approximately 50% of the increase in cardiac output has occurred by the eighth week of pregnancy.[6] Although this increase in cardiac output is due to an increase in both stroke volume and heart rate, the more important factor is stroke volume, which increases by 20% to 50% at term from nonpregnant values. Changes in heart rate are extremely difficult to reliably quantify, but it is thought that the approximately 20% increase in heart rate is present by the fourth week of pregnancy. Although the normal variability in heart rate does not change in pregnancy, there does appear to be a reduction in the sympathetic component.[7] Tachyarrhythmias are more common, especially later in pregnancy as a result of both hormonal and autonomic factors.[8]

Because of the decrease in peripheral vascular resistance, arterial blood pressure does not change in a normal pregnant woman. Cardiac output decreases during the third trimester due to effects of the supine position in the patient at term.[9] Ueland and colleagues found that the decrease in cardiac output was due to obstruction of the inferior vena cava by the gravid uterus, which did not occur when women were placed in the lateral position.[10] A venogram performed before and after cesarean delivery (Fig. 69-1) demonstrates this phenomenon. Despite the increase in blood volume and cardiac output, parturients at term are susceptible to hypotension, especially when in the supine position. Up to 10% of pregnant patients at term show signs of severe hypotension when assuming the supine position. This phenomenon has been termed the *syndrome of supine hypotension*. To compensate, collateral routes of venous return develop, including the paravertebral veins to the azygos vein. Unlike compression of the vena cava, compression of the aorta is generally not associated with maternal symptoms in a healthy parturient but it may be associated with decreased uteroplacental perfusion.[11] Anesthetics and drugs that cause vasodilation or anesthetic techniques that cause sympathectomy (e.g., neuraxial techniques) may exacerbate the impact of aortocaval compression. In the operating room, a small pillow or "wedge" should be used to provide left uterine displacement of 15 to 20 degrees. This angle can be increased as necessary by increasing the wedge or tilting the table. Although tilting the table will also accomplish uterine displacement, the amount of tilt necessary may prove too anxiety provoking to parturients and staff.

The changes in blood volume and cardiac output are often associated with clinically significant implications in parturients who have concomitant cardiac disease, but they may also have an impact on healthy parturients. Many pregnant patients will complain of symptoms suggestive of cardiovascular disease at term, including shortness of breath, palpitations, dizziness, edema, and poor exercise tolerance.[12] Physical examination of the term pregnant woman may also be abnormal when compared with the prepregnant state, with auscultation commonly revealing a wide, loud, split first heart sound, an S_3 sound, and a soft systolic ejection murmur. As illustrated in Table 69-2, pregnancy has numerous effects on cardiac evaluation, including changes in the electrocardiogram, chest radiograph, and echocardiogram. Although these minor changes occur in healthy pregnant women at term, symptoms and signs such as chest pain, syncope, severe arrhythmias, systolic murmur more than grade 3, or diastolic murmur suggest severe disease and warrant further investigation.[13] A gradual return to the prepregnancy blood volume occurs at 6 to 9 weeks post partum.

Table 69-1 Cardiovascular Changes in Pregnancy

Parameter	Change	Amount (%)
Heart rate	Increased	20-30
Stroke volume	Increased	20-50
Cardiac output	Increased	30-50
Contractility	Variable	±10
Central venous pressure	Unchanged	
Pulmonary capillary wedge pressure	Unchanged	
Systemic vascular resistance	Decreased	20
Systemic blood pressure	Slight decrease	Midtrimester 10-15 mm Hg, then rises
Pulmonary vascular resistance	Decreased	30
Pulmonary artery pressure	Slight decrease	

From Birnbach DJ, Gatt SP, Datta S (eds): Textbook of Obstetric Anesthesia. New York, Churchill Livingstone, 2000, p 34.

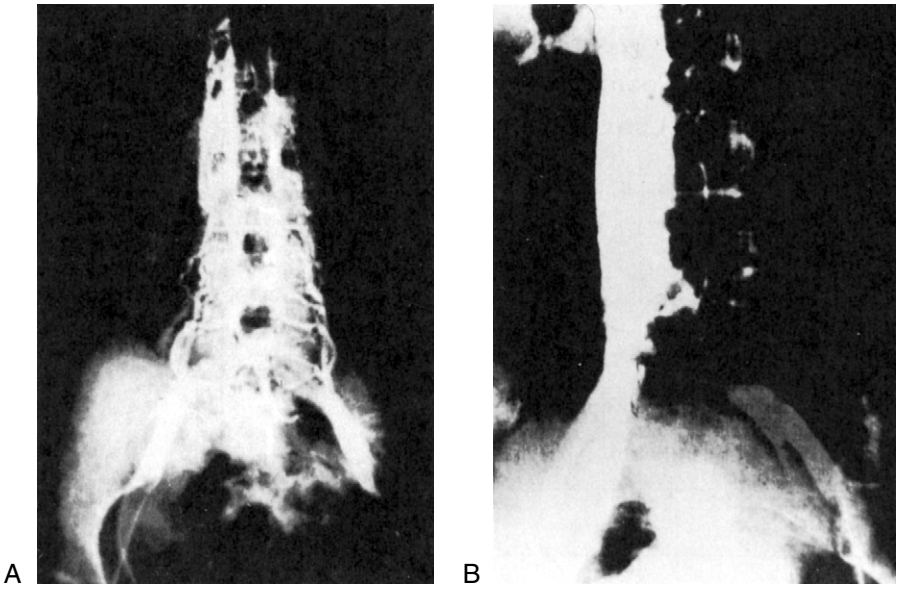

Figure 69-1 **A,** Venogram in a term patient in the supine position before cesarean section. Radiopaque dye injected into the femoral veins fails to reach the inferior vena cava (IVC) but reaches the paravertebral veins. **B,** After cesarean section, blood is seen in the IVC. (*From Kerr MG, Scott DB, Samuel E: Studies of the inferior vena cava in late pregnancy. BMJ 1:532, 1964.*)

Hematologic System

Maternal blood volume begins to increase early in pregnancy as a result of changes in osmoregulation and the renin-angiotensin system, causing sodium retention and increasing total body water to 8.5 L.[14] By term, blood volume increases by up to 45% whereas red cell volume increases by only 30%. This differential increase leads to the "physiologic anemia" of pregnancy with an average hemoglobin and hematocrit of 11.6 g/dL and 35.5%, respectively.[15] However, oxygen transport is not impaired by this relative anemia because the mother's body compensates for it by increased cardiac output, increased Pao_2, and a rightward shift in the oxyhemoglobin dissociation curve.

A state of hypercoagulability exists in pregnancy, with increased levels of most coagulation factors (Table 69-3). Fibrinogen and factor VII are markedly increased, whereas the other factors increase to a lesser extent. This increase in coagulation factors has been verified by thromboelastography[16] and is probably a protective adaptation to lessen the risks associated with the acute hemorrhage that occurs at delivery. This hypercoagulable state, however, may lead to thromboembolism, which remains a leading cause of maternal mortality. The platelet count remains unchanged throughout most of pregnancy, but it may be slightly reduced in the third trimester with increased activity in vivo. The platelet count increases in the postpartum period, probably because of activation of hemostasis at the time of delivery. The incidence of low platelet counts in normal pregnancy is approxi-

Table 69-2 Effect of Pregnancy on Cardiovascular Investigations

Investigation	Findings
Chest radiography	Apparent cardiomegaly Enlarged left atrium (lateral views) Increased vascular markings Straightening of left-sided heart border Postpartum pleural effusion
Electrocardiography	Right-axis deviation Right bundle branch block ST-segment depression of 1 mm on left precordial leads Q waves in lead III T-wave inversion in leads III, V_2, and V_3 Small decrease in PR and QT interval (heart rate dependent) Rotation ± 15 degrees (QRS axis)
Echocardiography	Trivial tricuspid regurgitation (up to 43%-93% at term) Pulmonary regurgitation (up to 94% at term) Increased left atrial size by 12%-14% Increased left ventricle end-diastolic dimensions by 6%-10% Inconsistent increase in left ventricle thickness Mitral regurgitation (28% at term) Pericardial effusion (40% postpartum)

Modified from Gei AF, Hankins GDV: Cardiac disease and pregnancy. Obstet Gynecol Clin North Am 28:465-512, 2001.

Table 69-3 Coagulation Factors in Pregnancy

Factor	Change
II	Unchanged
VII	Increased +++
VIII, IX, X, XII	Increased
XI	Reduced
Fibrinogen	Increased +++
Platelets	Stable

From Birnbach DJ, Gatt SP, Datta S (eds): Textbook of Obstetric Anesthesia. New York, Churchill Livingstone, 2000, p 41.

mately 8%.[17] However, thrombocytopenia during the latter part of pregnancy is not associated with adverse sequelae. Obstetric management of parturients with stable platelet counts above $50,000 \times 10^9$/L should be no different from that of normal parturients.[18] In addition, although the cutoff for initiation of neuraxial blocks was considered to be $100,000 \times 10^9$/L in the past, this level is no longer considered absolute. Currently, most anesthesiologists feel comfortable initiating a regional technique with platelet counts above $75,000 \times 10^9$/L and with counts between 50,000 and 75,000 if the level is stable and clinical laboratory abnormalities or signs of a coagulopathic state are absent.

Respiratory System

To accommodate the increased oxygen demand and requirement for carbon dioxide elimination, pregnancy is associated with an increase in the respiratory minute volume and work of breathing. Because of difficulties in performing clinical research on pregnant women, few investigations of respiratory changes in pregnancy have been conducted. Unfortunately, many of the findings quoted in the literature are inconsistent and often based on older techniques that were applied to a very limited number of subjects.[19]

The most impressive change in maternal lung dynamics is a decrease in functional residual capacity (FRC), which at term may have changed by as much as 20% of prepregnancy values. Minute ventilation increases by 45%, primarily as a result of an increase in tidal volume because the respiratory rate is essentially unchanged. Hormonal changes and an increase in the rate of carbon dioxide production are responsible for the increase in ventilation. Progesterone sensitizes the respiratory center to carbon dioxide. $Paco_2$ falls to approximately 30 mm Hg by the 12th week of gestation, and it remains at this level for the remainder of pregnancy. Tidal volume increases by 50%, with half of this increase occurring during the first trimester. The parturient's breathing pattern changes; it becomes more diaphragmatic as pregnancy progresses because of the effects of the gravid uterus and limitation of thoracic cage movement. Closing capacity (CC), however, remains unchanged. The resulting decrease in the FRC/CC ratio causes faster small-airway closure when lung volume is reduced; thus, parturients can desaturate at a much faster rate as compared with nonpregnant women. The rapid development of hypoxia as a result of decreased FRC, increased oxygen consumption, and airway closure may be minimized by administration of 100% oxygen for 3 to 5 minutes before the induction of anesthesia. In an emergency setting, four maximal capacity breaths with 100% oxygen should be sufficient.

Other changes in the respiratory tract and oropharynx during pregnancy may have profound anesthetic implications. Capillary engorgement of the mucosa and edema of the oropharynx, larynx, and trachea may result in a difficult intubation. Any manipulation of the upper airway such as suctioning, insertion of airways, or laryngoscopy may cause edema, bleeding, and upper airway trauma. Because of the particularly friable mucosa of the nasopharynx, instrumentation of the nose should be avoided if at all possible. In performing intubation of a pregnant patient, a smaller than usual endotracheal tube (size 6.0 to 7.0) should be used and repeated attempts at laryngoscopy minimized. Management of a difficult airway is discussed later in the chapter.

Gastrointestinal System

Gastrointestinal function in pregnancy and during labor is a topic that continues to be controversial. However, there is no doubt that the gastrointestinal tract undergoes significant anatomic and physiologic changes that increase the risk of aspiration associated with general anesthesia. Progesterone relaxes smooth muscle; consequently, it impairs esophageal and intestinal motility during pregnancy. Whether gastric emptying is delayed during pregnancy is controversial. Wong and coworkers suggest that the ingestion of 300 mL of water may actually enhance gastric emptying in healthy, term, nonobese, nonlaboring parturients.[20] However, the risk of pulmonary aspiration of gastric contents remains real in parturients, especially when undergoing an emergency cesarean delivery under general anesthesia. Even if gastrointestinal motility has not been affected during pregnancy, established labor and the administration of parenteral opioids delay gastric emptying.[21,22]

Epidural analgesia using local anesthetics without opioids does not affect gastric emptying, and the use of small doses of epidural fentanyl also has no effect on gastric function.[23-25] Large doses of fentanyl, however, may slow gastric emptying.

The pain of labor, however, may delay gastric emptying and promote emesis. These changes may be caused by the effects of placentally derived gastrin.[26] Because of the gastrointestinal alterations associated with pregnancy, the use of endotracheal intubation is warranted to reduce the risk of aspiration of gastric contents if general anesthesia is required.

Renal System

The renal system undergoes major changes in pregnant patients, mainly because of the effects of progesterone and the mechanical effects of compression of the enlarging uterus. Urea, creatinine, and uric acid clearance all rise in pregnancy (as illustrated in Table 69-4). Renal plasma flow and the glomerular filtration rate (GFR) both increase rapidly in pregnancy as a result of the increase in cardiac output. The GFR rises by almost 50%; this increase, accompanied by the dilutional effect of plasma volume expansion, accounts for the decrease in plasma creatinine and urea. Hence, "normal" renal indices in pregnancy are lower than in the nonpregnant state. Therefore, blood urea nitrogen and creatinine levels that would be considered marginally elevated in

Table 69-4 Values for Renal Function

Parameter	Pregnant	Nonpregnant
Creatinine clearance	140-160 mL/min	90-110 mL/min
Urea	2.0-4.5 mmol/L	6-7 mmol/L
Creatinine	25-75 µmol/L	100 µmol/L
Uric acid	0.2 mmol/L	0.35 mmol/L
pH	7.44	7.40
Bicarbonate	18-22 mmol/L	23-26 mmol/L

From Birnbach DJ, Gatt SP, Datta S (eds): Textbook of Obstetric Anesthesia. New York, Churchill Livingstone, 2000, p 37.

prepregnant patients are usually indicative of severe renal impairment in parturients. The increase in GFR generally precedes the expansion of blood volume and is considered to be a marker of pregnancy-induced vasodilation.[27] Glycosuria is a common finding that is attributable to the increase in GFR and reduced renal tubular resorption capacity.

Central Nervous System

Pregnant women demonstrate increased sensitivity to both regional and general anesthetics. From early stages, when neuraxial anesthesia is administered, pregnant women require less local anesthetic than nonpregnant women do to reach a given dermatomal sensory level. The minimum alveolar concentrations of halothane and isoflurane are reduced by 25% and 40%, respectively, during pregnancy.[28] The underlying mechanism of the decreased anesthetic requirements remains unclear. Furthermore, reduced local anesthetic requirements predate the mechanical effects of the gravid uterus.[29] In animal studies, chronically administered progesterone to reduced anesthetic requirements.[30] In addition, the increased concentrations of endorphins and dynorphins found in pregnant rats may be related to altered pain thresholds.[31,32] Obviously a multifactorial explanation for the decreased anesthetic requirements is likely.

The Fetus

The circulations of the mother and fetus amalgamate in the placenta; this organ has a variety of functions, including endocrine support of pregnancy and transport of nutrients. The pharmacologic and physiologic interactions at this site can be explained in terms of the maternal-placental-fetal unit. This model, as seen in Figure 69-2, can be compartmentalized into maternal, placental, and fetal components.

The placenta is composed of both maternal and fetal tissues that consist of a basal and a chorionic plate. In its simplest description, it can be viewed as a semipermeable membrane that provides an interface for the maternal and fetal circulation. The intervillous space separates the plates and is subdivided by decidual tissue. Chorionic villi and spiral arteries protrude into this intervillous space. Maternal blood flows into the intervillous space from the spiral artery while placental transfer from the mother to the fetus occurs. Approximately 80% of the uterine blood flow passes through the intervillous space.

Forty percent to 50% of fetal cardiac output goes to the placenta, and a similar amount returns to the heart through the umbilical vein (Fig. 69-3). Fetal blood enters the placenta through the two umbilical arteries, which arise from the internal iliac arteries. These arteries subdivide and eventually form umbilical capillaries that traverse the chorionic villi. Fetal blood flow is approximately 75 mL/kg/min, a rate far less than maternal flow. Although fetal and parturient pressures are uneven, placental transfer occurs rapidly for most drugs.

The umbilical-placental circulation is regulated by physiologic reflex changes and the neuroendocrine axis. Numerous substances, including prostaglandins, endorphins, catecholamines, and vasopressin, all play roles in fine-tuning of umbilical-placental perfusion.

Uterine Blood Flow

Uterine blood flow increases progressively during pregnancy and reaches a mean value of 500 to 700 mL by term. Blood flow through the uterine vessels is high and has low resistance; this change in resistance occurs most dramatically after 20 weeks of gestation.[33] Uterine blood flow lacks autoregulation (vessels are maximally dilated during pregnancy), and uterine artery flow is therefore dependent on maternal blood pressure and cardiac output. Consequently, factors that alter blood flow through the

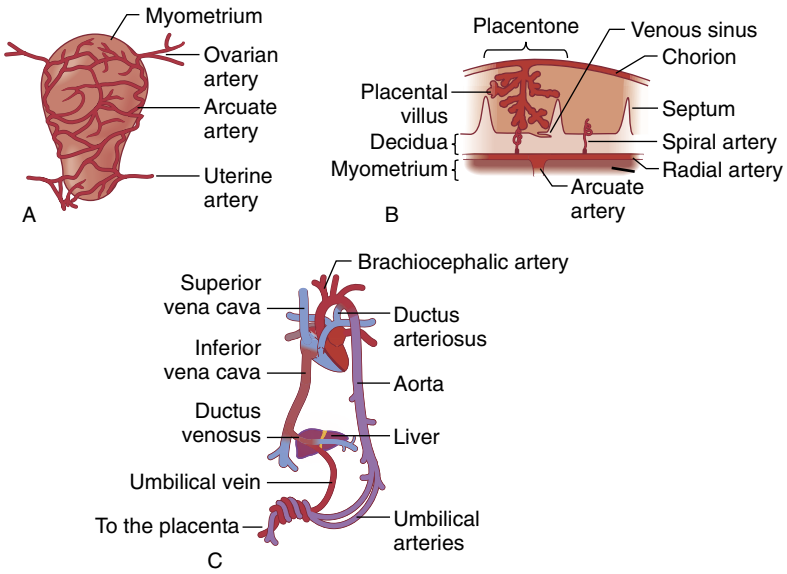

Figure 69-2 The maternal-placental-fetal unit. **A,** Maternal component. **B,** Placental component. **C,** Fetal component. (*From Birnbach DJ [ed]: Ostheimer's Manual of Obstetric Anesthesia, 3rd ed. New York, Churchill Livingstone, 2000, p 45.*)

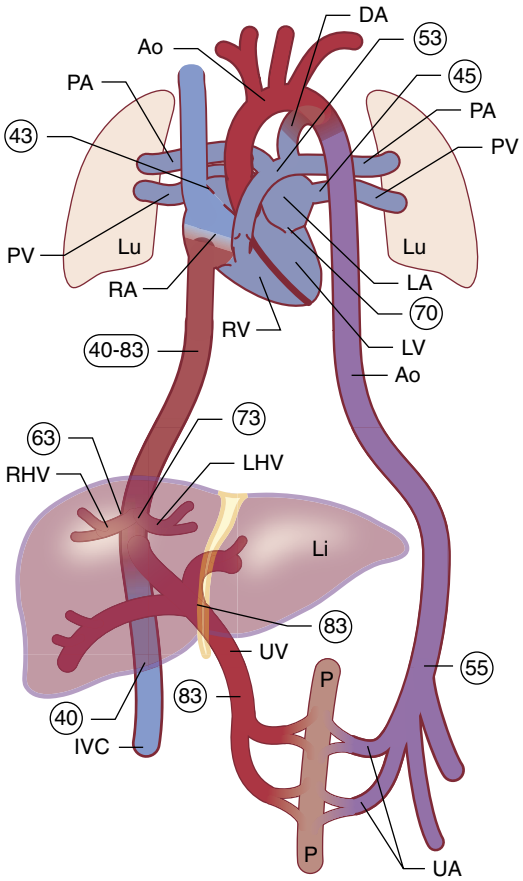

Figure 69-3 The fetal circulation demonstrating the major blood flow patterns and oxygen saturation values (*circled numbers* highlight percent saturation). Ao, aorta; DA, ductus arteriosus; DV, ductus venosus; IVC, inferior vena cava; Li, liver; Lu, lung; P, placenta; PA, pulmonary artery; PV, pulmonary vein; RA and LA, right and left atria; RHV and LHV, right and left hepatic veins; RV and LV, right and left ventricles; SVC, superior vena cava; UA, umbilical artery; UV, umbilical vein. (*From Birnbach DJ, Gatt SP, Datta S [eds]: Textbook of Obstetric Anesthesia. New York, Churchill Livingstone, 2000, p 51.*)

uterus will adversely affect the fetal blood supply. Uterine blood flow is determined by the following relationship:

$$\text{Uterine blood flow} = \frac{\text{Uterine artery pressure} - \text{Uterine venous pressure}}{\text{Uterine vascular resistance}}$$

Uterine blood flow decreases during periods of maternal hypotension, which can occur as a result of hypovolemia, hemorrhage, aortocaval compression, and sympathetic blockade. Similarly, uterine hypercontractility (or conditions that increase the frequency or duration of uterine contractions) and changes in uterine vascular tone, as seen in hypertensive states, may also adversely affect blood flow.

Anesthetics may dramatically influence uterine blood flow either by alterations in perfusion pressure or by changes in uterine vascular resistance. Sympathetic blockade after neuraxial techniques may reduce maternal blood pressure, and the decrease in pressure will affect uterine blood flow. This response may be exaggerated in patients who are not adequately prehydrated. Giving fluids intravenously (preloading) before neuraxial anesthesia does not completely prevent maternal hypotension, but it does increase maternal cardiac output; thus, it may help to preserve uteroplacental blood flow.[34] Maternal cardiac output correlates with the uterine artery pulsatility index and umbilical artery pH.[35,36] High concentrations of volatile anesthetics during general anesthesia may cause systemic vasodilatation and produce depressant effects on the myocardium. Aortocaval compression may further compound these effects.

Vasopressors with direct α-adrenergic receptor activity (e.g., phenylephrine) have been associated in animal studies with increased intrinsic vascular resistance and, as a consequence, a reduction in uterine blood flow.[37] There has been renewed interest in phenylephrine as a vasopressor for use in routine clinical practice; studies have demonstrated that this drug can be used safely in healthy parturients and is as efficacious as ephedrine in maintaining maternal blood pressure and umbilical artery pH values.[38-40] Although it has been suggested that combination therapy with ephedrine and phenylephrine may be optimal,[41] ephedrine is still the vasopressor of choice for many anesthesiologists.[42] Its mixed α- and β-adrenergic effects cause an increase in arterial blood pressure that is secondary to increased cardiac output and increased peripheral vascular resistance.

Traditionally, ephedrine has been the vasopressor of choice in pregnant women, on the basis of observations in pregnant sheep that showed that it was more effective for increasing arterial pressure with better preservation of uteroplacental blood flow compared with other vasopressors.[43,44] The use of α-agonists has generally been avoided since the 1970s because of concerns about their potential adverse effect on uterine blood flow. However, in a quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery, Lee and colleagues[45] showed that there was no difference between ephedrine and phenylephrine in efficacy. They did find, however, that women given phenylephrine had neonates with higher umbilical cord blood pH values than women given ephedrine, although the risk of true fetal acidosis (umbilical pH value of 7.20) was similar in both groups. Because acidotic changes in the umbilical arterial pH are sensitive indicators of reduced uteroplacental perfusion,[46] the authors concluded that their finding was indirect evidence that uterine blood flow may in fact be better with phenylephrine compared with ephedrine. In addition, a meta-analysis by Reynolds and colleagues[47] showed that spinal anesthesia for cesarean delivery is associated with lower cord pH, compared with general or epidural anesthesia. They suggested that the use of larger doses of ephedrine in patients who received spinal anesthesia largely contributed to these findings. There are two reasons why phenylephrine may be associated with a better fetal acid-base status than ephedrine. First, ephedrine readily crosses the placenta and has been shown to increase fetal heart rate.[48] Ephedrine may also stimulate fetal metabolism by a direct β-adrenergic effect as well as by stimulating endogenous release of fetal catecholamines. Thus, a direct metabolic effect on the fetus is a likely explanation for the acidosis associated with the use of ephedrine.[49] The second possible explanation for improved fetal acid-base status with phenylephrine compared with ephedrine is that the sympathectomy resulting from regional anesthesia shunts blood into the mesenteric bed and that α-agonists like phenylephrine have a greater selective vasoconstrictive effect on the mesenteric bed than on the uteroplacental vasculature.[50] Vasoconstriction in the mesenteric bed increases cardiac preload, which allows for improved uteroplacental perfusion.[51]

Placental Transfer of Anesthetic Drugs

Many medications administered to a pregnant woman cross the placenta, and these medications may have far-reaching effects on the fetus. Commonly used medications have both direct pharmacologic actions and indirect effects on the in utero environment. After administration of a medication to the mother, a certain amount will cross the placenta and enter the fetal circulation. Drugs cross the placenta by three main processes: simple diffusion, active transport, or pinocytosis. The extent of drug transfer is dependent on numerous factors, including molecular weight, protein binding, degree of lipid solubility, maternal drug concentration, and maternal and fetal pH. The Fick principle governs the rate of transfer of a drug across a membrane:

$$Q/t = \frac{K \times A \times (C_m - C_f)}{D}$$

where Q/t is the rate of diffusion, K is the diffusion coefficient, A is the surface area of membrane available for exchange, $C_m - C_f$ is the concentration gradient between the maternal and fetal circulations, and D is the thickness of the membrane.

Larger molecules are less likely to cross the placenta, but those with weights under 500 daltons will cross easily. Most drugs administered to a parturient in labor have low molecular weights; therefore, they transfer easily to the fetus. Drugs with high lipid solubility will also readily cross the placenta. Highly ionized substances with poor lipid solubility (e.g., nondepolarizing muscle relaxants) have limited transfer.

Once a drug crosses the placenta, fetal pH and protein binding affect drug disposition.[52] The degree of ionization greatly influences drug transfer because only nonionized portions of the drug can cross the placenta.

The degree of ionization of a drug is determined by the Henderson-Hasselbalch equation:

$$PH = pK_a + \log \frac{[base]}{[acid]}$$

where pK_a is the negative logarithm of the acid dissociation constant. The pK_a of a drug is the pH at which it is 50% ionized and 50% un-ionized. Most local anesthetic pK_a values range from 7.7 to 9.1, which is near physiologic pH values. Changes in maternal and fetal blood pH may alter the extent of ionization of a drug and its placental transfer. A phenomenon known as "ion trapping" may occur in a fetus with acidosis because lower fetal pH favors ionization of basic local anesthetics (e.g., lidocaine) and may explain the accumulation of drugs in a compromised fetus.[53]

Because of its unique characteristics, the fetal circulation can have a major impact on drug distribution within the fetus. After drugs cross the placenta, they enter the fetal circulation through the umbilical vein. The liver is the first fetal organ perfused by umbilical venous blood, and substantial hepatic uptake has been described for many drugs. However, approximately 40% of the umbilical venous blood bypasses the liver.[54] Hepatic drug uptake in the fetus may protect the fetus from the deleterious effects of certain drugs on the central nervous system.[55] Dilution of umbilical venous blood across the foramen ovale and ductus arteriosus may also modify fetal drug distribution.

Evaluation of the Fetus

Fetal well-being is of major importance to both the obstetrician and anesthesiologist and should be addressed in the preanesthetic evaluation of the parturient. An understanding of current methods available to evaluate fetal well-being allows better communication with other staff members of the labor delivery suite, especially when faced with emergency situations.

Electronic fetal heart rate (FHR) monitoring was first developed in the 1960s; it allows continuous monitoring during labor onto a paper chart.[56] Continuous FHR monitoring is now routinely used during labor for most women in developed countries. FHR can be monitored externally by surface ultrasound or internally with a fetal scalp electrode. The normal FHR varies between 120 and 160 beats/min. Variability of 5 to 25 beats/min occurs as a result of the opposing effects of the sympathetic and parasympathetic innervation of the atrial pacemaker. Reduced variability may be observed during quiescent phases of the fetal activity cycle (corresponding to "sleep") or be pharmacologically induced by drugs administered to the mother (e.g., meperidine). It also occurs during fetal hypoxia and acidosis.

FHR decelerations are classified according to their timing related to uterine contractions. If they occur in the absence of contractions, they are almost always pathologic. Early decelerations (type I) tend to mirror uterine contractions measured with a tocograph (internal or external) and are generally related to vagal discharge in response to fetal head compression. Variable decelerations vary in both configuration and timing of uterine contractions. These decelerations usually show an abrupt rise and fall and are caused by compression of the umbilical cord. Late decelerations (type II) occur after the peak of the uterine contraction and are an indication of fetal compromise. Fetal scalp blood pH sampling may be used in combination with evaluation of FHR patterns to assess the fetal status in labor. It should be noted, however, that there is not an exact correlation between the severity of fetal hypoxia and the depth of FHR deceleration.[57] In fact, although fetal monitoring is almost always used, it has been suggested that the only clinically significant benefit from continuous FHR monitoring is a reduction in neonatal seizures against an increased rate of instrumental deliveries and cesarean sections.[58] An increase in FHR may also indicate fetal asphyxia, but it may be due to maternal fever or drug effect.

Fetal pulse oximetry is a recent addition to the tools available to monitor the fetus and is still being investigated. A probe is inserted through the cervix and placed between the fetal cheek and uterine wall. To date, investigators have reported a wide range of fetal pulse oximetry values varying between 28% and 71%.[59] Values less than 30% are considered abnormal. Persistently low recordings lead to fetal acidosis.[60] This technology may allow early detection of acidosis when used in combination with continuous FHR monitoring. An American College of Obstetricians and Gynecologists' committee opinion, however, has stated that the Committee on Obstetric Practice "cannot endorse the adoption of this device in clinical practice at this time because of concerns that its introduction could further escalate the cost of medical care without necessarily improving clinical outcome."[61] A recent Cochrane review of randomized control trials of maternal and fetal outcomes when fetal pulse oximetry was employed in labor failed to reduce the overall cesarean section rate. The

authors concluded that a better method to evaluate fetal well-being in labor was required.[62]

Role of Intrauterine Resuscitation

Intrauterine resuscitation (IUR) refers to the application of certain measures in an attempt to improve both oxygen delivery to the placenta and umbilical blood flow for reversal of fetal hypoxia and acidosis. With a better understanding of the mechanisms at play during acute fetal "distress" in labor, specific IUR maneuvers may be applied to individual patients. Short-lived reductions in fetal oxygenation may be a result of aortocaval compression, uterine hyperstimulation, umbilical cord compression, or maternal hypoxemia. Maneuvers used during such situations include left lateral or knee-chest positioning, discontinuation of oxytocin infusion, supplemental maternal oxygen administration, rapid infusion of crystalloid solution, vasopressor administration to treat hypotension, and terbutaline- or nitroglycerin-induced tocolysis.[63] In addition, amnioinfusion may be initiated.

Although few studies have evaluated the use of IUR in a randomized fashion, its application is increasing dramatically. As anesthesiologists, we may become actively involved in IUR, especially during the establishment of regional analgesia and when urgent delivery of the fetus is required by cesarean section or instrumental delivery.[64] The ability to temporarily improve a problematic FHR can often allow the anesthesiologist to use a neuraxial technique in a setting that might otherwise require general anesthesia (e.g., late decelerations in a patient with a Mallampatti Class 4 airway).

Normal Progress of Labor

Labor can be defined as progressive dilatation of the cervix in association with repetitive uterine contractions. This process is illustrated in Figure 69-4. Labor can be either spontaneous or induced, and the activity of the uterus is measured in frequency, duration, and intensity of contractions. Although labor is a continuous process, it has traditionally been divided into three stages. The first stage of labor consists of at least two phases: a latent phase of variable duration (which is defined as the period between the onset of labor and the point at which a change in the slope of cervical dilatation is noted) and a phase of maximal dilatation (which usually begins at approximately 3-cm dilation).[65] During the active phase of labor, uterine contractions occur approximately every 3 minutes, have a duration of about 1 minute, and achieve an intrauterine pressure of 50 to 70 mm Hg. The most commonly used measure of uterine activity by obstetricians, however, is the Montevideo unit, which is defined as the average intensity frequency per 10 minutes. During the normal progress of labor, the cervix should dilate at a rate of approximately 1 cm/hr. When uterine activity is not optimal (contractions < 50 mm Hg every 3 minutes or <250 Montevideo units), an oxytocic drug is usually administered by the obstetrician. The second stage of labor is defined as the interval between full cervical dilation and delivery of the infant. The duration of this second stage is typically 1 to 2 hours, with allowances made for epidural analgesia. The third stage of labor encompasses delivery of the placenta. The

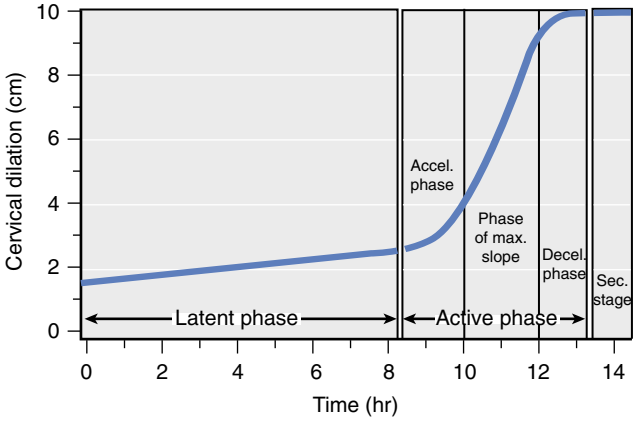

Figure 69-4 Composite of the average dilation curve for nulliparous labor based on analysis of the data derived from the patterns traced by a large, nearly consecutive series of gravidas. (*Redrawn with modification from Friedman EA: Primigravid labor: A graphicostatistical analysis. Obstet Gynecol 6:1567, 1955.*)

progress of labor may be abnormal and can be classified as a slow latent phase, arrest of active phase, and arrest of descent. Table 69-5 lists the diagnostic features of abnormal progress of labor.

The impact of neuraxial analgesia techniques on uterine activity and the progress of labor is a controversial issue. An association between epidural analgesia and cesarean delivery is based on uncontrolled and confounding variables. Actually, women with abnormal labor may have more than expected pain early in labor; therefore, they may require epidural analgesia for what is already a dysfunctional labor with a more frequent risk of cesarean section. Prospective randomized trials evaluated the controversy between epidural and cesarean deliveries; whereas earlier studies did show an association, more recent studies have demonstrated no significant differences between groups in the rate of cesarean delivery.[66] Furthermore, although methodologically limited, several studies of sentinel events that evaluated the impact of the introduction of an epidural service on stable labor and delivery units have failed to demonstrate a change in the cesarean section rate after initiation of an epidural service.[67] A meta-analysis of these sentinel event studies that included more

Table 69-5 Diagnostic Features of Prolonged Labor

Feature	Nulliparas	Multiparas
Slow latent phase	>20 hr	>14 hr
Slow-slope active	<1.2 cm/hr	<1.5 cm/hr phase
Active phase arrest	No cervical dilation for 2 hr	
Slow descent	<1 cm/hr	<2 cm/hr fetus
Arrest of descent	No descent for 1 hr	
Second Stage		
Nulliparous	More than 2 hr without regional analgesia More than 3 hr with regional analgesia	
Multiparous	More than 1 hr without regional analgesia More than 2 hr with regional analgesia	

than 37,000 parturients showed that the sudden availability and high utilization of an epidural service had no effect on the overall incidence of cesarean delivery or on the frequency of cesarean deliveries performed for dystocia.[68]

Anesthesia for Spontaneous Vaginal Delivery

Before deciding on one of the various analgesic options available to the parturient, it is important to understand the mechanisms and pain pathways of labor so that the most appropriate technique of labor analgesia will be utilized.

Pain perception by the parturient is a dynamic process that involves both peripheral and central mechanisms. Many factors have an effect on the degree of pain experienced by a woman during labor, including psychological preparation, emotional support during labor, past experiences, the patient's expectations of the birthing process, and induction or augmentation of labor with oxytocin. An abnormal presentation (e.g., occiput-posterior) may also cause early labor pain to be more intense. There is, however, no doubt that for most women, childbirth is associated with very severe pain, and it often exceeds all expectations.[69] In fact, as reported on the McGill pain questionnaire, labor pain is one of the most intense pains that a woman can experience, and it is typically worse than a toothache, back pain, and pain associated with a deep laceration (Fig. 69-5). A study of women in the first stage of labor reported that 60% of primiparous women described the pain of uterine contractions as being "unbearable, intolerable, extremely severe, or excruciating."[70]

During the first stage of labor, pain impulses arise primarily from the uterus. Uterine contractions may result in myometrial ischemia, which ultimately causes the release of bradykinin, histamine, and serotonin. In addition, stretching and distention of the lower uterine segment and cervix may stimulate mechanoreceptors. These noxious impulses follow the sensory nerve fibers that accompany sympathetic nerve endings; they travel through the paracervical region and the hypogastric plexus to enter the lumbar sympathetic chain.[71] These stimuli enter the spinal cord at the T10, T11, T12, and L1 spinal segments. Parturients describe this pain as dull in nature and often poorly localized. With onset of the second stage of labor and stretching of the perineum, somatic afferent nerve fibers transmit impulses through the pudendal nerve to the spinal cord at the S2, S3, and S4 levels (Figs. 69-6 and 69-7).

Analgesia for Labor and Vaginal Delivery

A variety of labor analgesia options are available, including psychoprophylaxis, transcutaneous electrical nerve stimulation (TENS), systemic medication, inhalational techniques, and neuraxial blocks. In addition, other regional techniques such as caudal or paracervical block are used infrequently.

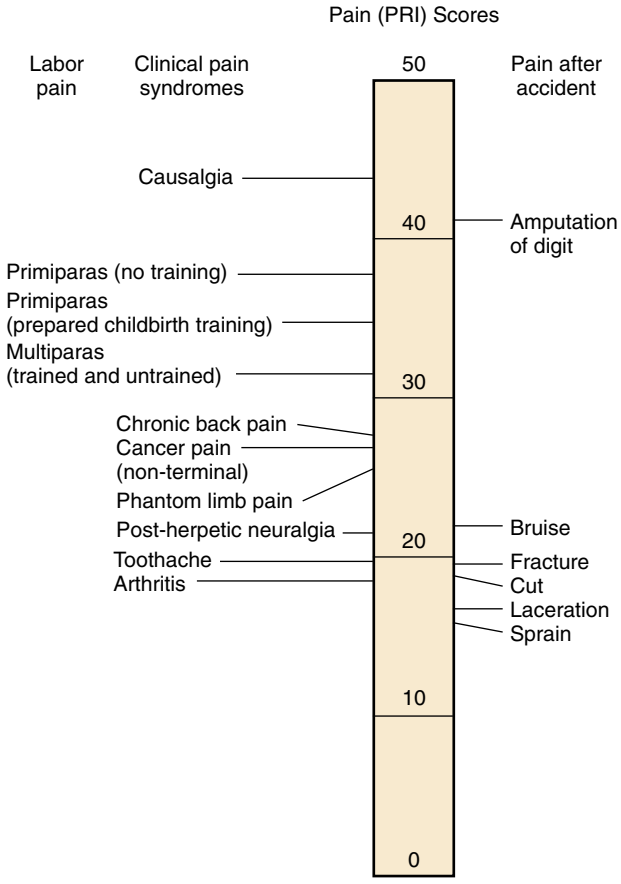

Figure 69-5 McGill pain questionnaire comparing pain scores for women in labor and those of patients in a general hospital pain clinic and emergency department for 20 conditions. (*Redrawn from Melzack R: The myth of painless childbirth. The John J. Bonica Lecture. Pain 19:321-337, 1984.*)

Psychoprophylaxis

"Natural childbirth" stems from a phrase coined by Grantley Dick-Read in 1933; he believed that childbirth was a painless process that did not need medical intervention if the mother was adequately prepared.[72] The Pavlovian methods of childbirth used in Russia were adapted by the French obstetrician Fernand Lamaze in the late 1950s, and "natural childbirth" was popularized as an option for parturients. This method focuses on teaching the mother conditioned reflexes to overcome the pain and fear of childbirth. It also uses an education program, human support during labor, breathing techniques, relaxation techniques of voluntary muscles, a strong focus of attention, and specific activities to concentrate on during contractions to block pain. Indeed, even the presence of another woman during labor to support the expectant mother has a positive effect on outcomes, including the duration of labor.[73]

Transcutaneous Electrical Nerve Stimulation

TENS is thought to reduce pain by nociceptive inhibition at a presynaptic level in the dorsal horn by limiting central transmission (see Chapter 58). Electrical stimulation preferentially acti-

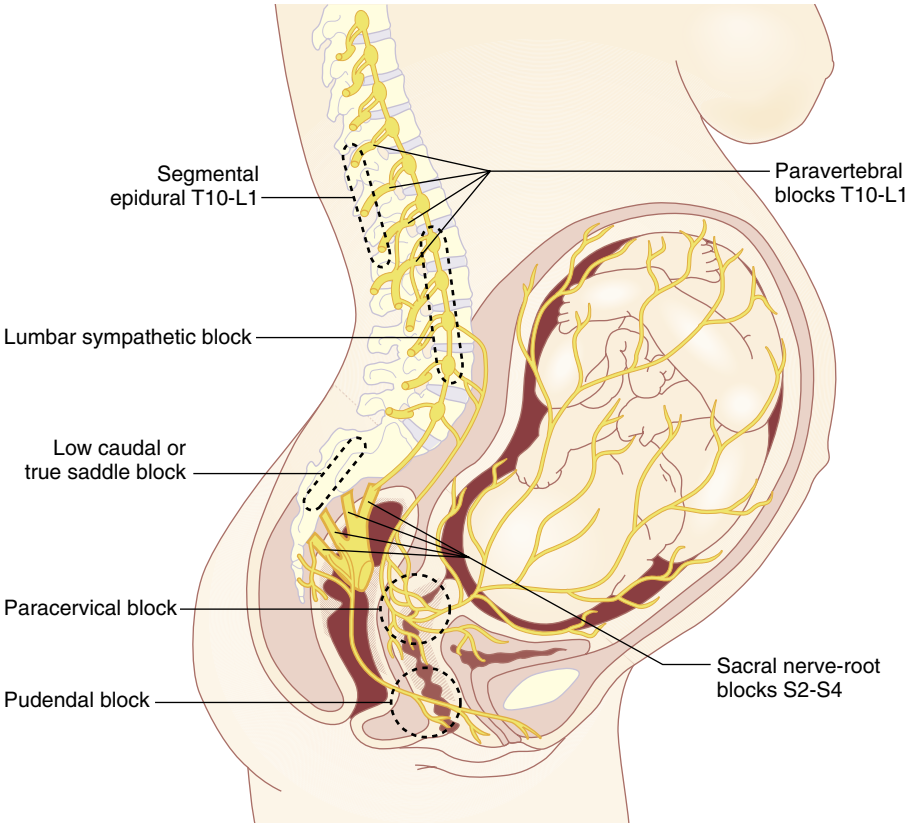

Figure 69-6 Pathways of labor pain illustrating the nerve pathways responsible for pain in the various stages of labor and the types of blocks that can block nerve impulse transmission through these pathways to alleviate labor pain. (*Redrawn from Eltzchig HK, Lieberman ES, Camann WR: Regional anesthesia and analgesia for labor and delivery. N Engl J Med 348:319, 2003.*)

vates low-threshold myelinated nerves. Afferent inhibition effects inhibit propagation of nociception along unmyelinated small c fibers by blocking impulses to target cells in the substantia gelatinosa of the dorsal horn. TENS is also thought to enhance release of endorphins and dynorphins centrally.[74] Placement of electrode pads over the lower back region in the distribution of T10-L1 may provide some analgesia for parturients in early labor.[75] However, Tsen and colleagues could not demonstrate its effectiveness for labor analgesia or as an adjunct to epidural analgesia.[76]

Systemic Medication

Opioids are the most commonly used class of drugs for systemic medication in laboring women (see Chapter 27). All opioids have various degrees of side effects, including respiratory depression, nausea, and vomiting, as well as mental status changes ranging from euphoria to excessive sedation. All opioids cross to the placental circulation freely because of their physicochemical characteristics, and they may cause respiratory depression in the newborn. However, when used appropriately, systemic opioids can partially alleviate labor pain for short periods. Other systemic drugs used in the treatment of labor pain include sedative-tranquilizers and ketamine.

Meperidine

Meperidine is the most commonly used parenteral opioid analgesic during labor. A recent survey carried out in the United States examined the use of parenteral opioids in obstetric units and reported their use in 39% to 56% of patients. In units with over 1500 deliveries per annum, parenteral opioids were administered to 39% of women; units with 500 to 1500 deliveries and units with under 500 per annum reported use in 56% and 50% of women, respectively.[77] The intramuscular dose ranges from 50 to 100 mg with a peak onset of effect at 40 to 50 minutes; intravenous doses of 25 to 50 mg start to act within 5 to 10 minutes. The analgesic effect lasts up to 3 to 4 hours. Fetal exposure to meperidine is highest between 2 and 3 hours after maternal administration,[78] as shown in Figure 69-8. Meperidine is thought to cause less respiratory depression in the neonate than morphine does; therefore, it is more commonly used.[79] It may, however, cause loss of beat-to-beat variability of FHR tracings.

A meta-analysis failed to prove that other tested opioids (tramadol, meptazinol, diamorphine, pentazocine, nalbuphine, and butorphanol) were superior to meperidine for labor analgesia[80]; however, some investigators have proposed fentanyl and remifentanil as superior choices.[81,82]

Fentanyl

Fentanyl is an alternative analgesic option for patients in whom neuraxial anesthesia is contraindicated. Its short half-life makes it suitable for prolonged use in labor, either as an intravenous bolus or as an analgesic administered by means of a patient-controlled analgesia delivery system.[83] It provides reasonable levels of analgesia with minimal neonatal depression.[84] Although it is a potent opioid, its use in labor has been limited by side effects and short duration of action. Fentanyl crosses the placenta; one study that evaluated intravenous fentanyl for labor reported that 4 of 11 fetuses whose mothers received fentanyl for analgesia during labor required naloxone treatment.[85] The usual dose of fentanyl

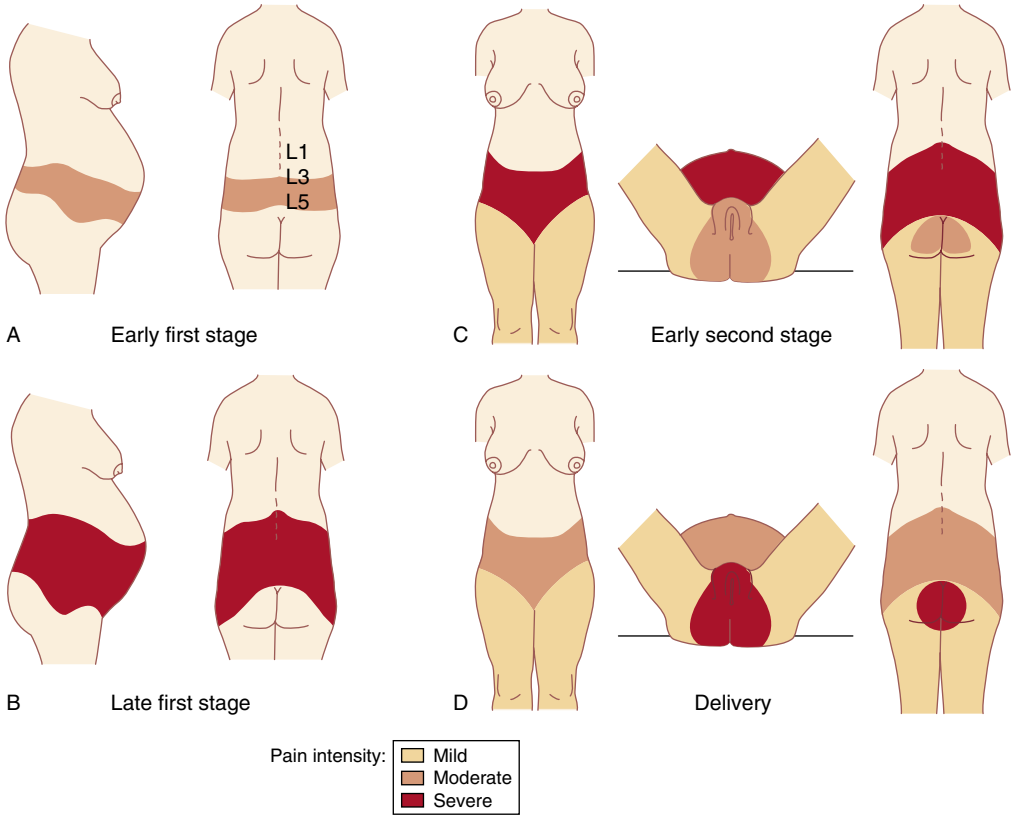

Figure 69-7 Distribution and intensity of labor pain during each stage of labor and delivery. In the early first stage (**A**), pain is referred to the T11 and T12 dermatomes. During the late first stage (**B**), pain also extends to the T10 and L1 dermatomes. In the second stage (**C**), in addition to the dermatomal distribution of late first stage, pain is also felt as pressure in the lower part of the back and perineum and the upper part of the legs. During the end of the second stage and for delivery (**D**), pain originates from the perineum. (*Redrawn from Bonica JJ: Obstetric Analgesia and Anesthesia. World Federation of Societies of Anesthesiologists. Seattle, University of Washington Press. As modified by Bonica JJ: The nature of pain in parturition. In Van Zundert A, Ostheimer GW [eds]: Pain Relief and Anesthesia in Obstetrics. New York, Churchill Livingstone, 1996, p 32.*)

for labor analgesia is 25 to 50 µg intravenously. The peak effect occurs within 3 to 5 minutes and has a duration of 30 to 60 minutes. Although adverse effects, as measured by acidotic umbilical cord blood gases or lower Apgar scores, have not been demonstrated after doses of 1 µg/kg, placental transfer is rapid.[86] A study evaluating fentanyl in labor has suggested that mild maternal sedation is apparent after the administration of 50 or 100 µg. In addition, a transient decrease in FHR variability was also noted.[87] Despite these limitations, several investigators have determined that intravenous fentanyl is preferable to meperidine as a labor analgesic.[84,88] Fentanyl offers another advantage in that it can be administered in nonparenteral modalities, including subcutaneously, orally, and by patch. These uses, however, have not been adequately evaluated in laboring patients.

Butorphanol and Nalbuphine

Butorphanol and nalbuphine are opioid agonist-antagonists that are structurally related to oxymorphone and naloxone. They have the potential advantages of producing less nausea and vomiting than other opioids do. Butorphanol is a κ-agonist and a µ-antagonist and has minimal affinity for σ-receptors. Its dose is 1 to 2 mg intramuscularly or intravenously, and it has a duration of action of up to 4 hours. Nalbuphine is a partial κ-agonist and a potent µ-antagonist with minimal σ-receptor activity. A dose of 10 mg intramuscularly or intravenously is equivalent to 10 mg of morphine with an onset of 2 to 3 minutes and 10 to 15 minutes for the intravenous and intramuscular routes, respectively. It can offer analgesia for up to 6 hours.

One advantage of these agents over µ-agonists is that they demonstrate a "ceiling effect" whereby increasing doses do not produce further respiratory depression.[89] Unfortunately, the use of these drugs is limited in clinical practice because they are rapidly transferred across the placenta and have produced ominous sinusoidal FHR patterns.[90,91] Although it appears that this FHR pattern is a "false positive" and does not signify life-threatening fetal jeopardy as is usually associated with such a pattern, obstetricians are loathe to allow a drug to be used that might produce such a potentially devastating FHR tracing. The use of antagonists or agonist-antagonists may precipitate acute withdrawal syndrome in the mother and the newborn of an opioid-dependent parturient. This syndrome has been reported after parenteral or neuraxial routes of administration.[92]

Remifentanil

Remifentanil is a potent, short-acting µ-opioid receptor agonist that has been approved for clinical use in the United States since 1996. It is a piperidine derivative with a normal opioid configuration, but it contains an ester linkage that allows metabolism by nonspecific esterases throughout the blood and muscles. This metabolism gives it a unique pharmacologic profile in compari-

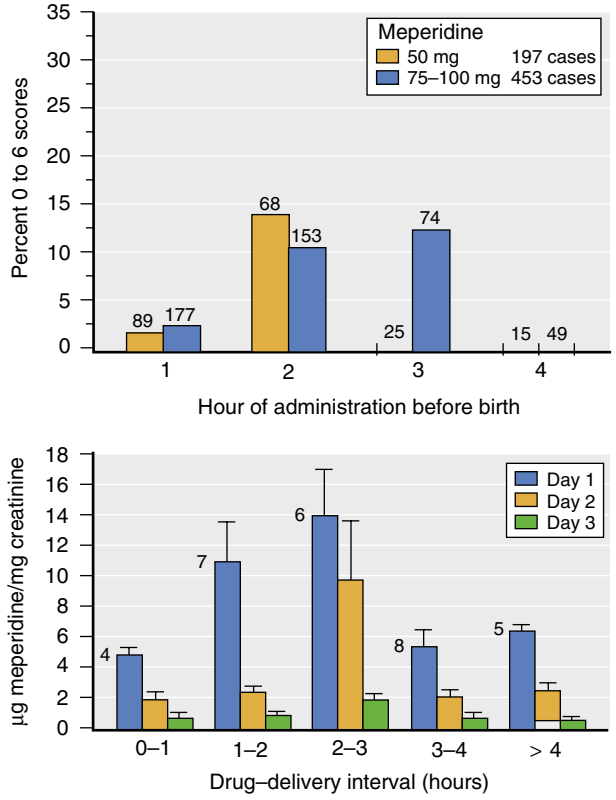

Figure 69-8 Effect of time of administration of meperidine before delivery on neonatal depression (Apgar scores of 0 to 6). (*Redrawn from Shnider SM, Moya F: Effects of meperidine on the newborn infant. Am J Obstet Gynecol 89:1009-1015, 1964.*)

son to other opioids. Consequently, remifentanil has an extremely rapid plasma clearance and offset of action. Its estimated half-life is 1.3 minutes,[93] and prolonged administration does not appear to cause accumulation of this drug. Studies have demonstrated an umbilical vein–to–maternal artery ratio of 0.88.[81] Thus, fetal exposure to the drug is minimized because of its rapid metabolism or redistribution, or both. These properties make it an attractive alternative systemic analgesic in parturients in whom regional anesthesia is contraindicated. Data in the literature from both case series and randomized trials are accumulating with regard to the use of remifentanil in obstetric anesthesia.[82,94] Dose-response studies using patient-controlled analgesia with intravenous remifentanil suggest that a median effective bolus dose of 0.4 µg/kg with a lockout time of 1 minute[95] or a continuous infusion of remifentanil at 0.05 µg/kg/min with a bolus of 25 µg and a lockout time of 5 minutes provides satisfactory labor analgesia.[82] Prolonged use for 34 hours has also been reported in a parturient with medical complications in whom regional techniques were contraindicated; no adverse effects occurred.[96] The studies in which remifentanil was administered, performed thus far, have not fully answered whether remifentanil will provide obstetric anesthesiologists with a superior systemic opioid analgesic for parturients.[97] Although preliminary reports have been promising, it is still somewhat premature to advocate the use of remifentanil until larger studies have fully evaluated its safety and optimum administration technique and dosing.

Sedative-Tranquilizers

Sedative-tranquilizers, including barbiturates, phenothiazines, hydroxyzine, and benzodiazepines, have been used for sedation, anxiolysis, or both during early labor and before cesarean delivery (see Chapter 28). Although barbiturates such as secobarbital were once popular, they are currently unfashionable because of antianalgesic effects in the mother and prolonged depressant effects in the neonate. Even with small doses of barbiturates that result in no depression of the Apgar score, the newborn's attention span may be depressed for more than 4 days.[98]

Promethazine is the most commonly administered phenothiazine in obstetrics. Used with meperidine, it can be given in doses of 25 to 50 mg to prevent emesis. Its ability to potentiate the analgesic effects of opioids, however, is in doubt.[99] Promethazine appears in fetal blood within 1 to 2 minutes after intravenous injection in the mother and reaches equilibrium within 15 minutes.[100]

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that produces dissociative anesthesia and has been used in pregnant patients. As a phenylcyclidine derivative, its mechanism of action may be mediated by an interaction with phencyclidine receptors located in the limbic and corticothalamic areas of the brain. Some evidence, however, suggests that NMDA antagonism is central to the effects of ketamine. Ketamine has been used in subanesthetic doses (0.5 to 1 mg/kg or 10 mg every 2 to 5 minutes to a total of 1 mg/kg in 30 minutes) during labor.[101] In addition to its use in labor, ketamine in a dose of 25 to 50 µg can be used to supplement an incomplete neuraxial blockade for cesarean section. Its main disadvantages are the potential for hypertension and emergence reactions. High doses (>2 mg/kg) can produce psychomimetic effects and increased uterine tone, which may cause low Apgar scores and abnormalities in neonatal muscle tone.[102]

Benzodiazepines such as diazepam (Valium), lorazepam (Ativan), and midazolam (Versed) can be used as sedatives and anxiolytics in labor. However, these drugs readily cross the placenta, with elimination half-lives as long as 48 hours for diazepam and upward of 120 hours for its main metabolite *N*-desmethyldiazepam.[103] Anecdotal evidence suggests that exposure to benzodiazepines early in utero may result in malformations such as cleft lip.[104] Closer analysis involving first-trimester administration of benzodiazepines shows that most infants were normal at birth and had normal postnatal development.[103] The use of these drugs during labor will obviously have no effect on fetal malformations, but they may be associated with other problems in the neonate, including sedation, hypotonia, cyanosis, and impaired metabolic responses to stress. In addition, because these drugs are potent amnestic agents, a parturient may not be able to remember her birthing experience.[105] Many of the adverse effects can be reversed by the administration of flumazenil, which is a competitive benzodiazepine receptor antagonist.

Inhaled Analgesia

Inhaled analgesia can be defined as the administration of subanesthetic concentrations of inhaled anesthetics to relieve pain during labor. This pain relief technique should not be confused with inhaled anesthesia that produces unconsciousness and loss of protective laryngeal reflexes. Although inhaled analgesia provides a limited amount of pain relief, it is not adequate to provide

sufficient pain relief for most mothers. It may, however, have a place as an adjunct to neuraxial techniques or in parturients in whom regional anesthesia is not possible. Inhaled analgesics can be administered either intermittently (during contractions) or continuously. They can be self-administered, but the patient should have a health care provider present to ensure an adequate level of consciousness and proper use of the equipment. Although inhaled analgesics continue to be used in parts of Europe as well as developing countries, they are seldom used for labor analgesia in the United States and scavenging of gases remains a concern.

Entonox (50:50 N_2O/O_2 mixture) has been used for many years as both a sole analgesic and an adjuvant to systemic and regional techniques for labor. Associated side effects include dizziness, nausea, dysphoria, and lack of cooperation. The maximum analgesic effect occurs after 45 to 60 seconds, and it is therefore important that the parturient use Entonox at the early onset of her contractions and discontinue its use after the peak of the contraction. The lack of scavenging systems in labor rooms may theoretically put staff at risk of exposure to excessive levels over a prolonged period. The administration of nitrous oxide and oxygen in a 50:50 combination appears to have no effect on hepatic, renal, cardiac, or pulmonary functions. A recent meta-analysis by Kronberg and Thompson[106] concludes that inhaled nitrous oxide relieves labor pain to a significant degree in most patients but does not provide complete analgesia for many. The analgesic effect of nitrous oxide does also seem to be dose dependent, which supports its analgesic efficacy during labor.

Desflurane (0.2%), enflurane, and isoflurane (0.2% to 0.25%) have also been used to provide labor analgesia, but their effectiveness is comparable to that of nitrous oxide. More recent studies suggest sevoflurane as an effective labor analgesic. An inspired concentration of 0.8% appears to be acceptable and effective for labor analgesia. Sevoflurane, when compared with Entonox, provided superior pain relief but with more intense sedation, without adverse effects and which was acceptable to mothers.[107-109] The use of these volatile analgesics, however, is limited by drowsiness, unpleasant smell, and high cost. The major risk when using volatile analgesics is accidental overdose resulting in unconsciousness and loss of protective airway reflexes.

Regional Analgesia

A variety of regional techniques are used in obstetric anesthesia to provide optimal analgesia with minimal depressant effects on the mother and fetus (see Chapters 51 and 52). These techniques are the most effective means of providing analgesia for labor and delivery. Regional techniques present the most flexible, effective, and least depressant options when compared with parenteral and inhalation techniques. Regional analgesia does not produce drug-induced depression in the mother or fetus. The most commonly performed regional techniques for labor are epidural, spinal, and combined spinal-epidural blocks. Less frequently, lumbar sympathetic blocks are performed.[110] Paracervical, pudendal, and local perineal infiltration techniques are occasionally performed by the obstetrician. Each technique has advantages and disadvantages and can be used to block pain transmission during parturition.

Patient Evaluation and Preparation

It is important to assess all patients before placement of a regional block by obtaining a focused medical and obstetric history, performing a clinical examination, and evaluating the airway. The use of herbal medications by the general population is gaining in popularity,[111] and obstetric patients are no different. A 7.1% incidence of herbal remedy use by parturients after 20 weeks' gestation has been reported.[112] Preparations containing garlic, ginkgo, ginseng, ginger, and feverfew may have anesthetic implications.

The obstetric plan and fetal well-being should be noted during this preoperative assessment. Informed consent must be obtained, and the anesthesiologist should explain the procedure and the potential complications of the technique. A retrospective study of patients' satisfaction with labor analgesia and their attitude toward the consent process revealed that distress during labor did not interfere with the women's ability to understand the information associated with the consent process before epidural placement. Furthermore, patients thought that the most valuable information received was either from the anesthesiologist who placed the epidural or from an antenatal course. Patients also wanted to know about the potential complications with the greatest morbidity and mortality before consenting.[113] A full check of emergency equipment should be performed to ensure the immediate availability of resuscitative drugs and equipment. An intravenous infusion should be started, and appropriate maternal and fetal monitoring should be in place before starting the procedure.

Epidural Analgesia

Lumbar epidural analgesia offers a safe and effective method of pain relief during labor. It is versatile and may be extended to provide anesthesia for instrumental or operative delivery. Low doses of local anesthetic or opioid combinations are administered (usually by infusion) to provide a continuous T10-L1 sensory block during the first stage of labor. Further supplementation may be required during the late first stage and second stage to achieve a sacral block. The benefits of epidural analgesia include effective pain relief without appreciable motor block, reduction in maternal catecholamines, and a means to rapidly achieve surgical anesthesia. Despite numerous relative contraindications, there are very few absolute contraindications to neuraxial analgesia. Such contraindications include patient refusal, overt maternal coagulopathy, frank infection at the needle site, and maternal hemodynamic instability. Other high-risk conditions, such as fixed cardiac output states (critical aortic stenosis), must be considered on a case-by-case basis, thereby allowing a risk-benefit analysis for each patient.

The use of ultrasound as aid when performing regional blocks and indeed for epidural placement is increasing (see Chapter 53). Ultrasound imaging of the lumbar spine can aid identification of necessary landmarks for epidural placement and estimate the depth of the epidural space in the pregnant patient. It may be especially beneficial in the obese parturient or in patients known to have previous difficult epidural placement.[114]

Epidural Test Dose

The issue of whether a test dose is needed when administering labor epidural analgesia is controversial. Because ultradilute solutions are commonly used and aspiration is often diagnostic, some authors believe that a test dose is unnecessary.[115] However, because catheter aspiration is not always predictive (especially when using a single-orifice epidural catheter), others maintain the importance of a test dose to improve detection of intrathecal or

intravascular placement of an epidural catheter.[116] Part of the controversy surrounding the testing of epidural catheters involves the use of epinephrine. Epinephrine has been shown to produce a reliable increase in heart rate in volunteers and surgical patients when the epidural has been sited in a blood vessel.[117] However, in a laboring patient, maternal heart rate variability from the pain of uterine contractions may confuse interpretation of the heart rate response, and intravenous epinephrine may have deleterious effects on uterine blood flow.[118] Means to improve the reliability of epinephrine include injecting the dose between uterine contractions and repeating the test dose when the response is equivocal. However, the lack of sensitivity and specificity of the test dose calls into question its usefulness as a diagnostic tool. Leighton and colleagues have described an alternative means of testing an epidural catheter for intravascular placement. They advocate the injection of 1 to 2 mL of air into the epidural catheter while listening over the precordium with the maternal external Doppler monitor for evidence of air.[119] If continuous infusion of dilute local anesthetic is administered and the patient remains comfortable without a motor block, proper epidural catheter placement is ensured. That is, after several hours, if the epidural catheter were intravascular the patient should have inadequate pain relief, and if the catheter were subarachnoid, a solid motor block would develop. Although infusions of ultradilute local anesthetics do not pose a serious threat, such is not true of concentrated local anesthetics used for operative delivery. Some authors have suggested that a test dose is essential for any parturient receiving epidural anesthesia (as opposed to "analgesia").[116] Regardless of the technique used, the safe practice of administering labor epidural analgesia dictates initial catheter aspiration, incremental injections, and continuous monitoring for evidence of local anesthetic toxicity.

Spinal Analgesia

A single-shot subarachnoid injection of local anesthetic or opioid provides effective and rapid onset of labor analgesia (see Chapter 51). It is particularly suitable in very early labor or in a distressed parturient to enable epidural placement under more controlled conditions. Single-shot spinal injections may also be used for instrumental deliveries in women who do not have an indwelling epidural catheter. Although used for routine labor analgesia in some hospitals, this technique does not provide the flexibility of an indwelling catheter. Continuous spinal analgesia with a "macrocatheter" may be considered in cases of accidental dural puncture or very high-risk parturients; it provides excellent analgesia and the assurance of a spinal catheter. This practice may also reduce the incidence of post–dural puncture headache (PDPH) after an accidental dural puncture with an epidural needle.[120] It is imperative to inform all personnel involved in the care of a parturient with a spinal catheter in place to avoid accidental overdose of local anesthetic. Small-bore spinal ("micro") catheters were introduced into clinical practice in the late 1980s and quickly gained popularity because of convenience, fast onset, and the potential for decreased risk of PDPH. However, reports of cauda equina syndrome associated with their use for cesarean section led the U.S. Food and Drug Administration (FDA) to withdraw these microcatheters from clinical practice. Possible explanations proposed for the occurrence of cauda equina syndrome included inadequate mixing of local anesthetic within the intrathecal space and the use of high concentrations of potentially neurotoxic local anesthetic (5% lidocaine) that can result in neural damage.[121,122] Recent work revisiting microcatheters in labor is still ongoing and may provide the necessary safety evidence to allow their reintroduction into clinical practice.[123]

Combined Spinal-Epidural Analgesia

The combined spinal-epidural (CSE) technique is widely used in obstetric practice to provide optimal analgesia for parturients (see Chapter 51). It offers effective, rapid-onset analgesia with minimal risk of toxicity or impaired motor block. In addition, this technique provides the ability to prolong the duration of analgesia, as required, through the use of an epidural catheter. Furthermore, should an operative delivery become necessary, that same catheter can be used to provide operative anesthesia. The onset of spinal analgesia is almost immediate, and the duration is between 2 and 3 hours, depending on which agent or agents are chosen. The duration of spinal analgesia, however, is decreased when administered to a woman in advanced labor versus one in early labor.[124] Patients may have greater satisfaction with CSE than with standard epidurals, perhaps because of a greater feeling of self-control.[125] The original description of spinal labor analgesia involved sufentanil or fentanyl,[126] but the addition of isobaric bupivacaine to the opioid produces a greater density of sensory blockade while still minimizing motor blockade.[127] Originally, 25 μg of fentanyl or 10 μg of sufentanil was advocated, but later studies have suggested using smaller doses of opioid combined with a local anesthetic.[128] For example, many clinicians are now routinely using 5 μg of sufentanil or 15 μg of intrathecal fentanyl. Other studies have suggested that ropivacaine and levobupivacaine can be substituted for intrathecal bupivacaine to provide labor analgesia.[129,130]

The CSE technique has also made ambulation possible for many women receiving neuraxial analgesia. Because of the minimal motor block with this technique, it has been termed "the walking epidural." This term, however, is imprecise because many neuraxial techniques allow ambulation in labor and many women who receive CSE never actually ambulate. In addition to the advantage of rapid onset of pain relief, the CSE technique may reduce the incidence of several potential problems associated with the conventional epidural technique, including incomplete (patchy) blockade, motor block, and poor sacral spread. Another potential advantage of the CSE technique is that early evidence suggests that it may be associated with a significantly reduced duration of the first stage of labor in primiparous parturients.[131,132]

Many methods may be used to perform a CSE block, including (1) epidural catheter insertion followed by spinal needle placement at a lower interspace; (2) an epidural needle beside the spinal needle at the same interspace with the use of specially designed needles; and (3) the most commonly used "needle-through-needle" technique, which involves identification of the epidural space and insertion of a long fine-bore atraumatic (pencil point) spinal needle through the epidural needle until the tip of the spinal needle pierces the dura, as shown in Figure 69-9. Free flow of cerebrospinal fluid (CSF) confirms correct placement, and the opioid, alone or in combination with a local anesthetic, is then injected. After spinal injection, the spinal needle is withdrawn and the epidural catheter is placed 4 to 5 cm into the epidural space via the epidural needle. Side effects of intrathecal opioid include pruritus, nausea and vomiting, and urinary retention. Respiratory depression as a result of cephalad spread of opioid is rare but has occurred when using lipid-soluble opioids. Use of a continuous

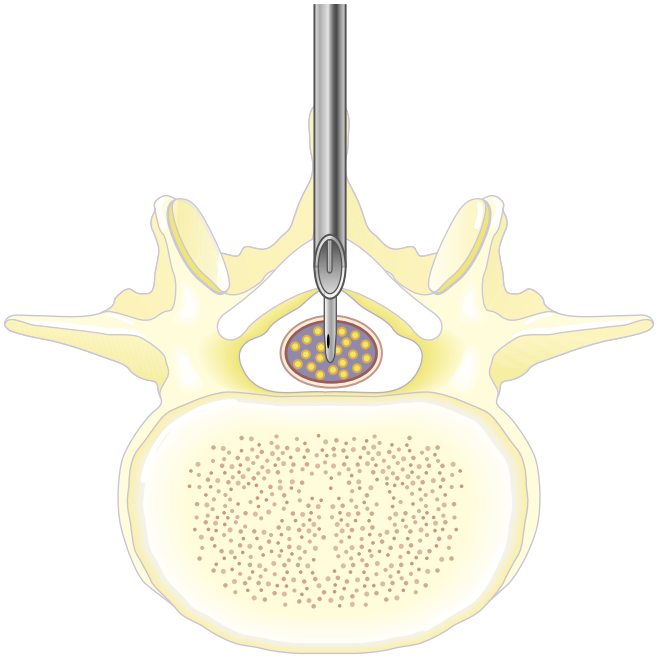

Figure 69-9 Illustration depicting the epidural and spinal spaces during combined spinal-epidural insertion.

epidural infusion of dilute local anesthetic plus opioid (e.g., 0.0625% to 0.1% bupivacaine) provides sensory analgesia without motor block; consequently, it permits many parturients to ambulate during labor. Before ambulation, however, women should be observed for the preceding 30 minutes to ensure maternal and fetal well-being, and they should be assessed for adequate motor function.

An increased frequency of nonreassuring FHR tracings and fetal bradycardia occurs with CSE.[133,134] The etiology of fetal bradycardia after CSE remains elusive, but it may be related to an acute reduction in circulating maternal catecholamine levels after the quick onset of analgesia. In addition, it has been postulated that an imbalance between epinephrine/norepinephrine levels causes unopposed α-adrenoceptor effects on uterine tone and decreases uterine blood flow. However, preliminary reports suggest that there may be no alteration in uteroplacental blood flow.[135]

The resulting fetal bradycardia is usually short in duration and typically resolves within 5 to 8 minutes.[133] A retrospective study of 1240 patients who received regional labor analgesia (mostly CSE) and 1140 patients who received systemic medication or no analgesia demonstrated no significant difference in the rate of cesarean delivery, with rates of 1.3% and 1.4%, respectively. That study also reported that no emergency cesarean deliveries for acute fetal "distress" were necessary in the absence of obstetric indications up to 90 minutes after intrathecal sufentanil administration.[64]

Continuous Epidural Infusion

Most obstetric anesthesiologists now advocate the use of continuous infusions of dilute local anesthetic solutions. Local anesthetics such as bupivacaine, ropivacaine, and levobupivacaine in concentrations ranging from 0.0625% to 0.125% are used either alone or in combination with opioid. The addition of epinephrine may enhance the quality of the analgesia by reducing vascular uptake and systemic absorption of local anesthetics and by a direct agonist effect on α_2 spinal receptors.[136,137] From a parturient's perspective, a continuous infusion offers numerous benefits because it allows for a continuous level of comfort rather than waiting for intermittent epidural top-ups. Typical doses for continuous infusions used for labor analgesia are reviewed in Table 69-6.

Table 69-6 Suggested Dosages for Continuous Lumbar Epidural Analgesia

Drug	Initial Injection	Continuous Infusion
Bupivacaine	10-15 mL of a 0.25%-0.125% solution	0.0625%-0.125% solution at 8-15 mL/hr
Ropivacaine	10-15 mL of a 0.1%-0.2% solution	0.5%-0.2% solution at 8-15 mL/hr
Fentanyl	50-100 µg in a 10-mL volume	1-4 µg/mL
Sufentanil	10-25 µg in a 10-mL volume	0.03-0.05 µg/mL
Epinephrine		1 : 200,000-1 : 800,000 concentration

From Birnbach DJ (ed): Ostheimer's Manual of Obstetric Anesthesia, 3rd ed. New York, Churchill Livingstone, 2000, p 92.

Patient-Controlled Epidural Analgesia

Patient-controlled epidural analgesia (PCEA) is a safe and effective technique. This method of delivery offers equally effective labor analgesia and excellent patient satisfaction. It reduces the total amount of local anesthetic used; consequently, it lessens unwanted effects such as motor block and hypotension. It also reduces the demands on staff on the labor floor, and it gives many parturients a feeling of empowerment. Typically, after analgesia is established by means of either a spinal or epidural block, the catheter is connected to the PCEA device and the patient can then self-administer further boluses as required. Some authors advocate a continuous infusion with patient-controlled top-ups, whereas others suggest a bolus-only technique.[138] Suggested regimens for PCEA settings are outlined in Table 69-7.

Paracervical and Pudendal Blocks

The paracervical block is an alternative technique for a pregnant woman who does not want or cannot receive a neuraxial block. It is a relatively simple block to perform, provides pain relief for the first stage of labor, and does not adversely affect the progress of labor. Local anesthetic is injected submucosally into the fornix of the vagina lateral to the cervix to block nerve transmission through the paracervical ganglion, which lies lateral and posterior to the junction of the cervix and uterus. Because this block does not affect somatic sensory fibers from the perineum, it offers no pain relief for the second stage of labor. Although this technique is still used by obstetricians for nonobstetric surgery, its use in obstetrics has been limited by profound fetal bradycardia, systemic local anesthetic toxicity, postpartum neuropathy, and infection.[139] The cause of this fetal bradycardia appears to be related to decreased uterine blood flow and high fetal blood levels of local anesthetic.[140,141]

The pudendal nerves are derived from the lower sacral nerve roots (S2-S4) and provide sensory innervation for the lower

Table 69-7 Suggested Regimens for Patient-Controlled Epidural Analgesia

	Basal Infusion			Lockout		
Mode	**Epidural Solution**	**Rate (mL/hr)**	**Bolus Dose (mL)**	**Interval (min)**		**Hourly Maximum (mL)**
Demand only	Bupivacaine	0	4	10-20	15-20	0.125%-0.25%
Continuous infusion plus demand	Bupivacaine	4-8	2-4	10-20	15-20	0.0625%-0.125%

From Birnbach DJ (ed): Ostheimer's Manual of Obstetric Anesthesia, 3rd ed. New York, Churchill Livingstone, 2000, p 93.

part of the vagina, the vulva, and the perineum, as well as motor innervation to the perineal muscles. The nerves are easily anesthetized through a transvaginal approach, which is accomplished by depositing local anesthetic behind each sacrospinous ligament.[142] This nerve block provides satisfactory analgesia for vaginal delivery as well as outlet forceps delivery, but it is not useful for labor analgesia. However, it is generally inadequate for midforceps delivery, repair of vaginal lacerations, or exploration of the uterine cavity.[143] Maternal complications from this technique are rare, but include systemic local anesthetic toxicity, infection, and hematoma formation.

Lumbar Sympathetic Blocks

Another nerve block that can be considered an alternative to central neuraxial blocks is the paravertebral lumbar sympathetic technique. This block can be used to impede transmission of pain from the uterus during the first stage of labor.[144] Although it is a technically difficult block to perform, it appears to be associated with far fewer complications than paracervical blockade.

Local Anesthetics

Bupivacaine

Bupivacaine is an amide local anesthetic commonly used for spinal and epidural anesthesia and analgesia in obstetric practice (see also Chapter 30). Its long duration of action, differential sensory to motor block,[145] and relative lack of tachyphylaxis make it a popular choice.

The placental transfer of bupivacaine, as with other amide local anesthetics, is governed by two factors: the degree of ionization at physiologic pH and the extent of protein binding. Bupivacaine has a pK_a of 8.05 (highly ionized at physiologic pH) and is 95% protein bound; thus, it has limited transfer to the placenta when compared with other local anesthetics. The UV/M ratio (the ratio at delivery of the concentration of local anesthetic in blood or plasma from the umbilical vein to the concentration of local anesthetic in maternal blood) for bupivacaine ranges from 0.31 to 0.44 and is much lower than that for lidocaine.[146] In the late 1970s and early 1980s, safety concerns were raised after reports of several deaths related to the cardiovascular or cardiac toxicity of bupivacaine.[147,148] After these reports, the FDA prohibited the use of a 0.75% epidural solution in obstetric practice. Changes in clinical practice have also lessened the risk of inadvertent intravascular local anesthetic injections with the increasing use of multiorifice catheters (which allow greater accuracy of aspiration of heme when the catheters have been placed intravascularly) and the practice of incremental dosing. Bupivacaine consists of two stereoisomers, S^- and R^+, and is marketed as a racemic mixture of these isomers. When separated, the R component was found to contribute to bupivacaine's unwanted toxicity.[149,150] This finding led researchers to develop the use of S isomers for clinical practice, which resulted in the introduction of ropivacaine (the S isomer of the propyl homolog of bupivacaine) and levobupivacaine (the S isomer of bupivacaine).

Lidocaine

Lidocaine has been used for many years in obstetrics. It has a quick onset of action with an intermediate duration of action. UV/M ratios reported in the literature are 0.4 to 0.6.[151] Even though lidocaine is very popular for use as an epidural local anesthetic for operative delivery (2% with epinephrine), it is not popular for labor analgesia because of motor block. Although early reports suggested that lidocaine compromises neonatal neurobehavioral function,[152] numerous follow-up studies have not substantiated this association.[153] Controversy has developed regarding the use of 5% hyperbaric lidocaine for spinal anesthesia because of reports of transient neurologic symptoms. In 1994, the FDA issued a letter concerning 5% hyperbaric lidocaine in which physicians were urged to dilute the lidocaine with saline or CSF before injection. These precautions were subsequently incorporated into the package insert for this drug. More recent data, however, indicate that the 2.5% and 2% solutions may still cause transient radicular irritation.[154] As a result, and despite many years of use without clinical evidence of neurotoxicity, many anesthesiologists have abandoned the use of spinal 5% hyperbaric lidocaine.

2-Chloroprocaine

2-Chloroprocaine is an ester local anesthetic with a rapid onset time and short-lived duration of action. Its rapid metabolism by ester hydrolysis (half-life, 45 seconds) makes it a safe agent for use in obstetrics because almost no drug crosses the placenta.[155] As a result of this property and its speed of onset, its primary role in obstetric anesthesia is for establishment of epidural anesthesia for emergency cesarean section when an epidural catheter is already in place. In addition to its short duration of action, a potential disadvantage of chloroprocaine is that it may interfere with the action of epidurally administered opioids.[156] This interaction with opioids may be due to antagonism at the μ- and κ-opioid receptors.[157] Furthermore, it has been reported that chloroprocaine may also interfere with the action of subsequently administered epidural bupivacaine.[158] Previous preparations of 2-chloroprocaine were considered to be neurotoxic because of reports of arachnoiditis after unintentional subarachnoid injection of this anesthetic.[159] Subsequent reports incriminated the low pH of the anesthetic along with the preservatives used for stabilization.[160] Replacement of metabisulfite and methylparaben has

eliminated the risk of neurotoxicity. However, caution is advised because despite the availability of preservative-free preparations marketed as MPF (methylparaben free), formulations containing preservatives are still commercially available.[161] Recent reports, in fact, even go so far as advocating the use of spinal chloroprocaine.[162]

Levobupivacaine

Based on data that the cardiotoxicity of bupivacaine was more pronounced with the R-enantiomer, the S-enantiomer (levobupivacaine) was developed for clinical use. Levobupivacaine is a long-acting local anesthetic with a clinical profile similar to that of bupivacaine. Both animal and human volunteer studies have demonstrated a safety profile greater than that of racemic bupivacaine. The lethal dose of levobupivacaine was 1.3- to 1.6-fold higher than that of racemic bupivacaine in most animal studies, thereby providing supportive evidence for the greater safety of levobupivacaine should accidental intravascular injection occur.[163] Like racemic bupivacaine, levobupivacaine crosses the placenta. The UV/M ratio for levobupivacaine was noted to be 0.3 in women undergoing elective cesarean section after the administration of 30 mL of 0.5% levobupivacaine by means of an epidural injection.[164] Levobupivacaine compares favorably with bupivacaine for epidural anesthesia for cesarean section.[164] Assessment of sensory block with 0.5% bupivacaine and 0.5% levobupivacaine demonstrated no difference in adequacy of the block or time taken to reach a surgically adequate block. Similarly, other authors have recently reported that they found no difference with regard to onset or duration of sensory block when patients received either 0.5% levobupivacaine or 0.5% bupivacaine for cesarean section. In addition, the onset and fade-out of sensory and motor blockade, the quality of anesthesia, and muscle relaxation were comparable between the two groups.[165] Levobupivacaine has also been used to provide epidural analgesia for labor. A multicenter study comparing levobupivacaine and bupivacaine reported that these drugs have equivalent analgesic efficacy. In addition, motor blockade was similar between the groups.[166] As with other local anesthetics, recent evidence suggests that fentanyl significantly reduces levobupivacaine requirements for epidural analgesia in labor.[167] Levobupivacaine is not currently being marketed in the United States but is available in many other countries.

Ropivacaine

Ropivacaine is a homolog of mepivacaine and bupivacaine. It was the first S (levo) isomer of a local anesthetic to be marketed. Ropivacaine is less soluble than bupivacaine; therefore, it may be less potent. Although clinical evidence suggests that the two drugs might be similar in potency,[168] minimum local anesthetic concentration (MLAC) studies have found that the analgesic potency of ropivacaine was 0.60 (0.47 to 0.75) relative to bupivacaine. Claims for reduced toxicity and motor block must be considered with differences in analgesic potency kept in mind.[169]

Anesthesia for Cesarean Section

The cesarean birth rate in the United States is now approximately 30% of all live births.[170] Increased use of the procedure has been attributed to the liberalization of indications for fetal "distress" as well as elective repeat cesarean sections.[171] The most common indications for cesarean delivery include "failure to progress," non-reassuring fetal status, cephalopelvic disproportion, malpresentation, prematurity, and previous uterine surgery. Although primary elective cesarean delivery without medical or obstetric indications has been previously considered inappropriate in the United States, a recent National Institutes of Health panel suggested that it should be considered under certain circumstances.[172] The choice of anesthesia for cesarean section depends on the indications for the surgery, the degree of urgency, maternal status, and desires of the patient.

Neuraxial Anesthesia

The use of neuraxial anesthesia has dramatically increased, and data since 1997 suggest that the use of general anesthesia for cesarean section has been steadily decreasing in the United States.[173] Neuraxial anesthesia techniques have several advantages, including a decreased risk of failed intubation and aspiration of gastric contents, avoidance of depressant agents, and the ability of the mother to remain awake and enjoy the birthing experience. In addition, it has been suggested that blood loss is reduced under regional anesthesia for cesarean delivery.[174]

Although epidural, spinal, continuous spinal, and CSE techniques have all been advocated, most straightforward cesarean sections are now performed with single-shot spinal anesthesia, which has been found to be faster, provides a superior block, and is more cost effective, especially as compared with epidural anesthesia.[175]

Spinal Anesthesia

Spinal (subarachnoid) anesthesia offers many advantages for cesarean delivery. It has a very rapid onset and provides a dense neural block. Because of the small doses used, there is little risk of local anesthetic toxicity and minimal transfer of drug to the fetus. In addition, failures (including incomplete or patchy blocks) are very infrequent with spinal anesthesia. Disadvantages of this technique include the finite duration of anesthesia and a higher incidence of hypotension.

Hyperbaric bupivacaine is the most commonly used agent in the United States for spinal anesthesia when performing cesarean sections. Its duration of action of 1.5 to 2 hours is well matched to the duration of surgery in most cases. Although some authors have advocated a sliding scale of doses that depend on patient height, most practitioners now use a set dose of hyperbaric bupivacaine.[176] As noted in Figure 69-10, neither patient height, weight, nor body mass index appears to correlate with block height.[176] Although increasing the dose of spinal anesthetic increases block height,[177] doses above 15 mg significantly increase the risk of complications, including high block, and are not recommended. Spinal hyperbaric bupivacaine is marketed in concentrations of 0.5%, 0.75%, and 1%; however, availability varies from country to country. Although the extent of the blockade does not appear to be greatly affected by concentration,[178] the density of the sensory block may be better with the 0.75% than the 0.5% concentration. However, there seems to be little advantage and potential disadvantage to use of the 1% concentration.

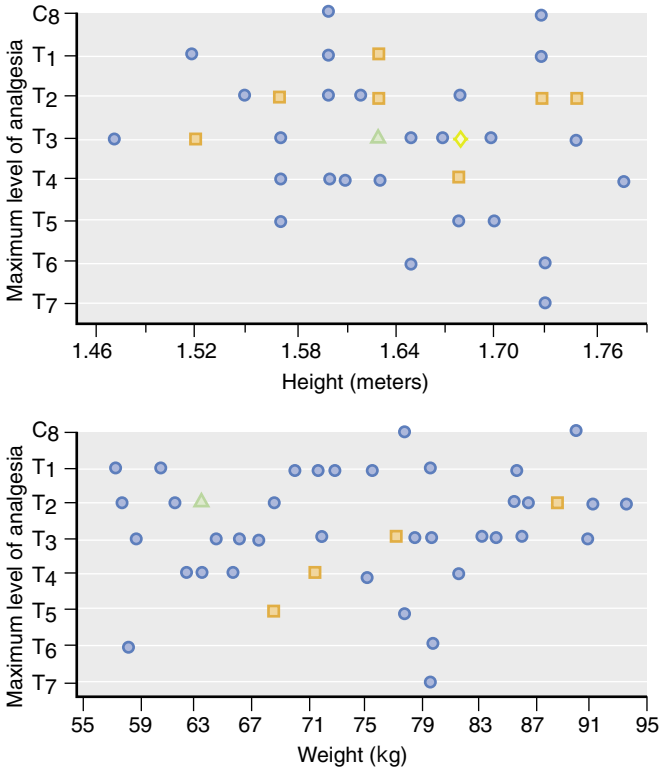

Figure 69-10 Relationship between patient weight and height and block height during spinal anesthesia with 12 mg of hyperbaric bupivacaine in 50 term parturients undergoing cesarean section. *Circles* represent one patient; *squares,* two patients; *triangles,* three patients; and *diamond,* four patients. (*From Shnider SM, Moya F: Effects of meperidine on the newborn infant. Am J Obstet Gynecol 89:1009-1015, 1964.*)

A comparison of 0.75% with 1% bupivacaine found no difference in onset time or quality of block, but an increased incidence of backache was reported in the 1% group.[179]

Spinal anesthesia can be initiated with the patient in either the sitting or the lateral position and with either plain or hyperbaric solutions. Each method has its advantages and disadvantages. The sitting position, however, appears to be optimal for placement of a neuraxial block in an obese parturient.[180] Hyperbaric solutions have the advantage of greater predictability of block height than plain solutions do, and they allow the anesthesiologist the ability to adjust block height by adjusting table position.[181]

Despite achieving an adequate (T4) block, some women under spinal anesthesia will experience some degree of visceral discomfort during cesarean section, particularly in situations in which the obstetrician exteriorizes the uterus. The quality of the spinal anesthesia has been reported to be improved by the addition of epinephrine,[182] morphine,[183] fentanyl, or sufentanil.[184]

Epidural Anesthesia

When flexibility is necessary (e.g., for a potentially prolonged cesarean section), a catheter technique is optimal and an epidural technique is often chosen. In addition, women with an indwelling epidural catheter for labor who require cesarean section usually receive the operative anesthetic through that catheter. In high-risk parturients, epidural catheters are often placed early so that they will be available for emergency cesarean section, again illustrating the importance of continual assessment of epidural catheters and their effectiveness during labor.

The ideal local anesthetic should provide rapid onset of sensory block with an appropriate duration of action. Commonly used agents include 2-chloroprocaine, lidocaine, and bupivacaine. When compared with spinal anesthesia, very large doses of local anesthetic are used to achieve adequate levels for cesarean section. Epidural catheters can migrate, and even negative aspiration of the catheter does not absolutely rule out intrathecal or intravascular placement. Because large volumes of potentially toxic local anesthetic are administered via an epidural catheter for cesarean section, several measures can be used to reduce the risk of local anesthetic toxicity. First, the catheter should be aspirated before use and an appropriate test dose administered. Second, the anesthetic should be administered in fractionated doses. Last, safer drugs (e.g., chloroprocaine and lidocaine) or the newer amide local anesthetics (e.g., ropivacaine and levobupivacaine) should preferably be used.

As with spinal anesthesia, adjuncts can be used to improve the quality of the block. Because local anesthetics are all weak bases and are commercially prepared in an acidic solution, they are ionized and do not readily cross lipid membranes. The addition of small quantities of bicarbonate increases the pH of the solution and the proportion of un-ionized local anesthetic; this practice shortens the time to onset of blockade.[185] The addition of bicarbonate to lidocaine and chloroprocaine clearly shortens their onset; however, not all studies have demonstrated this effect with bupivacaine.[186] In addition, bupivacaine may precipitate when alkalinized, so much smaller doses (0.1 mEq/20 mL local anesthetic) should be used.

Commercially prepared solutions of local anesthetics with epinephrine have a lower pH, so they may have a slower onset time. The addition of epinephrine to the local anesthetic immediately before injection may decrease the time of onset of the block for lidocaine,[187] but this effect does not seem to occur with bupivacaine.[188]

Intraoperative conditions under epidural anesthesia may be improved if fentanyl (50 to 100 μg)[189] or sufentanil (10 to 20 μg)[190] is added to the local anesthetic.

Clonidine has also been used as an additive to epidural local anesthetics, but it has been associated with sedation, bradycardia, and hypotension.[191]

Combined Spinal-Epidural Technique

The CSE technique, first reported as an option for cesarean section in 1984,[192] has recently increased dramatically in popularity. The advantage of this technique is that it provides rapid onset of dense surgical anesthesia while allowing the ability to prolong the block with an epidural catheter. In addition, because the block can be supplemented at any time, the CSE technique allows the use of smaller doses of local spinal anesthetics, which may in turn reduce the incidence of high spinal block and hypotension.[193] Potential problems of the CSE technique for cesarean delivery include an inability to test the catheter, the possibility of a failed

epidural catheter after spinal injection, and the risk of enhanced spread of previously injected spinal drug after use of the epidural catheter.[194] A recent study, however, found no difference in block height.[195] A detailed description of the CSE technique can be found in the section of this chapter on labor analgesia. Additionally, the reader is referred to a comprehensive review of the subject by Rawal and colleagues.[196]

Continuous Spinal Anesthesia

Continuous spinal anesthesia has many potential advantages when compared with single-shot spinal or epidural techniques. The classic technique required the use of large-bore epidural needles; newer techniques use a 32-gauge microcatheter inserted through a 26-gauge spinal needle.[197] The technique rapidly gained in popularity despite technical difficulties, but, as previously described, it was abandoned after withdrawal of these catheters by the FDA. The advantages of continuous spinal anesthesia, however, remain, and macrocatheters (e.g., placing an epidural catheter intrathecally) can be used in high-risk parturients. To perform continuous spinal anesthesia, the anesthesiologist pierces the dura with an epidural needle and then threads the epidural catheter 3 to 4 cm within the intrathecal space. Catheter placement can be tested by aspiration of CSF. Because a catheter is being used, smaller doses can be given in an incremental fashion. Such administration is particularly advantageous in high-risk parturients such as those with cardiac disease, respiratory disease, morbid obesity, and neuromuscular disease. To reduce the risk of headache after this technique, the epidural needle should be turned so that it is parallel to the dural fibers at the time of insertion. In addition, to further reduce the risk of headache, it has been suggested that several steps be taken, including leaving the epidural catheter in situ for more than 12 hours and injecting a bolus of preservative-free normal saline before removal of the catheter.[198]

General Anesthesia

Although the use of general anesthesia for cesarean delivery has dramatically declined during recent decades, it is still necessary for the management of several situations, including maternal hemorrhage, overt coagulopathy, life-threatening fetal compromise, or cases in which a patient refuses regional anesthesia. It has been reported that anesthesia-related maternal mortality associated with regional anesthesia has declined but that the number of deaths involving general anesthesia has remained relatively constant. Thus, the relative risk of fatality during general anesthesia has increased to more than 16 times that for regional anesthesia.[199] General anesthesia has the advantages of speed of induction, control of the airway, and superior hemodynamics. The frequency of the use of general anesthesia is dependent on many factors, including the number of patients who receive epidural analgesia for labor, the percentage of high-risk parturients, and the skills of the anesthesiologist. Although there are no absolute contraindications to general anesthesia, in certain conditions, such as malignant hyperthermia or a patient with a difficult airway, a modified anesthetic technique may be required. Potential problems associated with general anesthesia for cesarean section include failed intubation, pulmonary aspiration of gastric contents, neonatal depression, and maternal awareness. The technique for general anesthesia is outlined in Box 69-1. Although this "cookbook" recipe highlights the basics, it is essential that every anesthesiologist working on the labor and delivery floor be comfortable with the algorithm for the management of failed intubation, as illustrated in Figure 69-11.

Failed Endotracheal Intubation

A study of anesthesia-related deaths in the United States between 1979 and 1990 revealed that the case-fatality rate with general

Box 69-1 Suggested Technique of General Anesthesia for Cesarean Section

1. Administer a nonparticulate antacid. Additional agents such as metoclopramide or an H_2 blocker should be considered in patients at high risk for aspiration or failed intubation.
2. Apply routine monitors, including electrocardiography, pulse oximetry, and capnography. Ensure that suction is functioning and that equipment to correct failed intubation is readily available.
3. Position the patient in a manner to achieve left uterine displacement and optimal airway position.
4. De-nitrogenate with a high flow of oxygen for 3-5 minutes or 4 vital capacity breaths.
5. After the drapes are applied and the surgeon is ready, initiate a rapid-sequence induction with thiopental, 4.0-5.0 mg/kg, and succinylcholine, 1.0-1.5 mg/kg. Apply cricoid pressure and continue until correct position of the endotracheal tube is verified and the cuff is inflated. In hypotensive crises, ketamine, 1.0-1.5 mg/kg, should be substituted for thiopental. A defasciculating dose of muscle relaxant is not necessary.
6. Ventilate with 50% oxygen and 50% nitrous oxide and a volatile anesthetic as necessary. Maintain normocarbia and use muscle relaxation as necessary with either a nondepolarizing muscle relaxant or succinylcholine infusion.
7. After delivery, increase nitrous oxide to 70%, discontinue or reduce the volatile anesthetic, and administer an opioid and a benzodiazepine. Add oxytocin to intravenous fluids.
8. Insert an orogastric tube before completion of surgery.
9. Reverse neuromuscular blockade as necessary at completion of surgery.
10. Extubate when the patient is awake, the anesthesia is adequately reversed, and the patient is following commands.

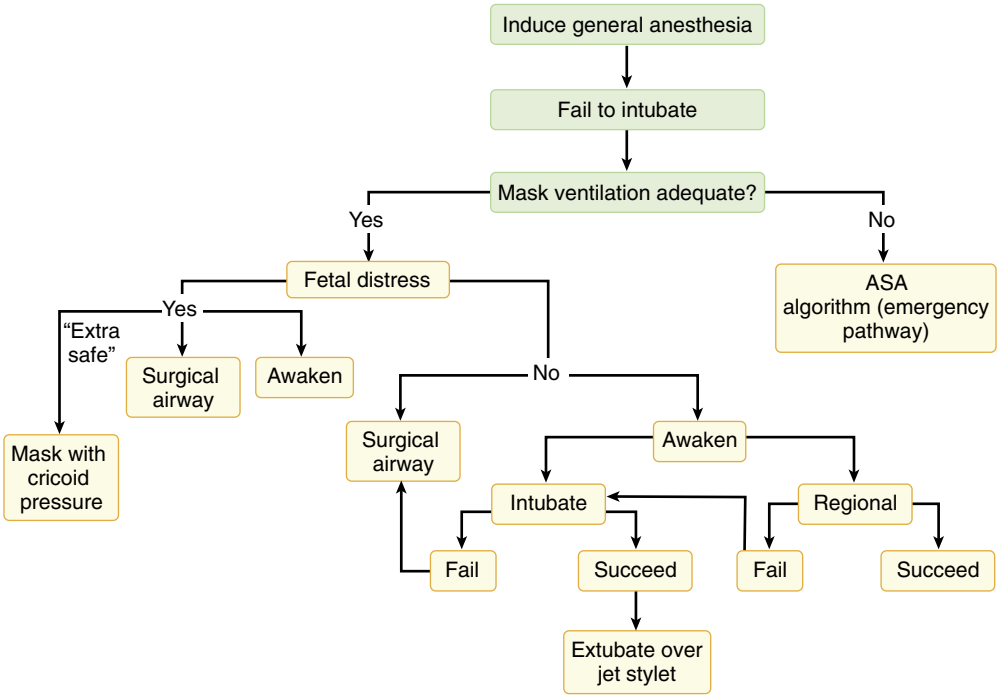

Figure 69-11 Management of failed intubation in pregnancy with reference to the presence or absence of fetal distress. ASA, American Society of Anesthesiologists. (*Redrawn from Reisner LS, Benumof JL, Cooper SD: The difficult airway: Risk, prophylaxis, and management. In Chestnut DH [ed]: Obstetric Anesthesia: Principles and Practice. St Louis, CV Mosby, 1999, p 607.*)

anesthesia was 16.7 times greater than that with regional anesthesia.[199] Most anesthesia-related deaths were due to hypoxemia when difficulty securing the airway was encountered. The most commonly occurring adverse respiratory events are failure to intubate, failure to recognize esophageal intubation, and failure to ventilate (see also Chapter 50). Physical changes associated with pregnancy, including weight gain, enlarged breasts, and oropharyngeal edema, can complicate endotracheal intubation. In addition, certain disease states such as preeclampsia may predispose to failed intubation. Central to decreasing the risk associated with general anesthesia is early assessment of the mother's airway. It has been reported that airway evaluation can often identify a parturient with a difficult airway, but it was not performed in upward of 10% of cases in which maternal mortality occurred.[200] Others have evaluated the risk factors associated with difficult intubation, and it has been suggested that the greatest risks are associated with a Mallampati class 4 airway, a short neck, protruding maxillary incisors, and mandibular recession.[201] From these data, an estimated prediction of a difficult airway has been calculated and highlighted in Figure 69-12. Regardless of the initial assessment, all patients must have a repeat airway examination performed before initiation of anesthesia for cesarean section because it has been demonstrated that labor may be associated with changes in the maternal airway.[202] A recent review of anesthesia-related maternal deaths over an 18-year period illustrated three key points: (1) anesthesia-related deaths from airway factors occurred during emergence and recovery and not during induction of general anesthesia; (2) system errors such as deficiencies in postoperative monitoring and in supervision of junior anesthesiologists contributed to fatalities; and (3) obesity and African American race were highlighted as risk factors for anesthesia-related maternal mortality.[203]

The series of triennial Confidential Enquiries into Maternal Deaths in the United Kingdom have documented numerous cases of maternal mortality associated with general anesthesia[204]; in particular, cases have been associated with difficult intubation and pulmonary aspiration. However, it has been suggested that the continuing downward trend of anesthetic mortality in the United Kingdom is associated with a stable number of general anesthetics.[205] Therefore, factors other than general anesthesia must also play a role.

Complications of Regional Anesthesia

Hypotension

Hypotension is present when systolic blood pressure decreases to less than 100 mm Hg or to more than 20% less than baseline readings, and it occurs in many patients after use of neuraxial anesthesia. The incidence and severity of hypotension depend on the height of the block, the position of the parturient, and whether prophylactic measures were taken to avoid such hypotension. Measures that decrease the risk of hypotension to varying degrees include intravenous administration of fluids, avoidance of aorto-

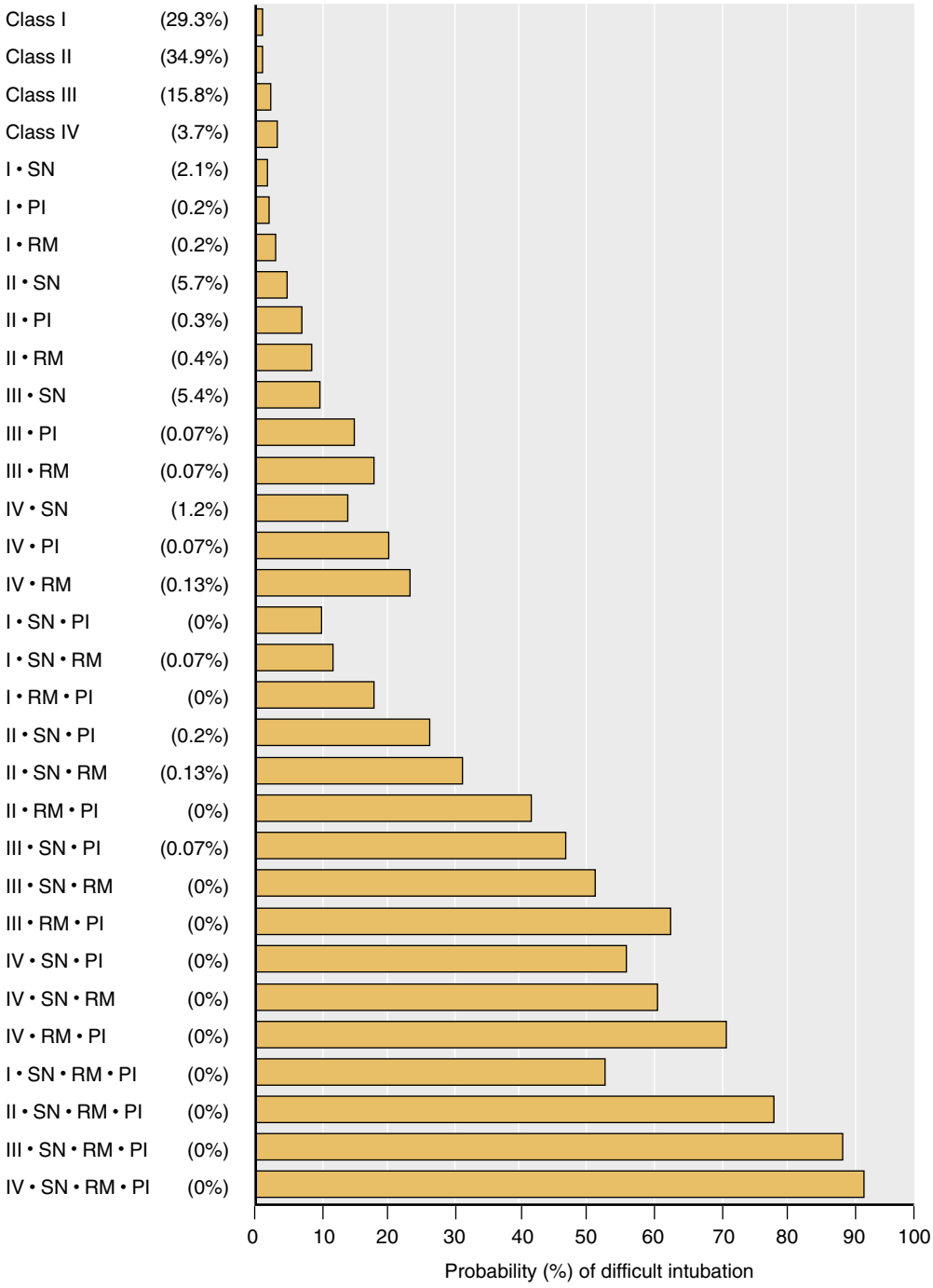

Figure 69-12 Graphic representation of the factors predictive of a difficult intubation. Such factors include Mallampati class, short neck (SN), protruding maxillary incisors (PI), and receding mandible (RM). Data were obtained from 1500 parturients undergoing cesarean section under general anesthesia. Values in parentheses represent observed incidences of risk factor combinations in the series. (*From Rocke DA, Murray WB, Rout CC, et al: Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. Anesthesiology 77:67, 1992.*)

caval compression (left uterine displacement), and vigilant monitoring of blood pressure at frequent intervals after placement of a regional anesthetic. In addition, FHR evaluation is helpful so that any adverse effects on the fetus can be corrected if possible. If recognized and treated promptly, transient maternal hypotension should not be associated with maternal or neonatal morbidity.[206] As previously discussed, although intravenous ephedrine in 5- to 10-mg increments remains the first-line treatment, recent evidence supports the use of phenylephrine.[41] The prophylactic administration of commonly used doses of ephedrine does not appear to be of benefit.[207,208]

Accidental Dural Puncture

A relatively common and problematic complication of epidural placement is accidental puncture of the dura ("wet tap"), which has an incidence of up to 3% (see also Chapter 51).[209] This complication can lead to the development of PDPH in up to 70% of cases.[210] The traditional management of accidental dural puncture is to reposition the epidural catheter at a different interspace. Recently, however, many anesthesiologists have advocated that the epidural catheter be passed into the spinal space to become a continuous spinal technique.[211] This technique establishes rapid and effective pain relief. Analysis of aggregate data from limited retrospective trials demonstrates a significant reduction in the incidence of PDPH and the need for an epidural blood patch in patients who receive continuous spinal analgesia after unintentional dural puncture.[120] In addition, the catheter provides excellent labor analgesia and a route toward almost instant onset of blockade for cesarean section. A recent review of seven cases in which epidural anesthesia was complicated by an unintentional dural puncture suggested that spinal headache could be reduced if five steps were followed: (1) injection of CSF from the epidural syringe back into the subarachnoid space through the epidural needle; (2) insertion of an epidural catheter into the subarachnoid space; (3) injection of preservative-free normal saline through the intrathecal catheter before its removal; (4) administration of continuous intrathecal labor analgesia; and (5) leaving the intrathecal catheter in situ for a total of 12 to 20 hours.[198]

Post–Dural Puncture Headache

As previously mentioned, PDPH will develop in 50% or more of patients after accidental dural puncture with an epidural needle. However, not all postpartum headaches occur as a result of dural puncture. A large analysis reported that headaches occurred in 15% of parturients who did not receive an epidural and in 12% of parturients who had an epidural but did not show evidence of dural puncture.[212] Other causes of headache in the postpartum period include nonspecific headache, migraine, hypertension, pneumocephalus, infection including sinusitis and meningitis, cortical vein thrombosis, and intracerebral pathology. In addition, because coffee and tea intake is so prevalent in our society, one should also consider caffeine withdrawal in the differential diagnosis. PDPH has the typical features of a postural headache that is worsened by standing or straining and relieved by lying down.

Generally, PDPH is initially treated conservatively with increased intake of both oral and intravenous caffeine and analgesics. No evidence, however, has shown that even dramatically increasing fluid intake will cause a greater production of CSF; recently, the use of intravenous fluid has been questioned.

Drugs that have been used to treat PDPH include caffeine, vasopressin, theophylline, sumatriptan, and adrenocorticotropic hormone (ACTH). Caffeine, a cerebral vasoconstrictor, has been used successfully, but the effects appear to be transient.[213] In addition, caffeine treatment seems to be more effective when headaches are the result of smaller rather than larger needles (e.g., spinal rather than wet-tap related). A negative aspect of caffeine treatment is that patients may feel anxious and unable to sleep. In addition, seizures and cardiac arrhythmias have been reported after caffeine administration.[214] Although some of the caffeine is present in breast milk, deleterious effects on the newborn have not been shown.[215] One recent study suggested that intravenous administration of caffeine may be effective for prophylaxis of PDPH.[216] Theophylline, which is also a cerebral vasoconstrictor and is available in long-acting formulations, may be useful in the pharmacologic treatment of PDPH. Unfortunately, the only study to evaluate this drug for PDPH has been published only in abstract form.[217] Sumatriptan, a serotonin agonist with cerebral vasoconstriction properties that is routinely used to treat migraine headaches, has also been used in the treatment of PDPH,[217] although not all studies support its use.[218]

ACTH has likewise been anecdotally reported as a treatment of PDPH.[219] If the symptoms are severe enough to limit a mother's activity or if evidence of cranial nerve involvement is noted, an epidural blood patch should be considered. The epidural blood patch was first described more than 40 years ago, and it continues to be the most effective treatment of PDPH. Although early reports suggested immediate and permanent cure of PDPH after an epidural blood patch, it has recently been suggested that complete success rates are approximately 75% and that the effectiveness of an epidural blood patch is decreased if the dural puncture was caused by a large-bore needle.[220] One study reported that although immediate relief occurred in almost all patients, permanent cure after an epidural blood patch was achieved in only 61%.[221] The success of an epidural blood patch is probably not as simple as the clotted blood obstructing the dural tear. CSF volume replacement is not rapid, yet the headache symptoms resolve almost immediately after injection of the blood. Other explanations for the effectiveness of an epidural blood patch include an increase in CSF pressure and cerebral vasoconstriction.[222] Some controversy has arisen regarding the optimal volume of blood to be injected; however, most practitioners use 15 to 25 mL and stop injection of the blood if severe back pain occurs. Although the incidence of complications (especially back pain) increases with increased volume, it appears that increased volume also increases the success rate.[223]

Radiologic studies using radiopaque dye while performing the blood patch have shown that blood inserted into the epidural space will travel one space below the level of insertion of the epidural needle and up to four spaces above the site.[224]

If inadvertent dural puncture occurs during epidural placement, there is growing evidence that placing a spinal catheter immediately and using continuous spinal analgesia may reduce the incidence of PDPH.[225]

Total Spinal Block

A total spinal block is a rare and life-threatening complication that occurs after excessive cephalic spread of the local anesthetic. It can occur during single-shot spinal anesthesia or as a result of inadvertent intrathecal spread of epidural medication after unintentional dural puncture or catheter migration.[226] Subdural spread of the local anesthetic can also cause a high block[227] characterized by a high sensory level, sacral sparing, and incomplete or absent motor block. Single-shot spinal anesthesia after a failed spinal or patchy epidural may also precipitate total spinal anesthesia.[228] There are several possible mechanisms for high spinal blocks when a spinal block is attempted after a failed epidural block. Expansion of the epidural space may compress the spinal canal and encourage cephalad spread of intrathecal drugs. Rapid transfer of local anesthetic from the epidural space across the dural hole may also occur. In addition, sufficient local anesthetic may be present in the nerve roots to decrease the dose requirements of subsequent spinal anesthesia.[229] In the case of a nonemergency cesarean section when a patchy block is present, several options are possible without resorting to a single-shot spinal block. An epidural catheter can be relocated and the drug titrated through the catheter. Alternatively, a CSE can be placed in which a fraction of the usual spinal dose can be administered; again, the catheter can be used to titrate to a desired level. Other options include repeating a spinal block after waiting for the original block to resolve or converting to general anesthesia.

Neurologic Complications

Neurologic complications after regional techniques in obstetric patients are fortunately rare, and often they are not due to the neuraxial block. They can be classified into three groups: (1) those relating directly to anesthesia, (2) those unrelated to anesthesia, and (3) those in which anesthesia is an incidental but possibly a contributory factor.[230] Neurologic examination of postpartum women has revealed transient postpartum sensory dysfunction in up to 21% of women who did not report any symptoms, and these symptoms were unrelated to regional anesthesia.[231] Neurologic complications are five times more common after childbirth itself than after regional blockade.[232] Most neurologic injuries after delivery that are obstetric in origin may be a result of the instrumentation, nonanatomic positioning during labor, or compression of sacral nerve roots by the fetal head during delivery.

Backache

Low back pain is common after delivery. Many patients believe that back pain is linked in some way to epidural analgesia administered for labor, and the alleged relationship between labor epidurals and postpartum backache has been suggested by two retrospective studies. One study reported new-onset long-term backache in 19% of women who delivered vaginally with labor epidural analgesia and in 10% of women who did not have an epidural catheter in situ.[233] A different group found an 18% incidence of new-onset postpartum back pain in women who delivered with epidural analgesia versus a 12% incidence in those who delivered without it.[234] More recently, however, prospective studies evaluating labor epidural analgesia and postpartum back pain failed to find a significant link between epidural analgesia and back pain. One study reported that the incidence of postpartum backache in women who received epidural anesthesia was equivalent to the incidence in those who did not (44% versus 45%). Further data analysis demonstrated an association of new-onset postpartum back pain with greater weight and shorter stature; postpartum back pain was also associated with a previous history of back pain, greater weight, and younger age.[235] Similarly, another study found no difference in the incidence of long-term low back pain in patients receiving epidural anesthesia for labor and controls who did not.[236]

Central Nervous System Infections

In routine anesthesia practice, the reported incidence of infection after regional anesthesia is extremely low. It is interesting to note that an epidural abscess may form spontaneously in up to 1 in 10,000 patients admitted to the hospital in the United States.[237] Typical signs and symptoms include fever, back pain, and localized infection at the level of the epidural site 2 to 3 days after the procedure.

Serious infectious complications after spinal/epidural analgesia and anesthesia are rare, but they can have devastating sequelae. Infection may be exogenous in origin and be caused by the contamination of equipment or pharmacologic agents or by colonization of the catheter. Endogenous spread may occur from a site of infection elsewhere in the body. There have also been reports of meningitis after spinal anesthesia in which the same phage type of organism (*Streptococcus viridans*) was isolated from the patient and the anesthesiologist who performed the procedure.[238] A recent comprehensive editorial by Reynolds highlights the risks and potential sources of infection associated with neuraxial techniques and discusses protective measures to reduce such potential complications.[239] Despite the lack of national guidelines on infection control precautions for neuraxial techniques in the U.S., most anesthesiologists believe that sterile precautions should be observed at all times.

Spinal and Epidural Hematoma

The incidence of neurologic injury resulting from hematoma associated with neuraxial anesthesia is very low, with estimates of 1 in 150,000 and 1 in 220,000 for epidural and spinal anesthesia, respectively.[240] A review of 61 cases of spinal hematoma associated with spinal or epidural anesthesia reported evidence of hemostatic abnormality in 68% of patients and difficult or bloody placement of needles and catheters in 25% of cases. In 15 of the reported cases the patients received spinal anesthesia, with the remaining 46 receiving epidural anesthesia.[241]

Another risk factor for the development of spinal hematoma is a high-risk parturient who is receiving low-molecular-weight heparin (LMWH). Recent guidelines by the American Society of Regional Anesthesia suggest that neuraxial techniques should be

deferred for 10 to 12 hours in a parturient who has received preoperative LMWH or 24 hours for parturients receiving higher doses of LMWH (e.g., enoxaparin, 1 mg/kg twice daily).[242]

Complicated Obstetric Conditions

Preeclampsia and Eclampsia

Preeclampsia complicates up to 8% of pregnancies.[243] It is the most common condition seen by obstetric anesthesiologists in which an otherwise healthy parturient can become critically ill. The classic triad of preeclampsia includes hypertension, proteinuria, and edema. Certain conditions predispose a woman to preeclampsia. In order of risk ratio, these conditions include homozygous angiotensin T-235, chronic renal disease, antiphospholipid syndrome, chronic hypertension, a family history of preeclampsia, multiple gestation, nulliparity, maternal age older than 40 years, diabetes, and African American race.[244] Preeclampsia has been defined as hypertension occurring after 20 weeks' gestation or in the early postpartum period and returning to normal within 3 months after delivery or onset after 20 weeks' gestation and at least one of the following[245]:

- Proteinuria higher than 300 mg/24 hr
- Oliguria or a serum-plasma creatinine ratio greater than 0.09 mmol/L
- Headaches with hyperreflexia, eclampsia, clonus, or visual disturbances
- Increased liver enzymes, plasma glutathione *S*-transferase-alpha 1-1, or serum alanine aminotransferase or right abdominal quadrant pain
- Thrombocytopenia, increased lactate dehydrogenase (LDH), hemolysis, disseminated intravascular coagulation (DIC)
- Intrauterine growth retardation

Preeclampsia may be classified as mild or severe according to the severity of symptoms and signs as illustrated in Table 69-8. It is misleading to assume a smooth progression from mild disease to severe preeclampsia to eclampsia, because 25% to 40% of patients will have normal blood pressure at the time of their first eclamptic seizure.[246]

In the most recent U.K. report "Why Mothers Die 2000-2002," hypertensive disease is now the fourth leading cause of direct deaths being surpassed by thromboembolic disease, hemorrhage, and deaths associated with early pregnancy, respectively. The report reiterates that "intra-cranial hemorrhage as the single largest cause of death indicates a failure of effective anti-hypertensive therapy."

Key recommendations from this report advocate the use of written guidelines for severe preeclampsia, effective treatment of severe life-threatening hypertension, and early involvement of senior obstetricians and intensive care specialists in the care of women with severe preeclampsia.[247]

Pathophysiology

Despite intensive research, the precise cause of preeclampsia remains unknown, thus making it "the disease of theories." Preeclampsia may be associated with abnormal placentation and failure of the normal invasion of trophoblast cells, thereby leading to maladaptation of maternal spiral arteries.[248] This aberration can result in abnormal villus development and potentially cause placental insufficiency. It has recently been proposed that the secondary pathology in preeclampsia is also linked to endothelial dysfunction and excessive activation of coagulation. This abnormality is accompanied by high circulating levels of fibronectin and endothelin, increased coagulation and fibrinolysis with increased platelet activation, and platelet consumption.[249] Figure 69-13 compares the balance in the biologic actions of prostacyclin and thromboxane in normal pregnancy with the imbalance of increased thromboxane and decreased prostacyclin in a preeclamptic patient. Based on this proposed mechanism, investigators have focused on various treatments to modulate this imbalance. The Collaborative Low-Dose Aspirin Study in Pregnancy (CLASP) trial involved pregnant women randomized to receive aspirin or placebo. Aspirin was not found to confer significant benefit in reducing the incidence of preeclampsia, but it did appear to delay the onset until a later gestational stage.[250]

Several studies have focused on the possible genetic basis of preeclampsia. It is thought that a single preeclampsia gene is unlikely, but that there are probably many modifier genes in conjunction with environmental factors.[251]

Clinical Features

The upper airway may become edematous in a preeclamptic woman and result in the potential for airway compromise or difficulty in intubation, which may be required for induction of general anesthesia, protection of the airway, or treatment of respiratory distress. Pulmonary edema occurs in up to 3% of these patients.[252] Its etiology is multifactorial, with high left atrial and

Table 69-8 Factors That Differentiate Mild from Severe Preeclampsia*

	Mild	Severe
Systolic arterial pressure	<160 mm Hg	≥160 mm Hg
Diastolic arterial pressure	<110 mm Hg	≥110 mm Hg
Urinary protein	<5 g/24 hr Dipstick + or 2+	≥5 g/24 hr Dipstick 3+ or 4+
Urine output	>500 mL/24 hr	≤500 mL/24 hr
Headache	No	Yes
Visual disturbances	No	Yes
Epigastric pain	No	Yes
Right upper quadrant abdominal pain	No	Yes
Pulmonary edema	No	Yes
Cyanosis	No	Yes
HELLP syndrome	No	Yes
Platelet count	>100,000/mm^3	<100,000/mm^3

HELLP, hemolysis, elevated liver enzymes, and low platelet count.
*Not all features need be present in the same patient.
From Birnbach DJ, Gatt SP, Datta S (eds): Textbook of Obstetric Anesthesia. New York, Churchill Livingstone, 2000, p 543.

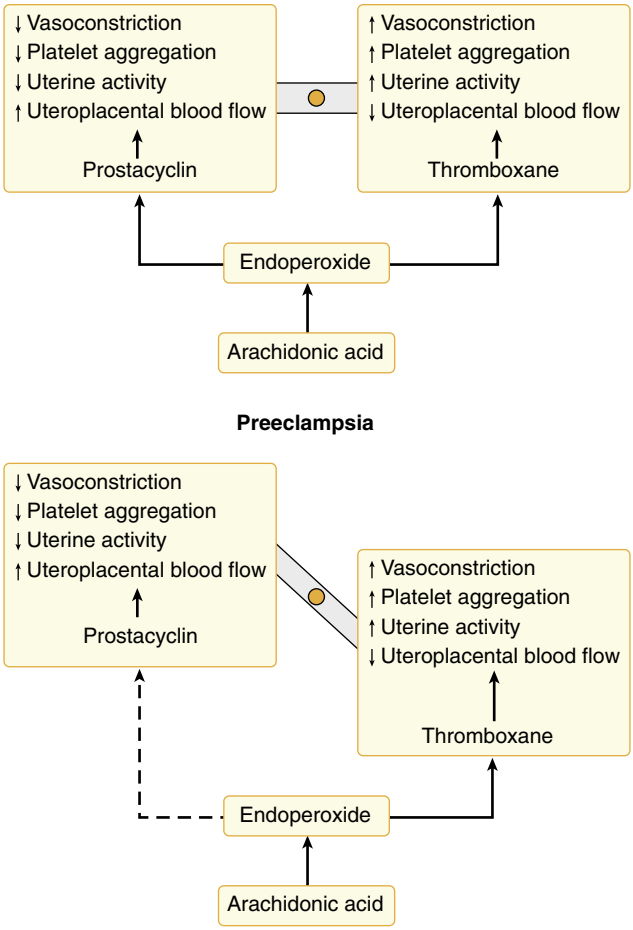

Figure 69-13 Comparison of the normal equilibrium and actions of thromboxane and prostacyclin in normal pregnancy with the dysequilibrium associated with preeclampsia. (*Redrawn from Walsh SW: Preeclampsia: An imbalance in placental prostacyclin and thromboxane production. Am J Obstet Gynecol 152:335, 1985.*)

pulmonary capillary wedge pressure, low plasma colloid and osmotic pressure, and increased capillary permeability often seen.

The cardiovascular effects of preeclampsia may vary. Cotton and colleagues[253] described three subsets of cardiovascular changes in women with severe untreated preeclampsia:

1. Hyperdynamic circulation, high cardiac output, normal to increased systemic vascular resistance (SVR), and normal or slightly decreased blood volume and filling pressures
2. Normal cardiac output and lower filling pressures, but increased SVR
3. Highly elevated SVR, but reduced blood volume and decreased left ventricular function

Figure 69-14 illustrates these hemodynamic subsets in untreated severe preeclampsia.

In preeclampsia, increased uric acid results from decreased renal excretion and reflects tissue ischemia and oxidative stress. Acute renal failure is rare, but it may occur, especially with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) and placental abruption. Hepatic impairment may also occur, but it is usually associated with HELLP syndrome. Liver rupture is a known, rare complication of preeclampsia. High levels of uric acid, LDH, or aminotransferases can be indicative of severe maternal disease.

HELLP Syndrome

As stated, this condition consists of hemolysis, elevated liver enzymes, and low platelets. Its severity ranges from a mild self-limiting condition to a fulminant process leading to multiorgan failure. Considerable debate, however, has centered around the definition, incidence, etiology, and management of this syndrome. Patients with HELLP syndrome may have various signs and symptoms, none of which is diagnostic and all of which may be found in patients with severe preeclampsia/eclampsia without HELLP syndrome.[254] Sibai, noting the lack of consensus regarding the diagnostic features of HELLP syndrome, recommended the following criteria: hemolysis (defined by an abnormal peripheral blood smear and an increased bilirubin level), increased liver enzymes (defined as an aspartate aminotransferase level ≥70 U/L and LDH >600 U/L), and a low platelet count (<100,000/mm^3).[255]

Assuming no other coagulopathy, hemostasis is typically not problematic unless the platelet count decreases below 40,000/mm^3.[256] The rate of fall in the platelet count is also of clinical significance, and regional anesthesia may be contraindicated if the platelet count has dramatically fallen over a short period. The

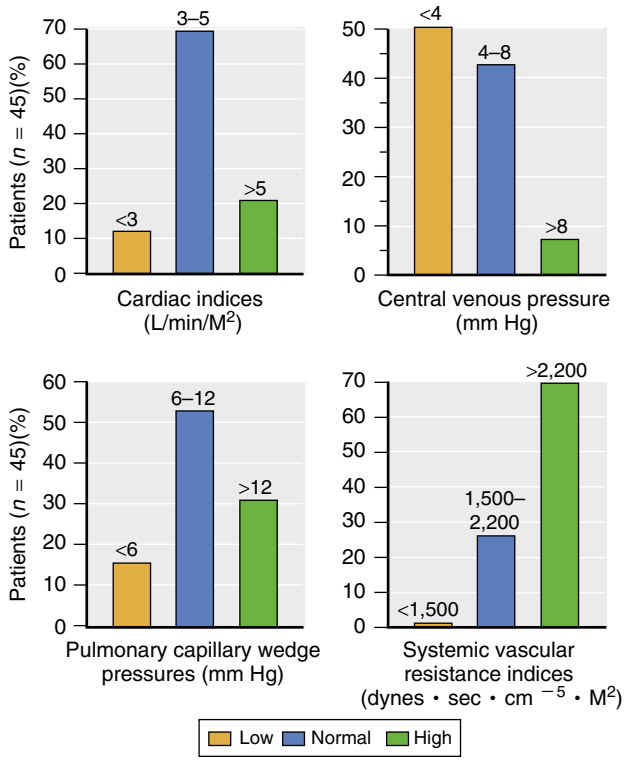

Figure 69-14 Hemodynamic subsets in 45 untreated parturients with severe preeclampsia. (*Redrawn from Cotton DB, Lee W, Huhta JC, et al: Hemodynamic profile of severe pregnancy induced hypertension. Am J Obstet Gynecol 158:523-529, 1988.*)

Table 69-9 Comparison of Properties of Hydralazine and Labetalol for Treatment of Hypertension

Drug	Hydralazine	Labetalol
Mode of action	Vasodilator	α- and β-blocker (1 : 3)
Speed of onset	Gradual	Quick
Dose	5-10 mg IV slowly	10-20 mg IV slowly
Interval	Repeat after 20 min	Titrate to effect
Infusion rate	2 mg/hr up to 20 mg/hr	20 mg/hr to maximum of 160 mg/hr
Effect on heart rate	Compensatory tachycardia	No effect

platelet count usually returns to normal within 72 hours of delivery, but thrombocytopenia may persist for longer periods.

Once preeclampsia is diagnosed, the goal of therapy is prevention and reduction of further complications by taking into account both maternal and fetal factors. Although the only definitive cure is delivery, management of maternal hemodynamics and prevention of the development of eclampsia are key to a favorable outcome for the mother and infant. There is now international consensus that magnesium is the treatment of choice for preeclampsia to prevent eclampsia, but the mechanism underlying its salutary effect remains debatable. Although magnesium is a direct smooth muscle relaxant at relatively high concentrations, it does not significantly reduce systemic blood pressure at the serum concentrations that are efficacious in treating preeclampsia.[257]

Treatment

The mainstay of therapy in preeclampsia is control of hypertension, prevention of seizures, and delivery of the fetus. Hydralazine and labetalol are commonly used as antihypertensives (Table 69-9). Other agents include nitroglycerin, nifedipine, and esmolol. Sodium nitroprusside may also be used, but only in the short term because of a risk of cyanide toxicity in the fetus.

Magnesium sulfate is the drug of choice for seizure control and prevention of recurrent eclamptic seizures.[258,259] The recently published Magpie trial demonstrated the efficacy of $MgSO_4$ in seizure prophylaxis. It reduced seizures by more than 50% and without any serious maternal morbidity.[260] A beneficial secondary effect in some patients may be vasodilatation and an increase in cardiac output by reducing SVR. Initial dosing is 4 g $MgSO_4$ given intravenously over a 10-minute period, followed by a maintenance infusion at 1 g/hr. In the presence of renal failure, the rate of infusion should be modified by evaluating serum magnesium levels. Magnesium has a narrow therapeutic index, with serum levels between 2 and 3.5 mmol/L being safe and effective. Levels should be monitored in conjunction with clinical signs to observe for toxicity (respiratory depression and reduced or absent tendon reflexes). If toxicity is present, 10 mL of 10% calcium gluconate given by slow intravenous injection should counteract its effects.

Anesthetic Considerations

Anesthetic management of a preeclamptic patient includes a detailed preanesthetic assessment that focuses on the severity of the condition, associated features and systemic involvement, evaluation of the airway, fluid status, and blood pressure control. Investigations should include a complete blood cell count, renal profile, and liver function tests. Routine coagulation screening is not recommended by all authors,[261] but if coagulopathy is suspected clinically, coagulation studies should be performed. However, before considering neuraxial analgesia or anesthesia, a recent platelet count should be evaluated. DIC may require the administration of whole blood, platelets, fresh frozen plasma, and cryoprecipitate. Initiation of neuraxial analgesia during DIC is contraindicated.

Although preeclampsia is accompanied by exaggerated retention of water and sodium, hypovolemia may be present because of a shift of fluids and proteins into the extravascular compartment. An inverse relationship between intravascular volume and the severity of hypertension has been demonstrated, and patients with very elevated diastolic pressure can be expected to have negative central venous pressure readings (Fig. 69-15).

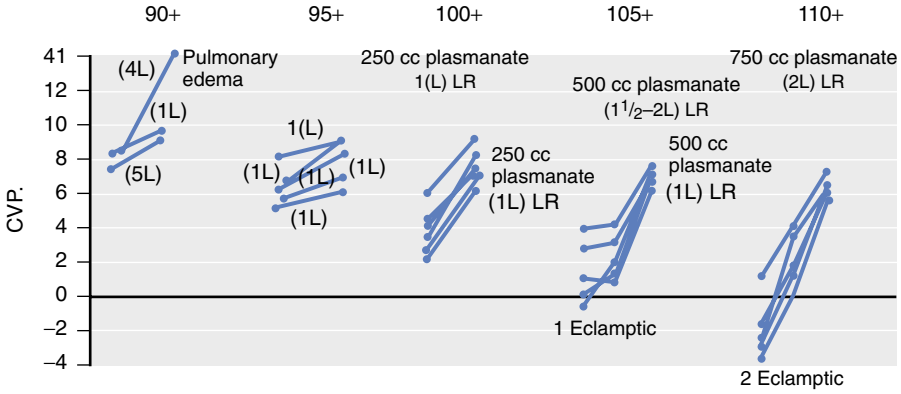

Figure 69-15 Initial central venous pressure (CVP.) readings (three or more recordings of maternal diastolic pressure) and intravascular volume replacement required to attain the range of 6 to 8 cm H_2O in five groups of women with preeclampsia classified according to the severity of the disease (by diastolic blood pressure). LR, lactated Ringer's solution. (*Redrawn from Joyce TH III, Debnath KS, Baker EA: Preeclampsia: Relationship of CVP and epidural analgesia. Anesthesiology 51[Suppl]:294, 1979.*)

Table 69-10 Hemodynamic Variables (Mean and Range) in Preeclamptic Patients and Control Subjects

Variable	Preeclamptic Patients (n = 10)					Control Subjects (n = 4)
	Initial	After Volume Expansion	P*	After Vasodilation	P†	
Diastolic blood pressure (mm Hg)	106 (100-120)	102 (90-120)	NS	85 (75-100)	<.01	77 (70-90)
Mean arterial pressure (mm Hg)	121 (113-136)	116 (103-136)	<.02	102 (97-116)	<.01	95 (93-106)
Heart rate (beats/min)	100 (90-130)	81 (60-110)	<.02	82 (70-100)	NS	84 (70-90)
Pulmonary capillary wedge pressure (mm Hg)	3.3 (1-5)	8 (7-10)	<.01	8 (7-9)	NS	9 (6-12)
Systemic vascular resistance (dyne•sec•cm^{-5})	1943 (1480-2580)	1284 (1073-1600)	<.01	947 (782-1028)	<.01	886 (805-1021)
Cardiac index (L/min/m^2)	2.75 (1.97-3.33)	3.77 (3.26-4.05)	<.01	4.40 (3.94-5.00)	<.01	4.53 (3.96-4.97)

NS, not significant, Wilcoxon signed-rank test (two-tailed).
*As compared with initial values.
†As compared with values after volume expansion.
From Groenendijk R, Trimbos MJ, Wallenberg HCS: Hemodynamic measurements in pre-eclampsia: Preliminary observations. Am J Obstet Gynecol 150:232, 1984.

Careful intravascular volume expansion may result in improved maternal tissue perfusion. As illustrated in Table 69-10, fluid administration is accompanied by a significant increase in pulmonary capillary wedge pressure and cardiac index and a decrease in SVR and maternal heart rate. In the presence of severe hypertension, central venous pressure may not be an acceptable measurement of right-sided preload.

Debate has been ongoing regarding the use of pulmonary artery catheters, and information about their use in the obstetric population is lacking. In 1997, the Pulmonary Artery Catheter Consensus recommended that the pulmonary artery catheter not be routinely used in the management of preeclampsia because of the lack of evidence supporting its use.[262] However, a retrospective study examining the safety and efficacy of pulmonary artery catheters in the management of severe preeclampsia and eclampsia reported a subjective benefit with their use in 93% of cases with a complication rate of 4%. The most common indications for insertion included renal failure (53%), pulmonary edema (30%), and eclampsia (17%).[263]

Epidural labor analgesia in a preeclamptic patient offers the advantage of a gradual onset of sympathetic blockade; it gives cardiovascular stability and avoids neonatal depression. The reduction in vasospasm and hypertension achieved potentially results in improved uteroplacental blood flow. Regional techniques also reduce the risk of airway complications and avoid the hemodynamic alterations associated with intubation. Ramanathan and coauthors reported the use of a CSE technique using 1.25 mg bupivacaine and 25 µg fentanyl in 39 severe preeclamptic parturients for labor analgesia. All patients had adequate analgesia, with a maximum decrease in mean arterial pressure of 16%. No correlation was found between low mean arterial pressure readings and umbilical artery pH values at birth.[264]

Although some authors have suggested that neuraxial anesthesia not be routinely performed in women with severe preeclampsia,[265] data suggest otherwise. A report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy from the National Heart, Lung, and Blood Institute has stated the following:

Neuraxial (epidural, spinal and combined spinal-epidural) techniques offer many advantages for labor analgesia and can be safely administered to the parturient with preeclampsia. Dilute epidural infusions of local anesthetic plus opioid produce adequate sensory block without motor block or clinically significant sympathectomy. When neuraxial techniques are used for cesarean delivery, however, there is a possibility of extensive sympatholysis with profound hypotension which may lead to decreased cardiac output and further diminished uteroplacental perfusion. This may be more likely with single shot spinal anesthesia, which although considered acceptable by some experts, is still considered by others to be relatively contraindicated for women with severe preeclampsia. A recent retrospective analysis, however, suggests that spinal anesthesia can be safely used in the patient with severe preeclampsia undergoing cesarean delivery because the magnitude of declines in maternal blood pressure after spinal and epidural anesthesia appear to be similar.[266] Newer prospective studies support the use of spinal anesthesia in severe pre-eclampsia demonstrating a lesser degree of hypotension when compared to healthy parturients for cesarean section using spinal anesthesia.[267,268] The incidence of hypotension can be reduced by meticulous attention to anesthetic technique and careful volume expansion. In one unblinded study of 80 women with severe preeclampsia randomly assigned to receive epidural, CSE, or general anesthesia, all three regimens appeared equally safe.[269] With general anesthesia, significant hypertension may occur at the time of laryngoscopy, at tracheal intubation, and again during emergence and extubation period. These responses can usually be blocked by appropriate pre-treatment with hydralazine, nitroglycerin, or labetalol. Remifentanil has also been safely used to modify such pressor responses in pre-eclamptic patients undergoing general anesthesia for cesarean section.[270]

Airway edema may be seen in the patient with preeclampsia and may increase the risks of a difficult airway situation, leading to failed intubation and ventilation. Because general anesthesia poses considerably greater risk to parturients than regional anesthesia, the risk of a failed endotracheal intubation

must be weighed against the risk of transient hypotension when deciding between general and regional anesthesia for cesarean delivery for the patients with severe preeclampsia-eclampsia. Although neuraxial techniques have become the preferred method to provide labor analgesia or anesthesia for cesarean delivery among women with severe preeclampsia-eclampsia, they are relatively contraindicated in the presence of coagulopathy. Early consultation with an anesthesiologist is suggested for parturients with severe preeclampsia.[271]

If general anesthesia becomes necessary in a preeclamptic patient receiving $MgSO_4$ therapy, the activity of succinylcholine will be enhanced; there is also enhanced sensitivity to nondepolarizing muscle relaxants. Magnesium offers another advantage in that it blunts the response to vasoconstrictors and inhibits catecholamine release after sympathetic stimulation.

Obesity (also see Chapter 64)

Obesity is an ever-increasing health problem in today's society. Recent data for the United States include prevalence rates for obesity and morbid obesity in nonpregnant women of childbearing age of 28.9% and 8%, respectively.[272] Both ACOG and the most recent Confidential Enquiries into Maternal Deaths (CEMD) report highlight the added risks of obesity and anesthesia.[247,273] Obesity is associated with comorbidities such as diabetes, hypertension, and obstructive sleep apnea. Obese parturients are at greater risk of developing gestational diabetes, preeclampsia, thromboembolic disease, and wound infections. Obesity is an independent risk factor for cesarean section, adverse neonatal outcome, and surgical and anesthetic risk. Exaggerated physiologic changes of pregnancy such as reduction in FRC, increased gastrointestinal reflux, and more pronounced aortocaval compression will have an impact on anesthesia care. Other factors such as difficult venous access, blood pressure monitoring, positioning of the patient, increased risk of cesarean section, and postpartum hemorrhage must also be considered.

Regional anesthesia techniques may prove difficult owing to inability to identify anatomic landmarks easily, and longer spinal or epidural needles may be necessary. ACOG practice guidelines encourage early placement of neuraxial catheters for high-risk patients (including twin pregnancy, difficult airway or obesity) even before a request for labor analgesia.[273] The presence of a "working catheter" may potentially reduce anesthetic and perinatal complications associated with provision of regional or general anesthesia in an emergency situation. Many obstetric anesthesiologists prefer a continuous spinal analgesia/anesthesia technique in obese patients. This can provide greater predictability and reliability, enabling titratable control of both level and duration of block. The incidence of PDPH is significantly decreased in morbidly obese parturients.[274] This may be due in part to the abdominal panniculus acting as an abdominal binder, elevating intra-abdominal pressures and thus reducing the degree of CSF leakage at the dural puncture site.

Many anesthesiologists use a reduced dose of local anesthetic in obese patients owing to a fear of unpredictable and exaggerated spread leading to possible high spinal block. The rationale for reduced local anesthetic dosing requirements includes a decrease in CSF volume with elevated abdominal pressure, thus decreasing the anesthetic solution. Hogan and associates observed a lower average CSF volume in subjects with higher body mass index.[275] A CSE technique for cesarean section may therefore be preferable over single-shot spinal anesthesia. CSE would allow a lower dose of local anesthetic and yet provide the quality of a spinal block with the flexibility of epidural supplementation of the block.

General anesthesia is associated with increased morbidity and mortality, [203,247] owing to factors such as rapid desaturation, increased risk of regurgitation, difficulty in maintaining mask ventilation, difficult intubation and difficulty in ventilating, intraoperative positioning, and prolonged surgery.

A multidisciplinary approach with effective communication and teamwork between obstetricians and anesthesiologists is vital for the care of obese patients. Early referral for anesthetic evaluation and adequate planning for labor and delivery can contribute to reducing anesthesia-related maternal morbidity and mortality.

Obstetric Hemorrhage

Although most patients tolerate the normal blood loss associated with delivery without hemodynamic consequences, occasionally blood loss may be excessive, leading to maternal and fetal compromise. The most common causes of third-trimester bleeding are abruptio placentae, placenta previa, and uterine rupture. Postpartum hemorrhage, which complicates approximately 10% of deliveries, is most often due to uterine atony, retained placenta, placenta accreta, or uterine inversion.

Placental Abruption

Placental abruption, a partial or complete separation of the placenta before delivery of the fetus, is estimated to occur in 1.3% to 1.6% of pregnancies. Figure 69-16 illustrates placental abrup-

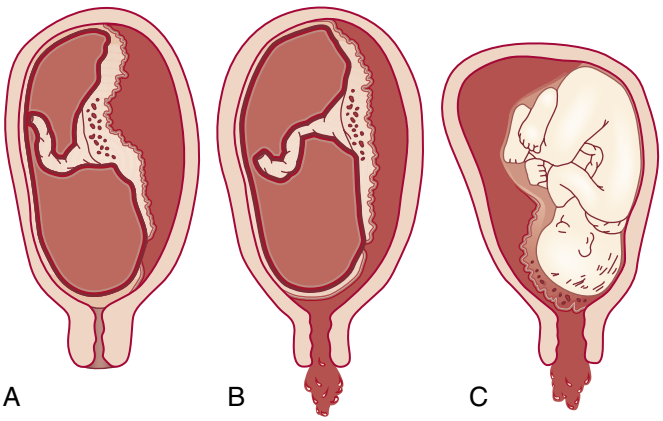

Figure 69-16 Illustration depicting degrees of abruptio placentae. **A,** Concealed hemorrhage. **B,** External hemorrhage. **C,** Complete placental separation. (*Redrawn from Bonica JJ, Johnson WL: Placenta previa, abruptio placentae or rupture of the uterus. In Bonica JJ [ed]: Principles and Practice of Obstetric Analgesia and Anesthesia, vol 2, 1st ed. Philadelphia, FA Davis, 1969, p 1164.*)

tion in its various forms. Certain preexisting conditions such as chronic hypertension, pregnancy-induced hypertension, preeclampsia, maternal cocaine use, excessive alcohol intake, smoking, and a previous history of abruption are all risk factors associated with placental abruption.

Placental abruption may be manifested as vaginal bleeding and uterine tenderness. However, as shown in Figure 69-16, blood loss can often be underestimated because of the potential for substantial hemorrhage concealed behind the placenta. Abruption may be mild, moderate, or severe, depending on the degree of placental separation. DIC may occur with abruptio placentae, and its incidence may be as high as 30% with an abruption large enough to result in fetal death.[276]

Obstetric management depends on the severity of bleeding and fetal status. Large-bore intravenous access should be established on admission and blood samples drawn for baseline hematocrit, coagulation studies, blood typing, and crossmatching. Treatment of associated DIC involves delivery of the fetus and placenta, restoration of maternal blood volume, and correction of coagulation with the use of blood components. Despite the lack of randomized controlled trials of the use of recombinant factor VIIa in uncontrolled obstetric hemorrhage, published reports in the literature supports the growing body of anecdotal evidence of the beneficial role of its use in the treatment of both massive obstetric hemorrhage and amniotic fluid embolism–related coagulopathy.[277] Recent European guidelines stress every attempt should be made to control bleeding by conventional methods, including administration of traditional blood products and correction of factors known to interfere with coagulation. Recombinant factor VIIa should not replace these treatments but should be given as an adjunct in the management of the bleeding patient.[278]

If an operative procedure is considered necessary, general endotracheal anesthesia is preferable to regional anesthesia in women with hemodynamic instability or coagulopathy. Direct arterial blood pressure and central venous pressure monitoring is useful to guide volume resuscitation.

Placenta Previa

Placenta previa occurs when implantation of the placenta is low in the uterus; it is either overlying or encroaching on the cervical os. Placenta previa is present in approximately 0.6% of all pregnancies. It may be categorized as *total* if the placenta completely covers the os, *partial* if there is some encroachment on the os by the placenta, and *marginal* if the placenta is not covering but is close to the internal os (Fig. 69-17). The condition is more common in multiparous women, and it is especially common in women who have had a previous cesarean section. Typically, in contrast with placental abruption, placenta previa is characterized by painless vaginal bleeding in the third trimester. Bleeding may stop spontaneously, in which case conservative management is recommended. However, if bleeding persists, stabilization of the mother and delivery of the fetus may be required.

Placenta Accreta

On occasion, the placenta can be adherent to the implantation site with an absent decidua, an abnormality that produces an absence of the physiologic line of cleavage through the decidual layer. This condition is termed *placenta accreta* and may produce life-threatening challenges. As shown in Figure 69-18, placenta accreta may be classified according to the degree of placental penetration of the myometrium. The condition occurs when the placenta is adherent to the myometrium. Placenta increta occurs when the placenta invades the myometrium. Placenta percreta occurs when the placenta extends through the myometrium and may adhere to surrounding structures. Patients with one or more previous cesarean sections have an increased likelihood of placenta accreta, as highlighted in Figure 69-19. With recent improvements in ultrasonography, it is now possible to diagnose most cases of placenta accreta antenatally.[279] The extent of trophoblast invasion can also be evaluated with magnetic resonance imaging

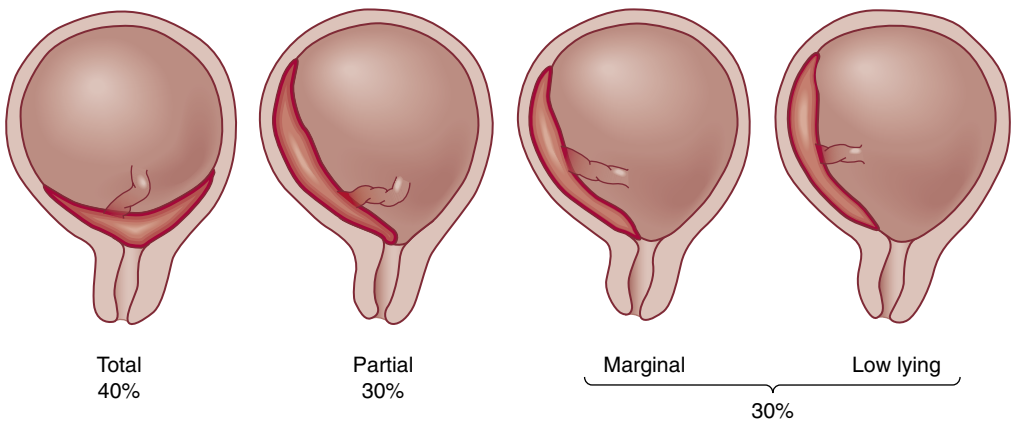

Figure 69-17 Types of placenta previa. (*Redrawn from Suresh MS, Belfort MA: Antepartum hemorrhage. In Datta S [ed]: Anesthetic and Obstetric Management of High Risk Pregnancy, 2nd ed. St. Louis, CV Mosby, 1996, p 93. Illustration copyright 1995. Baylor College of Medicine.*)

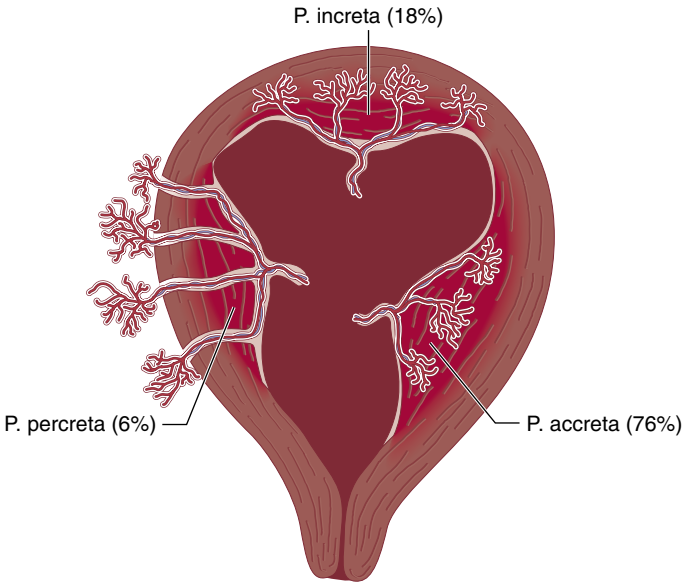

Figure 69-18 Classification of placenta accreta, increta, and percreta. (*From Birnbach DJ, Gatt SP, Datta S [eds]: Textbook of Obstetric Anesthesia. New York, Churchill Livingstone, 2000, p 406. Originally from Kamani AAS, Gambling DR, Christilaw J, et al: Anesthetic management of patients with placenta accreta. Can J Anaesth 34:613, 1987. Data from Miller DA, Chollet JA, Goodwin TM: Clinical risk factors for placenta previa-placenta accreta. Am J Obstet Gynecol 177:210, 1997.*)

(MRI).[280] If detected by radiologic studies, techniques such as arterial embolization under radiologic guidance may be used to decrease the extent of bleeding before or during cesarean hysterectomy.[281,282] Although controversy exists with regard to the use of cell salvage techniques during cesarean section, blood loss may be so massive in these cases that the benefits outweigh the potential risks of introduction of amniotic components into the maternal circulation. Two reports have described successful use of the cell salvage technique during cesarean hysterectomy.[283] This technique may also be of benefit to a Jehovah's Witness parturient, in whom a blood transfusion is not an alternative.

Optimal anesthetic management for cesarean hysterectomy is dependent on many factors, including the stability of the patient, the experience of the anesthesiologist, the availability of ancillary services, and patient wishes. In an early report by Chestnut and Redick, 7 of 25 patients undergoing cesarean hysterectomy required general anesthesia. Reasons for the use of general anesthesia included "patient discomfort" and "inadequate operating conditions."[284] A subsequent prospective multi-institutional study evaluated this subject and reported that continuous epidural anesthesia can be used safely for many cases of elective cesarean hysterectomy.[285] Because of the ever-present possibility that conversion to general anesthesia will be necessary, some anesthesiologists prefer to initially use general anesthesia in women with a high risk for placenta accreta. The timing of epidural catheter removal is controversial and warrants caution in cases in which massive hemorrhage and transfusion precipitate DIC.[286]

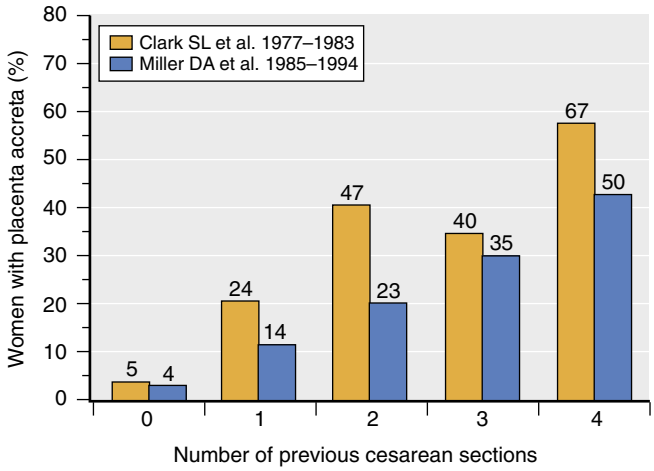

Figure 69-19 Relationship between the number of previous cesarean sections and the incidence of placenta accreta. (*Data from Clark SL, Koonings PP, Phelan JP, et al: Placenta previa/accreta and prior cesarean section. Obstet Gynecol 66:89, 1985; and Miller DA, Chollet JA, Goodwin TM: Clinical risk factors for placenta previa-placenta accreta. Am J Obstet Gynecol 177:210, 1997.*)

Vasa Previa

Vasa previa is an uncommon placental condition that carries with it high fetal mortality.[287] It occurs in pregnancies with a velamentous insertion of the umbilical vessels so that they run through amniotic membranes traversing between the fetal presenting part and the cervical os. These vessels have little support and are very susceptible to trauma during labor. A diagnosis of vasa previa is suspected when vaginal bleeding occurs immediately on rupture of the amniotic membranes and is accompanied by FHR abnormalities. The bleeding in vasa previa is fetal rather than maternal in origin; only a small amount of blood loss may result in fetal demise unless the problem is recognized quickly and an emergency cesarean section can be performed immediately.[288] Because this condition constitutes a true emergency, the fastest anesthetic technique should be used for cesarean section. For most patients (and most anesthesiologists), this would be general anesthesia.

Postpartum Hemorrhage

Postpartum hemorrhage remains a major contributor to maternal morbidity and mortality worldwide. The causes of postpartum hemorrhage can be divided into uterine and nonuterine causes. The most frequent uterine causes are atony and retention of pla-

cental products. Other uterine causes include uterine rupture and uterine inversion. Nonuterine causes include vaginal tears, perineal hematoma, and maternal coagulopathy.

Uterine Atony

Uterine atony is the most common cause of postpartum hemorrhage, and it is caused by ineffective uterine muscle contraction in the postpartum period. Risk factors include prolonged labor, an overdistended uterus (macrosomia or multiple births), infection, grand multiparity, and administration of drugs that relax the uterus (halogenated anesthetics, β-sympathomimetic agonists, and magnesium sulfate). Treatment includes oxytocin; however, boluses of this drug may precipitate hypotension, so continuous infusions are preferable.[289] Carboprost tromethamine (Hemabate), a 15-methyl analog of prostaglandin-$F_2\alpha$, is also a potent uterotonic that can be used. Side effects include nausea, vomiting, and bronchoconstriction. This drug is given intramuscularly either by the anesthesiologist or directly into the uterus by the obstetrician.[290] In addition, the ergot derivatives (ergonovine and methylergonovine) are also potent uterotonic agents that are given intramuscularly. Because profound hypertension may occur, this drug should be avoided in patients with severe hypertensive disease. Surgical compression suturing ("B-Lynch suture") is an important technique for treating postpartum hemorrhage associated with uterine atony and may avoid the need for cesarean hysterectomy.[291]

Other Complications

Umbilical Cord Prolapse

Cord prolapse is rare; it occurs in only 0.4% of cephalic term pregnancies. Abnormal presentations such as a complete breech or transverse lie carry a higher risk with an incidence of up to 6% or greater than 20%, respectively. The diagnosis may be suspected when there is a sudden fall in FHR, especially on rupturing the membranes in a patient with a known abnormal fetal lie or a patient with polyhydramnios. The diagnosis is confirmed by palpation of the umbilical cord on vaginal examination, with or without an associated fetal bradycardia. Management consists of manual replacement of the cord and avoidance of cord compression by the presenting fetal part against the pelvic rim. Urgent cesarean section should be performed. A regional technique may be considered if an epidural catheter is already in situ or if a spinal technique can be expeditiously performed in the lateral position. In the event that fetal compromise is noted, general anesthesia is usually chosen.

Multiple Births

The incidence of multiple gestations has increased with the increasing frequency of assisted reproduction. The frequency of higher-order multiple gestation has also increased significantly. Both perinatal and maternal morbidity and mortality are increased in these patients. These pregnancies are associated with a higher incidence of premature labor and delivery, abnormal presentation, preeclampsia, cord prolapse, need for operative delivery, uterine atony, and postpartum hemorrhage. Many of the maternal physiologic changes of pregnancy are exaggerated, which has significance for the anesthesiologist. FRC is greatly reduced because of the larger uterine size, and the reduced FRC results in a more rapid onset of hypoxemia during apnea or hypoventilation. In addition, aortocaval compression is more dramatic because of greater uterine weight and size. Uterine atony and the risk of postpartum hemorrhage are also greater than in singleton pregnancies. Depending on the fetal presentation, twins may be delivered vaginally; however, most obstetricians require vertex presentation of the presenting twin. If twin B has a nonvertex presentation, the obstetrician will perform either external cephalic version, breech extraction, or cesarean delivery. Epidural analgesia is useful in these situations because it can provide the necessary analgesia and be rapidly converted for use in an urgent cesarean section.

Uterine Rupture

Uterine rupture is a potentially life-threatening complication that is increasing in incidence. It may occur in a previously scarred uterus, or it may result from uterine manipulation, trauma, or overaggressive use of oxytocin. Of note, the incidence of rupture associated with vaginal birth after cesarean section (VBAC) appears to be higher than was once thought. The incidence of uterine rupture in VBAC labor is approximately 1%.[292] Among these ruptures, the rate of serious maternal or fetal morbidity or mortality is 10% to 25%. On the basis of this observation, the ACOG has recommended that for a trial of labor after cesarean section to occur, a physician capable of monitoring labor and performing an emergency cesarean section be immediately available throughout active labor. The ACOG recommendations also dictated that an anesthesiologist be immediately available.[293] The anesthesiologist for patients attempting VBAC should be aware of the signs and symptoms of uterine rupture. Symptoms can be nonspecific, but they almost always include fetal bradycardia. In addition, maternal hypotension along with loss of function of uterine pressure monitors often occurs. Treatment requires emergency laparotomy, and general anesthesia is usually indicated.

Uterine Inversion

Uterine inversion is a rare cause of postpartum hemorrhage in which the uterine fundus inverts through the cervix into the vagina.[294] Hypotension usually results before significant blood loss has occurred. Treatment of uterine inversion should include fluid therapy for the mother and restoration of the uterus to its normal position. Uterine relaxation may be necessary to replace the uterus; β-sympathomimetic agents, magnesium, and nitroglycerin all have been used to achieve this goal. The choice of agent may be dependent on the mother's hemodynamic stability. For example, in the case of profound maternal hypotension, magnesium sulfate may be a better choice than nitroglycerin. Should initial efforts to replace the uterus prove unsuccessful, rapid-sequence induction with cricoid pressure and endotracheal intubation should be undertaken. The use of volatile agents will also cause uterine relaxation, thereby assisting the obstetrician in replacing the uterus.

Anesthesia for Nonobstetric Surgery During Pregnancy

It is estimated that approximately 2% of pregnant women undergo nonobstetric surgery in the United States annually. Most of these

Table 69-11 Most Common Surgical Procedures Performed in Pregnant Women during Each Trimester of Pregnancy

Type of Operation	1st Trimester (%)	2nd Trimester (%)	3rd Trimester (%)
Central nervous system	6.7	5.4	5.6
Ear, nose, throat	7.6	6.4	9.5
Abdominal	19.9	30.1	22.6
Genitourinary-gynecologic	10.6	23.3	24.3
Laparoscopy	34.1	1.5	5.6
Orthopedic	8.9	9.3	13.7
Endoscopy	3.6	11	8.6
Skin	3.8	3.2	4.1

Adapted from Mazze RL, Kallen B: Reproductive outcome after anesthesia and operation during pregnancy: A registry study of 5,405 cases. Am J Obstet Gynecol 161:1178-1185, 1989.

procedures are nonelective and sometimes they are done for life-threatening reasons. Such situations are challenging to both the anesthesiologist and the surgeon. Anesthetic issues to be considered include maternal risk factors resulting from the physiologic and anatomic changes of pregnancy, the teratogenic potential of anesthetic agents, maintenance of adequate uteroplacental blood flow, and the direct and indirect effects of maternally administered agents on the fetus. Surgical management of such patients is also more complicated than in the nonpregnant state. The diagnosis of abdominal pathology is compounded by anatomic displacement of abdominal organs by the gravid uterus. Abdominal tenderness and leukocytosis are often normal findings during pregnancy.

A review of combined data from three Swedish health care registries from 1973 to 1981 by Mazze and Kallen detailed the types and rates of surgery during each trimester.[295] The most common abdominal procedures included appendectomy, cholecystectomy, and adnexal surgery (Table 69-11). Other, less frequent but more challenging situations include laparoscopic surgery, neurosurgery, cardiac surgery requiring cardiopulmonary techniques, and, more recently, fetal surgery.

Specific risks for the mother and fetus undergoing surgery include fetal loss, fetal asphyxia, premature labor, premature rupture of membranes, the potential for failed intubation, and thromboembolic phenomena. Surgery for obstetric indications is associated with a higher risk of perinatal mortality.

Trauma (also see Chapter 72)

Injury related to trauma occurs in up to 6% to 7% of all pregnancies and is perhaps the most common cause of nonobstetric maternal mortality. Motor vehicle accidents are responsible for most injuries, followed by domestic abuse and, to a lesser extent, falls. In contrast with nonpregnant women, abdominal injury during pregnancy is more likely than head injury.[296]

Rapid assessment, hemodynamic stabilization, and treatment of maternal injuries are essential for fetal survival. It is important to remember that the anatomic and physiologic changes associated with pregnancy may cause the clinician to underestimate the true extent of hypovolemia. For instance, shock in a pregnant patient may not be clinically evident until 25% to 30% of maternal blood volume is lost; at this point, the fetus may already be in jeopardy. In hemorrhagic shock, maternal blood is shunted away from the uterus to preserve perfusion to vital maternal organs at the expense of the fetus; such a physiologic response causes fetal hypoxemia and even death.[297]

Regardless of the clinical situation, a preoperative assessment that includes airway evaluation should be performed. The choice of regional or general anesthesia techniques should be based on the clinical status, surgical procedure, experience of the anesthesiologist, and the psychological condition of the patient.

Aspiration prophylaxis should be administered to all pregnant patients beyond 14 weeks' gestation because physiologic changes at the lower esophageal sphincter enhance the risk of aspiration. An H_2 antagonist should be given 1 hour before surgery if possible and a nonparticulate antacid such as sodium citrate given just before induction of anesthesia. Use of a prokinetic agent such as metoclopramide, 10 mg intravenously, may also enhance gastric emptying. It is imperative to position the patient correctly after the second trimester to avoid aortocaval compression by the gravid uterus; correct positioning may be accomplished by placing a wedge under the right hip.

Monitoring of the fetus perioperatively is important, but not always feasible, especially during abdominal surgery. External FHR monitoring is usually possible from 18 weeks onward. Whether intraoperative FHR monitoring can affect fetal outcome remains controversial. A literature review questioned the need to monitor FHR changes during surgery because of the lack of alterations in fetal outcome.[298] However, alterations in FHR may indicate adverse maternal conditions before they become apparent with standard monitoring. Such alterations should therefore encourage evaluation of maternal oxygenation, hemodynamics, acid-base status, and activities at the surgical field for compromise of uterine perfusion. It is advisable to document FHR before and after institution of both regional and general anesthesia and on completion of surgery. The decision to perform fetal monitoring should be individualized and may be based on gestational age, the type of surgery, and the facilities available.

If general anesthesia is necessary, a rapid-sequence technique with adequate preoxygenation, cricoid pressure, and endotracheal intubation should be used to minimize the risk of aspiration for any pregnant woman after 14 to 16 weeks' gestation. Drugs administered should be chosen for their known safety in pregnancy. Such agents include thiopental, depolarizing and nondepolarizing muscle relaxants, opioids (fentanyl, morphine, and meperidine), inhaled agents, and 50:50 O_2/N_2O mixtures. Maternal $Paco_2$ should be maintained in the normal range for pregnancy (30 mm Hg) because maternal hyperventilation may reduce placental blood flow. The patient should not be extubated until awake because there is still a risk of aspiration at the end of the procedure. Uterine activity should be monitored into the postoperative period, and tocolytic drugs may be required.

It has been suggested that nonsteroidal anti-inflammatory drugs should be avoided after the first trimester, because some of

these agents may constrict or close the fetal ductus arteriosus in the later stages of pregnancy.[299]

Cardiac Arrest in Pregnancy

Cardiac arrest in pregnancy is rare and carries a poor prognosis (see Chapter 97). Almost 10% of overall maternal deaths reported in the United Kingdom result from cardiac arrest.[247] Health care workers must be familiar with the physiologic changes of pregnancy that can make the diagnosis and treatment of cardiac arrest difficult in this population. Successful resuscitation of the mother requires prompt and effective CPR with some alterations in basic life support (BLS) and advanced cardiac life support (ACLS) principles. After 20 weeks' gestation, the gravid uterus may compress the inferior vena cava and impede venous return when in the supine position. The effects of aortocaval compression must be minimized by left lateral uterine tilt using manual uterine displacement or insertion of a wedge under the right hip.

Modification of Basic Life Support

Continuous cricoid pressure should be applied during positive-pressure ventilation for any unconscious pregnant patient to minimize the risk of regurgitation. As the diaphragm and abdominal contents are elevated by the gravid uterus, chest compressions should be performed higher than usual, slightly above the midpoint of the sternum.

Defibrillation should be performed as directed by standard ACLS guidelines. There is no evidence that shocks have adverse fetal cardiac effects. Fetal and maternal monitors should be removed before delivering any electric shocks.

Modification of Advanced Cardiovascular Life Support

The airway should be secured as early as possible in a cardiac arrest in order to minimize risk of regurgitation (see also Chapter 97). The airway may be edematous, and a smaller endotracheal tube may be required (0.5-1.0 mm smaller).

Pregnant patients can develop hypoxemia at a quicker rate than nonpregnant women owing to reduced FRC and increased oxygen requirements. The tidal volume of breaths delivered may need to be reduced because of elevation of the diaphragm.

There is a paucity of information in the literature on the use of resuscitative drugs. Current recommendations advise following standard ACLS guidelines regarding drugs and doses.[300]

Differential Diagnosis

One must consider standard causes of cardiac arrest and those specific to pregnancy. These may include amniotic fluid embolism, massive blood loss, complications of preeclampsia, acute coronary syndromes, aortic dissection, life-threatening pulmonary embolism, iatrogenic drug overdose (e.g., magnesium sulfate), or local anesthetic toxicity. Calcium gluconate, 1 g intravenously, is the drug of choice for magnesium toxicity. Cardiac arrest due to local anesthetic toxicity includes standard ACLS measures, and one should consider the use of 20% lipid emulsion therapy.[301]

Perimortem Cesarean Section

The best chance of fetal survival at 24 weeks' gestation and beyond is when delivery occurs no more than 5 minutes after the onset of maternal cardiac arrest. Therefore, the decision to perform an emergency cesarean section must be made early. There is little chance of maternal resuscitation until the uterus is emptied, which will restore venous return and cardiac output. Emptying of the uterus will also improve thoracic compliance and thus ability to improve maternal ventilation.[302]

Laparoscopic Surgery

Case series of successful diagnostic and operative laparoscopic procedures performed during pregnancy have been published (see Chapter 68).[303] A retrospective study of laparoscopic procedures versus open procedures during the first two trimesters of pregnancy demonstrated a significant reduction in opiate requirements and length of stay.[304] Certain physiologic changes of pregnancy may have an impact on anesthetic management during laparoscopic surgery. Mechanical ventilation of a pregnant patient can be difficult because of upward displacement of the diaphragm before abdominal insufflation. Capnography may be used to guide ventilation during CO_2 pneumoperitoneum with no increased risk of respiratory acidosis if the end-tidal CO_2 is maintained at 32 mm Hg.[305] The extent of Trendelenburg positioning may also be limited. Pneumoperitoneum pressure should be limited to 15 mm Hg.[306]

Analgesia for External Cephalic Version

Obstetricians have shown renewed interest in external cephalic version (ECV) in an attempt to decrease the cesarean section rate because of breech presentation. Recent published studies have demonstrated increased success rates for ECV, versus those in matched historical controls, when epidural or CSE analgesia is provided.[307,308] Provision of maternal analgesia with CSE creates a suitable environment for ECV; unlike older regional anesthesia techniques, it limits the use of excessive force by the obstetrician. If a serious complication occurs during ECV, the epidural catheter may be used to provide anesthesia for emergency cesarean section and avoid the complications of general anesthesia.

Fetal Surgery

Advances in prenatal diagnosis with the use of modern technology (ultrasonography, fetal echocardiography, fetal MRI, amniocentesis, umbilical blood sampling, and chorionic villus sampling) and the development of open fetal surgical techniques now permit the treatment of fetal conditions that would otherwise have caused progressive, irreversible damage and possible intrauterine fetal demise if left untreated.[309] Such abnormalities include congenital diaphragmatic hernia, hydronephrosis, twin-twin transfusion syndrome, and hydrothorax.

It is important for the anesthesiologist to understand the fetal lesion and the surgical approach because they determine the type of anesthetic care offered to the mother. Key issues for

the anesthesiologist include maternal safety, uterine relaxation, fetal immobility, and anesthesia. Intensive monitoring of uterine activity and the use of tocolytic agents (e.g., the volatile agents terbutaline and nitroglycerin) are often necessary to prevent the associated high risk of premature labor. The patient has an increased risk of pulmonary edema in the postoperative period as a result of aggressive tocolytic therapy; thus, close attention to fluid balance is warranted.

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Michael K. Urban

70 Anesthesia for Orthopedic Surgery

Key Points

1. Older age is a significant risk factor for poor outcome after orthopedic surgery. Elderly patients presenting for orthopedic surgery often have multiple comorbid conditions that must be considered in the perioperative anesthetic plan.
2. Patients with arthritis (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis) have special problems that must be addressed in an anesthetic plan.
3. For many orthopedic procedures, regional anesthesia may reduce perioperative complications compared with general anesthesia, and may provide superior analgesia.
4. Fat embolism syndrome is a well-recognized complication of orthopedic trauma and major joint replacement. Early intervention and stabilization of these patients may avoid significant morbidity.
5. Corrective surgery for spinal deformities (scoliosis, kyphosis, kyphoscoliosis) presents a significant challenge to the anesthesiologist. These patients are at risk for large blood loss, pulmonary complications, neurologic deficits, and postoperative loss of vision. Changes in anesthetic management may reduce the incidence of some of these complications.

Orthopedic patients can be particularly challenging for anesthesiologists. These patients represent a broad scope of problems, ranging from an elderly patient with multiple comorbid conditions to a young, deceptively healthy trauma patient who may have associated injuries that can have a significant impact on the type of anesthetic administered. It is imperative that the anesthesiologist examine the entire patient and not just focus on the area of surgery. In this regard, a complete medical history also is important because it may reveal chronic connective tissue diseases that may alter the anesthetic plan.

The field of orthopedics also is changing in many ways that affect the anesthetic care of these patients. There is increasing demand for joint replacements in the active aging population with the expectation of regional anesthesia, a postoperative pain management plan, and early hospital discharge. More orthopedic procedures are now performed as ambulatory surgery, and the anesthesiologist becomes responsible for which patients can be discharged and how their pain is to be managed. Adult spinal surgery also is dramatically increasing. These procedures can be the most challenging to the anesthesiologist because of difficult airways, hours in the prone position, large blood loss, and significant postoperative pain.

This chapter discusses the perioperative factors that potentially alter outcome after orthopedic surgery. Complications associated with specific procedures are emphasized with regard to recognition of such complications, avoidance when possible, and management. Choice of the best anesthetic based on current evidence for a given orthopedic procedure also is discussed. In many cases, the pros and cons of regional versus general anesthesia are presented, but this chapter does not concentrate on the technical aspects of regional anesthesia. This chapter provides guidance for anesthesia for patients undergoing common orthopedic procedures.

Preoperative Evaluation

All patients presenting for orthopedic surgery warrant a thorough preoperative medical evaluation. Any orthopedic patient could represent an anesthetic challenge. There are specific types of patients, however, who are more likely to have orthopedic surgery and are more likely to have perioperative complications.

Geriatric Orthopedic Patients

The population of the United States older than 65 years in 2006 was 37.3 million (1 in 8 of the population), and at least 16 million of these individuals had "advanced" osteoarthritis (see Chapter 71). In the same year, more than 300,000 hip replacements and 500,000 knee replacements were done. By 2030, the number of U.S. citizens older than 65 years is expected to almost double to 71.5 million (U.S. Department of Health and Human Services,

www.cdc.gov/aging). This means that older patients with multiple comorbid conditions will be having increasingly more orthopedic procedures, including total joint replacements.

Postmenopausal and age-associated osteoporosis affect older individuals, increasing their risk of fractures. Age-associated osteoporosis may be the result of increased circulating parathyroid hormone and decreased vitamin D, growth hormone, and insulin-like growth factors.[1] With osteoporosis, there is a disproportionate loss of trabecular (structural) bone, placing the patient at risk for stress fractures. Although all bones are theoretically at risk, the thoracic and lumbar spine, the proximal femur, the proximal humerus, and the wrist are at the highest risk.[2] Compression fractures of the thoracic and lumbar spine also are common and may require surgical intervention. Osteoporosis also compromises the incidence and quality of postoperative fusions. The National Osteoporosis Foundation recommends measuring bone mineral density in patients at risk and postmenopausal women. Osteoporosis can be treated with increased dietary calcium intake and weight-bearing exercises.

The mortality after hip and knee arthroplasty surgery ranges from 0.4% to 4.6%, depending on primary versus revision replacement.[3-6] The in-hospital mortality after repair of hip fractures is 4.8%, and mortality increases to 30% after the first year following hospitalization. The major risk factor for perioperative mortality in all of these studies was advanced age, and the most frequent perioperative complications involved cardiac problems. In their review of 1636 consecutive hip and knee replacements, Parviz and colleagues[5] reported a 6.4% incidence of serious postoperative complications, with the most frequent complication relating to cardiac problems. The reported incidence of a perioperative myocardial infarction at an orthopedic hospital was 0.6% of all nonambulatory procedures (approximately 8000), and 6.5% of those patients were at risk for myocardial ischemia.[8]

Postoperative Complications

Cardiac Complications. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend preoperative cardiac testing in patients at increased cardiac risk on the basis of clinical risk profile, functional capacity, and type of surgery.[9] The ACC/AHA classifies orthopedic surgery as intermediate-risk surgery, which in most cases involves intermediate-risk patients. Older patients have an increased risk of perioperative myocardial morbidity and mortality after orthopedic surgery (see Chapter 71). The possible reasons for this increased risk are as follows: (1) Many elderly patients have multiple medical comorbid conditions,[10] (2) elderly patients have limited functional capacity, (3) some orthopedic procedures initiate a systemic inflammatory response syndrome, (4) some orthopedic procedures are associated with significant blood loss and fluid shifts, and (5) postoperative pain is a major management problem after orthopedic surgery[11] (see Chapters 55 and 87). All of these factors can trigger a stress response leading to tachycardia, hypertension, increased oxygen demand, and myocardial ischemia.

Because there is a significant incidence of postoperative cardiac complications after orthopedic surgery, and it is difficult to assess the functional status of these patients owing to the limitations imposed by their orthopedic disease, many of these patients are subjected to preoperative cardiac testing. Data for orthopedic surgery showing that preoperative risk stratification or coronary revascularization, or both, has an effect on outcome are limited, however (see Chapters 33 and 34). A report by Salerno and associates[7] suggested that preoperative abnormal noninvasive cardiac testing rarely changed medical management before orthopedic surgery. The Decrease-II study questioned the value of preoperative cardiac testing in patients of intermediate risk before noncardiac surgery.[12] In the CASS registry, Eagle and colleagues[13] reported that coronary artery bypass graft surgery offered no advantage before orthopedic surgery in reducing cardiac mortality. Similar results have been obtained using percutaneous coronary intervention. Postoperative myocardial infarction and death have not been reduced for noncardiac surgery in patients at cardiac risk when preceded by percutaneous coronary intervention.[14,15] In patients in whom percutaneous coronary intervention involved the placement of stents, there are the added risks of restenosis and thrombosis if antiplatelet therapy has to be discontinued before surgery, and increased perioperative bleeding if these medications are not discontinued.[16]

If preoperative cardiac testing and revascularization does not decrease postoperative cardiac morbidity, hemodynamic stress reduction might be the answer. Numerous studies have indicated that the use of perioperative adrenergic β-blockers can reduce myocardial ischemia and postoperative myocardial infarctions.[12,17,18] Several more recent reports have questioned the efficacy of β-blockers in preventing postoperative cardiac complications, particularly in patients at intermediate risk.[19,20] In elderly patients undergoing orthopedic procedures, β-blockers should be continued perioperatively in the patients taking long-term β-blockers and initiated in the patients at the highest risk, with a target heart rate less than 80 beats/min.[17,21]

Orthopedic patients at risk for perioperative cardiac complications should be assessed postoperatively for myocardial ischemia. The diagnosis of a postoperative myocardial infarction is important because these events can be associated with significant cardiac morbidity and mortality if not treated appropriately. In addition, the decision to initiate postoperative physical therapy and rehabilitation, activities that are imperative for optimal mobility in orthopedic patients, depends on whether there has been a diagnosis of a postoperative myocardial infarction. The introduction of plasma cardiac troponin I analysis has markedly increased the ability to detect myocardial damage. Increases in the plasma concentrations of cardiac troponin I are highly specific for cardiac injury and are a more specific marker for a myocardial infarction after orthopedic surgery than the creatine kinase MB isoenzyme.[22,23]

Respiratory Complications. The changes in the respiratory system secondary to age may predispose elderly patients to increased postoperative pulmonary complications. These changes include a progressive decrease in arterial oxygen tension, an increase in closing volumes, and a decrease of approximately 10% in the forced expiratory volume in 1 second with each decade of life. Many of these changes are the result of alterations in chest wall mechanics, which are exacerbated in elderly patients with arthritis. Elderly patients who have sustained hip fracture have significantly lower P_{AO_2} values than other surgical patients of comparable ages.[24] The hypoxia in these patients may reflect the above-noted respiratory changes caused by age, and embolization of bone marrow debris to the lungs in these patients.

Neurologic Complications. After cardiac and pulmonary complications, confusion or delirium is the third most common

complication seen in elderly patients after orthopedic surgery. In 2004, $69 billion from Medicare was spent on the treatment of hospital-acquired delirium. Delirium is associated with an increased length of hospital stay, poor functional recovery, progression to dementia, and increased mortality.[24,25] Postoperative delirium manifests as attention and awareness deficits, including acute confusion, reduced ability to focus, change in cognition, irritability, anxiety, paranoia, and hallucinations. Delirium develops acutely, but generally has a fluctuating course over several days (see Chapter 71).[26] Some patients manifest a hypoactive form of delirium, confused but quiet and nondisruptive, which can be difficult to diagnose. The major risk factors for postoperative delirium are advanced age, alcohol use, preoperative dementia or cognitive impairment, psychotropic medications, and multiple medical comorbid conditions. Perioperative events that may trigger delirium include hypoxemia, hypotension, hypervolemia, abnormal electrolytes, infection, sleep deprivation, pain, and administration of benzodiazepines and anticholinergic medications.

Aging alters the pharmacokinetics and pharmacodynamics of most medications, including anesthetics and analgesics. The "usual" adult doses of these medications may have longer and more profound central nervous system (CNS) effects on elderly patients. Strategies used to reduce the incidence of postoperative delirium include identifying risk factors, and vulnerable and affected patients early; preserving orientation; early mobilization; adequate pain control; maintenance of normal sleep cycles; and avoidance of psychotropic medications.

Fat Embolism Syndrome

Fat embolization is a well-known complication of skeletal trauma and surgery involving instrumentation of the femoral medullary canal.[28] Fat embolism syndrome (FES) is a physiologic response to fat within the systemic circulation. Fat embolization and FES are not synonymous. The embolization of fat can be detected in almost all patients who sustain a pelvic or femoral fracture, but the incidence of FES is less than 1%.

The clinical manifestations of FES include respiratory, neurologic, hematologic, and cutaneous signs and symptoms. The presentation of FES can be gradual, developing over 12 to 72 hours, or fulminant leading to acute respiratory distress and cardiac arrest. Gurd and Wilson[29] in 1974 suggested major and minor criteria to be used for the diagnosis of FES (Table 70-1). The presence of any one major finding plus four minor criteria and evidence of fat macroglobulinemia was required for the diagnosis of FES. The requirement for fat droplets in the circulation has been criticized, however, because fat droplets can be detected in the blood of healthy volunteers, and their presence in trauma patients is not always associated with FES. In addition, Gurd and Wilson[29] recommended the daily assessment of fat droplets in blood, hypothesizing that a change in the quantity of fat would correlate with symptoms. More recent investigations have indicated that the quantity of fat in the circulation does *not* correlate with the severity of FES symptoms or the development of acute respiratory distress syndrome.[30]

A petechial rash is pathognomonic of FES, with the rash usually present on the conjunctiva, oral mucosa, and skin folds of the neck and axillae. This is reflected in the Schonfeld FES index, which ranks signs and symptoms of FES in relation to their incidence of presentation (Table 70-2).[31] Respiratory signs also are common in FES; approximately 75% of patients present with mild hypoxemia and radiologic evidence of bilateral alveolar infiltrates, but less than 10% progress to acute respiratory distress syndrome. Neurologic manifestations of FES range from drowsiness and confusion to obtundation and coma. CNS symptoms have developed in the absence of significant pulmonary complications and may represent the passage of fat droplets across an atrial septal defect or other atrioventricular shunt.[32] Magnetic resonance imaging of the brain of these patients has revealed characteristic lesions of fat embolization (Fig. 70-1).

The pathophysiology of FES is unclear, but it probably involves two processes: the embolization of fat and "bone marrow debris," which can mechanically obstruct the capillaries of end organs, and the triggering of a systemic inflammatory response.[28] Using transesophageal echocardiography during total hip arthroplasty (THA), embolization of bone marrow debris has been detected in the right heart at the time of insertion of the cemented femoral prosthesis (Fig. 70-2).[33,34] In some patients, this embolization resulted in segmental wall motion abnormalities, elevated pulmonary arterial pressures, decreased right ventricular function, and, in one case, cardiac arrest and death.[34,35]

In most cases, the embolic events during THA were clinically benign, but some patients still progressed to FES. The fat

Table 70-1 Gurd's Diagnosis of Fat Embolism Syndrome

Major Features (at least one)
Respiratory insufficiency
Cerebral involvement
Petechial rash
Minor Features (at least four)
Pyrexia
Tachycardia
Retinal changes
Jaundice
Renal changes
Laboratory Features
Fat microglobulinemia (required)
Anemia
Thrombocytopenia
High erythrocyte sedimentation rate

From Gurd AR, Wilson RI: The fat embolism syndrome. J Bone Joint Surg Br 56:408-416, 1974.

Table 70-2 Schonfeld Fat Embolism Syndrome Index*

Sign	Score
Petechial rash	5
Diffuse alveolar infiltrates	4
Hypoxemia Pao_2<70 mm Hg, FIo_2 100%	3
Confusion	1
Fever >38°C (>100.4°F)	1
Heart rate >120 beats/min	1
Respiratory rate >30	1

*Score >5 required for diagnosis of fat embolism syndrome.
From Schonfeld SA, Ploysongsang Y, DiLisio R, et al: Fat embolism prophylaxis with corticosteroids: A prospective study in high risk patients. Ann Int Med 99:438-443, 1983.

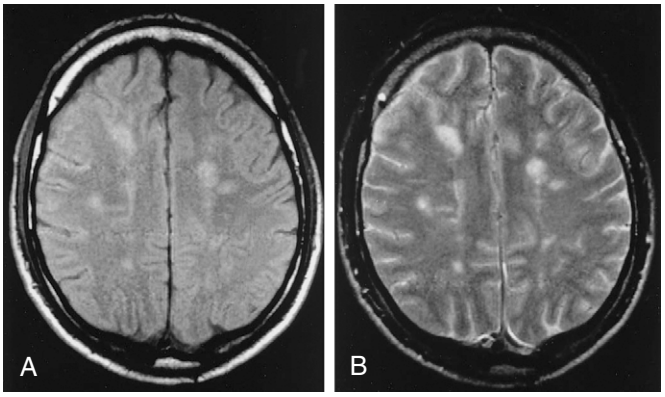

Figure 70-1 Cerebral fat embolism. **A** and **B,** Multiple hyperintensive lesions on proton density–weighted (**A**) and T2-weighted (**B**) MR images in the centrum semiovale. *(From Stoeger A, Daniaux M, Felber S, et al: MRI findings in cerebral fat embolism. Eur Radiol 8:1590-1593, 1998. Copyright Springer-Verlag.)*

emboli lodged in the microvasculature of the lung and other end organs were metabolized to free fatty acids, which triggered a systemic inflammatory response. This inflammatory response involves the invasion of inflammatory cells, the release of cytokines, and in the lung, pulmonary endothelial damage and acute respiratory distress syndrome.[36]

The treatment of FES is supportive with early resuscitation and stabilization to minimize the stress response to hypoxemia, hypotension, and diminished end-organ perfusion. Patients at risk for developing FES should be monitored with pulse oximetry, and tracheal intubation and mechanical ventilation should be instituted before respiratory failure. Although 10% of patients with FES may require mechanical ventilation, in most of these patients the symptoms resolve within 3 to 7 days. Corticosteroids have been studied extensively in the management of FES, with many investigators reporting beneficial effects, but other reports contradicting these results.[37] Well-controlled studies with defined outcomes are required before corticosteroids can be recommended in the treatment of FES.

Special Considerations in Conditions Leading to Orthopedic Surgery

Osteoarthritis

Approximately 22% of the U.S. population (46 million) have been diagnosed as having arthritis, and 8% (17 million) have limitations in physical activity because of arthritis.[38] Osteoarthritis is the most common type of arthritis and involves the loss of articular cartilage and associated inflammation. In most cases, osteoarthritis is a disease of aging with radiographic evidence in 90% of women and 85% of men of loss of articular cartilage after age 65 years.[39] Clinical manifestations include pain, crepitance, reduced mobility, and deformity of involved joints. Physical examination of the hands may reveal spurring and swelling of the distal interphalangeal joints (Heberden's nodes) and proximal interphalangeal joints (Bouchard's nodes).

Although there are no systemic manifestations of osteoarthritis, the anesthesiologist should be cognizant of previous orthopedic surgeries (including joint replacements) and which joints are painful and have limited mobility. This information is important for surgical positioning and the choice of an appropriate anesthetic. An axillary block of the brachial plexus for forearm

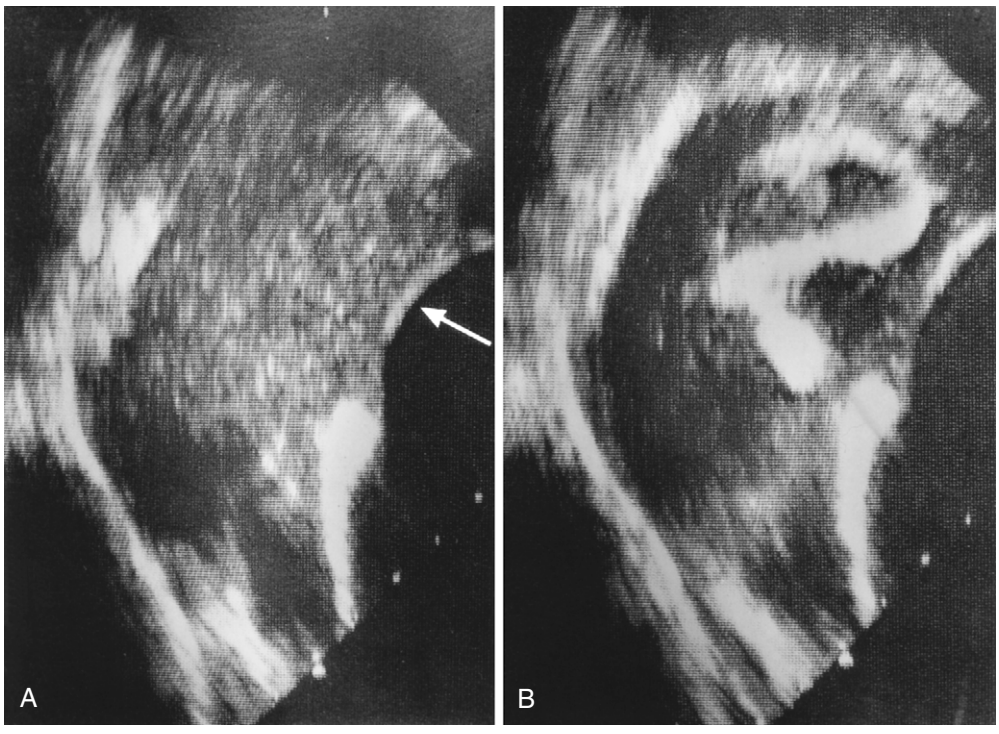

Figure 70-2 Right atrium during echocardiography. **A,** Multiple, small emboli (*arrow*) in the right atrium. **B,** Large embolus (7 cm long), which is probably a cast of the femoral vein. *(Adapted from Christie J, Burnett R, Potts HR, et al: Echocardiography of transatrial embolism during cemented and uncemented hemiarthroplasty of the hip. J Bone Joint Surg Br 76:409-412, 1994.)*

surgery is inappropriate in a patient with significant ipsilateral shoulder arthritis. Although the operative site would be completely anesthetized, the patient may complain of painful shoulder movement during the procedure. The appropriate regional anesthetic would include the arthritic shoulder; an appropriate anesthetic might be an interscalene block.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory form of arthritis, which affects about 1% of adults, with a prevalence two to three times higher in women than in men. RA is characterized by persistent joint synovial tissue inflammation leading to bone erosion, destruction of cartilage, and loss of joint integrity. RA also is a systemic disease, affecting multiple organ systems.[40] It often progresses through multiple exacerbations and remissions, but 20% to 30% of affected individuals become permanently disabled within 3 years of diagnosis.

The diagnosis of RA is primarily clinical. Patients commonly present with pain and stiffness in multiple joints. RA is characterized by morning stiffness often lasting more than 1 hour after initiating activity. Usually the wrists and metacarpophalangeal joints are involved; this distinguishes RA from osteoarthritis, which often affects distal interphalangeal joints. The symptoms may emerge over weeks and months, progressing from one joint to multiple joints, and may be accompanied by symptoms of anorexia, fatigue, and weakness. The rheumatoid joints are usually boggy, tender to the touch, and warm. Patients may have prominent epitrochlear, axillary, and cervical lymph node enlargement. Subcutaneous nodules (rheumatoid nodules) may surround joints, extensor surfaces, and bony prominences.

No single diagnostic laboratory test confirms the diagnosis of RA, but rheumatoid factor, an anti-immunoglobulin antibody, is elevated in 90% of patients with RA. In addition, C-reactive protein and erythrocyte sedimentation rate are elevated in patients with RA and are often used to monitor the course of the disease. RA also must be differentiated from other diseases that manifest as polyarthropathies, including seronegative spondylarthropathies, connective tissue diseases (scleroderma, lupus), fibromyalgia, hemochromatosis, polyarticular gout, polymyalgia rheumatica, and sarcoidosis.

Because joint destruction begins early with RA, disease-modifying antirheumatic drugs should be initiated immediately with the therapeutic goal of preservation of function and qualify of life. The most commonly used disease-modifying antirheumatic drugs include methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, infliximab (Remicade), and etanercept (Enbrel). All of these medications are associated with an increased risk of infection, which is a significant concern in patients with joint replacements. Pharmacotherapy also usually involves a nonsteroidal anti-inflammatory drug (NSAID) and oral or intra-articular glucocorticoids. RA patients taking NSAIDs should be assessed for gastrointestinal side effects and renal complications. Glucocorticoids, although highly effective at relieving symptoms, should be used at low doses and sparingly because of their side effects, which include osteoporosis, cataracts, cushingoid symptoms, and hyperglycemia. Patients taking significant quantities of glucocorticoids need stress-dose steroids for their operations.

Because of the myriad systemic problems associated with RA and the side effects of the medications administered to manage RA, the anesthetic considerations can be complex (Table 70-3). Airway management can be particularly challenging in RA patients and requires pre-planning even in patients receiving regional anesthesia because of the complexity of their airways (see later). Synovitis of the temporomandibular joint may significantly limit mandibular motion and mouth opening in these patients. Arthritic damage to the cricoarytenoid joints may result in diminished movement of the vocal cords, resulting in a narrowed glottic opening; this is manifested preoperatively as hoarseness and stridor. During laryngoscopy, the vocal cords may appear erythematous and edematous, and the reduced glottic opening may interfere with passage of the endotracheal tube.[41] There also is an increased risk of cricoarytenoid dislocation with traumatic endotracheal intubations.

Table 70-3 Anesthetic Considerations for Patients with Rheumatoid Arthritis

Airway	Limited TMJ movement Narrow glottic opening
Cervical spine	Atlantoaxial instability
Cardiac	Pericarditis Cardiac tamponade
Eyes	Sjögren's syndrome
Gastrointestinal	Gastric ulcers secondary to ASA, steroids
Pulmonary	Diffuse interstitial fibrosis
Renal	Renal insufficiency secondary to NSAIDs

ASA, acetylsalicylic acid; NSAIDs, nonsteroidal anti-inflammatory drugs; TMJ, temporomandibular joint.

Arthritis of the cervical spine is common in patients with RA. Anterior subluxation of C1 on C2 (atlantoaxial subluxation) may occur in 40% of patients with RA, with symptoms of progressive neck pain, headaches, and myelopathy (Fig. 70-3). Posterior and vertical migration of the odontoid process is less common. Flexion of the head in the presence of atlantoaxial instability could result in the displacement of the odontoid process into the cervical spine and medulla and compression of the vertebral arteries (Fig. 70-4). This may precipitate quadriparesis, spinal shock, and death. Preoperative cervical flexion-extension radiographs should be evaluated in RA patients with limited neck movement and neurologic symptoms. If the distance from the anterior arch of the atlas to the odontoid process exceeds 3 mm, the patient should undergo an awake fiberoptic tracheal intubation, and the cervical spine should be protected with a cervical collar during the procedure. These patients require postoperative monitoring with pulse oximetry and judicious administration of narcotic analgesics because emergent airway management, including tracheotomy, is extremely difficult.

The anesthesiologist also should be aware of several extra-articular manifestations of RA, which could potentially result in significant perioperative morbidity. RA patients frequently are affected with acute pericarditis. Restrictive pericarditis is characterized by dyspnea, right heart failure, fever, chest pain, pericardial friction rub, and pulsus paradoxus. RA patients with these symptoms should be evaluated by echocardiography. Pleural disease and intrapulmonary nodules can occur in RA, but are usually symptomatic. Some RA patients may have diffuse interstitial fibrosis with pneumonitis, producing symptoms of progressive dyspnea and a chronic cough. Pulmonary function tests show a restrictive ventilatory pattern. This pattern can progress to respiratory insufficiency, pulmonary hypertension, and right heart



Figure 70-3 MR image of a patient with advanced rheumatoid arthritis shows invagination of the odontoid process of C2 (*arrow*) through the foramen magnum, compressing the brainstem. Notice the degeneration of C4 and C5, a common problem in rheumatoid arthritis.

failure. These patients would be at higher risk for any orthopedic procedure.

Overlapping connective tissue syndromes also occur. RA patients can develop Sjögren's syndrome, which is associated with drying of the eyes and with corneal and conjunctival lesions. It is usually treated with artificial tears and ophthalmic ointments, which should be continued perioperatively. RA patients with chronic constitutional systems may develop Felty's syndrome, which includes splenomegaly, lymphadenopathy, anemia, thrombocytopenia, and leukopenia involving the neutrophils.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory arthritic disease that results in fusion of the axial skeleton. Ankylosing spondylitis involves ossification of the axial ligaments progressing from the sacral lumbar region cranially, resulting in a significant loss of spinal mobility (Fig. 70-5). These patients are a significant challenge to the anesthesiologist with regard to airway management because of the reduced movement of their cervical spines and their temporomandibular joints. In most cases, awake fiberoptic endotracheal intubation is required for general anesthesia. The increased rigidity of the thoracic spine in most cases also necessitates intraoperative controlled mechanical ventilation. Although sometimes neuraxial anesthesia can be an attractive alternative to general anesthesia, in these patients, the ossification of the spinal ligaments closes the intervertebral spaces, which may block access to the epidural space and prevent successful spinal anesthesia. In some cases, caudal epidural anesthesia may be a feasible alternative approach.

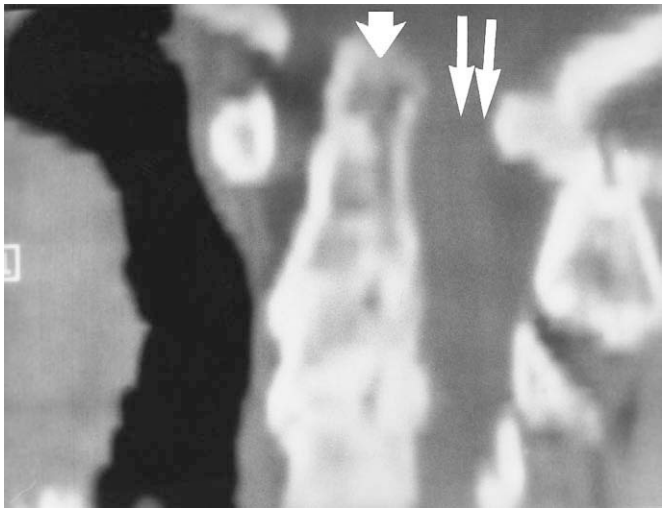

Figure 70-4 CT scan of the neck shows moderate subluxation of C1 and C2. The odontoid (*single arrow*) tends to compress the spinal cord (*double arrow*) against the posterior arch of C1, especially during neck flexion.

Extraskeletal manifestations of ankylosing spondylitis include aortic insufficiency, cardiac conduction abnormalities, iritis, upper lobe fibrobullous disease, and pleural effusions. Strict attention to intraoperative positioning is needed to avoid fracture of the fused spine with concomitant spinal cord trauma.

Achondroplasia

Achondroplasia is the most common cause of dwarfism, with short stature, short trunk, and disproportionate development. The estimated incidence is 1 in 26,000. Achondroplasia is transmitted by an autosomal dominant gene. Affected individuals are of normal intelligence and can lead a full and productive life. Their associated medical problems often require orthopedic surgical intervention, however, with the risk of perioperative complications.[42-44] The most serious complication of achondroplasia is premature fusion of the base of the skull resulting in a narrowed cervical canal or foramen magnum stenosis or both. Kyphoscoliosis with potential neurologic symptoms is another common complication associated with this genetic condition. These affected

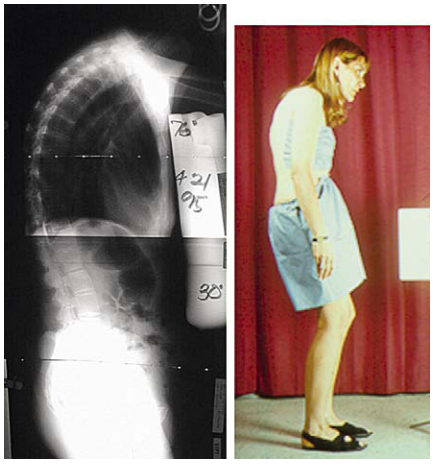

Figure 70-5 Patient with ankylosing spondylitis, exhibiting significant kyphosis of the spine. Note significant kyphosis in the lateral x-ray.

individuals undergo numerous orthopedic (spinal) procedures, including suboccipital craniotomy for foramen magnum stenosis, correction or stabilization of kyphoscoliosis, and laminectomies for spinal nerve root compressions.

Conventional laryngoscopy and tracheal intubation can be difficult and dangerous in achondroplastic dwarfs. Laryngeal exposure via direct visualization may be difficult in dwarfs with cervical kyphosis, and neck flexion should be avoided in dwarfs with atlantoaxial instability or foramen magnum stenosis. Awake fiberoptic tracheal intubation is the safest approach to securing the airway in these patients. Intravenous sedation should be administered judiciously during the preparation of the airway because many of these patients experience central sleep apnea owing to brainstem compression. Severe episodes of sleep apnea also can occur in these patients without any other clinical evidence of cord compression.

When the airway is secured, dwarfs can still represent an anesthetic challenge because of restrictive lung disease and pulmonary hypertension. Pulmonary hypertension develops from chronic hypoxemia and hypercarbia secondary to airway obstruction, sleep apnea, and thoracic kyphoscoliosis. Preoperative spirometry can be difficult to interpret in a dwarf, with successive changes in measurements more useful than absolute values.[45] An echocardiogram should be obtained before major surgery to assess the degree of pulmonary hypertension and intracardiac shunts. Pulmonary hypertension leading to cor pulmonale is the most common and devastating cardiovascular complication that develops in dwarfs. In these patients, the anesthetic must avoid aggravating pulmonary hypertension (hypoxemia and acidosis) and ensure adequate cardiac output and end-organ perfusion. In many cases, it is safer to allow the patient to remain intubated and monitored in the intensive care unit (ICU) until fully awake and spontaneously ventilating.

Orthopedic Procedures in Children with Special Conditions

The anesthetic management of pediatric patients undergoing orthopedic surgery is beyond the scope of this chapter (see Chapters 81 and 82). In most cases, care of pediatric patients would be similar as for other surgical procedures except that in many cases regional anesthesia might be a preferred alternative to general anesthesia. There are, however, a few pediatric diseases that predispose children to multiple orthopedic procedures.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is inflammation of the synovium of the joints that occurs before 16 years of age. JIA is classified into five types, as follows: (1) Oligoarthritis accounts for 50% of JIA and involves fewer than five joints; often these patients also have uveitis. (2) Polyarthritis involves arthritis in five or more joints. (3) Systemic arthritis accounts for 10% to 20% of JIA and is characterized by associated high fevers, rash, and nonarticular organ involvement. (4) Enthesitis-related arthritis affects the spine, hips, and attachment points of tendons to bones. (5) Psoriatic arthritis includes psoriasis and arthritis.

As in adult RA, the disease is chronic with quiescent periods interspersed with acute exacerbations. Also as in adult RA, airway issues can make tracheal intubation difficult and potentially dangerous. In most cases, fiberoptic intubation should be performed, and this can be done after the child has been anesthetized and is breathing spontaneously. Muscle relaxants should be reserved until the airway is secured. In contrast to adult RA, pulmonary disease is uncommon, but JIA patients can have associated pleuritis, pleural effusions, and pneumonitis. Pericarditis is common in patients with JIA, and it responds to steroid therapy. Some JIA patients also have myocarditis and conducting system abnormalities. In addition, vascular access in JIA patients can be extremely difficult because of fragile veins and a tendency to bruise and bleed easily. As with adult RA, JIA patients are managed with similar groups of medications with similar potential complications.

Osteogenesis Imperfecta

Osteogenesis imperfecta is a rare autosomal dominant inherited disease that results in extremely brittle bones because of a defect or deficiency in type I collagen production.[46,47] Repeated and multiple bone fractures are the most significant clinical manifestation of this disease (Table 70-4). In the most extreme form, multiple fractures occur during delivery, which are often fatal. In the milder variations, the individual is affected by multiple fractures produced with seemingly inconsequential force or trauma. Fractures are more common in the lower extremity, with the femur being the most commonly broken bone. Fracture deformities of the pelvis can lead to acetabular protrusions into the abdomen. Kyphoscoliosis is common secondary to decreased ligamentous stability. Affected children usually have a blue sclera because of defective collagen production. Impaired platelet function with increased perioperative bleeding also occurs.

Although osteogenesis imperfecta has been associated with malignant hyperthermia, this has not been verified by muscle biopsy (see Chapter 37).[48] Hyperthermia and metabolic acidosis can, however, be common intraoperative clinical manifestations of osteogenesis imperfecta. Associated cardiac abnormalities include patent ductus arteriosus, septal defects, and acquired aortic regurgitation and cystic degeneration of the proximal aorta (see Chapters 82 and 83).

The fragility of connective tissue and bones in osteogenesis imperfecta demands extreme care in positioning and padding during anesthesia. The area under the blood pressure cuff must be padded, and for longer procedures insertion of an arterial catheter avoids the repeated inflation of the cuff and the risk of a

Table 70-4 Anesthetic Considerations for Patients with Osteogenesis Imperfecta

Airway	Risk of fractures of the mandible, maxillary surface, and cervical spine
Bleeding	Platelet abnormalities
Cardiac	Congenital and valvular heart disease; cystic degeneration of proximal aorta
Eyes	Exophthalmos—prone positioning
Hyperthermia	Malignant hyperthermia; hydration; possible cooling
Positioning	Risk of repeated fractures
Pulmonary	Kyphoscoliosis—restrictive lung disease
Regional anesthesia	Fractures; intraosseous injections

humeral fracture. Because patients with osteogenesis imperfecta often have reduced mobility of the cervical spine, tracheal intubation must be achieved with minimal neck manipulation. Awake fiberoptic intubation in many cases would be the prudent approach. The administration of succinylcholine should be avoided for the induction of anesthesia because of the theoretical risk of malignant hyperthermia, and because muscle fasciculations may produce bony fractures. Osteogenesis imperfecta patients should have a preoperative echocardiogram and any abnormal findings should be managed accordingly.

The bleeding status of patients with osteogenesis imperfecta should be evaluated preoperatively to prepare for the perioperative transfusion of platelets. In some cases, desmopressin (DDAVP) may reverse the platelet abnormality. Because there is a risk of intraoperative hyperthermia and metabolic acidosis, osteogenesis imperfecta patients should be aggressively hydrated, and if necessary active cooling should be instituted. Regional anesthesia is an attractive alternative to general anesthesia, but must be approached with caution to avoid bone punctures and intraosseous injections (see Chapters 52 and 53).

Cerebral Palsy

Cerebral palsy is a nonprogressive motor impairment arising from lesions in the brain that occurred during the early stages of development—in utero (75%), at birth (10%), and soon after birth (15%) (see Chapter 82). The cause of cerebral palsy remains unclear; however, intrapartum asphyxia, which was originally thought to be the major etiology of the disease, may be responsible for only 10% of the cases. Perioperative infections and low birth weight may play a much more important role. Cerebral palsy is divided into four major classifications to describe the different movement impairments: spastic, athetoid/dyskinetic, ataxic, and mixed. Spastic cerebral palsy, which is the most common type, results from damage to the corticospinal tract, motor cortex, or pyramidal tract. Many of these affected children also have epilepsy and cognitive disorders.[49]

Although the neurologic deficit in cerebral palsy is nonprogressive, the secondary orthopedic consequences of the disease lead these patients to multiple surgical procedures. Normal skeletal developmental requires stress from the musculature to attain their proper shape and size. Without these stresses or with abnormal stresses as in cerebral palsy, various angular joint deformities and gracile (thin) shafts and abnormal articular joints develop. Orthopedic surgeries often involve loosening of tight muscles (hip adductor and iliopsoas release), releasing fixed joints, straightening abnormal twists (derotational osteotomy of the femur), rhizotomies to reduce spasm, and spinal surgery to correct kyphoscoliosis.

Cerebral palsy patients have significant gastroesophageal reflux and poor laryngeal reflexes. In most cases, surgical procedures on cerebral palsy patients require general anesthesia with tracheal intubation, even if also accompanied by regional anesthesia to reduce the need for systemic anesthetics and to provide postoperative analgesia. Postoperative epidural analgesia with local anesthetic alone eliminates the potential complications of narcotics, and permits continued dosing with diazepam to relieve spasms. Regional anesthesia also may shorten emergence from general anesthesia, which can be prolonged because of inherent cerebral damage and the effects of antiseizure medications. Postoperative pulmonary complications are common owing to multiple causes, including aspiration, poor respiratory effort, and thoracic compliance. After major surgical procedures, cerebral palsy patients should be observed in a monitored setting for several hours.

Regional Versus General Anesthesia

Many orthopedic procedures are well suited for regional anesthetic techniques (see Chapters 52 and 81). The controversy as to whether regional anesthesia has an advantage over general anesthesia has been debated for decades without clear evidence documenting superiority of one method. Regional anesthesia may reduce the incidence of major perioperative complications with certain surgical procedures, however, including deep vein thrombosis (DVT), pulmonary embolism (PE), blood loss, respiratory complications, and death.[50,51] In addition, postoperative pain management, a significant problem after orthopedic procedures with regional anesthetic techniques, leads to superior pain relief.[52] Peripheral nerve blocks employing long-acting anesthetics or catheters may provide excellent intraoperative anesthesia and superior postoperative analgesia.[53,54] Regional anesthesia may provide preemptive analgesia. In addition, severe acute pain after orthopedic surgery can develop into a chronic pain syndrome, which may be ameliorated by aggressive perioperative analgesia.[55]

As stated earlier, orthopedic patients often pose difficult airway management problems. Regional anesthesia avoids manipulation of the airway, and conscious patients can aid in the safest and most comfortable positioning for surgery. It is prudent, however, to recognize the warnings of Benumof: "Use of regional anesthesia in the patient with a recognized difficult airway does not solve the problem of the difficult airway; it is still there."[56] A well-defined plan must be devised for these patients for management of the airway in the event of a regional anesthetic failure or the need to secure the airway during an emergency.

A further advantage to the use of regional anesthetic techniques for orthopedic surgery has been the suggestion of decreased intraoperative blood loss. Since 1966, 17 randomized trials of patients undergoing THA have shown diminished blood loss with regional anesthesia compared with the same procedure performed under general anesthesia.[57] Modig[58] compared blood loss in THA patients randomly assigned to epidural anesthesia, general anesthesia with spontaneous ventilation, and general anesthesia with positive-pressure ventilation. The epidural group showed the smallest blood loss, but no significant relationship between arterial blood pressure and blood loss. The authors suggested that epidural anesthesia reduces venous blood pressure (measured in the operative wound), and this is the significant factor in determining surgical bleeding.

Perioperative Management of Orthopedic Patients

Thromboprophylaxis in Orthopedic Surgery

Thromboembolic complications remain one of the leading causes of morbidity and mortality after orthopedic surgery.[59,60] THA,

total knee arthroplasty (TKA), and hip and pelvic fracture surgery have the highest incidence of venous thromboembolism, including DVT and PE. Patients with DVT and PE are at risk for short-term and long-term morbidity and mortality. Patients with symptomatic PE have an 18-fold higher risk of death than patients with a DVT alone. The short-term complications of survivors of acute DVT and PE include prolonged hospitalization, bleeding complications related to DVT and PE treatments, local extension of DVT, and further embolization. Long-term complications include post-thrombotic syndrome, pulmonary hypertension, and recurrent DVT.

Because venous thrombi consist of fibrin polymers, anticoagulants should be administered for the prevention and treatment of DVT. Thrombolytics should be administered only in the event of a severe, possibly fatal PE. Treatment guidelines are based on the Seventh American College of Chest Physicians Conference document on DVT and PE.[61] Low-molecular-weight heparin (LMWH) is recommended over unfractionated heparin (intravenous or subcutaneous) for initial therapy of DVT and PE. LMWHs do not require monitoring of coagulation. Although DVT prophylaxis may be more efficient when started preoperatively, the risk of surgical bleeding also increases. Administration of LMWH 6 hours postoperatively was effective in DVT prophylaxis and did not increase bleeding; delaying prophylaxis until 24 hours was less effective.[62] Although the optimal duration of therapy is unknown, LMWH should be continued for at least 10 days in routine orthopedic procedures and in patients not considered high risk. Extended prophylaxis to 28 to 35 days would be supported in patients with evidence of a DVT or at higher risk for DVT. Risk factors for the development of PE after surgery are advanced age, obesity, previous PE and DVT, cancer, and prolonged bed rest. Factor V Leiden is the most common hereditary blood disorder associated with DVT. Warfarin is usually employed in the long-term treatment of DVT, with a target international normalized ratio (INR) of 2.5 maintained for the duration of therapy. In the United States, LMWH (enoxaparin) is administered at 30 mg every 12 hours; in Europe, it is administered at 40 mg daily. An alternative to LMWH is fondaparinux, a synthetic pentasaccharide that is a selective inhibitor of factor Xa and has a prolonged half-life of 18 hours. When administered once daily, fondaparinux produces a predictable anticoagulant response.[63] The American College of Chest Physicians guidelines do not recommend the sole use of aspirin for DVT prophylaxis after THA, TKA, and hip fracture surgery. More recent reports, however, have supported the use of aspirin, pneumatic compression, and early mobilization as effective prophylaxis for DVT after THA and TKA.[64]

The use of perioperative anticoagulants has a significant impact on the use of regional anesthesia, in particular neuraxial anesthesia with the potential risk of an epidural hematoma. The American Society of Regional Anesthesia (ASRA) has published and updated consensus conference recommendations with regard to the use of anticoagulants and regional anesthesia.[65] Full anticoagulation is a contraindication to regional techniques. The risk of an epidural hematoma is significantly increased with the use of LMWH, so the following recommendations have been made:

1. An interval of 12 hours should be observed after administration of the usual dose of LMWH and placement of a neuraxial block.
2. In patients receiving larger doses of LMWH (enoxaparin 1 mg/kg every 12 hours), the delay should be extended to 24 hours.
3. Epidural catheter removal should occur at least 8 to 12 hours after the last LMWH administration, or 1 to 2 hours before the next administration of LMWH.

Aspirin and NSAIDs do not seem to increase the risk of an epidural hematoma after neuraxial anesthesia. The American Society of Regional Anesthesia also recommends that for patients receiving warfarin, the prothrombin time and INR should be checked before neuraxial anesthesia, and an epidural catheter should not be removed if the INR is greater than 1.5. In a retrospective review of more than 12,000 TKAs in which warfarin was administered postoperatively, and an epidural catheter was maintained for analgesia, there were no reported epidural hematomas despite patients having an INR greater than 1.5.[66]

Lower Extremity Surgery

Arthroscopy

Arthroscopic procedures for the knee, hip, and ankle are increasingly performed as ambulatory procedures (see Chapter 78). These cases can be particularly challenging for the anesthesiologist who must decide on the appropriateness of the patient and procedure for outpatient surgery and an anesthetic that is adequate for the procedure, but provides the patient's expectation of an uncomplicated postoperative recovery with minimal pain.

Limited data are available to determine which patients are inappropriate adult ambulatory patients. In most centers, morbidly obese patients and patients with sleep apnea require monitored observation overnight after procedures in which systemic anesthetics and analgesics have been administered. The presence of stable preexisting diseases does not increase the incidence of postoperative complications in ambulatory patients, but American Society of Anesthesiologists grade 3 and 4 patients should have a medical clearance that documents the stability of their medical conditions. It follows then that medically unstable patients are not outpatient surgical candidates.

In a prospective study of 1088 patients for ambulatory surgery, Pavlin and coworkers[67] reported that the most important factors in determining discharge time were pain, nausea and vomiting, unresolved neuraxial blocks, and urinary retention. This study emphasizes the role of anesthesia in prolonging ambulatory surgical stay. General anesthesia is a safe and effective anesthetic for arthroscopic surgery, but it has been associated with increased postoperative nausea and vomiting and pain. A properly designed regional anesthetic may reduce the importance of some of these factors.

Arthroscopic knee surgery can be performed with a combination of extra-articular and intra-articular injections of local anesthetics. Short-duration local anesthetics are often combined with longer acting local anesthetics (bupivacaine) and morphine to provide postoperative analgesia. Intra-articular morphine probably does provide significantly additional analgesia after arthroscopic knee surgery. For more involved arthroscopic procedures, such as an anterior cruciate ligament repair, surgical relaxation is also required. Spinal anesthesia with pencil-point

atraumatic needles to prevent postdural puncture headaches provides excellent operating conditions for these procedures.

Problems related to neuraxial anesthesia for ambulatory surgery include unpredictable onset and regression of the spinal blockade, urinary retention, and transient neurologic symptoms. A dose of 45 mg of isobaric spinal mepivacaine results in a mean motor block of 142 ± 37 minutes. Using 30 to 40 mg of spinal chloroprocaine, Yoos and Kopacz[68] reported 155 ± 34 minutes to ambulation in outpatient surgical patients. Transient neurologic symptoms (TNS) are symptoms of pain in the gluteal region that can radiate down both legs and appear within a few hours to 24 hours after an uneventful spinal anesthetic.[69,70] The incidence of TNS is more frequent after outpatient surgery in the lithotomy position and in patients undergoing knee arthroscopy. The pain can vary from mild to severe, lasts 2 to 5 days, and is best treated with NSAIDs. TNS is more common after a spinal anesthetic with lidocaine (approximately 14%) than with mepivacaine (6.5%) and bupivacaine (<1%). For ambulatory patients, the benefit of short-acting spinal anesthetic must be weighed against the risk of developing transient neurologic symptoms. For postoperative analgesia after anterior cruciate ligament repairs, a femoral nerve block with a long-acting local anesthetic is superior to intra-articular injections. Because the quadriceps muscle is blocked, it is important for the patient to be fitted with a knee brace before ambulation.

Hip arthroscopy has become a common outpatient procedure for the diagnosis and treatment of hip pathology. The patient can be placed in either the supine or the lateral position (operative side up) with 50 to 75 lb of traction applied to the operative limb to gain access to the joint with the arthroscope. In positioning the patient, the anesthesiologist must ensure that the peroneal post is padded and not compressing the pudendal nerve, and that excessive traction for prolonged periods is not applied (see Chapter 36). Because complete muscle relaxation is required for the procedure, the patient must have either a general anesthetic or a neuraxial block. A lumbar-plexus block can be performed for postoperative analgesia.

Hip Fractures

Hip fractures in elderly individuals are common (1 in 50 individuals >60 years old), and as previously stated are associated with significant morbidity and mortality (1-year mortality of 30%).[4] The high perioperative complication rate is related to many factors, including cardiac conditions, pulmonary conditions, DVT, and delirium. Postoperative confusion and delirium is common, reported in 50% of elderly patients after the repair of hip fractures, and it is associated with increased mortality.[25-27] In many cases, dehydration and electrolyte abnormalities contributed to this delirium. In one study, the incidence of hyponatremia was 4%, and it was associated with a sevenfold increase in hospital mortality.[71]

These patients often arrive in the hospital in pain, under considerable stress, and possibly exhibiting signs and symptoms of myocardial ischemia. Although preoperative preparation is essential, delaying surgery may exacerbate these problems and increase the incidence of complications. Early surgery (<12 hours) has resulted in lower pain scores, decreased length of hospital stay, and reduced perioperative complications.[72] Compared with delayed surgery, however, early surgery has not been associated with increased overall survival. Early surgery for hip fractures should still be the goal for stable patients, combined with early mobilization, rehabilitation, and aggressive medical care.

Patients with hip fracture are often dehydrated and anemic because the fracture site can accommodate considerable extravasated blood. Blood hematocrit values are often normal because of this constricted blood volume in a dehydrated patient. A normal intravascular blood volume should be restored before anesthesia and surgery; this is best achieved with central venous catheter monitoring. Central venous catheter monitoring also may prevent overhydration, which can precipitate congestive heart failure. Placement of an arterial catheter permits accurate blood pressure monitoring during surgery and the ability to follow serial arterial blood gases. Hypoxemia, possibly owing to fat embolization, has been a major determinant of mortality in these patients.

Several studies have reported improved outcome with regional anesthesia compared with general anesthesia in these patients.[51] Patients undergoing hip fracture surgery have the greatest risk of death from a PE.[59] In a meta-analysis of patients undergoing the repair of femoral neck fractures, the incidence of DVT was almost four times greater in the patients who received general versus regional anesthesia.[73] A spinal anesthetic with isobaric 0.5% bupivacaine provides a stable regional anesthetic of sufficient duration to complete the surgical repair. Epidural anesthesia with postoperative analgesia is usually not indicated because in most cases aggressive postoperative anticoagulation is instituted.[61] Intravenous sedation during the procedure must be coupled with the ability of the patient to remain adequately oxygenated. Long-acting benzodiazepines should be avoided because of their association with postoperative confusion. In many cases, these patients require postoperative monitoring in an ICU-like setting.

Pelvic Fractures

Pelvic fractures are usually caused by significant trauma to the lower trunk and are often accompanied by chest (21%), head (16%), and liver and spleen (8%) injuries.[74] The 3-month mortality for pelvic fractures is almost 14%. Pelvic fractures also can result in fatal retroperitoneal bleeding. Hypotension and an increase in abdominal girth is an indication for emergent exploratory surgery. Injuries to the bladder and urethra also are often associated with pelvic fractures; urology clearance is usually indicated before inserting a Foley catheter. Because there is a significant risk of DVT and PE, many of these patients require a temporary inferior vena cava filter before surgery.

Most reports suggest that the optimal time for stabilization of pelvic fractures is within the first week of trauma, but associated injuries often delay the operation. Because iatrogenic sciatic nerve injury is the most frequent surgical complication (approximately 18%), many trauma surgeons advocate the use of neuromuscular monitoring during the operation. An optimal anesthetic may be the combination of a general anesthetic with the placement of an epidural catheter for postoperative analgesia after the preservation of lower extremity movement and sensation has been confirmed. In most cases, these patients require monitoring with arterial and central venous catheters, and the placement of large-gauge venous catheters in the event of sudden surgical hemorrhage.

Hip and Knee Arthroplasties

With the aging of the population, major orthopedic joint replacement procedures are becoming increasingly more common. The rate of major adverse events after hip and knee arthroplasties is 6.4%, and as stated earlier, the most important risk factor is advanced age (see Chapter 71).[3,5] The most common complications after THA and TKA are cardiac events, PE, pneumonia and respiratory failure, and infection.[3,75,76] Elderly patients with major comorbid conditions, including cardiac conditions, pulmonary conditions, and diabetes, should have a complete preoperative medical evaluation. In addition, obesity, particularly in a TKA patient, can be a problem anesthetically, and postoperatively with regard to obstructive sleep apnea and infections.[77] Many of these patients require prolonged postoperative monitoring in the postanesthesia care unit or ICU (see Chapter 85).

THA may be performed via an anterior or lateral approach. The anterior approach offers the advantage of exposure without violation of the muscles, but restricts full access to the femur with the risk of lateral femoral cutaneous nerve injury. The lateral posterior approach provides excellent exposure to the femur and the acetabulum with minimal muscle damage, but increases the risk of posterior dislocation. Most surgeons prefer the lateral posterior approach, which places the patient in the lateral decubitus position, surgical side up, for the operation. The anesthesiologist must be aware that this position may compromise oxygenation, particularly in obese and severely arthritic patients, owing to ventilation-perfusion mismatch. In addition, to prevent excessive pressure on the axillary artery and brachial plexus by the dependent shoulder, an anterior roll or pad must be placed beneath the upper thorax.

The nerve supply to the hip joint includes the obturator, inferior gluteal, and superior gluteal nerves. Regional anesthesia for THA is best achieved with a spinal or epidural anesthetic. Although most studies suggest decreased postoperative complications, particularly DVT and PE and respiratory problems, with regional anesthesia compared with general anesthesia, some controversy still remains.[51] A lumbar paravertebral block may be used for postoperative analgesia when postoperative anticoagulation requires removal of the epidural catheter.[78]

Blood loss during THA can be significant, and with revision procedures the patient can lose 1 to 2 L of blood. Several studies have shown that controlled hypotensive epidural anesthesia with mean arterial blood pressures of 50 to 60 mm Hg can reduce intraoperative blood loss for primary THAs to approximately 200 mL.[79] Elderly patients (mean age 72 years) were able to tolerate this degree of blood pressure reduction without cognitive, cardiac, or renal complications.[80] In addition to reduced overall blood loss during THA, hypotensive anesthesia may improve the cement prosthesis to bone fixation by limiting bleeding in the femoral canal.[81]

The femoral prosthesis can be fixed to the femoral canal through methyl methacrylate cement or bony ingrowth. Cemented fixation of the femoral prosthesis has been complicated by the "bone-cement implantation syndrome," which may result in intraoperative hypotension, hypoxia, and cardiac arrest and FES postoperatively (Fig. 70-6; see Fig. 70-2).[33-35] Several mechanisms have been suggested for these events, including embolization to the circulation of bone marrow debris during pressurization of the femoral canal, toxic effects of circulating methyl methacrylate monomer, and the release of cytokines during reaming of the femoral canal that promote microthrombus formation and pulmonary vasoconstriction. The cement monomer induces systemic hypotension, but not myocardial depression when intravenously injected in dogs.[82] The embolization of intramedullary debris is the most likely explanation because this debris can be visualized in the right heart using transesophageal echocardiography (see Fig. 70-2).

During THA, the hip is dislocated, and the femoral vein is probably obstructed. With hip relocation, embolic material generated during the insertion of the femoral prosthesis is released into the circulation after the relocation of the hip and unkinking of

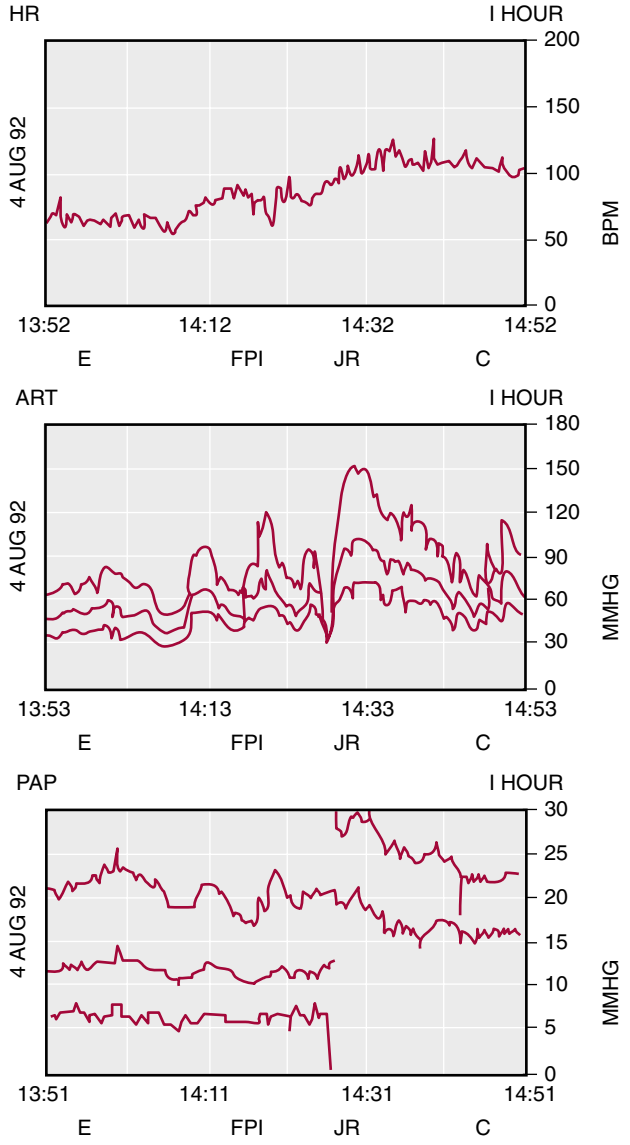

Figure 70-6 Intraoperative heart rate (HR), systemic arterial blood pressure (ART), and pulmonary arterial pressure (PAP) tracings of a patient undergoing revision total hip arthroplasty. E, induction of epidural anesthesia; FPI, insertion of a cemented femoral prosthesis; JR, reduction of prosthetic hip joint, producing hypotension with rebound from epinephrine injection; C, wound closure. *(From Urban MK, Sheppard R, Gordon MA, Urquhart BL: Right ventricular function during revision total hip arthroplasty. Anesth Analg 82:1225-1229, 1996.)*

the femoral vein. The hypotensive events that follow should be treated with epinephrine. Some of these hemodynamic consequences can be ameliorated through high-pressure pulsatile lavage of the femoral canal and drilling a vent hole in the femur before prosthesis insertion. Risk factors for this complication include revision surgery, a long-stem femoral prosthesis, THA for a pathologic fracture, preexisting pulmonary hypertension, and the quantity of cement used. These patients should be monitored with arterial and central venous catheters.

TKA also is becoming a major orthopedic procedure in the aging population, and these patients require the same preoperative medical evaluation as outlined for THA patients. The innervation of the knee includes the tibial nerve, the common peroneal nerve, the posterior branch of the obturator nerve, and the femoral nerve. Although general anesthesia can be safely provided for TKA, a prospective case-controlled study found general anesthesia and endotracheal intubation to be a major risk for nonsurgical complications after TKA.[50] Regional anesthesia in the form of a neuraxial block (spinal or epidural) or a combination of a femoral and sciatic block can be provided for the surgery. Sciatic nerve blocks may be a particular problem, however, in valgus knee deformities, where early detection of sciatic and peroneal nerve palsies is desired.

TKA patients have severe postoperative pain, and several studies have shown that management of this pain with regional analgesia has reduced complications and improved outcome.[83-85] Single-injection femoral nerve blocks in combination with intravenous and epidural patient-controlled analgesia have been employed to manage postoperative pain and improve functional recovery. When LMWH has been instituted for the prevention of DVT, patient-controlled epidural anesthesia cannot be continued postoperatively, and instead continuous femoral nerve catheters are used.

A pneumatic tourniquet is routinely inflated over the thigh during TKA to reduce intraoperative blood loss and provide a "bloodless" field for cement fixation of the femoral and tibial components. When the tourniquet is deflated, however, blood loss usually continues for the next 24 hours. Tourniquets are usually inflated to a pressure 100 mm Hg above the patient's systolic blood pressure for 1 to 3 hours. Nerve injury after extended tourniquet inflation (>120 minutes) has been attributed to the combined effects of ischemia and mechanical trauma. Peroneal nerve palsy, which is a recognized complication of TKA (incidence of 0.3% to 10%), may be caused by the combination of tourniquet ischemia and surgical traction.[86] Horlocker and colleagues[86] reported a combined tibial and peroneal nerve dysfunction of 7% of TKA patients associated with younger age, the presence of preoperative flexion deformities, and longer total tourniquet time. When prolonged tourniquet inflations are required, deflating the tourniquet for 30 minutes of reperfusion may reduce neural ischemia.

Pain related only to tourniquet inflation also may occur after 60 minutes, despite the presence of a regional anesthetic that is adequate for the surgery. It has been postulated that tourniquet pain is caused by the unblocking of unmyelinated C fibers during recession of a neuraxial block. The addition of narcotics to spinal or epidural anesthesia may ameliorate tourniquet pain. After tourniquet release, mean arterial blood pressure decreases significantly, partly owing to the release of metabolites from the ischemic limb into the circulation and the decrease in peripheral vascular resistance. In patients with known preexisting sciatic neuropraxias, neuropathic pain, and vascular disease in the operative leg, the operation can be performed without a tourniquet.

Many patients have symptomatic arthritis of both knees and require bilateral TKA to achieve functional improvement in pain and lifestyle. Controversy still exists as to whether both knees should be replaced sequentially in a single operation (simultaneous bilateral total knee arthroplasty [SBTKA]) or as a two-staged procedure, usually separated by several months. The advantages of SBTKA include exposure to the risks of one anesthetic, one postoperative course of pain, reduced rehabilitation and hospitalization, and an earlier return to baseline function. SBTKA has been associated, however, with a higher incidence of serious perioperative complications, including myocardial infarction, fat embolization, and thromboembolic events. Serious postoperative complications are more prevalent in elderly patients with cardiovascular disease.[87,88] SBTKA patients also require increased numbers of blood transfusions, are more likely to be transferred to a rehabilitation center, and have a higher incidence of postoperative ICU admissions.

Two more recent reports suggest that SBTKA can be performed without major complications.[89,90] Urban and associates[89] reported that with regional anesthesia and aggressive clinical management, which included 24-hour postoperative monitoring in an ICU, SBTKA patients had a major complication rate similar to matched control unilateral TKA patients. SBTKA patients exhibited a significantly higher incidence of FES and cardiac arrhythmias, however, than unilateral TKA patients did. Using published reports of SBTKA patients at risk for postoperative complications, Urban and associates[89] published guidelines for the exclusion of patients from SBTKA (Table 70-5).

Foot and Ankle Surgeries

Regional anesthesia that combines sciatic and femoral nerve blocks is sufficient for all surgical procedures below the knee that do not require a thigh tourniquet. The femoral nerve innervates the medial leg to the medial malleolus, and the remainder of the leg below the knee, including the foot, is innervated by the

Table 70-5 Patients Excluded for Single Operation for Bilateral Total Knee Arthroplasty

Age ≥ 75 yr
ASA class III
Active ischemic heart disease (positive stress test)
Poor ventricular function (LVEF < 40%)
Oxygen-dependent pulmonary disease
Patients considered at increased risk for morbidity and mortality
IDDM
Renal insufficiency
Pulmonary hypertension
Steroid-dependent asthma
Morbid obesity (BMI > 40)
Chronic liver disease
Cerebrovascular disease

ASA, American Society of Anesthesiologists; BMI, body mass index; IDDM, insulin-dependent diabetes mellitus; LVEF, left ventricular ejection fraction.

common peroneal nerve and tibial nerve, both branches of the sciatic nerve. The sciatic nerve is usually blocked high in the popliteal fossa to ensure anesthesia to the tibial and peroneal nerves. The nerves are identified through the use of a nerve-stimulating needle with foot inversion as the motor response or with ultrasound guidance. For procedures that also involve the medial aspect of the leg, the femoral nerve (saphenous nerve) can be blocked on the medial aspect of the leg, just below the knee. The popliteal sciatic nerve block also has been shown to reduce postoperative pain and narcotic requirements after foot and ankle surgery, when performed as a single preoperative injection or as a continuous catheter infusion.[91,92]

The acute compartment syndrome exists when edema and blood accumulate within a confined osseofascial space compromising the circulation and tissues within that space.[93,94] If not treated promptly, the pressure in the compartment leads to muscle and nerve ischemia and death, with potential loss of limb. Compartment syndrome occurs after fractures of the tibia, followed by the femur and ankle. Delay in diagnosis and treatment (surgical decompression) is the most common cause of serious complications. Pain out of proportion to the clinical situation is the usual early symptom. After the surgical repair of tibial and ankle fractures, a discussion with the surgeon with regard to the risk of compartment syndrome should occur before administering long-acting sciatic nerve blocks.

The ankle block is used for surgical procedures on the foot that do not require the use of a thigh tourniquet, although an ankle-level Esmarch tourniquet may be used. Because the block is primarily an infiltrative block, it usually is not performed by eliciting a paresthesia.

Five terminal nerves are usually blocked to provide complete anesthesia to the foot: (1) posterior tibial nerve, which provides sensation to the plantar surface; (2) saphenous nerve, which innervates the medial malleolus; (3) deep peroneal nerve, which supplies the interspace between the great and second toes; (4) superficial saphenous nerve, which supplies the dorsum of the foot and the second through the fifth toes; and (5) sural nerve, which supplies the lateral foot and lateral fifth toe (Fig. 70-7). Mineo and Sharrock[95] reported that the ankle block performed at the midtarsal level with 30 mL of 0.75% bupivacaine provided a mean duration of 17 hours of analgesia with safe blood levels of local anesthetic.

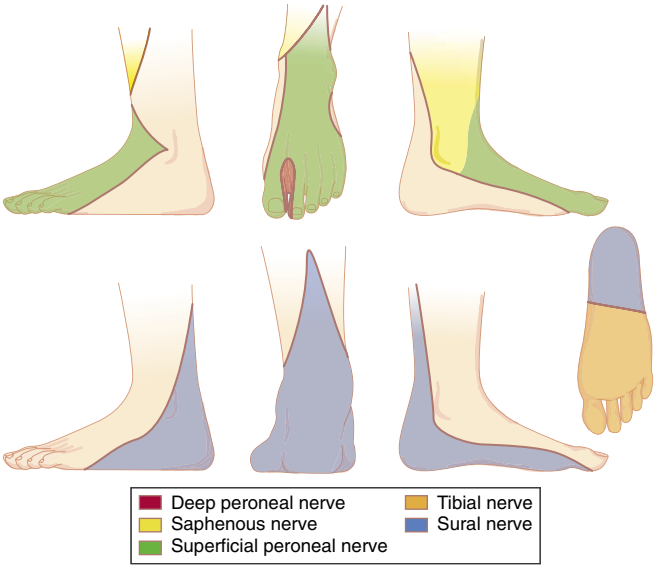

Figure 70-7 Cutaneous distribution of anesthesia produced by an ankle block. *(From Carron H, Korborn GA, Rowlingson JC: Regional Anesthesia: Techniques and Clinical Applications. New York, Grune & Stratton, 1984.)*

Upper Extremity Surgeries

Surgery for the upper extremity, from the shoulder to the hand, can be performed successfully by blocking the brachial plexus at several points until it branches into peripheral nerves (Table 70-6). Several methods are used to document the optimal location for neural blockade of the brachial plexus, including eliciting a paresthesia, motor nerve stimulation, ultrasound guidance, and perivascular infiltration. Regional anesthesia for the upper extremity also can provide postoperative analgesia using long-acting local anesthetics or continuous catheter techniques.

Regional anesthesia for shoulder surgery (see Chapters 52 and 53) has not gained wide acceptance because of the belief by anesthesiologists and surgeons that it is often inadequate for surgical anesthesia and the concern for postoperative neurologic symptoms (PONS). Several studies have reported 97% or greater successful surgical anesthesia using the interscalene block (ISB) approach to the brachial plexus with documentation of a paresthesia or the use of a nerve stimulator to locate the optimal site of injection.[96-98] The brachial plexus is formed from the ventral rami of C5-T1 nerve roots. After these roots pass between the anterior and middle scalene muscles, they fuse into three trunks (superior C5-6, middle C7, inferior C8-T1). During performance of the ISB, local anesthetic is injected between the scalene muscles at the level of the cricothyroid notch (C6) (Fig. 70-8).

The major acute complications and side effects associated with ISB are respiratory depression, intravascular injection with seizures and cardiac arrest, pneumothorax, epidural and spinal anesthesia, Horner's syndrome, hoarseness, and dysphagia. The ipsilateral phrenic nerve is blocked in all patients undergoing ISB, resulting in hemidiaphragmatic paresis.[99] Because hemidiaphragmatic paresis may result in a 25% reduction in pulmonary function, patients with severe respiratory disease may not tolerate an ISB without the addition of mechanical ventilation. An ISB would be contraindicated in patients after pneumonectomy on the contralateral side and for bilateral operative procedures. The

Table 70-6 Brachial Plexus Anesthesia

Site of Block	Simulated Brachial Plexus	Response
Interscalene	Roots; trunks	Shoulder to hand
Supraclavicular	Trunks (middle, inferior)	Upper arm to hand
Infraclavicular	Lateral cord	Forearm flexion Hand pronation
	Posterior cord	Wrist extension
	Medial cord	Fingers and thumb
Axillary	Median nerve	Forearm pronation Wrist flexion
	Ulnar nerve	Finger flexion Thumb opposition
	Radial nerve	Wrist extension

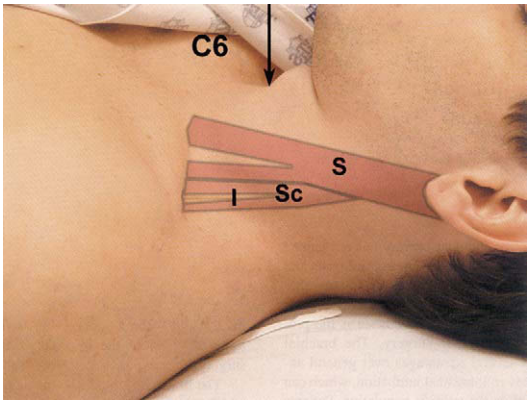

Figure 70-8 Interscalene approach to brachial plexus. At the level of the cricoid cartilage (C6), the anesthesiologist's finger is rolled laterally from the posterior border of the sternocleidomastoid muscle (S) into the interscalene grove (I) between the anterior and middle scalene muscles (Sc). The needle is inserted at point I and directed 45 degrees caudad and perpendicular to all planes. *(From Urban MK: The interscalene block for shoulder surgery. Tech Shoulder Elbow Surg 5:61-65, 2004.)*

supraclavicular block performed with ultrasound guidance may provide effective shoulder anesthesia without complete ipsilateral paresis of the phrenic nerve.

Because of the proximity to major vascular structures (vertebral artery, carotid artery, jugular vein), CNS toxicity is usually cited as a major risk of ISB. The reported incidence of CNS effects has been very low, however. Conn and associates[100] reported that ISB resulted in 3 of 100 patients experiencing CNS symptoms and one seizure. Urban and Urquhart[96] reported that 2 of 266 patients had CNS symptoms and no seizures.

PONS related directly to brachial plexus anesthesia is often cited as the reason to avoid regional anesthesia for shoulder and hand surgery. The few large studies that have attempted to ascertain the extent of nerve injury associated with ISB have concluded that although some patients may have neurologic complaints after surgery, many of them cannot be attributed to the anesthetic, and most of them resolve (Table 70-7). In the retrospective study by Conn and associates,[100] 2 of 100 patients had PONS, which persisted for 7 months and 18 months, respectively. In the prospective analysis of 266 patients by Urban and Urquhart,[96] 9% complained of paresthesias on the day after surgery, two thirds of which resolved after 2 weeks, and one persisted beyond 6 weeks. Liguori and colleagues[97] reported the incidence of PONS after ISB performed with either the documentation of a paresthesia (10 of 108) or the use of a nerve stimulator (11 of 109), with a median duration of 2 months and resolution of all cases of PONS within 1 year.

Arthroscopic shoulder surgery is often performed in the sitting (beach chair) position. Numerous hypotensive and bradycardic events, some progressing to asystolic arrest, have been associated with shoulder surgery in the sitting position under regional anesthesia.[102] There is some evidence that these events are the result of a cardiac inhibitory reflex, Bezold-Jarisch reflex, which occurs in response to diminished ventricular volume (venous pooling in the sitting position) and a hypercontractile ventricle. Prophylactic administration of β-blockers, anxiolytics, and intravenous fluids reduces the incidence of these events.[103]

For surgery from the elbow to the hand, the brachial plexus can be blocked via either the infraclavicular block approach or the axillary approach. Blockade of the nerves to the arm at the axilla can be achieved by a transarterial technique or the stimulation of a single nerve or multiple nerves. Advocates of the multiple paresthesia technique cite the report by Thompson and Rorie,[104] which states that within the axillary sheath the nerves are separated by discrete septa. Using a transarterial approach, Urban and Urquhart[96] reported a success rate of 93%. Advocates of the paresthesia or nerve stimulator technique for the axillary block argue that the transarterial approach may result in a hematoma with ischemic damage to the brachial plexus. Using the transarterial axillary block in 242 patients for forearm and hand surgery, 23% of the patients complained of tenderness and bruising at the axilla, and 19% had acute PONS.[96]

The infraclavicular block to the brachial plexus may be the best approach for elbow surgery, and it may result in less patient discomfort and PONS when used for forearm and hand surgery compared with the axillary approach, although objective evidence is still lacking.[105,106] Using the nerve stimulator technique, two large series of infraclavicular blocks reported 90% to 94% success with only posterior cord stimulation, whereas other reports still recommend a double stimulation technique. Performing the infraclavicular block with ultrasound guidance may avoid the need for multiple needle passes and the complications of vascular puncture and pneumothorax.[107]

Forearm and hand surgery also can be done under intravenous regional anesthesia. Intravenous regional anesthesia is a simple technique that involves exsanguinating the arm by wrapping it with a tight band, inflating an upper arm tourniquet to about 250 mm Hg, and injecting in a hand vein about 50 mL of a short-acting local anesthetic (0.5% lidocaine). A second tourniquet, proximal to the first, is often inflated 15 minutes later with subsequent deflation of the first, to minimize tourniquet pain. This technique is limited to short surgical procedures (approximately 1 hour). Complications occur when the tourniquet fails during initial anesthetic injection or the tourniquet is deflated early (<30 minutes), risking systemic local anesthetic toxicity.

Spinal Surgeries

In the United States with an active, aging population, 4.6 million individuals require spinal surgery at some time during their life. Spinal surgery includes a wide variety of procedures ranging from microdiskectomies for a herniated disk to complex reconstructive surgery for spinal deformities. These procedures can be simple or involve fusions at multiple levels, anterior or posterior approaches, and considerable blood loss. A few procedures, such as diskectomies, can be done under regional anesthesia.[108]

Table 70-7 Interscalene Block Complications: Postoperative Neurologic Symptoms

Reference	Acute Symptoms (%)	Chronic Symptoms (%)
Conn et al[100]	—	2
Urban and Urquhart[96]	9	0.4
Borgeat et al[101]	14	0.2
Faryniarz et al[98]	1.4	0
Liguori et al[97]	10	0

Table 70-8 Predictors of a Difficult Endotracheal Intubation

Facial dyssymmetry (trauma)
Tracheal deviation
Cervical fractures
Small mouth opening (interincisor gap)
Inability to visualize the faucial pillars and uvula (Mallampati)
Limited neck range of motion
Prominent incisors
Distance between thyroid cartilage and mandible <6 cm
Narrow maxillary arch

Table 70-9 Complications of the Prone Position*

Airway	ETT kinking, dislodgment Upper airway edema
Neck	Hyperextension or hyperflexion Cervical rotation—compromised blood flow to brain
Eyes	Orbital pressure—central retinal artery occlusion, supraorbital nerve Corneal abrasion
Abdomen	Pressure transmitted to epidural veins, increased bleeding
Upper extremity	Brachial plexus stretch—arms out Ulnar nerve compression—arms at the side
Lower extremity	Flexion of hips—occlusion of femoral vein, DVT, kinking of vascular grafts Pressure lateral to fibula—peroneal nerve palsy Pressure on iliac crest—lateral femoral cutaneous nerve

*See Chapter 36.
DVT, deep vein thrombosis; ETT, endotracheal tube.

Most spinal surgeries require general anesthesia. In this patient population with preexisting arthritic conditions, tracheal intubation often poses a challenge (Table 70-8). Awake, sedated fiberoptic intubation of many of these patients is the safest approach to general anesthesia. This is the standard of care in a patient with cervical spinal instability who requires posterior stabilization. These patients should be intubated first with a flexible fiberoptic bronchoscope, then positioned prone for surgery sedated but awake (if possible), and assessed for movements of upper and lower extremities before the induction of general anesthesia.

The careful positioning of patients for spinal surgery is an important shared responsibility of the anesthesiologist and surgeon (see Chapter 36). As stated previously, patients at risk for spinal cord compression should be positioned under light sedation, then observed for upper and lower extremity movement before inducing general anesthesia. Because some posterior cervical spine decompressions are done in the sitting position, preparations must be made for the possibility of a venous air embolism. Complex spinal deformity procedures often require anterior and posterior approaches to the spine. For a low lumbosacral approach, the patient is supine with the legs spread wide. Because pelvic retraction during this procedure may compromise blood flow to the legs, a pulse oximeter should be placed on a toe. Patients undergoing anterior thoracolumbar procedures are usually positioned in the lateral decubitus position where attention must be focused on the dependent arm and leg and the position of the neck. Table 70-9 outlines possible complications from prone positioning for these spinal procedures.

Complex corrective surgery of the spine includes patients with scoliosis, kyphosis, kyphoscoliosis, and revision surgery on patients with previous thoracolumbar fusions. Kyphosis is an exaggerated anterior flexion of the spine, as seen in ankylosing spondylitis. Scoliosis is defined as a lateral rotation of the spine greater than 10 degrees accompanied by vertebral rotation. Scoliosis is classified as idiopathic, congenital, or neuromuscular. Congenital scoliosis is the result of early embryonic errors in vertebral column formation, and half of the cases are associated with other organ system anomalies. Adolescent idiopathic scoliosis is common—present in 2% to 4% of children 10 to 16 years old. Only 10% of these adolescents have curves that require some type of medical intervention. Surgical intervention occurs when the curve magnitude estimated by the Cobb method is more than 40 degrees (Fig. 70-9), and there is a strong likelihood of curve progression. Most idiopathic scoliosis curves are right-sided; a left thoracic curve is more likely to be associated with other thoracic anomalies.

Thoracic scoliosis results in a narrowed chest cavity producing a decrease in chest wall compliance and restrictive lung disease. Cobb angles of greater than 65 degrees usually cause significant decreases in lung volumes. Although exercise tolerance is an important determinant of the effects of the severity of the curve on respiratory function, formal pulmonary function studies should be obtained before surgery. This information guides decisions regarding the extent of surgery permitted at one time and the requirement for postoperative ventilatory support. A vital capacity of less than 40% of the normal range is predictive of the requirement for postoperative ventilation. The major abnormality in arterial blood gases is hypoxemia, secondary to ventilation-perfusion inequalities caused by alveolar hypoventilation. Chronic hypoxemia produces elevated pulmonary vascular resist-



Figure 70-9 X-ray of a patient with scoliosis. Cobb angle is an angle formed by a line drawn perpendicular to the top of the superior vertebrae of the scoliotic curve and a similar perpendicular line drawn along the bottom of the inferior vertebrae. The Cobb angle in this patient is 62 degrees. *(From Reamy BV, Slakey JB: Adolescent idiopathic scoliosis: Review and current concepts. Am Fam Med 64:1-10, 2001.)*

ance, which ultimately leads to cor pulmonale. An echocardiogram should be assessed for pulmonary hypertension and right ventricular hypertrophy. In patients with pulmonary hypertension, the electrocardiogram may reveal evidence of right ventricular hypertrophy and right atrial enlargement.

Surgical spinal corrections involving high anterior thoracic levels or video-assisted thoracoscopic surgery require the isolation of one lung. One-lung ventilation traditionally has been achieved with a double-lumen endotracheal tube. In single-staged anterior then posterior spinal fusions and for postoperative ventilation, the double-lumen endotracheal tube must be replaced with a single-lumen endotracheal tube. A single-lumen endotracheal tube with an enclosed bronchial blocker also can provide one-lung ventilation, but has the advantage of being left in place as a single-lumen endotracheal tube with the blocker deflated at the end of the anterior procedure.[109] In patients with restrictive lung disease, adequate oxygenation may be difficult during one-lung ventilation and may require continuous positive airway pressure to the nonventilated lung and positive end-expiratory pressure to the ventilated lung.

Surgery for the correction of spinal deformities is usually associated with large blood losses. Multiple factors have been suggested to influence the magnitude of this blood loss, including: surgical technique, operative time, number of vertebral levels fused, anesthetics, mean arterial blood pressure, platelet abnormalities, dilutional coagulopathy, and primary fibrinolysis.[110] Several techniques have been employed to reduce this blood loss and limit the need for homologous blood transfusions, including proper positioning of the patient to reduce intra-abdominal pressure, surgical hemostasis, deliberate controlled hypotensive anesthesia, reinfusion of salvaged blood, intraoperative normovolemic hemodilution, use of pharmacologic agents that promote clot formation, and preoperative donation of autologous blood.

Controlled hypotensive anesthesia has been used commonly in limiting blood loss during idiopathic scoliosis corrections in adolescents, but must be used with caution in older patients.[111] In a young healthy patient, a mean arterial pressure of 50 to 60 mm Hg is well tolerated, but higher pressures may be required in adult patients with cardiovascular disease. In addition, perfusion of the spinal cord during deformity-correcting surgery may be exquisitely sensitive to low perfusion pressures. The adequacy of end-organ perfusion can be estimated with invasive monitoring, a urine output of 0.5 to 1 mL/kg/hr, and periodic blood gas analysis looking for evidence of metabolic acidosis.[112] In addition, central venous oxygen saturation analysis aids as an indicator of the patient's oxygen use. Although the increased heart rate associated with hypotensive anesthesia also may indicate anemia, hypovolemia, or "light" anesthesia, the use of a combined α/β-blocker for hypotensive anesthesia reduces the risk of myocardial ischemia and ameliorates rennin release with concomitant pressure rebound when the surgery has ended. Synthetic lysine analogs, such as aminocaproic acid and aprotinin, a polypeptide with serine protease inhibitor activity, also have been used to limit blood loss during these procedures by reducing fibrinolysis, but there may be concern because of more recent findings in postoperative cardiac cases.[113]

A postoperative neurologic deficit is one of the most feared complications of complex spinal reconstructive surgery. In a large survey of 97,586 spinal surgeries, neurologic deficits occurred in 0.55% of the cases.[114] To reduce this complication, Vauzelle and colleagues[115] introduced the concept of waking the patient up during surgery to determine the functional integrity of the spinal cord. This test is limited to gross motor movements of the lower extremities and can be influenced by anesthetics and the cognitive integrity of the patient. In addition, complications related to the test include inadvertent extubation of the patient during movement in the prone position, air embolism during a deep inspiration, and dislodgment of the instrumentation during violent movements.

Multimodal intraoperative monitoring has become the standard of care for complex reconstructive spinal surgery.[116] This monitoring includes somatosensory evoked potential (SSEP), motor evoked potential (MEP), and electromyogram monitoring. Electromyograms are used to monitor nerve root injury during pedicle screw placement and nerve decompressions (see Chapter 46). The posterior—sensory—portion of the spinal cord is evaluated using SSEP monitoring. MEPs assess the integrity of the anterior—motor—spinal cord. There are several potential adverse effects of MEP monitoring, including cognitive deficits, seizures, bite injuries, intraoperative awareness, scalp burns, and cardiac arrhythmias. It is advisable to employ a soft bite block during MEP monitoring to prevent tongue biting and dental damage. MEP monitoring should be avoided in patients with active seizures, vascular clips in the brain, and cochlear implants. In SSEPs, an impulse is sent from a peripheral nerve and measured centrally. In MEPs, an impulse is triggered in the brain and monitored as movement of a specific muscle group. SSEPs and MEPs are evaluated with regard to amplitude—strength—of the signal and latency—time it takes the signal to travel through the spinal cord—compared with the patient's nonsurgical control values.

Numerous physiologic factors attenuate SSEP and MEP monitoring, including hypotension, hypothermia, hypocarbia, hypoxemia, anemia, and anesthetics. The potent inhaled agents reduce the amplitude of the signal and increase latency in a dose-dependent manner. If a volatile anesthetic is used for the anesthetic, the concentration should be kept at about half minimum alveolar concentration and not varied throughout the procedure. Nitrous oxide produces a decrease in the amplitude of the signal and may have to be eliminated during MEP monitoring. Total intravenous anesthesia has been used successfully for MEP and SSEP monitoring. MEPs are the least affected by narcotics, midazolam, and ketamine, but are depressed by propofol. The depressant effect of propofol is diminished, however, with ketamine, such that the best total intravenous anesthetic may be an infusion of narcotic, ketamine (at low doses), and propofol.[117,118] Muscle relaxants cannot be administered during MEP monitoring.

Postoperative visual loss (POVL) is another devastating complication of spinal surgery (see Chapter 90). POVL is rare after spinal surgery (≤0.1%) and may be caused by ischemic optic neuropathy (ION), retinal artery or vein occlusion, and cortical brain ischemia. In an attempt to delineate the etiology of POVL, the American Society of Anesthesiologists Committee on Professional Liability established a POVL registry to collect detailed information on these cases.[119] Most patients with central retinal artery occlusion had evidence of unilateral ocular trauma, suggesting that improper positioning may have played a role. ION was the most common cause of POVL after spinal surgery. ION can be divided into anterior ION and posterior ION depending on the visual field cut, and whether edema to the optic disk is present early (anterior ION) or later (posterior ION). Both types are the result of reduced blood flow or oxygen delivery from end-arteriole branches of the ophthalmic artery.

The registry of 93 POVL cases after spinal surgery reported that most patients were relatively healthy and that blood loss greater than 1000 mL and duration in the prone position greater than 6 hours were present in 96% of the cases. ION occurs in the absence of direct pressure on the eye. Because ION occurred in the absence of vascular injury to other critical organs and in cases where neither hypotension nor anemia was reported, optic nerve blood supply may be uniquely vulnerable to hemodynamic perturbations in the prone position.

Patients experience considerable pain after multilevel spinal fusions with instrumentation (see Chapter 87). Most of these patients are initially treated with intravenous narcotics, but because of their multiple side effects, a multimodality approach with other agents has been recommended. For lumbar fusions, an epidural catheter placed at a level above the incision can be used for patient-controlled epidural anesthesia infusions of local anesthetics and narcotics. For procedures involving more extensive spinal levels, intrathecal morphine administered during surgery has been shown to provide reliable postoperative pain control.[120] NSAIDs may have a negative influence on the success of spinal fusions, however. For narcotic-tolerant patients, subanesthetic doses (0.2 mg bolus, then 2 μg/kg/hr) of ketamine reduced postoperative pain after posterior spine fusions.[121]

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Key Points

1. Two important principles must be kept in mind when discussing the physiology of aging. First, aging is associated with a progressive loss of functional reserve in all organ systems. Second, the extent and onset of these changes vary from individual to individual.
2. Generally, elderly patients are more sensitive to anesthetic agents. Less medication is usually required to achieve a desired clinical effect, and drug effect is often prolonged.
3. The greatest concern of the elderly patient is to maintain independence. The most important outcome and overall objective of perioperative care of geriatric patients is to speed recovery and avoid functional decline.
4. Surgical risk and outcome in patients 65 years old and older depend primarily on four factors: age, the patient's physiologic status and coexisting disease (American Society of Anesthesiologists class), whether the surgery is elective or urgent, and the type of procedure.
5. When performing preoperative evaluation of a geriatric patient, one should have a high index of suspicion for disease processes commonly associated with aging, and one should assess the degree of functional reserve of specific, pertinent organ systems, and the patient as a whole, before surgery.
6. Important issues of special concern in caring for elderly patients are cognitive dysfunction and perioperative delirium.
7. Current data suggest that routine testing on the basis of age alone is not indicated. Instead, selective testing should be done on the basis of the history and physical examination and the specific surgical procedure.
8. Preoperative comorbid disease is a greater determinant of postoperative complications than anesthetic management. Perioperative care should be tailored to comorbid disease and requirements of the surgical procedure.
9. Preoperative and postoperative management of pulmonary problems in elderly patients is of particular importance in the prevention of morbidity and mortality.

Although understanding anesthetic care for older patients can be related to the description of fundamental alterations in physiology and changes in the pharmacokinetics and pharmacodynamics of anesthetic medications, these issues are only starting points for defining the myriad factors influencing perioperative care of this heterogeneous population. This chapter reviews the relevant basics and discusses special considerations for optimizing care of elderly surgical patients.

Defining and implementing optimal perioperative care for elderly patients is of increasing importance to all stakeholders in health care, including consumers, insurers, and government agencies. The emphasis on cost containment and pay for performance initiatives is likely to drive many aspects of care in this arena. The demographic considerations alone are staggering. As of 2003, the number of individuals older than 65 years in the United States had increased to 35.9 million with 18.3 million 65 to 74 years old and 12.9 million 74 to 84 years old. In 2003, 4.7 million were older than age 85. In 2000, the average life expectancy was 76.5 years. In the United States, the first of the "baby boomers" will reach age 65 in 2011. It is estimated that by 2030, 72 million (20%) U.S. citizens will be older than 65 years. Worldwide, 974 million people will be older than 65 years with 70% residing in developing countries.[1]

Elderly individuals frequently access health care. In 2004, elderly patients represented roughly 12% of the health care population, accounted for 38% of discharges, and used 44% of all hospital days while receiving approximately one third of all surgical procedures in acute care hospitals in the United States.[2] Fifty percent of all individuals older than 65 years are estimated to have a surgical procedure.

Core Concepts in the Anesthetic Management of Elderly Patients

Two important principles must be kept in mind when discussing the physiology of aging. First, aging is associated with a progressive loss of functional reserve in all organ systems. Second, the

extent and onset of these changes vary from person to person. In most older patients, physiologic compensation for age-related changes is adequate, but the resultant limitation in physiologic reserve may become evident only during times of physiologic stress, including exercise, illness, and surgery. Anticipating the interaction of underlying disease, limited end-organ reserve, and the stress of the perioperative period should aid the perioperative physician in providing the best care possible.

Mechanisms of Aging

Aging is a universal and progressive physiologic process characterized by declining end-organ reserve, decreased functional capacity, increasing imbalance of homeostatic mechanisms, and an increasing incidence of pathologic processes.[3] Aging is now viewed as an extremely complex multifactorial process with interaction of various pathways to differing degrees and effect.[4] Theories of aging may be grouped into broad categories including evolutionary and physiologic mechanisms. These mechanisms also may be defined according to "programmed" or biologic clock theory, in which genetic mechanisms program declining function, and "error" theories, in which environmental damage leads to impaired function and progressive decline. These processes of aging overlap and may be defined further by the organizational level of an organism where a given process occurs. Changes at one level influence processes at another level. Molecular effects influence cellular function, which causes alterations in major organ systems and ultimately may exert evolutionary pressure by influencing survival and reproduction. Weinert and Timiras[3] recently reviewed major theories of aging. These are summarized in Table 71-1.

Table 71-1 Classification and Brief Description of Theories of Aging

Biologic Level/Theory	Description
Evolutionary	
Mutation accumulation	Mutations that affect health at older ages are not selected against
Disposable soma	Somatic cells are maintained only to ensure continued reproductive success; after reproduction, soma becomes disposable
Antagonistic pleiotropy	Genes beneficial at younger age become deleterious at older age
Molecular	
Gene regulation	Aging is caused by changes in the expression of genes regulating development and aging
Codon restriction	Fidelity/accuracy of mRNA is impaired owing to inability to decode codons in mRNA
Error catastrophe	Decline in fidelity of gene expression with aging results in increased fraction of abnormal proteins
Somatic mutation	Molecular damage accumulates primarily to DNA/genetic material
Dysdifferentiation	Gradual accumulation of random molecular damage impairs regulation of gene expression
Cellular	
Senescence-telomere theory	Phenotypes of aging are caused by an increase in frequency of senescent cells owing to telomere loss or cell stress
Free radical	Damage caused by free radical production from oxidative metabolism
Wear-and-tear	Accumulation of normal injury
Apoptosis	Programmed cell death
System	
Neuroendocrine	Alterations in neuroendocrine control of homeostasis leads to physiologic change
Immunologic	Decline in immune function leads to altered incidence of infection and autoimmunity
Rate-of-living	Assumes a fixed amount of metabolic potential for every living organism (live fast, die young)

Adapted from Weinert BT, Timiras PS: Invited review: Theories of aging. J Appl Physiol 95:1707, 2003.

Nervous System

With aging, several important processes occur that are of interest to the anesthesiologist.[5] These changes may be modified further by other underlying pathologic or age-related processes.[6] Memory decline occurs in greater than 40% of individuals older than age 60 years.[7] Memory decline in aging is not inevitable, however. Age-related memory decline is important because it can dramatically affect performance of the activities of daily living (ADL).

Structurally, cerebral atrophy occurs with aging in a selective and differential manner. There is a decrease in the volume of gray and white matter.[8] The decrease in gray matter volume is thought to be secondary to neuronal shrinkage as opposed to neuronal loss. More recent studies focusing on the effects of normal aging on the human cerebral cortex suggest that there is a small overall loss of neurons from the neocortex.[9] This decrease in neuron number is nowhere near as massive as older studies had indicated. Some neocortical areas do not lose any neurons with aging. There may be 15% loss, however, of white matter with aging.[9] Such loss results in gyral atrophy and increased ventricular size. Shrinkage in the subcortical white matter and the hippocampus may be accelerated by hypertension and vascular disease.

It is controversial whether the aging process alters the number of synapses present in the cortex. Data from nonhuman primates suggest significant regional reductions in the neurotransmitters dopamine, acetylcholine, norepinephrine, and serotonin with aging.[9] Levels of glutamate, the primary neurotransmitter in cortex, do not seem to be affected. Coupling of cerebral electric activity, cerebral metabolic rate, and cerebral blood flow remains intact in elderly individuals.

Although biochemical and anatomic changes have been described in the aging brain, the exact mechanisms causing changes in functional reserve are unclear. Decreases in brain reserve are manifested by decreases in functional ADL, increased sensitivity to anesthetic medications, increased risk for perioperative delirium, and increased risk for postoperative cognitive dysfunction.

Neuraxial changes include a reduction of the area of the epidural space, increased permeability of the dura, and decreased

volume of cerebrospinal fluid. The diameter and number of myelinated fibers in the dorsal and ventral nerve roots are decreased in elderly individuals. In peripheral nerves, inter–Schwann cell distance is decreased, as is conduction velocity. These changes tend to make elderly individuals more sensitive to neuraxial and peripheral nerve block.[10]

Cardiovascular System

The aging process is associated with primary and secondary changes in the heart, primary changes in the blood vessels, and alterations in autonomic control. As the heart ages, changes in morphology occur. Myocyte number decreases, left ventricular wall thickening occurs, and conduction fiber density and sinus node cell number decrease.[11] Functionally, these changes translate to decreased contractility, increased myocardial stiffness and ventricular filling pressures, and decreased β-adrenergic sensitivity.[11] Vascular stiffness increases with advancing age related to breakdown of elastin and collagen. Alterations in nitric oxide–induced vasodilation also contribute.[12]

Morphologically, one sees an increase in the diameter and stiffness of large elastic arteries. Functionally, these changes are readily observed in terms of an elevated mean arterial pressure and increased pulse pressure.[13] Increased vascular stiffness leads to important secondary responses in the heart. In youth, the cardiac pump and the blood vessels are optimally coupled to maximize efficiency. With increased resistance in the blood vessels, the velocity of conduction of pulse waves down the vascular tree increases. Increased pulse wave velocity results in earlier reflection of pulse waves from the periphery. In younger humans, wave reflection occurs later because of slower propagation, such that reflected waves reach the heart after aortic valve closure. In the setting of increased pulse wave velocity with early wave reflection, reflected pulse waves reach the heart during the latter phases of ejection, imposing an increased cardiac load.[11] Alterations in left ventricular afterload can lead to left ventricular wall thickening, hypertrophy, and impaired diastolic filling.[14]

Hypertrophy is not necessary for alterations in ventricular stiffness to occur.[15] Decreased ventricular compliance and increased afterload combine to cause a compensatory prolongation of myocardial contraction. This occurs at the expense of a decreased early diastolic filling time. Under these conditions, the contribution of atrial contraction to late ventricular filling becomes more important and explains why cardiac rhythm other than sinus is often poorly tolerated in elderly individuals.

Changes in the autonomic system with aging include a decrease in response to β-receptor stimulation and an increase in sympathetic nervous system activity.[16] Decreased β-receptor responsiveness is secondary to decreased receptor affinity and alterations in signal transduction.[17] Decreased β-receptor responsiveness assumes functional importance when increased flow demands are placed on the heart. Normally, β-receptor–mediated mechanisms act to increase heart rate, venous return, and systolic arterial pressure, while preserving preload reserve. In contrast, the attenuated β-receptor response in elderly individuals during exercise or stress is associated with decreased maximal heart rate and decreased peak ejection fraction. This response causes the increased peripheral flow demand to be met primarily by preload reserve, making the heart more susceptible to cardiac failure.[11]

It is well known that sympathetic nervous system activity increases with aging. Although changes in β-receptor responsiveness are well defined, it is controversial whether the aging process alters the α-receptor response. Clinically, these autonomic changes lead to a greater likelihood of intraoperative hemodynamic lability and decreased ability to meet the metabolic demands of surgery.

Although the age-related changes in cardiovascular physiology are generally well tolerated, several pathophysiologic states warrant mention. Impairment of diastolic relaxation leads to diastolic dysfunction in the aging heart. In its severest form, diastolic dysfunction may manifest as diastolic heart failure. Predisposing disease states for this condition include hypertension with left ventricular hypertrophy, ischemic heart disease, hypertrophic cardiomyopathies, and valvular heart disease. More recent population-based studies suggest that diastolic dysfunction is common and associated with an increase in all-cause mortality.[18] In patients with clinically evident heart failure, ejection fraction is preserved in more than half, with 40% manifesting overt diastolic failure. Mortality in the cohort with preserved ejection fraction is similar to patients with impaired ejection fraction.[19]

Clinically, diastolic failure occurs when decreased left ventricular compliance results in greatly increased left ventricular diastolic pressure. If this pressure is conducted retrograde to the pulmonary circulation, it results in pulmonary venous congestion and pulmonary edema. Diastolic dysfunction or failure is often related to systemic blood pressure and does not imply volume overload. Diagnosis can be difficult because the clinical picture appears identical to left ventricular systolic failure. Making the correct diagnosis is important because interventions commonly employed in systolic failure, such as diuretics and inotropes, may exacerbate diastolic dysfunction.[20] Echocardiography is the diagnostic modality of choice (see Chapter 34).[21] Classically, echocardiography shows preserved or hyperdynamic left ventricular systolic function and characteristic changes of flow velocity at the mitral valve.

Aortic valve sclerosis and mitral annular calcification are common echocardiographic findings in elderly patients. These represent non–flow-limiting calcifications around the aortic and mitral valves. Otto and colleagues[22] showed that aortic valve sclerosis is common in elderly patients and is associated with a 50% increase in the risk of cardiovascular death. It has been suggested that aortic valve sclerosis may represent a marker for coronary artery disease. A similar association has been postulated for mitral annular calcification.[23]

Respiratory System

Alterations in control of respiration, lung structure, mechanics, and pulmonary blood flow place elderly patients at increased risk for perioperative pulmonary complications. Ventilatory responses to hypoxia, hypercapnia, and mechanical stress are impaired secondary to reduced central nervous system activity.[24] In addition, the respiratory depressant effects of benzodiazepines, opioids, and volatile anesthetics are exaggerated.[24,25] These changes compromise the usual protective responses against hypoxemia after anesthesia and surgery in elderly patients.

Structural changes in the lung with aging include the loss of elastic recoil after reorganization of collagen and elastin in lung parenchyma. This loss of elastic recoil combined with altered

surfactant production leads to an increase in lung compliance. Increased compliance leads to limited maximal expiratory flow and a decreased ventilatory response to exercise.[26] Loss of elastic elements within the lung is associated with enlargement of the respiratory bronchioles and alveolar ducts, and a tendency for early collapse of the small airways on exhalation. There also is a progressive loss of alveolar surface area secondary to increases in size of the interalveolar pores of Kohn. The functional results of these pulmonary changes are increased anatomic dead space, decreased diffusing capacity, and increased closing capacity all leading to impaired gas exchange.

Loss of height and calcification of the vertebral column and rib cage lead to a typical barrel chest appearance with diaphragmatic flattening. The flattened diaphragm is mechanically less efficient, and function is impaired further by a significant loss of muscle mass associated with aging. Functionally, the chest wall becomes less compliant, and work of breathing is increased.

Although there are alterations in lung volumes with aging, total lung capacity is relatively unchanged. Residual volume increases by 5% to 10% per decade. Vital capacity decreases. Closing capacity increases with age. Change in the relationship between functional residual capacity and closing capacity cause an increased ventilation-perfusion mismatch and represent the most important mechanism for the increase in alveolar-arterial gradient for oxygen observed in aging (Table 71-2).[27] In younger individuals, closing capacity is below functional residual capacity. At 44 years of age, closing capacity equals functional residual capacity in the supine position, and at 66 years of age, closing capacity equals functional residual capacity in the upright position.[27] When closing capacity encroaches on tidal breathing, ventilation-perfusion mismatch occurs. When functional residual capacity is below closing capacity, shunt increases, and arterial oxygenation decreases. This results in impairment of preoxygenation. Increased closing capacity in concert with depletion of muscle mass causes a progressive decrease in forced expiratory volume in 1 second by 6% to 8% per decade.

Increases in pulmonary vascular resistance and pulmonary arterial pressure occur with age and may be secondary to decreases in cross-sectional area of the pulmonary capillary bed.[28] Hypoxic pulmonary vasoconstriction is blunted in elderly individuals and may cause difficulty with one-lung ventilation.

Renal and Volume Regulation

Renal mass may decrease 30% by age 80 years.[29] Loss of mass is most prominent in the renal cortex. This loss correlates with a decrease in the number of functioning glomeruli. Many confounders exist, however, in interpreting the data of older morphologic studies. Lower numbers of glomeruli have been associated with low birth weight, and rates of attrition are accelerated in hypertension.[30] Renal blood flow seems to decrease about 10% per decade. There is a progressive decline in creatinine clearance with age, yet with normal aging, serum creatinine remains relatively unchanged. This occurs because muscle mass also decreases with aging. Serum creatinine is a poor predictor of renal function in elderly patients. This concept is important in proper dosage adjustment for medications that are excreted by the kidneys.

Functional changes in the kidneys with aging include alterations in electrolyte handling and the ability to concentrate and dilute urine. Renal capacity to conserve sodium is decreased. Overall, older patients have a tendency to lose sodium in the setting of inadequate salt intake. This tendency, paired with a decreased thirst response, may place an elderly patient at risk for dehydration and sodium depletion. The elderly patient also has a diminished ability to handle a salt load, as evidenced by increased sodium retention and expansion of the extracellular volume during the perioperative period.[31] These changes assume particular importance under conditions of limited fluid intake.

Table 71-2 Normal Values for Arterial Po_2

Age (yr)	Mean; Range (mm Hg)
20-29	94; 84-104
30-39	91; 81-101
40-49	88; 78-98
50-59	84; 74-94
60-69	81; 71-91

From Nunn J: Nunn's Applied Respiratory Physiology, 4th ed. Oxford, Butterworth-Heinemann, 1995, p 269.

Hepatic Changes

Liver volume decreases approximately 20% to 40% with aging. Hepatic blood flow decreases about 10% per decade.[32] There also is a variable decrease in the liver's intrinsic capacity to metabolize drugs. Effects on phase I reactions predominate. Decreases in hepatic blood flow may decrease maintenance dose requirements in drugs that are rapidly metabolized. The pharmacokinetics of drugs that are slowly metabolized are more affected by innate liver capacity than by blood flow.[33]

Preventable Hazards and Special Perioperative Considerations for Elderly Patients

The greatest concern of the elderly patient is to maintain independence. The most important outcome and overall objective of perioperative care of the geriatric population is to speed recovery and avoid functional decline. Many factors must be considered in the preoperative planning that affect anesthetic management and recovery from surgery.

Consent, Surrogate Decision Makers, and Advance Directives

Autonomy is the most important principle in health care decision making with the elderly.[34] Autonomy implies mental competence, however. The legal standards for competence include the abilities to communicate a choice, understand relevant information, appreciate the current situation and its consequences, and manipulate information rationally.[35] Cognitive and sensory difficulties

frequently jeopardize informed consent in frail elderly patients. Dementia, depression, hearing difficulties, and stroke all may interfere with the ability to make independent decisions.

If one's ability to make decisions becomes severely impaired, a surrogate must give consent. Caution must be exercised in this situation. A low rate of agreement has been shown when comparing the health care decisions made by surrogates with the desires of the elderly patients involved.[36] Advance directives, when available, can be extremely helpful, but even with them difficult problems remain. Issues of consent and end-of-life decisions in elderly patients are complex and familiar to the practicing anesthesiologist. Addressing the specific desires of a patient who presents to the operating room with "do not resuscitate" orders is a common problem. Often there are no easy answers to these ethical dilemmas (see Chapter 9).[37]

Age and Age-Related Disease

It is well appreciated that aging is associated with an increased incidence of chronic systemic disease processes, such as hypertension, diabetes mellitus, ischemic heart disease, and malignancy. Some specific diseases, such as dementia and Parkinson's disease, have a significantly higher incidence in elderly individuals. It is often difficult to separate the effects of aging alone from the effects caused by concurrent disease. Acute and chronic pathologic insults occur in the setting of a decreased physiologic reserve that can have profound effects on the usual compensatory mechanisms and dramatically alter clinical presentation. These factors become especially confusing in considering perioperative risk in elderly patients.

Atypical Presentation of Disease

Recognizing acute illness and exacerbation of chronic disease in elderly patients can be challenging. Frequently, acute illness may have an atypical presentation.[38] The appearance of pneumonia in elderly patients may be heralded by uncharacteristic features such as confusion, lethargy, and general deterioration of condition.[39,40] There may be significant differences in the presentation of disease in demented versus nondemented patients. Studies suggest that the nonspecific presentation of disease in older individuals is primarily linked to the presence of dementia rather than a characteristic feature of the aging process.[41]

Dementia

Dementia is common in the geriatric population. Alzheimer's disease is present in 6% to 8% of patients 65 years old and older. Hospitalization and surgery represent a challenge to the demented patient. Agitation, in particular, is an issue in these patients.

It is important to determine the presence of cognitive deficit during the preoperative evaluation. Preoperative cognitive deficit has a direct bearing on postoperative emergence and perioperative morbidity. Cognitive deficits are associated with poorer rehabilitation outcomes and higher surgical mortality.[42,43] In terms of choice of anesthetic technique, it is controversial whether the administration of general anesthesia accelerates the progression of senile dementia because not all studies support this view.[44,45] Perhaps most important, dementia is a predictor of postoperative delirium.[46] Accurate diagnosis of dementia is not always easy. For the purposes of preoperative evaluation, the mini-mental status examination allows for quick screening of baseline cognitive status.[47] In addition, insight may be gained by speaking with the patient's family concerning baseline function and ADL.

Parkinson's Disease

The etiology of Parkinson's disease is unknown. Parkinson's disease is present in about 3% of the population older than age 66.[48] The classic triad of resting tremor, muscle rigidity, and bradykinesia results from destruction of dopaminergic neurons in the pars compacta of the substantia nigra. Patients may present for procedures related to treatment of Parkinson's disease or for treatment of common surgical diseases. More recent reviews emphasize the complexity of tailoring anesthetic care for patients with Parkinson's disease.[49] Parkinson's patients are at increased risk for postoperative pharyngeal dysfunction, leading to difficulty handling secretions and risk of aspiration. Autonomic instability may result from Parkinson's disease, as a complication of therapy, or as a combination of the two. Exacerbation of disease can lead to complications related to muscle dysfunction, including respiratory embarrassment and increases in tremor, akinesia, confusion, or frank hallucination.

Generally, the antiparkinsonian regimen should be continued up to the time of surgery. The commonly used agent levodopa has a short half-life, and therapeutic effects may wane by the end of the proposed surgery. Other agents frequently used in treatment of Parkinson's disease include monoamine oxidase inhibitors with well-known adverse interactions with opiates. Opiates may exacerbate muscle rigidity. Phenothiazines, butyrophenones, and metoclopramide all have potential to worsen symptoms and should be avoided. Propofol may have unpredictable effects on motor function and is best avoided during stereotactic procedures.

Polypharmacy

It has been estimated that the average patient older than age 65 takes eight different medications each day.[50] The number of medications used is directly proportional to the likelihood of having an adverse drug reaction with an incidence of 5% to 35% in outpatients older than age 65.[51] An expert panel identified risk factors for adverse drug reactions, including 12 medication-related factors and 9 specific patient characteristics.[51] Many of these adverse drug reactions represent classes of medications used in the perioperative period and common characteristics of elderly surgical patients. There is significant risk for interaction with medications introduced in the perioperative period.

Functional Status and Assessment of Functional Reserve

One end point in determining the success of surgical interventions in geriatric patients should be to return the patient to his or her previous level of activity and independence. Evidence suggests that current level of function is helpful in predicting long-term outcomes in medical patients.[52] Few studies in the surgical literature have attempted to address how preoperative level of function predicts postoperative quality of life (Table 71-3). Preop-

Table 71-3 Effect of Preoperative Level of Function on Postoperative Quality of Life

Study	Patient Population	Comment
Eisler et al*	Hip fracture	Low preoperative functional status predicts functional independence at 3 mo and 6 mo postoperatively
Falcoz et al†	Open heart surgery	Preoperative quality-of-life assessment is predictive of 1-yr cardiac functional status
Bo et al‡	General surgical patients	Functional measures are predictive of 30-day mortality in urgent procedures

*Eisler J, Cornwall R, Strauss E, et al: Outcomes of elderly patients with nondisplaced femoral neck fractures: 2002. J Orthop Trauma 17:S31-S37, 2003.
†Falcoz PE, Chocron S, Stoica L, et al: Open heart surgery: One-year self-assessment of quality of life and functional outcome. Ann Thorac Surg 76:1598-1604, 2003.
‡Bo M, Cacello E, Ghiggia F, et al: Predictive factors of clinical outcome in older surgical patients. Arch Gerontol Geriatr 44:215-224, 2007.

erative functional assessment provides a baseline to determine whether quality of life has been maintained by surgical intervention. Ideally, surgical decision making incorporates outcomes research on quality of life to an ever greater extent.

Various instruments are available to evaluate functional activity[53] and heath-related quality of life.[54] A commonly used screening tool for determining independence and functional level for the preoperative assessment is to question the patient concerning ADL and instrumental activities of daily living (IADL). ADL represent activities involved in physical day-to-day self-care, whereas IADL represent more complex tasks. These instruments are useful for indicating specifically how an individual is performing at the present time. When these instruments are used longitudinally over time, they serve as documentation of an individual's functional improvement or deterioration. IADL and ADL assessments are important for their predictive ability. Any ADL impairment is associated with a relative risk of 1.9 (1.2 to 2.9; 95% confidence interval) for 90-day mortality in medical patients. Any IADL impairment is associated with a relative risk of 2.4 (1.4 to 4.2; 95% confidence interval) for 90-day mortality in medical patients.[52] Any impairment of one to two ADL is associated with a relative risk of 1.47 (1.08 to 2.01; 95% confidence interval) hazard ratio of recovering independent function from a disability.[55]

For some anesthesiologists, a complete functional assessment can be an onerous task. Some data suggest that the entire battery of ADL and IADL questions is unnecessary, and the preoperative examination may entail a more focused approach. Self-reported walking ability may be the best predictor of overall mobility in community-dwelling older adults, even if they have existing difficulties with ADL and mobility.[56] Self-reported walking ability is important to assess because data suggest that walking-related items are predictive of mortality and nursing home admission.[57]

Frailty

Frailty refers to a loss of physiologic reserve that makes a person more vulnerable to disability during and after stress. The components of the frailty syndrome include mobility; muscle weakness; poor exercise tolerance; unstable balance; and factors related to body composition such as weight loss, malnutrition, and muscle wasting (Table 71-4).[58] It is estimated that the incidence of frailty in the community-dwelling population older than 65 years is 6.9%.[59] Patients who are frail are more likely than their peers to be hospitalized, fall, develop disability, and die. When followed over 3 years, frailty is predictive of disability, hospitalization, and death.[59] Data are scant concerning the effect of frailty on surgical outcomes. The concept of frailty assumes greater importance in assessment of surgical outcomes research.

Delirium

The incidence of postoperative delirium in elderly patients varies widely depending on the type of surgery. The incidence of delirium has been estimated to approximate 10% in elderly patients after major elective surgery, but to be higher after cardiac surgery and hip fracture repair.[60] In a review of 26 primary data collection studies conducted between 1966 and 1992, the incidence of postoperative delirium for all types of surgery was found to be 36.8% (range 0% to 73.5%).[46]

Incidence, but not prevalence, of delirium is an important predictor of longer hospital stay and increased costs.[61] Overall, 2 million to 3 million elderly patients per year experience delirium during their hospital stay, involving more than 17.5 million inpatient days and accounting for more than $4 billion in Medicare expenditures.[62] Milbrandt and associates[63] projected the yearly

Table 71-4 Criteria Used to Define Frailty*

Weight Loss Criterion
The patient is asked the question, "In the last year, have you lost more than 10 lb unintentionally (i.e., not due to dieting or exercise)?"
Patients answering yes are categorized as frail by the weight loss criterion.
Exhaustion Criterion
The patient is read the following two statements: (1) I felt that everything I did was an effort; (2) I could not get going. The question is asked, "How often in the last week did you feel this way?" The patient's response is rated as follows: 0 = rarely or none of the time (<1 day); 1 = some or little of the time (1-2 days); 2 = a moderate amount of the time (3-4 days); or 3 = most of the time.
Patients answering "2" or "3" are categorized as frail by the exhaustion criterion.
Physical Activity Criterion
The patient is asked about weekly physical activity.
Patients with low physical activity are categorized as frail by the physical activity criterion.
Walk Time Criterion
The patient is asked to walk a short distance and timed.
Patients who are slow walkers are categorized as frail by the walk time criterion.
Grip Strength Criterion
The patient's grip strength is measured.
Patients with decreased grip strength are categorized as frail by the grip strength criterion.

*Frailty is defined as a clinical syndrome in which three or more of the above frailty criteria are met.
Adapted from Fried LP, Tangen CM, Walston J, et al: Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56:M146-M156, 2001.

costs associated with delirium in a medical intensive care unit (ICU) patient to be $6.5 billion to $20.4 billion. Whether these costs apply to surgical ICU patients is yet to be determined. In a study cohort of 500 elective surgical patients at the Cleveland Clinic, the incidence of postoperative delirium was 11.4%, and average costs per patient were increased by $908, $1400, and $400 for nursing, technical services, and professional consultative fees, respectively. These individual increases accounted for a greater than $2500 cost increase per surgical patient experiencing delirium.[64]

Delirium is a syndrome characterized by acute onset of variable and fluctuating changes in level of consciousness accompanied by a range of other mental symptoms. By convention, the presence or absence of delirium is based on application of diagnostic criteria articulated in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV): "The essential feature of a delirium is a disturbance in consciousness that is accompanied by a change in cognition that cannot be better accounted for by a preexisting or evolving dementia" (Table 71-5).[65]

The Confusion Assessment Method (CAM)[66] is a bedside rating scale developed to assist non–psychiatrically trained clinicians in the rapid and accurate diagnosis of delirium in clinical settings. The CAM follows DSM-III-R criteria for delirium, but can be easily adapted to approximate DSM-IV criteria, which are similar. The CAM is designed to be administered by any clinician, including physicians or nurses, and may be administered by trained lay interviewers. Data suggest that geriatricians, nurses, and trained lay interviewers perform as well as psychiatrists in rating the CAM.[67] The sensitivity of the CAM versus psychiatric diagnosis is 94% to 100%, and specificity is 90% to 95%.[66]

There are many possible pathophysiologic mechanisms for delirium.[68] Although we do not yet fully understand the basic mechanisms of delirium, in the geriatrics paradigm, delirium epitomizes an atypical presentation of disease[69] in which acute illness is manifested in the most vulnerable organ system, or "the weakest link"—in this case, the brain. This theory holds that the normal aging process can be characterized as "homeostenosis," the progressive constriction of each organ system's ability to respond to stress.[70] In addition, the aging brain is more likely to be affected by diseases and drugs that cloud the sensorium. The sum of these effects leads some elderly to be teetering on the brink of neurodysfunction. Add any stressor, and these individuals develop acute worsening of their mental status. Based on the concept that "lack of brain reserve" predisposes elderly patients to delirium when exposed to stress, investigators have examined what preexisting vulnerability factors predispose elderly patients to delirium.

In medical patients, Inouye and Charpentier[71] developed a risk model for delirium that showed that the greater the number of preexisting vulnerability factors, the less acute the stressors required to invoke delirium. The important preexisting vulnerability factors defined in the medical model of delirium are visual impairment, severe illness, cognitive impairment, and dehydration. Kalisvaart and associates[72] attempted to validate the medical risk factor model of delirium in elderly hip surgery patients. Their study showed the usefulness of the medical risk factor model in predicting postoperative delirium in surgery patients and supports the concept that when more preexisting vulnerability factors are present, there is a higher risk for postoperative delirium.

A cornerstone of management of delirium is the recognition and treatment of any predisposing or precipitating factors for delirium (Table 71-6). More recent studies have shown that interventions consisting of standardized protocols for the management of known risk factors for delirium (e.g., cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration) result in significant reductions in the number and duration of episodes of delirium in hospitalized older patients.[73] Anesthetic-specific interventions include correction of metabolic and electrolyte disorders and perioperative continuation of pharmacologic therapy for neuropsychiatric disorders. Other interventions may be aimed at removing any triggering agents, such as drugs (e.g., anticholinergics) or inadequately controlled pain.[74] Type of anesthesia (regional versus general) and intraoperative hemodynamic complications have not been associated with delirium.[75] Alterations in blood transfusion practice may affect incidence because delirium has been associated with greater intraoperative blood loss, more postoperative blood transfusions, and postoperative hematocrit less than 30%.[75] Algorithms for pharmacologic treatment of delirium have been outlined in several more recent reviews.[76]

Table 71-5 DSM-IV Diagnostic Criteria for 293.0 Delirium

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention
B. A change in cognition (e.g., memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia
C. The disturbance develops over a short time (usually hours to days) and tends to fluctuate during the course of the day
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiologic consequences of a general medical condition

From American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision (DSM-IV-TR). Washington, DC, American Psychiatric Publishing, 2000.

Table 71-6 Predisposing and Precipitating Factors for Postoperative Delirium

Demographic characteristics—age >65 yr and male
Cognitive impairment or depression
Functional impairment
Sensory impairment, especially visual and hearing
Decreased oral intake
Drugs—polypharmacy, alcoholism, psychoactive, sedatives, narcotics, anticholinergic
Comorbidity—severe illness and neurologic disease
Some types of surgery—high-risk surgery (American Heart Association guidelines) and orthopedic
Intensive care unit admission
Pain
Sleep deprivation
Immobility/poor physical condition

Adapted from Inouye SK: Delirium in older persons. N Engl J Med 354:1157-1165, 2006.

Nutrition

In the community-dwelling elderly population, malnutrition has been reported to occur in 16.9% of women and 11.4% of men.[77] Among hospitalized elderly patients, the prevalence of malnutrition ranges from 15% to 26%.[78,79] Surgical patients who are malnourished have increased morbidity and mortality[80] and increased length of stay.[81] The diagnosis of malnutrition should be made on the basis of preoperative history and physical examination and laboratory tests (see Chapter 95).

Depression

Depression is estimated to occur in 10% of the community-dwelling population older than age 65 years.[82] Depression is an important issue because its presence may influence the occurrence of delirium[83] and length of stay,[84] and have a significant impact on postoperative quality of life.[85] Patients with baseline depression are at increased risk of death after coronary artery bypass graft (CABG) procedures.[86] Depression is easily treated with medications and psychological therapy. If possible, antidepressants should be continued during the perioperative period. Discontinuing antidepressants may increase symptoms of depression and confusion.[87]

Immobility

Bed rest leads to ventricular atrophy, hypovolemia, and orthostatic intolerance.[88] Prolonged bed rest causes decreases in muscle mass, which may influence ADL and pulmonary function.[89]

Dehydration

Dehydration accounts for approximately 6.7% of Medicare admissions.[90] Dehydration is often associated with hypernatremia and is accompanied by infection, such as pneumonia and urinary tract infection.

Alcoholism

Alcoholism is a common problem among elderly individuals.[91] Alcohol-related problems in elderly individuals often manifest as physical problems in the form of accidents or falls.[92] Alcoholism is an important predictor of postoperative pneumonia in noncardiac surgery patients.[93]

Hypothermia

Maintaining body temperature is important because unintentional hypothermia has been associated with myocardial ischemia, angina, and hypoxemia during the early postoperative period, particularly in high-risk patients undergoing lower extremity vascular surgery.[94] In patients with cardiac risk factors who are undergoing noncardiac surgery, the perioperative maintenance of normothermia is associated with a reduced incidence of morbid cardiac events and ventricular tachycardia.[95] Advanced age and general anesthesia are associated with hypothermia. During spinal anesthesia, a higher level of blockade is associated with a greater magnitude of core hypothermia.[96]

Trauma

Traumatic injury is an increasing problem for older adults and the individuals who care for them (see Chapter 72). Aside from the dramatic increase in the population at risk, in many circumstances older adults are enjoying a more active lifestyle that places them at risk for traumatic injury. There are important differences in patterns of injury and presentation of trauma in elderly patients.[97] In addition, evidence exists that elderly patients are often undertriaged. They are not initially transported to trauma centers even when appropriate criteria exist. This situation may occur because of inaccuracy of standard criteria in elderly patients or an age bias in referral patterns.

Age has been associated with increased mortality with various traumatic injuries. Cervical spine trauma is twice as likely in elderly patients with a greater likelihood of falls from sitting or standing height, multiple-level involvement, C1-2 involvement, and cervical instability compared with younger patients. Mortality and functional outcome after head injury is considerably worse in elderly patients, with preinjury anticoagulation or antiplatelet therapy dramatically worsening outcome.[98,99] Substance abuse is an often underappreciated factor.[100]

Falls are a common problem in and out of the hospital. As with any traumatic injury, prevention is the primary goal. Simple interventions, including identifying patients at risk, physical therapy, modification of the environment, and avoiding medications associated with orthostatic hypotension, may mitigate risk.[101]

Iatrogenic Complications

There are numerous hazards of hospitalization for elderly surgical patients. Iatrogenic complications are common and of increased severity in elderly patients.[102] The iatrogenic complications important to the anesthesiologist include adverse drug events, dehydration, delirium, and functional decline. Adverse drug events have a reported prevalence of 14.6% in hospitalized patients 70 years old and older, and are associated with the number of new inpatient medications and admission cognitive status. Patients experiencing an adverse drug event often incur a longer length of stay and a functional decline.[103]

Chronic Pain

The assessment of pain in elderly patients is often complicated by social, emotional, cognitive, and subjective issues (see Chapter 58).[104] At some time after age 65, 80% to 85% of individuals experience a significant health problem that predisposes them to pain. Chronic pain is frequently undetected, and it is important to evaluate the current use of pain medication.[105] Surveys of nursing home residents show arthritis is the most prevalent indication for analgesics (41.7% of residents), followed by bone fracture (12.4%) and other musculoskeletal conditions (9.7%). More residents

(76.8%) are reported to have chronic pain than acute pain (19.9%), and 3% have chronic and acute pain.[106]

Expected Outcomes

The successful end point of surgical intervention should be, at the very least, to return the patient to his or her previous level of activity and independence. Studies of certain high-risk patients reveal, however, that return to baseline function may be the exception rather than the norm. Thirty-nine percent of patients undergoing vascular surgery show a decline in capacity for independent function.[107] These types of findings suggest that physicians must begin to think about modification of treatment strategies in hopes of improving independent living status after vascular surgery. When achievement of return of function after major surgery and illness recovery is prolonged, many patients require extended assistance with ADL. This has important implications for discharge planning and rehabilitative care.

Disposition and Posthospital Care

Numerous factors are considered in determining the need for postacute care in a rehabilitation facility, including age, postoperative functional status, and home social situation.[108] Additionally, the availability of postacute care facility beds may drive the willingness to refer patients after discharge.[109] The decisions regarding disposition and the skill level required for care after discharge from the acute care hospital are complex. The effect of such care on overall outcome is largely unknown, however.[110]

Risk Assessment

Increased life expectancy, safer anesthesia, and less invasive surgical techniques have made it possible for a greater number of geriatric patients to be considered for surgical intervention. The decision to operate should not be based on age alone, but should reflect an assessment of the risk-to-benefit ratio of individual cases. Surgical risk and outcome in patients 65 years old and older depend primarily on four factors: (1) age, (2) the patient's physiologic status and coexisting disease (American Society of Anesthesiologists [ASA] class), (3) whether the surgery is elective or urgent, and (4) type of procedure (see Chapter 34).

Earlier studies suggest that anesthetic complications are related to age.[111] Surgical mortality increases with age.[112,113] Age also is an independent predictor of any serious adverse perioperative event.[114,115] These data emphasize that extremes of age do incur additional risk. The perioperative mortality in nonagenarians ranges from 0% to 20% depending on the type of procedure.[116,117] Compared with younger patients, patients 90 years old or older are more likely to die during hospitalization after hip fracture repair.[118] Age alone should not be a deterrent from surgery, however.

Prospective survival studies in surgical patients older than 75 years show that following an initial high mortality rate, the survival of this group as a whole approaches that of an age-matched population.[119] When surgical morbidity and mortality rates for nonagenarians are compared with age-matched, sex-matched, and calendar year of birth–matched peers from the general population, there is a decrease in patient survival at 1 year that reverses by 2 years, with observed survival at 5 years comparable to the rate expected.[120] In surgical patients 100 years old and older, the reported 48-hour, 30-day, and 1-year mortality rates are 0%, 16.1%, and 35.5%, respectively. Compared with survival rates for age-matched, sex-matched, and calendar year of birth–matched peers from the general population, the survival rate for centenarians who undergo surgery and anesthesia is comparable to the rate expected for nonsurgical patients.[121]

Although age has been shown to be a predictor of poor operative risk, the effect of age cannot be separated from ASA status or underlying comorbidity.[114] In carotid endarterectomy, mortality is greater in patients older than age 80 years. Illness severity has a greater impact on mortality after extracranial vascular surgery, however, than octogenarian status per se.[122] It is hard to pinpoint how aging alters surgical risk. It is likely that the association between age and surgical risk is related to the aging process and its ongoing decrease in functional organ reserve.

Emergency surgery is an independent predictor of adverse postoperative outcomes in older surgical patients undergoing noncardiac surgery.[120,123] Poorer preoperative physiology and preparation has a large influence on these results. Emergent care presents special problems, such as atypical presentations, impaired cardiopulmonary function, and fluid and electrolyte imbalance in the setting of decreased physiologic reserve.

Surgical mortality in elderly patients varies widely according to procedure.[113,124] The fact that risk varies widely depending on the type of surgery is well recognized. The current guidelines for cardiovascular evaluation of patients undergoing noncardiac surgery provide a useful means of categorizing procedures into low, intermediate, and high risk.[125]

Preoperative Evaluation

Two principles should be kept in mind when performing preoperative evaluation of a geriatric patient (see Chapter 34). First, one should have a high index of suspicion for disease processes commonly associated with aging. Common diseases of elderly patients may have a major impact on anesthetic management and require special care and diagnosis. Cardiovascular disease and diabetes are particularly prominent in this population. Pulmonary complications have an incidence of 5.5% and are the third leading cause of postoperative morbidity in elderly patients undergoing noncardiac surgery.[123] Pulmonary diagnosis and optimization cannot be overemphasized preoperatively. Management of cardiovascular disease, diabetes, and pulmonary disorders are discussed elsewhere in this textbook.

Second, one should assess the degree of functional reserve of specific, pertinent organ systems and the patient as a whole before surgery. Laboratory and diagnostic studies, history, physical examination, and determination of functional capacity should attempt to evaluate the patient's physiologic reserve. Laboratory testing should be guided by the patient's history, physical examination, and proposed surgical procedure, and should not be based on age alone. A prospective study of laboratory abnormalities in elderly patients failed to show any specific laboratory value as

predictive of adverse outcome. Only ASA physical status and surgical risk were significant.[126] Although electrocardiogram abnormalities are frequent, they also fail to predict postoperative cardiac complications.[127]

Although many questions remain, current evidence suggests cardiovascular risk may be mitigated by judicious perioperative β-blockade for patients with known coronary artery disease, particularly if begun at least weeks before surgery.[128] For elderly patients on long-term β-blocker therapy, long-acting β-blockers seem to be more effective than short-acting β-blockers in reducing risk of perioperative myocardial infarction.[129] A protocol involving acutely administering β-blockers beginning the day of surgery and continued perioperatively has been associated with an increased incidence of stroke and all-cause mortality.[129a]

Anesthetic Management

Clinical Pharmacology

Factors that affect the pharmacologic responses of elderly patients are well described and include changes in (1) plasma protein binding, (2) body content, (3) drug metabolism, and (4) pharmacodynamics.[130,131] The main plasma binding protein for acidic drugs is albumin and for basic drugs is α_1-acid glycoprotein. The circulating level of albumin decreases with age, whereas α_1-acid glycoprotein levels increase. The effect of alterations in plasma binding protein on drug effect depend on which protein the drug is bound to, and the resulting change in fraction of unbound drug. The relationship is complex, and generally changes in plasma binding protein levels are not a predominant factor in determining how pharmacokinetics are modified with aging.

Changes in body composition with aging reflect a decrease in lean body mass, an increase in body fat, and a decrease in total body water. We might infer that a decrease in total body water could lead to a smaller central compartment and increased serum concentrations after bolus administration of a drug. In addition, the increase in body fat might result in a greater volume of distribution, with the potential to prolong the clinical effect of a given medication.[33]

As discussed previously, alterations in hepatic and renal clearance occur with aging. Depending on the degradation pathway, decreases in liver and kidney reserve can affect a drug's pharmacokinetics profile.

The clinical response to anesthetic medications in elderly patients may be the result of alterations in sensitivity of the target organs (pharmacodynamics). A given agent's physical properties and alterations in receptor numbers or sensitivity determine the relative influence of pharmacodynamics alterations on anesthetic effect in elderly patients. Generally, elderly patients are more sensitive to anesthetic agents. Less medication is usually required to achieve a desired clinical effect, and drug effect is often prolonged. Undesired hemodynamic perturbations also tend to occur more frequently and in greater magnitude. Hemodynamic responses to intravenous anesthetics may be exaggerated because of interactions with the aging heart and vasculature. Expected compensatory or reflex responses are often blunted or absent because of physiologic changes associated with normal aging and age-related disease. Whatever the cause of altered pharmacologic effect, an elderly patient usually requires a downward adjustment in medication dose.

Clinical Pharmacology of Specific Anesthetic Drugs

Table 71-7 summarizes the clinical pharmacology of anesthetic agents in elderly patients.

Inhaled Anesthetics

The minimum alveolar concentration (MAC) decreases approximately 6% per decade for most inhaled anesthetics (see Chapter 21). A similar pattern is observed for MAC-awake.[132] The mechanism of action of inhaled anesthetics is related to altered activity of neuronal ion channels associated with nicotinic, acetylcholine, $GABA_A$, and glutamate receptors. Perhaps with aging alterations in ion channels, synaptic activity, or receptor sensitivity may occur to account for these changes in pharmacodynamics.

Intravenous Anesthetics and Benzodiazepines

There is no change in brain sensitivity to thiopental with age (see Chapter 26).[133] The dose of thiopental required to achieve anesthesia decreases with age, however. The age-related decrease in thiopental dose is related to an age-related decrease in the initial distribution volume of the drug. The decrease in initial distribution volume results in higher serum drug levels after a given dose of thiopental in elderly patients.[133] Likewise, in the case of etomi-

Table 71-7 Clinical Pharmacology of Anesthetic Agents in Elderly Patients

Drug	Brain Sensitivity	Pharmacokinetics	Dose
Inhaled agents	↑	—	↓
Thiopental	—	↓ Initial distribution volume	↓
Etomidate	—	↓ Initial distribution volume ↓ Clearance	↓
Propofol	↑	↓ Clearance	↓
Midazolam	↑	↓ Clearance	↓
Morphine	↑	↓ Clearance	↓
Sufentanil	↑	—	↓
Alfentanil	↑		↓
Fentanyl	↑		↓
Remifentanil	↑	↓ Clearance ↓ Central compartment volume	— ↓
Pancuronium	NA	↓ Clearance*	↓*
Atracurium	NA	—	—
Cisatracurium	NA	—	—
Vecuronium	NA	↓ Clearance	↓

*See text. NA, not applicable.

date, age-dependent changes in pharmacokinetics (decreased clearance and initial volume of distribution), rather than altered brain responsiveness, account for the decrease in etomidate dose requirement in elderly patients.[134] The brain becomes more sensitive to the effects of propofol with age.[135] In addition, clearance of propofol is reduced. These additive effects are associated with a 30% to 50% increased sensitivity to propofol in elderly patients.[33]

The dose requirement of midazolam to produce sedation during upper gastrointestinal endoscopy is decreased approximately 75% in elderly patients.[136] These changes are related to increased brain sensitivity and decreased drug clearance.[137]

Opiates

Age is an important predictor of postoperative morphine requirements, with elderly patients needing less drug for pain relief (see Chapter 27).[138] Morphine and its metabolite morphine-6-glucuronide have analgesic properties. Morphine clearance is decreased in elderly patients.[139] Morphine-6-glucuronide depends on renal excretion.[140] Patients with renal insufficiency may have impaired elimination of morphine glucuronides, and this may account for some of the enhanced analgesia from a given dose of morphine in an elderly patient.[141]

Shafer[33] provided a comprehensive review of the pharmacology of sufentanil, alfentanil, and fentanyl in elderly patients. Sufentanil, alfentanil, and fentanyl are approximately twice as potent in elderly patients. These findings are primarily related to an increase in brain sensitivity to opioids with age, rather than alterations in pharmacokinetics.

Aging is associated with changes in the pharmacokinetics and pharmacodynamics of remifentanil. There is an increase in brain sensitivity to remifentanil with age. Remifentanil is approximately twice as potent in elderly patients, and one half the bolus dose is required.[142] The volume of the central compartment, V1, and clearance decrease with age,[143] and approximately one third the infusion rate is required in elderly patients.[142]

Muscle Relaxants

Generally, age does not significantly affect the pharmacodynamics of muscle relaxants (see Chapter 29). Duration of action may be prolonged, however, if the drug depends on liver or renal metabolism. One would expect that pancuronium clearance would decrease in elderly patients because of its dependence on renal excretion. Changes in pancuronium clearance with aging are controversial.[144,145] Atracurium depends to a small extent on hepatic metabolism and excretion, and elimination half-life is prolonged in elderly patients. Clearance is unchanged with age, however, suggesting that alternative pathways of elimination (ester hydrolysis and Hofmann elimination) assume importance in elderly patients.[146] Cisatracurium undergoes Hofmann degradation and is unaffected by age. Plasma clearance of vecuronium is lower in elderly patients.[145] The age-related prolonged duration of action of vecuronium may reflect decreases in renal or hepatic reserve.[147]

Neuraxial Anesthesia and Peripheral Nerve Blocks

Age has no effect on duration of motor blockade with bupivacaine spinal anesthesia (see Chapters 33 and 51).[148] The time of onset is decreased, however, and spread is more extensive with hyperbaric bupivacaine solution.[148,149] Effects of age on duration of epidural anesthesia have not been shown with 0.5% bupivacaine. Time of onset is shorter, however, and extent of block is greater.[150] A reduced plasma clearance of local anesthetics is observed in elderly patients. This can become a factor during repeated dosing and continuous infusion techniques prompting a reduction in top-up doses and infusion rates.[10] When using 0.75% ropivacaine for brachial plexus block, age is a major factor in determining duration of motor and sensory blockade.[151]

Anesthetic Technique

Advantages of Specific Drugs in Elderly Patients

Data suggest that preoperative comorbid disease is a greater determinant of postoperative complications than anesthetic management.[152] Perioperative care should be tailored to comorbid disease and requirements of the surgical procedure. Several comments concerning pharmacologic and physiologic management are in order, however. There may be a role for shorter acting anesthetics in caring for elderly patients. A more predictable method of opioid titration may be to use a shorter acting opioid such as remifentanil. By adjusting the bolus and infusion doses, the variability in remifentanil pharmacokinetics is considerably less than for other intravenous opioids.[153] Similarly, it may be prudent to use shorter acting muscle relaxants. Studies show that there is an increased incidence of postoperative residual block and pulmonary complications in patients receiving pancuronium compared with atracurium or vecuronium.[154] The use of sugammadex as a reversal drug for rocuronium should improve muscle relaxant use in elderly patients (see Chapter 29). When comparing inhaled anesthetics, there does not seem to be a significant difference in recovery profile of cognitive function. Desflurane is associated with the most rapid emergence.[155]

Generally, it is unclear what constitutes the optimal physiologic management to produce the best surgical outcomes. What is optimal blood pressure during surgery? This issue has been addressed during cardiopulmonary bypass where the question concerning most favorable perfusion pressure remains unresolved.[156,157] Similarly, it is uncertain whether deliberate hypotension in elderly patients is detrimental. Studies have shown that elderly patients can safely receive controlled hypotensive anesthesia (mean arterial blood pressure range 45 to 55 mm Hg) during orthopedic procedures without increased risk.[158] Even more controversy surrounds the question of whether better outcomes are obtained when invasive hemodynamic monitoring is used to optimize hemodynamics and fluid therapy. The use of pulmonary artery catheters in high-risk patients has been called into question because large prospective randomized studies analyzing in-hospital mortality have found no benefit to therapy directed by pulmonary artery catheter over standard care in elderly, high-risk surgical patients requiring ICU care.[159]

Regional versus General Anesthesia

Most evidence suggests little, if any, difference in outcome between regional and general anesthesia in elderly patients (see Chapters 33 and 51).[160] These results have been reported in many types of surgery, including major vascular and orthopedic procedures.[161,162] Use of regional anesthesia does not seem to decrease the incidence of postoperative cognitive dysfunction compared with general anesthesia.[163]

Specific effects of regional anesthesia may provide some benefit. First, regional anesthesia affects the coagulation system

by preventing postoperative inhibition of fibrinolysis.[164] Deep vein thrombosis or pulmonary embolism may occur in 2.5% of patients after certain high risk procedures.[165] Regional anesthesia may decrease the incidence of deep vein thrombosis after total hip arthroplasty.[166] These findings are controversial, however, because similar results have not been reported with total knee arthroplasty.[167] In lower extremity revascularization, regional anesthesia is associated with a decreased incidence of postoperative graft thrombosis compared with general anesthesia.[168] Second, the hemodynamic effects of regional anesthesia may be associated with decreased blood loss in pelvic and lower extremity surgery.[169] Third, regional anesthesia does not require instrumentation of the airway and may allow patients to maintain their own airway and level of pulmonary function. Data suggest that elderly patients are more susceptible to hypoxemic episodes in the recovery room. Patients who undergo regional anesthesia may have a lower risk of hypoxemia.[170] It is unclear, however, whether fewer pulmonary complications occur with regional versus general anesthesia.

Postoperative Considerations

Common Problems in the Postanesthesia Care Unit

Preoperative and postoperative management of pulmonary problems is of particular importance (see Chapters 35 and 93). In general surgical patients 65 years old and older, the incidence of common postoperative morbidities is 17% for atelectasis, 12% for acute bronchitis, 10% for pneumonia, 6% for heart failure or myocardial infarction (or both), 7% for delirium, and 1% for new focal neurologic signs.[171] In higher risk procedures, such as vascular surgery, the incidence of major postoperative pulmonary complications is 15.2%.[172] Numerous predictors of postoperative pulmonary complications in elective noncardiac surgery have been identified,[173,174] and risk indices have been developed to forecast the development of postoperative pneumonia.[93] Elderly patients may be at higher risk for aspiration secondary to the progressive decrease in laryngopharyngeal sensory discrimination that occurs with aging.[175] In addition, dysfunctional swallowing predisposes elderly patients to aspiration. After cardiac operations, dysfunctional swallowing occurs in 4% of patients and is more common in older patients. Swallowing dysfunction after cardiac surgery is closely associated with the intraoperative use of transesophageal echocardiography and carries with it a 90% rate of pulmonary aspiration and pneumonia.[103]

Treatment of Acute Postoperative Pain

Experimental and clinical studies provide support for the notion of an age-related decrease in pain perception (see Chapter 87).[176,177] It is unclear, however, whether the observed changes are caused by the aging process or reflect other age-associated effects, such as an increased presence of comorbid disease.[178] A greater problem occurs in patients with cognitive impairment. Evidence suggests that evaluation of pain, especially in a severely cognitively impaired individual, is difficult even for a geriatrician.[179] Nonetheless, the basic principles of evaluation of pain in elderly patients are similar to those in other age groups. Verbal pain scales are superior to nonverbal methods in elderly patients.[180]

As discussed earlier in this chapter, aging alters functional organ reserve and pharmacokinetics. The combination of pain assessment and drug dose adjustment provides challenges in the management of postoperative pain in elderly patients. Several general principles should be kept in mind when managing frail elderly patients. First, it is important to try to incorporate multiple modalities of analgesia, such as intravenous patient-controlled analgesia and regional nerve blocks, to enhance analgesia and reduce narcotic toxicity. This principle is especially important in frail elderly patients, who often tolerate systemic narcotics poorly. Second, the use of site-specific analgesia is a helpful adjunct. Certain operative sites, such as the upper extremity, are especially amenable to local nerve blocks. Others, such as thoracotomy, are especially painful, and techniques such as neuraxial analgesia or intercostal nerve block might be considered. Third, whenever possible, nonsteroidal anti-inflammatory drugs should be used to spare narcotics, enhance analgesia, and decrease inflammatory mediators. Unless the patient has a contraindication, or there is a strong concern about hemostasis or peptic ulceration, nonsteroidal anti-inflammatory drugs should generally be administered.[181] Opioid-based postoperative pain management may be used in elderly patients. It is imperative to keep in mind, however, the alterations in dose requirements that occur with age.[138]

Postoperative Cognitive Dysfunction

Short-term changes in cognitive test performance during the first days to weeks after surgery are well documented and typically involve multiple cognitive domains, such as attention, memory, and psychomotor speed (see Chapter 89). Early cognitive decline after surgery is largely reversible by 3 months.[182] Cardiac surgery is associated with a 36% incidence of cognitive decline at 6 weeks postoperatively.[183] The reported incidence of cognitive dysfunction after major noncardiac surgery in patients older than 65 years is 26% at 1 week and 10% at 3 months.[184] Predictors of early postoperative cognitive decline include age, low educational level, preoperative cognitive impairment, depression, and surgical procedure.[185,186] Short-term cognitive dysfunction after surgery may be attributed to multiple etiologies, including microemboli (especially with cardiac surgery), hypoperfusion, systemic inflammatory response (cardiopulmonary bypass), anesthesia, depression, and genetic factors (E4 allele).

Whether or not anesthesia contributes to long-term postoperative cognitive dysfunction is controversial and an area of intense investigation. In noncardiac procedures, anesthesia has a modest impact on long-term cognitive decline, although this effect may be more robust with increasing age.[44] Postoperative cognitive decline after major noncardiac surgery is reversible in most cases, but may persist in approximately 1% of patients.[187]

In patients undergoing CABG procedures, Newman and colleagues[188] reported a 42% incidence of cognitive decline at 5 years postoperatively (see Chapter 60). In addition, lower 5-year overall cognitive function scores were associated with poorer general health and less productive working status. Newman's study did not contain a nonsurgical control group. Other investigations addressing the issue of neurocognition and CABG procedures using nonsurgical control groups suggest that long-term postoperative cognitive dysfunction may result from factors other than anesthesia and surgery. First, patients with underlying coronary artery disease have lower baseline cognitive test scores compared with controls without coronary artery disease.[189] Second, long-term cognitive outcome of on-pump and off-pump CABG procedures is similar.[190] Third, long-term neurocognitive per-

formance in patients undergoing CABG procedures and nonsurgical controls with comparable coronary artery disease is similar.[191] These data suggest that the etiology of long-term cognitive changes after anesthesia and surgery may be related to underlying cerebrovascular disease risk factors. Management of risk factors, such as blood pressure, cholesterol, and diabetes, may be important in attenuating long-term cognitive decline. In addition, the role of interim medical events, such as new stroke, surgery with general anesthesia, or cardiac catheterization, in long-term cognitive decline has yet to be defined.

Intensive Care Outcomes

A growing number of studies have examined long-term outcome after critical care in elderly patients (see Chapters 91 and 92).[192,193] Survival to discharge from an ICU seems to be most closely related to severity of illness at the time of admission, whereas age and prehospital functional status correlate most closely with long-term survival. Recovery is often a long process with many elders requiring assistance with IADL 1 year after discharge.

Future Directions

Future trends are toward less invasive surgery with shorter hospital stays, as evidenced in many surgical subspecialties. Video-assisted muscle-sparing minithoracotomy for major lung resection has been used to decrease mean length of hospital stay for elderly patients to 1 day.[194] Early extubation and critical pathways for accelerated discharge have been used successfully in elderly patients undergoing isolated CABG procedures.[195] Endovascular repair of abdominal aortic aneurysm is now being used in high-risk patients with good results.[196] Laparoscopic surgical approaches have been shown to provide benefits to elderly patients in the form of smaller scars, decreased postoperative pain, and more rapid return to normal activity.[197] In addition, there is a major thrust toward ambulatory surgery in elderly patients. Studies report, however, that with ambulatory surgery, elderly patients have higher rates of intraoperative events, in particular, events of a cardiovascular nature.[198] Although the ideal model for perioperative care for older patients is unknown, studies suggest multidisciplinary teams including geriatricians can influence outcome.[199] More outcome studies are needed across a wide range of perioperative issues including ambulatory surgery. The challenge of the future will be managing perioperative care of elderly patients with their associated comorbid diseases and increased risk in a cost-conscious environment.

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72 Anesthesia for Trauma

Key Points

1. Trauma anesthesiology is a unique subspecialty of our profession. Optimal anesthetic care of trauma patients depends on an understanding of trauma system design and surgical priorities.
2. Successful emergency airway management is based on having a clear plan, such as the American Society of Anesthesiologists algorithm for difficult airways. In general, rapid-sequence induction of anesthesia accompanied by cricoid pressure and in-line cervical stabilization, followed by direct laryngoscopy, is the safest and most effective approach.
3. Recognition of hemorrhagic shock is at the center of advanced trauma life support. Hemorrhagic shock indicates the need for rapid operative treatment, with the possibility of a "damage control" approach.
4. Resuscitation during acute hemorrhagic shock is controversial, but current recommendations are to maintain deliberate hypotension during active bleeding by limitation of crystalloid infusion and to emphasize maintenance of blood composition by early transfusion of red blood cells, plasma, and platelets.
5. Management of patients with severe traumatic brain injury poses unique challenges for the anesthesiologist. Monitoring and maintenance of cerebral perfusion are the keys to operative and intensive care of these patients.
6. Trauma anesthesiology includes a substantial component of critical care practice. Operating room use of advanced ventilator strategies, including permissive hypercapnia and facilitated spontaneous ventilation (bilevel or airway pressure release ventilation), may improve outcomes.
7. Prehospital, interhospital, and intrahospital transport of critically injured patients is the province of the trauma anesthesiology team and requires planning and attention to detail.

Injury is the leading cause of death between the ages of 1 and 45 years in the United States and the third leading cause of death overall.[1] Because it affects primarily the young, trauma is *the* leading cause of years of life lost before the age of 75. The World Health Organization (WHO) estimates that injury is the leading cause of death worldwide for both men and women from the age of 15 to 44 years, and by 2020, injuries will be the third leading cause of death and disability in all age groups.[2] Unlike in developed nations, where road traffic deaths are predicted to decrease by 2020, annual road traffic mortality is expected to rise by 80% in low- and middle-income countries.[3]

Globally, about 16,000 people die of injuries every day and about 5.8 million people every year, which corresponds to an annual mortality rate of 97.9 per 100,000 population. Mortality from injury under-represents the true burden of disease inasmuch as hundreds of people require hospital treatment for every death. According to the 2002 *World Report on Violence and Health*, injury accounts for 12.2% of the total burden of disease.[4] In comparison with other disease and health conditions, morbidity and disability as a result of injury account for a disproportionate number of deaths in children and young adults. This leads to a major burden on health sector and social welfare services, and the economic consequences include both the cost of care and a substantial amount of lost productivity.

A comprehensive review published by the WHO showed that more than 1.6 million people worldwide lost their lives to violence in the year 2000. About half the deaths were caused by suicide, nearly a third were homicides, and about a fifth were casualties of armed conflict.[5] In the post–Cold War period 1990 to 2001 there were 57 different major armed conflicts in 45 different locations. Terrorism, either transnational or domestic, is not new. In addition to the increasing global incidence of trauma, other major trends in trauma and its management include a growing emphasis on prevention and public health aspects of trauma, globalization of trauma practices because of rapid dissemination of new information, a critical emphasis on organizational aspects of trauma care and education, and the prominent role of efficacious and cost-effective management practices.[6]

Management of trauma patients presents unique challenges to the health care system because they require resource-intensive care, they have multiple injuries to multiple body systems, and their acute injuries overlie and interact with a variety of chronic medical conditions. Anesthesiologists in practice at designated

trauma centers are involved in the care of trauma patients beginning with airway and resuscitation management in the emergency department (ED) and proceeding through the operating room (OR) to the intensive care unit (ICU). Trauma patients represent a significant proportion of all OR cases handled during night and weekend shifts. Critical care and pain management specialists see trauma patients as a large fraction of their practice. Even practitioners at outpatient surgery centers will encounter trauma patients in need of reconstructive, orthopedic, or plastic surgery.

At the same time, very few anesthesiologists in the United States consider trauma their primary specialty. This is distinct from European practice, where it is not unusual to find an anesthesiologist working in the prehospital environment, as an ED director, or as leader of a hospital's trauma team. The U.S. model, in which all anesthesiologists treat trauma patients but few do so exclusively, has led to a relative dearth of research, publication, and education in this field. This situation is unfortunate because trauma is a rapidly evolving field of study that presents unique challenges to the clinician and one in which improvements in care can have a dramatic impact on society as a whole.

Anesthesia for trauma patients is different from routine OR practice. Most urgent cases occur during off-hours, when the most experienced OR and anesthesia personnel may not be available. In small hospitals and military and humanitarian practice, austere conditions may influence the resources available. Patient information may be limited, and allergies, genetic abnormalities, and previous surgeries may create sudden crises. Patients are frequently intoxicated, with full stomachs and the potential for cervical spine instability. Simple operations may become complicated, and specialty surgical and anesthesia equipment may be required on short notice. Patients often have multiple injuries requiring complex positioning, multiple procedures, and the need to consider priorities in management. Occult injuries, such as tension pneumothorax, can be manifested at unexpected times. Successful perioperative care of these patients requires a good understanding of the basics, supplemented by preparation, flexibility, and the ability to react quickly to changing circumstances.

As with other endemic diseases, successful treatment of trauma extends well beyond the boundaries of an individual hospital. Community-based prevention has included efforts to incorporate airbags in motor vehicles, mandate helmet use on motorcycles, encourage citizens to wear seat belts, punish intoxicated drivers, and promote responsible handgun ownership.[7] All of these measures have had an impact on the demographics of injury in much the fashion that smoking cessation, dietary modification, and routine mammography have affected the incidence of heart disease and cancer. When prevention fails, outcomes after injury are heavily influenced by the community's commitment to an organized system of trauma care.[8]

A "systems" approach to the delivery of trauma care has been shown to improve outcome. Trauma care systems represent a continuum of integrated care that is a coordinated effort between out-of-hospital and hospital providers with close cooperation of medical specialists in each phase of care. In 1998, the first Academic Symposium to Evaluate Evidence Regarding the Efficacy of Trauma Systems (the Skamania Conference) systematically reviewed the published literature in an effort to quantify the understanding of trauma system effectiveness at that time and to chart a course to outline future research endeavors.[9,10] The Skamania Symposium concluded that treatment at a trauma center versus a nontrauma center is associated with fewer inappropriate deaths and less disability. This conclusion was substantiated in 2006 by a *New England Journal of Medicine* study showing that mortality is reduced when care is provided at a trauma center versus a nontrauma center.[11] Studies in the United States have shown that a reduction in unnecessary deaths from greater than 30% to less than 5% occurred in trauma centers as compared with general hospitals and that a regionalized system with triage criteria and dedicated trauma centers also reduces the potentially preventable mortality rate to a low of 1% to 3%. However, based on a U.S. study evaluating rates of mortality after implementation of a statewide trauma system program, a mean of *9 years* elapsed after passage of enabling legislation before a significant benefit in survival was achieved.[12]

The degree to which the trauma system is organized and regulated varies widely from state to state across the United States. States such as Maryland, Pennsylvania, Connecticut, and Illinois have established protocols for the care of trauma patients that begin at the moment of first contact with the emergency medical system. In other states the system may be more fragmentary, and care may vary widely between one jurisdiction and another. Mature trauma systems include protocols for patient triage and transport, standards for hospitals providing trauma care, and data collection systems that facilitate benchmarking. Although some states have written their own standards for certifying trauma hospitals, the most influential national document is *Resources for Optimal Care of the Injured Patient*, published by the American College of Surgeons Committee on Trauma in 2006.[13] This reference offers standards for accreditation of trauma hospitals based on the availability of key resources, the volume of trauma patients treated, and the institutional commitment to prevention and education. The presence of an experienced anesthesiologist and the immediate availability of an open OR are both core resource standards for accreditation of a "level 1" trauma center. Prospective studies have demonstrated improved patient outcomes when a hospital pursues and attains designation as a trauma center.[14]

The need for ongoing education of providers is brought home by the numerous innovations in trauma care witnessed in just the past decade, including technologies for rapid volume resuscitation; "damage control" surgical techniques; diagnostic modalities such as high-speed computed tomography (CT), angiography, and focused abdominal ultrasound; and perfusion-focused strategies for managing traumatic brain injury (TBI). The coming decades will see new pharmacologic therapies for shock and reperfusion, new strategies for achieving hemostasis, and better patient monitoring. Improving patient outcomes requires a commitment to continuing education on the part of the anesthesiologist and every member of the trauma team.

This chapter provides an overview of important areas of trauma care for the anesthesiologist. We begin with a description of the initial approach to an injured patient, followed by discussions of emergency airway management, fluid volume resuscitation, and care of patients with central nervous system (CNS) injuries. We briefly cover the needs of orthopedic and reconstructive surgery patients and then conclude with a discussion of postoperative and critical care issues for the trauma anesthesiologist. New to this edition is a discussion of the anesthesiologist's role in battlefield medicine, including combat casualty assessment, stabilization, and transfer.

Prioritizing Trauma Care

The advanced trauma life support (ATLS) (see Chapter 97) course of the American College of Surgeons is the most widely recognized training program for trauma physicians of all disciplines.[15] Though not comprehensive in subspecialty areas, the ATLS curriculum nonetheless provides a framework and a common language for the care of injured patients. ATLS is based on a "primary survey" that includes simultaneous efforts to identify and treat life- and limb-threatening injuries, beginning with the most immediate. This focus on urgent problems first is captured by the "golden hour" catchphrase and is the most important lesson of ATLS. Put simply, better outcomes are achieved with faster diagnosis and treatment. Resolution of urgent needs is followed by a meticulous secondary survey and further diagnostic studies designed to reduce the incidence of missed injuries. Knowing the basics of ATLS is essential for *any* physician who interacts with trauma patients. Figure 72-1 is a simplified representation of the ATLS protocol.

ATLS emphasizes the ABCDE mnemonic: airway, breathing, circulation, disability, and exposure. Verification of an open airway and acceptable respiratory mechanics is of primary importance because hypoxia is the most immediate threat to life. Inability to oxygenate the patient will lead to permanent brain injury and death within 5 to 10 minutes. Trauma patients are at risk for airway obstruction and inadequate respiration for the reasons listed in Box 72-1. Endotracheal intubation, whether performed in the prehospital environment or in the ED, must be confirmed immediately by capnometry. Esophageal intubation or endotracheal tube dislodgement are common and devastating if not promptly corrected. Patients in cardiac arrest may have very low end-tidal CO_2 values; direct laryngoscopy should be performed if there is any question about the location of the endotracheal tube (see also Chapter 50).

If establishment of a secure airway and adequate ventilation requires a surgical procedure such as a tracheostomy, tube thoracostomy, or open thoracotomy, this procedure must precede all others. Indeed, these procedures are commonly performed in the ED, often before the arrival of an anesthesiologist. Subsequent surgery to convert a cricothyroidotomy to a tracheostomy or close an emergency thoracotomy may then follow in the OR.

Hemorrhage is the next most pressing concern inasmuch as ongoing blood loss is inevitably fatal. The symptoms of shock are presented in Box 72-2. Shock is presumed to result from hemorrhage until proved otherwise. Assessment of the circulation consists of an early phase, during active hemorrhage, and a late phase, which begins when hemostasis is achieved and continues until normal physiology is restored. In the early phase, diagnostic efforts focus on the five sites of bleeding detailed in Table 72-1, the only areas in which exsanguinating hemorrhage can occur. Any surgical procedure to diagnose or control active hemorrhage is an emergency case that must be brought to the OR as soon as possible. This includes exploration of the neck or pericardium to rule out hemorrhage in sensitive compartments. In the OR, the trauma surgeon focuses on anatomic control of hemorrhage, whereas the anesthesiologist is responsible for restoring the patient's physiology. Goals for early and late resuscitation are discussed in more detail later.

After management of the circulation is assessment of the patient's neurologic status by calculation of the Glasgow Coma Scale (GCS) score (Box 72-3)[16]; examination of the pupils for size, reactivity, and symmetry; and determination of sensation and motor function in each of the extremities. Significant abnormalities on the neurologic examination are an indication for immediate cranial CT. A majority of trauma patients with a diminished GCS score will have nonoperative conditions, but for the few who require operative evacuation of an epidural or subdural hematoma, timeliness of treatment has a strong influence on outcome. Patients with unstable spinal canal injuries and incomplete neurologic deficits will also benefit from early surgical stabilization.

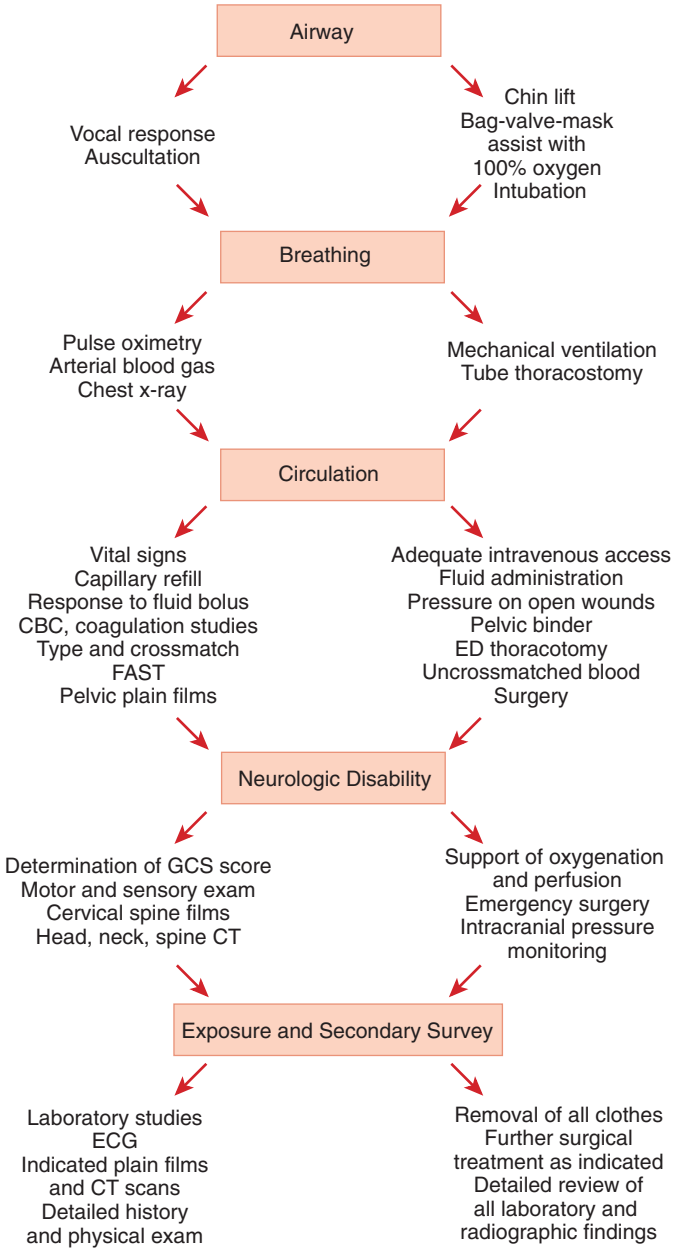

Figure 72-1 Simplified assessment and management of a trauma patient. CBC, complete blood count; CT, computed tomography; ECG, electrocardiogram; ED, emergency department; FAST, focused assessment by sonography for trauma; GCS, Glasgow Coma Scale. *(Adapted from the Advanced Trauma Life Support curriculum of the American College of Surgeons.)*

Box 72-1 Causes of Obstructed Airway or Inadequate Ventilation in A Trauma Patient

Airway Obstruction
Direct injury to the face, mandible, or neck
Hemorrhage in the nasopharynx, sinuses, mouth, or upper airway
Diminished consciousness secondary to traumatic brain injury, intoxication, or analgesic medications
Aspiration of gastric contents or a foreign body (e.g., dentures)
Misapplication of an oral airway or endotracheal tube (esophageal intubation)

Inadequate Ventilation
Diminished respiratory drive secondary to traumatic brain injury, shock, intoxication, hypothermia, or oversedation
Direct injury to the trachea or bronchi
Pneumothorax or hemothorax
Chest wall injury
Aspiration
Pulmonary contusion
Cervical spine injury
Bronchospasm secondary to inhalation of smoke or toxic gas

The final step in the primary survey is complete exposure of the patient and a head-to-toe search for visible injuries or deformities, including deformities of bones or joints, soft tissue bruising, and any breaks in the skin. The anesthesiologist can assist in this procedure by support of the head and neck, maintenance of the airway, and care in manipulating the spine.

After the primary survey a more deliberate secondary examination is undertaken that includes a thorough history and physical examination, diagnostic studies, and subspecialty consultation. Any remaining injuries are diagnosed at this time and treatment plans established. Indications for urgent or emergency surgery may also arise during the secondary survey. The presence of a limb-threatening injury as a result of either vascular compromise, compartment syndrome, or a severely comminuted fracture is one such indication. Although the ABCDE issues must be addressed first, a pulseless extremity, compartment syndrome, near-amputation, or massively fractured extremity must go to the OR as soon as the patient is otherwise stable.

Another category of urgency arises in patients with a time-dependent potential for systemic infection. Because sepsis is a leading cause of complications and death in trauma patients, open injuries should be thoroughly débrided—and closed if appropriate—at the earliest opportunity (see Chapters 91 and 92). Other

Box 72-2 Symptoms of Shock

Pallor
Diaphoresis
Agitation or obtundation
Hypotension
Tachycardia
Prolonged capillary refill
Diminished urine output
Narrowed pulse pressure

Table 72-1 Diagnostic and Therapeutic Options for the Management of Traumatic Hemorrhage

Site of Bleeding	Diagnostic Modalities	Treatment Options
Chest	Chest radiography Thoracostomy tube output Chest CT scan	Observation Surgery
Abdomen	Physical examination Ultrasound examination (FAST) Abdominal CT scan Peritoneal lavage	Surgical ligation Angiography Observation
Retroperitoneum	CT scan Angiography	Angiography
Long bones	Physical examination Plain radiography	Fracture fixation Surgical ligation
Outside the body	Physical examination	Direct pressure Surgical ligation

CT, computed tomography; FAST, focused assessment by sonography for trauma.

Box 72-3 Glasgow Coma Scale Score*

Eye-Opening Response
4 = Spontaneous
3 = To speech
2 = To pain
1 = None

Verbal Response
5 = Oriented to name
4 = Confused
3 = Inappropriate speech
2 = Incomprehensible sounds
1 = None

Motor Response
6 = Follows commands
5 = Localizes to painful stimuli
4 = Withdraws from painful stimuli
3 = Abnormal flexion (decorticate posturing)
2 = Abnormal extension (decerebrate posturing)
1 = None

*The Glasgow Coma Scale score is the sum of the best scores in each of three categories.

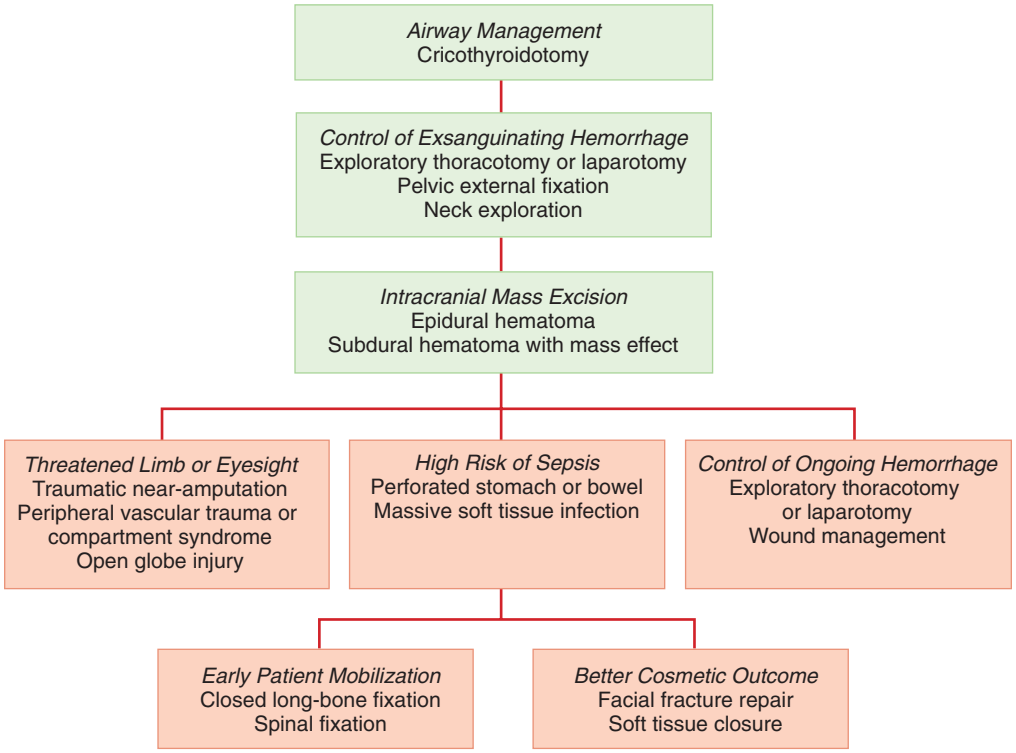

Figure 72-2 Surgical priorities in a trauma patient. *(Reprinted with permission from Dutton RP, Scalea TM, Aarabi B: Prioritizing surgical needs in the patient with multiple injuries. Probl Anesth 13:311, 2001.)*

urgent indications for surgery include perforation of the bowel, open fracture, and extensive soft tissue wounds. The frequency of infectious complications of open fractures increases in a linear fashion with time from the moment of injury until operative débridement[17]; the anesthesiologist must balance the need for early surgery against the need for diagnostic studies and adequate preoperative resuscitation and may be required to determine the priority of this procedure relative to other cases.

Figure 72-2, an algorithm for prioritizing surgical management in trauma patients, is presented with the understanding that individual situations will vary according to available resources and the patient's response to therapy. A trauma patient will often arrive at the OR with the need for more than one surgical procedure by more than one surgical service. A trauma patient may have injuries requiring emergency surgery coexisting with injuries that can be repaired at any time. The anesthesiologist plays an important role in determining which procedures to perform, in which order, and which procedures should be postponed until the patient is more stable.

Anesthesia in War and Austere Conditions

"While it is evident that the general principles of anesthesia are not affected by the circumstances of war, it is equally evident that it is our duty to assiduously seek those means in anesthesia which are especially suited to the exigencies of battle."[18]

Though written in 1942, these words are still true today and many of the principles developed from earlier wars still apply on the modern battlefield or in a large-scale disaster (see Chapter 74). Recent conflicts and events have allowed anesthesiologists, nurse anesthetists, and other providers to help improve management of traumatically injured patients in the areas of anesthesia, resuscitation, and damage control surgery. Management of battlefield casualties typically follows the same flow as outlined earlier, but with special consideration in the areas of prehospital interventions, resuscitation, technologic and logistic support, patient movement, mass casualty management, and surgical interventions.[19]

Modern advancements in battle armor, prehospital interventions, provision of forward surgical support, and resuscitative strategies have had an impact on survival from combat injuries. During the most recent conflicts in Iraq and Afghanistan, the killed-in-action rate has dropped to 13.9% from 20.2% in Vietnam and World War II.[20] This is mirrored by a similar reduction in the case fatality rate. Paradoxically, the ability to get many of the severely wounded patients to a hospital has led to an increase in the "died-of-wounds" rate. Most likely this rate would be even higher if not for improvements in surgical management such as damage control techniques, improved ICU care, earlier recognition of abdominal compartment syndrome, liberal use of fresh whole blood, and institution of a theater-wide trauma system approach.

One of the major advances in battlefield medical support has been the rapid movement of patients out of the theater of operations to more comprehensive medical facilities. In the most recent conflict, the time from injury in the Middle East until return to the United States is frequently less than 72 hours for even the most seriously injured patients.[21] This may include initial in-theater damage control surgery followed by one or two aeromedical evacuation missions lasting up to 12 hours with a critical care air transport team (CCATT). In preparation for such rapid movement, the anesthesiologist must ensure that perioperative

interventions such as airway management, pain control, and adequacy of resuscitation are addressed before transfer. In addition, anesthesiologists are frequently assigned to a CCATT as the physician team member based on their overall skill set and ability to provide en route support to critically ill or injured patients. Beyond the support provided during wartime, the CCATT has also proved useful for the movement of critical patients during large-scale disasters such as occurred after Hurricane Katrina in 2005.[22]

Mass casualty situations are not uncommon in wartime conditions, although the role of the anesthesiologist will vary depending on the number of patients and requirements for urgent surgical interventions. Given the limited number of anesthesia providers in most combat-related scenarios, it is unlikely that they will be directly involved in the triage process. If available, however, emergency airway management, establishment of venous access, and supervision of resuscitative efforts would be augmented by anesthesia support. Only 10% to 20% of arriving casualties require immediate lifesaving interventions, although a much larger percentage will ultimately require surgical procedures.[23] As a theater matures, a well-developed trauma system will evolve and management of mass casualty scenarios will become routine.[24]

Overall anesthetic management of battlefield casualties is similar to that for patients in a civilian trauma setting; however, a number of factors must be considered in the perioperative plan for a combat casualty.[25] Environmental considerations such as extremes of temperature, availability of water, contamination with sand, lack of consistent electricity, and other aspects may have to be taken into consideration. Logistic support chains may be long and not keep up with use of supplies in the early phases of a conflict. Deployable equipment, such as draw-over vaporizer systems or portable ventilators, may be different from those used during peacetime, so predeployment training is vital (Fig. 72-3).[26]

In addition, techniques such as total intravenous anesthesia and regional anesthesia/analgesia will frequently be used and thus require familiarity with their management and associated equipment (see Chapters 51 and 52).[25]

Optimal care of wartime casualties or victims of large disasters requires not only familiarity with a broad range of anesthetic principles and techniques but also the ability to be flexible in the face of a rapidly changing environment. With special training in airway management, provision of anesthesia and sedation, resuscitation, and pain management, anesthesiologists may find themselves involved in triage, emergency management, and perioperative and critical care.

Emergency Airway Management

The American Society of Anesthesiologists (ASA) algorithm for management of difficult airways (see Fig. 50-2) is a useful starting point for the trauma anesthesiologist, whether in the ED or the OR.[27] Although the options included will vary from institution to institution and provider to provider, the concept of the algorithm is an important one. The anesthesiologist should have a plan for the initial approach to the airway and for coping with any difficulties that might develop. Figure 72-4 is a typical algorithm for emergency intubation of an unstable trauma patient. Note that it differs from the ASA algorithm in that reawakening the patient is seldom an option because the need for emergency airway control will presumably remain. Once the decision to obtain a definitive airway is made, efforts will continue until a cuffed tube is in position in the trachea, whether by conventional intubation or via a surgical approach. Failure to commit to a surgical airway soon enough results in bad outcomes more commonly

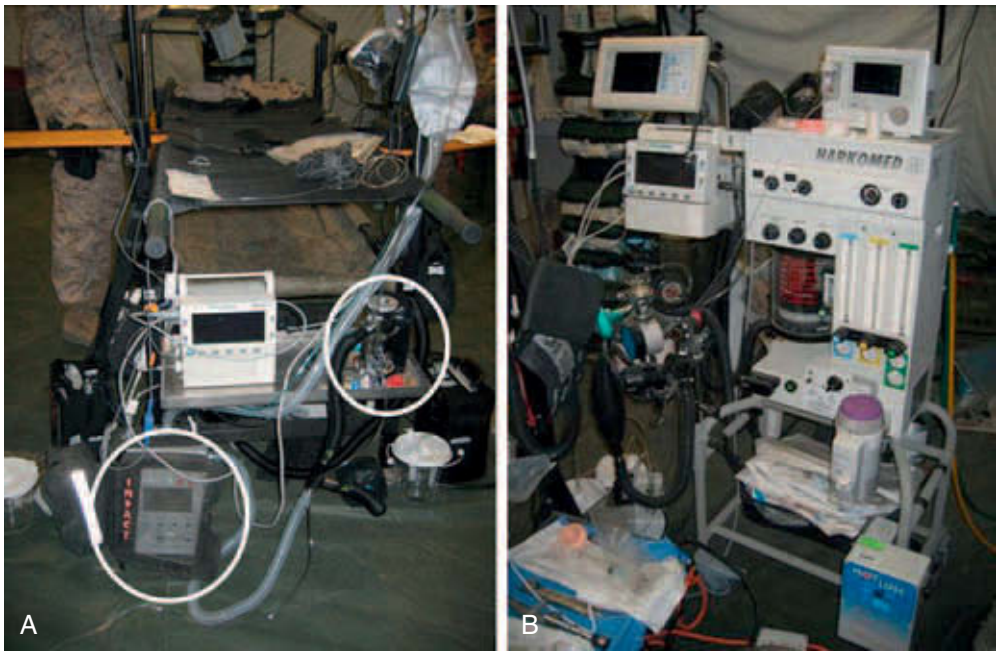

Figure 72-3 Deployable military anesthesia equipment. **A,** Draw-over vaporizer and portable ventilator (*circled*) in a field hospital. **B,** Portable anesthesia machine. *(Used with permission from CPT Bruce Baker, M.D., USN.)*

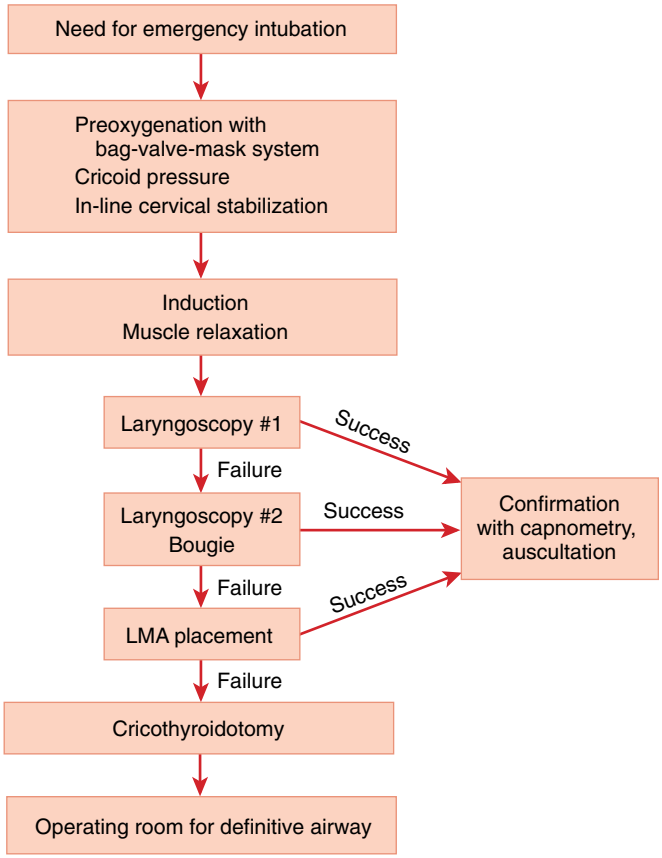

Figure 72-4 Emergency airway management algorithm used at the R Adams Cowley Shock Trauma Center, presented as an example. Individual practitioners and trauma hospitals should determine their own algorithm based on available skills and resources. LMA, laryngeal mask airway.

than do complications of a procedure that might have been unnecessary.

Indications

The goal of emergency airway management is to ensure adequate oxygenation and ventilation while protecting the patient from the risks of aspiration. Endotracheal intubation is commonly required and is specifically indicated in the following conditions:

- Cardiac or respiratory arrest
- Respiratory insufficiency (see Box 72-1)
- Airway protection
- The need for deep sedation or analgesia, up to and including general anesthesia
- Transient hyperventilation of patients with space-occupying intracranial lesions and evidence of increased intracranial pressure (ICP)
- Delivery of a 100% fraction of inspired oxygen (Fio_2) to patients with carbon monoxide poisoning
- Facilitation of the diagnostic workup in uncooperative or intoxicated patients

Approach to Endotracheal Intubation

In general, the anesthesiologist should insist on the same monitoring standards for airway management in the ED as in the OR, including an electrocardiogram (ECG), blood pressure, oximetry, and capnometry. Appropriate equipment, including an oxygen source, bag-valve-mask ventilating system, mechanical ventilator, suction, and a selection of laryngoscope blades, endotracheal tubes, and devices for managing difficult intubations, should be available in any location where emergency intubation is likely, including the ED.

Endotracheal intubation is best accomplished in almost all cases with a modified rapid-sequence approach by an operator with experience in this practice. Although concern may exist that the use of neuromuscular blocking drugs and potent anesthetics outside the OR will be associated with a higher complication rate,[28] in fact the opposite is more likely correct. Anesthesia and neuromuscular blockade allow the best intubating conditions on the first approach to the patient's airway, which is advantageous in an uncooperative, hypoxic, or aspirating patient. Attempts to secure the airway in an awake or lightly sedated patient increase the risk for airway trauma, pain, aspiration, hypertension, laryngospasm, and combative behavior. Experienced providers, supported by appropriate monitoring and equipment, have achieved results of medication-assisted intubation outside the OR that are equivalent to those for emergency intubation within the OR (Table 72-2).[29-31]

Prophylaxis Against Aspiration of Gastric Contents

A trauma patient is always considered to have a full stomach and to be at risk for aspiration during induction of anesthesia. Reasons include ingestion of food or liquids before the injury, swallowed blood from oral or nasal injuries, delayed gastric emptying associated with the stress of trauma, and administration of liquid contrast medium for abdominal CT scanning. As with obstetric anesthesia (see Chapter 69), it is reasonable to administer nonparticulate antacids to a trauma patient before induction if time and patient cooperation allow.

Cricoid pressure—the Sellick maneuver—should be applied continuously during emergency airway management from the time that the patient loses protective airway reflexes until

Table 72-2 Drug-Assisted Intubation outside the Operating Room (OR)

Author(s)	Number of Patients	Problems
Rotondo et al.[29]	204	No difference from the OR
Stene et al.[30]	>3000	None noted
Talucci et al.[31]	260	No hemodynamic or neurologic complications
Karlin*	647	No difference from the OR

*Unpublished data.
Adapted from Karlin A: Airway management of trauma victims. Probl Anesth 13:283, 2001.

endotracheal tube placement and cuff inflation are confirmed. The Sellick maneuver consists of elevating the patient's chin (without displacing the cervical spine) and then pushing the cricoid cartilage posteriorly to close the esophagus. Although the value of cricoid pressure in occluding the esophagus is debatable, it costs nothing to perform and may offer secondary benefits.[32,33] Posterior displacement of the larynx may improve the view for the intubator, whereas palpation of the larynx during intubation can provide a clue to anatomic distortions and an early suggestion that the endotracheal tube has been placed correctly. Some recent evidence, however, suggests that cricoid pressure may worsen the laryngoscopic grade of view in up to 30% of patients.[34] It is appropriate for the intubator to request that cricoid pressure be released if this problem is suspected.

In the traditionally defined rapid-sequence induction of anesthesia, any attempt at ventilation between administration of medication and intubation is avoided, presumably because positive-pressure ventilation may force gas into the patient's stomach, leading to regurgitation and aspiration. The reasoning for this is unclear inasmuch as appropriate application of cricoid pressure should prevent any entry of air into the esophagus. Indeed, Sellick's original paper described ventilation during cricoid pressure in patients with full stomachs.[35] Furthermore, the increase in oxygen consumption in trauma patients necessitates preoxygenation whenever possible, and because preoxygenation may be difficult in a trauma patient—as a result of facial trauma, decreased respiratory effort, or agitation—rapid desaturation is a possibility. Positive-pressure ventilation during all phases of induction provides the largest possible oxygen reserve during emergency airway management and will help mitigate hypoxia if intubation proves difficult.

Protection of the Cervical Spine

Standard practice dictates that all blunt trauma victims be assumed to have an unstable cervical spine until this condition is ruled out.[15] The airway management of these patients receives much attention from anesthesiologists because direct laryngoscopy causes cervical motion, with the potential to exacerbate spinal cord injury (SCI).[36] Stabilization of the cervical spine will generally occur in the prehospital environment, with the patient already having a rigid cervical collar in place. This collar may be kept in place for several days before the complete gamut of tests to rule out cervical spine instability have been completed (see later). The presence of an "uncleared" cervical spine mandates the use of in-line manual stabilization (not traction) throughout any attempt at intubation.[15] This approach allows removal of the front of the cervical collar to facilitate wider mouth opening and jaw displacement. In-line stabilization has been tested through considerable clinical experience and is the standard of care in the ATLS curriculum. Emergency awake fiberoptic intubation, though requiring less manipulation of the neck, is generally very difficult because of airway secretions and hemorrhage, rapid desaturation, and lack of patient cooperation and is best reserved for cooperative patients with known cervical instability under controlled conditions. Indirect video laryngoscopy with systems such as the Bullard laryngoscope[37] or GlideScope[38,39] offer the potential to enjoy the best of both worlds: an anesthetized patient and minimal cervical motion. However, it will require years of clinical experience to verify this hypothesis.



Figure 72-5 Emergency intubation of a trauma patient immobilized on a long spine board. The front of the cervical collar is removed once in-line manual stabilization of the spine is established to allow cricoid pressure and greater excursion of the mandible. *(Reprinted with permission from Dutton RP: Spinal cord injury. Int Anesthesiol Clin 40:111, 2002.)*

Personnel

Emergency intubation requires more assistance than an intubation performed under controlled conditions (see Chapter 6). Three providers are required to ventilate the patient, hold cricoid pressure, and provide in-line cervical stabilization; a fourth provider to administer anesthetic medications allows the intubating physician to maintain uninterrupted focus on the patient's airway. Figure 72-5 is an illustration of this approach. Additional assistance may be required to restrain a patient who is combative as a result of intoxication or TBI.

The immediate presence of a surgeon or other physician who can expeditiously perform a cricothyroidotomy is desirable. Even if a surgical airway is not required, additional experienced hands may prove useful during difficult intubations. The surgeon may also wish to inspect the upper airway during laryngoscopy if there has been trauma to the face or neck. Urgent tube thoracostomy may prove necessary in some trauma patients to treat the tension pneumothorax that develops with the onset of positive-pressure ventilation.

Anesthetics and Induction of Anesthesia

Any intravenous anesthetic administered to a trauma patient in hemorrhagic shock may potentiate profound hypotension and even cardiac arrest as a result of inhibition of circulating catecholamines. Although propofol and sodium thiopental are the mainstays of intravenous induction in the OR, their use in trauma patients is especially problematic because both drugs are vasodilators and both have a negative inotropic effect. Moreover, the effects of hemorrhagic shock on the brain appear to potentiate the effects of these anesthetics, with propofol doses as small as one tenth of normal producing deep anesthesia in animals in shock.[40] Etomidate is a frequently espoused alternative because of its cardiovascular stability in comparison with other intravenous

hypnotic drugs in the trauma population,[41-43] although its inhibition of catecholamine release may still produce profound hypotension.

Ketamine continues to be popular for induction of anesthesia in trauma patients because it is a CNS stimulant.[44] However, it is also a direct myocardial depressant.[45,46] In normal patients the effect of catecholamine release masks cardiac depression and results in hypertension and tachycardia. In hemodynamically stressed patients the cardiac depression may be unmasked and lead to cardiovascular collapse.[47]

Hypotension will develop in hypovolemic patients with the administration of any anesthetic because of interruption of compensatory sympathetic outflow and the sudden change to positive-pressure ventilation. Previously healthy young patients can lose up to 40% of their blood volume before experiencing a decrease in blood pressure, thereby leading to potentially catastrophic circulatory collapse with induction of anesthesia, regardless of the anesthetic chosen. The dose of anesthetic must be decreased in the presence of hemorrhage, down to none at all in patients with life-threatening hypovolemia. Rapid-sequence induction of anesthesia and endotracheal intubation may proceed with muscle relaxants alone, although onset time may be prolonged in a patient with circulatory impairment. Subsequent patient recall of intubation and emergency procedures is highly variable and affected by the presence of coexisting TBI, intoxication, and the depth of hemorrhagic shock (see Chapter 11). Decreased cerebral perfusion appears to inhibit memory formation but cannot be reliably associated with any particular blood pressure or chemical marker. Administration of 0.2 mg of scopolamine (a tertiary ammonium vagolytic) has been advocated to inhibit memory formation in the absence of anesthetic drugs in this situation, but it may interfere with subsequent neurologic examination because of its long half-life. Small doses of midazolam will reduce the incidence of patient awareness but can also contribute to hypotension. Although recall of ED and OR events is not unusual in this circumstance, anesthesia provider liability appears to be limited; a recent analysis of intraoperative awareness lawsuits in the ASA Closed Claims Database revealed no claims related to surgery in trauma patients.[48]

Neuromuscular Blocking Drugs

Succinylcholine remains the neuromuscular blocker with fastest onset—less than 1 minute—and shortest duration of action—5 to 10 minutes (see Chapter 29). These properties make it popular for rapid-sequence induction of anesthesia. Although the use of succinylcholine may allow return of spontaneous respiration before the development of significant hypoxia in the "cannot intubate, cannot ventilate" situation, this is unlikely to be of benefit in an emergency intubation in a trauma patient. The anesthesiologist should not rely on return of spontaneous breathing in time to salvage a difficult airway management problem but should instead proceed with efforts to obtain a definitive airway, including cricothyroidotomy if other possibilities have been exhausted.

Administration of succinylcholine is associated with several adverse consequences. Increases in serum potassium of 0.5 to 1.0 mEq/L are expected, but in certain patients potassium may increase by more than 5 mEq/L.[49] A hyperkalemic response is typically seen in burn victims and those with muscle pathology secondary to direct trauma, denervation (as with SCI), or immobilization. Hyperkalemia is not seen in the first 24 hours after these injuries, and succinylcholine may be used safely for acute airway management. Patients at risk are those with underlying pathology before their traumatic event or those undergoing subsequent surgery in the weeks to months after injury.

Succinylcholine causes an increase in intraocular pressure and should be used cautiously in patients with ocular trauma.[50] Succinylcholine may also increase ICP,[51] so its use in brain trauma victims is controversial. In both these cases, however, hypoxia and hypercapnia may be as damaging as the transient increase in pressure caused by the drug. If the use of succinylcholine will lead to faster intubation, its benefits may outweigh its risks. The provider must weigh the use of succinylcholine in each individual situation based on the acuity of CNS injury, the anticipated speed with which intubation can be accomplished, and the likelihood that hypoxia will develop.

Alternatives to succinylcholine include rocuronium (0.9 to 1.2 mg/kg) and vecuronium (0.1 to 0.2 mg/kg). Because these drugs have no significant cardiovascular toxicity, large doses can be administered to achieve rapid (1- to 2-minute) systemic relaxation. Unfortunately, at this dose the duration of action of either rocuronium or vecuronium will be 1 to 2 hours, which may be of significance if inadequate sedation leads to patient awareness of paralysis or if it prevents ongoing neurologic assessment. An exciting different approach could come about with the introduction of sugammadex as an antagonist of rocuronium-induced neuromuscular blockage. Specifically, instead of succinylcholine for rapid-sequence induction of anesthesia, rocuronium, 0.9 to 1.2 mg/kg, would be given, the trachea intubated, and then the profound block immediately reversed by sugammadex (see Chapter 29 for details).

There will always be specific situations in which maintaining spontaneous ventilation during intubation is the preferred manner in which to proceed. If patients are able to maintain their airway temporarily but have clear indications for an artificial airway (e.g., penetrating trauma to the trachea), slow induction with ketamine or inhaled sevoflurane through cricoid pressure will enable placement of an endotracheal tube without compromising patient safety.

Adjuncts to Endotracheal Intubation

Equipment to facilitate difficult intubation should be readily available wherever emergency airway management is performed. The particular equipment available depends on the preferences of the anesthesiologist; the usefulness of most special equipment depends more on previous experience than on any intrinsic properties of the device. Certain items deserve mention, however, because of their frequent citation as aids to management of a difficult airway.

The *gum elastic bougie*, or intubating stylet, is an inexpensive and easily mastered adjunct for management of a difficult airway. The stylet is placed through the vocal cords via direct laryngoscopy, and the endotracheal tube is then advanced over the stylet into the trachea. Placement of the bougie is easier than direct placement of an endotracheal tube because of both its smaller diameter and the ability of an experienced operator to feel it enter the trachea even when the glottic opening cannot be visualized. The bougie is passed under the epiglottis and gently advanced; if resistance is met, it is withdrawn, rotated slightly, and

advanced again. In this fashion the anesthesiologist can blindly "palpate" the larynx until the bougie advances into the trachea. The bougie can also be used with indirect video laryngoscopy systems such as the GlideScope and is especially useful in the ED when the sniffing position cannot be used because of uncertainty about the cervical spine. The GlideScope may provide improved visualization (based on the Cormack score) and facilitate safe intubation in patients wearing a cervical collar.[52]

The *esophageal Combitube* may be used by paramedics as a backup for failed intubation in the prehospital environment; in many jurisdictions it is the sanctioned airway rescue device for failed rapid-sequence intubation (RSI). Because placement of the Combitube has been associated with esophageal injury, its use should be reserved for emergency situations.[53-55]

The *laryngeal mask airway* (LMA) (LMA North America, San Diego, CA) is recommended in the ASA algorithm for management of a patient with a difficult airway. The LMA can be used as a guide for intubation when an unsuspected difficult intubation is encountered in a trauma patient; an endotracheal tube may be placed blindly through the lumen of the LMA and into the trachea, or a fiberoptic bronchoscope may be used to guide the tube through the LMA. The LMA is an appropriate rescue device for a difficult airway situation in trauma, provided that there is no major anatomic injury or hemorrhage in the mouth and larynx. In our practice the LMA has most commonly been used as a bridge to emergency tracheostomy because it allows more controlled conditions than a cricothyroidotomy does.

Oral Versus Nasotracheal Intubation

The most recent ATLS guidelines suggest that practitioners providing emergency airway management should proceed with the method of intubation with which they are most proficient.[15] In general, oral intubation is preferable to nasal intubation in the emergency setting because of the risk of injury to the brain from nasal instrumentation in the presence of a basilar skull or cribriform plate fracture. Furthermore, nasal intubation poses a risk for sinusitis in a patient who will be mechanically ventilated for longer than 24 hours, and use of a smaller-diameter tube will also increase the difficulty of subsequent airway suctioning and fiberoptic bronchoscopy. If nasal intubation is most likely to be successful in a given situation, however, this is the route that should be used. Change to an oral tube with a larger internal diameter can occur once the patient's condition has stabilized.

Facial and Pharyngeal Trauma

Trauma to the face and upper airway poses particular difficulties for the anesthesiologist. Serious skeletal derangements may be masked by apparently minor soft tissue damage. Failure to identify an injury to the face or neck can lead to acute airway obstruction secondary to swelling and hematoma. Laryngeal edema is also a risk in patients who have suffered chemical or thermal injury to the pharyngeal mucosa. Intraoral hemorrhage, pharyngeal erythema, and change in voice are all indications for early intubation.

In general, both maxillary and mandibular fractures will make ventilation by mask more difficult, whereas mandibular fractures will make endotracheal intubation easier. Palpation of the facial bones before manipulation of the airway will alert the anesthetist to these possibilities. Patients with injuries to the jaw and zygomatic arch often have trismus. Although the trismus will resolve with the administration of neuromuscular blocking agents, preinduction assessment of airway anatomy may be difficult. Bilateral mandibular fractures and pharyngeal hemorrhage may lead to upper airway obstruction, particularly in a supine patient, although intubation may be easier because of loss of skeletal resistance to direct laryngoscopy. A patient arriving at the ED in the sitting or prone position because of airway compromise is best left in that position until the moment of anesthetic induction and intubation.

Resuscitation from Hemorrhagic Shock

Resuscitation refers to restoration of normal physiology after injury. Resuscitation from hemorrhagic shock refers specifically to restoration of normal circulating blood volume, normal vascular tone, and normal tissue perfusion. Resuscitation begins immediately after injury, via the patient's own compensatory mechanisms, and continues through the prehospital, ED, OR, and ICU phases of care.

Pathophysiology of Hemorrhagic Shock

The initial response to hemorrhage takes place on the macrocirculatory level and is mediated by the neuroendocrine system. Decreased blood pressure leads to vasoconstriction and release of catecholamines. Heart, kidney, and brain blood flow is preserved, whereas other regional beds are constricted. Pain, hemorrhage, and cortical perception of traumatic injuries lead to the release of hormones and other inflammatory mediators, including renin, angiotensin, vasopressin, antidiuretic hormone, growth hormone, glucagon, cortisol, epinephrine, and norepinephrine.[56] This response sets the stage for the microcirculatory response that follows.

Individual ischemic cells respond to hemorrhage by taking up interstitial fluid, thus further depleting intravascular fluid.[57] Cellular edema may choke off adjacent capillaries and result in the "no-reflow" phenomenon, which prevents reversal of ischemia, even in the presence of adequate macroperfusion.[58] Ischemic cells produce lactate and free radicals, which accumulate in the circulation if perfusion is diminished. These compounds cause direct damage to the cell and form the bulk of the toxic load that washes back to the central circulation when flow is reestablished. Ischemic cells also produce and release inflammatory factors: prostacyclin, thromboxane, prostaglandins, leukotrienes, endothelin, complement, interleukins, tumor necrosis factor, and others.[59] Figure 72-6 shows the inflammatory response to shock, with an emphasis on immune system amplification. This inflammatory response, once begun, becomes a disease process independent of its origin. This is why a patient may die of multiple organ failure after traumatic hemorrhage even when bleeding has been controlled and fluid volume restored.

Specific organ systems respond to traumatic shock in specific ways. The *central nervous system* is the prime trigger of the

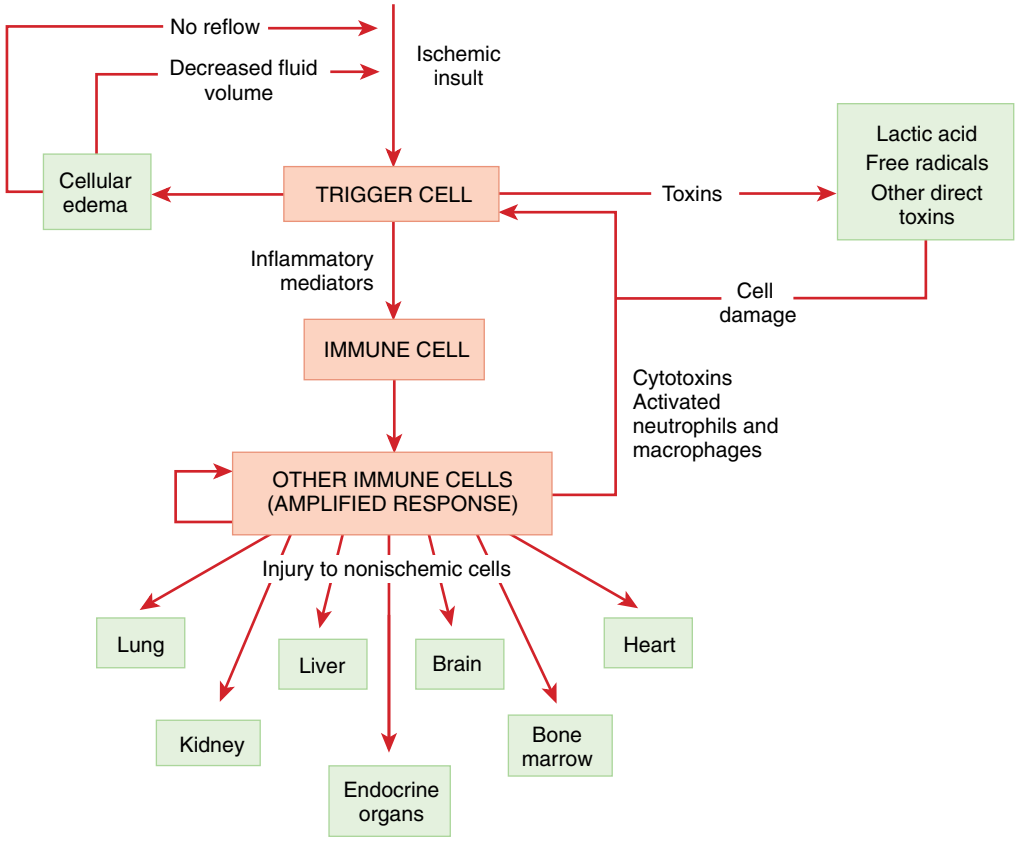

Figure 72-6 The "shock cascade." Ischemia of any given region of the body will trigger an inflammatory response that will have an impact on nonischemic organs even after adequate systemic perfusion has been restored. *(Reprinted with permission from Dutton RP: Shock and trauma anesthesia. In Grande CM, Smith CE [eds]: Anesthesiology Clinics of North America: Trauma. Philadelphia, WB Saunders, 1999, pp 83-95.)*

neuroendocrine response to shock, which maintains perfusion to the heart, kidney, and brain at the expense of other tissues.[60] Regional glucose uptake in the brain changes during shock.[61] Reflexes and cortical electrical activity are both depressed during hypotension; these changes are reversible with mild hypoperfusion but become permanent with prolonged ischemia. Failure to recover preinjury neurologic function is a marker for a poor prognosis, even when normal vital signs are restored.[62]

The *kidney* and *adrenal glands* are prime responders to the neuroendocrine changes associated with shock and produce renin, angiotensin, aldosterone, cortisol, erythropoietin, and catecholamines.[63] The kidney maintains glomerular filtration in the face of hypotension by selective vasoconstriction and concentration of blood flow in the medulla and deep cortical area. Prolonged hypotension leads to decreased cellular energy and an inability to concentrate urine (renal cell hibernation), followed by patchy cell death, tubular epithelial necrosis, and renal failure.[64]

The *heart* is preserved from ischemia during shock because of maintenance of or even an increase in nutrient blood flow, and cardiac function is well preserved until the late stages. Lactate, free radicals, and other humoral factors released by ischemic cells all act as negative inotropes and, in a bleeding patient, may produce cardiac dysfunction as the terminal event in the shock spiral.[65] A patient with cardiac disease or direct cardiac trauma is at great risk for decompensation because a fixed stroke volume inhibits the body's ability to increase blood flow in response to hypovolemia and anemia. Tachycardia is the patient's only option, with potentially disastrous consequences on the oxygen supply-demand balance in the heart itself. Shock in the elderly may therefore be rapidly progressive and not respond predictably to fluid administration.[66]

The *lung* is the filter for the inflammatory by-products of the ischemic body. Immune complex and cellular factors accumulate in pulmonary capillaries and lead to neutrophil and platelet aggregation, increased capillary permeability, destruction of lung architecture, and acute respiratory distress syndrome (ARDS).[67,68] The lung is the sentinel organ for the development of multiple organ system failure (MOSF) in a traumatic shock patient.[69,70] Pure hemorrhage, in the absence of hypoperfusion, does not produce pulmonary dysfunction.[71] This is evidence that traumatic shock is more than just a hemodynamic disorder.

The *gut* is one of the earliest organs affected by hypoperfusion and may be the prime trigger of MOSF. Intense vasoconstriction occurs early and frequently leads to a "no-reflow" phenomenon, even when the macrocirculation is restored.[72] Intestinal cell death causes a breakdown in the barrier function of the gut that results in increased translocation of bacteria to the liver and lung, thereby potentiating ARDS.[73]

The *liver* has a complex microcirculation and may experience reperfusion injury during recovery from shock.[74] Hepatic cells are also metabolically active and contribute to the ischemic inflammatory response and to irregularities in blood glucose.[75] Failure of synthetic function of the liver after shock is almost always lethal.

Skeletal muscle is not metabolically active during shock and tolerates ischemia better than other organs do. The large mass of skeletal muscle, though, makes it important in the generation of lactic acid and free radicals from ischemic cells. Sustained ischemia of muscle cells leads to an increase in intracellular sodium and free water, with an aggravated depletion of fluid in the vascular and interstitial compartments.[76]

Early Resuscitation

Fluid administration is the cornerstone of resuscitation (see Chapters 88 and 97). Intravascular volume is lost to hemorrhage, to uptake by ischemic cells, and to extravasation into the interstitial space. Administration of intravenous fluids will predictably increase cardiac output and blood pressure in a hypovolemic trauma patient. The ATLS curriculum advocates rapid infusion of up to 2 L of warmed isotonic crystalloid solution in any hypotensive patient with the goal of restoring normal blood pressure.[15]

This approach has been questioned in recent years because of a growing awareness that fluid administration during active hemorrhage may be counterproductive. Dilution of red cell mass reduces oxygen delivery and contributes to hypothermia and coagulopathy. Elevation of blood pressure leads to increased bleeding as a result of disruption of clots and reversal of compensatory vasoconstriction.[77] The result of aggressive fluid administration is often a transient rise in blood pressure, followed by increased bleeding, another episode of hypotension, and the need for more volume administration. This vicious circle has been recognized since the First World War and remains a complication of resuscitation therapy today. The ATLS manual characterizes such patients as "transient responders" with active, ongoing hemorrhage.[15] Resuscitation of these patients should be considered in two phases:

- *Early*, while active bleeding is still ongoing
- *Late*, once all hemorrhage has been controlled

Managing late resuscitation is driven by end-point targets and consists of giving enough fluid to maximize oxygen delivery. Early resuscitation is much more complex because the risks associated with aggressive volume replacement (see Box 72-4), including the potential for exacerbating hemorrhage and thus prolonging the crisis, must be weighed against the risk of hypoperfusion and ischemia.

Box 72-4 Risks Associated with Aggressive Volume Replacement during Early Resuscitation*

Increased blood pressure
Decreased blood viscosity
Decreased hematocrit
Decreased clotting factor concentration
Greater transfusion requirement
Disruption of electrolyte balance
Direct immune suppression
Premature reperfusion
Increased risk for hypothermia

*Most complications of volume resuscitation arise from increased hemorrhage volume or excessive hemodilution.

Deliberate hypotensive management is an accepted standard of anesthetic care for elective surgical procedures such as total joint replacement, spinal fusion, radical neck dissection, reconstructive facial surgery, and major pelvic or abdominal procedures.[78] Application of this technique to the initial management of hemorrhage is controversial and has been the focus of numerous laboratory and clinical research efforts. In 1965 Shaftan and colleagues published the results of a study of coagulation in dogs in which it was demonstrated that the formation of a soft extraluminal clot limits bleeding after arterial trauma.[79] This study compared the quantity of blood lost from a standardized arterial injury under a variety of conditions. The least blood loss occurred in hypotensive animals (whether hypotensive from hemorrhage or from administration of a vasodilator), followed by the control group and then vasoconstricted animals. The largest amount of blood was lost in animals that underwent vigorous reinfusion during the period of hemorrhage.

Laboratory data have shown the benefits of limiting intravascular fluid volumes and blood pressure in actively hemorrhaging animals.[80-83] In the most sophisticated models, direct assessment of cardiac output and regional perfusion showed no difference between moderate- or large-volume resuscitation in terms of cardiac output, arterial blood pressure, or regional perfusion of the heart, kidneys, and intestines. Moderate resuscitation (to a lower than normal blood pressure) improved perfusion of the liver.[84] Burris and coworkers studied both conventional resuscitation fluids and various combinations of hypertonic saline and dextran and found that rebleeding was correlated with higher mean arterial pressure (MAP) and that survival was best in groups resuscitated to lower than normal MAP. The optimum target blood pressure for resuscitation varied with the composition of the fluid used.[85] A 1994 consensus panel on resuscitation from hemorrhagic shock noted that mammalian species are capable of sustaining MAP as low as 40 mm Hg for periods as long as 2 hours without deleterious effects. The panel concluded that spontaneous hemostasis and long-term survival were maximized by reduced administration of resuscitation fluids during the period of active bleeding in an attempt to keep perfusion only just above the threshold for ischemia.[86]

To date there have been two published prospective studies of deliberate hypotensive resuscitation in trauma patients. The first was that of Bickell and colleagues in 1994.[87,88] The investigators randomized victims of penetrating torso trauma to one of two treatment groups: standard of care (up to 2 L of crystalloid infused in the prehospital setting) or delayed resuscitation (no fluid until the patient reached the OR). This well-managed 37-month study eventually included 598 patients. Average times of transport and care were 30 minutes from injury to the ED and then 50 minutes before reaching the OR; the fluid-restricted group received an average of about 800 mL of fluid during this time. The immediate-resuscitation group received an average of 2500 mL of crystalloid and 130 mL of blood over this same period. Though substantially different during the period of study, blood pressure on arrival at the OR was similar in both groups, which the authors took as evidence that the unresuscitated group had achieved spontaneous hemostasis. Survival to hospital discharge in the delayed-resuscitation group was significantly improved over the immediate-resuscitation group (70% versus 62% [$P = .04$]). No

Table 72-3 Results of a Randomized Trial of Deliberate Hypotensive Resuscitation*

	Conventional	Hypotensive	Total
Patients enrolled	55	55	110
Male	46	41	87
Blunt trauma	22	31	53
Penetrating trauma	33	24	57
Injury severity score	19.65	23.62 ($P = .11$)	
Predicted survival	0.94	0.90 ($P = .19$)	
Systolic blood pressure during study period	114	100 ($P < .001$)	
Survived to discharge	51	51	
Died	4	4	

*The probability of survival was calculated from published historical data.

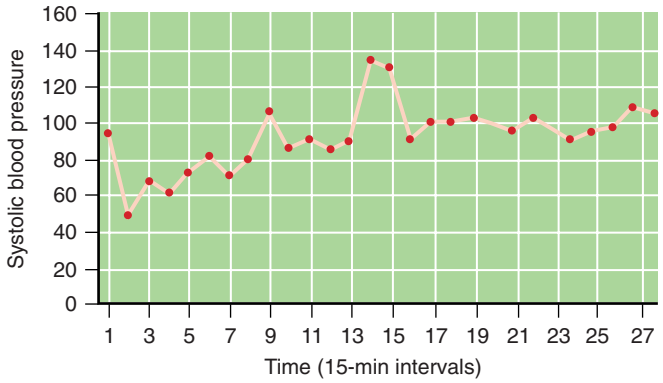

Figure 72-7 Typical systolic blood pressure measurements of a patient undergoing damage control surgery for a grade V liver injury during deliberate hypotensive management. Oscillations in blood pressure are common during early resuscitation because of ongoing hemorrhage and bolus fluid administration. Once hemorrhage is controlled, blood pressure will stabilize.

data were presented on the conduct of anesthesia after arrival at the OR but before control of hemorrhage or on the incidence of rebleeding after volume loading and induction of anesthesia in patients who had achieved hemostasis preoperatively.

A retrospective review of trauma admissions to the Los Angeles Medical Center published in 1996 supported these findings. Patients brought to the hospital by private conveyance fared substantially better than those delivered by paramedics, even with high levels of injury severity.[89] Further corroboration was provided by retrospective examination of outcomes in a population of hemorrhaging trauma patients who received fluids via a commercial rapid infusion system (RIS) (Haemonetics, Inc.) during initial resuscitation.[90] The survival rate of this group was compared with that predicted by the institution's trauma registry. RIS patients, when compared with case-matched controls, had a survival rate of only 56.8% versus 71.2% for patients of similar age with similar injuries ($P < .001$).

This retrospective review was followed in 2002 by the second prospective trial of delayed resuscitation in trauma patients.[91] Patients with systolic blood pressure lower than 90 mm Hg and clinical evidence of blood loss were randomized to fluid resuscitation titrated to a systolic blood pressure of 100 mm Hg (normal group) or 70 mm Hg (study group) until the end of surgical interventions to control hemorrhage. The results of this study are summarized in Table 72-3. As in the Bickell study, hypotension allowed spontaneous resolution of hemorrhage and autoresuscitation; blood pressure would increase without exogenous fluid administration once hemostasis was achieved. The typical patient began with a low initial pressure, followed by recovery to the vicinity of the target, overshoots and undershoots as bleeding and fluid administration continued, and an eventual rise above the target when the hemorrhage resolved, even in the absence of further fluid administration (Fig. 72-7). The 93% overall survival rate in this study was more frequent than predicted from historical data and substantially higher than seen in Bickell's group. This reflects the exclusion of patients who died in the prehospital phase or arrived at the trauma resuscitation unit in a moribund condition. It may also reflect improvements in overall care, an observation effect (i.e., patients in both groups received better care than patients not in the study did), or a bias in subject recruitment. Over the first 24 hours, lactate and base deficit cleared to normal in both groups and required similar amounts of fluid and blood products, thus suggesting that both groups were reaching an equivalent resuscitation end point. The authors concluded that administration of fluids to an actively hemorrhaging patient should be titrated to specific physiologic end points, with the anesthesiologist navigating a course between the Scylla of increased hemorrhage and the Charybdis of hypoperfusion.

The effect of anesthetic drugs on the body's response to hemorrhage is an important difference between deliberate hypotension occurring in the elective operative setting and hemorrhagic shock occurring in the ED. Hypotensive trauma patients receive a minimum of anesthetics, even for induction, because of the obvious effect of these drugs on arterial blood pressure. A hypotensive trauma patient is thus in a state of profound vasoconstriction, as opposed to a patient undergoing elective intraoperative hypotension, who is vasodilated by general anesthesia before any blood loss. Table 72-4 summarizes the physiologic contrasts between these two states. It should be noted that blood loss without shock does not produce systemic complications such

Table 72-4 Differences in Clinical Findings Between Surgical Patients Undergoing Elective Deliberate Hypotension and Emergency Trauma Cases*

Aspect	Elective	Trauma
Intravascular volume	Euvolemic	Hypovolemic
Temperature	Normal	Probably hypothermic
Capillary beds	Dilated	Constricted
Level of general anesthesia	Deep	Usually light
Preexisting mental status	Normal	May be impaired
Coexisting injuries	None	May be significant
Comorbid conditions	Known and managed	Unknown

*Each of these factors produces a real or perceived contraindication to the use of deliberate hypotensive technique in trauma patients.

Box 72-5 Goals for Early Resuscitation*

- Maintain systolic blood pressure at 80 to 100 mm Hg
- Maintain hematocrit at 25% to 30%
- Maintain the prothrombin time and partial thromboplastin time in normal ranges
- Maintain the platelet count at greater than 50,000 per high-power field
- Maintain normal serum ionized calcium
- Maintain core temperature higher than 35°C
- Maintain function of the pulse oximeter
- Prevent an increase in serum lactate
- Prevent acidosis from worsening
- Achieve adequate anesthesia and analgesia

*Fluid administration to limit hypoperfusion is balanced against an undesirable increase in blood pressure and thus bleeding.

as ARDS in experimental models.[71] Based on this physiology, the recommended goals for early resuscitation are expressed in Box 72-5, and an algorithm for management is presented in Figure 72-8. The emphasis in this situation must be on rapid diagnosis and control of ongoing hemorrhage; the anesthesiologist should attempt to restore vascular volume and provide anesthesia in equal measure by moving the patient from a vasoconstricted state to a vasodilated one while facilitating hemostasis by maintenance of lower than normal blood pressure.

Vulnerable Patient Populations

Clinical trials of deliberate hypotensive resuscitation have avoided the application of this technique to populations perceived to be at greater risk for ischemic complications,[87,91] including patients with known ischemic coronary disease, elderly patients, and those with injuries to the brain or spinal cord (see Chapters 35, 63, and 71). The prohibition against hypotension in patients with TBI is especially well established because of the observed disparity in outcome between TBI patients who experience hypotension and those who do not.[92,93] Older trauma patients suffer worse outcomes from similar injuries compared with younger patients, presumably because of their reduced physiologic reserve.[94] Clinical care of these patients is focused on avoidance of ischemic stress and rapid correction of hypovolemia. It may well develop, however, that deliberate hypotensive management to enable rapid control of hemorrhage is equally beneficial in vulnerable populations. There have been no clinical trials to date on this subject, but a laboratory study did find a benefit of deliberate hypotension in animals with both TBI and hemorrhagic shock.[95] Absent convincing human evidence, deliberate hypotension in older or brain-injured patients should generally be avoided.

Resuscitation Fluids

Isotonic crystalloids (normal saline, lactated Ringer's solution [LR], Plasma-Lyte A) are the initial resuscitative fluids administered to any trauma patient (see Chapter 88). They have the advantage of being inexpensive, readily available, nonallergenic, noninfectious, and efficacious in restoring total-body fluid. They are easy to store and administer, they mix well with infused medications, and they can be rapidly warmed to body temperature. Disadvantages of crystalloids include their lack of oxygen-carrying capacity, their lack of coagulation capability, and their limited intravascular half-life. More recent laboratory data have implicated specific crystalloid solutions as immunosuppressants and triggers of cellular apoptosis.[96] Unlike necrosis, apoptosis is highly regulated and involves gene modulation and complex pathways of signal transduction. It seems clear that apoptosis is an important element of reperfusion injury. In a rat model of controlled hemorrhage, animals receiving LR showed an immediate increase in apoptosis in the liver and small intestine after resuscitation.[97] Neither whole blood nor hypertonic saline increased the amount of apoptosis.

Hypertonic saline solutions, with or without the addition of polymerized dextran (HS or HSD), have been extensively studied in resuscitation from hemorrhagic shock.[98] In theory, HS will draw fluid into the vascular space from the interstitium and thereby reverse some of the nonhemorrhagic fluid loss caused by shock and ischemia. A given amount of HS will thus have an enhanced ability to restore intravascular volume when compared with an equivalent volume of an isotonic solution. This has made HS a popular choice for fluid resuscitation under austere conditions. HSD is licensed for prehospital use in a number of European countries and is used for resuscitation by units of the U.S. military. Multiple studies of otherwise lethal hemorrhage in animals have demonstrated improved survival after resuscitation with HSD versus either normal saline solution or the components of HSD alone. Studies of the efficacy of HSD in trauma patients have been inconclusive[99]; the most obvious benefit occurred in a subset of polytraumatized patients with both hemorrhage and TBI, in whom improved neurologic status was demonstrated in those who received HSD as a resuscitation fluid. Indeed, HS is commonly used as an osmotic agent in the management of TBI with elevated ICP.[100]

Colloids, including starch solutions and albumin, have been advocated for rapid plasma volume expansion. Like crystalloids, colloids are readily available, easily stored and administered, and relatively inexpensive. As with hypertonic solutions, colloids will increase intravascular volume by drawing free water back into the vascular space. When intravenous access is limited, colloid resuscitation will restore intravascular volume more rapidly than crystalloid infusion will and at a lower volume of administered fluid. Colloids do not transport oxygen or facilitate clotting; their dilutional effect will be similar to that of crystalloids. Recent studies have demonstrated no great benefit of colloids over crystalloids in a variety of resuscitation models.[101,102]

Many of the risks of aggressive intravascular fluid administration just summarized are related to dilution of the circulating blood volume. Recognition of this fact and continued improvement in the safety of donated blood have led to increased use of *blood products* in the management of early hemorrhagic shock (see Chapter 55). The risk of systemic ischemia is decreased by the maintenance of an adequate hematocrit, and the potential for dilutional coagulopathy can be avoided by the early administration of plasma. The composition of resuscitation fluids may be as important as the rate and timing of administration. A 4-year retrospective review of a cohort of critically injured patients who underwent emergency surgery examined the outcomes of

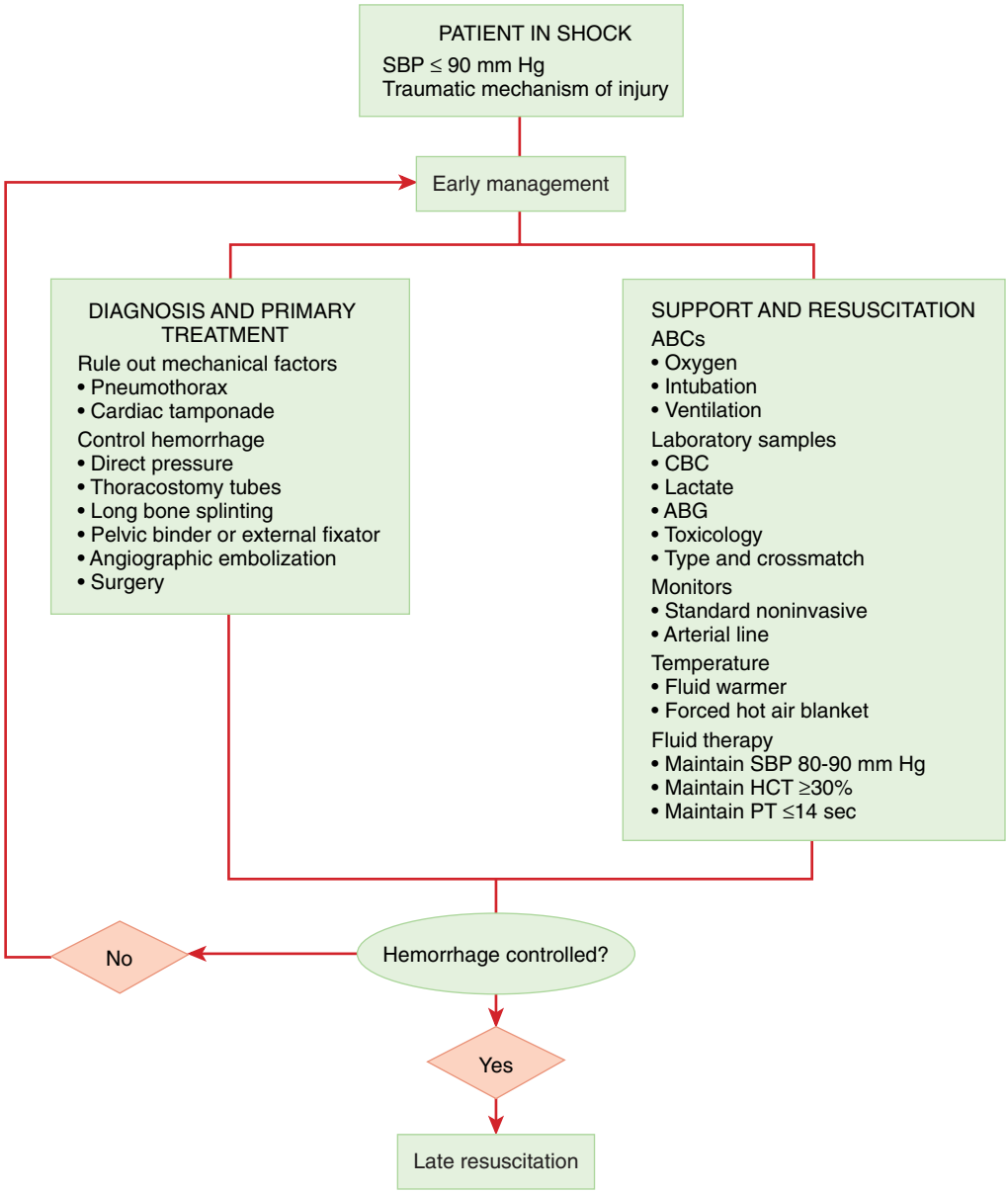

Figure 72-8 Algorithm for the management of early hemorrhagic shock. ABCs, airway, breathing, circulation; ABG, arterial blood gases; CBC, complete blood count; HCT, hematocrit; PT, prothrombin time; SBP, systolic blood pressure.

short-term care based on the number of units of blood transfused.[103] One hundred forty-one patients received massive blood transfusions (20 or more units of red blood cells [RBCs]) during preoperative and intraoperative resuscitation. The number of blood units did not differ between survivors (30%) and nonsurvivors (70%). Eleven variables were significantly different: aortic clamping for control of blood pressure, use of inotropic agents, time with a systolic blood pressure higher than 90 mm Hg, time in the OR, temperature lower than 34°C, urine output, pH lower than 7.0, Pao_2/Fio_2 ratio less than 150, $Paco_2$ greater than 50 mm Hg, potassium greater than 6 mM/L and calcium lower than 2 mM/L. Of these, the presence of the first three variables in the face of transfusion of more than 30 units of packed RBCs was invariably fatal. Total blood loss and the amount of transfused blood were less critical than the depth and duration of shock. These concerns led to the concept of damage control surgery, which emphasizes rapid control of active hemorrhage.[104]

Red blood cells are the mainstay of treatment of hemorrhagic shock. With an average hematocrit of 50% to 60%, a unit of RBCs will predictably restore oxygen-carrying capacity and expand intravascular volume *as well as any colloid solution.* RBCs of blood type A, B, or AB carry major incompatibility antigens that may precipitate a lethal transfusion reaction if given to a patient with the opposite blood type. Because RBCs also carry dozens of minor antigens that can cause reactions in susceptible patients, crossmatching is desirable when time allows (typically about 1 hour from the time that a sample reaches the blood bank until the RBCs reach the patient). Type-specific blood requires less time for delivery from the blood bank (usually about 30 minutes) and may be an appropriate alternative in some

situations. Type O blood—the "universal donor" type—can be given to patients of any blood type with little risk of a major reaction.[105] This is the preferred approach for patients who arrive at the ED in hemorrhagic shock. If O-positive blood is given to a Rhesus-negative woman who survives, prophylactic administration of anti-Rh_0 antibody is indicated.

Risks of RBC administration include transfusion reaction, transmission of infectious agents, and hypothermia (see Chapter 55 for details.) For example, RBCs are stored at 4°C and will decrease the patient's temperature rapidly if not infused through a warming device or mixed with warmed isotonic crystalloid at the time of administration.

Plasma requires blood typing but not crossmatching; delay in availability of plasma is caused by the need to thaw frozen units before they can be administered. Busy trauma hospitals will often maintain a supply of pre-thawed plasma (thawed fresh plasma [TFP] as opposed to fresh frozen plasma [FFP]) that can be issued quickly in response to an emergency need; in smaller hospitals it is important to request plasma early in resuscitation if it is likely to be needed. Very busy centers are experimenting with keeping 2 to 4 units of pre-thawed type AB (universal donor) plasma available in the trauma resuscitation unit. Units are kept ready in this way for 2 days at a time; if not used on an emergency basis, the units are returned to the blood bank and released to the next patient needing plasma. Whether this approach improves outcomes has not yet been studied.

Platelet transfusion should normally be reserved for clinically coagulopathic patients with a documented low serum level (<50,000 per high-power field). When the patient is in shock, however, and blood loss is likely to be substantial, platelets should be empirically administered in proportion to RBCs and plasma (1:1:1). Transfused platelets have a very short serum half-life and should be administered only to patients with active coagulopathic bleeding. Platelets should not be administered through filters, warmers, or rapid infusion systems because they will bond to the inner surfaces of these devices, thereby reducing the quantity of platelets actually reaching the circulation.

Rapid transfusion of banked blood carries the risk of inducing "citrate intoxication" in the recipient. Harvested blood units are treated with citrate to bind free calcium and thus inhibit the clotting cascade. Consecutive administration of multiple units of banked blood leads to a correspondingly large dose of citrate, which may overwhelm the body's ability to mobilize free calcium and have a profound negative inotropic effect on the heart. Unrecognized hypocalcemia is a cause of hypotension in patients after massive transfusion and persists despite an adequate volume of resuscitation. Ionized calcium levels should be measured at regular intervals in a hemorrhaging patient, and calcium should be administered as needed (in a separate intravenous line from transfusion products) to maintain serum levels in the normal range.

Resuscitation Equipment

Intravascular fluid resuscitation of any kind is impossible in the absence of intravenous access. Immediate placement of at least two large-bore catheters (16 gauge or larger) is recommended during the primary assessment of any trauma patient.[15] Practitioners should have a low threshold for placement of a large-caliber central line in any patient in whom antecubital or other peripheral placement attempts have been unsuccessful. Potential sites for central line placement include the internal jugular, subclavian, and femoral veins, each of which has its own benefits and potential risks. The internal jugular approach, though familiar to most anesthesiologists, will require removal of the cervical collar and manipulation of the patient's neck and is not recommended in the acute setting unless other options have been exhausted. The femoral vein is easily and rapidly accessed and is an appropriate choice in patients without apparent pelvic or thigh trauma who require urgent drug or fluid administration. Caution should be used in patients with penetrating trauma to the abdomen because fluids infused via the femoral vein may contribute to hemorrhage from an injury to the inferior vena cava or iliac vein; these patients should have intravenous access placed above the diaphragm if possible. Femoral vein catheterization carries a high risk for the formation of deep venous thrombosis,[106] thus limiting use of this approach to the acute setting. Femoral lines should be removed as soon as possible after the patient's condition stabilizes. The subclavian vein is the most common site for early and ongoing central access in a trauma patient because the subclavian region is easily visible and seldom directly traumatized. This approach carries the highest risk for the development of pneumothorax, although many patients will already have indications for tube thoracostomy in one or both chest cavities; when possible, this is the preferred side for placement of a subclavian line. Placement of an arterial line facilitates frequent laboratory analysis and allows close monitoring of blood pressure; this should be undertaken as soon as possible but should not impede other diagnostic or therapeutic maneuvers.

The anesthesiologist should work to maintain thermal equilibrium (see Chapter 48) in any trauma patient. Although deliberate hypothermia has been suggested as a management strategy for both hemorrhagic shock[107] and TBI,[108] there is insufficient evidence to support this approach. Hypothermia will potentiate dilutional coagulopathy and systemic acidosis, and shivering and vasoconstriction in response to cold will demand an additional metabolic effort that may predispose the patient to myocardial ischemia. Hypothermia also greatly increases the subsequent risk for sepsis. Because many trauma patients arrive at the ED cold from exposure to the elements, early active warming measures are required. All intravenous fluids should be prewarmed or infused through a warming device. The patient should be kept covered with warmed blankets whenever possible, and the environment should be kept warm enough to make the patient comfortable. If hypothermia has already developed, the use of forced hot air warming is strongly indicated to restore normothermia. Even though all these measures are routine and obvious in the OR, the anesthesiologist can perform a valuable service by ensuring that they are available and applied in the ED, CT scanner, and angiography suite as well.

Commercial rapid-infusion devices are of great benefit in trauma care, particularly in the presence of hemorrhagic shock. These machines offer a number of benefits whenever large quantities of fluid resuscitation are likely (Box 72-6). Early experience with these devices demonstrated higher patient temperature and reduced acidosis at the conclusion of the initial surgery,[109] although others have suggested that rapid infusers might contribute to overinfusion of fluids, inappropriately elevate blood pressure, and contribute to rebleeding.[90] Application of the principles described earlier can prevent this complication; basal fluid administration should be kept low (200 to 500 mL/hr), with small fluid

Box 72-6 Benefits of a Fluid Infusion System in Resuscitation from Hemorrhagic Shock

- An active mechanical pump enables fluid administration rates of up to 1500 mL/min
- Compatible with crystalloid, colloid, packed red blood cells, washed salvaged blood, and plasma (*not* platelets)
- The reservoir allows mixing of products in preparation for rapid blood loss
- Fluids infused at a controlled temperature (38°C to 40°C)
- Able to pump simultaneously through multiple intravenous lines
- Fail-safe detection systems to prevent infusion of air
- Accurate recording of fluid volume administered
- Portable enough to travel with the patient between units

boluses given in response to measured systolic blood pressure below 80 to 90 mm Hg. In practice, fluid boluses are given alternately with anesthetic agents, with the goal of reaching a normal depth of anesthesia without increasing systolic blood pressure.

Late Resuscitation

Box 72-7 summarizes end points for late resuscitation, and Figure 72-9 presents an algorithm for management. Fluid administration is an integral, mandatory component. The adequacy of resuscitation should not be judged by the presence of normal vital signs, but by normalization of organ and tissue perfusion. The role of the anesthesiologist-intensivist is to recognize the presence of ongoing shock after traumatic hemorrhage and to resuscitate the patient with the appropriate fluid, in the appropriate amount, at the appropriate time.

Late resuscitation begins once bleeding is definitively controlled by surgery, angiography, or the passage of time. The practitioner's goal at this time is to restore normal perfusion to all organ systems while continuing to support vital functions. Hypoperfusion caused by hemorrhagic shock triggers a predictable cascade of biochemical events that will cause physiologic derangements persisting long after adequate blood flow is restored. The extent of hypoperfusion—the depth and duration of shock—is highly correlated with the development of subsequent organ system failure. Unfortunately, traditional vital sign markers such as blood pressure, heart rate, and urine output are insensitive to the adequacy of resuscitation. Occult hypoperfusion syndrome is common in postoperative trauma patients, particularly young ones.[110] This syndrome is characterized by a normal blood pressure maintained by systemic vasoconstriction; intravascular volume is low, cardiac output is low, and organ system ischemia persists. The patient will be at high risk for MOSF if the hypoperfusion is not promptly corrected.

The search for the optimal end point of resuscitation has led to several different hemodynamic, acid-base, and regional perfusion targets. Table 72-5 summarizes modalities that are available to gauge the adequacy of resuscitation, along with the shortcomings of each technique. Although the flow of blood to tissue beds is a determinant of tissue perfusion, pressure should also be an important consideration. The left ventricular stroke work index is a variable that accounts for both flow and pressure. Furthermore, left ventricular power output has been used to quantify left ventricular performance. These indices were compared with purely flow-derived hemodynamic and oxygen transport variables as markers of perfusion and outcome in critically injured patients during resuscitation.[111] A consecutive series of 111 patients were monitored with a volumetric pulmonary artery catheter during the first 48 hours of resuscitation. The ability to clear lactate in less than 24 hours and survival were studied. Survivors exhibited significantly higher stroke work and left ventricular power output than nonsurvivors did. In addition to heart rate, these were the only variables that were significantly related to lactate clearance and survival. The higher stroke work and left ventricular power output in survivors were related to better ventricular-arterial coupling and therefore more efficient cardiac function.

Box 72-7 Goals of Late Resuscitation*

- Maintain systolic blood pressure higher than 100 mm Hg
- Maintain hematocrit above individual transfusion threshold
- Normalize coagulation status
- Normalize electrolyte balance
- Normalize body temperature
- Restore normal urine output
- Maximize cardiac output by invasive or noninvasive measurement
- Reverse systemic acidosis
- Document decrease in lactate to normal range

*Fluid administration should be continued until adequate systemic perfusion is restored.

Table 72-5 Modalities for Assessment of Systemic Perfusion

Technique	Shortcomings
Vital signs	Will not indicate occult hypoperfusion
Urine output	May be confounded by intoxication, diuretic therapy, circadian variation, or renal injury
Systemic acid-base status	Confounded by respiratory status
Lactate clearance	Requires time to obtain laboratory result
Cardiac output	Requires placement of a pulmonary artery catheter or use of noninvasive technology
Mixed venous oxygenation	Difficult to obtain, but a very accurate marker
Gastric tonometry	Requires time to equilibrate, subject to artifact
Tissue oxygenation	Emerging technology, appears beneficial
Stroke volume variation	Emerging technology, requires an arterial line
Acoustic blood flow	Investigational technology, unproven

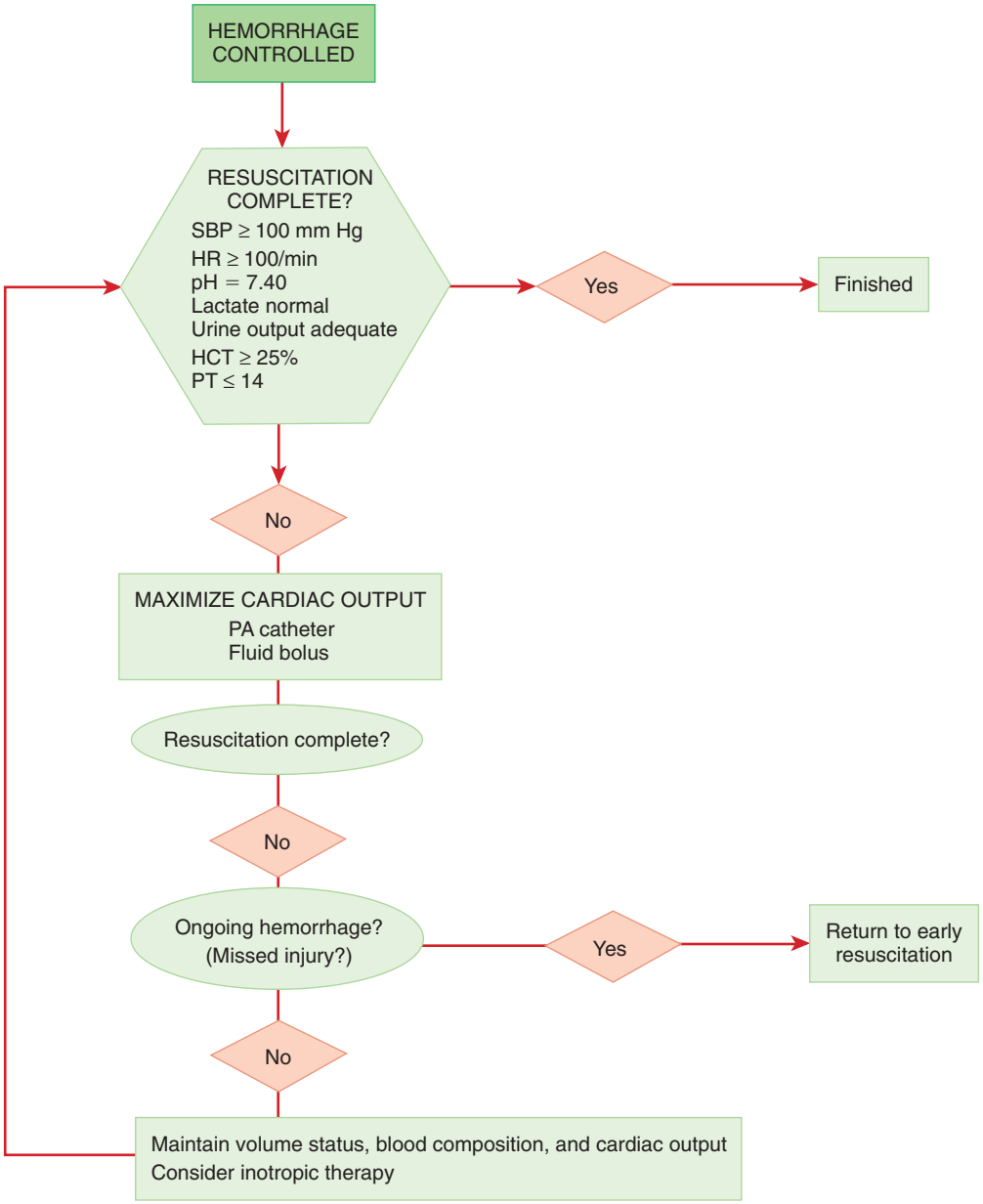

Figure 72-9 Algorithm for the management of late hemorrhagic shock. HCT, hematocrit; HR, heart rate; PT, prothrombin time; PA, pulmonary artery; SBP, systolic blood pressure.

Monitoring resuscitation with invasive monitors is changing at present to noninvasive approaches that assess the return of adequate metabolism, respiration, and oxygen transport in peripheral tissue beds. One such technique is tissue oxygen monitoring (skin, subcutaneous tissue, or skeletal muscle). Skeletal muscle blood flow decreases early in the course of shock and is restored late during resuscitation, thus making the skeletal partial pressure of oxygen a sensitive indicator of low flow.[112,113] Early "goal-directed" treatment of septic shock,[114] with an emphasis on measurement of mixed-venous oxygen saturation, has influenced the care of trauma patients, and many ICUs are now using continuously measured venous oxygenation to guide resuscitation. Stroke volume variation, the change in arterial pressure driven by the respiratory cycle, is emerging as another less invasive measure of fluid volume status; increased variation in arterial pressure during positive-pressure ventilation is a reliable predictor of decreased intravascular volume.[115]

Tissue hypercapnia has been suggested as a universal indicator of critically reduced perfusion. Measurement of gastric P_{CO_2} by gastric tonometry has been used in trauma patients as an indicator of restoration of splanchnic blood flow, and distal gut pH has shown promise as a reliable indicator.[116] The most proximal area of the gastrointestinal tract, the sublingual mucosa, is a useful site for measurement of P_{CO_2} (P_{SLCO_2}).[117] When P_{SLCO_2} exceeded a threshold of 70 mm Hg (normal, 45.2 ± 0.7 mm Hg), its positive predictive value for circulatory shock was 100%.[118] Inadequate tissue perfusion, as indicated by these specific monitors or by the traditional systemic markers of serum lactate, base deficit, and decreased pH, must be treated promptly once ongoing hemorrhage is controlled. The rate at which lactate returns to

normal after shock is strongly correlated with outcome; failure to normalize within 24 hours is associated with a greater risk for MOSF and eventual death.[110,119]

Future Developments in Resuscitation

Because resuscitation from hemorrhagic shock begins with control of bleeding, improvements in the ability to diagnose and treat hemorrhage are likely to prove beneficial after trauma. The past decade has seen the development and widespread use of focused assessment by sonography for trauma (FAST)[120] and high-resolution CT to improve the diagnosis of hemorrhage and of damage control surgery and angiographic embolization to correct it. Two different classes of prothrombotic agents have become increasingly popular adjuvants for use in hemorrhaging patients: topical clotting agents and systemic procoagulants.

Topical preparations are applied to open wound surfaces (such as a lacerated liver) to induce the immediate formation of clot. The ones that have seen the longest use are preparations of thrombin and fibrin. These "fibrin glues" will not work in the presence of brisk hemorrhage because they are rapidly washed away, but they are advantageous in the management of oozing surfaces and organs that are difficult to suture or cauterize, such as lung or liver.[121] Fibrin glue is assembled from recombinant or highly purified thrombin; it carries no risk of transmission of viral disease, although there have been reports of antibodies developing to bovine thrombin administered topically. Systemic uptake is also limited, which means that inappropriate coagulation remote from the site of application is unlikely. Formulations of thrombin and fibrinogen layered on collagen-based dressings, intended for rapid control of large-area injuries to solid visceral organs or the musculoskeletal system, have been developed and are in use by the military in Iraq and Afghanistan.[122] Also in use by the military are several newer topical hemostatics consisting of small hydrophilic particles (zeolite or chitosan) that rapidly absorb free water from injured tissue, thereby greatly concentrating clotting factors and platelets and thus enhancing the rate of clot formation.[123] At present, none of these compounds are licensed for internal use, although this is a probable future development.

Recombinant activated human coagulation factor VII (rFVIIa) is licensed for the treatment of hemophiliacs with active or anticipated hemorrhage and known antibodies to factor VIII (see Chapters 54 and 55). The observation of rapid hemostasis in this population led to the anecdotal use of rFVIIa in other congenital and acquired coagulopathies, including the dilutional coagulopathy of traumatic hemorrhage. Factor VIIa in pharmacologic doses works by triggering a burst of thrombin on the surface of platelets activated by exposed tissue factor, which produces rapid clot formation. Because tissue factor is required, coagulation is limited to the site of vascular injury, and inappropriate clotting of uninjured organs or vessels, though an acknowledged risk, occurs at only low frequency.[124] Prospective trials of rFVIIa have demonstrated decreased blood loss in patients undergoing elective open prostate surgery[125] and rapid reversal of coagulopathy in patients taking warfarin.[126] Retrospective reports have suggested a role for rFVIIa in the management of acute traumatic hemorrhage,[127] gastrointestinal hemorrhage secondary to cirrhosis,[128] hemorrhage after cardiovascular surgery[129] and liver transplantation,[130] and intracranial hemorrhage in both neonates[131] and the elderly.[132] One small placebo-controlled trial of rFVIIa in hemorrhaging trauma patients has demonstrated decreased blood loss, decreased transfusion requirements, and improved outcome.[133] A larger international trial is currently under way.

Other anticipated developments in the field of resuscitation include more specific management strategies for the consequences of shock and reperfusion (see Chapters 91 and 92). Hemorrhagic shock followed by resuscitation can be viewed as an ischemia-reperfusion injury involving the entire body. Prevention of organ ischemia or damage may be possible in the future through the administration of agents that regulate cellular function and humoral signaling. Possibilities include manipulation of shock-related pathophysiologic alterations such as complement and granulocyte activation, endothelial activation, leukostasis, and edema formation with resultant organ injury.[134] Modification of outcome may be possible through the use of oxygen carriers (fluorocarbons and modified hemoglobins), antioxidants, nitric oxide scavengers, and antiendotoxin compounds. Even more exciting is the possibility of tailoring treatment to the patient's individual genetic make-up, with controlled manipulation of a wide variety of proinflammatory and anti-inflammatory agents used to maintain optimal serum chemistry during recovery from injury. Though a distant possibility at present, the first steps in this approach are being taken with the recent recognition that patterns of genetic expression can predict outcome after major injury.[135]

Trauma to the Central Nervous System

CNS trauma accounts for almost half of all trauma deaths examined post mortem in population-based analyses[136] or after trauma center admission (see Chapter 63).[137] In addition, more than 90,000 Americans are disabled by TBI[138] and 8000 to 10,000 by SCI[139] each year. As with hemorrhagic shock, CNS trauma consists of both the primary injury, in which tissue is disrupted by mechanical force, and a secondary response, in which the body's reaction to the injury plays an important role. Mitigation of secondary CNS injury depends on prompt diagnosis and early, goal-directed therapy. Although there is no way to minimize primary CNS injury other than with preventive strategies, secondary brain injury accounts for much of the death and disability that follows trauma. The initial management of these patients can significantly affect outcome. Attention to the ABCDE approach is paramount to successful resuscitation, and the trauma anesthesiologist should be intimately involved in this process. Critical care management of TBI patients is covered elsewhere in this volume (see Chapter 94). What follows is a brief discussion of the early management of these patients.

Trauma produces shear forces that result in primary damage to neuronal cell bodies and axons and to the vasculature. The pathophysiology of secondary injury includes metabolic failure, oxidative stress, and a cascade of biochemical and molecular events leading to both delayed necrotic and apoptotic cell death.[140] Secondary injury is often exacerbated by tissue hypoxia/ischemia and by inflammatory responses, and outcomes from TBI are influenced by a large number of interacting factors. Individual

drugs such as free radical scavengers, anti-inflammatory agents, and ion channel blockers have been effective in animals but have had little impact or yielded disappointing results in human trials.

Patients with mild TBI (GCS score of 13 to 15) who maintain a stable GCS score for 24 hours after injury are very unlikely to deteriorate further, although they are at risk for a number of "postconcussive" effects, including headache, memory loss, emotional lability, and sleep disturbance.[141] Moderate TBI (GCS score of 9 to 12) may be accompanied by intracranial lesions that require surgical evacuation, and early CT is strongly indicated. Early intubation, mechanical ventilation, and close observation may be required in the management of patients with moderate TBI because of combative or agitated behavior and the potentially catastrophic consequences of respiratory depression or pulmonary aspiration occurring during diagnostic evaluation. Extubation of the trachea can be undertaken if the patient is hemodynamically stable and appropriately responsive after the diagnostic workup. Treatment of secondary brain injury is accomplished by early correction and subsequent avoidance of hypoxia, prompt fluid resuscitation, and management of associated injuries. The timing of indicated noncranial surgery in these patients is highly controversial in that early surgery has been associated with an increase in episodes of hypoxia and hypotension.[142] Whereas some studies have demonstrated a decrement in neurologic outcomes after early surgery,[143,144] others have shown an increased incidence of pulmonary and septic complications when orthopedic and soft tissue surgeries are delayed.[145,146] Recent reviews of surgical timing have not substantiated an increased risk with early surgery, although a definitive prospective trial has not yet been reported.

Neurologic monitoring of patients with moderate TBI consists of serial assessment of consciousness and motor and sensory function. Deterioration of the GCS score is an indication for urgent CT to establish the need for craniotomy or invasive monitoring of ICP. If frequent neurologic monitoring is not possible because of general anesthesia continuing longer than 2 hours, the need for aggressive analgesia, or prophylaxis against delirium tremens, invasive ICP monitoring is indicated.[93] Although mortality from moderate TBI is low, almost all patients will suffer significant long-term morbidity.

Severe TBI is classified as a GCS score of 8 or less at the time of admission and carries a significant risk for mortality. Early, rapid management focused on restoration of systemic homeostasis and perfusion-directed care of the injured brain will produce the best possible outcomes in this difficult population. Guidelines for all aspects of the management of patients with severe TBI have been published by the American Association of Neurological Surgeons, now in the third edition. The clinical pathway in place at our institution appears in Figure 72-10.

A single episode of hypoxemia (Pao_2 <60 mm Hg) occurring in a patient with severe TBI is associated with nearly a doubling of mortality.[147] The data on prehospital intubation are controversial. In the past it was thought that field intubation, by providing a "definitive" airway and adequate oxygen delivery to the brain, would benefit patients. However, there are no prospective data evaluating the impact of prehospital intubation in adult trauma patients, and two retrospective studies have shown worsened neurologic outcomes.[148,149] An expert panel examining this question concluded that (1) the existing literature regarding paramedic RSI is inconclusive and apparent differences in outcome can be explained by the use of different methodologies and variability in comparison groups; (2) use of the GCS score alone to identify TBI patients requiring RSI is limited, with additional research needed to refine screening criteria; (3) suboptimal RSI technique, as well as subsequent hyperventilation, may account for some of the increase in mortality reported with the procedure; (4) initial and ongoing training, as well as experience with RSI, appears to affect performance; and (5) the success of a paramedic RSI program is dependent on the particular characteristics of the emergency medical service and trauma system. The patient should be transported as rapidly as possible to a facility capable of managing severe TBI or to the nearest facility capable of intubating the patient and initiating systemic resuscitation. The sine qua non is adequacy of systemic oxygenation, by whatever means that this can best be accomplished.

Patients with isolated head injuries can be managed with traditional ventilatory strategies, but those with chest trauma, aspiration, or massive resuscitation after shock are at high risk for the development of acute lung injury. The classic teaching of no or low-level positive end-expiratory pressure (PEEP) to prevent elevated ICP is inappropriate because it may fail to correct hypoxemia. With adequate volume resuscitation, PEEP does not increase ICP or lower cerebral perfusion pressure (CPP)[150] and may actually decrease ICP as a result of improved cerebral oxygenation.[151] Hyperventilation therapy (e.g., at a $Paco_2$ of 25 mm Hg), long a mainstay in the management of patients with TBI, is no longer recommended as a prophylactic treatment. Current guidelines imply a range of $Paco_2$ between 30 and 35 mm Hg, with hyperventilation to 30 mm Hg only for episodes of elevated ICP that cannot be controlled with sedatives, drainage of cerebrospinal fluid, neuromuscular blockade, osmotic agents, or barbiturate coma.[92] Hyperventilation during the first 24 hours is of particular concern because of the critical reductions in perfusion during this timeframe. However, these recommendations should be taken in context and modified in the face of unstable clinical circumstances such as an expanding mass lesion or signs of imminent herniation.[152]

The most challenging of all trauma patients are those with severe TBI and coexisting hemorrhagic shock. A single episode of hypotension, defined as systolic blood pressure lower than 90 mm Hg, is associated with an increase in morbidity and doubled mortality after severe TBI.[147] Hypotension together with hypoxia is associated with a threefold increase in mortality. Systolic blood pressure less than 90 mm Hg should be avoided, with a goal of greater than 70 mm Hg MAP until ICP monitoring is instituted and CPP can be directly targeted. Contrary to practices in the past, current recommendations are to maintain a patient with severe TBI in a euvolemic state. Therefore, *fluid resuscitation is the mainstay of therapy*, followed by vasoactive infusions as needed. The ideal fluid has not yet been identified, but increasing evidence suggests that hypertonic saline solutions are optimal. Correction of anemia from blood loss is the first priority, with a goal of maintaining the hematocrit at greater than 30%. After the initial ABCDE management of a patient with severe TBI, a stepwise approach to maintenance of CPP is initiated, with a currently recommended goal range of 50 to 70 mm Hg, as discussed in Chapter 63.

Decompressive craniectomy is a surgical procedure used to control severely elevated ICP and prevent herniation after stroke, and it is now more widely used for the same indications after severe TBI.[153] Decompressive craniectomy is indicated for selected anatomic patterns of TBI, such as when CPP cannot be

Critical Pathway for Treatment of Cerebral Perfusion Pressure in Patients with Severe Traumatic Brain Injury

General parameters for ALL patients

- Maintain systolic BP > 90 mm Hg with transducer leveled at the phlebostatic axis
- Keep Hct 30%-33%
- Maintain serum sodium at 140-145 unless patient has ICP elevations
- Encourage use of P_{ETCO_2} monitoring
- Initiate DVT prophylaxis
- Initiate nutrition as soon as medically appropriate with full caloric replacement by 7 days after injury
- Initiate anticonvulsants for the first 7 days after injury; phenytoin is the agent of choice

Initial interventions

- Establish airway, breathing, and circulaton
- Ventilate to maintain $Paco_2$ to 35 mm Hg
- Provide supplemental O_2 to keep Pao_2 >70 mm Hg or Spo_2 >94%
- Maintain normothermia
- Maintain head of bed to optimize CPP and minimize ICP
- Ensure good head and neck alignment
- Reduce unnecessary noxious stimuli
- See sedation algorithm

Insert camino or IVC ICP monitor: Pbro2 monitor

Maintain CPP > 60 mm Hg

* When patient has an unexplained ICP elevation or there is a change in mental status:
– Check the ABG to ensure Pao_2 and $Paco_2$ are in the desired range
– Ensure that the patient's position is not limiting ventilation or causing increased ICP

Intracranial hypertension? ≥20 mm Hg or*

No

Yes

*>25 mm Hg after decompressive craniectomy

- Ensure all initial interventions are in place*
- Administer sedation (see algorithm)
- Consider repeating a brain CT scan

Carefully remove treatment for ICP

Intracranial hypertension? ≥20 mm Hg or*

No

Yes

- Ensure all initial interventions are in place*
- Insert IVC and drain CSF
- Consider repeating a brain CT scan

Intracranial hypertension? ≥20 mm Hg or*

No

Figure 72-10 Clinical pathway for the management of severe traumatic brain injury. The goal of therapy is to maintain cerebral perfusion pressure above 60 mm Hg by support of the circulation and control of intracranial pressure. Progressively more intensive therapies are added until this goal is achieved. ABG, arterial blood gases; BP, blood pressure; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CT, computed tomography; DVT, deep venous thrombosis; Hct, hematocrit; ICP, intracranial pressure; IVC, intraventricular catheter.

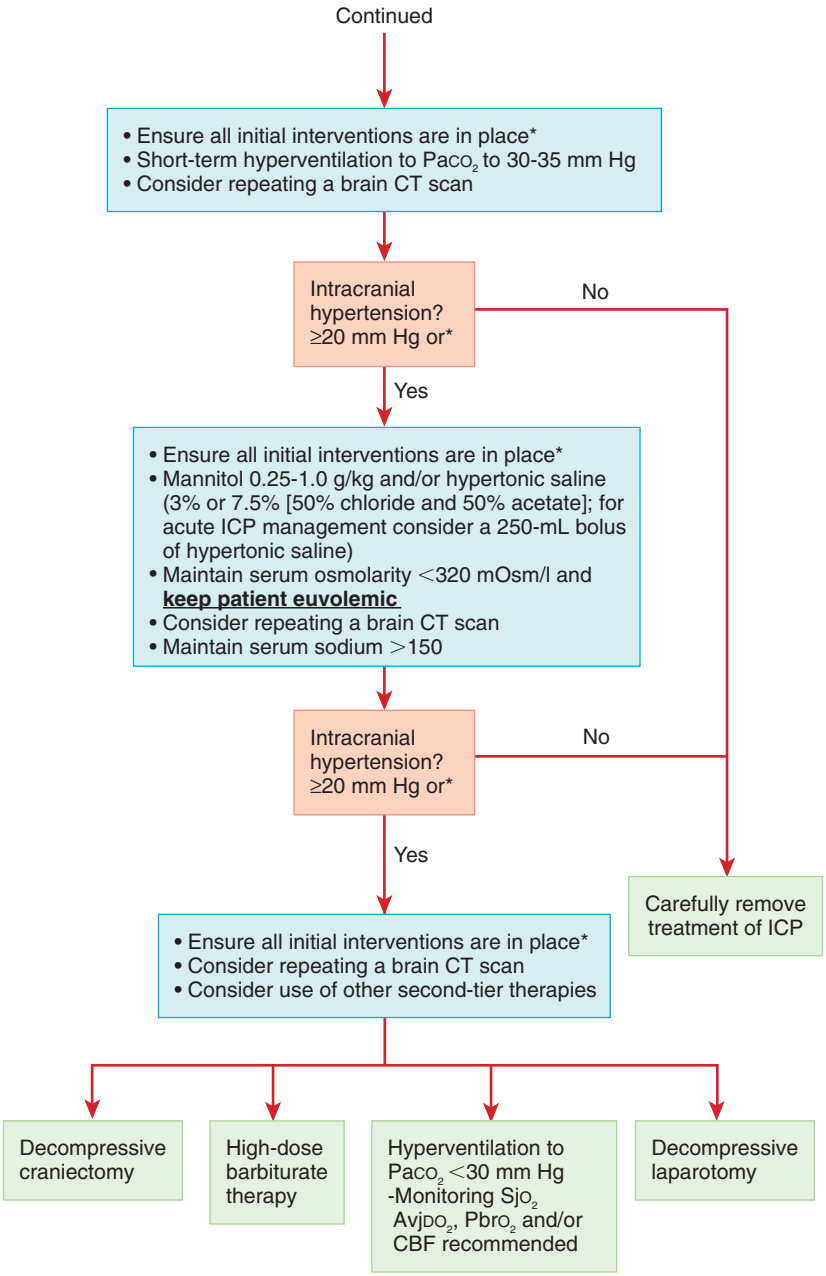

Figure 72-10, cont'd

maintained despite vigorous application of the previously described therapies, including barbiturate coma. Recent evidence suggests that relieving ICP by removal of a piece of cranium and use of a dural patch may improve mortality and morbidity in patients who might not otherwise survive.[154] Decompressive laparotomy may be also be indicated in patients with severe TBI if coexisting injuries or vigorous volume infusion have increased intra-abdominal compartment pressure to greater than 20 mm Hg. Elevated abdominal pressure worsens pulmonary mechanics, thus necessitating higher MAP to maintain arterial oxygen saturation. This increase in ventilating pressure will increase intrathoracic pressure and impair venous drainage from the head and consequently decrease CPP. The use of decompressive celiotomy as a therapy to reduce ICP was recently described.[155] More recently, a new concept of "multiple compartment syndrome" in patients with severe TBI has been proposed.[156] Fluid therapy or acute lung injury (or both) may increase intra-abdominal pressure and intrathoracic pressure, thereby increasing ICP. Further fluid

administration to support cerebral perfusion or increasing ventilatory support to treat acute lung injury further exacerbates this problem. This can create a cycle that ultimately produces multiple compartment syndrome and necessitates opening of the abdomen, even in the absence of primary abdominal trauma. Isolated TBI can thus become a multisystem disease.

Like hyperventilation therapy, there has been a progressive change in the use of hypothermia to treat severe TBI. Early studies demonstrated that moderate, systemic hypothermia reduces both the rate of cerebral edema and mortality after cortical injury in laboratory animals.[157,158] Small, clinical series in humans also suggested improved outcome in patients suffering TBI when hypothermia was maintained for 24 or 48 hours.[159,160] However, a recently published multicenter, randomized trial of hypothermia (33°C) versus normothermia demonstrated no improvement in outcome in a population of patients with severe TBI.[161] Of note, patients who were hypothermic on admission and then were randomized to the normothermia group had a worse outcome than those who were left hypothermic, thus leading to the recommendation that patients with severe TBI who are hypothermic on admission not undergo active rewarming.

Management of Intracranial Pressure in the Operating Room

Although most interventions for management of a patient with severe TBI will occur in the ICU, urgent cranial or noncranial surgery is frequently indicated.

All of the previously described therapies should be continued throughout the perioperative period, including positional therapy (when possible), aggressive hemodynamic monitoring and resuscitation, administration of osmotic agents (with attention to maintaining euvolemia), and deep levels of analgesia and sedation. Appropriate anesthetic choices include narcotics and low concentrations of volatile anesthetics.

Spinal Cord Injury

SCI after trauma affects some 10,000 Americans each year.[139] Blunt trauma accounts for the majority of SCI: 40% from motor vehicle collisions, 20% from falls, and the remainder as a result of penetrating trauma (14%).[162] Complete neurologic deficit occurs in approximately 3500 patients a year and partial deficit in an additional 4500.[163] The health care cost of SCI is staggering: $5.6 billion in direct and indirect costs to the government each year for medical care, rehabilitation, and lost wages.[164] Cervical spine injuries occur in 1.5% to 3% of all major trauma.

Most spinal injuries are found in the lower cervical spine, just above the thorax, or in the upper lumbar region, just below the thorax. Blunt SCI is most common in the regions of the cord that are most flexible, especially at the junctions between flexible and inflexible segments. SCI at midthoracic levels is less common because of the rotational stabilization provided by the rib cage and intercostal musculature.

SCI is commonly accompanied by radiographically visible injury to the bony spine and concomitant disruption of the muscles, ligaments, and soft tissues that support it. However, clinically significant injury to the cervical spinal cord can occur in the absence of visible skeletal injury. This entity, known as SCIWORA (spinal cord injury without radiographic abnormality) is more common in children and is presumably the result of temporary hyperdistraction or torsion of the neck insufficient to disrupt the bony skeleton.[165]

Primary injury to the spinal cord sustained at the moment of trauma may be exacerbated by a number of secondary factors (Fig. 72-11). SCI includes sensory deficits, motor deficits, or both. Incomplete deficits may be worse on one side than the other and may improve rapidly in the first minutes after injury. Complete deficits—representing total disruption of the spinal cord at one level—are much more ominous, with generally little improvement seen over time. Cervical spine injuries causing quadriplegia are accompanied by significant hypotension because of inappropriate vasodilatation and loss of cardiac inotropy (neurogenic shock). Functioning of the lower cord will gradually return, along with restoration of normal vascular tone. Diagnosing cervical spine instability can be difficult. The Eastern Association for the Surgery of Trauma has published guidelines regarding which patients require cervical spine radiographs, which views and studies should be obtained, and how to determine the absence of significant ligamentous injury in an unconscious patient.[166]

Evaluation of the ABCs (airway, breathing, circulation) is often followed by a glucocorticoid steroid bolus in patients with blunt SCI and complete or partial deficit. A bolus dose of 30 mg/kg of methylprednisolone, followed by a maintenance infusion of 5.4 mg/kg/hr, is given if the patient is less than 8 hours removed from the time of injury. This infusion is continued for 24 hours if started within 3 hours of injury and for 48 hours if started 3 to 8 hours after injury. High-dose glucocorticoid therapy has resulted in a small, but statistically significant improvement in neurologic level after SCI in two large multicenter trials: the National Acute Spinal Cord Injury Study (NASCIS) II and III.[167,168] Methylprednisolone has been shown to improve spinal cord blood flow, reduce intracellular calcium influx, and mitigate the formation of free radicals in ischemic spinal cord tissue. The NASCIS results have been challenged for several reasons.[169-171] The positive benefits seen with high-dose steroid administration were driven by results in a few subpopulations and were not present in a majority of patients. The improvement in spinal level seen after steroid administration has not been shown to lead to increased survival or improved quality of life, and the results have not been reproducible in other studies of acute SCI.

Patients with bony injury to the spinal cord will require surgery based on their neurologic symptoms and the anatomic stability of the injury. Magnetic resonance imaging is indicated to assess ligamentous and soft tissue injury in any patient with bony fracture or neurologic deficit. Surgery is more commonly required for cervical lesions, whereas supportive bracing or extension casting of the torso may be used for thoracic and lumbar fractures.

Early intubation is almost universally required for patients with cervical spine fracture and quadriplegia. Ventilatory support is absolutely required for patients with a deficit above C4 because they will lack diaphragmatic function. Patients with levels from C6 to C7 may still need support because of lost chest wall innervation, paradoxical respiratory motion, and an inability to clear secretions. Early intubation is recommended and can often be accomplished by awake fiberoptic bronchoscopy or use of the GlideScope before hypoxia renders the patient anxious and uncooperative.[172,173] Spontaneous ventilation and extubation are possible after surgical stabilization and resolution of neurogenic shock, although pneumonia is a common and recurrent

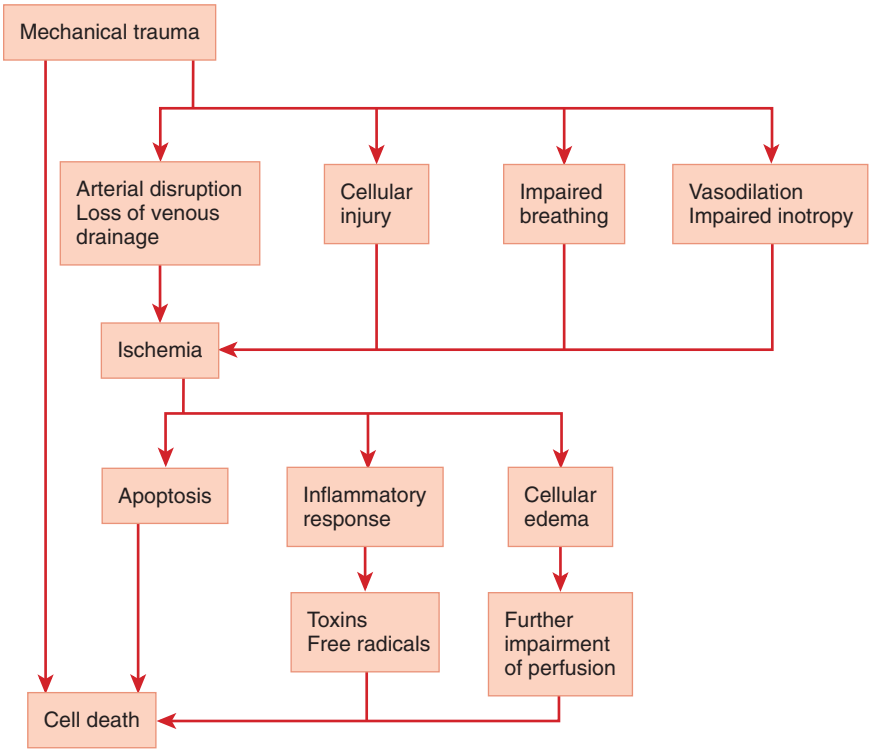

Figure 72-11 Mechanisms of spinal cord injury. Mechanical trauma to the spinal cord is exacerbated by systemic hypoperfusion or hypoxia. *(Reprinted with permission from Dutton RP: Spinal cord injury. Int Anesthesiol Clin 40:109, 2002.)*

complication that frequently necessitates tracheostomy to facilitate pulmonary toilet.

Intraoperative Management of Spinal Cord Injury

A patient about to undergo surgical reduction and fixation of a spinal column fracture presents a number of challenges for the anesthesiologist. First and foremost is the need for intubation of the trachea in a patient with a known injury to the cervical spine. Direct laryngoscopy with in-line stabilization is appropriate in the emergency setting and in unconscious, combative, or hypoxemic patients when the status of the spine is not known.[174] In the OR, an awake, alert, and cooperative patient can be intubated by a number of different methods known to produce less displacement of the cervical spine, presumably with less risk of worsening an unstable SCI. A common technique in current clinical practice is awake fiberoptic intubation. Although the nasal route is associated with an easier path to intubation in most patients, it can lead to an increased risk for sinusitis in the ICU if the patient is not extubated at the end of the procedure. Oral intubation is likely to be more challenging technically but will be of greater value if the patient remains mechanically ventilated. Blind nasal intubation, transillumination with a lighted stylet, and use of an intubating LMA, GlideScope or Bullard laryngoscope, and any of a variety of other instrument systems for indirect laryngoscopy are acceptable. The clinician is advised to use the equipment and techniques that are most familiar. The important concept is to successfully achieve tracheal intubation while minimizing motion of the cervical spine and preserving the ability to assess neurologic function after positioning.

Orthopedic and Soft Tissue Trauma

Musculoskeletal injuries are the most frequent indication for operative management in most trauma centers (see Chapter 70). Because many procedures can be appropriately managed under regional anesthesia, familiarity with these techniques is essential. The length of many procedures, particularly in patients with multiple extremity injuries, necessitates attention to body positioning, maintenance of normothermia, fluid balance, and preservation of peripheral blood flow.

For the last 15 years the emphasis in trauma management of a multiply injured patient has included early stabilization of long-bone, spine, pelvic, and acetabular fractures. Failure to do so results in increased morbidity, pulmonary complications, and length of hospital stay.[175,176] In one study, only 2% of patients with femoral shaft fractures stabilized within the first 24 hours of injury had pulmonary complications, as compared with 38% of patients in whom fracture stabilization was delayed for more than 48 hours.[176]

Specific Conditions

Dislocation of the hip is common after high-energy trauma and is frequently accompanied by fracture of the acetabulum. Whereas the fracture itself can be safely managed on a delayed basis, the

dislocation is a medical emergency that must be promptly addressed if the patient is to have a good functional outcome. Failure to promptly diagnose and reduce a dislocated hip joint is a significant risk factor for avascular necrosis of the femoral head. Reduction typically requires a very deep level of sedation, which may be facilitated by nondepolarizing neuromuscular blockade. For this reason the anesthesiologist is commonly involved.[177] Although it is possible to reduce a dislocated hip in a spontaneously breathing patient sedated with fentanyl, midazolam, ketamine, propofol, or a combination of two or more agents, an acutely injured patient is at high risk for aspiration. Any patient who will be undergoing surgery in the near future (as for an open long-bone fracture or exploratory laparotomy) should be intubated at the time of reduction and maintained with appropriate sedation and analgesia until reaching the OR. Other patients who may require intubation even for uncomplicated reductions include those who are inebriated or uncooperative, hemodynamically unstable, or suffering from pulmonary dysfunction.

Unlike acetabular fractures, fracture of the pelvic ring requires immediate recognition and management by the trauma team. Hemorrhage, even exsanguination, is common after a major pelvic ring fracture and is a leading contributor to early death after motor vehicle collisions. Bleeding occurs from multiply disrupted venous beds in the posterior pelvic bowl; if the pelvis as a whole is unstable, there is no anatomic barrier to continued expansion of this retroperitoneal bleeding. Surgical exploration by way of the peritoneum is usually unrewarding because the bleeding vessels are not easily accessed.[178] Therapy consists of supportive volume resuscitation, external fixation of the unstable pelvis, and angiography. Intubation is usually undertaken on an emergency basis in a hypotensive patient, and the anesthesiologist may remain with the patient throughout the initial hours of stabilization to manage sedation, analgesia, transport, and fluid resuscitation. In the absence of an orthopedic specialist, temporary stabilization and tamponade of some pelvic fractures can be accomplished with use of a specially made pelvic binder, the pelvic portion of military antishock trousers, or a bed sheet knotted tightly around the bony pelvis.[179]

Open fractures should be pulse-lavaged and débrided as soon as possible after injury to minimize the risk of infectious complications. If ongoing resuscitation or unstable TBI precludes the patient from early management in the OR, this procedure should be performed at the bedside.

The advantages and disadvantages of regional and general anesthesia are summarized in Boxes 72-8 and 72-9. For many orthopedic trauma cases a combined approach will provide an optimal solution by incorporating the hemodynamic and analgesic benefits of a regional anesthetic with the flexibility and increased anxiolysis of a general anesthetic.

One prevalent concern in the management of an orthopedic trauma patient is the concomitant use of regional anesthesia/analgesia and prophylaxis for venous thromboembolism, as discussed in Chapter 70.

Intraoperative transesophageal echocardiography (TEE) has shown that most patients undergoing long-bone fracture manipulation experience microembolism of fat and marrow.[180] Most patients suffer no discernible clinical impact from this phenomenon, but some will experience a significant acute inflammatory response. After long-bone fractures, some lung dysfunction occurs in almost all patients ranging from minor laboratory abnormalities to full-blown fat embolism syndrome (FES). A lack of universally accepted diagnostic criteria combined with concomitant pulmonary and cardiovascular dysfunction accounts for the varying incidence reported in the literature. Most studies suggest that clinically significant FES occurs in 3% to 10% of patients, although the presence of multiple long-bone fractures is associated with a higher incidence. Patients with coexisting lung injury are at additional risk for FES. Signs include hypoxia, tachycardia, mental status changes, and a petechial rash on the upper portions of the body, including the axillae, upper arms and shoulders, chest, neck, and conjunctivae. FES should be considered whenever the alveolar-arterial oxygen gradient deteriorates in conjunction with decreased pulmonary compliance and CNS deterioration. Under general anesthesia, the CNS changes will not be apparent but may be manifested as failure to awaken after

Box 72-8 Advantages and Disadvantages of Regional Anesthesia for Trauma Patients

Advantages
- Allows continued assessment of mental status
- Increased vascular flow
- Avoidance of airway instrumentation
- Improved postoperative mental status
- Decreased blood loss
- Decreased incidence of deep venous thrombosis
- Improved postoperative analgesia
- Better pulmonary toilet
- Earlier mobilization

Disadvantages
- Peripheral nerve function difficult to assess
- Patient refusal common
- Requirement for sedation
- Hemodynamic instability with placement
- Longer time to achieve anesthesia
- Not suitable for multiple body regions
- May wear off before procedure(s) conclude

Box 72-9 Advantages and Disadvantages of General Anesthesia for Trauma Patients

Advantages
- Speed of onset
- Duration—can be maintained as long as needed
- Allows multiple procedures for multiple injuries
- Greater patient acceptance
- Allows positive-pressure ventilation

Disadvantages
- Impairment of global neurologic examination
- Requirement for airway instrumentation
- Hemodynamic management more complex
- Increased potential for barotrauma

Box 72-10 Risk Factors for The Development of Compartment Syndrome

Orthopedic
Fractures and operative repair

Vascular
Reperfusion injury
Hemorrhage with hematoma formation
Ischemia from arterial and venous injuries

Soft Tissue
Crush injury
Burns
Prolonged compression in an immobile state

Iatrogenic
Casts and circular dressings
Use of pneumatic antishock garments
Intraosseous fluid replacement in an infant/child
Pulsatile lavage with extravasation
Extravasation from venous or arterial puncture sites

Miscellaneous
Snakebite
Acute exertion

surgery. If central hemodynamic monitoring is available, pulmonary artery pressure is elevated, often accompanied by decreases in the cardiac index. Diagnosis in the OR is largely based on the clinical findings after ruling out other causes of hypoxemia. Fat globules in urine are nondiagnostic, but lung infiltrates seen on chest radiography confirm the presence of lung injury and the need for appropriate ventilatory management with oxygen, higher PEEP, and possible longer-term mechanical ventilatory support.[181,182] Treatment includes early recognition, administration of oxygen, and judicious fluid management. A change in the orthopedic procedure may be indicated, such as converting intramedullary nailing of the femur to external fixation.

Acute compartment syndrome of the extremities is defined as a "condition in which increased pressure within a limited space compromises the circulation and function of the tissues within that space."[183] With orthopedic trauma the most common cause of compartment syndrome is edema secondary to muscle injury and associated hematoma formation. Though most commonly associated with traumatic injuries, compartment syndrome can also occur as a result of a number of causes associated with trauma, including reperfusion injury, burns, drug overdose, and prolonged limb compression (Box 72-10). The most common fractures associated with the development of compartment syndrome are those of the tibial shaft (40%) and forearm (18%).[184,185] A further 23% are caused by soft tissue injuries without fracture.[185]

The classic hallmarks of compartment syndrome have been described as pulselessness, pallor, paralysis, paresthesia, and pain—the "five P's." The presence of these findings, however, is associated with an established syndrome of ischemic injury, and fasciotomy at this stage is associated with a poor outcome. The early presence of pain out of proportion to the injury can be the first clinical indication of compartment syndrome and may easily be confused with pain associated with the injury or operative repair. In addition, pain with passive stretching or paresthesia may be the initial complaint. An altered level of consciousness because of associated conditions may easily mask this finding.

Fasciotomy is usually indicated when compartment pressure approaches 20 to 30 mm Hg below diastolic pressure in any patient with a worsening clinical condition, a documented rising tissue pressure, major soft tissue injury, or a history of 4 to 6 hours of total ischemia of an extremity. Prophylactic fasciotomy may be indicated in patients with warm ischemic time in excess of 4 to 6 hours, ligation of the major veins in the popliteal region or distal part of the thigh, and crush injuries.

Crush syndrome is the general manifestation of crush injury caused by continuous prolonged pressure on one or more extremities[186] and is commonly found in patients who have been trapped in one position for an extended period. Muscle injury secondary to ischemia causes myoglobinuria, which can lead to acute renal failure and subsequent profound electrolyte disturbances. The most critical treatment consists of crystalloid fluid resuscitation; a total-body fluid deficit of 15 L may occur in severe rhabdomyolysis.[187] Osmotic diuresis with mannitol and alkalinization of urine with sodium bicarbonate to prevent precipitation of myoglobin in the renal tubules are controversial.[188,189] The preferred therapy for renal failure secondary to rhabdomyolysis at the Shock Trauma Center is continuous renal replacement therapy and hemofiltration.[190] A majority of these patients eventually have full recovery of native renal function.[191]

Soft Tissue Trauma

Assessment of soft tissue injury is critical in the management of a trauma patient. Muscular coverage is necessary for the viability of any orthopedic repair, but it may be jeopardized by avulsion at the time of injury, ischemia from elevated compartment pressure, and ongoing bacterial infection in open wounds. Acute surgical management of soft tissue injury is straightforward: all dead or devitalized tissue must be débrided away and the wound thoroughly irrigated to reduce the load of bacterial contaminants. When muscle or fascia involvement is significant, serial débridement at 1- to 3-day intervals is necessary to establish a margin of completely viable tissue. Vacuum dressings for large soft tissue wounds are gaining in popularity because continuous negative pressure over the wound surface removes contaminants and encourages blood flow.[192] When serial débridement establishes viable tissue at all margins of the wound, arrangements for definitive closure can be made. Closure may be as simple as a split-thickness skin graft or as complex as free tissue transfer of muscle and fascia from an uninjured portion of the body, with attendant arterial and venous anastomoses.

Superficial vacuum dressings can be changed at the bedside under light sedation, but patients with deep wound dressings will require general anesthesia. The need for repeated surgeries is an important consideration for the anesthetic technique. When otherwise appropriate, the use of a continuous epidural catheter for both analgesia and operative anesthesia can greatly facilitate the care of these complex patients. Anesthesia for free tissue transfer surgery requires meticulous attention to detail because these operations can be quite protracted. Every effort should be made

to facilitate perfusion of the grafted vessels, including keeping the patient warm, euvolemic, and comfortable and maintaining the hematocrit in the rheologically favorable range of 25% to 30%. The use of epidural anesthesia and analgesia is controversial, with some surgeons favoring it for its vasodilatory effects and others being concerned that it will induce a "steal" phenomenon that will actually limit flow in the denervated free tissue.[193]

Amputation is occasionally necessary for massive crush injury, vascular injury, or progressive soft tissue infection. Anesthetic management is notable for the strong emotional overlay that accompanies this operation. Although regional anesthesia is physiologically appropriate and has been shown to limit the subsequent development of phantom limb pain, very few patients will be accepting. General anesthesia is usually required, although combining it with epidural analgesia may confer the benefits of both techniques.

Other Traumatic Injuries

Head and Neck Surgery

With the exception of emergency exploration of penetrating trauma to zone II of the neck (from the clavicles up to the angle of the mandible), most surgical repair of head and neck trauma will occur in the subacute phase, after complete resuscitation and secondary diagnostic studies (see Chapter 75). Anesthetic management of these patients is not substantially different from that for similar elective procedures, although coexisting injuries may influence patient positioning and ventilator settings. Surgery on the mandible and maxilla will be facilitated by nasotracheal intubation, but the anesthesiologist should not jeopardize a secure airway by attempting to switch from an oral to a nasal tube in a patient in whom visualization of the larynx might be difficult because of traumatic swelling or body habitus. It is safer in these cases for the surgeon to either work around an oral tube secured behind the second molar (to allow dental occlusion) or to place a tracheostomy if the need for intubation and mechanical ventilation is likely to be protracted. Surgery on the zygoma and the nasal, orbital, and ethmoid bones will be possible with an oral endotracheal tube. Securing the endotracheal tube to the molar with a fine-gauge wire will help stabilize it through the operation. All of these surgeries will lead to significant soft tissue swelling in the immediate postoperative period, often necessitating several days of continued intubation and sedation until sufficient venous drainage has occurred to allow safe extubation. Though not by itself definitive, the presence of an air leak when the endotracheal tube cuff is deflated is suggestive that the airway will remain patent once the tube is removed.

Chest Injuries—Pulmonary

Injuries to the lung parenchyma that produce pneumothorax can be managed by tube thoracostomy to relieve tension, drain accumulated blood, and apply suction to the pleural space until the air leak spontaneously resolves (see Chapter 59). Bleeding from the low-pressure pulmonary circulation is usually self-limited. Thoracostomy is uncommon but becomes necessary when there is evidence of mediastinal injury, chest tube output exceeds 1500 mL in the first hours after injury, tracheal or bronchial injury and massive air leak are apparent, or the patient is hemodynamically unstable with evident thoracic pathology.[15] Blood collected from the pleural space is generally free of clotting factors and can be directly reinfused with any of several commercial systems.[194] Hemorrhage necessitating surgery may be from injured intracostal or internal mammary arteries, as well as from the lung parenchyma. Staple resection of injured lung or even anatomic lobectomy is not uncommon, particularly after penetrating trauma.

Although double-lumen endotracheal intubation is desirable during urgent thoracotomy, this should not be the initial approach. RSI with a large-caliber (at least 8.0 mm in internal diameter) conventional endotracheal tube will allow diagnostic bronchoscopy and protect the patient from aspiration until passage of a gastric tube can reduce the stomach contents. The change to a double-lumen tube can then be made under controlled conditions in the presence of adequate oxygenation, anesthesia, and muscle relaxation. Tolerance of single-lung ventilation is variable in the trauma population and depends in large part on the absence of significant pathology in the ventilated lung. Many patients with blunt thoracic injury have bilateral pulmonary contusions and will require increased Fio_2 and high levels of PEEP to maintain adequate oxygenation, even when both lungs are ventilated.

Although chest trauma requiring pneumonectomy has historically resulted in mortality approaching 100%, a recent multicenter retrospective review reported on a series of survivors of this surgery.[195] Intraoperative deaths are the result of uncontrollable hemorrhage, acute right ventricular failure, and air embolism. Patients who survive the initial procedure are at risk for early postoperative morbidity and mortality. Fluid management may be complicated by the need to weigh ongoing resuscitation against the treatment of right ventricular failure. Blunt thoracic trauma requiring pneumonectomy is often associated with abdominal and pelvic trauma. Volume replacement must be judicious, and the use of a pulmonary artery catheter (placed with care in a postpneumonectomy patient) or TEE may be beneficial. Echocardiography will also play an important role in assessing right ventricular function and pulmonary hypertension. Treatment of right ventricular failure after traumatic pneumonectomy is difficult.[196] During hypovolemic shock there is a disproportionate increase in pulmonary vascular resistance with respect to systemic vascular resistance,[197] as well as high mortality with combined hemorrhagic shock and pneumonectomy.[198] With severe right heart dysfunction it is desirable to maintain a higher preload than normal. Several therapeutic approaches have been used to treat right ventricular failure, including close monitoring of pulmonary artery pressure, the use of diuretics for volume overload, and administration of pulmonary vasodilators. Because this injury is rare and the number of patients reported in the literature is small, it is impossible to definitively state which treatment option is superior. A recent case report describes the use of nitric oxide to successfully treat pulmonary hypertension after posttraumatic pneumonectomy.[199] Extracorporeal support has also been used to sustain patients through the perioperative period, although the technical challenges are substantial and successful weaning may require days to weeks on bypass. Early initiation has been beneficial in our experience, with a recent survival rate of approximately 60%.

Tracheal-bronchial injury can result from either blunt force or penetrating trauma. Penetrating injuries are usually more promptly diagnosed and treated. *Blunt* trauma most commonly results in an injury to the tracheobronchial tree within 2.5 cm of the carina and may initially be unrecognized. The presence of subcutaneous emphysema, pneumomediastinum, pneumopericardium, or pneumoperitoneum, without apparent cause, should alert the practitioner to possible tracheobronchial injury.[200] Despite bronchoscopy and helical CT scanning, a small injury may never be delineated. If the resultant injury is an incomplete tear, it may heal with stenosis, subsequent atelectasis, pneumonia, pulmonary destruction, and sepsis. When surgery is required for a delayed, incomplete tracheobronchial injury, pulmonary resection may be required if there is significant tissue destruction, whereas complete transection may be amenable to reconstruction with preservation of pulmonary tissue. The level of injury dictates the surgical approach. Cervical injuries are approached through a transverse neck incision, left bronchial injuries via a left thoracotomy, and tracheal or right main bronchial injuries via a right thoracotomy. In the cervical region it is sometimes possible to access a longitudinal tear of the posterior membranous trachea by opening the anterior trachea and operating around the endotracheal tube.

Chest Injuries—Traumatic Aortic Injury

Traumatic aortic injury (TAI) must be ruled out in any patient suffering a high-energy injury, such as from a motor vehicle accident or fall from a height. The incidence of TAI has decreased in recent years because of the increased presence of airbags in motor vehicles; a majority of cases in the past decade have been caused by side-impact collisions.[201] Aortic injury occurs most commonly just distal to the left subclavian artery and is the result of sheer forces between the mobile heart and aortic arch and the immobile descending thoracic aorta. TAI is manifested as a continuum of injury from a small intimal flap to free transection contained by the surrounding mediastinum and pleura. The diagnosis is made by screening chest radiography, followed by definitive angiography, CT, or TEE. Surgical or endovascular repair is indicated for most patients with TAI because of the high risk of rupture in the hours and days after injury.[202] Various techniques have been described for this highly morbid surgery, with the best results attributed to partial bypass techniques using inflow from the left atrium, a centrifugal pump, and outflow to the descending aorta.[203] There have been reports of selective nonoperative management of high-risk patients with TAI in the recent literature.[204,205] Treatment is similar to that in patients with uncomplicated type B aortic dissection and consists of β-blockade to minimize the cardiac rate-pressure product. Endovascular repair is becoming more common at centers with experience in this technique and is likely to become the standard practice as stent-grafting hardware continues to improve.

Chest Injuries—Rib Fractures

Rib fractures are the most common injury resulting from blunt chest trauma. The fracture itself generally requires no specific treatment and will heal spontaneously over a period of several weeks. Therapy is directed at minimizing pulmonary complications secondary to these fractures, such as pain, splinting, atelectasis, hypoxemia, and pneumonia. Of particular concern are rib fractures in the elderly (age >55). Elderly patients with rib fractures have twice the mortality and thoracic morbidity of younger patients with similar injuries. Epidural anesthesia should be used liberally in patients with severe pain, the elderly, and patients with preexisting compromised pulmonary function. There are data to support a 6% decrease in morbidity and mortality in the elderly when epidural anesthesia is used.[206] Epidural analgesia may minimize or avoid complications of splinting and pain such as hypoxemia, hypoventilation, the need for tracheal intubation, and the possibility of pneumonia. Endotracheal intubation is reserved for patients who are unable to oxygenate or ventilate or who require protection of the airway.

Fracture of multiple neighboring ribs will result in the flail chest syndrome, characterized by paradoxical chest wall motion during spontaneous ventilation. Not all patients with a flail chest require positive-pressure ventilation, and endotracheal intubation should be reserved for those who meet the usual criteria. Patients who are not initially intubated should be observed closely in the ICU for signs of worsening respiratory function. There are increasing reports of the use of noninvasive positive-pressure ventilation (NIPPV) for lung injury secondary to trauma.[207] For these patients who subsequently require intubation for a surgical procedure, the anesthesiologist will need to determine the safety of extubation postoperatively. NIPPV is associated with fewer cases of pneumonia, which may lead to fewer tracheostomies and decreased ICU length of stay. A successful technique has been early extubation to a mask delivering continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP).[208] Concomitant pulmonary injury, especially lung contusion, is commonly associated with flail chest. Pulmonary contusion will cause shunting, which will lead to hypoxemia. This syndrome may progress rapidly in the hours and days after injury. An initially clear chest radiograph does not exclude the possibility of a pulmonary contusion, and again, close observation is warranted if signs of significant chest wall trauma are present. As with all patients after traumatic injury, a high degree of suspicion along with a continuous search for missed injuries is warranted. There is no specific therapy for a pulmonary contusion, and therapy is directed at the associated injuries or resultant hypoxemia. Early and aggressive implementation of a lung protective strategy is crucial in the treatment of patients with significant pulmonary contusion to minimize progression to ARDS or concomitant ventilator-associated lung injury.

Chest Injuries—Cardiac Injury

Blunt cardiac injury is a rare and poorly understood phenomenon that must be considered in any patient who has sustained a frontal impact to the chest. Bruising or edema of the myocardium is functionally indistinguishable from myocardial ischemia and may be causally related in that the pathophysiology of cardiac contusion may involve forcible dislodgement of unstable atherosclerotic plaque. If the patient is hemodynamically stable and the ECG does not demonstrate conduction disturbances or tachyarrhythmias, blunt cardiac injury can be safely excluded.[209] If either a new tachyarrhythmia or conduction disturbance subsequently develops or the patient has unexplained hypotension, other causes (hypovolemia, renal failure) should be ruled out first. If the

workup is negative, transthoracic echocardiography (TTE) should be performed. Right ventricular dysfunction resulting in hypotension may be overlooked while more common causes of hypotension in the trauma patient are being evaluated. TEE is superior to TTE in obese patients or those with injuries to the chest wall that make it difficult to obtain adequate acoustic windows, but it will generally require intubation and deep sedation to perform. Once diagnosed, blunt cardiac injury should be managed as ischemic cardiac injury, with completion of resuscitation and then careful control of fluid volumes, administration of coronary vasodilators, and monitoring and symptomatic treatment of rhythm disturbances. Anticoagulation with aspirin or heparin may be helpful but should be approached on a case-by-case basis as determined by the patient's other injuries. Cardiology consultation is appropriate if there is a possibility that the patient would benefit from coronary angiography followed by angioplasty or stenting of stenotic vessels.

Patients with penetrating cardiac trauma and blunt trauma causing rupture of one or more chambers (usually the atria) will infrequently be seen by the trauma center because of high prehospital mortality. Those who do not die immediately of free exsanguination into the thoracic cavity will have pericardial tamponade and can be extremely unstable in the first minutes after admission. This condition is diagnosed by clinical suspicion, by FAST, and by direct inspection during ED thoracotomy. Relief of the tamponade and clamp or suture control of the cardiac injury may allow restoration of spontaneous circulation and necessitate urgent transition to the OR for definitive hemostasis and chest closure. Cardiopulmonary bypass may be required for support during repair of cardiac injuries.

Abdominal Injury

The need for exploratory laparotomy, once the mainstay of the trauma surgeon, has declined significantly in recent years. FAST and high-resolution CT have reduced the incidence of negative abdominal explorations, whereas angiographic embolization of hemorrhaging vessels in the liver and spleen has reduced the need for open procedures. Urgent celiotomy, when it does occur, will typically follow the principles of damage control.[104] The abdomen is opened and packed tightly in all four quadrants. Systematic exploration is undertaken in each quadrant in turn, with time taken only for control of hemorrhage and rapid staple closure of open gastrointestinal injuries. The abdomen is packed open at the conclusion of the procedure, a sterile drape is used to cover exposed viscera, and the patient is moved to the ICU to complete resuscitation. Definitive treatment of nonlethal injuries and restoration of bowel continuity are deferred until a second operation 24 to 48 hours later.

Anesthetic management of emergency celiotomy should follow the principles of early resuscitation outlined earlier. Adequate intravenous access is required, as well as continuous arterial pressure monitoring. Cell salvage devices can be used to reduce the patient's exposure to banked blood, although reinfusion is generally deferred if there has been significant contamination by bowel contents. A rapid infusion system is advantageous for preservation of intravascular volume and normothermia during periods of heavy bleeding. Subsequent abdominal surgeries will be needed in hemodynamically stable patients and should not present unusual anesthetic challenges. Subsequent reconstructive procedures can become technically difficult as scarring and adhesions develop; the anesthesiologist should be prepared for a long anesthetic procedure with the potential for significant hemodynamic compromise.

Selected Patient Populations

Trauma and Pregnancy

Trauma to pregnant patients is associated with a high risk for spontaneous abortion, preterm labor, or premature delivery, depending on the location and magnitude of the mother's injury (see Chapter 69). Early consultation with an obstetrician is desirable for any pregnant trauma patient, both for immediate management and for long-term follow-up. The best treatment of the developing fetus consists of rapid and complete resuscitation of the mother. Trauma patients in the first trimester of gestation may not realize that they are pregnant; for this reason human chorionic gonadotropin testing is part of the initial laboratory studies for any injured woman of childbearing age. Serious trauma occurring during the period of fetal organogenesis may induce birth defects or miscarriage because of hemorrhagic shock with uterine ischemia, pelvic irradiation, or the effects of medications. Indicated radiologic tests should not be deferred, but shielding of the pelvis should be provided whenever possible. Patients who do not spontaneously miscarry should be advised of the potential risks related to trauma and anesthesia and be referred for counseling if desired. Dilatation plus curettage of the uterus is advisable after miscarriage to avoid toxicity arising from retained products of conception.[210]

Trauma occurring in the second or third trimester of pregnancy necessitates early ultrasonographic examination to determine fetal age, size, and viability. Monitoring of the fetal heart rate is indicated if the pregnancy is sufficiently advanced that the fetus would be viable if delivered. Preterm labor is very common in this population and should be treated with β-agonist agents or magnesium at the direction of the obstetrician; delivery should be delayed as long as the fetus is not an unacceptable metabolic stress on the mother. Delivery by cesarean section is indicated if the mother is in extremis, if the uterus itself is hemorrhaging, or if the gravid uterus is impairing surgical control of abdominal or pelvic hemorrhage.[211] Placental abruption can occur in response to substance abuse or abdominal trauma and can precipitate life-threatening uterine hemorrhage. Emergency cesarean section is indicated. The Kleihauer-Betke blood test can be used to determine if fetal blood has leaked into the maternal circulation[211]; if positive, administration of anti-Rh_0 immune globulin is recommended for any Rh-negative mother carrying an Rh-positive fetus. By the third trimester the uterus is sufficiently enlarged to compress the inferior vena cava when the patient is positioned supine, thereby impairing venous return to the heart and contributing to hypotension. Left lateral uterine displacement is indicated to treat this problem. If the patient is immobilized on a long spine board because of concern for a thoracic or lumbar spinal fracture, the whole board can be tipped to the left.

Elderly Trauma Patients

Equivalent traumatic injuries will have a markedly more serious outcome in the elderly than in younger victims (see Chapter 71).[212] Decreased cardiopulmonary reserves lead to a higher incidence of postoperative mechanical ventilation in older trauma patients and a much greater risk for MOSF after hemorrhagic shock. Greater care must be taken with intraoperative positioning to avoid pressure injuries. A higher hematocrit achieved by tighter control of administered fluid is generally recommended to maintain maximized tissue oxygen delivery. Post-traumatic myocardial dysfunction is a significant risk, particularly if the heart rate is elevated secondary to blood loss, pain, or anxiety. Complex operations or large blood loss should encourage the use of TEE or pulmonary artery catheterization to guide fluid and inotropic therapy.[94] Although prophylactic β-antagonist therapy has been recommended for older patients undergoing major elective surgery,[213] its role in the early management of older trauma patients is unknown. Older patients will have diminished requirements for postoperative analgesia and may respond to sedative medications with inappropriate agitation. Prophylaxis against deep venous thrombosis is important in patients who cannot be immediately mobilized in the postoperative period, as is aggressive pulmonary physiotherapy.

Jehovah's Witness Patients

A trauma patient who refuses blood products requires special management. Early identification and control of hemorrhage are obviously important; deliberate hypotension to limit bleeding may be helpful. Preoperative and intraoperative phlebotomy should be minimized, possibly by using pediatric blood collection tubes. The use of salvaged red cells (from intraoperative collection or from a chest drainage system) should be discussed with the patient because some Jehovah's Witness patients will allow the use of salvaged blood provided that the entire system remains in continuity with the vasculature.[214] The use of albumin and other substances derived from circulating proteins should be addressed. Early hemodynamic monitoring is indicated to help determine the role of colloid therapy, pressors, and inotropes in maintaining tissue oxygen delivery at the highest possible level. Case reports have described the successful use of rFVIIa and hemoglobin-based O_2 carriers in Jehovah's Witness patients to rapidly correct bleeding and support oxygen delivery, but these agents are not approved for these uses and large case series are not available.[215] The use of erythropoietin to promote red cell growth will shorten the period of relative anemia.[216]

Postoperative Care

Emergence and Tracheal Extubation

Initial surgery in a trauma patient is followed by a period of monitoring and ongoing treatment in which the anesthesiologist is closely involved, either in the postanesthesia care unit (PACU) or in the ICU (see Chapter 85). The adequacy of post-traumatic resuscitation must be confirmed, as outlined earlier, and diagnostic studies of the secondary survey completed. Rapid termination of general anesthesia is highly desirable, particularly in patients with an altered level of consciousness or other evidence of TBI before surgery. Change in mental status from the preoperative baseline is an indication for repeat cranial CT and a search for possible metabolic or toxic derangements.[15]

Although it is imperative that neurologic function be assessed postoperatively, early extubation of a trauma patient should not be taken for granted. Many patients will require continued ventilator support because of CNS trauma, direct pulmonary or chest wall trauma, massive transfusion, upper airway edema, or ongoing intoxication. Box 72-11 lists the criteria for extubation after urgent or emergency trauma surgery. If there is any doubt about the patient's ability to meet these criteria, it is appropriate that the patient be transported to the PACU or ICU with the endotracheal tube in place. Appropriate analgesic medication should be administered, with sedation if necessary. Twelve to 24 hours of support allows confirmation of successful resuscitation and surgical repair, hemodynamic equilibration, titration of appropriate analgesia, and resolution of intoxication. Many patients can be extubated easily and safely at this time; those who cannot are at high risk for the development of MOSF—heralded by the development of post-traumatic ARDS—and will usually require days to weeks of subsequent intensive care.

Box 72-11 Criteria for Operating Room or Postanesthesia Care Unit Extubation of Trauma Patients

Mental Status
Resolution of intoxication
Able to follow commands
Noncombative
Pain adequately controlled

Airway Anatomy and Reflexes
Appropriate cough and gag
Ability to protect the airway from aspiration
No excessive airway edema or instability

Respiratory Mechanics
Adequate tidal volume and respiratory rate
Normal motor strength
Required Fio_2 less than 0.50

Systemic Stability
Adequately resuscitated (see above)
Small likelihood of urgent return to the operating room
Normothermic, without signs of sepsis

Acute Pain Management

Trauma patients present significant pain management challenges to the clinician because of multiple sites of injury, protracted episodes of care, complicating psychological and emotional issues, and prior or ongoing substance abuse (see Chapter 87). As with pain management practice in other diseases, trauma patients are

frequently undertreated, thus creating a significant source of dissatisfaction. Because trauma patients run the gamut of physiology from healthy young athletes to the debilitated elderly, anesthesiologists providing pain management for trauma patients must be prepared for a wide range of needs.

Individual trauma patients will have widely varying requirements for pain medication, so induction of analgesia must be titrated carefully, ideally in a closely monitored environment such as the PACU. Administration of rapidly acting intravenous agents in small doses at frequent intervals until pain relief is achieved is recommended. This allows the practitioner to determine the patient's basal requirements before starting long-acting medications or patient-controlled analgesia. Hypotension in response to analgesics is most commonly indicative of hypovolemia and should prompt a search for occult hemorrhage while further resuscitation occurs.

The need for analgesic medication and the duration of requirement for analgesics will be minimized if a comprehensive emotional support system is available to the patient. Trauma, because of its unexpected nature, carries with it a strongly negative psychological overlay that can have a profound effect on how anatomically based pain is perceived by the brain[217] and on how the patient reacts. After an injury the patient may have legal, financial, and family-based concerns, without the ability to immediately address them. The availability of counselors—religious, financial, or legal—who can help the patient and family with these issues is of enormous benefit. The anesthesiologist can help by communicating to the patient a clear description of the patient's injuries, the probable time required for recovery, and the plan for managing pain throughout the patient's course. The anesthesiologist should refer the patient to counseling services as needed and should be alert to the potential for post-traumatic stress disorder (PTSD) in any traumatized patient.[218] Referral to an experienced psychiatrist or psychologist is appropriate if PTSD is hindering the patient's recovery.

The need for analgesic medication is also influenced by the schedule of physical therapy prescribed for the patient. In general, the more active a patient can be after traumatic injury, the lower the risk of pulmonary complications, venous thrombosis, and decubitus ulcers. Though painful in the short term, the sooner the patient is mobilized, the lower the analgesic requirements in the long term. Early mobilization demonstrates to the patient the "path to recovery" and contributes to an improved emotional state. One of the goals of analgesia, therefore, is provision of adequate medication to facilitate physical therapy without so sedating the patient that participation is impossible.

Neuropathic pain arises when there is direct injury to a major sensory nerve and is common after spinal cord trauma, traumatic amputations, and major crush injuries. Neuropathic pain is characterized by burning, intermittent electrical shocks, and dysesthesia in the affected dermatomal distribution. It is important to identify neuropathic pain because it responds poorly to the analgesics used for somatic pain. This diagnosis should be considered whenever pain control is poor or the patient has a rising requirement for medications unexplained by anatomic injuries. First-line therapy for neuropathic pain has been revolutionized by the widespread use of gabapentin, an antiepileptic drug with very strong specificity for this problem.[219] Gabapentin therapy is typically initiated at a dose of 200 mg three times daily, with daily titration upward to a maximum of 2 to 3 g/day. If neuropathic pain persists, selective regional anesthesia or analgesia may be indicated in an effort to "break the cycle" of spinal cord receptor recruitment.[220]

Regional analgesia provided through an epidural or brachial catheter should be considered for any trauma patient with a potential to benefit from this approach because it will spare the use of systemic narcotics and facilitate early mobilization. Epidural analgesia has been shown to produce high levels of patient satisfaction and improved pulmonary function after major thoracoabdominal and orthopedic surgery in elective populations[221]; this is very likely true for the trauma population as well. Regional techniques are less useful when the patient has multiple sites of injury or when fractures or open wounds make placement difficult. Although epidural placement in anesthetized patients is relatively contraindicated because of the potential for occult SCI, the risk-benefit ratio in many trauma patients favors placement during surgery, when general anesthesia facilitates appropriate positioning and patient cooperation.

Summary

Trauma touches all ages and classes of patients, from young and vigorous to elderly and frail. Because of its great prevalence, practicing anesthesiologists will encounter trauma patients throughout their careers. Increased public recognition of the consequences of injury has sparked interest in trauma research and education, with the result that diagnostic and therapeutic techniques have evolved rapidly in recent years. The anesthesiologist, as a perioperative physician, is in the ideal position to understand and apply these new techniques.

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Peter Nagele and Michael Hüpfl

73 Anesthesia and Prehospital Emergency and Trauma Care

Key Points

1. Anesthesiology was instrumental in creating critical care and emergency medicine. In many countries, worldwide anesthesiology departments are responsible for prehospital emergency and trauma care. Physician-based emergency medical services (EMS) systems exist in many European countries, whereas paramedics are the mainstay of EMS in the United States.
2. The basics of prehospital care follow the general form of basic life support (BLS) and advanced life support (ALS), depending on the nature of the EMS system in place for a given region or country.
3. In major trauma, prehospital care must aim at limiting the time spent on the scene, controlling hemorrhage, and expediting transport to a trauma center, often ideally via rescue helicopter. Prehospital fluid resuscitation for major trauma is controversial and patients with penetrating torso injuries and hemorrhagic shock might benefit from limited fluid resuscitation, in particular in urban settings. Prevention of the lethal triad in trauma of hypothermia, acidosis, and coagulopathy is paramount.
4. In acute coronary syndrome (ACS), achieving rapid reperfusion of the ischemic myocardium is the main goal. Opioids (morphine), oxygen, nitrates, and aspirin (MONA) are the main components of prehospital therapy. Fibrinolysis for ACS has been used with much success in the prehospital setting but requires very close supervision by EMS physicians.
5. Prehospital endotracheal intubation and rapid-sequence induction (RSI) have been shown in more than 15 studies to be associated with increased mortality and poorer neurologic outcomes, in particular after traumatic brain injury. It appears that what anesthesiologists consider the standard of care in the operating room may not be the ideal approach for less experienced EMS providers. Perhaps reappraising intubation and RSI in favor of alternate airways such as the laryngeal mask airway or laryngeal tube can improve outcomes.
6. Medical simulation is rapidly becoming the future standard for teaching and training prehospital EMS personnel in the management of complex emergency scenarios.

Unbeknown to many current practitioners, anesthesiologists not only serve as the backbone of physician-staffed prehospital emergency medical services (EMS) in many countries[1-3] but also were instrumental in the creation of modern prehospital emergency medicine.[4,5] In several countries, emergency medicine is considered the fourth pillar of our specialty besides anesthesiology, critical care, and pain therapy.

After World War II, the inadequacy of the civilian ambulance service became all too apparent for wartime experienced physicians, as motor vehicle–related injuries and deaths increased sharply and ambulances provided only transport to the hospital. In Germany, this led to a call to "bring the doctor to the patient" rather than the more traditional converse arrangement.[1,5] As a consequence, the first surgeon-staffed ambulance, the "Klinomobil," was implemented in 1957 in Heidelberg and functioned as a mobile operating room,[5] a concept that was soon abandoned in favor of physician-staffed ambulances, sometimes referred to as mobile ICUs.[6] Similar developments occurred throughout Europe, for example, in Prague, Mainz, Munich, Moscow, and several Scandinavian countries where physicians began to staff ambulances to respond to motor vehicle crashes and other accidents.[3,4] In Belfast, Ireland, Frank Partridge was the first to implement a mobile coronary care unit (CCU) that brought a defibrillator to prehospital patients in cardiac arrest due to ventricular fibrillation.[7] Over the next decades, several European countries, such as France, Germany, Austria, and Norway, implemented nationwide physician-staffed ambulance services that were often complemented by physician-staffed helicopter

emergency medical services (HEMS).[1-3,8,9] Anesthesiology is currently the dominant medical specialty providing EMS physicians in Europe, and many anesthesiology departments are in charge of staffing ambulances and helicopters with physicians.[3,10]

In the United States, a different development took place. For various reasons, physician-staffed ambulances were not considered an option, so specifically trained emergency medical technicians (EMTs) and paramedics became the mainstay of EMS in North America. A landmark event for the creation of modern EMS systems was the publication of the report *Accidental Death and Disability: The Neglected Disease of Modern Society*, commonly referred to as *The White Paper*, published by the National Academy of Sciences in 1966.[11] Among several remarkable physicians, two anesthesiologists, Peter Safar, in Pittsburgh, the father of modern cardiopulmonary resuscitation (CPR), and Eugene Nagel, in Miami, were most influential in creating the first paramedic-based EMS system in the United States in the 1960s. Before emergency medicine became its own medical specialty, anesthesiologists were often involved in prehospital emergency care based on their unique expertise in resuscitation, airway management, and critical care. This involvement has dwindled over the past 2 decades, although it appears that anesthesiology could still play an important role in prehospital emergency care in the United States based on what the recent, widely cited Institute of Medicine report *Emergency Medical Services: At the Crossroads* identified as the major problems in prehospital care, such as prehospital airway management, fluid resuscitation, rapid-sequence induction (RSI), and pain therapy.[12]

In this chapter, we provide a concise overview of prehospital emergency and trauma care with a focus on the important role of anesthesiology.

Organizational Models of Prehospital Emergency Care

Levels of Care

Originally, the terms *basic* and *advanced life support* were only used to describe the two different levels of care for CPR (see Chapter 97) but were later expanded to all emergency situations, including trauma and pediatric emergencies. Currently, they denote the level of care in an organized EMS system and are usually divided into BLS and ALS. First responders, such as police officers and firefighters, are not part of an EMS system and they provide first aid, operating below the formal BLS level.

Basic Life Support

Prehospital care at the BLS level is usually provided by EMTs and does not include advanced and invasive techniques and skills.[13] BLS is focused on the classic ABCs (Airway, Breathing, Circulation) and includes simple airway maneuver, such as chin lift or jaw thrust, oral and nasal airways, bag-valve-mask ventilation, hemorrhage control, and administration of oxygen (Table 73-1). During CPR, the use of an automated external defibrillator is considered a BLS skill. BLS-only ambulances are often found

Table 73-1 Skill Set for BLS and ALS Providers and Prehospital Emergency Physicians

BLS
Basic patient evaluation
Vital signs and basic monitoring (noninvasive blood pressure, pulse oximetry, heart rate)
Hemorrhage control via direct pressure or pressure dressing
Cardiopulmonary resuscitation (BLS) with use of automatic external defibrillator
Bag-valve-mask ventilation
Oral and nasal airway
Oral suctioning
Administration of oxygen
Basic patient rescue, positioning, and transport skills
Cervical spine stabilization
Fracture splinting
Assisting a patient taking prescribed medication (e.g., albuterol inhaler)
ALS
Venous access and fluid therapy
Administration of select drugs*
Advanced monitoring (ECG, capnography)
Cardiopulmonary resuscitation (ACLS)
Manual defibrillation
Basic 12-lead ECG interpretation
External pacing
Endotracheal intubation* (without drugs; some EMS systems allow rapid-sequence induction)
Cricothyroidotomy
Sedation*
Needle decompression of tension pneumothorax
Knowledge of mass casualty incident management and triage
Knowledge of biological, chemical, and nuclear agents
Prehospital Emergency Physician
Unlimited administration of emergency drugs
Use of narcotics and controlled substances (e.g., fentanyl)
Prehospital rapid-sequence induction and anesthesia
Advanced airway management
Chest tube placement
Advanced 12-lead ECG interpretation
Advanced techniques (ultrasound, noninvasive ventilation)
Emergency surgery
Can assume role of medical incident commander in mass casualty event

*Not in all ALS-level EMS systems allowed.
ALS, advanced life support; BLS, basic life support.

in rural areas where the incidence of emergencies is low and volunteer EMTs frequently staff ambulances.

Advanced Life Support

ALS is usually provided by paramedics and flight nurses with a rigorous educational background and includes the use of advanced and invasive techniques (see Table 73-1). In many countries, ALS-level providers are allowed to work semi-independently with often only indirect physician control through the use of standing orders and protocols issued by the EMS medical director. The use of drugs is tightly regulated, and physician permission from the emergency department must be sought in cases where drugs outside the approved list are to be administered. Most urban EMS systems use ALS units to provide prehospital care. In EMS systems without EMS physicians responding directly to the scene, the scope of practice of ALS-level providers is usually greater and they are allowed to work more independently. Combat medics in the military frequently operate at the ALS level. EMS physicians, flight nurses, and critical care EMTs provide a level of care above and beyond ALS.

Models

Worldwide, a high degree of variability exists as to how prehospital care is organized and staffed. It would be beyond the scope of this chapter to describe all the nuances of the different EMS systems worldwide; rather, we will outline the differences between the two main models, which primarily differ by their level of direct physician involvement in prehospital emergency care: EMT-based models versus physician-based models. These two models are also known as the U.S. model and the "Franco-German" model.[14] Although controversy exists which model provides superior patient care and outcomes, the design of the EMS system is dictated by tradition and fiscal constraints.

Single-Tiered Versus Multi-Tiered EMS Systems

If an EMS system is composed only of units providing the same level of care—BLS or ALS—it is referred to as a *single-tiered* system. The advantage of a single-tiered EMS system is that it eliminates overtriage or undertriage by emergency medical dispatch. In rural areas with a low frequency of emergency calls, a single-tiered EMS system—often composed of volunteer EMTs at the BLS level—is the only possible model; and in dense urban areas with a high frequency of emergency calls, an all-ALS EMS system might be advantageous. The disadvantage of single-tiered all-ALS EMS systems is that the highly trained paramedics will not be exposed to the same number of high priority situations, making it difficult to maintain their skills and experience.

Multi-tiered EMS systems use priority dispatch to determine the adequate level of response; it would dispatch an ALS unit to a patient with myocardial infarction but a BLS unit to a patient with a broken wrist.

EMT- and Paramedic-Based EMS Systems

In North America, EMTs provide organized prehospital care.[15] Only rarely will physicians be directly involved in out-of-hospital patient care on the scene.[16] By U.S. law, physicians are required in most states to oversee the medical operations of EMS systems, either *online* through direct communication or *offline* as EMS medical directors responsible for developing and implementing standardized treatment protocols. Besides developing standard operating procedures and approving new medical devices, EMS medical directors are responsible for quality control and improvement and are an integral part of EMT education.[17] In the United States, EMS medical directors are often emergency physicians working in the emergency department of the local hospital.

In general, three levels of EMTs can be distinguished by their educational background and experience in the United States: EMT-basic (EMT-B), EMT-intermediate (EMT-I), and EMT-paramedic (EMT-P). EMT-basic providers usually spend between 80 and 120 hours of training and are only allowed to perform basic life support (BLS) skills. The basic level is the minimum level required to work in an organized ambulance service. Often, EMT-basic providers staff nonemergent ambulance transport but are also used to respond to non–life-threatening situations. EMT-I providers are regulated differently among the individual states, and their skills range between BLS and ALS. Often, EMT-I providers can be found in rural areas where it would be too expensive to employ paramedics only but where more advanced skills than those of an EMT-B level are needed. Most states do not allow EMT-I providers to perform endotracheal intubation or administer drugs, except very few deemed safe, such as albuterol for asthma, but allow the placement of an intravenous (IV) line. Paramedics (EMT-P), on the other hand, are the most advanced EMTs. They undergo intensive 1- to 2-year training in all different aspects of advanced prehospital emergency care. Their scope of practice is ALS, and they are allowed to perform advanced techniques such as endotracheal intubation, administration of selected drugs, and manual defibrillation. Most developed countries have training requirements for their EMT work force similar to the U.S. model.

Physician-Based EMS Systems

Germany and France represent the two most well-known examples of countries where doctors are an integral part of prehospital emergency care.[14] These integrated EMS systems combine BLS-level ambulances with physician-staffed ALS ambulances and helicopters in a noncompetitive but complementary fashion. Physician-based EMS systems are always part of a multi-tiered system and often use what is referred to as a "rendezvous system" to dispatch two units simultaneously to the scene, one unit staffed with EMTs (BLS or ALS level) and one ambulance carrying the doctor. Often, the physician-staffed vehicle will be a nontransport vehicle aimed to provide quick response to emergencies without having to move a large and slow truck through traffic. EMS physicians are licensed physicians from various medical specialties who undergo a specialized training in prehospital emergency care. The level of mandatory education varies from country to country. In many countries with direct physician involvement in prehospital care, anesthesiologists compose the largest fraction of physicians and often assume the role of chief emergency physician/medical director.[18,19]

Helicopter EMS

In many countries worldwide, helicopter EMS (HEMS) continues to expand as an integral component of EMS. Although being mostly privately organized and funded in the United States, several European countries have implemented a nationwide HEMS network that is strategically distributed to be able to respond to emergency calls from every location in the country. HEMS have historically been mostly associated with rapid



Figure 73-1 Train accident in Wampersdorf, Austria. Mass-casualty incident with 6 fatalities and 17 injured patients. In addition to more than 50 EMS personnel and EMS physicians on the ground, 5 EMS-physician–staffed helicopters provide invaluable EMS-physician level backup and transport capacity.

response to and fast transport from the scene of an accident, particularly from remote rural accident scenes. However, HEMS is now considered more and more as a vital ALS-level backup for all emergency situations in rural areas lacking local ALS-level response.[20] EMS helicopters are usually staffed with experienced personnel, either paramedic and flight nurse or EMS physician.[9,21] In mass-casualty incidents, all helicopters from a large area can be concentrated at the scene of the accident within a short period of time and provide several highly trained ALS teams to support local rescue operations and transport the victims quickly to trauma centers (Fig. 73-1). Another area where HEMS have become the most important means of evacuation is in mountain rescue operations. Pioneered in the Alps, helicopter evacuation by ALS teams specially trained in mountain rescue techniques is now considered the standard of care in countries such as Switzerland, Austria, Germany, and France (Fig. 73-2).

Communication

Starting with the emergency call, communications is a vital aspect of prehospital emergency care. The implementation of a universal emergency telephone number (911 in the United States and Canada, 112 in several European countries, 000 in Australia, and 999 in the United Kingdom)[17] was a milestone in prehospital care, and nowadays the location of the caller can be automatically identified by the system except if calling from a cellular phone. Emergency medical dispatchers will determine the type and priority of the response based on standardized questionnaires and will provide invaluable prearrival instructions to the caller to start potentially lifesaving interventions before the ambulance arrives. For example, dispatcher-assisted CPR has been shown to improve survival after cardiac arrest.[22] Two-way radio communication has long been an indispensable part of EMS communications, allowing not only fast communication between ambulance and dispatcher but also to the hospital and other emergency response teams such as fire department, police, and helicopters.

Basic Techniques and Skills

Patient Examination and Initial Assessment on the Scene

Emergency patients show a wide range of symptoms, challenging the prehospital care team to obtain a tentative diagnosis quickly and start a specific treatment. In contrast to the emergency department, fewer diagnostic tools are available in the prehospital setting. The classic approach of "look, listen, and feel" is still the most important aspect of the patient examination.

On approaching the patient, a rapid appraisal of the scene should assess potential hazards that could endanger patient and prehospital personnel. The initial assessment should take into account the surrounding circumstances such as environmental factors and should focus on the vital signs of the patient using a systematic approach.[23] Visual impressions from the scene help to understand the circumstances of an accident or medical emergency, such as intoxication. The medical history of the patient can guide the presumptive diagnosis. In case the patient is unresponsive, relatives or bystanders must be queried. The most common chief complaints encountered in the prehospital setting are dyspnea/respiratory distress, cardiac/circulatory dysfunction, altered level of consciousness, and trauma.

Basic Evaluation

Vital Signs

The first quick survey employs the A-B-C-D scheme well known by ALS.[24] The first step is to use acoustic and tactile stimuli to rule out unconsciousness in the emergency patient. The next step



Figure 73-2 In mountain rescue, helicopter EMS systems have become the standard of care for evacuating patients from alpine accidents and emergencies. Here, a rescue helicopter supports a complex mock rescue operation from a ski lift in alpine Austria.

is to identify airway (A) obstruction and, if necessary, to secure the airway. In trauma patients, manual in-line stabilization of the cervical spine should be performed at this point. While maintaining an open airway, breathing (B) is assessed by look, listen, and feel.[23] Respiratory rate, efficacy, work and pattern of breathing are also assessed. If indicated, supplemental oxygen or assisted ventilation will be administered to support oxygenation and ventilation. Circulation (C) is initially checked by feeling the pulse centrally at the carotid artery and can be extended to feel pulses proximally and distally on the extremities. The pulse should be assessed for rate, quality, and regularity. To complete C, the capillary refill time should be measured. The level of responsiveness and consciousness (D, disability) should be determined according to the Glasgow Coma Scale (GCS) and a quick pupil check performed to determine size and reaction to light. The GCS is a reliable prognostic tool for head trauma[25,26] and other forms of nontraumatic altered level of consciousness.[27] For children younger than the age of 3 years, the verbal component of the GCS score must be adjusted. In case of trauma, exposure and environment (E) are assessed to complete the primary survey. At this point, the patient should be checked from head to toe, and his or her back should be evaluated after a log-roll maneuver.[28]

Auscultation—Palpation—Percussion

Auscultation is a versatile and useful tool in most prehospital settings, limited primarily by ambient noise in the environment. Palpation, also an important tool, may be more useful in such settings. In trauma, the entire body can be examined by palpation only. During the primary and secondary survey in the field, the rescuer has to rely solely on palpation. Percussion is specifically helpful to detect abnormal air or gas collections, such as tension pneumothorax and large amounts of free intra-abdominal air.

Capillary Refill Time

Capillary refill time is a quick and reliable parameter to detect hypovolemia; 5% dehydration can be detected by capillary refill time with 87% sensitivity and 82% specificity.[29] After compression of the skin for at least 5 seconds, the time is measured until normalization of skin color occurs. Normal findings are less than 2 seconds. Capillary refill time may be especially useful to detect significant dehydration in children.[30]

Monitoring and Equipment

In a similar development compared with standard monitoring in operating room and intensive care, monitoring in the prehospital setting is now considerably standardized with noninvasive blood pressure monitoring, electrocardiography (ECG), and pulse oximetry regarded as the classic "trifecta." Capnography and temperature monitoring have begun to supplement the diagnostic and monitoring armamentarium in the field.

Pulse Oximetry

After the first prehospital uses in the 1980s,[31] pulse oximeters have become the universal, easy to attach and use monitor for the prehospital patient. The improvement of the devices led not only to smaller machines but also to pulse oximeters with better quality even in motion and the cold.[32,33] Additionally, new features such as detection of methemoglobin and carboxyhemoglobin[34,35] can help diagnose conditions such as carbon monoxide poisoning.

Arterial Blood Pressure

Noninvasive blood pressure measurement is the most common form of blood pressure monitoring in the prehospital setting. Automatic or manual cuffs are mostly used and use an oscillometric technique that has known limitations.[36] The precision and accuracy of noninvasive oscillometric blood pressure monitoring is reduced by movement during transport. During interhospital transfer of a critically ill patient, intensive care unit (ICU) monitoring with invasive blood pressure monitoring is frequently used.

Electrocardiography

ECG monitoring has two major goals in the prehospital setting. A quick 3- or 4-lead ECG or an ECG rhythm obtained from defibrillator paddles is sufficient for a rapid ECG rhythm diagnosis. This is of importance for treatment decisions during ALS in cardiac arrest to decide if a shockable rhythm is present. On the other hand, to identify myocardial ischemia or infarction, a 12-lead ECG is needed. It is more cumbersome to apply and requires more experience for interpretation. Prehospital ECG allows for a focused prehospital therapy in acute coronary syndrome[37] and has been shown to shorten the door-to-reperfusion time.[38-40] This benefit can be further improved by transmission of the ECG to medical oversight.[41]

Temperature Monitoring

Oral, esophageal, and some tympanic thermometers[42-45] are reliable tools in the field given the more extreme weather conditions in which they must operate. The most important aspect of measuring temperature on the scene is to identify hypothermia. Special temperature probes are required to assess severe hypothermia (<28°C) because most commercially available instruments become unreliable at these low temperatures. Trauma patients, patients at the extremes of age, disabled patients (stroke, coma), and intoxicated patients are especially vulnerable to hypothermia, particularly during winter months. Even relatively mild outside temperatures can result in hypothermia with long exposure times.[46,47]

Capnography

Colorimetric, main- or side-stream capnographs are primarily used in the prehospital setting for identification of the correct positioning of the endotracheal tube.[48-50] With a single measurement the correct tube position can be identified. Capnography became the standard for identifying the correct tube position in addition to auscultation and identifying chest movements. Continuous monitoring of end-tidal CO_2 allows the monitoring of hemodynamics and the success of resuscitation.[51] In cardiac arrest, low CO_2 levels are a predictor for fatal outcome.[52] Hyperventilation may also contribute to poor outcome[53] and may be preventable by controlling ventilation with the aid of end-tidal CO_2 monitoring.[54,55] Significant cardiorespiratory failure may limit the usefulness of capnography owing to significantly reduced pulmonary perfusion.

Prehospital Blood Tests

Despite proposals for prehospital point-of-care testing,[56] only blood glucose testing is routinely used. Troponin and blood gas analysis are examples of tests that may have potential utility.[53,57]

Ultrasonography

Small and portable ultrasound machines have been developed that are applicable in the prehospital setting. Diagnostic ultrasound requires a physician on the scene (or online through medical oversight if adequate transmission of the image can be achieved) but offers very interesting possibilities. Focused abdominal sonography for trauma (FAST) is a rapid and reliable technique even in inexperienced hands in the emergency department and could be used in the field.[58] It has the potential to improve the triage and management of trauma patients.[59] During resuscitation from cardiac arrest, cardiac activity is a predictor for return of spontaneous circulation (ROSC).[60] Nevertheless, diagnostic prehospital ultrasonography is still considered experimental and may interfere with management priorities.

Prehospital Airway Management and Ventilation

Early and adequate airway management and ventilation in the out-of-hospital setting are lifesaving interventions that define prehospital emergency and trauma care (see Chapter 50). For anesthesiologists who perform advanced airway management on a daily basis it is often difficult to comprehend why airway management is such a contentious issue in prehospital emergency medicine, particularly in the United States.[61-67] The reasons are many. The major difference from the operating room environment, as an EMS saying goes, is that *there is no easy airway in the field*. Challenges include nonstandard environments; difficult access to the patient's head; bad weather and lighting conditions; and blood, vomitus, secretions, and foreign bodies obstructing the airway. In a patient who is critically ill with limited oxygen reserves and a higher baseline oxygen consumption all of these factors contribute to a significantly more difficult prehospital airway management compared with the operating room, even for an experienced anesthesiologist.[68-72]

Airway Management at the BLS Level

Supplemental oxygen is the most important component in prehospital airway management, hence the saying "The patient does not die because of a lack of an endotracheal tube but because of lack of oxygen." EMTs are trained and qualified to administer supplemental oxygen, often via a non-rebreather facemask allowing for a significantly higher F_{IO_2}. Furthermore, EMTs are allowed to use nasopharyngeal or oropharyngeal airways to maintain a patent airway and to ventilate a patient by bag-mask-valve ventilation. The use of the Combitube (or Easytube), a double-lumen tube with a proximal and a distal balloon that was initially developed for ventilation during CPR, is considered a BLS skill.[73,74] The use of other alternate supraglottic airways, such as the King-LT (laryngeal tube) or laryngeal masks, is increasingly recommended at the BLS level if adequate training and experience are provided.[75] These alternate airways have been shown to be safe and easy to apply and have excellent success rates when used by EMTs and paramedics.[76-79] The limitations of these alternate airways are a disability to ventilate if misplaced in the larynx and lack of airway protection compared with a cuffed endotracheal tube. It is of note that many anesthesiologists who do not work in EMS medicine are currently not familiar with many new alternate airway devices used in prehospital care, such as the King-LT, which is rapidly becoming the standard alternate airway in the field.[75]

Ventilation in the prehospital setting is most commonly achieved by bag-mask-valve ventilation. Although fairly common in Europe, only a few EMS services in the United States currently use portable field ventilators to ventilate intubated patients. The major disadvantage of relying on bag-mask-valve ventilation is that minute ventilation and tidal volumes are uncontrolled, often leading to significant hyperventilation that has been shown to be detrimental in patients in cardiac arrest[53,80,81] and with head trauma.[82-88]

Airway Management at the ALS Level

Endotracheal intubation is considered the standard of care in prehospital airway management and a standard intervention for paramedics and EMS physicians because it provides a definitive airway and protection from aspiration of gastric contents. Compared with standard endotracheal intubation in the operating room, several differences exist. First, most prehospital intubations (50%-70%) are performed in patients with cardiac arrest, obviating the need for any anesthetic induction or muscle relaxation.[89] Most other intubations in spontaneously breathing patients require sedation or induction of general anesthesia, most commonly performed as RSI. Particular emphasis should be placed on adequate preoxygenation because these critically ill patients have little to no oxygen reserves,[90] as well as on maintaining cervical in-line stabilization in trauma patients. Oral, direct laryngoscopic, and tracheal intubation while maintaining cricoid pressure (Sellick's maneuver) is the recommended approach. Endotracheal intubation in the field requires confirmation by auscultation and end-tidal CO_2 monitoring.

Adverse intubating conditions in the field lead to more frequent incidences of difficult endotracheal intubations,[70] including higher incidences of multiple attempts[91] and of unrecognized esophageal or endobronchial intubation. This occurs even by experienced EMS physicians and anesthesiologists and is associated with a high mortality rate.[71] However, experienced physician "airway managers" and, in particular, anesthesiologists have more frequent success rates and lower complication rates after prehospital endotracheal intubation.[92-94]

A significant portion of failed field intubations results from inadequate operator training or experience. Less than one half of field intubation failures were remedied in the emergency department by the use of neuromuscular blocking agents.[95] Because of the higher complication rate, every prehospital provider performing advanced airway management must be trained also in alternate airway management, such as Combitube, King-LT, or laryngeal masks. A special training for managing the unanticipated difficult airway according to adapted international guidelines should be required.[96,97] Surgical airway access such as cricothyroidotomy is considered the last resort but can be lifesaving in patients when every other airway technique fails.[98]

Sedation, Anesthesia, and Pain Control in the Prehospital Setting

In this section, the focus will be on generally accepted strategies for providing prehospital sedation, induction, and maintenance of anesthesia and pain control (see Chapters 26 and 27). Drugs

commonly used in the field will be discussed with an emphasis on the differences from use in the hospital. There is hardly any area of greater controversy than RSI in the field.

Drugs Commonly Used for Prehospital Sedation, Anesthesia, and Pain Control

In general, not all drugs routinely used in the operating room for general anesthesia are safe in the prehospital setting.[99] Nonanesthesia personnel such as paramedics and nurses are much less experienced than anesthesiologists in the use of these drugs, and critical patients often require a more cautious approach and dosage titration. Therefore, drugs used for analgesia, sedation, and anesthesia in the field should have the following desirable properties[100]:

- Wide safety margin—even for inexperienced providers
- Hemodynamic stability
- Minimal respiratory depression
- Ease of administration via different routes (IV, IM, IO, rectal)
- Rapid onset
- Minimal side effects

Benzodiazepines, such as midazolam (0.05-0.2 mg/kg IV) and diazepam (3-10 mg IV), are well suited for sedation in adult and pediatric patients and can be administered via several different routes; however, the complete lack of analgesic properties usually requires the concurrent administration of a potent analgesic in patients with severe pain. *Ketamine,* on the other hand, is closer to an ideal agent for sedation and analgesia (0.5-2 mg/kg IV) and in higher doses for induction of anesthesia (2-5 mg/kg IV) in the field.[101] It provides potent analgesia and sedation, maintains hemodynamic stability in patients with hypovolemic shock, is a potent bronchodilator, and causes minimal respiratory depression. The use of ketamine in severe head trauma is controversial: some make a case for its use if ventilation is controlled.[102] Owing to its hallucinogenic properties, a benzodiazepine should be coadministered. The new isoform, S(+) ketamine, is twice as potent but has otherwise a similar profile as a racemic drug. Ketamine can be administered intramuscularly (IM) and is ideally suited to provide analgesia and sedation for entrapped trauma patients during extrication (4-12 mg/kg IM). *Etomidate* is rarely used for sedation but is often used as an anesthetic induction agent for RSI in the field (0.2-0.3 mg/kg IV). It maintains hemodynamic stability but frequently produces myoclonus, rendering intubating conditions less favorable. Furthermore, etomidate may cause adrenocortical suppression, but this is controversial and has not been sufficiently studied in the EMS setting.[103,104] *Propofol* has become the anesthetic induction agent of choice in the operating room but has several disadvantages for use in the field. It causes significant hemodynamic compromise and respiratory depression, both highly undesirable properties, especially for inexperienced nonanesthesiologists. *Barbiturates,* such as thiopental, share similar pharmacologic properties and side effects with propofol and should be used only by experienced providers and only in selected patients, for example, in those with status epilepticus. The prehospital muscle relaxant of choice is still *succinylcholine* (1-1.5 mg/kg IV) during RSI,[105] although rocuronium has been successfully used by anesthesiologists in EMS.[106] For pain control in the prehospital setting, *opioids* are useful owing to the rapid onset and the ability to control severe pain.[107] *Morphine* is considered the standard of care in acute coronary syndrome (0.1-0.2 mg/kg IV), but in trauma other opioids, such as *fentanyl* (1-3 µg/kg IV), *piritramide* (0.1-0.2 mg/kg IV, currently not available in the United States but widely used in Europe), and sometimes *tramadol* (50-100 mg bolus IV) are more frequently used. Nonopioid analgesics are infrequently used in the prehospital setting, although they offer a potential additive analgesic effect with opioids.

Box 73-1 Prehospital Rapid-Sequence Induction

1. Preparation of necessary equipment (suction, oxygen, laryngoscopes, endotracheal tube, Ambu bag plus masks, stylet)
2. Preoxygenation with 100% oxygen (at least 3 minutes)
3. Pretreatment (optional) with small defasciculation dose of a nondepolarizing neuromuscular blocking agent, such as vecuronium (0.01-0.015 mg/kg IV)
4. Pretreatment (optional) with sedative (midazolam) and/or opioid analgesic (fentanyl)
5. Induction agent (etomidate, 0.3 mg/kg IV, or ketamine, 2-3 mg/kg IV) plus succinylcholine (1.0-1.5 mg/kg IV)
6. Cricoid pressure (Sellick's maneuver), plus manual in-line stabilization for trauma patients
7. Direct laryngoscopy with oral intubation (use of stylet is recommended)
8. Confirmation of correct endotracheal tube placement: bilateral auscultation plus end-tidal CO_2 confirmation

Induction of Anesthesia

The management of prehospital induction of anesthesia will nearly always be performed as RSI, also known as drug-assisted intubation (DAI) in EMS literature (see Chapter 50). The goal is twofold: (1) the provision of a definitive airway and ventilation control and (2) the provision of potent analgesia and sedation. The actual principles of RSI do not differ from RSI in the emergency department, operating room, or ICU, only in the environment in which it is applied, as discussed earlier.[63] A standard RSI sequence consists of the steps presented in Box 73-1. Extremely important in the prehospital setting is to have a backup plan, if intubation fails. Bag-mask-valve ventilation, placement of an alternative airway such as a laryngeal mask airway or intubating laryngeal mask airway, or Combitube are acceptable options. EMS providers must understand that prehospital RSI is not trivial and is associated with significant morbidity and mortality if performed improperly.[108] Life-threatening hypoxemia will ensue if intubation is prolonged and ventilation is difficult (Fig. 73-3).

Prehospital Trauma Care

The management of a severely injured patient is one of the biggest challenges in prehospital care. Trauma represents a leading cause of death and disability among all ages but disproportionally affects the younger age groups. The potential for saving lives is probably nowhere more prevalent in EMS than in major trauma, which was also historically the driving force behind the creation of modern EMS systems. The challenges for EMS providers

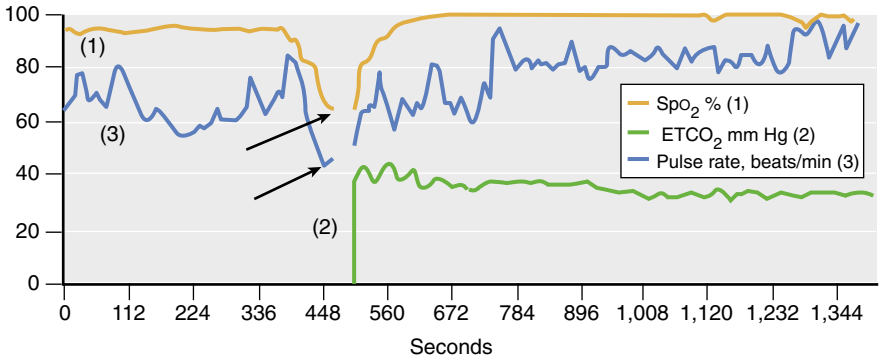

Figure 73-3 Potentially life-threatening desaturation and bradycardia after out-of-hospital rapid-sequence induction and endotracheal intubation. (*From Dunford JV, et al: Incidence of transient hypoxia and pulse rate reactivity during paramedic rapid-sequence intubation. Ann Emerg Med 42:721-728, 2003.*)

responding to major trauma begin with assessment of safety at the scene, scene assessment (number of injured patients, mechanism of injury, injury severity, difficult weather and lighting conditions), and coordination with other first-responder services (police, fire department). Significant pressure exists to minimize on-scene and transport times, based on the "golden hour" and "platinum 10 minutes" concept.[109] The most commonly used guideline for prehospital trauma care is Prehospital Trauma Life Support (PHTLS) developed by the National Association of Emergency Medical Technicians (NAEMT) in cooperation with the Committee on Trauma, American College of Surgeons.[28] PHTLS is based on the Advanced Trauma Life Support (ATLS) concept that is used as standard for in-hospital trauma care.[110]

Patient Evaluation on the Scene and Initial Management

Before turning the attention to the trauma patient, the EMS crew must ensure that the accident scene is safe. Crew protection is paramount, in particular in hazardous accidents involving fire, chemical agents, or electricity or on busy highways. Motor vehicle accidents often involve more than one patient; therefore, the EMS team must perform a quick but thorough scan of the entire accident scene and triage all victims. The overriding goal of the initial patient assessment on the scene is to identify life-threatening injuries. This usually follows the well-known A(irway), B(reathing), C(irculation), D(isability), and E(xposure/Environment) algorithm. Treatment is immediately initiated if a life-threatening injury is identified ("Treat what kills first"). This often involves emergent airway management to protect the airway or hemorrhage control for major bleeding. Supplemental oxygen via a nonrebreathing facemask should be started on the scene, as well as standard monitoring (ECG, pulse oximetry, blood pressure, capnography) applied. The goal is to maintain Spo_2 above 90%. If the patient's respiratory status deteriorates or if he or she is unable to protect the airway (due to unconsciousness, intoxication, hypoperfusion, or direct trauma), establishing a definitive airway is indicated. Endotracheal intubation in the field with or without RSI by paramedics has been intensely scrutinized over the past decade,[62,68] especially in traumatic brain injury,[111] and it is currently unclear if field airway management with RSI by paramedics decreases or contributes to trauma mortality.[67] It appears that experience of the provider in endotracheal intubation and RSI is a strong predictor for successful prehospital airway management,[112] and therefore it should not come as a surprise that success rates are higher and complication rates lower if anesthesiologists perform airway management in the prehospital setting.[93]

Hemorrhage control is probably the most critical aspect of prehospital trauma care, particularly in combat casualty care. A large fraction of traumatic deaths within the first hour can be attributed to exsanguination.[113] The recommended first step in controlling the bleeding is direct pressure to the wound, including application of an appropriate pressure dressing. Compressing the major artery proximal to the wound at pressure points is the next step, and tourniquets should only be used as a last resort in civilian trauma.[114] In military trauma, the use of tourniquets has recently surged again in Iraq and Afghanistan and has been accredited with having saved many lives.[115,116] Several different hemostatic wound dressings have been advocated and used in combat casualties suffering from severe hemorrhage[117]; their use in civilian EMS is currently not well defined.[118] In patients with hemorrhagic shock, it is currently recommended to start two large-bore IV lines and give a fluid bolus of 2 L of a warm crystalloid solution.[28] This practice, however, has been repeatedly questioned, particularly for penetrating trauma in an urban setting.[119,120] Newer concepts, such as small-volume resuscitation with either hypertonic saline or hypertonic-hyperoncotic hydroxyethyl starch solution,[121,122] permissive hypotension/hypotensive resuscitation,[123] or hemoglobin-based oxygen carriers,[124] are promising but currently still under investigation. The controversy regarding optimal fluid therapy goes hand in hand with the ongoing discussion of if a "scoop-and-run" (evacuate) or "stay-and-play" (resuscitate on site) or BLS versus ALS approach is superior in major trauma (see Controversies in Prehospital Emergency and Trauma Care).[125] There is evidence supporting a minimalistic on-the-scene management (BLS only) for penetrating trauma to the torso in an urban setting because transport times are very short, usually a younger age group is affected that will tolerate a period of hypotension well, and the injury can only be treated by emergent surgery. On the other hand, evidence is scant to support a scoop-and-run approach for blunt trauma, especially in the rural setting where transport times are much longer than in an urban setting. Irrespective of the current controversy regarding fluid resuscitation in major trauma, the goal is to minimize on-scene time to less than 10 to 15 minutes (or less than 5 minutes in a hypotensive penetrating trauma victim) as well as transport times. Helicopter transport has been advocated for major trauma patients because it was shown to reduce mortality as well as facilitate treatment in a trauma center.[126] Current criteria that patients should be transported to a trauma center can be found in Table 73-2. In major head trauma (see Chapter 63), a modified approach is required in the field: adequate oxygenation

Table 73-2 On-Scene Triage Criteria for Major Trauma Necessitating Transport to Trauma Center

Mechanism of Injury
Extrication time >20 minutes
High-speed crash with:
Intrusion into passenger compartment >20 cm
Speed >40 mph
Ejection
Death of another passenger in same car
Rollover
Pedestrian or bicyclist hit by motor vehicle
Motorcycle crash >20 mph or with separation of rider from motorcycle
Falls >3 m (9.8 ft)
Physiologic Criteria
Systolic blood pressure <90 mm Hg
Respiratory rate <10 or >29 breaths/min
Glasgow Coma Scale score <14
Pregnancy
Anatomic Criteria
Flail chest
Two or more proximal long bone fractures
Pelvic fracture
Penetrating injury to head, neck, torso, or extremities proximal to elbow or knee
Open or depressed skull fracture
Amputation proximal to wrist or ankle
Paralysis
Discretion of EMT
Per discretion of EMT, patients can be declared a major trauma patient. In addition, preexisting conditions of the patient can lead to an upgraded status, such as coronary artery disease, congestive heart failure, severe COPD, morbid obesity, or bleeding disorders.

COPD, chronic obstructive pulmonary disease.
From O'Connor RE: Trauma triage: Concepts in prehospital trauma care. Prehospital Emerg Care 10:307-310, 2006.

and avoiding hypoxemia (SpO_2 >90%), maintaining an adequate cerebral perfusion pressure >70 mm Hg with a systolic blood pressure of at least 90 mm Hg with isotonic or hypertonic fluids, endotracheal intubation for patients with a GCS less than 9, maintaining normoventilation (end-tidal CO_2 of 35-40 mm Hg) and avoiding hyperventilation or hypoventilation are considered the mainstays of prehospital therapy in traumatic brain injury.[127] However, if cerebral herniation is suspected, moderate hyperventilation (end-tidal CO_2 of 30-35 mm Hg) and hyperosmolar therapy with mannitol or hypertonic saline should be instituted.

Adult Medical Emergencies

Most textbooks on prehospital emergency medicine discuss adult medical emergencies under the patient's final diagnosis, such as congestive heart failure (CHF) or chronic obstructive pulmonary disease (COPD). This, however, is not how patients present to the EMS team on the scene; instead, patients usually present with a chief complaint (or lead symptom), such as dyspnea or chest pain. Most often, adult medical emergencies fall into only three separate chief complaints: dyspnea/respiratory distress, cardiac/circulatory emergencies, and altered level of consciousness. Therefore, we will discuss adult medical emergencies in this chapter by their respective chief complaint.

Dyspnea/Respiratory Distress

Dyspnea is one of the most common presenting symptoms in prehospital care, carrying a significant mortality rate of 12% to 18% in adults.[128] Each year in the United States alone, 2 million patients with respiratory distress are transported by EMS. As shown in a large Canadian outcome study (OPALS), prehospital ALS decreases mortality in these patients.[128] In adults, acute shortness of breath is most commonly caused by either bronchospasm or pulmonary edema secondary to CHF, but other differential diagnoses such as pulmonary embolism, pneumonia, and foreign body obstruction must be considered (Table 73-3).[129] Identifying the correct diagnosis on the scene is not always as straightforward as it may seem[130-132] because the etiology of dyspnea can be multifactorial, for example, in a patient with severe COPD and CHF who develops pneumonia.

Patient Evaluation

The most important aspect of the initial evaluation in a patient with acute dyspnea is to identify if the condition is life threatening with imminent respiratory failure and requires immediate treatment. Physical signs and symptoms indicating a life-threatening condition are cyanosis, tachypnea (respiratory rate <6 breaths/min or >30 breaths/min), stridor, tachycardia, inability to speak in full sentences (<5 to 6 words), and the use of accessory respiratory muscles.[133] The use of pulse oximetry has quickly become the standard of care in diagnosing hypoxemia and adds an objective measurement of the severity of respiratory distress.

Irrespective of the underlying cause, all patients with respiratory distress should receive high-flow oxygen, ideally through a non-rebreathing facemask. Owing to space constraints, we will focus on the two most common causes of respiratory distress in adults: bronchospasm due to asthma and COPD and pulmonary edema due to CHF.

Prehospital Management

Bronchospasm: COPD and Asthma

Bronchospasm as a cause for dyspnea is often suggested by the patient's medical history and current medications. Asthmatics and COPD patients often use inhaled β-agonists and corticosteroids and, in severe cases, also systemic agents. These patients tend to have frequent encounters with EMS and emergency departments. In addition to the clinical signs of dyspnea, wheezing and coughing are classic symptoms of bronchospasm. In extreme forms of bronchospasm, no breath sounds can be auscultated,

Table 73-3 Common Nontraumatic Causes of Acute Shortness of Breath in Adults

Exacerbated chronic obstructive pulmonary disease
Asthma
Cardiogenic pulmonary edema (congestive heart failure)
Noncardiogenic pulmonary edema (inhalational, sepsis-related)
Pneumonia
Pulmonary embolism
Foreign body obstruction
Aspiration

Adapted from Fowlkes TD: Shortness of breath. *In* National Association of EMS Physicians and Kuehl AE (eds): Prehospital Systems and Medical Oversight, Dubuque, IA, Kendall and Hunt, 2002, p 665.

resulting in a "silent chest." It has been a long-standing myth in EMS that patients with severe COPD should not receive high-flow oxygen to prevent respiratory arrest.[129] However, these patients often die as a result of hypoxemia and thus should be given the same oxygen therapy as any other patient in respiratory distress.

On-the-scene management for patients with asthma attacks or acute COPD exacerbations is very similar and follows the recommended guidelines.[134] Besides providing oxygen to prevent hypoxemia, the first line of treatment is inhaled β-agonists plus an anticholinergic agent such as albuterol or salbutamol plus ipratropium, either via nebulized aerosol or metered-dose inhaler. Often these patients will already have made extensive use of their inhalers before calling EMS, so in moderate to severe exacerbations the use of systemic corticosteroids, for example, an IV bolus of methylprednisolone, 60 to 125 mg, is clearly indicated. In life-threatening asthma and COPD exacerbations, IV β-agonists (epinephrine, 100-200 µg IV bolus—equals one tenth of the recommended resuscitation dose) are particularly helpful. In case of impending or actual respiratory arrest, endotracheal intubation is warranted, often after RSI with ketamine as the preferred induction agent owing to its favorable bronchodilating properties. The EMS crew must be vigilant for additional conditions that add to the severity of hypoxemia, such as pneumonia, pneumothorax, anaphylaxis, and pulmonary embolism.

Pulmonary Edema: Congestive Heart Failure

In addition to standard monitoring, a 12-lead ECG should be obtained to guide prehospital therapy for patients with acute pulmonary edema and rule out acute myocardial infarction. As a biomarker, brain natriuretic peptide (BNP) has become the mainstay in the clinical diagnosis of cardiogenic pulmonary edema, and some EMS systems now use point-of-care BNP testing on the scene to determine the cause of dyspnea.[132] Noninvasive positive-pressure ventilation (NIPPV) such as continuous positive airway pressure (CPAP) has become a standard therapy over the past several years in the treatment of acute pulmonary edema.[135] Recently published recommendations suggest NIPPV for every patient with acute pulmonary edema.[136,137] The subsequent therapy should be guided by the patient's systolic blood pressure (SBP):

- SBP greater than 140 mm Hg: NIPPV plus nitrates (nitroglycerin spray or continuous IV infusion; recommended starting dose: 5-20 µg/min)
- SBP 140 to 100 mm Hg: NIPPV plus nitrates plus diuretics (furosemide) if signs of systemic fluid retention
- SBP less than 100 mm Hg: hypoperfusion is predominant and signs of cardiogenic shock are present. These patients require inotropic agents such as dopamine and dobutamine and a carefully titrated volume challenge.
- Pulmonary edema with signs of acute coronary syndrome (ACS): these patients require ACS specific management in addition to NIPPV plus nitrates.[136]

The treatment goals are to stabilize the patient, improve oxygenation and perfusion, and reduce dyspnea.

Cardiac and Circulatory Emergencies

Chest pain and circulatory problems (e.g., syncope, hypertension) are encountered frequently in the prehospital setting (see Chapter 60). Much emphasis has been put on the role of EMS in the management of ST-segment myocardial infarction (STEMI), but other conditions such as pulmonary embolism, hypertensive emergencies, or dysrhythmias require a similar high quality of prehospital diagnostic and therapeutic skills. In this overview, we will focus on the most common emergencies resulting in chest pain—acute coronary syndrome (ACS) and pulmonary embolism—and also on hypertensive emergencies.

Patient Evaluation

The most important goal in evaluating a patient with acute chest pain or circulatory problems is to rule out a life-threatening condition such as ACS or pulmonary embolism. Because chest pain is a common complaint, identifying high-risk patients among all the patients with back spasm, esophageal acid reflux, or other gastrointestinal disorders is difficult. History and physical examination as well as a 12-lead ECG often guide the diagnosis. Prehospital 12-lead ECG can be quickly performed by the EMS crew and transmitted to physician oversight if required and prolongs on-scene time only 3 to 4 minutes while offering very high sensitivity and specificity for detecting myocardial ischemia and in particular for detecting patients with STEMI. Assessing the type and quality of chest pain (stabbing versus burning, radiation, severity, and provocation) is critical in determining the differential diagnosis (Table 73-4). However, some patients with ACS have atypical pain symptoms (epigastric discomfort, jaw pain) or no pain at all in case of silent myocardial ischemia in diabetic patients.

Prehospital Management

Acute Coronary Syndrome

Patients with acute coronary syndrome should immediately be put on continuous ECG monitoring in addition to blood pressure and oxygen saturation monitoring. Rapid access to a defibrillator is mandatory, especially for patients with STEMI. The most recent guidelines recommend starting supportive therapy on the scene consisting of morphine (pain control), high-flow oxygen, nitrates (if patient is not hypotensive), and oral aspirin, easily memorized as the well-known "MONA" acronym.[138,139] β-Blockers can be considered if the patient is tachycardic and/or hypertensive. The goal is to reduce myocardial oxygen demand while improving oxygen supply. The 12-lead ECG is a vital component of prehospital care for ACS because it is the only tool that can reliably identify patients who may benefit from prehospital reperfusion therapy (Fig. 73-4). The overarching goal is to limit myocardial ischemia time to less than 120 minutes (ideally <60 minutes). Early out-of-

Table 73-4 Differential Diagnosis of Acute Chest Pain in Adults

Acute coronary syndrome (unstable angina, myocardial infarction)
Pulmonary embolism
Gastroesophageal reflux
Peptic ulcer disease
Gastritis or esophagitis
Aortic dissection
Pericarditis
Pneumonia
Pneumothorax
Pleurisy
Boerhaave's syndrome (esophageal rupture)
Pancreatitis
Musculoskeletal pain

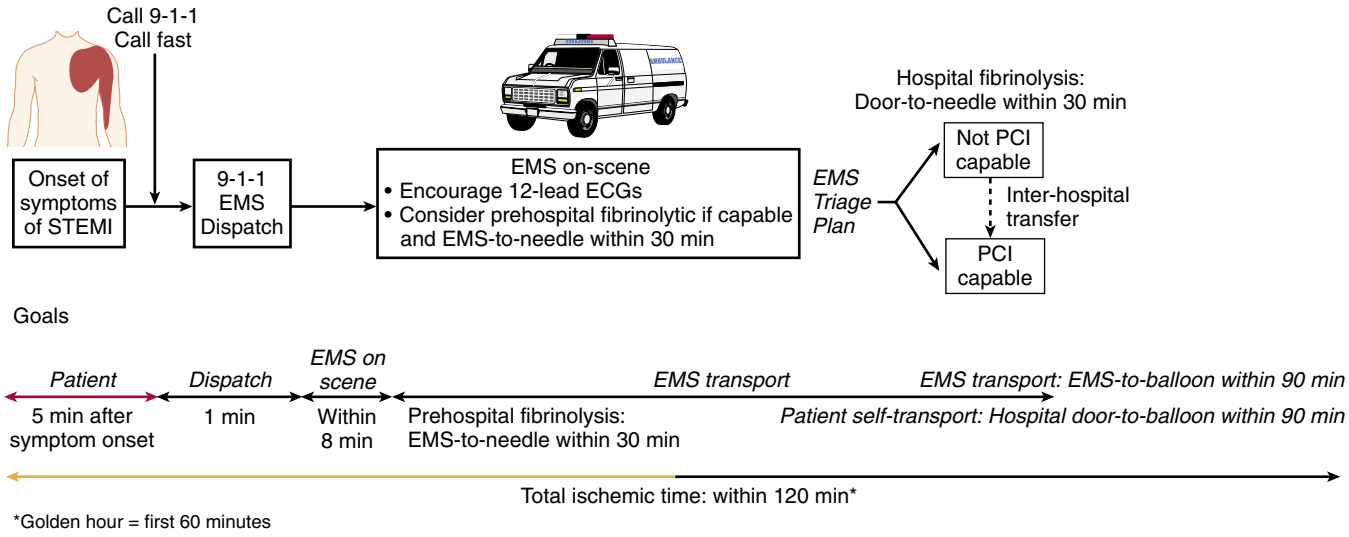

Figure 73-4 Prehospital management priorities in patients with ST-segment elevation myocardial infarction. ECG, electrocardiogram; EMS, emergency medical service; PCI, percutaneous coronary intervention; STEMI, ST-segment myocardial infarction. *(Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction]. J Am Coll Cardiol 44:e1-e211, 2004; and Armstrong PW, Collen D, Antman E: Fibrinolysis for acute myocardial infarction: The future is here and now. Circulation 107:2533-2537, 2003.)*

hospital fibrinolysis reduces mortality in patients with STEMI or new-onset left bundle branch block[140] and is the recommended standard for fibrinolysis-capable EMS systems.[138] Several fibrinolytic agents are available, and the choice is often based on the institution. Streptokinase was the first fibrinolytic agent but is now rarely used in prehospital care. Most EMS systems now use recombinant tissue plasminogen activator (rt-PA or t-PA) or modified forms of t-PA, such as reteplase or tenecteplase (TNKase). The latter offer convenient single- or double-bolus dosing, making them preferable fibrinolytic agents in the prehospital setting.[141] It is important to note, however, that fibrinolytic therapy has several contraindications (Table 73-5) and also carries the risk of intracranial hemorrhage, resulting in major disability or death in 1% to 2% of the patients. If fibrinolysis cannot be performed on the scene, rapid transport to a facility with percutaneous coronary intervention is warranted with the goal of EMS arrival-to-balloon time of less than 90 minutes.

Pulmonary Embolism

A definitive diagnosis of pulmonary embolism is difficult to establish on the scene because signs and symptoms are nonspecific and no rapid objective measure, such as the 12-lead ECG in STEMI, is available for on-site diagnosis. Often, the patient's medical history is telling; for example, an immobilized leg and signs of a preexisting deep venous thrombosis can be found, such as unilateral, tender swelling in one extremity. The severity of pulmonary embolism directly relates to the size of the clots and ranges from mild symptoms of dyspnea and coughing to acutely life-threatening states of cardiogenic shock due to acute right-sided heart failure. Classic symptoms of pulmonary embolism include distended neck veins, hypoxemia, tachycardia, tachypnea, and chest pain. More objective, but nevertheless unspecific find-

Table 73-5 Contraindications of Fibrinolytic Therapy in ST-Segment Elevation Myocardial Infarction

Absolute Contraindications
Any prior intracranial hemorrhage
Known structural cerebrovascular lesion (e.g., AVM)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head trauma or facial trauma within 3 months
Relative Contraindications
History of chronic, severe, poorly controlled hypertension
Severe uncontrolled hypertension on presentation (SBP > 180 mm Hg or DBP > 110 mm Hg)*
History of prior ischemic stroke < 3 months, dementia, or known intracranial pathologic process not covered in contraindications
Traumatic or prolonged (>10 minutes) CPR or major surgery (<3 weeks)
Recent (within 2 to 4 weeks) internal bleeding
Noncompressible vascular punctures
For streptokinase/anistreplase: prior exposure (<5 days ago) or prior allergic reaction to these agents
Pregnancy
Active peptic ulcer
Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

AVM, arteriovenous malformation; SBP, systolic blood pressure; DBP, diastolic blood pressure; INR, international normalized ratio.
*Could be an absolute contraindication in low-risk patients with myocardial infarction.
Adapted from American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 8. Stabilization of the Patient with Acute Coronary Syndromes. Circulation 112(24 Suppl):IV-89-110, 2005.

ings are new right bundle branch block, symmetric T-wave inversion in the anterior leads (V_1-V_4), and S_IQ_{III} pattern in the 12-lead ECG.[142] Often the 12-lead ECG is more useful to rule out other conditions as myocardial infarction than ruling in pulmonary embolism.

In absence of an objective means to reliably diagnose pulmonary embolism in the prehospital setting, the management is largely supportive. Applying standard monitoring, administration of high-flow oxygen, establishing an IV line, and pain control with opioid analgesics are considered standard therapy. In severe pulmonary embolism that is usually accompanied with systemic hypotension (SBP < 90 mm Hg), in other words with signs of shock, circulatory support with inotropic agents is often required. The prehospital use of heparin in pulmonary embolism is not universally recommended and must be determined on a case-by-case basis, taking into account the likelihood of pulmonary embolism and the severity of symptoms. Prehospital fibrinolysis in a patient with pulmonary embolism is not recommended, although it has been successfully used in extremis.[143]

Hypertensive Emergencies

EMS often responds to patients with acute hypertensive episodes, but these are rarely true hypertensive emergencies. The classification of hypertensive episodes is very helpful in determining the urgency of a prehospital intervention (Table 73-6). Acute end-organ damage in conjunction with a hypertensive episode, such as hypertensive encephalopathy, stroke, pulmonary edema, myocardial infarction, aortic dissection, acute renal failure, and preeclampsia must be immediately treated and progression must be stopped. The goal is to lower the blood pressure by 20% to 25% within 30 to 60 minutes.[144] However, in the setting of cerebral infarction, great care must be exercised in reducing blood pressure as needed because the ischemic territory may be critically dependent on collateral perfusion pressure; this is an area of controversy in need of further study. Evidence for benefits of antihypertensive treatment is scant; some argue that only excessively high SBP or diastolic blood pressure (DBP) should be treated.[145] On the other hand, patients with an aortic dissection require swift and aggressive treatment with a target blood pressure of SBP less than 120 mm Hg and DBP less than 80 mm Hg.[146] The choice of antihypertensive should take into account the underlying pathophysiology. For example, patients with acute hypertension plus acute coronary syndrome and tachycardia might benefit from a β-blocker and nitroglycerin, whereas in intracranial hemorrhage labetalol is the preferred agent. The antihypertensive agent of choice in many European EMS systems, urapidil, an α-adrenoceptor antagonist, is currently not available in the United States.

Table 73-6 Classification of Acute Hypertensive Episodes

Hypertensive emergency	Also termed *hypertensive crisis;* hypertension with acute end-organ dysfunction
Hypertensive urgency	Hypertensive episode with high risk of imminent end-organ damage that has not yet occurred
Acute hypertensive episode	SBP > 180 mm Hg or DBP > 110 mm Hg without signs of evolving or imminent end-organ dysfunction
Transient hypertension	Related to anxiety or primary complaint

SBP, systolic blood pressure; DBP, diastolic blood pressure.
Adapted from Chobanian AV, et al: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42:1206-1252, 2003.

Altered Level of Consciousness

Altered level of consciousness is often encountered in prehospital care. The differential diagnoses are vast; therefore, most patients will receive only supportive care in the field. The overarching goal is to stabilize the patient's vital signs, quickly identify and treat potentially life-threatening conditions, and determine a likely cause.[147] For example, rapid detection of severe hypoglycemia in an unconscious patient can be assessed by point-of-care testing and reversed by administration of an IV glucose bolus. In this section, we focus on general principles but briefly mention a few specific conditions, such as stroke or seizure.

Patients with an altered level of consciousness should immediately receive high-flow oxygen and IV access, be undressed, and undergo standard monitoring. The addition of continuous capnography, when available, is helpful to assess adequate ventilation. Level of unconsciousness and determination of the GCS score should be performed (see Chapter 46). In the prehospital setting, it is often sufficient to distinguish if the patient is alert (responsive to verbal commands), only responsive to painful stimuli, or is completely unresponsive (unconscious).[148]

Because patients with impaired consciousness are at risk for aspiration, the need for airway protection needs to be assessed. Recommended diagnostic steps on the scene include determining the pupil size and reaction to light, measuring core body temperature, and obtaining point-of-care blood glucose levels. During the initial neurologic examination, EMS providers must determine if the main neurologic symptoms are global or if there is a focal neurologic deficit. Nasal or oral airways equipment may be inserted to keep the airway open and to test for a gag reflex. Once these basic steps have been accomplished, the EMS team should try to obtain as much information about the patient and the circumstances as possible to narrow the possible causes for the patient's unconsciousness (Table 73-7). Often, this can only be accomplished by involving bystanders and family members. Important aspects are onset and progression of unconsciousness (quick or over a few hours), fever, the patient's status before the onset of symptoms, headache, medical history and medications (e.g., hypertension, diabetes, depression), signs of intoxication (open drug containers, needles, drug paraphernalia), and signs of trauma.

For patients with *hypoglycemia,* the recommended treatment plan is to immediately administer dextrose ($D_{50}W$, 50 mL = 1 ampule). If an IV cannot be established, IM glucagon (1-2 mg) is a viable alternative. On average, blood glucose levels rise after this treatment between 100-150 mg/dL and patients are fully awake within a few minutes. In cases where *opioid overdose* is suspected (miosis, respiratory rate <10 breaths/min), the opioid antagonist naloxone should be administered. The recommended starting dose is 0.4 mg IV, but it should be titrated to clinical effect, which in this case is restoration of spontaneous ventilation and not complete awakening. A wide range of required dosages may be required, sometimes requiring as little as 0.2 mg and sometimes up to 10 mg.[148] If too much naloxone is administered,

Table 73-7 Causes of Altered Level of Consciousness in Adults: AEIOU-TIPS

Alcohol and Airway (hypoxia)
Epilepsy, Electrolytes, Encephalopathy
Insulin—hypoglycemia
Opioids/Overdose
Urea (metabolic)
Trauma, Tumor
Infection
Psychiatric
Shock, Subarachnoid hemorrhage, Snake bite

Adapted from Wolfe RE, Brown DFM: Coma and depressed level of consciousness. *In* Marx JA (ed): Rosen's Emergency Medicine. Philadelphia, Mosby, 2006.

severe opioid withdrawal symptoms can result. Similarly, if patients with benzodiazepine overdose ("sleeping pills") are treated aggressively with the antagonist flumazenil, generalized seizures can result that may be unresponsive to further benzodiazepine treatment. Patients with hypoglycemia or opioid intoxication comprise probably the only category of patients with an altered level of consciousness that can be successfully identified and treated in the field.

Only over the past decade, *stroke* patients have received similar attention in prehospital care as patients with acute myocardial infarction. It is now clear that a similar "window of opportunity" exists in stroke patients as in patients with acute myocardial infarction.[149] The goal is to quickly identify stroke in the field and rapidly transport the patient to a facility that can perform computed tomography (CT) to aid in diagnosis and rule out the presence of intracranial hemorrhage. Ischemic stroke without hemorrhage may be treated with thrombolysis. Classic symptoms of stroke are hemiparesis, aphasia, and altered level of consciousness. Formal prehospital screening tools such as the Cincinnati Prehospital Stroke Scale are useful and should be used.[150] Stroke is a leading cause of death in the United States and is the number one cause for disability in adults. Rapid identification and treatment of stroke limits brain damage and improves survival after stroke.[145,151] Because of the inability to clinically distinguish between ischemic stroke (85% of cases) and hemorrhagic stroke (15%), prehospital thrombolysis cannot be performed as in patients with STEMI. Thus, supportive care to stabilize the patient's vital signs and to avoid risk factors that negatively influence outcome, such as hypoxia, hypotension, and hyperglycemia are main treatment goals in stroke in the prehospital setting.[152] Therefore, stroke patients require supplemental oxygen, IV access, continuous ECG monitoring, as well blood pressure monitoring. Hyperglycemia should be corrected to normal levels. Blood pressure management in stroke patients is controversial; it is clear that any aggressive lowering of SBP worsens outcome and that a certain degree of hypertension in acute stroke might be beneficial. If other end organ dysfunction is apparent, such as myocardial ischemia, or SBP greater than 220 mm Hg, cautious antihypertensive treatment can be started on the scene. One of the most important aspects of prehospital care for stroke patients is the expeditious transport to a facility that specializes in stroke treatment, ideally a stroke center.[153]

Seizure is a common disorder seen in EMS practice. Often, the seizure is over when EMS arrives and the patient will be found in a post-seizure state that seldom requires intervention. If the seizure is ongoing, however, the seizure may be usually treated by the IV administration of benzodiazepine and prevention of secondary complications such as hypoxia. IV access is difficult to establish during a generalized seizure. High-flow oxygen should be administered via a non-rebreathing facemask. Status epilepticus is a state of ongoing, refractory general seizure activity and is a true life-threatening emergency; sometimes treatment requires induction of general anesthesia.[154]

Pediatric Emergencies

Pediatric emergencies are one of the biggest challenges for a prehospital provider (see Chapter 82). Between 5% and 8% of emergency calls to an EMS are pediatric emergencies.[155,156] In the first years of age, common pediatric emergencies are respiratory problems and febrile seizures. Trauma increases in incidence in higher age groups.[155] Some of the skills, such as securing the airway and vascular access, are more difficult to perform for EMS providers in children than in adults.

In this section, the main differences in etiology, diagnostic procedures, and treatment are stressed and the chief symptoms and their relevance in the pediatric population are discussed.

Dyspnea/Respiratory Distress

Respiratory failure is the leading cause for cardiac arrest in children. The anatomy of the airway and the smaller respiratory reserve due to a smaller residual capacity as well as a higher basal metabolism make children more vulnerable to hypoxic events. Infections or an obstructed airways by foreign bodies dominates the respiratory problems in younger children; in older children the airway problems are usually due to direct trauma or altered level of consciousness after head trauma or shock.

Patient Evaluation

Assessing the child may be more difficult if the child is frightened. An agitated child interferes with many diagnostic procedures, and the resultant stress level increases oxygen consumption, potentially leading to a decompensation of the situation.

After assessing the airway, the work of breathing is estimated. Physical signs and symptoms indicating respiratory distress are tachypnea and intercostal, sternal, and subcostal retractions. Children use accessory muscles to support breathing, which may manifest as head bobbing and nasal flaring. An early sign of distress is use of chest wall muscles. Paradoxical breathing movements of chest and abdomen (see-saw respiration) indicate decompensated respiration. Abnormal sounds from the airway pinpoint the level of airway obstruction. Inspiratory stridor indicates an extrathoracic airway problem. In contrast, expiratory noises are signs of lower tracheal problems, whereas wheezing leads to a problem at the bronchial level. Hypoxia can cause vasoconstriction, and cyanosis can be masked by skin pallor. Pulse oximetry should be mandatory in respiratory distress.

Prehospital Management

Pediatric respiratory support may include facemask with supplemental oxygen, assisted bag-mask-valve ventilation, or controlled ventilation with a secured airway. Because of the different anatomy dependent on the age of the child and the limited skills in most nonanesthesiologist prehospital providers, difficulties in airway management occur more often than in adults.

Infection: Asthma

Laryngotracheobronchitis (croup) is a typical emergency of the 6-month- to 3-year-old child. Because of the dramatic onset, usually during the night with sudden loud inspiratory stridor and sometimes respiratory distress, it frightens both child and parents. Except for a minor infection of the upper respiratory tract, the medical history is usually noncontributory.

On-the-scene management of mild croup (without retractions) consists of psychological support by the EMS team, humidified oxygen via facemask in a nonthreatening manner, and transport to a pediatric emergency department. More severe cases with retractions and/or neurologic signs such as apathy or agitation require oral dexamethasone (0.15-0.6 mg/kg) and, as a next step, nebulized epinephrine (0.5 mL of 2.25% racemic epinephrine or 5.0 mL of epinephrine 1 : 1000, irrespective of the weight of the child).[157] The need for prehospital intubation is rare.

Another pediatric infection of the upper airway is much more dangerous but fortunately very rare: epiglottitis. Epiglottitis usually occurs in patients age 2 to 7 years and is characterized by inspiratory stridor, hypersalivation, high fever, and inability to swallow. The voice sounds muffled. Any anxiety-provoking maneuvers such as examination or IV access should be avoided. The child should be attended at all times by someone capable of establishing an airway and brought to a facility where endoscopy can be done. Cricothyroidotomy may be necessary in very severe cases.[158]

Bronchospasm is a frequent symptom in pediatric respiratory infections. Therapy ranges from supportive therapy only in mild cases to inhalational β-adrenergic agonists and corticosteroids and intravenous drug therapy sometimes requiring anesthesia and intubation in status asthmaticus. Ketamine is the anesthetic drug of choice in exacerbated bronchospasm.

Foreign Body Airway Obstruction

Foreign body airway obstruction is characterized by the sudden onset of respiratory distress associated with coughing, gagging, or stridor in a child with no other signs of illness.

If the child is coughing effectively, then no immediate action to remove the foreign body by the EMS is necessary. The child is monitored and brought to the hospital and advised to try to expel the foreign body by coughing. If the coughing becomes ineffective, intervention is required. With a series of back blows (5) in turn with thrusts (abdominal in children >1 year and chest thrusts in infants <1 year of age) attempts are made to remove the foreign body. If the child becomes unconscious, standard BLS must be started[159] and the airway must be rapidly checked with direct laryngoscopy. If the foreign body cannot be removed, an effort can be made to advance the foreign body into the bronchus and ventilate the remaining lung.

Cardiac Emergencies and Shock

Life-threatening cardiac rhythm disturbances in children are more frequently the result, rather than the cause, of acute emergencies. Nevertheless some arrhythmias are seen, especially in children with congenital problems.

Patient Evaluation

After assessing consciousness, airway, and breathing, the circulatory status is determined. Heart rate, pulse quality, and capillary refill time are quick tools for evaluation. Blood pressure and preload assessment complete the picture. To determine if the child is already decompensated, additional information of the neurologic status (apathetic or agitated) is taken into account.

Prehospital Management

Arrhythmia

Bradyarrhythmia is usually the result of hypoxia or poisoning. If the heart rate is below 60 beats/min and the child shows signs of inadequate perfusion (unconsciousness, apnea), resuscitation is started and the underlying cause can then be identified and reversed.

Most tachyarrhythmias are supraventricular and need only be treated if decompensated. After exclusion of causes for a reflex tachyarrhythmia, specific therapy starts with vagal maneuvers, adenosine, and, if the child is severely decompensated, cardioversion.

During resuscitation, epinephrine (10 µg/kg), atropine (0.02 mg/kg), and amiodarone (5 mg/kg) are given according to international guidelines (see Chapter 97).[160]

Recurrent ventricular tachycardia/ventricular fibrillation in an otherwise healthy child or a torsades de pointes pattern on an ECG suggests a long-QT syndrome, which follows a different path in the universal algorithm of resuscitation. In a long-QT syndrome, amiodarone is contraindicated and magnesium is given as a bolus (3-12 mg/kg).[161]

Shock

Hypovolemic shock due to acute blood loss or acute diarrheal disease is the most common type, followed by septic, cardiogenic, and distributive shock.[162,163]

Obtaining quick vascular access in a decompensated situation is essential, but difficult. Venous access is the first choice; but if it cannot be rapidly established, intraosseous access is the next alternative. Intraosseous access provides a quick and reliable venous access, adequate for all IV medications. An initial fluid bolus of 20 mL/kg of fluid should be given. Crystalloids are preferred.[164] After reassessing the child, a second bolus can be given. If shock persists after the second reassessment, packed red blood cells should be administered, especially in trauma victims, which usually can only be done in the emergency department.[159] This requires rapid transport to the nearest hospital and minimizing on-scene times.

Altered Level of Consciousness

Altered level of consciousness is one of the first signs for a decompensation of a respiratory or circulatory failure. Besides that, disorders of the brain (infection, ischemia, trauma, intoxication, metabolic disorders like diabetic coma, hepatic or nephrologic problems and tumors) will alter the level of alertness.

Patient Evaluation

After evaluation of the respiratory and circulatory status, a quick neurologic assessment should be made. The GCS examination is adapted to the age-related abilities of the child.[165] Especially, the

motor quality of the GCS has a good predictive value for the outcome after traumatic brain injury.[166] In unconscious children, the repeated assessments of the pupils can give information about intracranial injury and/or elevated intracranial pressure. Blood glucose measurement is mandatory.

Prehospital Management

Infection

If signs of meningeal irritation are seen, bacterial meningitis accounts for roughly 30%, whereas viral or aseptic meningitis is the cause in approximately 13% of cases. Other diagnoses are pneumonia (8%), other serious bacterial infections (2%), upper respiratory tract infections or other self-limiting diseases (46%).[167] Independent predictors of the presence of bacterial meningitis obtained from a patient's history and physical examination are the duration of the main complaint, a history of vomiting, and meningeal irritation, cyanosis, petechial bleeding, and altered consciousness at physical examination.[168] Identifying this potentially life-threatening disease is an important challenge for the prehospital provider. Airway management and fluid resuscitation may be necessary before transferring the child to a pediatric emergency department. If the diagnosis of bacterial meningitis is confirmed, antibiotic prophylaxis of all persons having had direct contact with the patient is necessary.

Seizures

Febrile seizures are the most common seizure disorder in childhood, occurring in 2% to 5% of children, typically between the age of 6 months to 5 years.[169] Usually the seizure has already terminated when the EMS team arrives and the patient is postictal. An antipyretic therapy may prevent a recurrence of the seizure.

To rule out other underlying conditions for a seizure, such as hypoxia, intoxication, infectious reasons, metabolic disorders, trauma, or sunstroke, the child should be hospitalized after stabilization of the vital signs. If seizures recur or are still ongoing (status epilepticus) the initial assessment should follow the ABC principle. High-flow oxygen should be given and blood glucose should be tested. For those children in whom intravenous access can immediately be established, lorazepam, 0.1 mg/kg, should be given intravenously. If a rapid IV access is not possible, diazepam (0.5 mg/kg) is given rectally. If after 10 minutes the initial seizure has not stopped or another seizure has begun, a second dose of lorazepam (0.1 mg/kg) should be given.[170] The child has to be repeatedly reassessed to verify that an unrecognized underlying cause has not been missed. During transport, epileptogenic maneuvers should be avoided, such as overzealous papillary examination with a strong light.

Trauma

Trauma is a leading cause of death from the ages 1 to 18. Boys are more at risk than girls are.

Patient Evaluation

Although the pattern of injury differs from that of the adult patient (more pelvis, chest, abdominal, and head trauma) the evaluation and the treatment principles are in accordance with the adult management guidelines.

Prehospital Management

Carrying out a quick primary survey, treating the life-threatening conditions according to the ABCDE approach, and organizing the communication and quick transport to an adequate facility are the main issues of trauma treatment of children.

The Abused Child

Child abuse is common and a major challenge for prehospital providers (see Chapter 82).[171] Typical injuries include evidence of injuries of different ages, atypical burns, abrasions and hematomas reflecting the form of the beating hand or instrument, shaken baby syndrome, and injuries at unusual locations and on the top of the head. A delayed or inconclusive patient history should arouse suspicion. A management goal is to guarantee the well-being of the child. In suspected cases of child abuse, the appropriate authorities are informed, depending on the local system, and the patient is transferred to a hospital or another safe facility.

Prehospital Mass Casualty Incident Management and Disaster Medicine

Prehospital providers are often faced with situations such as multiple vehicle accidents where the number of simultaneous patients initially exceeds the capabilities of the rescue squad or local rescue forces. This creates an inadequate ratio of rescuers to victims. In these mass casualty situations (Table 73-8; see Chapter 74), the concept of *triage* must be employed: trying to save as many patients as possible without being able to provide individual one-on-one care. During the mass casualty event, the boundaries between an emergency, a major incident (mass casualty situation), and a disaster are constantly in a state of flux. The first and most important duty of the first prehospital team at the scene is to communicate the dimension of the accident/disaster and the ongoing hazards to the dispatcher. A mass casualty situation creates many problems for EMS providers. Frequent errors included having multiple communicators on site (38%), misidentifying the number of victims (56%), and having unclear information for the resource physician (43%).[172] It has been estimated that prehospital triage information was deemed appropriate in only one third of mass casualty events. After alerting local backup resources, patients must be triaged.

In man-made and natural disasters, prehospital providers and their EMS systems have to shift their triage methodology from a daily operational framework of treating the most severely injured patient first and providing the highest level of care for each patient to the concept of providing the greatest good for the greatest number of casualties. This shift is necessary to identify those critically injured patients who can benefit from immediate, lifesaving interventions and to conserve resources.[173] In disasters such as hurricane Katrina, coordination of the rescue and relief effort on a national level is required. National disaster resources such as DMAT (disaster medical assistance teams) from unaffected states will be deployed as will be military forces (National Guard).

Table 73-8 Definitions in Disaster Medicine

Term	Definition	Level of Prehospital Medical Care Possible	Examples
Emergency	Incident that demands urgent action; impact: minutes to hours	Individual medicine	Patient with bicycle accident, stroke, angina
Mass casualty	Large number of casualties in a short period that initially exceed local logistic support capabilities; impact: hours to days	Triage; increasing level of medical treatment dependent on resources	Airplane crash, train collision, mass poisoning
Disaster	Large number of casualties and destroyed infrastructure; exceeds local response capabilities. Supraregional (national) forces are needed to solve the problem; damage and interruption last long-term (weeks to years)	Triage; first aid; significant delay until professional medical help available usually only after temporary infrastructure was set up	Hurricane, earthquake, tsunami, nuclear disaster (e.g., Chernobyl)

Different triage strategies (Simple Triage and Rapid Treatment-START, CareFlight Triage, modified START) show comparable results in identifying the severely injured (Table 73-9). Triage implies constant reevaluation of victims because conditions of the victims and of available resources change continuously.[174] Patients whose injuries are so grave (i.e., traumatic cardiac arrests) that their prognosis is dismal should not be classified as critical in the setting of a large mass casuality incident (MCI). They are likely to consume large quantities of resources in a futile resuscitative effort.[175] The motor score of the GCS and systolic blood pressure show good association with severe injury.[175] The emergency physician on the scene has to guarantee that the treatment priorities are followed by the EMTs rather than treating patients by himself or herself.

In the first phase, only BLS, such as opening the airway, recovery position, tourniquets, and positioning, should be done. Advanced procedures such as IV access, oxygen therapy, anesthesia, intubation, and ventilation can be performed as soon as resources are available. With incoming transport capacity, patients are stabilized and transported according to urgency priorities. For example, patients with intra-abdominal bleeding requiring emergent surgery have the highest transport priority. For disposition of the patients to adequate hospitals, a quick registration and documentation stage is necessary.

Table 73-9 Triage Groups in Mass Casualty Incidents

With the aid of triage tags or colored flags the patients are sorted into four groups:		
Green/minor	Minor injuries with no immediate need of treatment; psychological support needed; patients can walk	Wounds, minor fractures
Yellow/delayed	Urgent treatment, no vital threat	Fractures, joint injuries, amputation, major blood loss, burns
Red/immediate	Immediate vital threat	Respiratory insufficiency, shock, brain trauma, burns with immediate vital threat, abdominal trauma
Black/expectant	Dead or moribund	Respiratory arrest, cardiac arrest, head injuries with dismal prognosis

Controversies in Prehospital Emergency and Trauma Care

The EMS literature is full of conflicting opinions and recommendations about what the ideal EMS system and the ideal level of prehospital care are. The plethora of differing opinions is likely due to the vast differences in how EMS systems are organized around the world and probably also to a lack of reliable evidence from high-quality research. In the United States, one of the most important documents ever written on the current problems in EMS, *The Future of Emergency Care: Emergency Medical Services at the Crossroads,* was published in 2007 by the Institute of Medicine of the National Academy of Sciences.[12] It is the third part of a comprehensive study on the state of emergency medicine in the United States that also includes in-hospital emergency medicine[176] and pediatric emergency care.[177] It is likely that this report will have a similar effect on EMS as did *The White Paper* published in 1966.[11] Here, we focus on those areas in prehospital care engendering the fiercest debate and where anesthesiologists could, in our opinion, make the biggest impact.

The Optimal Level of Prehospital Care: BLS Versus ALS or "Scoop-and-Run" Versus "Stay-and-Play"

Numerous articles have been published over the past decades favoring either a minimalistic approach to prehospital care, basically BLS level only, or the opposite, an aggressive strategy trying to bring the level of care in an emergency department to the scene. In our opinion this discussion is misguided. It is unlikely that a country that currently employs a paramedic-level EMS system will abandon this system in favor of a BLS-only system or vice versa (see Chapter 97). More importantly, this discussion leads away from the most important determinant of the overall efficacy and efficiency of any EMS system: the outcome of the

patient. Whereas it makes perfect sense to argue in favor of a minimalistic prehospital approach in young patients in severe hemorrhagic shock after penetrating torso trauma in an urban area with transport times of only a few minutes,[119,125] the same approach might be detrimental in rural areas with long transport times, an older patient population with significant comorbidities, and a predominantly blunt trauma mechanism.[178-180] Therefore, in our view, it is overly simplistic to strongly argue for one or the other system. The condition of the patient, the environment, and the setting should determine the adequate EMS response and level of treatment. However, a well-trained physician or paramedic can easily "downgrade" his or her level of response on the scene and rush the patient to the hospital, whereas a basic level EMT cannot "upgrade" his or her response if required by the nature of the emergency.

A similar discussion is going on between advocates of paramedic-based EMS models and physician-based models.[14,94] Again, this is more a theoretical discussion about advantages and disadvantages of the two different systems rather than a realistic option for change. The discussion shows, however, the impact well-trained physicians and, in particular, anesthesiologists, can have on patient outcomes when directly involved in prehospital care.[8,19,181] Airway management immediately comes to mind.

Prehospital Endotracheal Intubation and Rapid-Sequence Induction

This area might be the one where the clearest difference between an anesthesiologist-run and a paramedic EMS system materializes. Success rates for out-of-hospital endotracheal intubation performed by paramedics are unacceptably low compared with standards in the operating room and are associated with a high complication rate.[182,183] More than 15 studies have shown that prehospital endotracheal intubation and RSI by paramedics are associated with an increased mortality rate or poorer neurologic outcomes compared with patients who were not intubated.[66,67] Most of the studies focused on prehospital airway management in patients with severe traumatic brain injury,[111,184,185] but also studies investigating prehospital pediatric intubation delivered sobering results.[186-188] These results should serve as a wake-up call among anesthesiologists, especially in the United States, but so far they have failed to do so. The central question is: why are endotracheal intubation and RSI, procedures that many consider the standard of care and lifesaving, associated with worse outcomes when performed in the out-of-hospital setting? The reasons are manifold, but over the past several years research has shown that not only is airway management in the field much more challenging and difficult than in the hospital[70] but also that paramedics and many nonanesthesiologist physicians are inexperienced in airway management and fail to maintain their airway skills learned during training because the actual numbers of intubations performed per year are very small.[61,65,67,189,190] Less experience equals more intubation attempts, a more frequent complication rate, including severe hypoxemia and bradycardia during field RSI and airway management, and a higher rate of failed intubations.[67,68,84,111,191] Unbeknown to many anesthesiologists, paramedics require only five successful endotracheal intubations in a clinical setting to graduate and not a single pediatric intubation, numbers that are significantly lower than any medical specialty training such as anesthesiology or emergency medicine.[66,67] Even in the landmark paper on out-of-hospital pediatric intubation by Gausche and colleagues,[188] paramedics who were previously not trained in advanced pediatric airway management received only 6 hours of classroom training including manikin intubations but not a single live intubation in a pediatric patient! Taken together, it appears that there is currently a great unmet need for our specialty to reach out to nonanesthesiologist airway providers and help define the ideal strategy for prehospital airway management focusing on the infrequent, occasional "airway manager." It may be the case that endotracheal intubation and RSI as a standard of care need to be reassessed with a clearer vision of to whom this standard applies. Perhaps, alternate airways are safer and more efficient for EMS personnel who lack the necessary training or who cannot maintain their skills.

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David Baker*

74 Chemical and Biological Warfare Agents: The Role of the Anesthesiologist

Key Points

1. The management of injury from chemical and biological warfare (CBW) is a continuing process from the site of release of noxious agents to the hospital. The anesthesiologist may be involved at all stages in the provision of essential early life support through intensive care unit care.
2. CBW management requires advanced life support and other specialized skills that are part of the anesthesiologist's sphere of operation.
3. CBW injury should not be approached in isolation from the many clinical lessons that already exist from accidental hazardous materials (HAZMAT) releases and natural epidemic infections. CBW release poses a risk to the medical responder, and he or she should be trained and equipped to operate safely in a contaminated or infected zone.
4. Chemical and biological hazards form part of a continuous hazard spectrum. Agents from different parts of the spectrum may have common effects on susceptible somatic systems. Because detection of a released agent may not be immediate, response should be based on presenting signs and symptoms and may require the provision of life support.
5. Each hazard in the spectrum has four key properties: toxicity, latency, persistency, and transmissibility. The first two determine the management of the patient, and the second two determine the management of the incident.
6. A wide range of potential hazards (often loosely described as threats) have been suggested in a climate of apprehension because of the possibility of terrorist attack. On the basis of preexisting military and intelligence information, these potential hazards can be refined down to provide a framework of genuine hazards and management protocols that can be applied across the hazard spectrum.
7. CBW agents should not be regarded medically as weapons of mass destruction (WMD); rather, they are agents that may cause mass injury. Early life support and specific therapy can break the link between mass injury and mass loss of life.
8. Most of the toxic hazards likely in civil life are part of the United Nations HAZMAT classification. Planning for accidental industrial releases is relevant to the management of deliberated CBW release.
9. Toxic agents have been used in military and civil releases over the past 30 years and currently should be regarded as a potential terrorist threat.
10. Management of exposed patients depends on the protection of medical responders, early provision of life support, and specific antidote and antimicrobial therapy. Decontamination of patients may cause delays in starting treatment and is not always necessary. Essential life support (TOXALS) should be given during decontamination if required. Mass ventilation capability in the hospital is important in the management of accidental and deliberate respiratory failure from chemical and biological causes.
11. Military chemical warfare agents, such as nerve agents, vesicants, pulmonary edemagens, cyanides, and certain toxins, pose the greatest hazard in civil releases. Many industrial chemicals are equally hazardous.
12. Classic biological warfare agents, such as anthrax and plague, are used in deliberately induced epidemics with far longer latencies than chemical warfare attacks. Anesthetic involvement is usually at the intensive care stage.
13. Lessons learned from the current fears of deliberate toxic release will have value for the management of the increasing number of accidental individual and mass toxic exposures that form the greater risk for human life in the 21st century.

*The views expressed in this chapter are those of the author and do not necessarily represent those of SAMU de Paris or the United Kingdom Health Protection Agency.

Until more recently, the effects of exposure to chemical and biological warfare (CBW) agents were a remote area of clinical practice, which concerned military specialists, microbiologists, and toxicologists. Since the World Trade Center attack in New York City in September 2001, there has been increased concern about the possible impact of CBW agents released by terrorists on a civilian population. The attacks in London in July 2005 involved the use of high explosive devices in a confined space. There were toxic effects, and the use of a chemical device by the terrorists was considered by the emergency responders. Anesthesiologists from the helicopter emergency service were among the first to treat the injured on site.[1] With the continuing real threat of the use of CBW agents by terrorists, anesthesiologists have become more involved in the prehospital and hospital management of CBW injuries. As a result, CBW casualty management, previously dominated by considerations only of toxicity and pathogenicity, now includes considerations of modification of outcome by provision of early and continuing life support.

This chapter discusses the anesthetic aspects of management of casualties involving injury or infection after a deliberate exposure to CBW agents. There are important lessons for management of CBW incidents from plans for accidental toxic releases. In some countries, anesthesiologists are part of the initial emergency medical response and are trained in the essentials of personal protection and decontamination.[2] They also may be involved in the initial reception of contaminated casualties at the hospital itself, particularly when autoreferral occurs.[3] Casualties with toxic injuries also may have conventional injuries requiring surgery, and this brings a whole new dimension to the management of operative anesthesia, modified by the effects of a toxic agent. Finally, many of the victims of a CBW attack require immediate and long-term ventilation and other intensive care, which is an area where anesthesiologists and intensivists are actively involved.

In this chapter, the nature and management of chemical and biological hazards are approached first by considering their definition and classification, and second by discussion of the properties of key representative agents in terms of pathophysiologic effects. There is a wide range of potential CBW hazards that have been the subject of exhaustive literature, and it is not the intention here to repeat specialized information. Instead, key features of representatives of various classes of hazard are discussed from the standpoint of anesthetic and intensive care practice. Finally, the practical aspects of the involvement of the anesthesiologist and intensivist in management of CBW agent release are considered. This discussion covers the management of the patients and safe operation during the incident, including detection of release, protection of responding personnel, and decontamination.

Nature of Chemical and Biological Warfare Hazards

Approaches to the Literature

Many different scientific and clinical specialties have been involved in the study of CBW for more than a century. The literature is very extensive and covers a wide clinical range. Of the specialties involved, toxicology, microbiology, and occupational health have been the most dominant and have left their particular influences. Much of the literature relevant to CBW agents predates the Medline era and is not readily accessible from this source. Many reviews and books exist, however, particularly in the exhaustively studied area of cholinergic transmission, which make the careful and relevant work of early researchers still accessible to modern anesthesiologists.[4-10] The reader is advised to consult these resources to gain a working background on the nature of CBW agents.

Evidence-Based Studies

The study of CBW agents in humans has been less extensive than human studies in other areas of clinical medicine. This is understandable because prospective studies that involve exposure of human subjects either willingly or otherwise have been strictly controlled or proscribed by international convention. There is a large amount of information in the literature, however, from early clinical volunteer studies and from accidental exposures to chemical warfare agents, and many unpublished or inaccessible reports are now openly available.[8] In the biological warfare field, there also are more recent reviews[11-13] and valuable continuing clinical study in the parallel field of accidental (rather than deliberate) infection together with literature on the development of antimicrobial and antiviral agents, which is of immediate relevance to biological warfare release.

Secrecy

Although considerable information about the pathophysiology and management of CBW cases exists in the open literature, it is highly likely that far more information is still classified by governments involved in the subject and is not easily accessible.[8] Nevertheless, much historical information is available from time-declassified government sources[14] and from searching the sources provided by the Freedom of Information Act in the United States. Other nongovernmental organizations, such as Stockholm International Peace Research Institute (SIPRI), also have published extensive information, although this information may have a certain political bias.[15] The most research on CBW agents was carried out by the Soviet Union (USSR) during the Cold War, and large amounts of this remain unpublished. Soviet scientists involved in programs such as Mikrobioprom[16] and the application of genetic engineering to CBW did publish many articles on techniques openly, however, and these can be readily accessed through the databases because the major part of the Soviet program started after the signing of the 1972 biological warfare treaty,[17] which led to the discontinuation of biological warfare research by the West.

Definitions

Classic Definitions of Chemical and Biological Agents

The accepted classic definition of a chemical warfare agent is a chemical substance that is intended for use in military operations to kill, seriously injure, or otherwise incapacitate humans through pathophysiologic effects.[18] Traditionally, riot control agents and herbicides were excluded from this definition, although they frequently have been used in a way that would be compatible with the definition of a chemical warfare agent. Biological agents were defined by the 1972 biological warfare treaty as living organisms,

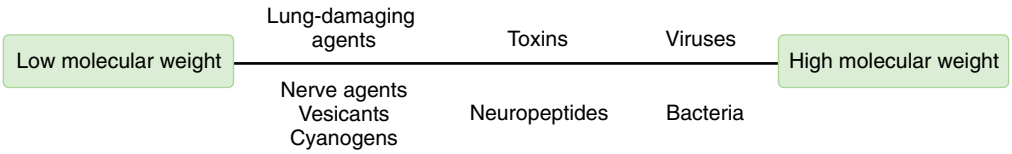

Figure 74-1 The chemical-biological hazard spectrum. Agents originally classified as chemical or biological are arranged in order of ascending molecular weight. Toxins, originally classed as biological agents, occupy the middle of the spectrum, together with neuropeptides, which normally act as transmitters in the central nervous system. These agents, sometimes called agents of biological origin, can be synthesized using genetic engineering techniques. (Adapted from Baker DJ: Anesthesia in extreme environmental conditions,. Part 2: Chemical and biological warfare. *In* Grande CG [ed]: Textbook of Trauma Anesthesia and Critical Care. St Louis, Mosby-Year Book, 1993, p 1331.)

whatever their nature, or infective material derived from them, which are intended to cause disease or death in humans, animals, or plants.[17] Toxins, which are an essential part of the pathophysiologic process in bacterial infection, were excluded from the biological warfare treaty and are regarded essentially as chemical agents.

Chemical-Biological Hazard Spectrum

Although chemical and biological agents traditionally have been separated, it is appropriate medically to regard them as part of a continuous spectrum of hazards[19]; this is shown diagrammatically in Figure 74-1. Agents in Figure 74-1 are arranged in ascending order of molecular weight from chemical toxic agents on the left to self-replicating agents such as bacteria and viruses on the right. The spectral approach to hazards is useful in emphasizing that agents from different parts of the line act in a similar way on the body. The failure of the neuromuscular junction caused by nerve agent anticholinesterases and botulinum toxin is a good example. Bacteria exert their toxic effects through toxins that may affect various somatic systems. The spectral approach serves as a reminder that medical management of CBW injury should respond primarily to system dysfunction, rather than to specific etiologic factors.

Essential Properties of Chemical and Biological Warfare Agents

There are four essential properties of hazards within the CBW spectrum: toxicity, latency, persistency, and transmissibility.[10] These four characteristics are common to chemical and biological agents, and determine the degree of risk and the appropriate response. Toxic effects of CBW agents seem to have a specific latent period. Generally, chemical agents and toxins have short periods of latency before the appearance of specific signs and symptoms. In contrast, classic biological warfare agents have extended latency periods (usually familiar as incubation periods) before the effects of the induced disease begin to appear.

Persistency relates to the ability of a toxic agent to remain in the environment into which it has been released and is a function of the physicochemical properties of the agent. For chemical agents, the persistency may vary, but for most biological warfare agents, with the exception of spore-forming agents such as anthrax, persistency is usually very short. Finally, transmission of a hazard may occur as a result of the physical contamination of the victim owing to a persistent chemical agent or as a result of infection in the case of an airborne agent. Chemical transmission can be contained by decontamination, but biological warfare agent transmissibility is more difficult to control because of continuing activity. Toxicity and latency determine the management of the casualty, whereas persistency and transmissibility determine the management of an incident involving the release of a CBW agent.

Toxicity and Its Modifications

Toxicity is usually expressed in terms of median lethal dose (LD_{50}) or LCt_{50}, where C is the concentration of agent inhaled for the time (t) required to produce lethality in 50% of the exposed population. LD_{50} usually relates to toxicity via injected routes. In the case of most chemical agents, the inhaled route is usual, so expressions of concentration and time are used.

Haber defined a *lethality coefficient* as follows:

$$W = C \cdot t$$

where C is the inhaled concentration of toxic agent, and t is the time of exposure. In practice, the absorbed amount of agent depends on the respiratory minute volume of the exposed individual. This is just one factor modifying the expression of toxicity. Others include life support responses in the case of respiratory failure and the effects of antidotes. The reader is referred to specialized texts for a more detailed discussion.[8]

NBC Classification

Since the end of World War II, nuclear, biological, and chemical weapons have by convention been classified together as "NBC" agents, which gave rise to a new subsection of warfare that was developed by both sides during the Cold War. Although all three components are "toxic," necessitating the development of detection, protection, and decontamination, the classification ignored the very intense level of physical damage caused by nuclear explosions. In more recent years, the term *weapons of mass destruction* (WMD) has been applied to NBC agents, although the term was originally used by the United Kingdom at the end of World War II.[14] The term *NBC* has been altered more recently to reflect the threat perception from the use of explosive devices that can spread radioisotopes (rather than create them as in a fission process) into chemical, biological, radiologic, and nuclear hazards. CBW agents are defined by their effects after mass release on large populations. The term *chemical and biological warfare* is not usually applied to the use of such agents for individual or small group poisonings, although agents have been used in assassinations in this way.

Myth and Reality of Chemical and Biological Warfare Agents as Weapons of Mass Destruction

At the end of World War II, the Tizard report[14] appeared, which looked at the future potential of nuclear and biological weapons, both of which had been used during the war. The term *weapons of mass destruction* apparently was used for the first time in this report because it seemed that both agents would cause mass loss of life. Chemical weapons were added to this group during the 1950s when the equilibrium of international power depended on analysis of the possession of the three WMD agents. In retrospect, the WMD classification is (at least medically) inappropriate. Consideration of the events of World War II showed that nuclear weapons should be classified with conventional weapons systems that cause mass loss of life and destruction to material and the environment, such as the conventional high explosive and fire bombing of Germany in the latter part of the war.

Civil Toxic Hazards (Hazardous Materials)

Parallel to the definitions of CBW agents, there is a classification of hazardous materials (HAZMAT) used in everyday industrial life. HAZMAT are usually released by accident. Many are as toxic as chemical warfare agents. Such toxic substances classified as HAZMAT are covered by the United Nations convention controlling the use and transportation of such materials.[20,21] HAZMAT are defined as materials that cause mass injury and death if released from a confined state. The civil equivalent of biological warfare agent release is natural infection expressed as an epidemic. Another term for HAZMAT is *toxic industrial chemicals*. These are substances that could be used as improvised chemical agents in a terrorist attack.

Background and Development of Agents of Chemical and Biological Warfare

World War I

Chemical agents were used from 1915 to 1918 in World War I. Their use was catalyzed by the battlefield stalemate of trench warfare; chemical warfare agents have usually been used in such conditions because they do not fit well with the tactics of a mobile war. Large-scale releases of chlorine and phosgene in 1915 had considerable effects against unprotected troops and caused large numbers of casualties, including deaths. These early attacks probably gave rise to the notion of CBW agents being weapons of mass destruction. (In fact, chemical agents had the lowest ratio of dead to wounded of all the arms used during the war at <4%,[14] whereas explosive shells had the highest at >15%. Artillery caused 59% of the overall mortality on all sides.)

Many different chemical agents were tried during World War I, delivered usually by shell fills, but there was difficulty in building high enough concentrations of agent to be lethal, and the continuing countermeasures meant that better-trained troops with masks were less affected. Although phosgene could be regarded as the most lethal of the agents used, causing untreatable toxic pulmonary edema, mustard agent, a vesicant disabling agent, probably caused the most injury and removed many soldiers from the field of battle (usually temporarily). One feature of the casualties from World War I that is overlooked is the possibility of mixed toxic and physical trauma. The exact figures are unavailable, but of 546 American soldiers who died after exposure to chemical warfare agents during the period March to November 1918, 6% also had ballistic injuries.[22] The figures for dead and wounded do not reveal the true extent of the disability caused by exposure to toxic agents, and it is likely that the long-term pathology was high, particularly given the limited postwar medical facilities at that time.

Development and Use of Chemical and Biological Warfare Agents during World War II

Organophosphate (OP) pesticide research by Schrader in 1936 led to the development of anticholinesterase "nerve agents" by Germany under conditions of the strictest secrecy during World War II. Although never used in action during that time, these agents became the major toxic hazard during the Cold War and beyond.[14] A major nerve agent plant was captured by the Russians and rebuilt in the USSR in 1945, giving the USSR a "mass-destructive" capability long before it possessed nuclear weapons. A lesson for military and civil anesthesiologists is that mixed casualties can be expected after the use of toxic agents, given it has been known for some time that Soviet commanders saw the use of chemical weapons as part of a normal armamentarium, rather than being exceptional weapons.[23]

There is some evidence of the use of biological warfare agents in China by the Japanese, who had a secret unit devoted to the subject since the early 1930s.[14] Plague and clostridia were used in tests on prisoners and against civilian populations. The considerable knowledge gathered was passed on to the United States by the head of the section after his capture and formed the basis of an offensive biological warfare development program, which was terminated in 1972 with the signing of the biological warfare treaty.

Cold War Development

It is now known that a major Soviet biological warfare program began in the early 1970s that used genetic engineering and other techniques to develop a whole new range of possible agents, including toxins and "agents of biological origin,"[15] which are probably deployed at the present time. There also was continued development of nerve and other agents during the Cold War and extensive research into an antidote-based approach to the management of the wounded. With the end of the Cold War, much of the expertise in USSR laboratories may have moved to other countries, increasing the risk that developed CBW agents and delivery technology may be more easily available to terrorist groups.

Iran-Iraq War

The Iran-Iraq War during the 1980s saw not only the sustained use of chemical agents, but also the first application of modern medical techniques to chemical warfare injuries. Extensive investigations by the United Nations established that sulfur mustard and lewisite, vesicant agents, had been used together with the nerve agent tabun and a toxin agent, mycotoxin.[24,25] Casualties were almost exclusively on the Iranian side and numbered about 27,000, with a mortality rate less than 1%. This continued the trend noted during World War I of the low mortality rate for chemical warfare compared with other weapons, and almost certainly reflects the impact of organized medical care for the casualties and techniques of protection. In comparison, the Iraqi attack against an unprotected Kurdish village at Hallabjah in 1989 produced 5000 dead.

Terrorist Chemical and Biological Warfare Releases during the Last Part of the 20th Century

In 1995, the first recorded terrorist use of a chemical warfare agent against a civilian population occurred with the use of the nerve agent sarin in attacks in Matsumoto and Tokyo, Japan, and for the first time hospital medical teams were brought into direct contact with a chemical warfare incident during the initial and continuing management of the casualties.[2,26] Because of lack of experience, there were numerous casualties among the attending emergency staff, but the number of fatalities was low. The incident brought home many lessons for medical responders, including anesthesiologists. The first was that the use of a hitherto military chemical warfare agent was possible by a terrorist group. Second, the incident management underlined all the lessons taught by the HAZMAT system, in that secondary casualties occurred among the attending staff because of lack of control, protection, and decontamination. Third, fatalities that occurred at the release site were essentially due to lack of on-site resuscitation. Fourth, the well-documented clinical management of the many thousands of victims who were admitted to the hospital provided for the first time a significant clinical database for a population exposed to a nerve agent.[27]

Hazards and Threats

There is often confusion regarding the concept of a hazard versus a threat. CBW agents are, by definition, hazardous and are strictly controlled by the provisions of the HAZMAT system. The term *threat* is usually used in the military context if a hazard has been weaponized, and the assailant has the capability and the intention to use the weapon. The relationship may be expressed by the following simple equation:

$$\text{Threat} = \text{hazard} + \text{capability} + \text{intention}$$

For a balanced medical response to a CBW attack, the reality is that many of the CBW hazards causing public concern are difficult to weaponize and deliver. Such understanding is important for the medical responder because it reduces the likelihood of encountering casualties from a CBW attack to a restricted number of agents, the properties and pathophysiology of which can be considered before casualties present.

Modes of Release of Chemical and Biological Warfare Agents

Chemical Agent Release

Military Release. In warfare, the release of CBW agents is a deliberate action achieved through the use of shells or missiles or through spraying. Agents that are active through the respiratory route are dispersed as an aerosol, but more persistent agents, designed to contaminate terrain, are usually spread by spray. These agents are active through the skin.

By the end of World War I, delivery of chemical warfare agents was almost exclusively through explosive shells, and by the end of the war, 40% of the fills were chemical, indicating the effectiveness of chemical warfare agents on the battlefield.[14] The advent of aerial bombardment before World War II brought great fears that cities would be wiped out by gas attacks, but these fears were never substantiated, and it is now understood that dissemination of chemical warfare agents over a wide area (rather than a limited tactical area) by explosion is not easy. During the Cold War, the Soviets developed considerable expertise in the use of BM21/24 multiple rocket launchers (Stalin Organs), which could deliver rapidly a high concentration of nonpersistent agents, such as hydrogen cyanide (HCN). Missiles such as the Scud also were developed for chemical warfare release at this time, and it was feared that they had been developed for chemical warfare use by Iraq before the Gulf War of 1991.

In the military context, release of toxic agents may be revealed or concealed. Attack, by whatever means, is usually predicted and detectable with the considerable resources that the military can bring to bear in this area for chemical and biological agents. Tuned detection systems are employed wherever there is perceived to be a threat, and the threat itself is usually supported by intelligence information about the hazards concerned, which means that the systems can be tuned. Broad detection systems such as mass spectrography also are employed by CBW reconnaissance units in the field.

Release on a Civilian Population. In civil life, toxic agent release is usually accidental and is usually revealed by the circumstances. Road and other transportation accidents, particularly when vehicles carrying HAZMAT plates are involved, give an immediate warning about the nature of the problem.[20] Accidental releases, particularly in nations with poor emergency response resources, still can be catastrophic, as in the case of the mass release of methyl isocyanate in the Indian city of Bhopal in 1984, which caused more than 5000 deaths and 50,000 casualties.[28] Civil populations, in contrast with military populations, are usually untrained and unprotected against release of toxic agents. In addition, the panic induced by the fear of the actions of CBW agents compounds the flexibility of the emergency medical response.

Biological Warfare Agent Release

The deliberate release of classic biological warfare agents such as bacteria or viruses may not be as easy as the media have led the public to believe. Effective mass release implies aerosol release, and very few biological warfare agents are capable of withstanding the environmental stresses involved. Some, such as anthrax spores, have long been recognized as being sufficiently robust and have attracted the most research attention. The only other bacterial diseases that have probably been used as biological warfare agents are tularemia, spread through infected fodder, and plague, which was said to have been used by the Japanese during the World War II campaign against China, and where the vector used was the traditional one of the rat-borne flea.[14]

Considerable research work was carried out by the USSR during the Cold War to try to find new ways of delivering biological agents and for their modification using genetic engineering.[16] This work also developed agents of biological origin that lie in the middle of the CBW spectrum, and that produce subtle pathophysiologic effects and are difficult to detect postmortem in the body. In military terms, biological warfare has always been seen as a debilitating weapon, self-propagating and of long latency, which could be used to degrade the capability of static enemy formations or key formations operating behind front lines, such as air fields. In the civil context, biological warfare agents have yet to be used in a terrorist attack, but there is evidence of continued interest.[29]

Role of the Anesthesiologist in the Clinical Management of Hazards and Threats from Chemical and Biological Warfare Agents

Extensive reviews[6-11,13,17] are available giving details of agents that are regarded as being CBW hazards. This section concentrates on selected hazards that can be regarded as being potential threats and that are likely to be encountered by the responding anesthesiologist.

In the management of CBW casualties, the anesthesiologist acts as part of a clinical team. To provide a safe and effective response, the following information is required for each toxic hazard:

1. Physical, pharmacologic, and immunologic methods of individual protection
2. Immediate measures for life support
3. Specific antidote therapy
4. Latent effects

In this section, specific agents have been selected that are representative of classes of hazards and have in some cases been used as weapons of warfare. They are hazards that either can be synthesized easily or are potentially available from stockpiles or from reference laboratories.

Nerve Agents

Nerve agents are OPs, a very large group of chemical compounds known since the 19th century, but first examined in detail in the 1930s.[7,8] More than 50,000 OP compounds have been synthesized, and several are in regular use as insecticides around the world, including parathion, malathion, and fenthion.[30] Although OPs were originally developed as insecticides, certain highly toxic members of the class, known as nerve agents, were developed before World War II specifically for military use. As a result of development by Germany and later by Russia, the United States, and Great Britain, at least five nerve agents have been produced. The formulas of the more common nerve agents are shown in Figure 74-2. Tabun (GA) was the first nerve agent to be produced, followed during World War II by sarin (GB) and soman (GD). VX, VR, and cyclosarin (GF) were developed during the Cold War. Cyclosarin (in which the isopropyl group in sarin is replaced by a cyclopropyl group) was found stockpiled in Iraq during the First Gulf War in 1992. Currently, the most important nerve agent hazard likely to face an anesthesiologist is sarin (isopropyl methyl phosphonofluoridate), which has been widely produced and stockpiled, and synthesized and used by terrorists.[3,27]

In terms of physical properties, GA, VX, and VR are persistent, whereas GB, GD, and GF are not. GD may be made in a thickened form, however, which is persistent. The relevance of the physicochemical data to the clinical situation is that the nonpersistent agents generally pose a respiratory risk, whereas the persistent agents are a danger because of absorption through the skin. Different agents pose specific risks to victims and to medical attendants.

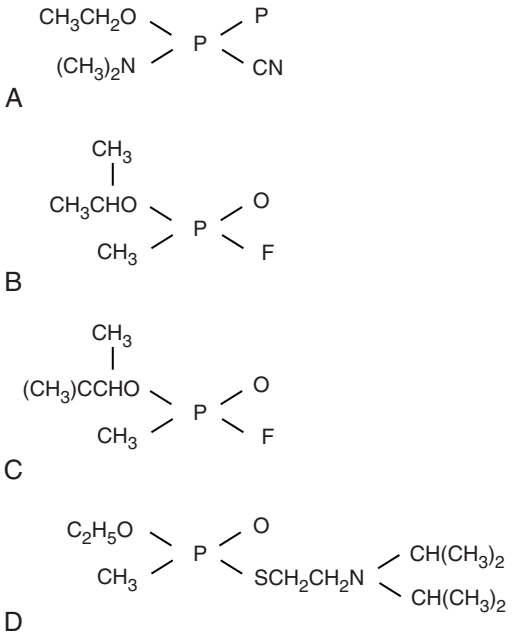

Figure 74-2 A-D, Chemical formulas of organophosphate nerve agents: tabun (GA) (**A**), sarin (GB) (**B**), soman (GD) (**C**), and VX (**D**). (From Baker DJ: Anesthesia in extreme environmental conditions, Part 2: Chemical and biologic warfare. *In* Grande CG [ed]: Textbook of Trauma Anesthesia and Critical Care. St Louis, Mosby-Year Book, 1993, p 1331.)

Nerve agents were originally termed *nerve gases,* but are liquids with volatilities varying between that of petrol and heavy lubricating oil. None of the agents freeze until −40°C. They are pale yellow to colorless in appearance, are odorless, and are soluble in water where they undergo slow hydrolysis. In the presence of strong alkalis and hypochlorite solution, the hydrolysis is rapid, and this is the basis of the field decontamination of the G agents. Decontamination of V agents with hypochlorite can itself produce toxic products and is not recommended. Nerve agents can penetrate clothing, skin, and leather. Rubber and synthetic materials, such as polyethylene and butyl rubber, are more resistant. The physical properties of the nerve agents are shown in Table 74-1.

Actions of Nerve Agents

The main effect of nerve agents is inhibition of acetylcholinesterase (AChE) and butaryl cholinesterase in the cholinergic nervous system. Both of these enzyme systems are familiar to anesthesiologists, who inhibit them on a daily basis using the carbamate anticholinesterase neostigmine to reverse the action of nondepolarizing neuromuscular blocking agents. OPs also inhibit other enzymes, notably neurotoxic esterase. This inhibition causes long-term neurologic effects unrelated to cholinergic changes. The interaction of OPs with AChE is complex and is analogous to the interaction of the enzyme with the natural substrate acetylcholine (Fig. 74-3).[4] Inhibition of AChE causes a buildup of acetylcholine at muscarinic and nicotinic synapses of the cholinergic nervous system. Central and peripheral signs and symptoms can be directly explained from the classic pharmacologic knowledge of how the cholinergic system operates.

Although the classic effects of OPs are cholinergic in nature, there are important effects on other receptor systems, notably γ-aminobutyric acid and *N*-methyl-D-aspartate, which gives rise to central excitation causing the initial convulsions seen in acute OP

Table 74-1 Physicochemical Properties of Nerve Agents

Properties*		**Tabun (GA)**		**Sarin (GB)**		**Soman (GD)**		**VX**	
Molecular weight (daltons)		162.3		140.1		182.18		267.36	
Specific gravity at 25°C		1.073		1.0887		1.022		1.0083	
Boiling point (°C)		246		147		167		300	
Melting point (°C)		–49		–56		–80		–20	
Vapour Pressure (VP) and Volatility (Vol)†‡	*°C*	*VP (mm Hg)*	*Vol (mg m^{-3})*	*VP (mm Hg)*	*Vol (mg m^{-3})*	*VP (mm Hg)*	*Vol (mg m^{-3})*	*VP (mm Hg)*	*Vol (mg m^{-3})*
	0	0.004	38	0.52	4279	0.044	470.9	—	—
	10	0.013	119.5	1.07	8494	0.11	1135.5	—	—
	20	0.036	319.8	2.10	16101	0.27	2692.1	0.00044	5.85§
	25	0.07	611.3	2.9	21862	0.40	3921.4	0.0007	10.07
	30	0.094	807.4	3.93	29138	0.61	5881.4	—	—
	40	0.23	1912.4	7.1	60959	—	—	—	—
	50	0.56	4512.0	12.3	83548	2.60	23516.0	—	—

*At room temperature, GB is a comparatively volatile liquid. GD also is significantly volatile. GA is less volatile. GD may be thickened to increase its persistence. VX is relatively nonvolatile and is regarded as presenting little vapor hazard.
†Vapor pressure in mm Hg.
‡Volatility in mg • m^{-3}. Volatility = concentration of saturated vapor at specified temperature. Volatility calculated from PV = nRT.
§Some authorities quote values 0.1 to 1 mg/m^{-3}.
In the equation:

$$\text{Vol} = \frac{\text{VP} \cdot 101325 \cdot \text{MW}}{760 \cdot 8.3143 \cdot A} = \frac{\text{VP} \cdot \text{MW} \cdot 16.035}{A}$$

Å = absolute temperature.
From Baker DJ: Anesthesia in extreme environmental conditions, part 2: Chemical and biologic warfare. ***In*** Grande CG (ed): Textbook of Trauma Anesthesia and Critical Care. St Louis, Mosby-Year Book, 1993, pp 1320-1354.

poisoning. The interaction of OPs with AChE is nonreversible after a certain time depending on the nerve agent. The formation of an irreversible complex is known as aging. Each nerve agent has an aging half-life. For GB, this is about 5 hours, whereas for GD, it is only 2 minutes. GA and VX have aging half-lives of 40 hours. After 5 half-lives, more than 95% of the enzyme AChE has aged and cannot be reactivated. This has important consequences on the window of clinical opportunity[31] for treatment to try to reverse the AChE inhibition (see section on oximes later).

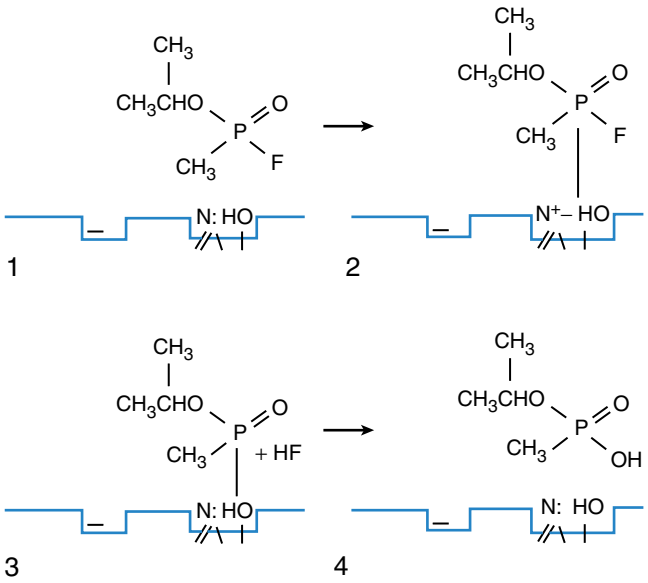

Figure 74-3 Reaction of acetylcholine and sarin with acetylcholinesterase. (From Baker DJ: Anesthesia in extreme environmental conditions, part 2: Chemical and biologic warfare. *In* Grande CG [ed]: Textbook of Trauma Anesthesia and Critical Care. St Louis, MO Mosby-Year Book, 1993, p 1341.)

Signs and Symptoms of Nerve Agent Poisoning

The classic signs and symptoms of nerve agent poisoning are shown in Table 74-2. Poisoning is caused by the accumulation of acetylcholine and not by the OP itself. As a result of stimulation of muscarinic synapses, there is miosis; ciliary body spasm causing pain[32]; glandular hypersecretion, including salivary, bronchial, and lacrimal; sweating; cardiac effects, including bradycardia, atrioventricular block, and Q–T prolongation; bronchoconstriction; vomiting; severe diarrhea; and fecal incontinence. The nicotinic effects are manifested by fasciculation and paralysis at the neuromuscular junction. Sometimes anomalous tachycardia may occur after nicotinic ganglionic stimulation in the sympathetic system. Central effects lead to apprehension, dizziness, amnesia, seizures, coma, and respiratory depression.[33] Lower long-term doses of OPs lead to irritability, fatigue, loss of concentration, and memory loss.

Clinical Experience with Intoxications from Organophosphates. Much of the information about actions of OPs in humans has been gathered from animal studies and from management of pesticide poisoning. Animal studies do not represent human reactions, and pesticide studies may not accurately represent the cholinergic syndrome after nerve agent exposure. Although there is some evidence from accidental exposure to sarin and from some human volunteer studies conducted early in

Table 74-2 Symptoms and Signs of Nerve Agent Poisoning by Type of Cholinergic Receptor and Target Organ

Receptor	Target Organ	Symptoms and Signs
Muscarinic	Iris muscle; ciliary muscle accommodation	Miosis; spasm leading to failure of pain in the eyes; nausea and vomiting; headache
	Conjunctival vessels	Vasodilation and hyperemia
	Nasal glands	Rhinorrhea and hyperemia
	Bronchial glands	Increased secretion
	Bronchial muscle	Bronchoconstriction; tightness in the chest; expiratory wheezing; dyspnea
	Gastrointestinal tract	Anorexia; nausea; vomiting; abdominal cramps; diarrhea; tenesmus; involuntary defecation
	Sweat glands	Increased activity
	Salivary glands	Increased activity
	Lacrimal glands	Lacrimation (not usually marked)
	Heart	Bradycardia; occasionally tachycardia
	Bladder	Frequency; involuntary micturition
Nicotinic	Skeletal muscle	Weakness; fatigue; fasciculations; cramps; flaccid paralysis (early effects on respiratory muscles may produce dyspnea)
	Autonomic ganglia	Pallor; occasional elevation of blood pressure
Muscarinic and nicotinic	Central nervous system	Anxiety; giddiness; restlessness; headache; withdrawal and depression; memory failure; impaired concentration; slurred speech; depression of respiratory and cardiovascular centers; Cheyne-Stokes respiration

From Baker DJ: Anesthesia in extreme environmental conditions, Part 2: Chemical and biologic warfare. *In* Grande CG (ed): Textbook of Trauma Anesthesia and Critical Care. St Louis, Mosby-Year Book, 1993, pp 1320-1354.

the Cold War, the clinical evidence base is smaller than that for pesticide poisoning. During the early stages of the Cold War, many experimental studies were done on human volunteers exposed to nerve agents; these studies have been reviewed by Marrs and colleagues.[8] The attacks in Japan in 1994 and 1995 also have provided important information concerning the signs and symptoms after sarin release.[3,27]

Clinical Evidence from More Recent Military Experience. The Iran-Iraq War produced first-hand clinical information about the effects and management of nerve agent poisoning.[24] Iranian casualties from nerve agents apparently fell into four broad categories. Individuals who had the greatest exposure died in the field; mask protection by Iranian troops was severely compromised by their having to wear beards for religious reasons. Despite the fact that Iraqi attacks were made against troops having compromised or poor protection, the number of deaths seems to have been low. The most severely injured individuals who reached medical care were unconscious and unresponsive and often in respiratory arrest. The next group who were seriously poisoned had symptoms of dizziness, disorientation, anxiety, salivation, and respiratory difficulty. Disorientation was a problem, and often cases with only mild symptoms were difficult to manage because of this (this parallels experience gained with the management of OP pesticides). Finally, the greatest number of casualties required only decontamination.

Individuals with nerve agent poisoning were treated with large doses of atropine, usually 50 to 200 mg intravenously. These patients were usually comatose, and the degree of advanced life support given was limited. Most patients received only 2 mg of atropine every 8 hours. Comatose patients with significant cardiovascular deterioration did not usually survive.

Clinical Evidence from Pesticide Poisoning. There is considerable clinical evidence about the effects of OP pesticides from the many thousands of cases that occur in agricultural areas of the world each year.[34] Although these cases give an overall picture that corresponds to the signs and symptoms described previously, there are considerable differences with nerve agents. It also is likely that different nerve agents have different effects on the central and peripheral nervous systems.

Cardiovascular Effects of Nerve Agents. Critical care management of OP pesticide poisoning has indicated short-term and medium-term cardiac changes.[35,36] After an initial tachycardia (mediated through the anomalous sympathetic nervous system) and a vagally induced bradycardia, there may be ventricular dysrhythmias, including torsades de pointes and prolongation of the Q–T interval. Dysrhythmias have been reported as a poor prognostic sign.

Treatment of Nerve Agent Poisoning: Antidotes and Life Support

Atropine. Atropine has long been a mainstay in the management of OP poisoning.[30,34] Its antagonistic action against acetylcholine at the muscarinic synapses allows control of the muscarinic effects, the most severe of which is bradycardia. Atropine has been used for many years in the management of OP pesticide poisoning. The relevance of the experience with pesticides to poisoning with nerve agents is uncertain, however.[8] The traditional military response to a confirmed or suspected attack with nerve agents is to use a self-administered autoinjector containing 2 mg of atropine, a benzodiazepine, and an oxime (Fig. 74-4). During the Cold War, NATO troops were provided with three such devices to be used sequentially.

Useful treatment indications have been gained from the Iran-Iraq War[37] and from the Japanese terrorist experience.[27] Atropine, 2 mg, is given intravenously (pediatric dose 0.02 to 0.05 mg/kg) with repeat doses every 5 to 10 minutes until pupillary dilation occurs, and the heart rate increases to greater than 80/min.[8,38] Atropine infusions may be used for persistent bradycardia in pesticide poisoning.[39]



Figure 74-4 Military automatic intramuscular injection device containing nerve agent antidotes (Combopen).

Oximes. Oximes are compounds capable of reactivating in some cases the complex formed by the OP and AChE. Clinically, this means that oximes can reverse the actions of OP at the nicotinic receptor and reduce the degree of paralysis.[40,41] Oximes are widely used in the clinical management of OP pesticide and nerve agent poisoning. Chemically, they are monopyridinium or bispyridinium compounds that can bind to the complex and cause the nerve agent molecule to separate from the enzyme. Oximes are a mainstay of the standard military response to nerve agent attacks and are widely used in the management of pesticide poisoning. Their effectiveness depends, however, (1) on the exact nature of the nerve agent involved and (2) on the length of time after the attack before they are given.

Chemical changes known as aging occur in the nerve agent–enzyme complex. Aging occurs very rapidly in humans after GD exposure, but less so after exposure to the other nerve agents. A major problem related to oxime research is the selection of a suitable animal model. Originally, monkeys and guinea pigs were thought to be good models for human OP intoxication, and human treatment protocols were developed from such studies. There are known to be major differences, however, between aging rates for primates and rates for rodents.[42] The rate of formation of aged enzyme in different species increases in the following order: mouse << rat < guinea pig < rabbit < dog < cow < monkey = human. From erythrocyte studies in humans, the rate of aging is known to be very rapid (half-life = 1.3 minutes), indicating that the guinea pig would not be a good model for humans.

Several oximes are available, and recent years have seen the development of new compounds.[40,41] The most commonly used is pralidoxime (as either the chloride or methane sulfonate [mesylate]). Obidoxime is used in some countries for OP pesticide poisoning and may be effective against GA. More recent research has concentrated on the rational use of a range of oximes in terms of the type of oxime used and dose and timing.[40,41,43] HI-6, a Hagedorn oxime, was thought to be able to reactivate the GD-enzyme complex, the most difficult clinical situation to treat. HI-6 may be useful because of other pharmacologic properties, and may be advantageous in the treatment of GF poisoning and other cases in which obidoxime was previously used.

For most anesthesiologists treating patients with symptoms of nerve agent poisoning, a civilian setting is the most likely. Exposure to sarin is the most probable situation, and treatment schedules logically should be based on this premise. Military anesthesiologists may face other hazards, but would be provided with specialized detection equipment and treatment modalities based on a threat assessment. In the civil context, all nerve agent casualties should receive pralidoxime mesylate initially in addition to atropine and ventilatory life support.

Practical Treatment Regimen. Oxime therapy should be given simultaneously with atropine.[38,40] Slow intravenous injection of pralidoxime is recommended to prevent laryngospasm, muscle rigidity, and hypertension. Pralidoxime, 15 to 30 mg/kg intravenously or intramuscularly is given over 20 minutes for adults and children. This dose may be repeated after 4 hours (or 1 hour if paralysis is worsening). The target therapeutic blood concentration should be 4 μg/mL. Studies by Worek and colleagues[41] have shown, however, that the full therapeutic effects of pralidoxime may be achieved at higher concentrations. The same group has shown that there is a possibility of reinhibition of AChE after pralidoxime treatment in human erythrocytes, but the relevance to the whole body is unclear. Sarin is broken down rapidly in the blood by hydrolysis. Oxime treatment in the hospital should continue for as long as atropine is required.

Benzodiazepines. The central actions of OPs lead to spike discharges and convulsions. Benzodiazepines have long been used to counter this action. Given the known action of OPs at the γ-aminobutyric acid receptor and the antagonistic action of benzodiazepines at this site, the action may be noncholinergic in nature.[44,45] Convulsions may be an early sign of severe nerve agent poisoning and must be controlled quickly to avoid long-term cerebral damage.

Pyridostigmine Pretreatment. The problem of aging of the OP AChE complex, particularly with GD and the ineffectiveness of oxime therapy, gave rise to a novel military approach to prophylaxis against nerve agent poisoning.[9] Pyridostigmine is a dimethyl carbamate compound with a quaternary nitrogen atom. As a result, it does not penetrate the blood-brain barrier to any extent. In common with other carbamates such as neostigmine and physostigmine, pyridostigmine is an anticholinesterase and has essentially the same action as OPs. In the case of carbamates, the complex formed with the enzyme is readily reversible. The normal treatment dose of pyridostigmine is 30 mg every 8 hours. There is no plasma protein binding and no drug interactions involving competition for binding sites. Of the absorbed dose, 79% to 90% is excreted unchanged in the urine. The reversibility of the complex formed with AChE is such that the enzyme returns to 90% of normal within 12 hours after the last dose. In addition, at the steady state, only 40% of the available AChE is complexed. Given the considerable safety margin that exists in the level of enzyme at cholinergic synapses, treatment with pyridostigmine does not produce any more than mild parasympathetic signs.[46]

The protective action of pyridostigmine against OPs is based on the fact that the carbamylate-complexed AChE is resistant to attack after subsequent exposure to OPs. If a person taking pyridostigmine is exposed to a subsequent potentially lethal dose of OP, there is a reserve of enzyme that is effectively autotransfused into the patient during the subsequent period. This process does not require the presence of an oxime. OP is rapidly hydrolyzed in the bloodstream after exposure and has no further action on the released AChE. The amount of enzyme released from the carbamylate complex is sufficient to restore neuromuscular transmission because of the safety margin that exists at the synapse. In severe cases of OP poisoning, life support measures are necessary, however, to bridge the gap between OP attack on the synapse and restoration of the AChE level through the autotransfusion.

Anesthetic Implications of Pyridostigmine Pretreatment. The anticholinergic actions of pyridostigmine have considerable relevance to normal anesthetic practice. Butaryl cholinesterase, a determinant of the metabolism of succinylcholine, also is inhibited, and prolonged action of this drug may be expected in patients taking pyridostigmine.[47] The carbamate neostigmine is usually given at the end of an operation to reverse the action of nondepolarizing neuromuscular blocking drugs. Pretreatment with a carbamate in a patient who is not subsequently exposed to OP may be expected to produce some resistance to the action of the neuromuscular blocker. Experimental studies[48] indicate that pyridostigmine does not alter the overall characteristics of neuromuscular block in an isolated human forearm, and the neuromuscular effects may be minimal, particularly because more central muscles of respiration such as diaphragm have a higher safety margin of neuromuscular transmission and are less affected by treatment with pyridostigmine. Estimations of the degree of neuromuscular block using fade relationships such as the train-of-four[49] theoretically may be affected by pyridostigmine pretreatment because the determinant of fade is feedback to the prejunctional cholinergic receptor.[50] The hysteresis loops for the onset and offset of fade and paralysis relationships in the isolated forearm are not affected, however, by pyridostigmine pretreatment.[48] The civilian anesthesiologist is referred to more specialized military texts[8,13] for a more complete discussion of pyridostigmine and its clinical actions.

Vesicant Agents

Vesicant agents were first used as chemical weapons during World War I.[14] The most well-known agent is sulfur mustard (1917, commonly known as "mustard gas"). It was used as a disabling agent and has a long latency of 2 to 4 hours. Its successor lewisite (1919), an arsenic-based compound (2-chlorovinyl dichloroarsine), is more volatile and has a short latency and causes immediate eye pain in addition to its vesicant properties.[18] Mustard gas is the most commonly encountered vesicant. Although an early chemical warfare agent, it is still widely distributed around the world, and its easy synthesis makes it a possible agent for use by terrorists. It has numerous pathologic properties that make it of concern to anesthesiologists. The overall management of mustard gas injury is the domain equally of the surgeon and specialized pulmonary physician.[8,51,52] Intensive care unit (ICU) management presents longer term problems, which are mainly respiratory. Eye and skin injuries fall within the aegis of other specialities.

Properties

Sulfur mustard (bis-2-chloroethyl sulfide) is a colorless or pale yellow, oily liquid that smells faintly of mustard. Its odor threshold is 1.3 mg/m^3, which is below the concentrations usually reached in a battlefield, and several minutes of detection are possible before incapacitating doses are reached. The LCt_{50} is about 1500 mg/min/m^3. Although the latency of action in cooler climates is about 4 hours, information from the Iran-Iraq War, the scene of its most recent use, [53,54] indicates that at higher ambient temperatures the agent has a far shorter latency and causes significant respiratory damage apart from its classic action as a skin vesicant.

Signs and Symptoms

After exposure to mustard gas, there is a latent period of 4 to 12 hours, following which ocular symptoms comprise eye pain, blurred vision, and lacrimation, accompanied by a diffuse erythema of exposed skin with edema and first-degree burns. The groin and genital areas are particularly susceptible. Exposure to high doses produces severe cutaneous injury with necrosis. The burns bear some resemblance to thermal burns, but are very slow to heal and are prone to secondary infection. The bullae that are characteristic of exposure to mustard agent are filled with a fluid that is not itself corrosive (Fig. 74-5). A feature of exposure is that fluid-filled bullae appear for several days afterward in an apparently random way (i.e., not cropped). The eyes are particularly vulnerable to mustard gas, causing usually a temporary blindness (Fig. 74-6). The fluid in the bullae has no vesicant effect.



Figure 74-5 Cutaneous vesication caused by mustard gas exposure. (Courtesy of Her Majesty's Stationery Office, London, United Kingdom.)

Respiratory Effects

The respiratory effects of mustard gas exposure are potentially serious, particularly when the ambient temperature is high.[54,56] After exposure, there is an early tracheobronchitis with dry cough and hoarseness. Heavy exposure produces severe damage to the tracheal and main bronchial architecture with necrosis, sloughing, and blockage (Fig. 74-7). A chemical bronchiolitis occurs at lower doses in high ambient temperatures and causes severe bronchospasm, requiring ventilation and intensive care.[54] Lung damage after mustard exposure can be severe and permanent with chronic obstructive pulmonary disease, bronchiectasis, and reactive airways dysfunction syndrome.

Cellular Action of Mustard Agent

Sulfur mustard agent acts at a cellular level forming highly reactive sulfonium ions, which attack DNA by alkylation of sulfhydryl



Figure 74-6 Eye injury caused by mustard gas exposure. (Courtesy of Her Majesty's Stationery Office, London, United Kingdom.)

and amino groups.[8] This causes the epithelial manifestations of exposure and long-term carcinogenesis, particularly of the skin, pharynx, and respiratory tract.

Treatment

There is no specific treatment for mustard gas exposure, but experimental studies in animals have shown that a combination of sodium thiosulfate, vitamin E, and dexamethasone can improve survival and reduce organ damage.[8] The key points of treatment are (1) the need for decontamination, (2) the latent period of action, and (3) respiratory support for exposure affecting the respiratory tract. Willems[52] reviewed information concerning the clinical management of mustard gas casualties, reporting that 87% of patients requiring ventilation died. The onset of severe respiratory symptoms is a serious development and underscores the need for a proactive approach to airway management and ventilation. Endotracheal intubation should be done early to allow adequate ventilation and access for débridement of the large airways. Another point of concern for longer term management is the leukopenia that follows exposure to mustard gas. This becomes evident 3 to 5 days after exposure and usually reaches its lowest point 7 to 9 days after exposure. Cellular replacement, either peripherally or as marrow, could be considered here because mustard gas is bound very quickly in the body after exposure and does not cause destruction of new cells.

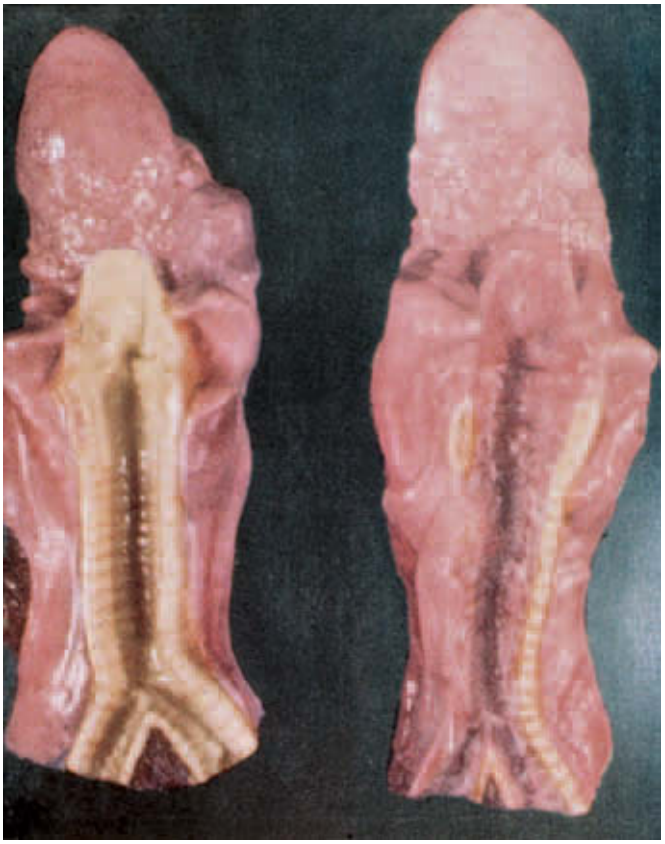

Figure 74-7 Tracheal injury caused by mustard gas. (Courtesy of Her Majesty's Stationery Office, London, United Kingdom.)

More Recent Clinical Evidence

Sulfur mustard was used extensively in the Iran-Iraq War during the 1980s, producing a significant amount of clinical information about casualties[53] with cutaneous and respiratory injuries. The treatment given reflects the experience gained in the treatment of burn injuries since its first use. Decontamination was achieved early to limit the contact time with the agent. Because of the long latency of mustard gas, vesicle formation often was not present at this time. Shaving of the affected areas was done, and the agent was diluted by irrigation. The management of the vesicles followed the pattern of aspiration, removal of necrotic tissue, and the use of silver sulfadiazine cream.

From the anesthetic standpoint, the respiratory effects found in casualties were important and unprecedented from the use of mustard gas in the lower temperature conditions of World War I. Chemical bronchiolitis giving rise to increased airway resistance was reported together with soiling of the larger airways secondary to sloughing. Intermittent positive-pressure ventilation with positive end-expiratory pressure was required with ICU support for cases of more serious injury. Many of these cases were managed in hospitals around Europe, introducing chemical warfare injury to many anesthesiologists and intensivists for the first time. For the casualties who reached definitive hospital care, the recovery period was often long, and patients had cachexia with significant negative nitrogen balance.

Lung-Damaging Agents

Lung-damaging agents were formerly known as choking agents, a term that does not adequately describe the many levels of the lung at which they act. Lung-damaging agents act at the upper and the lower respiratory levels, but their main lethal action is to cause toxic pulmonary edema. Lung-damaging agents were the first to be used as chemical weapons during World War I with the use initially of chlorine, followed by phosgene. These agents are a universal hazard in military and civilian populations because they also are used widely as industrial feedstocks in many chemical engineering processes. The isocyanates are widely used in this respect, and the accidental release of methyl isocyanate in Bhopal, India, in 1984 caused the largest number of casualties ever recorded after toxic release in either war or peace, with more than

5000 deaths from toxic pulmonary edema.[57,58] Chemical warfare and HAZMAT sources list many lung-damaging agents.[8,19]

Phosgene

Phosgene[59] has been used as a chemical warfare agent, is an established worldwide industrial hazard, and may be regarded as a potential terrorist threat. It is a model for consideration of other hazards in its class. Phosgene is carbonyl chloride, familiar to earlier anesthesiologists as the product of the reaction of trichloroethylene with soda lime. First synthesized in the 19th century, phosgene has been in industrial use for more than a century, but achieved notoriety during World War I when it was used extensively by both sides from 1915 onward. It caused greater than 85% of all deaths from chemical warfare agents.[14] Phosgene is a gas at normal temperatures and is nonpersistent (Table 74-3). It is less water soluble than chlorine, its immediate chemical warfare predecessor in 1915, a feature that results in the gas being taken further down the respiratory tree and into the alveoli. Phosgene has been known since World War I to have a dual latency of action, which underlies its essentially dangerous character. The stages after exposure are as follows:

1. Immediately after exposure, there is an intense upper respiratory irritation with coughing, retching, choking, and chest tightness. These symptoms are accompanied by eye irritation and lacrimation. In some cases, death has followed exposure to high concentrations of phosgene without the development of toxic pulmonary edema. The reason for this is obscure, but may be related to hypoxia as a result of intense laryngeal or bronchospasm.
2. The immediate choking symptoms are followed by a latent period of 2 to 24 hours before the onset of more serious symptoms and signs, including dyspnea, painful cough, and cyanosis, with increasing signs of pulmonary edema leading to circulatory collapse and cardiac arrest.

Pathophysiology of Toxic Pulmonary Edema

Phosgene reacts through covalent attack on many substrate groups, including NH_2 and SH.[60] Potential cell targets are type I and II pneumocytes and alveolar macrophages. Covalent binding can be seen as the primary attack leading to free radical release. This stage is followed by a secondary attack involving released inflammatory mediators, including prostaglandins (causing vasoconstriction, vasodilation, and platelet disaggregation), bradykinin (causing increased capillary permeability), 5-hydroxytryptamine (causing constriction of postcapillary vessels), and thromboxane A_2 (causing vasoconstriction), and the release of complement activating enzymes (leading to attraction of leukocytes and leukotriene release).

Table 74-3 Properties and Toxic Exposure Levels of Phosgene

Properties
Chemical name: carbonyl chloride ($COCl_2$), chloroformyl chloride
Boiling point: 8.2°C
Vapor pressure: 1215 mm Hg at 20°C
Vapor density: 3.5 × air
Breakdown: slow aqueous hydrolysis to HCl and CO_2
Toxic Exposure Levels
1 ppm chronically—chronic lung disease
>25 ppm/min—acute lung effects
50-100 ppm/min—initial inflammatory response that may be followed by pulmonary edema
>150 ppm/min—clinically significant and life-threatening pulmonary edema
Lethal exposure in humans—800 ppm for 2 min

Management of Phosgene Exposure

Patients who have been exposed to phosgene should be removed from the site of exposure as quickly as possible by protected emergency responders. There is usually no requirement for decontamination, unless liquid contamination has occurred. There is no specific antidote to phosgene, and treatment is based on use of supportive measures and pharmacologic modification of the effects of the inflammatory mediator cascade.[59] One of the firm rules for the management of phosgene exposure dating from World War I was complete bed rest and observation for 24 hours, and this still applies. No patient who has had a risk of significant exposure should be discharged from the hospital in less than 24 hours, unless accompanied by a responsible observer.

Provision of specialized respiratory care is at the prehospital and hospital level. Some cases may require early intubation and ventilation, and more require oxygen and supported ventilation in the early stages. The method of provision of emergency ventilation is a matter of interest. More recent work in physical trauma has indicated that the "open lung" strategy[61,62] is of value in the prevention of inflammatory cascades by opening the alveoli and keeping them open by use of the correct level of positive end-expiratory pressure. This technique follows the hypothesis that repeated opening and closing of alveoli causes kinin release through the action of shear forces in the alveolar walls. There may be an important lesson for the early management of lungs damaged by phosgene exposure, and the manner of emergency ventilation may be critical. Bag-valve ventilation, which can lead to very high inflation pressures and high flow rates, may be harmful. Emergency ventilation strategies that provide controlled flow rates with the early use of positive end-expiratory pressure are more appropriate. These can be provided by the use of small automatic gas-powered ventilators (Fig. 74-8).

Modern experience of the management of mass casualties with toxic pulmonary edema is limited, but it must be assumed that a considerable proportion who survive the acute toxic pulmonary edema would develop acute respiratory distress syndrome unless the appropriate measures are taken. A study by Parkhouse and colleagues[63] showed improved oxygenation, decreased shunt fraction, and decreased mortality in phosgene-exposed pigs that received a protective compared with a conventional ventilation strategy.

Use of Steroids. The use of inhaled and systemic steroids in the treatment of toxic phosgene exposure has been controversial for many years, and Diller,[64] a leading authority on phosgene poisoning, believed in 1985 that the case was unproven. More recently, there has been renewed experimental interest in the subject using chlorine injury, which has produced some encouraging results in pig and rat studies. Gunnarsson and colleagues[65] found in a study of 18 pigs subjected to 140 ppm chlorine for 10 minutes that inhaled beclomethasone dipropionate produced higher Pao_2 and ventilation-perfusion ratios, with less histologic damage, than in the control group. In another study, Wang and colleagues[66] exposed 24 pigs to a higher concentration of 400 ppm for 10 minutes. They found that the inhaled steroid budesonide,



Figure 74-8 The compPAC portable gas-powered emergency and transport ventilator for use in contaminated environments. (Courtesy of Pneupac Ltd, Luton, United Kingdom.)

0.1 mg/kg given within 30 minutes of exposure, was associated with more favorable cardiorespiratory symptoms and lower wet lung weights at autopsy. Demnati and coworkers[67] studied the effects of dexamethasone in rats exposed to high concentration of chlorine (1500 ppm for 5 minutes). They found that the dexamethasone group had significantly reduced pulmonary airway resistance and methacholine-induced bronchoconstriction than the controls.

There have always been noted species differences in challenges to chemical warfare agents, and these results should be applied with caution to humans. In a clinical area where few therapeutic options are available, however, the results provide encouragement for further research and for clinical intervention if the need arises. Borak and Diller[68] reviewed the available evidence for treatment regimens in human phosgene exposure.

Role of Cyclic Adenosine Monophosphate Diesterase Inhibitors. Kennedy and associates[69] suggested that aminophylline may protect against phosgene exposure as a result of its ability to increase cyclic adenosine monophosphate levels. Other compounds, including β-adrenergic agonists, also have this effect and may indicate a new therapeutic direction.

Phosgene and Glutathione Modification. Another promising therapeutic approach is provided by compounds that can increase intracellular reduced glutathione levels as a means of preventing lipid peroxidation–induced phosgene exposure. The rationale behind this approach is that phosgene reacts with cellular SH groups, reduces reduced glutathione redox state, and increases arachidonic acid mediator production and lipid peroxidation. Sciuto and coworkers[70] studied the effect of *N*-acetyl cysteine on anesthetized rabbits exposed to 1500 ppm phosgene. The *N*-acetyl cysteine–treated group had smaller increases in pulmonary wet weight, lower leukotriene levels, and higher glutathione levels. This work suggests that *N*-acetyl cysteine may protect against phosgene exposure by maintaining reduced glutathione levels and inhibiting production of inflammatory leukotrienes.

Hydrogen Cyanide

HCN is one of several agents known originally as *blood agents,* although the term is a misnomer because the agent acts at the cellular mitochondrial level.[71] HCN is a highly volatile liquid used widely in industry and potentially available to terrorists. It has been used since World War I as a chemical warfare agent. Its very short persistence means that decontamination is usually not required after release. It is not absorbed by the activated charcoal of level C respirators (see later), but is removed by impregnating the charcoal with silver salts with which HCN reacts. HCN in high concentrations is rapidly fatal. The LCt_{50} has been estimated at 200 mg/m^{-3} for 10 minutes. HCN acts by binding to the iron atom in cytochrome oxidase enzymes, inhibiting the catalytic function that allows oxygen to act as an electron receptor and produce adenosine triphosphate. Because of this mitochondrial uncoupling, the resulting lactic acidosis theoretically cannot be reversed by restoring oxygenation of the blood by resuscitation measures to improve tissue oxygenation.

Signs and Symptoms

After exposure in humans, the first sign is hyperventilation, which has the effect of increasing the absorbed dose. This is followed by dizziness, rapid loss of consciousness, and convulsions, followed by respiratory arrest. At levels that are not fatal, patients report a smell of almonds and a feeling of apprehension. There is a metallic taste in the mouth, and there may be dyspnea. Because of the rapid action of HCN, patients with acute intoxication are unlikely to be encountered in hospital. This is because antidote therapy plays a key role and, if successful, is curative. Long-term management of the consequences of HCN poisoning is unlikely, although survivors of near-fatal doses can have long-term effects, such as intellectual deterioration, mental confusion, and parkinsonism.

Treatment

In the body, HCN is broken down by rhodanase, which detoxifies cyanide to thiocyanate. This process can be accelerated by provision of sodium thiosulfate, which provides a store of sulfane sulfur for the enzyme.[72-74] The usual dose of sodium thiosulfate is 25 mL of 50% solution (pediatric dose 1.65 mL/kg of 25% solution). It is usually administered in conjunction with sodium nitrite (300 mg given intravenously over 10 minutes [pediatric dose 0.15 to 0.33 mL/kg of a 3% solution]), which causes the formation of methemoglobin. The methemoglobin acts as a scavenger for HCN and reduces its plasma levels. Sympathomimetic support may be required for hypotension produced by sodium nitrite. HCN also reacts with heavy metals, and this is the basis of the use of dicobalt edetate and hydroxycobalamin as cobalt providers for this reaction. Cobalt ions themselves are toxic, but

the toxicity can be countered by giving glucose, which is part of standard therapy. Dicobalt edetate is thought to be more effective in the binding of cyanide ions than methemoglobin despite its secondary effects of hypertension and nausea.

It has long been believed that oxygen therapy and ventilation has no role in the treatment of cyanide intoxication because the blood is fully oxygenated in this condition. This view has been challenged more recently because some studies have shown that oxygen enhances the antidotal effects of the classic cyanide antidotes.[75] Table 74-4 details current antidote treatment approaches.

Toxins

Toxins are high-molecular-weight compounds that are in the middle of the CBW spectrum.[19] They do not reproduce and have characteristics of chemical warfare agents, although they have been considered with biological agents by international convention. They are produced naturally by bacteria and by organisms ranging from protozoans to reptiles such as snakes and scorpions.[76] Toxins are hazardous to humans from natural and deliberate exposure, and this has fueled much research into their actions and treatment.[77] Scientifically, they are of considerable interest and are used as research tools to probe natural processes such as nerve conduction and neuromuscular transmission. In the context of toxic warfare, toxins often have been cited as *doomsday weapons,* and there is considerable public fear about their actions. More than 500 toxins have been described, but only a few are suitable for battlefield and terrorist attacks because of difficulties in production and lack of stability in a released aerosol. Table 74-5 presents the characteristics of common toxins.

In the chemical warfare context, the anesthesiologist may encounter toxins with short latency (neurotoxins, such as botulinum toxin) requiring immediate life support and treatment or with long latency (DNA toxins, such as ricin), which cause major organ dysfunction and present intensive care problems.

Botulinum Toxin

Botulinum toxin is produced by the anaerobe *Clostridium botulinum* and has the reputation of being the most toxic substance by weight known; it is at least 5000 times more toxic than sarin.[78] Botulism, the natural occurrence of the toxin in food poisoning, is a disease of humans and animals. Seven different functionally related neurotoxins (A through G) are produced by the parent organism. Botulism is essentially an intoxication, brought on by ingestion of the toxin produced by clostridial infection of food, usually incorrectly canned meats. Primary botulism, a direct infection, is rare and affects only infants among humans. The interest of botulinum toxin as a toxic agent is that it can be easily produced by fermentation processes (which have been developed to produce antitoxins), and that it is stable as an aerosol, making mass delivery a theoretical possibility. Calculations that 1 kg of the toxin would be sufficient to destroy every human on the planet have rested on this fact.

Botulinum intoxication can be treated, and this modifies the toxicity considerably. It is estimated that less than 10% of natural cases receiving ventilatory and antitoxin support are fatal. A consensus document has been published that examines the risks to civilian populations exposed to botulinum toxin.[80]

Botulinum toxin acts at the nerve terminal of cholinergic synapses. It blocks the release of acetylcholine by being taken up into the vesicles and translocated to the cytoplasm, where it catalyzes the proteolysis of components involved in the calcium-mediated exocytosis of acetylcholine. The inhibition is permanent, and recovery occurs only after the creation of new terminal boutons. The toxin blocks neurotransmission, parasympathetic synapses, and peripheral ganglia. The signs and symptoms of botulism can be explained on this basis.

Conventionally, after ingestion of the toxin (the usual route), there is a latent period of several hours, following which the parasympathetic action produces a dry mouth, followed by signs of a progressive bulbar palsy (dysarthria, dysphasia, and dysphagia) and ocular signs (diplopia and ptosis). These signs are followed by a progressive symmetric descending muscular weakness leading to respiratory failure requiring prolonged ventilatory support. Neuromuscular testing shows a classic presynaptic decremental pattern to repeated stimuli with post-tetanic facilitation. Single-fiber electromyography detects the neuromuscular changes before conventional nerve stimulation; there is increased jitter and blocking, which is reduced by increasing the nerve firing rate.[79] The pattern of signs and symptoms after a deliberate mass inhalation release is unknown, but botulinum toxin must be considered along with the nerve agents in any cases manifesting with sudden disturbances of cholinergic transmission.

Conventional level C protection (see section on personal protection) and decontamination procedures are effective against botulinum toxin, and several antisera exist. A heptavalent antitoxin exists for all the serotypes, but the human efficacy is not known with certainty.[80] Established cases require supportive treatment with antitoxin and positive-pressure ventilation. The latter may be required for a long time.

Saxitoxin

Saxitoxin has been suggested as a possible terrorist toxic agent, but there is no record of its production or use in a military context. In nature, saxitoxin is produced by dinoflagellate sea organisms (causing the "red tide"), including *Alexandrium tamarense, Gymnodinium catenatum,* and *Pyridonium hamense.* The toxin is concentrated in shellfish and is the cause of paralytic shellfish poisoning.[76] The toxin is about 20 times more toxic than sarin, having an LD_{50} in mice of 8 μg/kg. Saxitoxin is active by the inhaled route, causing bulbar palsy, respiratory failure, and cardiovascular failure. The toxin acts by blocking voltage-gated sodium channels.[82] Treatment is based on ventilatory and organ support. An antitoxin has been developed in guinea pigs.[82]

Ricin

Ricin is considered a serious terrorist threat because it can be extracted easily from the seeds of the castor bean plant, *Ricinus communis*. Waste from the production of castor oil contains about 5% ricin, making it a potential source for terrorists. Ricin has been used in assassination,[14] and high inhaled concentrations are thought to be fatal. There is a substantial latent period before generalized signs and symptoms of the inhibition of protein synthesis occur, including fever, abdominal pain, diarrhea, drowsiness, confusion, convulsions, coma, weakness, cardiovascular collapse, and respiratory failure, all progressing to multiple organ failure and death within 36 to 72 hours. Ricin poses a considerable

Table 74-4 Antidotes Used in the Treatment of Cyanide Poisoning

Antidote	Action	Route	Dose	Concurrent Drugs	Duration of Administration	Possible Side Effects
Oxygen	Increases arterial O_2 content, potentiates activity of other antidotes	Inhalation via mask or ETT	High flow via mask or 100% via ETT	Oxygen used as primary antidote in all cases	≤24 hr	Unlikely—possible in patients with COPD
Amyl nitrite	Methemoglobin formation	Inhalation	Adult: 0.2 mL Pediatric: 0.2 mL; may need repeating	Oxygen (not simultaneously)	30 sec/min	Difficult to achieve effective antidotal levels without cardiovascular collapse
Sodium nitrite	Methemoglobin formation	Intravenous injection	Adult: 300 mg (10 mL of 30 mg/mL 3%) Pediatric: 0.13-0.33 mL/kg of 30 mg/mL (3%) solution (i.e., 4-10 mg/kg body weight)	Adult: sodium thiosulfate 25 mL of 500 mg/mL, (50%) solution and oxygen Pediatric: sodium thiosulfate 1.65 mL/kg body weight of 250 mg/mL (25%) solution (approximately 400 mg/kg body weight) and oxygen	≥5 min, ≤20 min	Methemoglobinemia, vasodilation and cardiovascular collapse
Dicobalt edetate	Binding of cyanide ions by dicobalt edetate and by free cyanide ions	Intravenous injection	Adult: 300 mg (20 mL of 15 mg/mL (15%) Pediatric: 4-7.5 mg/kg (0.3-0.5 mL/kg of 15 mg/mL (15%)	50 mL dextrose (500 g/L) intravenously immediately after each dose and oxygen	1 min	Urticaria, edema of face and neck, chest pains, dyspnea, hypotension, convulsions
4-DMAP	Methemoglobin formation	Intravenous injection	Adult: 3.25 mg/kg Pediatric: 3.25 mg/kg	Oxygen and sodium thiosulfate	1 min	Methemoglobinemia, vasodilation and cardiovascular collapse, hemolysis, elevated bilirubin and iron (this is unlikely to be relevant to single-dose exposure)
Hydroxocobalamin	Binds cyanide ions	Intravenous injection	Adult: 5-10 g Pediatric: 70 mg/kg	5 g reconstituted in 100 mL 0.9% saline; oxygen	20 min	Reddish discoloration to skin and mucous membranes
Sodium thiosulfate	Sulfur donor for endogenous enzymatic conversion of cyanide to thiocyanate	Intravenous injection	Adult: sodium thiosulfate 25 mL of 500 mg/mL (50%) solution and oxygen Pediatric: sodium thiosulfate 1.65 mL/kg body weight of 250 mg/mL (25%) solution (approximately 400 mg/kg body weight) and oxygen	Oxygen and sodium nitrite *or* oxygen and DMAP	10 min	Excess administration may cause hypernatremia

COPD, chronic obstructive pulmonary disease; ETT, endotracheal tube.

Table 74-5 Characteristics of Common Toxins

Source	Toxin	Action
Bacteria		
Bacillus anthracis	Anthrax toxin	DNA toxin
Staphylococcus aureus	Staphylococcal enterotoxin B	Enterotoxin
Vibrio cholerae	Cholera toxin	Enterotoxin
Clostridium botulinum	Botulinum toxins	Prejunctional decrease in acetylcholine release
Clostridium perfringens	Perfringens toxin	Necrosis through phospholipase C
Clostridium tetani	Tetanus toxin	Neurotoxin increase in excitability of motor neurons
Protozoa		
Gonyaulax catenella	Saxitoxin	Depolarization block
Fungi		
Fusarium spp.	Tricothecenes	DNA toxin; hemorrhagic syndrome
Plants		
Ricinus communis (castor bean)	Ricin	DNA toxin; hepatorenal failure
Amphibia		
Colombian frog	Batrachotoxin	Irreversible; Na^+ channel blockade; depolarization block
Reptilia		
Asian cobra (*Naja naja oxiana*)	Cobra toxin	Postsynaptic neurotoxin via phospholipase A_2
Taiwan banded krait (*Bungarus multicinctus*)	α-Bungarotoxin	Acetylcholine receptor blocker
Fish		
Deadly pufferfish	Tetrodotoxin	Depolarization block

Adapted from Baker DJ: Anesthesia in extreme environmental conditions, Part 2: Chemical and biologic warfare. *In* Grande CG (ed): Textbook of Trauma Anesthesia and Critical Care. St Louis, Mosby-Year Book, 1993, pp 1320-1354.)

ICU problem. Treatment is supportive, but an antitoxin has been developed for use in animals.[83]

Pharmacologic Agents and Agents of Biological Origin

The events in the Moscow theater siege in 2002[84] have highlighted the possible use of substances that were originally developed as anesthetic agents or adjuncts as "knock-down" weapons. In the siege, a substance was released into the air conditioning system by special forces entering the theater, which led to the deaths from respiratory failure of 127 of 800 of the hostages. The event emphasized the need for immediate life support after toxic attack with short-latency agents. The Russian government, after challenge, declared that the agent used was "fentanyl." Many fentanyl agents have been synthesized apart from the agents familiar in clinical practice, and some are too toxic for general use. Another possibility is the use of a short-chain neuropeptide. Considerable research effect went into investigating such compounds during the last days of the USSR.[16] Agents such as BZ (also initially considered as a possible cause of the theater casualties) have been known for many years and are centrally acting anticholinergic agents. Phencyclidine compounds (related to ketamine) and other hallucinogens were tested during the early days of chemical warfare research during the Cold War and should be considered as part of the differential diagnosis of patients presenting with central nervous system symptoms after a possible toxic attack.

Classic Biological Warfare Agents

General Considerations

Although many organisms have been suggested as being capable of use as biological warfare agents, only a few have been studied to the point of being a threat rather than a hazard.[14] Management of deliberate epidemics is the role of specialist physicians, and anesthesiologists are likely to encounter only agents that have serious pulmonary effects and are likely to require ICU care. There are many analogies from normal epidemic outbreaks that are relevant to deliberate biological warfare attacks, particularly by terrorists. The SARS epidemic in 2004 was a valuable lesson about the spread of a new infectious pathogen in a world linked by fast air connections. Although previous slower forms of travel allowed the incubation of symptoms before arrival at the destina-

tion, air travel does not, and patients may be asymptomatic at the time of their arrival. All hospital practitioners must now be aware of the possibility of transmission of infection from distant locations. Recent travel history should be an essential part of the initial patient interrogation process.

Anthrax

Bacillus anthracis, an aerobic gram-positive, spore-forming, rod-shaped organism, is one of the few listed "standard" biological warfare agents that has been proven to be a hazard and a weaponized threat The natural reservoir of the disease is spores in the soil, and these highly resilient spores form the basis for its use as a biological warfare agent. During tests in World War II, a whole Scottish island was experimentally contaminated and remained in this condition for more than 40 years.[14] There has been evidence for weaponization of the bacillus by several other countries. An accidental release from a military installation in the USSR in 1979 claimed more than 100 lives.[15] The Iraq War in 2003 was fought under the shadow of a possible anthrax attack, although no such weapons were found. Although the standard biological warfare release is seen to be aerosolization spores, the agent was distributed in the United States by mail as a powder in 2001 and claimed several lives, showing its terrorist use.

Anthrax exists in cutaneous, gastrointestinal, and pulmonary forms. The pulmonary form is the major concern of the anesthesiologist and intensivist. In the natural state, pulmonary anthrax is rare, but deliberate release of spores in an aerosol would make the presentation more common.

Physical Findings. The physical findings in pulmonary anthrax are nonspecific, but chest radiography may show signs of effusion or phosgene exposure and mediastinal widening There is an immunoassay available that can detect circulating toxin. The infective dose of anthrax when inhaled is 8000 to 15,000 spores. Spores 2 to 5 µm reach the alveoli; spores greater than this size are trapped in the upper airways. After trapping, the spores are removed to the mediastinal and hilar lymph nodes by pulmonary macrophagocytes. After a germination period of 1 to 3 days, large amounts of anthrax toxin are released into the circulation, causing the clinical manifestations of the pulmonary form of the disease. An initial phase is insidious, lasting 1 to 4 days and consisting of general malaise, fatigue, myalgia, nonproductive cough, and fever. During the next phase of the pulmonary disease, a necrotizing hemorrhagic mediastinitis occurs causing chest discomfort, dyspnea, and stridor. In untreated cases, multiple organ failure follows, which is very refractory to treatment and causes death within 24 to 36 hours. In 50% of cases, hemorrhagic meningitis with coma occurs.

Pathogenesis. Considerable work has been done on the mechanism of the pathogenesis of anthrax infection and the effects of the toxin. The pathogenesis consists of three proteins with a central protective component binding the other two, known as the edema and lethal factors. After transfer to the cytoplasm, edema factor, a calmodulin-dependent adenyl cyclase, converts adenosine triphosphate to cyclic adenosine monophosphate,[85] which causes tissue edema and suppression of the oxidative burst associated with polymorphonuclear phagocytosis.[86] Lethal factor is thought to be associated with macrophage expression of tumor necrosis factor and interleukin-1, cytokines that are a fundamental part of the systemic inflammatory response.

Treatment. Treatment of anthrax infection classically has been founded on the use of benzyl penicillin, but there is evidence of resistance. The current antibiotic recommendation is to use ciprofloxacin, 400 mg every 8 hours, and this was widely used as prophylaxis during the 2001 U.S. terrorist scare. Other approaches may be more appropriate, including doxycycline (200 mg intravenously followed by 100 mg intravenously every 8 hours), gentamicin, erythromycin, and chloramphenicol (Table 74-6).

The recommended antibiotic prophylaxis is ciprofloxacin, 500 mg every 12 hours, or doxycycline, 100 mg every 12 hours. This should be started as soon as possible after exposure.[87] Vaccines have been studied, and the standard Michigan vaccine should be given at 0, 2, and 4 weeks and then at 6, 12, and 18 months, followed by annual boosters. If vaccines are unavailable, antibiotic prophylaxis should be continued for 60 days. For anesthesiologists, intensivists, and other staff involved in the longer term care of anthrax patients, prophylaxis is important, together with careful filter protection of ventilation and disinfection. Wherever possible, disposable circuits should be used.

Plague

Plague was the scourge of the medieval world, and natural outbreaks continued well into the 20th century. Plague has long been considered as a potential biological warfare agent and was researched extensively by the USSR.[16] The pulmonary form is very serious and requires ICU support. The causative organism, *Yersinia pestis,* is an anaerobic, gram-negative coccobacillus that is transmitted to humans via fleas carried by rodents or by animal-human or human-human droplet infection.[88,89] Bubonic, pneumonic, and septicemic forms of plague exist; the last two are fatal without treatment. Only about 100 to 5000 organisms constitute an infective dose. There is an incubation period of 2 to 3 days, following which a pneumonia develops with malaise, high fever, myalgia, hemoptysis, and finally septicemia. There is dyspnea, stridor, and cyanosis. With the worsening condition, intermittent positive-pressure ventilation is required with aggressive antibiotic treatment.

Confirmation of the diagnosis comes from the causative organism in blood, lymph nodes, or sputum cultures. An enzyme-linked immunosorbent assay also is available. Pneumonic plague has long been recognized as being fatal, but antibiotic treatment reduces the mortality to at least 60%. The first line of treatment is streptomycin, 30 mg/kg every 12 hours for 10 days. Alternatives are gentamicin or chloramphenicol. There is an inactivated vaccine (Greer vaccine), but its effectiveness is not thought to be high.

Cholera

Cholera is a widespread natural infection originating from the Far East, which caused several epidemics in Europe throughout the 19th century. Although cholera is the domain of a specialized physician, the profound fluid imbalances caused by the disease make admission of patients to the ICU likely in severe cases. Cholera has been suspected of being weaponized, but it can be spread effectively only by causing mass poisoning through the water supply. Outbreaks occurring in China during World War II were thought to be caused in this way.[14]

Pathogenesis. The infection is localized to the small bowel and causes a major outpouring of fluid and electrolytes. Paradoxi-

Table 74-6 Treatment for Patients Exposed to Biological Warfare Agents

Agent	Infective Dose	Incubation Period	Effects (after Inhalation)	Staff Protection	Specific Treatment	Chemoprophylaxis	Vaccine	Mortality if Untreated
Bacillus anthracis	8000-15,000 spores	1-5 days	Mediastinitis, meningitis, MOF	Isolation, vaccination, universal precautions	Ciprofloxacin 400 mg IV tid; doxycycline 200 mg IV once, then 100 mg IV tid; penicillin 2 MU IV 2 hourly + streptomycin 30 mg/kg IM qd	Ciprofloxacin 500 mg PO bid × 4 wk + vaccinate; doxycycline 100 mg PO bid × 4 wk + vaccinate	Michigan at 0, 2, 4 wk, 6, 12, 18 mo, then annually	Pneumonic, 100%
Yersinia pestis	100-500 organisms	2-3 days	Pneumonia, septicemia, MOF	Isolation, universal precautions	Streptomycin 30 mg/kg IM qd × 10 days; doxycycline 200 mg IV, then 100 mg IV tid × 14 days (chloramphenicol)	Doxycycline 100 mg PO bid × 7 days; tetracycline 500 mg PO qd × 7 days	Greer at 1-3 mo + 3-6 mo	Pneumonic, 100%
Viral hemorrhagic fevers	1-10 organisms	4-21 days	Coagulopathy, edema, MOF	Isolation, HEPA masks, universal precautions	Ribavirin 30 mg/kg IV once, then 15 mg/kg IV qd × 4 days, then 7.5 mg/kg IV tid × 6 days (immunoglobulin)	NA	None	90% (Ebola-Zaire)
Viral encephalitides	10-100 organisms	2-6 days (VEE) 7-14 days (EEE/WEE)	Encephalitis, convulsions, coma, CNS damage	Universal precautions	Supportive, anticonvulsants	NA	Available for VEE, EEE, and WEE	75% (EEE)
Francisella tularensis	10-50 organisms	2-10 days	Pneumonia, pleural effusions	Universal precautions	Streptomycin 30 mg/kg IV qd × 10-14 days; gentamicin 3-5 mg/kg IV od	Doxycycline 100 mg PO bid × 14 days	Live attenuated	35%
Variola organisms	10-100	7-10 days	Rash, secondary pneumonia	Isolation, universal precautions	Cidofovir 5 mg/kg IV once every 2 wk	Vaccinia immunoglobulin	Wyeth	Unvaccinated 30%, vaccinated 3%
Burkholderia mallei	1-10 organisms	10-14 days	Septicemia, pneumonia, lymphadenopathy	Universal precautions	Co-amoxiclav 20 mg/kg IV tid	Tetracycline 500 mg PO qd × 14 days	None	Uncertain: >30% if septicemic
Coxiella burnetii	1-10 organisms	10-14 days	Myalgia, malaise, fever	Barrier nursing	Doxycycline 100 mg PO bid × 5-7 days after exposure × 5 days	Doxycycline 100 mg PO bid for 8-12 days	Q vax	<1%
Brucella spp.	10-100 organisms	5-60 days	Malaise + cough, sacroiliitis, pancytopenia	Barrier nursing	Doxycycline 100 mg PO bid + rifampicin 900 mg tid PO for 6 wk	Doxycycline and rifampicin for 3 wk	None	<5%
Escherichia	10-100 organisms	1-5 days	Vomiting + diarrhea, renal failure	Barrier nursing	Antibiotics not required	NA	None	<5% *E. coli* O157:H2

CNS, central nervous system; EEE, eastern equine encephalitis; HEPA, high-efficiency particulate air filter; MOF, multiple organ failure; NA, not applicable; VEE, Venezuelan equine encephalitis; WEE, western equine encephalitis.
Adapted from White SM: Chemical and biological weapons: Implications for anaesthetic and intensive care. Br J Anaesth 89:306, 2002.

cally, fluid can still be absorbed, and this is the basis of the use of oral rehydration solutions in mass outbreaks in developing countries.

Treatment. The management of cholera essentially comprises fluid and electrolyte replacement. Traditionally, the intravenous route was used, but modern practice is to use oral rehydration solutions containing electrolytes and glucose.[90] Early rehydration in this way avoids the need for admission to the ICU. In the case of a deliberate cholera epidemic, early oral rehydration would be a high priority for mass casualties. Tetracyclines traditionally have been the antibiotic treatment of choice, but resistance has been reported.[91]

Glanders

Glanders is an equine disease caused by the gram-negative bacillus *Burkholderia mallei*. It has long been considered to be a potential biological warfare agent in a modified form because the organism is known to be highly infectious in the aerosolized form. There are acute and chronic forms in humans.[91] The septicemic form appears 10 to 14 days after exposure, making the agent one of long latency. There is a sudden onset of high fever, rigors, and myalgia with cervical lymphadenopathy, splenomegaly, leukopenia, or leukocytosis. In this form, septic shock and multiple organ failure occur, and the fatality rate without treatment is high.

After inhalation of the organism, the acute pulmonary form is seen with septicemia, bilateral pneumonia, and pulmonary nodular necrosis. The chest radiograph shows miliary shadowing. The severe acute forms of the disease are most likely to concern intensivists, but there is an oropharyngeal form with ulceration of the septum and turbinate and a blood-stained mucopurulent discharge and a macropapular or pustular rash similar to smallpox. In the chronic form, glanders can produce chronic lymphadenopathy, multiple musculocutaneous abscess formation, and oropharyngeal nodules. The first-line treatment of glanders is an antibiotic combination (co-amoxiclav and sulfadiazine, 30 mg/kg every 8 hours for 3 weeks). Doxycycline, rifampicin, and ciprofloxacin are second-line drugs. No vaccine against glanders exists.

Viral Diseases Regarded as Potential Biological Warfare Hazards

Numerous viral illnesses are considered to be potential biological warfare agents. They are the province of the specialized infectious disease physician, and the anesthesiologist is referred to specialized texts for a broader discussion.

Of the potential listed agents, smallpox is placed high on the potential terrorist hazard list because of the continuing presence of laboratory stocks of virus, which is normally promulgated only through human hosts. The success of the worldwide vaccination campaign led the World Health Organization to declare smallpox an extinct disease, and mass vaccination programs were stopped. Laboratory studies continued, however, and there is a fear at present that strains could be stolen and used to create a deliberate widespread epidemic in a largely unprotected population. Intensive care may be required for cases contracting overwhelming secondary infection. Although treatment is based on isolation and supportive therapy, there is current interest in the use of the antivirals cidofovir and ribavirin.[92]

Involvement of the Anesthesiologist in the Management of Casualties from Chemical and Biological Warfare Agents

Approaches to Management of Chemical and Biological Warfare Incidents

Anesthesiologists may be confronted with the management of victims from the deliberate or accidental release of CBW hazards inside and outside the hospital. It is important to have a system of management of such cases that allows for the safety of the medical responders and provides the correct treatment for the patient. Given the risks associated with CBW release, management should be considered in terms of (1) management of the incident and (2) management of the patient's condition. In terms of the four properties of agents in the CBW spectrum (see the section on agents of chemical and biological warfare—background and development), management of the incident is determined by persistency and transmissibility, and management of the patient's condition is determined by toxicity and latency.

Many chemical hazards have limited persistency, and decontamination is not required. "Limited persistency" means reduced risk of contact transmission to other individuals. Certain chemical agents have long persistency, however, and high transmissibility. Many such agents do not pose a significant threat by inhalation, but may be absorbed through the epithelia (e.g., nerve agent VX). For such agents, careful decontamination is essential.

Most classic biological warfare agents have low persistency, and are rapidly degraded by the environment and depend on host transmission via an incubation period. In such cases, transmissibility is high. Anthrax is a notable exception; its spores have very long persistency, but no infective transmissibility. At the other extreme, the viral hemorrhagic fevers have very short persistency, but high infective transmissibility.

Management of the Incident

Disaster planning, which is a process familiar to many anesthesiologists, provides a good model of how to approach toxic releases. A toxic release is a special case of disaster and may be either accidental or deliberate. Plans put in place for a terrorist release of a CBW agent would be equally valuable for the more likely case of accidental release. Moles[93] summarized the essential points of disaster planning as follows:

1. The importance of risk assessment—not all listed hazards are identifiable risks.
2. Preplanning—this essential stage should bring together all the different emergency agencies, such as fire, civil defense, and police, that would be involved in CBW incident management.
3. The importance of a phased response, based on exercises and assessment.

Personal Protection

Protection is a key feature of incident management, and anesthesiologists should be familiar with personal protection levels (Table 74-7) and protective suits and masks, and with techniques of decontamination. As Table 74-7 shows, several levels of protection are used in the management of toxic releases, but the appropriate level for medical intervention is level C, which allows reasonable tactile dexterity and contact with the patient to provide essential life support and antidote therapy on site.[21] Level C protection (Fig. 74-9) is equivalent to that used by the military to provide protection against the most toxic chemical warfare agents and virulent biological warfare organisms.

Table 74-7 Levels of Personal Protection in HAZMAT Incidents

Level A
Positive-pressure SCBA
Fully encapsulating chemical-resistant suit
Double layer of chemical-resistant gloves
Chemical-resistant boots
Airtight seal between suit and gloves and boots
Level B
Positive-pressure SCBA
Chemical-resistant, long-sleeved suit
Double layer of chemical-resistant gloves
Chemical-resistant boots
Level C
Full-face air-purification device (respirator)
Chemical-resistant suit
Chemical-resistant outer gloves
Chemical-resistant boots
Level D
Equipment does not provide specific respiratory or skin protection and usually consists of regular work clothes

SCBA, self-contained breathing apparatus.

Detection and Identification of the Hazard

In contrast with military CBW releases, civil incidents may not provide early information about the nature of the hazard. Patterns of signs and symptoms manifesting in victims may be the first indication of the nature of the causative agent. Detection and monitoring devices for established military chemical warfare hazards exist, but are not widely available in the civil context. Intelligence information may be available for terrorist attacks. In the case of accidental toxic agent release, information would be available from the HAZMAT system and the appropriate identification codes.

Early Patient Management after Chemical and Biological Warfare Release

If the released hazard is persistent and transmissible, decontamination is essential in the decontamination zone. In some countries, level C–protected medical staff or paramedics can now operate in this area and work alongside fire personnel in providing (1) triage, in terms of whether or not the patient requires decontamination and the patient's medical status; (2) immediate life support measures (TOXALS); and (3) immediate antidote and other pharmacologic support.

Figure 74-10 shows a medically operated chemical warfare casualty reception facility at a Parisian hospital. The importance of early life support measures in the decontamination zone has been recognized by many emergency services.[94] The concept of *TOXALS*, introduced in 1996,[95] expands the familiar *ABCs* of life support to relate to toxic releases as follows:

*A*irway of the casualty must be maintained at all times. In an unconscious patient, this may involve simple basic airway maneuvers plus suction of the copious secretions associated with chemical poisoning. Occasionally, there may be a requirement for advanced airway management, such as tracheal intubation, to protect the airway from the excessive secretions and to prevent aspiration of regurgitated stomach contents.

*B*reathing must be carefully observed until full decontamination and recovery have occurred. Supplemental oxygen speeds the recovery from volatile chemical poisoning. If breathing becomes compromised, it must be supported by



Figure 74-9 Civil (**A**) and military (**B**) level C protective respirators and suits. *(Courtesy of Service d'Aide Médicale Urgente [SAMU] de Paris, France.)*



Figure 74-10 Special triage, decontamination, and resuscitation center set up at a Parisian teaching hospital. *(Courtesy of Service d'Aide Médicale Urgente [SAMU] de Paris, France.)*

artificial ventilation with supplemental oxygen using a self-inflating resuscitation bag-valve-mask or automatic ventilator. Entrained air must be filtered when ventilating casualties in a contaminated environment.

*C*irculation must be carefully observed and monitored. Noninvasive blood pressure, pulse oximetry, and electrocardiogram monitoring all are useful indicators of circulatory function. The early establishment of intravenous access aids the administration of fluids and drugs.

*D*isability (conscious level) should be assessed using the simple *AVPU* scale (*A*lert, responds to *V*oice, responds to *P*ain, *U*nresponsive). This assessment should be repeated at frequent intervals to assess the progress of the casualty.

*D*rugs, especially the specific antidotes, should be administered when a specific agent has been identified.

*E*xposure of the casualty is essential not only to assess physical damage, but also to remove all clothes that have been contaminated by the chemical. Approximately 80% of surface contamination is removed by undressing.

*E*nvironment. The primary management as described may be severely limited by the need of the rescuer to wear protective clothing. Only individuals skilled in these techniques and trained in protective clothing should enter and treat casualties in a contaminated area. All others should await the casualties' arrival in cold/clean zone, following decontamination.

The identification of the chemical and its specific antidote might take some time. This situation must not delay the basic medical management of the casualty, however.

Somatic Systems Affected by Toxic Hazards

Early patient management is based on (1) identification information and (2) the presenting signs and symptoms. Usually, information is available to help with identification of the agent used. On the basis of presenting signs and symptoms, it is useful to consider attacks on the various systems as guide to the agent used (Table 74-8). A wide range of chemical agents affect the respiratory system and are summarized in Table 74-9.

Problems in Chemical and Biological Warfare Incident Management

The numerous recognizable problems in the medical management of CBW incidents include the following:

1. Failure to recognize CBW release
2. Failure to implement appropriate HAZMAT procedures to limit the number of secondary casualties
3. Release of the agent overwhelming the available emergency and medical resources
4. Insufficient planning and training
5. Lack of appropriate protective equipment
6. Lack of resuscitation skills for early life support
7. Lack of specific knowledge for the management of toxic or infectious hazards
8. Panic and hysterical reactions from a frightened general public fueled by irresponsible reporting

These problems may be minimized by careful planning, equipping, and training, with the objective of making a CBW release manageable in the same sense as for other mass disasters.

Effects of Chemical and Biological Warfare Agents on Anesthetic Practice

Management of Mixed Toxic and Physical Injury

Chemical warfare and HAZMAT release may be accompanied by explosion and fire causing associated injuries requiring surgical intervention. The effects of the release agent on the subsequent

Table 74-8 Effects of Chemical and Biological Warfare Agents on Somatic Systems

System Affected	Agents
Epithelial	Vesicants (e.g., sulfur mustard), smallpox, ricin
Respiratory	
Upper, lower airway	Vesicants, phosgene
Respiratory control system	Nerve agents, ABO
Gaseous exchange	Pulmonary edemagens
Mechanics of breathing	Nerve agents, neurotoxins
Central nervous system	Nerve agents, cyanide, neuropeptides, agents of anesthetic origin (phencyclidines, BZ)
Peripheral nervous system	Nerve agents, neurotoxins (e.g., botulinum, saxitoxin)
Immune system	Vesicants, ABO (provocation of immune responses, inflammatory responses, organ failure)
Cardiovascular	Nerve agents, ABO
Alimentary, renal	Nerve agents, toxins, infectious agents

ABO, agents of biological origin.

Table 74-9 Effects of Toxic Agents on Respiration

Respiratory Component	Effect	Toxic Agent
Central nervous system	Depression of respiratory drive and convulsions leading to apnea	Nerve agents, cyanide, neuropeptides
Peripheral nervous system	Neuromuscular paralysis of respiratory muscles	Nerve agents, neurotoxins
Nasopharynx	May become blocked by excess secretions Prodromal rhinitis and rhinorrhea Sneezing	Lung-damaging agents, nerve agents Vesicants Early symptom of mustard
Larynx	Irritation, laryngeal spasm	Upper respiratory irritant, lung-damaging agents Riot-control agents, particularly CS and CR (tear gas)
Large airways	Blocked by secretions Blocked by inhaled vomitus Sloughing of walls of trachea and main bronchi, produces "pseudodiphtheritic" membrane, serious cause of large airway obstruction, leading to bronchopneumonia and death	Nerve agents (theoretical) Various agents Nerve agents
Small airways	Blocked by secretions Cholinergic innervation affected; bronchospasm (relieved by atropine) Chemical bronchiolitis, followed by serious bronchospasm	 Nerve agents Mustard agents
Alveoli	Toxic pulmonary edema	Various agents, especially lung-damaging agents (latency 6-24 hr) Vesicant agents, particularly if inhaled at high ambient temperature*

*Data from Willems JL: Clinical management of mustard gas casualties. Ann Med Mil Belg 3(Suppl):1-61:47, 51, 1989.
From Baker DJ, Rustick JM: Anesthesia for casualties of chemical warfare agents. *In* Zaitchuk R, Grande C (eds): U.S. Army Textbook of Military Medicine, part IV, vol I. U.S. Department of the Army, Office of the Surgeon General Borden Institute, Washington, DC, 1995, pp 833-856.

conduct of general anesthesia are important. Many of the agents described earlier affect the condition of the patient and the action of anesthetic agents.

Effects on the Condition of the Patient

Shock and toxic airway injury can produce ventilation-perfusion inequality, which affects preoxygenation for emergency induction. The respiratory uptake of anesthetic vapors and alveolar ventilation itself are affected by degrees of shunt and pulmonary edema. Above all, the action of toxic agents may be expected to alter the balance and flow of general anesthesia and may cause delays in recovery, which would be manpower-intensive in management. In terms of postoperative intensive care, patients who have been exposed to pulmonary edemagens and to OPs may pose the greatest problem.

Intensive Care Implications

Exposure to chemical warfare agents may give rise to numerous syndromes that have already been mentioned that require medium-term or long-term ICU treatment. These include pulmonary edema and acute respiratory distress syndrome. In the case of OP exposure, there may be a possibility of developing the intermediate syndrome,[96,97] with a reparalysis of the patient requiring several days of ventilation. Experience with OP anticholinesterases in this area is lacking, although there is considerable evidence from pesticide poisoning.

Many of the infectious agents that are considered as biological warfare agents could give rise to infections that cause an overwhelming inflammatory response and organ dysfunction. Although the management of the infections caused by biological warfare agents is the domain of the specialized physician, intensive care is required for cases of systemic inflammatory response syndrome and multiple organ dysfunction syndrome. The continued possibility of an avian flu pandemic has highlighted the need to provide simple mass ventilation systems in high-dependency units. In such units, patients can be ventilated using simpler machines than the ones found in the ICU and that can be operated by non-ICU personnel. Mass procurement of devices and training is necessary. The ability of hospitals to provide intermittent positive-pressure ventilation for large numbers of casualties is a necessary step in managing not only respiratory epidemics, but also the consequences of the numerous CBW agents considered in this chapter in which respiratory failure is the end stage of the pathology.

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75 Anesthesia for Eye, Ear, Nose, and Throat Surgery

Key Points

Ear, Nose, and Throat

1. Patients can present with an acute onset of stridor from various conditions, including epiglottitis, laryngotracheobronchitis, inhaled foreign bodies, angioneurotic edema, tracheitis, burns, and bilateral vocal cord palsies after surgery.
2. Facial injuries can produce severe bleeding with the aspiration of blood, bone, loose teeth, and soft tissue fragments, so the priority is to clear and secure the airway.
3. For ear surgery, several anesthesia and airway management devices are available, all of which offer different advantages and disadvantages.
4. Bleeding from a tonsil after surgery usually occurs within the first 6 hours.
5. The optimal anesthetic technique for endoscopy procedures depends on the patient's general condition; the size, mobility, and location of the laryngeal lesion; the use of a laser; and surgical requirements.

Eye

1. Understanding ocular anatomy and physiology and the systemic effects of ophthalmic medications is essential to prepare an appropriate anesthesia plan.
2. Pressure on the globe or any orbital contents can result in a trigeminovagal or oculocardiac reflex with bradycardia, atrioventricular block, or asystole.
3. The blood supply to the retina is driven by the ocular perfusion pressure, which is determined by the arterial blood pressure and the intraocular pressure (IOP).
4. Deep inhaled anesthesia reduces IOP, whereas ketamine and succinylcholine can increase IOP.
5. Sudden increases in IOP in the setting of open globe injury can lead to vitreous loss and blindness.
6. Complications of retrobulbar block include retrobulbar hemorrhage, increased IOP, intra-arterial injection with convulsions, and subarachnoid injection via the optic nerve sheath with respiratory arrest.
7. Nitrous oxide should be avoided for 15 minutes before the use of intraocular gas. Nitrous oxide must be avoided for 7 to 45 days after use, or until the gas bubble is resorbed.
8. True ophthalmic emergencies, such as chemical burns and central retinal artery occlusions, must be treated within minutes to avoid permanent vision loss. Open globe injuries and other urgent procedures can be scheduled after appropriate NPO status.
9. Eye compression from a facemask or positioning can lead to central retinal artery occlusion.

General Principles of Ear, Nose, and Throat Surgery

Anesthesia for ear, nose, and throat (ENT) surgery encompasses a range of operations varying in duration, severity, and complexity from high-volume cases, such as myringotomy, tonsillectomy, and simple nasal procedures, to complex procedures in head and neck cancer patients. Probably in no other branch of surgery is the requirement for understanding between the surgeon and the anesthesiologist greater than in "shared airway" procedures, and careful planning, preoperative evaluation, and close cooperation are essential.

Airway Safety and Maintenance

The provision of a clear, free, and unobstructed airway is the principal concern for all ENT procedures. Numerous factors have an impact on the ability to maintain a safe and patent airway, and careful attention is mandatory during the whole procedure, including cessation of surgery if necessary. Chapter 50 contains a

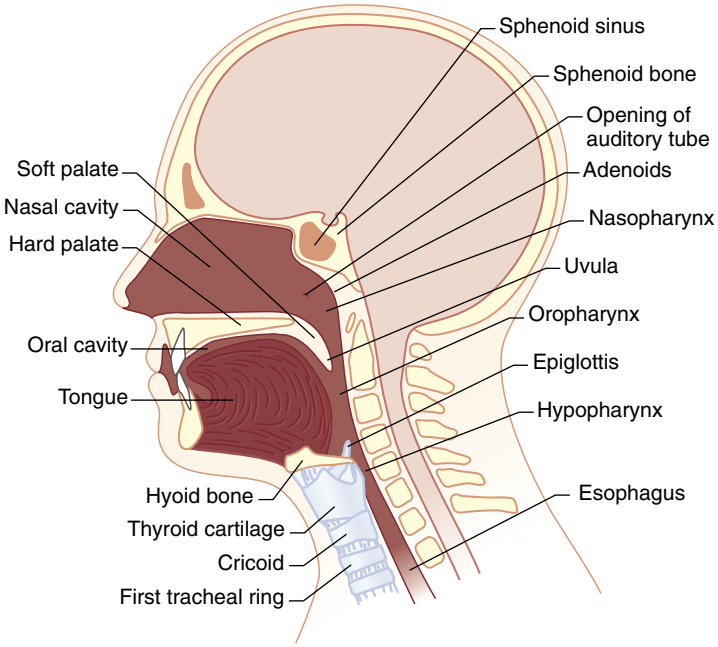

Figure 75-1 Anatomy of nasal cavity, oral cavity, nasopharynx, oropharynx, and hypopharynx.

thorough discussion of airway anatomy and management (Figs. 75-1 to 75-3).

Factors affecting airway safety and maintenance may be classified into the following four groups:

1. *Patient factors*: Patients may present with distorted upper airway anatomy or airway obstruction.
2. *Remote surgery*: After surgery has begun, the anesthesiologist is remote from the airway, making adjustments more difficult and disruptive.
3. *Surgical factors*: Significant lateral rotation of the head may be required for ear procedures, and head extension may be required for neck procedures. During intraoral procedures, instruments to keep the mouth open may obstruct the airway. For nasal and intraoral surgery, the airway requires protection from blood and secretions.
4. *Shared airway*: Shared airway procedures involving surgery of the glottis, subglottis, and trachea require an understanding of specialist equipment, techniques, and laser safety.

Physiology

Vocal Cord Palsy

Nerve damage can result from surgical trauma during operations on the thyroid gland, operations on the parathyroid glands, anterior approaches to the cervical spine, neck procedures, and left-sided thoracic procedures. Short-duration tracheal intubation for peripheral elective surgery is associated with unilateral vocal cord palsy, which has an incidence of approximately 1 per 1000 procedures.[1]

The superior laryngeal nerve provides innervation to the cricothyroid muscle, which tenses the vocal cord. Superior laryngeal nerve injury results in a loss of tension, with the vocal cord appearing wavy, or at a lower level during inspiration and a higher level during expiration. Bowing of the true vocal fold, prolapse of the false vocal fold, and altered waveform on videostroboscopy are seen with this injury. Patients are at a higher risk of aspiration because of their sensory deficit and have a lower pitched, weak, monotonous, and easily tired voice.[2]

The recurrent laryngeal nerve provides innervation to all the other intrinsic muscles of the larynx, including the only abductor of the vocal cords, the posterior cricoarytenoid. The recurrent laryngeal nerve supplies abductor fibers (posterior cricoarytenoid) and adductor fibers to the other intrinsic laryngeal muscles. The abductor fibers within the recurrent laryngeal nerve are more sensitive and vulnerable to trauma than the adductor fibers. A partial injury to the recurrent laryngeal nerve can produce a pure abductor paralysis, whereas complete transection of the recurrent laryngeal nerve produces an abductor and adductor fiber injury.[3] This variable sensitivity of the recurrent laryngeal nerve to either abductor injury or abductor and adductor injury accounts for the different clinical presentations of patients with nerve damage.

With a partial injury of the nerve in which only the abductor fibers have been damaged, the vocal cord on the affected side remains in the midline on phonation and inspiration, while the nonaffected vocal cord moves (adducts). With a complete unilateral palsy of the recurrent laryngeal nerve, abductor and adductor fibers are affected. In this case, the vocal cord assumes a paramedian position with the vocal cord neither abducted nor adducted. In this situation, on phonation the unaffected vocal cord crosses the midline to meet the affected vocal cord, and on inspiration the unaffected vocal cord moves to full abduction.

A bilateral complete recurrent laryngeal nerve palsy (affecting abduction and adduction) results in both vocal cords adopting a paramedian position. A partial bilateral recurrent laryngeal nerve palsy involving only the abductor fibers can result in bilateral adducted vocal cords, an inability to open the vocal cords on inspiration, serious compromise to airflow, and a critically obstructed airway, which may require immediate intervention. Bilateral incomplete palsy is more dangerous than complete palsy.[3]

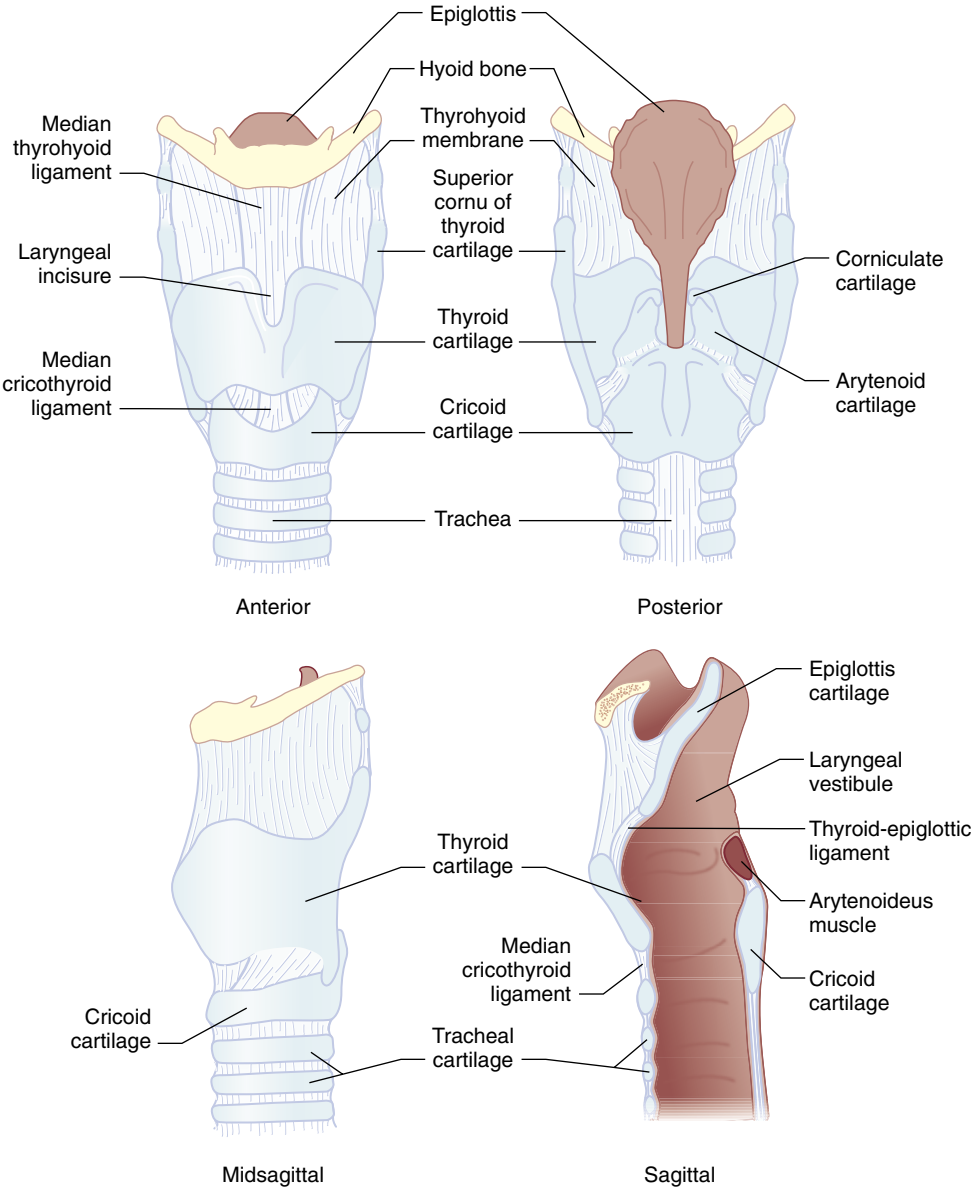

Figure 75-2 Schematic representation of the anatomy of the larynx: anterior, posterior, midsagittal, and sagittal views.

Laryngospasm

Laryngospasm is an exaggeration of the normal glottic closure reflex that persists long after the removal of the stimulus.[4] Reflex glottic closure is a dominant and stable reflex produced by the stimulation of the superior laryngeal nerve. Laryngospasm is an exaggeration of this response stimulated by the presence of blood, secretions, or surgical debris, particularly in the presence of a light plane of anesthesia. During light planes of anesthesia, buccal, pharyngeal, laryngeal, and upper abdominal stimulation or manipulation; smell; and nasal irritation all have been implicated in the production of laryngospasm. Laryngospasm is more common after upper airway procedures, particularly ENT procedures in which blood, secretions, and surgical debris are present. Typically, laryngospasm manifests with stridor that can proceed to complete airway obstruction and requires an immediate response. Strategies to reduce the incidence of postextubation laryngospasm, particularly in children undergoing ENT procedures, include intravenous lidocaine,[5] topical lidocaine,[6] intravenous magnesium,[7] and "deep" extubation.[8]

The management of laryngospasm involves immediate suctioning to remove obvious blood and secretions from the airway and the application of a tightly held facemask with 100% oxygen acting as a pneumatic splint to keep the airway open. Larson's maneuver, a forcible jaw thrust with bilateral digital pressure on the body of the mandible just anterior to the mastoid process, known as Larson's point, may resolve laryngospasm by clearing the airway and stimulation.[9]

The general principle for the management of laryngospasm is to apply 100% oxygen with either positive end-expiratory pressure or continuous positive airway pressure acting as a pneumatic splint. Any obvious secretions are suctioned out, and these maneuvers are used as a holding point to allow the patient's depth of anesthesia to lighten and the laryngospasm to resolve. If these holding maneuvers fail to provide enough airflow, and oxygen

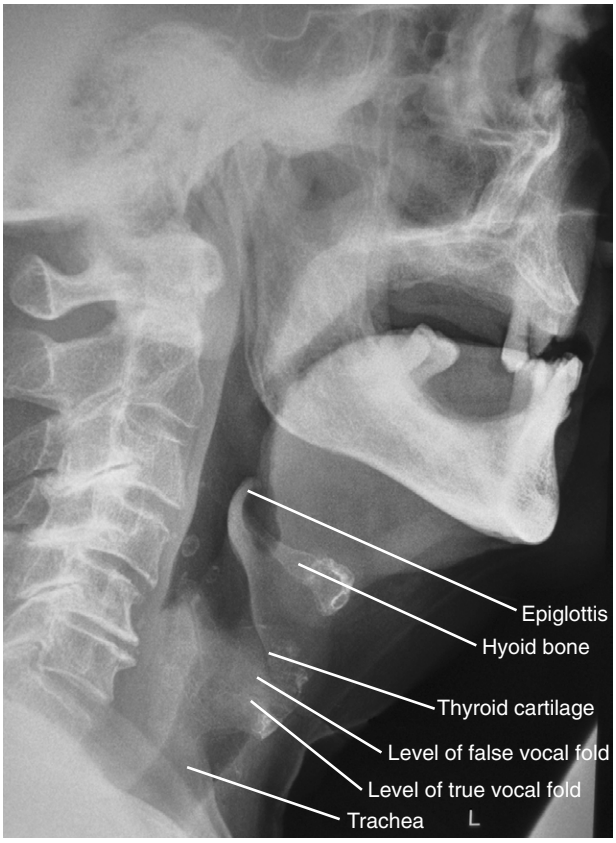

Figure 75-3 X-ray of larynx anatomy.

desaturation starts to occur, an increase in the depth of anesthesia is required with intravenous propofol or other intravenous drugs to diminish the exaggerated glottic closure reflex causing the laryngospasm. If, despite the application of 100% oxygen, positive end-expiratory pressure or continuous positive airway pressure, and intravenous agents, the laryngospasm continues, and oxygen saturation levels continue to decrease, a small dose of succinylcholine (0.1 to 0.5 mg/kg) should be considered. If laryngospasm does not resolve, other causes of postextubation stridor need to be assessed for, including laryngomalacia, tracheomalacia, vocal cord paralysis, airway edema, hematoma, soft tissue obstruction, and the presence of foreign material such as throat packs.

The incidence of laryngospasm is greater in children than in adults, and hypoxia develops more rapidly. This is a particular problem for children undergoing ENT procedures, requiring vigilance and immediate treatment.

Stridor

Stridor is a noisy, high-pitched, predominantly inspiratory sound from turbulent airflow secondary to upper airway obstruction and can be a medical emergency requiring immediate intervention. The initial management is the same regardless of the cause; 100% oxygen should be administered by a facemask with the patient sitting upright and nebulized, with racemic epinephrine, 1 mg of a 1 : 1000 solution (1 mL) in 5 mL of 0.9% saline, repeated every 30 minutes with monitoring. Epinephrine works by droplet deposition on inflamed swollen mucosa and its intense vasoconstrictor actions. Dexamethasone, 0.1 mg/kg intravenously every 6 hours, helps reduce airway edema, but takes 4 to 6 hours to work. Heliox (70% helium, 30% oxygen) greatly increases flow for any given pressure gradient, or allows the same flow for a smaller pressure gradient. In contrast with laminar flow, in which resistance depends on gas viscosity during turbulent flow, resistance depends on gas density. Heliox leads to a dramatic decrease in airway resistance and improvement in ventilation. The higher the concentration of helium in the mixture, however, the lower the F_{IO_2}.

Patients can present with an acute onset of stridor from various conditions, including epiglottitis, laryngotracheobronchitis, inhaled foreign bodies, angioneurotic edema, tracheitis, burns, and bilateral vocal cord palsies after surgery. Typically with acute-onset stridor, as the airway diameter decreases, a noisy inspiratory stridor is audible, and in a typical adult this is most pronounced as the airway diameter reaches about 4 mm. In chronic stridor, the patient slowly compensates for the reduction in airway diameter; it is possible to have a patient with an airway diameter of 3 to 5 mm, who at rest appears to have no stridor, although stridor becomes obvious on simple exertion. Although the presence of stridor in an acute setting is always an alarming sign, its absence does not imply the airway is not compromised. Chronic causes of stridor include subglottic stenosis, laryngomalacia, malignancy, mediastinal masses, webs, cysts, and vascular malformations.

Trauma (see also Chapter 72)

Airway Trauma

Trauma to the airway can result from blunt or penetrating injuries, burns, inhalational injury, and iatrogenic trauma. The initial response is influenced by the degree of airway compromise (Figs. 75-4, 75-5, and 75-6), and patients with obvious respiratory distress need immediate intervention to secure a patent airway. Immediate airway control may involve orotracheal intubation, intubation through a large open wound in the airway, or an emergency surgical airway, under local anesthesia. Fiberoptic intubation can be extremely difficult, or may not be possible when severe airway distortion is present with swelling, edema, and bleeding. Orotracheal intubation should be performed by an experienced practitioner, with the help of a skilled assistant.

In blunt laryngeal trauma, cricoid pressure may result in cricotracheal separation and should be avoided. A high index of suspicion should be maintained when assessing and observing patients with laryngeal trauma because late diagnosis and intervention can result in poor airway and voice outcome.[10] Symptoms that suggest laryngeal trauma include dyspnea, dysphonia, odynophagia, pain, dysphagia, and hoarseness.[11,12] Careful, gentle assessment should be undertaken to avoid accidental dislodgment of unstable cartilage fragments, which may cause further airway compromise. Examination may reveal abrasions over the anterior neck, subcutaneous emphysema, stridor, hemoptysis, bruits, loss of palpable landmarks, and signs of a pneumothorax. Flexible fiberoptic laryngoscopy may reveal edema, hematoma, and abnormal vocal cord position.

Patients with neck trauma who are hemodynamically unstable or who have an obvious injury to the aerodigestive tract require urgent surgery.[13] Iatrogenic trauma,[14] resulting in cricoarytenoid joint dysfunction,[15] vocal cord palsy,[1] granuloma formation, hematoma, or subglottic stenosis, is a significant cause of morbidity after routine tracheal intubation.[16]

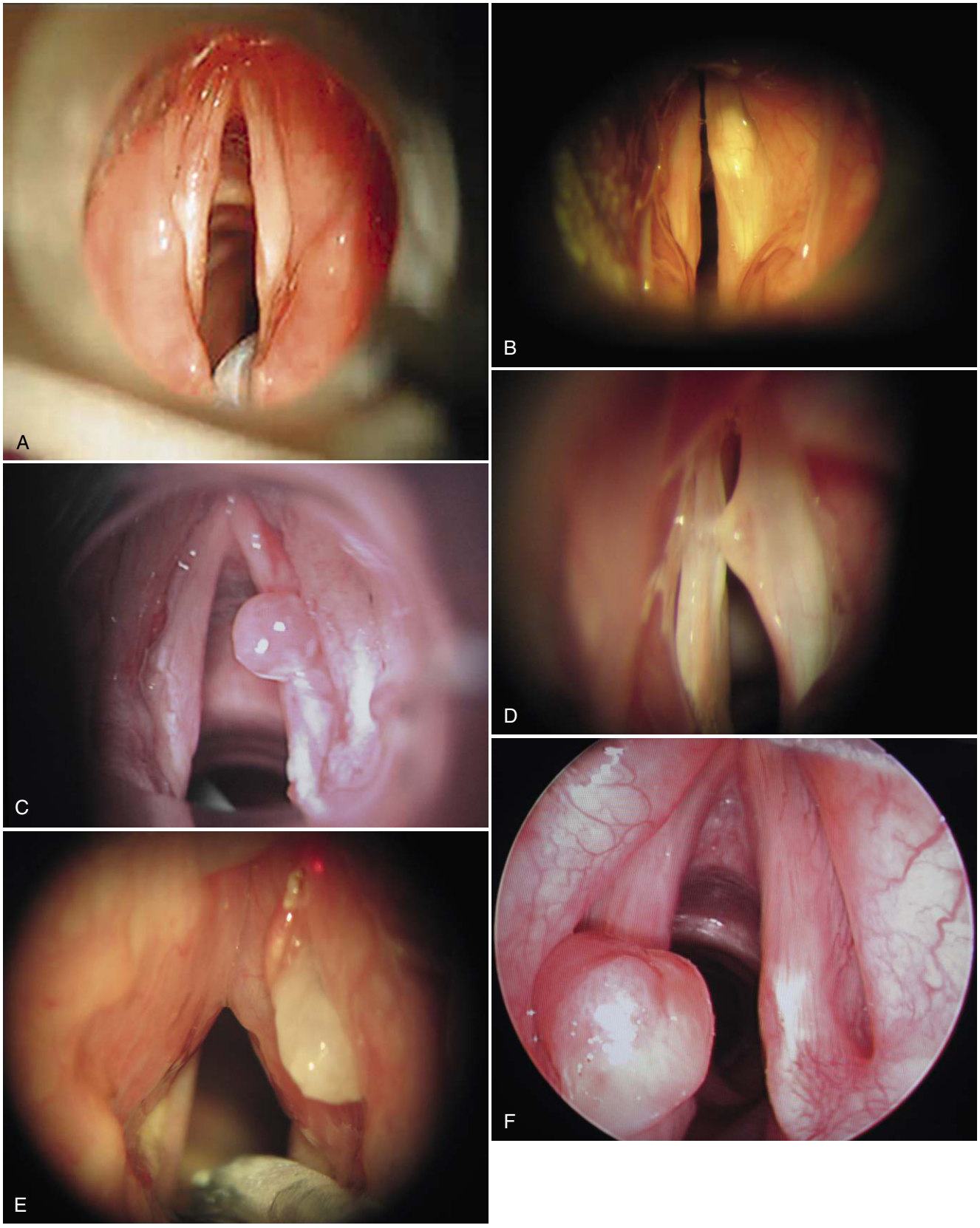

Figure 75-4 Vocal cords with little or no airway compromise. **A,** Normal vocal cord. **B,** Minor right cord lesion. **C,** Granuloma on mid right cord. **D,** Kissing nodule on right cord. **E,** Anterior webbing of vocal cord. **F,** Intubation granuloma.

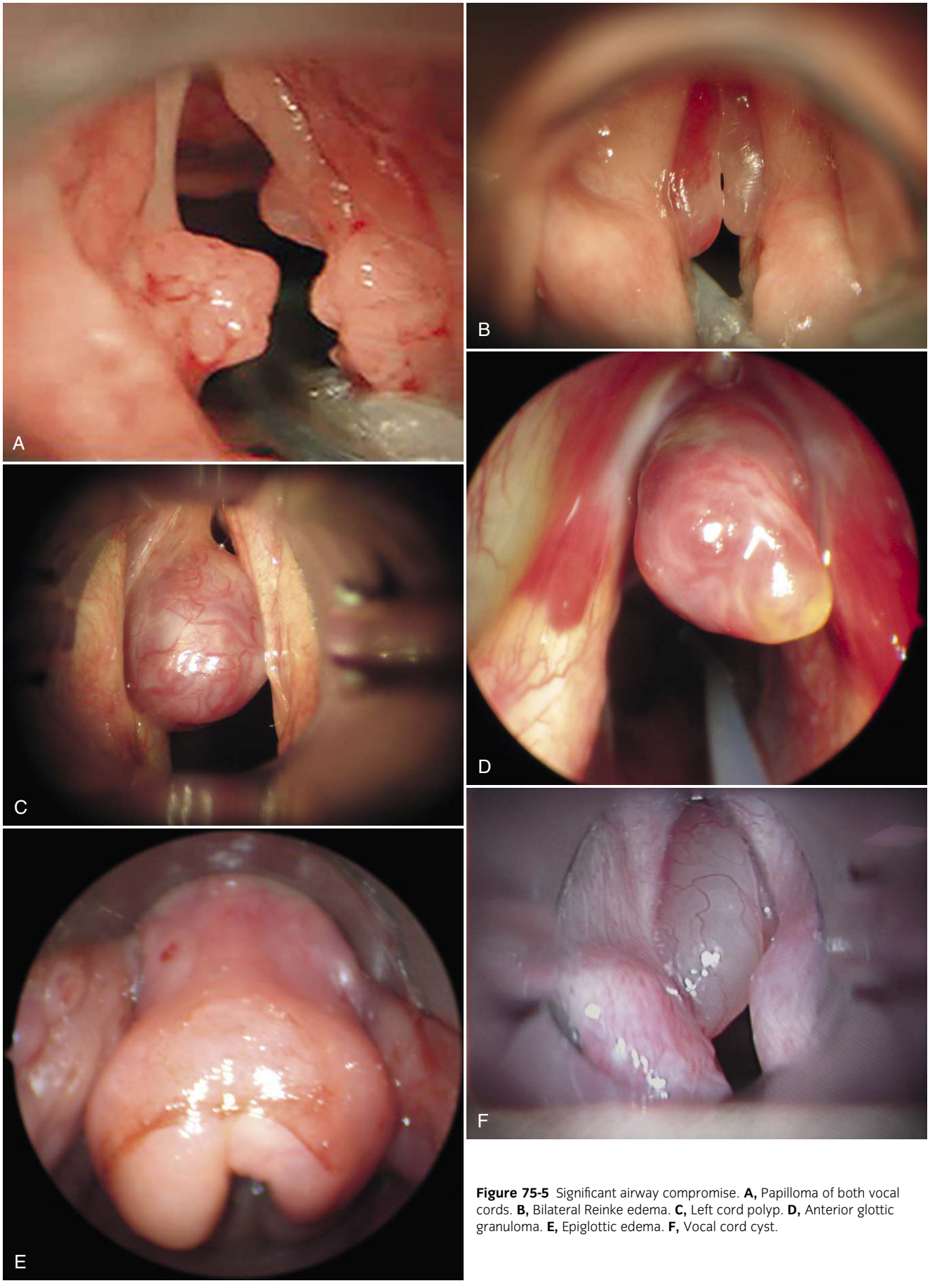

Figure 75-5 Significant airway compromise. **A,** Papilloma of both vocal cords. **B,** Bilateral Reinke edema. **C,** Left cord polyp. **D,** Anterior glottic granuloma. **E,** Epiglottic edema. **F,** Vocal cord cyst.

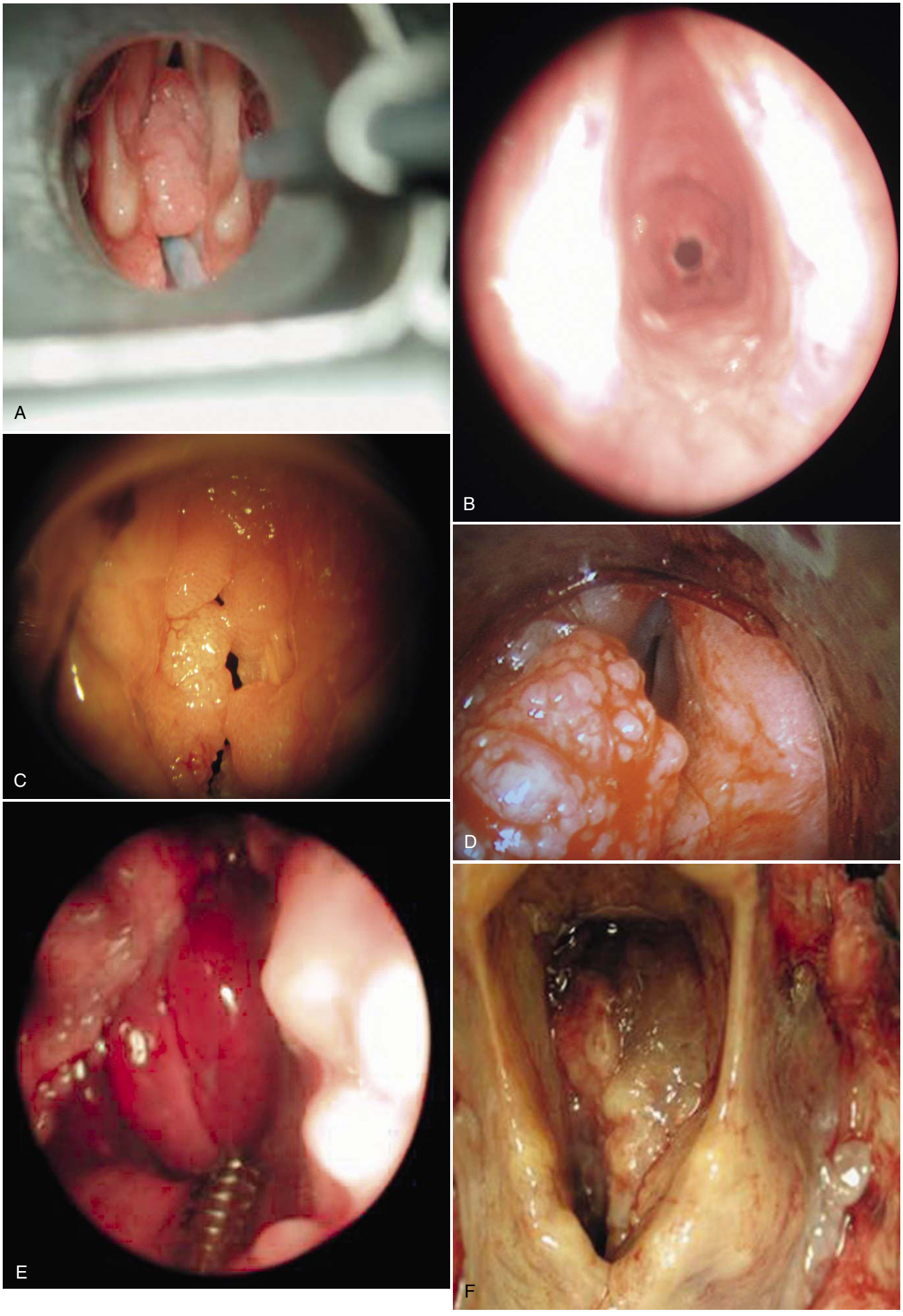

Figure 75-6 Severe airway compromise. **A,** Papilloma of vocal cord. **B,** Severe subglottic stenosis (2-mm airway). **C,** Bilateral papilloma. **D,** Extensive supraglottic carcinoma. **E,** Acute epiglottitis. **F,** Laryngeal carcinoma.

Facial Trauma

Facial injuries to the mandible, injuries to the midface, and Le Fort I, II, and III fractures can produce severe bleeding with the risk of aspiration of blood, bone, loose teeth, and soft tissue fragments. Clearing and securing the airway is the priority, but this may be complicated by cervical spine, vascular, and head injuries. Unilateral mandibular fractures are usually stable, whereas bilateral mandibular fractures are unstable.

Ear Surgery

Types of Ear Surgery

Operations on the ear range from high-volume, short-duration procedures such as myringotomy and ventilation tube placement to long, complex procedures such as mastoidectomy or skull-based procedures requiring ENT and neuroanesthetic attention. Ear procedures can be divided into external, middle ear, mastoid, and inner ear procedures.

External Ear

External ear procedures can be done under general or local anesthesia, and involve removal of simple lesions, foreign bodies in the external auditory canal, preauricular abnormalities, and exostoses and complex reconstruction of the external auditory canal.

Middle Ear and Mastoid

In children, otitis media can result in middle ear effusions with hearing loss and may require repeated procedures for fluid drainage and tube placement to allow ventilation of the middle ear. This is the second most common procedure undertaken in children,[17] and is often done with adenoidectomy or tonsillectomy, the most common procedure in children, or both.

Chronic infections can lead to a perforation of the tympanic membrane and damage to the middle ear ossicles, and with cholesteatoma can erode bone, spreading into the mastoid cavity, inner ear, lateral sinus, meninges, and brain. Facial nerve paralysis and intracranial extension is rare, but in the past this was a common cause of morbidity after chronic ear infections.

Myringoplasty involves the closure of a persistent perforation in the tympanic membrane using a graft of tissue from the temporalis muscle and fascia. A tympanoplasty involves a more extensive repair to the tympanic membrane and reconstruction of the damaged underlying ossicular chain. Stapedectomy involves the removal of a damaged stapes resulting in a conductive hearing loss and replacement by a prosthetic implant. Damage to the stapes results from otosclerosis, an inherited condition in which new bone formation occurs at the base of the stapes. A stapedectomy can be done under general anesthesia or with sedation in suitable patients and usually involves the use of a laser. A mastoidectomy is done to remove cholesteatoma and chronic infections and as part of a more complex procedure to allow surgical access to deeper structures.

Inner Ear

Inner ear procedures require complex specialist surgical intervention and include operations on the cochlea, endolymphatic sac, and labyrinth. Cochlear implants are used for patients with sensorineural hearing loss and are now being placed in increasingly younger children. Patients with disorders of the labyrinth and endolymphatic sac, such as Meniere's disease, can have severe vertigo and hearing loss. With all ear procedures, patients are more prone to nausea and vomiting perioperatively, but with inner ear disorders, this can be particularly difficult to treat.

Anesthesia for Ear Surgery

Local Anesthesia

Local anesthesia with or without sedation can be undertaken safely in suitable patients. Preoperative assessment and intraoperative monitoring should be the same as for general anesthesia. The choice of local anesthetic with or without sedation or general anesthesia depends on numerous factors, including patient cooperation, duration of procedure, patient preference, patient understanding, and surgical preference. Simple external ear and some middle ear procedures involving the tympanic membrane and stapes are suitable for local anesthesia with or without sedation. Patient understanding and cooperation are vital to prevent sudden movements at critical stages of the surgery, and usually most young children and uncooperative adults require a general anesthetic.

Light sedation during these procedures can be achieved by careful bolus doses of midazolam, titration or infusion of propofol, and, more recently, careful titration with an infusion of remifentanil. Local anesthetic can be administered by infiltration with lidocaine and epinephrine, topical instillation of lidocaine onto the tympanic membrane, and, more recently, topical application of EMLA cream onto the tympanic membrane.

Nerve Block

The sensory nerve supply of the ear comes from the auriculotemporal nerve, greater auricular nerve, auricular branch of the vagus nerve, and tympanic nerve. Local anesthesia involves infiltration of the anterior and posterior external meatal wall blocking the auriculotemporal and greater auricular nerve. Infiltration through an aural speculum blocks the auricular branch of the vagus, and topical infiltration of local anesthetic on the tympanic membrane blocks the tympanic nerve.

General Anesthesia

Nearly all surgery on the external, middle, and internal ear requires the use of an operating microscope, where movements, coughing, and straining are greatly magnified. Access to the airway during the procedure is limited, and a safe, unobstructed airway is essential. A thorough preoperative assessment, as for any general anesthetic, should be undertaken with specific attention paid to hypertension or other cardiovascular disease, which contraindicates or limits attempts to control blood pressure intraoperatively.

For most ear procedures, usually no specific preoperative medication is required. Anxiolytics, such as temazepam, are useful for anxious patients. Preoperative β-blocking drugs and clonidine have been used in the past as premedicants, but are not used commonly now. If β-blockade or clonidine is required, it can be given intravenously with intraoperative monitoring. Specific issues relating to general anesthesia for ear surgery are the choice of airway, use of nitrous oxide, head and body position, facial

nerve monitoring, adequate surgical field, nausea and vomiting, duration, deep vein thrombosis prophylaxis, and temperature control, and these are considered later.

Airway—Facemask, Tracheal Tube, or Laryngeal Mask Airway (see also Chapter 50)

The choice of facemask, tracheal tube, or laryngeal mask airway (LMA) depends on the duration of surgery, experience of the anesthesiologist, and patient factors (Fig. 75-7).

Facemask

Historically, a facemask was used for simple, short ear procedures, such as myringotomy and tube insertion. The patient retained spontaneous ventilation, but this required the anesthesiologist to hold the facemask and the surgeon to "work around" the anesthesiologist's hands and the facemask. Most of these short-duration procedures are now undertaken with an LMA. The quality of airway management with an LMA is superior to a facemask with better oxygenation,[18,19] improved seal with less oropharyngeal air leaks,[20,21] better monitoring of tidal gases particularly at low flow,[22] and less pollution.[23-25] Patients with features that make facemask ventilation difficult, such as beards, edentulism, and facial burns,[26-28] also are better managed with an LMA.

Tracheal Tube

For most long-duration procedures, a reinforced or armored tracheal tube is used to prevent kinking or partial compression with head rotation. Alternatively, south-facing preformed tracheal tubes are used. The advantages of using a tracheal tube are familiarity with its use and the ability to secure the airway and provide airway protection from above (debris and blood) and below (regurgitated gastric contents) during spontaneous and positive-pressure ventilation.

Laryngeal Mask Airway

Laryngeal mask airways also are used in ear surgery. The Flexible LMA (Laryngeal Mask Airway Company, San Diego, CA) is designed for ENT procedures. For minor ear surgery, the LMA has specific advantages over facemask ventilation, as has been discussed. The Flexible LMA has a flexible shaft and is better suited and tolerant to head rotation and flexion and extension during surgery. For longer duration procedures, a Proseal LMA (Proseal LMA North America, San Diego, CA) with a gastric drain tube and superior airway seal characteristics has allowed major ear surgery for 5 hours.[29]

Nitrous Oxide

Nitrous oxide diffuses from blood to airspaces within the body; the amount depends on the concentration of nitrous oxide and

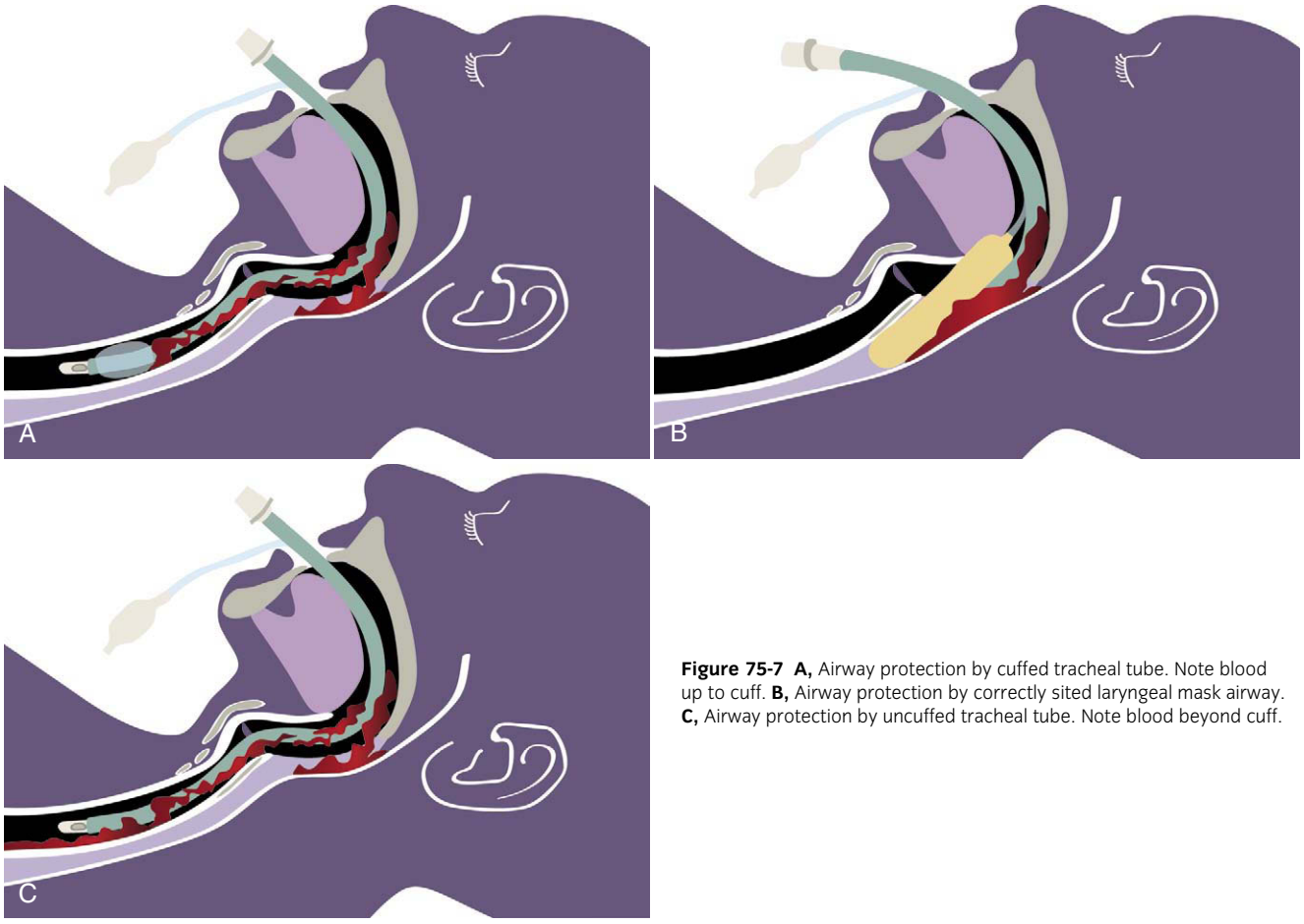

Figure 75-7 **A,** Airway protection by cuffed tracheal tube. Note blood up to cuff. **B,** Airway protection by correctly sited laryngeal mask airway. **C,** Airway protection by uncuffed tracheal tube. Note blood beyond cuff.

the duration of anesthesia. As nitrous oxide diffuses into the middle ear cavity, the pressure increases and is relieved only by reabsorption after discontinuation of nitrous oxide at the end of the procedure, or by eustachian tube opening allowing gas to escape into the nasal cavity. At the end of surgery after discontinuation, rapid reabsorption of nitrous oxide can produce negative middle ear pressures, particularly when there is eustachian tube dysfunction resulting in graft displacement. Nitrous oxide can displace grafts by causing the middle ear pressure to be too high or too low.

Early types of surgery to repair the tympanic membrane involved "overlay" grafts, in which a high middle ear pressure would displace and lift up the graft. Most ENT surgeons now use "underlay" grafts, in which increased middle ear pressures can help hold the graft in position. Many anesthesiologists do not use nitrous oxide during ear surgery for these reasons, and instead use a mixture of air and oxygen or limit nitrous oxide concentration to 50%.

Position

Rotation of the head and extension of the neck is necessary for most ear procedures, and measures to prevent significant compression of internal and external jugular veins and the carotid artery in vulnerable patients should be considered. A lateral tilt of the operating table may improve surgical access without the need for extreme head and neck rotation, which may reduce venous compression and improve arterial blood supply. Arms should be placed in a neutral position and well padded. A head-up tilt typically around 15 degrees is useful in reducing venous pressure and improving the operative field.

Facial Nerve Monitoring

Facial nerve monitoring is used during middle ear, mastoid, and inner ear procedures to identify the facial nerve and reduce the incidence of iatrogenic facial nerve injury. Various monitors are used; the general principle involves an audible and visible signal on the monitor to identify when surgical movement or stimulation is close to, or at, the facial nerve. When the nerve is stimulated, electrodes attached to the face detect nerve activity, and the monitor signals. Partial or complete neuromuscular blockade with muscle relaxants reduces or abolishes this nerve activity, and accidental transection of the facial nerve does not generate a signal. It is essential that neuromuscular blockade be stopped or reversed and peripheral nerve function be assessed to ensure adequate neuromuscular function before surgery proceeds in the vicinity of the facial nerve. With the introduction of remifentanil, an adequate depth of anesthesia can be maintained more easily with a tracheal tube in place and no neuromuscular blockade.

Surgical Field

During ear surgery, significant bleeding obscures the surgical field and makes surgery difficult under an operating microscope. Simple measures to limit bleeding and improve the surgical field should be used first. A head-up position to reduce venous pressure and bleeding is often successful. A smooth, balanced anesthetic with adequate analgesia (remifentanil infusion) avoids tachycardia and hypertension, and optimal ventilation avoids hypercapnia. For most patients, these maneuvers are sufficient to improve the operative field; however, additional measures may be needed. Induced hypotension requires a careful assessment of the risks and benefits, and should not be performed on patients with preexisting cardiovascular compromise.

For American Society of Anesthesiologists class I patients, a mean arterial pressure greater than 50 to 60 mm Hg, an intraoperative systolic pressure greater than the preoperative diastolic pressure, and a heart rate around 60 beats/min should provide an adequate surgical field. Drugs used include β-blockers (metoprolol, labetalol), α_2-agonists (clonidine), and opioids (remifentanil).

Antiemetics

Middle ear and inner ear procedures have a greater incidence of postoperative nausea and vomiting than general surgical procedures. Postoperative nausea and vomiting is particularly common after inner ear surgery involving the labyrinth and vestibular nerve. In addition to being unpleasant for the patient, retching and vomiting increase venous pressure, intracranial pressure, and bleeding, and dislodge or disrupt delicate surgical grafts and prosthesis. If possible, opioids should be avoided, the patient should be kept hydrated with intravenous fluids, and prophylactic antiemetics should be administered. Drugs are used alone or in combination; various regimens include serotonin antagonists[30,31] such as ondansetron and granisetron, butyrophenones such as droperidol, anticholinergics such as scopolamine,[32] dexamethasone, and gastrokinetic agents such metoclopramide.

Duration, Deep Vein Thrombosis Prophylaxis, and Temperature Control

The duration of surgery varies from 10 to 20 minutes for simple ear procedures such as myringotomy and tube insertion to 4 hours or more for complex middle ear and inner ear surgery. Standard deep vein thrombosis prophylaxis should be established for all procedures that are not very short duration. Temperature monitoring with avoidance of hypothermia and hyperthermia should be undertaken. For longer surgical procedures, urinary catheterization should be considered.

Recovery

Smooth emergence and recovery from anesthesia are important. Some anesthesiologists advocate changing tracheal tubes to a LMA for a superior recovery profile; this is known as the Bailey maneuver.[33]

Nasal Surgery

Types of Nasal Surgery

Surgery of the nose can be divided into (1) procedures on the external aspect of the nose, (2) procedures within the nasal cavity,

(3) procedures within the nasal sinuses, and (4) procedures involving the bony structures. Fractures of the nasal bones are usually corrected within 10 days when the initial swelling has resolved. If these fractures are corrected later, they can be more difficult to align and cause significant rebleeding. Septal surgery is undertaken to improve airflow through the nasal passages and ventilation of the sinuses. Patients can present with near-total nasal airway obstruction as a result of gross septal deviation blocking one nasal passage, and contralateral inferior turbinate hypertrophy blocking the other passage.[34] Nasal polyps can be single or multiple and cause significant obstruction of airflow within the nasal cavity or sinuses and even total nasal blockage.

Most sinus surgery nowadays is undertaken using endoscopes and is termed functional endoscopic sinus surgery. Intranasal antrostomy and Caldwell-Luc procedures, which allowed access to the maxillary sinuses, generally have been replaced by functional endoscopic sinus surgery.

Local or General Anesthesia

Some nasal procedures can be performed under local anesthesia with or without sedation,[35-37] and others usually require general anesthesia. The choice of general or local anesthetic depends on patient factors and duration, site, and complexity of the procedure. Generally, local anesthesia is suitable for procedures on the anterior septum, septoplasty, turbinectomy, cauterization, simple polypectomy, and reduction of simple nasal fractures. For more complex or longer procedures, including sinus surgery, rhinoplasty, septorhinoplasty, nasolacrimal surgery, frontal sinus surgery, anterior skull base procedures, and craniofacial resections, general anesthesia is preferred. During these procedures, movements under local anesthesia at critical stages of the operation can have serious consequences, causing blindness, carotid artery damage, and intracranial extension.[38]

Small children have a propensity to place foreign material into the nasal cavity. Some material, such as small batteries, can be corrosive to the nasal mucosa and septum and require urgent removal. In uncooperative children, attempts at foreign body removal carry the risk of inhalation of the foreign body, and general anesthesia may be necessary. Ideally, spontaneous ventilation should be maintained to reduce the risk of foreign material entering the lower airway.

Preoperative Evaluation (see also Chapter 34)

Preoperative evaluation and anesthetic assessment should be the same for local and general anesthesia. Specific assessment for obstructive sleep apnea (OSA), use of nasal continuous positive airway pressure, cardiovascular status, and suitability for topical nasal vasoconstrictors should be sought and a history of nonsteroidal anti-inflammatory (NSAID) drug use. Samter's triad, the association of NSAID sensitivity in patients with asthma and nasal polyps, who can have severe life-threatening bronchospasm, should be kept in mind.

Nasal Vasoconstrictors

Nasal vasoconstrictors are commonly used to reduce bleeding from vascular nasal mucosa, and many agents applied alone or in combination are used to vasoconstrict and provide local anesthesia. Some agents, such as cocaine, have local anesthetic and vasoconstrictor properties, and others, such as lidocaine, have local anesthetic properties. Commonly used vasoconstictors include cocaine, epinephrine, and phenylephrine. Cocaine has been used alone and in combination with epinephrine. Phenylephrine has been used in combination with lidocaine, and lidocaine has been used in combination with epinephrine.

Cocaine has a rapid onset of action and excellent vasoconstrictor properties. Small doses are vagotonic, producing a reduction in heart rate, whereas increasing blood concentrations cause tachycardia, hypertension, ventricular tachycardia, and direct cardiac muscle depression, any of which may cause sudden death,[39] myocardial infarction,[40] and ventricular fibrillation.[41] The cardiovascular effects of cocaine are attributed to its ability to block the reuptake of norepinephrine at sympathetic nerve terminals and potentiate sympathetic activity.[39] Cocaine use should be avoided in patients with a history of myocardial infarction, coronary artery disease, congestive heart failure, irregular heart rhythm, and hypertension, and in patients taking monoamine oxidase inhibitors.

Cocaine has been used as a nasal vasoconstrictor in a topical solution, paste or gel, and spray. The safe recommended maximum dose of cocaine is 1.5[34] to 3 mg/kg,[39,42-44] with a maximum dose of 200 mg. It is difficult to establish dosing with paste and gel, and these are not recommended.

Cocaine solution is available in various concentrations from 0.5% to 20%, but solutions of more than 4% are not required.[39] The addition of epinephrine, 1 mg (1 mL 1:1000), to cocaine solution is intended to provide additional vasoconstriction and to reduce the absorption of cocaine. In one study of 30 adults comparing serial plasma concentrations of cocaine between two groups, one with epinephrine and the other without, there were significantly lower plasma cocaine levels in the epinephrine group.[45] It also was noted, however, that in two patients in the cocaine and epinephrine group there were unusually high plasma concentrations, although these were below levels associated with toxicity. The cause of this idiosyncratic rapid absorption is unknown, although it has been suggested that decay in the adrenaline-induced vasoconstriction occurs in a few patients and may account for this.[34]

Phenylephrine is a potent α-adrenergic agonist and is used as a topical vasoconstrictor alone or in combination with lidocaine. Guidelines on the topical use of phenylephrine in the operating room recommend the following:[46]

1. Initial phenylephrine dose should not exceed 0.5 mg, and in children weighing 25 kg or less, it should not exceed 20 μg/kg.
2. Blood pressure and pulse should be closely monitored.
3. The dose should be administered in a calibrated syringe and should be verified by a physician.
4. The anesthesiologist should be aware of all medications given.
5. Severe hypertension should be treated immediately with direct vasodilators or α-receptor antagonists.
6. β-Receptor blockers and calcium channel blockers should be avoided. They can worsen cardiac output and result in pulmonary edema.
7. If a β-receptor blocker is used to treat hypertension, glucagon administration should be considered to counteract the loss of cardiac contractility.

Airway (see also Chapter 50)

Nearly all nasal surgery has the potential to contaminate the lower airway with blood or secretions, and it is essential that the anesthesiologist recognize this and take measures to prevent it. Significant nasal blockage can make facemask ventilation difficult, and an oral airway may be needed. Airway maintenance can be a particular problem in obese patients with OSA and nasal blockage.

Tracheal Tube or Flexible Laryngeal Mask Airway

The choice of a tracheal tube or Flexible LMA for nasal procedures depends on the experience of the anesthesiologist, duration of surgery, and patient factors. Using a Flexible LMA during nasal surgery is an advanced use of the device, and if there is incorrect sizing, insertion, malposition, dislodgment, or suboptimal recovery, there is the potential for airway obstruction and blood contamination of the lower airway.

A south-facing or reinforced tracheal tube is often used with a throat pack to reduce blood contamination of the lower airway. The advantages of using a tracheal tube are its familiarity and ability to secure the airway and provide airway protection during positive-pressure ventilation and spontaneous pressure ventilation.

It seems intuitive that that a tracheal tube would protect the airway more effectively than a Flexible LMA because of the seal offered by contact of the tracheal tube cuff on the tracheal wall; however, this may not be true. The tracheal cuff is below the glottic and subglottic airway, and blood can pass down from the nasopharynx, past a throat pack, along the outer surface of the tracheal tube to the level of the vocal cords and subglottis. In contrast, a correctly sited Flexible LMA covers and protects the supraglottic and glottic airway, and blood is diverted laterally to the piriform sinus and postcricoid region.

Direct comparisons of lower airway contamination by fiberoptic examination at the end of surgery show that patients managed with a Flexible LMA by experienced anesthesiologists are significantly less likely to have blood staining the airway (glottis and trachea) than patients managed with a tracheal tube.[47] The Flexible LMA effectively and satisfactorily protects the glottic and tracheobronchial airway from blood exposure during nasal and sinus surgery, and can offer better protection of the tracheobronchial airway than a tracheal tube in many instances.[47,48]

Extubation

Extubation of a tracheal tube is usually undertaken with the patient "awake" or "deep," and extubation of a Flexible LMA is undertaken when the patient can open the mouth to command. For nasal surgery, awake extubation involves removal of the tracheal tube when the patient responds to commands and makes purposeful attempts to remove the tracheal tube. The advantage of awake extubation for nasal surgery is the intrinsic airway control in an awake patient with return of laryngeal reflexes and protection from further airway contamination by blood and secretions. The disadvantage is the higher incidence of laryngospasm, coughing, bucking, oxyhemoglobin desaturation, and increased risk of bleeding.

Deep extubation is used in an attempt to improve the recovery profile; however, for nasal surgery, this leaves an unprotected airway. After surgery, the nasal airway is often blocked with surgical packs, and the patient is dependent on oropharyngeal airflow. In practice, this may make it extremely difficult to maintain an airway in an OSA patient extubated deep lying on his or her side.

Recovery with an LMA provides protection of the lower airway from blood from the pharynx[47,49] and a superior recovery profile compared with awake or deep extubation.[47-50] Compared with recovery with a Flexible LMA, awake tracheal extubation was accompanied by excessive coughing with increased risk of bleeding, increased incidence of oxyhemoglobin desaturation early after extubation, delay in patient fitness for discharge from the operating room, and increased incidence of oxyhemoglobin desaturation on admission to the postanesthesia care unit.[48] Compared with removal of the Flexible LMA, tracheal extubation in patients deeply anesthetized was accompanied by an increased incidence of coughing, laryngospasm, and oxyhemoglobin desaturation early after extubation.[48] Emergence quality and overall airway protection after nasal surgery seem to be better for a Flexible LMA than a tracheal tube.[47-50]

Coroner's Clot

A throat pack is often used around a tracheal tube in an attempt to absorb blood, limit blood from the nasopharynx entering the oropharynx, and prevent surgical debris pooling in the laryngopharynx. At the end of surgery, the pack should be carefully removed and noted. Laryngoscopy and pharyngoscopy should be undertaken in every patient, and a careful inspection of the oral cavity and postnasal space should be made. This inspection involves standard laryngoscopy, followed by neck flexion to encourage any clot to fall past the soft palate, and direct visualization of the passage of a suction catheter behind the soft palate. Any clot left behind can be inhaled after removal of a tracheal tube and lead to total airway obstruction and death—hence the term "coroner's clot."

Postoperative Considerations

Postoperatively, all patients with nasal packs have a partially or completely obstructed nasal airway, but this is particularly significant in OSA patients. OSA patients need high-dependency care for airway observation and can have nasopharyngeal airways incorporated into the nasal pack.

Severe pain postoperatively is not a feature of most nasal surgery, and analgesia usually can be provided with oral acetaminophen and an NSAID. An intravenous cannula should be retained until after removal of the nasal pack in case of unexpected bleeding.

Throat and Head and Neck Surgery

Throat and head and neck procedures can be divided as follows:

1. Intraoral procedures—tonsillectomy, adenoidectomy, and palatal surgery
2. Laryngeal procedures—benign, malignant, and stenotic laryngeal lesions; airway endoscopy; and laser surgery
3. Head and neck—parotid surgery, thyroid surgery, nasopharyngeal wall tumors, neck dissection, laryngectomy, and pharyngolaryngectomy

Intraoral Surgery

Tonsillectomy

The tonsils and adenoids are part of Waldeyer's ring of lymphoid tissue around the pharynx and are often the sites of acute and chronic inflammation. Tonsillectomy and adenoidectomy are not minor procedures; they involve a shared airway, often in a small child, with difficult access, obstructive airway symptoms, and the potential for blood contamination of the lower airway. Mortality associated with tonsillectomy ranges from 1:40,000[51] to 1:12,000.[52]

Tonsillectomy is one of the most frequently performed surgical procedures, and its main indication is severe recurrent tonsillitis. Other indications include chronic tonsillitis, peritonsillar abscess (quinsy), OSA, and tonsillar biopsy or resection for tumor. Adenoidectomy is usually performed in children when there is evidence of enlarged adenoids causing symptoms such as blocked nose, mouth breathing, or OSA. As a child grows, the postnasal space enlarges in proportion to the other pharyngeal structures, and adenoidectomy is seldom required.[34]

A large prospective tonsillectomy audit[51] with data from 277 hospitals and more than 40,000 tonsillectomy or adenotonsillectomy procedures described the indications for and complications of these operations. Children younger than 5 years of age accounted for 23% of procedures, children 5 to 16 years of age accounted for 49%, and individuals 16 years old and older accounted for 28%. A tonsillectomy was performed alone in 71%, and an adenotonsillectomy was performed in 27% of patients. For children younger than 5 years of age, 61% of tonsillectomies were performed for recurrent acute tonsillitis, and 33% were performed for pharyngeal obstructive symptoms. As age increased, indications for surgery changed with an increase in acute recurrent tonsillitis, chronic tonsillitis, and quinsy, but a reduction in pharyngeal obstructive symptoms. Generally, in children, the tonsils can be dissected and removed more easily than in adults, in whom the tissue is often scarred and fibrotic from repeated infections, and this may account for the greater postoperative hemorrhage rates seen in the older age group.

Obstructive Sleep Apnea

In children, enlarged tonsils and adenoids cause varying degrees of pharyngeal obstruction ranging from simple snoring to upper airway resistance syndrome, in which partial upper airway obstruction occurs. With very large tonsils and adenoids, OSA can be present with loud persistent snoring interrupted by gasping or choking episodes and silent periods of apnea. Children and adults with OSA are at increased risk for postoperative respiratory complications.[53] In severe OSA, hypoxemia, hypercarbia, pulmonary hypertension, and cor pulmonale can be present. These children should be looked after in specialist pediatric centers with appropriate postoperative monitoring and high-dependency care.

Preoperative Assessment

Preoperative evaluation aims to identify patients with OSA, loose teeth, vulnerable dental implants, bleeding disorders, anemia, active infection, and sickle cell disease status. Active respiratory tract infections increase the risk of bleeding, and surgery should be postponed. Some uncooperative children may require sedative medication, but this should not be given to patients with OSA, unless appropriate observation and care is available.

General Anesthesia

The principles of anesthesia for tonsillectomy are to maintain a sufficient depth of anesthesia to allow the introduction of a mouth gag, and prevent reflex-induced hypertensive responses, tachycardia, and hypertension. During the procedure, intermittent positive-pressure ventilation or spontaneous ventilation can be used; at the end, a careful inspection for blood should be performed. The timing and manner of extubation is crucial to reduce the incidence of laryngospasm, and high-quality recovery care is essential to identify problems in the immediate postoperative period.

Induction of anesthesia can be by inhaled or intravenous route. Intravenous induction with propofol and fentanyl with or without a short-acting muscle relaxant provides a smooth, quick induction with reduced airway irritability. Inhaled induction is used principally in uncooperative children with poor venous access and needle-phobic adults.

An inhaled induction in the presence of significant airway obstruction can be a difficult, lengthy procedure to undertake. Patients with OSA may have reduced hypoxic and hypercapnic ventilatory responses and may tolerate hypoxia and hypercapnia with little attempt to increase respiratory rate or tidal volume. Early loss of upper airway muscle tone exacerbates the hazards of inhaled induction further. During spontaneous ventilation, constant observation of the reservoir bag is required, particularly during mouth gag insertion to identify obstruction.

A tonsillectomy is usually more painful in adults and requires significant analgesia intraoperatively and postoperatively. Intraoperative opioids, including morphine, are usually necessary.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs are routinely used analgesics after tonsillectomy. Despite this fact, their use is controversial because of concerns about increased bleeding in the postoperative period owing to inhibition of platelet aggregation. Moiniche and colleagues,[54] in a meta-analysis with data from 25 studies, looked at four bleeding end points (intraoperative blood loss, postoperative bleeding, hospital admission, and reoperation because of bleeding), and concluded that the risk of bleeding after tonsillectomy was equivocal, but

there was some evidence for an increased likelihood of reoperation because of bleeding. Others also have found no significant increase in the risk of bleeding with NSAIDs,[55,56] although aspirin has been shown to increase the risk[56] and should not be used for tonsillectomy. NSAIDs seem to have no significant increase in postoperative bleeding,[54-56] to have less associated nausea and vomiting compared with other analgesics,[55] and to be generally well tolerated.

Steroids

The role of steroids with single intravenous doses of dexamethasone, 0.05 to 0.15 mg/kg, to improve recovery after tonsillectomy has been investigated.[57-59] Steroids decreased postoperative emesis,[57,58] increased tolerance to regular diet,[57,58] and reduced pain.[59]

Postoperative Nausea and Vomiting

Various prophylactic antiemetic interventions have been reported after tonsillectomy. Bolton and associates[60] found good evidence for the prophylactic antiemetic effect of dexamethasone and the serotoninergic antagonists ondansetron, granisetron, tropisetron, and dolasetron. Metoclopramide was found to be efficacious,[60] although ondansetron, 0.15 mg/kg, was superior to metoclopramide, 0.25 mg/kg.[61,62] Patients should be well hydrated, receive regular nonopioid analgesia, and have intravenous fluids continued until normal oral intake is resumed.

Antibiotics

The routine administration of antibiotics, although common, is controversial. No reduction in pain or analgesia requirements was seen; however, a reduction of halitosis, reduction in fever, and return to normal oral intake 1 day earlier was identified.[63,64]

Postextubation Laryngospasm and Stridor

For tonsillectomy, the incidence of laryngospasm and stridor after removal of a tracheal tube is greater than that after recovery with a Flexible LMA.[65-69] The incidence of laryngospasm after routine tracheal tube extubation following tonsillectomy in control groups is reported as 12% to 25%.[5-7,70-72] Attempts to reduce the incidence of laryngospasm involve either topical anesthesia to the upper airway,[6,71] limiting the exaggerated glottic closure reflex and subsequent laryngospasm, or intravenous agents administered close to extubation, increasing the depth of anesthesia and limiting glottic closure reflex–mediated laryngospasm.[5,7,70,72] Topical lidocaine (4 mg/kg) can be used in concentrations of 2% to 4% and is as effective as intravenous lidocaine (1 mg/kg)[6] without the sedative effects. Intravenous magnesium,[7] subhypnotic doses of propofol,[72] and lidocaine[5,6,70,71] all have been suggested as agents to reduce the incidence of postextubation laryngospasm.

Airway—Tracheal Tube or Flexible Laryngeal Mask Airway

The choice of tracheal tube or Flexible LMA depends on the experience of the anesthesiologist, the surgeon, and the recovery staff. The use of a Flexible LMA for tonsillectomy is an advanced technique; the Flexible LMA should be used only by an experienced anesthesiologist who is familiar with the insertion and maintenance of the device and by a surgeon who is competent at working around a Flexible LMA. In small children, an inexperienced anesthesiologist should not use a Flexible LMA.

Tracheal Tube. A south-facing tracheal tube is the most commonly used means of airway maintenance during tonsillectomy.[73] For an inexperienced anesthesiologist, a tracheal tube is easier to place than a Flexible LMA, is more resistant to compression from the mouth gag, is less likely to obstruct during the operation, and occupies less space in the oropharynx than a Flexible LMA.

At the end of the operation, extubation of a tracheal tube is undertaken after careful inspection and laryngoscopy to ensure no blood clots are present. The child is placed in a left lateral or semiprone ("tonsil position"), slight head-down position, and often a pillow is placed under the chest to allow blood or secretions to drain down and out. Extubation can be done "awake" or "deep." Deep extubation is associated with fewer airway complications,[8] but leaves an unprotected lower airway.

Flexible Laryngeal Mask Airway. The use of a Flexible LMA for tonsillectomy requires close cooperation and meticulous attention to detail by the anesthesiologist and the surgeon.[74] Particular care is required by the surgeon on placement and opening of the mouth gag and intraoperative manipulation of the gag. Mechanical obstruction during the use of a tonsillar gag occurs in 2% to 20% of cases,[65,67] and for most of these cases the obstruction is correctable. Access to the inferior pole of the tonsil also has been documented as being more difficult.[75] Advantages of using a Flexible LMA for tonsillectomy include (1) the avoidance of muscle relaxants; (2) the superior recovery profile with fewer episodes of bronchospasm, laryngospasm, bleeding, and desaturation; (3) less aspiration of blood compared with an uncuffed tracheal tube; and (4) better protection of the lower airway from blood and secretions until the patient is awake.[65-69]

The Flexible LMA is removed when patients open their eyes to command. The cuff should remain inflated allowing blood and secretions on the backplate to be suctioned out as the Flexible LMA is removed from the mouth.

Bleeding Tonsil

The incidence of postoperative hemorrhage increases with age.[51] In a national audit with more than 33,000 tonsillectomies, hemorrhage rates were 1.9% in children younger than 5 years old, 3% in children 5 to 15 years old, and 4.9% in individuals older than 16. The return to the operating room rate was 0.8% in children younger than 5 years old, 0.8% in children 5 to 15 years old, and 1.2% in individuals older than 16. Hemorrhage rates are higher in adults, patients with quinsy, and male patients.[51]

Primary bleeds usually occur within 6 hours of surgery[53] and may not be obvious in the immediate recovery period because the blood is swallowed. The bleeding is usually a venous or capillary bleed, rather than arterial, and problems arise because of hypovolemia, aspiration risk, and difficult laryngoscopy. Signs suggesting hemorrhage are an unexplained tachycardia, excessive swallowing, increased capillary refill time, pallor, restlessness, sweating, and airway obstruction. Hypotension is a late feature.

Anesthesia for these patients is challenging, and help from a senior anesthesiologist should be requested. Patients should be given oxygen; should be adequately resuscitated; should have hemoglobin, hematocrit, and coagulation checked; and should have blood typed and crossmatched. Large-bore reliable intravenous access should be established. Laryngoscopy can be difficult because of the presence of blood clots, continuous oozing of blood, and reduced venous and lymphatic drainage causing

intraoral swelling and edema. The case of a patient with an uneventful initial laryngoscopy can become difficult very quickly.

After resuscitation, options for anesthesia include a rapid-sequence induction, which is usually the preferred technique, or an inhaled induction. For a rapid-sequence induction, patients should be in a slightly head-down position, protecting the airway from aspiration of blood. Some patients may not tolerate lying supine, and preoxygenation, induction, and cricoid pressure may have to be applied with the patient semi-upright. The advantage of a rapid-sequence induction is the rapid induction and control of the airway with less chance of regurgitation during induction. The disadvantages are the potential to inhale blood and cardiovascular depression from induction. A difficult laryngoscopy should be anticipated and prepared for, and a selection of smaller tracheal tubes may be needed if airway and tracheal edema is significant. After tracheal intubation, a large-bore gastric tube should be placed to decompress the stomach and evacuate swallowed blood at the beginning and at the end of the procedure.

An inhaled induction may be an option for anesthesiologists experienced with the technique, but can be challenging in the lateral or head-down position. This technique can be slow, and blood can be inhaled and precipitate laryngospasm. For an inexperienced anesthesiologist, tracheal intubation in a lateral position is more difficult.

At the end of the procedure, extubation should be done with the patient fully awake. Careful postoperative monitoring with close observation and high-quality recovery care should be available, and hemoglobin levels should be rechecked.

Laryngeal Procedures

Operations on the airway are unique in that the anesthesiologist and the surgeon are working in the same anatomic field. Patients range from young, otherwise fit and healthy individuals presenting with minor vocal cord lesions to elderly patients with glottic carcinoma and stridor. During these procedures, the anesthesiologist has to maintain oxygenation, remove carbon dioxide, protect the airway, and keep the patient anesthetized, while the surgeon is operating in the same area. Close cooperation and communication between the anesthesiologist and the surgeon are essential for success.

Vocal Cord Pathology

Vocal cord pathology can be classified as follows:

1. Nodules are benign lesions of the vocal fold that can be bilateral and that are usually caused by vocal abuse.
2. Polyps are benign lesions of the vocal fold and are common in adults. They are usually unilateral.
3. Cysts are benign lesions commonly seen in professional voice users. They are caused by obstruction of a glandular duct resulting in a mucus retention cyst.
4. Granulomas are benign lesions induced by healing granulomatous tissue, which develops after microtrauma. They are usually found on the posterior third of the vocal process after trauma during intubation or extubation.
5. Papillomas are benign lesions caused by human papillomavirus infection and can undergo malignant transformation. In adults, hoarseness is usually the main symptom, whereas in children airway obstruction can occur. After laser resection, papillomas can recur, and some patients require repeated laser surgery at 3- to 12-monthly intervals.
6. Malignant tumors are usually unilateral and can occur mainly in the middle third of the vocal fold. Of tumors, 80% are found in men 45 to 65 years old. More than 97% of patients are smokers with a high alcohol intake. Treatment depends on tumor staging and involves local resection, radiotherapy, transoral laser resection, hemilaryngectomy, or laryngectomy.
7. Other lesions are caused by hemangiomas, submucous hemorrhage, Reinke edema, chronic laryngitis, amyloidosis, sarcoidosis, tuberculosis, and rheumatoid arthritis.

Preoperative Assessment

At the end of the preoperative assessment, the anesthesiologist should have some idea of the size, mobility, and location of the lesion (Table 75-1). Standard airway assessments to predict the ease of ventilation, visualization of the laryngeal inlet, and tracheal intubation should be performed. Airway pathology and its impact on airway management should be assessed. The severity and size of lesions at the glottic level are assessed by direct or indirect laryngoscopy, undertaken by surgeons in an outpatient setting, and a photograph of the findings is often included in the notes. Information about subglottic and tracheal lesions is provided by chest radiography, computed tomography (CT), and magnetic resonance imaging (MRI).

Size of the lesion gives an indication of potential airflow obstruction. Stridor indicates a significantly narrowed airway. In an adult, stridor implies an airway diameter of less than 4 to 5 mm, but the absence of stridor does not exclude a significantly narrowed airway.

Very mobile lesions (e.g., multiple large vocal cord polyps or papillomas) may cause partial airway obstruction after induction of anesthesia, but total airway obstruction is rare. Obstruction is worse with a spontaneously breathing patient because of the loss of supporting tone in the oropharynx and hypopharynx.

Supraglottic lesions, if mobile, can obstruct the airway or make visualization of the laryngeal inlet difficult. Subglottic lesions may allow a good view of the laryngeal inlet, but cause difficulty during the passage of a tracheal tube.

Anesthetic Techniques for Endoscopy

There is no ideal anesthetic technique for all endoscopy procedures. The technique depends on the patient's general condition; the size, mobility, and location of the lesion; the use of a laser; and the surgical requirements. An ideal technique would (1) be simple to use; (2) provide complete control of the airway with no risk of aspiration; (3) control ventilation with adequate oxygenation and carbon dioxide removal; (4) provide smooth induction and maintenance of anesthesia; (5) provide a clear motionless surgical field, free of secretions; (6) not impose time restrictions on the surgeon; (7) not be associated with the risk of airway fire or cardiovascular

Table 75-1 Preoperative Assessment

Assessment	Implication
History of endoscopic procedures	Any previous difficulty is significant, and anesthetic records should be reviewed to assess severity and site of obstruction, vascularity of lesion, and previous anesthetic techniques used
Hoarse voice	Nonspecific symptom; patients can be hoarse with only minor lesions on the vocal cord or have significant vocal cord pathology and airway compromise
Voice changes	Nonspecific symptom; minor lesions can result in significant voice changes
Dysphagia	Significant and suggests supraglottic obstruction; if associated with carcinoma implies upper esophageal extension
Altered breathing position	Significant; patients with partially obstructing lesions compensate by changing their body positioning to limit airway obstruction
Unable to lie flat	Significant; suggests severe airway obstruction, and patients may need to sleep upright
Breathing during sleep	Significant; difficulty in breathing at night or waking up at night in a panic suggests severe obstruction
Stridor	Significant; indicates critical airway obstruction with >50% reduction in airway diameter and in adults an airway diameter of 4-5 mm
Stridor on exertion	Significant; suggests airway obstruction is becoming critical; patients may have no stridor at rest
Stridor at rest	Significant; critical airway obstruction is present
Inspiratory stridor	Significant; suggests extrathoracic airway obstruction
Expiratory stridor	Significant; suggests intrathoracic airway obstruction
Absence of stridor	Generally reassuring, *but* in exhausted adults and children there are limited chest movements and insufficient airflow to generate enough turbulent flow for stridor; these circumstances suggest life-threatening compromise
Fiberoptic awake flexible laryngoscopy	All adult patients should have this to visualize the vocal cords; in patients with symptoms and signs of severe airway obstruction, great care must be taken to avoid local anesthetic and fiberscope contact with the vocal cords, precipitating total airway obstruction
Chest x-ray/CT/MRI scans	Can identify severity and depth of glottic, subglottic, tracheal, and intrathoracic lesions

instability; (8) allow safe emergence with no coughing, bucking, breath holding, or laryngospasm; (9) produce a pain-free, comfortable, alert patient at the end of the operation.

Some of these ideals conflict. The presence of a cuffed tracheal tube provides control of the airway and prevents aspiration, but may obscure a glottic lesion and is not laser safe. A cuffed laser tube provides some protection against laser-induced airway fires, but has a greater external-to-internal diameter ratio and may obscure laryngeal lesions. Jet ventilation techniques require specialist equipment and knowledge and an understanding of their limitations. Anesthetic techniques can be broadly classified into two groups: first, "closed" systems, in which a cuffed tracheal tube is employed with protection of the lower airway, and second, "open" systems, in which a cuffed tracheal tube is absent using either spontaneous ventilation and insufflation techniques or muscle paralysis and jet ventilation.

Closed System

The advantages of a closed system are (1) routine technique for all anesthesiologists, (2) protection of the lower airway, (3) control of the airway, (4) control of ventilation, and (5) minimal pollution by volatile agents. The disadvantages of a closed system are (1) surgical access and visibility of the lesion may be limited, (2) high inflation pressure may be required through small tubes, (3) tube-related damage to the vocal cords during intubation, and (4) risk of a laser airway fire.

Open System

The advantages of an open system are (1) laser safety, (2) reduced risk of tube-related trauma, and (3) complete laryngeal visualization. The disadvantages are (1) an unprotected lower airway and (2) specialist knowledge, equipment, and experience are required. The decision to use a closed or open technique depends on the experience of the anesthesiologist; the experience of the surgeon; the equipment available; the requirements for surgical access; and the size, mobility, vascularity, and location of the lesion.

The technique chosen for any given procedure is not absolute and may have to change as surgical and anesthetic requirements change. An open system using jet ventilation on a lesion thought to be avascular may have to change to a closed system employing a cuffed tracheal tube if the lesion is bleeding significantly, and there is a considerable risk of soiling of the tracheobronchial tree. Conversely, a system employing a cuffed tracheal tube may have to change during surgery to an open system if the tracheal tube obscures the lesion, making surgery very difficult or impossible.

For most benign vocal cord lesions and early malignant lesions (T1 and most T2 lesions), airway obstruction is not a feature, and most techniques described are appropriate. An intravenous induction technique is suitable for lesions in which airway obstruction is not anticipated. After preoxygenation and intravenous induction of anesthesia, laryngoscopy is undertaken to visualize the lesion, establish laryngoscopy grade, and administer

topical local anesthetic (lidocaine). Confirmation of pathology is important because the disease may have progressed since the last outpatient visit, and the anesthetic plan may have to be changed. Topical local anesthetic reduces airway reflexes, and improves the recovery profile.

Closed System—Intubation Techniques

Microlaryngoscopy Tubes

Microlaryngoscopy tubes are long, have a small internal and external diameter, and are designed specifically for endoscopy procedures. Typically, 4- to 5-mm internal diameter tubes with high-volume, low-pressure cuffs are used in nasal or oral versions. These tubes are not suitable for laser surgery.

Laser Tubes (see also Chapter 77)

Laser microsurgery of the airway allows precise surgical cutting, coagulation, and sealing with little postoperative edema. Lasers are used for the resection of papillomas, vascular lesions of the vocal cord, granulomas, and laryngeal carcinoma. Carbon dioxide lasers are the most commonly used in airway surgery and are targeted toward the glottis by aiming mirrors integral to the operating surgical microscope. Two main hazards exist from the use of a laser: first, the risk to the patient from a laser-induced airway fire, and, second, the risk to the operating room staff and patient from diverted laser radiation. Operating room staff should be aware of these risks, and specific precautions should be taken to avoid them. Before use, alignment of the carbon dioxide laser with the visible tracer beam should be confirmed. Unprotected areas of the patient's face and neck should have wet gauze swabs placed over them.

An airway fire occurs only if the three components of the fire triangle are present—fuel, oxidant, and ignition source. The transient flaring of fat deposits occasionally seen in the airway during laser surgery is self-terminating and would not produce a blow torch laser airway fire regardless of the ambient oxygen concentration. For a blowtorch airway fire to occur, a nonmetal foreign material, such as a tracheal tube, has to be present.

To minimize these risks, the inspired oxygen concentration should be the lowest that maintains adequate oxygen saturations, and air should be used in preference to nitrous oxide. The potential fuel source should have laser-resistant properties (laser tubes) or be removed (supraglottic jet ventilation technique). The only nonflammable, *laser-proof* tube is the all-metal Norton tube, which has no cuff. Most laser tubes have *laser-resistant* properties around the shaft, but can ignite with sustained laser energy strikes, particularly around the cuff, which is not protected. Commercially available laser tubes have product information leaflets that describe their laser-resistant properties at different power settings and with different types of laser. Anesthesiologists involved in procedures using lasers for airway surgery should be familiar with the causes of a laser airway fire, the limitations of laser-resistant tubes, and an airway fire drill.

Open Systems—Nonintubation Techniques

Spontaneous Ventilation and Insufflation Technique

Spontaneous ventilation and insufflation techniques are useful in the removal of foreign bodies, evaluation of airway dynamics (tracheomalacia), and removal of noncompromised glottic and subglottic lesions. The technique requires a spontaneously breathing patient and provides a clear view of an unobstructed glottis.

Inhaled induction is begun with sevoflurane in 100% oxygen. At a suitable depth of anesthesia as assessed by clinical observations on the rate and depth of respiration, pupil size, eye reflexes, blood pressure, and heart rate changes, laryngoscopy is undertaken, and topical lidocaine is administered above, below, and at the level of the vocal cords. One hundred percent oxygen is administered by facemask with spontaneous ventilation, and anesthesia is continued with inhalation (insufflation) or an intravenous route (propofol infusion). At a suitable depth of anesthesia, again assessed by clinical observations, the surgeon undertakes rigid laryngoscopy or bronchoscopy. Insufflation of anesthetic gases and agents can be via numerous routes: (1) a small catheter introduced into the nasopharynx and placed immediately above the laryngeal opening, (2) a tracheal tube cut short and placed through the nasopharynx emerging just beyond the soft palate, (3) a nasopharyngeal airway, and (4) the side-arm or channel of a laryngoscope or bronchoscope.

Movements of the vocal cords are usually minimal with a spontaneously breathing technique, provided that an adequate level of anesthesia is maintained. If the depth of anesthesia is too light, the vocal cords may move, the patient may cough, or laryngospasm may occur. If the depth of anesthesia is too great, the patient may become apneic with cardiovascular instability. Careful observation throughout the procedure, noting movements, respiratory rate and depth, cardiovascular stability, and unobstructed breathing, is vital, with the concentration of the volatile anesthetic adjusted accordingly.

The limitations of spontaneous ventilation or insufflation techniques include the lack of control over ventilation and the potential for airway soiling. Operating room pollution secondary to insufflation of volatile agents also is an issue and requires the presence of high-intensity suction catheters near the mouth. Insufflation techniques may be unsuitable for large, soft, floppy lesions, particularly in the supraglottis or glottis, which may obstruct the airway after the onset of general anesthesia with spontaneous ventilation.

Jet Ventilation Techniques

In 1967, Sanders first described a jet ventilation technique using a 16-gauge jet placed down the side-arm of a rigid bronchoscope, relying on air entrainment to continue ventilation with an open bronchoscope.[75a] Sanders used intermittent jets of oxygen (rate 8/min, 3.5-bar driving pressure) to entrain air and showed that the technique maintained supranormal oxygen pressure with no increase in the carbon dioxide partial pressure. Since 1967, modifications to Sanders' original jet ventilation technique have been made for endoscopic airway surgery. These modifications include the site at which the jet of gas emerges and the frequency of jet ventilation.

Supraglottic jet ventilation is a technique in which the jet of gas emerges in the supraglottis by attachment of a jetting needle to the rigid suspension laryngoscope. Subglottic jet ventilation involves placing a small (2 to 3 mm in diameter) catheter or specifically designed tube (Benjet, Baldwin Medical, Melbourne, Australia) through the glottis and into the trachea. Transtracheal jet ventilation involves the placement of specifically designed percutaneous transtracheal catheters through the cricothyroid membrane or trachea.

In addition to modifications to the site at which the jet of gas emerges, changes to the frequency of jet ventilation have been described. High-frequency (>1 Hz, 60 breaths/min) is used with ventilator rates typically around 100 to 150/min. This allows (1) continuous expiratory flow of air, enhancing the removal of fragments of blood and debris from the airway; (2) reduced peak and mean airway pressures with improved cardiovascular stability; and (3) enhanced diffusion and interregional mixing within the lungs, resulting in more efficient ventilation. These advantages are of particular importance in patients with significant lung disease and obesity. High frequencies are achieved by automated high-frequency jet ventilators, which have alarms and automatic interruption of jet flow when preset pause pressure limits have been reached (i.e., blockage of entrainment or exhalation has occurred).

Jet ventilation techniques are suitable for most benign glottic pathology and early malignancy where airway obstruction is not anticipated. A typical jet ventilation technique includes preoxygenation followed by intravenous induction and the administration of muscle relaxants. Laryngoscopy is undertaken, and topical local anesthetic (lidocaine) is administered. An LMA is inserted, and ventilation is continued with 100% oxygen until the surgeon is ready to site the rigid (suspension) laryngoscope onto which a jetting needle has been attached in preparation for supraglottic jet ventilation.[76] Alternatively, facemask ventilation is continued until the surgeon is ready to site the laryngoscope. Anesthesia is maintained with a target-controlled infusion of propofol, supplemented by bolus administration or infusion of alfentanil or remifentanil is undertaken. At the end of surgery, the LMA is reinserted before antagonism of residual muscle relaxation and cessation of intravenous anesthesia, to facilitate smooth emergence.[76]

During the procedure, the adequacy of jet ventilation should be assessed continuously by observation of chest movements, by oxygen saturation readings, and by listening for changes to the sound during air entrainment and exhalation. The patency of the airway and any surgical obstruction also can be assessed by watching the endoscopic image on a television screen.

Supraglottic Jet Ventilation. Supraglottic jet ventilation describes a technique in which the jet of gas emerges in the supraglottis by attachment of a jetting needle to the rigid surgical suspension laryngoscope. High-frequency or low-frequency ventilation can be used. Supraglottic jet ventilation techniques allow a clear, unobstructed view for the surgeon with no risk of a laser airway fire. If the surgeon places surgical swabs into the operating field, however, and these swabs are dry, there is a risk of an airway fire with the swab acting as a "fuel" source. The limitations of supraglottic techniques relate to (1) misalignment of the suspension laryngoscope to the glottic inlet, which results in poor ventilation and the risk of gastric distention with entrained air; (2) blood, smoke, and debris are blown into the distal trachea; (3) considerable vibration and movement of the vocal cords occurs, which may require ventilation to be stopped while operating; (4) inability to monitor end-tidal carbon dioxide concentration; and (5) risk of barotrauma with pneumomediastinum, pneumothorax, and subcutaneous emphysema.

Subglottic Jet Ventilation. Subglottic jet ventilation allows delivery of a jet of gas directly into the trachea by the placement of a small catheter through the glottis and into the trachea. The technique is more efficient than supraglottic jet ventilation and results in reduced driving pressures, minimal vocal cord movements, a good surgical field, and no time constraints for the surgeon in the placement of the rigid laryngoscope. The main disadvantages are the potential for a laser-induced airway fire because of the presence of a potential fuel source within the airway, and a greater risk of barotrauma than in supraglottic jet techniques.

Transtracheal Jet Techniques. Elective transtracheal catheter placement under local anesthesia in individuals with significant airway pathology or under general anesthesia for elective laryngeal surgery has been described. Transtracheal jet techniques carry the greatest risks of barotrauma. Other potential problems include blockage, kinking, infection, bleeding, and failure to site the catheter. The use of transtracheal jet ventilation techniques for endoscopic surgery of the larynx requires careful evaluation of the potential risks and benefits.

Recovery from Anesthesia

Smooth emergence and recovery from anesthesia is particularly important for patients who have undergone airway procedures where recovery profiles and reintubation rates are significantly greater than in the general surgical population. The recovery profile with an LMA provides smooth emergence from anesthesia, and many groups advocate the exchange of microlaryngoscopy tubes, tracheal tubes, and laser tubes for an LMA for recovery.[33]

Inhaled Foreign Bodies

Foreign body aspiration is the most common indication for bronchoscopy in children 1 to 4 years old. Inhaled foreign bodies can lodge in the larynx, trachea, main bronchi, or smaller airways, and their effects depend on the duration, degree, and site. Peanuts are commonly inhaled foreign bodies, and as they absorb water, they swell, become friable, cause a chemical irritation of the airway, and require urgent removal. Patients with foreign bodies within the larynx and trachea present with acute dyspnea, stridor, coughing, and cyanosis. The Heimlich maneuver may be needed to dislodge the obstruction. If the obstruction is in the bronchus, the child is more likely to be wheezy, coughing, and dyspneic with evidence of decreased air entry on the side of the obstruction. Chest radiographs may not reveal the lesion because most foreign bodies are radiolucent, so a positive history and clinical symptoms of aspiration may be the only guide to the diagnosis. A child may present much later if the obstruction does not pose a functional problem with mucosal irritation, edema, and pneumonitis distal to the obstruction.

Dislodging an inhaled foreign body can convert a partial obstruction to a more severe or even complete obstruction. The general principle of removal of inhaled foreign bodies during laryngoscopy and tracheobronchoscopy is to maintain spontaneous ventilation and reduce the chances of the foreign body being pushed distally into the airway. In practice, however, maintenance of spontaneous ventilation in a critically obstructed airway can be extremely difficult to sustain, and intermittent positive-pressure ventilation may be needed. Some centers routinely use controlled ventilation with muscle paralysis.[77]

Sedative premedication should be avoided because it may precipitate total airway occlusion. Induction is usually by an inhaled technique with sevoflurane or halothane in oxygen. At a deep plane of anesthesia, laryngoscopy is performed, and topical local anesthetic (lidocaine) is administered. Intravenous anticholinergic agents (atropine, 20 µg/kg, or glycopyrrolate, 10 µg/kg) can help reduce secretions and reflex bradycardia associated with airway instrumentation. Close observation and monitoring throughout the procedure is required to ensure a correct depth of anesthesia to prevent movement, coughing, and laryngospasm. Because of its shorter duration of effect, sevoflurane is often changed to isoflurane when a deep plane of anesthesia is achieved. Maintenance may be in the form of a propofol infusion.

Some bronchoscopes allow the attachment of a T-piece to a side arm on the bronchoscope through which oxygen and volatile agent can pass directly into the distal trachea. Here the bronchoscope acts in a similar manner to an uncuffed tracheal tube. Some bronchoscopes do not allow T-piece attachment, however, and insufflation techniques are required. Postoperative care requires observation for airway edema and intravenous steroids (dexamethasone, 0.1 mg/kg), antibiotics, and humidified oxygen; high-dependency postoperative care may be needed.

Epiglottitis

Acute epiglottitis is an acute inflammatory disease of the epiglottis, arytenoids, and aryepiglottic folds. The onset and progression of the symptoms can be rapid and lead to complete airway obstruction, hypoxemia, and death. In adults, the incidence has been around 1 per 100,000 adults per year,[78] although the incidence seems to be increasing because of the frequent use of antibiotics in childhood with an associated failure to develop immunity against *Haemophilus influenzae*. Adults and children present with a sore throat, fever, dysphagia, drooling, open mouth, muffled voice, stridor, and respiratory distress. Patients often assume the tripod position, sitting up with their hands outstretched. In children, the main differential diagnosis is laryngotracheobronchitis (croup). The diagnosis is made on the history and physical examination, and an experienced anesthesiologist and ENT surgeon should be available. In children, indirect laryngoscopy, placement of intravenous lines, oropharyngeal examination, intramuscular injections, and lateral neck radiographs should not be performed because further distress may precipitate complete airway obstruction. In cooperative adults, very careful flexible fiberoptic laryngoscopy, intravenous lines, and careful oropharyngeal examination by experienced personnel may be beneficial.

For adults and children, preparation for a difficult intubation and emergency tracheostomy should be made. Inhaled induction with sevoflurane or halothane in oxygen is begun with the child usually sitting or in the preferred position. Nitrous oxide is not used. After inhaled induction, further monitoring and intravenous access are established as anesthesia deepens. Intravenous fluids and atropine may be administered to reduce the likelihood of bradycardia associated with intubation. On laryngoscopy, the epiglottis and aryepiglottic folds are swollen, and the classic "cherry-red" epiglottis may be seen. Often, the glottic opening is not seen, and the only clue may be a small mucous bubble during spontaneous ventilation or by gentle pressure on the child's chest. An uncuffed tracheal tube usually 1 to 3 mm smaller than normal is placed. Initially, this is an oral tube, and when the child is stable, this is replaced with a nasal tube, which is less likely to become dislodged during the subsequent 24 to 72 hours of ventilation in a pediatric intensive care unit. Throat and blood cultures are taken, antibiotic therapy is started, and the child is transferred to a pediatric intensive care unit.

In adults, management follows similar principles[78,79]; however, inhaled anesthesia in an adult with a compromised airway is often unfamiliar, difficult, and slow, and the depth of anesthesia can be difficult to assess. The patient can become more hypoxic and hypercarbic with long periods of instability and arrhythmias. The traditional view is that the technique is safe because if the patient obstructs, the volatile agent is no longer taken up, and the patient lightens and wakes up. This may not always be reliable, and some centers use an intravenous induction technique in adults with epiglottitis.

Head and Neck Surgery

A large part of head and neck surgery involves treatment for patients with diseases of the upper airway, larynx, and pharynx. When airway compromise is not an issue, most procedures are routine and largely uneventful. When airway compromise is a feature, the anesthetic plan needs to change according to the severity and site of obstruction. All patients with airway compromise should be considered as a possible difficult intubation, whereas not all patients with a difficult intubation have airway compromise.

Major head and neck procedures include laryngectomy, pharyngolaryngectomy, radical neck dissection, and resection of large thyroid lesions. A laryngectomy involves the resection of the larynx and the creation of an end tracheal stoma. A pharyngolaryngectomy also resects structures within the pharynx, including part or all of the tongue and esophagus. A radical neck dissection resects sternomastoid, internal and external jugular veins, and cervical lymph nodes. The treatment of upper airway tumors depends on the staging (TNM [tumor, node, metastasis]) and site. Chemotherapy, radiotherapy, laser endoscopic resection, transoral laser surgery, major soft tissue and organ excision, radical neck dissection, and flap reconstruction alone or in combination are the principal treatment options.

The recognition of a compromised or anatomically distorted upper airway is paramount in the preoperative assessment of patients. For elective procedures, a detailed history, physical examination, and investigations should be undertaken, but for more urgent procedures with severe airway compromise, investigations may not be possible.

General Considerations

More than 80% of laryngeal and oropharyngeal cancers are found in men 40 to 75 years old, and greater than 97% of patients are smokers with a high alcohol intake. Patients may have had previous radiotherapy and surgery resulting in altered anatomy, tissue edema, induration, and "stiff" tissues. Preoperative evaluation includes assessment of alcohol intake, use of tobacco, nutritional status, and electrolyte disturbance. Patients with a significant alcohol intake require an alcohol withdrawal regimen and optimization of nutritional, electrolyte, and hematologic indices.

Cardiovascular and respiratory disease, including chronic obstructive pulmonary disease, hypertension, and coronary artery disease, should be assessed.

Major head and neck operations are long procedures lasting many hours with the potential for significant blood loss. Monitoring including intra-arterial blood pressure and central venous pressure should be strongly considered. After a radical neck dissection and removal of the jugular veins, head and neck venous drainage depends on jugular veins from the nonoperative side, and central venous pressure lines are usually placed in the femoral vein or antecubital fossa, avoiding the neck.

Surgical manipulation of the carotid sinus can produce vagal reflexes causing severe bradycardia, hypotension, and even asystole. When this occurs, the surgeon should stop manipulation of the carotid sinus immediately, which usually resolves the bradycardia, and intravenous atropine should be administered. Occasionally, with manipulation of the carotid sinus, persistent vagal reflexes occur, and local anesthetic infiltration with lidocaine is required. Air embolism is possible, although rare, in head and neck surgery during dissection with open neck veins.

Blood loss during head and neck surgery can be significant, and some degree of hypotension is usually required. This can be achieved with inhaled agents and a 10- to 15-degree head-up tilt aiming for systolic blood pressures of around 85 to 90 mm Hg. A remifentanil infusion also is very effective[80,81] in controlling the stress response during surgery, providing moderate hypotension. At the end of surgery, when the remifentanil infusion is discontinued, additional analgesia, usually morphine, is necessary to prevent hypertensive responses.

After a laryngectomy, a J-shaped laryngectomy (Montandon) tube is inserted into the distal trachea allowing the breathing circuit to be connected at some distance from the stoma, which helps the surgeon suture the end tracheal stoma to the anterior neck wall. The cuff in a laryngectomy tube is sited at the end of the tube, and there is no distal bevel to prevent accidental endobronchial intubation. At the end of the procedure, careful suctioning of the area above the cuff of the laryngectomy tube should be performed to prevent blood and secretions entering the trachea after cuff deflation and replacement by a new cuffed tracheostomy tube.

The presence of a new tracheostomy tube often produces coughing and irritation, which can be reduced by topical local anesthetic (lidocaine) around the stoma. Patients who have had previous laryngectomy procedures can present with stoma stenosis or recurrence of disease. The airway can be managed by local anesthetic (lidocaine) spray to the stoma and trachea, and the placement of a tracheostomy tube awake. Ventilation can be achieved through the stoma by applying a partially inflated LMA cuff over the stoma. Postoperative considerations for laryngectomy patients include humidification, regular suctioning for blood and secretions, and a head-up position to reduce edema.

Head and Neck Difficult Airway

The head and neck difficult airway is caused by numerous disease states at different levels within the airway, and no single anesthetic management technique can be used safely in all patients. Many investigators have provided guidelines for the management of patients with compromised airways, which also is reviewed in Chapter 50.[82-86]

Level of Obstruction

Generally, difficult airways can be divided according to the level at which a problem exists and include (1) oral cavity, (2) oropharynx, (3) tongue base and supraglottis, (4) glottis, (5) subglottic and upper tracheal, (6) midtracheal, and (7) lower tracheal and bronchial. Disease states are not confined to these anatomic areas and can pass through many levels.

Management Options

Anesthetic management depends on the urgency of the intervention, site of the lesion, size of the lesion, level of obstruction, extension of the lesion, and degree of airway compromise. Symptoms and signs of airway compromise include respiratory distress, tachypnea, accessory muscle use, sternal retraction, tracheal tug, stridor, hypoxia, tachycardia, and exhaustion.

Management options include (1) awake regional laryngeal blocks, (2) intravenous induction of general anesthesia, (3) inhaled induction with maintenance of spontaneous ventilation, (4) inhaled induction with "takeover" of ventilation, (5) awake fiberoptic intubation, (6) asleep fiberoptic intubation, (7) awake transtracheal catheter placement and jet ventilation, (8) awake tracheostomy under local anesthesia, and (9) asleep tracheostomy under general anesthesia. Whatever technique is chosen as the primary anesthetic technique, a backup plan should be thought through, discussed with the surgeon, and instituted when difficulties arise.

Oral Cavity and Oropharyngeal Lesions

Small oral cavity lesions, such as early tonsillar carcinoma, often have no features suggestive of airway compromise, and the upper airway is essentially normal. Many of the standard airway management techniques can be used successfully for these early noncompromised patients. For larger lesions in the oral cavity, partial or near-complete airway obstruction can be a feature. An intravenous induction in these patients may result in oral cavity airway obstruction secondary to the loss of supporting tone on the structures within the oral cavity, and an inability to ventilate or oxygenate. The normal techniques to prevent this obstruction, such as facemask ventilation with oral or nasal airways, may not be effective. Passage of an oral or nasal airway past large, obstructing, vascular, necrotic oral tumors causes trauma and bleeding. The glottis and lower airway are often normal in these patients, and the principal problem around intubation is one of bypassing a large obstructing mass without traumatizing it, while maintaining a patent airway. An awake fiberoptic intubation technique is often used in this group of patients.

Large obstructing lesions within the oral cavity are usually seen by anesthesiologists working with ENT and maxillofacial surgeons, and this may account for the experience within this group of awake fiberoptic techniques. Other anesthetic techniques include awake transtracheal catheter placement with jet ventilation and awake tracheostomy.

Abscess and Ludwig's Angina

Any abscess causes pain and swelling, but abscesses around the peritonsillar area also may lead to airway compromise with

obstruction, trismus, dysphagia, and severe pain. Aspiration under local anesthetic may be possible, but extensive surgery may need to be done under general anesthesia. For patients without symptoms and signs suggesting airway compromise, an intravenous induction with careful laryngoscopy and tracheal intubation, avoiding rupture of the abscess, can be done. If airway compromise or anatomic distortion is present, an awake fiberoptic intubation technique or tracheostomy under local anesthetic may be indicated.

Ludwig's angina is a bilateral, rapidly spreading submandibular cellulitis, originating usually from the second or third molars. It was originally described by Ludwig in 1836, and angina implies the suffocating sensation. The tongue is elevated and displaced with hard, firm induration of the floor of the mouth and perioral edema.

Spread of the infection can cause trismus and mediastinitis. Airway management involves the placement of a nasotracheal tube usually by an awake fiberoptic technique. Occasionally, in severe disease, an awake local anesthetic tracheostomy is indicated.

Tongue Base and Supraglottic Lesions

Even small lesions at the tongue base and supraglottis can have significant effects on the airway because of their location at the entrance to the glottis, and their effect on the epiglottitis. As a tongue base lesion expands, it fills the space in the valleculae and directs the epiglottis downward, increasing airway obstruction at the glottic inlet. A large epiglottic or vallecular cyst results in airway obstruction and compromise in a manner similar to epiglottitis. The danger of an intravenous induction in these patients is airway obstruction after the loss of supportive tone from the soft tissues. An oral or nasal airway may be ineffective in relieving the obstruction, and a strong jaw thrust maneuver displacing the mandible and tongue base forward, creating an airspace at the supraglottic inlet, may be required.

Standard curved blade laryngoscopy can traumatize any lesion at the tongue base and valleculae, causing bleeding and swelling with the potential for complete airway obstruction. Although straight blade laryngoscopy aims to pass below the epiglottic tip and lift the epiglottis upward, this can be difficult with a distorted epiglottis. Great care and attention need to be taken during attempted laryngoscopy with these lesions.

Any patient in whom there is concern about a lesion at the tongue base or supraglottis, or in whom there is evidence of significant airway obstruction, an awake fiberoptic intubation, awake transtracheal catheter, awake laryngeal block with direct laryngoscopy, or an awake local anesthetic tracheostomy should be considered.

Glottic Lesions

Laryngeal pathology with no symptoms or signs of airway compromise, such as early T1 and some T2 tumors, can be managed by numerous anesthetic techniques, including intravenous induction of general anesthesia and placement of a cuffed tracheal or laser tube. Alternatively, a supraglottic or subglottic jet ventilation technique can be employed for biopsy and laser resection. When airway symptoms or signs suggest airway compromise with significant airway obstruction or stridor, the options for anesthesia are limited.

Awake fiberoptic techniques are suitable for oral cavity, oropharyngeal, and tongue base lesions because they *pass around* the mass, but may be unsuitable for advanced obstructing laryngeal disease, in which the fiberscope has to *pass through* the mass, resulting in complete airway occlusion.[87] Good topical anesthesia is difficult to achieve, and technically fiberoptic intubation through an anatomically distorted large vascular friable necrotic tumor is difficult. Awake fiberoptic intubation techniques have an associated morbidity and mortality.[88]

Some investigators have used inhaled induction techniques for the obstructed airway in which spontaneous ventilation is maintained throughout.[87] Inhaled induction for advanced laryngeal tumors with airway obstruction is difficult and challenging. Physiologic problems include a reduction in airflow with spontaneous ventilation, an increased collapsibility of the airway, increased work of breathing, critical instability at points of narrowing leading to further airway collapse, and a reduction in functional residual capacity.[89] Induction is slow with apneic periods, and episodes of obstruction are common.

Controversy exists regarding the suitability of "taking over" the patient's own spontaneous ventilation with bag-mask ventilation. Retaining spontaneous ventilation throughout is the theoretical inherent advantage of this technique. Taking over ventilation allows a suitable depth of anesthesia for laryngoscopy to be achieved quicker, however, which avoids the long periods of spontaneous ventilation waiting for an adequate depth of anesthesia in which the patient may become unstable.

The administration of a muscle relaxant provides optimal ventilation and intubating conditions. Calder and Yentis[90] commented on the perceived "safe practice" of not giving muscle relaxants until facemask ventilation has been documented, and argued that the theoretical advantage is not fulfilled in practice. They commented on two studies[91,92] looking at the incidence and prediction of difficult and impossible mask ventilation in which no patient was woken up, and suggested that when a patient has an obstructed airway, it is not feasible to await awakening, and something has to be done to ventilate the lungs before catastrophic desaturation occurs.[90]

At a suitable depth of anesthesia, laryngoscopy is undertaken, and the best chance of success is usually at the first attempt when bleeding, trauma, and swelling are minimal. A gum elastic bougie or stylet may be useful. Failure to intubate requires an urgent tracheostomy, and the surgeon should be gowned and immediately ready.

Transtracheal catheter placement[93,94] under local anesthesia at a level below the distal margin of the tumor is a recognized technique for the difficult airway. The catheter is placed usually at the level of the second or third tracheal rings, avoiding the tumor and the risk of bleeding and tumor seeding. When catheter placement has been confirmed in an awake patient by an end-tidal capnography trace, intravenous induction is started. After induction, jet ventilation through the transtracheal catheter is begun, ideally with a high-frequency ventilator with automated cutoff at a preset pause pressure limit to reduce the incidence of barotrauma. An experienced anesthesiologist should remain at the head end of the patient ensuring a patent and adequate upper airway by chin lift, jaw thrust, or oral or nasal airway.

Subglottic and Upper Tracheal Lesions

Lesions in the subglottis are usually an extension of glottic lesions, and the anesthetic problems and principles are similar. Acquired laryngotracheal stenosis in the glottis, subglottis, and upper trachea has an incidence of around 1 in 200,000 adults.[95] After intubation, nonspecific changes in the glottis and subglottis occur that result in edema and superficial ulceration forming granulation tissue, which progresses to firm scar tissue. Surgical management of these patients involves (1) laser resection, (2) serial dilation, (3) stent insertion, (4) topical chemotherapy (mitomycin), (5) resection of stenotic areas with an end-to-end anastomosis, and (6) tracheal homografts. Patients with advanced laryngotracheal stenosis may have airway diameters of 2 to 4 mm, and airway management usually involves a supraglottic jet ventilation technique.

Mid and Lower Tracheal Lesions

Tracheal obstruction can be caused by lesions arising within the trachea itself or by compression from surrounding structures or tumors. The upper airway is usually normal at laryngoscopy, and the problems are secondary to an inability to pass a tracheal tube and difficulties placing a surgical airway below the obstruction. Awake fiberoptic intubation should be considered, but may be impossible. A rigid bronchoscope may be required to secure the airway. Lower tracheal lesions and large mediastinal masses should be managed in specialist thoracic centers.

Tracheostomy

With severe life-threatening airway compromise, a tracheostomy may be indicated. Ideally, tracheostomy should be performed under a general anesthetic allowing the surgeon optimal operating conditions; however, a general anesthetic may be unsafe and risk total airway occlusion, requiring an emergency surgical airway under suboptimal conditions. The decision to perform a tracheostomy under local anesthesia is made in conjunction with the surgeon and depends on many factors, including the experience of the anesthesiologist, the severity of airway disease, and surgical requirements after resection. Technically, tracheostomy with an awake local anesthetic in a patient with severe airway compromise is difficult. Ideal patient positioning with an extended head and supine is often not tolerated by the patient, and the procedure has to be undertaken in a semiupright sitting position. Surgical infiltration, manipulation, and dissection are often poorly tolerated with increasing airway compromise. Sedation should be avoided during this period because of the risk of total airway obstruction.

A tracheostomy tube change in a patient with a long-term tracheostomy in which the tract has been stable for many months is usually uncomplicated and can be performed at the bedside. Changing a fresh tracheostomy tube within the first week can be dangerous because the tract is unstable, and the soft tissues can easily close after the tracheostomy tube has been removed. Attempts to force a tracheostomy tube past the tract can result in false passages, subcutaneous emphysema, an inability to oxygenate, and a critical situation. Early tube changes should be avoided, but may be necessary to optimize size and reduce air leaks. These early tube changes with airway exchange catheters should be done after preoxygenation by an experienced clinician who can rescue the airway.

Anesthesia for Eye Surgery

Ocular Anatomy

The eye is a sphere about 24 mm in diameter. It sits in the pyramidal bony orbit. The wall of the globe has three layers—the sclera, the uveal tract, and the retina.

The sclera is the outermost layer. It is the tough, fibrous "white of the eye." The transparent cornea is the most anterior part of the sclera. Most of the focus power of the eye is from the curvature of the cornea.

The middle layer, the uveal tract, has three structures—the choroid, the iris, and the ciliary body. The choroid is a layer of blood vessels located posteriorly. Bleeding in this layer is one cause of intraoperative expulsive hemorrhage. The pigmented iris controls light entry with muscle fibers that change the size of the pupil. Sympathetic stimulation dilates the pupil by causing iris dilator muscles to contract, whereas parasympathetic stimulation causes miosis, or pupillary constriction, by causing the iris sphincter muscles to contract. The ciliary body lies just behind the iris; it produces aqueous humor. Ciliary muscle fibers adjust the focus by releasing tension on the suspensory fibers, or zonules, of the lens. Opacification of the lens causes a cataract. Uveitis is an inflammatory condition of these structures (iris, choroid, and ciliary body).

The innermost eye layer is the retina. Light stimulates retinal photoreceptors to produce neural signals that the optic nerve carries to the brain. There are no capillaries in the retina; the choroid layer provides the retina with oxygen. Retinal detachment from the choroid layer compromises the retinal blood supply and is a major cause of vision loss. The retinal layer ends about 4 mm behind the iris. The area between the limbus of the cornea and the retina is called the pars plana. Because there is no retinal layer there, it is a safe entrance site for vitrectomy procedures.

The center of the eye is filled with vitreous gel. This thick fluid has attachments to blood vessels and the optic nerve. Traction of the vitreous on the retina is a cause of retinal detachment. Scarring, bleeding, or opacification of the vitreous is treated by vitrectomy.

The extraocular muscles move the globe within the orbit. They arise from a fibrous ring near the apex of the orbit and insert on the sclera. The six extraocular muscles lie within a cone behind the eye surrounding the optic nerve, ophthalmic artery and vein, and ciliary ganglion.

The eyelids have an outer layer of skin, a muscle layer, a tarsal plate of cartilage, and a layer of conjunctiva. The conjunctiva is a mucous membrane that lines the inner eyelids and covers the globe up to the corneal-scleral junction.

The lacrimal gland sits in the superior temporal orbit. It releases tears across the surface of the globe. Tears drain via the puncta near the medial canthus of the eyelids. Tears flow through the canaliculi to the lacrimal sac and duct, to drain into the nasopharynx.

The ophthalmic artery provides most of the blood supply to the orbital structures. It is a branch of the internal

carotid artery, very close to the circle of Willis. The superior and inferior ophthalmic veins drain directly into the cavernous sinus.

Cranial nerves innervate the ocular structures. The optic nerve (CN II) carries the neural signals from the retina. The oculomotor (CN III), trochlear (CN IV), and abducens (CN VI) control the extraocular muscles. Touch and pain sensation is carried via the trigeminal nerve (CN V). Sensation to the lower lid is via the maxillary nerve. Sensation to the upper lid is via the frontal branch of the ophthalmic nerve. The nasociliary branch of the ophthalmic nerve sends sensory fibers to medial canthus, lacrimal sac, and ciliary ganglion.

The ciliary ganglion provides sensory innervation to the cornea, iris, and ciliary body. Parasympathetic fibers originate from the oculomotor nerve (CN III) and synapse in the ciliary ganglion before supplying the iris sphincter muscle. Sympathetic fibers originate from the carotid plexus and travel through the ciliary ganglion to innervate the dilator muscle of the iris. Local anesthetic blockade of the ciliary ganglion produces a fixed, mid-dilated pupil.

The facial nerve (CN VII) exits the base of the skull from the stylomastoid foramen. It supplies motor innervation to the orbicularis muscle via the zygomatic branch. Local anesthetic block of the facial nerve can prevent lid squeezing.

Oculocardiac Reflex

The oculocardiac reflex was first described by Aschner and Dagnini in 1908.[95a,95b] Traction on the extraocular muscles or pressure on the globe causes bradycardia, atrioventricular block, ventricular ectopy, or asystole. It is especially seen with traction on the medial rectus muscle, but can occur with stimulation of any of the orbital contents, including the periosteum.

The reflex is trigeminovagal. The afferent limb is from orbital contents to ciliary ganglion to ophthalmic division of the trigeminal nerve to the sensory nucleus of the trigeminal near the fourth ventricle. The efferent limb is via the vagus nerve to the heart.[96]

The reflex may be seen more often with procedures under topical anesthesia. Retrobulbar block is not uniformly effective, however, at preventing the reflex. Orbital injections can trigger the response. The response is exacerbated by hypercapnia or hypoxemia.

In the event of arrhythmia, the anesthesiologist first should ask the surgeon to stop manipulations. The ventilatory status is assessed. If significant bradycardia persists or recurs, intravenous atropine is administered in 7 μg/kg increments. Rarely, severe bradycardia or asystole occurs. Although chest compressions might be required to allow the atropine to circulate, usually the heart rhythm returns to normal with cessation of manipulation alone. The response fatigues with repeated stimulation.

Pretreatment with intravenous atropine or glycopyrrolate can be effective. Pretreatment may be indicated in patients with a history of conduction block, vasovagal responses, or β-blocker therapy.

Intraocular Pressure

The blood supply to the retina and optic nerve depends on the intraocular perfusion pressure.[97] This perfusion pressure is defined as the difference between the mean arterial pressure and the intraocular pressure (IOP). High IOP impairs the blood supply, leading to a loss of optic nerve function. After an incision in the globe is made, factors that would increase IOP can cause prolapse and loss of intraocular contents; this can cause permanent vision loss.

The globe is a relatively noncompliant compartment. The volume of the internal structures is fixed except for aqueous fluid and choroidal blood volume. The quantity of these two factors regulates IOP.

Two thirds of the aqueous fluid is actively secreted by the ciliary body by a sodium-pump mechanism. One third comes from passive filtration through vessels on the iris. Aqueous fluid is produced at a rate of 2 μL/min. Aqueous flows over the lens and through the pupil to bathe the inner corneal endothelium. It then enters the angle of the anterior chamber to flow through the trabecular meshwork to the canal of Schlemm. The canal of Schlemm is continuous with channels to the episcleral veins. IOP is primarily regulated by the resistance at the trabecular meshwork. Normal pressure is 10 to 20 mm Hg.

Impairment of aqueous drainage at any point can elevate the IOP. Sclerosis of the trabecular meshwork is believed to cause the chronic pressure elevation in open-angle glaucoma. Closed-angle glaucoma occurs when there is an obstruction to aqueous drainage from closure of the anterior chamber angle. This happens from peripheral iris swelling or anterior displacement. Patients with a preexisting narrow angle may be predisposed to this condition. The acute increase in pressure causes severe pain. This is an ophthalmologic emergency.

Changes in choroidal blood volume can increase IOP rapidly. Hypercapnia causes choroidal congestion.[98] Coughing, straining, or vomiting can increase IOP to 30 to 40 mm Hg. Endotracheal intubation can cause similar increases. These increases are transient and are relatively innocuous in a closed eye. In an open eye, such as after traumatic injury or during cataract surgery, these increases can lead to loss of intraocular contents, hemorrhage, and permanent vision loss.[99]

Extrinsic compression of the eye also increases the IOP. A normal blink increases the IOP by 10 mm Hg. A forceful lid squeeze can increase IOP to more than 50 mm Hg.[100] A poorly placed anesthesia mask can put enough pressure on the eye to reduce blood flow to zero.

Deep inhaled or thiopental anesthesia causes a dose-related reduction in IOP by 30% to 40%.[101] Opioids have little effect. Atropine in the usual doses does not cause a significant increase in IOP, even in patients with open-angle glaucoma. Ketamine may cause a modest increase in IOP.

Intravenous succinylcholine causes IOP to increase by 6 to 12 mm Hg.[102] This lasts for 5 to 10 minutes. The use of succinylcholine for induction in cases of open-globe injury with full stomach has been controversial. Loss of vitreous in patients from succinylcholine has not been reported.

Ophthalmologic Drugs

Ophthalmologic drugs are systemic medications. Eyedrops can have systemic effects and important drug interactions with anesthetics. Acetazolamide is a carbonic anhydrase inhibitor. It is used in the treatment of glaucoma to decrease chronically elevated IOP. It induces an alkaline diuresis that may result in potassium depletion. Patients taking acetazolamide should have electrolytes

checked preoperatively. Atropine eye drops can cause tachycardia, dry skin, fever, and agitation.[103] Overdosage can be treated with incremental doses of physostigmine.

Echothiophate is a topical anticholinesterase drug used to maintain miosis in the treatment of glaucoma. Systemic absorption leads to total body inhibition of plasma cholinesterase. Subsequent administration of succinylcholine can cause prolonged muscle paralysis.[104] Inhibition of the metabolism of ester-type local anesthetics may predispose a patient to local anesthetic toxicity. Echothiophate is very long-acting. Return toward normal enzyme activity may take 4 to 6 weeks after discontinuation of the drug.

Mannitol is an osmotic diuretic. It causes a decrease in IOP lasting 5 to 6 hours. Patients who receive the drug during surgery may need a urinary catheter to avoid overdistention of the bladder. Mannitol causes an increase in the circulating blood volume, which may lead to congestive heart failure in patients with poor ventricular function.

Phenylephrine is an α-adrenergic agonist applied topically to dilate the pupil. Systemic absorption of the 10% solution is associated with severe hypertensive reactions.[105] The 2.5% concentration is safer, but may exacerbate hypertension in some patients.

Pilocarpine and acetylcholine are cholinergic drugs used to constrict the pupil. Bradycardia and acute bronchospasm have been reported.

Timolol maleate is a topical β-blocker. It is used in the treatment of glaucoma. Systemic absorption causes β-blockade, with possible bradycardia, bronchospasm, or exacerbation of congestive heart failure.[106] Care should be taken especially in a patient with severe chronic obstructive pulmonary disease.

Tamsulosin hydrochloride (Flomax) has selective α-adrenoreceptor antagonistic properties and binds for a long period to nerves to the iris dilator muscle, affecting iris dilation and leading to complications in cataract surgery. The iris remains floppy even after 7- to 28-day interruption of the tamsulosin regimen.[107]

Preoperative Evaluation (also see Chapters 34 and 71)

Eye surgery is the most common surgery in the elderly. In 2005, the Medicare program paid for nearly 3 million claims for cataract surgery. These are quick outpatient procedures that do not involve blood loss or much postoperative pain. They are not minor procedures, however; ophthalmic surgery can be a major life event. Establishing a professional relationship reduces anxiety and helps the patient prepare for surgery. Giving information to the patient is just as important as getting information from the patient. An informed patient is more calm, comfortable, and cooperative. The patient needs to know what to expect.

Eye surgery patients are a high-risk group. Adults tend to be old. Most have other risk factors, such as diabetes, hypertension, and atherosclerosis.[108] Cataracts were shown to be a marker for increased mortality in the Nurses' Health Study.[108a] Ophthalmic surgery is low risk, however. Mortality after eye procedures is much lower than for the general surgical population. Backer et and colleagues[109] found that eye surgery did not pose the risk of myocardial reinfarction seen with general surgical procedures. Patients' chronic diseases have less effect on outcome with these procedures. In a study of unanticipated hospital admissions after outpatient ophthalmic surgery, age and American Society of Anesthesiologists physical status were not significant factors.[110]

There is controversy regarding the best preoperative management. Some clinicians say that because cataract extraction is a low-stress procedure with no blood loss, no preoperative evaluation is needed. Publication of a large, multicenter trial showed no effect of preoperative blood tests and electrocardiogram on postoperative outcome.[111] Another opinion is that every patient must receive a full evaluation to include every possible test, to detect every possible finding, to institute every possible therapy, and to delay as long as possible, so that the patient can be in the best possible condition and have the lowest possible risk. Appropriate preoperative medical consultation is important. A study of malpractice litigation in cataract surgery found that medical consultation accounted for 16% of the liability; this compared with 17% attributed to either local or general anesthesia.[112]

We do not want to ignore risk. Neither should we reduce every risk to the lowest conceivable minimum. The anesthesiologist's goal is to prepare the patient to present an acceptable risk at surgery. Acceptable risk is determined by the medical care team with the informed consent of the patient. If a patient's condition would indicate inpatient admission for medical treatment, or if a reversible condition would likely lead to a perioperative complication, the risk is unacceptable.

The goal is to develop guidelines that would encourage consistency of care and minimize disruption to patients and the operating room. The following guidelines are presented after review of literature and published guidelines.

Patient History

Previous hospitalizations and surgical procedures are reviewed. Allergies and drug sensitivities are noted. Latex allergy should be addressed specifically. A current list of medications is obtained. Patient factors that could influence anesthetic management include dementia, deafness, language difficulty, restless legs syndrome, obstructive sleep apnea, tremors, dizziness, and claustrophobia. A preoperative patient questionnaire can be very helpful. A thorough review of the patient history helps perioperative planning and establishing a physician-patient relationship.

Physical Examination

Check for signs of major cardiac or pulmonary decompensation. Particular attention should be paid to positioning issues, such as severe scoliosis or orthopnea.

Laboratory Studies

No routine screening tests have been shown to improve outcome. Laboratory studies should be determined on the basis of the results of the history and physical examination. Generally, the tests that a patient needs before ophthalmic procedures are the same tests a patient would require at a routine examination if surgery were not planned. Tests are chosen when the results are likely to change management. Urgent medical management is obtained for results reaching critical limits. Indications for laboratory studies and critical results are as follows:

Electrocardiogram: New chest pain, decreased exercise tolerance, palpitations, near-syncope, fatigue, or dyspnea. Tachycardia, bradycardia, or irregular pulse on examination. *Critical results*: Signs of acute ischemia or injury, malignant

arrhythmia, complete heart block, atrial fibrillation that is new, or heart rate greater than 100 beats/min.

Serum electrolytes: History of severe vomiting or diarrhea, poor oral intake, changes in diuretic management, or arrhythmia. *Critical results*: Sodium less than 120 mEq/L or greater than 158 mEq/L. Potassium less than 2.8 mEq/L or greater than 6.2 mEq/L.

Urea nitrogen: Signs or symptoms of renal decompensation. *Critical result*: Greater than 104 mg/dL.

Serum glucose: Polydipsia, polyuria, or weight loss. *Critical results*: Less than 46 mg/dL or greater than 484 mg/dL.

Hematocrit/hemoglobin: History of bleeding, poor oral intake, fatigue, decreased exercise tolerance, or tachycardia. *Critical results*: Hematocrit less than 18% or greater than 61%. Hemoglobin less than 6.6 mg/dL or greater than 19.9 mg/dL.

Ophthalmic Evaluation

Visual acuity of both eyes should be noted. Patients with poor vision in the nonoperative eye face much greater potential functional loss. These patients have a higher anxiety level. If the patient is to be patched overnight, the physician should anticipate the increased need for postoperative assistance for a temporarily blind patient.

The axial length of the globe should be assessed. When ultrasound measurements are available, the axial length should be noted. If no ultrasound is available, a myopic patient should be assumed to have an increased axial length. If a posterior staphyloma is present, the risks of injection anesthesia may be dramatically increased. Preoperative glaucoma history, increased IOP, and increased axial length are important risk factors for suprachoroidal hemorrhage. The risk may be reduced with tighter control of intraoperative heart rate and blood pressure. Preoperative softening with a compression device also may decrease risk.

Cardiovascular Evaluation

The American Heart Association and American College of Cardiology published guidelines for perioperative cardiovascular evaluation for noncardiac surgery.[113] Ophthalmic procedures such as cataract extraction are specifically identified as low-risk procedures. For these procedures, evaluation is focused on patients with major clinical predictors of risk. These major predictors and the evaluation of the patient are reviewed in Chapters 34 and 35.

Hypertension

Hypertension is a common problem in ophthalmic patients. Severe hypertension may lead to perioperative complications. Degrees of hypertension have been defined. Stage 3 of severe hypertension is defined as a systolic blood pressure of 180 mm Hg or more or a diastolic blood pressure of 110 mm Hg or more. It would be prudent to reschedule elective procedures in patients with sustained stage 3 hypertension until after 2 weeks of antihypertensive therapy.

Pulmonary Considerations

Ophthalmic procedures generally require that the patient lie flat comfortably and quietly. If the patient cannot lie flat, or if there is intractable cough, a perioperative complication is more likely. Preoperative risk reduction strategies include cessation of cigarette smoking, treatment of airflow obstruction with bronchodilators or steroids, and administration of antibiotics for respiratory infections.

Patients should be assessed for sleep apnea. Intravenous sedation is often contraindicated in these patients. For some patients, treatment with a mild stimulant such as caffeine can be helpful in keeping them awake and cooperative during a procedure.

Endocrine Considerations

Diabetes mellitus is very common in patients undergoing ophthalmic surgery.[112] It is best if these patients can be done early in the morning with as little disturbance as possible to their usual daily routine. Severe hyperglycemia and hypoglycemia should be avoided. A fasting blood glucose should be checked preoperatively. Insulin therapy should be used, if needed, to maintain blood glucose at 150 to 250 mg/dL. The potential for autonomic neuropathy needs to be considered, especially when elevating the patient from the supine position.

Patients on long-term steroid therapy generally do not require "stress-dose" steroid treatment for ophthalmic surgery. The patient should be given his or her normal steroid dose on the day of surgery. The physician should be alert to the occasional patient who may require additional glucocorticoid perioperatively. Unexpected hypotension, fatigue, and nausea may be signs of a patient who needs additional steroid.

Anticoagulation

Many patients undergoing ophthalmic surgery take anticoagulants. Perioperative management of anticoagulants involves weighing the relative risks of thrombotic against possible hemorrhagic complications. Either of these results can be devastating to the patient. In a study of more than 19,000 cataract procedures, the incidence of hemorrhagic and thrombotic complications was very low.[114]

The risk of thrombotic complications depends on the following:

1. The indication for anticoagulation. Serious complications from arterial thromboembolic disease, such as atrial fibrillation or valvular heart disease, are much more common than complications from venous disease, such as deep vein thrombosis.
2. The risk factors for thromboembolism, especially if and when the patient had a previous episode of thromboembolism.

The risk of hemorrhagic complications depends on the following:

1. The degree of anticoagulation.
2. The hemorrhagic potential of the surgical procedure. Serious hemorrhagic complications are most probable in orbital and oculoplastic surgery; of intermediate probability in vitreoretinal, glaucoma, and corneal transplant surgery; and least likely in cataract surgery.

A consensus is developing that cataract surgery may be safely performed while maintaining patients on warfarin. For intermediate-risk procedures, such as some glaucoma surgeries, stopping warfarin for 4 days preoperatively is indicated. For high-

risk cases for hemorrhage or thrombosis, conversion from warfarin to heparin may be required.

Anesthetic Techniques

Regional Techniques

Eye surgery usually requires immobility (or akinesia) of the eye and profound anesthesia of the surgical site. Any discomfort during the procedure can be magnified by the patient's anxiety and fear of possible vision loss.[115] Various regional anesthetic techniques have been developed that satisfy the requirements of ophthalmologic surgery and are generally reliable and safe. Discomfort and anxiety are associated with many of these blocks, and rare but severe complications. Supplementation with intravenous sedation and continuous patient monitoring are frequently preferred.[116,117] Intravenous sedation also may be associated with increased incidence of medical events.[118]

Regional anesthesia has several advantages over general anesthesia. The local block gives significant postoperative analgesia. Nausea and vomiting are infrequent. The patient can return to ambulation faster. Most patients meet recovery discharge criteria at the end of surgery, and can bypass a stay in the postanesthesia care unit.

An intravenous infusion is started. Blood pressure, electrocardiogram, and oxygen saturation monitors are placed. Supplemental oxygen is given by nasal prongs. A foam wedge is placed to keep the knees flexed to prevent lower back pain. An air blower is often placed with the outlet on the chest to eliminate carbon dioxide and oxygen buildup under the drapes and to prevent claustrophobia.

A combination of midazolam (0.5 to 1 mg), fentanyl (12.5 to 50 μg), and propofol (30 to 50 mg) provides excellent amnesia and sedation for the placement of the blocks. We omit midazolam and fentanyl in patients with limited cognitive reserve as a result of stroke or mild dementia. For local anesthesia, we use a 1 : 1 ratio of bupivacaine 0.75% and lidocaine 2% without epinephrine.[119] Hyaluronidase is added to speed tissue penetration.

Facial Nerve Blocks

A facial nerve block is done when complete akinesis of the eyelids is desired.[120] Three methods for the eyelid block are as follows:

1. *Modified van Lint block*: The needle is placed 1 cm lateral to the orbital rim, and 2 to 4 mL of anesthetic is injected deep on the periosteum just lateral to the superolateral and inferolateral orbital rim. The disadvantages of this block include discomfort, proximity to the eye, and common postoperative ecchymoses.
2. *O'Brien block*: The mandibular condyle is palpated inferior to the posterior zygomatic process and anterior to the tragus of the ear as the patient opens and closes the jaw. The needle is inserted perpendicular to the skin about 1 cm to the periosteum. As the needle is withdrawn, 3 mL of anesthetic is injected.
3. *Nadbath-Rehman block*: A 12-mm, 25-gauge needle is inserted perpendicular to the skin between the mastoid process and the posterior border of the mandible. The needle is advanced its full length, and after careful aspiration, 3 mL of anesthetic is injected as the needle is withdrawn. This blocks the entire trunk of the facial nerve. The patient should be told to expect a lower facial droop for several hours postoperatively. The major disadvantage to this block is the proximity of the injection to important structures such as the carotid artery and the glossopharyngeal nerve.

Retrobulbar Block

The retrobulbar block provides excellent akinesia and anesthesia of the eye.[121] A 3-cm, 23- to 25-gauge blunt Atkinson needle is recommended to protect against ocular perforation. The needle is placed at the junction of the inferior and lateral walls of the orbit just above the inferior orbital rim.[122] The needle is advanced about 15 mm along the wall of the orbit until it is past the equator of the eye. The needle is turned superiorly to aim toward the superior orbit. The needle is advanced until it enters between the extraocular muscles; 2 to 3 mL of anesthetic solution is injected. Some intorsion on downgaze is expected because the superior oblique muscle is outside the muscle cone and may not be blocked.

Retrobulbar hemorrhage is the most common complication of this block; proptosis and subconjunctival ecchymosis also are seen. Monitoring of the IOP is mandatory. If the pressure becomes elevated, a lateral canthotomy is performed to decompress the orbit. Bleeding outside the muscle cone is seen as subconjunctival ecchymosis without proptosis. After some monitoring, if no increased IOP develops, the surgical procedure may be done safely.

Intravascular injection can occur despite a negative aspiration test. The total dose of local anesthetic used is small, and even if the total dose is given intravenously, no systemic effects would be likely. Accidental intra-arterial injection can give high brain levels via retrograde flow in the internal carotid artery. Central nervous system excitation and seizures can be seen, but are usually very transient, as the local anesthetic redistributes out of the brain. Obtundation and respiratory arrest have been reported. These prolonged effects are thought to be due to injection into the optic nerve sheath, which is continuous with the subarachnoid space.

Optic nerve damage and ocular perforation with retinal detachment and vitreous hemorrhage also have been reported. Special care must be taken when injecting patients with high myopia. If the axial length of the globe is greater than 25 mm, the eye is larger, and the sclera is thinner, increasing the risk of ocular penetration. A different anesthesia technique may be advisable in such cases.

Posterior Peribulbar Block

To prevent retrobulbar hemorrhage, posterior peribulbar anesthesia has become more popular.[123] A blunt 23-gauge ⅞-inch Atkinson needle is placed at the junction of the middle and lateral thirds of the lower lid just above the inferior orbital rim; 1 mL of local anesthetic is put just below the orbital septum, 3 mL at the equator, and 2 mL posterior outside the muscle cone. If no bulging is noted at the superior nasal lid area, a second injection of 2 to 3 mL is administered inferonasally. Disadvantages of the technique include a longer onset time (9 to 12 minutes) and lower incidence of complete akinesia. Globe perforation from peribulbar injection has been reported.[124]

Sub-Tenon's Block

To avoid the complications of sharp needles, a technique was developed using a blunt cannula under Tenon's fascia.[125] Various

lengths of cannulas have been used. Under topical anesthesia with sedation, a speculum is placed to retract the lids. A 2- to 3-mm spot of cautery is made 5 mm from the limbus in the inferonasal or inferolateral quadrant. A 2-mm snip is made in the conjunctiva with blunt dissection through Tenon's fascia. A blunt cannula is directed under Tenon's fascia posteriorly, but not beyond the equator of the globe, with injection of 1 to 3 mL of local anesthetic. Some degree of conjunctival edema is often seen. Analgesia is usually excellent.

Topical Anesthesia

Cataract surgery can be done under topical anesthesia alone.[126] This technique arose with the increase in popularity of small incision surgery and phacoemulsification. Topical anesthesia avoids the potential complications associated with retrobulbar and peribulbar injections. In addition, patients have the most rapid visual rehabilitation, with improved vision almost immediately after the procedure. Disadvantages of the technique include the potential for eye movement during surgery, increased patient anxiety, and discomfort from the microscope light.[127] Tetracaine 0.5% and lidocaine 4% have been used successfully. Two drops of tetracaine are given initially. About three more doses of tetracaine or lidocaine are applied every 5 minutes just before surgery.

Appropriate patient selection is crucial. A confident, calm, and cooperative patient usually does well. A nervous, hypersensitive patient may be a better candidate for another technique. Other problems may be presented by photophobic patients, patients with small pupils, or patients who require a large incision.

General Anesthesia

The choice of general versus regional anesthesia is made on the basis of the duration of the surgery, the relative risks and benefits of each technique for the patient, and patient preference. Neither technique has been shown to be safer.

In the past, regional anesthesia had an advantage of greatly reduced postoperative nausea and vomiting. With the advent of shorter-acting general anesthetics and nonopioid analgesia, the incidence of nausea and vomiting has decreased dramatically. Droperidol has been used frequently as an antiemetic, although it has been associated with late postoperative anxiety in some individuals. Ondansetron may be as effective with fewer side effects. A comparison of memory function in patients after general anesthesia or local anesthesia with sedation showed no advantage to either technique.[128]

The goals of general anesthesia include a smooth intubation, stable IOP, avoidance of severe oculocardiac reflexes, a motionless field, and smooth emergence. These goals can be accomplished with inhaled anesthesia, balanced opioid anesthesia, or intravenous agents, with or without muscle relaxants. The LMA can be used for ophthalmologic surgery and may be associated with less coughing on emergence. Because of the inaccessibility of the airway during the surgery, and the risk of laryngospasm or aspiration, LMA should be used only by anesthesiologists very skilled in the technique. It may be more appropriate for extraocular surgery.

Nitrous oxide presents a special problem in some vitreoretinal procedures.[129] In the technique called fluid-gas exchange, the surgeon injects an intravitreal air bubble to tamponade the retina against the wall of the globe. Sulfur hexafluoride is a poorly soluble gas used to prolong the resorption of intravitreal air bubbles. Nitrous oxide diffuses and causes bubble expansion, with the potential for dangerous increases in IOP. Nitrous oxide should be shut off for 15 minutes before placing the sulfur hexafluoride bubble and should be avoided for 7 to 10 days thereafter.

This problem is potentially worse with a newer agent, perfluoropropane (C3F8), because this agent can persist for weeks. Here, nitrous oxide should be avoided for at least a month, or until the bubble is resorbed. If a patient presenting for nonophthalmic surgery has a history of a recent retinal procedure, it is critical to establish whether the patient has an intravitreal gas bubble before using nitrous oxide. Otherwise, blindness can result.

Anesthesia for Pediatric Ophthalmologic Procedures

(see also Chapter 82)

Anesthesia for pediatric eye surgery can be considered a subspecialty of its own.[130] Small children may need examination under anesthesia. Intramuscular ketamine sometimes can be a good choice; it can be used when intravenous access may be problematic. Some ophthalmologists prefer ketamine because it does not reduce IOP as barbiturates and deep inhaled anesthetics do.

The most common eye surgery in children is for strabismus, or misalignment of the eyes. There is generally no severe postoperative pain, but nausea and vomiting are significant 50% to 80% of the time without treatment. Droperidol 5 to 75 µg/kg seems to decrease nausea and vomiting significantly without undue delay of discharge. Ondansetron has similar effects without sedation. If forced duction testing is used to assess the muscle tightness, the surgeon should be notified if succinylcholine is used. Succinylcholine causes a tonic increase in eye muscle tone, which resolves in about 20 minutes.

Strabismus is a very common condition, and most children are otherwise healthy. There is a higher incidence of strabismus in trisomy 21 or Down syndrome, cerebral palsy, and hydrocephalus. Malignant hyperthermia and myotonic dystrophy also have been associated with strabismus. Myotonic dystrophy also is seen in patients with ptosis and cataracts.

Cataracts can be seen in children with Pierre-Robin syndrome and phenylketonuria. Patients with Marfan syndrome have a high incidence of subluxation or dislocation of the lens. Aniridia, the congenital absence of the iris, is associated with Wilms' tumor and hypertension. Congenital glaucoma also can be seen with Sturge-Weber syndrome and with seizures and angiomas of the mouth and larynx. Pediatric ophthalmic conditions associated with congenital syndromes are summarized in Table 75-2.

Ophthalmologic Procedures

General Procedures

Most general ophthalmologic procedures are done with topical or local anesthetic injection techniques. Enucleation can be done under block, but usually is done under general anesthesia.

Incision and Drainage of Chalazion

A chalazion is an eyelid mass that results from chronic inflammation of the meibomian gland. Surgical treatment is indicated when there is inadequate response to conservative methods.

Tarsorrhaphy

The partial or total suturing together of the eyelids is performed to protect the eye and to allow healing of ulcers or exposure problems.

Table 75-2 Ocular Manifestations and Pediatric Syndromes

Strabismus	Trisomy 21 Cerebral palsy Meningomyelocele Prematurity Retinoblastoma Craniopharyngioma Malignant hyperthermia Myotonic dystrophy Ehlers-Danlos syndrome
Ptosis	Malignant hyperthermia Myotonic dystrophy
Cataract	Trisomy 21 Myotonic dystrophy Pierre-Robin syndrome Phenylketonuria Homocystinuria Lowe's syndrome Rubella Sarcoidosis Galactosemia Hypoparathyroidism Diabetes mellitus Glucose-6-phosphate dehydrogenase deficiency
Lens subluxation	Marfan's syndrome Homocystinuria Ehlers-Danlos syndrome
Glaucoma	Homocystinuria Lowe's syndrome Rubella Aniridia Sturge-Weber syndrome Neurofibromatosis Ehlers-Danlos syndrome
Retinal hemorrhage	AIDS Multiple myeloma
Vitreal hemorrhage	Sickle cell syndromes
Orbital tumor	Multiple myeloma
Glioma of the optic nerve	Neurofibromatosis
Retinopathy	Diabetes mellitus Hypertension
Ophthalmopathy	Juvenile diabetes Graves' disease
Ocular muscle weakness	Myasthenia gravis
Ocular erosions	Stevens-Johnson syndrome (erythema multiforme)
Conjunctivitis or iritis	Reiter's syndrome Infectious mononucleosis Rheumatoid arthritis
Keratoconjunctivitis sicca	Sjögren's syndrome Sarcoidosis Systemic lupus erythematosus
Uveitis	Ankylosing spondylitis Juvenile arthritis Sarcoidosis
Optic neuritis	Multiple sclerosis

AIDS, acquired immunodeficiency syndrome.

Temporal Artery Biopsy

A biopsy of the temporal artery is performed to diagnose temporal arteritis.

Anterior Chamber Paracentesis

A tap of the anterior chamber fluid is done for diagnostic testing or to reduce IOP quickly.

Enucleation

Enucleation refers to the removal of the entire eyeball after the muscles and optic nerve have been cut. Indications for surgery are a blind painful eye and intraocular tumors.

Cataract Extraction

Cataracts are opacities of the crystalline lens of the eye. Cataract extraction is performed under topical or regional block. General anesthesia is rarely used.

Intracapsular Cataract Extraction. Intracapsular cataract extraction is the total removal of the opaque lens with the lens capsule. It may be done with a cryoprobe. Intracapsular cataract extraction is done in selected cases of lens subluxation, dislocation, or a lens containing a foreign body.

Extracapsular Cataract Extraction. Extracapsular cataract extraction refers to the removal of the lens, while leaving the posterior lens capsule and zonules intact. A rim of the anterior capsule also is preserved. This provides an excellent location for an intraocular lens implant.

Phacoemulsification

Phacoemulsification refers to the use of ultrasonic vibration of fragments of the lens with simultaneous irrigation and aspiration. This technique allows for very small incisions.

Glaucoma Procedures

Glaucoma is a general term for diseases of the eye characterized by an increase in IOP.

Filtration Procedures. Trabeculectomy is a surgical excision of the trabeculum to increase the drainage of aqueous humor. Baerveldt and Ahmed devices are glaucoma drainage implants that shunt aqueous fluid out of the eye to drain under the conjunctiva of the orbit.

Procedures for the Cornea

Penetrating Keratoplasty. A corneal transplant is done to replace an optically poor, infected, or traumatized cornea. Control of IOP and avoidance of patient movement are especially important in these open-globe procedures.

Radial Keratotomy. A series of incisions is made in the cornea in a spikelike manner to change the shape of the cornea to correct myopia.

Pterygium Excision. A pterygium is an abnormal fold of membrane in the interpalpebral fissure. An excision is generally performed when the abnormal tissue impinges on the cornea, affecting vision, or for cosmetic improvement.

Vitreoretinal Surgery

Retinal Cryotherapy. A cryoprobe is used for prophylaxis of certain retinal breaks and tears. It also is used in some patients with retinal tumors and vascular malformations.

Repair of Retinal Detachment. Retinal reattachment involves localizing all tears and holes, creating chorioretinal adhesions, and scleral buckling with silicone belts around the globe to pull the sclera in to support the retina.

Vitrectomy. Vitrectomy is the surgical extraction of the contents of the vitreous chamber and their replacement with a physiologic solution. A posterior vitrectomy is indicated for the removal of foreign bodies, to repair retinal detachments, to remove membranes and media opacities, and to alleviate vitreous traction on the retina. These may be prolonged procedures. Many patients have diabetes or severe chronic hypertension and offer difficult challenges to the anesthesiologist.

Oculoplastic Surgery

Most oculoplastic surgery is performed with local infiltration anesthesia. Some longer, more invasive procedures require general anesthesia.

Ectropion Repair. Ectropion usually results from the effects of aging on the eyelid. Other causes include mechanical or congenital lid pathology. The eyelid is turned outward.

Entropion Repair. Involutional entropion usually results from aging. The eyelid is inverted or turned inward.

Ptosis Repair. Ptosis, or drooping of the upper eyelid, can be congenital (dystrophy of the levator muscle) or acquired from aging or trauma.

Blepharoplasty. Blepharoplasty is plastic surgery of the eyelids to remove redundant tissue that is obstructing vision, or for improved appearance.

Dacryocystorhinostomy

Dacryocystorhinostomy refers to the formation of a communication channel between the lacrimal sac and the nasal cavity. This is performed for congenital or acquired nasolacrimal duct obstruction. It usually requires general anesthesia.

Orbital Surgery

Most orbital surgery is performed using general anesthesia. If the surgery is anterior, local anesthesia can be used. Examples of orbital surgery include the following:

Repair of blow-out fracture
Drainage of orbital abscess
Decompression of the optic nerve
Exenteration of the orbit for malignancy.

Ophthalmologic Emergencies

Most urgent ophthalmologic procedures do not need to be done on an emergency basis. This is important because the anesthetic plan must consider the NPO status and general medical condition of the patient. This does not apply to true eye emergencies. In these rare conditions, therapy should be started within minutes. Other urgent ophthalmologic conditions can start within 1 to several hours without change in outcome.

True Emergencies. Therapy should be started within minutes for chemical burns of the cornea and central retinal artery occlusion.

Urgent Situations. Therapy should be started in 1 to several hours. Urgent situations include open-globe injuries, endophthalmitis, acute narrow-angle glaucoma, acute retinal detachment, corneal foreign body, and lid laceration.

Semi-urgent Situations. Therapy should be started within days, but sometimes can be rescheduled for several weeks. Semi-urgent situations include ocular tumors, blow-out fractures of the orbit, congenital cataract, and chronic retinal detachment.

Open Globe and Full Stomach. A patient with eye trauma presents a challenge to the anesthesiologist. The dilemma is to protect the patient from aspirating stomach contents and to protect the eye from acute changes in IOP, which could cause vitreous loss, retinal detachment, and blindness. A rapid-sequence induction provides rapid airway control, but succinylcholine is associated with a modest increase in IOP. Other suggested strategies include precurarization, large-dose vecuronium or pancuronium, and succinylcholine using the priming principle. Regional anesthetic techniques also have been shown to be applicable.[131] Factors to consider include the following:

Size of the perforation: Small punctures have higher resistance to vitreous loss with changes in IOP.
Pulmonary status: Patients with decreased functional residual capacity become hypoxic faster, making a more rapid technique preferable.
NPO status: What is the magnitude of the aspiration risk?
Length of procedure: If the surgery is short, and a large dose of nondepolarizer is used, will the patient require postoperative mechanical ventilation?

Anesthesia-Related Eye Injuries

Anesthesiologists must be aware of possible ocular damage during anesthesia and surgery. If a patient emerges from a general anesthetic complaining of vision impairment, it must be considered an emergency because of the possibility of central retinal artery occlusion. When using a facemask, care must be taken to avoid applying undue pressure to the eye. Systemic hypotension and anemia also can be contributing factors in vision loss.

A second potential complication is corneal abrasion. General anesthesia has been shown to decrease basal tear production. Proper eye care with taping of lids with or without an ocular lubricant provides protection. If a patient emerges from general anesthesia with eye pain or a foreign body sensation, the patient must be followed up to ensure improvement. If left untreated, corneal abrasions can progress to form corneal ulcers.

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76 Anesthesia for Robotic Surgery

Key Points

1. Robotic surgery is accomplished by an autonomous, reprogrammable manipulator designed to move and articulate specialized instruments through programmed motions that achieve a specific task. A robot can be given three-dimensional coordinates from any imaging device (e.g., computed tomography) that allows it to recognize surfaces on which it will do a specific, programmed task.
2. Robotically assisted surgery involves mechanical devices that move by a motorized system under partially programmed control, and that can be instantly controlled or modified by a surgeon's intervention.
3. Computer-assisted surgery involves systems that are manually controlled by the surgeon, and that include a tracking system, sensors, and end-effector instruments. This system provides direct and continuous control of movements.
4. Telesurgery refers to the ability to perform surgery using computer-assisted instruments from a remote location.
5. Telemanipulation refers to the ability to produce electronically precise instrument movements at a distance from a remote location.
6. Telepresence refers to virtual projection of images from remote sites. This virtual projection allows the surgeon to visualize intended robotic movements at distant locations. It also enables telementoring, which is supervision and instruction from a distant location.
7. Initially, robotically assisted surgical thoracic procedures increased the duration of required general anesthesia. Concomitantly, the duration of one-lung ventilation has been taken to new time extremes, which has given us insight into the respiratory physiology of prolonged one-lung ventilation. As surgeons gain expertise with robotically assisted surgery, operative times are expected to shorten dramatically to approach those for traditional open surgery.
8. Because of the proximity of the side cart to the patient, the patient must be guarded against inadvertent contact from the motions of the robotic arms. Even more important, after the instruments are engaged to the arms of the robot and are inside the patient, the patient's body position cannot be modified unless the instruments are disengaged entirely and removed from the body cavity.

Robotic surgery is the resulting transformation of the minimally invasive surgical evolution. Robotic devices are being introduced to surgery because they allow unprecedented control and precision of surgical instruments in minimally invasive procedures. The anticipated benefits of robotic or robot-assisted surgery to the patient include less pain and trauma, shorter hospital stays, quicker recovery, and a better cosmetic result. With these technologic innovations, new anesthetic implications for patient care are being discovered. As surgery evolves into the robotic era, anesthesiologists must keep abreast of these changes and their impact on patient care and safety.

First-generation surgical robots are being installed in numerous operating rooms around the world. These are not true autonomous robots that perform surgical tasks; rather, they are mechanical "helping hands" that offer assistance in various fields of surgery. These machines still require human intervention to operate or to provide input instructions. Robotic devices are here to help surgeons, not to replace them.

History

The word *robot* was first used by Capek in his play *Rossum's Universal Robots* in 1921. It is derived from the Czech word *robota,* meaning "forced labor."[1] Robots were first developed by the National Aeronautics and Space Administration (NASA) for use in space exploration.[2] These devices, or telemanipulators, were capable of doing manual tasks aboard a spacecraft or out in space. The slave devices were controlled electronically from a remote master control on Earth or aboard a spacecraft. Telemanipulators were used extensively aboard NASA's space shuttle missions between 1983 and 1997. Research in trajectory and missile guidance systems eventually led to highly precise targeting mechanisms. Precision pointing at targets, such as the Earth and stars, was crucial for Spacelab telescope experiments. Telemanipulators such as the Instrument Pointing System were specifically designed for extreme accuracy (±1.2 arcsec). Scientists at NASA Ames

Research Center were responsible for developing virtual reality. The idea took root with contributions of VPL, a visual programming language, and Dataglove. Their integration made it possible to interact with three-dimensional virtual scenes. It took the integration of robotic engineering and virtual reality, however, to develop a dexterous telemanipulator for the anastomoses of nerves and vessels in hand surgery.

From these applications, it became apparent to the U.S. Department of Defense that virtual reality and telepresence might serve a useful function in treating wartime casualties on the battlefield. Through virtual reality, the surgeon could be brought to the patient's side, an idea described by the term *telepresence*. Data from wounded casualties of the Vietnam War estimated that, of all wounded soldiers, one third died of head and massive injuries, and another third died of exsanguinating hemorrhage, but had the potential to survive if they were treated in time.[2] The Department of Defense sought to improve medical presence on the battlefield given that one third of casualties could be saved. Telepresence allowed a surgeon located aboard an aircraft carrier to perform surgery (with the aid of telemanipulation) on wounded soldiers located in a remote location on the battlefield. With this idea in mind, the Department of Defense funded much of the research in telemanipulation for remote mobile surgical units that would allow for telepresence.

Another impetus for development of robotic surgery came from limitations of laparoscopic surgery. Mouret[3] performed the first videolaparoscopic cholecystectomy in Lyons, France, in 1987[3]; in 1988, Perissat and coworkers[4] presented the innovation to the Society of American Gastrointestinal Endoscopic Surgeons, and an exponential spread of laparoscopic surgical procedures began. Although laparoscopic surgery provided a great benefit for the patient, it brought tremendous surgical limitations, such as loss of three-dimensional vision, impaired touch sensation, and poor dexterity provided by the long instruments and the fulcrum effect. The fulcrum effect is a nonintuitive motion of the instrument tips in opposite direction around a fixed point, usually at the skin entrance site. New skills had to be learned. Initial attempts to surmount the burdens of endoscopic surgery provided the impetus for robotic support systems that can enhance surgical skills and control of instruments.

The first robotic devices appeared in the 1980s for use in stereotactic brain surgery. In 1992, ROBODOC (Integrated Surgical Systems, Sacramento, CA) was introduced for grinding bone to make space for prostheses in hip replacement surgery. By the mid-1990s, positioning robots were introduced. Automated Endoscopic System for Optimal Positioning (AESOP) (Computer Motion Inc, Goleta, CA) was introduced for voice-controlled optimal camera positioning, and Laparoscopic Assisted Robotic Systems (LARS) (John Hopkins University, Baltimore, MD), an automated robot, was introduced for organ retraction.[5] The master-slave telemanipulator concept was developed for medical use in the early 1990s. The first master-slave manipulator for medical use was developed at Stanford Research Institute in 1991. The goal was to have computer algorithms that translate a surgeon's master manual movements to end-effector slave instruments at a remote site. Early designs had only 4 degrees of freedom, but by 1992, a German prototype was developed with 6 degrees of freedom (Fig. 76-1).[6] In 1994, Intuitive Surgical obtained technologic rights from Stanford Research Institute, and a prototype DaVinci system was released in 1997.

Engineers realized that the distance between patient and surgeon had an upper limit, beyond which accuracy and dexterity of instrument control would become degraded. Latency is the time it takes to send an electric signal from a hand motion to actual visualization of the hand motion on a remote screen. The lag time to send an electric signal to a geosynchronous satellite at 22,300 miles above the Earth and return is 1.2 seconds. This transmission delay would prohibit practical surgery. Humans can compensate for delays of less than 200 msec. Longer delays compromise surgical accuracy. Tissue moves when force is applied to it, and with a visual delay greater than 200 msec, the movement would not be noticed fast enough to avoid cutting in an unintended place.

The most optimistic attempt to provide telesurgical presence over long distances was undertaken using high-bandwidth fiberoptic ground cable. The latency time of 155 msec allowed Marescaux and colleagues[7,8] to perform a robot-assisted laparoscopic cholecystectomy between New York City and Strausbourg, France, in 2001. In 2003, a telerobotic surgical service was established between a teaching hospital in Canada, and a community hospital 250 miles away. This service was designed to provide telerobotic assistance by an "expert" surgeon to a community-based surgeon. Some of the procedures performed include laparoscopic Nissen fundoplication, laparoscopic right hemicolectomy, laparoscopic sigmoid/anterior resection, and laparoscopic hernia repair.[9]

Recent years have witnessed a surge in robotic surgery. In 2000, 1500 robotic procedures were performed. In 2004, more than 20,000 robotic procedures were done. Urology accounted for the bulk of these procedures, with 8000 prostatectomies being done.

Robotic Systems

The word *robot* is a ubiquitous term that describes an autonomous device capable of various tasks (see the previous section on history). Industrial robots used in assembly lines perform highly precise, repetitive tasks. The robots are preprogrammed off-line, and tasks are invoked on command. Robots used in orthopedic surgery and neurosurgery are examples.[10] Precise tasks, such as drilling and probe insertion, are based on registration. Registration is a mathematical process that allows location and anatomic orientation in three dimensions based on data derived from preoperative computed tomography (CT) or magnetic resonance imaging (MRI).

A second type of robot is defined as an assist device, such as AESOP. These robots are used to control instrument location and guidance. Assist-device robots are not autonomous; they need input cues from the operator.

A third type of robot is a telemanipulator. These robots are under constant control of the operator. These devices mimic the operator's hand motions in an exact or scaled motion. Several telemanipulator robotic devices are available throughout the world. The da Vinci Robotic Surgical System (Fig. 76-2) has been approved by the U.S. Food and Drug Administration (FDA) for laparoscopy, thoracoscopy, and intracardiac mitral valve repair surgery, and the ZEUS Surgical System (Fig. 76-3) has been developed in parallel and approved by the FDA for general and

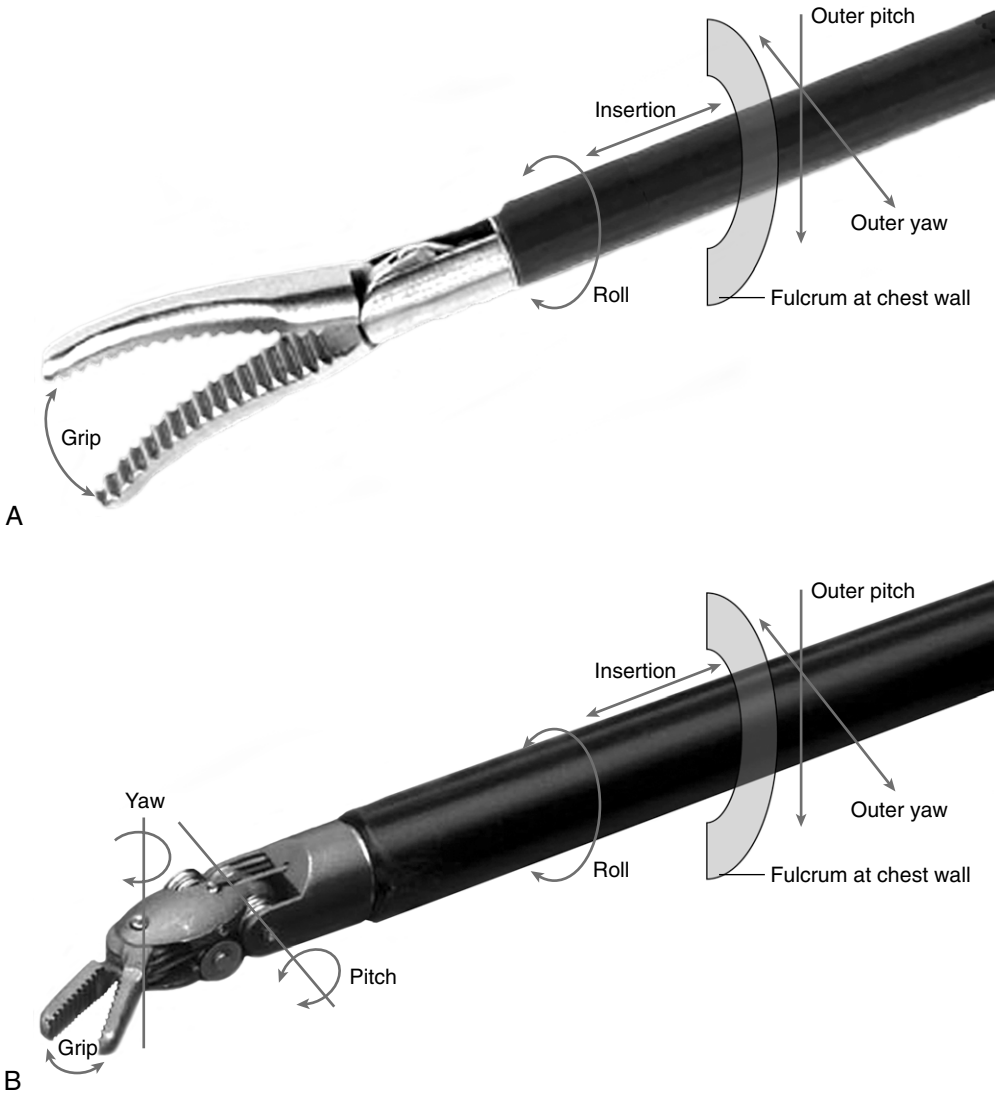

Figure 76-1 Degrees of freedom (DOF) in motion. **A,** Conventional laparoscopic instruments have only 4 DOF and grip. Insertion (i.e., movement in the *z* axis), roll, and movement along the *x* and *y* axis outside the body relative to a fulcrum point constitute the 4 DOF. **B,** Depiction of the EndoWrist instrument with two added intracorporeal joints, producing 7 DOF. *(**A** and **B,** Copyright © 1999 Intuitive Surgical, Inc, Sunnyvale, CA.)*

laparoscopic surgery. The two systems are very similar, with some minor differences. The ZEUS system was subsequently shelved after the company making it was acquired by its competitor, Intuitive Surgical, the makers of Da Vinci systems. The da Vinci Robotic Surgical System is described in this chapter as a representation of most modern surgical robots.

The da Vinci system has three components: a console, an optical three-dimensional vision tower, and a surgical cart (see Fig. 76-2). The surgical cart has four arms that can be manipulated by the surgeon through real-time computer-assisted control. The first two arms represent the surgeon's right and left arms, to hold the instruments, and the third arm positions the endoscope. The optional fourth arm enables the surgeon to hold another instrument or perform additional tasks, such as holding countertraction and following running sutures, eliminating the need for a patient-side surgeon. The system allows the surgeon to be physically remote from the patient (Fig. 76-4).



Figure 76-2 The da Vinci Robotic Surgical System: Surgical console, patient cart with four mounted surgical arms, and an optical tower. *(Courtesy of Intuitive Surgical, Inc, Sunnyvale, CA.)*

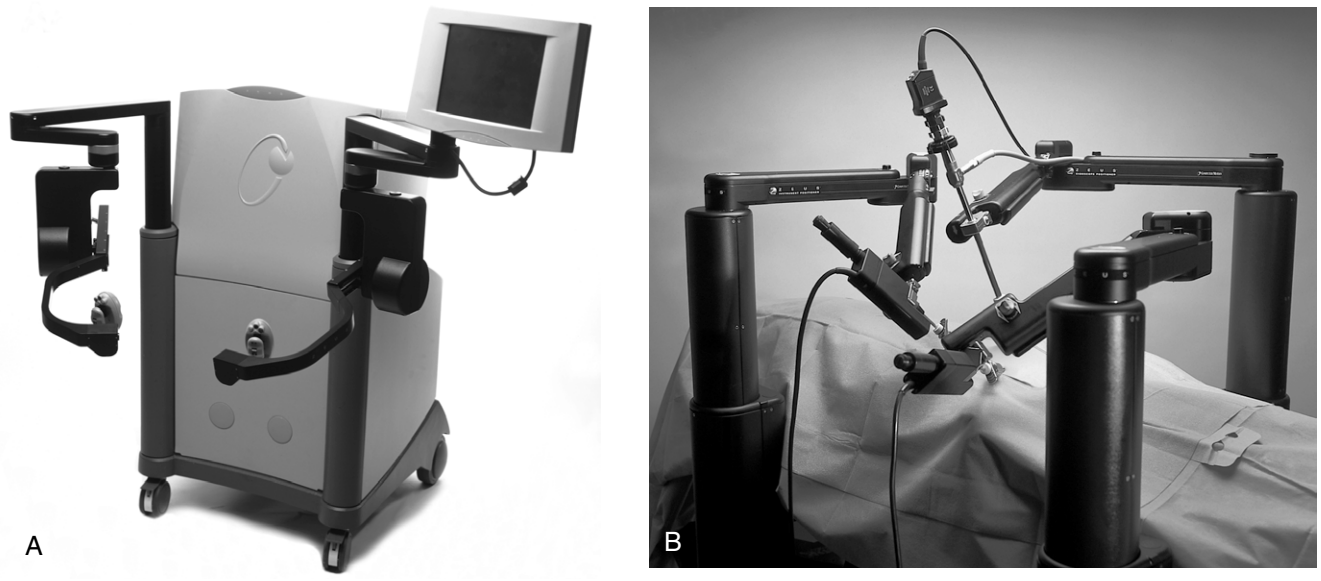

Figure 76-3 A, The console of the ZEUS robotic telemanipulation system consists of a video monitor and two instrument handles that translate the surgeon's hand motions into an electric signal that moves the robotic instruments. **B,** Two table-mounted AESOP arms hold instruments, and a third arm controls the camera. *(Courtesy of Computer Motion, Inc, Sunnyvale, CA.)*

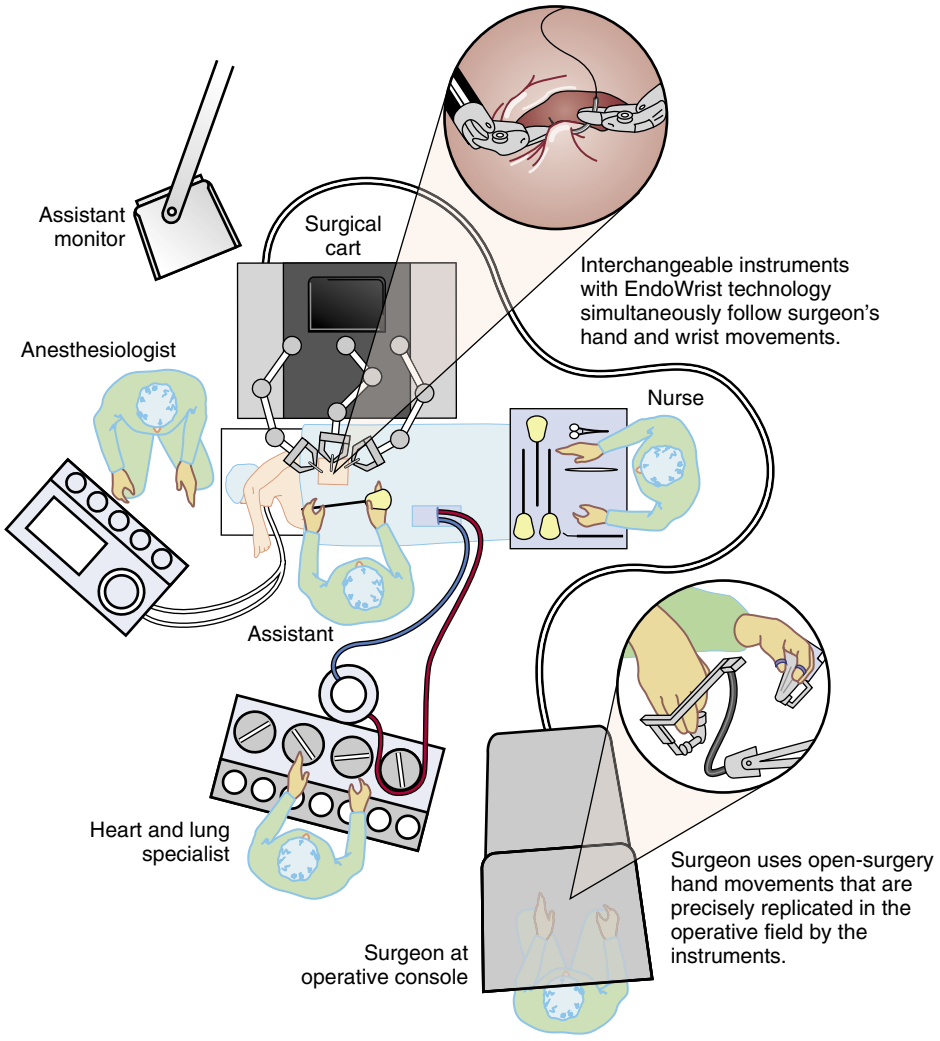

Figure 76-4 Operating room schematic of the use of a robotic surgical system in cardiac surgery. *(Courtesy of Intuitive Surgical, Inc, Sunnyvale, CA.)*

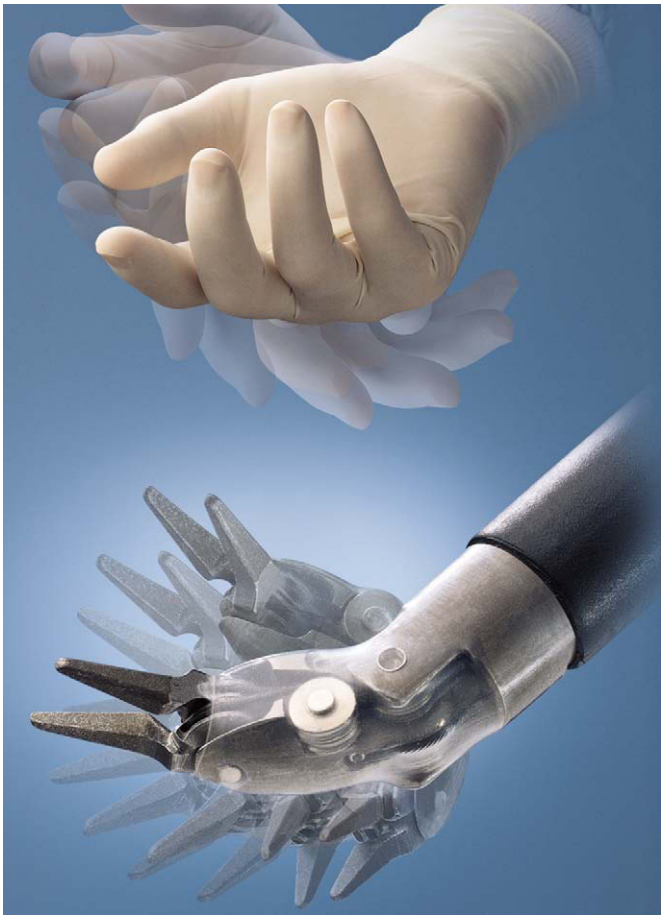

Figure 76-5 The da Vinci Robotic Surgical System: Master controls that translate the surgeon's hand, wrist, and finger movement into real-time movements of surgical instruments inside the patient. *(Courtesy of Intuitive Surgical, Inc, Sunnyvale, CA.)*

The system's instruments are designed to have 7 degrees of freedom, which enables it to approach the identical articulation of the human wrist (Fig. 76-5). Seven degrees of freedom include three arm movements (in out, up down, side to side), and three wrist movements—yaw (side to side, left and right), pitch (up and down), and roll or rotational. The seventh degree of freedom is grasping or cutting. The system design incorporates a frequency filter that eliminates hand tremor greater than 6 Hz. Motion scaling also can be invoked up to a ratio of 5:1 (i.e., the surgeon moves 5 cm, and the robot moves 1 cm). Scaling allows for work on a miniature scale. The console also provides a three-dimensional image of the surgical field. The endoscope consists of dual, independent optical channels capable of transmitting digital images to the console's visual monitor. At the console, the surgeon is actually looking at two separate monitors; each eye sees through an independent camera channel to create a virtual three-dimensional stereoscopic image. The images are controlled through two independent light sources found on the optical three-dimensional vision tower.

The surgeon sits at the console and controls the telescope arm and three robotic manipulator arms. The viewing space provided is similar to a double-eyepiece microscope (Fig. 76-6). Each eyepiece displays a mirror reflection of a computer monitor screen. Each monitor displays one channel of the stereo endoscope to an eye, creating a virtual three-dimensional stereoscopic image of the surgical field.



Figure 76-6 The da Vinci Robotic Surgical System: Stereo viewer that creates a virtual three-dimensional stereoscopic image. *(Courtesy of Intuitive Surgical, Inc, Sunnyvale, CA.)*

The surgeon controls the manipulators with two masters (Fig. 76-7). The masters are made of levers that attach to index fingers and thumbs of each hand. Wrist movements replicate the movements of the instruments at the end of the robotic arms. The console has a foot pedal that disengages the robotic motions (i.e., clutching), another that allows adjustment of the endoscopic camera, and a third pedal for controlling the energy of electric cauterization.

The side cart of the robotic device has four arms that respond to the manipulative controls of the surgeon while sitting at the console. The cart is bulky and very heavy. It has to be wheeled to the vicinity of the patient's surgical area and is locked into place. Because of the proximity of the side cart to the patient,



Figure 76-7 The EndoWrist instrument of the da Vinci Robotic Surgical System mimics the natural kinematics of the surgeon's hand and wrist. This design allows 7 degrees of freedom. *(Copyright © 1999 Intuitive Surgical, Inc, Sunnyvale, CA.)*

the patient must be guarded against inadvertent contact from the motions of the robotic arms. Even more important, after the instruments are engaged to the arms of the robot and inside the patient, the patient's body position cannot be modified unless the instruments are disengaged entirely and removed from the body cavity. Any patient movement from lack of muscle relaxant may be disastrous. The clutching buttons allow for the robotic arms to be grossly positioned without moving the instruments within the trocars or access ports. A clutching function allows surgical assistants to exchange various instruments.

The optical tower contains the computer equipment needed to integrate the left and right optical channels to provide stereoscopic vision and to run the software needed to control the kinematics of the robotic arms. The computer interfaces the translated motion of the surgeon's hands to a digital code that moves mechanical levers, motors, and cables that allow the robot to articulate the exact motions of the surgeon's hand.

The instruments in the body cavity must remain sterile, but interface with nonsterile robotic arms. Detachable disposable instruments facilitate this interface. Each type of instrument requires different forces and motion scaling intrinsic to the task at hand and requires specific computer software processing. Additional operating room staff is required for detaching and exchanging task-specific instruments throughout the case. Monitors are positioned on top of the tower so that all individuals in the operating room have a view of the surgical field.

An obstacle that still needs research is tactile sensing. The feedback that the robot offers for the surgeon's applied force is inferior. The robot offers some sensation, but the applied force does not correlate well with the force applied to the tissues. This correlation varies with the type of instrument and depends on the torque applied; the operator must rely on visual cues from tissue distortion to gauge how much pressure is being generated.

The ZEUS Surgical System is another example of a master-slave telemanipulator. It employs the assistance of the AESOP Robotic System for visualization. It is basically one mechanical arm used by the physician to position the endoscope, which is a surgical camera inserted into the patient. Foot pedals or voice-activated software allow the physician to position the camera, leaving his or her hands free to continue operating on the patient. The manipulators of the ZEUS system are freely mounted on the operating table, similar to the AESOP. It provides tremor filtering and motion scaling from 2:1 to 10:1.

General Surgery

Robotic technology has defined itself in the field of gastrointestinal laparoscopic surgery.[11] The first surgical operation using robotic telemanipulation was a laparoscopic cholecystectomy performed in 1997 in Brussels, Belgium.[12] Robot-assisted surgical techniques permit the surgeon to provide the smallest possible incision and lowest surgical stress. This technology allows surgeons to work on a very small scale in cramped spaces. Virtually all gastrointestinal procedures have been performed safely by surgeons using this technology. Procedures most commonly performed include cholecystectomy, fundoplication, Heller myotomy, bariatric surgery, and colectomy.[13]

Robotic surgery overcomes some of the disadvantages of conventional laparoscopic procedures with three-dimensional imaging, elimination of motion reversal, motion scaling, and filtering of resting tremors, while offering an ergonomically comfortable position. Other reported apparent advantages of robotic laparoscopic surgery are a short learning curve,[14] better quality of repair,[15] and ease of operation in morbidly obese patients because stiff instruments help counteract abdominal wall torque.[16] Robotic laparoscopic surgery also is associated with high patient satisfaction.[17] Because outcome data on laparoscopic robotic surgery are lacking, its higher costs may prove to be a deterrent to some surgical programs.

Anesthetic Considerations

In the operating room, the patient is monitored with an electrocardiogram, pulse oximetry, axillary temperature probe, and noninvasive blood pressure cuff. Bilateral peripheral intravenous access is valuable because the left upper extremity is not immediately available during the surgery. Anesthesia can be maintained with a volatile agent. Muscle relaxation is paramount in avoiding any movements by the patient while the surgical instruments are within the abdominal cavity. An orogastric tube and a urinary bladder catheter are placed. Convective-air body warmers are applied whenever possible.

With the patient in the supine position, the patient is prepared and draped, and the abdominal cavity is insufflated with carbon dioxide (CO_2) to a pressure not to exceed 20 mm Hg. The trocar for the camera is placed manually. Incision ports for Nissen fundoplication and cholecystectomy are shown in Figures 76-8 and 76-9. The side cart robot is brought very close to the patient's head to engage the other trocars with visual guidance from the robotic camera. Because of the proximity of the side cart to the patient's head, there is limited access to the patient's airway and neck, and the head must be guarded against inadvertent collision with the robotic arms when moving.[18,19] After the robot is engaged, the patient's body position cannot be changed. The surgical team should be capable of rapidly disengaging the robotic device if an

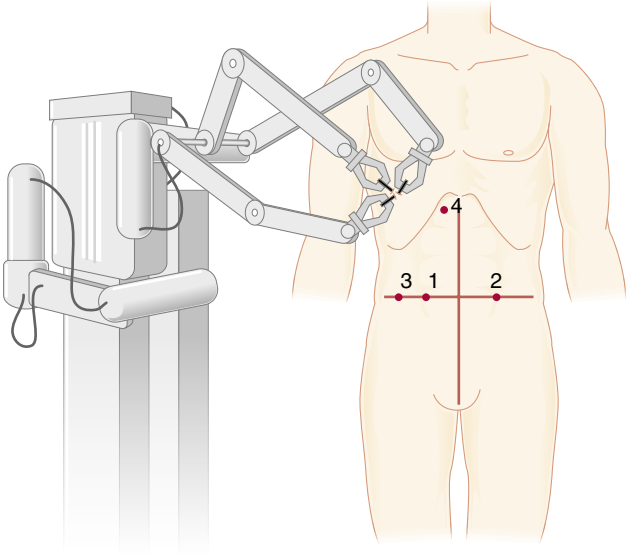

Figure 76-8 Numbered incision ports for Nissen fundoplication and location of the robotic arms.

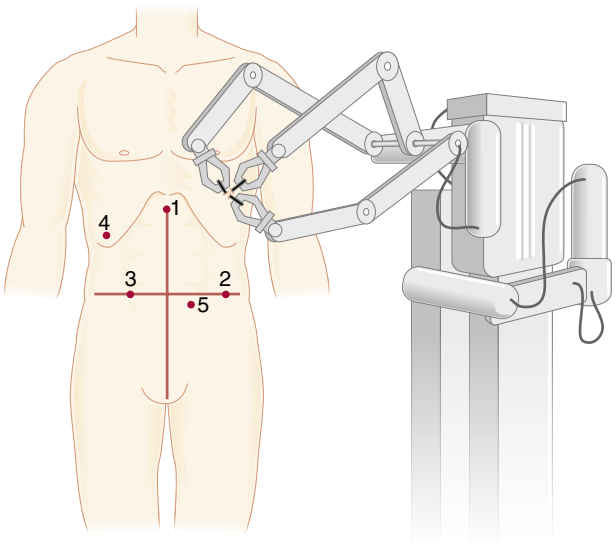

Figure 76-9 Numbered incision ports for cholecystectomy and location of the robotic arms.

airway or anesthesia emergency arises. As with any laparoscopic procedure that requires a pneumoperitoneum pressurized with CO_2, ventilator adjustments may be required to normalize the exhaled CO_2.[20] Some surgeons argue that the benefit of invasive arterial monitoring does not outweigh the risks.[19] This issue should be considered for each patient based on a risk/benefit analysis.

Cardiac Surgery

Application of conventional endoscopic instruments has paved the way for several cardiac procedures to be performed with robotic assistance (see Chapter 60). Internal mammary artery harvesting was successfully performed thoracoscopically in 1997 by Nataf.[21] In 1998, Loulmet and colleagues[22] reported the first totally endoscopic coronary artery bypass surgery. Cardiothoracic applications of robotically assisted surgery have expanded and include atrial septal defect closures,[23-25] mitral valve repairs,[26] patent ductus arteriosus ligations,[27] totally endoscopic coronary artery bypass grafting,[28,29] minimally invasive atrial fibrillation surgery,[30,31] and left ventricular pacemaker lead placement.[32]

Although technical advances in minimally invasive surgery have introduced techniques that are done through very small ports and may eventually make surgical sternotomy obsolete, surgeons still must be trained and prepared to convert to an open sternotomy if the need arises. Sternotomy alone carries a finite risk of morbidity from an inflammatory response, but it is less than that of exposure to cardiopulmonary bypass.[33-35]

Familiarity with and expertise in cardiac and thoracic anesthesia are imperative because both organ systems need to be managed safely. The ability to perform and maintain single-lung ventilation is mandatory, as is the management of the physiologic consequences (Table 76-1). Preoperative assessment of lung function is indicated if a patient has significant lung disease. Poor pulmonary function test results may be a contraindication to robotically assisted cardiac surgery because single-lung ventilation may be poorly tolerated. Robotic surgery may require unprecedented, prolonged one-lung ventilation, which challenges the extent of our understanding of respiratory physiology. Continuous monitoring of cardiac function with transesophageal echocardiography (TEE) has become a standard of care and has found a niche for several procedures required for safer robotically assisted surgery.

Mitral Valve Surgery and Anesthetic Implications

In 1997, two independent groups reported the first robotically assisted mitral valve repair.[36,37] In November 2002, the FDA approved the use of robot-assisted surgery for performing mitral valve repairs. Mitral valve repair, initially done through minithoracotomy incisions, could be done completely with a closed chest. Mitral valve replacements may still require a small thoracotomy, however, to introduce the new prosthetic valve.

Mitral valve surgery employing robotic devices is being done at a few cardiac centers in the United States and Europe. The anesthetic techniques and other relevant considerations have been described previously.[38] Patients are initially evaluated by cardiac catheterization to estimate the degree of coronary artery stenosis and to assess valve function. Severe mitral regurgitation is a mechanical problem that requires surgery for cure. Most patients are medically treated with afterload reducers, such as angiotensin-converting enzyme inhibitors if they are hypertensive. An enlarged left atrium is often susceptible to atrial fibrillation. Patients with persistent atrial fibrillation may be taking anticoagulants concomitantly with therapy for rate control. Chronic elevation of left atrial pressure may manifest with pulmonary hypertension, which may be exacerbated further by obstructive lung disease. Severe pulmonary hypertension renders a patient unsuitable for robotic surgery.[39]

Patients are provided with a large peripheral intravenous catheter. Light sedation with midazolam and local anesthesia is offered before the placement of bilateral radial arterial catheters. The patient is routinely monitored with electrocardiogram leads II and V_5, pulse oximetry, and a right radial arterial pressure catheter to exclude endovascular aortic balloon misplacement. Modern electrocardiogram monitors can provide automatic ST segment analysis for the detection of ischemia. After ample oxygenation, the patient is anesthetized with a combination of midazolam, fentanyl, and isoflurane, and a muscle relaxant is administered.

The trachea is intubated with a double-lumen endotracheal tube. Proper tube position is confirmed by bronchoscopy. A TEE probe is inserted to assess heart and valve function and to guide central line placement. A midesophageal, bicaval view at 90 degrees is used for guidance in positioning the superior vena cava (SVC) and inferior vena cava cannulas (Fig. 76-10). Initially, a left 9F introducer catheter is inserted by means of the Seldinger

Table 76-1 One-Lung Ventilation Strategy

1. Use $F_{IO_2} = 1.0$
2. Begin one-lung ventilation with pressure control ventilation, maintaining a plateau pressure of <30 cm H_2O
3. Adjust respiratory rate so that P_{aCO_2} approaches 40 mm Hg
4. Check arterial blood gas pressure
5. Apply continuous positive airway pressure to nonventilated lung
6. Apply positive end-expiratory pressure to ventilated lung

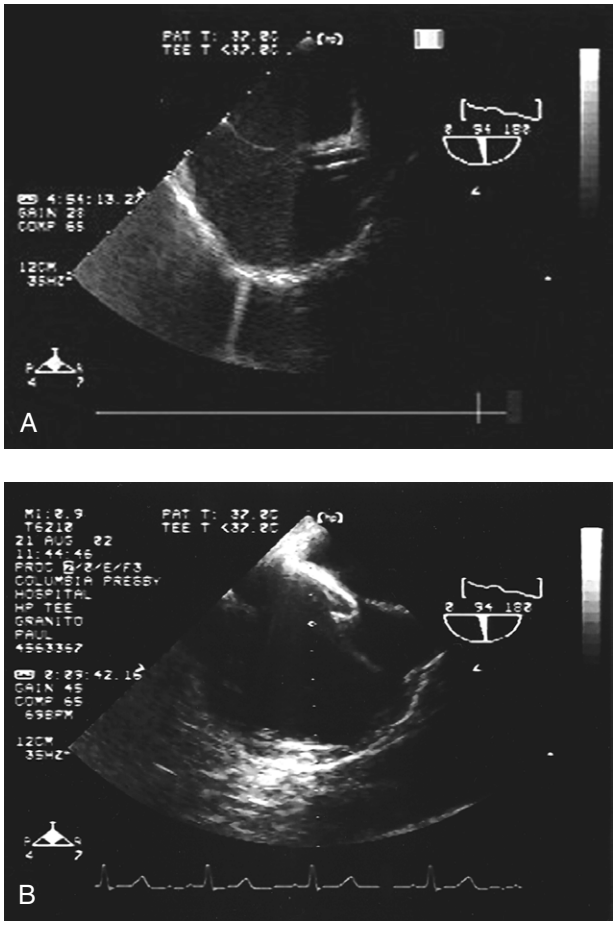

Figure 76-10 **A,** Ultrasound image of the superior vena cava cannula. **B,** Ultrasound image, bicaval view, depicting the inferior vena cava containing a J guidewire. Both views are helpful in correctly placing cardiopulmonary bypass venous cannulas.

technique, and an 8F pulmonary artery catheter is floated into the pulmonary artery. Next, the right neck is prepared for insertion of a percutaneous 17F Biomedicus cannula (Medtronics, Minneapolis, MN). It is inserted directly into the internal jugular vein using the Seldinger technique, and its proper placement is confirmed by TEE. Experience shows that the long transthoracic aortic cross-clamp may impinge and occlude the SVC. For this reason, an armored SVC neck cannula provides resistance to occlusion or kinking. At the time of insertion, the cannula is flushed with 5000 U of heparin to ensure its patency. The cannula is anchored with a purse-string suture at the skin and secured with Kerlix gauze wrapped around the patient's head.

After the patient's pelvis is positioned supine and the right shoulder is tilted 30 degrees to the left, transcutaneous defibrillation and pacing pads are applied. The surgeon can determine proper location for port access, which may vary according to a patient's body habitus.

After the right femoral vessels are exposed and left-sided, single-lung ventilation is established, a right-sided mini-thoracotomy incision is made. The heart is exposed after a pericardial opening is made. The pericardium is anchored open to the chest wall by two percutaneous stay sutures.

After the patient is heparinized according to an activated clotting time–guided protocol, the femoral vein and artery are cannulated in anticipation of femorofemoral cardiopulmonary bypass. First, the femoral vein is cannulated, and a 21F cannula is placed over a guidewire and passed into the inferior vena cava–radial artery junction with the aid of TEE. One end hole and 12 side holes resist collapse under the high negative pressure that is created by augmented venous return pumps. Likewise, the femoral artery is cannulated with a 24F cannula, and cardiopulmonary bypass is initiated with venous drainage from the femoral and jugular veins. Anterograde and retrograde cardioplegia cannulas are placed. Some surgical teams prefer to cannulate the ascending aorta using a Heartport Straight-shot (Heartport, Inc. Redwood City, CA).[39] A transthoracic aortic cross-clamp is passed percutaneously through the right axilla and applied to the ascending aorta. The robotic arms are engaged through their respective trocars lateral to the mini-thoracotomy incision, while the camera arm passes directly through the thoracotomy incision. The left atrium can be entered for mitral valve repair or replacement.

Before terminating cardiopulmonary bypass, TEE is used to evaluate the function of the mitral valve, to assess residual valvular regurgitation, and to confirm the disappearance of intracardiac air. The anterior leaflet of the mitral valve is inspected further for systolic anterior motion.

Patient selection is important for optimal results. Table 76-2 lists the risk factors that make patients unsuitable candidates for robotic mitral valve surgery.

Atrial Septal Defect Repair

Operations for atrial septal defects are similar to those for mitral valve repairs except that a mini-thoracotomy is not required. A closed-chest procedure is possible. Similar to all robotic procedures that demand entrance into the thoracic cavity, single-lung ventilation must be instituted during surgery. Atrial septal defect repairs also require opening the heart and preventing any blood from entering the heart; this is facilitated by jugular and femoral vein cannulation and snaring the inferior vena cava and SVC. Cardiopulmonary bypass with cardioplegia administration into the aortic root is used to arrest the heart. Methods of cardiopulmonary bypass using endovascular clamping are described in the section on coronary artery bypass grafting.

Internal Mammary Artery Harvest

Patients are monitored in the usual way for cardiac surgery. A central venous line and a radial artery cannula are placed on the same side as the harvested internal mammary artery. Single-lung ventilation with a double-lumen tube, a Univent tube, or a bronchial blocker is mandated; the position of the tube is confirmed by bronchoscopy. The patient is positioned supine, with the thorax rotated 20 degrees by placing a roll under the left scapula. External defibrillation and pacing pads are applied to the left posterior

Table 76-2 Exclusion Criteria for Robotically Assisted Mitral Valve Repairs

Severely calcified mitral annulus
Severe pulmonary hypertension
Ischemic heart disease
Surgery requiring multiple valve repairs
Previous surgery to right hemithorax
Severe aortic and peripheral atherosclerosis

Table 76-3 Exclusion Criteria for Robotically Assisted Endoscopic Coronary Artery Bypass Grafting

Contraindication to one-lung ventilation
Age >80 years
Ejection fraction ≤40%
Severe noncardiac health issues
Severe peripheral vascular disease
Myocardial infarction within last 7 days
Previous thoracic surgery, pleural adhesions, or emergency surgery
Calcified left anterior descending artery or diffuse disease
Intramyocardial left anterior descending artery
Morbid obesity (body mass index >32)
Large heart within left chest

chest and anterolateral right chest. Raising the left arm provides more exposure and stretches the skin overlying the left anterolateral chest. The opposite can be done to the right chest when harvesting only the right internal mammary artery.

CO_2 insufflation is needed to provide exposure and countertraction. CO_2 insufflation (5 to 10 mm Hg) into the left hemithorax pushes the mediastinal fat pad medially and enlarges the space between the sternum and heart to a small extent to provide a better view. For harvesting both internal mammary arteries, insufflation of the left hemithorax is sufficient to expose the right internal mammary artery because of the leftward position of the heart[40] and the improved angle of sight. Insufflation is begun in increments of 2 to 4 mm Hg. The insufflation flow rate is adjusted automatically to achieve a preset intrathoracic pressure limit. Caution should be exercised when insufflating the thorax in patients who have poor left ventricular function or are hypovolemic (central venous pressure <5 mm Hg).

Patients should have their volume status augmented before proceeding to full insufflation. CO_2 insufflation and one-lung ventilation increases central venous pressure and pulmonary artery pressure by a small amount.[41] Bilateral pneumothoraces are deliberately produced when doing bilateral internal mammary artery harvest. Most patients studied tolerate small bilateral pneumothoraces well for periods less than 1 hour.[42]

Coronary Artery Bypass Grafting

All patients undergoing coronary artery bypass grafting are evaluated preoperatively by TEE to exclude the possibility of persistent left SVC or patent foramen ovale. Table 76-3 lists the major exclusion criteria for robotic coronary artery bypass grafting. The iliac and femoral arteries also should be evaluated for their size by echo Doppler ultrasonography.

Patients are prepared and monitored for anesthesia in a manner similar to that for mitral valve surgery (see the section on mitral valve repair). Monitoring of the right radial artery pressure tracing is imperative with use of an endovascular balloon-occlusion catheter. After the patient is asleep, inspired oxygen tension and expired CO_2 are monitored. TEE is used routinely as the standard of care for determining cardiac function and for confirming catheter placement. Pulmonary artery catheters are used judiciously in the appropriate patient population, but the data that the catheter provide may be redundant when TEE data are available. The patient is positioned the same as for internal mammary artery takedown, and trocar positions are placed as depicted in Figure 76-11.

When cardiopulmonary bypass is anticipated, the left femoral artery is cannulated with a 17F or 21F Remote Access Perfusion catheter (Fig. 76-12) with an aortic occlusion balloon. Table 76-4 lists exclusion criteria for endovascular cardiopulmonary bypass. The Remote Access Perfusion catheter allows anterograde flow of 4 L/min or 5 L/min. The cannula has a separate lumen for delivering cardioplegia to the aortic root beyond the occlusion of the balloon. The aortic cannula is positioned in the ascending aorta, 2 cm above the aortic valve, with TEE guidance (Fig. 76-13). The endovascular balloon is inflated with a volume equal to the diameter (in milliliters) of the sinotubular junction of the aorta. A balloon pressure greater than 300 mm Hg usually provides complete occlusion of the aorta.[43] Residual flow around the balloon can be seen and monitored with color flow on TEE. The use of bilateral radial arterial lines is useful in detecting the migration of the occlusion balloon toward the innominate artery. Proximal migration of the balloon can be seen most easily with TEE, preventing balloon herniation through the aortic valve.

After full cannulation and being poised for cardiopulmonary bypass, the right lung is allowed to collapse, and left lung ventilation is begun. The ventilator is adjusted to provide an end-tidal CO_2 partial pressure of 35 to 40 mm Hg. Ports can be placed safely after the right-sided pneumothorax has formed. CO_2 is insufflated into the right hemithorax and continued at a pressure of 5 to 10 mm Hg; this allows the affected lung to collapse further and provides a larger visual field. It also may prevent mediastinal shifts during one-lung ventilation when large tidal volumes are used, such as in a patient with emphysematous lungs. Insufflation to produce a deliberate pneumothorax is ineffective at raising the sternum above the anterior surface of the heart. For this reason, some surgeons provide sternal lift retractors to increase the retrosternal space and provide better exposure.[44]

Robot-assisted, beating-heart coronary artery bypass grafting can be accomplished with appropriate patient selection. Articulating stabilizers passed through a subxiphoid port can stabilize the anterior surface of the heart to facilitate grafting.[45] Bilateral internal mammary artery grafting also has been accomplished using robotic assistance.

Atrial Fibrillation Surgery

Atrial fibrillation is a common rhythm disturbance encountered in clinical practice (see Chapter 61). The Cox maze procedure is often the first choice to treat medically resistant atrial fibrillation. Excellent long-term results have been reported with this procedure.[46] In this procedure, right and left atriotomies are combined

Table 76-4 Contraindications to Use of Endovascular Cardiopulmonary Bypass System

Major vascular disease of iliac, femoral, and abdominal aorta found by Doppler ultrasound imaging
Severe atherosclerosis
Aortic diameter >4 cm
Moderate to severe aortic valve incompetence

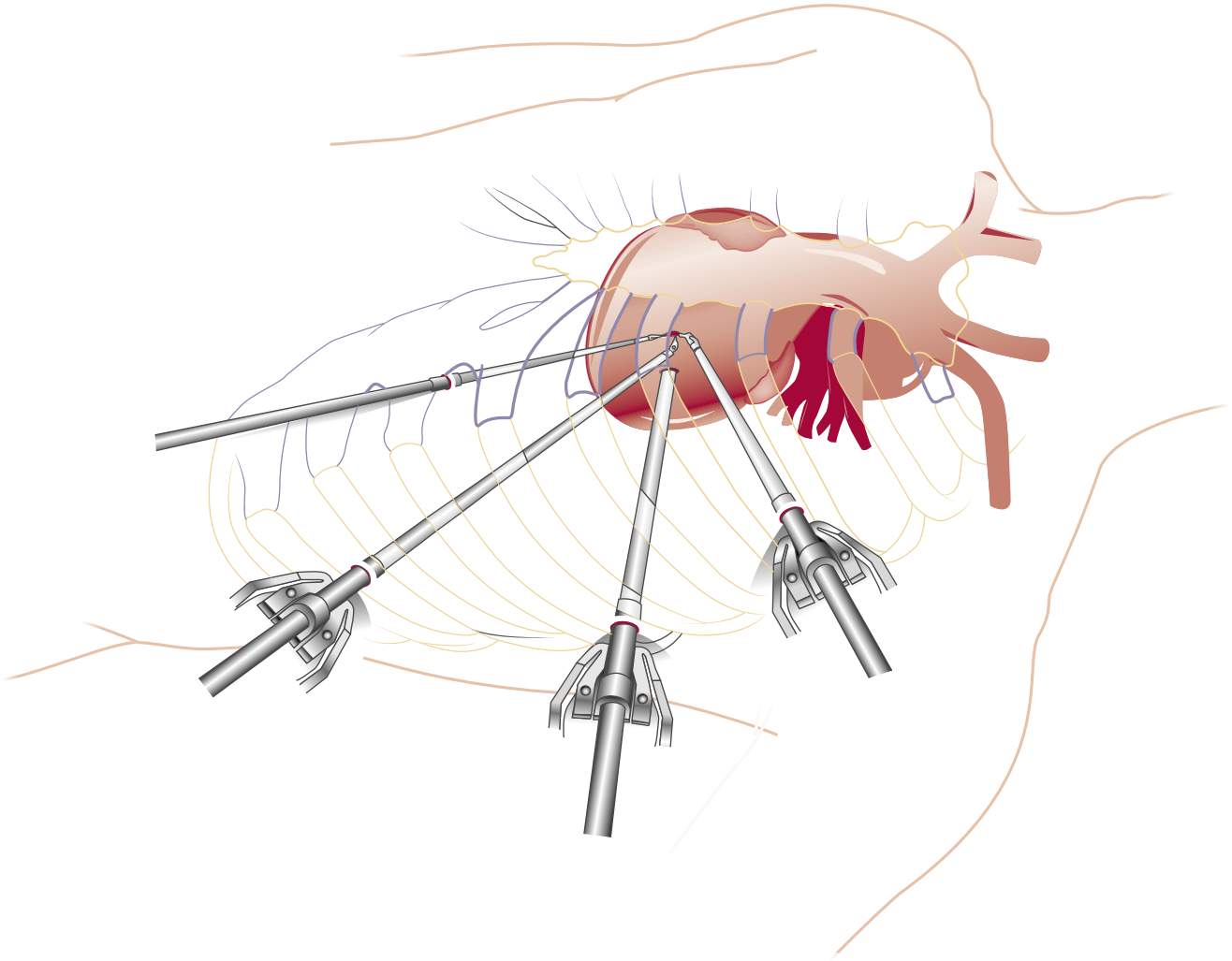

Figure 76-11 Incision ports for coronary artery bypass grafting. Trocars are placed in the third, sixth, and eighth intercostal spaces. Similar port positions are used for bilateral internal mammary artery dissection.

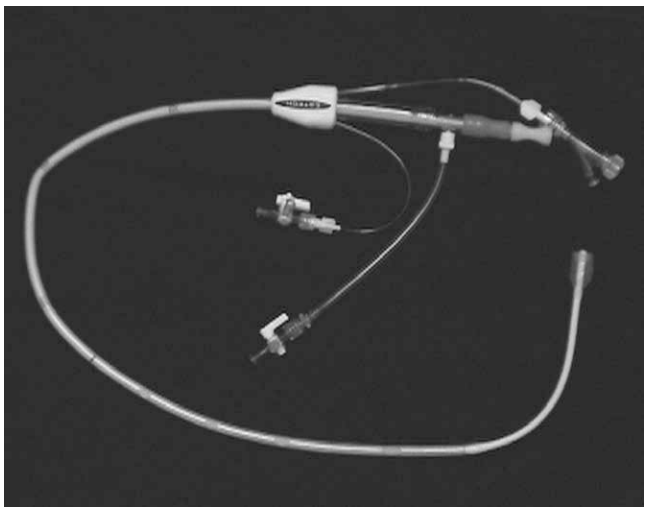

Figure 76-12 Remote Access Perfusion (Estech Systems, Inc, Plano, TX) catheter. The endovascular catheter has a cylindrical balloon for endovascular aortic clamping. The catheter provides anterograde perfusion of the aortic arch at a rate of 5 L/min and cardioplegia administration to the aortic root.

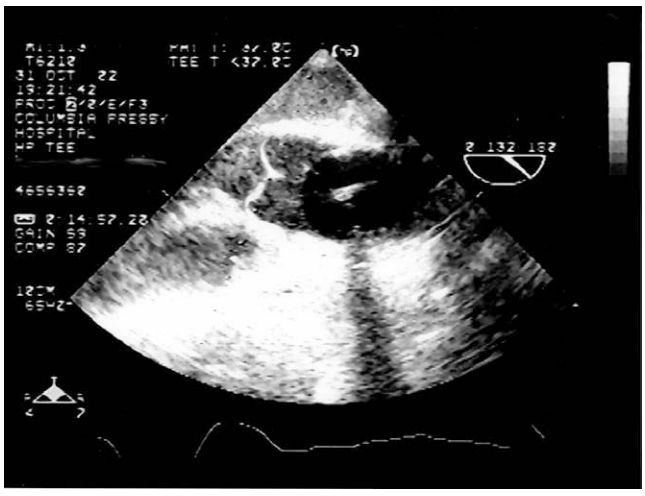

Figure 76-13 Ultrasound image of Remote Access Perfusion (Estech Systems, Inc, Plano, TX) catheter balloon in situ. Transesophageal echocardiography allows the anesthesiologist to keep track of migration of the catheter balloon. The balloon should be positioned in the ascending aorta 2 to 4 cm distal to the aortic valve. Right radial pressure catheter signal damping can detect balloon malposition when occlusion of the innominate artery occurs.

with cryoablation to interrupt re-entrant rhythms and restore sinus rhythm. Traditionally, this procedure has involved median sternotomy and cardiopulmonary bypass. With the evolution of technology such as cryotherapy, microwave, and radiofrequency, new hand-held devices have become available for use in minimally invasive surgery.

Many approaches have been used for minimally invasive atrial fibrillation ablation surgery. The approach employing the da Vinci system via right mini-thoracotomy with peripheral cannulation and cardiopulmonary bypass is the most commonly used approach.[30] A total endoscopic approach on a beating heart also has been described.[47]

This section describes the total endoscopic approach on a beating heart. The patient is placed in a supine position. In addition to the standard monitors, invasive arterial and central venous pressures are monitored. A pulmonary artery catheter can be used in appropriate patients. After induction of anesthesia, the trachea is intubated with a double-lumen endotracheal tube. The position of the tube is confirmed by a fiberoptic bronchoscope. A TEE probe is inserted for intraoperative cardiac monitoring and to rule out a clot in the left atrial appendage. External defibrillator pads are applied to the chest. One-lung (left) ventilation is instituted, the right lung is excluded, and the right hemithorax is insufflated with CO_2. Three 1-cm port access incisions are made at the level of the third, fourth, and fifth intercostal space on the anterior axillary line for the robotic arms and the endoscope. The heart is exposed after dissecting the pericardium. Using a microwave probe (Flex10, Boston Scientific, Natick, MA), a continuous circular lesion is produced encircling the pulmonary veins. Arrhythmias in the early postoperative period are treated with amiodarone and β-blocker therapy.[47,48]

Left Ventricular Lead Placement

Numerous patients with heart failure exhibit cardiac dyssynchrony secondary to delay in activation of the left ventricular free wall; this can result in a further decrease in ventricular function. This dyssynchrony may worsen mitral regurgitation and increases mortality.[49] Ventricular resynchronization has been shown to improve ventricular function, exercise capacity, and quality of life.[50] Standard biventricular pacing is done by inserting transvenous, right atrial, and ventricular endocardial leads. An epicardial left ventricular lead is inserted by cannulating the coronary sinus in the right atrium and advancing the lead via venous tributaries of coronary sinus to the ventricular surface. This approach has a failure rate of 15% to 20% because of inability to cannulate the coronary sinus. Left ventricular lead dislodgment also can contribute to a late failure rate of 5% to 10%.[32] In these patients, the only option is to place an epicardial lead via a left mini-thoracotomy. A mini-thoracotomy is associated with increased morbidity. Some surgical groups have developed a total endoscopic robotic approach.[51-53]

The total endoscopic approach is described in this section. After application of standard monitors and insertion of an arterial line, general anesthesia is induced, and the trachea is intubated with double-lumen endotracheal tube. The position of the endotracheal tube is verified with a fiberoptic bronchoscope. Subsequently, a TEE probe and a pulmonary artery catheter are inserted. The patient is placed in a posterolateral thoracotomy position. One-lung (right) ventilation is instituted. The left lung is excluded, and the left hemithorax is insufflated with CO_2 at a pressure of 8 to 10 mm Hg.

Robotic arms are inserted by incisions in the fifth and ninth intercostal spaces in the posterior axillary line, and the camera is inserted in the seventh intercostal space. The pacing lead is introduced through a working port and attached between the first and second obtuse marginal between the base and the apex. A second pacing lead is attached near the second obtuse marginal, and the pericardium is closed over the leads. Both leads are tunneled to an incision in the axilla and retested for threshold pacing requirements. The lead with the best threshold is connected to the pacemaker, whereas the other lead is capped and secured to the fascia for future use. If a right-sided pacing lead is needed, it is inserted transvenously at this time and connected to the biventricular pacemaker. This approach allows for reliable entry into the chest for left ventricular lead insertion, while allowing complete cardiac access for mapping.

Thoracic Surgery

Although video-assisted thoracoscopic surgery (VATS) is well established, its use is limited to simple procedures (see Chapter 59). Few centers perform complex procedures such as pulmonary lobectomies and thymectomies using VATS.[54] It is hoped that robotic surgery will be able to overcome some of the limitations of conventional VATS.

Compared with minimally invasive surgery performed in other regions of the body, robotic thoracic surgery presents a different set of challenges. The surgical challenges include rigidity of the chest wall and movement of heart, lungs, and mediastinum. The anesthesia-related challenges include prolonged one-lung ventilation and hemodynamic instability associated with CO_2 insufflation of the hemithorax.

Patient positioning plays a major role in exposing otherwise inaccessible areas because mediastinal structures are heavy and mobile, and change position in response to gravity. Supine or slight lateral decubitus (raising one side 15 to 30 degrees) position is ideal for anterior mediastinum pathology. A 90-degree lateral position may be optimal for hilar masses and lobectomies. A nearly prone position may create better exposure for posterior mediastinal masses.[55] CO_2 insufflation also has a big role in achieving adequate exposure by pushing the mediastinum to the opposite site, while compressing the lung away from the operative site. It also reduces fogging and removes cautery smoke. The disadvantage of CO_2 insufflation is hemodynamic instability.

As the use of robotics in surgery has increased, its role in thoracic surgery has evolved over the last few years. The procedures being performed include multiple esophageal procedures, including Heller myotomy, resection of esophageal masses,[56] and esophagectomy.[57] Other procedures being performed include resection of mediastinal masses and thymectomy.[54]

Neurosurgery

From the late 1980s to 1993, neurosurgeons investigated the use of robots to position resection probes and devices precisely within neural parenchyma to provide minimally invasive surgery and to protect normal tissue (see Chapter 63). Stereotactic navigation during neurosurgery has provided an image-guided system for real-time tracking of surgical instrument tips.

CyberKnife (Accuray, Inc, Sunnyvale, CA) is an image-guided frameless, stereotactic radiosurgery system for treatment of spinal tumors. A major potential benefit of radiosurgical treatment of spinal lesions is that this can be performed in an outpatient setting, with rapid recovery.[59] NeuroMate stereotactic robot (Renishaw plc, Gloucestershire, UK) is a frameless system that uses MRI data for treatment of movement-based disorders.[60] MRI-compatible robotic systems also have been developed for neurosurgery.

Medical robotics has yet to gain prominence in neurosurgery. The integration of various disciplines, such as robotics, machine intelligence, nanotechnology, and sophisticated computational networking, could revolutionize the practice of neurosurgery.

Urologic Surgery

The first use of robotics in urology began in the late 1980s, when a robotic frame was developed for transurethral resection of the prostate (see Chapter 65). The frame was constructed to support the six axes Unimate Puma robot (initially designed by Unimation, Inc., Danbury, CT). The safety of this device is derived from the steel circular frame that restricts and confines the robot to a precise arc of resection. Procedures can be done more quickly with a robotic instrument, and because hemostasis is required only once at the end of the procedure, there is less time for absorption of irrigation fluid. The Puma robot has been used to resect prostate tissue safely.[61]

The percutaneous access robot (PAKY-RCM) (URobotics, Baltimore, MD) was developed in 1996, and was later replaced by Tracker in 2003. This is used with fluoroscopy or CT guidance to improve the accuracy of needle placement in percutaneous nephrolithotomy and tissue biopsy. The AESOP system (see earlier) also has been used successfully in laparoscopic urologic surgery. The most advanced systems currently being used in urology are master-slave systems, such as the da Vinci Robotic Surgical System. The procedures that have been performed using da Vinci systems include radical prostatectomy,[62] radical cystectomy,[63] radical and simple nephrectomy, live donor nephrectomy, pyeloplasty, and adrenalectomy.[64]

Radical Prostatectomy

Guillonneau and Vallancien[65] were the first to show the feasibility and efficacy of laparoscopic radical prostatectomy. Since then, several centers have shown the feasibility of a robotically assisted radical prostatectomy (RAPR). RAPR has become the most common procedure performed with robotic assistance. Between 2000 and 2004, 5200 RAPRs were performed, and in 2005, more than 8000 procedures were performed.[66]

The learning curve seems to be much shorter with RAPR compared with the laparoscopic approach. The most common technique used for RAPR seems to be the transperitoneal and antegrade approach, developed by Ficarra and colleagues[62] at Vatikutti Institute of Urology in Detroit, Michigan. Outcome data, such as the transfusion rate, positive surgical margin rate, urinary continence recovery, and erectile function with RAPR, compare favorably with those for laparoscopic or traditional retropubic approaches.[67-69] The operating times also can be similar to the traditional retropubic technique after the operator has learned the technique.

After inducing anesthesia, an arterial line may be placed for frequent phlebotomy. An additional, large-bore intravenous line may be considered when the potential for large blood losses are foreseen. The patient is positioned in a supine lithotomy position with 30 degrees of Trendelenburg incline. The thighs are spread far enough apart to allow the approach of the robotic system between them. Patients shorter than 6 feet are not placed in a lithotomy position and have their legs in a frog-leg position. The prolonged Trendelenburg position may be relatively contraindicated in patients with history of stroke or cerebral aneurysm. Because of the long procedure, silicone gel pads are placed at every pressure point. Some surgeons advocate tucking the patient's arms while the patient is awake to maintain optimal comfort and avoidance of neurapraxia.[70] After a 14F Foley catheter is inserted, the body is prepared and draped. A pneumoperitoneum is created through an umbilical puncture needle, and the maximum pressure is set to 15 mm Hg. The trocar is inserted according to the standardized Heilbronn approach using a semilunar five-trocar arrangement, with a sixth in the suprapubic area.[71] A procedure with some modification of the Montsouris technique is used.[70]

Radical Cystectomy

The advantage of using the laparoscopic approach to perform radical cystectomy is decreased blood loss, improved postoperative pain control, and decreased length of hospital stay.[63] The drawback of the laparoscopic approach is that it is a technically challenging procedure requiring a high degree of surgical skill, and currently there is a paucity of data on long-term oncologic outcomes. The robotic approach might be able to bridge the gap between the open and laparoscopic approach. The first case series of robotic radical cystectomy was described in 2003. Since then, other case reports and small case series have been published.[72]

An arterial line may be placed depending on the comorbidities. The trachea is intubated with a single-lumen endotracheal tube. An additional, large-bore intravenous line may be considered when the potential for large blood losses is foreseen. Anesthesia can be maintained with a volatile agent. Muscle relaxation is paramount in avoiding any movements by the patient while the surgical instruments are within the abdominal cavity. An orogastric tube and a urinary bladder catheter are placed. Convective-air body warmers are applied whenever possible. The patient is positioned in an extended lithotomy position with 45 degrees of Trendelenburg incline. Because of the long procedure, silicone gel pads are placed at every pressure point.

Using the six-port approach and the da Vinci system, pelvic lymphadenectomy and cystoprostatectomy are performed. The specimen is removed in a bag through a 5- to 6-cm suprapubic incision. Through this incision, the bowel is exteriorized, and a neobladder is created extracorporeally. Subsequently, urethroneovesical anastomosis is performed with robotic assistance.[73] Compared with open radical cystectomy, the advantage of the robotic approach seems to be decreased blood loss and shorter hospital length of stay.

Gynecologic Surgery

Robotic surgery in gynecology was first described in 1999 for fallopian tubal anastomoses[74,75] after sterilization or tubal ligation. Subsequently, there have been small case series describing the use of robotic assistance in gynecology. The procedures that have

been performed with robotic assistance include sacral colpopexy, myomectomy, treatment of endometriosis, simple and radical hysterectomy, salpingo-oopherectomy, ovarian cystectomy, and repair of vesicovaginal fistula.[76,77] The advantages of robotic assisted surgery include three-dimensional visualization of surgical field, improved dexterity, and greater surgical precision. The disadvantages include increased cost and added operating room time for assembly of robotic equipment.

Orthopedic Surgery

Total Hip Arthroplasty

The first medical application of robotics was in orthopedic surgery (see Chapter 70). In 1992, Paul,[78] a veterinarian who worked in collaboration with International Business Machines (IBM), developed a robotic system that could be used for hip replacement in dogs. The research collaboration resulted in the first surgical robot—ROBODOC (Integrated Surgical Systems, Davis, CA). In this procedure, the femoral implant is placed into an axial canal of the proximal shaft of the femur. The femoral component can be glued or pressed into the femoral shaft as a tight fit. Long-term radiographs after hip replacement surgery have shown that adhesives are prone to cracking and loosening, with consequent osteolysis, which leads to surgical failure of the prosthetic hip. Modern femoral implants have a porous surface that allows for bone growth into the surface, promoting better hip longevity. For this reason, a tight fit of the implant into the femoral canal is essential.

This femoral canal is formed with higher precision by a robot than by the visual cues that are used in the manual method. The cavity it creates is 10 times more accurate than is achieved by manual methods.[78] The robot obtains its visual or coordinate cues from image-based information, such as from an MR image or CT scan. The accurate registration of the femoral coordinates in three-dimensional space is essential for precise bone milling of the femoral canal so that it can accommodate the surgical implant. Titanium pins are placed in the femoral condyles and the greater trochanter. The patient's leg is imaged by CT, and three-dimensional data about the femoral bone and registration pins are recorded in a computer.

In the operating room, the surgeon removes the native femoral head and places the acetabular cup into its place in the routine manual procedure. The femur is rigidly clamped and secured by the robot fixator. The robot is allowed to recognize the three titanium registration pins and compares their location relative to the data obtained from CT. In this manner, the robot has a perfect sense of where the femur lies in three-dimensional space and can perform precise milling of the femoral canal. The remainder of the surgery proceeds manually.

Four systems are commercially available for robotic orthopedic surgery, including the Acrobot system (Acrobot Co Ltd, London, UK), the ROBODOC system, the Pi galileo nav system (Precision Implants AG, Aarua, Switzerland), and the CASPER system (Ortho-Maquet/URS, Schwerin, Germany). The first randomized multicenter study compared the ROBODOC system with a control (manual) group for hip replacement. It showed that the ROBODOC group had fewer gaps between the prosthesis and bone, with no intraoperative femoral fractures.[79] The amount of blood loss and surgical time were significantly higher in the ROBODOC group. In 2001, the FDA approved the second multicenter U.S. trial of the ROBODOC system using the pinless system. The aim of this trial was to prove the efficacy of the pinless system and to decrease surgical time and blood loss associated with ROBODOC-assisted surgery. In the cases performed, there was a significant decrease in blood loss and surgical time[80] compared with the first multicenter trial.[79]

A more recent study[81] showed a higher rate of dislocations (18% in the ROBODOC group versus 4% in the control group) and revisions (13% in ROBODOC group versus 0% in the control group) in ROBODOC-assisted primary total hip arthroplasty compared with manual arthroplasty. These complications were thought to be due to injury to the abductor muscles. These complications have been attributed to human error because such a high rate of dislocations was not reported in the initial multicenter trial,[79] and has not been reported in the ongoing U.S. multicenter trial.[80]

Knee Replacement

Most total knee replacements depend on a jig system to guide bone sawing. The placement of the jig is based on the surgeon's visual cues from the exposed bone surfaces. These inaccuracies can produce patellofemoral pain and limited flexion in 40% of patients when conventional approaches are used.[82] Displacements of 2.5 mm can produce a 20-degree alteration in the range of motion of a joint.

Robotic surgical assistants have been developed to increase the accuracy of prosthetic joint alignment. For the robot to recognize specific landmarks, the pelvis and the ankle must be fixed to the surgical table. Osseous material is less likely to deform under pressure and can keep its shape. Small trials have shown increased accuracy of robotic systems in knee surgery.[83,84]

Ophthalmologic Surgery

The challenge of creating a robot that is accurate and has an extremely high level of dexterity and precision was mandated for laser retinal surgery (see Chapter 75). Because blood vessels in the retina are only 25 µm apart, high precision is necessary. Collaboration between Charles and the NASA Jet Propulsion Laboratory developed a Robot-Assisted Microsurgery System.[85] It is capable of performing laser microsurgery with 10-µm accuracy. The unaided human eye can discern an increment of only 200 µm. The Robot-Assisted Microsurgery System provides a 200-Hz gating system for eye tracking, and it eliminates the saccades of the eye, allowing the eye to appear perfectly still to the observer. The system also provides a 100:1 scaling that allows for 10-µm incremental movements. Tremor is filtered out between 8 and 14 Hz to eliminate inaccuracy.

The ability to work at such small scales is the robot's strength. Newer robotic devices intended for microsurgical application have an accuracy of 5 µm. This accuracy would be inconceivable without the dexterity of robotic technology.

Summary

The use of robots in surgery is likely to increase because of enhanced precision and control. Because of the minimally invasive nature of robotic surgery, the stress response, overall pain,

tissue trauma, and length of hospital stay are reduced; recovery from surgery is hastened; and cosmetic results are improved.[86]

Anesthesiologists need to be aware of this fast-changing field and how it affects anesthetic techniques and their delivery. Initially, robotically assisted surgical thoracic procedures increased the duration of required general anesthesia. Concomitantly, the duration of one-lung ventilation has been taken to new time extremes, which has given us insight into the respiratory physiology of prolonged one-lung ventilation. As surgeons gain expertise with robotically assisted surgery, operative times are expected to decrease dramatically to the point of traditional open surgery. The inability to move the patient while the robot is engaged with the patient is a challenge when attempting to alter cardiac filling pressures by gravity, causing pharmacologic agents to be used more often.

Anesthesiologists have experienced working in locations that are remote from the patient's airway. It should come as no surprise that robotically assisted surgery of the upper body also presents that challenge. Improved monitoring methods are needed to make remote anesthesia safe and practical. Perhaps the "minimally invasive" revolution will advocate earlier patient recovery and the increased implementation of regional anesthetic techniques. The extent of the surgical stress response may be attenuated, ultimately minimizing the inflammatory response.

We have entered a new age of practical robotic applications that ultimately will improve surgical care. In the future, the robot will be regarded less as a mechanical device and more as an information system to be used with other information systems. The latest innovation in robotics is that of image-guided surgery, in which a surgeon is able to see in real time the scanner images superimposed on the surgical field. The human anatomy will be rendered translucent, and the exact location of any vital structure will be clearly visible. Preoperative diagnostic imaging in combination with virtual reality simulators will allow the surgeon to rehearse the complex procedures in advance and program the robot to avoid any vital structures during the surgery. Visualization systems are being developed that will improve surgery on mobile structures, such as the beating heart. Advances in motion gating technology will allow the heart to appear as if it were standing still. A properly timed strobe light that is synchronized with the heart rate will achieve the proper virtual image of a heart standing still or of virtual stillness.[2]

Another area in which development in medical robotics may occur is nanotechnology. More recently, the world's smallest untethered robot was shown to measure 250 × 100 μm.[1] In the future, nano-scale robots will be used to deliver targeted gene therapy or chemotherapy to remote locations in the body. As with all new innovations, we make progress with optimistic caution.

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Ira J. Rampil

77 Anesthesia for Laser Surgery

Key Points

1. The energy of a photon depends on its frequency. Higher-frequency photons (toward ultraviolet) have more energy than lower-frequency photons (toward infrared).
2. Stimulated emission is the basis for laser phenomena. Stimulated emission creates a chain reaction leading to the creation of many photons of the same energy.
3. The biomedical application of laser light involves its ability to focus intense energy in a small area. Focus is determined by monochromicity, collimation, and phase synchrony, all of which are superior in laser light than in ordinary light.
4. Carbon dioxide (CO_2) lasers pose a high risk of remote fires. CO_2 laser light is invisible infrared and usually is transmitted to the surgical site in a beam through free air.
5. Potassium titanyl phosphate (KTP)–type lasers are not usually transmitted through air. These lasers are conducted by fiberoptics to a direct contact tip that creates heat from light, coagulating adjacent tissue.
6. Infrared laser light at 10.6 μm is strongly absorbed by water molecules. This frequency of laser light, generated by CO_2 lasers, explosively converts water to steam.
7. Different laser sources require different eye protection. Any glass or plastic lens can block CO_2 laser light, but other lasers require type-specific protection.
8. All nonmetal endotracheal tubes have the potential to burn in the airway.
9. Nitrous oxide should not be used to dilute the fraction of inspired oxygen (F_{IO_2}) during airway surgery. Nitrous oxide supports combustion similar to oxygen.
10. If possible, the F_{IO_2} should be held at less than 40% during airway surgery.

The word *laser* is an acronym for *l*ight *a*mplification by *s*timulated *e*mission of *r*adiation, and laser technology is one consequence of Nobel prize–winning developments in quantum mechanics, which are among the most important in 20th century physical sciences. In essence, lasers provide the ability to transfer large quantities of energy rapidly to remote locations. Applications in medicine have been sought since the creation of the laser. About 30 years later, lasers are an accepted and often preferred member of the surgical armamentarium. The rapid proliferation of this technology has been accompanied occasionally by severe complications, however, making it imperative that anesthesiologists understand the potential threat to their patients and themselves and be prepared to respond properly. This chapter reviews relevant highlights of the fundamental physics of lasers and laser light, rationales for the various lasers in clinical use, and important anesthesia-related concerns during laser surgery. Table 77-1 is a glossary of terms relevant to this topic.

Physics of Laser Light

Visual light is electromagnetic radiation, as are radio waves, x-rays, and gamma rays. These different classes of electromagnetic radiation are similar phenomena that occur at very different wavelengths. In 1864, Maxwell[1] explained that light is an electromagnetic wave with combined electric and magnetic oscillations that propagates at 299,792,458 m/sec. Planck[2] subsequently discovered the photoelectric effect: Light of a certain color (e.g., blue) causes metal to eject electrons at a rate proportional to the brightness of the light, whereas intense light of other colors (e.g., red, orange, yellow) cannot. Planck's discovery was the first step toward laser physics, because explaining the photoelectric effect required a new conceptual framework. Einstein[3] developed this framework, quantum mechanics, in 1905, establishing the theoretical basis for laser action. He explained that all electromagnetic

Table 77-1 Glossary of Laser Terminology

Ablation	Removal of tissue by vaporization
Absorption	The transformation, by interaction with matter, of radiant energy to a different form of energy
Active medium	A material that acts as a laser with the proper excitation
Aiming beam	A very low-powered laser beam that is collimated with the high-powered, often invisible therapeutic beam to illuminate the target site
Ångstrom unit (Å)	10^{-10} m
Anode	The positive terminal in a gas discharge laser
Attenuation	The reduction in beam energy by absorption or scattering as it passes through matter
Brewster windows	Transparent windows at the ends of a gas laser discharge tube set at such an angle to the optical axis of the tube (Brewster angle) as to provide maximum light transmission
Coherent light	Light in which the photons all have the same wavelength and maintain a constant in-phase relationship with each other
Collimation	The property of a light beam that describes the degree to which the constituent photons move in a single direction; highly collimated beams do not spread in diameter as they move away from the source
Continuous wave (CW) mode	A mode of operation in which the laser discharge is continuous
Diffraction	The modulation in intensity and apparent bending exhibited by photons as they pass through an opaque body
Dopant	A chemical added to a crystal matrix to serve as an active laser constituent
Energy density	The amount of energy per unit area arriving at a surface, usually expressed in joules per square centimeter
Excimer	Excited dimer; a type of laser based on the transition states of a diatomic molecule (e.g., ArF, KrF, XeCl); these lasers produce photons of very high energy
Extinction length	The thickness of a specified medium that absorbs 98% of the incident beam intensity (expressed as wave number in cm^{-1})
Infrared	Electromagnetic radiation whose wavelengths lie in the band 0.7 μm to 1 mm (i.e., longer than visible light, but shorter than microwaves or radio waves)
Interference	The phenomenon in which photons of like wavelength but different phase combine constructively and destructively to modulate the resulting intensity
Joule (J)	A unit of energy (1 joule = 1 watt-second)
Micrometer (μm)	10^{-6} m
Mode	A description of the intensity cross-section of a laser beam
Monochromatic light	Light of a single wavelength or color
Nanometer (nm)	10^{-9} m
Neodymium (Nd)	A rare earth metal, frequently chosen as a laser material within a substrate of glass or yttrium-aluminum-garnet (YAG)
Output power	Rate of energy discharge, usually measured in watts or joules per second
Photon	A quantum of electromagnetic energy possessing both wavelike and particle-like properties; photons travel at a constant speed of approximately 300 million m/sec
Power density	The amount of power (energy per second) per unit area arriving at a surface, usually expressed in watts per square centimeter
Pulsed mode	A mode of operation in which the laser delivers discrete (usually quite brief) bursts of photons
Pump	The means of including an electron population inversion so that stimulated emission may occur
Resonator	The combination of laser material and mirrors necessary to support laser activity
Spontaneous emission	The emission of a photon when an excited orbital electron decays back to its ground-state energy
Stimulated absorption	The process by which an orbital electron captures the energy of a colliding photon and is boosted to a higher-energy orbital
Stimulated emission	The process by which an electron in a high-energy orbital, if struck by an appropriate photon, emits a new photon of wavelength, phase, and direction equal to those of the original, colliding photon
Tunable laser	A laser that can be adjusted to provide a selected output wavelength from a range of possibilities
Ultraviolet	Electromagnetic radiation having wavelengths shorter than visible light, 0.01 to 0.38 μm
Wavelength	The distance from peak to peak of a photon wave; the usual units for light waves are nanometers (nm) or micrometers (μm)
YAG	A synthetic crystalline matrix composed of yttrium, aluminum, and garnet, with the chemical formula $Y_3Al_5O_{12}$

radiation (e.g., light, radio, x-ray) consists of photons, which may be described as follows:

1. Their properties are consistent with particles and waves.
2. They propagate in a vacuum, without diminishing, at a constant speed of 299,792,458 m/sec.
3. Their energy is proportional to their vibrational frequency, as follows:

$$E(J) = h\upsilon$$

In this equation, h is the Planck constant, 6.63×10^{-34} (joule-seconds), and υ is the frequency of the photon in Hertz.

4. Their wavelength (λ) can be calculated as follows:

$$2.998/\lambda(m) \times 10^8\ m/sec = \upsilon(Hz)$$

What we perceive as color is a property of the wavelengths of visible light, which ranges from 385 to 760 nm (nanometer = 10^{-9} m); shorter wavelengths are ultraviolet, and longer wavelengths are infrared. Einstein also explained that the photoelectric effect is independent of the number of photons present, occurring even if only one photon at a time struck the metal surface. Frequency is the key: Only photons of high enough energy (i.e., high enough frequency and short enough wavelength) can provide the energy necessary to stimulate electron emission; lower-energy photons, even arriving in large numbers at a given time (i.e., brightness), cannot. These findings precipitated the development of laser light.

Some additional aspects of quantum physics provide greater insight into the origin and nature of laser light. Electrons circling the nuclei of atoms are constrained to a few specific orbital patterns and radii (Fig. 77-1). Each orbital is associated with a specific energy level; the only way an electron can move from one orbital to another of higher or lower energy is to absorb or emit an amount of energy exactly equal to the difference in energy between the two orbitals. The process by which a photon's energy is captured by an electron, vaulting the electron into a higher-energy orbital, is called *stimulated absorption* (Fig. 77-2); the converse process, by which an electron drops to a lower orbital in the process sending out a photon to carry away the excess energy, is called *spontaneous emission*. In 1917, Einstein predicted that stimulated emission, the key to laser action,[4] also could occur. For this process, a photon of a particular wavelength (i.e., energy) must collide with an atom ready for spontaneous emission at that wavelength (i.e., having an electron already in the higher-energy orbital), stimulating immediate photon emission and electron descent to a lower orbital. The colliding photon leaves the electron with the emitted photon, with both photons having the identical wavelength, phase, and direction.

The energy differences between electron orbitals are specific to different atoms and are responsible for the fingerprint-like emission (i.e., absorption spectra) used in chemical identification. Under normal circumstances of thermodynamic equilibrium, most of a substance's electrons are in the lowest available (ground-state) energy orbitals. Normally, an electron is much more likely to engage in spontaneous than in stimulated emission (by a factor of 10^{33}:1). The key to the creation of the laser was the achievement of a population inversion, in which many electrons are "pumped up" to the higher orbital, waiting for a photon to come along and start a chain reaction (i.e., amplification) of stimulated emission. In 1958, the technology for pumping up electrons to achieve stimulated emission was introduced.[4] A method was found for enclosing the laser medium between parallel mirrors, so that laser-frequency photons could traverse the medium repeatedly and maximize the number of stimulated emissions. When one of the mirrors is partly transparent, a beam of laser light eventually exits through that mirror.

Laser light differs from ordinary light in three ways. First, it is highly monochromatic. It consists of photons that have a well-defined, very narrow band of wavelengths, whereas ordinary light contains a wide spectrum of wavelengths. Second, laser light is coherent, a property that implies that the electromagnetic fields of all photons in the laser beam oscillate synchronously (in identical phase). In ordinary light, the electromagnetic fields are phased randomly even at the same wavelength. Third, directed beams of laser light are collimated (i.e., have minimal dispersion). The light remains in a narrow, collimated beam, whereas ordinary light beams spread out in all directions from a point source. These three characteristics allow lasers to generate intensely powerful light beams, to send such beams efficiently and accurately through lenses, and to deliver intense energy to small target sites.

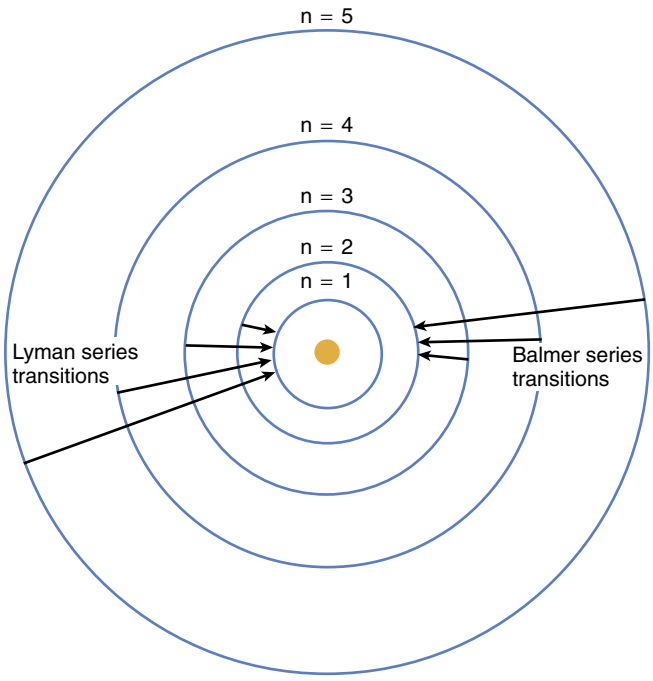

Figure 77-1 Electronic orbitals and energy levels are shown in this schematic diagram of the Bohr model of the hydrogen atom. The circular electron orbitals are a simplification of the probabilistic electron cloud structure. Superimposed on the electron orbitals are the energy transitions responsible for two of the line series in the emission spectrogram of hydrogen. The Lyman series of spectral lines occurs when electrons release photons as they jump down to the lowest energy orbital; the Balmer series of lines represents jumps to an orbital just above the lowest. The wavelength of the resulting photons is inversely proportional to the size of the jump. In the Balmer series, the jump from the n = 3 orbital to the n = 2 orbital releases a photon of wavelength 656.3 nm, whereas the jump from n = 5 to n = 2 is more energetic, releasing a 434-nm photon.

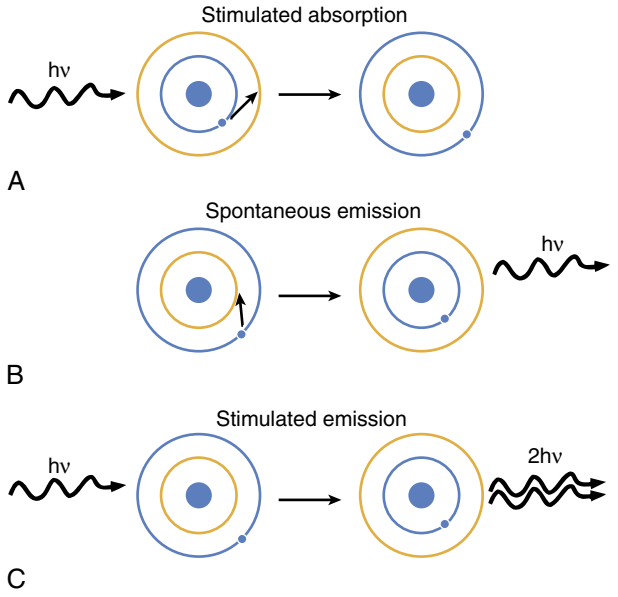

Figure 77-2 Absorption, emission, and stimulated emission. Photons may interact with orbital electrons in three ways. **A,** A photon striking an electron may transfer its energy to the electron, pushing the electron into a higher energy orbit. This interaction is known as absorption. **B,** An electron in an orbit higher than the ground (i.e., minimal energy) state may spontaneously lose energy in the form of an emitted photon. **C,** An incoming photon may interact with an electron that is already in a high-energy orbit, with the result that two perfectly coherent, collimated photons leave the electron; this is known as stimulated emission.

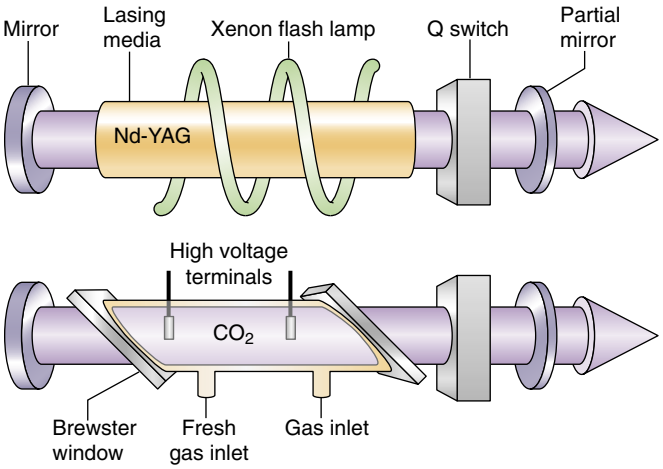

Figure 77-3 Generic laser hardware. A laser system consists of several components, regardless of whether the laser is a solid-based, liquid-based, or gas-based device. The central component is the laser medium itself, which may be a solid crystal of yttrium-aluminum-garnet (YAG) with a small concentration of neodymium as dopant, or may be a tube containing carbon dioxide (CO_2). The energy pump provides the means of obtaining a population inversion of orbital electrons; it may consist of a xenon flash lamp or an electric spark generator. A pair of axial mirrors permits repeated passes of collimated photons through the medium, allowing maximum amplification by stimulated emission. The mirror on the right is not 100% reflective, allowing the beam to escape eventually. The optional Q switch increases the efficiency of pulsed lasers by allowing a small delay to increase the pumping.

Laser System Hardware

The essential components of a laser system include a laser medium containing the atoms whose electrons create the laser light, resonating mirrors to boost laser efficiency, and an energy source to excite or pump the atoms of the laser medium into producing laser light (Fig. 77-3). The different types of lasers applied in clinical practice use a variety of laser media and energy pumps. Some clinical lasers use a gaseous medium, such as carbon dioxide (CO_2), argon, krypton, or helium-neon, and are pumped by electric discharge through the gas. Gas lasers may produce a continuous or an intermittently pulsed beam output. Other lasers use solid rods of laser-passive material containing small quantities of ionic impurities, known as dopants, which are the actual laser materials. Dopants commonly used for their laser potential include chromium (as in the ruby laser), neodymium (Nd), and holmium (Ho). A synthetic gem crystal known as yttrium-aluminum-garnet (YAG) is commonly used as a passive host matrix, but even glass has been used. Solid lasers usually are pumped by high-energy photons from a xenon flash lamp and produce a pulsed beam. Lasers also are made from dyes in liquid media and semiconductors, but these technologies have yet to appear to a significant extent in surgical practice. Table 77-2 summarizes medically relevant laser media and their respective output wavelengths.

Because lasers are inefficient at converting electricity into light, they require a large power supply. A laser with a 10-W output requires greater than 1000 W of alternating current from a wall socket; consequently, some laser systems may require special wiring for the high current load. This electrical energy is converted to very high voltages (5000 to 30,000 V) to drive the gas discharge or a xenon flash lamp. Many laser systems also require running water for cooling. Some power supply units contain nonmedical compressed gas (e.g., argon, krypton, CO_2) as a laser medium or as a coolant.

Frequency doublers convert laser light to a different wavelength, enhancing therapeutic flexibility. A beam of laser light passed through a crystal of potassium titanyl phosphate (KTP) emerges with a mixture of light of the original wavelength and light of a wavelength that is one half of the original (i.e., double the original frequency). In medical lasers, KTP is most often used with Nd:YAG. Truly "tunable" or frequency-adjustable lasers exist, but they are still low-powered devices. A light guide directs the laser beam to the surgical site, as illustrated in Figure 77-4. Fiberoptic bundles provide a convenient, flexible conduit for visible and near-infrared wavelengths. Wavelengths outside this range, such as the long infrared from a CO_2 laser, require an articulated arm containing front-surface mirrors at each joint or newly developed exotic materials in a fiberoptic bundle. After the laser beam is delivered in proximity to the surgical site, it is focused to the site by the lens of an operating microscope, or the shape of the beam is intentionally altered by passing it through a contact probe directly on the tissue to be ablated.

An operating microscope accurately aims a laser by directing a low-power (about 1-mW) visible beam (usually from a low-power helium-neon gas laser) through the same optical path as the surgical laser. Some surgical lasers can be focused

Table 77-2 Laser Media Wavelengths

Laser Medium	Color	Wavelength (nm)	Typical Application
Carbon dioxide	Far infrared	10,600	General, cutting
Erbium:YAG	Infrared	2930	Dental, arthroscopy
Holmium:YAG	Infrared	2060	Angioplasty
Neodymium:YAG	Near infrared	1064	General, coagulation, with fiberoptics
Ruby	Red	694	Tattoos, nevi
Krypton	Red	647	
Helium-neon	Red	632	Aiming beam
Gold (vapor)	Red	632	
Organic dye (liquid)	Red	632	Phototherapy
Organic dye (liquid)	Yellow	585	Dermatology, ophthalmology
Copper (vapor)	Yellow	578	
Organic dye (liquid)	Yellow	577	
Krypton	Yellow	568	Retina
KTP:neodymium-YAG	Green	532	General, pigmented lesions
Krypton	Green	521	
Argon	Green	514	Vascular, pigmented lesions
Copper (vapor)	Green	510	
Organic dye (liquid)	Green	504	
Argon	Blue	488	Vascular, pigmented lesions
Xenon fluoride	Ultraviolet	351	Cornea, angioplasty
Xenon chloride	Ultraviolet	308	Cornea, angioplasty
Krypton fluoride	Ultraviolet	248	Cornea, angioplasty
Krypton chloride	Ultraviolet	222	Cornea, angioplasty
Argon fluoride	Ultraviolet	193	Cornea, angioplasty

KTP, potassium titanyl phosphate; YAG, yttrium-aluminum-garnet.

to a spot size of 30 µm (0.030 mm), creating very-high-power densities.

For surgical procedures that do not require a "no-touch" technique, there are special heat-resistant (sapphire), direct-contact probes[5] (see Fig. 77-4) that are interchangeable and whose shapes can be designed as needed for sharp cutting or diffuse coagulation. These probes require active cooling, however, in the form of a compressed gas or liquid jet, a feature that has contributed significantly to laser-related morbidity and mortality.[6] The mechanism of action of the contact probe is probably a combination of thermal conversion of most of the laser energy within the sapphire (heating the surface to >800°C) and transmission of perhaps 20% of the near-infrared energy to the surrounding tissue.[7]

Clinical Applications

Lasers used as scalpels and electrocoagulators have some unique advantages. Lasers allow highly precise microsurgery, even in confined or difficult-to-reach sites. Two examples of procedures using the ability of a laser system to reach remote sites effectively are percutaneous diskectomy[8] and endovascular angioplasty.[9] The ability to focus laser beams on small target areas concentrates the intensity or power per area enormously. A 10-W beam, originally with an area of 1 cm^{-2}, has a power density of 10,000 W/cm^2 when focused on a target area of 0.001 cm^{-2}. This power density delivers approximately 2500 kcal/sec to the target site, producing heating at a rate of many thousand degrees per second, depending on the volume of energy absorption. This heating allows precise, rapid vaporization of tissue and most other materials. Even metals and ceramics are susceptible to high-energy lasers. Lasers do not increase the energy of a particular photon, but they place more photons at a given place and time than other light sources. Laser surgery is relatively "dry," providing near-instantaneous sealing of small blood vessels and lymphatics, even in the presence of clotting abnormalities. Early claims for faster-than-normal healing (see later) and lower infection rates have not been convincingly validated, however.[10]

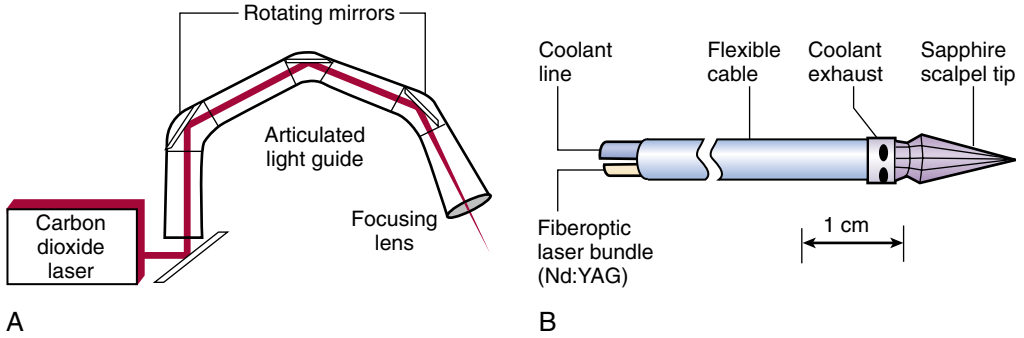

Figure 77-4 Light guides. **A,** Schematic representation of a carbon dioxide laser guide such as may be found in an operating microscope or a hand-held wand. The guide consists of rigid hollow tubes with hinged, aligned mirrors, which reflect the beam from its source through the focusing lens. **B,** Schematic of a flexible fiberoptic guide with a sapphire contact scalpel and a coaxial cooling system.

Biologic Effects of Laser Light

Living tissue is a complex aqueous solution containing a variety of molecules that absorb light. When an atom interacts with a photon whose energy does not exactly match a possible electron transition, the photon's energy may be translated into atomic vibrations that we recognize as heat. The degree to which a particular wavelength of light is absorbed and converted to heat in the target tissue determines its effect on that tissue.

Long infrared wavelengths are absorbed with great efficiency by water, the main constituent of tissue. Long-wavelength laser light, such as that from CO_2 (operating at 10,600 nm), is completely absorbed by water in the first few layers of cells. With powerful, focused CO_2 beams, this results in explosive vaporization of the surface tissue of the target with little damage to underlying cells. Excimer lasers have an extremely precise effect because they produce ultraviolet light that is absorbed more intensely by water and other molecules. These lasers are of great value in office-based refractive surgery. Near-infrared light from an Nd:YAG laser at 1064 nm is less absorbed by water, and the beam diffuses through several millimeters, scattering through a volume of tissue 100 to 1000 times the volume through which a CO_2 beam diffuses. Consequently, the energy of an Nd:YAG beam is more widely disseminated (Fig. 77-5), producing less vaporization and more thermal coagulation (i.e., a cooking effect). Some of the effects of this bulk coagulation may not be apparent for hours or days after exposure.

Nd:YAG or holmium laser energy delivered via a thin fiberoptic bundle has begun to replace traditional electrodessication in transurethral resection of the prostate. The anesthetic implication of this new modality includes the reduced incidence of transurethral resection of the prostate syndrome because saline irrigant can be used.[111] Some authors advocate the use of topical anesthesia with a digitally guided transperineal prostate block[112] in place of the more traditional subarachnoid block. Another area more recently developed around fiber-delivered Nd:YAG laser energy is office-based resection of laryngeal papillomatosis and dysplasia using only topical anesthesia.[113] Another application for outpatient surgery in the airway is the laser uvulopalatoplasty, which is at least moderately effective in reducing the symptoms of obstructive sleep apnea. The absence of an endotracheal tube in these outpatient cases would diminish the likelihood of an airway fire; however, risk of igniting drapes remains (see Chapter 78).

The red light produced by a ruby laser (694 nm) is poorly absorbed except by cells containing dark pigment. The green and blue light produced by argon (514 nm and 488 nm) or krypton (476 nm, 521 nm, and 568 nm) gas lasers is transmitted by water, but is intensely absorbed by hemoglobin, providing the ability to penetrate skin or ocular structures and selectively coagulate vascular or pigmented regions. Although lasers that produce infrared or visible light have exclusively thermal effects on tissue, the photons produced by ultraviolet excimer lasers are energetic enough to disrupt chemical bonds directly and cause ionization, which might result in mutation and carcinogenesis.

Excimer laser light, despite the high energy per photon, is very highly absorbed and capable of extremely fine focus, providing the exquisitely controlled vaporization and coagulation necessary for photorefractive surgery of the cornea. Photorefractive keratectomy and, more recently, laser-assisted in situ keratomileusis are now widely performed in outpatient clinics with only topical anesthesia, such as proparacaine or oxybuprocaine. Occasionally, children with severe refractive pathology also require laser keratoplasty, necessitating general anesthesia. In 2001, an interaction was discovered in such a case in which nitrous oxide leaking from a facemask absorbed a sufficient quantity of argon-fluoride beam at 193 nm to abort the photorefractive repair.[114]

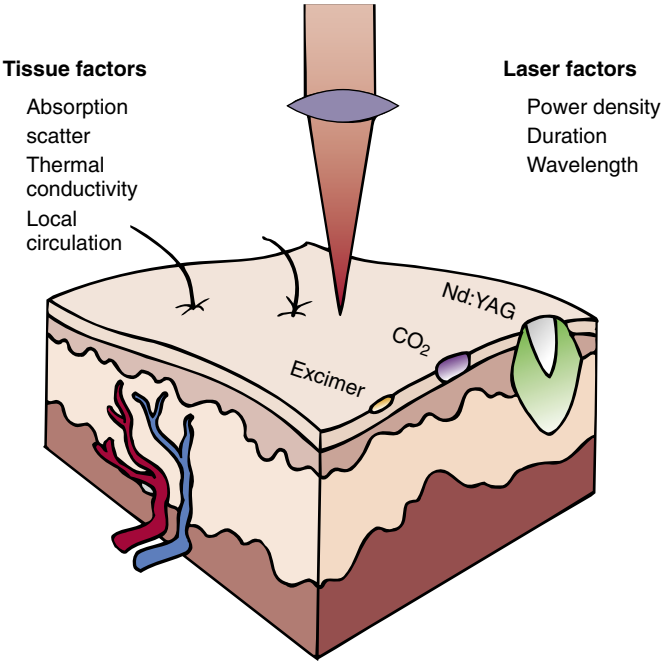

Figure 77-5 Different wavelengths of laser light cause different patterns of tissue destruction. The destructive effect of laser light on tissue depends on laser parameters and tissue factors.

Low-level laser irradiation has been posited for many years to increase the rate of wound healing as a result of hypothetical stimulation of immune function and fibroblast proliferation. A critical review of the relevant literature by the Agency for Healthcare Research and Quality found little evidence of clinical efficacy.[107] Laser light also has been studied as an analgesia-inducing stimulation of skin, over either painful areas or identified acupuncture sites. At best, the evidence for efficacy is mixed.[108]

Another application of laser light is in the use of an erbium:YAG (2930 nm) beam to disrupt the cutaneous diffusion barrier and enhance the delivery of topically applied drugs.[109] Singer and colleagues[110] showed that a single pulse from a hand-held laser followed by a 5-minute application of 4% lidocaine cream reduced pain associated with intravenous line placement by nearly two thirds over placement after sham laser plus the same exposure to lidocaine cream.

Risks of Laser Use: Standards and Regulations

Because lasers are potentially dangerous technologic devices, their clinical use is subject to some degree of federal regulation

and to voluntary consensus standards to minimize possible risks. The U.S. Food and Drug Administration (FDA) controls the manufacture and marketing of medical laser equipment. There are no mandatory federal safety precautions or regulations governing the clinical use of lasers, however. Institutions using lasers clinically should subscribe to the standards published in the American National Standard for the Safe Use of Lasers in Health Care Facilities (Z136.3-1988) by the American National Standards Institute (ANSI). ANSI Z136.3-1988 is available from ANSI (1430 Broadway, New York, NY 10018) or from the Laser Institute of America (5151 Monroe Street, 102W, Toledo, OH 43623). These standards reflect a consensus of governmental, industrial, and professional opinions on the methods used to define and control the risks of laser use, define and standardize training, and assess and ensure safety. The FDA also has suggested a set of regulations that have been adopted and modified by several states.[11] The safety guidelines proposed by ANSI and the FDA should be followed to the maximal extent possible.

Although patients are at most risk from the surgical use of lasers, injuries to staff members have occurred. The Occupational Safety and Health Administration is empowered to intervene if the medical use of lasers threatens the health of employees. Data regarding the true incidence of laser-related injury are limited. Manufacturers are required to report unusual incidents or injuries as they become aware of them. Until more recently, clinical reporting has been voluntary, however, except when complications of laser use occur in the course of a premarketing testing protocol. The passage by Congress of the Safe Medical Devices Act of 1990 requires reporting by clinicians of all serious injuries and should provide more accurate data regarding the prevalence of such injuries.

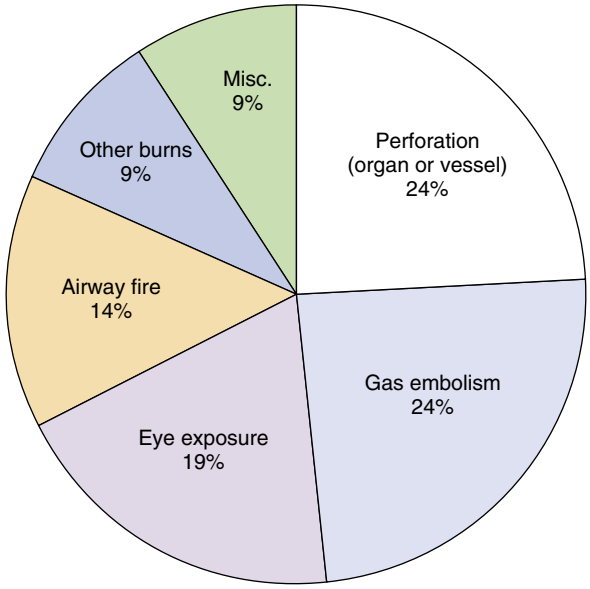

Figure 77-6 Distribution of laser injury type reported to the U.S. Food and Drug Administration from January 1989 to June 1990. *(Data from U.S. Food and Drug Administration: Special report: Laser safety. Laser Nurs 4:3, 1990.)*

Laser Hazards

The hazards associated with laser use can be divided into four major categories: atmospheric contamination, perforation of a vessel or structure, embolism, and inappropriate energy transfer. Twenty-one injuries were reported to the FDA—2 minor, 12 serious, and 7 fatal.[12] The distribution by type of injury is illustrated in Figure 77-6.

Atmospheric Contamination: Laser Plume

Vaporization of tissue, whether by electrosurgery or laser radiation, produces a plume of smoke and fine particulates (mean size 0.31 µm; range 0.1 to 0.8 µm),[13] sized within the range of particles that are efficiently transported and deposited in the alveoli. Many people find the odor of this plume objectionable, and sensitive persons have described headaches, tearing, and nausea as a consequence of inhalation. Deposition of laser plume particulates in rat lung seems capable of producing interstitial pneumonia, bronchiolitis, reduced mucociliary clearance, inflammation, and emphysema.[14,15]

Potentially, the laser plume also may be mutagenic,[16,17] teratogenic, or a vector for viral infection. In vitro, the mutagenic potential of laser condensate is one half that of electrocautery,[17] and the total mutagenic potential from 1 g of tissue is comparable to smoking three to six cigarettes. The role of the smoke plume as a viral vector is controversial. Viral DNA has been detected in plume from condylomas[18,19] and skin warts,[20] but not from laryngeal papillomas.[21] Human immunodeficiency virus (HIV) was not detected in electrosurgical smoke plume[22] in one study, and only noninfectious DNA fragments were found in a CO_2 laser plume from HIV-infected tissue pellets.[23] Competent transmission of any viral infection by a smoke plume has yet to be shown.[24] The laser plume does not seem to contain viable eukaryotic cells (i.e., tumor cells),[25,26] but it may contain viable bacterial spores.[27,28] CO_2 lasers seem to produce the most smoke because of vaporization of tissue, and Nd:YAG contact probes produce much less.

The most effective means of preventing dissemination of the plume is to use an efficient smoke evacuator at the surgical site.[29,30] Ordinary surgical masks efficiently filter particles only down to 3 µm, and special high-efficiency masks (e.g., The Protector II; Anago, Fort Worth, TX) are required to catch laser plume particulates. The high-efficiency masks are less effective when wet and may need to be changed periodically.

Tissue and Vessel Perforation

Misdirected laser energy may perforate a viscus[31-34] or a large blood vessel (vessels >5 mm are not coagulable by laser). Laser-induced pneumothorax has been reported after a laryngeal procedure.[35] With an Nd:YAG system, the depth of damage is impossible to assess accurately or immediately, and perforation and bleeding may not occur until edema and necrosis have become maximal several days postoperatively.

Embolism

The Nd:YAG laser system has been associated with venous gas embolism. Embolization has been a particular problem during

hysteroscopic surgery with Nd:YAG contact probes when the gas coolant for the sapphire probe tip has accidentally inflated the uterine cavity. In 1989, this technique resulted in five widely publicized cases involving four deaths.[6] In another report, uterine insertion of a sheathed quartz fiber (with coaxial coolant gas running) produced an immediate, massive, and fatal gas embolism.[36] The laser and its contact probe were not directly responsible for the injury, but a liquid (saline) coolant is strongly preferred during hysteroscopy. If a coolant gas must be used, CO_2 produces less damage after embolization than nitrogen or air. If uterine distention is achieved with saline rather than with gas, a fluid overload similar to that seen during transurethral prostate surgery is possible.[37]

Venous gas embolization also has been reported during Nd:YAG resection of tumor in the trachea,[38,39] and during various types of laparoscopic and endoscopic procedures.[40,41] A laser coolant malfunction during laparoscopic ablation of endometriosis at the University of California, San Francisco, resulted in complete subcutaneous air emphysema, from which the patient recovered after a benign course. During laparoscopic surgery with CO_2 insufflation, mechanical hyperventilation should be instituted and adjusted to compensate for intra-abdominal CO_2 absorption and cephalic displacement of the diaphragm. Continuous airway CO_2 monitoring is highly recommended for detection of embolization or hypercapnia.

Energy Transfer to an Inappropriate Location

All available medical laser wavelengths are transmitted transparently through air and are well reflected by smooth metal surfaces. Pressing the laser control trigger at the wrong time can deliver damaging laser light across the wound to sites at which surgical ablation was not desired or across the operating room into colleagues' eyes. Potentially tragic situations include laser ignition of surgical drapes[42,43] and, of special concern for anesthesiologists, accidental irradiation of an endotracheal tube during airway surgery.

Eye Protection

The ANSI standards and common sense dictate that the eyes of the operating room staff and the patient be protected during laser surgery (see Chapter 75). Errant infrared energy from a CO_2 laser can quickly cause a serious corneal injury,[44] whereas argon, KTP:Nd:YAG, or ruby lasers may burn the retina.[45] The lids of patients' nonoperated eyes should be taped closed and then covered with an opaque, saline-soaked knit or metal shield.[46-48] Operating room personnel must wear safety goggles or lenses specific for the specific laser wavelength in use. Using the wrong filter provides no protection. Safety goggles should provide wraparound protection from reflected light. For CO_2 lasers, any clear glass or plastic lenses suffice because they are opaque to far infrared. Regular eyeglasses may be sufficient, but contact lenses are not. Other lasers require color filters whose wavelength specificity and optical density are regulated. Nd:YAG lasers require special green-tinted goggles, which make assessment of patient skin color difficult, or clear lenses (Nd:YAG Protection Glass; Surgical Laser Technologies, Malvern, PA), which have a special coating opaque to near infrared. Argon or krypton lasers require an amber-orange lens filter, and KTP:Nd:YAG lasers require a red filter. Because lasers other than the far-infrared CO_2 produce beams that pass through glass, all windows into the operating room should be covered during laser procedures, and specific, specially designed warning signs should be posted as described in ANSI Z136.3.

Endotracheal Tube Fires

A feared complication of laser use during airway surgery is endotracheal tube fire. The estimated incidence of this complication during such operations is 0.5% to 1.5%.[49,50] Although a survey of otolaryngologists did not provide an incidence for fires, it did show that laser-induced ignition of endotracheal tube, cuff, or cottonoids was responsible for most (41%) perioperative complications, followed by postoperative laryngeal web (19%) and laser-related or laser-induced facial burns (11%).[51] The largest published (retrospective) series of CO_2 laser airway procedures documented 6 airway fires in 4416 cases (0.14% incidence),[52] confirming it as the most frequent laser-related complication in patients undergoing this type of procedure. Given the proximity of the endotracheal tube to surgical sites around the larynx, the potential for fire or other airway complications is clear. Electrosurgical devices also have caused airway fires when leaks from the breathing circuit raise the oxygen concentration in proximity to the cautery. Many of these fires, when appropriately handled, result in minimal or no harm to the patient,[49,53,54] but catastrophic consequences are possible.[55,56]

With the energy delivery rates described earlier, any hydrocarbon material, including tissue, plastic, or rubber, can ignite and burn, particularly in an oxygen-enriched atmosphere. Fires can result from direct laser illumination, reflected laser light, or incandescent particles of tissue blown from the surgical site.[57] Initially, most fires are located solely on the external surface of the endotracheal tube, where they can cause local thermal destruction. If a fire is unrecognized and burns through to the interior of the tube, the oxygen-enriched gas combined with the to-and-fro gas flow owing to ventilation produce a blowtorch-like flame, blowing heat and toxic products of combustion down to the pulmonary parenchyma (Fig. 77-7). Puncture and unrecognized deflation of the tube cuff also may permit oxygen-enriched gas to flood the operative site and increase the chance of a devastating fire after a laser burst.

Three strategies are used to reduce the incidence of airway fire: reduction of the flammability of the endotracheal tube, removal of flammable materials from the airway by using a metallic Venturi jet ventilation cannula or intermittent extubation with or without apnea, and reduction of the available oxygen content to the minimum required for reasonable arterial saturation. Each of these strategies is discussed next.

Relative Flammability: Effect of Tube Composition

Because all common endotracheal tubes are potentially flammable, the relative risks of the various types of construction material

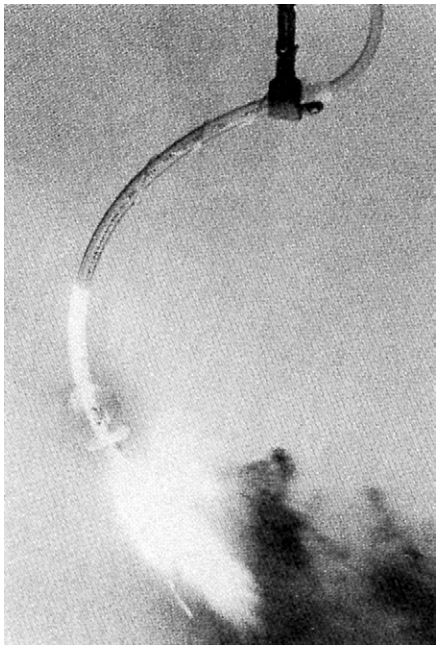

Figure 77-7 Blowtorch ignition of an endotracheal tube. *(From Emergency Care Research Institute: Airway fires: Reducing the risk during laser surgery. Health Devices 19:109, 1990.)*

have been well studied. For many years, reusable red rubber tubes were commonplace, but these were supplanted by clear polyvinyl chloride (PVC) plastic tubes. Modern PVC strongly absorbs far-infrared light and is very sensitive to CO_2 laser energy. PVC tubes seem to be ignited much more easily by CO_2 lasers than red rubber tubes[52,58,59] and to produce more toxic combustion products. In vitro, PVC is transparent and immune to Nd:YAG and visible laser light; however, a thin coating of mucus or blood in vivo can absorb energy and restore the hazard.[60] Commercially available tubes fabricated of PVC without opaque lettering or a barium stripe make claims of laser resistance based on the in vitro tests—however, *caveat emptor* (i.e., let the buyer beware).

Two studies of the effects of Nd:YAG laser energy on common types of tubes, including tubes designed to be resistant to laser irradiation, revealed that endotracheal tubes of all materials are quite vulnerable.[61,62] Ossoff and colleagues[58] compared the extent of acute damage to the trachea from blowtorch-type ignitions in dogs ventilated with 1% halothane and 70% nitrous oxide (balance oxygen) through PVC, rubber, or silicone endotracheal tubes. PVC ignited and developed intense flame the soonest, resulting in widespread deposit of carbonaceous debris and significant ulceration and inflammation of the trachea on postmortem analysis. Red rubber tubes were more resistant to ignition, and produced less debris and inflammation. Silicone tubes were the most resistant to ignition, but they produced copious white silica ash, suggesting the potential for late development of silicosis.

Ossoff[63] subsequently measured the time to intraluminal ignition during exposure CO_2 laser energy to determine resistance to ignition and reversed the ranking of silicone and red rubber, with PVC remaining the most vulnerable. He also found that addition of 2% halothane vapor retarded ignition. After ignition occurs, the index of flammability is the minimum inspired oxygen fraction (F_{IO_2}) necessary to maintain combustion. Wolf and Simpson[64] report that PVC is less flammable than silicone or red rubber, having a flammability index of 0.26 versus 0.19 for silicone and 0.19 for red rubber. When nitrous oxide was used as the oxidant, PVC retained the highest index (0.46), followed by silicone (0.41) and red rubber (0.37).

Despite the conflicting data, many physicians recommend the use of red rubber endotracheal tubes during laser surgery of the aerodigestive tract, and base this suggestion on criteria of resistance to ignition and least toxic combustion products. At the University of California, San Francisco, one surgeon has performed more than 4000 microdirect laryngoscopies using a CO_2 laser, incurring only two fires (0.005%), and no significant fire-related morbidity (H. H. Dedo, personal communication, 1992) with aluminum-taped PVC endotracheal tubes and moistened pledgets (discussed later). Regardless of the tube substrate, there are additional safety considerations and maneuvers to consider, as outlined later.

Effect of Respiratory Gas Mixture

The mixture of airway gases becomes an important issue when any type of potentially flammable endotracheal tube is used. Combustion is more vigorous when excess oxidizer is present, and most clinicians recognize the need to reduce the F_{IO_2} to less than 0.40 or to the minimum concentration consistent with patient oxygenation. That nitrous oxide also is a powerful oxidizer is less well recognized, but adding nitrous oxide as a diluent for oxygen is just as dangerous as having a high F_{IO_2}.[64] Use of an air-oxygen mixture seems to be acceptable. Some investigators prefer helium as a diluent to nitrogen because helium has a higher thermal conductivity, which may delay the ignition of an endotracheal tube for a few seconds.[63,65] Helium also has a lower density, allowing the use of a smaller endotracheal tube without turbulence and high flow resistance.[67-69] The index of flammability is reduced by only 1% to 2%, however, when oxygen-helium is substituted for oxygen-nitrogen.[66]

The volatile anesthetics used in clinical practice are nonflammable and nonexplosive in clinically relevant concentrations.[70,71] During an airway fire, they may undergo pyrolysis to potentially toxic compounds.[72] On this theoretical basis, the ANSI Z136.3 standard recommends not using volatile anesthetics during airway laser surgery. This is an extremely conservative stance given the low concentration of anesthetic gas compared with the products of combustion from an endotracheal tube, and the lack of evidence of toxicity because of the pyrolytic products. When Venturi ventilation is used, administration of volatile agents usually is not practical.

Protection of the Endotracheal Tube

After the possibility of endotracheal tube ignition was raised, extrinsic protection of the tubes was suggested.[73] Patil and colleagues[74] suggested wrapping tubes with moistened muslin. If allowed to dry, however, muslin becomes flammable. Kumar and Frost[75] suggested coating the vulnerable portion of the exterior of the tube with dental acrylic. This approach renders the tube rigid with a rough surface, however, which may traumatize the mucosal

surfaces. The most popular approach to the problem has been wrapping the tube with metallized foil tape.[50,59,61,63,73,76,77]

Three types of tape have been used: aluminum foil with adhesive backing, copper foil with adhesive backing, and plastic tape thinly coated with metal on one side and adhesive on the other. These tape products are widely available from electronics, arts and crafts, and building supply shops. Lead foil (commonly used on windows for burglar alarms) is similar in appearance, but is toxic and should never be used in the airway.

The aluminum and copper tapes have been evaluated for protection of different types of endotracheal tubes with various lasers. Although taping does not provide protection of the inflatable cuff portion of an endotracheal tube, these metal tapes do offer a measure of protection against inadvertent, brief, or unfocused far-infrared CO_2 laser hits to the taped portion of the tube shaft. Metallic tapes are a less certain shield, however, against the near-infrared beam from Nd:YAG. The solid copper (1-mm foil; Venture Tape Corp, Rockland, MA) and aluminum (no. 425 or no. 433; 3M Corp, Industrial Tape Division, St. Paul, MN) tapes were able to withstand at least 60 seconds of direct Nd:YAG laser exposure without penetration or ignition.[77] An Emergency Care Research Institute (ECRI) study[78] found that the 3M aluminum tape provided protection against CO_2 and KTP:Nd:YAG, but it did allow ignition of a PVC tube at the highest power setting of an Nd:YAG laser. Copper tape (no. 1181; 3M Corp, Electrical Products Division, St. Paul, MN) provided ignition protection from all three lasers. Sosis and Dillon[77] found that metallized plastic tape (Radio Shack no. 44-1155, Fort Worth, TX) was more easily ignited by Nd:YAG than an unwrapped red rubber tube, with a time to ignition of 6 seconds versus 13 seconds for the unwrapped control. The ECRI[78] also found that although the metallized plastic tape was most pliant and least likely to abrade the larynx, it provided protection only against CO_2 lasers, not against Nd:YAG or KTP:Nd:YAG.

Applying a protective metal foil wrap to an endotracheal tube requires some care. A clean tube should be wiped with alcohol to remove residue that could interfere with adhesion and then optionally wiped lightly with Mastisol or tincture of benzoin. The end of the tape should be cut at an angle of about 60 degrees, and the cut edge should be aligned with the proximal end of the cuff junction (Fig. 77-8). Tape should be wrapped in a spiral, with about 30% overlap, to the exit point of the cuff pilot tube. Wrinkles should be eliminated to avoid abrading the tracheal mucosa. The result should eliminate bare tubing or areas of exposed tape adhesive (which is quite flammable). Rewiping the wrapped tube with alcohol provides a degree of cleanliness before tracheal intubation.

Although this use is well supported in the medical literature, none of these metal foils has FDA approval because their manufacturers have not sought it. Physicians who devise a wrapped endotracheal tube using such tapes incur some product liability risk as a noncertified "manufacturer" should injury occur, especially because there are FDA-approved commercial products that claim laser resistance.

The Merocel Laser Guard (Medtronic Xomed Merocel Corp, Mystic, CT) is a commercial, FDA-approved endotracheal wrap consisting of an adhesive metal foil laminated to a synthetic sponge surface. Properly placed on an endotracheal tube and kept moist, the Merocel product provides protection against CO_2, argon, and KTP:Nd:YAG lasers, but not YAG lasers.[78] The manufacturer recommends this product only for use with CO_2 lasers. The shield material adds almost 2 mm to the diameter of the endotracheal tube. Similar to the nonapproved tapes, Laser Guard can be applied only to the shaft of the tube and provides no protection for the cuff.

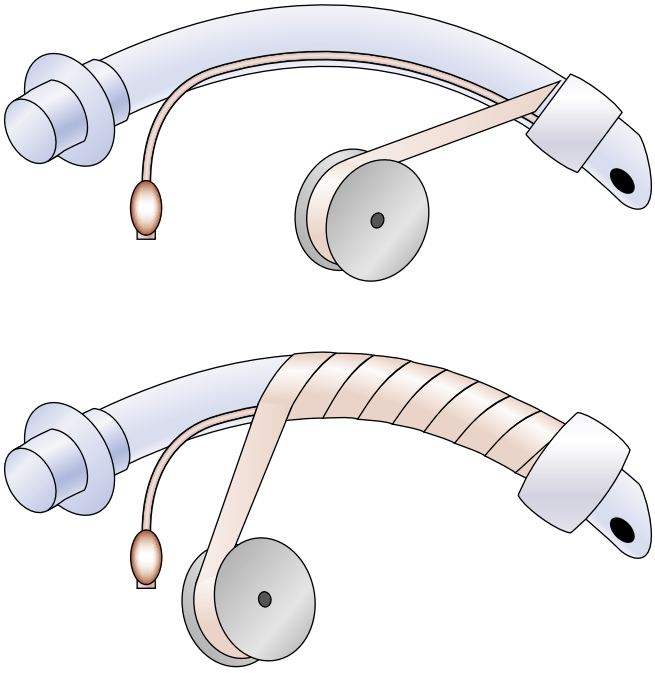

Figure 77-8 Cuff wrapping technique. If a wrapped endotracheal tube is the chosen method for laser protection, the technique for wrapping is crucial in ensuring protection from ignition and foil-induced mucosal abrasions. It is often helpful first to paint the tube sparingly with a medical adhesive, such as benzoin or Mastisol. The end of the tape should be cut with a scalpel to approximately 60 degrees. Wrapping is begun by aligning the cut end of the tape with the junction of the tube and the proximal end of the cuff and is done in a spiral with a 30% to 50% overlap between layers. Wrapping should include the inflation tube for the cuff and should be continued until just short of the pilot balloon, with care taken not to wrinkle the tape at any point.

The FDA also has approved the use of an integral laser-resistant coating in the manufacture of endotracheal tubes. The commercially available Xomed Laser shield tube (Medtronic Xomed, Jacksonville, FL) is fabricated from silicone with an outer layer of finely divided aluminum powder in silicone; the aluminized layer extends over the inflatable cuff. This tube is specified for use only with CO_2 lasers, a beam power density of less than 4900 W/cm^2, and an F_{IO_2} of less than 25%.

Although more resistant to far-infrared radiation than PVC or red rubber tubing,[79,80] the Laser Shield nonetheless burns vigorously when ignited in vitro,[63] producing friable silica dust. It also may ignite under typical surgical conditions, failing the ECRI flammability test.[78] In at least one case, an airway fire involving this tube occurred,[56] resulting in serious injury attributed to an intraluminal fire caused by laser penetration of the cuff; the laser power settings were within specified limits, but the respiratory gas mixture included an excessive F_{IO_2} and nitrous oxide. A newer version, the Laser Shield II, is approved for use with CO_2 or KTP lasers. The construction of this version includes a silicone-based tube that is smoothly wrapped by a coated aluminum

tape. The cuff is made of unshielded silicone elastomer, designed to be expanded with saline, and includes methylene blue dye to tint the saline. The tube wrap is specified to withstand (in vitro) 35,000 W/cm^2 of CO_2 laser energy or 11,000 W/cm^2 of KTP energy for 3 minutes. Blood or mucus on the tube can be expected to reduce its tolerance to laser irradiation by approximately 60%.

Protection of the Endotracheal Tube Cuff

The thin plastic envelope of a standard high-volume, low-pressure endotracheal cuff is extremely susceptible to misdirected laser energy. Although combustion is possible, simple puncture may be more common. Unrecognized cuff punctures lead to oxygen enrichment of the gas surrounding the surgical site and endotracheal tube and increase the likelihood of a catastrophic airway fire. Cuffs with significant laser resistance that maintain the mechanical properties necessary to minimize tracheal trauma are unavailable. Many physicians recommend filling the standard Hi-Lo cuff with colored saline to signal a puncture more clearly and potentially to quench a small cuff fire. The cuff should be placed as far distal in the trachea as possible, and the surgeon should completely cover the visible cuff with moistened cotton pledgets. The cotton strings attached to the pledgets should be replaced by uninsulated wire, and the pledgets should be remoistened as needed. The utility of moistened pledgets in preventing or delaying cuff ignition from CO_2 laser exposure has been confirmed.[81]

Metal Endotracheal Tubes

In 1978, Norton and De Vos[82] introduced a nonflammable endotracheal tube constructed as an interlocking stainless steel spiral coil, resembling electric cable armor (Baxter Healthcare Corp, Niles, IL). The manufacture of this endotracheal tube has been discontinued. Its walls were not airtight, and although this property allowed a cooling gas flow to the exterior surface, it could make ventilation difficult in patients with noncompliant lungs, particularly because the tube had no inflatable cuff. Jet ventilation with a modified Sanders Venturi coupler was suggested as a means to overcome this problem,[83] as was the use of a separate, slide-on cuff, but these are all flammable and pose an ignition risk.

Two other metal endotracheal tubes are commercially available and are approved for use with specific lasers. The Laser Flex tube (Mallinckrodt Inc, St. Louis, MO) is an airtight stainless steel spiral with two distal, saline-inflatable PVC cuffs (redundant in case of puncture of the proximal cuff). This tube is resistant to CO_2 and KTP laser energy,[84] but not the Nd:YAG laser.[78] The Bivona Fome-Cuf (Smith's Medical, Kent, UK) is an aluminum spiral tube with an outer covering of silicone and a unique, self-inflating foam sponge-filled cuff, which prevents deflation after puncture. This feature allows continued positive-pressure ventilation and segregation of airway gases from the operative site, but it may lead to injury if a puncture of the cuff or of the filling tube prevents deflation before removal. The Fome-Cuf is approved for use only with pulsed CO_2 lasers.

The use of laser-resistant endotracheal tubes requires particular care to prevent mucosal abrasions because these tubes tend to be bulkier and more rigid than conventional tubes. Surgeons should ensure that laser energy is not reflected from smooth metal surfaces and directed at sensitive structures. Use of a metal endotracheal tube does not imply absolute protection from ignition; 50 W of an Nd:YAG beam focused to 0.68 mm has been reported to ignite a Laser Flex tube in 6 seconds.[85]

Jet Ventilation

Some physicians contend that optimal surgical conditions and patient safety can be obtained with jet ventilation. This technique takes advantage of Bernoulli's principle to augment the ventilation produced by a narrow, high-speed gas stream in a Venturi tube. In practice, jet ventilation uses an intermittent high-pressure oxygen supply, directed at the glottis through a small metal tube, such as a ventilating bronchoscope or even a 12-gauge blunt needle.[86-91] A retrospective review of 942 cases of microdirect laryngoscopy using endolaryngeal jet ventilation found only four complications.[92] Jet ventilation with air also has been used through a bronchoscope when resecting distal tracheal and bronchial tumors.[93-96] It has been suggested that patients undergoing laser resections of airway tumors during jet ventilation may absorb carbon monoxide from entrained laser smoke in the pharynx. The carbon monoxide can result in an overestimate of arterial oxygen saturation by pulse oximetry. Goldhill and colleagues[95] found neither a significant increase in carboxyhemoglobin during Nd:YAG bronchoscopy nor a difference in pulse oximetry reading versus in vitro carbon monoxide–oximeter measurement of arterial oxygen saturation.

Although jet ventilation generally provides adequate ventilation without introducing flammable material or a large obstacle to the surgical field, potential disadvantages include the risk of barotrauma, pneumothorax, or crepitus; the restriction to use of intravenous anesthetic agents; gastric distention; and the relative requirement for compliant lungs. In the presence of papillomas, a common indication for laryngeal laser surgery, jet ventilation could cause distal bronchial seeding with active virus. Shikowitz and associates[92] found no evidence, however, of this phenomenon in 96 patients who had multiple laser procedures and were followed over time. Cozine and colleagues,[97] in a survey of 58 institutions (15,701 cases) performing CO_2 laser airway surgery, found a higher rate of ventilatory complications with jet ventilation than with a standard endotracheal tube (Fig. 77-9), but the only fatality was caused by an endotracheal tube fire.[97] The investigators concluded that no single mode of ventilation proved superior during laser surgery.

To reduce obstruction of the surgical field by ventilatory instrumentation even further, several researchers have advocated complete removal of such instrumentation combined with the technique of spontaneous ventilation or intermittent apnea, with general anesthesia provided by nasal insufflation or bronchoscopic delivery of a potent inhaled anesthetic[7,72,98,99] or use of an intravenous anesthetic.[100] Cohen and associates[101] and Hawkins and Joseph[102] advocated modest hyperventilation followed by intermittent tracheal extubation by the surgeon for periods of 90 to 120 seconds, during which the laser is used. Pulse oximetry adds a measure of safety by confirming adequate oxygenation from a denitrogenated pulmonary residual capacity during apnea.

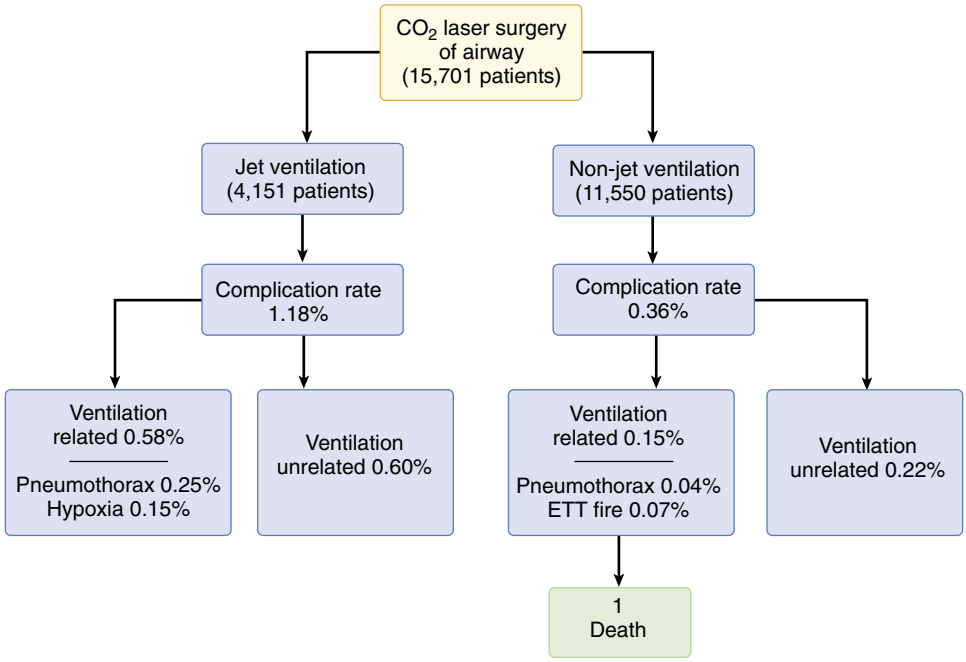

Figure 77-9 Complications of laser airway surgery. Pneumothorax was common with jet ventilation, but potentially lethal airway fires occurred with endotracheal intubation. ETT, endotracheal tube. *(Data from Cozine K, Stone JG, Shulman S, et al: Ventilatory complications of carbon dioxide laser laryngeal surgery. J Clin Anesth 3:20, 1991.)*

Other Considerations

Although not specifically related to laser procedures in the airway, vagal hyperactivity often occurs during instrumentation of the trachea. Immediate recognition and treatment are important. The paraneoplastic syndrome, occasionally observed with small cell and other types of endobronchial tumors, may lead to prolonged weakness after administration of neuromuscular relaxants.[103]

Airway Fire Protocol

If an airway fire or explosion occurs, the surgeon and the anesthesiologist must act quickly, decisively, and in a coordinated fashion. This may not be easy after an explosion because the event may be so traumatic as to incapacitate the operating room staff temporarily. Clear communication and emergency practice (at least a mental drill of the emergency procedure) are key to managing such a crisis. Schramm and coworkers[104] provided a useful review of the ensuing pathologic features and suggested emergency management.

A surgeon who detects an endotracheal or other source of airway fire should remove the source as quickly as possible and simultaneously inform the anesthesiologist, who should immediately, despite reflexive training to the contrary, stop ventilation. Temporarily disconnecting the breathing circuit from the anesthesia machine may be useful. These maneuvers remove the flame and the retained heat in the tube and stop the flow of oxygen-enriched gas. The flaming material should be extinguished in a bucket of water, which should always be available during laser surgery. Ventilation with 100% oxygen should be provided by mask, and anesthesia should be continued.

Direct laryngoscopy and rigid (Venturi-ventilating) bronchoscopy should be performed to survey damage and to remove debris. If the fire was of the "interior blowtorch" type, gentle bronchial lavage may be indicated, followed by fiberoptic assessment of the more distal airways. If any airway damage is apparent, the patient should be reintubated. Small fires involving only the exterior of the tube may not cause appreciable damage. If the damage is severe, a low tracheotomy may be indicated.

The pattern of damage in interior fires tends to be worst in the upper airway and diminishes as the surgeon approaches and passes the carina. The patient's oropharynx and face should be assessed, and a chest radiograph should be obtained. Pulmonary damage due to heat or smoke inhalation, or both, may necessitate prolonged intubation and mechanical ventilation. A brief course of high-dose steroids may be helpful.[105,106]

Summary

Lasers provide a useful tool in the surgical armamentarium, one for which anesthesiologists must prepare, with increasing frequency, their patients and themselves. Although some of the potential threats posed by clinical lasers are unique, most are extensions of the risks posed by the previous generation of surgical tools. As with most potentially dangerous procedures, the risks of laser use can be minimized by common sense and preconsidered contingency plans.

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78 Ambulatory (Outpatient) Anesthesia

Key Points

1. The continued growth in ambulatory surgery is related to expansion in minimally invasive surgical techniques and office-based procedures.
2. Pre-existing medical conditions are rarely an exclusionary criterion for ambulatory surgery.
3. Routine laboratory testing is not recommended before ambulatory surgery.
4. The choice of anesthetic technique has a significant effect on postoperative side effects and discharge time. The use of local anesthesia with sedation, so-called monitored anesthesia care, is associated with the fewest side effects and the shortest time to discharge home.
5. The use of propofol for induction or maintenance of anesthesia (or both) is associated with a reduced incidence of postoperative nausea and vomiting (PONV).
6. The use of desflurane or nitrous oxide (or both) in conjunction with antiemetic prophylaxis will facilitate the "fast-track" recovery process.
7. The use of potent opioid analgesics (e.g., fentanyl, sufentanil) in combination with local anesthetics will decrease the time to discharge home after spinal anesthesia.
8. Multimodal ("balanced") analgesic and antiemetic regimens will allow most outpatients to be fast-tracked after ambulatory surgery under general anesthesia.
9. Fast-tracking after ambulatory surgery is accomplished by taking the patient directly from the operating room to the day-surgery step-down unit ("bypassing the PACU") or simply discharging the patient home from the PACU ("PACU bypassing").
10. Outcomes after ambulatory (and office-based) surgery are no different than after inpatient (hospital-based) surgery procedures. Recent data suggest that for elderly patients the surgical outcome may be improved.

Over the past 4 decades, ambulatory surgery has grown from less than 10% to over 70% of all elective surgical procedures.[1] Ambulatory surgery has progressed from the practice of performing simple procedures on healthy outpatients to encompassing a broad spectrum of major procedures in outpatients with complex preexisting medical conditions. Formal development of ambulatory anesthesia as a respected subspecialty occurred with establishment of the Society for Ambulatory Anesthesia (SAMBA) in 1984 and the subsequent development of postgraduate subspecialty training programs recognized by the American Society of Anesthesiologists (ASA).

The expanding number of freestanding diagnostic and surgical treatment centers around the world reflects the global interest in reducing the need for hospitalization after elective surgery.[2] However, the growth in ambulatory surgery would have not been possible without the development of improved anesthetic and surgical techniques.[3] The availability of rapid, shorter-acting anesthetic, analgesic, and muscle relaxant drugs has clearly facilitated the recovery process after surgery, and the development of minimally invasive surgical techniques allowed more extensive procedures to be performed on an ambulatory basis, irrespective of the patient's preexisting medical conditions.[4]

The range of acceptable ambulatory surgical procedures continues to expand, and patients are presenting for outpatient surgery with increasingly complex medical problems. As a result, anesthesiologists must play a more active role in the preoperative assessment and preparation of these patients to avoid costly delays and last-minute cancellations.[5] The role of the anesthesiologist has evolved from that of a physician primarily concerned with providing optimal surgical conditions and minimizing pain immediately after the operation to that of a perioperative physician responsible for ensuring that patients with coexisting medical conditions are optimally managed before, during, and after surgery (Table 78-1).[6,7] In modern ambulatory facilities, complex surgical procedures can be safely performed without sacrificing quality while minimizing use of hospital resources.[8] In an era of cost containment, the savings inherent in providing increased ambulatory surgical services ensures that the number of outpatient surgical procedures will continue to grow in the 21st century.[1]

Table 78-1 Key Elements of Perioperative Anesthetic Management for Facilitating a Fast-Track Recovery after Elective Ambulatory Surgery

Preoperative Period
- Stabilize coexisting diseases (e.g., hypertension, diabetes) and encourage prehabilitation exercise program and smoking cessation.
- Optimize patient comfort by minimizing anxiety and discomfort.
- Ensure adequate rehydration by replacing fluid deficits.
- Use appropriate prophylactic therapies to prevent postoperative complications (e.g., nausea, vomiting, pain, ileus).

Intraoperative Period
- Utilize anesthetic techniques that optimize surgical conditions, while ensuring a rapid recovery with minimal side effects.
- Administer local analgesia via peripheral nerve blocks, wound infiltration, and/or instillation.
- Apply multimodal analgesia and antiemetic prophylaxis (including use of glucocorticoid steroids).
- Minimize use of nasogastric tubes and surgical drains, and avoid excessive fluid administration.

Postoperative Period
- Allow patients who meet discharge criteria to be fast-tracked (i.e., discharged earlier from recovery units).
- Ensure adequate pain control in the postdischarge period utilizing nonopioid analgesics to minimize need for opioid-containing analgesics.
- Encourage early ambulation and resumption of normal activities of daily living.

Modified from White PF, Kehlet H, Neal JM, et al: The role of the anesthesiologist in fast-track surgery: From multimodal analgesia to perioperative medical care. Anesth Analg 104:1380-1396, 2007.

Rationale for Ambulatory Surgery

Ambulatory surgery can offer a number of advantages for patients, health care providers, third-party payers, and even hospitals (Table 78-2). Most patients actually prefer to have their surgical procedures performed as outpatients because it decreases separation from their familiar home environment. Postoperative cognitive dysfunction was less frequent in elderly patients undergoing minor surgery on an ambulatory basis,[9] confirming that hospitalization should be avoided whenever possible. A survey of patient satisfaction after ambulatory surgery reported that 97% of the respondents would choose to have day surgery for a future surgical procedure.[1] Unlike inpatient surgery, ambulatory surgery does not depend on the availability of a hospital bed, and patients thus have a greater degree of flexibility in scheduling the timing of their operation.

Outpatient surgery has been performed safely with a remarkably low incidence of both minor and major morbidity.[10] Studies have shown that unanticipated admission to the hospital and return visits to the hospital occur in less than 3% of patients after ambulatory surgical procedures.[11-13] The majority of readmissions (and emergency department visits) were related to surgical complications.[12] Of the surgical subspecialties, otolaryngology had the highest, and gynecology the lowest, incidence of unanticipated admissions. The lower infection rate associated with outpatient surgery is particularly beneficial to pediatric, geriatric, and immunocompromised patients.[1] Risk factors associated with an increase in surgical site infections were the use of postoperative antibiotics and prolonged surgical times.[14] Finally, there is evidence that the incidence of respiratory complications (i.e., pulmonary embolus and pneumonia) also may be decreased.[15] Even outpatients with obstructive sleep apnea syndrome were not found to have an increased incidence of respiratory complications or unanticipated hospital admissions.[16]

Minimally invasive ambulatory surgery has clear economic benefits. For example, when compared with conventional "open" procedures, the use of minimally invasive surgical techniques can reduce overall hospital costs by almost 50%.[17] Another cost-saving benefit relates to the greater efficiency of ambulatory centers, which results in higher operating room utilization and faster turnover times.[8] The ability to care for larger volumes of patients can lead to reduced surgical waiting lists. When compared with similar procedures performed in hospitalized patients, less preoperative laboratory testing is ordered for ambulatory surgery and the patients have a reduced demand for postoperative medications. These factors all contribute to the 25% to 75% reductions in overall cost for most operations performed in the outpatient (versus inpatient) setting. However, procedures requiring specialized postoperative care (e.g., extensive physical therapy or complex pain management techniques) may be more costly when performed on an outpatient basis.[18] Patients who require postoperative blood transfusions or intravenous antibiotics and parenteral opioid analgesics are best handled as 23-hour admissions. Recent improvements in home health care and outpatient physical therapy may enable these services to be performed in the patient's home. Importantly, studies comparing minimally invasive (versus open) procedures have reported that patients can resume activities of daily living several days or even weeks earlier.[19] Assuming that the number of available hospital beds continues to decline in the future, the growth of ambulatory surgery will lead to an increased return on investment of the health care dollar.

Table 78-2 Benefits of Ambulatory Surgery

- Patient preference, especially children and the elderly
- Lack of dependence on the availability of hospital beds
- Greater flexibility in scheduling operations
- Low morbidity and mortality
- Lower incidence of infection
- Lower incidence of respiratory complications
- Higher volume of patients (greater efficiency)
- Shorter surgical waiting lists
- Lower overall procedural costs
- Less preoperative testing and postoperative medication

Modified from Snyder DS, Pasternak LR: Facility design and procedural safety. *In* White PF (ed): Ambulatory Anesthesia and Surgery. London, WB Saunders, 1997, p 61.

Facility Design and Safety

Ambulatory surgical facilities need to be well-designed to ensure efficient delivery of surgical services at the lowest possible cost. The first freestanding outpatient surgical facility was built and managed by an anesthesiologist, Wallace Reed, to provide surgical care to patients whose operations were deemed too demanding for a surgeon's office yet did not require overnight hospitalization.[20] Since that time, outpatient surgical facilities have continued to grow and evolve.[21] The prototypical ambulatory surgical units have four basic designs[1]:

1. *Hospital integrated:* Ambulatory surgical patients are managed in the same surgery facility as inpatients. Outpatients may have separate preoperative preparation and recovery areas.
2. *Hospital-based:* A separate ambulatory surgical facility within a hospital handles only outpatients.
3. *Freestanding:* These surgical and diagnostic facilities may be associated with a hospital or medical center but are housed in separate buildings that share no space or patient care functions. Preoperative evaluation, surgical care, and recovery occur within this autonomous unit.
4. *Office-based:* These operating and/or diagnostic suites are managed in conjunction with physicians' offices for the convenience of patients and health care providers.

Patient volume, types of patients (e.g., children, elderly), types of diagnostic and therapeutic procedures, organizational structure, and radiologic and laboratory testing requirements must all be considered during the initial planning of a new facility. To be optimally efficient, it is recommended that all the outpatient services be organized in one dedicated area. Designs that place the waiting room, preoperative evaluation area, preanesthesia room, operating suites, and recovery areas in close proximity have many advantages.[20] Surgeons and anesthesiologists are able to visit the patient and family before and after the operation without losing valuable time in transit. Patient transportation time is also reduced to a minimum, and extra personnel are unnecessary because the circulating nurse (or anesthesiologist) can transport the patient to and from the operating room (Fig. 78-1). In most office-based facilities, the patients can walk in and walk out of the operating room.

Quality assurance and total quality improvement are helpful in maintaining high standards for outpatient care and ensuring patient safety. Quality standards are set and enforced either by government regulation, through a licensing process, or by accreditation by private organizations such as the Accreditation Association for Ambulatory Health Care (AAAHC). The AAAHC is an independent accreditation organization whose principal activities are to develop standards, conduct surveys, and confer accreditation on ambulatory health care providers. In the United States and Canada, hospital-based ambulatory surgical facilities receive accreditation through The Joint Commission on Accreditation of Healthcare Organizations, which is the primary accreditation agency for hospitals. As a result of heightened public and practitioner concern over the safety and quality of office-based surgical procedures, the AAAHC has established new quality standards for office-based and so-called mobile or itinerant anesthesia organizations.[22] It has been recommended that all facilities where surgery is performed, as well as the health care providers, be accredited to ensure that patient safety is not being compromised.[23]

The ASA also provides guidelines for ambulatory surgical facilities. The availability of personnel and equipment for unexpected emergencies or a delayed return to the operating room is essential. In-service training of all staff members regarding skills that are infrequently required should be given regularly, including advanced cardiac life support, management of airway complications, emergency tracheotomy, and treatment of malignant hyperthermia (MH).[1] All facilities in which anesthesia is administered require a portable crash cart and suction device. General support services for routine laboratory tests, an electrocardiography (ECG) machine, and access to a blood supply should also be available. A mechanism should be in place for obtaining an emergency MH kit in locations where general anesthesia is performed.

Patient Selection Criteria

Selection of Procedures

Surgical procedures suitable for ambulatory surgery should be accompanied by minimal postoperative physiologic disturbances and an uncomplicated recovery.[24] The primary predictors of prolonged stay or unanticipated admission after day-case surgery are related to the type of surgical procedure and associated complications (e.g., blood loss, incisional pain, postoperative nausea and vomiting [PONV]).[25,26] With advances in surgical technologies and the rapid growth in minimally invasive surgical techniques, an even wider variety of operations can now be performed on an outpatient basis (Table 78-3). Many published reports have demonstrated that minimally invasive outpatient procedures such as parathyroidectomy and thyroidectomy, laparoscopically assisted vaginal hysterectomy, removal of ectopic tubal pregnancy, and ovarian cystectomy, as well as laparoscopic cholecystectomy and fundoplication, offer advantages over conventional "open" approaches.[27-31] In addition, procedures such as laparoscopic adrenalectomy, splenectomy, and nephrectomy, lumbar microdiscectomy, and video-assisted thoracic surgery significantly improve recovery and reduce costs compared with open procedures.[32,33] For superficial procedures (e.g., mastectomy), reductions in both cost and perioperative complications have been observed when these procedures are performed on an outpatient basis.[34]

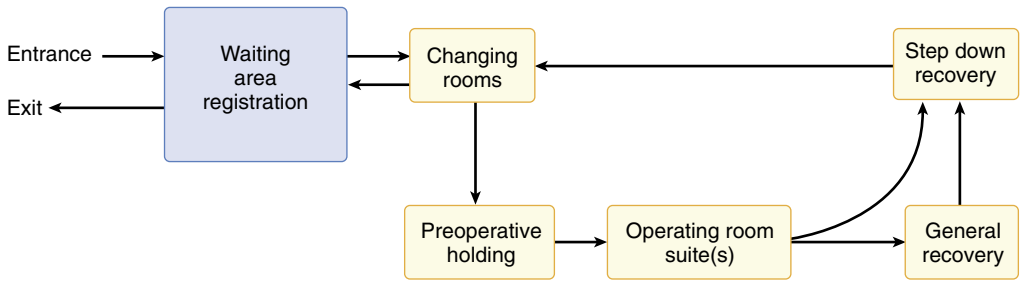

Figure 78-1 Essential components related to patient flow in an ambulatory surgery facility. (*Redrawn with modification from Snyder DS, Pasternak LR: Facility design and procedural safety. In White PF [ed]: Ambulatory Anesthesia and Surgery. London, WB Saunders, 1997, p 61.*)

Table 78-3 Operative Procedures Suitable for Ambulatory Surgery

Specialty	Types of Surgical Procedures
Dental	Extraction, restoration, facial fractures
Dermatology	Excision of skin lesions
General	Biopsy, endoscopy, excision of masses, hemorrhoidectomy, herniorrhaphy, laparoscopic cholecystectomy, adrenalectomy, splenectomy, varicose vein surgery
Gynecology	Cone biopsy, dilatation and curettage, hysteroscopy, diagnostic laparoscopy, laparoscopic tubal ligations, uterine polypectomy, vaginal hysterectomy
Ophthalmology	Cataract extraction, chalazion excision, nasolacrimal duct probing, strabismus repair, tonometry
Orthopedic	Anterior cruciate repair, knee arthroscopy, shoulder reconstructions, bunionectomy, carpal tunnel release, closed reduction, hardware removal, manipulation under anesthesia and minimally invasive hip replacements
Otolaryngology	Adenoidectomy, laryngoscopy, mastoidectomy, myringotomy, polypectomy, rhinoplasty, tonsillectomy, tympanoplasty
Pain clinic	Chemical sympathectomy, epidural injection, nerve blocks
Plastic surgery	Basal cell cancer excision, cleft lip repair, liposuction, mammoplasty (reductions and augmentations), otoplasty, scar revision, septorhinoplasty, skin graft
Urology	Bladder surgery, circumcision, cystoscopy, lithotripsy, orchiectomy, prostate biopsy, vasovasostomy, laparoscopic nephrectomy and prostatectomy

Modified from White PF (ed): Ambulatory Anesthesia and Surgery. London, WB Saunders, 1997.

Patients undergoing procedures that are likely to be associated with major postoperative surgical complications (e.g., bleeding) or major fluid shifts (e.g., extensive plastic surgery) should be admitted to the hospital overnight. Although autologous blood transfusions are used for extensive outpatient plastic surgery (e.g., reduction mammoplasty, liposuction), after lengthy procedures associated with excessive fluid shifts, patients should be admitted to an overnight (23-hour) recovery facility. Similarly, operative procedures requiring prolonged immobilization and parenteral opioid analgesic therapy are more ideally suited to a 23-hour stay. However, the availability of newer analgesic therapies (e.g., continuous local anesthetic infusions, nonparenteral opioid analgesic delivery systems), as well as ambulatory patient-controlled analgesic techniques (e.g., subcutaneous, intranasal, transcutaneous), is allowing more patients undergoing painful orthopedic procedures to be discharged home on the day of surgery.[35-37]

Duration of Surgery

The duration of surgery in the ambulatory setting was originally limited to procedures lasting less than 90 minutes because early investigators found that the operating and anesthesia times were strong predictors of postoperative complications (e.g., pain, emesis)[38] and delayed discharge,[25] as well as unanticipated admission to the hospital after ambulatory surgery.[11,38-40] However, surgical procedures lasting 3 to 4 hours are now routinely performed on an ambulatory basis.

Patient Characteristics

Originally, the majority of patients treated in ambulatory surgical facilities were classified as ASA physical status I or II. However, improved anesthesia and surgical care has allowed increasing numbers of medically stable ASA physical status III (and even some IV) patients to undergo operations away from conventional medical centers.[1] In a large, prospective outcome study by Warner and coworkers,[10] 24% of ambulatory surgical patients were ASA physical status III, and these patients had the same low incidence of morbidity as ASA I and II patients (Table 78-4). Other studies have shown that patients with preexisting medical conditions do not have an increased incidence of perioperative complications or unexpected admissions.[41] The comparable incidence of complications in outpatients of differing ASA status was attributed to prudent patient selection, careful preoperative evaluation, and close communication among surgeons, anesthesiologists, and primary care physicians.

The risk of complications can be minimized if preexisting medical conditions are stable for at least 3 months before the scheduled operation. Therefore, the ASA physical status should not be considered in isolation because the type of surgical procedure, the anesthetic technique, and a multitude of medical and social factors can also influence decisions regarding a patient's suitability for ambulatory surgery.[42] Even morbid obesity (body mass index >40 kg/m^2) is no longer considered an exclusionary criterion for day-case surgery.[43,44] However, morbidly obese patients with preexisting cardiovascular (e.g., hypertension, congestive heart failure, angina) and respiratory (e.g., asthma, chronic obstructive pulmonary disease) conditions had a higher incidence of perioperative morbidity than did healthy outpatients undergoing similar procedures on an ambulatory basis.[25] Elderly obese patients were more likely to experience natural oxygen desaturation and episodic airway obstruction after ambulatory surgery.[45] As expected, heavy smoking was associated with an increased risk of respiratory complications and postoperative wound infection in patients undergoing ambulatory surgery.[46]

Table 78-4 Relationship between American Society of Anesthesiologists Physical Status and Postoperative Morbidity and Mortality

ASA Physical Status	No. Patients (%)	Major Morbidity (No.)
I (healthy patient)	14,609 (32)	6
II (mild systemic disease)	19,614 (43)	17*
III (severe systemic disease with functional limitation)	10,867 (24)	8
IV (severe systemic disease, constant threat to life)	0	—
V (moribund, unlikely to survive 24 hr)	0	—

*A total of four deaths were reported within 30 days of the surgical procedure (two were related to motor vehicle accidents).
From Warner MA, Shields SE, Chute CG: Major morbidity and mortality within 1 month of ambulatory surgery and anesthesia. JAMA 270:1437, 1993. Copyright 1993, American Medical Association.

Yet, the presence of obstructive sleep apnea syndrome was not associated with an increased risk of unanticipated admission to the hospital.[16]

Susceptibility to Malignant Hyperthermia

MH-susceptible patients can be successfully managed with nontriggering anesthetics (e.g., local anesthesia) in the outpatient setting (see Chapter 37). The decision to admit a patient postoperatively should be based on clinical criteria because admission solely on the basis of MH susceptibility is no longer considered appropriate.[47] If the anesthesia and surgery were uneventful, MH-susceptible patients can be safely discharged home on the day of surgery. Patients at risk for MH and their families should be advised about the signs and symptoms of MH, in addition to the usual postoperative instructions.

Extremes of Age

Age alone should not be considered a deterrent in the selection of patients for ambulatory surgery (see Chapters 71 and 82). However, there is recent evidence to suggest that the rate of admission or death within 7 days of outpatient surgery increases with increased age.[48] Even the "elderly elderly" patient (>100 years) should not be denied ambulatory surgery solely on the basis of age.[49] In fact, elderly patients experience less postoperative pain, dizziness, and emetic symptoms than their younger counterparts.[50] A study found that elderly patients experienced less postoperative cognitive dysfunction and disorientation after ambulatory (versus inpatient surgery).[8] Nevertheless, elderly outpatients may experience a higher incidence of perioperative cardiovascular events, and recovery of fine motor skills may be slowed with increasing age. Furthermore, elderly outpatients may require a greater degree of supervision after discharge than their younger counterparts. Social factors, including lack of transportation, a responsible escort, and a caretaker at home, may make it difficult for some elderly patients to undergo ambulatory surgery procedures on a same-day basis.

At the other extreme, ex-premature infants (gestational age < 37 weeks) recovering from minor surgical procedures under general anesthesia have an increased risk for postoperative apnea. Controversy exists regarding the postconceptual age after which no further risk remains.[51] Most studies suggest that the risk is greatest in premature infants younger than 46 weeks' postconceptual age.[51,52] However, some authors have reported that the risk of apnea may persist until the 60th postconceptual week.[53] In addition, anemia (hematocrit < 30%) independently increases the risk of postoperative apnea in former preterm infants less than 60 weeks' postconceptual age.[54] Treatment with IV caffeine may prevent prolonged apnea and desaturation in this patient population.[55] There was no relationship between apnea and intraoperative use of opioid analgesics or muscle relaxants.[56]

Contraindications to Outpatient Surgery

Patients with the following conditions may be at increased risk for postoperative complications and should be offered the option of overnight hospitalization[24]:

1. Potentially life-threatening chronic illnesses (e.g., brittle diabetes, unstable angina, symptomatic asthma)
2. Morbid obesity complicated by symptomatic cardiorespiratory problems (e.g., angina, asthma)
3. Multiple chronic centrally active drug therapies (e.g., use of monoamine oxidase inhibitors such as pargyline and tranylcypromine) and/or active cocaine abuse
4. Ex-premature infants less than 60 weeks' postconceptual age requiring general endotracheal anesthesia
5. No responsible adult at home to care for the patient on the evening after surgery

Preoperative Assessment

Preoperative assessment of outpatients has become increasingly important because patients are presenting for ambulatory surgery with more complex medical conditions and may be taking multiple chronic medications (see Chapter 34). It is essential to develop an effective method of screening these patients preoperatively to avoid costly delays and last-minute cancellations.[5] Preoperative screening may be accomplished by means of a telephone interview by a trained nurse[57] or a visit to a preoperative evaluation clinic.[58,59] The use of a computerized questionnaire can also be a time-saving and efficient practice. Computerized questionnaires are more accurate in listing positive and negative historical information than a physician interview and can be used to guide preoperative laboratory testing.[60] Clinical studies suggest that these computerized questionnaires allow for more appropriate and cost-effective use of preoperative laboratory testing.

The use of a preoperative questionnaire along with a telephone screening interview was highly effective in reducing cancellations and surgical delays.[61,62] However, when the preoperative assessment is performed 1 to 2 weeks before surgery in a preadmission clinic, it was reported to provide a benefit for less than 10% of patients.[63] A trained nurse using a rule-based computer program in which the identified medical problems and abnormal laboratory findings were reviewed by an anesthesiologist was found to reduce cancellation from 5% to 2%.[64] It would appear that the quality of information obtained from the preanesthetic visit is improved by using computer-based standardized questionnaires.[65]

Preoperative Evaluation

The primary objective of the preoperative assessment is to identify patients who have concurrent medical problems requiring further diagnostic evaluation or active treatment before elective surgery. Patients with specific anesthetic concerns (e.g., difficult airway, active cardiac disease, MH susceptibility) and those at increased risk for perioperative anesthetic and surgical complications should be identified so that steps can be taken to prevent postoperative complications. Preexisting medical conditions that may be associated with adverse events include hypertension (e.g., perioperative cardiovascular events); obesity, asthma, and smoking (e.g., perioperative respiratory events); and gastroesophageal reflux disease (e.g., intubation-related events).[46,66] Of the three primary components of a preoperative assessment (i.e., history, physical examination, and laboratory testing), the patient's

medical history is clearly the most valuable.[67] Evaluations of medical consultations demonstrated that 86% of diagnoses depended entirely on the information obtained from the patient's history. A further 6% of diagnoses were discovered by careful physical examination, and only 8% were determined by additional laboratory investigations. Routine preoperative laboratory testing of patients before ambulatory surgery is unjustified and extremely wasteful of valuable health care resources.

For outpatients undergoing superficial surgical procedures (e.g., biopsy, dilatation and curettage, herniorrhaphy, arthroscopy, vein stripping), no laboratory tests appear to be indicated in males, and only a hemoglobin (or hematocrit) test is indicated for adult females of child-bearing age. Obviously, patients with chronic diseases (e.g., hypertension, diabetes) require additional laboratory studies (e.g., electrolytes, glucose). Patients with an unexplained hemoglobin concentration of less than 10 g/dL should be considered for further evaluation before elective outpatient surgery because a low hemoglobin level may be associated with diseases that could influence perioperative mortality and morbidity. Eliminating routine preoperative testing (even in elderly outpatients) will allow cost savings without compromising the safety or the quality of patient care.[68-71]

Preoperative assessment 1 to 2 weeks before surgery was found to reduce preoperative anxiety when compared with assessment on the evening before surgery.[72] In addition to the anesthesiologist's evaluation, the preoperative visit could be used by the nursing staff to assess, prepare, and educate the patient; by the facility's business office to perform a financial interview; and to familiarize the patient and family with the center's operating procedures. To avoid unexpected delays resulting from an incomplete assessment, all paperwork (including the consent form, history and physical examination, and laboratory test results) should be reviewed before the patient arrives for surgery. A well-planned and smooth-functioning ambulatory surgery program can yield many benefits to patients and their families, as well as to surgeons and nursing personnel. Appropriate patient preparation before the day of surgery can prevent unnecessary delays, absences ("no shows"), last-minute cancellations, and substandard perioperative care.

Preoperative Preparation

Optimal preoperative preparation of outpatients makes ambulatory surgery both safer and more acceptable for patients and the hospital staff (see Chapter 34). The preparation process is aimed at reducing the risks inherent in ambulatory surgery, improving patient outcome, and making the surgical experience more pleasant for the patient and their family. Simple procedures such as topical warming of an extremity before venous cannulation reduce both the time and number of attempts required.[72] Preoperative preparation should attempt to minimize patient anxiety using both pharmacologic (e.g., benzodiazepines) and nonpharmacologic (e.g., relaxation therapies) approaches. Patients should be encouraged to continue all their chronic medications up to the time that they arrive at the surgery center. Oral medications can be taken with a small amount of water up to 30 minutes before surgery. Practitioners need to be aware of the fact that an increasing number of outpatients are using nutraceuticals,[73] some of which may cause adverse effects during the perioperative period.[73]

Nonpharmacologic Preparation

The anticipation of undergoing anesthesia can cause psychological stress that is commonly manifested as acute anxiety. Preoperative anxiety has been shown to rise at least 1 week before surgery and return to normal levels in the postoperative period only after an uneventful recovery is ensured. The cause of patients' preoperative anxiety is multifactorial, but most commonly it is related to concerns about intraoperative awareness, not awaking after surgery, or postoperative pain and nausea. Not surprisingly, previous surgery reduces the degree of preoperative anxiety.[74] High levels of stress preoperatively are associated with slower recovery and greater analgesic and antiemetic requirements after surgery, but it can be effectively reduced by careful preoperative preparation (Fig. 78-2). Overall, well-informed patients tend to recover faster and experience less pain and fewer postoperative complications.

Nonpharmacologic preparation has many desirable characteristics. These methods are economic, lack undesirable side effects, and are associated with high patient acceptance. More than 40 years ago, Egbert and colleagues demonstrated that the anesthetist's preoperative visit was more effective than a sedative premedicant in relieving preoperative anxiety. Postoperative pain can also be reduced by preoperative educational programs. The timing of the preoperative interview is also important because anxiety is significantly decreased only when the interview takes place outside the operating room immediately before surgery.[75] Many centers have shown encouraging results with the use of instructional preoperative videotapes that offer a complete explanation of the events surrounding surgery.[76] Outpatients who listen to music before surgery reported significantly lower anxiety levels.[77] Self-hypnotic relaxation techniques have proved beneficial during invasive medical procedures.[78] Hypnosis and imagery may also have a positive effect in reducing pain and anxiety, as well as improving hemodynamic stability during the perioperative period.

The use of play-oriented preoperative teaching, books, pamphlets, and video programs are beneficial for pediatric patients.[79] Separation anxiety and postoperative behavioral changes (prominent in children 1 to 4 years of age) may be diminished when preparation programs are utilized. In the modern ambulatory surgery center, both psychological and pharmacologic means should be available to alleviate patients' anxiety and decrease postoperative morbidity.[80] Preoperative preparation should also include written and verbal instructions regarding arrival time and place, fasting instructions, and information concerning the postoperative course, effects of anesthetic drugs on driving and cognitive skills immediately after surgery, and the need for a responsible adult to care for the patient during the early postdischarge period (<24 hours).

Pharmacologic Preparation

The use of premedication in the outpatient setting has been a subject of considerable debate over the past 30 years. The primary indications for preoperative medication include anxiolysis, sedation, analgesia, amnesia, and prophylaxis against postoperative emesis and aspiration pneumonia.[81] Despite these well-recognized indications, benzodiazepine premedication is not routinely used at many ambulatory surgery facilities in the United States[1] because of concern that these drugs will prolong the recovery period. Interestingly, prospective studies have not found recovery to be prolonged after the use of appropriate doses of sedative

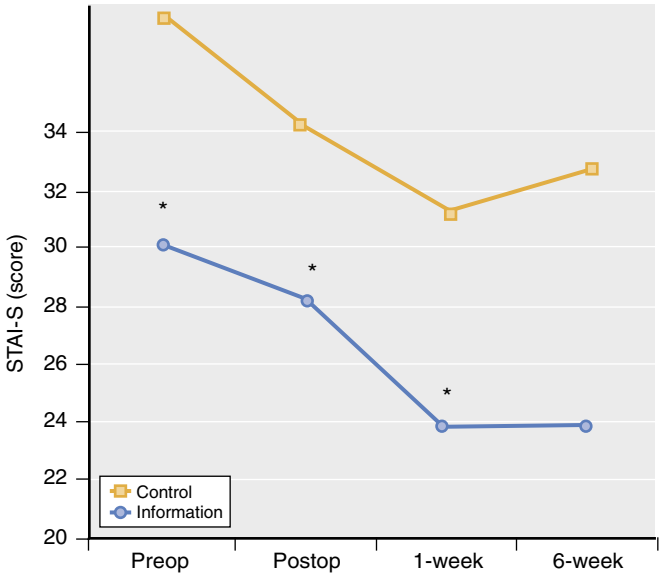

Figure 78-2 Preoperative psychological preparation reduces stress before and up to 1 week after surgery, as measured by the Spielberger state anxiety score. * = $P < .05$. (*Redrawn with modification from Wallace LM: Psychological preparation as a method of reducing the stress of surgery. J Hum Stress 10:62, 1984. Reprinted with permission of the Helen Dwight Reid Educational Foundation. Published by Heldref Publications, 1319 Eighteenth St, Washington, DC 20036-1802. Copyright 1984.*)

premedication in the outpatient setting (e.g., midazolam, 1-2 mg intravenously [IV]).[82,83] Van Vlymen and associates[84] found that premedication with a small dose of a benzodiazepine actually improved outcome in women undergoing needle-localized breast biopsies without delaying recovery. Midazolam premedication not only decreases preoperative anxiety but may also be associated with a reduction in postoperative pain.[85]

Anxiolysis and Sedation

Traditionally, the most widely used premedicants have been barbiturates and benzodiazepines. These drugs produce dose-related anxiolysis, sedation, and ultimately, unconsciousness (see Chapter 26). Barbiturates are not commonly used as premedicants in the outpatient setting because of residual sedation, which makes them less cost beneficial than nonbarbiturate sedative drugs (e.g., midazolam, propofol).[86] Methohexital and ketamine have been used for rectal premedication in children. However, side effects of ketamine (e.g., confusion, vivid dreams) are frequent unless this drug is combined with midazolam.[87] Melatonin has also been reported to produce sedation and anxiolysis comparable to oral midazolam when administered for premedication.[88]

Benzodiazepines

The amnesic and anxiolytic properties of small doses of benzodiazepines are also useful in the outpatient setting (Table 78-5). Oral diazepam, 0.1 mg/kg, given 60 to 90 minutes before surgery was found to reduce stress hormone levels after day-case surgery.[89] Diazepam was the most commonly used benzodiazepine; however, midazolam has become the drug of choice because its shorter elimination half-life and its anesthetic sparing effects and lack of significant side effects facilitate the recovery process after ambulatory surgery.[90-92] In addition to its well-known anxiolytic properties, midazolam may be effective in reducing postoperative nausea and improving patient satisfaction.[93] Although larger doses of midazolam are required when it is administered orally because of first-pass metabolism, it is a highly effective in both adults and children.[80,94] Midazolam (0.5 mg/kg PO) allowed children to be separated from their parents as early as 15 minutes after oral ingestion, without prolonging recovery even after brief surgical procedures.[81,94,95] Larger doses (1.0 mg/kg) of oral midazolam delay early recovery (emergence) but not discharge time after ambulatory surgery.[96] In geriatric patients, premedication with midazolam (0.5-1.0 mg IV) did not adversely affect mental and psychomotor recovery, even after brief ambulatory procedures.[97]

Temazepam and alprazolam also are effective oral premedicants for outpatient surgery.[94,98] Although oral triazolam can produce effective sedation and amnesia, it is less effective than diazepam or midazolam in decreasing preoperative anxiety. Lorazepam, because of its long duration of amnesia, is not recommended in the ambulatory setting. If a patient expresses significant anxiety during the preoperative interview, an oral benzodiazepine should be prescribed to be taken at home in the evening before or in the morning 1 to 2 hours before surgery or

Table 78-5 Use of Anxiolytic-Sedative Drugs for Outpatient Premedication

	Dosage Range	Onset (min)	Key Points
Benzodiazepines			
Midazolam	7.5-15 mg PO	15-30	Large first-pass effect
	5-7 mg IM	15-30	Water soluble, nonirritating
	1-2 mg IV	1-53	Rapid onset, excellent amnesia
Diazepam	5-10 mg PO	45-90	Long-acting metabolites
Temazepam	15-30 mg PO	15-40	Comparable anxiolysis to midazolam
Triazolam	0.125-0.25 mg PO	15-30	Prominent sedation
Lorazepam	1-2 mg PO	45-90	Prolonged amnestic effect
α2-Adrenergic Agonists			
Clonidine	0.1-0.3 mg PO	45-60	Prolonged sedative effect
Dexmedetomidine	50-70 μg IM	20-60	Bradycardia and hypotension
	50 μg IV	5-30	Reduced anesthetic/analgesic requirements

Modified from White PF: Ambulatory anesthesia and surgery: Past, present, and future. *In* White PF (ed): Ambulatory Anesthesia and Surgery. London, WB Saunders, 1997.

both. When significant anxiety develops after admission to the day surgery center, intravenous midazolam (1-3 mg IV) is the most useful drug.

α-Adrenergic Agonists

Premedication with α_2-adrenergic agonist drugs produce sedation and anxiolysis while also decreasing the heart rate and blood pressure during anesthesia and opioid requirements after surgery.[99] Oral clonidine, the prototypical α_2-agonist, has been successfully used for ambulatory premedication and may reduce intraoperative blood loss,[100] as well as the anesthetic and analgesic requirements. Dexmedetomidine is a more highly selective α_2-agonist that has a shorter duration of action than clonidine.[101] Because of its high potency and selective agonist action on α_2-receptors, dexmedetomidine may gain more widespread acceptance in outpatient anesthesia. Although the acute hemodynamic effects of this IV drug may limit its use for premedication, dexmedetomidine could prove to be a valuable adjunct during surgery because of its anesthetic and analgesic sparing effects and ability to decrease postoperative pain.[102]

When compared with oral midazolam, clonidine was less effective in reducing anxiety but produced greater anesthetic- and analgesic-sparing effects in children.[103,104] Interestingly, clonidine was also effective in decreasing emergence delirium after sevoflurane anesthesia.[105] In adults, adjunctive use of intravenous clonidine during general anesthesia reduced emetic symptoms after breast surgery.[106] Clonidine has also been found to facilitate glycemic control in type-2 diabetic patients[107] and reduce postoperative myocardial ischemia in patients with preexisting cardiac disease.[108]

β-Blockers

The role of β-adrenergic blockers appears to be increasing in ambulatory surgery because of their ability to control acute autonomic responses during surgery while minimizing the need for opioid analgesics.[109,110] Recent studies[110,111] have demonstrated improved postoperative pain control when esmolol is used as an adjuvant during ambulatory surgery. β-Blockers (e.g., atenolol, esmolol) suppress surgery-induced increases in circulating catecholamines and prevent untoward perioperative cardiovascular events in the elderly and patients with preexisting coronary artery disease undergoing noncardiac surgery.[112] Although labetalol has not been studied, it possesses both α-adrenergic and β-blocking properties and is highly effective in both the prevention and control of acute autonomic responses during ambulatory surgery procedures.

Preemptive (Preventative) Analgesia

Improving pain control after ambulatory surgery can accelerate normalization of activities of daily living and improve functionality.[113-115] Multimodal analgesic regimens involving the use of a combination of nonopioid analgesics to minimize the need for opioid analgesics after ambulatory surgery can optimize the recovery process and allow patients to resume normal activities more promptly after discharge home.[116] Although the value of preemptive analgesia has been questioned, the use of perioperative multimodal analgesia is helpful in facilitating a faster emergence from anesthesia and an earlier discharge.

Opioid (Narcotic) Analgesics

Use of opioid analgesics for premedication is not recommended unless the patient is experiencing acute pain (see Chapter 27). Opioid premedication can increase the incidence of PONV and urinary retention, which can contribute to a delayed discharge after ambulatory surgery.[82] Traditionally, fentanyl and its newer analogs have been given before induction of anesthesia because they can decrease the anesthetic requirement and minimize the hemodynamic response to airway stimulation and the surgical incision.[117] It is unclear whether the newer, shorter-acting fentanyl analogs (alfentanil and remifentanil) offer any significant advantages over the traditional compounds with respect to reducing perioperative side effects.[118-120] However, remifentanil may offer a significant advantage in situations in which rapid resumption of spontaneous ventilation is desirable.[121]

Nonopioid Analgesics

Controversy surrounds the preoperative use of the classic nonsteroidal anti-inflammatory drugs (NSAIDs) because of their side effect profile (e.g., antiplatelet effect) and limited efficacy in controlling acute postoperative pain.[122] Nevertheless, newer NSAIDs have proved to be valuable analgesic adjuvants as a result of their long-lasting opioid-sparing actions and lack of effect on platelet function. When administered as part of a balanced ("multimodal") analgesic technique in combination with local anesthetics and acetaminophen, NSAIDs can facilitate early recovery, decrease side effects, and reduce discharge times.[4,123] For many outpatient procedures, use of NSAIDs and local anesthetics for 2 to 3 additional days after surgery can eliminate the need for opioid analgesics postoperatively.[124] Ketorolac, a parenterally active NSAID, was more effective than acetaminophen with codeine in preventing pain after outpatient procedures in children.[125]

To achieve the optimal benefit of NSAIDs in the ambulatory setting, they should be administered on a "fixed" dosing schedule beginning in the preoperative period and extending into the postdischarge period.[126] To minimize the potential for operative site bleeding, as well as gastric mucosal and renal tubal toxicity, the more selective cyclooxygenase-2 (COX-2) inhibitors can be used as alternatives to the nonselective NSAIDs during the perioperative period. Perioperative celecoxib (400 mg) reduces pain and the opioid analgesic requirement in the postoperative period, thereby leading to improved patient satisfaction with the quality of recovery after ambulatory surgery.[127-129] The addition of dexamethasone to a COX-2 inhibitor leads to a further improvement in postoperative analgesia.[130] Gabapentin has also shown to offer a significant analgesic benefit in the ambulatory setting when administered for premedication.[131]

Prevention of Nausea and Vomiting

PONV remains a common problem after general anesthesia and contributes to patient dissatisfaction with their ambulatory surgery experience (see Chapter 86).[1,132] When patients undergoing a preanesthetic evaluation were asked which postoperative side effects were of greatest concern, PONV accounted for 49% of the responses.[132] Over 70% of patients considered avoidance of PONV to be very important, and patients were willing to pay a significant amount of money out-of-pocket to avoid PONV.[133] Emetic symptoms can delay discharge and result in unplanned overnight hospital admission.[11,25,134,135] The type of surgery, choice of anesthetic technique, and use of opioid analgesics can all influence the incidence of PONV (Table 78-6). Additional factors influence the incidence of PONV and include preexisting medical conditions (e.g., motion sickness), gender, smoking status, preg-

Table 78-6 Common Factors Associated with Nausea, Vomiting, and Retching during the Perioperative Period

Patient-Related Factors
Age
Gender
Preexisting diseases (e.g., diabetes)
History of motion sickness or postoperative nausea and vomiting
Smoking history
Level of anxiety
Intercurrent illness (e.g., viral infection, pancreatic disease)
Anesthesia-Related Factors
Premedication
Opioid analgesics
Induction and maintenance anesthetics
Reversal (antagonist) drugs
Gastric distention
Inadequate hydration
Residual sympathectomy
Surgery-Related Factors
Operative procedure
Length of surgery
Blood in the gastrointestinal tract
Forcing oral intake
Opioid analgesics
Premature ambulation (postural hypotension)
Pain

Data from Watcha MF, White PF: Postoperative nausea and vomiting: Its etiology, treatment, and prevention. Anesthesiology 77:162, 1992.

nancy, phase of the menstrual cycle, preoperative hydration status, and postoperative hypotension (due to residual sympathectomy, premature ambulation).[136] The incidence of emesis is low in infants, gradually increases toward adulthood, and then decreases again at advanced age (e.g., the elderly). The phase of the menstrual cycle may influence the incidence of PONV, with the highest incidence reported during the ovulatory and luteal phases of the woman's cycle.

A variety of risk scoring systems have been developed in an attempt to improve the use of antiemetic therapies.[137] These scores and the treatments are more fully discussed in Chapter 86, although studies specific to the outpatient setting are described here. Although the use of propofol for induction and maintenance of anesthesia significantly reduces the incidence of PONV after ambulatory surgery,[138,139] the cost-effective combination of droperidol, dexamethasone, and ondansetron is increasingly being used for antiemetic prophylaxis of outpatients undergoing a wide variety of surgery procedures.[140]

Butyrophenones

Droperidol is a butyrophenone neuroleptic drug with antiemetic properties as a result of its antagonistic effects at central dopamine receptors. Larger doses of droperidol (>20 μg/kg) enhance postoperative sedation and may prolong recovery and discharge in ambulatory surgical patients without improving on its antiemetic efficacy. In children undergoing strabismus surgery, droperidol, 80 μg/kg, was most effective in reducing emetics without prolonging time to discharge.[141] However, larger doses of droperidol can produce unwanted side effects, including dyskinesia, restlessness, and dysphoric reactions. Since the effect of droperidol in prolonging the QT interval appears to be dose-related, the lowest effective dose should be administered after induction of anesthesia.[141,142]

Phenothiazines

The antiemetic action of phenothiazines also results from their ability to block dopamine receptors in the chemoreceptor trigger zone of the brain.[143] Prochlorperazine suppositories are frequently used for treating PONV occurring after discharge. Premedication with phenothiazines can produce intraoperative hypotension along with significant residual sedation after surgery. In addition, these compounds may produce extrapyramidal effects ranging from restlessness to oculogyric crisis.[141] Therefore, this class of antiemetic is rarely used for prophylaxis in the outpatient setting.

Anticholinergics

Anticholinergic drugs (e.g., atropine, glycopyrrolate, and scopolamine) have traditionally been used for their antisialagogue and vagolytic properties. However, transdermal scopolamine (TDS), a centrally active anticholinergic, with potent anti–motion sickness properties has recently been found to be comparable to both droperidol and ondansetron when used for antiemetic prophylaxis in the ambulatory setting.[144] Preoperative placement of a TDS patch can reduce the incidence of severe PONV in both the early and late postoperative periods. However, when administered before outpatient gynecologic laparoscopy, transdermal scopolamine was associated with a higher incidence of adverse effects (including dry mouth, somnolence, mydriasis, and dizziness).

Antihistamines

Dimenhydrinate and hydroxyzine are antihistaminic compounds that also act on the central vomiting center and vestibular pathways to prevent PONV. These compounds are particularly useful for the prophylaxis and treatment of motion-induced emesis in outpatients undergoing middle ear and strabismus surgery.[145] A long-acting formulation of dimenhydrinate compared favorably with droperidol in reducing vomiting for up to 24 hours without delaying discharge from the ambulatory facility.[146]

Serotonin Antagonists

Given the important role of 5-hydroxytryptamine (5-HT) in the pathophysiology of drug-induced emesis, it is hardly surprising to learn that specific 5-HT antagonists are highly effective in the treatment and prevention of PONV. Ondansetron, granisetron, dolasetron, and palonsetron are all highly selective 5-HT_3 receptor antagonists that lack the sedative, dysphoric, or extrapyramidal effects of other commonly used antiemetics.[147-150] However, these compounds appear to produce headache and may be less effective in preventing nausea than other antiemetic drugs. Palonsetron is a 5-HT3 antagonist with a long half-life and a high receptor binding affinity[151] that may prove to be advantageous in the postdischarge period.

Neurokinin-1 Antagonists

The neurokinin-1 (NK-1) antagonists are effective in both the treatment[152] and prevention[153] of PONV. Preliminary studies suggest that NK-1 antagonists may have longer-lasting antiemetic properties than ondansetron.[152,153] In addition, these compounds may act synergistically with 5-HT_3 antagonists.[153] Premedication with oral aprepitant was comparable to IV ondansetron in preventing PONV in the early postoperative period and offered

an advantage in the postdischarge period.[154,155] Studies examining the cost-benefit of using an NK-1 antagonist as part of a multimodal antiemetic prophylactic regimen are clearly needed.[156]

Nonpharmacologic Techniques

Recent studies suggest that nontraditional therapies may be useful additions to the traditional antiemetic drug therapies.[157,159] Acupuncture, acupressure, and transcutaneous electrical nerve stimulation at the P-6 acupoint have all been used for the prevention of PONV.[136,158-161] Korean hand acupressure has been shown to be superior to ondansetron in reducing PONV in both adults and children.[158,162-164] In outpatients undergoing laparoscopic cholecystectomy procedures,[165] acupressure compared favorably with ondansetron (4 mg IV) in preventing PONV. Transcutaneous electrical acupoint stimulation at the P-6 acupoint with the ReliefBand device compared favorably to ondansetron, and the combination was more effective than either modality alone.[161] Compared with antiemetic drugs, most studies have suggested that the use of electro-acupoint stimulation is more effective in preventing nausea than vomiting (or emesis).[161,166,167]

Prevention of Aspiration Pneumonitis

Outpatients may have an increased risk of aspiration based on the observation that a larger percentage of patients had a residual gastric volume greater than 25 mL with a pH less than 2.5. However, carefully controlled studies have found no increased risk of aspiration in "fasted" outpatients (versus inpatients) undergoing elective surgery. Therefore, routine prophylaxis for acid aspiration is no longer recommended. However, outpatients with predisposing risk factors for pulmonary aspiration (i.e., pregnancy, scleroderma, hiatal hernia, nasogastric tubes, severe diabetics, morbid obesity) may benefit from the use of an H_2-receptor blocking drug or proton pump inhibitor in the preoperative period.

H_2-Receptor Antagonists and Proton Pump Inhibitors

H_2-receptor antagonists are effective in increasing gastric pH and decreasing gastric volume by reducing gastric acid secretion. Ranitidine offers an advantage over cimetidine because of a more prolonged period of protection and fewer side effects. When compared with fasted patients who did not receive ranitidine, patients who received oral fluids in combination with ranitidine 2 to 3 hours before induction of anesthesia had lower residual gastric volumes and higher gastric pH values and were less thirsty.[168,169] The use of effective doses of metoclopramide in combination with an H_2-receptor blocking drug has been advocated to decrease postoperative emesis and reduce the potential risk for aspiration pneumonitis in high-risk surgical populations (e.g., diabetics, the morbidly obese). Other studies have failed to demonstrate a significant advantage of this drug combination over an H_2-receptor antagonist alone. Premedication with the rapid-acting proton pump inhibitor pantoprazole (40 mg IV) was less effective than use of ranitidine (50 mg IV) in reducing gastric volume and increasing pH.[170]

NPO Guidelines

Prolonged fasting does not guarantee an empty stomach at the time of induction. Therefore, several investigators have questioned the value of even a 4- to 5-hour fast before elective surgery.[168,171-173] Due to short half-life of clear fluids in the stomach (10-20 minutes), residual gastric volume after 2 hours is less in patients ingesting small amounts of clear fluids than in fasted patients.[174] After an overnight fast, 50% and 44% of outpatients complained of moderate-to-severe hunger and thirst, respectively. More importantly, 14% of young female outpatients arriving at the operating room in the early afternoon after an overnight fast had a serum glucose concentration less than 45 mg/dL.[175] Drinking 150 mL of water 2 hours before surgery significantly decreased the severity of thirst without increasing gastric volume in fasted outpatients.[176] Furthermore, the ingestion of 150 mL of either coffee or orange juice 2 to 3 hours before induction of anesthesia had no significant effect on residual gastric volume or pH even in obese adults.[176,177] Similarly, preoperative ingestion of apple juice, 3 mL/kg, decreased gastric volume, thirst, and hunger in children and had no adverse effect on gastric contents.[178]

Arbitrary restrictions prohibiting outpatients from drinking fluids on the day of surgery are completely unwarranted. A national survey in the United States demonstrated that 69% of anesthesiologists had changed their NPO guidelines to allow the ingestion of clear fluids for children and 41% had changed their guidelines for adults.[179] Unless outpatients have delayed gastric emptying (e.g., diabetics), the requirement for a prolonged fast is not justified. Importantly, adequate hydration (e.g., allowing oral intake of clear liquids up to 2 to 3 hours before surgery and/or IV hydration before induction of anesthesia) is associated with a decreased incidence of postoperative side effects, including pain, dizziness, drowsiness, thirst, and nausea (Fig. 78-3).[38,180] Several recent studies[181-183] have confirmed the importance of ensuring adequate hydration. Liberal (versus restrictive) fluid administration during laparoscopic surgery also led to improved patient outcomes. Preoperative administration of glucose-containing fluids prevents postoperative insulin resistance and attenuates the catabolic responses to surgery while replacing fluid deficits.[184,185] However, effects of glucose-containing solutions on clinical outcomes including the length of hospital stay, incidence of PONV, muscle strength, and subjective well-being remains controversial.[186,187]

Basic Anesthetic Techniques

Quality, safety, efficiency, and the cost of drugs and equipment are all important considerations in choosing an anesthetic technique for ambulatory surgery. The ideal outpatient anesthetic should have a rapid and smooth onset of action, produce intraoperative amnesia and analgesia, provide optimal surgical conditions and adequate muscle relaxation with a short recovery period, and have no adverse effects in the postdischarge period. Ambulatory surgery requires the same basic equipment as inpatient surgery for delivery of anesthetic drugs, monitoring, and resuscitation. Standard intraoperative monitoring equipment for outpatient operations should include an electrocardiogram, blood pressure cuff, temperature probe, pulse oximeter, and capnograph. If nondepolarizing muscle relaxants are used, a neuromuscular monitor should also be available. The availability of a cerebral monitor can be useful for patients with a history of intraoperative recall and for improving the titration of anesthetic drugs, thereby facilitating a faster emergence from anesthesia.[188]

The choice of anesthetic technique depends on both surgical and patient factors. For many ambulatory procedures, general anesthesia remains the most popular technique with both patients

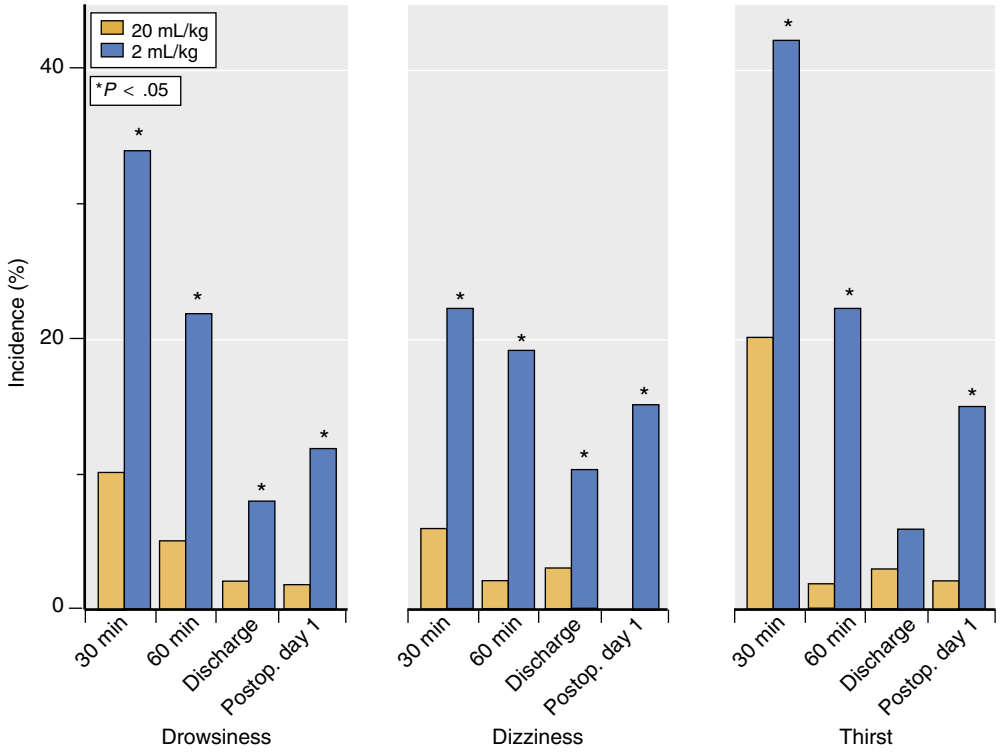

Figure 78-3 Preoperative hydration of 20-mL/kg versus 2-mL/kg decreases in postoperative morbidity in outpatients. (*Redrawn with modification from Yogendran S, Asokumar B, Cheng DC, et al: A prospective randomized double-blinded study of the effect of intravenous fluid therapy on adverse outcomes on outpatient surgery. Anesth Analg 80:682, 1995.*)

and surgeons despite the well-known advantages of local and regional anesthetic techniques. Although spinal and epidural anesthesia (i.e., central neuraxis blockade) has traditionally been used for lower extremity and abdominal-perineal procedures, its use in the ambulatory setting can delay discharge because of residual motor and sympathetic blockade. Local anesthesia and peripheral nerve blocks facilitate the recovery process by reducing postoperative pain and minimizing the need for opioid analgesics. Therefore, an increasing number of ambulatory cases are being performed using local anesthetic infiltration and/or nerve blocks in combination with intravenous sedation-analgesia (so-called monitored anesthesia care [MAC]). Although there is no single ideal anesthetic drug or technique for outpatients, a knowledge of the options available for each type of operation is critically important to produce the desired surgical conditions with an optimal fast-track recovery (Table 78-7).

General Anesthesia

The ability to deliver a safe and cost-effective general anesthetic with minimal side effects and rapid recovery is critical in a busy outpatient surgery unit. Despite a higher incidence of side effects than local or regional anesthesia, general anesthesia remains the most widely used anesthetic technique for ambulatory surgery. Effective use of ancillary equipment (e.g., protective padding, heated airway humidifiers,[189] blankets, forced air warmers,[190] passive heat and moisture exchangers, minimally invasive airway devices) will enhance patient comfort after general anesthesia. For example, devices that heat and humidify insufflation gases may improve maintenance of core body temperature while reducing pain after laparoscopic surgery.[191] Using a forced air warming device with standard cloth hospital blankets was found to be a cost-effective alternative to commercial forced air heating blankets in maintaining body temperature during surgery.[192] However, for ambulatory procedures lasting less than 90 minutes, forced warming devices are unlikely to be cost effective.[190]

Tracheal intubation causes a more frequent incidence of postoperative airway-related complaints, including sore throat, croup, and hoarseness than a facemask or laryngeal mask airway (LMA) (see Chapter 50). Most outpatients undergoing superficial procedures under general anesthesia do not require tracheal intubation unless they are at an increased risk for aspiration. The LMA device was introduced in 1983 as an alternative to tracheal intubation and the face mask for airway management. When compared with a facemask and oral airway, patients with an LMA had fewer desaturation episodes, fewer intraoperative airway manipulations, and fewer difficulties in maintaining a patent airway.[193] The incidence of postoperative sore throat after ambulatory surgery was 18% with an LMA compared with 45% with a tracheal tube and 3% with a facemask.[194] The LMA also frees the anesthesiologist's hands for record keeping, monitoring, and drug administration and avoids hand fatigue.

The LMA can be easily positioned without direct visualization or neuromuscular blocking drugs, and patients can ventilate spontaneously throughout the procedure if muscle relaxants are not needed.[195] Although desflurane is more pungent than sevoflurane or isoflurane, the LMA is equally well tolerated during the maintenance period with all volatile anesthetics.[196] However, coughing is more frequent with desflurane during the emergence

Table 78-7 Criteria Used to Determine Fast-Track Eligibility after Ambulatory Anesthesia

Criteria	Score
Level of Consciousness	
Awake and oriented	2
Arousable with minimal stimulation	1
Responsive only to tactile stimulation	0
Physical Activity	
Able to move all extremities on command	2
Some weakness in movement of the extremities	1
Unable to voluntarily move the extremities	0
Hemodynamic Stability	
Blood pressure < 15% of the baseline MAP value	2
Blood pressure between 15% and 30% of the baseline MAP value	1
Blood pressure > 30% below the baseline MAP value	0
Respiratory Stability	
Able to breathe deeply	2
Tachypnea with good cough	1
Dyspneic with weak cough	0
Oxygen Saturation Status	
Maintains value > 90% on room air	2
Requires supplemental oxygen (nasal prongs)	1
Saturation < 90% with supplemental oxygen	0
Postoperative Pain Assessment	
None or mild discomfort	2
Moderate to severe pain controlled with IV analgesics	1
Persistent severe pain	0
Postoperative Emetic Symptoms	
None or mild nausea with no active vomiting	2
Transient vomiting or retching	1
Persistent moderate to severe nausea and vomiting	0
Total score	14

A score over 12 with no individual score less than 1 is required for fast-tracking.
MAP, mean arterial pressure.
From White PF, Song D: New criteria for fast-tracking after outpatient anesthesia: A comparison with the modified Aldrete's scoring system. Anesth Analg 88:1069, 1999.

period.[197] Use of an LMA in children with a recent upper airway infection was also associated with increased coughing, laryngospasm, and oxygen desaturation.[198] When compared with tracheal intubation, insertion of the LMA causes minimal cardiovascular responses and is better tolerated at lighter levels of anesthesia. The incidence of sore throat is also reduced when an LMA is used as an alternative to a tracheal tube.[199] In the ambulatory setting, LMA devices can be re-used up to 200 times,[200] thus making the LMA a cost-effective alternative to other airway devices. The LMA does not completely protect the patient from having foreign material introduced into the airway and should not be used in patients at high risk of aspiration. If positive airway pressure is required for maintaining the airway or assisting ventilation, the risk of gastric dilatation and subsequent aspiration may be increased.[201] A variety of supraglottic devices are available as alternatives to the LMA (e.g., cuffed oropharyngeal airway [COPA]). Even though these devices are easy to insert after induction without muscle relaxants, their ability to maintain an obstruction-free airway is less adequate than other currently used airway devices.[202] Although supraglottic airway devices have been used in paralyzed patients undergoing laparoscopic surgery,[203,204] most practitioners in North America still prefer tracheal intubation in these situations to minimize the risk of gastric distention and aspiration for patients in the Trendelenburg position.

Anesthetic Drugs

Induction of general anesthesia is typically accomplished with a rapid-acting intravenous anesthetic (see Chapter 26). Propofol has replaced the barbiturates for induction of anesthesia in the ambulatory setting because of its favorable recovery profile.[205] However, the most popular technique for maintenance of anesthesia is a combination of a volatile anesthetic with or without nitrous oxide. The extremely low solubility of nitrous oxide and the newer volatile anesthetics (i.e., sevoflurane and desflurane) contributes to a more rapid recovery from general anesthesia. Although nitrous oxide can produce emetic symptoms, its clinical importance is questionable because nitrous oxide's anesthetic and analgesic-sparing effects offset its emetogenic potential.[206-209] Total intravenous anesthesia (TIVA) utilizing a combination of propofol and remifentanil (or alfentanil) has become extremely popular outside North America owing in large part to the availability of target-controlled, computer-based drug delivery symptoms.[210] Studies suggest that TIVA is as effective as spinal anesthesia for ambulatory surgery with the advantage of earlier home readiness.[211] When compared with a target-controlled infusion of propofol for maintenance of anesthesia, the use of desflurane or sevoflurane produced similar anesthetic conditions with shorter emergence times and lower drug costs.[212-215]

Barbiturates

Thiopental (3 to 6 mg/kg) was the prototypical intravenous induction drug because of its rapid onset and relatively short duration of hypnotic action (see Chapter 26). However, thiopental can impair fine motor skills for several hours after surgery and can produce a "hangover" effect.[216] Methohexital is associated with shorter emergence times, but complete recovery of fine motor skills may still require 2 to 4 hours after an induction dose.[217] When compared with thiopental, methohexital is associated with a higher incidence of pain on injection, involuntary muscle movement, and hiccoughing. Although propofol is associated with a faster emergence from anesthesia and a lower incidence of PONV than methohexital when used for both induction and maintenance of general anesthesia,[205] the barbiturate compared favorably with propofol when used for induction only in procedures lasting longer than 30 minutes.[218]

Benzodiazepines

Although midazolam (0.2 to 0.4 mg/kg IV) has been used for induction of anesthesia in outpatients, its onset of action is slower and recovery is prolonged in comparison to the barbiturate compounds and propofol.[219] When combined with nitrous oxide and a potent opioid analgesic, lower doses of midazolam (0.1-0.15 mg/kg IV) can be used to induce general anesthesia. If midazolam is used for induction and flumazenil, a specific benzodiazepine antagonist, is administered at the end of surgery, prompt recovery can be achieved after outpatient surgery.[220] Yet when compared with propofol, recovery after flumazenil antagonism of midazolam anesthesia offered no clinically significant advantages. Recurrence of sedation is a concern when flumazenil is used to facilitate emergence from anesthesia.

Etomidate

Etomidate (0.2 to 0.3 mg/kg) has also been used for induction and maintenance (1 to 3 mg/min) of general anesthesia during short outpatient procedures.[221] Recovery tends to be faster than after thiopental and compares favorably with methohexital. Disadvantages of etomidate include pain on injection, a high incidence of PONV, myoclonic movements, and transient suppression of adrenal steroidogenesis.[221,222] Given its side effect profile, the use of etomidate is restricted to clinical situations in which its hemodynamic stability offers a distinctive advantage over the other available induction drugs (e.g., elderly outpatients with clinically significant coronary artery or cerebrovascular disease).

Ketamine

Ketamine is a unique sedative-analgesic that can be used for both induction and maintenance of general anesthesia.[223] However, ketamine compares unfavorably with both the barbiturates and propofol for minor surgical procedures because of its prominent psychomimetic effects and higher incidence of PONV during the early postoperative period.[224] Use of the more potent S(+)-isomer of ketamine may decrease some of the adverse effects associated with the racemic mixture in the ambulatory setting.[87,225] Premedication with a benzodiazepine (e.g., midazolam, 0.05 mg/kg IV) and/or concomitant administration of propofol decreases the incidence of ketamine-induced emergence reactions.[223] Smaller doses of ketamine (10 to 20 mg IV) have been used as an alternative to potent opioid analgesics during induction of anesthesia with propofol,[226,227] as well as for sedation-analgesia in combination with propofol.[228] Furthermore, adjunctive use of 75-150 µg/kg intravenously during ambulatory surgery produced an opioid-sparing effect after painful orthopedic procedures.[229,230]

Propofol

Propofol is an intravenous anesthetic with an extremely high metabolic clearance rate (see Chapter 26).[231] Recovery after propofol anesthesia is superior to that from all other intravenous anesthetics in the outpatient setting.[232] Although propofol is more costly than the barbiturate anesthetics, the use of propofol may contribute to significant savings because of decreased recovery costs.[81] Recovery after induction of anesthesia with propofol is faster than with the barbiturate compounds, irrespective of the maintenance anesthetic (Fig. 78-4).[135,217,233] When compared with methohexital, use of propofol was associated with fewer perioperative side effects (e.g., hiccoughs, nausea, and vomiting) and faster overall recovery times.[205] The faster intermediate recovery with propofol may also yield savings with respect to nursing costs (e.g., less overtime).

The use of propofol is associated with less PONV and a decreased requirement for antiemetic medications.[205,234-237] When propofol was administered in subhypnotic doses (10-20 mg IV) to treat PONV, 81% of patients showed improvement compared with only 35% in the control group.[238] Unfortunately, 28% of patients experienced a relapse of their symptoms within 30 minutes. Small doses of propofol administered after a volatile anesthetic can reduce emesis in the early postoperative period.[239] Subhypnotic concentrations of propofol can produce other central effects, including perioperative mood alterations.[240] Patients emerging from propofol anesthesia were more likely to exhibit sensation-seeking tendencies (e.g., adventurous, daring, energetic) and to report feeling elated or even euphoric. IV administration of propofol is associated with a high incidence of venous pain and discomfort. Administration of lidocaine (40 mg IV) immediately before propofol injection (or mixed with propofol) reduces the incidence and severity of pain when it is injected into small hand veins.[241] Use of a bisulfite-containing formulation of propofol may also be associated with less pain on injection.[242] On the other hand, the low lipid formulation of propofol (Ampofol) is associated with more pain on injection.[243]

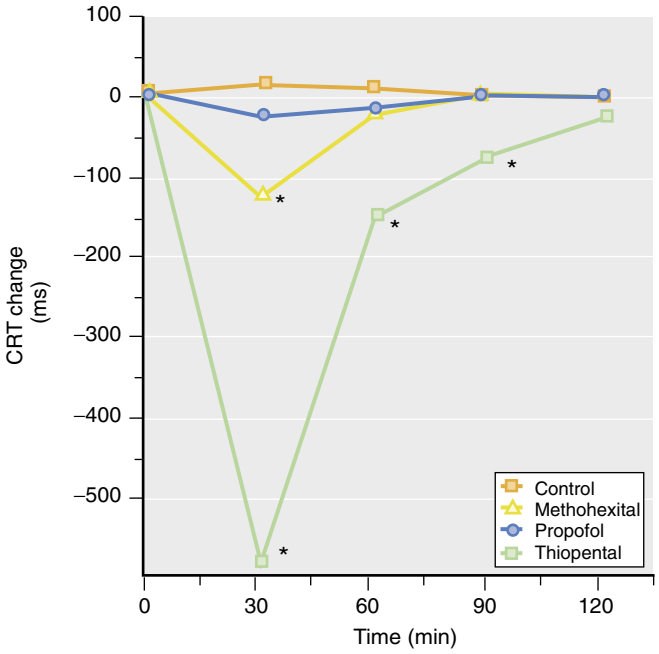

Figure 78-4 Comparison of mean changes in choice reaction time (CRT) postoperatively in untreated controls and outpatients who received thiopental, methohexital, or propofol for induction of anesthesia. * = $P < .5$. (*Redrawn with modification from Mackenzie N, Grant IS: Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anaesthesia in day cases. Br J Anaesth 57:725, 1985.*)

Inhaled Anesthetics

Volatile anesthetics are most commonly used for maintenance of ambulatory anesthesia (see Chapters 20, 21, 24, 25). Changes in the depth of anesthesia can be achieved readily because of the rapid uptake and elimination of these anesthetics. The rapid elimination of anesthetic vapors also provides for fast recovery and potentially earlier discharge from the outpatient facility. Although a similar spectrum of pharmacologic activity is produced by all of the available volatile anesthetics, halothane and isoflurane have largely been replaced by the less soluble sevoflurane and desflurane because of their superior recovery profiles. Studies involving pediatric patients have reported that sevoflurane (versus halothane) is associated with a higher incidence of postoperative complications (e.g., emergence delirium).[244,245] A single dose of propofol (1 mg/kg) at the end of surgery is effective in preventing agitation during emergence from sevoflurane without delaying discharge in children.[244]

Sevoflurane is widely used for inhaled induction in the outpatient setting because of its lack of pungency and more favorable recovery profile compared with halothane (Table 78-8).[1,246] However, when desflurane is used for maintenance of anesthesia, emergence (awakening) was significantly faster than with sevoflurane or other available agents (Table 78-9).[247-251] However,

Table 78-8 Recovery Profiles and Postoperative Side-Effects of Three Different Maintenance Anesthetic Techniques for Gynecologic Laparoscopic Surgery

	Propofol	Sevoflurane	Desflurane
Age (yr)	29 ± 7	30 ± 7	31 ± 8
Weight (kg)	69 ± 11	70 ± 11	71 ± 13
Aldrete score of 10 (min)	21 ± 14	13 ± 5*	12 ± 6*
Awakening time (min)	8 ± 4	5 ± 3*	5 ± 4*
Orientation time (min)	13 ± 6	9 ± 4*	9 ± 5*
Fast-track eligibility [n (%)]	7 (41)	13 (77)*	16 (94)*
Actually fast-tracked [n (%)]	6 (35)	9 (53)	8 (47)
Postoperative side effects			
Nausea/vomiting (%)	0/0	6/0	18/6
Pain [n (%)]	13 (77)	11 (65)	7 (41)*
Time to home readiness (min)	131 ± 48	116 ± 13	114 ± 51
Patient satisfaction (1-100)	94 ± 7	93 ± 10	92 ± 9

*$P < .05$; significantly different from the propofol group.
From Coloma M, Zhou T, White PF, Forestner JE: Fast-tracking after outpatient laparoscopy: Reasons for failure after propofol, sevoflurane and desflurane anesthesia. Anesth Analg 93:112, 2001.

Table 78-9 Effect of the Maintenance Anesthetic Drug on the Fast-Track Eligibility of Geriatric Patients Undergoing Brief Surgical Procedures

	Propofol	Isoflurane	Desflurane
Age (yr)	74 ± 5	73 ± 7	75 ± 67
Weight (kg)	74 ± 14	73 ± 11	74 ± 14
Surgical time (min)	22 ± 11	29 ± 13	24 ± 10
Anesthesia time (min)	47 ± 14	53 ± 15	48 ± 13
Emergence time (min)	10 ± 4	9 ± 3	7 ± 3
Orientation time (min)	11 ± 4	11 ± 3	9 ± 3
Fast-track eligible (%)	44	43	73*
Fast-track score of 14 (min)	33 ± 25	44 ± 36	22 ± 23*
Nursing interventions (n)	11	21	7*

*$P < .05$ vs propofol.
From Fredman B, Sheffer O, Zohar E, et al: Fast-track eligibility of geriatric patients undergoing short urologic surgery procedures. Anesth Analg 94:560, 2002.

intermediate and late recovery after sevoflurane and propofol is similar to that after desflurane (Fig. 78-5).[252] Compared with the volatile anesthetics, propofol anesthesia offered the advantage of a lower incidence of PONV (Fig. 78-6).[252,253]

Early comparative studies of propofol, sevoflurane, and desflurane were performed before the introduction of fast-track recovery paradigms involving the routine use of multimodal analgesic and antiemetic therapies for minimizing pain and emesis, respectively. As a result of its extremely low tissue solubility, desflurane is associated with the most rapid recovery of both cognitive and psychomotor function.[253-257] In morbidly obese outpatients, both emergence and intermediate recovery times were consistently more rapid after desflurane than after propofol.[258] In addition, desflurane was associated with better postural control than propofol in the early recovery period.[259] Desflurane can produce significant autonomic stimulation when administered at high inspired concentrations,[255,256,260] and its pungency precludes its use for routine induction of anesthesia.[261] However, sevoflurane's impressive lack of airway irritation makes it a very useful alternative to propofol for induction of anesthesia in both adults and children.[262-265] In the elderly, induction with sevoflurane was also associated with better hemodynamic stability compared with induction with propofol.[266]

Volatile anesthetics are associated with a more frequent incidence of vomiting in the early recovery period than propofol-based anesthetic techniques.[15,267] However, no difference in emesis was observed in the later recovery period because delayed (post-discharge) PONV is most commonly associated with oral opioid-containing analgesics. From a cost-minimization point of view, maintenance with a volatile anesthetic compares favorably with a propofol-opioid (i.e., TIVA) technique.[211] The use of nitrous oxide as an adjuvant during outpatient anesthesia significantly reduces the requirements for intravenous and volatile anesthetics and opioid analgesics during the maintenance period. Therefore,

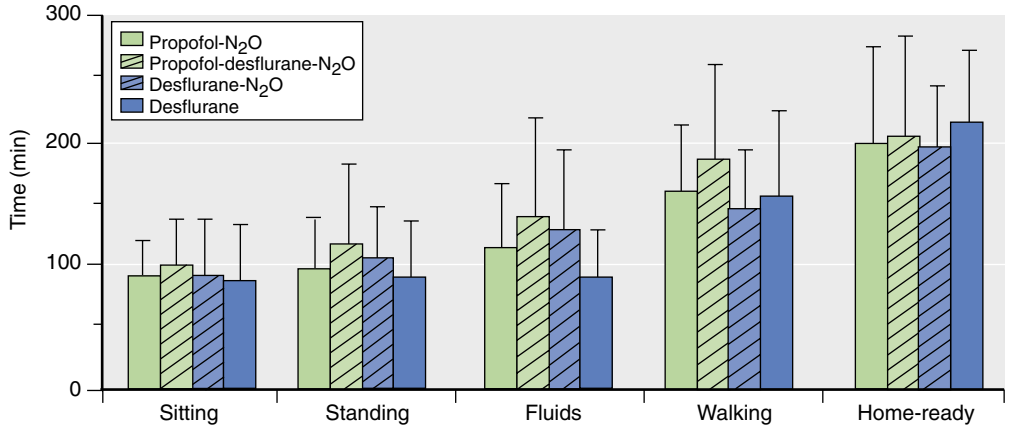

Figure 78-5 Intermediate recovery after propofol, desflurane, and propofol-desflurane anesthesia. (*Redrawn from Van Hemelrijck, J, Smith I, White PF: Use of desflurane for outpatient anesthesia: A comparison with propofol and nitrous oxide. Anesthesiology 75: 197, 1991.*)

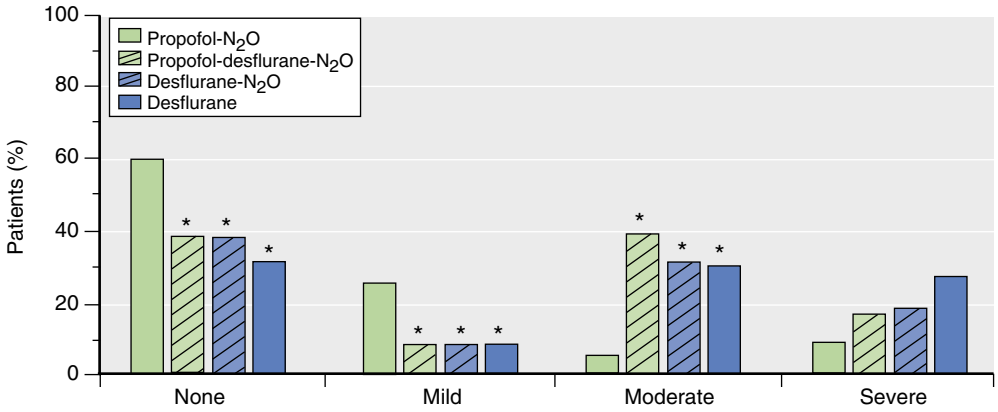

Figure 78-6 Postoperative nausea after propofol, desflurane, and propofol-desflurane anesthesia. (*Redrawn from Van Hemelrijck, J, Smith I, White PF: Use of desflurane for outpatient anesthesia: A comparison with propofol and nitrous oxide. Anesthesiology 75: 197, 1991.*)

recovery is faster and the cost of anesthesia is reduced when nitrous oxide is used as an adjuvant.[267,268]

Opioid Analgesics

Opioid compounds are frequently administered during anesthesia to suppress autonomic responses to tracheal intubation and painful (noxious) surgical stimuli (see Chapter 27). Opioids can also reduce the dosage requirements for sedative-hypnotic and volatile anesthetic drugs, thereby decreasing recovery times. Potent opioid analgesics have been shown to decrease the incidence of pain on injection and involuntary motor activity associated with intravenous methohexital, etomidate, and propofol. Fentanyl also reduces tachycardia observed during inhalational induction with desflurane and decreases emergence agitation after sevoflurane.[269]

Small doses of potent opioid analgesics (e.g., fentanyl, 1-2 µg/kg, alfentanil, 15-30 µg/kg, sufentanil, 0.15-0.3 µg/kg, or remifentanil, 0.5-1 µg/kg) can effectively attenuate the transient cardiostimulatory response to laryngoscopy and intubation, as well as skin incision. These drugs are also useful supplements to inhaled anesthetics during the maintenance period. Compared with inhaled anesthesia (i.e., volatile agents with nitrous oxide), adjunctive use of fentanyl or one of its newer analogs improves intraoperative conditions and provides for a more rapid emergence from anesthesia.[270,271] When a sufentanil infusion was compared with fentanyl for maintenance of outpatient anesthesia in combination with nitrous oxide, use of the more potent analog was associated with less nausea and postoperative pain. Because alfentanil has a more rapid onset and shorter duration of action than fentanyl does, emergence and recovery of psychomotor function are faster after an anesthetic technique based on alfentanil (versus fentanyl).[271] Alfentanil has also been alleged to cause less emesis than equipotent doses of fentanyl or sufentanil.[272]

Remifentanil is an ultrashort-acting opioid analgesic with potency similar to that of fentanyl but with a much shorter duration of action because it is rapidly metabolized by nonspecific tissue esterases. This metabolic process allows for rapid systemic elimination, with a half-life of 8 to 10 minutes and a context-sensitive half-life (the time for a 50% decrease in its effect site concentration after discontinuing an infusion) of 4 minutes regardless of the duration of infusion (Fig. 78-7).[273] In contrast, the context-sensitive half-life of alfentanil is 58 minutes because it depends on its small volume of distribution rather than metabolism for the rapid termination of its clinical effect.[273] When remifentanil was compared with alfentanil as part of a TIVA technique, remifentanil provided more effective suppression of acute autonomic responses and a faster emergence from anesthesia. However,[274] it can prolong postoperative recovery due to increased postoperative pain.[274] Studies involving the use of remifentanil in combination with the less-soluble volatile anesthetics suggest that a low-dose infusion (0.05-0.2 µg/kg/min) can produce a significant anesthetic-sparing effect and thereby contribute to a faster emergence from anesthesia.[275,276] Furthermore, bolus doses of remifentanil (0.5-1 µg/kg) were more effective than a standard dose of fentanyl in suppressing the acute

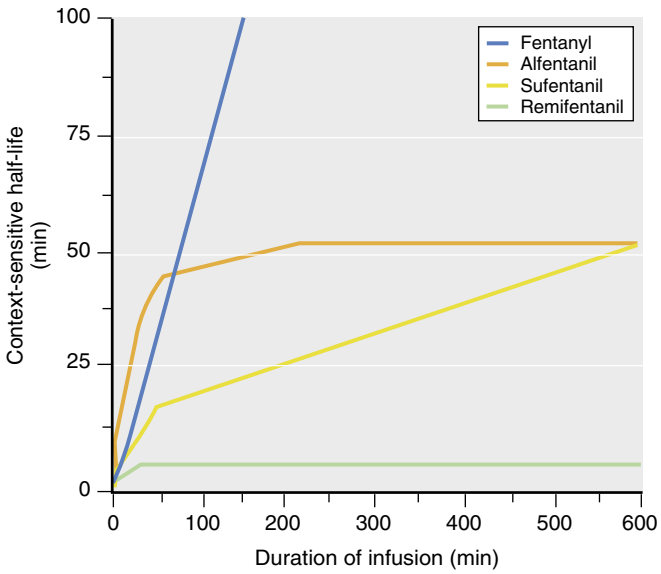

Figure 78-7 Computer simulation of the "context-sensitive" half-life (CSHT) for remifentanil (3.65 minutes), alfentanil (58.5 minutes), sufentanil (240 minutes), and fentanyl (262.5 minutes). Note that remifentanil's CSHT is independent of the duration of infusion. (*Redrawn with modification from Egan TD, Lemmens JH, Fiset P, et al: The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology 79:881, 1993.*)

hemodynamic response to laryngoscopy and tracheal intubation in outpatients undergoing laparoscopy procedures.[117] Smaller doses of remifentanil (0.25 μg/kg) have been used to facilitate placement of an LMA device.[277] However, remifentanil is less cost-effective than either fentanyl or alfentanil when administered as an adjuvant to general anesthesia unless drug wastage is minimized.[278,279]

Morphine, hydromorphone, oxymorphone, and meperidine have all been used in outpatient anesthesia. However, these classic opioid compounds are less popular than the more potent, rapid, and short-acting opioid analgesics because motion-induced emesis is a concern when morphine and its older congeners are used in the ambulatory setting. When intraoperative morphine and fentanyl were compared in ambulatory surgical patients, higher postoperative pain scores and greater oral analgesic use in the postdischarge period was reported in the fentanyl group.[280] However, morphine was associated with increased nausea and vomiting.

The opioid agonist-antagonist compounds (e.g., butorphanol, nalbuphine, dezocine, tramadol) have a theoretical advantage over the potent opioid compounds as adjuvants during general anesthesia because of their limited potential to produce severe ventilatory depression. Unfortunately, there is also a "ceiling effect" with respect to their analgesic efficacy. Although intraoperative use of dezocine provided significantly longer postoperative analgesia than fentanyl, it increased postoperative nausea and delayed discharge after outpatient anesthesia.[281] When nalbuphine (0.3-0.5 mg/kg) was compared with fentanyl (1.5 μg/kg) during outpatient surgery, it was found to produce more unpleasant dreaming during surgery and greater postoperative anxiety, drowsiness, and emetic symptoms.[120]

Muscle Relaxants

Many superficial outpatient surgical procedures do not require the use of neuromuscular relaxants. However, muscle relaxants are commonly used during laparoscopic surgery, ophthalmologic ("open globe") and ear/nose/throat procedures and operations performed in the prone position (see Chapter 29). When remifentanil is used in combination with propofol for induction of anesthesia, tracheal intubation can often be performed without any muscle relaxants.[282] Nevertheless, muscle relaxants are still commonly used to facilitate tracheal intubation and to optimize surgical conditions while minimizing the use of anesthetic and analgesic drugs.

Succinylcholine remains a commonly used muscle relaxant to facilitate tracheal intubation in the ambulatory setting because it has a rapid onset and its short duration of action obviates the need for reversal drugs. Prior to the introduction of short and intermediate-acting nondepolarizing muscle relaxants,[283] an infusion of succinylcholine was the most frequently used muscle relaxant technique during outpatient laparoscopic surgery. Although the administration of succinylcholine has been reported to cause myalgia after surgery, use of mivacurium or vecuronium as alternatives to succinylcholine failed to lower the incidence or severity of muscle pain after outpatient laparoscopy.[283,284] Pretreatment with small doses of rocuronium before succinylcholine also failed to reduce the incidence or severity of postoperative myalgia and is not recommended because it may cause uncomfortable muscle weakness before loss of consciousness.[285]

Use of the short-acting nondepolarizing muscle relaxants (e.g., mivacurium) allows spontaneous reversal of neuromuscular blockade even after relatively brief surgical procedures.[286] An intubating dose of mivacurium (0.15-0.20 mg/kg) has approximately twice the duration of action of succinylcholine (20-30 min) but a significantly more rapid spontaneous recovery profile than atracurium, vecuronium, or rocuronium.[287,288] A cost-effective technique involves the use of succinylcholine for tracheal intubation followed by small bolus doses of mivacurium during the maintenance period. This relaxant technique minimizes the need for muscle relaxant reversal drugs after short laparoscopic procedures.[283] The availability of sugammadex, a novel cyclodextrin compound, should allow for rapid reversal even from a "deep" block when a steroid-based muscle relaxant is used.[289] Compared with the standard reversal combinations of edrophonium-atropine and neostigmine-glycopyrrolate, use of sugammadex produced a more rapid and complete reversal of rocuronium-induced blockade.[290]

Antagonist (Reversal) Drugs

Pharmacologic antagonists (i.e., drugs that compete with agonists at specific receptor sites) may be useful in facilitating the recovery process after ambulatory anesthesia. However, antagonists frequently produce unwanted side effects (e.g., dizziness, headaches, nausea, vomiting). If the duration of action of the antagonist is shorter than the agonist (e.g., naloxone, flumazenil), a "rebound" agonist effect may occur later in the recovery period. This latter effect is a concern in the ambulatory setting because patients are frequently discharged home within 2 hours after surgery.

Opioid-induced rigidity and respiratory depression can be treated with small incremental boluses of naloxone. However, naloxone has its own intrinsic side effects (e.g., nausea and vomiting, hypertension, pulmonary edema, and arrhythmias); therefore, it is preferable to carefully titrate the opioid to achieve the desired effect during surgery without the need for the reversal drug. For treating opioid-induced muscle rigidity, small doses of succinylcholine (5 to 10 mg IV) are highly effective without adversely affecting the opioid's analgesic action.

The central effects of benzodiazepines (e.g., residual sedation and amnesia) can be promptly reversed with flumazenil (0.2-0.5 mg IV). Although flumazenil is a specific benzodiazepine antagonist, its use also leads to an increase in side effects. As with opioids, it is far more cost-effective to carefully titrate a benzodiazepine to the desired clinical effect rather than to rely on flumazenil to reverse the residual central depressant effects. Re-sedation can occur 1 to 2 hours after reversal because the elimination half-life of flumazenil (90 minutes) is shorter than that of any of the benzodiazepine agonists.

Intermediate-acting neuromuscular drugs are usually reversed at the end of an ambulatory surgery procedures using neostigmine and edrophonium in combination with an anticholinergic drug. Several studies have reported that the dosage of the reversal drug influences the frequency of PONV in the ambulatory setting.[283] When compared with patients receiving no reversal drugs, patients receiving neostigmine-glycopyrrolate had an increased frequency of PONV in the early postoperative period.[291] Mivacurium may be advantageous for use during the maintenance period because reversal is seldom required if the drug is properly titrated.[283] The novel cyclodextrin compound sugammadex[289] is capable of facilitating reversal of steroid-based, nondepolarizing neuromuscular blockers without uncomfortable anticholinergic side effects.[290] Use of this reversal agent may also

lead to earlier tracheal extubation after laparoscopic surgery procedures.

Pediatric Considerations

In unruly, frightened, or mentally retarded children, preoperative sedation is required before taking the patient into the operating room (see Chapter 82). Because of the aversion of children to needles, oral or rectal premedicants are more popular. Midazolam remains the most commonly used anxiolytic premedication for pediatric outpatients. After receiving oral midazolam, children can be separated from their parents within 30 minutes and dosages of 0.25 to 0.75 mg/kg do not prolong the discharge time even after short ambulatory procedures.[81] Use of rectal methohexital (20 to 30 mg/kg) for premedication before a volatile anesthetic can prolong recovery. Rectal etomidate (6 mg/kg) and ketamine (5 to 10 mg/kg) both produce a rapid onset of hypnosis without cardiorespiratory depression in children undergoing outpatient procedures. Although ketamine (2-4 mg/kg IM) can be an extremely useful drug for induction of anesthesia in an uncooperative or mentally retarded child, home readiness is delayed when larger doses of ketamine (>5 mg/kg) are administered before a volatile anesthetic.[292]

The practice of allowing parents to be present during induction of anesthesia is becoming more common. An informal survey indicated that 50% of pediatric anesthesiologists allow parents to be present during induction of anesthesia.[293] If the parents are calm and supportive, the number of upset children during the preinduction and induction periods is significantly decreased. Parents must be told exactly what to expect and must agree to leave immediately if asked to do so by the anesthesiologist. Unduly anxious or hysterical parents should not be encouraged to be present for induction because they will increase the child's anxiety.[294]

Regional Anesthesia

Regional anesthesia can offer many advantages for the ambulatory patient population (see Chapters 51 to 53). In addition to limiting the anesthetized area to the surgical site, common postoperative side effects of general anesthesia (e.g., nausea, vomiting, dizziness, lethargy) can be minimized.[295] Regional anesthesia offers advantages over general anesthesia with respect to speed of early recovery,[296] but recent data suggest that there are no significant differences in long-term outcomes after ambulatory surgery.[297] However, regional anesthesia can decrease the need for nursing care if it can provide more effective analgesia in the early postoperative period.[298] Simple regional anesthesia techniques (e.g., IVRA, peripheral nerve blocks) may be more cost effective in the outpatient setting because of the lower incidence of side effects and improved recovery profile compared with general and spinal/epidural anesthesia. Proper patient selection along with the skill and enthusiasm of the surgical and anesthesia teams will allow an even wider variety of procedures to be performed using regional anesthetic techniques in the future. While obesity is associated with higher block failure and complication rates,[299] use of newer ultrasound techniques may improve the success rates in this patient population.[300,301] Another important factor to successful implementation of a regional anesthesia program for ambulatory surgery is the availability of an induction room to perform the block before the patient enters the operating room.[302]

Spinal and Epidural Anesthetic Techniques

Spinal anesthesia is probably the simplest and most reliable regional anesthetic technique (see Chapter 51). Unfortunately, the incidence of side effects is surprisingly high and early recovery times are longer when subarachnoid block techniques are used in the ambulatory setting. The most troublesome complications of outpatient spinal anesthesia are related to residual effects of the block on motor, sensory, and sympathetic nervous system function. These residual effects can contribute to delayed ambulation, dizziness, urinary retention, and impaired balance.[303] Although the incidence of post–dural puncture headache can be minimized with the use of small-bore, 25-gauge pencil-point needles, the incidence of failed blocks appears to be higher.[304] When compared with general anesthesia, the use of spinal anesthesia with small doses of short-acting local anesthetics is also associated with a much higher incidence of backache (35% versus 14%).[303,305]

When central neuraxis block techniques are utilized for ambulatory surgery, it is important to select the most appropriate local anesthetic-adjuvant combination to avoid prolonged local anesthetic effects that negatively impact on the patient's "readiness for discharge."[306] Prolonging subarachnoid-induced analgesia with fentanyl rather than epinephrine avoids the prolonged time to micturition[307] and reduces the time to discharge from the hospital.[308] However, the adjunctive use of the opioid increases the incidence of pruritus and PONV. As compared with conventional intrathecal doses of local anesthetics, use of so-called mini-dose lidocaine (10-30 mg), bupivacaine (3.5-7 mg), or ropivacaine (5-10 mg) techniques combined with a potent opioid analgesic (e.g., fentanyl, 10-25 μg, or sufentanil, 5-10 μg) results in faster recovery of sensory and motor function.[309-311] The mini-dose spinal technique involving lidocaine and fentanyl achieved comparable recovery times to monitored anesthesia care (MAC) after knee arthroscopy.[312] For outpatient laparoscopic gynecologic surgery, this combination technique has also been reported to offer significant advantages over both conventional spinal and general anesthetic techniques with respect to hemodynamic stability and speed of recovery.[310,313,314] However, surgical conditions may be inadequate for lower abdominal procedures, and postoperative side effects (e.g., pruritus, nausea) are increased due to the intrathecal opioid.

Short-acting local anesthetics (e.g., lidocaine and procaine) are clearly preferable to bupivacaine, ropivacaine, and tetracaine in achieving a rapid recovery. However, the use of lidocaine is controversial because of numerous reports of transient neuropathic symptoms (i.e., radicular nerve root pain).[315,316] As a result, investigators are recommending the use of either isobaric lidocaine alone or combinations of small-dose hypobaric lidocaine with fentanyl or sufentanil. Intrathecal fentanyl-induced pruritus is more severe with procaine than with lidocaine or bupivacaine.[317] However, use of droperidol (0.625 mg IV) or nalbuphine (4 mg IV) can decrease these side effects.[312] Intrathecal bupivacaine and ropivacaine should be reserved for ambulatory procedures with an anticipated duration of more than 2 hours because of their more prolonged recovery times.[318] With longer procedures, Korhonen and colleagues[319] reported comparable recovery times after spinal anesthesia with hyperbaric bupivacaine (5 mg) and general endotracheal anesthesia. Compared with bupivacaine, the duration of sensory blockade with ropivacaine was two thirds and the duration of motor block was half.[320] Hyperbaric ropivacaine also produces a faster onset of analgesia compared with isobaric

ropivacaine.[321] Outpatients should be allowed to fully recover motor function before discharge home. After complete recovery of motor function, residual sympathetic blockade and orthostatic hypotension are less likely to be a problem with ambulation. However, functional balance is frequently impaired for 150 to 180 minutes after spinal anesthesia.[322]

Epidural anesthesia is technically more difficult to perform, has a slower onset of analgesia and a greater potential for intravascular or intrathecal injection, and is associated with a higher increase of incomplete sensory blocks compared with spinal anesthesia. The use of 3% 2-chloroprocaine epidural anesthesia achieved discharge times comparable to those of small-dose lidocaine spinal anesthesia for outpatient knee arthroscopy while avoiding post–dural puncture headache and transient neurologic symptoms.[323] Another advantage of epidural anesthesia is the ability to extend the duration of anesthesia by placing a catheter. Use of the short-acting local anesthetic 2-chloroprocaine for outpatient epidural anesthesia was associated with a high incidence of back pain from muscle spasm as a result of the preservative ethylenediaminetetraacetic acid (EDTA).[1] However, the newer formulations are preservative free and are associated with discharge times comparable to those for general anesthesia.[324] Epidural 3% 2-chloroprocaine enables readiness for discharge home 1 hour earlier than epidural 1.5% lidocaine after knee arthroscopy.[325] The preservative-free formulation of 2-chloroprocaine (50 mg) also offers advantages over lidocaine when administered in the subarachnoid space for short (<60 minutes) outpatient procedures.[326] The use of combined spinal-epidural anesthesia allows for the reliability of spinal anesthesia with the flexibility of continuous epidural anesthesia.[327,328] The small initial dose of intrathecal drug results in a more rapid onset, reduced side effects, and faster recovery from the sensorimotor blockade. If necessary, the epidural catheter could be used to extend the block beyond the duration of the spinal anesthetic.

Given that similar postoperative analgesia can be achieve using a perineural catheter technique (e.g., continuous femoral or popliteal nerve blocks) as with epidural local analgesia without the attendant risk of epidural-related complications (e.g., inadvertent dural puncture, hematoma formation, hemodynamic instability), continuous peripheral neural blockade would appear to be preferable to epidural techniques for lower extremity surgery in the ambulatory setting. Use of epidural anesthesia and analgesia for major laparoscopic surgery only facilitated recovery of bowel function when a traditional (nonaccelerated) perioperative care program was used.[329] Recent advances in fast-track surgery techniques and the availability of peripheral mu-opioid antagonists[330] will likely lessen the role of epidural analgesia in the postoperative period.

Intravenous Regional Anesthesia

The intravenous regional anesthetic (IVRA) technique with 0.5% lidocaine is a simple and reliable technique for short superficial surgical procedures (<60 minutes) limited to a single extremity (see Chapter 52). Intravenous regional anesthesia has been reported to be a more cost-effective technique for outpatient hand surgery than general anesthesia.[331-333] Ropivacaine is alleged to provide longer-lasting analgesia after deflation of the tourniquet cuff than lidocaine.[334] The addition of a wide variety of adjuvants (e.g., ketorolac, 15 mg; clonidine, 1 μg/kg; dexmedetomidine, 0.5 μg/kg; gabapentin, 1.2 mg; dexamethasone, 8 mg) has been reported to improve the quality of intraoperative and postoperative analgesia after IVRA.[333-339]

Peripheral Nerve Blocks

If more profound and prolonged anesthesia of the upper or lower extremity is required, a major regional block of the brachial plexus (e.g., axillary, subclavicular, or interscalene block) or femoral-sciatic-popliteal nerves can be extremely valuable in the ambulatory setting (see Chapter 52).[339,340] As supplements to general anesthesia, peripheral nerve blocks (versus local infiltration) improve postdischarge analgesia and reduce opioid-related side effects, thereby facilitating the fast-track recovery process.[7,341]

The "three-in-one block" (i.e., femoral, obturator, and lateral femoral cutaneous nerves) performed with the use of a perivascular technique is useful for outpatient knee arthroscopy and anterior cruciate ligament repairs because it provides excellent postoperative analgesia. Use of a simple femoral nerve block with 0.25% or 0.5% bupivacaine improves postoperative analgesia after arthroscopic anterior cruciate repairs.[340] Ultrasound guidance can provide reliable blockade of the infrapatellar nerve for arthroscopic knee surgery, although concomitant blockade of the saphenous nerve may occur.[342]

Ankle blocks are also effective techniques for surgery on the foot. However, these blocks require multiple injections that increase patient discomfort. In contrast, popliteal fossae nerve blocks are simple to perform and provide excellent postoperative analgesia after foot and ankle surgery.[343] More importantly, these peripheral blocks can be extended by using continuous local anesthetic infusions.[344,345] Continuous perineural techniques can be administered at home after discharge.[344-348] The beneficial effects of these techniques have been demonstrated in a recent multicenter trial that utilized patient-controlled perineural local analgesia as an alternative to IV patient-controlled analgesia (PCA).[349] A recent meta-analysis confirmed the advantages of a peripheral catheter technique over parenteral opioid-based analgesic techniques for painful extremity procedures.[350] As the primary analgesic technique, peripheral nerve blocks are associated with shorter discharge times, improved analgesia and reduced need for opioid analgesics, enhanced patient satisfaction and mobility (i.e. activity), and fewer side effects when utilized for hand,[341,351] shoulder,[352-354] anorectal,[355] hernia repair,[356,357] and knee surgery.[358] For example, when compared with general anesthesia, use of a pudendal nerve block in hemorrhoidectomy was associated with reduced postoperative pain, shortened hospital stay, and earlier return to normal activities of daily living.[359] Not surprisingly, continuous peripheral nerve blocks are becoming increasingly popular for painful orthopedic procedures.[344-347,360,361] The use of disposable nonelectronic (elastomeric) pumps may offer advances over mechanical pumps in the ambulatory setting.[362] Patient-controlled regional anesthesia has also been used effectively for pain control outside the hospital after hand[363] and breast augmentation surgery.[364]

Other popular peripheral nerve blocks include combined deep and superficial cervical plexus blocks, which reduce pain and opioid requirements after thyroid surgery.[365] When compared with intravenous regional and general anesthesia for carpal tunnel surgery, distal nerve blocks at the wrist were found to be more cost effective because they were associated with improved intraoperative cardiovascular stability, fewer postoperative side effects, and earlier discharge home.[366] Paravertebral somatic nerve blocks

can be used as an alternative to ilioinguinal-hypogastric nerve block for inguinal herniorrhaphy.[367] However, the additional time and expertise required to perform this block, as well as the risk of serious side effects (e.g., pneumothorax), are concerns when using paravertebral blocks rather than simpler peripheral blocks for this common operation.[367]

In pediatric patients, peripheral nerve blocks can be performed immediately after induction of general anesthesia to reduce the anesthetic requirement and provide postoperative analgesia (see Chapter 81). Historically, caudal anesthesia has been the most popular technique to reduce postoperative pain in children undergoing lower abdominal, perineal, and lower extremity procedures. However, this central neuraxis block is associated with more side effects (e.g., urinary retention) and a longer recovery time than simple peripheral nerve blocks. Popular peripheral blocks for children include blockade of the ilioinguinal and iliohypogastric nerves to minimize postherniorrhaphy pain[368] and use of the dorsal penial nerve block and subcutaneous ring block for postcircumcision pain. Using ultrasound guidance for ilioinguinal and iliohypogastric nerve blockade significantly reduced the volume of local anesthetic injected, as well as the intraoperative and postoperative requirements for opioid analgesics.[369] Interestingly, simple wound infiltration (or instillation) with local anesthetics may be as effective as a caudal or ilioinguinal nerve block in reducing pain after inguinal hernia repair.[370] Other studies suggest that systemic ketorolac (1 mg/kg) is also as efficacious as caudal blockade and has a lower incidence of side effects when combined with local anesthetic wound infiltration.[371] Topical lidocaine ointment is a simple and effective alternative to both a peripheral nerve block and opioid analgesics for postcircumcision pain.

Local Infiltration Techniques

Of all the anesthetic techniques suitable for outpatients, local infiltration of the operative site with dilute solutions of local anesthetics is the simplest and safest approach to reducing postoperative pain and the need for postdischarge opioid-containing analgesics.[372] Infiltration of local anesthetics at the surgical incision site should be a component of all ambulatory anesthetic techniques.[373,374] Outpatient urologic procedures (e.g., vasovasostomy, orchiopexy, and hydrocele and spermatocele repairs) performed with local anesthesia can significantly decrease the overall cost or surgical care. Local infiltration anesthesia alone can provide adequate analgesia for superficial procedures (e.g., inguinal herniorrhaphy, breast and anorectal surgery, shoulder and knee arthroscopy) but is vastly underutilized in clinical practice.[312,375-377] Compared with spinal anesthesia for anorectal surgery, local anesthesia with sedation resulted in a shorter hospital stay, reduced cost, and fewer side effects.[378] Patient comfort can be improved if IV sedation-analgesia is used to supplement local anesthetic infiltration, particularly when the local anesthesia is not completely effective.[355,376] However, use of IV adjuvants can also increase side effects (e.g., ventilatory depression, PONV).[379,380]

The benefits of local wound infiltration in patients undergoing more invasive major surgical procedures have not been as extensively studied. Although there is very little evidence that "preemptive analgesia" involving local anesthetic injections at the surgical wound reduces the risk for developing persistent postoperative pain syndromes,[381] it does lessen both intraoperative and postoperative opioid requirements, as well as opioid-related side effects.[382] Many studies have demonstrated improved analgesia, greater patient satisfaction with pain management, and reduced PONV and hospital stay when local anesthetics are administered at the surgical incision site.[383] For example, patients receiving a continuous infusion of bupivacaine at the incision site not only experienced improved postoperative pain management but also were able to ambulate earlier.[383] Infiltration of local anesthetic at portal sites and the gallbladder bed improves postoperative analgesia after laparoscopic cholecystectomy.[384] Compared with neuraxial or general anesthetic techniques, local anesthetic infiltration techniques reduce the risk of postoperative urinary retention associated with anorectal surgery[355] and inguinal herniorrhaphy.[380,385,386] A combination of local infiltration and intercostal nerve blocks has also been used for lithotripsy. Careful patient (and surgeon) selection is important for operations performed using local infiltration or a field block techniques. When used as the primary anesthetic technique, local anesthesia facilitates postanesthesia care unit (PACU) bypass, thereby reducing recovery costs.[331,355,356,376,380,387] Local anesthetic supplementation during general and spinal anesthesia (e.g., infiltration with bupivacaine, 0.25% to 0.5%) will also decrease incisional pain in the postdischarge period.[388]

Monitored Anesthesia Care

The combination of local anesthesia and/or peripheral nerve blocks with intravenous sedative and analgesic drugs is commonly referred to as MAC and has become extremely popular in the ambulatory setting.[379,389] Compared with general endotracheal and central neuraxis anesthetic techniques for superficial (noncavitary) surgical procedures, MAC-based techniques can facilitate recovery in the ambulatory setting.[355,356] The *simplest* local anesthetic technique that provides adequate analgesia is recommended to minimize the risk of side effects and complications.[366] These local anesthetic-based techniques are also the most cost effective for ambulatory surgery (Tables 78-10 and 78-11).[355,356]

The primary objective in providing MAC is to ensure patient comfort, safety, and satisfaction during surgery. MAC is the term used when an anesthesiologist monitors a patient receiving local anesthesia or administers supplemental drugs to patients undergoing diagnostic or therapeutic procedures.[389] The ASA defines MAC as *instances in which an anesthesiologist has been requested to provide specific anesthesia services to a particular patient undergoing a planned procedure, in connection with which a patient receives local anesthesia or, in some cases, no anesthesia at all.*[390] In such a case, the anesthesiologist is in control of the patient's vital signs and is available to administer anesthetics and provide other medical care as appropriate. The standard of care for patients receiving MAC should be the same as for patients undergoing general or regional anesthesia and includes a standard preoperative assessment, intraoperative monitoring, and postoperative recovery care. Vigilant monitoring is required because patients may rapidly progress from a "light" level of sedation to "deep" sedation (or unconsciousness) and, thus, may be at risk for airway obstruction, oxygen desaturation, and even aspiration.

Anesthetic drugs are administered during procedures under MAC with the goal of providing analgesia, sedation, and

Table 78-10 Comparison of Anesthetic Techniques for Outpatient Inguinal Herniorrhaphy

	Local Anesthesia with Sedation	General Anesthesia	Spinal Anesthesia
Age (yr)	42 ± 18	36 ± 16	29 ± 14
Weight (kg)	73 ± 9	75 ± 10	73 ± 14
Surgery time (min)	109 ± 23	119 ± 29	116 ± 24
Time to awakening (min)	2 ± 2	5 ± 2*	0
Time to orientation (min)	4 ± 4	10 ± 5*	0
Time in the PACU (min)	0	40 ± 13	35 ± 22
Time to home-readiness (min)	128 ± 68	171 ± 40*	283 ± 80†
Nausea and/or vomiting (%)	8	61†	13
Maximum pain (0-100)	14 ± 13	27 ± 22	31 ± 30*
Highly satisfied with anesthesia (%)	77	36*	63

*$P < .05$ versus local sedation.
†$P < .01$ versus local sedation.
From Song D, Greilich NB, White PF, et al: Recovery profiles and costs of anesthesia for outpatient unilateral inguinal herniorrhaphy. Anesth Analg 91:876-81, 2000.

anxiolysis and ensuring rapid recovery without side effects. Systemic analgesics are often used to reduce the discomfort associated with the injection of local anesthetics and prolonged immobilization[391] as well as procedure-related pain that is not amenable to local anesthesia (e.g., endoscopy). Sedative-hypnotic drugs are used to make procedures more tolerable for patients by reducing anxiety and providing a degree of intraoperative amnesia while allowing them to rest (or sleep) during the operation.[392] Patients often become restless, bored, or uncomfortable when forced to remain immobile for prolonged periods of time under local anesthesia. Perioperative anxiety can be reduced with benzodiazepines (e.g., midazolam, 2 mg IV), as well as by intraoperative verbal communication, keeping the patient warm and covered, and allowing him or her to listen to music during the procedure.[393]

Many different sedative-hypnotic drugs have been administered during MAC (including barbiturates, benzodiazepines, ketamine, and propofol) using a wide variety of delivery systems (e.g., intermittent boluses, variable-rate infusion, target-controlled infusion, and even patient-controlled sedation).[394,395] The most commonly used sedation technique is a propofol infusion at 50-100 μg/kg/min.[396-398] Methohexital has also been used during MAC when administered as intermittent boluses (10-20 mg) or as a variable-rate infusion (1-3 mg/min). Residual sedation is greater with methohexital compared with propofol. Nevertheless, discharge times were similar after infusions of methohexital (40 μg/kg/min) and propofol (50 μg/kg/min) during MAC.[399] Furthermore, the incidence of pain on injection is lower with methohexital.[205,218] Therefore, the short-acting barbiturate may be a cost-effective alternative to propofol for sedation during MAC.[399]

In women undergoing laparoscopic tubal sterilization with a MAC technique, anesthetic drug costs were significantly reduced in comparison with general anesthesia.[400] The MAC technique was also associated with less time in the operating room, a higher degree of "awakeness" on the evening of the day of surgery, and decreased postoperative pain and sore throat. Analogous to earlier studies involving patients undergoing unilateral hernia repair and anorectal surgery,[355,356] Patel and coworkers[401] reported that the use of MAC sedation resulted in a 6- to 7-minute decrease in operating room exit time when compared with general anesthesia, contributing to enhanced turnover of cases and improved operating room efficiency. This is an increasingly important consideration in the current practice environment that emphasizes "fast-tracking" after ambulatory surgery.[402]

Avramov and White[403] described the combined use of alfentanil (0.3 to 0.4 μg/kg/min) and propofol (25 to 75 μg/kg/min) infusions for MAC. Propofol produced a dose-related reduction in the opioid dose requirement (25% to 50%) and the incidence of PONV (0% to 17%) when compared with alfentanil alone (33%). Ketamine infusion has also been used as an alternative to the opioid analgesic.[404] Although an infusion of remifentanil, 0.05 to 0.15 μg/kg/min, can provide adequate sedation and analgesia during minor surgical procedures performed with the patient under local anesthesia, opioid-related side effects have limited the use of this drug as the primary IV adjuvant during MAC.[405] The addition of midazolam (2 to 4 mg IV) improved the quality of sedation and anxiolysis produced by remifentanil.[406] In

Table 78-11 Comparison of Anesthetic Techniques on Recovery Profile after Anorectal Surgery

	Local Anesthesia with Sedation	Spinal Anesthesia	General Anesthesia
Duration of anesthesia (min)	40 ± 15	72 ± 17	75 ± 19*
Duration of surgery (min)	26 ± 14	26 ± 13	26 ± 15
Phase 1 stay (min)	0	52 ± 18*	44 ± 27*
Phase 2 stay (min)	71 ± 17	136 ± 113*	120 ± 52*
Time or oral intake (min)	12 ± 5	59 ± 18*	60 ± 29*
Aldrete score (on arrival in recovery)	10 ± 0	9.1 ± 0.4*	8.3 ± 0.7*†
Time to Aldrete score of 10 (min)	0	19 ± 7*	30 ± 19*†
Time to home-readiness (min)	76 ± 17	103 ± 112*	171 ± 58*
Duration of hospital stay (min)	116 ± 21	266 ± 112*	247 ± 65*

*$P < .05$ versus local anesthesia with sedation.
†$P < .05$ versus spinal anesthesia.
From Li S, Coloma M, White PF, et al: Comparison of the costs and recovery profiles of three anesthetic techniques for ambulatory anorectal surgery. Anesthesiology 93:1225, 2000.

comparing the use of intermittent remifentanil boluses (25 μg) with a continuous variable-rate infusion (0.025 to 0.15 μg/kg/min) as part of a MAC technique consisting of midazolam (2 mg) and propofol (25 to 50 μg/kg/min), Sá Rêgo and colleagues[406] reported superior patient comfort when the remifentanil was administered by a variable-rate infusion. However, concomitant use of propofol and remifentanil infusions during MAC resulted in a higher incidence of episodic oxygen desaturation (30% versus 0%) compared with those given small intermittent boluses of remifentanil. When administered to spontaneously breathing patients in combination with propofol, remifentanil offered no benefits compared with propofol alone.[407] In a direct comparison of remifentanil and propofol infusions after premedication with midazolam (2 mg IV), a reduced level of sedation and a greater degree of respiratory depression were noted with remifentanil than with propofol.[408]

Given the increased risk of ventilatory depression when potent opioid analgesics are combined with sedative-hypnotics, a variety of nonopioid analgesics have been evaluated during MAC.[391] Ketorolac has been used as an analgesic supplement to propofol sedation during local anesthesia. The use of ketorolac was associated with a lower incidence of pruritus, nausea, and vomiting when compared with fentanyl.[126,409,410] However, ketorolac-treated patients required higher intraoperative dosages of propofol and more supplemental opioid analgesia.[126,391] Low-dose ketamine (0.25 to 0.5 mg/kg) combined with either midazolam or propofol has also been administered to outpatients undergoing cosmetic surgical procedures with local anesthesia.[226,411,412] Ketamine has the advantage over both opioid analgesics and NSAIDs because it produces less ventilatory depression and PONV than the opioid compound while providing more effective intraoperative analgesia than NSAIDs.[413] Small doses of either midazolam and propofol can be administered to attenuate the adverse psychomimetic reactions produced by ketamine.[229,411,412,414,415]

The α_2-agonists clonidine and dexmedetomidine reduce central sympathetic outflow and have been shown to produce anxiolysis and sedation. Kumar and associates[416] demonstrated that oral clonidine (300 μg) provided effective anxiolysis for elderly patients undergoing ophthalmic surgery under local anesthesia while also decreasing the incidence of intraoperative hypertension and tachycardia. Dexmedetomidine (1 μg/kg IV) significantly decreased anxiety levels and reduced the requirements for supplemental analgesic medications when given before intravenous regional anesthesia for hand surgery.[417] In comparing dexmedetomidine with midazolam for sedation, Aho and colleagues[418] reported faster recovery from sedation when dexmedetomidine was followed by reversal with the specific α_2-antagonist atipamezole. However, the slower onset and recovery from dexmedetomidine-induced sedation, as well as the occurrence of bradycardia, has limited its use for MAC in the ambulatory setting.[417-419]

Facilitating the Recovery Process

Cerebral Monitoring

The impact of monitoring the level of consciousness during general anesthesia in the ambulatory setting remains controversial (see Chapter 39).[420] Monitoring patient vital signs remains the most useful method for determining the "depth of anesthesia" during surgery. Although the value of cerebral monitoring as an adjuvant to monitoring autonomic responses to noxious surgical stimuli is limited, several studies have reported that the use of cerebral monitoring can improve early recovery after general anesthesia in the ambulatory setting because of its ability to minimize both "overdosing" and "underdosing" with both intravenous (e.g., propofol) and inhaled anesthetic (e.g., sevoflurane and desflurane) drugs during the maintenance period.[421-425] A meta-analysis confirmed that more precise dosing of intravenous and inhaled anesthetics during ambulatory surgery significantly reduced anesthetic consumption, the incidence of PONV, and the time in the recovery room.[426]

Several different electroencephalographic (EEG)-based algorithms have been evaluated in an attempt to improve the correlation between EEG-derived indices, anesthetic drug concentrations, and clinical signs of the depth of anesthesia.[427] The bispectral index (BIS), physical state index (PSI), spectral and response entropy, auditory evoked potential (AEP) index, and cerebral state index (CSI) are all processed variables derived from the EEG that have been used to quantify the sedative and hypnotic effects of anesthetic drugs on the central nervous system (CNS).[426] The BIS, PSI, and CSI values are dimensionless numbers that vary from 0 to 100, with values less than 60 associated with "adequate" hypnosis under general anesthesia and values greater than 75 typically observed during emergence from anesthesia.[428] In contrast to the BIS, PSI, and CSI monitoring devices, the AEP monitor uses the middle latency auditory evoked potential (MLAEP) response to assess the depressant effects of anesthetic drugs on the CNS. Studies suggest that the AEP index changes in a consistent and dose-dependent manner with the administration of sedative-hypnotic and volatile anesthetics but not with opioid analgesics.[428,429]

Despite the introduction of these cerebral monitoring devices, there is still no universally accepted "gold standard" for measuring the depth of anesthesia. For a monitor to be of the most clinical utility, it should display a strong correlation between the observed variable (index) and the patient's state of consciousness and physiologic responses (e.g., blood pressure, heart rate, catecholamine levels) to noxious stimuli during surgery independent of the anesthetic technique and with minimal interpatient variability. For example, the CSI failed to reliably predict autonomic or somatic responses to surgical stimuli.[430] In studies involving nonparalyzed patients, electromyographic activity has been found to interfere with the ability of these monitors to obtain reliable EEG-based index values. In their editorial on cerebral monitoring, Kalkman and Drummond[420] suggested that all of the currently available devices have deficiencies in monitoring "depth of anesthesia." This is hardly surprising because these monitoring devices only measure the hypnotic component of anesthesia.

The reported indices of the cerebral monitors are generally lower (reflecting "deeper" levels of sedation-hypnosis) in patients when using standard monitoring practices than in cerebral-monitored patients.[424,428,431] These data suggest that patients are maintained at a "lighter" level of anesthesia (or hypnosis) when the anesthesiologist has access to the information provided by one of these cerebral monitoring devices. The information provided by a cerebral monitor influences the anesthesiologist's use of not only volatile anesthetics but also opioid analgesic and

sympatholytic drugs during the maintenance period. As a result of the anesthetic and/or analgesic-sparing effects, monitored patients are able to more rapidly achieve surrogate recovery end points (e.g., fast-track eligibility) and to satisfy PACU discharge criteria (e.g., Aldrete score of 10), resulting in a 30- to 90-minute reduction in the length of the PACU stay and/or the time to discharge home after ambulatory surgery.[424] When cerebral monitoring is used to administer isoflurane, the speed and quality of recovery was similar to sevoflurane after outpatient gynecologic surgery.[432]

One of the concerns in "minimizing" the use of anesthetics relates to the possibility that patients may experience more purposeful movement during surgery (i.e., less optimal operating conditions) and even awareness. It has further been suggested that the use of cerebral monitors to minimize the administration of anesthetic and analgesic drugs may result in increased autonomic (stress) responses and adverse clinical outcomes (e.g., myocardial ischemia). Previous studies have demonstrated that patient outcome is similar whether supplemental general anesthetic, opioid analgesic, or sympatholytic drugs were used to control acute autonomic responses during surgery.[433,434] A study by Monk and colleagues[435] suggested that there was a correlation between the length of time during anesthesia that the BIS value was less than 45 and the incidence of adverse clinical outcomes in elderly surgical patients. Despite the emphasis on rapid recovery after ambulatory anesthesia, outpatients do not appear to be at increased risk for awareness when compared with inpatients receiving general anesthesia.[436] From the perspective of the patient, the quality of recovery appears to be improved with cerebral monitoring versus traditional monitoring practices.[424,431]

Optimal Anesthetic Techniques

In the ambulatory setting, the optimal anesthetic technique would provide for excellent operating conditions and rapid "fast-track" recovery to full activity without postoperative side effects or complications.[7] In addition to improving the quality and minimizing the cost of anesthetic services, the ideal anesthetic technique would also optimize operating room efficiency (e.g., turnover times) and provide for an earlier discharge home. Local anesthesia with intravenous sedation (i.e., MAC techniques), regional (peripheral) blocks, spinal anesthesia, and general anesthesia can all be used for ambulatory surgery. Opinions differ regarding the "best" anesthetic technique, even for superficial surgical procedures.[309,355,356,437-440] Rather than simply generalizing about the best anesthetic technique for ambulatory surgery, it would be far better to individually analyze each surgical procedure (i.e., procedure-specific approach).[306]

In the current cost-conscious environment, it is important to also examine the impact of anesthetic techniques on the perioperative process because prolonged recovery times and reduced efficiency contribute to the increased cost of surgical care.[355,356,387] In addition, patient satisfaction with the perioperative experience and quality of recovery is improved when the anesthetic technique chosen for the procedure is associated with a low incidence of postoperative side effects. For example, the routine use of prophylactic antiemetic drugs during general anesthesia has been found to increase patient satisfaction in "at-risk" outpatient surgical populations (e.g., nonsmoking women with a history of PONV or motion sickness).[140] Furthermore, the use of local anesthetic infiltration and/or peripheral nerve blocks decrease postoperative pain after ambulatory surgery procedures irrespective of the actual anesthetic technique.[402,441,442]

The time required to achieve a state of home readiness (i.e., "fitness" for discharge home) is influenced by a wide variety of surgical and anesthetic factors.[443,444] However, the major contributors to a delay in discharge after ambulatory surgery are nausea, vomiting, dizziness, pain, and prolonged sympathetic and motor blockade. Although the incidence of PONV can be decreased by the use of prophylactic antiemetic drugs,[402] it remains a common side effect after general anesthesia and prolongs discharge after ambulatory surgery.[138] The primary factor delaying discharge after spinal anesthesia is recovery from the residual motor and sympathetic blockade, which contributes to delayed ambulation and an inability to void. These side effects can be minimized by use of the so-called minidose lidocaine-fentanyl spinal anesthetic technique.[110,440] Other concerns with spinal anesthesia include back pain, post–dural puncture headache, and transient radicular irritation.[445,446] Although MAC is associated with the lowest incidence of postoperative side effects,[355,356] the possibility of transient nerve palsy is a concern when peripheral nerve block techniques are used.[447-449] Another issue relates to the fact that many patients simply prefer to "be asleep during the operation."

Use of the modern general anesthetics with an LMA for airway management combined with antiemetic prophylaxis and nonopioid analgesic techniques can achieve recovery times that compare favorably with MAC techniques.[450,451] Studies have demonstrated that outpatients undergoing hernia repair and breast surgery were able to ambulate within 30 minutes and were discharged within 60 minutes after general anesthesia. When tracheal intubation is required (e.g., laparoscopic procedures, risk factors for aspiration [e.g., diabetics, morbidly obese, esophageal dysfunction]), the use of minimally effective doses of a short-acting opioid analgesic (e.g., remifentanil) or sympatholytic (e.g., esmolol, labetalol) can facilitate the early recovery process and allow patients to achieve earlier discharge times after ambulatory surgery.[117,276,452]

Table 78-12 Effects of Intravenous Anesthetic and Cardiovascular Drugs on the Duration of Electroconvulsive Therapy–Induced Seizure Activity

	Increased	No Change	Decreased
Anesthetic Drugs	Etomidate	Methohexital,* ketamine, alfentanil,† remifentanil†	Thiopental, thiamylal, lorazepam, midazolam, propofol
Cardiovascular Drugs	Aminophylline, caffeine	Clonidine, esmolol, labetalol, dexmedetomidine, nifedipine, nicardipine, nitroglycerin, trimethaphan, nitroprusside	Diltiazem, lidocaine

*When compared with saline, methohexital decreases the seizure duration of electroconvulsive therapy.
†Increases seizure time because of an anesthetic-sparing effect.
From Ding Z, White PF: Anesthesia for electroconvulsive therapy. Anesth Analg 94:1351, 2002.

The cost savings associated with the newer anesthetic techniques are lost if institutional practices mandate minimum lengths of stay in the recovery units (i.e., PACU or "step-down" unit). Claims of reduced total costs with earlier discharge are commonly based on the assumption that there is a linear relationship between the cost of a clinical service and the time spent providing it. Because personnel costs are semifixed rather than variable, an additional 15- to 30-minute stay in the PACU may not be associated with increased cost to the institution unless the facility is working at or near its capacity.[453] Fast-tracking does not, however, reduce the overall nursing workload and the associated costs after ambulatory surgery.[454]

The relationship between decreasing costs and bypassing the PACU ("fast-tracking") appears to be much closer because the major factor in recovery care cost relates to the peak number of patients admitted to the PACU at any given time.[453] Fast-tracking can lead to the use of fewer nurses and a mix of less highly trained, lower-wage nursing aides and fully qualified recovery room nurses and, therefore, reduces "overtime" personnel costs for busy ambulatory surgery units. Shorter anesthesia times, the ability to bypass the PACU, and a decreased length of stay in the day-surgery unit will reduce total institutional costs.[455] Studies have demonstrated that "fast-tracking" ambulatory surgery patients can decrease the time to actual discharge.[456,457]

The combination of low cost and high patient satisfaction suggests that the highest-quality (cost/outcome) anesthetic may be achievable with a MAC technique if the surgical procedure is amenable to this anesthetic approach (e.g., superficial surgical and endoscopic procedures). However, the success of MAC techniques is dependent not only on the anesthesiologist but also on the skills of the surgeon in providing effective local anesthetic infiltration and gentle handling of tissues during the intraoperative period. Superficial operations can be performed under local anesthesia without any monitoring or intravenous adjuvants (so-called unmonitored local anesthesia) in situations in which the local anesthesia is able to provide complete analgesia and patients do not object to being awake and aware of events in the operating room.[458] However, in a prospective, randomized comparison of local infiltration with spinal and general anesthesia,[459] surgeons in Sweden suggested that technical difficulties and patient pain were "more intense" during surgery under local anesthesia alone.

Fast-Tracking Concepts

Ambulatory anesthesia is administered with the dual goals of rapidly and safely establishing satisfactory conditions for the performance of therapeutic or diagnostic procedures while ensuring rapid, predictable recovery with minimal postoperative sequelae. If careful titration of short-acting drugs permits safe transfer of patients directly from the operating room suite to a less labor-intensive recovery area, many outpatients can be discharged home within 1 hour after surgery, thereby resulting in cost savings to the institution.[450,460] Bypassing the PACU has been termed "fast-tracking" after ambulatory surgery.[461] In addition, fast-tracking can be accomplished directly from the PACU ("PACU fast-tracking") by creating a specialized area within an existing PACU where recovery procedures are organized along the lines of a step-down unit.[462] This approach represents a key component of the "total care" package for ambulatory surgery.[463]

The criteria used to determine fast-track eligibility (see Table 78-7) have been made even more stringent than the standard PACU discharge criteria to reduce the need for nursing interventions in areas with less nursing personnel.[464] The use of anesthetic techniques associated with more rapid recovery will result in fewer patients remaining deeply sedated in the early postoperative period[457,465] and decrease the risk for airway obstruction, episodes of oxygen desaturation, and cardiovascular instability, thereby reducing the number of nursing interventions.[457,466] By using anesthetic techniques associated with faster emergence times from anesthesia, it should be possible to reduce the need for "intensive" nursing care in the early postoperative period.[467] Therefore, a well-organized fast-tracking program may permit an institution to use fewer nurses in the recovery areas and could lead to significant cost savings.

The fast-track concept is gaining wider acceptance for outpatients of all ages.[468,469] Fast-tracking children after ambulatory surgery is feasible and beneficial (e.g., shorter recovery time) when specific selection criteria are used.[455] Similarly, elderly outpatients can be fast-tracked after general anesthesia if short-acting drugs are used.[465] The vast majority of outpatients no longer require admission to a conventional PACU recovery facility after ambulatory surgery.[470] Bypassing the PACU after outpatient knee surgery was associated with fewer unplanned hospital admissions.[471] The primary anesthetic-related cause of failure to fast-track outpatients after laparoscopic surgery was residual sedation on emergence from anesthesia (propofol > sevoflurane > desflurane).[457] Other important reasons included residual muscle weakness (due to nondepolarizing muscle relaxants) and surgical misadventures. If common side effects cannot be effectively prevented, bypassing the PACU may result in more nursing interventions in the day-surgery step-down unit.[471]

Improved titration of anesthetic drugs with the use of EEG-based cerebral monitors can lead to faster emergence from general anesthesia,[421,422] and by predicting the time required to achieve fast-track eligibility,[472] they may actually reduce discharge times.[424] Whereas the availability of more rapid and shorter-acting anesthetic drugs has clearly facilitated the early recovery process after general anesthesia, the "preemptive" use of nonopioid analgesics[126] and antiemetics[140] will reduce postoperative side effects and accelerate both the immediate and late recovery phases after ambulatory surgery. When compared with a conventional recovery pathway, fast-tracked patients are eligible to be discharged home 30 to 90 minutes earlier without compromising patient safety or satisfaction with their surgical experience.[452]

Multimodal Approaches to Minimizing Side Effects

As more complex procedures are performed utilizing minimally invasive surgical approaches (e.g., laparoscopic adrenalectomy and nephrectomy, arthroscopic knee and shoulder reconstructions), the ability to effectively control postoperative side effects such as pain and PONV may make the difference between performing a given procedure on an inpatient or ambulatory basis. The introduction of multimodal approaches to perioperative care has led to improved surgical outcomes.[473]

For preventing PONV, the most cost-effective antiemetic combination consists of droperidol (0.625-1.25 mg IV), dexame-

thasone (4-8 mg IV),[155,156] and generic ondansetron (4-8 mg IV).[474] Outpatients at the highest risk of PONV may also benefit from the addition of a long-acting 5-HT_3 antagonist (e.g., palonosetron, 75 µg IV), an NK-1 antagonist (e.g., aprepitant), a transdermal scopolamine patch, or an acu-stimulation device (e.g., SeaBand, ReliefBand).[159,161,166] Use of nonopioid analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], cyclooxygenase-2 [COX-2] inhibitors, acetaminophen, α_2-agonists, glucocorticoids, ketamine, and local anesthetics) as part of a multimodal analgesic regimen will minimize opioid-related side effects and enhance patient satisfaction.[139,382,475] In a study comparing ketorolac with the glucocorticoid steroids when administered as adjuvants during ambulatory surgery, the parenteral NSAID not only provided more effective postoperative analgesia but also was superior in preventing PONV in the early recovery period. However, the adjunctive use of dexamethasone does prolong the analgesic effects of NSAIDs.[476] In addition to using multimodal antiemetic and nonopioid analgesic therapy,[382,477] ensuring adequate hydration will minimize nausea and other side effects (e.g., dizziness, drowsiness, thirst) during the postoperative period.[180-183]

A multimodal (or "balanced") approach to providing postoperative analgesia is essential in the ambulatory setting.[4,35,478] Not surprisingly, pain has been found to be a major factor complicating recovery and delaying discharge after ambulatory surgery.[233] The addition of low-dose ketamine (75-150 µg/kg) to a multimodal analgesic regimen improved postoperative analgesia and functional outcome after painful surgical procedures.[229,414,479] In addition to effective multimodal analgesic regimens, nonpharmacologic factors can also influence control of postoperative pain. For example, when compared with the conventional CO_2 insufflation technique, reduced pain and shorter convalescence were achieved after mini-laparoscopic cholecystectomy simply by using a gasless technique.[29] Use of nitrous oxide for pneumoperitoneum and heated insufflation gases were also associated with less postoperative pain than the standard insufflation technique.[191,480]

After ambulatory surgery, pain must be controllable with simple oral analgesics (e.g., acetaminophen, ibuprofen, acetaminophen with codeine) when patients are discharged from the surgery facility. Although the potent rapid-acting opioid analgesics (e.g., fentanyl, sufentanil, remifentanil) are commonly used to treat moderate-to-severe pain in the early recovery period, these compounds increase the incidence of PONV and may contribute to delayed discharge after ambulatory surgery.[126,233] As a result of the concern regarding opioid-related side effects, interest has increasingly focused on the use of parenteral NSAIDs (e.g., diclofenac, ketorolac, parecoxib), which can effectively reduce the requirements for opioid-containing oral analgesics after ambulatory surgery and lead to an earlier discharge home.[481] However, less expensive oral nonsteroidal analgesics (e.g., ibuprofen, naproxen)[482,483] are also highly effective in the postdischarge period. The perioperative use of the oral COX-2 inhibitors has become more popular because they are devoid of adverse effects on platelet function (Tables 78-13 and 78-14).[122] Oral celecoxib (400 mg/day) is a simple and cost-effective approach to improving pain control and decreasing discharge times after ambulatory surgery.[127,129,484-486] A recent study demonstrated that the use of celecoxib, 400 mg/day, on the day of surgery and for the first 3 postoperative days can lead to significant improvements in clinically relevant patient outcome measures (e.g., gastrointestinal function, resumption of physical activities, patient satisfaction).[485] Furthermore, the addition of a glucocorticoid (e.g., dexamethasone, 4-8 mg IV) can prolong the duration of analgesia when

Table 78-13 Effect of Postoperative Celecoxib on Recovery after Outpatient Laparoscopy

	Control	Celecoxib (400 mg/day)
Age (yr)	39 ± 11	36 ± 10
Weight (kg)	80 ± 16	83 ± 16
Surgery time (min)	100 ± 56	97 ± 51
Pain scores (0-10)	4 (3-6)	2 (2-5)*
Rescue analgesic use (no., %)	32 (80)	18 (44)*
Quality of recovery scores (0-18)	16 (15-18)	18 (17-18)*
Patient satisfaction (0-100)	76 ± 26	92 ± 11*
Recovery Outcome Variables		
Normal diet (days)	3 (2-4)	2 (1-3)*
Normal bowel function (days)	2 (2-4)	1 (1-2)*
Resume normal activities (days)	6 (3-7)	4 (1-5)*

*P < 0.05 *versus* the conventional recovery pathway.
From White PF, Sacan O, Tufanogullari B, et al: Effect of short-term postoperative celecoxib administration on patient outcome after outpatient laparoscopic surgery. Can J Anaesth 54:342-348, 2007.

Table 78-14 Analgesic Efficacy of Premedication with Rofecoxib in the Ambulatory Setting

	Placebo	Rofecoxib (50 mg PO)
Surgery time (min)	63 ± 29	66 ± 36
Anesthesia time (min)	87 ± 29	91 ± 36
PACU fentanyl dose (µg)	101 ± 133	22 ± 42*
Max. pain score (0-10)	6 ± 3	3 ± 3*
Pain after discharge (0-10)	6 ± 3	1 ± 1*
Moderate to severe pain (%)	58	16*
No pain at discharge (%)	5	42*
Recovery times (min)		
Phase I (PACU)	70 ± 26	64 ± 18
Phase II (DSU)	194 ± 263	96 ± 43
Patient satisfaction (1-100)	73 ± 19	98 ± 4*
Completely satisfied with pain management (%)	6	69
Quality of recovery (1-100)	77 ± 16	95 ± 7*
Oral analgesics post discharge (no.)	5 ± 3	0.5 ± 1*

*$P < .05$ versus placebo group.
DSU, day-surgery unit; PACU, postanesthesia care unit.
From Issioui T, Klein KW, White PF, et al: Cost-efficacy of rofecoxib vs. acetaminophen for preventing pain after ambulatory surgery. Anesthesiology 97:931, 2002.

using a multimodal analgesic regimen that included an NSAID and local anesthesia.[130] Finally, acetaminophen is a cost-effective alternative to the traditional NSAIDs if an effective dose (40 to 60 mg/kg orally or rectally) can be given before the end of surgery.[487-489] A parenteral formulation of acetaminophen (1 g IV) has been developed and has quickly become a valuable adjuvant to standard multimodal analgesic regimens.

One of the keys to facilitating the recovery process is the routine use of local anesthesia as part of a multimodal regimen.[126,479] The use of local anesthetics for perioperative analgesia during MAC, as well as adjuncts to general and regional anesthesia, can provide excellent analgesia during the early recovery and postdischarge periods.[441,442] Even simple wound infiltration and instillation techniques have been shown to improve postoperative analgesia after a variety of lower abdominal, peripheral extremity, and even laparoscopic procedures. A wide array of peripheral extremity blocks have also been used to minimize postoperative pain;[340,490] however, the beneficial effects of local anesthetic blocks on patient outcomes are limited unless the local analgesia can be extended into the postdischarge period.[491] The use of continuous local anesthetic delivery systems has been found to improve pain control after major ambulatory orthopedic surgery by extending peripheral nerve blocks into the postdischarge period.[344,346,347]

For laparoscopic procedures, abdominal pain can also be minimized by the use of a local anesthetic at the portals and topical application at the surgical site. Shoulder pain is also common after laparoscopic surgery, and this pain has been reported to be reduced with subdiaphragmatic instillation of local anesthetic solutions. Topical intra-abdominal application at the surgical site (e.g., gallbladder bed, fallopian tubes) can also reduce both pain and PONV.[492] After arthroscopic knee surgery, instillation of 30 mL of 0.5% bupivacaine into the joint space reduces postoperative opiate requirements and permits earlier ambulation and discharge.[493] The addition of adjuvants (e.g., morphine, 1-2 mg; ketorolac, 15-30 mg; clonidine, 0.1-0.2 mg; ketamine, 10-20 mg; triamcinolone, 10-20 mg) to intra-articular local anesthetics can further reduce pain after arthroscopic surgery.[494-497] Novel compounds such as capsicum (the active ingredient in chili peppers!) have been found to produce analgesic effects because of their ability to alter nociceptive input at peripheral nerve ending.[498] Finally, simple electroanalgesic techniques (e.g., transcutaneous electrical nerve stimulation [TENS]) can also be used as a nonpharmacologic component of a multimodal analgesic regimen.[499] Future growth in the complexity of surgical procedures being performed on an ambulatory basis will necessitate further improvements in our ability to provide effective postoperative pain relief away from the surgical facility.

Bisgaard[500] suggested that "opioids should only be used when these other nonopioid analgesic techniques fail." Although so-called preemptive analgesic techniques have been postulated to provide superior analgesia by preventing the establishment of central sensitization,[501] this approach does not appear to offer any clinically significant advantages over simple preventative multimodal regimens administered immediately after surgery.[502] Administration of celecoxib after plastic surgery was as effective as administering the drug both before and after the operation.[503] Interestingly, perioperative administration of IV lidocaine improved patient outcomes after major laparoscopic surgery.[504] Safer, simpler, and more efficacious analgesic drug delivery systems are still needed to provide cost-effective pain relief in the postdischarge period as more major surgery is performed on an ambulatory basis in the future.[473,505]

Special Considerations

Office-Based Anesthesia

Office-based anesthesia is simply a variant of ambulatory anesthesia that has attracted growing attention around the world.[506] Ralph Waters opened the first office-based anesthetic practice (the Downtown Anesthesia Clinic) almost 100 years ago in Sioux City, Iowa. In response to an occasional call from a dentist for anesthesia, Dr. Waters set up "a modest office with a waiting room and a small operating room with an adjoining room containing a cot on which a patient could lie down after his anesthetic before going home."[20] In a series involving over 30,000 office-based ENT procedures with 72% receiving "deep sedation" or general anesthesia, the complication rate was only 1.3% and only two patients required overnight hospitalization.[507] In a review of over 4,000 consecutive patients who had undergone office-based surgery with MAC techniques, postoperative complication rates were less than 0.1% and only two patients required overnight hospitalization.[508]

For many years, simple minimally invasive surgical procedures have been performed in physicians' offices. Certified registered nurse anesthetists, dental anesthesiologists, and, increasingly, practicing anesthesiologists have been active in office-based surgery. It is currently estimated that only 5% to 10% of outpatient surgical procedures are performed in the office setting, and this number is anticipated to approach 20% by 2010. Both the numbers and the types of surgical procedures are steadily increasing. As pressure from third-party payers to reduce the overall cost of surgical procedures continues to increase, surgeons and anesthesiologists are moving cases to facilities where they have more direct control over costs. For example, a cost comparison of laparoscopic inguinal herniorrhaphy was performed by Shultz, who reported that the total cost for this procedure in the hospital was $5494 versus $1534 in an office facility.[509] Similarly, the hospital-based fee for a conventional "open" inguinal herniorrhaphy was $2237 versus $895 in an office facility.

Office-based facilities have lower overhead than hospital or freestanding ambulatory surgical centers and are often more comfortable and convenient for patients. It is important to select patients appropriately and to adhere to the usual guidelines for safe anesthetic care. The preoperative workup should be guided by the same clinical acumen and common sense that drives the decision-making process at freestanding surgery centers (i.e., coexisting diseases must be under good control). Patients with potentially difficult airways are not good candidates for office-based anesthesia. The selection criteria for patients should also consider the invasiveness of the surgical procedure.

The optimal anesthetic techniques for office-based surgical procedures are similar to those used for hospital-based and freestanding ambulatory surgery procedures. Most procedures involve the use of local anesthesia supplemented with intravenous sedation (e.g., propofol infusion) or "light" general anesthesia and an LMA or facemask for airway management.[450,451,510] Propofol is used for providing sedation, as well as for induction and mainte-

nance of anesthesia, along with sevoflurane and desflurane. Nitrous oxide was shown to decrease the propofol requirement and allow patients to be discharged within 60 minutes after office-based procedures without increasing the incidence of PONV. The use of larger doses of opioid analgesics has been found to enhance cardiorespiratory depression without improving the quality of perioperative patient comfort.[511] Most office suites do not have stretchers or recovery beds, and patients have to be able to get up from the operating room table and transfer themselves (with assistance) to a reclining chair or ambulate to an area where they can rest until they are ready to get dressed and go home.

Although the modern practice of office-based anesthesia is relatively new in the United States, a similar practice of office-based dental anesthesia has been in place for several decades in the United Kingdom. After a review of anesthetic deaths in dental offices in the United Kingdom, it was recommended that all anesthetics be administered by accredited anesthesiologists whose training included specific experience in dental anesthesia.[510] There were also recommendations regarding resuscitation equipment and the availability of drugs needed for emergency use. In the years after publication of the Poswillo report, the number of dental offices offering general anesthesia for office-based procedures significantly decreased.[512] The high cost required to equip and maintain such locations was the main reason for this change of practice. Based on the U.K. experience, it is obvious that if office-based anesthesia is going to be successful in North America, issues other than cost must be considered.[23]

Office-based surgery practice guidelines established by the ASA, the American Association of Nurse Anesthetists, and the Joint Commission on the Accreditation of Healthcare Organizations include the following:

1. Employment of appropriately trained and credentialed anesthesia personnel
2. Availability of properly maintained anesthesia equipment appropriate to the anesthesia care being provided
3. As complete documentation of the care provided as that required at other surgical sites
4. Use of standard monitoring equipment according to the ASA policies and guidelines
5. Provision of a PACU or recovery area that is staffed by appropriately trained nursing personnel and provision of specific discharge instructions
6. Availability of emergency equipment (e.g., airway equipment, cardiac resuscitation)
7. Establishment of a written plan for emergency transport of patients to a site that provides more comprehensive care should an untoward event or complication occur that requires more extensive monitoring or overnight admission of the patient
8. Maintenance and documentation of a quality assurance program
9. Establishment of a continuing education program for physicians and other facility personnel
10. Safety standards that cannot be jeopardized for patient convenience or cost savings

Beyond their responsibility to provide safe anesthesia care in the office, modern-day office-based anesthesiologists have an opportunity to expand their role as perioperative physicians. This practice has the potential to heighten public awareness of the vital role of anesthesiologists in the ambulatory setting and enhance the professional image of our specialty.[512] Patients and caregivers must be confident that the office setting adheres to the same standards of care required in a hospital-based or a freestanding ambulatory surgery facility.

Anesthesia for Procedures outside the Operating Room

Anesthesiologists are being called on to provide anesthetic care for an increasing number of procedures in remote locations (see Chapter 79). The most common of these procedures are electroconvulsive therapy (ECT), extracorporeal shock waves lithotripsy (ESWL), and neuroradiologic procedures, including magnetic resonance imaging (MRI) and computed tomography (CT). The anesthetic machines and monitors used in these locations may be old or unfamiliar models, and the monitoring equipment and supplies may be more limited in comparison to the operating room. Experienced assistants may be unavailable, and nursing staff members in these locations are frequently unaccustomed to the anesthetic drugs, equipment, and procedures used by anesthesiologists. Consequently, the anesthesiologist must be vigilant when checking the anesthetic machine and must know where to locate emergency resuscitation drugs and equipment.

As with any ambulatory or office-based surgical procedure, patients must be carefully selected and evaluated before any procedure involving the administration of anesthetic drugs if performed outside the operating room. The anesthetic techniques used for these procedures should provide for prompt recovery with minimal side effects, and patients must fulfill the same discharge criteria as those undergoing procedures in an operating room facility. Many of these procedures have specific anesthetic considerations and well-known complications. The anesthetic techniques used for ESWL procedures have changed dramatically over the past several years. With the development of newer lithotriptors, the water bath is no longer required and targeting is more precise, so fewer shocks are required. These improvements have essentially eliminated the use of general or epidural regional anesthesia, and the majority of these procedures can be performed with IV sedation-analgesic techniques.[482,512,513] These MAC techniques reduce anesthesia and recovery times without compromising patient safety and satisfaction.[514] MAC techniques involving midazolam-alfentanil, midazolam-ketamine, and fentanyl-propofol have been used for ESWL procedures with excellent patient satisfaction.[514,515] In addition, PCA with alfentanil and remifentanil has been described for lithotripsy of gallstones and urinary tract calculi.[516,517] A MAC technique involving midazolam (2 mg), propofol infusion (25 to 50 μg/kg/min), and a continuous infusion of remifentanil (0.025 to 0.15 μg/kg/min) has also been described.[406] Intercostal nerve blocks may improve patient comfort during ESWL. Even electro-acupuncture has been reported to produce sedation-analgesia during an ESWL procedure.[518]

In summary, nonoperating room anesthesia requires anesthesia providers to deliver sedation and anesthesia in a wide variety of venues (including radiology suites, cardiac and neurologic catheterization laboratories, and diagnostic centers) in addition to office-based facilities.[519] Nonoperating room anesthesia claims had a higher severity of inquiry and more substandard

care than operating room claims.[520] Inadequate oxygenation and an inability to adequately ventilate were the most common mechanisms of patient injury. Therefore, maintenance of minimum monitoring standards and airway management training should be required of all staff members involved in the administrations of sedative analgesic medications. When properly conducted, office-based surgery is both safe and highly cost effective.[521]

Magnetic Resonance Imaging

MRI has become an increasingly popular noninvasive radiologic diagnostic procedure because of the high-quality images provided. MRI requires that patients be confined for 30 to 60 minutes in a magnetic, closed noisy space. Because of their age, altered mental state, or pain, some patients cannot fully cooperate for this length of time and require either general anesthesia or intravenous sedation-analgesia to obtain a high-quality image. Patient movement during any part of the examination can compromise the quality of the image. Therefore, anesthesiologists are increasingly becoming involved in patient care for MRI and spectroscopy. Special anesthetic considerations are necessary for MRI because of the high magnetic field and the specialized rooms and buildings for housing the MRI scanners.[522-524] Problems in monitoring patients undergoing MRI include the following:

1. Ferromagnetic equipment must be removed from the magnetic field, including credit cards, key chains, paper clips, pins, and pens, as well as conventional monitoring devices.
2. While in the scanner, access to the patient and viewing of the patient are limited.
3. Malfunction of monitoring equipment or interference produced by the changing magnetic field (e.g., syringe infusion pumps) can occur.
4. Stray radiofrequency current produced by the monitoring equipment can degrade the quality of the images.

These issues make it difficult to achieve an adequate balance between meeting the ASA standards for monitoring during anesthesia and acquiring high-quality images.[522] Newer anesthesia machines and nonferrous pumps and monitoring equipment are available. Because the older monitors may have to be located far from the patient (e.g., outside the room), the chance of disconnection and kinks in the intravenous tubing, anesthesia breathing circuit, and monitoring leads is increased. The ideal situation is to have two anesthesia personnel: one close to the patient and an assistant outside the room with the monitoring equipment. Unfortunately, the personnel costs of this type of arrangement would be higher than most institutions are willing to accept.

Gastroenterology Suite

For many years, endoscopists have used conscious sedation techniques for gastroenterology procedures. Sedation improves not only patient comfort during the examination but also patient acceptance of follow-up examinations. Specific monitoring guidelines and sedation techniques for assisting the endoscopist are available.[525-527] However, situations arise that can benefit from the services of an anesthesiologist, such as endoscopic procedures performed on unruly patients with complex coexisting medical conditions or situations in which previous attempts at performing the procedure using operator-administered sedation were unsuccessful.

An important consideration in the planning of an anesthetic technique is the position of the patient during the examination. Patients undergoing endoscopic procedures are often positioned lateral or prone to facilitate the examination, and these positions may pose difficulty should resuscitative efforts be required due to cardiorespiratory depression. During upper endoscopic procedures or endoscopic retrograde cholangiopancreatography, the endoscope is inserted orally, which necessitates sharing the patient's airway with the endoscopist. Cooperation and a team approach by the endoscopist, the radiology staff, and the anesthesiologist are essential for the safe and expeditious performance of these procedures.

Electroconvulsive Therapy

The use of ECT to provoke a generalized epileptic seizure was first described in 1938 and was performed without anesthesia for almost 30 years. At the present time, the number of ECT procedures performed each year under general anesthesia in the United States exceeds the number of coronary revascularization, appendectomy, and herniorrhaphy procedures. ECT has assumed an increasingly important role in the treatment of acute and medication-resistant chronic depression and mania, as well as the management of schizophrenic patients with affective disorders, suicidal drive, delusional symptoms, vegetative dysregulation, inanition, and catatonic symptoms.[528] ECT is both extremely safe and highly effective in a wide variety of high-risk patient populations. Typically, the acute phase of ECT is performed three times a week for 8 to 12 treatments. Maintenance therapy can be performed at progressively increasing intervals from once a week to once per month.

Anesthetic management for ECT typically involves the use of an induction dose of an intravenous anesthetic (e.g., methohexital, thiopental, etomidate, or propofol), followed by a short-acting muscle relaxant (e.g., succinylcholine or mivacurium).[529] Although the overall recovery profiles are similar with all the intravenous anesthetics, methohexital remains the drug of choice because of longer seizure times (versus propofol), shorter awakening times (versus thiopental), and fewer side effects (versus etomidate). Of interest, patients who received propofol for anesthesia required a longer acute course of ECT.[530] However, if patients are experiencing excessively long seizures (>100 seconds), propofol may be a useful alternative to methohexital.[531] In situations in which the intravenous anesthetic precludes an adequate seizure (<30 seconds), adjunctive use of remifentanil (50 to 100 μg IV) can prolong the seizure duration because it produces an anesthetic-sparing effect[532] and has no direct effect on the ECT-induced seizure duration.[533] A wide variety of cardiovascular drugs (e.g., esmolol, labetalol, nicardipine) are commonly used to minimize the acute hemodynamic changes produced by the electrical stimulus and the resultant seizure activity (Table 78-12).

Standard noninvasive monitors are used during the procedure, and the airway is typically managed with a facemask and reusable airway circuit. An antisialagogue (e.g., glycopyrrolate) is administered to decrease oral secretions, and a Guedel airway device may be used in patients prone to upper airway obstruction (e.g., sleep apnea syndrome, morbid obesity). An LMA is an excellent option for airway management when fitting a facemask is difficult.[534] Tracheal intubation is rarely performed (e.g., late

pregnancy, obese diabetics). The availability of cerebral monitors may improve the ability of anesthesiologists to titrate anesthetic drugs and to optimize the timing of the ECT-induced seizure stimulus in refractory cases.[535,536]

The optimal dosage of anesthetic, muscle relaxant, and sympatholytic drugs requires careful titration to the needs of the individual patient, and further adjustments during the course of a series of ECT treatments should be based on the patient's earlier responses. Although a simple "modal" approach to anesthesia for ECT was advocated by Kellner,[537] patients vary widely in their sensitivity to these drugs, depending on their age, body habitus, concurrent drug therapy, and underlying medical conditions. Given the large number of elderly patients with underlying cardiovascular disease (e.g., hypertension, coronary artery disease, peripheral vascular disease), careful titration of the commonly used sympatholytic drugs (e.g., labetalol, esmolol, nicardipine, clonidine) is also important to maintain hemodynamic stability and obtain the best possible outcome with ECT. Anesthesiologists should be aware of anesthetic factors that influence the duration of seizure activity because the clinical effectiveness of ECT is predicated on achieving an adequate seizure at each treatment session.

Discharge Criteria

Discharge after General Anesthesia and Monitored Anesthesia Care

The three stages of recovery after ambulatory surgery are the early, intermediate, and late recovery phases (see Chapter 85). The early and intermediate recovery stages occur in the ambulatory or office-based surgical facility, whereas late recovery refers to the resumption of normal daily activities and occurs after the patient has been discharged home. Early recovery is the time interval during which patients emerge from anesthesia, recover control of their protective reflexes, and resume early motor activity. During this phase of recovery, patients are cared for in the PACU and day-surgery unit, where their vital signs and oxygen saturation are carefully monitored, and supplemental oxygen, analgesics, or antiemetics can be readily administered if necessary. The modified Aldrete or White score is commonly used to assess the fitness of patients to be transferred to the day-surgery recovery area.[464,538] Ideally, the vast majority of outpatients would complete the early recovery criteria in the operating room and be able to satisfy the White fast-track criteria.[539]

During the intermediate recovery period, patients are usually cared for in a reclining chair and progressively begin to ambulate, drink fluids, void, and prepare for discharge (see Fig. 78-1). The choice of anesthetic technique, as well as the appropriate use of postoperative analgesic and antiemetic drugs, all have an impact on the duration of the intermediate recovery period. Analogous to the use of IV caffeine in the past, a preliminary study[540] suggested that modafinil, a wakefulness promoting drug, could reduce postoperative fatigue and improved alertness in patients recovering from general anesthesia. A prolonged early (emergence) and intermediate recovery can significantly increase the overall cost of the patient's operation. Factors that predict a more prolonged stay in the day-surgery unit include female gender, advanced age, longer operations, large blood loss, use of opioid and nondepolarizing muscle relaxants, episodes of oxygen desaturation, postoperative pain and PONV, and spinal anesthesia.[25,541,542]

The late recovery period starts when the patient is discharged home and continues until complete functional recovery is achieved and the patient is able to resume normal activities of daily living. Although anesthetics, analgesics, and antiemetics can affect the patient's early and intermediate recovery, the surgical procedure itself has the highest impact on late recovery (i.e., the patient's ability to resume normal activities of daily living). Guidelines for safe discharge from an ambulatory surgical facility include stable vital signs, return to baseline orientation, ambulation without dizziness, minimal pain and PONV, and minimal bleeding at the surgical site.[47] The major accreditation bodies in the United States and Canada require that all ambulatory surgical patients receiving sedative and anesthetic drugs have an escort to transport them home, and they must receive written postoperative instructions, including advice on whom to contact if a problem develops in the postdischarge period.

A more objective discharge scoring system has been developed to evaluate and document the patient's readiness for discharge.[541,543] The so-called postanesthetic discharge scoring (PADS) system is a simple cumulative index that measures the patient's home readiness; it is based on five major criteria: (1) vital signs, including blood pressure, heart rate, respiratory rate, and temperature; (2) ambulation and mental status; (3) pain and PONV; (4) surgical bleeding; and (5) fluid intake/output.[538] Patients who achieve a score of 9 or greater and have an adult escort are considered fit for discharge (or "home ready"). The requirement for patients to drink and void before discharge is no longer considered mandatory. A modified postanesthetic discharge scoring system was developed that eliminated input and output as discharge criteria and resulted in earlier discharge for up to 20% of the outpatients studied (Table 78-15).[47]

Delays in discharge are typically related to persistent symptoms such as pain, PONV, hypotension, dizziness, unsteady gait, or the lack of an escort.[543] Excessive postoperative pain and emetic symptoms are the most common causes of delayed discharge from ambulatory surgical facilities and can lead to unexpected hospital admissions.[233] The highest incidence of moderate-to-severe pain occurred in patients undergoing orthopedic, general, and plastic surgery procedures.[373]

Discharge after Regional Anesthesia

Patients recovering from regional anesthesia must meet the same discharge criteria as patients recovering from general anesthesia. However, these outpatients must also fulfill additional criteria to ensure safe ambulation if they were administered a central neuraxis blockade or a major nerve block involving a lower extremity. With spinal or epidural anesthesia, it is generally accepted that motor and sensory function returns before sympathetic nerve function. Residual blockade of the sympathetic nerve supply to the bladder and urethra can cause urinary retention. It is advisable after spinal and epidural anesthesia for outpatients to void before discharge. Therefore, long-acting local anesthetics (e.g., bupivacaine, ropivacaine, tetracaine) should be avoided in the ambulatory setting. The use of shorter-acting local anesthetics (e.g., lidocaine, procaine) with the addition of a potent opioid

Table 78-15 Modified Postanesthesia Discharge Scoring (PADS) System

Vital Signs	
2	Within 20% of the preoperative value
1	20%-40% of the preoperative value
0	40% of the preoperative value
Ambulation	
2	Steady gait/no dizziness
1	With assistance
0	No ambulation/dizziness
Nausea and Vomiting	
2	Minimal
1	Moderate
0	Severe
Pain	
2	Minimal
1	Moderate
0	Severe
Surgical Bleeding	
2	Minimal
1	Moderate
0	Severe

From Chung F, Chan VW, Ong D: A postanesthetic discharge scoring system for home readiness after ambulatory surgery. J Clin Anesth 7:500, 1995.

analgesic can provide spinal anesthesia without significantly prolonging the time to discharge.[310,313] Before ambulation, patients receiving a central neuraxis block should have normal perianal (S4-5) sensation, have the ability to plantarflex the foot, and have proprioception of the big toe. Discharge criteria after spinal and epidural anesthesia should include the return of normal sensation, muscle strength, and proprioception, as well as the return of sympathetic nervous function.

Controversies Related to Discharge Criteria

There is still controversy regarding the requirement for all outpatients to tolerate fluids and void before discharge from an ambulatory surgical facility. It is clearly unacceptable to discharge a patient who is actively vomiting and unable to tolerate oral fluids. Interestingly, Schreiner and Nicolson[174] found that requiring children to drink before discharge actually increased the incidence of vomiting (>50%) and delayed discharge. On the other hand, children are more likely to vomit after discharge than during their stay at the surgical facility, and, therefore, tolerating clear fluids before discharge may prevent dehydration at home after discharge. At the Children's Hospital of Philadelphia, more than 20,000 day-surgery patients have been discharged home without requiring intake of oral fluids and there have been no readmissions for dehydration.[174] All these children (except those undergoing myringotomy tube placement) received the equivalent of 8 hours of intravenous fluid replacement during their hospital stay. Well-hydrated outpatients can be safely discharged home without demonstrating an ability to tolerate oral fluids after surgery.

The requirement to void before discharge has also been challenged.[544] The inability to void may be caused by pain (which inhibits normal bladder detrusor function) and opioid analgesics, spinal or epidural anesthesia, and anticholinergic drugs.[47] Patients may be discharged earlier if voiding is not a discharge requirement. Delaying discharge for voiding after spinal or epidural anesthesia with short-acting local anesthetics is unnecessary in low-risk patients (e.g., age < 70 years; no hernia, rectal, or urologic surgery; no history of voiding problems).[544] However, appropriate measures must be in place for urinary catheterization if the inability to void persists after discharge home. The use of ultrasound bladder monitoring before discharge may reduce voiding problems after discharge.[544]

Before leaving the outpatient facility, patients should have their dressings checked and be given both verbal and written instructions regarding their postoperative care. Most postoperative symptoms (e.g., pain, PONV, dizziness, headache, and myalgias) resolve within 24 hours. However, if these symptoms persist, the patient should be encouraged to contact the facility regarding appropriate follow-up care. All patients should be discharged from the surgical facility in the company of a responsible adult and should be aware of the recommendations regarding appropriate activities after discharge. Patients should be warned about the potential dangers of operating complex machinery, driving a car, or making important decisions for up to 24 hours after anesthesia.[545] However, when short-acting anesthetic drugs are used for 1- to 2-hour procedures, return of fine motor skills can occur in less than 4 hours.

It is important to have an efficient mechanism in place for admitting outpatients to the hospital if the need arises. Most well-organized outpatient facilities have an unanticipated hospital admission rate of less than 1%.[11,12] However, transfer rates are higher in ambulatory centers with a larger proportion of neonates, elderly (>80 years), and ASA physical status III patients. The Federated Ambulatory Surgery Association multicenter survey suggested that 70% of all perioperative complications occurred after discharge from the ambulatory surgery center.[1] This finding emphasizes the importance of providing clear, written discharge instructions and the availability of a responsible adult to monitor the patient at home. Most practitioners recommend that out-of-town patients spend their first postoperative night within a reasonable distance from the surgical facility. All outpatient facilities should also have a mechanism in place for collecting follow-up information regarding patient well-being after discharge (e.g., telephone interview or postcard questionnaire).

Outcome Measures

As outpatient surgery continues to grow and the types of surgical procedures become more complex, ambulatory surgical centers must develop methods to evaluate patient outcome during both the early and late recovery periods (see Chapter 33).[546] The overall risk of major morbidity and mortality is very low after ambulatory surgery. A large, retrospective study of more than 45,000 ASA I to III outpatients found that only 31 patients (1:1455) experienced major morbidity.[10] Four patients died, 2 as passen-

gers in automobile accidents within the first 48 hours and 2 of myocardial infarctions more than 48 hours after surgery. In a multicenter survey performed in the 1980s involving over 50 freestanding ambulatory centers in the United States, an increased risk of perioperative complications was reported in patients who had preexisting cardiovascular diseases.[1] A four-center prospective study involving 6,914 Canadian outpatients also found that patients with underlying medical conditions (e.g., hypertension, diabetes, and gastrointestinal disorders) were at higher risk for adverse events in the perioperative period.[547] No deaths were reported during the study period, and major morbid events were extremely rare. In a more recent analysis, ASA III outpatients undergoing ambulatory surgery demonstrate no significant difference in unplanned admission rates or complications in the first 24 hours after discharge compared with ASA I and II outpatients.[548]

Although the incidence of major morbidity is extremely low, minor complications remain problematic after ambulatory surgery, in particular, in the postdischarge period. In a survey of anesthesiologists,[549] the clinical anesthesia outcomes that were thought to be most important to avoid in the ambulatory setting were incisional pain, nausea, vomiting, preoperative anxiety, and discomfort from insertion of the intravenous line. One study found that 35% of outpatients discharged from freestanding surgical centers experienced PONV severe enough to prevent their return to normal daily activities.[550] Half these patients had not experienced PONV in the recovery room and became symptomatic only after they were discharged home. Incisional pain, PONV, drowsiness, dizziness, headache, and fever are the most frequent minor symptoms that occur after surgical outpatients are discharged home.[551] The type of surgical procedure clearly influences the occurrence of postdischarge symptoms, with laparoscopic, general, and orthopedic surgical procedures having the highest incidence and minor gynecologic and ophthalmologic procedures having the lowest incidence of postdischarge symptoms. Outpatients experiencing other postdischarge symptoms experienced delays in returning to their usual daily activities. Despite the frequent occurrence of minor morbidity after ambulatory surgery, patient satisfaction is remarkably high and most would choose to have their surgery performed on an outpatient basis in the future.[1]

Delayed discharge and unexpected hospital admission after outpatient surgery are the most commonly identified outcome measures after ambulatory anesthesia (Table 78-16). Not only does hospital admission add to the expense of the procedure, but it is also disruptive for the patient and the surgical facility. Ambulatory surgery facilities should have admission rates of less than 1%.[11-13] Orthopedic (3.2%), general surgery (3.1%), otolaryngology (3.1%), and urology (29%) have the highest rates of unanticipated hospital admissions.[15] However, freestanding and office-based units tend to have lower unanticipated hospital admission rates (<0.1%) because of differences in the types of patients and procedures, as well as the relative ease of admitting outpatients from hospital-based facilities.[12] The most common reasons for unexpected admission are pain, bleeding, intractable vomiting, surgical misadventure (e.g., bowel or uterine perforation), more extensive surgery than expected, urinary retention, or lack of an escort.[11]

The likelihood of an unexpected hospital admission is related more to the type of surgery performed than to specific patient characteristics or the type of anesthetic technique.

Table 78-16 Factors Alleged to Delay Discharge and Lead to Unanticipated Admissions after Ambulatory Surgery

Delayed Discharge

Preoperative

- Female gender
- Increasing age
- Congestive heart failure

Intraoperative

- Long duration of surgery
- General anesthesia
- Spinal anesthesia

Postoperative

- Postoperative nausea and vomiting
- Moderate-to-severe pain
- Excess drowsiness
- No escort

Unanticipated Admissions

Surgical

- Pain
- Bleeding
- Extensive surgery
- Surgical complications
- Abdominal surgery
- Otorhinolaryngology and urology surgery

Anesthesia

- Nausea and vomiting
- Somnolence
- Aspiration

Social

- No escort

Medical

- Diabetes mellitus
- Ischemic heart disease
- Sleep apnea

Modified from Awad IT, Chung F: Factors affecting recovery and discharge following ambulatory surgery. Can J Anaesth 53:858-72, 2006.

The frequency of return hospital visits after discharge from ambulatory units is another useful outcome measure. One early study found that 3% of patients returned to the hospital after discharge after ambulatory surgery,[13] with bleeding at the surgical site accounting for 42% of the patients who requested emergency medical care. Interestingly, patients undergoing varicocelectomy and hydrocelectomy were eight times more likely to return to the hospital. However, 77% of the outpatients who sought medical attention in the emergency department were treated and subsequently discharged home. These findings suggest that better preoperative and postoperative education may have prevented a return visit to the hospital in many of these cases.

Future Perspectives

Advances in anesthetic and surgical practices have facilitated the rapid growth in ambulatory surgery throughout the world.[505] With the availability of rapid, short-acting anesthetic, analgesic, sympatholytic, and muscle relaxant drugs, as well as improved cerebral monitoring techniques, it has been possible to minimize the adverse effects of anesthesia on the recovery process. Improvements in perioperative care has allowed surgeons to perform an increasing array of more invasive surgical procedures on outpatients with complex medical conditions on an ambulatory (day-case) basis.

Major surgical procedures (e.g., extensive knee and shoulder reconstruction, laparoscopically assisted vaginal hysterectomy, gastric fundoplication, nephrectomy, splenectomy, and adrenalectomy) are routinely performed at ambulatory centers. Even patients undergoing carotid endarterectomy, pulmonary lobectomy, prostatectomy, and minor craniectomy procedures are being discharged on a 23-hour admission basis. Although it is commonly assumed that the primary reason for the continued expansion in ambulatory surgery is related to pressure from third-party payers and governmental agencies to reduce health care costs, there may be other less obvious benefits for patients and their families. More aggressive rehabilitation leads to faster recovery of organ function, fewer surgical and anesthetic complications, reduced mental and physical disability, and, most importantly, earlier resumption of normal activities (e.g., return to work). For patients "at risk" for hospital-acquired infections (e.g., immunosuppressed patients), ambulatory surgery may also reduce postoperative infectious complications.

As perioperative physicians, anesthesiologists can play an important role in facilitating ambulatory (and short-stay) surgery by actively becoming involved in the preoperative, intraoperative, and postoperative care of this expanding patient population. To achieve the desired outcome, careful consideration must be given to each phase of the ambulatory surgical process. First, it is important to ensure that all patients are in "optimal" medical condition before their elective operation. Changes in NPO policies[552] have allowed patients to continue taking chronic medications and avoid the uncomfortable symptoms of dehydration, hypoglycemia, and caffeine withdrawal. In addition, oral premedication with preventive analgesics (e.g., NSAIDs, COX-2 inhibitors) can improve pain control during the postoperative period. The use of small doses of sedative-anxiolytic drugs (e.g., midazolam) for premedication has been found to improve the perioperative experience of patients without adversely affecting the early recovery process.

Second, the use of anesthetic techniques that optimize intraoperative surgical conditions while providing for rapid early recovery has assumed increased importance in the current health care environment.[464] The introduction of more rapid- and shorter-acting volatile anesthetics and opioid analgesics has allowed practitioners to improve titration and more consistently achieve a recovery profile that facilitates the "fast-tracking" process. Use of cerebral monitoring can further improve the titration of maintenance anesthetics. However, in spontaneously breathing (nonparalyzed) patients, the value of cerebral monitoring in facilitating the recovery process is limited.[553] Importantly, recent studies confirm that modern general anesthesia causes minimal delayed cognitive impairment.[554] Increasingly, practitioners are turning to MAC as an alternative to both general and spinal anesthesia. The availability of drugs such as propofol, remifentanil, and dexmedetomidine has clearly improved the intraoperative conditions for patients undergoing more extensive surgical procedures with local anesthesia-based techniques.

Third, preventing postoperative pain and other untoward side effects (in particular PONV) is critical to successfully implementing a fast-track program in the ambulatory setting and facilitating earlier resumption of normal activities of daily living.[555] The use of a multimodal approach to preventing postoperative pain will decrease the dependence on opioid analgesics. Importantly, NSAIDs (e.g., ketorolac, diclofenac, COX-2 inhibitors) and other nonopioid analgesics (e.g., local anesthetics, gabapentin, acetaminophen, ketamine, clonidine) have assumed an increasingly important role in controlling pain in the ambulatory setting. Similarly, the routine use of prophylactic antiemetic drugs is also extremely helpful in facilitating the recovery process and improving patient satisfaction. Multimodal strategies for minimizing side effects have assumed even greater importance because of rapid expansion in the variety of surgical procedures performed in the ambulatory setting.[424]

Finally, streamlining the recovery process and providing patients and their families with information on how to avoid problems after discharge will also facilitate the rehabilitation process.[462,505] The importance of discussing the implications of undergoing surgical procedures on an ambulatory basis with the patient and family before the operation will also increase acceptance and patient satisfaction with an early ("fast-track") discharge. As perioperative physicians, anesthesiologists will be required to assume an increasingly important role in minimizing postoperative pathophysiologic changes and facilitating the rehabilitation process. To optimize patient outcome, a care team approach involving the patient, the patient's family, the nursing staff, the surgeon, and the anesthesiologist is essential.[556] It has recently been reported that an anesthesiologist-led management team improved OR efficiency (resulting in a 48% reduction in "gap time" between cases) when defined scheduling policies were supported by surgeons, nurses, and hospital administrators.[557] In addition, the implementation of a multidisciplinary approach to minimizing common postoperative side effects can lead to a reduced recovery room and hospital stay as well as enhanced patient satisfaction after surgery.[558] As more extensive surgical procedures are performed on an ambulatory basis, more innovative "multimodal" approaches to providing postdischarge recovery care will assume increased importance.[7,556]

In summary, ambulatory surgery has become the predominate mode of surgical care delivery in both North America and Europe. However, the benefits of ambulatory anesthesia and surgery are yet to be appreciated in the developing countries around the world. The expanded use of ambulatory surgery has the potential to (1) increase patient access to surgical care in locations remote from major medical centers; (2) reduce surgery "waiting list" at public institutions; (3) provide basic surgical services at a reduced cost to patients, third party payers, and governmental agencies; (4) enhance patient satisfaction with their perioperative experience; (5) allow greater involvement of the patient's family in their postoperative care; and (6) facilitate an earlier resumption of normal activities of daily living, including returning to work. Therefore, the challenge for practitioners in the future will be to facilitate the practice of ambulatory surgery throughout the world to improve health care and optimize the use of increasingly limited healthcare resources.

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Paul E. Stensrud

79 Anesthesia at Remote Locations

Key Points

1. Standards of anesthesia care and patient monitoring do not vary with the anesthetizing location.
2. Open communication between anesthesiologists and physicians working in non–operating room anesthetizing locations is key to efficient and timely provision of anesthetic care to patients in these areas.
3. Anesthesiologists working in areas where radiology equipment is in use need to be knowledgeable regarding radiation safety and take adequate precautions to ensure their own safety.
4. The iodinated contrast media used in the radiology and neuroradiology suites, as well as the cardiac catheterization laboratory, may cause significant adverse reactions, and patients receiving contrast media require close monitoring.
5. The unique nature of the magnetic resonance imaging suite with its powerful magnetic fields mandates special care and training to avoid disastrous adverse events.
6. Provision of quality anesthetic management in the cardiac catheterization laboratory requires an understanding of the patient's underlying condition and the procedure to be performed.
7. Electroconvulsive therapy has profound physiologic effects that must be understood and dealt with by anesthesiologists providing care to patients undergoing such therapy.
8. Provision of anesthesia services in areas where therapeutic radiation is used requires further understanding of radiation safety and is facilitated by the installation of devices to allow remote monitoring of patients under general anesthesia.

Hospital-based anesthesiologists increasingly provide anesthetic care to patients at locations outside the operating suite. Such locations include radiology suites, cardiac catheterization laboratories, and psychiatric units. Care must be provided in these locations because of patient need and the logistic constraints of specialized equipment available only in these areas of the hospital, such as computed tomography (CT) and magnetic resonance imaging (MRI) machines. When providing care at such locations, anesthesiologists must maintain the same high standard of anesthetic care provided in the operating suite.[1] The anesthetizing location must be surveyed by the anesthesiologist to determine whether anesthetic care can be delivered safely in that location before delivery of that care.[2] The requirements for anesthesia and the patient's underlying condition do not vary merely because of location, but the conditions under which the anesthetic care is delivered may vary greatly because of the space and equipment available in these locations. Large, mobile pieces of radiologic equipment, radiation hazards, intense magnetic fields, paramedical personnel not familiar with the anesthesia team, and other factors may make the delivery of quality anesthetic care problematic. Despite the promulgation of detailed guidelines, a recent analysis of closed anesthesia claims demonstrated greater injury severity and more substandard care than seen with operating room closed claims.[3]

Guidelines for anesthetic care delivered outside the operating suite have been developed by the American Society of Anesthesiologists (ASA).[4] The 1994 Guidelines for Non–Operating Room Anesthetizing Locations include recommendations for (1) a reliable oxygen source with backup; (2) a suction source; (3) waste gas scavenging; (4) adequate monitoring equipment to meet the standards for basic anesthetic monitoring and, in addition, a self-inflating hand resuscitator bag; (5) sufficient safe electrical outlets; (6) adequate illumination of the patient and anesthesia machine with battery-powered backup; (7) sufficient space for the anesthesia care team; (8) an emergency cart with a defibrillator, emergency drugs, and other emergency equipment; (9) a means of reliable two-way communication to request assistance; and (10) compliance of the facility with all applicable safety and building codes. It is the responsibility of the anesthesiologist providing care to ensure that the anesthetizing location in which that care is delivered meets all applicable standards.

Monitoring

Appropriate patient monitoring is a universal requirement for delivery of safe anesthetic care (see Chapter 38). The ASA has

developed and published standards for basic anesthetic monitoring requiring that qualified anesthesia personnel be present throughout conduct of the course of anesthesia and that the patient's oxygenation, ventilation, circulation, and temperature be continually evaluated.[5] Provision is made for the absence of anesthetic personnel from the immediate vicinity of the patient if required for safety (i.e., in the presence of radiation hazards), provided that adequate patient monitoring is continued despite the physical separation of the anesthesiologist from the patient. Oxygen concentrations of inspired gas should be monitored with the use of a low-concentration alarm, blood oxygenation should be monitored with pulse oximetry, and ventilation should be monitored by observation of the patient. When present, the position of the endotracheal tube must be verified by observation and by detection of end-tidal carbon dioxide. Continuous end-tidal carbon dioxide analysis should be performed. When mechanical ventilation is used, a disconnect alarm with an audible signal must be present. Circulation is monitored by continuous display of the electrocardiogram, as well as by measurement of arterial blood pressure at a minimal interval of 5 minutes, in addition to other assessments such as auscultation, palpation of pulse, invasive blood pressure monitoring, or oximetry. When changes in body temperature are anticipated or suspected, patient temperature should be assessed.

Facilities and Equipment

Many features of non–operating room anesthetizing locations may render delivery of quality anesthetic care difficult (see Chapter 100). Such features may include an awkward layout from the perspective of the anesthesiologist, unfamiliar anesthetic equipment, the anesthetic implications of the procedure performed, the remoteness of available assistance, and personnel less familiar than the usual personnel in the operating suite with the anesthetic aspects of patient care.

Anesthetizing locations outside the operating suite are frequently designed for their primary role, with provision for the requirements of anesthesia being a seeming afterthought. Access to the patient for anesthetic care is hampered by diagnostic and therapeutic equipment such as C-arms, other angiographic equipment, ultrasound machines, and other devices. Space for anesthesia equipment and drugs may be limited and not conveniently located. Advance planning and communication with involved personnel are key to providing safe anesthetic care to patients in such locations.

Piped-in gases, suction, and isolated power are not always available in non–operating room anesthetizing locations. Anesthesia personnel must be familiar with the gas cylinder supply for anesthesia machines. The machines themselves may be older models relegated from the operating suite to areas where their use is less frequent. The ASA has developed and published "Guidelines for Determining Anesthesia Machine Obsolescence."[6] These guidelines have not been reviewed or approved as a practice parameter, but they are practical, instructive, and worthy of review. Briefly, the anesthesia machine should have essential safety features such as a minimum gas ratio device and oxygen failure alarm, not have unacceptable features such as measured flow vaporizers, and be maintained and serviced. Anesthesia machines that do not meet these standards should not be used in any anesthetizing location. Anesthesia personnel must perform standard machine checks before delivering anesthesia and should be familiar with operation of the machine, which may be quite different from the familiar operating room anesthesia machines. Ideally, familiarization and machine checks should be performed before the procedure. Grounded power outlets are a minimum electrical requirement.

Personnel and Staffing

Nonanesthesia personnel involved in patient care in non–operating room anesthetizing locations, including circulating nurses and radiology technicians (see Chapter 2), are frequently less familiar with the management of patients under anesthesia than their counterparts who care for patients in the operating suite. Consequently, they may be unable to provide the skilled assistance that anesthesia personnel may take for granted in other areas. Open communication between care teams is essential because skilled assistance for the anesthesia care team may be some distance away. Thus, the presence of an adequate number of anesthesia personnel in the immediate vicinity of the care site is vital. Educational programs for personnel in non–operating room anesthetizing locations may be helpful in this regard.

Many procedures in non–operating room anesthetizing locations may be performed with conscious sedation provided by practitioners not specialized in anesthesiology. The ASA has published "Practice Guidelines for Sedation and Anesthesia by Non-Anesthesiologists."[7] Numerous recommendations are provided. Patients must be evaluated before the procedure by qualified personnel to ensure that they are not compromised by coexisting medical conditions, are appropriately fasting, and have given informed consent. During the procedure, the level of consciousness, ventilation, oxygenation, and hemodynamics are to be monitored. The standard monitoring practice discussed earlier should be used. A designated individual, not the person performing the procedure, should be present to monitor the patient and ensure maintenance of an adequate level of sedation and analgesia. This designated individual should be trained to recognize complications of analgesia and sedation, and at least one individual trained in basic life support skills should be present continuously when moderate or deep sedation is used. Supplemental oxygen should be used for moderate and deep sedation, and emergency equipment, including pharmacologic antagonists, should be available. Defibrillators should be on hand for at-risk patients undergoing moderate sedation and for all patients undergoing deep sedation. Adequate recovery care should be provided, with the patient observed in an adequately staffed and equipped recovery area. The patient should be released only when acceptable discharge criteria have been met.

Efficient assignment of anesthesia personnel to multiple locations in the hospital is complex. Many factors come into play, including patient need, requirements for adequate preanesthetic evaluation by personnel working in multiple areas, and minimization of "downtime" during room turnover or waiting for the next patient. Organization of the anesthesia department to provide services both within and outside the operating suite is key to efficient provision of patient care. Specific recommendations for such organization are extremely dependent on the health care system under consideration. Non–operating room anesthetic

locations with predictable high utilization might have full-time assignment of anesthetic personnel. Areas with lower utilization may require block assignments of anesthesia times and centralized scheduling with the anesthesiology group to provide care in a timely, yet efficient manner. Benefits include optimal use of assigned anesthesia personnel and release of personnel who would be underused to areas that would otherwise be understaffed.[8] Additionally, provision of adequate anesthesia personnel to provide necessary services allows growth of these practices, with additional opportunities to benefit patients.[9]

Medications

Anesthesia techniques used in non–operating room anesthetizing locations range from no anesthesia; to minimal, moderate, or deep sedation/analgesia; to general anesthesia. The choice of personnel to deliver the anesthesia care depends on the desired level of anesthesia, the patient's underlying medical condition, and the procedure to be performed. Medications used to provide sedation/analgesia result in a continuum of depth of sedation ranging from anxiolysis to general anesthesia.[7] Sedation/analgesia is defined as the level of anesthesia at which patients are able to tolerate unpleasant procedures through relief of anxiety, discomfort, or pain and at which uncooperative patients are able to tolerate procedures requiring that they not move. Moderate sedation/analgesia is defined as the level of anesthesia at which the patient retains purposeful responses to stimulation, requires no airway intervention, and can maintain adequate ventilation and cardiovascular function. Nonanesthesia personnel may care for patients undergoing procedures that require minimal to moderate sedation/analgesia, provided that they are trained to rescue patients from deep sedation/analgesia. Deeper levels of sedation, general anesthesia, or complex underlying patient conditions require the presence of adequately trained anesthesia personnel. Most procedures conducted in non–operating room anesthetizing locations can be performed under minimal to moderate sedation/analgesia.

Combinations of sedative and analgesic medications, such as benzodiazepines and opioids, provide effective moderate sedation (also see Chapter 78).[7] It is recommended that the drugs be administered individually and the doses carefully titrated to achieve the desired effect in a given patient while recognizing that combinations of sedative and analgesic agents may cause more than additive respiratory depression. Patients receiving intravenous sedation/analgesia should have intravenous access maintained throughout the procedure. Otherwise, the need for intravenous access needs to be individually assessed according to the patient's condition, as well as the procedure planned. When oral agents are used (e.g., benzodiazepines, chloral hydrate), adequate time must be given to allow complete drug uptake before supplementation can be considered. Repeat nonintravenous dosing of sedatives/analgesics is specifically not recommended because of variability in drug absorption. Combinations of benzodiazepines (e.g., midazolam, diazepam) and opiates (e.g., alfentanil or remifentanil) have been the mainstay of intravenous sedation/analgesia. These drugs are titratable, and antagonists are available: flumazenil for antagonism of benzodiazepine-induced sedation and naloxone for antagonism of opiate effects. These antagonists should be reserved for emergency use only because their administration can result in patient discomfort, as well as adverse side effects. The ASA has noted that the use of barbiturates or propofol for analgesia/sedation can result in rapid onset of general anesthesia and that these agents are best reserved for the use of trained anesthesia personnel. Because ketamine may alter the signs of anesthetic depth, as well as cause airway obstruction and pulmonary aspiration, this agent should also be reserved for the use of anesthesia personnel.

Recovery Care

Frequently, anesthesia provided in remote locations requires transport of the patient over longer distances to the recovery location than similar care provided in the operating suite does (also see Chapter 85). The patient must be medically stable before transport. The patient must be accompanied to the recovery area by the individual providing the anesthesia or sedation/analgesia care, and monitoring commensurate with the patient's medical condition must be maintained. Provision of oxygen delivery and monitoring while the patient is on the transport cart may be required. Appropriate recovery facilities and staff must be provided.[7,10] In the recovery area, the patient's condition must be documented and continually assessed. Immediate availability of personnel trained in advanced cardiac life support should be ensured. Patients should not be discharged until they have met specific discharge criteria.

Radiology Suite

Radiologic procedures that may require sedation/analgesia include a number of imaging modalities such as radiology, ultrasonography, CT, and MRI, as well as various interventions that may be directed by the imaging modalities. Such interventions include percutaneous drain placement, nephrostomy tube placement, percutaneous placement of feeding tubes, placement of intravascular access catheters, thrombolysis, dilation of stenotic vessels, embolization of tumors or arteriovenous malformations (AVMs), and many other interventions. Tissue biopsy specimens may be obtained under radiologic guidance with the aforementioned techniques. For example, some solid tumors may be treated by guided tissue ablation.[11] Painful metastases may be treated by guided radiofrequency (RF) ablation.[12] Cerebrovascular lesions may be treated endovascularly with guidance by digital subtraction angiography.[13] Advances in imaging capability, as well as the availability of advanced endovascular devices and RF probes, have increased the use of radiology suites and the demand for anesthesia services in these areas.

General Considerations

In diagnostic and, especially, in therapeutic radiologic procedures, the patient must often remain immobile for prolonged periods. Most procedures may be accomplished with minimal to moderate sedation/analgesia.[14] Cooperative patients may be able to undergo procedures with no or minimal sedation, but obtunded patients or children will require, at a minimum, sedation/analgesia. In

some instances, however, cooperative patients may not tolerate the procedure because of anxiety or claustrophobia. Patients in the radiology suite may have severe underlying medical conditions such as cardiovascular, pulmonary, or neurologic disease. Indeed, they may be in the radiology suite, as opposed to the operating suite, precisely because their severe underlying disease precludes operative intervention. Finally, anesthesiologists may be summoned relatively late in the care episode, after failure of sedation/analgesia administered by the radiologist or nonanesthesia personnel. Clearly, this situation is undesirable, and open communication between the departments of radiology and anesthesiology is essential.

The work environment in the radiology suite is frequently ill adapted to safe anesthetic care of patients. The rooms may be crowded, especially in older radiology suites or those in which anesthesiologists were not consulted during the design phase. Patients and equipment are frequently moved during the procedures to facilitate imaging, and if such movement is not coordinated with the anesthesia team, airway devices or intravascular access may become dislodged, and the patient, or even the anesthesia provider, may be injured. High-voltage equipment or the presence of intense magnetic fields may result in current leakage being conducted to the patient by electrically conductive monitoring leads. Lack of gas scavenging may limit the options of the anesthesiologist should general anesthesia prove necessary for the procedure. Familiarity of the anesthesia personnel with the environment in the anesthetizing location is essential to provide safe patient care.

Radiation Safety

A unique hazard in the radiology suite is radiation exposure (see Chapter 101). Radiation exposure is potentially harmful in terms of its somatic effects during an exposed individual's lifetime (e.g., production of leukemia) and in terms of genetic injury resulting in fetal abnormalities caused by damage to gonadal cells or the developing fetus. In the environment of the radiology suite, anesthesia personnel must be aware of radiation safety and take precautions when possible to avoid radiation exposure. Dosimeters should be worn to monitor exposure. In the United States, the maximal permissible radiation dose for occupationally exposed persons is 50 millisieverts (mSv) annually, a lifetime cumulative dose of 10 mSv × age, and monthly exposure of 0.5 mSv for pregnant women.[15] Radiation exposure can be limited by wearing appropriate lead aprons and thyroid shields, using movable leaded glass screens, and applying innovative techniques such as video monitoring and remote mirroring of monitor data to allow remote conduct of anesthesia when appropriate and required for the safety of anesthesia personnel. Open communication and adequate warning of initiation of imaging by the radiology team allow the anesthesia personnel to take appropriate precautions in a timely fashion.

Iodinated Contrast Media

Iodinated contrast agents are often used in diagnostic and therapeutic radiologic procedures to assist imaging. Soluble contrast agents use iodine (atomic number 53) to absorb x-rays. Older ionized contrast media were hyperosmolar and relatively toxic.[16] Nonionized contrast media feature low osmolality, have improved side effect profiles, and are being used with increasing frequency.[17] Adverse reactions to contrast media range from mild to immediately life threatening, and causes include direct toxicity, idiosyncratic reactions, and allergic reactions, either anaphylactic or anaphylactoid (Table 79-1). Predisposing factors include a history of bronchospasm, history of allergy, underlying cardiac disease, hypovolemia, hematologic disease, renal dysfunction, extremes of age, anxiety, and medications such as β-blockers, aspirin, and nonsteroidal anti-inflammatory drugs.[18] Prompt recognition plus treatment of contrast media reactions is important to prevent progression of less severe reactions and lessen the impact of severe reactions. Treatment is symptomatic, for example, oxygen and bronchodilators to treat bronchospasm. Severe or resistant bronchospasm may require treatment with epinephrine. Typically, corticosteroids and antihistamines are given to symptomatic patients under the assumption that the cause is immunologic. Patients who have had previous reactions to contrast media may benefit from pretreatment with prednisolone, 50 mg 12 and 2 hours before a procedure requiring contrast media, and diphenhydramine, 50 mg immediately before the procedure.[17,19] Protocols should be in place both for treatment of acute contrast media reaction and for prophylaxis in patients with a history of such reactions.

Contrast-induced nephropathy is a significant complication of radiologic procedures and a leading cause of hospital-acquired acute renal failure.[18,20] High-osmolality contrast agents are associated with greater nephrotoxicity than low-osmolality agents are. Most cases of new or worsened renal function related to contrast media are self-limited and resolve within 2 weeks. However, some patients may progress to the point of requiring dialysis. Prevention of renal dysfunction related to contrast media has been based on hydration before, during, and after the procedure and the use of low-osmolality contrast media. Recent studies have demonstrated a reduction in contrast media–related nephrotoxicity by the administration of acetylcysteine[21-23] or ascorbic acid.[24] Life-threatening lactic acidosis may develop in non–insulin-dependent diabetic patients who are receiving metformin and have preexisting renal dysfunction if their renal function declines further.[18,25] Extra care is needed when patients taking metformin receive radiologic contrast media.

Anesthesia in the Radiology Suite

It is obvious from the preceding discussion that delivery of anesthesia care in the radiology suite is not to be undertaken

Table 79-1 Reactions to Iodinated Contrast Media

Mild	Severe	Life Threatening
Nausea, retching	Vomiting	Glottic edema/bronchospasm
Perception of warmth	Rigors	Pulmonary edema
Headache	Feeling faint	Life-threatening arrhythmias
Itchy rash	Chest pain	Cardiac arrest
Mild urticaria	Severe urticaria	Seizures/unconsciousness
	Bronchospasm, dyspnea	
	Chest pain	
	Abdominal pain/diarrhea	
	Arrhythmias	
	Renal failure	

lightly. Ideally, the anesthesiologist should be involved at the earliest possible stage in planning the delivery of such care. Careful communication with radiologists and early consultation with the anesthesiologist will maximize efficient operation of both departments by providing timely, quality anesthetic care and minimizing delays or cancellation of necessary procedures. The development of sedation/analgesia guidelines, as well as training of involved personnel, is an important step in providing quality anesthetic care.[7] Nonanesthesiologist providers of sedation/analgesia who know and understand the guidelines regarding sedation/analgesia become adept at recognizing patients who are at higher risk for either failure of sedation or complications and are thus able to provide more timely notification of appropriate anesthesia personnel that assistance is required.

In the past, much variability was noted in adherence to the modern guidelines regarding provision of anesthesia care, including lack of preoperative evaluation, lack of informed consent, and lack of sufficient dedicated personnel to monitor pediatric and adult patients during sedation/analgesia.[26,27] It would be hoped that increased involvement by anesthesiologists in this arena will improve the delivery of care.

A number of anesthesia techniques are used in the radiology suite. Minimal to moderate sedation/analgesia is the technique used for most patients undergoing these procedures.[14,27] For most adults, combinations of intravenous benzodiazepines and opioids (e.g., titration of midazolam and fentanyl) are sufficient to ensure comfort during the procedure. As noted earlier, the use of more potent anesthetic agents such as propofol, barbiturates, and ketamine is best reserved for specialists in anesthesia.[7] The patient's condition, the anticipated level of stimulation, and patient position during the procedure are all important considerations. As an example, a patient undergoing ultrasound-guided hepatic biopsy might have ascites, which would render that patient prone to aspiration if sedated, and penetration of the hepatic capsule by the biopsy needle would be anticipated to be quite painful. Such a patient might benefit from general anesthesia rather than sedation/analgesia. Procedures that might be anticipated to last several hours may best be performed with general anesthesia at the outset rather than late conversion after failure of sedation/analgesia, when patient access might be limited by catheter placement and radiologic equipment. Certain procedures performed in the radiology suite may necessitate specific anesthetic techniques for maximum patient benefit. It was found that patients undergoing RF ablation of painful osteolytic lesions seem to benefit from continuous regional anesthesia after the procedure, which is usually performed under general anesthesia.[12] The role of regional anesthetic techniques may be expected to grow in nonoperative anesthetizing locations as further advances in treatment modalities occur (also see Chapters 51 and 52).

Pediatric patients merit special consideration (see Chapter 82).[28] Some radiologic procedures require patients to remain still for prolonged periods, which may not be possible for infants and children, even with sedation/analgesia. When it is thought that the procedure can be performed with sedation/analgesia, healthier infants and children frequently receive chloral hydrate orally for radiologic procedures (25 to 50 mg/kg for infants younger than 4 months, 50 mg/kg for older children) (also see Chapter 82). Interventional procedures of longer duration or those that require more dermal punctures than placement of a single intravenous catheter may necessitate more intensive anesthetic regimens ranging from deeper sedation/analgesia to general anesthesia, with or without endotracheal intubation. Additionally, the patient's underlying medical condition may merit more intensive anesthesiology involvement than might otherwise be the case. Children's Hospital Boston has developed criteria to assist radiology nurses carrying out preprocedure evaluations to determine the necessity for anesthesiology referral before the planned procedure. Patient characteristics necessitating anesthesiology referral at that institution include a history of apnea, age younger than 1 month, respiratory compromise, Pierre Robin syndrome, Apert's or Crouzon's syndrome, severe gastroesophageal reflux, poor oral muscle development, sedative/analgesic allergy, new-onset illness, a history of cardiac disease, and mitochondrial or metabolic disease.[29] The development of similar referral triggers at other institutions seems prudent, to provide timely, quality anesthetic care and to avoid unnecessary cancellation or postponement of potentially beneficial procedures. The availability of anesthesia personnel familiar with the pediatric patient plus the availability of equipment for provision of pediatric anesthesia in all areas where pediatric anesthesia may be delivered is essential.

Patients with difficult airways, whether anticipated or not, can be problematic in settings outside the operating suite (also see Chapter 50). It is recommended that anticipated difficult endotracheal intubations be performed in the operating suite because of its greater availability of skilled assistants and specialized equipment. As soon as the airway is controlled, the patient can be transported to the site of the planned procedure, should it be necessary to perform the procedure outside the operating suite. Unanticipated difficult airways can place an anesthesiologist outside the operating suite in a difficult position.

Computed Tomography

CT is commonly used for diagnostic purposes, for example, to evaluate the status of a neoplastic process in the thorax or abdomen. It has proved valuable in studies of vascular malformations and tumors. Caregivers involved in imaging patients undergoing this examination should be mindful that some patients have limited reserve because of their disease process (e.g., compression of the upper airway or vena cava by a neoplastic process). CT is occasionally also used for invasive therapeutic procedures instead of fluoroscopy, such as to visualize drainage of a liver abscess. Contrast media are often used in conjunction with CT to enhance the quality of the image. If contrast media are to be introduced into the gastrointestinal system in patients who are sedated or anesthetized, it is usually done by nasogastric tube. When the airway is not protected in this situation, there is a risk of aspiration. It has also been suggested that the incidence of adverse sequelae associated with the use of contrast media is higher in patients undergoing CT than other types of radiologic studies because of limited access to the patient and consequent compromised monitoring and treatment if reactions do occur.[17]

Issues confronting anesthesiologists requested to anesthetize patients undergoing CT include inaccessibility of the patient during the procedure and control of movement artifact. Monitoring interference is not a problem in CT, however, as it is with MRI, as discussed later. With anesthetized patients, care needs to be taken to ensure that the sides of the scanning tunnel do not occlude or dislodge the breathing circuit or monitoring leads during the procedure. As with other radiographic procedures,

exposure to ionizing radiation occurs during CT scans. The patient can be monitored visually through a lead glass window, supplemented if necessary by closed-circuit television. Should the patient's condition merit closer monitoring by the anesthesiologist, radiation-monitoring badges and protective lead aprons and thyroid shields must be worn.

The anticipated procedure may necessitate special anesthetic techniques. Ablation of bony metastases may be conducted under CT guidance, and continuous postprocedure regional analgesia may be beneficial, as noted previously. Selection of the regional anesthetic technique and timing of placement of the catheter (if a catheter-based technique is selected) are dependent on the patient's condition, as well as the available space and equipment. For example, the CT room is not typically a suitable location for placement of an epidural catheter. If a recovery room or preanesthetic area is available in the radiology suite, it might be a convenient, safe location for placement of a regional anesthetic catheter. If such areas are not conveniently located or sufficiently equipped, these techniques might have to be performed in the operating suite before or after the CT-guided procedure.

Certain pulmonary neoplasms, usually metastases not suitable for surgical resection, are amenable to CT-guided RF ablation.[30,31] These procedures have been performed under both sedation/analgesia and general anesthesia. Reported complications of RF ablation of pulmonary masses include pleural effusion, pneumothorax, pneumonia, acute respiratory failure, and massive hemoptysis.[32,33] It may be desirable that these procedures be performed under general anesthesia. Some of the procedures, depending on perceived risk, have been conducted via one-lung ventilation with the use of double-lumen endotracheal tubes. Whatever the anesthetic method, anesthesia personnel caring for these patients must be vigilant for the occurrence of complications, which are not infrequent.

Magnetic Resonance Imaging

MRI can reveal subtle differences between areas of dissimilar anatomy, physiology, and pathology that are not possible with other imaging techniques. Other advantages include the following:

1. Unlike conventional radiographs and CT, MRI can obtain images in any plane (transverse, sagittal, coronal, or oblique).
2. MRI provides excellent soft tissue contrast.
3. It may provide intravascular contrast without the need for intravenous contrast media.
4. Very little patient preparation is required.
5. MRI does not produce ionizing radiation, is noninvasive, and does not in itself produce biologically deleterious effects.

Principles of MRI

A number of detailed descriptions of the technical aspects of MRI have been published.[34-37] Briefly, atomic nuclei with an odd number of protons or neutrons have the potential to act as magnetic dipoles. This property is possessed by all paramagnetic elements (^{1}H, ^{13}C, ^{19}F, ^{23}Na, and ^{31}P). Biologic tissues have a high water content. Thus, ^{1}H is present in high concentrations, and its detection is the basis of MRI. The single-proton ^{1}H can be understood to behave like a tiny bar magnet with north and south poles. Absent a strong magnetic field, the hydrogen protons are oriented randomly and do not exhibit any net magnetic field. If they are placed in a strong external magnetic field, the hydrogen protons will align themselves parallel or antiparallel to the applied magnetic field, and the tissue itself will exhibit slight net magnetism, with the magnetic vector aligned with the MRI field. This tissue magnetism results from the nuclei that are aligned antiparallel to the external magnetic field; they are in a slightly higher energy state than those aligned parallel to the field. This energy difference increases with the strength of the applied magnetic field. In MRI, tissue magnetized by the powerful static magnetic field is suddenly exposed to a second, transient magnetic field aligned perpendicular to the static field. This second magnetic field is generated by a pulse of RF energy. The RF pulse deflects the magnetic vector of ^{1}H by altering proton alignment. When the transient RF pulse is terminated, the nuclei return to their original alignment within the static magnetic field, which causes a weak transient RF signal as the protons return to their previous energy state. The RF signal emitted by the tissues is detected by an RF coil placed in close proximity to the patient. The intensity of the signals received is plotted in gray scale, and an image is built up by sophisticated computers. The characteristics of decay of the emitted signal, which is called "relaxation," provide most of the information for generating the image. Relaxation time is measured in two ways: T1 relaxation is the time taken to return to the resting magnetic vector, whereas T2 is the time taken to return to resting axial spin. Different tissues demonstrate different relaxation characteristics. Multiple, sequential RF pulses within the static field can thus be used to emphasize particular tissues or abnormalities by taking advantage of the difference in relaxation between tissues.

The magnetic field strength used in MRI scanners is measured in tesla units. One tesla (T) equals 10,000 gauss, with the strength of the earth's magnetic field at its surface being between 0.5 and 1.0 gauss. Field strengths used in most clinical MRI examinations vary from 0.05 to 2.0 T, but the use of 3-T units is increasing, and research units with 8 T or greater are in use.[38] The advantage of weaker-field MRI scanners is that more open construction can be used, and the advantage of scanners with stronger fields is that they produce better image quality. Stronger-field MRI scanners generally use cryogenic magnets with superconductive coils operating in liquid helium (4°K).

Hydrogen proton density and relaxation dynamics as detected by MRI vary in different tissues in accordance with the tissue's physical and chemical properties. Because the differences in water content and proton environment in gray and white matter are greater than the differences in electron densities as measured by CT, MRI can produce better resolution between gray and white matter, and the same is also applicable to soft tissue examinations. MRI permits evaluation of blood flow, cerebrospinal fluid flow, contraction and relaxation of organs, and because calcium does not emit a signal in MRI, images of tissues surrounded by bone. This lack of a calcium signal, however, prevents MRI from detecting pathologic calcification in soft tissue tumors and pathologic changes in cortical bone.[39]

The RF signal used during MRI scanning is of very low intensity and is subject to interference from stray high-frequency

electronic radiation such as FM radio signals and electromagnetic emissions from electronic equipment or monitoring devices.[34] For this reason, the scanning area is enclosed in an RF shield incorporated into the structure of the MRI suite. Preventing interference from monitoring devices situated within the RF shield can be challenging. Attempts have been made to overcome this problem by using isolated power sources or battery power, filtering, enclosing the monitoring device in its own small RF shield, or any combination of these measures. The implications of this problem for the anesthesiologist are obvious.

Limitations and Hazards of MRI

MRI scanning has a number of limitations. Imaging is time consuming, and individual scans may take up to 20 minutes, with an entire examination lasting more than 1 hour. Any patient movement, even that resulting from physiologic motion (e.g., cardiac and vascular flow pulsations, cerebrospinal fluid flow and pulsation, respiratory excursion, and peristalsis in the gastrointestinal tract), can produce artifacts on the image. To optimize information when imaging the cardiovascular system, the signal acquisition is synchronized or "gated" with phases of the cardiac cycle (electrocardiographic [ECG] R wave) to virtually freeze cardiac motion. The magnet generating the large static magnetic field has a small-diameter hollow bore, typically 50 to 65 cm in diameter. Obese patients cannot be examined in this small magnetic bore, and patients otherwise suitable for examination may not tolerate long periods inside the confines of the magnet. Switching the RF generators on and off produces loud noises (>90 dB). Hearing protection is mandatory for both the patient and health care personnel who must be present in the scanning room. Heating resulting from the RF energy of nonferromagnetic prosthetic devices has not proved to be a problem.[40] Body surfaces do absorb this RF energy, but it is unlikely that the patient's temperature will increase by more than 1°C.

Direct adverse biologic effects of the MRI field are not believed to exist. Nonetheless, a number of serious hazards are attributable to the intense magnetic fields necessary for MRI.[41] Although heating of the whole patient is not generally a concern, the potential exists for generation of heat within monitoring wires as a result of electromagnetic induction, circuit resonance, or an "antenna effect." Thermal injury in the area of ECG electrodes and pulse oximeter probes has been reported.[42] Recommendations for avoiding thermal injury include keeping monitoring wires straight (avoid loops), avoiding having conductors touch the patient at more than one location, and inspecting monitor wires before each use to avoid the use of worn or frayed wires.

The most significant risk posed in the MRI suite is the effect of the magnet on ferrous objects.[34,39-42] Dislodgement and malfunction of implanted biologic devices or other objects containing ferromagnetic material are also real possibilities. Such items include shrapnel, vascular clips and shunts, wire spiral endotracheal tubes, pacemakers, automatic implantable cardioverter-defibrillators (ICDs), mechanical heart valves, and implanted biologic pumps. Potential problems with cardiac pacemakers and ICDs include heating of leads by induced current, inhibition of the pacemaker output of rapid pacing, reed switch malfunction, ICD malfunction, or torque on the pacemaker pack.[43,44] Patients with such devices should not undergo MRI examination. Tattoo ink may contain high concentrations of iron oxide. Burns at tattoo sites have been reported after exposure to the magnetic fields of MRI, but such incidents are very rare and the presence of, for example, permanent eyeliner should not exclude the patient from MRI examination.[45,46] Intraocular ferromagnetic foreign bodies may migrate within the MRI field, and MRI examination of patients with suspected ferromagnetic ocular foreign bodies should not be undertaken.[47]

Death from torque of a vascular clip within the MRI field has been reported.[48] Manufacturers of some implantable devices, such as the clips used in vascular surgery and neurosurgery, are now trying to use alloys that have low ferromagnetic properties and are safe in the MRI suite. Clips with low ferromagnetic properties are safe in MRI systems with magnetic fields of 1.5 T or less. MRI systems of up to 3 T, which are increasingly being used, mandate that the clips be nonferrous (e.g., titanium) to avoid movement of the clip within the scanning magnet.[49] Before MRI examination, the radiologist and the surgeon who placed the vascular clip must confer, and a positive determination of the MRI safety of the particular clip implanted in the patient must be made. In the absence of positive knowledge of the exact composition of the clip in question, MRI examination should not be performed.

Although potentially significant, the relatively small movements of implanted ferromagnetic devices and local damage caused by heat generation within lead systems are overshadowed in the popular and medical literature by the large, rapid movements possible when iron-containing items are brought into the vicinity of the magnetic field of the MRI machine. Typical objects include scissors, pens, keys, and gas cylinders. When such objects are brought into the vicinity of the MRI scanner, the intense magnetic field may attract them into the scanner bore at high velocity. The result when a patient is present in the scanner bore may be fatal.[50,51] Even in the absence of a patient, health personnel, maintenance workers, or visitors to the MRI suite might be injured by objects flying at high velocity toward the scanner.[51] For this reason, ferromagnetic items must never be allowed in the vicinity of the MRI magnet.

Because of the numerous, severe hazards related to MRI, recommendations regarding MRI safety have been developed by the American College of Radiology.[41] To summarize, recommendations include the development of formal policies and procedures regarding MRI, which should be present at every MRI site. These policies should be under the direction of formally appointed competent personnel, and review mechanisms should be in place to ensure quality care. Importantly, the recommended policies include restriction of access to the site within the MRI suite. The MRI suite should be divided into four zones. Zone I is the public zone with free access. Zone II is the interface between the public zone and the MRI suite, where all movement by non-MRI personnel is supervised by MRI personnel. Zone III is the area within which the introduction of ferromagnetic objects may form a hazard. Zone II should be separated from zone III by physical restriction (locked doors). MRI personnel are responsible for controlling all movement into zone III by any personnel, including patients, the public, health care workers, maintenance workers, hospital administration, security, and fire department personnel. Note that this restriction specifically includes non–MRI-trained physicians. Zone IV is the scanner room itself, which should be further separated from zone III and clearly marked with lighted signs. Formal training programs are to be put in place for MRI personnel. No one is to be considered "MRI personnel" until they

have completed the formal training program. MRI personnel will screen all non-MRI personnel who request access to zone III and beyond and closely supervise their activities. It is important that anesthesiologists caring for patients understand the restrictions in place on access to the MRI suite and the reasons for these restrictions. Anesthesia personnel who may be called on to provide patient care in the MRI suite should complete the formal training program to become recognized MRI personnel.

Intraoperative MRI

Safety guidelines have been developed for "freestanding" MRI areas. The increasing use of intraoperative MRI complicates this picture further. Not only must the anesthesia team provide anesthesia for a potentially complex surgical procedure, but they must also intermittently provide an MRI-compatible anesthetic during episodes of intraoperative imaging. In addition to radiology and anesthesia personnel, intraoperative use of MRI means that a complete surgical team will also be in the vicinity of the MRI machine. All personnel on these teams must understand the special hazards associated with MRI and must be "MRI qualified." Radiology personnel must continue to monitor all involved staff to ensure compliance with safety guidelines, especially because anesthesia and operating room staff may be distracted by the surgical procedure and not be as cognizant of MRI safety requirements as they would be in a freestanding MRI area. In addition, anesthesia personnel must deal with moving anesthetized patients intraoperatively into the MRI torus, perhaps multiple times. Anesthesiologists must be involved from the beginning in the design of the MRI operating room to ensure that the needs of anesthetized patients can be met safely.[28]

Anesthetic Management for MRI

Patient acceptance of MRI examination is generally high. Most adults and small babies (if recently fed and well wrapped) tolerate the procedure without sedation/analgesia. Sedation/analgesia may be required in older children and adults who cannot cooperate. Sedation/analgesia is usually administered by radiologists and nurses in the MRI suite. This practice generally works well, as long as it conforms to the ASA recommendations for sedation by nonanesthesiologists.[7] The likelihood that a child can undergo the examination successfully under sedation/analgesia is enhanced if the child is deprived of sleep for several hours the previous night. All patients receiving sedation/analgesia need supplemental oxygen and standard monitoring. Anesthesia personnel become involved in these patients' care in the MRI suite when sedation fails, when it is impossible to control patient movement without general anesthesia, and when it is necessary to protect the patient's airway and control ventilation.

Several articles have discussed anesthetic management of patients undergoing MRI.[52-56] As might be inferred from the preceding discussion, provision of anesthesia in the MRI suite poses several unique problems, including the following:

1. Limited patient access and visibility, especially when the patient must be placed head first into the magnet (Fig. 79-1)

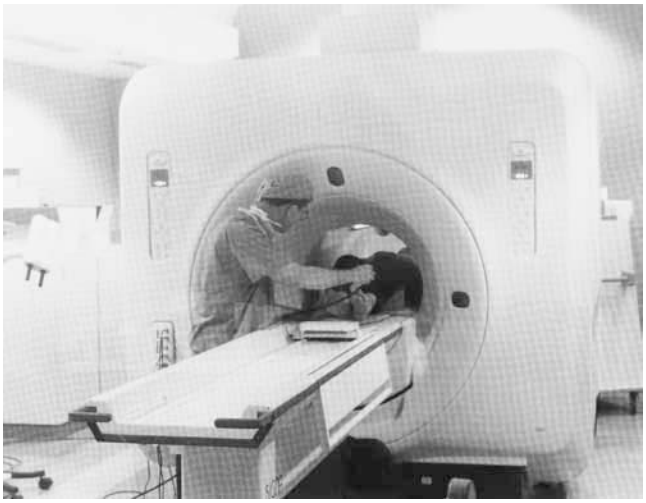

Figure 79-1 View of a magnetic resonance scanner through the window from the control desk. Note the limited patient access. The photograph appears grainy because of the radiofrequency shield embedded in the window. *(From Mackenzie RA, Southorn PA, Stensrud PE: Anesthesia at remote locations.* In *Miller RD* [*ed*]*: Anesthesiology, 5th ed. Philadelphia, Churchill Livingstone, 2000, p 2248.)*

2. Absolute need to exclude ferromagnetic components
3. Interference/malfunction of monitoring equipment produced by the changing magnetic field and RF currents
4. Potential degradation of the imaging caused by the stray RF currents produced by the monitoring equipment and leads
5. The necessity to not move the anesthetic and monitoring equipment when the examination has started to prevent degradation of magnetic field homogeneity
6. Limited access to the MRI suite for emergency personnel in accordance with the recommended policies noted earlier

Anesthesiologists must be involved in the planning and construction of MRI suites, as well as administration of the operation of these suites, to minimize the aforementioned issues. Satisfactory performance of the anesthetic and monitoring equipment and ensuring that this equipment does not interfere with the scanning need to be confirmed before clinical use. A common approach now is to induce anesthesia in an induction area adjacent to the MRI suite outside the magnetic field by using conventional equipment with the patient on a dedicated MRI transport table that is not ferromagnetic. This transport table is then used to bring the patient into the MRI suite, where anesthesia and monitoring are continued with MRI-compatible devices. The MRI transport table is also used to remove the patient rapidly from the scanner should an emergency arise. This is important because the ferromagnetic equipment used for patient resuscitation by the code team and others must never be brought into the MRI scanner room.[41]

Several manufacturers make MRI-compatible anesthetic machines.[56] Various breathing circuits have been used successfully in the MRI suite. They can be used to deliver breaths generated by an MRI-compatible mechanical ventilator or by manual inflation of an anesthesia bag. Because the patient's airway is not

easily accessed during the MRI scan and because patient assessment and communication are limited by both the magnet bore in which the patient is placed and the loud noise associated with MRI scanning, deep sedation/analgesia is not advisable. Patients requiring more than moderate sedation/analgesia are probably most safely administered a general anesthetic with airway control by either endotracheal intubation or a laryngeal mask airway (LMA). Endotracheal tubes and LMAs and their connections to the breathing circuit must contain no ferromagnetic material. Because conventional zinc batteries are strongly ferromagnetic, if a laryngoscope is needed in the MRI suite, it should be of plastic construction and equipped with lithium batteries and aluminum spacers. As noted, most emergency situations in the MRI scan room itself should be treated with basic life support techniques while the patient is rapidly moved out of the scanner vicinity for definitive treatment.

Given the patient's inaccessibility in the MRI scanner, observation of the patient by the anesthesiologist is limited (see Fig. 79-1). Chest excursion will probably be observable, but this is not guaranteed. A peripheral pulse will probably be amenable to palpation, but again, this is not guaranteed. Specific problems and solutions for monitoring each physiologic parameter in the MRI environment can be summarized as follows[52]:

1. Electrocardiography: Voltage induced by blood flow in the aorta when the patient is in a static magnetic field produces T- and ST-wave abnormalities. In addition, the rapidly changing magnetic fields can induce artifacts in the ECG trace. Furthermore, as noted previously, the patient may be subject to heating and thermal injury. ECG wires must be kept straight and contact of the wires with the patient must be minimized.
2. Pulse oximetry: The "antenna effect" in conventional pulse oximetry wires has resulted in thermal injury.[42] Typically, MRI-compatible pulse oximeters use fiberoptic signal linking between the sensor and monitor.
3. Noninvasive blood pressure monitoring: Such monitoring can be successfully accomplished, provided that the connections of the blood pressure cuff and hoses are plastic.
4. Precordial and esophageal stethoscopes: These instruments do not function well because of interference created by the noise of the scanner during operation.
5. Capnography: This monitor usually functions satisfactorily, but the length of the sample tube may cause a significant time delay in signal transduction.
6. Temperature: Temperature monitoring is not generally a problem if temperature probes with RF filters are used.

Meeting all the ASA recommendations for standard monitors in the MRI suite is thus problematic. Pulse oximetry should be used on all patients receiving sedation/analgesia or anesthesia, with the probe placed as far from the scanning site as possible to limit the potential for thermal injury, which still exists despite the use of nonferromagnetic connections.[56] Noninvasive blood pressure monitoring should likewise be used in all anesthetized patients. Capnography should be performed in all applicable cases. ECG monitoring in the MRI scanner should probably be limited to patients deemed to be at particularly high risk, if it is used at all, with precautions taken to limit the potential for thermal injury.[41]

No specific anesthetic technique is required for MRI. Most cooperative patients, as noted, will tolerate MRI with either no sedation or light to moderate sedation/analgesia. MRI is not painful, and the medication regimen may thus be biased toward sedation unless the patient's underlying condition or the long period in the scanner in the supine position requires analgesia. Patients with critical neurologic and cardiac problems, including congenital cardiac conditions, are frequently and safely anesthetized for MRI. Should the patient undergo sedation/analgesia, the anesthesia provider should be present in the scanner room. Hearing protection is mandatory for anesthesia providers if they must remain in the scan room. Critically ill patients, uncooperative adults, and children older than 3 years, who may not respond favorably to chloral hydrate, may best be managed with general anesthesia. Because patient access is limited during the scan, it has been suggested that the airway be secured with either an endotracheal tube or LMA and ventilation controlled. General anesthesia is induced in an induction area adjacent to the MRI room after standard monitors are placed and the airway is secured. Particular care is taken to ensure removal of the ECG electrodes before transfer to the scan room, as well as all other non–MRI-compatible monitoring devices. The patient is then transferred to the adjacent scan room, ventilation is resumed, and function of the airway device is reassessed. Airway disconnection is typically limited to 15 to 30 seconds. Anesthesia can be maintained with volatile anesthetics or propofol. MRI-compatible monitors are placed, and the examination proceeds. It is not mandatory that the anesthesia provider remain in the scan room during general anesthesia, assuming that remote mirroring of the monitors and direct observation of the anesthesia machine are feasible from the immediately adjacent control room. If such observation is not feasible, the anesthesia provider will need to remain in the scanner room with the patient. At the end of the examination, the patient is transferred back to the induction area and awakened there, where conventional monitoring may be resumed and conventional management of any untoward event can take place. At any point in the examination, the patient may be transferred on an emergency basis to the induction area for management of an emergency situation. After emergence from anesthesia, the patient is transferred to an appropriate recovery room and monitored. Patients are discharged when they are documented to have met conventional discharge criteria.

Anesthesia for Interventional Neuroradiology

The advances in interventional neuroradiology over the past 25 years have been remarkable (see Chapter 63).[57] Procedures that were once highly experimental are now routinely performed at many centers. Relatively commonly performed interventional neuroradiologic procedures include embolization of cerebral and dural AVMs, coil embolization of cerebral aneurysms, angioplasty of atherosclerotic lesions, and thrombolysis of acute thromboembolic stroke.[58] Interventional neuroradiologic procedures are sophisticated diagnostic and therapeutic endeavors involving complex manipulation of patient conditions to provide optimal operative outcomes. These procedures may involve deliberate

hypotension, deliberate hypercapnia, or deliberate cerebral ischemia as part of the procedure; a requirement for rapid transition between deep sedation/analgesia and the awake, responsive state; and severe potential procedural complications.[58] Accordingly, involvement of experienced anesthesiologists is valuable to ensure an optimal outcome.

Interventional neuroradiology (or endovascular neurosurgery) is the radiologically guided endovascular approach to lesions of the central nervous system or its related circulatory structures to deliver therapeutic devices or agents.[58] The development of digital subtraction angiography was the basis for growth in this field.[57] By the 1990s, microcatheters suitable for placement in intracranial blood vessels were available, as well as interventional devices such as detachable balloons and coils, and the horizons of interventional neuroradiology began to expand rapidly.[57]

Methods

High-resolution fluoroscopy and digital subtraction angiography are combined to obtain real-time images of the patient's vascular anatomy, through which catheters can be guided. Vascular access for the neuroradiologist is usually obtained through the femoral artery, but the carotid or brachial arteries may be used as well. The site of sheath placement is typically infiltrated with local anesthetic to minimize patient discomfort. Radiologic contrast media are used, with attendant potential complications. It must be noted that digital subtraction angiography delivers greater radiation doses than even fluoroscopy does; attention to radiation safety policies in the neuroradiology suite is therefore essential.[58] Blood pressure may need to be increased or decreased at various points during the procedure to facilitate the intended therapy. When the catheter or catheters have been placed in the vicinity of the lesion, the definitive procedure commences.

Many cerebral aneurysms are amenable to endovascular treatment. Current practice is to embolize the aneurysm with Guglielmi detachable metallic coils.[59] Middle cerebral artery aneurysms are difficult to treat endovascularly. Conversely, aneurysms of the posterior circulation or the cavernous segment of the internal carotid artery are more amenable to embolization. Aneurysms with large necks or large neck-to-aneurysm size ratios are more favorably treated surgically. Aneurysms associated with large intraparenchymal hematomas may be approached surgically to allow concomitant decompression.[59] Patients with unruptured aneurysms may undergo procedures electively or be seen on an emergency basis for repair after rupture with subarachnoid hemorrhage. Patients with subarachnoid hemorrhage may suffer further rupture, hydrocephalus, or cerebral vasospasm.[59-61] Anesthesiologists managing patients during these procedures must be prepared for aneurysm rupture at any time, and tight postprocedural blood pressure control will be essential to reduce the potential for rupture or rerupture after the procedure.[58,59] Rupture of an aneurysm may be treatable with further embolization.

Brain AVMs are another lesion amenable to endovascular therapy.[62] Techniques used to obliterate AVMs include coil embolization, detachable balloons, particulate material, and glue. Frequently, the endovascular approach to intracranial AVMs is combined with a surgical approach, with initial embolization followed by subsequent surgical resection.[63,64] Multiple episodes of embolization are often necessary to limit the occurrence of hemorrhagic complications. Complications of AVM embolization include embolization of foreign material to undesired locations, cerebral edema, and intracranial bleeding.[58] As in the case of rupture of cerebral aneurysms, hemorrhage may be treatable by further embolization.

Intracranial and extracranial vessels with stenotic atherosclerotic lesions have been treated with balloon angioplasty.[58,65,66] Increasingly, patients with extracranial carotid artery stenosis are undergoing carotid angioplasty/stenting rather than conventional carotid endarterectomy. However, at present, indications for selection of carotid angioplasty/stenting over carotid endarterectomy are not clear, and the results of definitive comparative outcome trials remain some years away. A notable feature of carotid angioplasty/stenting is that profound bradydysrhythmias often occur at the time of balloon inflation. Placement of transvenous pacing wires or a pulmonary artery catheter with the ability to accept pacing wires before the procedure may be reasonable in some patients.[58] Movement attributable to external temporary cardiac pacing is undesirable in the face of the ongoing endovascular procedure. Intracranial arterial angioplasty/stenting has been performed, but at this time the procedure remains risky, with complication rates reported to be 12% to 28%.[67,68]

Treatment of acute occlusive stroke, performed in timely fashion, may result in reversal of neurologic deficits. A single, controlled trial has demonstrated improved neurologic outcome after thrombolytic therapy for acute stroke (thrombolysis within 3 hours of the onset of stroke).[69] A meta-analysis of other studies confirmed improved neurologic outcome after prompt thrombolytic treatment of acute stroke.[70] Complications of thrombolytic stroke therapy include low recanalization rates with major occlusion and increased risk for symptomatic intracerebral hemorrhage.[70] Risk factors for complications after thrombolysis of acute stroke include severe hemispheric stroke, extended early infarction signs on preprocedural CT, delay in treatment of more than 3 hours, uncontrolled hypertension, aspirin use, diabetes mellitus, and old age.[71] Current endovascular approaches to ischemic stroke include intra-arterial thrombolytic treatment with tissue plasminogen activator, possibly combined with intravenous administration. Increasingly, thrombolytic therapy is being combined with mechanical disruption or removal of thromboemboli.[70]

Anesthetic Management

Preprocedure anesthetic evaluation is similar to that before neurosurgical procedures. Airway examination is important inasmuch as airway manipulation during the procedure is not possible because of interference with head positioning for imaging. Patients judged to be at special risk for airway compromise might benefit from early securing of the airway and general anesthesia. Particularly important is a history of previous experience with radiologic procedures and any history of contrast media reaction. Because blood pressure management is essential for these procedures, preoperative evaluation for hypertension is important, as is good preoperative control of existing hypertension.

As in other areas outside the operative suite, communication between anesthesiologists and interventional neuroradiologists is essential to ensure optimal patient management. Some

procedures may require awake neurologic assessment during the procedure. Superselective injection of sodium amobarbital into a limited area of the cerebral circulation may be used to assess functional dependence in an awake patient.[72-74] Alternatively, temporary balloon occlusion of vessels that may be embolized may be used to assess functional dependence in an awake patient. Clearly, management of patients during cases involving midprocedure neurologic assessment can be particularly challenging because the patient must remain completely immobile during all critical portions of these long procedures, yet be awake and responsive during neurologic testing. Preoperative training can assist in patient management. Patients who do not require neurologic testing during anesthesia may be managed with either sedation/analgesia or general anesthesia. General anesthesia may provide improved images (less motion artifact), afford better airway control, given the neutral head position required, and facilitate control of blood pressure.[58,65]

Whatever anesthetic technique is selected, standard anesthesia monitoring is established. Two intravenous catheters are placed, one for drug infusions and one for fluid administration and drug boluses. Invasive arterial blood pressure monitoring may be obtained through the side port of the neuroradiologist's introducer sheath, but if postprocedure blood pressure control is considered important, placement of a radial arterial catheter is reasonable for ongoing monitoring. A urinary catheter is placed because of the frequent use of large amounts of radiologic contrast media and administration of osmotic diuretic agents. Careful attention is paid to padding all pressure points to ensure patient comfort and to avoid positioning injury during a potentially long procedure. Sedation may be accomplished with a number of drugs alone or in combination: benzodiazepines, opiates, dexmedetomidine, or propofol. General anesthesia may likewise be accomplished by a number of techniques, from volatile to total intravenous anesthesia, always keeping in mind the desirability of prompt, gentle emergence to allow neurologic evaluation and avoid complications.[58]

Heparin is commonly administered during these procedures, with a target activated clotting time (ACT) of 2 to 2.5 times the baseline value. Deliberate hypotension is frequently used during embolization of AVMs to decrease flow to feeding vessels, as well as during some trial balloon occlusions. Agents such as esmolol, labetalol, or sodium nitroprusside are all useful in this situation. Deliberate hypertension is called for during cerebral ischemia in an attempt to maximize collateral flow. Phenylephrine is generally used, both as a bolus and as an infusion titrated to increase systolic blood pressure 30% to 40% above baseline. Vasopressin may be a superior alternative to phenylephrine in these cases and should be considered. Close monitoring of ECG parameters for signs of myocardial ischemia is critical during induced hypertension, especially in patients likely to have concomitant coronary artery disease (see Chapter 42). Smooth emergence from anesthesia is important because these patients may be prone to migration of the device or intracranial hemorrhage. Administration of antiemetics before emergence is certainly reasonable, and precautions to avoid coughing and "bucking" should be taken.[58]

Anesthetic management of patients undergoing interventional neuroradiologic procedures is challenging. The anesthesia care team must remain vigilant for the occurrence of complications and act decisively and in concert with the procedural team as complications occur.

Interventional Cardiology

Like interventional neuroradiology, interventional cardiology continues to be a rapidly expanding field. Interventional cardiology procedures include coronary angiography and cardiac catheterization, coronary artery angioplasty/stenting, valvotomy, endovascular closure of intracardiac defects, endovascular cardiac valve replacement, electrophysiologic studies with pathway ablation, and cardioversion. These procedures, both diagnostic and therapeutic, may benefit from the involvement of anesthesia personnel in terms of both procedural outcome and patient comfort. Anesthesiologists caring for these patients must be familiar with the patient's medical condition, as well as the planned procedure, to develop a coherent anesthetic plan. Whereas many procedures performed in the cardiac catheterization laboratory may be performed with mild to moderate sedation, others will require advanced anesthetic care and sedated patients may require emergency conversion to general anesthesia because of complications incurred. Consequently, staffing of this area by an anesthesiology group or department must account for potential sudden changes in staffing requirements.

The environment of the cardiac catheterization laboratory is not optimized for anesthetic management. The rooms, like other radiologic procedure rooms, are frequently darkened to allow better visualization of fluoroscopic images, and they are crowded with equipment and personnel. Radiation safety is as much a concern in the cardiac catheterization laboratory as it is in other areas where x-ray devices are used. Like other radiologic suites, the cardiac catheterization laboratory is frequently some distance from the operating suite. It is critical that the requirements for anesthetic equipment and monitoring discussed earlier be met and that the anesthesiologist remain vigilant for rapid changes in the patient's condition, which frequently occur in this distracting environment.

Coronary Angiography and Percutaneous Coronary Intervention

The coronary vasculature may be visualized with the use of radiographic contrast media to allow identification of coronary anatomy, precise determination of the presence and location of coronary artery stenoses, and detection of coronary vasospasm.[75] The American College of Cardiology and the American Heart Association have developed guidelines for the practice of coronary angiography.[76] Although other procedures, such as CT and MRI, may allow determination of the presence of coronary artery disease (and as noted, also possibly require anesthetics administered away from the operating suite), coronary angiography remains the "gold standard" for this diagnosis. In addition, percutaneous coronary intervention (PCI) to improve coronary blood flow may be performed as part of the same procedure.[77] Some patients undergoing diagnostic procedures may be inpatients, but many are outpatients, and the anesthetic plan must take this possibility into account. It is at present controversial whether PCI should be performed in the outpatient setting.

Coronary angiography and cardiac catheterization carry a less than 2% risk of significant complications.[76] Risks include complications related to vascular access, such as hemorrhage, infection, or ischemia; cardiac ischemia in patients with coronary

artery disease; catheter-related complications such as coronary dissection and thromboembolic events (including stroke); and contrast media–related reactions. The risk of significant complications is increased in patients with cardiogenic shock, acute myocardial infarction, unstable angina, renal failure, cardiomyopathy, valvular heart disease, congestive heart failure, hypertension, or inpatient hospital status.[76,78] Very ill, unstable patients considered at high risk of requiring cardiac surgery should be transferred to institutions with immediate cardiac surgical backup available.[76]

Coronary angiography is performed by passing a catheter in retrograde fashion through the arterial tree to the aortic root for the selective injection of contrast media into the ostia of the coronary arteries. Usually, the catheter has been inserted through the femoral artery, but occlusive arterial disease or cardiologist and patient preference may indicate access via the brachial, radial, or ulnar arteries. Increasingly, access is electively gained through the radial artery, with improvement in patient satisfaction and decreased cost.[79,80] Supplemental oxygen is administered, typically by nasal cannula, and standard ASA monitors are used. Arterial blood pressure can be directly transduced from the arterial introducer, and noninvasive blood pressure can be monitored as well. The ECG tracing must be scrutinized and the patient watched closely for the presence of angina or heart failure. Local anesthesia is used at the catheter insertion site to limit patient discomfort related to vascular access. Peripheral intravenous access is necessary for the administration of cardiac medications and sedative/analgesics. The usual anesthesia management is by sedation/analgesia, with general anesthesia reserved for failure of sedation, uncooperative patients, or those who require airway control to manage respiratory failure or other major complications. Anesthetic agents used commonly include fentanyl and midazolam, sometimes supplemented with propofol or dexmedetomidine. Sedation and analgesia are helpful in reducing the discomfort associated with injection of contrast material and remaining motionless and supine during long procedures. Sublingual and intravenous nitroglycerin should be readily available for administration if myocardial ischemia develops, and emergency resuscitation drugs and equipment must be immediately accessible. Heparin is frequently administered, even for diagnostic catheterization, and the effects are often reversed with protamine. Typical heparin doses range from 2500 to 5000 IU intravenously. For interventional procedures, higher heparin doses (i.e., 10,000 IU intravenously) are given, with a target ACT of greater than 300 seconds. Patients must be monitored carefully after protamine administration to detect the predictable peripheral vasodilation, as well as the less predictable anaphylactic and anaphylactoid reactions or the rare catastrophic pulmonary vasoconstrictive crisis associated with protamine administration. Care must also be taken to carefully monitor the patient for reaction to the contrast media. Finally, the patient must be observed closely after the procedure for bleeding or hematoma at the catheter site, as well as for ischemia of the limb distal to the site. Recovery should take place in a fully equipped and staffed recovery area, with the patient discharged only after meeting standard discharge criteria.

Platelet aggregation inhibitors and low-molecular-weight heparin are frequently administered during interventional cardiac catheterization and have resulted in improved outcomes despite the reduction in heparin dose.[81] Platelet aggregation inhibitors used have included abciximab, ticlopidine, and clopidogrel. Numerous studies have shown the benefits of antiplatelet therapy in acute and chronic coronary syndromes.[82-85] A notable side effect of abciximab is elevation of the ACT independent of heparin.[86]

Coronary artery disease is assessed by detection of stenoses after injection of contrast medium selectively into each main coronary artery. Stenoses greater than 50% to 70% of the normal arterial diameter are considered hemodynamically significant, although lesser stenoses may be clinically important. Coronary artery disease is classified as one-, two-, or three-vessel disease or left main coronary disease. An additional cause of myocardial ischemia is coronary arterial spasm. When the patient has typical symptoms without significant atherosclerotic disease at cardiac catheterization, coronary vasospasm should be investigated. Provocative agents, including ergonovine maleate, methylergonovine maleate, or intracoronary acetylcholine, may be given to provoke spasm while contrast medium is injected into the coronary artery. Intracoronary vasodilators such as nitroglycerin may be required when provocative agents are administered. Intracoronary diltiazem may be used to treat resistant vasospasm.[87,88]

When the presence and location of coronary artery stenoses are confirmed, interventional cardiologists can use a variety of methods to improve myocardial blood flow directly. Heparin is administered before the procedure, as noted earlier. Percutaneous transluminal coronary angioplasty (PTCA) involves traversing the stenotic area with a balloon-tipped catheter and compressing the stenosis with the balloon, thereby opening the coronary artery.[89] Transient coronary artery occlusion occurs during balloon inflation, and the patient's hemodynamic status must be monitored closely. Further analgesia may be necessary because angina may develop during this time. The obligate ischemia initially limited the stenotic sites that may be treated with this technique to the distal coronary vasculature and, usually, to one- or two-vessel coronary artery disease. These limitations changed as the technology of angioplasty, coronary stents, and extracorporeal circulation allowed treatment of more severely affected patients in the catheterization laboratory, as discussed later. More recently, PTCA has been supplemented by various techniques that remove rather than compress the atheromatous plaque causing coronary arterial stenosis, as well as by placement of coronary stents to improve long-term patency. Coronary atherectomy may be performed either with atherectomy catheters that "shave" the plaque or with the excimer laser.[90]

During ischemia and frequently during reperfusion after dilation of the stenotic coronary artery, ventricular arrhythmias may develop and require treatment. Hemodynamically significant premature ventricular contractions and nonsustained ventricular tachycardia should be initially treated with amiodarone. More severe arrhythmias may require cardioversion with the patient under general anesthesia. Rupture of the coronary artery may result in hemopericardium and pericardial tamponade. Pericardial tamponade must be treated promptly with emergency pericardiocentesis, typically guided by transthoracic echocardiography, and it may require emergency operative intervention. Another rare complication of PTCA is coronary artery occlusion, which may result from coronary artery dissection, thrombus within the coronary artery, or vascular spasm caused by dysfunctional coronary artery endothelium. Vascular spasm may often be relieved by the injection of 200 μg of nitroglycerin through the coronary artery. Thrombosis of the coronary artery may require multiple therapeutic approaches.[91] Thrombus formation is

retarded by prior administration of heparin. When a thrombus has formed, intracoronary injection of thrombolytic agents, such as urokinase, may dissolve the thrombus. Bleeding complications may result from thrombolytic therapy, especially if the patient requires an emergency surgical procedure. Platelet aggregation inhibitors will probably be administered during stenting, as discussed earlier. Again, bleeding disorders may result and complicate postprocedure care and management during emergency surgery. These patients may require relatively massive autologous platelet transfusions should emergency cardiac surgery be necessary.[92] It should be anticipated that further developments will continue to occur in regulation of the hemostatic system to reduce acute occlusion and chronic reocclusion. Acute coronary occlusion may not respond to transluminal treatment in the catheterization laboratory and may require emergency coronary artery bypass grafting (CABG). The anesthesiologist must be prepared to manage a very unstable patient if this should occur. The patient may have angina, hypotension, and arrhythmias and may benefit from the insertion of an intra-aortic balloon pump. In addition, the patient may require inotropic support and endotracheal intubation. Nitroglycerin is administered in an effort to improve collateral coronary flow and reduce preload. Adequate preload must be ensured, and monitoring of central pressures may be helpful. If the stenotic or dissected area can be traversed with a guidewire, the cardiologist may be able to leave a perfusing catheter in place to allow some coronary blood flow and limit myocardial ischemia pending surgical revascularization.[93] Great care must be taken in transport so that this catheter is not dislodged. Time is critical when the patient requires emergency CABG in this situation. The patient must be expeditiously transported to the operating suite and placed on cardiopulmonary bypass as soon as possible for maximal myocardial salvage. Multidisciplinary examination of institutional systems may result in streamlining of the procedure for rapid transport of the patient to the operating suite, thus improving patient outcomes.[94] Because these patients may be very hemodynamically unstable, their cardiovascular and respiratory status must be monitored. continuously.

Results after PTCA and atherectomy procedures are initially excellent. However, restenosis of the dilated coronary arteries has occurred in as many as 30% to 40% of patients and is due to both neointimal thickening and remodeling.[95] Expandable metallic stents are used to maintain coronary artery patency, with improvement in patency rates. The stents are placed across the area of stenosis after PTCA or atherectomy and remain in place after the procedure.[96] Current research is focused on further reducing the restenosis rate, including the use of novel mechanical strategies, new systemic drugs to inhibit neointimal proliferation, and drug-coated and drug-eluting stents.[97] Anesthesiologists caring for patients undergoing cardiac catheterization laboratory procedures must be aware of the current protocols for pharmacologic regulation of hemostasis and intimal proliferation for the various procedures performed at their institution because they are evolving constantly.

The use of intracoronary radiation therapy to prevent instent restenosis has anesthetic implications. The radiation is believed to prevent neointimal proliferation by breaking DNA strands and hence blocking mitosis.[98] Multiple trials have demonstrated the effectiveness and complication profile of coronary brachytherapy.[99] From an anesthesia perspective, the therapy has a significant implication. Because of concerns of radiation safety, during deployment of the radiation probe, which is otherwise shielded in a lead-lined case, personnel may be required to leave the intracoronary radiation room. Provision for remote monitoring needs to be ensured, similar to that for MRI discussed earlier and similar to the remote monitors for intraoperative radiation therapy (IORT) discussed later.

Patients with acute coronary syndromes benefit from thrombolytic therapy, from antiplatelet therapy, and possibly from PCI to restore myocardial blood flow.[97] Such treatment must be administered rapidly to maximize myocardial viability and reduce morbidity and mortality. Delays in PCI reperfusion of patients with acute coronary syndromes are monitored by the Joint Commission on Accreditation of Health Care Organizations (JCAHO) and the Center for Medicare and Medicaid Services (CMS) as a component of institutional quality assessment. These patients may have full stomachs and may be hemodynamically unstable. General anesthesia has been successful in patients who cannot tolerate the procedure because of pain, anxiety, or dyspnea.[100]

Developments in perfusion technology have increased the portability of temporary ventricular assist devices. Use of these devices maintains hemodynamic stability during procedures that would otherwise result in unacceptable degrees of hemodynamic instability, such as PCI of the left main coronary artery or interventional procedures performed on patients in cardiogenic shock. Currently, this procedure is most frequently performed on patients who are not otherwise candidates for CABG surgery, such as those with unacceptably poor ventricular function or distal coronary artery disease that would preclude CABG.[101,102] However, the use of these devices is expanding to other cardiac catheterization procedures such as complex endocardial and epicardial RF ablation.[103] Extracorporeal circulation is established through the femoral artery or vein (or both, depending on the machine technology used) after induction of general anesthesia and systemic heparinization. Monitoring is the same as for CABG in the operating suite and typically involves placement of arterial and central venous or pulmonary artery catheters. Transesophageal echocardiography is also used for ventricular monitoring, as well as cannula placement. Given the often tenuous nature of these patients' condition, a case can be made for awake placement of these invasive monitors. The induction and maintenance techniques should, of course, take into account the patients' underlying condition. After the procedure, extubation is performed as soon as the patient's condition allows. The anesthetic technique chosen must provide hemodynamic stability and the potential for early extubation. A balanced anesthetic regimen of fentanyl and a volatile agent with neuromuscular blockade provides these conditions. Patients must be closely monitored for bleeding complications because heparinization is frequently continued after the procedure. Platelet aggregation inhibitors are generally administered. Should complications occur in these patients, who are supported by extracorporeal circulation but are not surgical candidates, ethical dilemmas may occur. The possibility of complications and the potential treatment options, or lack thereof, must be clearly understood by the patient and by all medical personnel caring for the patient before undertaking such procedures. Clear and open communication is essential in this setting.

Cardiac Catheterization

Placement of transvenous and transarterial catheters into the heart and great vessels (cardiac catheterization) allows determi-

nation of cardiac anatomy, ventricular function, valvular anatomy, and pulmonary vascular anatomy. Pressure measurements in cardiac chambers and vascular structures may be made with these catheters. Injection of contrast medium allows radiologic visualization of various structures, and injection of an indicator with distal sampling allows determination of flow according to the Fick principle. In addition, blood samples may be withdrawn from various areas for determination of oxygen saturation to detect the presence and location of shunts. Although much (but by no means all) of this information can be obtained with echocardiography, cardiac catheterization remains the "gold standard" for detailed diagnosis of complex cardiac anatomic anomalies. It must be noted that because multiple measurements and samples are necessary for the complete cardiac catheterization procedure, the measurements cannot be performed simultaneously. For the hemodynamic and shunt calculations to be valid, a relatively constant cardiovascular and respiratory state is necessary.[104,105] The arterial pressure of oxygen (Pa_{O_2}) and CO_2 (Pa_{CO_2}) must be "normal" for the patient being studied and must remain so during the measurement periods. The anesthetic techniques used in a given institution should be consistent so that the cardiologist does not have to account for differences in anesthetic techniques when interpreting diagnostic data. These constraints can make anesthetic management of these patients extremely difficult.

Cardiac catheterization in adults is frequently performed in conjunction with coronary angiography. Access to the right side of the heart (pulmonary circulation) is through the venous system and usually involves placement of a catheter in the femoral vein. The left side of the heart (systemic circulation) is accessed as the coronary arteries are accessed, through the brachial, radial, or more commonly, the femoral arteries. Complications related to vascular access are similar to those outlined for coronary angiography. Because catheters are placed within the cardiac chambers, supraventricular and ventricular arrhythmias are common during this procedure. The procedure is usually performed under local anesthesia, but patients benefit from systemic analgesia and sedation. Medications frequently used for this purpose include fentanyl and midazolam, sometimes supplemented with propofol or dexmedetomidine. Oxygen is administered as needed, but care must be taken to maintain "normal" (for the patient) arterial blood gas values if pulmonary hemodynamics is to be measured during the procedure. As with coronary angiography, the anesthesiologist must be prepared to deal with acute hemodynamic and respiratory instability in patients who may have severe valvular and myocardial dysfunction.

Pediatric Cardiac Catheterization

Anesthetic management for cardiac catheterization in pediatric patients can be uniquely challenging (see Chapter 83). These patients range in age from premature neonates to the upper limits of the pediatric age group. Cardiac anomalies vary from relatively simple atrial septal defects to complex congenital cardiac anomalies such as hypoplastic left heart syndrome. Shunts may be present at multiple levels, and patients may be profoundly cyanotic. Ventricular dysfunction may be severe. Patients may also have coexisting noncardiac congenital abnormalities. In addition, these young patients may be uncooperative, and their parents may be severely stressed and thus of limited assistance. Neonatal studies are frequently performed on an emergency basis, and these patients are often deeply cyanotic and critically ill. Diagnosis of the cardiac anomaly is usually made by echocardiography before cardiac catheterization, but determination of surgical treatment or possible catheter-based intervention is dependent on the results of cardiac catheterization.

Anesthetic techniques used in these cases range from sedation and analgesia to general anesthesia. Again, it must be remembered that a "steady state" must be maintained for diagnostic accuracy. In general, older, cooperative patients are readily managed with intravenous sedation and analgesia. Even in cyanotic patients, supplemental oxygen is not administered unless oxygen saturation falls below baseline levels. Care must be taken to maintain ventilation and Pa_{CO_2} within normal physiologic limits to avoid alterations in pulmonary vascular resistance.[106] Medications administered for sedation include fentanyl, midazolam, propofol, and ketamine. Premedication with midazolam, 0.5 mg/kg orally, can be particularly helpful. Some evidence has indicated that ketamine can increase oxygen consumption, so care must be taken to ensure that it does not impair diagnostic accuracy.[107] Even small infants have been sedated in this manner for these procedures.

That said, infants and small children frequently cannot tolerate the procedure under intravenous sedation and are more readily managed with general anesthesia. As with intravenous sedation for these procedures, premedication with oral midazolam, 0.5 mg/kg, can be very helpful. If intravenous access is not present, induction with inhaled nitrous oxide, oxygen, and a volatile anesthetic such as sevoflurane is performed, and intravenous access is obtained after the patient is anesthetized. Alternatively, intravenous induction with thiopental, ketamine, etomidate, or propofol is performed. A nondepolarizing neuromuscular relaxant is administered, and endotracheal intubation is carried out when the patient is fully relaxed. Correct endotracheal tube position is confirmed by end-tidal CO_2 measurement, and position above the carina is readily confirmed with fluoroscopy. Anesthesia is maintained with volatile anesthetics and controlled ventilation with room air, as long as oxygen saturation does not fall below baseline levels. Controlled ventilation avoids the increases in Pa_{CO_2} frequently seen with levels of intravenous sedation adequate to allow performance of this invasive procedure in pediatric patients. Controlled ventilation has not been found to affect the diagnostic accuracy of cardiac catheterization.[104] Minute ventilation and the respiratory rate are adjusted to maintain normal Pa_{CO_2} based on analysis of arterial gases from blood drawn by the cardiologist from the arterial catheter. The end-tidal CO_2 determination can be used to subsequently adjust ventilation, but it must be remembered that physiologic dead space is highly variable in these patients. Infiltration of local anesthetic at vascular access sites limits postprocedure discomfort. Small amounts of an opioid such as fentanyl (i.e., 1 to 2 μg/kg intravenously) or midazolam may be administered to provide postprocedure sedation, thus allowing the patient to remain still and avoid bleeding complications at the femoral vascular access sites. As an alternative to a volatile anesthesia–based technique, the patient can be managed with total intravenous anesthesia using various combinations of opioids, benzodiazepines, propofol, and ketamine.[108-113] Again, steady-state conditions are essential, and the anesthetic plan at any institution should be consistent from patient to patient to provide reproducible patient conditions for the cardiologists and cardiac surgeons who must interpret the diagnostic data.

Close monitoring of these patients is required. Especially in neonates, deterioration can be rapid. These patients may be very sensitive to anesthetics, and hemodynamic instability may ensue. Repeated blood gas analysis is necessary because metabolic acidosis may be the initial sign of a low cardiac output state. Even mild degrees of metabolic acidosis should be treated in critically ill patients, and inotropic therapy may be necessary. Hypocalcemia and hypoglycemia may develop in neonates and require treatment. Hypothermia can be a problem in young patients, especially those under general anesthesia. The room may need to be warmed. In addition, inspired gases may need to be warmed and humidified, and a warming blanket or forced-air warming system should be available. Rectal temperature may need to be monitored in small patients because an esophageal or axillary probe may intrude into the cardiologist's imaging area. Blood loss during the procedure is less well tolerated than in larger patients because the loss may represent a significant fraction of a smaller patient's blood volume. Hematocrit must be monitored carefully and anemia must be treated appropriately. Deeply cyanotic patients tend toward polycythemia as they age, and sufficient fluids must be administered to balance the osmotic effects of contrast media, which could result in hemoconcentration and microembolic events.

Complications of cardiac catheterization include arrhythmias, bleeding at vascular access sites, perforation of cardiac chambers or great vessels by catheters, vascular dissection or hematoma, and embolic phenomena. Arrhythmias are the most frequent complication.[88] Supraventricular tachycardias are the most common and are often related to catheter tip placement, in which case the arrhythmias usually resolve on withdrawal of the catheter. Occasionally, vagal maneuvers, intravenous medication, or cardioversion may be necessary to terminate the arrhythmia. Second- or third-degree heart block may also be seen. Sinus bradycardia may require treatment with atropine. Profound bradycardia may necessitate temporary ventricular pacing if hemodynamic instability results.

Pericardial tamponade can be detected by characteristic hemodynamic alterations, as well as by a widened mediastinum and reduced cardiac motion on fluoroscopy. A definitive diagnosis of tamponade is best made by echocardiography, which is readily available and can be used to guide emergency pericardiocentesis. The pericardiocentesis catheter can cause arrhythmias by mechanical irritation. These arrhythmias can be supraventricular or ventricular, and they may be poorly tolerated in critically ill patients. As with coronary angiography, emergency surgical procedures may be necessary, and hospital systems must allow rapid, safe transport of these patients to the operating suite.

Interventions During Cardiac Catheterization

Balloon atrial septostomy (Rashkind procedure) is performed in infants requiring communication between the pulmonary and systemic circulations for survival (e.g., transposition of the great vessels). A balloon-tipped catheter is placed across the atrial septum. The balloon is inflated to rupture the septum, creating an atrial septal defect and allowing shunting at the atrial level. In the case of transposition of the great vessels, oxygenated blood flowing from the lungs to the left atrium would then mix in the right atrium with venous return blood and flow into the systemic circulation through the right ventricle. Neonates scheduled to undergo this procedure are usually receiving intravenous prostaglandin E_1 to maintain a patent ductus arteriosus. It is critical that this infusion be maintained to keep the ductus patent until the atrial septostomy is complete and is determined to be of adequate size to maintain systemic oxygenation. Anesthesia for the procedure is otherwise as described earlier.

Balloon-tipped catheters have been used to dilate stenotic heart valves and great vessels. The procedure has been performed to dilate congenital pulmonary valvular stenosis,[114] stenotic pulmonary arteries, and aortic coarctation.[115] Balloon valvuloplasty has also been used to ameliorate acquired stenosis of the tricuspid, pulmonary, mitral, and aortic valves.[88] The procedure is generally reserved for patients regarded as very high-risk surgical candidates.[116] During balloon inflation, the circulation is blocked, and severe hypotension may result that because of the tenuous condition of the patient, may not resolve immediately on deflation of the balloon. Inotropic and antiarrhythmic therapy may be necessary, and preload may need to be optimized with intravenous fluid administration. Complications of the procedure are similar to those of cardiac catheterization. In addition, valvular insufficiency may develop.

Older patients usually tolerate this procedure when local anesthetics are infiltrated at the site of catheter entry. Intravenous sedation with fentanyl, midazolam, and propofol attenuates discomfort related to the environment and balloon inflation. When the aortic valve is to be dilated, two intravenous catheters are inserted. Valvuloplasty of other valves requires only a single intravenous catheter. If the patient becomes hemodynamically unstable, the balloon must be deflated immediately. Vagal stimulation can occur with balloon inflation and may require treatment with atropine. Should major complications ensue, prompt surgical intervention may be necessary.

Recent developments have allowed closure of atrial and ventricular septal defects with devices deployed through catheters placed across the defects in the cardiac catheterization laboratory.[97,117] A number of different devices are either in use or being investigated. Teams undertaking such procedures must have plans in place to deal with failure or complications resulting from the procedure.[118] These and similar devices have been used to occlude perivalvular leaks of implanted valve prostheses, and devices to close other abnormal communications, such as ventricular septal defects occurring after myocardial infarction, are under development.[119,120]

Septal ablation for hypertrophic cardiomyopathy may be performed in the cardiac catheterization laboratory. This technique may be performed by septal injection of ethanol or by occlusion of the first septal penetrating artery, a branch of the left anterior descending coronary artery.[121-124] Criteria for selecting patients for transcatheter septal ablation rather than surgical resection are not yet clear. Patients generally tolerate these procedures with sedation/analgesia.

Repair or replacement of defective heart valves in the catheterization laboratory is an exciting recent development. Aortic valve replacement has been performed percutaneously.[125] New techniques to repair valves percutaneously are also in development.[126] Anesthesiologists caring for patients in the cardiac catheterization laboratory must remain abreast of these developments and understand the implications for intraoperative monitoring,

such as invasive lines and transesophageal echocardiography, as well as the anesthetic implications of these developing procedures. Again, timely, preprocedure communication with the cardiologists involved is essential.

Electrophysiologic Studies and Catheter Ablation of Abnormal Conduction Pathways

Electrophysiologic studies involve the placement of special multipolar catheters within cardiac chambers to define the mechanism, origin, and pathways of arrhythmias and to determine the best therapeutic options (see Chapters 34 and 61).[127] Vascular access is usually achieved through the femoral artery and vein, and frequently, additional catheters are placed through the internal jugular vein, with obvious implications for airway management. Programmed electrical stimulation is performed at various locations with the use of standard transvascular catheterization techniques. By using specifically timed electrical impulses, the arrhythmia is reproduced under controlled conditions and monitored through the catheters and the surface ECG leads. Electrical energy delivered through appropriately positioned catheters can then be used to ablate arrhythmogenic foci or accessory pathways. Another intervention that may also be performed in the laboratory is to place the electrodes precisely for subsequent connection to an implantable defibrillator.

Antiarrhythmic drugs are stopped before these studies and are avoided during the procedure because they may prevent detection of the accessory conducting pathways and arrhythmogenic foci. Formerly, these procedures were performed under sedation because the lead technology was exquisitely sensitive to subtle anesthetic drug effects on the conduction pathways. However, improvement in the technology has made this problem less of a concern, and we generally perform the more complex electrophysiology procedures under general anesthesia. It is important to avoid, if possible, the use of drugs that affect the sympathetic nervous system because they affect the ability to map the electrophysiologic pathways. Inotropic support may be required, but this must be discussed with the electrophysiologists, and the procedure may best be performed with temporary ventricular assist device support, as discussed earlier.

Pacemaker and Cardioverter-Defibrillator Implantation

Permanent pacemakers and ICDs are frequently implanted in the cardiac catheterization laboratory (also see Chapter 43). Implantation of both devices involves placement of transvenous leads into the cardiac chambers (usually the right atrium or ventricle or both) with tunneling of the leads to a subcutaneous pocket in which the device is placed. Many of these procedures are performed with sedation/analgesia. General anesthesia is necessary during testing of the ICD. When the ICD is tested, ventricular tachycardia or fibrillation is induced, and the ability of the device to sense the arrhythmia and deliver appropriate cardioversion-defibrillation energy is confirmed. Many patients undergoing ICD placement have poor ventricular function. Return of hemodynamic variables to baseline after cardioversion-defibrillation must be closely monitored. In addition to placement of devices, obsolete, malfunctioning, or infected pacemaker or ICD leads (or both) may need to be removed. Pacemaker or ICD lead extraction is not to be taken lightly.[128] Major complications are rare, but complications such as rupture of the superior vena cava, right atrium, or right ventricle obviously require prompt intervention. Additionally, severe tricuspid regurgitation may result from removal of right ventricular leads adherent to the valvular or subvalvular apparatus, but it generally requires less acute intervention. Leads in place for longer than 1 year may have extensive fibrosis, which may make removal difficult. Placement of additional leads may result in additional fibrosis and eventually lead to vascular occlusion. Therefore, lead extraction before replacement may be beneficial. Clearly, infected leads require extraction. Powered telescoping sheaths, which detach the leads from fibrotic attachments by means of lasers or mechanical means, have improved the ability to remove stubborn leads.

Elective Cardioversion

Cardioversion is used to convert supraventricular and ventricular arrhythmias to sinus rhythm by delivery of synchronized direct-current electric shock. Current evidence indicates that biphasic shock delivery is superior to the damped sinusoidal current formerly used.[129] When these arrhythmias are not causing hemodynamic instability or when the arrhythmia is of long-standing duration and has not responded to drug therapy, cardioversion can be performed on an elective and possibly an outpatient basis. The patient's cardiovascular status and medical therapy are optimized before elective cardioversion. In contrast, emergency cardioversion is often required when the arrhythmia causes hemodynamic instability and when time pressure and the patient's condition may not allow full evaluation or administration of anesthesia.

Elective cardioversion is uncomfortable, and general anesthesia is required. Many medications have been used, including barbiturates, propofol, etomidate, opiates, and benzodiazepines.[130-133] In the case of chronic atrial fibrillation, echocardiography is performed before cardioversion to rule out the presence of left atrial thrombi, which could cause stroke. Standard monitoring is used, and standards for the availability of equipment must be observed. When all is in readiness for cardioversion, the patient is preoxygenated and then given small incremental doses of anesthetic until the eyelid reflex is abolished. Immediately before the countershock, the mask is removed, and it is confirmed that no person is touching the patient or cart. More than one shock may be required to restore sinus rhythm, and it is important to keep the patient anesthetized until the procedure is successful or the attempt is terminated. After cardioversion, the patient is ventilated with 100% oxygen until consciousness is regained and the patient is able to maintain the airway. It should be noted that muscle relaxants are not typically needed for this procedure. If cardioversion is required on an urgent basis, it must be remembered that the patient may not have been fasting before the procedure. To prevent aspiration during anesthesia in this situation, it is appropriate to intubate the trachea with a rapid-sequence induction technique involving the use of cricoid pressure.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) was introduced in the 1930s as a treatment of schizophrenia. Although use of this therapy declined through the 1970s because of negative publicity, acceptance and use of ECT have again increased. Current acceptance of this procedure is in part due to the use of general anesthesia to reduce the physical and psychological trauma associated with ECT. Indications for ECT include major depression, mania, certain forms of schizophrenia, and perhaps Parkinson's syndrome.[134] Pheochromocytoma is a contraindication to ECT. Relative contraindications include increased intracranial pressure, recent cerebrovascular accident, cardiovascular conduction defects, high-risk pregnancy, and aortic and cerebral aneurysms.[135,136] In these conditions, the risk of the patient's psychiatric illness and the side effects of antidepressant medications must be weighed against the risk associated with ECT and anesthesia.

ECT consists of programmed electrical stimulation of the central nervous system to initiate seizure activity. The precise mechanism of the therapeutic effect of ECT remains unknown despite increasing research in this area.[137] After induction of general anesthesia and muscle relaxation to prevent traumatic injury during generalized seizure activity, two stimulus electrodes are applied to the patient's scalp. A series of programmed electrical pulses at precise energy levels are then delivered to induce a generalized seizure. The energy level selected for a given patient is based on an initial titration of stimulus dosage. The seizure is monitored both by observation of the patient and by an electroencephalogram on the ECT machine. Seizure duration is recorded. Treatment efficacy was believed to be related to a minimum seizure duration of 25 seconds and to the total seizure duration over the course of treatment, but this is no longer thought to be the case.[138] However, the efficacy of the treatment does depend on a seizure occurring. Delivery of energy is thus minimized and tailored to the condition of each patient. Treatments continue two to three times per week until either improvement is seen or the treatment is deemed unsuccessful. Successful treatment may be supported by continuation of ECT at weekly to monthly intervals for up to 6 months and by similar maintenance ECT continuing more than 6 months past initiation of treatment.[134]

Physiologic Effects

Direct brain effects of the stimulus and seizure include large increases in cerebral blood flow and intracranial pressure.[139] Seizure activity causes an initial parasympathetic discharge manifested by bradycardia, occasional asystole, premature atrial and ventricular contractions, or a combination of these abnormalities. Hypotension and salivation may be noted. The parasympathetic discharge is followed immediately by sympathetic discharge associated with tachycardia, hypertension, premature ventricular contractions, and rarely, ventricular tachycardia. The tachycardia peaks at 2 minutes after the stimulus and is normally self-limited.[140] ECG changes, including ST-segment depression and T-wave inversion, may also be seen after ECT without any of the myocardial enzyme changes consistent with myocardial infarction. These ECG changes are presumed to be secondary to the sympathetic discharge.[141,142] The arrhythmias associated with ECT, even in patients with preexisting arrhythmias, are self-limited and not in themselves a contraindication to treatment. ECT has been found to be relatively safe even in high-risk cardiac patients, if careful management is provided.[143,144]

Norepinephrine and epinephrine increase immediately after ECT, and epinephrine levels decrease more rapidly thereafter. Glucose homeostasis is variably affected by ECT. Improvement in control of non–insulin-dependent diabetes is generally noted, whereas hyperglycemia may be seen when the diabetes is insulin dependent. A single report noted hyperglycemia in a patient with no previous history of diabetes.[145]

Antidepressant Drug Therapy

Most patients scheduled to undergo ECT are receiving tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), serotonin reuptake inhibitors, lithium carbonate, or a combination of these drugs. Tricyclic antidepressants block the reuptake of norepinephrine, serotonin, and dopamine into presynaptic nerve terminals, thereby increasing central sympathetic tone.[146] Tricyclic antidepressants have antihistaminic, anticholinergic, and sedative properties and also slow cardiac conduction. These side effects are less common with the newer types of antidepressant drugs such as trazodone, bupropion, and fluoxetine.[147] The combination of centrally acting anticholinergics, such as atropine, with tricyclic antidepressants can increase postprocedure delirium.[148]

MAOIs inhibit monoamine oxidase by irreversibly combining with it to form a stable complex, thereby blocking the metabolism of norepinephrine, serotonin, and dopamine. The use of indirectly acting sympathomimetics in patients receiving MAOIs can result in hypertensive crises.[146] An exaggerated response to direct-acting sympathomimetics may also be seen. Hypotension in these patients should be treated with reduced doses of direct-acting sympathomimetic agents. MAOIs can inhibit hepatic microsomal enzymes. They may interact with opioid analgesics and cause excessive depression. Used concomitantly with meperidine, MAOIs may result in severe, possibly fatal excitatory phenomena.[149]

Lithium carbonate prolongs the action of neuromuscular blocking drugs (see Chapter 29).[150] Elevated lithium levels, higher than the therapeutic range, can prolong the action of benzodiazepines and barbiturates. Patients receiving lithium may demonstrate more cognitive side effects after ECT. The American Psychiatric Association recommends discontinuation of lithium therapy before ECT.[151]

Anesthetic Management of Electroconvulsive Therapy

Anesthesia for ECT has been the subject of recent reviews.[140,151,152] Anesthesia and neuromuscular blockade are necessary during ECT to prevent psychological and physical trauma. Rapid recovery is desirable. Careful preoperative evaluation is necessary, with particular attention paid to coexisting neurologic and cardiac disease, osteoporosis and other causes of bone fragility, and medications that the patient may be receiving. The patient may be a poor historian because of the psychiatric condition, and accom-

panying caregivers may need to provide the necessary history and assurance of fasting status. Standard monitors are used. Pretreatment with glycopyrrolate (0.2 mg intravenously), which does not cross the blood-brain barrier, can reduce the occurrence of bradycardia and the amount of oral secretions associated with ECT, as discussed later. After preoxygenation, anesthesia is administered by peripheral intravenous catheter, and neuromuscular blockade is induced. When relaxation is adequate and satisfactory mask ventilation with oxygen is ensured, a bite block is placed and a stimulus is delivered to induce the seizure. If the patient has a hiatal hernia and gastroesophageal reflux, or in the case of ECT for a pregnant patient, rapid-sequence induction and endotracheal intubation with cricoid pressure may be a reasonable approach. Adequate ventilation is ensured during the procedure. The peripheral seizure is monitored by patient observation, as well as by electromyography, and the central seizure is monitored by electroencephalography. It must be remembered that the duration of the central seizure may outlast peripheral clonic manifestations; this is monitored by the electroencephalogram. A blood pressure cuff inflated to isolate a limb before administration of a neuromuscular blocker can assist in monitoring the peripheral seizure. In patients undergoing their initial ECT treatment, more than one stimulus may be necessary because of titration of the stimulus, and additional anesthetic or neuromuscular blocking drug (or both) may need to be administered. After the procedure, ventilation with oxygen by mask is continued until the patient awakens and is breathing adequately. During this time, tachycardia and hypertension, if persistent or of hazardous magnitude, may require treatment. The patient should be monitored in a fully staffed and well-equipped recovery area after the procedure until specific discharge criteria are met, the same discharge criteria for any patient who has undergone general anesthesia. Some patients demonstrate significant oxygen desaturation after ECT, and oxygen should be given by nasal cannula until the patient is fully awake.[153]

Many intravenous anesthetics have been used to induce anesthesia for ECT, including methohexital, thiopental, propofol, and ketamine. Methohexital (0.75 to 1.0 mg/kg) is the most commonly used drug for ECT anesthesia and is considered the "gold standard."[152] Propofol (0.75 mg/kg) was found to reduce seizure duration, which was believed to decrease the efficacy of ECT. However, more recent studies have demonstrated no difference in outcome with propofol versus methohexital.[154-156] Administration of methohexital, as well as propofol, is associated with pain on injection, which may be poorly tolerated by psychiatrically fragile patients. The use of thiopental (1.5 to 2.5 mg/kg) avoids pain on injection, but it is associated with more hypertension and tachycardia than propofol is.[157] Etomidate may prolong seizures and recovery, but prolongation of the seizure may be useful in patients in whom seizures are difficult to elicit or whose seizure duration is deemed too short with other agents.[158] Benzodiazepines have anticonvulsant activity and should be avoided before ECT.[152] Ketamine has been demonstrated to not increase seizure length or produce excessive postprocedure agitation.[159] Given the hemodynamic response expected after ECT, ketamine would seem to be a less desirable agent.[140,152]

Volatile anesthetics have been used for ECT and may be helpful in treating patients in whom placement of an intravenous line is difficult because of patient resistance or poor peripheral veins. Sevoflurane has been studied, and although its use is more time consuming in terms of induction and recovery times, patient outcomes were similar to those of patients who received thiopental.[140,160] Use of sevoflurane obviously requires an anesthesia machine and waste gas scavenging.[152] Various opioids, used as adjuncts to the anesthesia induction regimen, have been studied in patients receiving ECT. The newer, short-acting opioid remifentanil has received the most recent interest. In a study comparing remifentanil, 1 μg/kg, plus methohexital with methohexital alone, no difference was found except for longer seizure duration in the methohexital group.[161] Remifentanil may be a useful adjunct in patients in whom seizures are difficult to elicit or in whom seizure duration is deemed too short.[140] That is, use of remifentanil with a barbiturate may be an alternative to use of etomidate in such patients.

Complete neuromuscular blockade is not necessary for ECT and may not be desirable because monitoring of peripheral seizure duration would be impeded. Partial neuromuscular blockade is necessary, however, to reduce the peripheral manifestations of the seizure and to prevent musculoskeletal trauma to the patient. More complete neuromuscular blockade may be accepted for high-risk patients who may be more likely to suffer fractures if the degree of neuromuscular blockade is overestimated. Succinylcholine has been used most frequently for neuromuscular blockade during ECT because of its short duration of action and low frequency of side effects. An initial dose of 0.5 mg/kg is administered and adjusted for subsequent treatments according to the patient's response. Use of a peripheral nerve stimulator to assess the degree of neuromuscular blockade before the seizure may be useful. Mivacurium has been suggested as an alternative to succinylcholine, but it may not be as effective as succinylcholine in preventing tonic-clonic muscle contractions, which could result in traumatic injury to the patient.[162,163] Mivacurium also necessitates prolonged postprocedure ventilatory support, thus increasing anesthetic requirements and costs.[164] Both succinylcholine and mivacurium are metabolized by plasma cholinesterase, and alternative nondepolarizing muscle relaxants such as atracurium or cisatracurium may be required in patients with pseudocholinesterase deficiency. Relatively prolonged neuromuscular blockade may need to be accepted in such patients to avoid trauma from the seizure. When these nondepolarizing agents are used, the neuromuscular blockade is routinely reversed after the treatment.[140]

Prophylactic medications have been advocated to avoid various side effects of ECT. Transient asystole secondary to parasympathetic discharge during delivery of the stimulus is rare during ECT, but it may be prevented with anticholinergic pretreatment. Glycopyrrolate is preferred over atropine because it produces less tachycardia after ECT.[140] In addition, glycopyrrolate is an effective antisialagogue. Both esmolol and labetalol have been successfully used to control hypertension and tachycardia after ECT.[165] Some evidence has shown that esmolol reduces seizure duration.[166,167] Routine treatment with esmolol or labetalol is not recommended because the hypertension and tachycardia are usually self-limited, as are premature ventricular contractions. Should treatment be necessary, these drugs can be administered immediately after the stimulus.[152] Use of labetalol has not been found to increase orthostatic hypotension during the recovery period.[168]

The anesthetics and neuromuscular blocking drugs administered to each patient should, as in other anesthetic procedures, be accurately recorded. Such recording is especially important with ECT because the treatment is repeated over a period of

several weeks to months and consistent patient conditions must be provided along with a predictable response to the ECT stimulus. Moreover, patients' responses to previous treatment, such as the development of arrhythmias or agitation, and to the additional medications that were required, such as β-antagonists or benzodiazepines, should be noted so that extra precautions can be taken during subsequent treatments. Proper anesthetic care allows safe administration of ECT in patients with multiple coexisting medical conditions, even in very elderly patients.[169]

Therapeutic Radiation

Intraoperative Radiation Therapy

IORT is the delivery of radiation during exposure of a tumor or tumor bed during an operative procedure. In its broadest sense, IORT includes brachytherapy with temporary or permanent implantation of radioactive seeds.[170] Radiation therapy plays a major role in the management of many malignant diseases. The usual method by which radiation is delivered is external beam treatment with high-energy photons. The external beam doses required to achieve local tumor control can exceed the radiation tolerance of some normal organs and other structures of the body.[171] IORT can be effectively used as a supplemental boost to external beam treatments. By delivering the radiation therapy during surgery, it is possible to remove normal structures from the radiation beam or to shield them with lead.[172]

This method of treatment is appealing, particularly for locally advanced malignant lesions when conventional modalities are unlikely to produce local tumor control. Theoretical advantages over conventional external radiotherapy are the ability to increase the tumor dose with less damage to adjacent healthy tissues and more accurate localization of the radiation field. Disadvantages of this technique are that an operation is needed, optimal dose combinations of external beam radiation and IORT are complex to calculate,[170] and complications are not infrequent. Complications include pain, nausea and vomiting, bowel dysfunction, ureteral obstruction, neuropathy, abscesses, and delayed wound healing.[173] Tumors treated with IORT have included locally advanced colorectal cancer, retroperitoneal sarcomas, limb sarcomas, gynecologic malignancies, and pediatric malignancies.[173-177]

Most of the advances in the use of radiation have been achieved by an improved dose distribution and better differentiation of the dose delivered to the tumor relative to normal tissue. Delivering the radiation during the surgical procedure permits direct observation of tumor size and density and the tissues at risk for microscopic spread of tumor. Patient selection for IORT should include no contraindications to surgery and the belief that surgical intervention alone will not result in local tumor control. The tumor should be a localized focus of disease, and no distant metastasis should be apparent.[170] IORT is seen as potentially curative.[178]

Ideally, anesthesia, incision, radiation delivery, and closure occur in a single dedicated IORT room. Alternatively, induction of anesthesia, surgical incision, and tumor isolation can be accomplished in a modified operating room within the radiation oncology area.[179] This alternative allows the linear accelerator room to be used without interruption for treating other patients while the patient who is to undergo IORT is being prepared. After preparation, the anesthetized and surgically draped patient is transported a short distance to the accelerator treatment room. Once radiation treatment is completed, the patient is returned to the modified operating room for closure of the incision. This situation would be subject to the limitations of all procedures requiring anesthesia in non–operating room settings.

Patients typically receive a conventional general anesthetic regimen with endotracheal intubation. Particular attention must be paid to the preoperative evaluation of these cancer patients, who may demonstrate anemia, cachexia, depression, and side effects of chemotherapy and external radiation treatments.[180] Standard monitors are used, as well as additional monitors as dictated by the patient's condition and the surgical procedure planned. Adequate intravenous access for a potentially major operation is necessary. After surgical incision and exploration, the tumor is exposed and isolated. A sterile Lucite cylinder is then inserted to cover the tumor mass, define the radiation beam, and displace normal structures outwardly circumferentially around its perimeter (Fig. 79-2). Radiation therapy may then be focused directly on the isolated tumor.

Throughout the actual radiation treatment period, all personnel must leave the treatment room to avoid high radiation exposure, and the patient, anesthesia equipment, and monitors are observed continuously by closed-circuit television (Fig. 79-3). After treatment, the patient is transported to the recovery room.

External Beam Radiotherapy for Cancer in Children

Optimal treatment of children with cancer often requires combined-modality therapy incorporating chemotherapy, surgery, and radiotherapy (see Chapter 82). Chemotherapy alone is not always sufficient to cure childhood solid tumors; either resection or radiation may be needed for local tumor control.[181] Children with radiosensitive malignant tumors typically require radiation therapy for a number of sessions over a period of several weeks. Although the treatments are painless, young children cannot be depended on to remain absolutely motionless in the strange and frightening surroundings of radiation therapy rooms. Because immobility during treatment is mandatory, sedation/analgesia or general anesthesia is usually necessary.[182]

Anesthetic regimens for external beam radiation in children should provide brief periods of anesthesia at a depth that ensures immobility and minimal time to recovery.[182] Airway management should be appropriate to whatever body position the patient requires for the radiation therapy. Because all personnel must leave the room during actual delivery of the radiation, the anesthetic technique should facilitate remote monitoring for continuous assessment of the patient. During the actual radiation treatment period, the patient and anesthesia equipment are observed continuously by closed-circuit television, and monitors are mirrored to the remote observation site outside the treatment room.

Typically, patients require a series of treatments and hence a series of anesthetic regimens. It is therefore desirable to avoid repeated invasive procedures to the degree feasible and to keep the anesthesia technique as simple as possible. The LMA has



Figure 79-2 Intraoperative radiation therapy room. A sterile Lucite cylinder is used to isolate the tumor mass and displace normal tissues to limit the radiation dose. *(From Mackenzie RA, Southorn PA, Stensrud PE: Anesthesia at remote locations.* In *Miller RD* [*ed*]*: Anesthesiology, 5th ed. Philadelphia, Churchill Livingstone, 2000, p 2261.)*



Figure 79-3 The patient and anesthetic monitors are viewed on closed-circuit television during an intraoperative radiation procedure. *(From Mackenzie RA, Southorn PA, Stensrud PE: Anesthesia at remote locations.* In *Miller RD* [*ed*]*: Anesthesiology, 5th ed. Philadelphia, Churchill Livingstone, 2000, p 2262.)*

proved to be a simple and safe airway device for use in children undergoing general anesthesia for external beam irradiation.[183,184] Intravenous propofol infusion has been used satisfactorily in these children.[182,185,186] If the patient does not have an intracranial mass lesion, intramuscular administration of ketamine has provided satisfactory conditions.[187] However, excessive salivation and postoperative nausea and vomiting make ketamine a less desirable alternative. Given the frequent need for repeated treatments over a period of days or weeks, intravenous access may become difficult. Placement of a peripherally inserted central catheter may provide ongoing intravenous access.[188,189] Repeated access of the central line can be accomplished without undue risk of line-related sepsis, provided that access protocols are scrupulously followed.[182]

Stereotactic Radiosurgery

Stereotactic radiosurgery is the delivery of a large radiation dose to ablate tissue localized stereotactically.[190] Sources of ionizing radiation include photon beams produced by either ^{60}Co gamma ray or linear accelerators and heavy-ion particle beams. The radiation is emitted as multiple beams that can be focused on the desired site. The radiation dose from each beam is small to limit exposure of normal tissue to radiation. However, the radiation dose at the focus of the beams is high to achieve tissue destruction in the desired area.[191] This technique has been used to treat AVMs, dural arteriovenous fistulas, pituitary adenomas, acoustic neuromas, trigeminal neuralgia, and malignant tumors.[192-196]

The procedure consists of the initial placement of a stereotactic head frame, usually under local anesthesia, followed by neuroradiologic imaging, most frequently MRI. Other imaging procedures performed in conjunction with stereotactic radiosurgery have included angiography and CT. After precise stereotactic localization of the target, the radiosurgical procedure commences. Most cooperative patients require only mild sedation/analgesia for the procedure. Because absolute head immobility is necessary, uncooperative adults, those with movement disorders, and pediatric patients may require general anesthesia for any or all components of the procedure. The total duration of the anesthesia may be several hours.[188] Attention to fluid status, maintenance of temperature, and padding of pressure points is particularly important during these potentially long procedures. If general anesthesia is required, intravenous anesthesia with propofol may provide advantages in maintenance during the multiple patient transfers entailed by the procedure.[188] Mechanisms to maintain consistent standard monitoring throughout the procedure and transfers need to be in place. After the procedure, the patient goes to a fully staffed and equipped recovery area and is discharged after meeting standard discharge criteria.

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Richard E. Moon and Enrico M. Camporesi

80 Clinical Care in Extreme Environments: At High and Low Pressure and in Space

Key Points

1. Hyperbaric oxygen (HBO) exposure (breathing oxygen at increased ambient pressure, typically 2-3 atmospheres absolute [ATA]) causes an increase in arterial and tissue P_{O_2} and no significant change in arterial pH or P_{CO_2}.
2. During HBO therapy, cardiac output is reduced, systemic vascular resistance is increased, and pulmonary vascular resistance is decreased.
3. Acute illnesses for which HBO is indicated include carbon monoxide (CO) poisoning (based on randomized, controlled studies), gas bubble disease (gas embolism and decompression sickness), and soft tissue necrotizing infections (the latter two based on clinical experience and meta-analysis).
4. The decision to use HBO to treat a patient with arterial gas embolism or decompression sickness should be based on clinical criteria, including the presence of symptoms, abnormal physical examination, or a history of arterial gas embolism within a few hours even in the absence of symptoms. Neither neurophysiologic testing nor radiographic imaging is useful except, rarely, to exclude other pathologic processes.
5. The decision to use HBO to treat a patient with CO poisoning should be based on clinical criteria, including a history of impaired consciousness or other neurologic manifestation, pregnancy, or severe exposure (e.g., peak carboxyhemoglobin [HbCO] > 25%). The HbCO level correlates poorly with the severity of the illness and is generally useful only to make the diagnosis.
6. Oxygen-induced seizures are rare and self-limited. Appropriate management includes discontinuation of inhaled oxygen. Chamber pressure should not be altered during the seizure. Decompression can result in pulmonary barotrauma.
7. The principles of treatment of acute altitude illness include descent and supplemental oxygen. If these options are not available, for acute mountain sickness (AMS) or high-altitude cerebral edema (HACE), dexamethasone and acetazolamide are recommended; for high-altitude pulmonary edema (HAPE), drugs that lower pulmonary artery pressure, such as nifedipine, are recommended.
8. When providing anesthesia for otherwise healthy acclimatized patients at altitude, supplemental oxygen should be used only to maintain arterial oxygen saturation at baseline (not normal levels). Liberal administration of oxygen may reverse acclimatization.
9. As ambient pressure is altered, anesthetic vaporizers deliver a variable concentration but fixed partial pressure. Therefore, there is no need to adjust vaporizer settings when delivering anesthesia in a hyperbaric chamber or at altitude.
10. Unexpected complications have been observed after anesthetics for minor procedures in primates after spaceflight. Physiologic and pharmacologic effects of neuraxial or general anesthesia during or after spaceflight are largely unknown but could include hypotension, resistance to nondepolarizing muscle relaxants, and exaggerated hyperkalemia due to succinylcholine.

Hyperbaric medicine began in the 19th century, when clinical improvement was observed after recompression of divers and compressed air workers with decompression sickness. Hyperbaric air treatment was subsequently used for a variety of diseases, including tuberculosis, heart failure, emphysema, bronchitis, asthma, croup, whooping cough, anemia, anorexia, dyspepsia, leukorrhea, menorrhagia, neuralgic pain, and depression, without any scientific basis. An exception was the use by Fontaine in 1879 of a mobile hyperbaric chamber for anesthesia and surgery.[1] Compressed to 1.25 to 1.33 atmospheres absolute (ATA), a nitrous oxide/oxygen mixture was provided to the patient (Fig. 80-1). Breathing air in Fontaine's chamber would have provided an inspired P_{O_2} equivalent to 26% to 28% O_2 at 1 ATA. This was probably the first use of an elevated P_{O_2} during anesthesia and certainly the first administration of hyperbaric nitrous oxide.

Use of O_2 at high pressure for the treatment of decompression sickness had been suggested[2] and reported for the treatment

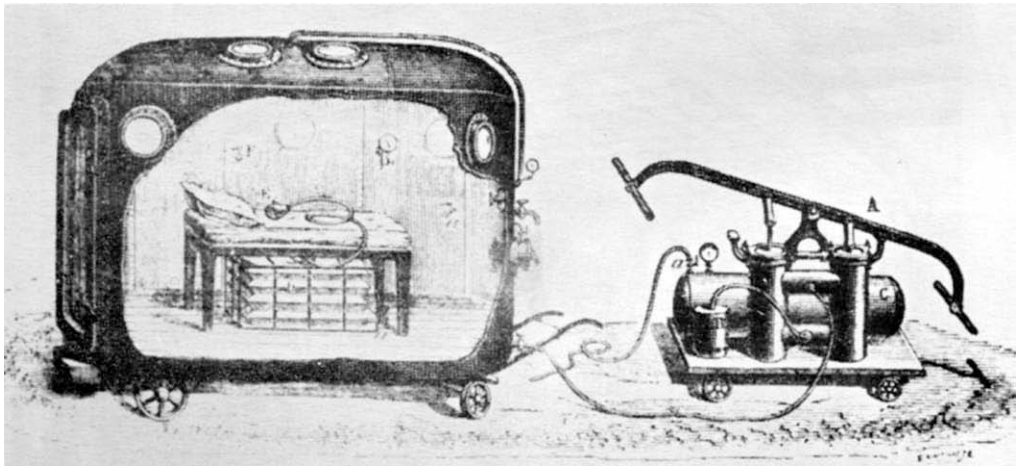

Figure 80-1 Mobile hyperbaric operating room described by Fontaine in 1879.[1] Nitrous oxide storage tanks can be seen under the operating table. Compressed to 1.25 to 1.33 atmospheres absolute (ATA) with air, a nitrous oxide/oxygen mixture was provided to the patient. Breathing air in this chamber would have provided an inspired P_{O_2} equivalent to 26% to 28% O_2 at 1 ATA.

of decompression sickness[3] but remained an isolated medical curiosity until the early 1960s. A few indications, such as support of oxygenation in hyaline membrane disease of the newborn[4] and during open heart surgery[5,6] were not useful. For other indications, such as carbon monoxide (CO) poisoning, arterial gas embolism, and decompression sickness, hyperbaric oxygen (HBO) proved to be effective, as evidenced by substantial clinical experience and randomized controlled studies. Indications are reviewed regularly by the Undersea and Hyperbaric Medical Society (Durham, NC). This medical organization publishes an extensive bibliography with a list of indications for hyperbaric oxygenation that is updated every 2 to 3 years.[7] Laboratory and clinical data support the use of HBO for a select number of acute and chronic illnesses (Table 80-1), and anesthesiologists are often called on to provide care of patients in this unusual environment.

Interest in the physiologic and medical aspects of altitude originated because of mountaineering and high-altitude balloon exploits in the 19th century.[8] An understanding of the physiologic response to altitude hypoxia has had wide application, as increasing numbers of people fly in aircraft, travel from low to high altitude, and live or work at higher elevations (Table 80-2). Significant effort has been devoted to techniques for prophylaxis and treatment of these illnesses in recent years.

The effects of space travel are mostly due to microgravity, radiation, and confinement. Understanding these effects and development of tools to deal with sick or injured astronauts are paramount for the medical support of long-range space missions, such as to Mars.

Table 80-1 Partial List of Conditions for Which Hyperbaric Oxygen Has Been Used

Gas-bubble disease
*Air embolism[7,83]
*Decompression sickness[83,291]
Poisoning
*Carbon monoxide[7,41,48-50,55]
Cyanide[41]
Carbon tetrachloride[292,293]
Hydrogen sulfide[41]
Infections
*Clostridial myonecrosis[7,99-101]
*Other soft tissue necrotizing infections[7,97,98,101]
*Refractory chronic osteomyelitis[7,90,294]
*Intracranial abscess[7,295]
Mucormycosis[296,297]
Acute ischemia
*Crush injury[7,298]
*Compromised skin flaps[7,299]
Central retinal artery occlusion, central retinal vein occlusion[300]
Chronic ischemia
*Radiation necrosis (soft tissue, radiation cystitis, and osteoradionecrosis)[7]
*Ischemic ulcers, including diabetic ulcers[7,11,301,302]
Acute hypoxia
*Exceptional blood loss anemia (when transfusion delayed or unavailable)[7]
Support of oxygenation during therapeutic lung lavage[103,104]
Thermal injury
*Burns[7,303-306]
Envenomation
Brown recluse spider bite[307,308]

*Approved by the Undersea and Hyperbaric Medical Society as an appropriate indication for HBO therapy.[7]

Physiologic Effects of Increased Gas Pressure

Increased Barometric Pressure

Some effects of altered ambient pressure are summarized in Figure 80-2.

Table 80-2 Range of Terrestrial Altitudes

Altitude*		Ambient Pressure		
ft	m	Atmospheres Absolute (ATA)	mm Hg	Comments
		0.32	246†	Lowest pressure to which volunteers have been continuously exposed (hypobaric chamber study: Operation Everest I)[309,310]
29,028	8848	0.35	263†	Mt. Everest, Nepal: highest point on earth
20,320	6194	0.45	345	Mt. McKinley (Denali): highest point in North America
19,521	5950	0.49	372†	Aucanquilcha mine, Chile: highest altitude known to have been continuously inhabited by humans.[311] Miners slept in a village at lower altitude (Quilcha, 5334 m).
17,716	5400	0.51	384	Everest base camp
17,060	5200	0.54	409	Chacaltaya ski resort, Bolivia (Elevation at the top of the ski hill: 5422 m)
16,733 5100 5050		0.55	414	La Rinconada, Peru: highest permanently inhabited town Atacama Large Millimeter Array telescope, Chile. The facility includes oxygen enrichment to 27%.[312]
14,110	4301	0.58	458	Pike's Peak, Colorado[194]
13,796	4205	0.60 (0.57-0.63)	460† (433-479)†	Mauna Kea, Hawaii (Keck Observatory)[313]
11,910	3630	0.65	497	La Paz, Bolivia
10,500	3200	0.69	524	Alta Ski Resort, Utah
10,430	3179	0.69	525	Leadville, CO, USA (highest altitude incorporated city in North America; population 3000)[314]
9,321	2841	0.67-0.68	507-516†	South Pole Station, Antarctica[315]
9,249	2819	0.72	549	Quito, Ecuador
7,546	2300	0.77	583	Mexico City, Mexico
5,280	1609	0.83	633	Denver, Colorado; Zermatt, Switzerland
4,500	1372	0.86	650	Banff, Alberta, Canada; Katmandu, Nepal
0	0	1.00	760	Sea level

*Altitudes and barometric pressures are shown for Mt. Everest and several locations inhabited at least part time. Barometric pressures have been calculated using an algorithm developed by West[316] except for values with a dagger (†), which were obtained by direct measurement.[310]

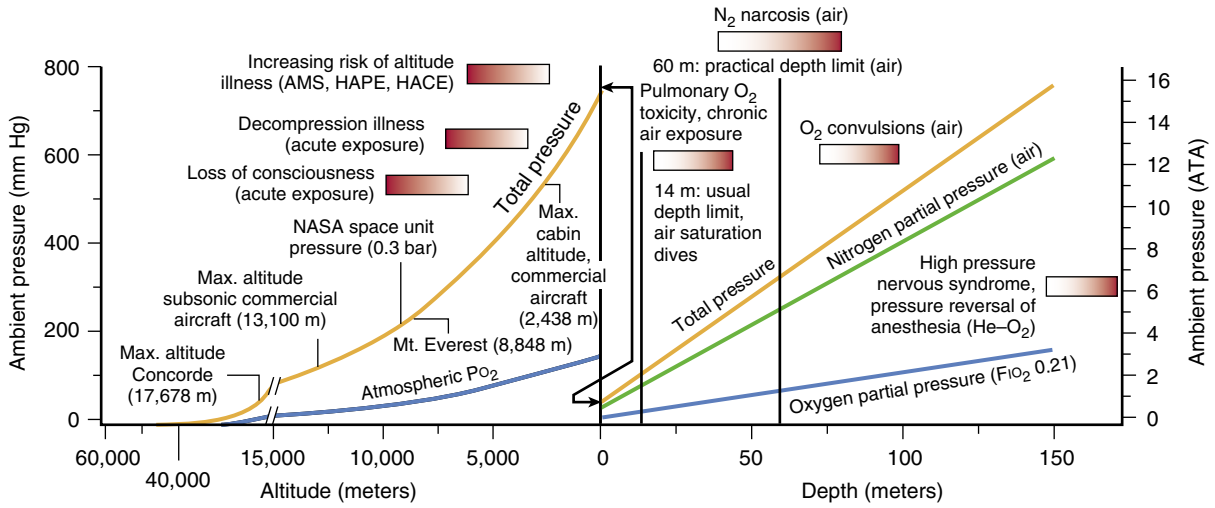

Figure 80-2 Ambient pressure as a function of altitude and water depth. Whereas ambient pressure increases linearly with depth, pressure and altitude are not linearly related. As air is inspired and humidified, there is a small and usually insignificant drop from atmospheric P_{O_2} to inspired P_{O_2}. At altitude, however, this decrease accounts for a greater proportion of the total ambient pressure. The O_2 partial pressure line in the water is shown for a constant F_{IO_2} of 21%. At increasing depth, the inspired P_{O_2} eventually exceeds the pulmonary toxic limit (~14 m in depth) and the central nervous system toxic limit (~70 m in depth). The threshold for high-pressure nervous syndrome and pressure reversal of anesthesia (observed in non-narcotic atmospheres) is 150 to 200 m in depth. The *shaded red bars* represent the depth or altitude ranges over which risk progresses from low (*light shading*) to high (*dark shading*). AMS, acute mountain sickness; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema.

An increase in environmental pressure is accompanied by significant adiabatic heat production, whereas decompression generates cooling. This results in an increase in chamber temperature during compression and in cooling and precipitation of water droplets during decompression. These phenomena may limit the rate of compression in manned chambers in order to maintain temperature within a comfortable range.

Additionally, pockets of trapped gas within the body will contract and expand on compression and decompression. Such pockets include gas in the middle ear, and paranasal sinuses, intestinal gas, pneumothorax, and gas pockets within monitoring and life-support systems. The changes in gas volume will occur according to Boyle's law:

$$PV = \text{constant}$$

such that a doubling of environmental pressure (P) will cause the volume (V) of a gas-filled cavity to decrease by half. This effect also underlies one of the major beneficial effects of hyperbaric treatment of pathologic gas, as in arterial gas embolism or decompression sickness (see later).

A comparison of pressure units used clinically with those in common use in hyperbaric environments is shown in Table 80-3.

Increased Partial Pressure of Oxygen

Breathing O_2 at increased ambient pressure will lead to elevation of alveolar O_2 tension (P_{AO_2}), which can be calculated according to the alveolar gas equation for O_2:

$$P_{AO_2} = F_{IO_2} \cdot (Pb - P_{H_2O}) - P_{ACO_2} \cdot \left(F_{IO_2} + \left[(1 - F_{IO_2})/R\right]\right)$$

where F_{IO_2} is the fractional inspired O_2 concentration; P_{H_2O} is saturated water vapor pressure at body temperature (typically 47 mm Hg); P_{ACO_2} is alveolar P_{CO_2}, assumed to equal arterial P_{CO_2} (Pa_{CO_2}); and R is the respiratory exchange ratio (usually ≈ 0.8 at rest). From calculated values of P_{AO_2}, arterial P_{O_2} (Pa_{O_2}) has been estimated, assuming that the arterial/alveolar P_{O_2} ratio remains constant.[9] Whereas at 1 atmosphere absolute (ATA) the fraction of O_2 in arterial blood that is carried dissolved in the plasma is minimal, it can be seen that at elevated Pa_{O_2} in the range of 1000 to 2000 mm Hg significant quantities of O_2 may exist in dissolved form (Table 80-4).

Increased Pa_{O_2} has at least four pharmacologic effects:

1. Increased blood O_2 content
2. Vasoconstriction
3. Antibacterial action, particularly against anaerobic bacteria
4. Inhibition of endothelial neutrophil adhesion in injured tissue

The increased arterial O_2 content underlies the rationale for administering HBO for the treatment of ischemic conditions, for example, ischemic, nonhealing wounds. The elevation in Pa_{O_2} leads to an increase in tissue P_{O_2}, which can be estimated using transcutaneous P_{O_2} electrodes, even in ischemic tissue.[10,11] The second effect is an explanation for the effectiveness of HBO in the treatment of traumatic edema (e.g., crush injury). The mechanism of HBO-induced vasoconstriction appears to be inactivation of nitric oxide due to increased production of superoxide[12] and possibly decreased release of NO from circulating S-nitrosohemoglobin.[12-14]

These two effects, increased O_2 content and vasoconstriction, lead to hemodynamic changes,[14,15] shown in Table 80-4. There is also a slight increase in mean arterial pressure. Studies of HBO effects on myocardial contractility using denervated hearts[16] or autonomically blocked animals[17] have indicated no intrinsic effect. In intact animals or humans heart rate and cardiac output are decreased and systemic vascular resistance is increased.[14,15,18] In both anesthetized dogs and awake humans pulmonary vascular resistance is decreased.[14,19] At 2 ATA 100% O_2 in conscious dogs has no effect on coronary flow,[18] whereas at 3 ATA both coronary flow and myocardial O_2 consumption are decreased.[17] Cerebral blood flow is decreased by O_2 administration over a range of pressures,[12,18] whereas at 2 ATA, hepatic, renal, and mesenteric flows are unchanged.[18]

HBO also has microcirculatory and cellular effects in various disease states (see later).

Increased Inert Gas Partial Pressure

Elevation of the partial pressure of the inert gas (usually nitrogen) present in a breathing mixture is associated with a narcotic effect, predictable by the Meyer-Overton hypothesis. Based on its solubility in olive oil, N_2 has 0.03 to 0.05 times the narcotic potency of nitrous oxide. At 3 ATA (breathing air) most people experience mild euphoria. At 6 ATA there may be memory loss and poor judgment. At 10 ATA some individuals lapse into unconsciousness. Nitrogen narcosis has been compared with alcoholic intoxication, an increase in ambient pressure of 1.5 ATA resulting in an effect that is said to be similar to drinking one martini. Argon and, to a lesser degree, hydrogen are narcotic, whereas helium has minimal if any narcotic effect. In animals exposed to high partial pressures of nitrogen there is evidence of activation of $GABA_A$ receptors of dopaminergic neurons in the nigrostriatal pathway, leading to a decrease in dopamine release.[20]

Table 80-3 Units of Pressure

Atmospheres Absolute (ATA)	Absolute Pressure (mm Hg)	Gauge Pressure (mm Hg)	Feet of Sea Water (fsw)	Meters of Sea Water (msw)
1	760	0	0	0
2	1520	760	33	10
3	2280	1520	66	20
6	4560	3800	165	50

Table 80-4 Mean Blood Acid-Base and Cardiovascular Responses to Altitude Exposure and Hyperbaric Oxygenation in 14 Normal Subjects

		Arterial						Mixed Venous									
Atmospheric Pressure (ATA)	Inspired Gas	Po_2 (mm Hg)	pH	Pco_2 (mm Hg)	O_2 Saturation (%)	Dissolved O_2 (mL/dL)	Total O_2* (mL/dL)	Po_2 (mm Hg)	pH	Pco_2 (mm Hg)	O_2 Saturation (%)	Cardiac Output (L/min^{-1})	Mean Arterial Pressure (mm Hg)	Mean Pulmonary Artery Pressure (mm Hg)	Pulmonary Artery Wedge Pressure (mm Hg)	Systemic Vascular Resistance ($dyne \cdot sec \cdot cm^{-5}$)	Pulmonary Vascular Resistance ($dyne \cdot sec \cdot cm^{-5}$)
0.56 (4572 m altitude)	Air	38	7.46	32	73.4	0.1	13.4	30	7.44	36	57.1	9.1	87	18	10	762	83
1	Air	94	7.40	37	95.7	0.3	17.6	43	7.39	42	75.5	6.5	86	13	9	1061	64
3	100% O_2	1542	7.42	36	99.1	4.6	22.5	399	7.37	43	97.7	5.8	95	12	9	1286	41

*Assuming Hb = 13 g/dL.

Data from McMahon TJ, Moon RE, Luschinger BP, et al: Nitric oxide in the human respiratory cycle. Nature Med 8:711-717, 2002.

Elevation of Absolute Pressure

High-Pressure Nervous Syndrome

High pressure induces a constellation of symptoms consisting of tremor, ataxia, nausea, and vomiting, known as the high-pressure nervous syndrome (HPNS).[21] It occurs at an ambient pressure greater than 15 to 20 ATA and was first described during the compression phase of deep dives with a helium-oxygen atmosphere. HPNS is ameliorated by slow compression and addition of a narcotic gas (e.g., nitrogen) to the breathing mix.[22] Its pathogenesis may be related to an increase in striatal dopamine.[23]

Pressure Reversal of Anesthesia

Studies in animals have demonstrated that high pressure has the tendency to reverse general anesthesia. Elevations in ambient pressure in the absence of a narcotic inert breathing gas will tend to decrease the effectiveness of both inhaled and intravenous anesthetics. At 50 ATA a 20% increase in the 50% effective dose (ED_{50}) has been observed in mice for a variety of inhaled anesthetics. At 50 and 100 ATA the effective dose of barbiturates increases by 30% to 60%.[24] The ED_{50} for diazepam in rats is markedly reduced at 90 ATA in a helium/oxygen atmosphere.[25] At 31 ATA, the effective concentration for half maximal effect (EC_{50}) of propofol for loss of righting reflex in tadpoles is increased by 19%, and, at 61 ATA, by 38%.[26] Using the same technique, the EC_{50} for dexmedetomidine at 31 ATA is nearly double the value at 1 ATA and increased 2.5-fold at 61 ATA.[27] At 80 ATA, the MAC of desflurane as assessed by response to a noxious stimulus is increased by 19%.[28] The mechanisms of pressure reversal are not fully understood but may be secondary to physical chemical effects of pressure on membranes[29] or due to alterations in neurotransmitter release.[23] However, within the range of pressures used for hyperbaric oxygen therapy (up to 3-6 ATA) the effects of pressure on sedative or anesthetic drugs are not clinically significant.

Effects of Hyperbaric Exposure on Drug Disposition

A few studies have examined the disposition of drugs and drug effects at increased environmental pressures. Studies in awake dogs at pressures up to 6 ATA and ambient Po_2 up to 2.8 ATA have shown that liver plasma flow decreased when either ambient pressure or Po_2 was raised. There was an apparent increase in plasma volume at 1.3 ATA and a return toward 1 ATA values at higher pressures. In the same studies, plasma volume was inconsistently affected by ambient pressure but reduced by increases in Po_2.[30]

There is no major pharmacokinetic or pharmacodynamic effect of hyperbaria for most drugs up to 6 ATA. Up to 6 ATA pressure and 2.8 ATA Po_2, the pharmacokinetics of meperidine,[31] pentobarbital,[32] theophylline,[33] and salicylate[34] are unaffected.

Use of benzodiazepines, chlorpromazine, and lithium carbonate has been reported for the treatment of agitation, auditory and visual illusions, and paranoia in a previously normal subject participating in an experimental dive to 650 m (66 ATA).[35] The symptoms, poorly controlled with diazepam, 120 mg/day, and temazepam, 60 mg/day, ultimately responded to chlorpromazine, 300 mg/day. Lithium carbonate administered in conventional doses appeared to display normal pharmacokinetics. While the effect of chlorpromazine appeared clinically to be appropriate, the authors were uncertain as to whether the failure of benzodiazepines to elicit a desired therapeutic response was due to the patient's condition or to a pressure-reversal phenomenon.

In summary, clinical experience and the published literature indicate that for a variety of drugs, conventional parenteral drug dosing schedules may be used safely under hyperbaric conditions at the pressures used for clinical treatment of patients with HBO therapy.

Rationale for the Treatment of Selected Specific Syndromes

Carbon Monoxide Poisoning

Hemoglobin (Hb) binds CO with an affinity much higher (by a factor of about 200) than that for O_2. This binding of CO with Hb to form carboxyhemoglobin (HbCO) has two major effects. First, the proportion of Hb that is occupied by CO molecules is unavailable for O_2 transport, resulting in a functional anemia. Second, the avidity with which the remaining Hb binds O_2 is increased (shift to the left of the Hb-O_2 dissociation curve). The result of this is a decreased ability to unload O_2 from blood to tissue at the capillary, and therefore a reduction in tissue Po_2. Previously it was believed that these effects were totally responsible for the toxicity of CO. However, evidence has since been presented to show that the binding of CO to intracellular pigments (e.g., cytochrome aa_3, myoglobin) and oxidative stress may contribute significantly to the toxicity of CO.[36-44] CO exposure also triggers intravascular platelet-neutrophil aggregation and neutrophil activation.[44] These mechanisms result in toxicity to multiple organ systems, including brain and heart.[41,45] Immune-mediated effects have also been described.[46]

Clinical effects include headache, nausea, vomiting, dizziness, myocardial ischemia, loss of consciousness, and, during pregnancy, fetal distress. Persistent or delayed neurologic sequelae can occur, often after a clear window of lucidity.[47-49] Increased risk factors for persistent sequelae include older age (≥36 years) and longer CO exposure.[50]

The diagnosis of CO poisoning is made by a history of exposure (internal combustion engine exhaust, fire, improperly adjusted gas or oil heating, charcoal or gas grills, or exposure to paint stripper containing methylene chloride, which is metabolized by the liver to CO). Confirmation of the diagnosis is made by finding an elevated HbCO level in either arterial or venous blood. HbCO concentration in anticoagulated blood samples is stable for several days. Therefore, if HbCO determination is not available at a referring facility the diagnosis can be confirmed using a blood sample obtained at the time of initial evaluation and transported with the patient. Fetal hemoglobin (HbF) can produce a falsely elevated reading for HbCO on certain four-wavelength laboratory co-oximeters.[51] In the first few weeks of life, blood from normal infants may therefore falsely indicate 7% to 8% HbCO.

Actual HbCO levels measured on arrival in the emergency department correlate poorly with clinical status and should not be used as the sole criterion to determine the need for treatment. Because of the lower intracellular Po_2, elimination of CO from

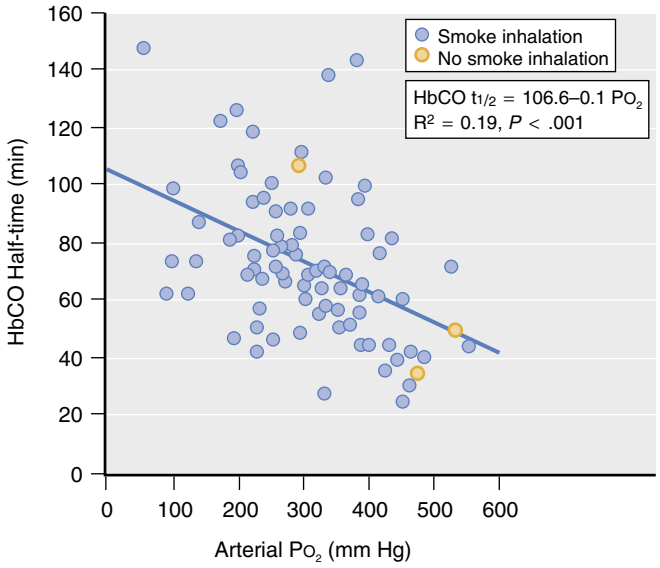

Figure 80-3 Elimination half-time of carboxyhemoglobin in 93 CO-poisoned patients. Although there is scatter in the data, it is apparent that CO dissociates from hemoglobin faster at higher PO_2. *(Redrawn from Weaver LK, Howe S, Hopkins R, Chan KJ: Carboxyhemoglobin half-life in carbon monoxide–poisoned patients treated with 100% oxygen at atmospheric pressure. Chest 117:801-808, 2000.)*

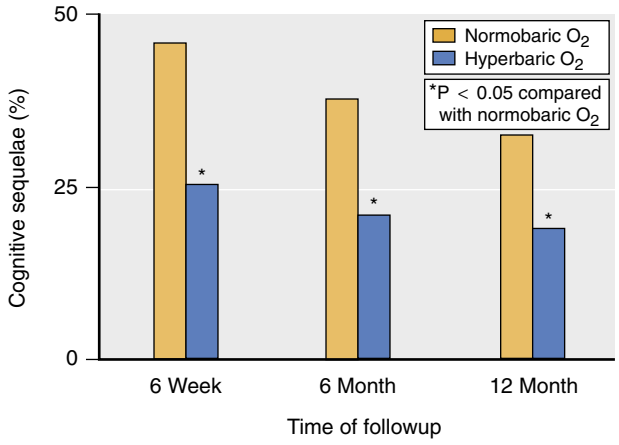

Figure 80-4 Cognitive sequelae in a randomized prospective trial of hyperbaric O_2 in CO poisoning. Cognitive sequelae were defined as any T score for a neuropsychological subtest more than 2 SD below the mean of demographically corrected standardized T scores or if two or more T scores for subtests were more than 1 SD below the mean. If the patient reported difficulties with memory, attention, or concentration, then cognitive sequelae were defined as a T score on any neuropsychological subtest more than 1 SD below the mean of demographically corrected standardized T scores. *(Drawn from data reported by Weaver LK, Hopkins RO, Chan KJ, et al: Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 347:1057-1067, 2002.)*

intracellular binding sites occurs more slowly. Significant mental obtundation, vomiting, and headache may remain even in the presence of a normal HbCO level.

Brain imaging may reveal a variety of abnormalities in patients with CO poisoning, including hypodensities in the globus pallidus and subcortical white matter, cerebral cortical lesions, cerebral edema, hippocampal lesions, and loss of gray matter/white matter differentiation and white matter hyperintensities.[52-54] Except to exclude other pathologic processes, brain imaging is not useful for determining who should receive HBO, but it may provide prognostic information.[52]

Oxygen is the primary treatment modality for CO poisoning. High Pao_2 hastens the removal of CO from blood, as indicated by a reduced half-life of HbCO. Figure 80-3 shows the HbCO half time in a series of CO-poisoned patients during normobaric O_2 administration; HBO reduces the half-time even further, to around 20 minutes at 2.5 ATA (Table 80-5).[55] Additionally, the increased dissolved O_2 in plasma may support tissue oxygenation pending removal of CO from Hb and other proteins important for O_2 transport. Although the treatment of CO poisoning with HBO remains somewhat controversial, there is mounting evidence that for poisoning in which neurologic symptoms occur, HBO treatment may decrease both early and late morbidity. The results of one randomized prospective trial of hyperbaric versus normobaric oxygen revealed no apparent benefit of HBO[56]; however, in four trials, HBO treatment has resulted in an improved outcome (Fig. 80-4).[48,49,57,58]

Commonly used guidelines for the application of HBO therapy in CO poisoning include the following:

- A history of neurologic impairment (including dizziness, loss of consciousness)
- Evidence of cardiac abnormalities (ischemia, arrhythmias, ventricular failure)
- An HbCO level that has been greater than 25%

Fetuses are particularly susceptible to CO toxicity. Pregnant women who fulfill the criteria just listed or in whom there is fetal distress should be treated with HBO. Case reports,[59-61] published series,[62,63] and a critical review[64] support the concept that inadequately treated CO poisoning is a serious risk to the mother and fetus, and the benefits of HBO outweigh the theoretical risks to the fetus of HBO treatment. Potential adverse effects of currently implemented HBO treatment protocols have not been confirmed in clinical practice.

Gas Embolism and Decompression Sickness

Introduction of gas into the arterial circulation (arterial gas embolism) has traditionally been associated with scuba divers and attributed to pulmonary barotrauma during ascent from a dive while breathing compressed gas. However, it may also occur iatrogenically in several clinical circumstances, such as during cardiopulmonary bypass or as a result of inadvertent injection of air during a diagnostic arteriogram or hemodialysis. Additionally, large amounts of gas may enter the venous system, for example, during neurosurgical procedures with the patient in the sitting position, hemodialysis, major back surgery, total hip replace-

Table 80-5 Carbon Monoxide Elimination Half-times While Breathing Air or 100% Oxygen at 1 ATA and at 2.5 ATA

Breathing Gas	Mean Half-life (min)*	No. Subjects
Air, 1 ATA	214	10
Oxygen, 1 ATA	43	15
Oxygen, 2.5 ATA	19	10

*Mean values from data of Pace N, Strajman E, Walker E: Acceleration of carbon monoxide elimination in man by high pressure oxygen. Science 111:652-654, 1950.

ment, cesarean section, laparoscopy, intrauterine laser surgery, arthroscopy (due to air escaping from faulty air-powered drill), and hydrogen peroxide irrigation or oral ingestion (due to elaboration of gaseous oxygen from tissue and blood catalase). Venous gas embolism can also occur when a central venous catheter is opened to air. Severe venous gas embolism has also occurred during orogenital sex after blowing air intravaginally.[65] Venous gas embolism has been reported in patients with acute respiratory distress syndrome (ARDS) being ventilated with positive end-expiratory pressure.[66] Venous gas embolism in sufficient quantity may overwhelm the ability of the pulmonary vasculature to filter the gas, allowing bubbles to pass into the arterial circulation. Even small amounts of venous gas (e.g., venous gas embolism due to decompression from diving) have recently been implicated in neurologic syndromes in scuba divers because of transatrial passage through a patent foramen ovale.[67,68]

The effects of gas embolism are not solely due to vessel obstruction by bubbles. Bubble-endothelial interaction causes increased capillary permeability and extravasation of fluid[69,70] and impairment of endothelial function.[71] Another effect has been demonstrated in a model of arterial gas embolism in anesthetized rabbits[72,73]: small doses of intracarotid air may pass through the cerebral microcirculation yet produce vasoplegia, delayed reduction of cerebral blood flow, and neurophysiologic impairment. This reduction in blood flow is abolished when there is neutropenia; thus, it has been concluded that leukocytes are required for this effect.[74] This phenomenon of delayed reduction of cerebral blood flow may be responsible for the clinical observation of initial neurologic improvement after arterial gas embolism, followed by delayed deterioration.[75]

A related syndrome that results from pathologic effects of tissue and blood gas bubbles is decompression sickness (DCS) seen in aviators and compressed gas divers. The gas bubbles in these situations occur because of a decrease in ambient pressure at a rate sufficient to induce local inert gas supersaturation, resulting in formation of bubbles in situ from tissue stores. Symptoms of arterial gas embolism classically consist of impaired consciousness, hemiparesis, or seizures but may be of a less severe nature. DCS most commonly presents as any combination of joint pain, paresthesias, motor weakness, bladder or bowel sphincter dysfunction, vertigo, tinnitus, or hearing loss.[76,77]

Treatment principles for both forms of gas bubble disease, arterial gas embolism and DCS, are the same in most instances. First aid includes therapy with oxygen.[78] High P_{O_2} results in increased rate of resolution of gas bubbles because of the resulting higher partial pressure gradient for diffusion of inert gas from the interior of the bubble into the surrounding tissue or blood. Intravascular bubbles cause endothelial leak, extravasation of plasma, and hemoconcentration.[69,79] Fluid resuscitation will replenish intravascular volume, reduce hemoconcentration, and facilitate microcirculatory flow,[80] principles that have been confirmed by both animal[81] and human observations.[69] However, excessive fluid administration can worsen pulmonary gas exchange in cardiorespiratory DCS (pulmonary edema due to venous gas embolism) and aggressive fluid therapy is not indicated for isolated arterial gas embolism.[80]

HBO therapy is the definitive treatment for arterial gas embolism and DCS. The increased pressure will cause a diminution in gas volume and thus further hasten resolution. The usefulness of HBO treatment of diving-related or aerospace-related gas embolism associated with rapid decompression is well documented.[82,83] HBO may effect neurologic improvement even after many hours and sometimes days between the embolic event and treatment,[84-86] although severe abnormalities are less likely to resolve if not treated promptly. Treatment of arterial gas embolism is usually performed at ambient pressures from 2.8 to 6 ATA (see the section "Treatment Schedules").

The decision to administer recompression treatment should be based entirely on clinical evaluation. The only appropriate role for brain or spinal imaging (e.g., computed tomography [CT], magnetic resonance imaging [MRI]) is to exclude other pathologic processes such as hemorrhage, and only if there is a high degree of suspicion that bubbles are not the cause of a patient's symptoms. Some authors have suggested that patients with arterial gas embolism should only be treated with HBO if CT of the brain reveals air[87]; however, brain imaging of patients with arterial gas embolism or DCS reveals abnormalities in only a minority of cases and the abnormalities on either CT or MRI are usually not specific. Intravascular gas is observed in a small fraction of cases,[86] and neither its absence nor presence predicts response to hyperbaric treatment. Neither single-photon emission tomography (SPECT) nor positron emission tomography (PET)[88] has yet been demonstrated to provide clinically useful information in the management of patients with gas bubble disease.

Acute Infections

Anaerobic bacteria are especially sensitive to increased tissue P_{O_2}. High O_2 tensions inhibit clostridial α-toxin production.[89] Other mechanisms include reversal of hypoxia-induced neutrophil function,[90-92] enhanced macrophage interleukin (IL)-10 expression,[93] and anti-inflammatory effects.[94-96] Evidence in favor of the use of HBO in clostridial and nonclostridial infections is provided by clinical series and a meta-analysis.[97-102]

Support of Arterial Oxygenation

HBO is a safe and effective method of supporting arterial oxygenation during therapeutic lung lavage, during which oxygenation has to be maintained by the contralateral (nonlavaged) lung.[103,104] In our experience of over 100 procedures, using this technique to treat arterial oxygenation has been uniformly successful with no resulting complications. A reversible simulation of pulmonary gas exchange during the lavage procedure can be provided by temporarily ventilating the lung to be lavaged with 5% to 6% O_2/balance N_2, which reduces P_{AO_2} in that lung to approximately the level of mixed venous P_{O_2} and confining O_2 exchange to the contralateral lung. Hypoxemia within 5 minutes is predictive of hypoxemia during the actual lavage.

Maintenance of Oxygen Transport in Severe Anemia

The ability of HBO to increase arterial O_2 content in plasma to clinically useful levels may allow support of tissue O_2 delivery even without hemoglobin. HBO can therefore be used for temporary support of severely anemic patients pending availability of definitive therapy in the form of crossmatched blood.

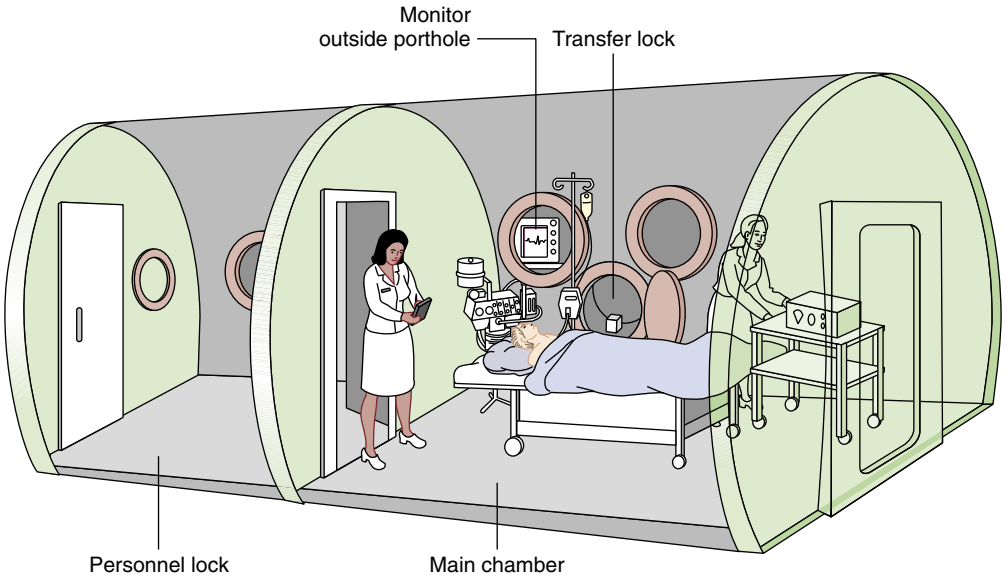

Figure 80-5 Multiplace hyperbaric chamber large enough for one or more patients and tenders. The chamber atmosphere is compressed air. The patient receives 100% O_2 by mask, head tent, or endotracheal tube. Monitors are usually kept outside the chamber because of electrical safety considerations. Monitoring is possible through a porthole. A personnel lock and a transfer lock allow physicians, nurses, or other personnel, in addition to medications, food, and blood samples, to be moved into and out of the chamber without repeated compression and decompression of the patient.

Therapeutic Systems

The traditional method of administering hyperbaric therapy is with a multiplace chamber, which accommodates two or more persons (Fig. 80-5). Size may vary from a small, portable two-person chamber used for transporting patients in the field to one 20 feet or more in diameter, in which up to 12 patients may be comfortably admitted, in addition to tenders. Multiplace chambers are compressed with air while the patient breathes O_2 with a head tent (Fig. 80-6), face mask, or endotracheal tube. Because of immediate access to the patient by accompanying nursing personnel or physicians, monitoring and resuscitative procedures are straightforward. However, multiplace chambers take up a lot of space and are expensive.

Monoplace chambers are large enough to accommodate only 1 patient (Fig. 80-7) or a tender with a small child. The chamber wall in most types is manufactured of Plexiglas, facilitating close visual observation of the patient. The chamber is usually compressed with 100% O_2. The advantage of monoplace chambers is their relatively low cost and ease of installation. Chamber operation can often be implemented by connecting the O_2 inlet to the hospital supply. Operation is relatively simple, but the patient inside is not directly accessible. Monitoring is somewhat more remote, and emergency airway management is not possible. Development of a pneumothorax during treatment, particularly a tension pneumothorax, could be fatal as pleural decompression with a needle or chest tube cannot be performed before decompression; however, this complication is extremely rare. A minor disadvantage of these chambers is that the ambient pressure limit is 3 ATA, and for practical reasons (psychological

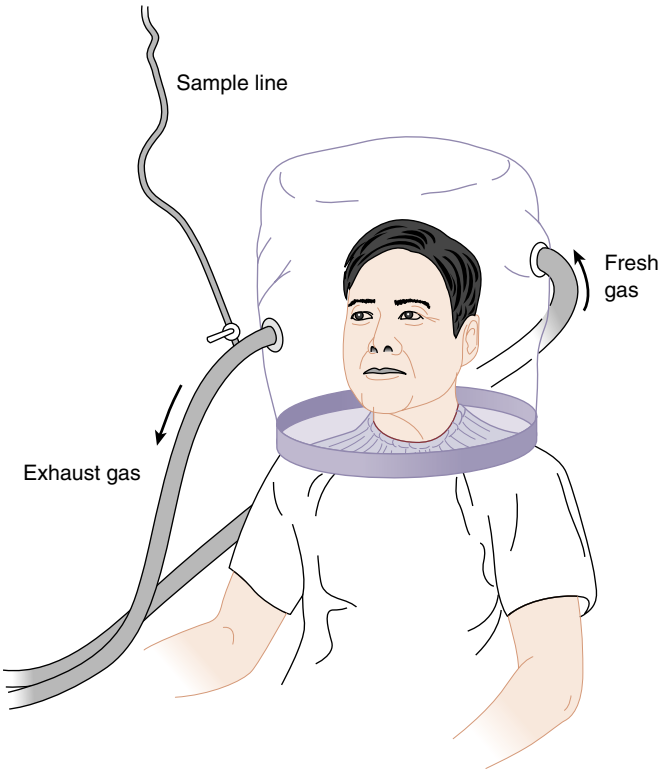

Figure 80-6 Head tent circuit for use in a multiplace chamber. Fresh gas (100% O_2) flows at a constant rate (>30 L/min) through the head tent. Exhaust gas may be either vented outside the chamber or recirculated through a CO_2 scrubber. The sample line attached to the exhaust hose allows monitoring of the patient's breathing gas.



Figure 80-7 Monoplace chamber. This type of chamber has room for one patient or a tender with a small child. The patient is moved into and out of the chamber on a wheeled gurney. The chamber atmosphere is usually 100% O_2. The chamber is constructed of transparent Plexiglas to allow observation. Through-hull penetrators in the door on the left can be seen and allow monitoring, intravenous fluid administration, and control of a ventilator inside the chamber. *(Photograph courtesy of Dr. Lindell Weaver.)*

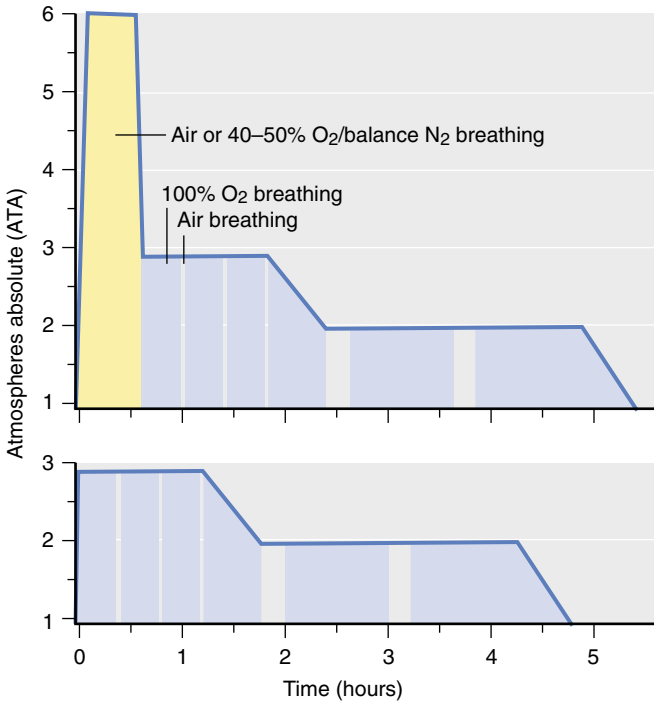

Figure 80-8 U.S. Navy treatment tables 6 (*top*) and 6a (*bottom*). Table 6a is occasionally used for the treatment of arterial gas embolism. During the 30-minute period at 6 ATA, air or 40% to 50% O_2 can be administered. Table 6 was originally designed for the treatment of decompression sickness but is now the most commonly used table for gas embolism as well. The *blue areas* represent 100% O_2 breathing; the *white areas* represent air breathing periods (see Fig. 80-10). *(Further details can be found in the Navy Department: US Navy Diving Manual. Revision 6. Vol 5: Diving Medicine and Recompression Chamber Operations. NAVSEA 0910-LP-106-0957. Washington, DC, Naval Sea Systems Command, 2008.)*

aversion to confinement) treatment times are limited. Moreover, intermittent periods of air breathing, in order to decrease the risk of O_2 toxicity during some types of treatment schedules (see later), requires installation of an additional gas delivery system. Nevertheless, monoplace technology now permits intravenous fluid administration from outside the chamber, invasive intravascular monitoring, mechanical ventilation, and utilization of pleural drainage systems incorporating regulated suction.[105,106]

Hyperbaric Treatment Schedules

Ideally, a patient who has therapeutic indication for hyperbaric O_2 would be exposed for an unlimited time until the condition resolves. Unfortunately, several factors limit the dose and duration of HBO:

- O_2 toxicity
- Decompression obligation for nursing staff (or other tenders) accompanying patient
- Adequacy of monitoring
- Patient isolation and boredom in a confined environment

Treatment schedules have been developed that are compromises between O_2 partial pressure and exposure time on one hand and O_2 toxicity and other practical limiting factors listed on the other. The original schedules (or "tables") were developed by the various navies of the world to treat DCS and gas embolism in divers (Fig. 80-8).

U.S. Navy Table 6 (see Fig. 80-8) prescribes an initial exposure to 2.8 ATA (equivalent to 60 feet of sea water [fsw] or 18 m of sea water [msw]), followed by slow decompression to 1.9 ATA (30 fsw). Periods of O_2 breathing are interspersed with 5- or 15-minute periods of air breathing to decrease O_2 toxicity (see later). This schedule remains the mainstay of treatment for DCS in multiplace chambers throughout the world. Incomplete relief of signs or symptoms can be treated with repeated applications described in Table 6 or a shorter treatment on a daily basis.

Table 80-6 Duke Modifications for Decompression of Tenders

Standard air decompression Within 2 ft of standard Navy depth divisions, use the next greatest depth. Within 2 min of standard Navy time divisions, use the next greatest time. During decompression of the chamber after a compressed air dive, breathe 100% O_2 from an equivalent depth of 50 fsw (2.5 ATA) to the surface or for 15 minutes, whichever is shorter.
Time for decompression: 68-30 fsw (3.06-1.9 ATA): 3 minutes 30-20 fsw (1.9-1.6 ATA): 1 minute 20-10 fsw (1.6-1.3 ATA): 1 minute 10 fsw (or last stop)—"surface" (1.3-1.0 ATA): 5 minutes
When USN Table 6 or 6a is extended, the tender should breathe 100% O_2 for the last 30-90 minutes at 30 fsw (1.9 ATA) according to the number of extensions at 60 fsw (2.8 ATA): 30 minutes (no extensions), 60 minutes (1 extension), 90 minutes (2 extensions). 100% O_2 is breathed by the tender for the entire period of decompression from 30 fsw (1.9 ATA) to "surface" (1 ATA).

fsw, feet of sea water.

"Saturation" treatment consists of an extended exposure to elevated pressure (e.g., 2.8 ATA) for an unspecified period of time (often 1-2 days) until manifestations have stabilized. Periodic O_2 breathing is given according to a recommended schedule as tolerated. Because saturation treatment results in a much larger degree of nitrogen uptake in both the patient and the tender, decompression must occur much more slowly, usually over 24 to 36 hours.[107-109] Although this therapy avoids the theoretical disadvantage of intermittent treatment—failure of resolution of gas bubbles—it is also considerably more labor intensive. Because hyperbaric chambers used for saturation treatments require additional hardware (e.g., CO_2 scrubbing capability) and personnel, their application outside military and commercial diving has been limited.

A schedule used for treatment of patients with clostridial myonecrosis or other life-threatening anaerobic infections is shown in Figure 80-9. This schedule consists of 85 minutes at 3 ATA followed by a 33-minute decompression stop for the tenders at 1.3 ATA. This treatment schedule has been designed to maximize Pao_2 (and hence tissue bactericidal activity due to O_2) without an undue risk of hyperoxic seizures.

Treatment schedules for CO poisoning have varied. However, the proven efficacy of the schedule reported by Weaver (60 minutes at 3 ATA, 60 minutes at 2 ATA in addition to air breaks and compression/decompression time) supports the use of 3 ATA for at least the first treatment.[49]

Administration of HBO to patients with chronic diseases (e.g., radionecrosis) is usually performed using shorter tables at lower ambient pressure, most commonly 1 to 2 hours at 2.0 to 2.5 ATA (see Fig. 80-9) once or twice daily. At this lower ambient pressure the risk of O_2 toxicity is minimal and treatments are well tolerated by most patients.

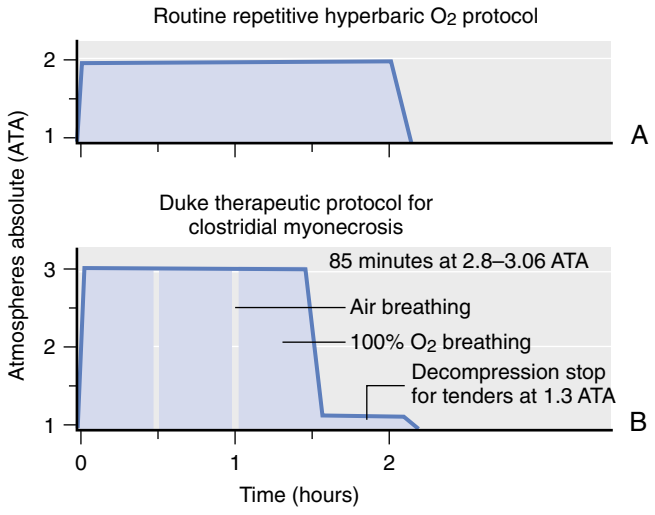

Figure 80-9 Examples of clinical hyperbaric O_2 treatment schedules. **A,** The patient breathes 100% O_2 for 2 hours at an ambient pressure of 2 ATA. Generally, this schedule is used for repetitive treatment of chronic conditions (e.g., osteoradionecrosis). **B,** Therapeutic schedule often used for treatment of clostridial myonecrosis. The patient and the tender spend 85 minutes at 2.8 to 3.06 ATA (3 ATA shown). The patient breathes 100% O_2, except during two 5-minute air breaks to reduce pulmonary and CNS O_2 toxicity. A decompression stop is made at 1.3 ATA, according to the U.S. Navy standard air decompression table. The stop is designed to facilitate safe decompression of the tender, who breathes air at 3 ATA.

Side Effects of HBO Therapy

Oxygen Toxicity

A wide body of evidence supports the notion that O_2 toxicity is caused by excessive production of oxygen free radicals (e.g., superoxide, hydroxyl radicals, and singlet oxygen). At high O_2 partial pressures scavenging mechanisms can be overcome by increased rates of free-radical production.[110] With the use of supplemental O_2 at 1 ATA, the manifestations of O_2 toxicity are almost exclusively confined to the lung; however, during hyperbaric oxygen exposure, other organs can be affected as well.

O_2 toxicity during HBO therapy can affect mainly the lung, the central nervous system (CNS), and the eye. Pulmonary toxicity in the conscious patient is heralded by symptoms of tracheobronchial irritation, namely, cough and burning chest pain. Prolonged exposure may result in a decrease in vital capacity and, if O_2 administration continues, ARDS. In the rare instances in which prolonged HBO is indicated, the rate of development of pulmonary O_2 toxicity can be slowed by intermittent air-breathing periods ("air breaks") (Fig. 80-10).

O_2 toxicity is related to the Po_2 of the inspired gas. At 1 ATA, 100% O_2 is as toxic as 16.7% O_2 at 6 ATA or 2% O_2 at 50 ATA. One method of quantification of O_2 exposure is the unit pulmonary toxic dose (UPTD).[111] In this system the number of UPTD units (U) is calculated by the formula:

$$U = t \cdot \sqrt[m]{0.5/(P-0.5)}$$

where t is the exposure time in minutes; P is the inspired Po_2 in ATA, and m is a slope constant that has an empirical value of 1.2. After 1425 UPTD units of O_2 exposure, there is an average 10% decrease in vital capacity; After 2190 UPTD units, there is an associated decrease of 20%. Complete reversal of vital capacity decrements as large as 40% of control has been observed after extended O_2 exposure at 2 ATA.[111]

Reanalysis of a larger data set than the one used for the UPTD model, which included those data, resulted in a different prediction equation:

$$\%\Delta VC = -0.009 \cdot (P - 0.38) \cdot t$$

where P and t are the same as for the previous equation.[112]

Using previously published data, Arieli and colleagues[113] developed the following equation:

$$\%\Delta VC = 0.0082 \cdot t^2 \left(Po_2/101.3\right)^{4.57}$$

where t is time in hours and Po_2 is measured in kilopascals (kPa).

Although these algorithms may be useful as an approximate guide to safe O_2 exposures in populations, interindividual variability is such that they cannot be relied on to predict accurately the development of pulmonary O_2 toxicity for a specific patient.[114] Furthermore, O_2 toxicity can be modified by humidity,[115] circulating catecholamine and corticosteroid levels, leukocyte accumulation in the lungs (e.g., with pneumonia), and circulating endotoxin. A more useful guide to the development of pulmonary toxicity is the patient's symptoms, which include cough and inspiratory central burning chest pain. These symptoms do not occur during routine repetitive HBO treatment but may become evident during extensive O_2 periods at 2.8 ATA, for example when treating neurologic decompression illness. Asymptomatic persons usually have minimal or no change in vital capac-

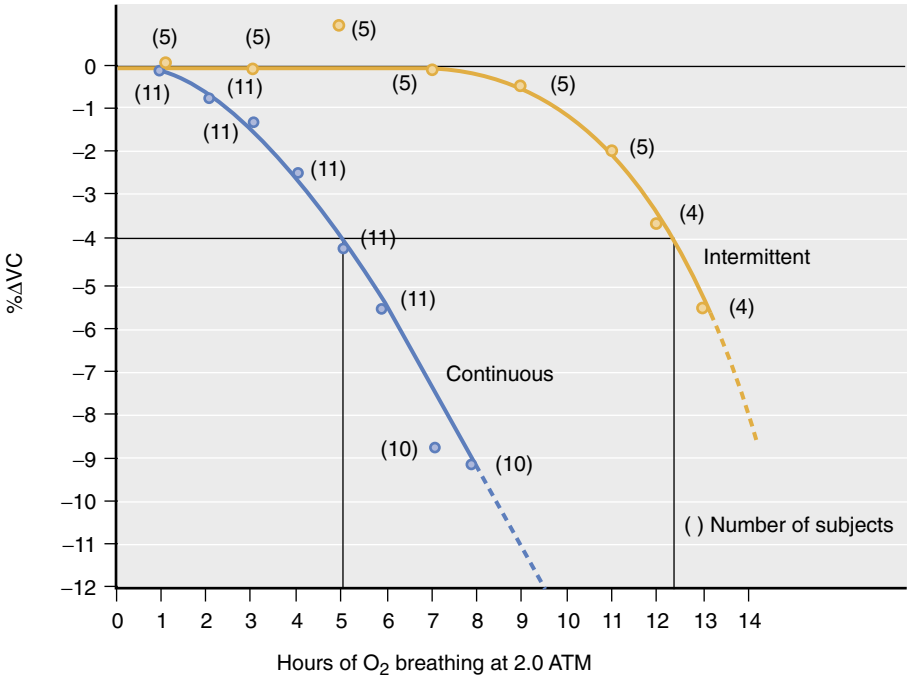

Figure 80-10 Decrease in vital capacity (VC) as a function of time breathing 100% O_2 at 2 ATA in humans. The figure illustrates the value of intermittent O_2 (20 minutes O_2, 5 minutes air) versus continuous administration in the prevention of pulmonary O_2 toxicity. The numbers in parentheses represent the number of subjects tested. *(From Clark JM: Oxygen toxicity.* In *Bennett PB, Elliott DH [eds]: The Physiology and Medicine of Diving. Philadelphia, WB Saunders, 1993, pp 121-169, with permission.)*

ity. Minor changes in forced expiratory volume in 1 second (FEV_1) reported during repetitive HBO treatments[116] are of uncertain clinical importance.

Some antineoplastic agents, such as bleomycin[117] and mitomycin C,[118,119] appear to predispose to fatal pulmonary O_2 toxicity (ARDS and respiratory failure) from what should otherwise have been well-tolerated doses of supplemental O_2. The risk of pulmonary O_2 toxicity due to HBO therapy in patients with previous exposure to such agents is unknown, although we have treated several such individuals with a remote history of bleomycin treatment with repetitive doses of HBO at 2 ATA for 2 hours (initially once daily, then increased to twice daily). Occasional mild pulmonary O_2 toxicity symptoms such as retrosternal chest tightness did occur, but none experienced severe O_2 toxicity. Propensity to pulmonary O_2 toxicity engendered by these drugs appears to diminish a few weeks after their discontinuation.

CNS O_2 toxicity manifests as nausea, vomiting, numbness, twitching, dizziness, olfactory, acoustic, or gustatory sensations, and, in its most severe form, as nonfocal tonic/clonic seizures.[120,121] The probability of seizures increases with increasing P_{O_2} and time of exposure. In a study of 36 divers breathing 100% O_2 at 3.7 ATA, all experienced one or more of these symptoms within 100 minutes or less.[120,121] In clinical practice, convulsions in patients undergoing HBO therapy are rare at ambient P_{O_2} up to 2.5 ATA (typically 0.008% to 0.035% of treatments[122]) and often have another predisposing factor. The probability of a convulsion is also greater when administered for acute indications such as carbon monoxide poisoning.[123] Metabolic factors may reduce the seizure threshold, such as the administration of high-dose penicillin (e.g., for clostridial infection), sepsis, and hypoglycemia.

The treatment of hyperoxic seizures is immediate reduction of the inspired P_{O_2} until the seizure stops. Some physicians then routinely administer an anticonvulsant such as phenobarbital, phenytoin, or a benzodiazepine. It is generally recommended that the chamber should not be decompressed while the patient is actively convulsing because airway closure and failure to exhale during this period may cause pulmonary barotrauma. Hyperoxic seizures otherwise have no sequelae and rarely recur even if HBO is continued. Thus the occurrence of CNS O_2 toxicity should not preclude further HBO. There is no evidence that hyperoxic seizures are more common in patients with preexisting seizure disorders.

An acute effect of HBO on the eye is narrowing of the visual fields,[124] which is generally only observed at a P_{O_2} of 3 ATA or greater and thus rarely during routine HBO treatments. A subacute or chronic ocular effect is a change in the refractive index of the lens, resulting in myopia.[125,126] Such refractive index change occurs during the course of intermittent HBO therapy over several weeks and usually resolves in a similar period of time. However, some patients may be left with residual myopia, particularly if elderly.[127]

Concern has been raised about the risk of retrolental fibroplasia in the unborn child of a woman who may require acute HBO therapy during pregnancy. Although many pregnant women have been treated with single exposures to HBO (e.g., for CO poisoning), we are not aware of any subsequent occurrence of retrolental fibroplasia in the child. Pregnancy is not a contraindication to HBO for appropriate acute indications (e.g., CO poisoning[60,62,64,128,129]), because the risk to the fetus of the underlying condition exceeds that of the treatment.

Table 80-7 Resting Blood Gas and Heart Rate Values in a Group of Normal Volunteers Acutely Exposed to Various Altitudes in a Hypobaric Chamber (mean ± SD)

Altitude (ft)	Barometric Pressure (mm Hg)	Pao_2 (mm Hg)	Sao_2 (%)	$Paco_2$ (mm Hg)	pH	HR (beats/min)
0	750	103 ± 11	99 ± 1	34 ± 5	7.44 ± .04	78 ± 15
5,000	632	78 ± 8	94 ± 4	33 ± 3	7.42 ± .04	92 ± 16
10,000	523	58 ± 8	88 ± 4	33 ± 4	7.42 ± .03	98 ± 16
15,000	429	42 ± 7	76 ± 8	28 ± 4	7.48 ± .03	107 ± 17

Sao_2, oxygen saturation. Data from experiment reported by Torre-Bueno JR, Wagner PD, Saltzman HA, et al: Diffusion limitation in normal humans during exercise at sea level and simulated altitude. J Appl Physiol 58:989-995, 1985.

Inert Gas Uptake

Breathing air at high ambient pressure can result in nitrogen narcosis, a dose-dependent decrement in cerebral performance due to the anesthetic properties of nitrogen. This only occurs to any significant extent at ambient pressures exceeding 4 ATA, a treatment pressure that is only utilized for severe arterial gas embolism or DCS. Nitrogen uptake can also result in DCS during or after decompression (see earlier). However, chamber decompression schedules are so conservative that this rarely occurs (most hyperbaric facilities use U.S. Navy compressed air decompression tables[109]). Additional safety for the tender can be provided by requiring the tender to breathe 100% O_2 for a period immediately before and during decompression (Table 80-7). Rare episodes of DCS in hyperbaric tenders are usually of a minor nature, generally consisting of mild joint pain. Nitrogen narcosis and DCS could only occur in tenders in a multiplace hyperbaric chamber; patients breathe 100% O_2 and are therefore not susceptible.

Barotrauma

As the ambient pressure is altered, the pressure within gas-containing spaces in the body must equilibrate with the ambient pressure or undergo a change in volume. Volume change can easily occur in compliant compartments such as the gastrointestinal tract, but if there is obstruction to free flow of gas into and out of containing spaces surrounded by a rigid shell, such as the lung, paranasal sinuses, and middle ear, then tissue disruption and hemorrhage can occur. Indeed, the most common patient side effect of hyperbaric chamber use is the difficulty with middle ear pressure equilibration.[130] In awake patients, equilibration may be accomplished using several techniques, such as performing intermittent Valsalva maneuvers, swallowing while the nose is pinched, thrusting the jaw forward, or simply swallowing intermittently during compression. Patients with prior irradiation of the head and neck and acute respiratory tract infections are at particular risk. Equilibration may be facilitated by application of a topical nasal vasoconstrictor (e.g., oxymetazoline, 0.05% [Afrin]). For patients who cannot equalize despite these measures, or for obtunded or intubated patients, myringotomy or tympanostomy tubes may be required. Theoretically, HBO exposure in a patient with obstructed eustachian tubes could cause labyrinthine window rupture, but to our knowledge this has not been reported during HBO treatment.

Pulmonary barotrauma is most likely during decompression. Areas of regional hypoventilation could lead to pulmonary overpressurization and alveolar rupture, causing pneumothorax, pneumomediastinum, or arterial gas embolism.[131,132] Pulmonary barotrauma during HBO therapy is extremely rare, probably due to slow decompression rates typically used.

Although a pneumothorax would be expected to diminish in size and resorb more quickly after compression, continuing leakage of air from the lung might result in tension pneumothorax during decompression.[131] Pneumothorax detected before treatment is usually treated by insertion of a chest tube and water seal or Heimlich-type valve. Caution must be exercised when using certain commercially available pleural suction regulators, which can exert high negative pleural pressures during chamber compression.[133] Such excessive suction can be relieved by an attendant inside a multiplace chamber by activating the manual pressure relief valve on the chest drainage unit.

Despite these potential adverse effects of HBO therapy, major complications are extremely rare.[130]

Practical Aspects of Hyperbaric Therapy

Patient Monitoring

Despite the changes in the acoustic properties of compressed air, blood pressure measurement may be performed without difficulty with a standard sphygmomanometer and stethoscope (see Chapter 38). Aneroid pressure gauges are preferred to mercury to avoid contamination of the closed environment. Monitoring of the electrocardiogram (ECG) and of intravascular pressures requires that transducer cables be plumbed through the chamber wall to preamplifiers outside the chamber. Standard intensive care monitors can be used to provide simultaneous measurement of arterial and pulmonary artery pressures and intermittent measurement of cardiac output by thermodilution. If pressure bags are used to drive continuous-flow systems, they must be repressurized during compression and vented before or during decompression. Pulmonary artery catheter balloon ports should also be left open to the chamber during compression and decompression.

Defibrillation could generate a fire if there is sparking and combustible materials in the vicinity of the paddles. Sparking and heat generation can be minimized by using a low resistivity conductive gel between the electrodes and the skin[134] or pre-applied

conductive disposable pads.[135] To avoid pressure-related malfunction of the device, the defibrillator can remain outside the chamber and connection to the patient via through-hull high voltage wiring. Despite the fear of causing fire, defibrillation has been carried out in multiplace chambers numerous times without arcing, fire, or explosion.[136,137] Defibrillation cannot be safely performed inside a monoplace chamber compressed with O_2.

Intravenous Fluid Administration

In multiplace chambers the air volume within the drip chamber will shrink during the compression phase of the HBO treatment and expand during decompression (which could force air into the intravenous line). Most intravenous infusion pumps work well inside a hyperbaric chamber at pressure (although there are electrical safety issues [see later]). Glass bottles are best excluded from the chamber because of the possibility of explosive rupture during decompression.

Administration of fluids to patients inside a pressurized monoplace chamber requires an infusion pump capable of handling the pressure differential (up to 3 ATA or 1500 mm Hg pressure gradient across the chamber wall). Check valves can prevent unintended backflow of blood from the patient in the event of disconnection of the pump. Rigid arterial-pressure transducer tubing will help to prevent kinking while the patient is inside the chamber.

Blood Gas Assessment and Ventilator Management

Blood gas measurement on arterial samples obtained from a patient inside a hyperbaric chamber can be erroneous. There are two reasons. At 1 ATA, oxygen tensions that exceed the ambient pressure will be supersaturated and thus O_2 will rapidly diffuse out of the blood, thus lowering its tension. An additional error (extrapolation error) is due to the impossibility of accurate P_{O_2} electrode calibration at P_{O_2} values exceeding around 700 mm Hg. Blood gas tension measurement should therefore ideally be performed inside the hyperbaric chamber using an appropriately calibrated analyzer. If such a capability is not available, rapid analysis at 1 ATA of decompressed samples can produce acceptably accurate values.[138]

Another approach is to estimate the hyperbaric Pa_{O_2} based on measurements obtained at 1 ATA. Using a measured Pa_{O_2} and a calculated alveolar P_{O_2} (P_{AO_2}) the ratio of the two (Pa_{O_2}/P_{AO_2}, or a/A ratio) is a constant.[9,139] On this basis, 1 ATA arterial blood gas values and the following equations can be used to predict Pa_{O_2} at pressure.

The alveolar gas equation is required to calculate P_{AO_2}:

$$P_{AO_2} = F_{IO_2} \cdot (Pb - P_{H_2O}) - P_{ACO_2} \cdot \left(F_{IO_2} + \left[(1 - F_{IO_2})/R\right]\right)$$

where Pb and P_{H_2O} are, respectively, ambient and saturated water vapor pressures, and R is the respiratory exchange ratio. If F_{IO_2} = 0.2, R = 0.8, and body temperature = 37°C, then this equation can be simplified to:

$$P_{AO_2} = (Pb - 47) \cdot 0.2 - 1.2 \cdot P_{CO_2}$$

Having calculated P_{AO_2} and measured Pa_{O_2}, the a/A ratio can then be obtained at 1 ATA. The predicted Pa_{O_2} at increased ambient pressure while breathing 100% O_2 may then be obtained from this next equation:

$$Pa_{O_{2(pred)}} = a/A \cdot \left[(760 \cdot ATA - 47) - Pa_{CO_2}\right]$$

where ATA is the chamber pressure in atmospheres absolute. Although as yet there are no dose-response curves for HBO, a reasonable aim is to achieve Pa_{O_2} greater than or equal to 1000 mm Hg for routine chronic therapy and to as high a level as possible for treatment of acute necrotizing infections (Fig. 80-11).

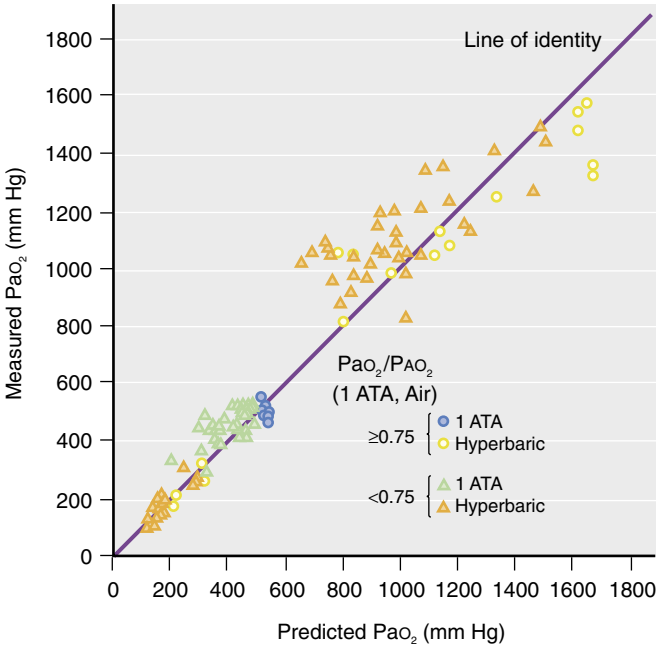

Figure 80-11 Measured versus predicted Pa_{O_2} at increased ambient pressure. Predicted Pa_{O_2} is calculated from room-air arterial blood gases, assuming that the arterial-alveolar P_{O_2} ratio (Pa_{O_2}/P_{AO_2}, or a/A ratio) is a constant. Data are shown both for persons with normal lungs (a/A ratio ≥ 0.75) and for patients with gas exchange abnormalities (a/A ratio < 0.75). It is evident that Pa_{O_2} predicted in this way is close to the actual measured Pa_{O_2}. *(From Moon RE, Camporesi EM, Shelton DL: Prediction of arterial P_{O_2} during hyperbaric treatment.* In *Bove AA, Bachrach AJ, Greenbaum LJ Jr [eds]: Underwater and Hyperbaric Physiology IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology. Bethesda, MD, Undersea and Hyperbaric Medical Society, 1987, p 1127.)*

A better monitor of tissue oxygenation may be mixed venous P_{O_2} ($P\bar{v}_{O_2}$), which, in the absence of left-to-right shunt, may be a reasonably accurate estimate of mean tissue P_{O_2}; thus a low value may indicate inadequate tissue oxygenation despite HBO, owing to insufficiently high cardiac output.[140]

Normal values for pH and P_{CO_2} under resting clinical hyperbaric conditions are the same as they are at 1 ATA.[14,15,141] P_{CO_2} (and hence pH) do not change significantly in blood samples that are decompressed.

Mechanical ventilation in a hyperbaric environment presents a variety of challenges. The ideal requirements for ventilation include small size, no electrical requirement, absence of flammable lubricants, ability to operate on a volume-cycled basis over a wide range of tidal volumes and respiratory rates, minimal modification requirement for installation, and ability to provide positive end-expiratory pressure, as well as to ventilate in inter-

mittent mandatory ventilation and assist/control modes.[142] Additionally, the ideal gas source to actuate the ventilator should minimize the risk of combustion caused by buildup of static electricity.

As ambient pressure increases, gas density is proportionately raised, whereas there is relatively little change in gas viscosity. Therefore, in regions of turbulent flow (i.e., in the large airways) airway resistance increases. Measurements of respiratory conductance (the reciprocal of resistance) during tidal breathing[143] indicate that it varies with gas density according to the following formula:

$$G = G_0\rho(\kappa)$$

where G is lung conductance at gas density ρ; G_0 is the conductance at gas density 1.1 g/L (1 ATA); and κ is a constant that was found to have a mean value of −0.39. At 6 ATA this equation predicts that lung conductance would decrease by 50%, which is equivalent to a doubling of pulmonary resistance. In addition, the higher gas density results in a less efficient distribution of ventilation, manifested by an increase in physiologic dead space.[144] The effects of these two phenomena include higher airway pressures during mechanical ventilation and an increased ventilatory requirement. If ventilator settings are not adjusted to compensate for the higher dead space, a rise in $Paco_2$ will occur.

Several types of ventilators have been used and tested in hyperbaric chambers. Pressure-cycled devices have been used with some success, because their compactness admirably fulfills the requirement for small size. However, continual adjustment of rate and cycling pressure is necessary with changes in ambient pressure. Volume-cycled ventilators seem to work well,[142,145] although at increased pressure some changes in rate may occur.

There are two specific safety considerations. First, in any ventilator delivering enriched O_2, a possible fire hazard can occur owing to O_2 buildup within the ventilator case or leakage of O_2 into the chamber. This can often be offset by minor alterations, for example, for a pneumatic ventilator using air versus oxygen to drive the bellows.[142] The risk of ignition can be substantially mitigated by purging the device with an inert gas such as 100% nitrogen (see later). Air-filled endotracheal tube cuffs will tend to lose volume during compression and reexpand during decompression. Appropriate cuff inflation volume can be maintained either by manual adjustment of the air pressure within the cuff during compression and decompression or filling the cuff with water.

Atmosphere Control

Chamber atmosphere safety includes management of levels of O_2, CO_2, and trace gases. In a multiplace chamber it is essential that the patient breathe as high a concentration of O_2 as possible (usually 98% or greater) while maintaining the chamber O_2 concentration close to 21% to minimize fire hazard. In some hyperbaric units, head-tent O_2 concentration is routinely monitored. In others, the concentration is assumed to be high because of a high rate of O_2 flow through the head tent. Leakage of O_2 from head tents, masks, and ventilators will tend to raise the chamber O_2 concentration. Typically, an upper limit of around 23% is used as a criterion for ventilating the chamber with air or small volumes of 100% nitrogen until the O_2 concentration decreases.

Significant elevations of inspired CO_2 concentration will increase the risk of CNS O_2 toxicity. Therefore, a typical standard for the upper limit for head-tent CO_2 is 1% "surface equivalent" CO_2, equal to a partial pressure of 7.6 mm Hg. Using a nonscrubbing (open circuit) system, head-tent O_2 flow rates of 40 to 60 L/min (measured at chamber pressure) are usually adequate to keep CO_2 levels at such a level. Chamber CO_2 is usually limited to less than 0.5% "surface equivalent" (3.8 mm Hg).

Trace gases that may enter the environment include carbon monoxide and hydrocarbons from improperly functioning compressors or from automobile exhaust that may be near the compressor air intake. Volatile gases such as alcohol vapor from skin disinfectant solutions and mercury vapor from spillage of sphygmomanometer columns may also pollute the atmosphere. Trace gas concentrations that are innocuous at atmospheric pressure can be toxic under hyperbaric conditions because their pharmacologic or toxic effects are related to partial pressure. Mercury in any form should be excluded from hyperbaric chambers, because spillage can cause acute toxicity in chamber occupants.

Considerations of battery use may have implications for chamber atmosphere control as well as fire hazards. All batteries release small quantities of hydrogen, although not usually in amounts that would be hazardous. Lithium/sulfur dioxide batteries carry a theoretical risk of sulfur dioxide discharge. Similarly, there is an objection to the use of mercury cells (now banned in the United States). Alkaline cells are considered safe, although temporary failure has been observed at extremely high ambient pressures (40 to 60 ATA).

Fire Hazards

Although fires in hyperbaric chambers are rare, they are usually lethal. The effects of fire at elevated ambient pressure are so devastating and so fast that fire extinguisher systems may not be effective (see Chapter 77). The very real risk of fire in hyperbaric chambers has been illustrated by recent accidents in which chamber fires were started by a hand warmer, a sparking toy, and other sources of ignition carried into the chamber in the patient's clothing. Minimization of these risks involves the following:

- Control of chamber O_2 concentrations (irrelevant in a monoplace chamber)
- Minimizing the use of combustible materials within the chamber
- Controlling sources of heat and spark
- Chamber fire extinguisher system

The geometric increase in burning rate with increases in O_2 concentrations mandates careful monitoring of chamber O_2, as already noted. At increased ambient pressure, burning occurs more rapidly, even when O_2 concentration is 21%. Cotton garments are recommended because of their reduced risk of static electricity. Elimination of hair grease and humidification of the O_2 within the head tent can reduce the risk of hair ignition. Hydrocarbon lubricants (e.g., for stretcher wheels) can spontaneously ignite on contact with aluminum in the presence of high O_2 tensions and should therefore be replaced with nonflammable fluorocarbon lubricants.

Sources of sparks from electrically powered equipment should be minimized. Cigarette lighters, matches, and other

sources of ignition should be excluded from the chamber. Plugging and unplugging electrical cables during hyperbaric treatments is a source of sparking that can be eliminated by taping all electrical plugs onto female receptacles before compression. In multiplace chambers the flammability of electrically powered devices (e.g., intravenous controllers) can be reduced by purging with 100% nitrogen via ports drilled in the covering, at a rate sufficient to keep O_2 concentration at a level that does not support combustion (typically at a flow rate of two to three times the internal volume per minute). Electrical systems used in monoplace chambers must comply with specific codes, which specify the types of switches, grounding, and insulation that can be used.[105]

Fluorinated anesthetics can be combustible at 1 ATA in high concentrations. However, isoflurane and sevoflurane Dräger vaporizers have been tested up to 3 ATA using 100% O_2, with no evidence of spontaneous combustion at room temperature. Given the experience with halothane under hyperbaric conditions, without any reported fires, and the resistance to combustion in 100% O_2 at 1 ATA, in the absence of a source of ignition it is unlikely that any of the modern fluorinated anesthetics pose a fire safety hazard in the hyperbaric environment.

Evaluation of a Patient for Safety of HBO Treatment

In addition to ensuring that HBO is indicated for the disease process in question, it is important to assess the patient in terms of general effectiveness and safety of HBO. The following issues are pertinent:

- Whether a sufficient elevation in Pao_2 can be obtained
- Whether the patient can equilibrate middle ear pressure
- Optimization of reversible obstructive lung disease and the presence of pulmonary bullae or blebs
- Whether the patient is susceptible to claustrophobia

The calculation of predicted Pao_2 in the hyperbaric chamber was described previously. For example, a patient who has sufficient lung disease or injury such that Pao_2 during treatment would not exceed 1000 mm Hg would probably obtain marginal benefit from HBO unless the reason for HBO is gas bubble disease.

The ability to vent the middle ears may be assessed before treatment by observing directly the tympanic membrane with an otoscope while the patient holds his or her nose or performs a Valsalva maneuver. Movement of the eardrums indicates a patent eustachian tube and the ability to equilibrate middle ear pressure. If otic barotrauma is unlikely to be avoided (e.g., with mental obtundation or the presence of an endotracheal tube) or because of a condition that may render the patient susceptible to inner ear injury (e.g., stapedectomy), myringotomy or tube placement can be performed before HBO treatment. The presence of pulmonary bullae or blebs represents a relative contraindication to HBO because of the possibility of barotrauma, although a large clinical experience suggests that the risk is extremely low.

For patients requiring more than 20 to 30 HBO treatments, periodic checks of visual acuity may be useful to assess hyperbaric myopia.

Because most hyperbaric chamber systems are small and cramped, patients who cannot tolerate enclosed spaces may require anxiolytic therapy to facilitate toleration of the HBO therapy.

Delivery of Anesthesia at Increased Ambient Pressure

A review of the problems of anesthesia under HBO was published as a report to a committee of the American Society of Anesthesiologists.[146] This report explored various issues, including the potential for nitrous oxide to be used as a sole anesthetic.

Anesthesia while breathing spontaneously in a 100% O_2 atmosphere at 3 ATA was reported in the 1950s for radiation therapy.[147] Patients were intubated after administration of pentobarbital, 250 to 750 mg, and meperidine, 100 mg; some patients also received chlorpromazine, 50 mg. Intubation was performed after succinylcholine and topical anesthesia of the airway. Patients breathed spontaneously.

Anesthesia may be required as a procedure incidental to the hyperbaric exposure. Ross and associates[148] discussed the challenges of anesthesia up to 35 ATA in order to provide care for injured divers while in a saturation diving system (e.g., in North Sea oil fields). They suggested using intravenous agents for general anesthesia rather than gaseous anesthetics because of the problems of pollution of the chamber environment with the latter. Regional anesthesia was recommended whenever possible. The authors noted that muscle relaxants should be titrated to effect because some degree of pressure reversal at around 10 ATA has been reported.

Since the 1960s anesthesia has been performed at increased ambient pressure using a variety of agents for carotid endarterectomy,[149] cesarean section,[150] therapeutic lung lavage for patients with alveolar proteinosis,[103,104] emergency surgery in a saturation dive,[151] open heart surgery,[152] and enhancement of the effectiveness of irradiation of carcinoma.[153]

Inhaled Anesthesia

Inhaled anesthesia of any type can pollute the enclosed chamber atmosphere with anesthetic gases, which may exert pharmacologic effects on medical personnel inside the chamber, particularly at high ambient pressures. Russell and colleagues[154] reported nitrous oxide concentrations in chamber air of 2500 ppm; ventilation of the chamber with air at a high rate (3500 L/min of air) was required to reduce the concentration to 25 to 75 ppm.

Nitrous Oxide

The increased ambient pressure in a hyperbaric chamber allows nitrous oxide to be used at partial pressures exceeding its minimum alveolar concentration (MAC).[154-156] Although in both studies induction of anesthesia by nitrous oxide was rapid (<60 seconds) it was accompanied by tachypnea, tachycardia, hypertension, diaphoresis, muscle rigidity, catatonic jerking of the extremities, eye opening, and opisthotonus. After 2 to 4 hours of anesthesia, most subjects emerged rapidly from the anesthetic; however, the majority subsequently experienced nausea and vomiting, which was often severe.

A potential problem associated with nitrous oxide anesthesia at high ambient pressures is the possibility that tissues could

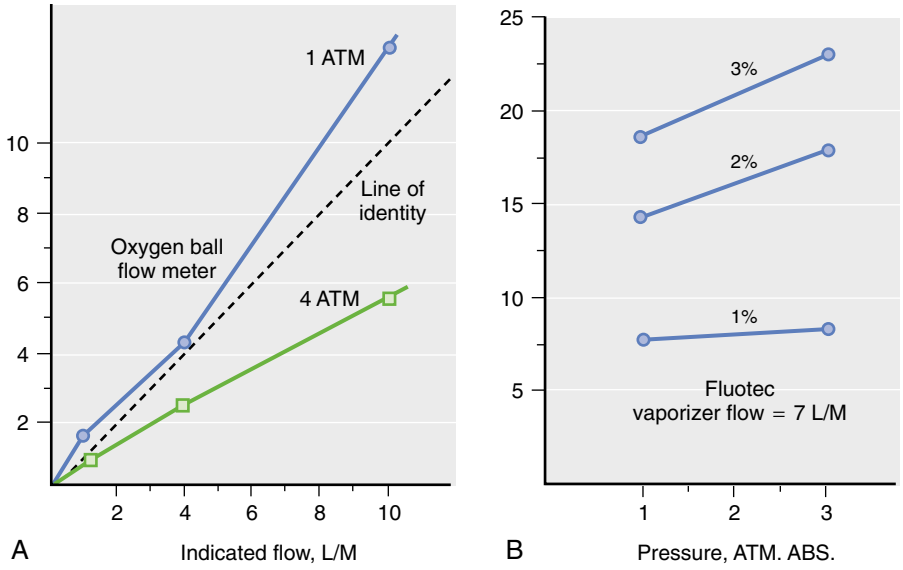

Figure 80-12 Performance of an anesthetic vaporizer system at increased ambient pressure. **A,** Flow characteristics of a rotameter system are shown. At 4 ATA the actual delivered flow is less than 60% of the flow indicated by the rotameter. **B,** Fluotec vaporizer output in partial pressure of halothane as a function of ambient pressure. Only small increases in delivered partial pressure are evident at 3 ATA, at the 2% and 3% settings. *(From Committee on Hyperbaric Oxygenation: Fundamentals of Hyperbaric Medicine [Publication No. 1298]. Washington, DC, National Academy Press, 1966.)*

become supersaturated during decompression, allowing N_2O bubbles to form during decompression. This was not observed by Russell and associates,[154] who used an empirical staged decompression schedule with a decompression stop for 30 minutes at 1.3 ATA while the patients breathed 100% O_2. Bubble formation can occur without decompression if the patient breathes one gas while surrounded by an atmosphere of another gas that is more diffusible. For example, breathing air while in a helium/O_2 environment at 5 to 7 ATA can lead to urticaria and vestibular dysfunction[157] owing to rapid diffusion of helium into tissues, causing local inert gas pressure to exceed ambient pressure (isobaric gas counterdiffusion). This phenomenon can even occur at normal atmospheric pressure if a person breathes nitrous oxide/O_2 while surrounded by helium.[158] Therefore, it is imperative that nitrous oxide never be administered in a helium/oxygen atmosphere.

Another risk of hyperbaric N_2O is the dilutional effect of large volumes of dissolved gas entering the lungs during decompression, causing dilutional hypoxia. This can be prevented by administration of an O_2-enriched breathing mix for several minutes before decompression.

In patients who have recently engaged in scuba diving or have suffered decompression illness, nitrous oxide should be avoided, even at 1 ATA, because its administration may result in tissue or blood bubble growth and recrudescence of pain or neurologic symptoms. Neurologic symptoms were reported after a nitrous oxide anesthetic after apparent spontaneous resolution of decompression illness.[159]

The effect of a volatile anesthetic on a patient is proportional not to the alveolar concentration but to the partial pressure of the anesthetic. For example, the effect of 1% halothane at 1 ATA (with a partial pressure of 7.6 mm Hg) will be equivalent to a 0.5% concentration at 2 ATA (with the same partial pressure). The anesthetic concentration of an anesthetic-specific calibrated vaporizer varies with ambient pressure, but in a manner such that delivered partial pressure remains constant (Fig. 80-12). Because of the effect of increased gas density on this flow ratio, in practice the delivered partial pressure is somewhat dependent on ambient pressure. A slightly increased partial pressure of halothane delivered by a Fluotec vaporizer at 3 ATA has been observed (see Fig. 80-12[146]). Our testing of a sevoflurane vaporizer revealed delivery of a constant partial pressure of anesthetic, up to the maximum tested ambient pressure: 3 ATA.

Rotameter flow meters calibrated at 1 ATA will indicate falsely high values at increased ambient pressure because of the increased gas density. McDowell[160] reported the following relationship for rotameter flow:

$$\text{Flow}_{\text{actual}} = \text{Flow}_{\text{read}} \cdot \sqrt{\rho_1/\rho_P}$$

where $\text{Flow}_{\text{actual}}$ and $\text{Flow}_{\text{read}}$ are the actual and scale reading flows and ρ_1 and ρ_P are the gas densities at 1 ATA and P ATA, respectively. This inaccuracy in rotameter performance up to 4 ATA has been confirmed by others (see Fig. 80-12).[146]

Intravenous Anesthesia

Intravenous anesthetics behave similarly and are unlikely to be affected within the usual clinical range of ambient pressure (see Chapter 26). There is no evident alteration in the pharmacokinetics of either meperidine[31] or pentobarbital[32] at ambient pressures up to 6 ATA. For therapeutic lung lavage we have provided general anesthesia at ambient pressures up to 3 ATA using conventional doses of ketamine and benzodiazepines or propofol and narcotics with nondepolarizing muscle relaxants.

Regional Anesthesia

Regional anesthesia is likely to be both safe and effective in a hyperbaric environment by avoiding the requirement for mechanical ventilation (see Chapters 51 and 52). A bowel resection has been performed at an ambient pressure 6.75 ATA in a helium/O_2 environment using local injection of lidocaine supplemented with

parenteral meperidine.[151] Extreme care should be taken to ensure sterile technique because of the propensity for enhanced bacterial growth in the warm, humidified environment of a hyperbaric chamber, particularly during saturation chamber exposures.

Effects of Altitude

There are approximately 140 million people worldwide living permanently at altitudes greater than 2500 m[161] and possibly an equal number who visit high altitudes each year, many of whom will require medical care. There is therefore clearly a need for anesthesia and critical care practitioners to understand the physiology of this environment.

Unlike the relationship between ambient pressure and water depth, the relationship between pressure and altitude is a nonlinear one (see Fig. 80-2). The physiologic effects of altitude exposure are mainly attributable to reduction in the following three variables: inspired P_{O_2}, ambient pressure, and gas density. Extreme or prolonged altitude exposure may be accompanied by additional factors, which may modulate physiologic responses, such as hypothermia, exertion, dehydration, sunburn, and polycythemia. Pregnant women and individuals with hypoxic conditions such as cerebrovascular disease, congenital heart defects, coronary artery disease, and hypoxic lung disease may carry additional risks that require medical evaluation.[162]

Hypoxia

Physiologic Changes

The major reason for hypoxemia at altitude is the reduction in inspired P_{O_2}, augmented by the failure of erythrocytes in the pulmonary circulation to equilibrate fully with alveolar gas (diffusion nonequilibrium)[163] and increased ventilation/perfusion ($\dot{V}_A/\dot{Q}$) mismatch.[164]

The acute blood gas and heart rate responses to acute hypoxia are shown in Tables 80-4 and 80-7. Heart rate and cardiac output are increased.[165] Systemic vascular resistance is decreased, and pulmonary vascular pressure is increased.[166] There is a corresponding increase in organ blood flow, including cerebral blood flow. Hypoxia also induces hyperpnea (due to increased breathing rate) to a degree that varies considerably among individuals. End-tidal P_{CO_2} measured in one subject breathing air at the summit of Mt. Everest (barometric pressure, 263 mm Hg) was 7.5 mm Hg while P_{AO_2} was 37.6 mm Hg.[167] This hypocapnia has several effects. It results in an increased affinity of Hb for O_2 (leftward shift of the Hb-O_2 dissociation curve), which enhances oxygenation of blood at the lung while simultaneously interfering with transport of O_2 from tissue capillary to mitochondrion. The overall effect on O_2 transport is beneficial.[168]

Hypoxemia may be particularly accentuated during sleep. Figure 80-13 depicts continuous pulse oximetry during transition from sleep to wakefulness at a simulated altitude of 4572 m in a hypobaric chamber, demonstrating periodic breathing and cyclic oscillation of Spo_2. Individuals with moderate obstructive sleep apnea at 1 ATA are at risk of severe central sleep apnea at altitude.[169]

Acute exposure to altitudes in the range of 4000 to 5000 m causes a decrease in arterial P_{O_2} to approximately 40 mm Hg and in arterial HbO_2 saturation to approximately 75%. Acute exposure to mild hypoxia appears to have only minor effects on CNS function. Crow and Kelman[170] found no decrement on free recall and visual scanning when normal subjects were exposed to a simulated altitude of 3658 m (inspired P_{O_2}, 92 mm Hg). Severe hypoxia can cause encephalopathy and loss of consciousness. A measure of this is the effective performance time, defined as the amount of time the individual is able to perform useful flying duties.[171] At 5500 m altitude the effective performance time is 20 to 30 minutes, which is reduced to 2.5 to 3 minutes at 8500 m and 1 to 2 minutes at 9100 m.

Gradual exposure to altitude or chronic exposure results in a series of adaptive changes, allowing individuals to function extremely well and do substantial physical work at altitudes at which newcomers can barely function. For instance, Mt. Everest has been climbed by adapted individuals without the benefit of supplemental O_2, whereas acute exposure to such an altitude would result in rapid loss of consciousness. Subjects exposed to a progressively lower barometric pressure, reaching to simulated

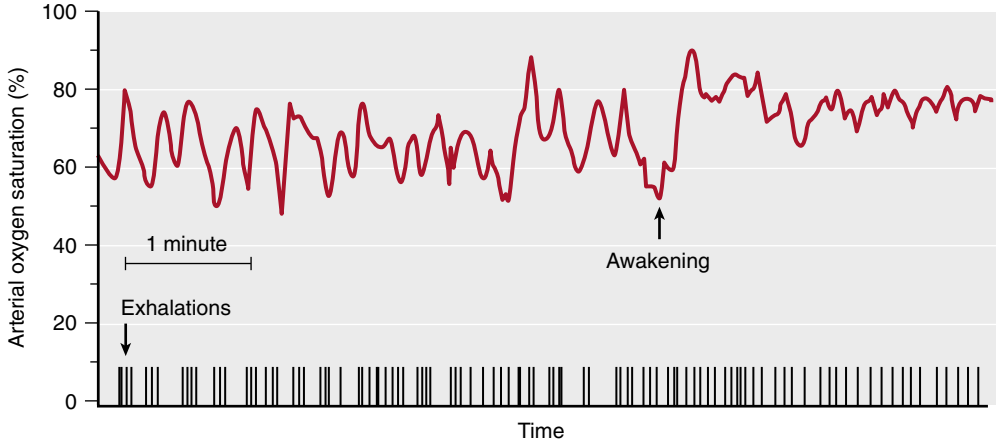

Figure 80-13 Pulse oximetry and breathing pattern (spikes at bottom represent exhalations) are shown in this subject in a hypobaric chamber at a simulated altitude of 4572 m. During sleep, periodic breathing and oscillatory alterations in Spo_2 change after waking up to a more regular breathing pattern and a steady Spo_2.

altitude of 8848 m in a hypobaric chamber over the course of 40 days, were able to work on an exercise ergometer at 120 W while their mean Pao_2 was only 30 mm Hg (arterial HbO_2 saturation, 58%).[172] In the same study, blood Hb concentration increased from 13.5 to 17.0 g/dL (hematocrit from 40.4% to 51.9%). The development of polycythemia may be one of many mechanisms by which tolerance to hypoxia occurs. However, the mechanisms of adaptation are still incompletely understood.

One of the adaptive mechanisms is a gradual reduction in plasma bicarbonate,[172] preceded by a decrease in cerebrospinal fluid (CSF) bicarbonate,[173] tending to offset the initial respiratory alkalosis. After a 40-day simulated "climb" of Mt. Everest in a hypobaric chamber, resting serum bicarbonate had decreased from 22.2 to 9.9 mM whereas pH had increased from 7.43 to 7.56.[172] Other adaptive changes include increases in hematocrit and capillary density, as well as undoubtedly other mechanisms as yet undiscovered.

Despite the adaptive mechanisms, careful neuropsychologic testing of subjects before and after mountaineering expeditions to extreme altitudes of 7000 m or greater has shown evidence of mild persistent performance impairment.[174,175] Such neuropsychologic impairment after prolonged extreme altitude exposure is correlated with a brisk hypoxic ventilatory response,[174] possibly owing to enhanced cerebral vasoconstriction and reduced brain O_2 delivery.

Effect of Maternal Hypoxia on the Fetus

Data on the fetal effects of maternal hypoxia are sparse (see Chapter 69). However, using changes in fetal heart rate (FHR) as an end point, the fetus appears to be relatively resistant to moderate degrees of maternal hypoxia. Administration of 15% O_2 (inspired Po_2 = 108 mm Hg, equivalent to 2500-m altitude) for 4 minutes to five primigravid women at 36 to 38 weeks' gestation resulted in an increase in FHR of only 2 to 3 beats/min.[176] The same investigator observed no change in FHR after administration of mixtures as low as 10% O_2 (inspired Po_2 = 71 mm Hg, equivalent to 5300-m altitude) for 20 minutes in 8 of 28 pregnant women. Administration of 10% O_2 for 10 minutes to pregnant women at 35 to 41 weeks' gestation had no significant effect on FHR, heart rate variability, or Doppler velocimetry in the umbilical and middle cerebral arteries of the fetus.[177] Acute hypoxia of this magnitude appears to exert no detectable effects on the healthy fetus because of augmentation of uterine blood flow; thus, it is unlikely that acute exposure to altitudes up to 2500 to 3000 m would have any adverse fetal effects.

Additional adaptations to chronic altitude exposure specific to pregnant women include an increase in placental capillary volume and a reduction in villous membrane thickness.[178] Infants born at altitude, even as high as 4329 m, have scalp vein O_2 tensions similar to values obtained from infants born at sea level.[179] Consequently, a significant reduction in maternal O_2 delivery can be tolerated without any impact on fetal O_2 consumption.

Infants Born at Altitude

As with adults, SpO_2 decreases with increasing altitude, but also depends on activity (lower during sleep), postnatal age (Fig. 80-14), and race.[180] Perinatal hypoxia appears to predispose to a blunted hypoxic ventilatory drive in adulthood.[181]

At sea level, pulmonary artery pressure decreases to normal levels within 24 hours after birth, whereas at altitude pulmonary artery pressure often remains elevated for several weeks or throughout infancy.[180] In a series of 35 consecutive infants born at term in Leadville, Colorado (altitude, 3179 m), during the first 3 months of life 17% experienced elevated pulmonary artery pressure or respiratory distress requiring supplemental O_2 or mechanical ventilation or both.[180] In infants born at altitude the transition to adult circulation occurs more slowly, with increased frequency of patent foramen ovale and patent ductus arteriosus.[182] Patent foramen ovale was present at 6 months in 7 of 16 infants studied after birth in La Paz, Bolivia (altitude, 3700 to 4000 m).[183] Acute hypoxia after birth (15% O_2 administration) in preterm infants paradoxically produced hypoventilation, periodic breathing, and apnea.[184] Infants with trisomy 21 (Down syndrome) are at

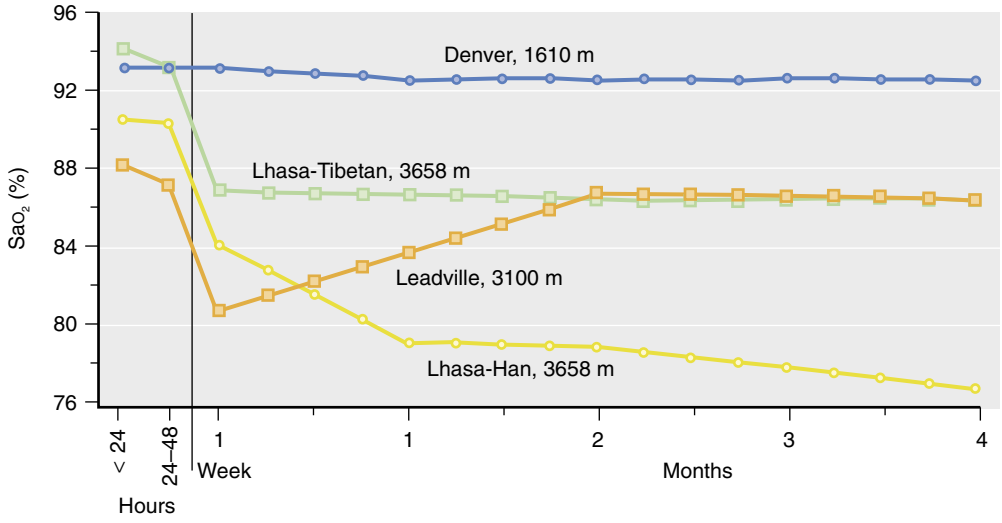

Figure 80-14 Pulse oximetry in infants born at various altitudes. In infants born in Lhasa (altitude of 3658 m), Han Chinese children have progressive arterial desaturation whereas Tibetan infants, following a slight drop shortly after birth, have a stable Spo_2. *(Redrawn from Niermeyer S: Cardiopulmonary transition in the high altitude infant. High Alt Med Biol 4:225, 2003.)*

increased risk of HAPE (see later).[182] Perinatal pulmonary hypertension seems to predispose to exaggerated hypoxic pulmonary vasoconstriction in adulthood.[185]

Effects of Altitude on Children

While Spo_2 is lower at higher elevations, children who reside at altitudes up to 3000 m generally maintain arterial oxygen saturation above 90%.[186] Exaggerated hypoxemia at altitude can suggest previously undiagnosed cardiorespiratory anomalies, such as Pierre-Robin syndrome or tracheomalacia-laryngomalacia.[182]

Altitude Illness

Altitude illness consists of a group of subacute and chronic syndromes, the underlying pathophysiology of which is triggered by continuous exposure to hypoxia. These are described here. Further information can be obtained from detailed reviews.[187,188]

Acute Mountain Sickness

The most common symptoms of AMS are headache, decreased appetite, nausea and vomiting, insomnia, ataxia, and peripheral edema.[189] AMS can occur after several hours of exposure to elevations greater than 2500 to 3000 m, although some people are more susceptible and can experience it at lower altitudes. Approximately 25% of visitors to ski resorts in the American Rockies (altitude, 1920 to 2960 m) develop AMS.[190]

Effective prophylactic measures against AMS in mountaineers include slow ascent (around 300 m/day) or "staging" in which several days are spent at an intermediate altitude of around 2000 m.[189] Pharmacologic prophylactic measures include the administration of acetazolamide,[191] which is believed to work in part by augmenting the ventilatory response to hypoxia due to the ensuing bicarbonate diuresis.[192] However, other purported mechanisms include tissue respiratory acidosis, improved sleep quality due to a reduction in periodic breathing (paradoxically due to its inhibition of the carotid body response to CO_2), and diuresis.[193] An effective dose range is 125 to 250 mg orally twice daily begun the day before ascent.[187]

Although most individuals recover spontaneously after several days at altitude, AMS can be treated effectively with oxygen and descent. A descent of only 500 to 1000 m usually leads to resolution of AMS. Simulated descent using a portable inflatable hyperbaric chamber (Gamow bag or similar) operated by foot pump (Fig. 80-15) is also effective. Depending on the altitude, inflation of such a chamber to only 2 psi (100 mm Hg) produces a decrease in equivalent altitude of 1500 to 2000 m.[187] AMS also responds to dexamethasone in a dosage of 4 mg every 6 hours, although symptoms may occur as soon as it is discontinued.[194,195] *Gingko biloba* has also been used, with mixed results.[196,197] Insomnia associated with AMS responds to treatment with acetazolamide. Sedative/hypnotic agents can depress ventilation and exacerbate hypoxia and should therefore be used cautiously. Both zolpidem (10 mg orally) and zaleplon (10 mg orally) improve sleep quality at altitude, and neither appears to depress ventilation in healthy young subjects.[198,199]

AMS symptoms could conceivably exist due to hypoxemia at sea level. It has been suggested that headache associated with obstructive sleep apnea and opioid-related headache may be due to a form of "AMS"—hypoxemia caused by respiratory depression.



Figure 80-15 Portable altitude chamber at Mt. Everest base camp. The pressure inside the bag can be raised to 2 psig (approximately 100 mm Hg) using a foot pump. This effectively reduces the "altitude" for the occupant of the chamber, thus raising the Po_2. These bags can be used to treat altitude illness when neither oxygen administration nor true descent is feasible. *(Photograph courtesy of Caudwell Xtreme Everest.)*

High-Altitude Pulmonary Edema

High-altitude pulmonary edema (HAPE) is much less common than AMS but more serious. It occurs in a small percentage of unacclimatized, susceptible people within a few days of reaching altitude.[166] A hemodynamic pathophysiology for HAPE is suggested by its tendency to occur when pulmonary vascular flows or pressures are particularly high, for example in the lung contralateral to unilateral absence of the pulmonary artery.[200] Measurements in patients with HAPE have revealed pulmonary hypertension, normal pulmonary artery wedge pressures, but elevated pulmonary capillary pressures (assessed using the single occlusion method).[201] Bronchopulmonary lavage fluid in subjects with HAPE has a high protein content, implicating an increase in permeability or alveolar-capillary disruption.[202-204]

Prophylaxis against HAPE includes slow ascent. People with known predisposing factors such as unilateral absence of the pulmonary artery should avoid high altitudes. For climbers with known HAPE susceptibility, prophylactic measures may include nifedipine (20 mg slow release formulation every 8 hours),[205] tadalafil (10 mg twice daily), or dexamethasone (8 mg twice daily).[206] Inhaled salmeterol also appears to be an effective prophylactic agent.[207] Whether acetazolamide prevents HAPE has not been established by randomized studies, but it is probably at least partly effective based on animal studies and its augmentation of Pao_2 during hypoxia.[208]

Treatment of HAPE consists of descent or supplemental oxygen or both.[187] If either descent is impossible or oxygen is unavailable, pharmacologic reduction in pulmonary artery pressure should be initiated. Nifedipine, 10 mg, sublingually followed by 20 mg of a slow-release preparation administered orally every 6 hours has been successful in HAPE.[209] Pulmonary artery pressure can also be lowered in patients with HAPE using hydralazine, phentolamine, or inhaled nitric oxide.[209-212] Other suggested treatments include agents that could lower pulmonary artery pressure, such as prostaglandins[213] and nitric oxide donors such as sildenafil,[213] or facilitate alveolar fluid clearance, such as β_2-adrenergic agonists,[207] recompression in a Gamow bag,[187] and application of expiratory airway pressure.[214]

High-Altitude Cerebral Edema

High-altitude cerebral edema (HACE) is the rarest but the most lethal form of high-altitude illness. Clinical diagnosis is made when there is ataxia or altered consciousness or both in a patient with AMS or HAPE.[215] Physical findings in patients with HACE may include papilledema, retinal hemorrhages, and, occasionally, cranial nerve palsies.[216] Focal abnormalities in the corpus callosum detected with MRI have been reported.[217] The pathophysiology of HACE is unknown. It has been hypothesized that individuals who develop AMS and HACE have a limited capacity to accommodate the associated increase in brain volume that accompanies the rise in cerebral blood flow during hypoxemia.[187,218]

Treatment of HACE is a medical emergency and ideally should include evacuation or descent and administration of supplemental O_2. Although a reduction in altitude of 500 to 1000 m is usually effective for AMS, treatment of HACE may require descent to a lower altitude. Use of a Gamow bag may also be effective. Recommended adjunctive treatment includes dexamethasone, 8 mg, immediately, then 4 mg every 6 hours. If descent is not possible, acetazolamide, 250 mg twice daily, may also be effective.[187]

Chronic Mountain Sickness (Monge's Syndrome)

Chronic mountain sickness has been defined as a clinical syndrome that occurs to natives or long-life residents above 2500 m. It is characterized by excessive erythrocytosis (females Hb ≥ 19 g/dL; males Hb ≥ 21 g/dL), severe hypoxemia, and, in some cases, moderate or severe pulmonary hypertension, which may evolve to cor pulmonale, leading to congestive heart failure.[219] Other manifestations include headache, dizziness, breathlessness and/or palpitations, sleep disturbance, fatigue, localized cyanosis, burning in the palms of the hands and soles of the feet and dilatation of the veins, muscle and joint pain, loss of appetite, lack of mental concentration, and alterations of memory.[219] The diagnosis requires the exclusion of other conditions that may produce hypoxemia, such as cyanotic heart disease and chronic lung disease. Clinical improvement and increased work capacity often result from phlebotomy, at least transiently, and descent to lower altitudes relieves the symptoms completely. Other suggested modalities for treatment of chronic mountain sickness include angiotensin-converting enzyme inhibitors, the D_2 dopaminergic receptor antagonist domperidone, acetazolamide, and the respiratory stimulants medroxyprogesterone and almitrine.[220] Both nifedipine and sildenafil may be effective to reduce pulmonary artery pressure.[220]

Reduction in Ambient Pressure

Acute ascent to altitude in an aircraft can cause decompression sickness (DCS) due to the reduced barometric pressure and supersaturation of nitrogen. Although symptoms have been reported to occur after rapid ascent in aircraft to only 2437 m[221] DCS usually occurs only in aircraft in which the cabin pressure is higher than 5000 to 6000 m,[222] which typically occurs only in military planes. Exposure to lower altitudes, including the cabin altitude of commercial aircraft (2400 m or less) within 12 to 24 hours after a scuba dive can also precipitate decompression illness.[223] To reduce this risk it is the practice of individuals planning a rapid decompression to low ambient pressure (e.g., military pilots, astronauts) to de-nitrogenate their tissues by pre-breathing 100% O_2 for periods ranging from a few minutes to several hours, depending on the altitude of the planned exposure.

Reduction in Gas Density

Reduction in gas density results in lower breathing resistance. Varene and associates[224] have examined the effect of ambient pressure from 0.5 to 5 ATA on airways resistance in normal subjects. Their data can be summarized by either of the following equations:

$$R_P/R_0 = 0.057 + 0.44 \cdot P_{ATA}$$

or

$$R_P/R_0 = P_{ATA}^{0.59}$$

where P_{ATA} is ambient pressure in ATA, R_P is airways resistance at ambient pressure, and R_0 is airways resistance at 1 ATA. For example, at an ambient pressure of 0.5 ATA (5486 m) airways resistance is reduced by approximately 20%. Under resting conditions, differences in breathing pattern during altitude exposure, compared with a similar degree of hypoxia at sea level, are minor.[225]

Other Environmental Stresses at Altitude

Individuals at altitude are subjected to low temperature, wind, and ultraviolet radiation. The effects of hypoxia may therefore be compounded by hypothermia, dehydration, frostbite, and sunburn. On the basis of a seemingly higher incidence of stroke,[226] thrombophlebitis, and pulmonary thromboembolism[227] at high altitude, it has been suspected that prolonged hypoxic exposure may cause a hypercoagulable state.[228] Indeed, rapid exposure to altitude in a hypobaric chamber has been associated with a decrease in partial thromboplastin time[229] and an increase in prothrombin fragments 1 and 2, thrombin-antithrombin complex, and factor VIIa activity.[230]

Anesthesia at Altitude

General Principles

Because of the reduced ambient P_{O_2} at high altitudes, the risk of perioperative hypoxia is likely to be magnified, particularly in newcomers to altitude. Opiates depress both the tachycardia and hyperpnea that normally occur in response to acute hypoxemia. Slow recovery of consciousness and postanesthetic headache have been reported after anesthesia using thiopental with air or nitrous oxide.[231] When ventilation was assisted or controlled during the anesthetic and when postoperative supplemental O_2 was administered, these complications did not occur, which suggests that intraoperative or postoperative hypoxemia may be a pathophysiologic factor. On the other hand, long-term residents at altitude may be more tolerant of hypoxemia; in such individuals other considerations may be important, including a higher hematocrit, pulmonary hypertension, and lower P_{aCO_2} and bicarbonate concentration.[172] To prevent renal retention of bicarbonate, which will reduce ventilatory drive, patients requiring controlled ventilation

should have their $Paco_2$ maintained at baseline value rather than in the traditionally normal range. Similarly, maintenance of Pao_2 within the sea level normal range will result in loss of adaptation and difficulty in readapting the patient to breathing room air.

Increased oozing of blood from surgical wounds at altitude has been reported[232] and attributed to higher venous pressure, blood volume, vasodilatation, and increased capillary density. Camporesi[233] has reviewed the topic of anesthesia at both high and low ambient pressures.

Anesthesia Equipment

Fluotec Mark II and Drager Vapor halothane vaporizer performance has been compared at sea level, 5000 ft (1524 m) and 10,000 ft (3048 m) altitude.[234] At any given setting the delivered percentage of halothane increased with altitude; however, its partial pressure remained constant. Therefore, when these devices are used at a given vaporizer setting, anesthetic will be delivered at a constant potency regardless of altitude (see Chapter 25).

The effect of altitude on floating-bobbin or floating-ball gas flow meters has also been examined.[234] At 10,000 ft (3048 m) simulated altitude, both nitrous oxide and O_2 flow meters underread the actual flow rate. The percentage error progressively increased up to 4 L/min, at which point both flow meters were approximately 20% in error. A hazard may therefore arise when a low flow of O_2 is mixed with a higher flow of nitrous oxide. Unless an O_2 analyzer is available, the delivered percentage of O_2 may be significantly lower than that calculated on the basis of the flow meter readings.

Venturi-type gas mixing devices tend to deliver higher concentrations of O_2 at altitude than they do at sea level[234]; at 10,000 ft (3048 m) altitude a mask designed to deliver 35% O_2 at sea level actually delivered 41% O_2.

Sedation

Standard sea level doses of sedatives/hypnotics may produce increased respiratory depression at altitude in unacclimatized subjects (see Chapters 78 and 79). A small dose of oral ethanol (50 g, producing an estimated blood alcohol concentration of 65 mg/dL, which was without ventilatory effect at ground level) increased blood Pco_2 by a mean of 1.5 mm Hg after acute ascent to 3000 m.[235] Both diazepam (5 mg orally) and temazepam (10 mg orally)[236] have been shown to have measurable effects on respiration at 3000 m. On the other hand, temazepam, 10 mg orally, improved sleep quality and reduced the number of desaturations during sleep in partially acclimatized mountaineers at 5300 m.[237] The difference in the studies is probably explained by different degrees of acclimatization to altitude. During acute altitude exposure in healthy young subjects neither zolpidem (10 mg orally) nor zaleplon (10 mg orally) adversely affected Spo_2 during sleep.[198,199]

General Anesthesia

The potency of anesthetic gases is proportional to their partial pressure. Therefore, as barometric pressure is reduced, fixed concentrations of inhaled anesthetics will have lower potency. At an altitude of 3300 m a significant reduction in efficacy of 50% nitrous oxide has been observed in reducing pain threshold in normal volunteers (Table 80-8).[238] Successful induction of general anesthesia with halothane in a hypobaric chamber has been reported at a barometric pressure of 375 mm Hg (equivalent altitude = 5490 m).[239] Recovery was rapid and uneventful.

Table 80-8 Effect of 50% Nitrous Oxide on Pain Threshold in Normal Volunteers at Altitude*

Altitude (m)	Barometric Pressure (mm Hg)	Increase in Pain Threshold (%)	Side Effects
0	760	71.5	3 subjects, nausea; 2 subjects, semi-comatose
1460	636	40.0	None
3300	517	19.0	None

*Pain threshold was measured in 20 subjects at each altitude by applying pressure to the anterior aspects of the tibia using a spring balance. Simulated altitude exposures were in a hypobaric chamber. At increasing altitudes a fixed concentration of N_2O is progressively less effective.
Data from James MFM, Manson EDM, Dennett JE: Nitrous oxide analgesia and altitude. Anaesthesia 37:285-288, 1982.

Because supplemental O_2 may not be available in some mountain locations it may be imperative to choose an anesthetic technique that is least likely to suppress ventilation. Ketamine anesthesia with spontaneous ventilation has been reported in 23 patients requiring general anesthesia at an altitude of 1830 m.[240] Two patients developed significant, although brief, desaturation, which resolved quickly. The authors concluded that this form of anesthesia is a practical method in a rural hospital setting at altitude without access to supplemental O_2.

Ketamine (total dose, 1-6 mg/kg) after intravenous premedication with atropine, 0.02 mg/kg, and midazolam, 0.05 mg/kg, was reported in a consecutive series of 11 patients (ASA Physical Status 1-2) requiring general anesthesia for short procedures at Kunde Hospital (Fig. 80-16) in Nepal (3840 m).[241] Nine patients required reduction of dislocations or fractures, one (9 years old) required suturing of a facial laceration, and one required drainage of an abscess. The induction dose of ketamine was 1 mg/kg administered intravenously over 1 to 2 minutes, followed by additional incremental doses, titrating to effect. Baseline Spo_2 on room air was 86% to 91%. Oxygen was administered in 3 of 11 cases via an O_2 concentrator if Spo_2 fell below 80% for 1 minute and was not correctable by forward jaw thrust or vocal and tactile stimulation. Both low-altitude residents required supplemental O_2 for 20 minutes during recovery, whereas only one of nine high-altitude residents required O_2. Use of ketamine has been reported at even higher altitude (4243 m) for control of postpartum hemorrhage in a 22-year-old woman.[242] Deep general anesthesia was obtained with only 25 mg of intravenous ketamine (approximately 0.5 mg/kg), which induced 5 minutes of apnea, requiring airway manipulation and supplemental oxygen. The total dose of ketamine required for the 20- to 25-minute procedure was 50 mg. The authors attributed the exaggerated response to a low dose of ketamine to a combination of hypoxemia and hemodynamic instability.

High-altitude natives anesthetized at 3500 meters above sea level (mean preoperative Spo_2 88.5%) appear to require significantly larger amounts of propofol when administered with fentanyl compared with lowlanders at 300 m.[243] Compared with the low-altitude residents, the highlanders had a lower resting heart rate, and heart rate responses to surgical stress were significantly attenuated.



Figure 80-16 Kunde Hospital, Nepal (altitude 3840 m), the site of the published series of general anesthetics described in the text.[241] The photo depicts Dr. David Murdoch assisted by Kami Temba Sherpa. *(Photo courtesy of Dr. Lynley Cook.)*

Regional Anesthesia

Spinal anesthesia has been reported to result in unacceptably high incidence of dural puncture headache,[231] possibly owing to chronically increased CSF pressure, dehydration, and altered sensitivity of the altitude resident's CNS to intracranial pressure changes.[231] Headaches were not reported in 20 young native mountain dwellers in whom CSF samples were obtained with 25-gauge needles.[231]

Perioperative Supplemental Oxygen

At high altitude, P_{AO_2} is normally increased by hyperventilation induced by the hypoxic ventilatory drive. Administration of anesthetics or narcotic analgesics, both of which blunt the hypoxic ventilatory drive, may therefore precipitate hypoxia. The resulting hypoxic symptoms of irritability, confusion, and restlessness may be misinterpreted as due to pain, and misguided administration of additional narcotics would only compound the problem. Analgesic-induced respiratory depression has been reported as a likely cause of death in a Sherpa who had débridement of frostbitten fingers at 4300-m altitude.[239] Therefore, if opiate analgesics are administered, supplemental O_2 may be required.

Monitoring

Oxygen analyzers, both electrochemical and paramagnetic, measure P_{O_2} rather than O_2 percentage. Thus, if the display is in "percent," the actual percentage will be falsely low unless the analyzer is calibrated at altitude. Nevertheless, it is the P_{O_2} that is physiologically important. CO_2 analyzers similarly measure partial pressure. Since end-tidal P_{CO_2} at altitude is within the normal range (or somewhat low), readings will be unaffected by altitude.

Air evacuation in an unpressurized or partially pressurized aircraft will engender expansion of the gas volume in enclosed spaces such as tracheal tube cuffs and pulmonary artery catheter balloons.

Commercial Air Travel

Clinical Effects of Aircraft Flight

During commercial aircraft flight the pressure within the cabin is mandated to be no less than the barometric pressure at 8000 ft altitude (typical cabin altitude 1500-2438 m). During flight the ambient air P_{O_2} would fall from 159 mm Hg at sea level to as low as 118 mm Hg. The ensuing mild hypoxemia (Sa_{O_2} usually above 90%) is generally well tolerated by normal individuals, although altitude-related symptoms such as discomfort and fatigue can occur.[244] Changes in ambient pressure can induce otic and sinus barotrauma and pain due to expansion of intestinal gas. Motion sickness is now rare. More serious manifestations that have been attributed to immobility and possible hypoxemia include phlebothrombosis.[245,246] Airborne spread of communicable diseases has also been reported.[246] Medical guidelines for air travel have been discussed in review articles.[246,247]

Prediction of Oxygenation during Commercial Flight

Patients with impaired gas exchange due to chronic obstructive pulmonary disease or restrictive disease during flight may experience significant hypoxemia[248,249] and symptoms of dyspnea, edema, wheezing, cyanosis, and chest pain.[250]

To predict the effect of altitude on arterial oxygenation the patient can be exposed to simulated altitude in a hypobaric

chamber with assessment of Spo_2 and/or arterial blood gases. Alternative measures include administering a hypoxic gas premixed to produce the same inspired Po_2 as air at the target altitude (typically 15% O_2)[251] or supplying a Venturi mask designed to deliver 35% to 40% O_2 with 100% nitrogen.[252,253] Prediction algorithms based on sea level blood gas values have also been used with success.[254] Predicted Pao_2 at altitude ($Pao_{2alt(predicted)}$) can be predicted from the ground level blood gases (Pao_{2GL}, $Paco_{2GL}$), ground level calculated alveolar Po_2 (PAo_{2GL}) and altitude alveolar Po_2 (P_Ao_{2alt}) using the following equation:

$$Pao_{2alt(predicted)} = PAO_{2alt} \cdot \left(Pao_{2GL}/PAO_{2GL}\right)$$

Systematic testing of a number of other prediction equations has been reported.[253,255]

It has been recommended that patients with baseline hypoxemia due to lung or heart disease be considered for in-flight O_2 administration.[256] Procedural details have been reviewed by Stoller.[254]

In-Flight Emergencies

From 1 to 75 in-flight medical events per million passengers have been reported by commercial airlines.[257] The most common are due to syncope, gastrointestinal complaints, minor trauma, or cardiac, pulmonary, or neurologic issues. Emergency care of severely ill passengers is facilitated by medical kits that are carried aboard all U.S. commercial aircraft requiring a flight attendant. In addition, automatic external defibrillators (AEDs) are aboard all U.S. commercial planes with a payload exceeding 7500 pounds. In-flight deaths are extremely uncommon (0.01-0.8 deaths per million passengers). In a study of 1 year's (1999-2000) experience of a U.S.-based airline it was estimated that an onboard physician was available in approximately half of all flights.[257] A system of ground-based physicians is available for consultation and to assist with decisions regarding flight diversion.

Medical Care in Space

Physiologic and Medical Issues During Space Flight

For a few minutes during launch of a space vehicle there is an increase in gravitational force as the space craft accelerates to orbital speed (typically 3 *G* for the NASA shuttle, 4 *G* for the Russian Soyuz). During the period in space the major physiologic stress on astronauts is the absence of gravitational stress (microgravity). This results in an increase in left ventricular end-diastolic volume, paradoxically accompanied by a decrease in central venous pressure.[258] The central redistribution of blood causes facial edema and initiates a diuresis, and thence plasma volume depletion (up to 20% or more), which persists until after landing.[259] Shortly after attaining orbit most astronauts experience self-limited dizziness, drowsiness, nausea, and vomiting.[260] During reentry, astronauts are reexposed to increased G force, typically 1.5 *G* for the shuttle and 3 to 4 *G* for the Soyuz craft. After landing, astronauts typically experience some degree of orthostatic intolerance[261] and often a recurrence of nausea and vomiting.[260] Postural hypotension has been attributed to hypovolemia, enhanced eNOS expression, and downregulation of α-adrenergic receptors.[262] Reduced ventricular mass has been observed after several days in orbit,[263] which may be due to cardiac atrophy[264] or dehydration.[265] Skeletal muscle atrophy can occur even after short missions.[266]

Cabin pressure in the Shuttle and International Space Station is 760 mm Hg. However, during extravehicular activity (EVA) space suit pressure is 4.3 psi (222 mm Hg). During EVA astronauts prevent hypoxia by breathing 100% O_2; however, the reduced pressure engenders the potential risk of DCS.[267] If the suit becomes disrupted during EVA, the astronaut's ambient pressure would quickly drop to zero, causing hypoxia and generalized bubble formation, referred to as *ebullism* (body fluids boiling due to ambient pressure lower than saturated water vapor pressure).

Gravitational unloading causes loss of calcium from bones, which during long space flights could produce significant osteoporosis. This problem, along with the resulting hypercalciuria and increased probability of nephrolithiasis, constitutes major obstacle to human interplanetary travel.

Emergency care during space includes numerous challenges.[267-272] Hypovolemia due to hemorrhage may not be adequately treatable due to limited quantities of supplies, and hypotension could be exacerbated by preexisting volume loss and increased G forces during reentry. Air-fluid interfaces in intravenous fluids generate bubbles (Fig. 80-17). Thus, intravenous fluid bags must be degassed before flight or bubbles must be removed by in-line filtration. The physiologic effects of general or regional anesthesia in microgravity are unknown. Conventional anesthesia vaporizers require gravity to confine the liquid to the bottom of the reservoir; thus, a different design would be required for use in space. Additional practical limitations include the need to prevent pollution of the enclosed environment by volatile anesthetics or exhaust oxygen (fire hazard).

Tracheal intubation may be difficult because of facial edema. The laryngeal mask airway (LMA), cuffed oropharyngeal airway, and intubating LMA have all been successfully demonstrated in microgravity simulated using a neutral buoyancy tank.[273] Studies using secured mannequins during short periods of microgravity in an aircraft have demonstrated successful intubation using laryngoscopy and standard tracheal tube (Fig. 80-18), Combitude (Nellcor, Pleasanton, CA), and an intubating LMA.[274,275] However, tracheal intubation in microgravity by a



Figure 80-17 Air in the bag of intravenous fluid in microgravity with an infusion pump. The lack of a gravitational field makes it difficult to remove gas. *(Courtesy of NASA.)*

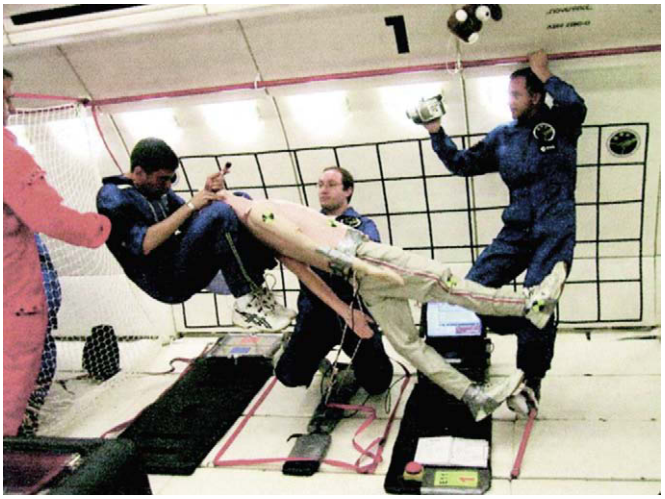

Figure 80-18 Tracheal intubation of a free-floating mannequin in microgravity. The intubator stabilizes the head by holding it between his knees. *(From Groemer GE, Brimacombe J, Haas T, et al: The feasibility of laryngoscope-guided tracheal intubation in microgravity during parabolic flight: A comparison of two techniques. Anesth Analg 101:1533-1535, 2005, with permission.)*

nonphysician using conventional laryngoscopy is frequently unsuccessful.[274] All intubation techniques require that both the patient and the intubator be secured.[274] Gastroesophageal reflux is more common in microgravity; thus, aspiration during general anesthesia may be more likely.

On-board diagnostic tools are being developed, such as remotely guided ultrasound examination (Fig. 80-19).

Remote robotic surgery has been considered as a substitute for an on-board surgeon. Indeed, a robotic laparoscopic cholecystectomy was successfully performed on a patient in Strasbourg, France, by surgeons operating from New York City. The total delay time between movement initiated by the surgeon and detection on the monitor was approximately 155 msec.[276] The limit of the acceptable time delay is believed to be around 330 msec. Whether training or technology will allow this to be increased to permit surgery during interplanetary flights (with a much longer delay time) is unknown.

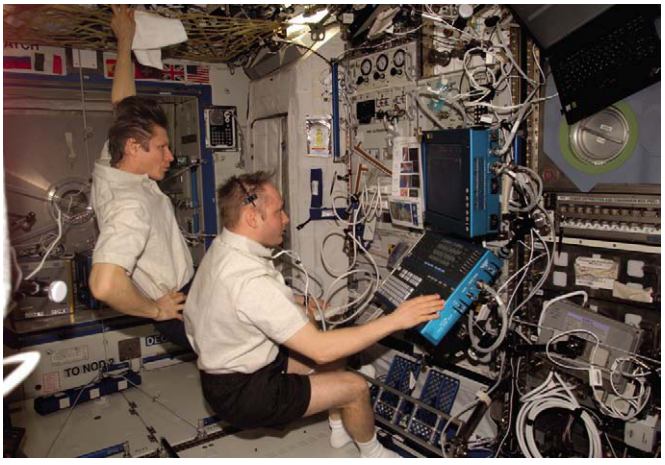

Figure 80-19 Testing diagnostic ultrasound on the space shuttle. Astronaut Mike Finke is operating the ultrasound imager while being guided by a ground-based physician. *(Courtesy of NASA.)*

Physiologic and Medical Issues after Return to Earth

Medical challenges may extend into the period after landing. After 14 days in space, in order to obtain biopsies, two rhesus monkeys were administered general anesthesia (ketamine, 10 mg/kg IM, then 1% to 1.5% isoflurane for 3½ to 4 hours) within 24 hours after landing by a competent veterinary anesthesiologist. One animal aspirated during emergence and could not be resuscitated. Three hours after recovery, the other inexplicably developed lethargy and facial edema.[277] From this experience it can be inferred that well-accepted standard-of-care techniques may not be safe when anesthetizing astronauts shortly after space flight.

Several specific challenges have been elucidated. Details can be found in two excellent reviews.[278,279] Some issues most pertinent to anesthetic risk are as follows.

Hypovolemia and Adrenergic Hyporesponsiveness

Following flight a large percentage of astronauts experience orthostatic intolerance. This is in part due to hypovolemia but also due to a dysfunctional adrenergic response.[280] In astronauts with post-flight orthostatic intolerance the pressor response to phenylephrine is not different from pre-flight; however, it is attenuated compared with astronauts who are tolerant of acute orthostasis.[281] Cardiovascular deconditioning, ventricular atrophy, and changes in arterial stiffness may also play a role.[264,265,282,283] The immediate post-flight hemodynamic response to general or neuraxial anesthesia could include unexpected hypotension but to date is unknown.

Electrolyte Disorders

Reductions in both serum potassium and magnesium have been reported after some space missions,[284,285] possibly owing to decreased dietary intake. Hypokalemia has been blamed for cardiac arrhythmias observed during Apollo 15.[286]

Hyperkalemic Response to Succinylcholine

Skeletal muscle atrophy due to immobilization and disuse causes proliferation of acetylcholine receptors, increased sensitivity to succinylcholine (see Chapter 29), and decreased cholinesterase activity.[287] Based on data from patients with neuromuscular disease and immobilized limbs, there may be a resistance to nondepolarizing neuromuscular blocking drugs.[288] Use of succinylcholine in immobilized intensive care patients has been associated with exaggerated hyperkalemia and cardiac arrest.[289,290] It has been suggested that skeletal muscle atrophy in astronauts may put them at a similar risk.[279]

Summary

Increasingly widespread use of HBO to treat critically ill patients has created a demand for individuals skilled in using this technology. Planning and design of monitoring capabilities will enable optimal control of hemodynamics and oxygenation. Careful

attention to detail will maximize patient safety in this environment. Optimized treatment schedules will evolve from further studies of mechanism of action. Advances in prevention and treatment of O_2 toxicity may allow more prolonged therapy than can currently be safely administered, and hence a more aggressive approach to ischemic and infectious syndromes.

The reduction in ambient pressure and ensuing hypoxia associated with acute altitude exposure result in well-described physiologic changes that are often associated with clinical symptoms. Methods for prophylaxis and treatment have been described. Safe anesthesia at altitude requires some modification of sea level techniques, not only because of the hypoxia and reduced ambient pressure but also because suboptimal equipment may be available under mountain conditions.

Anesthesia in space poses unique challenges that may extend even beyond return to earth.

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Bernard J. Dalens

81 Regional Anesthesia in Children

Over the past 30 years, regional anesthesia has progressively become a major technique of pain management in surgical and nonsurgical pediatric patients. It was made easier and safer by the development of needles and catheters specifically designed for pediatric patients. Over the years, many pediatric studies involving large series of patients from the neonatal period to the end of adolescence have evaluated virtually all techniques of nerve blockade, thus allowing precise delimitation of their indications, contraindications, and adverse effects. With the use of nerve stimulators, peripheral blocks can now be safely achieved in anesthetized patients provided that no muscle relaxants had been previously administered.

Ultrasound imaging techniques represent the second revolution of regional anesthesia (see Chapter 53). The advantage of ultrasonography over neurostimulation is to make visible the spread of the local anesthetic, thus allowing both adjustment of needle positioning in case of inappropriate spread and dose reduction when complete circumferential spread of the local anesthetics is clearly obtained.

Relevant Differences between Children and Adults

Anatomic Differences

Change in Body Size Due to Growth Process

The most obvious difference between children and adults pertains to body size: "Normal" full-term neonates weigh 3 to 3.5 kg with a height of 50 cm, and within 10 to 15 years they will multiply their weight by more than 12 (>1200%) and their height by more than 3 (>300%). During the early stages of development the spinal cord occupies the spinal canal entirely, but later on the growth of vertebrae exceeds that of the cord,[1] and the last spinal nerves, the cord, and its envelopes are "attracted" within the spinal canal. At birth the dura mater ends at the level of the third or fourth sacral vertebra and the cord (conus medullaris) at the L3 or L4 level. It is only at the end of the first year of life that adult level is attained, namely, L1 for the conus medullaris and S2 for the dural sac.

Anatomic relationships and landmarks are constantly changing throughout infancy and childhood, which interferes with regional procedures and requires quite a good knowledge of developmental anatomy and the assistance of accurate techniques for localization of anatomic spaces and nerve trunks.

Congenital malformations, genetic disorders, and consequences of fetal/neonatal asphyxia (cerebral palsy) are frequent and specific to the pediatric period. They result in abnormal development and deformities of bone/joint and neurologic structures that tend to worsen during childhood.

The main pediatric anatomic and physiologic factors that can influence indications for or performance of regional block procedures are listed in Table 81-1.

Delayed Ossification of Bones and Fusion of Sacral Vertebrae

Bones of neonates, including vertebrae, are mostly cartilaginous. They can be easily traversed by sharp needles because cartilage offers little resistance to penetration, and ossification nuclei can be severely damaged, thus compromising further bone/joint development. Consequently, bone contact should be avoided as often as possible during block procedures, especially in infants. This cartilaginous structure also allows easy penetration of x-rays and ultrasound (Fig. 81-1).

Delayed Myelinization of Nerve Fibers

Myelinization begins during the fetal period in cervical neuromeres and extends cephalad and caudad,[2,3] but the process is not finalized before the 12th year of life. Myelinization is especially poor in infants; this lack of fully developed nerve fibers is the main reason why they are unable to walk. A major pharmacologic consequence of this condition is that local anesthetics can penetrate and block nerve fibers more easily: Diluted solutions of local anesthetics provide the same quality of nerve blockade as with at least twofold more concentrated solutions in adults. Onset time is shortened but, on the other hand, duration of blockade is reduced because trapping of local anesthetics within myelin with subsequent progressive release is reduced and because local circulation and therefore vascular absorption are greater in infants.

Development of Flexures of the Spine

At birth, there is a single spinal flexure and the orientation of epidural needles is the same whatever the intervertebral space. Flexures, however, are not fixed and they can be easily counteracted by forced flexion almost throughout childhood due to

Table 81-1 Main Anatomic and Physiologic Factors in the Pediatric Period That Can Influence the Selection or Performance of a Regional Block Procedure

Pediatric Factors (Infants Mainly)	Resulting Danger	Implications for Regional Anesthesia
Lower termination of spinal cord	Increased risk of direct trauma to the spinal cord	Avoid epidural approaches above L3 whenever possible.
Lower projection of dural sac	Increased risk of inadvertent penetration of the dura mater	Check for cerebrospinal fluid reflux, including during caudal approaches. Favor low approaches to the epidural space.
Delayed myelinization of nerve fibers	Easier intraneural penetration of local anesthetics	Onset time is shortened, and diluted local anesthetic is as effective as more concentrated anesthetic in adults.
Cartilaginous structure of bones and vertebrae	Reduced resistance to penetration by sharp needles Danger of direct trauma and bacterial contamination of ossification nuclei compromising further bone/joint growth	Avoid use of thin and sharp needles; use short and short beveled ones instead. Do not apply excessive force on needle: if resistance is felt, stop trying to insert the needle farther.
Lack of fusion of sacral vertebrae	Persistence of sacral intervertebral spaces	Intervertebral sacral epidural approaches can be performed throughout childhood.
Delayed development of curvatures of the spine	Cervical lordosis (3-6 months) Lumbar lordosis (8-9 months)	Same orientation of epidural needles is appropriate whatever the spinal level before 6 months of age; then adapt needle orientation to spinal flexures.
Changing axis of coccyx and absence of growth of sacral hiatus	Sacral hiatus comparatively smaller with increasing age	Identification of sacral hiatus becomes more difficult above 6-8 years (increased failure rate of caudal anesthesia).
Delayed ossification and growth of iliac crests	Tuffier's line, which joins anterior superior iliac spinous processes, crosses the spine at L5 or lower in infants.	This line passes over L5-S1 interspace instead of L4-L5 interspace.
Increased fluidity of epidural fat	Increased diffusion of local anesthetic up to 6-7 years of age	Excellent blockade after caudal anesthesia can be achieved up to 6-7 years of age.
Loose attachment of sheaths and aponeuroses to underlying structures	Increased spread along nerve paths with danger of penetrating remote anatomic spaces and blocking distant nerves	Larger volume of local anesthetic is required for epidural blocks due to leakage along spinal nerve roots. Smaller volume of local anesthetic is necessary to produce excellent peripheral blocks.
Enzymatic immaturity	Slower metabolism of local anesthetics (usually compensated by other enzyme pathways)	Increased mean body residency time and half-life, with accumulation (especially after repeat injection and continuous infusions of local anesthetic), are characteristic.
Increased extracellular fluids	Increased distribution volume and mean body residency time of local anesthetic (and most medications)	Decreased Cmax after single injection but accumulation with repeat/continuous injections
Low plasma protein content (HSA and AAG)	Competition at nonspecific HSA binding sites Limited capacity of specific binding of local anesthetic by AAG, resulting in increased plasma concentration of the free fraction	Increased unbound free fraction of all local anesthetic: greater danger of systemic toxicity
Increased cardiac output and heart rate	Increased regional blood flow resulting in increased systemic absorption of local anesthetic	Increased systemic absorption of local anesthetic (decreased Tmax and shorter duration of blockade) Increased efficacy of epinephrine: vasoconstriction reduces absorption (thus toxicity) and prolongs duration of blockade.
Sympathetic immaturity, diminished autonomic adaptability of the heart, smaller vascular bed in lower extremities	Hemodynamic stability during neuraxial blocks	Fluid preloading and use of vasoactive agents are unnecessary.
Delayed acquisition of body scheme and conceptualization, anxiety	Inability of patients to locate precise body areas Concept of paresthesia not understandable Difficult cooperation	Nerve/space identification requires application of location techniques independent of patient's cooperation. Heavy sedation or general anesthesia is required in most patients (especially when a "dangerous" technique is planned to avoid detrimental consequences of panic attacks at a critical phase of the block procedure).

AAG, α_1-acid glycoprotein; Cmax, peak plasma concentration; HSA, human serum albumin; Tmax, time to reach Cmax.

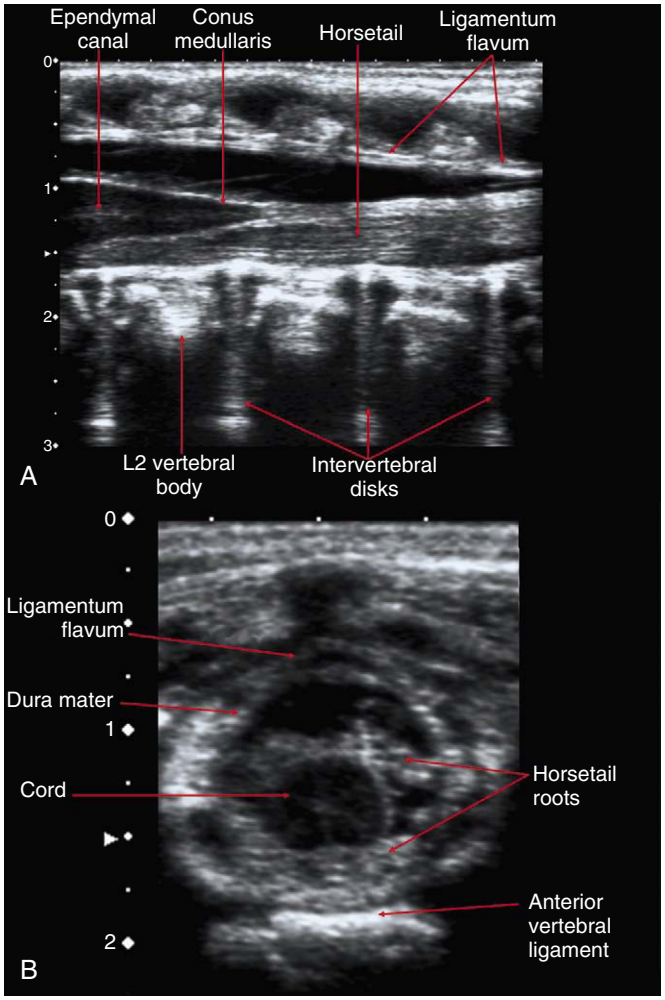

Figure 81-1 Ultrasound imaging of the caudal part of the spine in a 3-week-old infant. **A,** Long-axis view. **B,** Short-axis view (transverse echotomography).

persistent spinal flexibility, which is a major advantage in the pediatric period (in addition to the absence of osteophytes).

Loose Attachment of Fascias and Fluidity of Epidural Fat

Fascias and perineurovascular sheaths are loosely attached to underlying structures (e.g., nerves, muscles, tendons, vessels). This allows extended spread of local anesthetics, resulting in high-quality nerve blockade whatever the technique but also, occasionally, undesirable spread to distant nerves or anatomic spaces.

The epidural fat is very fluid in infants and young children (up to 6-7 years of age). This fluidity combined with the loose attachment of the sheaths surrounding the spinal roots favors consistent leakage of the local anesthetics injected within the epidural space; therefore, comparatively large volumes of epidural local anesthetics (up to 1.25 mL/kg) are required to reach desired levels of anesthesia.

Perception of Pain

Somatic pain is a subjective sensory experience resulting from the intermixing of three main components[4,5]: motivational-directive, sensory-discriminatory, and cognitive-evaluative. The motivational-directive component is conveyed by unmyelinated C fibers ("slow" pain or "true" pain). It leads to protective reflexes such as autonomic reactions, muscle contraction, and rigidity. C fibers are fully functional from early fetal life onward.

Connections between C fibers and dorsal horn neurons are not mature before the second week of postnatal life. However, nociceptive stimulations transmitted to the dorsal horn by C fibers elicit long-lasting responses,[6,7] probably owing to extensive depolarization of surrounding neurons in response to the production of large amounts of substance P. As the number of dorsal horn receptors to substance P decreases during the first 2 weeks of life, this exaggerated response of neonates to nociceptive stimulation progressively disappears. The inhibitory control pathways, which are immature at birth, develop concomitantly.

Painful procedures during the neonatal period modify subsequent pain responses in infancy and childhood,[8] depending on the developmental stage of the infant (full-term versus preterm) and his or her cumulative experience with pain. To later noxious procedures, full-term neonates react with heightened behavioral responsiveness whereas preterm neonates react with a damped response. When analgesic agents (local anesthetics or opioids) are administered before painful procedures, infants demonstrate less evidence of procedural pain and a reduction in the magnitude of long-term changes in pain behaviors.[8]

A major difficulty is assessment, and, at times, even identification of pain in children pertains to the inability of young patients to communicate with their caregiver and precisely express their distress and discomfort. During the past 2 decades, pediatric pain has received considerable attention, and reliable age-related pain scales have been developed to evaluate both the severity of pain and the efficacy of its treatment.

Pharmacology of Local Anesthetics and Additives

Two main factors influence pharmacologic properties of medications in children: (1) immaturity of some enzyme pathways and their replacement by other biochemical pathways and (2) progressive increase in body surface area concomitantly with the growth process. Drug prescriptions made according to body surface area are the same as (or in simple ratio with) adult dosing.[9] However, body surface area is not easily obtained and, in practice, doses are calculated according to body weight and require constant adaptation as the child grows up; dosage errors are not infrequent.

Local Anesthetics

Chemical properties and mechanisms of action of local anesthetics are detailed elsewhere in this textbook (see Chapter 30); they are basically the same during the pediatric period and only pharmacokinetic properties may notably differ, especially in neonates and infants.[10]

Local Fixation

Schematically, local fixation is reduced and spread is increased in infants as compared with adults, especially within the epidural space, because the epidural fat is more fluid and less densely packed. The main consequences are (1) shorter onset time of

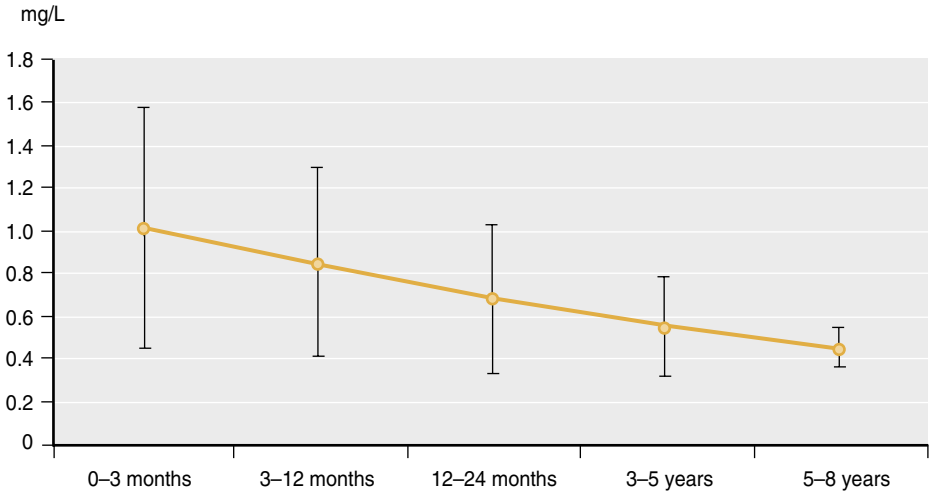

Figure 81-2 Cmax values of ropivacaine after caudal injection of 2 mg/kg in different age groups.

action; (2) more extended longitudinal and circumferential spread of local anesthetics; and (3) shorter duration of action because of reduced secondary release from local binding sites.

Regional Spread toward the Target

The target of local anesthetic action is voltage-dependent Na^+ channels located within nerve fibers. Penetration of biologic membranes can only be achieved by nonionized molecules, and the speed of the process depends on the number and thickness (increasing with age) of sheaths.

Systemic Absorption and Distribution

Plasma Protein Binding. Nonionized local anesthetics cross almost freely the capillary wall close to the injection site. Because cardiac output and local blood flow are two to three times greater in infants than in adults, systemic local anesthetic absorption is increased accordingly and vasoactive agents such as epinephrine are very effective in slowing down systemic uptake.

Once they have penetrated within the vascular bed, local anesthetics undergo plasma protein binding mainly to human serum albumin (HSA) and α_1-acid glycoprotein (AAG), or orosomucoid. HSA has a low affinity for local anesthetics, and many pharmacologic agents can compete at available binding sites. Furthermore, plasma levels of HSA are low during the first months of life, especially in premature and fasted infants; thus, the protection offered by HSA against systemic toxicity of local anesthetics is low and decreases postoperatively. The affinity of AAG for local anesthetics is 5,000 to 10,000 times greater than that of HSA, which makes AAG very effective to protect the patient from systemic toxicity (which depends on the nonbound free form of local anesthetics). However, again, plasma concentration of AAG is very low at birth (0.2-0.3 g/L) and does not reach adult levels (0.7-1.0 g/L) before 1 year of age.[11-13]

Because plasma concentration of the two proteins able to bind local anesthetics are low at birth, the free fraction of all local anesthetics is increased in infants; therefore, the maximum doses of all aminoamides must be significantly reduced in this age group even though the plasma concentration of AAG increases postoperatively except in case of liver insufficiency.[13]

Red Cell Storage. Once in the bloodstream, local anesthetics distribute to red blood cells, which retain 20% to 30% of the total dose, depending on the anesthetic agent and the hematocrit. Red cell storage usually has a minor impact on the pharmacokinetics of local anesthetics except:

- In neonates: high hematocrit values (which may exceed 70%) and enlargement of erythrocytes (physiologic macrocytosis) result in consistent "entrapment" of local anesthetics, thus lowering Cmax values after a single injection but increasing secondary release, thus increasing the half-life of all local anesthetics.
- In infants: physiologic anemia reduces red cell storage and its protective effect against systemic toxicity of local anesthetics (after a single-shot injection only) when the plasma protein binding sites are saturated, that is, close to toxic blood concentrations.

Absorption from the Epidural Space. Absorption has been rather well evaluated in the epidural space. In children and infants, the same kinetics of absorption is reported, but the younger the patient, the less accentuated is the biphasic shape of the plasma concentration curve. The peak plasma concentration and the slope of the decreasing concentration curve are increased,[14,15] whereas the time (Tmax) to reach peak plasma concentration (Cmax) remains basically unchanged; for example, the Tmax of bupivacaine is around 30 minutes whatever the patient's age.

Ropivacaine is a remarkable exception. After caudal or lumbar epidural injection, Tmax is prolonged up to 2 hours in infants and Cmax, too, is increased (Fig. 81-2).[16] This unusual pharmacokinetic profile is difficult to understand; some hypotheses have been tentatively considered, such as enzyme immaturity, slower systemic uptake, and decrease in distribution volume.[17,18] Intrinsic vasoconstrictive properties of ropivacaine may also play a role in the same way as addition of epinephrine. Anyway, such an increase in both Cmax and Tmax values cannot be ignored because many surgeries in infants are brief and the young patient may have left not only the operating room but also the postanesthesia care unit (PACU) less than 2 hours after the caudal/epidural was performed, that is, before peak plasma concentration were reached.

Levobupivacaine displays a similar pharmacokinetic profile. After caudal injection of 2 mg/kg of levobupivacaine in infants younger than 2 years of age, the Cmax range is 0.41 to 2.42 µg/mL

(0.91 ± 0.40 µg/mL), which is higher than the Cmax reported after caudal injection of the same dose of racemic bupivacaine.[19] Tmax values also are delayed (50 min versus 30 min) in infants younger than 3 months of age[20] owing to reduced plasma clearance.

When repeat injections are considered, the epidural dose must be reduced to keep Cmax values in the same range as that resulting from the first injection. For the second injection, either:

- Reduce the dose to a third of the initial dose and do not inject it less than 30 minutes (lidocaine, mepivacaine, prilocaine) or 45 minutes (bupivacaine, levobupivacaine, ropivacaine) after the first injection; or
- Inject half of the initial dose but 60 minutes (lidocaine, mepivacaine, prilocaine) or 90 minutes (bupivacaine, levobupivacaine, ropivacaine) after the first injection.

If more reinjections are necessary, dosing should be further reduced to half of the second dose (i.e., one sixth of the initial dose) while respecting the same delay as for the second injection.

Continuous infusions aim to produce a steady-state concentration at the 24th hour postoperatively. This goal is easily achieved in adolescents with infusion rates around 0.3 mg/kg/hr of bupivacaine and levobupivacaine or 0.4 mg/kg/hr of ropivacaine. In infants, infusion rates must be reduced[21-23]; they should not exceed 0.2 mg/kg/hr with bupivacaine (or equipotent doses of other local anesthetics) in infants younger than 4 months and 0.25 mg/kg/hr later on.

Infants younger than 4 months (occasionally up to 9 months) may develop systemic toxicity even at these "safe" infusion rates with racemic bupivacaine because no steady-state plasma concentration is reached, even at the 48th hour. In this age group, levobupivacaine[24] or ropivacaine[25] instead of racemic bupivacaine is preferred because stable plateau concentrations are obtained from the 24th hour onward.

Absorption from Other Injection Sites. Absorption of local anesthetics deposited along mucous membranes is increased in infants. Mucosal topical anesthesia has long been considered contraindicated in this age group. However, the technique can be safely used with certain precautions: selection of specific transmucosal patches[26] or sprays with diluted lidocaine[27,28] and recognition that topical lidocaine exaggerates laryngomalacia.[29]

After cutaneous application of EMLA cream, peak plasma concentrations occur 4 hours later and remain low[30]: less than 200 ng/mL for lidocaine and less than 131 ng/mL for prilocaine, even in infants younger than 6 months of age.

Absorption of local anesthetics from compartment blocks (e.g., fascia iliaca, umbilical, ilioinguinal, pudendal blocks) follows the same biphasic curve as for the epidural space.[31-35] Because of the extended surface of absorption, injection of highly concentrated solutions of local anesthetics often leads to high, occasionally potentially toxic peak plasma concentrations, especially with 0.5% ropivacaine[35] whereas use of more diluted solutions results in rather low plasma concentrations.

Absorption from peripheral conduction blocks also follows a similar biphasic curve with different Cmax and Tmax values depending on the local anesthetic, the addition of epinephrine, and the site of injection: The more distal the injection, the slower the absorption process (as in adults).

Pulmonary Extraction. After they have reached the venous bloodstream and undergone plasma protein linkage and erythrocyte storage, aminoamides reach the right cardiac cavities and then the pulmonary circulation from which they are extracted by the lung; their plasma concentration in pulmonary veins and then in systemic arterial circulation (especially coronary and cerebral arteries) is consistently decreased. Thus, pulmonary extraction represents a temporary protection against systemic toxicity. However, certain medical conditions suppress this protective effect. Some medications such as propranolol decrease pulmonary extraction in a clinically relevant way. Also, children with right-to-left shunts undergo considerable increase in arterial plasma concentration of local anesthetics due to pulmonary bypass: even with small doses of local anesthetics they can develop systemic toxicity.[36]

Distribution Volume. After intravenous (IV) injection, distribution volume at the steady state (Vd_{ss}) is 1 to 2 L/kg for all aminoamides (Table 81-2). After administration at other sites,

Table 81-2 Age-Related Differences in Pharmacokinetic Parameters of Aminoamides

Local Anesthetic	Protein Binding (%)	Vd_{ss} (L/kg)	Clearance (mL/kg/min)	Elimination Half-Life (hr)
Lidocaine				
Neonate	25	1.4-4.9	5-19	2.9-3.3
Adult	55-65	0.2-1.0	11-15	1.0-2.2
Mepivacaine				
Neonate	36	1.2-2.8	1.6-3	5.3-11.3
Adult	75-80	0.6-1.5	10-13	1.7-6.9
Bupivacaine				
Neonate	50-70	3.9 (± 2.01)	7.1 (± 3.2)	6.0-22.0
Adult	95	0.8-1.6	7-9	1.2-2.9
Levobupivacaine				
Infant	50-70	2.7	13.8	4
Adult	95	0.7-1.4	28-39	1.27 ± 0.37
Ropivacaine				
Infant	94	2.4	6.5	3.9
Adult	94	1.1 ± 0.25	4-6	1.15 ± 0.41

Table 81-3 Variation of Body Fluid Distribution by Age Group

Distribution of Body Fluids	Preterm Neonates	Full-Term Neonates	Infants	Children	Adults
Total body fluids	80-85%	70-75%	65%	55-60%	50-55%
Intracellular	20-25%	30-35%	35%	35-40%	40-45%
Extracellular	55-60%	45%	30%	20-25%	20%

calculated distribution is increased, often considerably, owing to the "flip-flop" effect, especially for long-lasting local anesthetics. In infants and neonates, owing to higher extracellular fluid content (Table 81-3), the distribution volume of all LA is greater than in adults, the consequences of which are (1) significant decrease in peak plasma concentration of all local anesthetics, thus decreasing the danger of systemic toxicity after a single dose, and (2) accumulation with reinjections, which increases drug plasma concentration and elimination half-life while concomitantly decreasing clearance.

Hepatic Extraction and Clearance of Aminoamides. Short-acting local anesthetics undergo high hepatic extraction (0.65-0.75 ratio for lidocaine), which depends mainly on hepatic blood flow and not much on their plasma concentration. Only limited pediatric data are available for levobupivacaine. After a single injection, the clearance of levobupivacaine increases during the first months of life, but during continuous infusion (even with 0.0625% levobupivacaine), it tends to decrease almost to the same extent as for racemic bupivacaine, and plasma concentrations do not reach a plateau.[20]

Placental Transfer. In pregnant women, placental extraction may consistently affect tissue distribution of local anesthetics. Protein binding influences placental transfer: the concentration ratio between umbilical venous blood and maternal arterial blood is around 0.73 for lidocaine, 0.85 for prilocaine, but only 0.32 for bupivacaine.[37] Chirality may play a role, too, at least for bupivacaine, because placental transfer of dextrobupivacaine exceeds that of levobupivacaine but only with solutions containing epinephrine.[38]

Most aminoesters undergo such a rapid plasma hydrolysis that placental transfer is not an issue. Tetracaine and cocaine, the hydrolysis of which is slow, are only used for topical applications or (tetracaine only) spinal anesthesia: systemic uptake is slow and plasma concentrations remain extremely low and, thus, are not issues again for placental transfer.

Metabolism

Aminoesters are rapidly hydrolyzed by plasma cholinesterases. This enzymatic activity is low at birth (but no adverse clinical consequences are to be feared) and gradually reaches adult levels by 1 year of age.[39] Chloroprocaine is eliminated at the fastest rate (4.7 mol/mL/hr), procaine at a slower rate (1.1 mol/mL/hr), but cocaine only at 0.3 mol/mL/hr. Procaine and chloroprocaine are also metabolized, in part, by hepatic cholinesterases.

Aminoamides are metabolized within the liver, where they are subjected to two types of enzymatic reactions: phase I reactions first, during which oxidation of the amide link is achieved within hepatic microsomes by the cytochrome P450 enzyme superfamily; then phase II reactions, during which glucuronic acid or aminoacids residues are appended to phase I metabolites, producing atoxic and hydrosoluble compounds, which are thus easily eliminated from the body.

Cytochrome P450 enzymatic activities are reduced during the first months of life. Bupivacaine is mainly metabolized by CYP_{3A4} in adults, but this enzyme is defective in infants. However, fetal CYP3A7 remains very active in infants, thus allowing metabolism of bupivacaine almost as effective as with CYP3A4. Ropivacaine and levobupivacaine[20] are metabolized by CYP1A2, which is not fully functional before the third year, and, to a minor extent, by CYP3A4. This enzyme immaturity is clinically relevant but with limited consequences (lower clearance, delayed Tmax and, for ropivacaine only, increased Cmax but within clinically acceptable levels): it does not preclude administering these local anesthetics in neonates and infants.

Phase II reactions, especially glucuroconjugation, are immature at birth and remain so until the third year of life. However, other conjugation pathways such as sulfoconjugation are active and quite effective during the first months of life.

Elimination Half-Life

Elimination half-life ($t_{1/2}\beta$) depends on both distribution and metabolism. It can be calculated using the formula below (Cp is the plasma clearance and Vd_{ss} the distribution volume at the steady state):

$$t_{1/2}\beta = (0.693 \times Vd_{ss})/Cp$$

Basically $t_{1/2}\beta$ is the same in children older than 1 year and in adults, mainly because the increase in Vd_{ss} is compensated by concomitant increase in Cp (related in part to higher hepatic blood flow in children, whose liver accounts for 4% of body weight, versus 2% only in adults). Before the age of 1 year, Cp is low and elimination half-life of all local anesthetics is prolonged (see Table 81-2), thus favoring accumulation with repeat injections. Nevertheless, no consistent differences in pharmacokinetic parameters between infants and adults were measured by Bricker and colleagues.[40]

Systemic Toxicity

Clinical signs of neurologic toxicity have been reported with plasma concentration ranging from 7 to 10 µg/mL for lidocaine or mepivacaine and 1.5 to 2 µg/mL (intraoperatively) to 2 to 2.5 µg/mL (postoperatively) with bupivacaine. However, plasma concentrations of bupivacaine higher than 4 µg/mL have been reported without any evidence of clinical toxicity. From studies in adult volunteers, the following thresholds of toxicity of the unbound form of local anesthetics have been defined:

- 0.3 µg/mL for unbound bupivacaine
- 0.6 µg/mL for unbound levobupivacaine or ropivacaine

Because plasma protein binding is lower in infants, hazards of systemic toxicity might be increased, the more so as cardiac toxicity is usually concomitant with, not preceded by, central nervous system toxicity.

Opioids

Elimination half-life of neuraxial opioids is considerably increased in neonates and infants.[41] After epidural injection, morphine reaches its peak concentration in plasma within 10 minutes, but

Table 81-4 Commonly Used Additives and Recommended Doses in Pediatric Regional Anesthesia

Additive	Recommended Doses	Maximum Doses
Morphine		
Epidural	30 µg/kg	50 µg/kg
Intrathecal	10 µg/kg	20 µg/kg
Fentanyl (epidural)	1-1.5 µg/kg	2.5 µg/kg
Sufentanil (epidural)	0.25-0.5 µg/kg	0.75 µg/kg
Clonidine (epidural or along peripheral nerves)	1-1.5 µg/kg	2 µg/kg
Ketamine* (epidural or occasionally along peripheral nerves)	0.5 mg/kg	1 mg/kg

*Preservative free-ketamine (preferably preservative-free *S*-ketamine).

this concentration is very low and unable to provide clinically relevant analgesia.[42,43] Elimination half-life from CSF is similar to that from plasma, but CSF concentrations are very high after epidural injection; therefore, it takes 12 to 24 hours before their decrease below minimal effective concentrations (near 10 ng/mL). Consequently, vital parameters of children given neuraxial opioids must be monitored for 24 hours and are not eligible for outpatient surgery. Usual doses of neuraxial narcotics are listed in Table 81-4.

Short-acting lipid-soluble opioids (fentanyl, sufentanil) can be used but, as in adults, they do not significantly prolong postoperative pain relief unless repeat injections are given or a continuous infusion is established. Their analgesic effect is mainly a systemic effect, and the patient may experience acute respiratory depression (sudden apnea); this condition is very different from the progressive and delayed respiratory depression, preceded by generalized pruritus, sedation, and bradypnea, reported after excessive doses of epidural/intrathecal morphine.

Other Additives

Epinephrine (5 mg/L or 1/200,000 concentration) is frequently co-administered with local anesthetics to decrease plasma peak concentration[31] and prolongs the duration of blockade, especially in children younger than 4 years of age.[44,45] Another benefit expected from epinephrine is early detection of accidental IV injection (test dose) because young children are very sensitive to arrhythmogenic properties of epinephrine. Neuraxial epinephrine has long been suspected to elicit spinal ischemia: Even though this fear proved to be unfounded,[46] many anesthesiologists recommend using lower concentrations of epinephrine (2.5 mg/L or 1/400,000) in local anesthetic solutions administered to neonates and infants; at such concentrations, the absorption rate of caudal bupivacaine is decreased by 25%.[45]

Clonidine, like epinephrine, is an α_2-adrenergic agonist that offers several benefits in children when added to local anesthetics either neuraxially[47-49] or peripherally (see Table 81-4)[50]: It increases (by a factor of 2 approximately) the duration of nerve blockade without eliciting hemodynamic disorders, decreases plasma peak concentration of the local anesthetics, and produces a slight sedation for 1 to 3 hours postoperatively (which does not preclude hospital discharge). Addition of clonidine often makes unnecessary the placement of a catheter to prolong postoperative pain relief, thus reducing morbidity and costs. However, its clearance in neonates is approximately one third that in adults owing to immature elimination pathways[51] and several instances of respiratory depression in neonates and small infants have been reported[52,53]; this additive should be avoided during the first 6 month of life.

Ketamine, especially *S*-ketamine, is an interesting adjuvant owing to its blocking effects on *N*-methyl-D-aspartate (NMDA) receptors and interaction with Na^+ channels in a local anesthetic–like fashion (it shares a binding site with local anesthetics). Coadministered at a dose of 0.25 to 0.5 mg/kg, ketamine prolongs the duration of analgesia for many hours[48,54] with no significant adverse effects.

Many other agents have been occasionally used as adjuvants to local anesthetics.[55] Even though some of them proved to have analgesic properties (corticosteroids, buprenorphine, neostigmine, tramadol, midazolam, and biodegradable bupivacaine/polyester microspheres), they all produce significant adverse effects that preclude their use in most patients. Furthermore, their administration to pediatric patients raises ethical questions, and they have no approval for pediatric use.

Physiologic Factors

Surgery generates a neuroendocrine stress response in neonates, infants, and children[5,56] resulting in undesirable alterations of the metabolic state and immune function.[57,58] Epidural anesthesia diminishes or even suppresses this stress response.[59-61]

Central blocks do not affect left ventricular function and are virtually free of measurable hemodynamic effects, at least up to the age of 8 years.[62-64] Epidural anesthesia does not result in systemic or pulmonary hemodynamic changes as measured by mean blood pressure, end-diastolic diameter of the left ventricle, ejection fraction of the left ventricle, and mean velocity circumferential fiber shortening.[65] However, pulmonary Doppler flow velocity is decreased during epidural anesthesia, probably owing to an increase in the pulmonary arterial resistance. Preloading with saline is not recommended in children and, even in adolescents, fluid therapy or injection of vasoactive agents is rarely required.

Psychological Factors

Children are frightened by new environmental conditions in the operating room and most of them cannot cope with their anxiety.[66,67] They feel abandoned by their parents and exposed to strangers who are threatening them with needles. Furthermore, children younger than 10 years of age have not acquired their complete body image and cannot clearly make a distinction between adjacent parts of their body such as forearm and arm. Young patients cannot understand the concepts of paresthesia and differential blockade ("touch" is not "pain"). Thus, localization of nerve trunks as well as anatomic spaces requires using physical methods independent of the patient's cooperation (loss of resistance seeking, neurostimulation, ultrasound techniques) (see Chapter 82).

Infants and most children cannot cope with their anxiety and fear of needles; therefore, sedation or light general anesthesia is mandatory before block procedure to avoid panic attacks and dangerous movements at the wrong point in the procedure.

Regional anesthesia has a significant psychologic impact. A pain-free postoperative course improves the morale of the patient, the family, and the nurses. Surgeons are happy to examine quiet, alert, and manageable patients. Occasionally, negative psychological effects can be observed: Persistent motor (even sensory) blocks postoperatively may be frightening to some children (3-5 years old especially) and their parents even though precise explanations had been given preoperatively as to the expected course of events during the postoperative period. This postoperative anxiety can be reduced by offering friendly environmental conditions, empathy, and additional explanations on local anesthetic pharmacology. In any case, it should be kept in mind that a motor block must be avoided when not absolutely required for surgery.

Indications, Contraindications, and Complications

Indications

Indications for regional anesthesia in children are not exactly the same as in adults, not only because surgical pathologic processes are quite different but also because regional block procedures are used as techniques of analgesia in anesthetized children rather than in conscious or lightly sedated patients.

Anesthetic Indications

Mature children and adolescents are occasionally willing to undergo their surgery under regional anesthesia while remaining conscious. If adequate analgesia can be provided by a regional block, there is no reason to refuse such management, especially for short-duration surgery.

Occasionally, such a management approach can be considered in children at risk of severe complications during general anesthesia from certain problems[68]:

- Testicular torsion or incarcerated hernia at immediate risk of rupture in nonfasted children
- Inguinal hernia repair in former preterm infants younger then 60 weeks of postconceptual age who are at risk of developing severe postoperative apneas
- Severe acute or chronic respiratory insufficiency
- Emergency conditions in children with severe metabolic or endocrine disorders
- Neuromuscular disorders, myasthenia gravis, or some types of porphyria
- Some types of polymalformative syndromes and skeletal deformities

Cervical instability (making tracheal intubation at risk of tetraplegia) is constant in Chiari syndrome and common in achondroplasia and Down syndrome. Patients with facial deformities, microstomia, and mandible abnormalities can be difficult to intubate, thus making general anesthesia a dangerous technique. Also, infants with epidermolysis bullosa are extremely difficult to manage under general anesthesia; occasionally, regional block procedures may represent an alternative with lower morbidity.[69,70]

Trauma patients with extremity lesions may greatly benefit from peripheral nerve block for alleviating pain without impeding monitoring of head trauma or hemodynamic disorders and allowing wound dressing as well as temporary stabilization of fractures, provided that appropriate precautions are taken to avoid hiding development of compartment syndromes (see later).

Intraoperative/Postoperative Analgesia and Procedural Pain

Analgesia is currently the main indication for regional blocks in children because they offer the best benefit/risk ratio for many outpatient and inpatient surgeries: orthopedic (including scoliosis surgery), thoracic, urologic, and upper and lower abdominal surgeries.[71-74] Cardiac surgery is a more controversial indication,[75,76] and many anesthesiologists are reluctant to perform neuraxial blocks in children scheduled to receive anticoagulants.

Procedural pain can easily be anticipated and thus prevented mostly by topical anesthesia or infiltration techniques.[77-79] A comparative evaluation of most regional techniques is provided in Table 81-5.

Management of Nonsurgical Pain

Relief of pain associated with some medical conditions such as herpes zoster, AIDS, mucosal/cutaneous lesions, and cancer can be achieved using regional block techniques.[80-82] Children with sickle cell disease may greatly benefit from epidural analgesia during vaso-occlusive crisis or thoracic syndromes with intractable pain by other means, provided that pain is localized to limited areas and concomitant fever is not due to bacteremia.[83,84]

Chronic Pain Relief and Palliative Care

Chronic pain is less unusual in children than commonly believed, and regional techniques such as epidural anesthesia, stellar ganglion blockade, or continuous peripheral nerve blocks may help treat this condition, especially in case of phantom limb pain and complex regional pain syndrome (CRPS).[85] Erythromelalgia, a rare but extremely painful condition, can be successfully relieved by continuous epidural analgesia.[86] Cancer pain resulting either from primary tumor or from metastases can also be controlled by regional techniques when other medications fail or produce too many adverse effects. Virtually all techniques of regional anesthesia have been reported in this ultimate management of pain in children, from epidural analgesia to intrathecal infusions to celiac or brachial plexus block.[87-89]

Nonanalgesic Indications

For certain medical conditions, analgesia is not the only benefit expected from regional blockade. Sympathetic blockade is essential to protect/improve blood supply to an upper or lower extremity in a context of severe trauma. Also, continuous epidural blockade proved to be effective in treating vascular insufficiency resulting from Kawasaki disease,[90] accidental intra-arterial injec-

Table 81-5 Evaluation of the Suitability and Benefits of Most Techniques of Regional Anesthesia in Children

Technique	Ease of Performance*	Benefit/Risk Ratio	Suitability for Catheter Placement
Neuraxial Block			
Spinal anesthesia	+ to +++	+++	No
Caudal anesthesia	+++	++++	Occasionally
Sacral epidural anesthesia	+++	+++	Yes
Lumbar epidural anesthesia	+++	+++	Yes
Thoracic epidural anesthesia	++	++	Yes
Cervical epidural anesthesia	Avoid	Very low	Avoid
Plexus and Peripheral Nerve Conduction Blocks			
Interscalene block	++	++	Occasionally
Parascalene block	+++	++++	Yes
Infraclavicular block	+++	+++	Yes
Axillary block	++++	++++	Occasionally
Psoas compartment block	+++	++	Occasionally
Femoral block	+++	++++	Yes
Proximal sciatic blocks	++ to +++	+++	Yes
Popliteal sciatic blocks	+++	++++	Yes
Distal blocks	++ to +++	+++	No (except tibial nerve at ankle)
Compartment Blocks			
Intercostal block	++	+	Occasionally
Intrapleural block	++++	0 to +	Yes
Thoracic paravertebral block	++	+ to +++†	Yes
Ilioinguinal/iliohypogastric/spermatic nerve block	++++	+++	Occasionally
Penile block	++++	++++	No
Other Techniques			
Bier block	++ to ++++	+	No
Topical anesthesia	++++	++++ (skin) + (pharyngeal/ tracheal mucosa)	No

0, nil; +, low; ++, average; +++, good; ++++, very good.
*Depends on the technique of localization.
†Intraoperative catheter placement under vision (by the surgeon).

tion of an anesthetic drug,[91] penile block with a local anesthetic containing epinephrine,[92] and severe frostbite.[93] Acute vascular insufficiency of the upper limb has also been successfully treated by axillary and stellate ganglion blocks.[94,95]

Contraindications and Limitations

Absolute Contraindications to Neuraxial Blocks

Seven medical conditions contraindicate neuraxial blocks in children: (1) severe coagulation disorders, which may be either constitutional (hemophilia), acquired (disseminated intravascular coagulation), or therapeutic; (2) severe infection such as septicemia or meningitis; (3) hydrocephaly and intracranial tumoral process; (4) true allergy to local anesthetics, a very rare condition even with aminoesters; (5) certain chemotherapies (such as with cisplatin) prone to induce subclinical neurologic lesions that can be acutely aggravated by a block procedure; (6) uncorrected hypovolemia; and (7) cutaneous or subcutaneous lesions, whatever their nature (infection, angioma, dystrophic or tumoral, tattoo) at the contemplated site of puncture. Parental refusal is a nonmedical absolute contraindication.

Depending on the clinical condition of the patient and the possibility to cure (at least temporarily) the impeding disorder, a regional block occasionally may be contemplated in spite of the existence of a medical contraindication. After correction of hypovolemia, injection of factor VIII to a hemophilic child, or effective antibiotic treatment of a septicemic patient,[96-98] a central block may be performed, provided that the expected benefits consistently outweigh the risks by comparison with other techniques of analgesia. Also, some authors consider it acceptable to perform a caudal block in children with shunt devices under protection of antibioprophylaxis.[99]

Absolute Contraindications to Peripheral Nerve Block Procedures

True allergy to local anesthetics is the only absolute medical contraindication to peripheral nerve blocks. Coagulation disorders are less hazardous than during neuraxial blocks, but it is prudent to avoid techniques with a danger of arterial trauma, especially in an area where compression is difficult or impossible (supraclavicular brachial plexus block, psoas compartment block). Septicemia does not necessarily contraindicate peripheral nerve blockade if expected benefits are significant. Hypovolemia should

preferably be corrected but does not preclude peripheral blocks because hemodynamic consequences are minimal.

Patients at Risk of Compartment Syndrome

Because pain is one of the cardinal symptoms of a compartment syndrome, any pain treatment, including regional anesthesia, is often claimed to be contraindicated because it can suppress this presenting symptom, thus delaying the rescuing surgery. Such a refusal of pain management is not acceptable both medically and ethically.[100] Fractures are very frequent in the pediatric population whereas compartment syndromes are very rare; whether or not a compartment syndrome is in progress, intense pain is a constant feature. Adequate pain management including continuous epidural analgesia[101] does not preclude early diagnosis, and this fact was confirmed by the national pediatric epidural audit in Great Britain.[102]

Excruciating pain is not a "presenting" symptom but a late—possibly too late—symptom of compartment syndrome. Patients at risk should be monitored adequately, which is not done most of the time even in university hospitals, and precautions must be taken: avoidance of closed plaster casts and elbow immobilization with an angle greater than 90 degrees,[103] closed reduction of supracondylar fractures of the humerus, repeat clinical evaluation of the distal perfusion and tissue oxygenation of the limb, and noninvasive monitoring of the intracompartmental pressure, even though this monitoring is not 100% reliable. If the risk is considered high (e.g., displaced humeral fractures, intramedullary nail fixation of tibia or radius, obtunded patients), intracompartmental pressure close to the fracture site should be invasively monitored: the procedure is easy and almost inexpensive, requiring only a venous cannula, an IV line, and a pressure gauge (as for central venous pressure measurement).[104,105]

Hemoglobinopathies

Children with sickle cell disease are prone to develop massive hemolysis in case of desaturation and undergo repeat episodes of extreme pain due to extended microthromboses when local blood flow slows down (e.g., hemoconcentration, shock, surgical tourniquet).[106,107] If there is a danger of hypoxemia (respiratory disease) or hemodynamic disorders (surgery known to produce significant blood loss, tourniquet placement), regional (especially neuraxial) blocks would better be avoided.[108]

Bone and Joint Deformities

Minor or localized malformations of the spine (hemivertebra, spina bifida occulta, Scheuermann's disease) do not preclude neuraxial blocks whereas extended malformations of vertebrae, spinal fusion, myelomeningoceles, open spina bifida, and major spondylolisthesis are contraindications. Tethered cord syndrome is not unusual and often misdiagnosed; neuraxial blockade may increase the overall morbidity of patient management because it facilitates excessive bending or extension of the spine that can occasionally damage the spinal cord forever. The diagnosis must be suspected if there is a clump of hairs or a dystrophic lesion of the skin at the lower extremity of the spinous process line or in case of minor neurologic disorders involving pelvic nerves (minimal sphincter disorders, perineal dysesthesia). Even though some authors consider that this condition is not a contraindication,[109] it is preferable to select another technique of analgesia than epidural blockade.

Many pediatric syndromes, cerebral palsy, and kyphoscoliosis are associated with bone and joint deformities that represent more of a technical difficulty than a contraindication to performing a regional block.

Preexisting Neurologic Disorders or Diseases

Controlled epilepsy is not a contraindication to regional anesthesia, including neuraxial blockade. Preexisting central nervous system disorders and degenerative axonal diseases have long been considered to be contraindications, at least relative, even though no data support the hypothesis that a regional block could worsen their course.[110] A recent pediatric study involving 139 patients showed that preexisting neurologic disorders were not associated with bad neurologic outcome (the reverse was observed) after central block procedures.[111]

Complications

Complications of regional anesthesia are basically the same as in adults. They can be classified as local, regional, and general (or systemic).

Local Complications

There are four main types of local complications:

1. Inappropriate needle insertion damaging the nerve and surrounding anatomic structures
2. Tissue coring and introduction of epithelial cells into tissues where they do not belong and where they can develop as compressive tumors (especially in the spinal canal)[112]
3. Injection of neurotoxic solutions (syringe mismatch, epinephrine close to a terminal artery)
4. Leakage around the puncture site, especially when a catheter has been introduced, which may cause partial block failure and favor bacterial contamination (very rare)

These local complications are easily avoidable by using adequate devices and applying standard precautions (appropriate dressing and bacterial precautions). Leakage around the catheter can be reduced by tunneling the catheter and applying a slightly compressive dressing.

Systemic Complications

Systemic complications usually result from accidental IV injection of local anesthetics or, less frequently, excessive dosing.[10,113] They can be life-threatening and should be managed in the same way as in adults. The major difference between adults and children is that cardiovascular complications are not preceded by neurologic signs but are concomitant with cerebral toxicity.[114]

Epidemiology

Available pediatric information is limited.[113,115] In the first report of the ASA closed malpractice claims, there were 238 pediatric cases (10% of claims) but only 7 involved children given a regional block procedure[116]; however, at that time regional anesthesia was not commonly used in American children, thus making this apparently low rate of complications meaningless. In 1996, the 1-year prospective study of the French-Language Society of Pediatric Anesthesiologists (ADARPEF) evaluated 85,412 pediatric anesthetic procedures, including 24,409 involving regional anesthesia.[117] There were 23 complications (no sequelae, no death, and no legal consequences), all following neuraxial blocks. In

2000, the Australian Incident Monitoring Study[118] included 2000 claims involving 160 pediatric cases with a regional block procedure (83 epidurals, 42 spinals, 14 brachial plexus, 4 Bier blocks, 3 ophthalmic blocks, and 14 local infiltrations); the largest single cause of complications was circulatory problems, and there were 24 drug errors (including 10 "wrong drugs" and 14 "inappropriate use"). In 2007, the British national pediatric epidural audit[102] reported 96 incidents in 10,633 epidural blocks performed:

- 56 (0.53%) were associated with the insertion or maintenance of epidural anesthesia and most were of low severity; only 1 child had residual effects from a cauda equina syndrome (following a programming error of the infusion pump).
- 40 (0.38%), mainly pressure sores (33), were believed to be associated with the epidural infusion technique.

There was a significantly higher rate of incidents in the neonatal age group, mainly because of drug errors (13) and local anesthetic toxicity (1); these incidents were not related to catheter insertion. There were 28 infection-related incidents, of which 85% were relatively minor skin infection; caudal catheters did not result in increased incidence of infections. Six children, all older than age 8 years, suffered from mild postdural puncture headache. Four patients developed a compartment syndrome, but the condition was not masked by the epidural infusion.

In conclusion, regional block procedures, mainly neuraxial blocks, are associated with the occurrence of adverse incidents (around 0.5%) that are mostly minor but occasionally severe. The majority of these complications results from insufficient precautions at the time of the block procedure (drug errors) and postoperatively (pressure sores). Also, of major importance is the fact that compartment syndrome is not hidden by a regional procedure provided that adequate monitoring is guaranteed.

Selection of Materials, Techniques, and Agents

Selection of a Suitable Block Procedure

Sound selection of block procedures is based on anatomic considerations first: sensory blockade must cover all areas from which noxious stimuli can originate (e.g., operative field, sites for skin or bone graft tissue, placement of tourniquet or drains). Then, the potential morbidity of the technique, either from the medical condition of the patient, the requested positioning, or the "intrinsic" morbidity of technique itself, must be evaluated. The anticipated duration of postoperative pain is the third most important factor to take into account because the regional technique should provide adequate analgesia until minor analgesics are sufficient. The anesthesiologist will select one of the following approaches:

- A single-shot technique with either a short-acting or a long-acting local anesthetic
- A single-shot technique with local anesthetic and adjuvants
- A catheter technique with repeat/continuous injections of local anesthetic

Equipment and Techniques Used to Identify Anatomic Spaces and Nerve Trunks

Quality of blockade depends on needle or catheter positioning in close proximity to the nerve.

These location techniques require some adaptations in infants. Cerebrospinal fluid (CSF) hydrostatic pressure is low, necessitating slow progression of the spinal needle so as not to miss CSF reflux. Ligaments are more hydrated and less densely packed, thus making the loss of resistance technique with saline less dependable than that with air (or preferably CO_2) in infants and young children. Nerve structures are more superficial, and infants' skin can be slenderized to such an extent that nerve stimulation with low current can elicit twitches even if the tip of the needle is still outside the epidermal layer. This property can be used to locate the relevant nerve ("surface mapping" or "percutaneous guidance"[119-121] and identify the cutaneous site at which twitches can be elicited with the lowest current, that is, closest to the nerve; this point will be the site of puncture. Application of ultrasound techniques in pediatric patients also requires some adaptations. For obvious reasons, small probes should be available ("jockey stick"). Because of poor mineralization of bones, especially vertebrae, ultrasound techniques allow excellent visualization of the spinal cord of neonates and small infants (see Fig. 81-1), which allows guiding the progression of an epidural needle and that of a catheter. At the same time, nerve structure is less echoic than in older patients, thus requiring both use of a good ultrasound machine and excellent knowledge of anatomy to correctly identify the relevant nerve (Fig. 81-3).

Other localization techniques are occasionally used, mostly for educational purposes. Penetration into the epidural space can be detected using an acoustic device. Electrostimulation can be used to locate the position of the needle tip or catheter within the epidural and subarachnoid space.[122-124] "Whoosh test" (injection of air into the epidural space via the sacral hiatus) and paresthesia seeking are techniques of the past that should no longer be used.

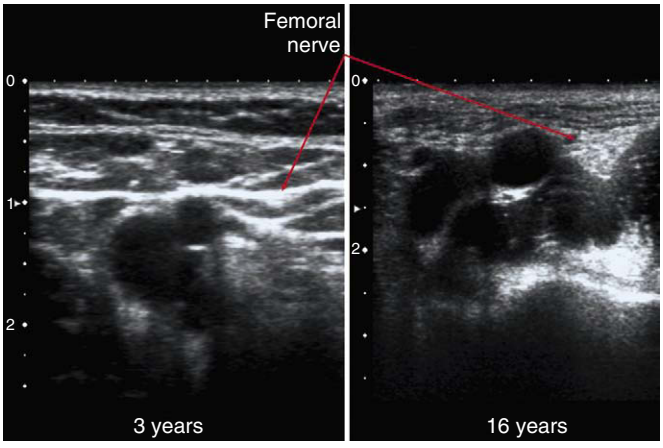

Figure 81-3 Ultrasound imaging of the inguinal area to locate the femoral nerve at different ages. The femoral nerve is clearly visible in the 16-year-old adolescent but difficult to identify in the 3-year-old child. Note the highly contrasted images of aponeuroses in the younger patient.

Selection of the Anesthetic Solution

The prerequisites for selecting a local anesthetic are not exactly the same in children as in adults because regional techniques are mostly used for analgesic purposes rather than anesthesia. The factors to be considered are (1) site and severity of surgery, (2) expected duration of intense postoperative pain, and (3) hospital stay versus early discharge. Usual doses are listed in Table 81-6.

Lidocaine and mepivacaine are preferred for outpatient surgery. For continuous infusion, levobupivacaine and ropivacaine are preferred to racemic bupivacaine owing to their safer pharmacokinetic profile. In infants younger than 3 months old, epidural infusion of ropivacaine should not be maintained for more than 36 hours.[125]

Addition of clonidine or ketamine helps improve the quality and duration of blockade without precluding early hospital discharge. In many cases, these drugs make it unnecessary to insert a catheter and establish a continuous infusion to provide adequate postoperative pain relief.

For many years, continuous epidural anesthesia was the only suitable technique for treating protracted pain. In recent years, peripheral nerve catheter techniques have proved to be effective,[72] with less morbidity and limitations than continuous epidural blockade, even allowing hospital discharge[85] and management at home in selected pediatric patients. For these techniques, continuous infusion (2 to 5 mL/hr) or on-demand injections (2 to 5 mL) of low-concentration levobupivacaine or ropivacaine (0.1 to 0.2%) represent the best and safest choice.

Selection of Block Needles and Catheters

Epidural anesthesia (sacral, lumbar, or thoracic) is performed using Tuohy needles ranging in size from 22 to 17 gauge and in length from 50 to 90 cm; shorter Tuohy needles (25 cm) would be more appropriate in neonates and infants but are not easily available. Caudal anesthesia has been performed in the past with almost all types of needles. This is no longer acceptable, and only short beveled needles (Crawford needles) with a guide sealing their lumen or IV cannulas with an introducer needle should be used.

Spinal anesthesia in premature infants can be performed using either a neonatal lumbar puncture needle (22 gauge) or, preferably, a thinner spinal needle (shorter than 50 mm). The distal end of the needle does not have the same importance as in adults because the incidence of postdural puncture headache remains (very) low in children and is not influenced by the design of the tip of the needle.[126,127] What matters the most is the distance separating the tip of the needle from its distal orifice: this distance must be as short as possible to avoid extradural leakage if the needle has not been introduced far enough through the dura mater. Pencil-point needles have no advantage in infants and young children; they do not improve the results and are even suspected to decrease the success rate by favoring subdural spread of the local anesthetic.

A summary of recommended needles for most regional block procedures in pediatric patients is provided in Table 81-7.

Safety Precautions and Discharge Criteria

Acceptable Environments for Performing a Regional Block

Regional techniques are techniques of anesthesia; therefore, they must be performed only in places where all the monitoring, anesthetic, and resuscitation equipments (including anesthetic and emergency drugs) are available. Additionally, the anesthesiologist must be assisted by staff members able to provide adequate patient monitoring and trained to help in emergency situations. The operating theater represents the best location to guarantee safe performance of any type of regional anesthesia.

Sedation and General Anesthesia

Regional procedures are performed in conscious adult patients, with or without sedation, but usually not under general anesthesia. In some pediatric patients, the same management can be offered and is sometimes requested by the child.[128] However, most children require being unconscious during the block procedure. If general anesthesia is not medically contraindicated, it is widely accepted that regional blocks be performed with the patient under light general anesthesia.[74,93,129]

Table 81-6 Usual and Maximum Recommended Doses of Local Anesthetic for Conduction Nerve Blocks (Excluding Bier Blocks and Spinal Anesthesia)

Local Anesthetics	Usual Concentrations	Maximum Dose of Plain Solutions (mg/kg)	Maximum Doses with Epinephrine (mg/kg)
Aminoesters			
Procaine	1-2	7	10
Chloroprocaine	2-3	7	10
Aminoamides			
Lidocaine	0.25-2	5 (or 400 mg)	10 (or 700 mg)
Mepivacaine	0.25-2	5-7 (or 400 mg)	Not available
Bupivacaine	0.125-0.5	2 (or 150 mg)	3 (or 200 mg)
Levobupivacaine	0.125-0.5	3 (or 200 mg)	4 (or 250 mg)
Ropivacaine	0.1-10	3 (or 300 mg)	Not available (and not recommended)

Table 81-7 Recommended Devices for Most Regional Block Procedures in Children

Block Procedure	Recommended Device	Alternate Device
Intradermal wheals and metacarpal blocks	Intradermal needles (25 gauge)	None
Subcutaneous infiltrations and field blocks	Standard intramuscular needles (21-23 gauge)	Intradermal needles (25 gauge)
Compartment blocks (thoracic paravertebral, rectus sheath, ilioinguinal-iliohypogastric, pudendal, penile)	Short (25-50 mm) and short beveled (45-55 degrees) needles	Epidural needles (intercostal block) Neonatal spinal needle
Peripheral mixed nerve blocks and plexus blocks	Insulated 21-23 gauge short beveled needles of appropriate length connected to a nerve stimulator (0.5-1 mA) Specific catheter (for continuous techniques)	Sheathed pencil-point needles Unsheathed needles only when ultrasound guidance is used Epidural catheter (for continuous techniques)
Spinal anesthesia	Spinal needle (24-25 gauge; 30, 50 or 100 mm long, Quincke bevel, stylet)	Neonatal lumbar puncture needle (22 gauge, 30-50 mm long) Whitacre spinal needle
Caudal anesthesia	Short (25-30 mm) and short beveled (45-degree) needle with stylet	IV cannula (22-18 gauge), especially for epidural catheter insertion Pediatric epidural (occasionally spinal) needle
Epidural anesthesia	Tuohy needle (22, 20, and 19/18 gauge); LOR syringe and medium epidural catheter	Crawford, Whitacre, or Sprotte epidural needles appropriately sized; LOR syringe and medium epidural catheter

LOR, loss of resistance.

Patient Monitoring and Safety Precautions During the Block Procedure

Monitoring and Anesthesia Chart

Even when general anesthesia is not used, regional techniques must be performed by an experienced anesthesiologist in an operating room environment with the usual monitoring recommended for pediatric general anesthesia, that is, electrocardiographic (ECG) tracings, blood pressure, temperature, respiratory rate, and oxygen saturation measurements. An IV line must be established before any injection of local anesthetic,[130] and vital parameters as well as the techniques and doses of local anesthetics have to be reported on a detailed anesthesia chart.

Technique of Injection

Techniques in adults and children are similar. Of prime importance is to evaluate the effects on ECG tracings of a test dose containing epinephrine (0.1 mL/kg up to 3 mL containing 0.5-1 µg/kg of epinephrine) for 30 to 60 seconds: Any elevation of ST segment or increase in T-wave amplitude,[131-135] followed by an increase in blood pressure[136] but only occasionally by tachycardia, suggests inadvertent IV injection and necessitates cessation of the procedure; when epinephrine is contraindicated, isoproterenol (0.05 to 0.1 µg/kg) should be used instead.[137]

Assessment of the Block

After every block procedure, the quality and extension of analgesia must be evaluated before surgical incision. However, this evaluation is difficult, even in conscious children. Gentle skin pinching is the most dependable technique of sensory testing, especially in lightly anesthetized children. Postoperatively, this evaluation should be comparative (blocked versus nonblocked areas) and requires that the child has gained the confidence of the caregiver, cannot see what he or she is doing, and is not influenced either by the caregiver or the family. Electrical stimulation using a nerve stimulator at different threshold intensities proved to be suitable in healthy volunteers but available data on children are limited. Skin temperature is not suitable, and whether pupillary reflex dilation of 0.2 mm is sensitive to the loss of analgesia it is not clinically useful.[138]

Prevention of Irrelevant Medicolegal Claims

Whenever something wrong happens to a patient after a regional procedure has been performed, the first condition incriminated is the block procedure even though on closer analysis it is rarely the cause of the alleged consequence or damage. To minimize irrelevant medicolegal claims, the recommendations listed in Table 81-8 should be followed whenever possible.

Postoperative Monitoring in the Recovery Room

After combined regional and general anesthesia, all children must be transferred to a PACU where the stability of their respiratory and hemodynamic status is checked as following any general anesthesia. In addition to this standard postanesthetic care, they require repeat evaluations of the anesthetized area. In case of motor blockade, which should be avoided as often as possible, it is important to verify that its distribution corresponds to the area supplied to the blocked nerve. Motor blockade is a stressful condition: The children (and their parents) should be comforted, and the information that it is just a time-limited condition should be repeated. Patient positioning must be carefully and regularly checked to avoid pressure points. Anesthetized areas must also be protected from patients' inadequate behavior, imprudence, or attempts to remove dressings. The possibility that a compartment syndrome is evolving must be always kept in mind, and both the

Table 81-8 Basic Safety Recommendations for Any Type of Regional or Local Anesthesia Aiming to Avoid Irrelevant Medicolegal Claims

1. Evaluate carefully the physical status of the patient and ask for complementary laboratory, radiographic, or any other examination whenever useful.
2. Select the least hazardous technique for a given block.
3. Provide detailed explanations concerning the scheduled anesthetic management, including beneficial as well as potentially detrimental effects, even in emergency situations.
4. Discuss the possibility of block failure and explain what replacement procedure(s) will then be used.
5. Obtain written consent for anesthesia care.
6. Manage the patient in the same way and with the same monitoring procedures as recommended for the same surgical procedure under general anesthesia.
7. Fill in an anesthesia chart detailing the monitoring procedures, vital parameters, techniques and doses used, and adverse effects if any.
8. Treat all complications and provide full details with precise timing.
9. Transfer all pediatric patients to a PACU requesting appropriate monitoring of vital function and repeat evaluations of the extension and quality of blockade; data are to be reported on a detailed postanesthetic chart, and discharge should be allowed only when objective signs of recovery are obtained.
10. Keep hospitalized at least overnight all patients given epidural or intrathecal morphine in units where their respiratory function will be regularly/continuously monitored (hourly for the first 6 hours, then every 2 hours).

hemodynamic status of the relevant limb and the quality of analgesia must be repeatedly evaluated.

Urinary retention can be of concern after neuraxial blocks. In many institutions, however, voiding is not requested before discharging the child. In infants and disabled children it may be prudent to keep them in the PACU until they have urinated or to check their bladder content with an ultrasound probe, especially after hypospadias repair, because the incidence of urinary retention is greater than usual in this surgery.[139]

Adults operated on under regional blockade often bypass the recovery room. In children, even if no sedative has been given, it is not wise to do so: Adequate monitoring and skilled assistance improve recovery from immediate postoperative incidents.[140] After short procedures especially, sudden cessation of external stimulation may unmask some compensated adverse effects (hemodynamic and respiratory especially) that will not be harmful if detected early. Also, as detailed earlier, ropivacaine and, to a lesser extent, levobupivacaine, have both a longer Tmax (up to 2 hr) and Cmax in infants; therefore, after short-duration surgeries, these patients may leave the operating room before local anesthetic plasma peak concentration has been reached. It is safer to keep them monitored in a PACU up to 2 hours after the block procedure.

Discharge Criteria After Single-Shot Procedures

Discharge from the PACU depends on the same criteria as following general anesthesia (pediatric adaptation of Aldrete score or specific scoring method in use in the relevant institution); in the absence of motor blockade, children may usually be discharged within 30 minutes. In other cases, discharge depends on the behavior of the child. Partial restoration of motor function is mandatory, even in quiet children with caring families. Boisterous children should not leave before motor functions have been fully restored; additionally, protective dressings (including casts) may be useful to prevent harm to the operated limb.

Persistence of sensory blockade is not a contraindication to early discharge unless the familial environment is really inadequate. Pain medication should be systematically prescribed and administered on a regular basis to prevent the return of intense pain at home, when the sensory block is no longer effective.[141]

Most additives do not preclude early discharge except for epidural/intrathecal opioids, especially morphine, which necessitate that the child stay hospitalized overnight.

Management and Follow-up of Continuous Techniques

Children with repeat, on-demand, or continuous epidural infusion should remain hospitalized to be adequately monitored. Occasionally, a few selected patients can be allowed to return home with an epidural catheter, mostly in a context of chronic pain or cancer pain in terminally ill children.

Adult patient with continuous techniques of peripheral nerve blockade can be returned home provided surgical care does not require hospital stay. These continuous techniques are rather new in pediatrics[73] and not yet widely used. In one institution, children suffering from complex regional pain syndrome were treated at home with peripheral nerve catheters.[85] Such management will probably gain wider acceptance in the near future but, currently, it should be considered under evaluation.

Neuraxial Blocks

Caudal Anesthesia

Caudal anesthesia is the oldest and still most commonly used technique of epidural blockade in children. It is performed via the sacral hiatus, through the sacrococcygeal membrane. Caudal anesthesia considerably decreases stress hormone response to surgery[142-144]; therefore, fasted infants are prone to develop hypoglycemia if intraoperative fluids do not contain any glucose.

Anatomy of the Sacral Hiatus

The sacral hiatus is a V-shaped aperture resulting from the lack of dorsal fusion of the fifth and often fourth sacral vertebral arches. It is limited laterally by two palpable bony structures, the sacral cornua, and it is covered by the sacrococcygeal membrane (sacral continuation of the ligamenta flava). The distance separating the summit of the sacral hiatus and the dural sac ending is 30 ± 10.4 mm (range: 13.6 to 54.7 mm) in children aged 10 months to 18 years.[145] Mean distance from skin to anterior sacral wall is 21 mm (extremes: 10 to 39 mm) between 2 months and 7 years of age.[146] The distance from skin to the epidural space is hardly influenced by the age and weight of the patient (Fig. 81-4): 25-mm-long needles are long enough to reach the sacral epidural space

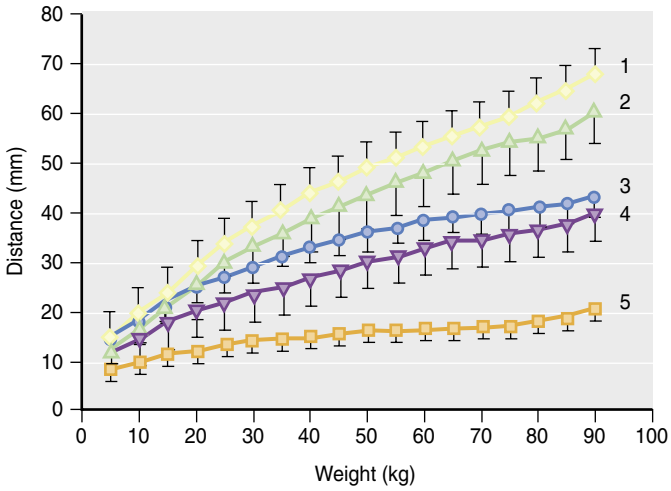

Figure 81-4 Distance from the skin to the epidural and subarachnoid spaces at different intervertebral levels and through the sacral hiatus. 1, Spinal anesthesia; 2, lumbar epidural approach (midline); 3, thoracic epidural approach (midline); 4, sacral epidural approach; 5, caudal approach.

and short enough to prevent inadvertent dural puncture in most patients.

With growth, the axis of sacrum changes: the sacral hiatus becomes more difficult to identify and may even close.[147] Concomitantly, the epidural fat becomes more densely packed, thus reducing the spread of local anesthetics. These changes make caudal anesthesia less suitable and more difficult to perform in children older than 6 to 7 years of age.

Indications and Contraindications

Caudal anesthesia is recommended for most surgical procedures of the lower part of the body (mainly below the umbilicus), including inguinal hernia repair, urinary and digestive tract surgery, and orthopedic procedures on the pelvic girdle and lower extremities.[148,149] It is usually performed in lightly anesthetized patients but can be used as the sole anesthetic regimen in fully awake ex-premature infants younger than 50 to 60 weeks of postconceptual age after local anesthesia of the skin covering the sacral hiatus, either as a single-shot technique[150,151] or after placement of an epidural catheter allowing repeat/continuous injection of local anesthetics.[152,153]

Specific contraindications include major malformations of the sacrum (myelomeningocele, open spina bifida), meningitis, and intracranial hypertension.

Technique

The technique is performed with the patient in the semiprone or, especially in nonanesthetized premature infants, in the prone position either with a rolled towel slipped under the pelvis or with the legs flexed in the "frog" position. The two sacral cornua limiting the V-shaped sacral hiatus are located by palpation along the spinal process line at the level of the sacrococcygeal joint (Fig. 81-5). The hiatus along with the two posterior superior iliac crests is claimed to form an equilateral triangle but, in clinical practice, this assumption does not help in locating the hiatus when palpation is not informative.

Caudal anesthesia is basically a single-shot technique. Occasionally, placement of an epidural catheter for repeat/continuous infusion is contemplated. The "normal" length of catheter to be introduced into the epidural space is 2 to 3 cm, as for any epidural block. Because the epidural fat is very fluid in infants, a longer distance can be inserted to reach lumbar or even thoracic levels: this technique should be considered with caution, by experts only, and the final position of the tip of the catheter must be controlled because it is misplaced in 28% of cases.[154] This is usually achieved by obtaining a contrast-enhanced radiograph, but other techniques are available:

- Neurostimulation at rather high intensities (however, safety of this technique is not established)[122,155]
- Recording ECG tracings from the metallic wire of the catheter and comparing them with those obtained from an electrode placed on the spinous process line, at the level where the tip of the catheter should be placed. The position is correct when the two tracings are identical.[156] This technique is very elegant and noninvasive, but the "second" ECG tracing is not easily readable in some patients (especially when they are conscious and moving).
- Ultrasound guidance,[157] which is the most promising noninvasive technique but still under evaluation

Catheter tunneling has been recommended to decrease the risk of bacterial contamination.[158] The dosage prescription scheme of Armitage that was published many years ago still remains the most dependable[159]:

- With 0.5 mL/kg, all sacral dermatomes are blocked.
- With 1.0 mL/kg, all sacral and lumbar dermatomes are blocked.
- With 1.25 mL/kg, the upper limit of anesthesia is at least midthoracic.

However, when 1.25 mL/kg is injected there is a danger of excessive rostral spread (above T4)[160]; it is therefore preferable not to administer more than 1.0 mL/kg of local anesthetic.

When a catheter has been inserted, repeat injections must be reduced, as detailed earlier (see "Pharmacokinetics") to avoid systemic toxicity. The second injection should be made no earlier

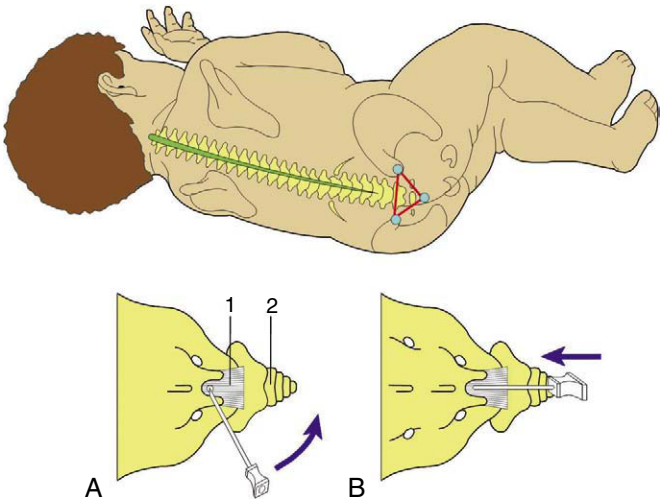

Figure 81-5 Caudal block procedure. **A,** Insertion of the needle at right angles to the skin. 1, Coccyx; 2, Sacrococcygeal membrane. **B,** Cephalic redirection of the needle after piercing the sacrococcygeal membrane.

than 60 minutes (for a short-duration local anesthetic) or 90 minutes (for a long-duration local anesthetic) after the first one and should consist of half of the initial dose. Further injections should be reduced to half of the second dose (i.e., one sixth of the initial dose) while respecting the same delays.

Specific Complications

Complications of caudal anesthesia are infrequent and usually minor[102,117] when adequate devices are used. Delayed postoperative voiding was an issue years ago when preoperative fasting was excessively prolonged, but this should not be an issue anymore and true urinary retention is (very) rare. Block failure is not unusual (3% to 5%), especially in children older than 7 years of age, but even in younger patients the failure rate can be rather high.[136]

Intervertebral Epidural Anesthesia

Anatomy and Physiology of the Epidural Space

The epidural space surrounds the spinal cord and the meninges from the foramen magnum to the sacral hiatus. Limited posteriorly by the vertebral laminae and the ligamenta flava, it communicates quite freely with both the paravertebral spaces and the root sleeves. In the "dural cuff" region, near the spinal ganglia, it is intimately connected with the subarachnoid space owing to protrusion of arachnoid granulations, which are easily traversed by local anesthetics. It contains blood vessels and lymphatics and is filled with loose fat in infants and in children up to 6 to 8 years of age.

The line joining the two iliac crests (Tuffier's line) crosses the spinous process line at the L5-S1 level up to 1 year of age instead of at L4-L5 as in older children and adults.[161] Bending the spine (as for performing an epidural block) does change the level at which Tuffier's line crosses the spine in 58.3% of patients.

Epidural injections result in considerable pressure changes. After placement of a 20-gauge epidural catheter in 20 infants, Vas and coworkers measured the following changes[162]:

- Pressure on penetrating the epidural space: 1 ± 10 mm Hg (extremes: −17 to +16 mm Hg)
- Peak pressure during injection of a local anesthetic at 1 mL/min: 27.8 ± 18.6 mm Hg with residual pressure of 12 ± 5.5 mm Hg 1 minute after completion of injection
- Peak pressure during injection of a local anesthetic at 0.5 mL/min: 15.2 ± 9.5 mm Hg with residual pressure of 14.8 ± 5.4 mm Hg 1 minute after completion of injection

As previously mentioned, young children tolerate epidural anesthesia well without any significant blood pressure change or bradycardia.[62,64]

Indications and Contraindications

Epidural anesthesia is recommended for all major abdominal, retroperitoneal, pelvic, and thoracic[163,164] surgeries, including pectus excavatum repair[165] and scoliosis surgery,[166] preferably with a two-catheter technique.[167] The technique is also used for cardiac surgery in a few institutions,[76,168] but this indication is controversial and most authors consider it contraindicated due to anticoagulation.

The intervertebral level at which the epidural space should be approached is a matter of debate and depends both on the patient's age and on the experience of the anesthesiologist. When a single-shot technique is planned for a surgery below the umbilicus, a caudal approach is most often selected in infants and young children and a lumbar approach is used in older patients. When catheter placement is contemplated it is preferable to select a lumbar approach in all patients to decrease the risk of bacterial contamination from anal proximity even though this is rare.[102]

When sensory blockade of high thoracic dermatomes is required, the most reliable approach is a thoracic epidural block, which requires expertise because the spinal cord could be damaged. When the anesthesiologist is not used to performing thoracic epidural blocks in infants, some authors recommend a caudal approach with cephalic insertion of a catheter over a long distance to reach thoracic levels.[169] This technique, however, requires experience, too, and luck: The catheter is misplaced in almost 30% of cases even in experienced hands,[154,170] serious complications are possible (e.g., spinal cord/vessel trauma during insertion, bacterial contamination, breakage or buckling around a nerve root on removal attempts).[171-173]

Specific contraindications to epidural anesthesia include severe malformations of the spine and the spinal cord (not spina bifida occulta), intraspinal lesions or tumors, and, for most authors, tethered cord syndrome. In most instances, epidural anesthesia should be avoided in children with a history of hydrocephalus, elevated intracranial pressure, unstable epilepsy, or reduced intracranial compliance, but these disorders are not absolute contraindications, depending on the context.[174] Also, previous surgery on the spine usually makes epidural (and spinal) anesthesia technically difficult or impossible, but they are not contraindications unless there are underlying lesions of the spinal cord.

Techniques

Lumbar Epidural Anesthesia

The lumbar epidural space is usually approached in anesthetized patients via a midline route below the L2-L3 interspace, which represents the lower limit of the conus medullaris. A paramedian approach can be used instead in cases of spinous process anomaly or spine deformity. The child is positioned in the semiprone position with the side to be operated lowermost and the spine bent to enlarge the interspinous spaces (Fig. 81-6). The sitting position can be used in conscious patients.

Medium selection for the loss of resistance (LOR) technique has elicited considerable debates in the past. In infants, the most dependable is gas (air or, preferably, CO_2), whereas in children older than 8 to 10 years saline is as reliable as it is in adults.

The distance from the skin to the epidural space is correlated with patient's age and size (see Fig. 81-4), but 1 mm/kg is a useful approximation between 6 months and 10 years of age. Use of an ultrasound probe allows precise measurement of the distance from skin to ligamenta flava (see Fig. 81-1).

When the tip of the needle has penetrated the epidural space, the LOR technique syringe is disconnected: no reflux of biologic fluid (blood or CSF) should appear at the hub. The next step consists of injecting the local anesthetic at a slow speed, either through the epidural needle or through a catheter. Progressive displacement of the dura mater can be visualized by placing an ultrasound probe in line with the spinous process line during injection in infants younger than 2 years of age.[175] When a catheter is inserted, it should not be introduced more than 3 cm in

Table 81-9 Usual Doses and Infusion Regimens for Epidural Anesthesia in Pediatric Patients

Agent	Initial Dose	Continuous Infusion (Max. Doses)	Repeat Injections
Bupivacaine, levobupivacaine	*Solution*: 0.25% with 5 µg/mL (1/200,000) epinephrine *Dose:* <20 kg: 0.75 mL/kg 20-40 kg: 8-10 mL (or 0.1 mL/year/number of metameres) >40 kg: same as for adults	*<4 mo:* 0.2 mg/kg/hr (0.15 mL/kg/hr of a 0.125% solution or 0.3 mL/kg/hr of a 0.0625% solution) *4-18 mo:* 0.25 mg/kg/hr (0.2 mL/kg/hr of a 0.125% solution or 0.4 mL/kg/hr of a 0.0625% solution) *>18 mo:* 0.3-0.375 mg/kg/hr (0.3 mL/kg/hr of a 0.125% solution or 0.6 mL/kg/hr of a 0.0625% solution	0.1 to 0.3 mL/kg every 6-12 hr of a 0.25% or 0.125% solution (according to pain scores)
Ropivacaine	*Solution:* 0.2% *Dose:* same regimen in mL/kg as for bupivacaine (see above)	Same age-related infusion rates in mg/kg/hr as for bupivacaine (usual concentration of ropivacaine: 0.1%, 0.15%, or 0.2%) Do not infuse for more than 36 hr in infants < 3 mo	0.1 to 0.3 mL/kg every 6-12 hr of a 0.15% or 0.2% solution (according to pain scores)
Adjuvants	Avoid in infants < 6 mo Fentanyl (1-2 µg/kg) or sufentanil (0.1-0.6 µg/kg) or clonidine (1-2 µg/kg)	*Select only one additive:* Fentanyl: 1-2 µg/mL Sufentanil: 0.25-0.5 µg/mL Morphine: 10 µg/mL Hydromorphone: 1-3 µg/mL Clonidine 0.3 at 1 µg/mL of solution	Morphine (without preservatives): 25-30 µg/kg every 8 hr

order to avoid buckling, knotting, and lateralization of blockade or erratic migration. Tunneling the catheter reduces the incidence of accidental removal and bacterial contamination.[176] Catheters inserted over a long distance have to be controlled in the same way as for caudal catheters.

The volume of anesthetic solution depends on the upper level of analgesia required for completion of the surgery; around 0.1 mL per year of age is necessary to block 1 neuromere.[177] Usual volumes of injectate range from 0.5 to 1 mL/kg (up to 20 mL), and the upper limit of sensory blockade ranges between T9 and T6 in more than 80% of patients.

Single-shot epidural blocks are appropriate for many pediatric surgeries, especially when adjuvants such as clonidine (1-2 µg/kg), preservative-free ketamine (0.25-0.5 mg/kg), and, in appropriate indications, morphine (30 µg/kg) are co-administered. Major operations resulting in long-lasting postoperative pain require placement of an epidural catheter and postoperative infusion of local anesthetics (Table 81-9).

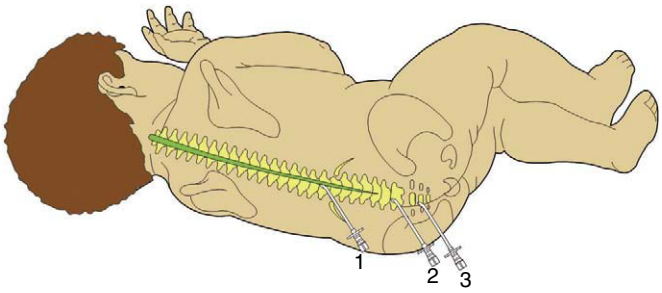

Figure 81-6 Epidural block procedures. 1, Thoracic approach (midline route); 2, lumbar approach (midline route); 3, sacral intervertebral approach.

In mature children understanding the concept of patient-controlled analgesia and willing to use it, patient-controlled epidural analgesia (PCEA) can be an interesting option. A prospective study involving 128 children older than 5 years of age reported a 90.1% success rate; PCEA was stopped in 6.1% of children because of adverse effects and only in 3.8% because of inadequate analgesia.[178] The local anesthetic was either 0.0625% or 0.125% bupivacaine with fentanyl (2 to 10 µg/mL); background infusion rate was less than or equal to 0.2 mL/kg/hr, and 1- to 3-mL bolus doses were permitted every 15 to 30 minutes with a 0.4-mg/kg/hr maximum dose of bupivacaine.

Another prospective study involving 58 children (age range: 7-12 years) undergoing lower extremity orthopedic surgery compared continuous epidural infusion of 0.2% ropivacaine (0.2 mL/kg/hr) with PCEA with background infusion of 1.6 mL/hr and 2-mL bolus doses (lock-out interval: 10 min) of the same solution. Pain scores were excellent and identical in both groups, but children from the PCEA group required half the doses of ropivacaine on a hourly basis as compared with the continuous infusion group.[179]

Sacral Epidural Anesthesia

Because sacral interspaces remain nonfused until early adulthood, the sacral epidural space of children can be approached from posteriorly via the S2-S3 interspace, which is identified by palpation 0.5 to 1 cm below the line joining the two posterior superior iliac spinous processes,[180] but any other sacral interspace can be used.[181] The procedure is the same as for a lumbar approach. Because sacral spinous processes are atrophic, the Tuohy needle can be oriented cephalad or, preferably, caudad to contact the dura mater with the convex part of the needle tip, thus reducing the danger of accidental dural penetration. Attention must be paid to the closer skin proximity of the epidural space as com-

pared with lumbar approaches (see Fig. 81-4). If mandatory, an epidural catheter can be inserted (using the same technique as for lumbar epidural catheter placement) to provide long-lasting postoperative pain relief.

Sacral epidural anesthesia is an alternative to caudal anesthesia, either in infants when skin lesions contraindicate a caudal approach or in children older than 6 to 7 years of age, in whom caudal anesthesia becomes more difficult and less reliable. The same volumes and doses of local anesthetic as for a caudal anesthesia are administered. Ultrasound imaging can be used to precisely evaluate the distance from skin to epidural space and, in infants mainly, visualize both the progression of the needle and catheter and the spread of the local anesthetic.

Thoracic Epidural Anesthesia

Thoracic epidural blocks are indicated for major operations requiring long-lasting pain relief, thus requiring placement of an epidural catheter to allow repeat injections or continuous infusion of local anesthetic. These are not commonly used techniques in children because indications are limited to thoracic and upper abdominal surgery and there is fear of spinal cord damage. In children younger than 1 year of age, the procedure is similar to that for a lumbar approach, with a needle insertion perpendicular to the spinous process line, because the spine displays a single flexure, especially when bent. As the patient grows and the flexure develops, the technique becomes progressively similar to thoracic approaches in adults, requiring cephalic orientation of the Tuohy needle up to a 45-degree angle to the skin. A paramedian approach can be used instead, but it is rarely required in children.

In infants, ultrasonography makes visible the dura mater, the progression of the Tuohy needle, and, in many cases, the progression and final position of the tip of the epidural catheter.[182]

Cervical Epidural Anesthesia

There are no surgical indications for cervical epidural blockade in children. Very rarely, the technique can be contemplated for chronic pain patients or to prevent phantom limb pain before an amputation of the upper arm at the scapular level (osteosarcoma of humerus), which is done almost exclusively in adolescents. The block procedure is the same as in adults.

Specific Adverse Effects and Complications

Specific complications are the same as those reported in adults but with a lower incidence and severity.[102,117]

Spinal Anesthesia

Anatomy and Physiology

The spinal cord and dural sac of infants younger than 1 year of age end at a lower level than in older patients (see "Caudal Anesthesia," earlier). Also, the volume of CSF varies considerably according to patient's age, from more than 10 mL/kg in neonates, to 4 mL/kg in infants weighing less than 15 kg, to 3 mL/kg in children, to 1.5 to 2.0 mL/kg in adolescents and adults. The spinal/cerebral distribution of CSF also varies with age: Half the CSF volume is located within the spinal subarachnoid space versus only 25% in adults. This has considerable pharmacokinetic consequences and explains why larger doses of local anesthetics are required for spinal anesthesia in infants and young children.

CSF hydrostatic pressure is lower in infants in the dorsal recumbent position[183] and further decreased during general anesthesia. In performing a spinal block, the progression of the needle must be slow to detect CSF reflux before the needle had been advanced farther.

Children older than 5 years of age behave like adults after spinal anesthesia, whereas younger patients remain hemodynamically stable, without significant hypotension or bradycardia,[184] even in case of cardiac malformations.[185] However, a decrease in mean arterial pressure during the first 10 minutes after injection of 0.8 mg/kg of 0.5% bupivacaine was reported in infants aged 1.5 to 5 months.[186] This decrease was time limited, well tolerated, and rapidly corrected by IV fluids. Similar results with concomitant decrease in cerebral blood flow were reported in former preterm infants of 41 weeks of postconceptual age.[187]

Indications and Contraindications

Spinal anesthesia has limited indications in pediatric patients. One of these is inguinal hernia repair in former preterm infants younger than 60 weeks of postconceptual age[188,189] who are prone to develop postoperative apnea after general anesthesia or even light sedation.[190] However, even after pure spinal anesthesia, apneas may occur postoperatively (as they may preoperatively) and it is prudent to keep at-risk infants hospitalized. Other indications are scarce, mainly for elective lower abdominal or lower extremity surgery[191-193] and, occasionally, for cardiac surgery or cardiac catheterization,[194,195] but these indications are controversial.

Technique

The technique of spinal anesthesia is that of lumbar puncture. It can be performed with the patient in the lateral decubitus position or sitting.

Currently, hyperbaric tetracaine and bupivacaine are the most commonly used local anesthetics.[196] Isobaric bupivacaine can be used instead.[191] Ropivacaine[197] and levobupivacaine[198] may become the standard of the future but are not currently approved for spinal administration in pediatric patients. Usual doses are given in Table 81-10 for infants and in Table 81-11 for children.

Adverse Effects and Complications

Spinal anesthesia is technically difficult in neonates and infants; the overall failure rate ranges from 10% to 25%.[190,199] Short dura-

Table 81-10 Usual Doses of Local Anesthetics for Spinal Anesthesia in Neonates and Former Preterm Neonates Younger than 60 Weeks of Preconceptual Age (up to a Weight of 5 kg)

Local Anesthetic	Dose (mg/kg)	Volume (mL/kg)	Duration (min)
Tetracaine 1%	0.4-1.0	0.04-0.1	60-75
Tetracaine 1% with epinephrine	0.4-1.0	0.04-0.1	90-120
Bupivacaine 0.5% isobaric or hyperbaric	0.5-1.0	0.1-0.2	65-75
Levobupivacaine 0.5%	1.0	0.2	75-88
Ropivacaine 0.5%	1.08	0.22	51-68

Table 81-11 Usual Doses of Local Anesthetics for Spinal Anesthesia in Children and Adolescents

Local Anesthetic	Usual Dose(s)
0.5% Isobaric or hyperbaric bupivacaine	5 to 15 kg: 0.4 mg/kg (0.08 mL/kg) >15 kg: 0.3 mg/kg (0.06 mL/kg)
0.5% Isobaric or hyperbaric tetracaine	5 to 15 kg: 0.4 mg/kg (0.08 mL/kg) >15 kg: 0.3 mg/kg (0.06 mL/kg)
0.5% Isobaric levobupivacaine	5 to 15 kg: 0.4 mg/kg (0.08 mL/kg) 15-40 kg: 0.3 mg/kg (0.06 mL/kg) >40 kg: 0.25 mg/kg (0.05 mL/kg)
0.5% Isobaric ropivacaine	0.5 mg/kg (max 20 mg)

tion of blockade and lack of residual analgesia are important limitations: Alternative (awake caudal anesthesia) or complementary techniques (ilioinguinal/iliohypogastric block) are often contemplated. Postdural puncture headache is rare in children younger than 8 years of age but not exceptional, and its incidence may be increased with use of pencil-point spinal needles.[200] All complications reported after lumbar epidural blockade can occur after spinal anesthesia.

Upper Extremity Conduction Blocks

Anatomic Considerations

Nerve supply to the upper extremity depends mainly on the brachial plexus formed by the union of the ventral rami of the fifth cervical to the first thoracic spinal nerves within the interscalene space. As in adults, brachial plexus nerve fibers redistribute first to three trunks (within the interscalene space), then to three divisions at the level of the clavicle under which they lie, then to three cords surrounding the axillary artery before splitting into terminal nerves in the axilla. Because of this complicated redistribution of nerve fibers, distribution of anesthesia varies considerably depending on the level at which the local anesthetic is injected.

The most important anatomic difference between infants and adults pertains to the upper part of the lung and apical pleura that penetrates the neck, above the plane formed by the clavicle and first rib (superior thoracic aperture). Subclavian vessels and the lower division of the plexus are impacted in the apical pleura, thus making any peri-subclavian approach at major risk of pleural penetration. The concept of peri-neurovascular sheath has been challenged in spite of strong embryological and anatomical evidences, but it received additional confirmation in a recent radiological study, and even the volume of the "axillary tunnel" could be precisely measured (5.1 to 9.5 mL in adults).[201]

Ultrasound imaging allows precise localization of the parietal pleura and subclavian/axillary vessels, thus improving the safety of supraclavicular as well as infraclavicular approaches, provided the tip of the block needle can be continuously seen during the procedure.

Indications and Contraindications

Indications for brachial plexus blocks include emergency as well as elective surgery of the upper extremity in conscious or anesthetized children.[202-205] These blocks are particularly useful for outpatient surgery and elicit a high degree of patient satisfaction. Axillary blocks are considered first, especially when the lesions involve the forearm and the hand, because they are virtually free of complications. Infraclavicular paracoracoid approaches are being increasingly used with the development of ultrasound guidance: The technique is easy and provides complete blockade of the upper extremity; catheter placement is easier and more comfortable than at axillary levels; catheter immobilization and protection against accidental removal are also easier.

Supraclavicular blocks are recommended when the lesion (or a tourniquet) is located on the proximal part of the arm, including the elbow. Peri-subclavian approaches should not be used in infants owing to the proximity of the apical pleura, even with the help of ultrasound imaging. Finally, the safest techniques are the parascalene and the modified interscalene approach (the tip of the block needle is placed virtually at the same place in the interscalene space with both techniques).

Distal nerve blocks are used either as complementary blocks when distribution of anesthesia is incomplete after a more proximal block or for distal lesions (surgery involving one finger only).

Brachial Plexus Blocks below the Clavicle

Axillary Blocks

Axillary block is the most common approach to the brachial plexus in pediatric patients, aiming to contact the cords and terminal nerves of the plexus in the axilla. The child is placed in the supine position[202] with the ipsilateral arm both supinated and abducted by 90 degrees. Depending on the technique used to identify the position of the nerves, muscle twitches (with neurostimulation) are elicited in the forearm and hand or the needle tip is visualized along the axillary artery, close to one of the three main cords (preferably the posterior one) and, often, close to the coracoid process of the scapula.

A most useful variant of this technique is the transcoracobrachialis approach.[202] The block needle is introduced posteriorly at the crossing of the coracobrachialis muscle with the lower border of the pectoralis major muscle (Fig. 81-7). The needle is advanced posteriorly toward the medial border of the humerus through the upper and lateral part of the coracobrachialis muscle (within which runs the musculocutaneous muscle).

With neurostimulation, the musculocutaneous nerve is usually the first nerve encountered (it will be preferably blocked on removal of the needle); the needle is moved deeper until it crosses the perineurovascular sheath[201] and elicits twitches in the muscles of the hand and forearm. At this level the cords have split into terminal nerves and the median nerve is usually contacted first: the local anesthetic is then injected and the needle is removed while a small volume (0.1 mL/kg up to 5 mL) is injected close to the musculocutaneous nerve. There is no need to try to locate each nerve and perform multiple injections.[206]

With ultrasound guidance, a high-frequency probe is placed perpendicular to the major axis of the arm ("short axis"

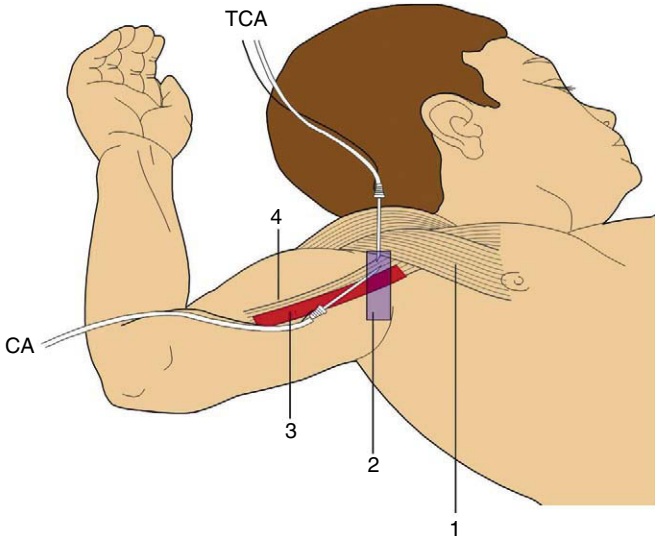

Figure 81-7 Axillary approaches to the brachial plexus. CA, classic approach; TCA, transcoracobrachialis approach; 1, pectoralis major muscle; 2, axillary artery; 3, coracobrachialis muscle.

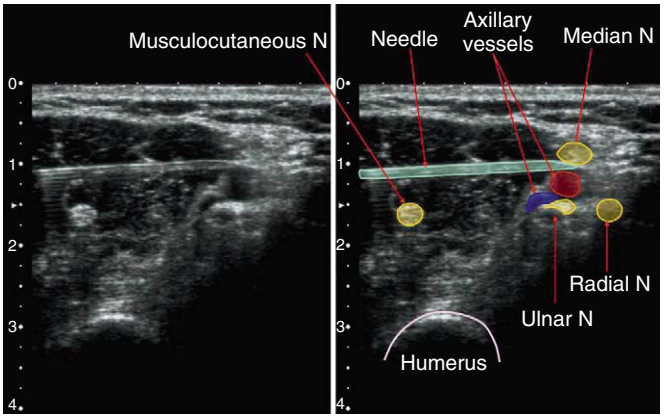

Figure 81-8 Ultrasound-guided axillary block (transcoracobrachialis approach).

[SA]). The needle can be visualized throughout the procedure as it progresses in the plane of the ultrasound beam (SAX-IP, "short axis—in plane") (Fig. 81-8); its tip can be precisely placed close to each of the three main nerves and, on removal of the needle, close to the musculocutaneous nerve. A catheter can be inserted in the axillary neurovascular sheath for continuous infusion, but its immobilization at this level is difficult and, usually, another approach is preferred when continuous infusion is contemplated.

Local anesthetics are selected according to the mandatory duration and intensity of sensory blockade (see earlier). The volume of injectate is critical and depends on the technique used to locate the nerves. With neurostimulation, no information is obtained regarding the circumferential spread around nerve trunks; thus, recommended volumes of injection are based on the probability to obtain complete blockade. These volumes are listed in Table 81-12 for single-shot techniques and in Table 81-13 for continuous infusions. With ultrasound-guided techniques, the circumferential spread of local anesthetics can be clearly seen and once a complete "donut" surrounding the relevant nerve trunk is obtained there is no need to inject additional volumes of local anesthetic.

Axillary blocks are very safe. Accidental arterial puncture is the most undesirable incident/accident, which may occasionally result in transient vascular insufficiency or a compressive hematoma.

Intraneural injection is the most feared complication. It is usually thought to be the main cause of permanent nerve damage and mostly undetected in the patient under general anesthesia. In a prospective study on 26 volunteers (that surprisingly got approval from an ethical committee), Biegeleisen deliberately attempted to penetrate axiallary nerve trunks under echoguidance. A total of 72 deliberate intraneural injections were made and the patients were evaluated after the injection and 6 months later. No motor or sensory deficits were observed. Whether the design of this study is debatable, the results are interesting in showing that intraneural injection might not be as detrimental as commonly believed and might even be innocuous provided no intrafascicular injection (which elicits strong resistance to injection and excruciating pain) is made. However, such intraneural injections should be avoided as often as possible, especially when US imaging is suggestive (tip of the needle within the nerve path and increase in nerve diameter when a fraction of the LA is being injected).

Thoracic Infraclavicular Blocks

Infraclavicular blocks have gained considerable interest in recent years, especially with the development of ultrasound guidance. They consist of approaching the divisions (close to the clavicle) or the cords (close to or below the coracoid process) of the brachial plexus. There are basically two main approaches: (1) midclavicular and (2) paracoracoid; both are performed with the patient in the dorsal recumbent position.[207] A catheter can be rather easily inserted and safely secured, which is not the case in the axilla. The same local anesthetics as for any peripheral conduction block can be used. Usual volumes of local anesthetics are listed in Table 81-12 for single-shot procedures and in Table 81-13 for infusion regimens.

Table 81-12 Recommended Volumes of Local Anesthetic for Single-Shot Upper Limb Blocks with Neurostimulation by Patient Weight*

	Patient Weight			
Conduction Block	**≤10 kg**	**11-30 kg**	**31-60 kg**	**>60 kg**
Brachial plexus above clavicle	1 mL/kg	10 mL + 0.5 mL/kg above 10 kg	20 mL + 0.25 mL/kg above 30 kg	30 mL
Brachial plexus below clavicle	0.5 mL/kg	5 mL + 0.25 mL/kg above 10 kg	10 mL + 0.15 mL/kg above 30 kg	15 mL
Any nerve trunk at elbow	0.2 mL/kg	0.15 mL/kg	0.15 mL	10 mL
Any nerve trunk at wrist	0.05 mL/kg	0.05 mL/kg	0.05 mL/kg	3-5 mL

*Volumes can usually be reduced with ultrasound imaging.

Table 81-13 Usual Local Anesthetic Infusion Rates with or without Bolus Doses of Either Ropivacaine 0.2%, Bupivacaine 0.125%, or Levobupivacaine 0.15% to 0.2% for Continuous Peripheral Nerve Blocks

Techniques	Plexus and Proximal Conduction Nerve Blocks*	Axillary and Popliteal Blocks
Infusion rate	0.2 mL/kg/hr up to 10 mL/hr	0.1 mL/kg/hr up to 5 mL/hr
Bolus doses	0.2 mL/kg up to 5 mL	0.1 mL/kg/hr up to 3 mL/hr
Maximum bolus doses per hour	3	3

*Including supraclavicular and coracoid approaches to the brachial plexus, femoral nerve block, fascia iliaca compartment block, and proximal approaches to the sciatic nerve.
From author's data.

Midclavicular Approaches

Two midclavicular approaches, vertical and anterolateral, have been described. The vertical midclavicular approach is performed by inserting a block needle at right angle to the skin, immediately below the midpoint of the lower border of the clavicle, until twitches are elicited in the upper extremity. Even though use of this technique was reported in pediatric patients without apparent complication,[208,209] the path followed by the needle threatens the apical pleura and lung, thus contraindicating this approach in children.

The anterolateral midclavicular approach can be safely used in children lying supine with the ipsilateral arm alongside the thorax. The landmarks are the coracoid process of the scapula, the lower border of the clavicle, and the deltopectoral groove (Fig. 81-9). The block needle is introduced 1 cm below the midpoint of the lower border of the clavicle at a 30- to 45-degree angle dorsally and a 30-degree angle laterally, aligned with the deltopectoral groove, in direction to the axilla. The objective is to enter the neurovascular sheath 1.0 to 1.5 cm medially to the coracoid process of the scapula until twitches are elicited in the arm, forearm, or hand. A catheter can be inserted along the nerve trunks and securely immobilized. Ultrasound guidance helps in locating the axillary vessels and parietal pleura; the tip of the needle should preferably be placed posteriorly to the artery to obtain good circumferential spread of the local anesthetic.

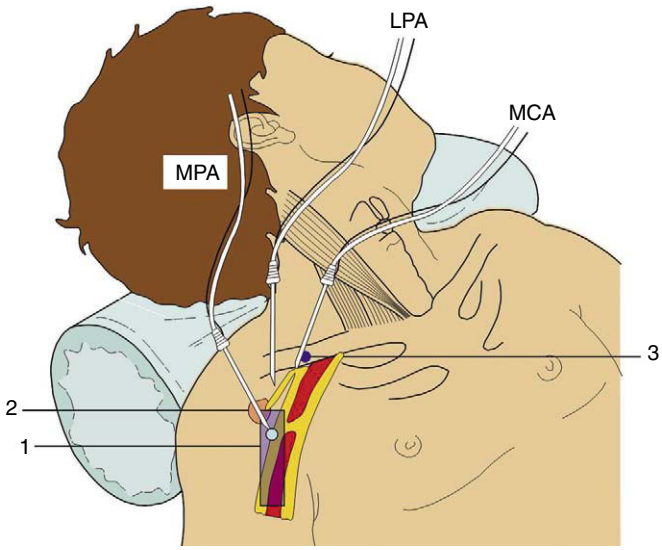

Figure 81-9 Infraclavicular approaches to the brachial plexus. MPA, median paracoracoid approach; LPA, lateral paracoracoid approach; MCA, midclavicular approach; 1, ultrasound probe; 2, coracoid process of the scapula; 3, midpoint of the clavicle.

Paracoracoid Approaches

Paracoracoid approaches are currently the most popular techniques of infraclavicular blockade in children. The medial approach is the reference technique with neurostimulation and the one with the lowest morbidity. The puncture site is located at the caudal extremity of the deltopectoral groove, 1 to 2 cm (according to patient's age) both caudally and medially to the coracoid (see Fig. 81-9). Abducting the upper arm at 90 degrees instead of placing it alongside the thorax brings the plexus closer to skin and favors circumferential spread of local anesthetic.[210] The needle is inserted perpendicularly to the skin until twitches are elicited in muscles of the upper extremity.

The lateral paracoracoid approach elicits considerable interest when ultrasound guidance is available (see Fig. 81-9). The technique can be performed with the arm extended alongside the thorax or abducted by 110 degrees and the elbow flexed by 90 degrees[207] to take away the neurovascular sheath from the parietal pleura and loosen it to favor circumferential spread of the local anesthetic. The puncture site is located 1 to 2 cm below the lower border of the clavicle on the parallel to the sternum drawn from the medial border of the coracoid process.[211] Needle repositioning might be necessary until complete circumferential spread is obtained; then the injection is stopped. Performing this technique under neurostimulation only is technically feasible but unsafe if concomitant ultrasound imaging is not available due to the danger of pleural penetration.

Cervical Brachial Plexus Blocks

Parascalene Approach

The parascalene approach[212] aims to penetrate the interscalene space at a distance from the apical pleura and great vessels of the neck. The child is lying supine with the ipsilateral arm extended alongside the thorax and a roll slipped under the neck to stretch and make more superficial the primary trunks of the brachial plexus. The landmarks are the midpoint of the upper border of the clavicle and the transverse process of C6 located by palpation in the interscalene groove, just posterior to the sternocleidomastoid muscle, at the level of the cricoid cartilage. The puncture site is identified at the junction of the upper two thirds, with the lower third of the line joining the skin projection of the C6 process and the midpoint of the clavicle (Fig. 81-10).

A catheter can be introduced in the interscalene space and safely immobilized at this level; the usual infusion regimens of local anesthetics are presented in Table 81-13.

The success rate for this approach is very high, with a good safety record. Occasionally, blockade of the lower cord (ulnar nerve and/or medial branch of the median nerve) can be incomplete when neurostimulation only is used. The morbidity of this technique is virtually nil.[213]

Posterior Approach

This technique was originally described in (conscious) adult patients in the sitting position. Even though no pediatric publication is available yet, it can be performed in anesthetized children

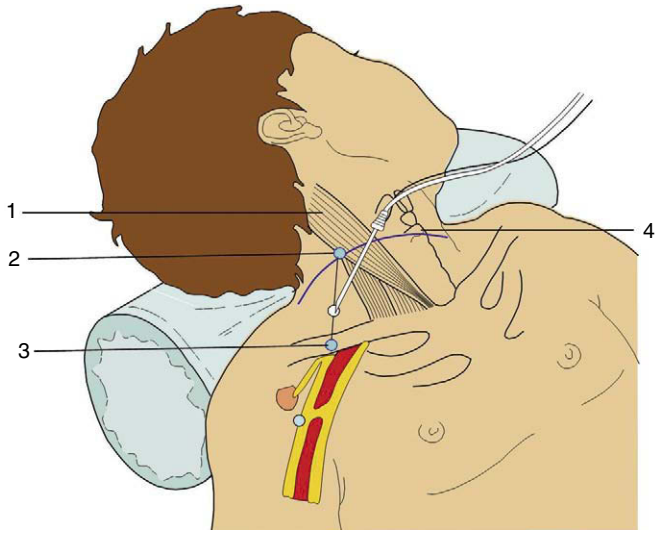

Figure 81-10 Parascalene approach to the brachial plexus. 1, Sternocleidomastoid muscle; 2, skin projection of Chassaignac's tubercle; 3, midpoint of the clavicle; 4, cricoid cartilage.

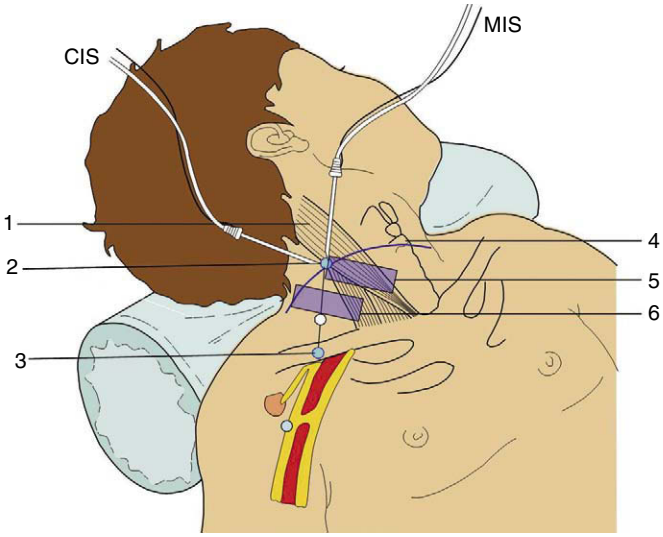

Figure 81-11 Interscalene approach to the brachial plexus. CIS, Classic interscalene approach (after Winnie); MIS, modified interscalene approach (after Borgeat); 1, sternocleidomastoid muscle; 2, skin projection of Chassaignac's tubercle; 3, midpoint of the clavicle; 4, cricoid cartilage; 5, probe positioning (classic approach); 6, probe positioning (Borgeat approach).

placed in the semiprone position with the head in neutral position to keep the anterior aspect of the neck freely accessible to palpation.

Interscalene Approach

This approach aims to enter the interscalene space at its upper extremity, close to the transverse process of C6. The child is placed in the dorsal recumbent position with the arms extended alongside the thorax and head slightly turned to the contralateral side. The landmarks are the cricoid cartilage, the anterior ramus of the C6 transverse process (Chassaignac's tubercle), and the interscalene groove. The puncture site is located at the skin projection of Chassaignac's tubercle in the interscalene groove, just posterior to the lateral border of the sternocleidomastoid muscle. The needle is inserted at an 80-degree angle (not perpendicularly) to the skin, that is, dorsally and slightly caudal in direction to the C6 transverse process until muscle twitches are elicited in the upper limb (Fig. 81-11). This technique is not very popular in children because of its adverse effects: ipsilateral phrenic nerve blockade, danger of vascular damage (vertebral artery and vein), and accidental cervical epidural/intrathecal penetration.

Ultrasound imaging improves the safety of this approach by showing the great vessels of the neck, aponeuroses of scalene muscles, and C5-C7 brachial plexus roots.[214,215] Borgeat and coworkers[216] described a modified technique in adults that can be used in children. The block needle is inserted at the same puncture site, but the needle is oriented laterally, pointing toward the midpoint of the clavicle until one of the primary trunks (instead of roots) of the brachial plexus is located and twitches are elicited in the upper arm. A catheter can be inserted if mandatory. The usual selection of local anesthetics and volumes of injectate is given in Tables 81-12 and 81-13.

Peri-subclavian Artery Approaches

The brachial plexus trunks gather at the lower part of the interscalene space where they surround the subclavian artery. They can be approached by several insertion routes that all begin with penetration of the interscalene space slightly above the first rib. All these techniques are very effective on virtually all branches of the brachial plexus, but they are dangerous in children, especially infants, as the apical pleura overpasses the clavicle in the neck. Ultrasound imaging allows precise identification of the pleura, subclavian vessels, and nerve trunks, thus making the technique less hazardous than with neurostimulation only. However, there are equally effective and safer alternatives to this approach; therefore, it should still be considered to be contraindicated even with ultrasound guidance.

Distal Conduction Blocks

In pediatrics, approaching the radial, median, or ulnar nerve at the elbow or wrist is still not very usual. These approaches are rather difficult with neurostimulation only, and their failure rate is relatively high when blind subcutaneous injections are made: Indications have long been limited to complementation of partially failed brachial blocks. Ultrasound imaging is currently widening the field of indications for these techniques because these superficial nerves are easy to identify and approach with ultrasound guidance, the more so as very small amounts of local anesthetic (1-3 mL usually, even less in infants) are sufficient to produce complete nerve blockade.

Metacarpal/Transthecal Blocks

These two techniques can be contemplated to treat or prevent finger pain whatever its cause without the limitations of digital ring blocks, which are almost never used in children, at least by anesthesiologists.

Transthecal Blocks

Transthecal blocks[217] consist of injecting a local anesthetic within the small space between the synovial sheath of each digital flexor

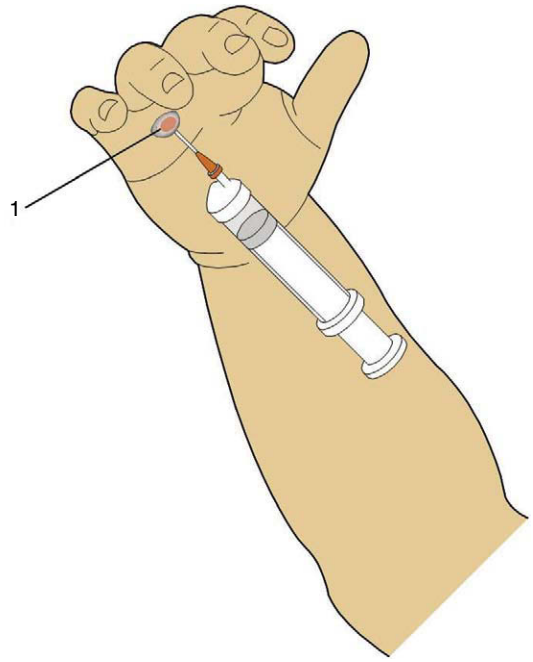

Figure 81-12 Metacarpal (or transthecal) nerve block. 1, Head of the metacarpal bone located by palpation.

tendon and the fibrous sheath that surrounds it and is attached proximally to the head of the metacarpal bone of the three median fingers (this sheath is more extended at the levels of the thumb and forefinger). Even though the procedure is moderately painful, it is reasonably well accepted by conscious children. The landmark is the head of the relevant metacarpal bone located by palpation of the palm while the hand is supinated. Then a 25- to 27-gauge intradermal needle is inserted perpendicularly to the palm, right in the center of the skin projection of this metacarpal head (Fig. 81-12), until bone contact is made. The needle is then slightly withdrawn (to avoid subperiosteal injection) and the local anesthetic (1% or 2% lidocaine without epinephrine) is injected until resistance is felt, which occurs after injection of a volume of

- 0.5 to 1.0 mL: index, middle, and fourth fingers
- 3 to 5 mL: little finger
- 5 to 10 mL: thumb

The last two phalanges and the ventral aspect only of the proximal phalanx are deeply anesthetized.

Metacarpal Blocks

The procedure consists of inserting at right angles to the skin a 25-gauge needle both lateral and then medial to the relevant head of the metacarpal bone, usually with the patient's hand in the prone position.[218] The anesthesiologist places his or her finger at the same level on the palmar aspect to feel tissue deformity produced by the tip of the needle on the palm. The needle is then immobilized, and 1 mL of local anesthetic without epinephrine is injected while the needle is slightly withdrawn. With this procedure, the two ipsilateral digital nerves are blocked. The procedure is then repeated on the other side of the finger. This two-injection procedure provides quick and excellent analgesia. Its morbidity is virtually nil, but, unfortunately, it is as painful as the classic four-injection technique for digital nerve blocks.

Lower Extremity Conduction Blocks

Lumbar Plexus Nerve Blocks

Anatomic Considerations

The lumbar plexus is formed by the union of L1 to L5 spinal nerves. It lies within the substance of the psoas muscle, in a fascial plane termed the *psoas compartment*, where it can be approached via a posterior route through the quadratus lumborum. It contributes four nerves to the lower extremity: the femoral, lateral cutaneous, obturator, and genitofemoral nerves. At their emergence from the psoas muscle, these nerves run a variable part of their course just below the fascia iliaca, which is the common fascia covering psoas and iliacus muscles. A sufficient volume of local anesthetic injected at the inner surface of this fascia will spread along it and reach these nerves, thus producing a fascia iliaca compartment block.

The main anatomic difference between children and adults pertains to the smaller size of nerve trunks and extensive spread of local anesthetic along fascial planes and perineural sheaths. Even though these nerves, especially the femoral nerve, are large, they are not very echoic (the younger the patient, the less echoic they are) (see Fig. 81-3), whereas aponeuroses (and blood vessels) are. Consequently, excellent knowledge of anatomy, especially relationships between muscle fascias and nerves, is required to avoid misidentification.

Indications, Contraindications, and Complications

Indications

Femoral nerve and fascia iliaca compartment blocks are commonly practiced both in emergency conditions (femoral shaft fractures) and for elective surgery of the thigh.[219,220] Conscious and slightly sedated children tolerate muscle biopsy quite well when the procedure is performed under femoral and lateral cutaneous nerve block.[221] Catheter placement allows long-lasting pain relief after surgery of the femur[222,223]; because bacterial contamination (but not infection) is reported in 57% of cases at 48 hours, such catheters should not be kept in place any longer, and aseptic techniques of catheter insertion and dressing are of critical importance.

Contraindications

There are no specific contraindications to femoral nerve blocks.

Complications

Psoas compartment blocks may result in direct trauma of retroperitoneal (right kidney mainly) and intraperitoneal content due to wrong needle insertion (too cephalic for the kidney, too medial for abdominal vessels). Also, accidental spread to neuraxial spaces, especially subarachnoid, may result in severe complications, including fatalities, if adequate monitoring and management of the patient are not achieved.

Nerve impalement is possible as in any nerve block procedure[224] and can result (rarely in fact) in permanent damage. Falls at home are mainly a problem in adults[225,226] but also can occur and be detrimental to children; strong recommendations to keep children in bed should be made.

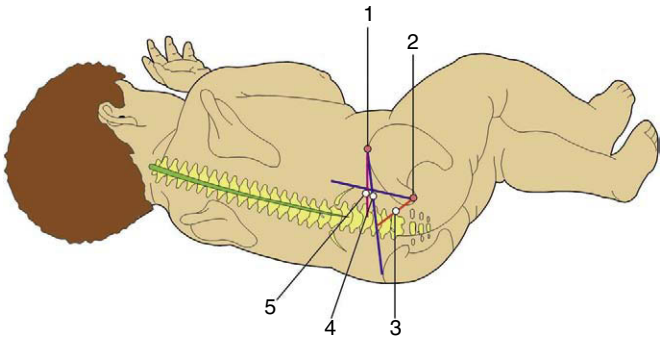

Figure 81-13 Direct lumbar plexus block. 1, Anterior superior iliac spine; 2, posterior superior iliac spine; 3, Chayen's puncture site (slightly modified); 4, Winnie's puncture site (slightly modified); 5, Shuepfer's puncture site.

Direct Lumbar Plexus Block (Psoas Compartment Block)

Psoas compartment block is performed with the child in the lateral decubitus position lying on the nonblocked side. The landmarks are the iliac crests, the ipsilateral posterior superior iliac spine, and the L5 spinous process. Three puncture sites can be used (Fig. 81-13)[227]:

- The midpoint of the line joining the posterior iliac spine to the L5 spinous process (modified Chayen's approach)[228]
- A point located on the intercristal line (Tuffier's line), 1 to 2 cm medial to its crossing by a perpendicular line[229] drawn from the posterior iliac spine (modified Winnie's approach)
- The point located at the union of the lateral third with medial two thirds of the line extending from the L4 spinous process to the ipsilateral anterior superior iliac spine

Whatever the puncture site used, the block needle is inserted perpendicularly to the skin until twitches are elicited in the ipsilateral quadriceps muscle. Medial orientation as well as excessive penetration of the needle must be avoided to prevent trauma of abdominal and retroperitoneal content (especially right kidney).

Femoral Nerve and Fascia Iliaca Compartment Blocks

Femoral Nerve Block

Femoral nerve blocks are performed while the child lies supine, preferably with the ipsilateral limb slightly abducted. The landmarks are the inguinal ligament and the femoral artery. The puncture site is located 0.5 to 1.0 cm both below the inguinal ligament (not the inguinal crease) and lateral to the femoral artery (Fig. 81-14). The block needle is inserted posteriorly, either perpendicular to the anterior aspect of the thigh or, especially when a catheter has to be inserted, at a 45-degree angle cephalad, pointing to the umbilicus, until twitches are elicited in the quadriceps muscle when neurostimulation is used (Fig. 81-15).

Ultrasound imaging makes the technique even easier.[230] The probe is placed slightly above and parallel to the inguinal ligament.

Usual doses of local anesthetic are displayed in Table 81-14. A catheter can be inserted and its position should preferably be controlled either by nerve stimulation (stimulating catheter) or

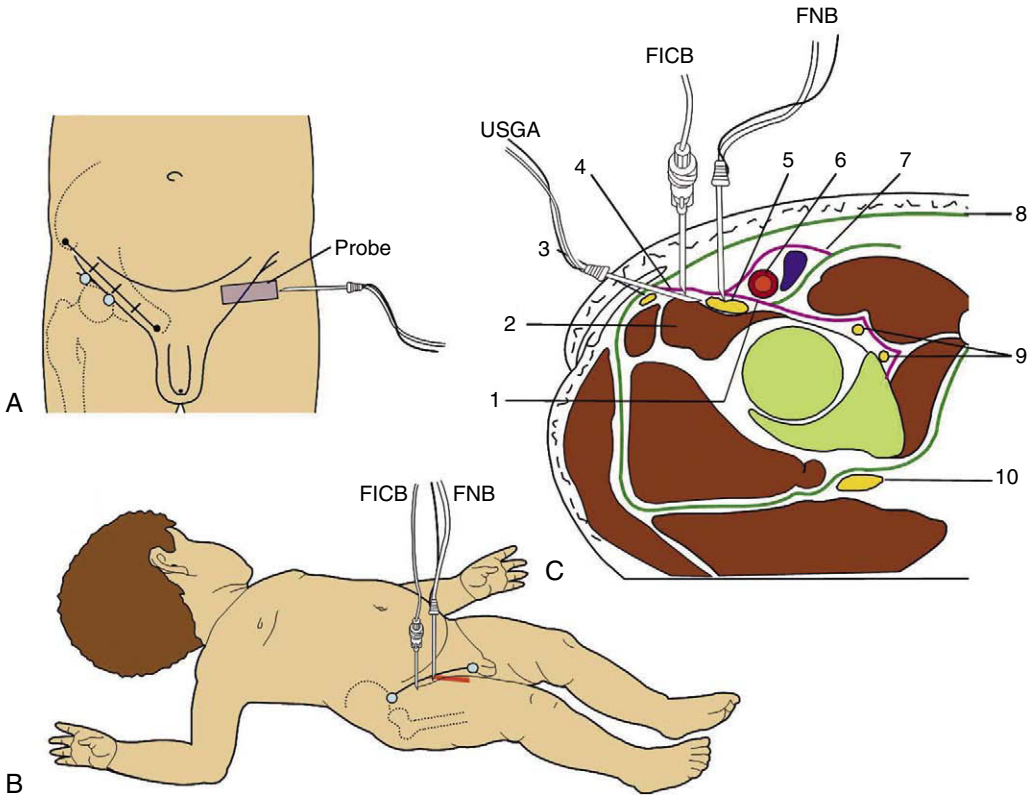

Figure 81-14 Femoral nerve and fascia iliaca compartment blocks. **A,** Landmarks and probe positioning. **B,** Patient's position. **C,** Transverse section of the thigh. USGA, ultrasound-guided approach; FICB, fascia iliaca compartment block; FNB, femoral nerve block; 1, iliopectineal arch; 2, psoas muscle; 3, lateral cutaneous nerve of the thigh; 4, fascia iliaca; 5, femoral nerve; 6, femoral artery; 7, femoral vessel sheath; 8, fascia lata; 9, division branches of the obturator nerve; 10, sciatic nerve.

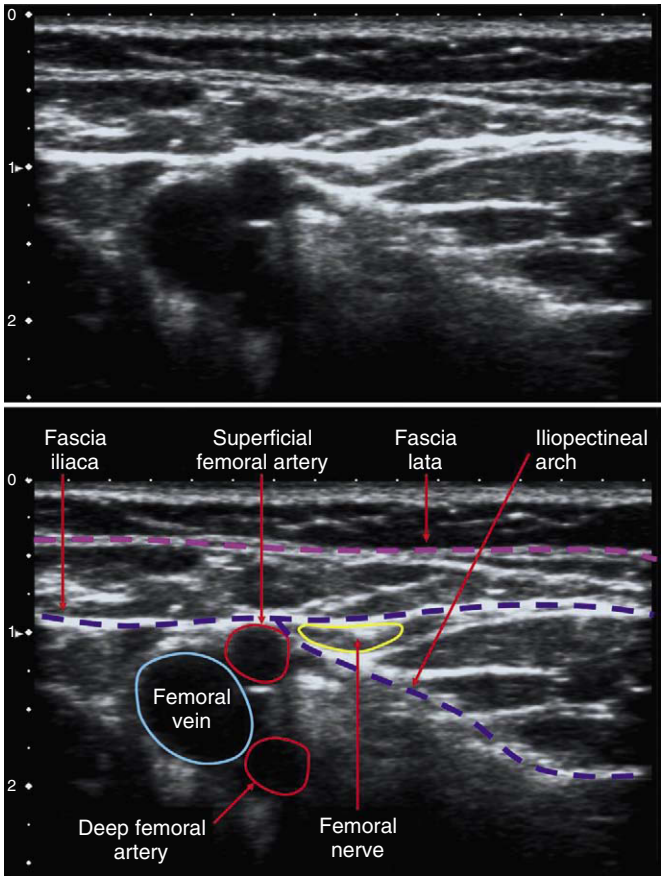

Figure 81-15 Femoral nerve block: ultrasound-guided tomography of the inguinal region (probe parallel to the inguinal ligament).

by ultrasonography. Usual regimens of repeat injections/continuous infusions are displayed in Table 81-13.

Fascia Iliaca Compartment Block

The technique consists of injecting a local anesthetic below the fascia iliaca.[231] The injectate will spread at the inner surface of the fascia and, depending on its volume, bathe the nerves emerging from the lumbar plexus that supply the lower extremity. The technique is performed with the child lying supine (see Fig. 81-14).

Placement of the catheter is improved by ultrasound guidance.

With this technique, the femoral and lateral cutaneous nerves are almost constantly blocked; the local anesthetic usually reaches the upper division branch of the obturator nerve, which is the branch giving a twig to the hip joint. The anesthetized area also includes areas supplied by upper branches of the lumbar plexus in more than 70% of procedures, such as the genitofemoral nerve. Usual doses of local anesthetic are displayed in Table 81-14. Local anesthetics with epinephrine produce significantly lower plasma concentrations and should be preferred whenever possible. Addition of clonidine (1-2 µg/kg) significantly prolongs the duration of analgesia.[50] Placement of a catheter is easy and allows long-lasting pain relief (see Table 81-13).

Other Lumbar Plexus Nerve Blocks

Saphenous Nerve Block

Saphenous nerve blocks are used to complement sciatic blocks with small amounts of local anesthetic. Because the saphenous nerve is a purely sensory nerve, it is not identifiable by neurostimulation. Many block procedures have been published, all resulting in high failure rate (30% or higher). Ultrasound imaging, currently underevaluated in this indication, is a promising technique.

The classic approach is performed at knee level with the patient supine. The anterior edge of the medial head of the gastrocnemius muscle and the tibial tuberosity are identified by palpation. A line is drawn at a 45-degree angle with the intercondylar line, from the tibial tuberosity to the anterior edge of the gastrocnemius muscle. The technique consists of subcutaneously injecting local anesthetic along this line. This very simple technique is virtually free of complications, but its failure rate is rather high.

The saphenous/vastus medialis nerve block takes advantage of the proximity of the vastus medialis and saphenous nerves within the adductor canal in the upper part of the thigh. Being a mixed nerve, the vastus medialis nerve can easily be located by neurostimulation and injecting a local anesthetic results in concomitant blockade of the two nerves. The landmarks are the femoral artery, the inguinal ligament, and the upper border of the sartorius muscle (Fig. 81-16). A short, short-beveled insulated needle is inserted perpendicularly to the skin, 0.5 cm lateral to the femoral artery just above the upper border of the sartorius until twitches are elicited in the vastus medialis muscle. Injecting 0.1 to 0.2 mL/kg of a local anesthetic is sufficient to block the two nerves and obtain complete analgesia of the medial aspect of the leg and foot.

The transsartorial approach aims to infiltrate the fat pad located between the inner aspect of the sartorius muscle and great adductor tendon. The puncture site is situated at the level of the upper border of the patella, on the medial aspect of the sartorius muscle located by palpation. The block needle is inserted medially and slightly posteriorly with a 45-degree angle caudally, in the direction of the medial femoral condyle until a loss of resistance

Table 81-14 Recommended Volumes of Local Anesthetic for Single-Shot Lower Limb Blocks with Neurostimulation*

Conduction Block	≤10 kg	11-30 kg	31-60 kg	>60 kg
Lumbar plexus (psoas compartment)	1 mL/kg	10 mL + 0.5 mL/kg above 10 kg	20 mL	20 mL
Femoral	0.5 mL/kg	5 mL + 0.35 mL/kg above 10 kg	12 mL + 0.3 mL/kg above 30 kg	25 mL
Fascia iliaca	1 mL/kg	10 mL + 0.5 mL/kg above 10 kg	20 mL + 0.25 mL/kg above 30 kg	30 mL
Proximal sciatic	1 mL/kg	10 mL + 0.5 mL/kg above 10 kg	20 mL + 0.3 mL/kg above 30 kg	30 mL
Sciatic in popliteal fossa	0.3 mL/kg	3 mL + 0.2 mL/kg above 10 kg	6 mL + 0.15 mL/kg	12.5 mL

*Volumes can usually be reduced with ultrasound imaging.

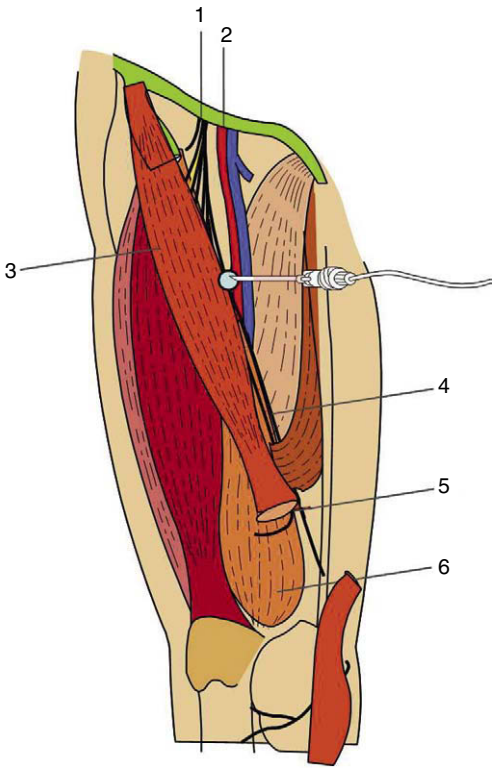

Figure 81-16 Saphenous/vastus medialis nerve block. 1, Femoral nerve; 2, femoral artery; 3, sartorius muscle; 4, saphenous nerve; 5, motor nerve supplying the sartorius muscle; 6, vastus medialis muscle.

is felt as the subsartorial fat pad (through which runs the saphenous nerve) is penetrated. The paravenous approach, originally described as a "blind" infiltration technique on both sides of the saphenous vein in the upper part of the medial aspect of the leg, is considerably improved by ultrasound imaging because the saphenous vein is very easy to locate. Inserting the needle along the major axis of the probe (SAX-IP) allows clear visualization of needle progression toward the vein and circumferential spread of the local anesthetic.

Lateral Cutaneous Nerve Block

A specific lateral cutaneous nerve block is rarely used in children; its main indication is as a technique complementary to a femoral block. Ultrasound guidance can be used.

Obturator Nerve Block

This procedure is performed with the child supine and the thigh slightly abducted and externally rotated (if possible). The landmarks are the groove between the tendon of the long adductor muscle and medial border of the pectineus muscle. The puncture site lies in this groove at the level of the greater trochanter of the femur.

With neurostimulation, the needle is inserted following a strict anterior posterior path until twitches are elicited in the long and short adductors muscles (stimulation of the anterior division branch of the obturator nerve). The needle is further advanced dorsally over 1 to 2 cm until twitches are elicited in the great adductor (posterior branch). Half of the local anesthetic solution (of a total of 0.1 mL/kg up to a maximum of 5 mL per nerve) is injected; the needle is then removed until stimulation of the anterior branch is obtained again and the second half the anesthetic is injected.

The same technique can be performed with ultrasound imaging. The probe is placed below the pubic tubercle, with its major axis parallel to the inguinal ligament. The aponeuroses of the sartorius and long and short adductors are easily identified. The anterior branch can be easily found between the long and short adductors while the posterior branch lies between the short and great adductors (Fig. 81-17).

Sciatic Nerve Blocks

Anatomic Considerations

The sacral plexus supplies the posterior aspect of the limb; it lies on the anterior aspect of the piriformis muscle, behind the posterior wall of the pelvic cavity, and cannot be directly approached by a block needle. It contributes two nerves to the lower extremity, the posterior femoral cutaneous nerve and the sciatic nerve. The sciatic nerve is the largest mixed nerve of the body. It is formed by two distinct nerves, the common peroneal nerve and the tibial nerve, enclosed in the same perineural sheath.

Indications and Contraindications

Sciatic nerve blocks are recommended for operations on the foot and the leg (a complementary saphenous nerve block is often required because this nerve provides cutaneous innervation of the medial aspect of the leg). Depending on the surgery, the sciatic nerve will be approached in the popliteal fossa or more proximally. Sciatic blocks have no specific contraindications. As with other extremity nerve blocks, patients at risk for compartment syndrome require close monitoring and use of diluted solution to avoid motor blockade (see earlier).

Proximal Sciatic Nerve Blocks

Numerous techniques have been described, for which the associated morbidity can differ significantly. When successful, they provide the same distribution of anesthesia. When contemplating a proximal sciatic block, the anesthesiologist must consider the following points: (1) morbidity of the technique; (2) positioning

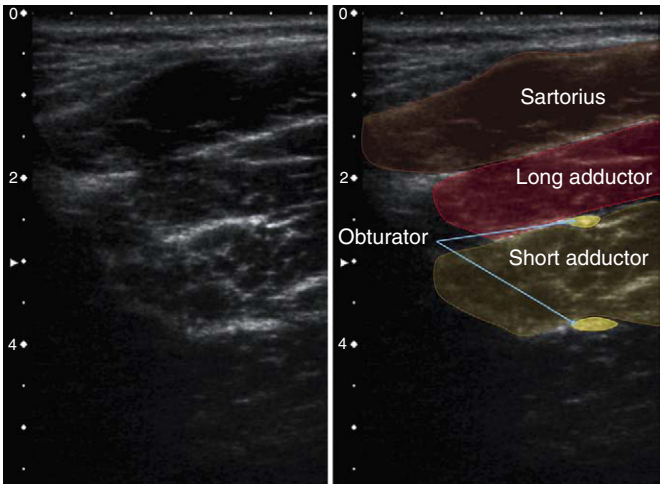

Figure 81-17 Obturator nerve block: ultrasound imaging of the anterior and medial aspect of the thigh.

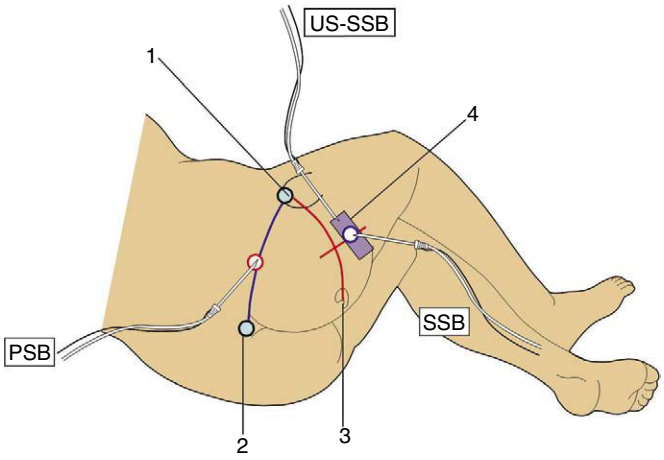

Figure 81-18 Proximal sciatic nerve block: posterior and subgluteal approaches. PSB, Posterior sciatic block; SSB, subgluteal sciatic block; US-SSB, ultrasound-guided sciatic subgluteal block; 1, greater trochanter of the femur; 2, coccyx; 3, ischiatic tuberosity; 4, probe.

of the patient; (3) technique used to locate the nerve; (4) necessity for catheter placement; and (5) experience of the anesthesiologist with this particular technique. Usual doses of local anesthetic are listed in Table 81-14, and usual regimens of repeat injections/continuous infusions after catheter placement are listed in Table 81-13.

Posterior Approach

This is the most classic approach. The child is placed in the semiprone position, resting on the nonoperated side. The site of puncture is located at mid-distance from the greater trochanter of the femur and the caudal extremity of the coccyx (Fig. 81-18). The block needle is inserted perpendicularly to the skin, that is, both medially and ventrally, pointing to the ischial tuberosity, until twitches are elicited in the leg or the foot or both. Ultrasound guidance is not easy at this level because of the distance from the skin at which the sciatic nerve runs.

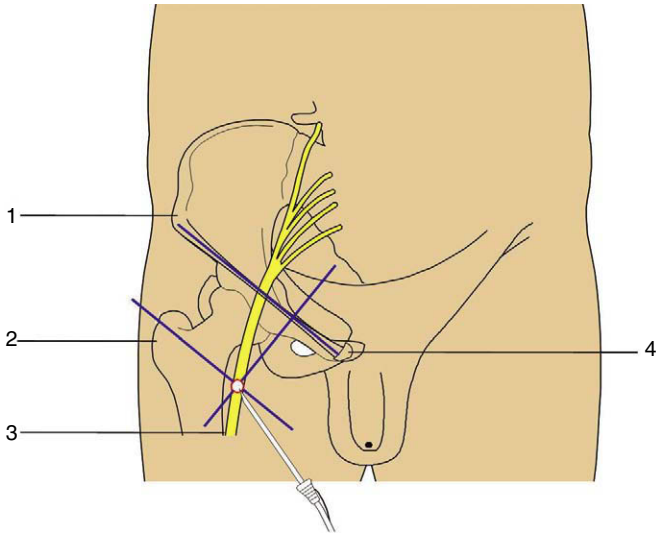

Figure 81-19 Proximal sciatic nerve block: anterior approach. 1, Anterior superior iliac spine; 2, greater trochanter of the femur; 3, sciatic nerve; 4, pubic tubercle.

Anterior Approach via the Femoral Triangle

This approach was developed to allow sciatic blockade in a patient who must remain in the dorsal position.[232] The landmarks are the inguinal ligament and the greater trochanter of the femur. The location of the site of puncture is rather complicated, requiring that two lines be drawn. The site of puncture is located at the crossing of the two lines (Fig. 81-19). This technique is the most difficult and hazardous approach to the sciatic nerve; it threatens the division branches of the femoral nerve, femoral vein, and femoral arteries. It should be the last option when a proximal sciatic block is contemplated.

Subgluteal Approach

The child is placed in the semiprone position with the operated side uppermost, the lower thigh and leg flexed by 90 degrees, and the upper thigh and leg extended. The landmarks are the ischiatic tuberosity and the greater trochanter of femur. At midpoint of the line joining the two landmarks, a perpendicular line is drawn and the puncture site is located on this line 2 to 4 cm caudally (see Fig. 81-18). The needle is inserted at right angles to the skin towards the femur until twitches are elicited in the foot. Echo guidance can be used instead of (or in conjunction with) neurostimulation.[233]

Lateral Approach

A lateral approach to the sciatic nerve has been described for use in patients lying supine[234] with the relevant leg slightly rotated medially. The needle is inserted horizontally toward the lower border of the femur (Fig. 81-20). If bone contact is made, the needle is withdrawn and reinserted slightly more posteriorly until twitches are elicited in the leg and the foot. The distance at which the sciatic nerve is found can be correlated with patient age (Fig. 81-21).[234]

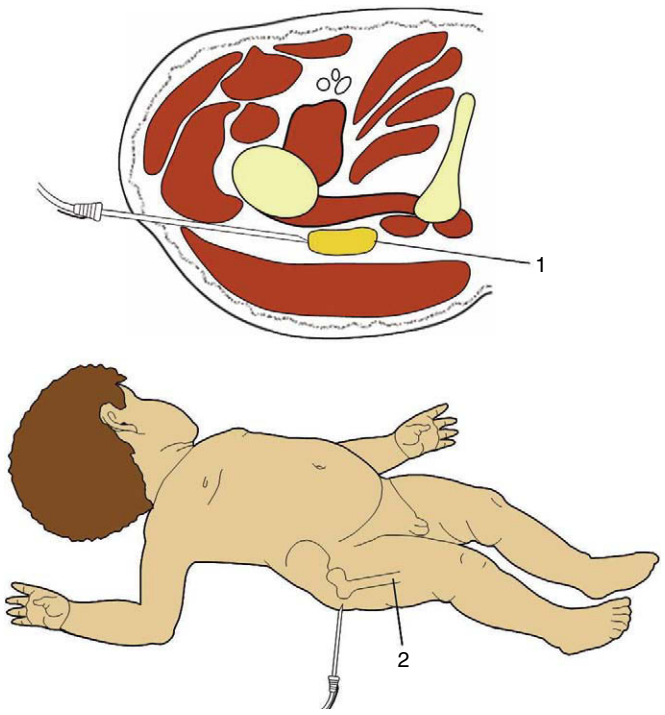

Figure 81-20 Proximal sciatic nerve block: lateral approach. 1, Sciatic nerve; 2, femur.

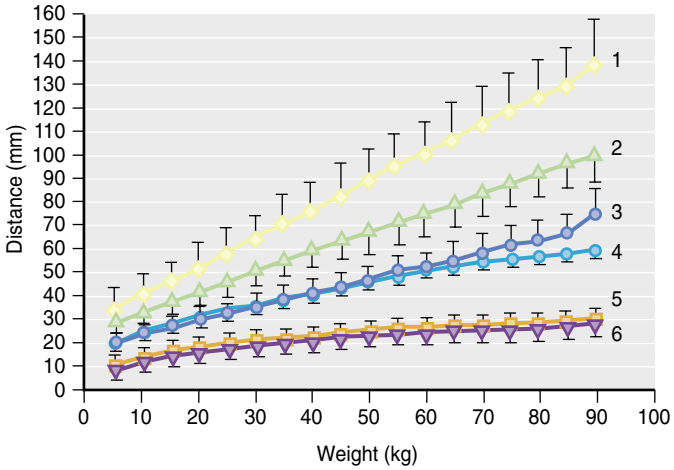

Figure 81-21 Distance from skin to plexus/nerve following the most commonly used techniques of peripheral nerve blocks. 1, Proximal anterior and lateral approach to sciatic nerve; 2, lumbar approach to lumbar plexus; 3, proximal posterior approach to sciatic nerve; 4, thoracic paravertebral; 5, axillary, femoral nerve, and fascia iliaca compartment blocks; 6, parascalene approach to brachial plexus.

Popliteal Sciatic Nerve Block

This approach is the easiest approach to the sciatic nerve. The child is placed in the prone or, preferably, the semiprone position (Sims position), resting on the nonoperated side (Fig. 81-22).[235]

Ultrasound guidance is easy at this level. Usual doses of local anesthetic are listed in Table 81-14, and usual regimens of repeat injections/continuous infusions after catheter placement are listed in Table 81-13.

Metatarsal and Transthecal Blocks

The metatarsal (or midtarsal) block is an easy technique for providing good pain relief for surgical procedures on the toes. The child is placed supine, and the head of the relevant metatarsal is palpated on the sole. The technique consists of inserting a standard intramuscular needle dorsally on the dorsum of the foot in close contact with the medial border of the base of the metatarsal until the tip of the needle is felt and seen as it pushes the skin of the sole. A volume of 1 to 3 mL of 0.25% to 0.5% plain bupivacaine or 0.2% to 0.5% ropivacaine is then injected while the needle is slowly withdrawn. The same procedure is repeated along the lateral border of the same metatarsal to provide full anesthesia of the relevant toe.

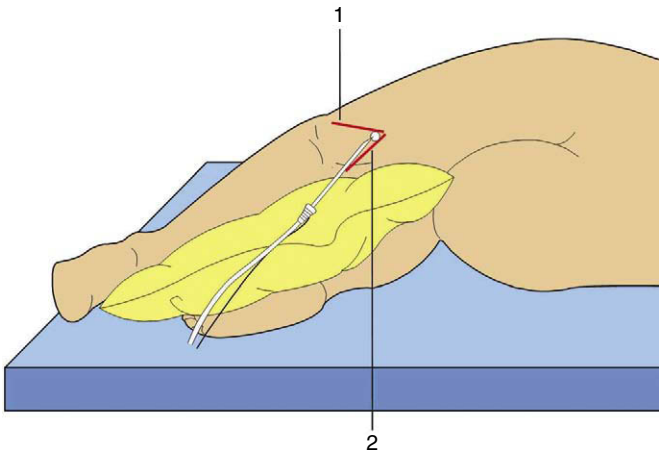

Figure 81-22 Popliteal sciatic nerve block. 1, Tendon of the biceps femoris. 2, Tendons of the semimembranosus and semitendinosus muscles.

The transthecal technique as described for finger procedures can be transposed to the sole of the foot by palpating the head of the relevant metatarsal bone and injecting a small volume of local anesthetic in the fibrous sheath surrounding the tendinous sheath of flexor tendons. However, except for the greater toe, the landmarks are more difficult to identify and, due to the thickness of the sole, the infiltration is technically more difficult and less precise.

Blocks of Nerves Supplying the Trunk

Intercostal Nerve Block

Intercostal nerves run along the lower border of each rib, within the intercostal space, a triangular space, with (1) a medial border formed by the posterior intercostal and innermost intercostal muscles, endothoracic fascia, and parietal pleura; (2) a lateral border formed by the internal and external intercostal muscles and intercostal membrane (thickening of the inner fascia of external intercostal muscles); and (3) a base formed by the lower rib. Intercostal nerve block is obtained by injecting a local anesthetic within the intercostal space and, provided several adjacent intercostal spaces are infiltrated, adequate intraoperative and postoperative pain relief is obtained for thoracotomy,[236] liver transplantation, pleural drainage, and management of rib fractures.

This block must be avoided in the presence of impaired blood or gas exchange, and it requires that all patients be kept under intensive medical observation because of the danger of clinically delayed pneumothorax: it is not suitable for outpatient surgery.

The safest approach to the intercostal space is along the midaxillary line with the child lying semiprone using a short 22- or 20-gauge Tuohy needle (intradermal needles are not appropriate) (Fig. 81-23).

A catheter can be introduced in the intercostal space located at the center of the area to be anesthetized to allow reinjections; the catheter can also be inserted intraoperatively under direct vision by the surgeon.[237,238] However, the safety of continuous techniques is questionable due to high systemic uptake of local anesthetic.[239] Spread of large-volume anesthetic solution can reach distant intercostal spaces (even contralateral ones), probably via the paravertebral space, thus providing adequate duration of pain relief with a single injection in a number of patients. Spread to the epidural space can also occur. Thus, the patient should be admitted to the intensive care unit for careful monitoring of respiratory function and for delayed pneumothorax.

Thoracic Paravertebral Space Block

This technique aims to penetrate the thoracic paravertebral space to provide unilateral thoracic anesthesia involving several der-

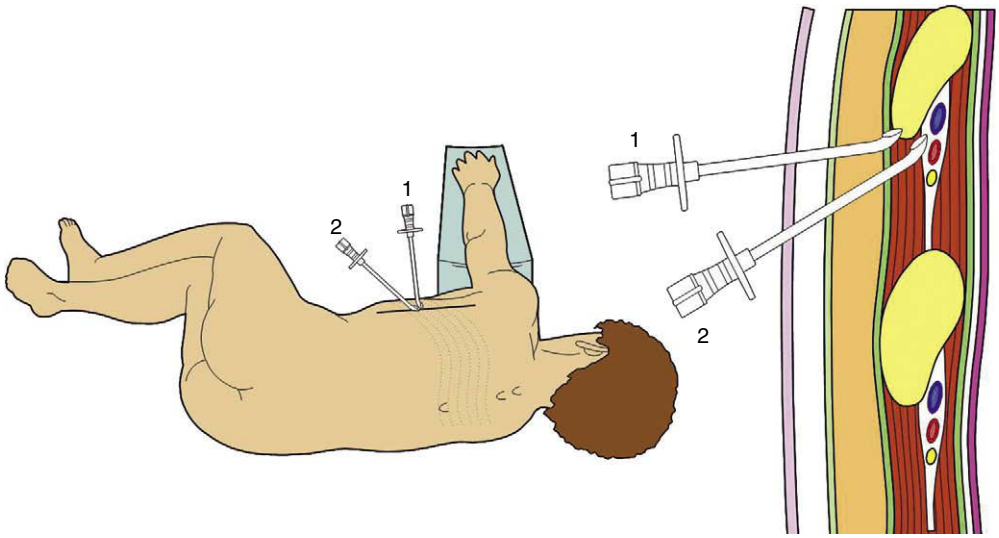

Figure 81-23 Intercostal nerve block. 1, Insertion of the needle at an 80-degree angle to the skin; 2, caudal and dorsal redirection of the needle.

matomes. The technique is the same as for adult patients (see Chapter 52) (Fig. 81-24).

Rectus Sheath/Paraumbilical Block

The technique consists of injecting a local anesthetic within the substance of the rectus abdominis muscle along the course of the terminal branch of the 10th intercostal nerve that supplies sensory innervation to the periumbilical area (Fig. 81-25).[240] It is indicated for any surgery involving the umbilical region (umbilical hernia repair especially) and can be modified to block other thoracoabdominal intercostal nerves for repair of hernias of the linea alba.

Ultrasound imaging is very demonstrative.[241] Both aponeuroses of the rectus muscle and the parietal peritoneum are very echoic. The probe is placed horizontally over the umbilicus, and the block needle is inserted medially in long-axis orientation. The superficial fascia is bent and then crossed by the tip of the needle that should be forwarded until it contacts the deep fascia (in order to favor the longitudinal spread of the anesthetic): the anesthetic is then injected and can be visualized in the form of an expanding biconvex black shadow (Fig. 81-26).

Some authors recommend injecting half the dose at the upper border and half at the lower border of the umbilical ring and to inject a small amount (1 mL) subcutaneously while the needle is withdrawn.[240] The technique is then repeated on the other side. The success rate is high and morbidity extremely low unless attempts are made to inject the drug between peritoneum and deep rectus fascia.

Block of the Ilioinguinal, Iliohypogastric, and External Spermatic Nerves

The inguinal area is supplied by three nerves: the ilioinguinal, iliohypogastric, and genitofemoral. In 50% of patients, sensory innervation of the inguinal canal depends exclusively on the genital branch of the genitofemoral nerve (also termed the external spermatic nerve in males). In recent years, several publications focusing only on the ilioinguinal and iliohypogastric nerves have appeared in the literature, especially with the development of

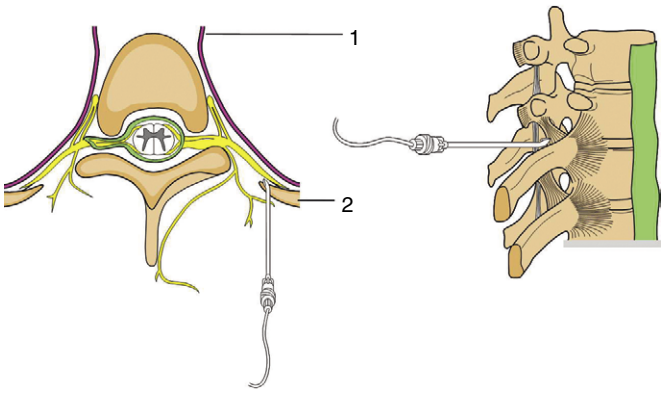

Figure 81-24 Block of the thoracic paravertebral space. 1, Parietal pleura; 2, rib.

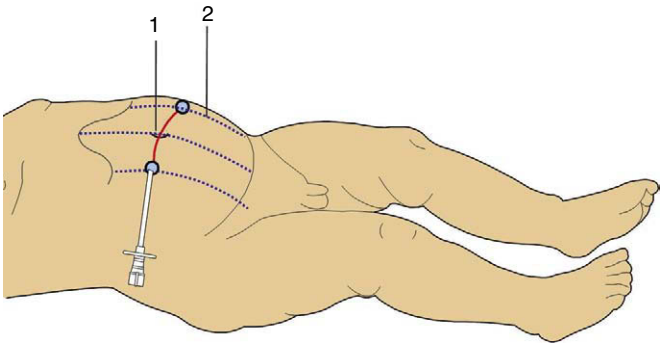

Figure 81-25 Umbilical/rectus sheath block. 1, Umbilicus; 2, lateral border of the left rectus muscle.

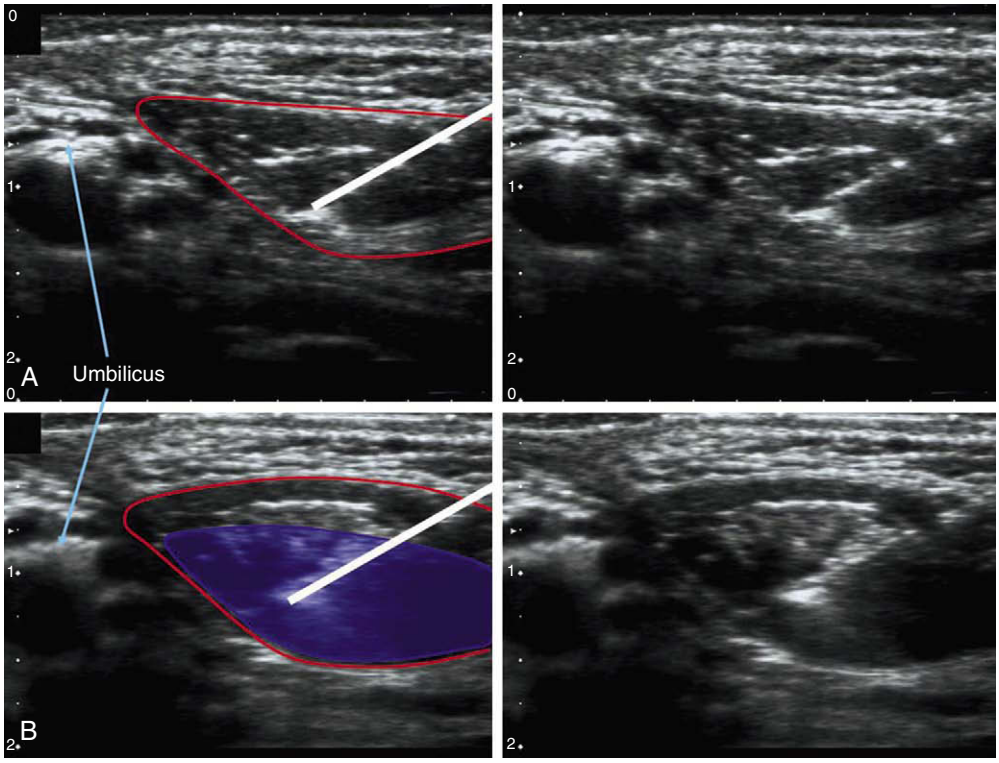

Figure 81-26 Ultrasound-guided insertion of umbilical/rectus sheath. **A,** Insertion of the needle close to the posterior fascia of the rectus muscle. **B,** Injection of the local anesthetic creating a biconvex black cloud. *Red line,* fascia of the rectus sheath muscle; *blue area,* spread of the anesthetic; *diagonal white line,* shadow of the needle.

ultrasound imaging.[242,243] Not surprisingly, the quality of analgesia produced is often unsatisfactory because a major contributor to sensory innervation remains unchanged.

A single injection technique can safely and reliably block the three relevant nerves at once because these nerves are located in the same fascial plane close to the subcutaneous inguinal ring formed by the aponeurosis of the external oblique muscle. The landmarks are the umbilicus, ipsilateral anterior superior iliac spine (ASIS), and midpoint of the inguinal ligament. The ASIS-umbilicus line is divided into four equal parts; the puncture site is located at the union of the lateral fourth with the medial three fourths (Fig. 81-27). The success rate of this technique is very high and its morbidity very low. Several complications have been reported with techniques attempting to locate the ilioinguinal nerve close to the ASIS. At this level, parietal abdominal muscles are slenderized and fibrous. Perceiving distinct losses of resistance, even with ultrasound imaging, is difficult and can be misinterpreted; a consequence may be abdominal penetration and damage to intestinal loops.[244-246] Also, the transverse fascia is continuous with the iliacus fascia; thus, spread of the anesthetic agent at the inner surface of the fascia iliaca can occur and produce a femoral block.[247-249] These adverse effects/complications are not seen with the technique described in this section.

Pudendal Nerve Block

The pudendal nerve provides sensory and motor innervation to the pelvic cavity and its content including external genital organs. Complete blockade of this nerve provides complete analgesia for all operations in this area (surgery of penis, genitourinary surgery below the bladder, anorectal surgery) and can be easily obtained by injecting a local anesthetic in the ischioanal (ischiorectal fossa) space. The patients are placed either in the dorsal decubitus position with the knees flexed and their soles conjoined as for bladder

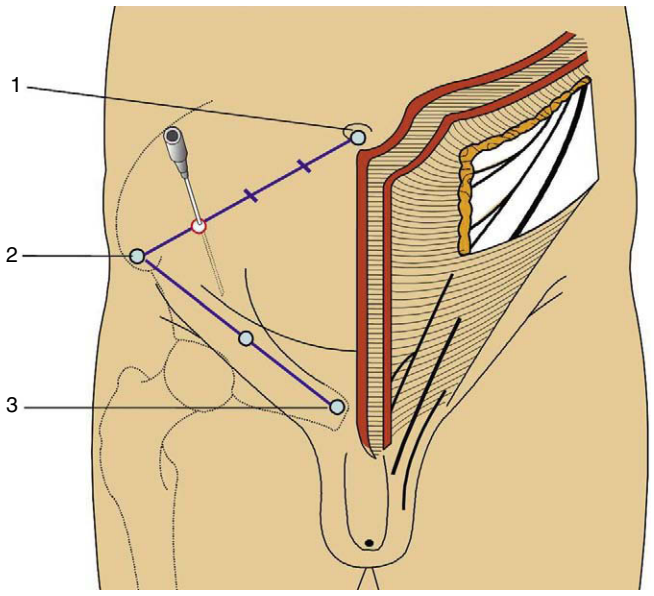

Figure 81-27 Iliohypogastric and ilioinguinal nerve blocks. 1, Umbilicus; 2, anterior iliac crest; 3, pubic spine.

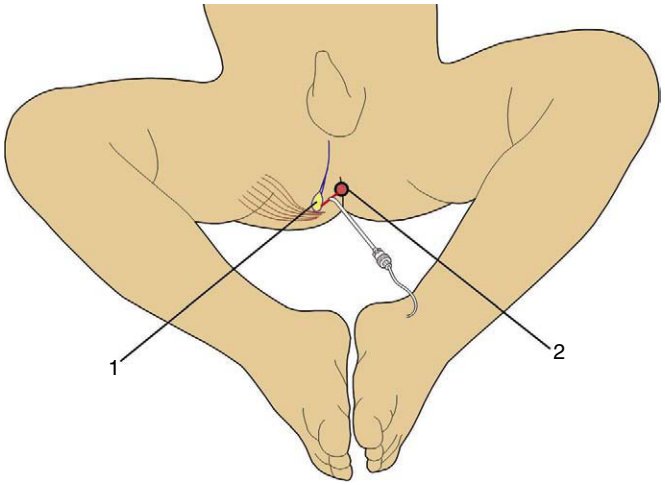

Figure 81-28 Perineal/pudendal nerve block. 1, Ischial tuberosity; 2, anus.

catheterization in girls (infants and young children) or in the lithotomy position (adolescents). The landmarks are the two ischial tuberosities and anus (Fig. 81-28). The distribution of anesthesia depends on the volume of injectate. With 0.1 mL/kg (up to 5 mL), anesthesia is usually limited to the perineal nerve that supplies the posterior part of the scrotum (this is enough to complement an ilioinguinal/iliohypogastric/genitofemoral nerve block when a scrotal incision is required). With 0.3 to 0.4 mL/kg on each side (up to 15 mL), all division branches of the pudendal nerve are blocked, thus providing complete analgesia of the perineum, including blockade of the dorsal nerve of the penis.

Because the pudendal nerve is a mixed nerve, a nerve stimulator can be used to locate it more precisely if this is deemed useful.[250] Ultrasound guidance has been used in adults, but identification of the pudendal nerve was possible in only one half of the procedures. Because this nerve is accompanied by a terminal artery (pudendal artery), only plain solution of local anesthetics must be injected.

Penile Block

Nerve supply to the penis depends mainly on the dorsal nerve of the penis, which is a terminal branch of the pudendal nerve. There is also a contribution of (1) the ilioinguinal nerve and genital branch of the genitofemoral nerve supplying the proximal part of the penis and (2) the perineal nerve, another terminal branch of the pudendal nerve, supplying the midline of the dorsal aspect and sometimes involving the frenulum (Fig. 81-29).

Crossing of Scarpa's fascia can also be verified by ultrasound imaging.[251]

This block procedure is easy and its learning curve is particularly short.[252] The morbidity is extremely low (almost nil when a local anesthetic without epinephrine only is used), whereas complications have been reported after attempts to block the nerves by infiltration of a local anesthetic below Buck's fascia at the dorsal part of the penis.[253,254]

A subcutaneous ring of local anesthetic at the base of the penis can provide satisfactory analgesia but requires relatively large amounts of drug (2 mg/kg bupivacaine) and fails to provide adequate analgesia in 20% of patients.[255] Topical anesthesia has been recommended for urethral meatotomy and even neonatal circumcision,[256] but the quality of analgesia is less than that obtained from "true" penile blocks.[255,257,258]

Other Blocks of Nerves of the Trunk

Interpleural (or intrapleural) blocks that consist of injecting a local anesthetic within the pleural cavity without creating a pneumothorax elicited some enthusiasm 15 years ago but they did not find an established place in pediatric anesthesia and fell into disuse. Other blocks of nerves of the trunk, including paravertebral ganglion, genitofemoral, paracervical (uterosacral), and transsacral nerve blocks are not used in pediatric patients.

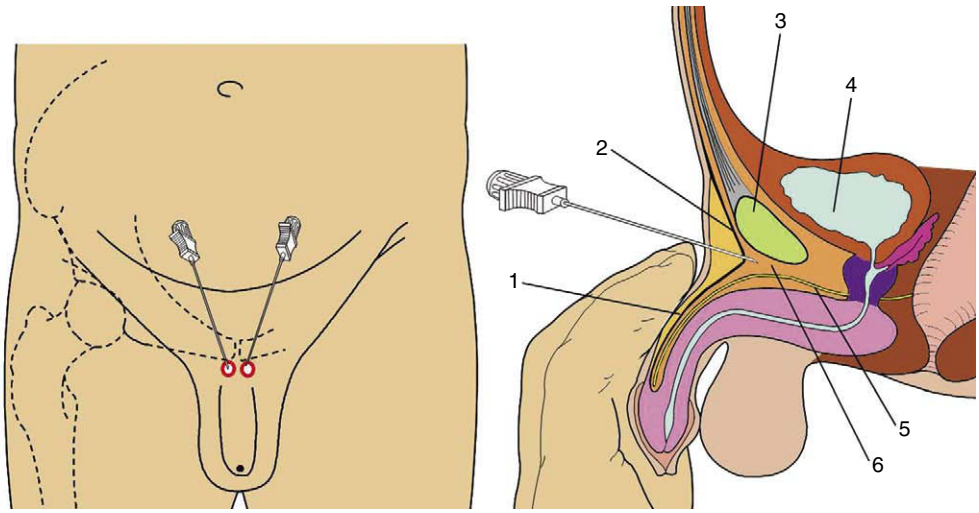

Figure 81-29 Penile block via the subpubic space. 1, Buck's fascia; 2, Scarpa's fascia; 3, pubic bone; 4, bladder; 5, dorsal nerve of penis; 6, subpubic space.

Block of Nerves Supplying the Head and Neck

Cervical Plexus Blocks

Cervical plexus blocks have few but specific indications in pediatric surgery: cervical lymph node biopsy, excision of thyroid nodules,[259,260] and surgery of vocal cords.[261] Only the superficial branches are blocked by a subcutaneous infiltration along the lateral border of the sternocleidomastoid muscle.

Laryngeal Nerve Block

Laryngeal nerve blocks can be used for short-duration laryngoscopic examinations in conscious patients or to facilitate awake intubation when difficult intubation is suspected. It also can be used to prevent or treat laryngospasm.[262] Several techniques have been described but the easiest consists of subcutaneous injection of a local anesthetic just lateral to the dorsal ending of the hyoid horns (on each side) (Fig. 81-30). An intradermal needle is inserted close to the hyoid horn ending until contact is made with cartilage. The needle is then slightly withdrawn and 0.1 to 0.2 mL/kg (up to a maximum of 8 mL) of 1% lidocaine is injected subcutaneously. Excellent laryngeal block is usually obtained.

Cervicothoracic (Stellate) Ganglion Block

Stellate ganglion block is a rather dangerous procedure with very few but very specific indications in children: (1) ventricular tachyarrhythmia due to congenital long QT syndrome[263,264] (a left stellate block is recommended) and (2) severe ipsilateral circulatory disorders of the upper extremity. Patients with certain acute pain syndromes such as herpes zoster ophthalmicus[265] or rare chronic pain syndromes such as sympathetically maintained pain syndrome[266,267] may benefit from the technique.

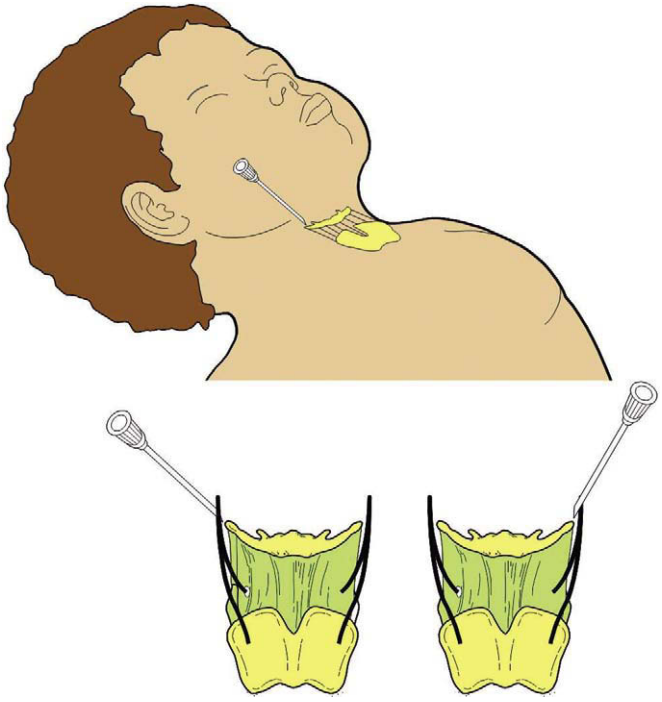

Figure 81-30 Laryngeal nerve block.

Blocks of Nerves Supplying Facial Sensory Innervation

Facial sensory supply is mainly provided by the fifth cranial (trigeminal) nerve. In pediatric patients, only three terminal branches of this nerve are commonly blocked by anesthesiologists, for either emergency (skin lacerations) or elective surgery procedures (cleft lip/palate repair, excision of skin lesions). Ultrasound guidance has not been reported yet, but the technique may be helpful in some patients. These block procedures have a low failure rate and are very safe, provided that no attempt is made to penetrate the foramen from which the relevant nerve emerges (danger of nerve trauma). Two complications can be observed very rarely: hematoma at the site of puncture and intravascular injection (but the volume of injectate is very small, so systemic toxicity is very unlikely).

Block of the Supraorbital and Supratrochlear Nerves

The supraorbital and supratrochlear nerves are terminal branches of the frontal nerve (V_1) that supply the upper eyelid, forehead, and scalp. Indications for blocking these nerves include frontal craniotomy, skin lesion removal of the eyebrow and medial part of the forehead, and placement of frontal ventroperitoneal shunts or an Ommaya reservoir.[268,269] The procedure consists of a subcutaneous infiltration below the eyebrow. The landmarks are the eyebrow and supraorbital foramen, which is located by palpation of the upper orbital rim, at its intersection with the vertical line passing over the ipsilateral centered pupil. The site of puncture is located at midpoint of the orbital rim (Fig. 81-31). An intradermal needle (25, 27, or 30 gauge) is inserted medially toward the supraorbital foramen where 1.0 to 1.5 mL of local anesthetic (1% lidocaine or 0.25% bupivacaine, with or without epinephrine) is injected. The needle is then removed, and strong pressure is exerted on the skin covering the supraorbital foramen to favor the spread of the drug and prevent the development of hematoma.

Block of the Infraorbital Nerve

The infraorbital nerve is a terminal branch of the maxillary nerve (V_2). It emerges from the infraorbital foramen and divides into four terminal subcutaneous branches (internal and external nasal nerves, inferior palpebral nerve, and superior labial nerve) that supply the nose, lower eyelid, and upper lip.

Infraorbital nerve blocks are indicated for surgery of cleft lip,[270,271] laceration of upper lip,[272] endoscopic surgery of sinus, surgery of nasal septum, and transsphenoidal hypophysectomy. The procedure is contraindicated in case of facial trauma with facture and displacement of the orbital floor, which prevents localization of the infraorbital foramen and increases the hazards of (additional) nerve damage.

The percutaneous technique consists of inserting an intradermal needle at the crossing of the vertical line passing over the ipsilateral centered pupil with the perpendicular line passing just

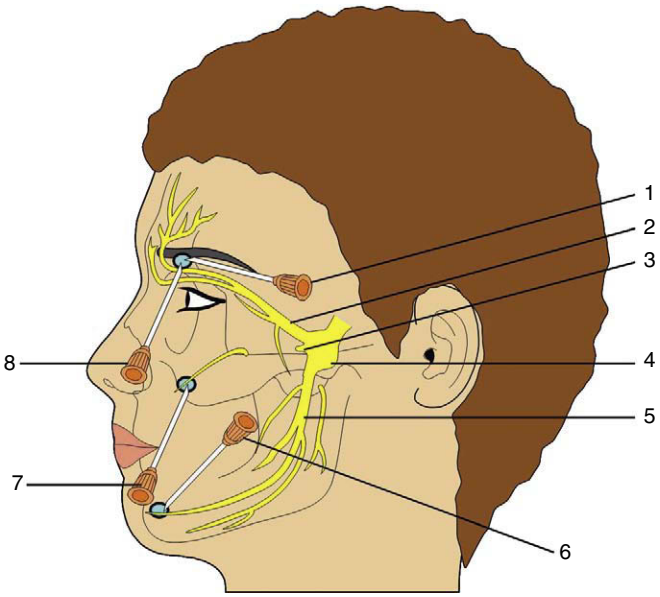

Figure 81-31 Block of nerve supplying the face: supraorbital, infraorbital, and mental nerve blocks. 1, Block of the supratrochlear nerve; 2, ophthalmic nerve; 3, maxillary nerve; 4, trigeminal ganglion (also gasserian ganglion or semilunar ganglion); 5, mandibular nerve; 6, block of the mental nerve; 7, block of the infraorbital nerve; 8, block of the supraorbital nerve.

below the nostrils.[270] The needle is directed cephalad toward the lower border of the infraorbital foramen (avoiding penetration into the foramen) until bone contact is made (see Fig. 81-31). The anesthetic is then injected following usual safety rules. The skin covering the infraorbital foramen is then gently massaged to promote homogeneous diffusion of the drug.

Both approaches provide excellent analgesia of the lower eyelid, jaw, palate, and ipsilateral nostril. They should be performed on both sides to provide excellent intraoperative and postoperative analgesia for cleft lip repair.

Block of the Mental Nerve

The mental nerve is the terminal branch of the mandibular nerve (V_3) that supplies the lower lip and chin. Main indications for mental nerve blocks are with surgery involving lower incisor and canine teeth; bilateral blocks allow pain-free procedures on the lower lip. The landmark is the mental foramen located by palpation on the line passing over the ipsilateral centered pupil. Again, two approaches can be used.

In the intrabuccal approach, after turning the lower lip outward, the lower incisor and first premolar are located. The intradermal needle is inserted into the gingival sulcus toward the mental foramen over which the anesthesiologist maintains his or her index finger. When the tip of the needle is close to the foramen, 1 to 2 mL of the anesthetic is slowly injected after a negative aspiration test. The skin covering the mental foramen is then gently massaged to favor homogeneous diffusion of the drug.

In the percutaneous approach the intradermal needle is inserted slightly below the skin projection of the mental foramen and directed toward its lower border (see Fig. 81-31). The drug is then injected as just described, and the infiltrated area is gently massaged.

Other Blocks

Several other conduction blocks of nerves supplying the head are commonly used in adults but only occasionally in children for extended laceration of the scalp (scalp blocks), ophthalmic surgery, operations involving the facial bones, or dental procedures. These blocks are not performed by anesthesiologists and are not described here.

Other Procedures

Intravenous Regional Anesthesia

Intravenous regional anesthesia (Bier block) has never been very popular in pediatric anesthesia. Currently, the technique is outdated, even though it is still used in some institutions mainly for fracture repairs (often in emergency departments).[273-275] The technique is the same as in adults. The limb is exsanguinated either by an Esmarch bandage or by simple gravitation. A tourniquet is placed around the proximal part of the arm and inflated at two to three times the systolic pressure before the Esmarch bandage is removed and 1 mL/kg of 0.5% lidocaine (not exceeding 3 mg/kg) is injected. Prilocaine can be used instead in adolescents. Children tolerate the pain produced by the inflated tourniquet very poorly, and this technique was responsible for several deaths in the past.

Local Infiltrations and Topical Anesthesia

Surface Anesthesia

Topical anesthesia has gained an established place for 15 years owing to the availability of new ointments containing mixtures of local anesthetics, such as EMLA cream, TAC cream, or lidocaine-epinephrine-tetracaine gel. When applied on the skin and maintained in place with a sterile dressing for 1 hour at least, these creams can provide complete analgesia of the skin and subcutaneous structures. The duration of application may vary among the different cream formulations. They allow pain-free performance of venous cannulation and most techniques requiring needle puncture, such as lumbar taps and repair of skin lacerations are made possible.[276-278] Recently, new devices and techniques have been developed to shorten the time necessary to obtain effective analgesia: iontophoresis,[279,280] heat-activated systems, high-pressure needle-free delivery systems,[281,282] and two techniques still under development, skin electroporation by application of high-frequency currents and sonophoresis by use of ultrasound waves.

Surface anesthesia of the larynx by local anesthetic sprays has long been contraindicated in children, but the efficacy and safety of the technique are now established,[28] provided that low doses of 5% lidocaine are administered (i.e., 8 mg in infants <10 kg and 16 mg in infants >10 kg). Topical anesthesia can be produced by instilling eye lotions containing a local anesthetic (oxybuprocaine) or using auricular lotion/ointment or viscous solutions on buccal mucosa and gums. Care must be taken to avoid administering excessive dosage and to prevent inadvertent swallowing of concentrated solutions of local anesthetics, especially in infants.

Intradermal Wheals

Intradermal wheals are routinely used in adult patients to anesthetize the skin covering deeper structures to be approached. The technique is used less often in children, except for anesthetizing the puncture site of a regional block procedure in nonanesthetized children. It consists of inserting a 25-, 27- or 30-gauge interdermal needle almost tangentially to the skin, with the bevel facing downward, without penetrating the subcutaneous layers. A small amount (<0.5 mL) of local anesthetic (0.5% to 1% lidocaine or prilocaine, with or without epinephrine) is then injected. The skin covering the wheal looks like an orange peel and almost immediate anesthesia of the relevant area is obtained. The only drawback of this technique is that the injection is moderately painful.

Local Infiltrations and Field Blocks

Infiltrations of local anesthetics (lidocaine, prilocaine, bupivacaine, or levobupivacaine with or without epinephrine or plain ropivacaine) in a fan-shaped manner in the subcutaneous fat and muscles surrounding the operative site (or the edges of a wound) provide adequate analgesia for surgery of soft tissues and wound stitching. Precautions must be taken to avoid bacterial contamination and overdosage, especially in case of extensive wounds or reinjections. In the latter instance, an important consideration is that plasma concentration of lidocaine after subcutaneous administration is linearly related to the dose per kilogram of body weight.[283]

Other Injections

Tracheal instillation of local anesthetics is regularly used in adults for awake tracheal intubation and prevention of laryngospasm but is not commonly practiced in children because of dangers of systemic toxicity and potential damage to the vocal cords.

The increasing use of laparoscopic surgery has generated new types of abdominal pain. Intraperitoneal injection of local anesthetics led to contradictory results in adult studies. The technique has not been evaluated in children, both in terms of safety and efficacy, and caution is recommended in considering its potential use.

Intra-articular injection of local anesthetics provides consistent analgesia of joint capsules. The technique can be used for diagnostic or therapeutic procedures (injection of painful joints), but it is almost never performed by anesthesiologists and its efficacy is inconstant.

Conclusion

The importance of regional anesthesia has considerably increased during the past 3 decades. Block procedures represent a major therapeutic option for preventing and treating pain both intraoperatively and postoperatively, especially for outpatient surgery (single-shot procedures) and for long-lasting postoperative pain relief (with catheter techniques). Over the years, there was a shift from neuraxial toward peripheral nerve blockade to reduce the incidence of adverse effects and allow early discharge from the hospital. Peripheral catheter techniques are becoming routine practice, and selected patients can be managed at home. The expansion of regional anesthesia was favored by the development of devices specifically designed for pediatric use and techniques, allowing precise localization of nerve trunks and not requiring the cooperation of the patient. Nerve stimulation is currently the gold standard for locating nerves and plexuses, but ultrasound guidance is an emerging technique that is currently challenging the primary role of neurostimulation. The growing number of publications based on regional anesthesia procedures, in children as well as in adults, is good testimony of the efficacy and safety of regional techniques if they are adequately performed. Provided that they are taught in detail to residents in anesthesia, these techniques will probably continue their expansion as the reference techniques for management of procedural, trauma, and surgical pain.

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Charles J. Coté

82 Pediatric Anesthesia

Key Points

1. During the first few weeks of life, neonates are vulnerable to the so-called flip-flop circulation, that is, going from an adult-type to a fetal-type circulation. Factors such as hypoxia, hypercapnia, acidosis, infection, hypothermia, and prematurity increase the potential for sudden increases in pulmonary artery pressure and subsequent shunting of blood past the lungs through a patent foramen ovale or the ductus arteriosus, which may reopen, particularly during the first 10 days of life.
2. The reduced cellular mass of the neonatal heart devoted to contractility results in less compliant ventricles. This leads to sensitivity to volume loading, poor tolerance of afterload (i.e., the development of biventricular failure), and rate-dependent cardiac output. In addition, the reduced cardiac calcium stores produces increased susceptibility to myocardial depression by potent anesthetic agents. This also makes neonates dependent on exogenous calcium (blood ionized calcium) values and vulnerable to the negative inotropic effects of ionized hypocalcemia, particularly that caused by infusion of citrated blood products such as fresh frozen plasma.
3. The neonatal airway differs from the adult airway in five ways: the tongue is larger, the larynx is located higher in the neck, the glottis is shaped differently and angled over the laryngeal inlet, the vocal cords are angled, and the narrowest portion is the subglottic region at the level of the cricoid cartilage. Accordingly, straight blades are more useful than curved blades in neonates, and uncuffed endotracheal tubes are commonly used.
4. Glomerular filtration and tubular function are immature but develop rapidly in the newborn period; adult levels are achieved at approximately the age of 2 years. The frequency with which medications excreted by the kidneys (e.g., antibiotics) can be administered during the first month of life changes rapidly. Particular attention is required in this period to avoid drug-induced toxicity (e.g., ototoxicity) caused by excessive plasma drug levels.
5. Hepatic metabolic capacity is immature at birth. Some cytochrome P450 enzymes (phase I reactions) are fully developed, whereas others are approximately 50% of adult values. Phase II reactions, that is, reactions that make a drug more water soluble, are usually impaired in neonates. Some of these reactions do not achieve maturity until the age 1 year. This hepatic immaturity can have important clinical implications regarding a neonate's ability to excrete some medications, such as benzodiazepines.
6. Cardiac dysfunction from anesthetic overdose is a particular danger for neonates and infants because of a combination of factors, including immaturity of the myocardium, decreased calcium stores of the neonatal myocardium, and the "systems issue" of the vaporizers for halothane and sevoflurane having different maximum minimum alveolar concentration (MAC) delivery capability; that is, nearly 6 MAC multiples of halothane may be delivered to a newborn, whereas only 2½ MAC multiples can be delivered with sevoflurane. Thus, anesthetic agent–induced cardiac arrest is a function of vaporizer design and vulnerability of the neonatal myocardium to anesthetic-induced cardiac depression, especially on changing from spontaneous to controlled respirations.
7. Remifentanil is a unique potent opioid in neonates. Unlike virtually every other medication used in newborns, its half-life is shorter rather than longer as in older children. This, then, makes the ability to rapidly induce or stop an intense opioid effect even easier to achieve in neonates than in older children. Careful attention to opioid-induced bradycardia and chest wall rigidity is obviously very important.
8. Former preterm infants younger than 60 weeks' postconceptual age are potentially at risk for postoperative apnea, and those who are anemic are at particular risk (i.e., hemoglobin <10 gm/dL). Both gestational age and postconceptual age at the time of surgery are independent risk factors. The use of regional anesthesia in these children may reduce but does not

eliminate the incidence of postanesthesia apnea. Postoperative apnea has been associated with all of the inhaled agents, including desflurane and sevoflurane.

9. Preoperative laboratory testing is minimal for most pediatric patients. The only groups of children who require routine hemoglobin measurement are infants younger than 6 months to assess the severity of the physiologic hemoglobin nadir (especially former preterm infants with a potential risk for apnea) and older children expected to experience significant blood loss. Preoperative chest radiographs are not generally indicated. Children who have undergone chemotherapy with anthracyclines, children with congenital heart disease, and neonates at risk for associated cardiac anomalies may require a preoperative echocardiogram. Children undergoing chemotherapy should usually have a complete recent hematology profile, including platelet counts. Children taking antiseizure medications will generally benefit from preoperative assessment to ensure therapeutic levels.
10. Temperature regulation is a particular issue for neonates and infants. Because of the large body surface–to–weight ratio, they are especially vulnerable to intraoperative hypothermia. Efforts to maintain a warm operating room, use of warming devices such as hot air mattresses, warm surgical skin preparation solutions, and transport in an appropriate transport device, as well as keeping the patient covered during transport, all help prevent dangerous hypothermia.

Provision of safe anesthesia for pediatric patients depends on a clear understanding of the physiologic, pharmacologic, and psychological differences between children and adults. Special consideration must be given to preterm infants, as well as to those with congenital malformations. This chapter describes how the unique characteristics of children influence the safe conduct of anesthetic procedures.

Developmental Considerations

Organogenesis takes place within 8 weeks of conception; organ function develops during the second trimester; and the infant gains weight, primarily muscle and fat, during the third trimester. Any physiologic or pharmacologic injury or stress during the first trimester may cause abnormal organogenesis; during the second trimester, abnormal functional development of organs; and during the third trimester, smaller organs or reduced muscle and fat mass. Injuries and stress take the form of congenital viral infections, exposure to drugs (therapeutic or recreational), nutritional insufficiency (caloric or vascular), or other maternal illness. A genetic predisposition to developmental malformations can also produce adverse effects. Such interruptions in normal growth and development may cause a variety of physiologic abnormalities ranging from simple preterm birth to a constellation of congenital malformations.

A preterm infant is one born before 37 weeks gestation; a postmature infant is one born after 42 weeks gestation. Any infant born at less than 2500 g is considered a low-birth-weight infant. Plotting weight against gestational age allows classification into three general categories: small for gestational age, appropriate for gestational age, or large for gestational age (Fig. 82-1). Infants who are small or large for gestational age often have developmental problems or difficulties associated with maternal disease (Table 82-1). Careful physical and neurologic examination at birth allows a fairly accurate estimate of gestational age. The anesthesiologist should be aware of this type of evaluation so that potential problems can be anticipated. Obtaining a perinatal history of problems during pregnancy (e.g., maternal drug abuse, maternal infection, eclampsia, diabetes) or during and after delivery (e.g., fetal distress, meconium aspiration, prematurity, postdelivery intubation) is also valuable for assessing possible anesthetic implications that may require specific considerations during and after anesthetic management. In the weeks after birth, measures of weight, height, and head circumference are plotted on standard developmental curves; deviations from normal (i.e., crossing developmental lines) usually indicate a severe physiologic insult. The anesthesiologist should examine the growth chart to evaluate how the child is developing.

The Cardiovascular System

The cardiovascular system undergoes dramatic physiologic and maturational changes during the first year of life. In utero, most

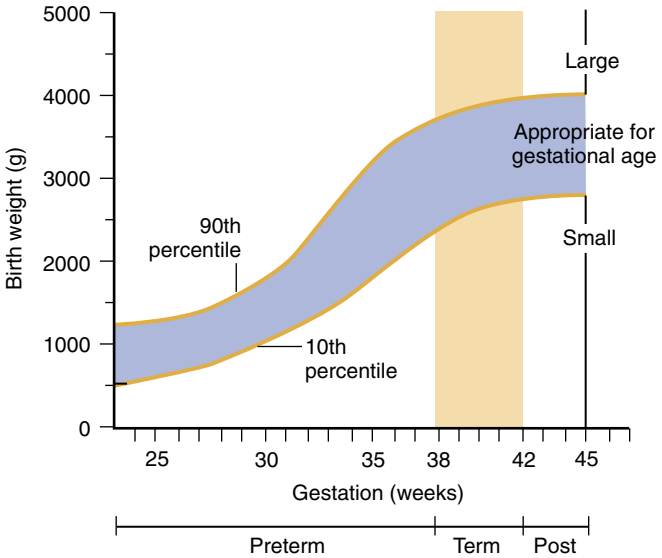

Figure 82-1 Plotting birth weight against gestational age for neonates determines whether infants are small, appropriate, or large for gestational age. Babies who are either small or large for gestational age are particularly likely to have a variety of problems such as metabolic, developmental, infectious, or structural abnormalities, as well as drug addiction and withdrawal. *(Modified from Battaglia FC: Intrauterine growth retardation. Am J Obstet Gynecol 106:1103-1114, 1970, with permission.)*

Table 82-1 Common Neonatal Problems Associated with Weight and Gestational Age

Gestational Age	Body Size	Neonatal Problems Occurring with Increased Frequency
Preterm	Small	Respiratory distress syndrome Apnea Hypoglycemia Hypomagnesemia Hypocalcemia Fetal alcohol syndrome Viral infection Thrombocytopenia Congenital anomalies Maternal drug addiction Neonatal asphyxia Aspiration pneumonia
Term	Small	Congenital anomalies Viral infection Thrombocytopenia Maternal drug addiction Neonatal asphyxia Hypoglycemia Fetal alcohol syndrome
Postmature	Small	Congenital anomalies Viral infection Thrombocytopenia Maternal drug addiction Neonatal asphyxia Aspiration pneumonia Hypoglycemia Fetal alcohol syndrome
Any gestational age	Large	Birth trauma Hyperbilirubinemia Hypoglycemia: infant of diabetic mother Transposition of great arteries

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of the cardiac output is directed from the placenta across the foramen ovale into the ascending aorta (oxygenated blood), whereas superior vena cava blood (deoxygenated) is directed to both the pulmonary artery and the ductus arteriosus. This pattern of circulation results in minimal intrauterine pulmonary blood flow. At birth, a number of events change hemodynamic interactions such that the fetal circulation becomes an adult-type circulation. Specifically, the placenta is removed from the circulation; portal blood pressure falls, which causes the ductus venosus to close; and blood becomes oxygenated through the lungs. Exposure of the ductus arteriosus to oxygenated blood induces ductal closure. As a result of the combined effects of lung expansion, exposure of blood to oxygen, and loss of low resistance through placental blood flow, pulmonary vascular resistance decreases while peripheral vascular resistance rises rapidly. The fall in pulmonary vascular resistance occurs on the first day of life and continues to decrease gradually during the next several years as the architecture of the pulmonary vessels changes. An increase in pressure on the left side of the heart (caused by the rise in peripheral vascular resistance) induces mechanical closure of the foramen ovale. Thus, all three connections between the right and left side of the circulation close. Although closure of the ductus arteriosus probably occurs primarily in response to a rise in arterial oxygen concentration, successful completion requires arterial muscular tissue. The fact that such tissue is less prevalent in preterm infants may account, in part, for the high incidence of patent ductus arteriosus in preterm infants. True mechanical closure by fibrosis does not occur until 2 to 3 weeks of age.

During this critical period, the infant readily reverts from the adult circulation to a fetal type of circulation; this state is called transitional circulation. Many factors (hypoxia, hypercapnia, anesthesia-induced changes in peripheral or pulmonary vascular tone) can affect this precarious balance and result in a sudden return to the fetal circulation. When such a "flip-flop" occurs, pulmonary artery pressure increases to systemic levels, blood is shunted past the lungs via the patent foramen ovale, and the ductus arteriosus may reopen and allow blood to shunt at the ductal level. A rapid downhill spiral may occur and lead to severe hypoxemia, which explains why hypoxemic events in infants are often prolonged despite adequate pulmonary ventilation with 100% oxygen.

Risk factors increasing the likelihood of prolonged transitional circulation include prematurity, infection, acidosis, pulmonary disease resulting in hypercapnia or hypoxemia (aspiration of meconium), acidosis, hypothermia, and congenital heart disease. Care must be directed to keeping the infant warm, maintaining normal arterial oxygen and carbon dioxide tension, and minimizing anesthetic-induced myocardial depression.

The myocardial structure of the heart, particularly the volume of cellular mass devoted to contractility, is significantly less developed in neonates than in adults. These differences, as well as developmental changes in contractile proteins, produce a leftward displacement of the cardiac function curve and less compliant ventricles. This developmental immaturity of myocardial structures accounts for the tendency toward biventricular failure, sensitivity to volume loading, poor tolerance of increased afterload, and heart rate–dependent cardiac output.[1,2] Another issue is that cardiac calcium stores are reduced because of immaturity of the sarcoplasmic reticulum; consequently, neonates have a greater dependence on exogenous (ionized) calcium and probably increased susceptibility to myocardial depression by potent inhaled agents that have calcium channel blocking activity.

The Pulmonary System

The pulmonary system is not capable of sustaining life until both the pulmonary airways and the vascular system have matured sufficiently to allow exchange of oxygen from "air" to the bloodstream across the pulmonary alveolar/vascular bed. Independent life is not generally possible until a gestational age of 24 to 26 weeks. Alveoli increase in number and size until the child is approximately 8 years old. Further growth is manifested as an increase in size of the alveoli and airways. At term, complete development of surface-active proteins helps maintain patency of the airways. If a child is born prematurely and these proteins are insufficient, respiratory failure (respiratory distress syndrome) may follow.

Several anatomic differences make respiration less efficient in infants. The small diameter of the airways increases resistance to airflow; resistance is inversely proportional to the radius raised

to the fourth power for laminar flow and to the fifth power for turbulent flow. The airway of infants is highly compliant and poorly supported by surrounding structures. The chest wall is also highly compliant, so the ribs provide little support for the lungs; that is, negative intrathoracic pressure is poorly maintained. Thus, each breath is accompanied by functional airway closure. Dead space ventilation is proportionally similar to that in adults; however, oxygen consumption is two to three times higher. In preterm infants, the work of breathing is approximately three times that in adults, and this work can be increased significantly by cold stress (increased metabolic demand for oxygen) or any degree of airway obstruction. Another important factor is the composition of the diaphragmatic and intercostal muscles. These muscles do not achieve the adult configuration of type I muscle fibers until the child is approximately 2 years old (Fig. 82-2).[3] Because type I muscle fibers provide the ability to perform repeated exercise, any factor that increases the work of breathing contributes to early fatigue of the respiratory muscles of infants. These differences partially explain the infant's high respiratory rate, the rapidity with which hemoglobin desaturation occurs, and their propensity for fatigue and apnea.

Differences in airway anatomy make the potential for technical airway difficulties greater in infants than in teenagers or adults. The airway of infants differs in five ways[4]: (1) the relatively large size of the infant's tongue in relation to the oropharynx increases the likelihood of airway obstruction and technical difficulties during laryngoscopy; (2) the larynx is located higher (more cephalic) in the neck, thus making straight blades more useful than curved blades; (3) the epiglottis is shaped differently, being short, stubby, omega shaped, and angled over the laryngeal inlet; control with the laryngoscope blade is therefore more difficult; (4) the vocal cords are angled, so a "blindly" passed endotracheal tube may easily lodge in the anterior commissure rather than slide into the trachea; and (5) the infant larynx is funnel shaped, the narrowest portion occurring at the cricoid cartilage (Fig. 82-3). Classic teaching has been that the adult larynx is cylindrical and the infant larynx is funnel shaped. However, recent autopsy data have demonstrated that the narrowest portion in approximately 70% of adults is also in the subglottic region at the level of the cricoid cartilage, but the opening is so large that commonly used endotracheal tubes are nearly always easy to advance past the glottic opening.[5] In infants or young children, an endotracheal tube that easily passes the vocal cords may be tight in the subglottic region because of the relatively greater proportional narrowing at the level of the cricoid cartilage. It is for this reason that uncuffed endotracheal tubes have generally been preferred for children younger than 6 years. However, the development of better endotracheal tube design and several prospective studies have combined to allow more common use of cuffed endotracheal tubes, even in infants.[6] It is vital to be certain that there is a leak around the cuff (with or without inflation) because injury to the tracheal mucosa is still possible. The recently introduced Microcuff tube may further improve the safety of cuffed endotracheal tubes; the new material is very soft, the shape of the cuff is more uniform (allowing a more uniform distribution of lateral sealing pressure), and the cuff itself is located more distally and thus perhaps beyond the cricoid cartilage (Fig. 82-4).[7] Unfortunately, at this time their cost is prohibitive (three to four times more expensive than current standard endotracheal tubes) for routine use. It is likely that for the present, the more expensive endotracheal tubes will be reserved for children with anticipated prolonged intubation and the lower-cost endotracheal tubes used for short-term intraoperative intubation.

Infants have often been described as obligate nasal breathers; however, approximately 8% of preterm neonates (31 to 32 weeks postconceptual age [PCA]) and 40% of term infants can

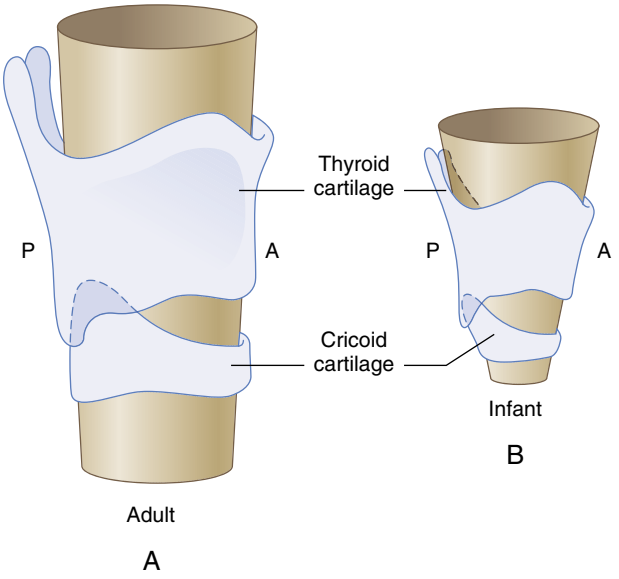

Figure 82-3 The narrowest part of the adult larynx and the pediatric larynx is at the level of the cricoid cartilage. Traditionally, the adult larynx was thought to be cylindrically shaped, but autopsy data suggest that the narrowing in adults (**A**) is not as pronounced as it is in infants (**B**). The narrowest part of the infant larynx occurs at the level of the cricoid cartilage; the normal adult configuration of the larynx is not achieved until the teenage years. This anatomic difference is one of the reasons why uncuffed endotracheal tubes have been traditionally preferred for children younger than 6 years. A, anterior; P, posterior. *(From Coté CJ, Lerman J, Todres ID [eds]: A Practice of Anesthesia for Infants and Children, 4th ed. Philadelphia, WB Saunders, 2008.)*

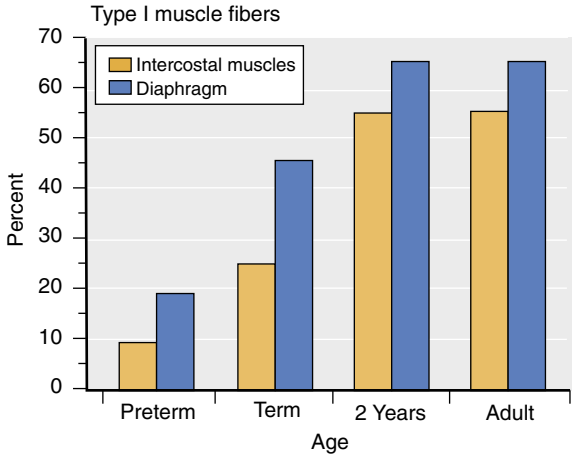

Figure 82-2 The composition of the diaphragm and intercostal muscles changes markedly during the first 2 years of life. The number of type I muscle fibers is inversely related to age and may account in part for the ease of inducing respiratory fatigue as the work of breathing increases. *(Data from Keens TG, Bryan AC, Levison H, Ianuzzo CD: Developmental pattern of muscle fiber types in human ventilatory muscles. J Appl Physiol 44:909-913, 1978.)*



Figure 82-4 The Microcuff endotracheal tube ((Microcuff; PET; I-MPEDC, Microcuff GmbH, Weinheim, Germany, Kimberly-Clark USA) (*right*) has a soft polyurethane cuff that inflates symmetrically and is located more distally than standard endotracheal tubes (*left*). This configuration results in more even pressure applied to the mucosa of the trachea and perhaps less potential for edema formation in the subglottic region because the cuff is located below the cricoid cartilage.

but not yet induced (stimulated) by the agents that they metabolize. As the infant grows, the ability to metabolize medications increases rapidly for two reasons: (1) hepatic blood flow increases and more drug is delivered to the liver, and (2) the enzyme systems develop and are induced.[8] The cytochrome P450 system is responsible for phase I drug metabolism of lipophilic compounds. This system reaches approximately 50% of adult values at birth, thus suggesting an overall reduced capacity for drug metabolism (e.g., caffeine). However, this generalization does not hold true for all lipophilic medications, and the ability of neonates to metabolize some drugs is dependent on specific individual drug cytochromes. CYP3A is generally present at adult values at birth,[9] whereas other cytochromes are absent or reduced.[10] Phase II reactions involve conjugation, which makes the drug more water soluble to facilitate renal excretion.[11] These reactions are often impaired in neonates and result in jaundice (decreased bilirubin breakdown) and long drug half-lives (e.g., morphine and benzodiazepines). Some of these reactions do not achieve adult activity until after 1 year of age.

A preterm infant's liver has minimal glycogen stores and is unable to handle large protein loads. This difference accounts for the neonate's tendency toward hypoglycemia and acidemia and for the failure to gain weight when the diet contains too much protein. Additionally, plasma levels of albumin and other proteins necessary for binding of drugs are lower in full-term newborns (and are even lower in preterm infants) than in older infants (Fig. 82-6). This condition has clinical implications regarding neonatal coagulopathy (e.g., the need for vitamin K at birth), as well as for drug binding and pharmacodynamics, in that the lower the albumin value, the less protein binding of some drugs with resultant greater levels of unbound drug (unbound drug is the portion available to cross biologic membranes). In addition, binding of

convert to oral breathing if the nasal airway is obstructed. Almost all infants can easily convert to oral breathing by 5 months of age. Most infants can convert to oral breathing if the obstruction lasts longer than 15 seconds.

The Kidneys

Renal function is markedly diminished in neonates and further diminished in preterm infants because of low perfusion pressure and immature glomerular and tubular function (Fig. 82-5). Nearly complete maturation of glomerular filtration and tubular function occurs by approximately 20 weeks after birth, although it is somewhat delayed in preterm infants. Complete maturation of renal function takes place by about 2 years of age. Thus, the ability to handle free water and solute loads may be impaired in neonates, and the half-life of medications excreted by means of glomerular filtration will be prolonged (e.g., antibiotics, hence the longer intervals between doses in neonates).

The Liver

At term, the functional maturity of the liver is somewhat incomplete. Most enzyme systems for drug metabolism are developed

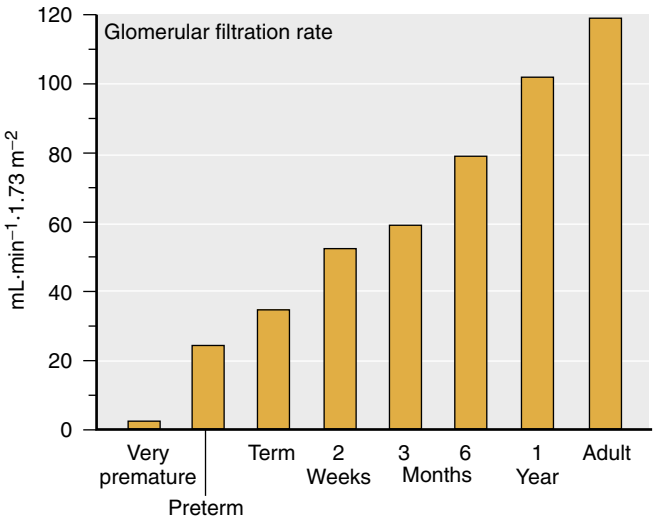

Figure 82-5 Glomerular filtration is markedly impaired at birth but develops rapidly during the first year of life. The ability of the kidney to handle large amounts of solutes and water is also limited during the first several months of life. These developmental changes have significant implications for drug excretion and fluid therapy, particularly during the first 4 weeks of life. Maturation of renal function may be delayed in sick neonates. *(Data from McCrory WW: Developmental Nephrology. Cambridge, MA, Harvard University Press, 1972.)*

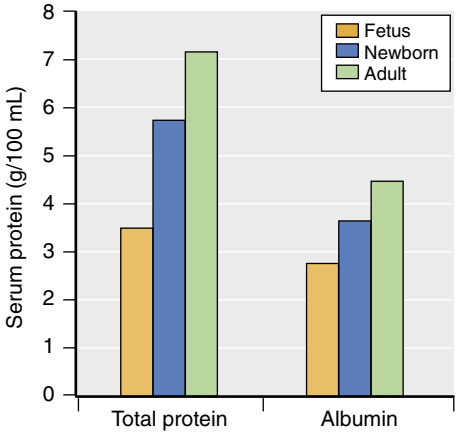

Figure 82-6 Changes in total serum protein and albumin values with maturation. Note that total protein and albumin are less in preterm than in term infants and less in term infants than in adults. The result may be altered pharmacokinetics and pharmacodynamics for drugs with a high degree of protein binding because less drug is protein bound and more is available for clinical effect. *(Abstracted from Ehrnebo M, Agurell S, Jalling B, et al: Age differences in drug binding by plasma proteins: Studies on human fetuses, neonates and adults. Eur J Clin Pharmacol 3:189-193, 1971. From Coté CJ, Lerman J, Todres ID [eds]: A Practice of Anesthesia for Infants and Children, 4th ed. Philadelphia, WB Saunders, 2008.)*

some drugs to albumin may be altered in the presence of hyperbilirubinemia in the neonatal period.

The Gastrointestinal System

At birth, gastric pH is alkalotic; by the second day of life, pH is in the normal physiologic range for older children. The ability to coordinate swallowing with respiration does not fully mature until infants are 4 to 5 months of age, thus resulting in a high incidence of gastroesophageal reflux in newborns. This problem is particularly common in preterm infants. In general, if a developmental problem occurs within the gastrointestinal system, symptoms will occur within 24 to 36 hours of life; upper intestinal abnormalities are manifested as vomiting and regurgitation, whereas lower intestinal abnormalities produce abdominal distention and failure to pass meconium.

Thermoregulation

Infants are especially vulnerable to hypothermia (see also Chapter 48) because of the large ratio of body surface area to weight, the thinness of the skin, and a limited ability to cope with cold stress. Cold stress will result in increased oxygen consumption and can cause metabolic acidosis. A preterm infant is more susceptible because of even thinner skin and limited fat stores. The infant may compensate by means of shivering and nonshivering (cellular) thermogenesis. The minimal ability to shiver during the first 3 months of life makes cellular thermogenesis (metabolism of brown fat) the principal method of heat production. It is very important to address all aspects of possible heat loss during anesthesia, as well as during transport to and from the operating room. Placing the baby on a warming mattress and warming the operating room (80°F or warmer) reduce heat lost by conduction. Keeping the infant in an incubator, covered with blankets, minimizes heat lost through convection. The head should also be covered. Heat lost from radiation is decreased with the use of a double-shelled Isolette during transport. Heat lost through evaporation is lessened by humidification of inspired gases, the use of plastic wrap to decrease water loss through the skin, and warming of skin disinfectant solutions. Hot air blankets are the most effective means of warming children. Anesthetic agents can alter many thermoregulatory mechanisms, particularly nonshivering thermogenesis in neonates.

Pharmacology and Pharmacodynamics

Developmental Pharmacology

The response of infants and children (and particularly neonates) to medications is modified by many factors: body composition, protein binding, body temperature, distribution of cardiac output, functional maturity of the heart, maturation of the blood-brain barrier, the relative size (as well as functional maturity) of the liver and kidneys, and the presence or absence of congenital malformations.[8]

The body compartments (fat, muscle, water) change with age (Fig. 82-7). Total body water content is significantly higher in preterm than in term infants and in term infants than in 2-year-olds. Fat and muscle content increases with age. These alterations in body composition have several clinical implications for neonates: (1) A drug that is water soluble has a larger volume of distribution and usually requires a larger initial dose (mg/kg) to achieve the desired blood level (e.g., most antibiotics, succinyl-

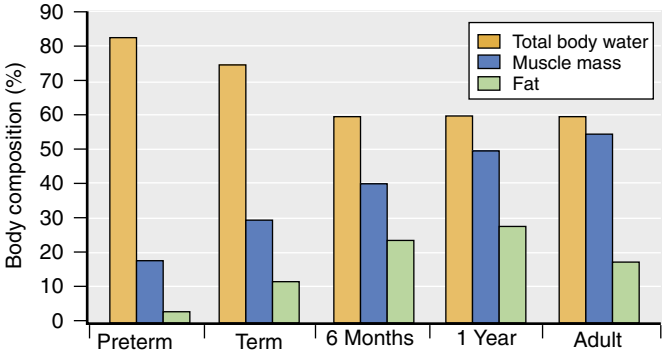

Figure 82-7 Body composition changes rapidly in preterm and term infants during the first 12 months of life. Their high water content provides a large volume of distribution for water-soluble medications, whereas their low fat and muscle content provides a small reservoir for drugs that depend on redistribution into these tissues for termination of drug effect. Thus, body composition may significantly affect pharmacokinetics and pharmacodynamics. *(Data from Friis-Hansen B: Body composition during growth. In vivo measurements and biochemical data correlated to differential anatomical growth. Pediatrics 47:169-181, 1971. From Coté CJ, Lerman J, Todres ID [eds]: A Practice of Anesthesia for Infants and Children, 4th ed. Philadelphia, WB Saunders, 2008.)*

choline); (2) because there is less fat, a drug that depends on redistribution into fat for termination of its action will have a longer clinical effect (e.g., thiopental); and (3) a drug that redistributes into muscle may have a longer clinical effect (e.g., fentanyl, for which, however, saturation of muscle tissue has not been demonstrated).

In addition to these very basic concepts, other important factors play a role in the neonate's response to medications: (1) delayed excretion secondary to the larger volume of distribution, (2) immature hepatic and renal function, and (3) altered drug excretion caused by lower protein binding. Further perturbations in drug pharmacodynamics and pharmacokinetics occur with extreme prematurity and with factors such as sepsis, congestive heart failure, increased intra-abdominal pressure, controlled ventilation, and poor nutritional state.[8] All of these factors lead to clinically important neonatal patient-to-patient variability in pharmacokinetics and pharmacodynamics.

Older children tend to have mature renal and hepatic function, with normal adult values for protein, fat, and muscle content. A greater proportion of cardiac output is diverted to the liver and kidneys—which also weigh more in relation to body mass—in older children than in infants. These factors usually mean that the half-life of most medications in children older than 2 years is shorter than in adults or equivalent. As the child approaches adulthood, the half-life of many drugs lengthens. In general, most medications will have a prolonged elimination half-life in preterm and term infants, a shortened half-life in children older than 2 years up to the early teen years, and a lengthening of half-life in those approaching adulthood.

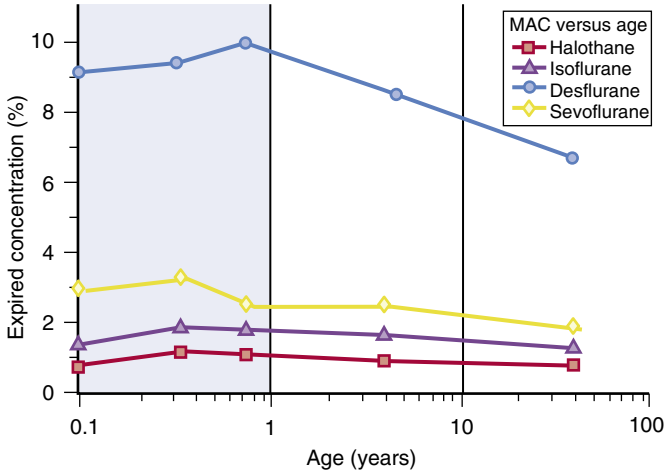

Figure 82-8 The minimum alveolar concentrations (MACs) of four commonly used inhaled anesthetics are plotted versus age. Note that MAC is highest in infants 3 to 6 months of age. The reasons for this are not clear. *(Extracted from data from references 12-19.)*

Inhaled Anesthetics

The expired minimum alveolar concentration (MAC) of an inhaled anesthetic required in pediatric patients changes with age (Fig. 82-8) (also see Chapters 20 and 21). Controlled studies show that the anesthetic requirement is lower for preterm than for term neonates and lower for term neonates than for 3-month-olds. Infants have a higher MAC than that noted in older children or adults, but the reasons have not been adequately explained. This fact, combined with the need for deeper planes of anesthesia to achieve satisfactory conditions for endotracheal intubation, places the infant in a precarious position because there is a small safety margin between anesthetic overdose (from a cardiovascular standpoint) and inadequate depth of anesthesia (for endotracheal intubation). Avoidance of controlled respirations until an intravenous line is inserted, rapid reduction in the delivery of inspired anesthetic drug, especially with the initiation of controlled respirations after the administration of a muscle relaxant, and in some cases, substitution of opioids for an inhaled agent are practices that improve safety.

Uptake of potent anesthetics is more rapid in children because of an increased respiratory rate and cardiac index and a greater proportional distribution of cardiac output to vessel-rich organs. This rapid rise in blood anesthetic levels combined with functional immaturity of cardiac development probably explains in part why it is so easy to deliver an inhaled anesthetic overdose to infants and toddlers. Age-related differences in blood-gas partition coefficients may also facilitate a more rapid rise in alveolar concentration in infants. Other factors include the state of hydration (e.g., excessive fasting would make a small infant relatively dehydrated) and the type of anesthesia circuit used. For example, a Mapleson D has a smaller volume than a circle system, so less volume is needed to achieve equilibration when the concentration of anesthetic agent exiting the vaporizer increases. With a Mapleson D circuit, the fresh gas flow is introduced into the system at the airway and enters directly into the child's lungs. Perhaps the most important factor influencing the potential for anesthetic overdose in neonates is the number of MAC multiples that can be delivered by the vaporizer (e.g., a halothane vaporizer can deliver up to 5.75 MAC multiples versus 2.42 MAC multiples for a sevoflurane vaporizer [Table 82-2]).

Sevoflurane

Sevoflurane has a gas partition coefficient similar to that of nitrous oxide (also see Chapters 20 and 21). Broad clinical experience has shown that it is less pungent than isoflurane and desflurane; some authors believe it to be superior or equivalent to halothane for gaseous induction. As with all potent volatile anesthetics, the MAC is highest in younger patients: 3.3% for neonates, 3.2% for infants 1 to 6 months old, and 2.5% for children older than 6 months.[12,13] When data from multiple studies are pooled, it is clear that sevoflurane and halothane are approximately equivalent in terms of airway complications during induction of anesthesia (laryngospasm, bronchospasm, breath-holding) but that the rate of induction is more rapid with sevoflurane. There is a lower incidence of coughing during induction with sevoflurane (~6% versus ~10%) and a 33% higher incidence of excitement during emergence (~21% versus ~15%) (Table 82-3). Both sevoflurane and halothane produce dose-related respiratory depression; however, halothane produces a decrease in tidal volume and an increase in respiratory rate, whereas sevoflurane decreases both the respiratory rate and tidal volume. I have often seen the need to assist respirations during the early induction stage in sevoflurane-anesthetized children. Unless the inspired concentration is markedly reduced (usually to ~3%), such assistance then increases the potential for anesthetic overdose while attempts are made to establish intravenous access.[20]

Table 82-2 MAC Multiples for a Neonate Allowed by Current Vaporizers

Agent	Maximum Vaporizer Output (%)	MAC (%)	Maximum Possible MAC Multiples
Halothane	5	0.87	5.75
Isoflurane	5	1.20	4.2
Sevoflurane	8	3.3	2.42
Desflurane	18	9.16	1.96

MAC, minimum alveolar concentration.
From Coté CJ, Lerman J, Todres ID (eds): A Practice of Anesthesia for Infants and Children, 4th ed. Philadelphia, Saunders, 2008.

Sevoflurane and halothane also have a different cardiovascular profiles. Children older than 3 years usually experience an increase in heart rate and no change in systolic blood pressure with sevoflurane, whereas with halothane, the heart rate does not change but systolic blood pressure decreases. It should be noted that the children most vulnerable to anesthetic overdose are the age groups shown to have the least increase in heart rate and the greatest decrease in systolic blood pressure (34% ± 16% and 26% ± 20%, respectively, for neonates and infants <6 months of age) during carefully conducted MAC studies.[13] These changes in systolic blood pressure are comparable to those produced by equi-MAC concentrations of halothane.[14] As described in the Pediatric Perioperative Cardiac Arrest (POCA) registry, there is an association between the use of controlled ventilation and cardiac arrest; generally, arrest occurs before the establishment of intravenous access.[20] It is important to respect the fact that even sevoflurane can cause catastrophic effects on the infant's cardiovascular system. One should not be lulled into thinking that because sevoflurane causes less myocardial depression than halothane does, it is much safer than halothane. Therefore, use of a muscle relaxant to facilitate endotracheal intubation and avoidance of high inspired concentrations of sevoflurane would seem to be the safest approach in this age group.

The safety of all potent anesthetics relates to how the drugs are used, the experience of the person administering anesthesia, and other less obvious factors. I generally induce anesthesia with sevoflurane, and if the infant becomes apneic, then I rapidly reduce the inspired concentration of sevoflurane while gently assisting respirations. After intravenous access is established, a decision must be made regarding continued management with just a facemask, with a supraglottic airway device (e.g., laryngeal mask airway [LMA], laryngeal tube, Cobra), or with an endotracheal tube. If I am going to place a supraglottic device, I usually administer propofol (1.5 to 2 mg/kg) and then insert the device 30 to 45 seconds later. Most children will become apneic and require assisted ventilation for several minutes. If I am going to place an endotracheal tube, two techniques seem reasonably safe: (1) If an endotracheal tube is required and the case is relatively brief or a nerve stimulator is to be used, I return to 8% sevoflurane and hyperventilate the child for a brief time (usually 1 to 2 minutes) to abolish spontaneous respirations and rapidly deepen the plane of anesthesia, administer approximately 1 mg/kg propofol, shut the vaporizer off (so that the 8% sevoflurane is not accidentally continued), and then insert the endotracheal tube; (2) if there is no need for a nerve stimulator or if muscle relaxation is necessary, I simply maintain the sevoflurane at approximately 3.5% to 4% (lower for a neonate), administer an appropriate muscle relaxant (based on the desired side effects or avoidance of undesired side effects and the duration of the procedure), and then insert the endotracheal tube. At this point I will further reduce the inspired concentration of sevoflurane or change to an appropriate concentration of halothane or isoflurane for maintenance to reduce cost. Because multiple studies have found no difference in time to discharge (street readiness), there seems to be little logic in using sevoflurane for the entire procedure except for very brief anesthesia.

Several other issues related to sevoflurane are worthy of mention. The most important is the risk of exothermic reactions with dry desiccant,[21-24] which has resulted in fires and explosions (sevoflurane and Baralyme). A number of cases have occurred in pediatric institutions (see also Chapter 100) (Fig. 82-9).[25-27] These incidents seem to most often be associated with high flow of oxygen through the circuit for extended periods and then the use of high inspired sevoflurane concentrations (e.g., the first procedure on a Monday morning). Another issue is the production of toxic metabolites as a result of interaction with the carbon dioxide absorbent.[28,29] Compound A appears to be nephrotoxic in animal models; however, conflicting data have been presented regarding the clinical importance of this observation. Studies of low-flow (2 L/min) and prolonged anesthesia have not demonstrated significant alteration in the usual markers of renal function. It appears that sevoflurane is a safe anesthetic even for prolonged surgical procedures. Fresh gas flows less than 1 L/min are not recommended. Use of new but more expensive carbon dioxide

Table 82-3 Summary Statistics for 17 Studies That Compared the Characteristics of Sevoflurane and Halothane

	Sevoflurane			Halothane			
Problem	Yes	No	Percent	Yes	No	Percent	Chi Square
Laryngospasm	22	773	2.8	22	601	3.5	.503
Breath-holding	33	635	4.9	34	439	7.2	.143
Coughing	42	662	6.0	52	454	10.3	.008
Excitement during induction	92	556	14.2	58	423	12.0	.338
Bronchospasm	2	604	0.33	2	436	0.46	.856
Excitement during emergence	169	645	20.8	102	573	15.1	.006



Figure 82-9 Sevoflurane-Baralyme interaction produced this fire in an anesthesia machine. *(From Coté CJ, Lerman J, Todres ID [eds]: A Practice of Anesthesia for Infants and Children, 4th ed. Philadelphia, Saunders, 2008. Reproduced with permission from Mr. A. Rich.)*

absorbents that do not contain a strong base seems to eliminate most of these issues.

The other concern is the apparent higher incidence of emergence agitation with sevoflurane than with halothane (see Table 82-3). Unfortunately, there is much confusion regarding the definitions and descriptions of agitation/delirium, thus making it difficult to compare studies. This response during emergence from sevoflurane anesthesia is not related to pain, appears to be inversely related to age, and is especially frequent in children 5 years or younger. Some investigators have reported a lower incidence with midazolam premedication and administration of clonidine (orally or epidurally), ketorolac, fentanyl, or dexmedetomidine. It is of interest that when one combines the data from many studies, the true difference in emergence agitation is quite small (~21% with sevoflurane and ~15% with halothane). It is my impression that the major reason that this is perceived to be such a problem is that the children often arrive in the postanesthesia care unit (PACU) in this agitated state. With halothane, children generally arrive in the PACU still partially anesthetized, the nurses are able to chart their initial vital signs, and then the children become agitated, but at this point it is less worrisome for the nurses so it is perceived as less of a problem. In either case, this condition does respond to low doses of fentanyl or propofol and is generally short-lived (~5 to 10 minutes). Another issue of interest is reports of seizure-like activity during induction with sevoflurane. At least one careful electroencephalographic (EEG) study has not documented seizure activity, thus suggesting that these abnormal movements are not central in origin.[30]

One personal observation is that airway reflexes are inadequately suppressed for performance of bronchoscopy during spontaneous respirations; supplementation with any combination of intravenous propofol, low-dose remifentanil, or a muscle relaxant is usually required with sevoflurane. Halothane appears to still be a superior inhaled agent for this procedure because higher MAC multiples may be used to maintain the concentration of inhaled drug, even in the face of large losses when the facemask is removed to allow insertion of the bronchoscope. The longer elimination half-life and maintenance of spontaneous respirations with halothane also contribute to its advantage for procedures in which the facemask will be applied intermittently, such as bronchoscopy or suture removal from a cleft lip repair.

Halothane

The use of halothane in the United States has fallen dramatically; however, it is still used widely in other parts of the world (also see Chapters 21 and 24). Halothane does not have a noxious smell and is still commonly used for the gaseous induction of anesthesia in places where budgetary concerns limit the availability of sevoflurane. There is nearly always a statistically significant, but clinically unimportant difference in the rapidity of awakening when comparing halothane with either desflurane or sevoflurane (usually 3 to 5 minutes). I often induce anesthesia with sevoflurane and then use halothane or isoflurane for maintenance to reduce cost. Most important, airway-related problems during induction occur less frequently with halothane and sevoflurane than with enflurane, isoflurane, or desflurane. Halothane and sevoflurane are the anesthetics of choice for the gaseous induction of anesthesia in children.

A 1987 report describing seven cases (one fatal) of "halothane hepatitis" concluded that children should not undergo repeated exposure to halothane (also see Chapter 24).[31] This report must be placed in proper perspective. To date, millions of children have been anesthetized with halothane. Perhaps a dozen instances of halothane hepatitis—and one or two deaths—have been reported in children. This is a remarkable safety record for any medication. Because "halothane hepatitis" appears to be primarily an adult issue, it may make sense to use other anesthetics or techniques in teenage patients. Halothane will probably remain the most commonly used potent anesthetic in undeveloped countries because of cost. It should be noted that hepatic dysfunction has been reported in children after all potent anesthetic agents, including sevoflurane and desflurane.

Another concern with halothane is sensitization of the myocardium to arrhythmias because of exogenous and endogenous catecholamines. Most arrhythmias associated with halothane anesthesia in children are caused by either hypercapnia or an inadequate level of anesthesia.[32] Up to 10 μg/kg of epinephrine may be used with minimal risk of cardiac arrhythmias in pediatric patients. In fact, I like the arrhythmogenic effects of halothane because the development of an arrhythmia suggests that the child is inadequately anesthetized or hypercapnic. In addition, the heart rate is generally stable or slightly decreased. If tachycardia develops in a halothane-anesthetized child, inadequate anesthesia or hypovolemia is usually the cause. This is distinctly different from isoflurane, desflurane, and sevoflurane, all of which can directly cause tachycardia.

Halothane is a potent myocardial depressant that can have profound effects on neonates and children with congenital heart disease. Such depression is responsible for the occasional inability to give critically ill children sufficient concentrations of halothane to provide "anesthesia" without inducing severe hypotension. In this circumstance, the liberal use of short-acting narcotics with light concentrations of halothane generally provides the desired response. The POCA study reported a greater number of anesthetic-induced cardiac arrests with halothane; the use of controlled ventilation (probably without reducing the inspired concentration of the anesthetic agent) was a common observation.[14] It is of interest that both halothane and sevoflurane have been shown to depress cardiac function but that sevoflurane is considered to be less of a myocardial depressant.[33,34] However, at both 1 and 1.5 MAC in children, there was no significant difference is mean arterial blood pressure[33]; in infants, there was no difference at 1 MAC but there was a difference at 1.5 MAC. It should be further noted that the simple administration of atropine would abolish these differences.

Isoflurane

Isoflurane is claimed to have some advantages over halothane: less myocardial depression, preservation of the heart rate, and a

greater reduction in the cerebral metabolic rate for oxygen (also see Chapters 21, 22, and 24). These properties may be beneficial in selected children. The major disadvantage of isoflurane is its noxious smell, which is unacceptable to many pediatric patients, and a greater incidence of airway-related events (laryngospasm, coughing). Hypertension is also observed occasionally, especially in teenagers, when the inspired concentration is rapidly increased or there is a sudden change from sevoflurane to isoflurane. The probable mechanism is similar to that of desflurane: stimulation of pulmonary irritant receptors causing increased sympathetic activity and stimulation of the renin-angiotensin system. In these children I have also occasionally observed a diffuse rash primarily on the torso. All signs and symptoms regress with a reduction in the inspired concentration of isoflurane.

Desflurane

Desflurane has a gas partition coefficient similar to that of nitrous oxide (also see Chapter 21). Unfortunately, it has been found to cause an unacceptable incidence of laryngospasm (~50%) during the gaseous induction of anesthesia in children.[35] Gaseous induction of anesthesia with halothane or sevoflurane and then changing to desflurane for maintenance and wake-up may be reasonable. This changeover, unlike a similar change to halothane or isoflurane, may be clinically important in that the gas partition coefficient clearly favors rapid excretion. However, it would appear to be more important to change to desflurane for longer procedures, where there is the potential for accumulation of potent agent within fat, than for brief cases, in which such accumulation is less likely. The more rapid awakening may also be advantageous for neurosurgical and spinal fusion procedures, for which early assessment of mental and neurologic status is important. One study of pediatric adenoidectomy patients demonstrated more rapid wake-up with desflurane than with sevoflurane or halothane, but this agent was also associated with the highest rate of emergence agitation.[36] Nasal fentanyl (2 μg/kg) reduces the incidence of emergence agitation, but my impression is that it also increases the incidence of postoperative vomiting.[37]

The MAC for desflurane is dependent on age: 9.2% for neonates, 9.4% for infants 1 to 6 months of age, 9.9% for infants 6 to 12 months of age, 8.7% for 1- to 3-year-olds, and 8% for 5- to 12-year-olds.[15] Interestingly, nitrous oxide does not appear to contribute to the MAC of desflurane to the same degree as it does with other potent inhaled agents.[38] There is virtually no hepatic metabolism of this agent, which clearly sets it apart from the other currently available potent anesthetics. Concern for the potential for carbon monoxide poisoning with desflurane as a result of dry carbon dioxide absorbent (also possible with isoflurane) can be prevented by rehydration before use. New carbon dioxide absorbents that do not contain a strong base may offer improved safety.

Drugs Used to Induce Anesthesia

Propofol

Propofol is highly lipophilic and promptly distributes into and out of vessel-rich organs; its rapid redistribution, hepatic glucuronidation, and high renal clearance account for the short duration of its effect (also see Chapter 26). As with barbiturates, the induction dose is higher in younger children (2.9 mg/kg for infants younger than 2 years) than in older children (2.2 mg/kg for children 6 to 12 years of age). This may be related in part to a larger central volume and greater clearance in younger children.[39] The major drawback of propofol is pain on intravenous administration, particularly through small veins. As little as 0.2 mg/kg of lidocaine (mixed with the propofol) is effective in reducing but not eliminating this discomfort. I will often place a tourniquet on the child and administer 1.0 mg/kg of lidocaine 15 to 20 seconds before administering the propofol. I then administer the propofol with the intravenous line running, and once most of it has entered the vein, I let the tourniquet down. This "mini–Bier block" technique seems to be quite effective in reducing pain. Another method for minimizing pain is to use a small-gauge catheter (22 to 24 gauge) and administer the drug through a large antecubital vein. Propofol is particularly useful for the brief and repeated sedation needed for radiotherapy in children with central venous lines. A constant infusion is useful for sedating children undergoing radiologic procedures and as a means of maintaining anesthesia during transport from one location to another, for example, from radiology to the operating room. A modest reduction in systolic blood pressure often accompanies bolus administration. Propofol has been associated with a reduced rate of postoperative vomiting. Because propofol contains egg and soy products, it should be used with caution in children with egg or soy allergies.[40,41]

The major concern with propofol is the potential for propofol infusion syndrome (lactic acidosis, rhabdomyolysis, cardiac and renal failure), which is generally associated with high-dose infusions for an extended period (usually days in an intensive care unit [ICU] environment).[42] Although no such cases have been reported in healthy children during routine anesthesia care, there is one case report in a child with a genetic defect in lipid metabolism who had received approximately 150 μg/kg/min (~9 mg/kg/hr) for 6.5 hours during scoliosis repair. This case report suggests caution in the use of propofol in children with known defects in lipid metabolism; this may include some forms of mitochondrial disease. It should be noted that propofol has been used safely in many children with mitochondrial disease and that this caution applies only to those with defects in lipid metabolism.[43]

Methohexital

Methohexital is generally administered intravenously at a concentration of 1% and a dose of approximately 1 to 2 mg/kg (also see Chapter 26). Problems associated with intravenous administration include burning, hiccups, apnea, and extrapyramidal-like movements. Methohexital has a shorter elimination half-life than thiopental does. It is also useful for providing sedation during radiologic procedures by rectal administration (10% solution). Usually, 25 to 30 mg/kg produces light sleep within 8 to 10 minutes that lasts for 20 to 40 minutes. Obstructive or central apnea may occur occasionally. Therefore, a means of ventilating the child must be available, and appropriate monitoring with pulse oximetry is important. Because it can cause seizures, methohexital is contraindicated in children with temporal lobe epilepsy. Children receiving seizure medications generally require larger doses.

Thiopental

Intravenous bolus administration of 2.5% thiopental (5 to 6 mg/kg) is sufficient to induce anesthesia in most healthy, unpremedicated pediatric patients (also see Chapter 26). Termination of effect occurs through redistribution of the drug in muscle and fat;

thiopental should be used in reduced doses (2 to 4 mg/kg) in children who have low fat stores, such as neonates or malnourished infants. Limiting the total dose to 10 mg/kg or less in older children minimizes the possibility of prolongation of anesthesia caused by residual barbiturate sedation. Thiopental (30 mg/kg in a 10% solution) may also be administered rectally if methohexital is contraindicated.

Ketamine

Ketamine causes central dissociation of the cerebral cortex while providing analgesia and amnesia (also see Chapter 26). In addition to the intravenous and intramuscular routes, ketamine may be administered rectally (10 mg/kg), orally (6 to 10 mg/kg), or intranasally (3 to 6 mg/kg). The combination of oral ketamine (4 to 6 mg/kg), oral midazolam (0.5 mg/kg), and oral atropine (0.02 mg/kg) provides a well-sedated child. Intravenous administration of doses as low as 0.25 to 0.5 mg/kg may be used to provide sedation/analgesia for painful procedures, whereas doses of 1 to 2 mg/kg produce sedation sufficient for a smooth transition to general anesthesia. Higher doses (up to 10 mg/kg intramuscularly) provide sufficient analgesia for the insertion of invasive monitoring devices before induction of anesthesia (cardiac surgery) or in children with limited venous access. Ketamine is useful for induction of anesthesia in hypovolemic children. Patient-to-patient variability in response to this drug is relatively large, however. A major side effect, increased production of secretions, usually requires the administration of an antisialagogue. Other undesirable side effects include vomiting and postoperative "dreaming" or hallucinations; the incidence of dreaming may be reduced by the concomitant administration of a benzodiazepine. Although spontaneous respirations and a patent airway are usually maintained, apnea and laryngospasm may occur.

Contraindications to the use of ketamine in children include the presence of an active upper respiratory tract infection (URI), increased intracranial pressure, open-globe injury, and a psychiatric or seizure disorder. Ketamine does not preserve the gag reflex and thus should not be used as the sole anesthetic for children with a full stomach or a hiatal hernia. Ketamine has also been used as an adjunct for epidural analgesia.[44] However, *because the preservative in usual ketamine preparations is neurotoxic, one must administer only preservative-free ketamine in the epidural space*.

Etomidate

Etomidate is a steroid-based hypnotic induction agent (also see Chapter 26). As with propofol, there is a high incidence of pain on intravenous administration. Concerns regarding anaphylactoid reactions and suppression of adrenal function resulted in most anesthesiologists avoiding this induction agent. Etomidate is very useful in children with head injury and those with unstable cardiovascular status, such as children with a cardiomyopathy, because of the virtual absence of adverse effects on the cardiovascular system.[45,46] This drug has gained increasing popularity for airway management in the emergency department setting.[47-49] Common doses are 0.2 to 0.3 mg/kg given before the administration of low-dose opioid and a muscle relaxant. Etomidate is often used to facilitate endotracheal intubation in critically ill children. Because a very high proportion of critically ill children, particularly those resistant to vasopressors, suffer from relative adrenal insufficiency, steroid supplementation may be indicated in such children in whom etomidate is deemed necessary for their safe airway management.[50,51]

Sedatives and Anxiolytics

Diazepam

Oral absorption of diazepam is more rapid in children than in adults, with 0.1 to 0.3 mg/kg orally usually providing excellent peak sedation within 1 hour (also see Chapter 26). Intravenous administration is painful and not well tolerated; diazepam may also be administered rectally. Because the liver is the main site of degradation, this medication should be given with caution to any child with hepatic disease. Diazepam has an extremely long half-life in neonates (80 hours) and may not be indicated until the infant is 6 months of age or until hepatic metabolic pathways have matured.

Midazolam

Midazolam is water soluble and therefore not generally painful on intravenous administration (also see Chapter 26). It should be noted that because of its water solubility, *it takes three times as long to reach a peak EEG effect as the more fat-soluble diazepam*. The clinical importance of this is that one should wait at least 3 minutes between intravenous doses to avoid "stacking" of effect.[52] The shorter elimination half-life (~2 hours) of midazolam than diazepam (~18 hours) offers an advantage for use as a premedicant in children. Midazolam is the only benzodiazepine approved by the Food and Drug Administration for use in neonates; in this population the half-life is much longer (6 to 12 hours).[53,54] In addition, severe hypotension has been reported in neonates after bolus administration, and the potential for this problem is apparently increased in neonates also receiving fentanyl. Midazolam is absorbed rapidly after intramuscular (0.1 to 0.15 mg/kg, maximum of 7.5 mg), oral (0.25 to 1.0 mg/kg, maximum of 20 mg), rectal (0.75 to 1.0 mg/kg, maximum of 20 mg), nasal (0.2 mg/kg), or sublingual (0.2 mg/kg) administration.[55] Nasal administration is uncomfortable for most children. Midazolam must always be used with caution when administered with narcotics because of the potential for respiratory depression. One important interaction is that erythromycin, calcium channel blockers, protease inhibitors, and even grapefruit juice produce a clinically important delay in midazolam metabolism because of inhibition of cytochrome P450.[56] In this circumstance either midazolam should be avoided or the dose reduced by 50%.[56] One further concern is that with nasal administration there is the theoretical possibility of central nervous system (CNS) toxicity as a result of drug entering the CNS along neural connections (olfactory nerves).[57] Because neurotoxicity has never been examined and most children cry with nasal administration, I believe that this route should generally be avoided.

Dexmedetomidine

Dexmedetomidine is a selective α_2-adrenergic agonist with anxiolytic, sedative, and analgesic properties (also see Chapter 26). The role of this new agent for the care of children awaits further investigation to clarify its exact advantages and disadvantages. At the time of this writing the drug is currently undergoing phase II and early phase III investigations; there are very limited well-controlled pediatric studies. A pharmacokinetic trial involving 36 children 2 to 12 years of age revealed a terminal elimination half-life of approximately 110 minutes with both heart rate (≤15%) and systolic blood pressure (≤25%) decreasing over time as the dose was increased; these observations are similar to those in

adults.[58] Infusions of 2, 4, or 6 µg/kg/hour (0.33 to 1.0 µg/kg) were administered over a 10-minute period, and there was no significant effect on the respiratory rate or oxygen saturation during the 1-hour period of observation before induction of anesthesia. Only one child initially demonstrated an increase in blood pressure, but it was unclear whether it was drug related. Transient sedation was noted in all children, and the authors recommend slow intravenous infusion to minimize any possible adverse hemodynamic events that might occur with bolus administration. Use of dexmedetomidine as the sole sedating agent or combined with other sedatives has been described in children undergoing cardiac catheterization and a variety of radiologic procedures.[59-64] Dexmedetomidine has also been used to facilitate fiberoptic intubation,[65] to sedate a child undergoing awake craniotomy,[66] to reduce the incidence of emergence agitation,[67,68] and to facilitate withdrawal from opioids.[69] In addition, this medication has been used to provide prolonged sedation in critically ill children.[70] Thus, the indications in children would seem to be the same as in adults.

Opioids

Morphine

Morphine is the oldest commonly used long-acting narcotic (also see Chapter 27). Its use in neonates (those younger than 10 days) remains controversial inasmuch as early studies in newborn infants suggested that morphine produces greater respiratory depression than meperidine does. Higher brain levels of morphine were found in neonatal than in adult rats, thus implying that permeability of the blood-brain barrier may account in part for the apparent sensitivity of the human neonate to morphine.[71] This rationale led to the common belief that infants are sensitive to the effect of narcotics. More recent studies have found age-dependent pharmacokinetics. Newborns have lower clearance of morphine, and therefore a lower dose will result in higher plasma values because of a longer elimination half-life.[72] Term infants older than 10 days may clear morphine more rapidly and at a similar rate as adults.

The issue of respiratory sensitivity and the age at which it decreases in humans have yet to be resolved; animal studies suggest that there appears to be a difference between morphine and fentanyl that may not relate to transport of drug into the brain.[73] Some of these effects may therefore be due to changes in pharmacodynamics rather than simply maturation of the blood-brain barrier. Morphine should be administered with caution to neonates and preterm infants who are not in a monitored setting. Infants older than 6 months probably have a normal adult response to morphine.

Meperidine

Meperidine received great attention when it was found on a milligram-per-kilogram basis to cause less respiratory depression in newborns than morphine does (also see Chapter 27).[74] This difference may be related in part to the fact that meperidine is much more lipophilic than morphine. Unlike morphine, the fraction of drug that enters the brain of neonates is similar to that entering the brain of older children. As with all drugs administered to neonates, there is large patient-to-patient variability in metabolism and response. Meperidine is not appropriate for long-term administration because of accumulation of the toxic metabolite normeperidine; this drug has been removed from the formulary of many children's hospitals.

Fentanyl

Fentanyl is the most commonly used narcotic in infants and children (also see Chapter 27). Its major advantages relate to its rapid onset and brief duration of action. This narcotic is more lipophilic than meperidine; the potential effects of the blood-brain barrier are of no importance with fentanyl. Termination of the effect of low doses of fentanyl results primarily from redistribution, whereas termination of the effect of high doses depends on elimination. High doses of fentanyl achieve the properties of long-acting narcotics.

Fentanyl induces a very stable cardiovascular response while providing an anesthetic state. The dosage required to produce anesthesia varies considerably, depending on the child's age, the surgical procedure, the health of the child, and the use of anesthetic adjuvants.[75] Neonates undergoing abdominal surgery have a longer fentanyl half-life than do those undergoing other procedures; hepatic blood flow—and factors that greatly increase or decrease hepatic blood flow, such as positive end-expiratory pressure (PEEP) or the use of vasopressors—may alter the pharmacokinetics. Impaired hepatic function may also play a role in the altered kinetics with increased intra-abdominal pressure.[76] Therefore, the pharmacokinetic and pharmacodynamic profile is very different and more variable for neonates than for older children. A dose of 12.5 µg/kg produces anesthesia in full-term neonates undergoing abdominal surgery, whereas higher doses (30 to 100 µg/kg) are used for cardiac surgery. These doses are safe in children whose ventilation will be controlled postoperatively; much lower doses (2 to 10 µg/kg) should be used with other anesthetics if ventilation is not to be controlled postoperatively. Because the cardiac output of neonates is determined by the heart rate, fentanyl-induced bradycardia may require administration of a vagolytic drug, such as atropine or pancuronium.

Alfentanil

Alfentanil is eliminated more rapidly than fentanyl; its pharmacokinetics is independent of dose (also see Chapter 27). This may provide a margin of safety because the greater the administered dose, the greater the elimination. Clearance of alfentanil may be increased in children in comparison to adults. As with any narcotic, there is important patient-to-patient variability in pharmacokinetics and pharmacodynamics in neonates and in children with impaired hepatic blood flow.

Sufentanil

Sufentanil has been used primarily for cardiac anesthesia; age-dependent kinetics is also evident, particularly in the first month of life (also see Chapter 27). Children are able to clear sufentanil more rapidly than adults do. This drug must be administered with caution because severe bradycardia and asystole have been reported when a vagolytic drug was not administered simultaneously.[77] Sufentanil has may be administered nasally as a premedicant or analgesic (2 µg/kg); however, desaturation may follow.

Remifentanil

Remifentanil is the most recent addition to the opioids available for the care of children (also see Chapter 27).[78] The main advantage of this opioid is its very brief half-life. Studies in adults have

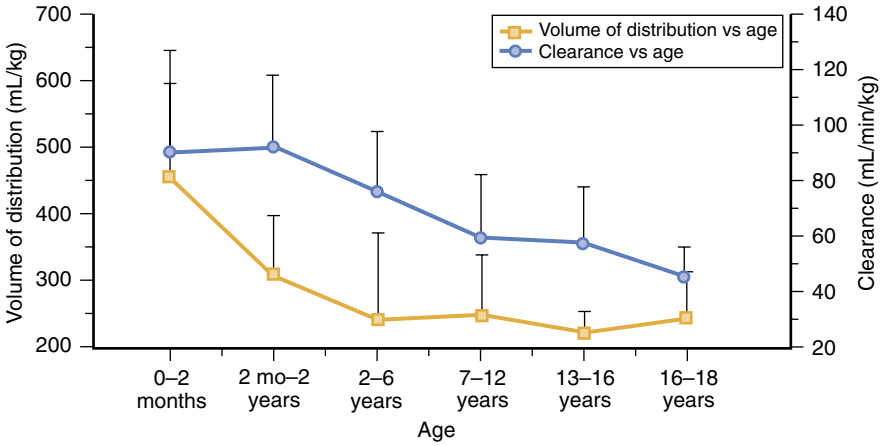

Figure 82-10 Remifentanil is the newest potent opioid available for the care of neonates. Note that unlike with virtually all other medications, its half-life is shorter in neonates than in older children, probably because of elimination of remifentanil by nonspecific plasma and tissue esterases, as well as the larger volume of distribution in neonates. The importance of this observation is that developmental immaturity of liver and renal function does not affect the pharmacokinetics of remifentanil. Because this was a single-bolus administration study, it is not clear whether similar pharmacokinetics would follow a long continuous infusion. *(Data abstracted from Ross AK, Davis PJ, Dear Gd GL, et al: Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. Anesth Analg 93:1393-1401, 2001.)*

found that even after prolonged infusions, the time to a 50% reduction in effect-site concentration (effect on respiration) is approximately 4 minutes. One study examining its pharmacokinetics in children found that there are age-related differences in the volume of distribution and clearance but not half-life (Fig. 82-10).[79] Contrary to the pharmacokinetics of most drugs, neonates are able to clear the drug more rapidly than older children! This difference may in part relate to the larger volume of distribution with equivalent half-life. Of further interest is the very small patient-to-patient variability in pharmacokinetic parameters when compared with similar studies examining other opioids, particularly in infants and neonates. Because remifentanil is broken down by nonspecific plasma and tissue cholinesterases, the importance of maturation of renal and hepatic function is minimal. This also helps explain the minimal differences in remifentanil's half-life between infants and adults. This drug has great utility in infants with hepatic or renal failure. The particularly favorable pharmacokinetics in neonates allows provision of a deep opioid-induced plane of anesthesia while avoiding cardiovascular depression and the need for postoperative ventilation. One multicenter study of infants undergoing pyloromyotomy found no difference in intraoperative hemodynamic parameters, time to extubation, PACU discharge times, need for pain medications, or adverse events when compared with halothane anesthesia.[80,81] In older children, remifentanil is very helpful in the anesthetic management of those in whom neurologic status must be rapidly assessed. This drug is also very useful for cardiac surgery in children as a means of providing adequate opioid analgesia, cardiovascular stability, and early extubation.

Several studies have examined bolus doses of remifentanil as an alternative to succinylcholine.[82,83] One study found that 1.25 µg/kg of remifentanil combined with 4 mg/kg of propofol allowed all children (2 to 16 years) to be intubated successfully, but there was more coughing and the duration of apnea was longer in the remifentanil group than in those who had received an equivalent dose of propofol combined with succinylcholine (1 mg/kg); in none of the children in the remifentanil group did chest wall rigidity develop.[82] Another study of infants 2 to 12 months old and children 1 to 6 years of age determined the 98% effective dose (ED_{98}) for successful intubation to be similar in both age groups (~2.9 µg/kg).[83] The second half of that study compared remifentanil, 3 µg/kg, combined with propofol, 4 mg/kg, in 2- to 12-month-old infants with succinylcholine and found similar intubating conditions; the duration of apnea was similar in both groups. It is my opinion that at this point data are insufficient to support the routine substitution of remifentanil for succinylcholine and that further study that truly mimics rapid-sequence intubation is needed. Because bolus doses of remifentanil are associated with hypotension and bradycardia, a vagolytic is indicated.

In neonates and toddlers, use of a more dilute concentration and bypassing the dead space of the injection port with a needle (or priming the dead space) are necessary so that the onset of drug effect is not delayed.[84,85] In older children, a standard solution of 50 µg/mL may be used. In general, a starting bolus dose of 0.1 to 0.25 µg/kg is followed by an infusion at 0.25 µg/kg/min. Increases or decreases in the infusion rate of 0.05 to 0.1 µg/kg/min are useful starting points for managing altered anesthetic requirements. Two studies have compared the somatic and autonomic responses to skin incision during continuous remifentanil infusion in adults and children.[86,87] The infusion rates to block somatic and autonomic responses in 50% of children were significantly higher (approximately twofold greater) than in adults. The reason for such a disparity in drug requirement between adults and children is not clear. However, this is certainly a clinically important observation because it suggests the possible need to (1) start at higher initial infusion rates, (2) rapidly increase infusion rates after initial assessment of responses, (3) supplement the anesthetic with nitrous oxide or a potent agent, or (4) add another analgesic. I have used a fix combination of 100 µg of remifentanil combined with 18 mL of propofol (final concentration, 5 µg/mL of remifentanil) run at a starting infusion rate equivalent to 150 µg/kg/min of propofol to provide excellent conditions for upper and lower endoscopic procedures. One study has demonstrated adequate stability of this mix for 6 hours.[88]

For practical purposes and for safety, it is vital that the drug be administered by continuous infusion and that it be carried into the vein by a second continuous infusion because variations in drug delivery related to differences in intravenous fluid delivery can have profound effects on the rate of opioid administration.[84,85] For neonates and small children, I generally use a continuous infusion pump for the maintenance intravenous fluid and "piggyback" the remifentanil infusion as close to the intravenous catheter as possible. In complex cases I will use a separate intravenous line for all other anesthetic management issues. A further very important concern is the need to provide analgesia once the use of remifentanil is discontinued. I usually accomplish this with morphine (0.05 to 0.2 mg/kg, depending on the severity of pain expected) or with a regional nerve block administered well before discontinuation of the remifentanil. I have also used remifentanil as a means of producing profound analgesia while taking advantage of its vagotonic effects to reduce blood pressure in children undergoing spinal instrumentation. This strategy avoids interference of evoked motor or sensory potentials because a low-dose inhaled agent or a propofol infusion may be used for anxiolysis and amnesia.

Muscle Relaxants

Depolarizing Muscle Relaxants

Succinylcholine

Succinylcholine is highly water soluble and rapidly redistributes into the extracellular fluid volume (also see Chapter 29). For this reason the dose required for intravenous administration in infants (2.0 mg/kg) is approximately twice that for older children (1.0 mg/kg). Succinylcholine is the only short-acting relaxant that is effective when given intramuscularly; reliable muscle relaxation occurs within 3 to 4 minutes after 5 mg/kg in infants and 4 mg/kg in children older than 6 months. The skeletal muscle relaxation produced by intramuscular administration may last up to 20 minutes; more rapid onset is not achieved by splitting the dose into two injections or by changing the concentration. In an emergency situation, succinylcholine may be administered intralingually (via a submental approach), which will further speed the onset of relaxation because the drug is more rapidly absorbed from the tongue than from peripheral skeletal muscle.

Cardiac arrhythmias frequently follow intravenous administration, especially during halothane anesthesia. Prior intravenous administration of atropine (but not intramuscular administration of atropine as a premedication) reduces the incidence of arrhythmias. Cardiac sinus arrest may follow the first dose of succinylcholine but is more common after repeated bolus administration; such arrest may occur in children of any age. Although the incidence of bradycardia is low in older children, I have observed one 13-year-old child in whom asystole developed for approximately 30 to 45 seconds after a single dose of succinylcholine administered with thiopental but not atropine; the asystole occurred before intubation and with 100% oxygen saturation and responded immediately to the administration of atropine and several chest compressions to circulate the atropine. Therefore, atropine should probably be given intravenously just before the first dose of succinylcholine in all children, including teenagers, unless there is a contraindication to tachycardia.

Succinylcholine has received much attention because of the severity of its possible complications. The potential for rhabdomyolysis and hyperkalemia (particularly in boys younger than 8 years, who may have unrecognized muscular dystrophy), as well as the risk for masseter spasm and malignant hyperthermia, suggests that succinylcholine should not be used routinely in children.[89,90] Increased jaw muscle tone after succinylcholine has been observed (masseter spasm), and this may be a normal variant. However, masseter tetany ("jaws of steel"), which prevents any mouth opening, may represent an extreme variation in increased masseter muscle tone and may be the reaction associated with malignant hyperthermia. I have observed this effect two times; in neither child did malignant hyperthermia develop, but one did have creatine kinase values greater than 20,000 IU the next morning.

With the foregoing cautions in mind, one should not yet completely abandon succinylcholine because it is the only commercially available ultrashort-acting muscle relaxant that provides a dependable, rapid onset of action. Intravenous use of this drug should be limited to children who have a full stomach or to treat laryngospasm; intramuscular or submental (intralingual) administration is indicated for children with difficult intravenous access when control of the airway is deemed essential.

There is hope on the horizon for a safer alternative for rapid-sequence intubation and for treatment of laryngospasm (i.e., high-dose rocuronium, 1.2 mg/kg).[91] If the new reversal agent sugammadex is demonstrated to be safe and effective in children (see further on) and its preliminary ability to antagonize profound neuromuscular blockade is confirmed in children, the vast majority of life-threatening adverse effects associated with succinylcholine will disappear (provided that the cost of sugammadex does not outweigh the potential benefits of avoiding succinylcholine).

Nondepolarizing Muscle Relaxants

A comparison of infants with older children or adults regarding their response to nondepolarizing muscle relaxants shows that infants are generally more sensitive to these drugs and that their response varies to a greater degree (also see Chapter 29). Although the initial dose per kilogram needed for neuromuscular blockade is often similar for children of all ages, the greater volume of distribution and reduced renal or hepatic function of neonates result in a slower rate of excretion and hence a prolongation of effect. Neuromuscular blockade occurs at a lower blood concentration.

The choice of nondepolarizing muscle relaxant depends on the side effects and the duration of muscle relaxation desired. If tachycardia is desired (e.g., with fentanyl anesthesia), pancuronium would be an appropriate choice. Vecuronium, atracurium, rocuronium, and cisatracurium are useful for shorter procedures in infants and children; they may also be administered as a constant infusion. The method of excretion of atracurium and cisatracurium (Hofmann elimination and ester hydrolysis) makes these relaxants particularly useful in newborns and children with liver or renal disease. Vecuronium is valuable because no histamine is released; however, its duration of action is prolonged in newborns, which makes it similar to pancuronium.

Rocuronium has a clinical profile similar to that of vecuronium, cisatracurium, and atracurium but offers the advantage that it can be administered intramuscularly. One study observed that acceptable conditions for intubation are produced by rocuronium within 3 to 4 minutes after 1 mg/kg intramuscularly in infants and

1.8 mg/kg intramuscularly in children older than 1 year; these effects were more dependable with deltoid than with quadriceps muscle injection.[92] This onset time is similar to that produced with intramuscular succinylcholine; however, the duration of action is approximately 1 hour, which could be a distinct disadvantage for a brief procedure. The onset of neuromuscular blockade with intravenous rocuronium (1.2 mg/kg) is also nearly the same as and intubation conditions are identical to those produced with intravenous succinylcholine (1.5 mg/kg).[91] I have used this intravenous rocuronium dose with thiopental (5 to 6 mg/kg) for rapid-sequence induction after preoxygenation in children in whom succinylcholine might present an added risk. Even better intubating conditions are achieved with the administration of lidocaine (1 mg/kg) and propofol (3.0 mg/kg) instead of thiopental just before rocuronium. Most children can be intubated at 45 seconds. The disadvantage is that the duration of action is 60 to 90 minutes, thus limiting its usefulness to either long procedures or accepting the fact that prolonged neuromuscular blockade is more desirable than the potential risk from but the shorter duration of succinylcholine. Conversely, at low doses of rocuronium (0.3 mg/kg), satisfactory conditions for intubation occur at about 3 minutes when combined with an inhaled drug, but successful reversal can usually be achieved within 15 to 20 minutes.

Table 82-4 provides commonly recommended guidelines for dosages. Because of the extreme variability in response, the doses of long-acting muscle relaxants used for infants should be titrated carefully, starting with one third to one half of the usual dose administered to older children. I recommend antagonism of neuromuscular blockade in all neonates and small infants, even if they have recovered clinically, because any increase in the work of breathing may cause fatigue and respiratory failure. Useful signs of reversal are the ability to lift the legs and arms and recovery of the train-of-four response to peripheral nerve stimulation.

Sugammadex

Sugammadex is a cyclodextrin whose endoskeleton forms a water-soluble complex with the exoskeleton of rocuronium; it was specifically designed to antagonize the effects of rocuronium (also see Chapter 29).[93-95] The purported advantage of this reversal agent is that antagonism occurs as a result of covalent bonding, and because sugammadex is made of sugars, the potential for adverse side effects would appear to be minimal.[94,96,97] This agent will also reverse the other steroidal relaxants vecuronium and pancuronium to a lesser extent. The mechanism of reversal is lowering of the plasma concentration and thus reversing the concentration gradient and pulling the rocuronium off the myoneural junction.[94,98,99] Data suggest more rapid antagonism than with neostigmine/atropine.[100] The importance of this new approach to antagonism of neuromuscular blockade is the ability to avoid all the side effects of neostigmine and anticholinergic medications, as well as the ability to antagonize profound neuromuscular blockade. This very exciting development could virtually eliminate the need for succinylcholine in pediatric practice, except perhaps for intramuscular use in children without intravenous access. Even in this circumstance, intramuscular rocuronium would be antagonized by sugammadex, provided that adequate doses are administered. Certainly, the adult data are very promising, and if it has a minimal adverse event profile, sugammadex may completely change our approach to anesthesia in children.

Anesthetic Considerations

Preoperative Preparation

The preoperative visit and preparation of the child for surgery are more important than the choice of premedication.[101] During this time the anesthesiologist evaluates the medical condition of the child, the needs of the planned surgical procedure, and the psychological makeup of the child and family. The anesthesiologist also formulates the approach to induction of anesthesia, explains the possibilities regarding induction, and helps soothe family concerns. Because the anxiety felt by the parents may be transferred to the child, any practice that reduces anxiety in the parents may also reduce anxiety in the child. Therefore, the anesthesiolo-

Table 82-4 Commonly Used Muscle Relaxants and Reversal Agents in Pediatrics

Drug	Average Intubation Dose (mg/kg)	Category	Approximate Duration
Muscle Relaxants*			
Pancuronium	0.1	Long acting	~45-60 min
Cisatracurium	0.1	Intermediate acting	~30 min
Vecuronium	0.1	Intermediate acting	~30 min
Rocuronium		Dose related:	
	0.3	Short acting	~15-20 min
	0.6	Intermediate acting	~30-45 min
	1.2	Long acting	~45-75 min
Reversal Agents†			
Edrophonium	0.3-1.0 mg/kg + atropine, 0.02 mg/kg		
Neostigmine	0.02-0.06 mg/kg + atropine, 0.02 mg/kg		

*The response of preterm and term neonates (who may be more sensitive to the drugs) to muscle relaxants varies greatly from patient to patient. Therefore, all doses should be titrated to response. The recommended intubation doses may be reduced 30% to 50% in the presence of a potent inhaled agent.
†The dose of reversal agent given to antagonize nondepolarizing neuromuscular blockade should be determined by the degree of residual neuromuscular blockade (i.e., the dose should be titrated to clinical effect).

gist should explain in great detail what the child and family can expect and what will be done to ensure the utmost safety. The more information that the parents and child have, the more easily they will deal with the stress of surgery and hospitalization. Presurgical programs such as videotapes, literature, and hospital tours also help.

After chart review, physical examination, and furnishing of information regarding the approximate time and length of surgery, the anesthesiologist should describe to the child what anesthesia is and what will be done to ensure good care. The purpose of all monitoring devices should be explained to both the child and family. Children need to understand that none of these devices will hurt and that they can watch during their application. If an intravenous line will be started, the child needs to be told that "numbing" medicine will be used. Any special monitoring devices, such as an arterial line, a central venous line, a nasogastric tube, or urine catheter, should also be described to the parents, with assurances that these devices will be inserted after induction of anesthesia. Part of this informed consent is also a description of our role in the operating room. It is vital to explain to the family that your anesthetic "prescription" will be tailored to meet their child's medical as well as surgical needs. I like to use the phrase "anesthetic prescription" because we are physicians, just as a surgeon or pediatrician, and it is important for families to clearly understand this.

Children think in very concrete terms, so care must be taken to avoid misunderstandings. It is important to explain to children that the "sleep" caused by anesthetic drugs differs from normal sleep They should know that the anesthesia medicines keep them from awakening during surgery and from remembering the operation. It should also be explained that the anesthesia medicines will be removed at the end of surgery and that they will then wake up and return to their parents. This kind of explanation does not require a significant amount of time and goes a long way toward reassuring the child and family about the quality of care provided.

The issue of pain must not be avoided. Children need to be reassured that everything possible will be done to minimize pain on awakening. Therefore, it should be stressed that pain medications will be administered and that local infiltration nerve blocks, continuous epidural or caudal infusions, child-controlled epidural analgesia, or patient/parent/nurse-controlled analgesia will be used (see also Chapter 87). The PACU or ICU must also be described so that there are no surprises.

The Fearful Child

There are some children who from either past experience or general lack of understanding are terrified to come to the operating room. When I see a child break into tears, if the child is old enough to talk with, I stop whatever is happening at the moment, sit on the bed next to the child, and ask what exactly is concerning them. Sometimes there is no response. In this situation I ask such children if they are afraid to go to sleep, afraid of feeling their operation, or afraid of pain afterward. Generally they are able to verbalize their concern, but even with no response at this point I reiterate that "*the sleep from anesthesia is different from sleep at home. At home if mom or dad shakes you, you would wake up. In the operating room no matter what we do you will not feel it, you will not remember it, and then at the end I will take the medicine away, you will breathe it all back out again, and then you will wake up and return to your family.*"

This explanation usually ends the tears. Sometimes the tears flow because they want a parent present for induction, even some of the older children. This is an easy request to grant, and it will also usually end the tears. If on the other hand there is a specific event in the past causing concern, it is important to investigate to see whether something was misunderstood or something can be carried out differently to avoid the issue. For some children with previous anesthetic experience, simply allowing them to hold the anesthesia mask themselves provides them with sufficient control of the situation to stop the tears. I once had a 7-year-old who wrote a will: "*leave my doll to, … leave my blanket to …*". When I asked her what this was all about, she responded that she was "*going to sleep today and that sometimes when people go to sleep they do not wake up.*" Because she had suffered a burn injury and needed many procedures, I explained to her that yes people can go to sleep and not wake up, but that this was usually an older person with a problem with the heart or the brain and that I had not seen this in someone her age having this operation. I asked her if she would feel better if she held the mask herself, and she in fact held the mask for a smooth anesthetic induction. In recovery she later thanked me as "*the first doctor that ever explained anything to me!*" This brief anecdote emphasizes the importance of talking directly to children regardless of their age. Finally, other children cannot be consoled and it is not possible to find the source of their concern. It is these children who will benefit from heavy premedication, such as the combined oral midazolam, ketamine, and atropine described earlier.

Fasting

A number of studies have found no difference in gastric residual volume or pH in children allowed to ingest unlimited clear liquids (water, apple juice) up until 2 to 3 hours before anesthetic induction versus standard fasting. This practice provides a more humane approach for both children and their parents without increasing the risk for pulmonary aspiration of gastric contents. Infants and young children have a higher metabolic rate and a larger body surface area–to-weight ratio than adults and become dehydrated more easily than adults. The major advantage of the liberalized fasting guidelines may be a reduced incidence of hypovolemia at the time of anesthetic induction. My approach is to restrict milk and solids after midnight but allow unlimited clear fluids up to 3 hours before induction; if there is a change in the operative schedule, I still feel comfortable with 2 hours of fasting (Table 82-5). Infants who are breast-fed may have their last breast milk 4 hours before induction of anesthesia. I consider breast milk to be equivalent to formula because the fat content varies with maternal diet and delayed gastric emptying may result. The American Society of Anesthesiologists (ASA) guideline also allows a "light meal" of toast and clear liquids up to 6 hours before induction of anesthesia, but I have found that parents frequently confuse this to mean any type of meal, including eggs and bacon![102]

Table 82-5 Fasting Guidelines for Pediatric Patients

	Fasting Time (hr)*	
Age	**Milk and Solids**	**Clear Liquids**
<6 months	4	2
6-36 months	6	3
>36 months	8	3

*Note that the American Society of Anesthesiologists guideline allows a "light breakfast" (tea and plain toast) 6 hours before anesthesia; however, it is difficult to determine what a "light breakfast" is for a child.

Premedication

The many published reports on premedication have produced approximately the same results: Almost all sedatives are effective. The important issue is effectiveness for individual anesthesiologists at their own institutions. The need for premedication must be individualized according to the underlying medical conditions, the length of surgery, the desired induction of anesthesia, and the psychological makeup of the child and family. Premedication is not normally necessary for the usual 6-month-old infant but is warranted for a 10- to 12-month-old who is afraid to be separated from parents. Oral midazolam is the most commonly administered premedication in the United States. An oral dose of 0.25 to 0.33 mg/kg (maximum, 20 mg) generally results in a very compliant child who will separate from parents without crying.[51] A review of previous anesthetic records is particularly helpful in ascertaining how the child has responded in the past.

Premedications may be administered orally, intramuscularly, intravenously, rectally, sublingually, or nasally. Although most of these routes are effective and reliable, each has drawbacks. Oral or sublingual premedication does not hurt but may have a slow onset or be spit out; drug taste and child cooperation are the main determinants of success. Intramuscular medications hurt and may result in a sterile abscess. Intravenous medications may be painful during injection or at the start of infusion. Rectal medications sometimes make the child feel uncomfortable, cause defecation, and occasionally burn. Nasal medications can be irritating, although absorption is rapid. Midrange doses of *intramuscular* ketamine (2 to 4 mg/kg) combined with atropine (0.02 mg/kg) and midazolam (0.05 mg/kg), or *oral* ketamine (4 to 6 mg/kg) combined with atropine (0.02 mg/kg) and midazolam (0.5 mg/kg, maximum of 20 mg), will result in a deeply sedated child.[103] This combination is generally reserved for children who refuse oral premedication or those in whom lighter premedication regimens have failed in the past. Higher doses of intramuscular ketamine (up to 10 mg/kg) combined with atropine and midazolam may be administered to children with anticipated difficult venous access or in whom an intravenous line is necessary for induction (e.g., infants with congenital heart disease) to provide better conditions for insertion of an intravenous line.

Anticholinergic drugs are not routinely administered intramuscularly to children because they are painful on administration and do not significantly reduce laryngeal reflexes during induction of anesthesia. On the other hand, atropine (0.02 mg/kg) administered orally or intramuscularly less than 45 minutes before induction does reduce the incidence of hypotension during induction with potent inhaled anesthetics, but only in infants younger than 6 months.[104]

The Child with an Upper Respiratory Tract Infection

A child with a URI is a major concern for the anesthesiologist because the anesthetic implications can be quite important. Unfortunately, data regarding URIs and the anesthetic implications are difficult to place in perspective because complications are not particularly common and the definition of what a URI consists of has varied from study to study. The decision whether to proceed with surgery and anesthesia is dependent on a number of factors. The URI may represent a prodrome of a much more serious illness, or it may simply be the usual viral infection so common in children, particularly in the wintertime. It is likely that a child with a URI has an irritable airway and is at increased risk for laryngospasm, bronchospasm, postintubation croup, atelectasis, pneumonia, and episodes of desaturation. Several studies have found an increased incidence of airway-related problems in children who are passively exposed to tobacco smoke.[105-107] These complications can be reduced by avoiding endotracheal intubation or using a supraglottic device such as an LMA. However, the incidence of adverse airway-related events is not reduced by the administration of anticholinergics or bronchodilators.[108,109] Because bronchial hyperreactivity may last for up to 6 weeks after a URI, cancellation will make a difference only if surgery is delayed for this amount of time or longer.[110,111] It is also known that there is virtually the same incidence of airway-associated complications in children who are recovering from a URI as for those in the acute phases of a URI.[105,111,112] The approach that I take with these children is rather commonsense. If the child is acutely ill and obviously getting worse, the case is canceled. If the child has rhonchi and a productive cough, the case is canceled. If the child is stable and afebrile and has had the URI for several days, I usually proceed. My main concern is with a child who is going to have a very long procedure or will be admitted to the hospital postoperatively, which may in turn result in exposure of other hospitalized children who may be immunocompromised. When faced with this dilemma for a child who will be going home postoperatively, I inform the family and the surgeon of the increased risks, and they generally end up making the decision to proceed. It is my feeling that we have the tools to successfully manage the reasonably common complications. We have oxygen to treat hypoxemia, we have albuterol and inhaled anesthetics to treat bronchospasm, we have muscle relaxants to treat laryngospasm, and we can usually find a way to avoid intubation for simple procedures. Cancellation of a procedure at the last minute is unfair to the family and upsets the operating room schedule. On the other hand, one should not place the child at risk merely for economic or social concerns. The best way of avoiding last-minute cancellations is a phone call by nursing staff the day before to inquire about the child's health. If the child has a URI, the anesthesiologist can call the family and take a history to determine how best to proceed. In this way wasted trips to the hospital are avoided and the father or mother, or both, do not take a day off work unnecessarily. Physicians are really left to their own best clinical judgment for an individual child on a particular day undergoing a specific procedure. If the decision is made to

proceed, it is helpful to write a note in the chart documenting the discussion.

Induction of Anesthesia

The method of inducing anesthesia is determined by a number of factors: the medical condition of the child, the surgical procedure, the level of anxiety of the child, the child's ability to cooperate and communicate (because of age, developmental delay, or language barrier), the presence or absence of a full stomach, and other factors.

Infants

Mask induction without premedication is generally used in infants younger than 10 to 12 months because this age group readily separates from their parents. Induction by mask is accomplished most easily by holding the end of the anesthesia circuit in a cupped hand over the infant's face or by holding the mask just off the surface of the face; the other hand can adjust the concentration of anesthetic. Allowing neonates and small infants to suck on a rubber nipple or on a gloved finger generally prevents crying during induction. As the infant loses consciousness, the anesthesia mask is adjusted to improve delivery and decrease operating room pollution. This phase is the most dangerous time because it is very easy to misjudge the depth of anesthesia and depress the heart. Once anesthesia has been induced, it is critical to rapidly reduce the inspired concentration of halothane (down to 1.0% to 1.5%) or sevoflurane (down to 2% to 4%) and to keep it at this level or less until an intravenous line is in place. After the intravenous line is inserted, one may either deepen the plane of anesthesia or add a muscle relaxant. It is dangerous to proceed directly to a deep plane of anesthesia without having an intravenous line in place; without this precaution, resuscitation would be difficult.

The second most dangerous point occurs immediately after endotracheal intubation. If the vaporizer has not been closed before laryngoscopy, it is easy to forget that a relatively high inspired concentration is being delivered and, during checking for breath sounds, to perhaps give an overdose of inhaled anesthetic. Therefore, the prudent clinician will discontinue all anesthetics until laryngoscopy and endotracheal intubation have been completed. With a Mapleson D circuit, a high concentration of anesthetic can be delivered more easily because the anesthetic enters directly at the airway. In contrast, changes made at the vaporizer of a circle system take a longer time to achieve equilibration with the circuit; therefore, the inspired concentration of anesthetic rises (or decreases) more gradually unless high fresh gas flow is being used. Particular caution should be used when changing from sevoflurane to halothane or isoflurane because the myocardial depressant effects of these drugs are additive.

Older Pediatric Patients

Successful, psychologically atraumatic induction of anesthesia by mask in an older pediatric patient requires that the child understand and cooperate. Premedication is particularly helpful in the 1- to 4-year-old age group. Several different techniques may be used. One method is to play a game. For example, a smaller child may be asked to "*blow up the balloon*." A slightly older child (4 years and older) may be receptive to hypnotic suggestions during induction. A young child may be susceptible to a suggestion that the anesthesia mask is an "*airplane pilot's mask*" and that the smell of halothane or sevoflurane is "*oxygen*" or "*aviation fuel*." Stating that the "*faster and higher the plane goes, the stronger the aviation fuel smell*" is one means of distracting the child. During this type of induction, the operating room must be free of distractions, and the anesthesiologist must be able to communicate with the child. The use of constant conversation and incremental increases in the inspired concentration of anesthetic every third or fourth breath usually produce a smooth transition to general anesthesia. Often the child will breath-hold. If so, the anesthesiologist should not attempt to assist respiration because this action often elicits coughing or laryngospasm. The anesthesiologist must be certain that airway obstruction and laryngospasm can be differentiated from breath-holding. Observing the chest wall and abdomen helps identify airway obstruction, which creates a rocking-type movement of the chest and abdomen (when the diaphragm descends, the abdomen appears to expand but the chest does not). As soon as the child loses consciousness, the inspired concentration of anesthetic can be reduced and an intravenous line inserted. Should partial laryngospasm or upper airway obstruction occur, closing the pop-off valve to create approximately 10 to 15 cm H_2O of positive pressure, while allowing the child to breathe spontaneously, often facilitates gas exchange. If this procedure is not effective, administration of rapid positive-pressure breaths, while avoiding inflation of the stomach, often disrupts the laryngospasm. Obviously, administration of a muscle relaxant will also break the laryngospasm; succinylcholine remains the agent of choice in an emergency situation.

A third method of induction involves the use of flavored masks. A variety of flavored scents (Loran Oils, Inc., Lansing, MI) are available to reduce the noxious smell of anesthetics; the child can select a favorite scent.

A fourth method, the single-breath technique, requires a very cooperative child who can follow instructions. Using an unattached anesthesia mask, the anesthesiologist should demonstrate the procedure to the child, who then rehearses the following steps: (1) take a big breath in and hold at full inspiration; (2) exhale completely, hold at full expiration, and place the mask on the child's face at exactly the end of expiration; (3) take another full inspiration held as long as possible; (4) and then resume normal breathing. Before induction, the anesthesia circuit is filled with either 5% halothane or 8% sevoflurane in 60% nitrous oxide. The circuit bag must be emptied and filled several times so that the entire circuit is filled with 5% halothane or 8% sevoflurane. Steps 1 to 4 are then repeated with the mask attached to the Y-piece of the anesthesia circuit. When placing the facemask, care should be taken to not direct the gas toward the eyes because this can frighten the child. If the child fully cooperates, this generally produces loss of the eyelid reflex in less than 1 minute. Occasionally, a child does not take a full breath or becomes frightened, or application of the facemask was not complete. If the child is partially anesthetized, induction takes slightly longer, but the child does not usually remember the induction. If the child panics before inhalation of anesthetic, induction should not be forced, and an alternative plan should be undertaken.

Parents in the Operating Room

It is very common for parents to request to be present during induction of anesthesia. I welcome their participation in this

process (usually limited to one parent) because on some occasions, the security of having a parent present and avoiding separation allows us to omit premedication. *Parental presence should not be substituted for premedication if the child needs premedication.* In other situations, parental presence reduces anxiety sufficiently so that light premedication is adequate. Decisions regarding parental presence must, however, take into consideration the developmental level of the child and the reason for their presence. It serves no purpose to have a parent present during induction of anesthesia in a newborn or a 6-month-old who is completely trusting of strangers. Likewise, it is unlikely to benefit a child who has been heavily premedicated. Certainly, parents must not be present for rapid induction in the presence of a full stomach. Parents are present for the benefit of their child, and if the child does not benefit or if it makes the physicians uncomfortable, a parent should not be present. The safety and care of the child are top priority. I sometimes even explain that their participation in this process is a privilege but not a right. Each physician and each institution must determine what works and what does not work for them. If I make a decision to allow a parent to be present, it is vital to explain to them what they might see so that there are no surprises. I explain that "*when anyone goes to sleep their eyes roll upward*." This is a normal response, and they might see their child do this a few times. I assure them that they should expect this and not to worry that something is wrong. I next warn them that as children fall asleep "*they often make noises from their throat*" (e.g., snoring) and that this is also normal and that they might hear noises from their child's throat as their child falls asleep (I do not explain that this might be airway obstruction or developing laryngospasm). Third, I point out that the "*brain often gets excited before it goes to sleep*"; thus, after their child breathes the anesthesia medicine for 15 to 30 seconds, it is common for the child to suddenly become restless and move the arms and legs. This response is expected, and shortly afterward their child will be completely anesthetized. I further explain that despite appearing to be awake, they do not remember this at all. Thus, the eye rolling, possible airway obstruction, and excitement are all explained and the parent is not frightened should any of these events occur. I also make sure that the parent is sitting in a chair and explain that as soon as we ask them to leave, they must do so because at that point we must completely focus on the care of their child.

For smaller children I like to anesthetize them on the parent's lap. I have the child facing straight forward with the parent's arms wrapped around the child and helping to hold the arms near the child's side to reduce the potential for them to reach up and grab the mask. I explain to the parent that they are going to be able to hug their child as they go to sleep. I also explain that the child will become limp and could fall unless they hold on tight. I further state that as their child looses consciousness, we will pick up their child and place him/her on the operating room table. They can then kiss their child and proceed to the family waiting area. If there is a language barrier, I will ask a translator to help explain this process and allow the translator in the operating room to assist in the communication that is needed to perform a nontraumatic mask induction.

Rectal Induction of Anesthesia

A number of medications may be administered rectally for induction/premedication of anesthesia (methohexital, thiopental, ketamine, midazolam). The main advantage of this approach is that the child falls asleep in the parent's arms or, as is the case with midazolam, separates atraumatically from the parents. This technique is no more intimidating than taking a rectal temperature but is generally reserved for children still in diapers. Care must be taken to not allow the child to see the rectal catheter or syringe, which would appear very large to the child. Rectal administration of 10% methohexital (20 to 30 mg/kg) reliably induces anesthesia within 8 to 10 minutes in 85% of young children and toddlers. Oxygen desaturation is not usually a problem unless the child's head is allowed to flex forward and cause obstruction of the airway. The main disadvantage of this technique is that there can be either markedly delayed or very rapid drug absorption. Other drugs administered rectally include 10% thiopental (20 to 30 mg/kg), midazolam (1 mg/kg up to 20 mg), and ketamine (6 mg/kg).

Intramuscular Induction of Anesthesia

Many medications, such as methohexital (10 mg/kg), ketamine (2 to 10 mg/kg combined with atropine [0.02 mg/kg] and midazolam [0.5 mg/kg]), or midazolam alone (0.15 to 0.2 mg/kg), are administered intramuscularly for premedication or induction of anesthesia. The main advantage of this route of administration is its reliability; its main disadvantage is that it is painful.

Intravenous Induction of Anesthesia

Intravenous induction of anesthesia is the most reliable and rapid technique. The main disadvantage is that starting an intravenous line can be painful and threatening for the child. Intravenous induction may be preferable when induction by mask is contraindicated (e.g., in the presence of a full stomach). A two-needle technique using a butterfly-type catheter with a 25-gauge needle is suitable for induction of anesthesia, followed by placement of an intravenous catheter once anesthesia is safely induced. Older children will often allow insertion of an intravenous catheter after the administration of 50% nitrous oxide and local anesthetic; topical anesthetic creams (e.g., EMLA, ELA-Max) are also well received. It is important to emphasize to the child that this procedure will not be excessively painful. Occasionally, children will cry with infiltration of local anesthetic and become hysterical when they see the intravenous catheter. Two maneuvers help minimize this response: (1) do not allow the child to see the catheter, and (2) puncture the anesthetized area with a needle, ask the child to look at the needle, and then ask if there is any sensation. Frequently the child is astounded at the lack of pain and stops crying.

Pediatric Airway Management

Endotracheal Tubes

For most children, the proper size of endotracheal tube and the proper distance of insertion relative to the alveolar ridge of the mandible or maxilla are moderately constant (also see Chapter 50). Published formulas are estimates that may need to be modified based on physical examination or unusual child size. Table 82-6 provides a guide to choosing the proper size of endotracheal tube and the recommended distance for insertion (from the alveolar ridge). Uncuffed endotracheal tubes were traditionally preferred for children younger than 6 years (see earlier discussion). Figure 82-4 illustrates a new cuffed endotracheal tube that may offer specific advantages over traditional cuffed endotracheal tubes. If one uses a cuffed endotracheal tube, a half-size smaller

Table 82-6 Recommended Sizes and Distance of Insertion of Endotracheal Tubes and Laryngoscope Blades for Use in Pediatric Patients

Age of Patient	Internal Diameter of Endotracheal Tube (mm)	Recommended Size of Laryngoscope Straight Blade	Distance of Insertion* (cm)
Preterm (<1250 g)	2.5 uncuffed	0	6-7
Full term	3.0 uncuffed	0-1	8-10
1 yr	3.5-4.0 cuffed	1	11
2 yr	4.5-5.0 cuffed	1-1.5	12
6 yr	5.0-5.5 cuffed	1.5-2	15
10 yr	6.0-6.5 cuffed	2-3	17
18 yr	7-8 cuffed	3	19

*Inserting the endotracheal tube this distance from the alveolar ridge of the mandible or maxilla places the distal end of the tube in the midtrachea.

than for an uncuffed endotracheal tube should be selected, and cuff pressure should be adjusted so that there is a small leak around the cuff at a peak inflation pressure of 20 to 30 cm H_2O. Cuff pressure should be checked periodically during anesthesia involving nitrous oxide. If an uncuffed endotracheal tube is used, the appropriate size allows a small gas leak at peak inflation pressures of 20 to 30 cm H_2O. If an uncuffed endotracheal tube (or a cuffed tube without the cuff inflated) does not leak at 40 cm H_2O, I will replace it with the next smaller size and recheck for a leak. It is always important to make this leak assessment to determine the size of the larynx. On average, several children per year in my practice have undiagnosed subglottic stenosis detected by the anesthesiologist at the time of intubation (Fig. 82-11).

Laryngoscope Blades

Any hospital that takes care of children must have a full selection of laryngoscope blades so that the blade most appropriate for the child is readily available. In general, straight blades are used in neonates and toddlers because of anatomic differences from older children (see earlier); the Wis-Hippel 1.5 is a particularly versatile blade because its surface is flat. Older children can be managed with either curved or straight blades. In some children a straight blade may offer advantage over curved blades because of midfacial hypoplasia or other anatomic deformity (Table 82-6). A laryngoscope blade with built-in oxygen delivery is available in sizes 0 and 1 and offers specific advantage for awake or sedated intubation of neonates (Fig. 82-12).

The Child with a Full Stomach

A child with a full stomach must be treated the same as for an adult with a full stomach; that is, both should undergo rapid-sequence induction of anesthesia with the application of cricoid pressure (also see Chapters 29 and 50). Because oxygen consumption is much greater, hemoglobin desaturation occurs more rapidly in a child than in an adult and more rapidly in an infant than in a child. Additionally, a child may be uncooperative and refuse to breathe oxygen before induction of anesthesia—that is, refuse preoxygenation. In this circumstance, the best that can be done is to enrich the environment with a high flow of oxygen because upsetting the child further is not desirable. Additional equipment that should be available includes two suction catheters (if one becomes blocked, another would be available immediately) and two appropriately sized laryngoscope blades (e.g., a Macintosh 2 and a Miller 2) with two handles (if the bulb, contact, or battery fails, another would be available immediately). While the child is breathing oxygen, atropine (0.02 mg/kg) is administered intravenously to prevent reflex- or succinylcholine-induced

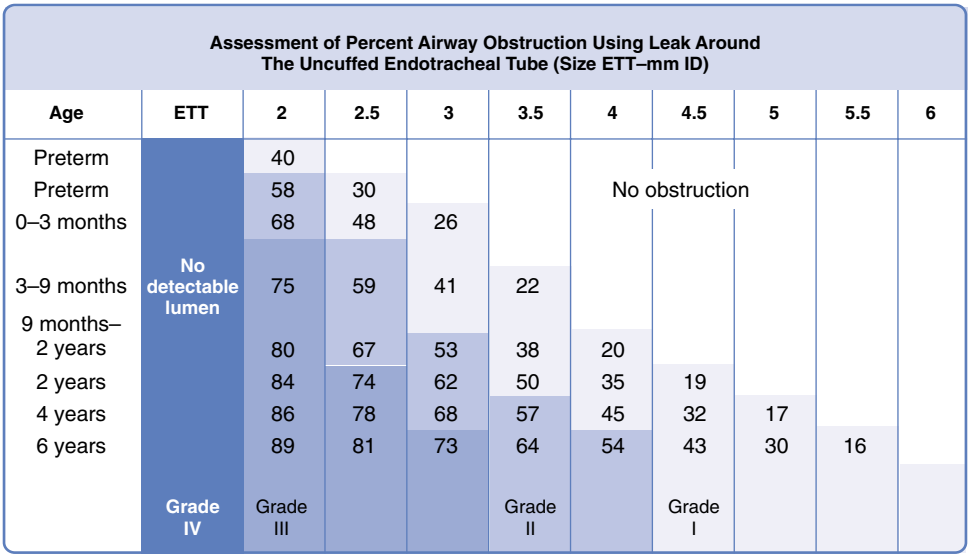

Figure 82-11 Method of determining the percentage of airway obstruction. After easy passage of an uncuffed endotracheal tube (ETT), a manometer is placed at the connection of the elbow of the anesthesia circuit and the ETT. A stethoscope is placed over the larynx and the circuit slowly pressurized. The pressure at which a leak is auscultated is matched with the age of the child and the size of the ETT to assess the degree of laryngeal narrowing. It should be noted that this chart is based on one institution's experience and the manufacturer of the ETTs was not described, so the actual external diameter of the ETTs used is unknown. *(Reproduced and modified with permission from Myer CM 3rd, O'Connor DM, Cotton RT: Proposed grading system for subglottic stenosis based on endotracheal tube sizes. Ann Otol Rhinol Laryngol 103:319-323, 1994.)*



Figure 82-12 The Oxyscope (Heine Optotechnik, D-82211 Herrsching, DE) is a Miller 1 laryngoscope blade with an insufflation channel along its length so that it may be attached to an oxygen source. An Oxyscope provides increased F_{IO_2} and is particularly useful for intubation in a conscious neonate whose oxygen consumption is high and in whom desaturation may develop rapidly.

bradycardia and to delay the bradycardia of hypoxemia should any of these events occur. Because of its rapid onset of neuromuscular blockade, succinylcholine is still the muscle relaxant of choice in this circumstance and should be administered at a dose of 1 to 2 mg/kg immediately after thiopental (5 to 6 mg/kg) or propofol (3 mg/kg). Cricoid pressure is gently applied after the child loses consciousness. Children should be told that they may "*feel someone touching you on the neck*" as they fall asleep and that this is "*normal*." In children, the head-up position does not significantly increase protection from pulmonary aspiration of acid gastric contents. If succinylcholine is contraindicated, rocuronium (1.2 mg/kg) will provide conditions for intubation similar to those provided with succinylcholine within 30 seconds of administration.[91] However, the duration of neuromuscular blockade will be 60 to 90 minutes (see earlier and Chapter 29). In the hypovolemic child, ketamine (2 mg/kg) may be used for induction, whereas in a child with hemodynamic instability, e.g., cardiomyopathy, etomidate (0.2-0.3 mg/kg) may be a better choice.

The Difficult Airway

The approach to a difficult airway depends in part on whether it is a known difficult airway and previous records are available for review or whether the child has an unexpectedly difficult airway. In the former situation, a difficult-airway cart with age- and size-appropriate airway equipment (Table 82-7) is brought into the operating room, and the assistance of a colleague with pediatric airway skills is arranged. In the latter situation, the difficult-airway cart may need to be brought into the room and skilled help summoned. The most common errors that I have observed in a number of malpractice cases are lack of equipment or inappropriately sized equipment, inadequate skilled help, failure or delay in calling for help, and failure of the anesthesiologist to attempt cricothyrotomy soon enough. Accordingly, the importance of having a dedicated pediatric difficult-airway cart, the need to be familiar with its contents and how to use the devices that it contains, and the availability of skilled help cannot be overemphasized.

A child facing a potentially difficult laryngoscopic procedure should receive, at most, light sedation before induction of anesthesia by mask to maintain spontaneous respirations. In this way the airway can be secured before "burning bridges" by administering a muscle relaxant and losing the help of spontaneous respirations. With the child breathing spontaneously, breath sounds can be used to guide successful tracheal intubation. When normal airway anatomy cannot be confirmed visually, placing a stylet in the endotracheal tube and bending the tip of the endotracheal tube acutely (90 degree bend) allows placement of the tip

Table 82-7 Suggested Equipment for a Difficult-Airway Cart

Equipment Category	Recommended Equipment
Airways	Oral and nasopharyngeal (trumpet) airways in all sizes for preterm infants to adults
Endotracheal tubes	Cuffed and uncuffed endotracheal tubes of various size (uncuffed down to size 2.0 mm ID)
Stylets	Stylets in several sizes
Laryngoscopy	Laryngoscope blades in multiple sizes and configurations Several handles, extra batteries Oxyscope (Heine Optotechnik, D-82211 Herrsching)
Laryngeal mask airways	All sizes 1.0 to 6.0 ProSeal LMAs for patients with a full stomach or those who require higher peak inflation pressure for successful ventilation Large-volume syringes for the larger masks
Fiberoptic intubation	Fiberoptic scopes—several sizes, including one that will fit through a 2.5-mm ID endotracheal tube Light source Teeth protectors Oral airways designed for fiberoptic intubation Silicon lubricant
Retrograde equipment	Retrograde intubation equipment (needle with guidewire)
Optical stylet	Available in a variety of sizes, including one that will fit through a 2.5-mm ID endotracheal tube (Storz, Karl Storz GmbH & Co. KG, Tuttlingen, Germany) or a 3.0-mm ID endotracheal tube (Shikani, Clarus Medical, Minneapolis, MN)
Endotracheal tube exchangers	Various sizes for the full array of pediatric patients
Cricothyrotomy equipment	Percutaneous cricothyrotomy kits designed for older and larger children (needles, guidewire, and dilator) Jet ventilation–type device, which is similar to an intravenous catheter (18, 14, and 13 gauge) and useful in infants
Jet ventilation equipment	Jet ventilation stylets and jet injector with an appropriate hookup for wall oxygen
Carbon dioxide detector	For use in non–operating room venues

ID, internal diameter.

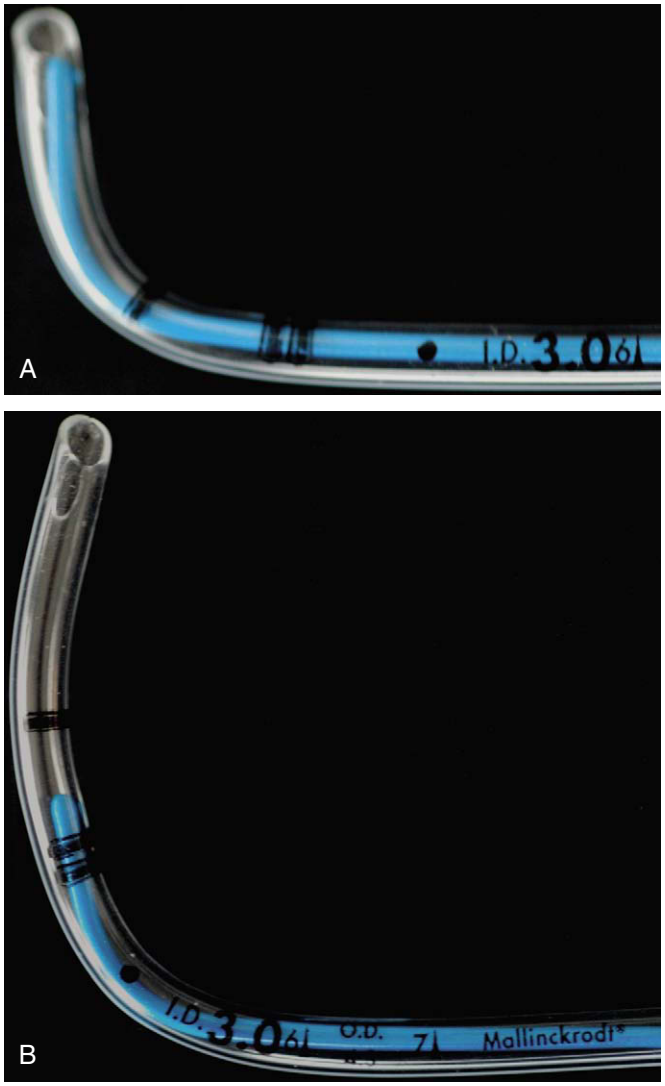

Figure 82-13 In patients with midfacial hypoplasia or those in a cervical collar, it is necessary to make a nearly 90-degree bend around the base of the tongue to enter the larynx. If one inserts a stylet into an endotracheal tube with a 90-degree bend (**A**), listens for breath sounds emerging from the proximal end of the endotracheal tube, and then when good breath sounds are heard, threads the endotracheal tube off the stylet (not advancing the stylet), the tube will make the bend around the base of the tongue and pass into the trachea (**B**).

of the endotracheal tube in the midline just posterior to the epiglottis. One can then listen for breath sounds exiting from the end of the endotracheal tube, and once good air exchange is heard, the endotracheal tube is advanced off the stylet (not inserted with the stylet) (Fig. 82-13). This technique allows advancement of the endotracheal tube at an acute angle without causing trauma to anatomic structures. If the child is not breathing spontaneously, this advantage may be lost. Spontaneous respiration with a facemask designed to allow fiberoptic intubation is another approach. Having a skilled assistant pull the tongue forward out of the mouth with a dry gauze or plastic retractor will also aid visualization of the glottic opening. Fiberoptic intubation through an LMA requires the use of two endotracheal tubes threaded on the fiberoptic scope (the second to hold the first in position while removing the LMA). The LMA is perhaps the most important adjunct to airway management because it can

Table 82-8 Laryngeal Mask Size versus Patient Weight*

Laryngeal Mask Size	Patient Weight
1	≤5 kg
1.5	5-10 kg
2	10-20 kg
2.5	20-30 kg
3	30-50 kg
4	50-70 kg
5	70-100 kg
6	>100 kg

*Manufacturer's recommendations (LMA North America).

establish a patent airway before the airway is secured more definitively with an endotracheal tube or a cricothyrotomy (Table 82-8). In neonates with difficult airways such as those with Goldenhar, Treacher-Collins, or Pierre Robin syndrome, awake topicalization of the airway with lidocaine (1% nebulized to avoid excessive doses) followed by placement of an LMA is very helpful in guiding awake/sedated fiberoptic intubation. A skilled assistant who can hold the head in proper position and assist with the difficult airway is critical to the success of most of these approaches to a difficult airway. It should be noted that in children the ProSeal LMA will allow ventilation at significantly higher peak inflation pressures (~25 cm H_2O) than possible with the classic LMA (~15 cm H_2O); thus, this device may be preferable in a difficult airway situation, especially since the stomach can be suctioned.[113]

If the child should progress to a "cannot ventilate, cannot intubate" situation, one must immediately establish a surgical airway. It is vital to properly position the child with a roll of towels under the shoulders to force the larynx anteriorly so that the best access to the larynx is provided. It is also important to have a variety of cricothyrotomy devices available, because some are appropriate for infants, whereas others are appropriate only for older children and teenagers. Devices appropriate for older children include some using the Seldinger technique (cricothyroid puncture, passing a guidewire, skin incision, then passing a dilator/catheter over the wire) (e.g., Arndt and Melker kits, Cook Critical Care, Inc., Bloomington IN) or use of an armored transtracheal catheter (Cook Critical Care). The simplest cricothyrotomy devices that can be used in children of all ages, including infants, is an intravenous catheter, which can then be interfaced with the 15-mm connector of a 3-mm internal diameter (ID) endotracheal tube.[114] Alternatively, a preformed device designed exactly like an intravenous catheter but with a built-in 15-mm connector is available. This device comes in three sizes (18, 14, and 13 gauge) and also has a Luer-Lok connection to allow transtracheal jet ventilation (Fig. 82-14) (Ventilation-Catheter, VBM Medical, Noblesville, IN). Other emergency airway devices include a stiletted endotracheal tube changer (used as a bougie) that has both 15-mm and Luer-Lok adapters (Cook, Inc., Bloomington, IN) (Fig. 82-15). A simple method for administering oxygen to the Luer-Lok without the high pressure of a jet ventilator is to use standard oxygen tubing with a hole cut in the side; occlusion and unocclusion of the hole will direct oxygen (1 to 5 L/min) through the catheter. Note that whenever

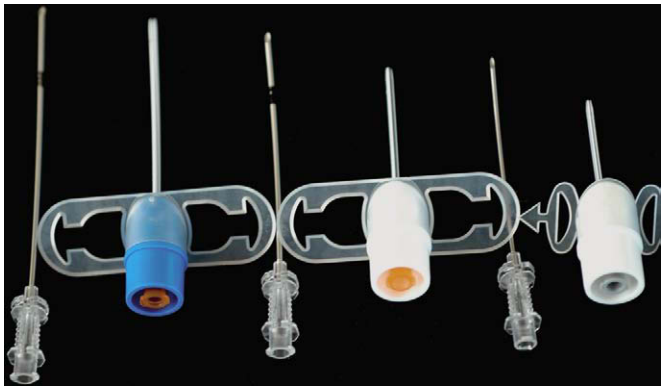

Figure 82-14 This device designed for transtracheal ventilation provides one of the best systems for emergency airway management in a child with a "cannot ventilate, cannot intubate" airway situation (Ventilation-Catheter, VBM Medical, Noblesville, IN). Note that the design is similar to that of an intravenous catheter, which means that the principles for use are familiar to all anesthesiologists, and the device is small enough to allow use even in neonates. In addition to a secure 15-mm adapter for interface with any standard bag ventilation device, there is a Luer-Lok connection that allows jet ventilation. Three sizes are available: 16 gauge (infant), 14 gauge (child), and 13 gauge (adult).

such a technique is applied, it is vital to ensure that the catheter is correctly positioned within the trachea to avoid barotrauma and that the chest is deflating between breaths.

The Child with Stridor

A child with intrathoracic airway obstruction has expiratory stridor and prolonged expiration (bronchiolitis, asthma, intrathoracic foreign body). In contrast, a child with extrathoracic upper airway obstruction has inspiratory stridor (epiglottitis, laryngotracheobronchitis, laryngeal or subglottic foreign body). When agitated or crying, such children exhibit dynamic collapse of the airway (Fig. 82-16), which can markedly worsen airway obstruction and lead to respiratory failure and hypoxemia. Therefore, events that can upset the child (drawing of blood for analysis of gases, venipuncture for blood tests, and separation from parents) must be minimized. The difficult-airway cart should also be present in the room. The surgical team should be mobilized and be prepared to perform an emergency tracheotomy should total airway obstruction occur and mask ventilation or endotracheal intubation not be possible.

I have found the following procedure to be effective for inducing anesthesia in a child with stridor. To minimize upsetting the child, the child is brought to the operating room with the mother or father, who holds the child during induction. Induction of anesthesia with halothane or sevoflurane in oxygen by mask is the preferred method because maintaining spontaneous respirations is critical. As soon as the child loses consciousness, the parent is escorted out of the operating room. With the child lightly anesthetized and after infiltration of local anesthetic, an intravenous line is inserted. This allows withdrawal of blood samples if indicated. Hydration is begun with lactated Ringer's solution (15 to 30 mL/kg), and atropine (0.02 mg/kg) is given. At this point the plane of anesthesia can be deepened with greater safety. If the stridor worsens or mild laryngospasm occurs, the pop-off valve is closed sufficiently to develop 10 to 15 cm H_2O of PEEP. This procedure relieves most instances of airway obstruction caused by dynamic collapse of the airway and loss of pharyngeal muscle tone when the child attempts to inspire against an obstructed airway (Fig. 82-17). As the level of anesthesia deepens, gentle assistance with ventilation may be necessary; however, maintaining spontaneous respiratory effort is important if possible.

Any child with airway obstruction will have a long, slow induction of anesthesia before becoming sufficiently anesthetized

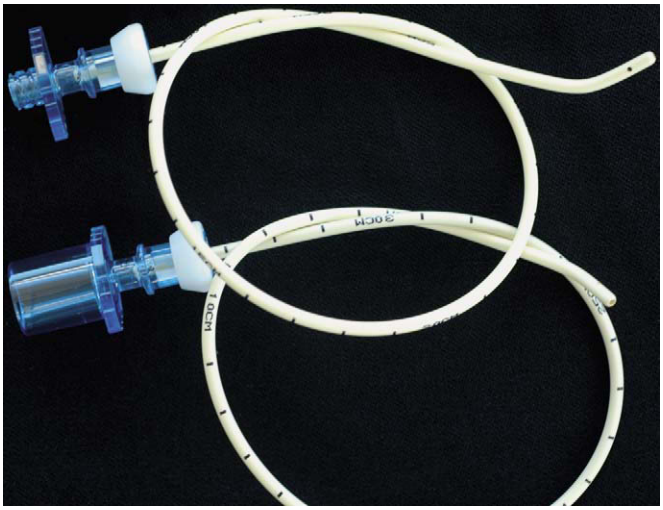

Figure 82-15 Endotracheal tube exchangers are available that will fit 3.0-mm internal diameter endotracheal tubes. They have side holes at the tip that allow delivery of oxygen and may be attached to either a jet ventilation system or standard adaptors with a 22-mm outside diameter. This device is also available with a stylet and slight bend to be used as an intubation bougie. *(Courtesy of Cook, Inc., Bloomington IN.)*

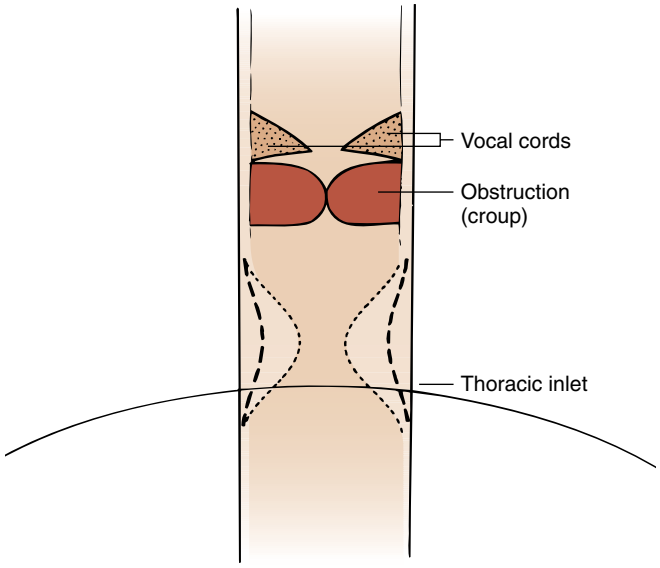

Figure 82-16 Infants and young children have highly compliant airway structures. With normal respiration, some dynamic collapse of the extrathoracic upper airway occurs (*broken line*). When a child has upper airway obstruction (as in epiglottis, laryngotracheobronchitis, or extrathoracic foreign body) (*dark orange*) and struggles to breathe against this obstruction, dynamic collapse of the trachea increases. This increase in dynamic collapse (*dotted line*) augments the mechanical obstruction of the airway. Therefore, until the airway is secured, it is important to avoid procedures that will upset the child. *(Modified from Coté CJ, Lerman J, Todres ID [eds]: A Practice of Anesthesia for Infants and Children, 4th ed. Philadelphia, Saunders, 2008.)*

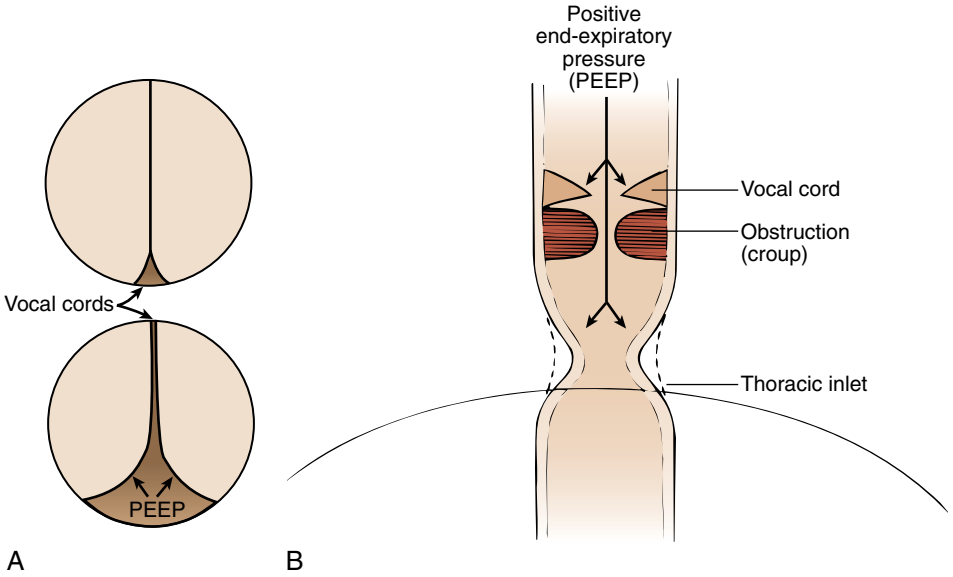

Figure 82-17 When a child has upper airway obstruction caused by laryngospasm (**A**) or mechanical obstruction (**B**), application of approximately 10-15 cm H_2O of positive end-expiratory pressure (PEEP) (*arrows*) during spontaneous breathing often relieves the obstruction. That is, PEEP helps keep the vocal cords apart (**A**) and the airway open (**B,** *broken lines*). If this simple maneuver does not relieve the obstruction, more vigorous positive-pressure ventilation may be necessary. Airway obstruction caused by the tongue requires insertion of an appropriately sized oral airway.

to permit laryngoscopy and endotracheal intubation. Because a sevoflurane vaporizer allows only 2.5 to 3 MAC concentrations to be delivered whereas a halothane vaporizer allows 5 to 6 MAC concentrations, halothane would be my drug of choice in this circumstance (if available). In addition, the slower excretion of halothane than of sevoflurane would also provide better conditions for airway manipulation for a longer time. The issue of a full stomach is secondary to the airway problem; rapid induction of anesthesia is contraindicated in these children. A child with laryngotracheobronchitis or epiglottitis usually requires an uncuffed endotracheal tube that is 0.5 to 1.0 mm (ID) smaller than normal; use of a stylet facilitates its insertion. Management of a difficult airway is also discussed in Chapter 50.

Intravenous Fluid and Transfusion Therapy

Intravenous Fluids

The approach to intravenous fluid therapy in children must consider their high metabolic demands and high ratio of body surface area to weight (also see Chapters 54 and 55). The basis for calculating maintenance fluids derives from data by Holliday and Segar,[115] who found that daily fluid requirements depend directly on metabolic demand—specifically, that 100 mL of water is required for each 100 calories of expended energy. Relating this to weight produces hourly fluid requirements of 4 mL/kg for children up to 10 kg, an additional 2 mL/kg for each kilogram above 10 kg up to 20 kg, and an additional 1 mL/kg for each kilogram above 20 kg (Table 82-9). Thus, a 25-kg child would require 65 mL/hr—that is, $(10 \times 4) + (10 \times 2) + (5 \times 1) = 65$ mL. This amount does not include fluid deficits, third-space losses, modifications because of hypothermia or hyperthermia, or requirements caused by unusual metabolic demands. In general, deficits caused by restriction of food and fluids are calculated by multiplying the hourly maintenance rate by the number of hours of restriction; 50% of the resulting deficit is replaced in the first hour and 25% in each of the next 2 hours. Third-space losses are replenished according to the surgical procedure and may vary from 1 mL/kg/hr for a minor surgical procedure to as much as 15 mL/kg/hr for major abdominal procedures (e.g., surgical repair of gastroschisis).

The composition of the intravenous fluid is also a concern. Because greater hypoxic brain damage was found to occur in animals with high blood glucose levels, we no longer recommend routine use of glucose-containing solutions, especially for brief operative procedures. However, a concern about unrecognized hypoglycemia was the motivating factor regarding the routine use of glucose-containing solutions in children, particularly those who have not had food or fluids for a longer than usual time or those who have diminished glycogen stores. Data are inadequate to eliminate glucose completely because the relevance of the animal data is not clear and the true incidence of hypoglycemia is not known in all populations of food-restricted children. This issue is further complicated by the fact that different values are used to define hypoglycemia, depending on the child's age.

Despite limited data, a balanced salt solution (e.g., lactated Ringer's solution) should be used for all deficits and third-space losses. If a child is thought to be at risk for hypoglycemia, 5% dextrose in 0.45% normal saline should be administered by "piggyback" infusion at maintenance rates. This minimizes the chance of a bolus administration of glucose and satisfies the concern for unrecognized hypoglycemia or accidental hyperglycemia. The routine use of 5% dextrose or 5% dextrose in 0.45% normal saline as the initial replacement for fluid deficit, third-space losses, and

Table 82-9 Calculation of Maintenance Fluid Requirements for Pediatric Patients

Weight (kg)	Hourly Fluid Requirements (mL)
<10	4 mL/kg
11-20	40 mL + 2 mL/kg for each kilogram above 10
>20	60 mL + 1 mL/kg for each kilogram above 20

blood loss is discouraged. For most children, lactated Ringer's solution is the only fluid required.

Children receiving intravenous alimentation present a special problem. Transition to 10% glucose is often recommended to avoid intraoperative hyperglycemia with continuation of the current alimentation fluid and to avoid hypoglycemia if it is stopped suddenly. However, this change to 10% glucose has not been adequately studied. In my practice I reduce the established intravenous alimentation fluid infusion rate by 33% to 40% (to account for the reduced metabolic rate under anesthesia) and periodically check blood glucose values. This then does not waste the current alimentation fluid and involves only a simple change in infusion rate. Another population of children who will require specific intravenous fluid management consists of those with mitochondrial disease. In general, glucose-containing solutions are administered at maintenance rates and lactate-containing solutions are avoided. Some children with mitochondrial disease have enormous glucose requirements that may necessitate the use of 10% glucose. Management of such patients must be individualized.

Fluid management of term and preterm infants must take into account other variables. The amount of insensible water loss is inversely proportional to gestational age. The younger and more physically immature the infant, the higher the skin permeability, the ratio of body surface area to weight, and the metabolic demand. In addition, the use of radiant warmers and phototherapy increases insensible water loss. On the other hand, preservation of body heat with warming devices reduces insensible water loss.

The fact that the neonatal kidney is unable to excrete large amounts of excess water or electrolytes must also be considered. As described earlier, the volume of extracellular fluid in a newborn is very large. During the first days of life, some of this excess water is excreted. Therefore, term newborns have reduced fluid requirements for the first week of life. The daily fluid requirements for a term newborn in the days after birth are 70 mL/kg on day 1, 80 mL/kg on day 3, 90 mL/kg on day 5, and 120 mL/kg on day 7. Daily fluid requirements would be slightly higher for preterm infants. Sodium and potassium concentrations are usually kept at 2 to 3 mEq/100 mL. Newborns are generally started on 10% glucose to prevent hypoglycemia. This fluid is continued for the first several days of life until glucose values are stable. Infants of diabetic mothers or those given large amounts of glucose just before delivery may require greater concentrations of glucose for protection against rebound hypoglycemia. Infants unable to tolerate oral feeding may continue to receive 10% glucose solutions and may even require peripheral or central alimentation. A number of infants have been transferred to our institution with severe and potentially life-threatening hyperglycemia (i.e., blood glucose levels of 700 to 900 mg/dL) as a result of overzealous use of this type of glucose therapy. This solution should be administered with a rate-limiting device and used with caution if infants require surgery; every effort should be made to reduce bolus administration of glucose. Blood sugar levels should be periodically monitored and the solution infused at maintenance rates only.

Packed Red Blood Cells

The use of blood products in pediatric surgical patients has diminished greatly because of the fear of transmission of disease—particularly human immunodeficiency virus (HIV). Because HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), and a number of other disease-causing viruses can be transmitted with as little as 10 mL of packed red blood cells (PRBCs), administration of any blood product requires clear, medically defensible clinical indications that are preferably recorded on the anesthetic record (also see Chapter 55). The current estimated risk for transmission of HIV, HBV, or HCV is 1 in 81,000 to 1 in 1,600,000 units (see www.aabb.org/All_About_Blood/FAQs/aabb_faqs.htm). Because of these concerns it is common for families to donate blood for their child or relative; in this situation the blood product should be irradiated to prevent possible graft-versus-host disease.

When caring for children, it is very important to think in terms of blood volumes and portions of blood volumes lost rather than units because a unit of blood may constitute several blood volumes in a preterm infant but only a fraction of the blood volume of a robust teenager. These considerations govern calculation of the maximal allowable blood loss (MABL) resulting in an acceptable hematocrit. MABL takes into account the effect of patient age, weight, and starting hematocrit on blood volume. In general, blood volume is approximately 100 to 120 mL/kg for a preterm infant, 90 mL/kg for a full-term infant, 80 mL/kg for a child 3 to 12 months old, and 70 mL/kg for a child older than 1 year. These are merely estimates of blood volume. The individual child's blood volume is calculated by simple proportion by multiplying the child's weight by the estimated blood volume (EBV) per kilogram. Although several formulas are available, a simple relationship is easiest to remember:

$$\text{MABL} = \frac{\text{EBV} \times (\text{Starting hematocrit} - \text{Target hematocrit})}{\text{Starting hematocrit}}$$

Thus, if a 3-year-old child weighs 15 kg and has a starting hematocrit of 38% and if clinical judgment estimates the desired postoperative hematocrit to be 25%, the calculation would be as follows:

$$\text{MABL} = (15 \times 70) \times (38 - 25)/38 = 1050 \times 13/38 = \sim 360 \text{ mL}$$

MABL would be replaced with 3 mL of lactated Ringer's solution per milliliter of blood loss; that is, 3 mL of lactated Ringer's solution times the 360 mL of blood loss equals approximately 1080 mL of lactated Ringer's solution. If blood loss is less than or equal to MABL and no further significant blood loss occurs or is anticipated in the postoperative period, there is no need for transfusion of PRBCs. If, however, significant postoperative bleeding occurs or is anticipated, discussion of potential transfusion needs with the surgeon is very important. Normally, a child who has had adequate replacement of intravascular volume deficits will tolerate anemia very well. There is sufficient time to make the decision to transfuse by observing postoperative urinary output, heart rate, respiratory rate, and overall cardiovascular stability. Unfortunately, no one formula permits a definitive decision. The development of lactic acidosis is a late sign of inadequate oxygen-carrying capacity.

If the child has reached the MABL and significantly more blood loss is expected during surgery, the child should receive PRBCs in sufficient quantity to maintain the hematocrit in the 20% to 25% range. The entire loss of red cell mass should not be replaced unless clinically indicated if these additional PRBCs would expose the child to additional units of blood products. Hematocrit values in the low 20% range are generally well tolerated by most children, the exception being preterm infants, term

newborns, and children with cyanotic congenital heart disease or those with respiratory failure in need of high oxygen-carrying capacity. Because the incidence of apnea is higher in neonates and preterm infants who have hematocrit values below 30%, it would be prudent to discuss with both the surgeon and neonatologist the minimal target hematocrit for such children and to document the discussion in the child's record.[116] Older children with a history of sickle cell disease may require preoperative transfusion and should be managed in conjunction with their attending hematologist. A simple formula for intraoperative or postoperative estimation of the volume of PRBCs needed in a 15- kg child with a hematocrit of 20% as an example is

$$\text{Volume of PRBCs to be transfused} = \frac{\left[\text{Desired Hct}\,(35) - \text{Present Hct}\,(20) \times \text{EBV}\left(70\ \text{mL/kg} \times 15\ \text{kg}\right)\right]}{\text{Hematocrit of PRBCs}\left(\sim 60\%\right)}$$

$$\frac{(35-20)\times(70\times15)}{60} = \sim 262\ \text{mL PRBCs}$$

Fresh Frozen Plasma

Fresh frozen plasma (FFP) is administered to replenish clotting factors lost during massive blood transfusion (usually defined as blood loss exceeding one blood volume), for disseminated intravascular coagulopathy, or for congenital clotting factor deficit. The anesthesiologist initiates and guides therapy with FFP during massive blood loss, whereas the hematologist's advice is sought when either of the other two conditions exists.

Children with known clotting factor deficits, such as those with massive thermal injury or coagulopathy, may require transfusion of FFP before blood loss exceeds one blood volume. In contrast, healthy children who do not have coagulation factor deficits at the beginning of surgery do not need FFP until blood loss exceeds 1 and probably 1.5 blood volumes.[117,118] This generalization applies to children given PRBCs; children given whole blood will not need FFP, even when blood loss exceeds several blood volumes. Despite loss of one blood volume, prolongation of the prothrombin time (PT) and the partial thromboplastin time (PTT) will only be minor.[119,120]

Blood loss exceeding 1 to 1.5 blood volumes (replaced entirely with PRBCs and crystalloid, albumin, or other non–blood-related products) often necessitates transfusion of FFP. However, the decision to administer FFP should be based on observed coagulopathy and documented prolongation of the PT and PTT. Obtaining these test results from the laboratory often takes longer than desired. In this circumstance, a note should be written that blood loss has exceeded one blood volume and that abnormal oozing has occurred in the surgical field. A child should never be given FFP to correct bleeding that is surgical in nature.

No studies on children have yet clearly defined what values of PT and PTT are associated with pathologic bleeding requiring transfusion of FFP to replace clotting factors. However, if associated with abnormal oozing, a PT exceeding 15 seconds (international normalized ratio [INR] >1.4) or a PTT greater than 60 seconds (>1.5 times baseline) seems to warrant correction. If these abnormalities exist but oozing does not occur and the surgical field is relatively safe from the complications of hematoma formation (e.g., as in orthopedic surgery versus neurosurgery), it seems appropriate to observe the child and withhold transfusion of FFP.

The volume of FFP required to correct prolongation of the PT and PTT depends on the severity of the clotting factor deficit and the presence or absence of consumptive coagulopathy. In general, FFP therapy may require replacement of 30% or more of the child's blood volume. Transfusion of FFP at rates exceeding 1.0 mL/kg/min is sometimes followed by severe ionized hypocalcemia and cardiac depression with hypotension, especially if FFP is administered during anesthesia with a potent inhaled anesthetic (Fig. 82-18).[121,122] Therefore, exogenous calcium chloride (2.5 to 5 mg/kg) or calcium gluconate (7.5 to 15 mg/kg) should be administered during rapid transfusion of FFP.[123] Ionized hypocalcemia occurs very frequently in neonates given FFP, possibly because of their decreased ability to mobilize calcium and metabolize citrate; children undergoing liver transplantation or those with compromised hepatic function or perfusion may also be at increased risk because of a decreased ability to metabolize citrate.

Platelets

Thrombocytopenia may occur as a result of disease processes (idiopathic thrombocytopenic purpura, chemotherapy, infection, disseminated intravascular coagulopathy) or dilution during massive blood loss. Children whose platelet count has fallen because of idiopathic thrombocytopenic purpura or chemotherapy generally tolerate platelet counts as low as 15,000/mm^3 without a need for platelet transfusion. In contrast, children whose platelet count has decreased because of dilution (massive blood loss) generally require platelet transfusion when the count is 50,000/mm^3 or less (also see Chapter 55). The reason for this disparity is not known. However, in my experience, the preoperative platelet count has been extremely valuable in predicting intraoperative platelet requirements.[124] Children who begin surgery with elevated platelet counts may not require platelet transfusion despite blood loss of four or more blood volumes. Conversely, children who begin surgery with low platelet counts (approximately 100,000/mm^3) may require platelet transfusion when blood loss is one or two blood volumes. Children who begin surgery with a normal platelet count (150,000 to 350,000/mm^3) usually do not require platelet transfusion until two blood volumes or more is lost (Fig. 82-19).

Whenever platelets are administered, the anesthesia record should document the reason for the transfusion, and every effort should be made to obtain a platelet count before transfusion. Clinical oozing is the typical indication for platelet transfusion, unless the potential for bleeding would be critical to survival, such as during neurosurgery, cardiac surgery, or major organ transplantation. The initial volume of platelets transfused is approximately 0.1 to 0.3 U/kg; the increase in platelet count achieved with this amount of transfusion varies considerably and depends on the presence or absence of platelet antibodies and the rate of platelet consumption.

Blood Warmers

A fluid/blood warmer is essential for any child who might require rapid correction of intravascular volume. There is no benefit in using such devices for maintenance intravenous fluid therapy because the rate of infusion is so slow that the intravenous fluid returns to room temperature between the time that it exits the warmer and enters the child. New warming devices that use countercurrent or microwave warming methods are superior to the older water bath coiled tubing devices. Low-capacity passive flow

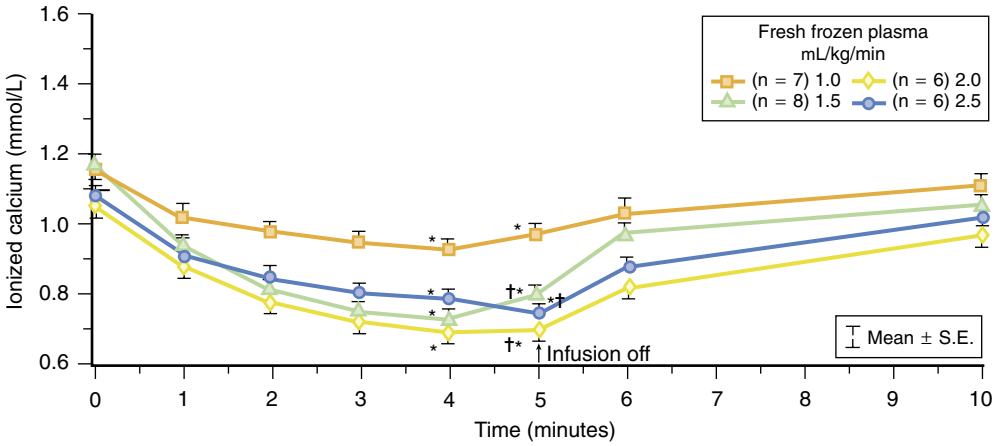

Figure 82-18 Ionized hypocalcemia always accompanies the administration of citrated blood products (fresh frozen plasma, citrated whole blood). Fresh frozen plasma has the highest concentration of citrate per unit volume of any blood product and is the most likely to cause ionized hypocalcemia during rapid infusion. Studies in children with severe thermal injuries suggest that rates exceeding 1.0 mL/kg/min produce severe ionized hypocalcemia. If there is no further administration of citrated blood products, this abnormality corrects itself because of metabolism of the citrate. However, children with impaired hepatic blood flow (infants, liver transplant patients, trauma patients) may need exogenous calcium therapy. *$P < .001$; †$P < .0021$ versus baseline. *(From Coté CJ, Drop LJ, Hoaglin DC, et al: Ionized hypocalcemia after fresh frozen plasma administration to thermally injured children: Effects of infusion rate, duration, and treatment with calcium chloride. Anesth Analg 67:152-160, 1988, with permission.)*

through devices such as the Hot Line (Level 1 Technologies, Inc., Rockland, MA) is useful but not for warming a patient with maintenance rate administration. One exception might be the Belmont Buddy fluid warmer (Belmont Instrument Corp., Billerica, MA). The manufacturer claims a warming capacity of "cold fluids to 38°C at flow rates as low as keep vein open (KVO) and as high as 100 mL/min." High-capacity systems such as the Level 1 System 1000 (Level 1 Technologies, Inc.), which uses countercurrent warming technology, is capable of warming blood starting at 5°C to 6°C to 33°C at rates as high as 250 mL/min. Another high-capacity blood warmer, the Belmont FMS (Belmont Instrument Corp.) uses microwave warming and is capable of fluid delivery at rates of 10 to 750 mL/min. This device is simple to set up. A comparison of several devices used with pediatric intravenous catheters found that technology similar to the Belmont FMS was superior to the Level 1 for maintaining temperature and high-volume transfusions through intravenous catheters larger than 18 gauge.[125] Thus, the Hot Line or Belmont Buddy seems appropriate for neonates and infants, the Level 1 would appear to be appropriate for massive rapid transfusion in children less than 30 kg, but the Belmont FMS would be superior for larger children.

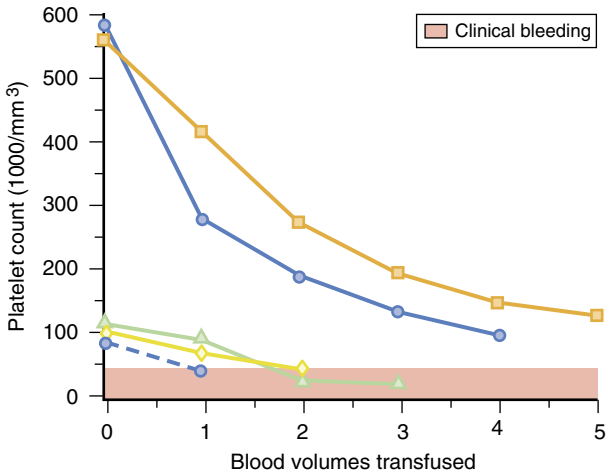

Figure 82-19 Dilutional thrombocytopenia occurs whenever massive blood loss takes place. The need for platelet transfusion, however, depends on the starting platelet count. In children who started with low platelet counts, dilutional thrombocytopenia developed after blood loss of one or two blood volumes, whereas children who started with very high platelet counts did not require transfusions of platelets. The *blue dashed*, *solid yellow*, and *solid green lines* represent three children with initial low platelet counts; the *blue* and *orange lines* represent two children with initial high platelet counts. *(Data from Coté CJ, Liu LM, Szyfelbein SK, et al: Changes in serial platelet counts following massive blood transfusion in pediatric patients. Anesthesiology 62:197-201, 1985.)*

Monitoring and Safety Issues for Pediatric Patients

The complexity of monitoring applied to pediatric patients must be consistent with the severity of the underlying medical condition and the planned surgical procedure. My philosophy is that if I would place an arterial line or central venous line in an adult undergoing a particular operation, the same should be carried out for a child or an infant.

Routine Monitoring and Safety Issues

Minimal monitoring during anesthesia should include a precordial or esophageal stethoscope, a blood pressure cuff, an electrocardiogram, a temperature probe, a pulse oximeter, an end-tidal carbon dioxide monitor, and if possible, an anesthetic agent analyzer. The noninvasive blood pressure cuff (NIBP) is particularly useful because frequent blood pressure measurements can be made even when the anesthesiologist is preoccupied with other tasks. The end-tidal carbon dioxide monitor, NIBP, and pulse oximeter all provide an early warning of impending disaster that may go unobserved until the appearance of late clinical signs such as cyanosis, bradycardia, severe hypotension, or absence of breath

sounds. Simultaneous loss of the pulse oximeter signal and inability to measure blood pressure usually indicate low or no cardiac output. If the pulse oximeter continues to function but the NIBP has changed from measuring to nonmeasuring, the likelihood of hypovolemia or anesthetic overdose must be addressed immediately, but one can have some assurance that perfusion is still taking place.

The pulse oximeter carries a high incidence of false alarms from movement artifact, light interference, and other factors. The newest generation of pulse oximetry software and new devices minimize these artifacts, but because they continue to function in very low-flow states and the software is designed to read through motion, it may no longer be possible to use the pulse oximeter as a rapid determinant of perfusion, and some devices may continue to indicate a pulse for some seconds even when no pulse is present (personal observation). It is therefore vitally important to understand the pluses and minuses of the devices used in one's institution.

Capnography is the gold standard for confirmation of successful endotracheal intubation. However, the capnograph is useful in a number of other ways as well. Changes in the shape or magnitude of the CO_2 waveform may indicate bronchospasm, endobronchial intubation, a kinked endotracheal tube, or low pulmonary blood flow. One of the main drawbacks of capnography in small children is the inaccuracy of the recording obtained with use of non-rebreathing circuits. The best method of avoiding artifacts is to sample the expired gases at some point within the endotracheal tube or to use the circle system, even in small infants but at lower fresh gas flow rates. In general, the concentration of carbon dioxide in expired gas is within 2 to 3 mm Hg of that in arterial blood. However, severe pulmonary disease or atelectasis may produce a large difference in these two values. In this type of child, the gradient between arterial and expired carbon dioxide levels may be used to estimate the severity of the shunting. When such shunts exist, measurement of expired carbon dioxide levels may be used only to monitor trends. Ultimately, the most important monitors are the eyes, ears, and hands of the anesthesiologist, who must gather all the information provided by observation of the child and by the monitors applied to the child, consolidate the information into an accurate picture, and respond accordingly.

Prospective studies have shown that children younger than 6 months have a higher incidence of critical events.[20,126-129] The incidence of critical events is higher in ASA physical status 3 and 4 children than in ASA physical status 1 and 2 children. A number of factors may account for these results: the high metabolic rate of small children, the technical difficulty of caring for infants, the difficulty of estimating actual delivered ventilation when a variety of circuit configurations are available, and unfamiliarity with the care of small children. The POCA registry, a voluntary reporting system, estimated that the incidence of pediatric cardiac arrest was 1.4 ± 0.45 per 10,000 cases. Of the 289 cases, 83 occurred in children younger than 12 months. Emergency procedures and ASA status of 3 or greater were predictive of death. Of the anesthesia-related cardiac arrests, 55 were thought to be related to medications, and halothane alone or in combination with other drugs was associated with 37 of these events. It should be noted that two were associated with sevoflurane and that at the time of data collection sevoflurane had not been widely used in the United States. The use of high inspired concentrations of halothane (≥3%) accounted for 14 of the arrests, and other associated factors were controlled ventilation ($n = 18$) and difficult intravenous access ($n = 4$). The most common preceding events were bradycardia and hypotension ($n = 25$). Three infants had an unrecognized cardiomyopathy and one had congenital heart disease. Airway-related events accounted for only 20% of cases, and most involved airway obstruction and laryngospasm. Several lessons can be taken from these data: (1) Children younger than 1 year are particularly vulnerable to adverse events in the perioperative period, (2) the combination of high inspired concentrations of an inhaled agent and controlled ventilation contributed to the critical event, (3) high inspired concentrations of an inhaled agent should be avoided until intravenous access is established, (4) it is not the inhaled agent but the way that the agent is used that is most likely the major contributing factor to these arrests, (5) particular attention should be paid to frequent monitoring of blood pressure and heart rate during induction, (6) monitoring with pulse oximetry and capnography may have reduced the incidence of airway-related events that were avoidable when compared with earlier studies, and (7) children with congenital heart disease are particularly vulnerable to the cardiac depressant effects of potent inhaled agents. One study that supports these conclusions was a multi-institutional, highly controlled drug trial that compared remifentanil-based anesthesia and halothane-based anesthesia for pyloromyotomy.[80,81] In that study of 60 infants (38 receiving remifentanil and 22 receiving halothane), there were no cases of significant bradycardia, no differences in hemodynamic variables, and no differences in extubation times, PACU time, or rate of adverse events. There basically was no difference between halothane (a slow-onset, slow-offset potent anesthetic) and remifentanil (a very potent opioid with rapid onset and rapid offset). This study suggests that when anesthesiologists pay careful attention to details, adverse outcomes and severe adverse events can be avoided. The presence of an intravenous line before induction also probably provided an additional measure of safety.

Invasive Monitoring

Arterial and central venous catheters should be used in pediatric patients whenever such monitors contribute to the management of safe anesthesia. Placement of these monitors should not be avoided simply because the child is small or the anesthesiologist is uncomfortable applying the technique to a child. A variety of manufactured kits are available, most often using a thin-walled needle and a guidewire for venous access. If these monitors are indicated, the anesthesiologist, surgeon, cardiologist, or neonatologist should insert them. Peripherally inserted central catheters (PICC lines) offer a less invasive procedure that can provide accurate measures of central venous pressure.

Multilumen catheters are very valuable in the care of critically ill children. These devices facilitate the simultaneous intravenous administration of a variety of fluids, vasopressors, and antibiotics. However, these catheters can also lead to a false sense of security created by having three intravenous ports. Specifically, if a rapid infusion of colloid or even crystalloid is necessary, the long, narrow lumen would severely limit the rate of infusion preventing adequate rapid volume replacement. If the need for rapid volume expansion arises, a separate large-bore intravenous catheter should be inserted. Short-term cannulation of the femoral or brachiocephalic vein is reasonable and may be lifesaving.

Pediatric Equipment

The Dedicated Pediatric Equipment Cart

Anesthesiologists caring for pediatric patients must be prepared for the unexpected, particularly an undiagnosed congenital malformation or difficult endotracheal intubation. Having designated pediatric carts containing pediatric equipment is a convenient way of providing optimal care in a variety of locations in and outside the operating room. These carts contain pediatric-specific intravenous administration sets, intravenous catheters of various size, butterfly needles (scalp vein needles), electrocardiographic pads, various infant- to adult-sized blood pressure cuffs, precordial stethoscopes, adult and pediatric esophageal stethoscopes, armboards, intravenous fluids in pediatric-size containers, preterm infant– to adult-sized laryngoscope blades and handles, preterm infant– to adult-sized oral airways, endotracheal tubes (2.5 to 6.0 mm ID uncuffed and 3.0 to 7.0 mm ID cuffed), stylets, facemasks in preterm to adult size, size 1 to 5 LMAs, tape, drugs for resuscitation as well as commonly administered medications, and syringes, especially tuberculin syringes, for more precise administration of drugs. An intraosseous needle can be a lifesaving means of establishing emergency venous access for administration of drug or crystalloid and should be present in the pediatric cart. In addition, an interface that allows the administration of albuterol down an endotracheal tube should be readily available and preferably in the drug drawer (Fig. 82-20).

Anesthesia Circuits

Much has been written about the advantages and disadvantages of various anesthesia circuits for use in pediatric patients (also see Chapter 25).[130] Most of the attention has been directed to neonates and ways of reducing the work of breathing while preventing rebreathing. Non-rebreathing circuits provide the advantage of minimal work of breathing because they have no valves to be opened by the child's respiratory effort. The rate of induction of anesthesia may be more rapid because the volume of the non-rebreathing circuit is less, no equilibration with the carbon dioxide canister is required, and anesthetic gases are delivered immediately at the airway. Additionally, because the volume of the non-rebreathing circuit is small in comparison to the circle system, the compression and compliance volume will be significantly less.[130] This improves the ability to observe respiratory effort, as reflected by movement of the anesthesia bag, as well as the ability to estimate pulmonary compliance. Thus, the actual delivered ventilation, when used in conjunction with a ventilator, may be greater with a Mapleson D system than with a circle system if no compensatory adjustment in tidal volume is made (Fig. 82-21). The Mapleson D circuit will be more sensitive to changes in fresh gas flow (i.e., an increase or decrease in minute ventilation) or to the addition of a humidifier (decreased minute ventilation because of added compression volume) during mechanical ventilation. The most recent generation of ventilators are less susceptible to these types of issues because they automatically compensate for changes in fresh gas flow.

A pediatric circle system can be used safely in neonates as long as one understands the clinical implications: large compression volume losses, longer time to equilibrate, and perhaps a decreased ability to determine changes in compliance. I have used pediatric circle systems exclusively for the past 14 years, and as long as pressure-limited ventilation with the same peak inflation pressure is used, the same tidal volume is delivered as with a non-rebreathing system.[131-133]

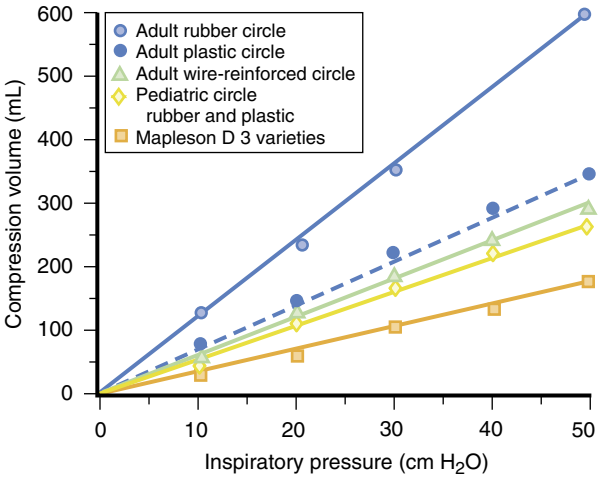

Figure 82-21 Eight types of anesthesia circuits were compared regarding ventilatory losses (circuit efficiency) as a result of compression of anesthetic gases (compression volume) and stretching of the circuit (compliance volume). Compression volume and compliance volume losses vary by as much as a factor of 5, depending on the volume of the circuit and the material from which it is constructed. Low-volume, low-compliance circuits (Mapleson D systems) are the most efficient and give the anesthesiologist the greatest amount of tactile feedback on tidal volume and lung compliance in small children. Although large-volume, high-compliance circuits (adult circle systems) can be used in small children, it is very difficult to estimate tidal volume and lung compliance because circuit-related losses in compression and compliance volume are so large. *(From Coté CJ, Petkau AJ, Ryan JF, Welch JP: Wasted ventilation measured in vitro with eight anesthetic circuits with and without inline humidification. Anesthesiology 59:442-446, 1983, with permission.)*



Figure 82-20 Adaptor that allows the administration of albuterol through an endotracheal tube and timing of that dose with inspirations to provide maximum delivery; note that use of a long intravenous catheter that extends beyond the tip of an endotracheal tube may further improve drug delivery. *(From Coté CJ, Lerman J, Todres ID [eds]: A Practice of Anesthesia for Infants and Children, 4th ed. Philadelphia, WB Saunders, 2008.)*

Considerations for Neonatal Anesthesia

The neonate has unique requirements for equipment, intravenous access, fluid and drug therapy, anesthetic dosage, and environmental control. The many possible neonatal procedures are too numerous to describe in this limited space. However, the basic anesthetic management is the same for all neonates. An understanding of the basic differences in physiology, pharmacologic and pharmacodynamic responses, and the underlying pathology of the surgical problem is essential for the development of a safe anesthesia plan. Most of the complications that arise are attributable to a lack of understanding of these special considerations before induction of anesthesia. Care of neonates is fraught with danger, sudden changes, unexpected responses, and unknown congenital problems. If anesthesiologists are to deliver optimum pediatric anesthesia care, they must always be prepared for the unexpected, have the proper size and variety of equipment available, and obtain the highest level of support, both in the operating room and in the ICU. If the anesthesiologist only occasionally cares for infants, the likelihood of a problem increases dramatically.

Children younger than 1 year have a higher incidence of complications than older children.[20,126-129,134,135] These complications relate to oxygenation, ventilation, airway management, and response to anesthetic agents and medications; they also occur more frequently in ASA physical status 3 and 4 children. Neonates—particularly preterm infants—function on a marginal basis, so any type of stress is usually poorly tolerated. This vulnerability may relate to the technical difficulty of taking care of small children, the immaturity of their organ systems (especially the cardiovascular, pulmonary, renal, hepatic, and nervous systems), their high metabolic rate, the large ratio of body surface area to weight, and the ease of miscalculating a drug dose.

When caring for infants and neonates, special attention must be paid to all aspects of anesthesia and surgical management. The anesthesiologist must devote particular care to the calculation of drug dosage and dilution of drugs. Prevention of paradoxical air emboli requires that all air be vented from intravenous devices and syringes before use (aspirate each intravenous injection port to remove air trapped at these junctions and eject some drug before intravenous administration to clear air from the dead space of the needle). A volume of air that is clinically unimportant in an adult may prove catastrophic in an infant. Warming of skin preparation solutions and irrigation fluids before application minimizes heat loss. Intravenous fluids should be administered with volume-limiting devices; infusion pumps are particularly helpful in preventing overadministration of intravenous fluid. The composition and infusion rate of flush solutions should be noted and calculated into maintenance fluid therapy.

Every effort must be made to maintain the infant's temperature so that thermal stress is minimized. The operating room environment should be warmed so that the whole operating room constitutes a giant incubator. Heated air mattress devices are particularly useful for maintaining temperature.

Monitoring of expired concentrations of carbon dioxide can be less accurate in small infants but is still very useful for diagnosing changes over time and issues such as bronchospasm, a kinked endotracheal tube, or endobronchial intubation. Pulse oximetry is useful not only for the usual data that it provides but also for preventing extreme hyperoxia. Maintaining oxygen saturation at 93% to 95% keeps preterm infants on the steep side of the oxygen-hemoglobin dissociation curve. This consideration may be important to infants still susceptible to retinopathy of prematurity (ROP), that is, those younger than 44 weeks PCA, although a multicenter trial of tight control of supplemental oxygen failed to show any change in risk for the development of ROP.[136] However, because these infants have the highest oxygen consumption, oxygen saturation in the 93% to 95% range can change to severe hypoxemia within seconds. When managing such a delicate balance and in view of the slight inaccuracies of these monitors, the anesthesiologist must be extremely vigilant and prepared to respond rapidly to changes in oxygen saturation. Keeping arterial carbon dioxide values within the normal range (35 to 45 mm Hg) may also be important in preventing ROP. Many other factors well beyond the control of the anesthesiologist contribute to the development of this condition.

Apoptosis

One very important concern that must be mentioned is the fear of apoptosis caused by medications used to provide sedation, analgesia, and anesthesia for infants and toddlers (~2- to 3-year-olds), a population still undergoing rapid brain growth. Anesthesiologists must be up to date on this issue because with the current widespread use of the Internet, more and more parents are asking "*Is it safe for my baby to have anesthesia?*" and specifically mention apoptosis! All of the potent inhaled agents—nitrous oxide, ketamine, propofol, etomidate, barbiturates, benzodiazepines, chloral hydrate, ethanol—and others have been associated with an increased rate of apoptosis in laboratory animals.[137-140] The majority of animal studies have examined drugs doses far outside the clinical range. Others have not controlled for blood pressure, ventilation, or oxygenation. To further confound the issue, the period of rapid brain growth is different in each animal species, and the time of exposure in some is longer than what would occur in clinical practice. To date, there are limited data in primates (monkeys) and none that have convincingly demonstrated that these observations are transferable to humans. In fact, the preliminary data that have focused on ketamine "suggest that there might be a margin of safety for the use of ketamine in vivo and that there may be safety margins for other anesthetics currently used in the clinical setting."[138] Given the fact that thousands of infants and toddlers undergo general anesthesia for diagnostic and therapeutic procedures each year, certainly if this were a major issue for humans, by now we would have evidence that our most vulnerable children, neonates, infants, and toddlers, would demonstrate adverse developmental outcomes consistent with the animal models. In addition, many preterm and term infants receive these same medications for days and often weeks in the neonatal ICU without obvious adverse outcomes.[139]

At present, I believe the issue of drug-induced apoptosis to be a very valid concern and an area of research that must be vigorously pursued. However, what is quite unclear is at what age or what developmental level this is no longer a concern. Is it just preterm infants, full-term infants, toddlers, teenagers, or even adults? Is the plasticity of the human brain able to overcome a (potential) short-term insult? If we remove this list of drugs from our armamentarium, how are we to provide adequate amnesia,

analgesia, and anxiolysis? Until more convincing data are available, it is prudent to continue our current level of care with the drugs now available to us.[141,142] It would not make sense and it would be irresponsible to change current practice without adequate science to support such a drastic change in child care.

The Stress Response

There is little doubt that neonates, even extremely preterm infants, are capable of feeling pain and responding to painful stimuli; however, what actually constitutes a state of "anesthesia" has yet to be proved. No child should be denied analgesia or anesthesia because of size or age. Clearly, the cardiovascular system of a preterm infant rarely tolerates the cardiovascular depressant effects of potent inhaled anesthetics. However, the synthetic narcotics (e.g., fentanyl, sufentanil, alfentanil, remifentanil) are usually well tolerated by even critically ill infants. These potent narcotics must be carefully titrated to response, and the anesthesiologist must always be wary of narcotic-induced bradycardia and its consequences on cardiac output. Low concentrations of potent inhaled anesthetics can be used with narcotics to provide a means of controlling hemodynamic responses without significantly depressing the myocardium. The relative merits of one anesthetic technique over another are not clear, and the few studies examining this issue are poorly controlled. Narcotics and inhaled anesthetics suppress the hormonal responses to pain. The important result of the provocative studies undertaken to clarify this issue is that they have heightened everyone's awareness of the need to provide adequate anesthesia and analgesia to neonates. As described earlier, it is not so much the drugs but how they are used that make the difference in terms of outcomes. In the hands of skilled pediatric anesthesiologists, no differences were found in adverse events or recovery from anesthesia for pyloromyotomy managed with halothane or remifentanil.[80]

Specific Neonatal and Surgical Procedures

Meningomyelocele

Meningomyelocele (hernial protrusion of a part of the meninges and spinal cord through a defect in the vertebral column) is a relatively common neonatal abnormality. The following should be considered in addition to the usual concerns for the management of neonates: (1) special positioning for endotracheal intubation (defect placed on a "doughnut" and towels under the head), (2) the possibility of underestimating fluid and blood loss from the defect, (3) the high association of this condition with hydrocephalus, (4) the possibility of cranial nerve palsy resulting in inspiratory stridor, and (5) the potential for brainstem herniation. The anesthesiologist must establish adequate intravenous access and invasive monitoring if appropriate; replace all fluid deficits, including loss from the defect (usually with normal saline); and ensure that crossmatched blood is available. Latex allergy precautions should be used with these children for their first and all subsequent anesthetics.

Omphalocele and Gastroschisis

Omphalocele and gastroschisis are major defects in closure of the abdominal wall that result in exposure of viscera that are either covered (omphalocele) or not covered (gastroschisis) by peritoneum (Fig. 82-22A and B; Table 82-10). The major problems with these defects include (1) severe dehydration and massive fluid loss, both from the exposed visceral surfaces (gastroschisis—chemical peritonitis) and from third-space losses caused by partial bowel obstruction; (2) heat loss; (3) the difficulty of surgical closure; and (4) the high association of this condition with prematurity and other congenital defects, including cardiac abnormalities (with omphalocele, ~20%). These children should not be rushed to the operating room without an echocardiogram before anesthesia.

Infants with omphalocele or gastroschisis must be cared for expeditiously to reduce the potential for infection and compromise of bowel function and to minimize the loss of fluid and heat; optimizing fluid and electrolyte balance before surgery is

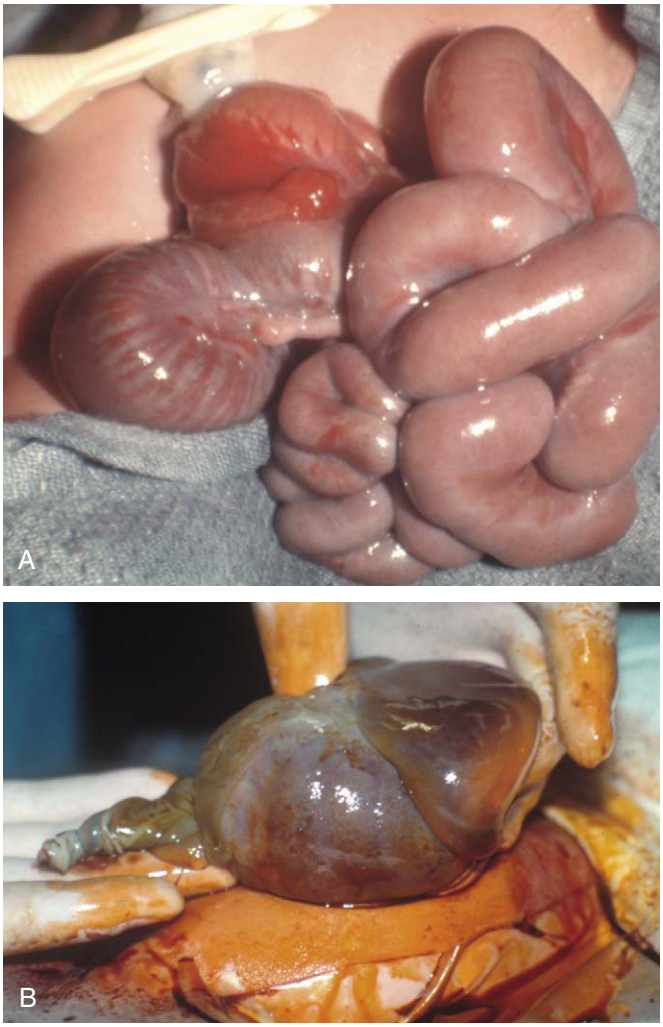

Figure 82-22 **A,** Gastroschisis malformation. Note that the viscera have herniated outside the peritoneum. **B,** Omphalocele malformation. Note that the viscera are still covered by peritoneum.

Table 82-10 Comparison of Gastroschisis and Omphalocele Malformations

	Gastroschisis	Omphalocele
Pathophysiology	Occlusion of the omphalomesenteric artery	Failure of gut migration from the yolk sac into the abdomen
Incidence	~1 in 15,000 births	~1 in 6000 births
Incidence of associated anomalies	~10%-15%	~40%-60%
Location of defect	Periumbilical	Within the umbilical cord
Problems associated with the defect	Inflammation of exposed gut Edema Dilated and foreshortened gut (chemical peritonitis)	Congenital heart disease (~20%) Exstrophy of the bladder Beckwith-Wiedemann syndrome (macroglossia, gigantism, hypoglycemia, hyperviscosity)

From Coté CJ, Lerman J, Todres ID (eds): A Practice of Anesthesia for Infants and Children, 4th ed. Philadelphia, WB Saunders, 2008.

recommended. Adequate intravenous access must be ensured, and occasionally invasive monitoring is necessary if an associated cardiac defect is present. The liberal use of muscle relaxants provides optimal surgical conditions for closure of the defect; hypotension secondary to tension on a major organ (liver) or caval compression is common. If the surgeon is unable to close the defect in one procedure, a staged procedure is planned, usually in the neonatal ICU. In either situation, postoperative ventilation will be necessary until the abdominal wall has had time to stretch to accommodate the viscera. Intravenous alimentation may also play a vital role in the rapid recovery of these children.

A small percentage of children with omphalocele will also have Beckwith-Wiedemann syndrome, a condition characterized by profound hypoglycemia, hyperviscosity syndrome, and associated visceromegaly. It should be noted that increased abdominal pressure after a tight closure may compromise hepatic function and markedly alter drug metabolism. Staged closure with a premade spring-loaded Silastic silo is being used with increasing frequency, thus minimizing repeat trips to the operating room and the need for postreduction ventilation.

Tracheoesophageal Fistula Anomaly

A tracheoesophageal fistula anomaly can have five or more configurations, most of which are manifested as an inability to swallow because of esophageal atresia (ending of the esophagus in a blind pouch). The characteristic diagnostic test is an inability to pass a suction catheter into the stomach. Neonates may have aspiration pneumonitis from a distal fistula connecting the stomach to the trachea through the esophagus or from a proximal connection of the esophagus with the trachea. Additionally, this anomaly may be a part of a larger constellation of anomalies known as the VATER association (V, vertebral; A, anal; TE, tracheoesophageal; R, renal) or the VACTERL association (VATER + C, cardiac; and L, limb). Any child with a tracheoesophageal fistula or esophageal atresia should be suspected of having the other anomalies described. An echocardiogram to examine for a right-sided aortic arch and the presence of congenital heart disease should be performed before anesthesia.[143]

The major anesthetic issues include (1) evaluation for aspiration pneumonia; (2) overdistention of the stomach from entry of air directly into the stomach through the fistula; (3) inability to ventilate the child because of the large size of the fistula; (4) problems associated with other anomalies, particularly a patent ductus arteriosus (shunting) and other forms of congenital heart disease; and (5) the need for postoperative intensive care.

For management of anesthesia the infant's feedings are withheld, a catheter is placed in the esophagus to drain saliva, and the infant is placed prone in a head-up position. If the infant has pneumonia, treatment should be initiated; surgery may be postponed until the pneumonitis improves or clears. The infant may be a candidate for gastrostomy to provide a means of nutrition during recovery from pneumonitis. Anesthesia evaluation centers on the pulmonary and cardiovascular systems. Generally, an "awake sedated" intubation is performed. I usually administer 0.5 to 1 μg/kg of fentanyl and 25 to 50 μg/kg of midazolam and topicalize the tongue, larynx, and vocal cords with no more than 5 mg/kg of lidocaine (1.0%). The endotracheal tube is intentionally passed into the right main bronchus and then slowly withdrawn until breath sounds are heard on the left. Often this technique ensures that the tip of the endotracheal tube is placed beyond the origin of the fistula, thus avoiding massive distention of the stomach. Care must be taken to avoid rupturing the stomach, so spontaneous and gently assisted ventilation may be appropriate until the fistula is ligated or a gastrostomy is completed. A change in the distance of insertion of the endotracheal tube of as little as 1 to 2 mm may determine whether the anesthesiologist is ventilating both lungs, one lung, or the fistula. Therefore, because a change in oxygen saturation may be the first indication that all is not well, the pulse oximeter is one of the most useful monitors in managing these children. A preductal and postductal location (two pulse oximeters) will diagnose intracardiac shunting. Taping the stethoscope to the left side of the chest in the axilla also decreases the possibility of unrecognized endobronchial intubation. Some surgeons prefer that the infant remain intubated postoperatively, whereas others prefer an attempt at extubation; it should be noted that approximately 30% will require reintubation for clearing of secretions.

Postoperative pain may be managed with a caudal catheter threaded up to the thoracic level and either intermittent bupivacaine (1 to 2 mL of 0.125% with epinephrine 1:200,000) administered every 6 to 8 hours or a continuous infusion of chloroprocaine (1.5%) with fentanyl (0.4 μg/mL) infused at 0.3 to 0.8 mL/kg/hr. Note that such management may be undertaken only with the full support of a pediatric pain service.

Diaphragmatic Hernia

A diaphragmatic hernia is usually manifested on the first day of life by respiratory distress and a scaphoid abdomen. The abnormality consists of herniation of the abdominal viscera through a defect in the diaphragm, most commonly the foramen of

Bochdalek on the left side. Almost all of the abdominal viscera, including the liver and spleen, may be above the diaphragm. The gestational age at which herniation occurs may determine the degree of lung hypoplasia.

Anesthesia concerns include (1) hypoxemia and hypotension caused by overdistention of the stomach and herniation across the midline, (2) hypoxemia due to primary pulmonary hypoplasia, (3) hypoxemia due to pulmonary hypertension, (4) pneumothorax of the contralateral lung during attempts at high-pressure ventilation, and (5) systemic hypotension caused by kinking of major blood vessels, particularly those of the liver. In general, the anesthesiologist's ability to control arterial carbon dioxide tension ($Paco_2$) reflects the severity of the lung pathology and therefore survival. An inability to reduce $Paco_2$ is associated with a poor prognosis. Extracorporeal membrane oxygenation (ECMO) and the use of nitric oxide have reduced the mortality associated with this condition, and the urgency for surgical intervention has diminished and given way to a desire to stabilize the infant and minimize stress. It is common practice to postpone surgery on infants with a diaphragmatic hernia until their condition has been stabilized for several days. In some centers the closure is accomplished at the bedside in the neonatal ICU.

Anesthestic management of children with a diaphragmatic hernia includes the following: (1) Awake intubation without bag-and-mask ventilation prevents overdistention of the stomach and herniation across the midline (now uncommon because they generally do not come to the operating room for several days); (2) insertion of an arterial line for heartbeat-to-heartbeat blood pressure monitoring and close observation of the surgical field are most helpful in diagnosing impairment of venous return or cardiac output; (3) blunting of the stress response is accomplished by providing analgesia with narcotics (usually high-dose fentanyl, 25 μg/kg or more) and by controlling respirations with a muscle relaxant (usually pancuronium); (4) careful control of ventilation and oxygenation prevents sudden increases in pulmonary artery pressure ($Paco_2$ is kept below 40 mm Hg and Pao_2 above 100 mm Hg); pulse oximetry is helpful in diagnosing subclinical episodes of hypoxemia; (5) hypothermia is avoided to decrease the oxygen consumption needed for thermogenesis; (6) anesthetic agents that might depress the myocardium are avoided until the chest is decompressed; (7) to prevent bowel distention, nitrous oxide is not given; (8) awareness for the development of barotrauma-induced pneumothorax on the ipsilateral or contralateral side should be heightened; (9) adequate intravenous access for maintenance of a constant circulating blood volume should be ensured; and (10) postoperative intensive care is necessary.

In most centers the approach to these children has changed to supportive care initially with permissive hypercapnia, ECMO, high-frequency ventilation, and inhaled nitric oxide.[144,145] The infant is no longer rushed to the operating room soon after birth, and this approach appears to have reduced mortality.[145,146] Review of long-term outcomes seems to indicate that all of these measures have not significantly improved mortality.[147]

Pyloric Stenosis

Pyloric stenosis is normally manifested in the first 3 to 6 weeks of life. The following are major concerns for the anesthesiologist: (1) a full stomach, occasionally filled with contrast material; (2) metabolic alkalosis with hypochloremia and hypokalemia; and (3) severe dehydration.

This operation is never a surgical emergency. Children should be evaluated carefully, and severe metabolic imbalance should be corrected before surgery. Even if the child arrives with a nasogastric tube in place and although the diagnosis is now most commonly made by ultrasound rather than barium swallow, the stomach should still be suctioned with a wide-bore catheter in the supine and the right and left lateral positions immediately before induction of anesthesia and as much of the stomach contents removed as possible.[148] This suctioning technique will remove 98% of the gastric contents![149] Children with pyloric stenosis can be managed with awake endotracheal intubation followed by low-dose rocuronium (0.3 mg/kg) or rapid-sequence induction of anesthesia with cricoid pressure after atropine (0.02 mg/kg), propofol (3 mg/kg), and succinylcholine (2 mg/kg). Arguments can be made for either type of induction, and selection depends on the skill and familiarity of the anesthesiologist with that technique, but one study in a teaching institution demonstrated fewer attempts and half the time for successful intubation when a muscle relaxant was used.[150] Postoperative analgesia is generally provided by local infiltration of the skin incision with bupivacaine (maximum dose, 1 mL/kg of 0.25% bupivacaine) and acetaminophen (40-mg/kg initial dose followed by 20 mg/kg every 6 hours rectally or 10 to 15 mg/kg by mouth every 4 to 6 hours for a total 24-hour dose of ~100 mg/kg). There have been conflicting reports of apnea events after pyloromyotomy.[151,152] One well-controlled clinical trial described new-onset apnea after halothane anesthesia in 3 of 13 children.[81] Until larger studies are carried out, it may be prudent to observe these children with apnea monitors and pulse oximetry postoperatively.

The Former Preterm Infant

Since the early retrospective reports noting a high incidence of postoperative apnea in former preterm infants (gestational age less than 37 weeks), a number of studies have tried to define the population at risk. Most studies have found that the majority of infants in whom postanesthesia apnea develops are younger than 46 weeks PCA; however, apnea has been reported up to 60 weeks PCA.[153] The conclusions reached by each of these studies were limited by the relatively small number of children. I had the opportunity to obtain and analyze the original data from eight prospective studies. A combined analysis examining risk for apnea included only children undergoing inguinal hernia repair and not receiving special treatment such as caffeine or regional anesthesia.[116] The only two risk factors that stood out across all ages were gestational age and PCA. The incidence of apnea was inversely related to both postconceptual and gestational age. For example, if two infants were now 42 weeks PCA yet one was born at 28 and the other at 36 weeks gestational age, the 28-week gestational age infant would have approximately twice the potential for apnea (Fig. 82-23). In addition, the younger the child at the time of surgery (weeks PCA), the higher the incidence of apnea. The incidence of apnea was higher in institutions that collected data with continuous recording devices than in those that relied on impedance pneumography or nursing observations. Anemia (hematocrit <30%) is an independent risk factor associated with apnea in former preterm infants (see Fig. 82-23). What makes this risk factor unique is the fact that the risk for apnea in anemic

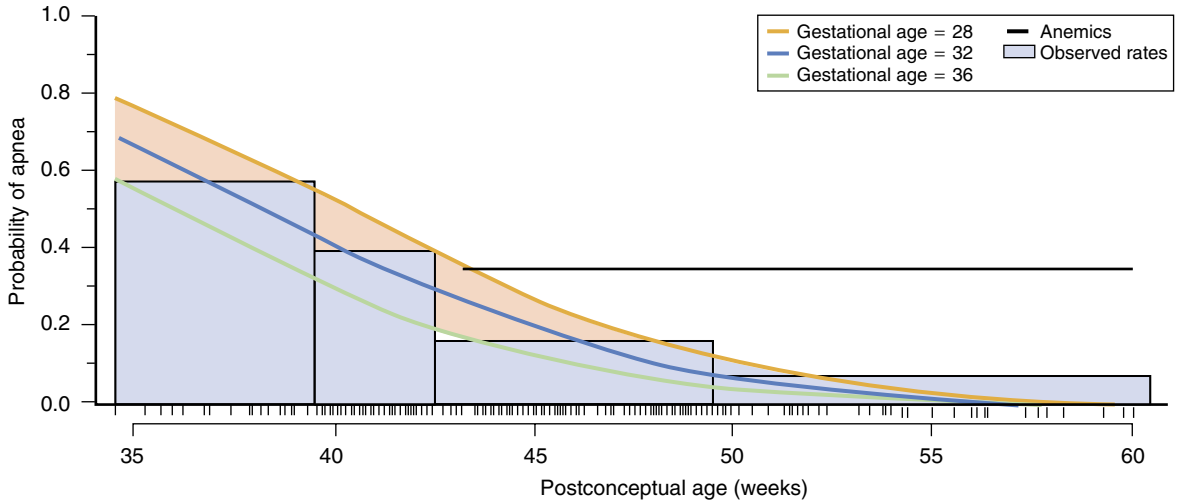

Figure 82-23 Predicted probability of apnea for all children by gestational age and weeks postconceptual age. Children with anemia are shown as the *horizontal hatched line*. *Bottom marks* indicate the number of data points by postconceptual age. The risk for apnea diminishes in infants born at a later gestational age. The *shaded boxes* represent the overall rates of apnea for infants within that gestational age range. The probability of apnea was the same regardless of postconceptual age or gestational age for infants with anemia (*horizontal hatched line*). *(Reproduced with permission from Coté CJ, Zaslavsky A, Downes JJ, et al: Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis. Anesthesiology 82:809-802, 1995.)*

former preterm infants is not altered by postconceptual or gestational age; that is, the risk for apnea would appear to be the same for an anemic 60-week PCA infant as for an anemic 45-week one. Even after eliminating infants with an obvious apnea spell in recovery and infants who were anemic, the risk for apnea does not decrease to less than 1% (with 95% statistical confidence) until a PCA of 56 weeks with a gestational age of 32 weeks or until a PCA of 54 weeks with a gestational age of 35 weeks. In general, it is simplest to just admit all former preterm infants younger than 60 weeks PCA to monitored beds and to be aware that anemic former preterm infants are at particular risk.

Although the risk of apnea may be less with regional anesthesia, apnea may still occur and may even be increased if regional anesthesia is combined with sedation (ketamine, midazolam).[154-161] There are insufficient numbers of well-controlled studies of regional versus general anesthesia to determine whether the risk is significantly reduced. It is also clear that apnea still occurs even with sevoflurane or desflurane anesthesia, so the more modern inhaled agents have not eliminated this concern.[162]

Part of the problem of how to treat these children is the fact that we do not know the clinical importance of brief apnea/bradycardia spells that do not require intervention. Because cerebral blood flow is markedly reduced at heart rates below 80 beats/min, even brief apnea associated with bradycardia may have adverse effects.[163] The dilemma faced by the clinician is how to manage former preterm infants scheduled for outpatient procedures. More prospective studies need to address whether regional techniques are safer than general anesthesia. Pulse oximetry would help define the severity of desaturation and electrocardiographic monitoring would help define episodes of bradycardia, which may reduce cerebral blood flow. It would seem reasonable that the combination of desaturation and bradycardia is of more physiologic importance than simple documentation of pauses in respiration.

If appropriate monitoring facilities are not available postoperatively, a preterm infant who is less than 60 weeks PCA should be referred to an institution that has such facilities. High-dose caffeine (10 mg/kg) has been recommended.[164] This may be an effective therapy, but the half-life of caffeine in older former preterm infants is only 6 hours and the first apnea spells after anesthesia may not be manifested until 12 hours.[116] Therefore, one cannot administer caffeine and then send the infant home and assume that the problem is treated.

To make the issue even more complex, I have observed a full-term infant who became apneic after general anesthesia. This infant had periodic breathing, which is distinctly unusual in a full-term infant.[165] We still do not know with certainty which children are truly anesthetized safely on an outpatient basis and at what postconceptual and gestational age. Because most organ systems are still rapidly developing during the first month of life (44 weeks PCA), it is reasonable to delay elective surgery during the first month of life and consider postoperative admission and apnea monitoring even in full-term infants younger than 1 month. Alternatively, performing the case as the first of the day and then observing for an extended period may permit safe discharge in the late afternoon or early evening.

Children with Repaired Heart Disease

Frequently, anesthesiologists assume that children have normal cardiac function after "correction" of congenital heart defects. Although the circulation may be normal, there is never assurance that cardiac function is normal. Any child who has undergone a ventriculotomy would be expected to have some ventricular dysfunction caused by the incision; there is less potential for dysfunction if the surgical approach was through an atriotomy.[166] Likewise, even relatively benign procedures such as closure of ventricular or atrial septal defects can be associated with the later develop-

ment of dysrhythmias.[166] Some children, particularly those with repaired single-ventricle physiology, have a marked predisposition to sudden death as a result of pathologic arrhythmias; a careful history is particularly important in these children. Should an arrhythmia develop intraoperatively, consultation with the child's cardiologist is essential because this may be the first indication of a serious underlying arrhythmogenic foci. A radiofrequency ablation procedure may be life saving. Cardiac transplant children need particular attention to rule out small vessel coronary artery disease.[167,168]

Children with Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is defined as a "disorder of breathing during sleep characterized by prolonged upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep." Children at particular risk include those with craniofacial abnormalities, neuromuscular disorders, obesity, and adenotonsillar hypertrophy.[169-176] The difficulty that we face is determining which children are at risk because not all children will undergo formal polysomnogram evaluation, which is considered the gold standard.[169] Abnormal sleep oximetry values (clusters of desaturation to <80%) have also been shown to correlate with the severity of OSA.[171,177] Even children undergoing surgery in the afternoon may be at greater risk than those operated on in the morning.[178] The apnea index (AI) and the respiratory disturbance index are measurements of the presence and severity of OSA syndrome. These indices reflect the frequency of occlusive and partially occlusive respiratory events per hour of sleep. OSA syndrome is considered to be present if the AI is 1 or greater (i.e., one or more apnea events per hour of sleep) and can be classified as mild if the AI is between 1 and 5, moderate if the AI is between 5 and 10, and severe if the AI is greater than 10 events per hour of sleep. Of particular concern are children in whom cardiac dysfunction (cor pulmonale) has developed and those in whom postobstructive pulmonary edema could develop. These children may require overnight ventilation in an ICU. In general, risk factors for postoperative complications include (1) age younger than 3 years; (2) abnormal coagulation values; (3) evidence of OSA; (4) systemic disorders that place the child at increased perioperative risk (e.g., cor pulmonale, metabolic diseases); (5) presence of craniofacial or other airway abnormalities; (6) performance of the procedure is for peritonsillar abscess; and (7) living a long distance from an adequate health care facility, adverse weather conditions, or home conditions not consistent with close observation, cooperativeness, and ability to return quickly to the hospital (e.g., substance-abusing parents, teenage mother).[179] The main problems that we face as anesthesiologists are when it is safe to send these children home and what we should do to provide postoperative analgesia. Some day-surgery centers send tonsillectomy children home immediately; others hold the children for at least 4 hours (the interval most likely for bleeding or respiratory compromise to occur). Hospitals tend to admit the children to a 23-hour unit (to avoid the 24-hour "hospital admission"), thus observing the child for an extended time (usually not the full 23 hours) while minimizing expense to the insurance provider. Though inefficient in cost, this provides the best safety net for these children. Analgesia is generally provided with a combination of oral acetaminophen given preoperatively or rectally after induction and low-dose morphine (50 μg/kg). Some anesthesiologists prefer short-acting opioids such as fentanyl to minimize respiratory depression and then supplement the analgesia with an additional longer-acting opioid in the PACU. Ketorolac provides analgesia without adverse respiratory effects, but it is associated with an increased incidence of postoperative bleeding if given before achieving hemostasis.[180] Postoperative nausea and vomiting are generally treated with serotonin 5-HT_3 antagonists, whereas postoperative swelling (plus vomiting) is treated with dexamethasone (0.0625 to 0.15 mg/kg).[181] The most common at-home analgesic is acetaminophen with codeine. One issue that requires further evaluation is the possibility of alteration of opioid receptors (upregulation of μ-receptors) in response to repeated minor hypoxemic events, as well as of response to carbon dioxide.[182-185] These altered responses result in increased sensitivity to the respiratory depressant effect of opioids.[186] It addition to these factors, it has been shown that children with OSA have a structurally narrowed airway because of an increased propensity for upper airway collapsibility.[187] These factors explain in part why children with OSA are at markedly increased risk for postoperative respiratory complications.[170,177,188,189]

Regional Anesthesia and Analgesia

Most regional anesthesia techniques used in adults can be administered safely to pediatric patients so long as strict attention is paid to the dose of local anesthetic, the dose of epinephrine, the route of administration, and the use of proper equipment. Perhaps the greatest advance in pediatric anesthesia has been the development of methods producing postoperative analgesia (also see Chapters 81 and 87). Caudal anesthesia, caudal narcotics, regional blocks, and child-parent-nurse–controlled analgesia have all been accepted by anesthesiologists and children. Recent advances in ultrasound equipment have further improved the accuracy of nerve blocks. Even pediatric patient–controlled epidural analgesia has been used successfully in children as young as 5 years.[190] Each institution and practitioner must decide which method works best given each particular practice setting. Obviously, until dosage guidelines and safety standards for monitoring are well established, some of these techniques must be limited to medical centers familiar with their use in children.[191]

It is my practice to supplement the analgesia of either opioid or regional techniques with 40 mg/kg of acetaminophen rectally at the beginning of the procedure. Several studies have demonstrated that 40 mg/kg of acetaminophen rectally will place a majority of children in the therapeutic range for antipyresis (we do not know the plasma levels associated with analgesia in children) within 60 to 180 minutes, hence the need to insert the suppositories at the beginning of the procedure rather than at the end.[192] It should be noted that suppositories should not be cut open because the drug may not be evenly distributed within the matrix; combinations of suppository doses are the best means of achieving a dose close to 40 mg/kg. Repeat rectal dosing should be approximately 20 mg/kg every 6 hours until transition to oral acetaminophen (total 24-hour limit, ~100 mg/kg either orally or rectally).[192]

Regional nerve blocks and direct local infiltration of surgical wounds with long-acting local anesthetics are simple yet very effective methods of providing pain relief for all children. In most institutions it is now rare for a pediatric patient to awaken from anesthesia without some form of regional block. This practice has been especially helpful in the outpatient population; parents are encouraged to start analgesics when they observe their child becoming irritable but before complete dissipation of the block. This approach usually provides a smooth transition from general anesthesia and a pain-free child. Chapters 51 to 53 discuss regional anesthesia and analgesia in detail, and in Chapter 81 special emphasis is placed on pediatrics.

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83 Anesthesia for Pediatric Cardiac Surgery

Key Points

1. Organ system maturation, from birth through adolescence (e.g., cardiovascular, central nervous system [CNS], pulmonary, renal, hematologic), affects physiologic function and therefore anesthetic and surgical management and outcome.
2. Physiologic understanding of congenital heart disease and consequent anesthetic management are based on the pathophysiologic determinants of four categories of defects: shunts, mixing lesions, stenotic lesions, and regurgitant lesions.
3. The chronic sequelae of congenital heart disease—repaired, palliated, or unrepaired—affect anesthetic management: ventricular failure, residual hemodynamic effects (e.g., valve stenosis), arrhythmias, and pulmonary blood flow changes (e.g., pulmonary artery hypertension).
4. Preoperative assessment of cardiac status (e.g., review of history and physical examination, echocardiography, and catheterization data and consulting with the patient's cardiologist) and planning are the keys to a successful anesthetic outcome.
5. Intraoperative transesophageal echocardiography and CNS monitoring enhance surgical outcome and reduce morbidity.
6. Selecting an induction technique is dependent on the degree of cardiac dysfunction, the cardiac defect, the degree of sedation provided by the premedication, and the presence or absence of an indwelling venous catheter. The maintenance of anesthesia depends on the age and condition of the patient, the nature of the surgical procedure, the duration of cardiopulmonary bypass (CPB), and the need for postoperative ventilation.
7. The physiologic effects of CPB on neonates, infants, and children are significantly different from the effects on adults. During CPB, pediatric patients are exposed to biologic extremes not seen in adults, including deep hypothermia (18°C), hemodilution (threefold to fivefold greater dilution of circulating blood volume), low perfusion pressures (20 to 30 mm Hg), and wide variation in pump flow rates (ranging from 200 mL/kg/min to total circulatory arrest).
8. After the repair of complex congenital heart defects, the anesthesiologist and surgeon may have difficulty separating patients from CPB. Under these circumstances, the underlying cause must be determined, which may be (a) an inadequate surgical result with a residual defect requiring repair, (b) pulmonary artery hypertension, or (c) right or left ventricular dysfunction.
9. The use of modified ultrafiltration (MUF) reverses the deleterious effects of hemodilution and the inflammatory response associated with CPB in children. Perioperative blood loss and blood use are significantly reduced when MUF is used. MUF also improves left ventricular function and systolic blood pressure and increases oxygen delivery. Pulmonary compliance and brain function after CPB are also improved.
10. Neonates, infants, and children undergoing cardiac surgery with CPB have a higher rate of postoperative bleeding than that seen in older patients. This is due to several factors: (a) There is disproportionate exposure to the nonendothelialized extracorporeal circuit, which produces an inflammatory-like response. This inflammatory response to CPB is inversely related to patient age; the younger the patient, the more pronounced the response. (b) The type of surgery performed in neonates and infants usually involves more extensive reconstruction and suture lines, creating more opportunities for surgical bleeding than in adult cardiac patients. (c) Operations are frequently performed using deep hypothermia or circulatory arrest, which may further impair hemostasis. (d) The immature coagulation system in neonates may also contribute to impaired hemostasis. (e) Patients with cyanotic heart disease demonstrate an increased bleeding tendency before and after CPB.
11. The guiding principle in the management of the postoperative patient is an understanding of both

normal and abnormal convalescence after anesthesia and cardiac surgery. The immediate postoperative period, even that of normal convalescence, is one of continuous physiologic change because of the pharmacologic effects of residual anesthetic agents and the ongoing physiologic changes secondary to abrupt alteration in hemodynamic loading conditions, surgical trauma, and extracorporeal circulation.

12. There are additional anesthetic considerations in patients with congenital heart disease who undergo transplantation, closed heart operations without CPB, cardiac interventional procedures, and noncardiac surgery.

Cardiac surgery is an established and effective treatment for children with congenital heart defects. Early successes in surgical treatment have led to a new therapeutic era in the management of congenital heart disease and have fostered the development of the subspecialties pediatric cardiology and cardiac surgery and their collaboration. Through this cooperative effort, tremendous progress in medical diagnosis and surgical treatment has been achieved. In turn, these accomplishments gave rise to the development of pediatric cardiac anesthesiologists, individuals who understand the pathophysiology of congenital heart malformations, the diagnostic and surgical procedures used to treat heart disease, and the principles of pediatric and cardiac anesthesia as well as of intensive care medicine. Pediatric cardiac anesthesia continues to evolve as an exciting and technically demanding subspecialty in which anesthetic management is based on physiologic principles.

Congenital cardiovascular surgery and anesthesia are often performed under unusual physiologic conditions. Rarely in clinical medicine are patients exposed to such biologic extremes as during congenital heart surgery. Commonly, patients are cooled to 18°C, are acutely hemodiluted by more than 50% of their extracellular fluid volume, and undergo periods of total circulatory arrest lasting up to 1 hour. Management of patients under these physiologic extremes is a vital function of the pediatric cardiovascular anesthesiologist. As with other areas of medicine, the application and management of technology preceded a comprehensive understanding of its physiologic effects.

Clearly, the perioperative management of these complex cases requires a group of physicians (surgeon, anesthesiologist, cardiologist, critical care specialist), nurses, and perfusionists to work as a team. This team orientation is essential to the achievement of an optimal outcome. Although the quality of the surgical repair, the effects of cardiopulmonary bypass (CPB), and postoperative care are the major determinants of outcome, meticulous anesthetic management is also imperative. Ideally, despite the complexity of the cases and the marked physiologic changes attributed to CPB and the surgical procedures, anesthetic care should never contribute substantially to morbidity or mortality.[1] The challenge is to understand the principles underlying the management of patients with congenital heart disease and to apply them to clinical anesthesia. We assume that the reader already understands the fundamentals of adult cardiac (see Chapter 60) and general pediatric anesthesia (see Chapter 82).

Unique Features of Pediatric Cardiac Anesthesia

Pediatric cardiovascular management is unique. Important differences from adult cardiac surgery do exist (Table 83-1). These differences are attributable to normal organ system maturation in the neonate and young infant, differing pathophysiologic conditions in congenital heart disease, the diversity of surgical repairs, and the use of specialized CPB techniques such as deep hypothermia and total circulatory arrest.

Table 83-1 Unique Characteristics of Pediatric Cardiac Anesthesia

Patient
Normal organ system development and maturational changes of infancy
Cardiovascular: blood flow patterns of circulation at birth, myocardial compliance, systemic and pulmonary vasculature, and β-adrenergic receptors
Pulmonary: respiratory quotient, closing capacity, chest compliance
Central nervous system: brain growth, cerebral blood flow, autonomic regulation
Renal: glomerular filtration rate, creatinine clearance
Hepatic: liver blood flow, microsomal enzyme activity
Disease/growth interrelationship
Effects of systemic disease alter somatic and organ growth
Compensatory ability of developing organs to recover from injury
Immunologic immaturity of the infant
Obligatory miniaturization (i.e., small patient size and body surface area)
Congenital Heart Disease
Diverse anatomic defects and physiologic changes
Altered ventricular remodeling owing to myocardial hypertrophy and ischemia
Chronic sequelae of congenital cardiac disease
Surgical Procedures
Diversity of operations
Frequent intracardiac and right ventricular procedures
Use of deep hypothermia and circulatory arrest during repair
Trend toward repair in early infancy
Evolution of surgical techniques to avoid residua and sequelae
Trend toward wider application of certain operations

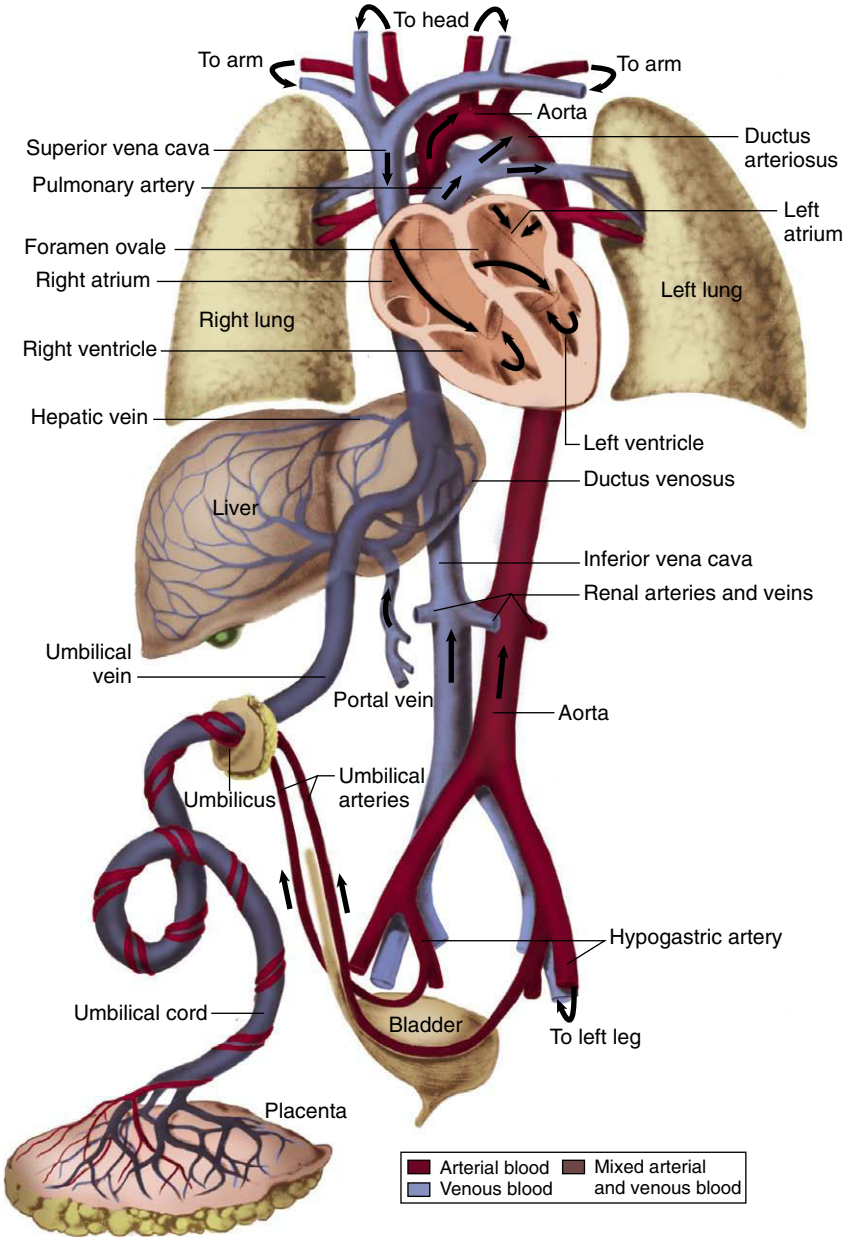

Figure 83-1 Course of the fetal circulation in late gestation. Note the selective blood flow patterns across the foramen ovale and the ductus arteriosus.

Physiologic Considerations and Maturational Features of the Pediatric Patient

The cardiovascular system changes markedly at birth because of a dramatic alteration in blood flow patterns (Fig. 83-1). During fetal life, blood flow returning to the right atrium bypasses the unventilated fluid-filled lungs. Blood is then preferentially shunted across the patent foramen ovale into the left atrium or passes from the right ventricle (RV) across the patent ductus arteriosus (PDA) to the systemic circulation. At birth, physiologic closure of the PDA and of the foramen ovale brings about the normal adult circulatory pattern. The presence of certain congenital heart defects or pulmonary disease can disrupt this normal adaptive process, creating a transitional circulation in which right-to-left shunting persists across the foramen ovale or the PDA. Under such circumstances, the continued presence of a transitional circulation can lead to severe hypoxemia, acidosis, and hemodynamic instability, which are poorly tolerated in the neonate. In contrast, when initially treating some forms of congenital heart disease, the prolongation of this transitional circulation is actually beneficial, promoting systemic or pulmonary blood flow (PBF) and postnatal viability. An example of the latter is pulmonary atresia, in which PBF is supplied via the PDA. In the absence of collateral vessels, closure of the PDA eliminates the principal source of PBF, resulting in hypoxemia and death. Ductal patency can be maintained with the administration of prostaglandin E_1. Importantly, the transitional circulation can be manipulated by pharmacologic ventilatory strategies, thereby promoting hemodynamic stability in the young patient.

Another unique feature of the normal neonatal and infant cardiovascular system is the reduced myocardial reserve compared with that in the healthy adult. The newborn left ventricular

function is restricted by a reduced number of α-adrenergic receptors, high resting levels of circulating catecholamines, limited recruitable stroke work, an immature calcium transport system, and decreased ventricular compliance.[2] This limits contractile reserve and results in a left ventricle (LV) with a high level of resting tone. Although the resting performance of the neonatal myocardium may be greater than in adults and older children, there is a greater sensitivity to β-blockade and only modest increases in cardiac performance after administration of the β-agonist drugs dobutamine and isoproterenol.[3]

On the ultrastructural level, a variety of cellular synthetic functions are occurring in immature myofibrils that dominate the newborn heart. Large nuclei, mitochondria, and surface membranes predominate within the myofibrils. In neonates, there is a 50% reduction in the number of myofibrils and the myofibrils are arranged in a nonlinear, disordered array. As a direct result, the contractile mass of the heart is effectively reduced, resulting in a ventricle with low compliance.[4] Preload augmentation is effective at low filling pressures (1 to 7 mm Hg). However, when left-sided filling pressures exceed 7 to 10 mm Hg, further increases in left ventricular stroke volume are minimal.[2] As a consequence, neonates are more dependent on heart rate and, to a lesser extent, on preload, to maintain cardiac output at filling pressures of 7 to 10 mm Hg or greater.[5]

In addition to a reduced contractile mass, the calcium transport system in the neonatal myocardium is underdeveloped. The transverse tubular system is absent, and the sarcoplasmic reticulum, which has to store and release calcium, is small and inefficient. The neonatal heart is therefore more dependent on extracellular calcium levels than the adult myocardium.[6-9] Because intracellular calcium concentrations play a central role in myocardial contractility, normal or even elevated plasma levels of ionized calcium may be necessary to augment or maintain an effective stroke volume.[10] This is in contrast to adult cardiac patients in whom calcium use during cardiac surgery has fallen into some disfavor, owing to direct concerns over myocardial ischemia and reperfusion injury.

Another unique feature relates to the pulmonary circulation. The pulmonary circulation undergoes significant changes during the first months of life. These changes are largely characterized by regression of the hypertrophied medial smooth muscular layer in the pulmonary arteries that exists in utero, resulting in a concomitant drop in pulmonary vascular resistance (PVR). In the immediate newborn period, the large decrease in PVR is due to lung expansion and the vasodilatory effects of a higher Pao_2 than existed in utero. Further decline in PVR throughout the next 2 months of life is attributable to regression of the smooth muscle layer in the pulmonary arterioles. A corresponding decrease in pulmonary artery pressure occurs as PVR declines. Acute physiologic stress in the newborn period, such as hypoxemia or acidosis, can increase pulmonary artery pressure and thus PVR. If the resulting right ventricular hypertension causes reduced right ventricular compliance, right-to-left shunting can occur at the foramen ovale. Once PVR exceeds systemic vascular resistance (SVR), right-to-left shunting develops at the PDA. Either phenomenon will worsen the hypoxemia and eventually limit tissue oxygen delivery to the point of lactic acidosis. In contrast, left-to-right shunts, such as with a ventricular septal defect (VSD), produce intimal changes in the pulmonary vasculature and delay regression of medial muscle hypertrophy. This results in persistent elevation of PVR.

Size differences between adult and pediatric cardiac patients require different anesthetic techniques and miniaturization. Anatomically, pediatric patients have small upper and lower airways, small veins and arteries, and a decreased body surface area, as compared with adult patients. There are several anesthetic implications related to patient size. Some centers believe that the placement of arterial catheters by cutdown in neonates and infants represents the most expedient approach, particularly when optimal sites are limited. Pulmonary artery catheters are used infrequently, both because of the technical difficulties in positioning the tip in the pulmonary artery and because of the fundamental fact that pulmonary flow bears no obligatory relationship to systemic output in children with either intra- or extracardiac communications. Transthoracic catheters for pressure monitoring and delivery of vasoactive substances are commonly placed from the surgical field instead of percutaneous approach via the neck. Adequacy of the repair and function can be assessed by transesophageal echocardiography with Doppler color flow imaging with miniaturized probes.[11,12] CPB serves as another example of the influence of patient size on management. The ratio of pump priming volume to patient blood volume is considerably higher in small children than in adults, resulting in a greater degree of hemodilution. Several studies have demonstrated a heightened inflammatory response to CPB in children compared with adults.[13] This effect is related to the disproportionate exposure to the nonendothelialized surfaces of the pump circuit per body surface area. Greater damage to the formed blood elements and plasma proteins is incurred, resulting in activation of mediators of inflammation.

In pediatric patients with congenital heart disease, the cardiovascular system often represents the sole cause of the medical problem. This is in contrast with the multiplicity of diagnoses and organ system involvement frequently found in adults with acquired cardiovascular disease. Moreover, there is a special disease/growth interrelationship unique to growing infants and children that does not exist in adults. This special interrelationship permits developing organs to compensate for and modify existing disease processes. Reparative and recuperative processes in children are greater as a result of this compensatory ability of developing organ systems. Adult cardiac patients unfortunately do not exhibit the same recuperative ability. Although children adapt well to cardiovascular pathology, there are some negative aspects to long-standing heart disease. Congenital heart disease has detrimental effects on somatic growth as well as on the growth and development of the brain, myocardium, and lung.

Other unique considerations are issues surrounding the premature infant (see Chapter 84). Premature infants are classified as low birth weight infants (31-34 weeks, 1-1.5 kg), very low birth weight infants (26-30 weeks, 600 g–1 kg) and extremely low birth weight infants (<26 weeks, 400-600 g). This population of infants manifests unique anesthetic challenges. Cardiorespiratory failure is common and multifactorial. The small airways are prone to obstruction, which results in increased airway resistance and work of breathing with easy fatigability. Diseases of the upper airway such as subglottic stenosis, tracheomalacia, and tracheal stenosis are poorly tolerated, and the use of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) is often necessary to stent open the airway. Lung compliance is reduced because of a deficiency of surfactant, resulting in intrapulmonary shunt and ventilation-perfusion mismatch. Mechanical ventilation prevents alveolar collapse, maintains

patency of the airway, and maintains lung volume, preventing hypoxia. Premature lungs are susceptible to barotrauma and oxidant injury. Ventilation should utilize measures to reduce peak inspiratory pressures and barotrauma, and the inspired oxygen concentration should be reduced to avoid generation of free radicals. Premature infants are also prone to perioperative periods of apneas. Such apneas might be central in origin or obstructive, both of which can be aggravated by anesthetic agents. Apnea can be precipitated by abrupt changes in oxygenation, pulmonary mechanics, brain hemorrhage, and hypothermia. Sustained apnea can result in desaturation and usually begins after emergence from anesthesia and persists for up to 48 hours. Continuous apnea and saturation monitoring with correction of anemia (hematocrit > 30) and intravenous administration of caffeine are therapeutic options. The incidence of postoperative apnea is related to postconceptional and gestational age, the presence of anemia, and the type of surgical procedure. The premature heart is a poorly contractile organ, sensitive to changes in intracellular calcium, with poor diastolic function. Cardiac output is dependent on heart rate, with marginal reserve. The premature infant also has a relatively low absolute blood volume and tolerates blood loss poorly. Autoregulation is not well developed and blood loss compromises cerebral and coronary flow prior to other manifestations of hypovolemia. It is also imperative to avoid fluid overload in these patients. Patency of the ductus arteriosus results in pulmonary overcirculation with heart failure and a large left-to-right shunt. If uncorrected, this would result in pulmonary hypertension secondary to the development of pulmonary vascular occlusive disease. Thermoregulation by nonshivering thermogenesis is also poor owing to inadequate stores of brown fat in prematurity. It is critical to maintain normothermia by increasing the operating room temperature, using incubators for transport, warming and humidification of respiratory gases, and warming all intravenous fluids. Glycemic control is poor with a tendency to hypoglycemia and hyperglycemia. It is important to monitor and maintain euglycemia. Typically, these infants receive higher concentrations of parenteral glucose solutions, which need to be continued in the perioperative period. Premature infants are also prone to retinopathy of prematurity with high inspired oxygen concentrations and intraventricular hemorrhage. Every attempt should be made to avoid hemodynamic perturbances and fluctuation in oxygen saturations. In general, immaturity of organ systems results in both increased drug effect and duration of action, warranting careful titration of drugs.

Prematurity is associated with a twofold increase in cardiovascular malformations compared with infants born at term.[14] One in 6 infants with congenital heart disease not including those with PDA or ASD are born prematurely. Some malformations such as tetralogy of Fallot, pulmonary stenosis, pulmonary atresia with ventricular septal defect, complete atrioventricular septal defect, large ventricular septal defects in isolation or associated with coarctation, and aortic stenosis are more prevalent in this population.[15] There is a significant increase in the likelihood of being small for gestational age among infants with tetralogy of Fallot, complete atrioventricular septal defect, hypoplastic left heart, pulmonary stenosis, or large ventricular septal defect.[16]

Cardiac catheterization, intervention, and complete surgical repair in the very-low-birth-weight newborn (<1.5 kg) can be successfully undertaken with low risk, although longer-term follow-up remains necessary to determine growth and development patterns. However, because of the complexity of premature organ systems and superimposed cardiorespiratory pathophysiology, morbidity and mortality are increased.[17-19] Surgical adaptations have been described that enable the use of CPB in low-birth-weight infants. However, low birth weight remains a significant risk for mortality in neonates with complex single ventricle disease undergoing surgical palliation.[20,21] Interventional catheterization is associated with higher risk of complications, especially related to problems with vascular access, arrhythmias, and respiratory compromise.[18] Premature infants are electively intubated and ventilated for both catheterization and surgical procedures. Adequate intravenous access and invasive monitoring can be challenging but are necessary in most cases. Maintenance of euglycemia and normothermia and attention to fluid and electrolyte balance are important. Oxygen delivery should be optimized by maintaining age-appropriate blood pressures, adequate intravascular volume, and hematocrit. Any acidosis must be sought and aggressively corrected. Generally, such infants should recover in a specialized pediatric cardiac intensive care unit.

Congenital Heart Disease

The marked array of anatomic and physiologic conditions seen with congenital heart disease distinguish these processes from acquired adult cardiac disease. The spectrum of intracardiac shunts, valve pathology (stenoses, regurgitation, or atresia), and disrupted great artery connections and the absence of one or more chambers of the heart preclude a uniform anesthetic approach to patients with congenital heart disease. Moreover, there are myocardial changes resulting from the hemodynamic impact and increased cardiac work incurred by these defects. Functionally, these myocardial changes place the ventricles at great risk for the development of intraoperative ischemia and failure. Therefore, an understanding of the isolated defect, associated myocardial changes, and hemodynamic consequences is fundamental to planning an appropriate anesthetic regimen.[4] Too often, because of the complexity and diversity of the defects, the anesthesiologist, cardiologist, and surgeon are focused on the specific anatomic considerations and the physiologic implications are overlooked. Distilling congenital heart disease into a finite number of physiologic categories enables the anesthesiologist to construct a strategy that employs the qualitatively predictable impact of pharmacologic agents, ventilatory management, and fluid administration to optimize cardiovascular performance. Although an isolated heart malformation may be identified, the entire cardiopulmonary system is usually affected.

Physiologic Approach to Congenital Heart Disease

Although the structural variations seen in congenital heart disease constitute an encyclopedic list of malformations, anesthetic management is more logically designed to achieve physiologic goals. A general physiologic classification is listed in Table 83-2. Fortunately, although structurally complex, these defects can be understood within a more limited physiologic spectrum. Identification and classification on the basis of physiology provide an organized framework for the intraoperative anesthetic management and postoperative care of children with complex congenital cardiac defects. In general, congenital heart lesions fit into one of four categories: shunts, mixing lesions, flow obstruction, and regurgitant valves (see Table 83-2). Each category imposes at least one

Table 83-2 Classification of Congenital Heart Defects

Physiologic Classification	Pulmonary Blood Flow	Comments
Left-to-right shunts		
VSD	↑	Volume-overloaded ventricle
ASD		Development of CHF
PDA		
AV canal		
Right-to-left shunts		
Tetralogy of Fallot	↓	Pressure-overloaded ventricle
Pulmonary atresia/VSD		Cyanotic
Eisenmenger complex		Hypoxemia
Mixing lesions		
Transposition/VSD	Generally ↓ but variable $\dot{Q}p/\dot{Q}s$	Variable pressure versus volume loaded
Tricuspid atresia		Usually cyanotic
Anomalous venous return		
Univentricular heart		
Obstructive lesions		
Interrupted aortic arch		Ventricular dysfunction
Critical aortic stenosis		Pressure-overloaded ventricle
Critical pulmonic stenosis		Ductal dependence
Hypoplastic left heart syndrome		
Coarctation of the aorta		
Mitral stenosis		
Regurgitant lesions		
Ebstein's anomaly		Volume-overloaded ventricle
Other secondary causes		Development of CHF

ASD, atrial septal defect; AV canal, atrioventricular canal; CHF, congestive heart failure; PDA, patent ductus arteriosus; $\dot{Q}p$, pulmonary blood flow; $\dot{Q}s$, systemic blood flow; VSD, ventricular septal defect.

of three pathophysiologic states: ventricular volume overload, ventricular pressure overload, or hypoxemia. Ultimately, these pathophysiologic conditions can result in myocardial failure or pulmonary vascular disease. Medical and surgical perioperative management strategies should be focused on minimizing the pathophysiologic consequences of these lesions.

Shunt Lesions

Shunts are intracardiac connections between chambers or extracardiac connections between a systemic and pulmonary artery; examples are an atrial septal defect (ASD), a VSD, and a PDA. The direction of blood flow through the shunt is dependent on the relative resistances on either side of the shunt and on the size of the shunt orifice.[22] With a nonrestrictive VSD or PDA that does not impede blood flowing freely in each direction, the main determinant of blood flow is the resistance of the pulmonary and systemic vascular beds. The direction and magnitude of shunt at the atrial level are governed by the relative differences in ventricular compliance and respective atrioventricular (AV) valve function. The effect that a shunt lesion has on the cardiovascular system depends on its size and direction, either right-to-left or left-to-right. Left-to-right shunts occur when the PVR is lower than the SVR and blood flow is preferentially directed toward the lungs, resulting in increased PBF.

In patients with large left-to-right shunts and low PVR, a substantial increase in PBF can occur. This results in three pathophysiologic problems: (1) congestion of the pulmonary circulation; (2) volume overload with resulting increased cardiac work for the LV, which is required to increase stroke volume and heart rate to ensure adequate systemic perfusion; and (3) excessive PBF, resulting in progressive elevation in PVR. Volume overload causes ventricular dilation that places the heart at a mechanical and physiologic disadvantage, resulting in reduced diastolic compliance. These diastolic changes lead to engorgement of the respective venous beds, which produces the signs and symptoms of clinical congestive heart failure early in the natural history of volume-overload condition. The demand for increased cardiac output placed on the LV is limited in the infant by virtue of its immature structure, so that large left-to-right shunts may outstrip the capacity of the left side of the heart to maintain adequate systemic perfusion, and congestive heart failure will result. Surgical closure of a hemodynamically significant VSD usually provides immediate benefit by dramatically lowering left ventricular volume output demands.

Occasionally, the sudden increase in wall stress imposed on a dilated ventricle that must now pump solely against SVR can produce worsening ventricular failure during the early postoperative period after eliminating the low resistance "popoff" into the pulmonary circulation. If the left-to-right shunt is not repaired, prolonged exposure to increased PBF results in progressive elevations in PVR. Fixed changes in pulmonary arterioles may occur, leading to pulmonary vascular obstructive disease. Table 83-2 lists common left-to-right shunt lesions.

Right-to-left shunts occur when pulmonary vascular or right ventricular outflow tract resistance exceeds SVR, thereby reducing PBF. The systemic circulation receives an admixture of

deoxygenated blood via the shunt and manifests clinically as cyanosis and hypoxemia. Pure right-to-left shunting due to increased PVR is seen in the Eisenmenger complex and in persistent pulmonary hypertension of the newborn with atrial and ductal level shunting. More commonly, PVR is low, and a more complex lesion with obstruction of pulmonary outflow, proximal to the pulmonary vasculature, produces right-to-left shunting. Defects such as tetralogy of Fallot represent classic right-to-left shunts. The shunting occurs through the VSD because of pulmonary outflow obstruction. Systemic perfusion is generally normal with right-to-left shunting lesions unless hypoxemia becomes severe enough to impair oxygen delivery to tissue. Thus, there are two pathophysiologic problems: (1) reduced PBF resulting in systemic hypoxemia and cyanosis and (2) an increased impedance to right ventricular ejection resulting in pressure overload, which may ultimately lead to ventricular dysfunction and failure of the RV. However, the physiologic mechanisms designed to compensate for pressure overload rarely create abnormalities in systolic or diastolic function early in the natural history of the disease process. In contradistinction to lesions that produce ventricular volume overload, ventricular dysfunction and failure typically take years to develop in the context of isolated pressure overload.

Mixing Lesions

Mixing lesions constitute the largest group of cyanotic congenital heart defects (see Table 83-2). In these defects, the mixing between the pulmonary and the systemic circulation is so large that the systemic and pulmonary artery oxygen saturations approach each other. The pulmonary-to-systemic flow ratio $\left(\dot{Q}p/\dot{Q}s\right)$ is independent of shunt size and totally dependent on vascular resistance or outflow obstruction. The pulmonary and systemic circulations tend to be in parallel with one another rather than in series (see Table 83-2). In patients with no outflow obstruction, flow to the systemic or pulmonary circulation is dependent on the relative vascular resistances of both circuits, such as with univentricular hearts or double-outlet RV. If SVR exceeds PVR, as in the typical circumstance, the tendency is toward excessive PBF, and the predominant pathophysiologic process is left-to-right shunting. These patients have increased PBF, ventricular volume overload, and a gradual elevation of PVR over time. If PVR exceeds SVR, as may occur episodically in ductal-dependent lesions such as hypoplastic left heart syndrome, systemic blood flow predominates and PBF dramatically decreases, causing progressive hypoxemia (Table 83-3).

In patients with a mixing lesion and left ventricular outflow obstruction, PBF may be sufficiently excessive to impair systemic perfusion. In patients with mixing lesions and a right ventricular outflow obstruction such as a single ventricle with subpulmonic stenosis, systemic-to-pulmonary flow can vary from balanced flow to significantly decreased PBF in which the severity of hypoxemia depends on the degree of obstruction. Typical mixing lesions include truncus arteriosus, univentricular heart, total anomalous pulmonary venous return, pulmonary atresia with large VSD, and single atrium.

Table 83-3 Ductal-Dependent Lesions

PDA Provides Systemic Flow	PDA Provides Pulmonary Flow
Coarctation of the aorta	Pulmonary atresia
Interrupted aortic arch	Critical pulmonary stenosis
Hypoplastic left heart syndrome	Severe subpulmonic stenosis with VSD
Critical aortic stenosis	Tricuspid atresia with pulmonic stenosis

PDA, patent ductus arteriosus; VSD, ventricular septal defect.

Obstructive Lesions

Obstructive lesions range from mild to severe. Severe lesions present in the newborn period with a pressure-overloaded, diminutive, or profoundly dysfunctional ventricle proximal to the obstruction. These lesions include critical aortic stenosis, critical pulmonic stenosis, coarctation of the aorta, and interrupted aortic arch. Although aortic and pulmonary atresia represent the most extreme variants of outflow tract obstruction, they are associated with such extreme hypoplasia of the ventricle (hypoplastic left heart syndrome and pulmonary atresia with intact ventricular septum, respectively) that the ventricle's function does not contribute to the circulatory physiology. As with other critical obstructive lesions, these extreme variants have ductal-dependent circulations, but beyond that similarity they are perhaps better understood as univentricular hearts for which the management characteristics of a mixing lesion dominate in importance. In critical neonatal left-sided obstructive defects, systemic perfusion is dependent on blood flow (desaturated) from the RV via the PDA and the coronary perfusion is supplied by retrograde flow from the descending aorta (see Table 83-3). In right-sided lesions, PBF is supplied from the aorta via the PDA and right ventricular function is impaired.

Pathophysiologic problems in critical neonatal left-sided heart obstructive lesions include (1) profound left ventricular failure, (2) impaired coronary perfusion with an increased incidence of ventricular ectopy, (3) systemic hypotension, (4) PDA-dependent systemic circulation, and (5) systemic hypoxemia. The pathophysiologic problems in critical neonatal right-sided heart obstructive lesions include (1) right ventricular dysfunction, (2) decreased PBF, (3) systemic hypoxemia, and (4) PDA-dependent PBF. Apart from the most extreme variants that become evident in the neonatal period, infants and children with outflow obstruction (e.g., mild to moderate aortic or pulmonary stenosis, coarctation of the aorta) manifest the effective compensatory mechanisms for pressure overload, often remaining clinically asymptomatic for many years.

Regurgitant Valves

Regurgitant valves are uncommon as primary congenital defects. Ebstein's malformation of the tricuspid valve is the only pure regurgitant defect presenting in the newborn period. However, regurgitant lesions are frequently associated with an abnormality of valve structure, such as incomplete or partial AV canal defect, truncus arteriosus, and tetralogy of Fallot with an absent pulmonary valve. The pathophysiology of regurgitant lesions includes (1) volume-overloaded circulation and therefore (2) progression toward ventricular dilation and failure.

In summary, when considering the incidence of all the congenital heart defects, three uncomplicated left-to-right shunts (VSD, ASD, PDA) and two obstructive lesions (pulmonic stenosis, coarctation) constitute 60% of all congenital cardiac defects. Mixing lesions, complicated obstructive defects, and right-to-left

shunting lesions account for the vast majority of the remaining 40%. The latter group of defects, which are more difficult to manage, are more labor intensive and have a significantly higher morbidity and mortality rate. This observation is directly attributed to the complexity of the cardiovascular abnormalities seen in this group, in which there is an absence of a chamber or a major ventricular-arterial connection.

Chronic Consequences of Congenital Heart Disease

The chronic effects of congenital heart disease are a consequence of the imposed hemodynamic stress of the defect or the residua and sequelae after cardiac surgery. These effects continue to alter normal growth and development of the cardiovascular system as well as other organ systems throughout life. Complete surgical cures are rarely achieved, and some repairs are palliative rather than corrective; therefore, abnormalities before and after repair produce long-term effects in patients with congenital heart disease.[23] Although the overall outlook for these patients is good in most instances, every defect has associated myocardial changes and every repair leaves certain obligatory abnormalities. Many of the abnormalities are trivial and have no major import. Others affect major organ system processes, such as ventricular function, central nervous system growth, the conduction system of the heart, or PBF. Under these circumstances, the long-term quality of life is affected. Whether anesthetizing these patients for their primary or subsequent cardiac repair or for noncardiac surgery, these chronic changes should be ascertained and reflected in the anesthetic plan.

The myocardium is continually remodeled by specific hemodynamic stresses in utero and throughout life. Right ventricular growth and development are influenced by the low-resistance afterload of the pulmonary circulation. The LV is coupled to the high-resistance systemic circulation, which accelerates its rate of growth and development. This situation gives rise to the adult condition in which left ventricular dominance of myocardial muscle mass occurs. This entire developmental process is referred to as dynamic ventricular modeling.[4] Abnormal hemodynamic loading conditions associated with congenital heart disease interrupt the normal ventricular modeling process (Fig. 83-2).[24] Abnormal ventricular remodeling typically begins in utero and stimulates an increase in ventricular mass. Increased ventricular mass is due to both hyperplasia and hypertrophy of myocytes in response to altered wall stress on the developing ventricle. The resultant biomechanical deformation of the ventricle alters its geometry, affecting normal systolic and diastolic function.

Abnormalities of ventricular performance at rest and with exercise can be detected in patients with chronic hemodynamic overload and complex cyanotic lesions. These abnormalities in ventricular function are the consequences of chronic ventricular overload, repeated episodes of myocardial ischemia, and residua or sequelae of surgical treatment (ventriculotomy, altered coronary artery supply, inadequate myocardial protection). The physiologic adaptive responses to chronic hypoxemia and ventricular pressure or volume overload are the primary stimuli producing the long-term ventricular dysfunction. Although chronic volume overload of the LV as seen with left-to-right shunts or a chronic pressure-loaded LV due to left-sided obstructive lesions results in congestive heart failure, the compensatory mechanisms for pressure overload create less physiologic disturbance, particularly in diastolic function. Consequently, congestive heart failure occurs later in the natural history of isolated obstructive lesions that do not require treatment in the neonatal period. Similarly, chronic right ventricular volume overload as seen in pulmonic insufficiency after tetralogy of Fallot repair is more likely to be associated with chronic ventricular dysfunction and failure than a pressure-loaded RV that manifests with residual pulmonic stenosis. In fact, the most potent combination for inducing ventricular dysfunction and failure occurs when a pressure overload is superimposed on a dilated, volume-overloaded ventricle (e.g., postoperative tetralogy of Fallot with pulmonary insufficiency and branch pulmonary artery stenosis). The mechanism for the dysfunction and failure is multifactorial.

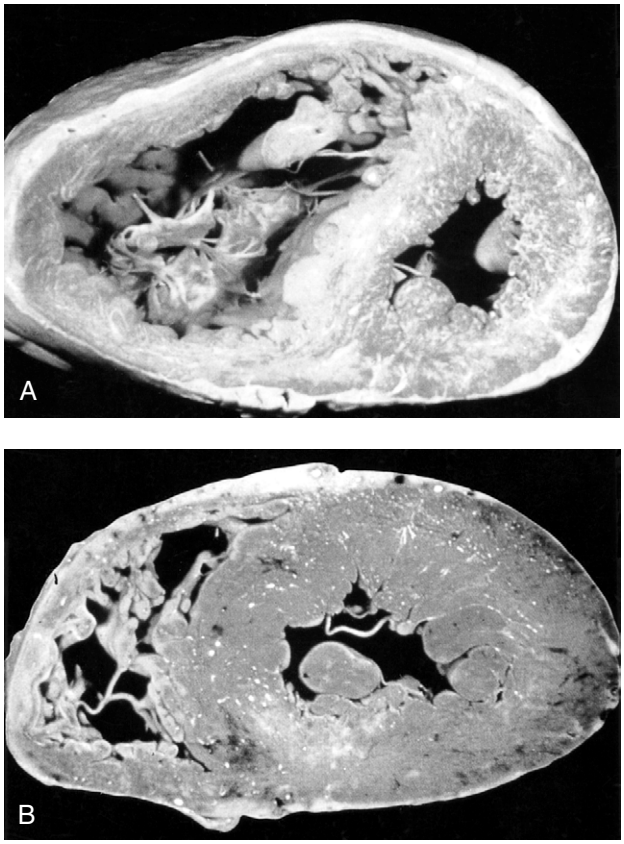

Figure 83-2 Comparison of ventricular hypertrophy patterns demonstrating altered ventricular remodeling in two different congenital heart defects. **A,** Note the right ventricular hypertrophy and the diminutive left ventricle in tetralogy of Fallot. **B,** Note the severe left ventricular hypertrophy and septal bulging into the right ventricle in aortic stenosis.

Initial manifestations of congestive heart failure reflect alterations in ventricular compliance that result from a variety of biophysical responses to abnormal loading conditions. The ventricular dilation and compensatory hypertrophy that accompany volume overload provide effective compensation to preserve normal systolic wall stress, but alterations in diastolic wall stress become evident (Fig. 83-3). Ultimately, chronic or severe pressure loads manifest similar changes as the resultant myocardial hypertrophy outgrows vascular supply and results in ischemia and fibroblast proliferation. Permanent changes in myocardial structure and function are the end result.

In patients with cyanotic conditions, the long-term compensation for chronic hypoxemia shows a major redistribution of



	Normal	Pressure overload	Volume overload
LVp	117 ± 7 / 10 ± 1	220* ± 6 / 23* ± 3	139 ± 7 / 24* ± 2
h	.8 ± .1	1.5* ± .1	1.1* ± .1
r	2.4 ± .1	2.8 ± .2	3.3* ± .1
h/r	.34 ± .02	.58* ± .05	.34 ± .02
σ_s	151 ± 14	161 ± 24	175 ± 7
σ_p	17 ± 2	23 ± 3	41* ± 3

Figure 83-3 Changes in ventricular physiology that accompany abnormal pressure and volume loading in human adolescents and adults. Schematic diagram represents the changes in cross-sectional ventricular geometry that accompany abnormal pressure and volume loads. Data are measured and derived from catheterization and echocardiography of 30 adolescent and adult human subjects. Pressure overload triggers significant increases in wall thickness and wall thickness : radius ratio (h/r), but these compensatory mechanisms preserve σ within normal limits. Whereas volume overload causes dilation and enough hypertropy to preserve normal σ_s, diastolic function deteriorates significantly. LVp, left ventricular pressure; r, radius of the LV chamber; σ_D, end-diastolic wall stress; σ_S, peak systolic wall stress; *$P = .01$. (*From Grossman W, Jones D, McLaurin LP: Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 56:56, 1975.*)

organ perfusion with selected blood flow to the heart, brain, and kidney and decreased flow to the splanchnic circulation, skin, muscle, and bone. Chronic hypoxemia is associated with increased work of breathing in an attempt to increase oxygen uptake and delivery. The most dramatic complications are decreased rate of somatic growth, increased metabolic rate, and an increase in hemoglobin concentration seen in children with palliated or unrepaired defects.

There may also be congenital syndromes with associated congenital heart disease that will influence long-term outcome (Table 83-4).

Surgical Procedures and Special Techniques

The ultimate objectives for congenital heart surgery are (1) physiologic separation of the circulation, (2) relief of outflow obstruction, (3) preservation or restoration of ventricular mass and function, (4) normalization of life expectancy, and (5) maintenance of quality of life. The available surgical procedures to accomplish these objectives are diverse and complex (Table 83-5). Compared with cardiac operations in adult patients, pediatric congenital heart repairs involve more intracardiac surgery, with a greater preponderance performed via the right atrium and RV. In general, operations performed for congenital heart defects can be divided into palliative and corrective procedures. The type and timing of repair depend on the age of the patient, the specific anatomic defect, and the experience of the surgeon and the team (see Table 83-5).

Palliation in infancy is usually performed when there are missing anatomic parts, as in pulmonary atresia (absent RV and pulmonary artery), tricuspid atresia (absent RV and tricuspid valve), hypoplastic left heart syndrome (aortic atresia and hypoplastic LV), univentricular heart (absent RV or LV), and mitral atresia (absent LV). These palliative procedures can be further subdivided into those that will increase PBF, those that decrease PBF, and those that increase mixing (see Table 83-5). Palliative procedures that increase PBF include shunts (Blalock-Taussig, central, and Glenn), outflow patch, and enlargement of the VSD. Those that decrease PBF include pulmonary artery banding and ligation of a PDA. Those that improve intracardiac mixing include atrial septostomy (balloon, blade, and Blalock-Hanlon).

The improvements in surgical technique, coupled with advancements in anesthetic and technologic support, make repair in early infancy not only feasible but in many cases preferable.[25] Currently, repair in infancy can be offered for a number of congenital heart defects, as shown in Table 83-5. The timing of surgical intervention reflects medical necessity, physiologic and technical feasibility, and optimal outcome. Cardiac defects that require a PDA to sustain sufficient systemic blood flow or PBF (e.g., pulmonary atresia, hypoplastic left heart syndrome, interrupted aortic arch, critical aortic stenosis, and critical pulmonic stenosis) require an intervention in the neonatal period. A variety of defects are optimally repaired in early infancy. Lesions such as transposition of the great arteries may exhibit better left ventricular function if the arterial switch operation is performed in the first few weeks of life when the PVR has recently been high enough to increase left ventricular systolic pressure, whereas other repairs may manifest less volatile postoperative physiology if deferred a few weeks or months until PVR has consistently fallen (e.g., tetralogy of Fallot, AV canal defect). Each defect may have mitigating factors for which deferred definitive repair will enable optimal surgical result (e.g., tetralogy of Fallot with aberrant coronary branching pattern or multiple VSDs; transposition of the great arteries with VSD and severe left ventricular outflow tract obstruction).

Although some lesions merit repair whenever they are diagnosed (e.g., total anomalous pulmonary venous return, coarctation of the aorta), others exhibit such a wide spectrum of physiologic disturbance that the timing of an intervention must be made individually (e.g., VSD, aortic stenosis, pulmonic stenosis). A few cardiac malformations produce pathophysiologic changes that are sufficiently mild that repair is typically deferred to later infancy or childhood (e.g., isolated ASD). Palliative surgery is entertained when a physiologic derangement requires intervention but circumstances preclude definitive repair.

In general, the recent trend in pediatric cardiovascular surgery has been to repair defects in infancy rather than palliate.[24] This trend reflects improved technical capabilities coupled with a desire to limit the morbidity and mortality associated with long-term medical management and the sequelae of multiple palliative operations. Early corrective surgery is expected to decrease the incidence of the chronic complications of congenital heart disease, such as the problems associated with ventricular overload, cyanosis, and pulmonary vascular obstructive disease.[26] Early infant repair may also have the selective advantage of enhancing organ system protection during repair because of poorly understood factors promoting resistance to injury and enhanced recovery potential (i.e., enhanced plasticity). With the continued improvement in surgical techniques and the early treatment of congenital heart disease, specific organ systems such as the brain, heart, and

Table 83-4 Syndromes Associated with Congenital Heart Disease (CHD)

Syndrome	Lesion	Cardiac Lesion	Comments
Syndromes with Airway Issues and CHD			
CHARGE association		VSD, ASD, PDA, TOF	Micrognathia, possible difficult airway
Edwards' syndrome	Trisomy 18	VSD, ASD, PDA	Micrognathia, small mouth, difficult intubation
Di George sequence	Microdeletion 22q11.2	Aortic arch and conotruncal lesions	Short trachea—tendency to endobronchial intubation
Goldenhar's syndrome		VSD, PDA, TOF, CoA	Maxillary and mandibular hypoplasia, C-spine anomalies—difficult intubation
Hurler's syndrome	MPS 1, storage disorder	Multivalvular disease, CAD, cardiomyopathy	Macroglossia, short neck—extremely difficult intubation
Noonan's syndrome		PS, ASD, cardiomyopathy	Short webbed neck, macrognathia—difficult intubation
Turner's syndrome	Monosomy X	LVOT O, AS, HLHS, CoA	Micrognathia, webbed neck—difficult intubation
VATER association		VSD, TOF, ASD, PDA	Potential for difficult intubation
Syndromes with Risk of Arrhythmias			
Long QT syndrome (LQTS)		Torsades de pointes, SCD	
Brugada's syndrome		VT/VF/SCD	
Arrhythmogenic right ventricular dysplasia (ARVD)		VT/SCD	
Catecholaminergic polymorphic ventricular tachycardia		Polymorphic VT/SCD	
Wolff-Parkinson-White syndrome		SVT	
Maternal lupus		CCHB in the newborn	
Chromosomal Disorders Associated with CHD			
Down syndrome	Trisomy 21	VSD, ASD, CAVC	
Edwards' syndrome	Trisomy 18	VSD, ASD, PDA	
Patau's syndrome	Trisomy 13	VSD, PDA, ASD	
Turner's syndrome	Monosomy X	LVOT O, AS, HLHS, CoA	
3p– syndrome	Deletion 3p	CAVC	
Cri du chat syndrome	Deletion 4p	Variable	
8p– syndrome	Deletion 8p	CAVC	
9p– syndrome	Deletion 9p	VSD, PDA, PS	
Williams syndrome	Microdeletion 7q11	SVAS, SVPS, branch PS	
Smith-Magenis syndrome	Microdeletion 17p11.2	ASD, VSD, PS, AV valve malformations	
Miller-Dieker syndrome	Microdeletion 17p13.3	TOF, VSD,PS	
CHARGE association		VSD, ASD, PDA, TOF	Coloboma, heart, choanal atresia, retardation, genital and ear anomalies

lungs will be spared the detrimental effects of chronic derangements of hemodynamics and oxygen delivery.

Procedures for the treatment of congenital heart disease continue to evolve to decrease long-term morbidity and enhance survival. For example, the long-term problems with right ventricular dysfunction and failure associated with the Mustard procedure for repair of transposition of the great arteries encouraged many surgical groups to develop the neonatal arterial switch operation.[27] Early indications suggest that the latter procedure provides an anatomic correction with better long-term results. A second example of the continuing evolution of technique is surgery for tetralogy of Fallot. Long-standing pulmonary insufficiency after right ventricular outflow repair for tetralogy of Fallot is associated with right ventricular dysfunction and failure. Preservation of the pulmonary valve at initial repair using a combined transatrial and transpulmonary approach during correction and the early insertion of a pulmonary homograft in the setting of pulmonary insufficiency are techniques being used in an attempt to avoid the long-term problems of right ventricular dysfunction and failure.[28]

Surgery for hypoplastic left heart syndrome, once considered a fatal disease, has achieved significant long-term survival in a growing number of institutions after a series of staged reconstructive procedures.[29,30] The use of right ventricular to pulmonary artery (RV-PA) conduits as an alternative to traditional systemic-to-pulmonary shunts has been shown to confer some advantage in survival after stage 1 palliation owing to elimination of diastolic runoff into the pulmonary circulation with concurrent unloading of the systemic RV. There seems to be an improvement in myocardial perfusion, with higher diastolic pressures, lower aortic saturations, and decreased myocardial work. The long-term impact of a right ventriculotomy in a univentricular

Table 83-5 Congenital Cardiac Defects and Their Repair

Anatomic Defects	Palliation	Complete Repair
Tetralogy of Fallot		VSD closure and RVOT patch
With PA atresia	Shunt	
With anomalous right coronary artery	Rastelli	
HLHS	Norwood I/transplant	
Transposition of the great arteries		Arterial switch
Unfavorable coronary anatomy	Atrial switch (Senning)	
Tricuspid atresia	Shunt followed by Fontan	
Pulmonary atresia with VSD	Shunt followed by Fontan	
With intact septum	Shunt followed by Fontan	
Critical aortic stenosis		Aortic valvotomy
Interrupted aortic arch		End-end anastomosis/reverse subclavian flap/tube graft
Total anomalous pulmonary		Anastomosis of pulmonary veins to left atrium venous return and ASD closure
Single ventricle/normal PAs	Band followed by Fontan	
With small PAs	Shunt followed by Fontan	
Truncus arteriosus		RV-PA conduit and VSD closure
Atrioventricular canal		Repair valve clefts/patch closure of ASD/attach valves to patch

ASD, atrial septal defect; HLHS, hypoplastic left heart syndrome; PAs, pulmonary artery; RV, right ventricle; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

heart is unknown.[31-33] The use of a low-resistance strategy has been advocated for a stable postoperative course with use of vasodilators such as phenoxybenzamine on CPB and optimal reduction of PVR with inhaled nitric oxide and 100% oxygen after CPB.[34,35]

Several factors considered to be associated with an increased risk for single ventricle palliation include anatomic variants such as aortic atresia, mitral atresia, ascending aorta less than 2.0 to 2.5 mm, restrictive atrial septum, obstructed pulmonary venous return, the presence of other congenital anomalies, prematurity, birth weight less than 2.5 kg, older age at time of surgery (>14 days), surgical inexperience, and prolonged CPB and arrest times. Perioperative factors can adversely affect outcome and include preoperative metabolic acidosis, preoperative inotrope support, morphologic RV in the systemic circuit, right ventricular dysfunction, presence of severe tricuspid regurgitation, pulmonary valve regurgitation (beyond mild), and low $S\bar{v}O_2$ (<30%) after a Norwood procedure.[36-42] Neurologic outcome after surgical repair is an ongoing concern. Preoperative cerebral blood flow (CBF) was shown to be diminished in patients with a variety of congenital heart defects, and low CBF values were associated with periventricular leukomalacia.[43] Some centers routinely advocate regional low-flow cerebral perfusion and measurement of regional cerebral oxygen saturation index and CBF velocity using transcranial Doppler during arch reconstruction in this population. Reductions in the regional cerebral oxygen saturation index or CBF greater than 20% of baseline are treated aggressively in an attempt to increase cerebral oxygen delivery by increasing the mean perfusion pressure, red blood cell transfusion, and maintenance of high normal levels of $PaCO_2$ to achieve cerebral vasodilation.

Surgical management has evolved in a broader application of certain surgical procedures initially designed for a specific defect. For example, modifications of the Fontan operation, which was originally devised for patients with tricuspid atresia, are now being used to repair a variety of univentricular hearts, including hypoplastic left heart syndrome.[44,45] Initially, the wider application of the Fontan operation to include complex defects once considered inoperable was associated with a rise in morbidity and mortality. However, this trend has been reversed in recent years by several groups who have demonstrated improved outcome with the staging of the operation (superior cavopulmonary anastomosis, subsequent completion of the Fontan operation), the creation of a fenestration between the right and left atrium at the time of the Fontan operation, and the use of modified ultrafiltration (MUF) (see later).[46] The communication allows for right-to-left shunting, thereby preserving cardiac output at lower systemic venous pressure in the early postoperative period. When necessary, once the patient has convalesced from the acute postoperative changes, the fenestration can be closed at the bedside with a snare placed at the time of the operation or in the catheterization laboratory with a clamshell device. In a substantial proportion of cases, these fenestrations close spontaneously without further intervention.

Ingenuity and innovation such as demonstrated with the difficult Fontan procedure have permitted continued improvements in survival for all patients with congenital heart disease. As incisions in the myocardium become smaller and sutures more precisely placed, and as improvements in surgical techniques continue to evolve, the complications of ventricular dysfunction, arrhythmias, and residual obstruction should decline, contributing to improved patient quality of life.

One final difference unique to congenital heart surgery that has a major impact on anesthetic management relates to the type of cardiopulmonary support. Because of the complexity of repair in small patients, surgery often requires significant alterations in the bypass techniques, such as the use of deep hypothermic CPB at temperatures of 18°C and total circulatory arrest. Many operations are undertaken in this setting of extreme biologic conditions of temperature and perfusion. Current methods of CPB management in neonates, infants, and children involve extensive alterations in temperature, hemodilution, systemic perfusion pressure, and flow. Despite widespread use of these techniques during CPB, their physiologic effects on major organ system function are just beginning to be understood. These effects are discussed in subsequent sections.

In summary, there are unique features that need to be considered in caring for children with congenital heart disease who are undergoing pediatric cardiac surgery. These features include the patient's growth and development, the developing cardiovascular system of the young, the pathophysiology of congenital heart disease, the surgical procedures, and the CPB techniques. A basic understanding of these differences coupled with the fundamental knowledge of adult and pediatric cardiac anesthesia principles underlies the approach to the perioperative management of these patients.

Anesthetic Management

Preoperative Management

Anesthetic Evaluation

Caring for children with congenital heart disease presents the anesthesiologist with a wide spectrum of anatomic and physiologic abnormalities. Patients range from young, healthy, asymptomatic children who are having closure of a small ASD to the neonate with hypoplastic left heart syndrome requiring aggressive perioperative hemodynamic and ventilatory support. Intertwined with the medical diversity of these patients are the psychological factors affecting both the patient and the parents. Preparation of the patient and the family is time-consuming, but omitting or compromising this aspect of patient care is a major deterrent to a successful outcome and patient/parental satisfaction. This team-oriented approach also serves as a safeguard to prevent errors and omissions in the exacting perioperative care necessitated by the complexity of cardiac surgery for congenital heart disease. The preoperative visit offers the family the opportunity to meet the surgeon and anesthesiologist.

Parents should be questioned about the general health and activity of their child. Fundamentally, a child's general health and activity will reflect cardiorespiratory reserve. Deficiencies may point toward cardiovascular or other systems that may influence anesthetic or surgical risk. It is important to determine whether the child has an impaired exercise tolerance. Is he or she gaining weight appropriately or exhibiting signs of failure to thrive on the basis of cardiac cachexia? Does the child exhibit signs of congestive heart failure (diaphoresis, tachypnea, poor feeding, recurrent respiratory infections)? Is there progressive cyanosis or new onset of cyanotic spells? Any intercurrent illness such as a recent upper respiratory tract infection or pneumonia must be ascertained. Lower respiratory tract infections may require a delay in proposed surgery, based on the negative impact that airway reactivity and elevations in PVR may have on surgical outcome. Recurrent pneumonia is frequently associated with pulmonary overcirculation and altered lung compliance in patients with increased PBF.

A good history must delineate previous surgical and cardiologic interventions. These may have an impact on both surgical and anesthetic plans for the current procedure. Patients who have had their subclavian artery sacrificed for a subclavian flap angioplasty to correct coarctation or a Blalock-Taussig shunt will not accurately display systemic arterial pressure or perhaps even pulse oximetry readings when the monitoring is applied to the left arm. Likewise, children who have femoral venous occlusion after catheterization are not candidates for femoral venous access, particularly for femoral CPB should sternotomy prove impossible. It is equally important to ascertain current medications, previous anesthetic problems, or family history of anesthetic difficulties.

In the modern era of echocardiography and cardiac catheterization, physical examination rarely contributes additional anatomic information about the underlying cardiac lesion. However, it is extremely useful in assessing the overall clinical condition of the child. For example, an ill-appearing, cachectic child in respiratory distress has limited cardiorespiratory reserve and the use of excessive premedication or a prolonged inhalational induction could result in significant hemodynamic instability.

Concurrent Medications and Drug Interactions

Drug interactions are common both among the co-therapeutic cardiovascular agents and between the cardiovascular drugs and anesthetic drugs. An understanding of the mechanisms and of the interactions is useful to the pediatric cardiovascular anesthesiologist. Some common cardiovascular medications and anesthesia considerations are shown in Table 83-6.

Pediatric oncology patients presenting for cardiac or noncardiac procedures may manifest higher cardiovascular risk due to cardiotoxic chemotherapy.[47] Common cardiotoxic agents include the antimetabolite 5-fluorouracil, the anthracycline antibiotics doxorubicin and daunorubicin, and the alkylating agent cyclophosphamide. The acute form is characterized by acute ST segment/T wave changes on the electrocardiogram (ECG), serious dysrhythmias, and congestive heart failure associated with pericardial effusion. Chronic cardiotoxic heart failure is cumulative, dose related, and unresponsive to digoxin therapy. Serious cardiomyopathy can occur and is related to dose, irradiation, and use of an anthracycline. Mortality rate can exceed 50%. These patients should undergo thorough preoperative evaluation, including a full blood cell count, assessment of renal and hepatic function and coagulation parameters, and an echocardiogram. An isoflurane/N_2O-based anesthetic might confer better hemodynamic stability than opioid-based anesthesia in such patients.[48]

Anesthetic agents can cause torsades de pointes, a malignant arrhythmia. Risk factors for torsades de pointes include female gender, electrolyte imbalances such as hypokalemia and hypomagnesemia, genetic ion channel polymorphisms of congenital long QT syndrome (LQTS), subclinical LQTS, baseline QT prolongation, and use of QT-prolonging drugs especially in high concentrations or as rapid intravenous infusions. Conditions

Table 83-6 Common Perioperative Cardiovascular Medications and Considerations

Cardiac Drug Class	Interactions	Considerations
Angiotensin-converting enzyme inhibitors	Hypotension with induction of general anesthesia	Consider withholding AM dose, or reducing dosage, in hypotensive patients; avoid fixed dose induction regimens with drugs having a profound vagomimetic effect
β-Blockers	Acute withdrawal can precipitate tachycardia and arrhythmias; can potentiate hypotension with volatile anesthesia; can decrease response to inotropic agents	Continue in the perioperative period
Calcium channel blockers	May augment the negative inotropic and chronotropic effects of volatile anesthesia	Continue in the perioperative period
Diuretics	Hypovolemia/hypokalemia; may augment effect of neuromuscular blocking agents	Discontinue preoperatively
Antiarrhythmics	Can be proarrhythmic with inotropes, electrolyte disturbances; high catecholaminergic states; can interact with other antiarrhythmics and precipitate bradycardia	Avoid electrolyte imbalance Avoid drugs that are proarrhythmic Monitor carefully
α_2-Agonists	Reduces perioperative shivering, ischemia, anesthetic and analgesic requirements	Continue into the perioperative period with appropriate monitoring

with reduced repolarization reserve such as congestive cardiac failure or digoxin toxicity can precipitate torsades de pointes. Drugs that may cause torsades in patients with congenital LQTS are shown in Table 83-7.

Laboratory evaluation should include analysis of hemoglobin, hematocrit, pulse oximetry, and, in selected patients (e.g., those on diuretics or with renal impairment), serum electrolytes. An elevated hematocrit in a normovolemic child gives an indication of the magnitude and chronicity of their hypoxemia. Levels above 60% may predispose to capillary sludging and secondary end organ damage, including stroke. Despite these risks, liberalized nothing-by-mouth guidelines that permit children to consume clear liquids up to 2 hours before anesthetic induction have virtually eliminated the need to admit these patients for preoperative intravenous hydration.[49,50]

Echocardiography with Doppler color flow imaging (echo-Doppler) is an invaluable tool that provides a noninvasive means of assessing intracardiac anatomy, blood flow patterns, and estimates of physiologic data.[51] For many cardiac defects, more invasive studies are generally not required if a good echocardiographic assessment is made. Echo-Doppler is especially helpful for defining intracardiac abnormalities. Extracardiac abnormalities, such as pulmonary artery or vein stenosis, are more difficult to define by echo-Doppler and often require cardiac catheterization. The ability to interpret anatomy and physiology accurately requires a skilled echocardiographer, reaffirming the need for a well-integrated interactive team. Although the complexities posed by extreme anatomic variation and changing loading conditions render intraoperative echo-Doppler challenging even for experienced echocardiographers, the pediatric cardiac anesthesiologist should develop some familiarity with its capabilities and limitations so as to participate in critical intraoperative management decisions.

Magnetic resonance imaging (MRI) of the heart and major vessels has become a very useful noninvasive imaging tool in children with heart disease. Typically, MRI is used for segmental description of cardiac anomalies; evaluation of thoracic aortic anomalies; noninvasive detection and quantification of shunts, stenoses, and regurgitations; evaluation of conotruncal malformations and complex anomalies; identification of pulmonary and

Table 83-7 Drugs That May Cause Torsades de Pointes in Patients with Congenital Long QT Syndrome

Drug Category	Drug Name
Antiarrhythmics	Amiodarone Procainamide Disopyramide Ibutilide Quinidine Sotalol
Antipsychotics	Chlorpromazine Haloperidol Thioridazine Mesoridazine
Antimicrobials	Erythromycin Clarithromycin
Miscellaneous	Cisapride Arsenic Methadone Droperidol Domperidone Dolasetron Ondansetron Glycopyrrolate

systemic venous anomalies; and postoperative studies and evaluation of congenital heart disease in adult patients.[52] MRI is particularly useful in quantifying ventricular function, regional wall motion, valvar competence, and velocity flow mapping. It is especially useful for imaging the aortic arch, pulmonary arteries, and the mediastinal vessels in children with complex congenital heart disease. Lesions for which MRI provides accurate and useful information include coarctation of the aorta, anomalies of the pulmonary arteries, anomalous pulmonary venous connections and persistent left superior vena cava, and intracardiac baffles, conduits, and shunts. MRI is also useful in older patients with poor acoustic windows and patients with chest wall deformities.[52] It can be used as an alternative to cardiac catheterization in select patients. However, physiologic data such as oxygen saturations cannot be obtained. Adenosine stress cardiac MRI is used to delineate areas of inducible ischemia.

Cardiac catheterization remains the gold standard for assessing anatomy and physiologic function in congenital heart disease. Although many anatomic questions can now be reliably answered noninvasively, cases that present complex anatomic questions or those for which physiologic data are required, catheterization remains a vital tool. Important catheterization data for the anesthesiologist include the following:

1. Child's response to sedative medications
2. Pressure and oxygen saturation in all chambers and great vessels
3. Location and magnitude of intracardiac and extracardiac shunt $\left(\dot{Q}p/\dot{Q}s\right)$
4. Pulmonary vascular resistance, systemic vascular resistance
5. Chamber size and function
6. Valvular anatomy and function
7. Distortion of systemic or pulmonary arteries related to prior surgery
8. Coronary artery anatomy
9. Anatomy, location, and function of previously created shunts
10. Acquired or congenital anatomic variants that might have an impact on planned vascular access or surgery

Careful review of the cardiac catheterization data and an understanding of their potential impact on the operative and anesthetic plan are essential. Not all the medical problems can be evaluated and corrected preoperatively; the surgeon, cardiologist, and anesthesiologist must discuss the potential management problems and any need for further evaluation or intervention before arrival in the operating room. Appropriate communication and cooperation between the two physicians will optimize patient care and facilitate perioperative clinical management. Typically, institutions have a regularly scheduled combined cardiology/cardiac surgery meeting to discuss candidates for surgery, during which all essential information is displayed and discussed. Such a meeting provides an invaluable opportunity for learning about specific patients proposed for surgery as well as a continuing educational forum that promotes an interdisciplinary exchange directed at contemporary concepts in congenital heart disease and its treatment, both medical and surgical.

Premedication

See Chapter 82.

Intraoperative Management

Operating Room Preparation

Advance, careful preparation of the operating room is essential. The anesthesia machine must have the capacity to provide air, oxygen, carbon dioxide, and nitric and nitrous oxide to help balance pulmonary and systemic blood flow. Intravenous tubing must be free from air bubbles to prevent paradoxical air embolism. Resuscitative drugs, labeled and ready for administration, should include succinylcholine, calcium gluconate or calcium chloride, sodium bicarbonate, atropine, phenylephrine, lidocaine, and epinephrine. An inotropic infusion, usually dopamine, should be premixed and ready for administration in high-risk cases, but additional infusions are prepared if their need is strongly suspected. For all pediatric cases, certain anesthetic drugs should be available (thiopental, propofol, ketamine). In pediatric cardiac anesthesia, many patients have limited reserve as well as high endogenous catecholamine levels released in an adaptive response to their underlying cardiac disease. The resuscitative drugs should therefore be prepared and immediately available before anesthetic induction.

For congenital heart surgery, the ability to alter body temperature rapidly for cooling and rewarming is essential. During deep hypothermic CPB, patients are cooled to 18°C. Surface cooling with a heating/cooling water mattress and an efficient room/ambient temperature control system is important in the operative management of these patients.

Physiologic Monitoring

The monitoring used for any specific patient should depend on the child's condition and the magnitude of the planned surgical procedure. The perioperative monitoring techniques available are listed in Table 83-8. Noninvasive monitoring is placed before induction of anesthesia. In the crying pediatric patient, the anesthesiologist may elect to defer application of monitoring devices until immediately after the induction of anesthesia. Standard monitoring includes an electrocardiographic system, pulse oximetry, capnography, precordial stethoscope, and an appropriate-sized blood pressure cuff (either oscillometric or Doppler). Additional monitoring includes an indwelling arterial catheter, temperature probes, and an esophageal stethoscope. Foley catheters are generally employed when surgical intervention entails CPB or might produce renal ischemia or when the anesthetic management includes a regional technique associated with urinary retention. Some centers routinely employ central venous pressure (CVP) monitoring for major cardiovascular surgery. Alternatively, we typically use directly placed transthoracic atrial lines to obtain that information for separation from CPB and the postoperative period. In that setting, the benefits of the information or access provided by percutaneous CVP catheters in the pre-bypass period must be weighed against the risks they pose.

Continuous monitoring of arterial pressure is only possible through an indwelling intra-arterial catheter. In young children, cannulation of the radial artery with a 22- or 24-gauge catheter

Table 83-8 Monitoring of Organ Systems

Cardiopulmonary System
Esophageal stethoscope
Electrocardiogram
Standard seven-lead system, ST-T wave analysis, esophageal electrocardiographic lead
Pulse oximetry
Automated oscillatory blood pressure
Capnograph
Ventilator parameters
Indwelling arterial catheter
Central venous pressure catheter
Pulmonary artery catheter
Transthoracic pressure catheter
Left or right atrium, pulmonary artery
Echocardiography with Doppler color flow imaging
Epicardial or transesophageal
Central Nervous System
Peripheral nerve stimulator
Processed electroencephalography
Specialized
Cerebral blood flow—xenon clearance methodology
Cerebral metabolism—near-infrared spectroscopy, oxygen consumption measurements
Transcranial Doppler
Jugular venous bulb saturations
Temperature
Nasopharyngeal, rectal, esophageal, tympanic
Renal Function
Foley catheter

is preferred. In older children and adolescents, a 20-gauge catheter may be substituted. Careful inspection, palpation, and four-extremity noninvasive blood pressure determinations help ensure that previous or currently planned operative procedures (e.g., a previous radial artery cutdown, subclavian flap for coarctation repair, or Blalock-Taussig shunt) do not interfere with the selected site of arterial pressure monitoring. Other sites available for cannulation include the ulnar, femoral, axillary, and umbilical (in neonates) arteries. Cannulation of the posterior tibial or dorsalis pedis arteries is not usually sufficient for complex operative procedures. Peripheral arterial catheters, principally of the distal lower extremities, function poorly after CPB and do not reflect central aortic pressure when distal extremity temperature remains low.[53]

Myocardial and cerebral preservation is maintained principally through hypothermia; therefore, the accurate and continuous monitoring of body temperature is crucial. Rectal and nasopharyngeal temperatures are monitored because they reflect core temperature and brain temperature, respectively. Monitoring of esophageal temperature is a good reflection of cardiac and thoracic temperature. Tympanic probes, although a useful reflection of cerebral temperature, can cause tympanic membrane rupture.

Pulse oximetry and capnography provide instantaneous feedback concerning adequacy of ventilation and oxygenation. They are useful guides in ventilatory and hemodynamic adjustments to optimize $\dot{Q}p/\dot{Q}s$ before and after surgically created shunts and pulmonary artery bands. Peripheral vasoconstriction in patients undergoing deep hypothermia and circulatory arrest renders digital oxygen saturation probes less reliable. In the newborn, the use of a tongue sensor has been advocated to provide a more central measure of oxygen saturation, with less temperature-related variability.[54]

The use of transthoracic (in the right or left atrium, pulmonary artery) or transvenous pulmonary artery catheters is determined on an individual basis based on the disease process, physiologic state, and surgical intervention. For example, in children undergoing a Fontan procedure for tricuspid atresia or a univentricular heart, catheters in the Fontan pathway and the pulmonary venous atrium are especially useful. After a Fontan operation, PBF must occur without benefit of a ventricular pumping chamber. Subtle changes in preload, PVR, and pulmonary venous pressure will influence PBF and thus systemic cardiac output. Data derived from systemic venous pressure and left atrial pressure (LAP) help identify the relative importance of intravascular volume (CVP), PVR (CVP-LAP gradient), or ventricular compliance (LAP), each of which requires a different therapeutic approach.

As a general guideline, a transvenous pulmonary artery catheter may be placed using the internal jugular approach in children weighing more than 7 kg. A 5.0-Fr catheter is used for children weighing between 7 and 25 kg, and a 7.0-Fr one is used for children weighing more than 25 kg. For infants weighing less than 7.0 kg, percutaneous placement of a pulmonary artery catheter can be performed from the femoral vein. Occasionally, the latter technique will require fluoroscopy. The use of intraoperative transthoracic monitoring lines and echo-Doppler limits the need for transvenous pulmonary artery catheters in most cases.

Special Monitoring

Intraoperative Echocardiography

Of the newer techniques available for monitoring patients during pediatric cardiovascular surgery, the most promising is echo-Doppler imaging. Several reports have described the usefulness of intraoperative echo-Doppler imaging during congenital heart surgery.[55-57] Two-dimensional echocardiography combined with pulsed-wave Doppler ultrasonography and color flow mapping is able to provide detailed morphologic as well as physiologic information in the majority of operative cases. Using echo-Doppler in the operating room, anatomic and physiologic data can be obtained before CPB, thus refining the operative plans. Prebypass echo-Doppler precisely defines anesthetic and surgical management.[12,56] Because of the unrestricted epicardial and transesophageal echocardiography (TEE) approaches in anesthetized patients, new findings are frequently discovered and management plans changed accordingly (Fig. 83-4).

Postbypass echo-Doppler evaluation is able to immediately assess the quality of the surgical repair as well as assess cardiac function by examining ventricular wall motion and systolic thickening.[12,56] This technique can show residual structural defects after bypass, which can be immediately repaired in the same operative setting and avoids leaving the operating room with significant residual structural defects that will require reoperation at a later time (Fig. 83-5). By identifying patients with new right ventricular and left ventricular contraction abnormalities after bypass, as determined by a change in wall motion or systolic thickening, echo-Doppler provides guidance for immediate phar-

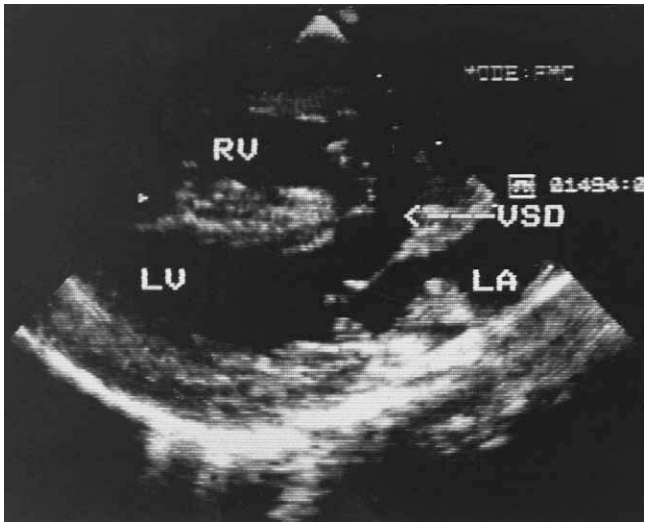

Figure 83-4 Intraoperative pre–cardiopulmonary bypass epicardial echocardiogram in the long-axis view. Note the insertion of the papillary muscle of the tricuspid valve on the interventricular septum. On the basis of this view, the surgeon decided that ventricular septal defect (VSD) closure was possible in a child thought preoperatively to be only a candidate for palliation. LA, left atrium; LV, left ventricle; RV, right ventricle.

macologic interventions. Importantly, postbypass ventricular dysfunction and residual structural defects identified by echo-Doppler are associated with an increased incidence of reoperation and higher morbidity and mortality rate.[58] Thus, this monitoring tool is helpful in assessing surgical outcome and identifying operative risk factors. Whether early identification of these abnormalities, which directs appropriate medical and surgical interventions, will improve outcome remains to be determined.

Two techniques for intraoperative echo-Doppler have been described: epicardial and transesophageal echocardiography (TEE). Using TEE, the probe is placed after induction of anesthesia and intubation and is then available for monitoring of the patient. The advantage of this technique is its utility as a continuous monitor of cardiac structure and function, without interrupting surgery.[12,59] Because of its ideal imaging location, TEE has been especially helpful in evaluating pulmonary venous return and the integrity of the left AV valve after mitral valvuloplasty, complete AV valve repair, and correction of complex congenital heart disease. Early limitation in views has been virtually eliminated as a result of clinical experience and improved biplane images. Pediatric biplane TEE probes have now extended the patient weight limits to neonates between 2.5 and 3 kg.[60] Potential hazards of TEE that merit particular vigilance include descending aorta and airway compression due to probe size or during probe flexion. If a pre-repair TEE is indicated, the probe is removed during the procedure because of concerns about esophageal damage during hypothermia and low or no flow states.

A second technique for intraoperative echocardiographic analysis in children is the epicardial approach.[56,60] This approach requires passing a clean, short-focused 5.0- or 7.0-MHz transducer over the anesthesia screen into a sterile sheath, where it then can be placed on the epicardial surface of the heart. This technique best facilitates the probe manipulations necessary for thorough interrogation of the major structures and dynamic function of the heart. The advantage of this approach is that all views can be obtained in patients of any size. Among the disadvantages are the need for sufficient operator skill and experience to perform the manipulations,[58] the need to interrupt surgery to manipulate the probe, and the possible deleterious impact of direct myocardial mechanical manipulation. With the current TEE capabilities, epicardial imaging is rarely employed.

Specialized Central Nervous System Monitoring

The primary goal of brain monitoring is to improve our understanding of cerebral function and dysfunction during cardiac surgery so that effective brain protection strategies can be developed. Because many of the determinants of normal brain perfusion become externally controlled by the cardiac team during CPB, such as flow rate (cardiac output), perfusion pressure, temperature, hematocrit, and $Paco_2$, a knowledge of the effect of these factors on the brain in neonates, infants, and children is essential. Furthermore, the examination of the brain under unusual biologic circumstances, such as after deep hypothermic circulatory arrest (DHCA) or during continuous-flow CPB at deep hypother-

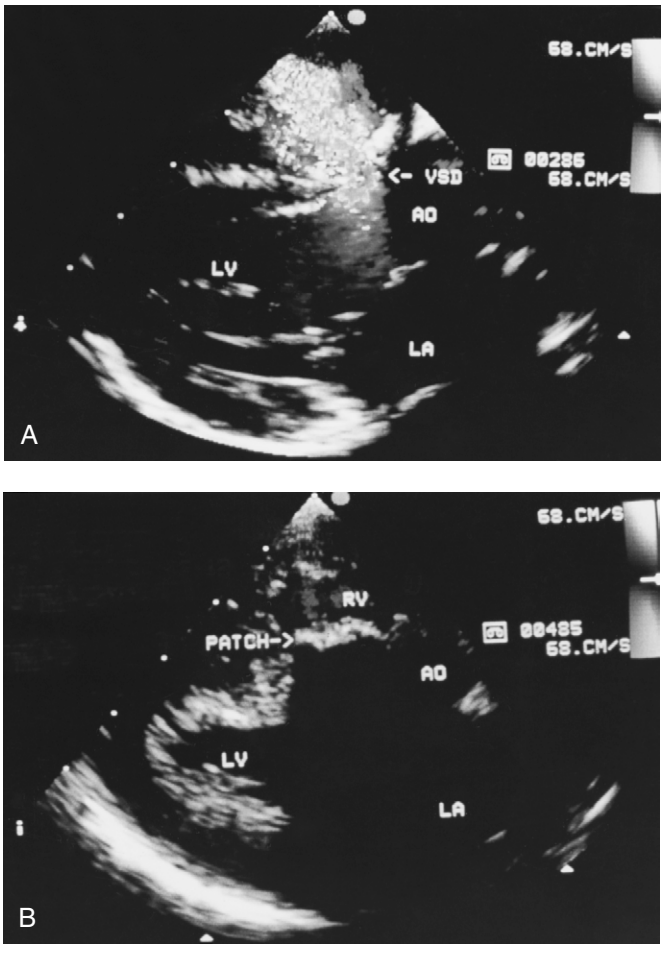

Figure 83-5 **A,** Echocardiogram with a Doppler flow map in the long-axis view illustrating a residual ventricular septal defect (VSD) resulting from patch dehiscence after initial repair. Turbulent flow through the VSD appears as a mosaic of white particles (*arrow*). This finding necessitated immediate reinstitution of cardiopulmonary bypass and re-repair. **B,** Repeat Doppler flow map in the long-axis view illustrates patch closure (*arrow*) of the VSD after re-repair. Note the absence of turbulent flow with the loss of the mosaic of white particles. AO, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

mia (18°C), permits a unique opportunity to describe cerebrovascular physiology and pathophysiology. Numerous intraoperative techniques have been used for monitoring the brain to prevent secondary brain injury due to hypoxia, ischemia, emboli, and electrophysiologic derangements (see Chapter 46). These have primarily included the following three modalities in isolation or combination: (1) near-infrared spectroscopy (NIRS) to provide a measure of venous-weighted, tissue oxyhemoglobin saturation; (2) transcranial Doppler to measure arterial flow and resistance; and (3) electroencephalography (EEG) to assess perfusion-related changes in cortical activity.[61] Additionally, the measurement of CBF and metabolism with specialized clinical research tools has been very important in furthering our understanding of brain function during and after surgery. Multimodal neurologic monitoring is also used to guide the conduct of CPB, DHCA, and regional low flow cerebral perfusion (RLFP) techniques in neonatal arch reconstruction.[62-64]

Electroencephalographic monitoring allows detection of ischemia or recognition of an adequate decrease in cerebral metabolic activity during hypothermia before DHCA. Electroencephalography is helpful in monitoring physiologic functions of the CNS during deep hypothermic bypass and total circulatory arrest. For example, during deep hypothermia and before total circulatory arrest, the processed electroencephalogram (EEG) can identify residual cerebral electrical activity.[65] Isoelectric silence can then be induced by further cooling and any further brain activity detected by electroencephalography. Because this residual electrical activity during arrest is associated with ongoing cerebral metabolism, an isoelectric state may prevent ischemic injury to the brain during circulatory arrest. Electroencephalography may also be useful in detecting the level and depth of anesthesia. Postoperative electroencephalographic analysis has demonstrated subclinical seizure activity in a number of high-risk patients, potentially linking these abnormalities to poorer neuropsychologic outcome. The value of intraoperative electroencephalographic monitoring after CPB and the significance of the findings remain to be determined.

Transcranial Doppler imaging has been used primarily for research purposes in infants and allows detection of venous or arterial flow abnormalities and the detection of microemboli.[66] This technology uses the Doppler principle to detect shifts in the frequency of reflected signals from blood in the middle cerebral artery to calculate blood flow velocity.[67] Because the diameter of this large cerebral artery is relatively constant, flow velocity should approximate that of CBF. Transcranial Doppler imaging has several advantages: (1) It is noninvasive, (2) it does not require radiation exposure, and (3) it is a continuous monitor. An additional advantage of this technique is the capability of assessing rapid alterations in blood flow velocity caused by temperature or perfusion changes, as commonly occur during cardiac surgery. The limitations of transcranial Doppler monitoring include (1) reproducibility, especially at low flows, when minute movement of the patient's head can dramatically alter signal intensity and alter baseline measurements, and (2) the lack of validating studies during hypothermic CPB, when temperature, reduced flow rates, and the laminar flow characteristics of nonpulsatile perfusion may limit the accuracy of CBF velocity measurements. CBF velocity measurements by TCD have reasonable correlation with more standard measures of CBF during normothermia, and some studies have examined its validity during hypothermic CPB.[68]

Transcranial Doppler imaging has been used to investigate the effect of CPB and deep hypothermic circulatory arrest on cerebral hemodynamics in children, as well as to assess the incidence of cerebral emboli. Recent studies examining the brain using TCD have enabled several investigative groups to provide important information regarding questions of normal and abnormal brain perfusion during cardiac surgery in children. Questions regarding cerebral perfusion pressure, autoregulation, effect of $Paco_2$, and temperature have been addressed using transcranial Doppler imaging in children and are discussed subsequently.[68-70] This technique has also provided qualitative information regarding the presence of gaseous emboli in the middle cerebral artery during cardiac surgery.[71,72] Quantification of this important mechanism of cerebral injury during cardiac surgery would be instructive. Future investigations using transcranial Doppler should address this mechanism of injury as well.

Centers with excellent outcomes may report "never" or "always" using NIRS during the perioperative care of neonates with congenital heart disease. Given that cerebral NIRS values have been shown to correlate with jugular venous bulb saturations, the interest in using NIRS as a way to noninvasively assess oxygen delivery to the brain is sensible.[73] Austin and associates have reported the value of monitoring cerebral NIRS intraoperatively. They noted that cerebral oxyhemoglobin desaturation accounted for a majority of neurophysiologic abnormalities during multimodality neuromonitoring using NIRS, transcranial Doppler, and electroencephalography.[74] Over two thirds of the patients in their study had detectable neuromonitoring events, and a similar percentage of these events required intervention by the perfusionist, surgeon, or anesthesiologist. Surgical interventions, such as cannula repositioning, were performed in one fourth of the events, and the perfusionist intervened in over one half of the events. The incidence of postoperative neurologic sequelae was also higher in those patients who had untreated events. During some specific surgical techniques, such as regional cerebral perfusion, NIRS monitoring has also been reported to be of benefit in guiding intraoperative care.[75,76] However, no studies have yet shown that use of NIRS in the postoperative period is associated with improved neurodevelopmental outcomes.

CBF studies using xenon clearance technology have improved the understanding of cerebrovascular dynamics in young children during CPB and especially during deep hypothermia and after periods of circulatory arrest.[77-80] In general, this investigational tool has described the effects of CPB, temperature, and various perfusion techniques on CBF and, indirectly, on brain metabolism (Fig. 83-6). Studies using this methodology have shown that some of the mechanisms of CBF autoregulation, such as pressure-flow regulation, are lost with deep hypothermia and that cerebral reperfusion is impaired after a period of total circulatory arrest.

Induction and Maintenance of Anesthesia

The principles of intraoperative management of cardiothoracic surgical procedures are based on an understanding of the pathophysiology of each disease process and a working knowledge of the effects of the various anesthetic and other pharmacologic interventions on a particular patient's condition. Selecting an induction technique is dependent on the degree of cardiac dysfunction, the cardiac defect, the degree of sedation provided by

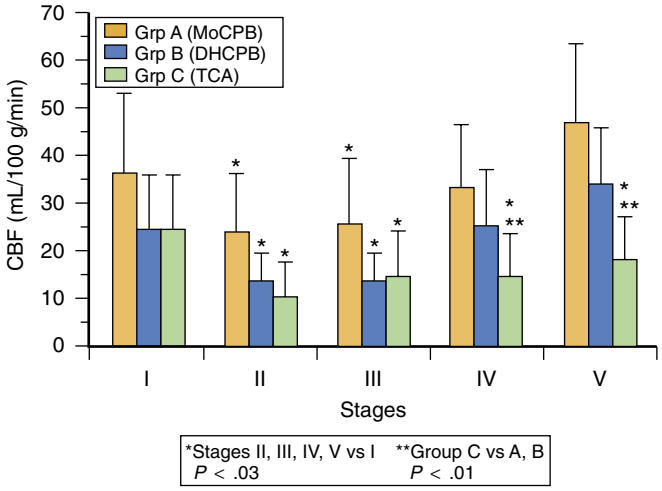

Figure 83-6 Bar chart of the changes in cerebral blood flow (CBF) before, during, and after cardiopulmonary bypass (CPB) in 67 infants and children (mean ± SD). Group A underwent repair with moderate hypothermic bypass (MoCPB) at 28° to 32°C; group B, with deep hypothermic bypass (DHCPB) at 18° to 22°C; and group C, with total circulatory arrest at 18°C. Note the impaired cerebral reperfusion after total circulatory arrest (group C). Stage I, pre-bypass; stages II and III, during hypothermic bypass; stage IV, rewarmed on bypass; stage V, after bypass. (*From Greeley WJ, Brusino FG, Ungerleider RM, et al: The effects of cardiopulmonary bypass on cerebral blood flow in neonates, infants, and children. Circulation 80:I209, 1989.*)

the premedication, and the presence or absence of an indwelling catheter. In children with good cardiac reserve, induction techniques can be quite varied so long as induction is careful and well monitored. The titration of anesthetics for induction of anesthesia is more important than the specific anesthetic technique in patients with reasonable cardiac reserve. A wide spectrum of anesthetic induction techniques have been used safely and successfully, such as sevoflurane, isoflurane, and nitrous oxide; intravenous and intramuscular ketamine; and intravenous propofol, fentanyl, midazolam, and thiopental.[81] For neonates undergoing open-heart surgery, opioid-relaxant inductions are most prevalent, whereas older children with sufficient cardiac reserve typically receive inhalation inductions with either sevoflurane or halothane. Ketamine is often used in anesthetic induction in patients with cyanotic conditions because it increases SVR and cardiac output, thereby diminishing the magnitude of right-to-left shunting. Administration of ketamine can be intravenous or intramuscular. An intramuscular injection may result in pain, agitation, and subsequent arterial desaturation.

Inhalation inductions are generally well received and tolerated by most children. An inhalation induction with sevoflurane can easily and safely be performed even in cyanotic patients such as those with tetralogy of Fallot (Fig. 83-7). In these patients, who are at risk for right-to-left shunting and systemic desaturation, oxygenation is well maintained with a good airway and ventilation despite halothane-induced reduction in systemic arterial pressure.[82] Skilled airway management and efficiency of ventilation are equally essential components of anesthetic induction. Although it is essential to understand the complexities of shunts and vascular resistance changes, airway and ventilation effects on the cardiovascular system are of primary importance during the induction of anesthesia.

After anesthetic induction, intravenous access is established or augmented as appropriate. A nondepolarizing muscle relaxant is usually administered and an intravenous opioid or inhalation agent or both chosen for maintenance anesthesia. The child is preoxygenated with 100% F_{IO_2}, and a lubricated nasal endotracheal tube is carefully positioned. A nasal tube is usually selected because in most patients who require an intraoperative TEE or postoperative mechanical ventilation or both a nasotracheal tube provides greater stability and patient comfort compared with the oral route. Some degree of alveolar preoxygenation is recommended, even in the infant whose systemic perfusion might be jeopardized by lowering PVR with resulting increase in PBF. This maneuver delays desaturation during intubation. If the child arrives in the operating room with an endotracheal tube in place, it is our practice to change it. Inspissated secretions in a tube with a small internal diameter can cause significant obstruction to gas flow. During periods of bypass when humidified ventilation is discontinued, significant endotracheal tube obstruction can occur. This can be minimized by placing a new endotracheal tube at the beginning of the procedure.

Because of the diverse array of congenital heart defects and surgical procedures, an individualized anesthetic management plan is essential. The maintenance of anesthesia in these patients depends on the age and condition of the patient, the nature of the surgical procedure, the duration of the CPB, and the need for postoperative ventilation. An assessment of the hemodynamic objectives designed to lessen the pathophysiologic loading conditions should be developed for each patient, taking advantage of the known qualitative effects of specific anesthetic agents and ventilatory strategies. These individualized plans must also be integrated with the overall perioperative goals to configure the optimal anesthetic. In patients with complex defects requiring preoperative inotropic and mechanical ventilatory support, a carefully controlled hemodynamic induction and maintenance

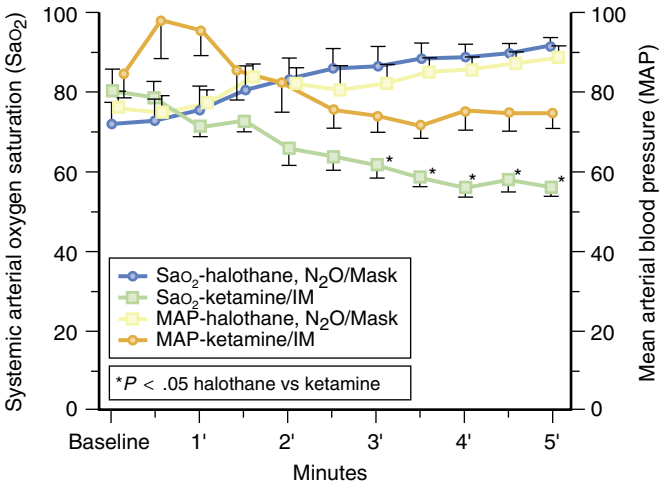

Figure 83-7 Comparative changes in arterial oxygen saturation (Sao_2) and mean arterial pressure (MAP) during mask halothane N_2O ($n = 7$) and intramuscular ketamine ($n = 7$) inductions in children with tetralogy of Fallot at risk for right-to-left shunting. Note the maintenance of Sao_2 in the halothane group despite the significant drop in MAP. (*From Greeley WJ, Bushman GA, Davis DP, Reves JG: Comparative effects of halothane and ketamine on systemic arterial oxygen saturation in children with cyanotic heart disease. Anesthesiology 65:666, 1986.*)

anesthetic with a potent opioid is generally chosen. In patients with a simple ASD or VSD, a potent inhalation agent is preferred as the principal anesthetic agent. This allows for early postoperative extubation and a less prolonged period of intensive care monitoring. More important than the specific anesthetic techniques and drugs is the skilled execution of the anesthetic plan, taking into account patient response to drugs, the changes associated with surgical manipulation, and early recognition of intraoperative complications.

The reported changes in arterial blood pressure and heart rate from the inhaled anesthetic in normal children are observed in pediatric cardiac surgical patients as well. Although both halothane and isoflurane decrease blood pressure in neonates, infants, and children, the vasodilatory properties of isoflurane may improve overall myocardial contractility, compared with the effects of halothane.[83] Despite improved cardiac reserve with isoflurane, the incidence of laryngospasm, coughing, and desaturation during induction of anesthesia limits its use as an induction agent in children with congenital heart defects.[84] The use of potent inhalation agents as primary anesthetics should be reserved for the child with adequate cardiovascular reserve who is a candidate for early postoperative extubation. In these patients, the myocardial depression and hypotension associated with the use of inhalation agents are well tolerated. Examples include closure of an ASD or VSD, excision of a discrete subaortic membrane, pulmonic or aortic stenosis, tetralogy of Fallot, shunts, ligation of a PDA, and repair of coarctation of the aorta.

Desflurane has cardiorespiratory properties similar to those of isoflurane.[85] Its main advantage is low blood gas and tissue solubility. This allows for rapid equilibration between the inspired and alveolar concentrations and rapid decrease of alveolar concentrations during elimination.[86] This provides greater precision in drug dosing during the operative period and may make desflurane a more titratable adjunctive drug for pediatric cardiac anesthesia. The three main disadvantages of desflurane are potency, pungency, and negative inotropic effect.[87,88] Studies in normal infants and children suggest that 1 minimum alveolar concentration (MAC) of desflurane requires concentrations of 8% to 10%.[89,90] Desflurane is also quite pungent and, although its uptake is rapid, early experience with this drug for inhalation induction in children has reported a fairly high incidence of airway reactivity and laryngospasm.[89,91,92] Although its negative inotropic effect is significantly less potent than that of halothane, desflurane should not be used as the sole anesthetic in patients with significant cardiac dysfunction.[92]

Sevoflurane offers a more tolerable aroma without the magnitude of myocardial depression that accompanies halothane.[93] In addition, its blood gas solubility is nearly as low as that of desflurane. Hemodynamically, sevoflurane tends to produce some tachycardia, particularly in older children, and preserve systemic arterial pressure.[94] Reductions in heart rate and systemic arterial pressure are more modest in infants anesthetized with sevoflurane than in control subjects anesthetized with halothane, and the former exhibit echocardiographic evidence of normal contractility and cardiac index.[95,96] Controversies continue to surround the potential toxic by-products of sevoflurane anesthesia, related both to patient metabolism and to the production of Compound A in the anesthesia breathing circuit. Although the importance of Compound A in adult practice remains uncertain, evidence suggests that production of this toxin is significantly diminished in children.[97]

Children with complex congenital heart disease and limited cardiac reserve demand an anesthetic technique that provides hemodynamic stability. Inhalation agents are less well tolerated as a primary anesthetic in patients who have limited cardiac reserve, especially after CPB. Fentanyl is an excellent induction and maintenance anesthetics for this group of patients. Low to moderate doses of this opioid can be supplemented with inhalation anesthetics. Adding low concentrations of inhalation agents to smaller doses of opioids shortens or eliminates the need for postoperative mechanical ventilation while maintaining the advantage of intraoperative hemodynamic stability. Postoperative mechanical ventilation will be required when a high-dose opioid technique is used. The hemodynamic effects of fentanyl at a dose of 25 μg/kg with pancuronium given to infants in the postoperative period after operative repair of a congenital heart defect include no change in LAP, pulmonary artery pressure, PVR, and cardiac index and a small decrease in SVR and mean arterial pressure.[98] Higher doses of fentanyl at 50 to 75 μg/kg with pancuronium result in a slightly greater fall in arterial pressure and heart rate in infants undergoing repair for complex congenital heart defects.[99] Despite the wide safety margin exhibited by this opioid, a selected population of infants and children with marginally compensated hemodynamic function sustained by endogenous catecholamines may manifest more extreme cardiovascular changes with these doses. Fentanyl has also been shown to block stimulus-induced pulmonary vasoconstriction and contributes to the stability of the pulmonary circulation in neonates after congenital diaphragmatic hernia repair.[100] Thus, the use of fentanyl may be extrapolated to the operating room, where stabilizing pulmonary vascular responsiveness in newborns and young infants with reactive pulmonary vascular beds is crucial to weaning from CPB and stabilizing shunt flow.

Sufentanil and pancuronium provide the same cardiovascular stability as with fentanyl and pancuronium in pediatric cardiovascular patients. Children receiving a sufentanil induction as a single dose of 5 to 20 μg/kg have a stable preintubation period.[101,102] Intubation and other stimuli such as sternotomy do not produce clinically significant alterations in hemodynamics, although changes are greater than with equipotent doses of fentanyl. The use of fentanyl as an infusion (0.1 μg/kg/min) produces fewer alterations in heart rate and blood pressure. This is particularly important in infants, in whom significant hemodynamic changes are poorly tolerated. For neonates with critical congenital heart disease, sufentanil anesthetic and postoperative infusion have been shown to reduce morbidity after cardiac surgery when compared with a halothane anesthetic and routine morphine postoperatively.[103] The blunting of the stress response observed in this study probably accounted for the differences in morbidity; there was no comparison group representing a more typical dose of a phenylpiperidine opioid (e.g., fentanyl, 0-75 μg/kg) to permit conclusions as to whether such large opioid doses are optimal.

Compared with other agents in its class, remifentanil, a newer ultrashort-acting opioid, offers the unique advantage of metabolism via nonspecific and tissue esterases, thereby limiting the potential for accumulation related to protracted elimination.[104] Remifentanil may provide advantages in the selected group of patients for whom the blunting of endogenous responses is desirable intraoperatively but potentially deleterious at the end of the procedure. A randomized controlled trial comparing equipotent doses of alfentanil and remifentanil for outpatient pediatric surgery revealed delayed emergence, requiring naloxone only

in the alfentanil group.[105] In both adults and children, remifentanil is associated with qualitative hemodynamic changes similar to other opioids, a variable tendency to bradycardia, and a small reduction in systolic blood pressure.[105-107]

Because of the widespread use of the opioids for pediatric cardiac surgery and the availability of invasive monitoring, the pharmacokinetics and pharmacodynamics of these drugs have been well studied.[102,108] In general, the clinical pharmacology of fentanyl and sufentanil share the same age-related pharmacokinetic and pharmacodynamic features. For example, sufentanil has increased clearance in patients aged 1 month to 12 years, comparable adult clearance in adolescents (12 to 16 years of age), and decreased clearance during the neonatal period (newborn to 1 month) (Table 83-9).[91,96] Furthermore, sequential sufentanil anesthetics in neonates with congenital heart disease show marked increases in clearance and elimination between the first week and the third or fourth week of life (Fig. 83-8).[97] The latter observation is most likely attributable to maturational changes in hepatic microsomal activity and improved hepatic blood flow from closure of the ductus venosus. The variability in clearance and elimination, coupled with limited cardiovascular reserve in the neonate during the first month of life, makes opioid dosing difficult in this age group. Careful titration of 5 to 10 µg/kg of fentanyl or 1 to 2 µg/kg of sufentanil or a continuous infusion technique provides the most reliable method of achieving hemodynamic stability and an accurate dose response. CPB, different institutional anesthetic practices, and individual patient differences influence pharmacokinetic and pharmacodynamic disposition of the opioids in ways that are not predictable. Even certain disease states such as tetralogy of Fallot[98] or pathophysiologic conditions such as increased intra-abdominal pressure[99] alter pharmacokinetic processes.

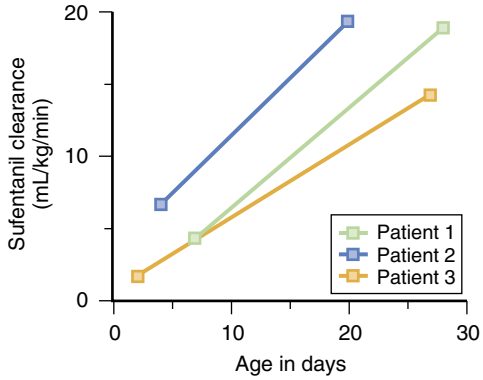

Figure 83-8 Sequential sufentanil clearance during the first month of life in three neonates with congenital heart disease. Clearance of sufentanil increases above adult rates within the neonatal period. (*Data from Greeley WJ, de Bruijn NP: Changes in sufentanil pharmacokinetics within the neonatal period. Anesth Analg 67:86, 1988.*)

Cardiopulmonary Bypass

Differences between Adult and Pediatric Cardiopulmonary Bypass

The physiologic effects of CPB on neonates, infants, and children are significantly different than the effects on adults (Table 83-10). During CPB, pediatric patients are exposed to biologic extremes not seen in adults, including deep hypothermia (18°C), hemodilution (threefold to fivefold greater dilution of circulating blood volume), low perfusion pressures (20 to 30 mm Hg), wide variation in pump flow rates (ranging from highs of 200 mL/kg/min to total circulatory arrest), and differing blood pH management techniques (α-stat or pH-stat, or both sequentially). These parameters significantly differ from those of normal physiology and affect preservation of normal organ function during and after CPB. In addition to these prominent changes, subtle variations in glucose supplementation, cannula placement, presence of aortopulmonary collaterals, and patient age may be important factors affecting organ function during CPB.

Adult patients are infrequently exposed to these biologic extremes. In adult cardiac patients, temperature is rarely lowered below 25°C, hemodilution is more moderate, perfusion pressure is generally maintained at 50 to 80 mm Hg, flow rates are maintained at 50 to 65 mL/kg/min, and pH management strategy is less influential because of moderate hypothermic temperatures and rare use of circulatory arrest. Variables such as glucose supplementation rarely pose a problem in adult patients owing to large hepatic glycogen stores. Venous and arterial cannulas are larger and less deforming of the atria and aorta, and their placement is more predictable. Although superficially similar, the conduct of CPB in children is considerably different from that in adults. One would therefore expect marked physiologic differences in the response to CPB in children. Additionally, there are several modifiable intraoperative factors that can influence neuropsychologic morbidity (Table 83-11).

Table 83-9 Sufentanil Pharmacokinetics in Pediatric Cardiovascular Patients*

Age Group	t½α (min)	t½β (min)	Clearance (mL/kg/min)	Vd_{ss} (L/kg)
1-30 days	23 ± 17	737 ± 346	6.7 ± 6.1	4.2 ± 1.0
1-24 mo	16 ± 5	214 ± 41	18.1 ± 2.7	3.1 ± 1.0
2-12 yr	20 ± 6	140 ± 30	16.9 ± 2.2	2.7 ± 0.5
12-18 yr	20 ± 6	209 ± 23	13.1 ± 0.4	2.7 ± 0.5

t½α, slow distribution half-life; t½β, elimination half-life; Vd_{ss}, volume of distribution at steady state.
*All values are mean ± standard deviations (see reference 39).

Priming Volume

The priming solutions used in pediatric CPB take on great importance because of the disproportionately large priming volume/blood volume ratio in children. In adults, the priming volume is equivalent to 25% to 33% of the patient's blood volume, whereas in neonates and infants the priming volume may exceed the patient's blood volume by 200%. With contemporary low-volume bypass circuits (e.g., small volume oxygenators, smaller tubing), priming volume is not more than one blood volume in a small neonate. Care must be taken, therefore, to achieve a physiologically balanced priming solution and limit the volume as much as possible. Most pediatric priming solutions, however, have quite

Table 83-10 Differences between Adult and Pediatric Cardiopulmonary Bypass

Parameter	Adult	Pediatric
Hypothermic temperature	Rarely below 25-30°C	Commonly 15-20°
Use of total circulatory arrest	Rare	Common
Pump prime Dilution effects on blood volume Additional additives in pediatric primes	 25-33%	 150-300% Blood, albumin
Perfusion pressures	50-80 mm Hg	20-50 mm Hg
Influence of α- vs. pH-stat management strategy	Minimal at moderate hypothermia	Marked at deep hypothermia
Measured $Paco_2$ differences	30-45 mm Hg	20-80 mm Hg
Glucose regulation Hypoglycemia Hyperglycemia	 Rare—requires significant hepatic injury Frequent—generally easily controlled with insulin	 Common—reduced hepatic glycogen stores Less common—rebound hypoglycemia may occur

variable levels of electrolytes, calcium, glucose, and lactate. Electrolytes, glucose, and lactate levels may be quite high if the solution includes large amounts of banked blood or quite low if a minimal amount of banked blood is added. Calcium levels are generally very low in pediatric priming solutions; this may contribute to the rapid slowing of the heart with the initiation of bypass.

The main constituents of the priming solution include crystalloid, banked blood (to maintain a temperature-appropriate hematocrit), and colloid. Other supplements that may be added to the prime are mannitol, a buffer (sodium bicarbonate or trishydroxymethylaminomethane [THAM]), and steroids. Many institutions add colloid or fresh frozen plasma to the pump prime in neonates and small infants or use whole blood in the priming solution. Low concentrations of plasma proteins have been shown experimentally to impair lymphatic flow and alter pulmonary function by increasing capillary leak.[109] Although adding albumin to the pump prime has not been shown to alter outcome in adults during CPB, one study suggested that maintaining normal colloid osmotic pressure may improve survival in infants undergoing CPB.[110,111]

Table 83-11 Central Nervous System Injury and Potential Modifiable Intraoperative Factors

Air or particulate embolus
Rate and depth of core cooling (if utilized)
Deep hypothermic circulatory arrest (if utilized)
Reperfusion injury and inflammation
Rate of core rewarming/hyperthermia
Hyperglycemia
Hyperoxia
pH management during cardiopulmonary bypass
Hematocrit management during cardiopulmonary bypass

The addition of fresh frozen plasma or whole blood (see Chapter 55) is an attempt to restore the level of procoagulants, which are severely diluted with CPB in infants. For neonates and infants, blood must be added to the priming solution. Most institutions use packed red blood cells, but some use whole blood. The use of whole blood supplements both red blood cells and the coagulation factors with a single donor exposure. In fact, low-volume bypass circuits may enable perfusionists and anesthesiologists to share a single unit of whole blood, thereby limiting the donor exposure to one throughout the entire perioperative course.

The addition of any blood products will cause a much higher glucose load in the priming solution. Hyperglycemia may increase the risk of neurologic injury if brain ischemia occurs. Mannitol is added to promote an osmotic diuresis and to scavenge oxygen free radicals from the circulation. Steroids are added to stabilize membranes to produce the theoretical advantage of reducing ion shifts during periods of ischemia. Steroids, however, may raise glucose levels, and this may be detrimental if there is a period of cerebral ischemia. Steroids remain one of the more controversial additives in priming solutions.

Temperature

Hypothermic CPB is used to preserve organ function during cardiac surgery. Three distinct methods of CPB are used: moderate hypothermia (25°C to 32°C), deep hypothermia (18°C), and DHCA. The choice of method of bypass is based on the required surgical conditions, patient size, the type of operation, and the potential physiologic impact on the patient.

Moderate hypothermic CPB is the principal method of bypass employed for older children and adolescents. In these patients, venous cannulas are less obtrusive and the heart can easily accommodate superior and inferior vena cava cannulation. Bicaval cannulation reduces right atrial blood return and improves the surgeon's ability to visualize intracardiac anatomy. Moderate hypothermia may also be chosen for less demanding cardiac repairs in infants, such as an ASD or an uncomplicated VSD. Most surgeons are willing to cannulate the inferior and superior venae cavae in neonates and infants. In these patients, however, this approach is technically more difficult and likely to induce

brief periods of hemodynamic instability. Additionally, the pliability of the venae cavae and the rigidity of the cannulas may result in caval obstruction, impaired venous drainage, and elevated venous pressure in the mesenteric and cerebral circulation.

Deep hypothermic CPB is generally reserved for neonates and infants requiring complex cardiac repair. However, certain older children with complex cardiac disease or severe aortic arch disease benefit from deep hypothermic temperatures. For the most part, deep hypothermia is selected to allow the surgeon to operate under conditions of low-flow CPB or total circulatory arrest. Low pump flows (50 mL/kg/min) improve the operating conditions for the surgeon by providing a nearly bloodless field. DHCA allows the surgeon to remove the atrial or aortic cannula. If this technique is used, surgical repair is more precise because of the bloodless and cannula-free operative field. Arresting the circulation, even at deep hypothermic temperatures, introduces the concern of how well deep hypothermia preserves organ function, with the brain being at greatest risk.[112]

Hemodilution

Hemodilution has been used during CPB to decrease homologous blood use and has been thought to improve microcirculatory flow by reducing blood viscosity. Although hemoconcentrated blood has an improved oxygen-carrying capacity, its viscosity reduces efficient flow through the microcirculation. With hypothermic temperatures, blood viscosity increases significantly and flow decreases. Hypothermia, coupled with the nonpulsatile flow of CPB, impairs blood flow through the microcirculation. Blood sludging, small vessel occlusion, and multiple areas of tissue hypoperfusion may result. Therefore, hemodilution is an important consideration during hypothermic CPB. The appropriate level of hemodilution for a given hypothermic temperature, however, is not well defined. However, hemodilution also reduces perfusion pressure, increases CBF thereby potentially increasing the microembolic load to the brain, and reduces the oxygen-carrying capacity of blood.[113] Using an animal model, one group of investigators found that extreme hemodilution to a hematocrit less than 10% resulted in inadequate oxygen delivery, but with higher hematocrit levels of 30% there was improved cerebral recovery after DHCA.[114] Jonas and colleagues[115] confirmed these findings in a randomized trial using two hemodilution protocols (20% versus 30% hematocrit) in infants younger than 9 months of age. Developmental outcomes were assessed at follow-up at 1 year of age with the Bayley Scales of Infant Development. In the short term, the lower-hematocrit group had lower nadirs of cardiac index, higher serum lactate levels 1 hour after CPB, and a greater increase in total body water on the first postoperative day. At 1 year of age, mental development index scores were similar but psychomotor development index scores were significantly lower in the lower hematocrit group. Also, infants in the lower hematocrit group had psychomotor development scores that were 2 standard deviations below the mean. Because red blood cells serve as the major reservoir of oxygen during circulatory arrest, especially during rewarming, hematocrit values closer to 30% are generally preferred for deep hypothermia when this technique is contemplated. Currently, most centers maintain hematocrit levels around 25% to 30% during CPB, enhancing oxygen delivery to vital organs such as the brain. Cerebral oxygen delivery is an especially important consideration, because cerebral autoregulation is impaired at deep hypothermic temperatures and after DHCA.

To achieve a hematocrit level of 25% to 30% in neonates and infants, banked blood should be added to the priming solution. The mixed hematocrit level on CPB (the hematocrit level of the total priming volume plus the patient's blood volume) can be calculated by the following formula:

$$HCT_{CBP} = \frac{BV_{pt} \cdot HCT_{pt}}{BV_{pt} + TPV}$$

where Hct_{CPB} is the mixed hematocrit (TPV + BV_{pt}), BV_{pt} is the patient's blood volume (weight in kilograms × estimated blood volume in milliliters per kilogram), TPV is the total priming volume, and Hct_{pt} is the starting hematocrit level of the patient. This calculation allows an estimate of the hematocrit level of the patient using an asanguineous priming solution and is therefore useful for older children and adolescents. In neonates and infants, the perfusionist must add blood to the pump prime to achieve a desired hematocrit level during hypothermic CPB. The following formula estimates the amount of packed red blood cells (RBCs) in mL that must be added to the prime volume to achieve this hematocrit level:

$$\text{Added RBCs (mL)} = \left(BV_{pt} + TPV\right)\left(Hct_{desired}\right) - \left(BV_{pt}\right)\left(Hct_{pt}\right)$$

where BV_{pt} is the patient's blood volume, TPV is the total priming volume, $Hct_{desired}$ is the desired hematocrit level on CPB, and Hct_{pt} is the starting hematocrit level of the patient.

Currently, no evidence exists for defining the optimal hematocrit level after weaning from CPB. Decisions concerning post-CPB hematocrit levels are made based on the patient's post-repair function and anatomy. Patients with residual hypoxemia or those with moderate to severe myocardial dysfunction benefit from the improved oxygen-carrying capacity of hematocrit levels of 40% or higher. Patients with a physiologic correction and excellent myocardial function may tolerate hematocrit levels of 25% to 30%.[116] In children with mild to moderate myocardial dysfunction, accepting hematocrit values between these levels seems prudent. Therefore, in patients with physiologic correction, moderately good ventricular function, and hemodynamic stability, the risks associated with blood and blood product transfusion should be strongly considered during the immediate postbypass period.

Blood Gas Management

The theoretical benefit of α-stat versus pH-stat blood gas management during hypothermic CPB has been a topic of great debate (see Chapter 49). Although the pH-stat strategy may not be optimal for adults in whom the principal risk for brain injury is microembolism, this risk is thought to be lower in infants due to the lack of atherosclerotic disease. With pH-stat management, the addition of CO_2 to the inspired gas mixture during cooling on CPB increases CBF and may improve cerebral tissue oxygenation and outcomes.

The controversial issue of pH management during CPB has been addressed in a large study from Boston Children's Hospital. In this study, infants younger than 9 months of age were randomized to α-stat versus pH-stat during deep hypothermic CPB with excellent long-term follow-up.[117,118] Neurodevelopmental

outcomes were evaluated in infants undergoing biventricular repair for a variety of cardiac defects when younger than 9 months of age. The short-term benefits identified with the pH-stat strategy included a trend toward less postoperative morbidity and shorter recovery time to first electroencephalographic activity. In patients with transposition of the great arteries, there was a shorter duration of intubation and intensive care unit stay in patients.[118] However, the use of either the α-stat or pH-stat strategies was not consistently related to either improved or impaired neurodevelopmental outcomes at 2- and 4-year follow-up.[117]

Initiation of Cardiopulmonary Bypass

Arterial and venous cannula in the heart before initiating CPB may result in significant problems in the peri-bypass period. A malpositioned venous cannula has the potential for vena cava obstruction. The problems of venous obstruction are magnified during CPB in the neonate because arterial pressures are normally low (20 to 40 mm Hg), and large, relatively stiff cannulas easily distort these very pliable venous vessels.[109,110] A cannula in the inferior vena cava may obstruct venous return from the splanchnic bed, resulting in ascites from increased hydrostatic pressure or directly reduced perfusion pressure across the mesenteric, renal, and hepatic vascular beds. Significant renal, hepatic, and gastrointestinal dysfunction may ensue and should be anticipated in the young infant with unexplained ascites. Similar cannulation problems may result in superior vena cava obstruction. This condition may be more ominous during bypass. Under these circumstances, three problems may ensue: (1) cerebral edema, (2) a reduction in regional or global CBF, and (3) reduced proportion of pump flow reaching the cerebral circulation, causing inefficient brain cooling.

In the operating room, superior vena cava pressures via an internal jugular catheter should be monitored by examining the patient's head for signs of suffusion after initiating bypass. Discussions with the perfusionist regarding adequacy of venous return and large cooling gradients between the upper and lower body should alert the anesthesiologist and the surgeon to potential venous cannula problems. Patients with anomalies of the large systemic veins (persistent left superior vena cava or azygous continuation of an interrupted inferior vena cava) are at particular risk for problems with venous cannulation and drainage.

Problems with aortic cannula placement can also occur. The aortic cannula may slip beyond the takeoff of the innominate artery and therefore selectively flow to the right side of the cerebral circulation. Also, the position of the tip of the cannula may promote preferential flow down the aorta or induce a Venturi effect to steal flow from the cerebral circulation. This problem has been confirmed during CBF monitoring by the appearance of large discrepancies in flow between the right and left hemispheres after initiating CPB. The presence of large aortic to pulmonary collaterals, such as a large PDA, may also divert blood to the pulmonary circulation from the systemic circulation, thereby reducing CBF and the efficiency of brain cooling during CPB. The surgeon should gain control of the ductus either before or immediately after instituting CPB to eliminate this problem and, if possible, large aortopulmonary collaterals should be embolized in the cardiac catheterization laboratory before the operative procedure. Neonates with significant aortic arch abnormalities (e.g., aortic atresia, interrupted aortic arch) may require radical modifications of cannulation techniques, such as placing the arterial cannula in the main pulmonary artery and temporarily occluding the branch pulmonary arteries to perfuse the body via the PDA, or even dual arterial cannulation of both the ascending aorta and main pulmonary artery. Such adaptations require careful vigilance to ensure effective, thorough perfusion and cooling of vital organs.

Once the aortic and venous cannulas are positioned and connected to the arterial and venous limb of the extracorporeal circuit, bypass is initiated. The arterial pump is slowly started, and, once forward flow is ensured, venous blood is drained into the oxygenator. Pump flow rate is gradually increased until full circulatory support is achieved. If venous return is diminished, arterial line pressure high, or mean arterial pressure excessive, pump flow rates must be reduced. High line pressure and inadequate venous return are usually caused by malposition or kinking of the arterial and venous cannulas, respectively. The rate at which venous blood is drained from the patient is determined by the height difference between the patient and the oxygenator inlet and the diameter of the venous cannula and line tubing. Venous drainage can be increased by using vacuum-assisted drainage under certain circumstances.

In neonates and infants, deep hypothermia is commonly used. For this reason, the pump prime is kept cold (18°C to 22°C). When the cold perfusate contacts the myocardium during the institution of CPB, heart rate slows immediately and contraction is impaired. The contribution of total blood flow pumped by the infant's heart rapidly diminishes. Therefore, to sustain adequate systemic perfusion at or near normothermic temperatures, the arterial pump must reach full flows quickly.

CPB is initiated in neonates and infants by beginning the arterial pump flow first. Once aortic flow is ensured, the venous line is unclamped and blood is siphoned out of the right atrium into the inlet of the oxygenator. Flowing before unclamping the venous line prevents the potential problem of exsanguination if aortic dissection or misplacement of the aortic cannula occurs. Neonates and infants have a low blood volume/priming volume ratio, and intravascular volume falls precipitously if the venous drainage precedes aortic inflow. Once the aortic cannula position is verified, pump flow rates are rapidly increased to maintain effective systemic perfusion. Because coronary artery disease is rarely a consideration, the myocardium should cool evenly unless distortion caused by the cannulas compromises the coronary arteries. When a cold prime is used, caution must be exercised in using the pump to infuse volume before initiating CPB. Infusion of cold perfusate may result in bradycardia and impaired cardiac contractility before the surgeon is prepared to initiate CPB.

Once CPB is begun, careful observation should be focused to ensure appropriate circuit connections, myocardial perfusion, and optimal cardiac decompression. Ineffective venous drainage can rapidly result in ventricular distention. This is especially true in infants and neonates, in whom ventricular compliance is low and the heart is relatively intolerant of excessive preload augmentation. If ventricular distention occurs, pump flow must be reduced and the venous cannula repositioned. Alternatively, the heart may be decompressed by placing a cardiotomy suction catheter or small vent in the appropriate chamber.

Pump Flow Rates

Recommendations for optimal pump flow rates for children have historically been based both on the patient's body mass and on evidence of efficient organ perfusion as determined by arterial blood gases, acid-base balance, and whole-body oxygen consumption during CPB.[65,119] At hypothermic temperatures, metabolism is reduced, and CPB flow rates can therefore be reduced and still meet or exceed the tissue's metabolic needs (see the discussion of low-flow CPB in the following section).

Special Techniques

Deep Hypothermic Circulatory Arrest

There are a certain subset of neonates, infants, and children with congenital heart disease who require extensive repair of complex congenital heart defects using DHCA. This technique facilitates precise surgical repair under optimal conditions and free of blood or cannulas in the operative field, providing maximal organ protection and often resulting in shortened total CPB time. The scientific rationale for the use of deep hypothermic temperatures rests primarily on a temperature-mediated reduction of metabolism. Whole-body and cerebral oxygen consumption during induced hypothermia decreases the metabolic rate for oxygen by a factor of 2 to 2.5 for every 10°C reduction in temperature.[120] These results are consistent with in-vitro models, which relate temperature reduction to a decrease in the rate constant of chemical reactions, as originally described by Arrhenius using the equation $k = Ae^{-RT}$. The reduction in oxygen supply during deep hypothermic low-flow CPB is associated with preferential increases in vital organ perfusion (e.g., to the brain) and increased extraction of oxygen.[121] Therefore, to some extent, deep hypothermic low-flow CPB exerts a protective effect by reducing the metabolic rate for oxygen, promoting preferential organ perfusion, and increasing tissue oxygen extraction.

The duration of the safe period of DHCA has not clearly been delineated.[122] Although all organ systems are at risk for the development of ischemic and reperfusion injury, as manifested by lactate and pyruvate production during DHCA, the brain appears to be the most sensitive to and the least tolerant of these effects. Brainstem and cortical evoked potentials as well as processed electroencephalograms are altered after DHCA.[122-124] The abnormalities in the evoked potentials appear to be related to the duration of DHCA and are attributed to altered metabolism. During reperfusion after the arrest period, CBF and metabolism remain depressed in neonates and small infants (Fig. 83-9; also see Fig. 83-6).[77] Importantly, during the use of these extremes of temperature, it appears that autoregulation is lost and cerebral perfusion becomes highly dependent on the conduct of extracorporeal perfusion and presumably post-bypass hemodynamic performance.

The potentially deleterious effects of prolonged DHCA in infants and neonates are well described. In general, it is agreed that very prolonged periods of uninterrupted DHCA may have adverse neurologic outcomes. However, there is considerable disagreement if a "safe" period of DHCA exists and whether patient-specific, procedure-specific, or postoperative management strategies may attenuate or promote CNS damage from DHCA. There are some reports of detrimental effects of DHCA

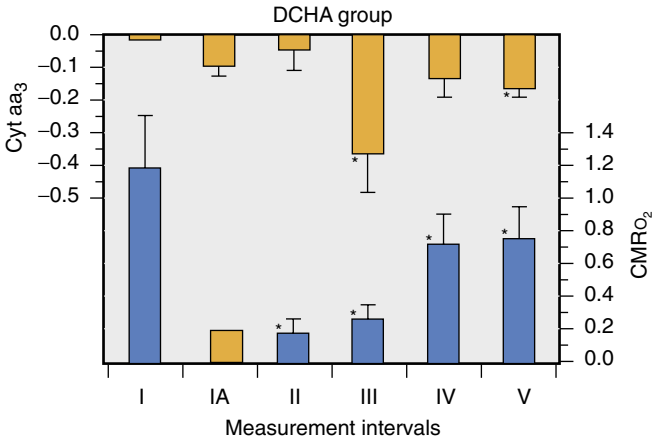

Figure 83-9 Bar graph of variations in cytochrome oxidase (cyt aa_3) near-infrared spectroscopic signals and cerebral metabolic rate for oxygen ($CMRO_2$) in subjects with deep hypothermic circulatory arrest (DHCA). Each point of cyt aa_3 represents mean ± SE in six subjects; $CMRO_2$ values are mean ± SD. Negative values in cyt aa_3 represent relative decreases in quantity of oxidized enzyme. *, $CMRO_2$ and cyt aa_3 are significantly different from control, $P \pm .05$.

on a variety of outcomes regarding the central nervous system and others on either an inconsistent effect or no effect.[118,125-128] Three issues have become clear over time: (1) The effects of short durations of DHCA are inconsistently related to adverse outcomes, (2) the effect of DHCA is not a linear phenomenon, and (3) the effects are most likely modified by other patient-related, preoperative, and postoperative factors.[128-130] Because many studies suggest a negative effect, some surgeons have developed innovative and challenging strategies to provide continuous cerebral perfusion during complex reconstruction of the aortic arch or intracardiac repair to avoid or minimize the use of DHCA. It should be emphasized that by avoiding DHCA, the duration of CPB is necessarily lengthened and longer durations of CPB have been shown to adversely effect both short- and long-term outcomes.[130] The relative risks and benefits of longer CPB versus less (or no) DHCA remain a subject of continued controversy.

Regional Cerebral Perfusion

Some surgeons have developed innovative and challenging strategies to provide continuous cerebral perfusion during complex reconstruction of the aortic arch or intracardiac repair to avoid or minimize the use of DHCA. However, avoiding DHCA, the duration of CPB is necessarily lengthened and longer durations of CPB have been shown to adversely effect both short and long-term outcomes.[59,60] The relative risks and benefits of longer CPB versus less (or no) DHCA remain a subject of continued controversy. In efforts to study this newer strategy, two recent studies have evaluated the technique of regional cerebral perfusion. In one nonrandomized study from Boston, Wypij and colleagues followed 29 infants who underwent a stage I palliation, 9 of whom received regional cerebral perfusion at 30 to 40 mL/kg/min.[131] The authors reported no difference in mental or psychomotor developmental indices at 1 year of age between the regional cerebral perfusion group and those who received DHCA as a primary strategy. A group from the University of Michigan has published a larger, randomized trial of DHCA ± regional cerebral perfusion

at 20 mL/kg/min in patients with a functional single ventricle, with long-term studies that are in the planning stages.[132] A total of 77 patients were enrolled with similar survival to hospital discharge (88%) and at 1-year follow-up (75%). No significant difference was seen in either the psychomotor development index or the mental development index scores between the two groups at any time points, although the scores tended to be lower in the regional cerebral perfusion group.

Glucose Regulation

A substantial amount of clinical and experimental data has shown conclusive evidence of the detrimental effects of hyperglycemia during complete, incomplete, and focal cerebral ischemia.[133,134] The role of glucose in potentiating cerebral injury appears to rest on two factors: adenosine triphosphate (ATP) utilization and lactic acidosis.[135,136] The anaerobic metabolism of glucose requires phosphorylation and the expenditure of two molecules of ATP before ATP production can occur. This initial ATP expenditure may result in a rapid depletion of ATP and may explain why hyperglycemia worsens neurologic injury. Lactic acidosis is also important in glucose-augmented cerebral injury. Its important role, however, may be as a glycolytic enzyme inhibitor. Lactate slows anaerobic ATP production by inhibiting glycolysis immediately after ATP is consumed in the phosphorylation of glucose.[137]

A strong scientific argument can be made for the detrimental effects of hyperglycemia during ischemia, but there is very little evidence supporting a relationship between a worsening neurologic outcome and hyperglycemia during CPB or DHCA in children. Although a retrospective review of 34 children undergoing DHCA suggested a worse neurologic outcome in the hyperglycemic children, the results were reported as a nonsignificant statistical trend.[138] A review of acquired neurologic lesions in patients undergoing the Norwood stage I procedure for hypoplastic left heart syndrome suggested hyperglycemia as a significant associated finding in patients with extensive cerebral necrosis or intraventricular hemorrhage. A host of other potentially damaging factors (e.g., periods of hypoxia, low diastolic and systolic pressure, thrombocytopenia) were statistically associated with the observed neuropathology.[139] Because hyperglycemia accompanies a generalized stress response, this literature failed to distinguish whether glucose directly contributes to neurologic injury or merely serves as a marker for a high-risk population that ultimately suffers neurologic insult as a result of other factors.

Hypoglycemia is a frequent concern in neonates during the perioperative period. Reduced hepatic gluconeogenesis coupled with decreased glycogen stores places the newborn at increased risk for hypoglycemic events. In newborns with congenital heart disease, reduced systemic perfusion (e.g., critical coarctation, hypoplastic left heart syndrome, critical aortic stenosis) may result in worsening hepatic biosynthesis, further impairing glucose production. These patients may be fully dependent on exogenous glucose; therefore, it is not uncommon for them to require 20% to 30% dextrose infusions to maintain euglycemia in the pre-bypass period. Older children are not immune to hypoglycemic events and are therefore susceptible to hypoglycemia-induced neurologic injury. Patients with low cardiac output states (cardiomyopathies, pretransplant patients, critically ill postoperative patients) requiring reoperation and when on substantial inotropic support are at risk for reduced glycogen stores and intraoperative hypoglycemia.[140]

The impact of hypoglycemia during CPB is further complicated by the consequences of hypothermia, CO_2 management, and other factors that may modify normal cerebrovascular responses during bypass. In a dog model, insulin-induced hypoglycemia to 30 mg/dL did not alter the electroencephalographic findings. However, after 10 minutes of hypocapnic hypoglycemia, the EEG became flat.[141] When regional blood flow was examined in these animals, cortical and hippocampal blood flow remained normal whereas other regions of the brain had reduced flow. The loss of electroencephalographic activity from hypoglycemia alone does not normally occur above glucose levels of 8 mg/dL.[142]

During deep hypothermic CPB and DHCA, CBF and metabolism are altered. The additive effect of hypoglycemia, even if mild, may cause alterations in cerebral autoregulation and culminate in increased cortical injury.[139] The common practice of using hyperventilation to reduce PVR in neonates and infants during weaning from CPB and in the early post-bypass period can further exacerbate hypoglycemic injury. Glucose monitoring and rigid maintenance of euglycemia are an important part of CPB management in the patient with congenital heart disease.

Renal Effects

After CPB, the combined effects of hypothermia, nonpulsatile perfusion, and reduced mean arterial pressure cause release of angiotensin, renin, catecholamines, and antidiuretic hormones.[143-145] These circulating hormones promote renal vasoconstriction and reduce renal blood flow. However, despite the negative impact of CPB on renal function, studies have been unable to link low-flow, low-pressure, nonpulsatile perfusion with postoperative renal dysfunction (Table 83-12).[143] The factors that best correlate with postoperative renal dysfunction are preoperative renal dysfunction and profound reductions in post-CPB cardiac output. Preoperative factors include primary renal disease,

Table 83-12 Sequelae of Pediatric Cardiopulmonary Bypass

End-Organ Injury	Etiology/Signs
Renal injury	Organ immaturity, preexisting renal disease Post-cardiopulmonary bypass low CO, use of DHCA Renal dysfunction characterized by reduced GFR and ATN
Pulmonary injury	Endothelial injury, increased capillary leak, complement activation, and leukocyte degranulation Pulmonary dysfunction characterized by reduced compliance, reduced FRC, and increased A-a gradient
Cerebral injury after DHCA	Loss of autoregulation, suppressed metabolism and cerebral blood flow, cellular acidosis, and cerebral vasoparesis CNS dysfunction characterized by seizures, reduced developmental quotients, choreoathetosis, learning disabilities, behavioral abnormalities

A-a, alveolar-arterial; ATN, acute tubular necrosis; CNS, central nervous system; CO, cardiac output; DHCA, deep hypothermic circulatory arrest; FRC, functional residual capacity; GFR, glomerular filtration rate.

low cardiac output, and dye-related renal injury after cardiac catheterization.[145]

The incidence of acute renal insufficiency after pediatric cardiac surgery is approximately 8%. Multiple causative factors are involved, and the final common result is oliguria and an elevated serum creatinine. Diuretics have been the mainstay of promoting urine flow after pediatric CPB. Furosemide in a dose of 1 to 2 mg/kg or ethacrynic acid 1 mg/kg every 4 to 6 hours, or both, induces a diuresis and may reverse renal cortical ischemia associated with CPB. After DHCA, it is not unusual to observe a 24-hour period of oliguria or anuria that resolves over the next 12- to 24-hour period. The use of diuretics is effective only after spontaneous urine output has been initiated in these patients.

Glomerular filtration rate, creatinine clearance, and medullary concentrating ability are substantially reduced in neonates and young infants. Therefore, the use of CPB in these patients is associated with greater fluid retention than is typically seen in older children and adult patients. The net result may be increased total body water, increased organ weight (e.g., lungs, heart), and greater difficulty with postoperative weaning from ventilatory support. The use of ultrafiltration during rewarming or after CPB is effective in reducing total body water, limiting the damaging effects of CPB, and decreasing the postoperative ventilation period.[146,147]

Pulmonary Effects

Cardioplegia protects the heart, but there is no parallel protection afforded the lung during bypass. Pulmonary dysfunction is common after CPB, and its pathogenesis is poorly understood (see Table 83-12). In the broadest terms, lung injury is mediated in one of two ways: first, by an inflammatory response due to leukocyte and complement activation and, second, by a mechanical effect culminating in surfactant loss, atelectasis with resultant ventilation-perfusion mismatch, loss of lung volumes, and altered mechanics of breathing.

Pulmonary function after CPB is characterized by reduced static and dynamic compliance, reduced functional residual capacity, surfactant deficiency, and an increased A-a gradient.[148,149] Atelectasis and increased capillary leak due to hemodilution and hypothermic CPB are the most likely causes. Hemodilution reduces circulating plasma proteins, reducing intravascular oncotic pressure, and favors water extravasation into the extravascular space. Hypothermic CPB causes complement activation and leukocyte degranulation.[150] Leukocytes and complement are important in causing capillary-alveolar membrane injury and microvascular dysfunction through platelet plugging and release of mediators, which increase PVR. The technique of modified ultrafiltration (MUF) is highly effective in reducing lung water and pulmonary morbidity during the postoperative period.

Stress Response and Cardiopulmonary Bypass

The release of a large number of metabolic and hormonal substances, including catecholamines, cortisol, growth hormone, prostaglandins, complement, glucose, insulin, endorphins, and other substances, characterizes the stress response during hypothermic CPB.[13,151] The likely causes of the elaboration of these substances include contact of blood with the nonendothelialized surface of the pump tubing and oxygenator, nonpulsatile flow, low perfusion pressure, hemodilution, hypothermia, and light anesthesia depth. Other factors that may contribute to elevations of stress hormones include delayed renal and hepatic clearance during hypothermic CPB, myocardial injury, and exclusion of the pulmonary circulation from bypass. The lung is responsible for metabolizing and clearing many of these stress hormones. The stress response generally peaks during rewarming from CPB. There is strong evidence that the stress response can be blunted by increasing the depth of anesthesia.[13,151]

It is unclear at what level elevated circulating stress hormones, a normal neonatal adaptive response, become detrimental. There is little question that these substances could mediate undesirable effects such as myocardial damage (catecholamines), systemic and pulmonary hypertension (catecholamines, prostaglandins), pulmonary endothelial damage (complement, prostaglandins), and pulmonary vascular reactivity (thromboxane). The benefits of controlling the stress response with fentanyl in premature infants undergoing PDA ligation and with sufentanil in neonates with complex congenital heart disease have been demonstrated.[103,152] Although blunting the stress response seems warranted, there is additional evidence suggesting that the newborn stress response, especially the endogenous release of catecholamines, may be an adaptive metabolic response necessary for survival at birth.[153] Thus, the complete elimination of an adaptive stress response may not be desirable. To what extent acutely ill neonates with congenital heart disease are dependent on the stress response for maintaining hemodynamic stability is currently unknown.

It is, therefore, prudent to maintain a depth of anesthesia adequate to attenuate the stress response but to attempt to block the response altogether may not be necessary. Acceptable anesthesia during CPB may be best accomplished by the continuous administration of an inhalation anesthetic via a vaporizer connected to the pump oxygenator, careful titration of incremental doses of opioids, or the precise administration of an opioid or opioid and benzodiazepine by a continuous infusion technique. Primary opioid anesthetic techniques result in reduced stress hormone release and decreased postoperative metabolic acidosis and lactate production compared with primary halothane anesthesia and may therefore be a preferred technique in complex congenital heart disease.[103] If an adequate depth of anesthesia is accomplished by the administration of excessively large doses of opioids (e.g., fentanyl or sufentanil), postoperative mechanical ventilation will be necessary. By contrast, residual levels of inhalation anesthetic drugs (e.g., halothane or isoflurane) can produce transient myocardial depression at the termination of CPB, complicating separation from CPB. Because of the improved surgical techniques coupled with the reduced morbidity of CPB, the use of high doses of an opioid anesthetic is infrequent in our current practice.

Discontinuation of Cardiopulmonary Bypass

In separating the patient from CPB, blood volume is assessed by direct visualization of the heart and monitoring right atrial or left atrial filling pressures. When filling pressures are adequate, the patient is fully warmed, acid-base status is normalized, heart rate is adequate, and sinus rhythm has been achieved, the venous drainage is stopped and the patient can be weaned from bypass. The arterial cannula is left in place so that a slow infusion of

residual pump blood can be used to optimize filling pressures. Myocardial function is assessed by direct cardiac visualization and by a transthoracic left or right atrial catheter, by a percutaneous internal jugular catheter, or by the use of intraoperative echocardiography. Pulse oximetry can also be used to assess the adequacy of cardiac output.[154] Low systemic arterial saturation or the inability of the oximeter probe to register a pulse may be a sign of very low output and high systemic resistance.[155]

After the repair of complex congenital heart defects, the anesthesiologist and surgeon may have difficulty separating patients from CPB. Under these circumstances, a diagnosis must be made and includes (1) an inadequate surgical result with a residual defect requiring repair, (2) pulmonary artery hypertension, and (3) right or left ventricular dysfunction.

Two general approaches are customarily used, either independently or in conjunction. An intraoperative "cardiac catheterization" can be performed to assess isolated pressure measurements from the various great vessels and chambers of the heart (i.e., catheter pullback measurements or direct needle puncture to evaluate residual pressure gradients across repaired valves, sites of stenosis and conduits, and oxygen saturation data to examine for residual shunts).[156] Alternatively, echo-Doppler imaging may be used to provide an intraoperative image of structural or functional abnormalities to assist in the evaluation of the postoperative cardiac repair.[12,157] If structural abnormalities are found, the patient can be placed back on CPB and residual defects can be repaired before the patient leaves the operating room. Leaving the operating room with a significant residual structural defect adversely affects survival and increases patient morbidity (see Fig. 83-5).[12,157] Echo-Doppler imaging can rapidly identify right and left ventricular dysfunction and suggest the presence of pulmonary artery hypertension. In addition, echo-Doppler imaging can identify regional wall motion abnormalities caused by ischemia or intramyocardial air that will direct specific pharmacologic therapy and provide a means of assessing the results of these interventions (Fig. 83-10).[158]

Ultrafiltration

Institution of CPB in neonates, infants, and young children results in a profound proinflammatory response as well as significant hemodilution. This may lead to post-CPB morbidity and mortality resultant from poor organ function. The organ systems most affected by this are the heart, lungs, and brain. Although contact between the patient's blood and the foreign surface of the bypass circuit is a potent stimulus to trigger the inflammatory cascade, other factors including ischemia, profound hypothermia, rewarming, and surgical trauma are also important in its genesis. These inflammatory mediators include complement anaphylotoxins, vasoactive amines, and cytokines (e.g., tumor necrosis factor-α [TNF-α]) that lead to an increase in vascular permeability.[159] Hemodilution occurs at the onset of CPB despite the use of physiologically balanced priming solutions that include blood, crystalloid, albumin, and buffer and smaller volume circuits. Hemodilution may, however, be advantageous in those patients where the surgery is performed under hypothermic conditions ranging from mild hypothermia down to deep hypothermic circulatory arrest. Initiation of CPB will change the viscoelastic properties of blood, and these changes have been shown to continue into the post-CPB period.[160] Although the mode of perfusion, cardiotomy suction, arterial roller pump type, and shear forces of the CPB circuit are important, it is the temperature and hematocrit of the blood that play the most important role in changing viscoelasticity. It has been shown that low temperature with a high hematocrit leads to a higher viscosity.[161] This elevated viscosity may lead to altered organ perfusion particularly in the brain. It is thus for the reason of these alterations in blood viscosity that hemodilution is tolerated in the cooling phases of CPB. Although advantageous early, this hemodilution combined with the inflammatory response will lead to transudation of fluid into the extravascular space, which in turn leads to the potential for organ dysfunction as eluded to earlier. Prevention of organ dys-

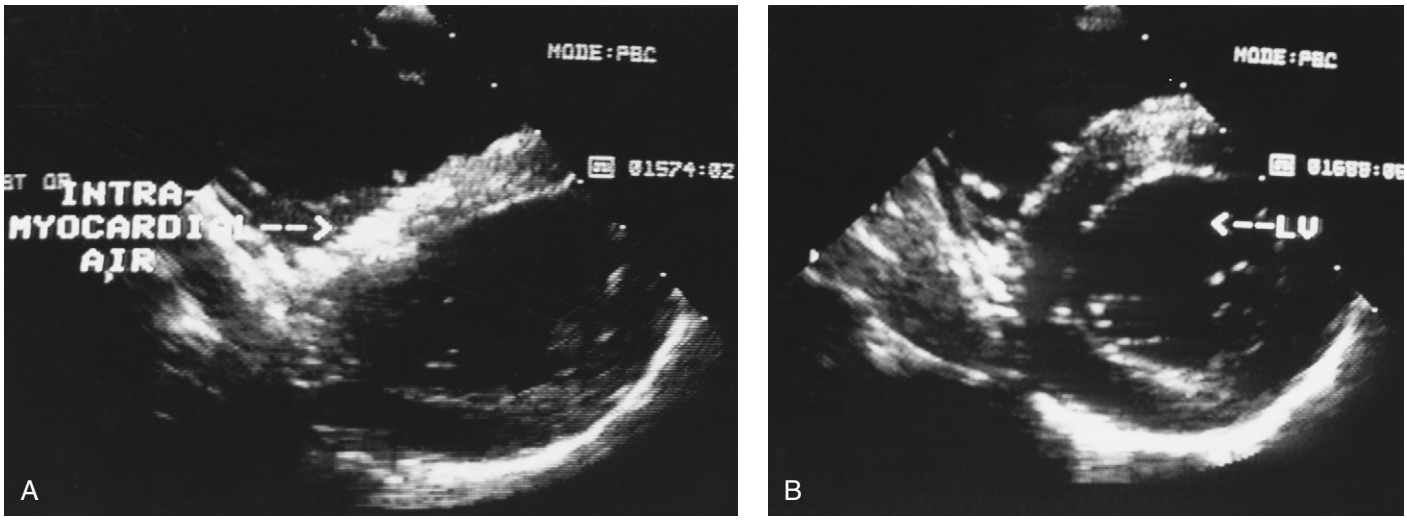

Figure 83-10 A, Two-dimensional echocardiogram in the short-axis view across the ventricles demonstrating the presence of intramyocardial air (*arrow*) in the ventricular septum and right ventricular wall. The intramyocardial air appears as a dense, "snowy" echogenic area. Note the associated wall motion abnormality appearing as flattening of the ventricular septum. **B,** The patient was treated with phenylephrine, increasing systemic and coronary perfusion pressure, resulting in clearance of the air, normalization of the echogenic density, and restoration of normal left ventricular (LV) wall motion and configuration.

function and improved oxygenation by the removal excess fluid and inflammatory mediators are the rationale, therefore, in the use of ultrafiltration. The end result thus is the removal of plasma water and low-molecular-weight solutes across a semipermeable membrane.

Essentially, five forms of ultrafiltration are utilized in modern perfusion practice, three of which are while the patient is on CPB. Prime ultrafiltration (PUF) is utilized when packed red blood cells are added to the prime solution and is performed in the pre-bypass phase. Its aim is to replace crystalloid prime with blood prime, adjust pH, alter electrolyte concentration to safer levels, and remove inflammatory mediators potentially present in the donor blood.[162] Conventional ultrafiltration (CUF) involves the removal of fluid at any time while the patient is being supported by CPB. A common use for this method is the removal of the volume of clear fluid equal to the volume of cardioplegia used. Conventional ultrafiltration can be performed during all phases of CPB. It involves the placement of an ultrafilter within the circuit and connected either to the venous line or to the venous reservoir. The problems associated will be the removal of an excess of ultrafiltrate, resulting in low reservoir volumes. In zero balance ultrafiltration (ZBUF), once fluid has been removed it is replaced with crystalloid to avoid the problems of inadequate reservoir volumes, and thus there is no net removal of volume. The third method of on-bypass ultrafiltration is dilutional ultrafiltration (DUF), which is employed when the concentration of a given electrolyte (e.g., potassium) is deemed elevated. The method thus involves removal of ultrafiltrate with its replacement by one-half normal saline, thus diluting the concentration of the given electrolyte to safer levels. From the description of on-bypass ultrafiltration it can be appreciated that although these methods have different names their end point is similar, that is, attempted removal of excess clear fluid resulting in hemoconcentration, removal of inflammatory mediators, and manipulation of electrolyte concentrations to safe levels.

First described by Nakik and associates[146] in 1991, MUF involves filtration of blood once the patient has been weaned from bypass. This can be achieved either by a venovenous technique in which blood is removed and returned to the atrium once concentrated or by an arteriovenous technique in which blood is removed via the aortic cannula and returned via the venous line.[147,163-165] In more detail, in this technique blood is removed in a retrograde fashion via the aortic cannula and passes through the ultrafilter along with remaining circuit volume from the venous reservoir and oxygenator. Flow through the ultrafilter is maintained by a roller pump at flows of between 10 and 30 mL/kg, with the slower rates resulting in a more gradual change in the intravascular fluid compartment and thus potentially better tolerated. A constant atrial pressure is maintained throughout the procedure by adding crystalloid into the venous reservoir as needed. Suction is applied to the filtrate port to achieve a maximal transmembrane pressure, thus allowing for ultrafiltration rates of between 100 and 150 mL/min.[166] End points for the process of MUF are time (15-20 minutes) and reaching of a target hematocrit (usually 40%) once the circuit volume has been replaced by crystalloid or should the patient's hemodynamics not tolerate the procedure.

Cardiac surgeries in the very young may be complex with potentially protracted CPB and cross-clamp times. It is not surprising, therefore, that myocardial performance is depressed after weaning from CPB. Although ultrafiltration is used during CPB in an attempt to remove excess body water, it appears from studies

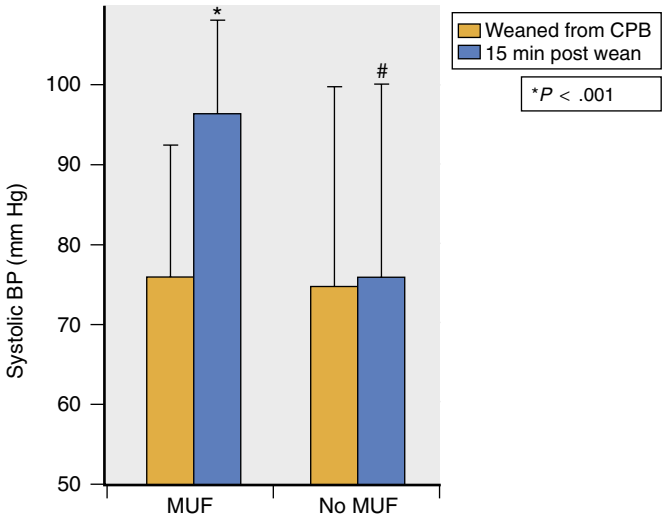

Figure 83-11 Systolic blood pressure (BP) after separating from cardiopulmonary bypass (CPB) and 15 minutes after separating with and without modified ultrafiltration (MUF). Note the significant improvement in systolic BP with the use of MUF. (*From Ungerleider RM: Effects of cardiopulmonary bypass and use of modified ultrafiltration. Ann Thorac Surg 65:S35, 1998; reprinted with permission from the Society of Thoracic Surgeons.*)

that it is the use of MUF that significantly improves myocardial performance (Fig. 83-11).[166-168] Using echocardiographic measurements in a study of infants undergoing corrective surgery under nonhypothermic arrested conditions, Davies and associates found that there were improvements in both systolic and diastolic function in the children studied.[169] They found that the preload recruitable stroke work, which is load independent, improved after MUF and was thus a good indicator of improved systolic function. The same study showed that after MUF there was a decrease in the myocardial wall thickness and cross-sectional area that was not present in the control group of patients who received no ultrafiltration. These reductions result in an increase in end-diastolic length and a fall in end-diastolic pressure, both of which are indicators of improved diastolic function. Although presumably it was the decrease in myocardial edema that was the cause for these improvements, the increased hematocrit also observed could well have also contributed, owing to the associated improvement in oxygen-carrying capacity. Of interest, however, in the Davies study was that these positive effects were not seen past 24 hours, when urine output and inotropic support were the same in both treatment groups. This has led some commentators to question the absolute benefit of MUF.[169]

Pulmonary dysfunction is one of the most common negative effects of CPB.[170] The use, therefore, of ultrafiltration and MUF is to improve oxygenation and decrease the effects of inflammatory mediators on the alveolar capillary membrane and pulmonary vascular reactivity. Studies have demonstrated that in patients in whom ultrafiltration and MUF were used improvements in pulmonary compliance, decreased airway resistance, pulmonary arterial reactivity, and improved oxygenation were demonstrated.[171-175] It is therefore obvious why these methods have thus found such wide acceptance in pediatric cardiac surgery, particularly in those patients in whom normal compliance with low PVR is vital (i.e., those with single-ventricle physiology).

Although these studies commonly find that there is improvement in pulmonary function immediately after weaning from CPB and the completion of MUF, there is disagreement as to whether these effects result in improved function much beyond 6 hours, with some showing little if any benefit at 24 hours. A conclusion, however, from these studies is that combination of on-bypass ultrafiltration coupled with MUF has the best results in the early postbypass period.

Studies into the long-term effects of CPB and indeed DHCA on the brain of children are ongoing. As has been mentioned previously, the initiation of CPB will affect the major organs. In a study performed on a piglet model of DHCA, the use of MUF after CPB improved hematocrit, cerebral oxygen delivery, and cerebral oxygen consumption, thus representing a potential reduction in cerebral injury.[27] Further studies have made similar conclusions. In these studies it was shown that four variables are of importance in improving cerebral oxygenation: P_{CO_2}, mean arterial pressure, hematocrit, and MUF flow rate.[176,177] Increasing all except MUF flow rate improved oxygen delivery. Increasing the flow rate appeared to cause a steal-like phenomenon in which there was an apparent diastolic runoff into the MUF circuit from the aortic cannula. Thus, although the process of MUF is important for recovery of normal cerebral function, care must be used not to negate the benefits by decreasing the time on MUF by increasing the flow rates (Fig. 83-12).

Common to the improvement in cardiac and pulmonary function are the associated decrease in inflammatory mediators seen after ultrafiltration. Studies have shown that the ultrafiltrate contains a wide variety of low-molecular-weight inflammatory mediators, including C3a, C5a, interleukin (IL)-6, IL-8, TNF, myocardial depressant factor, and endothelin.[172,174,178] It is the removal of endothelin-1 after MUF that results in the improvement of pulmonary vascular reactivity, which is of great importance particularly in infants younger than 4 to 6 months of age when pulmonary vascular reactivity is high and in those patients who are having staged cavopulmonary reconstructions. TNF, a potent inflammatory mediator implicated in the development of capillary leak syndrome seen after CPB, has been shown to be removed best by MUF. Despite these positive effects of MUF the literature does not give a clear advantage of one form of ultrafiltration over the other, and it may be the combination of these methods that once again shows the best potential results.

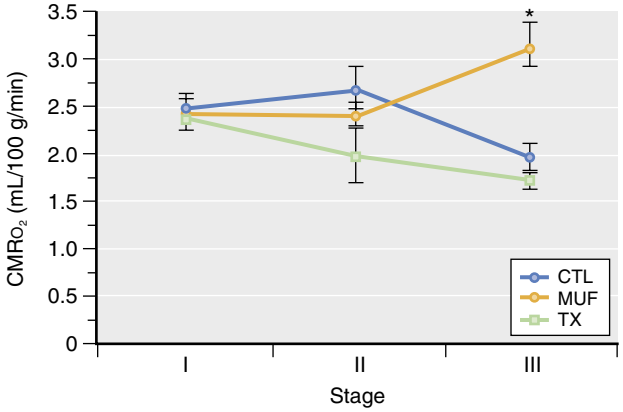

Figure 83-12 Cerebral metabolic rate for oxygen measurements ($CMRO_2$) before and after deep hypothermic circulatory arrest. Note the significant increase in $CMRO_2$ in the MUF animals compared with the control and transfusion groups at stage 3. CTL, control; MUF, modified ultrafiltration; TX, transfusion. (*From Skaryak LA, Kirshbom PM, DiBernardo LR, et al: Modified ultrafiltration improves cerebral metabolic recovery after circulatory arrest. J Thorac Cardiovasc Surg 109:744, 1995.*)

Another important post-CPB issue is ongoing blood loss. There is little doubt that the use of MUF will result in an elevation of the patient's hematocrit secondary to the removal of the excess body water, as already discussed. This further results in decreased blood use and the observation that there is less postoperative bleeding.[179] Indeed, in older children attempts can thus be made to avoid the use of donor blood altogether.

Disadvantages to these techniques are noted. The addition of an ultrafilter to the CPB circuit adds a level of complexity to the circuitry and, thus, another potential area in which circuit-related complications may occur. Antagonists of MUF note also the following potential problems: the potential for air entrainment into the arterial cannula, additional time in which the patient is anticoagulated, potential for hypovolemia as volume is drawn off from the patient, hypothermia as the filtered volume does not pass through the heater/oxygenator, and the potential for the increase in the plasma concentration of drugs (e.g., fentanyl).[180] Another interesting complication potentially associated with ultrafiltration was the reduction in thyroid hormone. This acute hypothyroidism may lead to depressed function, manifesting as decreased contractility, heart rate, cardiac output, and elevated SVR, all of which will clearly effect the immediate post-CPB period.[181] As with other techniques in medicine the benefit versus risk must be seriously considered, but from the presented evidence the use of ultrafiltration both on and off CPB is extremely beneficial and these methods are thus commonly used in modern pediatric cardiac surgery with good result and little complication.[165,168,182,183]

In the preceding paragraphs the discussion has concluded that there is no clear advantage of one method of ultrafiltration over the other. Unfortunately, comparing a wide range of patients having different surgeries under different conditions is difficult, and thus it appears that from the articles referenced the best strategy would include both the use of on-CPB ultrafiltration and the use of MUF once the patient has been separated from bypass to achieve the goals of decreasing total-body water, removal of inflammatory mediators, improved hematocrit, and thus oxygen-carrying capacity, and the preservation of vital organ function.

Specific Problems Encountered in Discontinuing Cardiopulmonary Bypass

Left Ventricular Dysfunction

The contractile state of the LV may be reduced after pediatric cardiac surgery. This is due to surgically induced ischemia during the repair, the preoperative condition of the myocardium, the effects of deep hypothermia and circulatory arrest on myocardial compliance, and new, altered loading conditions on the LV caused by the repair.[184,185] Left ventricular dysfunction can be treated by optimizing preload, increasing heart rate, increasing coronary perfusion pressure, correcting ionized calcium levels, and adding inotropic support. The neonate's heart rate–dependent cardiac output, reduced myocardial compliance, and diminished response to calcium and catecholamines are factors influencing the need for inotropic support. Inotropic support is usually begun with

dopamine (3-10 μg/kg/min). Several studies suggest that the effect of dopamine in children is age dependent. After cardiac surgery in young children, dopamine increases cardiac output, which correlates more with elevations in heart rate than augmentation of stroke volume, whereas, in young adults, dopamine clearly increases stroke volume.[10] Nonetheless, infants and neonates respond favorably to dopamine infusions with increased systemic blood pressure and cardiac output and improved systemic perfusion.

Calcium supplementation is important in augmenting cardiac contractility. Although calcium supplementation has fallen into some disfavor because of concerns over reperfusion injury, it remains an important therapy after pediatric cardiac surgery. Fluctuations in ionized calcium levels occur commonly in the immediate post-CPB period in children. This is most often due to the relatively large transfusions of citrate- and albumin-rich blood products, such as whole blood, fresh frozen plasma, platelets, and cryoprecipitate necessary for hemostasis, all of which bind calcium.[186] Routine calcium supplementation during the early post-CPB period is especially helpful in patients with diminished left ventricular function. In patients with a slow sinus or junctional rate, calcium must be administered cautiously because marked slowing of AV conduction may occur.

Epinephrine (0.02-0.2 μg/kg/min) is useful in patients with significant left ventricular dysfunction who remain hypotensive with high left atrial filling pressures or echo-Doppler imaging evidence of reduced contractility or regional ischemia.[187]

Milrinone, a potent phosphodiesterase-3 inhibitor, is also an effective inotrope-vasodilator in infants and children. Studies in neonates after open-heart surgery reveal significant reductions in SVR and PVR and increases in cardiac index, primarily due to larger stroke volume.[188] Infants and children demonstrate a larger volume of distribution and clearance of milrinone compared with adults; thus, the loading dose necessary to achieve therapeutic levels may be as high as 100 μg/kg.[189] In neonates, the loading dose of milrinone on CPB is 100 μg/kg, followed by a continuous infusion to be started within 90 minutes of the load dose at a rate of 0.2 μg/kg/min to maintain a therapeutic level. In older infants and children, the rate of continuous infusion is higher, usually 0.5 to 1.0 μg/kg/min.

Dobutamine is an effective, albeit weaker, inotropic agent in children. Although it is reported to have fewer chronotropic effects than dopamine in neonates, significant tachyarrhythmias may occur. This may be related to structural similarities between dobutamine and isoproterenol.[187] In children after cardiac surgery, dobutamine increases cardiac output primarily through increased heart rate. The efficacy of dobutamine seems to be reduced in immature animals. This is consistent with reduction in α-receptors and a higher level of circulating catecholamines in newborns.

Right Ventricular Dysfunction

Primary right ventricular dysfunction is a common finding after CPB in neonates, infants, and children. For example, after repair of tetralogy of Fallot, preexisting right ventricular hypertrophy, a right ventriculotomy, and the placement of a transannular patch across the right ventricular outflow tract, resulting in acute pulmonary regurgitation and right ventricular volume overload, are common causes of postoperative right ventricular dysfunction.[23] The treatment of right ventricular dysfunction consists of measures directed at lowering PVR and preserving coronary perfusion without distending the RV. Metabolic acidosis should be addressed and inotropic agents selected for their vasodilating properties (e.g., dopamine, amrinone, or milrinone). In cases of extreme ventricular dysfunction, low-dose epinephrine (0.01 to 0.03 μg/kg/min) may provide inotropy without vasoconstriction.[184,190] Mechanical ventilation should be adjusted to assist right ventricular function and minimize PVR.

In contrast with the LV, the low intracavitary pressure of the normal RV receives two thirds of its coronary filling during ventricular systole.[191] In patients with right ventricular dysfunction, maintaining a normal or slightly elevated systolic arterial pressure maximizes coronary perfusion to the RV and augments contractility. If the need for inotropic support persists after the early post-CPB period, a critical evaluation for other structural and functional abnormalities should be aggressively pursued. Preload should be maintained at a normal to slightly elevated level. Because right ventricular contractility is reduced, it is important to maximize preload to the highest portion of the Starling curve. Overdistention of the RV, however, is not well tolerated, owing to diminished ventricular compliance and diastolic dysfunction. Excessive volume loading may result in significant diastolic dysfunction, tricuspid regurgitation, and worsening forward flow. Generally, CVP much above 12 to 14 mm Hg is poorly tolerated in neonates and infants with right ventricular dysfunction.[192] If right ventricular dysfunction is severe, the sternum should be left open.[193] This eliminates the impedance imposed by the chest wall and mechanical ventilation, allowing the RV to maximize its end-diastolic volume. An additional strategy in neonates, infants, and children with significant post-CPB right ventricular dysfunction is to allow right-to-left shunting at the atrial level. Typical patients who would benefit from this strategy include neonates undergoing repairs for tetralogy of Fallot and truncus arteriosus. Allowing an atrial communication to remain open, with blood shunting in a right-to-left direction, preserves cardiac output and oxygen delivery to the systemic circulation. Although these patients have somewhat diminished systemic oxygen saturation, as their effective cardiac output and tissue oxygen delivery are enhanced, systemic perfusion pressure improves and coronary perfusion of the RV is maintained. As right ventricular function improves, right atrial pressure falls, right-to-left shunting decreases, and systemic arterial saturation rises.

If right ventricular dysfunction persists to the extent that systemic cardiac output is compromised, consideration should be given to extracorporeal life support (extracorporeal membrane oxygenation [ECMO]). When ECMO is used for circulatory support, venoarterial cannulation is preferred. Venous and arterial access may be achieved through a large central artery and vein, usually the carotid artery and internal jugular vein, or by direct chest cannulation. Recovery from severe ventricular dysfunction is predicated on the concept that the myocardium has sustained a transient injury (i.e., "stunned myocardium") and is capable of recovery with time.[194,195] ECMO is used to decrease ventricular wall tension, increase coronary perfusion pressure, and maintain systemic perfusion with oxygenated blood. ECMO may also be used for left ventricular failure, although success with this condition is less common than that seen with right ventricular dysfunction or pulmonary artery hypertension. Patients placed on ECMO because they fail to separate from CPB demonstrate significantly greater mortality than do those for whom ECMO was instituted later in the postoperative course.[196] The children

who consistently have the lowest survival rate are those who require ECMO after a Fontan operation.[197] The role of ECMO in patients with myocardial injury or pulmonary hypertension is to provide adequate systemic oxygen transport and systemic perfusion while allowing the ventricles to rest and recover. ECMO may even provide an effective means of resuscitation for postoperative cardiac patients, particularly if instituted promptly.[198] In larger infants and children with predominantly right ventricular dysfunction and satisfactory pulmonary function, a selective right ventricular assist device may be preferable to ECMO.[199]

Pulmonary Artery Hypertension

Primary pulmonary hypertension is a devastating disease. The progressive and sustained elevation in PVR eventually leads to right-sided heart failure and death.[200,201] Pulmonary arterial hypertension (PAH) is defined by the presence of mean pulmonary arterial pressure greater than 25 mm Hg at rest or 30 mm Hg during exercise.[202] In two recent studies, presence of PAH was shown to be a significant predictor of major perioperative cardiovascular complications including pulmonary hypertensive crises, cardiac arrest, and death in patients undergoing cardiac catheterization or noncardiac surgery under anesthesia.[203,204] Suprasystemic pulmonary artery pressure was predictive of major complications. Complications, however, were not associated with age, etiology, type of anesthetic, or airway management. Preanesthesia evaluation should evaluate disease severity. A history significant for chest pain, syncope, and dizziness, with signs of dyspnea at rest, low cardiac output state, metabolic acidosis, hypoxemia, and signs of right-sided heart failure warrants caution. Acute increases in PVR resulting in pulmonary hypertensive crises cause an increase in right ventricular afterload, right ventricular dysfunction, and hemodynamic decompensation. Suprasystemic pulmonary artery pressure results in inadequate PBF, inadequate left ventricular preload, low cardiac output, and biventricular failure. The associated hypotension results in coronary ischemia, which worsens this cycle. Perioperative factors thought to precipitate a pulmonary hypertensive crisis include hypoxia, hypercarbia, acidosis, hypothermia, pain, and airway manipulations in patients with pulmonary hypertension. Such patients present for hemodynamic catheterization, drug study, and noncardiac and cardiac surgical procedures. Although each anesthetic has to be tailored to the patient's pathophysiology and surgical procedure, certain common principles remain. Pulmonary vasodilator therapy and inotropes must be continued in the perioperative period. Investigations include a comprehensive echocardiogram with occasional chest CT angiography to exclude pulmonary thromboembolic disease. In our center, premedication is avoided and intravenous induction is performed with carefully titrated doses of ketamine. Procedures with potential for blood loss, hemodynamic instability, and changes in ventilatory status mandate invasive arterial monitoring. Care should be taken to avoid systemic hypotension while achieving general anesthesia. Ventilation and oxygenation are controlled, and acidosis is treated aggressively. Hypotension in the presence of euvolemia may need to be treated with inotropes and, if necessary, with α_1-agonists.[205,206]

Therapy for elevated pulmonary artery pressures is directed at lowering PVR and unloading the RV. Reduction of PVR is accomplished by altering ventilation pattern, inspired oxygen concentration, and blood pH. Specifically, manipulating the pulmonary vascular bed in newborns and infants is a matter of regulating $Paco_2$, pH, Pao_2, PAo_2, and ventilatory mechanics.[207,208] $Paco_2$ is a potent mediator of PVR, especially in the newborn and young infant. Reducing $Paco_2$ to 20 mm Hg and increasing pH to 7.6 produces a consistent and reproducible reduction in PVR in infants with pulmonary artery hypertension. Manipulating serum bicarbonate levels to achieve a pH of 7.5 to 7.6 while maintaining a $Paco_2$ of 40 mm Hg has equal salutary effects on PVR.[209] Both the Pao_2 and the PAo_2 decrease PVR as well. In the circumstance of intracardiac shunts, changes in Fio_2 have little effect on Pao_2. Thus, by inference, a reduction in PVR induced by increasing the inspired oxygen concentration is probably a direct pulmonary vasodilatory effect of PAo_2 rather than Pao_2.

Ventilatory mechanics also play a major role in reducing PVR. Neonates and infants have a closing volume above functional residual capacity. Thus, at the end of a normal breath, some airway closure occurs. This process results in areas of lung that are perfused and yet underventilated. As these lung segments become increasingly hypoxemic, secondary hypoxic vasoconstriction occurs. The net effect is an increase in PVR. Therefore, careful inflation of the lungs to maintain functional residual capacity will selectively reduce PVR. In practice, this is accomplished with relatively large tidal volumes and low respiratory rates, which produce an exaggerated chest excursion. Generally, tidal volumes of 15 to 25 mL/kg are required. Respiratory rates of 15 to 25 breaths/min are used for neonates and infants. A reduced ventilatory rate with large tidal volumes reduces mean airway pressure and provides a longer expiratory phase of ventilation.

Because PBF occurs predominantly during the expiratory phase of the respiratory cycle, the ventilatory pattern should be adjusted to allow an adequate distribution of gas throughout the lung during inspiration and a more prolonged expiratory phase to promote blood flow through the lungs. End-expiratory pressure must be applied cautiously during the post-CPB period. Low positive end-expiratory pressure (3 to 5 mm Hg) prevents narrowing of the capillary and precapillary blood vessels, thereby reducing PVR. Higher positive end-expiratory pressure or excessive mean airway pressure results in alveolar overdistention and compression of the capillary network in the alveolar wall and interstitium. This condition elevates PVR and reduces PBF.[148]

The final and perhaps the least well-recognized use of the mechanical ventilator is to assist in unloading the RV. During inspiration, intrathoracic pressure increases and creates an increased pressure gradient from the lung to the left atrium, promoting cardiac output. This ventilatory assist is commonly seen in patients with PAH or right ventricular dysfunction. An augmentation of the arterial pressure trace during inspiration is seen. The use of the ventilator to augment systemic blood flow is very similar to the thoracic pump concept used to explain blood flow during CPR.[210] The inspiratory assist must be balanced by the potential negative effects of increased mean airway pressure on PVR and right ventricular afterload. To maximize these cardiopulmonary interactions, high tidal volume with low respiratory rates should be employed.

Attempts to manipulate PVR through pharmacologic interventions have been generally unsatisfactory. Drugs that have shown the greatest promise in decreasing PVR both clinically and experimentally have been the phosphodiesterase inhibitors. Amrinone and milrinone are the only drugs of this class currently available in the United States. Both reduce PVR and SVR and increase RV contractility.[211,212] Isoproterenol has mild pulmonary

artery–vasodilating properties in the normal pulmonary circulation.[213] It reduces PVR in adults after cardiac transplantation, but there are very few data to support PVR reduction in infants and young children after cardiac surgery. In immature animals, the myocardium is less responsive to isoproterenol and causes tachycardia and increased myocardial oxygen consumption. These latter effects may reduce coronary perfusion and result in relative myocardial ischemia. Both prostaglandin E_1 and prostacyclin have a pulmonary vasodilating effect[214,215]; however, both drugs produce systemic hypotension, which severely limits their use.

Because of the lack of specificity of vasodilator drugs on the pulmonary bed, newer pharmacologic methods of controlling pulmonary artery hypertension and elevated PVR are being sought. Two new concepts include ultrashort-acting intravenous vasodilators and inhaled vasodilating agents such as nitric oxide. Ultrashort-acting intravenous vasodilators are nonspecific potent vasodilators, with a half-life measured in seconds. Infusion of these drugs into the right side of the circulation produces a potent short-lived relaxation of the pulmonary artery smooth muscle.[216] Once the drug reaches the systemic circulation it is no longer functional. Adenosine and ATP-like compounds have these properties and may have clinical applicability in pulmonary artery hypertension in the future.[217]

Beginning in the past decade, several potent therapies for pulmonary hypertension have evolved.[207,208] A continuous intravenous infusion of prostacyclin improves pulmonary vascular hemodynamics, exercise tolerance, and survival in pulmonary hypertension.[218] Sildenafil is a selective phosphodiesterase type 5 inhibitor. Phosphodiesterase type 5 breaks down cyclic guanosine monophosphate. Sildenafil produces acute and relatively selective pulmonary vasodilatation and acts synergistically with nitric oxide.[219-221] Bosentan is a dual endothelin receptor blocker. Preliminary reports indicate that bosentan improves symptoms, exercise tolerance, and hemodynamics in patients with pulmonary hypertension. The drug is well tolerated and free of side effects apart from a dose-dependent increase in liver enzymes.[222] Lung transplantation is the only available surgical therapy for primary pulmonary hypertension; however, the 5-year survival remains less than 50%, and bronchiolitis obliterans remains the single most common cause of death.[223,224] Prior to listing for transplantation all patients undergo a hemodynamic cardiac catheterization and drug study in which reversibility of pulmonary hypertension with increased inspired oxygen concentrations and nitric oxide is determined.[225] Inhaled iloprost, although used in adult centers, has not become routine in pediatric practice.

CPB with associated endothelial injury predisposes to the development of postoperative pulmonary hypertension in patients with congenital heart disease. Anatomic factors that impose either obstruction to PBF or residual left-to-right shunting need to be surgically addressed. Elevated LAP resulting from mitral valve disease or left ventricular dysfunction, pulmonary venous obstruction, branch pulmonary artery stenosis, or surgically induced loss of the pulmonary vascular cross-sectional area all raise right ventricular pressure and impose a burden on the right side of the heart.

Nitric oxide, an endothelium-derived vasodilator that is administered as an inhaled gas, represents the most promising development in the therapy for elevated PVR in patients with congenital heart disease (see Chapter 31). Although nonselective, it is rapidly inactivated by hemoglobin and, when inhaled, produces no systemic vasodilation.[226] Nitric oxide reduces pulmonary artery pressure in adult patients with mitral valve stenosis and in selected pediatric cardiac patients with PAH.[227-229] The congenital cardiac patient population in whom nitric oxide appears to be effective is those patients with acute PVR elevation after open-heart surgery, as well as preoperative pulmonary hypertension accompanying specific anatomic conditions (e.g., total anomalous pulmonary venous return, congenital mitral stenosis).[228,229] Because it acts directly on vascular smooth muscle, nitric oxide remains effective despite the post-CPB endothelial injury frequently encountered in children.[230] Some centers routinely employ nitric oxide in low dose (1 to 5 ppm) after a Fontan operation when the CVP-LAP gradient exceeds 10 mm Hg.[231] Finally, nitric oxide can provide diagnostic information that helps distinguish reactive pulmonary vasoconstriction from fixed anatomic obstructive disease either in the postoperative surgical patient or in the patient undergoing pretransplant evaluation.[232,233] In the latter, the distinction between pulmonary vasoconstriction and advanced pulmonary vascular occlusive disease will influence the prediction as to whether a child with pulmonary hypertension in association with either congenital heart disease or cardiomyopathy will survive a heart transplant or requires replacement of both heart and lungs.

Management strategies for postoperative pulmonary hypertension and treatment of pulmonary hypertensive crises include sedation, moderate hyperventilation (maintaining P_{CO_2} between 30 and 35 mm Hg), moderate alkalosis (pH > 7.5), increased inspired oxygen, optimization of positive end-expiratory pressure (to maximize functional residual capacity), pulmonary vasodilators (e.g., nitric oxide), and the creation or maintenance of an intracardiac right-to-left shunt in an attempt to maintain cardiac output.[234-236] Nitric oxide is also useful in the manipulation of PVR after Fontan-type procedures.[237] Care should be exercised in weaning nitric oxide in patients, because abrupt withdrawal can precipitate rebound pulmonary hypertension and pulmonary hypertensive crises.[237,238]

Anticoagulation, Hemostasis, and Blood Conservation

Modern pediatric cardiac anesthesia must include the principles and practice of effective anticoagulation, hemostasis, and blood conservation. Bleeding after CPB remains a significant problem in pediatric cardiac surgery.[239] Continuing blood loss after CPB requiring blood component replacement is associated with hemodynamic compromise as well as morbidity from multiple donor exposures. In pediatric patients, restoration of hemostasis has proved difficult; diagnosis of the problem and treatment are marginally effective.

Neonates, infants, and children undergoing cardiac surgery with CPB have a higher rate of postoperative bleeding than that seen in older patients.[239] This is due to several factors. First, there is disproportionate exposure to the nonendothelialized extracorporeal circuit, which produces an inflammatory-type response. This inflammatory response to CPB is inversely related to patient age; the younger the patient, the more pronounced the response.[13] Because complement and platelet activation are linked to the activation of other protein systems in the blood (i.e., fibrinolytic), it is probable that this hemostatic activation, which results in

impaired hemostasis and increased bleeding tendency, plays a major role during pediatric cardiac surgery. Second, the type of operation performed in neonates and infants usually involves more extensive reconstruction and suture lines, creating more opportunities for surgical bleeding than in adult cardiac patients. Operations are also frequently performed using deep hypothermia or circulatory arrest, which may further impair hemostasis.[240] Third, the immature coagulation system in neonates may also contribute to impaired hemostasis.[241] Although procoagulant and factor levels may be reduced in young patients with congenital heart disease due to immature or impaired hepatosynthesis,[242] functional bleeding tendencies are usually not present before surgery. Finally, patients with cyanotic heart disease demonstrate an increased bleeding tendency before and after CPB.

CPB is a significant thrombogenic stimulus requiring anticoagulation with heparin before its initiation. Heparin is usually administered empirically based on patient weight, and its effect is followed by activated clotting time monitoring. Because the heparin effect is primarily due to coupling with antithrombin III and because there are age-related differences and quantitative differences in procoagulants and inhibitors, variability of heparin dosing and its effect has been a concern. High heparin sensitivity is observed in the first week of life and then decreases progressively until about 3 years of age, when values approach those observed in adults.[243] These findings are consistent with evidence in infants of variable quantities of both procoagulants and inhibitors, especially prothrombin and antithrombin III.[244] Heparin administration must also include a consideration of the quantity and composition of the priming volume for CPB, especially if fresh frozen plasma is added. The authors recommend a heparin dose of 200 U/kg plus an additional dose of 1 to 3 U/mL of priming solution and maintaining the activated clotting time above 480 seconds.

Heparin is neutralized with protamine dosed according to the quantity of heparin administered or based on body weight. Protamine excess may actually contribute to postoperative bleeding.[245] It appears that the protamine dose requirement is high for neonates and decreases with increasing age of the patient. The relatively increased protamine requirement for young as compared with older children and adults is indicative of higher circulating heparin levels after CPB.[246] Delayed hepatic clearance of heparin due to organ immaturity and the predominant use of hypothermic circulatory arrest in the young will decrease metabolism and excretion of heparin. We typically administer 4 mg/kg protamine in neonates, whereas 2 mg/kg usually restores the activated clotting time to baseline values in adolescents and adults. Interpatient variability mandates some form of individual assessment to guide drug dose, in order to prevent excess protamine.[245]

Neonates and young infants with congenital heart disease will have low circulating levels of procoagulants and inhibitors. The thrombogenic and dilutional effects of CPB further contribute to hemostatic abnormalities after CPB. Formed blood elements such as leukocytes and platelets may be activated, and procoagulants may be diluted by CPB. Furthermore, deep hypothermic circulatory arrest causes increased clotting and fibrinolytic activity. The lower the temperature, the higher the degree of hemostatic activation. Therefore, the causes of bleeding after CPB are many. Injudicious use of blood products to correct individual coagulation abnormalities separately can further exacerbate dilution of existing procoagulants, as well as carrying the risks of multiple donor exposure. Because the transfusion of blood products is associated with numerous complications, transfusion is to be assiduously avoided, unless specifically indicated by an impairment in tissue oxygenation or documented coagulopathies with clinically significant bleeding. All efforts at blood conservation during cardiac surgery should be routinely employed by all members of the operative team, intraoperatively as well as postoperatively.

Bleeding after CPB is not an unusual occurrence. The surgeon should first attempt to identify any obvious source of surgical bleeding at the sites of repair. Next, adequate protamine reversal of heparin is assessed by measuring an activated clotting time. In general, standard coagulation tests show a prolongation of the partial thromboplastin time, prothrombin time, hypofibrinogenemia, and dilution of other procoagulants as well as a prolonged bleeding time in many pediatric patients, with and without bleeding (Fig. 83-13). The most common reason for persistent bleeding is platelet dysfunction.[247,248] Under such circumstances, administration of platelets is warranted in the presence of bleeding. Routine administration of blood products to correct laboratory coagulation abnormalities in the absence of bleeding is never clinically indicated. After platelets have been given and if bleeding is still present, reassessment and repeat platelet infusion or the administration of cryoprecipitate or fresh frozen plasma may be beneficial. Under most circumstances, meticulous surgical technique, appropriate administration of protamine, adequate patient temperature, and platelet infusion will correct excessive bleeding. In neonates, excessive bleeding, as well as the escalating dilutional effects of selective component therapy on the remaining procoagulants, makes the treatment of bleeding difficult. The use of fresh whole blood may be warranted under these

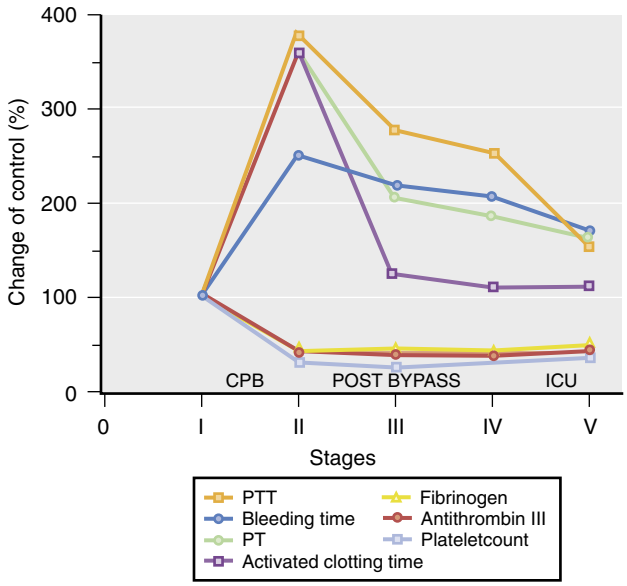

Figure 83-13 Plot of blood coagulation profile changes before, during, and after cardiopulmonary bypass (CPB) in 25 children. Clotting times and coagulant factors are shown as percent change from control. Stage I, baseline, before CPB; stage II, post-CPB, before protamine reversal of heparin; stage III, after protamine; stage IV, just before leaving the operating room; stage V, after 3 hours in the intensive care unit (ICU). PTT, partial thromboplastin time; PT, prothrombin time.

circumstances. The administration of fresh whole blood (<48 hours old) after CPB can meet all the hematologic requirements with minimum donor exposure. The efficacy of whole blood in restoring hemostasis and reducing blood loss after CPB has been demonstrated in patients younger than 2 years of age undergoing complex surgical repairs.[239]

Many attempts have been made to reduce bleeding after CPB by pharmacologic interventions. Desmopressin acetate[249,250] and the antifibrinolytics aminocaproic acid and tranexamic acid[251] have been tried with variable success in significantly reducing postoperative blood loss after cardiac surgery. Royston and associates have demonstrated this with the use of aprotinin.[252] A proteinase inhibitor, aprotinin has antifibrinolytic properties in low concentrations and acts as a kallikrein inhibitor at higher levels. CPB causes increased kallikrein by contact activation, promoting thrombus and fibrin generation, which promotes fibrinolysis. The inhibition of kallikrein results in inhibition of the contact phase of coagulation, and the inhibition of fibrinolysis reduces bleeding. Reduced thrombin generation leads to a diminished platelet stimulation. Better-preserved platelet function has been described in patients receiving aprotinin.[252] Aprotinin has been demonstrated to reduce the intraoperative and postoperative blood loss in cardiac surgery.[253-256] Aprotinin use during pediatric cardiac surgery attenuates fibrinolytic activation in a dose-dependent fashion, reducing the formation of fibrin-split products.[240,257] Higher doses of aprotinin reduce thrombin/antithrombin III complex and F1/F2 fibrin fragments, supporting the hypothesis of suppression of clotting activation with higher aprotinin doses and plasma concentrations. To date, the use of aprotinin for congenital heart surgery has been generally confined to certain patients requiring reoperation, patients undergoing a Ross procedure, and patients undergoing cardiac/lung transplantation procedures. Of note, because of current concerns about aprotinin being associated with increased thrombosis and morbidity, we no longer use this drug in our practice.

The techniques of blood conservation must be continued during the postoperative period. Isolated coagulation abnormalities are often present in the uncomplicated postoperative cardiac patient (see Fig. 83-13). Usually, these coagulation abnormalities self-correct during the first postoperative day and are not associated with excessive bleeding. Therefore, routine correction of these abnormalities with infusion of blood products is not warranted. Administration of blood products should not occur in the absence of clinical evidence of bleeding and the identification of a specific defect requiring targeted component therapy. Routine use of blood products for volume replacement is also to be avoided; lactated Ringer's or saline solution can be satisfactorily administered at a reduced cost without the hazards associated with transfusion.

Postoperative Management

Immediate postoperative care of the pediatric patient who has undergone cardiothoracic surgery is an important period in the overall sequence of anesthetic and surgical management. Although the primary influence on outcome is determined by the conduct of the operation, postoperative care is an important factor. As a member of the operative team, it is necessary that the anesthesiologist understand and become involved during the immediate postoperative period. Detailed principles of postoperative management of the pediatric cardiac surgical patients are beyond the scope of this chapter. However, a few general guiding principles and approaches are given to provide fundamental knowledge for the anesthesiologist.

The postoperative period can be characterized by a series of physiologic and pharmacologic changes as the body convalesces from the abnormal biologic conditions of CPB and cardiac surgery. During this period, the effects of the cardiac operation, any underlying disorders, the effects of hypothermic CPB, and special techniques such as DHCA may create special problems. In the immediate postoperative setting, abnormal convalescence and specialized problems must be recognized and managed appropriately. Fortunately, most patients are able to balance the cost imposed by the physiologic trespass created by the surgical repair and the effects of CPB against the benefit of reduced pathophysiologic loading conditions, resulting in low morbidity and mortality.

Therefore, the guiding principle in the management of the postoperative patient is an understanding of both normal and abnormal convalescence after anesthesia and cardiac surgery. The immediate postoperative period, even that of normal convalescence, is one of continuous physiologic change because of the pharmacologic effects of residual anesthetic agents and the ongoing physiologic changes secondary to abrupt alteration in hemodynamic loading conditions, surgical trauma, and extracorporeal circulation. Anesthesia and surgery affect not only the patient's conscious state but also cardiovascular, respiratory, renal, and hepatic function; fluid and electrolyte balance; and immunologic defense mechanisms. Despite all these changes, postoperative care should be predictable and standardized for most patients undergoing cardiac procedures.

In general, there are four temporal phases of postoperative management in the cardiac patient: (1) transport to the intensive care unit (ICU), (2) stabilization in the ICU, (3) weaning from inotropic and ventilatory support, and (4) mobilization of fluids. Patients proceed through these phases at variable rates based on such factors as the underlying disease process, preoperative medical condition, sequelae of the surgical procedure, duration of CPB, and presence or absence of intraoperative complications. One of the most important functions of the ICU team is to identify postoperative complications in the patient who convalesces abnormally and to provide interventional therapy. Because physiologic change after cardiac surgery is dramatic but self-limiting during normal convalescence, recognition of abnormal processes can be difficult. Under such circumstances a uniform, multidisciplinary approach with experienced clinicians and nurses facilitates the identification of any abnormalities in convalescence. These abnormalities often are indications for closer observation, more invasive monitoring, pharmacologic intervention, and increased cardiopulmonary technical support. Complications include hypovolemia, residual structural heart defect, right and left ventricular failure, hyperdynamic circulation, pulmonary artery hypertension, cardiac tamponade, arrhythmias, cardiac arrest, pulmonary insufficiency, oliguria, seizures, and brain dysfunction. It is critical to detect these departures from the normal convalescent course and to treat them aggressively.

One important area in which the anesthesiologist can aid the recovery of the cardiac patient is pain control. Pain and sedation are among the most common problems requiring ICU intervention. Many factors influence the onset, incidence, and severity

of postoperative pain. The attenuation of the stress response in the immediate postoperative period using infusions of potent opioids in the critically ill infant reduces morbidity.[103] Attenuation of postoperative pain can be attempted with a preoperative medication and an intraoperative anesthetic management technique that includes the use of potent opioids. Patients who receive no opioids preoperatively or during the operative procedure will require analgesics in the immediate postoperative period once the inhalation anesthetic is eliminated. Most cases of postoperative pain can be managed by the administration of small intravenous doses of opioids, usually morphine. This is important in a patient being weaned from the ventilator during the early postoperative period. Patients who are intubated and ventilated overnight should receive adequate sedation and pain control until ventilatory weaning is begun. This is usually accomplished by a continuous infusion of a benzodiazepine and an opioid. Continuous infusion of sedatives and analgesics results in a more consistent and reliable control of postoperative pain. When separated from mechanical ventilation, the patient is concurrently weaned from the sedatives and analgesics. Under these circumstances, careful titration of opioids often results in prompt pain relief. In patients with reactive pulmonary artery hypertension, opioids have been shown to prevent hypertensive crisis.[100]

Regional anesthesia may be used for postoperative pain control in infants and children after thoracotomy (see Chapter 81). This method avoids opioid-induced respiratory depression from intravenous doses of these drugs. The administration of opioids in the epidural space is a very effective approach to pain management. This technique is used in children for postoperative pain control when given in the epidural space via the caudal route as a "single shot" or via a small caudal catheter. Morphine or hydromorphone provides effective analgesia with a duration of 6 to 12 hours, with no significant respiratory depression. Caudal morphine diluted in 0.05 to 0.075 mg/kg delivered in a total volume of 1.25 mL/kg of sterile saline has been used with good success in our practice. The use of regional anesthesia for postoperative pain appears to be best suited for the child extubated in the early postoperative period. Relative contraindications of this technique include hemodynamic instability and patients with abnormal clotting profiles with continued active bleeding. Using this regional technique, better arterial oxygenation, a more rapid ventilator weaning, and decreased postoperative respiratory complications may be expected. However, urinary retention occurs frequently in patients without a bladder catheter. Generally, no treatment is required.

Children requiring large thoracotomies or a bilateral thoracosternotomy (i.e., "clamshell") incision merit consideration for thoracic epidural analgesia. This technique significantly reduces the respiratory depression and pulmonary mechanics abnormalities that accompany the quantity of systemic opioids that would be necessary to provide adequate analgesia for these excruciatingly painful incisions. If the procedure requires systemic heparinization, we will typically defer placement of these catheters until the heparin effect is neutralized. For the patient undergoing coarctation repair via a left thoracotomy, we place the caudal or epidural catheter after demonstration of motor function in the lower extremities. For patients undergoing heart/lung transplantation, a thoracic epidural catheter is placed at a time in the postoperative period when the patient can be weaned from intravenous medications that will adversely impact on the patient's ability to breathe in close proximity to the planned extubation. It is common for these patients to need a functioning thoracic epidural catheter for several days.

Postoperative Neuropsychologic Morbidity

Neurologic morbidity has been identified to be increasingly problematic in neonates and infants with congenital heart disease as surgical mortality rates have improved. Although early postoperative CNS sequelae such as stroke and seizures occur in a small percentage of neonates with congenital heart disease, the importance of more subtle neurologic abnormalities at long-term follow-up is being increasingly recognized.[223,258-266]

These findings may include fine and gross motor impairments, speech and language delays, disturbances in visual-motor and visual spatial abilities, attention-deficit disorders, learning disorders, and impaired executive functioning. The presence of "congenital brain disease" in patients with congenital heart disease represents a challenge in improving long-term neurologic outcomes. Many neonates with CHD have congenital structural brain abnormalities or chromosomal abnormalities or both, as well as physiologic abnormalities that may impair brain development. Brain abnormalities on head ultrasonography have been noted in one fifth of full-term infants undergoing heart surgery, with half of the abnormalities being present preoperatively.[266]

Postoperatively, secondary neurologic injury may be related to post-CPB alterations in cerebral autoregulation and additional hypoxic-ischemic insult, seizures, or other issues associated with prolonged ICU stay. In addition to prenatal and modifiable perioperative factors, genetic and environmental factors are known to be important. Unfortunately, modifiable perioperative factors may explain less of the variability in long-term outcomes than do patient-specific factors.

New, postoperative neurologic injury may be detected clinically in over 10% of infants,[7] and in over 50% using more sensitive brain imaging techniques such as MRI.[267,268] Given that new neurologic injury can occur at various time points during the neonate's hospitalization, perioperative attention to reducing known risk factors is critical. Mechanisms of CNS injury in infants undergoing cardiac surgery include hypoxia-ischemia, emboli, reactive oxygen species, and inflammatory microvasculopathy. Preoperatively, the primary focus is on preventing hypoxic-ischemic injury and thromboembolic insults. Modifiable intraoperative factors associated with CNS injury include, but are not limited to, pH management, hematocrit during CPB, regional cerebral perfusion, and the use of DHCA. The adverse effects of CPB may be greater in infants compared with larger children or adults given their immaturity in organ function and tissues as well as the size of the CPB circuit relative to their body size.[269] However, a significant amount of research has been conducted in the area of intraoperative prevention of neurologic injury. With ongoing changes in technology and new therapies, the conduct of CPB and other support techniques have been actively under investigation

Mechanical Assist Devices

Survival in children with congenital cardiac as well as pulmonary defects has improved over recent decades due to improved preoperative management, surgical techniques, anesthesia

management, drug therapies, and postoperative management. Despite these advances patients may still require therapies for both acute and chronic heart failure that are refractory to medical therapy. Mechanical support in the form of ECMO or ventricular assist devices (VADs) may then need to be instituted. Examples of conditions that may require support include failure to wean from CPB, acute cardiac arrest, malignant arrhythmia, and worsening myocardial function secondary to the underlying congenital defect or related to acquired cardiomyopathy. Fortunately, however, the numbers are small, with less than 2% of post-CPB patients requiring this intervention.[270] Mechanical support can thus be used as a treatment option to allow for recovery of ventricular function, as a bridge to transplant, or to support the heart in those with marginal functional reserve requiring invasive diagnostics or treatments (e.g., Williams' syndrome with severe supravalvar pulmonary or aortic stenosis). As with any therapy, contraindications must be excluded before embarking on the use of a mechanical assist device. These contraindications may include extreme prematurity, severe and irreversible multiorgan failure, incurable malignancy, and preexisting neurologic devastation.[270] Anesthetic management in the use of ECMO is supportive with management limited to assistance in the resuscitative efforts and hemorrhage associated with the cardiac surgery that was ongoing at the time of conversion to ECMO. Once the patient is on full ECMO support, ventilation is continued but at a slower rate of ventilation in the order of 10 breaths/min with peak pressure of 20 cm H_2O with PEEP set at 5 to 10 cm H_2O and F_{IO_2} also decreased to about 40%. These settings will aid in the prevention of atelectasis with management of CO_2 and O_2 related to flow across the circuit membrane. This is very different from the patient into whom a VAD is placed. Here the anesthesiologist continues to manage the patient as for routine CPB weaning. Obviously differences exist in this scenario. If a systemic VAD is placed, careful attention must be given to the ventricle pumping blood into the pulmonary bed because failure of this ventricle will have disastrous consequences. Thus, management tailored to unload this pulmonary ventricle is vitally important and will include inodilators in the form of phosphodiesterase inhibitors, inotropic support, and possibly even inhaled nitric oxide to decrease PVR and promote forward flow. In association with the perfusionist, intravascular volume loading is assessed and maintained for effective functioning of the VAD and thus adequate offloading of the assisted ventricle. Careful attention to pulmonary function is also vital. Adequate pulmonary toilet, recruitment maneuvers, and appropriate ventilatory parameters must be utilized. As will be alluded to later, bleeding is a potential in the implantation of the VAD and thus a clear strategy must be planned for in the form of antifibrinolytics, adequate volumes of blood and blood products, and even possibly the use of activated clotting factors (e.g., factor VII).[271]

As can be seen from Table 83-13 there are a number of differences that can be appreciated between the just-mentioned assist devices. The potential for bleeding exists at the time of insertion of both of these modalities; however, it would seem from clinical experience that due to the extensive dissection and need for sizeable ventriculotomy that implantation of a VAD (and especially Bi-VAD) is more problematic. That being said, however, the requirements of anticoagulation to keep the activated clotting time in the range of 180 to 200 for ECMO may also lead to ongoing and significant bleeding, especially if placed into a patient who requires support in the immediate perioperative phase. The use of an ECMO circuit with a membrane oxygenator requires ongoing intravenous anticoagulation with maintenance of the ACT in the aforementioned range. Apart from the immediate postoperative phase, patients with VAD systems can be transitioned to oral agents. A two-part therapy is recommended. Antiplatelet therapy includes aspirin or clopidrogel. The second part of the therapy will entail the use of anticoagulation with either warfarin (Coumadin) or subcutaneous low-molecular-weight heparin.[270]

Table 83-13 Comparison of ECMO versus VAD

	ECMO	VAD
Bleeding at insertion	++	++
Sternotomy	Not required	Required
Left atrial venting	±	–
Blood product use	+++	+
Number of cannulae for biventricular support	2	4
Pulmonary support	+	–
Intravenous anticoagulation	+	±
Duration of support	Weeks	Months
Emergent support	Yes	No
Patient mobility	–	+

ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.

As previously mentioned these modalities are used as a potential bridge to transplant and, as such, exposure to donor antigens is of great importance. In a study by Stiller and associates comparing the volume of blood products used, it was shown that the volume was less in those treated with a VAD in a period up to 8 days after insertion. Importantly, the authors pointed out that this difference remained even when support was started at a time remote from surgery.[272]

Three potential disadvantages exist in the use of the VAD system. There is no pulmonary support when using the VAD, and this limits its use to patients whose lung function is adequate. From Table 83-13, when biventricular support is needed the patient will require two separate VAD devices necessitating the placement of four cannulae that may be technically difficult in a very young child. The third disadvantage is that VAD placement cannot be performed in a code situation or at the bedside as with ECMO.

Important advantages of the VAD system are the ability of patients to ambulate while on support and that VAD support can be maintained for months in comparison to the weeks only of ECMO support. Another important advantage over ECMO is that these patients will not require further venting of the left atrium. In ECMO patients this is achieved by the placement of a left atrial vent at the time of sternotomy or a balloon atrial septectomy, which may require transfer to the catheterization laboratory with the possible complications associated with transport of a patient on an ECMO circuit.

Despite successful resuscitation and placement onto mechanical assist devices, morbidity and mortality remain high, with ECMO appearing to have worse outcomes. The mortality rate for ECMO in the 1990s was on the order of 47%, with survival in series published in the early 2000s not showing much

improvement.[274-277] In contrast, the survival in those into whom a VAD is placed appears to be superior within the quoted series up to 80% of patients surviving to transplantation or being successfully weaned from support.[274,278] In the study by Blume and coworkers,[275] it was, however, noted that associated congenital heart disease, and patients who are younger and smaller, have a higher mortality when compared with those with fulminant myocarditis and cardiomyopathy. Alongside survival data, the next most important marker is neurologic outcome and it appears that this is better in the VAD group.[279,280] Risk factors for poor neurologic outcome were once again low weight and duration of DHCA, both of which place ECMO patients at a survival disadvantage because ECMO patients will be smaller and a number of those who undergo DHCA for repair of congenital anomalies will require emergent ECMO support to wean from CPB or in the immediate postoperative phase.[281]

Survival predictors are important in our management of these patients. It appears that one common variable that can predict survival is the return of ventricular function between 3 and 5 days after the initiation of support; and should the support be required for longer periods of time, morbidity and mortality increases.[276,281] As mentioned earlier, both of these modalities have been used successfully as a bridge to transplantation, with VAD patients having a greater than 80% survival to transplantation and ECMO patients showing a less than 60% survival. These data, however, may be skewed because ECMO is used often in the infant population and in those with complex congenital heart disease, both of which are factors known to increase mortality among VAD patients.[278] The important causes of morbidity and mortality in patients on both of these modalities include cerebrovascular events secondary to either hemorrhagic or embolic phenomena, circuit-related issues (e.g., circuit thrombosis), renal failure requiring hemofiltration, sepsis, ongoing hemorrhage, and multiple-organ failure.

Although these modalities are often compared alongside each other, they both have unique places in the care of children with cardiac disability. ECMO has a great advantage in that it can be employed rapidly in a code situation for a patient of any age or size. In the past, size has been the limiting factor for implantation of VAD systems into pediatric patients. The Berlin Heart VAD (Berlin Heart AG, Berlin, Germany) is available for use even in neonates. The system has been employed in Europe for over 10 years and has pump sizes from 10 to 80 mL. At this time the device is available only for emergency compassionate use in the United States. From this, however, it can be appreciated that these two modalities can certainly complement each other, with ECMO being used acutely; once the patient is physiologically stable, but still requiring support, a VAD can be used should long-term support be warranted.

Anesthesia for Heart and Lung Transplantation

Although perioperative management for thoracic organ transplantation is considered elsewhere in this text, the application of these procedures to children requires some specific modification. Differences include the characteristics of the candidates, preparation of these children, anesthetic management, surgical considerations, post-CPB management, and outcome. Even though some of the earliest heart transplant procedures were performed for congenital heart malformations, this indication became rare by the early 1980s. In 1984, over 60% of the few pediatric heart transplant procedures were performed in patients with cardiomyopathy, usually adolescents. In the next decade, a dramatic rise in the number of infants and young children with congenital heart malformations treated with heart transplantation resulted in a marked shift in the demographics (Fig. 83-14).[282] By 1995, over 70% of the children receiving heart transplants were younger than 5 years of age, with half of those younger than age 1. The overwhelming majority of these infants received transplants for congenital heart malformations for which reconstructive options either had failed or were not believed to exist (Fig. 83-15).[282] The implications of this shift reach into every element of perioperative management.

Children considered for heart transplantation are more likely to have pulmonary hypertension than adults. Most adult transplant programs will not offer heart transplant therapy to patients with PVR over 6 Wood units/m^2.[283] The exclusion threshold in infants and children remains controversial. Some programs accept patients with PVR as high as 12 Wood units/m^2, particularly if the pulmonary vasculature responds to vasodilators such as oxygen, nitric oxide, calcium channel blockers, or prostacyclin.[284] Neonates are generally assumed to have elevated PVR, but outcome data from some programs suggest that the importance

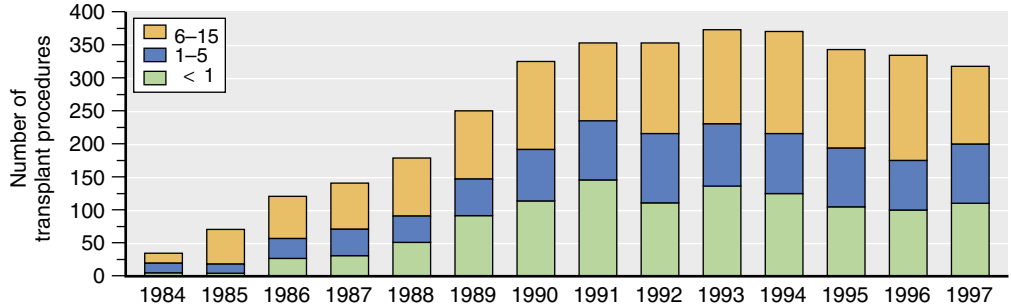

Figure 83-14 Demographic data for pediatric heart transplantation by age. Stacked bar graph illustrates the total number and age distribution for heart transplantation in patients younger than 16 years of age. Note the rapid rise in transplant procedures performed during the late 1980s, with particular growth in the population of children aged 5 years and younger. Having peaked in the mid 1990s, the total number of transplant procedures (both adult and pediatric) has declined slightly, but the relative age proportions within the pediatric population remain relatively constant. (*Data from the Registry of the International Society for Heart and Lung Transplantation.*[282])

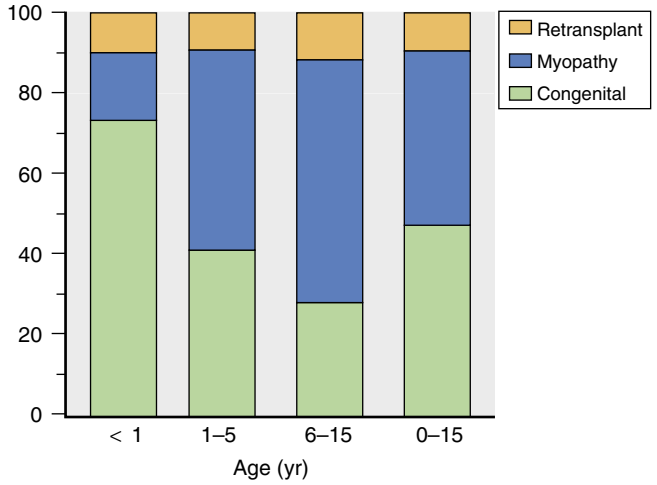

Figure 83-15 Indication for heart transplantation in children. Over the past 2 decades, the major indications for pediatric heart transplantation were nearly equally divided between congenital malformation and cardiomyopathy. In later years, pediatric recipients with congenital malformations assumed a slight plurality due to shifting age demographics. As illustrated, younger children are more likely to undergo heart transplantation because of congenital malformation. (*Data from the Registry of the International Society for Heart and Lung Transplantation.*[282])

of this factor for postoperative outcome is substantially less in the first year of life, perhaps because the infant donor hearts, having recently undergone transitional circulation, are better prepared to cope with the right ventricular pressure load that elevated PVR imposes.[285]

The anesthetic plan for pediatric heart transplantation must accommodate a wide spectrum of pathophysiology. Recipients with congenital heart malformations benefit from the analysis of loading conditions and optimizing hemodynamics discussed previously. Although a few of these patients undergo heart transplantation because the natural history of reconstructive heart surgery poses greater risk despite reasonable ventricular function, most candidates exhibit some manifestations of impaired ventricular performance. Accordingly, they require careful titration of anesthetic agents with minimal myocardial depressant characteristics to avoid cardiovascular collapse. In this fragile population, even modest doses of opioids can be associated with marked deterioration in systemic hemodynamics, presumably by reducing endogenous catecholamine release. As with most congenital heart patients, skilled management of the airway and ventilation represents crucial elements in a satisfactory induction, particularly in the presence of elevated PVR. No matter how elegant the anesthetic plan in conception and implementation, a certain proportion of these children will decompensate on induction, necessitating resuscitative therapy.

Although orthotopic heart transplantation poses some technical challenges in neonates and young infants, the replacement of an anatomically normal heart is less complex than several reconstructive heart procedures commonly performed in patients at this age. However, the need to adapt this procedure to incorporate repair of major concurrent cardiovascular malformations requires the consummate skill and creativity that remain the province of a few exemplary congenital heart surgeons.[286,287]

Having withstood extended ischemic periods, heart grafts are extraordinarily intolerant of superimposed residual hemodynamic loads that may accompany imperfect vascular reconstruction. The extensive vascular repair and, particularly in older children with longstanding hypoxemia, the propensity to coagulopathy together elevate hemorrhage to a major cause of morbidity and even mortality in pediatric heart transplantation. Nevertheless, once successfully implanted, these grafts will respond to physiologic factors that stimulate growth and adaptation in the developing infant and child.[288]

Management considerations during separation from CPB and the early postoperative period are primarily focused on three pathophysiologic conditions: myocardial preservation, denervation, and PVR. Even expeditious transplant procedures usually force the heart to endure ischemic periods that exceed those encountered during reconstructive surgery. Although some researchers believe the infant heart is more tolerant of extended ischemia,[285] these hearts will demonstrate a period of reperfusion injury, and virtually all require pharmacologic and, in some cases, mechanical support. In addition, endogenous adaptive responses and exogenous pharmacologic agents that act via myocardial sympathetic activation are ineffective in the denervated graft. Because the majority of children presenting for heart transplantation exhibit some element of elevated PVR, even with isolated end-stage cardiomyopathy, the RV of a newly implanted heart is particularly vulnerable to failure.

As such, ventilatory and pharmacologic interventions are usually configured to exert a favorable impact on PVR and provide inotropic and chronotropic support. Once the lungs are fully expanded, we ventilate to $Paco_2$ values in the low 30s using an Fio_2 of 1. Virtually all recipients receive low-dose dopamine (3-5 μg/kg/min) and isoproterenol (0.02-0.05 μg/kg/min) to promote inotropy, chronotropy, and lower PVR. In the event that these do not provide sufficient inotropy in the presence of more significant postischemic dysfunction, additional agents are added (e.g., milrinone, epinephrine). Most transplant centers have a specific regimen for immunosuppression to be initiated in the perioperative period. As with adults, pediatric transplant programs typically employ triple-drug immunosuppression with a calcineurin inhibitor (e.g., cyclosporine, tacrolimus), antimetabolite (e.g., azathioprine), and steroid. After an interval without rejection, some pediatric programs will taper and discontinue one or even two of these agents, particularly in neonates, in whom some element of tolerance is thought to develop.[289,290]

National statistics indicate that the outcome from pediatric heart transplantation is slightly less favorable than comparable adult results.[282] The principal risk factors are age younger than 1 year and congenital heart defects. Because these factors are closely related (i.e., the vast majority of infants younger than age 1 undergo transplantation for a congenital heart defect), it is difficult to determine the independent effect of age. Concurrent repair of structural cardiovascular anomalies substantially increases perioperative risk of hemorrhage, residual hemodynamic loading conditions, and right-sided heart failure from elevated PVR. When these two factors are taken together, infants younger than 1 year of age have an operative mortality rate of 24%, more than twice that of older children.[282] Beyond the early postoperative period, mortality rates are quite comparable for all age groups. Nevertheless, the sequelae of rejection and the consequences of the requisite immunosuppression result in significant ongoing morbidity and mortality. Because even the best transplant recipi-

ents have achieved only a 28% 14-year survival rate, these procedures must be considered palliative for children.[282]

Lung and heart-lung transplantation have achieved respectable operative survival rates in children.[291,292] They remain the only viable surgical therapy for infants and children with severe pulmonary vascular disease and selected progressive pulmonary diseases. These remain uncommon procedures in pediatrics. Lung transplantation carries the additional morbidity of obliterative bronchiolitis, a debilitating small airway disease that results in gradual deterioration in flow-related pulmonary functions over time. Despite an operative mortality rate that is currently less than 20%, the 3-year survival rate is only 50% to 60%.[282,292]

Patients with transplanted hearts also present for surveillance cardiac catheterizations, biopsies, and other procedures.[270,293-295] The anesthesia plan in these patients should take into effect the physiologic and pharmacologic problems of allograft denervation, the side effects of immunosuppression, the risk of infection, and the potential for rejection.[293-295] Cardiac allograft vasculopathy is the leading cause of morbidity and mortality after transplantation, leading to progressive graft dysfunction with heart failure, an increased risk of dysrhythmia, and the possibility of arrhythmogenic sudden death. Conventional revascularization procedures are ineffective because cardiac allograft vasculopathy is caused by intimal proliferation; thus, retransplantation is the only therapeutic option. Hyperlipidemia after heart transplantation is a common occurrence in both adults and children and is aggravated by chronic steroid therapy and other immunosuppressive agents. Statins are used with good results in controlling hyperlipidemia after transplantation and are likely to manifest inherent immunosuppressive effects. Risk factors for post-transplant renal dysfunction are the use of calcineurin inhibitors, mechanical circulatory support, prolonged inotropic support, and preexisting renal dysfunction. Newer, more potent immunosuppressive agents (e.g., tacrolimus) have led to steroid-sparing regimens late after transplantation, eliminating the detrimental effects of long-term steroid administration. Agents such as sirolimus may now be used in combination with lower levels of calcineurin inhibitors, thus minimizing long-term nephrotoxicity. Post-transplant lymphoproliferative disorders represent a pathologic spectrum of abnormal lymphoid proliferation ranging from localized early lesions to polymorphic disease or, in some cases, monomorphic lymphomatous disease. From a clinical perspective, the most common sites of disease and presenting symptoms included the gastrointestinal tract and pulmonary systems. Patients with polymorphic disease are treated primarily by a reduction or temporary cessation of immunosuppression along with adjunctive surgical therapy for tissue diagnosis or obstructive lesions. Most centers reserve traditional chemotherapeutic regimens for patients with nonresponsive polymorphic disease and monomorphic disease. As a result of cardiac denervation, autonomic regulatory mechanisms are not available to prevent the wide swings in a patient's hemodynamic state, and the stress response is slower than usual. Cardiac parameters are significantly altered, and patients may experience a decrease in systemic blood pressure and cardiac filling pressures. Compensatory mechanisms are delayed, and reductions in cardiac output lead to decreased coronary and cerebral perfusion, especially on the background of hypertension. Drugs with direct myocardial and vascular effects are the mainstay of therapy. Most immunosuppressive agents affect hepatic and renal functions and interact with anesthetic drugs.

Anesthesia for Closed-Heart Operations

Early corrective repair in infancy has significantly reduced the number of noncorrective, palliative closed-heart operations. Corrective closed-heart procedures include PDA ligation and repair of coarctation of the aorta. Noncorrective closed-heart operations include pulmonary artery banding and extracardiac shunts such as the Blalock-Taussig shunt. These procedures are performed without CPB. Therefore, venous access and intra-arterial monitoring are important in evaluating and supporting these patients. A pulse oximeter remains an invaluable monitor during intraoperative management.

Ligation of a PDA is typically performed through a left thoracotomy, although video-assisted thoracoscopic techniques are increasingly common.[296,297] Physiologic management is that of a left-to-right shunt producing volume overload. Patients with a large PDA and low PVR generally present with excessive PBF and congestive heart failure. Neonates and premature infants also run the risk of having substantial diastolic runoff to the pulmonary artery, potentially impairing coronary perfusion. Thus, patients range from an asymptomatic healthy young child to the sick ventilator-dependent premature infant on inotropic support. The health of the former patient allows a wide variety of anesthetic techniques culminating in extubation in the operating room. The latter patient requires a carefully controlled anesthetic and fluid management plan. Generally, a trial of medical management with indomethacin and fluid restriction is attempted in the premature infant before surgical correction. Transport of the premature infant to the operating room can be especially difficult and potentially hazardous, requiring great vigilance to avoid extubation, excessive patient cooling, and venous access disruption. For these reasons, many centers are now performing ligation in the neonatal ICU.

There is a subset of premature infants with PDAs at institutions without cardiac surgical teams. Ligation of the PDA in these patients requires either transfer of these high-risk neonates to a center that has a team that routinely performs the procedure or the availability of a team capable of performing the procedure that is willing to travel to perform the procedure in the neonate's home neonatal intensive care unit (NICU). Gould and associates[298] reviewed the experience with on-site and off-site ligations of a team composed of a pediatric cardiac attending anesthesiologist, a certified registered nurse anesthetist, an attending pediatric cardiothoracic surgeon and fellow, and cardiac operating room nurses. There were no anesthetic-related complications in their group. No differences were found in the incidence of perioperative complications in the procedures in the two sites. This study showed PDA ligations can be performed safely in the NICUs of hospitals lacking on-site pediatric cardiac surgical units, without incurring the risk inherent in transport of critically ill infants. In addition, patient care is continued by the neonatology team most familiar with the child's medical and social history and the patient's family is minimally inconvenienced.

Complications of PDA ligation include inadvertent ligation of the left pulmonary artery or descending aorta, recurrent laryngeal nerve damage, and excessive bleeding due to inadvertent PDA disruption. After ductal ligation in premature infants, worsening pulmonary compliance can precipitate a need for increased

ventilatory support; and manifestations of an acute increase in left ventricular afterload should be anticipated, especially if left ventricular dysfunction has developed preoperatively. PDA ligation has been performed in infants and children using thoracoscopic surgical techniques. This approach has the advantage of limited incisions at thoracoscopic sites, promoting less postoperative pain and discharge from the hospital the same day of surgery.

Coarctation of the aorta is a narrowing of the descending aorta near the insertion of the ductus arteriosus. Obstruction to aortic flow results and may range from severe obstruction with compromised distal systemic perfusion to mild upper extremity hypertension as the only manifestation. Associated anomalies of both the mitral and aortic valves can occur. In the neonate with severe coarctation, systemic perfusion is dependent on right-to-left shunting across the PDA. In these circumstances, left ventricular dysfunction is very common and prostaglandin E_1 is necessary to preserve sufficient systemic perfusion. Generally, a peripheral intravenous line and an indwelling arterial catheter, in the right upper extremity, are recommended for intraoperative and postoperative management. In patients with left ventricular dysfunction, a central venous catheter may be desirable for pressure monitoring and inotropic support.

The surgical approach is through a left thoracotomy, whereby the aorta is cross-clamped and the coarctation repaired with an end-to-end anastomosis, patch aortoplasty, or subclavian patch. During cross-clamping, we usually allow significant proximal hypertension (20% to 25% increase over baseline), based on evidence that vasodilator therapy may jeopardize distal perfusion and promote spinal cord ischemia. Intravascular volume loading with 10 to 20 mL/kg of crystalloid is given just before removal of the clamp. The anesthetic concentration is decreased, and additional blood volume support is given until the blood pressure rises. Post-repair rebound hypertension due to heightened baroreceptor reactivity is common and often requires medical therapy. After cross-clamping, aortic wall stress due to systemic hypertension is most effectively lowered by institution of β-blockade with esmolol or α/β-blockade with labetalol.[299] Recent work indicates that patients younger than 6 years of age should receive a loading dose of 250 to 500 μg/kg of esmolol, followed by an infusion of 250-750 μg/kg/min, depending on the blood pressure. Despite an esmolol infusion, 25% to 50% of patients have a blood pressure that is above the targeted range, requiring a second drug. Sodium nitroprusside, which increases the calculated aortic wall stress in the absence of β-blockade, is usually chosen as the second drug. Other agents that may have a greater likelihood of achieving the targeted pressure include nitroglycerin and nicardipine. Propranolol is useful in older patients but can cause severe bradycardia in infants and young children. Although it actually increases calculated aortic wall stress in the absence of β-blockade by accelerating dP/dT (contractile force), the addition of sodium nitroprusside may be necessary to control refractory hypertension. Captopril or an alternative antihypertensive regimen is begun in the convalescent stage of recovery in those patients with persistent hypertension.

The management of infants undergoing placement of extracardiac shunts without CPB centers on goals similar to those of other shunt lesions: balancing pulmonary and systemic blood flow by altering $Paco_2$, Pao_2, and ventilatory dynamics. Central shunts are usually performed through a median sternotomy, whereas Blalock-Taussig shunts may be performed through a thoracotomy or sternotomy. In patients in whom PBF is critically low, partial cross-clamping of the pulmonary artery required for the distal anastomosis causes further reduction of PBF and desaturation, necessitating meticulous monitoring of pulse oximetry. Careful application of the cross-clamp to avoid pulmonary artery distortion will help maintain PBF. Under circumstances in which severe desaturation and bradycardia occur with cross-clamping, CPB will be required for the procedure.

Intraoperative complications include bleeding and severe systemic oxygen desaturation during chest closure, usually indicating a change in the relationship of the intrathoracic contents that results in distortion of the pulmonary arteries or kink in the shunt. Pulmonary edema may develop in the early postoperative period in response to the acute volume overload that accompanies the creation of a large surgical shunt. Measures directed at increasing PVR, such as lowering inspired O_2 to room air, allowing the $Paco_2$ to rise, and adding positive end-expiratory pressure are helpful maneuvers to decrease PBF until the pulmonary circulation can adjust. Decongestive therapy such as diuretics and digoxin may alleviate the manifestations of congestive heart failure. Under such circumstances, early extubation is inadvisable.

Pulmonary artery banding is used to restrict PBF in infants whose defects are deemed uncorrectable for either anatomic or physiologic reasons. These patients are generally in congestive heart failure with reduced systemic perfusion and excessive PBF. The surgeon places a restrictive band around the main pulmonary artery to reduce PBF. Band placement is very imprecise and requires careful assistance from the anesthesia team to accomplish successfully. Many approaches have been suggested. We place the patient on 21% inspired oxygen concentration and maintain the $Paco_2$ at 40 mm Hg, to simulate the postoperative state. Depending on the malformation, a pulmonary artery band is tightened to achieve hemodynamic (e.g., distal pulmonary artery pressure 50%-25% systemic pressure) or physiologic (e.g., $\dot{Q}p:\dot{Q}s$ approaching 1) goals. Should the attainment of these objectives produce unacceptable hypoxemia, the band is loosened.

Anesthesia for Interventional or Diagnostic Cardiac Procedures

Advances in interventional and diagnostic cardiac catheterization techniques are significantly changing the operative and nonoperative approach to the patient with a congenital heart defect. Common interventions in the cardiac catheterization laboratory are shown in Table 83-14. Nonoperative interventional techniques are being used instead of procedures requiring surgery and CPB for safe closure of secundum ASDs, VSDs, and PDAs. Stenotic aortic and pulmonic valves, recurrent aortic coarctations, and branch pulmonary artery stenoses can be dilated in the catheterization laboratory, avoiding surgical intervention.[300,301] These techniques shorten the hospital stay and are particularly beneficial to patients with recurrent coarctation and muscular or apical VSDs, who are at a higher risk of operative intervention. Many patients

Table 83-14 Common Interventions in the Cardiac Catheterization Laboratory

Simple Interventions	
Device Closures	**Coil Embolization**
Atrial septal defect (ASD)	Decompressing veins
Ventricular septal defect (VSD)	Aortopulmonary (AP) collaterals
Patent ductus arteriosus (PDA)	Surgical shunts
Patent foramen ovale (PFO)	Coronary/atrioventricular fistulas
Balloon valvuloplasty	Balloon angioplasty
Aortic stenosis (AS)	Branch pulmonary artery stenosis
Pulmonary stenosis (PS)	Coarctation of the aorta
Complex Interventions	
Hypoplastic Left Heart Syndrome (HLHS)	
Post Norwood	
Pulmonary artery stenosis	Angioplasty
Shunt thrombosis	Dilation/thrombectomy
Restrictive ASD	Balloon septostomy
Aortic arch obstruction	Angioplasty
AP collaterals	Coil embolization
Post Glenn/Fontan	
Decompressing veins	Coil embolization
Baffle leaks	Device/coil embolization
Systemic vein stenosis/thrombosis	Angioplasty/thrombectomy
RV failure	Creation of fenestration
Exercise intolerance	Closure of fenestration
AP collaterals	Coil embolization
Obstructive Fontan pathway	PA angioplasty, balloon septostomy)
Transposition of Great Arteries	Balloon atrial septostomy
Tetralogy of Fallot	
Shunt thrombosis	Thrombectomy
Pulmonary artery stenosis	Angioplasty
AP collaterals	Coil occlusion
Miscellaneous Interventions	
Severe pulmonary hypertension	Atrial septostomy
ECMO left heart decompression	Atrial septostomy
Stenosis of pulmonary veins	Balloon angioplasty stent
Stenosis/thrombosis of systemic veins	Balloon angioplasty/thrombectomy

with complex cardiac defects are poor operative risks. Innovative interventional procedures improve vascular anatomy, reduce pressure loads on ventricles, and decrease the operative risk for these patients. For example, in tetralogy of Fallot with hypoplastic pulmonary arteries, balloon angioplasty and vascular stenting procedures create favorable pulmonary artery anatomy and reduce pulmonary artery pressure and right ventricular end-diastolic pressure. Complications are more common during interventional catheterization and include arterial thrombosis, arrhythmias (especially heart block), hemodynamic instability, embolization of devices or coils, bleeding, and perforation of the major vessels or heart.[302] Complications are more common in infants younger than 6 months and with smaller infants. Constant vigilance, correction of electrolyte imbalance, maintenance of acid-base status, and appropriate heparinization will mitigate some of the morbidity. Appropriate and early transfusion with deployment of rapid-response ECMO in the resuscitation of an infant in cardiac arrest improves outcome. High-risk patients undergoing diagnostic evaluation of pulmonary artery hypertension in anticipation of heart-lung transplantation also require anesthetic management. Despite the attendant high risks of the procedure in patients with suprasystemic right ventricular pressure, these patients are best managed with general anesthesia and controlled ventilation.

Anesthetic management of interventional or diagnostic procedures in the catheterization laboratory must include the same level of preparation that applies in caring for these patients in the operating room. These patients have the same complex cardiac physiology and, in some cases, greater physiologic complexity and less cardiovascular reserves. Interventional catheterization procedures can impose acute pressure load on the heart during balloon inflation. Large catheters placed across mitral or tricuspid valves create acute valvular regurgitation or, in the case of a small valve orifice, transient valvular stenosis. When catheters are placed across shunts, severe reductions in PBF and marked hypoxemia may occur. The anesthetic plan must consider the specific cardiology objectives of the procedure and the impact of anesthetic management in facilitating or hindering the interventional procedure. In general, there are three distinct periods involved in an interventional catheterization: the data acquisition period, the interventional period, and the postprocedural evaluation period.

During the data acquisition period, the cardiologist performs a hemodynamic catheterization to evaluate the need for and extent of the planned intervention. Catheterization data are obtained under normal physiologic conditions; that is, room air, physiologic $Paco_2$, and spontaneous ventilation are preferred. Increased Fio_2 or changes in $Paco_2$ may obscure physiologic data. During the procedural period, the patient is usually intubated and mechanically ventilated. A secured airway allows the anesthesiologist to concentrate on hemodynamic issues. Positive-pressure ventilation also reduces the risk of air embolism. During spontaneous ventilation, a large reduction in intrathoracic pressure can entrain air into vascular sheaths and result in moderate to large pulmonary or systemic air emboli. Precise device placement is also facilitated with muscle relaxants that eliminate patient movements and controlled ventilation, thereby reducing the respiratory shifting of cardiac structures. Substantial blood loss and changes in ventricular function occur commonly during the intervention. Blood volume replacement and inotropic support may be necessary during or immediately after the interventional procedure.

In the postprocedural period, the success and the physiologic impact of the intervention are evaluated. Blood pressure, mixed venous oxygen saturation, ventricular end-diastolic pressure, and cardiac output, when available, are used to assess the impact of the intervention. Persistent severe hemodynamic derangement indicates the need for ICU monitoring and respiratory or cardiovascular support. Because of the hemodynamic variability of many of these patients, as well as changing anesthetic requirements, continuous intravenous infusion with ketamine/midazolam or propofol is appropriate. Potent inhaled anesthetics are generally not used as the primary anesthetic and are reserved for adjunctive anesthesia.

A brief description of some of the interventional procedures and the associated anesthetic implications follows. The success of these interventions will undoubtedly result in widespread availability and use over the next few years.

Transcatheter Technique for Atrial Septal Defect Closures

In the transcatheter technique for ASD closures, a collapsed double-umbrella clamshell device is loaded into a large introducer sheath placed through the femoral vein, advanced to the right atrium, and placed across the ASD into the left atrial chamber. Each side of the device consists of a Dacron mesh patch suspended in six spring-loaded arms that open like an automatic umbrella. Using biplane fluoroscopy and TEE, the catheter is positioned in the left atrium away from the mitral valve.[303] The sheath is pulled back to open the six distal arms and its Dacron mesh cover into the left atrium. The sheath and device are then pulled back so the distal arms contact the left atrial septum. Fluoroscopy and TEE are used to confirm that the arms are on the left atrial side and do not interfere with mitral valve motion. Once adequately seated, the sheath is pulled farther back to expose the proximal side of the device and the proximal arms, which spring open to engage the right side of the atrial septum. When proper positioning is certain, the device is released.[303] In a review of data for 122 children undergoing transcatheter ASD closures, there was a 9% incidence of procedural complications that resulted in hemodynamic complications requiring treatment.[304]

Device closure of secundum ASD is the preferred therapeutic approach. Data continue to support closure of small to moderate size defects (<8-20 mm) in appropriate-size patients with appropriate septal length and device diameter.[305-307] The procedure is well tolerated with minimal long-term complications. Complications such as cardiac erosions and heart block can occur in patients who receive a large device for patient size, especially those who have a deficient anterosuperior rim.[308-309] Thrombus is a rare problem that can usually be treated medically, and its incidence appears to be device-dependent.[310] Despite nearly a decade of experience, these devices remain under investigational protocol and are therefore available only at a limited number of study centers.

Transcatheter Ventricular Septal Defect Closures

Most VSDs that are electively closed in the catheterization laboratory are mid-muscular or apical VSDs that are either difficult to close in the operating room or would require a left ventriculotomy. Left ventriculotomies are associated with a high incidence of left ventricular dysfunction and have been relegated to a position as the least desirable surgical option. The preferred therapeutic approach for VSD is surgical closure. Transcatheter closure of muscular VSDs can be performed safely. However, there is a significant incidence of complications including heart block, blood loss, and hemodynamic instability.[311,312] Device closure of membranous VSD is in early stages of investigation, and the incidence of complications remains to be determined.[313-314] The transcatheter approach requires a blade atrial septostomy and a retrograde catheter placed through the femoral artery and advanced to the left atrium. This catheter is pulled across the atrial septum into the right atrium and is used to guide a superior vena cava catheter (placed through the internal jugular vein) across the ASD into the left atrium, across the mitral valve, and into the LV. The VSD defect is approached from the left ventricular side. The large sheath containing the double-umbrella clamshell device prevents closure of the mitral valve, resulting in acute mitral regurgitation or, in cases in which the VSD is large or the mitral annulus small, acute severe mitral stenosis. In this latter case, systemic output is decreased and a period of severe hypotension is unavoidable. Judicious use of vasoconstrictors to maintain coronary perfusion may be required during the catheter placement, followed by volume and inotropic resuscitation after the VSD device is deployed. This highly specialized application of the clamshell device is confined to only a few pediatric centers in the United States.

Angioplasty of Branch Pulmonary Artery Stenosis

One of the most important areas of interventional catheterization has been the dilation and stenting of hypoplastic or stenotic branch pulmonary arteries. In patients with tetralogy of Fallot with hypoplastic pulmonary arteries, pulmonary atresia, or single ventricle with surgically induced peripheral stenoses, the use of balloon angioplasty and stenting procedures creates favorable pulmonary artery anatomy and reduces the risk of subsequent surgical repairs (Fig. 83-16). Peripheral pulmonary artery stenosis is not a surgically amenable lesion and is particularly suited to catheterization and angioplasty. Balloon angioplasty is accomplished by tearing the vascular intima and media, allowing the vessel to remodel and heal with a larger diameter. The balloon is placed across the stenotic lesion so that the middle of the balloon is at the stenosis. The balloon is inflated until the waist of the balloon is eliminated. Ideally, the most stenotic lesions are dilated first to minimize the impact on PBF and cardiac output. When the balloon is inflated, PBF is reduced, right ventricular afterload is increased, and cardiac output falls. In patients with an associated VSD or ASD, right-to-left shunting and desaturation occur with balloon inflation. In patients without a shunt, acute increase in right ventricular afterload can cause systemic hypotension and right ventricular failure. The large vascular sheaths required for these procedures can introduce tricuspid regurgitation, which is poorly tolerated in patients with severe RV hypertension. Occasionally, balloon catheters must be placed across aortopulmonary shunts, significantly reducing PBF.

The procedure is successful in approximately 60% of patients. In an early series, complications included hypotension (40%), pulmonary artery rupture (3%), unilateral reperfusion pulmonary edema (4%), aneurysmal dilation of the dilated pulmonary vessel (8%), death (1.5%), and transient postprocedural right ventricular dysfunction.[315] Improved techniques and patient selection have favorably influenced the results with superior balloon catheters and stents while significantly reducing serious complications. Anesthetic support minimizes hemodynamic compromise by anticipating changes in blood flow patterns, treat-

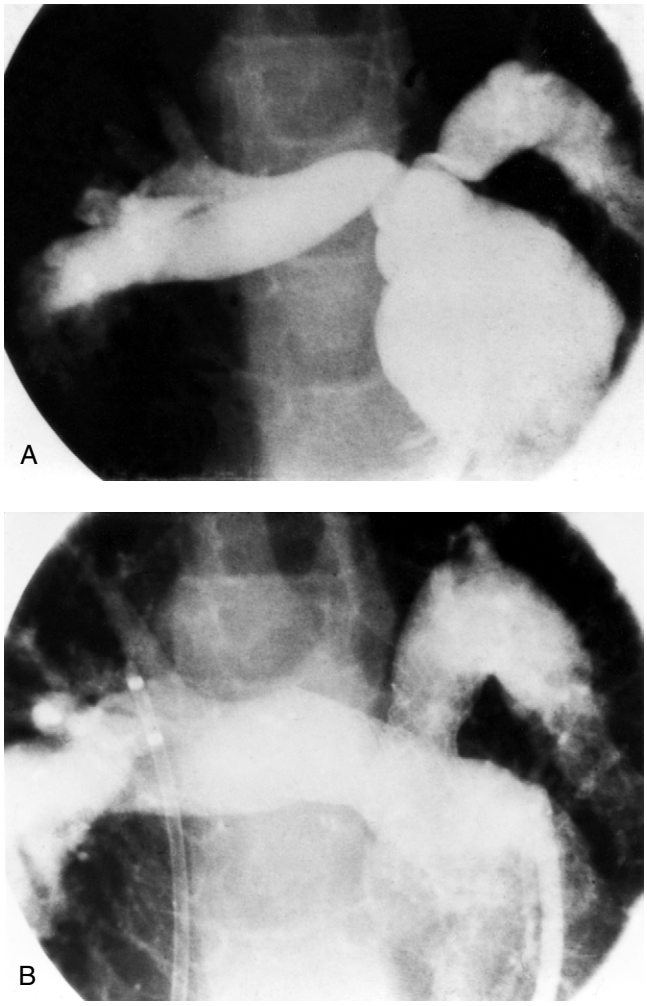

Figure 83-16 A, Severe bilateral branch pulmonary artery stenoses at the distal end of a conduit in a patient with pulmonary trunk atresia and ventricular septal defect. Stents were placed in the right and left pulmonary arteries. **B,** Follow-up angiogram in the same projection and magnification showed marked improvement of both right and left stenoses.

ing transient hypotension, and providing airway support to minimize the risks associated with pulmonary artery disruption and acute unilateral pulmonary edema.[315]

A unique group of patients are those with Williams' syndrome with supravalvar aortic and pulmonary stenosis. Such patients can have multiple areas of severe branch pulmonary artery stenosis, with resultant systemic or suprasystemic right ventricular pressures and right ventricular dysfunction. Patients can also have coronary stenosis and develop subendocardial ischemia from hemodynamic disturbances in the setting of biventricular hypertrophy. The presence of supravalvar aortic stenosis, biventricular outflow tract obstruction, and coronary stenosis is associated with increased perioperative risk. Typically, such patients undergo general anesthesia with positive-pressure ventilation and recover in the cardiac ICU for angioplasty of branch pulmonary artery stenosis.[316] Care must be exercised in maintaining SVR, myocardial oxygenation, and contractility. Tachycardia and subendocardial ischemia should be avoided in the presence of ventricular hypertrophy.

Balloon Valvulotomies

Balloon valvulotomies conducted in well-compensated infants and children can often be accomplished without anesthetic support. Exceptions include neonates with critical aortic or pulmonary stenosis and patients with significant ventricular dysfunction who exhibit unstable hemodynamics. Balloon valvuloplasty is indicated in valvular pulmonary or aortic stenosis with valvular gradients more than 50 mm Hg. Balloon dilation is effective in most patients except those with dysplastic valves (e.g., Noonan's syndrome); post-dilation pulmonary incompetence is anticipated and does not pose a problem in the immediate and intermediate period. There is a need for prophylaxis for subacute bacterial endocarditis long-term. Only 8% of patients require re-interventions. Typically, patients recover in the ICU and may require transfusion depending on hemodynamic stability. Valvular aortic stenosis is associated with poor surgical outcome in the neonatal period. All therapies are palliative with a high incidence of re-interventions, and balloon valvuloplasty is often the initial treatment. Residual obstruction or regurgitation is common after balloon dilatation and can require re-intervention. There is a real risk of damage to the aortic valve and subaortic septum with the consequence of acute aortic insufficiency and coronary ischemia. Hypotension and bradycardia commonly occur during valvuloplasty, and many centers have a policy of ECMO standby for these high-risk interventions in the catheterization laboratory. Ready availability of a surgical and perfusion team is crucial to a good outcome. Neonates with critical aortic stenosis often require stabilization with inotropes and prostaglandins to maintain systemic perfusion before the procedure. Balloon dilation of recurrent coarctation is often the therapy of choice in older children with re-coarctation after surgery. Such patients are often hypertensive. The procedure can be performed with the patient under deep sedation or general anesthesia. In infants after Norwood palliation for hypoplastic left heart syndrome, coarctation can occur in the distal arch anastomotic site. Catheters placed antegrade via the right side of the heart into the neoaorta can induce hemodynamically significant tricuspid and neoaortic regurgitation, resulting in hemodynamic instability. Careful monitoring and aggressive hemodynamic intervention result in a good outcome.

Coil Embolization

Transcatheter methods can be adapted to occlude undesired vascular structures. Intravascular coils have been used to close PDAs, aortopulmonary collaterals, surgical systemic/pulmonary artery shunts, venous collaterals in single ventricle lesions, coronary fistulas, and some arteriovenous malformations (e.g., vein of Galen malformation). In selected instances, to minimize the risk that coils may escape to threaten vital organ perfusion, cardiologists request the use of general anesthesia with a muscle relaxant.

Depending on the lesion, patients might manifest severe cyanosis, low or high output cardiac failure, or coronary ischemia. Extra care should be exercised in patients with coronary fistulas to maintain myocardial oxygen supply and reduce demand. Mate-

rials used for embolization can include surgical gel (Gelfoam), alcohol, and coils. Some of these substances can induce severe allergic reactions with hemodynamic collapse. Antibiotic prophylaxis is mandatory to prevent bacterial endocarditis. Angiography is used to demonstrate successful occlusion of the vascular structure and ascertain appropriate placement.

Valve Prostheses

Transcatheter bioprosthetic valve replacement of the pulmonary and aortic valves is being performed. The pulmonary valve is a bovine jugular venous valve mounted on a balloon-expandable Cheatham platinum stent. The technique is limited by the maximum size of 22 mm of the bovine jugular venous valve. Percutaneous placement of bioprosthetic valve in the pulmonary position is a reality, and further refinement and miniaturization will lead to its application in aneurysmal right ventricular outflow tract. The development of transcatheter placement in the aortic position is still in its very early stages, but animal studies and initial adult studies show that it is feasible.[317-318]

Emergent Procedures

Emergent interventions such as balloon atrial septostomy to ensure adequate mixing in patients with transposition physiology and in patients who have restrictive atrial septal defect with single ventricle physiology are lifesaving and enable planning surgery at a suitable time. The procedure can be performed at the bedside with echocardiography or in the catheterization laboratory with fluoroscopic confirmation of balloon position. Access is via the femoral or umbilical vein, and the balloon catheter is advanced through the foramen ovale into the left atrium. The balloon is inflated with contrast and pulled back via the septum until a satisfactory atrial septal defect is created. If the procedure is successful, the left and right atrial pressures should equalize and adequate mixing should occur. Oxygenation and pulmonary venous drainage should improve. Complications include atrial perforation, laceration of the mitral or tricuspid valves and pulmonary veins, and low cardiac output state. Balloon atrial septostomy is also performed emergently in patients receiving ECMO therapy for left-sided heart decompression.

Endomyocardial Biopsy

Typically, endomyocardial biopsies are performed both as part of post-transplant surveillance catheterizations at regular intervals to ascertain absence of rejection in patients after orthotopic heart transplantation. Right-sided heart catheterization is usually performed via access of the right internal jugular vein, through which the long sheath and biotome are introduced. Usually five to eight samples are taken. Endomyocardial biopsies are also used to confirm a diagnosis of myocarditis or cardiomyopathy; sedation or general anesthesia is required for smaller children, although older children can undergo this procedure with local anesthesia alone. Children who undergo catheterization during a period of acute rejection are at high risk of malignant arrhythmias during endomyocardial biopsy and might require resuscitation. A clinical history suggestive of an episode of rejection includes fever, gastrointestinal disturbances, and arrhythmias. Complications include perforation, tricuspid valve damage, and the development of coronary to right ventricular fistulas.

Cardiac Catheterization of Patients Supported by Extracorporeal Membrane Oxygenation

Booth and associates have reported on the Boston experience of cardiac catheterization in pediatric patients supported on ECMO. Indications included assessment of surgical repair, left-sided heart decompression, myocarditis/cardiomyopathy, hemodynamic assessment, catheter interventions, and ablation of arrhythmias.[319] The most common interventions were left-sided heart decompression in patients with left atrial hypertension, balloon angioplasty of the pulmonary arteries, and endomyocardial biopsy. The anesthesiologist coordinates safe transport of the patient on mechanical support with the perfusion and nursing team. The logistics of the transport, availability of surgeon, and blood need to be addressed before the transfer. Anesthesia is provided using isoflurane or sedatives on the ECMO circuit, and paralysis must be achieved before transport. Rest ventilation of the lungs is continued. The anesthesiologist's role is in managing a safe transport and attending to emergency mechanical, cardiorespiratory, and hematologic issues.

At present, hybrid techniques find a niche in lesions where cardiac surgery is problematic, such as apical muscular or anterior muscular VSDs or in high-risk patients with more complex lesions where immediate surgery is contraindicated or is associated with significant morbidity and mortality. Close collaboration is required so that a surgical approach is modified to facilitate subsequent interventional approach. The hybrid approach has been used in the management of hypoplastic left heart syndrome (HLHS). Stage 1 palliation is performed by creation of an atrial septal communication and stent placement in the ductus arteriosus during catheterization to maintain ductal patency with surgically applied external right and left pulmonary artery bands or transcatheter placed internal bands.[320,321] A modified Norwood procedure with a bidirectional Glenn anastomosis is performed with CPB during stage 2 palliation.[322] Stage 3 (Fontan operation) is performed entirely by transcatheter techniques.[323] In the current surgical climate, it seems difficult to promote ductal stenting as a method of choice but in patients with contraindications to immediate surgery this provides an attractive bridge.[324]

Pediatric Cardiac Electrophysiology

Diagnostic Evaluation

Cardiac Event Monitoring

Most patients with cardiac arrhythmias present with infrequent or episodic symptoms. These symptoms may include chest pain, palpitations, syncope, and presyncope. Transtelephonic

electrocardiographic event monitors (TTMs) may yield documentation of the arrhythmia because they are portable and patient activated.[325]

Insertable Cardiac Recorders

Insertable loop recorders implanted subcutaneously allow continuous rhythm monitoring that is stored either when manually activated by a patient/parent or automatically when high or low rate parameters are met.[326] These insertable loop recorders have value in correlating arrhythmias with symptoms when noninvasive means do not make a diagnosis. Typically, loop recorders are inserted under general anesthesia as an outpatient procedure and cause minimal pain.

Radiofrequency Ablation of Accessory Pathways

Radiofrequency ablation is a nonsurgical approach designed to eliminate atrial or ventricular reentrant tachyarrhythmias. The technique requires pathway mapping and precision ablation of the aberrant pathway, using a radiofrequency ablation catheter. Catheter ablation is offered to patients with refractory arrhythmias that are bothersome and the focus or pathway is amenable to ablation. In pediatrics, the EP catheters are introduced via femoral venous catheterization and the tips are positioned in the right atrial appendage, the His bundle area, right ventricular apex, and the coronary sinus. Occasionally, right internal jugular venous access is used for placement of the coronary sinus catheter. Rapid atrial pacing and, occasionally, an isoproterenol infusion are required during the mapping procedure to induce the arrhythmia. An ablation catheter is used to map the substrate, and, subsequently, the pathway is ablated. During the ablation, unexpected patient movement may result in catheter dislodgment and damage to normal conducting tissue; therefore, general anesthesia is usually required in younger children. Anesthetic agents and techniques should be chosen to maintain circulating catecholamines and avoid suppression of arrhythmogenesis, for identification of the aberrant pathway. Our current preference is a propofol continuous intravenous anesthetic, although low-dose volatile anesthetics are equally satisfactory. Rapid atrial pacing and, occasionally, an isoproterenol infusion are required during the mapping procedure.

Severe postprocedural cardiomyopathy has been described but is very unusual. An underlying cardiomyopathy from frequent episodes of supraventricular tachycardia and myocardial oxygen imbalance caused by prolonged periods of rapid atrial pacing and isoproterenol infusions are the presumed causative factors. An arterial line is helpful during these lengthy procedures for continuous monitoring of blood pressure and blood gases. Complications of the procedure include radiation exposure, tamponade, pericarditis, groin hematoma, arterial thrombosis, AV block, systemic embolization, coronary artery dissection, trauma to the mitral and tricuspid valves, and endocarditis.

Intra-atrial Reentrant Tachycardia

Intra-atrial reentrant tachycardia (IART) is associated with significant morbidity and mortality for many patients with repaired congenital heart disease, particularly after extensive atrial surgery, such as Fontan and atrial switch operations. Therapeutic options for IART include antiarrhythmic medications, catheter ablation, surgery, and pacing. The arrhythmia occurs along with long-standing myocardial dysfunction and residual lesions. Careful choice of anesthetic, monitoring, and early management of low cardiac output, especially in patients with single-ventricle physiology, are important. Prolonged periods of arrhythmia induction during mapping can result in low cardiac output state, necessitating inotropic therapy. Such patients may need to undergo recovery in the cardiac ICU. Despite reports of high acute success rates with catheter ablation, arrhythmia recurrence continues to be problematic in this population.[327] Acute success was reported in 93% of patients and was defined as no inducible, sustained IART. Recurrence occurred in 34% of patients, 88% within 1 year. Patients with Fontan physiology had the highest recurrence rate. Inadequate lesion size and depth with conventional radiofrequency ablation catheters are the principal reasons for recurrence. Intraoperative cryoablation within the right atrium for patients with IART and/or left atrium for atrial fibrillation using preoperative and intraoperative mapping can be used successfully. A new generation of antitachycardia pacemaker (AT500) has been used for treating IART. This device was able to successfully terminate 54% of treatable tachycardias by use of antitachycardia pacing, with no incidence of ventricular proarrhythmia.[328] In patients who are either unsuitable candidates for catheter ablation or in whom ablation has been unsuccessful, surgical ablation may be successfully combined with repair of congenital heart disease. This is particularly true of patients with complex physiology (e.g., Fontan revision with a maze procedure).[329-331]

Arrhythmias and Sudden Cardiac Death

Certain cardiomyopathies and channelopathies are associated with an increased risk of sudden cardiac death due to lethal arrhythmias. There is usually a history of syncope, near-syncope, or aborted sudden death. Such patients present for insertion of automated internal cardioverter-defibrillators (AICDs) for either primary or secondary prevention.

Implantation of Pacemakers and Defibrillators

Pacemakers are indicated for complete heart block or sinus node dysfunction with symptomatic bradycardia and hemodynamic decompensation. Children usually require general anesthesia with endotracheal intubation. It should be noted that the anesthetic can be associated with worsening bradycardia. Transthoracic pacing pads are applied before induction of anesthesia, and an isoproterenol (Isuprel) infusion might be required for chronotropic effect. External transthoracic, esophageal or emergent transvenous pacing might be necessary until placement of a permanent pacing device is achieved. In small children the pacemaker generator is typically placed in the upper abdomen, and in older children and teenagers it is placed in the subclavicular region. Epicardial leads are used in small children due to inadequate size of the veins, and in those in whom transvenous access to the heart is impossible (e.g., the Fontan circulation). Epicardial pacemaker placement usually is performed by a cardiac surgeon, with electrophysiologists readily available to program the device. Adequate peripheral venous access is mandatory in the event of

major hemorrhage, and blood should be readily available. A mode of monitoring mechanical capture of electrical pacing activity is also necessary and can include invasive arterial monitoring or pulse plethysmography. Transvenous pacing can be achieved in the operating room with surgical backup or in the cardiac catheterization laboratory by the cardiologists. In the latter situation it is important to address the need for surgical backup during case planning.

AICDs are placed for life-threatening ventricular arrhythmias, which include LQTS, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular dysplasia. Of note, the device is tested after placement, with induction of ventricular fibrillation. It is absolutely essential to have external modes of defibrillation available, as well as antiarrhythmics such as amiodarone, magnesium, and lidocaine, in the event of device failure. These devices are placed with the patient under general anesthesia with endotracheal intubation and controlled ventilation. Invasive arterial pressure monitoring is typically used. Adequate analgesia can be provided with local infiltration with local anesthetics and short-acting intravenous opioids. Patients are admitted overnight with telemetry monitoring. Appropriate antibiotic therapy is provided for a 24-hour period.

Advances in Resynchronization Therapy

Bundle branch block or interventricular conduction delay often accompanies heart failure as well as some forms of congenital heart disease, either preoperatively or postoperatively, and may result in ventricular dysfunction caused by asynchronous myocardial contraction. Biventricular pacing is an attempt to resynchronize ventricular contraction by pacing both ventricles, thereby improving overall ventricular function. In patients with left bundle branch block, cardiac resynchronization therapy counteracts the underlying electrical and mechanical dyssynchrony, leading to improved contractility, function, exercise tolerance, and quality of life. Multisite pacing has been attempted in pediatric patients.[332] Two atrial and three ventricular epicardial leads were placed at the time of surgery, with the ventricular leads placed as far from one another as possible. Atrial synchronous ventricular pacing was established postoperatively, and the AV interval was adjusted to yield the narrowest QRS complex while simultaneously pacing two ventricular sites. Multisite pacing resulted in significant narrowing of the QRS complex, improved cardiac index, and increased systolic blood pressure overall. Multisite pacing after surgery for congenital heart disease in children may facilitate weaning from inotropic agents, thereby limiting side effects such as increasing myocardial oxygen consumption. There have also been reports of biventricular pacing with improved outcome in infants with dilated cardiomyopathy and complete AV block.[333,334] Long-term improvements need to be studied. Right bundle branch block is a common outcome after surgery for congenital heart lesions. Right ventricular pressure and/or volume loading may also be present, with attendant right ventricular enlargement and dyskinesis. The QRS duration decreased in all patients during dual-chamber pacing. Cardiac index also increased during resynchronization with dual-chamber pacing. The pacing site yielding the narrowest QRS duration also improved the cardiac index the most.[335,336]

Anesthesia for Noncardiac Surgery

Infective Endocarditis Prophylaxis: American Heart Association Guidelines

Guidelines for IE prophylaxis have been updated by the American College of Cardiology and the American Heart Association in 2008. A detailed discussion of the changes is beyond the scope of this chapter.

Procedures for which prophylaxis for infective endocarditis is recommended include the following:[337]

- Dental procedures involving manipulation of the gingival tissue or periapical region of the teeth or involving perforation of the oral mucosa
- Respiratory procedures that involve incision of the respiratory mucosa
- Infected skin, skin structure, or musculoskeletal tissue

Prophylaxis is no longer routinely recommended for gastrointestinal/genitourinary procedures. For elective procedures, coexisting enterococcal urinary tract infections should be treated before genitourinary/gastrointestinal procedures; for emergent procedures, in patients at highest risk of infective endocarditis, prophylaxis can be considered.

Conditions for which prophylaxis is recommended for dental procedures include the following (Table 83-15):

- Prosthetic cardiac valve
- Previous infective endocarditis
- Unrepaired congenital heart disease including palliative shunts/conduits
- Completely repaired congenital heart disease with prosthetic material or device within the first 6 months after the procedure
- Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or device
- Cardiac transplant recipients who develop cardiac valvulopathy

These are guidelines only. The authors' practice at the current time is to consult the child's cardiologist and make a decision based on the child's condition, the operative procedure, risk of bacteremia, and the cardiologist's opinion.

Magnetic Resonance Imaging of the Heart

Apart from the usual considerations of providing general anesthesia in a remote location, when working in a magnetic field necessitating the use of magnet-safe equipment, the anesthesiologist needs to be prepared to provide resuscitative care in these patients. Patients with implanted devices and hardware need to be assessed to ensure magnet compatibility and safety. Generally, pacemakers, implanted defibrillators, and aneurysm clips are contraindications to MRI. Other coils, stents, and surgical clips produce interference and artifact with imaging but do not constitute a

Table 83-15 Infective Endocarditis Prophylaxis

Situation	Drug	Single Dose 30-60 min before Dental Procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin *or*	2 g IM/IV	50 mg/kg IM/IV
	Cefazolin/ceftriaxone	1 g IM/IV	50 mg/kg IM/IV
Allergic to penicillins/oral	Cephalexin *or*	2 g	50 mg/kg IM/IV
	Clindamycin *or*	600 mg	20 mg/kg IM/IV
	Azithromycin/clarithromycin	500 mg	15 mg/kg
Allergic to penicillins/unable to take oral medication	Cefazolin/ceftriaxone *or*	1 g IM/IV	50 mg/kg IM/IV
	Clindamycin	600 mg	20 mg/kg

Vancomycin is an alternative for patients who are unable to tolerate a β-lactam or when the infective agent is considered to be methicillin-resistant *Staphylococcus aureus*.

threat to patient safety. Usually an MR screening form is part of the evaluation and needs to be discussed with the MR technologist/radiologist. In a majority of patients, the scan can be performed as an outpatient procedure. Patients who are younger, uncooperative, or claustrophobic require sedation or general anesthesia. Total intravenous anesthesia can be provided with a propofol infusion and a natural airway, avoiding the need for scavenging and allowing rapid recovery.[338] Anesthesia has been provided with a range of inhalational agents, such as dexmedetomidine, ketamine, and midazolam.[339] In patients in whom breath holding is necessary, or there is a potential for airway compromise, general endotracheal anesthesia with positive-pressure ventilation may be required. Irrespective of technique chosen it is mandatory to maintain continuous monitoring of heart rate, pulse oximetry, capnography, noninvasive blood pressure, and temperature. Supplemental oxygen should be delivered until the patient is fully recovered from the anesthetic. In the event of hemodynamic compromise, the patient needs to be removed from the MR scanner into a safe environment where resuscitation equipment can be safely used. With the development of compatible catheters and devices, MRI will be a useful tool in minimizing x-ray exposure, particularly in patients whose congenital heart disease necessitates numerous catheterization procedures. Razavi and associates have described their experience of MRI used in combination with fluoroscopy to decrease radiation exposure and improve soft tissue visualization during cardiac catheterization of congenital heart disease patients.[340]

Offsite Anesthesia in Cardiac Surgery Patients

Patients with cardiac disease are no different from any other group of patients who require procedures or investigations in areas outside the operating room. As such, anesthesiologists should always be prepared for any eventuality and follow guidelines such as those set out by the American Society of Anesthesiologists.[341] This discussion will exclude those procedures performed in the cardiac catheterization laboratory because this has already been addressed elsewhere. The nature of congenital cardiac surgery will result in a number of patients' requiring emergent chest exploration for ongoing hemorrhage or as part of resuscitation to relieve tamponade or for ECMO placement, all of which may take place in the ICU setting. It is obvious that we cannot predict which patients will have problematic postoperative courses with absolute certainty, but the practitioners who have participated in the operative phase will gain an accurate sense of which patients may require possible further exploration or surgery. Accordingly, it is best to plan ahead, and it cannot be stressed enough that even if as a group of practitioners we are overprepared, this is the best option to have. This being said, it is imperative that the patient have enough blood and blood products available to perform surgery at any given time. Successful treatment of these patients is dependent on a team approach to their care and thus surgeons, anesthesiologists, intensivists, perfusionists, and operating room nurses must be immediately available. When the decision is made to perform a procedure within the ICU, speed of preparation is of the essence. We are fortunate in our practice that we can obtain a set of premade drugs, electrolytes, and infusions within a 15-minute period. Invariably, if a patient is within a few hours' window from returning from the operating room this same set of drugs will have accompanied the patient from the operating room to the ICU and can thus be accessed. Emergent preparation includes ensuring that blood is checked and that a warmer is set up ready for use, emergency drugs are present as mentioned, and the code cart (with internal paddles) is readily available. The blood that will be used for these procedures will include fresh whole blood (<48 hours old and remaining from the operating room) or packed red blood cells, which in our practice is less than 7 days old, or for blood older than this we would prefer it to be washed to avoid the possibility of acute hyperkalemia with transfusion. An anesthesiologist's role here is thus one of facilitation of the entire procedure from sedation of the patient, positioning and preparation, readying the blood, and continuing ongoing volume resuscitation, resuscitative drug use, and airway management.

The premature infant with a patent ductus arteriosus poses an interesting management problem to cardiac surgery teams because frequently these ill neonates are at hospitals remote from major centers where the team is normally assembled. As referenced in an article by Gould and associates, our team has been

performing these ductal ligations with great success at hospitals remote from ours.[298] The philosophy is thus to take the cardiac team to the neonate instead of having these fragile infants transported to us. In this article neonates operated on in our home hospital NICU were used as the controls, and it was found that the success and complication rates were comparable in the two groups. Thus, from an anesthetic perspective we travel with a full complement of airway equipment and drugs as described earlier, with packed red cells being made available at the host hospital. The anesthetic regimen for this procedure comprises a high-dose narcotic, muscle relaxant, antibiotic, and a continuation of any preoperative vasoactive infusions. We have found that this is a stable and well-tolerated anesthetic regimen.

The requirement for anesthesia services is ever-widening and in patients with pediatric heart disease this is also the case. Thus the patients will require radiologic investigations, including computed tomography, MRI, and nuclear medicine scans; interventional radiology procedures; and gastrointestinal procedures, to name a few. Prior to discussion of the patient and the anesthetic it is important for the practitioners to have a thorough knowledge of the environment into which they are taking the patient with regard to magnetic fields, closest code cart, and the ability to get help quickly if needed. Without going into the specifics of every potential clinical scenario, a few basic points are discussed.

As with any anesthetic procedure, a thorough preoperative evaluation is vital. Most patients with pediatric heart disease have long and complex histories, so this assessment should include a detailed description of their cardiac status, including prior surgeries, catheterization findings, and associated conditions (e.g., neurocognitive function, pulmonary status, renal function). Depending on the patient's underlying condition a recent echocardiogram will give very important clinical details related to overall function, valve pathology, presence or absence of intracardiac shunt, patency of surgical shunts, and presence of pericardial fluid. Although this may be ideal, often the echocardiographic examination may be remote from the anesthetic encounter and thus the clinical history and examination are important. The group of heart transplant patients, however, requires an echocardiogram within a short time of the planned procedure because it will give vital information that may indicate worsening function in an otherwise asymptomatic patient. The last point is the nil per mouth period. Many patients in this group have physiology in which dehydration may be very deleterious (e.g., single-ventricle physiology, presence of surgical shunts, unrepaired tetralogy of Fallot). In these patients it is important that the patient stay orally hydrated up to 2 hours before the planned procedure, and if this is not possible, then intravenous fluids must be used. The anesthetic course will be dependent on the duration of the planned procedure, the patient's physiology (i.e., spontaneous versus controlled ventilation), airway management (natural versus laryngeal mask airway versus endotracheal tube airway), anesthetic maintenance, travel to and from the procedural area, and maintenance of the patient's temperature. Before leaving the induction area the anesthetic team must be prepared for airway misadventures and even a code situation; thus, the team must travel with auxiliary airway equipment and resuscitative drugs. The very number of these different venues may make it difficult to have an anesthesia machine present in each; however, an anesthetic cart with additional airway equipment, intravenous materials, and resuscitative drugs should be present. The anesthetic that is delivered may vary among practitioners and institutions, but the common details of importance are a thorough knowledge of the patient and the ability to treat expeditiously should any difficulty ensue in a remote venue.

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84 Pediatric and Neonatal Intensive Care

Key Points

1. Critically ill children cared for in pediatric intensive care units have improved outcomes when compared with children treated in intensive care units that do not specialize in the treatment of children.
2. The autonomic nervous system has predominantly a parasympathetic vagal tone at birth and gradually shifts to a sympathetic tone in older children.
3. Because the Frank-Starling mechanism is less effective in the newborn, a greater but not exclusive dependence on heart rate is necessary for maintenance of cardiac output.
4. Improvements in ventilation strategies for children with acute lung injury have led to decreased mortality.
5. Microprocessor technology in ventilators has made volume-preset modes of ventilation possible in babies and small children.
6. A multidisciplinary task force has developed a set of guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents.
7. The leading causes of death in children 1 to 14 years of age are accidents and trauma.
8. Pediatric critical care transport systems not only provide a means of transferring a sick patient to a more appropriate facility but also initiate appropriate intensive care monitoring and treatment of the patient before leaving the referring hospital.
9. Mortality from sudden infant death syndrome dropped threefold with institution of the "Back to Sleep" campaign.
10. Pediatric cardiopulmonary arrest is usually manifested initially as respiratory compromise or arrest, followed by secondary cardiac arrest.

Pediatric intensive care requires surveillance, evaluation, and support of vital systems in infants and children who have acute, often reversible, life-threatening disease. In contrast to adults, fewer children who require pediatric intensive care suffer from chronic or degenerative organ system disorders. Most children have a potentially reversible life-threatening illness or injury that if successfully treated, will restore the child to a normal, productive life.[1]

The principles of intensive care for children are similar to those for adults. However, the spectrum of ages (infancy through adolescence) requires that the staff have special expertise in developmental physiology and psychology. All critically ill children, regardless of diagnosis or subspecialty category, should be treated in units dedicated to children. Specific guidelines describing minimum criteria for pediatric intensive care units (PICUs) and services have been published.[2]

When patients are cared for in PICUs, mortality is lower than it is when children are cared for in nonpediatric intensive care units (ICUs).[3] Hospitals without specialized facilities for pediatric intensive care should seriously consider transferring critically ill children to a regional PICU. Regional PICUs must have transport systems that facilitate the safe and timely transport of critically ill children to the referral center and must develop educational programs in emergency and critical care pediatrics for primary care and referring physicians and nurses.[4]

Organization of the Pediatric Intensive Care Unit

Medical and nursing directors, hospital administrators, and representatives from pediatric medicine, anesthesia, surgery, and the pediatric subspecialties should be responsible for policy and procedures pertaining to the PICU and should make recommendations regarding personnel staffing, equipment purchases, and structural and design changes within the unit.

The medical director oversees the quality of patient care, patient triage, implementation of policy and procedures, in-

service education, and coordination of consultants. Physician coverage should be full-time geographic at the resident, fellow, and attending staff level and should include in-house, full-time coverage at night.

The nursing director should have special skills in pediatric intensive care, education, and personnel management. The nursing staff must be trained in all aspects of pediatric critical care and resuscitation. Staffing should be flexible enough to provide one-on-one patient care when necessary. A multidisciplinary in-service program is essential for continuing education and orientation.

Other team members include respiratory therapists, physical therapists, nutritionists, social workers, laboratory technologists, pharmacists, and psychiatrists and psychologists for the patients and staff. All medical and support personnel should be encouraged to participate in rounds, educational endeavors, and team meetings whenever possible.

There must be adequate work space around each bed and enough storage space to keep life support equipment within reach. Space for reading, meeting, sleeping, and showering should be available for the staff. Space should be provided for parents to remain with their children during the day and for parents to sleep overnight. Parents should be encouraged to participate as much as possible in the care of their child.

Each bed space should be standardized so that it can be used to provide any level of care. Private rooms are ideal, but if shared rooms are necessary, the distance between beds must be adequate to ensure privacy and minimize nosocomial infection. Isolation rooms should be available within the confines of the unit.

Devices for diversion and entertainment should be available for conscious children. Television and computer games are often better than heavy sedation.[5,6] Adequate nurses and nursing involvement at the bedside will prevent potentially life-threatening events. Because sick children require close personal observation, centrally monitored nursing stations have little place in the PICU.

Cardiovascular System

Circulation

Infants and children continually undergo structural and functional maturational changes (see Chapter 82). Understanding these age-dependent processes is essential for the diagnosis and treatment of circulatory failure in young children.

Structural and Functional Development

The shape of the heart is complete by 6 weeks' gestation, but myofibrillar density and maturation increase through the first year of postnatal life. During this time, myocytes engage in rapid protein synthesis and rapid cell growth, which requires a high intracellular concentration of nuclei, mitochondria, and endoplasmic reticulum. The greater number of nonelastic and noncontractile elements makes the neonatal myocardium less compliant and it contracts less efficiently than the adult myocardium. In the fetus and newborn, the decreased ventricular compliance causes small changes in end-diastolic volume to induce large changes in end-diastolic pressure. In addition, augmentation of stroke volume by the Frank-Starling mechanism is less effective in young children. The newborn is more dependent on heart rate for maintenance of cardiac output.[7,8] Cardiac output increases only about 15% with volume loading; it increases much more by increasing the heart rate.[9]

Development of the Circulation

The adult and fetal circulation differs in many ways. The fetal circulation is distinguished by (1) the placenta as the organ of respiration, (2) high pulmonary vascular resistance (PVR), (3) low systemic vascular resistance (SVR), and (4) fetal ventricles that pump in parallel with right ventricular dominance. While the fetus lives in a low oxygen environment, the oxygen content of the blood of the fetus is similar to that of adults (20 mL of oxygen/100 mL of blood) because of a higher concentration of hemoglobin that has high affinity for oxygen. The neonatal circulation has several shunts—the ductus arteriosus, ductus venosus, and foramen ovale—that direct more oxygenated blood to the brain and heart and bypass the lungs. Changes then occur that allow the parallel circulation of the fetus to convert to the series circulation of the adult:

1. With the first breath, expansion of the lung, increased alveolar oxygen, an increase in pH, and neurohumoral mediators and nitric oxide (NO) relax the pulmonary vasoconstriction.[10,11]
2. When the placenta separates from the uterine wall, the placental blood vessels constrict, and SVR and left ventricular afterload increase. The decrease in PVR plus increase in SVR raises left atrial pressure above right atrial pressure and functionally closes the "flap valve" of the foramen ovale. The foramen ovale may not close anatomically for months to years, if ever. It is patent in at least 15% of adults.[12,13]
3. The decrease in PVR causes flow through the ductus arteriosus to reverse. This exposes the ductus to oxygenated systemic arterial blood, which along with the rapid decrease in prostaglandin E_2 (PGE_2) after birth, closes the ductus. Anatomic closure of the ductus requires several weeks.[14]
4. The ductus venosus closes passively with removal of the placental circulation and readjustment of portal pressure relative to inferior vena cava pressure.
5. There is a further gradual decline in PVR secondary to structural remodeling of the muscular layer of the pulmonary blood vessels. During fetal life, the central pulmonary vascular bed has a relatively thick muscle layer. After birth, the muscle coat thins and extends to the periphery of the lung, a process that takes months to years to complete.[15]

Development of Autonomic Control of the Circulation

The functional integrity of autonomic circulatory control during fetal and perinatal development is still a matter of considerable speculation. The fetal heart has reduced catecholamine stores and increased sensitivity to exogenously administered norepinephrine.

Adrenergic innervation of the human myocardium is complete between 18 and 28 weeks' gestation. Human newborns have low cardiac stores of norepinephrine and decreased numbers of sympathetic nerves after birth. Adrenergic responses are apparently present but diminished in newborn humans.

Table 84-1 Age-Related Circulatory Variables

Age	Heart Rate (Beats/min)	Systolic Blood Presssure (mm Hg)	Diastolic Blood Pressure (mm Hg)	Stroke Volume (mL/Beat)	Cardiac Index (L/min/m^2)	Oxygen Consumption (mL/kg/min)	Hemoglobin Concentration (g/dL)	P_{50} (mm Hg)
Term newborn	133 ± 18	80 ± 16	46 ± 16	4.5 ± 5.0	2.5 ± 0.6	6.0 ± 1.0	16.5 ± 1.5	18
6 mo	120 ± 20	89 ± 29	60 ± 10	7.4 ± 2.0	2.0 ± 0.5	5.0 ± 0.9	11.5 ± 1.0	24
12 mo	120 ± 20	96 ± 30	66 ± 25	11.5 ± 3.0	2.5 ± 0.6	5.2 ± 0.9	12.0 ± 0.75	—
2 yr	105 ± 25	99 ± 25	64 ± 25	16.9 ± 4.5	3.1 ± 0.7	6.4 ± 1.2	12.5 ± 0.5	27
5 yr	90 ± 10	94 ± 14	55 ± 9	27.8 ± 7.5	3.7 ± 0.9	6.0 ± 1.1	12.5 ± 0.5	—
12 yr	70 ± 17	113 ± 18	59 ± 10	53.5 ± 14.5	4.3 ± 1.1	3.3 ± 0.6	13.5 ± 1.0	—
Adult	75 ± 5	—	—	85.5 ± 6.0	3.7 ± 0.3	3.4 ± 0.6	14.0 ± 1.0	27

P_{50}, oxygen half-saturation pressure of hemoglobin.
From Crone RK: Pediatric Intensive Care. ASA Refresher Courses in Anesthesiology, vol 9. Philadelphia, JB Lippincott, 1981.

In human neonates, the cholinergic system is completely developed at birth, and the heart is sensitive to vagal stimulation. Bradycardia is the probable response to an increase in autonomic tone.

The baroreceptor reflex is present, but incompletely developed at term in humans. In preterm infants, postural changes elicit no change in heart rate, suggesting an incomplete or attenuated baroreceptor response.[16] The chemoreceptor response is well developed in utero. The fetal bradycardia that occurs in response to hypoxia is thought to be mediated through chemoreceptors and may be similar to the oxygen-conserving mechanisms of diving animals.[17]

Myocardial Metabolism

Fetal myocardial metabolism differs from that of adults. Relative "hypoxia" is normal in utero, and infant hearts tolerate hypoxia better than the hearts of adults do. This difference may be due in part to high concentrations of glycogen in fetal myocardial tissue and to the ability to more effectively use anaerobic metabolism.[18] Because of the high glycogen stores and the ability to use anaerobic metabolism efficiently, the fetal/newborn heart is relatively resistant to hypoxia and can be resuscitated more easily if oxygenation and perfusion are reestablished reasonably quickly.

Oxygen consumption increases precipitously after birth, presumably because neonates are required to maintain their own temperature. A full-term infant's oxygen consumption in a neutral thermal environment is approximately 6 mL/kg/min; it increases to 7 and 8 mL/kg/min at 10 days and 4 weeks, respectively.

Age-Related Circulatory Variables

Common Cardiovascular Disease States

Congenital Heart Disease

Congenital heart disease causes significant alterations in oxygenation, perfusion, and myocardial function after birth (Table 84-1; also see Chapter 83). These abnormalities can be divided into hypoxic and normoxic lesions. The latter include obstructive lesions of the left side of the heart (mitral valve stenosis, aortic valve stenosis, aortic stenosis, anomalous pulmonary venous return, ventricular septal defect, or patient ductus arteriosus with a right-to-left shunt), whereas hypoxic lesions include tricuspid valve stenosis, pulmonary valve stenosis, pulmonary artery stenosis or aplasia, and the tetralogy of Fallot. Right-sided lesions cause hypoxia if the left-to-right shunting of blood is sufficient to cause congestive heart failure (CHF) and pulmonary edema.

Newborns with significant congenital heart disease commonly have either cyanosis or CHF. The degree of dysfunction usually changes during the first few months of life as PVR decreases to adult levels. As PVR decreases, left-to-right shunting of blood usually increases, and the symptoms of CHF become more apparent. Many neonates with a significant ventricular septal defect have no left-to-right shunting for several weeks after birth; however, induction of alkalosis during surgery can increase shunting. In the newborn, the usual signs and symptoms of CHF include poor feeding, irritability, sweating, tachycardia, tachypnea, decreased peripheral pulses, poor cutaneous perfusion, and hepatomegaly. Many patients with pulmonary edema exhibit tachypnea without retractions. Cyanosis occurs with structural cardiac disease, but other causes such as respiratory disease, increased PVR (persistent pulmonary hypertension), and methemoglobinemia must also be considered (Box 84-1).

Box 84-1 Common Congenital Heart Lesions in the Newborn

Cyanotic congenital heart lesions
- Tetralogy of Fallot
- Transposition of the great arteries
- Hypoplastic left heart syndrome
- Pulmonary atresia with an intact ventricular septum
- Single ventricle
- Total anomalous pulmonary venous return
- Tricuspid atresia

Congenital heart lesions manifested as congestive heart failure
- Ventricular septal defect
- Patent ductus arteriosus
- Hypoplastic left heart syndrome
- Critical aortic stenosis
- Coarctation of the aorta

Congenital heart disease is diagnosed by physical examination, electrocardiogram (ECG), chest radiograph, and echocardiogram. Cardiac catheterization is occasionally performed as interventional therapy or as a diagnostic tool. Magnetic resonance imaging (MRI) is used to define the anatomy of congenital heart lesions before cardiac surgery.

Initial treatment of congenital heart disease is aimed at relieving CHF, improving systemic perfusion, and improving or maintaining pulmonary blood flow. The ductus arteriosus must be maintained open in instances of hypoplastic left heart syndrome, aortic stenosis or atresia, interrupted aortic arch, and symptomatic neonatal coarctation of the aorta. In many cases, infusion of PGE_1 sustains life until definitive surgical correction can be performed.[19]

Acute Circulatory Failure in Children

Acute circulatory failure is defined as insufficient systemic blood flow to meet the metabolic demands of the body.[20] The clinical syndrome of shock includes the signs and symptoms of both an inadequate circulation and an attempt by the patient to compensate for the circulatory failure. Children compensate for inadequate circulation by releasing endogenous catecholamine and increasing peripheral autonomic tone. The earliest signs of shock include anxiety or irritability, cool and pale extremities, and unexplained tachycardia. Tachypnea, moderate metabolic acidosis, oliguria, and somnolence are signs of inadequate tissue perfusion. Obtundation, periodic breathing, and apnea are signs of impending cardiopulmonary arrest. Arterial blood pressure is seldom a good indicator of the adequacy of perfusion in children because the pressure decreases late in the course of the disease. The child's ability to vasoconstrict is so effective that central blood pressure may remain normal despite impending circulatory collapse. Circulatory failure may be caused by pump failure, intravascular hypovolemia, hypoglycemia, and hypocalcemia. Hypovolemia is the result of either volume loss (blood, plasma, water) or an alteration in SVR (Table 84-2).

Hypovolemia is the most common cause of circulatory failure in children. These children have decreased ventricular preload, reduced stroke volume, and reduced cardiac output. Acute hypovolemia is caused by blood loss (trauma, gastrointestinal [GI] bleeding), plasma loss (capillary leak syndrome, hypoproteinemia, burns, peritonitis), and water loss (vomiting and diarrhea, glycosuric diuresis from diabetic ketoacidosis [DKA]). Children with acute hypovolemia have marked peripheral vasoconstriction and cool, poorly perfused extremities. Peripheral pulses may be thready, and the capillary refill time is prolonged unless the child has a fever.

Inadequate intravascular volume can also be caused by anaphylaxis, septic or endotoxic shock, spinal cord injury, or the ingestion of vasodilating drugs. In the case of vasodilation, peripheral perfusion is usually maintained (despite the presence of hypotension), and the extremities remain warm.[20,21]

Cardiogenic shock is relatively uncommon in pediatric patients. When it does occur, the usual causes are congenital heart disease with outflow obstruction or systemic-to-pulmonary shunting in neoates, although it might also occur as a result of viral or bacterial sepsis. In any child, extrinsic inflow or outflow obstruction (tension pneumothorax, hemopericardium, pneumopericardium, pericardial effusion) must be considered. Finally, viral or infiltrative cardiomyopathies, collagen vascular or Kawasaki's disease, and metabolic derangements such as hypoglycemia, sepsis, or uremia can produce circulatory failure and primary pump failure.[22-24] Arrhythmias, such as paroxysmal atrial tachycardia or atrioventricular (AV) block, can also precipitate circulatory failure in children.

Treatment The cause of shock can frequently be identified from the history and physical examination. Immediate therapy includes assessment of the airway, administration of oxygen, establishment of an airway (if necessary), and adequate ventilation. Vascular access must be obtained early and be of sufficient size to rapidly administer fluids if necessary. Percutaneous peripheral venous cannulation may be difficult because of peripheral vasoconstriction. The intraosseous (IO) route is used for fluid and drug administration if venous access cannot be obtained quickly.[25] A short-beveled trocar needle is used to place an IO line into the proximal third of the tibia (Fig. 84-1) or the distal end of the femur after approprialte sterilzation of the skin. IO needles, 18-gauge spinal needles, and bone marrow aspirate needles work well for this purpose. The needle must not be placed into the epiphysis. When the IO needle is properly positioned, its shaft is anchored in the bone cortex and the tip of the needle is in the marrow cavity. The cortex supports the needle. Blood and bone spicules can be aspirated, and infusion of fluid is easy. There is no distortion of the soft tissues of the leg with fluid injections. IO lines are effective for obtaining blood samples, delivering fluids, and administering the resuscitation medications traditionally

Table 84-2 Circulatory Failure: Hypotension

Low Central Venous Pressure: Intravascular Hypovolemia		
Vasoconstriction: Loss of Volume	**Vasodilation: Loss of Resistance**	**Normal or High Central Venous Pressure: Cardiogenic**
Blood loss	Anaphylaxis	Pump failure
Plasma loss	Sepsis	Shunting
Extracellular fluid loss	Drug intoxication	Outflow, inflow obstruction Arrhythmias

Modified from Crone RK: Acute circulatory failure in children. Pediatr Clin North Am 27:525, 1980.

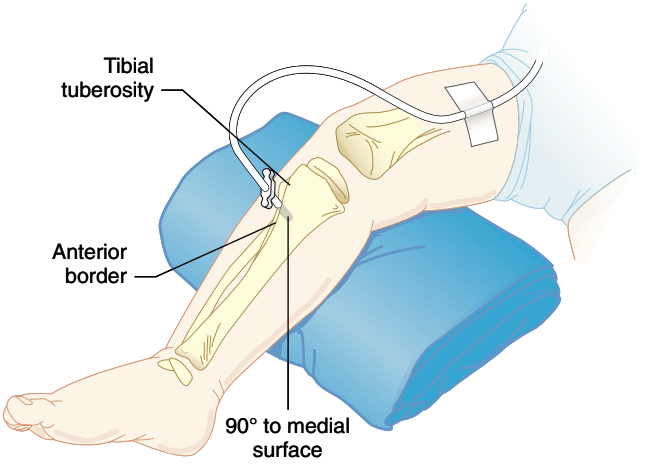

Figure 84-1 Intraosseous cannulation technique.

given intravenously. Standard intravenous access should be achieved as soon as possible because osteomyelitis can occur. Percutaneous cannulation of the jugular[26,27] and subclavian veins is relatively easy but carries a slight risk of carotid puncture, hemothorax, pneumothorax, or perforation of the superior vena cava or right atrium. The smaller size of the child increases the risk associated with cannulating any vessel.

Treatment of circulatory failure includes improving cardiac output and normalizing peripheral organ perfusion. Cardiac output is the result of heart rate and stroke volume, and an increase in either is usually beneficial. If tachycardia is not present, the heart rate may be increased by vagolysis or by α-adrenergic stimulation (positive chronotropy). Atropine (0.02 mg/kg—up to 1 mg), isoproterenol, and epinephrine are the most commonly used drugs for this purpose. In children, a 30% to 50% increase in heart rate above control is well tolerated and usually increases cardiac output substantially.[8] Stroke volume can be augmented by increasing preload, decreasing afterload, improving contractility, or a combination of these therapies.

Because most children in shock are hypovolemic, preload augmentation with an isotonic crystalloid or colloid solution is generally effective. A good starting point is 20 mL/kg given over a period of 2 to 10 minutes. The bolus should be repeated until perfusion improves or 60 mL/kg has been infused. If no improvement has occurred with this volume, other causes of shock should be sought, including ongoing losses, myocardial dysfunction, sepsis, anaphylaxis, and others.[20,21] Intravascular volume is assessed by physical examination, chest radiography, echocardiography, and the use of central venous pressure (CVP) and arterial catheters.

Echocardiography is rapid and noninvasive, but it requires the immediate availability of sophisticated equipment and personnel skilled in interpreting pediatric echocardiograms. Structural cardiac abnormalities can be ruled out and myocardial function may be qualitatively assessed.[28] Hypovolemia can also be diagnosed by echocardiography.[29] Most infants and children who need ongoing assessment and cardiovascular support require a central venous catheter for volume administration and measurement of CVP. Although a CVP of 5 cm H_2O is a reasonable estimate of adequate intravascular volume, there is no single optimal number for CVP. Several extracardiac factors, including lung compliance, the level of positive end-expiratory pressure (PEEP), peak inspiratory pressure, and increasing abdominal pressure, affect CVP or right ventricular filling pressure; thus, each patient's optimal CVP may differ considerably. If there is no improvement in blood pressure, cutaneous perfusion, or urine output with adequate CVP, cardiogenic causes of circulatory failure must be sought. Arterial blood gases (ABGs), hematocrit, serum electrolytes, glucose, and calcium concentrations should be determined. Correction of acidosis, hypoxemia, or other metabolic derangements is essential. Blood and other appropriate sites must be cultured and broad-spectrum parenteral antibiotics must be administered if sepsis is a possibility. Urine output in excess of 1 mL/kg/hr usually indicates adequate renal blood flow and cardiac output. Patients whose urine output is less than 0.5 mL/kg/hr should be evaluated for circulatory failure, renal failure, and obstruction to urine flow.

Myocardial contractility can be improved by correcting hypoxia, acidosis, and hypoglycemia and by administering positive inotropic agents, such as sympathomimetic amines (β-agonists), xanthines, and cardiac glycosides.

Pulmonary artery catheters are used less frequently in children than in adults because these catheters are often too large for the size of the pulmonary artery, especially in infants. Most conditions causing circulatory failure in children are associated with biventricular failure, not left ventricular failure, as occurs in adults. Consequently, left ventricular filling pressure reflects right atrial pressure, and CVP is an adequate indicator of left- and right-sided filling pressure. The pulmonary artery catheter, if used, allows the ICU team to continuously measure pulmonary artery pressure and intermittently measure cardiac output.[30,31]

Afterload reduction is often indicated when "pump failure" coexists with an elevated SVR.[32] The decrease in SVR permits the ventricle to pump more efficiently, increases stroke volume, and improves tissue perfusion. Afterload reduction is induced with a direct vasodilator (sodium nitroprusside), a β-agonist (isoproterenol), a phosphodiesterase III inhibitor (milrinone), or an α-antagonist (phentolamine or tolazoline). The effects of afterload reduction are often unpredictable. If the associated hypotension sufficently reduces coronary perfusion, cardiac efficiency may be reduced rather than improved. Vasoconstricting agents (phenylephrine or norepinephrine) must be available for immediate treatment of severe hypotension.

Vasoconstriction is instituted when anaphylaxis and warm septic shock cause inappropriate vasodilation.[20] Vasoconstricting drugs increase myocardial work and oxygen consumption and may worsen existing myocardial decompensation.

Cardiovascular Pharmacology in Children

Pharmacologic support of the circulation includes positive inotropic and chronotropic agents, vasoconstrictors and vasodilators (afterload reduction), and antiarrhythmics (see Chapters 12 and 82). Most currently used drugs have not been adequately tested in children, so dosage recommendations and anticipated effects must be extrapolated from adult doses and clinical experience.

Positive inotropic drugs are used to augment the cardiac output of patients with circulatory failure. Most inotropic agents also affect the heart rate and vasomotor tone. Tachycardia in a child is usually well tolerated and is frequently beneficial.[20] In a neonate whose ventricles are relatively noncompliant and whose stroke volume is less variable, tachycardia is an important means of augmenting cardiac output. Because drugs that increase the heart rate or contractility also increase myocardial oxygen consumption, adequate arterial oxygenation and sufficient metabolic substrates are required when these drugs are administered. The cardiovascular response to sympathomimetic amines is attenuated in the presence of severe acidosis and possibly sepsis; higher infusion rates of these drugs are required and need readjustment as the acidosis improves. Commonly used inotropes are listed in Table 84-3. Brief comments regarding their use in pediatric intensive care are provided in the following paragraphs.

Epinephrine

Epinephrine has become the first choice for the treatment of hypotension of many causes because of its cardiac stimulatory effects.

Dopamine

Dopamine is the most commonly infused inotrope in pediatric patients. Its effects are dose dependent, with dopaminergic activity at low doses, β-adrenergic activity with intermediate doses, and some α-adrenergic activity at higher doses. Young children

Table 84-3 Vasoactive and Inotropic Agents in Pediatrics

Drug	Effect	Dose*	Inotropy	Chronotropy	Vasodilation	Vasoconstriction
Epinephrine (Adrenalin)	α, β	0.05-2.0	++	++		++
Isoproterenol (Isuprel)	β_1, β_2	0.05-2.0	++	++	+	
Dopamine (Inotropin)	δ β > α β, α	1-3 5-15 >15	 + +	 + +	+Renal splanchnic	 +/– +
Milrinone		Bolus: 50 μg/kg over 10-min period Infusion: 0.375-0.75	+		+	
Norepinephrine	α >> β	0.05-1.0	sl+	+		++
Nitroprusside		0.5-10			++ Arterial > venous	
Nitroglycerin		1-20			++	

*All infusions are μg/kg/min.
sl, slight.

require higher doses of dopamine than adults do to produce the same effect. In one study, an infusion of 15 μg/kg/min was required to increase cardiac output above control levels after cardiac surgery.[33] This may reflect the decreased releasable myocardial stores of norepinephrine in immature ventricles.

Isoproterenol

Isoproterenol is a pure β-agonist with strong chronotropic effects and is usually well tolerated in children. However, high doses of isoproterenol can cause myocardia ischemia.[34] Isoproterenol also induces vasodilation that is responsive to acute volume administration.

Dobutamine

Dobutamine provides positive inotropy and afterload reduction. In children but not in adults it causes tachycardia.[35,36]

Norepinephrine

Norepinephrine, a drug with α- and β-agonist effects, has had a resurgence of use in infants and children.[37] Children with nearly normal cardiac function and marked peripheral vasodilation have good responses to this drug. It is expecially useful in instances of warm septic shock, anaphylaxis, liver failure, and sympathetic blockade with regional anesthesia.

Milrinone

Milrinone is a phosphodiesterase III inhibitor that increases cyclic adenosine monophosphate. Its has both inotropic and vasodilator effects. This drug has improved the outcome of children who have low cardiac output syndrome after cardiac surgery.[38] The loading dose of milrinone is 25 to 75 μg/kg administered over a period of 10 minutes; the maintenance infusion rate is 0.25 to 0.75 μg/kg/min. Hypotension and tachycardia occur primarily with the loading dose of the drug and generally respond to an infusion of fluid. Renal failure significantly increases the elimination half-life of this drug.[39-41]

Digitalis

Digitalis is useful for the long-term treatment of myocardial failure in children but may not be effective in neonates.[42] Because of its long half-life and unpredictability, digitalis should be administered cautiously to children who have changing levels of serum potassium, calcium, and pH. In these cases, it is more appropriate to use rapid-acting, titratable inotropic agents.

Calcium

When serum ionized calcium levels are below normal, administration of calcium produces a positive inotropic effect. If the patient's ionized calcium levels are normal, less marked inotropic effects occur. Low ionized calcium levels most commonly occur in patients with DiGeorge's syndrome, when large volumes of citrate-containing blood products are rapid administered, and in neonates with relatively unstable calcium metabolism. Calcium also has effects on the cardiac conduction system. Rapid administration of calcium can cause severe bradycardia or asystole. This effect may be exaggerated in hypokalemic children or in those receiving digitalis. The vasomotor effects of calcium are controversial, but most reports show an increase in both SVR and PVR when the drug is administered.[43]

Bicarbonate Therapy

Severe acidosis decreases myocardial function and tissue perfusion. Correction of acidosis with 1 to 2 mEq/kg of sodium bicarbonate is indicated for a pH below 7.20 if ventilation is adequate (P_{CO_2} <40 mm Hg if possible). Treatment is necessary because the circulatory system is refractory to sympathomimetic amines when the pH is less than 7.00. After initial correction of pH, persistence or reappearance of metabolic acidosis suggests a continuing underperfused state and the need for further therapy. Administration of sodium bicarbonate is only a stopgap measure to improve the response to drugs. Repeat infusions of sodium bicarbonate can cause hypernatremia and hyperosmolarity. Every 50 mEq of bicarbonate administered produces 1250 mL of CO_2 when the bicarbonate is fully reacted with acid. Consequently, adequate ventilation must be ensured while the drug is administered to avoid worsening the acidosis. Trishydroxymethylaminomethane (THAM) is an alternative to sodium bicarbonate, but larger volumes of THAM are required to produce the same amount of acid-base correction, which may be a problem in patients who have CHF. THAM does not increase P_{aCO_2}.

Vasodilators

Vasodilators are used to control systemic hypertension, increase cardiac output by decreasing afterload, control pulmonary hypertension, and control cardiac shunting. Vasodilators are effective treatment of systemic hypertension and increase cardiac output in children with CHF. Treatment of pulmonary hypertension and intracardiac shunting with vasodilators has met with limited success because they decrease both PVR and SVR, which may increase extrapulmonary right-to-right shunting and further reduce pulmonary blood flow.

Sodium Nitroprusside Sodium nitroprusside relaxes arteriolar and venous smooth muscle, which decreases afterload and preload. The half-life of sodium nitroprusside is only minutes, making it safe to titrate the drug to a desired effect. Nitroprusside is commonly used to control severe systemic hypertension, to provide controlled hypotension to reduce blood loss, and to increase cardiac output in children with low cardiac output syndromes (myocarditis, post–cardiac surgery status).[44] Sodium nitroprusside can generally be used for days without problems, although cyanide and thiocyanate poisoning develops in some children, especially those with renal failure or reduced renal perfusion. Serum thiocyanate levels of 10 mg/dL are associated with weakness, hypoxia, nausea, muscle spasms, and disorientation. When these symptoms occur, nitroprusside administraton should be discontinued immediately.

Nitroglycerin Intravenous nitroglycerin has effects similar to those of sodium nitroprusside, except that nitroglycerin has more effect on venous capacitance than on the arterial bed.

Hydralazine Hydralazine is used to control systemic hypertension because it relaxes arterial smooth muscle more than it relaxes veins. Administration of the drug can cause headache, nausea, dizziness, sweating, and tremors. The most important acute side effect is tachycardia, which may increase cardiac output; labetalol, a β-antagonist, can counteract this effect.[45]

Tolazoline and Phentolamine These competitive α-adrenergic blockers have had varied success in the treatment of pulmonary hypertension.[46] However, they are effective in treating the symptoms of pheochromocytoma preoperatively. Serious side effects of these drugs include tachycardia, ventricular arrhythmias, hypotension, and tissue edema.

Prostaglandin E_1 PGE_1 acts directly on vascular smooth muscle and has greatly improved the care of neonates with heart disease. At infusion rates of of 0.1 µg/kg/min, patency of the ductus arteriosus is maintained and a closed ductus reopens in some neonates. The drug is indispensable in the care of patients with ductus-dependent cardiac lesions, such as interrupted aortic arch, critical aortic stenosis, or hypoplastic left heart syndrome, where systemic blood flow is supplied through the ductus arteriosus. It is equally important for the care of patients who have pulmonary atresia or critical pulmonic stenosis.[19] PGE_1 has been used with varying degrees of success to treat pulmonary hypertension. Apnea, fever, and hypotension are common side effects of this drug.

Nitric Oxide NO is an endothelium-derived relaxing factor that selectively vasodilates the pulmonary vasculature.[47] When administered by inhalation to patients with pulmonary hypertension, NO reduces PVR. It improves the survival of neonates who have reactive pulmonary hypertension.[48-50] This compound is inactivated by hemoglobin before it reaches the systemic circulation. On rare occasion, NO causes systemic vasodilation or clinically significant methemoglobinemia when administered at 5 to 80 ppm.[49]

Sildenafil Sildenafil is a pulmonary vasodilator that increases intracellular cyclic guanosine monophosphate. The drug can be administered orally or intravenously to outpatients. Because it appears to treat pulmonary hypertension of several causes, it will potentially be a treatment of choice in the future.

Arrhythmias

Arrhythmias occur less commonly in children than in adults, probably because children do not have atherosclerosis. However, a few arrhythmias commonly occur in infants and children and must be considered.

Sinus bradycardia is the most common arrythmia in children and is frequently caused by hypoxemia. Hence, an open airway, oxygen, and ventilation are the treatments of choice. If such treatment does not increase the heart rate, atropine, 20 to 30 µg/kg (up to 1 mg), should be given. Heart block is a common form of bradycardia that occurs in children who have undergone surgical repair of congenital heart lesions. If heart block persists for more than 2 weeks after surgery, insertion of a pacemaker is indicated. Connective tissue disease, such as systemic lupus erythematosus, has induced heart block in utero.

Sick sinus syndrome is usually due to surgery, myocarditis, or myocardiopathy. Prolonged QT syndrome, an abnormality in ventricular repolarization, is a familial disorder that can cause sudden cardiac death. Supraventricular tachycardia (SVT), a narrow QRS complex with a regular R-R interval, is also a common arrhythmia of childhood. In infants and neonates, the heart rate may be 200 to 300 beats/min, and in older children it can be 150 to 250 beats/min. Older patients with SVT frequently complain of palpitations or a racing heart rate and seek medical care before CHF occurs. In contrast, younger nonverbal children are often initially seen with CHF. Treatment of SVT includes vagal maneuvers, adenosine by rapid intravenous bolus (0.1 to 0.2 mg/kg, with a maximum single dose of 12 mg), and direct-current cardioversion (0.25 to 1 J/kg).[51,52]

Hypertension

Essential hypertension is uncommon in children, but when it occurs, it is often associated with another disease process (Box 84-2) and is frequently difficult to control. The acute onset of severe systemic arterial hypertension is a medical emergency that has the potential of causing cardiovascular decompensation, encephalopathy, seizures, and intracranial hemorrhage. In older children, the neurologic manifestations of hypertension are more likely to precede cardiovascular decompensation. Neonates with severe hypertension are frequently initially found to have CHF. Treatment of hypertension is tailored to the disease process, the absolute degree of hypertension, and the presence of cardiovascular or neurologic symptoms.[53,54]

Classes of antihypertensive drugs are listed in Box 84-3. If malignant hypertension is the admitting diagnosis, close cardiac monitoring and insertion of an arterial line in an ICU are required. In emergency situations, diazoxide is often the drug of choice. This potent vasodilator rapidly reduces blood pressure, but its short half-life necessitates administering another drug with a longer duration of action. Nitroprusside infusions are also useful in the acute setting.

Box 84-2 Causes of Severe Hypertension in Children

Renal
Acute glomerulonephritis (e.g., poststreptococcal, Henoch-Schönlein purpura)
Hemolytic-uremic syndrome
Chronic glomerulonephritis (all types)
Acute and chronic pyelonephritis
Congenital malformations (dysplasia, hypoplasia, cystic diseases)
Tumors (e.g., Wilms', leukemic infiltrate)
Post–renal transplantation status; also rejection
Oliguric renal failure
Trauma
Obstructive uropathy
After genitourinary surgery
Blood transfusions in children with azotemia

Cardiovascular
Coarctation of the aorta
Renal artery abnormalities (e.g., stenosis, thrombosis)
Takayasu's disease

Endocrine
Pheochromocytoma
Neuroblastoma
Adrenogenital disease
Cushing's syndrome
Hyperaldosteronism
Hyperthyroidism
Hyperparathyroidism

Iatrogenic
Intravascular volume overload
Administration of sympathomimetic drugs (e.g., epinephrine, ephedrine)
Administration of corticosteroid
Rapid intravenous infusion of methyldopa

Miscellaneous
Immobilization (e.g., fractures, burns, Guillain-Barré syndrome)
Hypercalcemia (e.g., hypervitaminosis D, metastatic disease, sarcoidosis, some immobilized patients)
Hypernatremia
Stevens-Johnson syndrome
Increased intracranial pressure (any cause)
Dysautonomia
After resuscitation

Specific Pediatric Diseases

Kawasaki Disease

Kawasaki disease (mucocutaneous lymph node syndrome) occurs primarily in children 4 years of age or older. The disease is divided into three stages: an acute febrile stage (1 to 2 weeks), a subacute phase, and finally, the convalescent stage (typically 6 weeks after onset). The cause is uncertain, but it is presumed to be infectious.

Although the disease affects many organ systems, cardiovascular involvement is the usual cause of ICU admission. Forty percent of patients with this disease have myocarditis, pericardial effusions, arrhythmias, or any combination of these findings. Coronary aneurysms, with and without thrombosis, develop in 20% of cases. Acute myocardial infarction is responsible for the death of 3% to 4% of patients.

Laboratory tests reveal an elevated leukocyte count with a left shift, increased acute-phase reactants, and a platelet count that is often grossly elevated after the first few weeks of the disease. An echocardiogram is required for any child with this presumed diagnosis.

Treatment includes high-dose aspirin (20 to 25 mg/kg every 6 hours) and intravenous gamma globulin, 2 g/kg administered as a 10- to 12-hour infusion. Some patients require inotropic support. There is considerable controversy about whether children with thrombosed coronary arteries should receive anticoagulants. Survivors frequently resolve their aneurysms, although some require coronary artery bypass surgery to provide adequate myocardial blood flow.[55,56]

Box 84-3 Antihypertensive Medications

Converting enzyme inhibitors to decrease angiotensin II
  Caution in the face of renovascular disease
    Captopril
    Enalapril
Calcium channel blockers, usually type II blockers
  Caution: Myocardial decompensation
    Nifedipine
    Nimodipine
Diuretics, usually as an adjunct
β-Adrenergic blockers
  Caution: Reactive airway disease
    Propranolol
    Esmolol
α_2-Antagonist
  Prazosin
Central α-agonist
  Clonidine
α- and β-adrenergic blocker
  Labetalol
Dilators
  Hydralazine
  Diazoxide

Anomalous Origin of Coronary Arteries

Vascular causes of myocardial ischemia are uncommon in pediatric patients. An anomalous origin of the left coronary artery in which the coronary artery originates from the pulmonary artery occurs in 1 in 300,000 births. During the first weeks or months of life, coronary perfusion may be adequate because PVR is elevated. As PVR decreases, however, coronary perfusion may decrease. By 6 weeks of life, these infants usually have overwhelming myocardial failure. Patients with large collateral vessels can survive into adulthood. Treatment is surgical.[57]

Respiratory System

Age-Dependent Respiratory Variables: Structural and Functional Development

Airways and Alveoli

The lungs appear in the fourth to eighth weeks of gestation. At this time, the lung buds divide into the mainstem bronchi; by 6 weeks all subsegmental bronchi are present; and by 16 weeks, the number of airway generations is similar to that of adults. When airway development is complete, the terminal airways remodel and multiply to form a cluster of large saccules, or alveolar precursors, that can support gas exchange. True alveoli appear before and after birth, and the respiratory saccules are thin and septate during postnatal growth.

At birth, children have approximately 24 million alveoli; by 8 years of age, the number has increased to 300 million (Table 84-4). After that, further lung growth is primarily the result of increased alveolar size.

There is less elastic tissue in the neonatal lung than in the lungs of adults, and the elastin extends only to the alveolar duct. By 18 years of age, elastin extends to the alveolus and is at its maximum. It then slowly decreases over the next 5 decades. Lung compliance is integrally related to the amount of elastin; hence, compliance peaks in adolescence. It is lower in the very young and the very old. Airways close in the tidal volume range until about 5 years of age.

Pulmonary Circulation

The main axial arteries of the lungs are present at 14 weeks' gestation. By 20 weeks' gestation, the pattern of branching is similar to that of adults, and collateral supernumerary vessels are present. During fetal life, additional arteries develop to accompany the respiratory airways and saccules. Bronchial arteries appear between the 9th and 12th weeks of gestation. The arterial wall develops a fine elastic lamina by 12 weeks' gestation, and muscle cells are present as early as 14 weeks of gestation. By 19 weeks, the elastic tissue extends to the seventh generation of arterial branching, and muscularization extends distally. In the fetus, muscularization of the arteries ends at a more proximal level than in childen and adults. The muscularized arteries have thicker walls than arteries of similar size in adults. The pulmonary arteries are actively constricted until the latter part of gestation. In the fetal lamb, pulmonary blood flow is only 3.5% of the combined

Table 84-4 Age-Dependent Respiratory Variables: Normal Values*

	Newborn	6 mo	12 mo	3 yr	5 yr	12 yr	Adult
Respiratory rate (breaths/min)	50 ± 10	30 ± 5	24 ± 6	24 ± 6	23 ± 5	18 ± 5	12 ± 3
Tidal volume (mL)	21	45	78	112	270	480	575
Minute ventilation (L/min)	1.05	1.35	1.78	2.46	5.5	6.2	6.4
Alveolar ventilation (mL/min)	385	—	1245	1760	1800	3000	3100
Dead space–tidal volume ratio	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Oxygen consumption (mL/kg/min)	6 ± 1.0	5 ± 0.9	5.2 ± 0.9	±	6.0 ± 1.1	3.3 ± 0.6	3.4 ± 0.6
Vital capacity (mL)	120	—	—	870	1160	3100	4000
Functional residual capacity (mL)	80	—	—	490	680	1970	3000
Total lung capacity (mL)	160	—	—	1100	1500	4000	6000
Closing volume as a percentage of vital capacity	—	—	—	—	20	8	4
Number of alveoli (saccules) × 10^6	30	112	129	257	280	—	300
Specific compliance: CL/FRC (mL/cm H_2O/L)	0.04	0.038	—	—	0.06	—	0.05
Specific conductance of small airways (mL/sec/cm H_2O/g)	0.02	—	3.1	1.7	0.12	8.2	13.4
Hematocrit	55 ± 7	37 ± 3	35 ± 2.5	40 ± 3	40 ± 2	42 ± 2	43-48
pH_a	7.30 ± 7.40	—	7.35-7.45	—	—	—	7.35-7.45
$Paco_2$ (mm Hg)	30-35	—	30-40	—	—	—	30-40
Pao_2 (mm Hg)	60-90	—	80-100	—	—	—	80-100

*Also see Chapter 82.
CL, compliance of lung; FRC, functional residual capacity.
From O'Rourke PP, Crone RK: The respiratory system. *In* Gregory G (ed): Pediatric Anesthesia, 2nd ed. New York, Churchill Livingstone, 1989, p 63.

ventricular output at 0.4 to 0.7 of gestation and is just 7% near term. Immediately after birth, pulmonary blood flow increases to near adult levels. Development of the pulmonary venous system mirrors that of the arterial system.

The pulmonary arteries continue to develop after birth; new artery formation follows airway branching up to about 19 months of age, and supernumerary arteries continue to grow until 8 years of age. As alveolar size increases, the acinar branching pattern becomes more extensive and complex. The arterial structure also changes as preexisting arteries increase in size; the thickness of the muscular arteries decreases to adult levels during the first year of life.

Biochemical Development

By 24 weeks of gestation, the alveolar cuboidal epithelium flattens, and type I pneumocytes become the lining and supporting cells for the alveoli. The larger type II cells, which manufacture and store surfactant, also develop at this time. Surfactant initially appears at 23 to 24 weeks' gestation in humans and increases in concentration during the last 10 weeks of gestational life.[58] Surfactant is released into the alveoli at about 36 weeks' gestation, thus making normal extrauterine life possible.

Respiratory Transition: Placenta to Lung

By approximately 24 weeks' gestation, the lungs are capable of extrauterine gas exchange. However, several important circulatory and mechanical changes must occur immediately after birth for pulmonary gas exchange to be adequate.

Ventilation begins to match perfusion within the first hours of life. Initially, there is right-to-left intrapulmonary shunting through atelectatic areas of the lung, as well as left-to-right shunting through the ductus arteriosus and some right-to-left shunting through the foramen ovale. The resultant Pao_2 of 50 to 70 mm Hg indicates a right-to-left shunt that is three times that of normal adults.

Transition from fetal to neonatal respiration and circulation is dynamic. Postnatally, the pulmonary vascular bed remains constricted if it is exposed to acidosis, cold, or hypoxia. If pulmonary artery constriction occurs, right-to-left shunting of desaturated blood through the foramen ovale and ductus arteriosus increases and consequently reduces pulmonary blood flow. Maintenance of this active pulmonary vasoconstriction is called persistent pulmonary hypertension of the newborn or persistent fetal circulation. It also occurs in patients who have congenital diaphragmatic hernia, meconium aspiration, and sepsis.[59]

Mechanics of Breathing

For ventilation of the lungs, the respiratory muscles must overcome the lung's static-elastic and dynamic-resistive forces. Changes in these opposing forces during postnatal development affect lung volume, the pattern of respiration, and the work of breathing.

Lung Compliance Versus Age

Lung compliance changes with age because of the changing alveolar structure, amount of elastin, and amount of surfactant. At birth, compliance is low because alveolar precursors have thick walls and decreased amounts of elastin. A deficiency of surfactant (e.g., hyaline membrane disease) further decreases lung compliance. The improved lung compliance occurring over the first years of life is the result of continued development of alveoli and elastin.

Chest Wall

The chest wall of infants is very compliant because their ribs are cartilaginous. Because of the box-like configuration of an infant thorax, there is less elastic recoil than there is with the dorsoventrally flattened thoracic cage of adults. Adults have a high proportion of slow-twitch, high-oxidative, fatigue-resistant fibers in their diaphragm and intercostal muscles. Whereas adults have 65% of these fibers in the intercostal muscles and 60% in the diaphragmatic muscles, neonates have only 19% to 46% of these fibers in their intercostal muscles and 10% to 25% in the diaphragm.[60] Consequently, infants are more vulnerable to muscle fatigue and decreased stability of the chest wall. The net effect of the compliant chest wall and the poorly compliant lungs is alveolar collapse and lower resting lung volume (functional residual capacity [FRC]). Despite this tendency for lung collapse, a child maintains a large dynamic FRC via rapid respiratory rates, laryngeal breaking, and stabilization of the chest wall with increased intercostal tone during exhalation.[61]

Upper Airway

The upper airways of children and adults have several anatomic differences that affect their ability to maintain a patent airway. The more anterior and cephalad position of the larynx in children makes the "sniffing position" ideal for mask ventilation and endotracheal intubation. Extreme neck extension can actually obstruct the airway. The narrowest part of the adult airway is the vocal cords. Up to the age of 5 years, the narrowest portion of a child's airway is at the cricoid cartilage because the posterior larynx is positioned more cephalad than the anterior larynx, which causes the cricoid ring to be an ellipse rather than a circle. By 5 years of age, the posterior larynx has descended to the adult level.[62,63] An endotracheal tube (ETT) that passes easily through the vocal cords of a young child may cause ischemic damage to the distal airway. The cricoid narrowing and very pliant tracheal cartilage provide an adequate seal around an uncuffed ETT. Children younger than 5 years rarely require a cuffed ETT, although some practitioners use cuffed tubes regularly in these patients.[64,65]

Closing Capacity

The elastic properties of the lung closely correlate with closing capacity. Closing volume is the lung volume at which the terminal airways close and gas is trapped behind the closed airways.[66] Large closing volumes increase dead space ventilation, which leads to atelectasis and right-to-left shunting of blood. Elastic tissues help keep the airways open, so the greater the elastic stroma in the small airways, the lower the lung volume required to close small, noncartilaginous airways. Closing volume is small in late adolescence and relatively large in the elderly and the very young. Children overcome the complications of large closing volumes and secondary atelectasis by breathing rapidly, by constant activity, and by crying. Closing volume becomes a significant problem in infants who are inactive, sedated, or anesthetized.

Resistive Forces

Neonates have small airways with high resistance or low conductance (conductance = 1/resistance). The diameter of the small

airways does not significantly increase until about 5 years of age; hence, young children have elevated airway resistance at baseline and are particularly vulnerable to diseases that cause further narrowing of the airways (i.e., smooth muscle constriction, airway edema/inflammation). The normal high airway resistance of neonates and young children helps maintain FRC.

Control of Breathing

The newborn's respiratory control is unique. Hypoxia initially increases ventilation for a short time. This increase is followed by a sustained decrease in ventilation.[67] The response is more exaggerated in preterm neonates. In full-term infants, it disappears after several weeks. Periodic breathing is also more common in infants, particularly preterm infants, and is probably due to inadequate development of the medullary respiratory centers.

Oxygen Transport: Oxygen Loading and Unloading

Fetal hemoglobin has low levels of 2,3-diphosphoglycerate and an oxygen half-saturation pressure of hemoglobin (P_{50}) of 18 mm Hg, which is much lower than the 27 mm Hg in adults. This lower P_{50} allows the fetus to load more oxygen at low placental oxygen tension, but it makes unloading oxygen in tissues more difficult. Three to 6 months after birth, fetal hemoglobin has been replaced with adult hemoglobin. The increased oxygen content of fetal hemoglobin and the increased fetal hemoglobin concentration are advantageous to the fetus because it allows an oxygen content of 20 mL of oxygen/100 mL of blood to be delivered to the brain and heart. This is the same oxygen content that adults have when breathing room air. The oxygen concentration of neonates at birth is 6 to 8 mL/kg/min. It decreases to 5 to 6 mL/kg/min over the first year of life. The decreased ventilation-perfusion ratio, the decreased P_{50} of fetal hemoglobin, and the progressive anemia characteristic of infants can make it difficult to deliver adequate oxygen during the first few months of life. Infants compensate by having a cardiac output of approximately 250 mL/kg/min for the first 4 to 5 months of life.

Respiratory Failure

Respiratory failure is the inability of the lungs to adequately oxygenate and remove CO_2 from pulmonary arterial blood. There are many causes of respiratory failure, including a low environmental oxygen concentration, parenchymal lung desease, and pulmonary vascular disease.

A complete history of the severity and chronicity of the respiratory problem helps formulate a differential diagnosis and an approach to treatment. Specific data should include a history of prematurity, previous airway instrumentation, previous mechanical ventilation, nonpulmonary organ dysfunction, and a family history of respiratory disease. A detailed feeding history and up-to-date growth chart may provide valuable information because growth failure may increase the need for oxygen. Usually, 1% to 2% of the total oxygen consumed is used for breathing. During respiratory illneses, as much as 50% of the total oxygen consumption may be used for breathing.

Infants and children with respiratory failure often have intercostal and suprasternal retractions, signs that the work of breathing and oxygen consumption are increased. Patients grunt during expiration in an attempt to maintain FRC. Most infants and children have tachypnea, which also helps maintain FRC by decreasing the time for exhalation. Less energy is required to breath rapidly and shallowly than to take deep breaths. Infants with respiratory failure often have cyanotic lips, skin, and mucous membranes. However, it is often difficult to recognize skin color changes unless the Pao_2 is below 70 mm Hg. Symmetry of chest movement should be noted. Differences in movement may indicate pneumothorax or blockage of a bronchus. The small thoracic volume allows easy transmission of breath sounds from one side to the other. Breath sound may be normal, even when pneumothorax is present. Abdominal distention can dramatically impede breathing in infants and young children.

Radiologic evaluation of the nasopharynx, neck, and thorax can provide meaningful information regarding the cause and severity of the respiratory dysfunction. Fluoroscopy can be used to evaluate the airways and movement of the diaphragm in an uncooperative child. If a child must leave the ICU for these examinations, someone capable of providing ventilatory support should accompany the patient.

Pulmonary function tests help assess respiratory function, but because of lack of cooperation, these tests are difficult to perform in children younger than 5 years without sedation, which may be dangerous for an unintubated child with respiratory failure. Most pulmonary function testing requires the use of a tight-fitting mask, and this in and of itself can be problematic.[68] If the trachea is intubated, lung volumes, expiratory flow rates, compliance, and inspiratory forces can be measured easily; in fact, most mechanical ventilators are now equipped with monitors that allow these variables to be measured routinely.

Analysis of ABGs is used to determine the effectiveness of gas exchange. Pao_2 measurements allow calculation of the alveolar/arterial oxygen gradient and right-to-left shunting of blood across the lung.

Elimination of CO_2 from arterial blood is another indicator of lung function. Failure to remove CO_2 from pulmonary arterial blood indicates maldistribution of blood flow in the lungs; specifically, there is increased dead space.

Umbilical artery cannulation is common in neonates, so those caring for such children can obtain arterial blood and continuously measure arterial blood pressure. These catheters are relatively simple to insert and reasonably easy to maintain.[69] The tip of the catheter ideally should be at or just above the level of the aortic bifurcation and below the level of the renal arteries (L2). Once the child's condition is stable, a peripheral artery catheter should be inserted and the umbilical artery catheter should be removed. All intra-arterial catheters have the potential to cause distal thromboembolic disease. Care must be taken to flush arterial catheters gently to prevent cerebral or cardiac emboli. With proper insertion and maintenance, serious complications of arterial lines are rare. Although arteries that are cannulated for a long time may occlude, they recanalize within a short period.[70]

Less invasive techniques for monitoring gas exchange have been developed. Transcutaneous electrodes accurately measure oxygen and CO_2 in infants and young children, but they lose accuracy during hypoperfusion. The electrodes require some warm-up time, which makes "spot checks" difficult. These monitors are best used as trend monitors in older children and adults.[71,72] Pulse oximeters are routinely used to care for critically ill infants and children because they are accurate, require no warm-up time, and need little skill to apply. The probe is easily wrapped around an infant's or young child's entire hand or foot.[73] End-tidal CO_2 monitoring allows CO_2 elimination to be meas-

ured continuously. However, this technology has limited application in small children because of the increased dead space and the weight of the sampling device on the end of the ETT, which can kink the ETT and cause accidental extubation. The volume of gas withdrawn for sampling (about 75 mL/min) can alter the tidal volume of an extremely small child.[74]

Causes of Respiratory Failure

The cause of respiratory failure depends to some degree on the age of the patient. Newborn respiratory failure is often the result of congenital anomalies and immaturity of the lungs and their blood vessels. Congenital anomalies can include airway malformations, dysgenesis or malfunction of the lung or nonpulmonary organs, and abnormalities of the pulmonary vessels. Lesions of immaturity include apnea of prematurity, hyaline membrane disease, and abnormalites of surfactant production and secretion. During the perinatal period neonates are subject to infections and stress. Persistent pulmonary hypertension can complicate neonatal pulmonary and nonpulmonary problems. These and other important causes of respiratory failure in the newborn are listed in Table 84-5. A wide variety of disorders cause respiratory failure in older children (Box 84-4). Regardless of the specific cause, respiratory failure can be categorized as hypoventilation syndromes in patients with normal lungs, intrinsic alveolar and interstitial disease, and obstructive airway disease.

Hypoventilation Syndromes in Children with Normal Lungs

Causes of hypoventilation include neuromuscular disease, central hypoventilation, and structural/anatomic impairment of lung expansion (i.e., upper airway obstruction, massive abdominal distention). These clinical conditions are characterized by inadequate lung expansion, secondary atelectasis, intrapulmonary right-to-left shunting, and systemic hypoxia. Atelectasis and the secondary reduction in FRC increase the work of breathing. The child's response to the increased work of breathing and lower lung volumes is to breathe faster with a smaller tidal volume. This pattern of breathing eventually increases the amount of atelectasis and shunting. As a result, children with intrinsically normal lungs and hypoventilation syndromes exhibit tachypnea, small tidal volumes, increased work of breathing, and cyanosis. Chest radiographs reveal small lung volumes and miliary or lobar atelectasis. Positive-pressure ventilation and PEEP quickly reverse the pathologic processes.

Primary Pulmonary Alveolar or Interstitial Disorders

Intrinsic lung disease involving the alveoli or pulmonary interstitium decreases lung compliance and increases airway closure, both of which cause atelectesis and increase the work of breathing. Edema or inflammation of the alveoli or fibrosis of the interstitium decreases lung compliance. The stiffer lung requires a greater negative intrapleural pressure for air movement, thereby increasing the work of breathing and the risk for pneumothorax.

Obstructive Airway Disease

Airway obstruction can be extrinsic or intrinsic. Intrinsic small airway obstruction commonly occurs with bronchiolitis, bronchopneumonia, asthma, and bronchopulmonary dysplasia (BPD).

Table 84-5 Classification of Causes of Neonatal Respiratory Failure

	Congenital Abnormalities	Developmental Immaturity	Specific Neonatal "Stress"
Impaired control of ventilation	Central nervous system dysgenesis Ondine's curse	Apnea of prematurity Intracranial hemorrhage	Drug intoxication (note maternal drugs) Sepsis Central nervous system infections Seizures
Neuromuscular disorders	Congenital myopathies		High cervical cord injuries
Structural impairment	Thoracic deformities Lung hypoplasia Diaphragmatic hernia Potter's syndrome Abdominal malfunction Gastroschisis Omphalocele		Severe abdominal distention Pneumothorax or other air leak
Airway obstruction	Choanal atresia		Massive meconium aspiration
Upper airway	Pierre Robin syndrome Laryngeal web/cleft Congenital tracheal/laryngeal stenosis Recurrent laryngeal palsy Hemangioma Lymphangioma		Vocal cord paralysis secondary to myelodysplasia
Lower airway	Tracheoesophageal fistula Lobar emphysema		Meconium/blood aspiration
Alveolar disorders		Respiratory distress syndrome	Bronchopulmonary dysplasia
Cardiovascular disorders	Congenital cardiac malformations Congestive heart failure (critical coarctation or aortic stenosis) Total anomalous pulmonary venous return		Persistent pulmonary hypertension

Box 84-4 Causes of Respiratory Failure in Children

- Impaired control of ventilation
  - Head trauma
  - Intracranial hemorrhage
  - Increased intracranial pressure secondary to tumor, edema, hydrocephalus, Reye's syndrome, etc.
  - Central nervous system infections
  - Ondine's curse
  - Drug intoxication
  - Status epilepticus
- Neuromuscular disorders
  - High cervical cord injury
  - Poliomyelitis
  - Guillain-Barré syndrome
  - Neurodegenerative diseases (e.g., Werdnig-Hoffmann syndrome)
  - Muscular dystrophies and myopathies
  - Myasthenia gravis
  - Botulism
  - Tetanus
  - Phrenic nerve injury
- Structural impairment
  - Severe kyphoscoliosis
  - Flail chest
  - Large intrathoracic tumor
  - Pneumothorax or pneumomediastinum
  - Large pleural effusion, hemothorax, empyema
  - Severe abdominal distention
  - Severe obesity (pickwickian syndrome)
- Airway obstruction
  - Upper airway
    - Congenital anomalies
    - Tumor—intrinsic or extrinsic
    - Epiglottitis
    - Croup (laryngotracheobronchitis)
    - Foreign body
    - Postintubation edema, granulation tissue, or scarring
    - Vocal cord paralysis
    - Burns
    - Vascular ring
  - Lower airway
    - Asthma
    - Bronchiolitis
    - Foreign body
    - Lobar emphysema
    - Cystic fibrosis
- Alveolar disorders
  - Pneumonia
    - Infectious—bacterial, viral, fungal, *Pneumocystis*
    - Chemical—aspiration, hydrocarbon, smoke inhalation
  - Pulmonary edema—cardiogenic, near-drowning, capillary leak syndrome
- Massive atelectasis
- Oxygen toxicity
- Pulmonary contusion
- Pulmonary hemorrhage

Airway obstruction decreases conductance and increases airway resistance and the work of breathing. Partial obstruction impedes expiration more than inspiration and causes gas trapping or regional emphysema. Complete airway obstruction results in atelectasis and right-to-left shunting of blood within the lung. Patients with disease of the small airways usually have a mixture of total and partial airway obstruction and inhomogeneous collapse and overdistention of the lung. The areas of collapse cause intrapulmonary right-to-left shunting of blood, and the overdistended areas increase the amount of dead space. If the entire lung is overdistended, compliance is decreased and the work of breathing is increased. The clinical and radiographic picture varies with the different degrees of collapse and overdistention of the lung.

In summary, all causes of respiratory failure share similar pathophysiology: atelectasis and decreased FRC with intrapulmonary right-to-left shunting of blood or alveolar overdistention with increased dead space and decreased CO_2 elimination, or both. The increased work of breathing associated with all forms of respiratory dysfunction can cause fatigue and a breathing pattern that further complicates the initial process. It may also lead to apnea, hypoxia, and cardiac arrest in young childeren if the increased work of breathing is not quickly detected and treated.

Treatment of Respiratory Failure

Treatment of respiratory failure includes ensuring an open airway, increasing the inspired oxygen concentration, relieving airway obstruction, treating infection, correcting fluid overload, correcting abnormalities of all nonpulmonary systems, and instituting mechanical ventilation. Exogenous surfactant, high-frequency ventilation, lung-protective mechanical ventilation strategies,[75] inhalation of NO, prone positioning, liquid ventilation,[76] and extracorporeal membrane oxygenation (ECMO) may be effective in particular clinical situations.

Infants and young children often require help to maintain airway patency. Specific maneuvers include keeping the child in a semiupright position to avoid aspiration or gastroesophageal reflux and to minimize the effects of abdominal distention. It is usually appropriate to keep the head in a midline position and to minimize excessive neck flexion.

The inspired oxygen concentration can be increased by a tight-fitting anesthesia mask. Nasal prong oxygen often helps but may agitate some children and negate any beneficial effects of the increased F_{IO_2}. Blow-by oxygen, space masks, croup tents, and head boxes are less invasive and generally are better tolerated by children.

Upper airway obstruction can be relieved by inserting a laryngeal mask, an ETT, a tracheostomy, or an oropharyngeal or nasopharyngeal tube. Inhaled racemic epinephrine and intravenous steroids often decrease subglottic edema,[77,78] antibiotics decrease infectious swelling, and β-agonists and inhaled anticholinergic medications relax bronchial smooth muscle.[79] Patients with pneumonitis should have cultures for bacterial, viral, or fungal pathogens and be treated with appropriate antibiotics. Pulmonary edema is treated by limiting fluid intake and administering diuretics and cardiotonic or vasoactive drugs. Good oral or

intravenous nutrition, fluid and electrolyte balance, and adequate cardiovascular and renal function are part of pulmonary support.

Mechanical ventilation is the main treatment of respiratory failure. The following are several nonpulmonary reasons for mechanical ventilation:

1. Resuscitation from circulatory collapse. In situations in which the cardiovascular system is unstable, it is safest to mechanically ventilate the lungs. During cardiac arrest, respiratory support is mandatory, although bag-and-mask ventilation may initially be effective. *Patients seldom die of lack of an ETT. They usually die of lack of oxygen, which is sometimes forgetten in our haste to place an ETT.* Mechanical ventilation is used after cardiac surgery to ensure adequate gas exchange until the circulation is stable. Mechanical ventilation also reduces the risk of untoward cardiovascular decompensation.
2. Respiratory assistance. Intentional hyperoxia is occasionally used to dilate the pulmonary vascular bed of some newborns while initiating other therapies.[46] Mechanical ventilation is also used to reduce intracranial pressure (ICP) by inducing mild respiratory alkalosis and decreasing cerebral blood volume.[80] When this is done, mean arterial pressure must be kept at pre-hyperventilation levels or higher to prevent further cereberal ischemia. Children with underlying conditions that predispose them to respiratory failure (morbid obesity, sepsis, nutritional debilitation, and kyphoscoliosis) may also require mechanical ventilation.
3. Reduced work of breathing. Reducing the oxygen cost of breathing by mechanically ventilating patients may improve some patients' ability to survive a major physiologic insult. Childern with BPD may require long-term mechanical ventilation to conserve the energy expended for breathing and use this energy for growth.[81]

Ventilatory Therapy

Respiratory assistance is provided by continuous positive airway pressure (CPAP), intermittent positive-pressure ventilation, and negative-pressure ventilation. Positive-pressure ventilation is usually applied through an ETT or a tracheostomy. Some infants and children can be supported with mask CPAP, noninvasive ventilation, or nasal prongs with high flow. Oral intubation is easier than nasal intubation is, especially in emergency situations.

The size of ETT required should be selected carefully. One formula that estimates the appropriately sized tube for children older than 2 years is (age + 16)/4.

This formula provides the internal diameter of the appropriately sized ETT. The correct size should have a slight air leak when a positive pressure of 20 to 30 cm H_2O is applied.[82] Serious lifelong laryngeal and subglottic damage can result from using inappropriately large ETTs, particularly in children with inflammatory lesions of the upper airway such as laryngotracheobronchitis. Because of the more flexible tracheal cartilage and the relative subglottic narrowing of children, uncuffed ETTs generally provide an adequate seal in those younger than 5 years. However, if the patient has lung disease that requires high ventilation pressure, a cuffed tube is more appropriate. Small cuffed ETTs are frequently used in the ICU in younger patients,[65] but care should be taken to ensure that there is a small leak of air at 25 to 30 cm H_2O. Cuffed tubes will usually eliminate the air leak around an ETT, but overinflation of the cuff may occlude venous flow and injure the airway. There are presently no data on the long-term safety of using cuffed ETTs in young children.

With endotracheal intubation, it is important to correctly position the ETT. If correctly positioned, chest movements should be symmetric, and breath sounds should be equal when auscultated in the axillae. An electronic or colorimetric CO_2 detection system helps confirm whether the ETT is in the trachea or the esophagus.[83] If the double lines on the ETT are at the level of the vocal cords, the ETT is usually in the correct position. Another way to correctly position the ETT is to advance it into the right mainstem bronchus and listen for breath sounds in the left axilla. Breath sounds will be diminished. Withdraw the ETT slowly. When breath sounds are heard on the left, pull the tube out an additional 1 to 2 cm, depending on the size of the child. If the breath sounds are equal, fix the tube in place. The tip of the ETT should be midway between the vocal cords and the carina on the chest radiograph. In small infants, the distance between the carina and the vocal cords is very short. Consequently, it is easy to inadvertently place the ETT in a mainstem bronchus. Flexion of the head moves the ETT into the airway. Extension moves it toward the vocal cords. Turning the head to the side may obstruct the tip of the ETT if it comes in contact with the tracheal wall, which may cause CO_2 retention or hypoxemia, or both (unpublished data).

It is common to leave a child's trachea intubated for more than 2 weeks before performing a tracheostomy. This is possible with proper humidification of the inspired gases, improved endotracheal suctioning and monitoring (Sao_2), and excellent nursing care.

Everyone caring for the child must be constantly alert to the possiblity that the ETT will become obstructed by secretions or that accidental extubation or mainstem bronchus intubation will occur. In neonates, ETTs with a "Murphy" eye become obstructed more often with secretions than those without a Murphy eye do (unpublished data). The Murphy eye is very near the end of the ETT. Once the ETT enters the mainstem bronchus, it is impossible for the infant to effectively breath through the "eye." Because the ETT is almost the same size as the trachea, it is nearly impossible for the infant to breath around the tube. Thus, ETTs with Murphy eyes are dangerous and probably should not be used in young infants. Tracheostomy is indicated when children require a long-term artificial airway for mechanical ventilation, for endotracheal suctioning, or to bypass an upper airway obstruction. Accidental dislodgement of the tracheostomy tube before the tract is well healed can be life threatening. Reinsertion of a tracheostomy tube during the first 72 hours after insertion can be very difficult and can create false passages that can make it impossible to ventilate the lungs or can cause pneumothorax.

Continuous Positive Airway Pressure and Positive End-Expiratory Pressure With CPAP, the child breathes spontaneously through a system that maintains constant PEEP during exhalation. With PEEP, the lungs are mechanically ventilated while a constant end-expiratory pressure is maintained.

CPAP is applied by ETT, nasal cannula, or facemask. Because most newborns are obligate nose breathers, nasal CPAP is often effective, even for small premature infants. Successful application of CPAP depends on the size and condition of the infant and on whether the infant is mouth breathing. Crying and mouth breathing reduce the efficiency of nasal CPAP because

both reduce pharyngeal pressure. Gaseous distention of the abdomen occurs with nasal or mask CPAP. An orogastric tube is required to vent the stomach.[84] Facemask CPAP is effective for short periods in children and adults. Use of mask CPAP for prolonged periods may cause pressure necrosis of the face or eyes (or both). Low to moderate levels of PEEP can be maintained in children with an uncuffed ETT, but large gas leaks around the ETT make the PEEP level unstable. Using a larger ETT or a cuffed ETT solves this problem.

The optimum level of CPAP or PEEP is difficult to determine but is usually thought to be the lowest level of pressure that maintains a normal Pao_2 without elevating $Paco_2$ excessively. Too little pressure does not effectively increase Pao_2, whereas too much pressure overdistends the lungs and increases dead space ventilation. Low levels of CPAP or PEEP (2 to 5 cm H_2O) are advocated for any child with an artificial airway.[85]

The goal is to use the lowest level of CPAP or PEEP that adequately improves oxygenation while minimizing the effects on ventilation. One approach is to use the level of CPAP or PEEP that improves oxygenation and allows Fio_2 to be reduced to 0.6 or less. A second approach is to increase end-expiratory pressure until maximal improvement in compliance occurs.[86]

Suter and colleagues[87] proposed that the best PEEP (or CPAP) is the level of end-expiratory pressure required to produce maximal oxygen transport, which is the product of cardiac output and arterial oxygen content. This requires repeated cardiac output measurements and a Swan-Ganz thermodilution catheter, which is seldom done in young children. Most clinicians approximate the best CPAP or PEEP by using the CPAP or PEEP that gives an adequate Pao_2 and $Paco_2$ and allows Fio_2 to be reduced.

Positive-Pressure Ventilation Positive-pressure mechanical ventilators are classified according to their method of control as (1) volume preset, (2) pressure preset, and (3) time-flow preset.[88] As a general rule, time-flow or pressure-preset ventilators are more convenient to use in infants and young children (<10 kg), whereas volume-preset ventilators are commonly used in older children (>10 kg) and adults. Time-flow and pressure-preset ventilators have several advantages in infants and young children. Most of these patients are intubated with an uncuffed ETT, which causes a variable leak around the ETT. This leak, along with the relatively large compression volume of the circuit relative to the tidal volume of infants, makes volume-preset ventilation unreliable. The main problem with pressure-preset or time-flow–preset ventilators is that the volume delivered depends on the child's thoracic and lung compliance and on airway resistance. Improved lung and chest wall compliance may overdistend the alveoli and cause alveolar rupture. Alternatively, decreased compliance may cause atelectasis and hypoventilation.

Intermittent mandatory ventilation (IMV) allows the child to breathe spontaneously from a fresh gas source at low resistance while intermittently receiving a tidal volume from the mechanical ventilator at preset intervals.[89] Between ventilator breaths, children can breathe with the same Fio_2 and PEEP that they receive from the ventilator. IMV is produced either by a continuous-flow circuit or by a series of demand valves. Continuous-flow IMV circuits are simpler and require no additional patient effort during spontaneous breathing. Demand-valve systems may be ineffective in children who have relatively high respiratory rates because the sensitivity of the valve and the valve's response time may not allow the ventilator to function in synchrony with the patient's breaths. During pressure-support ventilation, each spontaneous breath is augmented by delivery of gas at a preset pressure. The patient determines the respiratory rate and the inspiratory time, and the machine determines the inspiratory pressure. Pressure-support ventilation increases tidal volume, may decrease the work of breathing, and may improve patient comfort. This mode of ventilation is commonly used to wean patients from mechanical ventilation. Pressure support will not work if patients have an abnormal respiratory drive.[90-92]

Box 84-5 outlines the salient features of the pathophysiology of acute respiratory distress syndrome (ARDS). Better understanding of the pathology of this disease has led to ventilator strategies that use relatively long inspiratory times, high end-expiratory pressures, and low tidal volumes. This lung-protective ventilator strategy results in lower minute ventilation and elevated $Paco_2$. It also decreases the shear forces acting on the terminal airways and recruits lung units that are below closing volume.[93] Acid-base status can be kept relatively normal by inducing a metabolic alkalosis by retaining bicarbonate in the kidney and administering sodium bicarbonate or THAM.

The optimal ventilation pattern for patients with obstructive airway disease is a faster inspiratory flow rate, a shorter inspiratory time, and a longer expiratory time to better ventilate relatively normal lung and to allow gas to escape from obstructed portions of the lung. Pharmacologic dilation of the bronchi is the principal treatment of disease of the small airways. Barotrauma and alveolar rupture occur commonly during mechanical ventilation of these patients.

Initiation of Mechanical Ventilation An inspiratory-to expiratory ratio of 1.5 : 1 or 1 : 1 and a relatively slow ventilation rate (<24 cycles/min in infants and <16 cycles/min in children) are useful starting points for many patients. Based on blood gases, pH, and oxygen saturation, the ventilator settings are changed.

Chest expansion, auscultation of the chest, and the adequacy of alveolar ventilation (as determined by $Paco_2$) are important criteria when determining the adequacy of ventilation. Peak airway pressure should be measured frequently and as near to the ETT as possible.

PEEP is begun at 3 to 4 cm H_2O and increased in 2–cm H_2O increments until the Sao_2 is appropriate. Few pediatric patients require end-expiratory pressure greater than 20 cm H_2O.

Initiation of positive-pressure ventilation may cause systemic arterial hypotension, which usually improves with the infusion of 10 to 20 mL/kg of crystalloid, colloid, or blood. CVP should be measured when a PEEP of 10 cm H_2O or greater is required. Measurement of intravascular arterial pressure and

Box 84-5 Pathophysiology of Acute Respiratory Distress Syndrome

- Disruption of endothelial barriers with leakage of protein-containing fluid and inflammatory cells into alveoli
- Inactivation of surfactant resulting in increased surface tension of the alveolar lining layer
- Atelectasis and loss of lung volume
- Shunting of blood through nonventilated areas of the lung resulting in hypoxemia and tissue hypoxia
- Decreased pulmonary compliance

CVP helps detect detrimental effects of mechanical ventilation and positive airway pressure on the cardiovascular system.

Adjunctive Pharmacologic Therapy: Sedatives and Analgesics Sedation is often required to help conscious children cooperate with mechanical ventilation. The amount of sedation required depends on the child's age, size, underlying disease, and amount of respiratory support needed. Some infants are sufficiently depressed and require no sedation. Sedation allows patients to breathe "in phase" with the ventilator, which reduces the peak airway pressure and eliminates coughing and straining, all of which can cause pulmonary gas leaks. A continuous infusion of fentanyl (1 to 2 µg/kg/hr) provides pain relief and sedation. However, it may be necessary to increase the infusion rate of fentanyl on subsequent days to maintain the same level of sedation.[94] Other drugs, such as lorazepam (0.1 to 0.2 mg/kg administered intravenously every 4 to 6 hours) or an infusion of midazolam (0.05 to 0.2 mg/kg/hr), can be useful adjuncts to opioid administration. These drugs usually have minimal cardiovascular effects if intravascular volume is adequate.[95] However, administering lorazepam to premature neonates for several days may cause steroid-responsive hypotension as a result of buildup of drug in the body. The half-life of lorazepam is approximately 72 hours in premature infants. Giving the drug every 4 to 6 hours causes accumulation of the drug in blood and tissues.

Neuromuscular blocking agents increase chest wall compliance, reduce oxygen consumption,[96] and facilitate mechanical ventilation. If neuromuscular blocking drugs are used, they should be administered in conjunction with medications that cause amnesia and anxiolysis and control pain.

Pancuronium and vecuronium are the most commonly administered muscle relaxants used in the PICU (also see Chapter 29). The usual dose of pancuronium is 0.1 mg/kg administered intravenously every 1 to 1½ hours or 40 to 100 µg/kg/hr as an infusion. The tachycardia associated with pancuronium is an undesired side effect in adults, but it is generally desirable in infants and children because it helps maintain cardiac output. Vecuronium (0.08 to 0.2 mg/kg, followed by an infusion of 60 to 150 µg/kg/hr) produces less tachycardia than pancuronium does; cisatracurium (0.1 to 0.2 mg/kg followed by an infusion of 60 to 120 µg/kg/hr) is often useful because its elimination is not dependent on renal or hepatic function. If these drugs are given for more than a day, provision of regular drug holidays should be considered to avoid serum buildup of the drug and prolonged paralysis.

Weaning from Mechanical Ventilation The criteria for weaning are ill defined. In general, weaning from respiratory support begins when the child's cardiovascular system is stable and the child is awake and alert. Mechanical ventilation should not be withdrawn if there is still significant risk for acute cardiac decompensation. It is also best to correct severe anemia, hypoglycemia or hyperglycemia, hypernatremia, hypochloremia, or malnutrition before initiating weaning because these metabolic disorders impair the child's ability to be weaned from mechanical ventilation. The child should be able to generate at least −20 cm H_2O pressure at the airway (inspiratory force) and inhale at least 10 mL/kg of gas with maximal effort (vital capacity) before weaning is considered.

When pressure-limited or time-flow–limited ventilators are used, the peak inspiratory pressure must be reduced when lung compliance improves because failure to do so may cause pneumothorax or pneumomediastinum (or both).

Ventilator rates are not usually decreased before ABGs are stable, the inspired oxygen concentration is less than 0.6, PEEP is less than 10 cm H_2O, and peak airway pressure is below 30 to 35 cm H_2O.

There should not be any residual effects of neuromuscular blocking drugs, and the level of sedation should be minimal. Neuromuscular blockade can be reversed with intravenous neostigmine (0.05 to 0.07 µg/kg) and glycopyrrolate (0.01 mg/kg); acceptable neuromuscular function should be confirmed with a peripheral nerve stimulator. When all these factors are in place, the ventilator rate is gradually decreased over a period of hours to days.

Weaning should continue as long as ABGs remain within an acceptable range and the child's clinical condition is stable. As spontaneous ventilation increases, the increased work of breathing may worsen the child's condition. Tachycardia, hypertension or hypotension, tachypnea, increased work of breathing, and anxiety are danger signs. If these signs occur, weaning should be discontinued and ventilatory support should be increased. Frequent assessment of ABGs and the child's clinical condition is essential throughout the weaning process. If a child has residual lung disease and decreased lung compliance, a further decrease in FRC and increased hypoxemia may delay weaning. These potential problems can be minimized by using moderate levels of CPAP or PEEP (5 to 10 cm H_2O) during weaning. FRC is similar in mechanically ventilated infants with a PEEP of 2 cm H_2O as it is after tracheal extubation.[97]

Tracheal extubation should be performed by an individual skilled in tracheal intubation because reintubation of the trachea may be necessary. Once tracheal extubation has occurred, it is usual to increase F_{IO_2} by 20%. Patients old enough should be encouraged to deep-breathe, cough, and clear secretions as often as possible. Incentive spirometry, early mobilization, and chest physical therapy are important adjunts when recovering from respiratory failure.[98]

Before tracheal extubation, the quality and volume of tracheal secretions should be assessed. Large volumes of thick secretions may make it difficult for the patient to clear the secretions after extubation. It is usually best to extubate the trachea while a full staff is available so that the child can be observed closely and a chest radiograph can easily be obtained. If weaning and tracheal extubation have been carefully planned and executed, reintubation is relatively uncommon.

High-Frequency Ventilation High-frequency ventilation provides smaller than anatomic dead space tidal volumes at high respiratory rates (150 to 3000 breaths/min). Several different types of ventilators, including high-frequency jet ventilators, high-frequency oscillating ventilators (HFOVs), and flow interrupters, are effective.[99] Each of these machines differs in technical design and clinical application and may differ in the mechanism of gas exchange.[100]

HFOVs are commonly used for neonates and children with severe lung disease and respiratory failure. Use of HFOVs has reduced the number of infants requiring ECMO.[101,102] HFOV is also successful in the treatment of children with acute homogeneous interstitial and alveolar disease.[103] This form of ventilation has been less successful in the treatment of large children and adults because of physical limitations of the equipment. Jet ventilation is used to treat respiratory failure of many causes, although the main indication for its use is to treat barotrauma or bronchopleural fistula.

Exogenous Surfactant

Administration of exogenous surfactant is now routine therapy for surfactant deficiencies of premature infants and has improved the survival of these children and decreased their need for aggressive mechanical ventilation and ECMO.[104] Exogenous surfactant has not been as effective in older children and adults, primarily because the type of lung disease is different. Older patients more often have abnormal surfactant function than they have an absolute decrease in the amount of surfactant.

Extracorporeal Membrane Oxygenation

ECMO is the standard of care for infants older than 34 weeks' gestation who have acute respiratory failure (ARF) that is unresponsive to standard therapy. More than 24,000 infants with a predicted mortality of 80% to 85% with conventional management have been treated by ECMO, and more than 80% of these patients survived.[105] Approximately 30% of infants with cardiac lesions, especially stunned myocardium, are saved by ECMO. The majority of ECMO has been venoarterial (VA), where blood is drained from the venous system and returned to the ascending aorta. VA ECMO supports respiratory and cardiac function. Venovenous (VV) ECMO is less efficient than VA ECMO, but it preserves pulmonary flow and avoids cannulation of a major artery. VV ECMO is less effective in patients with myocardial dysfunction. However, VV ECMO is rapidly gaining in popularity and is being used as commonly or more commonly than VA ECMO.[106] Target neonatal ECMO populations are also changing. Exogenous surfactant, inhaled NO, and HFOV have significantly reduced the need for ECMO greater preponderance of sepsis and multiorgan system failure. Today's ECMO candidates are sicker and have a greater preponderance of sepsis and multiorgan system failure.

ECMO support for older children and adults with ARF continues to be investigated. Approximately 7000 pediatric ECMO patients have been reported worldwide. All were patients who had a presumed 80% predicted mortality. About 50% of ECMO-treated patients survived. The reason for this difference in outcome in the two age groups is related to the marked heterogeneity in age, diagnoses, conventional management, and criteria for ECMO. In addition, neonates have only a few causes of ARF, and most are reversible. Older patients have multiple causes of ARF that are not always reversible.[107,108]

Common Respiratory Disorders

Laryngotracheobronchitis (Croup)

Croup is the most common cause of acute upper airway obstruction in otherwise healthy children (see Chapter 82). It occurs most frequently in the 3-month-old to 3-year-old age group. Croup is a viral infection (parainfluenza, influenza, adenovirus) that causes edema of the tissues in the upper airway, particularly in the immediate subglottic region. There is usually a history of a few days of upper respiratory tract infection symptoms followed by hoarseness, a croupy cough, and possibly stridor. The degree of respiratory distress and the child's ability to compensate for the increased work of breathing are best assessed clinically.

These patients are initially treated with mist and aerosolized racemic epinephrine to reduce swelling of upper airway mucosa.[109] Steroid administration is common yet controversial.[77] Tracheal intubation is required when the child can no longer sustain the increased work of breathing and CO_2 increases. When the trachea is intubated, the ETT should be 0.5 to 1.0 mm smaller than usual for age. The ETT must be of sufficient size that the patient can breathe easily during spontaneous ventilation and the nurses can effectively suction secretions from the airways. Croup usually resolves spontaneously in 3 to 7 days. The average duration of tracheal intubation is approximately 5 days. Laryngotracheobronchitis is less common in children older than 4 years.

Epiglottitis

Epiglottitis is an inflammation of the mucosa of the supraglottic structures that was previously caused by *Haemophilus influenzae* type B but is now commonly caused by *Staphylococcus aureus* and streptococcal organisms because immunizatiion against the *Haemophilus* organism has been so effective. In the past, epiglottitis was a disease of 4- to 6-year-old children. Now, it occurs more commonly at older ages (even in adults).[110] In young children, epiglottitis is a true airway emergency because it may rapidly progress to complete and fatal airway obstruction. Providing a secure airway is the first priority. Children with epiglottitis appear toxic and have a fulminant onset of fever and respiratory distress. Tracheal intubation during anesthesia is commonly required until antibiotic therapy (ampicillin and chloramphenicol or ceftriaxone) is initiated and the signs of systemic toxicity subside. Introduction of the *H. influenzae* vaccine has dramatically decreased the incidence of *H. influenzae* infection, as well as that of other *H. influenzae* processes.[111]

Bronchiolitis

Bronchiolitis is an acute viral infection of the lower respiratory tract that occurs primarily during the first 2 years of life. The signs and symptoms of this malady are air trapping, wheezing, mild to moderate systemic hypoxemia, increased work of breathing, and increased airway resistance. The cause is usually an infection with respiratory syncytial virus (RSV).[112]

Patients at high risk for respiratory failure from this disease include infants and young children with a history of prematurity, chronic lung disease, or congenital heart disease. Apnea is frequently the first sign of decompensation in neonates, which often occurs before significant hypercapnia appears. Fatigue is a common indication for mechanical ventilation. Treatment is primarily supportive and includes endotracheal intubation and mechanical ventilation for respiratory failure.[113]

RSV immune globulin (RespiGam) is a prophylactic intravenous drug that is administered to patients at risk for seasonal RSV disease (ex-premature infants, infants with congenital heart disease, immunosuppressed patients, or those with multiple congenital anomalies); it has dramatically decreased the incidence of illness in this population. Ribavirin is a virostatic drug available for the treatment of children with RSV and congenital heart disease, immunosuppressive disease, or multiple congenital anomalies.

Status Asthmaticus

Asthma, a disease of airway hyperreactivity, is the most common chronic respiratory disorder of childhood and is a frequent cause of admission to emergency rooms and hospitals. Acute attacks are generally associated with intercurrent viral infections, exposure to allergen, stress, or noncompliance with therapy.[114]

A stepwise approach to the treatment of asthma includes inhaled aerosolized β-agonists, cromolyn/nedocromil, leuko-

triene pathway modifiers, and inhaled glucocorticoids.[115] The number of asthmatic patients and the mortality rate associated with asthma are increasing. This increase is associated with a number of risk factors, including teenage years, black race, history of previous life-threatening episodes, hospitalization within the last year, poor long-term medical care, and psychological and psychosocial problems.

Most episodes of status asthmaticus respond to emergency department management with oxygen, nebulized/inhaled β-agonists, anticholinergic agents, and intravenous steroids.[116]

Even with this therapy, some children fail to improve or their condition worsens. Signs of respiratory failure include tachypnea and tachycardia; prolonged expiration; marked intercostal, supracostal, and infracostal retractions; nasal flaring; pulsus paradoxus; and anxiety or depression. Despite the increased minute ventilation, $Paco_2$ is normal or elevated, and moderate to severe hypoxemia is present. Treatment of impending respiratory failure requires maximizing conservative therapy, starting an infusion of intravenous terbutaline at 0.1 μg/kg/min, and increasing the dose until clinical improvement occurs or significant tachycardia develops. When aminophylline is used, blood levels should be monitored closely. Both phosphodiesterase inhibitors and adrenergic agonists increase myocardial oxygen consumption and may cause myocardial ischemia and ventricular arrhythmias; hence, hypoxia must be prevented and the ECG must be closely monitored. Children tolerate drugs used to treat asthma better than adults do, probably because children have relatively normal coronary arteries and better myocardial reserve. Heliox (a 70:30 helium-oxygen mixture) is about one third as dense as room air and decreases the work of breathing of some asthmatics. Heliox cannot be used if high oxygen concentrations are required. Intravenous magnesium sulfate is a smooth muscle relaxant that has been used to treat asthma. When 25 to 40 mg/kg (maximum of 2 g) is infused over a period of 20 minutes, pulmonary function frequently improves. Hypotension, decreased reflexes, and drowsiness may occur.[117,118]

Most clinicians tolerate $Paco_2$ values of 70 or 80 mm Hg as long as there is no evidence of cardiovascular or neurologic problems.[119] Tracheal intubation is seldom required in pediatric patients with asthma and is avoided when possible because the ETT may further irritate the airway and increase bronchoconstriction. It may also be difficult to remove the ETT later. Mechanical ventilation is frequently ineffective in patients with disease of the small airways and may cause barotrauma. Halothane and isoflurane have been used in mechanically ventilated asthma patients who have respiratory failure and are unresponsive to conventional therapy.[120] Usually, the severe bronchospastic state returns when the inhaled anesthetic is discontinued. ECMO has been used in some asmatic patients when gas exchange could not be achieved with conventional ventilators.[121]

Cystic Fibrosis

Cystic fibrosis is a fatal autosomal recessive disease carried on chromosome 7. Although it affects the pancreatic, hepatic, pulmonary, GI, and reproductive systems, 90% of the reported morbidity and mortality is pulmonary.[122] The pulmonary pathology consists of severe airway obstruction, bronchiectasis, emphysema, and terminal respiratory failure.

Survival of patients with cystic fibrosis has improved dramatically over the past 30 years. More than one third of patients survive to greater than 30 years of age.[123] This change is the result of improved antibiotic therapy, nutritional support, and aggressive treatment of complications. Lung transplantation has been performed in patients with chronic respiratory failure with varied success.[124,125]

Bronchopulmonary Dysplasia

BPD is a form of chronic lung disease that occurs in patients who have survived severe neonatal lung disease. The cause of this disease is uncertain, but usually patients were premature, had hyaline membrane disease, and required prolonged and aggressive respiratory support with high inflating and distending pressure and high oxygen concentrations. Inflammation appears to be an important component of this disease.[126] Children with BPD have decreased dynamic compliance, increased airway resistance, increased physiologic dead space, and markedly increased work of breathing. The lungs are hyperinflated, and there are intercostal retractions, nasal flaring, and wheezing. Chest radiographs demonstrate large lung volumes and fibrosis as well as cystic and atelectatic areas. Hypercapnia and hypoxia are present to varying degrees.[127,128]

Therapy for BPD includes providing enough calories to meet the higher energy expenditure required for the increased work of breathing. Respiratory support (mechanical ventilation, CPAP) is required for some patients. Diuretics and bronchodilators are frequently used and may be associated with electrolyte abnormalities. Most long-term survivors have subjectively normal pulmonary function. However, some survivors have severe chronic physiologic changes.[129,130] During the first years of life, viral or bacterial pulmonary infections often increase the need for respiratory support; these infections may prove to be fatal.

Great effort is being made to prevent BPD. Because the trauma of mechanical ventilation on an immature lung is thought to be the major cause of BPD, alternative modes of ventilatory support are being evaluated, including exogenous surfactant, high-frequency ventilation (especially HFOV),[101] ECMO, and liquid ventilation.[127,131]

Sleep Apnea

Normal ventilation during sleep requires normal upper airway anatomy and normal intact reflexes. The latter include central responses to hypercapnia and hypoxia, response to airway irritation, and dynamic phasic contraction of the pharyngeal and hypopharyngeal muscles. Sleep apnea usually occurs when one or more of these protective responses is abnormal.

In infancy, sleep apnea is relatively common. Numerous causes have been postulated, the most attractive of which is immaturity of the medullary chemoreceptors. Patients with Ondine's curse, the most severe form of central apnea, have complete apnea when asleep. Lesser breathing disorders may be present during sleep in patients with sudden infant death syndrome (SIDS). Treatment of sleep apnea consists of respiratory stimulants (theophylline), cardiorespiratory monitoring during sleep, and in some severe cases, tracheotomy and nighttime mechanical ventilation.[132]

Obstructive sleep apnea occurs in all pediatric age groups. It may be associated with an identifiable anatomic disorder, such as enlarged tonsils and adenoids, the Pierre Robin syndrome, and tracheal and laryngeal malacia. Signs and symptoms of obstructive sleep apnea include loud snoring, obstructive episodes with frequent arousal, behavior disorders caused by sleep deprivation, and cor pulmonale. The diagnosis is made by the history, ECG,

and formal sleep studies. Bronchoscopy may also be helpful in defining the problem. In young children, an enlarged liver may suggest that the child has pulmonary hypertension.

Treatment of sleep apnea includes removal or bypass of an obstruction. Although tonsillectomy and adenoidectomy may improve the airway, there may still be significant airway obstruction for the first few days after surgery. Rarely does such a child require a tracheostomy.

Foreign Body Aspiration

Foreign body aspiration is a relatively common and often catastrophic event in children. Although it can occur at any age, the peak incidence of foreign body aspiration occurs at 6 months to 3 years of age. Vegetable matter (peanuts) and other foodstuff (hot dogs) or coins and small pieces of toys are the most commonly aspirated material. Many of these objects are radiolucent. The symptoms of aspiration are related to the location of the foreign body within the airway and the time since the object was aspirated. Acute symptoms may include total airway obstruction, stridor, wheezing, or acute onset of coughing, whereas more chronic symptoms include bloody sputum, chronic coughing, or wheezing. The diagnosis of a foreign body in the airway is made from the history and physical examination and, in some cases, by radiologic imaging.

The efficacy and safety of abdominal thrusts have been questioned. Heimlich's maneuver and back slaps are reserved for acute upper airway obstruction with no air movement. Treatment of less acute or lower airway foreign body aspiration includes bronchoscopy, postural drainage, chest physical therapy, bronchodilators, and surgical removal of the object.[133]

Upper Airway Obstruction and Meningomyelocele

Vocal cord paralysis is a common result of several disorders, including brainstem abnormalities and myelodysplasia. Children with meningomyelocele usually have an Arnold-Chiari malformation and may have stridor. This lesion allows caudal displacement of the medulla, stretching of the cranial nerve tracts, and abnormal arterial architecture of the brainstem.

Vocal cord paralysis may result from pressure on the brainstem (i.e., with hydrocephalus) or from focal infarcts of the brainstem. Treatment of these brainstem abnormalities includes relief of the hydrocephalus and, if the paralysis persists, cervical decompression of the Arnold-Chiari lesion. Despite these surgical procedures, some children require a tracheotomy and long-term mechanical ventilation.

Central Nervous System

Systemic illness is a common cause of central nervous system (CNS) dysfunction in infants and children. Seizures, head trauma, CNS infections, and hypoxic or metabolic encephalopathy commonly cause acute neurologic dysfunction in the PICU. Assessment of neurologic function depends on an understanding of the age-dependent progression of motor and cognitive skills. Table 84-6 lists the developmental milestones.

Functional Postnatal Neurologic Development

Motor function in the newborn depends on gestational rather than postnatal age.[134] That is, an infant born at 28 weeks' gestation exhibits motor responses similar to those of a full-term newborn when the former is 3 months old. Although potentially modifiable by cortical influence, most neonatal motor behavior is subcortically controlled, which permits normal motor behavior in newborns who have severe cortical damage.

Table 84-6 Normal Ages for Major Developmental Milestones

Age	Motor Function	Language	Adaptive Behavior
4-6 wk	Lifts head from prone position and turns from side to side	Cries	Smiles
4 mo	Shows no head lag when pulled to sitting from supine position; tries to grasp large objects	Utters sounds of pleasure	Smiles, laughs aloud, and shows pleasure to familiar objects or persons
5 mo	Grasps voluntarily with both hands; plays with toes	Makes primitive sounds	Smiles at self in mirror (ah, goo)
6 mo	Grasps with one hand; rolls prone to supine; sits with support	Has increased range of sounds	Expresses displeasure and food preferences
8 mo	Sits without support; transfers objects from hand to hand; rolls supine to prone	Combines syllables (baba, dada, mama)	Responds to "No"
10 mo	Sits well; crawls; stands holding; finger-thumb apposition in picking up small objects		Waves bye-bye; plays patty-cake and peek-a-boo
12 mo	Stands holding; walks with support	Says two or three words with meaning	Understands names of objects; shows interest in pictures
15 mo	Walks alone	Utters several intelligible words	Requests by pointing; imitates
18 mo	Walks up and down stairs holding; removes clothes	Says many intelligible words	Carries out simple commands
2 y	Walks up and down stairs by self; runs	Makes two- or three-word phrases	Engages in organized play; points to some parts of the body

Modified from Crone RK: Pediatric critical care: Supporting the developing organ system. *In* Shoemaker WC (ed): Critical Care: State of the Art, vol 5. Fullerton, CA, Society of Critical Care Medicine, 1984, p D1.

Assessment of intellectual development is difficult in a newborn; initially, it is based on the absence of reflexes and the acquisition of new motor skills. Adaptive or interactive behavior is first seen with accommodation to repeated stimuli and eye contact. The infant's intellectual development depends on the presence of external stimulation and social interaction, preferably from one or a few individuals. This is why infants and children who require long-term intensive care must have parental input and exposure to a limited number of caregivers.

Monitoring of Neurologic Function

Clinical examination is the most important tool we have for assessing neurologic function in children. In an awake child, interactions with the examiner and caretakers are sensitive indicators of high or integrative cortical function. When the child's cognitive function is depressed from disease or drugs, examination of the general level of activity and peripheral and brainstem reflexes becomes an important, albeit crude measure of CNS function. The Glasgow Coma Scale (GCS) is a tool to evaluate the level of function of neurologically impaired patients (Table 84-7).[135] Table 84-8 presents the pediatric GCS for children without language skills.

Laboratory Assessment of Neurologic Function

The electroencephalogram (EEG) is used to diagnose seizures and isoelectric brain death and to monitor the effects of barbiturates administered to induce coma. Otherwise, the EEG is so nonspecific that it is not very helpful. Brainstem evoked potentials (auditory, visual, and somatosensory) allow neurologic assessment of comatose or anesthetized patients. Evoked potentials define marginally functioning neurons that are undetectable clinically. Asymmetry, abnormality, or absence of conduction of auditory, visual, or tactile stimuli through the brainstem to the cortex provides useful information regarding the progress or recovery from neurologic injury. Although evoked potentials are only mildly affected by barbiturates, a flat EEG during barbiturate coma cannot be regarded as diagnostic of brain death.

Table 84-7 Glasgow Coma Scale Score*

Sign	Evaluation	Score
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best verbal response	Oriented	5
	Confused	4
	Inappropriate	3
	Incomprehensible	2
	None	1
Best motor response	Obeys commands	6
	Localizes pain	5
	Withdrawal to pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1

*Also see Chapters 46 and 63.
Modified from Teasdale G, Jennett B: Assessment of coma and impaired consciousness: A practical scale. Lancet 2:81, 1974.

Table 84-8 Modified Coma Score for Infants

Activity	Best Response	Score
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Verbal	Coos and babbles	5
	Irritable cries	4
	Cries to pain	3
	Moans to pain	2
	None	1
Motor	Normal spontaneous movements	6
	Withdraws to touch	5
	Withdraws to pain	4
	Abnormal flexion	3
	Abnormal extension	2
	None	1

From Ramondi AJ: Head injury in the infant and toddler. Childs Brain 11:12, 1984.

Computed tomography (CT) allows rapid detection of CNS lesions, the extent of structural injury, and noninvasive assessment of ICP. Cranial ultrasound is a bedside technique used to assess ventricular size and intracranial anatomy in infants with nonfused cranial sutures. MRI permits intraorbital and ocular injuries and brainstem and spinal cord lesions to be examined; it is also good for defining soft tissue abnormalities.[136] MRI's major drawback is the length of time required for each examination and the relative inaccessibility of the patient while in the scanner. Maintaining body temperature can also be a problem in small children during MRI scanning because the room must be cold. It may be difficult to safely perform MRI in patients who have significant cardiorespiratory compromise because many of the pumps and ventilators cannot enter the scanner.

Doppler ultrasound allows bedside assessment of cerebral blood flow (CBF) velocity in the ICU. Although it does not directly measure CBF, Doppler ultrasound is a useful bedside guide to therapy. CBF scans are the "gold standard" and are usually required to diagnose brain death during barbiturate coma.

ICP can be monitored by inserting a catheter into a lateral ventricle or by inserting a subarachnoid screw or transducer into the epidural space or cerebral parenchyma. The ventricular catheter provides an accurate waveform and permits withdrawal of cerebrospinal fluid (CSF) to reduce ICP. The other devices used to measure ICP provide less consistent pressure waves and do not permit removal of CSF.

Pathophysiology of Neurologic Disease

The pathophysiology of critical neurologic disease includes increased ICP, abnormal electrical discharge (status epilepticus), and focal loss of functioning neurons (see Chapter 63).

Increased Intracranial Pressure

With severe neurologic diseases, increased ICP increases morbidity and mortality. Such diseases include head trauma, Reye's

syndrome, hypoxic-ischemic encephalopathy, metabolic encephalopathies, intracranial space-occupying lesions, and hydrocephalus. ICP increases when the intracranial volume of one of the four compartments (CSF, blood, brain, and supporting tissues) within the cranial vault increases. An increase in one compartment can occur without raising ICP if an equal volume is displaced from another compartment. When displacement is no longer possible, ICP rises in proportion to the added volume.[137] In older children and adults who have a rigid calvaria, the cranial cavity is a closed container, and the contents are noncompressible.

Intracranial Compliance Curve

Intracranial hypertension causes neurologic injury by two mechanisms: (1) a sufficiently high ICP that reduces cerebral perfusion pressure and causes brain ischemia and (2) a sufficiently elevated ICP that compresses and herniates the brainstem or other vital structures. Monitoring of ICP and anticipatory treatment of intracranial hypertension may improve outcome, particularly in patients with head trauma.[138]

It is often difficult to determine who is at risk for intracranial hypertension. A normal cranial CT scan does not always rule out the development of intracranial hypertension, and open fontanelle/sutures do not preclude it from occurring. One study found an ICP higher than 20 mm Hg in 86% of children with a GCS score of 3 to 8.[139] Although certainly not a substitute for careful neurologic assessment, ICP monitoring may suggest that further intervention is necessary. In head-injured patients, intracranial hypertension can occur with or without a surgical lesion, or it may occur after a hematoma is evacuated. Although the outcome of children is better than that of adults with similar head injuries, children may still have significant long-term CNS injury.[140] Prompt recognition and treatment of increased ICP increase survival and improve neurologic outcomes.[141]

Hypoxic-Ischemic Encephalopathy

There is little evidence that increased ICP or correction of ICP alters the outcome of patients with hypoxic-ischemic encephalopathy. The clinical impression is that the outcome is less favorable in patients who have trauma or metabolic encephalopathy and that aggressive management of ICP, at best, prevents further CNS damage, which is important. The GCS score provides a reasonable assessment of neurologic function in these patients.

Hydrocephalus

Another cause of increased ICP is an increase in CSF volume (i.e., hydrocephalus). Common causes of hydrocephalus include obstructed ventricular shunts, aqueductal stenosis/compression as a result of congenital malformations, infection, posterior fossa tumors, or intracranial bleeding. Inserting an external or internal shunt to reduce the volume of CSF can be lifesaving.

Tumors

Brain tumors are common in children and many occur in the posterior fossa. The initial symptoms may include focal deficits, ataxia, or symptoms of increased ICP.

Guidelines for Monitoring Intracranial Pressure

Patients with head trauma, Reye's syndrome, or metabolic encephalopathy are candidates for ICP monitoring if they have a GCS score of 8 or less, clinical signs of increased ICP, or evidence of increased ICP on CT. Coagulopathies must be corrected before inserting an ICP monitor.

Treatment of Increased Intracranial Pressure

When intracranial hypertension is present, therapy should be initiated promptly. Although removing CSF acutely decreases ICP, the underlying cause of the elevated ICP must be sought and treated (i.e., hematomas should be evacuated, antibiotics should be administered when appropriate, and plans should be made to remove tumors or other masses). Treatment of increased ICP includes positioning, oxygenation, and administration of hypertonic solutions.

Positioning Elevating the head of the bed 15 to 30 degrees while keeping it in the midline position enhances cerebral venous outflow. Even slight movement of the head to a few degrees off midline may double the ICP.

Adequate Oxygenation Children with increased ICP should undergo tracheal intubation after being given appropriate premedication to mitigate further increases in ICP. Pao_2 should be kept at or above 100 mm Hg and $Paco_2$ between 30 and 35 mm Hg (when possible) by mechanical ventilation. The lowest airway pressures possible should be used to achieve these goals to avoid interfering with venous drainage from the head. Mean arterial pressure should be kept at the preintubation level.

Mannitol and Hypertonic Saline Mannitol reduces ICP by decreasing blood viscosity and transiently increasing CBF and oxygen transport. The adenosine concentration decreases and CBF is maintained in areas that have intact autoregulation.[142] CBF remains constant despite a decrease in cerebral blood volume and ICP. Mannitol also reduces ICP by withdrawing water from the brain parenchyma and excreting the water as urine.[143] It takes 20 to 30 minutes for this osmotic effect of the drug to develop. Intermittent boluses of 0.25 to 1 g/kg of mannitol are administered intravenously to control ICP. The drug eventually enters the CSF and can increase ICP.

Use of 3% saline to treat increased ICP is gaining in popularity[144] because the sodium does not cross the blood-brain barrier quickly and it has an osmolar gradient similar to that of mannitol. Three percent saline has additional theoretical beneficial effects, including enhancement of cardiac output, reduction of inflammation, restoration of normal cellular resting membrane potential and cell volume, and stimulation of the release of atrial natriuretic peptide.

Muscle Relaxants

Paralysis of striated muscles may decrease ICP by reducing the increased intrathoracic and venous pressure caused by coughing, straining, or "bucking against the ventilator."

Sedation

Fear, anxiety, and the response to painful stimuli may increase CBF and ICP. Sedation of unconscious patients can obscure the neurologic examination, but the reduction in ICP may outweigh this risk in many cases. Most intravenous sedatives, including benzodiazepines, butyrophenones, and barbiturates, decrease CBF and ICP. Ketamine increases CBF and should be avoided in most cases. Opioids can be used if the patient's respiration is controlled.

Steroids

Steroids decrease vasogenic edema around brain tumors and reduce eighth nerve swelling and associated hearing loss caused by bacterial meningitis.[145] Steroids play no role in the treatment of traumatic brain injury or global cerebral edema.[146] If steroids are administered, care should be taken to prevent the development of gastric ulcers.

Temperature Control

Hyperthermia may be detremental to patients with brain injury. Even an increase of a few degrees in body temperature significanlty increases CNS injury in patients with head injuries and other causes of cerebral injury. The cerebral metabolic rate increases 5% to 7%°C. Antipyretic agents (acetaminophen) and cooling devices are used to decrease the brain temperature. Hypothermia reduces the cerebral metabolic rate. For example, at 30°C, the cerebral metabolic rate is about 50% below control values.[147] Inducing hypothermia before a cerebral ischemic insult takes place allows longer periods of inadequate CBF before CNS injury occurs, but there is some evidence that inducing hypothermia after an insult improves neurologic outcomes.[148] Decreasing the body temperature to 35°C reduces long-term CNS injury.[149] Temperatures below 33°C are associated with increased morbidity and mortality related to an increased metabolic rate, increased bleeding, and increased rates of infection. Hypothermia should be used only if the patient is paralyzed and anesthetized to prevent shivering.

Glucose Control

Hyperglycemia can worsen neurologic outcome after head injury in adults and children.[150,151] In animals, hyperglycemia increases CNS injury, possibly by causing lactic acidosis.[152-154] Giving sufficient insulin to maintain the glucose concentration near normal was associated with fewer neurologic deficits than in hyperglycemic animals.[155] Hypoglycemia should also be avoided. Dextrose-containing solutions should be administered to patients with head injury only if there is clear evidence of hypoglycemia and just in sufficient quantities to maintain normoglycemia.

Seizure Control

Seizures increase the metabolic requirements of the brain and increase CBF, cerebral blood volume, and ICP.[156] Paralyzed patients should have an EEG to determine the presence or absence of seizures. Aggressive treatment of seizures with anticonvulsants is mandatory.

Barbiturates

Barbiturates reduce CBF and cerebral metabolism. Thiopental, 1 to 5 mg/kg by intravenous bolus, reduces ICP for 5 to 10 minutes. A bolus of pentobarbital (Nembutal), 3 mg/kg or more intravenously, plus a continuous infusion of 1 to 2 mg/kg/hr, effectively reduces ICP. Blood levels of 20 to 40 mg/L are generally required to produce a significant reduction in ICP. Higher concentrations may be necessary to achieve burst suppression. In these doses, barbiturate metabolism and excretion may be altered, so blood levels must be monitored closely. Myocardial depression and hypotension are common complications of barbiturate administration. Consequently, cardiovascular function should be monitored closely, and steps must be taken to improve cardiac function and arterial blood pressure.[157] Although barbiturate administration decreases ICP, it may not improve survival or neurologic outcome.[158-160]

Lidocaine

A bolus of intravenous lidocaine, 1 mg/kg, may minimize increases in ICP associated with noxious airway stimulation (i.e., endotracheal suctioning).

Status Epilepticus in Children

Status epilepticus is a continuous motor seizure that lasts for more than 20 minutes or a series of seizures without intercurrent awakening. Although it is common for physicians to never find a cause of the seizures, the most commonly diagnosed causes are infections (meningitis or encephalitis) and metabolic abnormalities (toxins, head trauma, and hypoxic and ischemic injury). Because seizure activity increases with status epilepticus, brain and skeletal muscle metabolism and oxygen consumption increase and place the child at risk for cellular hypoxia. During a seizure, airway obstruction and ineffective chest wall and diaphragmatic excursion can limit ventilation and worsen arterial hypoxemia and hypercapnia.

Treatment of a seizure begins with establishing a patent airway, administering oxygen, and ensuring adequate ventilation. Intravenous anticonvulsant drugs are given to stop the seizure. Commonly used anticonvulsants include lorazepam, phenobarbital, paraldehyde, and phenytoin.

Lorazepam is a rapid and reliable drug used to stop seizures. Boluses of 0.1 mg/kg are given intravenously or rectally when there is no intravenous access. Phenobarbital, 5- to 10- mg/kg boluses (maximal dose of 20 mg/kg), also stops seizures. The main complication of lorazepam is respiratory depression when administered in high doses. Giving both phenobarbital and lorazepam together exaggerates the respiratory depression. Fosphenytoin is also given intravenously in doses of up to 20 mg/kg and should be administered slowly to avoid cardiovascular depression. Paraldehyde, 0.3 mL/kg, can be given rectally. Finally, an intravenous injection of 1 to 4 mg/kg of sodium thiopental stops most intractable seizures; higher does of the drug may cause apnea, and the risk of vomiting and aspiration of gastric contents is real. Once the seizures are under control, the cause of the seizures must be determined.

Brain Death

Irreversible cessation of cardiorespiratory function is the most common definition of death (also see Chapter 98). However, the advent of organ transplantation and the need for organs have made the definition of death less clear. The problem is that it is possible to maintain cardiopulmonary function indefinitely, even after brain function has ceased. Consequently, brain death is the clinical and legal definition of death, "a permanent cessation of brain function."

Criteria for brain death include irreversibly absent cerebral and brainstem functions. Absent cerebral function is defined as lack of cortically mediated responses to external stimuli.[161] Absent brainstem function is defined as absent brainstem reflexes, including absent pupillary response to light and absent corneal,

oculocephalic, oculovestibular, oropharyngeal, and respiratory reflexes.

Irreversible brain death occurs when the cause of coma is sufficient to account for the loss of brain function and when the possibility of recovery is excluded by clinical observation, laboratory studies, or both. Laboratory studies include analysis of blood and urine for toxic substances, EEG, radionuclide brain scans, cerebral angiography, and brainstem evoked potentials. These tests are supplementary to the clinical history and physical examination. Factors that can simulate the clinical or laboratory criteria for absent brain function (a core temperature <30°C and high blood barbiturate concentrations) must be ruled out. Both hypothermia and barbiturates can significantly depress electrical activity in the brain and render an EEG meaningless. In such cases, a technetium 99m radionuclide angiogram will demonstrate the presence or absence of CBF. Brain-dead patients have no arterial blood flow in the anterior and middle cerebral arteries and no venous flow in the sagittal sinus; blood flow in extracranial tissues is usually preserved. This study is independent of the patient's core temperature or barbiturate level. Two or more physicians should concur on the clinical or laboratory diagnosis of brain death (or both) before care is discontinued. All evidence of brain death and all related discussions must be clearly documented in the patient's record.

Whenever a patient is declared brain-dead, the family should be approached for organ donation. Tissue donation (e.g., eyes and heart valves) is also possible after death. Regional procurement agencies can provide protocols and support to the ICU staff and families.

Renal System

Structural and Functional Development of the Excretory System

Embryologic development of the renal system begins in the middle of the third week of gestation with development of the pronephric tubules. By 10 weeks' gestation, a functioning kidney and collection system exist, and fetal urine is discharged into the bladder. At 32 to 36 weeks' gestation, each kidney has a full complement of nephrons. Table 84-9 presents normal values for pediatric renal function.

Table 84-9 Normal Values for Pediatric Renal Function

	Age	Value
Creatinine (mg/dL)	1 yr 10 yr 18 yr	0.41 ± 0.1 0.61 ± 0.22 0.91 ± 0.17
Glomerular filtration rate (mL/min/1.72 m^2)	2-8 days 6-12 mo 2-12 yr	39 (range, 17-60) 103 (range, 49-157) 127 (range, 89-165)
Urine concentration (mOsm/L)	1 mo 2-16 yr	600-1100 1089 (range, 870-1309)

Modified from Goldsmith DI: Clinical and laboratory evaluation of renal function. *In* Edelman CM Jr (ed): Pediatric Kidney Disease. Boston, Little, Brown, 1978, p 213.

Functional Development of the Kidney

Because the placenta is the major excretory organ of the fetus, renal growth is not governed by functional requirements. Renal growth increases linearly with body weight and body surface area during the third trimester of pregnancy. The glomerular filtration rate (GFR) increases rapidly from 28 to 35 weeks of gestation. At term, the GFR is 10 mL/min/m^2 and increases to 20 mL/min/m^2 by 2 weeks of age. Although the GFR of premature infants is lower, the rate of increase is the same as that in a term infant.[162] Tubular function is not fully mature in full-term newborns. The newborn kidney is sensitive to antidiuretic hormone (ADH) and vasopressin, and urine osmolarity can vary from only 50 up to 780 mOsm/L.[163] The tubular function of premature infants is less mature.

The newborn's renal threshold for bicarbonate is about 20 mEq/L, which means that standard acid-base nomograms do not apply to infants because their serum bicarbonate concentration of 20 mEq/L is not indicative of metabolic acidosis. The renal tubular glucose threshold of term infants is similar to that of adults, but it is only 125 to 150 mg/dL in premature infants. A full-term infant has 1% or less fractional excretion of sodium by the third day of life. Fractional excretion of sodium can be much higher (5%) in premature infants.[164] Renin, angiotensin, and aldosterone concentrations are high in newborns and decrease over the first few weeks of life. Normal values for pediatric renal function are presented in Table 84-9.[165]

Renal Failure

Acute renal failure is defined as an abrupt, often temporary loss of renal function (see Chapters 65 and 67). Oliguria is the rule, polyuria is the exception, and anuria is uncommon. Urine volume and composition are altered, and fluid, electrolyte, and acid-base disorders are common. Therapy is directed at maintaining normal metabolic and fluid homeostasis, supporting nutrition, and exhibiting patience. Acute renal failure is caused by prerenal, postrenal (obstructive), or intrinsic renal disorders. Prerenal causes are due to reduced renal blood flow. Reduced cardiac output or renal blood flow is a common cause of reduced urine output and results in azotemia and ischemic renal damage. The adequacy of circulating blood volume is assessed by CVP and cardiac output measurements and by estimating renal blood flow with Doppler flow studies or nuclear imaging techniques. These studies help differentiate prerenal from renal causes of azotemia, but they may be difficult to obtain in sick neonates.

Postrenal obstruction of urine flow can occur anywhere within the collecting system but it occurs most commonly as partial obstruction of the bladder neck or the ureterovesical or ureteropelvic junction. All these malformations cause obstructive nephropathy and renal injury or renal failure. Signs of obstruction may be subtle and require radiologic, ultrasonic, or endoscopic evaluation to detect. Recurrent urinary tract infections are frequent clinical manifestations of obstructive lesions.[166]

Intrinsic renal failure is caused by disorders of the renal glomeruli, tubules, or blood vessels. Glomerular diseases include hemolytic-uremic syndrome (HUS), poststreptococcal glomerulonephritis, Henoch-Schönlein purpura, and other inflammatory and immune complex diseases. Acute tubular injury is most commonly caused by hypoxia and ischemia; other causes are rhabdomyolysis, sepsis, hyperthermia, hemolysis, and a myriad of

nephrotoxins, including mercury, carbon tetrachloride, and ethylene glycol. Vascular diseases, including arterial embolism, venous thrombosis, and congenital malformations, are also causes of acute renal failure.

Hemolytic-Uremic Syndrome

HUS is one of the most common causes of acute renal failure in children. This syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal injury. In North America, HUS is most often associated with infection by cytotoxin-producing *Escherichia coli* O157, but other serotypes and other Shiga-like toxin–producing bacteria have been implicated.[167]

E. coli O157 resides in the intestinal tract of cattle and may contaminate beef during processing.[168] The organism is killed by cooking. Infections can be spread by person-to-person contact in daycare centers, institutions, and the military. There is also a familial form of the disease that accounts for a small percentage of the total cases.[169]

HUS is seen predominately in 0.5- to 4-year-old children but it can occur in all age groups.[170] It shares many laboratory and clinical features with the adult disease, thrombotic thrombocytopenic purpura. In fact, some investigators consider the two disorders a continuum of the same disease. The abnormalities that develop in HUS are believed to be caused by cytotoxins and lipopolysaccharide, a bacterial endotoxin. Toxin-induced damage to renal endothelial cells, the vasculature, and other organs is directly or indirectly associated with the activation of leukocytes.[171] Cytokines such as interleukin-1 and tumor necrosis factor, prostaglandin I_2, thromboxane A_2, and von Willebrand factor (vWF) multimeres probably play a role in the pathogenesis of this disease.[172]

The time from exposure to the organism to initial evaluation of the patient varies from 3 to 12 days. Symptoms last for about a week. Patients usually have abdominal cramping, bloody diarrhea, tenesmus, and vomiting.[173] On average, about 10% of children with *E. coli* O157–induced bloody diarrhea progress to HUS. Mildly affected patients exhibit anemia, thrombocytopenia, azotemia, and decreased urine output and have an uncomplicated course. In severely affected patients, anuria is common, hypertension and seizures may occur, and the duration of illness is prolonged. A small number of children exhibit progressive and permanent renal insufficiency, severe and recurrent hemolysis, thrombocytopenia, and neurologic impairment.

Hematologic abnormalities include hemolysis and thrombocytopenia. Hemolysis often causes hyperbilirubinemia and, despite reticulocytosis, severe anemia with hemoglobin concentrations of 4 to 5 g/dL. Thrombocytopenia is the result of platelet destruction and sequestration in the liver and spleen.[174] The remaining platelets show evidence of impaired aggregation.[175] Disseminated intravascular coagulation (DIC) is relatively common. Glomerular capillary endothelial injury is the most consistent renal finding in HUS. Acute renal failure with oliguria or anuria usually lasts less than a week but may linger for more than 10 weeks.[176] Glomerular or arterial injury, or both, may predominate, depending on the presence and extent of renal insufficiency (glomerular injury) and hemolysis and hypertension (arterial injury). CNS abnormalities are manifested as decreased levels of consciousness, seizures, irritability, ataxia, hypotonia, hemiparesis, hyperreflexia, and hallucinations; these problems may be caused by severe hypertension, electrolyte disturbances, microthrombi, or cerebral edema and increased ICP.[177] Abdominal cramping is common and may be difficult to distinguish from intussusception, intestinal stricture or bowel perforation, colonic gangrene, or other surgical emergencies.[178] Pancreatitis is common in patients with HUS. CHF may occur if there is fluid overload, hypertension, anemia, or myocardial depression caused by circulating endotoxins.

Treatment of HUS is primarily supportive. Meticulous attention should be paid to volume status, electrolyte and acid-base balance, nutrition, antisepsis, and treatment of hypertension and coagulopathies. Enteric isolation is mandatory to prevent secondary spread of the disease. Accurate fluid intake and output measurements and frequent assessment of weight and volume status are important for management of these patients. A central venous catheter is useful for CVP measurements, blood sampling, and administration of intravenous medications and nutrition. Nephrotoxic drugs should be avoided if possible. If nephrotoxic drugs must be given, the drug dose should be adjusted and serum concentrations monitored closely. Daily fluids should be restricted to the amounts required to replace insensible losses, urine output, and other ongoing losses. Fluids administered should reflect the electrolyte content of the fluid losses. Caloric support is essential. Enteral feedings are preferred, but parenteral feeding may be necessary if ileus develops. Antidiarrheal medications prolong the duration of colitis, and antibiotics may increase the risk for HUS.[179,180] No specific treatment has been effective to date. Heparin, fibrinolytic agents, aspirin, dipyridamole, corticosteroids, vitamin E, and furosemide have not affected the outcome of HUS.[181] Immunoglobulin therapy, plasmapheresis, and infusions of fresh frozen plasma have had mixed results, but no long-term therapeutic benefit has been demonstrated.

Dialysis, improved nutrition, and supportive care have decreased the mortality rate from 100% in the original report to less than 10% in the last 30 years. Mortality rates remain high in developing countries and in children with a genetic predisposition for HUS.

Peritoneal dialysis requires the insertion of a soft, multiholed catheter into the peritoneal cavity. When patency of the catheter is confirmed, a dialysate solution is infused that equilibrates with plasma and extracellular fluids. The parietal and visceral surfaces function as semipermeable dialysis membranes. The composition of the dialysis fluid is similar to that of plasma and consist of approximately 130 mEq/L of sodium, 100 mEq/L of chloride, 35 mEq/L of acetate or lactate as a buffer, 3.5 mEq/L of calcium, and 1.5 mEq/L of magnesium. The glucose concentration of the solution can be either isosmotic or hyperosmotic. Hyperosmotic solutions remove fluid and electrolytes. Respiratory compromise may occur with peritoneal dialysis because the increased abdominal pressure caused by the dialysate in the abdomen may prevent effective spontaneous ventilation. Mechanical ventilation will be required if this occurs. Bacterial or fungal peritonitis is common. Severe dehydration, circulatory collapse, and metabolic derangements are other complications of peritoneal dialysis. The principles of hemodialysis are essentially the same as those of peritoneal dialysis, but the blood interfaces with a semipermeable membrane rather than with the peritoneum. Hemodialysis is more efficient than peritoneal dialysis and is more appropriate in the acute setting. Hemofiltration and ultrafiltration are processes in which blood is cleansed by convective

solute transport. During this procedure, an ultrafiltrate of plasma is created by hydrostatic pressure exerted across a highly permeable membrane. Simultaneous blood volume replacement with modified lactated Ringer's solution is required.[182]

Outcome

The prognosis with acute renal failure depends on the patient's age, underlying disease, and the extent of the precipitating insult (also see Chapter 18). In general, children do better than adults; in fact, children usually recover completely from a renal insult if the hypoxia or ischemia lasted only a short time and other organ systems are not involved.[183] Children with chronic renal failure require long-term outpatient peritoneal dialysis or hemodialysis until they can undergo renal transplantation.[184]

Endocrine System

It is beyond the scope of this chapter to discuss chronic endocrine diseases in detail, but the acute disorders most commonly encountered in the PICU are discussed in the following sections.

Adrenal

Abnormalities of the adrenal axis result in deficient or excessive production of glucocorticoids, mineralocorticoids, or both. Many of these disorders are diagnosed and treated as they are in adults. Congenital adrenal hyperplasia, pheochromocytoma, and iatrogenic chronic adrenal insufficiency will be discussed briefly.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia is an autosomal recessive disorder that is associated with deficiencies in either 21-, 11-, or 17-hydroxylase. 21-Hydroxylase deficiency in children can be partial (simple virilizing form) or more complete (salt-losing form); at birth, affected children demonstrate masculinization of the external genitalia, and those with the more complete deficiency show a progressive salt-losing state (i.e., loss of sodium and elevation of potassium). This condition is usually manifested in the first few weeks of life as feeding difficulty, vomiting, and failure to thrive. The clinical and historical course is suggestive of pyloric stenosis. If the deficiency is not diagnosed and treated early in life, affected children may suffer severe cardiovascular collapse. A blood sample should be obtained for electrolytes, glucose, and if the diagnosis has not been established, adrenocorticotropic hormone (ACTH), cortisol, aldosterone, and plasma renin activity.

Treatment requires aggressive support of intravascular volume and myocardial function, glucose, and replacement of the deficient hormones. Cortisol can be replaced by oral administration of hydrocortisone at a dose of 25 mg/m^2/day divided into three doses; if the child cannot tolerate oral medication, cortisone acetate can be administered intramuscularly at a dose of 37.5 mg/m^2/day once every 3 days. For emergency therapy, when the oral route is not possible and perfusion of the muscle is poor, hydrocortisone acetate is used intravenously at a bolus dose of 1.5 to 2.0 mg/kg and then 25 to 250 mg/day in divided doses. Mineralocorticoid is replaced with cortisone acetate, 0.05 to 0.2 mg/day orally; these patients usually require the addition of salt to their diet. Deficiencies of 11- and 17-hydroxylase do not result in salt wasting; masculinization and hypertension are the common initial signs.[185]

Pheochromocytoma

Less than 5% of pheochromocytomas are diagnosed in childhood. As a rule, these tumors are confined to the adrenal medulla, but they can occur anywhere throughout the sympathetic chain. The clinical signs and symptoms of excessive catecholamines are the same as those in adults.

Iatrogenic Chronic Adrenal Insufficiency

Long-term daily use of steroids for the treatment of asthma, nephrotic syndrome, and malignancies is common. Such use may cause a hypoadrenal state and increase the risk for cardiovascular collapse during a severe illness or stress. In children, topical steroids can also depress the production of ACTH. Replacement of stress-level steroids (three times the daily replacement dose) is required.

Anterior Pituitary

Panhypopituitarism is usually secondary to a tumor or to aggressive dissection of a tumor.[186] Acute ICU problems related to this lesion include support of the adrenal axis and abnormalities of ADH.

Diabetes Insipidus

Diabetes insipidus can be of central, renal, or psychogenic origin. The central mechanism is the most common form in ICU patients. Absence of ADH results in polyuria and polydipsia; patients with a severe form of this disease may not be able to drink sufficiently to meet their requirement, and severe hypovolemia may develop. Diabetes insipidus is precipitated by brain tumors, head trauma, neurosurgery, and clinical brain death.[187,188] Treatment, in the setting of the ICU, is fluid replacement or, if unwieldy, hormone replacement with aqueous vasopressin (Pitressin), 0.1 to 1.0 mL intramuscularly (duration, 4 to 6 hours); Pitressin tannate in oil, 0.25 to 1.0 mL intramuscularly (duration, 24 to 72 hours); or desmopressin acetate intranasal, 2.5 to 10 µg twice daily (duration, 10 to 11 hours). The clinical syndrome may be transient or chronic. In either case, close supervision of fluid intake and output is essential.

Syndrome of Inappropriate Secretion of Antidiuretic Hormone

The syndrome of inappropriate ADH secretion is associated with hyponatremia and hypo-osmolality caused by inappropriate urinary loss of sodium and free water in patients with normal kidneys. Urine osmolality is greater than serum osmolality. This syndrome is precipitated by a number of mechanisms, including head trauma, neurosurgery, meningitis, hypoxia, and any major surgical procedure in which there is large-volume fluid shifts and fluid replacement.[189,190]

This disease is usually self-limited, and the only real problem occurs if the diagnosis is not considered and the level of hyponatremia is low enough to cause CNS dysfunction. Seizures are rare unless serum sodium is less than 120 mEq/dL. Care should be taken to raise the serum concentration of sodium

slowly. This syndrome is treated by fluid restriction and, in severe cases, by the infusion of hypertonic or isotonic saline.

Pancreas/Insulin

Hypoglycemia

Hypoglycemia is a common problem in ICU patients. What constitutes hypoglycemia in children has been disputed. However, it is uncommon to find a blood glucose level below 40 mg/dL in normal, nourished premature or term neonates.

The usual symptoms of hypoglycemia include tachycardia, diaphoresis, weakness, mental clouding, seizures, and coma. The causes of hypoglycemia can be subdivided into disorders of increased utilization and disorders of decreased production. Transient hypoglycemia of the newborn is caused by decreased or immature hepatic gluconeogenesis and it self-corrects within hours to days. If the hypoglycemia persists, hepatic enzyme deficiencies, endocrine problems, or hyperinsulinism (i.e., pancreatic cell abnormalities, infants of diabetic mothers) must be considered. Other causes of hypoglycemia in the neonatal period include sepsis, hypothermia, hypoxia, and transplacental exposure to maternal hypoglycemic drugs.

In older children, hypoglycemia is associated with ketotic hypoglycemia,[191] hepatic enzyme abnormalities, hyperinsulinism, hepatic failure, and Reye's syndrome, and it is a side effect of certain drugs. Regardless of cause, the initial treatment of hypoglycemia is glucose administration. The initial dose is 0.5 g/kg given as 50% dextrose in water ($D_{50}W$). This dose should be followed by an infusion of dextrose that is sufficient to meet the metabolic requirements of the child (see the later section on the gastrointestinal system).

Diabetic Ketoacidosis

The most serious acute complication of diabetes mellitus is DKA, a syndrome of glucose and ketone overproduction and underutilization that causes hyperglycemic ketoacidosis. The clinical syndrome includes dehydration and hypovolemic shock from hyperglycemic osmotic diuresis, compensatory hyperventilation (Kussmaul pattern), life-threatening electrolyte depletion, and in cases of severe metabolic imbalance, neurologic obtundation and coma.[192] Laboratory evaluation demonstrates elevated blood glucose concentrations, severe metabolic acidosis and compensatory hypocapnia, increased osmolality, hyperlipidemia, and a normal or low sodium level (usually fictitiously low because of the hyperlipidemia). Total-body depletion of potassium and possibly phosphate occurs. Levels of both may be falsely normal because of the metabolic acidosis.

Treatment of DKA requires careful correction of the metabolic derangements with meticulous monitoring of the multisystem complications of DKA, as well as the complications of therapy. Adequate intravascular volume is restored with an isotonic glucose-free solution. Regular insulin is given as an intravenous infusion of 0.1 U/kg/hr. The goal is to decrease blood glucose by 75 to 100 mg/dL/hr. This infusion is continued until the blood glucose reaches 250 to 300 mg/dL, at which time 5% dextrose in normal saline (D_5NS) is added to the infusate. This regimen of simultaneous glucose and insulin infusion can be continued until the patient can tolerate oral feedings and routine subcutaneous insulin administration. Most clinicians continue the insulin infusion until the acidosis is nearly corrected. Potassium concentrations should be monitored closely. These children have total-body potassium depletion, but potassium should not be added to any infusion until there is urine output. The need for phosphate may be more theoretical than real, but in most situations, half the potassium is given as a phosphate salt. The severe metabolic acidosis is usually corrected with volume and insulin administration.

The use of bicarbonate to correct acidosis is generally avoided because bicarbonate may precipitate or worsen the child's neurologic dysfunction. In severe DKA, the intracellular volume of brain cells is reduced by hyperosmolar dehydration. In an attempt to maintain their normal size, brain cells generate osmotically active idiogenic osmoles (e.g., inositol) that attract more water into the intracellular compartment. As systemic rehydration and correction of the hyperosmolar state begin, the brain cells may swell until the idiogenic osmoles are metabolized or cleared. Consequently, rapid correction of osmolarity can cause significant brain edema[193] and may also worsen the neurologic dysfunction. The pH of the brain is determined by the CSF bicarbonate level and by the CO_2 content; the CSF CO_2 content equilibrates much more rapidly with the vascular space than bicarbonate does. Therefore, correcting the systemic acidosis decreases the level of hyperventilation and causes a rise in $PaCO_2$; if this rise is precipitous, the CSF acidosis could worsen before the bicarbonate equilibrates with CSF. Because rapid correction of pH is problematic, bicarbonate administration is not advocated in DKA unless cardiovascular instability is present. Even then, the doses administered are small. Unfortunately, despite very careful and slow correction of the hyperosmolar and acidotic state, hyperosmolar coma and fulminant brain edema can occur.[194] The pathophysiology of brain swelling in DKA is poorly understood. Subclinical brain swelling may be relatively common in children with DKA.[195] If the swelling is significant, mannitol should be administered immediately and therapy for intracranial hypertension begun. The goal is to prevent secondary injury to the brain.

Gastrointestinal System

GI problems in the ICU include organ dysfunction and failure from acquired disease and from congenital anatomic malformations and dysfunction. Delivery of adequate nutrition to critically ill patients is necessary.

Structural and Functional Development of the Intestine

Knowledge of fetal midgut development makes it easier to understand a number of severe congenital anomalies. Although the intestine begins as a hollow tube, it is occluded by 7 to 10 weeks' gestation by rapidly growing epithelial cells. The lumen is later reconstituted when vacuoles within the epithelial cells coalesce. Some of the neonatal intestinal atresias are the result of abnormalities of this recanalization process. At 3 to 10 weeks' gestation, the midgut lies outside the abdominal cavity, with only the hindgut fixed in the left side of the abdomen. The gut rotates 270 degrees counterclockwise and re-enters the abdominal cavity at 10 weeks' gestation. If the midgut fails to migrate back into the

abdominal cavity, an omphalocele occurs. Abnormalities in midgut rotation result in abnormal intra-abdominal relationships, the most important being malrotation and volvulus of the intestine.

Development of the Liver

The liver begins as an outgrowth of the foregut at approximately 3 weeks' gestation. During fetal life it is relatively large in comparison to the adult liver. Although the fetus relies on the maternal liver and placenta for detoxification and excretory function in utero, the fetal liver is necessary for both prenatal and postnatal survival. As early as 10 to 12 weeks' gestation, the fetal liver is involved in glucose regulation, protein synthesis, and lipid synthesis and is capable of some drug metabolism.

The fetal liver contains approximately three times the amount of glycogen as the adult liver, but the glycogen is nearly completely released within hours of birth to compensate for interruption of the placental supply of nutrients.[196] It takes several weeks for the newborn to reestablish the store of liver glycogen, putting the infant at risk for hypoglycemia during this vulnerable period.

Congenital Malformations

Gross anatomic malformations are usually diagnosed during the first few days of life. Some, such as omphalocele, gastroschisis, diaphragmatic hernia, and imperforate anus, are apparent on the initial physical examination. Others manifest themselves in the first few days of life as failure to feed enterally, intestinal atresia, microcolon, tracheoesophageal fistula, and meconium ileus. Other malformations present difficult diagnostic and therapeutic dilemmas after the neonatal period. Specific clinical problems are discussed in the following sections.

Intestinal Malrotation and Midgut Volvulus

Malrotation of the intestine is caused by incomplete rotation of the fetal midgut when the gut migrates into the abdominal cavity. This abnormal rotation can cause partial or complete duodenal obstruction by peritoneal (Ladd) bands or, more importantly, midgut volvulus. The midgut (duodenum to transverse colon) and its vascular supply hang on a single pedicle; if the pedicle twists, the entire midgut may infarct. Infants with omphalocele almost invariably have associated malrotation of the gut. Symptomatic infants and children have signs of high intestinal obstruction (bilious vomiting) or signs of an acute abdomen, intestinal perforation, and sepsis. Treatment is surgical reduction and fixation of the volvulus and resection of nonviable bowel. Postoperative respiratory support and total parenteral nutrition are often necessary in infants who were severely compromised before surgery.

Meckel's Diverticulum

Meckel's diverticulum represents persistence of the omphalomesenteric or vitelline duct and is brought to the attention of the physician because of painless lower GI bleeding. The bleeding site is due to ulceration of the bowel mucosa caused by secretion of gastric acid. Although usually self-limited, massive and life-threatening hemorrhage has been reported.[197] The diagnosis can be difficult to make because it is often one of exclusion. The technetium pertechnetate isotope scan demonstrates gastric mucosa in the diverticulum. Therapy is supportive, but particular attention must be paid to blood replacement. Definitive therapy is surgical resection.

Hirschsprung's Disease

Hirschsprung's disease (congenital aganglionic megacolon) is characterized by the absence of parasympathetic ganglion cells in the rectum and colon and occasionally in the small bowel.[198] Lack of ganglia cause narrowing of the distal bowel and distention of the normal proximal bowel. The clinical symptoms can be relatively minor, with abdominal distention and stool retention, or severe, with toxic megacolon, peritonitis, and intestinal perforation. Toxic megacolon is usually manifested in younger children; reported mortality rates are as high as 75% with toxic megacolon.

The diagnosis of Hirschsprung's disease is occasionally made by the history and physical examination. A barium enema reveals a narrowed segment with ballooning of the proximal part of the bowel. The definitive diagnosis is made by finding no ganglion cells on rectal or colon biopsy (or both). Treatment of toxic megacolon is both supportive (volume re-expansion and antibiotic administration) and definitive (surgical decompression via colostomy).

Other Intestinal Disorders

Intestinal disorders can cause bleeding, obstruction, or inflammation, and there can be secondary problems such as malabsorption and bowel perforation. GI bleeding in children is caused by inflammatory diseases (gastritis), ulcers, varices, or vascular malformations. Although ulcer disease is an uncommon initial complaint in pediatric patients, stress gastritis or stress ulcers occur in critically ill children. Prophylactic antacids or an H_2 antagonist should be considered. Bowel obstruction can be caused by intussusception, twisting of the bowel around congenital or postsurgical bands, and twisting of the bowel on itself (volvulus). Intussusception is relatively common in the pediatric age group and usually occurs in the distal part of the ileum. In only a few cases can a leading point, such as a polyp or localized edema (as seen in Henoch-Schönlein purpura) be identified. Treatment of intussusception can be surgical or, in patients with no evidence of necrotic bowel, with barium, air, or saline enema.[199] Inflammatory bowel diseases include Crohn's disease and regional enteritis.[200] Infectious agents to be considered include *Salmonella*, *Shigella*, and *Yersinia*. These patients often have diarrhea, malabsorption (especially lactose intolerance), and bloody diarrhea. They also can have a toxic acute abdomen.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is an often fulminant neonatal disease characterized by ulceration and necrosis of the small bowel and colon. Its cause is unknown but is probably multifactorial. Prematurity is the greatest risk factor for NEC. It is probably due to a combination of intestinal ischemia, oral feeding, and pathogenic organisms. Umbilical artery catheters, perinatal asphyxia, respiratory distress syndrome, and persistent patent ductus arteriosus have all been implicated.[201] The incidence of NEC is on the rise, with 1% to 5% of infants in neonatal ICUs affected. The most common initial signs are feeding intolerance, abdominal distention, and bloody stools. Intestinal obstruction, bowel perforation, and sepsis may follow. Treatment consists of withholding enteral feeding, nasogastric decompression, intrave-

nous fluids, hemodynamic support, administration of appropriate antibiotics, and surgical exploration if there is evidence of an acute abdomen with free air. Peritoneal drainage may be helpful for very-low-birth-weight babies and for those in extremis.[202] Total parenteral nutrition is frequently required for several weeks, and intestinal obstruction may occur weeks to months after a relatively benign course.[203]

Hepatic Failure

Hepatic failure occurs with chronic or acute liver disease. Chronic liver failure can be caused by biliary atresia, inborn errors of metabolism (tyrosinosis, Wilson's disease, galactosemia, cystic fibrosis), or chronic inflammatory hepatitis. Children with chronic disease often have signs and symptoms of synthetic dysfunction (malnutrition, hypoalbuminemia, abnormal coagulation), degradation dysfunction (icterus and hyperammonemia), and portal hypertension (hypersplenism and varices). Acute liver failure is most commonly caused by infectious hepatitis A and B.

Evidence of bleeding, edema, and other organ dysfunction, including identification of liver and spleen size, is sought on physical examination. Laboratory evaluation should include screening for synthetic function (albumin, prothrombin time [PT], partial thromboplastin time [PTT]), degradation products (bilirubin, ammonia), and liver enzyme concentrations. Hepatic ultrasound, radiographic contrast studies, and liver biopsy are indicated on an individual basis.

Life-threatening complications of liver failure include acute bleeding and cardiovascular compromise (from massive intravascular hypovolemia as a result of fluid shifts) and intracranial hypertension from toxic encephalopathy. Treatment is expectant and supportive. A 10% dextrose infusion will provide adequate carbohydrate intake. Low-protein diets minimize ammonia production. Coagulation is supported with vitamin K, fresh frozen plasma, and platelets as required. Plasmapheresis with fresh frozen plasma and platelets improves coagulation and maintains normovolemia. Oral lactulose and neomycin enemas decrease the enterohepatic cycle of ammonia production and absorption.[204] Cardiovascular and respiratory function should be monitored closely and supported as required.

The development of intracranial hypertension must be anticipated. Serum ammonia levels are used to monitor neurologic dysfunction,[204] but it is unknown whether ammonia is the primary CNS toxin or whether it is just one of many chemical markers. Steroids have been used for some forms of inflammatory hepatitis. Exchange transfusions and plasmapheresis have been used to decrease the toxin load,[205] but there is no strong evidence that such measures reduce morbidity and mortality.[206] Patients with certain forms of acute hepatic failure, including those resulting from toxic and infectious causes, may be considered candidates for liver transplantation.[207,208]

Extrahepatic Biliary Atresia

Extrahepatic biliary atresia occurs once in every 8000 to 10,000 live births.[209] The extent of atresia differs from patient to patient and involves variable degrees of obstruction or discontinuity of the biliary tree between the duodenum and the proximal branches of the hepatic ducts. Treatment is surgical (jejunal Roux-en-Y and portoenterostomy) and is tailored to the amount of extrahepatic bile duct present. The Kasai procedure is most successful in patients operated on before they are 6 to 9 months of age. However, this procedure is associated with many acute and chronic complications, including hepatic failure, ascending cholangitis, and cirrhosis with portal hypertension and varices. Despite these complications, the Kasai procedure persists because there are not enough suitable donor organs.[210]

Liver Transplants

Improved immunosuppressive drugs and surgical techniques have increased the success of liver transplantation (see Chapter 67). For transplantation to be successful, the perioperative and postoperative periods require a coordinated approach among surgery, gastroenterology, anesthesia, immunology, and the ICU staff. Most of the clinical issues that arise can be anticipated. Large blood losses occur and massive replacement therapy is required in the operating room. Accordingly, intravascular volume status, renal status, and hematology/coagulation profiles must be closely monitored. The immunosuppression required puts the patient at risk for infection with both "normal" and opportunistic organisms. Surveillance cultures and early aggressive antibiotic therapy are indicated. Systemic hypertension, which appears to be unrelated to elevated CVP or pulmonary capillary wedge pressure, is due to the antirejection drugs. Many patients require aggressive antihypertensive therapy (hydralazine, diazoxide, captopril).[211,212]

Nutritional Support in Critically Ill Children

Adequate nutritional support of a critically ill child is of paramount importance to decrease morbidity and mortality (see Chapter 95). The caloric and mineral requirements of these patients must be met when possible. The nutritional requirements of healthy children have been defined, but the requirements of critically ill children are not well understood; measurements of oxygen consumption and nitrogen balance are not easly done at the bedside.

It may be difficult to deliver adequate nutrition because of bowel compromise, severe fluid restriction for renal or CNS disease, or glucose intolerance. All avenues of nutrition (enteral and parenteral) must be followed to prevent a catabolic state from developing.

Using the GI tract for alimentation when possible is the safest and most efficient approach. Numerous commercial formulas with variable sources and quantities of protein, fat, and carbohydrate are available. Protein requirements can be met with whole protein, protein hydrolysates, or individual amino acids. Whole protein, which has the least osmotic effect, has greater nutrient density. However, it can be used only in children with normal pancreatic function and no allergy. Children with protein allergy, pancreatic deficiency, or severe intestinal mucosal disease may benefit from a protein hydrolysate. However, these formulas have high osmolarity. Free amino acid formulas are used in chemically defined diets restricted by specific requirements or intolerances.

The high caloric density of fat makes it an important component in nutritional support. Long-chain triglycerides (LCTs) yield approximately 9 kcal/g, and medium-chain triglycerides (MCTs) yield 8.3 kcal/g. Although of greater caloric density, LCTs are less readily absorbed. MCTs are hydrolyzed more rapidly and are converted almost exclusively to free fatty acids and glycerol. MCTs are absorbed, even in the absence of lipase, because of their relative water solubility and emulsification properties. However,

MCTs contain no essential fatty acids. Consequently, linoleic acid is required to supplement the diet.[213]

Parenteral Alimentation

Parenteral nutrition is used for children who cannot tolerate enteral feedings because they have acute respiratory or GI disease; it is also used as primary treatment of chronic short-bowel syndrome, Crohn's disease, and renal failure.

Procedure for Implementation of Parenteral Nutrition in Children

When intravenous alimentation is considered, $D_{10}W$ is administered at 1 to 1.5 times maintenance for 24 hours (also see Chapter 95). The patient is closely monitored for glycosuria, hyperglycemia, and edema. If the glucose load is tolerated, a $D_{10}W$ solution with amino acids (PN-10) can then be initiated. Administration of $D_{10}W$ with or without amino acids is done through a central or peripheral catheter. Because concentrated solutions sclerose peripheral veins, they must be given through a central line. If a central line is in place and the patient is tolerating 1.5 times maintenance with PN-10 or $D_{10}W$, the dose of glucose can be increased to 20% and the fluid rate can be reduced to maintenance. The patient should gain little weight until 1.5 times maintenance with PN-20 is achieved. In general, if a patient is malnourished (<0.80 weight for height), fluid rates must be adjusted downward to roughly 80% of those for normal children of the same weight. After 1 week of nutritional rehabilitation, regular maintenance fluids may be used (Table 84-10).

Intravenous Lipid Alimentation

Lipid in Central Intravenous Alimentation

With central intravenous alimentation, lipid is required to prevent essential fatty acid deficiency and should be given as 5% to 10% of the total calories (see Chapter 95). The following fluid rate permits rough determination of the lipid rate necessary to prevent essential fatty acid deficiency during central intravenous alimentation: 5 to 10 mL/kg for the first 10 kg, 2.5 to 5 mL/kg for the second 10 kg, and 1.25 to 2.5 mL/kg for weight greater than 20 kg. Lipids are usually introduced several days after parenteral nutrition is begun. Tolerance of lipids is improved if the patient has had a period of adequate caloric intake. Fatty acids may impair the patient's ability to tolerate large doses of dextrose. Serum lipid concentrations should be checked whenever lipids are infused.

Lipid in Peripheral Intravenous Alimentation

With peripheral intravenous alimentation (10% concentration), lipid often constitutes a major portion of the caloric intake because it is the only isomolar product with sufficient caloric density to provide significant caloric intake by peripheral vein.

Table 84-10 Maintenance Fluid Rates in Pediatric Patients Receiving Parenteral Nutrition

Regular Maintenance Weight	Malnourished Body (mL/kg/day)	Maintenance (mL/kg)
1st 10 kg	100	80-90
2nd 10 kg	50	40
Weight >20 kg	20	20

Table 84-11 Calculated Caloric Density of Lipid Products Used in Pediatric Peripheral Intravenous Alimentation

Lipid Product	Caloric Density
Amino acids	3.33 cal/g
10% dextrose	0.34 cal/mL
20% dextrose	0.68 cal/mL
PN-10	0.39 cal/mL
PN-20	0.73 cal/mL
Lipid 10%	1.1 cal/mL
Lipid 20%	2.0 cal/mL

Thus, once a patient who is receiving peripheral alimentation has reached a maximum rate of PN-10, Intralipid is added at 10 mL/kg/day and advanced by 10 mL/kg/day to a maximum of 40 mL/kg/day. Lipid calories should not exceed 60% of the total calorie intake.[214] Lipid clearance is facilitated by administering lipid continuously over a 24-hour period. For calculations, the caloric densities shown in Table 84-11 may be used.

Peripheral versus Central Alimentation: Energy Considerations

Peripheral intravenous alimentation is a stopgap measure that rarely allows caloric intake to exceed maintenance requirements. Therefore, few extra calories will be available for growth. Peripheral intravenous alimentation should be limited to 2 weeks' duration. Central alimentation, on the other hand, can provide caloric and nitrogen requirements for growth and maintenance. However, central indwelling catheters carry a risk of infection.

Caloric requirements represent the energy intake necessary for maintenance, growth, and activity. Whatever net energy is left after allowing for maintenance and activity is available for growth. The caloric cost of growth is at least 5 cal/g weight. Normal growth is approximately 25 to 30 g/day for the first 6 months of life, 10 to 15 g/day for the next 6 months, and roughly 7 to 10 g/day thereafter. Representative maintenance energy requirements for the nonstressed state are listed in Table 84-12. By using these data, intravenous alimentation can be adjusted to produce normal or moderate catch-up growth rates. Weight gain, in the face of inadequate caloric intake (less than maintenance), inevitably means that the child is edematous. If the goal of nutritional therapy is merely supportive over a period of 1 to 2 weeks, there is less concern about growth; peripheral alimentation will be adequate. If significant catch-up growth or long-term support is required, growth and activity requirements should be met.

Table 84-12 Maintenance Energy Requirements for Nonstressed Patients

Age (yr)	Maintenance Energy (kcal/kg/day)
<2	75-80
2-5	70-75
5-10	55-70
10-17	40-55
Adult	40

Monitoring of Children Receiving Total Parenteral Nutrition

Intake, output, and body weight should be assessed daily. The site of alimentation, either peripheral or central, should be evaluated regularly for signs of obstruction, extravasation, or occlusion. The skin and mucous membranes are evaluated for evidence of trace metal deficiency. Liver size and function must be monitored; intrahepatic cholestasis, excessive fat and glycogen deposition, and elevated liver function have been documented in patients receiving parenteral nutrition. Other metabolic studies should include routine screening of electrolytes, glucose, blood urea nitrogen, and creatinine, as well as ammonia. Total protein, albumin, hemoglobin, and triglycerides should be checked regularly, but less frequently.[214]

Outcome

Survival of children depends on adequate nutritional intake. Infants with a nonfunctioning GI tract can survive on total parenteral nutrition for years, but this is clearly a stopgap measure.[215] The risk of complications from central venous cannulation increases over time, and vascular access becomes increasingly limited as sites are used up.

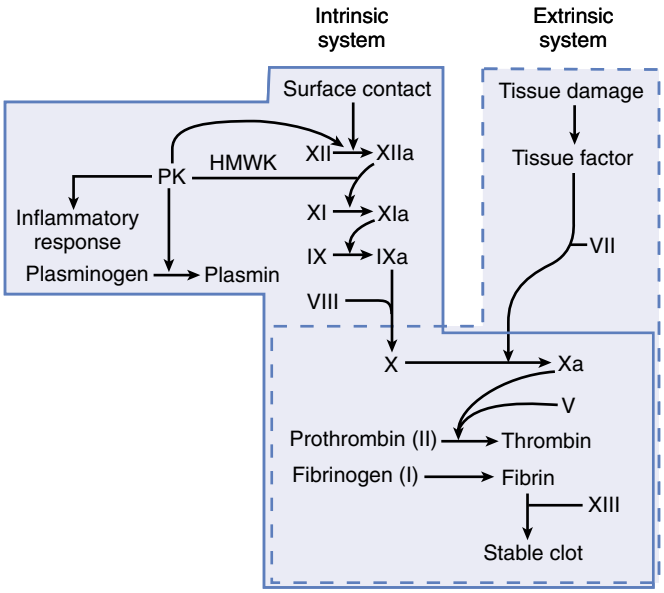

Figure 84-2 Scheme of blood coagulation. The suffix "a" denotes the activated factor with enzyme activity. HMWK, high-molecular-weight kininogen; PK, prekallikrein. *(Redrawn from Hathaway WE: Hemostasis.* In *Rudolph AM [ed]: Pediatrics, 17th ed. East Norwalk, CT, Appleton-Century-Crofts, 1982, p 1110.)*

Hematology

Hematologic emergencies in the ICU include abnormalities in coagulation, immunity, and red blood cell (RBC) mass. They can be primary isolated defects, or they can be caused by multiorgan system failure. The immune system is discussed in the section on infectious disease.

Coagulation System

Normal clotting includes initial platelet hemostatic plug formation and fibrin production (intrinsic or extrinsic pathways) (Fig. 84-2). For both to occur, platelets, coagulation factors, and an intact blood vessel are essential.[216,217] Neonates have a number of measurable coagulation abnormalities that rarely have clinical manifestations. Full-term and most preterm infants have normal platelet-vessel interaction, but platelet aggregation is transiently impaired. In addition, many coagulation factors show decreased activity or concentration in the fetus and newborn. Of greatest importance are the vitamin K–dependent factors: factors II, VII, IX, and X. These factors are low at birth and decrease to even lower levels during the first week of life unless vitamin K is administered. The amounts of factor V and VIII are close to adult levels in all but the most premature of infants. Although routine screening tests for coagulation activity are prolonged in infants, the newborn's blood clots more rapidly in vitro because neonates lack sufficient naturally occurring protease inhibitors, principally antithrombin III.[216]

Diagnosis of Hemostatic Disorders

Coagulation disorders are diagnosed by the history, physical examination, and laboratory data. It is important to elicit a history of easy bleeding, bruising, drug ingestion, and associated illnesses or a family history of bleeding. The patient should be examined closely for evidence of petechiae or bruising, bleeding gums, or hepatosplenomegaly. Bleeding or venipuncture sites should be observed for fresh clot or oozing. Laboratory evaluation of the PTT, PT, thrombin time, platelet count, and bleeding time gives valuable information on the nature of the hemostatic defect.

Specific Coagulation Disorders

Congenital Disorders

Hereditary deficiencies of most coagulation factors have been described, but classic hemophilia (factor VIII) and Christmas disease (factor IX) account for most deficiencies (see Chapter 35). Since the advent of modern factor replacement therapy, these disorders seldom cause life-threatening hemorrhage requiring ICU management.[218]

Factor VIII Deficiency or Hemophilia A Factor VIII deficiency, or hemophilia A, is transmitted by sex-linked recessive inheritance and occurs in 1 in 10,000 male infants.[219] The severity of the clinical disease is determined by the amount of circulating factor: severe disease is associated with less than 1% of normal levels, moderately severe disease with 1% to 5%, and very mild disease with 5% to 30% of normal levels. The most common sites of bleeding are the joint spaces, but hemorrhage may also occur in the peritoneal cavity, GI tract, muscle, skin, or CNS. Severe trauma or surgery can cause extensive bleeding. The diagnosis of hemophilia is made by demonstrating an elevated PTT and decreased levels of factor VIII. Treatment with plasma-derived factor VIII or recombinant proteins is necessary.

von Willebrand's Disease von Willebrand's disease occurs nearly as commonly as hemophilia A and is transmitted to both sexes by autosomal dominant inheritance. vWF is a multimeric glycoprotein that is produced by megakaryocytes and endothelial cells. vWF adheres to the subendothelial matrix after vascular injury. Changes in its conformation cause platelets to adhere and activate. von Willebrand's disease is classified into

three types. Type I has a quantitatively reduced amount of normal vWF and accounts for 85% of cases. Type II has qualitatively abnormal vWF, and type III has no vWF. Skin and mucous membrane bleeding, particularly nosebleeds and menorrhagia, are the most frequent clinical problems. The PTT and bleeding time are prolonged, as are some tests of platelet function. Desmopressin increases plasma vWF in patients with type I and some patients with type II disease. Cryoprecipitate or other plasma derivatives of vWF can be used when patients are unresponsive to desmopressin and if there is severe bleeding.[220]

Hereditary Thrombocytopenia Hereditary thrombocytopenia is an uncommon congenital defect. Most cases are associated with familial sex-linked immunodeficiency diseases, such as Wiskott-Aldrich syndrome.[221] Platelet transfusions help control bleeding. Splenectomy often corrects the thrombocytopenia, and successful bone marrow transplantation cures Wiskott-Aldrich syndrome.

Acquired Disorders

A variety of circumstances can impair the production of coagulation factors. The vitamin K–dependent factors are most commonly affected. These factors are decreased with liver disease, warfarin therapy, and malabsorption syndromes secondary to either bowel disease or altered bowel flora caused by long-term antibiotic therapy. In addition, untreated neonatal vitamin K deficiency results in hemorrhagic disease of the newborn. In these disorders, the PT is prolonged and there are low levels of factors II, VII, IX, and X. Administration of vitamin K usually reverses these deficiencies unless the synthetic function of the liver is markedly compromised.

Acquired platelet abnormalities include decreased production, increased destruction, and decreased function. Decreased production or hypoproliferative states include marrow diseases, such as leukemia and aplastic anemia, and the side effects of chemotherapeutic agents. Increased destruction can be immune mediated (i.e., idiopathic thrombocytopenic purpura[222]) or the result of consumption (i.e., microangiopathic states, HUS, or thrombotic thrombocytopenic purpura[223]). Finally, platelet dysfunction has been found with uremia and chronic polycythemia in patients with cyanotic heart disease.[224]

Treatment of acquired thrombocytopenia includes platelet transfusions and, if possible, correction of the underlying disorder. Therapeutic splenectomy will increase platelet survival in some patients with severe immune-mediated diseases.

DIC is characterized as a consumptive coagulopathy with decreased platelets and fibrinogen; increased PT, PTT, and thrombin time; and elevated fibrin degradation products. DIC complicates a number of nonspecific conditions: sepsis, anaphylaxis, shock, acidosis, massive tissue trauma, sickle cell disease, and certain malignancies, particularly acute myelogenous leukemia (AML) in childhood.[225] Purpura fulminans is a particularly severe form of DIC that is associated with ecchymosis and thrombosis of the skin, subcutaneous tissue, and distal ends of the extremities. This condition is seen with acute meningococcemia and with other bacterial, viral, and fungal septicemias. Purpura fulminans is associated with high morbidity and mortality; the main morbidity is ischemic loss of the distal ends of the extremities.

Treatment of DIC requires removal of the triggering event as soon as possible. Support of vascular volume and oxygen transport is essential. When active bleeding is present, transfusion of platelets (0.2 U/kg) and fresh frozen plasma (10 mL/kg) every 4 to 6 hours replenishes platelet and clotting factors. Coagulation antagonists, such as antithrombin III, may also be required. Heparin administration has been advocated by some clinicians; however, it has not improved outcome and may enhance bleeding. Transfusion with factor concentrates is helpful when the volume of fresh frozen plasma that can be administered is limited by intravascular hypervolemia. Occasionally, exchange transfusion with fresh whole blood or plasma exchange/plasmapheresis with fresh frozen plasma and platelets may be necessary to effectively treat severe DIC.[226]

Red Blood Cell Abnormalities

RBC abnormalities include either a decrease in RBC mass or RBCs that do not function normally. RBC mass is reduced by either decreased production or increased loss. Decreased RBC production is associated with factor deficiencies (iron, folate, vitamin B_{12}), bone marrow disease (aplastic anemia, leukemia), chronic diseases (infection, neoplasm, renal disease), and rarely, a congenital deficiency of RBC precursors (Diamond-Blackfan syndrome). RBC loss is caused by extracorporeal blood loss (hemorrhage) or cell destruction (hemolysis). Hemolysis can be caused by intrinsic RBC abnormalities or by extrinsic factors. Intrinsic anomalies include membrane defects (spherocytosis, elliptocytosis), enzyme defects (glucose-6-phosphate dehydrogenase, pyruvate kinase deficiencies), and hemoglobinopathies (hemoglobin S, C, D, and E and thalassemia). Extrinsic abnormalities can be immune mediated or infection and toxin mediated, or they may occur secondary to microangiopathic destruction.[227]

Regardless of what causes the decrease in RBC mass, the signs, symptoms, and therapy depend on the acuity and severity of the blood loss. Acute loss of large amounts of blood (hemorrhage) may cause hypovolemic shock. Treatment consists of oxygen, intravascular volume re-expansion, and replacement of RBCs. In the absence of hypovolemia, acute and chronic RBC loss is tolerated until the loss of oxygen-carrying capacity is critical and results in high-output cardiac failure. Treatment of these severe anemias includes oxygen and replacement of the RBC mass, which should be done cautiously and slowly to avoid the complications of fluid overload. Partial exchange transfusions are sometimes necessary to replace RBCs without causing volume overload.

Patients with hemoglobinopathies have RBCs that cannot carry oxygen appropriately; sulfhemoglobinemia and methemoglobinemia are the most common of these abnormalities. These disorders can be congenital or acquired. The congenital forms are usually asymptomatic and require no therapy; the acquired or toxic forms may be fatal. Treatment includes oxygen, intravenous administration of methylene blue, and occasionally, exchange transfusion.

Complications of Transfusion Therapy

Although the administration of blood products can be lifesaving, a number of potential complications should be anticipated (also see Chapter 55). Whenever massive transfusion therapy is used, the risks of citrate toxicity, transfusion reactions, and leukocyte

and platelet sensitization must be kept in mind, especially when large volumes of blood and products must be given rapidly to small children. In addition, depending on the age and type of the administered blood component, electrolyte disturbances such as hypocalcemia, hyperkalemia, and hypernatremia can occur. Whenever in doubt, a sample of the infusate should be sent for electrolyte analysis. Serum electrolytes and ionized calcium should be monitored during therapy. Transfusion-acquired infections, including hepatitis, cytomegalovirus, and acquired immunodeficiency syndrome, have decreased with improved screening of blood donors and extensive testing of units of blood.[228]

Finally, hemochromatosis complicates the care of patients who require long-term transfusion therapy to treat an RBC abnormality. Efforts to decrease this often lethal complication include aggressive iron chelation therapy and transfusion of young RBCs to increase the time interval between transfusions.[229]

In addition to RBC loss and abnormal oxygen binding, grossly deformed RBCs can cause vaso-occlusive disease. Sickle cell anemia is the best example of this pathology. Sickle cell anemia is a hemoglobinopathy. The major ICU complication is vaso-occlusive disease, which can be manifested as a painful crisis; if vaso-occlusion occurs in the cerebral vessels or in other vital organs, it is usually manifested as stroke or infarction.[230] Vaso-occlusive disease of the lung is referred to as acute chest syndrome and is clinically manifested as ARDS. Treatment consists of hydration, oxygen, and when severe, exchange transfusion and mechanical ventilation.[231] The other potentially fatal crisis of sickle cell disease is splenic sequestration, which occurs in infants and young children who have not undergone autosplenectomy. Splenic sequestration is manifested as severe anemia and hypovolemic shock. Treatment consists of aggressive supportive therapy with emergency surgical splenectomy. Other children with sickle cell disease have had a functional autosplenectomy as a result of multiple splenic infarcts. These "splenectomized" children are at risk for severe infection from encapsulated organisms. Pneumococcal vaccine is given to these children.

Oncology

Neoplastic disease in children usually involves the hematopoietic system, CNS, sympathetic nervous system, soft tissue, bone, and kidney. Much of oncologic care is performed on an outpatient basis, but some patients still require hospitalization and intensive care.

Blast Crisis in Leukemia

Children with an initial white blood cell (WBC) count of greater than 100,000 are at high risk for leukostasis and metabolic crisis (tumor lysis syndrome [TLS]).

Leukostasis

Leukostasis (vascular obstruction) results from high viscosity caused by elevated cell counts or by the WBCs themselves. This syndrome is anticipated in patients with acute lymphoblastic leukemia when the WBC count exceeds 500,000 and in AML patients with WBC counts greater than 200,000/mm^3. In AML, leukemic cells are less deformable than lymphoblasts, so a lower WBC count produces the same syndrome.

The brain and lungs are the two major target organs for leukostasis; vascular plugging and organ infarction are the usual manifestations. Initial symptoms include tachypnea, cyanosis, increased work of breathing, altered mental status, and focal neurologic deficits. Besides supportive therapy, reducing the circulating tumor load and viscosity are the primary goals of therapy. Leukapheresis and exchange transfusion transiently accompish these goals. Cranial irradiation may reduce the CNS tumor load, and chemotherapy will interrupt cell production and possibly destroy circulating cells. The initial goal of chemotherapy is to stop cell production without producing massive cell lysis; this halts the increase in tumor load without causing a severe metabolic crisis before adequate perfusion is reestablished.[232,233]

Tumor Lysis Syndrome

TLS is a metabolic crisis precipitated by acute lysis of a large number of tumor cells. Serum uric acid, potassium, and phosphate concentrations are elevated; the elevated phosphate concentrations cause hypocalcemia. The hyperkalemia and hypocalcemia can be life threatening; increased uric acid may cause acute renal failure.[234]

Therapy for TLS consists of alkalinization of urine, fluid administration, and diuresis. Before any chemotherapy is administered, the patient's renal function should be assessed. If renal function is normal, allopurinol or rasburicase therapy is begun. In most cases, this conservative approach of forced diuresis and allopurinol or rasburicase will prevent renal failure, but occasionally dialysis must be instituted. Indications for the initiation of dialysis include

1. Potassium >6 mEq/L and rising despite resin exchange
2. Uric acid >19 mg/L
3. Creatinine >10 mg/L
4. Phosphorus >10 mg/L or rapidly rising
5. Volume overload
6. Symptomatic hypocalcemia

If dialysis is necessary, it is usually required for only a few days.

Respiratory Distress and Mediastinal Mass

Children with a mediastinal mass and respiratory distress often complain of coughing, difficulty breathing, stridor, and shortness of breath. They prefer to sit upright and cannot lie supine. The chest radiograph usually shows a large mediastinal mass, often with obliteration or obscuring of the tracheal air column. These masses can also cause positional obstruction of vascular structures such as the superior vena cava or a pulmonary artery. These tumors can be malignant (87% Hodgkin's and non-Hodgkin's lymphoma) or benign; the prognosis and therapy rely on adequate diagnosis, which is best made by obtaining a tissue sample before treatment is begun.[235] However, obtaining a sample of the mediastinal mass may require anesthesia and surgery, and the airway must be manipulated and instrumented. All these manuevers may cause the patient to die. Local anesthesia with fine-needle biopsy under radiographic guidance allows tissue sampling without anesthesia in some patients. Irradiation of the

tumor before obtaining a tissue sample may reduce the size of the tumor and make biopsy easier and safer under anesthesia.

Obstruction of the intrathoracic trachea is a major anesthetic risk for these patients; it is often impossible to maintain a patent airway when the patient lies supine, is deeply anesthetized, or is paralyzed with muscle relaxants.[236,237] Care of these patients clearly requires individualized and creative approaches. Pulmonary function tests with flow-volume loops help identify patients at increased risk and guide response to treatment before anesthetic care. However, the patient must cooperate sufficiently to perform the test, which is often difficult for them because of respiratory distress. Induction of anesthesia and tracheal intubation are usually done with the patient in the sitting position and breathing spontaneously. If the airway compromise is severe, the tumor should be irradiated and the child given steroids before a tissue diagnosis is made. Sometimes, a peripheral node or mass can be biopsied under local anesthesia, or if the tumor mass is very large, some of the tumor can remain outside the field of radiation. In summary, although diagnosis is the key to treatment of neoplastic disease, the risk associated with biopsy may far outweigh the benefit of tissue diagnosis.

Fever and Neutropenia

The most common admitting diagnoses for children with neoplastic disease are fever and neutropenia. Neutropenia increases the child's risk for life-threatening infections.

Infectious Disease: Life-Threatening Infections in Infants and Children

Infections in the Newborn

Neonates with developmental immunologic deficiencies have increased susceptibility to infection. Depressed cell-mediated immunity makes the fetus and infant more susceptible to viral and fungal infection. In addition, infants have depressed B-cell function and diminished production of immunoglobulins. The latter is partially offset by increased maternal immunoglobulin G (IgG). By 2 to 3 months of age, which is before infants can adequately produce their own antibodies in sufficient quantity, the level of maternal antibodies reaches a nadir.[238] The time during which the circulating antibody concentration is low is a time when the risk for infections is increased.

Perinatal infections are either congenitally or postnatally acquired. Congenital infections occur with prenatal exposure to viral, protozoal, or rarely, bacterial pathogens. Common diseases include the TORCH infections: *Toxoplasma gondii* (T); "other" (O), including human immunodeficiency virus (HIV), syphilis, and tuberculosis; rubella (R); cytomegalovirus (C); and herpes simplex virus type 2 (H). Only rarely do these infections cause overwhelming sepsis, but they can be confused with bacterial infection when profound CNS depression, circulatory collapse, or thrombocytopenia occurs. When a TORCH infection develops in the first trimester of pregnancy, it causes fetal wastage or major organ malformation.[239]

Premature infants have a high incidence of acute infections in the newborn period. Regardless of gestational age, the signs and symptoms of infection are often subtle. Therefore, a very high index of suspicion and low threshold for diagnosing and treating infection are required.[240] Box 84-6 lists the common signs and symptoms of neonatal sepsis.

Box 84-6 Common Signs and Symptoms of Neonatal Sepsis

- Temperature instability (hypothermia and hyperthermia)
- Lethargy and poor feeding
- Respiratory distress and apnea
- Hypoglycemia and metabolic acidosis
- Poor cutaneous perfusion, hypotension
- Rashes or petechiae
- Seizures

The most common acquired pathogens are those that colonize the mother's genital tract: group B streptococci, *E. coli*, *Listeria monocytogenes*, and herpesvirus. Herpes is such a fulminant infection in neonates that the presence of active herpes lesions in the birth canal is an indication for cesarean section, although this may not prevent herpes in all children. Group B *Streptococcus* is the most common bacterial pathogen that causes neonatal sepsis. Infection with group B streptococci is manifested as severe cardiorespiratory instability and meningitis in 30% of cases. By 2 to 3 weeks of age, this organism is more commonly associated with meningitis and less commonly with pulmonary disease.

Whenever sepsis is suspected, cultures of blood, urine, and CSF should be obtained. Because it is difficult for the physician to localize the infection in an infant, repeated complete sepsis workups are often required. When appropriate cultures are obtained, treatment with ampicillin and an aminoglycoside, such as gentamicin, is usually begun until specific bacteriologic information becomes available. Only about 50% of neonates thought to be septic have positive cultures.

The Older Child: Sepsis and Septic Shock

Infectious diseases that require intensive care include sepsis with organ dysfunction and septic shock. In a previously well child, sepsis is frequently associated with an obvious primary site or source of infection. Although older children generally localize an infection as well as adults do, younger children do not. CNS infections may be difficult to diagnose in children younger than 2 years because they cannot give an adequate history of headache and because meningismus or other signs of meningeal irritation are unreliable.

Common clinical manifestations of sepsis in neonates include fever or hypothermia, tachypnea and tachycardia, poor cutaneous perfusion, altered level of neurologic function (agitation and irritability followed by apnea or coma), petechiae, purpura or other rashes, DIC, and the metabolic abnormalities associated with metabolic acidosis, hypoglycemia, and hypocalcemia. Sepsis can also cause septic shock. In septic shock, endotoxin, exotoxin, or other endogenously liberated vasoactive substances produce an endothelial lesion that causes increased vascular permeability, ARDS, increased use of metabolic substrate, depressed myocardial function, and profound DIC.[241]

The primary goal of therapy for any infection is eradication of the organism. Rationally chosen parenteral broad-spectrum antibiotic coverage should be initiated immediately and any septic focus or abscess should be drained surgically. Treatment of septic shock often requires early cardiorespiratory support. Endotracheal intubation and positive-pressure ventilation with PEEP may be required to treat the ARDS that often accompanies septic shock. Inotropic drugs may be used to maintain adequate cardiac output and tissue perfusion. Cardiovascular assessment with echocardiography, CVP monitoring, and sometimes a pulmonary artery catheter provide useful information that guides therapy. Because coagulopathies, including thrombocytopenia and generalized clotting factor deficiencies, are common in septic shock, fresh frozen plasma and platelet transfusions are frequently required. Steroids have few positive and possibly deleterious effects in septic shock.[242] Use of these drugs is therefore not advocated, except as steroid replacement in purpura fulminans and Waterhouse-Friderichsen syndrome.

Immunocompromised children may not have a specific primary focus of infection and may have repeated infections with different pathogens. Immunocompromised children may also have polymicrobial sepsis that is the result of bacterial seeding from the GI tract. There are few if any premonitory signs or symptoms before shock develops. Fever is the most common and often the earliest sign of opportunistic infection in immunocompromised children. Bacterial, fungal, and viral cultures should be obtained and broad-spectrum antimicrobial therapy should be initiated immediately. Antifungal drugs should also be considered. Granulocyte transfusions may benefit septic, neutropenic patients.[243] Table 84-13 lists the most common predisposing

Table 84-13 Opportunistic Infection in Inherited and Acquired Disorders

Predisposing Causes: Inherited and Acquired Disorders of Inflammation or Immunity	Opportunistic Organism Isolated Most Frequently	Suggested Mechanisms
Chronic granulomatous disease	*Staphylococcus*, gram-negative enteric organisms, *Serratia*, *Nocardia*	Impaired production of H_2O_2 with defective bactericidal function
Job's syndrome	*Staphylococcus aureus*	Unknown
Myeloperoxidase deficiency	*Candida*	Failure to kill *Candida*
Glucose-6-phosphate dehydrogenase deficiency	*Staphylococcus*, *Serratia*	Deficient cellular NADH and NADPH, deficient HMPS activity, decreased H_2O_2 production, defect in bacterial killing
Chédiak-Higashi syndrome	Pyogenic infection	Defective bactericidal activity, impaired chemotaxis, neutropenia
Congenital neutropenia	*Herellea*, *Serratia*, *Pseudomonas*, *Staphylococcus epidermidis*	Insufficient number of neutrophils
Complement deficiencies (C3, C3 inactivator)	Pathogens (e.g., *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Neisseria meningitidis*)	Defective chemotaxis, impaired opsonization
Splenic insufficiency	*Streptococcus pneumoniae*, *Salmonella*	Defective opsonization, defective clearing of organisms
Sickle cell disease and other hemoglobinopathies	*Streptococcus pneumoniae*, *Salmonella*, *Edwardsiella*	Reticuloendothelial blockade, defective opsonization
Humoral immunodeficiency syndrome (predominantly B-cell defects)	Bacterial pathogens, *Pseudomonas*	Reduced phagocytic efficiency, failure of lysis and agglutination of bacteria, inadequate neutralization of bacterial toxins
Cellular immunodeficiency syndromes (predominantly T-cell defects)	*Mycobacterium*, *Listeria*, *Nocardia*, cytomegalovirus, varicella, *Cryptococcus*, *Candida*, *Pneumocystis*	Absence of or impaired delayed hypersensitivity response, absent T-cell cooperation for B-cell synthesis of antibodies to T-cell–specific antigens
Severe combined immunodeficiency syndrome	Many bacteria, fungi, viruses, and *Pneumocystis*	Absence of T- and B-cell responses
Cancer	*Pseudomonas*, *Klebsiella*, *Escherichia coli*, *Listeria*, *Cryptococcus*, varicella-zoster, herpes simplex, *Pneumocystis*, *Mycobacterium*; incidence of infection with gram-negative organism increases in the presence of neutropenia	Granulocytopenia, decreased neutrophil chemotaxis, decreased bactericidal activity of neutrophils, lymphopenia, defective cell-mediated immunity, impaired antigenic response to challenge
Immunosuppression	*Pseudomonas*, *Klebsiella*, *Escherichia coli*, *Herellea*, *Serratia*, herpes simplex, varicella-zoster, cytomegalovirus, Epstein-Barr virus, papovavirus, hepatitis virus, *Candida*, *Aspergillus*, *Mucor*, *Cryptococcus*	Dependent on the agent used

Table 84-13 Opportunistic Infection in Inherited and Acquired Disorders—cont'd

Predisposing Causes: Inherited and Acquired Disorders of Inflammation or Immunity	Opportunistic Organism Isolated Most Frequently	Suggested Mechanisms
Transplantation	*Staphylococcus*, *Pseudomonas*, *Klebsiella*, *Candida*, *Aspergillus*, *Nocardia*, *Pneumocystis*, cytomegalovirus, hepatitis viruses, herpes simplex, varicella-zoster	Probably related to the use of immunosuppressive agents
Malnutrition	Measles, herpes simplex, varicella-zoster, *Mycobacterium*	Impaired T-cell function, reduction in complement activity, impaired migration of phagocytes, reduced bacterial activity
Cystic fibrosis	*Staphylococcus*, *Pseudomonas*	Presence of ciliary dyskinesia factor, impaired phagocytosis of *Pseudomonas*
Diabetes mellitus	*Staphylococcus*, *Escherichia coli*, *Proteus*, *Clostridium*, *Actinomyces*, *Candida*, *Mucor*, *Torulopsis*	Impaired phagocytic activity, decreased serum opsonizing capacity, decreased chemotaxis of neutrophils
Polyendocrinopathy	*Candida*	Unknown
Nephrotic syndrome	*Streptococcus pneumoniae*, enteric bacteria	Unknown
Uremia	*Bacteroides*, *Serratia*, *Enterobacter*, *Staphylococcus*, *Candida*, *Mucor*, herpes, varicella-zoster	Defects in early phases of the inflammatory response, lymphopenia, impaired T-cell function
Exudative enteropathy	*Streptococcus pneumoniae*, enteric bacteria, *Giardia lamblia*	Low levels of IgG, depressed T-cell function in intestinal lymphangiectasia
Inflammatory bowel disease	*Candida*, *Mucor*, herpes, varicella-zoster	Probably not related to basic disease but rather to the use of corticosteroids
Collagen diseases	*Candida*, *Mucor*, *Aspergillus*, *Pneumocystis*, diphtheroids, *Listeria*, *Pseudomonas*, *Serratia*, *Staphylococcus*, *Nocardia*, *Aspergillus*, cytomegalovirus, herpes, varicella-zoster	Probably related to the use of immunosuppressive agents; may relate to involvement of the reticuloendothelial system

HMPS, hexose monophosphate shunt; H_2O_2, hydrogen peroxide; NADH, reduced nicotinamide-adenine dinucleotide; NADPH, reduced NADH phosphate.
From Feigin RD, Matson DO: Opportunistic infections: The compromised host. *In* Feigin RD, Cherry JD (eds): Textbook of Pediatric Infectious Diseases, vol 1, 2nd ed. Philadelphia, WB Saunders, 1987, p 1013.

causes of immunosuppression, along with the most frequently associated opportunistic organisms.[244]

Human Immunodeficiency Virus

Major improvements in the treatment and management of HIV disease have decreased the incidence of new infections in children in North America and Western Europe. In young chidren, HIV infection is the result of vertical transmission from a seropositive mother. HIV-infected adolescents are affected in much the same way as adults; therefore, this discussion is limited to HIV in younger children.

A mother who has an untreated HIV infection has a 12% to 30% chance of infecting her child. Perinatal treatment of infected mothers with antiretroviral drugs dramatically decreases these rates. Vertical transmission of HIV can occur in utero (30% to 40%), in the intrapartum setting by exposure to infected blood or cervicovaginal secretions (60% to 70%), or in the postpartum setting by breastfeeding. Diagnosis of perinatal infection may be difficult because most infants have passively acquired maternal IgG antibodies, which prevents serodiagnosis. In developed countries, nucleic acid–based detection methods are the preferred virologic assay. Testing is performed during the first 2 days of life, and antiretroviral therapy is initiated when needed. False negatives can occur, and repeat testing through 4 to 6 months of age is recommended. The usual clinical manifestation of HIV infection in the very young includes failure to thrive, hepatosplenomegaly, and chronic interstitial pneumonitis. Toddlers have a higher incidence of lymphadenopathy, recurrent bacterial infections, delay in neurologic development, and progressive encephalopathy. Some children may remain asymptomatic for years.

Pneumocystis carinii pneumonia (PCP) is seen in all age groups, but it occurs more commonly and is associated with a higher mortality rate in children younger than 1 year. The mainstay of treatment remains trimethoprim-sulfamethoxazole and supportive care.

Lymphocytic interstitial pneumonitis is a slowly progressive disease characterized by chronic cough and slight to moderate hypoxemia. It is more common in children younger than 1 year. Radiographic findings include small nodules and fine reticular densities. Treatment is supportive. The efficacy of steroids is uncertain.

Children with HIV infection are most commonly admitted to an ICU because they have pulmonary disease, usually PCP. Aggressive care is provided. Antibiotic prophylaxis and prevention have drastically decreased the incidence of disease and improved survival after respiratory failure from PCP.[245]

Pediatric Trauma

Prenatal and Perinatal Injuries

Perinatal trauma occurs before or immediately after birth (also see Chapter 72). The most common prenatal injuries are due to maternal gunshot wounds and blunt trauma. Fetal mortality in both cases is at least twice that of the mother,[246] with fetal death being attributable to maternal shock and fetal oxygen deprivation rather than direct injury. Birth injuries occur more commonly in large full-term infants and in infants born by breech presentation. Injuries to the head include linear or depressed skull fractures, cephalohematomas, subdural or subarachnoid hematomas, and intraparenchymal or intraventricular hemorrhage. Intracranial injuries can increase ICP and cause cerebral ischemia, neurologic injury, and death. Injury to the sternocleidomastoid muscle may cause torticollis; traction on the neck may transect the cervical spinal cord. Less devastating nerve injuries caused by cervical traction are phrenic nerve paralysis and Erb's or Klumpke's palsy, which is caused by brachial plexus stretching or tearing (or both).

Shoulder dystocia is commonly associated with clavicular and humoral fractures; femoral shaft fractures occur with breech deliveries. Injuries to the liver, spleen, adrenal glands, and kidneys can cause life-threatening hemorrhage or thrombosis. Vaso-occlusion causes tissue loss in the cerebral, coronary, or renal vascular beds. Emergency instrumentation of the airway in the delivery room on rare occasion leads to tracheal and esophageal perforation, particularly in a premature infant.

Trauma in Children

Accidents and trauma are the leading causes of death in children 1 to 14 years of age.[247] Children are frequently victims of falling or being dropped, drowning, near-drowning, motor vehicle accidents (pedestrian), ingestions, and burns. Head injuries are common, especially in younger children, who have disproportionately large heads and relatively poor neck muscle support.[248] Young children are less likely to be victims of gunshot or knife attacks; blunt injuries are more usual. Blunt trauma to the abdomen can cause solid organ injury (liver and spleen) rather than a perforated viscus. Hypothermia is a frequent complication of trauma; children lose heat rapidly because they have a relatively large surface-to-volume ratio. Drowning and near-drowning are the prototypical hypothermic injuries.

Management of trauma patients of all ages requires an organized approach that permits rapid diagnosis and treatment. Most preventable deaths in pediatric trauma patients are caused by airway obstruction, pneumothorax, and shock; shock is often the result of inadequate treatment of bleeding or secondary brain injury from an expanding intracranial hematoma.[249] The American College of Surgeons recommends a four-step approach to pediatric trauma patients: (1) primary survey, (2) resuscitation, (3) secondary survey, and (4) definitive care.[250] The primary survey requires rapid assessment of the airway, breathing, and circulation (ABCs). A disproportionately large tongue, in relation to a narrow oropharynx, easily obstructs the airway in an unconscious child. Proper jaw positioning enables bag-and-mask ventilation until the trachea is intubated. Ventilation through an inadequate airway may lead to gaseous distention of the stomach, vomiting, and aspiration of gastric contents. Cervical spine injuries are less common in children than in adults, but the child's neck should be immobilized until spinal injury is excluded. After establishing an airway, adequacy of respiration should be verified by observation of symmetric chest movement, auscultation of normal and equal breath sounds, and an early chest radiograph. Tension hemopneumothorax can be diagnosed clinically and treated by needle aspiration. Aspiration will alleviate the tension and stabilize the patient's condition until a chest tube can be inserted. Circulation can be quickly assessed by looking for tachycardia, poor peripheral perfusion, weak peripheral pulses, and hypotension (which may not occur until blood loss exceeds 25% of the circulating blood volume).[251] A severely hypovolemic child requires rapid insertion of a central venous catheter. If a peripheral venous catheter cannot be inserted expeditiously, an IO cannula should be placed.[252] The amount of volume resuscitation is dictated by the clinical condition of the child and the estimated volume of blood or plasma lost.

During the secondary survey, a thorough head-to-toe examination is performed, and a plan of definitive treatment is developed. Diagnostic measures in a pediatric trauma patient are similar to those in adult patients, but there should be consideration of special problems that occur in children. Most intra-abdominal injuries requiring laparotomy are recognized clinically because they produce peritonitis or cause increasing abdominal girth.[253] Diagnostic peritoneal lavage may be of help in children who are hemodynamically unstable despite administering more than 40 mL/kg of blood. Peritoneal lavage may locate the site of occult bleeding in a child too unstable to undergo CT, or it can be used to evaluate abdominal injury in a child about to undergo emergency nonabdominal surgery. Many practitioners forego this procedure if surgery is imminent. Indications for surgical intervention for abdominal trauma include free peritoneal air, evidence of a ruptured viscus, and acute uncontrolled bleeding. A ruptured spleen or a liver laceration is not an indication for surgery in and of itself; the preferred treatment is supportive, blood volume replacement, and re-evaluation.[254]

A careful head and neurologic examination is done to quickly detect intracranial trauma. The most important indicator of intracranial trauma is a decrease in the level of consciousness. Rapid diagnosis and treatment of intracranial mass lesions will reduce ICP and may prevent secondary brain injury.

Child Abuse

The diagnosis of child abuse is made by finding an acute injury that may have a plausible explanation and signs of past trauma, including healing bruises, contusions, and fractures. Child abuse may also take the form of psychological or sexual abuse and failure to meet a child's need for food, clothing, shelter, hygiene, medical care, education, or supervision.

Suspicion of child abuse begins with an inappropriate or inadequate explanation for the child's injuries or when the degree of trauma exceeds the stated cause. Multiple hospital admissions, emergency department visits, doctor or hospital "shopping," and a history of previous trauma should be of concern. Frequently, the story regarding the injury changes over time. Certain clinical features are common to child abuse, but they are by no means pathognomonic. Most abused children are older than 3 years and may have poor hygiene and delayed somatic or psychological development. The injuries most commonly include bruises, welts,

lacerations, scalds, and burns from cigarettes, stoves, heating grates, or irons. Long-bone fractures, often of varying age, abdominal injuries, signs of smothering, and multiple soft tissue or genital bruises are also common. Head injuries can occur. Shaking an infant can cause neck injuries, intracranial hemorrhage, and contra-coup injuries without necessarily producing external manifestations of trauma. The approach to a suspected victim of child abuse includes a meticulous and nonjudgmental history, written in detail in the chart. All allegations are recorded and changes in the reported history are documented. The physical examination includes growth parameters, descriptions of soft tissue bruising or burns, and diagrams or preferably photographs of all injuries. The color, shape, placement, and estimated age of all injuries should be catalogued. Laboratory studies should include the following: a skeletal survey of all long bones, ribs, and the skull; a coagulation profile, including hematocrit, platelet count, PT, and PTT; and genital and throat cultures for venereal disease if sexual abuse is suspected. If child abuse is suspected, it must be reported to the authorities.

Ingestion Injury

Despite the success of various preventive public health programs, poisoning continues to occur commonly in pediatric patients. Fortunately, the vast majority of presumed poisonings in young children can be managed by telephone consultation with a regional poison control center. In one study, acute poisoning accounted for approximately 5% of all medical admissions to a PICU.[255] Approximately half of these admissions were accidental ingestions and half were attempted suicides. The median age for the accidental poisoning group was 2 years. For the suicide group it was 15 years. Although many different toxic substances are ingested by children and adolescents, management of poisoning has three main goals: (1) identifying, decontaminating, and eliminating the toxic agents[256]; (2) minimizing the toxic effects on the child; and (3) providing close observation and organ system support until detoxification is complete. Procedures for drug elimination include emesis, gastric lavage, activated charcoal, and magnesium citrate. Toxic effects can be minimized with specific antidotes when available, by hemodialysis, or by charcoal hemoperfusion. Examples of specific antidotes are deferoxamine for iron ingestion, ethanol infusion for methanol ingestion, naloxone for narcotic overdose, and *N*-acetylcysteine for acetaminophen ingestion. Because many ingestions, particularly those for attempted suicide, include multiple drugs, specific antidote therapy is only occasionally successful. Organ system support usually includes airway protection and mechanical ventilation, intravenous fluids, cardiovascular monitoring for arrhythmias and myocardial depression, and anticonvulsive therapy for patients who are seizing. Consultation with clinical pharmacologists or with the regional poison control center and contacting a social worker or psychiatrist are essential aspects of the care of an acutely toxic child. Common complications of ingestions and their therapy include aspiration pneumonia with hydrocarbon ingestion or loss of glottic function, sepsis, respiratory depression, myocardial depression, arrhythmias, seizures, and coma. The psychosocial environment that allowed or precipitated the ingestion must also be considered. Families should be counseled about proper supervision and "child-proofing" their home. Psychiatric intervention should be introduced early; unsuccessful suicide attempts are often repeated.

Transporting Critically Ill Infants or Children

With regionalization of neonatal pediatric intensive care, emergency interhospital transport systems were developed to provide rapid, safe, and effective transfer of critically ill children from community hospitals to regional intensive care facilities. Transport systems not only transfer sick patients to a facility where a patient can receive needed care but also initiate appropriate monitoring and treatment of the patient before leaving the referring hospital. Care of the patient begins as soon as the referring physician telephones the referral hospital. The ICU physician offers advice regarding immediate treatment and then mobilizes the transport team and alerts the appropriate consultants and hospital resources required for the incoming patient. The transport team usually consists of a physician and nurse specially trained in neonatal or pediatric intensive care. Other personnel may include respiratory therapists, anesthesiologists (particularly in the case of a pediatric upper airway problem), emergency medical technicians, or additional nursing or physician trainees. Portable intensive care equipment must include cardiovascular monitoring devices, an infant transport device to maintain a neutral thermal environment during transport, resuscitation equipment (including airway and breathing devices and a defibrillator), and additional equipment to institute intensive care on arrival at the referral hospital.

Problems that may arise during transport must be anticipated and treated before the patient is transported, which usually requires a careful assessment of the airway, breathing, and the adequacy of gas exchange, plus monitoring the adequacy and stability of the circulation. Because procedures are so difficult to perform in transit, tracheal intubation and placement of venous or arterial catheters are completed at the referring hospital if the transport team believes that these procedures may be required during transport. Medications required during transport should be anticipated and should be available. Transport can be carried out by ambulance, helicopter, or fixed-wing aircraft, depending on local circumstances. The environment during helicopter transport is difficult inasmuch as it is hard to provide surveillance and treatment because of poor temperature and noise control and limited operating space. Communication between the transport team and regional center is essential. Consultation with senior staff members helps the ICU anticipate the nature and degree of the illness. The most serious flaws in the transport system are usually the response time of the transport team after a referral call is made and the availability of adequately trained on-call transport team members. An institutional commitment of funds, personnel, and equipment, along with excellent organization, can ensure that neonatal and pediatric transport systems have a significant impact on patient care, community physician education, and regional hospital referrals.[257,258]

Sudden Infant Death Syndrome

SIDS is defined as the unexplained, sudden death of an infant younger than 1 year. It is the third leading cause of infant mortality in the United States, and the incidence was stable at 2 to 3 deaths per 1000 live births per year until advent of the "Back to Sleep" campaign in 1994. The rate is now 0.7 death per 1000 live births. The incidence peaks at 3 to 4 months of age and can be

temporally, but not causally associated with an upper respiratory tract infection, recent immunization, and rarely, anesthesia and surgery. Potential causes of SIDS include abnormalities in the cardiac conduction system, such as prolonged QT interval syndrome and Wolff-Parkinson-White syndrome, and abnormalities in the respiratory system, such as central or peripheral chemoreceptor abnormalities, upper airway obstruction, and the central hypoventilation associated with sleep.[259] In most cases, SIDS appears to be a "quiet" death in that breathing appears to stop without evidence of arousal or struggle. Occasionally, an infant is observed to be apneic and cyanotic and responds to tactile stimulation or to more vigorous resuscitative efforts. These infants are often admitted to the PICU for intensive monitoring and observation and may require treatment of hypoxic-ischemic injury to multiple organ systems.

Future treatment and monitoring of survivors of unexplained, apparent life-threatening events remain controversial; home cardiorespiratory monitoring does not decrease the incidence of SIDS. Caretakers should be thoroughly instructed in infant cardiopulmonary resuscitation (CPR) techniques. Parent groups and the National Foundation for Sudden Infant Death are helpful to some families.

The Asphyxiated Child

An asphyxiated patient, whether an older child or an infant with aborted SIDS or birth asphyxia, poses an important challenge for the intensivist. Asphyxia injures a number of target end organs.

Asphyxial Injury to Organ Systems

Cardiovascular System

The hypoxia and mixed metabolic and respiratory acidosis associated with asphyxia decreases cardiac output by depressing the medullary cardiac regulation center and by causing bradycardia and decreased myocardial contractility. As compensation for the decreased cardiac output, blood flow is preferentially redistributed to the cerebral and coronary circulations at the expense of the kidneys and GI tract. Asphyxiated children are cold and mottled and have evidence of a low-output shock state. Specific therapy for asphyxia-induced cardiovascular dysfunction consists of correcting the respiratory abnormality, correcting the acidosis, and administering chronotropic and inotropic agents as needed. (Appropriate monitoring and general treatment of circulatory failure are discussed in the section on acute circulatory failure in children.)

Respiratory System

Asphyxia-induced respiratory decompensation is commonly manifested as pulmonary edema, increased microvascular pressure, hypoxic myocardial failure, capillary endothelial damage, and capillary leak. Treatment of both conditions includes cardiovascular support, positive-pressure ventilation, and PEEP.

Central Nervous System

CNS complications of asphyxia include intraventricular hemorrhage, cortical infarction, and cerebral edema. Intraventricular hemorrhage in premature infants is a consequence of hypoxic-ischemic necrosis of the paraventricular germinal matrix, which undergoes liquefaction. The vessels rupture into the ventricular system hours to days after the initial asphyxic injury.[260]

Cortical infarction occurs in children of all ages. This condition usually develops in a watershed area and affects the motor cortex controlling the upper extremities and the visual cortex.

Cerebral edema is a relatively late consequence of asphyxia that occurs 8 to 72 hours after injury. Because the ultimate neurologic outcome depends principally on the degree of cortical injury that occurs with asphyxia, aggressive management of cerebral edema may prevent or reduce secondary damage. Measures that ensure adequate oxygenation and hemodynamic stability should be instituted. Patients who have purposeful movements and a normal brainstem examination 24 hours after their hypoxic insult generally have a good neurologic recovery. Children without these findings 24 hours after injury are more likely to have severe neurologic deficits or die.[261] (Treatment of cerebral edema is discussed in the CNS section.)

Renal and Metabolic Effects

Asphyxia may cause renal ischemia, tubular or glomerular necrosis, and renal vein or glomerular capillary thrombosis. Metabolic complications of asphyxiated infants and children may also include hypoglycemia, hypocalcemia, hypomagnesemia, and metabolic acidosis. These complications of asphyxia often produce profound myocardial depression and systemic hypotension. Hypervolemia and hypo-osmolality and the syndrome of inappropriate ADH secretion can occur with fluid resuscitation. Free water overload should be avoided if at all possible.

Hematologic System

The major hematologic complication of asphyxia is DIC. In the newborn, as well as in older children, levels of vitamin K–dependent factors (II, VII, IX, X) may be low because of asphyxia-induced hepatic dysfunction; these conditions may respond to vitamin K.

Gastrointestinal System

Splanchnic ischemia may cause necrosis, ulceration, or perforation of the GI tract.[262] Monitoring includes testing nasogastric secretions and stool for blood, measuring abdominal girth, and evaluating abdominal radiographs for intraluminal, intramural, intraportal, or extraluminal air. NEC is a common problem after asphyxia in premature infants. In severe cases, bowel perforation, peritonitis, and sepsis can lead to death. Management of NEC consists mainly of treatment with appropriate antibiotics, maintenance of intravascular volume, and minimizing the osmotic load of feedings until the GI tract has fully recovered. Oral or gastric alimentation is avoided for several days to several weeks after injury. When feedings are initiated, low-osmolality solutions should be used. While the bowel is recovering, intravenous alimentation should be provided through a central venous catheter. Gastric pH should be monitored and abnormalities should be treated with antacids or an H_2 blocker. Hypoxia and hypoperfusion of the liver may cause hepatocellular damage. The extent of the injury is directly related to the duration and severity of the insult. Elevated transaminase levels, abnormal coagulation, elevated bilirubin, and unstable carbohydrate metabolism are common; all functional and laboratory abnormalities should be corrected if possible.[263]

Approach to Death from Asphyxia

Because the CNS is very sensitive to asphyxia, it is relatively common to have full cardiovascular recovery and profound CNS damage or brain death. In situations in which meaningful neurologic recovery is hopeless or when brain death has occurred, life support can be terminated. The parents and siblings of children who die require support, counseling, and understanding. They often react with guilt, denial, or hostility for not having been more vigilant. These issues must be addressed directly by trained professionals.

Cardiopulmonary Resuscitation

Resuscitation of the Newborn

Profound changes occur in the cardiovascular and respiratory systems at birth. Failure to successfully make these changes may result in death or CNS injury (also see Chapter 97). Consequently, someone capable of performing neonatal resuscitation must be present at every delivery. Wasting time finding someone to resuscitate the neonate may be disastrous for the infant. This section discusses the causes and effects of cardiorespiratory insufficiency at birth and the techniques of resuscitation. When possible, the recommendations of the American Academy of Pediatrics have been followed.

Guidelines for neonatal resuscitation have been issued by many orgaizations, including the American Heart Association and the American Academy of Pediatrics. Guidelines are helpful for remembering the sequence for resuscitation. Failure to follow the guidelines has resulted in bad outcomes.[264] However, slavish adherence to guidelines without thinking may also result in bad outcomes. Understanding the physiology of delivery and birth is the keystone to success.

Resuscitation of the newborn requires education and practical experience. Unfortunately, there is little opportunity to learn and refresh the neonatal resuscitation skills of most anesthesiologists because few of their patients require resuscitation. Simulators solve this problem. In the near future, those who resuscitate babies will be required to train with a neonatal simulator and to repeat this training several times a year to maintain board certification.[265]

Detecting potential problems and preparing to treat them before birth increase the likelihood of successfully resuscitating patients. Fetal heart rate monitoring is a moderately reliable and widely used means of detecting early, serious fetal problems. Analysis of fetal blood gases and pH can be used to detect asphyxia and may help decide whether early, rapid delivery of the fetus is required.

Asphyxia (i.e., decreased Pa_{O_2} and pHa and increased Pa_{CO_2}) occurs when gas exchange by the placenta (fetus) and by the lung (neonate) is inadequate or when there is right-to-left shunting of blood in the heart or lungs after birth. It also occurs with myocardial dysfunction.

During fetal asphyxia, Pa_{O_2} decreases from its normal of 25 to 40 mm Hg to less than 5 mm Hg in about 2 minutes (Fig. 84-3) and is followed by anaerobic metabolism. Five minutes of asphyxia reduces the pH to 6.90 or less, increases Pa_{CO_2} to greater than 100 mm Hg, and reduces Pa_{O_2} to unmeasurable levels.[266,267] Blood flow to the liver, kidney, gut, skin, and muscle is reduced, and flow

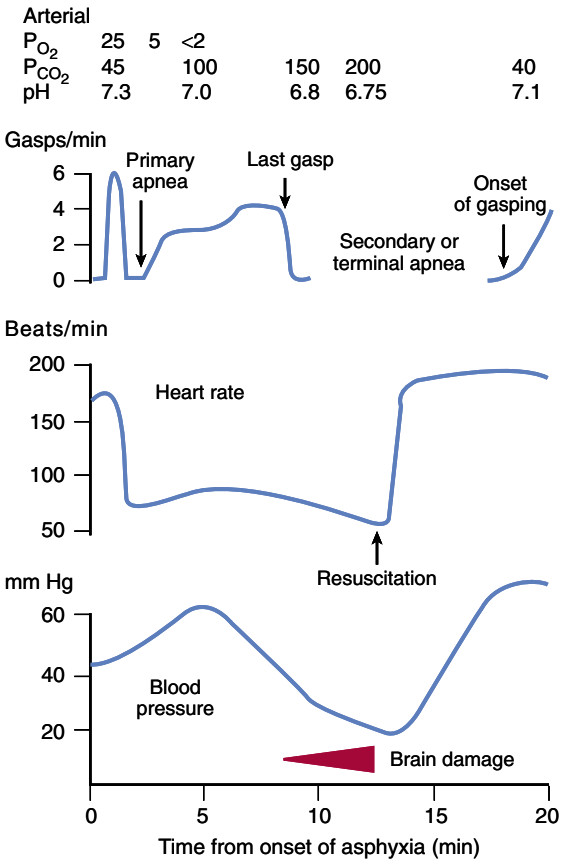

Figure 84-3 The response of newborn monkeys to asphyxia. *(From Dawes GS: Foetal and Neonatal Physiology. Chicago, Year Book Medical Publishers, 1968.)*

to the heart, brain, adrenal glands, and placenta is constant or increased. Oxygen extraction from blood is greatly increased.[268] Myocardial function is maintained by myocardial glycogen and lactic acid metabolism.[269] A heart rate of less than 100 beats/min significantly decreases cardiac output. Catecholamines are also important for survival from asphyxia. Intrapartum asphyxia may result in hypervolemia or hypovolemia.

Assessment of the Fetus at Birth

The Apgar score, if done properly, is a simple, useful guide to neonatal well-being and resuscitation (Table 84-14), but it is only a guide. The 1-minute score correlates well with acidosis and survival. The 5-minute score may or may not be predictive of neurologic outcome.[270,271] To be of value, each variable must be evaluated at 1 and 5 minutes. However, some very acidotic neonates have relatively normal Apgar scores at 1 and 5 minutes and are peripherally vasoconstricted, exhibit pallor, and have a relatively normal heart rate and arterial blood pressure.

Heart Rate

The heart rate of normal fetuses and neonates ranges from 120 to 160 beats/min. When the heart rate is less than 100 beats/min, cardiac output and tissue perfusion are reduced.

Respiratory Effort

Breathing usually begins by 30 seconds after birth and is sustained by 90 seconds of age. A few minutes after birth, the respira-

Table 84-14 The Apgar Scoring System

	Score*		
Sign	**0**	**1**	**2**
Heart rate	Absent	Less than 100/min	More than 100/min
Respiratory effort	Absent	Slow, irregular	Good, crying
Color	Blue, pale	Body pink, extremities blue (acrocyanosis)	Completely pink
Reflex irritability (response to insertion of a nasal catheter)	Absent	Grimace	Cough, sneeze
Muscle tone	Limp	Some flexion of extremities	Active motion

*Each variable is evaluated individually and scored from 0 to 2 in an infant at 1 and 5 minutes of age. The total score at each time is the sum of the scores of the individual variables. A total score of 10 is perfect.

tory rate of normal neonates is between 30 and 60 breaths/min. The absence of a pause between inspiration and expiration helps develop and maintain FRC. Apnea and bradypnea prolong exhalation, reduce FRC, and cause hypoxia. Causes of apnea and bradypnea include severe acidosis, asphyxia, maternal drugs, infections, and CNS damage. Tachypnea (>60 breaths/min) occurs with hypoxemia, hypovolemia, metabolic and respiratory acidosis, CNS hemorrhage, pulmonary gas leaks, pulmonary disease (e.g., hyaline membrane disease, aspiration syndromes, infections), pulmonary edema, and maternal drugs (e.g., narcotics, alcohol, magnesium, barbiturates).

Resuscitation with 100% oxygen can be detrimental.[272] Neonates resuscitated with room air do equally well as those resuscitated with added oxygen.[273] Animals resuscitated with air had less cerebral hydrogen peroxide than did those resuscitated with oxygen.[274] Polymorphonuclear cells were less activated with room air.[275] Oxygen administration in excess of room air increases the likelihood of an inflammatory response. When possible, room air rather than oxygen should be used to resuscitate neonates.

Muscle Tone

Most neonates, including those born preterm, are active at birth and move all extremities in response to stimuli. Asphyxia, maternal drugs, CNS damage, amyotonia congenita, and myasthenia gravis decrease muscle tone. Flexion contractures and absent joint creases are signs of in utero CNS damage.

Reflex Irritability

Normal neonates move with stimulation and grimace or cry when a catheter is inserted into a nostril. Neonates who have hypoxia, acidosis, CNS injury, and congenital muscle disease or are sedated by maternal drugs may not move.

Color

Essentially all neonates have a blue-tinged cast to their skin at birth. By 60 seconds of age most of them are entirely pink, except for their hands and feet, which remain blue. If central cyanosis persists beyond 90 seconds of age, asphyxia, low cardiac output, pulmonary edema, methemoglobinemia, polycythemia, congenital heart disease, arrhythmias, and pulmonary disorders (e.g., respiratory distress, airway obstruction, hypoplastic lungs, diaphragmatic hernia) should be considered, especially if the infant remains cyanotic despite oxygen and controlled ventilation.

Neonates who are pale at birth are often asphyxiated, hypovolemic, acidotic, or anemic, or they have congenital heart disease. A neonate whose skin is entirely pink within 2 minutes of birth may be intoxicated with alcohol or magnesium or may be alkalotic (pH >7.50). Rubrous neonates are usually polycythemic.

Resuscitation Equipment

Resuscitation beds should allow positioning of the neonate's head below the level of the lungs to promote drainage of lung fluid and reduce the likelihood of aspirating gastric contents. A servocontrolled infrared heater should be used to maintain the neonate's temperature between 36°C and 37°C unless there is evidence of asphyxia. If asphyxia is noted, body temperature should be reduced to 34°C to 35°C for brain protection. A suction device should be available and should allow the suction pressure to be varied; pressures below −100 mm Hg should not be used.

Equipment required for tracheal intubation includes 0 and 00 straight laryngoscope blades; a pencil-type laryngoscope handle; 2.5-, 3.0-, and 3.5-mm ETTs; and a suction catheter that easily fits through each size tube.

The ventilation system must permit ventilatory rates of at least 150 breaths/min and make it possible to maintain PEEP. One-way valves can stick in the closed position, especially when high gas flow and high respiratory rates are used. The modified Jackson-Rees or Ayres system works well when appropriately trained people use it. Overexpansion of the lungs with large tidal volumes injures the lungs and activates inflammatory processes that may cause chronic lung disease.[276] Gentle inflation of the lung is less injurious to the lung. Airway inflation pressures should be measured continuously during assisted or controlled ventilation in the delivery room, and excessive pressures and tidal volumes should be avoided.

As in any critical care situation, patient care should be guided by information. Consequently, blood gas and pH measurements are mandatory, and the results of these tests must be available within 10 minutes of drawing the blood sample. Umbilical arterial catheters are useful for measuring arterial blood pressure and withdrawing blood for blood gas analysis and pHa. They can also be used to infuse emergency fluids.

Arterial oxygen saturation (Sao_2) can be measured immediately after birth by attaching a pulse oximeter to a hand or foot.[277] Pulse oximeters permit rapid detection of changes in oxygenation and rapid reduction of Fio_2. The normal Sao_2 of neonates is usually 87% to 95%, which is associated with a Pao_2 of 55 to 70 mm Hg.[278]

Pulmonary Resuscitation

If the heart rate is below 80 beats/min and Sao_2 is less than 85%, tracheal intubation should be considered and positive-pres-

sure ventilation should be initiated at 30 to 60 breaths/min. For the first several minutes every fifth breath should be held for 2 seconds to expand the atelectatic lung and remove lung fluid. PEEP at 3 to 5 cm H_2O should be maintained. Excessive airway pressure is to be avoided. As few as six large breaths at birth markedly increased lung injury in premature lambs and prevented a response to surfactant.[279] Excessive inspiratory volumes are also associated with inflammation and chronic lung disease.[276] Measuring airway pressure helps prevent us from using excessive pressure and volumes.

Tracheal Intubation

The head should be placed in a neutral or "sniffing" position during bag-and-mask ventilation and tracheal intubation. An appropriately sized ETT is inserted and its tip is placed 1 to 2 cm below the vocal cords, depending on the size of the neonate. Usually, this means that the distance from the tip of the tube to the gums is 7, 8, 9, or 10 cm in 1-, 2-, 3-, and 4-kg infants. A small gas leak should be present between the ETT and trachea when the ventilation pressure is 15 to 25 cm H_2O. This usually entails the use of a 2.5-mm (internal diameter) tube for neonates weighing less than 1.5 kg, a 3.0-mm tube for those between 1.5 and 2.5 kg, and a 3.5-mm tube for those weighing more than 2.5 kg. Successful tracheal intubation is confirmed by observing the ETT pass through the vocal cords, by observing bilateral chest movement with each mechanical inspiration, and by observing condensation in the ETT during exhalation. Breath sounds should be much louder over the chest than over the abdomen, and the skin color, heart rate, and Sao_2 should improve with positive-pressure ventilation. Carbon dioxide should be present during exhalation.

However, the small tidal volumes and low pulmonary blood flow of some infants at birth may make it difficult to use capnography effectively.

Adequacy of Ventilation

Both sides of the chest should rise equally and simultaneously with inspiration, but the amount of rise should not exceed that associated with the neonate's normal spontaneous breathing. The presence of breath sounds may be misleading because they are well transmitted within the neonate's small chest. A difference in breath sounds between the two sides of the chest should raise suspicion of endobronchial intubation, pneumothorax, atelectasis, or a congenital anomaly of the lung. The presence of loud breath sounds over the stomach suggests esophageal intubation or a tracheoesophageal fistula. If ventilation is adequate, the neonate will become pink, initiate rhythmic breathing, and have a normal heart rate.

Because most asphyxiated neonates have no lung disease, they can be effectively ventilated with peak airway pressures lower than 25 cm H_2O, even for the first few breaths. Those with stiff lungs (e.g., erythroblastosis fetalis, congenital anomalies of the lung, pulmonary edema, severe meconium aspiration, diaphragmatic hernia) may require higher inspiratory pressure to ventilate their lungs and are more likely to have pulmonary gas leaks. To reduce this likelihood, the lungs should first be ventilated with an inspiratory pressure of 15 to 20 cm H_2O and inspiratory rate of 150 to 200 breaths/min. If low-pressure (low-volume), high-rate ventilation does not improve the oxygenation, higher pressure and volume may be required. Failure to adequately ventilate the lungs at birth may worsen hypoxemia and lead to CNS damage or even death. If Pao_2 exceeds 70 to 80 mm Hg or Sao_2 exceeds 94%, the inspired oxygen concentration should be reduced (if increased concentrations of oxygen are used) until Sao_2 and Pao_2 are normal for age. Oxygenation is maintained at the low range of normal in neonates 34 weeks' or less gestation to avoid the retinopathy of prematurity.[280,281] The neonate's heart rate should be monitored continuously during endotracheal intubation because the process of tracheal intubation may cause arrhythmias in hypoxic neonates.

Routine Tracheal Suctioning

The trachea should be suctioned before the lungs are ventilated if there is thick meconium in the amniotic fluid or major vaginal bleeding has occurred. Meconium aspiration has been reviewed elsewhere.[282-285]

Particulate meconium should be removed from the lung before breathing is established. The mouth and pharynx are suctioned as soon as the head is delivered. An ETT is inserted, a suction device especially designed for this purpose is applied to the ETT, and suction is applied to the ETT as it is withdrawn from the trachea.[286] The laryngoscope is left in place as the ETT is removed. If meconium is retrieved from the airway, the ETT should be quickly reinserted and the airway suctioned again. The lungs are then gently ventilated. The heart rate should be continuously monitored during laryngoscopy and suctioning and 100% oxygen blown over the neonate's face. The stomach should be suctioned to remove meconium that can be regurgitated and aspirated later. Neonates with Apgar scores of 9 or 10 do not require tracheal suctioning. Removing thin watery meconium at birth has no beneficial effect, whereas removing thick meconium is effective.[287]

Other Causes of Respiratory Failure

Pneumothorax

Pneumothorax occurs in 1% of all vaginal deliveries, in 10% of meconium-stained neonates, and in 2% to 3% of neonates who require mechanical ventilation in the delivery room. The hemithorax containing free air is usually hyperexpanded and moves poorly with ventilation. The point of maximum cardiac impulse is shifted toward the side without the pneumothorax. Heart tones may be muffled.

If a small, high-intensity cold light is placed directly on the skin of the neonate's chest, the involved side of the chest will glow if a pneumothorax is present.[288] Pneumothoraces are relieved by needle or chest tube drainage.

Administration of Surfactant

Surfactant administration has significantly reduced the incidence of pulmonary gas leaks, hyaline membrane disease, deaths, BPD, and interstitial emphysema.[289-292] Surfactant is administered as 5 mL of solution per kilogram into the trachea at or shortly after birth, which briefly reduces oxygen saturation. Sao_2 then increases rapidly in most instances, as does compliance of the lung. The improved lung compliance will result in overinflation of the lung and lung injury or a pulmonary gas leak if the ventilation pressure is not reduced.

Premature infants are often supported with nasal CPAP shortly after birth to reduce the need for tracheal intubation and mechanical ventilation.[265] However, this does not reduce the incidence of CNS hemorrhage or chronic lung disease.[293] The

duration of oxygen administration and chronic lung disease is unchanged.

Vascular Resuscitation

Vascular resuscitation is a neglected aspect of neonatal resuscitation. If the neonate's condition does not improve with ventilation, oxygen (if needed), and tactile stimulation, an umbilical artery catheter should be inserted so that blood gases and pH and arterial blood pressure can be measured and blood volume can be expanded if necessary.

Correction of Acidosis

Respiratory acidosis is corrected by mechanical ventilation. Metabolic acidosis is corrected by administering sodium bicarbonate. Sodium bicarbonate solutions consist of about 1800 mOsm/L. Rapid administration of this solution (>1 mEq/kg/min) may possibly cause intracranial hemorrhage in premature infants. The complete reaction of hydrogen ions with 50 mEq of bicarbonate generates approximately 1250 mL of CO_2. If ventilation is adequate, there is no increase in $Paco_2$; if ventilation is inadequate, $Paco_2$ increases significantly and may cause cardiac arrest or intracranial hemorrhage, or both. *Sodium bicarbonate should be infused only to correct metabolic acidosis if ventilation is adequate.* Administration of bicarbonate may also induce hypotension in hypovolemic infants (Fig. 84-4) by relaxing acidosis-induced intense peripheral vasoconstriction. THAM is an alternative to sodium bicarbonate. It reduces $Paco_2$ rather than increases it.

If the Apgar score is 2 or less at 2 minutes or is 5 or less at 5 minutes despite tactile stimulation and controlled ventilation, consider giving 2 mEq/kg of sodium bicarbonate while the lungs are being ventilated. If the pH is below 7.00, $Paco_2$ is below 35 mm Hg, and blood volume is adequate, correct a fourth of the base deficit. If the pH is above 7.10, administration of base should

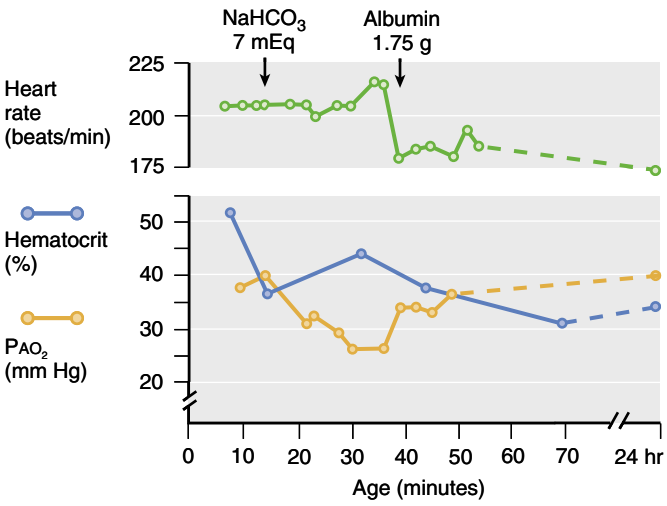

Figure 84-4 Effects of sodium bicarbonate on aortic blood pressure (PAO), heart rate, and hematocrit level. Notice that hypotension occurred after the administration of sodium bicarbonate. The hematocrit level decreased as fluid was "pulled" into the intravascular space to compensate for the hypovolemia that was present since birth. Raising the pH decreased the peripheral vasoconstriction produced by the preexisting acidosis. Giving albumin increased the aortic pressure to normal. On the basis of the final hematocrit level, the initial blood volume was approximately 30% less than predicted. *(Adapted from Phibbs RH: Problems of neonatal intensive care units.* In *Lucey JF [ed]: Report on the 59th Ross Conference on Pediatric Research. Columbus, OH, Ross Laboratories, 1969.)*

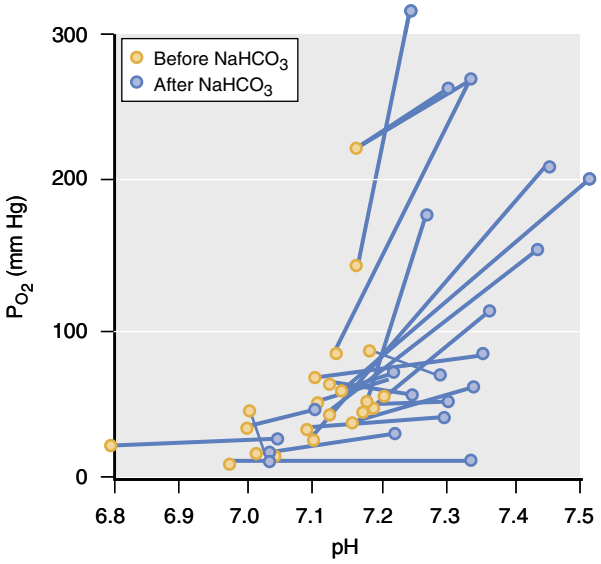

Figure 84-5 Effects of rapid infusion of sodium bicarbonate on Pao_2 and pH when ventilation was held constant. Pao_2 increased when the pH increased above 7.10 to 7.20. *(Adapted from Gregory GA: Resuscitation of the newborn. Anesthesiology 43:225, 1975.)*

be delayed and lung ventilation should be continued. Five minutes later, arterial pH and blood gas analysis should be repeated. If the pH is 7.15 or higher, ventilate the lungs and again delay bicarbonate therapy. If the pH has decreased or is unchanged, correct a fourth of the base deficit with bicarbonate or THAM while continuing artificial ventilation. Figure 84-5 shows the effects of sodium bicarbonate on the Pao_2 of a group of asphyxiated neonates whose ventilation was held constant. No significant increase in Pao_2 occurred until the pH exceeded 7.10 to 7.20, the point at which Rudolph and Yuen[294] found the most significant decrease in PVR.

Metabolic acidosis is usually caused by poor tissue perfusion that is the result of hypovolemia or heart failure. Acidosis-induced heart failure generally occurs when the pH is 7.00 or less. When the pH is above 7.15, cardiac output improves. Congenital bradycardia-induced heart failure is usually treated with isoproterenol (starting with 0.05 µg/kg/min and increasing the dose as necessary) or insertion of a transvenous pacemaker. Hypoglycemia may also cause heart failure. Thus, the glucose concentration should be measured during resuscitation of the child.

Expansion of Intravascular Volume

If the umbilical cord is clamped early or if it is wound tightly around the neck of the fetus and the umbilical cord must be cut for delivery, the baby may be hypovolemic. The baby may also be hypovolemic with intrauterine asphyxia, placental abruption, or transection of the placenta.

Detection of Hypovolemia

Hypovolemia is detected by measuring arterial blood pressure and by physical examination (i.e., skin color, perfusion, capillary refill time, pulse volume, and extremity temperature) (Table 84-15). Table 84-16 shows the systolic, diastolic, and mean arterial pressure during the first 12 hours after birth.

CVP measurements are useful in detecting hypovolemia and in determining the adequacy of fluid replacement. The venous

Table 84-15 Relationships of Skin Color, Capillary Refill Time, Pulse Volume, and Extremity Temperature to Hypovolemia

Amount of Volume Depletion (%)	Skin Color	Capillary Refill Time (sec)	Posterior Tibial Pulse Volume	Skin Temperature
None	Pink	<2	Full	Warm
5	Pale	3-4	Moderately full	Cold from the midcalf and midforearm out
10	Gray	4-5	Markedly diminished or absent	Cold from the midthigh and upper arm out
15	Mottled	>5	Markedly diminished or absent	Entire extremity cold

pressure of normal neonates is 2 to 8 cm H_2O. If CVP is less than 2 cm H_2O, hypovolemia should be suspected.

Treatment of Hypovolemia

Treatment of hypovolemia requires expansion of intravascular volume with blood and crystalloid. Albumin may also be used, but evidence of its effectiveness is limited. If it is suspected that the neonate will be hypovolemic at birth, Rh-negative type O packed RBCs should be available in the delivery room before the the neonate is born.

Occasionally, enormous volumes of blood and fluid are required to raise arterial blood pressure to normal. At times, more than 50% of the blood volume (85 mL/kg in term neonates and 100 mL/kg in preterm neonates) must be replaced (Fig. 84-6), especially when the placenta is transected or abrupted during birth. In most cases, less than 10 to 20 mL/kg of volume restores mean arterial pressure to normal.

Overexpansion of intravascular volume should be avoided because sudden systemic hypertension may disrupt the intracerebral vessels and cause intracranial hemorrhage, particularly in premature infants.[295]

Other Causes of Hypotension

Hypoglycemia, hypocalcemia, and hypermagnesemia also cause hypotension in neonates. Hypotension induced by alcohol or magnesium intoxication usually responds to blood volume expansion or dopamine, or to both. Hypermagnesemic neonates generally respond to 100 to 200 mg/kg of calcium gluconate administered over a 5-minute period.

Cardiac Massage

If the heart rate at 1 minute or less of age is less than 80 beats/min despite stimulation and ventilation, the trachea should be intubated, the lungs ventilated with oxygen, and closed chest massage begun. Place both thumbs on the sternum and allow the fingers to support the back (Fig. 84-7). Compress the sternum about 2 to 2.5 cm at a rate of 100 to 120 times per minute. It is not necessary to interrupt ventilation of the lungs during cardiac massage. The effectiveness of cardiac massage is determined by measuring blood gases and pH, by the arterial pressure generated, and by examining the pupils, which should be in the midposition or constricted. If the pupils are dilated and no atropine has been given, CBF and oxygenation are inadequate.

Resuscitation Drugs

Table 84-17 lists the drugs and their usual starting doses used during resuscitation of the newborn. Severe acidosis (pH < 7.0) may decrease the effectiveness of these drugs. Thus, the pH must be raised above 7.20 as soon as possible. All drugs should be infused in the smallest volume of fluid possible to reduce the risk of inducing hypervolemia.

Table 84-16 Average Systolic, Diastolic, and Mean Arterial Blood Pressure during the First 12 Hours of Life in Normal Infants

Blood Pressure Measures by Birth Weight	Blood Pressure (mm Hg) during the First 12 Hours of Life											
	1	2	3	4	5	6	7	8	9	10	11	12
Birth Weight 1001-2000 g												
Systolic	49	49	51	52	53	52	52	52	51	51	49	50
Diastolic	26	27	28	29	31	31	31	31	31	30	29	30
Mean	35	36	37	39	40	40	39	39	38	37	37	38
Birth Weight 2001-3000 g												
Systolic	59	57	60	60	61	58	64	60	63	61	60	59
Diastolic	32	32	32	32	33	34	37	34	38	35	35	35
Mean	43	41	43	43	44	43	45	43	44	44	43	42
Birth Weight >3000 g												
Systolic	70	67	65	65	66	66	67	67	68	70	66	66
Diastolic	44	41	39	41	40	41	41	41	44	43	41	41
Mean	53	51	50	50	51	50	50	51	53	54	51	50

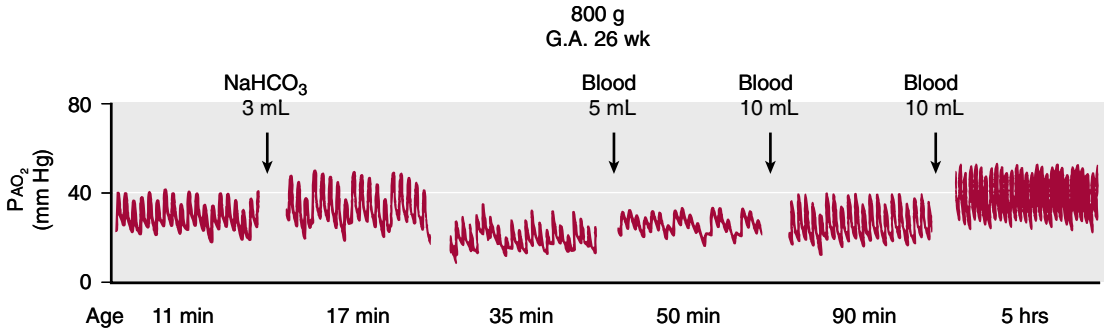

Figure 84-6 Aortic blood pressure (PAO) during the first 5 hours of life of a premature infant with hypovolemia. PAO values equal mean aortic pressure. G. A., gestational age. *(From Gregory GA: Resuscitation of the newborn. Anesthesiology 43:225, 1975.)*

When to Discontinue Resuscitation

The decision to stop resuscitation is usually based on the physician's experience, the condition of the patient, and the desires of the parents. If the chances of a productive, useful life are very poor, discontinuing all resuscitative efforts should be considered. Whether to resuscitate micropremies is questionable[296,297] because the outcome of neonates born before 26 weeks' gestation is abysmally poor.[298,299] Frank discussions should be undertaken with the family before the baby is born when possible. If this cannot be done, it may be necessary to initiate resuscitation and then discontinue it after talking with the parents.

Resuscitation of Children

Pediatric cardiopulmonary arrest differs in a number of ways from arrest in adults. Cardiac arrest in adults is usually caused by severe cardiac ischemia and malignant arrhythmias. Children seldom have primary malignant arrhythmias. The more commom cause of cardiac arrest in children is respiratory compromise or respiratory arrest. Another difference is the character of the arrhythmia observed. Adults generally display ventricular arrhythmias, whereas children are more likely to have a bradyarrhythmia that degenerates into asystole.

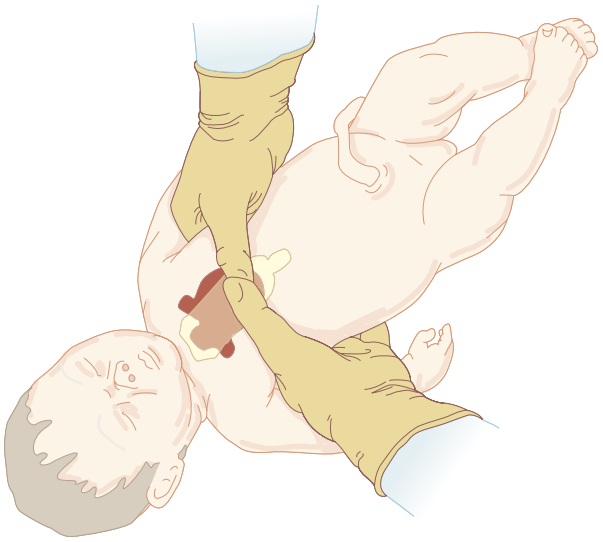

Figure 84-7 Closed chest massage. For simplification, ventilation is not shown. *(From Gregory GA: Resuscitation of the newborn. Anesthesiology 43:225, 1975.)*

Identifying patients at risk for cardiopulmonary arrest is just as important as providing good CPR. This requires constant clinical evaluation and identification of risk factors. Critically ill patients are often at increased risk for cardiac arrest during airway manipulation, any change in therapy, or manipulation of the patient or bed and when doctors and nurses change shifts.

The basic ABCs of resuscitation must be sufficiently familiar that no thought is required to begin the initial resuscitative efforts. Despite the evolving literature regarding new CPR, the standard American Heart Association CPR is still advocated as the appropriate method.[300] If despite ventilation there is no evidence of a pulse, external cardiac compressions are initiated immediately and the lungs are ventilated. The rate of compression should be 80 to 100/min in children and adults. One hand can be placed behind the back for support while the child's sternum is compressed with two fingers of the other hand. The adult-style two-handed massage is preferable in older children. Pressure should always be completely released between forceful compressions to permit filling of the cadiac chambers, and a pulse should be sought to assess the adequacy of compressions.

Vascular access is attained as soon as possible. Although a number of medications (atropine, epinephrine, lidocaine) have been given through the ETT, bicarbonate, calcium, fluid, and pressors require vascular access. The evidence that endotracheal administration of drugs is better is inconclusive. Common drugs used for CPR include the following:

1. Atropine (0.02 to 30 mg/kg with a minimum dose of 0.1 mg and a maximum dose of 1.0 mg) is used to treat bradycardia.
2. Sodium bicarbonate corrects the metabolic component of the acidosis. The recommended initial dose is 1 mEq/kg in association with adequate ventilation. Because the acidosis is primarily respiratory, inadequate ventilation during bicarbonate administration will only increase $Paco_2$ and decrease the pH. Overzealous use of bicarbonate lowers the threshold for ventricular fibrillation and causes a left shift of the oxygen dissociation curve. Present guidelines suggest that bicarbonate administration be guided by ABG results.
3. Calcium is a positive inotrope and peripheral vasoconstrictor; it may decrease the threshold for ventricular

Table 84-17 Drugs Used during Resuscitation

Drug	Indication	Dose*	Route	Response	Complications
Atropine	Bradycardia	0.03 mg/kg	IV	Increased heart rate	Marked tachycardia, diminished cardiac output
Calcium gluconate	Low cardiac output	100 mg/kg over 5-10 minutes (ECG monitoring)	IV	Improved cardiac arrhythmias	Bradycardia
Epinephrine	Flat-line ECG	0.1 mL of a 1 : 10,000 solution per kg	IV	Flat-line ECG converted to some rhythmic response	Hypertension, ventricular fibrillation
Isoproterenol	Bradycardia, hypotension, low cardiac output	4 mg/250 mL of 5% dextrose; start at 0.01 μg/kg/min and increase until the heart rate increases	IV	Increased heart rate, improved cardiac output	Arrhythmias, low cardiac output if the heart rate is greater than 180-220/min
Dopamine	Hypotension	40 mg/100 mL; start at 5 μg/kg/min and increase until the desired effect is achieved	IV	Increased arterial pressure; improved cardiac output, perfusion, and urine output	Arrhythmias (uncommon)

*In general, doses given are starting doses and may have to be increased. Most drugs tend to be more effective when the pH is higher than 7.15.
ECG, electrocardiogram.

arrhythmias. In pediatric patients, ventricular arrhythmias seldom cause cardiac arrest. Thus, administration of calcium may be safer. Ten to 20 mg of elemental calcium per kilogram of body weight is appropriate in patients who have hypocalcemia, hyperkalemia, or an overdose of calcium channel blockers.

4. Dextrose (0.5 to 1.0 g/kg) is given to correct hypoglycemia, which may be a precipitating cause of the arrest. It is available as $D_{50}W$ (1 to 2 mL/kg) and $D_{25}W$ (2 to 4 mL/kg). $D_{50}W$ and $D_{25}W$ are also osmotic diuretics. Dextrose (0.5 g/kg) in combination with insulin (0.1 U/kg) is administered to treat hyperkalemia. Hyperglycemia should be avoided during resuscitation for fear of increasing CNS damage.
5. Epinephrine is usually given intravenously or intraosseously, but it can also be administered through the ETT (0.1 mL/kg of a 1 : 1000 solution). Epinephrine is supplied as a 1 : 10,000 solution (0.1 mg/mL); the dose is 0.1 mL/kg and is repeated every 3 to 5 minutes as needed. The maximum recommended dose is 1 mg intravenously/intraosseously or 10 mg by ETT.
6. Lidocaine is used to decrease ventricular irritability and to help maintain a normal rhythm after defibrillation. It decreases myocardial contractility and should therefore be given only when absolutely necessary, such as when a stable rhythm cannot otherwise be maintained. The dose is 1 mg/kg as a single dose; this dose can be repeated several times or the drug can be given as an infusion of 20 to 50 μg/kg/min.
7. Amiodarone, 5 mg/kg intravenously/intraosseously, is used to treat ventricular tachydysrhythmias by slowing AV conduction, prolonging the AV refractory period and QT interval, and slowing ventricular conduction. The drug can be administerd rapidly to patients in cardiac arrest, but it should be administered more slowly to patients with a pulse—blood pressure should be monitored. The ECG should be monitored for evidence of bradycardia.
8. Adenosine is administered rapidly for diagnosis and treatment of narrow-complex tachycardias in doses of 0.1 mg/kg (maximum dose of 6 mg), which can be repeated as 0.2 mg/kg (maximum of 12 mg). ECG recording during adenosine administration is very useful to determine whether the drug is effective or if more drug is needed.
9. Vasopressin is used frequently in resuscitation of adults, but there is limited experience with the use of vasopressin in pediatric patients (dosing is not well established, but the drug has been administered in doses of 1 U/kg intravenously/intraosseously).[301] The American Heart Association believes that there is insufficient evidence to make a recommendation for or against the routine use of vasopressin during cardiac arrest.
10. It is common to infuse an inotrope or chronotrope during resuscitation. Cardioversion is indicated if ventricular fibrillation or ventricular tachycardia is present or if either one develops. The pediatric dose is 1 to 3 W-sec/kg or 10 to 15 W-sec/yr of life. The synchronized mode is used for ventricular tachycardia, and the nonsynchronized mode is used for fibrillation. If small paddles are not immediately available for use with small children, adult paddles can be placed in an anteroposterior position. If resuscitation efforts are unsuccessful, the primary event that precipitated the arrest should be re-evaluated to determine whether there are correctable mechanical or metabolic problems (or both). Possible reasons for unsuccessful resuscitation include tension pneumothorax/hemothorax, disruption of a major vessel, cardiac tamponade, profound hypovolemia, profound metabolic imbalance, toxin ingestion, and hypothermia. A patient with a core temperature lower than 30°C may appear dead and be unresponsive to pharmacologic management. The patient must be warmed as part of the resuscitation. It may be necessary to open the chest and bathe the heart in warm water to increase its temperature sufficiently so that it will be responsive to drugs. A hypothermic patient can be pronounced dead only if there is no electrical activity on the ECG and the core temperature is at least 30°C or if it is impossible to warm the patient to 30°C with aggressive methods, including peritoneal dialysis.

Iatrogenic complications, including traumatic pneumothorax from attempted vascular cannulation, pericardial tamponade

from intracardiac injections, splenic or hepatic rupture from closed-chest compressions, pneumothorax from overzealous positive-pressure ventilation, and placement of the ETT into the esophagus, may also make resuscitation unsuccessful. Because patients in cardiorespiratory distress or arrest have an excellent chance of full recovery with adequate resuscitation, speedy, orderly direction, cooperation of all personnel, and continuous assessment of the effectiveness of resuscitation are key. Keeping the brain alive is the objective of every resuscitative effort, and rapid institution and maintenance of ventilation and cardiac massage increases the chance of this occurring.

Parent/Family Support

Numerous unavoidable stresses occur in any intensive care setting. In a PICU, the difficulty of dealing with the illness or death of a child often magnifies the amount of stress. To adequately support the ICU staff, children, and families, potential problems should be discussed and understood. ICU staff members are exposed to extremes of frustration and success, and this has an emotional and psychological impact on everyone. Support systems for patients, parents, and staff are a necessity.

Pediatric patients range from premature infants to adults, and each patient must be approached in an age-appropriate manner. Diseases, procedures, and treatments should be discussed with the patient when appropriate; children should participate in their own care to the degree that age, sedation, and disability permit. Parents of a child with a critical illness often progress through the stages of grief reaction described by Kübler-Ross.[302] Their interaction with the ICU staff and with their child is dramatically influenced by the character of their grief reaction. In addition, the ICU may be very confusing. The hectic pace and the numbers of physicians and nurses often leave parents feeling that they lack control and direction. ICUs are also very intimidating and isolating. They are frequently geographically isolated and have a separate dedicated staff, a level of technology not seen in other parts of the hospital, and a terminology of numbers and abbreviations that can render conversations uninterpretable. All these factors make it difficult for parents to maintain a parenting role. Too often, parents assume the role of an absent or passive parent, an angry critical parent, or a parent who wants to assume the role of physician. Some parents can never be directed into a more productive role, but frequently, careful explanations of ICU operational procedures and generous use of social and clerical services can help parents maintain their parenting roles. Other members of the family, especially the patient's siblings, should also be considered. Many parents need help and encouragement before they can involve their children at home in the events taking place at the hospital. Sibling visits should be encouraged and supported by the ICU staff.

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Dorre Nicholau

85 The Postanesthesia Care Unit

Key Points

1. Emergence from general anesthesia and surgery may be accompanied by a number of physiologic disturbances that affect multiple organ systems. Most common are PONV, hypoxia, hypothermia and shivering, and cardiovascular instability.
2. In a prospective study of more than 18,000 consecutive admissions to the PACU, the complication rate was found to be as high as 24%. Nausea and vomiting (9.8%), the need for upper airway support (6.8%), and hypotension (2.7%) were the most common problems.
3. The most frequent cause of airway obstruction in the immediate postoperative period is the loss of pharyngeal muscle tone in a sedated or obtunded patient. The persistent effects of inhaled and intravenous anesthetics, neuromuscular blocking drugs, and opioids all contribute to the loss of pharyngeal tone in the PACU patient.
4. Pharyngeal function is not normalized until an adductor pollicis train-of-four ratio is greater than 0.90.
5. The ability to strongly oppose the incisor teeth against a tongue depressor is a reliable indicator of pharyngeal muscle tone. This maneuver correlates with an average train-of-four ratio of 0.85 as opposed to 0.60 for the sustained head lift.
6. An estimated 8% to 10% of patients who undergo abdominal surgery subsequently require intubation and mechanical ventilation in the PACU. Respiratory failure in the immediate postoperative period is often due to transient and rapidly reversible conditions such as splinting from pain, diaphragmatic dysfunction, muscular weakness, and pharmacologically depressed respiratory drive.
7. Although a combination of leads II and V_5 will reflect 80% of the ischemic events detected on a 12-lead ECG, visual interpretation of the cardiac monitor is often inaccurate. Because of human error, the American College of Cardiology guidelines recommend that computerized ST-segment analysis be used (if available) to monitor high-risk patients in the immediate postoperative period.
8. In one study, urinary retention was defined as bladder volume greater than 600 mL in conjunction with inability to void within 30 minutes and the incidence of postoperative urinary retention in the PACU was 16%. The most significant predictive factors were age older than 50 years, intraoperative fluid greater than 750 mL, and bladder volume on entry to PACU greater than 270 mL.
9. Perioperative attention to adequate hydration is indicated in any patient who has received an intravenous contrast agent. Aggressive hydration with normal saline provides the single most effective protection against contrast nephropathy.
10. Rhabdomyolysis has been reported to occur in 22.7% of 66 consecutive patients undergoing laparoscopic bariatric surgery. Risk factors include increased body mass index and duration of operation.
11. The incidence of postoperative shivering may be as high as 65% (range, 5% to 65%) after general anesthesia and 33% after epidural anesthesia. Identified risk factors include male gender and the choice of induction agent; propofol is more commonly associated with shivering than pentothal is.
12. Approximately 10% of adult patients older than age 50 who undergo elective surgery will experience some degree of postoperative delirium within the first 5 postoperative days. The incidence is much higher for certain procedures, such as repair of hip fracture (>35%) and bilateral knee replacement (41%).
13. PACU Standards of Care require that a physician accept responsibility for the discharge of patients from the unit (Standard V). This is the case even when the decision to discharge the patient is made at the bedside by the PACU nurse in accordance with hospital-sanctioned discharge criteria or scoring systems.

The postanesthesia care unit (PACU) is designed and staffed to monitor and care for patients who are recovering from the immediate physiologic effects of anesthesia and surgery. PACU care spans the transition from one-on-one monitoring in the operating room to the less acute monitoring on the hospital ward or, in some cases, independent function of the patient at home. To serve this unique transition period, the PACU is equipped to resuscitate unstable patients while providing a tranquil environment for the "recovery" and comfort of stable patients. Its location in close proximity to the operating rooms facilitates rapid access to physician consultation and assistance.

Admission to the PACU

The PACU is staffed by specially trained nurses skilled in the prompt recognition of postoperative complications. On arrival to the PACU, the anesthesiologist provides the PACU nurse with pertinent details of the patient's history, medical condition, anesthesia, and surgery. Particular attention is directed to monitoring oxygenation (pulse oximetry), ventilation (breathing frequency, airway patency, capnography), and circulation (systemic blood pressure, heart rate, electrocardiogram [ECG]). Vital signs are recorded as often as necessary but at least every 15 minutes while the patient is in the unit. Vital signs and other pertinent information are recorded as part of the patient's medical record. Specific requirements and recommendations for patient monitoring and therapeutic intervention can be found in the Practice Standards and Guidelines drafted by the American Society of Anesthesiologists.[1,2]

The Standards for Postanesthesia Care

Practice Standards delineate the required *obligation* of *minimal* care in the clinical setting. As such, they serve as a threshold that can be exceeded when indicated by the clinical judgment of the practitioner. The Standards for Postanesthesia Care are updated on a regular basis to keep up with changing practice parameters and technologic advances. The most recent revision published in 2004 is summarized here.

I. All patients who have received general anesthesia, regional anesthesia or monitored anesthesia care shall receive appropriate post anesthesia management.
II. A patient transported to the PACU shall be accompanied by a member of the anesthesia care team who is knowledgeable about the patient's condition. The patient shall be continually evaluated and treated during transport with monitoring and support appropriate to the patient's condition.
III. Upon arrival in the PACU, the patient shall be re-evaluated and a verbal report provided to the responsible PACU nurse by the anesthesia care team who accompanies the patient.
IV. The patient's condition shall be evaluated continually in the PACU. *The patient shall be observed and monitored by methods appropriate to the patient's medical condition. Particular attention should be given to monitoring oxygenation, ventilation, circulation, level of consciousness and temperature.*
V. A physician is responsible for the discharge of the patient from the postanesthesia care unit.

Table 85-1 Summary of Recommendations for Assessment and Monitoring in the PACU

Respiratory
Respiratory rate
Airway patency
Oxygen saturation
Cardiovascular
Pulse rate
Blood pressure
Electrocardiogram*
Neuromuscular
Physical examination
Neuromuscular blockade*
Nerve stimulator*
Mental status
Temperature*
Pain
Nausea and vomiting
Urine*
Voiding
Output
Drainage and bleeding*

*Selected patients.
PACU, postanesthesia care unit.
From Practice Guidelines for Post Anesthetic Care. Anesthesiology 96:742, 2002.

Unlike Practice Standards, Practice Guidelines are not requirements. They are recommendations designed to assist the health care provider in clinical decision-making. The ASA Practice Guidelines for Post Anesthetic Care are the result of a multiple-step process that incorporates input from three groups: (1) an ASA-appointed task force consisting of private practice and academic anesthesiologists and epidemiologists, (2) PACU consultants, and (3) ASA members at large. The guidelines are based upon literature review, expert opinion, open forum commentary, and clinical feasability. They recommend the appropriate assessment, monitoring, and treatment of the major organ system functions during recovery from anesthesia and surgery (Table 85-1).[2]

Early Postoperative Physiologic Changes

Emergence from general anesthesia and surgery may be accompanied by a number of physiologic disturbances that effect multiple organ systems. Most common are postoperative nausea and

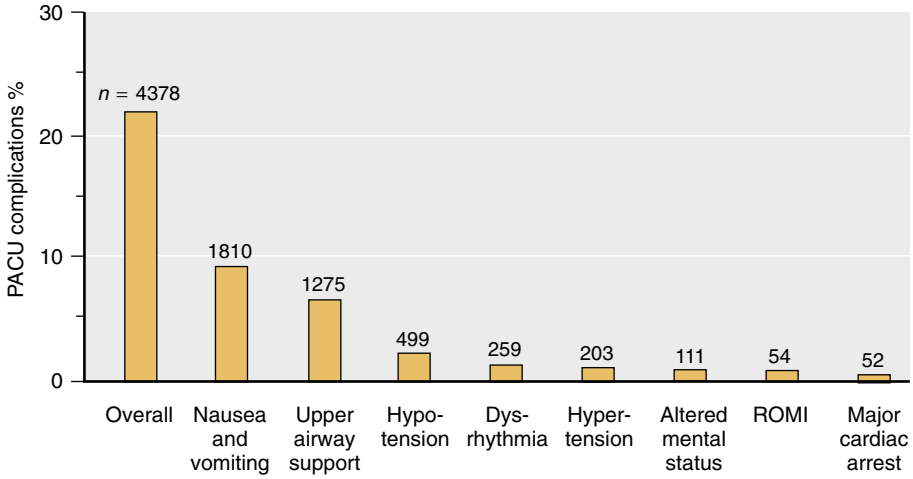

Figure 85-1 The overall complication rate in 18,473 consecutive patients entering a postanesthesia care unit (PACU) was 23.7%. Nausea and vomiting, the need for upper airway support, and hypotension were the most frequent individual complications. (*From Hines HR, Barash PG, Watrous G, et al: Complications occurring in the postanesthesia care unit: A survey. Anesth Analg 74:503-509, 1992, with permission.*)

vomiting (PONV), hypoxia, hypothermia and shivering, and cardiovascular instability. In a prospective study of more than 18,000 consecutive admissions to the PACU, the complication rate was found to be as high as 24%. Nausea and vomiting (9.8%), the need for upper airway support (6.8%), and hypotension (2.7%) were the most common (Fig. 85-1).[3]

Over a 4-year period ending in 1989, 7.1% of the 1175 anesthesia-related malpractice claims in the United States were attributed to recovery room incidents.[4] Despite the significant incidence of nausea and vomiting in the PACU, serious adverse outcomes correlate more closely with airway/respiratory and cardiovascular compromise. In 2002, airway/respiratory problems (183 [43%]) and cardiovascular events (99 [24%]) accounted for the majority of 419 recovery room incidents reported to the Australian Incident Monitoring Study (AIMS) database (Table 85-2).[5] Similar data were obtained from the U.S. closed claims database in 1989, in which critical respiratory incidents accounted for more than one half of the recovery room malpractice claims.[4]

Transport to the PACU

Upper airway patency and the effectiveness of the patient's respiratory efforts must be monitored when transporting the patient from the operating room to the PACU. Adequate ventilation can be confirmed by watching for the appropriate rise and fall of the chest wall with inspiration, listening for breath sounds, or simply feeling for exhaled breath with the palm of one's hand over the patient's nose and mouth.

With rare exception, patients who undergo general anesthesia should receive supplemental oxygen during their transport to the PACU. In an observational study of 502 patients admitted to the PACU, breathing room air during transport was the single most significant factor to correlate with hypoxemia (O_2 sat < 90%) on arrival. Other significant factors included elevated body mass index (BMI), sedation score, and respiratory rate.[6]

Although the majority of otherwise healthy patients undergoing ambulatory surgery can be transported safely breathing room air, the decision to do so must be made on a case-by-case basis. In the ambulatory setting, advanced age (>60 years) and weight (>100 kg) identifies adults who are at increased risk for oxygen desaturation when breathing room air on transport to the PACU.[7] Hypoventilation alone may cause hypoxemia even in healthy patients who undergo minor procedures.

Table 85-2 Primary Presenting Problem in 419 Recovery Room Incidents Reported to AIMS

Primary Presenting Problem	No. (%)
Cardiovascular	99 (24)
Respiratory	97 (23)
Airway	86 (21)
Drug error	44 (11)
Central nervous system	32 (8)
Equipment	27 (6)
Communication problems	7 (2)
Hypothermia	6 (1)
Regional block problems	4 (1)
Inadequate documentation	4 (1)
Hyperthermia	3 (1)
Trauma	3 (1)
Dental problems	2 (0.5)
Renal	1 (0.2)
Skin	1 (0.2)
Blood transfusion	1 (0.2)
Facility limitations	1 (0.2)
Gastrointestinal problems	1 (0.2)

From Kluger M, Bullock M: A review of the Anesthetic Incident Monitoring Study. Anesthesia 57:1060, 2002.

Upper Airway Obstruction

Loss of Pharyngeal Muscle Tone

The most frequent cause of airway obstruction in the immediate postoperative period is the loss of pharyngeal muscle tone in a sedated or obtunded patient. The persistent effects of inhaled and intravenous anesthetics, neuromuscular blocking drugs, and opioids all contribute to the loss of pharyngeal tone in the PACU patient.

In an awake patient, opening of the upper airway is facilitated by the contraction of the pharyngeal muscles at the same time that negative inspiratory pressure is generated by the diaphragm. As a result, the tongue and soft palate are pulled forward, tenting the airway open during inspiration. This pharyngeal muscle activity is depressed during sleep, and the resulting decrease in tone can promote airway obstruction. A vicious cycle then ensues wherein the collapse of compliant pharyngeal tissue during inspiration produces a reflex compensatory increase in respiratory effort and negative inspiratory pressure that promotes further airway obstruction.[8]

The effort to breathe against an obstructed airway is characterized by a paradoxical breathing pattern consisting of retraction of the sternal notch and exaggerated abdominal muscle activity. Collapse of the chest wall and protrusion of the abdomen with inspiratory effort produces a rocking motion that becomes more prominent with increasing airway obstruction. Obstruction secondary to loss of pharyngeal tone can be relieved by simply opening the airway with the "jaw thrust maneuver" or continuous positive airway pressure (CPAP) applied via a facemask (or both). Support of the airway is needed until the patient has adequately recovered from the effects of drugs administered during anesthesia. In selected patients, placement of an oral or nasal airway, laryngeal mask airway, or endotracheal tube may be required.

Table 85-3 Factors Contributing to Prolonged Nondepolarizing Neuromuscular Blockade

Drugs
Inhaled anesthetic drugs
Local anesthetics (lidocaine)
Cardiac antidysrhythmics (procainamide)
Antibiotics (polymyxins, aminoglycosides, lincosamines [clindamycin], metronidazole [Flagyl], tetracyclines)
Corticosteroids
Calcium channel blockers
Dantrolene
Metabolic and Physiologic States
Hypermagnesemia
Hypocalcemia
Hypothermia
Respiratory acidosis
Hepatic/renal failure
Myasthenia syndromes
Factors Contributing to Prolonged Depolarizing Blockade
Excessive dose of succinylcholine
Reduced plasma cholinesterase activity
Decreased levels
Extremes of age (newborn, old age)
Disease states (hepatic disease, uremia, malnutrition, plasmapheresis)
Hormonal changes
Pregnancy
Contraceptives
Glucocorticoids
Inhibited activity
Irreversible (echothiophate)
Reversible (edrophonium, neostigmine, pyridostigmine)
Genetic variant (atypical plasma cholinesterase)

Residual Neuromuscular Blockade

When evaluating upper airway obstruction in the PACU, the possibility of residual neuromuscular blockade should be considered in any patient who received neuromuscular blocking drugs during anesthesia (Table 85-3) (see Chapter 29). Residual neuromuscular blockade may not be evident on arrival in the PACU because the diaphragm recovers from neuromuscular blockade before the pharyngeal muscles do. With an endotracheal tube in place, end-tidal carbon dioxide concentrations and tidal volumes may indicate adequate ventilation while the ability to maintain a patent upper airway and clear upper airway secretions remains compromised. The stimulation associated with tracheal extubation, followed by the activity of patient transfer to the gurney and subsequent mask airway support, may keep the airway open during transport to the PACU. Only after the patient is calmly resting in the PACU does upper airway obstruction become evident. Even patients treated with intermediate- and short-acting neuromuscular blocking drugs may manifest residual paralysis in the PACU despite what was deemed clinically adequate pharmacologic reversal in the operating room.

Measurement of the train-of-four ratio is a subjective assessment that is often misleading. A decline in this ratio may not be appreciated until it reaches a value less than 0.4 to 0.5, whereas significant signs and symptoms of clinical weakness persist to a ratio of 0.7.[9] Pharyngeal function is not restored to normal until an adductor pollicis train-of-four ratio is greater than 0.90.[10]

In the anesthetized patient, 5 seconds of sustained tetanus to 100-Hz stimulation is the most reliable indicator of adequate reversal of drug-induced neuromuscular blockade.[9,11] In an awake patient, clinical assessment of reversal of neuromuscular blockade is preferred to the application of painful train-of-four or tetanic stimulation. Clinical evaluation includes grip strength, tongue protrusion, the ability to lift the legs off the bed, and the ability to lift the head off the bed for a full 5 seconds. Of these maneuvers, the 5-second sustained head lift has been considered to be the standard, reflecting not only generalized motor strength but, more importantly, the patient's ability to maintain and protect the airway. However, the ability to strongly oppose the incisor teeth against a tongue depressor is a more reliable indicator of pharyngeal muscle tone. This maneuver correlates with an average train-of-four ratio of 0.85 as opposed to 0.60 for the sustained head lift.[9]

Weakness in the PACU patient may manifest as respiratory distress and/or agitation. If one suspects the persistence or return of neuromuscular weakness in the PACU, prompt review of pos-

sible etiologic factors is indicated (see Table 85-3). Common etiologic factors include respiratory acidosis and hypothermia, alone or in combination. Upper airway obstruction as a result of the residual depressant effects of volatile anesthetics or opioids (or both) may result in progressive respiratory acidosis after the patient is admitted to the PACU and external stimulation is minimized. Simple measures such as warming the patient, airway support, and correction of electrolyte abnormalities can facilitate recovery from neuromuscular blockade. It is hoped that the use of sugammadex, instead of neostigmine, will lead to a reduced incidence of residual neuromuscular blockade.

Laryngospasm

Laryngospasm refers to a sudden spasm of the vocal cords that completely occludes the laryngeal opening. It typically occurs in the transitional period when the extubated patient is emerging from general anesthesia. Although it is most likely to occur in the operating room at the time of tracheal extubation, patients who arrive in the PACU asleep after general anesthesia are also at risk for laryngospasm on awakening.

Jaw thrust with CPAP (up to 40 cm H_2O) is often sufficient stimulation to "break" the laryngospasm. If jaw thrust and CPAP maneuvers fail, immediate skeletal muscle relaxation can be achieved with succinylcholine (0.1 to 1.0 mg/kg IV or 4 mg/kg IM). It is not acceptable to attempt to forcibly pass a tracheal tube through a glottis that is closed because of laryngospasm.

Edema or Hematoma

Airway edema is a possible operative complication in patients undergoing prolonged procedures in the prone or Trendelenburg position. It can be particularly significant in procedures that involve a large blood loss and require aggressive fluid resuscitation. Although facial and scleral edema is an important physical sign that can alert the clinician to the presence of airway edema, significant edema of pharyngeal tissue may not be accompanied by visible external signs. In addition to the generalized edema just described, surgical procedures on the tongue, pharynx, and neck, including thyroidectomy,[12,13] carotid endarterectomy,[14] and cervical spine procedures,[15] can produce more localized tissue edema or hematoma. If tracheal extubation is to be attempted in these patients in the PACU, evaluation of airway patency must precede removal of the endotracheal tube. The patient's ability to breathe around the endotracheal tube can be evaluated by suctioning the oral pharynx and deflating the endotracheal tube cuff. With occlusion of the proximal end of the endotracheal tube, the patient is then asked to breathe around the tube. Good air movement suggests that the patient's airway will remain patent after tracheal extubation.[16] An alternative method involves measuring the intrathoracic pressure required to produce a "leak" around the endotracheal tube with the cuff deflated. This method was originally used to evaluate pediatric patients with croup before extubation.[17] When used in patients with general oropharyngeal edema, the "safe" pressure threshold can be difficult to identify. Lastly, when ventilating patients in the volume control mode, one can measure the exhaled tidal volume before and after cuff deflation. Patients who require reintubation generally have a smaller leak (less percentage difference between exhaled volume before and after cuff deflation) than those who do not. A difference greater than 15.5% is the advocated cutoff value for extubation of the trachea.[18] The presence of a cuff leak demonstrates the likelihood of successful extubation, not a guarantee, just as a failed cuff leak does not rule out a successful extubation. The cuff leak test does not take the place of sound clinical judgment.

It may not be possible to mask-ventilate a patient with severe upper airway obstruction resulting from edema or hematoma. In the case of hematoma after thyroid or carotid surgery, an attempt can be made to decompress the airway by releasing the clips or sutures on the wound and evacuating the hematoma. This maneuver is recommended as a temporizing measure, but it will not effectively decompress the airway if a significant amount of fluid or blood (or both) has infiltrated the tissue planes of the pharyngeal wall. If emergency tracheal intubation is required, it is important to have ready access to difficult airway equipment and, if possible, surgical backup for performance of an emergency tracheostomy. If the patient is able to move air by spontaneous ventilation, an awake technique is preferred because visualization of the cords by direct laryngoscopy may not be possible.

Obstructive Sleep Apnea

Because most patients with obstructive sleep apnea (OSA) are not obese and a vast majority are undiagnosed at the time of surgery, obstructive sleep apnea syndrome is often an overlooked cause of airway obstruction in the PACU (see Chapter 64).[19,20]

Patients with OSA are particularly prone to airway obstruction and should not be extubated until they are fully awake and following commands.[8,21] Any redundant compliant pharyngeal tissue in these patients not only increases the incidence of airway obstruction but also often makes intubation by direct laryngoscopy difficult or impossible.[22,23] Once in the PACU, a patient with OSA whose trachea has been extubated is exquisitely sensitive to opioids and, when possible, continuous regional anesthesia techniques should be used to provide postoperative analgesia.[24,25] Interestingly, benzodiazepines can have a greater effect on pharyngeal muscle tone than opioids, and the use of benzodiazepines in the perioperative setting can contribute significantly to airway obstruction in the PACU.[8,26]

When caring for a patient with OSA, plans should be made preoperatively to provide CPAP in the immediate postoperative period. Patients should be asked to bring their CPAP machines with them on the day of surgery so that the equipment can be set up before the patient's arrival in the PACU. Patients who do not routinely use CPAP at home or who do not have their machines with them may require additional attention from the respiratory therapist to ensure proper fit of the CPAP delivery device (mask or nasal airways) and to determine the amount of positive pressure needed to prevent upper airway obstruction.[27,28]

Management of Upper Airway Obstruction

An obstructed upper airway requires immediate attention. Efforts to open the airway by noninvasive measures should be attempted

before reintubation of the trachea. Jaw thrust with CPAP (5 to 15 cm H_2O) is often enough to tent the upper airway open in patients with decreased pharyngeal muscle tone. If CPAP is not effective, an oral, nasal, or laryngeal mask airway can be inserted rapidly. After successfully opening the upper airway and ensuring adequate ventilation, the cause of the upper airway obstruction should be identified and treated. In adults the sedating effects of opioids and benzodiazepines can be reversed with persistent stimulation or small titrated doses of naloxone (0.3 to 0.5 μg/kg IV) or flumazenil (0.2 mg IV to maximum dose of 1 mg), respectively. Residual effects of neuromuscular blocking drugs can be reversed pharmacologically or by correcting contributing factors such as hypothermia.

$$P_{A}O_2 = Fi_{O_2}(PB - PH_2O) - \frac{P_{CO_2}}{RQ}$$

$$P_{aCO_2} = 40 \text{ mm Hg}$$
$$P_{AO_2} = 21(760 - 47) - \frac{40}{0.8} = 150 - 50 = 100 \text{ mm Hg}$$

$$P_{aCO_2} = 80 \text{ mm Hg}$$
$$P_{AO_2} = 21(760 - 47) - \frac{40}{0.8} = 150 - 100 = 50 \text{ mm Hg}$$

P_{AO_2} = alveolar oxygen pressure
Fi_{O_2} = fraction of inspired oxygen concentration
PB = barometric pressure
PH_2O = vapor pressure of water
RQ = respiratory quotient

Figure 85-2 Hypoventilation as a cause of arterial hypoxemia. (*From Nicholau D: Postanesthesia recovery. In Stoelting RK, Miller RD [eds]: Basics of Anesthesia, 5th ed. Philadelphia, Elsevier, 2002.*)

Differential Diagnosis of Arterial Hypoxemia in the PACU

Atelectasis and alveolar hypoventilation are the most common causes of transient postoperative arterial hypoxemia in the immediate postoperative period.[29] Clinical correlation should guide the workup of a postoperative patient who remains persistently hypoxic.[30] Review of the patient's history, operative course, and clinical signs and symptoms will direct the workup to rule in possible causes (Table 85-4).

Alveolar Hypoventilation

Review of the alveolar gas equation demonstrates that hypoventilation alone is sufficient to cause arterial hypoxemia in a patient breathing room air (see also Chapter 15) (Fig. 85-2). At sea level, a normocapnic patient breathing room air will have an alveolar oxygen pressure (P_{AO_2}) of 100 mm Hg. Thus, a healthy patient without a significant alveolar-arterial gradient will have a Pa_{O_2} near 100 mm Hg. In the same patient, an increase in Pa_{CO_2} from 40 to 80 mm Hg (alveolar hypoventilation) results in a P_{AO_2} of 50 mm Hg. Hence, even a patient with normal lungs will become hypoxic if allowed to significantly hypoventilate while breathing room air.

Normally, minute ventilation increases linearly by approximately 2 L/min for every 1-mm Hg increase in Pa_{CO_2}. In the immediate postoperative period, the residual effects of inhaled anesthetics, opioids, and sedative-hypnotics can significantly depress this ventilatory response to carbon dioxide. In addition to depressed respiratory drive, the differential diagnosis of postoperative hypoventilation includes generalized weakness due to residual neuromuscular blockade or underlying neuromuscular disease. The presence of restrictive pulmonary conditions, such as preexisting chest wall deformity, postoperative abdominal binding, or abdominal distention, can also contribute to inadequate ventilation.

Arterial hypoxemia secondary to hypercapnia can be reversed by the administration of supplemental oxygen (Fig. 85-3)[31] or by normalizing the patient's Pa_{CO_2} by external stimulation of the patient to wakefulness, pharmacologic reversal of opioid or benzodiazepine effect, or controlled mechanical ventilation of the patient's lungs.

Table 85-4 Factors Contributing to Postoperative Arterial Hypoxemia

Right-to-left intrapulmonary shunt (atelectasis)
Mismatching of ventilation to perfusion (decreased functional residual capacity)
Congestive heart failure
Pulmonary edema (fluid overload, postobstructive)
Alveolar hypoventilation (residual effects of anesthetics and/or neuromuscular blocking drugs)
Diffusion hypoxia (unlikely if receiving supplemental oxygen)
Inhalation of gastric contents (aspiration)
Pulmonary embolus
Pneumothorax
Increased oxygen consumption (shivering)
Sepsis
Transfusion-related lung injury
Adult respiratory distress syndrome
Advanced age
Obesity

Decreased P_{AO_2}

Diffusion hypoxia refers to the rapid diffusion of nitrous oxide into alveoli at the end of a nitrous oxide anesthetic. Nitrous oxide dilutes the alveolar gas and produces a transient decrease in P_{AO_2} and Pa_{CO_2}. In a patient breathing room air, the resulting decrease in P_{AO_2} can produce arterial hypoxemia while decreased Pa_{CO_2} can depress the respiratory drive. In the absence of supplemental oxygen administration, diffusion hypoxia can persist for 5 to 10 minutes after discontinuation of a nitrous oxide anesthetic; therefore, it may contribute to arterial hypoxemia in the initial moments in the PACU.

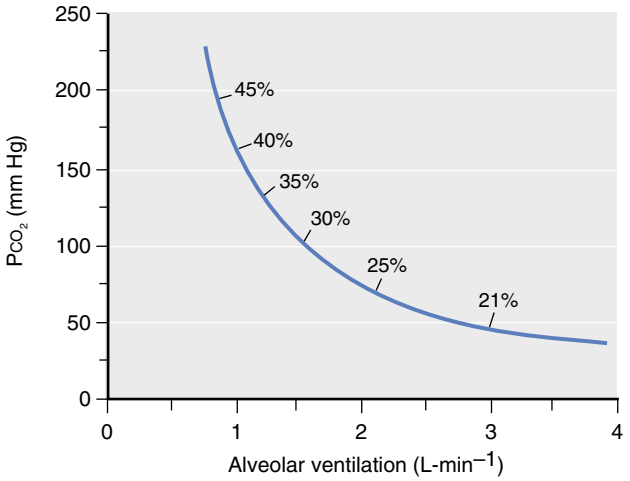

Figure 85-3 Alveolar P_{CO_2} as a function of alveolar ventilation at rest. The percentages indicate the inspired oxygen concentration required to restore alveolar P_{O_2} to normal. (*Adapted from Nunn JF: Nunn's Applied Respiratory Physiology, 6th ed. Philadelphia, Butterworth-Heinemann, 2005, with permission.*)

Ventilation-Perfusion Mismatch and Shunt

Hypoxic pulmonary vasoconstriction refers to the attempt of normal lungs to optimally match ventilation and perfusion (see also Chapters 15 and 44). This response constricts vessels in poorly ventilated regions of the lung and directs pulmonary blood flow to well-ventilated alveoli. In the PACU, the residual effects of inhaled anesthetics and vasodilators such as nitroprusside and dobutamine used to treat systemic hypertension or improve hemodynamics will blunt hypoxic pulmonary vasoconstriction and contribute to arterial hypoxemia.

Unlike a $\dot{V}/\dot{Q}$ mismatch, a true shunt will not respond to supplemental oxygen. Causes of postoperative pulmonary shunt include atelectasis, pulmonary edema, gastric aspiration, pulmonary emboli, and pneumonia. Of these, atelectasis is probably the most common cause of pulmonary shunting in the immediate postoperative period. Mobilization of the patient to the sitting position, incentive spirometry, and positive airway pressure by facemask can be effective in treating atelectasis.

Increased Venous Admixture

Increased venous admixture typically refers to low cardiac output states. It is due to the mixing of desaturated venous blood with oxygenated arterial blood. Normally, only 2% to 5% of cardiac output is shunted through the lungs, and this shunted blood with a normal mixed venous saturation has a minimal effect on P_{AO_2}. In low cardiac output states, blood returns to the heart severely desaturated. Additionally, the shunt fraction increases significantly in conditions that impede alveolar oxygenation, such as pulmonary edema and atelectasis. Under these conditions, mixing of desaturated shunted blood with saturated arterialized blood decreases P_{aO_2}.

Decreased Diffusion Capacity

A decreased diffusion capacity may reflect the presence of underlying lung disease such as emphysema, interstitial lung disease, pulmonary fibrosis, or primary pulmonary hypertension. In this regard, the differential diagnosis of arterial hypoxemia in the PACU must include the contribution of any preexisting pulmonary condition.

Finally, keep in mind that inadequate oxygen delivery may result from an unrecognized disconnection of the oxygen source or empty oxygen tank.

Pulmonary Edema

Pulmonary edema in the immediate postoperative period is often cardiogenic in nature secondary to intravascular volume overload or congestive heart failure. Less frequently, pulmonary edema may result from airway obstruction (postobstructive pulmonary edema), sepsis, or transfusion (transfusion-related lung acute lung injury [TRALI]).

Postobstructive Pulmonary Edema

Postobstructive pulmonary edema and the resulting arterial hypoxemia are rare, but significant consequences of upper airway obstruction that may follow tracheal extubation at the conclusion of anesthesia and surgery. Postobstructive pulmonary edema is a transudative edema produced by the exaggerated negative intrathoracic pressure generated by an inspiratory effort against a closed glottis. The resulting negative intrathoracic pressure and increased venous return increase the hydrostatic pressure gradient across the pulmonary vascular bed, promoting the transudation of fluid. Muscular healthy patients are at increased risk of postobstructive pulmonary edema because of their ability to generate significant inspiratory force.

Laryngospasm is likely the most common cause of postobstructive pulmonary edema in the PACU, but postobstructive pulmonary edema may result from any condition that occludes the upper airway.[32,33] The resultant arterial hypoxemia is usually manifested within 90 minutes of the upper airway obstruction and is accompanied by bilateral fluffy infiltrates on the chest radiograph. Treatment is supportive and includes supplemental oxygen, diuresis, and, in severe cases, positive-pressure ventilation of the patient's lungs.

Transfusion-Related Lung Injury

The differential diagnosis of pulmonary edema in the PACU should include transfusion-related lung injury in any patient who received blood products intraoperatively (see Chapter 55).[34,35] Transfusion-related lung injury is typically manifested within 1 to 2 hours after the transfusion of plasma-containing blood products, including packed red blood cells, whole blood, fresh frozen plasma, or platelets. Because reactions can occur up to 6 hours after transfusion, the syndrome may develop during the patient's stay in the PACU after a transfusion in the operating room. The

Table 85-5 Criteria for the Diagnosis of Transfusion-Related Acute Lung Injury: The American-European Consensus Conference Recommendations

1. Acute lung injury evidenced by:
   a. Acute onset of signs and symptoms
   b. Hypoxemia:
      i. $Pao_2/Fio_2 < 300$ or
      ii. Room air $Spo_2 < 90\%$, or
      iii. Other clinical evidence of hypoxemia
   c. Bilateral infiltrates on chest radiography without cardiomegaly
   d. No clinical evidence of left atrial hypertension
2. No preexisting acute lung injury before transfusion
3. Onset of lung dysfunction within 6 hours of transfusion
4. No temporal association of onset to alternative causes of acute lung injury

Adapted from Swanson K, Dwyre DM, Krochmal J, Raife TJ: Transfusion-related acute lung injury (TRALI): Current clinical and pathophysiologic considerations. Lung 184:177-185, 2006.

resulting noncardiogenic pulmonary edema is often associated with fever and systemic hypotension. If a complete blood cell count is obtained with the onset of symptoms, it is possible to document an acute drop in the white blood cell count (leukopenia), reflecting the sequestration of granulocytes within the lung and exudative fluid.[36,37] Treatment is supportive and includes supplemental oxygen and drug-induced diuresis. Mechanical ventilation may be needed to support hypoxemia and respiratory failure. Vasopressors may be required to treat refractory hypotension.[38]

In past years, the lack of specific diagnostic criteria has resulted in the underdiagnosis and underreporting of the syndrome. Recently, implementation of diagnostic criteria developed by the American-European Consensus Conference, a group of transfusion experts, has raised the awareness of the syndrome (Table 85-5).[39,40]

Monitoring and Treatment of Hypoxemia

Oxygen Supplementation

In the era of cost containment, it has been suggested that the routine delivery of supplemental oxygen to all patients recovering from general anesthesia is a costly and unnecessary practice.[41] The argument against the use of routine oxygen supplementation relies on the fact that continuous pulse oximetry, now a PACU standard, readily identifies those patients who will require oxygen therapy.[42] Supporting this argument is the observation that a majority of patients after general anesthesia do not become hypoxic (63% at threshold of $Sao_2 < 90\%$—and 83% at threshold of $Sao_2 < 94\%$) when breathing room air in the PACU.[42] Although the authors of this observational study predict that the elimination of routine oxygen supplementation in the PACU would result in significant cost savings, others assert that the economic benefit of limited oxygen therapy is likely to be offset by the cost of complications.[43,44]

Although the practice of prophylactic oxygen therapy to all patients after general anesthesia is controversial, most would argue that the benefits outweigh the risks. Even with oxygen supplementation, a significant percentage of patients will become hypoxic at some point during their PACU stay.[45,46] Russell and associates studied 100 patients who were transferred to the PACU breathing room air before receiving at least 40% oxygen by aerosol face tent in the unit. All patients had an Sao_2 greater than 97% before the 2-minute transport to the PACU. Fifteen percent of patients experienced transient desaturation on arrival in the PACU (<92% saturation for >30 sec). This immediate desaturation correlated positively with patient age, body weight, ASA classification, general anesthesia, and increased volume of intravenous fluid greater than 1500 mL. An even larger percentage of patients (25%) desaturated 30 to 50 minutes later in their PACU stay despite prophylactic oxygen administration. These later desaturations were more severe (71%-91%) and lasted longer (5.8 ± 12.6 min) than those that occurred on admission. Additional correlating factors included duration of anesthesia and female gender.

The safe practice of postanesthesia care without oxygen supplementation requires ideal conditions at all times, that is, functioning oxygen delivery apparatus at every bedside as well as sufficient manpower for observation and immediate intervention. Gravenstein argues that this degree of vigilance is likely unrealistic and the risk of adverse outcome to even a small number of patients is unwarranted.[47]

Limitations of Pulse Oximetry

The ASA Standards for Post Anesthesia Care require that patients be observed and monitored with "particular attention given to" both oxygenation and ventilation. The pulse oximeter is a standard monitor in the PACU for the detection of hypoxemia, but it does not reflect the adequacy of ventilation.[69] Although several studies have demonstrated oximetry's limited ability to detect hypoventilation in patients breathing room air,[70,71] they confirm that it does not reliably detect hypoventilation in patients breathing oxygen.[71] When monitoring ventilation in the PACU, pulse oximetry is not a substitute for close observation by trained personnel.

Optimal Perioperative Oxygenation

Postoperative Nausea and Vomiting

A number of studies have asked whether perioperative supplemental oxygen administration can reduce the incidence of PONV (see also Chapter 86). In the first such study, Grief and colleagues randomized 231 patients undergoing elective colon resection to receive either 30% or 80% oxygen (balanced with nitrogen). In this study, the administration of 80% supplemental oxygen intraoperatively and 2 hours postoperatively reduced the incidence of PONV nearly twofold (30% to 17%).[48] In a subsequent study of 240 patients undergoing laparoscopic gynecologic surgery, the same group found that perioperative supplemental oxygen (80%) was as effective as ondansetron (with 30% oxygen) in preventing

PONV. When compared with 30% oxygen alone, both oxygen and ondansetron decreased the incidence of PONV by 50% in the first 24 hours postoperatively (44% to 22%).[49]

Increased oxygen supplementation did not reduce the incidence of PONV in children undergoing elective dental surgery,[50] adults undergoing thyroid surgery,[51] or patients undergoing strabismus surgery.[52] In 210 patients (aged 4-79 years) undergoing strabismus surgery, the incidence of PONV was the same among three groups: those who received 30% oxygen/air (+ ondansetron on induction), 80% oxygen/air, or 30% oxygen/air. Finally, in patients undergoing laparoscopic cholecystectomy, the elimination of nitrous oxide, not increased oxygen fraction, was found to correlate with decreased PONV. In this study, increasing the oxygen concentration from 40% in air to 80% in air offered no further benefit.[53]

The mechanism by which the elimination of nitrous oxide and increased oxygen fraction may contribute to a reduction in PONV is unknown. Whereas there is evidence that perioperative oxygen administration may reduce PONV in patients undergoing colorectal procedures, the data do not support its use for surgical procedures that do not directly involve the bowel.[55] This lack of efficacy of supplemental oxygen in patients undergoing peripheral procedures argues for a local effect on the gastrointestinal tract where the elimination of nitrous oxide and nitrogen together with hyperoxia work to decrease bowel distention and reduce gastrointestinal ischemia.

Studying elderly patients transported by ambulance after minor trauma, Kober and colleagues found that hyperoxia reduced the incidence of nausea and vomiting fourfold over patients breathing air. In this double-blind study, patients were randomized to receive room air or 100% facemask O_2 delivered at 10 L/min. Here the authors propose a central mechanism for the effect of oxygen on motion sickness.[54]

Wound Infections

Supplemental oxygen appears to reduce the incidence of surgical wound infections in patients undergoing colorectal surgery. Grief and colleagues randomized 500 patients undergoing colon resection to receive either 30% or 80% oxygen (in air). In this study the higher concentration of oxygen reduced the incidence of surgical site infection by 6% (11.2% to 5.2%).[56] More recently, a randomized controlled multicenter study of 300 patients in 14 Spanish hospitals found that patients who received supplemental oxygen had a 30% reduction in surgical site infections.[57] This study compared 30% to 80% oxygen administration intraoperatively and 6 hours postoperatively. The perioperative care was standardized, and surgical site infections were identified by criteria delineated by the Centers for Disease Control.

These results were not consistent with a study of patients undergoing major intra-abdominal surgical procedures where patients who received 80% oxygen had a significantly higher infection rate (25%) than those who received 35% oxygen. It is notable that this study has been widely criticized for failure of randomization because the patients receiving 80% oxygen were more obese, underwent a longer duration of surgery, and had a larger blood loss than those receiving 35% oxygen. Unlike the Spanish study, the diagnosis of surgical site infection was made by chart review rather than standardized criteria.[58]

Nitrous Oxide

The role of nitrous oxide in the risk of wound infection remains controversial. When controlling for oxygen concentration (35%) in patients undergoing colon resection, the Outcomes Research Group found that the elimination of nitrous oxide did not decrease the incidence of surgical site infection.[59]

The largest multicenter trial to date comparing nitrous oxide–based anesthesia with nitrous oxide–free general anesthesia included 2050 patients who underwent major surgery. Exclusion criteria included cardiac and thoracic surgery. The exclusion of patients undergoing colon surgery or those who had a history of PONV was left to the discretion of the anesthesiologist. Patients were randomized to receive 30% oxygen and 70% nitrous oxide or 80% oxygen with 20% nitrogen. In this study, the elimination of nitrous oxide significantly decreased the incidence of PONV and major complications within 30 days of surgery. Major complications included pneumonia, pneumothorax, pulmonary embolism, wound infection, myocardial infarction, venous thromboembolism, stroke, and awareness. It did not decrease the length of hospital stay, the study's primary endpoint.[60] Significantly, this study did not control for inspired oxygen concentration; therefore, it is not clear whether the beneficial effects were the result of the elimination of nitrous oxide or the increase in F_{IO_2}.[61]

Oxygen Delivery Systems

Supplemental Oxygen

The choice of oxygen delivery system in the PACU is determined by the degree of hypoxemia, the surgical procedure, and patient compliance. Patients who are status post head and neck surgery may not be candidates for facemask oxygen owing to the risk of pressure necrosis on incision sites and microvascular muscle flaps, whereas nasal packing prohibits the use of nasal cannulas in others. Face tent oxygen or blow-by setups are viable alternatives in cases in which tight-fitting masks and straps are contraindicated.

The delivery of oxygen through a traditional nasal cannula with bubble humidifier is usually limited to a maximum flow of 6 L/min to minimize the discomfort and complications that result from inadequate humidification. As a general rule, each liter per minute of oxygen flow through nasal cannula increases the F_{IO_2} by 0.04, with 6 L/min delivering an F_{IO_2} of approximately 0.44. Until recently, maximum oxygen delivery to extubated patients required delivery by facemask through a nonrebreather system or high flow nebulizer. These systems can be inefficient, however, because of inadequate mask fit and/or high minute ventilation requirements that result in significant entrainment of room air. The newer high-flow nasal cannula devices can comfortably deliver oxygen at 40 L/min, 37°C, and 99.9% relative humidity.[62] The delivery of high flow oxygen directly to the nasopharynx produces an F_{IO_2} equal to that delivered by traditional mask devices. In fact, the Vapotherm system has been shown to deliver a higher F_{IO_2} than a nonrebreather mask at similar flow ranges (10-40 L/min). Unlike the nonrebreather mask, these devices

deliver high flow oxygen directly to the nasopharynx throughout the respiratory cycle. The efficacy of these devices may be enhanced by a CPAP effect resulting from the high gas flow.[63]

Continuous Positive Airway Pressure

An estimated 8% to 10% of patients who undergo abdominal surgery subsequently require intubation and mechanical ventilation in the PACU. As discussed elsewhere in this chapter, respiratory failure in the immediate postoperative period is often due to transient and rapidly reversible conditions such as splinting from pain, diaphragmatic dysfunction, muscular weakness, and pharmacologically depressed respiratory drive. Readily reversible hypoxemia may be due to hypoventilation, atelectasis, or volume overload. The application of CPAP in this setting can potentially decrease hypoxemia due to atelectasis by recruiting alveoli. The resulting increase in functional reserve capacity may also improve pulmonary compliance and decrease the work of breathing. In a recent randomized controlled trial, 209 consecutive patients undergoing major elective abdominal surgery were randomized to receive supplemental oxygen alone or in conjunction with CPAP (at 7.5 cm H_2O pressure) in the PACU. In this study, the application of CPAP in the PACU significantly reduced the incidence of intubation, pneumonia, infection, and sepsis. The study was halted due to efficacy after the enrollment of 209 patients (Table 85-6).[64]

A large percentage of obese patients undergoing Roux-en-Y gastric bypass surgery have OSA and stand to benefit significantly from postoperative CPAP therapy (see Chapter 64). Yet surgeons were initially hesitant to embrace this modality for fear that application of positive pressure to the airway would inflate the stomach and proximal intestine and result in anastomotic disruption. In a single center study of 1067 patients undergoing gastrojejunostomy bypass, 420 with diagnosed OSA, CPAP did not increase the risk of postoperative anastomotic leaks.[65]

Noninvasive Positive-Pressure Ventilation

Even with the application of CPAP in the PACU there will be a number of patients who will require additional ventilatory support. Noninvasive positive-pressure ventilation (NIPPV) (see Chapter 93) has been shown to be an effective alternative to endotracheal intubation in the ICU setting. Although the use of NIPPV in both chronic and acute respiratory failure is well established, there is a limited experience in its application in the PACU.

In the past, the use of NIPPV was avoided in the immediate postoperative period because of the potential for gastric distention, aspiration, and wound dehiscence. This is especially true in patients who have undergone esophageal or gastric surgery. The decision to use noninvasive modes of ventilation in the PACU must be guided by careful consideration of both patient and surgical factors. Relative contraindications include hemodynamic instability or life-threatening arrhythmias, altered mental status, high risk of aspiration, inability to use nasal or facial mask (head and neck procedures), and refractory hypoxemia.[66] Several case reports describe the successful application of NIPPV in lieu of endotracheal intubation in both adults and children in the PACU. In 2000, Tobias reported the successful application of NIPPV in two patients, one after gastrostomy tube placement and another after cholecystectomy.[67] A larger case series (8 patients) reported by Albala and Ferrigno did not include intra-abdominal procedures.[68] The authors of both studies agree that the successful application of NIPPV is dependent on appropriate patient selection and careful instruction.

NIPPV can be delivered by facemask using the pressure support mode of a mechanical ventilator. Alternatively, the use of a BiPap machine allows the delivery of positive pressure by either nasal cannula or facemask. An example protocol for instituting NIPPV in patients with acute respiratory failure is shown in Table 85-7.

Hemodynamic Instability

Hemodynamic compromise in the PACU patient manifests in a number of ways (systemic hypertension, hypotension, tachycardia, or bradycardia) alone or in combination. Hemodynamic instability in the PACU has a negative impact on long-term outcome. Interestingly, postoperative systemic hypertension and tachycardia are associated with an increased risk of unplanned critical care admission and a higher mortality than hypotension and bradycardia.[72]

Table 85-6 CPAP for Postoperative Hypoxemia: Secondary Outcomes

	Control (*n* = 104)	CPAP (*n* = 105)	Difference of Means (95% CI) Relative Risk (95% CI)	*P* Value*
Pneumonia, No. Patients (%)	10 (10)	2 (2)	0.19 (0.04 to 0.88)	.02
Infection, No. Patients (%)	11 (10)	3 (3)	0.27 (0.07 to 0.94)	.03
Sepsis, No. Patients (%)	9 (9)	2 (2)	0.22 (0.04 to 0.99)	.03
Anastomotic leakage, No. Patients	6	1		
Pneumonia, No. Patients	3	1		
Deaths, No. Patients (%)	3 (3)	0 (0)		.12

*All *P* values are two-tailed. Comparisons between control and CPAP by Fisher exact test for categorical variables and two-tailed *t* test for continuous variables.
CI, confidence interval; CPAP, continuous positive airway pressure.
Modified from Squadrone V, et al: Continuous positive airway pressure for treatment of postoperative hypoxemia: A randomized controlled trial. JAMA 293:589-595, 2005.

Systemic Hypertension

Patients with a history of essential hypertension are at greatest risk for significant systemic hypertension in the PACU.[73] Additional factors include pain, nausea and vomiting, hypoventilation and associated hypercapnia, emergence excitement, advanced age, urinary retention, and preexisting renal disease (Table 85-8). The surgical procedures most commonly associated with postoperative hypertension are carotid endarterectomy and intracranial operations. A significant number of patients, especially those with a known history of hypertension, will require pharmacologic blood pressure control in the PACU.

Table 85-8 Factors Leading to Postoperative Hypertension

Preoperative hypertension
Arterial hypoxemia
Hypervolemia
Emergence excitement
Shivering
Drug rebound
Increased intracranial pressure
Increased sympathetic nervous system activity
Hypercapnia
Pain
Agitation
Bowel distention
Urinary retention

Systemic Hypotension

Postoperative systemic hypotension may be characterized as (1) hypovolemic (decreased preload), (2) distributive (decreased afterload) (see Table 85-7), or (3) cardiogenic (intrinsic pump failure) (Table 85-9).

Hypovolemic (Decreased Preload)

Systemic hypotension in the PACU is often due to decreased intravascular fluid volume and preload, and as such, it responds favorably to intravenous fluid administration. Common causes of decreased intravascular fluid volume in the immediate postoperative period include ongoing third-space translocation of fluid, inadequate intraoperative fluid replacement (especially in patients who undergo major intra-abdominal procedures or preoperative bowel preparation), and loss of sympathetic nervous system tone as a result of neuraxial (spinal or epidural) blockade.

Table 85-7 Example Protocol for Instituting Noninvasive Positive-Pressure Ventilation in Patients with Acute Respiratory Failure*

1. Choose the appropriate patient based on the surgical procedure and the patient's risk of aspiration, ability to protect their airway, and ability to comply with the mask fit.
2. Position the head of the bed at ≥45-degree angle.
3. Choose the correct size mask and connect mask to ventilator.
4. Explain the modality to the patient and provide reassurance.
5. Set initial ventilatory settings (CPAP, 0 cm H_2O; pressure support, 10 cm H_2O).
6. Hold mask gently on face until patient is comfortable and synchronous with ventilation.
7. Apply wound care dressing on nasal bridge and other pressure points.
8. Secure mask with head straps.
9. Slowly increase CPAP.
10. Adjust pressure support to achieve adequate tidal volumes and maximal patient comfort.
11. In hypoxic patients, increase CPAP in increments of 2 to 3 cm H_2O until $F_{IO_2} \leq 0.6$.
12. Avoid peak mask pressures > 30 cm H_2O.
13. Set ventilator alarms and apnea backup parameters.
14. Ask the patient and nurse to call for needs (repositioning mask, pain, or discomfort) or if complications occur (respiratory difficulties, abdominal distention, nausea, vomiting).
15. Monitor with oximetry and adjust ventilator settings after blood gas results.

*Protocol at the University of Tennessee, Memphis.
CPAP, continuous positive airway pressure.
Adapted from Abou-Shala N, Meduri U: Noninvasive mechanical ventilation in patients with acute respiratory failure. Crit Care Med 24:705-715, 1996.

Ongoing bleeding should be ruled out in hypotensive patients who have undergone a surgical procedure in which significant blood loss is possible. This is true regardless of the estimated intraoperative blood loss because the measured blood loss may be inaccurate. If the patient is unstable, hemoglobin can be measured at the bedside to eliminate laboratory turnover time. It is also important to remember that tachycardia may not be a reliable indicator of hypovolemia or anemia (or both) if the patient is taking β-blockers or calcium channel blockers.

Table 85-9 Differential Diagnosis of Hypotension in the PACU

Intravascular volume depletion
Persistent fluid losses
Ongoing third spacing of fluid
Bowel preparation
Gastrointestinal losses
Surgical bleeding
Increased capillary permeability
Sepsis
Burns
Transfusion-related acute lung injury
Decreased cardiac output
Myocardial ischemia/infarction
Cardiomyopathy
Valvular disease
Pericardial disease
Cardiac tamponade
Cardiac dysrhythmias
Pulmonary embolus
Tension pneumothorax
Drug induced (β-blockers, calcium channel blockers)
Decreased vascular tone
Sepsis
Allergic reactions (anaphylactic, anaphylactoid)
Spinal shock (cord injury, iatrogenic high spinal)
Adrenal insufficiency

PACU, postanesthesia care unit.

Distributive (Decreased Afterload)

Distributive shock in the PACU may be the result of a number of physiologic derangements, including iatrogenic sympathectomy, critical illness, allergic reactions, and sepsis. Iatrogenic sympathectomy secondary to regional anesthetic techniques is an important cause of hypotension in the perioperative period. A high sympathetic block (to T4) will decrease vascular tone and block the cardioaccelerator fibers. If not treated promptly, the resulting bradycardia in the presence of severe hypotension can lead to cardiac arrest even in young healthy patients.[74] Vasopressors, including phenylephrine and ephedrine, are pharmacologic treatments of hypotension caused by residual sympathetic nervous system blockade.

Critically ill patients may rely on exaggerated sympathetic nervous system tone to maintain systemic blood pressure and heart rate. In these patients, even minimal doses of inhaled anesthetics, opioids, or sedative-hypnotics can decrease sympathetic nervous system tone and produce marked systemic hypotension.

Allergic (anaphylactic or anaphylactoid) reactions may be the cause of hypotension in the PACU. Epinephrine is the drug of choice to treat hypotension secondary to an allergic reaction. Increased serum tryptase concentrations confirm the occurrence of an allergic reaction, but this change does not differentiate anaphylactic from anaphylactoid reactions. The blood specimen for tryptase determination must be obtained within 30 to 120 minutes after the allergic reaction, but the results may not be available for several days. Neuromuscular blocking drugs are the most common cause of anaphylactic reactions in the operative setting (Table 85-10).[75,76]

If sepsis is suspected as the cause of hypotension in PACU, blood should be obtained for culture and empirical antibiotic therapy should be initiated before transfer of the patient to the ward. Urinary tract manipulation and biliary tract procedures are examples of interventions that can result in a sudden onset of severe systemic hypotension secondary to sepsis. Although fluid resuscitation is the most important immediate intervention, pressor support is often required—at least transiently. Vasopressin deficiency has been shown to contribute to vasodilation in septic shock[77] and low dose vasopressin (0.01-0.05 unit/min) improves mean arterial pressure, decreases catecholamine vasopressor requirement, and may spare renal function in severe septic shock.[78]

Table 85-10 Drugs Involved in Perioperative Anaphylaxis

Substance	Incidence of Perioperative Anaphylaxis (%)	Most Commonly Associated with Perioperative Anaphylaxis
Muscle relaxants	69.2	Succinylcholine, rocuronium, atracurium
Natural rubber latex	12.1	Latex gloves, tourniquets, Foley catheters
Antibiotics	8	Penicillin and other β-lactams
Hypnotics	3.7	Propofol, thiopental
Colloids	2.7	Dextran, gelatin
Opioids	1.4	Morphine, meperidine
Other substances	2.9	Propacetamol, aprotinin, chymopapain, protamine, bupivacaine

From Hepner DL, Castells MC: Anaphylaxis during the perioperative period. Anesth Analg 97:1381-1395, 2003.

Cardiogenic (Intrinsic Pump Failure)

Significant cardiogenic causes of postoperative hypotension include myocardial ischemia and infarction, cardiomyopathy, cardiac tamponade, and cardiac dysrhythmias. The differential diagnosis depends on the surgical procedure and patient's preoperative cardiac risk and medical condition. To determine the cause of the hypotension, central venous pressure monitoring, echocardiography, and, rarely, pulmonary artery catheter monitoring may be required.

Myocardial Ischemia: Evaluation and Treatment

Low-Risk Patients

Interpretation of changes on the electrocardiogram in the PACU is influenced by the patient's cardiac history and risk index. In low-risk patients (<45 years of age, no known cardiac disease, only one risk factor), postoperative ST-segment changes on the ECG do not usually indicate myocardial ischemia. Relatively benign causes of ST changes in these low-risk patients include anxiety, esophageal reflux, hyperventilation, and hypokalemia. In general, low-risk patients require only routine PACU observation unless associated signs and symptoms warrant further clinical evaluation. A more aggressive evaluation is indicated if the changes are accompanied by cardiac rhythm disturbances, hemodynamic instability, or both.

High-Risk Patients

In contrast to low-risk patients, ST-segment and T-wave changes on the ECG in high-risk patients can be significant even in the absence of typical signs or symptoms. In this patient population, any ST or T-wave changes that are compatible with myocardial ischemia should prompt further evaluation to rule out myocardial ischemia. Determination of serum troponin levels is indicated when myocardial ischemia or infarction is suspected in the PACU. Once blood samples for measurement of troponin are obtained and a 12-lead ECG is completed, arrangements must be made for the appropriate cardiac monitoring and cardiology follow-up.

Cardiac Monitoring

In the immediate postoperative period, myocardial ischemia is rarely accompanied by chest pain, and confirming myocardial ischemia in a PACU patient is dependent on the sensitivity of the cardiac monitoring (see Chapters 40, 41, and 42). Although a combination of leads II and V_5 will reflect 80% of the ischemic events detected on a 12-lead ECG, visual interpretation of the cardiac monitor is often inaccurate. Because of human error, the American College of Cardiology guidelines recommend that

computerized ST-segment analysis be used (if available) to monitor high-risk patients in the immediate postoperative period.[79,80] A recent small scale single-center study by Goldman and associates suggests that a postoperative 12-lead ECG obtained in the PACU may be a valuable tool to adjust risk stratification in low-risk patients older than 50 years.[81] However, at this time a routine postoperative 12-lead ECG is recommended only for patients with known or suspected coronary artery disease who have undergone high- or intermediate-risk surgery.

Cardiac Dysrhythmias

Perioperative cardiac dysrhythmias are frequently transient and multifactorial (see Table 85-8). Reversible causes of cardiac dysrhythmias in the perioperative period include hypoxemia, hypoventilation and associated hypercapnia, endogenous or exogenous catecholamines, electrolyte abnormalities, acidemia, fluid overload, anemia, and substance withdrawal.[82]

Tachycardia

Common causes of sinus tachycardia in the PACU include pain, agitation, hypoventilation with associated hypercapnia, hypovolemia, and shivering. Less common but serious causes include bleeding, cardiogenic or septic shock, pulmonary embolism, thyroid storm, and malignant hyperthermia.

Atrial Dysrhythmias

The incidence of new postoperative atrial dysrhythmias may be as high as 10% after major noncardiothoracic surgery. The incidence is even higher after cardiac and thoracic procedures when the cardiac dysrhythmia is often attributed to atrial irritation.[83] The risk of postoperative atrial fibrillation is increased by preexisting cardiac risk factors, positive fluid balance, electrolyte abnormalities, and oxygen desaturation.[84] These new-onset atrial dysrhythmias are not benign because they are associated with a longer hospital stay and increased mortality.[85]

Ventricular Dysrhythmias

Premature ventricular contractions (PVCs) and ventricular bigeminy occur commonly in the PACU. PVCs most often reflect increased sympathetic nervous system stimulation that may accompany tracheal intubation, pain, and transient hypercapnia. True ventricular tachycardia is rare and is indicative of underlying cardiac pathology. In the case of torsades de pointes, QT prolongation on the electrocardiogram may be intrinsic or drug related (amiodarone, procainamide, or droperidol).

Bradydysrhythmias

Bradycardia in the PACU is often iatrogenic. Drug-related causes include β-blocker therapy, anticholinesterase reversal of neuromuscular blockade, opioid administration, and treatment with dexmedetomidine. Procedure- and patient-related causes include bowel distention, increased intracranial or intraocular pressure, and spinal anesthesia. A high spinal block that blocks the cardioaccelerator fibers originating from T1 through T4 can produce severe bradycardia. The resulting sympathectomy, bradycardia, and possible intravascular fluid volume depletion and associated decreased venous return can produce sudden bradycardia and cardiac arrest, even in young healthy patients.

Atrial Fibrillation

Control of the ventricular response rate is the immediate goal in the treatment of new-onset atrial fibrillation. Hemodynamically unstable patients may require prompt electrical cardioversion, but most patients can be treated pharmacologically with an intravenous β-adrenergic blocker or calcium channel blocker.[87] Diltiazem is the calcium channel blocker of choice for patients in whom β-blockers are contraindicated. If hemodynamic instability is a concern, the short-acting β-blocker esmolol is an option. Rate control with these agents is often enough to chemically cardiovert the postoperative patient whose arrhythmia may be catecholamine driven. If the goal of therapy is chemical cardioversion, an amiodarone load can be initiated in the PACU with the knowledge that QT prolongation, bradycardia, and hypotension may accompany the intravenous infusion of this drug.

Treatment

The urgency of treatment of a cardiac dysrhythmia depends on the physiologic consequences of the dysrhythmia, principally hypotension or cardiac ischemia or both. Tachydysrhythmias decrease coronary perfusion time and increase myocardial oxygen consumption. Their impact depends on the patient's underlying cardiac function, and they are most harmful in patients with coronary artery disease. Bradycardia has a more deleterious effect in patients with a fixed stroke volume, such as infants and patients with restrictive pericardial disease or cardiac tamponade. For the most part, treatment relies on identifying and correcting the underlying cause (i.e., hypoxemia or electrolyte abnormalities).[86] The possible role of myocardial ischemia or the occurrence of pulmonary embolism must be considered when contemplating treatment options.

Renal Dysfunction

The differential diagnosis of postoperative renal dysfunction includes prerenal, intrarenal, and postrenal causes (Table 85-11). Frequently, the cause is multifactorial, with a preexisting renal insufficiency that is exacerbated by an intraoperative insult. In the PACU, diagnostic efforts should focus on identification and treatment of the readily reversible causes of oliguria (urine output < 0.5 mL/kg/hr). For example, urinary catheter obstruction or dislodgment is easily remedied and often overlooked (see Table 85-10). When appropriate, one should confer with the surgical team regarding the details of the surgical procedure (urologic or gynecologic) to rule out anatomic obstruction or disruption of the ureters, bladder, or urethra.

Table 85-11 Postoperative Oliguria

Prerenal
Hypovolemia (bleeding, sepsis, third-space fluid loss, inadequate volume resuscitation)
Hepatorenal syndrome
Low cardiac output
Renal vascular obstruction or disruption
Intra-abdominal hypertension
Renal
Ischemia (acute tubular necrosis)
Radiographic contrast dyes
Rhabdomyolysis
Tumor lysis
Hemolysis
Postrenal
Surgical injury to the ureters
Obstruction of the ureters with clots or stones
Mechanical (urinary catheter obstruction or malposition)

Oliguria

Intravascular Volume Depletion

The most common cause of oliguria in the immediate postoperative period is depletion of intravascular fluid volume. In this regard, a fluid challenge (500 to 1000 mL of crystalloid) is usually effective in restoring urine output. A hematocrit measurement is indicated when surgical blood loss is suspected and repeated volume boluses are required to maintain urine output. Volume resuscitation to maximize renal perfusion is particularly important to prevent ongoing ischemic injury and the development of acute tubular necrosis.

Renal perfusion may be altered by a number of perioperative events. Preoperative or intraoperative angiography can result in ischemic injury secondary to renal vasoconstriction and direct renal tubular injury. Perioperative volume depletion can exacerbate hepatorenal syndrome or acute tubular necrosis caused by sepsis. The surgical procedure itself can alter renal vascular patency decreasing renal perfusion. Finally, increased intra-abdominal pressure can impair renal perfusion.

If a fluid challenge is contraindicated or oliguria persists, assessment of intravascular fluid volume status and cardiac function is indicated to differentiate hypovolemia from sepsis and low cardiac output states. Fractional excretion of sodium can be useful in determining the adequacy of renal perfusion (assuming that diuretics have not been given), but the diagnosis of prerenal azotemia will not differentiate between hypovolemia, congestive heart failure, or hepatorenal syndrome. Further evaluation with central venous monitoring or echocardiography, or both, may facilitate the differential diagnosis.

Postoperative Urinary Retention

Postoperative urinary retention can cause bladder overdistention and permanent detrusor damage. Ultrasonography can measure bladder volume and identify urinary retention in the PACU.[88] Using this technique, Keita and associates attempted to identify high-risk patients by measuring bladder volume in 313 adult inpatients on admission to and before discharge from the PACU. They collected data on age, sex, history of urinary retention, intraoperative administration of anticholinergics, amount of intraoperative fluid administration, and intravenous use of morphine. Urinary retention was defined as bladder volume greater than 600 mL in conjunction with inability to void within 30 minutes. In this study, the incidence of postoperative urinary retention in the PACU was 16%. The most significant predictive factors were age older than 50 years, intraoperative fluid more than 750 mL, and bladder volume on entry to PACU greater than 270 mL.[89] This study argues for the use of ultrasound in high-risk patients to identify possible urinary retention.

Contrast Nephropathy

Angiography with intravascular stent placement is replacing open surgical procedures to treat carotid stenosis, aortic aneurysm, and peripheral vascular disease. As a result, contrast nephropathy will be more frequently included in the differential diagnosis of postoperative renal dysfunction. Perioperative attention to adequate hydration is indicated in any patient who has received an intravenous contrast agent. Aggressive hydration with normal saline provides the single most effective protection against contrast nephropathy. Alkalinization of the urine with sodium bicarbonate has been shown to provide additional protection.[90] If bicarbonate is used for renal protection, 154 mEq/L should be infused at a rate of 3 mL/kg/hr for 1 hour before injection of a contrast agent followed by 1 mL/kg/hr for 6 hours.[90] Mucomyst is a relatively inexpensive and easily administered medication (single oral dose before and after procedure) that may also provide protection.[91] Although a number of studies support the efficacy of Mucomyst, meta-analysis does not consistently confirm its usefulness.[92,93]

Intra-abdominal Hypertension

Intra-abdominal hypertension should be considered in any oliguric patient with a tense abdomen on examination after abdominal surgery. An intra-abdominal pressure greater than 30 cm H_2O can impede renal perfusion and lead to renal ischemia and postoperative renal dysfunction. In a prospective study of patients undergoing major abdominal surgery, intra-abdominal hypertension accounted for 40% of new-onset renal insufficiency. In this study, postoperative renal impairment was independently associated with four factors: hypotension, sepsis, older age, and increased abdominal pressure.[94] Bladder pressure should be measured in patients in whom intra-abdominal hypertension is suspected so that prompt intervention can be initiated to relieve intra-abdominal pressure and restore renal perfusion.

Rhabdomyolysis

Rhabdomyolysis may complicate the postoperative course of patients who have suffered major crush or thermal injury. The incidence is also significantly increased in morbidly obese patients who undergo bariatric surgery. It has been reported to occur in 22.7% of 66 consecutive patients undergoing laparoscopic bariatric surgery.[95-97] Risk factors include increased BMI and length of operation. Patient history and the operative course should guide your decision to measure creatine phosphokinase in the PACU.[95] Early aggressive hydration to maintain urine output is the main-

stay of treatment. Loop diuretics can be used to flush the renal tubules and avoid fluid overload.[98] The infusion of mannitol to enhance the elimination of myoglobin casts from the renal tubules and bicarbonate to protect against myoglobin toxicity is commonly practiced but may not provide further benefit. In a study of more than 2000 trauma patients with rhabdomyolysis, the infusion of bicarbonate and mannitol did not further decrease the incidence of acute renal failure.[99] There is no evidence that renal dose dopamine affords renal protection in this setting.[100]

Body Temperature and Shivering

Postoperative shivering often occurs after general and epidural anesthesia (see Chapter 48). The incidence of postoperative shivering may be as high as 65% (range, 5% to 65%) after general anesthesia and 33% after epidural anesthesia. Identified risk factors include male gender and the choice of induction agent; propofol is more commonly associated with shivering than pentothal is.[101]

Mechanism

Postoperative shivering is usually, but not always, associated with hypothermia. Although thermoregulatory mechanisms can explain shivering in the hypothermic patient, a number of different mechanisms have been proposed to explain shivering in normothermic patients. One proposed mechanism is based on the observation that the brain and spinal cord do not recover simultaneously from general anesthesia. The more rapid recovery of spinal cord function is thought to result in uninhibited spinal reflexes manifested as clonic activity. This theory is supported by the fact that doxapram, a central nervous system stimulant, is somewhat effective in abolishing postoperative shivering. Other proposed mechanisms include the action of kappa opioid, *N*-methyl-D-aspartate (NMDA), and 5-hydroxytryptamine receptors.

Treatment

Intervention includes the identification and treatment of hypothermia if present. Accurate core body temperatures can be most easily obtained at the tympanic membrane. Axillary, rectal, and nasopharyngeal temperature measurements are less accurate and may underestimate core temperature. Forced air warmers are used to actively warm the hypothermic patient. A number of opioids, ondansetron,[102] and clonidine[103] have been shown to be effective in abolishing shivering once it starts, but in adults meperidine, 0.35 to 0.4 mg/kg (12.5 to 25 mg IV), is most commonly used. The infusion of low-dose ketamine (0.5 mg/kg IV) before general[104] and regional anesthesia[105] has been shown to be an effective prophylactic measure.

Clinical Effects

In addition to significant patient discomfort, postoperative shivering increases oxygen consumption, CO_2 production, and sympathetic tone. It is associated with increased cardiac output, heart rate, systemic blood pressure, and intraocular pressure. Patients who are hypothermic on arrival in the PACU should be actively warmed to avoid these immediate complications as well as delayed consequences of hypothermia. Mild to moderate hypothermia (33°C to 35°C) inhibits platelet function, coagulation factor activity, and drug metabolism. It exacerbates postoperative bleeding, prolongs neuromuscular blockade, and may delay awakening. Whereas these immediate consequences are associated with a prolonged PACU stay,[106] long-term deleterious effects include an increased incidence of myocardial ischemia and myocardial infarction, delayed wound healing, and increased perioperative mortality.

Postoperative Nausea and Vomiting

Without prophylactic intervention, roughly one third of patients who undergo inhalational anesthesia will develop PONV (range: 10% to 80%) (see also Chapter 86).[107] The consequences of PONV include delayed discharge from the PACU, unanticipated hospital admission, increased incidence of pulmonary aspiration, and significant postoperative discomfort. The ability to identify high-risk patients for prophylactic intervention can significantly improve the quality of patient care and satisfaction in the PACU. From a patient's perspective, PONV may be more uncomfortable than postoperative pain.

Prevention and Treatment

Prophylactic measures to prevent PONV include modification of anesthetic technique and pharmacologic intervention. In a randomized controlled multicenter multifactorial trial, Apfel and associates studied the efficacy of six prophylactic interventions in high-risk patients (PONV risk > 40%).[107] Interventions were both pharmacologic and technique related. Pharmacologic intervention included droperidol, 1.25 mg; dexamethasone, 4 mg; or ondansetron, 4 mg. Anesthetic intervention included propofol in lieu of volatile anesthetic, nitrogen in lieu of nitrous oxide, or remifentanil in lieu of fentanyl. More than 4000 patients were assigned to one of 64 possible combinations. The study found that each of the three antiemetics reduced the relative risk of PONV to the same degree (26%). Together, propofol (19% decrease) and nitrogen (12% decrease) reduced the relative risk of PONV to a similar degree.

Although prophylactic measures to prevent PONV are more effective than rescue, a subset of patients will require treatment in the PACU even after appropriate prophylactic treatment. There is no convincing evidence that any of the serotonin receptor antagonists commonly prescribed at this time are more effective than any others. Table 85-12 lists the different classes of antiemetic medications commonly prescribed in the PACU. If an adequate dose of antiemetic given at the appropriate time is ineffective, simply giving more of the same class of drug in the PACU is unlikely to be of significant benefit.

Delirium

Approximately 10% of adult patients over the age of 50 who undergo elective surgery will experience some degree of post-

Table 85-12 Commonly Used Antiemetics (Adult Doses)

Anticholinergics
Scopolamine (0.3-0.65 mg IV)
Scopolamine (1.5 mg) transdermal patch to a hairless area behind the ear before surgery (remove 24 hours postoperatively)
Antihistamines
Hydroxyzine (12.5-25 mg IM)
Phenothiazines
Promethazine (12.5-25 mg IM)
Butyrophenones
Droperidol (0.625-1.25 mg IV); monitor the ECG for prolongation of the QT interval for 2-3 hours after administration; preoperative 12-lead ECG recommended
Prokinetic
Metoclopramide (10-20 mg IV; avoid if any possibility of gastrointestinal obstruction)
Serotonin Receptor Antagonists
Ondansetron (4 mg IV 30 minutes before the conclusion of surgery)
Anzemet (12.5 mg IV 15-30 minutes before the end of surgery)
Vasopressors
Ephedrine (25 mg IM with hydroxyzine, 25 mg)
Corticosteroids
Dexamethasone (4-8 mg IV with induction of anesthesia)

operative delirium within the first 5 postoperative days (see Chapters 70 and 71).[108] The incidence is much higher for certain procedures, such as repair of hip fracture (>35%)[109] and bilateral knee replacement (41%).[110] Although the majority of these are elderly patients who develop delirium within the first several postoperative days, the percentage who become delirious while they are recovering in the PACU is not well known. This is because many studies of postoperative delirium and postoperative cognitive dysfunction (POCD) do not evaluate the PACU stay.[111] The American Psychiatric Association defines *delirium* as an acute change in cognition or disturbance of consciousness that cannot be attributed to a preexisting medical condition, substance intoxication, or medication[112]; however, the risk of immediate postoperative delirium is influenced by preexisting conditions such as age, functional status, and substance abuse.

Risk Factors

Persistent postoperative delirium is generally a condition of elderly patients.[113] It is a costly complication in both human and monetary terms because it increases the length of hospital stay, pharmacy costs, and mortality. In adults, patients at risk for postoperative delirium can be identified before surgery. The most significant preoperative risk factors include (1) advancing age (>70 years), (2) preoperative cognitive impairment, (3) decreased functional status, (4) alcohol abuse, and (5) a previous history of delirium. Intraoperative factors that are predictive of postoperative delirium include surgical blood loss, hematocrit less than 30%, and the number of intraoperative blood transfusions.[108,113] In adults, intraoperative hemodynamic derangements (hypotension),[114] the administration of nitrous oxide,[115] and the anesthetic technique (general versus regional)[116] have not been shown to increase the risk of postoperative delirium or longer-term POCD.

Clinical evaluation of a delirious patient in the PACU includes a thorough evaluation of any underlying disease or metabolic derangement, such as hepatic and/or renal encephalopathy. The workup for postoperative delirium must exclude or treat iatrogenic factors, including inadequate hydration, perioperative medications, arterial hypoxemia, hypercapnia, pain, sepsis, and electrolyte abnormalities.

Management

It is useful to identify the high-risk patient before admission to the PACU.[113,117] Severely agitated patients may require restraints and/or additional personnel to control their behavior and avoid self-inflicted injury. Early identification of high-risk patients can also guide pharmacologic therapy postoperatively. Elderly patients older than 60 years who are to undergo minor surgery should be scheduled in an outpatient center whenever possible to minimize the incidence of POCD.[118]

Emergence Excitement

Persistent postoperative delirium should not be confused with emergence "excitement," a transient confusional state that is associated with emergence from general anesthesia. Emergence excitement is common in children, with more than 30% experiencing agitation or delirium at some period during their PACU stay.[119] It usually occurs within the first 10 minutes of recovery but can have onset later in children who are brought to the recovery room asleep. The peak age of emergence excitement in children is between 2 and 4 years. Unlike delirium, emergence excitement typically resolves quickly and is followed by uneventful recovery.[120]

In children, emergence excitement is most frequently associated with rapid "wake up" from inhalational anesthesia. Although it has also been reported after isoflurane[121] and, to a lesser extent, halothane[122] anesthesia, it is most often associated with the less-soluble vapors sevoflurane[123] and desflurane. Several studies suggest that the incidence of emergence excitement is more a reflection of the anesthetic agent used rather than the rapidity of emergence.[124] In studies comparing sevoflurane and propofol, propofol resulted in a much smoother awakening than sevoflurane despite rapid emergence. Furthermore, delaying emergence by a slow reduction in the inhaled concentration of sevoflurane did not reduce the incidence of emergence excitement.[125]

In addition to rapid emergence, the literature supports a number of possible etiologic factors, including intrinsic characteristics of the anesthetic, postoperative pain, type of surgery, age, preoperative anxiety, underlying temperament, and adjunct medications. Awareness of these contributors allows one to identify and treat children who are at increased risk.[120]

Simple preventative measures should be taken to treat children at risk. These include reducing preoperative anxiety, treating postoperative pain, and providing a stress-free environment for recovery. Medications that have been used to prevent and treat emergence agitation/delirium in children include midazolam,[126]

clonidine,[127-129] dexmedetomidine,[130,131] fentanyl,[132,133] ketorolac,[134] and physostigmine.[135] In children, the most common preoperative anxiolytic, midazolam, has produced conflicting data. Although midazolam is generally associated with a decrease in the incidence and duration of postoperative delirium, not all studies are in agreement. In studies in which it has not been shown to be beneficial, it is unclear whether midazolam is an independent factor or merely a reflection of other preoperative variables.[136]

The incidence of emergence excitement in adults is significantly less than in children. It is estimated to be between 3% and 4.7%.[137] One study found that significant surgical- and anesthesia-related risk factors included preoperative medication with midazolam (OR 1.9), breast surgery (OR 5.190), abdominal surgery (OR 3.206), and, to a much lesser extent, length of surgery.[137]

Delayed Awakening

Even after prolonged surgery and anesthesia, a response to stimulation in 60 to 90 minutes should occur.[138] When delayed awakening occurs, it is important to evaluate the vital signs (systemic arterial blood pressure, arterial oxygenation, ECG, body temperature) and perform a neurologic examination (patients may be hyperreflexic in the early postoperative period). Monitoring with pulse oximetry and analysis of arterial blood gases and pH can detect problems of oxygenation and ventilation. Additional blood studies may be indicated to evaluate possible electrolyte derangements and metabolic disturbances (blood glucose concentration).

Residual sedation from drugs used during anesthesia is the most frequent cause of delayed awakening in the PACU. If residual effects of opioids are a possible cause of delayed awakening, it is appropriate to administer carefully titrated intravenous doses of naloxone (20- to 40-μg increments in adults) while keeping in mind that this treatment will also antagonize opioid-induced analgesia. Physostigmine may be effective in reversing the central nervous system sedative effects of anticholinergic drugs (especially scopolamine). Flumazenil is a specific antagonist for the residual depressant effects of benzodiazepines. In the absence of pharmacologic effects to explain delayed awakening, it is important to consider other causes, such as hypothermia (especially <33°C), hypoglycemia, and increased intracranial pressure. Computed tomography may be indicated in patients in whom a central nervous system cause of delayed awakening is a consideration. A stat measurement of serum glucose is indicated if hypoglycemia is a possibility, as in patients with known insulin-dependent diabetes mellitus. Residual neuromuscular block may appear to be delayed awakening. Confirmation with peripheral nerve stimulation and sugammadex administration should correct this situation.

Discharge Criteria

Although specific PACU discharge criteria may vary, certain general principles are universally applicable (Table 85-13).[2] To summarize, a mandatory minimum stay in the PACU is not required. Patients must be observed until they are no longer at risk for ventilatory depression and their mental status is clear or has returned to baseline. Hemodynamic criteria are based on the patient's baseline hemodynamics without specific systemic blood pressure and heart rate requirements. An assessment and written documentation of the patient's peripheral nerve function on discharge from the PACU may become useful information should a new peripheral neuropathy develop in the later postoperative period.

Table 85-13 Summary of Recommendations for Discharge

1. Patients should be alert and oriented or mental status returned to baseline.
2. A minimum mandatory stay is not required.
3. Vital signs should be stable and within acceptable limits.
4. Discharge should occur after patients have met specified criteria.
5. Use of scoring systems may assist in documentation of fitness for discharge.
6. The requirement to urinate before discharge and drink and retain clear liquids should *not* be part of a routine discharge protocol although they may be appropriate for selected patients.
7. Outpatients should be discharged to a responsible adult who will accompany them home.
8. Outpatients should be provided with written instructions regarding postprocedure diet, medications, activities, and a phone number to call in case of emergency.

Adapted from Practice Guidelines for Postanesthetic Care. Anesthesiology 96:742-752, 2002.

Postanesthesia Scoring Systems

In 1970, Aldrete and Kroulik developed a postanesthesia scoring system to monitor recovery from anesthesia. The original Aldrete score assigned a number of 0, 1, or 2 to five variables: activity, respiration, circulation, consciousness, and color. A score of 9 out of 10 was considered adequate for discharge from the PACU.[139] Over the years, this system has been modified to keep up with advances in technology and anesthesia practice, including the expansion of ambulatory surgery. In 1995, pulse oximetry replaced visual assessment of oxygenation and additional assessments were added to accommodate patients undergoing ambulatory surgery (Tables 85-14 and 85-15).[140]

With the increase in number and complexity of outpatient surgeries, discharge criteria have been amended by various authors to include assessment of home readiness. The resulting PADSS, or postanesthesia discharge scoring system, continues to evolve. It was initially based on five criteria: vital signs, ambulation and mental status, pain and nausea/vomiting, surgical bleeding, and fluid intake/output. The current version has been modified to separate pain and nausea/vomiting and to eliminate the need to urinate before discharge.[141-145] In the ambulatory surgery setting, postoperative pain is the most significant cause of delayed discharge and unplanned hospital admission (see Chapter 78). In an effort to improve patient satisfaction and timely discharge, Chung and associates identified a subset of high-risk patients who are likely to benefit from intense prophylactic analgesic therapy. This study of 10,008 consecutive ambulatory surgical patients found that the incidence and intensity of postoperative pain increased with increasing BMI and duration of anesthesia. Orthopedic and urologic procedures were the most significant surgical factors.[146]

Table 85-14 Criteria for Determination of Discharge Score for Release from the Postanesthesia Care Unit

Variable Evaluated	Score
Activity	
Able to move four extremities on command	2
Able to move two extremities on command	1
Able to move no extremities on command	0
Breathing	
Able to breathe deeply and cough freely	2
Dyspnea	1
Apnea	0
Circulation	
Systemic blood pressure ≠ 20% of the preanesthetic level	2
Systemic blood pressure is 20% to 49% of the preanesthetic level	1
Systemic blood pressure ≠ 50% of the preanesthetic level	0
Consciousness	
Fully awake	2
Arousable	1
Not responding	0
Oxygen Saturation (Pulse Oximetry)	
>92% while breathing room air	2
Needs supplemental oxygen to maintain saturation >90%	1
<90% even with supplemental oxygen	0

Adapted from Aldrete JA: The post anaesthesia recovery score revisited. J Clin Anesth 7:89-91, 1995.

PACU Standards of Care require that a physician accept responsibility for the discharge of patients from the unit (Standard V).[1] This is the case even when the decision to discharge the patient is made at the bedside by the PACU nurse in accordance with hospital-sanctioned discharge criteria or scoring systems. If discharge criteria are to be used, they must first be approved by the department of anesthesia and the hospital medical staff. A responsible physician's name must be noted on the record.

Infection Control

Limitations in space,[147] staffing,[148,149] and time contribute to the transmission of infectious organisms in the PACU. The PACU is typically an open unit without physical barriers between bed stations. Nurses and respiratory therapists care for more than one patient simultaneously, and admissions to the unit are transient with a length of stay measured in hours rather than days. Complicating infection control monitoring is the fact that an infection resulting from a lapse in infection control in the PACU will not be identified by routine monitoring until days later on the surgical ward. In 1999, serial hand washing audits in a large metropolitan hospital cited the physical design of the PACU (open patient bays) as a significant barrier to improvement in hand washing compliance.[147]

With these limitations in mind, it is not surprising that the PACU has been described as the "weakest link" in the chain of care that bridges the sterile technique practiced in the operating room with infection control protocols practiced on the surgical unit. Despite awareness of the factors that increase the risk of infection in the PACU, until recently there have been no studies addressing the problem. A recent study of hand cleansing during postanesthesia care documents the poor compliance of PACU nurses with this standard infection control procedure.[150,151] In this observational study of 3143 patient care activities, the average compliance with hand cleansing was only 19.6% on patient admission to the unit and 12.5% in patients already admitted to the unit. In this study, the intensity of patient care activities was an independent predictor of noncompliance, that is, the greater the work load the less likely the nursing staff would comply with infection control measures. Additional independent factors included patients of advanced age and (>65 years) and those recovering from clean (surgical sites where the respiratory, alimentary, and urinary tracts are not entered) and clean-contaminated (surgical sites in which respiratory, alimentary, genital or urinary tracts are entered under controlled conditions without unusual contamination) surgery. As expected, compliance was best in patients with contaminated or known infected wounds.

The installation of bedside alcohol-based cleansers increases compliance of hand hygiene among heath care workers in the intensive care unit (ICU).[152-155] While no equivalent study has been done in the PACU, the unit is similar to the ICU in work load and intensity of patient care. The Centers for Disease Control

Table 85-15 Criteria for Determination of Discharge Score for Release Home to a Responsible Adult

Variable Evaluated	Score*
Vital Signs (stable and consistent with age and preanesthetic baseline)	
Systemic blood pressure and heart rate within 20% of the preanesthetic level	2
Systemic blood pressure and heart rate 20% to 40% of the preanesthetic level	1
Systemic blood pressure and heart rate >40% of the preanesthetic level	0
Activity Level	
Steady gait without dizziness or meets the preanesthetic level	2
Requires assistance	1
Unable to ambulate	0
Nausea and Vomiting	
None to minimal	2
Moderate	1
Severe (continues after repeated treatment)	0
Pain (minimal to no pain, controllable with oral analgesics)	
Yes	2
No	1
Surgical Bleeding (consistent with that expected for the surgical procedure)	
Minimal (does not require dressing change)	2
Moderate (up to two dressing changes required)	1
Severe (more than three dressing changes required)	0

*Patients achieving a score of at least 9 are acceptable for discharge.
Modified from Marshall SI, Chang F: Discharge criteria and complications after ambulatory surgery. Anesth Analg 88:508-517, 1999.

and Prevention *Guideline for Hand Hygiene in Health-Care Settings* recommends that an "alcohol based hand rub [be made] available at the entrance to the patient's room or at the bedside, in other convenient locations, and in individual pocket-sized containers to be carried by HCWs."[156] Although the convenience of appropriately placed alcohol based cleansers is expected to improve hand cleansing compliance, no followup studies in the PACU have been published.

Future Considerations

Intensive Care

In recent years, the demand for ICU beds has increased significantly within the United States and Europe. Because the PACU possesses the equipment and expertise to monitor, ventilate, and resuscitate patients recovering from general anesthesia, it has become the logical choice to provide care for critically ill patients for whom ICU beds are not available.[157] Although it is now common to care for critically ill patients in the PACU, the maintenance of quality patient care continues to challenge hospital administrators and staff.[158]

One obstacle to efficient ICU care in the PACU is the diversity of physician coverage required. Whereas the proximity of the operating room and the patient population recovering from anesthesia dictate that an anesthesiologist be the responsible physician for the majority of patients in the unit, nonsurgical ICU patients often require physician coverage by specialists who are unfamiliar with the unit and whose practices are located in distant areas of the hospital. As a result, PACU nurses must identify and contact physicians with whom they rarely interact.

Physician coverage (who will be primarily responsible for patient care—internist, anesthesiologist, or surgeon), privacy for family visitation (lack of space in a traditionally open unit), infection control (the proximity of patient beds and rapid turnover of patients), and nursing competencies (ongoing ICU training of staff) are some of the challenges facing the PACU today.[159] In a study of 400 ICU overflow patients admitted to the PACU in the United Kingdom, Ziser and colleagues identified insufficient medical and nursing coverage, inadequate communications, and visiting facilities for patient's families as the most significant problems facing the unit. The ICU patients in this study were on average 53 years of age with a mean length of stay of 12.9 hours. Seventy percent were mechanically ventilated, 77.8% required invasive monitoring, and 4.5% died in the PACU while awaiting placement in the ICU. The busiest hours of admission were 1 AM to 11 AM.[160]

In an effort to ensure the quality of patient care in the PACU, the professional societies responsible for the delivery of care in the unit have collaborated to develop standards for the care of ICU overflow patients. The "Joint Position Statement on ICU Overflow Patients" issued in 2000 is the result of this collaboration. It specifically requires that PACU staffing meet the nursing staffing ratios and competencies required in the critical care units.[161]

The Joint Position Statement reproduced here recommends that the following criteria be met:

- It must be recognized that the primary responsibility for Phase 1 PACU is to provide the optimal standard of care to the postanesthesia patient and to effectively maintain the surgery schedule.
- Appropriate staffing requirements should be met to maintain safe, competent nursing care of the postanesthesia patient as well as the ICU patient. Staffing criteria for the ICU patient should be consistent with ICU guidelines and based on individual acuity and needs.
- Phase 1 PACUs are by their nature critical care units and as such should meet the competencies required for the care of the critically ill patient. These competencies should include, but are not limited to, ventilator management, hemodynamic monitoring, and medication administration, as appropriate to their patient population.
- Management should develop and implement a comprehensive resource utilization plan with ongoing assessment that supports the staffing needs for both the PACU and ICU patients when the need for overflow admission arises.
- Management should have a multidisciplinary plan to address appropriate utilization of ICU beds. Admission and discharge criteria should be utilized to evaluate the necessity for critical care and to determine the priority of admission.

In addition to increasing the acuity of patient care in the PACU, the shortage of ICU beds has encouraged the de-escalation of care in selected patient populations. Postoperative patients who were historically admitted directly to the ICU from the operating room for intensive or specialized monitoring have had successful recovery by routine postoperative care in the PACU. Examples include postoperative craniotomy,[162] liver transplantation,[163,164] and cardiac surgery patients. The neurosurgical group at the University of Florida has shown that uncomplicated craniotomy patients can be safely cared for in the PACU at a significant savings of hospital-days and cost without increased morbidity or mortality.[162] Likewise, the trend to early extubation of liver transplant patients in the operating room has lead to the successful uncomplicated recovery of these patients in the PACU. Finally, in an effort to protect ICU bed availability and reduce the number of cardiac surgery cancellations, a group in Melbourne established a cardiac surgery recovery unit within the PACU.[165] Each of these examples requires adequate space and specialized nursing skills to be successful.

Outpatient Procedures

Finally, the PACU has responded to the economic restrictions that currently limit hospital resources by accommodating the performance of simple outpatient procedures (see Chapter 78).[166] The PACU is uniquely equipped to care for patients who are undergoing noninvasive and minimally invasive procedures such as electroconvulsive therapy,[167,168] cardioversion,[169] epidural blood patch,[166] and liver biopsy.[166] Ambulatory patients undergoing such procedures can be admitted directly to the PACU for the procedure and discharged to home after a brief recovery period. In order to do so, the PACU must be appropriately staffed and scheduled so as to not interfere with routine operating

room scheduling and postoperative recovery. Electroconvulsive therapy is somewhat unique in that it requires general anesthesia that is delivered by an anesthesia care practitioner. Typically these are short procedures that can be scheduled before the routine operating room cases. One successful electroconvulsive therapy program schedules the procedure at 5:30 AM with nurse-to-patient ratio of 2:1 and estimated PACU length of stay of 2 hours.[168]

Summary

The PACU is more than a postanesthesia observation unit. It is unique in its ability to support the care of patients of all ages and in every stage of illness. Since its inception more than 50 years ago, the PACU has proved to be an exceptionally adaptable unit that is equipped to meet the demands of an evolving health care system.

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Christian C. Apfel

86 Postoperative Nausea and Vomiting

Key Points

1. Postoperative nausea and vomiting (PONV) may be triggered by various pathways through peripheral and/or centrally located receptors; however, the exact etiology is unknown.
2. Numerous patient-, anesthesia-, and surgery-related risk factors are associated with a high incidence of PONV, but this association may not be causal. For example, the high incidence of PONV after gynecologic surgery is likely observed because the surgery is conducted in women, who are more susceptible to PONV, and not because of the surgery itself.
3. Instead of assessing a wide range of associated risk factors, a patient's risk for PONV is best predicted by a simplified risk score using independent predictors (statistically corrected for confounders).
4. In adult inpatients undergoing a general inhaled anesthesia, Apfel's simplified risk score includes female gender, nonsmoking status, history of PONV/motion sickness, and the use of postoperative intravenous opioids as the main independent predictors. When 0, 1, 2, 3, or 4 of these factors are present, the risk for PONV is about 10%, 20%, 40%, 60%, or 80%, respectively.
5. In children, a similar simplified risk score exists for postoperative vomiting (POV) with duration of surgery greater than or equal to 30 minutes, age older than or equal to 3 years, strabismus surgery, and a positive patient history of POV or POV/PONV in relatives as the main predictors.
6. Because main triggers for PONV appear to be inhaled anesthetics and opioids, strategies to avoid or reduce exposure (e.g., regional or total intravenous anesthesia) are effective means to reduce the risk for PONV.
7. A PONV prophylaxis strategy should be tailored based on a patient's baseline risk, which can be determined using a simplified risk score. Patients at greatest risk will experience the greatest absolute risk reduction from interventions (absolute risk reduction = baseline risk x relative risk reduction).
8. Effective antiemetics to reduce PONV are cyclizine, dimenhydrinate, droperidol, dexamethasone, metoclopramide, ondansetron, dolasetron, tropisetron, and granisetron. The relative risks (RR) of these antiemetics versus placebo for nausea and for vomiting vary between approximately 0.60 and 0.80.
9. Neurokinin (NK1) antagonists are similarly effective against nausea compared with other antiemetics but are considerably more effective against postoperative vomiting.
10. While the minimally effective dose for prophylaxis with ondansetron is 4 mg, the minimally effective dose for rescue treatment with ondansetron is only 1 mg. Based on this observation, it has been generalized that about a quarter of the prophylactic dose is needed for rescue treatment.
11. Patient who suffer from PONV in spite of intraoperative prophylaxis with ondansetron do not respond to rescue treatment with a second dose of ondansetron or granisetron in the postanesthesia care unit. It is therefore concluded that rescue treatment targeting an already blocked receptor is ineffective so that an antiemetic strategy using a different mechanism should be used instead.

Nausea and vomiting in the postoperative period occurs in 20% to 30% of patients[1] and together are the second most common complaints reported (pain is the most common).[2-8] After the landmark 1992 review from Watcha and White,[9] *postoperative nausea and vomiting (PONV)* became the more commonly used clinical term; and in 1999, PONV became a medical subject heading in the National Library of Medicine. The term *PONV* will be used throughout this chapter to reflect its current widespread usage to describe the composite postoperative symptoms of nausea and/or vomiting and/or retching. However, the description of these symptoms as "postoperative" should not be construed to suggest that surgery is their most important direct cause, although this is a widely held belief. Several large prospective cohort studies now suggest that the varying incidences of PONV observed after dif-

ferent types of surgeries are largely a reflection of important patient-specific and anesthesia-related risk factors rather than surgery itself.[4,5,8]

PONV can be such an unpleasant experience that patients often rate it worse than postoperative pain.[10] Patients' "willingness to pay" out of pocket for effective antiemetic treatment of PONV, as measured by well-designed studies, is $56 in the United States[11] and €65 in Europe.[12] Prevention of PONV in high-risk patients significantly improves postoperative ratings of well-being and satisfaction.[13] While the experience of PONV is generally self-limited, postoperative vomiting/retching (POV) can lead to rare but serious medical complications, such as aspiration of gastric contents, suture dehiscence, esophageal rupture, subcutaneous emphysema, or pneumothorax (the actual incidence due to PONV has not been quantified).[14,15] PONV may delay patient discharge from postanesthesia care units (PACUs) and can be the leading cause of unexpected hospital admission after ambulatory anesthesia.[16] Annual PONV-related health care costs approach several hundred million dollars in the United States alone.[17,18]

The ongoing need to improve understanding, prevention, and treatment of PONV is reflected in the literature: over 2000 randomized controlled PONV trials have been published in peer-reviewed journals, and almost 200 new studies are published each year. This is in part due to the interest of the pharmaceutical industry in developing new and more effective treatments for this condition. The purpose of this chapter is to provide an up-to-date review of PONV by a deepened methodological understanding that allows resolution of discrepancies between traditional beliefs and the best available evidence. This more current understanding and knowledge shall then enable the reader to better manage PONV in daily clinical practice.

Etiology: Pathways for Nausea and Vomiting

Nausea and vomiting may be induced through various pathways (Fig. 86-1).[19,20]

Toxic Materials in the Gastrointestinal Lumen

Ingestion of toxic substances (e.g., hypertonic saline or copper sulfate) results in the release of serotonin (5-hydroxytryptamine [5-HT]) from enterochromaffin cells in the gut wall.[21] These enterochromaffin cells hold over 90% of the body's serotonin and appear to release it under various chemical and mechanical stimuli. Serotonin may also be released indirectly via M_3-receptors, β-adrenoceptors, and H_3-receptors; conversely, the stimulation of $GABA_B$-receptors, 5-HT_4-receptors, and α_2-adrenoceptors and the presence of vasoactive intestinal polypeptide and somatostatin have been proposed to reduce the release of serotonin.[19] Serotonin is secreted in close proximity to afferent vagal nerve endings of the gut wall that travel to the dorsal brainstem via the nucleus tractus solitarius, as demonstrated in animal models in which vagotomy blocks cisplatin-induced emesis.[22] However, large amounts of serotonin released by neuroendocrine carcinoid tumors lead to flushing, diarrhea, wheezing, and abdominal cramps but typically not to nausea and vomiting. This finding suggests that serotonergic emetogenic stimuli are primarily mediated through the autonomic nervous system rather than the bloodstream. Therefore, even though renal secretion of 5-hydroxyacetic acid (a metabolite of serotonin, with a much longer half-life) is associated with PONV after abdominal surgery,[23] a causal relationship to PONV remains unclear.

Absorbed Toxins and Drugs

Absorbed toxins or drugs circulating in the blood can cause nausea and vomiting via stimulation of the chemoreceptor trigger zone (CRTZ).[24] The CRTZ is located in the area postrema, a circumventricular organ at the bottom of the fourth ventricle. Even though the CRTZ resides anatomically in the central nervous system, its uniquely permeable endothelium (i.e., lack of a blood-brain barrier) allows it to detect emetogenic substances in the bloodstream as if it were a peripheral organ.[25] Based on a series

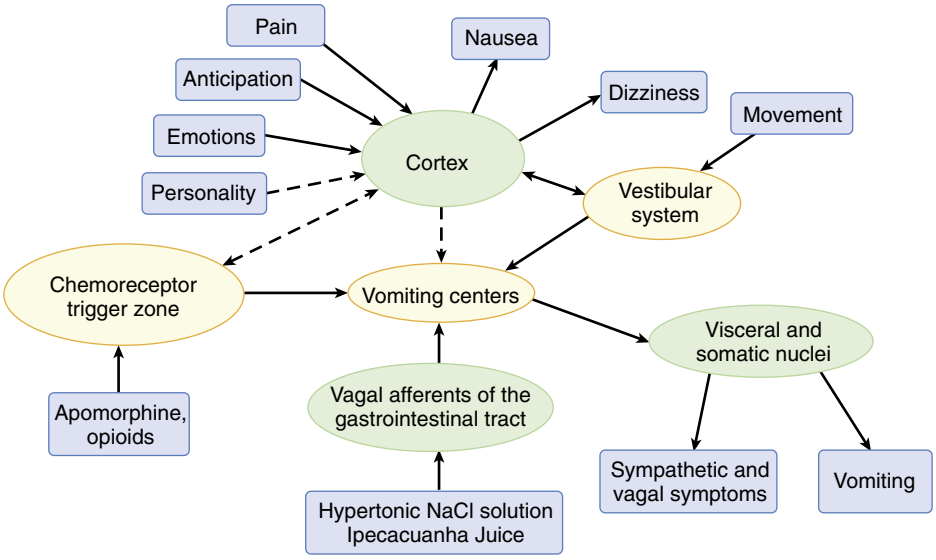


Figure 86-1 Pathways for nausea and vomiting. Dotted lines are hypothetical pathways with only indirect evidence. (*Created by Christian Apfel, MD, PhD.*)

of papers, Borison and Wang were able to demonstrate in the early 1950s that the CRTZ has an abundance of receptors and that its stimulation can send emetogenic triggers to the brainstem's vomiting center to activate the vomiting reflex (Fig. 86-2).[26-30] Although this mechanism explains how apomorphine (a fairly selective dopamine [D_2] agonist) provokes emesis, and why droperidol (a D_2 antagonist) will reverse apomorphine's emetogeneic effect, it remains unclear how the CRTZ senses or transduces emetic stimuli and why nausea and vomiting are not typical side effects of dopamine infusions. Again, it remains unclear why certain receptor agonists circulating in the blood fail to trigger nausea and vomiting while corresponding receptor antagonists prevent or reduce nausea and vomiting.

Stimulation of the Vestibular System

The vestibular system is another source of emetogenic stimuli, as observed in motion sickness or Ménière's disease.[31-33] Motion sickness is a risk factor for PONV.[2-8] Whether vestibular

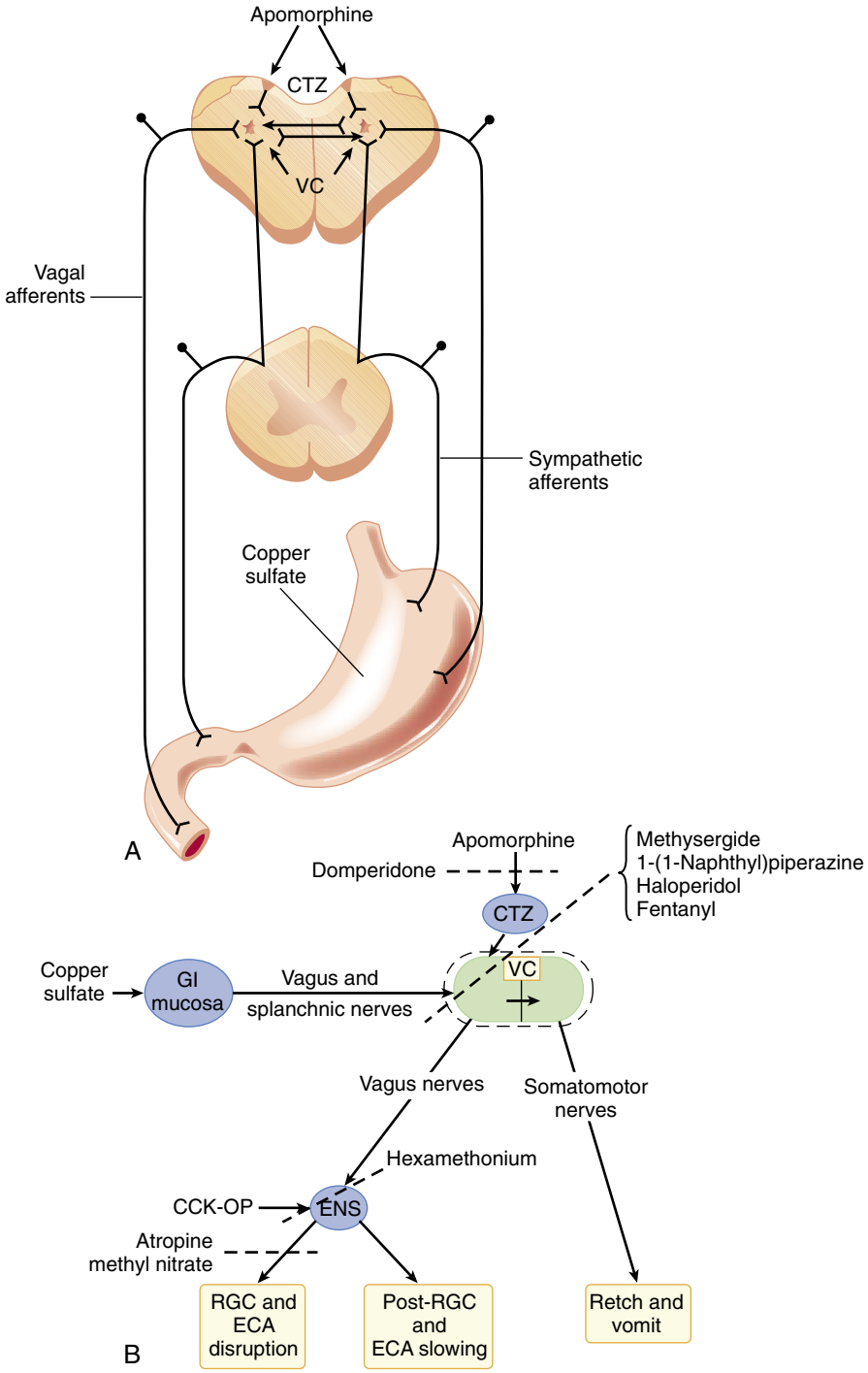


Figure 86-2 Different types of schematic representation of the organization of the emetic reflex from the original Wang and Borison (**A**) 1952 model and Lang and Marvig (**B**) in 1989, Borison and McCarthy (**C**) in 1981, and Andrews, Rapeport, and Sanger (**D**) in 1988. Note that all the models contain essentially the same key elements. GI, gastrointestinal; CTZ, chemoreceptor trigger zone; VC, vomiting center; CCK-OP, cholecystokinin octapeptide; ENS, enteric nervous system; RGC, retrograde giant contraction; ECA, electrical control activity; NTS, nucleus tractus solitarius; PCRF, parvicellular reticular formation; 5-HT, 5-hydroxytryptamine; SP, substance P.

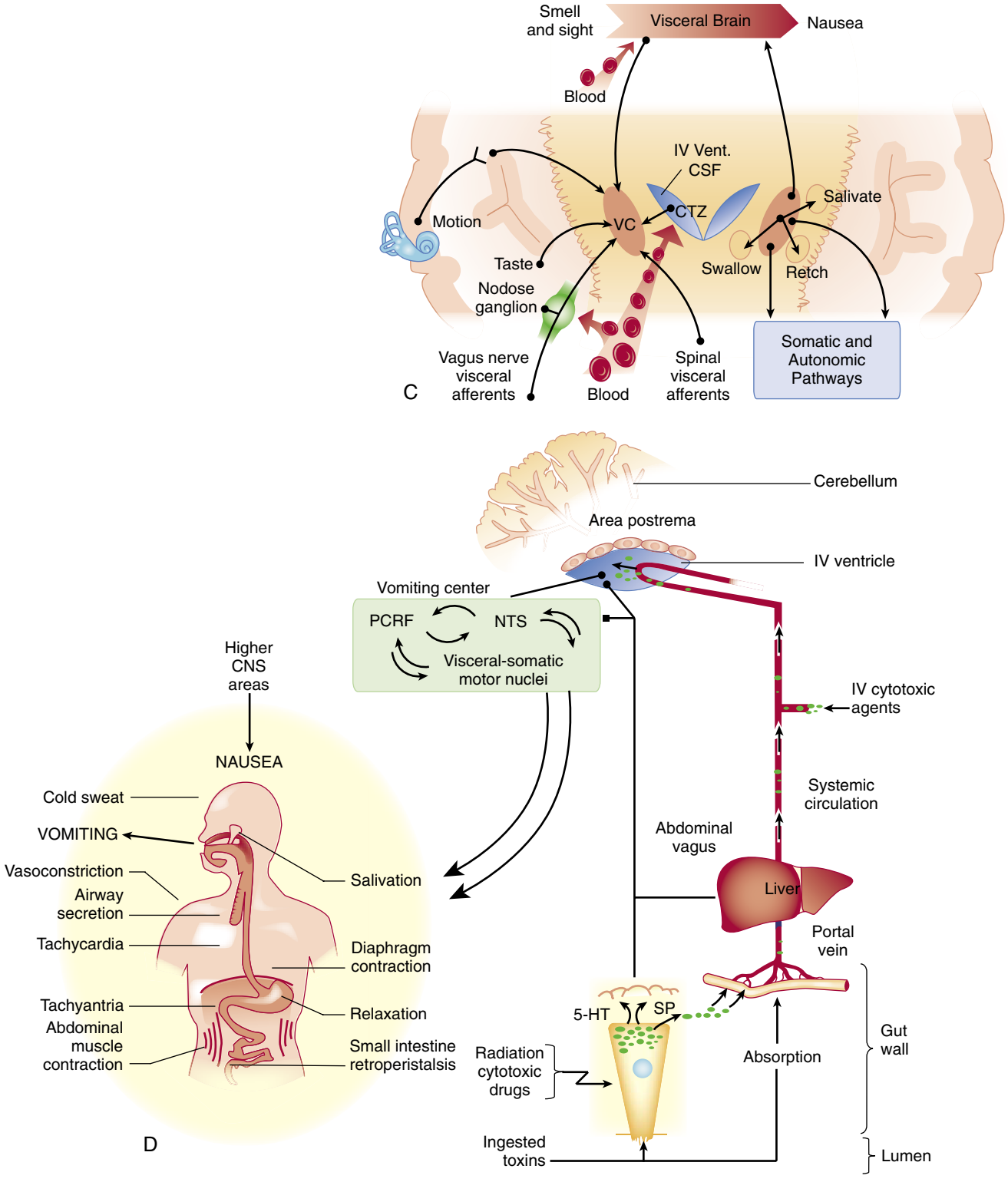


Figure 86-2, cont'd

input contributes to the emetogenic state in the vomiting center or whether anesthetics or opioid analgesics contribute to the susceptibility of the vestibular organ or signal processing is not clear.

Risk Factors and Independent Predictors

Distinguishing Association from Causality

The recognition of risk factors plays a critical role in making diagnostic and therapeutic decisions in medicine. The term *risk factor* was likely first coined in the Framingham study, where risk of heart disease was associated with specific conditions such as hypertension, high cholesterol, and smoking. To know which of the risk factors is most likely *causal* or merely *correlational* can be critical for the development of valid risk assessment tools to be used for clinical decisions. For example, women are more susceptible than men to certain emetogenic stimuli (motion, chemotherapy, inhaled anesthetics, and opioids).[34,35] If we consider that the average incidence of PONV is about 30% overall and females are about three times more likely to develop PONV,[3,5] the average incidence in male and female patients should be in the range of 15% and 45% (assuming the same number of men and women are anesthetized).[36] It is therefore not surprising that approximately one in two women undergoing gynecologic surgery suffers from PONV. From this perspective, the type of surgery can be considered a risk factor for PONV. However, establishing a policy for the routine use of antiemetics for the prevention of PONV for women having gynecologic surgery, but not other surgeries, would not acknowledge that lengthy non-gynecologic surgeries in women are associated with incidences of PONV well over 50%,[4,5] whereas short gynecologic procedures such as dilatation and curettage may be associated with PONV incidences as low as 7%.[37] Therefore, the current categories of surgeries are generally too broadly defined to be reliable predictors for PONV.[38] It is more useful to consider PONV multifactorial in its origin, that is, as a consequence of emetogenic agents (inhaled anesthetics, opioids) applied to susceptible patients (females, those with a history of motion sickness, nonsmokers). These have been shown not only to be associated with an increased incidence of PONV but also to be important independent predictors of PONV. A better prediction can be obtained by focusing on these well-established independent predictors that appear to cause PONV.[38] Therefore, the following text distinguishes between factors that are merely associated with increased risk (risk factor or associated risk factors) and factors that appear to be causally related to PONV (independent risk factors or independent predictors). Table 86-1 lists the relative importance (as delineated by the odds ratio) of independent predictors as determined in large cohort studies.

Factors That May Not Be Relevant

Many reviews or book chapters list large numbers of PONV risk factors, irrespective of the evidence or the magnitude of effect. This has contributed to a divergence between commonly held clinical beliefs about PONV risk factors and the published evidence. For example, Eberhart and colleagues reported that over 80% of German anesthesiologists considered obesity to be a risk factor for PONV.[39] Yet Kranke and coworkers found that an increased body mass index was not associated with an increased incidence of PONV.[40] Similar discrepancies exist for the influence of facemask ventilation,[41,42] use of a nasogastric or orogastric tube,[43-45] intravenous use of neostigmine to reverse neuromuscular blockade,[46,47] phase of menstrual cycle,[48] and even weather or phase of the moon.[49,50] Thus, the following discussion of risk factors for PONV will focus on these factors, which are well supported in the literature. Of course, other unknown or insufficiently studied PONV risk factors may yet be found. For example, it may be possible that rapid patient transport from the operating room to the PACU, especially fast turns or decelerations, can trigger nausea and vomiting. However, this has never been formally studied and therefore its importance cannot be determined. Accordingly, the following discussion focuses on the best available evidence.

Patient-Related Independent Predictors

Female Gender

Most prospective cohort studies using logistic regression analyses have identified female gender (in adults) as the strongest independent predictor for postoperative nausea,[3,8] vomiting,[8,51,52] use of antiemetic rescue treatment,[53] and overall PONV (see Table 86-1)[2,4-6,37,54-61] independent of anesthetic technique. Yet women have a lower threshold for motion sickness[62] and for hyperemesis gravidarum.[63] The reason for increased female susceptibility to nausea and vomiting is unclear but persists well after menopause and most of the rest of a woman's life.[64]

Not Smoking

Individuals often experience nausea and diarrhea when smoking their first cigarette.[65] This is likely an acute effect of nicotine, because nausea is a known side-effect of nicotine patches.[66] While one might predict that smokers have a higher risk of PONV than nonsmokers,[39] Cohen and associates found that nonsmokers were 1.8 times more likely than smokers to have PONV.[3] These findings were subsequently confirmed by several but not all other large-scale studies.[4-6,37,54-58] The mechanism by which a smoking habit reduces the risk of PONV is not entirely clear, but one may speculate that chronic smokers are desensitized to nausea. Nicotine stimulates indirect GABA-mediated cerebral dopamine release,[67] and nicotine withdrawal in the perioperative period may lead to low postoperative cerebral dopamine levels, reducing activation of dopaminergic circuits in the CRTZ known to be associated with nausea and vomiting (my conjecture).

History of PONV, Motion Sickness, or Migraine

Susceptibility to emetogenic stimuli varies among individuals according to history of PONV,[2,4,6,8,37,54,55,57] history of motion sickness,[2,4,6,55,57] and history of migraine.[4,8] Although one would intuitively expect that a history of PONV is the strongest predictor for subsequent PONV, it is important to realize that this is not the case. In fact, in the majority of studies, female gender is a stronger predictor than a history of PONV.

Table 86-1 Odds Ratio for Independent Predictors Shown to Be Statistically Significant in at Least Two Multivariable Analyses

	First Author and Year								
First Author and Year	**Palazzo 1993**[2]	**Cohen 1994**[3a]	**Koivuranta 1997**[4]		**Apfel 1998**[51]	**Apfel 1998**[52]	**Sinclair 1999**[37]	**Apfel 1999**[5]	**Junger 2001**[53]
Risk factors	**PONV**	**PN**	**PN**	**PV**	**PV**	**PV**	**PONV**	**PONV**	**Treat.**
Female gender	11	2.6	2.4	2.7	3.6	1.7	2.8	3.6	2.4
History of PONV,[P] motion sickness,[M] or both[B]	53[P] 2.2[M]		2.3[P] 1.7 [M]	1.9[P] 1.5 [M]	1.9[BB]	4.3[B]	3.1[P]	1.9	
Nonsmoker		1.8	2.1	1.7	2.1	(1)	1.5	2.1	1.9
Hx. of migraine			1.6	(1)					
Age (per decade)	(1)	(0.90)[c]	(1)	1.2[d]	0.75	0.88	0.87	(1)	0.95
ASA		0.66[g]	0.66[h]	0.49[i]					(1)
Body mass index (BMI)	(1)[j]	(1)	1.6	1.4	(1)	(1)			(1)
General vs. regional anesthesia		1.5	1.7	(1)			11		(1)
Inhaled vs. IV									2.5
Nitrous oxide									2.2
Opioids Intraoperative Postoperative Perioperative	 9.4	 1.3	 1.7	 (1)	 (1) (1)	 (1)		 2.1	 4.2 (1)
Duration (per hr)	(1)	1.5	2.0	2.1	1.3	(1)	2.5	(1)[n]	1.4
Surgery duration									
Ophthalmology		1.8	(1)	(1)		(0.69-0.78)[t]	5.9	(1)	(1)
ENT, head and neck surgery		(1.7)	(1)	(1)	(1)	2.7[v]	4.4	(1)	(1)
Urology									(1)
Plastic							6.6		
Neurosurgery									(1)
Gynecology/Hysterectomy		1.3	(1)	(1)		(1)	3.3	(1)	(1)
Breast surgery						(2.2)			
Abdominal surgery		(0.9)[y]	(1)	(1)		(0.89)		(1)	(1)
Cholecystectomy									
Laparoscopic surgery		2.3	(1)	(1)		0.4		(1)	(1)
Orthopedic surgery	(1)		(1)	(1)		(0.9)	2.6-5.9	(1)	(1)
Anxiety	(1)								
Additional factors	0.04[dd]	0.60[ee] 0.77[ff] 1.15[gg]			(1)[hh]	(1.62)[ii]			(1)[ii]

Numbers in parentheses are not statistically significant. Odds ratio for variables that were tested in the model but failed statistical significance and were thus not available are displayed as "(1)". The fields are left blank when variables were not investigated.
[a]From inpatients of hospital A.
[b]Data in parentheses are based on the univariate analyses.
[c]Original data: odds ratio of 0.74 for > 50 yr compared with < 50 yr. Converted by assuming difference of 30 yr.
[d]Original data: odds ratio of 1.51 for > 50 yr compared with < 50 yr. Converted by assuming difference of 20 yr.
[e]Derived from adults vs. children by assuming 40 years of difference.
[f]Original data: odds ratio of 0.57 for > 50 yr compared with < 50 yr. Converted by assuming difference of 20 yr.
[g]For ASA III+IV vs. ASA I+II.
[h]For ASA II vs. ASA I.
[i]For ASA II vs. ASA I.
[j]Weight.
[k]For BMI ≥ 25 kg/m^2.
[l]For BMI > 30 kg/m^2.
[m]For an average morphine consumption of 11.4 mg.
[n]Correlated with postoperative opioids.
[o]Converted from $1.77^{0.67}$ (to account for > 90 min vs. ≤ 90 min).
[p]Converted from –0.075 × 0.5 (assuming 2-hr difference in anesthesia time).
[q]Converted from –0.33 × 0.5 (assuming 2-hr difference in anesthesia time).
[r]Converted under the assumption that anesthesia time is about 30 longer than surgery time, $1.9^{0.67}$.

First Author and Year										
Apfel 2002[55]	**Pierre 2002**[54]	**Apfel 2002**[76]	**Stadler 2003**[8]		**Apfel 2004**[38]	**Apfel 2004**[56]	**Bosch 2005**[68,b]	**Choi 2005**[194]	**Wallenborn 2006**[117]	**Wallenborn 2007**[58]
PONV	**PONV**	**PONV**	**PN**	**PV**	**PONV**	**PONV**	**PONV**	**PONV**	**PONV 0-12 hr**	**PONV**
2.9	2.44	1.48	2.7	3.78	2.73	3.13	1.58	2.9	2.3	2.51
1.7,[P] 1.7,[M] 1.8[B]	4.46[P]	2.02[B]	(1.75)[P]	(1.95)[P]	1.79[P]	1.70[B]	2.13[B]	2.4	2.0	2.05[B]
1.8	(1.6)	2.29	2.4	3.00	1.76	1.57	1.88	2.0	2.2	1.95
			(2.2)	(1.3)						
(0.96)	0.81	0.84[e]	(0.86)	(0.90)			0.80		0.74[f]	
							(0.89), (0.63)			
(0.8)			(1.0)	(0.94)				0.85[k]	(1.07)[l]	(1.02)
			2.5	3.67					(1.2)-5.9	
		3.1				1.45	2.05	1.96		
						1.23				
(1.9) 1.3 (1.9)	4.8	(1.47) 2.32	1.15[m]	1.23[m]	1.50[P]	2.14[P]	(1.01) (1.07)	1.28	1.31[p]	(0.97)[P]
1.4	(0.98)	1.46[o]	(0.96)p[q]	(0.84)[q]		1.20	(1.82)	1.5[r]		6.33[s]
(1.4)		1.78[u]	(9.5)	(2.14)	(1.45)		(1)			
(1.0-1.6)	(0.51)	(1.04-1.22)	(5.0)	(1.77)	(1.60)	(1.08) (1.22)[v]	1.84[w]		1.38, 2.00[v]	
			8.08	6.17						
	(0.38)		(2.94)	(1.70)						
			(4.8)	(0.99)						
(1.1)	(0.39)		9.30	(0.84)	(1.8)	(0.91) 1.78[x]			1.77[x]	
						(0.74)				
(1.2)			5.8	(1.21)	2.0	(1.04)[z]	(1)		0.89[z]	
2.9[aa]					3.2	1.49			1.45	
(1.6)								1.33		
(0.93-1.4)			(2.7)	(0.98)	(1.3)	(0.91)			(0.85-1.28)	
(1.3)	(1.4)[bb]						1.01[cc]			
						1.97[jj]			0.30[kk]	

[s]Additional anesthesia time minus duration of surgery.
[t]Cataract and strabismus surgery in adults.
[u]Strabismus surgery, also in children.
[v]Thyroidectomy.
[w]Together with lower abdominal surgery.
[x]Hysterectomy.
[y]Digestive surgery.
[z]Hernia repairs.
[aa]Laparoscopic cholecystectomies.
[bb]No use of midazolam.
[cc]Stait-trait anxiety inventory (only the state component was significant).
[dd]Gender X history of PONV.
[ee]For emergency compared with elective surgery.
[ff]For one preoperative comorbid condition,
[gg]With resident.
[hh]Ease of facemask ventilation.
[ii]Vascular surgery.
[jj]Droperidol and male interaction (this cancelled out the antiemetic effect of droperidol in males).
[kk]More than 14 alcoholic drinks per week.

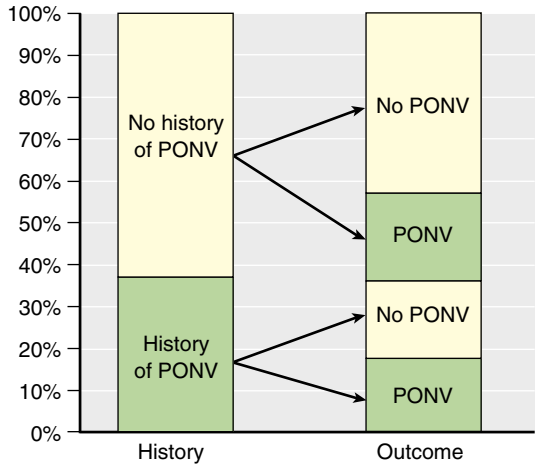


Figure 86-3 Limited sensitivity of a single predictor to identify patients at risk for PONV, with history of PONV as an example. (*From Apfel CC, Kranke P, Eberhart LH: Comparison of surgical site and patient's history with a simplified risk score for the prediction of postoperative nausea and vomiting. Anaesthesia 59:1078-1082, 2004.*)

This is illustrated by a study of 1566 patients (Fig. 86-3).[38] About a third of patients (569) presented with a history of PONV, of whom every second patient (280) experienced PONV. Two thirds of patients (997) did not have a history of PONV, of whom one third (320) experienced PONV. Clearly, patients with a history of PONV were at higher risk for experiencing PONV. However, of the total 600 patients who developed PONV, fewer than half (280 of 600) would have been correctly identified if the history of PONV had been used as a single predictor. Indeed, the use of PONV history as a single predictor has been associated with a sensitivity of less than 50% to identify patients at risk for PONV, that is, fewer than half the patients who develop PONV were correctly identified in advance (which is less than one would expect from a random guess).[38]

Age

In adults, although the incidence of PONV decreases with age, it has not always been a strong risk factor.[3,37,51-54,57,64,68] In children, however, Eberhart and coworkers have shown that an age of 3 years or older is associated with an increased risk for PONV.[69]

Anxiety

Anxiety may influence PONV, although this was not supported in a study with a small cohort of children.[70] However, in secondary analyses of the considerably larger AIDA trial in adults conducted by the group around Kalkman,[7] anxiety was assessed using two standardized psychometric instruments and a statistically significant but fairly weak association was demonstrated.[68] Although anxiety increases PONV, a preoperative assessment of anxiety is unlikely to result in a significant improvement in prediction for PONV.

Anesthesia-Related Independent Predictors

Preoperative Opioids

Only few studies compared different opioids given in conjunction of premedication. Eger and colleagues found no difference between morphine and meperidine.[71] Of note, in the same study, the $GABA_A$-enhancing drug pentobarbital was associated with a less frequent incidence of PONV compared with placebo.

Intraoperative Opioids

No large prospective cohort study has demonstrated that type or dose of intraoperative opioid influences PONV in adults. In children, the liberal intraoperative use of morphine (analgesic ED_{50} 0.18 mg/kg) is associated with a frequent incidence of POV in children undergoing tonsillectomies (see Chapter 82).[72]

Whether the type of intraoperative opioid used is a relevant consideration remains controversial. One recent paper has suggested that alfentanil is associated with less PONV compared with fentanyl or sufentanil.[73] Another group hypothesized that the ultra-short half-life of remifentanil would result in less carryover effect into the postoperative period and thereby decrease PONV. However, there was no significant difference in the overall incidence of PONV when remifentanil was compared with fentanyl, probably because the study design included predominantly larger operations requiring significant amount of opioids for postoperative pain relief, masking any potential benefit.[47] Finally, morphine-6-glucuronide, an active metabolite of morphine, has been reported to be associated with less PONV compared with morphine,[74] although it was not statistically significant in another study.[75] In conclusion, regardless of whether opioids are used intraoperatively or postoperatively, the available evidence suggests that the dose of opioid, rather than type, is one of the main predictors (or causes) for PONV.

Postoperative Opioids

Most large studies using multivariable analyses demonstrate that use of postoperative opioids doubles the risk for PONV.[2,4,5,38,54,56,76] The dose of postoperative opioid appears to be important[77] but not the type (e.g., morphine versus piritramide).[78] As a consequence, opioid-sparing strategies should reduce the incidence of PONV. Indeed, PONV tended to be decreased when cyclooxygenase-2–selective nonsteroidal anti-inflammatory drugs (NSAIDs) reduced opioid use by 20% to 40%. However, regional anesthesia definitely reduces the incidence of PONV (see also Chapters 51 and 52).[79]

Propofol and Inhaled Anesthetics

Propofol is widely believed to have antiemetic properties. By using propofol in patient-controlled analgesia (PCA) pumps in the PACU as "patient-controlled antiemesis," Gan and associates found that "non-sedating" plasma concentrations of 343 ng/mL reduced nausea in 50% of cases.[80,81] However, using a similar design, Scuderi and colleagues were unable to demonstrate any antiemetic effect of propofol.[82] In another study, healthy volunteers were randomized to propofol, midazolam, or placebo and then exposed to an infusion of apomorphine.[83] At nonsedative doses, neither propofol nor midazolam provided protection. However, at sedative doses, both propofol and midazolam increased the threshold for nausea. As a result, the antiemetic activity of propofol-induced sedation is not clear.

Compared with a purely regional anesthetic technique, general anesthesia is associated with a significantly higher incidence of PONV.[37] This raises the question of the individual contribution of the drugs used for the general anesthetic, namely, opioids, inhaled anesthetics, and nitrous oxide. Although previous meta-analyses have demonstrated a lower incidence of nausea

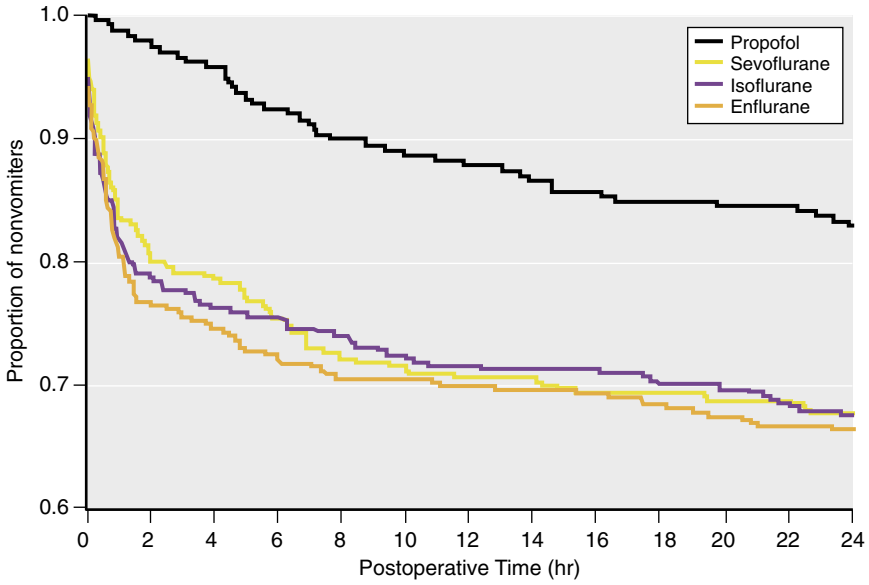


Figure 86-4 Kaplan-Meier chart for postoperative vomiting after isoflurane, enflurane, sevoflurane, and propofol. (*From Apfel CC, Kranke P, Katz MH, et al: Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: A randomized controlled trial of factorial design. Br J Anaesth 88:659-668, 2002.*)

and vomiting with propofol compared with inhaled anesthetics,[84,85] in volunteer studies an 8-hour anesthetic with sevoflurane was associated with nausea and vomiting in over 80%, strongly suggesting the emetogenicity of volatile anesthetics.[86] In addition, a large clinical single center study with patients demonstrated that (1) the difference in vomiting between inhaled anesthetics and propofol occurs predominantly in the first 2 to 6 hours postoperatively (Fig. 86-4) and, more importantly, (2) the difference in early vomiting is clearly dose related (Fig. 86-5) so that the difference is not due to propofol but rather related to the dose-dependent emetogenic effect of the volatile anesthetics.[76] There are no differences in PONV among the volatile anesthetics isoflurane, enflurane, and sevoflurane. This finding is consistent with a meta-analysis by Gupta and coworkers (comparing propofol, isoflurane, sevoflurane, and desflurane),[87] a meta-analysis by Macario and associates (comparing sevoflurane with desflurane),[88] and a very recent study by Wallenborn and colleagues (comparing isoflurane, sevoflurane, and desflurane).[58]

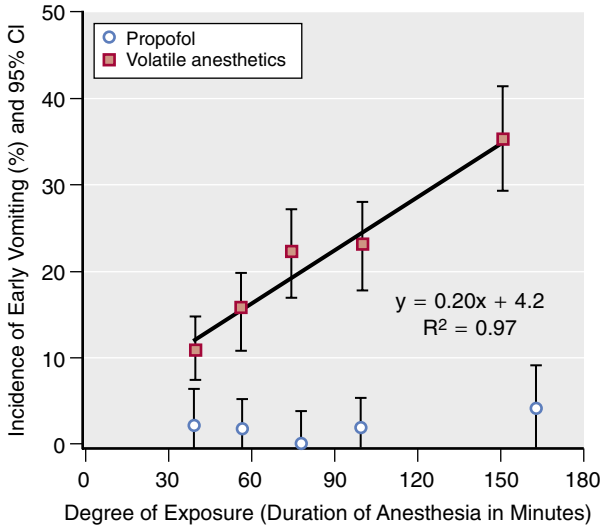


Figure 86-5 Incidence of early vomiting (0-2 hr) after maintenance with volatile anesthetics or propofol. (*From Apfel CC, Kranke P, Katz MH, et al: Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: A randomized controlled trial of factorial design. Br J Anaesth 88:659-668, 2002.*)

Nitrous Oxide

Numerous studies in the 1980s and meta-analyses in the 1990s emphasized the emetogenic effect of nitrous oxide.[89,90] However, the emetogenic effect of nitrous oxide may not be quite as strong as that associated with volatile anesthetics.[56] Moreover, the emetogenic effects of nitrous oxide and volatile anesthetics are independent, that is, they are additive.[56] What is probably more notable than the emetogenic effect of nitrous oxide is the recent landmark trial from the Australian group led by Paul Myles comparing a nitrous oxide group (70% N_2O, 30% O_2) with an oxygen-enriched air group (80% O_2, 20% N_2) that found not only more PONV but also significantly more severe adverse events (pulmonary complications, wound infections, and fever) in the nitrous oxide group.[91] A second large multicenter study comparing a nitrous oxide group (70% N_2O, 30% O_2) and nitrous oxide–free group (70% N_2, 30% O_2) is attempting to provide further evidence regarding nitrous oxide and the association with more severe medical complications.

Duration of Anesthesia

The effect of duration of anesthesia on PONV is described in a number of studies.[4,37,55,56,58,76] The magnitude of this time-dependent dose response varies widely as reflected in odds ratios per hour ranging from 1.15[56] to 2.53.[37] As referenced earlier, the effect size may be large when inhaled anesthetics are used and small when propofol is used (see Fig. 86-5) and depend on the amount of opioids used.[56] In any event, it is generally correct to assume longer and more invasive surgeries to be associated with more PONV. In fact, in a cross validation that developed a simplified risk score, there was a co-linearity between the duration of anesthesia and the postoperative intravenous use of opioids. Because intravenous opioid use was the slightly stronger predictor, that variable remained an independent predictor as opposed to duration of anesthesia.[5]

Surgery-Related Independent Predictors

Many surgeries are associated with a high incidence of PONV.[9] This has led to many hypothesized causal mechanisms for various types of surgeries—tympanoplasty and vestibular stimulation, adenotonsillectomy and swallowed blood, breast surgery and emotional load, laparoscopic surgery and peritoneal irritation, abdominal surgery and serotonin release, and hysterectomy and vagal stimulation[92-94]—all resulting in a tendency to narrowly specify the type of surgery in antiemetic trials. There is no question that patients undergoing large abdominal and gynecologic surgeries have increased risk for PONV, with incidences of at least 50%. However, in many instances, these incidences may often be a reflection of other underlying factors, in this example most likely prolonged exposure to emetogenic volatile anesthetics and/or large doses of intraoperative opioids. In fact, if volunteers are exposed to volatile anesthetics (without any surgery) for an extended period of time, almost all experience nausea or vomiting afterward.[86] Therefore, risk assessment should be based on the underlying independent predictors rather than the type of surgery. In addition, several studies support the notion that the type of surgery is not an independent predictor for postoperative nausea,[4] vomiting,[4,8,51] PONV,[5,54] or need for rescue treatment (see Table 86-1).[53] However, there are other studies that have identified several types of surgery as independent predictors for postoperative nausea,[3,8] vomiting,[52] or PONV.[37,55,56,68] Nevertheless, most types of surgery have not consistently been shown to be independent predictors for PONV in the majority of studies; possible exceptions to this rule are laparoscopic cholecystectomy and hysterectomy.[3,56] Of note, although strabismus surgery is not a risk factor in adults,[95] it is a well-established and clinically relevant independent predictor for POV in children.[69,96]

One might argue that it would be enough to know which types of surgeries are risk factors, whether or not they are independent predictors of PONV, to decide on the need for prophylactic antiemetics. The incidence of PONV in many so-called emetogenic procedures (laparoscopy, adult strabismus surgery, middle ear surgery, herniorrhaphy, tonsillectomy, adenoidectomy, and uvulopalatopharyngoplasty) is not much higher than for other types of surgery. In fact, when Scuderi and colleagues stratified patients according to "emetogenic procedures," the incidence of PONV in the PACU was 37% (80/215) compared with 31% (112/360) for all other surgeries, which is not significantly different.[97] These findings are also consistent with a study in which the PONV incidence over 24 hours was 42% (283/681) for "emetogenic procedures" and 36% (317/885) for other procedures.[38] In conclusion, although certain types of surgeries are associated with a more frequent incidence of PONV, causality has not been clearly established. With the exception of strabismus surgery in children, the incidence of PONV with most surgeries likely reflects underlying patient- and anesthesia-related factors.

Risk Assessment

PONV is multifactorial. Therefore, a patient's risk can better be estimated by accounting for several independent predictors simultaneously.

Palazzo and Evans in the United Kingdom were the first who applied multiple logistic regression analysis to 148 patients undergoing minor orthopedic procedures, thus developing a predictive model for "postoperative sickness."[2] One year later, logistic regression analysis was applied to data from a Canadian four-center survey of 16,000 inpatients.[3] Of note, the binary logistic regression analysis is a multivariable statistical method that quantifies the relative impact of *independent* predictors (e.g., female gender, nonsmoking) of a dichotomous outcome (here PONV) by determining their coefficients according to

$$p = 1/(1+e^{-z})$$

with $z = \alpha \bullet x_1 + \beta \bullet x_2 + \gamma \bullet x_3 + \ldots + \omega$, and α, β, γ, etc., being the coefficients for the factors x_1, x_2, x_3, etc. These coefficients are directly related to the odds ratio of a predictor through the formula odds ratio$_{(a)} = e^a$, a measure that is similar to the previously mentioned relative risk or risk ratio.

This is important to realize when comparing papers that report the coefficients with those that report the odds ratio.[8] Table 86-1 thus displays the odds ratios that quantify the impact as independent predictors and not only as risk factors for PONV.

Subsequently, two groups independently started to conduct large surveys and to apply logistic regression analyses to develop more generalizable predictive models.[4,51,52] Koivuranta and colleagues were the first to publish predictive models for PONV based on logistic regression analyses and developed a simplified model by selecting the five strongest predictors: female gender, previous PONV, duration of operation over 60 minutes, history of motion sickness, and nonsmoking.[4] When 0, 1, 2, 3, 4, or 5 of these independent predictors were present, the risk for PONV was 17%, 18%, 42%, 54%, 74%, and 87%. One year later, a predictive model for POV in patients undergoing ENT surgery was published that showed a tight correlation between predicted and observed incidence in a validation cohort (Fig. 86-6).[51] Because the latter model was developed in patients undergoing ENT surgery its applicability for other type of surgeries was unclear. In a subsequent study that included a wide range of surgeries, type of surgery turned out to be an *independent* predictor (at the

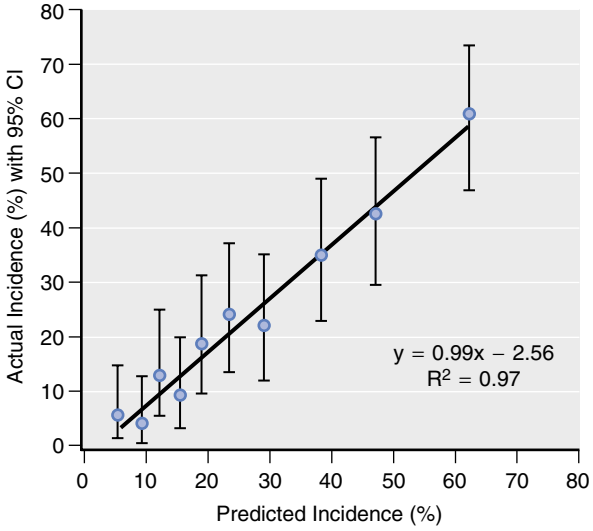


Figure 86-6 Correlation between average predicted and actual incidence of postoperative vomiting in 10 percentile groups. (*From Apfel CC, Greim CA, Haubitz I, et al: The discriminating power of a risk score for postoperative vomiting in adults undergoing various types of surgery. Acta Anaesthesiol Scand 42:502-509, 1998.*)

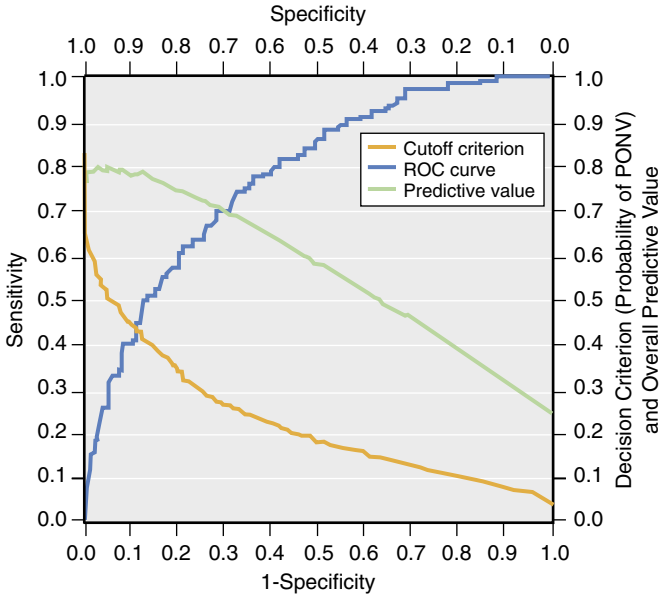


Figure 86-7 Receiver operating characteristic (ROC) curve characterizing the relationship between sensitivity and specificity. (*From Apfel CC, Greim CA, Haubitz I, et al: The discriminating power of a risk score for postoperative vomiting in adults undergoing various types of surgery. Acta Anaesthesiol Scand 42:502-509, 1998.*)

expense of duration of anesthesia) but the discriminating power as described by the area under the receiver operating characteristic (ROC) curve was at least as good using the prior risk score (independent of surgery type). Notably, the area under the ROC curve (ROC-AUC) was 0.77 (Fig. 86-7), meaning that on average the prediction was correct in about three fourths of cases.[52] The two groups then performed a cross-validation and found that risk scores derived from one center were able to predict PONV from the other center (ROC-AUC = 0.65 to 0.75) and that simplification of the score did not weaken the discriminating power (ROC-AUC = 0.63 to 0.73).[5] The final score consisted of four predictors: female gender, history of motion sickness or PONV, nonsmoking, and the use of postoperative opioids; if none, one, two, three, or four of these risk factors were present, the incidences of PONV were 10%, 21%, 39%, 61%, and 79% (Fig. 86-8).[5] While this score was developed for the prediction of PONV over 24 hours in inpatients, Chung's group developed a fairly complex predictive model for PONV in outpatients.[37] That score included type of surgery as a predictor, but it appeared to be inferior to the simplified risk scores[54,55]; however, this may have occurred, in part, because the validations were performed in inpatients. A recent validation from the Kalkman group in the Netherlands found that the predictive characteristics of the simplified risk scores were rather limited, with ROC-AUCs of only 0.63 to 0.66.[57] In their patient population, however, use of postoperative opioids—invariably shown to affect the risk for PONV in previous studies and a key independent predictor in the simplified risk models—was not associated with an increased incidence of PONV, likely accounting for the limited predictive power.

These models have been developed for prediction in adults and are not applicable for pediatric patients.[98] However, the risk for POV can be predicted with a simplified risk score in children by Eberhart and colleagues taking the following four variables into consideration: duration of surgery greater than or equal to 30 minutes, age older than or equal to 3 years, strabismus surgery, and a personal history of POV or PONV in immediate relatives.[69] The presence of 0, 1, 2, 3, and 4 risk factors was associated with a POV incidence of 9%, 10%, 30%, 55%, and 70% (and an ROC-AUC of 0.72) (see also Chapter 82).[69]

Prophylactic Antiemetic Strategies

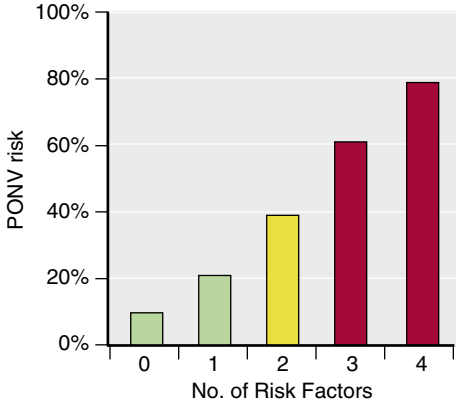
Methodological Background

Measurement of Nausea and Vomiting/Retching

Understanding the various definitions and methodologies used in publications is critical for interpretation of results. For instance, even though the occurrences of nausea and vomiting are correlated, they can occur independently and should therefore be assessed and reported separately so that results can be compared across publications. This is true for both inhaled and intravenous anesthesia in both inpatient and outpatient procedures (Fig. 86-9).[7] Failure to realize this essential point has resulted in difficulties in assessing results for a significant portion of the available literature. Similar difficulties have arisen from the use of various scales that are generally inadequate to properly assess PONV. For example, assessing PONV on a 4-point severity scale ranging from "*no symptoms, mild nausea, severe nausea or up to two*

Risk factors	Points
Female gender	1
Nonsmoker	1
History of PONV	1
Postoperative opioids	1
Risk score =	0...4

Figure 86-8 The simplified risk score for adults. (*From Apfel CC, Laara E, Koivuranta M, et al: A simplified risk score for predicting postoperative nausea and vomiting: Conclusions from cross-validations between two centers. Anesthesiology 91:693-700, 1999.*)



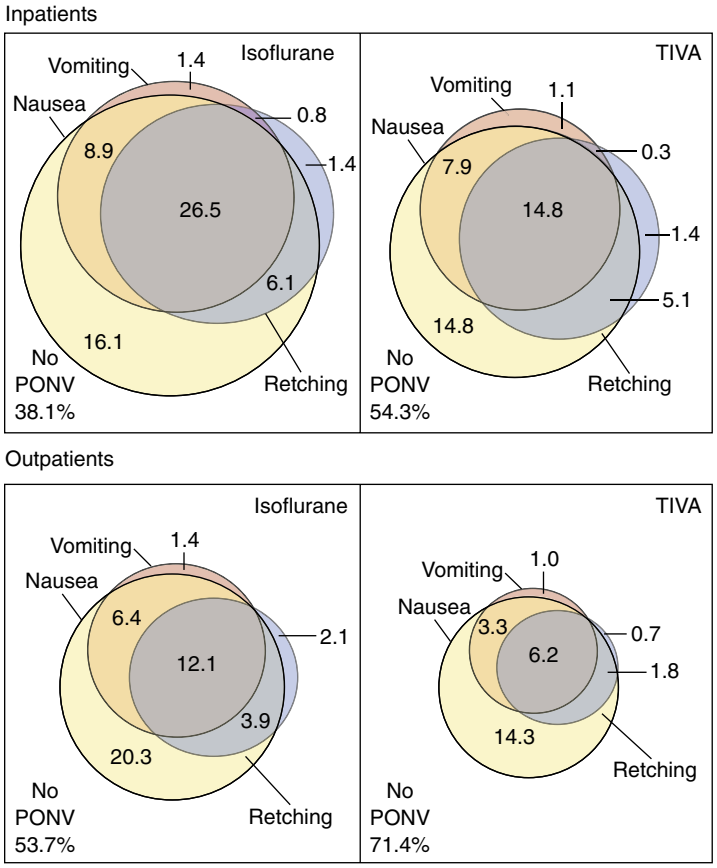


Figure 86-9 Venn diagrams for nausea, vomiting, and retching in patients after general inpatient or outpatient anesthesia with inhalational or propofol anesthesia. (*From Visser K, Hassink EA, Bonsel GJ, et al: Randomized controlled trial of total intravenous anesthesia with propofol versus inhalation anesthesia with isoflurane-nitrous oxide: Postoperative nausea with vomiting and economic analysis. Anesthesiology 95:616-626, 2001.*)

vomits, or more than two vomits" fails to reflect the underlying physiology and presentation of these symptoms and does not allow determination of the proportion of patients experiencing nausea, vomiting, or both.[99]

Nausea (from the Greek *nautia* meaning "seasickness") is often described as a "sensation of unease and discomfort in the stomach with an urge to vomit." Nausea may present at different intensities, may last a variable period of time, and may be waxing and waning (cyclic change of intensity over time). There are three ways to assess the intensity of these symptoms.

The most widely accepted measurement technique for intensity utilizes a Visual Analog Scale (VAS). The VAS consists of a 10-cm horizontal line with the left end corresponding to *no nausea* and the right end corresponding to *worst imaginable nausea.* Patients are asked to choose a point on the line that represents the intensity of their current state. VAS is considered the criterion standard, because its reliability and sensitivity have been well established in pain studies.[100] Another common approach is the use of a written or verbal 11-point numeric rating scale (NRS), with which the patient is asked to rate severity of nausea between 0 and 10, with 0 corresponding to *no symptoms* and 10 corresponding to *worst possible symptoms.* The NRS approach has the advantage of ease of use and maintains a sensitivity similar to the VAS gold standard.[101] The easiest approach appears to be a categorical verbal rating scale (VRS), in which patients describe their symptoms as *none*, *mild*, *moderate,* or *severe*. Unfortunately, even though Boogaerts and colleagues have demonstrated a good correlation between VRS and VAS for nausea,[102] pain studies have found that VRS is not as sensitive as the VAS.[101] All told, the NRS approach may provide the best balance between sensitivity and ease of use.

Usually, the intensity of nausea varies over time so that repeated measurements would be needed for an overall severity assessment. Thus, nausea assessment may not be accurate if the intervals between assessments are considerably longer than the duration of nausea episodes. As a rule of thumb it might thus be advantageous to have patients estimate their *average* and/or *severest* level of nausea, rather than limit the patient to rating the current nausea at the time of questioning. Therefore, assessments of nausea should be performed covering a time *interval* rather than assessing a time *point*.

Vomiting, as a clinical symptom, is the forceful expulsion of gastric contents through the mouth or nose. *Retching* is similar to vomiting with the exception that no gastric content enters the pharynx (dry heaves). An *emetic episode* is often operationally defined as one or more instances of vomiting and/or retching separated by no more than 1 minute of respite. However, for the sake of simplicity and because vomiting is much more frequent than retching, many authors' reports of *vomiting* will include both vomiting and retching. In such instances, use of the term *emetic episode* is preferable. The measurement of vomiting and emetic episodes is simpler than that of nausea, because the former involves a distinctive and recognizable muscular reflex. Severity is therefore best evaluated by number of episodes, and recording of the times of each individual episode allows secondary analysis with regard to the time course.

Because there is no universally accepted standard for how to measure and report nausea and vomiting, publications should at the minimum report separate incidences for nausea and for vomiting, even if the primary outcome is a combined measure such an incidence of PONV. Whenever possible, the frequency and success of rescue treatment should be reported as well, to allow comparison of treatment effects in subsequent meta-analyses.[99] It should also be kept in mind that patients may experience benefit as mild (instead of severe) nausea, and this is not reflected by the crude incidence, a dichotomous outcome. This may also be a reason why a joint severity score that considers the severity of nausea and vomiting may be a valuable adjunct to be reported and analyzed with more statistical power than the binary variables.

Measures of Efficacy and Effectiveness

From an epidemiologic perspective, *efficacy* refers to the impact of an intervention in a clinical trial while *effectiveness* refers to the impact in real world situations. For PONV trials, *efficacy* of a prophylactic strategy is probably best described by the relative risk (a synonym would be the risk ratio [RR]) or the odds ratio (OR) that measures the drug-specific antiemetic potential. In contrast, the *effectiveness* of a prophylactic intervention is probably best measured by the absolute risk difference (ARD; synonym: absolute risk reduction) or number-needed-to-treat (NNT) that describes the actual benefit of that intervention when given to patients of a population with a certain risk for PONV. To fully appreciate the meaning of the different measures of treatment effects described in the literature, it is essential to conceptualize the fundamental differences between measures of *efficacy* and *effectiveness*, that is, relative risk and absolute risk difference. Understanding this difference is key when comparing the efficacy between antiemetic trials and when determining the effectiveness of interventions in specific clinical situations.

Absolute Risk Difference and Number-Needed-to-Treat

When using binary outcomes such as the incidence of PONV, the clinical benefit or *effectiveness* of prophylactically administered antiemetics for an individual (or a population) with a particular underlying risk profile is best described by the absolute risk difference (ARD). For example, when a patient is at very high risk for PONV, say 80%, the use of an antiemetic such as ondansetron may reduce the risk to 60%, that is, the ARD is 20% (Fig. 86-10A). Thus, ondansetron given to 100 individuals with a baseline risk of 80% will prevent PONV in 20% of cases, and therefore 1 of 5 such patients will benefit from the intervention. To put it another way, 5 high-risk patients would need to be treated prophylactically to prevent 1 of those 5 patients from experiencing PONV: the NNT is 5. Thus, the following formula applies:

$$NNT = 1/ARD$$

However, when ondansetron is given for prophylaxis to patients at low risk for PONV, say 10%, the risk will only be reduced to 7.5%; thus the ARD is only 2.5% and the NNT is 40. Thus, ARD and NNT, both measures of *effectiveness,* are critically dependent on the patient's baseline risk. As a corollary, ARD or NNT determined in one study cannot be taken as a measure of *efficacy* for patients in a population with a different (higher or lower) baseline risk. This emphasizes the importance of an objective risk assessment to tailor the use of prophylactic antiemetic treatment to those patients who benefit most.

Relative Risk Reduction and Risk Ratio

The aforementioned examples have one characteristic in common. The use of ondansetron reduced the risk by about a fourth. Thus, in both examples the relative risk reduction (RRR) was 25% and the risk ratio (RR) was 0.75.

$$RR = 1 - RRR$$

The fact that the RR is a relatively robust measure of efficacy for a wide range of baseline event rates has been described in other medical areas[103] but was first described in the field of PONV in the IMPACT (an **I**nternational **M**ulticenter **P**rotocol to assess **A**ntiemetic **C**ombinations in a controlled Clinical **T**rial of factorial design) study.[56,161] In addition, this study demonstrated that the *efficacy* of each of the three antiemetics tested (ondansetron, dexamethasone, and droperidol) was independent of one another and by and large of other risk factors.[56] In other words, RR and RRR were reliable measures for the *efficacy* of prophylactic antiemetics and were independent of the patient's baseline risk.

As a consequence, the *effectiveness* in terms of an absolute risk reduction (ARD) of an antiemetic that can be expected in

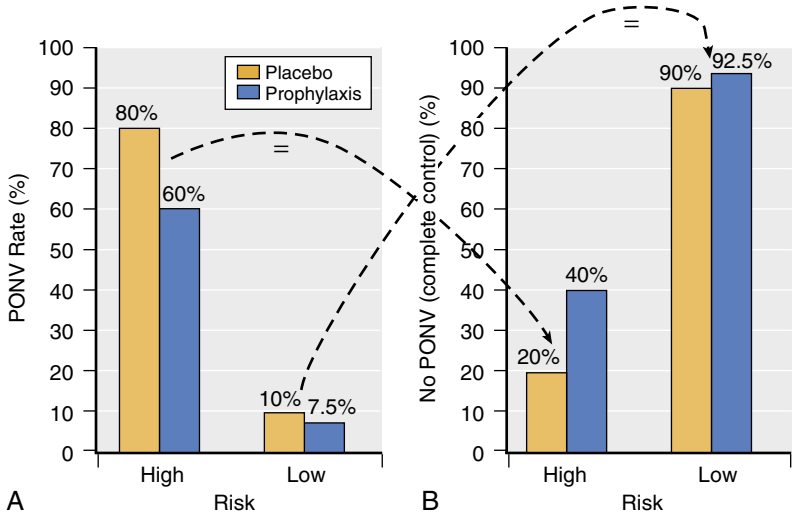


Figure 86-10 **A** and **B,** Relative risks (risk ratios) or relative risk ratios are independent of the patient's baseline risks. Note, that both **A** and **B** represent the same data, yet efficacy of a drug can be judged only from the risk ratio of the events (e.g., PONV) but not from the risk ratio of the absence of events (e.g., no PONV).

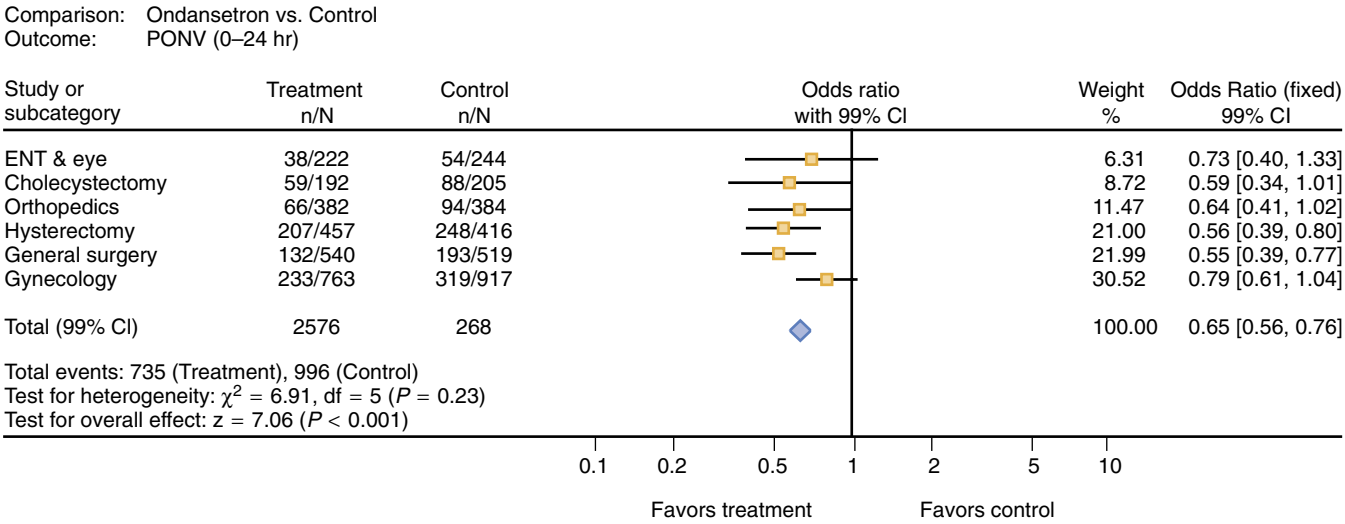


Figure 86-11 Efficacy of ondansetron is independent of the type of surgery. (*Based on data from Apfel CC, Korttila K, Abdalla M, et al: A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 350:2441-2451, 2004.*)

clinical practice can be estimated from the baseline risk multiplied by the RRR using the formula:

$$\text{ARD} = \text{baseline risk} \cdot \text{RRR}$$

Alternatively, the remaining risk can be estimated using the formula:

$$\begin{aligned}\text{Remaining risk} &= \text{baseline risk} - \text{ARD}\\ &= \text{baseline risk} \cdot (1 - \text{RRR})\\ &= \text{baseline risk} \cdot \text{RR}\end{aligned}$$

Relative Benefit for Freedom from Symptoms

However, it is important to note that the RRR or RR is only independent of the patient's baseline risk when the outcome is "PONV" but not "no PONV." In the first example (i.e., in the high-risk group), the incidence of no PONV was 20% without prevention and 40% with prevention (see Fig. 86-10B), so that twice as many patients were free of PONV; that is, the relative benefit (RB) for no PONV was 2. However, in the second example (i.e., in the low risk group), the incidence of no PONV was 90% without prevention and 92.5% with prevention; that is, the RB for no PONV was only 1.03 (92.5/90) even though there was a 25% decrease in the incidence of PONV. This demonstrates that the RB for "no PONV" or "freedom from symptoms" is again highly dependent on the patient's baseline risk. Similarly, this applies to complete response (no vomiting and no rescue treatment) or complete control (no nausea, no vomiting, and no rescue treatment). Thus, a ratio cannot be taken as a measure for drug *efficacy* when the reported outcome is a measure of freedom from symptoms such as "no nausea," "no emesis," "complete response," or "complete control." For this reason, future publications should report vomiting or nausea rather than no vomiting or no nausea and compound measures should report PONV or rescue treatment rather than complete response or complete control.

Generalizability of Study Results

As described earlier, the number of patients required to demonstrate antiemetic efficacy of a drug in a clinical trial depends critically on the baseline risk (often described as control event rate). A table for sample size estimations for PONV trials can be found in the article "How to Study Postoperative Nausea and Vomiting."[99] Fewer patients need to be studied when the control event rate is high, that is, when patients at high risk are selected. In addition, patients at high risk are much more likely to benefit from prevention given that their absolute risk difference will be larger. Therefore, most PONV trials specify certain types of surgeries that are assumed to be "high risk procedures." However, as pointed out earlier, patients at risk are more reliably identified by using a simplified risk score.[38]

The other rationale for the selection of just one type of surgery is to increase study strength by minimizing heterogeneity. Although this is a well-recognized approach for any continuous outcome, it does not apply to binary outcomes where the confidence interval is solely a function of the number and proportion of patients.

The third reason why most studies are limited to a certain type of surgery is the notion that type of surgery might play a critical pathophysiologic role for PONV. If that were true, study results for one type of surgery might not be applicable to other surgical populations. Carlisle and Stevenson addressed this question in a subgroup analysis of their meta-analysis but could not find any evidence that the type of surgery affects the efficacy of an antiemetic.[104] One theoretical limitation of their subanalysis is that it is based on "inter-study" comparisons. However, two large sufficiently powered randomized controlled trials were also unable to identify any interaction between antiemetics and type of surgery (Fig. 86-11).[56,76]

In conclusion, currently published data suggest that the efficacy of an antiemetic is independent of the type of surgery. Therefore, the clinician may assume similar antiemetic *efficacy* for

other types of surgeries or similar settings from those in the randomized trials. For the clinical researcher, it would be better to address more novel questions rather than repeating PONV trials that have already been studied in other types of surgeries. As a corollary, it appears that separate meta-analyses on PONV for specific types of surgeries[105,106] are unlikely to advance our knowledge and understanding.

Perioperative Pain Management

Local Anesthesia

Data from multivariable analyses suggest that the main cause of PONV is exposure to emetogenic triggers, namely, inhaled anesthetics and opioids. If both can be avoided, PONV incidence can be expected to be quite infrequent. In fact, a 5-year review of 1264 cases using an opioid-free propofol/ketamine sedation technique for a wide range of ambulatory surgeries under local anesthesia reported only 7 patients (0.6%) with vomiting and 21 patients (2%) requiring postoperative antiemetics.[107] However, the lack of a control group in this study necessitates a cautious interpretation. Nevertheless, this result is in accordance with small-scale, high-quality randomized controlled trials, such as the comparison of anesthetic techniques by White and colleagues.[108] In that study, ilioinguinal-hypogastric nerve block, spinal anesthesia, or general anesthesia (with volatile anesthetics and opioids) was associated with PONV incidences of 7%, 12%, or 62%, respectively.

Regional Anesthesia

Consistent with the low incidence of PONV after primarily regional techniques (with or without sedation) (also see Chapters 51 and 52) are the results of a meta-analysis from Liu and associates that compared single-shot regional anesthesia (peripheral nerve block or central neuraxial blockade) versus general anesthesia as the primary anesthetic technique for ambulatory surgery.[79] Patients who were randomized to receive a peripheral nerve block had a more than fourfold lower incidence of nausea than those receiving a general anesthetic (6.8% versus 30%). The RR was 0.23, which corresponds to an RRR of 77%, an antiemetic efficacy that can only be achieved by a quadruple antiemetic combination (see later).[56]

Similarly, a central neuraxial blockade was also associated with a numerically lower incidence of nausea (5% versus 14.7%), an RR of 0.34, and an RRR of 66%; however, it needs to be noted that this failed statistical significance and that further research is needed to confirm this finding ($P < .06$). Of note, anesthetic solutions for epidural anesthesia often contain opioids to increase the density of the block, which may be the reason why opioid-free paravertebral blocks are associated with a lower incidence of PONV compared with epidural anesthesia.[109]

In this respect, intraoperative nausea and vomiting after spinal anesthesia is different. Two large cohort studies of spinal anesthesia have been conducted[59,60] and identified the following independent predictors for nausea and vomiting in the perioperative period: female gender, history of motion sickness, preoperative tachycardia, preoperative intravenous opioids, intrathecal procaine, use of phenylephrine or epinephrine, and hypotension or high intrathecal block (T4 or higher).

Non-opioid Analgesics

Although individual studies have been able to demonstrate a reduction in pain and/or opioid consumption by NSAIDs (see also Chapter 26), most were unable to demonstrate benefits in their secondary outcomes, such as incidence of PONV. Bonnet's group conducted a quantitative systematic review (of randomized controlled trials), and although there was insufficient evidence to demonstrate a significant reduction of pruritus, urinary retention, or respiratory depression, they were able to demonstrate an RR of 0.7 for PONV, that is, an RRR of 30%.[110] Although the efficacy of NSAIDs is not as high as that of regional anesthetic techniques, they are equal to antiemetics such as 4 mg of ondansetron.

Antiemetics

To date, more than 2000 articles on PONV have been published, with over 200 articles added yearly. Most are reports of randomized controlled trials for the prevention of PONV, yet it is apparent that the elusive "holy grail" of how to prevent PONV has yet to be found.

One reason might be that relatively little effort has been made to understand the causes of PONV. For example, few reviews acknowledge that the strongest known causes of PONV are inhaled anesthetics and opioids and that an opioid-free regional anesthetic technique is probably the most effective way to prevent PONV. However, for a particular patient there may be medical and logistical reasons why a local or regional anesthetic technique may not be practical. Therefore, even though the efficacy of antiemetics is limited, and avoiding the causes for PONV appears to be more effective, antiemetics remain important tools for the prevention of PONV in many other clinical situations.

Meta-analyses

Given the abundance of published PONV studies, it is highly desirable to (1) identify all available evidence and, if possible (2) reconcile controversial results and (3) determine the treatment effect based on the best available evidence. This can be achieved through a systematic review such as a Cochrane review with prespecified study question, inclusion/exclusion criteria, and well-established search algorithms to ensure identification of all relevant papers. Of note, the term *systematic review* characterizes the scientific rigor to identify and consider all available evidence while the term *meta-analysis* characterizes the statistical approach to synthesize the various study results to come up with the most accurate point estimate for the treatment effect. Thus, a systematic review that uses a meta-analysis to quantify the treatment effect is often described as a "quantitative systematic review."

The first systematic review on PONV was by Tramer and associates on the effect of nitrous oxide.[89] Because systematic reviews tend to focus on a well-defined, specific question, dozens of other systematic reviews have been subsequently published requiring reviews on the systematic reviews.[111,112]

Fortunately, Carlisle and Stevenson have created a comprehensive Cochrane review for all drugs that have been studied for the prevention of PONV.[104] The first edition encompasses 737 studies involving 103,237 patients: the largest PONV meta-analysis to date and clearly the most important for clinicians seeking a single reference for drugs that may prevent PONV. In addition, in contrast to many previous systematic reviews that focused on the NNT, that—as described above—is not a useful estimate to characterize the efficacy, the Cochrane review from Carlisle and Stevenson used the RR.

Antiemetics (Table 86-2)

Dopamine Antagonists

Metoclopramide has been used for decades to prevent PONV. Its antiemetic properties are primarily mediated through its antidopaminergic action and it also probably has prokinetic properties.[113] In the past, use of large doses of metoclopramide (e.g., 200 mg every 6 hours) was a mainstay for prevention of chemotherapy-induced nausea and vomiting. These large doses likely have anti-serotoninergic properties.[114] Unfortunately, these large doses cause extrapyramidal side effects in more than 10% of patients, which can be treated with antihistamines and benzodiazepines.[115]

As a result, small doses of metoclopramide (10 mg) became established in clinical practice. However, this amount has been not proven to be clinically effective.[116] Consequently, Wallenborn and associates conducted a large randomized placebo-controlled trial comparing 8 mg dexamethasone alone or combined with either 10, 25, or 50 mg metoclopramide.[117] The risk ratios for the prevention of PONV for these three combinations compared with dexamethasone alone were 0.89, 0.74, and 0.63, respectively. Thus, the efficacy of 25- or 50-mg doses seems to be comparable to that of other well-established antiemetics. Efficacy needs to be balanced against the potential side effects (the most frequent ones were treatable hypotension and tachycardia) and the incidence of dyskinetic and/or extrapyramidal symptoms, which were 0.1%, 0.4%, 0.8%, and 0.8% in those four groups. Of note, in children undergoing tonsillectomies a moderate dose of 0.5 mg/kg of metoclopramide was not equivalent to 0.1 mg/kg of ondansetron.[118]

Droperidol is a highly potent D_2-antagonist with well-proven antiemetic properties at intravenous doses as small as 0.625 to 1.25 mg[104,119,120] and an overall RR of 0.65, 0.65, and 0.62 for nausea, vomiting, and PONV, respectively.[104] Furthermore, it is similarly effective compared with ondansetron,[56,121] with an RR for PONV of 0.99.[104] Compared with placebo, droperidol is associated with increased sedation (RR, 1.32) but with a decreased incidence of headache (RR, 0.79).[104] Although droperidol has been investigated in over 200 papers, its minimal effective dose and optimal time of administration have not yet been established. Because of its relatively short plasma half-life of about 3 hours, it should be given at the end of surgery and at the lowest effective dose of 0.625 mg to minimize potential sedative side effects. For the same pharmacokinetic reason, the supplementation of a morphine-loaded PCA pump with droperidol appears to be a highly effective approach to reduce opioid-induced nausea and vomiting. In a dose response study by Tramer and colleagues, adding 5, 15, or 50 μg to 1 mg of morphine led to an RR of 0.88, 0.63, and 0.44.[122] Although 50 μg of droperidol per milligram of morphine appears to be the most effective dose, it was associated with sedative side effects, so the authors concluded that a dose of 25 μg droperidol per milligram of morphine was optimal.

Low-dose droperidol has also been reported to lead anxiety and restlessness,[123] akathisia,[124] and dystonia.[125] However, data are conflicting.[126] In addition, the U.S. Food and Drug Administration (FDA) has received reports of severe arrhythmias (torsades de pointes) and deaths in association with the use of low-dose droperidol, leading to the following black box warning:

> Droperidol is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome. In patients who fail to show an acceptable response to other adequate treatment, a 12-lead ECG must confirm the absence of QT prolongation (440 ms for males, 450 ms for females) prior to administration of droperidol, and ECG monitoring should be continued for 2-3 hours after drug administration. Also, it should be administered with extreme caution to patients who may be at risk for the development of a prolonged QT syndrome, such as in patients with electrolyte disturbances or those receiving volatile anesthetics and IV opioids.

The FDA black box warning for droperidol has created controversy among physicians who continue to see a value in its low-dose use for PONV prevention. According to the study from White and associates, general anesthesia itself leads to a QT prolongation from about 400 to 430 msec and the mean maximal QT prolongations when placebo, 0.625 mg, or 1.25 mg droperidol was administered during anesthesia were 12, 15, and 22 msec.[127] Of note, the anesthetic had a much stronger overall effect on the average QTc interval compared with droperidol and was associated with considerably more interindividual variability. On the other hand, one instance of QT prolongation of 133 msec was observed in a single patient who received 1.25 mg of droperidol. Charbit and colleagues investigated the effect of 0.75 mg of droperidol or 4 mg of ondansetron on the QTc interval when given as rescue treatment in the PACU.[128] Over 40% of patients had a prolonged QTc interval after anesthesia, and the mean maximal additional QTc prolongation was 17 msec after droperidol and 20 msec after ondansetron (Fig. 86-12). This raises a question about the clinical relevance of QT prolongation. In general, the Committee for Proprietary Medicinal Products in the United Kingdom considers QT prolongation less than 30 msec unlikely to be clinically relevant. Furthermore, based on data from patients with congenital prolonged QT syndrome, a prolongation of 10 msec corresponds to a hazard ratio of 1.056, which translates to an 18% increased risk (RR, 1.18) with 30 msec but doubles the risk (RR, 2.06) at 133 msec.[129] Based on these data, the risk of droperidol for healthy patients with a normal electrocardiogram appears to be negligible. It is, however, difficult to exclude the possibility that the addition of droperidol in a clinical context of an unrecognized conduction abnormality alongside other QTc-prolonging drugs may be the trigger of a clinically relevant QT prolongation leading to torsades de pointes.[130]

Because of the droperidol black box warning, haloperidol has garnered more interest, with recent studies showing an efficacy similar to ondansetron.[131,132] However, cardiac arrhythmias and death associated with haloperidol have also been reported to health agencies so that the FDA has issued an alert that it is only approved for the intramuscular route and that intravenous injection is off-label use.

Alizapride, perphenazine, (Decentan, Trilafon) and prochlorperazine (Compazine) (the latter two are highly potent neuroleptics) are less frequently used dopamine antagonists that have further mechanism of actions. Although their efficacy appears comparable to that of other antiemetics these drugs have not been studied extensively so that the limited number of patients provides insufficient power to detect all treatment effects.[104] A main reason for their rather infrequent use may be sedative side effects that can delay recovery.

Table 86-2 Mechanisms, Doses, and Measures of Efficacy of all Investigated Antiemetics with Statistically Significant Outcome

Antiemetic (U.S. Trade Name)	Primary (Other) Actions, Mechanisms	Frequently Studied Adult Doses, Given Intravenously Unless Noted Otherwise	Risk Ratio (RR) Compared with Placebo That Met Statistical Significance			Evidence Comment
			Nausea	Vomiting	PONV	
Metoclopramide (Reglan)	D_2, prokinetic, (5-HT_3)	10 or 20 mg	0.82	0.76	0.76	
		10 mg		0.80	0.78	SR[116]
		25 mg	0.75	0.71	0.74	Large RCT[117]
		50 mg	0.57	0.60	0.63	Large RCT[117]
Droperidol (Inapsine)	D_2 (α_1)	0.625-1.25 mg	0.65	0.65	0.62	Sedation RR = 1.32, decreased headache RR = 0.79, FDA black box warning
Haloperidol (Haldol)	$D_{2,3,4}$ (D_1), 5-HT_2	0.5 mg IM, 1 mg	0.48	0.23, 0.38		[195,196] FDA safety alert
Alizapride (Vergentan)	D_2, prokinetic	50-200 mg	0.65	0.49		No evidence for dose-response
Perphenazine (Trilafon)	D_2, (D_1), H_1, 5-HT_2	2.5-5 mg IM or IV		0.70		
Prochlorperazine (Compazine)	D_2 (M, α_1, H_1)	6.25-12.5 mg IM or IV or 3-6 mg buccal	0.73	0.68	0.68	
Dimenhydrinate (Dramamine) or Diphenhydramine (Benadryl)	H_1 (M)	31.25-62.5 mg IV, 50-mg suppository		0.61	0.71	Drowsiness RR = 9.0
Cyclizine (Marezine)	H_1 (M)	50 mg IV or IM	0.67	0.55	0.67	
Promethazine (Phenergan)	H_1 (M)	12.5-25 mg or 12.5-50 mg IM			0.46	Risk of vascular necrosis
Hyoscine (Scopoderm)	M	1.5-mg patch	0.63	0.65	0.71	Dry mouth RR = 1.25
			0.49	0.43	0.46	SR of small trials[135]
			0.71	0.68	0.78	SR of large trials[135]
Ondansetron (Zofran)	5-HT_3	4 mg	0.68	0.54	0.56	Headache RR = 1.16. Preferably at the end of surgery
Dolasetron (Anzemet)	5-HT_3	12.5-50 mg	0.82	0.62	0.72	Arrhythmia warning (Canada)
Granisetron (Kytril)	5-HT_3	1 mg	0.67	0.42	0.56	Data from one center excluded[146]
Tropisetron (Navoban)	5-HT_3	All doses	0.77	0.60	0.72	Decreased dizziness RR = 0.37
		2 mg	0.75	0.67	0.71	SR[197]
		5 mg	0.69	0.56	0.69	SR[197]
Diazepam, Lorazepam (Ativan)	$GABA_A$, modulation	10 mg PO, 2-2.5 mg PO	0.50, 0.55			
Midazolam (Versed)	$GABA_A$, modulation	2-5 mg IV, 7.5-15 mg PO		0.73		
Dexamethasone (Decadron)	Unknown	4-8 mg	0.58	0.51	0.48	Slow onset, preferably after induction
Aprepitant	NK_1	40-mg PO capsule				Active control with ondansetron: Similarly effective against nausea but significantly more effective against vomiting: RR = 0.38 (0.13-0.64),[158] 0.55 (0.32-0.79)[159]

RCT, randomized controlled trial; SR, systematic review.
Data are primarily based on the Cochrane Review from Carlisle and Stevenson[104] unless indicated otherwise. Original papers are quoted if data are based on ≤3 RCTs or if a more specific meta-analysis was believed to provide more detailed information. Efficacy fields were left blank if data were not available or did not meet statistical significance.

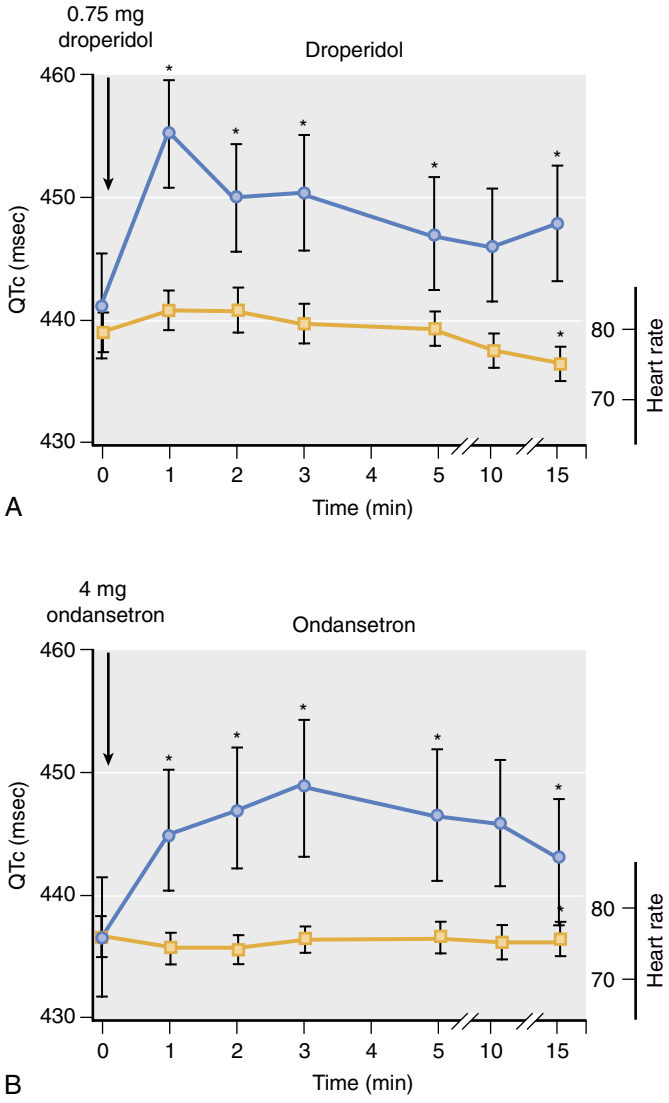


Figure 86-12 Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. (*From Charbit B, Albaladejo P, Funck-Brentano C, et al: Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. Anesthesiology 102:1094-1100, 2005.*)

Histamine Antagonists

Diphenhydramine (Benadryl) and dimenhydrinate (an aminophylline salt of diphenhydramine) are histamine (H_1)-receptor antagonists known for their effectiveness against motion sickness and relatively weak anticholinergic (antimuscarinic) activities (see Table 86-2).[104,133] Cyclizine (Marezine) and promethazine (Atosil, Phenergan) seem to have equal antihistaminic and anticholinergic properties, which poses a contraindication for patients with glaucoma and prostate hypertrophy. All relatively nonspecific histamine receptor antagonists have sedative side effects that may delay recovery when given immediately before the end of anesthesia. Diphenhydramine, cyclizine, and promethazine are effective for the prevention of PONV, with RRs of 0.71, 0.67, and 0.46, respectively.[104] Side effects include drowsiness (RR, 9.0)[104] but also urinary retention, dry mouth, blurred vision, and extrapyramidal symptoms reported too infrequently to draw conclusions.[104,133] Promethazine has also been reported to cause vascular necrosis requiring plastic surgery of skin lesions and/or limb amputations, leading to the FDA safety alert in 2006.

Anticholinergics

Data on the potential antiemetic properties of atropine are conflicting. For example, when coadministered with neostigmine to reverse neuromuscular blockade, atropine was associated with less postoperative vomiting compared with glycopyrrolate.[47,104] One plausible explanation is that atropine, unlike glycopyrrolate, crosses the blood-brain barrier. However, comparisons of atropine versus placebo have been negative,[104] perhaps owing to the drug's short half-life. Scopolamine is another central-acting anticholinergic (antimuscarinergic) that, like atropine, has a relatively short half-life. This limitation is overcome by a transdermal formulation that allows a more favorable pharmacokinetic profile to cover up to 72 hours. Its antiemetic properties are well established for the prevention of motion-induced nausea and vomiting,[134] and the scopolamine patch has also been shown effective for the prevention of PONV, with RRs of 0.63 and 0.65, respectively.[104] Its long duration of action might be especially useful for the prevention of postdischarge nausea and vomiting in ambulatory patients; however, scopolamine is associated with an increased incidence of side effects, such as blurred vision (18%), dry mouth (8%), dizziness (2%), and agitation (1%).[135]

Serotonin Antagonists

Ondansetron was the first serotonin antagonist, and its introduction was a milestone in the prevention of early chemotherapy-induced nausea and vomiting. It was considerably more effective and had fewer side effects (no extrapyramidal symptoms or sedation) compared with all previous antiemetics. Given its superior efficacy for chemotherapy-induced nausea and vomiting, it is not surprising that ondansetron quickly established a reputation as the most effective antiemetic for prevention of PONV. This perception was further nurtured by duplicate publication of positive studies that, according to analyses by Tramer and coworkers, would lead to a 23% overestimation of ondansetron's effectiveness if included in a meta-analysis.[136] In fact, according to the meta-analysis from Carlisle and colleagues the risk reduction for nausea and vomiting are 0.68 and 0.54.[104] This is comparable to the efficacy determined in meta-analyses of other antiemetics such as dexamethasone or droperidol (note that the results from meta-analyses tend to be more positive than subsequent large studies due to publication bias). For example, in IMPACT (a large multicenter randomized controlled factorial-design trial), 4 mg of ondansetron, 4 mg of dexamethasone, and 1.25 mg of droperidol had risk ratios of 0.76, 0.76, and 0.74. That is, each drug led to an RRR of about 25%.[56] Of note, ondansetron has a plasma half-life of 4 hours and is metabolized via CYP2D6 such that select genetic polymorphisms of the P450 enzyme can lead to decreased efficacy due to ultrarapid metabolism.[137] These polymorphisms may also be the reason why ondansetron appears to be more effective when given at the end of surgery rather than immediately after induction of anesthesia.[138,139]

Dolasetron mesylate, and its liver-converted active metabolite hydro-dolasetron, are other highly specific $5HT_3$ antagonists

with plasma half-lives roughly twice as long as ondansetron. In general, all highly selective serotonin antagonists are considered to be equally effective when given at equipotent doses. For ondansetron, 4 mg is well documented to be the minimal effective dose (the minimal dose where any further increase fails to produce additional clinically relevant benefit). For dolasetron, the data from Korttila and associates suggest that 50 mg is superior to 25 mg and equivalent to 4 mg of ondansetron.[140] However, this contrasts to a pooled analysis of three trials by Philip and coworkers that suggests that 12.5 mg is the minimum effective dose, which is the dose approved by the FDA for the prevention of PONV.[141]

Granisetron is another highly specific $5HT_3$ antagonist, with a half-life that is about twice as long as that of ondansetron. The FDA-approved dose for the prevention of PONV is 1 mg. This is based on a dose range study from Wilson and associates in which 0.1, 1.0, and 3.0 mg were associated with risk ratios for postoperative vomiting of 0.94 (not significant), 0.56, and 0.66.[142] A second dose-response study investigated the efficacy of 2, 5, 10, and 20 μg/kg and found that 5 μg/kg appears to be the minimal effective dose, which corresponds to roughly 0.35 mg for a 70-kg adult patient.[143] Despite results from these relatively large randomized controlled trials, some recent studies have reexplored the possibility that doses as low as 0.1 mg are effective for the prevention of PONV. One study compared 0.1, 0.2, and 0.3 mg with placebo in patients undergoing abdominal hysterectomies.[144] Although all three doses were associated with less vomiting within the first 6 hours, no significant difference could be demonstrated over 24 hours. Another study compared the combination of 8 mg of dexamethasone plus either 0.1 mg of granisetron or 4 mg of ondansetron in laparoscopy patients.[145] However, that study was not sufficiently powered to demonstrate a statistically significant difference for the main outcome, that is, vomiting in the first 2 postoperative hours, which was 6% in the granisetron group and 3% in the ondansetron group. Of note, the majority of studies on granisetron suggest that 3 mg is superior to 1 mg for prevention of PONV, but those were published by a single center[146] and there have been serious concerns about the validity of the data.[147] The current evidence suggests that the FDA approved dose of 1 mg—but not 0.1 mg—is an effective does for the prevention of PONV.

Whereas all serotonin antagonists have generally been considered to be similarly effective, palonosetron might be an exception, not only because of the long half-life of about 40 hours but also because it seems to be able to prevent delayed chemotherapy-induced nausea and vomiting for which serotonin antagonists are usually not effective. Whether this will translate into higher efficacy for the prevention of PONV, and perhaps postdischarge nausea and vomiting, has yet to be shown.

Dexamethasone

Dexamethasone is well documented as an effective antiemetic,[56,104] and animal experiments suggest that it exerts its antiemetic effects through central inhibition of the nucleus tractus solitarii but not the area postrema.[148] Most early studies were conducted with 8 to 10 mg of dexamethasone,[120,149] but there is now convincing evidence from several smaller dose-response trials that 2.5 to 5 mg can be considered the minimum effective dose.[150-152] Dexamethasone has a slow onset of action, which might be the reason why its application at the beginning of a case appears to be superior to later use.[153] According to Carlisle and Stevenson, the RR of dexamethasone is 0.58 for nausea and 0.51 for vomiting[104] and direct head-to-head comparisons suggest its efficacy is similar to that of ondansetron or droperidol.[56,104]

Neurokinin-Antagonists

Substance P is a regulatory peptide that binds to neurokinin-1 (NK1) receptors found in vagal afferents in the gastrointestinal tract. More importantly, in the 1950s it was shown to reside in areas of the central nervous system that are thought to be involved in the vomiting reflex.[154] Nevertheless, it took over 40 years before it became apparent that NK1 antagonists could be highly effective against a wide range of emetic stimuli in animal studies.[155] A few years later, Diemunsch and colleagues showed the clinical feasibility for control of established PONV after major gynecologic surgery in a pilot study with the NK1 antagonist GR205171.[156] This was followed by a multicenter study by White's group with CP-122,721.[157] In that study, 200 mg reduced the incidence of postoperative emesis from 50% to 10%, which corresponds to an RR of 0.2 and an RRR of 80%, significantly more effective against vomiting than all other previous antiemetics. The strong antiemetic property of NK1 receptor antagonists is confirmed by studies of aprepitant, the first drug in its class approved for clinical use by the FDA. In a three-arm multicenter study, 4 mg of ondansetron, given intravenously, was compared with 40 mg and 125 mg of orally administered aprepitant.[158] Although the incidence of nausea was similar between the groups, the incidences for vomiting were 26%, 10%, and 5%, respectively. Considering that ondansetron reduces the risk for vomiting by about 26%,[56] if a placebo group had been included in this study, the incidence in the placebo group would likely have been in the range 35%. In that case, the RRs for 40 and 125 mg of aprepitant would have been in the range of 0.3 and 0.15 compared with placebo, that is, an RRR in the range of 70% or 85%, again clearly more effective than other antiemetics. A similar international trial (again without a placebo control group) yielded similar (though less striking)

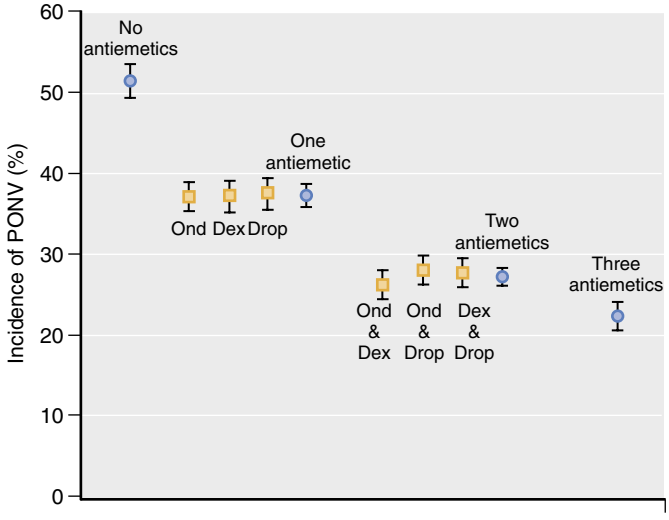


Figure 86-13 Reduction of PONV with ondansetron, dexamethasone, and droperidol when given alone or in combination. (*From Apfel CC, Korttila K, Abdalla M, et al: A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 350:2441-2451, 2004.*)

results for aprepitant.[159] In that study, the incidence of vomiting for 4 mg of ondansetron given intravenously, 40 mg of aprepitant, and 125 mg of aprepitant orally were 29%, 16%, and 14%. For the prevention of PONV, 40 mg of aprepitant is the dose approved by the FDA. In the future, it is likely we will see other NK1 receptor antagonists on the market, such as casopitant and rolapitant. However, it should be noted that although NK1 receptor antagonists appear to be superior for prevention of vomiting this may not be true for the prevention of nausea. And because novel drugs are inherently more expensive than generics, it is likely that the use of these drugs will focus on patients at high risk for PONV. Nevertheless, their excellent antiemetic profiles make NK1 antagonists ideal drugs to reduce the medical risk that may be associate with vomiting after certain procedures (e.g., wired jaw, neurosurgical procedures, and upper gastrointestinal surgery).

Combinations and Multimodal Therapy

None of the currently available antiemetics is capable of completely eliminating the incidence of PONV. In fact, according to the meta-analysis from Carlisle and Stevenson, the overall RR for FDA-approved "effective" antiemetics is 0.65, that is, the RRR is 35%.[104] Considering that smaller studies tend to be more often published if they are positive (publication bias), the "true" RRR is likely to be smaller than 35%. In fact, in a large multicenter trial, the RRs for ondansetron, dexamethasone, and droperidol were in the range of 0.75; that is, the RRR was 25% rather than 35%.[56]

Given the limited antiemetic efficacy of prophylactic antiemetics, Scuderi and coworkers were the first to investigate a multimodal approach.[160] In patients undergoing outpatient laparoscopy, they studied a combination antiemetic regimen (group I, n = 60) that consisted of both preoperative interventions (10-30 µg/kg midazolam for anxiolysis, 10 mL/kg crystalloid fluid administration) and intraoperative interventions (0.625 mg of droperidol, 10 mg of dexamethasone, induction and maintenance with remifentanil/propofol, gastric decompression, 30 mg of ketorolac, 1 mg of ondansetron at the end of surgery, and 25 µg of fentanyl 10 minutes before end of surgery). Patients in groups II and III received balanced anesthesia with sevoflurane/nitrous oxide/fentanyl with (n = 42) or without (n = 37) 4 mg of ondansetron. With the multimodal group I regimen, no patients vomited and only 1 of 60 patients (1.7%) experienced nausea before discharge from the hospital. In contrast, 10 patients in group II (24%), and 15 in group III (42%) experienced nausea. Although this study demonstrated an impressive reduction in PONV, the study design could not identify to what extent each individual intervention contributed to the reduction in PONV. Furthermore, it was unclear what interactions might exist among the various antiemetic interventions, for example, whether there is a certain synergistic combination that contributes the most to these positive results.

Inspired by this, IMPACT, "an **I**nternational **M**ulticenter **P**rotocol to assess **A**ntiemetic **C**ombinations in a controlled clinical **T**rial of factorial design (IMPACT) was developed.[56,161] In this trial, 4123 patients were randomly assigned to 1 of 64 possible combinations of six prophylactic interventions: 4 mg of ondansetron or no ondansetron; 4 mg of dexamethasone or no dexamethasone; 1.25 mg of droperidol or no droperidol; propofol or a volatile anesthetic; nitrogen or nitrous oxide; and remifentanil or fentanyl. Ondansetron, dexamethasone, and droperidol each reduced the risk of PONV by about 26% (RR, 0.74).[56] Propofol reduced the risk by 19%, and nitrogen, by 12%; the combined RRR of propofol with no nitrous oxide (i.e., total intravenous anesthesia) was thus similar to that observed with each individual antiemetic. This study provided two major insights. First, it was demonstrated that all interventions acted independently of each other; therefore, the RRs associated with combined antiemetic interventions can be estimated by multiplying the relative risks associated with each intervention. For example, the RR for a triple combination of ondansetron plus dexamethasone plus droperidol is $0.74 \times 0.74 \times 0.74 = 0.41$; that is, the application of three antiemetics that each reduce the risk by about a fourth will result in an RRR of $1 - 0.41 = 59\%$. Figure 86-13 demonstrates that all three antiemetics are similarly effective, and all three double combinations are similarly effective because there are no interactions. Second, it was demonstrated that the efficacy of the drugs as measured by the OR or RR is independent of the patient's risk. As a consequence, the effectiveness (in terms of absolute risk difference or NNT) is primarily dependent on the patient's baseline risk rather than the choice of antiemetic, and each addition of an antiemetic to a combination regimen adds less and less additional benefit as the patient's risk decreases. As an example, a female nonsmoker without a history of PONV or motion sickness expected to require postoperative opioids has a PONV risk of about 60%.[5] If she receives an antiemetic (e.g., 4 mg of dexamethasone), her risk will decrease to 44% (Table 86-3, $0.6 \times 0.74 = 0.44$), which means that the absolute risk difference will be 16%.

$$\begin{aligned} \text{RRR} &= 1 - \text{RR} \\ \text{Absolute risk difference} &= \text{Patient's risk} \times \text{RRR} \\ &= \text{Patient's risk} \times (1 - \text{RR}) \end{aligned}$$

If she receives a triple antiemetic therapy, her risk will decrease to about 24%, and a fourth antiemetic would reduce the risk to 18% (see Table 86-3). Adding a fourth antiemetic would thus result in an absolute risk difference of only 6%, that is, less than half as much reduction as for the first antiemetic. Apparently, the first antiemetic has the greatest effectiveness and additional prophylactic antiemetics are associated with a decreased effectiveness because of the already decreased baseline risk. Another example

Table 86-3 Estimated PONV Incidence as a Function of Baseline Risk, Assuming Each Intervention Reduces Relative Risk by 26% (values given as %)

Number of Interventions				
None*	One	Two	Three	Four
10	7	5	4	3
20	15	11	8	6
40	29	22	16	12
60	44	33	24	18
80	59	44	32	24

*The exemplified baseline risk levels of 10%, 20%, 40%, 60%, and 80% reflect 0, 1, 2, 3, and 4 risk factors considered in a simplified risk score.[5]
Table from Apfel CC, Korttila K, Abdalla M, et al: A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 350:2441-2451, 2004.

would be a male smoker with a short procedure that will not require postoperative opioids who will start off with a risk of about 10%.[5] Even the first antiemetic will at best reduce the risk by no more than 3% (see Table 86-3). The key message here is that the patient's baseline risk is the main determinant of the effectiveness of antiemetic interventions, so prophylaxis is rarely justified in patients at low risk, a single antiemetic is likely to be reasonable for patients with a moderate risk, and patients at high risk are likely to benefit from combination treatment.[56]

Alternative or Adjuvant Approaches

Ginger is frequently assumed to have antiemetic properties, even though there are few studies, most of which are negative, and meta-analyses came to conflicting conclusions.[162-164] However, based on data from a comprehensive review from Carlisle and Stevenson, there appears to be a lack of evidence for ginger to be an effective intervention for the prevention of PONV.[104]

Liberal crystalloid fluid supplementation was first described to reduce nausea by Chung's group.[165] However, it is interesting that there appears to be little effect in the early postoperative period[166,167] while the effect becomes stronger in the late period.[165,168] One could speculate that balancing out the preoperative fluid deficit reduces the need to drink larger amounts in the later postoperative period, thereby reducing PONV. Future studies may lend clarity.

Various reports have investigated stimulation of the classic acupuncture P6 point (the 6th point on the pericardial meridian at the volar side of the wrist) for the prevention of PONV.[169-173] A Cochrane review by Lee and associates in 2004 identified 26 trials and found RRs of 0.72 for nausea and 0.71 for vomiting compared with sham.[174] As shown by White and associates, this effect is comparable to that of conventional antiemetics.[175] These positive results bring up the question of why P6 stimulation is only rarely used for the prevention of PONV. Because most studies were small, Lee and colleagues conducted a secondary simulation analysis that suggested that the effect for nausea, but not for vomiting, may be due to publication bias.[176] Based on the published evidence it appears that stimulation of the P6 wrist point by means of acupuncture, electro-acupuncture, transcutaneous nerve stimulation, laser stimulation, acu-stimulation device, and acupressure are effective measures for the prevention of PONV.

Special Settings

Pediatric Anesthesia (See Also Chapter 82)

Fewer studies have been conducted in children, and these generally focus on postoperative vomiting (POV) because the assessment of nausea can be difficult in younger children.[177,178] A limited number of studies have investigated risk factors,[179] but only one well-designed multicenter prospective survey developed a predictive model for POV (see also section "Risk Assessment").[69] Of note, while the impact of the type of surgery remains somewhat controversial in adults, strabismus surgery and especially myopexy (Faden surgery)[96,180] appear to be independent predictors for POV in children as determined by Eberhart and colleagues.[69] At the same time, against widely held belief, there is little evidence to suggest that ENT surgeries or appendectomies are independent predictors for POV.

Regarding antiemetics, it appears that efficacy is comparable to that known for adults. There are few thoroughly conducted dose response studies for antiemetics in adults and even fewer in children. Thus, most pediatric doses are arbitrarily set at about 1/50th to 1/25th of the common adult per kilogram dose.

Postdischarge Nausea and Vomiting

In the United States, more than 60% of surgeries are now performed on an outpatient basis (ambulatory surgery). In addition to being a major cause for delayed discharge and unanticipated readmissions, PONV may also pose a significant problem to the patient after discharge (see also Chapter 78).[181,182] To date, the incidence of postdischarge nausea and vomiting has not been studied on a large scale but a systematic review from Wu and colleagues suggest it to be 8% for emesis and 17% for nausea[183]; moreover, Carroll and colleagues found that 35% of patients were significantly distressed by postdischarge nausea and vomiting such that it delayed resumption of their normal daily activities.[184] Most patients await spontaneous resolution of symptoms without contacting health care professionals for interventions or antiemetics. Thus, the magnitude of the problem has not been fully recognized as yet and studies are ongoing to characterize patients at risk.

Interestingly, the RRR of antiemetics seems to be similar for postdischarge nausea and vomiting as for PONV. For example, according to a systematic review from Gupta and colleagues, the RR for postdischarge nausea is 0.77 for 4 mg of ondansetron, 0.68 for more than 1 mg of droperidol, and 0.55 for dexamethasone.[185] Note that shorter-acting drugs are not as effective, especially when used at the minimally effective dose, and that antiemetics with a longer duration of action appear favorable. Therefore, dexamethasone, scopolamine (due to the sustained release of the patch), palonosetron, and the NK1-receptor antagonists may be reasonable first choices for the prevention of postdischarge nausea and vomiting. Of course, further studies, especially with the novel compounds, are needed to support this hypothesis.

Rescue Treatment

While numerous studies have investigated antiemetics for prevention of PONV, relatively few have addressed their use for rescue treatment of established PONV. In fact, when Tramer and coworkers conducted a quantitative systematic review of rescue treatments for established nausea and vomiting, a total of only 18 randomized placebo-controlled trials met inclusion criteria.[186] They reported an absolute risk reduction between 20% and 30%, consistent with the 20% to 30% RRR known for prevention of PONV in large trials[56] (of note, in studies of rescue treatment, absolute risk reduction and RRR are equivalent measures because all patients who receive treatment have prior symptoms). In fact, Scuderi and colleagues demonstrated that early rescue treatment of PONV results in outcomes including time to discharge, unanticipated admission, and time to return to normal daily activities that are similar to those achieved with routine prophylactic treatment.[97] This finding does not, however, account for patient

comfort even thought this might be difficult to measure in terms of patient satisfaction.

With regard to dosage, early rescue treatment with 1 mg of ondansetron seems to have comparable efficacy and better effectiveness than 4 mg of prophylactic ondansetron.[187,188] Thus only a quarter dose is needed for rescue as opposed to preventive treatment.

Serotonin antagonists are not only the most commonly used antiemetics for prevention but also the most commonly used antiemetics for rescue treatment.[189] One reason may be that serotonin antagonists are currently the only class of intravenously available antiemetics that may have a rapid onset for rescue treatment while being without sedative side effects. As mentioned previously, serotonin antagonists are highly selective and tend to block almost all available receptors. Thus, one can predict that once ondansetron is used for prophylaxis, subsequent use for rescue treatment in the PACU would be ineffective. This has been confirmed by a well-powered study with 428 patients from Kovac and coworkers.[190] Nevertheless, ondansetron is still commonly used as first-line rescue treatment after previous prophylaxis, even though this is contrary to both theoretical considerations and available evidence. Similarly, one would predict that use of rescue granisetron, another serotonin antagonist, would be ineffective in patients who previously received ondansetron for PONV prevention, as has been shown by Candiotti and colleagues.[191] Therefore, as a rule of thumb, it is currently assumed that after administering an antiemetic it is most effective to choose an antiemetic of another class for later rescue treatment. This is corroborated by a secondary analysis from Habib and associates that shows that after prophylaxis with either ondansetron and droperidol, promethazine rescue treatment is significantly more effective than repeat dosing with the same agent.[192]

Dexamethasone has been shown to be as effective as ondansetron for the prevention of PONV.[56] Clinically, it appears to have a fairly slow onset, as supported by observations that it has better efficacy when given at the beginning rather than at the end of the procedure.[153] Nevertheless, Rusch and associates were able to show that adding dexamethasone to either ondansetron or haloperidol for rescue treatment increases the overall RRR during a 24-hour period.[193]

In conclusion, drugs for rescue treatment appear to have the same efficacy and thus, better effectiveness compared with when they are given for prevention. In addition, lower doses are needed for rescue treatment than for prevention and it is preferable to administer drugs that have not been used previously.

A Rational Guideline for the Management of PONV

The wealth of published information poses a challenge for the anesthesia provider to develop a comprehensive and valid strategy for the prevention and treatment of PONV. To this end, consensus guidelines have been developed. However, the fact that a group of individuals agree or compromise on a certain content or wording does not guarantee infallibility. For example, some guidelines report the NNT for various interventions as if this would allow a comparison of drug efficacy among trials even though that would methodologically not be sound (see earlier section to appreciate the difference between efficacy and effectiveness).

Therefore, instead of summarizing various consensus guidelines, this last section describes a rational approach for the prevention and treatment of PONV that is based on the current knowledge and understanding outlined in this chapter. This should be taken as a guide for clinicians but not as a rigid rule because there are certainly a number of other similarly valid approaches. To this end, the rule of three would be helpful: (1) assess the need for prevention, (2) titrate preventive measures (that includes a modification of the anesthetic technique) according to the patient's need, and (3) follow up on your patient and use rescue treatment immediately by targeting mechanisms that have not been tried before.

Consider the Importance of the Prevention of PONV

This is influenced by the patient's risk for PONV, the potential medical problem associated with it, and the perspective and values of both the patient and the health care provider. It is advisable to estimate the patient's risk using a risk score, that is the score from Apfel and associates or Koivuranta and colleagues for adults and the score from Eberhart and coworkers for children.[4,5,69] Even though these scores are far from being perfect, they provide a better prediction compared with the history of PONV or the type of surgery.[38]

Titrate to the Patient's Needs

Patients with Limited Need for Preventive Measures

In general, the use of prophylactic antiemetics is rarely justified when the patient's risk is low (e.g., 10%-20%) (Fig. 86-14).[56] The reason is the low effectiveness at low risk so that many patients need to be treated for one patient to benefit and are thus unnecessarily exposed to an antiemetic that may have—even though it might be rare—associated side effects (e.g., sedation, headache, QT prolongations, torsades de pointes). However, as mentioned earlier, the use may be justified if this is a patient's preference or there are concerns about medical or surgical complications due to vomiting.

Patients Who Require Some Preventive Measures

At moderate risk, one or two antiemetic measures are often appropriate but these do not need to be antiemetic drugs. One approach could be a total intravenous anesthetic (TIVA with propofol, air, and fentanyl) or the use of 4 mg of dexamethasone or both after the induction of anesthesia supplemented with measures to minimize opioid consumption (NSAIDs, lidocaine, low-dose ketamine).

Patients in Whom Significant Preventive Measures Should Be Undertaken

At high or very high risk, avoidance of general anesthesia and minimization of perioperative opioids may be the most effective approach (e.g., peripheral nerve block, spinal anesthesia).[79] However, if a general anesthetic is needed, a TIVA with 4 mg of

Risk factors	Points
Female gender	1
Nonsmoker	1
History of PONV	1
Postoperative opioids	1
Risk score =	0...4

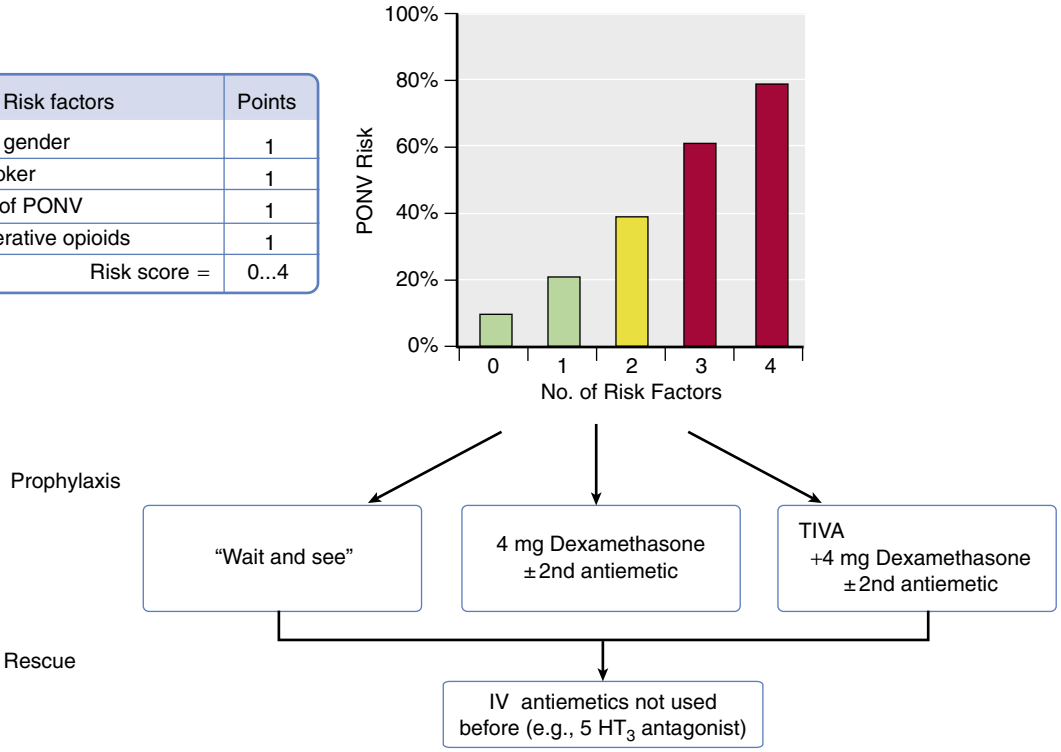


Figure 86-14 Algorithm for the management of PONV.

dexamethasone[56] and an additional antiemetic (e.g., 12.5 to 25 mg of promethazine, 31.25 to 62.5 mg of dimenhydrinate, or 25 to 50 mg of metoclopramide) can be recommended. Which partner drug to choose is most likely not relevant because most drugs appear similarly effective[104] and indirect evidence suggests that interventions with different mechanisms are additive, that is, work independently.[56] Of course, a TIVA could be substituted by an inhaled anesthetic with an additional antiemetic, but this eliminates one rescue treatment option should PONV occur in the PACU. This is particularly true for the use of a serotonin antagonist, which may otherwise be an effective rescue option without sedative side effects.

Rescue without Delay

Options for rescue treatment are interventions that have not been applied before or where the half-life suggests that it is no longer active.[190] Serotonin antagonists, if they were not given in the operating room, may be first choice in the PACU because of their lack of sedative side effects. Also, the addition of dexamethasone to dolasetron or haloperidol might increase the overall risk reduction for rescue treatment (again if it has not been given before).[193] Finally, stimulation of the P6 acupressure point may be another option, given that its efficacy has been demonstrated for the prevention of PONV.

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Robert W. Hurley and Christopher L. Wu

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Key Points

1. The process of nociception is not a hard-wired characteristic but a plastic and dynamic process (i.e., neuroplasticity) with multiple points of activation and modulation. Persistent noxious input may result in relatively rapid neuronal sensitization and possibly chronic pain.
2. Postoperative pain, especially when poorly controlled, results in harmful acute effects (i.e., adverse physiologic responses) and chronic effects (i.e., delayed long-term recovery and chronic pain).
3. By preventing central sensitization, preemptive analgesia may reduce acute and chronic pain. Although experimental studies overwhelmingly support the concept of preemptive analgesia, the evidence from clinical trials is equivocal because of methodologic issues.
4. By allowing individual titration of analgesic agents, use of patient-controlled anesthesia (intravenous or epidural) may provide several advantages over traditional provider-administered analgesia (e.g., intramuscular injections) in the management of postoperative pain.
5. The incidence of respiratory depression from opioids does not appear to be significantly different among the various routes of administration (i.e., intravenous versus intramuscular versus subcutaneous versus neuraxial). Appropriate monitoring of patients receiving opioid analgesics is essential to detect those with opioid-related side effects such as respiratory depression. Whether patients receiving neuraxial opioid analgesics require monitoring in an intensive care unit is debatable, although there is literature demonstrating the relatively safe use of single-dose and continuous-infusion neuraxial opioids on routine surgical wards under appropriate monitoring conditions.
6. Judicious use of adjuvant agents, such as nonsteroidal anti-inflammatory drugs, may improve postoperative analgesia and diminish analgesic-related side effects.
7. When compared with systemic opioids, perioperative epidural analgesia may confer several advantages, including a facilitated return of gastrointestinal function and decrease in the incidence of pulmonary complications, coagulation-related adverse events, and possibly cardiovascular events, especially in higher-risk patients or procedures. However, the risks and benefits of epidural analgesia should be evaluated for each patient, and appropriate monitoring protocols should be used during postoperative epidural analgesia.
8. Epidural analgesia is not a generic entity because different catheter locations (catheter-incision congruent versus catheter-incision incongruent), durations of postoperative analgesia, and analgesic regimens (local anesthetics versus opioids) may differentially affect perioperative morbidity.
9. Postoperative pain management should be tailored to the needs of special populations (e.g., ambulatory surgical, elderly, opioid-tolerant, pediatric, and obese patients, as well as those with obstructive sleep apnea) who may have different anatomic, physiologic, pharmacologic, or psychosocial issues.

Fundamental Considerations

A revolution in the management of acute postoperative pain has occurred during the past 3 decades. Widespread recognition of the undertreatment of acute pain by clinicians, economists, and health policy experts has led to the development of a national clinical practice guideline for management of acute pain by the Agency for Healthcare Quality and Research (formerly the Agency for Health Care Policy and Research) of the U.S. Department of Health and Human Services.[1] This landmark document includes acknowledgment of the historical inadequacies in perioperative pain management, importance of good pain control, need for accountability for adequate provision of perioperative analgesia by health care institutions, and a statement on the need for involvement of specialists in appropriate cases. In addition, several professional societies (e.g., American Society of Anesthesiologists,[2] Joint Commission on Accreditation of Healthcare Organizations) have developed clinical practice guidelines for

acute pain management or provided new pain management standards.

With their knowledge of and familiarity with pharmacology, various regional techniques, and the neurobiology of nociception, anesthesiologists are continually in the vanguard of clinical and research advances in acute postoperative pain management. Anesthesiologists are leaders in the development of acute postoperative pain services, application of evidence-based practice to acute postoperative pain, and creation of innovative approaches to acute pain management, all of which are a natural part of the anesthesiologist's functions as a "perioperative physician," consultant, and therapist throughout an institution, and as a highly skilled expert in the operating room. Provision of effective analgesia for surgical and other medical patients is an important component of this multidimensional role.

Pain Pathways and the Neurobiology of Nociception

Surgery produces tissue injury with consequent release of histamine and inflammatory mediators such as peptides (e.g., bradykinin), lipids (e.g., prostaglandins), neurotransmitters (e.g., serotonin), and neurotrophins (e.g., nerve growth factor).[3] Release of inflammatory mediators activates peripheral nociceptors, which initiate transduction and transmission of nociceptive information to the central nervous system (CNS) and the process of neurogenic inflammation in which release of neurotransmitters (i.e., substance P and calcitonin gene–related peptide) in the periphery induces vasodilatation and plasma extravasation.[3] Noxious stimuli are transduced by peripheral nociceptors and transmitted by Aδ and C nerve fibers from peripheral visceral and somatic sites to the dorsal horn of the spinal cord, where integration of peripheral nociceptive and descending modulatory input (i.e., serotonin, norepinephrine, γ-aminobutyric acid, enkephalin) occurs. Further transmission of nociceptive information is determined by complex modulating influences in the spinal cord. Some impulses pass to the ventral and ventrolateral horns to initiate segmental (spinal) reflex responses, which may be associated with increased skeletal muscle tone, inhibition of phrenic nerve function, or even decreased gastrointestinal motility. Others are transmitted to higher centers through the spinothalamic and spinoreticular tracts, where they induce suprasegmental and cortical responses to ultimately produce the perception of and affective component of pain.

Continuous release of inflammatory mediators in the periphery sensitizes functional nociceptors and activates dormant ones.[4] Sensitization of peripheral nociceptors may occur and is marked by a decreased threshold for activation, increased rate of discharge with activation, and increased rate of basal (spontaneous) discharge.[4] Intense noxious input from the periphery may also result in central sensitization ("persistent postinjury changes in the CNS that result in pain hypersensitivity"[5]) and hyperexcitability ("exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage"[5]). Such noxious input may lead to functional changes in the dorsal horn of the spinal cord and other consequences that may later cause postoperative pain to be perceived as more painful than it would otherwise have been. The neural circuitry in the dorsal horn is extremely complex, and we are just beginning to elucidate the specific role of the various neurotransmitters and receptors in the process of nociception.[3,6] However, it seems that certain receptors (e.g., *N*-methyl-D-aspartate [NMDA]) may be especially important for the development of chronic pain after an acute injury, although other neurotransmitters or second messenger effectors (e.g., substance P, protein kinase C-γ) may also play important roles in spinal cord sensitization and chronic pain.[7] Our understanding of the neurobiology of nociception has progressed from the hard-wired system proposed by Descartes in the 17th century to the current view of neuroplasticity in which dynamic integration and modulation of nociceptive transmission take place at several levels. There still are many gaps in our knowledge of the specific roles of various receptors, neurotransmitters, and molecular structures in the process of nociception.

An understanding of the neurobiology of nociception is important for appreciating the transition from acute to chronic pain. The traditional dichotomy between acute and chronic pain is arbitrary inasmuch as animal and clinical studies demonstrate that acute pain may quickly transition into chronic pain.[4] Experimental studies show that noxious stimuli can produce expression of new genes (which are the basis for neuronal sensitization[7]) in the dorsal horn of the spinal cord within 1 hour and that these changes are sufficient to alter behavior within the same timeframe.[6] Clinical studies also suggest that the intensity of acute postoperative pain is a significant predictor of chronic postoperative pain.[8] Control of perioperative pain (e.g., preventive analgesia) and the fashion in which it is implemented (e.g., multimodality perioperative management) may be important in facilitating short- and long-term patient convalescence after surgery.

Acute and Chronic Effects of Postoperative Pain

Uncontrolled postoperative pain may produce a range of detrimental acute and chronic effects. The attenuation of perioperative pathophysiology that occurs during surgery through reduction of nociceptive input to the CNS and optimization of perioperative analgesia may decrease complications and facilitate recovery during the immediate postoperative period[9] and after discharge from the hospital.

Acute Effects

The perioperative period is associated with a variety of pathophysiologic responses that may be initiated or maintained by nociceptive input. Although these responses may have had a beneficial teleologic purpose, the same response to the iatrogenic nature of modern-day surgery may be harmful. Uncontrolled perioperative pain may potentiate some of these perioperative pathophysiologies and increase patient morbidity and mortality. Attenuation of postoperative pain, especially with certain types of analgesic regimens, may decrease perioperative morbidity and mortality.[10]

Transmission of nociceptive stimuli from the periphery to the CNS results in the neuroendocrine stress response, a combination of local inflammatory substances (e.g., cytokines, prostaglandins, leukotrienes, tumor necrosis factor-α) and systemic mediators of the neuroendocrine response. The dominant neuroendocrine responses to pain involve hypothalamic-pituitary-adrenocortical and sympathoadrenal interactions.

Suprasegmental reflex responses to pain result in increased sympathetic tone, increased catecholamine and catabolic hormone secretion (e.g., cortisol, adrenocorticotropic hormone, antidiuretic hormone, glucagon, aldosterone, renin, angiotensin II), and decreased secretion of anabolic hormones.[11] The effects include sodium and water retention and increased levels of blood glucose, free fatty acids, ketone bodies, and lactate. A hypermetabolic, catabolic state occurs as metabolism and oxygen consumption are increased and metabolic substrates are mobilized from storage depots.[11] The extent of the stress response is influenced by many factors, including the type of anesthesia and intensity of the surgical injury, with the extent of the stress response being proportional to the degree of surgical trauma.[12] The negative nitrogen balance and protein catabolism may impede convalescence; however, attenuation of the stress response and postoperative pain may facilitate and accelerate the patient's recovery postoperatively.

The neuroendocrine stress response may potentiate detrimental physiologic effects in other areas of the body. The stress response may be an important factor in the postoperative development of hypercoagulability.[10] Enhancement of coagulation (i.e., decreased levels of natural anticoagulants and increased levels of procoagulants), inhibition of fibrinolysis, and increased platelet reactivity and plasma viscosity may contribute to an elevated incidence of postoperative hypercoagulable-related events such as deep venous thrombosis, vascular graft failure, and myocardial ischemia.[10,13] The stress response may also potentiate postoperative immunosuppression, the extent of which correlates with the severity of surgical injury.[4] Hyperglycemia from the stress response may contribute to poor wound healing and depression of immune function.

Uncontrolled postoperative pain may activate the sympathetic nervous system and thereby contribute to morbidity or mortality. Sympathetic activation may increase myocardial oxygen consumption, which may be important in the development of myocardial ischemia and infarction,[10,13] and may decrease myocardial oxygen supply through coronary vasoconstriction and attenuation of local metabolic coronary vasodilation.[10] Activation of the sympathetic nervous system may also delay return of postoperative gastrointestinal motility, which may develop into paralytic ileus. Although postoperative ileus is the result of a combination of inhibitory input from central and local factors,[10,13] an increase in sympathetic efferent activity, such as from uncontrolled pain, may decrease gastrointestinal activity and delay return of gastrointestinal function.

Nociceptors are activated after surgical trauma and may initiate several detrimental spinal reflex arcs. Postoperative respiratory function is markedly decreased, especially after upper abdominal and thoracic surgery. Spinal reflex inhibition of phrenic nerve activity is an important component of this decreased postoperative pulmonary function.[10,13] However, control of postoperative pain is also important because patients with poor pain control may breathe less deeply, have an inadequate cough, and be more susceptible to the development of postoperative pulmonary complications.[10] Activation of nociceptors may also initiate spinal reflex inhibition of gastrointestinal tract function and delay return of gastrointestinal motility.[10,13]

Many detrimental pathophysiologic effects occur in the perioperative period and are associated with activation of nociceptors and the stress response. Uncontrolled pain may result in activation of the sympathetic nervous system, which can cause a variety of potentially harmful physiologic responses that may adversely influence the extent of morbidity and mortality. Nociceptor activation may also result in several detrimental inhibitory spinal reflexes. Control of the pathophysiologic processes associated with acute postoperative pain may attenuate the stress response, sympathetic outflow, and inhibitory spinal reflexes and contribute to improvements in morbidity, mortality, and patient-reported outcomes (e.g., health-related quality of life [HRQL], patient satisfaction).[13]

Chronic Effects

Chronic postsurgical pain [CPSP] is a largely unrecognized problem that may occur in 10% to 65% of postoperative patients (depending on the type of surgery), with 2% to 10% of these patients experiencing severe CPSP.[14] Poorly controlled acute postoperative pain may be an important predictive factor in the development of CPSP.[8,15] Increasing experimental and clinical evidence suggests that the transition from acute to chronic pain occurs very quickly and that long-term behavioral and neurobiologic changes occur much earlier than was previously thought.[4] CPSP is relatively common after procedures such as limb amputation (30% to 83%), thoracotomy (22% to 67%), sternotomy (27%), breast surgery (11% to 57%), and gallbladder surgery (up to 56%).[8] Although studies suggest that the severity of acute postoperative pain may be an important predictor in the development of CPSP,[8] a causal relationship between the severity of acute postoperative pain and subsequent CPSP has not been definitively established, and other factors (i.e., area of postoperative hyperalgesia) may be more important in predicting the development of CPSP.[16]

Control of acute postoperative pain may improve long-term recovery or patient-reported outcomes (e.g., quality of life). Patients whose pain is controlled in the early postoperative period (especially with the use of continuous epidural or peripheral catheter techniques) may be able to actively participate in postoperative rehabilitation, which may improve short- and long-term recovery after surgery.[17] Optimizing treatment of acute postoperative pain can improve HRQL.[18] Postoperative chronic pain that develops as a result of poor postoperative pain control may interfere with patients' activities of daily living.

Preventive Analgesia

Central sensitization and hyperexcitability develop after the surgical incision and result in amplification of postoperative pain. Preventing the establishment of altered central processing by analgesic treatment may result in short-term (e.g., reduction in postoperative pain and accelerated recovery) and long-term (e.g., reduction in chronic pain and improvement in HRQL[18]) benefits during a patient's convalescence. Although experimental studies convincingly confirm the concept of preemptive analgesia in decreasing postinjury pain, the results of clinical trials are mixed.[19,20]

The precise definition of preemptive analgesia is one of the major controversies in this area of medicine and contributes to the question of whether preemptive analgesia is clinically relevant. Definitions of preemptive analgesia include what is administered before the surgical incision, what prevents the establishment of central sensitization resulting from incisional injury only (i.e., intraoperative period), what prevents central sensitization resulting from incisional and inflammatory injury (i.e., intraoperative

and postoperative periods), or the entire perioperative period encompassing preoperative interventions, intraoperative analgesia, and postoperative pain management (i.e., preventive analgesia).[5] The first two definitions are relatively narrow and may contribute to the lack of a detectable effect of preemptive analgesia in clinical trials. Timing of the intervention[19] may not be as clinically important as other aspects of preventive analgesia (i.e., intensity and duration of the intervention). An intervention administered before the surgical incision is not necessarily preemptive if it is incomplete or insufficient such that central sensitization is not prevented. Incisional and inflammatory injuries are important in initiating and maintaining central sensitization. Confining the definition of preemptive analgesia to only the intraoperative (incisional) period may not be clinically relevant or appropriate because the inflammatory response may last well into the postoperative period and continue to maintain central sensitization. Other methodologic and study design issues may also complicate the question of whether preventive analgesia is clinically relevant.

A variety of drugs and techniques[19] have been used to study preemptive analgesia. Using the broader definition of preventive analgesia that covers incisional (intraoperative) and inflammatory (postoperative) injury, the combination of experimental data and positive clinical trials strongly suggests that preemptive analgesia is a clinically relevant phenomenon. Maximal clinical benefit is observed when there is complete blockade of noxious stimuli with extension of this block into the postoperative period. By preventing central sensitization, preemptive analgesia along with intensive multimodal analgesic interventions[19] could theoretically reduce acute postoperative pain/hyperalgesia and chronic pain after surgery.[8]

Multimodal Approach to Perioperative Recovery

The analgesic benefits of controlling postoperative pain are generally maximized when a multimodal strategy to facilitate the patient's convalescence is implemented.[21] Postoperative pain treatment may not be enough to provide major improvements in some outcomes because it is unlikely that a unimodal intervention can be effective in addressing a complex problem such as perioperative outcomes.[9,22] Principles of a multimodal strategy include control of postoperative pain to allow early mobilization, early enteral nutrition, education, and attenuation of the perioperative stress response through the use of regional anesthetic techniques[9] and a combination of analgesic agents (i.e., multimodal analgesia). The use of epidural anesthesia and analgesia is an integral part of the multimodal approach because of the superior analgesia and physiologic benefits conferred by epidural analgesia.

A multimodal approach to perioperative recovery to control postoperative pathophysiology and facilitate rehabilitation may result in accelerated recovery and decreased length of hospitalization.[23] Patients undergoing major abdominal or thoracic procedures and who participate in a multimodal strategy have a reduction in hormonal and metabolic stress, preservation of total-body protein, shorter times to extubation, lower pain scores, earlier return of bowel function, and earlier fulfillment of intensive care unit discharge criteria.[23] By integrating the most recent data and techniques from surgery, anesthesiology, nociceptive neurobiology, and pain treatment, the multimodal approach may be seen as an extension of "clinical pathways" or "fast tracks" by revising traditional care programs into effective postoperative rehabilitation pathways.[23] This approach may potentially decrease perioperative morbidity, reduce the length of hospital stay, and improve patient satisfaction without compromising safety. However, widespread implementation of these programs requires multidisciplinary collaboration, change in the traditional principles of postoperative care, additional resources, and expansion of the traditional acute pain service, which may be difficult in the current economic climate.

Treatment Methods

Many options are available for the treatment of postoperative pain, including systemic (i.e., opioid and nonopioid) analgesics and regional (i.e., neuraxial and peripheral) analgesic techniques. By considering patients' preferences and making an individualized assessment of the risks and benefits of each treatment modality, the clinician can optimize the postoperative analgesic regimen for each patient. Essential aspects of postoperative monitoring of patients receiving various postoperative analgesic treatment methods are listed in Box 87-1.[2]

Systemic Analgesic Techniques

Opioids

Advantages and Characteristics

Opioid analgesics are one of the cornerstone options for the treatment of postoperative pain. These agents generally exert their analgesic effects through μ-receptors in the CNS, although there is evidence that opioids may also act at peripheral opioid receptors.[24] A theoretical advantage of opioid analgesics is that there is no analgesic ceiling. Realistically, the analgesic efficacy of opioids is typically limited by the development of tolerance or opioid-related side effects such as nausea, vomiting, sedation, or respiratory depression. Opioids may be administered by the subcutaneous, transcutaneous, transmucosal, or intramuscular route, but the most common routes of postoperative systemic opioid analgesic administration are oral and intravenous. Opioids may also be administered at specific anatomic sites such as the intrathecal or epidural space (see later sections, "Single-Dose Neuraxial Opioids" and "Continuous Epidural Analgesia").

There is wide intersubject and intrasubject variability in the relationship of opioid dose, serum concentration, and analgesic response in the treatment of postoperative pain.[25] Serum drug concentrations may exhibit wider variability with certain routes of administration (e.g., intramuscular) than with others (e.g., intravenous). In general, opioids are administered parenterally (intravenously or intramuscularly) for the treatment of moderate to severe postoperative pain, in part because these routes provide a more rapid and reliable onset of analgesic action than the oral

Box 87-1 Monitoring and Documentation of Postoperative Analgesia

Analgesic Medication*
Name, concentration, and dose of drug
Settings of PCA device: demand dose, lockout interval, continuous infusion
Amount of drug administered (including number of unsuccessful and successful doses)
Limits set (e.g., 1- and 4-hour limits on dose administered)
Supplemental or breakthrough analgesics

Routine Monitoring
Vital signs: temperature, heart rate, blood pressure, respiratory rate
Analgesia
Pain at rest and with activity, pain relief
Use of breakthrough medication

Side Effects
Cardiovascular: hypotension, bradycardia, or tachycardia
Respiratory status: respiratory rate, level of sedation
Nausea and vomiting, pruritus, urinary retention
Neurologic examination
Assessment of motor block or function and sensory level
Evidence of epidural hematoma

Instructions Provided
Treatment of side effects
Concurrent use of other CNS depressants
Parameters for triggering notification of the covering physician
Provision of contact information (24 hours/7 days per week) if problems occur
Emergency analgesic treatment if the PCA device fails

*Postoperative analgesia includes systemic opioids and regional analgesic techniques. This list incorporates some of the important elements of preprinted orders, documentation, and intravenous PCA and epidural analgesia daily care described in the ASA Practice Guidelines for Acute Pain Management.[2]
CNS, central nervous system; PCA, patient-controlled analgesia.

route does. Parenteral opioid administration may be necessary in patients who are unable to tolerate oral intake postoperatively. The transition from parenteral to oral administration of opioids usually occurs after the patient initiates oral intake and postoperative pain has been stabilized with parenteral opioids. Although oral opioids (typically formulated as part of a combination product that includes an adjuvant such as acetaminophen) are generally prescribed on an "as needed" (PRN) basis postoperatively, there may be a role for sustained-release oral opioids, which may provide analgesia superior to that with conventional PRN regimens.[26] Although the traditional form (passive) of transdermal fentanyl is not indicated for the routine treatment of acute postoperative pain, a newer version involving patient-activated electrically facilitated delivery of transdermal fentanyl has been introduced for use in hospitalized adult patients.[27]

Intravenous Patient-Controlled Analgesia

Various factors, including the aforementioned wide interpatient and intrapatient variability in analgesic needs, variability in serum drug levels (especially with intramuscular injection), and administrative delays, may contribute to inadequate postoperative analgesia. It may be difficult to compensate for these factors with the use of a traditional PRN analgesic regimen. By circumventing some of these issues, intravenous patient-controlled analgesia (PCA) optimizes delivery of analgesic opioids and minimizes the effects of pharmacokinetic and pharmacodynamic variability in individual patients. Intravenous PCA is based on the premise that a negative-feedback loop exists; when pain is experienced, analgesic medication is self-administered, and when pain is reduced, there are no further demands. When the negative-feedback loop is violated, excessive sedation or respiratory depression may occur.[28] Although some equipment-related malfunctions have been reported, the PCA device itself is relatively free of problems, and most problems related to PCA use result from user or operator error.[28]

A PCA device can be programmed for several variables, including the demand (bolus) dose, lockout interval, and background infusion (Table 87-1). An optimal demand or bolus dose is integral to the efficacy of intravenous PCA because an insufficient demand dose may result in inadequate analgesia whereas an excessive demand dose may result in a higher incidence of undesirable side effects such as respiratory depression.[29] Although the optimal demand dose is uncertain, the data available suggest that the optimal demand dose is 1 mg for morphine and 40 μg for fentanyl in opioid-naive patients; however, the actual dose for fentanyl (10 to 20 μg) is often less in clinical practice.[28,29] The lockout interval may also affect the analgesic efficacy of intravenous PCA. A lockout interval that is too long may result in inadequate analgesia and decrease the effectiveness of intravenous PCA. A lockout interval that is too short allows the patient to self-administer another demand dose before feeling the full analgesic effect of the previous dose and thus may contribute to an increase in medication-related side effects. In essence, the lockout interval is a safety feature of intravenous PCA, and although the optimal lockout interval is unknown, most intervals range from 5 to 10 minutes, depending on the medication in the PCA pump; varying the interval within this range appears to have no effect on analgesia or side effects.[28]

Most PCA devices allow administration of a continuous or background infusion in addition to the demand dose. Initially, routine use of a background infusion was thought to confer certain advantages, including improved analgesia, especially during sleep; however, subsequent trials failed to demonstrate any analgesic benefits of a background infusion in opioid-naïve patients.[30] Many studies show that use of a background infusion only increases the analgesic dosage used and the incidence of side effects such as respiratory depression.[31] Use of a nighttime background infusion does not improve postoperative sleep patterns, analgesia, or recovery profiles.[32] Although routine use of continuous or background infusion as part of intravenous PCA in adult opioid-naive patients is not recommended, there may be a role for use of a background infusion in opioid-tolerant or

Table 87-1 Intravenous Patient-Controlled Analgesia Regimens

Drug Concentration	Size of Bolus*	Lockout Interval (min)	Continuous Infusion
Agonists			
Morphine (1 mg/mL)			
Adult	0.5-2.5 mg	5-10	—
Pediatric	0.01-0.03 mg/kg (max, 0.15 mg/kg/hr)	5-10	0.01-0.03 mg/kg/hr
Fentanyl (0.01 mg/mL)			
Adult	10-20 μg	4-10	—
Pediatric	0.5-1 μg/kg (max, 4 μg/kg/hr)	5-10	0.5-1 μg/kg/hr
Hydromorphone (0.2 mg/mL)			
Adult	0.05-0.25 mg	5-10	—
Pediatric	0.003-0.005 mg/kg (max, 0.02 mg/kg/hr)	5-10	0.003-0.005 mg/kg/hr
Alfentanil (0.1 mg/mL)	0.1-0.2 mg	5-8	—
Methadone (1 mg/mL)	0.5-2.5 mg	8-20	—
Meperidine (10 mg/mL)	5-25 mg	5-10	—
Oxymorphone (0.25 mg/mL)	0.2-0.4 mg	8-10	—
Sufentanil (0.002 mg/mL)	2-5 μg	4-10	—
Agonist-Antagonists			
Buprenorphine (0.03 mg/mL)	0.03-0.1 mg	8-20	—
Nalbuphine (1 mg/mL)	1-5 mg	5-15	—
Pentazocine (10 mg/mL)	5-30 mg	5-15	—

*All doses are for adult patients unless noted otherwise. Units vary across agents for size of the bolus (mg versus mg/kg versus μg versus μg/kg) and continuous infusion (mg/kg/hr versus μg/kg/hr). The anesthesiologist should proceed with titrated intravenous loading doses if necessary to establish initial analgesia. Individual patient requirements vary widely, with smaller doses typically given to elderly or compromised patients. Continuous infusions are not initially recommended for opioid-naive adult patients.

pediatric patients (see later sections, "Opioid-Tolerant Patients" and "Pediatric Patients").

When compared with traditional PRN analgesic regimens, intravenous PCA provides superior postoperative analgesia and improves patient satisfaction, but it is unclear whether intravenous PCA can provide any economic benefits.[33] A meta-analysis (55 studies, 2023 subjects) revealed that intravenous PCA (versus PRN opioids) provides significantly greater analgesia and patient satisfaction; however, patients used more opioids and had a higher incidence of pruritus than those treated with PRN opioids, but there was no difference in the incidence of adverse events.[33] With regard to economic outcomes, it is not clear whether intravenous PCA is superior to traditional PRN intramuscular opioid administration because the calculations of cost are complex. Although there appears to be no improvement in hospital length of stay with intravenous PCA, it does require less nursing time than intramuscular injections do, which may be important with the shift toward using a higher percentage of less skilled providers on surgical and medical wards.[34]

Intravenous PCA may provide advantages when assessing other patient-related outcomes such as patient satisfaction; these outcomes have become more important as health care organizations use them as a measure of quality and a tool for marketing purposes. Patients tend to prefer intravenous PCA over intravenously, intramuscularly, or subcutaneously administered PRN opioids.[35] Greater patient satisfaction with intravenous PCA may be the result of superior analgesia and perceived control over the administration of analgesic medications and avoidance of disclosing pain or securing analgesic medication from nurses.[36] However, the reasons for patient satisfaction are complex, and many factors contribute to or predict satisfaction with intravenous PCA.[35,36] Patients' willingness to pay for and the timing of cessation of intravenous PCA may also influence satisfaction ratings.[37] Although intravenous PCA use overall appears to be associated with greater satisfaction, there are many methodologic issues in the proper assessment of patient satisfaction.[38]

The incidence of opioid-related adverse events from intravenous PCA does not seem to differ significantly from that of PRN opioids administered intravenously, intramuscularly, or subcutaneously. The rate of respiratory depression associated with intravenous PCA is low (<0.5%) and does not appear to be higher than that with PRN systemic or neuraxial opioids.[31,39] Factors that may be associated with the occurrence of respiratory depression with intravenous PCA include use of a background infusion, advanced age, concomitant administration of sedative or hypnotic agents, and coexisting pulmonary disease such as sleep apnea.[31,39] Intravenous PCA–related respiratory depression may also be caused by errors in programming or administration (i.e., operator error).

Nonopioids

Nonsteroidal Anti-inflammatory Agents

Nonsteroidal anti-inflammatory drugs (NSAIDs), which include aspirin and acetaminophen, consist of a diverse group of analgesic compounds with different pharmacokinetic properties. The primary mechanism by which NSAIDs exert their analgesic effect

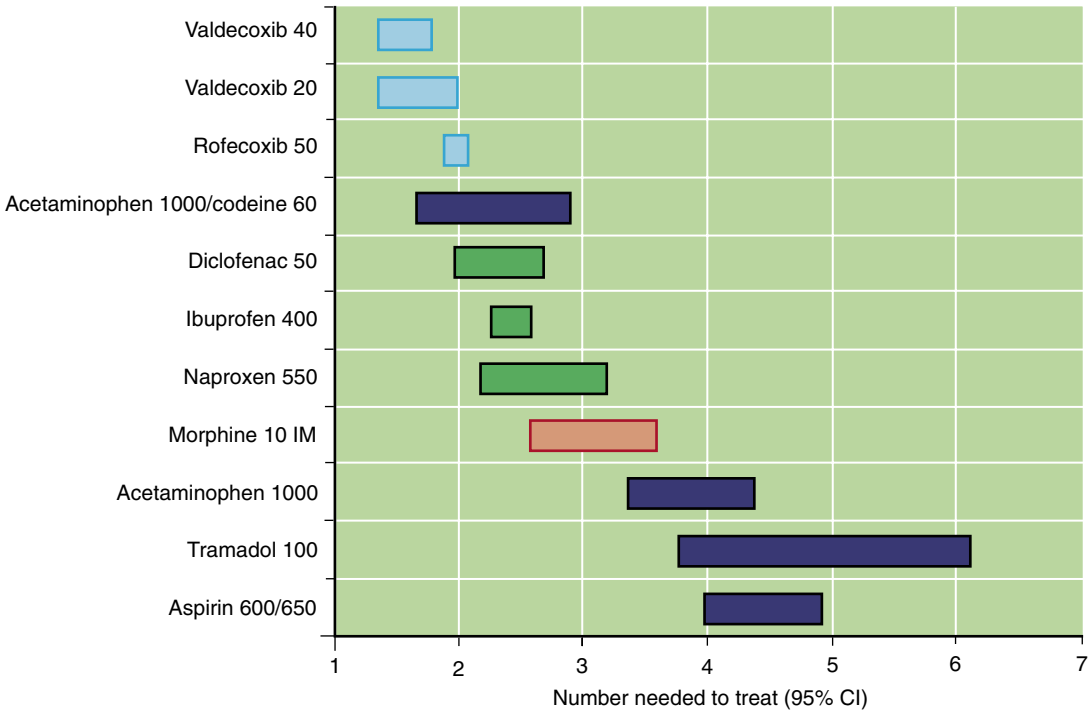


Figure 87-1 Number needed to treat (NNT) for at least 50% pain relief in patients with moderate to severe pain. The mean and 95% confidence interval (CI) for the NNTs are shown for several opioid and nonopioid analgesics from Table 87-2. The NNTs are derived from trials investigating the efficacy of a single dose of nonopioid analgesic versus placebo in providing more than 50% pain relief for moderate to severe postoperative pain. Numbers with drug names are doses in mg. *(From Bandolier. Available at http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/Leagtab.html/ Accessed February 8, 2008.)*

is through inhibition of cyclooxygenase (COX) and synthesis of prostaglandins, which are important mediators of peripheral sensitization and hyperalgesia. Though traditionally viewed primarily as peripherally acting agents, NSAIDs can also exert their analgesic effects through inhibition of spinal COX.[40] The discovery of at least two COX isoforms (i.e., COX-1 is constitutive and COX-2 is inducible) with different functions (i.e., COX-1 participates in platelet aggregation, hemostasis, and gastric mucosal protection, whereas COX-2 participates in pain, inflammation, and fever) has led to the development of selective COX-2 inhibitors that differ from traditional NSAIDs, which block both COX-1 and COX-2.[41] The discovery of a COX-3 variant may represent a primary central mechanism by which acetaminophen and other antipyretics decrease pain and fever; however, the precise relationship between COX-3 and acetaminophen is still uncertain.[42]

Used as a sole agent, NSAIDs generally provide effective analgesia for mild to moderate pain. NSAIDs are also traditionally considered a useful adjunct to opioids for the treatment of moderate to severe pain, although some quantitative, systematic reviews suggest that NSAIDs, alone or in combination with opioids, may be more beneficial than previously thought (Table 87-2 and Fig. 87-1). NSAIDs may be administered orally or parenterally and are particularly useful as components of a multimodal analgesic regimen by producing analgesia through a different mechanism from that of opioids or local anesthetics. However, several meta-analyses have examined the analgesic efficacy of NSAIDs (including COX-2 inhibitors) and acetaminophen when added to intravenous PCA with opioids. Only NSAIDs,[44] not acetaminophen,[45] resulted in a statistically significant (but probably not clinically meaningful) reduction in pain scores.[46,47] Although all regimens significantly decreased morphine consumption, only NSAIDs (but not acetaminophen) reduced risk for the opioid-related side effects of nausea, vomiting, and sedation.

Perioperative use of NSAIDs is associated with a number of side effects, including decreased hemostasis, renal dysfunction, gastrointestinal hemorrhage, and deleterious effects on bone healing and osteogenesis. Many of these side effects are related to inhibition of COX and the formation of prostaglandins, which mediate many diverse processes throughout the body. Decreased hemostasis from NSAID use is attributed primarily to platelet dysfunction and inhibition of thromboxane A_2 (generated by COX-1), an important mediator of platelet aggregation and vasoconstriction.[48] Evidence of the effect of NSAIDs on perioperative bleeding is equivocal, and a surveillance study of perioperative ketorolac did not demonstrate a significant increase in operative site bleeding.[49]

Perioperative NSAID-induced renal dysfunction may occur in high-risk patients, such as those with hypovolemia,

Table 87-2 Relative Efficacy of Single-Dose Analgesics in Providing Greater than 50% Relief of Moderate to Severe Postoperative Pain

Drug*	Mean NNT†	95% CI
Diclofenac (100 mg PO)	1.9	1.6-2.2
Rofecoxib (50 mg PO)	1.9	1.8-2.1
Codeine (60 mg) + acetaminophen (1000 mg PO)	2.2	1.7-2.9
Diclofenac (50 mg PO)	2.3	2.0-2.7
Ibuprofen (600 mg PO)	2.4	1.9-3.3
Oxycodone (15 mg PO)	2.4	1.5-4.9
Oxycodone (5 mg) + acetaminophen (325 mg PO)	2.5	2.0-3.2
Ketorolac (10 mg PO)	2.6	2.3-3.1
Meperidine (100 mg IM)	2.9	2.3-3.9
Morphine (10 mg IM)	2.9	2.6-3.6
Ketorolac (30 mg IM)	3.4	2.5-4.9
Acetaminophen (1000 mg PO)	3.8	3.4-4.4
Aspirin (1000 mg PO)	4.0	3.2-5.4
Codeine (60 mg) + acetaminophen (600 to 650 mg PO)	4.2	3.4-5.3
Aspirin (600 to 650 mg PO)	4.4	4.0-4.9
Dextropropoxyphene (65 mg) + acetaminophen (650 mg PO)	4.4	3.5-5.6
Acetaminophen (600 to 650 mg PO)	4.6	3.9-5.5
Tramadol (100 mg PO)	4.8	3.8-6.1
Dextropropoxyphene (65 mg PO)	7.7	4.6-22
Dihydrocodeine (30 mg PO)	8.1	4.1-540
Codeine (60 mg PO)	16.7	11.0-48.0

CI, confidence interval; IM, intramuscular; NNT, number needed to treat; PO, oral route.

*Data obtained in part and modified from Bandolier with permission. Available at http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/Leagtab.html.

†NNT in this case refers to the number of patients who must be treated to obtain greater than 50% relief of moderate to severe postoperative pain.[43] NNT conveys statistical and clinical significance, is useful in comparing the efficacy of different interventions, and summarizes treatment effects in a clinically relevant manner.[43] A lower mean NNT implies greater analgesic efficacy in this example. See Figure 87-1 for a graphic presentation of these data.

abnormal renal function, or abnormal serum electrolytes, because prostaglandins dilate the renal vascular beds and mediate diuretic and natriuretic renal effects.[50] Euvolemic patients with normal renal function are unlikely to be affected; a meta-analysis did not demonstrate any significant reduction in urine volume or cases of postoperative renal failure requiring dialysis, and there does not appear to be a benefit in using COX-2 inhibitors instead of traditional nonselective NSAIDs in reducing the incidence of renal complications.[51] NSAIDs may also have an adverse effect on bone healing and spinal fusion, but preliminary evidence suggests that COX-2 inhibitors may be an alternative when attempting to avoid the detrimental effects of nonselective NSAIDs on bone healing.[52] Perioperative use of NSAIDs is associated with a higher incidence of gastrointestinal bleeding[49] because of NSAID-inhibition of COX-1, which is required for the synthesis of cytoprotective gastric mucosal prostaglandins. Bronchospasm may be induced by NSAIDs (including aspirin) or acetaminophen, and there may be cross-sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects.[52]

Because expression of peripheral COX-2 is increased during inflammation, selective inhibition of COX-2 could theoretically provide analgesia without the side effects associated with COX-1 inhibition. COX-2 inhibitors are associated with a lower incidence of gastrointestinal complications[53] and exhibit minimal platelet inhibition, even when administered in supratherapeutic doses.[54] However, long-term use of COX-2 inhibitors has been associated with excess cardiovascular risk such that rofecoxib was withdrawn from the market.[55] Although cardiovascular toxicity appears to be a class effect of all COX-2 inhibitors, the cardiovascular risks of COX-2 inhibitors appear to be heterogeneous and influenced by many factors such as the specific medication, dosage, and patient characteristics.[55] Issues surrounding the perioperative use of COX-2 inhibitors are slightly different from those of longer-term use of COX-2 inhibitors.[56] Nussmeier and colleagues performed a randomized trial of valdecoxib and its intravenous prodrug parecoxib versus placebo to assess the safety of these drugs in patients undergoing coronary artery bypass grafting (CABG).[57] When compared with the group given placebo alone, both the group given parecoxib and valdecoxib and the group given placebo and valdecoxib had a higher proportion of patients with at least one confirmed adverse event.[57] The use of parecoxib and valdecoxib after CABG was associated with an increased incidence of cardiovascular events, thereby arousing serious concern about the use of these drugs in such circumstances.

Ketamine

Ketamine is traditionally recognized as an intraoperative anesthetic agent; however, increasing interest in the use of low-dose ketamine for postoperative analgesia has developed in part because of its NMDA-antagonistic properties, which may be important in attenuating central sensitization and opioid tolerance.[58] A systematic review of perioperative ketamine use found that perioperative subanesthetic doses of ketamine reduce rescue analgesic requirements or pain intensity.[59] In addition, perioperative ketamine reduced 24-hour PCA morphine consumption and postoperative nausea or vomiting and had minimal adverse effects.[59] In other studies, low-dose ketamine infusion does not appear to cause hallucinations or cognitive impairment, and the incidence of side effects, such as dizziness, itching, nausea, and vomiting, is comparable to that seen with opioids.[60] Ketamine has also been administered epidurally and intrathecally,[61,62] but racemic mixtures of ketamine have been found to be neurotoxic, and therefore the use of neuraxial ketamine is discouraged.

Tramadol

Tramadol is a synthetic opioid that exhibits weak μ-agonist activity and inhibits reuptake of serotonin and norepinephrine. Although tramadol exerts its analgesic effects primarily through central mechanisms, it may have peripheral local anesthetic properties.[63] Tramadol is effective in treating moderate postoperative pain[64] and comparable in analgesic efficacy to aspirin (650 mg) with codeine (60 mg) or ibuprofen (400 mg) (see Table 87-2 and Fig. 87-1).[64] Advantages of tramadol for postoperative analgesia

include a relative lack of respiratory depression, major organ toxicity, and depression of gastrointestinal motility and a low potential for abuse.[65] Common side effects (overall incidence of 1.6% to 6.1%) include dizziness, drowsiness, sweating, nausea, vomiting, dry mouth, and headache.[64] Tramadol should be used with caution in patients with seizures or increased intracranial pressure and is contraindicated in those taking monoamine oxidase inhibitors.[64]

Regional Analgesic Techniques

A variety of neuraxial (primarily epidural) and peripheral regional analgesic techniques may be used for the effective treatment of postoperative pain. In general, the analgesia provided by epidural and peripheral techniques (particularly when local anesthetics are used) is superior to that with systemic opioids,[66] and use of these techniques may even reduce morbidity and mortality.[10,13] However, there are risks associated with the use of such techniques, and the clinician should evaluate the risks and benefits of these techniques on an individual basis in determining the appropriateness of neuraxial or peripheral regional techniques for each patient, especially in light of some of the controversies about the use of these techniques in the presence of various anticoagulants.

Single-Dose Neuraxial Opioids

Administration of a single dose of opioid may be efficacious as a sole or adjuvant analgesic agent when administered intrathecally or epidurally. One of the most important factors in determining the clinical pharmacology for a particular opioid is its degree of lipophilicity (versus hydrophilicity) (Table 87-3). Once they have reacted the cerebrospinal fluid (CSF) through direct intrathecal injection or gradual migration from the epidural space, hydrophilic opioids (i.e., morphine and hydromorphone) tend to remain within the CSF and produce a delayed but longer duration of analgesia, along with a generally higher incidence of side effects because of the cephalic or supraspinal spread of these compounds.

Table 87-3 Properties of Neuraxial Opioids

Property	Lipophilic Opioids	Hydrophilic Opioids
Common drugs	Fentanyl, sufentanil	Morphine, hydromorphone
Onset of analgesia	Rapid onset (5-10 min)	Delayed onset (30-60 min)
Duration of analgesia*	Shorter duration (2-4 hr)	Longer duration (6-24 hr)
CSF spread	Minimal CSF spread	Extensive CSF spread
Site of action	Spinal ± systemic	Primarily spinal
Side effects		
Nausea and vomiting	Lower incidence with lipophilic than with hydrophilic opioids	
Pruritus	Lower incidence with lipophilic than with hydrophilic opioids	
Respiratory depression	Primarily early; minimal delay	Both early (<6 hr) and delayed (>6 hr) possible

CSF, cerebrospinal fluid.
*The duration of analgesia varies.

Neuraxial administration of lipophilic opioids, such as fentanyl and sufentanil, tends to provide a rapid onset of analgesia, and their rapid clearance from CSF may limit cephalic spread and the development of certain side effects such as delayed respiratory depression.[67] The site of analgesic action for hydrophilic opioids is overwhelmingly spinal, but the primary site of action (spinal versus systemic) for single-dose neuraxial lipophilic opioids is not as certain.[68]

The differences in pharmacokinetics between lipophilic and hydrophilic opioids may influence the choice of opioid in an attempt to optimize analgesia and minimize side effects for a particular clinical situation. Single-dose intrathecal administration of a lipophilic opioid may be useful in situations (e.g., ambulatory surgical patients) in which rapid analgesic onset (minutes) combined with a moderate duration of action (<4 hours) and minimal risk of respiratory depression is needed.[69] Single-dose hydrophilic opioid administration provides effective postoperative analgesia and may be useful in patients monitored on an inpatient basis, for whom a longer duration of analgesia would be beneficial.

Single-dose epidural administration of lipophilic and hydrophilic opioids is used to provide postoperative analgesia, with considerations generally being similar to those discussed for single-dose intrathecal administration of opioids. A single bolus of epidural fentanyl may be administered to provide rapid postoperative analgesia; however, diluting the epidural dose of fentanyl (typically 50 to 100 μg) in at least 10 mL of preservative-free normal saline is suggested to decrease the onset and prolong the duration of analgesia, possibly as a result of an increase in initial spread and diffusion of the lipophilic opioid.[70] Single-dose epidural morphine is effective for postoperative analgesia and may decrease postoperative patient morbidity in selected patients.[71,72] Use of a single-dose hydrophilic opioid may be especially helpful in providing postoperative epidural analgesia when the epidural catheter's location is not congruent with the surgical incision (e.g., lumbar epidural catheter for thoracic surgery). Lower doses of epidural morphine may be required for elderly patients and thoracic catheter sites. Commonly used dosages for intrathecal and epidural administration of neuraxial opioids are provided in Table 87-4.

An extended-release formulation of (single-dose) epidural morphine encapsulated within liposomes that results in up to 48 hours of analgesia has recently been introduced.[73] There are some precautions in using this newer formulation of epidural morphine. To resuspend the particles immediately before withdrawal from the vial, the vial should be gently inverted with avoidance of aggressive or excessive agitation. Concurrent administration of liposomal extended-release morphine and local anesthetics may increase peak concentrations of morphine. Accordingly, the manufacturer has recommended that clinicians increase the interval between administration of local anesthetic (including test doses) and liposomal extended-release morphine to at least 15 minutes to minimize this pharmacokinetic interaction. In addition, because the liposomal extended-release morphine does not contain any bacteriostatic agents, it should be administered within 4 hours after withdrawal from the vial. Finally, as with traditional single-dose neuraxial opioids, clinicians should administer a lower dose of liposomal extended-release morphine to the elderly or those with decreased physiologic reserve or coexisting disease. At this time, liposomal extended-release morphine has not been studied or approved in pediatric patients.

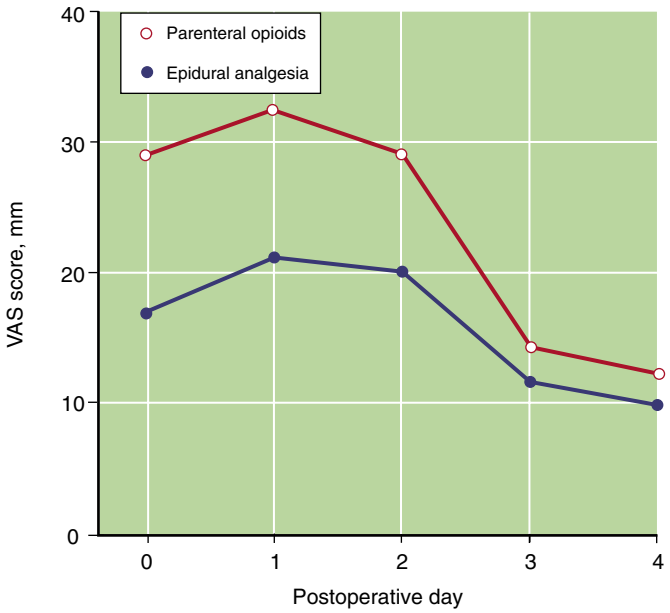
Table 87-4 Dosing of Neuraxial Opioids*

Drug	Intrathecal or Subarachnoid Single Dose	Epidural Single Dose	Epidural Continuous Infusion
Fentanyl	5-25 μg	50-100 μg	25-100 μg/hr
Sufentanil	2-10 μg	10-50 μg	10-20 μg/hr
Alfentanil	—	0.5-1 mg	0.2 mg/hr
Morphine	0.1-0.3 mg	1-5 mg	0.1-1 mg/hr
Diamorphine	1-2 mg	4-6 mg	—
Hydromorphone	—	0.5-1 mg	0.1-0.2 mg/hr
Meperidine	10-30 mg	20-60 mg	10-60 mg/hr
Methadone	—	4-8 mg	0.3-0.5 mg/hr
Extended-release morphine†	Not recommended	5-15 mg	Not recommended

*Doses are based on the use of a neuraxial opioid alone. No continuous intrathecal or subarachnoid infusions are provided. Lower doses may be effective when administered to the elderly or when injected in the cervical or thoracic region. Units vary across agents for single dose (mg versus μg) and continuous infusion (mg/hr versus μg/hr).
†See package insert for details on dosage and administration.

Continuous Epidural Analgesia

Analgesia delivered through an indwelling epidural catheter is a safe and effective method for management of acute postoperative pain.[74] Postoperative epidural analgesia can provide analgesia superior to that with systemic opioids (Fig. 87-2).[75,76] Of note, however, epidural analgesia is not a generic term but incorporates a wide range of options, including the choice and dose of analgesic agents, location of catheter placement, and onset and duration of perioperative use.[74] Although this section focuses on the postoperative management of epidural analgesia, it is important to realize that intraoperative use of the epidural catheter as part of a combined epidural-general anesthetic technique results in less pain and faster patient recovery immediately after surgery than general anesthesia followed by systemic opioids does.[77] Each of



No. of patient observations

Parenteral opioids	1104	2635	1496	794	536
Epidural analgesia	1010	2618	1527	822	566

Figure 87-2 Mean and standard deviation of visual analog pain scores (*y* axis) for both epidural analgesia (represented by *dark blue circles*) and parenteral opioids (represented by *open red circles*) for each postoperative day (*x* axis) up to the fourth day after surgery. *(From Block BM, Liu SS, Rowlingson AJ, et al: Efficacy of postoperative epidural analgesia: A meta-analysis. JAMA 290:2455-2463, 2003, with permission.)*

these options may affect the quality of postoperative analgesia, patient-reported outcomes, and even rates of morbidity and mortality.

Analgesic Drugs

Local Anesthetics. Epidural infusion of local anesthetic alone may be used for postoperative analgesia, but in general it is not as effective in controlling pain as local anesthetic–opioid epidural analgesic combinations are.[75,76] The precise location of action of local anesthetics in the epidural space is not clear, and potential sites include the spinal nerve roots, dorsal root ganglion, or spinal cord itself.[68] Although some anatomic data suggest that the initial site of epidural local anesthetic block is at the nerve root sheath and dorsal root ganglion,[78] experimental data demonstrate that the initial site of action may not be at the spinal nerve root sleeve.[79] Epidural infusion of local anesthetic alone may be warranted for postoperative analgesia in an attempt to avoid opioid-related side effects; however, the sole use of local anesthetics is less common than the use of a local anesthetic–opioid combination because of a significant failure rate (from regression of sensory blockade and inadequate analgesia) and relatively high incidence of motor block and hypotension.[74]

Opioids for Epidural Infusion. Opioids may be used alone for postoperative epidural infusion and do not generally cause motor block or hypotension from sympathetic blockade.[74] There are differences between continuous epidural infusion of lipophilic (e.g., fentanyl, sufentanil) and hydrophilic (e.g., morphine, hydromorphone) opioids. The analgesic site of action (spinal versus systemic) of continuous epidural infusion of lipophilic opioids is not clear, although several randomized clinical trials suggest that it is systemic[80] because there were no differences in plasma concentrations, side effects, or pain scores between those who received intravenous or epidural infusion of fentanyl.[80] Although some data suggest a benefit from epidural (versus intravenous) infusion of lipophilic opioids,[81] the overall advantage of administering continuous epidural infusion of lipophilic opioids alone is marginal.[74]

The analgesic site of action for continuous hydrophilic opioid infusion is primarily spinal.[82] Continuous infusion of a hydrophilic opioid may be especially useful for providing postoperative analgesia when the site of catheter insertion is not congruent with the site of surgery or when side effects (e.g., hypotension, motor block) are attributed to the epidural local anesthetic. Use of a continuous infusion rather than intermittent boluses of epidural morphine may result in superior analgesia with fewer side effects.[82] Continuous epidural infusion of hydrophilic opioids may provide analgesia superior to that of traditional PRN administration of systemic opioids.[83]

Local Anesthetic–Opioid Combinations. Use of a local anesthetic and an opioid in an epidural infusion may have advantages over infusions consisting of a local anesthetic or opioid alone. When compared with a local anesthetic or opioid alone, a local anesthetic–opioid combination provides superior postoperative analgesia (including improved dynamic pain relief), limits regression of sensory blockade, and possibly decreases the dose of local anesthetic administered, although the effect on the incidence is uncertain.[74] Continuous epidural infusion of a local anesthetic–opioid combination also provides analgesia superior to that of intravenous PCA with opioids.[75] It is unclear whether the analgesic effect of the local anesthetic and opioid in epidural analgesia is additive or synergistic. Experimental studies demonstrate a synergistic effect between local anesthetics and opioids[84]; however, clinical trials suggest an additive effect.[85]

The choice of local anesthetic for continuous epidural infusion varies. In general, bupivacaine, ropivacaine, or levobupivacaine is chosen because of the differential and preferential clinical sensory blockade with minimal impairment of motor function.[86] Concentrations used for postoperative epidural analgesia (≤0.125% bupivacaine or levobupivacaine or ≤0.2% ropivacaine) are lower than those used for intraoperative anesthesia. The choice of opioid also varies, although many clinicians prefer a lipophilic opioid (fentanyl, 2 to 5 μg/mL, or sufentanil, 0.5 to 1 μg/mL) to allow rapid titration of analgesia.[74,82] Use of a hydrophilic opioid (morphine, 0.05 to 0.1 mg/mL, or hydromorphone, 0.01 to 0.05 mg/mL) as part of a local anesthetic–opioid epidural analgesic regimen may also provide effective postoperative analgesia.[82]

Although the optimal local anesthetic and opioid dose that provides the lowest pain scores with the fewest medication-related side effects is unknown, a direct search method incorporating various epidural analgesic agents in patients undergoing major abdominal surgery revealed that the two optimal epidural bupivacaine-fentanyl combinations were 8 mg/hr of bupivacaine plus 30 μg/hr of fentanyl and 13 mg/hr of bupivacaine plus 25 μg/hr of fentanyl at a continuous infusion of 9 mL/hr.[87] Further investigation is needed to determine the optimal combinations for other types of surgical procedures with different epidural catheter insertion sites and to compare the efficacy of these optimal continuous infusions with patient-controlled epidural analgesia (PCEA).

Adjuvant Drugs. A variety of adjuvants may be added to epidural infusions to enhance analgesia while minimizing side effects, but none has gained widespread acceptance. Two of the more studied adjuvants are clonidine and epinephrine. Clonidine mediates its analgesic effects primarily through the spinal dorsal horn α_2-receptors on primary afferents and interneurons, as well as the descending noradrenergic pathway, and the epidural dose typically used ranges from 5 to 20 μg/hr.[87,88] Clinical application of clonidine is limited by its side effects: hypotension, bradycardia, and sedation.[88] Hypotension and bradycardia are both dose dependent. Epinephrine may improve epidural analgesia, can increase sensory blockade, and is generally administered at a concentration of 2 to 5 μg/mL.[89,90] Epidural administration of NMDA antagonists, such as ketamine, can theoretically be useful in attenuating central sensitization and potentiating the analgesic effect of epidural opioids, but additional safety and analgesic data are needed.

Location of Catheter Insertion

Insertion of the epidural catheter congruent to the incisional dermatome (i.e., catheter-incision–congruent analgesia) (Table 87-5) results in optimal postoperative epidural analgesia by infusing analgesic agents to the appropriate incisional dermatomes, providing superior analgesia, minimizing side effects (e.g., lower extremity motor block and urinary retention), and decreasing morbidity.[13,74] Observational and randomized data suggest that when compared with catheter-incision–congruent epidural analgesia, catheter-incision–incongruent epidural analgesia (e.g., low lumbar catheter placement for thoracic procedures) results in increased pain and early removal of the epidural catheter because of ineffective analgesia.[91] By targeting delivery of analgesic agents to the appropriate dermatomes, catheter-incision–congruent

Table 87-5 Recommended Catheter Insertion Sites for Surgical Procedures

Location of Incision	Examples of Surgical Procedures	Congruent Epidural Catheter Placement
Thoracic	Lung reduction, radical mastectomy, thoracotomy, thymectomy	T4-8
Upper abdominal	Cholecystectomy, esophagectomy, gastrectomy, hepatic resection, Whipple procedure	T6-8
Middle abdominal	Cystoprostatectomy, nephrectomy	T7-10
Lower abdominal	Abdominal aortic aneurysm repair, colectomy, radical prostatectomy, total abdominal hysterectomy	T8-11
Lower extremity	Femoral-popliteal bypass, total hip or total knee replacement	L1-4

L, lumbar level; T, thoracic level.

epidural analgesia may result in lower drug requirements and decreased medication-related side effects. There is a higher incidence of lower extremity motor block with the use of lumbar epidural catheters, and an earlier-than-anticipated termination of epidural analgesia may also result.[92] Use of a high thoracic epidural does not inhibit sympathetic nerve activity in the lower extremities, which are supplied by sympathetic nerve fibers from T9 to L1.[93] Use of thoracic epidural analgesia for abdominal or thoracic surgery may result in a relatively low incidence of urinary retention and diminish the need for routine bladder catheterization.[94] Placement of thoracic epidural catheters appears to be relatively safe, and there is no evidence of a higher incidence of neurologic complications with placement of a thoracic (versus lumbar) epidural catheter.[95] The benefits of epidural analgesia in decreasing morbidity in patients undergoing abdominal and thoracic surgery are seen only with thoracic (congruent), not lumbar (incongruent) epidural catheter placement.[96,97]

Side Effects of Neuraxial Analgesic Drugs

Many medication-related (opioid and local anesthetic) side effects can occur with the use of postoperative epidural analgesia, but before automatically ascribing the cause to the epidural analgesic regimen, it is important to first consider other causes, such as low intravascular volume, bleeding, and low cardiac output leading to hypotension and cerebrovascular accident, pulmonary edema, and evolving sepsis leading to respiratory depression. Standing orders and nursing protocols for analgesic regimens, neurologic monitoring, treatment of side effects, and physician notification about critical parameters should be standard for all patients receiving neuraxial and other types of postoperative analgesia (see Box 87-1).

Hypotension. The local anesthetics used in an epidural analgesic regimen may block sympathetic fibers and contribute to postoperative hypotension. Although the incidence of postoperative hypotension with postoperative epidural analgesia may be as high as approximately 7%, the average may be closer to 0.7% to 3%.[74,98] Strategies to treat noncritical hypotension caused by epidural analgesia include decreasing the overall dose of local anesthetic administered (by decreasing the rate or concentration), infusing an opioid epidural alone because it is unlikely that neuraxial opioid administration would contribute to postoperative hypotension, and treating the underlying cause of the decrease in blood pressure.[74]

Motor Block. Use of local anesthetics for postoperative epidural analgesia may also contribute to lower extremity motor block in approximately 2% to 3% of patients,[74,98] and this may lead to the development of pressure sores in the heels.[99] A lower concentration of local anesthetic and catheter-incision–congruent placement of epidural catheters for abdominal or thoracic procedures may decrease the incidence of motor block.[100] Although motor block resolves in most cases after stopping the epidural infusion for approximately 2 hours, persistent or increasing motor block should be evaluated promptly, and spinal hematoma, spinal abscess, and intrathecal catheter migration should be considered as part of the differential diagnosis.[74]

Nausea and Vomiting. Nausea and vomiting associated with neuraxial administration of single-dose opioid occurs in approximately 20% to 50% of patients,[101] and the cumulative incidence in those receiving continuous infusions of opioid may be as high as 45% to 80%.[102] Clinical and experimental data suggest that the incidence of neuraxial opioid–related nausea and vomiting is dose dependent.[103] Nausea and vomiting from neuraxial opioids may be related to the cephalad migration of opioid within the CSF to the area postrema in the medulla.[101] Use of fentanyl alone or in combination with a local anesthetic in an epidural infusion is associated with a lower incidence of nausea and vomiting than infusions of morphine are.[102,104] A variety of agents have been used successfully to treat neuraxial opioid–induced nausea and vomiting, including naloxone, droperidol, metoclopramide, dexamethasone, ondansetron, and transdermal scopolamine.[105,106]

Pruritus. Pruritus is one of the most common side effects of epidural or intrathecal administration of opioids, with an incidence of approximately 60% versus about 15% to 18% for epidural local anesthetic administration or systemic opioids.[107] Although the cause of neuraxial opioid–induced pruritus is uncertain, it does not appear to be associated with peripheral histamine release but may be related to central activation of an "itch center" in the medulla or activation of opioid receptors in the trigeminal nucleus or nerve roots with cephalad migration of the opioid.[101] It is unclear whether the incidence of neuraxial opioid–related pruritus is dose dependent because a quantitative systematic review[107] suggested no evidence of a relationship whereas other clinical and experimental studies have indicated a significant correlation.[108] Use of an epidural infusion of fentanyl alone or as part of a local anesthetic–opioid combination appears to generally be associated with a lower incidence of pruritus than is the case with morphine.[104] A variety of agents have been evaluated for the prevention and treatment of opioid-induced pruritus. Intravenous naloxone, naltrexone, nalbuphine, and droperidol appear to be efficacious for the pharmacologic control of opioid-induced pruritus.[107] Although pruritus is a common side effect, it

is relatively easy to treat and not considered an important clinical outcome to avoid.[109] The use of epidural morphine is associated with postpartum reactivation of herpes simplex labialis.[110]

Respiratory Depression. Neuraxial opioids used in appropriate doses are not associated with a higher incidence of respiratory depression than that seen with systemic administration of opioids. The incidence of respiratory depression with neuraxial administration of opioids is dose dependent and typically ranges from 0.1% to 0.9%.[39,111] The incidence of respiratory depression with continuous infusion of epidural opioids appears to be no greater than that seen after systemic opioid administration.[39,111] Although some institutions require that patients with continuous epidural infusion of hydrophilic opioids be monitored in an intensive care unit setting, many large-scale trials have demonstrated the relative safety (incidence of respiratory depression <0.9%) of this technique on regular surgical wards.[112]

Neuraxial lipophilic opioids are thought to cause less delayed respiratory depression than hydrophilic opioids are, although administration of lipophilic opioids may be associated with significant, early respiratory depression.[113] Delayed respiratory depression is primarily associated with the cephalad spread of hydrophilic opioids, which typically occurs within 12 hours after injection of morphine.[114] Risks factors for respiratory depression with neuraxial opioids include increasing dose, increasing age, concomitant use of systemic opioids or sedatives and possibly prolonged or extensive surgery, the presence of comorbid conditions, and thoracic surgery.[114] Clinical assessments, such as the respiratory rate, may not reliably predict a patient's ventilatory status or impending respiratory depression. Treatment with naloxone (and airway management if necessary) is effective in 0.1- to 0.4-mg increments; however, because its clinical duration of action is relatively short in comparison to the respiratory depressant effect of neuraxial opioids, continuous infusion of naloxone (0.5 to 5 µg/kg/hr) may be needed.[115]

Urinary Retention. Urinary retention associated with the neuraxial administration of opioids is the result of an interaction with opioid receptors in the spinal cord that decreases the detrusor muscle's strength of contraction.[101] The incidence of urinary retention seems to be higher with neuraxially administered opioids than when given systemically. However, the exact incidence of urinary retention seen clinically may be difficult to determine because patients who undergo major surgical procedures are often routinely catheterized. Urinary retention does not appear to depend on the opioid dose and may be treated with the use of low-dose naloxone, though at the risk of reversing the analgesic effect.[115] Epidural administration of local anesthetics is also associated with urinary retention, with a reported rate of approximately 10% to 30%.[116] Higher epidural infusion rates of local anesthetics (with a greater extent of sensory block and a higher incidence of motor block) may be associated with a higher incidence of urinary retention.[117]

Patient-Controlled Epidural Analgesia

Epidural analgesia has traditionally been delivered at a fixed rate or as a continuous epidural infusion (CEI); however, the administration of epidural analgesia through a patient-controlled device (PCEA) has become more common. Like intravenous PCA, PCEA allows individualization of postoperative analgesic requirements and may have several advantages over CEI, including lower drug use and greater patient satisfaction.[43] PCEA may also provide analgesia superior to that afforded by intravenous PCA.[75]

PCEA is a safe and effective technique for postoperative analgesia on routine surgical wards. Observational data from two series of over 1000 patients each reveal that more than 90% of patients with PCEA receive adequate analgesia, with a median pain score of 1 (of a possible 10) at rest and 4 with activity.[98,118] The incidence of side effects is 1.8% to 16.7% for pruritus, 3.8% to 14.8% for nausea, 13.2% for sedation, 4.3% to 6.8% for hypotension, 0.1% to 2% for motor block, and 0.2% to 0.3% for respiratory depression.[98,118] These rates are favorable and comparable to those reported with CEI, which is associated with an incidence of 10.2% to 22% for pruritus, 3.1% to 22% for nausea, 7.4% for sedation, 0.7% to 6.6% for hypotension, 3% for motor block, and 0.1% to 1.6% for respiratory depression.[112,119]

The optimal PCEA analgesic solution and delivery parameters are unclear. Use of a continuous or background infusion in addition to the demand dose is more common with PCEA than with intravenous PCA and may provide analgesia superior to that with the use of a demand dose alone.[120] In general, most acute pain specialists have gravitated toward a variety of low-concentration local anesthetic–opioid combinations (Table 87-6) in an attempt to improve analgesia while minimizing side effects, such as motor block and respiratory depression. As for CEI, addition of an opioid to the local anesthetic can provide analgesia superior to that with either agent alone.[121] A lipophilic opioid is usually chosen because its rapid analgesic effect and shorter duration of action may be more suitable for use with PCEA.[98] The roles

Table 87-6 Patient-Controlled Epidural Analgesia Regimens

Analgesic Solution*	Continuous Rate (mL/hr)	Demand Dose (mL)	Lockout Interval (min)
General Regimens			
0.05% bupivacaine + 4 µg/mL fentanyl	4	2	10
0.0625% bupivacaine + 5 µg/mL fentanyl†	4-6	3-4	10-15
0.1% bupivacaine + 5 µg/mL fentanyl	6	2	10-15
0.2% ropivacaine + 5 µg/mL fentanyl	5	2	20
Thoracic Surgery			
0.0625%-0.125% bupivacaine + 5 µg/mL fentanyl†	3-4	2-3	10-15
Abdominal Surgery			
0.0625% bupivacaine + 5 µg/mL fentanyl†	4-6	3-4	10-15
0.125% bupivacaine + 0.5 µg/mL sufentanil	3-5	2-3	12
0.1%-0.2% ropivacaine + 2 µg/mL fentanyl	3-5	2-5	10-20
Lower Extremity Surgery			
0.0625%-0.125% bupivacaine + 5 µg/mL fentanyl†	4-6	3-4	10-15
0.125% levobupivacaine + 4 µg/mL fentanyl	4	2	10

*Regimens listed are samples of local anesthetic–lipophilic opioid combinations from the literature.
†Patient-controlled epidural analgesic regimens commonly used at the Johns Hopkins Hospital.

of other adjuvant agents, including clonidine, have begun to be addressed. In one study, clonidine added to a mixture of bupivacaine and morphine administered into the epidural space was found to provide improved analgesia with few side effects after total-knee arthroplasty.[122]

Benefits of Epidural Analgesia

Use of perioperative epidural anesthesia and analgesia, especially with a local anesthetic–based analgesic solution, can attenuate the pathophysiologic response to surgery and may be associated with a reduction in mortality and morbidity when compared with analgesia with systemic (opioid) agents.[10,13] A meta-analysis of randomized data (141 trials enrolling 9559 subjects) demonstrated that perioperative use of neuraxial anesthesia and analgesia (versus general anesthesia and systemic opioids) reduced overall mortality (primarily in orthopedic patients) by approximately 30%.[123] Use of epidural analgesia can decrease the incidence of postoperative gastrointestinal, pulmonary, and possibly cardiac complications.[10,13]

By inhibiting sympathetic outflow, decreasing the total opioid dose, and attenuating spinal reflex inhibition of the gastrointestinal tract,[10] postoperative thoracic epidural analgesia can facilitate return of gastrointestinal motility without contributing to anastomotic bowel dehiscence.[124] Randomized clinical trials demonstrate that use of postoperative thoracic epidural analgesia with a local anesthetic–based analgesic solution allows earlier return of gastrointestinal function and fulfillment of discharge criteria.[125] When compared with those who receive epidural opioids for postoperative analgesia, patients who receive epidural local anesthetics have an earlier return of gastrointestinal motility after abdominal surgery.[125]

Perioperative use of epidural analgesia with a local anesthetic–based regimen in patients undergoing abdominal and thoracic surgery decreases postoperative pulmonary complications,[126,127] presumably by preserving postoperative pulmonary function by providing superior analgesia and thus reducing "splinting" behavior and attenuating the spinal reflex inhibition of diaphragmatic function.[10] A meta-analysis of 48 randomized clinical trials[128] and another large, randomized clinical trial[129] demonstrated that use of thoracic epidural analgesia with a local anesthetic–based regimen decreased the incidence of pulmonary infections and complications. However, patients who received postoperative epidural opioids, intercostal blocks, wound infiltration, or intrapleural analgesia did not have a significant decrease in the incidence of pulmonary complications.[128]

Use of postoperative thoracic, but not lumbar epidural analgesia may decrease the incidence of postoperative myocardial infarction,[97] possibly by attenuating the stress response and hypercoagulability, improving postoperative analgesia, and providing favorable redistribution of coronary blood flow.[10] The finding that only thoracic epidural analgesia decreases the incidence of postoperative myocardial infarction corroborates experimental data on the physiologic benefits of thoracic epidural analgesia, such as a reduction in the severity of myocardial ischemia or size of infarction, attenuation of sympathetically mediated coronary vasoconstriction, and improvement of coronary flow to areas at risk for ischemia.[10]

Although postoperative epidural analgesia appears to decrease postoperative gastrointestinal, pulmonary, and possibly cardiac morbidity, the benefits of postoperative epidural analgesia are not as clear in other areas, such as postoperative coagulation, cognitive dysfunction,[130] and immune function. Despite the fact that many randomized clinical trials and meta-analyses show that use of *intra*operative regional anesthesia decreases the incidence of hypercoagulable-related events (e.g., deep venous thrombosis, pulmonary embolism, vascular graft failure),[123,131] evidence of a beneficial effect of *post*operative epidural analgesia in decreasing the incidence of hypercoagulable-related events is not compelling.

The benefits of postoperative epidural analgesia are optimized when the epidural catheter is inserted in a location corresponding to the dermatomes covered by the surgical incision (i.e., catheter-incision–congruent analgesia), which results in a lower dose of drug administered and decreased incidence of drug-induced side effects, such as pruritus, nausea, vomiting, urinary retention, motor block, and hypotension.[98,132] When compared with catheter-incision–incongruent epidural analgesia, catheter-incision–congruent analgesia[132] provides earlier return of gastrointestinal function,[96] a lower incidence of myocardial infarction,[97] and superior analgesia.[91] The ability of postoperative epidural analgesia to attenuate postoperative pathophysiology and improve outcomes also depends on the type of drugs used (opioids versus local anesthetics). Maximal attenuation of perioperative pathophysiology occurs with the use of a local anesthetic–based epidural analgesic solution. The use of a local anesthetic–based (versus opioid-based) analgesic solution is associated with earlier recovery of gastrointestinal motility after abdominal surgery[125] and less frequent occurrence of pulmonary complications.[128] Epidural analgesia is not a generic entity because different catheter locations and analgesic regimens may differentially affect perioperative morbidity.

Use of postoperative epidural analgesia may be associated with an improvement in postoperative analgesia and patient-reported outcomes such as patient satisfaction[38] and HRQL.[18] When compared with systemic opioids, epidural local anesthetics consistently provide superior analgesia.[75,76] The data on the analgesic superiority of postoperative epidural analgesia reflect that seen with epidural analgesia during labor.[133] Although the concept of satisfaction is complex and difficult to measure accurately, the analgesic benefits of postoperative epidural analgesia may contribute to greater patient satisfaction[38] and improved HRQL.[18]

Risks with Epidural Analgesia

The benefits of perioperative epidural anesthesia-analgesia must be weighed against the risks associated with this technique. Risks and benefits should be evaluated for each patient. Some complications are associated with placement of an epidural catheter, and several risks related to the use of indwelling epidural catheters (e.g., epidural hematoma and abscess) should be discussed in the context of postoperative epidural analgesia. A review of neurologic complications after regional anesthesia revealed that the rate of neurologic complications after central neuraxial blockade is less than 4 in 10,000 (0.04%); the rate of neuropathy after a peripheral nerve block is less than 3 in 100 (3%).[134] However, permanent neurologic injury after either central neuraxial or peripheral nerve block is rare in contemporary anesthetic practice.[134] Elements of routine monitoring of patients receiving neuraxial analgesia are presented in Box 87-1.

The concurrent use of anticoagulants and neuraxial anesthesia and analgesia has always been a relatively controversial

issue but has been highlighted over the past decade by the increased incidence of spinal hematoma after the introduction of low-molecular-weight heparin in North America in 1993. Traditionally, the incidence of spinal hematoma is estimated to be approximately 1 in 150,000 for epidural blocks, with a lower incidence of 1 in 220,000 for spinal blocks.[135] Before its introduction in North America, low-molecular-weight heparin was used in Europe without significant problems; however, the incidence of spinal hematoma rose to as high as 1 in 40,800 for spinal anesthetics and 1 in 6600 for epidural anesthetics (1 in 3100 for postoperative epidural analgesia) in the United States between 1993 and 1998.[136] The estimate of the higher incidence of spinal hematoma after removal of the epidural catheter is based in part on the Food and Drug Administration's MedWatch data, which suggest that removal of an epidural catheter may be a traumatic event, although this issue is still relatively controversial.[137]

Different types and classes of anticoagulants have different pharmacokinetic properties that affect the timing of neuraxial catheter or needle insertion and catheter removal. Despite a number of observational and retrospective studies investigating the incidence of spinal hematoma in the setting of various anticoagulants and neuraxial techniques, no definitive conclusion regarding the absolute safety of neuraxial anesthesia and anticoagulation has been reached. The American Society of Regional Anesthesia and Pain Medicine (ASRA) lists a series of consensus statements based on the available literature for administration (insertion and removal) of neuraxial techniques in the presence of various anticoagulants, including oral anticoagulants (warfarin), antiplatelet agents, fibrinolytics-thrombolytics, standard unfractionated heparin, and low-molecular-weight heparin.[138] The ASRA consensus statements include the concepts that the timing of neuraxial needle or catheter insertion or removal should reflect the pharmacokinetic properties of the specific anticoagulant, that frequent neurologic monitoring is essential, that concurrent use of multiple anticoagulants may increase the risk of bleeding, and that the analgesic regimen should be tailored to facilitate neurologic monitoring, which may be continued in some cases for 24 hours after removal of the epidural catheter. An updated version of the ASRA consensus statements on neuraxial anesthesia and anticoagulation[138] can be found on their website (www.asra.com), and some of these statements address the newer anticoagulants.

Infection associated with postoperative epidural analgesia may result from exogenous or endogenous sources.[74] Serious infections (e.g., meningitis, spinal abscess) associated with epidural analgesics are rare (<1 in 10,000),[139] although some researchers report a higher incidence (approximately 1 in 1000 to 2000).[139] Closer examination of the studies that reported a higher incidence of epidural abscess reveals that the patients had a relatively longer duration of epidural analgesia or coexisting immunocompromising or complicating diseases (e.g., malignancy, trauma).[74,140] Use of epidural analgesia in the general surgical population with a typical duration of postoperative catheterization (approximately 2 to 4 days) is not generally associated with epidural abscess formation.[98] A trial of postoperative epidural analgesia (mean catheterization of 6.3 days) in more than 4000 surgical cancer patients did not reveal any abscesses.[122] Even though serious infectious complications appear to be rare after short-term (<4 days) epidural infusions, there may be a relatively higher incidence of superficial inflammation or cellulitis (4% to 14%) and an even higher rate of catheter colonization (20% to 35%), with the proportion of positive cultures increasing with longer duration of catheterization; however, the catheter colonization rate may not be a good predictor of infection of the epidural space.[141]

Although epidural analgesia may provide superior postoperative analgesia, migration of the epidural catheter out of the epidural space and into the intrathecal, intravascular, or subcutaneous space decreases the effectiveness of this technique. The failure rate (i.e., earlier-than-anticipated discontinuation of the catheter for any reason, placement of a nonfunctioning epidural catheter or "sham dural") ranges from approximately 6% to 25%, with many centers reporting a rate between 10% and 20%, but the incidence of actual premature epidural catheter dislodgment may be lower (mean, 5.7%; 95% confidence interval, 4.0% to 7.4%).[66,98,122] Fortunately, the rate of intrathecal (~0.15%) and intravascular (0.07% to 0.18%) migration of an epidural catheter is much lower than the failure rate.[142] Despite the less frequent occurrence of intravascular and intrathecal migration of postoperative epidural catheters, use of an epinephrine-containing test dose, administration of local anesthetic in fractionated doses, and aspiration of the catheter before bolus administration of local anesthetics may prevent complications (e.g., high or total spinal, seizures, neurotoxicity) associated with accidental administration of local anesthetics into the intravascular or intrathecal space.[74] The issue of whether lower extremity compartment syndrome can be consistently masked by the use of a local anesthetic–based epidural analgesic regimen is unresolved because use of systemic opioid analgesia has also been associated with a delayed diagnosis of compartment syndrome.[143]

Peripheral Regional Analgesia

The use of peripheral regional analgesic techniques as a single injection or continuous infusion can provide analgesia superior to that with systemic opioids[144] and may even result in improvement in various outcomes.[145] A variety of wound infiltration and peripheral regional techniques (e.g., brachial plexus, lumbar plexus, femoral, sciatic-popliteal, and scalp nerve blocks) can be used to enhance postoperative analgesia. Peripheral regional techniques may have several advantages over systemic opioids (i.e., superior analgesia and decreased opioid-related side effects) and neuraxial techniques (i.e., decreased risk for spinal hematoma).[146]

A one-time injection of local anesthetic for peripheral regional techniques may be used primarily for intraoperative anesthesia or as an adjunct to postoperative analgesia. When compared with placebo, peripheral nerve blocks with local anesthetics provide superior analgesia and are associated with reduced opioid use, decreased opioid-related side effects, and improvement in patient satisfaction.[146] The duration of postoperative analgesia resulting from the local anesthetic in the peripheral nerve block varies but may last up to 24 hours after injection. Local anesthetics may also provide effective wound infiltration analgesia postoperatively for a variety of procedures.[147,148]

Continuous infusions of local anesthetics can be administered through peripheral nerve catheters. When compared with systemic opioids, use of continuous infusions or patient-controlled peripheral analgesia results in superior analgesia, decreased opioid-related side effects, and greater patient satisfaction.[144,146] The optimal parameters (i.e., local anesthetic, concen-

tration, opioid, adjuvants, and continuous versus PCA versus intermittent boluses) for peripheral analgesia have not been determined.

Thoracic or Nonepidural Analgesia

Several nonepidural regional analgesic techniques can be used for the management of postoperative thoracic pain, including paravertebral and intercostal blocks, interpleural (intrapleural) analgesia, and cryoanalgesia. The most promising technique appears to be a thoracic paravertebral block, which has been used for thoracic, breast, and upper abdominal surgery and for the treatment of rib fracture pain.[149] Possible sites of analgesia for a thoracic paravertebral block include direct somatic nerve, sympathetic nerve, and epidural blockade.[149] A thoracic paravertebral block can be administered as a single injection or as continuous infusion through a catheter, may provide analgesia equal or superior to that with thoracic epidural analgesia, and is a valuable alternative to thoracic epidural analgesia.[150]

The analgesic efficacy of interpleural analgesia is controversial, as is its mechanism of action (i.e., sensory or sympathetic block, or both).[151] Interpleural analgesia appears to be inferior to epidural and paravertebral analgesia for control of postoperative pain, preservation of lung function after thoracotomy, and reduction of postoperative pulmonary complications.[128,151] Intercostal blocks may provide short-term postoperative analgesia and may be repeated postoperatively; however, the incidence of pneumothorax increases with each intercostal nerve blocked (1.4% per nerve, with an overall incidence of 8.7% per patient).[152] Like interpleural analgesia, intercostal blocks do not reduce the incidence of pulmonary complications postoperatively when compared with epidural analgesia.[128] Cryoanalgesia can be used for postoperative analgesia after thoracotomy but, like interpleural analgesia and intercostal blocks, does not appear to provide any analgesic advantage over epidural analgesia, is not effective for other types of postoperative pain, and is short-lived.[153]

Intra-articular Analgesia

Local peripheral administration of opioids (e.g., intra-articular injection after knee surgery) may provide analgesia for up to 24 hours after surgery[154] and decrease the incidence of chronic pain.[155] Peripheral opioid receptors are found on the peripheral terminals of primary afferent nerves and are upregulated during inflammation of peripheral tissues.[24] Results of the several randomized clinical trials investigating this topic have been summarized.[154] Use of a higher dose of intra-articular morphine (5 versus 1 mg) results in superior analgesia; however, there may be no advantage in the degree of analgesia provided between intra-articular and systemic opioids.[154] A systemic effect of intra-articularly injected morphine cannot be excluded. Intra-articular injection of local anesthetics may provide a limited duration of postoperative analgesia, but the clinical benefit from intra-articular injection of local anesthetics is unclear.[156]

Other Techniques

Other nonpharmacologic techniques, such as transcutaneous electrical nerve stimulation (TENS), acupuncture, and psychological approaches, can be used in an attempt to alleviate postoperative pain. The mechanism by which TENS produces analgesia is unclear but may be related to modulation of nociceptive impulses in the spinal cord, release of endogenous enkephalins, or a combination of these and other mechanisms.[157] Although the analgesic efficacy of these techniques is controversial, TENS and acupuncture may provide postoperative analgesia, decrease postoperative opioid requirements, reduce opioid-related side effects, and attenuate activation of the sympathoadrenal system.[157] In general, both these approaches to postoperative pain are relatively safe, noninvasive, and devoid of the systemic side effects seen with other analgesic treatment options.[157,158] However, there are methodologic issues with many of the available trials, and the precise role of these treatments in postoperative pain management is not clear. It is possible that TENS and acupuncture may be useful adjuncts to the more traditional pharmacologic analgesic drugs, but they may not be effective as the sole technique for severe postoperative or labor pain.[159]

Although this chapter has focused on the neurobiology of nociception and pharmacologic treatments available for the treatment of postoperative pain, the experience of pain is complex, multifaceted, and "an unpleasant sensory and emotional experience," as defined in part by the International Association for the Study of Pain. The differential behavior response to surgical incision may be related to global (i.e., personality, gender, age, and culture) and specific (i.e., fear, depression, anger, and coping) psychological factors.[160] Cognitive behavior therapy and behavior therapy may be efficacious in reducing pain and alleviating psychological factors associated with pain.[161] Identifying and addressing psychological factors can reduce pain, improve the efficacy of pharmacologic analgesics, and diminish patients' distress, in part through enhancement of the placebo effect.[160] Although the placebo effect has traditionally been thought to have a psychological origin, the placebo response may exert part of its effects through activation of endogenous opioids and be useful in reducing the intensity of pain.[162]

Postoperative Analgesia in Special Populations

This foregoing discussion has provided a general approach to the principles and practice of acute postoperative pain management, but this approach may need to be modified for certain populations that may have unique anatomic, physiologic, pharmacologic, affective, and cognitive issues. Management of acute pain should be tailored to the specific needs of a particular population. Although each topic by itself could merit a separate chapter in some textbooks, the general principles and essence of the issues associated with each population are outlined, and references are made to other more extensive sources.

Ambulatory Surgical Patients

The percentage of surgical procedures being performed on an outpatient basis continues to rise. There has been an increase in the number of outpatient surgical procedures, in the complexity of operations being performed, and in comorbid conditions of the surgical outpatients (also see Chapter 78). Optimizing treatment of postoperative and postdischarge pain is especially important in patients undergoing outpatient surgery because inadequate

control of postoperative pain is one of the leading causes of prolonged stays or readmission after outpatient surgery.[163] Although there has been much effort to minimize symptoms such as pain and nausea in the postanesthesia care unit and subsequent (phase II) recovery area to facilitate discharge after outpatient surgery, increasing data suggest that postdischarge pain (i.e., pain that occurs after discharge) is common and may interfere with patients' recovery and the overall health-related cost of outpatient surgery.[164] Despite advances in surgical techniques that minimize surgical trauma and postoperative pain, the incidence of moderate to severe postdischarge pain is still approximately 25% to 35%,[165] and it can be especially troublesome for certain patients, such as those undergoing tubal ligation and orthopedic procedures.[166] After discharge, poorly controlled nausea and vomiting may interfere with the intake of oral analgesics.

In light of these considerations, the traditional reliance on opioid analgesia may not be appropriate for patients undergoing ambulatory surgery because of opioid-related side effects that may delay hospital discharge and postdischarge recovery after outpatient surgery. A multimodal or "balanced" analgesic approach using a combination of opioid and nonopioid analgesic techniques (i.e., NSAIDs or acetaminophen, local anesthetics, and other nonpharmacologic therapies) may be more appropriate in this surgical population. Using nonopioid analgesic techniques with different mechanisms of analgesia diminishes opioid-related side effects, synergistically enhances postoperative analgesia, and facilitates patient recovery. For instance, use of local anesthetics has decreased postoperative pain, and the drugs can be administered as peripheral nerve blocks, tissue infiltration, wound instillation, or topical analgesics. Similar results have been achieved with the use of systemic NSAIDs and acetaminophen.

Although multimodal analgesia may be especially effective in the immediate postoperative period, not all of the options may be routinely available after the patient is discharged home. For example, use of local anesthetics in peripheral nerve blocks, tissue infiltration, or wound instillation may be effective in the immediate postoperative period; however, a single dose of local anesthetic rarely provides more than 24 hours of analgesia. Realistically, most outpatients rely on a combination of short-acting analgesics (e.g., an opioid and acetaminophen) for control of postoperative pain after discharge from the hospital. However, there are several strategies to optimize postdischarge pain, including the routine use of NSAIDs (if there are no contraindications) and the use of small doses of sustained-release opioids in certain surgical populations.[26] Routine use of acetaminophen, especially when an NSAID is added to the regimen, is recommended to maximize postoperative analgesia,[167] although it is important to remember that acetaminophen is a coanalgesic agent in many combination products, which may limit the number of combination analgesic tablets that the patient may consume. The future of postoperative pain control in ambulatory surgical patients may include postdischarge (home) use of continuous infusion of local anesthetic solutions or even use of long-acting, "sustained-release" local anesthetics.

Elderly Patients

The elderly population, which is expected to increase by 33% over the next 2 decades, accounts for approximately 12.5% of the total U.S. population and 38% of all health care spending (approximately 5% of the U.S. gross domestic product) (also see Chapter 71).[168] Changes in the physiology, pharmacodynamics, pharmacokinetics, and processing of nociceptive information that occur with aging may influence the effectiveness of postoperative pain control in the elderly. This group may have communication, affective, cognitive, social, and ideologic barriers to effective postoperative pain control. The elderly generally have decreased physiologic reserves and increased comorbid conditions in comparison to their younger counterparts, which may result in a higher incidence of postoperative complications (e.g., postoperative delirium), especially in the presence of severe or uncontrolled postoperative pain.

There is a clinically significant reduction in the intensity of pain perception or symptoms with increasing age.[169] For instance, silent myocardial ischemia is more common in the elderly, who may instead be seen initially with other anginal equivalents. Experimental studies demonstrate a decrease in Aδ and C fiber nociceptive function, delay in central sensitization, increase in pain thresholds, and decrease in sensitivity to low-intensity noxious stimuli.[169,170] However, elderly patients may have an increased response to higher-intensity noxious stimuli, decreased pain tolerance, and decreased descending modulation (i.e., serotoninergic and noradrenergic), which may contribute to the relatively high incidence of chronic pain in elderly patients.[169,171] Despite the methodologic issues in available studies evaluating age-related differences in the perception of pain, there appears to be a clinically relevant decrease in pain perception with increasing age. However, this should not be interpreted that elderly patients experience less pain than younger patients when they do report the presence of pain.

The physiologic and pharmacokinetic effects of aging on acute pain management are complex, and clinical implications include slow titration of opioids, which produces longer circulation times; smaller total doses because of increased sensitivity; and expectation of a longer duration of action because of reduced clearance. In general, analgesic requirements decrease with increasing age. Age has been shown to be the best predictor of postoperative requirements for intravenously and neuraxially administered morphine.[172] Similar to that seen in younger patients, there is large interpatient variability in postoperative analgesic requirements.[172] Use of intravenous PCA in the elderly is appropriate to compensate for the wide interpatient variability, although postoperative titration of intravenous morphine can also allow successful and safe administration to elderly patients.[173] Age itself is not an impediment to effective postoperative use of intravenous PCA or PCEA.[174] Use of postoperative epidural analgesia for elderly patients, especially those with decreased physiologic reserves, may attenuate the perioperative pathophysiology and is reported to improve postoperative outcomes, such as facilitating return of gastrointestinal function after abdominal surgery, decreasing the incidence of myocardial ischemia, lowering pain scores, and decreasing pulmonary complications.

Postoperative pain management in the elderly may be especially challenging because of some of the affective, cognitive, social, and ideologic barriers. Health care providers treating geriatric patients tend to have an unfounded level of fear of complications associated with treating perioperative pain, as reflected by the inadequate treatment of pain in elderly patients, even relative to younger patients.[171] Elderly patients may also contribute to inadequate pain control by their own reluctance to report pain or take opioid medications. Elderly patients have a higher incidence

of affective or cognitive impairment (e.g., depression, dementia) that may interfere with effective pain management.[171]

One of the most devastating complications in elderly surgical patients is postoperative delirium, which is associated with increased mortality rates and longer hospital stays.[175] The cause of postoperative delirium is unknown, although it is believed to result from an imbalance of neurotransmitters (particularly acetylcholine and serotonin) in the presence of decreased neurophysiologic reserve and inflammatory mediators.[176] Although the cause of postoperative delirium is multifactorial, uncontrolled postoperative pain may be an important contributor to its development.[177] Higher pain scores predict a decline in mental status and an increased risk for delirium.[178] Opioids other than meperidine[178] have not been associated with the development of postoperative delirium.[177,179] A multimodal analgesic approach may be useful in elderly patients but must be used with caution because adverse drug reactions in the elderly increase (to a greater extent than in younger patients) as the number of medications administered increases. Although the benefits of intraoperative regional anesthetic techniques on postoperative cognitive function are unclear, the postoperative use of epidural analgesia may diminish postoperative delirium in part through superior analgesia and a decrease in pulmonary complications.

Opioid-Tolerant Patients

Postoperative pain may be difficult to manage in opioid-tolerant patients because the standard approaches used for assessment and therapy in opioid-naive patients are inadequate for opioid-tolerant patients. Although opioid-tolerant patients typically require higher doses of analgesic medications in the immediate postoperative period, many health care providers still do not provide adequate postoperative pain relief, in part because of the fear of addiction or medication-related side effects. In dealing with patients with chronic opioid use, health care providers often mistakenly interchange several pharmacologic terms (i.e., tolerance, physical dependence, and addiction), a practice that may contribute to misunderstanding and inappropriate treatment decisions.

Tolerance refers to the pharmacologic property of an opioid in which an increasing amount is needed to maintain a given level of analgesia. *Physical dependence* is another pharmacologic property of opioids characterized by the occurrence of a withdrawal syndrome on abrupt discontinuation of the opioid or administration of an antagonist. Tolerance and physical dependence are pharmacologic properties of opioids and are not synonymous with the aberrant psychological state or behavior associated with *addiction*, a chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological, or social harm to the user and continued use despite that harm. The exaggerated fear of addiction contributes to the undertreatment of postoperative pain by health care providers; however, data suggest that there is minimal risk of iatrogenic addiction with use of opioids for pain control in patients who do not have a prior history of addiction.[180,181]

Several principles of pain assessment and treatment can be applied to the postoperative management of opioid-tolerant patients. The physician should expect high self-reported pain scores[182]; base treatment decisions on objective pain assessment (e.g., ability to breathe deeply, cough, ambulate) in conjunction with patients' self-reported pain scores[182]; recognize the need to identify and treat two major problems, maintenance of a basal opioid requirement and control of incisional pain; and recognize that detoxification is not usually an appropriate goal in the perioperative period. Likewise, several general strategies can be used for the treatment of postoperative pain in an opioid-tolerant patient. The physician can create a treatment plan early and discuss it with the patient, surgical team, and nursing staff; replace the patient's baseline or basal opioid requirements postoperatively; anticipate an increase in postoperative analgesic requirements[182]; maximize the use of adjuvant drugs; consider the use of regional analgesic techniques; and plan for the transition to an oral regimen. Although chronic pain patients are not synonymous with opioid-tolerant patients, many of these patients are opioid tolerant, and the same general principles and strategies may be applied to chronic pain patients who are opioid tolerant. Recognizing and addressing non-nociceptive sources of distress may be especially important for chronic pain patients.[160]

Even though there is no specific threshold or timeframe for when a patient becomes opioid tolerant, after an opioid-tolerant patient is identified, a perioperative strategy for postoperative pain control should be created and discussed with the patient. Such a strategy may include anticipation or arrangement for a longer than normal length of hospital stay, consultation with the anesthesiology or pain service, and confirmation of the patient's daily opioid intake to facilitate calculation of the patient's basal or maintenance opioid requirement in the postoperative period. Administration of a PRN analgesic regimen alone for opioid-tolerant patients is highly discouraged because replacing the basal opioid requirement in the postoperative period can optimize pain relief and possibly prevent opioid withdrawal. Basal opioid requirements can be administered systemically (typically intravenously or transdermally) until the patient can tolerate an oral analgesic regimen.[28] For example, 50% to 100% of the patient's baseline opioid requirement can be administered by continuous infusion as part of an intravenous PCA regimen, with a demand dose to cover the additional incisional pain. Conversion tables (Table 87-7) may facilitate equianalgesic conversion of opioids (i.e., different routes of administration of one opioid or conver-

Table 87-7 Guidelines for Equianalgesic Dosing of Opioid Agonists

	Equianalgesic Dose (mg)	
Drug	**Parenteral**	**Oral**
Morphine	10	30
Codeine	130	200
Fentanyl	0.1	—
Hydromorphone	1.5-2	6-7.5
Levorphanol	2	4
Meperidine	75	300
Methadone	10	20
Oxycodone	15	20-30
Oxymorphone	1	—

Equianalgesic doses are approximate and intended to serve only as an estimate of opioid requirements. Actual doses may vary, in part because of wide interpatient variability in response to opioids. Doses should be individualized and gradually titrated to effect.

sion between two different opioids); however, these tables provide only estimations to assist health care providers in initiating opioid titration.[183]

Opioid-tolerant patients generally require increased postoperative analgesic levels, including a larger demand dose.[28,182] Patients may need frequent adjustment (e.g., two to three times each day) of the intravenous PCA demand dose or continuous infusion, depending on the analgesic requirements. There is individual variability in response to different opioids, and if a decision is made to switch opioids, the choice of opioid is probably not as important as using an equianalgesic dose. Patients may experience different side effects with different opioids, and rotating to another opioid may be reasonable if the patient is not tolerating the first opioid.[184] Adjuvant agents such as NSAIDs should be administered on a regularly scheduled basis to optimize analgesic efficacy and possibly provide an opioid-sparing effect. Use of regional analgesic techniques with neuraxial opioids may provide excellent analgesia in opioid-tolerant patients while preventing withdrawal symptoms.[185]

After the patient is tolerating oral intake, conversion from intravenous opioids to a form (i.e., oral or transdermal, or both) that would be more suitable for discharge home may be initiated. Opioid-tolerant patients can generally be converted to a combination of a regularly administered, controlled-release formulation of opioid (i.e., sustained-release morphine or transdermal fentanyl) and short-acting, immediate-release opioid on a PRN basis. Although conversion of intravenous opioid to an oral or transdermal form can be accomplished over a period of 1 to 2 days in opioid-tolerant patients, this process may take several days in extremely difficult cases. Converting from an intravenous to an oral or transdermal form of opioid is not an exact science, and the conversion tables available can serve only as a rough guide because of significant interpatient and intrapatient variability in the sensitivity to opioids, lack of complete cross-tolerance between opioids (which may lead to greater than anticipated potency of a new opioid), and changes in the level of pain, which may rapidly decrease in the immediate postoperative period.[183] Because of these factors, conversion of approximately 50% to 75% of the equianalgesic dose to a sustained-release preparation of opioid or a transdermal fentanyl patch, with the remainder converted to a short-acting opioid delivered on a PRN basis, may be a reasonable starting point in patients whose pain is reasonably controlled, although additional titration may be necessary.

Pediatric Patients

As in adults, undertreatment of acute pain occurs in a substantial percentage of children (also see Chapter 82).[186] In addition to anatomic, physiologic, pharmacodynamic, and pharmacokinetic differences between children and adults, there are barriers unique to pediatric patients that may interfere with effective postoperative pain control. Control of postoperative pain is important in pediatric patients because poor pain control may result in increased morbidity or mortality.[181,187]

Some of the most important barriers to pain control in pediatric patients are the myths that children and infants do not feel pain, that pain is not remembered, and that there is no untoward consequence of experiencing pain.[186] These myths and other incorrect assumptions about pain in pediatric patients may hinder management of pain. Because of developmental, cognitive, and emotional differences, assessment of pain in pediatric patients can be difficult. Pediatric patients may have difficulty conceptualizing and quantifying a subjective experience such as pain. The lack of routine assessment and reassessment of pain may interfere with effective acute pain management.[186] Special scales are available to assist young children in self-reporting of pain; however, interpretation of behavior and physiologic parameters may be used to estimate pain intensity in preverbal children or those who cannot self-report their pain.

A plan for postoperative pain management should be discussed with the family and patient before surgery because pediatric patients may have many anxieties about pain and analgesic use after surgery. In general, the oral route of analgesic administration is preferred for mild to moderate pain. Intravenous or regional analgesia is appropriate for moderate to severe postoperative pain.[186] Use of intramuscular injections is strongly discouraged because of the pain associated with injection and variable absorption of analgesic medications. Fear of needles may inhibit control of postoperative pain because pediatric patients may choose to suffer in silence rather than receive a painful and anxiety-provoking intramuscular injection. Addressing medication-related side effects is important to alleviate patient-related distress and improve compliance with the postoperative analgesic regimen.

Use of an intravenous PCA device allows individualization of analgesic requirements and offers pediatric patients autonomy. Children as young as 4 years have the cognitive and physical capability to appropriately use an intravenous PCA device.[188] Although morphine is the standard by which other opioids are compared, morphine does not appear to have an analgesic advantage over other opioids (e.g., hydromorphone) when given in equianalgesic doses.[189] Because of toxicity from its metabolite, meperidine is not an opioid of choice in the acute pain management of pediatric patients.[186] Unlike adult patients, initial use of a background or continuous infusion in addition to the intravenous PCA demand dose appears to be more acceptable in pediatric patients.[188] Some data suggest that addition of an intravenous PCA background infusion is associated with improved sleep,[190] but other studies demonstrate a higher incidence of nausea, sedation, and hypoxemia with the addition of a background infusion.[191] None of these trials demonstrated superior analgesia with the addition of a background infusion. Nurse- or parent-controlled analgesia is also effective and may be used in certain circumstances, but close monitoring of the patient may be needed because significant respiratory depression occurs in approximately 1.7% of patients.[192]

For pediatric patients unable to use intravenous PCA, continuous infusions or intermittent intravenous administration of opioids is effective in providing postoperative analgesia.[193] Although respiratory depression may occur with opioids regardless of the route administered, clinically significant respiratory depression in pediatric patients is rare.[188] Unlike adults, pediatric patients do not appear to exhibit multiple episodes of clinically significant oxygen desaturation postoperatively when treated with neuraxial, intravenous, or intramuscular opioids.[194] Use of nonopioid analgesic agents, such as NSAIDs or acetaminophen, may improve overall analgesia, reduce the amount of opioid used postoperatively, and decrease some opioid-related side effects.[195] Some data suggest that for rectal administration of acetaminophen postoperatively, a higher dose (40 mg/kg followed by three doses of 20 mg/kg at 6-hour intervals) than that previously

recommended may result in appropriate serum analgesic levels.[195,196]

Peripheral and neuraxial regional analgesic techniques are commonly used and effective for acute pain management in pediatric patients. One of the most frequently used techniques is epidural analgesia, which can be delivered as a single dose or by using a continuous-infusion catheter technique. The catheter may be inserted (typically using general anesthesia[197]) anywhere along the epidural space (e.g., thoracic, lumbar, caudal), but the caudal approach seems to be the most common technique because the catheter can be easily advanced cephalad to the appropriate dermatome.[198] Local anesthetics or opioids, or both, can be administered through the epidural catheter or needle to provide effective postoperative analgesia. Although epidural (caudal) analgesia may be safely administered to neonates, the clinician should recognize that the maximal continuous infusion dose is probably lower than that in older children because of lower levels of α_1-acid glycoprotein (which binds local anesthetics) and diminished ability of the relatively immature liver to metabolize amide local anesthetics.[198] The addition of adjuvant drugs such as clonidine in the epidural infusion may enhance postoperative analgesia.[199]

Continuous epidural (caudal) analgesia may be used safely in the postoperative setting,[200] and the infection rate associated with continuous epidural analgesia is extremely low despite the relatively high colonization rate.[141] Continuous peripheral catheter techniques can be used effectively in pediatric patients. Regional analgesic techniques may be useful in providing analgesia for wound incision (e.g., herniorrhaphy or orchiopexy), thoracotomy, and orthopedic procedures.[189] Local anesthetics may also be administered topically to provide analgesia. Despite a lack of data comparing outcomes for regional analgesia versus systemic opioids in the pediatric population, some evidence suggests that the use of epidural analgesia is associated with improvement in some outcomes such as earlier tracheal extubation, return of gastrointestinal function, and length of hospital stay.[201]

Obesity, Obstructive Sleep Apnea, and Sleep

Patients with obesity and obstructive sleep apnea (OSA) may be at higher risk for postoperative complications (see Chapter 64). Obesity and OSA are separate disease states, but there is some association between the two because OSA occurs in a relatively higher percentage of obese than nonobese patients.[202] Although some data suggest that epidural analgesia may decrease postoperative complications in obese patients,[203] the optimal postoperative analgesic and monitoring regimen for patients with OSA is not clear. Data suggest that sleep is disrupted in the immediate postoperative period and may influence postoperative morbidity and patient-oriented outcomes.

Obesity is defined as a body mass index (BMI) of greater than 30 kg/m^2, with morbid and supermorbid obesity defined as a BMI of greater than 35 and 55 kg/m^2, respectively. The prevalence of obesity has increased to include approximately 22.5% of the U.S. population.[204] Although obese patients do not necessarily have OSA, obesity is the most important physical characteristic associated with OSA. Approximately 60% to 90% of OSA patients are obese, and at least 5% of morbidly obese patients have OSA, which is defined as more than five episodes per hour of cessation of airflow for more than 10 seconds despite continued ventilatory effort.[202] It is estimated that approximately 4% of men and 2% of women (18 million Americans overall) have OSA and that OSA is underdiagnosed in up to 95% of persons.[202] Patients with OSA are generally at higher risk for chronic cognitive impairment, pulmonary hypertension, cardiomyopathy, systemic hypertension, and possibly myocardial infarction.[205,206] The pathophysiology of airflow obstruction is related primarily to upper airway pharyngeal collapse, including the retropalatal, retroglossal, and retroepiglottic pharynx, during sleep, especially during rapid eye movement sleep.[202] During these obstructive episodes, OSA patients may exhibit hypoxia, bradyarrhythmias or tachyarrhythmias, myocardial ischemia, abrupt decreases in left ventricular stroke volume and cardiac output, or increases in pulmonary and systemic blood pressure.[206]

Based on our understanding of the pathophysiology of OSA, it is easy to see how postoperative pain management can be difficult in this population. Patients with OSA are at higher risk for respiratory arrest.[207] Use of sedative doses of benzodiazepines and opioids may result in frequent hypoxemia and apnea, which may be especially dangerous in OSA patients.[207] Avoiding respiratory depressants by optimizing the use of NSAIDs and epidural analgesia with a local anesthetic–based regimen may attenuate the risk for respiratory depression and arrest, because the use of epidural and systemic opioids is associated with sudden postoperative respiratory arrest.[207,208]

The American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea created guidelines that include recommendations for postoperative analgesia in patients with OSA.[209] Although the consultants acknowledged that the conclusions regarding postoperative analgesic options were based on insufficient literature evaluating the effects of various analgesic techniques, the presence of equivocal literature regarding the use of epidural opioids versus intramuscular or intravenous opioids in reducing respiratory depression, and insufficient literature regarding the addition of a basal infusion to systemic patient-controlled opioids, the consultants nevertheless recommended that regional techniques rather than systemic opioids be used in an attempt to reduce the likelihood of adverse outcomes in patients at increased perioperative risk from OSA.[209] In addition, the consultants recommended the exclusion (versus inclusion) of opioids from neuraxial postoperative analgesia to reduce perioperative risk and the use of NSAIDs to reduce adverse outcomes through their opioid-sparing effect. The consultants were equivocal regarding whether avoiding a basal infusion of opioids in patients with OSA reduces the likelihood of adverse outcomes.[209] Unfortunately, there is a paucity of randomized clinical trial data to provide definitive high-quality evidence-based recommendations for the provision of postoperative analgesia to OSA patients.

Postoperative Pain Services

Although dedicated health care professionals can improve postoperative pain control for a few patients, more comprehensive perioperative pain management programs (i.e., acute pain services) developed specifically to treat this problem can address the

needs for all patients within an institution. The organizational aspects of such comprehensive services are considerable and necessary for effective and safe care and may include issues such as education, administration, nursing, and documentation (Box 87-2; see also Box 87-1). With skills in regional anesthetic techniques and knowledge of the neurobiology of nociception and the pharmacology of analgesics and local anesthetics, anesthesiologists have been leaders in postoperative pain relief and the development of acute pain services. Provision of perioperative analgesia, along with other services such as critical care medicine and preoperative evaluation, is highly compatible with the emerging identity of anesthesiologists as perioperative physicians and enhances the role of anesthesiologists as valued consultants outside the operating room.

Although there are several models for the development of acute pain services,[210,211] the key organizational aspects are similar (see Box 87-2). Development and maintenance of acute pain services require a commitment and financial support at the national and local (institutional and departmental) level. In the United States there appears to be a dichotomy at the national and third-party payer level between the call for improved postoperative pain control, along with the introduction of practice guidelines or expanded roles for acute pain services, and decreased reimbursement for the provision of such services. Because there are financial burdens associated with the establishment of an acute pain service, high-volume or larger hospitals may be more likely to have acute pain services and access to more high-tech analgesic techniques such as epidural analgesia.[212,213]

Whether acute pain services actually improve outcomes is unclear. Two systematic reviews have examined the impact of acute pain services on patient outcomes,[214,215] and although both systematic reviews suggest that the introduction of acute pain services is associated with a decrease in pain scores, the effect of acute pain services on the incidence of analgesic-related side effects (e.g., nausea, vomiting), satisfaction, and overall costs is uncertain. Despite the direct costs (e.g., personnel, equipment, medication) associated with managing an acute pain service, there is no properly conducted pharmacoeconomic study available to examine the cost-effectiveness (or lack) of an acute pain service. Use of postoperative epidural analgesia in the context of acute pain services may decrease the cost of patient care through shorter intensive care unit stays and a decreased rate of complications.[13] Despite the costs associated with implementation of an acute pain service and acute pain management practice guidelines, acute pain services provide a valuable service at the individual, institutional, and societal levels.

Box 87-2 Organizational Aspects of an Acute Pain Service

Educational Activity
Anesthesiologists
Health insurance carriers
Hospital administrators
Nurses
Patients and families
Pharmacists
Surgeons

Administrative Activity
Economic issues
Evaluation of equipment
Human resources: pain service personnel, administrative-secretarial support
Institutional administrative activity
Quality improvement and assurance
Research (if applicable)
Residency-fellowship teaching (if applicable)

Nursing
Continuing education and in-service training
Defining of roles in patient care
Nursing policies and procedures
Pain service nurse (if applicable)
Quality improvement and assurance

Documentation
Bedside pain management assessment flow sheet
Daily consultation notes
Educational packages
Policies and procedures
Preprinted orders

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88 Postoperative Intravascular Fluid Therapy

Key Points

1. Water is the most abundant component in the body: total body water accounts for approximately 50% of the lean body weight in women and 60% in men. Derangements in the fluid homeostasis are common in the postoperative period.
2. The goal of fluid management in the postoperative period is to provide the optimal amount and type of fluid to the patient. Thus, patients should remain euvolemic with a normal electrolyte distribution.
3. Besides physical examination and routine patient monitoring, different devices are available for advanced hemodynamic monitoring. They can be clinically used in a stepwise escalating approach—from invasive blood pressure measurement, to central venous cannulation, to less invasive, advanced hemodynamic monitoring, to pulmonary artery catheterization, to transesophageal echocardiography.
4. For adequate assessment of a patient's fluid balance, all available variables (i.e., cardiac filling, heart function, or end-organ perfusion) have to be considered like the "pieces of a puzzle."
5. Maintenance fluid therapy in the postoperative period aims at preserving the water and electrolyte balance. It should replace the ongoing losses of water and electrolytes under normal physiologic conditions.
6. Replacement fluid therapy in the postoperative period corrects any existing and additionally occurring water and electrolyte deficits. These deficits result from bleeding, third space sequestration, evaporative losses (e.g., mechanical ventilation without humidifier, surgical field if wound is left open), profuse sweating, and additional gastrointestinal as well as other fluid losses.
7. Fluid therapy must be individualized to each patient and balanced according to the benefits and risks of intravascular fluid administration. Therefore, the patient's characteristics and the type of procedure that has been performed should determine whether to choose a more liberal or a more restrictive fluid regimen.
8. To optimize the fluid status and to avoid fluid overload, frequent re-evaluations are required, especially during a "fluid trial," which is the intravenous administration of a specified amount of fluid over a short period of time.
9. A variety of manufactured fluid formulations exist for intravenous fluid therapy that differ in two fundamental ways: the *component electrolyte solution* and the *suspended material* providing colloid osmotic (oncotic) pressure.

Intravascular fluid therapy is of prime importance for maintenance of and to correct various alterations in normal fluid balance. Several other chapters (see Chapters 49, 54, and 55) also deal with fluid therapy.

The emphasis in this chapter is on fluid therapy in the postoperative period, especially in patients who have complications. After a brief review of basic fluid balance physiology, the assessment and the treatment of abnormalities with regard to the postoperative period are discussed.

Basic Physiology of Fluid Balance

Total Body Water and Fluid Compartments

Water is the most abundant component in the body. Total body water (TBW) accounts for approximately 50% of the lean body weight in women and 60% in men. This difference is attributable to variations in the relative proportions of adipose (water content

Table 88-1 Body Water Distribution (%) Relative to Lean Body Weight

	Men	Women	Term Infant
Intracellular compartment	40	33	50
Extracellular compartment	20	17	25
Intravascular space	5	4	6
Interstitial space	15	12	19
Total body water	60	50	70-75

10%) and muscle tissue (water content 75%) in women and men. TBW is distributed in two major compartments: the intracellular and extracellular compartments. The latter is further divided into the intravascular and interstitial spaces. Their relative size in men, women, and infants is summarized in Table 88-1. In children, the contribution of the TBW to weight varies with age and constitution: it ranges from 80% or greater in the premature infant, to 70% to 75% in the term infant, to 65% to 70% in toddlers. The higher percentage in TBW mainly reflects an increased extracellular fluid (ECF) compartment that is even more pronounced in preterm infants. In the elderly, TBW decreases with increasing age. This decrease is mainly due to losses in the intracellular fluid (ICF) compartment, preserving the ECF compartment.

Composition of Body Fluids and Distribution of Fluid

The ICF and ECF compartments are separated by the cell membranes. The composition of solutes in each compartment is markedly different based on disparities in permeability and the presence of transporters and active pumps. The major ECF particles are sodium (Na^+) and its accompanying anions chloride (Cl^-) and bicarbonate (HCO_3^-). Minor contributions come from potassium (K^+), magnesium (Mg^{2+}), and plasma proteins (mainly albumin). In the ICF compartment, however, K^+ is the main cation and electroneutrality is preserved by organic phosphate esters (adenosine triphosphate [ATP], creatine phosphate, and phospholipids) (see Chapter 54).

Osmotic forces are the primary determinants of the water distribution in the body. Osmolality is determined by the number of moles of a chemical compound that contributes to the solution's osmotic pressure and is expressed as milliosmoles per kilogram of water (mOsm/kg). Solutes that cannot freely cross the cell membrane are restricted to a specified compartment, determine the *effective osmolality (or tonicity),* that is, the osmotic pressure of that compartment, and generate fluid shifts. On the other hand, solutes that passively equilibrate across the cell membranes (e.g., urea with its high lipid solubility) are called *ineffective osmoles* and do not contribute to water shifts across cell membranes.

The *distribution of water between ECF and ICF compartment* depends largely on Na^+ and K^+ content of each compartment. Because Na^+ and K^+ are the predominant ions in, and largely restricted to, the ECF and ICF compartments, respectively, the effective osmolality of each compartment is primarily determined by the content of Na^+ and K^+ salts. Because water can freely cross almost all cell membranes, the osmolalities of the ECF and ICF compartment are kept in an osmotic equilibrium: a change in osmolality in one compartment will trigger water movement across the cell membranes from the compartment of low osmolality to the one of a higher osmolality.

Although the total-body Na^+ content is a reflection of the ECF compartment, there is not necessarily a positive correlation between plasma Na^+ concentration and ECF volume. These parameters change in parallel when Na^+ salts are administered but in an opposite direction when water administration or retention occurs (low plasma Na^+ concentration, high ECF volume). However, the ICF volume typically varies inversely with the plasma Na^+ concentration, decreasing with hypernatremia and increasing with hyponatremia. This may have important clinical relevance, because acute changes in the plasma Na^+ concentration alter brain cell volume and may therefore cause neurologic symptoms.

The distribution of water between the intravascular and interstitial space differs from that across cell membranes. The primary sites of exchange are the capillaries and small postcapillary venules. Because these "exchange vessels" are freely permeable to Na^+, K^+, and glucose, Na^+ and K^+ become ineffective osmoles and do not contribute to the water distribution between the intravascular and interstitial spaces. However, several other mechanisms are involved in this exchange, most importantly, bulk flow and diffusion. The rate of exchange in either direction (i.e., net filtration) can be calculated by the law of Starling.[1,2] Net filtration is determined by the physical factors hydrostatic pressure (P) and oncotic pressure (π) multiplied by the reflection coefficient of proteins across the capillary wall (σ, with values ranging from 0 if completely permeable to 1 if completely impermeable), and the physical nature of the barrier separating the blood and the interstitium (i.e., permeability of the capillary barrier, $C_{Permeability}$, and the surface area available for fluid movement).

$$\text{Net filtration} = C_{Permeability} \times \text{Area} \left[\left(P_C - P_T \right) - \sigma \left(\pi_C - \pi_T \right) \right]$$

There are two important, opposing hydrostatic forces: capillary (P_C) and tissue (P_T) hydrostatic pressure. Because P_C is much greater than P_T under normal circumstances, the net hydrostatic pressure gradient across the capillaries is positive, meaning that hydrostatic forces are driving fluid out of the capillaries. Furthermore, proteins (primarily albumin) have a limited ability to traverse the capillaries and act as effective osmoles influencing the fluid exchange. Normally, capillary plasma oncotic pressure (π_C) is much greater than tissue (interstitial) oncotic pressure (π_T), thereby reabsorbing fluid from the interstitium into the capillaries, if unopposed by hydrostatic forces. Altogether, there is a slightly positive net filtration across the capillary beds (i.e., filtration exceeds reabsorption), with the filtrate being returned to the systemic circulation by the lymphatic system. Edema results if net filtration exceeds the capacity of the lymphatics to clear excess interstitial fluid.

Capillaries in different organs have different hemodynamic and permeability characteristics. The hydrostatic pressure in glomerular capillaries of the kidneys is uniquely high, owing in part to a low precapillary resistance. This is physiologically important because the high pressure gradient *plus* the high capillary permeability allows the glomerula to maintain a very high rate of filtration. By contrast, in skeletal muscle, the capillary pressure is much lower than the systemic pressure (high precapillary resistance) and the capillary wall is relatively impermeable to proteins. Alveolar capillaries in the lungs on the other hand have both a lower capillary hydrostatic pressure (low pressure pulmonary circulation) and a lower transcapillary oncotic pressure gradient (because of a higher permeability to proteins). The result is a

small gradient favoring filtration, which is slightly larger than that in skeletal muscles.[2] The smaller transcapillary oncotic pressure gradient across the alveolar capillary wall has important clinical implications, because the rate of filtration is relatively unaffected by changes in the plasma oncotic pressure. As an example, a fall in the plasma albumin concentration might be expected to promote fluid movement into the interstitium as a result of the reduced plasma oncotic pressure. However, if the onset of the hypoalbuminemia is subacute or chronic, the interstitial oncotic pressure will undergo a parallel decline, attributable in part to less albumin movement from the vascular space into the interstitium. The net effect with mild to moderate hypoalbuminemia is therefore an unchanged transcapillary oncotic pressure gradient without the development of pulmonary edema.

Body Fluid Homeostasis

Under normal circumstances, the water and electrolyte content in the body is maintained within narrow limits as variations in dietary intake are exactly matched by corresponding changes in urinary excretion. Nevertheless, it is important to understand the potential physiologic effects of alterations in solute or water balance, because these disturbances often occur in the perioperative period. Body fluid homeostasis is being maintained by two different mechanisms, the volume regulation and osmoregulation (Table 88-2). Preservation of an effective circulating volume is critical for adequate tissue perfusion, and maintenance of a physiologic osmolality is essential for best cell function.

Intravascular Volume Regulation

The effective circulating volume is a nonmeasurable entity and refers to that part of the ECF that is perfusing the tissues.[3] Under physiologic circumstances, the effective circulating volume is dependent on and varies directly with the ECF volume and both parameters are proportional to the total body Na^+ content. Therefore, maintenance of the effective circulating volume is primarily related to the regulation of the Na^+ balance.

In the body, the effective circulating volume is indirectly being measured and regulated by three groups of baroreceptors sensing changes in pressure or stretch rather than volume. First, receptors in the carotid sinuses and aortic arch regulate the sympathetic activity and, to a minor degree, the release of arginine vasopressin (AVP, formerly antidiuretic hormone). Because these receptors are indirectly sensing blood flow to the brain, their major goal is to maintain cerebral perfusion. Second, receptors in the juxtaglomerular apparatus of the kidneys (glomerular afferent arteriole) and macula densa affect the volume balance by influencing the activity of the renin-angiotensin-aldosterone system and the release of endothelin and nitric oxide. Third, the atria and ventricles can release natriuretic peptides in response to increased wall pressure as a result of volume overload. These effector systems will be discussed in detail later (see "Effector Systems for Volume Regulation and Osmoregulation").

Table 88-2 Volume Regulation and Osmoregulation

	Volume Regulation	Osmoregulation
Variables	Effective circulating volume	Plasma osmolality
Sensors	Baroreceptors	Osmoreceptors
Location	Carotic sinus, aortic arch Afferent glomerular arteriole Atria, ventricles	Hypothalamus (supraoptic and paraventricular nuclei)
Effectors	Sympathetic nervous system Renin-angiotensin-aldosterone Natriuretic hormones Pressure natriuresis Arginine vasopressin	Thirst Arginine vasopressin
Results	Sodium excretion	Water intake and excretion

Osmoregulation

The normal plasma osmolality (Posm) is kept within a narrow range (275-295 mOsm/kg) by osmoreceptors located in the hypothalamus, capable of sensing a 1% to 2% change in tonicity. Posm is measured in the laboratory by analyzing the freezing point of the plasma (the freezing point of a solution inversely correlates with the amount of osmotic active particles). Furthermore, Posm can be calculated as follows[4]:

$$\text{Plasma osmolality}\left(\text{mOsm/kg}\right) = 2 \cdot \left[Na^+\right] + [\text{Urea}] + [\text{Glucose}]$$

Na^+ is multiplied by the factor 2 to account for accompanying anions that provide electroneutrality (mostly Cl^- and HCO_3^-). Urea and glucose are entered in millimoles per liter (mmol/L) (if these values are reported in milligrams per deciliter, they have to be converted to mmol/L [i.e., BUN/2.8 and glucose/18]). The contributions of urea and glucose to Posm are small, except in conditions such as diabetes mellitus and renal failure. However, to calculate the effective Posm, the formula can be rewritten omitting the urea concentration, because urea is an ineffective osmole, as mentioned earlier. The osmolar gap in the plasma (i.e., laboratory measured plasma osmolality minus calculated plasma osmolality; normal: < 10 mOsm/kg) increases under certain clinical situations when large amount of osmotic active substances are present. Causes of a raised osmolar gap may be recalled by the mnemonic "I AM DEEEP" (Isopropyl alcohol, Acetone, Methanol, Diuretics [e.g., mannitol], Ethanol, Ethylene glycol, Ethyl ether, Paraldehyde). Acid-base disturbances may accompany an increased osmolar gap. To consider a list of causes that may otherwise be overlooked, further evaluation of the acid-base status is necessary and includes the calculation of the anion gap (i.e., $Na^+ - (Cl^- + HCO_3^-)$; normal range: 8-16 mEq/L). An increased anion gap combined with a metabolic acidosis may typically result from ingestion of methanol, ethanol, ethylene glycol, and paraldehyde. Other causes include lactic acidosis, diabetic ketoacidosis, uremia, and excessive salicylate intake.

Regulation of the plasma Na^+ concentration, and therefore the plasma osmolality, occurs by changes in water intake (via thirst) and excretion (via AVP). Although it is tempting to assume that the maintenance of the plasma Na^+ concentration must be related to Na^+ balance, this is not the case. Alterations in Na^+ balance are used to maintain the plasma volume and tissue perfusion, not the plasma Na^+ concentration.

Effector Systems for Volume Regulation and Osmoregulation

Sympathetic Nervous System

Sympathetic neural tone and the secretion of catecholamines from the adrenal medulla (norepinephrine and epinephrine) are

the key regulators of vascular tone and cardiac function. Sympathetic volume regulation is mediated through baroreceptors (stretch-sensitive mechanoreceptors) located in the heart and the arterial system (carotid sinuses, aortic arch). They are part of the baroreceptor reflex, providing a negative feedback loop in which an elevated blood pressure causes blood pressure to decrease. In contrast, a decreased blood pressure depresses the baroreceptor reflex, causing blood pressure to rise. Because hypovolemia typically results in a low blood pressure, hypovolemia indirectly induces an increase in peripheral sympathetic tone, initiating a series of events that act to restore normal tissue perfusion: enhanced venous return (venous constriction), rise in cardiac output (myocardial contractility and heart rate), and increase in systemic vascular resistance by arteriolar constriction. Furthermore, sympathetic activation enhances renin secretion, resulting in the generation of angiotensin II, which contributes to the systemic vasoconstriction. Finally, renal tubular Na^+ reabsorption is increased because of a direct adrenergic effect and an increase in angiotensin II and aldosterone secretion.

Renin-Angiotensin-Aldosterone System

A major physiologic stimulus to renin secretion is renal hypoperfusion; it is initiated by hypotension or volume depletion and is sensed by baroreceptors in the wall of the afferent glomerular arteriole. A second important mechanism is sympathetic neural activity and the level of circulating catecholamines, both of which enhance renin secretion via β_1-adrenergic receptors. Third, the release of renin is governed by macula densa cells in the early distal tubule, which appears to be stimulated by a reduction in the Cl^- concentration. Renin initiates a sequence of steps that begins with cleavage of angiotensin I from angiotensinogen, an α_2-globulin produced in the liver (and other organs including the kidneys). Angiotensin I is then converted into angiotensin II and catalyzed by the angiotensin-converting enzyme (ACE), which is primarily located in the lungs. Angiotensin II has two major actions: (1) it increases blood pressure by arterial vasoconstriction, both directly and by enhancing the norepinephrine release and effect, and (2) it induces renal Na^+ retention, directly and by increasing the secretion of aldosterone.

Natriuretic Hormones

Atrial natriuretic peptide (ANP) is primarily released from myocardial cells in the atria (and ventricles in some cases) in response to volume expansion, which is sensed as an increase in atrial stretch. Although both atria appear to participate, there is suggestive evidence that the right atrium may be quantitatively more important. There is also evidence that the carotid and renal baroreceptors contribute to ANP release. ANP directly lowers the systemic blood pressure and increases urinary Na^+ and water excretion. Besides ANP, there are other ANP-like hormones, such as B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). BNP is homologous to ANP and was initially identified in the brain but can also be found in ventricles of the heart. The circulating concentration of BNP is 20% lower than that of ANP in normal subjects but can equal or exceed ANP levels in patients with congestive heart failure. Because of this relationship, measurement of plasma BNP, which is available as a rapid bedside assay, is increasingly being used in the differential diagnosis of dyspnea and as a guide to the therapy and prognosis of heart failure.[5] Furthermore, CNP is structurally similar to the other natriuretic peptides and is produced by vascular endothelial cells and in the kidneys. Initial studies suggested that its major function may involve regulation of local blood flow. However, its exact pathophysiologic role in humans remains to be determined. In addition to ANP and related hormones, there is evidence of other natriuretic hormones presenting with a potential digitalis-like effect (ouabain-like hormone reduces Na^+/K^+-ATPase pump activity, thereby decreasing renal tubular Na^+ reabsorption).[6]

Pressure Natriuresis

The phenomenon of pressure natriuresis is an essential "backup" feature of the volume regulatory system that can compensate for an abnormality in the humoral control of Na^+ excretion. In contrast to other mediators of tubular Na^+ transport, pressure natriuresis does not require neural or humoral sensor and effector mechanisms. The exact mechanism, however, is incompletely understood. It is possible that the increase in systemic pressure is transmitted via the vasa recta capillaries to the medullary interstitium. This rise in interstitial pressure can impair NaCl transport with the net effect of a decreased loop NaCl reabsorption. Furthermore, increased release of renal prostaglandins and nitric oxide may contribute to pressure natriuresis.[7]

Arginine vasopressin is the primary physiologic determinant of the rate of free water excretion. AVP is a polypeptide hormone that is synthesized in the hypothalamic supraoptic and paraventricular nuclei. Secretory granules containing AVP migrate down the axons into the posterior lobe of the pituitary, where they are stored and subsequently released after appropriate stimuli. Some of the synthesized AVP of the paraventricular nuclei enters the cerebrospinal fluid or the portal capillaries in the median eminence and has therefore access to the systemic circulation. This finding may explain why lesions of the posterior pituitary below the median eminence do not usually lead to permanent diabetes insipidus. Factors affecting AVP secretion are summarized in Table 88-3. The most important stimuli to release AVP are increased plasma osmolality and decreased effective circulating volume. The osmotic threshold for AVP release is 280 to 290 mOsm/kg in humans. Below this level there is little if any circulating AVP and the urine is maximally diluted to an osmolality less than 100 mOsm/kg. Above the osmotic threshold, there is a linear rise in AVP secretion. The osmoreceptors are sensitive, responding to alterations in the Posm of as little as 1% to 2%.[8,9] Interestingly, the osmotic threshold for thirst has been reported to be 5 mOsm/kg higher than that for AVP release.[10] The sensitivity of changes in effective circulating volume is different from that of osmolality. Small, acute reductions in volume that are sufficient to increase the secretion of renin and norepinephrine have little effect on the release of AVP. However, if there is a large enough change in the effective circulating volume to produce a significant reduction in systemic blood pressure, AVP is markedly being

Table 88-3 Factors Regulating the Secretion of Arginine Vasopressin

Stimulate Release	Inhibit Release
Hyperosmolality	Hypo-osmolality
Reduced effective circulating volume	Increased effective circulating volume
Angiotensin II	Cortisol
Stress, pain, nausea	Drugs, e.g., caffeine, ethanol, phenytoin
Hypoglycemia	
Pregnancy	
Drugs, e.g., morphine, nicotine	

released, resulting in circulating hormone levels that can substantially exceed levels induced by hyperosmolality.

There are two classes of AVP receptors, V2 and V1a/b receptors (V2R and V1a/bR, respectively), both of which are seven transmembrane G protein–coupled receptors. V2R are located primarily at the apical membrane of the cells lining the collecting ducts of the kidneys (especially the cortical and outer medullary collecting ducts). Stimulation of V2R leads to insertion of aquaporin-2 (water channels) into the cell membrane, thereby allowing water to be reabsorbed down an osmotic gradient and mediating the antidiuretic response of AVP. Activation of V1aR induces vasoconstriction and enhancement of renal prostaglandin production (particularly prostaglandin E_2 and prostacyclin), and stimulation of V1bR facilitates the release of ACTH in the pituitary gland. AVP, when secreted into the plasma, is rapidly metabolized in the liver and kidneys (half-life in circulation: 15-20 min).[11]

Thirst is the most important mechanism for water intake in the conscious patient. Plasma osmolality and effective circulating volume are the main determinants of regulating the thirst mechanism. Additionally, other signals may stimulate (e.g., angiotensin II, relaxin) or inhibit (e.g., ANP) thirst.[12]

Fluid Balance in the Postoperative Period

Maintaining an optimal fluid balance is challenging in the perioperative period. Patients arrive in the operating room with a negative fluid balance after a certain fasting period. The intervention may cause bleeding, evaporative fluid losses, and third space fluid sequestration. Furthermore, anesthesia may affect the fluid balance by interactions of anesthetic drugs with normal fluid physiology and distribution; for example, neuraxial anesthesia may induce a sympathicolysis with vasoplegia of the dependent part of the body. Additionally, the regulation of the fluid balance by thirst is ineffective in the perioperative period because patients may not be fully awake and alert. Although the occurring fluid deficits are being treated during the interventions with various fluids (crystalloid, colloids, blood products), derangements in the fluid homeostasis are common when patients arrive in a recovery place (e.g., recovery room, intermediate care, or intensive care unit).

The goal of fluid management in the postoperative period is to provide the optimal amount and type of fluid to the patient. Thereby, patients should remain euvolemic with a normal electrolyte distribution. Hypovolemia and hypervolemia are the extremes of a disturbed fluid balance and will be discussed in this section, because the pathophysiology of these clinical syndromes has to be well understood for optimal fluid management. The focus of this chapter is on fluid balance, not electrolyte balance. For further reference on the electrolyte balance, see Chapter 54.

Hypovolemia

Absolute hypovolemia, or true volume depletion, generally refers to a state of combined Na^+ and water loss exceeding fluid intake or administration, leading to a reduced ECF volume. Dehydration, by contrast, relates to an isolated water loss that results in an elevation of plasma Na^+ and subsequent intracellular water deficit (osmotic movement of water from ICF to the ECF compartment). *Relative* hypovolemia, on the other hand, refers to a state with decreased effective circulating volume but normal or expanded ECF volume. Depending on the patient (age, physical status, coexisting disease), some volume depletion is usually well tolerated. However, with an increase in degree of hypovolemia (absolute or relative) and progressive dehydration, tissue perfusion may become limited, resulting in a clinical syndrome referred to as *shock* (Table 88-4). The oxygen delivery no longer matches tissue oxygenation needs, and a metabolic acidosis develops. In the early stage, the acidosis is the result of a decreased clearance (not overproduction) of lactate by the liver, kidneys, and skeletal muscle.[13] However, as shock progresses and circulatory failure with tissue hypoxia occurs, anaerobic cell metabolism is increased with an enhanced production of lactate, worsening the acidemia. Although the effects of inadequate tissue perfusion are initially reversible, prolonged oxygen deprivation leads to generalized cellular hypoxia and derangement of critical biochemical processes, including impaired function of ion pumps of the cell membrane, intracellular edema, and leakage of intracellular contents into the extracellular space. These abnormalities rapidly become irreversible and result sequentially in cell death, end organ damage, multiple organ system failure, and death.

Table 88-4 Causes of Impaired Effective Circulating Volume and Classification of Shock Syndromes

Pathophysiology	Clinical Syndrome
ECF Volume Reduced	**Hypovolemic shock**
Extrarenal volume/Na^+ loss	Nonhemorrhagic shock
Skin and respiratory	
Gastrointestinal	
Third space sequestration	
Hemorrhage	Hemorrhagic shock
Renal volume/Na^+ loss	Nonhemorrhagic shock
Osmotic diuresis, diuretics	
Salt-wasting nephropathies	
Hypoaldosteronism	
Diabetes insipidus	
ECF Volume Normal or Expanded	**Cardiogenic, distributive shock**
Cardiac and extracardiac pathology	Cardiogenic shock
Myocardial: pump failure	
Mechanical: valvular defects, ventricular septal defect, tumors	
Arrhythmias	
Extracardiac (obstructive): pericardial diseases, massive pulmonary embolism, severe pulmonary hypertension, tension pneumothorax	
Redistribution of fluids	Distributive shock
SIRS, sepsis	SIRS, septic shock
Bacterial and other toxins	Toxic shock syndrome
Anaphylaxis and anaphylactoid reactions	Anaphylactic shock
Injury of central nervous system or spinal cord	Neurogenic shock
Myxedema coma, addisonian crisis	Endocrine shock
Chronic liver disease	

SIRS, systemic inflammatory response syndrome.

Therefore, it is obvious that derangements of the fluid balance have to be recognized early and treated promptly.

The clinical presentation of shock varies with both the type and the cause of the shock, but all shock syndromes have several factors in common. The syndrome is associated with a marked increase in sympathetic activity characterized by tachycardia. Relative (compared with the patient's baseline, early stages) or absolute (systolic blood pressure <90 mm Hg, advanced stages) hypotension occurs in most shock patients. As a compensatory mechanism to the decreased effective circulating volume, efficient vasoconstrictive mechanisms redirect blood flow from the periphery to the vital organs, thereby maintaining cerebral, coronary, and splanchnic perfusion, causing the cold and clammy skin of the shock patient. However, an exemption is the peripheral vasodilation in early distributive shock and terminal shock states (failure of the mechanisms maintaining peripheral vasoconstriction) resulting in a hyperemic, flushed skin. As a consequence of shunting blood to vital organs, the urinary output drops and the patient becomes oliguric to anuric. With ongoing depletion of the intravascular volume, the cerebral blood flow is finally impaired and the patient presents with agitation, confusion, and frank coma. However, it has to be emphasized that several confounding factors profoundly alter the clinical presentation, including the classic hemodynamic response to acute intravascular volume depletion. These factors include the patient's age, medications used for chronic conditions, the type and location of the fluid loss, the time lapse between volume loss and initiation of treatment, and previous fluid treatment.

Hypovolemia Due to Decreased ECF Volume

Extrarenal Volume or Na^+ Loss

Insensible, nonmeasurable fluid losses from the skin and respiratory tract (water evaporation) account for 600 mL/day and 200 mL/day under normal conditions, respectively. During febrile illnesses, fluid losses increase significantly and lead to volume depletion. Losses from the skin by sweating increase with each 1°C above 37°C (additional loss of 200-1000 mL/day). The Na^+ concentration of sweat is normally 20 to 50 mEq/L and decreases with profuse sweating due to the action of aldosterone (Table 88-5). Because sweat is hypotonic, the loss of water exceeds that of Na^+. Furthermore, evaporative water loss from the respiratory tract may be enhanced in febrile patients especially associated with mechanical ventilation and with hyperventilation. Finally, burns and exudative skin disorders may result in large losses of fluid and a depletion of the intravascular volume (see Chapters 54 and 72).

Table 88-5 Sweat and Gastrointestinal Fluids: Electrolyte Composition and Common Sources of Losses in the Perioperative Period

		Composition (mEq/L)			
Common Losses	**Body Fluid**	**Na^+**	**K^+**	**Cl^-**	**HCO_3^-**
Sweating (fever)	Sweat	20-50	5-10	45-55	
Gastrointestinal					
Nasogastric tube, vomiting	Gastric	40-80	5-15	90-130	
Tracheostomy tube, fistula	Biliary	130-150	5-10	80-120	30-40
Fistula	Pancreatic	120-140	5-10	60-90	90-110
Duodenal tube, fistula	Duodenal	130-140	5-10	70-90	0-50
Ileostomy, fistula	Ileal	100-140	5-10	80-110	20-30
Diarrhea, colostomy	Colon	50-70	20-40	30-50	20-30

Na^+, sodium; K^+, potassium; Cl^-, chloride; HCO_3^-, bicarbonate.

Approximately 9 L of fluid enters the gastrointestinal tract daily, 2 L by ingestion and 7 L by secretion. Almost 98% of this volume is reabsorbed so that fecal fluid loss accounts only for 100 to 200 mL/day. External drainage of gastrointestinal fluids, fistulas, impaired gastrointestinal reabsorption, or enhanced secretion leads to volume depletion (see Table 88-5). Because gastric secretions have a low pH (high H^+ concentration) and biliary, pancreatic, and intestinal secretions are alkaline (high HCO_3^- concentration), vomiting and diarrhea are often accompanied by metabolic alkalosis and acidosis, respectively.

Hypovolemia can occur by the sequestration of interstitial and intravascular fluid into a third space, not in equilibrium with either the ECF or the ICF compartment. Although this fluid may be moved back into the ECF compartment over a period of days to weeks, the acute reduction in blood volume, if not corrected, can lead to severe volume depletion. Examples of third space losses include the retroperitoneal space in acute pancreatitis, bowel lumen in gastrointestinal obstruction, the peritoneal cavity in peritonitis, crush injuries, and the hematoma in the adjacent tissue to a long bone or pelvic fracture.

Hemorrhage from any source is a frequent cause of volume depletion in the postoperative period. Careful postoperative evaluation of the patient and a high index of suspicion are often required for a successful diagnosis of occult bleeding. The different classes of hemorrhage and hemorrhagic shock are summarized in Table 88-6. Class I hemorrhage is a minor blood loss resembling a condition of an individual who has donated a unit of blood, and class II is an uncomplicated hemorrhage but crystalloid fluid resuscitation is required. Class III, however, is a complicated hemorrhagic state, and class IV hemorrhage should be considered a preterminal event for which very aggressive measures have to be taken to restore the volume status and control the bleeding.

Renal Volume or Na^+ Loss

In a healthy adult, 130 to 180 L of plasma is filtered across the capillary membranes of the glomerula each day. More than 98% of the filtrate is reabsorbed by the renal tubule, resulting in a urinary output of 1 to 2 L/day. Many conditions are associated with excessive urinary NaCl and water losses, including diuretic intake. Diuretics inhibit specific pathways of Na^+ reabsorption along the nephron with a consequent increase in urinary Na^+ excretion. Enhanced filtration of nonreabsorbed solutes, such as glucose or urea, can impair tubular reabsorption of Na^+ and water, resulting in an osmotic or solute diuresis. This often occurs in poorly controlled diabetes mellitus and in patients receiving high-protein hyperalimentation. Mannitol is a diuretic that produces an osmotic diuresis because this drug cannot be reabsorbed in the renal tubule. Healthy subjects are able to maximally conserve Na^+ and to reduce Na^+ excretion less than 5 mEq/day. However, renal function may be impaired de novo in the postoperative period as a result of anesthesia- and surgery-related events, such as impaired renal perfusion due to hypovolemia, vasodilation, positive-pressure ventilation, surgical manipulation, impaired autoregulation, and perioperatively administered nephrotoxic medications. Furthermore, many preexisting tubular and

Table 88-6 Classification of Hemorrhage/Hemorrhagic Shock*

Variable	Class I	Class II	Class III	Class IV
Blood loss, mL (% blood volume)	<750 (<15%)	750-1500 (15-30%)	1500-2000 (30-40%)	>2000 (>40%)
Pulse rate	Normal	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Respiratory rate	Normal	20-30	30-40	>35
Urine output	Normal	20-30 mL/h	5-15 mL/h	Anuric
Mental status	Slightly anxious	Mildly anxious	Confused, anxious	Confused, lethargic
Response to fluid bolus	Yes	Yes	Transient	No

*Based on 70-kg man.
Adapted from American College of Surgeons, Committee on Trauma: Advanced Trauma Life Support for Doctors, 6th ed. 1997, p 98.

interstitial renal disorders may deteriorate postoperatively and are associated with Na^+ wasting. Patients with renal insufficiency (glomerular filtration rate < 25 mL/min) may have an obligatory Na^+ loss of 10 to 40 mEq/day. In rare cases of tubular and interstitial renal diseases, a higher degree of Na^+ wasting may be present and obligatory urinary losses may exceed 100 mEq of Na^+ and 2 L of water per day.[14] Excessive renal Na^+ and water losses may also occur during the diuretic phase of acute tubular necrosis and after the relief of bilateral urinary tract obstruction. Finally, mineralocorticoid deficiency (hypoaldosteronism) causes salt wasting in the presence of a normal intrinsic renal function. Massive renal water excretion can also lead to hypovolemia. Conditions associated with excessive urinary water loss include central diabetes insipidus (impaired secretion of AVP) and nephrogenic diabetes insipidus (renal unresponsiveness to AVP). For details on renal function, renal dysfunction, and replacement therapy see Chapters 45 and 96.

Disturbed renal fluid regulation with hyponatremia is also a common late complication of transsphenoidal pituitary surgery, occurring in 21% to 35% of cases.[15,16] Although relative cortisol deficiency may contribute, the major cause is inappropriate AVP release from the injured posterior pituitary gland. The fall in the plasma Na^+ concentration is most severe on the sixth to seventh postoperative days. This form of isolated hyponatremia (or isolated second phase) appears to be a subset of the classic triphasic cycle in which initial polyuria is followed by transient syndrome of inappropriate AVP secretion (SIADH) and then either recovery or, in severe cases, a third phase of permanent central diabetes insipidus. Rarely, the hyponatremia after pituitary surgery is due to cerebral salt wasting (see Chapter 13).

Hypovolemia Due to Normal or Increased ECF Volume

Cardiac and Extracardiac Pathology

The effective circulating volume may be decreased in patients with cardiac disease, owing to an impaired systolic or diastolic function (or both) with a reduction in cardiac output (relative hypovolemia).[17] Myocardial pathogenesis includes infarction involving more than 40% of the left ventricular myocardium, right ventricular infarction, stunned myocardium after prolonged ischemia or cardiopulmonary bypass, dilated cardiomyopathies, myocarditis, myocardial contusion, and the myocardial depression of advanced shock. Furthermore, mechanical complications of a myocardial infarction (acute mitral regurgitation caused by papillary muscle rupture, ventricular septal defect, free wall rupture, pericardial tamponade), valvular pathologic processes (critical aortic stenosis, acute aortic insufficiency caused by dissection of the ascending aorta into the aortic valve ring), and tumors obstructing ventricular filling (e.g., atrial myxoma) may impair cardiac function. Finally, arrhythmias and obstructive, extracardiac factors may reduce cardiac output (see Table 88-4).

In clinical conditions with a reduced cardiac output, the sympathetic nervous and renin-angiotensin-aldosterone systems become activated. These systems together with a reduced renal perfusion then promote Na^+ and secondary fluid retention. Initially, these changes may be appropriate because the retained fluid increases plasma volume and therefore may normalize preload, cardiac output, and the effective circulating volume. However, with progressive, chronic disease (e.g., chronic heart failure) low cardiac output can no longer be compensated and the effective circulating volume remains low despite an expanded ECF volume. As a result of a continuing stimulus to retain Na^+ and water, the retained solute and volume ultimately extravasates from the repleted intravascular space and causes peripheral or pulmonary edema or both.

Redistribution of body fluids is another cause of decreased effective circulating volume despite normal or expanded ECF volume (see Table 88-4). The distributive fluid pathology typically results from a severe decrease in systemic vascular resistance (vasodilation) or endothelial barrier dysfunction or both and is often associated with an increased cardiac output (at least in early stages).

Noninfectious disorders (e.g., acute pancreatitis, burns, multiple traumatic injuries) may be complicated by tissue injury secondary to activation of the inflammatory system. The term *systemic inflammatory response syndrome* (SIRS) is used in this setting to refer to the consequences of a dysregulated inflammatory response in absence of infection with the release of proinflammatory mediators creating a chain of events that leads to widespread tissue injury. SIRS is characterized by vasodilation, increased microvascular permeability, and leukocyte accumulation in tissues remote from the original insult. For example, cardiac surgery with cardiopulmonary bypass may result in overt activation of the inflammatory cascade owing to the extracorporeal circulation. Therefore, SIRS is frequently observed in the postoperative period of cardiac surgery patients.[18] In sepsis, the clinical signs that define SIRS are present and are due to either a

culture-proven infection or an otherwise identified infection. The severity of sepsis is graded according to the associated hemodynamic compromise and organ dysfunction.[19,20] Hypotension is the most severe expression of circulatory dysfunction in sepsis (i.e., septic shock) and is caused by a redistribution of the intravascular fluid volume: sepsis is characterized by a reduced arteriolar vascular tone leading to increased capillary pressure and increased endothelial permeability. Other changes that occur include venous dilation (thereby diminishing venous return to the heart) and the release of myocardial depressant substances.[21] When hypotension complicates sepsis, anomalies in the distribution of flow at the regional and microregional circulation are accentuated, thereby accelerating the progression of tissue injury. Isolated bacterial and other toxin exposure (e.g., toxic shock syndrome) may result in a similar inflammatory response and has many characteristics in parallel with SIRS and sepsis.

Anaphylaxis describes allergic, IgE-mediated, immediate hypersensitivity reactions to protein substances. In contrast, anaphylactoid responses are clinically indistinguishable reactions that are not IgE mediated. Both syndromes are most frequently mediated through neuromuscular blocking agents, antibiotics, and latex in the perioperative period. They are characterized by a decreased peripheral vascular resistance, increased vascular permeability, and consequently a reduced effective circulating volume. In addition, cardiac output is initially elevated but may become depressed at later stages.

Fluids may be redistributed by a sudden loss of the sympathetic outflow due to a severe trauma to the spinal cord or brain resulting in a sudden decrease in peripheral vascular resistance, hypotension and, eventually, decreased cardiac output (i.e., neurogenic shock). Furthermore, endocrine disorders may lead to a distributive fluid pathology: acute adrenal insufficiency (addisonian crisis) is frequently the result of discontinuing corticosteroid treatment without tapering the dosage. However, stress (e.g., surgery) may also induce an acute adrenal insufficiency in patients on corticosteroid therapy if the dosage has not been adjusted to accommodate for the increased requirements perioperatively. In addition, long-standing hypothyroidism can lead to diastolic hypertension due to increased systemic vascular resistance and a reduction in blood volume. However, myxedema coma is associated with bradycardia, decreased myocardial contractility, low cardiac output, fluid retention, and generalized edema.[22]

Finally, hepatic cirrhosis deserves special consideration when summarizing clinical entities with a redistributed fluid volume status. Splanchnic vasodilatation and portosystemic shunts are responsible for the hyperdynamic circulation and abnormal distribution of the blood volume. The effective circulating blood volume is reduced and the baroreceptors and volume receptors activated. Patients with hepatic cirrhosis have an increased perioperative risk. Enhanced perioperative vasodilatation and hypotension may impair perfusion of vital organs, finally ending with multiorgan failure.[23]

Hypervolemia

Fluids are being administered intraoperatively to correct for preoperative and intraoperative deficits and to substitute the ongoing blood losses. Furthermore, certain anesthetic techniques (anesthetics per se, neuraxial blockades) may decrease the peripheral vascular resistance and impair cardiac function. To maintain an effective circulating volume intraoperatively, excess fluids or sympathomimetic therapy (vasoconstrictive or inotropic agents) have to be administered. However, because part of the negative impact of anesthetics on cardiovascular physiology is transient (adverse effects during administration of anesthetic drugs only), these effects are no longer present in the postoperative period and the body has to deal with an increased effective circulating volume. Patients with preexisting disease (e.g., congestive heart failure, valvular disease, renal disease) and patients at the extremes of the aging scale (infants, elderly) are at particular risk to develop a clinically relevant hypervolemia, most likely presenting as acute heart failure with pulmonary edema.

Assessment of the Fluid Balance

Incorrect fluid therapy is associated with a considerable morbidity and mortality.[24] Multiple factors have to be considered when devising a rational approach to fluid management for patients in the postoperative period. All available information related to a patient's preexisting diseases, preoperative fluid status, surgical interventions, and intraoperative anesthetic management have to be known. To complete the picture, in-depth clinical examination, hemodynamic monitoring, and laboratory tests have to be performed (Table 88-7). Different fluid compartments cannot be measured easily in the clinical setting, except for the intravascular fluid space. Therefore, intravascular volume status (normovolemia, hypovolemia, and hypervolemia) is most frequently assessed according to cardiac filling, heart function, and end-organ perfusion. Because every single variable is nonspecific, these variables may best complement each other and the clinical evaluation. For adequate assessment of a patient's fluid balance, all available data have to be taken into account like the pieces of a puzzle. Furthermore, to optimize the fluid status and to avoid fluid overload, frequent re-evaluations are required, especially during a "fluid trial," which is the intravenous administration of a specified amount of fluid over a short period of time.

Table 88-7 Assessment of Fluid Balance in the Postoperative Period

Patient's History
Preoperative history
Medical history, preexisting diseases
Preoperative volume status
Surgery/intervention
Type and duration of surgery/intervention
Blood loss
Third space loss
Anesthesia
Type and duration of anesthesia
Fluid replacement including transfusion
Type of monitoring
Intraoperative course of physiologic variables (trends)
Patient's Current Clinical Condition
Physical examination
Physiologic variables from routine, advanced monitoring
Laboratory parameters, medical imaging

Physical Examination and Routine Monitoring

There is a sequence of compensatory mechanisms of the body after intravascular fluid loss (i.e., hypovolemia due to dehydration or bleeding) to maintain adequate tissue perfusion and end-organ oxygenation. In the acute phase, this is mediated predominantly by an increased sympathetic outflow. At fluid losses more than 15% of the blood volume, filling of the jugular veins, preload, and stroke volume decrease. To maintain optimal cardiac output, the heart rate raises more than 100 beats/min. Simultaneously, afterload is being increased by peripheral vasoconstriction. Therefore, blood pressure is sustained during ongoing volume losses and decreases only with a loss greater than 30% to 40% blood volume (see Table 88-6). The mucous membranes become increasingly dry, and turgor of the skin decreases. As signs of a reduced tissue perfusion and end-organ oxygenation, a decreased urinary output (<0.5 mL/kg/hr) and an impaired mental status (confusion, somnolence, or coma in severe fluid losses) are observed. Unfortunately, some of these typical pathophysiologic signs of hypovolemia are not reliable indicators of a reduced intravascular fluid status in the postoperative period. Anesthetic drugs and stress reactions (due to pain, postoperative nausea and vomiting, body temperature derangements, or respiratory insufficiency) alter pulse rate, blood pressure, and cerebral function. Nevertheless, thirst in an awake patient, dry or parched mucous membranes, collapsed jugular veins, and reduced urinary output are still important signs of hypovolemia in the postoperative clinical setting.

In contrast with the evaluation of the fluid balance in adults, the assessment in children requires additional understanding of the age-specific physiology (see Chapters 82 to 84). Cardiac output is regulated primarily via heart rate and not stroke volume, owing to the relative myocardial stiffness. Furthermore, elasticity of the child's vessels is higher than that in the adult. Under normal circumstances, the heart rate of children is higher and the blood pressure is lower than those of adults, thus limiting the validity of these parameters to assess hypovolemia in pediatric patient. Evaluation of the capillary refill (i.e., the microcirculation of the skin) is an important test to assess the volume status in children. For its assessment, the skin is examined after pressure relief performed by the index finger. Delayed restoration of the skin color (>3 seconds after pressure release) indicates a prolongation of capillary refill and therefore reduced skin and end organ perfusion. The formation of a skin fold at the child's back of the hand between the examiner's thumb and index finger and its persistence after pressure relief indicates a decreased skin turgor and is another sign of hypovolemia in the child. However, this may be rarely seen in the postoperative period.

Postoperative hypervolemia may become manifest as arterial hypertension, increased urinary output, and pulmonary edema (especially in patients with cardiovascular compromise). Signs of pulmonary edema include crackles, wheezing, and frothy sputum. The diagnosis is confirmed by a chest radiograph showing edema of the alveoli, increased vascular filling, and upper lobe diversion. Decreased pulmonary gas exchange may lead to hypoxemia with cyanosis. Ankle edemas and anasarca (edema at the back of a bedridden patient) are chronic signs of hypervolemia and prompt the re-evaluation of the patient's history in the postoperative period.

Advanced Hemodynamic Monitoring

Different devices are available for advanced hemodynamic monitoring. They can be clinically used in a stepwise escalating approach—from invasive blood pressure measurement, to central venous cannulation, to pulmonary artery catheterization, to less invasive, advanced hemodynamic monitoring, to transesophageal echocardiography (see Table 88-8). Indications are primarily based on the patient's physical status, related cardiovascular and pulmonary comorbidities, and the scheduled intervention. For example, invasive blood and central venous pressure monitoring are typically applied to a patient with the ASA classification I to III undergoing a surgical intervention with anticipated large fluid shifts and losses. Additional sophisticated monitoring including assessment of cardiac output is highly desirable for the same interventions in a patient with considerably limited cardiac function. The standard technique for the past 30 years to measure cardiac output is pulmonary artery catheter monitoring. Its routine use, however, is being questioned and a matter of debate based on studies demonstrating conflicting results for its impact on patient's outcome.[25,26] Today, several less invasive advanced hemodynamic monitoring techniques are commercially available. They can replace the pulmonary artery catheter under certain clinical circumstances, and some of these techniques allow an even more refined fluid assessment by measuring additional fluid variables.[27]

In this section, traditional and newly available techniques of hemodynamic monitoring are discussed with the aim of evaluating a patient's fluid status. For a profound technical overview, indications and related complications, we refer the reader to Chapters 40 and 41.

Invasive Blood Pressure Monitoring

Invasive blood pressure measurement is very important in the evaluation of a patient with ongoing intravascular volume losses or limited cardiac function or both. It allows continuous measurement and is more reliable at hypotonic states than intermittent noninvasive blood pressure measurement. Additionally, in the patient whose ventilation is controlled mechanically, the observation of increased respiratory variations of the arterial blood pressure waveform may help in the assessment of the fluid balance. During inspiration, increased intrathoracic pressure reduces venous return, that is, preload, and thus diminishes stroke volume. As a result, systolic and diastolic pressure decreases and increases with a short delay after inspiration and expiration, respectively (Fig. 88-1A). The effect is more pronounced for the systolic pressure and is typically amplified with progressive hypovolemia. Furthermore, arterial cannulation allows convenient withdrawal of blood for repeated blood gas analysis and additional laboratory parameters.

Cardiac Output Measurement

Continuous cardiac output measurement may help to evaluate the volume status and to guide fluid resuscitation in patients with impaired cardiac function. As mentioned earlier, the standard device for its assessment is the pulmonary artery catheter. Alternatively, less invasive devices can be used considering their specific characteristics and limitations. The most frequently applied techniques are pulse contour/wave analysis and transesophageal Doppler flow measurements.[27]

Table 88-8 Advanced Hemodynamic Monitoring to Assess the Fluid Status

Measured Parameter	Abbreviation	Standard Value
Monitoring Device		
Invasive blood pressure		
Visual evaluation of pressure variation		
Arterial blood gas analysis		
Central venous catheter		
Central venous pressure	CVP	2-8 mm Hg
Central venous oxygenation	$Sc\bar{v}o_2$	>70%
Invasive, Advanced Hemodynamic Monitoring ("Gold Standard")		
Pulmonary artery catheter		
Pulmonary capillary wedge pressure	PCWP	8-18 mm Hg
Cardiac index	CI	2-3.5 L/min/m^2
Stroke volume index	SVI	35-50 mL/m^2
Continuous end-diastolic volume index	CEDVI	100-200 mL/m^2
Mixed venous oxygen saturation	$S\bar{v}o_2$	>75%
Less Invasive, Advanced Hemodynamic Monitoring		
Transpulmonary thermodilution		
Global end-diastolic volume index	GEDVI	700-800 mL/m^2
Intrathoracic blood volume index	ITBVI	875-1000 mL/m^2
Extravascular lung water	EVLW	≤10 mL/kg
Pulse contour/wave analysis		
Pulse pressure variation	PPV	<10-13%
Stroke volume variation	SVV	<10-13%
Transesophageal Doppler		
Aortic flow measurements		
Transesophageal, transthoracic echocardiography		
Visual evaluation		
End-diastolic area	EDA	
End-diastolic volume	EDV	

More important than a single value for cardiac output is the analysis of the time course of these values (trends), such as the response of cardiac output to fluid administration. Furthermore, cardiac output has to be evaluated in context with clinical examination and other hemodynamic parameters. For example, when cardiac output is low, fluid administration should only be performed when other signs of hypovolemia coexist. However, if the patient is hypervolemic (cardiac failure), treatment with β-sympathomimetic catecholamines is required to improve cardiac function.

Cardiac Filling Pressures: Central Venous and Pulmonary Artery Occlusion Pressure

Traditionally, central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) have been considered to indirectly reflect heart filling, that is, right and left ventricular preload (Fig. 88-2A). CVP is widely being used to assess the fluid status in patients without significant right ventricular dysfunction and pulmonary alterations when large and rapid changes of the volume status occur. Recent studies, however, revealed only a weak correlation between cardiac filling pressures and volumes.[28] These findings may be primarily explained by the fact that transduced intrathoracic as well as intra-abdominal pressures interfere with these pressure measurements. Preload, according to the Frank-Starling law, is defined as end-diastolic myocardial fiber tension.[29] Because this cannot be measured in a clinical setting, only surrogate markers of preload can be determined. Although pressure is a determinant of a compliant system like the heart, this refers to transmural but not intravascular pressure. Moreover, frequently observed alterations of the cardiac valves or obstructions of the heart cavities may introduce false measurements.

Despite these limitations, CVP and PAOP are still being used in clinical practice worldwide. It is important that interpretation of these parameters has to be done in the clinical context. Furthermore, trends toward low or high values are more predictive for hypovolemia or hypervolemia than absolute values, and the dynamics of changes are essential: for example, a small increase in filling pressures during a fluid trial in a hypovolemic patient may indicate the need for additional fluid administration whereas a dramatic increase in filling pressures may indicate imminent fluid overload and restriction of fluid administration.

Volumetric Preload Parameters

Because cardiac filling pressures do not necessarily reflect the patient's volume status, easy accessible parameters to determine end-diastolic volumes are highly desirable. Two thermodilution-based techniques provide volumetric preload parameters, which are calculated from cardiac output using the modified

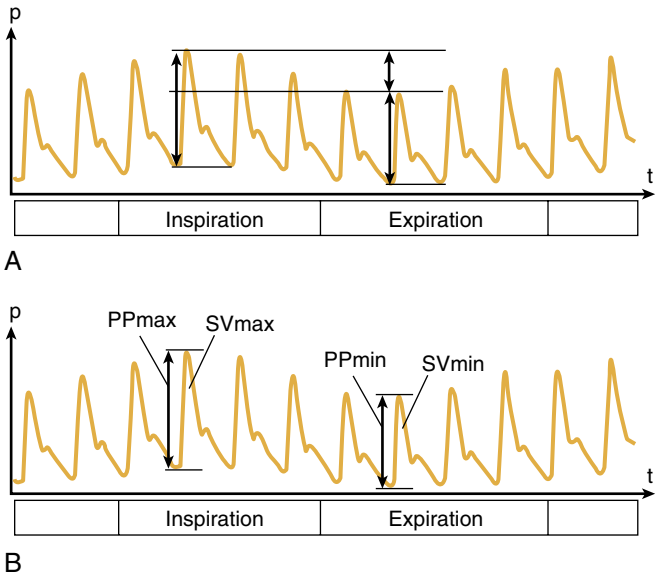

Figure 88-1 Arterial waveform analysis. **A,** Visual assessment of pulse pressure variation. Typical pulse pressure variation caused by hypovolemia as a result of intermittent positive-pressure ventilation. Note the changes in both the systolic and diastolic arterial pressures, with a higher decrease of the systolic pressure than of the diastolic pressure as a result of a reduced preload caused by mechanical inspiration, that is, an increase in intrathoracic pressure. p, pressure; t, time. **B,** Quantitative assessment of pulse pressure (PPV) and stroke volume (SVV) using less invasive hemodynamic monitoring device (pulse contour analysis). PPmax, maximal pulse pressure; PPmin, minimal pulse pressure. PPV is assessed as the percentage of change during the ventilatory cycle according to the following equation:

$$PPV\ (\%) = (PPmax - PPmin)/PPmean$$

PPmax/PPmin = means for the four extreme values of pulse pressure; PPmean, average value for this time period. SVmax, maximal stroke volume; SVmin, minimal stroke volume. SVV as the percentage of change of stroke volume (SV) can be determined during the same time interval:

$$SVV\ (\%) = (SVmax - SVmin)/SVmean$$

SVmax/min, means for the four extreme values of stroke volume during a period of 30 sec; SVmean, average value for this time period; p, pressure; t, time.

Stewart-Hamilton equation and indicator passage times.[30] Continuous end-diastolic volume index (CEDVI) is assessed by a modified pulmonary artery catheter (CCOmbo CCO/$S\bar{v}O_2$/CEDV catheter 774HF75, Edwards Lifescience LLC, Irvine, CA). Based on the site of measurement, CEDVI reflects right-sided heart end-diastolic volume (see Fig. 88-2B). Global end-diastolic volume index (GEDVI) and the closely related intrathoracic blood volume index (ITBVI) are determined via transpulmonary thermodilution (see Fig. 88-2C), which is used for the calibration of one of the less invasive cardiac output monitoring systems based on pulse contour analysis ($PiCCO_{plus}$, Pulsion Medical Systems, Munich, Germany). This concept assumes that the thermal indicator travels from the site of injection (central venous catheter) through different central compartments connected in series (i.e., right atrium and ventricle, pulmonary vessels and lungs, left atrium and ventricle) to the indicator detection site (a thermistor-tipped arterial catheter typically inserted in the femoral artery). Based on different indicator passage times through these compartments, different volumes can be calculated (Fig. 88-3). Thus, GEDVI includes the volume of all heart cavities and of the descending aorta. ITBVI additionally includes the volume of the pulmonary vessels. All volumetric preload parameters have shown to be superior preload indicators than cardiac filling pressures.[31-33]

Apart from to the assessment of GEDVI and ITBVI, the PiCCO system further allows calculation of the extravascular lung water (EVLW) (see Fig. 88-2D). EVLW may be useful to better characterize pulmonary edema and acute respiratory distress syndrome (ARDS), to evaluate the success of different ventilatory strategies, and to predict outcome in ARDS. However, careful interpretation of EVLW data is required in the presence of significant pulmonary vascular obstruction (e.g., pulmonary emboli), focal lung injury, or lung resection.[30,34]

Pulse Pressure and Stroke Volume Variation

Variations in pulse pressure (PPV) and stroke volume (SVV) occur due to cyclic changes of intrathoracic pressure induced by mechanical ventilation. The major determinant is a reduced venous return during inspiration of positive-pressure ventilation. PPV and SVV were recognized as potential parameters for guiding fluid replacement therapy more than 20 years ago. However, automated quantification of this phenomenon only became clinically available recently with the introduction of cardiac output monitoring devices based on pulse wave/contour analysis (see Fig. 88-1B). The method appears to visualize the individual cardiac response (changes in stroke volume) related to myocardial contractility due to diastolic volume loading: in the presence of hypovolemia, high stroke volume variations can be observed and the preload dependence of left ventricular function is pronounced; that is, the ventricle operates on the ascending limb of the Frank-Starling curve. During volume expansion, there is a rightward shift of left ventricular function on the Frank-Starling curve, which is thought to correspond to the observed decrease of stroke volume variation (Fig. 88-4). PPV and SVV have been used to assess fluid responsiveness and have shown to be sensitive in predicting the ventricular response to fluid administration (i.e., sensitive detection of fluid responders). However, alteration of vasomotor tone may influence PPV more than SVV. Moreover, the fact has to be stressed that this dynamic preload assessment is only reliable in fully sedated, mechanically ventilated patients with a regular heart rhythm.[35,36]

Transesophageal Echocardiography

Different echocardiographic approaches allow preload quantification either by measuring and calculating left ventricular end-diastolic area (LVEDA) or volume (LVEDV). LVEDA is determined at midpapillary level in a short-axis view. However, different echocardiographic positions and measurements are required for the volumetric calculation of LVEDV. These calculations are typically based on the Simpson algorithm assuming that the ventricle consists of a sum of small cylinders and a truncated ellipse.[37] Conflicting results have been reported using the Simpson algorithm; and, in daily practice, LVEDA is widely used as surrogate of left ventricular preload.[38] However, because this technique is highly operator dependent, the real benefit of echocardiography is the visualization of ventricular function, wall motion abnormalities, and cardiac filling and the "real-time" guiding of fluid therapy in acute, critical hemodynamic situations. The detection of "kissing papillary muscles," that is, the end-systolic contact of these structures, is highly pathognomonic for a hypovolemic state, whereas in hypervolemia a distended left ventricle with

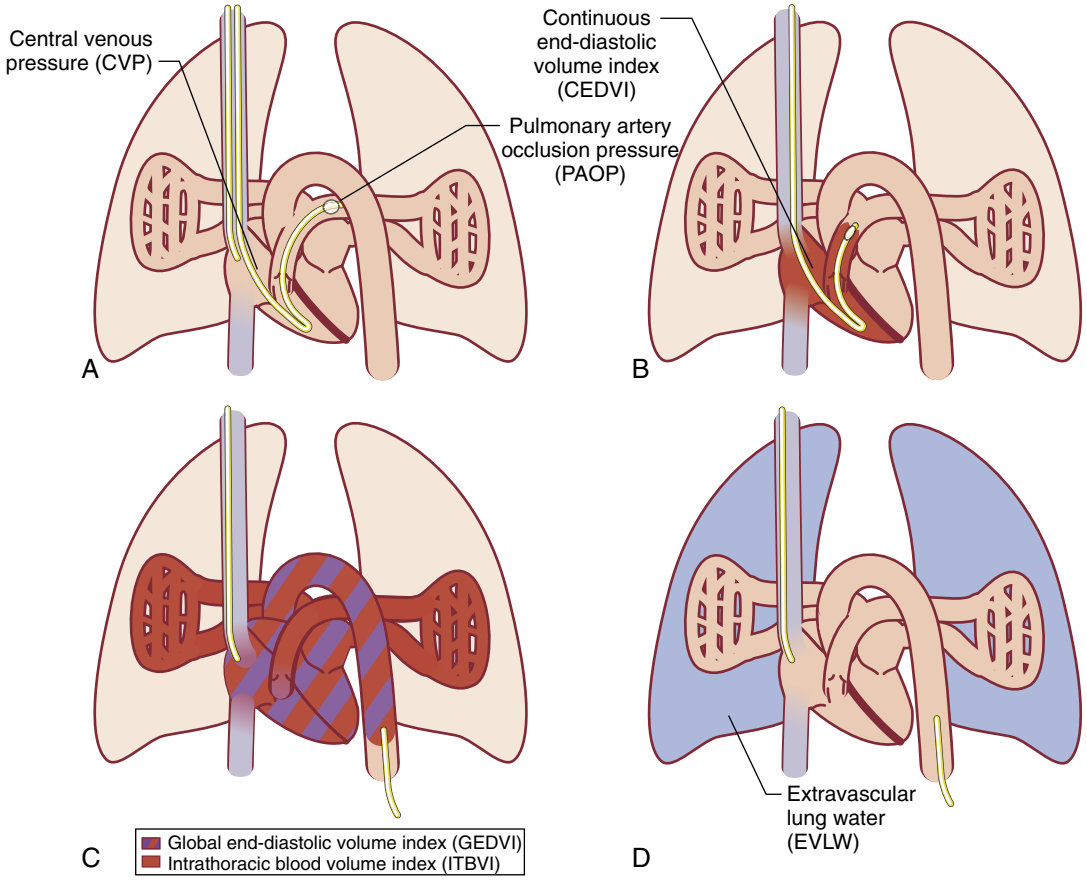

Figure 88-2 Basic and advanced hemodynamic monitoring. **A,** Right- and left-sided heart filling pressures: central venous and pulmonary artery occlusion pressure. Central venous pressure (CVP) is measured at the transition of the superior vena cava and the right atrium. For pulmonary artery occlusion pressure (PAOP) measurement, the balloon at the tip of the pulmonary artery catheter is inflated and floats to the wedge position. The blood flow ceases, and a hydrostatic column is created between the tip of the catheter and the left atrium. **B,** Continuous end-diastolic volume index (CEDVI). Continuous end-diastolic volume is determined from continuous cardiac output monitoring and the indicator travel time in the right side of the heart (indicator: intermittent release of small heat quantities from the thermal filament). **C,** Global end-diastolic volume index (GEDVI) and intrathoracic blood volume index (ITBVI). Global end-diastolic volume and intrathoracic blood volume are calculated from cardiac output and different indicator passage time after injection through a central venous catheter and the detection by a thermistor-tipped arterial catheter in the femoral artery (see Fig. 88-3). **D,** Extravascular lung water (EVLW). EVWL is calculated from cardiac output and different indicator passage time after injection through a central venous catheter and the detection by a thermistor-tipped arterial catheter in the femoral artery (see Fig. 88-3).

decreased function and mitral insufficiency as expression of an enlarged mitral annulus can be seen. Furthermore, echocardiography is of invaluable help as a diagnostic tool (e.g., detection of a papillary muscle rupture, pericardial tamponade, acute valvular pathologies, and dissection of the ascending aorta).[39,40]

Microcirculation and Regional Blood Flow

The maintenance of microcirculatory perfusion aims at providing an adequate tissue oxygenation. Consequently, different methods to directly visualize microcirculation have been developed in the past years. Nailfold microvideoscopy was the first technique available for bedside measurement. Unfortunately, local alterations of the vascular structure due to temperature changes and influences of vasoactive substances rendered these readings unreliable. Furthermore, results may fail to represent microcirculation of target organs like the intestines or the brain. The recently introduced orthogonal polarization spectral imaging and the sidestream dark-field technique are applied to the sublingual mucosal surface. The significance of these techniques has also been questioned for the same reasons as those of nailfold microvideoscopy. However, the use of these monitoring techniques revealed interesting insights into the hemodynamic pathophysiology of macrocirculation and microcirculation; for example, in sepsis, when microcirculatory alterations are most likely to occur, microcirculation improved as a result of a dobutamine infusion unrelated to cardiac output and mean arterial pressure.[41] Furthermore, in a comparative model of septic and hemorrhagic shock, changes of microcirculation were also observed in hemorrhagic shock but they were less pronounced than in septic shock. Resuscitation and restoration of the macrocirculation resulted in an increased microcirculation in hemorrhagic shock, whereas treatment failed to improve capillary blood flow in septic shock.[42] It seems that these techniques of microcirculation monitoring provide additional and necessary information for the optimization of end organ perfusion. However, because they are time-consuming and because clearly defined end points are lacking, they have to be considered experimental.[43]

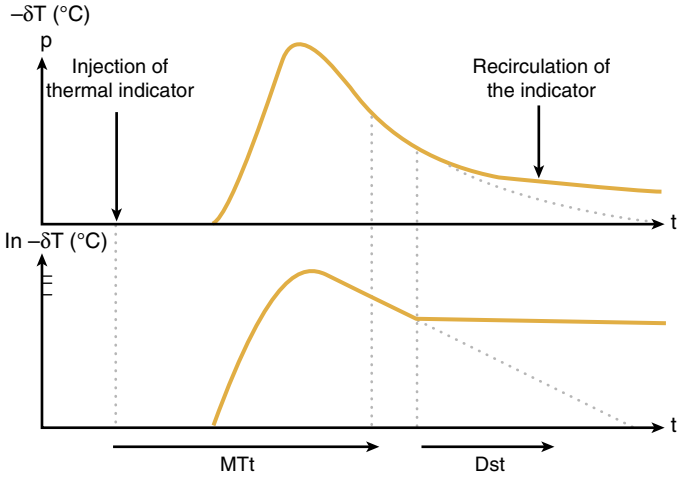

Figure 88-3 Transpulmonary thermodilution curve and typical indicator passage time required for the calculation of global end-diastolic volume index (GEDVI), intrathoracic blood volume index (ITBVI), and extravascular lung water (EVLW). MTt, Mean transit time of the indicator; DSt, downslope time of the indicator; δT, temperature change as result of thermal indicator injection; BSA, body surface area. GEDVI, ITBVI, and EVLWI are calculated according to the following formulas:

$$GEDVI = CO \times (MTt - DSt) \times BSA$$

$$ITBVI = 1.25 \times GEDVI \qquad EVLW = CO \times (MTt - 1.25 \times [MTt - DSt])$$

Laboratory Evaluation

Laboratory evaluation supports the assessment of a patient's fluid status primarily by providing information on the effects of an inadequate end organ perfusion. Parameters assessed by blood gas analysis reflect global tissue hypoperfusion but also allow the calculation of tissue oxygen extraction (in combination with cardiac output measurement). Furthermore, renal function and the electrolyte composition of the urine provide information on the global fluid status and end organ perfusion of the kidneys. Finally, hormones released from myocardial cells in response to volume expansion and possibly increased wall stress (e.g., BNP; see earlier section on natriuretic hormones) may provide some information on the patient's volume status and help to differentiate noncardiogenic and cardiogenic pulmonary edema (Table 88-9).

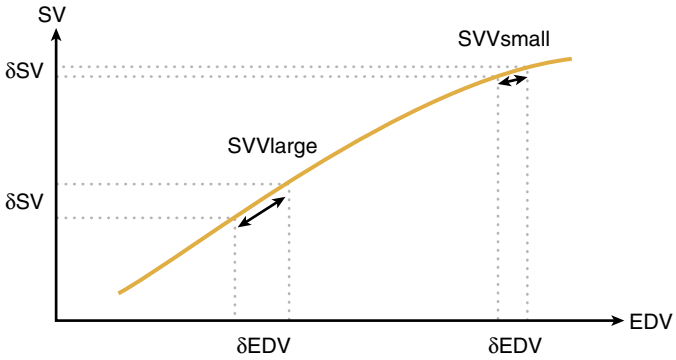

Figure 88-4 The concept of fluid responsiveness based on the assessment of stroke volume variation (SVV). EDV, end-diastolic volume; δEDV, change of end-diastolic volume induced by fluid administration; SV, stroke volume; δSV, change of stroke volume induced by fluid administration; SVVlarge = stroke volume variation typically higher than 15%; SVVsmall, stroke volume variation smaller than 12%. Fluid administration in a patient with a large SVV typically results in an increased EDV and an increased SV (so-called fluid responder). During additional fluid administration, SVV decreases and travels up along an imaginary individual Frank-Starling curve. If SVV becomes low, further fluid administration will induce only small changes in both EDV and SV (shallow part of the Frank-Starling curve) (so-called fluid nonresponder).

Table 88-9 Laboratory Parameters to Assess the Fluid Balance

Arterial blood gas analysis		
Metabolic acidosis (pH)	7.36-7.44	
Lactate	<2 mEq/L	
Base excess (BE)	–2 to +2 mEq/L	
Laboratory parameters of renal function		
Creatinine (Creat)	70-110 mmol/L (0.8-1.25 mg/dL)	
Blood urea nitrogen (BUN)	2.1-8.9 mmol/L (6-25 mg/dL)	
	PRA	**ATN**
BUN:creatinine ratio	≥20:1	10:1-20:1
Fractional sodium excretion (FENa) $= (Na_U \times Creat_P):(Na_P \times Creat_U) \times 100$	<1%	>2%
Urinary sodium (Na_U)	<10-20 mEq/L	>20-40 mEq/L
Urinary osmolality (Osm_U)	>450 mOsm/kg	<350 mOsm/kg
Laboratory parameter of cardiac failure		
Brain natriuretic peptide (BNP)	<125 pg/mL	

ATN, acute tubular necrosis; P, plasma; PRA, prerenal azotemia; U, urinary.

Arterial Blood Gas Analysis

Inadequate tissue perfusion, that is, impairment of oxygen delivery and regional hypoxia, induces a change of the energy supply from aerobic to anaerobic metabolism: instead of 36, only 2 ATP molecules are produced per metabolized glucose molecule, while pyruvate is converted to lactate. Anaerobic metabolism results in the formation of large amount of hydrogen ions, and a metabolic lactic acidosis develops with decreased pH and increased lactate level (>2 mEq/L). Independent of global hypoperfusion and anaerobic metabolism, lactate levels may also be elevated during administration of large amounts of lactated Ringer's solution and reduced hepatic clearance of lactate. On the other hand, pH is a function of the available amount of plasma HCO_3^- and arterial CO_2. The interaction between pH, HCO_3^-, and $Paco_2$ is explained by the Henderson-Hasselbalch equation:

$$pH = pK + \log HCO_3^- / 0.03(Paco_2)$$

For clinical purposes a simplification may be sufficient:

$$pH \approx HCO_3^- / Paco_2$$

Typically, levels of bicarbonate and base excess decrease during the development of tissue hypoperfusion and progressive metabolic lactic acidosis, because plasma HCO_3^- acts as a hydrogen ion buffer. *Base excess* is defined as the amount of base required to raise 1 L of blood to a pH predicted from actual Pco_2 and is a derived parameter from HCO_3^- and pH:

$$\text{Base Excess} = HCO_3^- - 24.8 + \left(16.2 \times [pH - 7.4]\right)$$

Base excess has shown to be a better indicator of global hypoperfusion and the development of metabolic acidosis than pH, primarily because of the compensatory physiologic mechanisms to maintain the pH in a normal range.[44,45] However, base excess can also be altered by causes other than global hypoperfusion. For example, hyperchloremic metabolic acidosis induced by infusion of normal saline, diabetic ketoacidosis, and acidosis due to chronic renal failure may result in a decreased base excess (increased base deficit).[46]

Apart from these main parameters indicating global hypoperfusion, arterial blood gas analysis together with advanced hemodynamic monitoring may further allow calculation of how much oxygen is being delivered into the tissue of the body, expressed as the oxygen delivery index (Do_2I):

$$Do_2I\left(mL/min/m^2\right) = CI \cdot 13.4 \cdot Hb \cdot Sa_{O_2}$$

where CI = cardiac index, Hb = hemoglobin concentration, and Sa_{O_2} = arterial oxygen saturation.

Do_2I may help to estimate a deficit in oxygen supply. Several studies demonstrate an improved outcome, when supranormal Do_2I levels (>600 mL/min/m^2) have been achieved during preoperative resuscitation.[47] However, conflicting results have been reported in studies applying this concept to trauma and septic patients.[48,49]

Venous Blood Gas Analysis

The oxygen saturation of venous blood is either measured in the pulmonary vein (mixed venous oxygen saturation [$S\bar{v}O_2$]) or in the superior vena cava (central venous oxygenation saturation [$Sc\bar{v}O_2$]) using co-oximetry to determine the balance between systemic oxygen delivery and consumption (i.e., tissue oxygen extraction). Hypoperfusion due to hypovolemia, for example, results in a decreased oxygen delivery. The determination of $S\bar{v}O_2$ requires the placement of a pulmonary artery catheter and, in order to avoid the inherent risk related to its use, assessment of $Sc\bar{v}O_2$ via a central venous catheter is advocated.[50] $S\bar{v}O_2$ reflects the oxygen extraction of the total body, with $Sc\bar{v}O_2$ only that of the brain and the upper part of the body. Under physiologic conditions $Sc\bar{v}O_2$ values are lower than $S\bar{v}O_2$ values (higher oxygen extraction by the brain), whereas in a sedated patient after major abdominal surgery $S\bar{v}O_2$ values may be significantly lower (higher oxygen extraction by the intestines). Thus, it has been argued that $S\bar{v}O_2$ and $Sc\bar{v}O_2$ may not necessarily be used interchangeably.[51] However, because trends of these two parameters show a good correlation,[52] $S\bar{v}O_2$ and $Sc\bar{v}O_2$ are helpful tools for the fluid assessment and resuscitation in complex hemodynamic situations. Because frequent blood gas analyses are required, the use of a modified pulmonary artery or central venous catheter (with fiberoptic sensors to measure oxygen saturation) has to be considered.

Parameters of Renal Function

In a patient without renal disease and diuretic therapy, hypovolemia and renal hypoperfusion leads to increased urea reabsorption and a proportionately greater elevation in BUN than plasma creatinine. Therefore, the BUN:creatinine ratio can increase from 10:1 to greater than or equal to 20:1 and help to assess this patient's volume status. However, increased urea production (hyperalimentation, glucocorticoid therapy, gastrointestinal bleeding) may also increase this ratio.

Because the appropriate response to fluid deficits is an enhanced renal Na^+ and water reabsorption, the urine composition typically reflects the patient's fluid status. In a hypovolemic patient, the urine osmolality and specific gravity are generally greater than 450 mOsm/kg and 1.015 g/mL because of maximal concentration of the urine (enhanced AVP secretion). Furthermore, the urine Na^+ concentration is usually less than 20 mEq/L in hypovolemia. For example, if the urine Na^+ concentration remains less than 20 mEq/L after fluid therapy, then the kidneys are sensing persistent intravascular volume depletion and more fluids should be given. However, the use of urine Na^+ concentration cannot be applied to an edematous patient with heart failure or cirrhosis. In these patients, the urine Na^+ concentration is a marker of effective circulating volume depletion but not necessarily an indicator for the need of more fluid. Additionally, urine Na^+ concentration does not reflect the volume status in conditions associated with impaired Na^+ reabsorption, as in acute tubular necrosis. Another exception is hypovolemia due to vomiting, because the associated metabolic alkalosis and increased filtered HCO_3^- impair proximal Na^+ reabsorption. In this case, the urine Cl^- is low (<20 mEq/L). Finally, in hypovolemia due to a diabetes insipidus, urine osmolality and specific gravity are indicative of inappropriately dilute urine.

Therapy for Alterations in Fluid Balance

Maintaining an optimal fluid balance is challenging but critical in the postoperative period to adequately perfuse tissue and organs. If the fluid homeostasis is altered, therapeutic interventions are required to bring the patient back to an optimal fluid balance. The goal of fluid therapy in postoperative patients is to maintain the effective circulatory volume while avoiding interstitial fluid overload whenever possible. The appropriate type and amount of fluid and or cardiac support should be provided if the effective circulating volume is low (absolute and relative hypovolemia). On the other side, fluid restriction and removal (pharmacologic, renal replacement therapy) need to be considered if a patient has excessive intravascular fluid volume.

Maintenance Fluid Therapy

Maintenance fluid therapy in the postoperative period aims at preserving the water and electrolyte balance. It should replace the ongoing losses of water and electrolytes under normal physiologic conditions. Because these losses account for 30 to 35 mL/kg/day (approximately 2100-2500 mL/day for a 70-kg adult), the same amount of fluids have to be provided to maintain the physiologic fluid balance. Maintenance fluid requirements may be calculated according to the 4-2-1 rule in the postoperative period and replaced intravenously with isotonic crystalloid solutions as long as the patient remains NPO (Table 88-10).

Besides estimating and measuring the net fluid input and output (according to the amount of fluids administered and lost), the patient should be weighed on a daily basis to estimate net gain or loss of fluids because gastrointestinal, urine, and insensible

Table 88-10 Empirical Maintenance and Replacement Fluid Therapy

Maintenance Fluid Therapy	
Ongoing losses of water and electrolytes under physiologic conditions	
4-2-1 Rule*	
≤10 kg	4 mL/kg/hr
11-20 kg	*Add* 2 mL/kg/hr
≥21 kg	*Add* 1 mL/kg/hr
Replace with balanced, isotonic crystalloid solutions (e.g., lactated Ringer's solution)	
Replacement Fluid Therapy	
Hemorrhage	Replace 1 mL of blood loss with 3 mL balanced, isotonic crystalloid solution or 1 mL colloid solution/blood.
Third space losses	Replace with balanced isotonic crystalloid solutions (e.g., lactated Ringer's solution).
Profuse sweating	Replace with D_5W ¼ NS with 5 mEq KCl/L.
Gastric and colonic losses	Replace with D_5W ½ NS with 30 mEq KCl/L.
Bile, pancreas, and small bowel losses	Replace with balanced isotonic crystalloid solutions (e.g., lactated Ringer's solution).

D_5W, 5% dextrose (glucose) in water; NS, normal saline (0.9% NaCl); KCl, potassium chloride.
*Example: Empirical maintenance fluid therapy per hour for a 70-kg person is approximately 110 mL/hr, i.e., 40 mL/hr *plus* 20 mL/hr *plus* 50 mL/hr.

losses may be unpredictable and difficult to monitor in patients after surgery.

Replacement Fluid Therapy

Replacement fluid therapy in the postoperative period corrects any existing and additionally occurring water and electrolyte deficits. These deficits result from bleeding, third space sequestration, evaporative losses (e.g., mechanical ventilation without humidifier, surgical field if wound is left open), profuse sweating, and additional gastrointestinal as well as other fluid losses (see Table 88-6). There is no formula that can be used to accurately estimate the total fluid deficit (as is the case for maintenance fluid requirements). Estimated and measured fluid losses, clinical examination, and laboratory values must be used to assess the severity of intravascular volume depletion. The plasma concentration of Na^+ provides the best estimate for water balance in relation to Na^+ but does not give any information on the volume status.

To preserve fluid homeostasis, the type of fluid given for replacement therapy is largely dependent on the type of fluid that has been lost and any concurrent fluid and electrolyte disorders (see Table 88-10). Thus, patients with blood loss usually require isotonic fluids and or blood if the hemorrhage is severe. Other examples are patients with hypernatremia in whom hypotonic solutions are preferred. The choice of replacement fluid in hypernatremia depends on the source of fluid loss: D_5W alone (5% dextrose in water) can be given if there has been only water loss (as in diabetes insipidus), whereas a hypotonic saline solution (such as D_5W ¼ normal saline [NS] or D_5W ½ NS) should be administered in patients who have lost both salt and water (as with profuse sweating, gastric losses, and diarrhea). Patients with hyponatremia should be administered isotonic or hypertonic saline. In addition, K^+ replacement may be required in patients who have developed K^+ depletion as evidenced by hypokalemia. It is important to emphasize that K^+ is as osmotically active as Na^+. Thus, the addition of 30 mEq of KCl to 1 L of D_5W ½ NS (containing 77 mEq/L of each, Na^+ and Cl^-) creates a solution that is essentially a two-thirds normal saline solution and therefore contains less free water. This could be important in patients with hypernatremia.

The optimal rate of volume repletion for mild to moderate volume deficits is somewhat arbitrary. However, severe volume deficits (e.g., hypovolemic shock) require immediate repletion in an attempt to restore tissue perfusion, and fluid administration has to be continued at a rapid rate until clinical signs of hypovolemia normalize. Clinical and laboratory parameters must be followed to assess the efficacy and adequacy of volume repletion. Repletion of intravascular volume in patients with hyponatremia or hypernatremia requires extra attention, because overly rapid correction of the plasma Na^+ concentration can lead to potentially irreversible neurologic damage. The preferred rate at which the plasma Na^+ concentration should be elevated in hyponatremia varies with the clinical presentation. Acute hyponatremia (e.g., hyponatremia during transurethral resection of the prostate due to massive reabsorption of free water) can and should be corrected faster than chronic hyponatremia. The rate of correction over the first 24 hours is more important than the maximum rate in any given hour. Demyelinating lesions in the central nervous system are most common when the plasma Na^+ concentration in severe hyponatremia is raised more than 15 mEq/L/day and are rare at a rate below 10 to 12 mEq/L/day.

Controversies of Liberal, Restrictive, and Optimal Intravascular Fluid Therapy

Perioperative fluid therapy has a direct bearing on patient's outcome, and prescriptions should be tailored to the needs of the patient. Too much or too little fluid can both adversely affect clinical status, with increased morbidity and mortality. The goal of fluid therapy in postoperative patients is to maintain the effective circulatory volume while avoiding interstitial fluid overload whenever possible.[24,53]

Liberal Intravascular Fluid Therapy

During outpatient surgery in healthy patients the administration of relatively liberal amounts of crystalloids perioperatively (up to 20-40 mL/kg crystalloids) appears to both improve the quality of a patient's recovery and decrease the time after surgery until ready for discharge.[54,55] Applying these protocols has led to fairly consistent results across studies. Therefore, they can be recommended with the caveat that they may apply only to healthy individuals undergoing minor surgical procedures.

Perioperative hypovolemia (absolute and relative) induced by many forms of anesthesia, and the use of vasoconstrictors, is considered the most important trigger for perioperative acute renal failure in patients with comorbid conditions and in patients undergoing major surgery. Therefore, a liberal fluid regimen has been proposed and has been clinically used for many years to prevent anesthesia-induced hypotension and to protect organ function, especially the kidneys.[56] However, this regimen is not evidence based and it has not been shown to decrease the incidence of acute renal failure. By contrast, excess fluid administration may result in adverse clinical outcomes from tissue edema

formation with compromised pulmonary gas exchange, impaired microvascular perfusion and tissue oxygenation, coagulation abnormalities, and acid-base disturbances. As a result, the traditional liberal perioperative fluid regimen has been questioned.[24] Furthermore, patients with one-lung ventilation after thoracic surgery are at risk for postoperative pulmonary complications (see Chapter 59). Excess positive fluid balance has been shown to be the strongest risk factor for postoperative pulmonary complications and increased in-hospital mortality rate in these patients.[57]

Restrictive Intravascular Fluid Therapy

As a result of the adverse effects of a liberal fluid regimen in some patients, restrictive fluid protocols have been developed and applied perioperatively with conflicting results. Protocol based fluid restriction has been shown to reduce the incidence of perioperative cardiopulmonary complications and disturbances of bowel motility while improving wound healing and decreasing the occurrence of anastomotic insufficiency in major abdominal procedures.[58,59] Other studies, however, did not confirm these findings.[60] The most likely cause for these controversial findings is the lack of a standardized definition of liberal and restrictive fluid therapy. To date, different studies used different definitions, making any pooling of data impossible. However, there is consensus in most studies that fluid overload in major surgical procedures may be harmful.[59]

Optimal Fluid Intravascular Therapy

The idea behind goal-directed fluid therapy and optimization is to obtain normal to supranormal values of tissue oxygen delivery.[61] With this concept transferred to the general surgical patient, a maximum stroke volume, achieved by esophageal Doppler-monitored fluid boluses, was considered to represent the optimum intravascular fluid load. Indeed, compared with fluid substitution at the discretion of the anesthesiologist, this goal-directed approach led to a significantly reduced hospital stay and fewer intermediate and major postoperative complications after elective colorectal surgery.[62] Additionally, patients treated intraoperatively with colloid boluses to maintain a predefined minimum aortic flow and to optimize stroke volume individually tolerated diet significantly earlier.[62] Also, several indirect variables were tested as predictors of fluid responsiveness. Less invasive measurements, such as variation in the systolic arterial or pulse pressure (on the principle that intrathoracic pressure changes cyclically during mechanical ventilation, decreasing venous return and consequently stroke volume, preferentially in hypovolemic patients) strongly distinguish between responders and nonresponders to fluid challenge.[63] However, circulatory optimization, achieved by optimizing these easily applicable surrogate variables, has not yet been reliably translated into improved outcomes and, for practical reasons, esophageal Doppler imaging cannot be routine.[64]

In summary, fluid therapy to each patient must be individualized and balanced according to the benefits and risks of intravascular fluid administration. Therefore, the patient's characteristics and the type of procedure should determine whether to choose a more liberal or a more restrictive fluid regimen. With more invasive or traumatic surgery and with increasing blood losses, greater alterations in fluid balance are expected and the fluid therapy should be optimized with a rational concept, that is, protocol-based, goal-directed fluid therapy under careful and continuous assessment of the fluid balance.

Types of Fluids: Crystalloids, Colloids, and Blood Products

A variety of manufactured fluid formulations exist for intravenous fluid therapy (see Chapters 49, 54, 55, and 57) that differ in two fundamental ways: the component electrolyte solution and the suspended material providing colloid osmotic (oncotic) pressure. Crystalloids are aqueous solutions of inorganic and small organic molecules, the main solute being either normal saline or glucose. Depending on the concentration of the solute, manufactured crystalloid solutions are isotonic, hypotonic, and hypertonic. Colloids, in contrast, are homogeneous noncrystalline substances containing large molecules. Because colloids have much greater capacity to remain within the intravascular space, these solutions may restore the plasma volume more efficiently and may act as volume expanders. Colloids used in clinical practice include hydroxyethyl starch (HES), gelatin, and dextran preparations dissolved in crystalloids and human plasma products such as albumin or blood products (fresh frozen plasma) (see Chapter 55).

Crystalloids

Crystalloid solutions are safe, nontoxic, reaction free, and inexpensive. Multiple different formulations are commercially available; the most commonly used are summarized in Table 88-11. Besides different tonicity, crystalloids can be further categorized into unbalanced (unphysiologic electrolyte composition, no buffers) and balanced (physiologic mixture of electrolytes with buffers) formulations. A major disadvantage of hypotonic and isotonic crystalloids is the limited ability to remain within the intravascular space. Therefore, to maintain an effective circulating volume, administration of large volumes of crystalloid solutions is required. Accumulation of fluid in the interstitial space with edema formation occurs as a typical side effect.

Isotonic crystalloids are favored in the perioperative period. Because NaCl is the predominant salt in crystalloids and because Na^+ equilibrates over the whole ECF compartment, only 25% of the administered crystalloid solution remains intravascular. Therefore, to completely replace an intravascular fluid loss with isotonic crystalloid solutions, three to four times the volume lost has to be administered. The major consideration in selecting a solution is its specific electrolyte composition (mainly Na^+, K^+, and Cl^-) and buffer capacity. Normal saline may induce a nongap, hyperchloremic metabolic acidosis associated with impaired end organ perfusion and function if large volumes are given intravenously.[65] On the other hand, buffers in lactated Ringer's solution (i.e., lactate) or Plasma-Lyte (i.e., acetate and gluconate) are being metabolized to HCO_3^- in the liver and may result in a metabolic alkalosis. These balanced crystalloid solutions should be used with caution in patients with preexisting hyperkalemia (e.g., end-stage renal disease) because of their K^+ content. Alternatives are normal saline or balanced, K^+ free solutions. Furthermore, calcium present in lactated Ringer's solution prohibits its use in the presence of citrated blood products and may precipitate different drugs (e.g., amphotericin B, thiopental).

Hypotonic crystalloids are being used to provide free water to patients with hypertonic dehydration or hypernatremia. Several formulations are available, such as D_5W, ½ NS, and ¼ NS with or without D_5W. The intravascular volume effect is minor in comparison with that of isotonic crystalloids. As an example, D_5W

Table 88-11 Composition of Plasma and Routinely Used Crystalloids

	Electrolytes, Buffers (mEq/L)						Glucose		Posm
Fluid	**Na^+**	**K^+**	**Ca^{2+}**	**Mg^{2+}**	**Cl^-**	**Buffers$^-$**	**(g/L)**	**pH**	**(mOsm/L)**
Plasma	141	4.5	5	2	103	Bic 26 Prot 16	0.7-1.1	7.4	290
Isotonic									
Normal saline (NS)*	154				154			6.0	308
Lactated Ringer's solution	130	4	3		109	Lac 28		6.5	274
Plasma-Lyte	140	5		3	98	Acet 27 Gluc 23		7.4	294
Hypotonic									
D_5W							50	4.5	252
D_5W ½ NS	77				77		50	5.0	406
Hypertonic									
7.5% NaCl	1284				1284			6.0	2568

*Normal saline, 0.9% NaCl.
Acet, acetate; Bic, bicarbonate; D_5W, 5% dextrose (glucose) in water; Gluc, gluconate; Lac, lactate; Prot, plasma proteins; Posm, calculated osmolarity.

consists entirely of free water because glucose is being metabolized and water equally distributes in the ICF and ECF compartments. Therefore, only 8% of the administered D_5W remains in the intravascular space. As a general rule, dextrose-containing solutions should be used with caution in the absence of disease states affecting glucose metabolism because hyperglycemic-induced hyperosmolality, osmotic diuresis, and cerebral acidosis are known complications.

Hypertonic solutions such as 7.5% NaCl are being used in the postoperative period to treat severe hyponatremia. Furthermore, hypertonic saline alone or combined with colloids refers to the concept of "small volume resuscitation" in patients with severe hemorrhage.[66] The theory of a rapid restoration of an effective circulating volume is convincing, and animal studies are promising so far, demonstrating an improved microcirculation, decreased intracerebral pressure, induction of stress protein response and cellular protection, as well as a balanced inflammatory response. However, these effects have been difficult to replicate clinically and a systematic review of hypertonic saline in resuscitation of patients with trauma, burns, or those undergoing surgery was unable to reach a conclusion regarding benefit or harm.[67]

Hydroxyethyl Starches

Hydroxyethyl starches are modified natural polysaccharides similar to glycogen (Fig. 88-5). They are derived from amylopectin, a highly branched corn or potato starch. Starches are rapidly being cleaved by α-amylase, and, as a result, plasma levels of α-amylase may significantly increase after administration of starches (typically twofold to fivefold). To delay α-amylase breakdown with subsequent elimination from the blood, natural starches are being substituted with hydroxyethyl groups (carbon position C2, C3, and C6), resulting in the clinically used HES preparations. Their most important physicochemical characteristics are the molar substitution, C2/C6 ratio, and molecular weight. Molar substitution (MS) is defined as the mol hydroxyethyl residues per mol glucose subunits. According to the MS, hydroxyethyl starch preparations can be classified into solutions with high (hetastarch, hexastarch; 0.7 and 0.6, i.e., 7 and 6 hydroxyethyl groups for every 10 glucose units, respectively), medium (pentastarch; 0.5), and low substitution (tetrastarch; 0.4). High MS prolongs degradation. The C2/C6 ratio refers to the pattern of hydroxyethylation at the carbon atoms of the glucose rings and is considered high (>8) or low (<8). Substituted hydroxyethyl groups at

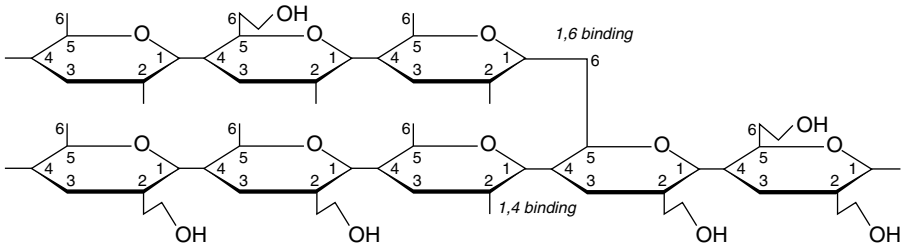

Figure 88-5 Molecular structure of hydroxyethyl starch solutions. Hydroxyethyl starches are modified natural polysaccharides similar to glycogen. The glucose units are bound together primarily by 1,4 and occasionally by 1,6 linkage. To delay α-amylase breakdown with subsequent elimination from the blood, natural starches are being substituted with hydroxyethyl groups (carbon positions C2, C3, and C6). Their most important physicochemical characteristics are the molar substitution, C2/C6 ratio, and the molecular weight.

the C2 position are being cleaved much more slowly than at position C6. Therefore, formulations with high C2/C6 ratio are being slowly degraded and have longer plasma half-lives. The low-molecular-weight fraction (<60-70 kD) is rapidly excreted by the kidneys, whereas the larger molecules have to be hydrolyzed by serum α-amylase before elimination. As a result, the plasma half-life of an HES preparation increases with increasing molecular weight. HES has recently become the subject of renewed interest in Europe and some non-European countries because of the introduction of a new, rapidly degradable formulation with reduced side effects (i.e., HES 130/0.4).[68] Furthermore, HES 670/0.75 and HES 130/0.4 are now clinically available in a carrier solution other than 0.9% NaCl (i.e., in a balanced electrolyte formulation; see later).

The plasma expanding effect (volume effect) primarily depends on the concentration of the HES solution. Specific physicochemical properties affect primarily the extent and duration of plasma volume expansion, their effects on blood rheology, and the coagulation system. The rheologic effects of HES are determined by their high hemodilutional capacity in combination with their specific pharmacologic effects on red cell aggregation, platelet function, plasma viscosity, and blood corpuscle/endothelial cell interactions. Vascular resistance is reduced by lowering whole blood viscosity, which will enhance venous return and increase cardiac output. The net result would be improved blood fluidity, which might beneficially influence tissue perfusion and oxygenation. Negative effects on coagulation have been reported after the use of HES, especially by first-generation preparations with high MS (hetastarches).[69] HES solutions decrease the levels of von Willebrand factor (vWF) and associated factor VIII activity (acquired, type I von Willebrand–like syndrome), impair platelet function (coating), and may induce platelet damage.[70] Patients with blood group O have significantly lower levels of vWF/VIII than patients with other blood groups, and these levels are further reduced significantly after HES administration.[71] Administration of HES solutions may be associated with renal dysfunction probably because of hyperviscosity of the urine in dehydrated patients. Glomerular filtration of hyperoncotic colloid molecules causes hyperviscous urine and stasis of tubular flow, resulting in the obstruction of the tubular lumen. Additionally, tubular cells may swell and show vacuolization ("osmotic nephrosis–like lesions"). In the case of HES, the risk of high plasma oncotic pressure and thus the risk of acute renal failure is probably increased by high concentrations of the colloid (10% HES) or repeated administration of HES with a high MS and molecular weight (slowly degradable HES). However, the critical creatinine level when HES should be avoided is not known. Depending on their physicochemical characteristics, HES molecules may pass the endothelial barrier and enter the interstitial space. Most of the extravasated HES will be collected by the lymph system and reenter circulation. A smaller amount is taken up by the reticuloendothelial system where the starch is broken down slowly. Thus, trace amounts of the preparations can be detected for several weeks after administration. The degree of plasma and tissue accumulation is highly dependent on the type of HES used for volume replacement. Especially HES solutions with a high MS and molecular weight are associated with considerable accumulation, particularly after multiple dosing. Pruritus after administration of HES has been described in some reports and seems to be associated with extravascular HES deposition after large volume administration. This may occur after a latency period and may persist for weeks to months. Allergic reactions may occur after administration of HES; however, the incidence is lowest compared with the other colloids. The following recommendations for maximum daily administration have been established: 1.5 (slowly degradable, e.g., HES 670, 0.75), 2.0 (intermediate degradable), and 3.0 (rapidly degradable, e.g., HES 130/0.4) g/kg body weight, respectively.

Gelatins

Produced by degradation of bovine collagen and chemical modifications, gelatins are polydispersed colloidal solutions. Three types of gelatins are available: oxy-crosslinked, urea-crosslinked, and succinylated gelatins. Different gelatin molecules have comparable molecular weight (average 30-35 kD), and the commercially available preparations have similar gelatin concentrations (3.5%-5.5%) and volume-restoring efficacy (volume effect 70%-100%). Because of the small molecular weight, gelatins are rapidly being cleared from the bloodstream by glomerular filtration (>80% are being excreted unchanged by the kidneys) and, to a minor extent, undergo cleavage by proteases into small peptides in the reticuloendothelial system. Therefore, repeated infusions of gelatins are necessary to maintain adequate blood volume. Gelatins do not accumulate in the body, have no dose limitations, and appear to be almost without adverse effects on the kidneys. Although gelatins were considered for a long time to have only an influence on blood coagulation via dilution, this has been questioned lately.[72] It seems that hemostasis could be impaired by an interference of gelatin with the function of coagulation factors and by a disturbance in the quality of fibrin polymerization. The exact mechanism however remains to be elucidated.[73]

Disadvantages of gelatins are their bovine origin with the hypothetical potential of transmitting prion diseases (e.g., bovine spongiform encephalopathy). Furthermore, they have the most frequent incidence of allergic reactions among all colloids (six times higher compared with HES; incidence 0.35%).[74]

Dextrans

Dextrans are polydispersed colloids that are biosynthesized from sucrose by the bacterium *Leuconostoc mesenteroides*. The formulations most frequently selected are dextran 40 and dextran 70, with molecular weights of 40 and 70 kD, respectively. After intravenous administration, small dextran molecules less than 50 kD are rapidly eliminated by the kidneys (filtration). All other molecules are being metabolized to carbon dioxide and water by cell-bound enzymes in the kidneys, liver, and spleen. Dextran solutions improve blood rheology, especially by decreasing blood viscosity, which should ultimately translate into improved microcirculatory blood and tissue perfusion. The rheologic effect of dextran 40 is especially pronounced because these solutions reduce whole blood viscosity more for any given degree of hemodilution than all other plasma substitutes. Indeed, dextran 40 is frequently used by vascular and plastic surgeons to assist in keeping microvascular anastomoses patent.

Dextran infusion induces a dose-dependent hyperfibrinolysis and an acquired von Willebrand's syndrome with decreased levels of vWF and associated factor VIII (VIII:c) activity. Consequently, there is a maximal daily dosage recommendation of 1.5 g dextran/kg body weight to avoid serious bleeding complications.

Impaired renal function may be a further problem with the use of dextrans. Because there is no known nephrotoxic effect of dextrans, the most likely mechanism of a dextran-induced renal dysfunction may be a tubular obstruction, swelling, and vacuolization of tubular cells (osmotic nephrosis–like lesions) due to the production of hyperviscous urine. Dextrans may cause severe anaphylactic reactions. A high frequency of preformed antibodies against dextrans has been noted in patients with prior exposure to high-molecular-weight dextrans in food or from bacteria and bacterial products. To prevent these anaphylactic reactions, dextran 1 (Promit), a low-molecular-weight hapten, has to be administered a few minutes before any dextran infusion. In summary, dextran 70 is generally preferred for volume expansion whereas dextran 40 is thought to improve blood flow in the microcirculation, presumably by decreasing blood viscosity. Despite these positive macrohemodynamic and microhemodynamic effects, the use of dextrans is declining in most countries because of their significant adverse effects.

Human Albumin

Albumin is purified from pooled human plasma and is commercially available as a 5% (iso-oncotic), 20%, or 25% (hyperoncotic) solution. Because albumin is heated and sterilized by ultrafiltration, the risk of bacterial or viral disease transmission should be eliminated.

Albumin is the most abundant plasma protein. It is essential for maintaining the plasma oncotic pressure needed for proper distribution of body fluids between intravascular and interstitial space. Furthermore, albumin acts as a transport protein by binding, for example, several hydrophobic steroid hormones and fatty acids and is an important buffer in the plasma. Serum albumin concentration is an independent predictor of mortality risk in patients with acute and chronic illness. A systematic review estimated that for each 2.5-g/L decrement in serum albumin concentration the risk of death increases by 24% to 56%.[75] The association persists after adjusting for other known risk factors and preexisting illness, suggesting a direct protective effect of the albumin molecule. Largely as a result of these observations, human albumin solutions have been used in the management of a diverse range of medical and surgical problems, including the acute restoration of an effective circulating volume due to hemorrhage, the acute management of burns, and clinical situations associated with hypoproteinemia. However, there is no evidence that albumin reduces mortality rates in patients with hypovolemia, burns, or states of hypoproteinemia.[76] In a large, multicenter trial on fluid resuscitation performed in a heterogeneous population of patients in an intensive care unit, use of either 4% albumin or normal saline for fluid resuscitation resulted in similar outcomes at 28 days (SAFE study).[77] Furthermore, for patients with burns and hypoproteinemia, albumin administration may even increase mortality rates.[76] As a result of these recent findings and the high costs of albumin, routine use of albumin for volume replacement should be reconsidered and reserved for selected patients only. The relative risk of albumin to develop an allergic reaction is 3.4 times less than that of gelatins and almost identical to that of HES.[74]

Controversy on Crystalloids Versus Colloids

There has been an ongoing debate for decades on whether crystalloids or colloids are superior in perioperative volume replacement therapy. The supporters of crystalloids argue that crystalloids are inexpensive and that adverse effects are rare or absent: There is no renal impairment, only minimal interaction with coagulation other than dilution, no tissue accumulation, and no allergic reactions. Colloid supporters, on the other hand, emphasize the much better volume-expanding properties, minor edema formation, and improved microcirculation with the use of colloid. For example, intravascular volume replacement with colloids has been shown to improve tissue oxygenation in patients undergoing major abdominal surgery. In contrast, administration of equivalent volumes of lactated Ringer's solution were associated with a significantly impaired microcirculation with decreased tissue oxygen tensions as a result of edema with subsequent capillary compression.[78]

However, a recent review by the Cochrane Collaboration in critically ill patients showed that there is no evidence from randomized controlled trials that resuscitation with colloids reduces the risk of death, compared with resuscitation with crystalloids, in patients with trauma or burns or after surgery.[79] Because colloids are not associated with an improvement in survival, and because they are more expensive than crystalloids, the routine and liberal use of colloids in the perioperative period should be questioned.

Controversy on Balanced Versus Unbalanced Fluids

The optimal electrolyte formulation of intravenous solutions has been questioned recently.[80,81] Large volume resuscitation with normal saline (unbalanced, unbuffered solution) causes hyperchloremic metabolic acidosis,[82] which, in turn, has been associated with organ hypoperfusion and increased morbidity, especially gastrointestinal, neurologic, and renal damage, as well as blood loss.[65,83] By contrast, buffered balanced electrolyte formulations (e.g., lactated Ringer's solution, Plasma-Lyte) maintain a higher plasma pH and less chloride load, leading to fewer incidences of hyperchloremic metabolic acidosis.[84] Low concentration electrolytes present in buffered solutions (e.g., Ca^{2+}, K^{+}) may also be responsible for a reduction in postoperative morbidity. Therefore, balanced crystalloid solutions are often preferred in the perioperative period.

The majority of colloids are suspended in unbalanced crystalloid solutions, mainly normal saline. However, the newest generation of HES preparations is now available in balanced crystalloid solutions (balanced HES 670/0.7 [Hextend] and balanced HES 130/0.4 [Voluven balanced]).[85] In addition to maintain a normal acid-base status, colloids suspended in these solutions may also have fewer adverse effects on coagulation and improved gastrointestinal microcirculation.

Treatment of Hypervolemia

Volume overload in the postoperative period may be the result of excess intraoperative and postoperative fluid administration and or impaired renal fluid excretion. Besides fluid restriction, nonspecific pharmacologic therapies may relief the patient from symptoms of pulmonary edema (i.e., morphine, nitroglycerin). Furthermore, diuretics may help to correct the positive fluid

balance by increasing the urine production. Patients with end-stage renal disease, however, may require dialysis to remove excess fluid. Intermittent or continuous hemodialysis should be started (see Chapter 96).

End Points of Intravascular Fluid Resuscitation

The primary end points of fluid therapy are improved patient outcome with reduced mortality and morbidity, especially reduced organ dysfunction and shortened recovery. These end points are being used in clinical trials to compare different fluid resuscitation protocols and to make a clinically relevant conclusion. For clinical use, however, protocols with secondary end points such as hemodynamic and metabolic parameters (see Tables 88-8 and 88-9) to achieve should help the clinician to provide optimal fluid therapy: immediate restoring or maintaining an optimal effective circulating volume with sufficient oxygen-carrying capacity and normal electrolyte composition is the primary goal (fluid and electrolyte balance). Measurement of end organ function (e.g., urinary output, mental status) indirectly reflects adequate effective circulating volume. If the effective circulating volume is not restored in a timely manner, and if the patient remains in global hypoperfusion, acute tubular necrosis may develop. This is independently associated with an increased mortality in the postoperative and critically ill patient.[86,87]

Currently, there is no single end point that universally diagnoses hypovolemia and hypoperfusion or identifies when the goals of resuscitation have been met. Neither pH, bicarbonate, base excess, lactate, nor regional perfusion end points have been demonstrated to be superior in the diagnosis of hypovolemia. The trends of the resuscitation end points over time and their ability to be restored to normal values within 24 hours after severe trauma have definitively been proved more useful. Only with frequent reevaluation of end point parameters can the resuscitation be tailored specifically to the individual patient and change a "nonresponder" into a "responder." Serum pH, bicarbonate, base deficit, and lactate are all metabolic indicators of the severity of hypovolemia and help determine the adequacy of resuscitation. They are more useful than estimated blood loss, heart rate, and blood pressure.[88] Which end point is used to guide resuscitation is less important than how the results are interpreted and how the therapy is altered to return the patient to adequate global tissue oxygenation.[46]

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Lars Rasmussen, Jan Stygall, and Stanton P. Newman

89 Cognitive Dysfunction and Other Long-Term Complications of Surgery and Anesthesia

Key Points

1. The selection, measurement, and analysis of neuropsychological tests (NP tests) will influence findings with postoperative cognitive dysfunction (POCD).
2. Patients' subjective reports after surgery are unrelated to assessed neuropsychological change and appear to be driven by mood.
3. There is good evidence of POCD after cardiac surgery where the mechanism is multifactorial but includes microemboli.
4. POCD after noncardiac surgery is evident in larger studies with good methodology although the mechanisms are less clear than after cardiac surgery.
5. Increased age is a risk factor for POCD.

Brain function is clearly affected during the immediate period after anesthesia, with depressed level of consciousness and impairment of attention, memory, and reaction time often being reported. Patients may experience complete amnesia for several hours after general anesthesia in spite of being apparently completely awake, and as a consequence it is not uncommon for patients to ask the same questions over and over again. Because of these issues, when patients are discharged from the hospital or outpatient clinic on the day of surgery, it is common practice, in many institutions, to ensure that the patient is accompanied by an adult during transportation and throughout the first postoperative night.

There is no simple answer to the question as to when brain function is back to normal after anesthesia. If all the difficulties were due to the anesthetic, one would expect cognitive function to have recovered to a preoperative level of functioning when any drugs affecting cognition have been cleared. One may expect that inhaled anesthetics and propofol differ from hypnotics such as barbiturates and benzodiazepines, which are much more slowly eliminated. It is clear, however, that anesthetic agents and their concentrations are only among many factors of importance for recovery. The duration of the recovery of cognition after anesthesia and surgery is multifactorial and among other factors is dependent on the type of anesthesia used, the type of surgery, and the patient. In some individuals, cognitive recovery is fast (within a matter of hours), whereas, in others, brain function may be disturbed for a much longer time.

The concept of postoperative disturbance in cognition is not new and has often been referred to as *postoperative cognitive dysfunction (POCD)*. The term is, however, used variably, and it is useful to distinguish among three types of cognitive deterioration after surgery:

1. Delirium is usually easily recognized, being an acute condition with fluctuating course, characterized by change in level of consciousness and primarily disturbance in attention. The duration is variable and the degree of severity ranges from mild to very severe.
2. Short-term cognitive disturbance may be apparent in the days after surgery. This occurs relatively frequently and may be due to a combination of factors, including surgery and anesthetic agents. This cognitive disturbance is short term, and it does not persist beyond a few days after surgery. It is best assessed by neuropsychological assessment, but frequently screening tests such as the Mini Mental State Examination (MMSE) are used. Studies have often attempted to assess POCD in the first few hours and days after anesthesia. Some results are reported in this chapter, but it must be remembered that although there are sometimes significant differences occurring between groups these changes are usually transitory and do not represent any lasting condition.
3. What we consider true POCD is a subtle deterioration in cognitive function, lasting for weeks, months, or longer; and neuropsychological testing is needed for verification. It can be considered to be a mild cognitive disorder characterized by impairment of memory, learning difficulties, and reduced ability to concentrate.

All of these different forms of cognitive disturbance that can occur after surgery are to be distinguished from dementia. *Dementia* is a syndrome that is due to disease of the brain, usually

of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Consciousness is not clouded. The impairments of cognitive function can be accompanied, and occasionally preceded, by deterioration in emotional control, social behavior, or motivation.

Detection of Postoperative Cognitive Dysfunction

The reported incidence of POCD varies widely between studies of the same form of surgery and anesthesia. Besides individual patient differences, this may also be due, in part, to methodological issues such as the choice of test battery, the time of postoperative assessments, and the method of analysis of dysfunction.

Neuropsychological Testing in Surgical Patients

Neuropsychological assessments (NP tests) are used to objectively measure cognitive function. The tests used in the detection of POCD, unlike those usually employed in a clinical assessment, need to be sensitive to change. It is important that the assessment tools be sensitive to potentially diffuse brain injury; therefore, these measures should form a battery of tests that attempt to cover a range of cognitive domains, such as memory, attention, concentration, and perceptual-motor ability. Because of the time constraints imposed by the surgical environment the time set aside to conduct these tests is often limited; therefore, the battery of tests, by necessity, frequently represents a compromise. A recent review of POCD studies in noncardiac surgery[1] indicated that 70 different NP tests had been used in this area in conjunction with 9 composite batteries, with between 1 and 13 tests used per study. The domain most often assessed was memory and learning. However, the number of tests used can be problematic; when more tests are used, dysfunction is more likely to be detected (although this also relates to the definition used to determine whether POCD is present). There is also a problem of fatigue in patients caused by their condition or surgery. Therefore, it is important not to make the assessments too long, and an attempt should be made to reduce test fatigue by alternating paper and pencil, computerized, manual, and verbal tasks.

Early studies investigating POCD often used traditional intelligence tests such as the Wechsler Adult Intelligence Scale (WAIS) or screening tests such as the MMSE. Although these batteries tend to be highly reliable they have been shown to be insensitive to the more subtle changes that may occur after surgery.[2,3] More recently, these have been replaced by a wide variety of NP tests designed for repeated assessments, many of which have been computerized to ease administration and improve standardization.

It is common to find studies in which the assessments have been performed by a range of health care and non–health care professionals. The assessment of brain function does require expertise particularly in how to present the tests and how to respond to the responses the patient makes, with an attempt at having the patient present his or her best performance. Ideally, the tests should be administered by the same trained neuropsychologist in the same quiet environment at each testing session.

Timing of Assessments

A very important issue regarding the measurement of POCD is the timing of the assessments. The timings of preoperative assessments have varied widely in studies, with some conducted within weeks of surgery, but many have been conducted at the time of admission into hospital for surgery; this may be 1 day before surgery or even on the day of their operation. Patients are frequently anxious about the surgery they are about to undergo. Although there is little evidence of the impact of preoperative anxiety on the NP tests that have been employed in most POCD studies it remains important to examine whether levels of both anxiety and depression have an impact on the cognitive tests employed. As a result, on each occasion neuropsychological performance is assessed both anxiety and depression should be assessed.

Cognitive problems are frequently observed in patients in the days immediately after surgery and are often transitory. These early assessments may well be detecting a transient disturbance of cognition, and the assessments conducted within days of surgery are likely to be influenced by general postoperative readjustment as well as analgesics, pain, and fatigue. Assessments conducted later in the recovery period (approximately 4 weeks after surgery) are more likely to detect a persistent or permanent change.

An important question is whether the early indications of cognitive disturbance are in any way predictive of longer-term difficulties in cognition. There is an indication that the early predischarge assessments may predict longer-term decline,[4-6] but the exact relationship remains to be clarified.

Analysis

In the POCD literature a number of different methods have been employed to measure and define dysfunction. Some studies have used a significant difference between postoperative and normative scores[7] and others a cut-off on a screening measure.[8-11] In a third approach, researchers have made a comparison between two different surgical/anesthetic groups,[2,13] and in a fourth approach between a surgical and control group.[14,15] In other studies a fifth approach has been to analyze NP test data as multiple comparisons of variables in the test battery. This approach provides the sensitivity to detect even small differences, but the risk of type 1 error is high. In addition, this analysis is not well suited to address whether deterioration has occurred because the analysis is based on group means rather than individual change and no incidence of cognitive decline can be calculated.[11,16]

Many researchers have selected to adopt a sixth method that uses an "individual change" approach in which each participant acts as his or her own control. Here the participant's score postoperatively is compared with the preoperative score. Then a statistically defined criterion is used to rate the participant as having or not having POCD. However, this statistically defined criterion is not uniform over studies; for example, Shaw and associates[17] have defined POCD as a decline in performance equal to or greater than 1 standard deviation (SD) from the preoperative score in 1 or more NP tests, whereas this same decline needed to be present in two or more tests before Treasure and coworkers[18]

rated the participant as having POCD. Other investigators have used the same decline of 1 SD but in 1 of 21 tests or 4 of 21,[19] and yet others have defined POCD as being a 20% decline in 20% of tests.[20] The advantage of this binary approach is that it defines and categorizes individual performance into an entity that appears meaningful in a clinical environment and is easily understood. However, these definitions are statistically derived and have no intrinsic meaning or relationship to brain injury. Another disadvantage is that these methods only take into account deterioration without considering improvement.

Because the NP tests used in studies of the detection of POCD should be sensitive to change, they are amenable to repeated administration. However, as patients undergo at least two assessments with often only a short time separation it is common for some learning to be found. This may be due to an increased familiarity with the tests or differing strategies employed when completing the assessments. Although many attempts are made to reduce these learning effects, such as use of parallel equivalent forms, these effects are almost impossible to remove from repeat testing. It could be argued that one measure of cerebral damage is the inability to learn a task or strategy that is the underlying basis of practice effects. This learning has been apparent in many POCD studies.[9,21] Therefore, it is important that the form of analysis used should take into account any learning, or failure to learn, occurring postoperatively. One such study that took learning into account was that of Williams-Russo and associates,[22] who examined individual change after establishing a clinically important difference (CID) score for each test. Here, the participants' raw change score was converted to a score of −1 (worse than the CID), 0 (within one CID), or +1 (better than the CID). A summed score of −3 or less was defined as a deficit. However, the improvement score was not used in the analysis.

When studies have employed a control group the effect of learning can be assessed. The multicenter International Study of Post-Operative Cognitive Dysfunction (ISPOCD) group[23] compared the mean of the NP test score change obtained from a healthy control group over three assessment intervals to that of a surgical group. The mean of the control group changes were used as an estimation of learning. The mean was subtracted from the surgical participants' change score and the result divided by the SD of the corresponding change in the control group to obtain a Z score for each test. Using a Z score allows for the scores for each individual test to be combined to obtain a composite NP score. The authors also applied a cutoff score to identify POCD, which they defined as when the Z scores on two individual tests or the combined Z score reached 1.96 or more (the higher the score, the more deterioration).

Using a control group strengthens a study considerably and allows for the influence of variables such as learning to be accounted for, but it is important to consider what constitutes an *appropriate* control group. POCD studies have utilized various types of control groups such as healthy volunteers, friends, and relatives of the participants under study, patients with other conditions, and patients with the same condition but not undergoing surgery. However, in POCD there is no "ideal" control. For example, using healthy volunteers fails to take account of any nonspecific effects of having the condition on cognition. Using patients with different conditions as controls assumes equivalence in cognition and learning between the conditions of the control and that of the groups of interest. When considering participants with the same condition who do not undergo surgery because of either a surgical decision or patient choice, then the groups could differ on important clinical factors because the allocation to groups is not random.

Limitations of Neuropsychological Studies

Patients need to be cognitively able to complete NP tests at baseline; therefore, only patients without preoperative brain disease have been included in these studies. Also, patients undergoing emergency procedures have not been studied owing to difficulties with obtaining a reliable evaluation preoperatively.

In all these studies, especially the long-term follow-up studies, some patients die or are too ill to return to be assessed and, in addition, some choose not to be followed up. In some cases those who are particularly well and back working may see no purpose in returning and be lost to follow-up. The attrition is unlikely to be random but may be more influenced by distance to be traveled and inconvenience. Not unexpectedly, attrition rates are lower for shorter follow-ups.[1] Some reports on attrition in the cardiac POCD literature have indicated that sicker patients are more likely to be unavailable for follow-up[24] and that attrition is higher among those with lower IQ[5] and lower education.[25] It is possible that the incidence of POCD may be higher/different if all patients could have been assessed.

Typically, patients with a known large intake of alcohol have been excluded from POCD studies; however, alcohol intake is rarely noted after surgery. Patients' cognitive performance at the follow-up assessment may be affected if their alcohol intake had increased substantially after surgery. It must, however, be considered rather unlikely that alcohol abuse would develop during the first postoperative weeks. In a large Danish sample of the normal population with no or moderate intake of alcohol, Jensen and colleagues[26] found that approximately 7% reported being heavy drinkers (>21 drinks per week for men and >14 drinks per week for women) at follow-up after at least 5 years after the first interview. Thus, although it is unlikely that many patients will have changed their drinking habits it may be interesting to obtain this information at follow-up.

Subjective Cognition and Proxy Ratings of Cognitive Change

Although NP tests are the most frequently used approach to detect POCD, another method sometimes employed is to ask the patients about self-perceived cognitive changes.[27-30] These studies have used measures such as the Cognitive Failures Questionnaire, the Cognitive Behavior Rating Scale, the Cognitive Difficulties Scale, or interviews and have reported subjective cognitive dysfunction after surgery. For example, Khatri and coworkers,[28] using the Cognitive Difficulties Scale, found that 16% of patients rated themselves as having cognitive difficulties 6 weeks after coronary artery bypass graft (CABG) surgery. Also, comparing local anesthesia with general anesthesia, Ward and associates[30] found that a statistically significant impairment of perceived cognitive function using the Cognitive Failures Questionnaire was reported by those patients who had undergone general anesthesia but not those who had undergone local anesthesia 3 days previously.

Although studies have been conducted to ascertain the reliability of proxy respondents in relation to quality of life of patients in a range of clinical cohorts,[31] very little research has been conducted regarding cognition. Thornton and associates[32] examined proxy ratings of cognitive change and found that cognitive changes were likely to be noticed by the patient's spouse or a close relative. Another study by Bergh and associates[33] found that a spouse's ratings of the patient's concentration and memory were in agreement with that of the patient.

However, the relationship between patients' subjective reports and formally assessed cognition is unclear. Many studies have found a stronger correlation between mood and patients' perception of cognitive difficulties than between NP test scores and subjective reports,[28,34-37] with those patients who are more anxious and depressed reporting more cognitive problems. It has been argued that this is due to patients who are emotionally distressed forming a negative information processing bias, which, in turn, leads to distorted perceptions of cognitive performance.[28,34,36]

Incidence and Risk Factors for Postoperative Cognitive Dysfunction after Cardiac Surgery

The incidence of POCD after cardiac surgery (coronary artery bypass and/or valve replacement or repair) has been reported as 50% to 70% in the first postoperative week, 30% to 50% after 6 weeks, and 20% to 40% at months and 1 year (see Chapter 60).[38] This variability is, as discussed previously, due in part to the problems of methodology, such as differing NP tests used, timings of assessments, and definitions of decline. In an attempt to reduce this variability a consensus meeting was held and guidelines were drawn up regarding NP tests conducted to assess cardiac POCD.[39]

Despite variability in incidence, timing, types of tests, and analysis there appears to be a general consensus that POCD after cardiac surgery does appear to exist in a proportion of patients. Several factors have been cited as accounting for this decline, which is often presented as competing hypotheses; however, it is likely that the cause is multifactorial, although the use of cardiopulmonary bypass (CPB) is often implicated.

Interventions to Reduce the Incidence of Cognitive Decline in Connection with Cardiac Surgery

Strategies to reduce the incidence of cerebral complications after cardiac surgery have been based on what was thought to cause these problems. Early research has suggested significant risk factors, including advanced age, poor left ventricular function, and duration of CPB. Of these only the last is modifiable either by changing the management of CPB and the related techniques or by avoiding CPB.

CPB involves numerous violations of normal physiology. The length of time on bypass has tended to be related to POCD, which suggests that there is something in the CPB procedure that is deleterious to the brain.[40,41] Important intraoperative causative agents are cerebral microemboli, which can be either particulate (e.g., atheroma, fat, platelet aggregates) or air. Microemboli occurring in the cerebral circulation can be detected noninvasively using continuous transcranial Doppler (TCD) of the middle cerebral artery (MCA). By using this technique, the numbers of microemboli have been found to be associated with length of time on bypass. A positive relationship has also been reported between microemboli found in the brains of patients who have died soon after cardiac surgery and the length of time on CPB.[42] However, the relationship between POCD in cardiac surgery and microemboli is not always clear cut, with some studies finding an association[43-45] and others not.[46,47] This relationship is complicated by a range of factors, including the size and final distribution in the brain of the microemboli. This final location of the microemboli is an important factor because they may be lodged in an area not covered by the NP tests used or be in an area less important for cognition. The composition of the microemboli has been an ongoing puzzle because it has been presumed that solid microemboli are more likely to cause damage than gaseous microemboli. Currently, techniques have become available that can distinguish between gaseous and particulate microemboli, and the relative importance of air emboli in POCD may soon be established.

Management of Cardiopulmonary Bypass

pH Management

Management of pH during hypothermia can be carried out as pH-stat or α-stat management (see Chapter 60).[48] There is evidence that α-stat management leads to better neurologic and cognitive outcome. Stephan and coworkers[49] found marked cerebral hyperemia and an increase in neurologic events at 7 days after surgery when using pH-stat management. Although Bashein and colleagues[50] found no difference in NP test outcome between these two techniques, both Murkin and associates[51] and Patel and coworkers[48] have shown that α-stat is associated with less NP test result deterioration than that with pH-stat management.

Temperature

Since the early days of cardiac surgery when it was shown that hypothermia could prolong the safe period of circulatory arrest, hypothermic perfusion has been used routinely by the majority of surgeons for both valve and coronary artery bypass graft (CABG) surgery (see Chapter 48). Recently, normothermia and normothermic cardioplegia have been considered as a means of myocardial protection, but this has led to concerns that neuroprotection may be compromised. Studies conducted to investigate this issue have produced conflicting results, some showing that normothermic perfusion may be potentially harmful,[52-54] with others finding no difference.[55-57] Because a small reduction in temperature is known to be neuroprotective, the failure to find an advantage for hypothermia in clinical trials may be surprising. However, brain hypothermia may not be guaranteed in all patients and the process of rewarming to normothermia may be harmful. Neurons may be injured by rewarming to 38°C, and it has been suggested that rapid rewarming may force anesthetic and other gases out of solution and thereby produce microemboli. However,

Buss and associates[58] found no effect on NP test outcome on rewarming to 38°C as compared with lower temperatures. Nathan and colleagues[59] maintained patient temperatures between 34°C and 36°C for 12 hours after surgery and found that avoiding hyperthermia during rewarming may be cognitively beneficial. At a 5-year follow-up study, Nathan and colleagues[60] reported that while fewer participants in the hypothermia groups had deficits at 5 years the difference did not reach significance.

Very little work has been conducted into temperature in the postoperative period. Grocott and coworkers[61] examined POCD in relation to temperature in the first 24 hours after surgery. Although they found no association between the area under the curve above 37°C during this period they did find a direct relationship between POCD at 6 weeks after surgery and maximum temperature achieved.

Arterial Line Filtration

Arterial line filters, which are an optional addition to the CPB circuit, are designed to prevent extraneous matter in the circuit from entering the patient. Two studies[62,63] found that the number of microemboli detected in the middle cerebral artery was significantly reduced when an arterial line filter was used. Although, two earlier studies[64,65] had reported that arterial line filters made no difference to cognitive outcome, a further study by Pugsley and coworkers[63] found less POCD in the filter group (46% filter versus 71% nonfilter; $P = .05$) 8 days after surgery and (8% filter versus 27% nonfilter, $P = .03$) at 8 weeks. The two earlier studies conducted their assessments only during the acute in-hospital phase, which may have confounded the results, whereas Pugsley and coworkers[63] were able to demonstrate an even more pronounced effect at 8 weeks.

Pulsatile Versus Nonpulsatile

Although nonpulsatile CPB is the most commonly practiced form of perfusion, pulsatile flow has been recommended for being more physiologic. A study by Murkin and colleagues[51] examined the neuropsychological benefits of pulsatile over nonpulsatile flow and found no significant differences in outcome.

Hematocrit

Recently, studies have examined the relationship between hematocrit and outcome after CABG. Habib and associates[66] found that the lowest quintile of hematocrit was related to vital organ dysfunction, morbidity, and 6-year survival in a survey of 5,000 consecutive operations. Also, Karkouti and coworkers[67] found a positive association between the risk of perioperative stroke and the lowest operative hematocrit. However, in a study examining cognitive dysfunction Harrison and associates[68] found no correlation between cognitive outcome and level of hematocrit.

Blood Glucose Management

Little research has been conducted into hyperglycemia during CPB. Most of the studies that have been conducted have been small and not of sufficient power to demonstrate any meaningful relationship between POCD and hyperglycemia after cardiac surgery.[69] However, a study conducted by Puskas and associates[70] of 525 patients undergoing CABG found that hyperglycemia was associated with a decrease in cognitive performance at 6 weeks after surgery in nondiabetic patients whereas hyperglycemia had no effect on cognition in the diabetic patients.

Type of Oxygenator

Oxygenators have undergone considerable development over the years. Early studies compared the two types of oxygenators (bubble versus membrane). Padayachee and colleagues[71] demonstrated that membrane oxygenators produced fewer cerebral microemboli on transcranial Doppler when compared with bubble oxygenators. Also, two studies have suggested that POCD is reduced when membrane oxygenators are used compared with bubble oxygenators.[72,73] The almost universal use of membrane oxygenators these days is likely to have a beneficial effect on NP test outcome.

Avoiding Cardiopulmonary Bypass

The resurgence of off-pump coronary artery bypass (OPCAB) surgery as a common technique for multivessel revascularization has paved the way for research into isolating the role that CPB plays in neurologic and neuropsychological decline after CABG surgery. Although many of the early studies conducted were retrospective in design and therefore potentially biased in that the patients were specially selected to undergo OPCAB surgery, they provided some evidence that OPCAB surgery may lead to a reduction in microemboli and strokes. Three recent meta-analysis studies,[74-76] while showing a trend toward an advantage for OPCAB over conventional CABG for incidence of stroke, failed to find a significant difference.

Studies reporting neuropsychological outcome are equally inconsistent. Poorer cognitive outcome at both 1 and 10 weeks was reported in patients undergoing on-pump surgery compared with OPCAB.[77] A large ($N = 281$) randomized study also found that neuropsychological performance at 3 months after surgery was better in patients undergoing OPCAB; however, these differences had disappeared by the 12-month[78] and 5-year[79] follow-up assessments. Subjective accounts of cognitive outcome have also been found to be similar at 1 year after surgery.[80] A further study by van Dijk and colleagues in 2004[6] found that early cognitive decline in patients undergoing first-time CABG predicted cognitive outcome after 3 months but suggested that this early cognitive decline was not significantly influenced by the use of CPB.

Management of Atherosclerosis of the Ascending Aorta

Embolization may result from dislodgment of atheromatous material during handling of the aorta, for instance when cannulation is conducted. Identification of plaques may therefore be advantageous to change the site of cannulation or carry out a coronary artery bypass as an off-pump procedure. That identification is often based on palpation, but ultrasound is clearly more sensitive, and the use of epiaortic ultrasound to detect atheroma has been found to be associated with a reduction in the incidence of POCD.[81]

Pharmacologic Techniques to Protect the Brain in Cardiac Surgery

A number of studies have been performed to attempt to protect the brain from any possible damage by using putative neuroprotective agents. These studies have had variable results (Table 89-1), and it is important to note that many have been underpowered, making the findings of a number of the studies unreliable.

Table 89-1 Randomized Trials of Pharmacologic Intervention to Reduce Cognitive Dysfunction after Cardiac Surgery

Authors	Year	Drug	No.	Result
Nussmeier et al.[136]	1986	Thiopental	182 complete	Neuropsychological test results showed no difference at 5 days
Roach et al.[137]	1999	Propofol	99 complete	No significant difference at days 5-7 or days 50-70
Legault et al.[138]	1996	Nimodipine	149 recruited, complete in 65-69%	No significant difference, at 1 week, 1 month, or 6 months (study terminated early)
Fish et al.[139]	1987	Prostacyclin	74 complete	No significant difference at 1 week or 2 months
Grieco et al.[140]	1996	GM_1 ganglioside	25 complete	No significant difference at 1 week or at 6 months
Arrowsmith et al.[46]	1998	Remacemide	159 complete	Using incidence, no significant difference; but using Z-change score, significantly less POCD with remacemide
Butterworth et al.[141]	1999	Pegorgotein	58 complete	No significant difference at days 5-7 or weeks 4-6
Mitchell et al.[142]	1999	Lidocaine	42 complete	Significantly less POCD with lidocaine at 10 days (40% vs. 75%) and at 10 weeks (46% vs. 75%)
Wang et al.[143]	2002	Lidocaine	88 complete	Significantly less POCD with lidocaine (19% vs. 40%) at 9 days
Kong et al.[144]	2002	Clomethiazole	219 complete	No significant difference at 4-7 weeks
Taggart et al.[145]	2003	Lexipafant	135 complete	No significant difference at discharge or 3 months
Mathew et al.[146]	2004	Pexelizumab	800 recruited	No significant difference at day 4 or at day 30
Harmon et al.[147]	2004	Aprotinin	35 complete	Significantly less POCD in the aprotinin group: 94% vs. 58% at day 4 and at 6 weeks 23% vs. 55%

Incidence and Risk Factors for Postoperative Cognitive Dysfunction after Noncardiac Surgery

For more than 50 years numerous research groups have tried to assess if cognitive function deteriorates postoperatively in noncardiac surgery. The earliest study is that of Bedford performed in 1955. It is a remarkable study that began work in the field, but it is important that his findings were based on subjective observation and questioning of relatives or caretakers. Using these techniques he reported that 7% (18/251) of elderly patients older than age 65 years became "demented" (not in the way it is used earlier) after undergoing general anesthesia. Clearly, there was a lack of objective verification, which, for this purpose, means testing of cognitive function by neuropsychological testing. Subsequently, Simpson and associates[82] reported no significant connection between anesthesia and decreased mental performance in 620 elderly patients, whereas Blundell and colleagues[83] found a significant deterioration in 50% of tests after surgery in 51 patients aged 70 and older.

Many of the early investigations into POCD tended to recruit a small number of participants. Therefore, many of these early studies did not have the statistical power to detect POCD. In addition, a number examined participants on a limited number of NP tests and the analysis was often unclear and different between the studies. Nonetheless, the evidence for POCD after noncardiac surgery began to grow. For example, Grinchnik and coworkers[20] found POCD in 45% of a sample of 29 patients with a mean age of 60 years at 6 to 12 weeks after thoracic or vascular surgery. The definition of POCD was similar to earlier studies in cardiac surgery, using a 20% deterioration in 20% of the tests (11 test variables considered). In a larger study of 98 patients with a mean age of 73 years, Ancelin and associates[19] found deterioration in at least 1 test of 28 in 71% of patients 9 days after surgery and in 56% of patients at 3 months. After knee replacement, POCD was seen in 41% of patients at 1 week and in 18% at 3 months.[84] In a much larger study (228 patients) that examined very early assessment in patients older than the age of 64 years, POCD was found in 16.8% 1 to 2 days after noncardiac surgery. The definition of POCD was based on deterioration in 2 of 3 test variables.[85] Further evidence that POCD does exist after noncardiac surgery was provided by Williams-Russo and colleagues,[22] who reported POCD in 5% of 231 patients older than age 65 at 6 months after knee replacement. In this study POCD was defined by a panel agreeing on what constituted a "clinically important deterioration" in each of the applied tests; however, there was no control group to allow a comparison. One of the important criticisms of these studies is that they investigated a simple incidence using a conventional definition but failed to include any control group.

In contrast, the ISPOCD study[23] recruited 1218 elderly patients and 176 healthy volunteers. The patients underwent major noncardiac surgery with general anesthesia. POCD was found in 25.8% after 1 week and 9.9% after 3 months. This was significantly higher than in the control group in whom the diagnostic criteria were fulfilled in only 3.4% and 2.8%, respectively. These findings were further supported in a single-center study using the same methodology where POCD was found in 41.4% of those older than 60 years of age at discharge and in 12.7% after 3 months.[88] Also, Iohom and colleagues[15] detected POCD more

commonly in patients than in controls, with 53% of patients exhibiting POCD at 6 weeks after laparoscopic surgery compared with 23% of controls.

Risk Factors for POCD after Noncardiac Surgery

In most studies investigating POCD the mean age of the participants assessed has been 60,[1] with many studies specifically selecting participants of an "older" age group. This is in part due to early reports of cognitive dysfunction being associated with "older people." However, age has been shown to be a significant and independent risk factor for POCD; for example, after 3 months, POCD in the ISPOCD study[23] was seen in 7% of those aged 60 to 69 compared with 14% in those older than 69. Also, Ancelin and colleagues[19] found a relationship between increasing age and POCD. However, few studies of POCD have included younger patients. The largest study was conducted by the ISPOCD2 group and included 508 middle-aged patients (40-59 years) and 185 control subjects of similar age.[35] POCD was found in 89/463 (19.2%) of the patients at 7 days and in 26/422 (6.2%) at 3 months; this is compared with 7/176 (4.0%) in the controls at 1 week and in 7/169 (4.1%) at 3 months. The difference in incidence of cognitive dysfunction between patients and controls was statistically significant ($P = .001$) at 1 week but not at 3 months ($P = .33$). Interestingly, when the surgical participants were compared with a previous group older than 60 years they found the younger group showed significantly less POCD at both 7 days ($P = .0064$) and 3 months ($P = .026$) after surgery.[35] These findings are similar to those in a recent study by Monk and coworkers[86] that examined 1064 participants undergoing major noncardiac surgery. A comparison was made between 331 patients aged 18 to 39, 378 patients aged 40 to 59, and 355 patients aged 60 and older. At discharge, POCD was found in 36.6% of the youngest, 30.4% of the middle aged, and 41.4% of those older than 60, with a significant difference between all groups. By 3 months, POCD incidence was similar in the young and middle-aged groups (5.7% and 5.6%, respectively) but a significantly higher rate was detected in the older age group (12.7%).

Risk factors for POCD other than age have been identified. Duration of anesthesia, respiratory complications, infectious complications, second operation, and level of education were all important factors in the ISPOCD1 study.[23] Although episodes of hypoxemia or hypotension have often been presumed to be important, no statistically significant correlation with POCD was found in this study. The most important results from the risk factor analyses of this study are shown in Table 89-2. Other investigators have also examined potential risk factors for POCD. Previous cerebrovascular accident has been identified as a significant risk factor for POCD at 3 months.[86] Ancelin and associates[19] found a relationship between postoperative cognitive deterioration and increasing age, low level of education, poor preoperative test performance, depression, and type of anesthesia (general versus epidural). However, in another study by Leung and coworkers,[85] no significant differences were found between types of general anesthesia used or use of nitrous oxide.

Table 89-2 Proportion of Elderly Patients with Cognitive Dysfunction after Major Surgery with General Anesthesia at 1 Week and 3 Months Postoperatively by Selected Patient, Surgical, and Anesthetic Factors

	1 Week		3 Months	
	No. of Patients	Patients with POCD	No. of Patients	Patients with POCD
Age (yr)				
60-69	586	135 (23%)	532	39 (7%)
≥70	425	125 (29%)	378	52 (14%)
Education				
< High school	576	153 (27%)	518	49 (9%)
High school	290	76 (26%)	260	26 (10%)
> High school	145	31 (21%)	132	16 (12%)
Benzodiazepines before surgery	116	32 (28%)	105	5 (5%)
Duration of anesthesia (min)				
≤120	196	37 (19%)	179	20 (11%)
121-240	503	121 (24%)	448	40 (9%)
≥241	312	102 (33%)	283	31 (11%)
Complication				
Hypoxemia*	115	30 (26%)	98	11 (11%)
Hypotension†	229	59 (26%	214	20 (9%)
Respiratory complication	99	40 (40%)	88	12 (14%)
Infectious complication	91	30 (33%)	138	13 (9%)
Second operation	24	13 (54%)	50	7 (14%)

*One or more episodes of oxygen saturation ≤ 80% for >2 min.
†One or more episodes of mean arterial pressure ≤ 60% for ≥30 min.
Data from ISPOCD1 study.[23]

Type of Surgery

Minor Surgery

Studies of POCD after minor surgery have focused primarily on early outcomes after outpatient surgery. Heath and associates[87] randomized 60 patients aged 18 to 60 years to receive thiopentone or propofol anesthesia. In addition, 30 age-matched control subjects were included. Although significant differences in neuropsychological performance between patients and controls were found at 1 and 2 hours after surgery, this difference had disappeared by 24 hours. In another smaller study of outpatient surgery patients no significant differences in NP tests results were found between 20 patients (aged 21-45 years) and 10 control subjects from the waiting list. Both groups underwent testing on two occasions with an interval of approximately 4 hours.[88] The ISPOCD group recruited 372 patients undergoing minor surgery either as an inpatient or outpatient procedure.[89] At 7 days, POCD was found in 22/323 (6.8%); in 164 inpatients, 16 (9.8%) had POCD and 5 of 141 (3.5%) outpatients had POCD ($P = .033$) but the group allocation was not randomized. At 3 months no significant difference was found in the incidence of POCD between the two groups (8.8% for inpatients and 4.5% for outpatients).

In a smaller more recent study 30 patients aged 65 to 86 years were assessed at 24 hours after surgery and POCD was found in 47% of participants with no difference found between propofol and sevoflurane.[90]

To summarize, POCD after 1 week seems to be much less common after minor surgery than after major surgery. Several factors may be important in explaining this difference in incidence of POCD, including the obvious difference in surgical trauma, postoperative stress response, postoperative pain, and need for analgesia. There is some evidence to suggest a relationship between the inflammatory response and the extent of recovery after surgery. Hall and colleagues[91] report a relationship between inflammatory response as measured by interleukin (IL)-6 and the extent of functional recovery after hip arthroplasty. The relationship between cognitive recovery and the inflammatory response is an area of current research activity.

Carotid Endarterectomy

Carotid endarterectomy has been considered a procedure that calls for special attention (see Chapter 62).

It is performed in patients with a tight (>70% or >90%) stenosis of the internal carotid artery. Postoperatively, neurologic complications may arise as a result of brain ischemia, embolism, or brain hyperperfusion. On the other hand, some authors have suggested that an improvement in brain function could be found if brain perfusion was corrected or perhaps because the carotid plaque is a source of brain emboli. However, neuropsychological studies conducted in this area have produced inconsistent findings that have been highlighted in two systematic reviews.[92,93] Improvement in cognitive performance after carotid endarterectomy was reported in over 50% of studies, with 43% showing no change or decline in one study.[93]

Regional Versus General Anesthesia

If general anesthesia is an important factor leading to the development of POCD, then it would be expected that regional anesthesia would reduce the incidence (see Chapter 51). One early study on 60 patients (mean age, 70 years) reported a significant difference between general and regional anesthesia undergoing hip replacement. They were randomized to receive general versus epidural anesthesia. Although no formal NP testing was performed, they reported "mental changes" (e.g., lack of orientation and amnesia for personal data) in 0/29 in the epidural group and in 7/31 in the general anesthesia group ($P = .01$).[94]

In the randomized studies that have been conducted using NP testing after surgery no clear picture emerges during the first postoperative week. Whereas significantly better NP test performance has been reported at examination from the first 6 hours to 4 days with regional anesthesia[12,95,96] after the first week after surgery, which is a more relevant time point to detect POCD (see earlier), no significant advantage of regional anesthesia has been detected (Table 89-3). Methodologic limitations could be an important confounding factor because in these types of studies blinding of patients and even blinding of examiners may be difficult.

The largest study conducted to date found no significant difference in POCD between general or regional anesthesia at either 1 week (general anesthesia = 37/188 (19.7%), regional anesthesia = 22/176 (12.5%), $P = .06$), or 3 months (general anesthesia = 25/175 (14.3%), regional anesthesia = 23/165 (13.9%), $P = .93$) after surgery.[97] Regional anesthesia was unsuccessful in 24 patients allocated to regional anesthesia for whom general anesthesia was therefore necessary. Also, 35 patients allocated to general anesthesia actually received spinal or epidural anesthesia. Not all of these 59 patients completed the study, but when excluded in a *per protocol analysis*, there was a significant difference in the incidence of POCD between general anesthesia in 33/156 (21.2%) versus regional anesthesia in 20/158 (12.7%) after 1 week ($P = .04$); however, there was no difference at 3 months.

Although there is no firm evidence that cognitive function is less affected after regional anesthesia as compared with general anesthesia, other complications have been shown to be less common after this regimen.[98-100]

Today, such randomized studies are difficult to conduct because many patients, surgeons, and anesthetists have firm opinions regarding which type of anesthesia should be used. The underlying reasons vary greatly but include reduced incidence of deep venous thrombosis or bleeding with regional anesthesia.

Etiologic Considerations

The etiology of POCD has not been elucidated, but perhaps POCD is the result of brain cell damage caused by toxic substances or hypoxia. Toxic substances could be drugs such as general anesthetics or analgesics, but also the surgery-induced release of hormones or inflammatory mediators could be important. Hypoxia may result from arterial hypoxemia or low perfusion either caused by low cardiac output, inappropriate blood flow distribution, thrombosis, or embolism.

Drugs

Anesthetic central nervous system toxicity has been discussed in recent years as a possible explanation for POCD. It is generally

Table 89-3 Randomized Studies Comparing General and Regional Anesthesia using Neuropsychological Testing

Authors	N = Completed	Age	Interval Post Surgery	Type of Surgery	Results
O'Dwyer et al.[148]	255	Mean 55 yr	6 hr, 24 hr, and 3 days	Hernia repair	No significant difference
Casati et al.[149]	30	Median 84 yr	1 and 7 days	Hip fracture repair	No significant difference
Rasmussen et al.[97]	340	Median 71 yr	3 mo	Mixed	No significant difference at 3 months using intention to treat but significant difference at 1 week 21% versus 13% in favor of regional when using per protocol
Somprakit et al.[150]	120	Group 1 = mean 37 yr Group 2 = mean 67 yr	1 and 3 days	Mixed	No significant difference in whole group but the older group had significantly more POCD
Williams-Russo et al.[22]	231	Median 69 yr	1 wk and 6 mo	Knee replacement	No difference between groups
Campbell et al.[151]	157	Mean 77 yr	24 hr, 2 wk, 3 mo	Cataract	No differences between groups
Haan et al.[13]	37	Mean 72 yr	4 days and 3 mo	Urology	No significant difference
Nielson et al.[152]	64	Mean 69 yr	3 mo	Knee replacement	Improvement: no difference between groups
Jones et al.[153]	129 50 controls	>60 yr	3 mo	Knee or hip replacement	Significant improvement in 2/5 variables in general anesthesia group, no change in regional anesthesia group ($P = .03$ and .04 between groups)
Chung et al.[10]	44	Mean 72 yr	6 hr, 1, 3, and 5 days and 1 mo	Urology	No difference
Asbjørn et al.[96]	40	Mean 69 yr	4 days and 3 wk	Prostatectomy	No difference
Ghoneim et al.[154]	105	Mean 61 yr	1-7 days and 3 mo	Mixed	No difference
Hughes et al.[12]	30	Mean 68 yr	24 hr, 48 hr, and 1 wk	Hip arthroplasty	No difference after 1 week
Chung et al.[95]	44	Mean 72 yr	6 hr, 1, 3, and 5 days and 1 mo	Prostate resection	Significantly higher in regional at 6 hr
Bigler et al.[155]	38	79 yr	1 wk and 3 mo	Repair of hip fracture	Improvement in both, with no difference between the two regimens
Riis et al.[156]	30	>60 yr	1 wk and 3 mo	Hip replacement: general, epidural or combined	Initial decline from baseline at 4 days and then improved, with no group differences
Karhunen and Jöhn[157]	47	Mean 73 yr	1 wk	Cataract surgery	After 1 week significantly more deterioration in local anesthesia group in one of two combined scores

assumed that general anesthesia is a completely reversible condition, but this cannot be proved. Exposure of animals to anesthetics has resulted in the detection of several types of changes in the brain. Jevtovic-Todorovic and coworkers have shown histologic changes in the brain after exposure to isoflurane, nitrous oxide, ketamine, and midazolam. In developing rat brain, apoptosis was found in thalamic nuclei and the parietal cortex after exposure to isoflurane and this effect was more pronounced if midazolam or nitrous oxide was added.[101] Memory testing using a water maze revealed inferior performance in the anesthetized rats as compared with controls animals. Also, infant mice showed signs of apoptosis in brain cortex after subcutaneous administration of midazolam or ketamine[102] and after propofol or combinations of ketamine with propofol or thiopental.[103] In adult rat brain cortex, neuronal vacuolization and neuronal degeneration with necrosis have been found after nitrous oxide. The neuronal vacuolization, however, seemed to be reversible with no vacuolated neurons already after 3 hours of recovery and the addition of diazepam or isoflurane blocked the neurodegeneration.[104] These findings are interesting but do not provide convincing evidence for induction of persistent neuronal changes after general anesthesia in humans, where nitrous oxide is not used as the only anesthetic. Finally, neuronal changes could only be demonstrated in adult animals given anesthesia under hyperbaric condition with an inspiratory carbon dioxide concentration of 1% to 3%.

Apoptosis occurred in human neuroglioma cells that were exposed to isoflurane, and increased levels of amyloid precursor protein were also found.[105] Abnormal processing of amyloid precursor protein with accumulation of β-amyloid protein is a feature of Alzheimer's disease, and it is therefore interesting if general anesthetics influence the processing of this protein.

Another possible effect of anesthetics could be related to long-term changes in brain receptor function. A decrease in cholinergic function has been found in Alzheimer's disease, and cholinesterase inhibitors may be beneficial for patients with this condition. In one study, changes in cholinergic binding were found in rat brains after repeated pentobarbital anesthesia given by intraperitoneal injection.[106]

Anesthetics have also been shown to cause changes in gene expression in the brain and in the protein synthesis pattern, as detected by comparison of brain tissue protein contents in anesthetized and control animals.[107-109] These findings in animals or cell cultures are difficult to apply to the clinical situation with POCD in humans. One important limitation in animal studies of anesthetic drug toxicity is that it may be difficult to ensure proper oxygenation, ventilation, perfusion, and temperature regulation. In addition, hypoglycemia may occur in infant rodents exposed to general anesthesia. The brain cell damage of anesthesia in this situation may therefore be caused by mechanisms other than drug effects.

In humans, it is much more difficult to study central nervous system toxicity consequent on anesthetic exposure. Although, large epidemiologic studies have not resulted in the detection of a major long-term effect of anesthesia on cognitive function, such research is associated with important limitations. For example, in a study of 1257 healthy subjects, 946 participants had been previously exposed to at least one general anesthetic and they found no significant correlation between exposure to anesthesia and performance in cognitive tests.[110] However, as with the collection of any retrospective data, subjects may not recall reliably the type and number of anesthetics they have received or the exact date they received the anesthetic. It is therefore difficult to take age at time of exposure into consideration.

Apart from anesthetic drugs, many other drugs are given in connection with surgery. As an example, analgesics may have important effects on cognitive function, but a recent systematic review concluded that the type of postoperative analgesia was not significantly related to cognitive decline in elderly surgical patients.[111] This is in accordance with the findings of Johnson and associates[35] that opioid administration within the 24 hours before the test had no significant influence on the performance. Still, other psychoactive medication cannot be excluded as a potential influence on NP test data obtained in patients during the weeks to months after surgery.

Hormones

Major surgery causes an endocrine response with release of hypothalamic-pituitary-adrenal (HPA) and sympathetic nervous system hormones. Cognitive impairment has been associated with high levels of glucocorticoids, as documented in a variety of experimental and clinical settings.[112,113] Cortisol has been found to be toxic to cells in the hippocampus, and this structure plays a critical role in the consolidation of short-term into long-term explicit memory as well as descending control of the HPA axis. This gave rise to the hypothesis that repeated episodes of stress cause decreased hippocampal inhibition of the HPA axis and, thus, prolonged hyperactivation.[114] This aspect was studied in 187 patients older than 60 years of age undergoing major noncardiac surgery. Saliva cortisol levels were measured preoperatively and at 1 day, 7 days, and 3 months postoperatively in the morning (8 AM) and in the afternoon (4 PM) using Salivettes. After surgery, salivary cortisol concentrations increased significantly. The preoperative ratio between the AM and PM cortisol (AM/PM ratio) concentration was 2.8 and 2.7 in patients with POCD at 1 week versus those without POCD, respectively. The AM/PM ratio decreased significantly postoperatively to 1.9 and 1.6 at 1 week, respectively ($P = .02$ for both). In an analysis considering all AM/PM ratios, it was found that the persistent flattening in AM/PM ratio was significantly related to POCD at 1 week.[115]

In the clinical setting, it is difficult to assess the possible association between cognitive dysfunction and high levels of glucocorticoids, but it seems that cortisol secretion pattern is profoundly affected (i.e., flattened) by major surgery and this flattening is significantly related to the occurrence of early postoperative cognitive dysfunction.

Inflammatory Mediators

Surgery is associated with an important tissue reaction involving an activation of the immune system with release of inflammatory mediators from lymphocytes. Important mediators include cytokines that are able to initiate the activation of other inflammatory mediators and to affect brain function either directly or indirectly.[116,117] A very pronounced inflammatory response is seen in connection with cardiac surgery using CPB, and significantly higher levels of the cytokines IL-1 and IL-10 have been reported in patients with POCD after such procedures.[118]

Hypoxia

Brain hypoxia may lead to irreversible damage depending on the level, duration, and susceptibility. Oxygen delivery to the brain is dependent on blood flow and arterial oxygen concentration, which is primarily related to hemoglobin concentration and arterial oxygen saturation. Brain hypoxia may be caused by a decrease in blood flow or arterial hypoxemia. In connection with anesthesia, inability to ventilate the patient or unrecognized esophageal intubation may cause profound and long-lasting hypoxemia[119] and, subsequently, brain damage. Modest perioperative reductions in arterial oxygen saturation are common, but the importance has probably been overemphasized when compared with the wide fluctuations in cerebral blood flow and blood hemoglobin level.[120] One possible explanation for this is the ease of measuring arterial oxygen saturation continuously by pulse oximetry. It has not been possible to show any connection between modest arterial hypoxemia and postoperative complications, including POCD.[23,121]

Brain Hypoperfusion

A temporary reduction of cerebral blood flow can cause neurologic or cognitive dysfunction without occlusion of cerebral vessels (see Chapter 63). Cerebral blood flow is regulated according to brain metabolism and nearly unchanged within wide variations in blood pressure (autoregulation) mediated through changes in diameter of resistance vessels. This autoregulation has a lower limit at approximately a mean arterial blood pressure of 50 mm Hg in healthy adults but is higher in hypertensive subjects.[122] Below this limit, further dilatation of vessels cannot compensate and cerebral blood flow decreases. Measuring cerebral blood flow or brain oxygenation during surgery is complicated. The techniques used include xenon-133, near-infrared spectroscopy, transcranial Doppler (which really measures velocity), and jugular bulb oxygen saturation. All of these techniques are associated with important limitations. Brain perfusion pressure is therefore frequently used to evaluate brain perfusion in clinical practice. During anesthesia, brain metabolism is reduced and, therefore, a lower brain blood flow may be acceptable. In earlier studies of cardiac surgery prolonged episodes of low blood pressure were found to be a risk factor for brain dysfunction,[40,123] but subsequent studies have not been able to confirm this.

Thrombosis or Embolism

Cerebral infarction can be caused by an embolic or a thrombotic occlusion of a cerebral artery, and necrosis of brain tissue including neurons as well as glial cells may result. Thus, tissue architecture is lost and a well-defined infarct can be identified by autopsy or brain imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI). Cerebral infarcts may cause no symptoms at all, depending on the size and location, but the usual clinical presentation is a stroke. Several risk factors have been identified in studies of stroke in the general population as well as in relation to surgery. Age is an important factor and other important risk factors include type of surgery, cardiac disease, especially atrial fibrillation, peripheral vascular disease, former cerebrovascular attacks, and diabetes.[124,125] The incidence of major cerebral complications presenting as stroke after general surgery varies between 0.2% and 0.7%. Most cerebral infarcts in the perioperative period are caused by emboli. Macroemboli are more than 200 μm in diameter and typically consist of atheromatous material or thrombi. These may rise from the left atrium, left ventricle, or aorta.

Microemboli are less than 200 μm in diameter and, as stated earlier, are common in cardiac surgery. As opposed to macroemboli, they may often consist of air introduced into the venous circulation for instance through tubings used in the CPB circuit or through arterial lines. In addition, paradox embolization may occur through an open foramen ovale from the venous side because of subatmospheric pressure in veins or bone marrow if the surgical field is above heart level and venous structures are noncollapsible, as in procedures such as back surgery, craniotomy in the sitting position, and knee replacement.

Microemboli have been found to occur in joint replacement surgery. It was specifically assessed in 37 patients in whom cognitive function was studied with a battery of 13 tests at 1 week and at 3 months; POCD was found in 41% and 18%, respectively, but no significant association with microemboli was detected using transcranial Doppler imaging.[84]

Genetic Aspects

Recently, it has been realized that polymorphic genetic variation may explain individual differences in susceptibility to medication, inflammation, trauma, and other harmful factors. Such genetic factors are important for the development of dementia but do not uniquely determine the phenotype.

Apolipoprotein E (ApoE) is a protein that is important for recovery after central nervous system injuries.[126] There are important differences in the three different isoforms of ApoE—E2, E3, and E4, which are encoded by the alleles ε2, ε3, and ε4 of the ApoE gene, respectively. The ε3 allele is the wild-type and present in 75% of the native European population, whereas ε2 and ε4 are less frequent.[127] The ε4 allele seems to increase the risk of Alzheimer's disease, and it is also associated with a poor prognosis after head injury.[128-130] The possible association between the ε4 allele and POCD after cardiac surgery has been studied, but literature presents conflicting information.[131,132] The possible relationship between the ε4 allele and POCD after noncardiac surgery was studied in 976 patients aged 40 and older: the ε4 allele was not a risk factor at 1 week ($P = 0.49$) or 3 months after noncardiac surgery ($P = .28$).[133] It seems, however, that there is a significant relationship between POCD and the presence of the ε4 allele in carotid surgery patients.[134]

Other genetic factors could be important in the general surgical population; for instance, individual differences in inflammation and drug metabolism, with polymorphism of the drug metabolism systems cytochrome P-450, are well described. Very slow metabolism of certain drugs could be associated with prolonged recovery, and very fast metabolism could lead to high concentrations of intermediary degradation products.[135] Both situations could result in a disturbance of receptor function, but the relationship, if any, with POCD remains to be established.

Clinical Significance of POCD

We have discussed the detection of POCD and the likely causes, but what affect does this dysfunction have on the patient? An often-told story is about an elderly patient whose cognitive function has deteriorated profoundly after surgery, especially regarding memory. The relatives describe a loss of function and lack of initiative and interests in activities that previously meant a lot to this particular person. In a retired individual this could be playing cards or doing crossword puzzles. The deterioration may be most noticeable in patients returning to work, when usual tasks may be impossible to carry out in the same manner and at the same speed as before surgery. Such difficulty is also not uncommon in middle-aged or young patients, who also may experience some degree of dysfunction in cognition.

One relevant question is whether POCD in fact results in impairment of function as reflected in activities of daily living. In a study of elderly patients undergoing major noncardiac surgery with general anesthesia, a statistically significant correlation was found between POCD at 3 months and a decline in activities of daily living.[23] This is in contrast with studies of elderly patients after minor surgery in which POCD was not related to instrumental activities of daily living (IADL).[89,97] Another study of middle-aged patients by Johnson and associates[35] found a statistically significant correlation between POCD at 1 week and a decline in IADL at 1 week reported by relatives at 3 months. There was also a statistically significant correlation between POCD at 3 months and the Subjective Cognitive Functioning (SCF) questionnaire both assessed by patients and relatives at 3 months, but only 7% of those with increased SCF scores had POCD. No correlation was found between POCD and depression as assessed by the Geriatric Depression Scale (GDS). However, Moller and colleagues,[23] in common with other investigators in studies in cardiac surgery,[36] found no correlation between subjective reports of cognitive decline and POCD or POCD and depression as measured by the Zung depression rating scale.

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Steven Roth

90 Postoperative Visual Loss

Key Points

1. Visual loss after anesthesia is a rare but devastating injury that appears more frequently after cardiac, spine, and head and neck surgery.
2. The causes of perioperative visual loss include central or branch retinal artery occlusion, anterior and posterior ischemic optic neuropathy, cortical blindness, and acute glaucoma. Transient visual loss may be experienced after transurethral resection of the prostate. Retinal vascular occlusion in patients who receive nitrous oxide–containing gas mixtures after a vitrectomy procedure with vitreal gas bubble tamponade is caused by acute expansion of the gas bubble and increased intraocular pressure.
3. Signs and symptoms of visual loss in the postoperative period may be subtle and can be incorrectly attributed to the residual effects of anesthetic agents. Any patient complaining of eye pain, an inability to perceive light or motion, complete or partial loss of visual fields, decreased visual acuity, or loss of pupil reactivity must be evaluated immediately by an ophthalmologist.
4. The most common causes of central and branch retinal artery occlusion are emboli from the operative site and compression of the eye. External pressure on the eyes must be scrupulously avoided.
5. The causes of ischemic optic neuropathy have not been clearly determined. This disease may be related to, among other factors, hypotension, blood loss, fluid replacement, patient positioning, emboli, the use of vasopressors, disturbed autoregulation in the optic nerve circulation, anatomic variation in the optic nerve, and systemic patient factors such as hypertension and atherosclerosis.
6. Patients who undergo prolonged operative procedures in the prone position with anticipated large blood loss are at higher risk for the development of ischemic optic neuropathy. There is controversy with respect to the appropriate level of blood pressure and hemoglobin, fluid replacement, and use of vasopressors in these patients. The anesthesiologist should consider the potential risk for ischemic optic neuropathy in the design of the anesthetic plan and weigh the risks versus benefits of interventions that decrease blood pressure and hemoglobin concentration perioperatively. Anesthesiologists should consider informing patients of the risk of visual loss accompanying lengthy surgical procedures with the patient positioned prone and with anticipated large blood loss. Because surgeons may be in a better position to discuss this complication with their patients, anesthesiologists should consider asking surgeons to mention the risk of visual loss at their preoperative visit with the patient.
7. Perioperative visual loss in the presence of focal neurologic signs or the loss of accommodation reflexes or abnormal eye movements suggests a diagnosis of cortical blindness. Neurologic consultation should be obtained.

Visual loss after anesthesia and surgery is a rare but unexpected and devastating complication. In recent years there has been an impression among clinicians, though yet unproven, that the incidence is on the rise, particularly in the setting of spinal fusion surgery. Hence, a major emphasis of this chapter is on perioperative visual loss associated with spine surgery. In this chapter the focus is on familiarizing anesthesiologists with the incidence, suspected risk factors, diagnosis, and treatment of eye injuries leading to visual loss in the perioperative period. The discussion is confined to visual loss that follows nonocular surgery because eye damage after ocular surgery is well described in the ophthalmology literature. Injuries to the retina and optic nerve and the visual connections to the brain are discussed.

Because of the infrequent occurrence of this complication, few clinical studies have been conducted and most incidents in the literature are contained within case reports and small case series. No prospective studies of perioperative visual loss have yet been performed. Case reports have the disadvantage of reporting bias. But case reports over a lengthy period and a few retrospective studies and published surveys largely provide much of the

current knowledge on postoperative visual loss. Two large retrospective studies showed that perioperative ischemic optic neuropathy (ION) is rare, occurring in approximately 1/60,000 to 1/125,000 anesthetic procedures in the overall surgical population.[1,2]

Spine and cardiac surgery appear to be associated with a higher incidence of perioperative visual loss than other operative procedures. The incidence after these procedures is difficult to define precisely, because the studies have far fewer patients than the larger studies of the overall surgical population, and because these studies have been derived from experiences at single institutions. Stevens and associates found 4 ION cases in 3,450 spine surgeries (0.1%),[3] and we reported 2 cases in 3,300 patients after spine surgery (0.06%).[4] Chang and Miller reviewed 14,102 cases of spine surgery over 20 years at Johns Hopkins Hospital, identifying 4 cases of ION, for an incidence of 0.028%.[5] After cardiac surgery, incidence was estimated as high as 1.3% in one study[6] but 0.06% and 0.113% in two more recent larger retrospective studies.[7,8]

Myers and associates[9] conducted a retrospective case-control study of 28 patients with visual loss after spine surgery. The ASA Postoperative Visual Loss Registry reported on 93 cases of visual loss after spine surgery submitted anonymously to the ASA Closed Claims Study (http://depts.washington.edu/asaccp/eye/index.shtml).[10] Nuttall and associates performed a retrospective case-control study of cardiac surgery patients at the Mayo Clinic.[7] Each of these studies is described in detail in subsequent sections of this chapter.

Retinal Ischemia: Branch and Central Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) decreases the blood supply to the entire retina, while occlusion of a retinal arterial branch (BRAO) is a localized injury affecting only a portion of the retina. In most instances this injury is unilateral. Four causes can be distinguished: external compression of the eye; decreased arterial supply to the retina (embolism to the retinal arterial circulation or decreased blood flow from a systemic cause); impaired venous drainage of the retina; and arterial thrombosis from a coagulation disorder.

The most common cause of perioperative retinal arterial occlusion is improper patient positioning resulting in external compression of the eye that produces sufficient intraocular pressure (IOP) to stop flow in the central retinal artery. It is the typical cause of the injury during spine surgery performed with the patient in the prone position. Pressure within the orbit also can be increased internally after retrobulbar hemorrhage, which is associated with vascular injuries during sinus or nasal surgery.

Although rare in most surgical procedures, emboli can directly impair blood flow in the central retinal artery (CRA) itself or a branch of it. Paradoxical embolism originating from the operative site and reaching the arterial circulation through a patent foramen ovale has rarely been reported as a cause of perioperative retinal vascular occlusion.[11] Retinal microemboli, however, are common during open-heart surgery.[12,13] Hypotension itself seems to be a rare cause of retinal ischemia. In a multicenter questionnaire, the incidence of retinal ischemia after hypotensive anesthesia was only 3 cases in 27,930 hypotensive anesthetic procedures.[14]

Venous drainage can be impaired after radical neck surgery by jugular vein ligation.[15] Studies measuring IOP, either in normal volunteers or in those who had spine surgery while positioned prone, show increased IOP, greater increases with the head-down position, and attenuation of the increases by head-up positioning, although extent of the changes differs, and there are some important technical issues in these studies.[16,17] The clinical significance of the changes remains unknown.

Clinical Findings

Patients have painless visual loss and abnormal pupil reactivity. Funduscopic examination shows opacification or whitening of the ischemic retina, and narrowing of retinal arterioles may be visible.[18,19] BRAO is characterized by cholesterol emboli (bright yellowish, glistening), calcific emboli (white, nonglistening), or migrant pale emboli of platelet fibrin (dull, dirty white). A cherry-red macula with a white ground-glass appearance of the retina and attenuated arterioles is a "classic" diagnostic sign in CRAO (Fig. 90-1). The red appearance from pallor in the ischemic, overlying retina makes visible the color of the intact, underlying choroidal circulation. Differential diagnosis from other causes of visual loss appears in Table 90-1.

Mechanisms of Retinal Ischemia

Findings of increased extracellular glutamate concentrations during retinal ischemia[20] and attenuation of ischemic injury in vitro and in vivo by glutamate receptor antagonists[21] support a

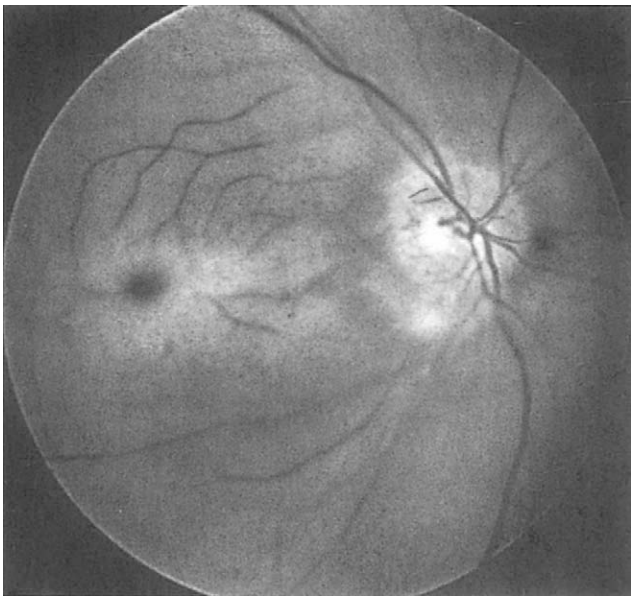

Figure 90-1 Funduscopic appearance of retinal vascular occlusion. Note the pallor of the retina and the cherry-red spot, the clinical hallmark of retinal arterial occlusion, visible in the fovea near the center of the photograph. The ischemic retina loses its normal transparency; and because the fovea is thinner than the surrounding retina, the underlying choroid is visible as a cherry-red spot. (*From Ryan SJ: Retina, 2nd ed. St Louis, CV Mosby, 1995.*)

Table 90-1 Differential Diagnosis: Eye Examination in Retinal, Optic Nerve, or Visual Cortex Injury*

	AION	PION	Cortical Blindness	CRAO	BRAO
Optic disc	Pale swelling, peripapillary flame-shaped hemorrhages, edema of optic nerve head. Late: optic atrophy	Initially normal Late: optic atrophy	Normal	Normal Late: optic atrophy	Normal Late: optic atrophy
Retina	Normal; may have attenuated arterioles	Normal; may have attenuated arterioles	Normal	Cherry-red macula†; pallor and edema, narrowed retinal arteries	Emboli may be present‡; partial retinal whitening and edema
Light reflex	Absent or RAPD	Absent or RAPD	Normal	Absent or RAPD	Normal or RAPD
Fixation and accommodation	Normal	Normal	Impaired	May be impaired with external compression	May be impaired with external compression
Opticokinetic nystagmus	Normal	Normal	Absent	Normal	Normal
Response to visual threat	Yes	Yes	No	Yes	Yes
Object tracking	Normal	Normal	Absent	Normal	Normal
Ocular muscle function	Normal	Normal	Normal	May be impaired if due to external compression	May be impaired if due to external compression
Perimetry	Altitudinal defect; scotoma	Altitudinal defect; blind; scotoma	Hemianopia (depending on lesion location); periphery affected usually	Usually blind	Scotoma; usually normal periphery

*Typical symptoms and signs are listed. Some patients may have varying findings.
†Because of a lack of overlying inner retinal cells in the fovea, the intact choroidal circulation is visible as a cherry-red spot.
‡Cholesterol, platelet-fibrin emboli, calcified atheromatous material.
AION, anterior ischemic optic neuropathy; BRAO, occlusion of a retinal arterial branch; CRAO, central retinal arterial occlusion; PION, posterior ischemic optic neuropathy; RAPD, relative afferent pupillary defect.

role for excitotoxicity. It is believed that an increased intracellular Ca^{2+} concentration as a result of enhanced glutamate release ultimately initiates mechanisms that result in cellular destruction.

Two distinct blood flow patterns follow a period of ischemia. In cats, retinal and choroidal blood flow increase dramatically (hyperemia) immediately after the end of ischemia.[22] Hyperemia is of clinical relevance in reperfusion after a period of ischemia; increasing flow when vessels or the blood-retinal barrier is damaged might lead to macular edema.[23] Hypoperfusion is the other extreme in blood flow derangement. Delayed retinal hypoperfusion 1 to 4 hours after the end of a period of ischemia has been shown in adult rats,[24] and these results resemble the low-flow state found in other models after global cerebral ischemia.[25] The mechanism of these changes in blood flow has not been clearly established, although depletion of vasodilators such as adenosine or nitric oxide may be responsible.

The retinal blood supply is derived from the retinal and choroidal vessels.[26] Therefore, after retinal vascular occlusion, some oxygen may still be supplied by diffusion from the outer retinal layers by way of the choroid. In monkeys, eyes with CRAO showed little damage in the macular retina after 97 minutes of ischemia. After 240 minutes, damage was profound and irreversible.[27] These studies were conducted by clamping the central retinal artery (CRA).[28] Interestingly, the same investigators reported that atherosclerosis did not increase sensitivity to ischemia in monkeys and actually may have "preconditioned" the animals against ischemic insult.[27]

Increased IOP from external compression of the eye is a more severe insult than ligation of the CRA because of the profound simultaneous decreases in both retinal and choroidal blood flow[22] and the differential susceptibility of the inner retinal cells to damage from pressure.[29] Ischemic tolerance time is probably shorter with external compression as evident in studies of injury in animal models of retinal ischemia (Table 90-2).

Central Retinal Artery Occlusion

The cause of perioperative CRAO is usually external compression resulting in sufficient IOP to occlude the arterial circulation to the retina. Patient characteristics may increase the risk of CRAO. Those with altered facial anatomy may be predisposed to damage from the external pressure of anesthesia masks or headrests. In osteogenesis imperfecta, fibrous coats of the eye are thin and immature because of a deficiency of collagen fibers, persistent reticulin fibers, and increased mucopolysaccharide ground substance. Sclerae and corneas are unusually thin, and exophthalmos is common as a result of bony facial abnormalities, factors that may render the eye more vulnerable to damage from external

Table 90-2 Animal Studies of Retinal Ischemia and Time Required to Produce Injury

Author(s)	Animal	Ischemia Method	Ischemia Time
Hayreh et al. (1980, 2004)	Monkey	Central retinal artery ligation	>100-240 min
Ettaiche et al. (2001)	Rat (brown-Norway)	Increased intraocular pressure	20 and 40 min
Roth (1998, 2002)	Rat (S-D)	Central retinal artery ligation, increased intraocular pressure	45 and 60 min
Zhu et al. (2002)	Mouse (ND4)	Increased intraocular pressure	30, 45, 60 min

pressure. Those of Asian descent tend to have lower nasal bridges, which may increase the risk of external compression.[30]

Improper positioning of the head with external pressure on the eyes may compress ocular contents and, consequently, occlude retinal blood flow. Most reports of improper positioning involve patients positioned prone for surgery. Two reports described CRAO from improperly fitting face masks. CRAO was found after mask-administered inhalational anesthesia in combination with corneal abrasion, chemosis, and eyelid edema. Some of the patients had profound decreases in blood pressure or were described as being in a shock state.[31,32] These cases, from more than 50 years ago, have not been reported again, either because of changes in anesthetic practice or equipment.

The eye can be compressed directly when the patient is positioned prone for surgery. The horseshoe headrest is of particular concern because improper head position or unintended head movement may place the eye in contact with the headrest. In most of the reports of CRAO in patients positioned prone for surgery, the horseshoe headrest or a similar device (e.g., a rectangular headrest[33]) was used.[30,34,35] Kumar and colleagues[36] reviewed published case reports of CRAO after spine surgery. Signs and symptoms included unilateral loss of vision usually with loss of light perception, afferent pupil defect, periorbital and/or eyelid edema, chemosis, proptosis, ptosis, paresthesias of the supraorbital region, hazy/cloudy cornea, and corneal abrasion. Loss of eye movements, ecchymosis, or other trauma near the eye were also reported. On funduscopic examination, findings included macular/retinal edema, a cherry-red spot, or attenuated retinal vessels. Two reports describing 4 patients who sustained external compression documented the development of retinal pigmentary alterations, suggesting simultaneous choroidal circulatory ischemia.[37,38] Early orbital computed tomography (CT) or magnetic resonance imaging (MRI) showed proptosis and extraocular muscle swelling, although most cases did not have imaging studies to confirm the diagnosis.[36] Findings were similar to the syndrome of "Saturday night retinopathy" in intoxicated individuals who slept while their eyes were compressed.[39]

Hollenhorst and coworkers, who described unilateral blindness in patients positioned prone for neurosurgery, replicated the human findings in monkeys with 60 minutes of elevated IOP by exerting a pressure of 200 mm Hg on the eye together with hypotension. Hypotension was not a feature in 6 of the 8 human subjects in their report. In the monkey, histologic findings were edema of the retina and dilated vascular channels, followed by severe loss of retinal structure and axonal loss in the optic nerve 4 months later, owing to retrograde degeneration after death of retinal ganglion cells.[35]

More recent studies of the effects of increased IOP have been performed on rodents. Bui and colleagues documented that during acute increases in IOP in the rat, changes in visual function assessed by electroretinography progressed from the inner to the outer retina. In other words, retinal ganglion cells were the most sensitive to raised IOP, showing abnormalities on the electroretinogram (ERG) at IOPs of 30 to 50 mm Hg; the photoreceptor cells were not affected until IOP was higher.[40] The duration of increased IOP that injures the retina (see Table 90-2) appears to vary depending on rat or mouse strain, with studies reporting ischemic times between as short as 20 minutes or as long as 30 or 45 minutes.[41-43] The mechanisms of injury with increased IOP from external compression are summarized in Figure 90-2.

Proper use of modern head-positioning devices such as square or circular foam headrests with cutouts for the eyes as well as a mirror to view the eyes (i.e., Prone View, Dupaco, Inc.) should prevent compression of the eyes (see Chapter 36). However, we recently reported a case of unilateral retinal arterial occlusion in a prone-positioned patient whose head was placed in a square foam headrest with goggles to cover the eyes. This practice may be hazardous because of the limited amount of space between the headrest and the goggles and the risk of compression of the eye

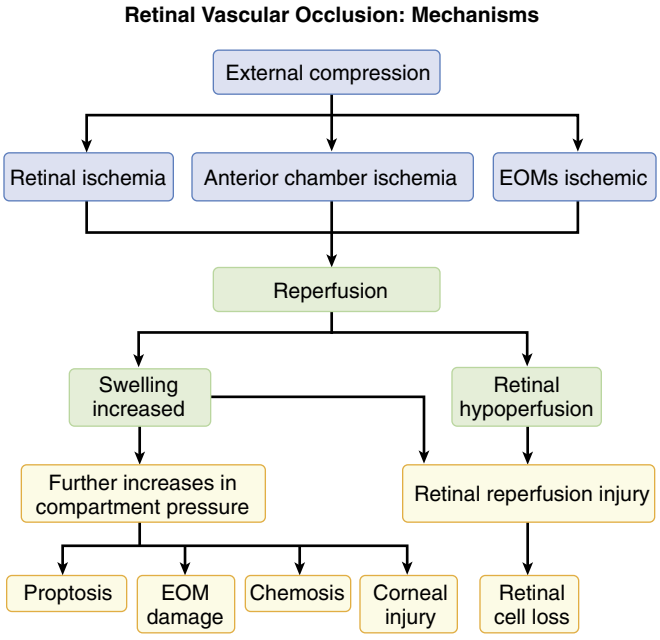

Figure 90-2 Mechanisms of retinal injury after external compression of the eye. EOM, extraocular muscle.

by the goggles. The patient exhibited signs of direct compression of the eye by the goggles, which ironically had been designed by the manufacturer (Dupaco, Inc., Oceanside, CA) to function as eye protectors.[44]

Ischemic ocular compartment syndrome, more typical in the setting of retrobulbar hemorrhage after nasal sinus surgery, was reported in a patient undergoing spine surgery in the prone position.[45] The patient's head had been positioned on a silicone head rest for surgery that lasted 8 hours during which the patient received only 1 L of crystalloids. Postoperatively, he had left ocular pain, no light perception from the eye, facial edema, 4 mm of left proptosis, and a tight orbit. There was corneal edema with a large abrasion, mid-dilated and fixed pupil, advanced cataract, pale optic nerve, retinal hemorrhages, and complete inability to move the eye. The IOP was 45 mm Hg. MRI showed proptosis, extraocular muscle enlargement, and severe globe tenting. Despite lateral canthotomy to relieve the pressure, vision did not improve. The cause in this patient was believed to be related to positioning with possible direct pressure on the eye.

Others have reported orbital compartment syndrome from perioperative intraorbital hemorrhage, orbital emphysema, or intraorbital bacitracin ointment in association with endoscopic sinus surgery.[46] This syndrome is different from cases of ION after spine surgery but may be similar to the early descriptions of ocular compression by Hollenhorst and coworkers.[35] Orbital compartment syndrome is an acute ophthalmologic injury, requiring prompt decompression to relieve the increased IOP.

Head and Neck Surgery

CRAO has occurred after neck and nasal/sinus surgery (see Chapter 75), although most reported cases of visual loss in neck dissection are from ION.[47] The incidence of orbital complications after endoscopic sinus surgery is 0.12%.[48] Orbital hemorrhage from blunt trauma during the procedure can result in orbital compartment syndrome with compression of the arterial and venous circulations and in CRAO and optic nerve injury.[49,50] Indirect damage to the CRA from intra-arterial injections of 1% lidocaine with epinephrine has also been described; the mechanism of action is speculated to be arterial spasm or embolism.[51]

Branch Retinal Artery Occlusion

BRAO usually leads to permanent ischemic retinal damage with partial visual field loss. Symptoms may not be noticed by the patient immediately if the visual field loss is peripheral or if a small scotoma is present. BRAO is primarily the result of emboli, but vasospasm has been reported in a few cases. Most case reports describe embolization of material from intravascular injections and circulating embolic material from the surgical field or cardiopulmonary bypass (CPB) equipment in cardiac surgery.

Microemboli to the retina during CPB have been shown by retinal fluorescein angiography (see Chapter 60). The occurrence and extent of perfusion defects were related to oxygenator type. When a bubble oxygenator was used, all patients had perfusion defects indicative of microemboli; when a membrane oxygenator was used, retinal perfusion defects were found in only half the patients. Neurologic outcome was not reported.[13] In patients who have coronary artery bypass graft (CABG) surgery, multiple calcific emboli in branches of the CRA are not unusual, and these emboli may produce visual field deficits of varying size and location. In pigs, mechanisms of air embolism during CPB included nonperfusion, vascular leakage and spasm, red blood cell sludging, and hemorrhage. Priming with perfluorocarbons blocked many of these mechanisms.[52]

Case reports have described sudden irreversible blindness with BRAO in patients after the injection of various drugs into the head and neck region. Loss of vision was nearly instantaneous when steroids were injected into the nasal mucosa.[53] In approximately half of cases, crystalline emboli could be seen at funduscopy, and one incident appeared to be complicated by vasospasm. Use of other agents, such as superselective injection of carmustine into the internal carotid artery to treat gliomas, or fat injected into the orbit for cosmetic surgery, has also been complicated by visual loss from retinal arterial occlusion.[54] Anesthesiologists providing care for neuroradiologic or angiographic/embolism procedures in the head and neck should be aware of the possibility of this complication.

Local infiltration anesthesia with lidocaine or bupivacaine in combination with epinephrine (1:100,000 or 1:200,000) for nasal septal surgery can cause partial or total visual field defects postoperatively attributable to BRAO (see Chapter 78).[51] No emboli were visible at funduscopy in these cases. It was speculated that the cause of BRAO was vasospasm induced by accidental intra-arterial retrograde injection of epinephrine or the combination of lidocaine and epinephrine into branches of the external carotid artery. Another possible contributing factor might have been epinephrine-induced platelet aggregation with retrograde embolization.[51]

BRAO was described in a patient in the prone position for spine surgery (see Chapters 63 and 70). After surgery a patent foramen ovale was discovered and it was believed that he had sustained a paradoxical air, fat, or bone marrow embolization from the operative site in the lumbar spine.[11]

Prognosis

Perioperative retinal artery occlusion results in permanent loss of vision in most cases. In monkeys, Hayreh and Weingeist[28] found that the critical time limit of irreversible retinal damage is approximately 100 minutes. CRAO lasting 105 minutes produced irreversible damage; recovery was possible if ischemic time was limited to 97 minutes. However, these studies involved surgical occlusion of the CRA. Retinal artery occlusion caused by external compression and increased IOP may produce a greater degree of ischemia and correspondingly shorter retinal survival times. In rodents, when the retinal artery was occluded by increasing IOP, periods of retinal ischemia as short as 20 minutes have produced damage.

Treatment

Currently available methods of treatment are not satisfactory. Treatment with ocular massage to lower IOP (contraindicated if glaucoma cannot be ruled out) and thereby dislodge an embolus, if present, to more peripheral arterial branches could be instituted by the anesthesiologist.[19] Intravenous acetazolamide can be administered to increase retinal blood flow, and the patient may inhale 5% CO_2 in oxygen to enhance dilation and increase oxygen delivery from retinal and choroidal vessels.[26] Further treatment

should be prescribed by the ophthalmologist and may include thrombolysis, although such treatment may be contraindicated after certain surgical procedures. A preliminary clinical study showed that fibrinolysis through a catheter in the ophthalmic artery within 6 to 8 hours after spontaneous CRAO was associated with improved visual outcome. An ongoing multicenter study is testing efficacy.[55] Localized application of hypothermia to the affected eye is a simple technique that has decreased injury in animal studies after ischemia,[56] and it is probably reasonable to institute in humans because of its minimal risk.

Prevention

Because retinal arterial occlusion in the perioperative period is most often caused by unintended application of external pressure to the eye, the anesthesiologist must take steps to avoid compression of the globe. Pressure on the eye from anesthetic masks is avoidable. If surgery is near the face, the surgeon's arm must not be allowed to rest on the patient's eye. In patients positioned prone for surgery, a foam headrest should be used with the eyes properly placed in the opening of the headrest; the position of the head and the eyes should be checked intermittently by palpation or visualization. The horseshoe headrest for the prone-positioned patient must be used with great caution, and there are safer choices available today. For the patient positioned prone for cervical spine surgery, this headrest should not be used because of the greater chance of head movement by the surgeon, leading to compression of the eye.

Intermittent examination of the eyes is advisable while the patient is prone. There are no data from human studies to establish the exact frequency of these checks. Considering results in rodent models of elevated IOP, it is advisable to examine eyes for change in position and the absence of external compression at least every 20 minutes. If the patient's head does not fit the headrest adequately (e.g., it is too large) or for surgery on the cervical spine, consideration should be given to securing the head with a pin head holder. Some surgeons now routinely place the patient's head in a pin head holder even for lumbar spine surgery, which eliminates opportunity for pressure on the eyes. This use must be weighed against the associated risks. For most procedures in which the patient is prone, I recommend any of the commercially available square foam headrests. The head is positioned straight down in the neutral position. The eyes and nose are then placed in the open portion of the headrest, and the anesthesiologist may easily reach underneath to check for pressure intermittently. When a transparent head piece is in use on the operating table, a mirror can be positioned underneath to indirectly view the eyes on the headrest. The ProneView is useful because it combines a foam headrest with a mirror immediately below, which enables the eyes to be seen easily during surgery. The use of goggles to cover the eyes is not advised when the head is positioned prone in a conventional square foam head rest.

In nasal and sinus surgery and in neuroradiologic procedures, the most important principles are avoidance of inadvertent injections into or compromise of the ocular circulation. After endoscopic sinus surgery, patients should be checked for signs of acutely elevated IOP suggestive of orbital hemorrhage. If present, immediate ophthalmologic consultation should be obtained. Embolization during CPB remains a cause of retinal vascular occlusion. Better means of detecting and preventing this complication are needed. Some surgical maneuvers may lower the incidence of arterial emboli.[57,58]

Ischemic Optic Neuropathy

Ischemic optic neuropathy, which primarily presents spontaneously without warning signs, is the leading cause of sudden visual loss in patients 50 years of age or older. The estimated annual incidence of nonarteritic ION in the United States is 2.3/100,000.[59] The two types of ION, anterior (AION) and posterior (PION), can be arteritic or nonarteritic. Arteritic AION, caused by temporal arteritis, responds to steroids. It is a systemic disease, generally occurs in patients 60 years of age or older, and has a female preponderance. Spontaneously occurring ION, unrelated to surgical procedures, is usually caused by AION. The specific mechanism and location of the vascular insult remain uncertain.[60] Only recently has a rodent model for AION been described.[61]

Nonarteritic ION, more common than arteritic, is overwhelmingly the type found perioperatively. It has been reported after a wide variety of surgical procedures, with most after cardiothoracic surgery,[62,63] instrumented spinal fusion operations,[9,10,64-66] head and neck surgery,[67,68] and surgery on the nose or sinuses.[69,70] Cases also have been described after vascular surgery, general surgical and urologic procedures, cesarean section and gynecologic surgery, and liposuction.[1,71-76] Most perioperative cases of ION are in adults, although there are some reports in children.[77]

Although there are many clinical studies of spontaneously occurring AION, there are few concerning PION. The lack of controlled studies, the absence of an animal model, and poorly defined pathology and risk factors limit our understanding of perioperative ION. Most of our knowledge is derived from individual case reports and case collections, of which the largest and best described single series is the ASA Postoperative Visual Loss Registry.[10] There have been one case-control study in spine surgery patients[9] and two in cardiac surgery.[6,7]

Mechanism

Simulated ischemia in optic nerve axons in vitro[78] culminates in axonal destruction. When oxygen delivery decreases, adenosine triphosphate is depleted, leading to membrane depolarization, influx of Na^+ and Ca^{2+} through specific voltage-gated channels, and reversal of the Na^+-Ca^{2+} exchange pump.[79] Ca^{2+} overload damages cells from activation of proteolytic and other enzymes. ION may lead to neuronal injury by apoptotic cell death, which may be stimulated in vitro with reduced oxygen delivery.[80]

Disruption of the blood-brain barrier is an early event in AION, and, as a result, fluorescein angiography in affected patients shows dye leakage in the optic nerve head.[81] Dye leakage correlates with the early onset of optic disc edema, seen even before the onset of symptoms.[82] The relationship between disruption of the blood-brain barrier and ischemic injury is not known. Earlier studies showed classic blood-brain barrier properties in the optic nerve head[83]; however, more recent immunohistochemical studies of microvessels in the monkey and human optic nerve head suggest a lack of classic blood-brain barrier characteristics in the prelaminar region[84] that could explain the early edema in the optic nerve head after ischemia.

Little is known about the in vivo cellular mechanisms leading to ischemic injury in the optic nerve. Guy showed that 30-minute occlusion of the carotid artery in rats produced ischemia and a swollen optic nerve within 24 hours.[85] The positive nitrotyrosine immunostaining found in the ischemic optic nerve[85] suggests a possible role for nitric oxide and perhaps oxygen free radicals, which would be expected to increase with disruption of the blood-brain barrier. Berstein and associates described a rodent model of AION.[61] After AION induction by a photothrombotic method, circulation to the optic nerve was lost within 30 minutes; edema peaked 1 to 2 days later and resolved by 5 days. A pale, shrunken optic nerve was found, similar to that in limited pathologic studies of human AION.[86] By 37 days after ischemic insult, the percentage of retinal ganglion cells was reduced by about 40%. After 6 days, the optic nerve showed axonal swelling and collapse. Permanent changes included septal thickening and axonal loss, most evident in the center, also similar to that found in the human optic nerve.

Clinical studies of AION with fluorescein angiography showed delayed filling of the prelaminar optic disc when disc edema was evident. Delayed filling was present in 76% of subjects and was not found in normal eyes. This suggests that delayed filling is the primary process in AION, and it is not caused by disc edema.[60] Hayreh attributed AION to individual variations in blood supply to the optic nerve.[87] This theory is supported not only by anatomic studies but also by the variability of visual loss in patients with AION. The "watershed concept," that impaired perfusion and distribution within a posterior ciliary artery predisposes the optic disc to infarction, is disputed. Arnold and Hepler showed that delayed filling of watershed zones was more common in normal eyes than in patients with AION.[81] Thus, reduced perfusion pressure in the region of the paraoptic branches of the short posterior ciliary arteries (PCAs) results in optic disc hypoperfusion, rather than a watershed event.[88] Histopathology in AION showed that the infarction was mainly in the retrolaminar region.[89] This implicates as the source of decreased blood flow the short PCAs directly supplying the optic disc.

Some have suggested that variability in blood pressure or IOP may predispose patients to the development of AION. Nocturnal hypotension in patients treated with antihypertensive agents may expose patients to low-level, albeit repeated decreases in perfusion to the optic nerve.[90] The importance of IOP fluctuations in the pathogenesis of AION has not been established.[91] Anatomic or physiologic variations in the circulatory supply of the optic nerve may predispose some patients to the development of AION,[92] especially if systemic arterial blood pressure is decreased. These variations in blood supply could result in underperfused areas.[93]

Hayreh reported nocturnal decreases of 25% to 30% in blood pressure in patients with AION.[94] There was no control group, but the decrease was larger than in age-matched normal subjects. Landau and associates[95] compared blood pressure decreases in normal and AION subjects and found no difference, although daytime blood pressures were slightly lower in those with AION. Thus, the role of chronically or intermittently low blood pressures in the pathogenesis of AION remains controversial. Interestingly, another study suggested an association between AION and sleep apnea syndrome,[96] but whether the mechanism depends on repeated hypoxia, increased IOP, decreased blood pressure, or altered autoregulation of blood flow in the optic nerve is still unclear.

A small optic disc (affected eyes commonly are referred to as having a small "cup-to-disc ratio") may play a role in a subject's susceptibility to AION[97] because axons of the optic nerve pass through a narrower opening as they exit the eye and are therefore prone to injury in the presence of edema or decreased blood flow. Mechanisms of injury due to a crowded disc include mechanical obstruction of axoplasmic flow, axoplasmic stasis, stiff cribriform plate, and decreased availability of neurotrophic factors to retinal ganglion cells after ischemia.[60] Tesser and colleagues reported that in a patient with spontaneous AION, axonal loss was in the superior part of the nerve, largely encircling the central retinal artery. The infarct was in the intrascleral portion of the nerve, extending 1.5 mm posteriorly. From this limited histopathologic evidence, the authors suggested that a tight scleral canal contributed to a "compartment syndrome" in the anterior optic nerve.[86]

The role of systemic diseases such as hypertension and diabetes has been examined in several studies. Hypertension was found in 34% to 47% of subjects with AION but was significantly different from non-AION patients only in those 45 to 64 years of age. Hayreh found increased prevalence of vascular risk factors in all age groups. Increased prevalence of diabetes is present in most studies of AION, but AION has not been consistently associated with stroke and myocardial infarction, cigarette smoking, and elevated cholesterol.[60] Among patients in the Ischemic Optic Neuropathy Decompression Trial (IONDT), 47% were hypertensive, 24% diabetic, 11% had a previous myocardial infarction, and 3% had a stroke.[98] These proportions of patients with "vascular risk factors" might, however, be similar to those in the general population. For ethical reasons, the IONDT could not include a non-ION control group. Smoking might also be a risk factor for the development of ION, but large numbers of patients have not been reported.[99] An association has been suggested between AION and prothrombotic factors, such as deficiencies of protein C, protein S, or factor V Leiden, but reports are conflicting.[60,100,101]

Patient Characteristics

Most of the cases occurring after spine surgery have a diagnosis of PION.[10,64,102] A diagnosis of AION has been more frequently reported after cardiac surgery (see Chapter 60). The onset of perioperative visual loss is typically within the first 24 to 48 hours after surgery, frequently noted on awakening, although later onset has been described, particularly in sedated patients whose lungs were mechanically ventilated postoperatively.[10,64,103] Patients present typically with painless visual loss, afferent pupil defect or nonreactive pupils, complete visual loss, no light perception, or visual field deficits. Color vision is decreased or is absent. In AION, altitudinal visual field deficits may be present. Optic disc edema and hemorrhages are seen on symptom onset in AION; in PION, the optic disc appears normal even though the patient complains of visual loss. Later, over a span of weeks to months, optic atrophy develops. The lesion may be unilateral or bilateral, but most post–spine surgery ION cases have bilateral involvement. In ION, orbital MRI is frequently nondiagnostic,[104] although some reports have described changes such as enlargement of the nerve from edema or perineural enhancement.[105] Visual evoked potential is abnormal, while the electroretinogram is unaffected.[106]

Recently, several reviews of case reports have appeared and a few case series have been published. It is worth reviewing some of the individual case reports where at least some patient-specific data were provided. After presentation of this information, I will discuss the more recent case series and summaries of case reports. There were 51 patients described in case reports in the literature from 1968 to 2002 in whom perioperative AION was diagnosed.[103] Among this group, 59% of subjects underwent open heart surgery; 12%, nasal, head, or neck surgery; and 12%, spine surgery. The average age was 53 years, and 72% were male. In many cases there are missing data concerning the patients and variability in the types of data reported. These patients tended to undergo lengthy operations, with an average operative time of 508 minutes. In patients for whom blood pressure was reported, mean arterial pressure averaged 92 mm Hg preoperatively and the lowest mean arterial pressure averaged 65 mm Hg intraoperatively. Preoperative hemoglobin averaged 13.7 g/dL, the lowest intraoperative value was 8.7 g/dL, and the postoperative hemoglobin concentration was 8.1 g/dL. The patients received considerable amounts of fluid intraoperatively; they averaged 1.4 L of blood replacement, 8.2 L of crystalloid, and 1.0 L of colloid. In 20% of cases, blood loss exceeded 2 L. Coronary artery disease was present in 61%, hypertension in 27%, and diabetes mellitus in 24% of patients. Because of the predominance of patients who underwent CABG surgery, these data may be weighted toward a higher prevalence of these disorders in this group.

In 67% of patients, symptoms of visual loss were not evident until more than 24 hours after surgery, either because of delayed onset of the disease or delayed recognition of the symptoms and signs of AION in the perioperative period due to mechanical ventilation and sedation postoperatively. Virtually all patients had disc edema, pallor, or both. Over 60% of patients had an afferent pupil defect or nonreactive pupils. The visual field deficit was altitudinal in 14%; there was central scotoma in 20%, and in 20% blindness was the initial symptom. Visual loss was bilateral in 55% and unilateral in 45% of patients. Some treatment was attempted in 15 patients, including steroids, aggressive volume replacement, vasopressors, or a combination of these therapies. Treatment did not necessarily result in improvement. Overall, in the 51 patients, 47% had no improvement or a worsening of symptoms, 29% improved, and in 25% the outcome was not described.

Between 1968 and 2002, case reports described 38 patients with perioperative PION.[103] The nature of the surgical procedures that these patients underwent tended to differ from those in the patients reported with AION. In this group, 8% of subjects underwent open-heart surgery; 24%, nasal, head, or neck surgery; and 39%, spine surgery. The average age was 50 years, and 63% were male. Although AION is rarely reported in children, four cases of perioperative PION occurred in children 13 years or younger. As with the AION cases, surgery tended to be lengthy, averaging 448 minutes. In patients for whom blood pressure was reported, mean arterial pressure averaged 90 mm Hg preoperatively, with an average lowest mean arterial pressure intraoperatively of 61 mm Hg. Preoperative hemoglobin averaged 12 g/dL, the lowest intraoperative hemoglobin concentration was 8 g/dL, and postoperative values averaged 10 g/dL. These values are similar to those reported in the AION cases. Hematocrit decreased from 44% to 27% intraoperatively and increased to 29% postoperatively. The patients also received considerable amounts of fluid intraoperatively; they averaged 2.3 L of blood replacement, 8.8 L of crystalloid, and 1.6 L of colloid. In 37% of cases, intraoperative blood loss exceeded 2 L. Coronary artery disease was present in only 8%, hypertension in 32%, and diabetes mellitus in 21%. When compared with patients with AION, the incidence of coronary artery disease was much lower. The onset of symptoms was typically within 24 hours postoperatively. Blindness was reported in 47%, an altitudinal defect in 8%, and a central scotoma in 26%. Twenty-seven (71%) patients had an afferent pupil defect or nonreactive pupils. A normal optic disc on initial funduscopic examination was evident in 92% of patients. Visual loss was bilateral in 63% and unilateral in 34% of patients. Forty-five percent of patients had no improvement, 29% improved, and for 18% the outcome was not described.

In summary, case reports showed similar intraoperative characteristics of patients with AION or PION. Most patients with AION had undergone open-heart surgery. The largest single group of patients with PION had spine fusion surgery. The main differences were a lower incidence of coronary artery disease in the group with PION; the occurrence of PION in younger patients; and somewhat more intraoperative blood replacement, more rapid onset or recognition of visual loss, and a greater likelihood of complete blindness initially in PION cases than in AION cases.

Retrospective Case Series

Sadda and associates retrospectively collected a series of 72 cases of ION from two large academic institutions over a 22-year period. In 38 subjects, PION developed spontaneously, and in 28, it developed in the perioperative period.[107] In the remaining 6, the diagnosis was arteritic PION. For the 38 patients with spontaneous nonarteritic PION the average age was 68 years; 39% had hypertension, 24% had diabetes, 18% had coronary artery disease, and 32% had a history of cerebrovascular disease. Bilateral involvement was evident in 21%, and 90% had some form of visual field deficit. Only 30% improved; 35% worsened. Unlike AION, where there may be a structural difference in the optic nerve such as a small cup-to-disc ratio, these authors could identify a structural abnormality in the optic nerve in only 4% of patients with PION. The 14 patients who had spinal surgery tended to be younger and to have a lower incidence of coronary artery disease and diabetes, but not hypertension, relative to the other two groups. Unfortunately, intraoperative data were not included but the postsurgical patients were more likely to have bilateral involvement (54%) and a worse visual outcome at initial examination and later follow-up compared with PION in nonsurgical cases.

Buono and Foroozan[108] reviewed 83 cases of PION reported in the literature. In 36 cases, there were details of clinical features; in the other 47, aggregate data had been reported. About 54% of the cases followed spine surgery, 13% radical neck dissection, and 33% other surgery. Mean age was 52 years; patients who had spine surgery were younger (mean age, 44 years) than those in the other groups. About two thirds of patients were men. In three fourths of cases, visual loss was apparent within 24 hours of surgery. Visual acuity was "counting fingers" or worse in 76%, and 54% of eyes had an initial visual acuity of no light perception. Over 60% of cases were bilateral. In 38% of patients, vision improved, but of 14 with no light perception initially, 12 (85%) had no improvement. Among patients with PION, 65% had one or more of the following: hypertension, diabetes, cigarette use, hypercholesterolemia, coronary artery disease, congestive heart failure,

arrhythmia, cerebrovascular disease, or obesity. Mean lowest hemoglobin value was 9.5 g/dL (5.8 to 14.2 g/dL). Mean lowest systolic blood pressure was 77 (48-120 mm Hg). Mean intraoperative blood loss was 3.7 L (0.8-16 L). Mean operative duration was 8.7 hours (3.5-23 hours).

Spine Surgery

Cheng and colleagues surveyed neurosurgeons in the United States who performed spine surgery.[65] There were 24 cases of visual loss reported by 22 surgeons. The mean age was 47 ± 15 years. Lumbar spine surgery was the procedure performed most frequently, and mean duration of surgery was 4.8 ± 3.5 hours. Mean hematocrit changed from 42 ± 5% to 35 ± 7%. Mean estimated blood loss was 793 ± 1142 mL. In 5 patients, estimated blood loss exceeded 1800 mL; 3 received blood transfusions. Of the 24 patients, 21 were normotensive intraoperatively and 2 had deliberate hypotension; 4 had diabetes mellitus, 1 had peripheral vascular disease, and 1 had diabetes and peripheral vascular disease.

Ho and associates[64] reviewed reported cases of AION and PION in the literature after spine surgery. There were 5 cases of AION and 17 of PION; median ages were 53 and 43 years, respectively. Most of the cases followed lumbar spine fusion surgery. Mean operative time for AION cases was 522 minutes, and for PION cases, 456 minutes. For AION, range of the lowest mean arterial pressure was 62 to 78 mm Hg; for PION, it was 52 to 85 mm Hg. Lowest mean intraoperative hematocrit was 27% in the PION cases. Mean blood loss was 1.7 L and 5 L for AION and PION, respectively. Crystalloid/colloid volumes averaged 6.0/0.8 L and 8.0/2.2 L for AION and PION, respectively. Sixty percent of patients with AION and 27% with PION had diabetes mellitus; coronary artery disease was noted in 20% of patients with AION and in none with PION. Prevalence of hypertension was similar (40% or 53%). Symptoms were reported within 24 hours of surgery in 40% of AION cases; 59% of PION cases reported symptoms immediately on awakening and 88% within 24 hours. Visual acuity improved somewhat in 60% of AION and 65% of PION cases.

Data from spine surgery patients in the ASA Postoperative Visual Loss Registry[10] showed striking differences between patients with ION ($n = 83$) and those with CRAO ($n = 10$). The average blood loss in ION cases was 2.0 versus 0.75 L with CRAO. The lowest hematocrit was 26% with ION and 31% with CRAO. With ION, decreases in blood pressure varied widely from preoperative baseline: in 33% of cases, lowest systolic blood pressures were greater than 90 mm Hg; in 20%, the lowest was less than or equal to 80 mm Hg. About 57% of patients had systolic or mean arterial blood pressure 20% to 39% below baseline, and 25% of patients were at 40% to 49% below preoperative baseline. Deliberate hypotension was used in about a fourth of the patients. Nearly all cases involved surgery longer than 6 hours. In the majority of the cases, estimated blood loss was greater than 1 L, the median estimated blood loss was 2 L, and the median lowest hematocrit was 26%. Large-volume fluid resuscitation was typical in these patients, with median crystalloid administration of about 10 L. Most of the patients underwent thoracic, lumbar, or lumbar-sacral fusion procedures that were often repeat operations that mostly involved multilevel surgery. Surgical positioning devices for these patients were the Wilson frame (30%), Jackson spinal table (27%), and soft chest rolls (20%). A foam pad was used for head positioning for 57%; 19% had the head positioned in a Mayfield head holder. PION accounted for the majority of the cases compared with AION. Patients of ASA class 1 or 2 accounted for 64% of cases. The mean age was 50 ± 14 years. About 41% had hypertension, 16% had diabetes mellitus, and 10% had coronary artery disease. The POVL Registry does not have a control group of unaffected spine surgery patients for comparison to enable a case-control study of risk factors.

In a retrospective case-control study of 28 patients with visual loss after spine surgery, Myers and colleagues found no difference in the lowest systolic blood pressure or hematocrit in the affected versus unaffected patients, suggesting that hypotension and anemia do not completely explain the occurrence of ION. About 40% of these patients had no risk factors for vascular disease preoperatively; a similar percentage in the two groups were hypertensive or smokers.[9]

Cardiac Surgery

Two retrospective case control studies of blindness after cardiac surgery (see Chapter 60) have been reported. Shapira and colleagues studied 602 patients at a single institution.[6] Patients underwent CPB under moderate systemic hypothermia (25°C) with pulsatile flow and a membrane oxygenator. Neo-Synephrine was used if perfusion pressure could not be maintained above 50 mm Hg despite a flow index of 2 L/m^2/min, and alpha-stat was used for pH management. There were 8 patients (1.2%) affected by AION. There were no differences in preoperative risk factors for vascular disease between patients with or without visual loss. CPB time was longer in patients with AION (252 versus 164 minutes), and minimum hematocrit was lower (18% versus 21%) compared with unaffected patients. There were no differences in flow indices, perfusion pressures, and P_{CO_2} levels intraoperatively. Patients with AION had a greater 24-hour postoperative weight gain (18% versus 11% increase) and required more epinephrine and amrinone postoperatively to maintain hemodynamics than did patients with unaffected vision. Visual symptoms were usually reported between days 1 and 3 postoperatively, soon after removal of mechanical ventilatory support.

Nuttall and colleagues performed a larger retrospective case-control study of about 28,000 patients who had cardiac surgery at the Mayo Clinic from 1976 to 1994.[7] They found 17 cases of ION (0.06%). By univariate analysis, significant risk factors for ION included lower minimum postoperative hemoglobin, history of clinically severe vascular disease, preoperative angiogram within 48 hours of CPB, longer duration of CPB, red blood cell (RBC) transfusions, and any use of non-RBC blood components. Patients with ION underwent longer CPB runs; there were no differences in pre-CPB or post-CPB systemic blood pressures. There were 9 cases of bilateral ION; disc edema was not found in 5 patients (29%), which may have been cases of PION, not AION. Small cup-to-disc ratio (<0.3) was identified in 5 patients (29%) with ION.

Kalyani and colleagues retrospectively reviewed cases of ION after 9701 cardiac surgeries over a 9-year period at a single institution.[8] Specific risk factors could not be determined from the 11 patients (0.11%) with ION in this series.

Trauma (see also Chapter 72)

Cullinane and coworkers retrospectively reviewed the medical records of over 18,000 trauma cases at a single institution between 1991 and 1998.[109] Of these, 350 required massive resuscitation with more than 20 L of fluid during the first 24 hours after

admission. Volume resuscitation consisted of 21 to 50 L (mean 33 ± 8 L) in the first 24 hours. Incidence of ION was 2.6% (9 patients). Four patients had bilateral blindness. No information was provided on funduscopic examinations. The mean age was 34 ± 13 years. Patients were acidotic, with serum lactate levels ranging from 2.5 to 17.5 mEq/L. Mean lowest hematocrit was 7.5% to 28% (mean 20 ± 8%); blood products included 9 to 39 units of packed RBCs (mean 22 ± 10 units). All patients had coagulopathy, and all developed acute respiratory distress syndrome that required high levels of inspired oxygen and positive end-expiratory pressure (mean level 29 ± 9 cm H_2O). All patients had systemic inflammatory response syndrome, and 66% had compartment syndrome at some location in the body remote from the eye. Mean time until detection of visual loss was 36 days because patients needed prolonged mechanical ventilation and sedation.

Blood Supply to the Optic Nerve

ION affects the anterior portion of the optic nerve in AION or beyond the retrolaminar region behind the eye in PION. The ischemic insult is presumably of vascular origin but has not been conclusively shown. Anatomy of and blood supply to the anterior and posterior optic nerves differ.[26,87] The pathophysiology of PION is even less well understood than that of AION.

The anterior portion of the optic nerve is proximal to the lamina cribrosa, an elastic, collagenous tissue through which the optic nerve and the central retinal artery and the central retinal vein pass as they enter the optic disc. The anterior portion of the optic nerve includes the superficial nerve fiber layer and the prelaminar region. The prelaminar area is a thick tissue that constitutes most of the optic disc volume.[110] The superficial nerve fiber layer, composed of axons extending from the retinal ganglion cells, is anterior to the plane extending across the optic nerve from the peripapillary Bruch membrane. Immediately posterior is the prelaminar region, adjacent to the peripapillary choroid. The laminar region is a transition zone between columns of glial cells and dense connective tissue plates. Astrocytes are predominant in the anterior optic nerve, and oligodendrocytes and microglial cells are more common in the posterior or retrobulbar optic nerve. Neural fibers transit the laminar region through fenestrations. The retrolaminar region is the posterior portion of the optic nerve and consists of meningeal sheaths and myelinated axons. The diameter of the optic nerve is enlarged in this area to about 3 mm.

The superficial nerve fiber layer derives its blood supply mainly from arterioles in the retina, although in the temporal regions it may receive blood from the posterior ciliary arteries. The prelaminar region is perfused by centripetal branches of the peripapillary choroid and vessels from the circle of Zinn-Haller (Fig. 90-3), which are not found in every eye.[87] Whether the region has a choroid-derived source of blood is controversial. The laminar region is supplied by centripetal branches from the short posterior ciliary arteries or by the circle of Zinn-Haller, but the short posterior ciliary arteries are the primary input. Longitudinal anastomoses of capillaries can be seen in the prelaminar and laminar regions and may provide some additional protection against ischemic insult, although their functional importance is not clearly known.

The retrolaminar, posterior portion of the optic nerve, which is affected in PION (Fig. 90-4), is perfused by two main

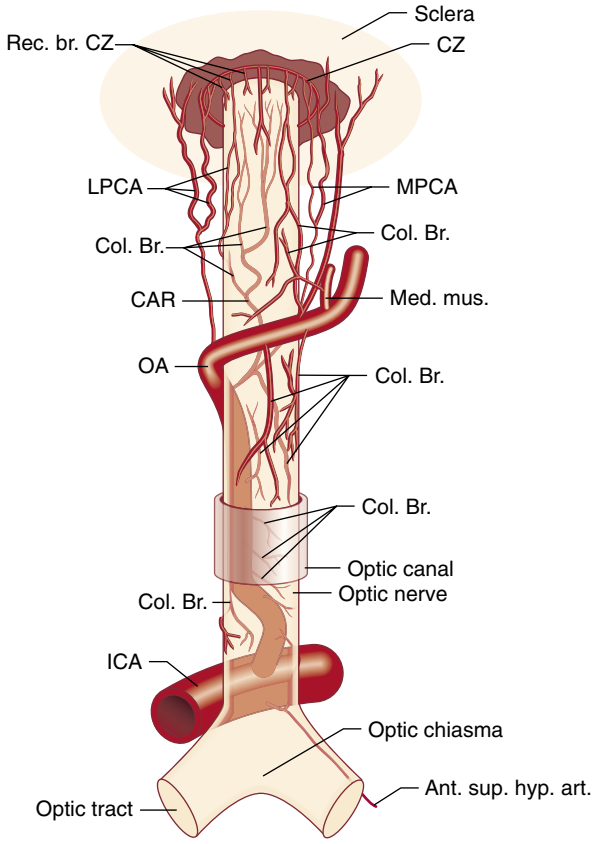

Figure 90-3 The origin, course, and branches of the ophthalmic artery, including the posterior ciliary arteries, as seen from above. Ant. sup. hyp. art., anterior superior hypophyseal artery; CAR, central retinal artery; Col. Br., collateral branches; CZ, circle of Zinn and Haller; ICA, internal carotid artery; LPCA, lateral posterior ciliary artery; MPCA, medial posterior ciliary artery; OA, ophthalmic artery; Rec. br., recurring branches. (*From Pillanut LE, Harris A, Anderson DR, Greve EL [eds]: Current Concepts on Ocular Blood Flow in Glaucoma. The Hague, Netherlands, Kugler, 1999.*)

vascular supplies. The peripheral centripetal vascular system is the major supply and is found in all optic nerves. It is formed by recurrent branches of the peripapillary choroid and the circle of Zinn-Haller. Pial branches of the central retinal artery and other orbital arteries, the ophthalmic artery, and the posterior ciliary arteries also contribute. Branches of the pial vasculature run in the septa of the nerve. The axial centrifugal vascular system is formed by small branches from the intraneural part of the central retinal artery and is not present in every eye; thus, differences in blood supply in the posterior optic nerve may render some individuals more susceptible to PION.[111]

Control of Blood Flow

Studies of autoregulation of blood flow in the optic nerve head have yielded conflicting results because measurement techniques are limited.[87] Blood flow in the optic nerve head is autoregulated within a range of perfusion pressures similar to those in the brain of monkeys and sheep. In a small sample of atherosclerotic monkeys, however, autoregulation was defective.[112] This study did not directly measure blood flow; rather, it measured glucose consumption, and the sample size was small. There is other evidence of autoregulation in the posterior portion of the optic nerve. In

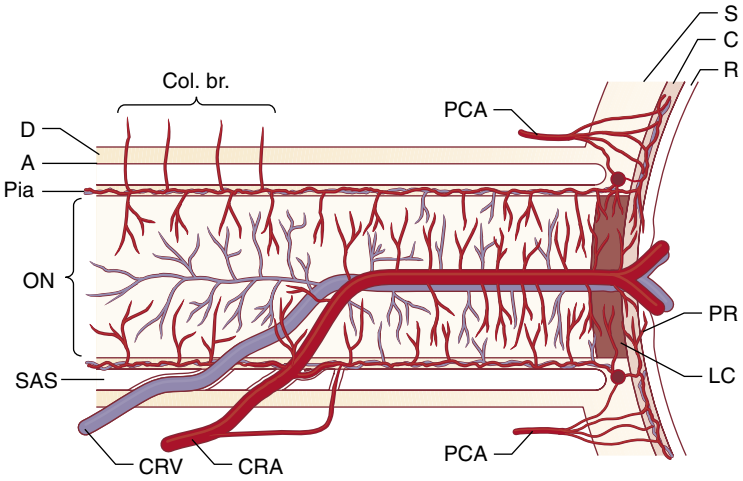

Figure 90-4 The blood supply to the optic nerve is illustrated. The anterior portion of the optic nerve is located to the left, whereas the posterior portion (closer to the brain) is on the right. The anterior portion of the nerve derives its blood supply from the posterior ciliary arteries (PCA) and the choroid (C), whereas the posterior optic nerve derives its blood supply from penetrating pial arteries (collateral branches [Col. br.]) and branches of the central retinal artery (CRA). A, arachnoid; C, choroid; CRV, central retinal vein; D, dura; LC, long ciliary artery; ON, optic nerve; PR, short posterior ciliary artery; R, retina; S, sclera; SAS, subarachnoid space. (*From Hayreh SS: Ischemic optic neuropathy, University of Iowa, Department of Ophthalmology Internet Site. http://webeye.ophth.uiowa.edu/dept/aion/ion_fg2.jpg.*)

cats, blood flow in the optic nerve measured directly by autoradiography remained constant in the prelaminar, laminar, and postlaminar nerve across a range of systemic mean arterial blood pressure values from 40 to more than 200 mm Hg.[113]

In one study in 13 healthy volunteers, blood flow in the optic nerve head measured by laser Doppler flowmetry was constant between ocular perfusion pressures of 56 to 80 mm Hg[114]; in another study, flow was preserved at extremely high IOP that resulted in a minimal perfusion pressure of 22 mm Hg.[115] Other investigators found that flow was preserved in the optic nerve head until ocular pressure reached levels of 40 mm Hg. However, 2 of 10 healthy young volunteers in the study failed to demonstrate autoregulation.[92] Using color Doppler imaging in humans, another group showed that flow velocity in the posterior ciliary arteries decreased at extremely high IOP. These findings seem to support the theory that "watershed" areas in the distribution of the posterior ciliary arteries predispose some patients, including otherwise healthy ones with no known vascular disease, to damage to the anterior portion of the optic nerve when perfusion pressure is decreased, either after systemic blood pressure decreases or IOP is elevated. At present, however, no clinical technique can reliably detect such patients.

Histologic Findings

Only a few cases report histopathologic examination of the optic nerve in ION. Of 3 PION cases evaluated after surgical procedures, all of the patients showed infarcts in the intraorbital portion of the optic nerve, but results were not completely consistent. Two patients had lesions in the central axial portion with peripheral axonal sparing; the other patient had the opposite pattern in one eye and complete axonal loss in the other.[108] Despite a larger autopsy series in AION, the location of the infarct has not been documented. Tesser and colleagues showed that in a patient with spontaneous AION the axonal loss was in the superior part of the nerve, largely encircling the central retinal artery. The infarct was in the intrascleral portion of the nerve, extending 1.5 mm posteriorly.[86]

Possible Pathogenic Factors

Among the possible factors in perioperative ION are decreased systemic blood pressure; blood loss; anemia or hemodilution; altered venous hemodynamics; flow of cerebrospinal fluid in the optic nerve (including the influence of patient positioning and perioperative fluid resuscitation); abnormal autoregulation in the optic nerve; anatomic variants in blood supply to the optic nerve; small cup-to-disc ratio; the use of vasopressors; the presence of systemic vascular risk factors including hypertension, diabetes, atherosclerosis, hyperlipidemia, and smoking history; prone positioning; lengthy surgery for spinal fusion; and other preexisting systemic abnormalities, such as sleep-apnea syndrome and hypercoagulability.[96,101-103,108]

It seems that one or more of the these factors are often present in an individual patient in an unpredictable fashion. In most cases there has been some degree of hypotension or anemia and fluid resuscitation. Many of the patients with ION after spine surgery have been relatively healthy preoperatively. Hypotension, blood loss, lengthy surgery, and large quantities of fluid administration seem to occur frequently in many patients undergoing complex spine surgery.[9,64,65,107,108] As a result, it is possible that combinations of these factors, perhaps together with abnormal autoregulation in the posterior optic nerve, prothrombotic tendencies, and other patient-specific factors lead to decreased oxygen delivery to the optic nerve sufficient to cause ischemic injury.

Current Knowledge and Controversies

Because of the paucity of case-control studies, and the absence of prospective studies, risk factors for ION have not yet been well defined. However, a number of potential factors warrant discussion. Myers and associates showed that *length of surgery* and *estimated blood loss* were higher in patients with postoperative blindness after spine surgery versus unaffected patients.[9] Therefore, patients undergoing anticipated long-duration surgery with large blood loss are recognized as higher-risk patients.[116] Staging

of spinal fusion procedures, particularly those for anterior and posterior surgery, may be advisable. Of course, this is not the primary decision of the anesthesiologist, but it is worth discussing with the surgeon for appropriate cases. Revision spinal fusion procedures are common, and these operations may be expected to be longer and involve greater blood loss.

Intraoperative hypotension has been cited as a risk factor by a number of authors of case reports,[71,117] but because it is not always present, and because some degree of hypotension frequently occurs in anesthetized patients, hypotension itself might not be responsible.[6,118-120] In Cheng and colleagues' survey of 24 cases of visual loss after spine surgery, deliberate hypotension was used in only 2 cases.[65] In a retrospective case-control study of patients undergoing spinal fusion, Myers and colleagues showed that levels of hypotension and anemia were equivalent in patients in whom ION developed after spinal surgery and in those in whom it did not.[9] In the ASA Postoperative Visual Loss Registry, which contains the largest series of visual loss after spine surgery, there was a wide variation in blood pressure decreases intraoperatively among the patients with ION; in 33% of cases, lowest systolic blood pressures were more than 90 mm Hg, while in 20%, the lowest were 80 mm Hg or less. About 57% of patients had systolic or mean arterial blood pressure 20% to 39% below baseline, and in 25% of patients it was 40% to 49% below preoperative baseline. Deliberate hypotension was used in 27% of the patients.[10]

Similarly, in Shapira and associates' retrospective case-control study of 602 patients who underwent open-heart surgery at one institution during a 2-year period, the lowest perfusion pressure intraoperatively was no different between affected and normal patients.[6] Nutall and coworkers' larger case-control study did not report the blood pressures during CPB, but there were no differences in pre- or post-bypass blood pressures between patients with ION and unaffected patients.[7] In open-heart surgery, hypothermia during CPB, and other systemic alterations such as systemic inflammatory syndrome might play a role in the development of ION but these mechanisms have not been studied.

Hypotension can potentially lead to decreases in perfusion pressure in the optic nerve and to ischemic injury either because of anatomic variation in the circulation or because of abnormal autoregulation and an inability to adequately compensate for decreased perfusion pressure. The degree of hypotension that is potentially dangerous is difficult to quantitate because of the lack of data in the literature.[116]

Blood loss may be considerable in reports of perioperative ION. It is apparent that, on average, patients sustained considerable blood loss and had a decreased hemoglobin concentration intraoperatively. Clinical blood transfusion practice in surgical patients, based on ASA practice guidelines,[121] suggests that transfusion is not generally required for hemoglobin values higher than 8.0 g/dL (see Chapter 55). The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists, which reviewed the available evidence base for these practices in cardiac surgery in particular, has issued a recent, similar clinical practice guideline.[122]

Some authors have suggested that allowing *hemoglobin* to decrease, as is common in anesthesia practice, may be putting patients at increased risk for ION[71,102]; however, whether practice should be changed in surgical procedures such as spine or heart surgery—or in any operative procedure—remains controversial. Two retrospective case-control studies examined whether decreased hemoglobin or hematocrit relates to the occurrence of ION. In spine surgery patients, Myers and associates[9] determined that the lowest levels of hematocrit did not differ between patients sustaining ION and those who were not affected. In cardiac surgery patients, Nuttall and coworkers[7] found a somewhat different result. The presence of a lower minimum postoperative hemoglobin was associated weakly with ION (odds ratio, 1.9; $P < .047$). Looked at another way, 13 of 17 patients with ION in their study had a minimum postoperative hemoglobin value less than 8.5 g/dL, versus 14 of 34 control patients with this level. The type of ION sustained by the patients was not specified, and the study had numerous statistical comparisons and a small sample size. Because spine and open-heart surgery patients are different, it is doubtful that the results can be extrapolated to types of surgery other than cardiac. Although visual loss after cardiac surgery is a rare but dreaded complication, the possibility of a relationship among blood loss, hemoglobin value, and visual loss was not a consideration in the clinical practice guideline for blood transfusion in cardiac surgery.[122]

In uncontrolled *hemorrhage* in which blood volume is not maintained, decreased oxygen delivery to the optic nerve could result in either AION or PION.[123] Just how low or for how long the hemoglobin concentration must decrease to lead to this complication is not known. However, the presence of recurrent and profound hemorrhage has been described in many reports. The argument that blood loss in the presence of maintained intravascular volume (hemodilution) is harmful seems less scientifically grounded. It has been shown experimentally in minipigs that blood flow in the optic nerve head, as measured by laser Doppler imaging, was maintained during isovolumic hemodilution with a 30% decrease in hematocrit. Moreover, oxygen tension at the vitreal surface increased 15%.[124] Hemodilution in cats resulted in a nonsignificant decrease in choroidal oxygen delivery[125] and an increase in preretinal oxygen tension.[126] Healthy volunteers tolerated very deep levels of hemodilution (hemoglobin, 50 g/L) without any disturbance in systemic oxygen delivery.[127] The multicenter prospective randomized trial conducted by Hebert and coworkers provided data justifying clinical use of a liberal transfusion strategy (lower hematocrit) in critically ill patients.[128] The effects of combined hypotension and hemodilution on hemodynamics and oxygen delivery in the optic nerve have not been reported.

AION and PION have been reported in the setting of *massive fluid replacement*, and many reports include patients who were operated on in the *prone position*, raising the possibility that positioning itself contributes to altered venous hemodynamics within the optic nerve. It is advisable to position the patient's head level with or above the heart, when possible, and in a neutral position during spine surgery performed with the patient in the prone position. Several studies have measured IOP and found that it increased in the prone position and was influenced by the position of the operating room table. However, there has been no correlation between IOP changes and visual outcome or visual function changes.[16,17] Cheng and colleagues[17] found that in anesthetized patients, IOP increased significantly on initial prone positioning relative to supine (27 ± 2 versus 13 ± 1 mm Hg). After 5 hours in the prone position, IOP remained elevated at 40 ± 2 mm Hg. None of the 20 patients in the study experienced visual loss. The largest increases in IOP were evident near the time that patients were awakening. Although these data suggest that ocular perfusion pressure may decline even during maintenance of normotension,

some experimental design issues must be considered in interpreting these results. The main issue is that the largest increases in IOP were evident near the time of awakening. Accordingly, IOP could have risen because of light anesthesia. Moreover, the study did not include a supine group to control for the effects of fluid administration on IOP. Such control is important because prone positioning itself may not explain the large increases in IOP. These results are valuable as well as of concern, but further studies are needed to fully evaluate their significance.

External pressure on the eye is a potential concern when a patient is positioned prone for surgery. Many cases of ION have been reported in which it was impossible for pressure to have been placed on the eye. Such cases include patients in pin head holders[65,120] and those in whom the head was turned with the affected eye placed upward.[129] But ION would not occur without retinal damage in a situation in which external compression was applied (see earlier). While we showed that high IOP decreased retinal and choroidal blood flows in cats,[22] Geijer and Bill[130] specifically measured the impact of graded increases in IOP on blood flow in the retina and optic nerve in monkeys. When IOP was elevated such that perfusion pressure was decreased to levels above 40 cm H_2O, there were small effects on retinal blood flow and in the prelaminar portion of the optic nerve. When perfusion pressure was below 40 cm H_2O, retinal and prelaminar flows were proportional to the perfusion pressure. At very high IOP, blood flow stopped in the retina and the prelaminar area but flow in the retrolaminar region increased. High IOP results in a redistribution of blood flow that favors the retrolaminar portion of the optic nerve. Therefore, an increase in IOP would not produce an isolated ION without also causing retinal damage. Further support is that sustained increases in IOP significantly decreased both retinal and choroidal blood flow, and even small increases in IOP damaged the retinal ganglion cells, which are sensitive to pressure alterations.[22,40]

The theory that massive *fluid resuscitation* could be a pathogenic factor in perioperative ION remains speculative, but it does have some merit. Fluid resuscitation is a necessity during lengthy, complex spine surgery associated with substantial blood and fluid losses at the operative site.[118,119] Conceivably, fluid administration could result in increased IOP or accumulation of fluid in the optic nerve, or both. Because the central retinal vein exits out of the optic nerve, an internal "compartment syndrome" may occur in the optic nerve. Alternatively, fluid accumulation in the vicinity of the lamina cribrosa may compress axons as they transit this region. In the report of Cullinane and associates,[109] trauma patients received massive blood replacement who were acidotic, and most had abdominal compartment syndrome. Analysis of these patients is complicated because of the presence of numerous systemic alterations. Sullivan and associates described a retrospective series of 13 burn patients with 25% or greater body surface area burns and massive fluid resuscitation. IOP was elevated more than 30 mm Hg in 4 patients at 48 hours after admission, all of whom received more than 27 L of intravenous fluid. Eye findings and vision diagnoses were not described.[131] Large-volume fluid replacement is generally seen in many case reports of ION.[103] Patients in the ASA Postoperative Visual Loss Registry received on average 9.7 L of crystalloid intraoperatively,[10] and increased postoperative weight gain was identified in a case-control study of visual loss after heart surgery,[6] suggesting, although not proving, that fluid replacement may play a role.

Further support of an idea that *increases in venous pressure* within the optic nerve are potentially deleterious can be seen in reports of ION after head and neck surgery in which the internal jugular veins were ligated.[15,67,68] However, there are venous drainage bypass pathways from the head and neck when the internal jugular veins are ligated. Although the relationship to fluid therapy is not clear, Myers and colleagues found that longer surgery was associated with ION.[9] However, cases of ION have been found after widely varying operative times.[10]

Some have speculated that *facial edema* indicates a risk for ION after spine surgery.[132] However, in clinical practice, facial edema is often seen after spinal fusion in many patients in whom ION does not develop, and, therefore, its relevance remains unclear and the notion that facial edema is a risk factor is unproved.

Killer and coworkers sampled cerebrospinal fluid (CSF) from the subarachnoid space of the optic nerve and from the lumbar region in patients with idiopathic intracranial hypertension undergoing optic nerve sheath fenestration.[133] The authors compared content of albumin, IgG, beta-trace protein, and brain-derived protein lipocalin-like prostaglandin D-synthase (L-PDGS). MRI and CT-cisternography were performed. From differences in the ratios of the CSF proteins in the optic nerve versus the CSF proteins in the lumbar region, and the results of cisternography, they concluded that CSF flow was compartmentalized in the optic nerve under these pathologic conditions. The implication of this conclusion is that relatively high CSF pressures in the intraorbital optic nerve can result in compression. Because CSF pressure may increase with fluid resuscitation, this may explain optic nerve compression. However, this theory has not been tested.

Although various theories concerning the role of intraoperative fluids in perioperative ION have been postulated, including extravasation from the central retinal vein, influence of directional CSF flow in the optic nerve, and changes in intracranial pressure, among others, none of these has been examined in either animal or human studies. MRI of the orbit in humans with ION has provided no evidence for any of these theories.[104] No study has shown any relationship among periorbital edema, IOP, and ION. Fluid administration could be a pathogenic factor in ION, especially in patients positioned prone or undergoing cardiac surgery, but the mechanisms involved, as well as the amounts and nature of fluid required, remain undefined.

Anatomic variation in the circulation of the optic nerve may potentially predispose patients to the development of ION. The location of potential watershed zones in the anterior and posterior circulation and the presence of disturbed autoregulation, even in normal patients,[92] are of concern but at present cannot be predicted clinically. There are few human studies of the relationship between perfusion pressure and changes in blood flow in the optic nerve. Human studies generally show preserved blood flow at clinically used or even lower ranges of perfusion pressure, but these studies have focused primarily on the anterior portion of the optic nerve.[92,114] In the studies that utilized laser Doppler flowmetry, depth of penetration of the measuring device is critical. Measurements might have been closer to the retinal blood vessels rather than the optic nerve head, and these do not measure optic nerve circulation. It is not currently feasible to measure blood flow in the human retrolaminar optic nerve. In animal studies blood flow is preserved in various layers of the optic nerve, including the retrolaminar area, at a mean arterial blood pressure as low as 40 mm Hg.[113]

Hayreh and associates theorized that AION is related to excessive secretion of vasoconstrictors, which in turn could lower optic nerve perfusion to dangerously low levels.[134] However, the theory was based on the development of AION in patients who sustained massive hemorrhage. *Vasopressors* are used to maintain blood pressure in circumstances such as after cardiac surgery and where there is decreased vasomotor tone. Shapira and coworkers showed an association between prolonged use of epinephrine or long bypass time and ION in patients undergoing open heart surgery.[6] Lee and Lam[120] reported a case of ION in a patient after lumbar spine fusion during which a phenylephrine (Neo-Synephrine) infusion was used to maintain blood pressure. They later presented a series of four case reports of ION in critically ill patients with significant systemic illness who required prolonged use of vasopressors and inotropic agents to maintain blood pressure and cardiac output.[135] However, α-adrenergic receptors are not known to be located in the optic nerve and the blood-brain barrier prevents entry of systemically administered agents, except possibly in the prelaminar zone of the nerve. Therefore, a role of vasopressor use in ION remains unclear and no clear guidance with respect to risk of ION can be provided at this time.

A *medical history* of high blood pressure, diabetes, and coronary artery or cerebrovascular disease has been cited in case reports but is not present in all patients in whom ION has developed. Moreover, hypertension and coronary artery disease are nearly always found in patients undergoing CABG but ION develops in few of these patients. No case-control data show an association of these factors with the development of ION in spine surgery patients. Case series show that many perioperative PION patients have few vascular disease risk factors.[107] In a prospective study of nonsurgical patients, ION was not associated with the presence of carotid artery disease.[136] Although a basis for the notion that perioperative ION is related to atherosclerosis is that the optic nerve vasculature would respond abnormally to changes in perfusion pressure (i.e., demonstrate disturbed autoregulation), this association has not been studied in humans, and animal data are sparse and inconclusive.[112]

AION has been described in patients who used *erectile dysfunction drugs.* Cause and effect has been debated,[137] but because of the possible increased risk and unknown impact on events in the perioperative period, it seems sensible to discontinue use of these agents 1 or 2 days before surgical procedures.

Because the sphenoidal sinus and ethmoidal cells are close to the orbit and optic nerve and the bone is fragile, *surgery on the nose and paranasal sinuses* poses a special risk of ocular damage. Retrobulbar hemorrhage may follow surgical damage to the fragile lateral wall of ethmoidal cells, the lamina papyracea. Blindness has occasionally been reported after endoscopic sinus surgery[138] due to direct surgical damage to the optic nerve, but indirect damage by compression from retrobulbar hematoma leading to ION is more commonly reported. Paresis of eye muscles (mostly the medial rectus muscle), including ptosis, is often seen; an ocular compartment syndrome may be present, necessitating immediate surgical decompression to preserve vision.[70] The outcome is poor; in only one case was blindness temporary,[139] whereas all other reported cases of retrobulbar hematoma resulted in permanent blindness. The anesthesiologist should maintain a high degree of vigilance for possible retrobulbar hemorrhage so that, if present, rapid surgical decompression can be accomplished.

In summary, the pathogenesis of perioperative ION is incompletely understood. Multiple factors that could contribute are frequently present in patients undergoing open-heart surgery, spine surgery, or head and neck operations. A patient may have anatomic variation and abnormal autoregulation in the optic nerve, but these anomalies are currently undetectable in the preoperative period. Preexisting as well as intraoperative factors may interact in an unpredictable fashion and lead to ION. Clinicians should be aware of the higher risk of visual loss with prolonged spine surgery with the patient positioned prone and in which large blood loss is anticipated. Although there is concern regarding factors such as blood pressure and fluid resuscitation during lengthy spine surgery, further studies are necessary to gain a better understanding of the mechanisms leading to ION in the perioperative period.

Prognosis, Treatment, and Prevention

Unfortunately, there is no proven treatment of ION. There are a few case reports of the outcome of attempts to treat perioperative ION. Williams and coworkers[102] reviewed the attempted treatments. Acetazolamide lowers IOP and may improve flow to the optic nerve head and retina.[140] Diuretics such as mannitol or furosemide reduce edema. In the acute phase corticosteroids may reduce axonal swelling, but in the postoperative period they increase the risk of wound infection. Because steroids are of unproven benefit, their use must be carefully weighed. Increasing ocular perfusion pressure or hemoglobin concentration may be appropriate when ION is found in conjunction with significant decreases in blood pressure and hemoglobin concentration. Maintaining the patient in a head-up position if increased ocular venous pressure is suspected may be advantageous. But its use has to be balanced against decreased arterial supply with the head-up position. Similarly, IOP should be lowered if an increase is documented. Clearly, if a patient has visual loss from ocular compartment syndrome, immediate decompression (lateral canthotomy) is indicated.

In their review of perioperative PION reports in the literature, Buono and Foroozan summarized the lack of proof that treatment altered the course of PION.[108] In a few anecdotal case reports, increasing blood pressure or hemoglobin, or applying hyperbaric oxygen, improved visual outcome.[103] The use of neuroprotective agents or drugs that lower IOP, valuable in theory, has never been shown to result in improvement.[141] Stevens and associates, who compiled a report of ION in patients after spine surgery, showed apparent improvement of vision in two patients when anemia and hypotension were corrected. One patient demonstrated partial improvement that subsequently regressed, and one patient showed more clear signs of improvement.[3] However, as Buono and Foroozan mentioned, it is difficult to ascertain if improvement came from treatment, because some patients recover vision spontaneously after PION.[108]

Prevention strategies depend on the status of the patient's optic nerve circulation, which is not known preoperatively and which cannot be monitored intraoperatively at present. Some general recommendations could be made for spine surgery, but whether any of these can prevent ION remains unknown at this time.

The head should be positioned neutral relative to the back, and head-down positioning is discouraged. In patients with

poorly controlled hypertension or significant atherosclerosis, maintaining systemic blood pressure near baseline seems sensible. Recommendations to maintain blood pressure have to be weighed against possible surgical needs for deliberate hypotension to decrease blood loss and maintain adequate operative exposure. In cardiac surgery, there are special considerations regarding the optimal systemic perfusion pressures to be maintained during CPB. In addition, it is evident that arterial blood pressure management is only one part of the care of the anesthetized patient, considering, of course, the entire patient and not the optic nerve alone. Increasingly, anesthesiologists are encountering patients whose hypertension is controlled with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, often together with β-adrenergic blockers or calcium channel blockers. These patients frequently become hypotensive intraoperatively, and treatment of hypotension may required.[142] In situations in which blood pressure declines intraoperatively, particularly during spine surgery, vasopressors may be required. Patients may be refractory to ephedrine and Neo-Synephrine and require vasopressin to maintain blood pressure.[142] There are systemic risks of increasing blood pressure with vasoactive agents or by infusion of intravenous fluids, such as decreased renal, liver, and intestinal perfusion, congestive heart failure, and myocardial ischemia. These risks are important considerations in decisions regarding the appropriate range for blood pressure and fluid resuscitation requirements.[143]

Whether hematocrit should be maintained at or near its baseline value is controversial. However, although scientific evidence to guide practice is incomplete, anesthesiologists are advised to be cautious during simultaneous deliberate hypotension and hemodilution to hematocrit less than 25%. Whereas contemporary practice is to conserve blood by initially replacing lost blood with fluids, the effect of such hemodilution will often be a large fluid resuscitation, in some instances further amplifying an already high volume resuscitation, particularly in repeat operations for spine fusion, which typically involve large fluid and blood requirements. A relatively "dry" fluid strategy has been tested in abdominal surgery, but its use is controversial, and outcomes have not been tested in any other surgery.[144] Either earlier blood replacement or greater use of colloids may potentially decrease the volume of infused crystalloids, although the impact of this practice on the occurrence of visual loss is not known. Withholding fluids is inadvisable because of many other risks, including multiple organ failure.[143]

Another strategy not under the direct control of the anesthesia provider is to consider staging of complex spine procedures. However, in some instances the anesthesiologist may be able to persuade a surgeon to follow a less ambitious surgical plan. This decision requires an assessment of the associated risks of multiple surgeries (infection, spinal instability) but may significantly shorten the duration of each procedure. However, ION has still occurred despite use of staging.

A summary of recommendations of the ASA Task Force on Perioperative Blindness that is applicable to patients undergoing spine fusion surgery appears in Box 90-1. The advisory has been endorsed or supported by the North American Neuro-ophthalmological Society and the North American Spine Society.[116]

Whether patients should be warned about the possibility of ION during the process of informed consent, especially those undergoing apparently higher-risk operations such as CABG and complex instrumented spinal fusion surgery, is controversial. The Task Force recommended considering informing high-risk patients, that is, those undergoing prolonged spine fusion surgery with large anticipated blood loss, about this risk.[116] This is difficult to accomplish in the often few rushed minutes of a preanesthetic interview on the day of surgery, typical of modern anesthetic practice in the United States. Accordingly, anesthesiologists may wish to consider requesting that the surgeon discuss the possible complication at an earlier, more relaxed preoperative visit.

Box 90-1 Recommendations of the ASA Task Force on Perioperative Blindness

The consensus of the Task Force is that a high-risk patient's vision should be assessed when the patient becomes alert (e.g., in the recovery room, intensive care unit, or nursing floor). If there is concern regarding potential visual loss, an urgent ophthalmologic consultation should be obtained to determine its cause. Additional management may include optimizing hemoglobin or hematocrit levels, hemodynamic status, and arterial oxygenation. To rule out intracranial causes of visual loss, consider magnetic resonance imaging. The Task Force believes that there is no role for antiplatelet agents, steroids, or intraocular pressure–lowering agents in the treatment of perioperative ischemic optic neuropathy.

- There is a subset of patients who undergo spine procedures while they are positioned prone and receiving general anesthesia who have an increased risk for development of perioperative visual loss. This subset includes patients who are anticipated preoperatively to undergo procedures that are prolonged, have substantial blood loss, or both (high-risk patients).
- Consider informing high-risk patients that there is a small, unpredictable risk of perioperative visual loss.
- The use of deliberate hypotensive techniques during spine surgery has not been shown to be associated with the development of perioperative visual loss.
- Colloids should be used along with crystalloids to maintain intravascular volume in patients who have substantial blood loss.
- At this time there is no apparent transfusion threshold that would eliminate the risk of perioperative visual loss related to anemia.
- High-risk patients should be positioned with the head level with or higher than the heart when possible. In addition, the head should be maintained in a neutral forward position (e.g., without significant neck flexion, extension, lateral flexion, or rotation) when possible.
- Consideration should be given to the use of staged spine procedures in high-risk patients.

Available from http://www.asahq.org/publicationsAndServices/BlindnessAdvisoryFinal.pdf.

Cortical Blindness

Complete cortical blindness is bilateral visual loss with an absence of optokinetic nystagmus and of the lid reflex response to threat.

The pupillary response, eye motility, retina, and optic nerve are normal. Complete blindness implies damage to both the left and right occipital cortex, whereas a more localized injury produces homonymous hemianopia.

Total blindness from bilateral occipital infarction is rare. Because the visual pathway travels through the parietotemporal lobes, a perioperative cerebrovascular accident affecting the internal carotid, or middle, basilar, or posterior cerebral arteries is the more common cause of cortical blindness. Yet because of collateral circulation, the degree of visual damage is difficult to predict.[145] About 80% of cases of cortical blindness postoperatively have followed cardiac or other thoracic surgery. Depending on the sensitivity of the neuropsychological testing, these patients frequently show evidence of postoperative neurologic sequelae.[146]

Initially, total cortical blindness is usually accompanied by signs of stroke in the parieto-occipital region. The patient may suffer agnosia, an inability to interpret sensory stimuli. Often, vision improves over time, with incomplete lesions in the visual field combined with visual disorientation. Pupillary reflexes are preserved and most of the visual field is restored within days, but impairment in spatial perception and in the relationship between sizes and distances may remain. Visual attention may be restricted, and images formed on all parts of retina may not be visualized at one time.

The incidence of cortical blindness after cardiac surgery was 10 in 808 CABG surgeries in one hospital, with brain scans in 5 patients showing occipital infarcts (see Chapter 60).[147] In a retrospective series of 700 CABG surgeries and valve replacements by a single surgeon, 2 patients had unilateral occipital cortical infarcts.[148] Shaw and colleagues[149] prospectively studied 312 patients who had undergone CABG surgery and found a 5% incidence of cortical blindness. At least 50% of the patients had associated neurologic deficits. In another study, the onset of visual deficits followed a time course similar to that of neurologic damage.[150] Among the largest studies of neurologic dysfunction after cardiac surgery is that of Roach and coworkers.[151] In a prospective study of 2108 patients who had CABG at one of 24 different hospitals, incidence of neurologic complications was 6%. Specific incidence of eye complications within this figure was not indicated. Results of subsequent studies are similar and have been reviewed by Newman and associates. Associated factors included age, unstable angina, diabetes, prior stroke or transient ischemic attack, previous CABG surgery, and history of vascular or pulmonary disease.[152] The incidence of visual disorders was not reported in any of these studies.

In case reports of cortical blindness, 55% of cases were reported after CABG surgery and 23% after other thoracovascular operations.[153] Cases have been reported in children. Hypotension was found in 45% of patients and anemia/hemodilution in 23%. Over half the patients had coronary artery disease, but cortical blindness was found in patients with a wide range of systemic disorders, including congenital heart disease, liver failure, postpartum pulmonary embolism, and hypercholesterolemia. Unfortunately, the time of onset of symptoms was not reported in about half the cases. For the remaining 50%, onset was within the first postoperative day. As would be expected, funduscopy was normal in virtually all patients when reported, except one, in whom AION was combined with cortical blindness. Visual defects were bilateral in all but one patient, who had a lesion near the lateral geniculate nucleus. The incidence of other objective neurologic findings was 38%. Confusion was present in 25% of patients. Visual outcome improved in 65% of cases.

Mechanism and Pathophysiology

Cortical blindness can result from global ischemia, cardiac arrest, hypoxemia, intracranial hypertension and exsanguinating hemorrhage, focal ischemia, vascular occlusion, thrombosis, intracranial hemorrhage, vasospasm, and emboli. If blood and oxygen deprivation persists long enough, the cellular energy supply ceases and a series of biochemical events are initiated that ultimately lead to cell death. The pathways responsible for neuronal injury in the cerebral cortex have been reviewed extensively.[154]

CABG surgery is the most common operation associated with cortical blindness, but the pathophysiology of cortical blindness after CABG surgery remains incompletely understood. The major source of brain and visual damage is believed to be embolism from the surgical field, such as fat and atheroma or microemboli of lipid and fibrin-platelet aggregates.[155] A high incidence of emboli in the retinal circulation of patients undergoing CABG surgery has been documented.[156] Patients with aortic atherosclerosis appear to be at particular risk.[151] Cerebral edema also may be responsible for cortical blindness, but a study of MRI of the brain soon after CABG surgery showed cortical swelling within 20 to 40 minutes that was not found on follow-up 1 to 3 weeks later, thus questioning its pathogenic role.[157] Edema may somehow contribute to the vague visual disturbances found in up to 25% of patients after CABG.[158] Another suspected factor is transient decreases in blood flow to border zones of perfusion between the middle and posterior cerebral arteries, especially in patients with preexistent cerebrovascular disease.[159]

Prognosis, Treatment, and Prevention

Visual recovery from cortical blindness may be prolonged, but previously healthy patients are likely to show a considerable degree of recovery. Therefore, when cortical blindness is accompanied by focal neurologic signs, treatment should be directed toward preventing progression of stroke. The optimal strategy to prevent neurologic injury during cardiac surgery remains controversial. Several different techniques have been advocated to decrease intraoperative manipulation of the aorta and embolization.[57,58] Adequate removal of air and particulate matter from the heart during valvular operations may decrease the risk of embolism. In patients younger than 70 years without evidence of cerebrovascular disease, the use of an arterial line filter during CPB significantly reduced the number of microemboli detectable by transcranial Doppler ultrasonography. The frequency of subtle neuropsychological and neurologic changes (including nystagmus) was also reduced. No visual defects were found in the study patients.[160] Maintenance of adequate systemic perfusion pressure may prevent episodes of hypoperfusion in patients with cerebrovascular disease, but no controlled studies have associated visual loss and perfusion pressure in open-heart surgery. The development of better transcranial Doppler techniques may enhance detection of embolic events. As yet, no proven neuroprotective agents whose use is feasible in these patients are available. Nonbypass heart surgery would be expected to avoid, but not eliminate, many embolic complications.[161]

Acute Glaucoma

Acute angle-closure glaucoma is a well-known disease that has been described rarely after general anesthesia. It usually occurs spontaneously and is more common in women and the elderly. Genetic predisposition, a shallow anterior chamber, and increased thickness of the lens are frequently found. The peak age for acute glaucoma is between 55 and 65 years.[162] Three case series in surgical patients have been reported. Gartner and Billet described acute angle-closure glaucoma in 4 of 3437 patients (0.1%) undergoing general or spinal anesthesia.[163] Subsequently, Wang and colleagues reported 5 cases in 25,000 surgical patients (incidence, 0.02%).[164] The highest incidence was found by Fazio and coworkers[165] after reviewing the records of 913 patients who had general or spinal anesthesia. Nine cases were detected, two of which were bilateral (1%). In these studies, no association was made between acute glaucoma and an anesthetic technique or drug.

Acute angle closure results in glaucomatous damage to the optic nerve and occurs when the passage of aqueous humor from the posterior to the anterior chamber is obstructed by apposition of the iris to the anterior surface of the lens. The pupil is mid-dilated, with an associated pupillary block. The diagnosis should be suspected in a patient with a painful red eye and cloudy or blurred vision, possibly accompanied by headache, nausea, and vomiting. This condition is often bilateral. It is distinguished from corneal abrasion, which also produces pain but without the papillary signs, increased IOP, subjective visual loss, and headache.[2] Symptoms may not appear for hours to days after a surgical procedure. Acute glaucoma is an emergency, and ophthalmologic consultation should be obtained immediately. Patients are treated with β-adrenergic antagonists, α-adrenergic agonists, carbonic anhydrase inhibitors, cholinergic agonists, and corticosteroids. Systemic analgesic agents are given as needed. A peripheral iridectomy should be performed later to create a permanent opening between the anterior and posterior chambers.[162]

Visual Changes after Transurethral Resection of the Prostate

Visual changes after transurethral resection of the prostate (TURP) have been recognized for nearly 40 years (see Chapter 65).[166] Changes appear alone or as part of a syndrome after excessive absorption of irrigating fluid (usually 1.5% glycine) with subsequent hyponatremia, cerebral edema, seizures, coma, and cardiac failure from fluid overload.[167] Although utilization of TURP is declining because of economic and regulatory constraints and noninvasive alternatives,[168] complications still occur. Absorption of the irrigant is the major source of nonsurgical complications. Determinants of the amount of irrigant absorbed include the duration of the resection, the extent of the opening of the prostatic venous sinuses, the hydrostatic pressure of the irrigation fluid, and venous pressure at the "irrigant-blood interface."[169] Hamilton-Stewart and Barlow disputed the effect of operative time; they found that a longer resection time did not increase absorption. The veins and capsule of a smaller prostate may be exposed earlier in the resection, so greater absorption during a quick resection leads to the same amount of irrigant absorption as slower absorption during a long resection.[170] Nonetheless, significant quantities of irrigant may be absorbed even if the surgeon believes that no venous sinuses are open, and the operator thus cannot predict or estimate the amount absorbed.

Signs and Symptoms

Visual deficits may occur during the resection, several hours after, or rarely on the second postoperative day as the patient awakens from a TURP-related coma.[171] The range of signs and symptoms is wide, from complete loss of light perception to more subtle defects. The first complaint may be visual halos and a blue visual hue.[172] Dilated pupils that are nonreactive to light, a normal IOP, normal extraocular muscle movement, and normal fundus examination without evidence of papilledema are the objective findings in these cases.[172] Visual changes may resolve over a few hours or persist for up to 80 hours.[171] Permanent visual loss has not been reported.

Mechanisms of Visual Dysfunction

Proposed mechanisms of the visual changes include cerebral edema,[173] glycine toxicity involving the retina and cerebral cortex,[172] ammonia toxicity,[174] and increased IOP.[175] Glycine, the smallest amino acid, enters cells primarily through a carrier-mediated process, but its rate of transport is relatively slow. It easily crosses the blood-brain barrier, and it depresses the spontaneous and evoked activity of retinal neurons and hyperpolarizes cells through blockade of chloride channels.[176] The highest glycine concentration is in the amacrine cells, inner plexiform, and ganglion cell layers of the retina.[177] Because of a profound effect on oscillatory potentials of the electroretinogram, the predominant site of action may be amacrine cells,[178] although other inner retinal cells are probably involved. Glycine altered visual evoked potentials in dogs and in humans, thus suggesting an effect on the optic nerve. The threshold for visual symptoms is a plasma glycine concentration over 4000 μmol/L.[179]

Hyponatremia/hypo-osmolality during TURP produces occipital cortical edema, but such an association has not been confirmed. Segmental vascular disease in the blood supply to the occipital cortex may have placed that portion of the brain at risk for swelling.[167] Ocular hypertension causes enlarged blind spots and paracentral scotoma. In the presence of water overload, it seemed logical that an increase in IOP is part of the TURP syndrome. Yet in a prospective study of 22 patients who had TURP, Peters and colleagues found no change in IOP in the patients with visual changes.[175] Such changes after TURP are transient and often associated with TURP syndrome. The most important means of prevention is to maintain intense vigilance to avoid excessive absorption of irrigating solution.

Visual Loss after Vitrectomy and Vitreal Gas Bubble Tamponade

Patients who have undergone vitrectomy with perfluorocarbon gas tamponade (C_3Fl_8) are at risk of gas bubble expansion and loss

of vision from acutely increased IOP (see Chapter 75). Patients anesthetized for a subsequent surgical procedure with gas mixtures containing N_2O after vitrectomy sustained retinal vascular occlusion from acute gas bubble expansion. N_2O anesthesia affects the size of the intraocular gas bubble. Wolf and coworkers showed that N_2O and oxygen resulted in a more than threefold increase in SFl_6 gas bubble volume, compared with a 50% increase with air ventilation and 35% increase with oxygen ventilation alone.[180] Perfluorocarbon gas remains in the eye for at least 28 days. Visual loss has been reported with N_2O anesthesia administered as long as 41 days after vitrectomy and gas bubble tamponade. Therefore, patients should wear a warning tag to alert the anesthesiologist to the presence of the gas bubble in the vitreous, and N_2O should not be used in patients who have had recent vitrectomy and gas bubble tamponade.[181,182]

Conclusion

Visual loss can result in the perioperative period from retinal arterial occlusion, ION, cortical blindness, or acute glaucoma. Visual loss after TURP is transient; visual loss in patients anesthetized with N_2O after a vitrectomy and placement of a gas bubble tamponade may be permanent. The most serious injuries that are likely to result in blindness are retinal arterial occlusion and ION. Even if unintended pressure on the eye is avoided, these complications may still occur, particularly after spine, cardiac, or head and neck surgery. The risk factors for ION in particular remain incompletely explained.

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Linda Liu and Michael A. Gropper

91 Overview of Anesthesiology and Critical Care Medicine

Key Points

1. By the year 2030, only 35% of the intensivists needed will be available to staff intensive care units.
2. Mandatory intensivist consultation may reduce intensive care unit mortality by as much as 29%.
3. Cortisol replacement, tight glycemic control, and activated protein C are actively being studied in randomized controlled trials as therapy for sepsis.
4. Patients with acute lung injury or acute respiratory distress syndrome should be mechanically ventilated with tidal volumes of 6 mL/kg of ideal body weight.
5. Without liver transplantation, mortality from acute liver failure is high and mainly due to multisystem organ failure, sepsis, and cerebral edema.
6. Earlier institution of dialysis and higher filtration volumes appear to be associated with reduced mortality among patients with acute renal failure.
7. Quality improvement initiatives can reduce nosocomial infections, mortality, and cost.
8. Proposals to prevent ventilator-associated pneumonia include maintenance of gastric pH with sucralfate, positioning the head of the bed at 30 degrees, and subglottic aspiration of secretions.
9. A comprehensive approach to central venous catheter insertion, including ultrasound guidance, maximum sterile barrier precautions, and antibiotic-coated catheters, can reduce the rate of catheter-related bloodstream infections.

The practice of critical care medicine, which originated in the 1940s with anesthesiologists providing life support to patients with polio, has undergone revolutionary changes. The development of new equipment, procedures, and medications has enabled intensivists to treat critically ill patients and support them through increasingly invasive procedures. In the past decade, another revolution has taken place, the introduction of evidence-based medicine into intensive care unit (ICU) practice. In this chapter we discuss the structure of ICU staffing, including studies examining the value of intensivist staffing. We then review how intensivist staffing may lead to improved outcomes, specifically through the implementation of evidence-based practice. Particular attention is paid to the implementation and cost-effectiveness of new clinical practices. Finally, we review the management of some common diagnoses that are encountered while caring for critically ill patients.

Intensive Care Unit Organization

With an aging population and increasing availability of medical technology, ICUs have become a critical component of modern hospital care. It is estimated that 0.5% to 1% of the U.S. gross domestic product is spent on critical care.[1] Given the magnitude of this expense, extensive research has focused on how the most cost-effective care can be delivered. Although ICUs started as open wards where any physician could admit patients, they have increasingly become managed. Most ICUs now have a designated medical director who is responsible for overall management of patient care and policies.

Role of the Medical Director

Each ICU should have a physician who is board certified or board eligible in critical care medicine to function as medical director.[2] The role of the medical director is to ensure the quality and safety of patient care in the ICU. Responsibilities often include patient triage decisions, education of house staff, development of clinical protocols, and improvement of performance. Anesthesiologists frequently serve as medical directors, primarily of surgical ICUs. As hospital-based physicians, anesthesiologists are particularly well placed to appreciate the issues that affect patient care and efficient flow of patients from operating rooms through the ICUs. In 1994, the Society of Critical Care Medicine described the seven organizational duties of an ICU administrator[3]:

1. Triage of admissions and discharges
2. Development of treatment protocols or guidelines
3. Collection of data
4. Involvement in unit budget approval
5. Updating of equipment and unit practices
6. Promotion of efficient use of material and personnel resources
7. Responsibility for coordination and dissemination of continuing education of hospital- and ICU-based personnel

Because of the increasing importance of the medical director and the time commitment required, salary support should be provided by the hospital to allow adequate investment of time in the position.

Staffing

The Committee on Manpower for Pulmonary and Critical Care Societies (COMPACCS) was commissioned by the American Thoracic Society, the American College of Chest Physicians, and the Society of Critical Care Medicine to determine current patterns of care of critically ill patients. More specifically, the committee examined the current and projected demand for critical care services and the supply of physicians based on current supply and training. The survey identified that intensivists provided care to 37% of all ICU patients in American hospitals in 1997.[4] The demand for intensivists is expected to increase, with supply being equal to 35% of demand by the year 2030 (Fig. 91-1). Table 91-1 describes the contribution of various specialties in providing critical care services.

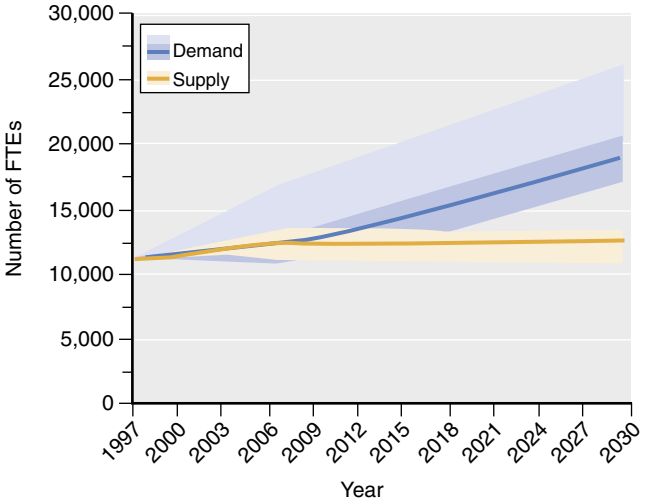

Figure 91-1 Forecast of supply and demand for intensivists through 2030. FTE indicates full-time equivalent. The *lines* represent the base model, whereas the margins of the *shaded areas* represent the widest upper and lower bounds of the sensitivity analysis. *(From Angus DC, Kelley MA, Schmitz RJ, et al: Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease. Can we meet the requirements of an aging population? JAMA 284:2762-2770, 2000.)*

Anesthesiologists in Critical Care Medicine

Although anesthesiologists originated critical care medicine, they represent a shrinking percentage of critical care physicians. The COMPACCS survey, performed between 1996 and 1999, found that anesthesiologists accounted for only 6.1% of all intensivists in the workforce,[4] even though they are particularly well trained to manage critically ill patients and do so on a regular basis in the operating room. A number of factors, however, have led to diminishing numbers of anesthesiologists practicing in the ICU. This trend comes at a time when there is an increasing need for intensivists. The most recent data available from the Accreditation Council for Graduate Medical Education show that there are 53 anesthesia trainees in 52 critical care medicine fellowships whereas there are 1087 pulmonary/critical care medicine trainees in 128 fellowships.[5]

The reason for decreasing representation of anesthesiologists in critical care is multifactorial. Reimbursement for critical care services is generally less than that for surgical anesthesia services. Subspecialty training in critical care medicine for anesthesiologists creates a unique situation in which additional subspecialty training results in lower compensation. In Europe, where there is not such a payment discrepancy between the operating room and the ICU, anesthesiologists provide the majority of critical care services.[6] The American Board of Anesthesiology and American Society of Anesthesiologists have begun to address the diminishing role of anesthesiologists in critical care medicine. Proposed changes include an increasing component of training in critical care medicine during anesthesia residency. There are also proposals for "experimental residencies" that will offer training for anesthesia and critical care concurrently in a blended residency/fellowship.

Rapid-Response Teams

Rapid-response teams (RRTs) were initially developed to identify and treat patients exhibiting physiologic deterioration on the general care hospital floor. The premise was that if appropriate intervention could be initiated early enough, a critical event such as cardiac or respiratory arrest could be prevented. RRT programs can consist of a myriad of personnel ranging from physicians, nurses, and respiratory therapists to pharmacists. A large number of articles have been published on RRT programs, but most are descriptive. Only a handful have compared outcomes between control and intervention groups.[7] Among the five observational studies that examined in-hospital mortality after institution of an RRT program, two studies reported a statistically significant improvement in mortality,[8,9] two had a lower but nonstatistically significant reduction in mortality,[10,11] and one reported equivocal data.[12] Of the two randomized studies looking at in-hospital mortality and RRT programs, one based from a single institution found a significant result favoring RRT programs (odds ratio of mortality, 0.52; 95% confidence interval [CI], 0.32 to 0.85),[13] but the larger multicenter study was unable to show a significant benefit (odds ratio of mortality, 1.03; 95% CI, 0.84 to 1.28).[14]

Despite the paucity of existing data, several organizations have advocated the implementation of RRT programs. The Institute for Healthcare Improvement added RRT programs as one of its six interventions for the 100,000 Lives Campaign,[15] and the

Table 91-1 Characteristics of the Critical Care and Pulmonary Specialist Workforce

Characteristic	Pulmonary*	Internal Medicine†	Anesthesiology	Surgery	All
Total number (%)	8080 (78.9)	1220 (11.9)	620 (6.1)	324 (3.2)	10,244
Mean age (yr)	48.9	42.1	44.8	43.3	47.7
Number of women (%)	727 (9.0)	144 (11.8)	61 (9.8)	45 (13.8)	977 (9.5)
Base specialty certification (%)	86.1	91.6	99.2	94.9	87.8
Critical care certification (%)	50.2	65.6	59.9	80.5	53.2
Type of practice group (%)					
University affiliated	13.4	13.9	35.4	46.0	15.7
Private solo or single specialty	50.8	47.6	50.0	31.7	49.9
Private multispecialty	21.7	26.0	6.2	3.7	20.8
Hospital or health maintenance organization	9.4	5.4	8.0	11.5	9.0
Other‡	4.6	7.2	0.4	6.0	4.7

*Includes physicians whose only specialty practice was pulmonary medicine and physicians who practiced both pulmonary and critical care medicine.
†Includes internal medicine physicians who practice critical care but do not practice pulmonary medicine.
‡Includes Veterans Affairs staff.
Data from Angus DC, Kelley MA, Schmitz RJ, et al: Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: Can we meet the requirements of an aging population? JAMA 284:2762-2770, 2000.

Joint Commission on Accreditation of Healthcare Organizations is making RRT programs one of its patient safety goals.[16] Many hospital organizations have invested in these teams because of public scrutiny of patient safety. The critical care service is most often asked to staff these teams, and they represent an opportunity for anesthesia critical care providers.

Although the rationale behind RRT programs seems logical, other approaches to achieve the same end point may be equally or more cost-effective. The presence of hospitalists, nurse practitioners, nurses, physician assistants, or automated monitoring systems may be viable alternatives.[7] It could also be that the benefit of the RRT program lies not in the availability of the team but rather in education of staff on how to recognize physiologic deterioration and a patient who is in trouble.[17] Ultimately, each institution needs to critically review its own system for taking care of patients deteriorating on the medical or surgical floor and determine what interventions would be the most beneficial for its patients.

Structure: Open versus Closed Intensive Care Units

ICUs are typically described by their patient population (i.e., medical or surgical), and they are now described by their staffing structure (i.e., open or closed). Most ICUs in the United States are classified as open, which means that a variety of physicians admit patients to the ICU, where they are cared for by their primary physician, with or without the assistance of a critical care specialist. The increasing complexity of caring for critically ill patients, however, has led to recognition of the need for dedicated critical care specialists.

The COMPACCS survey classified ICUs in four categories:

1. ICUs with full-time intensivists, where all or most care is delivered by the intensivist in a role greater than that of a consultant
2. The consultant intensivist model, whereby an intensivist serves as consultant but does not have primary responsibility for patients
3. ICUs with multiple consultants, wherein multiple consultants serve the patient (e.g., a pulmonologist may provide ventilator management) but no one physician is identified as an intensivist consultant
4. The single-physician model, in which the primary physician provides all the care in the ICU without consultation from an intensivist or other consultants

ICUs in larger hospitals tend to have full-time intensivists, with smaller community hospitals more likely to use the single-physician model.[18] The reasons for this tend to be economic inasmuch as smaller ICUs may not have adequate patient volume to support a full-time intensivist. What is the evidence that a particular ICU structure improves patient outcomes? Many studies are small, retrospective reviews of the impact of the addition of an intensivist to an existing ICU. For example, Carson and colleagues[18] performed a prospective cohort study of a single ICU that made the transition from an open to a closed form. They found that risk-adjusted mortality scores decreased in the closed ICU despite higher severity of illness and without additional resource use. Ghorra and coworkers[19] showed in a retrospective review comparing two time periods that mortality and complications were decreased when their open surgical ICU was converted to a closed model. These two studies suggest that there may be an advantage to a closed ICU structure, but a truly randomized, prospective study comparing open with closed ICUs has never been completed.

Rather than "open" versus "closed" ICU structure, the probable determinant of quality care is the presence of intensiv-

ists to implement patient safety and quality programs that reduce patient harm and, in return, improve efficiency. This structure leverages all the personnel present in the ICU to improve outcomes.[20]

The Leapfrog Group Recommendations

Despite the lack of definitive data about the preferred structure of ICUs, there is much more evidence supporting the role of the intensivist in the management of critically ill patients. For general and subspecialty patient populations, most studies suggest that critically ill patients should be cared for by an intensivist. For example, Pronovost and associates[21] studied whether the organizational characteristics of ICUs could influence outcome in patients undergoing surgery for an abdominal aortic aneurysm. They analyzed almost 3000 patients who underwent repair in the state of Maryland and found that in risk-adjusted patients, not having daily ICU rounds by an intensivist was associated with a threefold increase in mortality.[21] In addition to increased mortality, the patients not seen by an intensivist also had an increased risk for cardiac arrest, renal failure, septicemia, platelet transfusion, and reintubation.

In a large meta-analysis examining physician staffing and outcomes of critically ill patients, Pronovost and colleagues[6] compared "low-intensity" ICU staffing consisting of no or elective intensivist consultation with "high-intensity" staffing consisting of mandatory intensivist consultation or a closed ICU. This study found that the relative risk for hospital mortality was reduced by 29% and the relative risk for ICU mortality was reduced by 39% with high-intensity staffing. Table 91-2 demonstrates the overall impact of intensivist staffing on ICU mortality. This and other studies have led to significant consumer and regulatory pressure mandating that intensivists staff all ICUs. The Leapfrog Group (www.leapfroggroup.org) was established by the Business Roundtable, which consists of the chief executive officers of several large corporations. These corporations purchase health insurance for more than 34 million health care consumers and therefore have considerable influence on health policy. The Business Roundtable established the Leapfrog Group to "work with medical experts throughout the United States to identify problems and propose solutions that it believes will improve hospital systems that could break down and harm patients." One of the first recommendations by this group was that trained intensivists should staff ICUs. Although this recommendation has a strong evidence base, the other Leapfrog recommendations are not as strongly supported.[29] In addition to the factors discussed earlier, these pressures will create a significant demand for trained intensivists.

Despite evidence supporting intensivist staffing of ICUs, the number of intensivists from all areas of training is inadequate to meet this mandate. Recognition of this shortage has led to innovations such as the "eICU," whereby a small number of intensivists can monitor and consult on a large number of ICU beds from a remote location. Indeed, the eICU is stated to meet the requirements of the Leapfrog Group.

Table 91-2 Impact of Intensivist Staffing on Intensive Care Unit Mortality

Source	Risk Ratio	95% Confidence Interval
Brown and Sullivan[22]	0.48	0.32-0.72
Baldock et al.[23]	0.69	0.52-0.91
Kuo et al.[24]	0.60	0.49-0.73
Ghorra et al.[19]	0.42	0.20-0.90
Manthous et al.[25]	0.71	0.54-0.94
Pollack et al.[26]	0.53	0.17-1.64
Rosenfeld et al.[27]	0.15	0.05-0.50
Goh et al.[28]	0.38	0.27-0.53

Data from Pronovost PJ, Angus DC, Dorman T, et al: Physician staffing patterns and clinical outcomes in critically ill patients: A systematic review. JAMA 288:2151-2162, 2002.

Table 91-3 Levels of Evidence

Level	Description
1a	Systematic review of randomized, controlled trials (with homogeneity)
1b	Individual randomized, controlled trial with a narrow confidence interval
1c	All-or-none trial*
2a	Systematic review of cohort studies (with homogeneity)
2b	Individual cohort study (including low-quality randomized, controlled trials)
2c	"Outcomes" research
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series (and poor-quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles"

*Met when all patients died before the treatment became available but some now survive with it or when some patients died before the treatment became available but none now die with it.
Levels of evidence were provided by the Centre for Evidence-Based Medicine, Oxford, UK. Available at http://www.cebm.net/levels_of_evidence.asp/ Accessed December 25, 2003.

Quality Measurement in Critical Care

Quality of Evidence

To determine the value of a clinical intervention, it is important to evaluate the quality of the study on which it is based. A number of groups have developed criteria with which evidence can be graded. The Oxford Centre for Evidence-Based Medicine has strict criteria for grading the level of evidence. These criteria are described in Table 91-3. After the evidence level has been determined, specific practices can be graded by using the previously

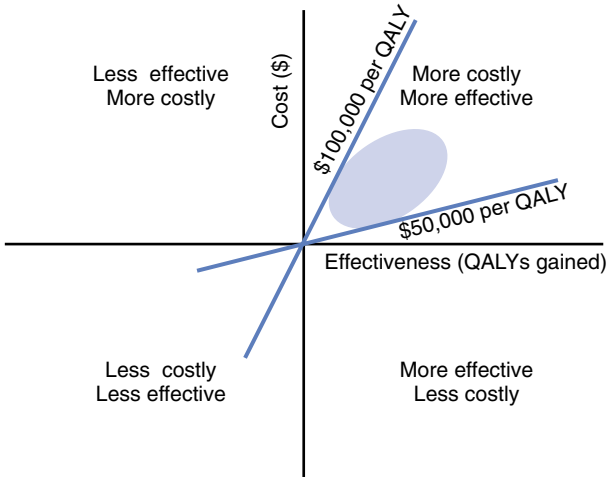

Figure 91-2 Graphic display of the cost-effectiveness of a theoretical treatment that adds additional cost but is effective in extending quality-adjusted life. A quality-adjusted life-year (QALY) is a year of life gained for which the quality of life is judged to be acceptable. The *lines* represent cost per QALY. Cost per QALY depends on the patient population that receives the intervention. For example, patients with a low severity of illness receiving activated protein C have a much higher cost per QALY than do those with a higher severity of illness.

described criteria. Only through rigorous clinical experimentation can we determine practices that will improve the outcomes of critically ill patients. Equally important is analysis of the cost-effectiveness of these interventions. Implementation may require fiscal and personnel expenditure, and it is the role of the medical director to convince hospital administrators of the cost-effectiveness of new interventions. Figure 91-2 describes the cost-effectiveness relationship for a theoretical treatment.

Care of critically ill patients has been revolutionized by technology and drug development, but an equally important contribution has come with the application of evidence-based medicine to critical care practice. Although critical care initially focused on trying to restore homeostasis, there is increasing recognition that normal physiology is not always the most desirable therapeutic target. An important example of this principle is found in the management of patients with acute respiratory distress syndrome (ARDS). When patients with ARDS are mechanically ventilated with higher tidal volumes (12 mL/kg ideal body weight), they improve their oxygenation ratio.[30] However, these patients had significantly higher mortality rates than those mechanically ventilated with lower tidal volumes (6 mL/kg ideal body weight). This example and others illustrate the need for randomized, prospective trials of new and existing therapies.

Implementation of Evidence-Based Practice

Application of evidence-based practice resulting in protocols to standardize patient care has been shown to improve the efficiency of care and reduce resource use.[31,32] Hospitals must customize the protocols to fit their practice, but protocols should not be used in place of good clinical judgment. They should be used as a complementary tool, and physicians should be able to justify departures from the protocol. These departures should be used to further refine the protocol so that it is not viewed as a static entity, but rather as an evolving guideline.[33] For protocols to be effective, the hospital must be willing to invest the resources necessary for implementation, such as providing adequate staffing. For example, inadequate nurse-to-patient ratios have been associated with a longer period of mechanical ventilation for patients.[34] Key personnel such as physicians, respiratory therapists, and nursing staff should be enlisted so that the entire patient care team helps define the standards on which the protocol is based.

Perhaps the most difficult task in the application of evidence-based practice is determining whether a given patient with a particular clinical scenario will benefit from that practice. Are there pathophysiologic differences in a particular patient's illness that may lead to a diminished treatment response? Are there important differences in systems or provider compliance that may diminish the safety or efficacy of the treatment? Does a patient have comorbid conditions that would lead to exclusion from a clinical trial? Despite these limitations, when applied to large populations of patients, these practices decrease mortality and usually reduce cost.

Severity-of-Illness Scoring Systems

Over the past 20 years, numerous efforts have been made to design a model that can objectively quantify physiologic derangements and comorbid conditions to estimate mortality, length of stay, and ICU resource use. The systems allow comparison between groups of patients and provide a means to adjust for differences between groups in nonrandomized or observational studies. Most models estimate the risk for hospital mortality from clinical variables measured near or at the time of ICU admission. Among the scoring systems, the most accepted and used in clinical studies are the Acute Physiology and Chronic Health Evaluation (APACHE), the Simplified Acute Physiology Score (SAPS), and the Mortality Prediction Model (MPM). These scoring systems and the variables measured are listed in Table 91-4.

Acute Physiology and Chronic Health Evaluation Scoring System

The APACHE system was the first illness severity model widely used by ICUs. It was developed in the early 1980s and involved a complex measure of 34 physiologic variables and a chronic health evaluation.[35] The score correlated well with mortality, but it was difficult to administer and complex to score. APACHE II was developed as a simplification of the first version and uses only 12 physiologic variables, patient age, and chronic health evaluation.[36] A 1-point increase in score equates to an increase of about 1% in mortality, but it cannot be transformed to a specific risk for death because the scoring system does not take into account the admission diagnosis. For example, an asthmatic with a score of 25 has mortality different from that of a patient with severe sepsis and the same score.[37] APACHE III was developed in 1991 and now includes weighting for ICU readmission, patient location, and hospital length of stay before ICU admission.[38] The score also consists of points for 17 physiologic abnormalities, age, and chronic health evaluation. This system is complex, more difficult to administer, and proprietary.

Simplified Acute Physiology Score

First reported in 1984, the variables collected for SAPS represent the most deranged values in the first 24-hour period in the ICU.

Table 91-4 Description of Scoring Systems

APACHE II Score = Acute Physiology Score + Age Points + Chronic Health Points									
	+4	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**
Rectal temperature (°C)	≥41	39-40.9		38-38.9	36-38.4	34-35.9	32-33.9	30-31.9	<29.9
MAP (mm Hg)	>160	130-159	110-129		70-109		50-69		<49
HR (beats/min)	>180	140-179	110-139		70-109		55-69	40-54	<39
RR (beats/min)	>50	35-49		25-34	12-24	10-11	6-9		<5
O_2 delivery (mL/min)	>500	350-499	200-349		<200				
Po_2 (mm Hg)					>70	61-70		55-60	<55
pH	>7.7	7.6-7.69		7.5-7.59	7.3-7.49		7.25-7.3	7.15-7.2	<7.15
Na	>180	160-179	155-159	150-154	130-149		120-129	111-119	<110
K	>7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Cr	>3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hct	>60		50-59.9	46-49.9	30-45.9		20-29.9		<20
WBC count	>40		20-39.9	15-19.9	3-14.9		1-2.9		<1

Age	**Points**
<44	0
45-54	2
55-64	3
65-74	5
>75	6

History of Severe Organ Insufficiency	**Points**
Nonoperative patients	5
Emergency postoperative patients	5
Elective postoperative patients	2

Organ Insufficiency or Immunocompromised State (Must Have Preceded the Current Admission)

Immunocompromised If:	**Hepatic Insufficiency If:**	**Cardiovascular Insufficiency If:**	**Respiratory Insufficiency If:**	**Renal Insufficiency If:**
• Receiving therapy reducing host defenses (immunosuppression, chemotherapy, radiation therapy, long-term steroid use, high-dose steroid therapy) • Has a disease interfering with immune function, such as malignant lymphoma or leukemia	• Biopsy-proven cirrhosis • Portal hypertension • Episodes of upper GI bleeding caused by portal hypertension • Prior episodes of hepatic failure, coma, encephalopathy	• New York Heart Association class IV	• Severe exercise restriction secondary to chronic restrictive, obstructive, or vascular disease • Documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension • Ventilator dependency	• Maintained on chronic dialysis

SAPS Scoring System—Variables to Measure (Use the Worst Value in 24 Hours)

Type of admission (unscheduled surgery, medical, scheduled surgery)
Chronic disease (none, metastatic cancer, hematologic malignancy, AIDS)
Glasgow Coma Scale score
Age
Systolic blood pressure
Heart rate
Temperature
Pao_2/Fio_2 ratio

Table 91-4 Description of Scoring Systems—cont'd

SAPS Scoring System—Variables to Measure (Use the Worst Value in 24 Hours)
Urine output
Blood urea nitrogen
WBC count
Potassium
Sodium
Serum bicarbonate
Bilirubin
MPM II Scoring System—Variables to Measure at Admission (Scored As 1 for "Yes," 0 for "No")
Type of admission (medical or unscheduled surgical admission)
Metastatic neoplasm
Cirrhosis
Chronic renal insufficiency
CPR before admission
Glasgow Coma Scale score of 3-5
Heart rate ≥150 beats/min
Systolic blood pressure ≤90 mm Hg
Acute renal insufficiency
Cardiac dysrhythmia
Cerebrovascular incident
Gastrointestinal bleeding
Intracranial mass effect
Mechanical ventilation
Age

AIDS, acquired immunodeficiency syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; CPR, cardiopulmonary resuscitation; Cr, creatinine; GI, gastrointestinal; Hct, hematocrit; HR, heart rate; MAP, mean arterial pressure; MPM, Mortality Prediction Model; RR, respiratory rate; SAPS, Simplified Acute Physiology Score; WBC, white blood cell.

Its second iteration, SAPS II, was published in 1993.[39] This score is composed of 12 physiologic variables, patient age, type of admission, and variables related to specific diseases such as hematologic malignancy, metastatic cancer, and acquired immunodeficiency syndrome. Unlike APACHE, the variables used in SAPS are readily available, and the calculations are simple. However, similar to APACHE, there is no correction for the patient's admitting diagnosis.[37]

Mortality Prediction Model

The most recently developed scoring system, MPM II, is less physiologically based than APACHE or SAPS. Each variable is entered as present or absent ("1" or "0"), except age, which is entered in years. The scoring system was designed to estimate mortality risk at 24 and 48 hours after ICU admission, so it gives a revised risk based on the patient's response to resuscitation and early treatment.[40]

Accuracy of Scoring Systems

There are subtle differences between APACHE, SAPS, and MPM in terms of their ability to predict mortality, but no data suggest that one system is substantially better than the others.[41,42] In comparison to a physician's clinical judgment, the data are mixed. Some studies favor the clinician,[43] whereas others favor the scoring system.[44,45] Overall, neither physicians nor scoring systems are sufficiently accurate to rely on these predictions in triage or end-of-life decisions. The scoring systems facilitate comparisons across ICUs and patient populations and allow us to characterize and stratify a patient population for research purposes. They cannot be used for decision-making in individual patients because the systems were designed to predict outcome in a population of patients. If the probability of mortality is 0.53, it means that 53 of 100 patients will be expected to die, but the scoring systems cannot distinguish which individual patient will be in the 53 who will die or the 47 who will live.

Organ Dysfunction Scores

Organ dysfunction scores may be measured daily, unlike prognostic models, which are usually performed near or at the time of ICU admission. They have the ability to capture the dynamic nature of a patient's clinical course in the ICU. These scores and the measured variables are listed in Table 91-5.

Sequential Organ Failure Assessment Score

Developed in 1994 initially as a sepsis-related organ failure assessment, the Sequential Organ Failure Assessment (SOFA) score was renamed when it was found to be applicable to nonseptic patients.[46] This system includes six organ systems (pulmonary, hematologic, hepatic, cardiovascular, central nervous, and renal), records the most abnormal value on each day, and scores the abnormality from 1 (normal) to 4 (most abnormal).

Multiple Organ Dysfunction Score

Published in 1995, the Multiple Organ Dysfunction Score (MODS) includes six organ systems, records the most representative value of the day, and scores the abnormality from 0 (normal) to 4

Table 91-5 Sequential Organ Failure Assessment (SOFA) and Multiple Organ Dysfunction Score (MODS) Scoring Systems

SOFA Scoring System				
Variable	**1**	**2**	**3**	**4**
Pao_2 (mm Hg)	<400, ± MV	<300, ± MV	<200, + MV	<100, + MV
Platelet count ($10^3/mm^3$)	<150	<100	<50	<20
Cardiovascular	MAP <70 mm Hg	Dopa/dobutamine ≤5 μg/kg/min	Dopa >5 μg/kg/min, Epi/NE ≤0.1 μg/min	Dopa >15 μg/kg/min, Epi/NE >0.1 μg/min
Glasgow Coma Scale score	13-15	10-12	6-9	<6
Bilirubin (mg/dL)	1.2-1.9	2-5.9	6-11.9	> 12
Cr (mg/dL) or UO	1.2-1.9	2-3.4	3.5-4.9 or <500 mL/day	>5 or <200 mL/day

MODS Scoring System					
Variable	**0**	**1**	**2**	**3**	**4**
Pao_2/FIo_2	>300	226-300	151-225	76-150	≤ 5
Platelet count ($10^3/mm^3$)	>120	80-120	50-80	21-50	≤20
Bilirubin (mg/dL)	≤1.2	1.2-3.5	3.5-7.0	7.0-14	≥14
HR × CVP/MAP	≤10	10.1-15	15.1-20	20.1-30	>30
Glasgow Coma Scale score	15	13-14	10-12	7-9	≤6
Cr (mg/dL)	≤1.1	1.1-2.3	2.3-4	4.0-5.7	>5.7

Cr, creatinine; CVP, central venous pressure; Dopa, 3,4-dihydroxyphenylalanine; Epi, epinephrine; HR, heart rate; MAP, mean arterial pressure; MV, mechanical ventilation; NE, norepinephrine; UO, urine output.

(abnormal).[47] MODS uses a pressure-adjusted heart rate rather than the dose of vasoactive agents administered, as used in the SOFA score. Another difference between scores is that SOFA uses urine output as the measure of renal dysfunction whereas MODS uses serum creatinine.

Accuracy of Organ Dysfunction Scores

Both organ failure measures (SOFA and MOD) give a more complete picture of the entire ICU course as opposed to the first 24 hours after admission. A potentially important application for organ dysfunction scores is their ability to capture the impact of a therapeutic intervention. For example, Vincent and colleagues[48] demonstrated more rapid resolution of cardiovascular dysfunction in patients who received drotrecogin alfa (activated) than in the group that received placebo. These scoring systems may also be used in innovative ways to predict long-term morbidity and help us move beyond survival as the sole measure of ICU outcome.

Management of Critically Ill Patients

The following sections examine the care of patients with some common diagnoses in critical care: sepsis, ARDS, renal failure, and hepatic failure. Many management plans have data supporting the use of protocol-base therapy. Several of these protocols are discussed in detail in Chapter 92. Others are introductory management ideas that may lead to integration into future protocols but are discussed here because of their importance in critical care.

Sepsis and Multisystem Organ Failure

Sepsis is the leading cause of death in critically ill patients in the United States and develops in 750,000 people annually.[1] Mortality from severe sepsis has remained steady at 30% to 50% despite improvements in critical care, including those discussed in this chapter.[49,50] The economic costs of sepsis are large, with annual expenditures totaling nearly $17 billion.[1] The high mortality rate and economic costs have led to considerable interest in the development of effective therapies for sepsis. As with other areas of medicine, adoption plus integration of new treatment strategies into routine clinical practice has been slow. After many years of unsuccessful clinical trials, randomized, controlled trials have begun to show efficacy. We now discuss three areas that have been intensively studied: cortisol replacement, tight glucose control, and activated protein C (APC).

Cortisol Replacement

With the recognition that severe sepsis represents a state of overwhelming inflammation, corticosteroids were among the first therapies tested in randomized trials of patients with sepsis. At large doses and with short courses, the studies showed a negative effect.[51,52] The adverse effects from large-dose steroids, commonly 30 mg/kg methylprednisolone, were an increased incidence of

gastrointestinal bleeding, secondary infections, and steroid psychosis. Annane and coworkers proposed a different hypothesis in 2002.[53] Prompted by studies showing significantly improved time to withdrawal of vasopressor therapy in patients with sepsis who received small doses of hydrocortisone over a longer period (>5 days),[54,55] they administered low-dose steroids for 7 days. All patients with septic shock received a short corticotropin test and then were randomized to receive hydrocortisone, 50 mg every 6 hours, plus fludrocortisone, 50 μg/day, or placebo. Their results showed that among patients who did not respond appropriately to the short corticotropin test, 63% in the placebo group versus 53% in the corticosteroid group died (P = .02). Vasopressor therapy was withdrawn in 40% of patients in the placebo group as opposed to 57% in the corticosteroid group (P = .001). Although there was no difference in adverse events between the groups, a slight, but not statistically significant trend toward increased mortality was noted in patients who did not have adrenal insufficiency as determined by the corticotropin test but who did receive glucocorticoids.[56]

Administration of steroids to patients with sepsis remains controversial. A large randomized trial recapitulating the study of Annane and coworkers has been completed and documents the lack of efficacy of even low-dose steroids and the association of increased infections with steroid administration.[56] The Corticosteroid Therapy of Septic Shock (CORTICUS) study was carried out to assess whether low-dose corticosteroids improve survival in patients with septic shock and sepsis. A total of 499 patients were enrolled over a period of 3 years from 52 European ICUs.[56] Patients received a tapering steroid regimen over an 11-day period, but no mineralocorticoids. The results were disappointing. The 28-day mortality rate in patients receiving low-dose steroids was not significantly improved from that in the placebo group (34% versus 31%, P = .57).[58]

In summary, large doses of corticosteroids should not be used in patients with severe sepsis. Although it initially appeared that low-dose steroids with mineralocorticoids may be beneficial, the results have not been reproducible in a large multicentered randomized study. One issue raised by these investigations was the role of etomidate in causing adrenal suppression. Patients who received etomidate for endotracheal intubation had worse outcomes, thus leading to suggestions that either etomidate not be used or if it is used, steroid replacement for several days be considered.[57]

Glycemic Control in the Critically Ill

Critically ill patients admitted to the ICU with severe injury or infection, such as burns, trauma, or sepsis, commonly enter into a hypermetabolic state. This state is associated with enhanced peripheral glucose uptake and use,[59] hyperlactatemia,[60] increased glucose production,[61] depressed glycogenesis,[62] and insulin resistance.[61] Glucose intolerance develops after uptake of glucose in skeletal muscle, adipose tissue, liver, and the heart becomes saturated,[63] and hyperglycemia occurs because of defective suppression of gluconeogenesis and resistance to the peripheral action of insulin. These mechanisms all work to generate a hyperglycemic state to satisfy an obligatory requirement for glucose as an energy substrate. The intensity of the metabolic response peaks several days after the initial insult and then diminishes as the patient recovers.[60] However, a prolonged hyperglycemic response may occur in patients who continue to have tissue hypoperfusion or persistent infection, which then predisposes them to progressive metabolic derangements and multisystem organ failure.

"Tight" Glycemic Control

Traditionally, hyperglycemia secondary to sepsis was viewed as a beneficial response because it promoted cellular glucose uptake when cells were energy deprived. A glucose concentration of 160 to 200 mg/dL was commonly recommended and was thought to maximize cellular glucose uptake without causing hyperosmolarity.[64,65] However, neutrophil function is impaired in patients with hyperglycemia because of decreased bacterial phagocytosis.[66] Hyperglycemia in diabetics is associated with an increased rate of postoperative infections.[67] Hyperglycemia is also associated with a poorer prognosis after stroke or head injury.[68,69] Better glycemic control (blood glucose <215 mg/dL) in diabetics with myocardial infarction has been shown to improve long-term outcome in several studies.[70,71]

van den Berghe and coworkers[72] hypothesized that even mild hyperglycemia (i.e., blood glucose level between 110 and 200 mg/dL) could be harmful by predisposing critically ill patients to increased morbidity and mortality. They performed a prospective, controlled study involving 1548 surgical ICU patients randomized to receive intensive insulin therapy (i.e., blood glucose maintained between 80 and 110 mg/dL) or conventional treatment (i.e., blood glucose maintained between 180 and 200 mg/dL). In patients who remained in the ICU for more than 5 days, intensive insulin therapy reduced the mortality rate from 20.2% with conventional therapy to 10% with intensive therapy (P = .005). The group receiving intensive insulin therapy also had a lower incidence of bloodstream infections (4.2% versus 7.8%, P = .003), renal failure requiring dialysis (4.8% versus 8.2%, P = .007), and critical illness polyneuropathy (28.7% versus 51.9%, P < .001). Patients in the intensive insulin group were also less likely to require prolonged mechanical ventilation and intensive care. The results of this trial make a persuasive argument for tighter glucose control, at least in surgical ICU patients.

Opponents of the use of strict glycemic control in critically ill patients argue that the risks of hypoglycemia should be seriously considered and that the therapeutic effect of insulin rather than glycemic control leads to the beneficial outcome. Insulin has multiple effects, including inhibition of tumor necrosis factor-α,[73] which triggers procoagulant activity and fibrin deposition and inhibits macrophage inhibitory factor, thereby contributing to endotoxemia and toxic shock.[74] To determine whether it was insulin effect or glycemic control, van den Berghe and colleagues[75] used multivariate analysis to reanalyze their previous data. It appeared that lowering of blood glucose levels rather than the actual amount of insulin given was most closely correlated with the beneficial reductions in mortality, polyneuropathy, and bloodstream infections. They reported no adverse effects from hypoglycemia in their study. Instead of the glucose level, the dose of insulin was found to correlate with the incidence of renal failure. Investigators thought that this difference might result from a direct effect of insulin on the kidney or the need for less exogenous insulin in patients with renal failure because insulin is cleared through the kidney. Finney and associates,[76] in a prospective, observational study, provided additional evidence that it was glycemic control rather than insulin administration that provided benefit. They examined the effects of glucose control in 523 patients admitted to a single surgical ICU. In this trial the primary determinant of a bad outcome was hyperglycemia rather than

hypoinsulinemia, and a lower mortality rate was associated with glycemic control rather than a protective effect of insulin administration. Increased insulin dosing resulted in an increased mortality rate across all ranges of glycemia. With regression analysis, their data also suggest that keeping blood glucose below 145 mg/dL may provide a survival benefit similar to that achieved with the "tighter" range of 80 to 110 mg/dL used by van den Berghe and colleagues.[75]

A major criticism of the original van den Berghe study was that it was performed on relatively homogeneous surgical populations. Recently, the same group published a follow-up study examining tight glucose control in 1200 medical ICU patients. The results showed reduced morbidity defined as a reduction in newly acquired renal injury, earlier weaning from mechanical ventilation, and earlier discharge from the ICU and the hospital, but no difference in mortality. With subgroup analysis, they were able to determine a mortality benefit from tight glucose control if the patient was admitted to the ICU for 3 days or longer (43% versus 52.5%, $P = .009$).[77] From the study design it is unclear whether intensive insulin therapy for less than 3 days causes harm or perhaps the benefit from intensive insulin therapy requires time to be realized.

A recent study was stopped early due to the increased incidence of hypoglycemia that occurs with tight glucose control.[78] Based on the current studies, it appears that improved glycemic control should be considered for critical care patients, but needs to be instituted carefully because of the risk of hypoglycemia. The optimal glucose target may not be the same for all patients and all clinical scenarios. A sample insulin titration order form used at the University of California, San Francisco, is provided in Figure 91-3.

Activated Protein C

Patients with severe sepsis have systemic inflammation resulting in coagulation abnormalities that range from subtle elevations in plasma D-dimer levels to frank disseminated intravascular coagulation.[79,80] Recognition that sepsis can cause microthrombosis and that patients with sepsis have low circulating levels of APC led to the investigation of APC as a specific therapy for sepsis.[81] APC is a naturally occurring anticoagulant that inactivates factors Va and VIIIa and prevents the generation of thrombin,[82] which is capable of stimulating multiple inflammatory pathways. Additional effects of APC include a permissive effect on thrombolysis that allows clearance of systemic microthrombi.[80] APC also decreases expression of tissue factor and can bind selectins, which activate neutrophils on the endothelial surface.[83] Recent data suggest that APC levels can predict outcome from multisystem organ failure, regardless of the inciting event.[84]

Recombinant human APC (Xigris, Eli Lilly, Indianapolis, IN) is the first pharmacologic drug that has demonstrated efficacy in the treatment of severe sepsis.[83] In a study of 1690 patients with severe sepsis randomized to receive APC or placebo, the mortality rate was 30.8% in the placebo group and 24.7% in the APC group ($P = .005$). Intravenous infusion of APC at 24 μg/kg/hr for 96 hours was associated with a 6.1% absolute reduction in the risk for death. The most important adverse effect was serious bleeding (3.5% versus 2%, $P = .06$), as would be expected because of its anticoagulant effect.[83]

APC is recommended for use in patients with severe sepsis, greater severity of illness (APACHE II score of ≥25), and a reasonable life expectancy if they survive the episode of sepsis.[85] The cost per quality-adjusted life-year gained by APC treatment was estimated to be about $33,000 for patients with an APACHE II score of 25 or higher and more than $958,000 for patients with an APACHE II score of less than 25. Caution is advised with the use of APC in patients with thrombocytopenia (platelet count <30,000) or a coagulopathy (international normalized ratio >3) because of the increased risk of bleeding.

Use of APC remains controversial.[86] A new randomized, placebo-controlled trial of Xigris is currently under way (clinicaltrials.gov, study No. NCT00279214)and may help finally determine the efficacy of this drug in the treatment of severe sepsis.

Acute Respiratory Failure

ICUs were first developed to manage patients with acute respiratory failure as a result of polio. Since then, management of patients with acute respiratory failure has been revolutionized by the development of modern mechanical ventilators. ARDS was first reported in adults in 1967 by Ashbaugh and coworkers.[87] They described 12 patients with acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance, and diffuse bilateral infiltrates on chest radiography. Because this initial definition lacked specific criteria that could be used to identify patients for research, the American-European Consensus Conference Committee recommended new definitions in 1994.[88] The consensus definition included the following:

1. Acute onset
2. Bilateral infiltrates on chest radiography
3. Pulmonary artery wedge pressure of 18 mm Hg or less or the absence of clinical evidence of left atrial hypertension
4. Pao_2/Fio_2 ratio of 300 or less for acute lung injury (ALI) or Pao_2/Fio_2 ratio of 200 or less for ARDS

The first epidemiologic study to use this consensus definition reported an annual incidence of 13.5 per 100,000 people for ARDS in Sweden, Denmark, and Iceland.[89]

Treatment of ALI or ARDS is primarily supportive and consists of mechanical ventilation, which allows time for treatment of the underlying cause of the lung injury and for natural healing.[90] Until recently, most studies of ALI or ARDS reported a mortality rate of 40% to 60%, with death attributed to sepsis or multiorgan failure rather than primary respiratory causes.[91-93]

Several clinical trials have addressed one of the hallmarks of ALI or ARDS—decreased lung compliance. The definitive study on protective mechanical ventilation was reported in 2000 by the National Institutes of Health (NIH) ARDS network.[30] In this prospective study of patients with ALI, the mortality rate was reduced from 40% in patients receiving tidal volume ventilation of 12 mL/kg to 31% in those receiving 6 mL/kg. The low–tidal volume group also had more ventilator-free and organ failure–free days than the higher–tidal volume group did.[30] Several reasons have been postulated for the discrepancy between this study and the previous inconclusive studies.[94] First, the NIH study may have been better able to show a difference because it used lower tidal volumes than the other studies did. Second, the NIH study allowed treatment of respiratory acidosis with high respiratory rates or with sodium bicarbonate. Treatment of respiratory acidosis may have prevented deleterious effects. Third, the NIH study enrolled 861 patients, which was by far the largest study and

UCSF
Medical Center

INSULIN INFUSION ORDER FORM
FOR ADULT CRITICAL CARE ONLY
For Hyperglycemic Patients

Addressograph

Ht: cm or in	**Instructions: "✓" in box to activate order**
Wt: kg or lbs	
Allergies:	

1. **Discontinue all previous orders for:**
   - ☐ Insulin orders
   - ☐ Oral antidiabetic medications. Name(s):_____
2. **Maintenance IV FLUIDS:** *IV dextrose infusion must be maintained while the patient is on an insulin infusion (minimum rate of 10 mL/hr)*
   - ☐ D5 NS at _____ mL/hr
   - ☐ D5 _NS at _____ mL/hr
   - ☐ D10 W at _____ mL/hr (for patients with fluid restrictions or renal failure)
   - ☐ Other____ at _____ mL/hr
   - ☐ Add KCl _____ mEq/L (generally 20 mEq/L)
3. **Insulin Infusion Bags** ICU Concentration 1 unit/mL*
   Use 100 units of REGULAR human insulin in a 100 mL NS bag.* ***Before connecting to the patient**—Flush and discard the first 20 mL through tubing or whenever tubing is changed. Concentrated insulin infusion must be piggybacked with IV fluid chaser to ensure delivery.*
4. **Start Insulin Infusion Rate.** Blood glucose (BG) level must be ≥ 120 mg/dl before starting.

☐ If patient's normal insulin daily use is 0–30 units/day (or on diet, oral antidiabetic medications or no history of diabetes)	0.5	unit/hr
☐ If patient's normal insulin daily use is > 30 units/day	1	unit/hr
☐ Other (especially if BG > 300)	_____	units/hr

5. **Blood Glucose Goal:** 80–120 mg/dL (Follow monitoring parameters & dose adjustments on page 2)
6. **If the TPN or tube feeds are interrupted for longer than 30 minutes, start $D_{10}W$ at 50 mL/hr and notify MD about change and further action.**
7. **Converting or starting subcutaneous (SQ) insulin:** The first SQ dose should be administered 30 minutes prior to discontinuing insulin infusion (see transition plan for converting to subcutaneous insulin from insulin infusion).

MD Name:	Provider ID # __ __ __ __ __	Pager # __ __ __ - __ __ __ __
MD Signature:	Date:	Time:
RN Signature:	Date:	Time:

Continued

Figure 91-3 Protocol for "tight" glycemic control in critically ill patients in use at the University of California, San Francisco. This protocol involves significant nursing intervention because changes in the infusion rate require rapid measurement of fingerstick glucose concentrations. Changes in the insulin infusion rate are based on the rate of change in glucose concentration over the preceding interval.

increased the statistical power to find a positive effect of low–tidal volume ventilation.

In a second study using the same patient database, Eisner and associates[95] did not find any evidence that the efficacy of the low–tidal volume strategy varied according to the clinical cause of ARDS. Although the mortality rate was highest (43%) in patients with sepsis, intermediate (36%) in patients with pneumonia and aspiration pneumonitis, and lowest (11%) in patients with trauma, there was no evidence of differential efficacy of low–tidal volume ventilation in different groups with ALI or ARDS. The investigators concluded that the recommendations for low–tidal volume ventilation should be applied to all patients with ALI or ARDS regardless of the inciting cause.

Important advances in the ventilatory management of patients with ALI or ARDS have led to improvements in the care of ICU patients. With the impressive 9% reduction in mortality demonstrated by the ARDSnet trial, low–tidal volume mechanical ventilation should be considered the standard of care for patients

ICU INSULIN DOSE ADUSTMENT TABLE

ICU Blood Glucose (BG) GOAL: 80–120 mg/dL

A. If current BG is <60, then

- **STOP** insulin infusion
- Give 50 mL D50 IV push
- Notify MD/HO
- Check BG every 15 minutes and repeat treatment until BG > 80 mg/dL; then, check BG every 30 minutes until BG is 120 mg/dL
- When BG ≥ 120 mg/dl, restart drip at **40%** of previous rate (0.40 × previous rate)

B. If current BG is 60 to 80, then

- **STOP** insulin infusion
- Check BG every 30 minutes until BG is 120 mg/dl
- When BG ≥ 120 mg/dl, restart drip at 50% of previous rate (0.50 × previous rate)
- If 2 episodes of BG below 80 in 4 hours, call HO to reevaluate rate

C. If current BG is 81 to 120 and previous BG was:	Action Step 1	Action Step 2: Check BG in
81–100	↓rate by 0.2 unit	1 hr
101–120	No change	1–2 hr
121–160	↓rate by 0.5 unit	1 hr
161–200	↓rate by 1 unit	1 hr
201–250	↓rate by 1.5 units	1 hr
251–400	↓rate by 2 units	1 hr
> 400	↓rate by 3 units	30 mins
D. If current BG is 121 to 160 and previous BG was:	**Action Step 1**	**Action Step 2: Check BG in**
120	↑rate by 0.2 unit	1 hr
121–160	↑rate by 0.4 unit	1 hr
161–200	No change	1 hr
201–250	↓rate by 0.5 unit	1 hr
251–400	↓rate by 1 unit	1 hr
>400	↓rate by 2 units	30 mins
E. If current BG is 161–200 and compared with previous BG it has	**Action Step 1**	**Action Step 2: Check BG in**
Remained the same or increased	↑rate by 0.5 unit	1 hr
Decreased by ≥1 but <10 then	↑rate by 0.4 unit	1 hr
Decreased by ≥10 but <50 then	No change	1 hr
Decreased by ≥50 but <100 then	↓rate by 0.5 unit	1 hr
Decreased by ≥100	↓rate by 1.5 units	30 mins
F. If current BG is >200 and compared with previous BG it hasa	**Action Step 1**	**Action Step 2: Check BG in**
Remained the same or increased	↑rate by 1.2 unit	1 hr
Decreased by ≥1 but <30 then	↑rate by 1 unit	1 hr
Decreased by ≥30 but <100 then	No change	1 hr
Decreased by ≥100	↓rate by 1 unit	30 min
NOT decreased below 200 after 3 adjustments in infusion rate	Call HO	1 hr

Individualize algorithm for very insulin resistant subjects (insulin infusion > 20 units/hr or BG > 300 for more than 4 hr).

Figure 91-3, cont'd

with ALI or ARDS unless a more efficacious strategy is demonstrated. Figure 91-4 shows the protocol used at the University of California, San Francisco, for mechanical ventilation of patients with ALI or ARDS.

Nontraditional Ventilatory Interventions

In addition to low tidal volume, other therapies have been used for the care of patients with ALI. Most have tried to improve the $\dot{V}/\dot{Q}$ mismatching and hypoxemia that result from ALI. The following sections discuss data associated with recruitment maneuvers, prone positioning, inhaled nitric oxide (iNO), and early tracheostomy.

Lung Recruitment Maneuvers

Gravity-dependent atelectasis is invariably seen in patients with ARDS. The atelectatic lung areas lead to intrapulmonary shunting, ventilation-perfusion mismatching, and regional differences in compliance. Recruitment maneuvers, which involve periods of sustained increased airway pressure, have been proposed to re-expand atelectatic alveoli and avoid atelectrauma.[96] These maneu-

ARDSnet
NIH NHLBI ARDS Clinical Trials Network
Mechanical Ventilation Protocol Summary
UCSF Division of Critical Care Medicine

INCLUSION CRITERIA Acute onset of:
1. $Pao_2/Fio_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: Ventilator setup and adjustment
1. Calculate ideal body weight (IBW)
   Male = 50 + 2.3 [height (inches)–60]
   Female = 45.5 + 2.3 [height (inches)–50]
2. Select Assist Control Mode
3. Set initial TV to 8 mL/kg IBW
4. Reduce TV by 1 mL/kg at intervals ≤ 2 hours until TV = 6 mL/kg
5. Set initial rate to approximate baseline $\dot{V}_E$ (not > 35 bpm)
6. Adjust TV and RR to achieve pH and plateau pressure goals below
7. Set inspiratory flow rate above patient demand (usually > 80 L/min)

PART II: Weaning

Definition of weaning tolerance
1. RR ≤35 (may exceed 35 for ≤5 minutes) and:
2. Spo_2 ≥88% (< 15 minutes at <88% may be tolerated) and
3. Respiratory distress is absent (< 2 of the following)
Pulse >120% of usual rate for >5 minutes; marked use of accessory muscles; abdominal paradox, diaphoresis; marked complaints of dyspnea.

A. Conduct a CPAP Trial daily when:
1. $Fio_2 \leq 0.40$ and PEEP ≤ 8.
2. PEEP and $Fio_2 \leq$ values of previous day.
3. Patient has acceptable spontaneous breathing efforts. (May decrease vent rate by 50% for 5 minutes to detect effort.)
4. Systolic BP ≥ 90 mm Hg without vasopressor support.

CONDUCTING THE TRIAL:
Set CPAP = 5 cm H_2O, $Fio_2 = 0.50$
If RR ≤ 35 for 5 min.: advance to Pressure Support Weaning below.
If RR > 35 in <5 min.: may repeat trial after appropriate intervention. (e.g.: suction, analgesia, anxiolysis)
If CPAP trial not tolerated: return to previous A/C settings.

B. Pressure support (ps) weaning procedure
1. Set PEEP = 5 and $Fio_2 = 0.50$.
2. Set initial PS based on RR during CPAP trial:
   a. If CPAP RR < 25: set PS = 5 cm H_2O and go to step 3d.
   b. If CPAP RR = 25-35: set PS = 20 cm H_2O then reduce by 5 cm H_2O at ≤5 min. intervals until RR = 26-35, then go to step 3a.
   c. If initial PS not tolerated: return to previous A/C settings.
3. REDUCING PS (No reductions made after 1700 hrs.)
   a. Reduce PS by 5 cm H_2O q 1-3 hr, then go to step 3d.
   b. If PS ≥ 10 cm H_2O not tolerated, return to previous A/C settings. (Reinitiate last tolerated PS level next AM and go to step 3a.)
   c. If PS = 5 cm H_2O not tolerated, return to PS = 10 cm H_2O. If tolerated, 5 or 10 cm H_2O may be used overnight with further attempts at weaning the next morning.
   d. If PS = 5 cm H_2O tolerated for ≥2 hrs, assess for ability to sustain unassisted breathing below.

Continued

Figure 91-4 Protocol for low–tidal volume mechanical ventilation of patients with acute lung injury or acute respiratory distress syndrome in use at the University of California, San Francisco. The protocol is based on that used in the ARDSnet trial. A/C, assist/control; BP, blood pressure; CPAP, continuous positive airway pressure; ICU, intensive care unit; I:E, inspiratory-to-expiratory ratio; PEEP, positive end-expiratory pressure; RR, respiratory rate; TV, tidal volume; $\dot{V}_E$, minute ventilation.

vers must be performed with caution because venous return may decrease significantly, thereby leading to hypotension, and alveolar ventilation may decrease, thereby resulting in hypercapnia and respiratory acidosis. Other clinically significant events can include pneumothorax, arrhythmias, and bacterial translocation. The optimal pressure, duration, and frequency of recruitment maneuvers have not been defined. In the ARDSnet ALVEOLI trial, patients randomized to the high–positive end-expiratory pressure (PEEP) group also received recruitment maneuvers with airway pressures of 35 to 40 cm H_2O for 30 seconds to assess the effect on oxygenation.[97] After the first 80 patients, recruitment maneuvers had only a modest effect on oxygenation and were not continued for the remainder of the study. At this time, routine use of recruitment maneuvers cannot be recommended because they have been shown to increase oxygenation only transiently without improving mortality.

Prone Positioning

Because atelectasis and ventilation-perfusion mismatching appear to be dependent on gravity, one assumption is that turning a patient from the supine to the prone position would change these relationships and improve gas exchange (see Chapter 36). Prone positioning is fraught with difficulty and can result in accidental extubation, dislodgement of the line or chest tube, and patient

C. Unassisted breathing trial
1. Place on a T-piece, trach collar, or CPAP < 5 cm H_2O.
2. Assess for tolerance as below for two hours.
3. If tolerated, consider extubation.
4. If not tolerated, resume PS 5 cm H_2O.

Definition of Unassisted Breathing Tolerance:
1. RR ≤ 35 and
2. SpO_2 ≥ 90 % and/or PaO_2 ≥ 60 mm Hg and
3. Spontaneous TV ≥ 4 mL/kg IBW and
4. Respiratory distress is absent (< 2 of the following):
   pulse > 120% of usual rate for > 5 minutes, marked use of accessory muscles;
   abdominal paradox, diaphoresis, marked complaints of dyspnea.

OXYGENATION GOAL:
PaO_2 55-80 mm Hg or SpO_2 88-95%
Use incremental FiO_2/PEEP combinations below to achieve goal:

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
FiO_2	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24

PLATEAU PRESSURE GOAL: ≤30 cm H_2O
Check Pplat (0.5 sec insp. Pause), SpO_2, total RR, TV and pH at least q4h and after each change in PEEP or TV

If Pplat > 30 cm H_2O: decrease TV by 1 mL/kg steps (min = 4 mL/kg)
If Pplat < 25 cm H_2O: increase TV by 1 mL/kg until Pplat > 25 cm H_2O or TV > 25 cm H_2O or TV = 6 mL/kg

pH GOAL: 7.25-7.45
Acidosis Management:
pH < 7.25 but ≥ 7.20
1. Notify ICU resident of pH < 7.25
2. Increase RR until pH > 7.25 or $PaCO_2$ < 25
3. If RR = 35 and/or $PaCO_2$ < 25, MAY give $NaHCO_3$ or choose to leave as is until pH < 7.20

pH < 7.20
1. Increase RR to 35 (if not already 35)
2. If pH remains < 7.20 and $NaHCO_3$ considered or infused, TV may be increased in 1 mL/kg steps until pH > 7.20 (Pplat target may be exceeded)

Alkalosis Management (pH > 7.45)
1. Decrease ventilator rate if possible.

I:E RATIO GOAL: 1:1 to 1:3. Adjust flow rate to achieve goal.
If FiO_2 = 1.0 and PEEP = 24 cm H_2O, may adjust I:E to 1:1.

Figure 91-4, cont'd

injury, but it can lead to higher functional residual capacity, better drainage of secretions, and improved oxygenation. Gattinoni and colleagues performed a multicenter, prospective randomized trial in patients with ARDS to compare supine positioning with prone positioning for 6 or more hours per day for 10 days.[98] Three hundred four patients were enrolled. Oxygenation was improved in the prone group, but again, mortality did not differ between the two groups. Although there may be specific patients who can benefit from this technique, routine use of prone positioning is not supported by the data. The use of specialized beds that can provide significant side-to-side rotation may be an alternative to prone positioning, but these beds have not been tested in prospective trials.

Inhaled Nitric Oxide

Numerous cells synthesize endogenous nitric oxide (NO) in the human body, including macrophages, mast cells, and smooth muscle cells. NO modulates vascular tone and neurotransmission, inhibits platelet aggregation and cell cytotoxicity, and interacts with free radicals (see Chapter 31).[99,100] It binds to hemoglobin and is then metabolized by conversion to nitrites and nitrates, which are excreted in urine.[101] This process is extremely rapid and results in a half-life on the order of seconds, so the effect of NO is limited to the immediate area in which it is released. Selective delivery of NO by inhalation (iNO) to well-ventilated areas of the lung improves ventilation-perfusion mismatching and improves oxygenation by dilating the local pulmonary capillaries. This

effect is in contrast to other pulmonary vasodilators, which usually worsen gas exchange by indiscriminately dilating vessels. In particular, iNO is inactivated in the lung by hemoglobin, which minimizes harmful systemic vasodilation.

Initially, iNO was used as salvage therapy to improve oxygenation in patients with severe ARDS.[102] Further studies then used iNO earlier in the course of ARDS and were able to demonstrate decreased pulmonary artery pressure, decreased venous admixture, and increased oxygenation with no change in systemic blood pressure, systemic vascular resistance, or cardiac output.[103,104] The average improvement in the Pao_2/Fio_2 ratio was 42%.[105] The beneficial effects appear to be sustained during long-term therapy, but a rebound phenomenon has been reported after abrupt removal of iNO therapy.[106]

Three randomized controlled trials of iNO in patients with ARDS were published in 1998. Two of the studies were small (<40 patients) and the results were consistent with the larger multicenter placebo-controlled, double-blinded trial.[107] Initially in that study, patients in the iNO group had an acute improvement in oxygenation, but no differences in Fio_2 were seen between the iNO and placebo groups from days 2 through 7. Most importantly, no differences in mortality or number of days alive and not requiring mechanical ventilation were found through day 28. In patients who were responders to iNO, defined as a 20% or greater increase in Pao_2, no differences in 30-day mortality were reported between responders given iNO and responders given conventional therapy.[105] A recent meta-analysis examining 12 trials involving 1237 patients also found an increased Pao_2/Fio_2 ratio in the iNO group and, again, no significant effect of iNO on hospital mortality, duration of ventilation, or ventilator-free days. There was, however, an increased risk for renal dysfunction (risk ratio, 1.5; 95% CI, 1.11 to 2.02) in the patients receiving iNO.[108]

Because of the data available, routine use of iNO in patients with ARDS cannot be recommended. However, there are no data to address the use of iNO as rescue therapy for patients with critically low oxygenation. Further randomized studies of patients with specific disease states (i.e., rapidly progressive hypoxia, severe pulmonary hypertension, or right ventricular failure) may identify the subgroup that could potentially benefit from iNO.

Tracheostomy

Tracheostomy is a common procedure in the ICU that is performed in about 10% of critically ill patients who require mechanical ventilation (see Chapter 50).[109] Placement of a tracheostomy is thought to allow a more secure and manageable airway, earlier and safer enteral feeding, easier oral care, and enhanced patient comfort while reducing sedation needs. Complications from tracheostomy include stoma infection, pneumothorax, subcutaneous emphysema, tracheomalacia, and tracheostenosis.[110] Major questions about tracheostomy include which patients with acute respiratory failure should have the procedure done and when should it be performed.

A review published in 1998 concluded that there was insufficient evidence to support the view that timing of a tracheostomy can alter the duration of mechanical ventilation or prevent airway injury in critically ill patients.[111] Since then, individual researchers have reported decreased days of mechanical ventilation,[112] decreased duration of ICU and hospital length of stay,[113] and less damage to the upper airway[112] with early tracheostomy. A meta-analysis attempted to answer this question definitively. Unfortunately, they were able to find only five trials with 406 patients that met their inclusion criteria.[114] They reported that the timing of tracheostomy did not alter mortality or increase the risk for hospital-acquired pneumonia. Early tracheostomy did, however, lower the duration of mechanical ventilation and the overall length of stay in the ICU. Their data are shown in Table 91-6. The results were far from conclusive. Heterogeneity was high in the meta-analysis because of variability in inclusion and exclusion criteria, definitions of "early" and "late" tracheostomy, characteristics of enrolled patients, and diagnostic criteria for hospital-acquired pneumonia.

Table 91-6 Data Comparing Early with Late Tracheostomy

	Relative Risk	95% Confidence Interval	*P* Value
Timing of tracheostomy	0.79	0.45-1.39	.42
Development of pneumonia	0.9	0.66-1.21	.48
Time on ventilator	8.5 days	−15.3 to −1.7 days	.03
Length of intensive care unit stay	15.3 days	−24.6 to −6.1 days	.001

From the results it appears that early tracheostomy may have benefit over late tracheostomy, but the difficulty comes in identifying patients who may have a simple subsequent weaning process after failing the first attempt. Tracheostomies should be performed in patients who will encounter difficult or prolonged weaning. Unfortunately, no validated specific and sensitive test or scoring system is available that can predict the need for prolonged ventilation, so selection of patients for tracheostomy remains a subjective decision.

Percutaneous versus Open Tracheostomy

Percutaneous techniques are emerging as a method of securing the airway of adult critical care patients. Advantages include smaller skin incision, less tissue trauma, lower incidence of wound infection, reduced risk associated with transfer of patients to the operating room, and fewer personnel requirements. Two meta-analyses showed a trend toward fewer complications, cost-effectiveness by releasing operating room resources, and greater feasibility than the open surgical approach in terms of the capability of performing the percutaneous procedure at the bedside.[115,116] One important caveat of these results is to remember the exclusion criteria for most of these studies (i.e., emergency tracheostomy, suspicion or evidence of a difficult airway, previous airway problems, coagulopathies, and previous tracheostomies). Consequently, although the procedure appears to be safe and effective, the favorable data exist only for a particular subset of patients admitted to the ICU.

Fluid Management and Monitoring

The use of pulmonary artery catheters (PACs) in critically ill patients remains controversial. Most studies have failed to show efficacy or have demonstrated harm (see Chapters 88 and 96). The best known of these investigations was the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT), which was a retrospective, observational study involving 5735 critically ill patients.[117] In these patients, use of a PAC was associated with increased mortality and cost. Richard and coworkers[118] completed a prospective, observational trial of

PACs versus central venous catheters (CVCs) in patients with ARDS or shock. Clinical management was left to the discretion of the treating physician. In 676 patients in 36 French ICUs, there was no difference in any of the outcome variables measured.[118]

Recently, the Fluids and Catheters Treatment Trial (FACTT) conducted by the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network compared hemodynamic management guided by a PAC with hemodynamic management guided by a CVC in 1000 patients with established ALI.[119] Patients were treated by clinicians at select academic ICUs who were trained in interpreting hemodynamic data and who were following a very specific management protocol. Although serious catheter-related complications were rare, the PAC group did have a higher incidence of arrhythmias and conduction blocks. The investigators were unable to demonstrate prevention or reversal of organ failure, reduced need for support (e.g., vasopressors, assisted ventilation, or renal replacement therapy), faster discharge from the ICU, or decreased 60-day mortality in the PAC group versus the CVC group. Possibly because of this growing evidence, use of the PAC has decreased by 65% during the last decade in the United States.[120]

The PAC is a monitoring device that can be difficult to interpret, especially in the setting of critical illness. More concerning than the device itself is the therapy that can be driven by misinterpretation of the numbers obtained from the PAC. A recent guideline on hemodynamic monitoring recommends against routine PAC placement in patients in shock and does not specifically recommend it for any clinical scenario.[121]

Recently, in one of the factorial assessments the FACTT study examined whether a conservative or a liberal strategy of fluid management was more effective in patients with established ALI.[122] Although the 60-day mortality was similar in both groups, patients in the conservative fluid management group had improved lung function, improved central nervous system function, and a decreased need for sedation, mechanical ventilation, and intensive care. The patients in the conservative fluid management group also did not have an increased incidence of complications, such as nonpulmonary organ failure or shock.

Perhaps the most prudent approach is to base management on clinical examination findings and appropriately titrate fluid according to the patient's phase of illness. There are important benefits of goal-directed, liberal fluid administration during the acute phase of sepsis. However, excess fluid is not beneficial when it is not needed physiologically during the established phase of ALI.[123]

Acute Liver Failure

Epidemiology

Acute liver failure (ALF) is an uncommon disorder that leads to jaundice, coagulopathy, and multisystem organ failure. It is defined by the development of hepatic encephalopathy within 8 weeks after the onset of jaundice in patients with no known chronic liver disease.[124] ALF affects approximately 2000 people per year in the United States,[125] with 20% to 39% of cases caused by acetaminophen overdose.[126] Mortality from fulminant hepatic failure (FHF) can be high (60% to 80%) in the absence of liver transplantation, depending on the etiology.[127] Causes of death are mainly multisystem organ failure, sepsis, and cerebral edema. Liver transplantation for ALF generally has a worse outcome than transplantation for chronic liver disease does because of the high postoperative mortality caused by sepsis and multiorgan failure.[128]

Table 91-7 Causes of Fulminant Hepatic Failure

Etiology	%
Acetaminophen	39
Idiosyncratic drug reaction	13
Hepatitis B	6
Hepatitis A	6
Other	19
Indeterminate cause	17

Prognostic Factors in Acute Liver Failure

The timing of transplantation and selection of patients are crucial because transplantation is the only therapeutic intervention proved to be beneficial.[129] Although scoring systems have been proposed, the myriad causes of ALF limit their accuracy (Table 91-7). Most case series are limited in number, and some span long periods during which supportive therapies may have changed. The King's College criteria have been shown to have good specificity (92%) for patients who will die without transplantation, but lower sensitivity (69%), thus suggesting that a proportion of patients will die and not fulfill the criteria. The criteria also have low negative predictive value, which could lead to transplantation in a patient who would have recovered without surgery. Other predictors include the Model for End-Stage Liver Disease (MELD),[130] which has been shown to be an excellent predictor of outcome in patients with ALF of various causes, excluding acetaminophen. Also promising are blood lactate levels[131] and hyperphosphatemia.[132]

Management of Fulminant Liver Failure

General Supportive Measures

Patients with ALF should be monitored closely, usually in an intensive care setting. The cause of the ALF should be identified, and suitable candidates for orthotopic liver transplantation should be moved early to a transplantation center. Early intubation may be necessary if neurologic status deteriorates and leads to airway compromise. Volume expansion with crystalloids and colloids is probably required to help maintain blood pressure. Correction of acid-base disturbances, treatment of hyperthermia, and close glucose monitoring are important to prevent cerebral edema. Hyponatremia is a negative prognostic sign, and values of less than 125 mmol/L can be a contraindication to transplantation.[133] Continuous renal support is often required in cases of advanced ALF to help with renal insufficiency, volume status, and cerebral edema.[134] Prophylactic antibiotics are used widely and have been shown to lower infection rates.[135] Current recommendations are to correct the coagulopathy with fresh frozen plasma when bleed-

ing occurs or an invasive procedure is planned. Recombinant factor VIIa has been shown to reverse the coagulopathy in patients with FHF.[136]

Management of Increased Intracranial Pressure

The development of cerebral edema and intracranial hypertension is probably the most devastating complication associated with ALF (see Chapters 46, 63 and 94). Osmotically active compounds, normally cleared by the liver, accumulate in blood and diffuse into the brain parenchyma. Movement of water into neurons and glia results in swelling and can cause herniation. The exact compounds responsible for cerebral edema are unknown, but ammonia is probably a major contributor.

Diagnosis of cerebral edema can be difficult. Serial neurologic examination is essential, and frequent computed tomography of the head can identify early signs of edema. Many centers implement early monitoring of intracranial pressure, although this practice has not been shown to improve outcome.[137] This can be achieved with either cranial or lumbar epidural monitors because traditional intraventricular monitors carry an unacceptable risk of bleeding.

Techniques to reduce intracranial pressure include removal of ammonia with continuous renal replacement therapy (CRRT), hypothermia, barbiturate coma, and administration of mannitol and hypertonic saline.[138]

Liver Support Devices

Bioartificial Livers. Bioartificial livers use hepatocytes to mimic the synthetic, detoxifying, and excretory function of the dying liver. Porcine hepatocytes are used preferentially because human hepatocytes are difficult to grow in culture.[139] The device works by passing the patient's plasma through hollow-fiber capillaries while the hepatocytes are placed in the extracapillary space. Molecules are exchanged between hepatocytes and plasma across a membrane that prevents passage of immunoglobulin, complement, and cells. A prospective, multicenter, randomized controlled trial using the HepatAssist liver support system was published in 2004.[140] The results did not show any improvement in survival in the treated group. Only during subgroup analysis were patients with fulminant/subfulminant liver failure found to have improved survival, but the results were marginal.

Artificial Extracorporeal Devices. Artificial extracorporeal devices have received renewed interest because of technology allowing the production of membranes that can increase selectivity through small pores. The system can be tailored for albumin-bound substances, which include most of the toxins that accumulate in FHF. Larger molecules such as immunoglobulins cannot cross.[139] Recent studies have found that this system is associated with significant improvements in encephalopathy in patients with acute-on-chronic liver failure,[141] but controlled clinical data in patients with FHF are lacking.

Overall, the systems appear to be safe, but adverse events can include bleeding, systemic infection, disseminated intravascular coagulation, and allergic shock. A meta-analysis of the use of artificial and bioartificial life support systems in eight randomized controlled trials involving only 139 patients concluded that the support systems evaluated have no significant effect on mortality in patients with ALF.[142] Randomized clinical trials are limited given the patient's severity of illness. More controlled trials addressing survival are warranted before this therapy can be strongly recommended.

Acute Renal Failure

Epidemiology

The incidence and outcomes of acute renal failure (ARF) in the ICU are highly variable. Reported incidences range between 1% and 31%,[143,144] and mortality ranges between 28% and 82%[144,145] Part of the variability is due to the fact that there is no consensus on the diagnostic criteria or clinical definition of ARF. A recent survey determined that at least 35 definitions were used in the literature.[146]

Diagnosis

A group of experts consisting of nephrologists and intensivists have proposed new criteria for describing renal dysfunction. They recognized the clinical importance of milder forms of renal insufficiency and that stratifying renal dysfunction (mild to severe) would better describe the disease. They proposed the RIFLE criteria (Table 91-8), which stands for risk, injury, failure, and two outcome classes (loss and end-stage kidney disease). For each increasing RIFLE class, there is a stepwise increase in mortality[147] and an increasing proportion requiring renal replacement therapy.

Management of Acute Renal Failure

General Supportive Measures

Patients with ARF should be monitored closely. The cause of the ARF should be identified by looking at prerenal, renal, and postrenal causes. Laboratory evaluations should include serum and urine electrolytes, urinalysis, and examination of urinary sediment. Careful assessment of volume status is necessary to determine hypovolemia leading to prerenal azotemia versus hypervolemia from oliguria. Correction of acid-base disturbances may be necessary, as well as correction of electrolyte abnormalities. Continuous renal support is often required in patients with advanced renal failure to help with volume overload and electrolyte disturbances. Antibiotics and other medications should be dosed according to creatinine clearance, and serum levels, if available, should be monitored closely. Platelet dysfunction may occur as a result of uremia and require desmopressin (DDAVP) for support if bleeding is problematic.

Table 91-8 The RIFLE Criteria

	GFR criteria	UO Criteria
Risk	Cr increased × 1.5 or GFR decreased >25%	UO <0.5 mL/kg/hr × 6 hr
Injury	Cr increased × 2 or GFR decreased >50%	UO <0.5 mL/kg/hr × 12 hr
Failure	Increased Cr × 3, GFR decrease >75%, or Cr ≥ 4 mg/dL	UO <0.3 mL/kg/hr × 24 hr or anuria × 12 hr
Loss	Complete loss of renal function >4 wk	
ESRD	End-stage disease	

Cr, creatinine; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RIFLE, risk, injury, failure, and the two outcome classes loss and ESRD; UO, urine output. Data from Hoste EAJ, Kellum JA: Acute kidney injury: Epidemiology and diagnostic criteria. Curr Opin Crit Care 12:531-537, 2006.

Renal Support

ARF in the ICU often requires some type of renal replacement therapy (see also Chapter 96). Commonly, this is accomplished by continuous venovenous hemofiltration (CVVH), a form of CRRT. The timing and dosing of this therapy and the patients most likely to benefit from it remain unclear.[148,149] Recently, it appears that the difference in efficacy lies not in the type of dialysis (intermittent hemodialysis versus CVVH) but in the dialysis dose. Undertreatment appears to be harmful,[150] whereas earlier application and higher filtration volumes appear to be associated with decreased mortality in patients with ARF.[151] Extended daily dialysis offered hemodynamic stability and small solute control comparable to that achieved with CRRT.[152] Even with intermittent hemodialysis, when studies are controlled for dialysis dose, polymer membrane, and bicarbonate-based buffer, 60-day mortality did not differ between the groups (CRRT versus intermittent hemodialysis).[153] Although there has been a trend to use CRRT, the favorable data with intermittent hemodialysis is intriguing because it would allow more ICU resources to be allocated elsewhere.

Complications of Intensive Care Unit Management

Even though ICU care has advanced and improved, some limitations on our ability to further reduce mortality are due to complications of the ICU care that we give. Nosocomial infections occur in approximately 10% of ICU patients at a rate of 21 to 25 infections per 1000 ICU patient-days.[154,155] The most common nosocomial infections in medical ICUs are urinary tract infections (31%), followed by pneumonia (27%) and primary bloodstream infections (19%).[156] Several studies have shown that quality improvement initiatives can reduce nosocomial infections, mortality, and cost.[157,158] The next section reviews the data available for the prevention of ventilator-associated pneumonia (VAP) and catheter-related bloodstream infections (CRBSIs).

As of 2008, the Center for Medicaid and Medicare Services, which administers federal-sponsored health care, will no longer reimburse hospitals for additional costs associated with common ICU complications, including urinary and CVC-associated infections. This pay-for-performance measure, in addition to the widespread adoption of public reporting of infection rates, will catalyze significant scrutiny of these infections.

Ventilator-Associated Pneumonia

VAP is defined as pneumonia developing in mechanically ventilated patients after more than 48 hours of intubation, with no clinical evidence suggesting the presence or probable development of pneumonia at the time of initial intubation.[159] VAP is a leading cause of morbidity and mortality in mechanically ventilated, critically ill patients. The incidence of VAP is estimated to be 10% to 25%,[160] and the estimated mortality rate from VAP is 5% to 27%.[161,162] VAP also increases hospital length of stay and cost.[161,163] Additional hospitalization cost because of an episode of VAP has been demonstrated to be as high as $40,000.[164,165] The pathogenesis of VAP probably involves microaspiration of oropharyngeal or gastric secretions contaminated with bacteria. Risk factors include previous exposure to antibiotic therapy and the presence of invasive devices.[166]

The diagnosis of VAP is challenging. Frequently, a presumptive diagnosis of pneumonia is made when fever, leukocytosis, purulent secretions, and a new infiltrate on chest radiography develop and when bacteria are isolated by nonquantitative analysis of endotracheal aspirates.[167] These nonspecific diagnostic criteria may lead to unnecessary antibiotic use, increased hospital cost, emergence of resistant microorganisms, and a potential delay in diagnosis of the true cause of the fever. These problems led several investigators to propose an invasive management strategy for the diagnosis of VAP.

Fagon and colleagues[168] used fiberoptic bronchoscopy to obtain protected specimen brush samples or bronchoalveolar lavage samples for quantitative culture. Patients were considered to have VAP if at least 10^3 colony-forming units (CFU)/mL of bacteria grew from the protected specimen brush sample or at least 10^4 CFU/mL of bacteria grew from the bronchoalveolar lavage fluid. The patients in the invasive management group had reduced mortality at day 14 (16.2% versus 25.8%, $P = .022$) and an increased number of antibiotic-free days (5.0 ± 5.1 versus 2.2 ± 3.5 days, $P < .001$). This study makes a compelling argument for a more definitive diagnosis of VAP before initiating antibiotic therapy. Along the same idea but with a less invasive approach, other studies[169,170] have shown that nonbronchoscopically guided placement of protected brush catheters or protected bronchoalveolar lavage is just as sensitive as directed bronchoscopy in detecting bacteria in the lungs.

Prevention of Ventilator-Associated Pneumonia

Gastric pH

As in all nosocomial infections, prevention is the most efficacious approach. Excessive use of gastric pH–altering medications for stress ulcer prophylaxis increases gastric pH and the risk for VAP.[171] The use of sucralfate, an agent that does not increase gastric pH, may be preferable to H_2 receptor antagonists or proton pump inhibitors. Three studies found decreased mortality rates in patients treated with sucralfate rather than H_2 receptor antagonists or proton pump inhibitors.[171-173]

Positioning

Positioning of the head of the bed at 30 degrees is the most cost-effective intervention for prevention of VAP. This position results in decreased gastroesophageal reflux. With this intervention, Drakulovic and coworkers[174] found a decreased rate of VAP with no adverse effects. This intervention is easily implemented and monitored.

Subglottic Aspiration of Secretions

Pooling of secretions above the endotracheal tube cuff may increase the volume of bacteria that enter the airways. Removal of these secretions by continuous aspiration in the subglottic region requires the use of a specialized endotracheal tube with a second lumen that permits a suction catheter to exit proximal to the endotracheal tube cuff. Three randomized, controlled trials have examined the efficacy of aspiration of subglottic secretions. Mahul and associates[175] studied 145 patients randomly assigned to prevention of aspiration by hourly drainage of subglottic secretions or prevention of gastric colonization with sucralfate or ant-

acids. Drainage of subglottic secretions was associated with a lower incidence of VAP (13% versus 29.1%), a prolonged time to onset of VAP (16.2 days versus 8.3 days), and a decrease in the colonization rate of subglottic secretions (2.1% versus 33.4%). Valles and colleagues[176] randomized 153 patients to subglottic aspiration or usual care. The intervention group had a reduced incidence of VAP (19.9 episodes per 1000 ventilator days versus 39.6 episodes per 1000 ventilator days). They also found that episodes of VAP occurred later (12 ± 7 versus 5.9 ± 2.1 days, P = .003) in the continuous aspiration group.[176] The third trial by Kollef and coworkers[177] randomized 340 patients undergoing cardiac surgery to continuous aspiration of subglottic secretions. VAP was seen in 5% of the interventional group as opposed to 8.2% of the control group (P = .238), but episodes of VAP occurred statistically later in patients receiving subglottic aspiration (5.6 ± 2.3 days) than in those who did not (2.9 ± 1.2 days, P = .006).[178] Unfortunately, none of the studies were able to show a mortality benefit from continuous aspiration of subglottic secretions. At this time, aspiration of subglottic secretions looks promising for prevention of VAP but cannot be recommended because of the mixed results from randomized studies.

Catheter-Related Bloodstream Infections

It is estimated that more than 5 million CVCs are inserted every year in the United States.[179] Unfortunately, more than 15% of patients have complications from these lines.[180] Infectious complications are reported to occur in 5% to 26% of patients with CVCs.[181,182] The mortality rate attributable to CRBSIs ranges from 12% to 25%,[183,184] and the attributable cost is estimated to be between $3700 and $29,000 per episode.[184,185]

Prevention of Central Venous Catheter Infections

Antibiotic-Impregnated Central Venous Catheters

Several studies have been conducted to examine the efficacy of antimicrobial-impregnated catheters in an effort to decrease the incidence of CRBSI. CVCs coated with the antimicrobials chlorhexidine and silver sulfadiazine or impregnated with the antibiotics minocycline and rifampin are commercially available. Chlorhexidine/sulfadiazine-coated catheters lowered the rate of bloodstream infection from 7.6 to 1.6 infections per 1000 catheter-days (P = .03).[186] A cost-effectiveness analysis conducted by Veenstra and associates[187] concluded that these catheters would decrease cost by $196 per catheter inserted if the institutional CRBSI rate was higher than 2%.

Later evidence suggests that minocycline/rifampin-impregnated catheters are even more efficacious. In a randomized trial performed in 12 university hospitals in which minocycline/rifampin-impregnated catheters were compared with chlorhexidine/silver sulfadiazine–coated catheters, the catheters with minocycline/rifampin were a third as likely to be colonized as those coated with chlorhexidine or silver sulfadiazine (7.9% versus 22.8%, P < .001) and half as likely to lead to CRBSI (0.3% versus 3.4%, P < .002).[188]

The use of antimicrobial-impregnated catheters should be considered in all critically ill patients who require long-term (at least 3 days) indwelling central venous access. Immunocompetent patients who will be catheterized for less than 3 or 4 days may not need these catheters because infection is rare during this period. Additional studies are required to further elucidate the benefit of catheters impregnated with minocycline/rifampin over chlorhexidine/silver sulfadiazine.[189] Although theoretically possible, no studies have shown the development of significant antibiotic resistance with these catheters. However, continued surveillance for resistance is recommended as part of the increased use of these devices.[182,188]

Sterile Technique

Optimal sterile technique is the most cost-effective means of reducing the incidence of central line colonization and CRBSI. Use of maximal sterile barrier precautions such as mask, cap, sterile gown, sterile gloves, and a large sterile drape as opposed to small towels has been shown to reduce the rate of CRBSIs and to save $167 per catheter inserted.[190,191] Use of chlorhexidine solution for skin decontamination reduces the risk of catheter colonization and is therefore preferred over the use of povidone-iodine solution.[192] With widespread implementation of these sterile techniques, Pronovost and associates were able to markedly reduce CRBSI rates in 108 ICUs in the state of Michigan.[193]

Ultrasound Guidance

With the development of portable, inexpensive ultrasound machines, use of real-time ultrasound guidance has been promoted as a technique for reducing the complications associated with central venous cannulation (see Chapter 40). Ultrasound guidance has been shown to reduce the number of complications, unsuccessful attempts, and time required for insertion of an internal jugular vein catheter,[194] but it has not been demonstrated to be efficacious for subclavian venous access.[195] Clinical trials assessing whether use of ultrasound can decrease the incidence of central venous line infections remain to be completed, but this technology can decrease the number of attempts required to locate the internal jugular vein and should be used routinely when available.[189] All three practices—maximum sterile barrier precautions, antibiotic-coated catheters, and ultrasound guidance—have been recommended as among the top 11 patient safety practices by the Agency for Healthcare Research and Quality in its report Making Health Care Safer: A Critical Analysis of Patient Safety Practices.[196]

Duration

The need for a CVC should be reassessed daily, and unnecessary catheters should be removed because the probability of catheter-related infections increases with time. The risk of infection with catheterization stays relatively low until about the fifth to seventh days and then increases exponentially.[197,198] Several trials have studied scheduled replacement of catheters over a guidewire or in a new site, but none of these strategies were able to show an improved outcome.[199,200] Optimal catheter insertion technique and maintenance can minimize infectious risks, but the most efficacious maneuver is to remove CVCs as soon as they are no longer required. The need for central venous access should be reassessed again before discharging the patient from the ICU because this is often an opportune time to remove any indwelling lines, including bladder catheters.

Conclusion

Critical care medicine is a growing specialty as the population ages and new procedures and technologies are brought into practice. Anesthesiologists represent a small proportion of intensivists in the United States but constitute the majority in Europe and other parts of the world. Critical care training represents a significant opportunity for anesthesia practitioners. We have reviewed management of a number of commonly encountered clinical conditions in the ICU, and the reader should refer to Chapters 92 through 98 for additional information related to critical care practice. The ICU is a nexus not just for promising therapies but for complications of treatment as well. To avoid patient harm, all practitioners must be aware of best practices, from the simplest interventions such as hand hygiene to the latest technologic advances.

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92 Critical Care Protocols

Key Points

1. Protocols allow for standardization of research protocols and minimization of confounding variables.
2. A multidisciplinary team is required and a specific educational plan is necessary to properly implement all facets of a protocol.
3. Protocols must be devised with the intention of not only improving the quality of patient care but also improving patient outcome and the efficiency of care, while at the same time decreasing practice variation and costs.
4. The ability to measure the effect of a particular protocol and adapt appropriately is the key to successful protocol application.
5. Quality measures that were found to be valuable (based on effect, feasibility, and strength of evidence) included: (a) percentage of patients with ventilator-associated pneumonia, (b) percentage of patients with resistant infections, (c) percentage of patients with central venous catheter infections, (d) number of complications per patient, (e) average days of mechanical ventilation, (f) rate of gastrointestinal bleeding, (g) average intensive care unit (ICU) length of stay, and (h) patient satisfaction.
6. With appropriate standards, definitions, defined pathways, and explicit interventions, the interpretation of research findings, whether prospective randomized or observational, will enhance clinical equipoise.

The demand for critical care services in the United States is estimated to increase dramatically in the coming years.[1] Because the future supply will unlikely be able to match this demand, intensivists will undoubtedly face a larger, sicker population with fewer resources.[2,3] While few would argue that an intensivist-led unit benefits from decreased morbidity and mortality, the impending staffing shortage and population growth will necessitate care paradigms that maximize efficiency, reduce practice variation, and standardize patient care.[4-6] Increasingly, intensive care units (ICUs) have adopted and implemented pathways and clinical protocols to achieve this goal. Designing such protocols, however, is not trivial. Protocols must be devised with the intention of not only improving the quality of patient care but also improving patient outcome and the efficiency of care, while at the same time decreasing practice variation and costs. Lohr and colleagues defined *quality* as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[7] It is imperative that health care providers maintain this characterization whether creating new or implementing known protocols. Furthermore, it is critical that clinicians not view protocol-driven care as a constraint on clinical judgment. To the contrary, protocols require a greater consideration of individual subtleties among patients and it is the attentive clinician who understands the need to deviate from protocol. The goal then becomes a process: a process of learning, a process of observation, and a process of educated response. Without this goal, critical care becomes "cookbook medicine" and protocols become recipes for disaster.

In this chapter we will discuss the rationale for care protocols in the context of achieving five goals: (1) enhancing quality of care, (2) improving efficiency, (3) decreasing cost, (4) decreasing errors, and (5) enabling rigorous clinical research. The focus is on more technical aspects of protocol design, including team development, evaluation of best evidence and/or consensus, preservation of flexibility, and continuous quality improvement. Factors necessary to implement protocols are also discussed. This process begins with identifying priorities and setting goals and culminates with the ability to continuously revise as new evidence builds. We will discuss three protocols that have been embraced among ICUs widely, all of which illustrate an important concept in protocol design. Finally, we will discuss the future of protocolized medicine including the role of computer-driven decision models and handheld computers in addition to areas that likely will see protocol implementation in the near future. As has been shown repeatedly in the literature, protocol development and implementation, for all its intricacies and details, will fail without the help, understanding, and sense of ownership of a large multidisciplinary team.

Rationale for Protocol Development

Critical care protocols or clinical practice guidelines (CPGs) were borne out of the need to establish a reduction in practice variability while improving the quality of care and patient outcome using the best available evidence. A 1994 editorial in the *British Journal of Medicine* predicted: " 'Evidence based medicine' is a phrase that is currently familiar to only a few doctors, but all will know it by the millennium."[8] While it turns out this forecast was accurate, no one could have predicted the care paradigm shift this would create. Rather than treating patients based on empirical evidence or anecdote, today's intensivists are faced with a plethora of objective data from which they must determine what will work best for their particular patient or population. The quality of this objective data and robustness of statistical analysis continues to improve. While many current protocols are based on data from multiple randomized controlled trials (RCTs), it is interesting to note that over one half of the clinical guidelines published before the year 2000 were based on no RCT evidence.[9]

There are a large number of interventions in critical care that have been shown to improve morbidity and mortality while at the same time decreasing costs.[10-14] Despite this, there continues to be a disparity between best evidence and best practice.[15,16] This may be due to physicians' respect for mentors or an inability to incorporate new evidence into traditional dogma. Evidence-based medicine and the inevitable consequence, protocol development, are a result of new types of evidence being generated. As new evidence accrues, it is incumbent on practitioners to critically analyze the data in a way that is fair and equitable to others performing similar research. Using a uniform approach for each piece of evidence has advantages and disadvantages (Table 92-1).[17] Protocol or guideline development should explicitly state what, if any, objective grading system was used to categorize and classify the data.

Table 92-1 Advantages and Disadvantages of Using the Same System for Grading Evidence to Implement ICU Protocols

Advantages	Disadvantages
• Having different systems for evaluation of various interventions might be confusing. • There is less chance for individuals with vested interests to bias results by selecting a particular grading scheme. • Limitations of the evidence become more apparent when comparing two disparate conclusions with a similar grading scheme. • Better research can be generated as a result of identifying gaps in evidence.	• Interventions that cannot be studied with randomized trials may not be evaluated or may lead to a false-negative conclusion. • A single system that can adequately grade evidence across a broad range of interventions may be overly complex.

Adapted from Schunemann HJ, et al: Improving the use of research evidence in guideline development: 9. Grading evidence and recommendations. Health Res Policy Syst 4:21, 2006.

The basis of CPG development includes (1) improving patient outcome; (2) establishing standards of care (either institutionally or within a specialty); and (3) changing practice patterns.[18] While these points form the rationale for CPGs, the primary goal of any new protocol is enhancement of the quality of care. Defining quality is a subject of debate; however, we will use the Institute of Medicine's definition: "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.[7,19]" Continuous quality improvement (CQI) is a term that originated in the business realm and was coined by W. Edward Deming. Deming was a trained statistician but is best known for the positive impact he had on production in the United States during World War II. He taught management executives how to improve design and product quality through objective evaluation, testing, and re-evaluation. CQI contrasts to the traditional, reactive, root-cause analysis, which focuses on recognizing a problem and then identifying a "seminal event" (or events) causally related to this event. In CQI, all facets of the critical care setting are evaluated and considered as potential targets for improvement initiatives.[20,21] Once an initiative is identified, a system is devised to measure the efficacy or outcome of a particular intervention.[22] This change is then continuously re-evaluated and modified via an internal evaluation system.[23] Depending on the goals of a particular critical care unit, interventions can be targeted appropriately.

Selecting a particular goal for quality improvement is not to be taken lightly, because an inappropriate goal may lead to incorrect conclusions and thus unsuitable interventions. One example may be a goal of "decreasing ICU readmission." Although there are certainly good data to support that patients who are readmitted to the ICU have significantly increased mortality and length of stay, readmissions may more likely represent a quality issue in the post-ICU setting or may represent an epiphenomenon associated with severity of illness.[20,24-27] Quality goals need not be limited to outcome measures such as morbidity and mortality. A "change in process" goal may be equally as important, such as use of aspirin or β-blockers in patients with acute coronary syndrome. Similarly, "perceptions of care" goals (e.g., patient satisfaction, pain relief, nausea) are appropriate and require the same process of re-evaluation as any other outcome.[28] A recent review identified interventions and quality measures that, after a systematic review of the literature, improved patient outcome.[11] Quality measures that were found to be valuable (based on effect, feasibility, and strength of evidence) included the following:

1. Percentage of patients with ventilator-associated pneumonia
2. Percentage of patients with resistant infections
3. Percentage of patients with central venous catheter infections
4. Number of complications per patient
5. Average days of mechanical ventilation
6. Rate of gastrointestinal bleeding
7. Average ICU length of stay
8. Patient satisfaction

Once a protocol has met the standard of "quality," it is necessary to evaluate the effect this process will have on efficiency and cost. Inefficient protocols (or protocols that create a systems

inefficiency) are undesirable and unlikely to be adhered to by clinicians. Efficiency refers not only to the ease of implementation but also to the overall financial impact and the timing of intervention. Additionally, efficient protocols reduce management variability and, at least theoretically, reduce errors and save lives.[4,29] Protocol development, while inundated with evidence-based practice, is at a local level a trial-and-error process. Systems theory provides us with many of the crucial aspects inherent in protocol design and necessary to maximizing practicality.[30,31] Testing a new process and then evaluating the impact on the overall system was first described by Walter Shewhart, founding theorist of the field of statistical process control. Shewhart described a form of learning through action termed the Plan-Do-Study-Act (PSA) cycle.[32] One of the best examples of using the PSA cycle to implement a change in practice comes from work done by the Northern New England Cardiovascular Disease Study Group over a decade ago.[33] By continuously reevaluating variations in practice and morbidity and mortality from large databases, members of the group were able to develop protocols for such practices as anesthesia, hemostasis, and cardiopulmonary bypass pump management, achieving a 24% reduction in mortality from coronary artery bypass graft surgery within the region.

Paradoxically, protocol development and implementation can have undesirable effects, if, by impacting negatively on other high-cost therapies, overall inefficiencies result. An example of this can be seen with ICU protocols that were designed to optimize sedation and analgesia efficacy. While the initial goals of anxiolysis and pain relief were attained, adverse effects include prolonged mechanical ventilation, increased risk of nosocomial pneumonia, and hemodynamic instability.[34,35] The final aspect of protocol efficiency that deserves mention is the timing of intervention. Ill-timed implementation of evidence-based practices is at best useless and at worst harmful. An example includes protocols designed to aggressively treat severe sepsis in the emergency department.[36] The execution of these practices late in the disease process (even by 1 day) is now known to increase mortality.[37] Thus, a protocol designed to treat a disease without identifying, or at least addressing, at-risk populations and diagnosis is wasteful and potentially unsafe.

Finally, protocols facilitate rigorous clinical research. Without standards, definitions, defined pathways, and explicit interventions, the interpretation of research findings, whether prospective randomized or observational, will enhance clinical equipoise. Protocols define a standard that attempts to control for confounding variables. As they are tested and replicated, new research is being generated. There is a wealth of RCTs demonstrating improved outcome with protocol implementation.[38-42] For meaningful advances in critical care, protocols must continually embrace new findings and intensivists must be willing to adhere to guidelines. The ability to discern the applicability of a particular guideline or protocol based on the population studied is a challenge faced by all.

Protocol Design

Protocol design usually requires a multidisciplinary team[29]; however, the process mandates an appreciation of the affected variables, the ability to grade the data, a method for continual reevaluation, and inherent flexibility (Table 92-2). Affected variables are factors that will be affected indirectly (positively or negatively) by the proposed protocol. An example would be a sedation/anxiolysis protocol that does not take into account time on ventilator, incidence of nosocomial pneumonia, nausea, vomiting, and so on. In other words, they are by-products of a purposeful change in practice. Affected variables can be universal, as in the example above, or institutional. A ventilator weaning protocol may look good on paper but practically is unrealistic depending on the local staffing paradigm of respiratory therapists at a particular institution. Similarly, an ICU glycemic control protocol may work at one institution but not be as effective in another or even be deleterious.[43,44]

Table 92-2 Process for Developing Guidelines

Establishing the Process
Prioritize problems
Select a panel
Declare conflicts of interest
Agree on processes
Preparatory Steps
Systematic review of problem
Defining outcomes of interest
Preparing evidence for outcomes
Grading Quality of Evidence and Strength of Recommendations
Define quality of evidence for each outcome
Define the relative importance of outcomes
Judge *overall* quality across all pieces of evidence
Balance benefit and harm
Balance net benefits and costs
Determine strength of recommendation
Subsequent Steps
Implementation and evaluation

Reprinted from The GRADE Working Group: Grading quality of evidence and strength of recommendations. BMJ 328:1490, 2004.

Evaluating and grading the literature involves an appreciation of the various affected variables measured in a study. Additionally, the appraisal of "best evidence" must take into consideration patient population to be relevant to protocol design. Protocol committee members must understand inclusion and exclusion criteria as well as the prevalence and incidence of disease in a particular study. Only after critically analyzing studies in this fashion can practitioners begin to grade the quality of evidence. Quality of evidence traditionally refers to four components: study design, study quality, consistency, and directness.[45]

Study design refers to the basic format and aim of an investigation. Case-control, cohort, and randomized-controlled trials are all examples of study designs. The aim of case-control and cohort studies is to establish an association between some potential risk factor (i.e., hyperglycemia) and morbidity (i.e., infection) or mortality. While cohort studies can be either retrospective or prospective, case-control studies are, by definition, retrospective. RCTs are prospective and aim to identify causality rather than association. For various reasons, RCTs are considered the most decisive test and are frequently deemed definitive.[46] However RCTs are often not feasible and, particularly with regard to rare diseases or outcomes, may not be as applicable as observational studies. Many have in fact challenged the traditional hierarchical study design paradigm that places RCTs at the top and expert opinion and anecdote at the bottom.[47,48] Regardless, study design must be evaluated and graded based on the merit it holds for a specific population and a consideration of a particular outcome.

Table 92-3 Items to Consider in Evaluating Study Quality

Section/Topic	Descriptor
Title/abstract	How participants were allocated to interventions
Introduction/background	Scientific background and explanation of rationale
Methods	
Participants	Eligibility criteria for participants and the settings and locations where the data were collected
Interventions	Precise details of the interventions intended for each group and how and when they were actually administered
Objectives	Specific objectives and hypotheses
Outcomes	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements
Sample size	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules
Randomization	
Sequence generation	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification)
Allocation concealment	Method used to implement the random allocation sequence clarifying whether the sequence was concealed until interventions were assigned
Implementation	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups
Blinding (masking)	Whether or not participants, those administering the interventions and those assessing the outcomes were blinded to group assignment; if done, how the success of blinding was evaluated
Statistical methods	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses
Results	
Participant flow	Flow of participants through each stage. Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome.
Recruitment	Dates defining the periods of recruitment and follow-up
Baseline data	Baseline demographic and clinical characteristics of each group
Numbers analyzed	Number of participants in each group included in each analysis and whether the analysis was by "intention-to-treat"
Outcomes and estimation	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval)
Ancillary analyses	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.
Adverse events	All important adverse events or side effects in each intervention group
Comment	
Interpretation	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes
Generalizability	Generalizability (external validity) of the study findings
Overall evidence	General interpretation of the results in the context of current evidence

Reprinted from Moher D, et al: The CONSORT Statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 285:1987-1991, 2001.

Study quality is altogether different from the "quality" referred to earlier. Study quality refers to the methodology and study implementation. Adequacy of blinding, method of randomization, selection of placebo, statistical analysis, and reduction of bias would all be examples of factors to be scrutinized when evaluating study quality. The revised CONSORT statement provides a useful template on which study quality indicators can be measured (Table 92-3).[49] The ability to discern adequacy of quality is neither precise nor has it been shown to be consistent among reviewers.[50] This fact has culminated in a collaborative effort to address these shortcomings and develop a process whereby intraobserver and interobserver variability in evaluation and grading of study quality is reduced.[51] Furthermore, study quality does not necessarily equate with superiority of study design. RCTs, for example, are not necessarily of highest quality. Indeed, RCTs can have significant inherent bias.[52,53] Although bias is difficult to eliminate completely from a study, it must be sufficiently reduced for a study to be of high quality. Jadad and colleagues defined study quality as "the likelihood of the trial design to generate unbiased results."[54] However, as Verhagen and associates indicate, although the reduction of bias enhances the internal validity of a study, study quality must take into account a study's external validity.[55] That is, consideration of the applicability and consequence of a study's result to the population as a whole must be deemed a variable when measuring quality. One of the ways to measure external validity is by examining the consistency and directness of an investigation.

Consistency refers to the reproducibility of results among different investigators. Consistency in the magnitude of effect, the direction of effect, and the statistical and clinical significance of a particular effect must be considered. Major inconsistencies among similar populations, by definition, decrease the quality of evidence and generalizability for a particular outcome and should be considered when grading evidence for protocol implementation. *Heterogeneity* is a statistical term used to measure consistency among studies and is frequently used in meta-analyses.

Traditionally, *Cochran's Q* statistic has been calculated by summing the squared deviations of each study's estimate from the overall meta-analytic estimate.[56] However, because this test has been shown to be poor at detecting significant heterogeneity when the number of studies is small, Higgins and colleagues have devised a more widely applicable test statistic, I^2, that describes the *percentage* of total variation across studies that is due to heterogeneity rather than chance alone.[57,58] Values of I^2 range from 0% (no observed heterogeneity) to 100%. Consideration of this value must be taken into account when designing evidence-based protocols.

Finally, the directness of a study more specifically addresses the generalizability and applicability aspect of external validity. This is an important aspect to consider later in this chapter when considering such protocols as tight glycemic control. Does the reduction of mortality seen in a single-center translate into reduced mortality for all surgical ICU patients, or do the results merely represent the consequences of improved patient care at a single institution? The same can be said of high-volume hemofiltration studies and the incidence of sepsis. It has been said that, "most patients to whom we would like to generalize the results of randomized trials would, for one reason or another, not have been enrolled in the most relevant study."[59] Despite this sentiment, *the data are what the data are*, and it is imperative the intensivist employ methods such as evaluation of directness to make decisions.[60] Evaluation of patient population, diagnostic criteria, and surrogate outcomes all must be scrutinized before application of principles or implementation of protocols based on such evidence.[61]

Protocol design must, in some fashion, address each of the above areas and rank them based on importance of outcome, severity of illness, risks and benefits of implementation, and cost. There are a plethora of systems designed to grade the literature; and most address these issues, in some way or another. A review of over 100 of these systems found that there was no single best scheme but rather that application of the *process* of evidence assessment was what was most important.[62]

Protocol Implementation

Designing a critical care protocol and *implementing* a change in practice are very different. Design is based on data review, judgment of applicability, and ranking the strength of evidence, as reviewed previously. Implementation, however, is *real world* and necessitates communication and collaboration among various members of the ICU team. Some of the more important concepts to be addressed before implementing a new protocol are education, defining targets/goals, data collection, analysis of variance, and measurement of impact.

The importance of thoughtful selection of a multidisciplinary task force to evaluate strategies for critical care protocol development and implementation cannot be understated. Most often, such groups will include both physician and nursing leadership as well as selected ancillary professionals (depending on the protocol), such as respiratory therapists, nutritionists, pharmacists, or physical therapists. Particular to the surgical ICU, physician leadership should involve both members from the critical care team and primary surgical representation.

Passive educational approaches such as didactics and dissemination of protocols have generally been shown to be ineffective implementation strategies.[63-65] Changes in physician behavior require outreach, dialogue, and discussion. Protocols that are integrated within a computerized algorithm such that warnings, reminders, and suggestions are generated when appropriate have been shown to be useful.[64] Education must address key points such as the evidence supporting a change in practice, the advantage of a new practice paradigm, and the compatibility of a novel protocol to the existing practice.

Targets and goals are usually related, although defined differently. *Targets* are frequently measured as continuous data points and often set a limit, outside of which patients are not considered to be "within protocol." *Goals* define a realistic outcome presumably obtainable if targets are met. Examples of *targets* would be maintaining glucose levels less than or equal to 150 mg/dL, elevation of the head of the bed greater than or equal to 30 degrees, administration of antibiotics within 3 hours of presentation, and maintaining inspiratory plateau pressures less than 30 cm H_2O for mechanically ventilated patients. Examples of *goals* may be decreasing sternal wound infection rate, decreasing ventilator-associated pneumonia, decreasing progression of sepsis to septic shock, and decreasing ventilator-associated lung injury. Targets and goals must be defined at the outset so that analysis of protocol compliance and effect can be objectively measured.

ICU Protocols

The focus of this section is on three protocols currently being utilized in critical care units. The purpose is not to define a particular care algorithm but rather to illustrate the process that various groups have gone through to devise best care practices. Each topic presented demonstrates a different facet of protocol development and implementation.

Glycemic Control

Since the publication of the landmark "Leuven" study, literally hundreds of protocols implementing tight glycemic control (TGC) have been published (see Chapter 91).[12] Furthermore, this single study has changed the standard of care in surgical ICUs and TGC has since been adopted by various professional societies.[66,67] How to best achieve euglycemia has been the real debate, and groups must identify, within their own infrastructure, a protocol that will work for them. An illustrative example of rational protocol design can be seen with the Stamford Hospital experience (Fig. 92-1).[68] Although the actual protocol devised by this group may be different from others, the process of design and the steps taken should serve as a model for those wishing to do similar work. The problem (i.e., "hyperglycemia is associated with increased hospital mortality") is stated at the outset. A review of the pertinent literature was undertaken and the problem was confirmed. A system was put in place to accurately quantify the problem at their institution, measure pertinent variables, and evaluate outcome. A multidisciplinary team undertook the task of devising a protocol to rectify the problem. Finally, successful implementation of the protocol was established and a statistical analysis was performed to validate the impact of the protocol.

ICU Protocol for Glycemic Management

Approved by the ICU Committee 2/01/03
Last modified by the ICU Multidisciplinary Committee 9/26/03

Rationale

Hyperglycemia is strongly associated with increased hospital mortality as well as organ system dysfunction among critically ill patients.

Goal

The goal of this protocol is to maintain serum glucose <140 mg/dL

Monitoring

Glucose levels will be evaluated *by blood testing or fingerstick testing,* using the following schedules.

Diet	Frequency of monitoring
NPO	Q8 hours: 6AM, noon, 6PM, midnight
PO diet	1 hour AC and QHS
Tube feedings, TPN	Q6 hours: 6AM, noon, 6PM, midnight

For most patients, the 6AM glucose evaluation will be obtained from the morning BMP. If glucose <140 for two consecutive days without treatment, glucose levels can be checked Q12 hours (6AM, 8PM).

Treatment of Hyperglycemia

Glucose value	Action (subcutaneous insulin dose)
<140	No treatment
140–169	3 units Regular insulin, Recheck glucose value in 3 hours
170–199	4 units Regular insulin, Recheck glucose value in 3 hours
200–249	6 units Regular insulin, Recheck glucose value in 3 hours
250–299	8 units Regular insulin, Recheck glucose value in 3 hours
300+	10 units Regular insulin, Recheck glucose value in 3 hours

*If glucose value exceeds 200 on two successive measurements, a continuous insulin infusion will be initiated. Hourly FSG or blood glucose measurements will be obtained in all patients receiving insulin infusions. The sliding scale noted above is a guideline: it can be modified if the patient requires more or less intensive therapy.

Management of Insulin Infusion

1. Initial infusion rate

Glucose value	Insulin dose
200–249	4 units/hour
250–299	6 units/hour
300–399	8 units/hour
400+	10 units/hour

Important points

*All patients receiving continuous insulin must receive a continuous source of glucose either via IV (D5W or TPN), or enteral feeds.

*The insulin infusion is discontinued if the patient has to leave the ICU for a diagnostic test as well as upon discharge from the ICU.

2. Subsequent management, based on hourly glucose checks

Glucose value	Insulin dose
<140	Stop infusion or continue low dose to avoid "rebound"
140–169	2 units/hour
170–199	3 units/hour
200–249	6 units/hour
350–399	8 units/hour
400+	10 units/hour

If this treatment plan does not lead to a decrease in the patient's glucose values, contact the house officer.

Figure 92-1 Example of rational protocol design. (*Reprinted from Krinsley JS: Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 79:992-1000, 2004.*)

Transfusion

It is estimated that as many as one third of patients admitted to an ICU in the United States will receive a blood transfusion (see Chapter 55).[69,70] Although the etiology of anemia in critical care patients is certainly multifactorial and not always obvious, the implications of treatment are becoming evident.[71-73] The risk of transfusion-related infections has decreased but remains. What have become more apparent, however, are the multitude of non-infectious complications associated with allogeneic transfusions, including acute lung injury and immunomodulation.[74,75] Accumulation of these negative data has resulted in the abandonment of the once well-accepted "10/30" rule, first proposed in 1942.[76] How then do intensivists decide on an appropriate transfusion "trigger"?

The best evidence regarding the efficacy of red blood cell transfusion in critically ill patients comes from the Canadian Critical Care Trials Group.[38] Patients who were managed with a restrictive transfusion strategy (maintenance of hemoglobin 7.0-9.0 g/dL, with a transfusion trigger of 7.0 g/dL) had equivalent outcomes (with a trend toward improved outcome) compared with a liberal transfusion strategy (maintenance of hemoglobin 10-12 g/dL, with a transfusion trigger of 10 g/dL). Since that time, there have been two large multicenter studies evaluating the practice of transfusion. The ABC (Anemia and Blood transfusion in Critically ill patients) trial explored the risks and benefits of transfusions in a large European population.[77] The authors were able to show a positive correlation between receipt of any blood transfusion and 28-day mortality (22.7% versus 17.1%, $P = .02$). Furthermore, the mortality risk increased in a dose-related fashion with increased transfusions. A second study, the CRIT trial, performed a similar analysis in the United States.[70] Again, transfusion was independently associated with mortality, and increased blood cell transfusion was associated with increased mortality.

Implementation of a transfusion protocol, however, requires more than a cursory understanding of the literature. As has been reviewed earlier, implementation necessitates an understanding of infrastructure, organization of a multidisciplinary team, a systematic grading of the literature, and a means to measure effect and variability in practice. What one begins to realize when reviewing the literature on this subject is that developing a transfusion "protocol" is meaningless without addressing a comprehensive blood conservation strategy. This is a point not to be overlooked in protocol design. The net effect of protocol implementation may be inconsequential if confounding variables are not addressed. Such variables impacting on the risk of transfusion include, but are not limited to, the following: contribution of phlebotomy,[72,78] inadequate salvage techniques,[79,80] and an inattentiveness to proper pharmacologic hemostatic agents.[81] One of the most cohesive and logical plans to address this topic has been published and should be used as a model for proper protocol implementation.[82]

Ventilator Weaning

There are few process-based interventions that are made in the ICU that have been more rigorously studied than the weaning of mechanical ventilation (see Chapters 91 and 93). Indeed, protocols in this area have been tested and validated, culminating in evidence-based guidelines.[83-88] Given the plethora of data, including three large randomized controlled studies that have demonstrated reduction in duration of mechanical ventilation, intensivists would be remiss if they did not currently have a protocol in place to address this issue.[41,89,90] The reason ventilator weaning protocols are being highlighted, however, is because they illustrate a critical point to understand when designing protocols: regardless of the design and the involvement of personnel, an ICU protocol will ultimately fail if confounding factors are not addressed and included within the protocol. In regard to mechanical ventilation in the ICU, one confounding factor is sedation and analgesia. Without some interface between the timing of ventilator weaning and the interruption of sedation, the compliance and success of the protocol is at jeopardy.[40,91]

The Future of Protocolized Medicine

One of the most frequent barriers to the implementation of established protocols is practitioner compliance. As was reviewed earlier in the chapter, anecdotal experience is often the enemy of evidence-based practice. Some groups have now begun looking at the removal of humans, altogether, from the decision-making process and, instead, relegating the assessments to computers and handheld devices.[86,92-95] What is more important, however, will be physicians' understanding of current technology and of recent literature, an appreciation of their limitations, and the ability to cohesively and continuously review these elements and outcomes in a pragmatic manner aimed at developing best practice guidelines.[96] Several groups have already initiated such reviews in areas such as traumatic brain injury,[97] nutritional support,[98] glycemic control,[99] and sedation/analgesia.[100] The real question that must be answered, however, is whether intensive care has become too complex to rely on a physician's ability to sort through and interpret the thousands of pieces of information that must be addressed each day.

Although protocols inevitably decrease the variability in practice, they do not address the multifaceted approach to ICU care. Some have advocated systematic development of checklists to remind team members of the multitude of goals for every patient, rather than increased protocol generation. An example is the FAST HUG mnemonic developed by Vincent[101]:

F—Feeding
A—Analgesia
S—Sedation
T—Thromboprophylaxis
H—Head of bed elevation
U—Ulcer prophylaxis
G—Glycemic control

Each component of the mnemonic should be addressed with each patient, every day. Whereas protocols may pertain and be applicable to any of the systems, the checklist helps prevent intensivists from oversight.

Conclusion

Protocol development and implementation is a complex and labor-intensive process. A multidisciplinary team is required and a specific educational plan is necessary to properly implement all facets of a protocol. Although evidence-based medicine is at the heart of the process and a detailed analysis of the literature is required, clinical acumens and anecdotes need not be ignored. Protocols are designed for the masses, and it requires a thoughtful and educated intensivist to identify those patients who may not be applicable. Protocols also allow for standardization of research protocols and minimization of confounding variables. The ability to measure the effect of a particular protocol and adapt appropriately is the key to successful protocol application. The future of critical care will certainly see an increase in the number of pro-

tocols based on quality evidence. These protocols will likely interface with various computers and handheld devices to help ensure compliance and more easily interpret the flood of information obtained on a daily basis. Intensivists will need to learn which patients are appropriate for such interventions and, with the help of checklists, ensure comprehensive patient care.

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93 Respiratory Care

Key Points

1. Acute respiratory failure requiring ventilatory support occurs if a pathologic process, or a pharmacologic intervention (a) impairs the capacity of the respiratory muscles to generate sufficient Pmus; (b) increases the ventilatory requirements above the muscle capacity; (c) increases the workload associated to the act of breathing.
2. Ventilator-induced lung injury (VILI) acts as the "engine" of multiple organ dysfunction syndrome (MODS).
3. In normal subjects at rest, the end-expiratory lung volume (EELV) closely corresponds to the elastic equilibrium point of the respiratory system (functional residual capacity [FRC]). Whenever the time available for expiration is shorter than the time required for passive emptying back to FRC, air trapping will develop. Consequently, alveolar pressure will remain positive at the end of expiration, which generates a "dynamic hyperinflation," that is, a positive end-expiratory alveolar pressure, called intrinsic PEEP (PEEPi) or auto-PEEP.
4. Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is characterized by abnormal mechanical properties of the respiratory system with the hallmark features of a reduced FRC and a reduced static compliance of the respiratory system. Measurements of the inspiratory volume-pressure curves of the respiratory system have been used in mechanically ventilated patients with ALI/ARDS as a means of assessing their status and progress and to optimize the use of PEEP and mechanical ventilation.
5. The ARDSNet study was to enroll up to 1000 patients, but accrual was stopped at 861 patients when an interim analysis revealed that the mortality rate in the lung protective group was 22% lower than in the control group. The beneficial results using 6 mL/kg ventilation (predicted body weight) occurred in all patient groups, including septic and nonseptic patients, and those with different degrees of lung dysfunction as assessed by respiratory system compliances.
6. At present the optimal level of PEEP and the best method used to set PEEP have not been definitively established for ARDS and ALI patients. Prone positioning has been demonstrated to improve oxygenation in patients with acute hypoxic respiratory failure but does not improve mortality, so that this therapeutic option might be considered useful only for ARDS patients with refractory hypoxemia. Similarly, inhaled nitric oxide led to improvements in oxygenation in ARDS patients but there was no beneficial effect on mortality. Thus, inhaled nitric oxide cannot be recommended for the routine treatment of ALI/ARDS but it may be useful as a rescue therapy in patients with refractory hypoxemia.
7. Applying noninvasive pressure support ventilation (PSV) (to unload inspiratory muscles and to increase tidal volume [V_T]) and PEEP (to counterbalance the inspiratory threshold load for the inspiratory muscles posed by PEEPi) in the early course of exacerbations of chronic obstructive pulmonary disease (COPD) reduces intubation rates, the frequency of complications, the in-hospital mortality, and the length of stay.
8. Noninvasive techniques, both continuous positive airway pressure (CPAP) and noninvasive positive-pressure ventilation (NIPPV), have been shown to reduce the need of intubation and improve outcomes in patients with acute cardiogenic pulmonary edema (ACPE). Some authors suggest that CPAP should be considered as the first-line treatment in patients with ACPE because it is less expensive and easier to implement and as efficacious as NIPPV. However, it might be better to use NIPPV in hypercapnic patients with ACPE.

Definitions

The target of ventilation is to generate flow and volume to provide adequate alveolar ventilation with the minimal work of breathing. Contraction of the respiratory muscles provides the "power" required for ventilation. The phrenic nerve regulates the timing and the intensity of this power integrating inputs from chemoreceptors, pulmonary stretching receptors, variations in metabolic demands, and so on. During "spontaneous breathing" the respiratory muscles generate a pressure (Pmus) that produces flow against the resistive and volume against the elastic properties of the respiratory system. Under these circumstances, the act of spontaneous breathing can be described at any instant as follows:

$$\text{Pmus} = \text{Pres} + \text{Pel} \quad (1)$$

where Pres represents the resistive pressure and is a function of flow (Pres = flow × resistance) and Pel represents the elastic recoil pressure and is a function of volume (Pel = volume × elastance). Assuming that resistance and elastance are linear, equation 1 becomes:

$$\text{Pmus} = (\text{flow} \cdot \text{ resistance}) + (\text{volume} \cdot \text{ elastance}) \quad (2)$$

Acute respiratory failure requiring ventilatory support occurs if a pathologic process or a pharmacologic intervention (1) impairs the capacity of the respiratory muscles to generate sufficient Pmus; (2) increases the ventilatory requirements above the muscle capacity; or (3) increases the workload associated to the act of breathing. Application of "positive" pressure (i.e., a pressure higher than the atmospheric pressure) to a patient's airway opening during the inspiratory phase is currently the main method to administer "assisted breathing" and restore adequate ventilation. The resulting pressure gradient between a patient's airway opening and alveoli generates a "positive" flow (i.e., directed from the ventilator to the patient). The expiratory phase, which is passive, depends on the end-inspiratory pressure gradient between alveolar pressure (which is positive, due to the elastic recoil pressure stored during the inspiratory phase into the respiratory system) and airway opening pressure. Under these circumstances, the pressure applied at the airway opening of the patient (Pao) includes the pressure generated by the ventilator (Pappl) plus the pressure generated by the contraction of the respiratory muscles according to the following equation:

$$\text{Pmus} + \text{Pappl} = (\text{flow} \cdot \text{ resistance}) + (\text{volume} \cdot \text{ elastance}) \quad (3)$$

Based on the relative contribution of the patient's Pmus to the total pressure applied at the airway opening, modes of mechanical ventilation can be described as "totally" or "partially" ventilator controlled.

- *Total ventilator-controlled ventilatory support:* Patient's own breathing pattern is totally replaced by the ventilator and Pmus is abolished by sedation and respiratory muscle paralysis and the ventilator imposes flow, volume, and/or pressure.
- *Partial patient-controlled ventilatory support:* The ventilator provides a fixed amount of support and the patient's Pmus is preserved. The ventilator delivers a preset VT/inspiratory flow/Pappl in response to the patient's inspiratory effort, and the patient is able to set his or her own respiratory rate and, in some cases, also the duration of inspiratory time and expiratory time and the ratio of inspiratory time to total breath cycle duration.

The capability of restoring gas exchange, unloading respiratory muscles, and relieving a patient's dyspnea with these modes of partial ventilatory support depends on the match between the ventilator settings and the patient's ventilatory demands, that is, on the "patient-ventilator interactions."[1]

Modes of Mechanical Ventilation

Positive-pressure breaths on the ventilator can be categorized by three variables: (1) the *trigger* variable (what initiates the breath), (2) the *limit* variable (what governs the gas delivery), and (3) the *cycle* variable (what terminates the breath). The variables that can regulate the triggering of ventilation include time (during controlled mechanical ventilation) or flow and pressure (during assisted mechanical ventilation). Ventilator gas delivery can be regulated to deliver flow, volume, or pressure. The ventilator can cycle from inspiration to expiration based on a preset time or on a flow/pressure threshold level. These three variables that can be set on the ventilator then affect three physiologic variables involved with breathing: (1) the ventilatory drive, that is, when inspiration starts, (2) ventilatory requirements (how much flow and volume are necessary to satisfy the metabolic demands), and (3) the timing of the integrated circuits generating the respiratory rhythm as measured by the duration and ratio of inspiratory time to the total breath cycle duration.[2]

Total Ventilator-Controlled Ventilatory Support (Controlled Mechanical Ventilation)

The main characteristic of controlled mechanical ventilation is that the variable used by the ventilator (and set by the health care provider) to *trigger* and to *cycle off* the breath is time. The *limit* variable that governs gas delivery during ventilator-controlled ventilatory support is flow and volume (controlled mechanical ventilation [CMV]) or pressure (pressure-controlled ventilation [PCV]) (Fig. 93-1). With the former, the ventilator applies either a constant (square shaped) or nonconstant (in the majority of the cases decelerating) flow to deliver a preset tidal volume (VT). Flow is the independent variable (i.e., the ventilator maintains the predetermined flow pattern whatever the patient's impedance), and the airway opening pressure (Pao) profile during inflation depends on the mechanical characteristics of patient's respiratory system. With the latter, the ventilator applies a preset positive-pressure level (commonly, square shaped) to the patient's airway opening. Pao is therefore the independent variable held constant by the ventilator, whereas delivered VT will depend on the inspiratory time and on the mechanical characteristics of the respiratory system. The inspiratory flow starts with a peak followed by the exponential flow decay and becomes nil as soon as the applied pressure equals alveolar pressure.

The choice between volume- and pressure-cycled modes is not supported by randomized controlled trials. Volume-cycled modes are to be preferred when maintaining minute ventilation is crucial, such as in head-injured patients. Physiologic studies have suggested a more homogeneous distribution of VT when

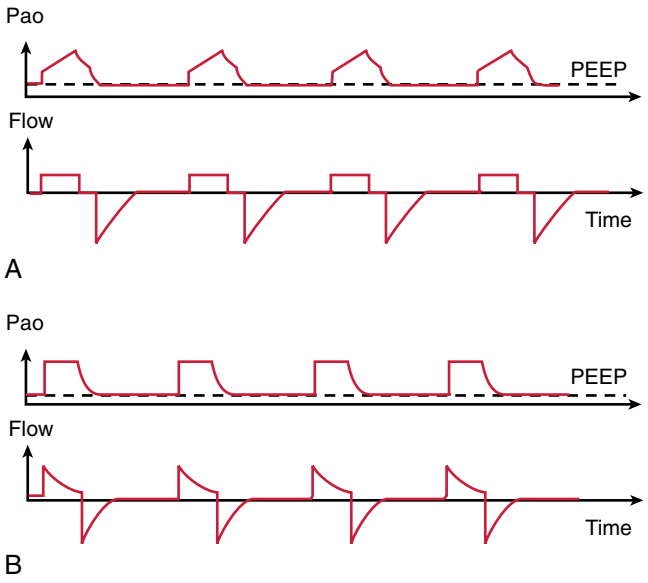


Figure 93-1 Tracings of flow and airway opening pressure (Pao) during the two basic controlled intermittent positive-pressure ventilation (IPPV) modes. Volume-cycled (**A**) and pressure-cycled (**B**) IPPV. PEEP, positive end-expiratory pressure.

ventilating patients with acute respiratory distress syndrome (ARDS) with the pressure-cycled mode.[3]

A controlled mode able to share the theoretical advantages of constant pressure with the guarantee of delivering a preset VT has been recently offered in newer mechanical ventilators ("pressure-regulated volume control" or "volume plus"). It consists of a closed-loop algorithm that, based on the measurement of static compliance of the respiratory system, changes the level of applied pressure on a breath-by-breath basis to match a "target" tidal volume. There are no data documenting superiority of the newer ventilator modalities.

Partial Patient-Controlled Mechanical Support (Assisted Mechanical Ventilation)

Partial ventilatory support techniques are intended to unload the respiratory muscles and relieve dyspnea in patients with impaired neuroventilatory coupling. The main characteristic of assisted mechanical ventilation is that the ventilator provides ventilatory support while the patient's Pmus is preserved. The patient will therefore be able to contribute some degree of ventilator support. The "degree of freedom" gained by the patient may include setting the respiratory rate and establishing the breathing pattern (inspiratory time, expiratory time, duration and ratio of inspiratory time to total breath cycle duration). The capability of restoring gas exchange, unloading respiratory muscles, and relieving a patient's dyspnea with these modes of partial ventilatory support depends on how well there is a match between the ventilator settings and the patient's ventilatory demand.[1,2,4]

The rationale for preserving diaphragmatic activity in the critically ill patient needing ventilatory support is to reduce the need for sedation and paralysis, avoid disuse atrophy of the respiratory muscles, and minimize the cardiovascular side effects of mechanical ventilation.[5] Moreover, as compared with controlled modes, partial ventilatory support has been shown to improve ventilation/perfusion $\left(\dot{V}/\dot{Q}\right)$ mismatch by reaerating dependent lung areas, perhaps through the effects of contraction of the diaphragm. However, if patient-ventilatory asynchrony develops it may even cause harm and delayed weaning from mechanical ventilation or both.

Assist/Controlled Mechanical Ventilation

The patient is allowed to set his or her own respiratory rate by activating the inspiratory trigger function (as a safety measure, if no spontaneous effort occurs, the ventilator will deliver controlled breaths at a preselected backup rate). The variable used by the ventilator to *cycle off* the breath is time. The *limit* variable that governs gas delivery is flow and volume (assisted/controlled mechanical ventilation [A/CMV]) or pressure (assisted pressure controlled ventilation [A/PCV]).

To activate a pressure trigger, the patient needs to decrease pressure in the respiratory circuit at a preset threshold level, whereas with a flow trigger system the patient needs to generate a preset amount of inspiratory flow. The inspiratory effort necessary to trigger a breath has been estimated to be about 17% and about 12% of the total inspiratory effort during pressure and flow triggering, respectively.

Several studies have questioned the ability of A/CMV to meet patient inspiratory demand. Marini and coworkers showed that during patient-triggered breaths, effort does not cease with the onset of gas delivery and that total inspiratory workload during A/CMV may even exceed the work performed during spontaneous breathing.[6] Physiologic studies have shown that patient-ventilator synchrony during A/CMV critically depends on the quality of the trigger mechanism (pressure versus flow-triggers) and on the kind of controlled breath delivered (volume versus pressure-cycled): combining flow-trigger and A/PCV improves patient ventilator interactions owing to the higher inspiratory peak flow as compared with the volume-cycled mode.[7]

However, with A/CMV, by definition, the neuroventilatory coupling is not restored and the amount of work performed by the ventilator will decrease at expense of patient's effort. This ventilatory mode is in general poorly tolerated by awake subjects and may induce respiratory alkalosis and air trapping, particularly in patients with dynamic hyperinflation.

Synchronized Mandatory Ventilation

Synchronized mandatory ventilation (SIMV) allows the patient to breathe spontaneously between a preset number of assist/controlled breaths. Depending on the SIMV modality, controlled breaths may be volume or pressure cycled. Spontaneous breathings may be supported by a variable degree of pressure support (see next section). Varying the rate of mandatory breaths allows either nearly total ventilatory support or fully spontaneous breathing. Regarding patient-ventilator interactions, SIMV shares the same limitations as A/CMV

Pressure Support Ventilation

Pressure support ventilation (PSV) is at present the most popular partial ventilatory support technique either to wean patients from controlled ventilatory modes or to ventilate patients who have acute respiratory failure.[8] During PSV, the patient's spontaneous effort triggers the ventilator and is assisted by a constant positive

pressure (Pappl; see Equation 3). VT depends on the interplay between Pmus, Pappl, and respiratory system impedance (see equations 2 and 3). As a consequence, PSV unloads respiratory muscles and improves the interaction between the patient efforts and VT, in the sense that, for a given inspiratory effort, the patient generates a greater volume than during spontaneous breathing. The ability of PSV to relieve dyspnea, unload the inspiratory muscle effort, and improve gas exchange has been clearly shown.[9] However, the patient is relatively unable to modulate the ventilatory pattern through changes in inspiratory effort while on PSV.[9]

Cycling from the inspiratory to the expiratory phase in PSV occurs when the inspiratory flow rate decreases to a preset level (which, depending on the ventilator, is a fixed or adjustable percentage of peak inspiratory flow). Expiratory sensitivity can be fixed or can vary from 5% to 90% or from 5 to 25 L/m. Modifying the pressure rise time at the beginning of inflation (inspiratory pressure-slope) can influence the expiratory threshold by its effect on the peak inspiratory flow value. There is some evidence that the rapid pressure rise that occurs during PSV might reduce the work of breathing in patients.[10] The decay of inspiratory flow is clearly a surrogate signal to the patient's neural network.[11] If the patient performs weak inspiratory efforts or the applied pressure is relatively high as compared with patient's needs, or both, the ventilator will prolong its inspiratory assistance well beyond the duration of spontaneous inspiration, generating a severe discrepancy between the "neural" and "mechanical" inspiratory time.[12] Adjusting applied pressure to maintain a respiratory rate between 20 and 35 breaths/min and VT between 5 and 8 mL/kg has been recommended as a clinical means to optimize ventilatory support during PSV.[13]

Proportional Assisted Ventilation

During proportional assisted ventilation (PAV), the ventilator amplifies the patient's effort in generating pressure in proportion to the patient's generated flow and volume. What is preset is not a target pressure but the proportion between the patient's inspiratory muscle effort and the ventilator-applied pressure.[9,14]

To realize a proportional assistance, the ventilator measures the spontaneous patient's instantaneous flow and volume through its internal sensors while the intensivist is required to measure and then set the values for elastance and resistance. Knowing all these parameters, the ventilator processor then estimates Pmus (see Equation 2) and assists the patient's effort in a proportional fashion. To do so, the ventilator delivers a pressure assist in proportion to the ongoing administered volume summed with another pressure assist in proportion to the instantaneous inspired flow.

The difference between PAV and PSV is a larger degree of tidal volume variability over time with PAV.[15] A sudden hypercapnic stimulus during PAV triggers a compensatory increase in minute ventilation mostly obtained by an increase in tidal volume, with no change in respiratory rate. In contrast, patients ventilated with PSV react by increasing respiratory rate but are unable to significantly increase VT. Thus, as compared with PSV, PAV better mimics the physiologic response to hypercapnia.[7] PAV has been shown to significantly unload the inspiratory muscles and improve the breathing pattern in patients with chronic obstructive pulmonary disease (COPD).[16]

To correctly set PAV a reliable estimation of elastance and resistance needs to be done (see Equation 2). If the estimate is correct, the pressure generated by the ventilator will be lower than the pressure required to offset the passive properties of the respiratory system: the patient will maintain his or her spontaneous respiratory activity, and the ventilator will continue to work by proportionally amplifying the patient's efforts. Both underestimation and overestimation of elastance and resistance may critically impair these patient/ventilator interactions. If elastance and resistance are *underestimated,* the level of assistance provided by PAV would be insufficient to relieve the patient's dyspnea, while, in contrast, if elastance and resistance are *overestimated,* a positive feedback will develop and the ventilator will continue to deliver flow and volume while the patient stops his or her inspiratory effort (the "*run-away*" phenomenon). The full potential benefits of PAV may be obtained only with a correct estimation of the elastic and resistive properties of the respiratory system and a continuous adaptation of the level of assistance to the changes in respiratory mechanics over time. To ameliorate these problems, PAV plus (PAV+) allows an automatic and noninvasive measure of elastance and resistance through a ventilator's internal sensors, and thus the ventilator continuously adapts the proportional assistance according to these measurements. The noninvasive assessment of the respiratory system mechanics is based on the application of brief (100 to 300 msec) occlusions on airway opening at end inspiration during PAV.[17,18]

Neurally Adjusted Ventilatory Assist

Neurally adjusted ventilatory assist (NAVA) consists of an innovative system able to measure electrical activity of the diaphragm by means of an electrode array inserted into a nasogastric tube that is placed in the lower esophagus and then is able to sense the diaphragmatic activity. This signal from the diaphragm is used both to trigger the ventilator ("neural" trigger function) and to assist the patient's inspiratory effort in proportion to the diaphragmatic electrical activity. With NAVA, the patient's respiratory drive controls the assisted positive breaths in all phases of the ventilatory cycle, from triggering to cycling between the inspiratory and the expiratory phase (Fig. 93-2). Any change in the patient's ventilatory output is matched on a breath-by-breath basis. Although several preclinical and experimental studies documented the potential advantages of NAVA to correctly restore the neuroventilatory coupling,[19,20] this promising technique is not yet available on current ventilators and there are a number of technical issues that have to be resolved before it can be used routinely.

Positive End-Expiratory Pressure/ Continuous Positive Airway Pressure

Positive end-expiratory pressure (PEEP) is the positive pressure applied at the end of expiration during mechanical ventilation. A constant level of positive pressure applied to a spontaneous breathing cycle is named continuous positive airway pressure (CPAP). Physiologic consequences of PEEP/CPAP depend on its effects on gas exchange, pulmonary compliance, and systemic hemodynamics.

Effects on Gas Exchange

PEEP/CPAP may improve arterial oxygenation by reexpanding functionally collapsed alveoli, redistributing lung water, and thereby, reducing $\dot{V}/\dot{Q}$ mismatch.

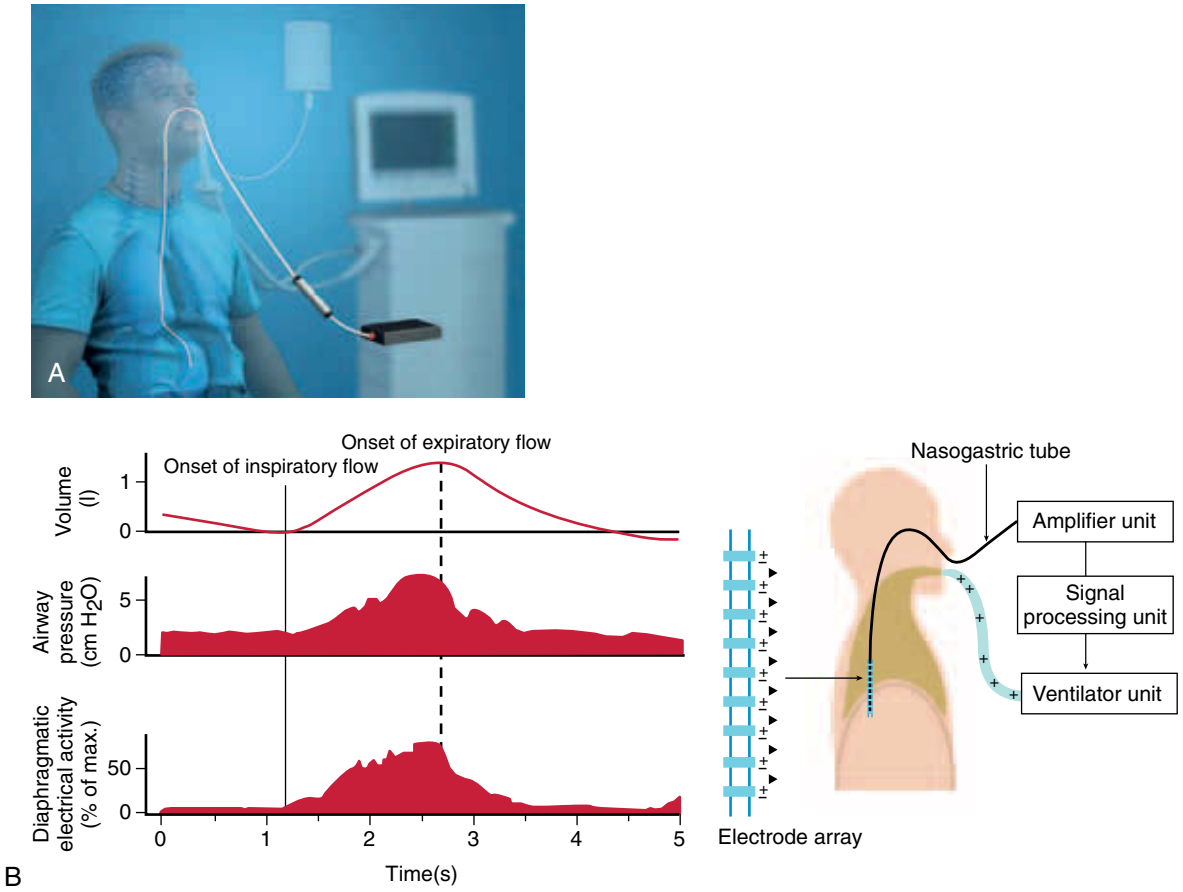


Figure 93-2 **A** and **B,** The neurally adjusted ventilatory assist (NAVA) concept. An electrode array, inserted into a nasogastric tube and placed in the lower esophagus, is able to sense the diaphragmatic activity. This signal is used both to trigger the ventilator ("neural" trigger function) and to assist patient inspiratory effort in proportion to the diaphragmatic electrical activity.

Alveolar recruitment, defined as the amount of noninflated tissue that is reexpanded by a given level of PEEP/CPAP, results in a more homogeneous distribution of the V_T and an increase in the functional residual capacity (FRC). Moreover, the application of PEEP/CPAP leads to the redistribution of lung water from the alveolar space to the perivascular interstitial space and improves $\dot{V}/\dot{Q}$ mismatch by diverting blood flow from shunt regions to normal regions.

All these effects depend on whether the applied PEEP/CPAP recruits previously collapsed alveoli.[21,22] If the applied PEEP/CPAP induces alveolar recruitment, a reduction in shunt with improvement in oxygenation and a reduction in dead space will be seen. On the other hand, if hyperinflation of normal alveoli occurs predominately, a rise in $Paco_2$ due to the increase in dead space will be seen while the Pao_2 could decrease, depending on whether the applied PEEP/CPAP deceased cardiac output.

PEEP/CPAP Effects on Respiratory Mechanics

Compliance of the respiratory system (i.e., $V_T \div$ Ppl − PEEP) represents a good estimate of the elastic properties of the respiratory system. Application of PEEP/CPAP may lead to the following effects on compliance:

- Increase in compliance, suggesting alveolar recruitment
- No change in compliance, indicating that ventilation is occurring on the linear portion of the volume/pressure relationship of the respiratory system
- Decrease in compliance indicating lung overdistention

The interpretation of the effects of PEEP/CPAP on the respiratory system requires assessment of both the lung and chest wall mechanics.

PEEP/CPAP Effects on Hemodynamics

The application of PEEP/CPAP may affect hemodynamics through several different mechanisms: decreased venous return to the right side of the heart, increased right ventricular afterload, decreased ventricular compliance, and decreased ventricular contractility.[23-25] Overall, the hemodynamic consequences of the application of PEEP/CPAP depend on the prior ventricular loading conditions and the ventricular function and on the effect of PEEP/CPAP on lung mechanics.

In patients with normal cardiac function, the main consequence of increased intrathoracic pressure is the reduction of venous return and a reduction of cardiac output. Because the right ventricular preload decreases, an adequate circulating blood volume is required before the application of PEEP/CPAP to

prevent depression of right ventricular output. In patients with poor left ventricular function or congestive heart failure, the increase in intrathoracic pressure reduces the left ventricular transmural pressure, leading to a reduction in left ventricular afterload and an improvement in left ventricular function. In these patients, cardiac output is relatively insensitive to the reduction in venous return because diastolic volume is elevated.[26]

Noninvasive Ventilation

Mechanical ventilation is usually applied through a endotracheal tube or a tracheotomy. An impressive series of studies have demonstrated the efficacy of mechanical ventilation noninvasively applied to patient's mouth or nose to restore respiratory function minimizing the side effects associated with invasive ventilation. Noninvasive ventilation is delivered almost exclusively through partial ventilatory support techniques. Potential advantages of avoiding endotracheal intubation include less patient discomfort, reduced need for sedation, and a lower incidence of ventilator-associated pneumonia and sepsis.[27] Clinical trials have shown that in specific clinical situations there is a significant improvement in patient outcomes when endotracheal intubation can be avoided.[28] However, the success of noninvasive ventilation critically depends on the correct patient selection and on the expertise of the team applying it, because recent data suggest that patients intubated after an unsuccessful trial of noninvasive ventilation can experience a longer duration of invasive mechanical ventilation and a longer intensive care stay.[29]

The established indications for noninvasive ventilation, supported by large randomized controlled trials, are acute COPD exacerbation, acute cardiogenic pulmonary edema, postoperative respiratory failure, and respiratory failure in immunocompromised patients (e.g., solid organ transplant recipients and bone marrow transplant patients; see later).[29]

In other clinical situations, noninvasive ventilation should be applied with caution. Lower intubation rates and shorter hospital lengths of stay were reported in patients with community acquired pneumonia treated with noninvasive ventilation.[30] In experienced centers the application of noninvasive ventilation to ARDS patients as a first-line intervention avoided intubation in approximately 54% of the cases,[31] whereas CPAP was not associated with better survival nor with a decreased length of hospital stay.[32] The use of noninvasive ventilation as a means to accelerate weaning from invasive ventilation has been the object of extensive, although inconclusive, clinical investigations. Its use as a weaning technique in "difficult to wean" COPD patients when the standard criteria for spontaneous breathing were not met was associated with conflicting results on the duration of mechanical ventilation and mortality in two clinical studies.[33,34] Recently, it has been shown that noninvasive ventilation does not prevent reintubation in patients developing acute respiratory failure after extubation.[35] There are too few studies available to establish a place for noninvasive ventilation in acute asthma, upper airway obstruction, and trauma. Other possible fields of application are during fiberoptic bronchoscopy in hypoxemic or hypercapnic patients[36] and as a palliative therapy in patients who are not candidates for invasive ventilation.[37]

Two recent publications evaluated the efficacy on noninvasive ventilation in two large and distinguished hospitals (Massachusetts General Hospital, Boston, and Molinette Hospital, Turin, Italy).[38,39] Both studies indicated that noninvasive ventilation as routine standard medical care resulted in the intubation of a similar percentage of patients with respiratory failure due to cardiogenic pulmonary edema and COPD exacerbation as shown in randomized controlled trials but in a higher percent of patients with hypoxemic respiratory failure than reported in these trials. Failure of noninvasive ventilation was associated with high hospital mortality for patients with hypoxemic respiratory failure.

Predictors of success for noninvasive ventilation include younger age, lower acuity of illness (as quantified by the Acute Physiology and Chronic Health Evaluation II [APACHE II] or SAPS [Simplified Acute Physiology Score] II score), ability of the patient to cooperate, intact dentition, technical ability to minimize air leaks, moderate hypercapnia (i.e., between 45 and 90 mm Hg), and moderate acidosis (i.e., pH between 7.35 and 7.10).[40] A successful trial of noninvasive ventilation should induce a trend toward slower respiratory rates and decrease in $Paco_2$ within 30 to 60 minutes.

The ideal interface for noninvasive ventilation should allow optimal patient comfort and minimal air leaks. Both masks (oronasal or nasal) and helmets are currently available. The oronasal mask induces air leaks in 80% to 100% of the patients, facial skin reddening in 20% to 34%, mask intolerance in 8% to 32%, nasal-mouth dryness and nasal congestion in 10% to 20%, nasal bridge ulceration in 2% to 31%, eye irritation in 16%, gastric distention in 8%, and aspiration in 6% All these side effects may be minimized by using the helmet, but this interface may induce delay in ventilatory assistance with PSV and cause significant acoustic noise.[41]

Patient monitoring during noninvasive ventilation includes frequent checking of the interface to evaluate CO_2 rebreathing, accidental disconnection from the ventilator, air leaks, skin necrosis, and the ability of the patient to clear secretions. Monitoring of physiologic parameters (oximetry, arterial blood gases, exhaled Vt, respiratory rate, use of accessory respiratory muscles, paradoxical abdominal motion, gastric distention, heart rate, and blood pressure) and of subjective parameters (mental alertness, comfort, dyspnea) is of paramount importance for patient safety. It has been estimated that respiratory therapists spent more time with patients treated with noninvasive ventilation when compared with the time they spend with patients who are endotracheally intubated in the first 8 hours, but this trend is reversed in the subsequent 8 hours.[42]

Nonconventional Ventilatory Support

Modalities of ventilatory support described previously are defined as "conventional" because they are based on two principles: (1) they deliver a Vt higher than the dead space volume; and (2) they apply a positive pressure at the airway opening. Hereafter we will describe modalities of ventilatory support that are defined as nonconventional when they are based on the application of a Vt lower than the dead space volume (*high-frequency oscillation*) and on the use of external gas exchangers that bypass the lung and the heart so they provide ventilator support without the need (or with limited need) of positive pressure (*extracorporeal support*).

High-Frequency Oscillation

High-frequency oscillation (HFO) is an open ventilator system that maintains continuous exchange with the atmosphere and

escape of ventilated gases through an open port. A bulk flow provides fresh air to the circuit, and small tidal volumes delivered by the strokes of the device sustain alveolar ventilation. During conventional mechanical ventilation, V_T is higher than alveolar dead space (V_{DS}) and alveolar ventilation can be described by the following equation:

$$f V_A = f (V_T - V_{DS})$$

where V_A is the alveolar volume, V_{DS} the dead space volume, and f the frequency. This equation predicts that the minute alveolar volume is a positive value if V_T is higher than dead space. During HFO a V_T lower than the anatomic dead space (1-3 mL/kg) with a very high frequency is delivered (3-15 Hz).[43]

An important concept during HFO is that it provides an *active* expiration. In other words, during HFO, inspiration and expiration are independent of the level of applied pressure and CO_2 removal and oxygenation are not coupled to the inflation/deflation of the lung. Alveolar gas exchange is therefore entirely due to the bulk flow of fresh air delivered through the circuit through different mechanisms, including (1) direct ventilation by low V_T of those alveoli located more proximally; (2) pendelluft occurring between nearby lung units with different time constants; (3) streaming of inspiratory/expiratory flow in diverging alveolar ducts; and (4) axial convection and lateral mixing.

Extracorporeal Support

Extracorporeal support (ECMO) was proposed to maintain the lung "at rest" while providing adequate gas exchange, but a randomized clinical trial did not show a decrease in mortality.[44] A modified technique (low-frequency positive-pressure ventilation with extracorporeal CO_2 removal [LFPPV-ECCO2R]) was later proposed to inflate the lungs to moderate pressures to maintain FRC while CO_2 removal was ensured by a low flow partial veno-venous bypass. Although the first studies showed promising results, further studies failed to confirm beneficial effects.[45] Consequently, this technique is considered only in patients with severe hypoxemia and hypercapnia unresponsive to optimal management. Results of an ongoing randomized clinical trial comparing patients treated locally with conventional techniques or transported to a center that offers ECMO are expected (www.cesar-trial.org).

Recent advances in technology have proposed new extracorporeal CO_2 removal devices as rescue therapy in severe ARDS to optimize a protective ventilatory strategy. The arteriovenous pumpless devices use the arteriovenous pressure gradient to force blood through a very low-resistance heparinized circuit.[46] The main advantages are lower anticoagulation requirements, small priming volume, little mechanical damage to blood components, and absence of recirculation. On the other hand, it does not offer direct blood flow control, it increases left-to-right shunt, and it could lead to lower-limb ischemia owing to prolonged arterial cannulation. Recently, a new venovenous bypass has been proposed and found to be efficient in removing 20% of CO_2 in the experimental setting.[47]

Monitoring Controlled Mechanical Ventilation

The analysis of the airway opening—time (Pao-t) signal obtained when applying volume-cycled constant-flow ventilation with a brief end-inspiratory pause allows monitoring of the mechanical properties of the respiratory system. The Pao-t during constant flow includes the following information (Fig. 93-3):

- *Resistive pressure increase* (AB tract in Fig. 93-3) represents the step increase in Pao that occurs at the beginning of inspiratory flow delivery. It is not perfectly perpendicular to the time axis but shows a discrete slope owing to the inability of the ventilator to generate a sudden increase in flow and to the inhomogeneities of different lung regions.
- *Elastic pressure increase* (BC tract in Fig. 93-3) represents the increase in Pao generated by the progressive inflation of respiratory system, whose slope depends on the elastic properties of the respiratory system. It is not always linear, because its profile may be curvilinear when the respiratory system compliance varies with lung inflation (see later).
- Pao_{peak} (point C in Fig. 93-3) is the peak in Pao reached at end inspiration. For a given flow rate and inspiratory time, Pao_{peak} expresses both the "resistive" and "elastic" pressure increase. After Pao_{peak}, the Pao-t profile during the end inspiratory pause (when both the inspiratory and the expiratory valves are closed) can be divided into two regions: (1) an immediate pressure drop from Pao_{peak} to $Pao_{occlusion}$ (point D in Fig. 93-3) owing to the interruption of flow that makes the "resistive" pressure nil and (2) a slower decay from $Pao_{occlusion}$ to the end-inspiratory pressure (Pao_{plat}) (point E in Fig. 93-3) that depends on a gas redistribution process between areas with different elastic and resistive characteristics and on the inertial properties of lung tissue. For a given V_T, Pao_{plat} expresses the elastic properties of the respiratory system. After the end-inspiratory pause, the expiratory valve is open while the inspiratory valve is closed and the respiratory system is allowed to passively exhale to the elastic equilibrium point of the respiratory system (EF tract in Fig. 93-3). If an end-expiratory valve is added to the expiratory limb of the ventilatory circuit, the FG tract is equal to the value of the *applied PEEP*.

The rate of change of the airway pressure-time curve during constant flow inflation has been shown to correspond to the rate of change of the compliance of the respiratory system during tidal inflation: a progressive increase in slope of the curve indicates that compliance is progressively increasing, whereas a progressive decrease in slope of the curve indicates that compliance is decreasing with tidal inflation; a linear increase of pressure indicates that compliance is constant throughout inflation.[48,49] Progressive increase or decrease in compliance during inflation is associated with tidal alveolar opening and collapse and tidal alveolar hyperinflation, respectively,[50] that is, with the main mechanisms responsible for mechanical ventilation-induced lung mechanical stress.[51] Hence, by analyzing the Pao-t profile during a period of constant-flow inflation (BC; see Fig. 93-3) the occurrence of tidal alveolar recruitment/de-recruitment or overinflation or both may be detected noninvasively (the *stress index* concept; Fig. 93-4). Recent data indicate that titrating the PEEP level according to the *stress index* analysis can minimize ventilator-induced lung mechanical stress in ARDS patients and suggest that continuous monitoring of the *stress index* may be useful to set up a lung-protective ventilatory strategy.[52]

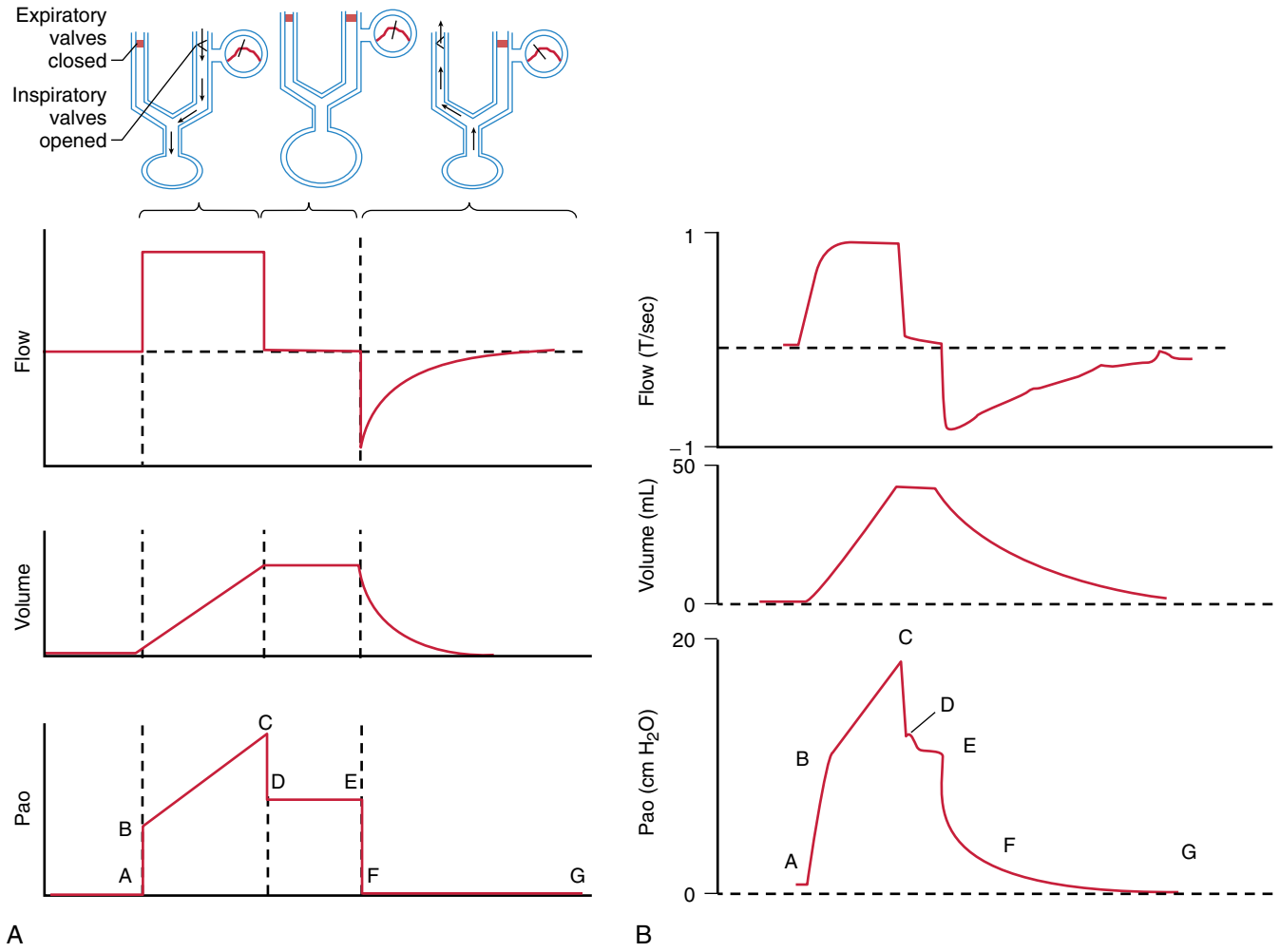


Figure 93-3 Flow, volume, and airway opening pressure (Pao) tracings recorded during controlled constant-flow mechanical ventilation applied. Theoretical traces related to the different phases of the ventilator duty cycle (**A**) and to a monocompartmental lung model (**B**). Mechanical ventilators are not able to generate a perfectly square inspiratory flow tracing such as in the model and the model does not take into account the respiratory system viscoelastic and inertial properties and the inhomogeneities among different lung regions. Accordingly, the AB tract ("resistive" pressure increase) is not perfectly perpendicular to the time axis and a transient phase of pressure slope variation substitutes a discrete B point. The BC elastic pressure increase is not always linear, but its profile may be curvilinear because respiratory system compliance and resistances may be nonlinear in the range of the delivered volume. Finally, after the C point (Pao_{peak}), the Pao-t profile from Pao_{peak} to Pao_{plat} (E) can be divided into two regions: (a) an immediate pressure drop from Pao_{peak} to $Pao_{occlusion}$ and (b) a slower decay from $Pao_{occlusion}$ to Pao_{plat} that take place in 2 to 5 seconds. The latter is principally due to alveolar gas redistribution between areas with different elastic and resistive characteristics (whose pressures at end-inspiration are not in equilibrium). Hence, the $Pao_{occlusion} - Pao_{plat}$ difference is proportional to the inhomogeneities between different lung regions.

Respiratory resistance is the opposition to gas flow through the respiratory system and is quantified as the amount of pressure required to cause a unit rate of gas flow, according to Ohm's law:

$$\text{Resistance} = \text{driving pressure}/\text{flow rate}$$

where driving pressure is the "resistive" pressure applied to generate a given constant laminar flow in the airways. The total resistance of the respiratory system is the sum of pulmonary resistance (airway resistance plus lung tissue resistance) and chest wall resistance (essentially tissue resistances) and is expressed in cm H_2O/L/sec. The total resistance of the respiratory system (*Rmax,rs*) is therefore proportional to the Ppeak-Pplat pressure decay when the constant flow is suddenly interrupted, according to the equation:

$$\text{Rmax,rs} = (\text{Ppeak} - \text{Pplat})/\text{Flow}$$

Rmax,rs may be further partitioned into the airway resistance (Rmin) and additional resistances (ΔR). The immediate drop of pressure from Ppeak to $Pao_{occlusion}$ is proportional to the airway resistances:

$$\text{Rmin} = (\text{Ppeak} - Pao_{occlusion})/\text{Flow}$$

while the slower decay from D to Pplat is proportional to the "additional" resistances:

$$\Delta R = \text{Rmax,rs} - \text{Rmin}$$

In normal subjects during general anesthesia, for a flow of 0.4 L/sec and in the normal VT range, Rmax,rs is 5 to 6 cm H_2O/L/sec and Rmin is 2 to 3 cm H_2O/L/sec.

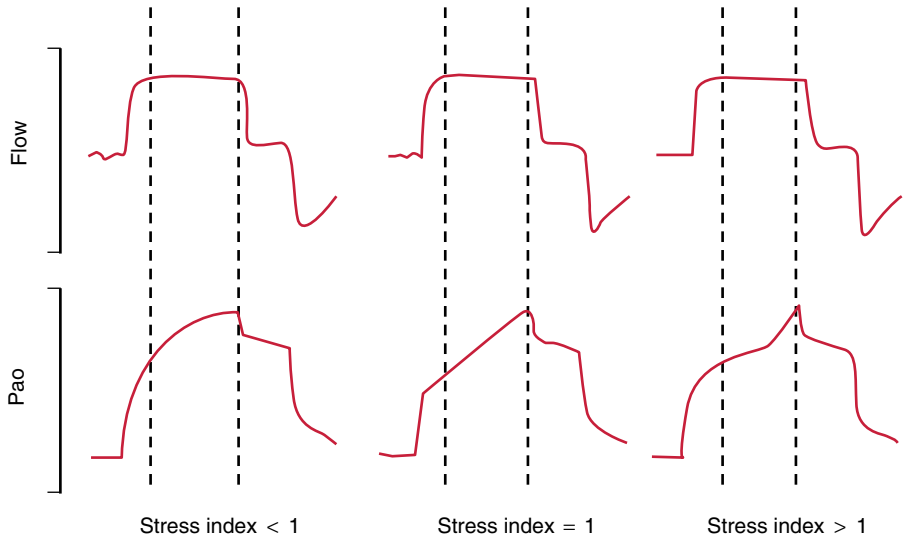


Figure 93-4 The stress index concept. Tidal alveolar recruitment/de-recruitment or overinflation or both may be detected through the analysis of the Pao-t profile during the period of constant flow inflation. A downward Pao-t concavity indicates progressive increase in compliance during tidal inflation, owing to ongoing alveolar recruitment with inflation, whereas an upward Pao-t concavity indicates progressive decreases in compliance during tidal inflation owing to ongoing alveolar overinflation with inflation. To measure the stress index a power equation ($Pao = a \cdot t^b + c$) is fitted on the Pao-time profile. Here, the coefficients a and c are constants and the coefficient b is a dimensionless number that describes the shape of the Pao-t profile (stress index). For a coefficient $b < 1$ the Pao-t profile has a downward concavity (compliance increases with inflation), whereas for a coefficient $b > 1$ the Pao-t profile has an upward concavity (compliance decreases with inflation). Finally, when $b = 1$ the Pao-t profile is straight and compliance remains constant during inflation.

Rmin,rs is increased in pathologic conditions characterized by the increase in airway resistances, such as asthma, acute cardiogenic pulmonary edema, ARDS, and COPD. However, because Rmin,rs is the sum of airway resistances and ventilatory circuit and endotracheal tube resistances, the possibility of an endotracheal tube obstruction should be always considered in the differential diagnosis. Both lung and chest wall inertial properties and lung inhomogeneities (expressed by ΔR) may be increased in some pathologic conditions, such as in patients with severe COPD or in morbidly obese patients.

Measuring PEEPi in passive patients during controlled mechanical ventilation (static intrinsic PEEP, PEEPi,st) is easily accomplished using a 5- to 10-second end-expiratory hold maneuver (during the contemporary closure of both inspiratory and expiratory valves at end-expiration), which allows the ventilator's pressure transducer to read the end-expiratory alveolar pressure (Fig. 93-5). This is the total respiratory system positive end-expiratory pressure (PEEPtot). In patients with dynamic hyperinflation, the value of PEEPtot is higher than the value of the applied PEEP (PEEPext) and PEEPi,st is the difference between PEEPtot and PEEPext.

When using partial ventilatory support techniques, PEEPi needs to be measured in a dynamic fashion (PEEPi,dyn). The gold standard method is based on continuous recording of flow, Pao, esophageal pressure, and eventually gastric pressure (Fig. 93-6).

Static respiratory system compliance (Cst,rs) is defined as the change in respiratory system volume per unit change in applied pressure (expressed in mL/cm H_2O):

$$Cst,rs = V_T / \left(Pao_{plat} - PEEPtot\right)$$

where Pao_{plat} is measured at the end of a 2- to 5-second end-inspiratory pause (point E). Elastance, the mathematical inverse of compliance, is expressed in cm H_2O/mL as:

$$Est,rs = \left(Pao_{plat} - PEEPtot\right) / V_T$$

For a correct calculation of Cst,rs, PEEPtot must be used instead of PEEPext, to discriminate between an increase in Pao_{plat} due to dynamic hyperinflation (where PEEPtot is higher than PEEPext and Cst,rs is not affected) and an increase in Pao_{plat} due to reduction of Cst,rs (where PEEPtot is equal to PEEPext).

Role of Chest Wall Mechanics

Lung and the chest wall are "in series": hence, Cst,rs is the sum of lung and chest wall compliance (respectively, Cst,L and Cst,cw) and Est,rs is the sum of lung and chest wall elastance (respectively, Est,L and Est,cw):

$$1/Cst,rs = 1/Cst,L + 1/Cst,cw$$

and hence

$$Est,rs = Est,L + Est,cw$$

Cst,cw and Est,cw are calculated as:

$$Cst,cw = V_T\left(Pes_{end\text{-}inspiratory} - Pes_{end\text{-}expiratory}\right)$$

and

$$Est,cw = \left(Pes_{end\text{-}inspiratory} - Pes_{end\text{-}expiratory}\right) / V_T$$

From a theoretical point of view, pleural pressure variations should be used instead of esophageal pressure to measure the pressure surrounding the lungs. However, pleural pressure measurements are virtually impossible in clinical practice whereas the esophageal pressure recording is commonly used as a substitute.

Pes is recorded with the patient in a semi-recumbent position through an air balloon–equipped catheter inserted in the

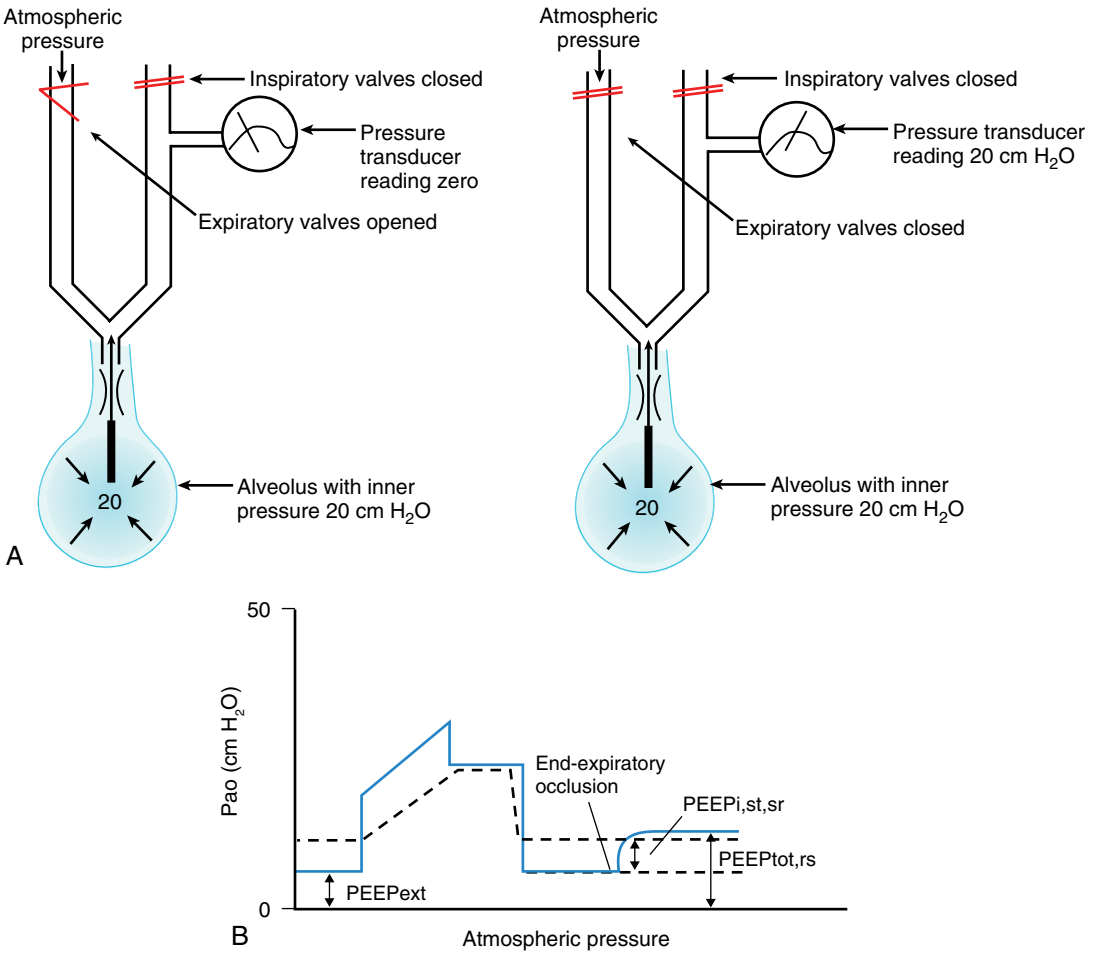


Figure 93-5 Static intrinsic PEEP (PEEPi,st) measurement: schematic representation of the end-expiratory hold maneuver. **A,** Schematic representation of the respiratory system and of a ventilatory circuit. During the expiratory phase, the ventilator opens the expiratory valve while the inspiratory valve is closed. Consequently, the pressure transducer reads atmospheric pressure. When the end-expiratory hold maneuver is performed, both inspiratory and expiratory valves are closed at end expiration. As a consequence, the pressure transducer reads the end-expiratory alveolar pressure. **B,** Recording of the Pao tracing obtained during a cycle of constant-flow mechanical ventilation, followed by an end-expiratory hold maneuver. At the end of the maneuver, the PEEPtot value is obtained. The *dotted line* refers to the theoretical value of alveolar pressure.

lower third of the esophagus and connected to a pressure transducer. Partitioning elastic properties between the lungs and the chest wall may be useful in the differential diagnosis of the decrease in respiratory compliance. Because chest wall and abdomen are coupled through the diaphragm, the increased abdominal pressure is one the most important factors leading to chest wall stiffness. However, patients without increased abdominal pressures may still have chest wall mechanical impairment related to chest wall deformities, fluid overload, or pleural effusions.

Monitoring Assisted Mechanical Ventilation

The main parameters to be clinically monitored during assisted mechanical ventilation include evaluation of patient-ventilator interactions and the occurrence of patient-ventilatory asynchronies.

Inspiratory Trigger Asynchrony

A "phase lag" between the beginning of inspiratory muscle activity and the beginning of mechanical inflation is virtually always present, although its amount is minimized with the neural trigger of NAVA.[53] The presence of PEEPi may complicate patient-ventilator interaction during the triggering phase.[54] Ineffective triggering is due to the inability of the ventilator to detect a patient's request of an assisted breath despite his or her production of a substantial inspiratory effort. This phenomenon usually occurs with high levels of ventilator assistance and short expiratory time. Mechanical characteristics that may facilitate ineffective triggering include low elastance, high resistance, and PEEPi.[55]

Ventilatory Requirement/Gas Delivery Asynchrony

Asynchrony occurs when the ventilator-delivered flow, volume, and pressure are insufficient to meet a patient's ventilatory requirements. Pressure-targeted breathing may better satisfy a patient's ventilatory requirements because the rapid pressuriza-

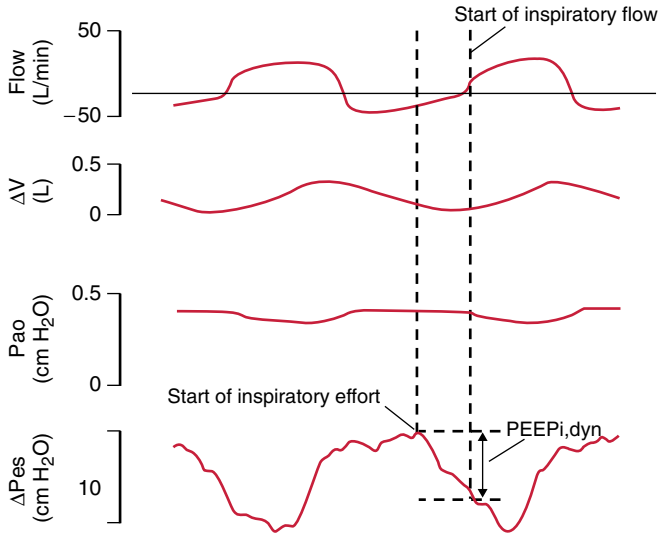


Figure 93-6 Flow, volume Pao, and Pes tracings recorded in a spontaneously breathing patient receiving positive continuous airway pressure. PEEPi,dyn is the value of Pes deflection from the beginning of the inspiratory effort to the point in which a positive inspiratory flow begins. See text for definition of abbreviations.

tion of the airways is coupled with high inspiratory flow just at the beginning of inspiration, reproducing the normal physiologic flow profile.

Cycling Asynchrony

This asynchrony occurs when the patient is trying to exhale but the ventilator continues to deliver gas. Parthasarathy and coworkers demonstrated that prolonging the mechanical inflation during the neural expiration reduces the time available for unopposed exhalation.[56] When PSV is delivered noninvasively, air leaks may cause an abnormal prolongation of the inspiratory time, preventing inspiratory to expiratory cycling off. In this condition, the patient keeps trying to exhale against the ventilator or to inhale without receiving any ventilatory support (inspiratory hang-up).[57]

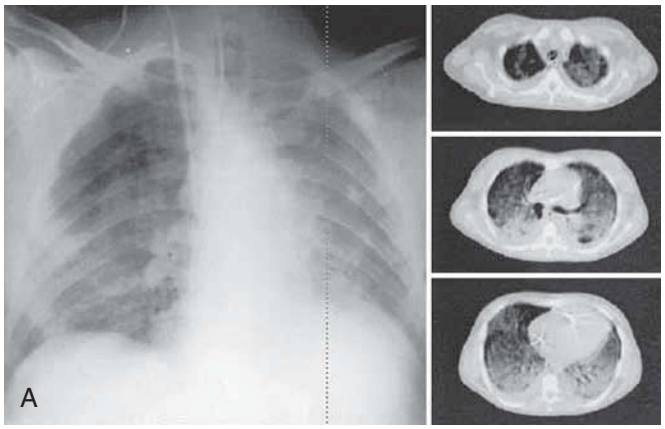
Work of Breathing

Estimating a patient's work of breathing during partial ventilatory support modes allows the setting of an optimal level of mechanical support in which inspiratory muscles work at a near-normal level, avoiding excessive muscle work or overassistance. Unfortunately, it requires a complex apparatus, continuous measurement of esophageal and gastric pressures, and a great deal of physiologic expertise. As described earlier, the PAV+ algorithm allows a continuous estimate of the work of breathing and the NAVA technology allows a continuous detection of diaphragmatic electrical activity. Although work of breathing may be referred to as a single breath, from a clinical standpoint it is more useful to measure the work of breathing per minute and the work of breathing per liter of minute ventilation (WOB/L = WOB/min ÷ minute ventilation). In a normal subject, the WOB/L at rest is between 0.3 and 0.6 Joules/L, whereas during any available partial ventilatory support technique the patient is subjected to additional "iatrogenic" work to overcome the endotracheal tube and the ventilatory circuit resistances and to trigger the ventilator.[58]

Clinical Problems Associated with Mechanical Ventilation

Elastic Properties of Nonhomogeneous Lung and Ventilator-Induced Lung Injury

Mechanical ventilation is almost invariably used in patients with acute respiratory distress syndrome (ARDS) or acute lung injury (ALI) or to ARDS. In the majority of those patients, once mechanical ventilation is applied, the gas exchange parameters improve as does the overall clinical condition. Unfortunately, since the mid 1980s, a large number of studies have shown that mechanical ventilation can worsen preexisting lung injury (ventilator-induced lung injury [VILI]).[51,59] The main feature of ARDS that predisposes to VILI is the heterogeneous distribution of lung disease. Pivotal computed tomography scan studies have clearly documented that in the ARDS lung normally aerated areas coexist with poorly aerated, consolidated, and hyperinflated areas (Fig. 93-7).[60] A systematic review of the pattern of distribution of these areas allowed classification of the distribution pattern of atelecta-



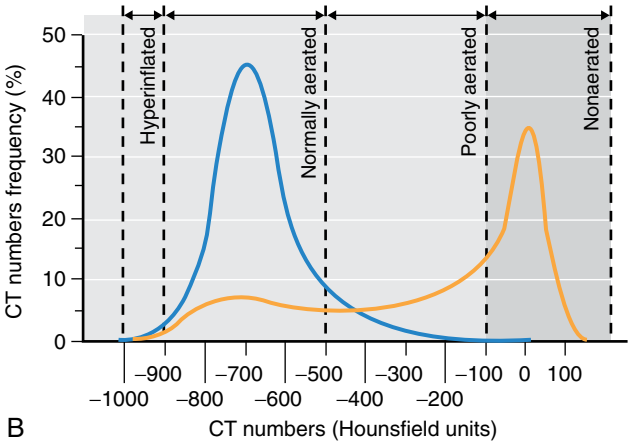


Figure 93-7 **A,** Anteroposterior chest radiograph and the CT scans (apex, hilum, and base) in acute respiratory distress syndrome. The chest radiograph shows diffuse ground-glass opacification, sparing the right upper lung. The CT scans show inhomogeneous disease and both the craniocaudal and sternovertebral gradients. **B,** The lung compartments, as defined by CT numbers, in normal condition (*blue line*) and in typical ALI/ARDS (*orange line*).

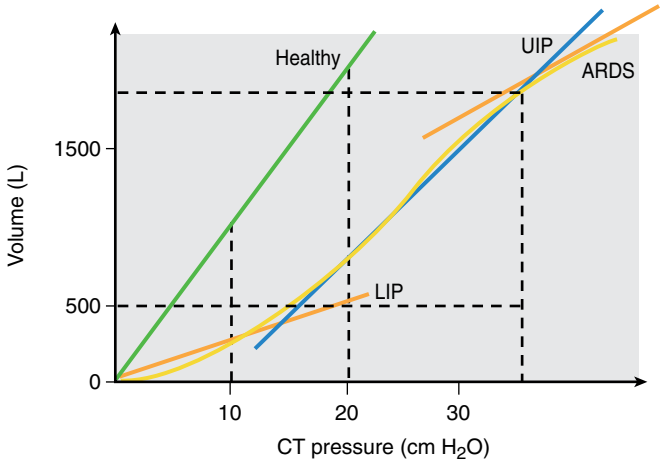


Figure 93-8 Static volume-pressure curves of respiratory system recorded in a healthy patient and in a patient with ARDS. LIP and UIP both occur within tidal ventilation and indicate the pressure at which recruitment of collapsed alveoli and alveolar hyperinflation start to occur, respectively. See text for definition of abbreviations.

sis into focal (≈36% of patients, where consolidated dependent areas coexisted with normally aerated nondependent areas), diffuse (≈23%, with a generalized opacification of the lung), and patchy (≈41%, where consolidated areas were unevenly distributed in the whole lungs).[60-62] This heterogeneity profoundly affects the mechanical characteristics of the respiratory system, as documented by the shape of the "static" or "quasi-static" inspiratory volume-pressure curve of the respiratory system.[63] When inflating the respiratory system in discrete volume steps, or in a very slow fashion, the increase in airway opening pressure will reflect the variations in elastic properties of the respiratory system. A progressive increase in compliance at the beginning of lung inflation ("lower inflection point" [LIP]) suggests that alveoli collapsed at end expiration are being progressively reopened during inflation (alveolar recruitment), whereas a progressive decrease of compliance toward the end of inflation ("upper inflection point" [UIP]) suggests that a number of alveoli are progressively stretched (hyperinflated) toward the end of inflation. In normal subjects, LIP occurs below the elastic equilibrium point of the respiratory system and UIP occurs at a volume close to total lung capacity. In patients with ARDS, LIP and UIP both occur within tidal ventilation and indicate the pressure at which recruitment of collapsed alveoli and alveolar hyperinflation start to occur, respectively (Fig. 93-8). However, recent studies suggest that lung recruitment along the incremental limb of the volume-pressure curve is a progressive phenomenon and a significant hysteresis between the inspiratory and the expiratory volume-pressure curve has been observed by constructing the decremental (i.e., the expiratory) limb of the volume-pressure curve. This means that, once recruited, atelectatic areas tend to collapse at a lower pressure than the pressure required to open alveoli during inspiration.[64,65]

According to the concept of "baby lung," originally proposed by Gattinoni and colleagues, mechanical ventilation delivering "standard" tidal volumes (i.e., the V_T that "normalizes" arterial P_{CO_2}) will generate cyclic tidal alveolar hyperinflation in the normally aerated areas in ARDS patients.[66] In addition, lung units collapsed at end expiration will reopen during inflation if low levels of PEEP are applied, generating a cyclic tidal alveolar opening and collapse phenomenon (or tidal recruitment). Tidal alveolar recruiting and tidal hyperinflation have been shown to activate proinflammatory intracellular signal pathways in epithelial and endothelial cells of the alveoli and in the lung's resident macrophages. As a consequence, genes responsible for the transcription of proinflammatory and anti-inflammatory mediators are respectively upregulated and downregulated, leading to alveolar inflammation.[67] This ventilator-induced "biotrauma" may arise after even relatively a short period of mechanical ventilation, leading to a local inflammatory response, further amplified by the recruitment of neutrophils, macrophages, and fibroblasts that occurs from the lung injury (Fig. 93-9).[59] In addition, mechanical stimuli posed on the alveolar wall are able to shed thrombomodulin (the surface molecule that proteolytically activates protein C) from the alveolar cell surface, depressing protein C activation at the alveolar level. Therefore, VILI may also exacerbate the intraalveolar procoagulative and antifibrinolytic state.[68] Other expressions of "biotrauma" include impairment of alveolar edema clearance by inactivation of the type I and II alveolar cells Na^+/K^+-ATPase,[69] inhibition of surfactant secretion by epithelial type II cells,[70] and the upregulation of the production of matrix metalloproteinases.[71] All these proposed mechanisms support the idea that VILI could act as the "engine" of multiple organ dysfunction syndrome (MODS), as originally proposed by Slutsky[59] and recently confirmed.[72]

Several "lung protective" ventilatory strategies have been proposed to minimize VILI. Initial studies were based on the measurement of the *inspiratory* volume-pressure curves of the respiratory system. Applying a PEEP level slightly above the LIP to avoid the end-expiratory collapse and a V_T to obtain an end-inspiratory plateau pressure just below the UIP reduced VILI-related lung and systemic inflammatory reactions[73] and VILI-related mortality.[74,75] However, selecting the PEEP level based on the incremental limb of the volume-pressure curve may be misleading, owing to the fact that alveolar recruitment has been shown to increase above the LIP (i.e., a pan-inspiratory phenomenon).[76] Furthermore, in the majority of the ARDS patients there is a significant hysteresis between the incremental and decremental limbs of the pressure-volume curve. Some authors have therefore suggested the selection of the PEEP level based on the *expiratory* limb of the volume-pressure loop. This would be done where a vital capacity maneuver is done to completely recruit the lung, followed by a decremental PEEP trial.[65]

Expiratory Flow Limitation and Intrinsic PEEP (PEEPi)-AUTOPEEP

In normal subjects at rest, the end-expiratory lung volume (EELV) closely corresponds to the elastic equilibrium point of the respiratory system (the FRC). Whenever the time available for expiration is shorter than the time required for passive emptying back to FRC, air trapping will develop. Consequently, alveolar pressure will remain positive at the end of expiration, which generates a "dynamic hyperinflation," that is, a positive end-expiratory alveolar pressure, called intrinsic PEEP (PEEPi) or auto-PEEP.[77,78] The trapped air volume may be assessed by measuring the amount of

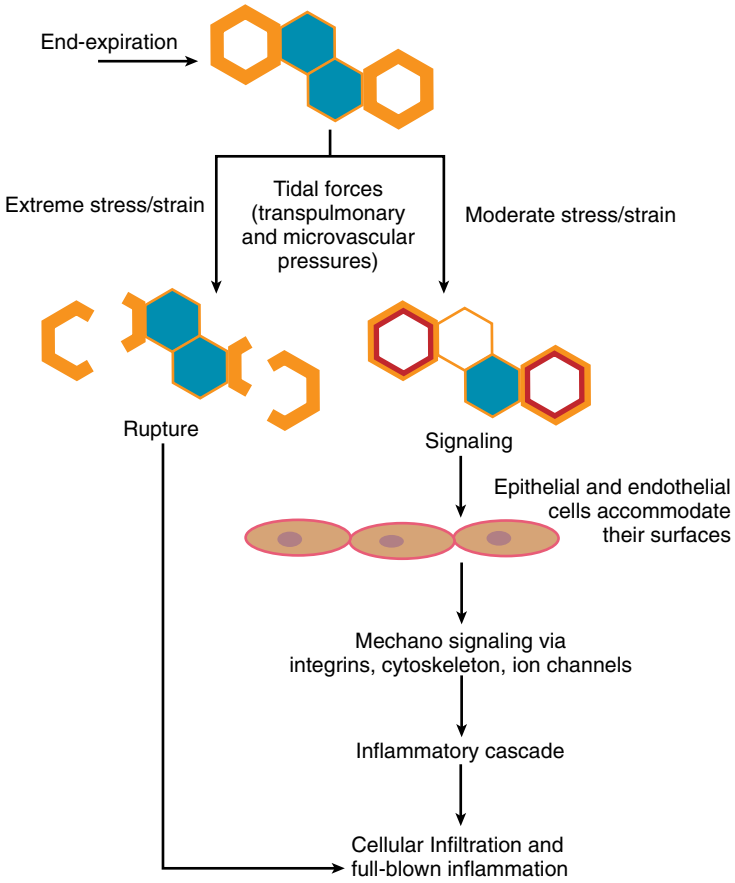


Figure 93-9 The concept of "biotrauma" related to ventilator-induced lung injury. The transduction of a mechanical stimulus posed on the alveolar walls (tidal alveolar opening/collapse and/or tidal alveolar stretch) leads to a biologic signaling that translates into pulmonary inflammation. (*From Marini JJ, Gattinoni L: Ventilatory management of acute respiratory distress syndrome: A consensus of two. Crit Care Med 33:250, 2004.*)

expired volume during a prolonged, passive emptying from EELV to FRC (30-60 sec) (Fig. 93-10).

PEEPi Due to Flow Limitation

Because of the expiratory collapse of distal airways, expiratory flow is severely limited.[79] This condition is peculiar to the patient with COPD, whereas in normal subjects it occurs only during forced maximal expiratory maneuvers. The pathophysiology of expiratory flow limitation has been originally explained by the waterfall model (Fig. 93-11).[80] Accordingly, increasing the pressure downstream from the waterfall by applying an external

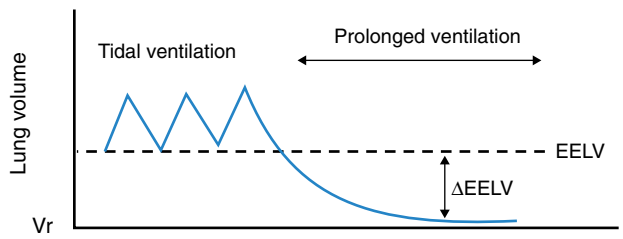


Figure 93-10 Difference (ΔEELV) between the end-expiratory lung volume (EELV) during mechanical ventilation and elastic equilibrium volume of the respiratory system (Vr) in a patient with dynamic hyperinflation. A complete lung emptying is obtained by disconnecting the patient from the ventilator at the end of mechanical expiratory time and allowing a prolonged (15-20 seconds) passive exhalation to atmospheric pressure.

PEEP will have no influence on either the expiratory flow or the pressure upstream of the site of critical airway closure, that is, until the value of external PEEP does not exceed the value of PEEPi.

Acting as an inspiratory threshold load, PEEPi places a burden on the inspiratory muscles, which are forced to develop sufficient force to overcome the opposite recoil pressure before inspiratory flow can begin. The work of breathing necessary to overcome PEEPi to initiate an inspiratory flow may be as high as 40% of total work of breathing in patients with COPD exacerbations[16] and may be significantly reduced by applying an appropriate level of external PEEP.[81] According to the waterfall analogy, the application of an external PEEP in the range of measured levels of PEEPi will decrease the inspiratory work of breathing without inducing further alveolar hyperinflation.[82] However, the waterfall analogy assumes a single value of critical closing pressure for all the distal airways (Pcrit) whereas a significant heterogeneity among regional lung units has been documented.[83] On this basis, the simple waterfall analogy may be not accurate. In terms of mechanically ventilated COPD patients, this implies that the value of external PEEP that can be safely applied without the risk of worsening dynamic hyperinflation should be somewhat less than the measured PEEPi. Experimental data suggest that applying a PEEP level equal to 75% of PEEPi is below Pcrit in the majority of COPD patients.[84]

PEEPi without Flow Limitation

This occurs when the expiratory time is shorter than the time required for passive lung emptying to FRC. The time needed to

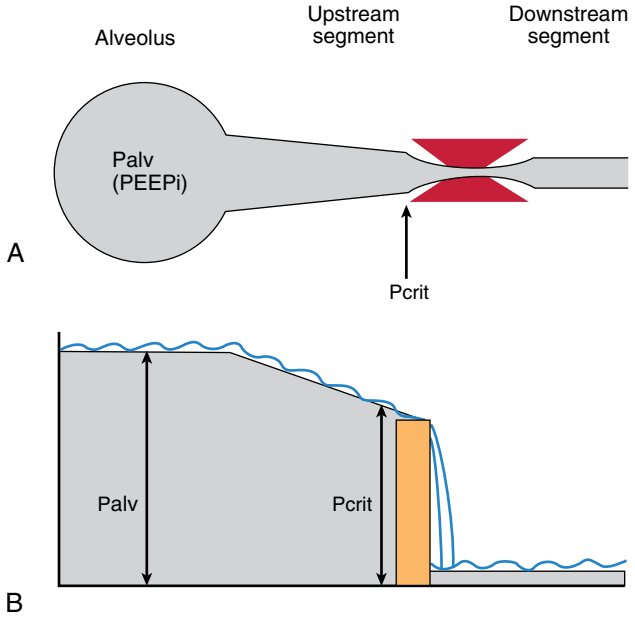


Figure 93-11 The waterfall model. Because of the dynamic expiratory collapse of distal airways, and in COPD patients the expiratory flow is severely limited and at end-expiration, and alveolar pressure (Palv) remains positive, generating intrinsic positive end-expiratory pressure (PEEPi). Because of the dynamic collapse, increasing the pressure in the downstream airway segment will not have influence on the pressure upstream of the site of critical airway closure until the applied pressure exceeds the pressure level in the upstream airway segment (Pcrit).

empty the lung depends on the interplay of several variables: VT, end-inspiratory elastic recoil pressure of the respiratory system, and expiratory resistances. Moreover, in the ventilated patient the resistances of endotracheal tubes, exhalation valves, and PEEP devices must be taken into account. Consequently, under conditions of high minute ventilation, high respiratory system compliance, and high expiratory resistance, the lungs do not have time, during passive deflation, to reach their equilibrium point at FRC. This is different than the problems that occur with flow limitation, because the application of an external PEEP in this condition worsens dynamic hyperinflation, providing a "back pressure" to expiratory airflow.[85]

In the ventilated patient, dynamic hyperinflation may cause severe hemodynamic impairment because it critically impairs venous return and increases right ventricular afterload, leading to a low cardiac output state. This phenomenon, originally described by Pepe and Marini,[86] is more likely to occur when applying controlled mechanical ventilation to patients with COPD or asthma. A rather different scenario occurs in spontaneous breathing patients who develop significant dynamic hyperinflation.[87] PEEPi acts as an inspiratory threshold load in the sense that the patient must create an opposite negative intrathoracic pressure to generate an inspiratory flow. Such a decrease in pleural pressure with no change in lung volume is theoretically similar to a Muller maneuver (Fig. 93-12). When COPD patients experience a severe exacerbation of their disease or when a ventilator-dependent COPD patient is suddenly disconnected from the ventilator, this mechanism has a marked improvement on venous return and cardiac output. Because the pulmonary vascular bed is relatively nonrecruitable in severe COPD, pulmonary artery pressure will increase and right ventricular engorgement ensues. Furthermore, acute right ventricular engorgement has been shown to induce a leftward interventricular septum shift, leading to impairment of left ventricular diastolic relaxation and pulmonary congestion.[88-90] Besides decreasing work of breathing, applying a PEEP/CPAP level lower than Pcrit will limit the hemodynamic consequences of PEEPi in spontaneously breathing patients.[87]

Although PEEPi and dynamic hyperinflation are usually thought to be synonymous, PEEPi does not necessary imply dynamic hyperinflation or air trapping. When expiratory muscles are recruited during expiration, alveolar pressure will be positive at end expiration without dynamic hyperinflation.[91]

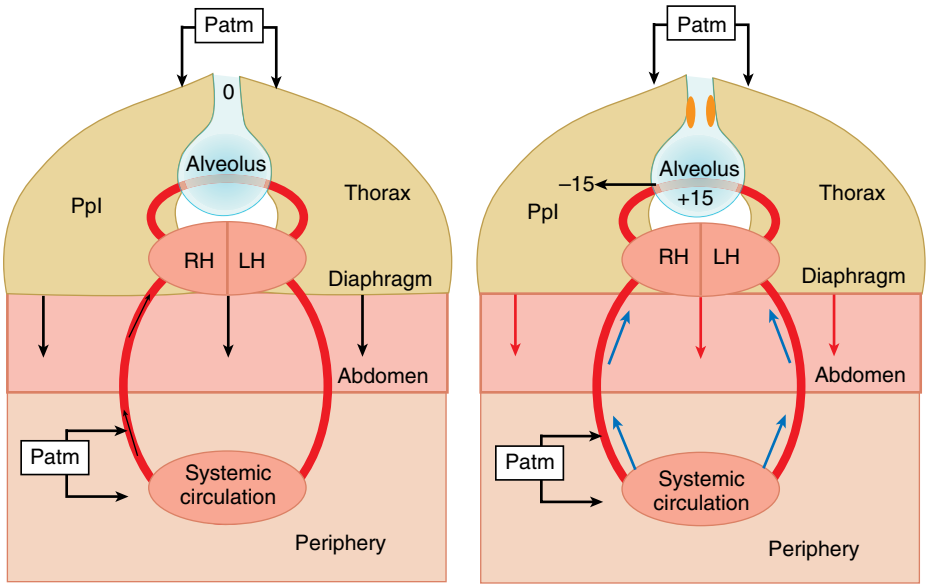


Figure 93-12 Hemodynamic consequences of dynamic hyperinflation and intrinsic PEEP (PEEPi). The physiologic increase in venous return during spontaneous inspiration, due to the generation of a slightly negative pleural pressure (Ppl) as compared with atmospheric pressure (Patm), is pathologically magnified in patients with dynamic hyperinflation. To initiate inspiratory flow (i.e., to generate a negative alveolar pressure), the hyperinflated patient needs to counterbalance PEEPi, generating an opposite negative pleural pressure. This has a marked fostering effect on venous return.

Mechanical Ventilation for Specific Clinical Entities

Acute Respiratory Distress Syndrome

ARDS is an inflammatory response of the lung to both direct and indirect insults defined according to the following criteria: acute onset, presence of bilateral infiltrates on chest radiography consistent with pulmonary edema, pulmonary artery wedge pressure less than 18 mm Hg or clinical absence of left atrial hypertension, and hypoxemia with a Pao_2/Fio_2 ratio less than 200.[92] Patients meeting these criteria but with Pao_2/Fio_2 ratios less than 300 are diagnosed with ALI. Although this definition is simple, limitations have been recently identified: the radiographic criterion has a high interobserver variability among experienced clinicians and no specific radiographic findings are agreed upon,[93] the presence of multiorgan dysfunction is not considered in the definition, and the cause of the lung injury is not identified. Although in the past ARDS was considered rare,[94] a recent population-based study showed an age-adjusted incidence of 86.2 per 100,000 persons/year.[95] Mortality due to ARDS has been reported to decline from 60% to 70% in the late 1980s to 30% to 40% over the past 2 decades with improved management.[96-98] Risk factors linked to increased mortality in ALI/ARDS include advanced age, a low Pao_2/Fio_2 ratio, the presence of septic shock, a high Acute Physiology and Chronic Health Evaluation II (APACHE II) score, a high Sequential Organ Failure Assessment (SOFA) score, a low Glasgow Coma Scale score, and the presence of chronic liver disease.[99] The most common long-term impairments are muscle wasting and weakness, significant neurocognitive and emotional morbidity, and decreased quality of life persisting after 2 years from hospital discharge. This is true despite the fact that pulmonary function generally returns to normal by 6 months, with the exception of a persistent reduction in the carbon monoxide diffusion capacity.[100,101]

The inciting factors for lung injury can be divided into those associated with direct insult to the lungs, such as pneumonia or aspiration, and indirect causes, such as sepsis or severe trauma (Fig. 93-13). This "first hit" to the lungs incites a pulmonary inflammatory response, which may lead to worsening of the pathologic manifestations of ARDS if coupled with injurious mechanical ventilation.[59,67] Clinical studies have suggested that there is an increased mortality in patients who continue to have elevated bronchoalveolar lavage concentrations of interleukin (IL)-6, IL-8, IL-1, and tumor necrosis factor (TNF) cytokine levels during their clinical course, precluding resolution of the pulmonary and systemic inflammatory processes.[96,102,103] An important source of these inflammatory mediators are the neutrophils, which play a pivotal role in the pathogenesis and progression of ALI/ARDS,[104] although it may develop in patients with profound neutropenia, suggesting that several parallel and interacting mechanisms are involved.[105]

ALI/ARDS is characterized by abnormal mechanical properties of the respiratory system with the hallmark features of a reduced FRC and a reduced static compliance of the respiratory system.[106] Measurements of the inspiratory volume-pressure curves of the respiratory system have been used in mechanically ventilated patients with ALI/ARDS as a means of assessing their status and progress and to optimize the use of PEEP and mechanical ventilation.[63]

In the past, mechanical ventilation with a large V_T of 10 to 15 mL/kg was recommended to guarantee a normal pH and $Paco_2$.[107] The use of a large V_T has now been shown to lead to shear stress injury of the lungs, from overdistention and local and systemic inflammatory responses due to this mechanical injury. The multicenter randomized controlled trial carried out by the ARDSNet included 10 academic centers with 75 intensive care units and enrolled patients with ARDS to compare a control ventilatory strategy using a V_T of 12 mL/kg (based on predicted body weight (PBW) versus a lung-protective strategy using a V_T of 6 mL/kg PBW.[96] The study set out to enroll up to 1000 patients, but accrual was stopped at 861 patients when an interim analysis revealed that the mortality rate in the lung-protective group was 22% lower than in the control group. These beneficial results occurred in all patient groups, including septic and nonseptic patients and those with different degrees of lung dysfunction as assessed by respiratory system compliances. The ARDSNet study set PEEP levels and inspired oxygen fractions (Fio_2) according to traditional criteria, using a standardized PEEP-Fio_2 combination table. Moreover, the ARDSNet study aggressively maintained $Paco_2$ close to the normal range, employing higher respiratory rates and a liberal use of bicarbonate. The study is very important from a clinical perspective because it demonstrated that a specific intervention (the reduction of V_T) was able to improve mortality in these patients. Recent investigations testing the effects on mortality of "higher" PEEP titration criteria did not show any

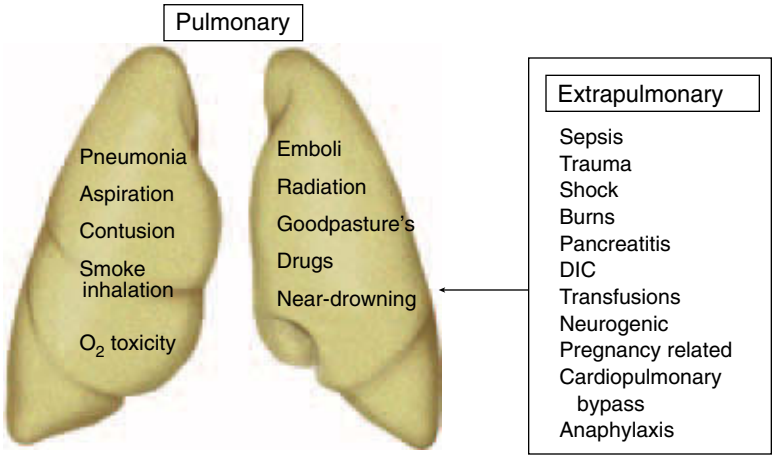


Figure 93-13 Pulmonary (primitive) and extrapulmonary (secondary) triggers of the acute respiratory distress syndrome.

improvement in terms of survival rates,[108-110] although they suggested beneficial effects of higher PEEP in terms of ventilator-free days and need for nonconventional therapy. At present the optimal level of PEEP and best method used to set PEEP has not been definitively established.[22] Prone positioning has been demonstrated to improve oxygenation and to decrease the incidence of ventilator-associated pneumonia in patients with acute hypoxic respiratory failure but does not improve mortality, so that this therapeutic option might be considered useful only for ARDS patients with refractory hypoxemia.[111,112]

Inhaled nitric oxide (iNO) has been shown to be a selective pulmonary vasodilator without systemic effects. It was suggested that this agent might improve gas exchange and reduce pulmonary hypertension, optimizing the $\dot{V}/\dot{Q}$ matching. Nevertheless, despite the improvement in oxygenation, there was no beneficial effect on mortality.[113] Thus, iNO cannot be recommended for the routine treatment of ALI/ARDS but it may be useful as a rescue therapy in patients with refractory hypoxemia.

Chronic Obstructive Pulmonary Disease

COPD is a syndrome of chronic lung inflammation characterized by chronic, not fully reversible, airflow limitation.[114] It is the fourth leading cause of death in the world, and its prevalence has been estimated to be around 9/1000 in men and 7/1000 in women, although recent data indicate that prevalence of the disease in developed countries is similar in the two genders.[115,116] The severe $\dot{V}/\dot{Q}$ mismatch that is associated with the late phase of COPD leads to chronic CO_2 retention, hypoxemia, and compensatory polycythemia. These conditions, together with an extensive destruction and remodeling of pulmonary vasculature, lead to pulmonary hypertension and chronic cor pulmonale.[117] Emphysema critically impairs lung elastic recoil and alters the alveolar attachments to small airways, compromising their stability. Either reduced alveolar driving pressure or susceptibility to dynamic expiratory collapse generates the phenomenon of "expiratory flow-limitation."[78]

Acute exacerbations of COPD are defined as worsening of dyspnea and increase in sputum purulence and volume.[118] Most COPD exacerbations are caused by tracheobronchial infections, exposure to air pollution, or concomitant diseases, although in some instances the cause remains unknown.[119] The exacerbation-induced increase in airways obstruction and worsening of dynamic hyperinflation acutely limits the ability of respiratory muscle to maintain the minute ventilation level. As a consequence, acute-on-chronic hypercapnia, hypoxemia, and hemodynamic impairment develops. Severe, life-threatening COPD exacerbations are characterized by pH below 7.30 and Pa_{O_2} below 60 mm Hg (breathing room air) and require intensive oxygen supplementation and pharmacologic and ventilatory treatment. The target of oxygen supplementation is to maintain Pa_{O_2} slightly above the 60 mm Hg threshold, because a moderate hypoxic stimulus is useful to stimulate the ventilatory drive in the presence of chronic hypercapnia.

Applying noninvasive PSV (to unload inspiratory muscles and to increase V_T) and PEEP (to counterbalance the inspiratory threshold load for the inspiratory muscles posed by intrinsic PEEP) in the early course of COPD exacerbations reduces intubation rates, the frequency of complications, the in-hospital mortality, and the length of stay.[120,121] Experiences with other NIPPV ventilatory modalities (e.g., PAV), although encouraging, are limited to physiologic studies.[122,123] Physiologic studies suggest there are benefits of CPAP in acute COPD exacerbation, but no clear-cut clinical indication for CPAP exists.[124] If controlled mechanical ventilation needs to be used, targeting minute ventilation to the pre-decompensation CO_2 level is important to minimize alveolar hyperinflation and to avoid rebound respiratory acidosis at the reinstitution of spontaneous breathing. In this context, measuring PEEPi and trying to minimize it by selecting the appropriate ventilatory pattern (low VT, low respiratory rate, and high expiratory time) is of paramount importance.[125]

Acute Cardiogenic Pulmonary Edema

ACPE results from any pathologic condition leading to the inability of the left ventricle to handle the pulmonary venous return. The resulting rise in hydrostatic pressure at the capillary level causes a leakage of fluid (with the characteristics of a transudate) in the interstitium and subsequently in the alveolar space. Both interstitial and alveolar edema leads to surfactant inactivation and thickening of small airways walls, resulting in increased lung elastance, resistance (cardiac asthma), and hypoxemia. A positive feedback develops, because hypoxemia and increased work of breathing increase a stress response, which, in turn, increases left ventricular workload and possibly induces left ventricular ischemia, further limiting the ability of the left ventricle to manage venous return.[126] Moreover, the stiffer edematous lung requires the patient to develop larger negative pleural pressure swings, increasing venous return and promoting further capillary fluid leakage. Finally, the more negative the pleural pressure during inspiration, the more transmural left ventricular pressure increases, leading to an increased left ventricular afterload (Fig. 93-14).[26]

Noninvasive techniques, both CPAP and NIPPV, have been shown to reduce the need of intubation and improve outcomes in patients with ACPE.[127-130] Of note, a small clinical trial raised serious warnings on the risk of myocardial ischemic events when ACPE patients are treated with bilevel positive airway pressure

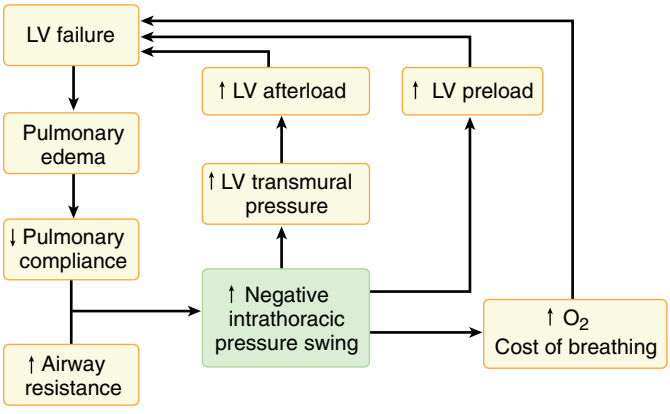


Figure 93-14 The vicious cycle of cardiopulmonary interactions during left ventricular (LV) failure leading to acute cardiogenic pulmonary edema (see text for further details).

(BiPAP, a form of PSV), as compared with CPAP.[131] Recently, two meta-analyses showed that both CPAP and NIPPV significantly reduce the need for intubation but CPAP significantly decreases mortality, whereas NIPPV is associated with a strong but nonsignificant trend toward better survival.[132,133] The same meta-analysis did not show significant differences in myocardial ischemic events between CPAP and NIPPV. Overall, some authors suggest that CPAP should be considered as the first-line treatment in patients with ACPE because it is less expensive and easier to implement and as efficacious as NIPPV.[133]

Several issues regarding noninvasive ventilation in patients with ACPE remain unresolved: Does the mechanism leading to ACPE (systolic versus diastolic heart failure)[134] influence the response to noninvasive ventilation? To what extent is the use of CPAP or NIPPV advisable in patients with acute myocardial infarction? Is there a different indication for CPAP or NIPPV in subgroups of these patients? However, it might be better to use NIPPV in hypercapnic patients with ACPE.[130] Finally, studies investigating the optimal settings of CPAP and NPPV in ACPE patients are needed.

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Michael J. Souter and Arthur M. Lam

94 Neurocritical Care

Key Points

1. Critical care of the nervous system is based on support of cerebral and spinal cord physiology and the prevention of secondary insult. This, in turn, depends on the comprehensive maintenance of cardiopulmonary, gastrointestinal, renal, and endocrine functional adequacy.
2. Cerebral function is critically dependent on perfusion and oxygenation. Increased intracranial volume beyond the capacity of compensatory mechanism will increase intracranial pressure (ICP) and may diminish perfusion adversely. Resulting cellular energy failure will both initiate and propagate edema and inflammation.
3. The resolution of cerebral edema depends on hydrostatic and osmolar forces applied to the blood-brain barrier. Excesses of perfusion pressure or intravascular hypotonicity will worsen edema and must be avoided. Blood-brain barrier disruption will vary over time and will markedly affect the ability of hypertonic agents to exert an osmotic effect.
4. Fever is frequently overlooked in the neurocritical care unit but significantly affects outcome across a range of pathologic processes.
5. Neurologic monitoring comprises placement of appropriate monitoring devices as well as prompt response and institution of therapy to changes detected. The goal is to optimize the physiologic environment, despite the current lack of level 1 evidence to support the majority of monitors in common use. Clinical examination of neurologic function remains a crucial part of monitoring and care.
6. Incidence of traumatic brain injury has declined but remains a disease of the young, with enormous long-term socioeconomic impact. Prompt surgical appraisal is mandatory; and although hypothermia remains controversial, decompressive craniotomy may be lifesaving in patients with elevated ICP refractory to medical treatment. Corticosteroids are contraindicated.
7. After the initial hemorrhage, mortality and morbidity from subarachnoid hemorrhage (SAH) arise chiefly from subsequent vasospasm. Medical therapy for this complication involves augmentation of perfusion pressure, maintenance of blood volume, and optimization of oxygen delivery. Endovascular therapy with angioplasty with or without chemical vasodilation plays an increasingly important role. SAH may be accompanied by significant pulmonary, cardiovascular, or endocrine effects.
8. Successful therapy for ischemic stroke is contingent on a time window of viability. Urgent appraisal and rapid treatment is crucial to good outcome.
9. Injury to the spinal cord necessitates careful observation of respiratory adequacy, because conditions may deteriorate before any observed improvement. Fatigue is frequently a factor.
10. Infectious disease of the central nervous system demands an aggressive approach to resuscitation, cerebrospinal fluid sampling, and early empirical antibiotic therapy, similar to that in the patient with septic shock.

Critical care of the central nervous system (CNS) involves collaboration between many disciplines—neurosurgery, neuroanesthesia, neurology, neuroradiology, and electrophysiology. Each discipline offers unique contributions, which in partnership, provide optimal care, not only to the injured brain but also to the cardiopulmonary, endocrine, gastrointestinal, and renal systems that support cerebral physiology. Integration of the complex goals of this care relies on the neurocritical care physician, which increasingly is recognized as an important subspecialty.[1]

The use of a neurocritical care team rather than single specialty care has been associated with reduced in-hospital mortality and length of stay.[2] Although the brain has a certain preeminence among the organs of the body, it relies on a stable platform of organ function elsewhere, to enable homeostatic control and mechanisms of repair and recovery to occur. Injury to the brain is associated with and precipitates a wide spectrum of dysfunction of other organ systems (Table 94-1). Although other specialties can train to be neurointensivists, anesthesiolo-

gists with training in neuroanesthesia and critical care are particularly well suited to demonstrate the combination of airway and cardiovascular support skills that, together with understanding of the physiology and pharmacology of the nervous system, may improve outcome.

Intracranial Physiology and Cerebral Autoregulation

The cerebrovascular circulation is constrained by a rigid perimeter of bone. After exhaustion of limited compensatory mechanisms, the bony confines of the skull mandate increasing intracranial pressure (ICP) consequent to increasing intracranial volume. The change in ICP with change in intracranial volume is often referred to as the intracranial compliance curve, but it is more appropriately termed the intracranial elastance curve (Fig. 94-1).

Thus, an increase in elastance implies poor compliance and a small change in volume can lead to an inordinate increase in pressure. These changes in volume arise from increments in intracranial tissue or fluid content, that is, blood, interstitial fluid, or cerebrospinal fluid (CSF). Tissue content is relevant insofar as mass lesions will reduce intracerebral compliance and accentuate the effects of fluid changes.

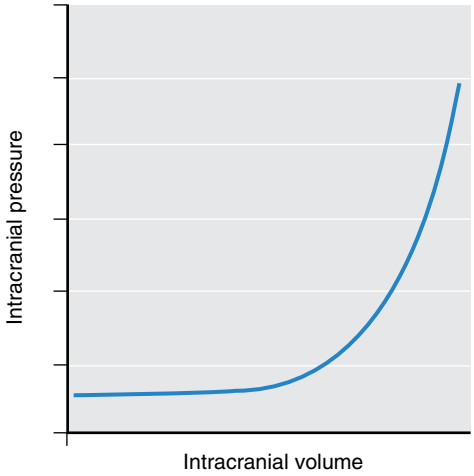

Figure 94-1 Intracranial pressure-volume relationship.

Small increases in volume can be accommodated by an outflow of CSF from the cranial cavity into the spinal canal, producing the exponential pressure-volume relationship (see Fig. 94-1).

The cranial vault is compartmentalized by the falx cerebri and tentorium cerebelli, which creates the possibility of internal pressure gradients (Fig. 94-2). This may induce physical protrusion of brain tissue through the "apertures" of the compartments—herniation. Brain tissue may be injured directly but also indirectly by deforming and compressing vasculature adjacent to the dural margin.[3] This is typically seen in severe lateral herniation—"midline shift"—when the anterior cerebral vasculature may be obstructed, producing frontal lobe infarction.

Pressure gradients are initially hydraulically equilibrated, with CSF moving from the ventricular chambers to the cranial vault. The compensation achieved is limited by the CSF volume available to be displaced; and, ultimately, changes in volume will induce tissue displacement. This displacement may also contribute to impedance of CSF drainage either by occlusion of the foramina of Monro in the case of lateral herniation or by occlusion of the third ventricle and aqueduct by supratentorial herniation through the tentorial gap. This typically gives rise to clinical features of midbrain structures being compressed. Unilateral papillary dilation, ipsilateral or even contralateral paralysis (Kernohan's notch phenomenon), and abnormalities of respiration are apparent in the spontaneously breathing patient. If the herniation continues, it will result in cerebellar descent through the foramen magnum with consequent compression of the brainstem, producing bilateral papillary fixation, either tachycardia or bradycardia, and systemic hypertension.[4] Changes in cerebral mass secondary to increase in venous blood volume will also arise from obstruction to venous drainage by compression of the easily susceptible bridging veins draining from cortex to venous sinuses. Once an individual threshold of compliance is crossed, changes in volume exert a mass effect on the draining veins, which act as Starling resistors. This decreases drainage, which, in turn, amplifies and

Table 94-1 Potential Systemic Complications Associated with Serious Brain Injury

Global	Pyrexia Inflammatory activation
Cardiovascular	Arrhythmia—bradycardia, tachycardia, atrial fibrillation Hypertension Hypotension Left ventricular dysfunction
Respiratory	Apnea Pneumonia—aspiration, hypostatic, ventilator associated Pulmonary edema ARDS
Gastrointestinal	Gastric erosion Ileus Constipation Perforation Malabsorption
Renal	Dehydration Acute renal failure Urinary tract infection
Hematologic	Anemia Leukocytosis Coagulopathy, disseminated intravascular coagulation Deep venous thrombosis, pulmonary embolism
Metabolic/Endocrine	Hyponatremia, hypernatremia Hyperglycemia Hypokalemia, hyperkalemia Hypomagnesemia Hypophosphatemia Catabolic azotemia Rhabdomyolysis

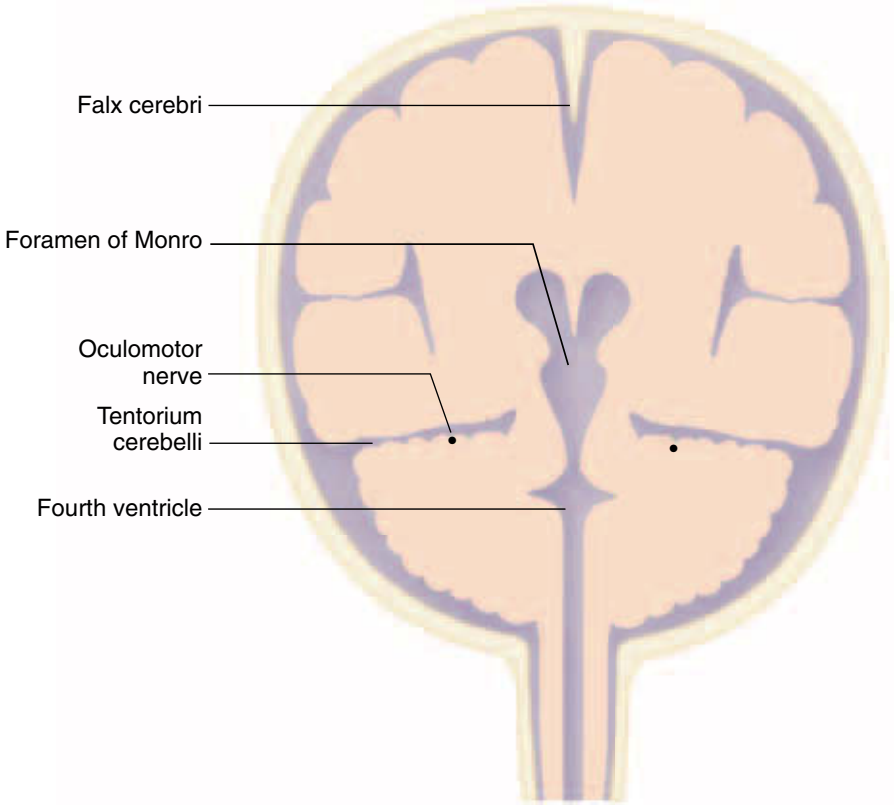

Figure 94-2 Schematic of intracranial compartments—coronal section.

prolongs pressure increases. Blood volume increases may be extravascular (i.e., hemorrhage) or intravascular (i.e., accumulation within a predominantly venous capacitance circulation). (Venous circulation comprises approximately 75% of the cranial blood volume, whereas approximately 25% of vessels are arteries, arterioles, and capillaries.)

The other main fluid mass effect is via edema. This may take the form of cytotoxic or vasogenic edema.[5,6] Cytotoxic edema occurs as a result of hypoxia, with swelling of the intracellular compartment, whereas vasogenic edema in the interstitium usually develops from a breach of the blood-brain barrier, often in response to high blood pressure.[7]

Thus, changes in the control of cerebral blood volume may have significant effects on ICP. Autoregulation of cerebral blood flow (CBF) responds to changes in arterial pressure, arterial P_{CO_2}, or P_{O_2}, by dynamically altering arteriolar caliber so as to maintain a constantly matched cerebral perfusion sufficient to meet metabolic demands (Fig. 94-3). pH, Pa_{CO_2}, potassium, and adenosine are among many purported metabolic mediators of flow.[8]

CBF control may be directly compromised by brain injury or by abnormalities of respiration and blood pressure. In turn, this may increase venous volume by allowing an excessive arterial inflow that venous drainage cannot match, increasing ICP. Consequently, untoward events, including hypotension, airway obstruction, fever, and seizures, produce what is termed a *secondary physiologic insult*. This has been demonstrated to induce further harm to the vulnerable brain and, in so doing, worsen outcome.[6,9]

A reduction in substrate delivery (i.e., oxygen and nutrients) below that threshold necessary to maintain cellular viability

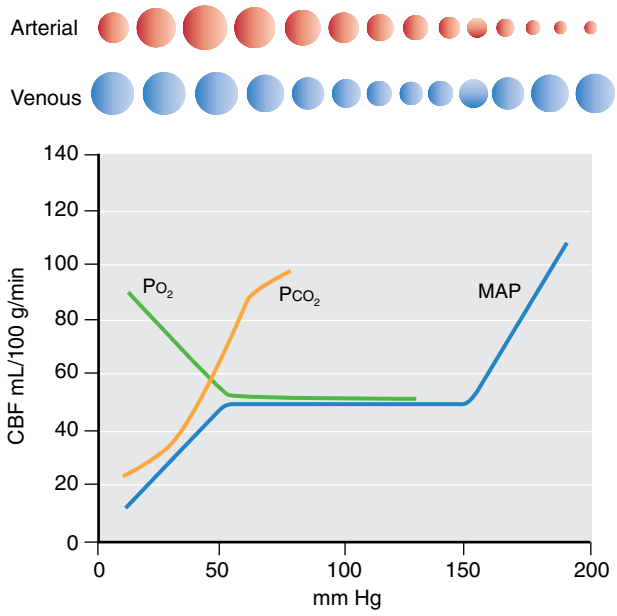

Figure 94-3 Graph of autoregulatory control of cerebral blood flow (CBF) and vascular diameter, in response to changes in mean arterial pressure (MAP), arterial partial pressure of oxygen (P_{O_2}), and arterial partial pressure of carbon dioxide (P_{CO_2}).

produces cell injury with cytokine and chemokine release. This inflammatory amplification expands the injury,[10] disrupts the blood-brain barrier function, and may directly lead to apoptosis. The disruption of the blood-brain barrier creates vasogenic edema and allows serum proteins to cross into brain parenchyma with prolonged effects. This is more evident in the more metabolically gray matter than white matter.[5] Most changes peak in the first 48 hours, but one study identified up to 25% of ICP peak increases occurring after day 5.[11]

General Cardiopulmonary Considerations

Any deterioration in ventilatory efficacy may adversely affect cerebral compliance (elastance) through CO_2-induced vasodilation. There have been concerns on the effect of positive end-expiratory pressure (PEEP) in this situation, but the decreased pulmonary compliance necessitating the PEEP will also limit intrathoracic pressure transmission to the cerebral circulation.[12] The net benefit of improved ventilatory efficacy from PEEP outweighs any mild disadvantages from its use. However, it should be remembered that injudicious PEEP in circumstances of hypovolemia may reduce functional venous return and hence reduce cardiac output with consequent effects on cerebral perfusion.[12]

Reductions in cardiac output can initiate reflex cerebral vasodilation, in an attempt to preserve cerebral blood flow. Hypotension is a well-documented source of worsened morbidity[13,14] whether it occurs by under-resuscitation or iatrogenic mechanisms. This vasodilation will increase venous blood volume and further diminish cerebral perfusion pressure (CPP).[15]

Hypoxemia can cause direct as well as indirect injury to the brain. Hypoxemia below 60 mm Hg is a significant contributor to secondary insult from secondary ICP effects, in addition to the reduction in the oxygen gradient to the cell. The resultant reduction in cerebral perfusion, irrespective of the primary cause, may cause further deterioration by depressing the level of consciousness, in turn leading to airway compromise, hypoventilation, and further decrease in oxygenation (Fig. 94-4). Consequently, pulmonary compromise is often seen in neurologic patients with altered mental status, as a result of impaired airway reflexes and repeated aspiration episodes, culminating in a significant incidence of pneumonia, irrespective of the initiating pathologic process.[16]

Another potential mechanism is the release of cytokines from the brain in response to the inflammatory process triggered by an injury, which may be sufficient to induce acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS).[17,18] Moreover, the large tidal volume ventilation delivered during initial hyperventilation can enhance the development of ARDS.[19] This may create a therapeutic dilemma in the presence of cerebral pathophysiology. However the "open lung" concept (i.e., small tidal volumes, high frequencies, and high PEEP) developed to minimize alveolar distention and reduce lung injury appears to be feasible in neurosurgical patients despite theoretical concerns for adverse effects on ICP.[20]

The relationship between $Paco_2$ and CBF can be exploited in examining the response of ventilated patients to tests of spontaneous breathing. Normalization of $Paco_2$ may increase ICP, indicating limited craniovascular compliance. Such an insight may guide subsequent therapy and ventilatory strategy, and ICP effects should be considered during any weaning strategy.

Fluids and Electrolytes

Normally, capillary fluid shift is a function of hydrostatic pressure pushing fluid out and the balance of osmotic forces retaining fluid within[21]:

$$Jv = Kf([Pc - Pi] - \sigma[\pi c - \pi i])$$

where Jv is the net fluid movement between compartments, Pc is the capillary hydrostatic pressure, Pi is the interstitial hydrostatic pressure, πc is the capillary osmotic pressure, πi is the interstitial osmotic pressure, Kf is the filtration coefficient (this is a product of surface area and hydraulic conductivity), and σ is the reflection coefficient (the membrane impermeability toward osmotically active particles). In extracranial capillaries, these osmotic forces derive from oncotic pressure, as smaller solutes can cross the capillary basement membrane following concentration gradients and only large protein molecules remain to exert effect.

However, in the brain, because of the presence of "tight junctions" in the endothelium, this intact blood-brain barrier

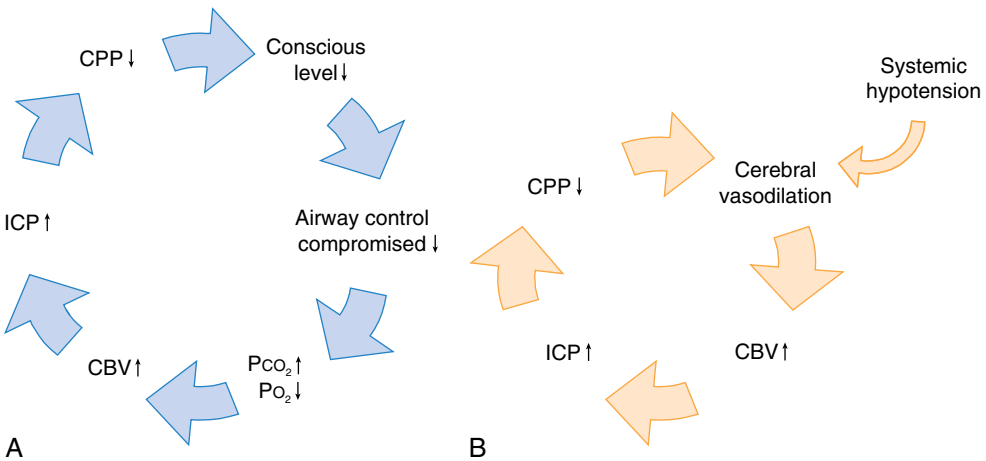

Figure 94-4 A, Ventilatory-neurologic circle of dysfunction. Induced changes in Pco_2 and Po_2 produce changes in cerebral blood volume (CBV), intracranial pressure (ICP), and cerebral perfusion pressure (CPP). This, in turn, impairs ventilatory control. **B,** Hemodynamic-neurologic circle of dysfunction. Similar to the diagram in **A**, systemic hypotension induces cerebral vasodilation, with increased CBV, increased ICP, and reduced CPP, which, in turn, increases vasodilation.

Table 94-2 Sodium Content, Osmolality, and Oncotic Pressure of Commonly Used Intravenous Fluids

Fluid	Osmolality (mOsm/kg)	Oncotic Pressure (mm Hg)	Na^+ (mEq/L)
Plasma*	289	21	141
Crystalloid			
0.9% NS	308	0	154
0.45% NS	154	0	77
3% NS	1030	0	515
Lactated Ringer's	273	0	130
Plasma-Lyte	295	0	140
Mannitol (20%)	1098	0	0
Colloid			
Hetastarch (6%)	310	31	154
Albumin (5%)	290	19	

reflects smaller solutes (e.g., sodium and chloride ions) and this relative impermeability renders cerebral capillary fluid shift a function of hydrostatic and *total* osmolar forces, with the oncotic pressure playing a very small part and the fluid shift most dependent on the osmolar gradient. In the absence of externally administered osmotically active substances (e.g., mannitol), this gradient is largely determined by sodium concentration, as serum osmolality.

$$\text{Serum osmolality} = (\text{serum Na}) \cdot 2 + \text{glucose}/18 + \text{BUN}/2.8$$

Thus, in general, hypotonic solutions should not be used in the neurosurgical patient when edema is a significant consideration. The osmolalities of commonly used solutions are listed in Table 94-2.

At the same time, the tighter endothelial connections and lipid bilayers also serve to reduce water permeability and, hence, the filtration coefficient. This physiologically limits the water shift across the vascular bed in response to changes in tonicity, as otherwise the brain volume would be significantly reduced by the large osmotic forces created by changes of only a few milliosmols per kilogram. Net fluid shift across the blood-brain barrier therefore depends on water permeability, as defined by the filtration coefficient, and the solute permeability, as defined by the reflection coefficient.

This permits osmotic diuresis, in which substances reflected by the blood-brain barrier can exert a significant effect on brain water (e.g., mannitol and hypertonic saline).

Inadequate perfusion and supply of substrate, whether it be relative or absolute, induces energy failure. This translates into real effects on the integrity and function of the blood-brain barrier, which is an energy-dependent physiologic construct as opposed to a purely anatomic structure. Ischemia and rapid reperfusion are associated with the generation of matrix metalloproteinases that directly attack the proteins sealing the connections between the endothelial processes that make up the blood-brain barrier.[22] This creates a loss of integrity and increased porosity of the blood-brain barrier, pathologically affecting the permeability and reflection coefficients. This acute blood-brain barrier disruption may allow solute shifts into the parenchyma and result in brain swelling, the extent of which depends on the "leakiness" of the blood-brain barrier as well as the size and concentration of the osmotically active molecules on either side of the barrier.

Hence, fluid therapy needs to be carefully considered under circumstances of cerebral ischemia and inflammation.

The brain exerts homeostatic control on metabolic and endocrine activity, and neurologic dysfunction can manifest as untoward changes in fluid and electrolyte balance. Diabetes insipidus is a florid example of this with polyuria and subsequent hypovolemia, and, if left untreated, systemic hypotension. Iatrogenic causes may also arise with the use of osmotic diuretics, sedation, and analgesics. Sympathetic denervation as a consequence of brainstem or spinal cord injury may also contribute to reductions in venous return as a result of increased vasodilatation and peripheral venous pooling.[23]

The increased sympathetic discharge commonly accompanying cerebral insults can also manifest as extracerebral stress on the entire body with increased incidence of gastric stress erosion, hypercatabolism, hyperglycemia, and impaired glucose tolerance.[24]

Nutrition requirements are often increased after brain injury, and there is evidence to suggest improved outcome with the early use of enteral nutrition (see Chapter 95).[25]

Hyperglycemia is a potent aggravator of cerebral insult.[26] It remains to be proven whether the widespread use of tight glycemic control with aggressive insulin therapy produces improvements in neurologically compromised patients. There are some suggestions that it may be deleterious.[27]

Fever and Infection

Over 50% of patients in neurologic intensive care units (ICUs) develop fever.[28] This is an often overlooked insult to the compromised brain, increasing oxygen utilization and metabolic stress.[28] Patients within the ICU have multiple risk factors for infection and sepsis, including the presence of a variety of indwelling catheters (e.g., arterial, venous, CSF). Other potential causes of fever include intracranial hemorrhage and idiosyncratic drug effects (e.g., the anticonvulsant phenytoin).[28,29] Fever is associated with a worsened outcome after neurologic injury, including intracranial hemorrhage, subarachnoid hemorrhage (SAH), and stroke. A meta-analysis of available studies demonstrated an increase in neurologic morbidity and mortality associated with fever.[30]

Although hypothermia has not proved to be a successful intervention for patients with traumatic brain injury[31] or SAH,[32] this does not equate to a lack of beneficial effect of normothermia compared with hyperthermia, and many clinicians are increasingly aggressive in preventing and treating fever.[33]

To provide appropriate treatment for fever, it is necessary to perform daily reappraisal to delineate the source of fever, given the large number of potential causes. However, in many cases a cause cannot be determined, and empirical treatment including scheduled administration of acetaminophen, application of cooling blankets, and increasingly, more invasive methods of cooling are required.

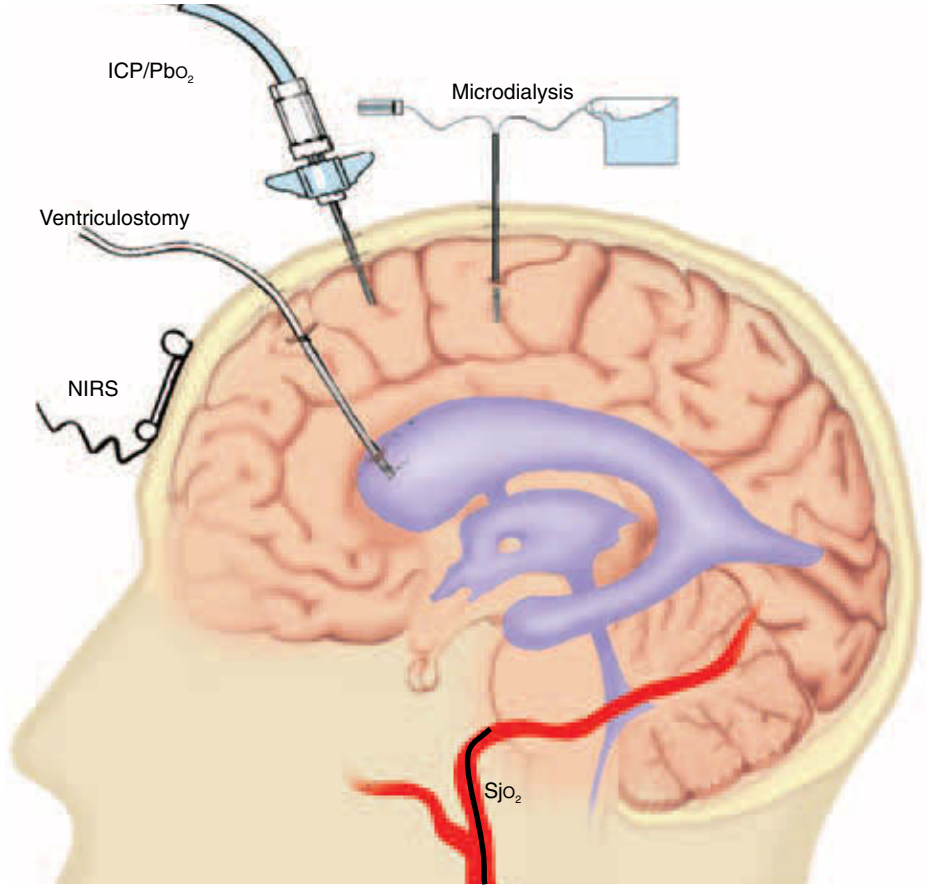

Figure 94-5 Schematic of available intracranial monitoring, with near-infrared oximetry (NIRS), intracranial pressure (ICP, either via ventriculostomy or parenchymal probe), brain tissue oximetry (Pbo_2), microdialysis, and jugular venous oximetry (Sjo_2).

Monitoring

The avoidance or correction of secondary physiologic insults necessitates the aggressive use of physiologic monitors (see Chapter 46 and Fig. 94-5). This does not obviate the need for regular clinical examination of the CNS, because monitors measuring the function of the brain (e.g., processed electrical activity, cerebral oxygenation, and ICP) are merely surrogates and do not integrate the information in a cogent manner. Similarly, attention should be paid to the basics of fluid volume status, respiratory rate, cardiovascular stability, and metabolic consumption.

Intracranial Pressure

ICP monitoring quickly became a standard of care after introduction to clinical use in the 1970s,[34] making subsequent determinations of utility and effectiveness with a randomized controlled clinical trial almost impossible. Noninvasive monitors have not established sufficient reliability to date and remain the subject of research.[35] Despite the broad acceptance of ICP monitoring, some have challenged its use as having no effect on outcome.[36] Nonetheless, the majority of neurosurgical centers insert such devices routinely in the management of traumatic brain injury and SAH, using defined thresholds (e.g., ICP > 25) to trigger treatment interventions, including osmotic agents (e.g., mannitol, or hypertonic saline) or operative treatments (e.g., decompressive craniotomy or CSF drainage).

ICP sensors may only represent the compartment pressure where they were placed (see Fig. 94-2) and may not be sensitive to acute transients in pressure on the other side of the falx or tentorium.[37] Intraparenchymal fiberoptic devices are less invasive and easier to place but may only be calibrated ex vivo and cannot drain CSF. Thus, provided the ventricles are accessible, ventricular catheters remain the gold standard of measurement but at the expense of an increased risk of infection of around 6%.[38]

When the ventricles are small, this becomes technically difficult, and the risks of hemorrhage and contusion are increased.

ICP devices can be quickly placed with a minimum of morbidity in experienced hands and, provided suitable attention is paid to the issue of potential drift from calibration,[39] generally offer useful insights to guide therapeutic interventions.

Observation of their trends reveals characteristic patterns that may have prognostic implications (e.g., the Lundberg "A" or "plateau" ICP wave indicating critical cerebral compliance[40] and impending herniation.

Cerebral Blood Flow

Important threshold values for function were identified by Symon and others (Table 94-3).[41] The initial methods of quantitative CBF measurements were laborious and time consuming and did not offer accurate regional estimates.[42] They were replaced by the use of isotopic tracers that allow basic regional flow measurement

Table 94-3 Functional Thresholds of Cerebral Blood Flow (CBF)

CBF (mL/100 g/min)	Result
50	Normal
20	EEG slowing
15	Isoelectric EEG
6-15	Ischemic penumbra
<6	Neuronal death

EEG, electroencephalogram.

(e.g., inhaled or intravascular xenon-133) or a combination of imaging and qualitative assessment (i.e., single photon-emission computed tomography [SPECT]). Calibrated imaging techniques such as positron emission tomography (PET) and stable xenon or contrast CT perfusion[42] have now become standard in many centers.

Although providing potentially useful information on regional perfusion, these methods often involve transporting the patient outside the ICU, which may be clinically inappropriate in unstable circumstances.

Recently, invasive probes using laser collimated light and the Doppler principle have been introduced to measure the capillary "flux" of red blood cells, providing focal measurements of tissue blood flow. Criticism has centered on their small measurement area, which may not be representative of global conditions.[43]

Thermodilution is a similarly focal technique in which small thermocouples are placed cortically. Blood flow is related to temperature diffusion at the probe.[44] An alternative approach has been to use jugular venous temperature diffusion to assess flow. Whether this reflects CBF reproducibly may depend on the ratio of jugular venous drainage to overall cerebral venous flow.[45] It remains to be seen whether these devices can be developed into reliable and consistent monitoring tools.

Transcranial Doppler Monitoring

Transcranial Doppler monitoring uses the Doppler shift effect to assess flow velocity in insonated arteries.[46] This is often used as a surrogate of flow in examining accessible vessels and in skilled hands offers considerable insights into dynamic flow. This technique has the advantage of being a bedside, relatively speedy and noninvasive monitor of flow within the main components of the circle of Willis via ophthalmic, temporal, and foramen magnum acoustic windows. It has excellent temporal resolution, and, being noninvasive, allows repetitive measurements with little or no risk. In a small proportion of patients, predominantly older women, temporal bone thickness may prevent monitoring.[47] Extrapolation of velocity to flow relies on an assumption of relatively constant diameter of the large conductance vessels. Under different circumstances, changes in velocity can be used to assess alterations of vascular caliber (e.g., arterial vasospasm after subarachnoid hemorrhage)[48] or intracranial stenosis (Fig. 94-6). For the middle cerebral artery, vasospasm can be distinguished from hyperemia by examining the ratio between the intracranial flow velocity to extracranial carotid artery flow velocity (the Lindegaard index). A ratio greater than 3 is generally indicative of vasospasm whereas a ratio less than 3 is consistent with hyperemia.[49]

Autoregulation and Vasomotor Reactivity

Monitors of CBF can assess the response of the cerebral vasculature to changing circumstances of metabolism and blood pressure (i.e., autoregulation).[50,51] Static cerebral autoregulation can be determined with sustained manipulation of blood pressure using either a tilt test or a direct vasopressor as clinically appropriate, whereas dynamic autoregulation can be assessed using rapid deflation of previously inflated thigh cuffs above systolic blood pressure. Alternatively, autoregulation can be assessed by monitoring CBF velocity via TCD in response to spontaneous fluctuation of blood pressure using transfer function analysis, although these are likely to be less reliable than the stimulus-response paradigm.[52] The presence or lack of autoregulation may guide subsequent treatment and prognosis, because frequently the loss of autoregulation is associated with a poor outcome.[53,54] Cerebrovascular reserve or vasomotor reactivity, as determined by CBF response to changes in $Paco_2$, can be assessed either with rebreathing or addition of carbon dioxide to the breathing circuit, or with administration of acetazolamide.[52]

Jugular Bulb Oximetry

The Fick principle may be reversed to examine the venous oxygen saturation that, assuming a constant hematocrit and metabolism, can offer an assessment of the adequacy of CBF and associated oxygen delivery relative to cerebral oxygen consumption—that is,

$$\text{If } AVDo_2 = \left(CMRo_2/CBF\right), \text{ then } Cao_2 - Cjvo_2 = \left(CMRo_2/CBF\right)$$

Ignoring the contribution of dissolved O_2, then

$$\left(Sao_2 - Sjvo_2\right) \times Hgb \times 1.34 = \left(CMRo_2/CBF\right)$$

where $CMRo_2$ is the cerebral oxygen metabolic rate, Cao_2 and $Cjvo_2$ are the arterial and jugular venous oxygen content respectively, Sao_2 and $Sjvo_2$ are the arterial oxygen and jugular venous oxygen saturation respectively, Hgb is the hemoglobin concentration, and 1.34 is the oxygen affinity constant.

In vivo, catheters are placed retrogradely through the internal jugular vein to its jugular bulb at the foramen or even beyond it to the large sinuses (Fig. 94-7).[55,56]

These catheters provide information related to both perfusion and oxygen consumption, in a manner analogous to the use of mixed venous oximetry for shock management. Both desaturation (<50%—suggesting inadequate delivery/excess consumption) and abnormally high saturation (>75%—suggesting hyperemia or stroke) have been associated with poor outcome.[57,58] The derivable arteriovenous oxygen content difference is possibly a more accurate assessment of the adequacy of flow and has been shown to relate to outcome.[59] Jugular venous oximetry has been criticized as being insensitive to focal changes, because it reflects the averaged global cerebral venous oxygen saturation from the confluence of hemispheric venous drainage. Consequently, some authors have suggested using oxygen consumption in combination with the cerebral arteriovenous gradient of lactate to make stoichiometric assessments of aerobic versus anaerobic

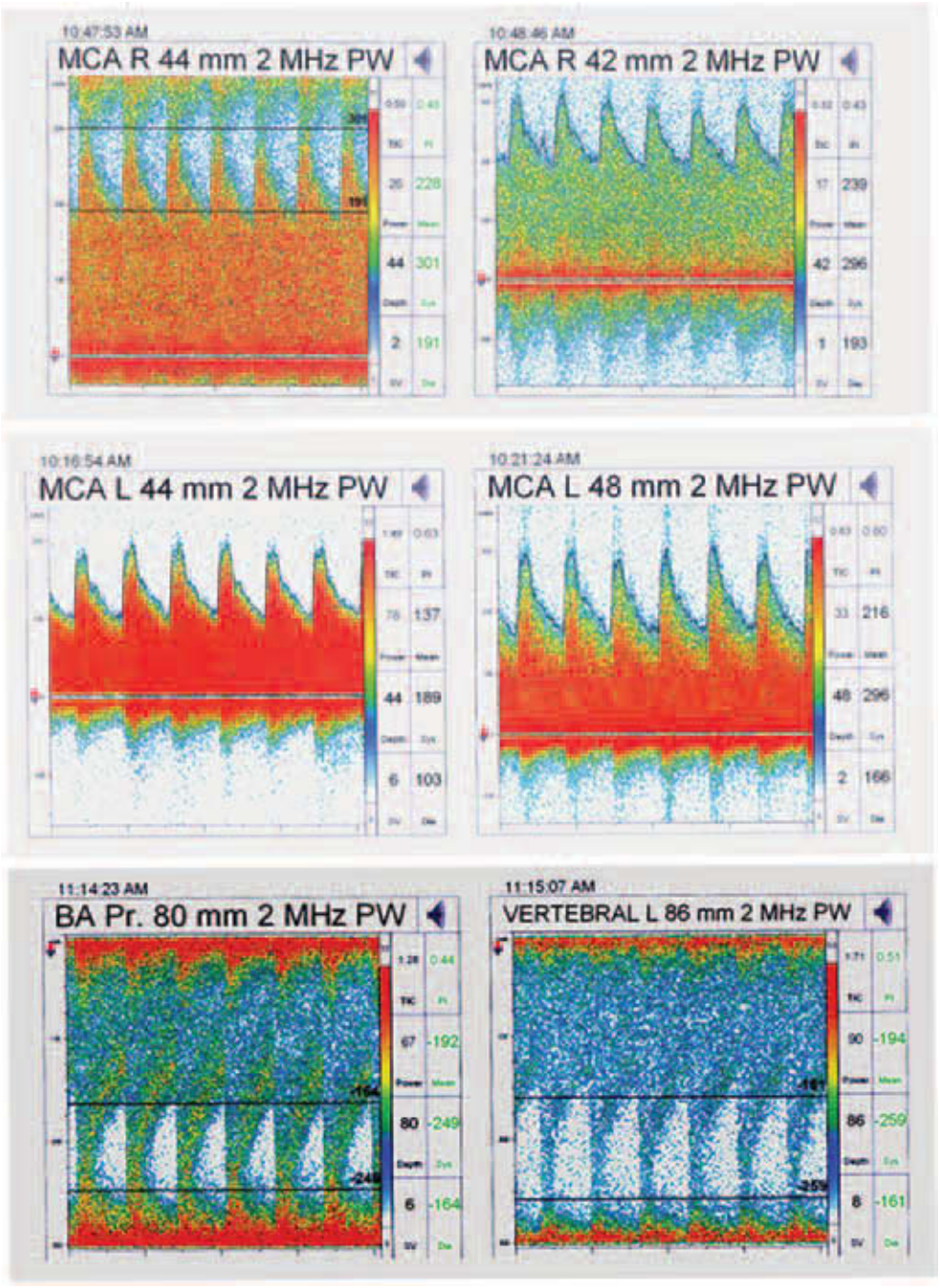

Figure 94-6 Transcranial Doppler images of elevated cerebral blood flow velocities in middle cerebral and vertebrobasilar vessels.

metabolism.[60] They have gone on to suggest metabolically directed management strategies as opposed to management of cerebral hemodynamics,[61] that is, goal-directed therapy based on metabolic indices (jugular venous oxygen saturation), rather than on hemodynamic indices (ICP and CPP).

Brain Tissue Oxygen Tension (Pbo_2)

In conceptually similar assessments of in vivo oxygenation, miniaturized Clark electrodes have been developed and combined with ICP catheters to provide simultaneously estimations of tissue oxygen tension and ICP. Pathologic levels are thought to be below 15 mm Hg with normal values in the 20- to 45-mm Hg range.[62] These Pbo_2 devices have been used in a variety of pathologic conditions, and many authors found them useful in guiding therapy and providing insight into adequacy of cerebral perfusion and have reported improved outcome.[62] However, there is a paucity of adequately powered randomized controlled trials, and many limitations including measurement errors, calibration drifts, and uncertainty of the generalizability of the local measurement remain.[63,64] Nevertheless, in patients without focal lesions, it can provide important physiologic feedback in response to therapeutic manipulations of blood pressure and oxygenation. Thus, a critical component of the utility of Pbo_2 or any of the monitors mentioned here, is a well-thought-out treatment proto-

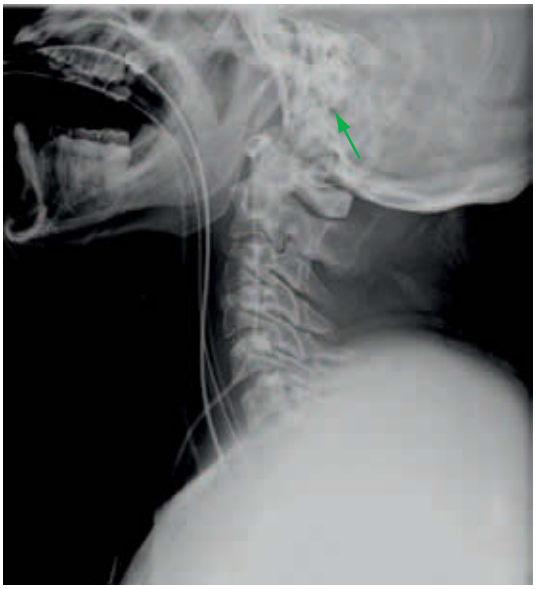

Figure 94-7 Lateral cervical spine radiograph showing appropriate positioning of the SjO_2 catheter above the lower border of the C1 vertebra (*arrow tip* is actually within the jugular foramen).

col with appropriate strategies for intervention guided by information provided by the monitor.[65]

Cerebral Microdialysis

There is significant interest in the use of cerebral microdialysis probes to assess the biochemical milieu of the brain. These probes are placed through a burr hole and cycle small volumes of dialysate through the catheter to an extracranial collection system. Consequently, various substances can diffuse across the semipermeable membrane (e.g., lactate. pyruvate, glucose, glycerol, glutamate)[66] for collection and subsequent analysis using a bedside high-pressure liquid chromatography device. This gives graphical and numerical displays of trended concentrations for the preceding collection interval (usually 1 hour). This then relates to the in vivo biochemistry of the brain. While intuitively attractive, there have been a number of unresolved questions hampering wider implementation, not the least of which is the question on the optimal site of placement, in relation to disease pathology, as well as to anatomic region of gray matter versus white matter.[66]

These issues were recently addressed by a consensus statement on placement of microdialysis catheters, with the aim of improving accuracy in the comparison of results and to allow generalization from accumulated experience.[67] Improvements in membrane technology now permit larger molecules to cross into dialysate, creating the possibility of research into microvascular peptidomics.[66]

Electroencephalography

The EEG records electrical activity generated and detected by appropriately placed electrodes in a radial and axial array, as defined by the 10/20 system, an internationally standardized system of recording. The consequent waveforms are displayed and recorded. The spectrum of component frequencies together with amplitude and power can be quantified and analyzed in a variety of fashions by what are termed processed EEG monitors. These devices can provide important diagnostic information in patients in the neurocritical care unit who cannot be otherwise assessed. The EEG tends to be used in a diagnostic snapshot mode for isolated assessments, and it is underutilized as a continuous monitor within the ICU. This is a function of the difficulty involved in its application and interpretation, which necessitates dedicated equipment and personnel. A 24-hour continuous recording of EEG is, in general, more fruitful than a snapshot recording.

Moreover, both in traumatic brain injury and SAH, there are significant numbers of patients who develop nonconvulsive status epilepticus,[68,69] and this constitutes a regularly overlooked but significant source of morbidity and stress on the brain. Whereas the EEG is a difficult monitor to use, there are definite indications for its deployment and the neurocritical care physician should be familiar with the basic principles of its function and use.

A number of related devices have also been developed from processed EEG to monitor the "depth of anesthesia." Although they have been utilized to monitor the level of sedation in critically ill patients, they are not designed for—and should not be used to—monitor neurologic integrity or seizure activity

Near-Infrared Spectroscopy

The idea of "pulse oximetry for the brain," as conceptualized in the early 1990s, is an attractive one. It relies on the principle of reflectance spectroscopy, in which near-infrared light traverses bone transparently, to be scattered and reflected to a degree inversely proportional to the concentration of light-absorbing materials in tissue (e.g., hemoglobin and other tissue chromophores). The surface detector is constructed and calibrated so as to detect light that has ostensibly traversed down to cerebral cortex and back. An adjacent detector is positioned to detect a signal from superficial tissues and both signals then used in an algorithm to derive an estimated tissue saturation. However, the devices employed have been troubled by issues of reliability, specificity, and cross contamination from other cytochrome-containing tissues.[70,71] There is slightly more enthusiasm for their role as trend monitors of flow, especially in children and patients with extracranial carotid artery disease.[72,73]

Radiologic Imaging

Imaging can be employed as a monitoring technique, albeit on a protracted time scale.[74] The two major modalities are computed tomography (CT) and magnetic resonance imaging (MRI). CT is by far the most useful and commonly used technique, because it is the most efficient method. MRI, although more time consuming, is more sensitive for brainstem lesions as well as for axonal injuries. Both CT and MRI can provide information on the vascular tree, but conventional contrast angiography remains the gold standard. Assessment of intracranial masses, diffuse injury, or hemorrhage can be subsequently used to guide therapy, triage, and prognosis.[75]

Table 94-4 Marshall Scale: Computed Tomography Categories for Head Injury

Category	Definition
Diffuse injury I	No visible intracranial pathologic process
Diffuse injury II	Cisterns are present with midline shift of 0-5 mm and/or lesion densities present; no high or mixed density lesions at ≥25 mL
Diffuse injury III	Cisterns compressed or absent, with midline shift of 0-5 mm; no high or mixed density lesions of ≥25 mL
Diffuse injury IV	Midline shift of >5 mm; no high or mixed density lesion of ≥25 mL
Evacuated mass lesion (V)	Any lesion surgically evacuated
Nonevacuated mass lesion (VI)	High or mixed density lesion of ≥25 mL; not surgically evacuated

To provide meaningful comparison of therapeutic modalities in clinical trials, it is important to standardize and categorize the CT images. The Marshall scale has been used in traumatic brain injury to stratify degrees of hemorrhage within the cranial vault and correlates to outcome (Table 94-4).[76,77] The Fisher scale assesses the volume of subarachnoid blood after a diagnosis of SAH.[78] There again is a strong relationship to outcome regarding the development of vasospasm (Table 94-5).[79] Both scales rely on experienced interpretation for accuracy. A recent paper documenting 18 neurosurgical centers in Italy found inconsistent application of the Marshall scale, suggesting an urgent continued need for standardization.[80]

Clinical Examination

Comprehensive neurocritical care encompasses the ability to perform a competent neurologic examination. Reproducible and objective assessment of neurologic function is just as important a monitor as some of the sophisticated technology mentioned earlier, with the advantage that it offers better insight into global function of the nervous system and allows integration of information in an inherently complex dynamic system. One of the most basic yet important examinations is the pupillary light reflex, the unilateral absence of which may indicate midbrain compression from uncal herniation and neurologic emergency. Bilaterally absent papillary reflexes signify imminent or established cerebellar herniation, but this might be reversible with rapid efficacious treatment.

Table 94-5 Fisher Scale (CT Scan Appearance)

Group 1	No blood detected
Group 2	Diffuse deposition of subarachnoid blood, no clots, and no layers of blood >1 mm
Group 3	Localized clots and/or vertical layers of blood ≥1 mm in thickness
Group 4	Diffuse or no subarachnoid blood, but intracerebral or intraventricular clots are present

Clinical scales have been devised for the common neurologic settings. The Glasgow Coma Scale (GCS) is a well-known, universally if inconstantly applied scale (Table 94-6). It relies on independent assessment of eye opening, speech, and best motor movement in response to progressive trials of command, voice, and noxious stimuli.[81] The Hunt and Hess scale (Table 94-7) when applied to patients with SAH offers classification and prognostication of mortality.[82] The World Federation of Neurologic Surgeons Scale (WFNS) is the preferable rating because it uses the more prevalent GCS but with a modifying component of focal deficit (Table 94-8).[83] Knowing and using these scales are crucial to understanding the terminology and practice of neurocritical care.

Multimodality Monitoring

No single monitor credibly and reliably offers insight into the functioning physiology of the brain. Instead, various surrogates of function are offered. Many criticisms can be directed at each individually, but an interesting concept is that of multimodality monitoring, that is, using a combination of parameters to improve on accuracy of diagnosis and response to management.[84] Although an attractive concept, the precise implementation of this idea is still in its early days, with little methodologic standardization; this may be facilitated by rapidly approaching commercial development.

Common Diseases in the Neurocritical Care Unit

Head Injury

The treatment of traumatic brain injury was one of the initial emphases of neurocritical care. Recent changes in road traffic

Table 94-6 Glasgow Coma Scale

	6	5	4	3	2	1
Eyes	N/A	N/A	Opens eyes spontaneously	Opens eyes in response to voice	Opens eyes in response to noxious stimuli	Does not open eyes
Verbal	N/A	Oriented, converses normally	Confused, disoriented	Utters inappropriate words	Incomprehensible sounds	Makes no sounds
Motor	Obeys commands	Localizes to noxious stimuli	Flexion to noxious stimuli	Abnormal flexion to noxious stimuli	Extends to noxious stimuli	Makes no movements

Table 94-7 Hunt and Hess Grading System

Grade	Clinical Presentation	Survival (%) (approximate)
Grade 1	Asymptomatic or mild headache	70
Grade 2	Moderate to severe headache, nuchal rigidity, and no neurologic deficit other than possible cranial nerve palsy	60
Grade 3	Mild alteration in mental status (confusion, lethargy), mild focal neurologic deficit	50
Grade 4	Stupor and/or hemiparesis	20
Grade 5	Comatose and/or decerebrate rigidity	10

legislation and enhancements in passenger protection have led to a decline in the incidence of traumatic brain injury in the United States, to the degree that motor vehicle accidents have been replaced by falls as the chief cause of injury.[85] These causes, together with assaults and off-road and sporting injuries, still contribute to what is referred to as a "silent epidemic,"[85] accentuated by ongoing military conflicts and their recent hallmark blast injuries[86] and a prevalence consequent on concentration in a predominantly youthful population. Outside of wartime, these causes usually share a common factor in the contribution from alcohol consumption.[87,88]

In all circumstances, brain structure is deformed by the transmission of kinetic energy, severing blood vessels and nerve fibers. The distribution of this damage covers a wide spectrum from localized contusion to diffusely scattered foci, varying with the circumstances of the incident and the architecture of the victim's brain. Typically, cerebral contusions are located at the bony prominences of the skull, at the sphenoid wing and petrous ridge.[89] The variability in inflicted pathology renders some of the broader assumptions about cerebral injury questionable, because a temporal lobe injury may behave very differently from a posterior fossa lesion.

Traumatic brain injury may also be classified according to whether it is blunt or penetrating. Penetrating injury may again have widely varying consequences depending on site, depth, and energy but is generally fatal if it bilaterally traverses the midbrain.[90] While initial mortality from penetrating injury is higher, outcome in survivors is similar to that for nonpenetrating injury.[91]

Vascular injury may affect more superficial arterial blood vessels, as seen in the middle meningeal artery injury typical of pterional fracture. This commonly results in an extradural hematoma.[92] These rapidly expanding collections can result in swift neurologic deterioration and devastating results, if not treated quickly. The mortality is between 15% and 20%.[93] Alternatively, cortical bridging veins between cortex and the dural venous sinuses are often torn by rotational or acceleration/deceleration forces to produce an accumulating subdural hematoma. This may manifest slowly and may even be unaccompanied by signs of external trauma. In the time taken for the venous hematoma to develop, symptoms may be subtle and, unfortunately, may be disregarded. The slow expansion exerts a cumulatively damaging effect, which by the time severe signs eventually manifest, may be just as or even more destructive than a rapidly expansile lesion.[94] This is prevalent in the elderly where the process of senile cerebral atrophy results in greater tension on the bridging veins crossing an increasing distance, consequently rendered all the more susceptible to rupture.

In all these scenarios, the primary pathology is accentuated by secondary features of elevated ICP, diminution of arterial inflow, and consequent reduction in CPP, with resulting tissue hypoxia and cell death, as previously described in the intracranial pressure-volume relationship (see Fig. 94-1).

This can also be modified adversely by loss of autoregulation, which may result in further increases in ICP. This is often seen in diffuse injury, where although individual foci may be small, they additively combine to produce a total burden of inflammatory change sufficient to overwhelm autoregulation.[95]

Traumatic SAH (tSAH) is seen on up to 60% of admissions for traumatic brain injury.[96] There is some variability of detection and reporting, but despite this, tSAH has a substantial effect on outcome.[97] There is an interesting relationship with prolongation of the QTc interval seen in 67% of patients with tSAH.[98] About 20% of patients with tSAH may also develop vasospasm, which can lead to secondary ischemic insult. The diagnosis and management of the vasospasm is facilitated with the use of transcranial Doppler imaging.

A crucial part of the management of traumatic brain injury in the ICU should be a comprehensive examination and assessment utilizing such principles as outlined in Advanced Trauma and Life Support,[99] because it is not unknown for occult injuries to escape initial screening but subsequently exert a delayed physiologic compromise on the arrival of the patient in the ICU, or worse, in the CT scanner. These injuries may accentuate the primary brain injury by contributing to secondary physiologic insult.[14]

Overall, the common goal of treatment of traumatic brain injury is to maintain cerebral perfusion. In patients with mass lesions resulting in anatomic distortion with mass effect, surgical removal is indicated. Although unproven by randomized controlled trial, early decompressive craniectomy for patients with elevated ICP refractory to medical treatment, without or without mass lesions, may improve outcome.

Medical management may be required both before and after surgical intervention or as an alternative in circumstances of diffuse injury. Such treatment strategies within the ICU revolve around the reduction of ICP and the maintenance of cerebral perfusion, which may not be compatible goals. While therapeutic resolution of ICP with osmotic diuresis is a logical approach, it may have unintended consequences on central vascular volume and myocardial function.[100] After an initially beneficial effect in reducing intracerebral volume, mannitol will then go on to leave

Table 94-8 World Federation of Neurologic Surgeons Scale

Grade 1	Glasgow Coma Score (GCS) of 15, motor deficit absent
Grade 2	GCS of 13-14, motor deficit absent
Grade 3	GCS of 13-14, motor deficit present
Grade 4	GCS of 7-12, motor deficit absent or present
Grade 5	GCS of 3-6, motor deficit absent or present

the vasculature via the kidney. This will also reduce the cardiovascular volume, diminishing cardiac output and blood pressure—possibly replacing one physiologic insult for another.

Mannitol has diminished in popularity over recent years to be supplanted by the increasing use of hypertonic saline (HTS).[101] This agent demonstrates a good resuscitation profile, with none of the delayed hypotension observed with mannitol.[102] Some of the same concerns apply to the use of hypertonic saline as exist with the use of mannitol (i.e., diffusion of osmotically active particles into the brain interstitium in circumstances of injury or compromise of the blood-brain barrier).[103] This may create "rebound" effects on reduction of plasma osmolarity as hypertonic saline administration is reduced, with an increase in brain water. This has been observed with differential effects in contused versus noncontused brain.[104] While bolus usage of hypertonic saline has been shown to be useful, it remains to be seen whether sustained infusions or the practice of persistent-induced hypernatremia offer any improvement in outcome.

While the choice of resuscitation fluid has not been shown to have any effect in a large study of trauma victims,[105] a post-hoc analysis of subgroup data demonstrated increased mortality associated with the use of albumin in traumatic brain injury.[106] This is somewhat at odds with the demonstration of potential benefit in stroke[107] and a prospective trial is needed.

Control of the vascular blood volume may also be regulated by manipulation of the Pco_2, which most frequently requires intubation of the trachea and mechanical ventilation.

Controlled hyperventilation is frequently practiced to reduce blood volume, and hence ICP.[108] Recent studies have demonstrated adverse consequences of aggressive hyperventilation, and most authorities agree on limiting the reduction in Pco_2 to avoid ischemia.[109]

The Brain Trauma Foundation publishes guidelines on the management of brain trauma, which are regularly updated. These concentrate on the principles outlined previously, namely reduction of ICP while preserving perfusion pressure.[110] They also provide statements of consensus on the merits of these strategies. They recommend a target Pco_2 of between 30 and 35 mm Hg[108] with a CPP of more than 60 mm Hg. This reflects the perfusion-oriented approach popularized by Rosner and others in which once ICP manipulation has reached its effective limit, mean arterial pressure may be accentuated through the use of fluids and inotropic support to maintain cerebral perfusion at or above 70 mm Hg.[15] This formed the basis of the initial Brain Trauma Foundation recommendations on cerebral perfusion.[111]

However, a subsequent clinical trial optimizing cerebral perfusion could not substantiate improvements in outcome[112] and, coupled with evidence that suggests an excessive CPP may worsen outcome,[113] the current recommendation is for a CPP of 60 to 70 mm Hg.[110]

Hypertension in excess of autoregulatory control can induce both excess blood volume and the formation of vasogenic edema across a compromised blood-brain barrier.[7] This concept underpins the Lund group protocol, which gives priority to limiting the Starling forces across the capillary bed to avoid the formation of edema.[114] These investigators recommend a CPP of 50 mm Hg using β-blockers as required, the reduction of metabolic demand with barbiturates, and intravenous colloid administration.[115]

There are no randomized controlled trials to support one strategy over the other. Nonetheless, a number of case series have now accumulated, offering comparable outcomes to CPP-oriented management.[116,117] There are almost certainly subsets of pathologic processes that may respond to the differing approaches, depending on the precise pathophysiology, determined in part by lesion volume, inflammatory burden, and blood-brain barrier integrity. A challenge lies in identifying which patient would better respond to each therapeutic strategy, perhaps using multimodality monitoring and imaging techniques.

Currently, ICP/Pbo_2 and ventriculostomy are frequently used in the management of patients in severe traumatic brain injury. However, these invasive monitors are contraindicated if coagulopathy is present. The occurrence of coagulopathy in traumatic brain injury is associated with a poor prognosis and should be vigorously treated with clotting factors, fresh frozen plasma, and platelets.

Hyperglycemia has also been reported to be associated with poor outcome in multiple retrospective studies.[26] To date there has been no randomized controlled trial on the influence of tight glycemic control on outcome in patients with traumatic brain injury, although it may be prudent to keep glucose below 140 mg/dL.

Corticosteroids have not been recommended for use in brain injury for some time, and any lingering suggestions that early steroid use may diminish inflammatory consequences of brain injury were finally dismissed by the publication of the CRASH study, which, in a multicenter evaluation of over 10,000 patients, showed an adverse effect of steroids on mortality and morbidity.[118]

Hypothermia, despite its failure to demonstrate a beneficial effect on outcome, may still have a role in the management of patients with traumatic brain injury in which ICP cannot be controlled with conventional means or when decompressive craniectomy is not otherwise available. Moderate hypothermia to 33° to 34°C generally facilitates control of ICP to a manageable level. Rewarming to normal temperature, however, runs the risk of rebound in ICP.

The timing of prophylaxis against deep venous thrombosis (DVT) has been an issue of controversy. There is general agreement on the need for prophylaxis, because up to 25% of patients with isolated traumatic brain injury develop DVT[119] and most clinicians will agree with its implementation 48 hours after injury. There is some evidence to suggest that immediate postoperative use of heparin prophylaxis is safe and does not confer additional risk of bleeding.[120]

Subarachnoid Hemorrhage

In contrast to declining numbers of patients with traumatic brain injury, the incidence of SAH remains consistent at 8 to 10 per 100,000 per year[121] and a major critical care challenge. Ethnic variations on incidence are reported, with the incidence in Finland and Japan being up to three times that in the United States.[121,122] Women have a greater risk than men by a factor of 1.6.[122] A majority of cases of SAH occur in the fourth to sixth decades of life, with a peak at age 55.[123] The majority of cases arise from aneurysms[124] that have a relatively severe morbidity and mortality. Ten percent of patients will die before hospitalization, and 25% will die within the first 48 hours, with initial hemorrhage being the primary cause of death, followed by rebleeding.[125] Subsequent morbidity and death is attributable to neurologic deficits due to ischemia induced by arterial vasospasm.[126]

Significant improvements in mortality and morbidity have occurred in the past 2 decades.[127,128] This suggests that further reductions may be achievable with continued changes in surgical practice and further concentration of expertise in regional centers. Paralleling this has been the development of neuroimaging and endovascular technologies, which have played a large part in improved outcome.[129,130]

Early Versus Late Treatment

Mortality and morbidity from SAH are mostly secondary to rebleeding of unsecured aneurysms and the delayed ischemic deficit or infarction from arterial vasospasm. Rebleeding peaks within the first 24 hours after the initial hemorrhage and declines progressively thereafter, reaching a plateau of 2% by 6 months. In contrast, vasospasm tends to develop by the third day, peaks between 5 and 7 days, and generally wanes by 14 days. This led to some debate on the timing of treatment—where rebleeding may averted by early intervention but at a risk of an increased risk of vasospasm, which may induce devastating neurologic ischemic deficit. Surgically, early treatment is also associated with less optimal brain relaxation conditions. Although no difference in outcome was reported, aggressive vasopressor therapy and endovascular support have tipped the balance in the favor of early clipping in the first 72 hours after bleeding.[131]

In addition to rebleeding and vasospasm, acute hydrocephalus develops in 25% to 30% of patients after SAH, and emergent ventriculostomy may be lifesaving as well as offering a more accurate prognosis.[132]

Antifibrinolytics

Antifibrinolytics to decrease the risk of bleeding increase the risk of stroke[133] and, with the advent of early treatment, are seldom used today. Many clinicians, however, will control blood pressure with the use of vasoactive infusions (e.g., nicardipine) to reduce the risk of rebleeding until the aneurysm is secured.[134]

Vasospasm

Vasospasm is thought to derive from the attenuation of nitric oxide–induced vasodilation, with an associated enhanced production of endothelin production and consequent vasoconstriction. The extravascular heme molecule is the leading candidate in a long list of possible culprits.[135] Seventy percent of patients with SAH develop angiographic vasospasm, although only 30% to 40% of patients will become symptomatic. Patients with a large amount of subarachnoid blood are at higher risk for the development of vasospasm. The Fisher grade is frequently used clinically to prognosticate the risk of vasospasm.[78] A recent meta-analysis of treatment techniques suggests no difference in the incidence of vasospasm between treatments.[136]

Denny-Brown first suggested increasing blood pressure to combat vasospasm in 1951,[137] but it was not until the demonstrated reversal of ischemic deficits with the use of pressors[138] that this approach developed into the subsequent use of what has been termed "triple H" therapy, where induced hypertension (up to and sometimes beyond 180 mm Hg systolic) and aggressive fluid infusion (4-5 L/day) (hypervolemia) could reverse the neurologic deterioration apparent in the patient with severe spasm.[139]

The third "H"—hemodilution to a theoretical optimal hematocrit of 30—is largely a passive result of hypervolemia and is thought to be less important, and possibly even harmful.[140] Despite a significant anecdotal history of effect there has been little evidence of benefit in randomized control trials and meta-analysis.[141,142] Triple H therapy may also be associated with an increased frequency of complications[143] thought to be related to the use of hypervolemia.[142]

There is more evidence to support the effect of hypertension used singly, an effect that can be undermined by the use of additional hypervolemia.[144]

Although hematocrit is considered as less of an issue with triple H therapy, in a retrospective study, it was shown that a higher hemoglobin level is associated with less cerebral infarction and better outcome,[140] and many clinicians will maintain a hematocrit of 30%. Disappointingly, benefit is not seen with deliberate transfusion to increase oxygen delivery. It has, on the contrary, been associated with increased vasospasm and poor outcome.[140,145] The general critical care literature reinforces these deleterious effects of transfusion.[146] A prospective trial is awaited.

The only level 1 evidence from randomized control trials in SAH is regarding the use of nimodipine. This agent, when administered prophylactically from diagnosis for 21 days, offers modest improvement in outcome and incidence of ischemic deficit. Interestingly, it does not have a readily apparent effect on the incidence of angiographic vasospasm.[147]

Other therapeutic approaches to vasospasm include trials on antiplatelet medications,[148] statins, where some small studies have suggested improved neurologic outcome,[149,150] and endothelin antagonists.[151]

Management of vasospasm is facilitated with appropriate use of imaging, including the use of transcranial Doppler monitoring, SPECT, and cerebral angiography when indicated. Institution of triple H therapy necessitates the use of invasive monitoring, including that for arterial blood pressure and central venous pressure (or other indices of preload).

The use of mechanical balloon dilation of blood vessels—angioplasty—has added a major weapon to the armamentarium against vasospasm.[152,153] Angioplasty is limited by the caliber of blood vessels, as well as their accessibility, and carries a risk of catastrophic rupture.[152]

Pharmacologic angioplasty with intra-arterial injection of a vasodilator is gaining in popularity. First established using papaverine, use of calcium channel blockers such as nicardipine and verapamil is being increasingly reported and has fewer adverse effects. All current agents are limited by the transient nature of their effects—less than 24 hours.[154] Vasodilators may be used in vessels too small to be accessible by balloons.

Cardiac Dysfunction

As suggested previously, significant autonomic disturbance may arise in association with SAH, resulting in changes in the electrocardiogram and myocardial performance. Electrocardiographic changes are frequent but do not appear to relate to outcome.[155] However, one series described a 32% incidence of abnormal perfusion scans, independent of the clinical history, electrocardiogram pattern, or neurologic condition.[156]

Abnormal echocardiography has been described in up to 8% of SAH patients, mostly in those with blood in basal cisterns, frequently accompanied by hypotension and pulmonary edema, and is associated with a poor neurologic grade. A typical pattern of symmetric T wave inversion and severe QTc prolongation was described, although multiple electrocardiographic patterns had been observed.[157]

Table 94-9 Suggested Cardiovascular Management Strategies in Subarachnoid Hemorrhage

General

1. Manage hypertension in unsecured aneurysms (with nicardipine titrated to systolic BP < 140 mm Hg.
2. Maintain euvolemia prophylactically; no role for prophylactic hypervolemia.
3. Nimodipine (possibly statins)

Cardiovascular Instability

1. Blood pressure and cardiac output goals will alter as aneurysm is secured.
2. ECG
   If abnormal: QTc prolongation, ST-segment changes; check troponins.
   If troponins elevated: echocardiography.
3. Perform echocardiography if any manifested hypotension or heart failure is suspected.
4. Monitor cardiac output (e.g., LiDCO, PICCO, PABC).
5. Support on dobutamine for cardiac output and norepinephrine for blood pressure.
6. Consider coiling as soon as practicable.
7. Reserve coronary catheterization for isolated wall motion deficit and rising troponins (coil first if possible).
8. Avoid β-blockers unless there is active coronary artery disease.
9. Vasospasm: treat with euvolemia/mild hypervolemia, pressors, and cardiac output monitoring: adjust targets as perfusion tests suggest.
10. Transfusion: maintain hematocrit above 25%. Avoid use of stored blood if possible.

The phenomenon of neurogenic stunned myocardium is a definite clinical entity, with what can be a severe limitation of cardiac contractility. It is, however, a reversible condition, in contrast to myocardial infarction, and has a good recovery profile. Obvious abnormalities of function start to recede within 72 hours; but when stunning is severe, endovascular management rather than surgical treatment may be indicated (if the aneurysm is suitable). Cardiac dysfunction may complicate and limit the active treatment options for vasospasm and render early mechanical angioplasty more appropriate.[158] It has morphologic, epidemiologic, and functional similarities to Tako-tsubo cardiomyopathy, which is an acute transient dysfunction resulting from sympathetic overactivity in postmenopausal women[159] that has also been reported in SAH. Troponins are frequently increased in acute SAH. Whether this release of troponin represents a frank cardiac injury or "myocardial leak" remains unknown, and clinically it does not appear to have prognostic significance.[160] Interestingly, adrenoreceptor polymorphism was implicated in myocardial stunning, in which different receptor genotypes denoted an increased sensitivity to and release of catecholamines, in turn associated with a 3- to 4.8-fold increase in risk of cardiac injury and dysfunction.[161]

A typical strategy for cardiovascular management is given in Table 94-9.

Respiratory Dysfunction

Pulmonary injury is a frequent complication in the clinical course of the patient with SAH, with nearly 17% of patients experiencing severe dysfunction. This is associated with a poor neurologic outcome.[162] Transfusion has been associated with an increased risk of lung injury, which in turn affects mortality.[163] Acute pulmonary edema can also occur in patients in poor grade SAH, and this can be either neurogenic or cardiogenic.

Endocrine and Metabolic Derangements

Hyperglycemia has been identified as a risk factor for poor outcome, especially in SAH.[164,165] However, aggressive glucose control has not been proved to be useful in SAH; and in other critical care settings (e.g., intraoperative control in cardiac patients), this was associated with worse outcome.[166] As in traumatic brain injury, there is also no basis for the use of corticosteroids.[167]

Hyponatremia is observed in 30% to 40% of patients with SAH.[168] The most frequent mechanism is that of cerebral salt-wasting syndrome in which sodium is actively excreted from the body in high concentration and there is an accompanying diuresis despite ongoing hyponatremia.[169]

Berendes and colleagues demonstrated increased brain natriuretic peptide (BNP) release, thought at that time to derive exclusively from the brain.[170] Given the increasing evidence for the ventricle as the main source of production of BNP, it is unclear whether BNP arises from a stressed ventricle at the time of the hemorrhage and associated sympathetic discharge or from a brain experiencing abnormal perfusion states of homeostatic areas. Hyponatremia is also associated with cerebral infarction[171] in keeping with the clinical observation that hyponatremia predicts the onset of vasospasm by around 24 hours.[172]

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been implicated in some cases of hyponatremia, and although the predominant force of opinion is with cerebral salt-wasting syndrome, argument still exists.[173] The distinction is crucial given the very different management. Cerebral salt-wasting syndrome may indicate replacement with sodium and fluids whereas SIADH may indicate fluid restriction, which may aggravate vasospasm. The situation is rendered all the more complex by the consideration that volume loading will itself induce natriuresis.[174] A suggested algorithm for resolving diagnostic uncertainty is given in Figure 94-8.

Feeding and Nutrition

SAH induces a profound stress response, where the hypercatabolic state relates to the severity of neurologic insult. Resting energy expenditure may reach a peak of 172% that of normal on day 10 after hemorrhage. This, coupled with the tendency to suffer from headache, nausea, and vomiting leads to relative hypoalbuminemia that may compound the tendency for hypovolemia.[175]

Ischemic Stroke

Stroke is the third leading cause of death in the United States after heart disease and cancer and a major source of disability, with some 700,000 cases per year.[176]

The deprivation of oxygen and nutrients to the brain beyond the combined thresholds of severity and time will induce cellular death in neuronal tissue. In complete occlusion this will start within minutes. Around the dead tissue, an area of marginally sufficient blood supply exists, where the probability of cell death is related to ischemic time. This is the ischemic penumbra and is potentially salvageable with aggressive intervention. In a similar fashion to the motto of cardiologists "time is muscle," it can also be said that "time is neurons."

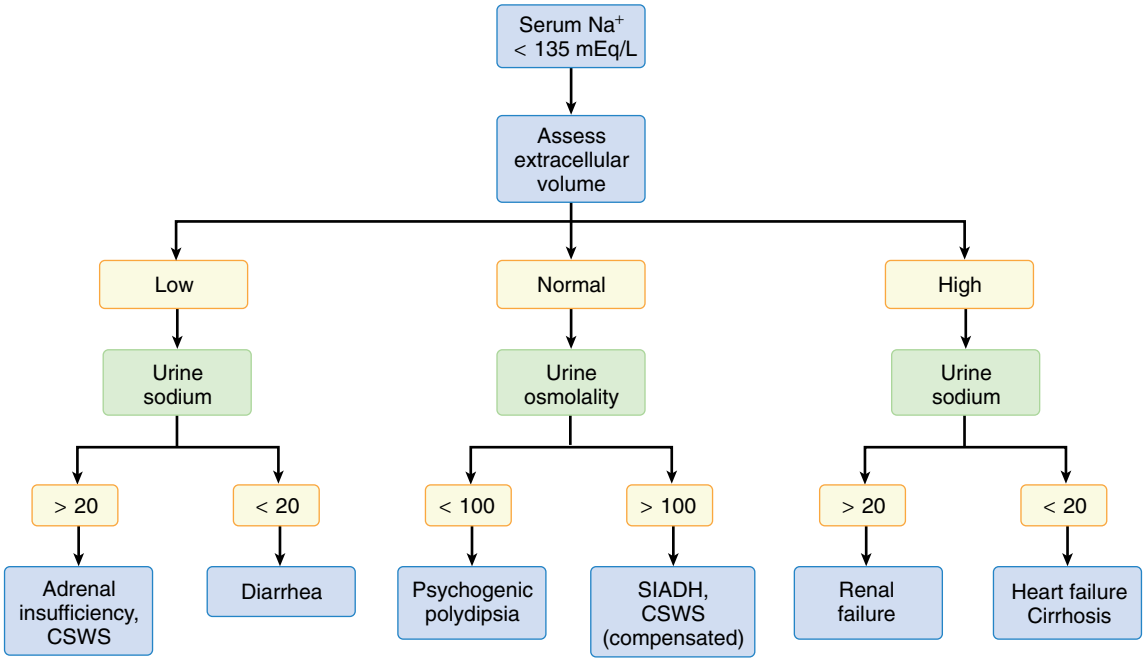

Figure 94-8 Algorithm for the differential diagnosis of hyponatremia in the neurosurgical patient. CSWS, cerebral salt-wasting syndrome; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Thus, the goals of treatment have moved away from physiologic stabilization and risk factor avoidance, toward accelerated reperfusion and retrieval of threatened brain tissue.

This was rendered feasible by the introduction of intravenous thrombolytics, paralleling aggressive cardiac management in threatened infarction. Treatment should start in the emergency department but will continue into the ICU. A window of opportunity of 3 hours has been identified, but this may be adjusted in the light of perfusion- and diffusion-weighted MRI. Intra-arterial thrombolysis is confined to specialist centers, which has limited the acquisition of data on efficacy, but suggestions are that it is effective with a lower incidence of systemic adverse events. It may be particularly advantageous in vertebrobasilar occlusion.[177]

It is crucially important to maintain vigorous perfusion until thrombolysis has been attempted. Consequently, hypertension should not be treated unless it is inducing myocardial damage or where intracerebral hemorrhage has already occurred (hemorrhagic conversion). This latter circumstance would also preclude thrombolysis.

Once thrombolysis has been attempted, this increases the risks of hemorrhage and hypertension should be moderated.[178] Unwanted side effects obviously center around hemorrhage, which is associated with higher thrombolytic doses and later treatment.[179] Keen attention should be paid to postprocedural CT scans and any signs of systemic hemorrhage such as lower abdominal pain, which may indicate retroperitoneal bleeding. Areas of brain that cannot be salvaged will swell, causing compressive ischemia in adjacent regions. Just as the effects of traumatic brain injury and SAH may vary by anatomic site, so, too, will the effects of ischemic stroke vary with the particular vascular area of occlusion.

In addition to control of cerebral volume, recent interest has revived in the early use of decompressive surgery in circumstances of "malignant" swelling. Edema can induce ICPs in excess of 30 mm Hg, with a correspondingly high mortality. Completed studies to date have relatively small sample size, but suggest treatment benefit if decompressive craniectomy is carried out in the first 24 hours after onset of symptoms, with aggressively sized bone flaps.[180] There is a adverse effect of increasing age, but hemispheric dominance seems less important.[177]

In many ways, management is similar to that of mass lesion after traumatic brain injury. Larger studies of efficacy are underway to examine not just mortality but also functional outcome, given a significant body of concern on the possibility of increased survival with increased disability and suffering.

Postoperative Neurosurgical Care

Many neurosurgical procedures are lengthy and involve significant insult to the brain; thus postoperative admission to the ICU for avoidance of secondary insult and a more graduated withdrawal of ventilatory support is common, although objective evidence is lacking. This entails careful control of blood pressure to minimize edema formation, taking account of potential compromise of autoregulation and cerebrovascular compliance. However, the importance of neurologic examination cannot be overemphasized, and early withdrawal or intermittent interruption of sedation to allow appropriate clinical examination is a prudent approach to follow these patients.

Vascular lesions such as arteriovenous malformations and vascular tumors predisposed to the development of hyperemia benefit from careful attention to blood pressure management, as does carotid endarterectomy. In both arteriovenous malformation and carotid disease, areas of the brain adjacent to the malformation or ipsilateral to the tight carotid stenosis may have absent autoregulatory control or autoregulate only at a significantly lower range of blood pressure. Until the autoregulatory

mechanism returns to normal, blood pressure should be carefully and tightly controlled to present what has been termed "normal pressure perfusion breakthrough." This can be accomplished with intravenous nicardipine or esmolol infusion or both, which will allow titratable adjustment of the blood pressure.

Aneursymal clipping does not fall into this category except in cases of vascular graft bypass procedures, where attention should be paid to minimum as well as maximum pressure targets, in what has been termed the *Goldilocks approach*. If pressure is kept too low, then this may risk graft thrombosis. If pressure is too high, then the graft may rupture. Although the range maintained is arbitrary, and there are no supporting data, it is customary to maintain the systolic blood pressure in a narrow range between 100 and 120 mm Hg.

Although not common, patients treated with lumbar CSF drainage may develop central herniation syndrome. The diagnosis is not always apparent, and the sudden decline in mental status, with a history of CSF drainage, should prompt appropriate imaging of the brainstem. Treatment is with fluid hydration and keeping the patient in Trendelenburg position.

Intracerebral Hemorrhage

Nontraumatic intracerebral hemorrhage may arise from ruptured aneurysm, ruptured arteriovenous malformation, hemorrhagic stroke (amyloid angiopathy, hypertension), conversion from ischemic stroke, tumor, substance abuse (alcohol, cocaine, methamphetamines), and the use of warfarin (Coumadin). This wide range of differential diagnoses can swiftly be refined by the CT scan, with accompanying clinical signs aiding localization and the assessment of pathophysiologic effect. Angiography may be required to rule out aneurysmal rupture.

Management is to avoid secondary insult by reducing the incidence of rebleeding, hypoxemia, hypercarbia, or edema.[181,182] Essential care is directed toward the airway and circulation. If the initial CT or MRI appearance is suggestive of arteriovenous malformation, then care should be taken to limit blood pressure to reduce the risk of rebleeding. The addition of ICP monitoring would allow one to set the CPP target and provide a more physiologic approach to the management of systemic blood pressure. If the intracranial hemorrhage is in the posterior fossa or midbrain, consideration should be given to the insertion of a ventriculostomy to reduce the risk of hydrocephalus. Patients with lesions in these regions are prone to airway and respiratory problems and may need early tracheal intubation to protect their airway and prevent aspiration.

Nimodipine does not have an established role in these circumstances. Corticosteroids are also not indicated. If the patient is on warfarin, it should be reversed with fresh frozen plasma and vitamin K.

Most intracranial hematomas expand in volume during the first 24 hours, and the volume of expansion is correlated with outcome. In a dose escalation trial, the use of activated recombinant factor VII led to a reduction in the size of intracranial hemorrhage expansion and an improvement in outcome. However, preliminary results from a phase 3 trial showed that while hemorrhage volume is decreased, outcome is not improved. The role of recombinant factor VIIa in intracranial hemorrhage is therefore uncertain, although it may be useful for rapid reversal of patients on warfarin.

The management of intracranial hemorrhage is generally medical and supportive, with control of blood pressure below 180 mm Hg. Surgery is rarely indicated.[182] However, in patients with cerebellar hemorrhage, and brainstem compression, or in those showing acute neurologic deterioration or obstructive hydrocephalus, surgical evacuation of clots may be indicated.[181,182]

Brain Injury after Cardiac Arrest

Although the therapeutic cerebroprotective value of induced moderate hypothermia has been disappointing in both traumatic brain injury and SAH, its efficacy in improving neurologic outcome has been demonstrated in patients who suffered global hypoxia secondary to ventricular fibrillation. Neurologic morbidity is common in those patients experiencing global cerebral ischemia as a consequence of cardiac arrest and is thought to be related to the generation of free radicals and cellular injury on reperfusion of the ischemic brain.

Two studies reported improved neurologic outcome and reduced mortality in patients with ventricular fibrillation who were resuscitated but remained in coma and immediately treated with mild hypothermia in the 32° to 34°C range.[183,184] These results have been confirmed in a wider population, and 12 to 24 hours of mild hypothermia is now recommended treatment for all post–cardiac arrest patients with neurologic dysfunction.[185]

Whereas initial studies induced hypothermia using cooled intravenous solutions, more sophisticated methods/devices have since been introduced. These include noninvasive methods such as forced air cooling with limb and trunk blankets, topical adhesive cooling pads, as well as invasive methods deploying intravascular heat exchange catheters. Water-cooled adhesive pads connected to heat exchange units are the most commonly used methods at present.

Some clinicians consider the use of somatosensory evoked potentials (particularly the N20 and N70 latencies) to be helpful in the prognosis of coma after cardiac arrest.[186]

Status Epilepticus

This condition has been defined as "repeated seizures occurring frequently without recovery between attacks" and has a significant morbidity and mortality, with around 50,000 deaths per year for an estimated annual incidence of 126,000 to 195,000 cases.[187] Some clinicians have attempted to refine this condition by using a stricter definition of continuous seizure lasting at least 30 minutes. Irrespective of the definition of status epilepticus, prompt treatment of seizure should be instituted, because a seizure lasting beyond 5 minutes is unlikely to stop spontaneously. There are variants of seizure type, but all may present in status, including nonconvulsive types, which present their own particular diagnostic challenges.[188]

Seizure activity may arise from any major insult affecting the cerebral cortex, whether that be infectious, mechanical, metabolic, or toxic. Even mild insults may provoke status where the seizure threshold is reduced by preexisting parenchymal disease or comorbidity (e.g., alcohol withdrawal). Given the previously outlined emphasis on the avoidance and termination of secondary insult to the brain, the metabolic disadvantage of status

epilepticus is readily apparent. Goals of treatment include seizure termination, physiologic support, and prevention of recurrence. This may involve intubation and ventilation, where long-term paralytic agents should not be used for fear of masking ongoing or recurrent seizure. Electroencephalographic control is highly recommended. Preferred anticonvulsants for termination include lorazepam and midazolam, in view of their relatively benign cardiovascular profile. Phenytoin remains a commonly used agent but takes time to administer because it can provoke hypotension and bradycardia if given rapidly. Hypotensive effects may also limit the usefulness of thiopental, pentobarbital, and propofol.[189]

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) occurs at a rate of 1 to 4 cases per 100,000 population per year. The incidence increases with age, and it is one of the most common neurologic causes of admission to critical care units.[190,191]

The classic form of GBS is an acute inflammatory demyelinating polyneuropathy that appears as a progressively ascending muscle weakness. This can manifest as flaccid paralysis and respiratory failure. There are a number of clustered conditions associated with the syndrome, including acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), and Miller-Fisher syndrome (MFS), with the latter affecting the cranial nerves first. AIDP is the most common variant seen in the United States, and more than 50% of all cases have a recent history of bacterial or viral infection. *Campylobacter jejuni* is the most frequently observed pathogen, along with cytomegalovirus, Epstein-Barr virus, and herpes simplex infections. GBS may display sensory and autonomic features, depending on the subtype, and there is some variation in speed of onset and offset. Commonly, symptoms progress over several days to reach their peak at 2 weeks, with a plateau thereafter. Around 5% of patients will progress more rapidly than that with maximal loss of function within 72 hours of symptom onset. At 4 weeks, the majority of patients will have progressed to the limit of their symptomatology and improvement is observed to start soon thereafter. Recovery, however, may be protracted for up to 6 months. There is some debate as to whether speed of onset relates to a slower rate of recovery and outcome limitation.[190,191]

Loss of ventilatory efficacy is the main reason for admission to the ICU, with a forced vital capacity of less than 20 mL/kg being a sensitive indicator of need for observation, and 15 mL/kg for probable intubation, along with clinical signs of fatigue and airway compromise. Hypercarbia is a relatively late sign, and should not be relied on.

Bulbar dysfunction, while less common, may appear before ventilatory compromise, particularly in patients with the MFS variant.

Dysautonomia is seen in up to 20% of patients and is a source of morbidity.[192] It should be monitored carefully, because there is a significant mortality of arrhythmia in the elderly. It can vary from urinary retention to fixed tachycardia to both severe hypotension and paroxysmal hypertension.

Investigations should include electrocardiography, CSF protein (for acellular protein elevation), electromyography (axonal degeneration is associated with poorer recovery), and antibody status/screening for possible causative pathogens and also prognosis, because GM_1 antibody is associated with worsened recovery whereas MFS is associated with anti-GQ1b antibody.[191]

Particular challenges to management are the problems of deafferentation pain and psychiatric depression. The pain can be severe, is truncal in distribution, and may respond to anticonvulsants more than opiates. It will certainly contribute to the frequently observed depression. This is often worsened by immobility, boredom, and the limited ability of busy staff to actively engage with a (relatively unusual for the neurocritical care unit) cognitively intact patient. Early tracheostomy in identifiably prolonged cases is appropriate.

Both symptom limitation and recovery from GBS have been improved with the use of plasmapheresis or the intravenous administration of gamma globulin. There is no advantage seen by one over the other, nor in combination. However, many physicians will try them sequentially in cases of treatment failure.

Neither interferon nor corticosteroids have been shown to improve outcome, either alone or in combination with immunotherapy.[190]

Spinal Cord Injury

In contrast with GBS, spinal cord injury (SCI) is much more common (11,000 cases/year), is intractable to treatment, and almost inevitably has permanent effects. The number afflicted in the United States in 2006 was 253,000. The degree of dysfunction is similar to GBS in that as the level of injury ascends there is a high level of motor paralysis of the lower limbs, trunk, upper limbs, and diaphragm. Additionally, there is also a traumatic sympathectomy, producing bradycardia, hypotension, and gastrointestinal paralysis. This latter aspect is often overlooked, and subsequent abdominal distention can embarrass an already compromised diaphragm into inefficacy. The cardiovascular effects of sympathectomy, particularly above T5, will manifest as bradycardia and hypotension.[193] This can be supported by fluid and pressor therapy, and the tachycardic effect of dopamine may be a useful attribute. Unopposed vagal stimuli, as well as hypoxia, may induce bradycardia.[193] Resuscitation targets are controversial with recent interest in maintaining spinal perfusion analogous to the CPP of traumatic brain injury. Patients with injuries below T5 may still manifest hypotension but usually only on the provocation of posture, hypovolemia, or comorbidities.

Ventilatory support is dependent on the level of injury. If the injury is below C5, although the diaphragm remains functional, in the acute stage respiratory embarrassment due to abdominal and intercostal paralysis can still occur, because flaccidity in these muscles significantly decreases the functional efficiency of the diaphragmatic contraction. Thus, paradoxical respiration with chest indrawing during inspiration occurs. With complete cervical spinal cord injury, acute respiratory failure is common, secondary to the sudden loss of functional residual capacity and the inability of the sternocleidomastoid muscle to stabilize the chest wall. With time, many patients can regain the ability to breathe spontaneously, except those with high cervical lesions. There is controversy regarding the ventilatory pattern used for spinal patients. Some clinicians suggest that a larger tidal volume should be used, because this might maintain the alveoli open and prevent atelectasis, although this has not been established by a randomized clinical trial.

Lower limb blood flow is reduced with increased arterial and venous pooling. This is associated with a higher incidence of thromboembolic disease, and early prophylaxis with low molecular weight heparin is recommended.

As with GBS, the patient with spinal cord injury is commonly aware, and this constitutes an additional burden of psychological stress. Consequently, the best approach taken is truly a holistic one, tending to psychological needs as well as to cardiopulmonary, gastrointestinal, renal, and integumental support. Significant advances have been made in the critical care and rehabilitation support afforded to these patients, and 2-year survival has increased significantly in the past 3 decades. Unfortunately, this has not translated to increased long-term survival.[194]

Myasthenia Gravis

Although myasthenia gravis is a relatively uncommon disease (prevalence of 10-20 per 100,000), it is relevant to neurocritical care in that patients can present acutely with rapid deterioration of muscle function, predisposing to ventilatory failure—the "myasthenic crisis." Myasthenia itself has a strong association with various autoimmune conditions (e.g., thyroid disease, pernicious anemia, rheumatoid arthritis), as well as being linked to women with certain HLA types.[195,196]

The myasthenic crisis can be precipitated by a progression in severity of the disease state or often by amplification by another factor. This can include infection, recent surgery, or interruption of immunosuppressants. There are a large number of drugs that can exacerbate myasthenic crisis, including aminoglycosides, fluoroquinolones, anticonvulsants (including phenytoin), steroids, β-blockers, calcium antagonists, ketamine, lidocaine, neuromuscular blockers, and anticholinergic agents.[196]

Diagnosis should exclude GBS, brainstem stroke, organophosphate poisoning, and botulism. Tests should include electrophysiology, CSF protein, edrophonium response, and antibodies to acetylcholine and muscle tyrosine kinase receptors.

The presentation is typically that of acutely worsening weakness of either respiratory or pharyngeal muscles, or both. The patient should be observed closely for signs of impending failure. Forced vital capacity is again useful with 15 mL/kg being a useful trigger for intubation.[196]

The other mainstay of therapy is by immunomodulation. Typically, intravenous immunoglobulin or plasmapheresis is started quickly to limit progression of symptoms and avert frank crisis. Corticosteroids do have a role in establishing longer-term control of immunosuppression, because IgG and plasmapheresis have limited duration of efficacy. Corticosteroids alone are associated with a transient worsening of symptoms, before improvement, so are best introduced immediately after plasmapheresis or IgG.[196]

Meningitis

Meningitis is a serious condition producing inflammation of the leptomeninges covering the CNS. The causative pathogens differ among different patient populations. Community infections are frequently caused by *Streptococcus pneumoniae, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis,* and group B streptococci. *N. meningitidis* is particularly evident in teenagers. Since the advent of a childhood vaccination program, *H. influenzae* affects chiefly adults, but the other organisms tend to affect all age groups. Nosocomial infection, on the other hand, predominantly arises in the neurosurgical patient, especially with the use of ventricular devices, and the pathogens here comprise gram-negative rods and staphylococci. Diagnostic features include fever almost invariably with the classic nuchal rigidity and change in mental status; less often, photophobia, papilledema, and new-onset seizures may be seen. A rash is typical of meningococcal infection, whereas arthritis occurs in a significant minority. Tests should include CSF Gram stain and culture by lumbar puncture, but any previous antibiotic dosing can diminish sensitivity. Under this circumstance polymerase chain reaction (PCR) testing is the method of choice, displacing the more variable latex agglutination test. A CT scan should only delay the lumbar puncture when there is history suggesting previous mass lesion, stroke, or focal infection, recent seizures, or immunocompromise. Similarly, signs of papilledema, depressed level of consciousness, or focal deficit indicate a need for a CT examination to avoid herniation. Cerebral edema not infrequently develops in patients with meningitis and can lead to acute deterioration in mental status. ICP monitoring might be indicated.

Treatment should be delivered swiftly, pausing only to get emergent samples for Gram stain and culture. If no identification is possible on Gram stain, empirical antibiotic therapy should be delivered with third-generation cephalosporins (e.g., ceftriaxone or cefotaxime), along with vancomycin until organism and sensitivities are obtained. This will cover the community-acquired pathogens. Nosocomial or trauma-associated infections can be effectively covered with cefepime and vancomycin.

The outcome of meningitis is a function of patient factors, the pathogenicity of the organism, and the time to effective treatment. An interesting study examined admission hypotension, altered mental status, or seizures for an effect on outcome. There was a 9% mortality if one factor was present, increasing to 33% for two factors, and 57% for all three being evident.[197]

Encephalitis

Encephalitis presents with fever, headache, and alteration of consciousness. There may also be delirium, focal deficit, and, commonly, seizures. Nuchal rigidity may be present in a mixed meningoencephalitis picture but should be absent in isolated encephalitis. Accompanying identifiers may be a vesicular rash associated with zoster (although its absence does not remove zoster from suspicion), bilateral paralysis typical of West Nile disease, parotitis if mumps is suspected, and, of course, the hyperactivity, hydrophobia, and pharyngeal spasm of rabies. West Nile disease is swiftly increasing in incidence from 62 cases in 1999 to 4219 in 2006 and seems to be clustering in rural states.[198] There are a large number of both nonviral and noninfectious causes of encephalitis that may confound the diagnosis. These include vasculitis, systemic lupus erythematosus, stroke, rickettsial and parasitic infection, and drug-induced meningitis (e.g., IgG). Careful examination of clinical features, history, and laboratory data are necessary. CSF should be drawn for viral DNA polymerase chain reaction as well as the routine biochemistry, culture, and cell count. MRI is useful in identifying the demyelination and edema that can be difficult to see on CT. Serum serology is helpful for the diagnosis of Epstein-Barr virus, mumps, and West Nile

disease, as sources of encephalitis. Paired samples are to be recommended to allow later comparison if CSF PCR is unhelpful. Brain biopsy was considered the gold standard but is now very much a last option after CSF PCR, culture, and serology have proven negative.

Herpes simplex type 1 carries a very poor outlook if not treated expeditiously, and a course of intravenous acyclovir is recommended as soon as samples are drawn.

The pathogen remains unidentified more often than not, and outcome usually then depends on classification of the clinical features, with intractable seizure and cerebral edema carrying a poor prognosis. Self-limiting seizure usually indicates a swift recovery.

Brain Death

It is crucially important that the physician understand the principles of the diagnosis of brain death and be able to apply them assiduously and without compromise (see Chapter 98). There are many unfortunate instances of poor understanding leading to imperfect examination, misdiagnosis, and considerable distress to all concerned.

Declaration of brain death was originally codified by the Harvard criteria with subsequent modification to allow separation of cerebral death from death of the entire nervous system including spinal cord.[199] This was later expanded to include the diagnosis of brainstem death as equivalent to whole-brain death.[200]

All such diagnoses are built on a solid clinical examination of nervous system function, examining the reflex response of the brain and cranial nerves to varying stimuli of hypercarbia, pain, light, temperature change, attitudinal change of the middle ear, and detection of the blink, cough, and gag reflexes. There should be clear mechanisms for cause of neurologic dysfunction. As with the operation of the GCS scale, the examination has to be done in circumstances of adequate systemic oxygenation and perfusion. Confounders, such as hypothermia, metabolic/endocrine compromise, and persistent sedative or neuromuscular drugs should be avoided, corrected, or removed. There should be two tests done by independent physicians, of whom at least one should have had training in neurology, neurosurgery, or neurocritical care. Time between tests is less important for diagnosis than for the opportunity to start communicating with and preparing the family. One of the tests should include an appropriately conducted apnea trial in the presence of the physician, with confirmation of adequate changes in P_{CO_2}. If for any reason any test cannot be completed in a safe manner, or to the satisfaction of either physician, then a confirmatory test of cerebral blood flow should be performed.

The hospital should have an institutionally approved protocol for the conduct of these tests and mechanisms in place for review and quality improvement.

Ethical Considerations

Ethical issues are frequently encountered in a neurologic ICU setting (see Chapter 9). Unfortunately, as well as the mortality described previously, there is significant life-altering morbidity, to the extent that many patients and families would not desire aggressive therapy.[201] This can be a difficult concept to accept for the physician, whose aim is to heal and preserve life. However, the ethical imperative in Western culture is to preserve the autonomy of the individual (along with the principles of nonmaleficence, beneficence, and justice), and this has been extended to health care decision-making. This may lead to uncomfortable decision-making and communication within the health care team, who may have differing opinions on goals, and from there to the patient and relatives, who, again, may think very differently.

There are a number of strategies that can avoid or minimize these difficulties:

- Prognosis should be made on the basis of the best available evidence. This may involve planning and discussion between the team members in advance of meeting with families. The personal anecdote should be avoided, even if solicited.
- The relationship within the team should be open and collegial, with mutual respect given to the principle of open discussion. This avoids misperception of goals and attitudes and enables more consistent communication with families, who often find dissonance between members of the ICU team disturbing.
- The presence of an advance directive offers major benefits, and the neurocritical care unit should have an admissions protocol that includes asking all competent conscious patients to consider making their attitudes or wishes known.
- Regular family/patient conferences allow communication of prognosis as it is appropriate and offer the opportunity for correction of any misconceptions, as well as progressive education of the family to anticipated problems.
- There should be internal institutional mechanisms for raising concerns and conducting reviews. This is often facilitated by the presence of an institutional ethics committee, who can examine the issues, promote educational discussion, and help achieve a consensus.
- All decision-making should be documented carefully and completely.
- Orders for limitation or withdrawal of care should be written explicitly and institutional protocols used wherever possible.

There are other important areas of possible conflict that it is not possible to address within the confines of this text, but readers are advised to educate themselves on the following:

- The issues surrounding organ donation from the brain dead and the non–heart-beating donor
- Withdrawal of care for the incompetent patient without family
- Hospital bylaws and state legislation on the certification of death, whether that be by neurologic or cardiovascular criteria

Summary

Neurocritical care demands a thorough comprehension of the physiology, pharmacology, and pathology of the nervous system, as well as for the organ systems supporting it. The best care is

provided in circumstances that allow multidisciplinary collaboration and appropriate attention to detail of often complex and demanding pathologic processes, but integrating them optimally under the direction of the critical care physician.

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95 Nutrition and Metabolic Control

Key Points

1. Sepsis, trauma, and surgery activate complex metabolic and inflammatory responses that affect all body systems.
2. The metabolic response to stress response is characterized by catabolism, hypermetabolism, hyperglycemia (diabetes of injury), and enhanced lipolysis.
3. The counterregulatory hormones (cortisol, glucagon, catecholamines) along with the cytokines (e.g., IL-1, TNF) are major mediators of this response.
4. Certain intraoperative anesthetic and postoperative analgesic techniques can modulate the stress response.
5. During the acute phase of illness, patients unable to eat should receive parenteral or enteral nutritional support.
6. Nutritional support during the acute phase of critical illness is a supplementary therapy designed to provide patients suffering from underlying metabolic disarray with sufficient nutrients to aid cellular biochemical functions and attenuate further loss of body mass.
7. Only once the ravages of the stress response have abated can lost lean and fat mass be repleted.
8. Overfeeding or aggressive refeeding should be avoided.

The human body is an adaptable organism that has many interrelated mechanisms designed to identify, respond, and neutralize both internal (e.g., infection) and external (e.g., temperature extremes) events that threaten or upset homeostasis (stressors). Anesthesiologists must be knowledgeable about these mechanisms because they routinely care for patients with acute and chronic homeostatic changes. Furthermore, anesthesia and surgery involve much manipulation and disruption of body physiology, anatomy, and biochemistry, leading to the activation of the body's responses to stress.

The stress response evolved as a mechanism for assisting organisms in reacting to immediate danger. The outpouring of catecholamines and other hormones increases the outputs of the respiratory, cardiovascular, and metabolic systems and improves the organism's ability to flee from an enemy and maintain perfusion to vital organs after blood loss. The metabolic alterations caused by change in the hormonal milieu increase the availability of certain substrates and reduce the availability of others. The organism thus attempts to improve conditions for wound healing, blood coagulation, and humoral immunity, a response that is beneficial in acute events such as bleeding and infection. Although once regarded positively as the body's defense mechanism, today the stress response is regarded more equivocally since its physiologic consequences, especially increasing the output of various organ systems, may lead to increased morbidity and mortality by overtaxing already compromised organ systems.[1] For example, among patients with underlying coronary artery disease, the tachycardia and increased myocardial oxygen demand resulting from catecholamine stimulation can cause myocardial ischemia.

The stress response was initially described by Hans Selye as "the nonspecific response of the body to any demand upon it."[2] However, contemporary research demonstrates that the nature of response varies depending on the type and intensity of the stressor and is only nonspecific when the stress is overwhelming.[3,4] Furthermore, chronic activation of the stress response has been implicated as contributing to a variety of conditions, such as atherosclerosis and depression. Although the chronic stress often is not the cause of the disorder it contributes to its pathogenesis, exacerbations, and duration.[5]

Metabolic Control Systems and the Response to Surgical Stress

Living organisms constantly undergo adjustments to adapt to ever-changing internal and external conditions. These natural alterations have been termed *allostasis* and include diurnal variations in temperature and cortisol production, changes in metabolism due to eating and drinking, and the cardiopulmonary responses to exercise.[6] Stress occurs when allostatic mechanisms are insufficient for maintaining homeostasis, thus causing the

organism to significantly alter many of its functions to reduce and contain the stressful threat.[7]

The response to surgical and traumatic injury was classically described by Cuthbertson as having three phases:

1. The ebb phase (<24 hours), also called the resuscitative phase, during which there is tissue hypoperfusion that requires treatment
2. The flow phase (duration depends on injury severity), which has a milieu characterized by catabolism, hypermetabolism, hyperglycemia, and an inflammatory response
3. The anabolic phase (may last for months) when anabolism facilitates the repair of injuries and a return to a normal metabolic environment.

However, the improved survival from major injury, occasioned by modern surgery and critical care, blurs this classic scheme. Today, critically injured patients often undergo multiple surgeries within a few days of their injury and suffer from iatrogenic infections during extended stays in an intensive care unit (ICU). These surgeries and infections add further stresses ("second hit") to an already highly stressed system.[8] The consequences of these second hits are problematic because they perpetuate or intensify metabolic changes that increase the chance of developing multiple organ failure.[9,10]

The Hypothalamus-Pituitary Axis

Many allostatic, as well as homeostatic, changes are controlled by feedback control systems centered on the hypothalamic-pituitary axis. The response to surgical and traumatic stress is triggered by hypothalamic activation secondary to afferent neuronal input from an area of injury or emotional activity centered in the limbic system and humoral factors, such as the inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6.[11] Hypothalamic activation increases the activity of the sympathetic nervous system, which increases the output of the cardiovascular system and stimulates the adrenal medulla to secrete epinephrine and the pancreas to secrete glucagon (Fig. 95-1). Hypothalamic activation also stimulates or reduces the secretion of the various hypothalamic releasing factors (e.g., corticotropin-releasing hormone [CRH], growth hormone–releasing hormone [GHRH]). The hypothalamus, the body's thermostat, also controls body temperature. Stimulation by mediators such as IL-1β (endogenous pyrogen) causes fever via a biphasic mechanism; the first phase is mediated by increased intracellular ceramide and the second by cyclooxygenase-2 (COX-2)–mediated prostaglandin E_2.[12,13] CRH is also produced peripherally in the adrenal medulla, gastrointestinal tract, skin, nerve fibers, and immune cells. At inflammatory sites CRH acts as a paracrine/autocrine inflammatory mediator (Fig. 95-2) via peripheral CRH receptors.[14]

During stress, the releasing factors, along with other stimuli, stimulate the posterior pituitary gland (neurohypophysis) to release arginine vasopressin (AVP, antidiuretic hormone [ADH]) and the anterior pituitary (adenohypophysis) to secrete prolactin (PRL) and growth hormone (GH) into the circulation. CRH, acting synergistically with AVP, stimulates secretion of proopiomelanocortin by the anterior pituitary. In the stressed state, IL-6, working through IL-6 receptors present on the pituitary corticotrophic cells, also acts synergistically with CRH. Proopiomelanocortin is cleaved to adrenocorticotropic hormone (ACTH), β-endorphin, and α-melanocyte-stimulating hormone (MSH), thus linking endogenous opioids with the hypothalamic pituitary-adrenal axis. ACTH, in turn, stimulates the zona fasciculata of the adrenal cortex to secrete glucocorticoids. A meta-analysis showed that the cortisol response increases with age and is greater in women than men.[15] Glucocorticoids, including those administered exogenously, constitute a negative feedback system suppressing hypothalamic CRH and AVP secretion. In the unstressed state the hypothalamic-pituitary control mechanism regulates cortisol secretion in a circadian rhythm, with peak concentrations occurring in the early morning and the nadir around 11 PM. In the postoperative stressed state, cortisol secretion increases twofold to threefold with disruption of the circadian rhythm, specifically, longer peak to nadir intervals.[16]

Arginine Vasopressin

AVP is vital for maintaining intravascular homeostasis and is secreted when there is increased osmolality, decreased arterial pressure, and reduced blood volume.[17] It causes vasoconstriction (V1 receptors) and renal water retention (V2 receptors) by stimulating aquaporin-2. Plasma AVP concentrations are elevated after a variety of stresses, including surgery, pneumonia, myocardial infarction with or without left ventricular failure, and electroconvulsive therapy. Plasma AVP concentrations increase after the start of surgery and often remain elevated for days after its completion. The magnitude and duration of the elevated plasma vasopressin concentrations are proportional to the degree of stress. In septic shock there is an initial increase in AVP concentrations followed by a decrease to very low concentrations.[18]

Growth Hormone

Secretion of GH secretion by the anterior pituitary is stimulated by hypothalamic GH-releasing factor and inhibited by somatostatin. GH, vital in the regulation of growth during the prenatal period and childhood, has a biphasic effect when secreted during stress. Initial exposure (2-3 hours) produces insulin-like effects, but longer exposure cause anti-insulin and anabolic effects. The latter results in increased incorporation of amino acids into structural proteins, glucose intolerance due to insulin resistance, and increased lipolysis due to increased sensitivity to the lipolytic effects of catecholamines. GH stimulates the secretion of insulin growth factors 1 (IGF-1) and 2 (IGF-2) by the liver and other peripheral tissues. IGF-1 has insulin-like actions and also mediates the anabolic and skeletal growth–promoting activity effects of GH. IGF-1 facilitates anabolism by directly reducing protein oxidation and enhancing insulin sensitivity so that insulin and GH stimulate protein synthesis.[19] A 5-day infusion of IGF-1 into normal subjects did not change the glucose oxidation rate but increased lipid oxidation, raised resting energy expenditure, and reduced protein oxidation. The six IGF-binding proteins modify the availability and actions of IGF-1. Most circulating IGF-1 is bound to IGFBP-3, whereas IGFBP-1 plays a major role in regulating unbound (free) IGF-1.

Immediately after major traumatic injury, burns, and surgery, GH blood concentrations are elevated, with the increases being roughly proportional to the degree of trauma. However, after a day the preoperative/preinjury GH concentrations start to decline. In severely traumatized patients the pulsatile nature of GH secretion persists but the bursts occur less frequently. IGF-1, IGF-2, and IGFBP-3 are reduced 40% to 60% after trauma and

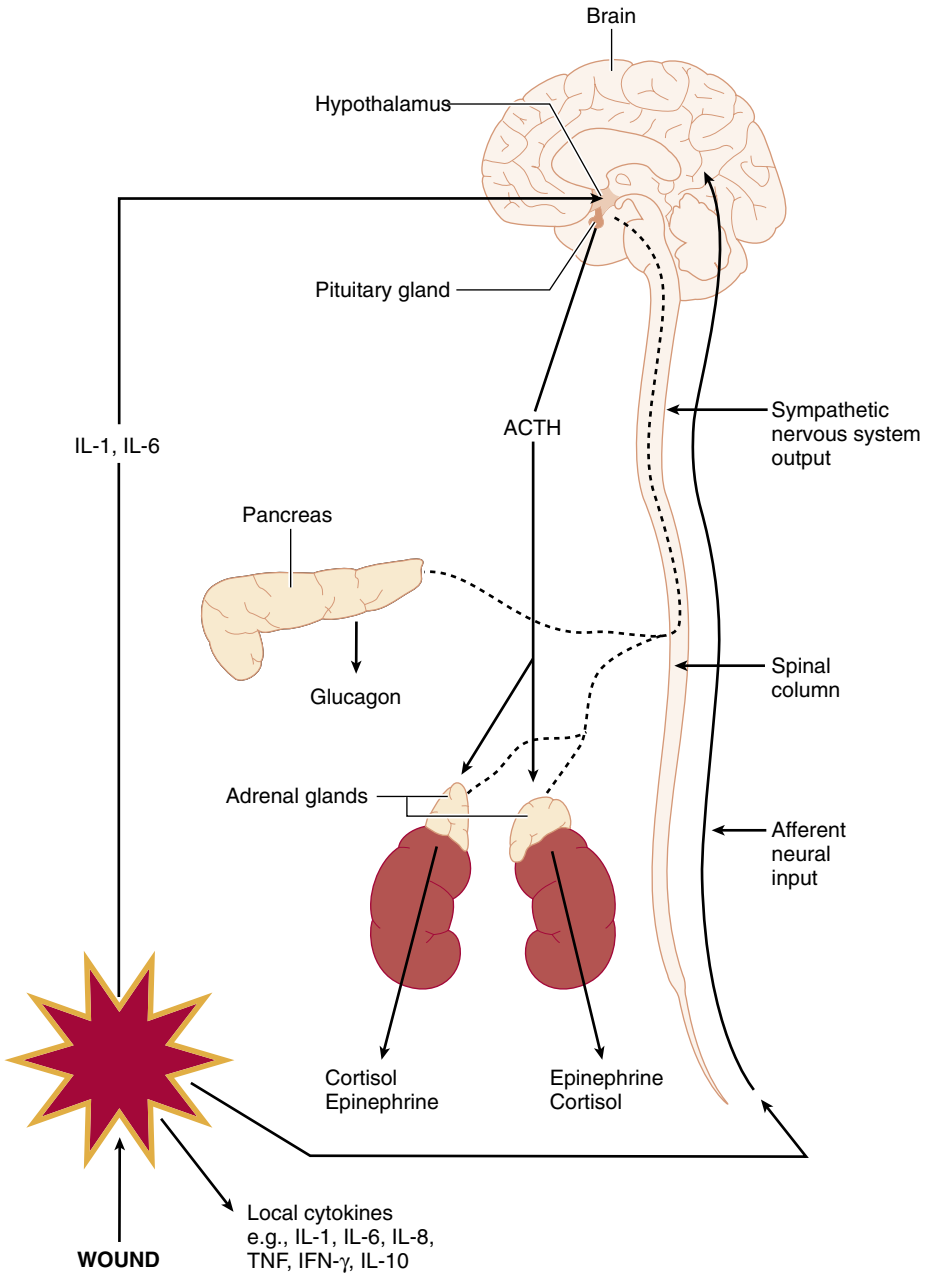

Figure 95-1 Mechanisms that initiate the stress response are shown. Afferent neural input plus cytokines such as IL-6 and IL-1 stimulate the hypothalamic-pituitary axis leading to secretion of adrenocorticotropic hormone (ACTH) (which stimulates the adrenal cortex to release cortisol) and activation of the sympathetic nervous system (which stimulates the pancreatic alpha cells to secrete glucagon and the adrenal medulla to secrete epinephrine). Cytokines and growth factors act locally in the area of the wound and some also have endocrine effects. IL, interleukin; TNF, tumor necrosis factor.

burns, whereas IGFBP-1 and IGFBP-4 are increased. The decreases in GH and IGF-1 concentrations are ascribed to inhibition by interleukin-1β.[20] The consequence of these decreases is protein catabolism.

The Endocrine System

The hypothalamic-pituitary axis is the main controller of the endocrine system, which, in turn, controls much of the body's metabolic functioning (see Fig. 95-1). The endocrine hormones are major mediators of the metabolic response to stress. The hormones glucagon cortisol, and catecholamines oppose the effects of insulin on glucose and lipid metabolism and are thus called the counter-regulatory hormones.

Sympathoadrenergic System

The sympathoadrenergic system, composed of the sympathetic nervous system and adrenal gland, produces and secretes the catecholamines: norepinephrine, epinephrine, and dopamine. Serum concentrations of these hormones increase after stresses such as anxiety, hypotension, hypothermia, surgery, burns, hypercarbia, and accidental injury. In severely burned patients, norepinephrine concentrations increase 2- to 10-fold in parallel with burn size.[21] Concurrent with the activation of the sympathetic system response there is acute suppression of parasympathetic activity. This suppression is important because the parasympathetic nervous system reduces proinflammatory responses.[22]

Epinephrine is secreted into the bloodstream by the adrenal medulla in response to sympathetic nervous system activation, whereas most norepinephrine is released from sympathetic nerve

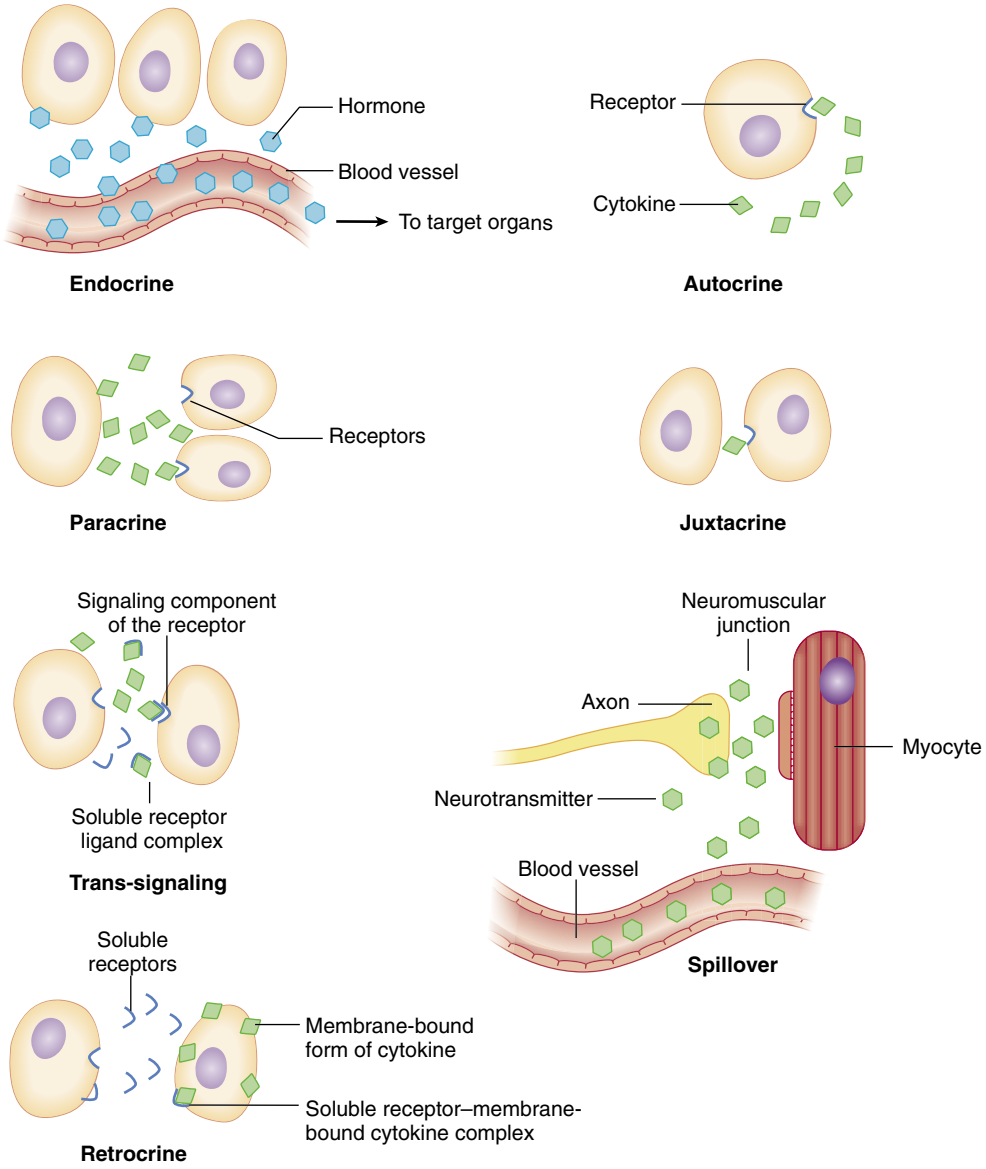

Figure 95-2 Various mechanisms used by hormones, cytokines, and other bioactive substances to affect end-organ function. *Endocrine*—transport to end organs of hormones and other substances via the bloodstream. *Autocrine*—secreted substances affect the cell that produced them. *Paracrine*—mediators act locally within the same tissue bed. *Juxtacrine and cell-to-cell communication*—mediators act on adjacent cells. *Trans-signaling*—a soluble receptor binds in the presence of its ligand to the signaling component of a multimeric receptor complex. *Spillover*—Neurotransmitter not taken up by nerve endings enters blood vessels. *Retrocrine*—soluble receptors interact with membrane-bound forms of cytokines and are used to control cytokine effects.

endings. Therefore, plasma epinephrine concentrations reflect adrenomedullary secretion whereas plasma norepinephrine levels are an index of sympathetic nervous system activity. Plasma concentrations of epinephrine and norepinephrine do not necessarily increase simultaneously. Most norepinephrine released by sympathetic ganglia is removed from the synapse by reuptake into the nerve ending. Therefore, only the norepinephrine that "spills" over into the plasma is assayed (see Fig. 95-2). Plasma norepinephrine concentrations are thus the difference between the spillover and plasma clearance rates. Besides the increased secretion of endogenous catecholamines, many critically ill patients receive vasopressor and inotropic support with infusions of exogenous catecholamine, which can have additive metabolic and other affects. For example, dopamine infusions depress thyroid-stimulating hormone (TSH), prolactin (PRL), and GH secretion.[23]

In addition to their cardiovascular effects, catecholamines have major metabolic effects. Hepatic gluconeogenesis, glycogenolysis, and glucagon release are increased by β_2-adrenergic stimulation, whereas lipolysis is increased by β_2- and β_3-adrenergic stimulation but inhibited by α_2-stimulation.[24] Epinephrine infusion in normal subjects does not affect protein metabolism.[25] The lesser role of the catecholamines, as opposed to glucagon in instigating and maintaining the abnormal glucose metabolism of burn patients, was demonstrated by the failure of propranolol to reduce the rates of glucose production and glucose cycling.

The sympathoadrenal system also affects the immune system. There are neuronal pathways that release neurotransmitter directly into the lymphoid parenchyma so that the lymphocytes and macrophages in these lymphoid regions are directly affected by sympathetic output. In general, this output acts to reduce the proinflammatory response, by decreasing the secretion of proinflammatory cytokines, possibly by a β-receptor–mediated mechanism.[22] However, β-receptor activation by circulating catecholamines seems to increase TNF-α secretion, especially during sepsis. Therefore, the sympathoadrenergic system appears to be both a major mediator of the stress response and also part of its negative feedback arm.

Glucocorticoids

Cortisol is a major stress hormone whose plasma levels are markedly elevated after surgical and traumatic stress. This is mainly due to enhanced secretion by the adrenal cortex. However, in some situations the increased concentrations are also due to reduced renal function and reduced hepatic clearance secondary to decrease hepatic blood flow.[26] In addition, this cortisol production is minimally suppressed by exogenous glucocorticoid administration. This was demonstrated by the inability of 24 mg/day of dexamethasone administered for 2 days after craniotomy to suppress the elevated concentrations of either ACTH or cortisol. Elevated plasma cortisol concentrations stimulate gluconeogenesis, sensitize adipose tissue to the action of lipolytic hormones (GH and catecholamines), and increase proteolysis by blocking the anti-proteolytic actions of insulin.[27] Cortisol is thought to cause insulin resistance by decreasing the rate of insulin activation of the glucose uptake system (inhibiting translocation of glucose tranporter-4 to the cell membrane) and increasing 11β-hydroxysteroid dehydrogenase activity.[23] Additionally, cortisol has anti-inflammatory and immunosuppressive actions. The anti-inflammatory actions include negative feedback to ACTH and proinflammatory cytokine production, as well as stimulation of the secretion of IL-10, an anti-inflammatory cytokine.[28] These anti-inflammatory and immunosuppressive actions are thought to prevent stress-activated defense mechanisms from overshooting and damaging the organism. Unlike elevated concentrations, basal concentrations of cortisol are anti-lipolytic and probably facilitate normal immune responses.

Cortisol is a vital mediator of the stress response because it facilitates catecholamine action and secretion, thus helping to maintain cardiovascular stability during surgical stress. The importance of glucocorticoids is demonstrated by the excessive mortality during stress observed in adrenalectomized animals and patients with Addison's syndrome. Furthermore, increased mortality was observed when etomidate was used to sedate critically ill patients. Etomidate blocks adrenal steroidogenesis by inhibiting 11β-hydroxylation and 17α-hydroxylation. Similarly, patients receiving or having received exogenous steroids within the 6 months before a stressful event should receive steroid replacement therapy to avoid the problems of adrenal insufficiency.

The magnitude and duration of the increases in both intraoperative and postoperative ACTH and cortisol levels correlate well with the degree of surgical trauma. Cortisol concentrations may remain elevated for up to 2 weeks after femoral fractures and burns. The increased ACTH secretion during surgery is often far greater than that required to produce a maximal adrenocortical response, as demonstrated by the observation that administering exogenous ACTH during surgery did not increase plasma cortisol concentrations. In prolonged critical illness (7-10 days), serum ACTH concentrations are low despite elevated cortisol levels, indicating other mechanisms stimulate the adrenal cortex.[29]

Cortisol is 80% bound to cortisol-binding globulin (CBG), which has a high affinity but low capacity for binding cortisol, and 10% to serum albumin, which has a low affinity but a high capacity for this process. The remaining unbound cortisol, referred to as free cortisol, is biologically active.[30] Direct measurement of the free cortisol concentration accounts for the binding effects of albumin, whose concentration is reduced after major surgeries and during sepsis.[31] After major surgery, during sepsis, and after burn injury, free cortisol concentrations are elevated due to both increased total cortisol concentrations and reduced CBG.[32] After major elective surgery, serum total cortisol increased by 55% and CBG decreased by 30%.[33] The reduced CBG is likely caused by inhibition of CBG production by IL-6 and/or increased CBG degradation due to elevated neutrophil-released esterase.

Glucagon and Insulin

Glucagon and insulin are both secreted by the pancreas, the former by alpha cells and the latter by beta cells. These hormones enter the portal vein, exposing the liver to high concentrations of both. The principal action of glucagon is to stimulate hepatic glycogenolysis and gluconeogenesis. Glucagon increases hepatocyte cyclic adenosine monophosphate (cAMP), promoting gluconeogenesis; insulin has the opposite effect: it decreases intracellular cAMP concentrations, preventing gluconeogenesis. Glucagon increases intracellular cAMP via a different receptor–secondary messenger mechanism than used by adrenergic mediators. Glucagon also increases hepatic glycogenolysis and ketogenesis during starvation and diabetic ketoacidosis. There is debate whether glucagon also stimulates lipolysis. In the unstressed state, glucagon secretion is stimulated by hypoglycemia, protein/amino acid intake, endorphins, exercise, GH, epinephrine, and glucocorticoids. Glucagon secretion is suppressed by somatostatin, insulin, and glucose infusion or ingestion.

Insulin is an anabolic hormone with many effects. In addition to increasing glucose transport across the cell membranes of adipocytes and myocytes, it stimulates glycogen production, promotes glucose oxidation, inhibits lipolysis in adipose tissue and skeletal muscle, inhibits net fatty acid oxidation, inhibits hepatic and muscle ketogenesis, and increases the rate of amino acid transport and protein synthesis in muscle, adipose tissue, and liver.[33] The plasma glucagon:insulin ratio is the major determinant of the degree of gluconeogenesis. During fasting and starvation, the ratio is increased secondary to increased glucagon and decreased insulin concentrations. This increased ratio promotes gluconeogenesis and facilitates glycogenolysis. In the fed state the reverse is true, with insulin predominating.

Serum glucagon concentrations rise after most types of major surgery. The glucagon:insulin ratio increases because insulin concentrations decrease during surgery. The decreased insulin concentrations are attributed to suppression of insulin secretion by elevated catecholamine concentrations or increased urinary losses. This suppression can be abrogated by α-adrenergic blockade. The hormonal milieu of low insulin with elevated catecholamines, cortisol, and glucagon stimulates gluconeogenesis. In septic patients this mechanism may fail, resulting in hypoglycemia, a situation associated with very poor survival rates. Postoperatively, insulin concentrations increase because of increases

in both plasma glucose and epinephrine-induced β-adrenergic stimulation. Unlike starvation, the plasma insulin concentrations are often markedly increased above basal values, although they are inappropriately low for the prevailing level of glycemia.

Somatostatin

Somatostatin, a hormone secreted by pancreatic D cells and the hypothalamus, suppresses GH, insulin, and glucagon secretion. When somatostatin was infused into postoperative patients, the rate of glucose production (gluconeogenesis) decreased, as did the rate of glucose clearance. If insulin is infused into patients receiving somatostatin, the rate of glucose clearance returns to basal level, normalizing glucose kinetics. However, there was still increased gluconeogenesis. It thus appears that glucagon is a major mediator of gluconeogenesis.

The Counter-regulatory Hormones

The hormones glucagon, catecholamines, and cortisol are called counter-regulatory hormones because they oppose the effects of insulin and act synergistically to increase hepatic glucose production. Shamoon and associates[34] explored the short-term effects in normal subjects of the combined infusion of hydrocortisone, glucagon, and epinephrine designed to simulate the plasma levels found in moderate injury. They observed increased glucose production (gluconeogenesis) and decreased glucose clearance; the effect was more pronounced when all three hormones were administered together than when they were infused individually or in groups of two, suggesting that they act synergistically.[34] Catecholamines and glucagon act synergistically: when either one is infused into normal subjects, only transient elevations in gluconeogenesis occur; when they are infused simultaneously, gluconeogenesis is more prolonged. A possible reason for this synergism is that glucagon increases intracellular cAMP, especially in the liver, by a non–β-receptor mechanism. This could amplify the actions of epinephrine. Cortisol acts synergistically with epinephrine and other β-adrenergic agonists (an action employed in the treatment of asthma). Proposed mechanisms include cortisol-induced inhibition of catechol-*O*-methyltransferase and blockade of catecholamine reuptake. Glucocorticoids also prevent β_2-adrenergic receptor downreglation by increasing both β_2-receptor expression and increasing β_2-receptor gene transcription.[35] Additionally, glucocorticoids reduce cytokine concentrations, which is important because both IL-1 and TNF can downregulate β-receptors. In addition, prolonged postoperative adrenergic stimulation downregulates and desensitizes β-receptors which is partially reversed by the glucocorticoids.[36] Simultaneous infusion of the three hormones also caused negative nitrogen and potassium balances, glucose intolerance, hyperinsulinemia, insulin resistance, sodium retention, and peripheral leukocytosis. The nitrogen losses appear to be mainly due to cortisol, because nitrogen balance during cortisol infusion was similar to that during the infusion of all three hormones. The nitrogen losses were also not of the magnitude observed after accidental injury. With hormone infusions, there were significant alterations in leucine flux and oxidation but only small increases in 3-methylhistidine excretion, indicating little muscle breakdown. Therefore, other mediators must cause the proteolysis and massive nitrogen loss observed after major injury. Also, the normal subjects were not febrile, failed to increase acute-phase proteins, and did not have decreased serum iron. When the pyrogenic (stimulates IL-1 secretion) steroid etiocholanolone was injected into normal subjects there was fever, leukocytosis, and hypoferremia without elevations in the counter-regulatory hormones, hyperglycemia, or negative nitrogen balance. Infusion of the counter-regulatory hormones plus etiocholanolone simulated more of the features of the response to injury than when they were administered individually. Therefore, both endocrine and inflammatory mediators are active during the response to injury and sepsis.

Reproductive Hormones

The response to surgical and traumatic injury is characterized by hypogonadotropic hypogonadism. The mechanism is reduced response of the pituitary gland to gonadotropin-releasing hormone (Gn-RH) secreted by the hypothalamus, resulting in decreased release of luteinizing (LH) and follicle-stimulating hormone (FSH). Concentrations of FSH and LH change little during surgery but decrease on the first postoperative day. Elevated concentrations of CRH and cortisol may also contribute to the suppressed reproductive function.[37] In males, testosterone concentrations are markedly decreased in direct relationship to illness severity. In burn patients, this was due to lowered biologic activity of LH and suppressed response to the peaks in the pulsatile LH secretion. In males, the adrenal androgens, dehydroepiandrosterone (DHES) and its sulfate (DHEA-S), are suppressed after surgery. In premenopausal women, decreased estrogen concentrations during stress are associated with amenorrhea. However, in postmenopausal women, DHEA and DHEA-S were increased after cholecystectomy. This is an interesting finding because adrenal androgen concentrations are in decline after menopause.

Thyroid Hormones

During postoperative convalescence, after trauma, after extensive burns, and during sepsis (i.e., during nonthyroidal acute illnesses) there are profound alterations in thyroid homeostasis with decreased serum T_3 concentrations, low or normal T4, normal free T_4, increased reverse T_3, and normal TSH. This is often called the "sick-euthyroid syndrome." There is less conversion of T_3 to T_4 because of reduced type-1 deiodinase activity. Although TSH concentrations are within the normal range there are lower nocturnal surges that resemble the pattern found in central hypothyroidism. Additionally, sialylation (by oligosaccharide) of TSH is decreased, possibly explaining the altered TSH bioactivity. The mechanism of sick-euthyroid syndrome development is still unclear, especially in prolonged critical illness in which T_4 concentrations also decrease.[29] Some have pointed to the lack of TSH elevation in the presence of a low serum T_3 concentration and questioned if the problem is too little stimulation by thyroid-releasing hormone (TRH). This view was reinforced by a postmortem study of the paraventricular nuclei of patients with antemortem sick-euthyroid syndrome. There was a positive correlation between low antemortem serum T_3 and TSH concentrations with total postmortem TRH messenger RNA in the nuclei. However, infusion of TRH in stressed patients increased TSH and peripheral thyroid concentrations.[38]

Elevated serum levels of IL-6 are associated with the low serum T_3 concentrations during illness. However, normal subjects infused with endotoxin indicated that TNF does not play a role in endotoxin-induced thyroid hormone changes. Short-term (4-hr) and long-term (42-day) infusions of recombinant IL-6 decrease T_3 but not T_4 concentrations. It is unclear whether elevation of IL-6 is one of the causes of the sick euthyroid syndrome or is just an associated phenomenon. Dopamine infusion

decreases basal TSH concentrations, inhibits the TSH response to TRH, decreases both serum T_4 and T_3 levels, and may aggravate sick-euthyroid syndrome. Cessation of dopamine infusion results in increases in TSH, T_4, and T_3. There has been interest in treating sick-euthyroid syndrome with thyroid hormone and TRH. In a randomized double-blind, placebo-controlled trial of T_3 administration in cardiac surgery patients, although there were lesser decreases in T_3 concentrations during cardiopulmonary bypass, T_3 did not have dramatic effects on hemodynamics.

In the sick-euthyroid syndrome, plasma free-T_4 concentrations remain normal despite reduced total T_4 concentration because of reduced thyroxine-binding globulin (TBG) concentrations. During stress, hepatic synthesis of TBG is reduced and clearance may also be accelerated (protease cleavage). The most intriguing aspect of thyroid metabolism in stressed patients is that they are hypermetabolic despite low T_3 and T_4.

Cytokines

The response to injury and sepsis includes both neuroendocrine and inflammatory/immune responses. Cytokines, the main mediators of the inflammatory response, are produced by cells of the immune system (e.g., lymphocytes, macrophages) and many have multiple functions (Table 95-1). The pattern of cytokine release is genetically and environmentally (type and intensity of the stress) determined. These patterns control the severity of the inflammatory response and the degree of immune response.[39] Some cytokines (e.g., TNF-α, IL-1α/β, IFN-γ, IL-6, IL-8) are proinflammatory (type I), whereas others (e.g., IL-4, IL-10, TGF-β, IL-13) are anti-inflammatory (type II). Some (e.g., IL-12) induce cellular immunity by directing uncommitted helper T cells toward the T_H1 phenotype, whereas others (e.g., IL-10) induce the T_H2 phenotype and enhance humoral immunity. The inflammatory response is controlled by the balance between the proinflammatory and anti-inflammatory cytokines. For example, survival from sepsis was correlated with the recurrent secretion of proinflammatory, rather than anti-inflammatory, cytokines, indicating that the inflammatory response's stimulation of the immune system is necessary to overcome sepsis. Furthermore, after trauma the suppression of proinflammatory cytokines IFN-γ and IL-12 along with elevation of anti-inflammatory cytokine IL-10 was associated with immunosuppression and sepsis.[39]

Cytokines interact closely with the endocrine system, as demonstrated by marked elevations in ACTH and cortisol after IL-6 administration to cancer patients.[40] Alternately, endocrine hormones affect cytokine secretion (e.g., cortisol suppresses the secretion of IL-1 and TNF-α).

Cytokines operate via local paracrine, autocrine, and juxtacrine mechanisms, as well as through endocrine effects (see Fig. 95-2). Therefore, plasma concentrations do not necessarily reflect cytokine activity. Cytokine actions are also modulated by a complex network of receptors, receptor-antagonists, and cytoplasmic signaling molecules. For example, the effects of IL-1 are moderated by the simultaneous secretion of IL-1 receptor antagonist (IL-1ra), which blocks its actions. Furthermore, soluble cytokine receptors are generated by the proteolytic cleavage of membrane-bound receptors or by de-novo production. These circulating soluble receptors bind cytokines and may either neutralize cytokine actions or act as carrier proteins that protect the cytokine from proteolysis. Therefore, they may have either proinflammatory or anti-inflammatory functions.

The local actions of cytokines are demonstrated by the acute wound healing process that occurs in overlapping phases: hemostasis, inflammation, proliferation, angiogenesis, and resolution. The inflammatory phase involves infiltration of neutrophils, macrophages, and lymphocytes that secrete growth factors and cytokines. These mediators, acting locally, are active at all stages of wound healing through chemotactic, mitogenic, and other effects. During the first 24 hours, cytokines in elective incisional hernia repair wound drainage include high concentrations of both proinflammatory (IL-1α, IL-6, and IFN-γ) and anti-inflammatory (IL-10, IL-1ra) cytokines. The concentrations decline over the next few days. It appears that the two types of cytokines balance each other, with the proinflammatory cytokines stimulating immune cells to prevent infection while the anti-inflammatory cytokines modulate their actions and promote healing.[41]

Despite cytokine actions being mainly autocrine, paracrine, and juxtacrine, much research has explored their blood concentrations in stressful situations. In general, the blood concentrations are proportional to the degree of stress. After the moderate stress of total hip replacement surgery, IL-6 was significantly elevated above preoperative levels during the first 6 postoperative hours but began returning toward baseline by the first postoperative day. In contrast, IL-1β, IL-12, IL-10, and IL-8 levels were not elevated.[42]

Many cytokines have multiple functions (see Table 95-1). For example, IL-1 causes fever, induces hepatic acute-phase protein synthesis, upregulates prostanoid synthesis, induces the maturation of B lymphocytes, and activates NK lymphocytes.[41] IL-6 (also called B-cell–stimulating factor and hepatocyte-stimulating factor) has endocrine, as well as local, functions. Many cells produce IL-6, including monocytes, fibroblasts, glial cells, and lymphocytes. Its production is stimulated by endocrine hormones such as catecholamines and suppressed by cortisol and estrogens. The soluble receptors of the IL-6 family (e.g., sIL-6R, sIL-11R) are agonists capable of transmitting signals through interaction with the universal signal-transducing receptor for all IL-6 family cytokines, gp130 (see Fig. 95-2).[43]

TNF-α, a multifunctional proinflammatory cytokine secreted predominantly by monocytes/macrophages, affects lipid metabolism, immunity, hematopoiesis, coagulation, and endothelial function (see Table 95-1). TNF-α has seeming contradictory properties. For example, it induces neutrophil proliferation during inflammation but it can also induce neutrophil apoptosis.[44] Moreover, TNF-α intensifies the inflammatory response by prolonging the survival of inflammatory cells through the suppression of Fas-mediated apoptosis (Fig. 95-3). The multiple roles of TNF are demonstrated by the TNF blockers etanercept, adalimumab, and infliximab, which are used to treat rheumatoid arthritis. However, these drugs increase the risk for developing tuberculosis because TNF plays a crucial role in the body's immune defense against the mycobacteria causing this disease.[45]

Endothelial Cells

Endothelial cells lining blood vessels are metabolically active and play an active role in the stress response by synthesizing a variety of important mediators such as nitric oxide and adhesion molecules (Fig. 95-4).

Table 95-1 Cytokines

Cytokine	Function
TNF-α (tumor necrosis factor, cachectin) Proinflammatory	• Stimulates T and B cells and macrophages • Chemotactic agent for neutrophils • Stimulates neutrophil respiratory burst and proliferation • Stimulates release of tissue factor from endothelium and monocytes • Stimulates monocytes to release other proinflammatory cytokines • Has anti-tumor activity • Mediates cancer and AIDS cachexia • Inhibits synthesis of lipoprotein lipase; suppresses lipogenesis in adipocytes • Stimulates synthesis of acute-phase proteins • Mediates part of the cell-mediated immunity against obligate and facultative bacteria and parasites • Involved in the development of insulin resistance • Decreases erythropoietin production that leads to the anemia of inflammation • Promotes the proliferation of fibroblasts
IL-1 Proinflammatory	• Stimulates myelopoiesis via stimulation of G-CSF and GM-CSF • Endogenous pyrogen • Stimulates T (NK-cells) and B lymphocytes and macrophages • Attenuates anticoagulatory mechanisms and promotes thrombotic processes; induces production of tissue factor • Induces monocytes to release various mediators • Stimulation of T-helper cells, which are induced to secrete IL-2 and to express IL-2 receptors • Promotes the adhesion of neutrophils, monocytes, T cells, and B cells by enhancing the expression of adhesion molecules such as ICAM-1 (intercellular adhesion molecule-1) and ELAM (endothelial leukocyte adhesion molecule) • Mediator of inflammatory reactions. Enhances the metabolism of arachidonic acid (in particular of prostacyclin and PGE_2)
IL-4 Anti-inflammatory	• Inhibits macrophage activity • B-cell proliferation and activation • Enhances Th2 differentiation • Inhibits cell activation of NK cells induced by IL-2
IL-6 Pro- and anti-inflammatory	• Stimulates the acute-phase protein response • Stimulates the hypothalamus to secrete CRF • In sick euthyroid syndrome inhibits 5′-deiodinase, which converts T_4 to T_3 • Stimulates B lymphocytes and is involved in their differentiation into plasma cells • In the presence of IL-2, induces the differentiation of mature and immature T cells into cytotoxic T cells • Stimulates the secretion of antibodies
IL-8 Proinflammatory	• Neutrophil chemotactic agent • Synthesis strongly stimulated by IL-1 and TNF-α • Activates neutrophils; releases enzymes from granules • Chemotactic for all known types of migratory immune cells; enhances the expression of adhesion molecules
IL-10 Anti-inflammatory	• Produced by and downregulates the function of Th1 and Th2 cells • Inhibits antigen-presenting cell activity • Suppresses macrophage activity • Inhibits production of pro-inflammatory cytokines such as IFN-γ, IL-2, and TNF-α in T_H1 T-helper subpopulations • In macrophages stimulated by bacterial lipopolysaccharides, IL-10 inhibits the synthesis of IL-1, IL-6, and TNF-α by promoting the degradation of cytokine mRNA • Prevents the activation of macrophages
IL-13 Anti-inflammatory	• Downregulates macrophage activity, reducing production of proinflammatory cytokines (IL-1, IL-6, IL-8, IL-10, IL-12) and chemokines (MIP-1, MCP) in response to IFN-γ or bacterial lipopolysaccharides • Enhances the production of IL-1ra • Strongly inhibits tissue factor expression induced by bacterial lipopolysaccharides and reduces the pyrogenic effects of IL-1 or TNF, thus protecting endothelial cells and monocytes against inflammatory mediator–induced procoagulant changes
IFN-γ Anti-inflammatory	• IFN-γ has antiviral and antiparasitic activities • Main biologic activity is as an immunomodulator • A major function is to activate macrophages • Influences cell-mediated mechanisms of cytotoxicity • Modulator of T-cell growth and functional differentiation • IFN-γ is the hallmark cytokine of T_H1 cells

IL, interleukin; IFN, interferon.

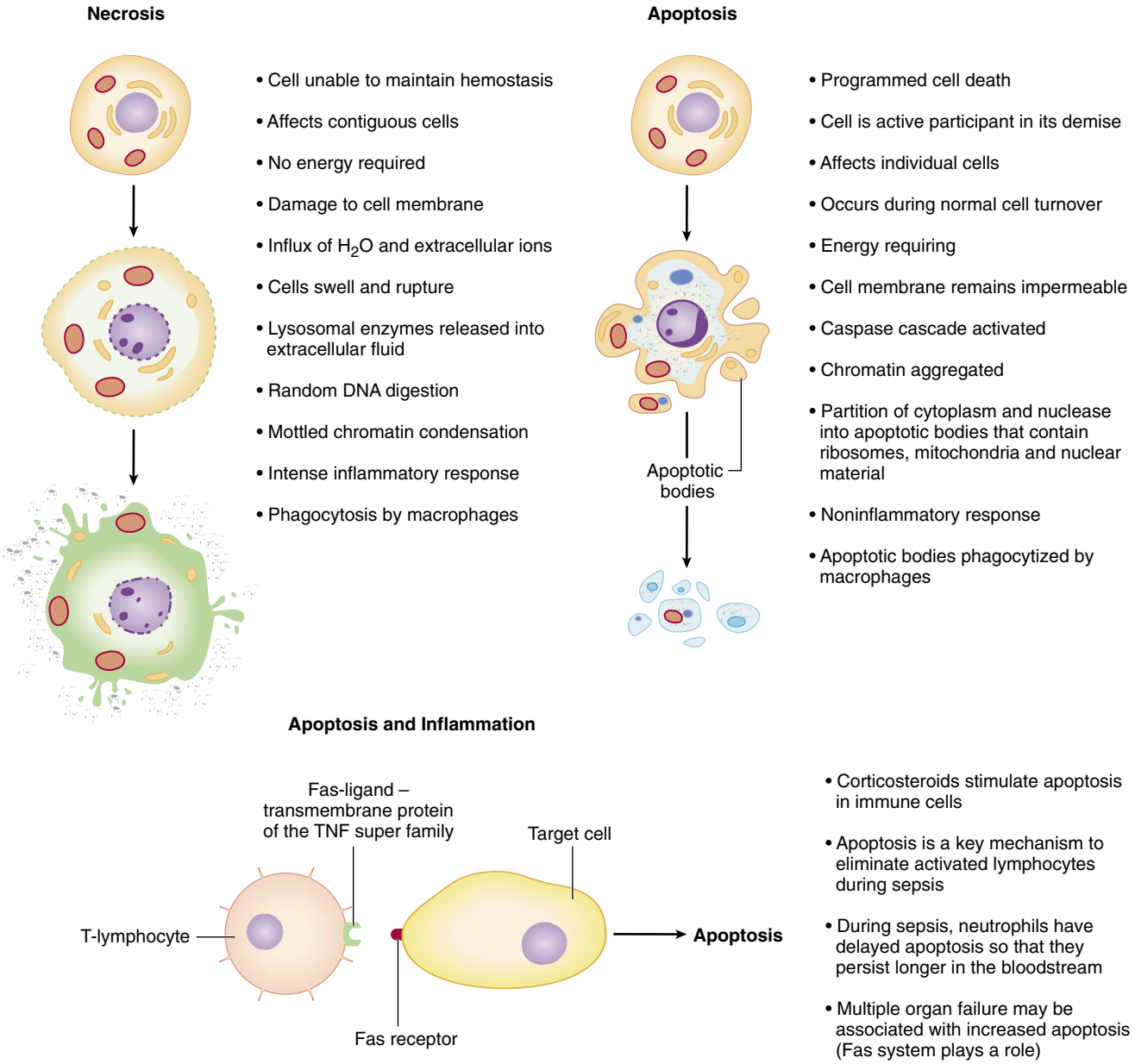

Figure 95-3 The differences between necrosis and apoptosis are shown. The importance of apoptosis during inflammation is also diagrammed.

The Immunologic/Coagulation Connection

Surgical, septic, and traumatic stress produce leukocytosis, thrombocytosis, and anemia. The granulocytosis seen with surgery and infections is mediated by cytokine-induced release of the hematopoietic growth factor granulocyte colony-stimulating factor (G-CSF). G-CSF increases neutrophil, monocyte, and T-lymphocyte production and is elevated above preoperative levels for at least a week after major surgery.[46] Thrombocytosis is induced by thrombopoietin, which increases in concert with IL-6 and acute-phase reactants.[47] Anemia of inflammation occurs during acute and some chronic stressed states. Erythropoiesis is suppressed because of an inability to incorporate iron into erythrocyte precursors despite the presence of adequate bone marrow iron stores. This is secondary to both decreased erythropoietin secretion and reduced sensitivity to its actions.

There is much bidirectional cross-talk between the inflammatory and coagulation systems.[48] During the perioperative period there is marked hypercoagulability secondary to both an increased procoagulant state and reduced fibrinolysis. The former is caused by a combination of decreased antithrombin, tissue factor pathway inhibitor (TFPI), and protein C coupled with increased tissue factor (TF) causing increased thrombin generation and fibrin deposition. This results in microvascular thrombosis. Decreased fibrinolysis is due to reduced t-PA (tissue plasminogen activator) and increased PAI-1 (plasminogen activator inhibitor-1). Cytokines, secreted by immune cells, are the responsible mediators; TNF-α upregulates PAI-I, monocytes express TF, and IL-6 stimulates TF. In addition, especially during

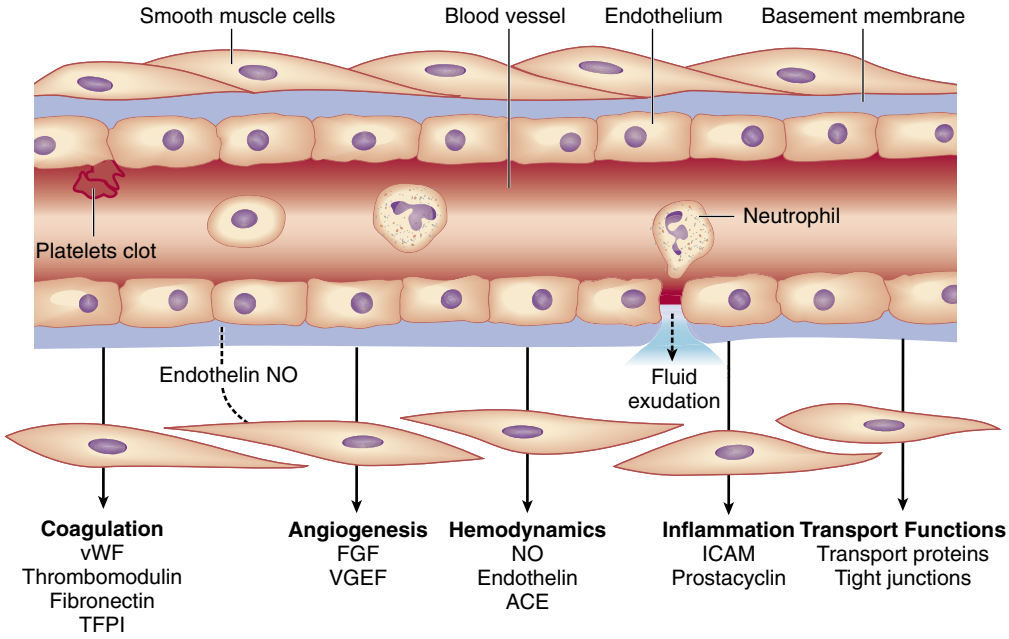

Figure 95-4 Endothelial cells have many functions. Nitric oxide (NO) produced by endothelial cells vasodilates blood vessels by relaxing adjacent myocytes, while endothelin causes vasoconstriction. The NO-endothelin system is the local controller of vascular tone. During sepsis, inflammatory cytokines, such as TNF, upregulate inducible NO synthetase (iNOS), increasing endothelial production of NO and resulting in vasodilation. During sepsis, endothelial disruption occurs because of increased expression of adhesion molecules, resulting in white blood cell attachment and disruption of the basement membrane. This results in exudation of fluid into the extracellular space. Adhesion molecules and selectins recruit leukocytes to enter tissues. vWF, von Willebrand factor; TFPI, tissue factor pathway inhibitor; FGF, fibroblast growth factor; VGEF, vascular endothelial growth factor; ACE, angiotensin-converting enzyme; ICAM, intercellular adhesion molecule; VCAM, vascular cellular adhesion molecule.

sepsis, ex vivo platelet reactivity increases. Acute-phase proteins contribute to the procoagulant state. Fibrinogen concentrations are elevated as are those of α_1-antitrypsin and α_2-macroglobulin, which inhibit protein C. Increased C4 binding protein lowers free protein S, whereas C-reactive protein (CRP) increases the expression of TF by monocytes and neutrophils.[49] The hypercoagulable state is also induced by other factors, including local tissue damage (PAI is secreted by endothelial cells) and materials such as methyl methacrylate monomers and bone marrow debris. During postoperative convalescence (days 3 to 7) hypercoagulability gradually abates. Hypercoagulability is not triggered by the counter-regulatory hormones. Instead, when a cocktail of these hormones plus angiotensin II and vasopressin was infused into normal volunteers, fibrinolytic and anticoagulant activity increased (fibrinogen, t-PA, and protein C concentrations increased, as did platelet activity). These results are reinforced by the anticoagulant effects of an epinephrine infusion begun before an endotoxin infusion in normal subjects.[50]

Regional anesthesia, especially after lower body surgery, causes less hypercoagulability than general anesthesia and is associated with less deep vein thrombosis. Laparoscopic cholecystectomy appears to cause less hypercoagulability than open cholecystectomy and may actually cause hypocoagulability by selectively increasing tPA.

The procoagulant state, in turn, accelerates the inflammatory response. Thrombin, acting through protease-activated receptors, upregulates cytokines (e.g., IL-6, IL-8, monocyte chemotactic protein-1) and increases adhesion molecule expression. The TF/factor VII complex increases inflammatory responses of macrophages and neutrophils, as evidenced by increased plasma concentrations of IL-6 and IL-8 on infusion of recombinant factor VII into normal subjects.[51] Inflammation plus microvascular thrombosis is thought to be a cause of multiple organ system dysfunction and thus is the rationale for activated protein C (APC) treatment in sepsis. APC is approved for treatment of sepsis, whereas trials of TFPI and antithrombin III were unsuccessful.

Fasting and Malnutrition

Fasting results in adaptive responses that permit the body to continue functioning despite a lack of nutrient intake.[52] During the 24 to 48 hours after cessation of nutrient intake glycogen stores are broken down (glycogenolysis) to provide glucose to the tissues. This glucose is vital for the brain, red blood cells, skin, and renal medulla, which have obligatory glucose requirements. Glycogenolysis is mediated by an increased glucagon/insulin ratio (increased glucagon and decreased insulin), which also promotes endogenous glucose production (gluconeogenesis). In addition to the increases in glucagon and decreases in insulin, hypoglycemia is avoided by small increases in catecholamine and cortisol secretion.[53] The increase in catecholamine-induced β-adrenergic stimulation accelerates lipolysis so that triglycerides stored in adipose tissue are broken down to free fatty acids (FFA) and glycerol. Some of the FFA undergo hepatic conversion to ketones (β-hydroxybutyrate and acetoacetate), which are then utilized as an energy source. As glycogen is depleted, glucose is increasingly provided by gluconeogenesis, which provides more than 90% of

the glucose after 42 hours of fasting.[54] Among the substrates for gluconeogenesis are glycerol released during lipolysis and lactate produced by glycolysis.

As starvation continues, skeletal and smooth muscle tissues undergo proteolysis to amino acids. The amino acids alanine and glutamine are transported mainly to the liver but some also to the kidneys, to be used as substrates for gluconeogenesis. This muscle breakdown results in a negative nitrogen balance (catabolism). As starvation progresses, the body adapts by reducing the rate of gluconeogenesis and muscle breakdown, which, along with decreases in free T_3 and catecholamines, reduce resting energy expenditure. This reduced muscle protein breakdown is accompanied by reduced nitrogen losses so that nitrogen balance becomes less negative. The decrease in gluconeogenesis is possible because the brain adapts to using ketones for some of its energy needs.[55] During this time much ATP is produced from fatty acids released by lipolysis.

Prolonged starvation leads to weight loss secondary to major losses of fat and lean (muscle) body mass. Marked weakness and fatigue develop as the result of proteolysis and reduced muscle protein synthesis. Sodium and water retention also occurs. Prolonged starvation reduces immune function and results in increased adherence of gram-negative bacteria to nasopharyngeal and pulmonary endothelial cells. This bacterial adherence along with weakness of the respiratory muscles and immune system makes these patients susceptible to pneumonia, the leading cause of death in starved or severely malnourished patients.

Eating

Eating sets into motion a series of steps that digest, absorb, and metabolize the ingested food. Gut hormones initiate a sequence of systematic events by signaling the body to secrete hormones such as insulin.[56] Ingested carbohydrates are converted to glucose and stimulate insulin secretion, and the glucose not immediately needed for energy is stored as glycogen or converted to fat (lipogenesis). Ingested proteins are digested and broken down into amino acids, used to synthesize proteins, and serve as precursors for neurotransmitters and other substances. Fats are stored and used for energy or as precursors for prostaglandins and other substances. Food ingestion increases metabolic rate—diet-induced thermogenesis or thermogenic effect of food—and contributes 10% to 15% of total daily energy expenditure.[57] Protein ingestion increases metabolic rate more than isoenergetic amounts of carbohydrates or fat.[58] The postprandial rise in energy expenditure lasts for 3 to 4 hours.

The Metabolic Responses to Surgical and Traumatic Injury

The metabolic responses to surgical and traumatic stress differ greatly from the response to starvation. Unlike the adaptive responses aimed at preserving body mass that occur during starvation, the response to stress has been called "auto-cannibalism."[59] This categorization is occasioned by loss of fat and lean body mass caused by an obligate catabolic state with proteolysis, gluconeogenesis, lipolysis, hypermetabolism, and insulin resistance. Autocannibalism is not reduced to any great extent by exogenous nutrients.

The intensity and duration of the metabolic response to surgery and trauma depend on the magnitude of injury, total operating time, amount of intraoperative blood loss, and degree of postoperative pain. The smaller injury of laparoscopic surgery, compared with open surgery, results in lower concentrations of IL-1, IL-6, and the acute-phase reactant CRP.[60] The greatest metabolic responses are observed after severe (>40% body surface area) burn injury with metabolic rates twice normal and catabolism that lasts for many months, leading to immunodepression, recurrent infections, and poor wound healing.[21]

Carbohydrate Metabolism

Surgical and accidental injury increase secretion of the counterregulatory (to insulin) hormones cortisol, catecholamines, and glucagon,[61] resulting in elevated endogenous glucose production secondary to accelerated hepatic gluconeogenesis (Fig. 95-5). This increased glucose production coupled with peripheral tissue resistance to insulin results in reduced glucose utilization and hyperglycemia. Serum insulin concentrations are normal or elevated but are insufficient to prevent hyperglycemia but do prevent ketosis. Hyperglycemia is thought to ensure a ready supply of glucose to predominantly glucose-consuming cells, such as the wound inflammatory cells and immune cells.

Insulin resistance is defined as impaired glucose disposal in the presence of either normal or elevated serum insulin concentrations.[62] This insulin resistance occurs in peripheral tissues, causes a 50% to 70% reduction in insulin sensitivity compared with healthy controls, and is likely due to a postreceptor defect that hinders cellular glucose uptake.[62] This defect is possibly caused by impaired activity of the intracellular glucose transport system or nonoxidative glucose disposal, that is, reduced muscle glycogen synthetase activity.[63] In postoperative patients the magnitude of the insulin resistance is proportional to the magnitude of the surgery. Insulin resistance occurred after both elective open and laparoscopic cholecystectomy and persisted for at least 5 days. In medical ICU patients the severity of insulin resistance was associated with the severity of illness, body mass index, and degree of hypermetabolism.[62]

In stressed patients, the overall amount of glucose oxidized (especially given the overall hypermetabolism) may be decreased despite a glucose oxidization pathway that is intact, because the rate of glucose uptake into the cell is limited by insulin resistance. The incremental response to increases in insulin concentration is maintained, but the ability to reduce blood glucose concentration per insulin concentration is markedly diminished. Despite the insulin resistance, the overall peripheral uptake of glucose is often normal or mildly elevated owing to increased non–insulin-mediated glucose uptake and the large amounts of glucose (due to hyperglycemia) being presented to the resistant insulin pathway. However, relative to the blood glucose concentration and hypermetabolism, the uptake is low.

Glucose can be oxidized to produce ATP, water, and CO_2; converted to glycogen for storage in the liver and muscles; or converted to fat. The latter process is called lipogenesis and occurs in both liver and adipose tissue, although the latter appears to be the main site for lipogenesis. Under normal circumstances carbo-

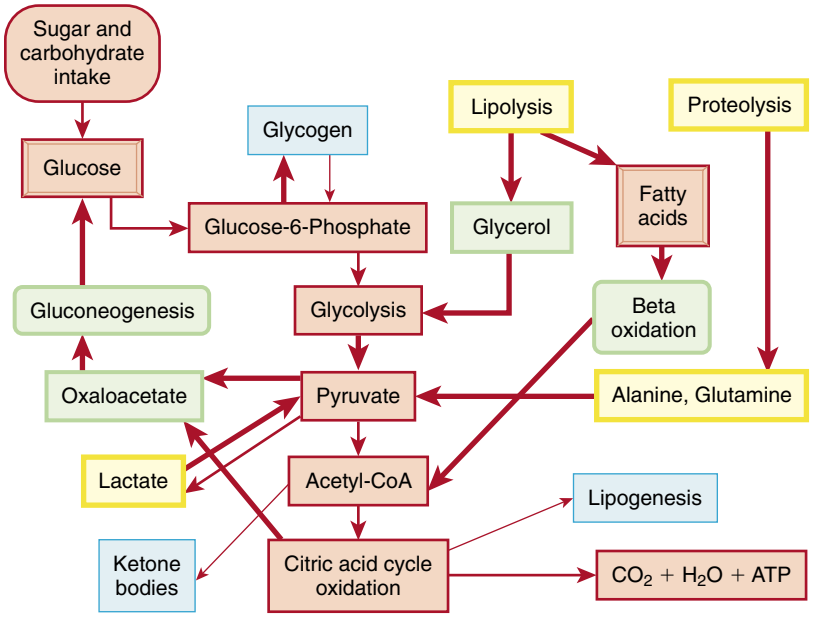

Figure 95-5 The metabolic milieu during stress. The rate of endogenous glucose production (gluconeogenesis) is greatly increased. Glycerol (from lipolysis), alanine (from proteolysis), and lactate (from the wound) are the substrates. Because of insulin resistance less glucose is used to produce energy (ATP) and, thus, β-oxidation of fatty acids becomes the major energy-producing pathway. Exogenous glucose intake does not decrease the rate of gluconeogenesis. The production of ketones is not greatly increased because of normal to elevated concentrations of insulin. Acetyl-CoA, acetyl coenzyme A; ATP, adenosine triphosphate.

hydrate intake inhibits fat oxidation, increases glucose oxidation, and promotes fat storage. Lipogenesis is quantitatively unimportant in humans because the rate of lipogenesis does not exceed the rate of lipid oxidation. Yet, when carbohydrate intake exceeds total energy expenditure, lipogenesis becomes a more important pathway, and respiratory quotients (RQs) may exceed 1.0, indicating net lipogenesis (see Table 95-3). Critically ill patients administered intravenous glucose at 4 mg/kg/min as part of glucose-based total parenteral nutrition (TPN) exhibited some increased hepatic de novo lipogenesis, despite achieving an RQ of only 0.90.[64] This lipogenesis occurred even though lipogenetic capability is thought to be reduced in surgical or septic stress. The reduced lipogenesis is possibly secondary to TNF, which among other things can induce apoptosis of pre-adipocytes and adipocytes. IL1-β may also inhibit lipogenesis in human adipocytes.

Lipid Metabolism

Stressful situations (e.g., injury, sepsis, and congestive heart failure) alter lipid metabolism. The major change is accelerated lipolysis due to increased β_2-adrenergic stimulation.[65] Stimulation of the β_2-receptors increases cAMP concentrations, which, in turn, stimulates the activity of hormone-sensitive lipase (Fig. 95-6). The lipolytic response to β_2 stimulation is greater in lean, than obese, subjects; β_3-adrenergic receptors also appear to play a role in human lipolysis. Elevated concentrations of glucagon, TNF-α, IL-1, interferon-α, and interferon-γ likely have roles in stimulating lipolysis. Insulin resistance contributes to the lipolysis because the anti-lipolytic effect of insulin is attenuated.[62] There are regional variations in the lipolytic rate, with visceral fat cells having the greatest rate due to increased activity of β_2 and β_3 receptors and reduced activity of α_2-adrenergic receptors. Subcutaneous fat has less lipolytic activity due to greater activity of insulin receptors and α_2 adrenoreceptors. The RQ in injured patients is consistently lower than normal subjects for a given level of intake, indicating greater fat oxidation (Table 95-2). Infusion of glucose in amounts that lead to net fat synthesis in normal subjects fails to suppress fat oxidation in injured and septic patients, leading to negative fat balance. Plasma free fatty acid concentrations are high because the lipolytic rate exceeds the rate of fat oxidation.

Rapid glycerol and free fatty acid turnover rates reflect the accelerated lipolysis seen during stress. The increased lipolysis increases the systemic supply of circulating free fatty acids (FFA). However, the turnover rates are greater than those expected from the increases in the plasma concentrations of these substrates. This indicates that there is both increased re-esterification of FFA to triglycerides (TG) and increased lipolysis of TG to FFA. This increased activity of the TG-FFA/glycerol substrate cycle is thought to be one of the causes of the hypermetabolism seen during stress (Fig. 95-7). β-Adrenergic receptor blockade with propranolol decreases lipid oxidation and the resting metabolic rates of burn patients. Glucose infusions further increase lipolysis during abdominal surgery because they increase sympathetic nervous system activity.

In the stressed state the relative contribution of fat oxidation to resting energy expenditure is increased while the contribution of glucose oxidation is decreased. FFA acids released by lipolysis undergo β-oxidation, which in the stressed patient is the predominant ATP-producing pathway (see Figs. 95-5 and 95-6). This situation is reflected in observations made after esophagectomy where there was a gradual decrease in the contribution of fat oxidation to energy production and an increase in the contribution of glucose oxidation as patients convalesced.

Protein Metabolism

One of the hallmarks of the metabolic response to injury and sepsis is catabolism (negative nitrogen balance). Catabolism is caused by accelerated proteolysis of skeletal muscle, which provides some of the substrate for increased hepatic gluconeogenesis (see Fig. 95-5). Reducing the rate of hepatic gluconeogenesis with

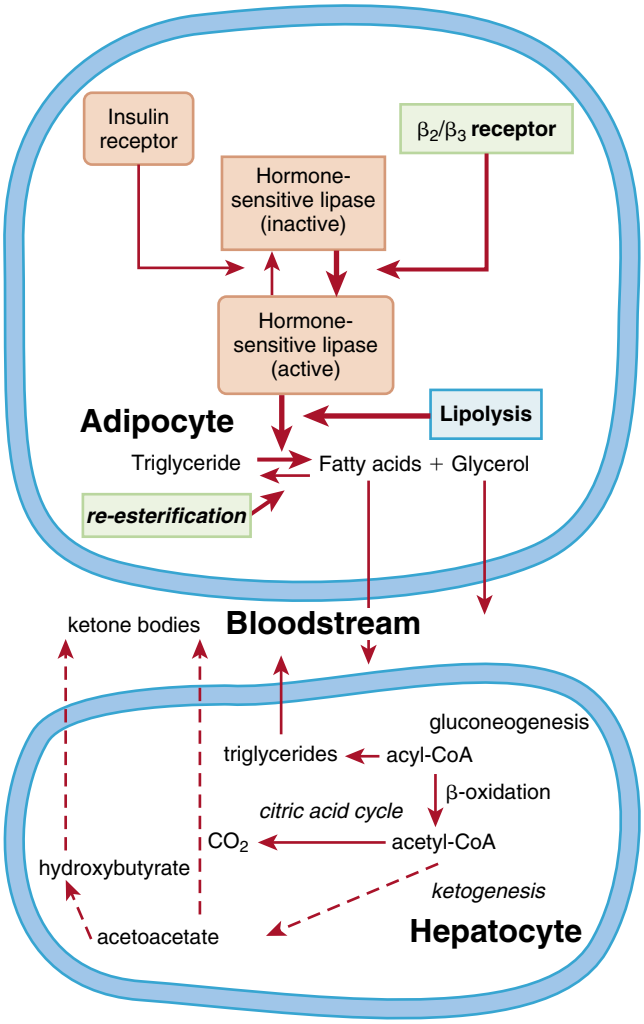

Figure 95-6 Lipid metabolism during the stressed state. Catecholamines stimulate β_2 and β_3 receptors, activating hormone-sensitive lipase, leading to lipolysis. Free fatty acids are transported to the liver where they undergo β-oxidation and are the main source of energy during stress (palmitoyl-CoA yields a net of 130 ATP). Glycerol released by lipolysis is a substrate for gluconeogenesis and is converted to glucose. Because insulin concentrations are elevated, ketone production is not increased. Both lipolysis and re-esterification are increased, leading to a futile cycle.

somatostatin does not decrease the rate of peripheral protein breakdown, demonstrating that the accelerated rate of hepatic glucose production is not linked to increased level of peripheral protein breakdown. The degree of nitrogen loss is proportional to the degree of stress and abates as the patient convalesces. After severe burns, protein breakdown and subsequent amino acid efflux from muscle is increased almost twofold. The increased protein breakdown is thought to be modulated only partially by the endocrine stress hormones, specifically cortisol. Instead, other mediators such as TNF-α, IL-1, IL-6, and interferon-γ mediate catabolic activity. It is the balance between these catabolic mediators and anabolic hormones, such as insulin and insulin-like growth factors, that determine the magnitude of catabolism. A number of metabolic pathways are responsible for skeletal muscle proteolysis including the lysosomal Ca^{2+}-activated, ATP-ubiquitin–dependent proteolytic pathway.[66] The liver also contributes to catabolism through increased clearance of α-amino nitrogen (urea). After surgery the rate of this conversion is doubled. Blockade of glucagon and cortisol secretions with a combination of etomidate, somatostatin, and thoracic epidural anesthesia decreased this clearance, thus indicating roles for glucagon and possibly cortisol and afferent neural reflexes in this process.

There are conflicting data regarding skeletal muscle protein synthetic activity during stress. Some studies indicate reduced (e.g., 31% decrease 24 hours after open cholecystectomy) skeletal muscle protein synthesis whether saline or TPN is infused. Liver biopsies taken during surgery demonstrated depressed hepatic protein synthesis after 20 minutes of surgery that decreased further as surgery progresses.[67] Tissues with rapidly replicating cells, such as enterocytes, immune cells, and keratinocytes, also exhibit reduced protein synthesis. Other investigators claim that the net negative nitrogen balance is due an accelerated rate of protein breakdown that is in excess of an increased protein synthetic rate. Furthermore, the derangement of protein metabolism is profound because administering TPN after open cholecystectomy did not prevent the decline in muscle protein synthesis observed 24 hours after surgery.

The detrimental affects of prolonged bed rest further contribute to the derangements in protein metabolism caused by the stress hormones and cytokines after injury and surgery. In normal volunteers, 28 days of bed rest resulted in a 0.4-kg loss of leg

FUTILE CYCLES

Glucose metabolism

Glycolysis ⟷ Gluconeogenesis

↓

"Wastes" 4 ~P bonds/cycle

Glycolysis

$$\text{Glucose} + 2\ \text{NAD}^+ + 2\ \text{ADP} + 2\ \text{P}_i \rightarrow 2\ \text{Pyruvate} + 2\ \text{NADH} + 2\ \text{ATP}$$

Glycolysis yields 2 ~P bonds of ATP

Gluconeogenesis

$$2\ \text{Pyruvate} + 2\ \text{NADH} + 4\ \text{ATP} + 2\ \text{GTP} \rightarrow \text{Glucose} + 2\ \text{NAD}^+ + 4\ \text{ADP} + 2\ \text{GDP} + 6\ \text{P}_i$$

Gluconeogenesis expends 6 ~P bonds of ATP and GTP

FAT METABOLISM

Lipolysis ⟷ Re-esterification

↓

"Wastes" 8 mol ATP/cycle

Lipolysis

↓

Triglycerides ⇌ Free fatty acids + Glycerol

↑

Re-esterification

Figure 95-7 Two futile cycles that contribute to the hypermetabolism of the stress response. A futile cycle is a set of opposing reactions catalyzed by different enzymes acting simultaneously, with at least one of the reactions driven by adenosine triphosphate (ATP) hydrolysis so that heat is produced. In the lipid metabolism cycle there is net lipolysis whereas in the glucose metabolism cycle there is net gluconeogenesis. ~P, high-energy phosphate bond, generally from ATP.

Table 95-2 Energy Expenditure and Caloric Requirements

Energy Expenditure

Basal energy expenditure (BEE)—also called basal metabolic rate (BMR)—the energy expenditure on awakening from a 12-hour fast measured in a thermoneutral environment (25°C).

Thermogenic effect of food—also called specific dynamic action—the energy expenditure after the ingestion of food. After a meal, energy expenditure may increase 5% to 10%.

Resting energy expenditure (REE)—the energy expenditure while resting in the supine position with eyes open. Includes the thermogenic effect of food if performed within a few hours of a meal or during continuous infusions of nutrients such as during continuous TPN administration. About 10% greater than BEE.

Sleeping energy expenditure (SEE)—the energy expenditure during sleep; it is usually 10% to 15% lower than REE.

Activity energy expenditure (AEE)—the energy expended during physical activity. During maximum exercise it can be 6- to 10-fold greater than the BEE.

Environmental temperature—energy expenditure increases to warm patients placed in a cold environment. Warming occurs through shivering and increased metabolism of brown fat (neonates).

Fever—Fever increases metabolic rate 10% per °C (or 7% per °F).

Total energy expenditure (TEE)—total energy expended over 24 hours: the sum of energy expended during periods of sleep, resting, and activity.

Estimating Resting Energy Expenditure (Harris-Benedict Equation)

Males: eBEE (kcal/day) = 66 + (13.7 • W) + (5 • H) – (6.8 • A)

Females: eBEE (kcal/day) = 655 + (9.6 • W) + (1.7 • H) – (4.7 • A)

eREE = eBEE • stress factor

eTEE = eREE • activity factor

eBEE, estimated basal energy expenditure; W, weight (kg); H, height (cm); A, age (years); eREE, estimated resting energy expenditure; eTEE, estimated total energy expenditure.

Stress Factors

Spontaneously breathing, nonsedated patients:

- Major surgery: 15%-25%
- Infection: 20%
- Long bone fracture: 20%-35%
- Malnutrition: Subtract 10%-15%
- Burns: Up to 120% depending on extent
- Sepsis: 30%-55%
- Major trauma: 20%-35%
- COPD: 10%-15%
- Sedated mechanically ventilated patients: Subtract 10%-15%.

Activity Factors

Sedated mechanically ventilated patients: 0-5%

Bedridden, spontaneously breathing nonsedated patients: 10%-15%

Sitting in chair: 15%-20%

Ambulating patients: 20%-25%

Measuring Energy Expenditure

Indirect calorimetry involves measuring oxygen consumption (Vo_2) and carbon dioxide production (Vco_2). The gas exchange method is used to measure Vo_2 and Vco_2, whereas the Fick method can be used to measure only Vo_2.

Weir equation: EE (kcal/day) = 1.44 (3.9 • Vo_2) + (1.1 • Vco_2)

Measurements made at rest provide the REE. To determine the TEE: REE • activity factor.

Continuous measurement made over 24 hours provides the TEE.

Measuring Nitrogen Balance

N balance = [N intake]–[N output]: Negative balance—catabolism; positive balance—anabolism.

Where [N intake] = all protein/amino acid intake over 24 hours whether enteral or parenteral

[N output] = [UUN + 4 + EL]

UUN, urine urea nitrogen over 24 hours; 4 g average fecal and cutaneous losses; EL, excessive losses, such as protein rich drainages (e.g., pus).

6.25 g protein/amino acids = 1 g nitrogen.

Table 95-2 Energy Expenditure and Caloric Requirements—cont'd

Daily Caloric Requirements	Using Measured or Estimated REE	Using Body Weight
Sedated mechanically ventilated patients	1.0-1.2 • REE	20-24 kcal/kg
Unsedated mechanically ventilated patients	1.2 • REE	22-24 kcal/kg
Spontaneously breathing critically ill patients	1.2-1.3 • REE	24-26 kcal/kg
Spontaneously breathing ward patients (maintenance)	1.3 • REE	24-26 kcal/kg
Spontaneously breathing ward patients (repletion)	1.5-1.7 • REE	25-30 kcal/kg

To gain 1 pound of body weight, one needs an excess above TEE of approximately 3500 kcal.

Respiratory Quotients	Energy (kcal/g)	Respiratory Quotient (RQ)*
Carbohydrate	4.0	1.00
Dextrose (glucose monohydrate)	3.4	1.00
Fat	9.0	0.70
Protein	4.0	0.80
Ethanol	7.0	0.67
Lipogenesis		*8.00*

RQ, ratio of resting CO_2 production to resting O_2 consumption.
*Whole-body RQ is influenced by the relative amounts of carbohydrate, fat, and protein oxidation and lipogenesis. For example, a patient who has received a 5% dextrose infusion of 100 mL/hr (440 kcal/day) for 4 days has a whole-body RQ of 0.77 to 0.80, reflecting the predominance of fat and protein oxidation as the energy source. Whole-body RQ above 1.0 indicates net lipogenesis. In humans, RQs above 1.2 to 1.3 are generally not seen even with very high carbohydrate intakes.

muscle mass and a reduction of 23% in leg extension strength.[68] When hydrocortisone was administered to such bed-rested volunteers, in doses intended to reproduce cortisol concentrations encountered during illness or trauma, there was a threefold greater loss of lean leg mass (1.4 kg), which represents a 6% loss of muscle mass from the legs and a 4-kg loss of whole-body lean mass. There was also a 28% reduction in leg extension strength. The muscle protein synthesis rate was decreased while muscle protein breakdown was unchanged from rates before bed rest.[69] In contrast, blunt trauma patients had a greater mean 6.4 kg loss of whole-body lean mass because they suffered from proteolysis in addition to reduced protein synthesis.[70] Extended periods of immobilization in bed contribute to loss of muscle mass and the weakness suffered by stressed patients. Early mobilization and exercise are thus important aspects of care.

During stress there is increased hepatic synthesis of the acute-phase proteins such as fibrinogen, haptoglobin, complement, immunoglobulins, serum amyloid A, and CRP. The secretion of the acute-phase proteins is stimulated by elevated concentrations of endogenous corticosteroids (which by themselves do not initiate the response) in concert with IL-1β, TNF-α, and IFN-γ. These cytokines induce the secretion of IL-6 by the hepatic Kupffer cells, which also initiates and stimulates the production of acute-phase proteins.[60] Simultaneously, IL-6 and the corticosteroids initiate a negative feedback loop, suppressing IL-1β and TNF-α production by mononuclear phagocytes. Bacterial infections tend to trigger a stronger acute-phase response than viral infections. The increase in the acute-phase proteins leads to greater ability to fight infection, stimulation of the wound healing process, and improved hemostasis. The increase in fibrinogen is responsible for the increased hemostatic ability and also increased plasma viscosity. The latter is the reason the erythrocyte sedimentation rate is used as a nonspecific diagnostic test for disease activity. CRP is often used as a measure of the acute-phase response and the degree of stress because of enormous concentration increases (e.g., on the second day after hip replacement concentrations increased from <6 to >200 mg/L).[42] It is often used as a marker of low-grade inflammation in obesity and cardiac disease because of its proatherosclerotic effects.

Occurring simultaneously with the increased synthesis of acute-phase proteins is reduced synthesis of binding proteins, such as albumin, transthyretin (prealbumin), retinol-binding protein, and transferrin. This reduction in the synthesis and plasma concentrations of binding proteins elevates the plasma concentrations and bioavailability of free hormones and electrolytes. As discussed previously, decreased plasma concentrations of cortisol binding globulin and albumin increase the concentrations of free cortisol. Albumin concentrations (half-life, 21 days) decrease because of reduced synthesis, redistribution in the expanded extracellular fluid, and a greater fractional catabolic rate. Therefore, short-term changes in albumin concentrations do not reflect changes in synthesis. For nutritional evaluation a protein with a short half-life (e.g., transthyretin) is measured. However, it, too, has limitations because concentrations are decreased in hepatic failure and increased in renal failure.

Energy Expenditure

Metabolism consumes fuels, such as glucose and fatty acids, to produce energy-containing compounds (e.g., ATP) for use in many energy-consuming body functions. Among the major func-

tions of eating is replenishing this fuel. The amount of fuel burned is reflected directly by the amount of energy released as heat (direct calorimetry) and indirectly by the amount of O_2 consumed, CO_2 produced, and urine urea nitrogen excreted (indirect calorimetry). The components of the daily total energy expenditure (TEE) are outlined in Table 95-2. Daily caloric intake should be sufficient to meet the daily energy expenditure. Intakes in excess of TEE result in the deposition of fat and weight gain, whereas sustained intakes less than TEE result in weight loss.

In stressed patients the altered metabolic milieu increases resting energy expenditure (REE). Most studies of spontaneously breathing postoperative, trauma, septic, and burn patients have reported that REE is above the estimated resting energy expenditure (eREE) estimated by the Harris-Benedict equation (see Table 95-2). This is in contradistinction to the starved or semi-starved state where the energy expenditure decreases as part of an adaptive response.

Studies performed in spontaneously breathing surgical patients showed that measured (via indirect calorimetry) REE was greater than eREE. The greater REE ranged from 10% to 20% after elective surgery to 20% to 40% during sepsis (although values as high as 80% have been reported after sepsis). Patients with fractures of the long bones tend to have higher REE/eREE than those with similar degrees of injury without fractures. Peak REE occurs about the third postoperative day, and hypermetabolism may last as long as 3 to 4 weeks in critically ill trauma and longer in burn patients. Burn patients can be extremely hypermetabolic (with REE as much as 120% greater than eREE) with the degree of hypermetabolism proportional to the extent and severity of the burns. Elderly patients (>60 years) have less of a hypermetabolic response.[71]

Mechanically ventilated postoperative and trauma patients have lower increases in REE than spontaneously breathing patients because they are receiving sedatives and/or muscle relaxants, which both decrease REE by as much as 20%.[72] In such patients, measured REE is often within ±10% to 16% of the eREE.[73] Another cause of this lack of hypermetabolism is that they have no or minimal work of breathing when ventilation is controlled by the mechanical ventilator. As they begin to breathe spontaneously the REE rises because of increased work of breathing and reduced sedation. During weaning from mechanical ventilation, energy expenditure rises further as the patient sustains more of his or her breathing, sedation is stopped, and anxiety sets it.[74] However, it is important to note that these very ill ICU patients retain much resuscitation fluid ("third space") that increases their body weight by as much as 10% to 12%. Because edema fluid has no metabolic activity, using their current, instead of preinjury, weight in the Harris Benedict equation may overestimate eREE and thus underestimate the degree of hypermetabolism.[75]

The causes of hypermetabolism during stress are multifactorial. Fever results in an increase of 11% in energy expenditure for each degree C increase in body temperature. In addition, the rate of metabolism is increased by the effects of the increase in energy-consuming processes such as gluconeogenesis and ureagenesis. Catecholamines infused into normal subjects increase the metabolic rate. This increase is even greater when cortisol, glucagon, and catecholamines are infused together. The significant hypermetabolism in head-injured patients has been ascribed to major sympathetic nervous system activation. This also occurs with other types of intracranial pathology. For example, for at least 5 days after subarachnoid hemorrhage, REE was 18% above eREE. The increased energy expenditure has also been ascribed to increased protein oxidation and synthesis. Yet this may not always be the case because after elective surgery there was only a modest change in energy expenditure, despite increased protein turnover. Another process that contributes to hypermetabolism is "futile substrate cycling" (see Fig. 95-7). Reducing the rate of the lipolysis/re-esterification futile cycle with β-adrenergic blockade reduced REE in burned children. The teleologic reason for the increase in futile cycling is that it affords patients the flexibility to adapt quickly to changes in energy substrate demands.

Environmental factors may also affect energy expenditure. Elevated ambient temperature (and humidity) has been shown to reduce the REE of burn patients by reducing evaporative losses and, in turn, reducing the need to generate energy to maintain body temperature.[76]

The Metabolic Responses to Sepsis

Unlike elective surgery, with the short-term stress of the surgery followed by a recovery period, sepsis is characterized by an ongoing stressful stimulus with systemic effects that can lead to multiple organ system dysfunction. The basic metabolic response observed during sepsis is similar to that after major surgery, burns, and trauma and in major nonseptic illnesses such as pancreatitis and serious transfusion reactions (e.g., blunting of the inhibitory effects of insulin on lipolysis and gluconeogenesis).[77] However, sepsis is further characterized by the presence of bacteria and bacterial components that initiate and sustain additional metabolic, inflammatory, immunologic, and coagulation responses.[78] This is demonstrated by the greater number of complement and coagulation proteins found in the plasma proteome profile of infected, as opposed to uninfected, critically ill trauma patients.[79] Such biochemical differences are important because they may serve as biomarkers to use in the early detection of active infection and for differentiating between sepsis/septic shock and the systemic inflammatory response syndrome (Table 95-3).

As part of the innate immune host defenses, Toll-like receptors recognize alarmins, either pathogen-associated molecular patterns (PAMP), which are products of bacteria, viruses, fungi, and protozoa, or intracellular proteins (damage-associated molecular patterns [DAMPs]) released by damaged cells.[80] Stimulation of Toll-like receptors (a group of pattern recognition receptors) activates transcription factor NF-κB and JNK (c-*Jun* N-terminal kinase) in immune cells, which initiate transcription of genes encoding proinflammatory cytokines. Interestingly, mice deficient in Toll-like receptors still succumb to sepsis, indicating that multiple pathways are active during sepsis. The type of infection influences the nature of the inflammatory response. Endotoxins (lipopolysaccharide) from gram-negative bacteria induce the production of TNF-α, IL-1, and IL-6, whereas exotoxin from gram-positive organisms increases IL-8 much more than TNF-α, IL-1, and IL-6.[81] Furthermore, septic shock produced a different cytokine profile than severe sepsis.[82] Viral infections produce different profiles from those produced by bacterial ones.

Table 95-3 Criteria for the Systemic Inflammatory Response Syndrome and Sepsis

Systemic Inflammatory Response Syndrome (SIRS)
Two or more of the following are required:
1. Body temperature > 38°C or < 36°C
2. Heart rate > 90 beats/min
3. Respiratory rate > 20 breaths/min or arterial $Paco_2$ < 32 mm Hg
4. WBC > 12,000 mm^3 or < 4000 mm^3 or > 10% immature forms

Sepsis
SIRS plus a documented infection site (documented by positive culture for organisms from that site). Blood cultures do *not* need to be positive. Although SIRS, sepsis, and septic shock are often associated with bacterial infection, bacteremia may not be present.

Severe Sepsis
Sepsis plus associated with organ dysfunction, hypoperfusion abnormalities, *or* hypotension. Hypoperfusion abnormalities include but are not limited to:
- Lactic acidosis
- Oliguria
- Acute alteration in mental status

Septic Shock
Sepsis-induced hypotension despite fluid resuscitation plus hypoperfusion abnormalities

Critical illness–related corticosteroid insufficiency—inadequate serum corticosteroid activity for the severity of illness—is reported to occur with some frequency in septic patients.[83] The cortisol concentration may be in the supranormal range and may or may not increase in response to additional ACTH stimulation. Annane and associates[84] found an incidence of 60% using metyrapone testing in severe sepsis and septic shock. The clinical presentation of this problem is usually reduced responsiveness to fluid and vasopressor therapy. It is also associated with increased mortality.[85] This relative adrenal insufficiency is acute and self-limited because it reverses on resolution of the acute illness. Its etiology is unknown but might be due to decreased ACTH or cortisol secretion and/or reduced end-organ sensitivity to glucocorticoids.[83] Therefore, the challenge is to find ways to easily and rapidly identify patients with this problem and determine whether glucocorticoid replacement improves outcome.[83] In a multicenter, randomized, double-blind, placebo-controlled trial of septic shock patients, 251 patients received 50 mg of intravenous hydrocortisone every 6 hours for 5 days which was then tapered over 5 days and 248 patients received placebo. There was no difference in either group in mortality between those who did and those who did not respond to an ACTH challenge. Although hydrocortisone did reverse shock more quickly than the placebo, it was associated with more episodes of superinfection.[83a] However, hydrocortisone did not improve survival.

Modulation of the Stress Response

Although the stress response evolved as a mechanism for assisting organisms in reacting to immediate danger, its effects may be detrimental to patients undergoing surgery or suffering from sepsis. For example, the hypercoagulable state intended to stem acute bleeding may lead to deep vein thrombosis and pulmonary emboli in immobilized patients. Furthermore, in extended stress situations the prolonged catabolism resulting from cytokine and stress hormone production leads to loss of fat and muscle with ensuing weakness and fatigue. This weakness and fatigue coupled with stress-related disordered immunologic function increases vulnerability to infections.

The detrimental consequences of the stress response have increased interest in aborting its appearance and/or actions. However, it is necessary to consider whether the goal of stress response modulation is full elimination or just attenuation. By eliminating the stress response, its beneficial effects, such as support of blood pressure by catecholamines in the face of hypovolemia or stimulation of cytokine production to enhance immunity, may be lost. Therefore, partial or selective suppression of the response may be more reasonable. In this manner some responses may be partly preserved, for instance the cardiovascular response to hypovolemia. Additional advantages of reducing certain consequences of the stress response include diminishing the degree of catabolism and lipolysis, thus reducing loss of muscle and fat mass. One approach tried in septic patients was selective mediator blockade. A prime example was anti-cytokine therapy (e.g., anti-TNF antibodies, IL-1 receptor antagonists) during sepsis and septic shock. The results of such therapy were disappointing because they not only failed to demonstrate any improvement in survival but, in some instances, even reduced survival. Postulated mechanisms for these failures include the possibility that targeting a single mediator may not be sufficient to block the wide-ranging ongoing biologic cascade. Another possible reason is that cytokines have beneficial immunoenhancing effects that assist the organism in combating infection. Impeding these effects thus leads to decreased immune function, causing increased mortality. Therefore, any attempt at modulating the stress response must be monitored for detrimental effects.

The Preoperative Stress Response

Patients undergoing elective surgery often suffer from preoperative anxiety, a state of psychological stress involving low-level activation of the hypothalamic-pituitary axis and possibly cytokines.[86] Evidence for such early activation comes from the observation that salivary cortisol increases by 50% after receipt of information about surgery.[87] Other studies show that both β-endorphin and epinephrine concentrations increase preoperatively. It is unclear whether this preexisting activation of the stress response has an additive effect on the subsequent stress response induced by surgery.

Preoperative medication is given to temper anxiety, thus attenuating the stress response. Midazolam as a premedication reduces anxiety and limits increases in intraoperative epinephrine and, possibly, norepinephrine and cortisol. Although it is unknown how benzodiazepines exert their activity, patients receiving benzodiazepines produce cortisol in response to exogenous ACTH, supporting the contention that the benzodiazepines exert their effect at a higher level, that is, on the hypothalamus or pituitary. Heavy premedication with a combination of opioid and antihistamine or opioid, anticholinergic agent, and benzodiazepine more successfully blunted serum catecholamine, AVP, ACTH, and cortisol increases than benzodiazepines alone.[88] Nonpharmacologic approaches to anxiety reduction have also been investigated. A number of studies have shown that music

reduces preoperative anxiety and thus may have practical applications.[89]

The Intraoperative Stress Response

Modulating the intraoperative stress response with anesthetics depends on various factors, including the type of anesthesia and surgery. Because it is nearly impossible to separate the effects of the anesthetics themselves from the stress response generated by the surgical injury, studies generally compare the effects of two or more anesthetic regimens on the overall stress response during a specific surgical procedure.

Inhaled Anesthetics

Volatile anesthetics minimally suppress the stress response. There is conflicting evidence as to whether volatile agents prevent surgically induced catecholamine secretion, although, among the volatile agents, enflurane is most capable of blocking intraoperative catecholamine surges. Both in the absence and presence of surgery, halothane and isoflurane failed to affect serum cortisol concentrations. However, sevoflurane attenuated the cortisol and ACTH responses to laparoscopic ovarian cyst removal.[90] During extended (>10 hours) inhaled anesthesia for head and neck surgery there were no differences in plasma cortisol, ACTH, insulin, or glucagon concentrations between isoflurane/nitrous oxide or sevoflurane/nitrous oxide anesthesia, although with sevoflurane, epinephrine and norepinephrine concentrations were attenuated during surgery and rose only after surgery.[91] Volatile anesthetics are generally ineffective in counteracting the metabolic responses (e.g., lipolysis) induced by surgical stimulation.

Intravenous Anesthetics

Some intravenous anesthetics partially modify the endocrine and metabolic components of the stress response. Sodium thiopental (5.0-5.1 mg/kg) does not prevent increases in catecholamine concentrations after intubation. However, many studies show lower epinephrine and norepinephrine concentrations when propofol (2.0-2.2 mg/kg), rather than pentothal, is used for intubation.[92] This finding is attributed to propofol's intrinsic ability to inhibit catecholamine secretion, possibly by decreasing catecholamine release from chromaffin cells. Propofol (1.5-2.5 mg/kg) also decreases cortisol concentrations during intubation. Etomidate does not affect metabolic responses except to decrease hyperglycemia. This is attributed to etomidate suppressing the adrenocortical response by blocking cortisol and aldosterone synthesis.

Compared with benzodiazepines, the α_2-adrenergic agonists clonidine and dexmedetomidine are more successful at blunting the hemodynamic and catecholamine responses to intubation and intraoperative stress. The α_2-agonists blunt the stress response by reducing norepinephrine release from central and peripheral nerve endings.[93] When 4.5 μg/kg of oral clonidine was given preoperatively, intraoperative plasma catecholamine concentrations were reduced. Similar doses reduced not only plasma but also cerebrospinal fluid (CSF) concentrations of TNF-α and norepinephrine.[94] Such doses also attenuated the intraoperative and postoperative hyperglycemic responses to minor surgery. Whether clonidine also attenuates the cortisol response is unclear.[95] Moreover, α_2-agonists, such as dexmedetomidine, do not suppress steroidogenesis.[96]

Opioids

Opioids are capable of blunting the stress response. Fentanyl (50 μg/kg) plus halothane and nitrous oxide abolished the elevations in cortisol, GH, and glucose normally seen during hysterectomy. Morphine (1 mg/kg) reduced GH and cortisol elevations during abdominal surgery. However, other studies show that the same dose of morphine was unable to suppress increased GH secretion during similar surgery. Opiates also decrease cytokine production. Propofol/alfentanil anesthesia when compared with isoflurane anesthesia caused lower IL-6 concentrations. These lower IL-6 concentrations are thought to occur because opioids bind to monocyte receptors and reduce intracellular cAMP concentrations. cAMP is necessary for monocyte secretion of IL-6.[97]

The limitation of the stress-reducing effects of opioids is most evident during cardiac surgery. Although high-dose fentanyl (50-200 μg/kg) and morphine (2-4 mg/kg) prevent pre–cardiopulmonary bypass increases in catecholamines and cortisol, during cardiopulmonary bypass both catecholamine and cortisol concentrations increase. Similarly, high-dose sufentanil (12 μg/kg induction, 3 μg/kg before skin incision, and 5 μg/kg before bypass) limited pre-bypass increases in catecholamines, cortisol, and AVP but failed to attenuate their elevation both during bypass and postoperatively. The reversal of the opioid-related stress-reducing effects by bypass is attributed to nonpulsatile blood flow, artificial surfaces of the bypass circuit, renin and angiotensin release, hypothermia, and dilution of the plasma opioid concentration.[98]

The mechanism by which opiates curb the stress response is unknown. One theory is that this action is mediated through hypothalamic and pituitary opiate receptors. This theory has been questioned because of the similar effects of fentanyl and sufentanil on the stress response despite the much greater affinity of sufentanil for brain opiate receptors. Both intravenous (50 μg then 20 μg every 30 minutes) and intrathecal high-dose (150 μg) sufentanil attenuated the intraoperative epinephrine and norepinephrine responses in patients undergoing general anesthesia for major abdominal surgery. However, only in the intrathecal group were the intraoperative ACTH and cortisol responses attenuated. Therefore, the unique actions of sufentanil may only be apparent on intrathecal administration.[99]

Although general anesthesia undoubtedly prevents an even greater stress response by rendering patients insensate to the discomfort and pain of surgery, it is unable to completely eliminate many manifestations of the stress response. This is ascribed to the inability of anesthesia to diminish or abolish the afferent nervous input from the area of the injury. Additionally, general anesthesia does not alter the effects of cytokines such as IL-6 and TNF, which are produced within the area of the wound.

Neuraxial Anesthesia

Neuraxial anesthesia is more effective than general anesthesia in attenuating the stress response (see Chapter 51). The ability of

such anesthesia to modify the intraoperative stress response depends on the level of the blockade, the location of the surgery, and the drugs used. Lower extremity surgery with epidural anesthesia results in lower intraoperative catecholamine concentrations when compared with general anesthesia.[100] These reductions in catecholamines may be caused by blockade of afferent nerve stimuli, reducing hypothalamic activation of the sympathetic nervous system and adrenal medulla. Further evidence for reduced hypothalamic activation is that epidural anesthesia to a T4 level successfully blunts increases in TSH. Similarly, during vaginal surgery, epidural anesthesia attenuates the usual increases in AVP.

Neuraxial anesthesia for lower abdominal and lower extremity surgery reduces or abolishes the hyperglycemic response to surgery, likely because of the lack of stimulation of hepatic glycogenolysis due to a reduced epinephrine response or blockade of hepatic sympathetic pathways or both. Reduced sympathetic and adrenal activity with epidural blockade also prevents normal intraoperative increases in free fatty acids and glycerol (lipolysis) during lower abdominal surgery. Further evidence that sympathetic blockade reduces intraoperative lipolysis is that during inguinal hernia repair lipolysis was reduced only once spinal anesthesia reached the T1-T3 sensory level. The influence of neuraxial blockade on cortisol secretion is less clear. Although neural blockade during lower abdominal surgery reduces the stress-induced cortisol response, whether the degree of suppression is similar to that of other hormones is still unclear. This may be due to the inability of epidural anesthesia to alter the IL-6 response to abdominal surgery,[101] suggesting that IL-6 secretion is neither mediated by nociceptive stimuli nor affected by sympathetic blockade. IL-6 increases pituitary ACTH secretion and thus stimulates cortisol secretion. Similar attenuation of catecholamine and cortisol secretion occurred when spinal cord–injured patients had surgery below their lesions.[102]

Neuraxial anesthesia more successfully reduces the stress response during lower abdominal than upper abdominal or thoracic surgery. There is a controversy whether T3-T4 epidural blockade can suppress surges in cortisol and catecholamine concentrations during upper abdominal surgery. Epidural blockade as high as C6 does not influence the cortisol response during upper abdominal or thoracic surgery. This was disputed when blockade extending from T3-T4 to L1-L2 significantly reduced the cortisol response during gastrectomies. Similarly, it remains uncertain whether epidural blockade for upper abdominal surgery alters lipid or protein metabolism, although it seems to partially suppress the hyperglycemic response.[103] These studies support the idea that regional anesthesia is unable to suppress the stress responses induced by upper abdominal stimulation. This lack of suppression is attributed to inadequate afferent sympathetic blockade, unblocked vagal afferent pathways, unblocked phrenic afferents, or locally released humoral substances. Others suggested that regional anesthesia that does not completely block afferent stimuli will not affect the hypothalamic-pituitary-adrenal axis because epidurally induced sympathetic block does not completely block neural traffic but just reduces it. Supporting this hypothesis, Tsuji and coworkers[104] found that the combination of epidural and splanchnic blockade (injection of 45 mL of 0.5% bupivacaine directly into the splanchnic plexus) during upper abdominal surgery reduced both the catecholamine response and plasma cortisol concentrations more effectively than epidural alone. Similarly, continuous spinal local anesthetic infusion more successfully attenuated the cortisol and glucose responses to upper abdominal surgery than epidural anesthesia presumably by better blockade of afferent nerves.

Another possible explanation for the inability of epidural anesthesia to attenuate the response to upper abdominal surgery is stimulus transmission through unblocked vagal afferent nerves. However, no attenuation of the stress response is seen after either vagal blockade or surgical vagotomy. Evidence for phrenic nerve involvement comes from Segawa and associates who showed that epidural blockade to the C3-C4 dermatome level during upper abdominal surgery more successfully blunted increases in ACTH and AVP than did C8-T2 blockade.[105]

The drugs used for regional anesthesia also influence the ability to affect the stress response. Epidural opiates are unable to prevent catecholamine surges. Increases in catecholamine concentrations were limited by 2-chloroprocaine and bupivacaine but not by lidocaine. This difference may be due to the central stimulatory effects of lidocaine.

Combined General and Neuraxial Anesthesia

Combined general anesthesia and neuraxial anesthesia should reduce the stress response if the general anesthetic is sufficiently deep to attenuate the stimulation of the endotracheal tube. For example, both desflurane/epidural (sensory block T4-S1 with 10 mL/hr infusion of 0.25% bupivacaine) and desflurane/remifentanil (bolus 1 μg/kg then an infusion of 0.125 μg/kg/min) anesthesia for colorectal surgery resulted in less glucose production and less hyperglycemia compared with desflurane alone.[106]

The effect of combined general and epidural anesthesia in patients undergoing coronary artery bypass grafting has been extensively studied. Patients receiving fentanyl anesthesia plus thoracic epidural bupivacaine (10 mg [5 mg/mL] every 4 hours) during coronary artery bypass grafting have lower epinephrine and norepinephrine levels both intraoperatively (including during bypass) and postoperatively compared with controls receiving only large doses of fentanyl. There are conflicting results as to whether the cortisol response is also reduced, although the cytokine response is not affected. Combined general and epidural anesthesia for cardiac surgery lessened myocardial damage, as evidenced by decreased troponin-T release. This effect may be secondary to the ability of epidural anesthesia to attenuate myocardial sympathetic stimulation, although a meta-analysis did not show fewer myocardial infarctions or lower mortality.[107]

Thermoregulation

Another way of minimizing the stress response is maintaining perioperative normothermia (see Chapter 48). Intraoperative hypothermia followed by postoperative rewarming stimulates the response. Hypothermic patients (35.3°C core temperature) had higher postoperative plasma norepinephrine and epinephrine concentrations than their warmer counterparts.[108] These elevated catecholamine concentrations are partially the result of postoperative rewarming with shivering and vasodilatation that leads to hypotension. Elevated catecholamines have been postulated to be among the reasons for the greater incidence of myocardial

ischemia after vascular surgery in hypothermic patients. There are thus several reasons to maintain intraoperative normothermia.

The Postoperative Period

The intraoperative attenuation of the stress response by anesthesia is often lost on emergence from anesthesia because of pain and awareness coupled with a series of stress-producing events (tracheal extubation, shivering). This postoperative response was demonstrated by extreme elevations in plasma ACTH and cortisol immediately after surgery with isoflurane anesthesia. Likewise, after sevoflurane-nitrous oxide anesthesia, peak cortisol, ACTH, and catecholamine concentrations occurred after tracheal extubation, implicating anesthesia emergence as more stressful than surgery. This phenomenon may be especially marked with sevoflurane anesthesia because of its typical rapid emergence. Associated with these markedly elevated catecholamine concentrations is an increased incidence of myocardial infarction that peaks 24 to 48 hours after surgery.

Like inhaled anesthetic, general anesthesia with intravenous drugs does not prevent the postoperative stress response. Intravenous opioid anesthesia did not blunt the stress response in the late postoperative period (>3 hours). Abrogation of the suppressive effects of anesthesia on the stress response on emergence was further demonstrated when patients were deeply sedated with propofol for 12 hours after cardiac surgery with bypass. This sedation attenuated the rise in cortisol and catecholamines and was associated with less tachycardia and hypertension than in a control group. However, once propofol was discontinued, hormone concentrations rose, indicating that deep sedation only delayed the appearance of the stress response.[109] Therefore, unless therapy that suppresses the stress response is continued during and after emergence and extubation, the postoperative period is marked by full appearance of the stress response.

After lower abdominal surgery, continuous postoperative analgesia via an epidural catheter using local anesthetics reduced the stress response. For example, continuous epidural analgesia (sensory block of T4-S5) for 24 hours after colorectal surgery successfully blunted increases in catecholamine, but not cortisol, concentrations. A similar regimen given for 24 hours after hysterectomy resulted in lower glucose and free fatty acid concentrations than did general anesthesia. Furthermore, better nitrogen economy was seen in hip replacement patients provided with 24 hours of epidural local anesthetics (sensory level: T10), than in patients administered only general anesthesia. This occurred with postoperative local anesthetic doses that provided only analgesia and not anesthesia. Similarly, combined spinal-epidural anesthesia during hip replacement with postoperative epidural analgesia (ropivacaine/sufentanil) resulted in reduced leucine oxidation rate on the first postoperative day while hyperglycemia was prevented only intraoperatively.[110] Attenuating the stress response with continuous postoperative epidural analgesia was more successful in lower than upper abdominal surgery, a finding similar to the observations during intraoperative epidural anesthesia. Yet, there are reports of stress response reduction after upper abdominal surgery. For example, after abdominal aortic surgery epidural morphine reduced the postoperative sympathetic, but not adrenal epinephrine, response, thus reducing the incidence of postoperative hypertension. However, neither epidural ropivacaine nor epidural morphine analgesia suppressed the catabolic response when administered to postoperative colonic surgery patients but ropivacaine did increase the carbohydrate oxidation rate, likely reflecting reduced insulin resistance.[111] The reduced insulin resistance coupled with decreased gluconeogenesis led to less hyperglycemia.[111] Therefore, pain control with epidural opioids or local anesthetics is unable to lessen many of the metabolic changes associated with such surgery.[112] However, combined epidural opioid/local anesthetic analgesia appears more effective in attenuating catabolism.[112a]

Whether modifying the stress response improves outcome is unclear. Ideally, one of desired effects of anesthesia is a "stress free" state, and achieving such an effect has become increasingly important as the stress response is more frequently implicated in the development of postoperative complications, especially among chronically ill and aging patients.[113] However, contemporary anesthesia practice can only partially modify this response and then only under specific conditions. General anesthesia has a very limited ability to attenuate the stress response whereas regional anesthesia is more effective. Therefore, it stands to reason that outcome would improve with regional anesthesia. A meta-analysis showed decreased mortality with regional anesthesia as opposed to general anesthesia in a variety of surgical procedures. However, this analysis has been criticized because it seems that only orthopedic patients had improved outcomes. Furthermore, morbidity studies demonstrated that under some circumstances epidural anesthesia reduces postoperative complications, such as deep vein thrombosis.

Attempts to modulate the perioperative stress response include nonanesthetic approaches (e.g., using β-adrenergic antagonists to block cardiovascular end-organ receptors) and α_2-adrenergic agonists to stimulate central receptors. These approaches have met with some success. Using β-adrenergic antagonists in patients with ischemic heart disease does not reduce the perioperative neuroendocrine or endocrine stress response but just blocks the end-organ response. Such end-organ blockade also has metabolic affects. Administering propranolol to severely burned children decreased their resting energy expenditure, attenuated muscle catabolism, reduced lipolysis, preserved lean body mass, and reduced TNF and IL-1 concentrations without increasing infections.[114] Hepatomegaly due to fatty liver was prevented because reductions in both lipolysis and hepatic blood flow decreased fatty acid delivery to the liver.[115] Mortality was unaffected by propranolol.[114] In severely septic patients selective β_1-adrenergic blockade had no affect on REE or muscle protein kinetics,[116] indicating that attenuation is due mainly to β_2-receptor blockade. However, it is important not to continue the β-blockade into the anabolic period because β-adrenergic activity might be important in muscle tissue restoration.[117]

Another nonanesthetic modulation of the stress response is administering a single preoperative dose of exogenous glucocorticoids. Administration of intravenous methylprednisolone (30 mg/kg) 60 to 90 minutes before the start of major abdominal, hepatic, and esophageal surgery reduced the stress response with lesser increases in IL-6, CRP, norepinephrine, and AVP and increased secretion of IL-10. A meta-analysis of 51 studies in which a single dose of methylprednisolone (15 or 30 mg/kg) was given showed no increase in complication rates.[118] Further study is needed to determine whether this approach significantly affects outcome. Similarly, methylprednisolone treatment before cardiac surgery attenuated cytokine secretion.

The inability of any one modality to reduce the stress response and significantly alter outcome has spawned the "multimodal" approach. The aim is to shorten the convalescence period and reduce the postoperative decline in functional status by improving pain control, early return of gut function, and early mobilization. This approach involves combining some or all of the following: premedication (benzodiazepines, β-blockers, α_2-agonists), preoperative carbohydrate intake, glycemic control, maintenance of normothermia, combining epidural anesthesia/analgesia and nonsteroidal anti-inflammatory drugs, avoiding opioids, early oral feedings or parenteral nutrition, and early mobilization after major abdominal surgery.[119,120] Such a regimen permitted 32 of 60 colorectal resection patients to go home within 48 hours of surgery and in a study of anterior colon resection reduced the hospital length of stay from 10 to 7 days.[121] Radical cystectomy patients anesthetized with general and thoracic epidural anesthesia and postoperative thoracic epidural analgesia and treated with early oral nutrition and forced mobilization had lower urinary catecholamines, less negative nitrogen balance, earlier return of bowel function, and a lower acute-phase response than conventionally treated patients.[119] The multimodal approach to modulating the perioperative stress response has much logic and practicality and, coupled with noninvasive surgery, has the potential to change postoperative care.

Glucose Control

Hyperglycemia appears almost immediately after the start of a major stress secondary to insulin resistance and accelerated endogenous glucose production. Administering exogenous catecholamines and glucocorticoids exacerbates this hyperglycemia. The teleologic explanation for the elevated blood glucose concentration is that it provides the wound and other glucose-dependent tissues with a ready supply of glucose. Experience gained from diabetic care showed the many problems caused by chronic hyperglycemia and the advantages of tightly controlling blood glucose concentrations. This experience was the impetus for exploring whether tight glucose control is also advantageous in the acute hyperglycemia associated with surgical, traumatic, and septic stress.

Acute hyperglycemia is associated with immunosuppression, stimulated sympathoadrenergic activity, increased mortality, increased infections, reduced skin graft success, increased catabolism in burn patients, and osmotic diuresis leading to volume depletion.[121-124] These effects are ascribed to the proinflammatory actions of glucose attributed to increased secretion of TNF-α and IL-1, greater adherence and sequestration of neutrophils in peripheral tissue, impaired microvascular relaxation in the presence of nitric oxide, and decreased monocyte HLA-DR expression reflecting reduced innate immunity.[125] The proinflammatory cytokine response to endotoxin infusion in normal subjects was enhanced by concomitant hyperglycemia.[126] These observations question whether elevated blood glucose concentrations are themselves detrimental or whether hyperglycemia is just a marker of severe stress. Hyperglycemia on hospital admission in trauma victims portends greater mortality, whereas hyperglycemia in both diabetic and nondiabetic cardiac surgery patients is associated with a higher incidence of infections. Moreover, Van den Berghe and associates[122] showed reduced mortality in surgical (mainly cardiac surgical) patients treated with intensive insulin therapy to maintain euglycemia (≤110 mg/dL). Compared with conventional therapy, the aggressive insulin therapy reduced ICU mortality (especially from multiple organ failure) by 43%, sepsis by 46%, and acute renal failure requiring dialysis or hemofiltration by 41%. Also, aggressively treated patients in the ICU for more than 7 days had less critical illness polyneuropathy/myopathy.[127] These results led to the additional question of whether it is the lowering of the blood glucose concentration or the administration of insulin, an anabolic and anti-inflammatory hormone, that reduces morbidity and mortality. Further studies suggest that avoiding hyperglycemia is associated with beneficial effects, since the total amount of insulin administered correlated with increased mortality regardless of the blood glucose concentration.[128] The latter observation indicates that a major determinant of mortality and morbidity is the severity of the critical illness, as demonstrated by the degree of tissue insulin resistance and hence the amount of insulin needed to control blood glucose. Therefore, it is the avoidance of hyperglycemia rather than the insulin administered for its correction that is beneficial.

The beneficial effects of lowering blood glucose concentrations with intensive insulin therapy are ascribed to abrogation of the proinflammatory actions of hyperglycemia (e.g., when somatostatin inhibited insulin release during the infusion of glucose in normal subjects, TNF-α and IL-6 concentrations increased[129]) along with the anti-inflammatory effects of insulin; protection of the mitochondrial compartment and endothelium; lower serum cortisol concentrations; and increased secretion of anti-inflammatory hormones such as IL-4 and IL-10.[130,131] Insulin is also thought to interfere with IL-6 signal transduction. In patients with myocardial infarctions, insulin suppresses the secretion of acute-phase reactants such as serum amyloid A and CRP.[132]

The enthusiasm for tight control of blood glucose in stressed patients must be tempered. There is the possibility of unrecognized hypoglycemia especially in sedated and mechanically ventilated patients. This concern is occasioned by the Van den Berghe study in which 5% of patients suffered a hypoglycemic episode, leading to recommendations that glucose be controlled to higher concentrations (<140 mg/dL).[122] Also, under some circumstances insulin appears to have proinflammatory actions and upregulates NF-κB.[133] The increased insulin doses could also increase resting energy expenditure (REE) further. Another issue is whether all or only specific populations benefit from tight glucose control or from the increased glucose utilization caused by the high insulin doses. In patients staying 3 or more days in a medical ICU, tight control reduced mortality from 53% to 43%.[134] Hyperglycemia is especially problematic in head trauma, and settings of cerebral ischemia. Glucose-insulin treatment might be beneficial in myocardial infarction/ischemia. A meta-analysis incorporating 8432 patients in 29 studies concluded than in critically ill patients, tight glucose control (<110 mg/dL and <150 mg/dL) was not associated with significantly decreased mortality, but increased risk of hypoglycemia.[134a]

Nutritional Support

The Perioperative Period

During the perioperative period there are many nutritional considerations. Patients are routinely fasted for 6 to 8 hours before surgery and thus present to the operating room in a postabsorp-

tive state with decreased insulin/glucagon ratios, utilizing their glycogen stores to provide tissues with glucose. Whether this is an appropriate metabolic milieu to surgically stress an individual has been questioned. Therefore, the utility of providing carbohydrates (50 g) either orally (maltodextrins) or intravenously (glucose) 2 hours before surgery was examined. Such carbohydrate intake increased insulin concentrations to those observed after a meal, reduced postoperative insulin resistance by about 50%, and decreased postoperative gluconeogenesis and nitrogen loss. However, the degree of postoperative hypermetabolism and cytokine activity was unchanged, whereas hospital stay after colorectal and other surgery appeared to be reduced.[135,136]

Immediately after surgery patients traditionally receive infusions of 5% dextrose (glucose monohydrate), which provide 50 g/L dextrose or 170 kcal/L (dextrose provides 3.4 kcal/g). Therefore, patients receiving 2 to 3 L/day of 5% dextrose are essentially being semi-starved. The rationale for infusing small amounts of dextrose is its protein-sparing effects (i.e., reduced gluconeogenesis, which decreases the need for proteolysis, leading to lower urinary nitrogen losses). In normal subjects, nitrogen losses decrease linearly as the amount of dextrose administered increases, up to an intake of 150 g/day. More than 150 g/day of dextrose results in no further protein sparing unless protein and fat are also provided. In addition, small amounts of carbohydrate (100 g/day) prevent ketosis.[55] However, the ability of exogenous glucose to suppress gluconeogenesis is diminished during stress. An infusion of 2 g/kg/min glucose during the first 3 hours of surgery reduced endogenous glucose production by 60%, as opposed to 90% reduction in preoperative patients.[120] In addition, 5% dextrose infusions contribute to hyperglycemia. Dextrose regimens should only be continued for a few days (4-6 days) after surgery, until the patient can resume oral intake. Patients unable to begin oral intake after such time should be evaluated for enteral or parenteral nutritional support.

Efforts have been directed at finding ways to improve the effectiveness of hypocaloric amounts of glucose administered during the postoperative period. When compared with an intravenous pain regimen, the greater pain relief provided after abdominal surgery by continuous intraoperative and postoperative epidural blockade with local anesthetics and opioids (0.1% bupivacaine plus 2 μg/mL fentanyl to a T7-L3 sensory block) further decreased endogenous amino acid oxidation and increased whole-body glucose uptake by decreasing insulin resistance.[137,138] These results are not unexpected because pain itself induces insulin resistance and contributes to the catabolic state after surgery.[139] Furthermore, epidural analgesia reduces the duration of postoperative ileus (thoracic > lumbar, local anesthetics > opioids), allowing earlier resumption of oral intake.[140]

Postoperative protein sparing has been attempted with hypocaloric amino acid infusions. The idea is to provide small amounts of exogenous amino acids as gluconeogenic substrate (1 g produces 0.5 g of glucose) while avoiding the hyperglycemia seen during 5% dextrose infusions. However, there is a limit to how much protein can be used as an energy source and postoperative amino acid infusions decreased gluconeogenesis only slightly (8%-12%), although they suppressed protein breakdown, reduced IGF-1 decreases, and stimulated protein synthesis.[141,142] There appear to be no advantages of administering amino acids instead of 5% dextrose.

Another use of intraoperative amino acid infusions are as thermogenic agents that are started either a few hours before surgery or after anesthesia induction to prevent or attenuate intraoperative hypothermia.[143] During anesthesia, the central thermoregulation is silenced, leading to exaggerated amino acid thermogenesis. Amino acid–induced heat generation during anesthesia occurs mainly in extrasplanchnic tissues, such as skeletal muscle, and is attributed to greater amino acid turnover because both protein breakdown and synthesis are energy-consuming (heat-generating) processes.[144] Such infusions reduced the body temperature decline during spinal anesthesia by 0.5° to 0.8°C.[145,146]

Indications for Nutritional Support

The primary indication for initiating nutritional support is preventing or treating malnutrition among patients unable or unwilling to sustain sufficient oral intake. From 20% to 35% of hospitalized patients suffer from malnutrition on admission or during their stay. Therefore, nutritional assessment and decisions about nutritional support should be a routine part of the ongoing care of all hospitalized patients. A major consideration when contemplating providing nutritional support to an individual patient is whether the nutrition will improve prognosis or the quality of life, since nutritional wasting is the inevitable consequence of many terminal diseases.[147] Another important aspect of providing nutritional support to stressed patients is that their already altered metabolic milieu greatly affects nutrient utilization and metabolism. In addition, critically ill patients with recurrent bouts of sepsis have an ongoing proinflammatory response that contributes to continued catabolism. Therefore, during the acute phase of stressful illness, nutritional support is an adjunctive therapy whose goal is to provide energy substrates to aid cellular functions and attempt to stem losses of lean and fat mass. Repletion of lost fat and muscle tissue must wait until the anabolic phase of the illness.

Preoperative malnutrition is associated with poor surgical outcome owing to a more severe systemic inflammatory response and more postoperative infections.[148] Yet it has been difficult to demonstrate any benefit of preoperative parenteral nutrition in malnourished patients except those severely malnourished, who had fewer noninfectious postoperative complications after 7 to 10 days of preoperative nutritional repletion. In such patients it is also beneficial to continue TPN during and after surgery. A systematic literature review found that the only preoperative TPN that was beneficial was the TPN administered to patients undergoing curative surgery for upper gastrointestinal cancer because it reduced major postoperative complications.[149] Postoperative nutritional support is not indicated unless it is anticipated that patients will be unable to resume adequate oral intake within 7 to 8 days after surgery. Patients not expected to resume adequate oral feedings by this time should begin nutritional support soon (2-4 days) after surgery. Evidence includes a study in which enteral nutrition started within 3 to 4 days of surgery reduced infectious complications after hepatectomy. A meta-analysis of 11 studies of patients after elective gastrointestinal surgery showed that early oral/nasoenteral/jejunostomy feeding started within 24 hours after surgery, compared with no nutrient intake, decreased infection rate and demonstrated a trend to less anastomotic breakdown but an increase in vomiting.[150] Similarly, a systematic literature review concluded that although many patients undergoing pancreaticoduodenectomy are nutritionally depleted before

surgery, routine postoperative TPN is not recommended because of the complication rate. However, postoperative EN is recommended.[151]

Mechanically ventilated ICU patients have a malnutrition rate of 38% to 100%.[141] Therefore, nutritional support guidelines recommend starting enteral nutrition early, that is, within 24 to 48 hours of ICU admission, to reduce infectious complications and duration of hospitalization.[152] Patients unable to tolerate enteral intake should be considered as candidates for TPN.

Parenteral versus Enteral Nutrition

A major decision when designing a nutritional support regimen is the route of administration. If patients are eating on their own, it is necessary to monitor their intake to ascertain its adequacy. Many patients have little appetite and thus may need nutritional supplementation between meals (snacking) to increase their caloric intake. Patients may be unable to feed themselves because of confusion or weakness and may need to be fed. During eating the intake of patients with severe chronic obstructive pulmonary disease (COPD) may be limited by arterial oxygen desaturation, causing fatigue. Such patients may require supplemental oxygen via nasal cannula while eating. Patients who fail to sustain adequate caloric intake by eating require either supplemental enteral or parenteral nutrition.

The enteral route is generally favored over the parenteral one because it is the natural portal of entry for exogenous nutrients. However, current evidence does not fully support this view except that enteral nutrition costs less.[153] The enteral route obviates the need for intravascular access with its attendant risk of infections and sepsis. In addition, the array of nutrients that can be administered via the gastrointestinal tract is greater than what is available for parenteral use, allowing for better tailoring of nutrient intake. Other advantages of enteral nutrition are ease of preparation and maintenance of gut function. The importance of maintaining gut integrity (the gut derives up to 70% of its nutrients from luminal food) is to reduce the translocation of bacteria from the gut. Animal studies showed that translocation of bacteria from intestines with reduced integrity and increased permeability leads to local activation of the gut's immune inflammatory system (Peyer's patches and hepatic Kupffer cells). These cells then release cytokines that intensify the already existing systemic inflammatory response, increasing the risk for multiple organ failure. However, there is no overwhelming evidence of significant translocation in humans.[154] Lack of enteral intake, such as occurs among postoperative and critically ill patients receiving no nutrition or only TPN, is associated with small intestinal villous atrophy, decreased villous cell count, and reduced mucosal thickness. Intestinal permeability, measured using the urinary lactulose-mannitol ratio, is increased. These changes reverse with enteral feeding. Interestingly, there was no evidence of mucosal atrophy among patients who had received 10 days of preoperative parenteral nutrition. It is thought that atrophy itself does not lead to bacterial translocation but that a further insult is needed. One such insult is small intestinal ischemia-reperfusion injury after resuscitation from an episode of shock, which by itself can change gut integrity.[155] This is supported by the observation that the incidence of bacterial growth from surgically removed mesenteric lymph nodes was higher in patients undergoing emergency surgery. Patients with such lymph nodes more commonly had postoperative sepsis.[156] Moreover, in a stressed patient it is possible that constantly proliferating gut epithelial and lymphoid tissues may have an insufficient nutrient supply, further compromising gut integrity. The fear of reduced gut integrity along with studies showing preserved xylose absorption in enterally, but not parenterally, fed neurosurgical patients has been among the reasons for recommending that enteral nutrition begin early even if only very small amounts can be administered. In the latter case, concomitant TPN is indicated to provide adequate caloric intake.[156a]

A major decision with enteral nutrition is the delivery method. Most patients are initially fed via nasoenteric tubes, including large-bore tubes. The advantages of the latter include the ability to quantify residual feedings and quickly reinitiate nasogastric suction. The disadvantages are the potential for pulmonary aspiration occasioned by gastroparesis and incompetence of the gastroesophageal junction due to the diameter of the tube. Additionally, long-term use of large-bore tubes can lead to sinusitis and otitis media. Therefore, the type of feeding tube and the location of its distal end are major issues. For medium and long-term feeding it is best to use a small-bore (8 to 12 Fr), soft (e.g., Silastic), long (to reach the jejunum) feeding tube with a weighted distal end. Such tubes reduce nasal and pharyngeal trauma and minimize gastroesophageal junction incompetence. Gastroparesis is common in critically ill patients so that placing the tube distal to the ligament of Treitz (small intestinal function generally remains intact) prevents pooling of feeds in the stomach with its risk of pulmonary aspiration.[145] Yet, there is controversy as to whether jejunal feeding actually reduces the risk of aspiration. Compared with gastric feedings, jejunal feedings facilitate higher caloric intakes. Passing the tube through the pylorus is often problematic because of gastroparesis and a supine and immobile state. Therefore, if possible, the tube should be passed through the pylorus during abdominal surgery. In nonsurgical situations an attempt may be made to pass a weighted tube through the pylorus by placing the tube in the stomach, turning the patient on the right side, and administering a prokinetic drug (e.g., metoclopramide). If that fails, the tube should be placed endoscopically or fluoroscopically.

Placing a jejunostomy tube during surgery is recommended in patients not expected to eat soon after surgery (e.g., severe trauma, major head injury, and esophageal surgery). Patients fed through nasoenteric tubes who will require prolonged enteral feeding (>4 weeks) should have either gastrostomies or jejunostomies placed surgically or percutaneously with endoscopic assistance. Percutaneous endoscopic gastrostomies (PEG) are commonly performed, and a modification is to place a jejunal tube through the PEG.

Parenteral nutrition is used when the enteral route is unable to provide or sustain sufficient caloric intake. Although it is preferable to use the gut, there are situations where parenteral nutrition is essential. Patients with short bowel syndrome require TPN after surgery and even for life if their residual bowel does not undergo sufficient adaptation to sustain adequate oral intake. Other absolute indications for TPN are small bowel obstruction, active gastrointestinal bleeding, pseudo-obstruction with complete intolerance to food, and high-output enteric-cutaneous fistulas (unless a feeding tube can be passed distal to the fistula). In partial large bowel obstruction it may or may not be possible to feed with a low residue diet. Relative indications for parenteral nutrition include nonhealing moderate-output enteric-cutaneous

fistulas; the need for bowel "rest" such as during inflammatory bowel flare-ups and acute radiation enteritis; marked abdominal distention and ileus due to intra-abdominal sepsis; continued distention after relief of intestinal obstruction; and chylothorax unresponsive to a medium-chain triglyceride diet. TPN is also indicated when the enteral route cannot provide enough nutrition.[157] In ICU patients this occurs because of diarrhea, vomiting, poor stomach emptying, feeding tube displacement, and interruption of feeding for diagnostic tests, procedures, and surgery.[158]

Parenteral nutrition is administered through either central or peripheral venous catheters. Peripheral veins cannot tolerate an osmolarity of more than 750 mOsm/L (the equivalent of 12.5% dextrose) so that the fluid volume that can be tolerated limits the caloric intake. Therefore, this route is used mainly for supplementation or short-term feeding. Central venous catheters are the main route of TPN administration. The preferred entry location is the subclavian vein, which provides a stable site, good patient acceptability, and lower infection rates than either the internal jugular or femoral routes. To minimize insertion and infectious complications a skilled individual should insert subclavian catheters under sterile conditions. The catheter should be a single-lumen catheter used only for TPN. Multiple-lumen catheters and multiple-purpose single-lumen catheters have high infection rates. For long-term use, tunneled Silastic Hickman-Broviac catheters, which have Dacron cuffs located at the proximal end of the tunnel to reduce infections, should be inserted.

Formulations

Glucose and Carbohydrates

In injured and septic patients exogenous glucose and carbohydrates minimally reduce the rates of gluconeogenesis and lipolysis.[159] This differs from refeeding starved patients when carbohydrate administration reduces gluconeogenesis and lipolysis. Despite the reduced glucose utilization, it is still important to administer carbohydrates to stressed patients because some body tissues do not readily use other substrates. Furthermore, glucose and carbohydrate intakes stimulate the secretion of insulin, which has anabolic properties that promote protein synthesis and decrease lipolysis. However, hyperglycemia, even with aggressive insulin treatment, often limits how much glucose and carbohydrate can be administered. The severity of TPN-induced hyperglycemia is directly proportional to the rate of glucose infusion and degree of injury. The elderly are more predisposed to hyperglycemia.

It is important to recognize that patients often receive carbohydrates that are frequently administered from sources other than the glucose in TPN or carbohydrates in enteral nutrition. Patients usually receive 5% dextrose infusions (170 kcal/L) while intravenous lipid emulsions contain at least 22 g/L of glycerol, which enters the gluconeogenic pathway. Overfeeding glucose (>4 mg/kg/min) to acutely stressed patients receiving a total caloric intake greater than REE results in a thermogenic response, further elevation of blood glucose concentrations, and production of additional CO_2. This added CO_2 must be excreted by the lungs and if insufficiently excreted can lead to elevated $Paco_2$. Such overfeeding is not uncommon, as revealed by a survey of U.S. teaching hospitals where many patients are fed with more than 4 mg/kg/min of glucose.[160]

Lipids

Intravenous lipid is usually administered as a long-chain triglyceride (LCT) emulsion. These emulsions contain soybean oil and an emulsifier (egg phospholipid) and are calorically dense (e.g., 10% and 20% solutions contain 1.0 and 2.0 kcal/mL, respectively). Once infused, the lipid emulsion is converted to both triglyceride-rich particles with sizes similar to that of chylomicrons and phospholipid-rich particles produced from the emulsifier called liposomes. The chylomicron-like particles are hydrolyzed by lipoprotein lipase to fatty acids and glycerol. The liposomes stimulate cholesterogenesis, incorporate cholesterol, and accumulate in the blood as the long-lived abnormal lipoprotein-X.[161] To minimize liposome formation, lipid emulsions should be administered slowly. Lipid emulsions are also the vehicle for many lipid-soluble drugs such as propofol, amphotericin B, and etomidate. Therefore, propofol infusion for sedation can provide significant amounts of lipid calories, which should be included when calculating caloric intake.

Exogenous fat is required to prevent essential free fatty acid deficiency, so at a minimum patients receiving TPN should receive lipid emulsion (500 mL of a 10% LCT emulsion) two to three times a week. Lipid emulsion is also utilized for energy because lipid oxidation is the predominant energy-producing pathway during stress. Fat emulsions are well oxidized when administered to septic and trauma patients even when glucose is provided. Even patients with chronic hepatic failure suffering from sepsis and multiple organ dysfunction efficiently metabolize intravenous lipid emulsions. The current practice is to consider lipid emulsions as energy substrates and administer them as 30% to 40% of total TPN calories.

There is concern that lipid emulsions may have immunosuppressive effects. Ex vivo studies showed decreased neutrophil bacterial killing, depressed monokine expression, and other immune-depressant effects. A study of trauma patients attributed increased infections to lipid emulsion administration. However, a meta-analysis found no evidence that LCT lipid emulsions are detrimental to immune function.[162]

The soybean-derived LCT emulsions traditionally used for parenteral nutrition have high proportions of omega-6 polyunsaturated fatty acids, specifically linoleic acid (53%). Linoleic acid is the precursor of thromboxane A_2 and prostaglandin E_1, which cause platelet aggregation and inflammation. Alternatively, fish oils containing omega-3 fatty acids (e.g., eicosapentaenoic and linolenic acids) are precursors of different prostaglandins (e.g., thromboxane A3), which have less platelet aggregating activity and cause less inflammation. Platelets from patients infused for 7 days after surgery with fish oil–enriched lipid emulsions aggregated less than those of patients administered non-enriched emulsions.[163] Also, omega-3 fatty acids decreased the ex vivo production of IL-1, IL-6, and TNF by peripheral blood mononuclear cells. Oral eicosapentaenoic acid intake after surgery improved lymphocyte proliferation and NK cell activity. Enteral nutrition regimens enriched with eicosapentaenoic acid and γ-linolenic acid (which promotes production of anti-inflammatory prostaglandin E_1) have been used in the acute respiratory distress syndrome (ARDS) to reduce pulmonary microvascular permeability and decrease prostaglandin, IL-8, and leukotriene synthesis by alveolar macrophages.[164,165] These formulations are associated with shorter mechanical ventilation, decreased ICU stay, and lower mortality.[166]

The purported limitations of intravenous LCT emulsions has heightened interest in substituting medium-chain triglycer-

ides (MCT) for some of the LCT. MCT do not need carnitine to enter mitochondria and may be advantageous when there is decreased carnitine, such as during sepsis. MCT are essentially an energy substrate, and it is unclear whether they can be stored. MCT appears to have fewer immunosuppressive effects than LCT and do not participate in eicosanoid synthesis.[167] Many commercial enteral formulas contain both MCT and LCT, supposedly because MCT is better absorbed. Intravenous MCT/LCT emulsion is not available in the United States.

Protein and Amino Acid

Amino acids and protein are essential ingredients of nutritional support regimens. TPN contains commercially prepared amino acid mixtures, whereas enteral formulas contain free amino acids, peptides, or whole proteins. The purpose of administering protein or amino acids to stressed patients is to decrease the breakdown of endogenous proteins by providing an alternative source of amino acids for gluconeogenesis and protein synthesis. Unfortunately, in the stressed state, exogenously administered amino acids and protein are not well utilized because proteolysis is relatively unresponsive to the usual negative feedback mechanisms, such as the administration of exogenous glucose, protein, or amino acids. Nitrogen balance remains negative well into the convalescent stage. In the catabolic state an intake of 1.2 to 1.5 g/kg/day of protein/amino acids is recommended because higher amounts do not promote further nitrogen retention and are metabolized to urea, so the blood urea nitrogen may rise. Situations with large external losses of protein, such as extensive burns and large draining abscesses, make it necessary to increase protein/amino acid intake. Adequate nonprotein calories (i.e., glucose and fat) must be administered concomitantly so that the protein/amino acids are not used as an energy source.

The inability of protein/amino acids to significantly attenuate nitrogen losses led investigators to explore ways of decreasing proteolysis and increasing protein synthesis. An initial attempt was to use branched-chain–enriched amino acid solutions as a component of TPN. This resulted in some improvement in nitrogen balance[168] but no improvements in outcome. Some enteral nutrition formulas for highly stressed patients are so enriched.[169] Other attempts focused on administering anabolic substances to reduce protein oxidation and improve protein synthesis. One such substance is insulin, which at lower doses decreases protein breakdown by inhibiting the major catabolic pathway, the ATP-ubiquitin proteasome proteolytic pathway.[170] At higher doses it is thought to also stimulate protein synthesis. Administering small doses of insulin to burn patients increased skeletal muscle protein synthesis and improved wound matrix formation. However, the anabolic effects of insulin on protein metabolism were not observed in enterally fed trauma patients. Therefore, the route of nutrient intake may play a role in insulin's anabolic effects.

To help maintain gut integrity it has been recommended that glutamine be added to both enteral and parenteral nutrition. Glutamine is the most abundant free amino acid in the blood and skeletal muscle and is a primary fuel for rapidly dividing cells such as enterocytes and immunocytes and a precursor of purines, pyrimidines, and nucleotides. It is synthesized primarily in skeletal muscle and is involved in the interorgan transport of nitrogen. Plasma glutamine concentrations decrease during severe stress, probably secondary to decreased glutamine synthesis, providing a possible explanation why alanine is the major interorgan nitrogen transporter. Animal studies indicate that glutamine may become an essential amino acid during catabolic illness when de novo synthesis is insufficient. These studies also show that parenteral and enteral glutamine-supplemented nutrition may prevent gut bacterial translocation, induce neutrophilic phagocytic activity, reduce neutrophil apoptosis, and increase concentrations of the antioxidant glutathione. The data in humans are less compelling.

Glutamine is rather insoluble, so it is difficult to administer. Some success was achieved by infusing it as the L-amino acid, glutamine dipeptides, α-ketoglutarate, or alanyl-glutamate. TPN solutions enriched with glutamate, arginine, and aspartate increased glutamine concentrations. After elective abdominal surgery, TPN with added glutamine dipeptide reduces infections and shortens hospital stays.[171] A systematic review found a trend that TPN and enteral nutrition supplemented with glutamine reduce mortality, infections, and organ failure in critical illness. However, the evidence was of limited quality.[172]

Nutritional regimens require many ingredients (see Tables 95-2 and 95-4). Choosing the route of administration is the key decision, because the type and composition of the formula are wholly dependent on the route. With use of the parenteral route, protein intake is limited to commercial mixtures of amino acids, carbohydrate to glucose, and lipids to the available emulsions. With enteral nutrition, more options are available because a variety of commercial formulas exist. It is possible to supplement enteral formulas with modular protein, lipid, and carbohydrate products. Caloric intake may be determined by either measuring REE using indirect calorimetry or estimating requirements (see Table 95-2).

Complications

Complications of nutritional support can result from problems with the delivery system or the nutrition itself. Morbidity related to the delivery system or the nutrients occurs more often with enteral nutrition than with parenteral nutrition. However, infectious complications are more frequent greater with parenteral nutrition.

Complications of central venous catheterization occur with parenteral nutrition. These complications include pneumothorax secondary to subclavian or internal jugular vein catheterization. The pneumothorax rate for subclavian catheterization is 1% to 5% but is lower if performed by an experienced operator. Other complications include hemorrhage causing hemothorax, brachial plexus injury, and catheter misplacement in the azygos vein, right ventricle, or retrograde into the jugular vein. Peripherally inserted (via an arm vein) central venous catheters (PICC) have the advantage of obviating pneumothoraces but are more difficult to place and have a higher incidence of poor position and skin site irritation. Catheter tips should be above the left atrium and confirmed by chest radiography before starting nutrition. Peripheral venous access whether via a short peripheral venous catheter or a PICC line can result in thrombophlebitis. With short catheters the osmolarity of the solution must be limited to less than 750 mOsm to prevent phlebitis. To further prevent phlebitis, some clinicians add heparin and hydrocortisone to the solution, whereas others place a nitroglycerin patch over the catheter site. It is imperative that peripheral parenteral nutrition catheter sites be inspected regularly and catheters changed when evidence of phlebitis develops.

Table 95-4 Considerations When Designing Nutritional Support Regimens

Considerations	Requirements	Issues
Route of administration	Enteral vs. parenteral or both	
Caloric requirements	Measure REE with indirect calorimetry Estimate REE with established equations Use weight-based formula	See Table 95-3
Protein/amino acids	Evaluate degree of stress, measure nitrogen balance Parenteral nutrition—amino acid solutions Enteral nutrition—standard or high-protein formulas; amino acids (elemental diet) vs. peptides vs. protein hydrolysates. If protein losses are excessive, then need increased protein intake.	Unstressed patients: 0.8-1.2 g/kg/day protein Stressed patients: 1.0-1.5 g/kg/day protein
Calorie/protein ratio	Expressed as calorie/nitrogen ratio	Standard formulas: 150:1 Stress formulas: 125-100:1
Carbohydrates	Parenteral nutrition: glucose is only available nutrient Enteral nutrition: oligosaccharides and starches	Glucose intake not to exceed 4 mg/kg/min during stress.
Lipid	Parenteral nutrition: LCT emulsions (in some countries LCT/MCT emulsions are available) Enteral formulas: contain LCTs or LCTs/MCTs; some enriched with omega-3 fatty acids	Sufficient LCT to prevent fatty acid deficiency
Lipid/carbohydrate (CHO) ratio	Parenteral nutrition: lipid/CHO ratio 30:70 to 60:40 Enteral nutrition: depends on formula. Calorie-dense formulas (1.5-2.0 kcal/mL) have higher lipid/CHO ratios.	
Electrolytes	Parenteral nutrition: sodium (NaCl, Na acetate), Potassium (KCl, K acetate), PO_4 (KPO_4, $NaPO_4$) $MgSO_4$, calcium (Cagluconate) Enteral nutrition: as per formulation; may add electrolytes, if needed	Potassium: 1-1.2 mEq/kg/day Magnesium: 8-20 mEq/day Calcium: 10-15 mEq/day Phosphate: 20-30 mmol/day
Trace elements	Parenteral nutrition: copper, molybdenum, selenium, zinc, manganese, chromium Enteral nutrition: also contain iron, iodine	
Vitamins	Parenteral nutrition: commercial multivitamin preparations contain all vitamins (some do not include vitamin K). Enteral nutrition: contains all vitamins including vitamin K; the volume of formula that provides the recommended daily requirements depends on the formula. Fat-soluble vitamins: A, D, E, K Water-soluble: B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5 (pantothenic acid), B_6 (pyridoxine), folate, B_{12}, C	Need to monitor prothrombin time weekly and give vitamin K, if indicated. Vitamin C: increased requirements for wound repair
Water	Parenteral nutrition: dilute vs. concentrated formulas Enteral nutrition: standard (1.0 kcal/mL) vs. calorie-dense (2.0 kcal/mL)	Dilute for peripheral vein administration. Concentrated for fluid restriction or high caloric intakes
Disease-specific considerations	Renal failure Hepatic failure Pulmonary disease Burns Diabetes	See “Special Considerations” in text. See “Special Considerations” in text. Reduce absolute carbohydrate intake; substitute lipid for carbohydrates with high total caloric intake See “Special Considerations” section Control blood glucose and monitor serum triglycerides.
Congestive heart failure	Concentrated formulas, low sodium intake	

LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

Catheter-related infections are the major venous access complication encountered with TPN. Microbial colonization and bacteremia result from the interaction of four factors: (1) the hydrophobicity and exopolysaccharide production of the microbe, (2) the amount of fibrin and fibronectin attached to the catheter surface, (3) the catheter material (hydrophobicity, surface charge, thrombogenicity), and (4) iatrogenic factors such as sterile technique and immunocompetence. Infections are uncommon during the first 72 hours after insertion but then increase in incidence. The incidence of central venous catheter–related bloodstream infections ranges from 0.3 to 30 per 1000 catheter-days and are most often caused by *Staphylococcus epidermidis* or *Staphylococcus aureus* or *Candida* species. Mortality attributed to catheter-related infections is as high as 25%. A major part of TPN care is aimed at reducing infections. Therefore, solutions are prepared under laminar flow hoods. Once they are prepared, nothing may be added to the solution, they must be refrigerated until use, any manipulation of the catheter or line must be performed using sterile procedures, manipulation of the line should be kept to a minimum, and the site must be examined regularly for signs of erythema and infection.

Inserting nasoenteric tubes for enteral nutrition can result in complications because such tubes can enter the pulmonary airways, can coil and knot in the stomach, and fail to enter the stomach and thus remain in the esophagus. Therefore, it is vital to confirm the feeding tube location with chest and/or abdominal radiographs before starting the feeding. Nasoenteric tubes can be withdrawn into the stomach (in case of jejunal feeding) or the esophagus, increasing the risk for aspiration. Such tube misplacement occurs because of patients pulling on the tube and during suctioning of the mouth. Therefore, the tube should be securely fastened to the nose and if any dislodgment is suspected, a radiograph should be obtained. The major problem with enteral nutrition is frequent decreases or discontinuations of the intake, which prevent administering of all the daily caloric requirements. These decreases and discontinuations have been ascribed to high gastric residuals, mechanical problems with the feeding tubes (e.g., dislodgment into the esophagus and obstruction), medical or surgical procedures, sepsis, and vomiting. As many as a third of patients receiving enteral nutrition are unable to achieve a target intake of 25 kcal/kg/day. Therefore, it is important to closely monitor the actual enteral nutrition intake so that measures can be taken to ensure adequate caloric intake. These include establishing more secure access to obviate or prevent tube dislodgment (e.g., placing a PEG) and placing the tube tip distal to the ligament of Treitz to avoid gastric residuals. In cases in which the enteral intake remains inadequate, supplementing with parenteral nutrients should be considered.[173] A cumulative caloric debt may occur in patients not fed early and adequately. Therefore, it is important to monitor caloric intake and try to avoid caloric deficits.[153]

In general, surgically placed needle jejunostomies provide safe and effective access for postoperative enteral feeding. However, complications may occur, including tube dislodgment, local cellulitis, and obstruction. Obstruction can be avoided by frequent flushing and limiting the viscosity of the feeds. Major complications were seen in 4% of 220 trauma patients who had jejunostomies placed during laparotomy. These complications included small bowel perforations, small bowel volvuli with infarction, intraperitoneal leaks, and small bowel necrosis.[174,175] Small bowel necrosis has a mortality rate approaching 100%.[176] These complications occurred more often with larger diameter tubes than needle jejunostomies.[174] Others have reported intra-abdominal and subcutaneous abscesses and small bowel obstruction. Other complications include catheters breaking especially at the hub and jejunocutaneous fistulas on removal.

Metabolic Complications

Nutrition support should be initiated slowly and increased only if the patient tolerates the feeding. Because metabolic complications of nutritional support occur frequently, it is important to monitor electrolytes and glucose daily in acutely ill patients, particularly when starting the nutrition. If necessary, adjustments should be made in the formulation. Hyperglycemia is a common problem, especially with severe stress, steroid use, and diabetes mellitus requiring treatment with insulin. It is preferable to administer insulin than to reduce the glucose intake unless there is excessive hyperglycemia (>250 mg/dL) despite high insulin doses. Insulin treatment can reduce serum potassium and phosphate concentrations, which require repletion. Importantly, as the stress response abates, the degree of glucose intolerance lessens and insulin requirements drop. Therefore, it is imperative to monitor blood glucose closely to prevent hypoglycemia.

Hypoglycemia can occur on the abrupt discontinuation of continuous feedings containing significant amounts of carbohydrate. Continuous feedings result in high blood insulin concentrations so that hypoglycemia intervenes when the carbohydrate intake stops. Therefore, when stopping continuous parenteral and enteral nutrition, any concomitant insulin infusion must be stopped, intravenous glucose should be infused, and blood glucose monitored frequently. The practice of using TPN solutions containing lower glucose:lipid ratios (70:30 to 50:50) has reduced the incidence of hypoglycemia after abrupt discontinuation. TPN should be continued during surgery, whereas enteral nutrition should be discontinued 8 hours before surgery and a glucose infusion begun to prevent hypoglycemia.

Refeeding

Refeeding nutritionally depleted patients (≥10% loss of body weight over ≤6 months) must be done carefully so as not to overload a metabolic system that has adapted to minimal or no food intake. Feeding such patients must begin with balanced diets of carbohydrates, fats, and proteins at intakes below REE. The intake should be increased stepwise over a week to 10 days. Intake must be monitored to prevent overindulgence because these patients may be hyperphagic. Patients must be monitored for signs of fluid overload, pulmonary edema, and electrolyte disturbances. Hypophosphatemia occurs when tissues begin to rebuild and is especially problematic if inadequate phosphate intake is provided ("the refeeding syndrome"). Hypophosphatemia may lead to major muscle (including respiratory muscle) weakness and glucose intolerance because phosphate is a vital component of tissue membranes, enzymes, and nucleosides, especially ATP. Concurrent hypomagnesemia, hypocalcemia, and hypokalemia may exacerbate the muscle weakness. Thirty-four percent of 62 patients who had not received nutritional intake for at least 48 hours after ICU admission developed hypophosphatemia (serum levels < 0.65 mmol/L or a drop of 0.16 mmol/L) on refeeding. Chronic alcoholics are especially prone to hypophosphatemia.

Nitrogen balance may take a while to turn positive because of the need to gradually increase protein intake and because glu-

coneogenesis continues for some time after the beginning of refeeding. Generally, nutritionally depleted individuals efficiently replete fat and glycogen stores and rebuild muscle tissue. To rebuild muscles requires exercise so that it is virtually impossible to rebuild the muscles of bedridden or immobile patients.

Overfeeding

Overfeeding stressed patients has many consequences (Table 95-5).

Table 95-5 Consequences of Overfeeding in Parenteral and Enteral Nutrition

Caloric Intake	Substrate in excess of energy needs and synthetic function
>1.5-1.7 REE in stressed patients	Increased fat storage, CO_2 production, urea production and thermogenic effects
Carbohydrates	
>4.5 mg/kg/min	*Lungs:* Increased CO_2 production leads to: Increased $\dot{V}_E$, which may lead to breathlessness. If increase in $\dot{V}_E$ insufficient, then increased $Paco_2$. *Liver:* Fatty liver: increased AST, ALT, and alkaline phosphatase, hepatomegaly *Hyperglycemia*: may lead to osmotic diuresis and prerenal azotemia *Increased intracellular potassium*: decreased serum potassium *Increased intracellular phosphate*: decreased serum phosphate *Increased REE* due to increased thermogenesis caused by increased catecholamine secretions
Lipids	
>2 g/kg/day	*Liver:* cholestasis, fatty liver *Increased congestion of RES with fat* *Increased serum triglycerides*
Protein	
>2 g/kg/day	*Kidneys:* Increased ureagenesis With decreased renal function BUN increases. With normal renal function, diuresis may occur due to increased BUN secretion. This may lead to prerenal azotemia. *Lungs:* Amino acids/proteins increase respiratory drive and might cause breathlessness.
Fluid Intake	If excessive may lead to fluid overload; is especially problematic with reduced cardiac or renal function.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; REE, resting energy expenditure RES; reticuloendothelial system; BUN, blood urea nitrogen; $\dot{V}_E$, minute ventilation.

Gastrointestinal System Complications

Parenteral nutrition is associated with hepatobiliary complications whose causes are often multifactorial. Factors related to their development include underlying diseases and their severity, intercurrent sepsis, and drugs. The role of TPN may be additive, if not primary. Large glucose loads (>4 mg/kg/min) can result in hepatic steatosis and steatohepatitis with "portal triaditis" on biopsy. The latter is accompanied by elevations in γ-glutamyl transpeptidase, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. Intrahepatic cholestasis with elevated alkaline phosphatase and bilirubin may occur 3 to 6 weeks after TPN is started. Large lipid loads (≥2 g/day) administered for prolonged periods may also cause cholestasis.

Enteral nutrition is frequently associated with gastrointestinal tract dysfunction. There is delayed gastric emptying in about 50% of mechanically ventilated patients. Therefore, feeds are usually administered continuously and gastric residuals are measured at frequent intervals. Among patients fed intragastrically, gastric residuals, vomiting, and regurgitation occur more frequently than among those being fed into the small intestines. In a multicenter prospective study of 400 ICU patients fed mainly via nasogastric tubes, gastrointestinal complications occurred in 62.8% and were due to diarrhea (14.7%), constipation (15.7%), high gastric residuals (39%), abdominal distention (13.2%), vomiting (12.2%), and regurgitation (5.5%). Enteral nutrition was withdrawn in 15% of patients because of gastrointestinal complications.[176] With gastroparesis and large volume (150-220 mL) residuals, prokinetic agents (e.g., metoclopramide) should be considered. In a randomized study, intravenous erythromycin was more effective than metoclopramide (improvement 87% versus 62%) but the effectiveness of both treatments declined over time. Rescue therapy using both drugs was effective.[177] To decrease aspiration, patients should be fed in the semi-recumbent position and promotility agents used if residual gastric volumes are high. It is yet unclear whether postpyloric feeding reduces aspiration.[152] With enteral nutrition it is important to be aware that drug-nutrient interactions can occur.

Diarrhea is a particularly unpleasant (for patient and staff) complication of enteral nutrition. Its reported incidence, depending on its definition, ranges from 2% to 53% of patients and 38% of feeding-days. The definition of diarrhea used is important because many enteral products are "low residual," that is, they do not contain fiber and may not cause formed stools. Formula-related causes of diarrhea include hyperosmolar feedings, too rapid administration, and contamination of feedings with toxigenic or pathogenic organisms. Therefore, feeds should be sterile and not be allowed to hang for more than 8 hours. Non–formula-related causes include concomitant administration of drugs constituted in sorbitol elixirs, mannitol, or polyethylene glycol; *Clostridium difficile* enterocolitis; intra-abdominal infection; receipt of broad-spectrum antibiotics; and hypoalbuminemia. Hypoalbuminemia-associated diarrhea has been attributed to small bowel wall edema, leading to malabsorption. Yet, diarrhea-free feeding has been achieved in hypoalbuminemic patients by using elemental and peptide diets. Fiber-containing formulations might reduce diarrhea, but not consistently.[178] Most enteral formulas are lactose free, eliminating lactose intolerance as a problem. In patients without infectious diarrhea, pectin and anti-motility drugs may reduce the diarrhea. However, such patients must be monitored for the development

of constipation. Hepatobiliary complications of enteral nutrition are rare (<5%).

Special Considerations

Burns

Burn patients present special problems because of their very high energy expenditures, transcutaneous losses of protein, and great fluid requirements. If patients are unable to eat, enteral nutrition is the preferred modality. A number of trials indicate that enteral nutrition started within a few hours of admission reduces the magnitude of the stress response to burns. Therefore, it is common practice with significant burns (>20%) to begin nutrition early, that is, within less than 16 hours of admission. However, on systemic review there was insufficient evidence to show the advantage of early versus late enteral nutrition or that enteral nutrition reduces the stress response.[179] To ensure successful administration of many calories of a high-protein diet, nasoenteric feeding tubes should be placed into the jejunum. Caloric intake must be closely monitored in burn patients. If inadequate calories are being ingested, then supplementation is needed. In patients who are eating, this may be in the form of nutritional supplements ingested between meals. In enterally fed patients, supplementation can be provided with parenteral nutrition.

Hepatic Dysfunction

Hepatic dysfunction, especially cirrhosis, with intercurrent acute illness presents a complex metabolic scenario (see Chapters 66 and 67). Patients with cirrhosis are frequently nutritionally depleted secondary to anorexia, large loses of protein into ascites, and hypermetabolism. They have hyperinsulinemia, insulin resistance, accelerated gluconeogenesis, increased lipid oxidation, and, possibly, reduced glycogenesis. Essential fatty acid, zinc, and selenium deficiencies also occur. After liver transplantation, glucose clearance improves owing to correction of the hyperinsulinemia and insulin resistance. However, patients receiving corticosteroids as part of their immunosuppressive therapy continue to have abnormal glucose metabolism.

Because of their depleted state, cirrhotic patients would appear to be candidates for nutritional repletion. Yet, because of their poor prognosis, especially when complicated by serious illness, enteral nutritional support of seriously ill hospitalized cirrhotic patients was associated with reduced survival. However, the success of liver transplantation renewed interest in nutritionally supporting transplant candidates. These patients require fluid and sodium restriction and diuretics to control their fluid overload. They need increased protein/amino acid intakes (1.2-1.5 g/kg/day) to replace the losses due to ascites formation and high caloric intake to account for hypermetabolism (25-40 kcal/day).[180] Some cirrhotic patients develop hepatic encephalopathy, which limits protein intake. If patients develop encephalopathy while receiving a standard protein intake of 0.8 g/day plus lactulose, then branched-chain amino acid–enriched solutions and feedings should be considered. In cirrhosis, the plasma concentrations of these amino acids are low. Furthermore, they are not metabolized in the liver so are available for protein synthesis. When administered intravenously they are thought to counter the effects of intracerebral aromatic amino acids, which are involved in hepatic encephalopathy.[181] A Cochrane review showed a decreased rate of hepatic encephalopathy without reduction in mortality rate or adverse events.[182]

Renal Dysfunction

Preexisting chronic renal disease and newly developed acute renal failure present special nutritional challenges (see Chapters 65 to 67). Acute renal failure is especially problematic in the surgical arena because of its association with shock and sepsis. Such patients are insulin resistant, catabolic, and hypermetabolic, like other stressed patients. However, uremia exacerbates catabolism because it exacerbates insulin resistance, metabolic acidosis, and circulating proteases. The kidney interconverts various amino acids and also degrades specific peptides so that there also are major abnormalities in protein/amino acid handling. Cytokines liberated during hemodialysis may further aggravate the catabolic state. Renal failure patients are intolerant of large fluid loads, especially when oliguric, are unable to self-regulate electrolyte concentrations, and are unable to tolerate large protein/amino acid loads because of an inability to excrete urea. Because these patients require about 30 kcal/kg/day and 1.0 to 1.5 g/kg/day of protein, frequent dialysis is needed to remove wastes and excess fluid. The protein/amino acid intake may need to be increased because of dialysis-related loss of amino acids. In the past, essential amino acid–enriched solutions were used to reduce the urea production. However, current recommendations are to provide a combination of essential and nonessential amino acids based on the theory that normally nonessential amino acids may become essential in diseased states.[183]

Hemodialysis, continuous venovenous (and arteriovenous) hemodiafiltration (CVVHD), and peritoneal dialysis facilitate enteral nutrition and parenteral nutrition by removing excess fluid and urea, as well as balancing electrolyte concentrations, thus permitting patients to receive a full complement of calories and amino acids/protein. However, these therapies result in the loss of amino acids (10-15 g/d) unrelated to amino acid intake but related to plasma amino acid concentrations, volume of dialysate effluent, and filter efficiency. The concentrations of most amino acids are equal in plasma and dialysate. Therefore, the amino acid/protein content of the nutritional support should be increased. With aggressive CVVHD, patients required as much as 2.5 g/kg/day of protein to achieve positive nitrogen balance.[184] Dialysis also results in losses of peptides, proteins (with peritoneal dialysis), and water-soluble vitamins. Therefore, some renal enteral nutrition formulations have added B vitamins.

Peritoneal dialysis and CVVHD solutions usually contain 1.5% glucose, although concentrations as high as 4.25% are used. Up to 35% to 45% of this glucose can be absorbed and is a source of carbohydrate calories. With peritoneal dialysis, as much as 500 g/day of dextrose may be absorbed. Similarly, glucose-containing solutions used as replacement solutions during hemofiltration can be a source of glucose calories, in one study providing 300 g/day of glucose. This glucose load must be considered when

designing nutritional regimens and glucose/carbohydrate contents reduced accordingly. Additionally, glucose concentrations need to be monitored because of both the profound stress state and dialysis-associated glucose absorption. Insulin therapy may be needed to reduce the hyperglycemia. However, renal failure patients may be especially sensitive to insulin.

Generally, nutritional regimens for renal failure patients should not contain phosphate, potassium, or magnesium because concentrations of these electrolytes are already elevated. Calcium intake may need to be increased, whereas sodium content should be nearly isotonic because of an inability to regulate serum sodium concentrations. During dialysis, serum electrolytes must be closely monitored and deficiencies corrected as indicated.

Pancreatitis

Traditional treatment of acute pancreatitis and of acute exacerbations of chronic pancreatitis is to exclude all oral intake, institute nasogastric suction, and deliver all nutritional support parenterally. However, contemporary practice is to begin enteral nutrition early (within 48-72 hours) in the course of the disease. A meta-analysis of seven trials showed that compared with TPN, enteral nutrition is associated with less infectious morbidity, shorter hospital lengths of stay, and less organ failure, with no effect on mortality.[185] In addition, another meta-analysis reported that compared with TPN, enteral nutrition caused less hyperglycemia and reduced insulin requirements in acute pancreatitis.[186] Therefore, enteral nutrition is the preferred route of nutritional support in patients with acute pancreatitis and TPN should be used only when enteral nutrition is not tolerated.[187]

Conclusion

A key question is whether nutritional support improves patient outcome, that is, whether it lowers mortality and mobility and reduces ICU and hospital lengths of stay. Although no definitive large prospective multicenter studies have examined this issue, a few meta-analyses and large studies examined selected aspects of nutritional support. Some studies concluded that starting enteral nutrition within 3 days of ICU admission reduces the duration of mechanical ventilation and improves outcome and is superior to parenteral nutrition. A meta-analysis of 13 studies in critically ill patients showed lower infectious complications with enteral nutrition versus parenteral nutrition, but no difference in mortality.[188] However, more recent meta-analyses suggest that the benefits of enteral nutrition may not be so pronounced and that TPN actually improves survival when compared with delayed (>5 days) enteral nutrition despite a higher infection rate among patients receiving TPN.[189,190] The recent evidence for equal or better survival with TPN versus early enteral nutrition might be due to better glucose control and the ability to reach caloric goals more readily with TPN.[189] This is in contradistinction to an earlier meta-analysis that examined the relationship between TPN and standard care (usual oral diet plus intravenous dextrose) where TPN had no effect on mortality but lowered complication rates in malnourished patients.[191] Complication rates, but not mortality, were lower among patients who did not receive intravenous lipids. Another meta-analysis of 27 randomized trials in surgical patients showed that TPN did not affect mortality and possibly reduced complication rates.[192] This and other analyses did not show any detrimental effects of intravenously administered lipids.[162,192] The five-center prospective SUPPORT study of 6298 seriously ill patients showed that nutritional support was not associated with improved survival in any group (COPD, acute respiratory failure, multiple system organ failure, cirrhosis) except those in coma.[193] Moreover, a systematic review of 11 trials showed better outcomes in terms of survival and disability in head-injured patients fed early versus late (enteral nutrition or TPN) after the injury.[194] Delayed feeding was associated with poorer outcomes and the advantages of TPN disappear when feeding was delayed. Contemporary practice is to begin enteral nutrition (when not contraindicated) within 1 to 3 days of ICU admission while monitoring caloric intake and institute TPN if the enteral nutritional caloric intake is insufficient. However, beginning TPN early to provide sufficient calories while simultaneously beginning enteral nutrition is also supported by evidence.[195]

Caring for surgical and critically ill patients requires that clinicians consider the consequences of the metabolic and inflammatory responses to injury and sepsis. This translates into practical actions such as modulating the response itself (e.g., with epidural anesthesia), modifying end-organ responses (e.g., β-adrenergic blockade), and treating its consequences (e.g., blood glucose control, nutritional support). The aims of these interventions are to improve patient outcome by decreasing the deleterious (e.g., increased nitric oxide production) effects of the response without reducing its beneficial (e.g., immune enhancing) actions. Yet, further basic and clinical research is needed to further examine the stress response and its modulation. This will involve using system biology incorporating genomic, transcriptomic (mRNA), proteomic, and metabolomic information to better understand the complexity of this response. The importance of genomics is underlined by research that reveals that the secretion of cytokines and end-organ responses due to activation of Toll-like receptors during sepsis differ depending on an individual's genetics.[196] Similarly, gender plays a role in the response. For example, young girls with burns have less hypermetabolism and higher anabolic hormone concentrations than boys, whereas healthy adult women appear to have lower susceptibility to sepsis than men, possibly because of more pronounced proinflammatory innate immunity and a lesser decrease in norepinephrine sensitivity when exposed to endotoxin.[197] Therefore, future clinical approaches to stressful situations could involve genetic and proteomic screening (e.g., with microarrays) to better tailor treatment.

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Zaccaria Ricci and Claudio Ronco

96 Renal Replacement Therapies

Key Points

1. The removal of sodium and water cannot be dissociated when using diuretics or in certain renal replacement techniques. Diuretics lead to a natriuresis, whereas dialysis may result in hypotonia or hypertonia, depending on the effect of dialysis on the diffusion and on the removal of molecules, including urea and other electrolytes.
2. Slow continuous ultrafiltration (SCUF) produces an ultrafiltration (UF) that varies from plasma water minimally due to Donnan effects. The UF from SCUF is iso-osmotic and isonatremic because sodium elimination is linked to the sodium concentration in plasma.
3. The ultrafiltrate composition produced from continuous venovenous hemofiltration (CVVH) and from hemofiltration in general is similar to plasma water, but the sodium concentration in the UF can be significantly affected by the sodium concentration in the replacement solution.
4. Sodium removal can be dissociated from water removal in CVVH, thus obtaining a real change of the sodium pool in the body. This effect on sodium cannot be achieved with any other technique.
5. The best evidence to date supports a renal replacement therapy dose of at least 35 mL/kg/hr—spKt/V 1.4—for CVVH, continuous venovenous hemodiafiltration (CVVHDF), or daily intermittent hemodialysis (IHD).
6. There is evidence that, when the circuit set-up is perfectly optimized, anticoagulants are only a relatively minor component of circuit patency: in fact, when patients have bleeding disorders (i.e., prolonged clotting times, thrombocytopenia), renal replacement therapy can be safely performed without the utilization of any anticoagulant.
7. The UNLOAD trial is the first randomized comparison of intravenous diuretic therapy alone against an alternative therapy, ultrafiltration, in hypervolemic patients. The principal findings of this trial were (a) in hypervolemic patients with congestive heart failure (CHF), ultrafiltration led to greater weight and fluid loss than intravenous diuretics at the doses used in this trial; (b) volume removal with ultrafiltration at the index hospitalization was associated with significant reductions in the rate and durations of subsequent hospitalizations and fewer unscheduled medical visits for CHF; and (c) the benefits from the short-term use of ultrafiltration over 90 days was achieved without significant adverse effects.
8. It is now possible to generate ultrapure replacement fluid and administer it in the intensive care unit (ICU) with a lower cost than continuous renal replacement therapy (CRRT), in greater amounts and for shorter periods of time. The choices are now almost limitless; 3 or 4 hours of IHD with standard settings or CRRT at 35 mL/kg/hr of effluent flow rate can be selected. Slow low-efficiency extended daily dialysis (SLEDD) at blood and dialysate flow rates of 150 mL/min for 8 hours during the day or SLEDD for 12 hours overnight can be considered as an alternative.

Acute kidney injury (AKI) is a complex disorder without a clear-cut, universally accepted definition.[1,2] Renal replacement therapy (RRT) is the fundamental part of AKI management. Although there are a number of different strategies of extracorporeal renal support that are available, a definite standard has not been defined and there is no evidence regarding the superiority of one technique over another in obtaining superior efficacy or outcomes. The best time to initiate and stop RRT is controversial. In this chapter we review AKI and provide theoretical and practical bases for RRT prescription with the goal of helping anesthesiologists and intensive care unit (ICU) clinicians to understand critical care nephrology.

Epidemiology of Acute Kidney Injury

A recent multinational, multicenter, prospective, epidemiologic survey of AKI was conducted in ICU patients[3] who were either

treated with RRT or fulfilled at least one predefined criteria for AKI, either oliguria (urine output < 200 mL/12 hr) or marked azotemia (blood urea nitrogen [BUN] level > 30 mmol/L). The data were collected at 54 hospitals in 23 countries. Of 29,269 critically ill patients admitted during the study period, 1,738 (5.7%) had AKI during their ICU stay, including 1,260 (4.3%) who were treated with RRT. Overall hospital mortality was 60.3%. The most common contributing factor to AKI was septic shock (47.5%). Approximately 30% of patients had preadmission renal dysfunction. At hospital discharge, 86.2% survivors were independent from dialysis. Independent risk factors for hospital mortality included the use of vasopressors, mechanical ventilation, septic shock, cardiogenic shock, and hepatorenal syndrome.

Crude mortality assessment shows that the overall hospital outcome of patients with AKI has remained high, and it has not changed in the past 30 years. The explanation for this finding is that patients with AKI 30 years ago were mostly treated outside the ICU and did not require or receive mechanical ventilation or vasopressor drugs, and they were 20 to 30 years younger. Their outcomes were typically assessed retrospectively, and these patients were only in academic centers. More recent data document that patients have much higher scores for severity of illnesses and yet the mortality of AKI has not increased and may have even decreased slightly. Also, the duration of treatment has clearly decreased in terms of need for dialysis, length of stay in the ICU, and length of stay in the hospital. The techniques for artificial renal support have also changed markedly.[4] Despite these advances, there remains a 50% to 60% crude mortality rate associated with AKI, suggesting that the present therapy is still inadequate.

In modern health care systems, patients with AKI are able to obtain acute RRT. It has been estimated that the incidence of AKI needing extracorporeal support is approximately 11 per 100,000 population/year. The annual mortality rate is 7.3 per 100,000 patients, with the highest rates in males older than age 65 years. Renal recovery occurs in 78% (68/87) of survivors at 1 year; although a great number of patients with severe AKI will die, most survivors will become independent from RRT within a year.[5] The increasing number of acute dialytic treatments in the ICU has led to the development of a new specialized branch of nephrology in the past 10 years: critical care nephrology. AKI requires a multidisciplinary approach with intensivists and nephrologists sharing their respective knowledge. Fluid balance, vasopressor dosage, mechanical ventilation support, and arterial blood gas exchange including Pao_2/Fio_2 ratio need to be linked to RRT prescription, dialysis dose, ultrafiltration (UF) requirement, and anticoagulation strategy The theoretical and technical aspects of critical care nephrology are also necessary parts of an intensivist's curriculum.

History of Renal Replacement Therapy

From the initial description of continuous arteriovenous hemofiltration (CAVH) in 1977 by Peter Kramer and colleagues,[6] RRT has progressively evolved in the ICU from a therapy of desperation for AKI to a standardized, widely used, fully independent form of artificial kidney support in critically ill patients. Older CAVH machines had the blood flow depend on the patient's spontaneous arteriovenous pressure gradient. Therefore, the UF was totally dependent on the generated transmembrane pressure (TMP) gradient. If a patient had a low mean arterial pressure or the intrinsic resistance of the circuit was elevated, there was very little UF formed. Nonetheless, often CAVH provided a very slow, continuous fluid removal and did maintain a steady solute concentration so that there were no peaks of waste products. The increased utilization of CAVH led to fully staffed, independent teams that functioned in ICUs without the usual staff of dialysis units.

CAVH was useful in that it did not generate the same problems associated with hemodialysis, including hypotension, rapid fluid shifts, increased cerebral edema, or rapid reductions in plasma osmolality. However, the limitations of CAVH included the requirement for both arterial and venous access. Solute clearance in CAVH is limited by the low UF rates and the pure convective nature of this treatment. Thus, the patients with the lowest mean arterial pressures would have the lowest clearances and early clotting of the circuit. CAVH can maximally achieve approximately 20 mL/min of clearance, which is insufficient to meet the needs of severely catabolic patients.

To overcome these technical limitations associated with CAVH, new filters were designed with increased cross-sectional area and inner hollow fiber diameter that reduced unit length so that there was a lower resistance to blood flow. These improvements optimized the UF that could be achieved with this technique. Highly biocompatible membranes mounted on parallel plate devices were also utilized because they had lower intrinsic resistance (ensuring higher extracorporeal blood flows at a given arteriovenous pressure gradient) and they were equipped with a second port in the filtrate compartment to achieve counter-current dialysis (CAVHD), rather than just convective filtration.

However, the most important innovation was the addition of a peristaltic pump to the extracorporeal circuit. This innovation, the addition of a pump to the CVVH circuit, basically created a dialysis machine in the ICU, without importing the expertise of the dialysis team. Blood flow is now programmed and delivered with reasonable precision. The new continuous venovenous therapies require negative pressure measurement and alarms in the arterial line before the pump, as well as positive-pressure measurements and alarms in the venous return line. A bubble trap is required In the venous return line to prevent air embolism (this was not necessary in CAVH where positive pressure existed in the entire length of the circuit). The higher blood flows induced by the addition of the peristaltic pumps led to higher filtration and higher clearances. It also became necessary to add roller pumps to the fluid replacement section of the circuit, and external scales had to be utilized to provide accurate estimates of fluid balance during treatment. It soon became evident that an ideal extracorporeal circuit should have incorporated continuous pressure measurements of inlet and outlet lumens of the catheter inlet and outlet of the filter and ultrafiltrate and dialysate ports. This information is now integrated with adequate alarms to allow the ICU staff to maintain filter efficiency and circuit patency, to detect potential sources of clotting, and to ensure patient safety.[7]

Other innovations that have helped establish CVVH as the RRT for the ICU is the creation of standardized dialysates for the ICU and double-lumen catheters that can be placed in single

veins, thus decreasing the high rate of complications associated with the placement of large arterial cannulas.

Indications to Start and Stop Renal Replacement Therapies

There is no consensus as to the indications for the initiation of RRT. Some of the indications espoused by various authors include azotemia, anuria, and complications of AKI, including pulmonary edema, severe fluid overload, hyperkalemia, and uncontrolled metabolic acidosis. An algorithm for RRT indication has been suggested (Table 96-1).[8] Unfortunately, once RRT has started there is no generally accepted biochemical or clinical marker that is achieved by the therapy. A routine clinical practice is to "adequately" control fluid balance and to maintain a serum urea concentration below 30 mg/dL, a serum creatinine value below 2 mg/dL, and normal electrolytes values.

Techniques and timing of weaning patients from RRT are poorly described in the literature. We recommend that, when the patient has reached hemodynamic stability or the need for vasopressors has been reduced or the severity of illness has decreased, the need for RRT can be ascertained. This process can be accelerated when urine output increases and fluid balance becomes manageable without RRT.

Techniques and Modalities

All renal replacement therapies consist of blood purification by having the blood flow though semi-permeable membranes. Blood flows into hollow fibers composed by porous biocompatible synthetic materials. A wide range of substances (water, urea, and low- middle-, and high-molecular-weight solutes) allow the blood across such membranes, by diffusion (solutes) and by convection (water and solutes) (Fig. 96-1).

During *diffusion,* solutes move from blood across the membrane in an attempt to reach the same concentration on each side of the membrane; this leads to the passage of solutes from the compartment with the highest concentration to the compartment with the lowest concentration. Other components of the semipermeable membrane that affect the rate of diffusion include the thickness and surface of the membrane, temperature of the blood, and diffusion coefficient. *Dialysis* occurs when a solution flows through a semi-permeable conduit counter current to the blood, allowing maximal solute diffusion, because the solute concentration is lower in the solution than in the blood.

Table 96-1 Indications for Renal Replacement Therapy*

- Anuria-oliguria (diuresis ≤ 200 mL in 12 hr)
- Severe metabolic acidosis (pH < 7.10)
- Hyperazotemia (BUN ≥ 80 mg/dL) or creatinine > 4 mg/dL
- Hyperkalemia (K^+ ≥ 6.5 mEq/L)
- Clinical signs of uremic toxicity
- Severe dysnatremia (Na^+ ≤ 115 or ≥ 160 mEq/L)
- Hyperthermia (temperature > 40°C without response to medical therapy)
- Anasarca or severe fluid overload
- Multiple organ failure with renal dysfunction and/or systemic inflammatory response syndrome, sepsis, or septic shock with renal dysfunction

*The presence of one indication suggests, two indications strongly suggest, and three indications mandate initiation of renal replacement therapy.

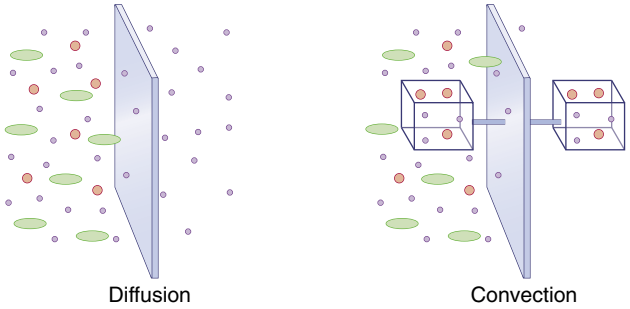

Figure 96-1 Diffusion and convection are schematically represented. During diffusion, solutes flux (Jx) is a function of solutes concentration gradient (dc) between the two sides of the semipermeable membrane, temperature (T), diffusivity coefficient (D), membrane thickness (dx), and surface area (A) according to the following equation:

$$Jx = D \cdot T \cdot A\,(dc/dx)$$

Convective flux of solutes (Jf) requires instead a pressure gradient between the two sides of the membrane (transmembrane pressure [TMP]) that moves a fluid (plasma water) with its "crystalloid" content (a process called ultrafiltration, whose entity is also dependent on membrane permeability coefficient [Kf]). Colloids and cells will not cross the semi-permeable membrane, depending on the size of the pores:

$$Jf = Kf \cdot TMP$$

where TMP = Pb – Pd – π, with Pb, blood hydrostatic pressure, Pd, hydrostatic pressure on ultrafiltrate side of the membrane, and π, blood oncotic pressure.

During *convection,* the movement of solute across a semi-permeable membrane takes place in conjunction with significant amounts of *ultrafiltration* (water transferring across the membrane). In other words, as the solvent (water in plasma) is pushed across the membrane in response to the TMP by UF, solutes are carried with it, as long as the porosity of the membrane allows the molecules to be sieved from blood. The process of UF is governed by the UF rate (Qf), the membrane UF coefficient (Km), and the TMP gradient generated by the pressures on both sides of the hollow fiber, according to the following formula:

$$Qf = Km \cdot TMP$$

The hydrostatic pressure in the blood compartment is dependent on blood flow (Qb). The greater the Qb, the greater the TMP. In modern RRT machines, UF is maximized by applying a pump, which generates control of the UF rate. As blood is processed, the membrane fibers can become soiled, and a negative pressure becomes necessary to maintain a constant Qf. Molecules cleared during convection are physically dragged to the UF side, but this function is seriously limited by a protein layer that progressively develops and closes fiber pores during convective treatments.[9] Membrane capacity, or a defined adsorption, has been shown to have a major role in the clearance of higher-molecular-weight toxins.[10] Membrane adsorptive capacity is generally saturated in the first hours of RRT treatment. Therefore, diffusion and convection are very important for the efficacy of RRT.[11]

As UF proceeds over time, plasma water and solutes are filtered from the blood, hydrostatic pressure within the filter is lost, and oncotic pressure is gained because blood concentrates

and the hematocrit increases. The fraction of plasma water that is removed from blood during UF is called the filtration fraction. The filtration fraction should be kept in the range of 20% to 25% to prevent excessive hemoconcentration within the filtering membrane and to avoid a critical point where oncotic pressure is equal to TMP and where filtration/pressure equilibrium is reached. Finally, replacing plasma water with a substitute solution completes the *hemofiltration* (HF) process and returns the now purified blood to the patient. The replacement fluid can be administered after the filter, with a process called postdilution HF. Otherwise, the solution can be infused before the filter to obtain predilution HF. Although postdilution HF allows a urea clearance equivalent to therapy delivery (i.e., 2000 mL/hr, see later), the administration of the solution before dilution leads to a prolonged circuit lifespan by reducing hemoconcentration and the protein caking effects described earlier. Conventional HF is performed with a highly permeable membrane with a surface area of about 1 m^2, steam sterilized, with a cut-off point of 30 kD. The difference between the volume of ultrafiltered plasma water and reinfused substitution solution gives the net UF, which is the fluid that is eventually removed from the patient. Prescriptions for net UF are based on the individual patient needs and can range from more than 1 L/hr (pulmonary edema in a patient with congestive heart failure who is resistant to diuretics) to zero (sepsis with catabolic state with increased creatinine levels). A net UF rate must be added to dialysis to achieve fluid balance during diffusion that does not allow water movements.

Dose and Prescriptions for Renal Replacement Therapies

Like any other therapy administered in the ICU, dialysis should be administered in an appropriate amount. Nephrologists estimate an appropriate RRT dose by measuring the elimination of a representative marker solute, such as creatinine. This estimate has two major flaws. First, the marker solute cannot and does not represent all the solutes that accumulate during AKI because kinetics and volume of distribution are different for each solute. Therefore, the removal of creatinine during RRT is not necessarily representative of the removal of other solutes. This is true both for patients who have end-stage renal failure and patients with AKI. Nevertheless, despite all of these limitations, a significant body of data[12] suggests that single solute marker assessment of dose of dialysis appears to have a clinically meaningful relationship with patient outcomes and, therefore, is of clinical utility.

During RRT, clearance of creatinine and urea depends on circuit blood flow (Qb), hemofiltration (Qf) or dialysis (Qd) flow, solutes' molecular weights, and hemodialyzer type and size. Qb, as a variable in delivering the RRT, is mainly dependent on vascular access and the operational characteristics of the machines utilized in the ICU. Qf is strictly linked to Qb, during convective techniques, by filtration fraction. Filtration fraction does not limit Qd, but when the Qd/Qb ratio exceeds 0.3 it can be estimated that dialysate will not be completely saturated by blood diffusing solutes. During UF, the driving pressure jams solutes, such as urea and creatinine, against the membrane and into the pores, depending on membrane sieving coefficient (SC) for that molecule. SC expresses a dimensionless value and is estimated by the ratio of the concentration of the solutes in the filtrate divided by that in the plasma water, or blood. An SC of 1.0, as is the case for urea and creatinine, demonstrates complete permeability, and a value of 0 reflects complete rejection. Molecular size over approximately 12 kD and filter porosity are the major determinants of SC. The clearance (K) during convection is measured by the product of Qf times the SC. Thus, differently from diffusion, there is a linear relationship between K and Qf, the SC being the changing variable for different solutes. During diffusion, the linear relationship is lost when Qd exceeds about a third of Qb. As a rough estimate, we can consider that during continuous slow efficiency treatments, RRT dose is a direct expression of Qf or Qd, independently of which solute must be removed from blood.

During continuous treatment in the ICU, the goal is to deliver at a minimum, a urea clearance of 2 L/hr. There is some evidence that 35 mL/kg/hr might be better (i.e., about 2.8 L/hr in a 70-kg patient (see later). Evaluations of chronic dialysis in end-stage renal disease patients have been described by the fractional clearance of a given solute, Kt/V, where K is dialysis clearance, t is the time of dialysis administration, and V is the solute marker volume of distribution. Kt/V is an established marker of adequacy of dialysis for small solutes correlating with medium-term (several years) survival in chronic hemodialysis patients.[13,14] Urea is typically used as a marker molecule in end-stage kidney disease to guide treatment dose, and a Kt/V_{UREA} of at least 1.2 is currently recommended. As an example, we can consider the case of a 70-kg patient who is treated 20 hours per day with a postfilter hemofiltration of 2.8 L/hr at a zero balance: his K_{UREA} will be 47 mL/min (2.8 L/hr = 2800 mL/60 min) because we know that during postfilter hemofiltration ultrafiltered water from plasma will drag all the urea across the membrane, making its clearance identical to UF flow. This treatment time (t) will be 1200 minutes (60 minutes for 20 hours). His urea volume of distribution will be approximately 42,000 mL (60% of 70 kg, 42 L = 42,000 mL), which is roughly equal to total body water. Simplifying our patient's Kt/V_{UREA} we will have $47 \times 1{,}200/42{,}000 = 1.34$.

Application of Kt/V_{UREA} to patients with AKI has not been rigorously validated.[15] In fact, although the application of Kt/V to the assessment of dose in AKI is theoretically intriguing, many concerns have been raised because problems intrinsic to AKI can hinder accuracy. These problems include the lack of a metabolic steady state, uncertainty about the volume of distribution of urea (V_{UREA}), a high protein catabolic rate, labile fluid volumes, and possible residual renal function, which changes dynamically during the course of RRT in the ICU. Finally, hypotension and vasopressors requirements can be responsible for solute disequilibrium within tissues and organs.

These observations highlight the current inadequacies of applying the paradigms utilized in end-stage renal failure patients to patients with AKI in the ICU. They also indicate that, unlike the field of chronic hemodialysis, only major changes in dose (e.g., changing from second daily to daily dialysis) can truly deliver a "different" therapy in the setting of AKI. More subtle adjustments such as prescribing a calculated Kt/V of 1.0 versus 1.2 can easily be criticized as being within the calculation error around each prescription in these patients and not necessarily representing a reliable change in dose delivery.

The therapeutic needs in the patients with AKI that can be or need to be affected by the "dose" of RRT are not only the simple control of small solutes as represented by urea. The features that can be affected include control of acid-base balance, tonicity, potassium, magnesium, calcium, phosphate, intravascular volume,

Table 96-2 Algorithm for Renal Replacement Therapy

Clinical Variables	Operational Variables	Setting
Fluid balance	Net ultrafiltration	A continuous management of negative balance (100-300 mL/hr) is preferred in hemodynamically unstable patients. Complete monitoring (CVC, S-G, arterial line, ECG, pulse oximeter) is recommended.
Adequacy and dose	Clearance/modality	2000-3000 mL/hr (or 35 mL/kg/hr) for CRRT; consider first CVVHDF. If IHD is selected, an every-day/4 hr prescription is recommended. Prescribe a Kt/V > 1.2.
Acid-base	Solution buffer	Bicarbonate-buffered solutions are preferable to lactate-buffered solutions in case of lactic acidosis or hepatic failure or both.
Electrolyte	Dialysate/replacement	Consider solutions without K^+ in case of severe hyperkalemia. Manage accurately with $MgPO_4$.
Timing	Schedule	Early and intense renal replacement therapy is suggested.
Protocol	Staff/machine	Well-trained staff should routinely utilize renal replacement therapy monitors according to predefined institutional protocols.

CVC, central venous catheter; S-G, Swan-Ganz catheter; ECG, electrocardiogram; CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis.

extravascular volume, and temperature and the avoidance of unwanted side effects associated with the delivery of solute control. Examples of these issues include the use of RRT in the setting of coagulopathic bleeding after cardiac surgery or in liver failure. RRT will allow the administration of large volumes of fresh frozen plasma, cryoprecipitate, and platelets to be administered rapidly without inducing fluid overload because 1.0 to 1.5 L of ultrafiltrate is removed in 1 hour. Another example is a patient with right ventricular failure, AKI, and ARDS who is receiving lung-protective ventilation with permissive hypercapnia and has acidemia. RRT will allow acid-base control and normalization of pH 24 hours per day, which will improve lung function and right- and left-sided heart function by maintaining a normal volume status and possibly decreasing pulmonary arterial pressures. Other examples include the use of RRT for potassium control in patients with rhabdomyolysis. Clearly, RRT is utilized for more than clearance of any one solute.

Tables 96-2 and 96-3 show potential flow charts that could be followed each time an RRT prescription is indicated.

Does Receipt of More Dialysis Improve Patient Outcomes?

The hypothesis that higher doses of dialysis may be beneficial in critically ill patients with AKI has been investigated by several authors. Brause and coworkers[16] used continuous venovenous hemofiltration (CVVH) and found that higher Kt/V values (0.8 versus 0.53) correlated with improved uremic control and acid-base balance. No other clinically important outcome was affected by this change. Investigators from the Cleveland Clinic[17] retrospectively evaluated 844 patients with AKI requiring continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD) over a 7-year period. They found that when patients were stratified for severity of disease, the dose of dialysis did not affect the outcomes of patients with very high or with very low scores but was associated with improved survival in patients with intermediate degrees of illness. A mean Kt/V greater than 1.0 was associated with increased survival. This study was retrospective

Table 96-3 Example of Possible Prescription for Continuous Treatment in a 70-kg Patient (V_{UREA} = 42 L) during an Ideal Session of 24 Hours (t = 1440 min)

	Estimated Urea Clearance (K_{CALC})*	Notes	Value of Q to Obtain 35 mL/kg/hr	Value of Q to Obtain a Kt/V of 1
CVVH postdilution	K_{CALC} = Qrep	Always keep filtration fraction < 20% (Qb must be 5 times Qrep)	Qrep: 41 mL/min or 2450 mL/hr	Qrep: 29 mL/min or 1750 mL/hr
CVVH predilution	K_{CALC} = Quf/(1 +[Qrep/Qb])	Filtration fraction computation changes (keep < 20%)	For a Qb of 200 mL/min: Qrep: 53 mL/min or 3200 mL/hr	For a Qb of 200 mL/min: Qrep: 35 mL/min or 2100 mL/hr
CVVHD	K_{CALC} = Qdo	Keep Qb at least thrice Qd	Qdo: 41 mL/min or 2450 mL/hr	Qdo: 29 mL/min or 1750 mL/hr
CVVHDF postdilution (50% convective and diffusive K)	K_{CALC} = Qrep + Qdo	Consider both notes of CVVH and CVVHD	Qrep: 20 mL/min + Qdo: 21 mL/min	Qrep: 14 mL/min replacement solution + Qdo: 15 mL/min

*Net ultrafiltration (patient fluid loss) is considered zero in K_{CALC} for simplicity.
Urea volume of distribution: V (L) = patient's body weight (kg) × 0.6.
Estimated fractional clearance: $Kt/V_{CALC} = K_{CALC}$ (mL/min) × prescribed treatment time (min)/V (mL).
35 mL/kg/hr roughly corresponds to a Kt/V of 1.4. A Kt/V of 1 approximately corresponds to 25 mL/kg/hr.
Filtration fraction calculation (postdilution): Qrep/Qb × 100.
Filtration fraction calculation (predilution): Qrep/Qb + Qrep × 100.
Qb, blood flow rate; Qrep, replacement solution flow rate; Quf, ultrafiltration flow rate (Quf: Qrep + Qnet); Qnet, patient's net fluid loss; Qdo, dialysate solution flow rate.

so there was a post-hoc selection bias. The validity of these observations remains controversial.

Daily IHD compared with alternate-day dialysis also seems to be associated with improved outcomes in another recent trial.[18] Daily hemodialysis resulted in significantly improved survival (72% versus 54%, $P = .01$), better control of uremia, fewer hypotensive episodes, and more rapid resolution of AKI. However, several limitations affected this study: sicker, hemodynamically unstable patients were excluded and underwent CRRT instead. Furthermore, it appears that patients receiving conventional IHD were underdialyzed. Finally, second daily dialysis was associated with significant differences in fluid removal and dialysis-associated hypotension, suggesting that other aspects of "dose" beyond solute control (inadequate and episodic volume control) might have explained the findings. These observations suggest that further studies should be undertaken to assess the effect of dose of IHD on outcomes.

In a randomized controlled trial of different doses of CRRT in 425 critically ill patients with AKI, those who either received CVVH at 35 mL/hr/kg or at 45 mL/hr/kg were found to have improved survival compared with the patients who received CVVH at 20 mL/hr/kg.[19] Many technical and/or clinical problems, however, make it difficult to apply the exact protocol utilized in this investigation. A survey of several ICUs worldwide found that very few units deliver this intensive CRRT regimen. Uchino and coworkers found that median unadjusted CRRT dose was 2000 mL/hr and the corrected dose was 20.4 mL/hr/kg. Only 11.7% of patients are being treated with a corrected dose of more than 35 mL/kg/hr.[20]

In a study conducted by Ronco and associates, the technique of CRRT was CVVH with postdilution, whereas current practice includes other techniques, including continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemodiafiltration (CVVHDF). Also, Ronco and associates' study was conducted over 6 years in a single center, uremic control was not reported, the study was unblinded, and the incidence of sepsis was low compared with other incidences in the literature.[3] Therefore, confirmatory studies are needed.

Another prospective randomized trial conducted by Bouman and colleagues[21] assigned patients to three different groups: early high volume hemofiltration (72 to 96 L/24 hr), early low volume hemofiltration (24 to 36 L/24 hr), and late low volume hemofiltration (24 to 36 L/24 hr). These investigators found no difference in terms of renal recovery or 28-day mortality. Unfortunately, prescribed doses were not standardized by weight, making the potential variability in RRT dose large. Furthermore, the number of patients studied was small, making the study insufficiently powered. Finally, the incidence of sepsis in the patients studied was low compared with other populations with AKI.

Recently, Saudan and coworkers[22] enrolled 371 patients with AKI (102 to CVVH and 104 to CVVHDF) and prescribed 25 mL/hr/kg UF in the CVVH group and 24 mL/hr/kg in the CVVHDF group. Patients receiving CVVHDF were prescribed an adjunctive mean dialysis dose of 18 mL/hr/kg. The CVVHDF patients had significant reductions in their creatinine and urea within 48 hr of the initiation of continuous RRT compared with the patients who received CVVH alone (50% versus 40%, $P < .009$ and 46% versus 38%, $P < 0.014$, respectively). Survival rates at 28 days and at 90 days were higher in the patients who had received CVVHDF than in the patients who received CVVH. Criticisms include that the study was underpowered. Also, the investigators compared a modality with dialysis to one without dialysis. Nevertheless, pooled results from the last four studies[19-22] seem to indicate a significant effect on survival in patients who receive more dialysis.[23] Although these data may still not be definitive, the best evidence to date supports the use of a minimum of 35 mL/hr/kg for CVVH, CVVHDF, or 1.2 Kt/V daily IHD.

Treatment interruptions due to patient need for surgery or other diagnostic procedures affect the results of CRRT. In a prospective observational trial,[24] it was shown that "down" time (amount of hours spent off an active treatment) adversely affected control of azotemia. There was a significant correlation between down time and creatinine concentrations ($P < .0001$). According to these authors, the down time should be less than 8 hours per day to maintain creatinine and urea concentrations (2 L/hr of UF). For example, if one prescribed a UF rate of 35 mL/hr/kg, only 23 mL/hr/kg would actually be delivered when there was a down time of 8 hr/day.

Evanson and coworkers[25] found other factors that diminished IHD administration, including high patient weights, male sex, and low blood flow, limited IHD administration and that about 70% of dialysis delivered a Kt/V of less than 1.2. A retrospective study by Venkatarman and associates[26] also showed that patients receive only 67% of prescribed CRRT therapy due to all these factors. Of note, in the CVVH dose trial,[19] only patients who achieved more than 85% of the prescribed dose were included in the analysis. To obtain this goal, compensation for interruptions in CRRT treatments due to ICU procedures were made by increasing effluent flow rates in the subsequent hours. A recent observational trial, where the CRRT prescribed/delivered ratio was monitored, an average 10.7% ($P < .05$) reduction of therapy delivery was found when compared with the prescribed dose.[15] This delivery reduction was sometimes due to the estimation error brought by the use of dose calculator software but more often was due to the short operative treatment time. Therefore, if at all possible, interruptions in CRRT should be minimized.

Continuous Versus Intermittent CRRT

When the critical parameter of dialysis efficacy is metabolic control, an acceptable mean BUN concentration of 60 mg/dL can be reached only after days of 2 L/hr CVVH in a 100-kg patient. Computer-based simulation documents that this goal is difficult to achieve even with intensive IHD regimens.[27] In the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock,[28] it is suggested that based on the present scientific evidence continuous RRT is equivalent to IHD for treatment of AKI. In a large comparative trial randomizing 166 critically ill patients with AKI to either CRRT or IHD,[29] the authors found that the CRRT population, despite randomization, had significantly greater severity of illness scores. This could in part explain why, despite better control of azotemia and a greater likelihood of achieving the desired fluid balance, patients receiving the CRRT had an increased mortality. Vinsonneau and colleagues[30] recently conducted a large, prospective, randomized multicenter study in 21 ICUs over a 3.5-year period. The primary end point was the 60-day mortality after the randomization of 360 patients with ARF to either CVVHDF or IHD in centers that were familiar with both techniques. The eligibility criteria changed after 8 months owing to the poor recruitment rate. No difference in 28-, 60- (CVVHDF 33%; IHD 32%), or 90-day mortality rates was

found between the two groups. The study was well conducted, and, at the moment, it is the best example of a randomized controlled study comparing effectively the two techniques. Nonetheless, the study was started more than 7 years ago, during which time the practices in both CVVHDF and IHD have changed considerably. As stated by Vinsonneau and colleagues, this may have led to changes in investigator practices during the study period, particularly with respect to the delivered dose of renal support. This possibility, however, is hard to ascertain given that the investigators, by protocol, started therapy with "initial standardized settings" and then adapted these settings to meet individual patient requirements to obtain the metabolic control objectives. Interestingly, the mortality decreased in the IHD arm of the study over the time of recruitment, which reflected a change in practice toward an increased dialysis prescription. Given the lack of control regarding the dosage in both arms of the study, definitive conclusions cannot be made. As remarked in the accompanying editorial,[31] the question of which treatment is better is influenced by the nature of the task. CRRT might be better in terms of total water and solute removal over 24 hours and for hemodynamically unstable patients, but IHD can remove much more water and solute per hour and does not require continuous anticoagulation or complete patient immobilization.

Other investigators have drawn similar conclusions.[32,33] Over the past 2 decades, technical advances in the delivery of IHD have dramatically decreased the propensity of IHD to cause intradialytic hypotension. These advances include the introduction of volume-controlled dialysis machines, the routine use of biocompatible synthetic dialysis membranes, the use of bicarbonate-based dialysate, and the delivery of higher doses of dialysis. Schortgen and coworkers demonstrated that there was a lower rate of hemodynamic instability and better outcomes after implementation of a clinical practice algorithm designed to improve hemodynamic tolerance to IHD.[34] Recommendations included priming the dialysis circuit with isotonic saline, setting dialysate sodium concentration at above 145 mmol/L, discontinuing vasodilator therapy, and setting dialysate temperature to below 37°C. These changes may have made IHD as good if not better than forms of CRRT.

Randomizing patients to receive one therapy or the other regardless of the conditions might yield results that are difficult to generalize to clinical practice. About 10 years ago, a similar passionate debate on ventilation weaning strategies (pressure support ventilation versus T-piece spontaneous ventilation versus continuous pressure airway pressure versus synchronized intermittent mandatory ventilation) was ongoing. The scientific community finally agreed that it is difficult to select one method over the other and that the *manner* in which the mode of weaning is applied may have a greater effect on the likelihood of weaning than the *mode* itself.[35]

Hybrid techniques are now available. These include slow low-efficiency extended daily dialysis (SLEDD),[36] prolonged daily intermittent RRT (PDIRRT),[37] extended daily dialysis (EDD),[38] or simply extended dialysis,[39] depending on variations in schedule and type of solute removal (convective or diffusive). These therapies were developed to offer the best aspects of both CRRT and IHD, including efficient solute removal with minimum solute disequilibrium, reduced UF rate with hemodynamic stability, optimized delivered to prescribed ratio, low anticoagulant needs, diminished cost of therapy delivery, efficiency of resource use, and improved patient mobility. Initial case reports have shown that these hybrid approaches are feasible and they do have high clearances. A single short-term single center trial compared these hybrid therapies to CRRT and showed that the dose delivery and hemodynamic stability were acceptable.[39] Recently, Baldwin and coworkers randomized 16 patients to 3 consecutive days of treatment with either CVVH (8 patients) or extended daily dialysis with filtration (EDDf) (8 patients) and compared small solute, electrolyte, and acid-base control.[40] They did not find a significant difference between these two techniques in urea or creatinine concentrations over 3 days. All electrolyte derangements before treatment were corrected by either treatment, except for 1 patient in the CVVH group who developed hypophosphatemia (0.54 mmol/L) at 72 hours. After 3 days of treatment, there was a mild but persistent metabolic acidosis in the EDDf group compared with the CVVH group.

It is now possible to generate ultrapure replacement fluid and administer it in the ICU with a lower cost than CRRT, in greater amounts and for shorter periods of time. The choices are now almost limitless; 3 or 4 hours of IHD with standard settings or CRRT at 35 mL/kg/hr of effluent flow rate can be selected. SLEDD at blood and dialysate flow rates of 150 mL/min for 8 hours during the day or SLEDD for 12 hours overnight can be considered as an alternative.[41-47]

The Role of Renal Replacement Therapies in Different Clinical Conditions

Sepsis and Multiple Organ Dysfunction Syndrome

Extracorporeal blood purification therapies (EBPT) have been proposed as adjuvant therapies for sepsis and multiple organ dysfunction syndrome (MODS) (see Chapters 91 and 92). RRT has been the most frequently utilized type of therapy. There are some animal and patient data that show that RRT has some benefit in this clinical setting. Animal models of severe sepsis[47-49] demonstrated a beneficial effect of high-volume hemofiltration (HVHF) on hemodynamics, proportional to the intensity of UF that was used. The benefit found in the animal experiments has led to the use of HVHF as a "ideal model of therapy to be started when endotoxemia is present or suspected, or even before it" in patients. HVHF protocols have been developed by different authors: 4 to 10 L/hr UF sessions in most of cases lasting only 4 to 8 hours and followed by traditional CVVH have been suggested.

The first reports of using HVHF for the treatment of patients with septic shock and MODS have just appeared: Lonnemann[50] demonstrated that the use of HVHF led to improved macrophage function in that macrophages regained their ability to produce tumor necrosis factor-α (TNF-α) in response to endotoxin exposure. Oudemans-van Straaten and colleagues[51] conducted a prospective cohort analysis in 306 patients who received HVHF at a mean UF rate of 4 L/hr. They found improvements in hemodynamics, including cardiac index, blood pressure, and stroke volume in patients who had presented with abnormal parameters. They also documented an increase in patients' systemic vascular resistance that allowed a decrease in the doses of

dopamine administered to these patients. Honore and coworkers[52] evaluated the effects of short-term high-volume hemofiltration (STHVH) in 20 patients. In this investigation, STHVH lasted 4 hours and the 9-L/hr sessions were followed by conventional CVVH in these patients with severe septic shock. Eleven of the 20 patients responded to the therapy, because they had increases in cardiac index, mixed venous saturation, and arterial pH and reductions in their doses of epinephrine. The study also documented that the rate of survival to 28 days in the patients who responded was significantly higher (9 of 11) than in the patients who did not respond to this treatment. Because all the patients received STHVH, it is not clear what the mechanism was for the response and why some of the patients responded and others did not.

Cole and coworkers[53] measured hemodynamics, serum cytokines, and complement concentrations in 11 patients with septic shock and MODS. These patients were randomly assigned to HVHF (8 hr; 6 L/hr) or to standard CVVH. The decrease in vasopressors requirement was significantly higher in the patients who received HVHF. Cole noted that the patients in the HVHF group had insignificant concentrations of the measured soluble mediators in the ultrafiltrate, suggesting the filter may have adsorbed some of the mediators.

These studies are limited because they enrolled small numbers of patients.[53,54] The results show that HVHF techniques can be utilized in these unstable, critically ill patients and that some of the patients appear to derive benefit from the therapy. Larger randomized trials are needed before the routine use of these therapies in septic patients.[54-58]

Coupled plasma filtration adsorption (CPFA)[59,60] separates plasma from blood using a plasma filter and then the plasma is passed through a synthetic resin cartridge and returned to the blood. A second blood filter is used to remove excess fluid and small-molecular-weight toxins. The resin was chosen based on its adsorption capacity for important inflammatory mediators, low levels of extractable toxins, and an acceptable pressure flow performance profile. In a randomized clinical trial, this technique removed almost 100% of the circulating concentrations of TNF-α and interleukin-β (IL-β), allowing significant reductions of vasopressor drugs in the intervention patients compared with the patients who received CVVH. Therefore, more research is necessary to evaluate similar techniques in patients with septic shock.

Ultrafiltration During Cardiopulmonary Bypass

Ultrafiltration has been used for many years in pediatric cardiac patients in an effort to attenuate the effects of hemodilution that occur after cardiopulmonary bypass (CPB) (see Chapter 60). Reported benefits of UF include decreased total body water, higher systemic arterial blood pressure, decreased duration of postoperative inotropic support, improved preload, recruitable stroke work, improved oxygenation, better pulmonary compliance, decreased duration of ventilatory support, higher postoperative hematocrit value, lower postoperative blood loss and requirement for blood transfusion, higher concentrations of plasma proteins and fibrinogen, less production of thromboxane B_2 and less activation of complement, decreased pleural effusions, and shorter duration of hospitalization. Other studies have documented removal of vasoactive substances and inflammatory cytokines in the UF effluent.

There have been nine studies that have, in various manners, evaluated UF in perioperative pediatric cardiac patients.[57-66] Four studies evaluated the concentrations of inflammatory markers with UF; three found a postoperative reduction in the concentration of inflammatory markers including IL-8 and IL-6 in patients who received UF, and one study found no differences in the concentrations. Three other studies evaluated postoperative bleeding, and two found a reduction in postoperative bleeding with UF and one study found no difference. Three studies reported improved hemodynamics after UF, including improved cardiac index and blood pressure. Five studies found improved hematocrits and reduced patient weights after hemofiltration. Individual studies also found an increased variability in heparin concentration but no change in aprotinin concentrations. These studies included very few patients and so the effects of UF on mortality or morbidity cannot be assessed.

There have been two basic approaches to UF in pediatric cardiac patients. First, conventional ultrafiltration (CUF) performs UF during the rewarming phase of CPB. Because the patient is still on CPB, the volume of fluid removed with CUF is limited by the volume of the CPB circuit and the requirements of the venous reservoir for adequate arterial inflow. Modified ultrafiltration (MUF) is performed after the discontinuation of CPB and is, therefore, independent of the circuit volume. To perform MUF the patient is weaned off bypass and then the hemofilter pressure is maintained by the difference in pressure between the arterial inflow and the right atrial outflow. Because of this technical difference, more fluid can be removed with MUF than with CUF, assuming that no or minimal additional volume is added to the circuit during CUF. This difference may translate into greater efficacy in attenuating the deleterious effects of hemodilution and systemic inflammatory reaction. Although a number of studies have investigated the potential advantages of MUF, the issue of whether MUF has any intrinsic benefit over CUF aside from the potentially greater volume of fluid removed has yet to be investigated.[67,68]

A third approach is a combination of the CUF and MUF, which starts CUF as soon as 3 to 5 minutes after the discontinuation of bypass. After the complete weaning from bypass, UF is switched to the modified method. During the MUF period blood from the venous reservoir is transfused to compensate for the lost water, keeping the arterial blood pressure above 60 mm Hg.[69] This aggressive strategy was evaluated and found to decrease inflammatory mediators (IL-6, endothelin-1, thromboxane B_2), attenuate lung edema and inflammatory pulmonary injury, and improve pulmonary function.

Journois and coworkers conducted a randomized, controlled study of zero-balanced high volume UF in 20 children (UF rate equivalent to 7 to 9 L/hr in a 70-kg adult) undergoing cardiac surgery.[70] The study documented a significant reduction in postoperative blood loss and time to extubation and improved alveolar-arterial oxygen gradient.

Congestive Heart Failure

Fluid overload occurs in patients with congestive heart failure (CHF) and is usually treated with diuretics and, if necessary, inotropic support. Extracorporeal UF is a possible solution to

help restore fluid balance close to normal. Several new technologies have made UF available today in all centers and easy to be instituted. The largest study on the use of ultrafiltration in patients with CHF was the prospective, randomized, multicenter trial UNLOAD (UF versus intravenous diuretics for acute decompensated CHF). Two hundred patients were recruited and randomized to receive UF or diuretics.[71] Inclusion criteria required the presence of at least two signs of fluid overload defined by a standard physical examination or simple diagnostic tests: distended neck veins, edema or ascites, pulmonary congestion on a chest radiograph or on chest auscultation, a history of paroxysmal nocturnal dyspnea, or hepatomegaly. Those randomized to the UF arm did not receive any diuretics within the first 48 hours of randomization. Those randomized to standard therapy were on loop diuretics at a dose level that was at least twice that of their daily diuretic dose. The duration and rate of UF were not predefined and were carried out based on the clinical judgment of an investigator. The UNLOAD trial is the first randomized comparison of intravenous diuretic therapy alone against an alternative therapy, UF, in hypervolemic patients. The principal findings of this trial were (1) in hypervolemic patients with CHF, ultrafiltration led to greater weight and fluid loss than intravenous diuretics at the doses used in this trial; (2) volume removal with ultrafiltration at the index hospitalization was associated with significant reductions in the rate and durations of subsequent hospitalizations and fewer unscheduled medical visits for CHF; and (3) the benefits from the use of short-term UF over 90 days was achieved without significant adverse effects.

The removal of sodium and water cannot be dissociated when using diuretics or in certain renal replacement techniques. Diuretics lead to a natriuresis, whereas dialysis may result in hypotonia or hypertonia, depending on the effect of dialysis on the diffusion and on the removal of molecules, including urea and other electrolytes. Therefore, water removal is always associated with the removal of other solutes and the amount of solutes lost depends on the technique used. Slow continuous UF (SCUF) produces an UF that varies from plasma water minimally due to Donnan effects. The UF from SCUF is iso-osmotic and isonatremic because sodium elimination is linked to the sodium concentration in plasma. In contrast, the ultrafiltrate composition produced from CVVH and from hemofiltration in general is similar to plasma water but the sodium concentration in the UF can be significantly affected by the sodium concentration in the replacement solution. Sodium removal can be dissociated from water removal in CVVH, thus obtaining a real change of the sodium pool in the body. This effect on sodium cannot be achieved with any other technique. The advantage is that not only plasma concentrations can be normalized but also the electrolyte content in the extracellular and possibly intracellular volume are changed by this technique.[72]

Technical Notes

Nomenclature

- *Intermittent hemodialysis (IHD):* The most common technique utilized for chronic renal failure. A diffusive treatment in which blood and dialysate are circulated in countercurrent manner and usually a low permeability, cellulose-based membrane is employed. Dialysate must be pyrogen free but not necessarily sterile, because dialysate-blood contact does not occur. The UF rate is equal to the scheduled weight loss. This treatment can be typically performed 4 hours thrice weekly or daily. Qb: 150-300 mL/min; Qd: 300-500 mL/min.
- *Peritoneal dialysis (PD):* A diffusive treatment in which blood, circulating along the capillaries of the peritoneal membrane, is exposed to a dialysate. Access is obtained by the insertion of a peritoneal catheter, which allows the abdominal instillation of dialysate. Solute and water movement is achieved by the means of variable concentration and tonicity gradients generated by the dialysate. This treatment can be performed continuously or intermittently.
- *Slow continuous ultrafiltration (SCUF):* A technique in which blood is driven through a highly permeable filter via an extracorporeal circuit in a venovenous mode. The ultrafiltrate produced during membrane transit is not replaced so it corresponds to the weight loss. It is used only for fluid control in overloaded patients (i.e., CHF patients who do not respond to diuretic therapy). Qb: 100-250 mL/min; Quf: 5-15 mL/min (Fig. 96-2).
- *Continuous venovenous hemofiltration (CVVH):* A technique in which blood is driven through a highly permeable filter via an extracorporeal circuit in venovenous mode. The ultrafiltrate produced during membrane transit is replaced in part or completely to achieve blood purification and volume control. If the replacement fluid is delivered after the filter, the technique is defined as postdilution hemofiltration. If the replacement fluid is delivered before the filter, the technique is defined as predilution hemofiltration. The replacement fluid can be delivered both pre and post filter. Clearance for all solutes is convective and equals UF rate. Qb: 100-250 mL/min; Quf: 15-60 mL/min (see Fig. 96-2).

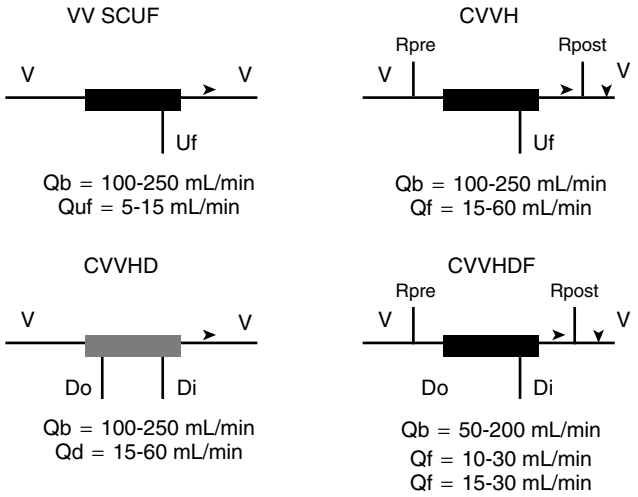

Figure 96-2 Schematic representation of most common continuous renal replacement therapy setups. *Black triangles* represent blood flow direction. VV, venovenous; Uf, ultrafiltration; Rpre, replacement solution prefilter; Rpost, replacement solution postfilter; Do, dialysate out; Di, dialysate in; Qb, blood flow; Quf, ultrafiltration flow; Qf, replacement solution flow; Qd, dialysate solution flow.

- *Continuous venovenous hemodialysis (CVVHD):* A technique in which blood is driven through a low permeability dialyzer via an extracorporeal circuit in venovenous mode and a countercurrent flow of dialysate is delivered in the dialysate compartment. The ultrafiltrate produced during membrane transit corresponds to the weight loss. Solute clearance is mainly diffusive and efficiency is limited to small solutes only. Qb: 100-250 mL/min; Qd: 15-60 mL/min (see Fig. 96-2).
- *Continuous venovenous hemodiafiltration (CVVHDF):* A technique in which blood is driven through a highly permeable dialyzer via an extracorporeal circuit in venovenous mode and a countercurrent flow of dialysate is delivered in the dialysate compartment. The ultrafiltrate produced during membrane transit is in excess of the patient's desired weight loss. A replacement solution is needed to maintain fluid balance. Solute clearance is both convective and diffusive. Qb: 100-250 mL/min; Qd: 15-60 mL/min; Qf: 15-60 mL/min (see Fig. 96-2).
- *Hemoperfusion (HP):* The patient's blood is circulated on a bed of coated charcoal powder to remove solutes by adsorption. The technique is specifically indicated in cases of poisoning or intoxication with agents that can be effectively removed by charcoal. This treatment may cause platelet and protein depletion.
- *Plasmapheresis (PP):* A treatment that uses specific plasma filters. The molecular weight cut-off of the membrane is much higher than that of hemofilters (100,000-1 million kD): thus, plasma as a whole is filtered and blood is reconstituted by the infusion of plasma products such as frozen plasma or albumin. This technique is performed to remove proteins or protein-bound solutes.
- *High-flux dialysis (HFD):* A treatment that utilizes highly permeable membranes in conjunction with a UF control system. Because of the characteristics of the membrane, UF occurs in the proximal part of the filter that is counterbalanced by a positive pressure applied to the dialysate compartment. This causes a phenomenon called backfiltration in the distal part of the filter from convective passage of the dialysate into the blood. Diffusion and convection are combined, but the necessity of a pyrogen-free dialysate replacement is avoided.
- *High-volume hemofiltration (HVHF):* A treatment that utilizes highly permeable membranes and hemofiltration with a high-volume setting: Qb > 200 mL/min; Qf > 45 mL/kg/hr.[41]
- *High-permeability hemofiltration (HPHF):* A treatment that utilizes high cut-off (60 kD) permeable membranes and hemofiltration. High treatment flows are not necessary, but a strict control of bigger molecules, like albumin, is recommended.[42]

Anticoagulation

The need for anticoagulation of the CRRT circuit is due to the contact between blood and the tubing of the circuit and the membrane of the filter. This contact induces activation of the coagulation cascade. This activation inevitably results in clotting of the filter or circuit. The quantity and duration of anticoagulation changes depending on the schedule of RRT; anticoagulation is necessary for continuous treatments, where the blood-artificial surface interaction is maximal.

Circuit Set-up Optimization

Several technical features of each RRT circuit affect the need for anticoagulation. Vascular access has to be of adequate size, kinking of the circuit tubing needs to be avoided, and the blood flow rate should exceed 100 mL/min, Pump flow fluctuations are mainly due to increased resistances in the circuit. The venous bubble trap is where air/blood contact occurs and so must be monitored. The plasma filtration fraction should be kept as far as possible below 20% and, when possible or considered correct, predilutional hemofiltration should be utilized. There is evidence that, when the circuit set-up is perfectly optimized, anticoagulants are only a relatively minor component of circuit patency: in fact, when patients have bleeding disorders (i.e., prolonged clotting times, thrombocytopenia) RRT can be safely performed without the utilization of any anticoagulant.[43]

Unfractioned Heparin

Unfractioned heparin (UFH) is the most widely used anticoagulant. It is easy to use and an antidote is available (protamine). Heparin doses range from 5 to 10 IU/kg/hr. In patients who require limited RRT, it can also be used in combination with protamine (regional heparinization) with a 1:1 ratio (150 IU of UFH per milligram of protamine), monitoring activated prothrombin time (aPTT). The problems with the use of UFH include its unpredictable bioavailability, the necessity for antithrombin III (ATIII) levels for optimal use, and the occurrence of heparin-induced thrombocytopenia (HIT).

Low-Molecular-Weight Heparins

Some centers now utilize low-molecular-weight heparins (LMWH) for RRT. Prospective studies have not yet shown LMWH to be superior in prolonging the life of RRT circuits. LMWH have better bioavailability than UFH and a lower incidence of HIT and they cost about 10% more than UFH.

Prostacyclin (PGI_2)

This agent is a potentially useful drug for anticoagulation for RRT, because it is the most potent inhibitor of platelet aggregation with a short half-life. PGI_2 is infused at a dose of 4 to 8 ng/kg/hr with or without the addition of low-dose UFH. Hypotension might be induced by higher doses of PGI_2. Some studies have demonstrated PGI_2 efficacy, but its high cost and harmful side effects might limit the use of this agent.[44]

Citrate

Citrate chelates calcium, which prevents clot formation. A calcium-free sodium citrate containing replacement solution or dialysate solution or both is prepared and is administered at the appropriate rate to achieve the desired aPTT (60 to 90 seconds). Calcium chloride is then administered to replace the chelated/dialyzed calcium and maintain normocalcemia. This approach is effective in maintaining excellent filter patency and compares favorably with heparin. It also avoids the risk for HIT and does not lead to systemic anticoagulation. The drawbacks of this anticoagulation management include the risks of hypocalcemia, metabolic alkalosis, and the cumbersome preparation of the replacement/dialysate fluid.[45,46]

Table 96-4 Anticoagulation Strategies

Drug	Pro	Con
No anticoagulation	High risk of bleeding patients	Relative shorter circuit lifespan
Unfractionated heparin	Routine	HIT
Low-molecular-weight heparin	Routine (alternative to UH)	HIT
Prostacyclin	Very short circuit lifespan	Hypotension
Citrate	Routine/very short circuit lifespan	Hypocalcemia
Danaparoid	HIT	Insufficient data available
Argatroban	HIT	Insufficient data available
Irudine	HIT	Insufficient data available
Nafamostat mesylate	HIT	Insufficient data available
Heparin-coated circuits	Routine	Insufficient data available

UH, unfractionated heparin; HIT, heparin-induced thrombocytopenia.

Other Strategies

Alternatives to the techniques presented here are listed in Table 96-4 for completeness.

Vascular Access

The fundamental role played by vascular access must be emphasized. Circuit failure is more often due to inadequacy of the vascular access than to insufficient anticoagulation. Thus, the optimal dialysis catheter can save the patient from an inappropriate increase in anticoagulation. Venovenous RRT relies on the use of a temporary double-lumen catheter. Such catheters are inserted in a central vein and available in various shapes and sizes. The site chosen for insertion of the double-lumen catheter should be done on the basis of clinical expertise, the body habitus of the patient, and the presence of other intravenous catheters that can be exchanged for the dialysis catheter. Cannulation of the right internal jugular vein, with the tip of the catheter reaching the right atrium, is associated with circuit blood flow rates of up to 300 mL/min. Catheter size for adult patients ranges from 12 to 14 French and the lengths from 16 to 25 cm. A 20-cm long catheter is used for the femoral vein location and has its tip positioned close to the inferior vena cava, allowing optimal flows within the circuit. When an inadequate blood flow in a catheter is suspected, venous and arterial lumens should be flushed with saline with the goal of testing resistance to injection. Limb clotting of the line versus kinking due to patient's position must be distinguished. Administration of heparin or urokinase into the catheters can be tried for a few hours to de-clot the catheter. The catheter can also be exchanged for a new catheter.

Summary

The mechanisms involved in RRT are founded on the principles of water and solute transport via diffusion and convection. These mechanisms have been applied and lead to different techniques (intermittent, extended, or continuous RRT) and modalities (hemofiltration, hemodialysis, hemodiafiltration, plasma filtration, hemoperfusion, coupled plasma filtration and adsorption). A precise understanding of technical and clinical implications of such therapies is important to achieve the desired results. Different RRT prescriptions, modalities, and schedules can be administered to critically ill patients with AKI. Clinical effects on critically ill patients depend on the selected RRT strategy and on the severity/complexity of the patients' clinical picture. A specific dose of RRT has not been adopted in clinical practice owing to a lack of enough clinical evidence. The best evidence to date supports an RRT dose of at least 35 mL/kg/hr—spKt/V 1.4—for CVVH, CVVHDF, or daily IHD.

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97 Cardiopulmonary Resuscitation: Basic and Advanced Life Support

Key Points

1. Chest compressions performed with minimal interruption are critically important in improving the chance of survival from sudden cardiac arrest.
2. Thirty chest compressions followed by two rescue breaths is the recommended ratio for single rescuers resuscitating children and adults.
3. Chest compressions should be performed at a rate of 100/min for children and adults.
4. The American Heart Association 2005 guidelines recommend that a single shock be delivered when a shockable dysrhythmia exists, followed by resumption of chest compressions as soon as the shock is delivered. Two minutes of chest compressions and ventilation should be performed before reassessing the underlying cardiac rhythm.
5. Automated external defibrillators (AEDs) may follow an outdated defibrillation protocol (e.g., three defibrillation shocks before resumption of cardiopulmonary resuscitation [CPR]). In this circumstance, the rescuer should allow the AED to function as programmed until a manual defibrillator becomes available.
6. When a rescuer is unfamiliar with the type of manual defibrillator used during resuscitation, a default energy of 200 J is a reasonable energy level for defibrillation.
7. In an unwitnessed cardiac arrest or in situations in which initiation of CPR has been delayed, 2 minutes of CPR before the first defibrillation has been shown to have survival benefit.
8. Hyperventilation during resuscitation increases intrathoracic pressure, impairs venous return to the heart, and has a negative impact on survival from cardiac arrest. The resuscitation team leader must ensure that only 8 to 10 breaths per minute are being delivered during resuscitation attempts.
9. Therapeutic hypothermia has demonstrated benefit in improving the neurologic outcomes of victims resuscitated from out-of-hospital ventricular fibrillation who remain comatose on hospital admission. This therapeutic intervention should be considered for victims of in-hospital ventricular fibrillation cardiac arrest with decreased neurologic function after resuscitation.
10. Resuscitation knowledge declines rapidly, even in anesthesia providers. Review of advanced cardiac life support (ACLS) resuscitation protocols may be necessary in the interim between ACLS certification. ACLS protocols should be made available on resuscitation carts to ensure that more uniform and accepted resuscitation interventions are followed during resuscitation attempts.

Although the history of resuscitation can be traced to at least biblical times,[1] contemporary approaches to cardiopulmonary resuscitation (CPR) date back to 1966, when a National Academy of Sciences National Research Council conference generated consensus standards for the performance of CPR.[2] Since that time, successive conferences have reviewed the practice of CPR in the light of available experimental and clinical data and have prepared revisions of previous standards.[3-9] The most recent recommendations, the "2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care" (Guidelines 2005), represent the second internationally recognized resuscitation guidelines developed by experts from the American Heart Association (AHA) and the European Resuscitation Council; accordingly, these guidelines represent a variety of countries, cultures, and medical specialties. Each intervention included in the new guidelines has undergone comprehensive evidence-based evaluation of the scientific information available supporting its uses in emergency cardiovascular care and resuscitation, as well as a structured and transparent process for managing potential conflicts of interest. Both basic life support (BLS) and advanced cardiac life support (ACLS) are established on credible foundations and have enjoyed widespread acceptance in the emergency cardiovascular care community. Indicative of this acceptance is the widespread popularity of the AHA BLS and ACLS training programs and related training materials. The intent of this chapter is to review the premise, rationale, and techniques

for the performance of both BLS and ACLS in light of current understanding and as published in AHA textbooks on BLS[10] and ACLS.[11] It is not the intent of this chapter to restate the performance of all BLS CPR procedures, which can be reviewed in the guidelines and also in the AHA BLS text.[10] Rather, both BLS and ACLS are reviewed within the context of their application by anesthesiologists in operating rooms, intensive care units (ICUs), and other patient care environments.

Basic Life Support

BLS involves early recognition of medical emergencies, activation of an emergency response system (e.g., dialing 911 in the United States), and interventions made in response to sudden cardiac arrest (SCA), heart attack, stroke, and airway obstruction by a foreign body. Airway, breathing, and circulation are BLS assessments readily performed without equipment. Rescue breathing, the Heimlich maneuver, CPR, and the application-use of an automated external defibrillator (AED) are BLS interventions. All BLS interventions are time sensitive for preventing SCA, terminating SCA, or supporting the circulation until restoration of spontaneous circulation occurs after SCA. For those performing BLS interventions, particularly CPR, the importance of prompt initiation and expert performance of these skills cannot be overemphasized. AEDs are included in BLS interventions because of their widespread availability in public spaces (i.e., airports, schools, shopping centers, hospitals, casinos, sporting arenas), their uncomplicated application, and automated analysis of cardiac rhythm and administered shocks (if indicated based on analysis of cardiac rhythm by the AED). The interdependency of BLS components will be reviewed in light of current understanding and the 2005 AHA recommendations.

Cardiopulmonary Resuscitation

SCA is a complex and dynamic process. Antegrade systemic arterial blood flow continues after cardiac arrest until the pressure gradient between the aorta and right heart structures reach equilibrium. A similar process occurs during cardiac arrest with antegrade pulmonary blood flow between the pulmonary artery and the left atrium.[12-14] As the arterial-venous pressure gradients dissipate, the left heart becomes less filled, the right heart becomes more filled, and the venous capacitance vessels become increasingly distended (Fig. 97-1). When arterial and venous pressure equilibrates (approximately 5 minutes after cardiac arrest), coronary perfusion and cerebral blood flow stop.

In the absence of native cardiac function and systemic circulation, CPR is performed until return of spontaneous circulation occurs, the patient is pronounced dead, or in some special circumstances, the patient is placed on extracorporeal circulation and membrane oxygenation (ECMO). Although CPR is far less efficient than the native circulation, when properly performed, it can provide coronary circulation and cerebral blood flow sufficient to afford full recovery in many cases if return of spontaneous circulation can be reestablished.

"Push hard and push fast" are the recommendations for chest compressions during CPR from the 2005 International Consensus conference.[15] Although there is insufficient evidence from human studies to identify an ideal chest compression rate, chest compressions performed at a rate of 100/min and with enough force to generate a palpable carotid or femoral pulse are considered ideal. Chest compressions are frequently interrupted during resuscitation attempts.[16-18] These interruptions have a negative impact on coronary and cerebral perfusion, as well as on return of spontaneous circulation.[14,19] Current recommendations for CPR reflect these observations by placing increased emphasis on limiting interruptions in chest compressions, even for other resuscitative measures (i.e., rescue breaths, attempts at defibrillation, tracheal intubation). During single- and two-person CPR, Guidelines 2005 recommends compression-ventilation ratios of 30:2 in both scenarios with minimal interruption in chest compressions for rescue breaths.

Physiologic Considerations

Since the early 1960s, when CPR became a widespread clinical technique, it has been assumed that blood is ejected as a direct result of actual compression of the heart between the sternum and the vertebral column. This is commonly referred to as the "*cardiac pump mechanism*." Transesophageal echocardiography during CPR in humans provides an opportunity to assess changes in cardiac dimensions and valve positions during chest compressions, as well as the direction of blood flow. Observations made with echocardiography during CPR describe a reduction in left and right ventricular volume, closure of the tricuspid and mitral valves during chest compression, and ejection of blood into the arterial system, all of which are consistent with the cardiac pump mechanism (Fig. 97-2).[20-23]

Repeated, forceful coughing (cough CPR) can sustain consciousness during ventricular fibrillation (VF) for as long as 100 seconds when the arrhythmia (or any arrhythmia capable of rapidly compromising cardiac output) is immediately recognized and the patient can respond to verbal prompts to cough. This observation suggests that mechanisms other than direct cardiac compression may account for forward blood flow during cardiac arrest.[24] Vigorous coughing produces an arterial pressure pulse associated with forward blood flow that opens the aortic valve during the generation of pressure and flow.[25] These findings

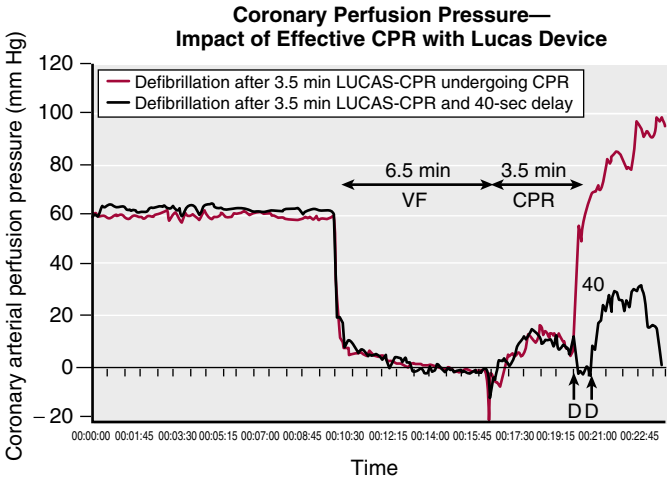

Figure 97-1 Effect of ventricular fibrillation on coronary perfusion pressure followed by CPR and defibrillation. CPR, cardiopulmonary resuscitation; D, defibrillation; VF, ventricular fibrillation. *(From Steen S, Liao Q, Pierre L, et al: The critical importance of minimal delay between chest compressions and subsequent defibrillation: A haemodynamic explanation. Resuscitation 58:249, 2003.)*

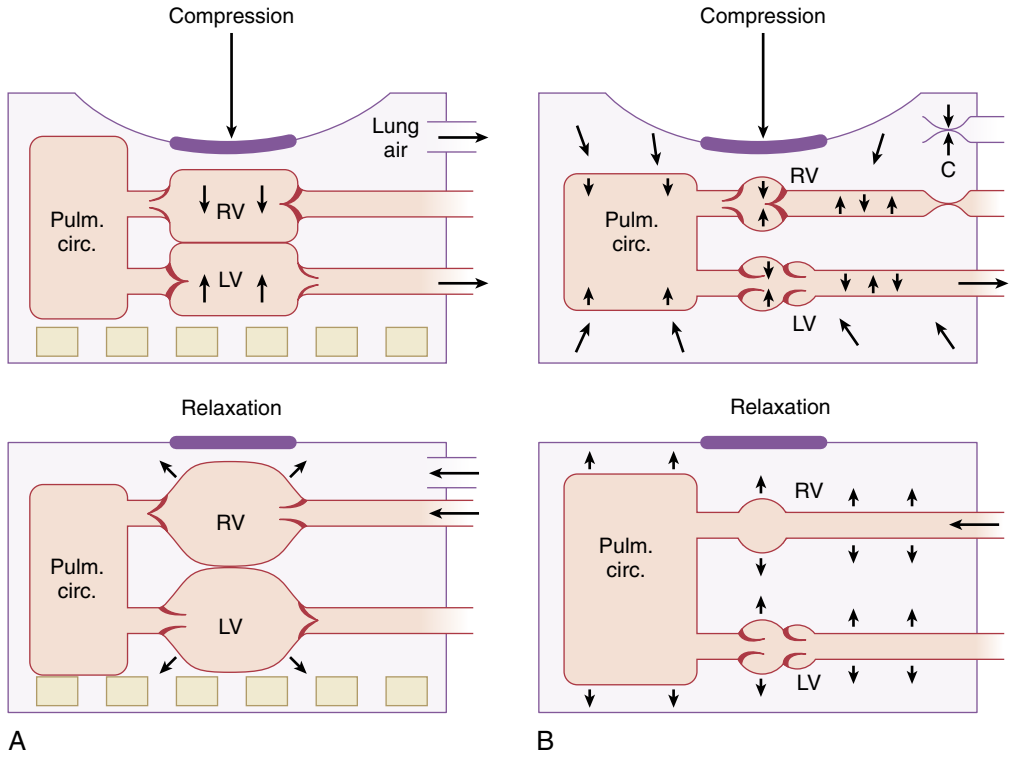

Figure 97-2 **A,** Schematic representation of the cardiac compression pump. **B,** The intrathoracic pressure pump. C, in panel **B** represents collapse of airways and venous structures. LV, left ventricle; RV, right ventricle. *(Redrawn with modification from Halperin HR: Mechanisms of forward flow during external chest compression.* In *Paradis NA, Halperin HR, Nowak RM [eds]: Cardiac Arrest: The Science and Practice of Resuscitation Medicine. Baltimore, Williams & Wilkins, 1995, p 252.)*

support the proposal that increases in intrathoracic pressure generate forward blood flow,[26] which is commonly referred to as the "*thoracic pump mechanism*" (see Fig. 97-2). The increasing intrathoracic pressure during chest compression equalizes intravascular pressure within the thorax. On the venous side, valve and venous collapse at the thoracic inlet limits the transmission of retrograde pressure or flow. The arterial system, which is relatively resistant to collapse, transmits pressure and flow into the extrathoracic arterial tree. A peripheral arteriovenous pressure difference is thus established that permits blood to flow forward in the extrathoracic vascular system. Some studies suggest that during compression or vigorous coughing the left side of the heart may act as a passive conduit for transfer of pulmonary venous blood out into the peripheral arterial circulation. During compression, blood flows from the lungs through the left ventricle toward the periphery. The pulmonary valve is closed and the mitral and aortic valves are open during periods of high intrathoracic pressure when the chest is compressed.[27]

There is evidence that both cardiac pump and thoracic pump mechanisms exist at times during resuscitation attempts. Echocardiographic evidence clearly demonstrates findings consistent with the cardiac pump theory. Cough CPR is effective in maintaining consciousness, at least in the early period after the onset of lethal arrhythmia, consistent with the thoracic pump theory. Chest compressions during cardiac arrest may initially promote a cardiac pump mechanism as a result of the presence of blood in the left heart. As pressure gradients between the arterial and venous systems equilibrate during prolonged resuscitation, pulmonary blood volume increases and probably supports a thoracic pump mechanism.

Systemic, coronary, and cerebral blood flow during CPR is dependent on effective chest compressions, as well as on return of venous blood to the heart. At chest compression rates of 80 to 100/min, the compression-relaxation ratio approaches 50:50. The time available for return of blood to the thorax is limited. Venous blood returns to the thorax at very low pressure during cardiac arrest. Modest increases in intrathoracic pressure will impair return of venous blood and have a negative impact on systemic, coronary, and cerebral perfusion, in addition to reducing the chance of spontaneous circulation.[28]

Cardiac output during CPR with effective, uninterrupted chest compression is 25% to 30% of the normal spontaneous circulation. Systemic and pulmonary perfusion during CPR reflects the decreased cardiac output as demonstrated by weak carotid pulses with compression and low carbon dioxide excretion (as will be addressed later). In cardiac arrest without a hypoxic etiology (e.g., drowning, suffocation), oxygen content in the lungs at the time of cardiac arrest is usually sufficient for maintaining an acceptable arterial oxygen content during the first several minutes of CPR. Rescue breaths are less important than initiating chest compressions immediately after the onset of SCA. Blood flow rather than arterial oxygen content is the limiting factor for delivery of oxygen to the coronary, cerebral, and systemic circulation during CPR. Multiple modifications to standard CPR exist, as well as mechanical adjuncts to improve circulation during CPR. A few will be reviewed here in light of current understanding.

Interposed abdominal compression (IAC) is a form of CPR in which the abdomen is compressed midway between the xiphoid process and the umbilicus during the upstroke of the chest com-

pression phase in an attempt to sustain aortic diastolic pressure and thus improve coronary perfusion pressure, a critical determinant of successful restoration of spontaneous circulation. Experimental evidence has shown that carotid blood flow[29] and end-diastolic arteriovenous pressure differences,[30] indexes of coronary perfusion pressure, are increased with IAC-CPR. In a recent evidence-based review of IAC-CPR, Babbs[31] reported evidence of improved immediate resuscitation when this technique was applied to in-hospital cardiac arrest victims based on the results of three randomized human studies. Though accepted by the AHA as an satisfactory adjunct to standard CPR, this intervention is rarely used despite recognition of its benefits, minimal risk, and easy application. When sufficient personnel trained in the technique are available, AIC-CPR can be considered a reasonable alternative to standard CPR.

Active compression-decompression CPR (ACD-CPR) accomplishes compression and active decompression of the thorax by means of a device containing a suction header, bellows, and a compression area within the bellows. Preliminary data in arrested humans comparing ACD-CPR with standard CPR have provided evidence of hemodynamic benefit, with higher systolic arterial pressure and end-tidal carbon dioxide pressure (P_{ETCO_2}) and echocardiographic demonstration of an increased velocity-time integral, an analog of cardiac output. In humans studied during implantation of cardioverter-defibrillators, ACD-CPR increased systemic arterial pressure, coronary perfusion pressure, and minute ventilation when compared with standard CPR.[32] Although these observations provided clinical support for experimental studies indicating improved hemodynamic (and perhaps ventilatory) function with ACD-CPR versus standard CPR, still lacking was evidence of benefit on patient outcome.

Several studies of ACD-CPR have been performed in patients after out-of-hospital cardiac arrest,[33-35] but none have demonstrated an improvement in patient outcome in terms of hospital discharge when ACD-CPR was compared with standard CPR. The largest study comparing ACD-CPR with standard CPR included 1784 adults after in-hospital and prehospital cardiac arrest. This study, like its predecessors, concluded that ACD-CPR does not improve survival or neurologic outcomes.[36] Thus, despite the earlier experimental and clinical evidence that ACD-CPR may confer benefit to victims of cardiac arrest by virtue of enhanced hemodynamic variables, no evidence supports the hypothesis that ACD-CPR improves outcomes after cardiac arrest in humans when compared with standard manual CPR. The ACD-CPR device may also expose patients to harm.[37] Currently, no ACD-CPR devices are approved by the Food and Drug Administration for sale in the United States.

The impedance threshold device (ITD) limits entry of air into the lungs during the recoil phase after chest compression, thereby creating greater negative intrathoracic pressure and drawing greater blood volume into the chest than with standard CPR. What results appears to be greater coronary blood flow (occurring during the diastole/chest recoil phase of chest compressions), greater cerebral blood flow, and improved hemodynamics in comparison to standard CPR. The results of animal and clinical studies endorse the benefits of this device, which include improved resuscitation and short-term survival when compared with standard CPR.[38-40] Although this device is most effective with endotracheal tubes, if a rescuer can maintain a good seal with a facemask, the ITD can be used. Even though long-term survival has not been documented after use of the ITD during resuscitation, if the device is available, there are no compelling reasons to not consider using this technology.

Circumferential compression of the chest with a load-distributing band (LDB) has been described as a mechanism for generating fluctuations in intrathoracic pressure and thereby improving blood flow by exploiting the thoracic pump mechanism beyond that possible with standard CPR.[41,42] This device wraps circumferentially around the patient's torso, is closed with Velcro, and then automatically adjusts the length of the belt to fit snuggly around the patient's chest. Repetitive shortening of the belt compresses the chest and generates forward blood flow. Chest recoil occurs as the belt relaxes. As with the other devices already mentioned, the LDB has been shown in a preliminary study to increase both aortic and coronary perfusion pressure in animals, which has resulted in improved survival and neurologic outcome.[43,44] However, a recent multicenter, randomized prehospital clinical trial to evaluate the effectiveness of an LDB was halted early because of markedly reduced neurologic recovery in cardiac arrest victims on whom the LDB was used when compared with cardiac arrest victims who received standard CPR.[45] The authors speculate that application of the device probably delayed or interrupted CPR and also noted that the time to first defibrillation in the LDB group occurred on average 2.1 minutes after the standard CPR group.

Although the devices mentioned here all demonstrate improved circulation and blood flow in comparison to standard CPR during cardiac arrest in humans, none of the devices demonstrate improved hospital discharge rates after resuscitation from cardiac arrest. What is certain is that CPR, regardless of the mechanism of blood flow and technique, is only a temporizing procedure in need of rapid supplementation with ACLS, most critically, rapid defibrillation of the fibrillating heart.

Monitoring Performance of Cardiopulmonary Resuscitation

Until recently, palpation of the carotid or femoral pulse and observation of pupillary size were the standard and very indirect measures for assessing the apparent adequacy of CPR. Obviously, a palpable large-artery pulse indicates only the transmission of a pressure wave into the arterial tree during chest compression and provides no objective evidence of the effectiveness of cardiac output. Initial *pupillary* size and changes during CPR are of some prognostic value.[46] Pupils that are persistently contracted or initially dilated but subsequently contracting are associated with a greater likelihood of successful resuscitation and neurologic recovery than persistently dilated or subsequently dilating pupils are.[47]

Monitoring systemic arterial pressure directly, as can usually be accomplished during in-hospital CPR, is helpful in optimizing the rate and depth of chest compressions.[48] Aortic diastolic pressure in particular, an index of coronary perfusion pressure, should be monitored whenever possible and optimized with appropriate changes in manual compression technique and early and repeated injection of epinephrine and vasopressin before restoration of spontaneous circulation.

In 1978, Kalenda[49] described the use of capnography as a guide to the effectiveness of external chest compressions. He demonstrated the value of monitoring P_{ETCO_2} in three patients in cardiac arrest and confirmed changes in P_{ETCO_2} with restoration of spontaneous circulation. Kalenda proposed that when ventilation is constant, as during controlled mechanical ventila-

tion, "the expired CO_2 is a precise and continuous mirror of lung perfusion and hence of cardiac output."[49]

Despite the potential clinical importance of Kalenda's well-documented observations and conclusion, it was several years before monitoring of P_{ETCO_2} during cardiac arrest and CPR was explored further. In 1984, using a porcine model of cardiac arrest, Grundler and colleagues[50] demonstrated a rapid decrease in P_{ETCO_2} with the onset of arrest and its immediate increase with resuscitation. Based on these preliminary experimental observations, this group suggested that P_{ETCO_2} monitoring may be a relatively simple and noninvasive guide to advanced life support interventions during CPR.[50,51] Severe reductions in pulmonary blood flow during cardiac arrest and CPR and therefore an acute failure of delivery of O_2 to the lungs explained the very low P_{ETCO_2} and increased venous CO_2 pressure (P_{VCO_2}) observed (see the discussion of sodium bicarbonate).[52] Subsequent studies in dogs provided confirmation of the possible utility of P_{ETCO_2} in that expired P_{VCO_2} correlated very closely with coronary perfusion pressure, which itself was shown to be a determinant of survival from cardiac arrest in this model.[53,54] In a porcine model of VF, the onset of VF was associated with a rapid decline in P_{ETCO_2} from a mean (±SEM) of 4.0% ± 0.2% to less than 0.7% ± 0.2%.[55] With external chest compression and constant-volume mechanical ventilation, P_{ETCO_2} increased to 1.9% ± 0.3%, with an immediate increase to 4.9% ± 0.3% after successful defibrillation and 12 minutes of CPR. Close correlation was found between changes in cardiac output and P_{ETCO_2} during both closed-chest and open-chest CPR.[55]

P_{ETCO_2} monitoring has been reported in arrested humans undergoing CPR.[56-59] In a study of 10 patients in whom spontaneous circulation returned, P_{ETCO_2} increased immediately on restoration of spontaneous circulation from a mean (±SD) of 1.7% ± 0.6% to 4.6% ± 1.4%.[56] The rapid increase in P_{ETCO_2} was often the first clinical evidence of resumption of spontaneous circulation.

In 10 critically ill patients, 9 of whom were in septic or cardiogenic shock at the onset of cardiac arrest, P_{ETCO_2} decreased from a mean (±SD) of 1.7% ± 0.9% to 0.4% ± 0.4% shortly after the onset of cardiac arrest.[59] The very low pre-arrest value is indicative of low cardiac output and therefore low pulmonary blood flow. During external chest compression, this value increased to 1.0% ± 0.5%. In seven patients in whom circulation was restored, P_{ETCO_2} rapidly increased from 1.3% ± 0.5% to 3.7% ± 2.1% and then declined to a stable volume of 2.4% ± 1.8% 4 minutes after resumption of spontaneous circulation. In patients with whom resuscitation failed to restore spontaneous circulation, P_{ETCO_2} remained at 0.7% ± 0.4%.[59]

Evidence is increasing that P_{ETCO_2} measurements obtained during cardiac arrest and CPR may have predictive value relative to the likelihood that spontaneous circulation will be restored. In one study, patients who later had a pulse had a mean P_{ETCO_2} of 19 ± 14 (SD) mm Hg at the beginning of resuscitation, whereas those who never regained a spontaneous pulse had a mean P_{ETCO_2} of 5 ± 4 mm Hg ($P < .0001$).[58] Other investigations have observed similar significant differences in P_{ETCO_2} during CPR between patients in whom spontaneous circulation develops and those in whom it does not.[60-62] Two of these studies were conducted in patients after out-of-hospital cardiac arrest.[61,62] P_{ETCO_2} was significantly higher during CPR in patients who subsequently regained spontaneous circulation than in those who did not. For example, 1 minute after the initiation of measurement, P_{ETCO_2} was 23.0 ± 17.4 mm Hg in those who regained pulses and 13.2 ± 14.7 mm Hg in those who did not ($P = .0002$) (Table 97-1). Differences of similar magnitude were noted at 2 minutes, as well as differences in the maximum value observed during resuscitation.[61] Although more such data are needed to quantitate the predictive power of these differences, it seems certain that P_{ETCO_2} measurements during cardiac arrest and CPR will become an objective index to predict the likelihood that persistent resuscitative effort will result in restoration of spontaneous circulation.

The major determinants of P_{ETCO_2} are CO_2 production, alveolar ventilation, and pulmonary blood flow.[63-66] In the presence of constant-volume ventilation and apparently unchanged CO_2 production immediately after cardiac arrest, the changes in P_{ETCO_2} observed both experimentally and clinically during cardiac arrest and CPR and during resumption of spontaneous circulation indicate that P_{ETCO_2} reflects pulmonary blood flow and therefore cardiac output.[56-60] Monitoring of both systemic arterial pressure by arterial catheter and P_{ETCO_2} with controlled ventilation should provide optimal hemodynamic assessment of the adequacy of the resuscitative effort and response to interven-

Table 97-1 End-Tidal Carbon Dioxide in Cardiopulmonary Resuscitation

	P_{ETCO_2} (mm Hg)					
	With ROSC			Without ROSC		
Patients	No. of Patients	Mean ± SD	95% CI	No. of Patients	Mean ± SD	95% CI
All						
1 minute	14	23.0 ± 7.4	18.7-27.3	13	13.2 ± 14.7	10.4-16.1
2 minutes	12	26.8 ± 10.8	20.0-33.7	12	15.4 ± 5.7	11.8-19.0
Maximum during CPR	14	30.8 ± 9.5	25.3-36.3	13	22.7 ± 8.8	17.4-28.0
Ventricular fibrillation						
1 minute	8	24.3 ± 6.8	18.5-30.0	5	12.0 ± 4.2	6.8-17.2
2 minutes	6	28.2 ± 11.4	16.2-40.1	5	12.4 ± 4.3	7.0-17.8
Maximum during CPR	8	33.0 ± 10.2	24.5-41.5	5	20.6 ± 11.1	6.8-34.4

CPR, cardiopulmonary resuscitation; P_{ETCO_2}, end-tidal carbon dioxide pressure; ROSC, restoration of spontaneous circulation.
Adapted from 2005 AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 112 (Suppl I):IV-1-IV-203, 2005.

tions such as changes in depth, rate, and location of manual chest compressions, as well as response to drugs such as epinephrine and vasopressin.[48]

Compelling evidence confirms major deficiencies in the provision of CPR, particularly by trained health care professionals, in both out-of-hospital and in-hospital settings.[16,17,67,68] Long pauses without chest compressions and compressions that are suboptimal in both rate and depth are frequent in both settings and result in decreased blood flow. Animal studies have shown that inadequate blood flow from poorly performed CPR during cardiac arrest has a negative impact on both restoration of spontaneous circulation and survival.[14,69,70] Clinical evidence also suggests that excessive ventilation occurs during resuscitation attempts and likewise has a negative impact on resuscitation outcomes.[28] In light of these observations, the major focus in Guidelines 2005 simplified CPR for the purpose of prolonging uninterrupted chest compression.

Airway Control and Ventilation

Ventilation is critical for restoration of spontaneous circulation and organ preservation during cardiac arrest. The AHA ACLS training program has effectively conveyed this treatment priority.[9] The techniques used for providing ventilation are obviously dependent on the clinical situation. The head tilt–chin lift maneuver is recommended for initial airway control.[9,71,72] The epiglottis rather than the tongue is the major cause of upper airway obstruction in unconscious humans.[73] Because of its ligamentous attachments to the hyoid bone, the epiglottis can be lifted by manual maneuvers that displace the hyoid bone anteriorly. These observations provide anatomic confirmation of the efficacy of the head tilt–chin lift technique for opening an obstructed airway. The head tilt–jaw thrust maneuver accomplishes the same purpose in restoring airway patency.[74]

When rescue breathing is indicated for a nontracheally intubated cardiac arrest victim, two 1-second breaths are delivered after the 30th compression during both one- and two-person CPR.[9] Rescue breaths should provide only enough force and volume to cause chest rise. Excessive ventilation force or tidal volumes run the risk of overcoming esophageal opening pressure and thereby contributing to gastric inflation[75] and its consequences.[76,77] Once a tracheal tube is in place, ventilation can occur at a rate of 8 to 10 breaths per minute independent of chest compressions.[9] Ventilation should minimally disrupt chest compressions.

During the first few minutes after the onset of cardiac arrest, chest compressions are more important than rescue breathing (provided that the cardiac arrest is not secondary to asphyxiation, as with drowning or suffocation). Delivery of oxygen to tissues with CPR is limited more by blood flow and low cardiac output than by arterial content.[9] The low cardiac output associated with CPR results in low oxygen uptake from the lungs, which in turn reduces the need to ventilate the patient during this low-flow state.[78] In view of this information, uninterrupted chest compressions must be given the highest priority early in resuscitation efforts.

Anesthesiologists use advanced life support procedures and devices early in resuscitation, whether in the operating room or elsewhere; these procedures are reviewed here within the context of early control of the airway and ventilation. In the traditional BLS/ACLS format, these procedures are all considered ACLS techniques and adjuncts.

Endotracheal intubation is the usual and expected standard of airway control in the critical care setting.[79] Alternative airways that may be useful in gaining rapid control of the airway and ventilation while reducing the risk of pulmonary aspiration of gastric contents in situations in which tracheal intubation is not possible include the laryngeal mask airway (LMA) and the esophageal-tracheal Combitube[80-82] (also see Chapter 50). These devices are classified in Guidelines 2005 as acceptable and possibly helpful, especially when the rescuer is inexperienced in placing tracheal tubes.[9] Although they may be helpful as temporizing devices, endotracheal intubation remains the optimal technique for controlling the airway and ventilating the lungs during CPR. Regardless of the device used, once an advanced airway is inserted and placement confirmed, ventilation can be provided at a rate of 8 to 10/min without interruption of chest compressions.

Confirmation of proper placement of an endotracheal tube can be difficult in a patient who has undergone cardiac arrest. Observation of the rise and fall of the thorax and auscultation of lung fields in this situation can be misleading. Likewise, because of the very low pulmonary blood flow during CPR, P_{ETCO_2} detection devices may not readily distinguish tracheal from esophageal intubation. For these reasons, esophageal detector devices based on the description by Wee[83] have been introduced and advocated for use in emergency situations such as cardiac arrest. Both a syringe and a self-inflating bulb have been used. The efficacy of these devices in distinguishing esophageal from tracheal intubation is based on the principle that the trachea remains patent during aspiration of air whereas the esophagus collapses because of its fibromuscular structure. The effectiveness of the self-inflating bulb in distinguishing esophageal from tracheal tube position[41,42,84] and in confirming proper position of the esophageal-tracheal tube has been documented.[85] In an emergency patient population, an esophageal detector device as described by Wee was observed to be more accurate than detection of P_{ETCO_2} because of its greater accuracy in patients in cardiorespiratory arrest.[83] False-negative results with the self-inflating bulb occur more frequently in emergency intubations than in anesthetized patients undergoing elective procedures. Causes include partial tube obstruction with secretions, atelectasis, bronchospasm, and endobronchial intubation.[86] A high incidence of false-negative results was observed in morbidly obese patients.[87] In these patients, reduced functional reserve capacity and large-airway collapse secondary to invagination of the membranous posterior tracheal wall after the application of subatmospheric pressure with the self-inflating bulb were identified as the cause of the false-negative results.[87] With these limitations in mind, the self-inflating bulb or syringe-type esophageal detector is useful in emergency situations such as cardiac arrest, particularly when used in combination with P_{ETCO_2} detection.

Despite extensive experience with the LMA in fasted patients undergoing general anesthesia, its role during CPR remains somewhat controversial.[88-92] In anesthetized patients, positive-pressure ventilation with the LMA is safe and effective, but concern was expressed that gastric inflation could be a problem in the presence of increased inflation pressure.[93] This problem, of course, is common in patients who sustain cardiorespiratory arrest because they typically have a full stomach and frequently require high inflation pressure during ventilation. The

LMA has been used successfully in arrested patients who have no evidence of regurgitation or aspiration.[94] In patients in whom endotracheal intubation is not possible, the LMA is more secure than a facemask and offers an alternative to control the airway and ventilate the patient.[90,95] Importantly, placement of an LMA by an inexperienced provider cannot result in unrecognized esophageal intubation in a patient requiring emergency airway management.

The esophageal-tracheal Combitube is an acceptable alternative airway device for use in cardiac arrest. The Combitube is a double-lumen device with proximal pharyngeal and distal inflatable cuffs that is introduced blindly into the airway. One lumen of the device has a closed distal lumen and ventilation holes at the level of the hypopharynx. The second lumen is open ended with a balloon cuff at its distal end. Both lumens of the airway can accommodate ventilation. Once inserted and followed by inflation of the pharyngeal and distal cuffs, confirmation of the proper ventilation port is mandatory. Auscultation and P_{ETCO_2} detection must demonstrate that tracheal rather than esophageal ventilation has been achieved.[96] When the esophageal-tracheal Combitube is properly placed, the airway is isolated and the risk for aspiration of gastric contents is reduced.

If these devices and techniques are unsuccessful in securing an airway, immediate cricothyroidotomy may be necessary. A 12-, 13- or 14-gauge catheter-over-needle device can be inserted quickly into the trachea through the cricothyroid membrane. Equipment permitting transtracheal jet ventilation from a 50-psi oxygen source through such a catheter should be available in the operating room and ICU.[97,98] Benumof and Scheller[98] provided specific guidelines for acceptable transtracheal jet ventilation systems. These guidelines should be considered for the implementation of an effective jet ventilation system in operating rooms or ICUs. Ventilation of an arrested patient can be accomplished with a variety of devices, including anesthesia bags, self-inflating bags, oxygen-powered, manually cycled demand valves with peak flow rates of 40 L/min, and time cycled, constant inspiratory flow rate generators known as automatic transport ventilators.

Increasingly, airway management and ventilation conducted in the setting of resuscitation has come under scrutiny.[16,17,67,68] Clinical studies support the concept that circulation, not ventilation, has the greatest impact on survivability after cardiac arrest.[67,99,100] Yet chest compressions are frequently interrupted for prolonged periods to allow either ventilation or placement of an advanced airway in both the in-hospital[16] and prehospital environments.[17] Ventilation during resuscitation, with or without the advanced airway in place, is often excessive and associated with increased intrathoracic pressure, lower coronary perfusion pressure, impaired venous return, and ultimately, decreased survival.[28,101] The team leader must be attentive to the rate and vigor of ventilation performed during resuscitation attempts, in addition to other components of therapy.

Automated External Defibrillators and Manual Defibrillation

The most frequent cardiac rhythm responsible for witnessed cardiac arrest in adults is VF. CPR prolongs the duration of VF but cannot convert the arrhythmia to an organized rhythm. Successful termination of this arrhythmia requires prompt electrical defibrillation, not medications. The most recent AHA guidelines include early defibrillation with an AED as part of BLS training and the concept of public-access defibrillation, which endorses the policy of making defibrillation available to victims of cardiac arrest through nonconventional providers (e.g., police, security guards, and others).[9] The AED, when applied to a patient, is capable of analyzing cardiac rhythm, detecting VF and rapid ventricular tachycardia (VT), and then delivering a defibrillatory shock. A trained rescuer's role is to apply the defibrillator pads to the patient's chest, activate the AED, and if the device indicates that a shock is indicated, deliver the shock by pushing a button when prompted to do so by the AED.

Previous guidelines addressing AED use in cardiac arrest recommended administering up to three consecutive uninterrupted shocks if needed to terminate VF. Chest compressions were not performed during the shock sequence. Current experimental and clinical evidence suggests that success in defibrillation and survival are negatively influenced by frequent or prolonged interruptions in chest compressions during cardiac arrest.[14] In light of this most recent information, Guidelines 2005 recommends a single shock from an AED followed immediately by a 2-minute period of CPR, the equivalent of five cycles of 30:2 chest compression-ventilation, before reanalysis of the cardiac rhythm. Chest compressions are continued until the AED is charged and ready to deliver the shock. In most instances, the heart is at least transiently "stunned" by defibrillation shocks and is benefited by a period of coronary blood flow with chest compressions. For the exceptional patient with invasive monitoring present at the time of cardiac arrest, if an organized cardiac rhythm with a perfusing arterial waveform follows defibrillation, chest compressions may not be indicated.[70] The recommended sequence of actions to minimize interruptions in CPR during treatment of cardiac arrest with AED technology is shown in Figure 97-3.

VF is a highly metabolically active state of the myocardium. In the presence of VF, myocardial stores of oxygen and metabolic

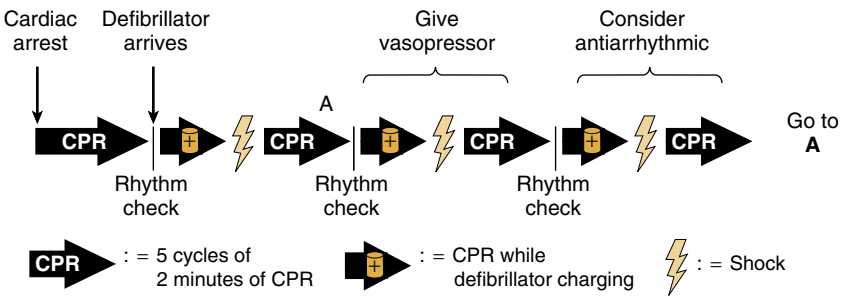

Figure 97-3 Pulseless arrest: treatment sequences. CPR, cardiopulmonary resuscitation. *(From CPR and ECC Guidelines 2005. Handbook of Emergency Cardiovascular Care for Healthcare Providers. Dallas, American Heart Association, 2006, p 8.)*

substrates are depleted rapidly. Chest compressions deliver oxygen and energy substrates to the myocardium, thus making defibrillation more likely. Experimental animal[102] and prehospital evidence from Seattle[103] and Oslo[104] demonstrate increased defibrillatory success when CPR is provided before defibrillation, particularly if the cardiac arrest was unwitnessed or if the time between cardiac arrest and arrival of rescuers exceeds 4 minutes. Guidelines 2005 recommends 2 minutes of CPR (five cycles of 30:2 compression-ventilation) before the first rhythm analysis of the cardiac arrest in the setting of unwitnessed cardiac arrest or delays in initiation of CPR. In settings in which defibrillation technology (manual defibrillator or AED) is immediately available (i.e., <3 minutes), rescuers should begin CPR and then defibrillate as soon as possible.[9]

The first AED was introduced in 1979.[105] In 1986, the first microprocessor-based AED was introduced; this AED used three successive, nonescalating, 180-J monophasic damped waveform shocks. Advances in defibrillator technology, including conversion from monophasic to biphasic defibrillator waveforms, resulted in smaller, lighter units with more accurate rhythm analysis. Impedance-compensated, nonescalating low-energy biphasic waveforms (150 J) were first introduced in 1996 and have been shown to achieve success in terminating VF in comparison to traditional, escalating-energy monophasic waveforms (200 to 300 J) in the controlled setting of an electrophysiology laboratory.[106-108] Biphasic waveforms deliver energy first in one direction and then reversed for the duration of the impulse. One of two biphasic waveforms is used in modern AEDs and defibrillators: biphasic truncated and rectilinear biphasic. Both waveforms have proved effective in terminating VF, with the energy levels used being specific to each waveform. Impedance compensation allows the defibrillator to change waveform morphology based on the impedance measured during delivery of a shock (typically 70 to 80 Ω) to generate transthoracic current capable of defibrillation. Biphasic defibrillation waveforms and impedance compensation together allow effective defibrillation at lower energies than with monophasic, non–impedance-compensated monophasic waveforms.[109-112] Defibrillation success is defined as termination of VF into an organized rhythm or asystole 5 seconds after shock, regardless of the hemodynamic response.[113]

Guidelines 2005 recommends a single AED shock (as determined by the AED), followed immediately by CPR for 2 minutes as part of BLS with the availability of an AED.[9] An issue probably faced by trained rescuers is the wide variability of AED devices encountered in both health care facilities and public-access defibrillation settings. Given the cost, longevity, and low-maintenance nature of AEDs, replacement of previous-generation devices programmed with outdated defibrillation protocols will probably have low priority by those responsible for managing the devices. As a result, a rescuer applying an AED may find an outdated rhythm analysis (i.e., prolonged interruption of chest compressions) and defibrillation protocol (i.e., three stacked shocks). At this time, deferring to the AED protocol, even if outdated, is probably more helpful than attempting to circumvent the protocol and "trick" the AED into following a current protocol. Effort should be made to obtain a manual defibrillator at the earliest opportunity if an outdated AED protocol interferes with the resuscitation attempt.

In circumstances in which standard defibrillators rather than AEDs are used for resuscitation, the rescuer must recognize the technology inherent in the defibrillator. When a manual defibrillator is activated, the rhythm screen typically identifies the defibrillation technology as either monophasic or biphasic. The manual defibrillator should be managed with a protocol identical to current AED protocols: an emphasis on delivering uninterrupted chest compressions while the defibrillator pads are being applied and for periods when rhythm analysis is not occurring, resumption of chest compressions immediately after delivery of a shock, reanalysis of cardiac rhythm as indicated after 2 minutes of chest compressions and rescue breathing, and an attempt at defibrillation for only VF and rapid VT. If a monophasic defibrillator is available, defibrillation energy should begin at high energy (300 to 360 J).[9] Prospective human clinical studies have failed to identify the optimal biphasic energy levels for first or subsequent defibrillation attempts.[112,114,115] Although first-shock energies specific to the defibrillation waveform have been recommended (150 to 200 J with a biphasic truncated exponential waveform, 120 J with a rectilinear biphasic waveform), a rescuer encountering an unfamiliar device should choose an energy setting of 200 J for the first shock and may increase the energy as needed for subsequent shocks when indicated.[116] In addition, when biphasic waveform defibrillation is used, the body weight of the patient does not influence the energy delivered because the waveforms compensate for transthoracic impedance to allow uniform delivery of energy and thus obviate the need to vary from the recommended defibrillation energy. This concept has been demonstrated in a study by White and colleagues.[117] Time to the first shock remains the most important factor influencing successful resuscitation.

Additional discussion related to cardioversion and defibrillation is included in the treatment algorithms for specific arrhythmias presented later.

Advanced Cardiac Life Support

Although it is commonly understood and accepted that all physicians, regardless of specialty, should be able to perform CPR, it must be emphasized that CPR almost invariably necessitates rapid interventional follow-up care with ACLS procedures. Anesthesiologists should be capable of rendering such definitive follow-up intervention, whether in the operating room, ICU, emergency department, delivery room, or hospital ward. In the operating room, cardiac arrest is rare. In two studies, cardiac arrests occurring within 12 hours[118] and 24 hours[119] of induction of anesthesia were reviewed to evaluate the role that anesthesia may have contributed to the cardiac event. The somewhat reassuring observation that intraoperative cardiac arrests are rare (1.1/10,000 and 1.4/10,000 in the aforementioned two studies) does not dismiss the need for anesthesiologists to be thoroughly acquainted with ACLS equipment and interventions because when these methods are needed, they must be executed skillfully and decisively. The need for skillful and knowledgeable ACLS intervention in intraoperative cardiac arrest is recognized.[120] Failure to intervene rapidly with ACLS pharmacologic therapy was identified as a major cause of poor outcome in other reports of intraoperative cardiac arrest.[120,121] It is evident that ACLS is a body of knowledge and skill with which anesthesiologists must be thoroughly familiar.

In a study using a computer program that simulates critical patient incidents such as cardiac arrest, it was observed that only 30% of participants, who consisted of anesthesiology residents,

faculty, and private practitioners, managed a simulated cardiac arrest in accordance with the AHA ACLS guidelines.[122] Timing since the last ACLS training was noted to be an important predictor of proper management of simulated cardiac arrest. Of those trained in ACLS within 6 months preceding the assessment, 71% managed cardiac arrests successfully, whereas successful management decreased to about 30% in those whose ACLS training occurred 6 months to 2 years earlier. No participant who had been trained in ACLS longer than 2 years before the assessment used ACLS guidelines correctly in the simulated cardiac arrest management.[122] These findings are consistent with a recent report assessing anesthesiologists' retention of resuscitation skills and knowledge after ACLS training.[123] These authors found a significant decline in skill (i.e., time to first defibrillation, defibrillation sequence, administration of medicine, tracheal intubation) and knowledge by 6 months. These findings support the position that some form of periodic training and retraining in ACLS is necessary for maintaining the level of knowledge and skills essential for management of cardiorespiratory arrest in accord with contemporary principles as incorporated in the ACLS training program.

Monitoring and Recognition of Arrhythmia

Prompt recognition and treatment of potentially life-threatening (pre-arrest) cardiac arrhythmias are essential components of ACLS.[124] Early recognition and immediate pharmacologic intervention necessitate the full application of BLS and ACLS and can frequently prevent the onset of fatal arrhythmias. In this context, supraventricular arrhythmias that may cause hemodynamic compromise are discussed first, followed by recognition and management of those that are ventricular in origin.

Supraventricular Bradyarrhythmia

Supraventricular bradyarrhythmias may be sinus or junctional in origin, or they may be caused by second-degree (types I and II) or third-degree atrioventricular (AV) block. Sinus (or junctional) bradycardia and type I (AV nodal) second-degree block are usually manifestations of increased vagal tone. Sinus bradycardia and type I second-degree AV block (Wenckebach phenomenon) may be observed during high-dose narcotic anesthesia. During spinal anesthesia, reduced venous return and unopposed vagal tone may produce bradycardia and hypotension of sufficient severity to progress to cardiac arrest.[125] Treatment is indicated whenever the bradycardia, regardless of type, leads to a significant decrease in systemic arterial pressure, produces clinical signs of reduced cardiac output (or a decrease in measured output), or is accompanied by ventricular ectopic depolarization. Any of these signs should be taken as evidence of hemodynamic or electrophysiologic deterioration with the propensity to progress to lethal arrhythmias, either asystole or VF. Initial treatment is atropine, 0.5 to 1.0 mg intravenously and repeated as needed at 3- to 5-minute intervals up to 0.04 mg/kg.[126] If such treatment is ineffective in producing an increase in heart rate and hemodynamic (increased systemic pressure, cardiac output, or both) or electrophysiologic (elimination of ventricular ectopy) improvement, alternatives include external or transvenous pacing or, during spinal anesthesia, low-dose (0.2 mg) intravenous epinephrine.[127] The availability of intraoperative cardiac pacing equipment and techniques has diminished the need for isoproterenol for the treatment of bradyarrhythmias. The increase in myocardial oxygen demand imposed by isoproterenol makes its use potentially hazardous in the presence of acute myocardial ischemia. If transvenous or transcutaneous pacing is not available for treating atropine-refractory bradyarrhythmias, an infusion of dopamine (5 to 20 μg/kg/min) or epinephrine (2 to 10 μg/min) would be a better choice than isoproterenol.

Pulmonary artery catheters that permit the insertion of atrial or ventricular pacing probes are available (also see Chapter 40). If such a catheter is in place, emergency pacing can be instituted rapidly. Pacing probes can be advanced into position quickly to permit rapid control of the cardiac rate by ventricular, atrial, or AV sequential pacing. Atrial pacing wires require an intact AV nodal conduction system. Ventricular pacing is indicated when AV nodal conduction is disrupted.

External transcutaneous pacing can be used to rapidly treat atropine-resistant bradyarrhythmias. These devices have been described as safe and effective, and intraoperative experience has been favorable.[128,129] They should be readily available for emergency use along with a defibrillator. External pacing is not beneficial in bradyasystolic arrest.

Transesophageal atrial pacing has been effective in treating intraoperative supraventricular bradyarrhythmias such as sinus or junctional bradycardia.[130,131] In its present configuration, however, it cannot be used to pace the ventricles and therefore is not useful in the management of any form of bradycardia caused by AV conduction disturbances.

Supraventricular Tachyarrhythmia

Supraventricular tachyarrhythmias include atrial flutter, atrial fibrillation, AV junctional tachycardia, multifocal atrial tachycardia, paroxysmal reentrant tachycardia, and other much less frequent arrhythmias. Paroxysmal supraventricular tachycardia (PSVT), atrial fibrillation (or flutter) with rapid ventricular rates, and multifocal atrial tachycardia are discussed here because not only can they produce hemodynamic compromise, they can also present diagnostic and therapeutic challenges.

An example of PSVT is shown in Figure 97-4. If such a tachyarrhythmia produces hemodynamic deterioration, cardioversion is the treatment of choice. The recommended initial dose for cardioversion of atrial tachyarrhythmias is 100 to 200 J if a monophasic defibrillator is used or 100 to 120 J with a biphasic device. Energy can be increased as needed if the arrhythmia is resistant to therapy. If the patient is hemodynamically stable, vagal maneuvers can be attempted (e.g., Valsalva maneuver in awake patients) before initiating pharmacologic interventions. Vagal maneuvers alone will terminate about 20% to 25% of reentry supraventricular tachyarrhythmias.[132] If vagal maneuvers are unsuccessful, adenosine is the drug of choice for termination of organized rapid supraventricular arrhythmias.[133-135] Adenosine slows sinoatrial and AV nodal conduction and prolongs refractoriness, which is very effective in terminating PSVT, the most common cause of which is reentry within the AV node.[136-138] The drug is of diagnostic usefulness in revealing the underlying mechanism in tachyarrhythmias of uncertain origin (e.g., atrial fibrillation, atrial flutter) by inducing transient block of AV nodal conduction (see Fig. 96-4).[139-141] Because of rapid cellular uptake and metabolism, adenosine must be injected rapidly into a venous catheter proximal enough to the heart to ensure delivery of a sufficient concentration of the drug at the AV node to induce an AV nodal conduction block. Adenosine can be used initially in a

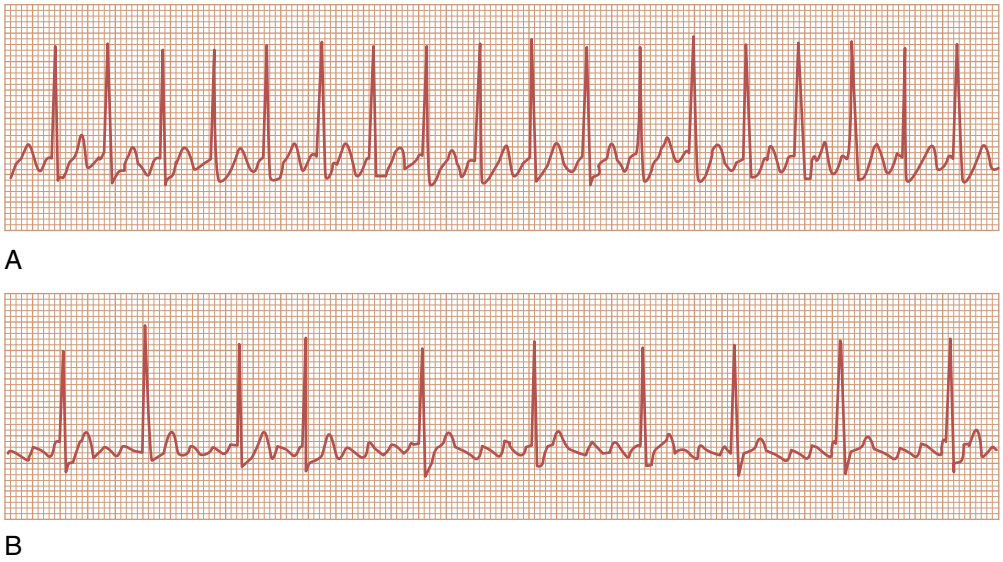

Figure 97-4 **A,** A supraventricular tachycardia at a rate of 180 beats/min is present; the origin of the tachycardia is not evident. **B,** After injection of 6 mg adenosine, atrial flutter waves are clearly visible, thus establishing the diagnosis.

dose of 6 mg, and if necessary, a second dose of 12 mg can be given in 1 to 2 minutes. If a central venous catheter is used, these doses can be reduced to 3 and 6 mg, respectively.[142] If the drug is injected more distally and slowly (e.g., into a small-bore catheter in a dorsal hand vein), not only may therapeutic failure result, but transient acceleration of the tachyarrhythmia may occur as well (Fig. 97-5).[143] This paradoxical acceleration of the rate is a manifestation of the increase in sympathetic nervous system traffic induced by adenosine in the presence of inadequate AV nodal blockade. Likewise, conversion of 2:1 or 1:1 conduction in atrial flutter has been observed.[144-146] This adverse effect indicates that an attempt to establish the diagnosis of atrial flutter should be made electrophysiologically, with vagal maneuvers used if necessary to unmask the flutter waves. Rate acceleration has also been observed after the administration of adenosine to patients with atrial fibrillation and preexcitation (Wolff-Parkinson-White syndrome).[147] As with verapamil in this setting, the acceleration in rate is a result of the AV nodal block with diversion of fibrillation wave fronts through the accessory connection. Even though the short half-life of adenosine may reduce this hazard, it seems prudent to avoid adenosine, as well as other AV node–blocking drugs, in patients with atrial fibrillation and preexcitation.

Adenosine's very short half-life (<5 seconds) is both advantageous and disadvantageous: side effects such as flushing,

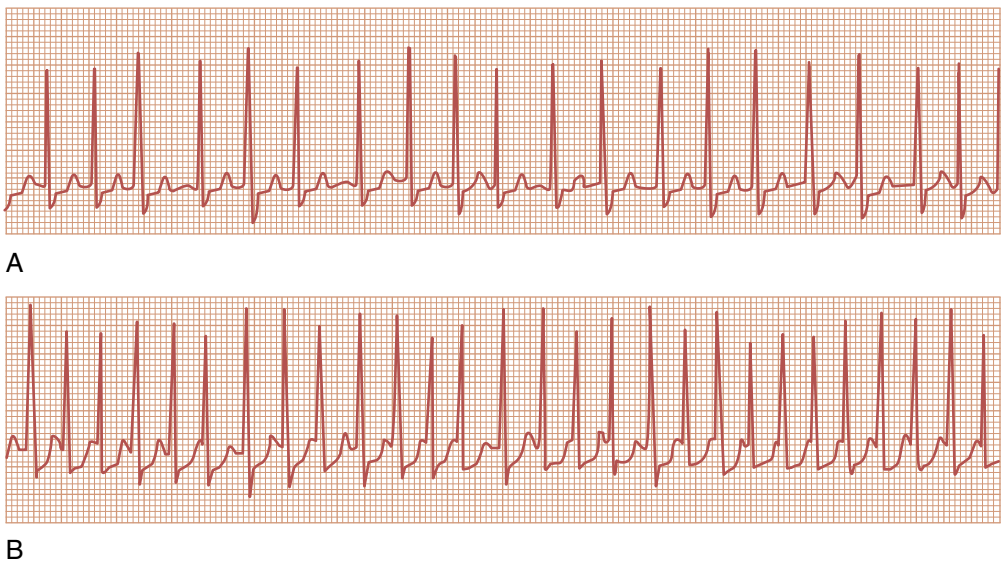

Figure 97-5 **A,** Atrial fibrillation with a ventricular response of 190 beats/min. **B,** After injection of 6 mg adenosine, the ventricular response increased to 240 beats/min. *(From White RD: Acceleration of the ventricular response in paroxysmal lone atrial fibrillation following the injection of adenosine. Am J Emerg Med 11:245, 1993.)*

Table 97-2 Administration of Adenosine*

Peripheral (antecubital)	6 mg, then 12 mg if needed
Central	3 mg, then 6 mg if needed
If taking theophylline-containing drugs	9 mg peripherally, 6 mg centrally
If taking dipyridamole	2 mg peripherally, 1 mg centrally

*Use with caution in asthmatic patients and those taking carbamazepine.

dyspnea, and chest pain are short lived, but the tachyarrhythmia may recur and necessitate the use of another drug. The AV nodal–blocking action of adenosine is antagonized by theophylline or related methylxanthines and is potentiated by dipyridamole and carbamazepine.[133-135,148,149] A suggested scheme for the use of adenosine, including dosing adjustments, is presented in Table 97-2.

Bronchospasm has also been described after the injection of adenosine, including intraoperatively.[150-153] This complication has occurred in patients with bronchial asthma or chronic obstructive pulmonary disease (COPD). The mechanism is unknown, but the bronchospasm may result from stimulation of bronchial smooth muscle adenosine receptors or stimulation of mast cell–derived mediators of bronchoconstriction. Aminophylline, an adenosine receptor antagonist, has been used successfully intraoperatively to treat adenosine-induced bronchospasm.[153] In light of this experience, adenosine should not be used or should be used with caution in patients with a history of bronchial asthma or COPD with a bronchospastic component.

If the PSVT does not respond to adenosine or if it recurs, verapamil is the drug of choice. A dose of 5 mg produces a more sustained block of AV nodal conduction. Verapamil can also be used to slow the ventricular response in atrial fibrillation or flutter.[154] However, it should not be used in patients with Wolff-Parkinson-White syndrome in whom atrial fibrillation or flutter develops. In this setting, verapamil-induced increases in conduction over the accessory pathway may produce alarming acceleration of the ventricular rate or VF.[155-157] If atrial flutter or fibrillation results in hemodynamic deterioration because of the rapid ventricular response, cardioversion is the treatment of choice. Atrial flutter can be terminated with low-energy synchronized shocks.

Atrial flutter or fibrillation with a rapid ventricular response can cause rate-related hemodynamic compromise manifested perioperatively as hypotension, decreased cardiac output, or both. In hemodynamically unstable patients, cardioversion should be used. Recent-onset atrial flutter is typically very sensitive to low-energy shocks (e.g., 50 J, monophasic or biphasic waveforms) (Fig. 97-6). Atrial flutter can also be terminated by overdrive pacing with external generators that have this capability. For atrial fibrillation, the initial dose for cardioversion is 100 to 200 J with monophasic waveforms or 100 J to 120 J with biphasic waveforms. Escalation of energy doses for the second and subsequent doses is indicated.[9]

In hemodynamically stable patients with rapid ventricular rates secondary to atrial fibrillation or flutter, treatment is pharmacologic. With acute onset of these tachyarrhythmias, ibutilide given intravenously has the most rapid onset of effect in restoring sinus rhythm.[158,159] Ibutilide is a class III antiarrhythmic drug that prolongs the action potential duration and effective refractory period without effects on action potential upstroke. The dose is 1 mg given over a 10-minute period. A second dose can be administered 10 minutes after the first, if necessary. Conversion to sinus rhythm is more frequent with atrial flutter than with atrial fibrillation (63% versus 31%) and more frequent with atrial fibrillation of shorter duration.[158] Prolongation of the QT interval reflects the pharmacologic action of the drug; polymorphic ventricular tachycardia (PVT) accompanied by increases in the QT interval has been reported in 8.3% of patients receiving ibutilide, so clinicians should be prepared to manage this arrhythmia[158] (see discussion of ventricular tachyarrhythmias).

Alternative options for the treatment of supraventricular arrhythmias include diltiazem, verapamil, β-blocking medications, procainamide, and amiodarone. By slowing conduction and increasing refractoriness in the AV node, calcium channel–blocking agents result in control of the ventricular rate in patients with atrial flutter, atrial fibrillation, and multifocal atrial tachycardia. Diltiazem is given in an initial dose of 0.25 mg/kg over a 2-minute period, followed, if needed, in 10 to 15 minutes by 0.35 mg/kg. An infusion at a rate of 5 to 15 mg/hr can be used to maintain rate control. If verapamil is used, 5 mg can be given initially and then 5 to 10 mg in 15 to 30 minutes if needed. β-Adrenergic–blocking drugs are helpful in controlling the ventricular rate when no contraindications to use are present. Amiodarone is a complex agent with antiadrenergic effects in the presence of supraventricular arrhythmias and tachycardias resulting from accessory pathways or rapid AV node transmission of atrial impulses and in situations in which other agents have failed to control the heart rate. It is given as a 150-mg intravenous bolus over a 10-minute period, followed by a 1-mg/min infusion for 6 hours to a maximum daily dose of 2 g.

Multifocal (multiform) atrial tachycardia is a quite common tachyarrhythmia that is often misdiagnosed as atrial fibrillation.[160-162] Increased automaticity in multiple atrial foci results in a need for therapy different from that for reentrant supraventricular arrhythmias (atrial flutter, atrial fibrillation, PSVT). Multifocal atrial tachycardia is diagnosed by observing the presence of at least three morphologically different P waves in the same lead of a 12-lead electrocardiogram (ECG) and a ventricular rate more rapid than 100/min (Fig. 97-7). It is usually described as occurring in patients with COPD, especially during exacerbations, and ICU management is necessary. However, it occurs in other settings as well, such as hypokalemia, catecholamine administration, and acute myocardial ischemia.[163,164] Treatment of underlying conditions probably contributing to myocardial irritability is important. Digitalization and cardioversion, sometimes helpful in other supraventricular arrhythmias, are ineffective in multifocal atrial tachycardia. Digitalis toxicity or repeated and futile attempts at cardioversion can follow misdiagnosis. Acceptable rate control treatment in patients with preserved ventricular function includes calcium channel blockers, β-adrenergic blockers, and amiodarone. In the presence of impaired ventricular function, diltiazem and amiodarone may be useful.

Ventricular Bradyarrhythmia

In the setting of emergency cardiovascular care, the bradyarrhythmia arising within the ventricles that is in need of urgent treatment is complete heart block with a very slow idioventricular escape rhythm (e.g., 15 to 30 beats/min) (Fig. 97-8). In this situation, atropine can be tried, but the treatment of choice is external or transvenous pacing as soon as it can be accomplished. If an external pacemaker is available, pacing should be instituted quickly.

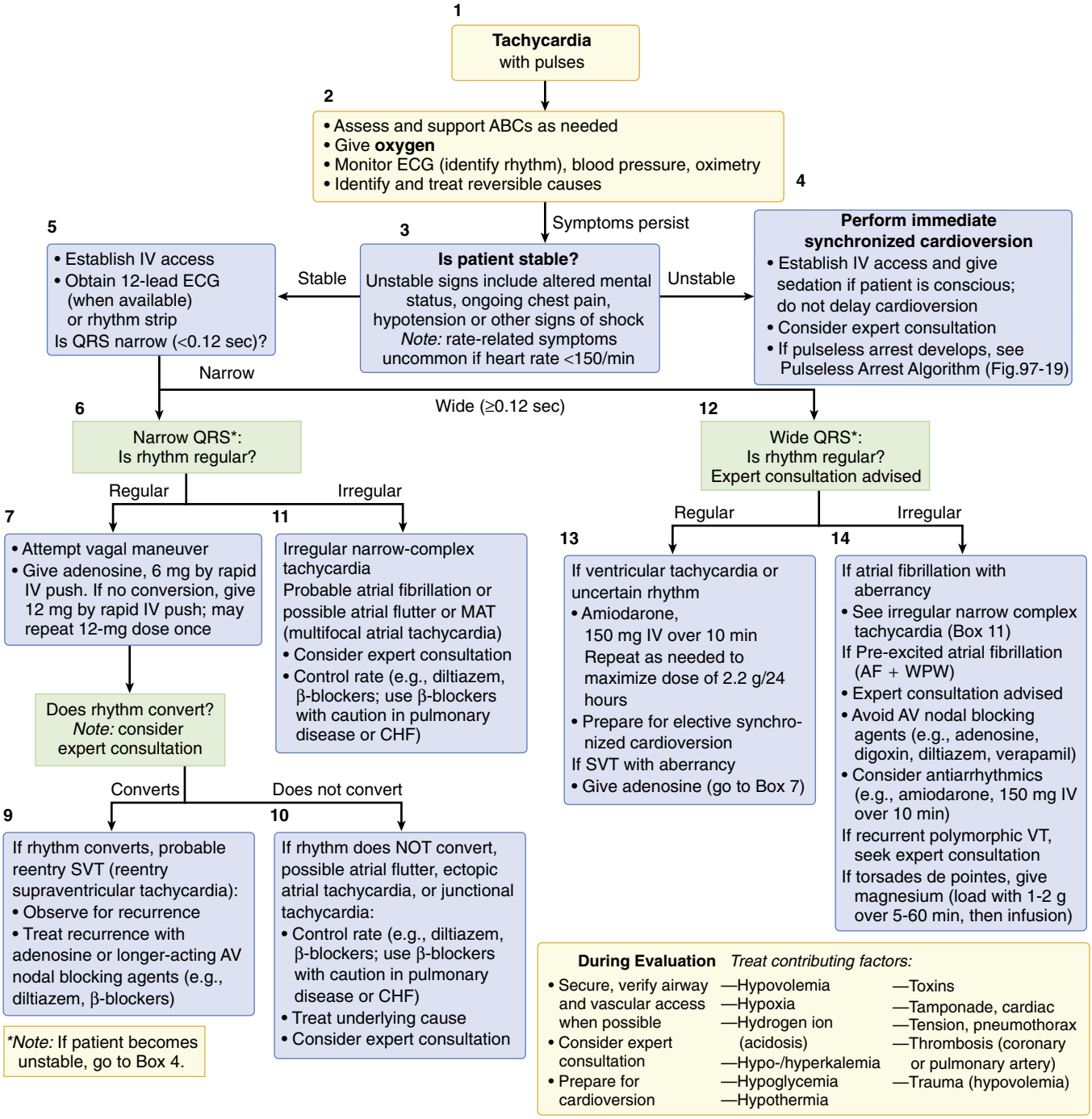

Figure 97-6 Advanced cardiac life support algorithm for tachycardia. ABC, airway, breathing, circulation; AV, atrioventricular; CHF, congestive heart failure; ECG, electrocardiogram; IV, intravenous; SVT, supraventricular tachycardia; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome. *(From 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 112:IV-70, 2005.)*

Ventricular Tachyarrhythmia

In the category of potentially life-threatening and sometimes pre-arrest arrhythmias, VT (Fig. 97-9) is commonly in need of urgent intervention. VT that produces cardiac arrest (pulseless VT) is discussed with VF. Treatable causes of VT should always be sought before or during pharmacologic or electrical interventions. Hypoxemia, hypercapnia, hypokalemia or hypomagnesemia (or both), digitalis toxicity, and acid-base derangements are obvious considerations.

Treatment of VT is dependent on the degree of hemodynamic compromise induced by the tachycardia. If the patient remains stable and ventricular function is preserved (no evidence of pulmonary edema or a known history of left ventricular function), procainamide and synchronized cardioversion are the treat-

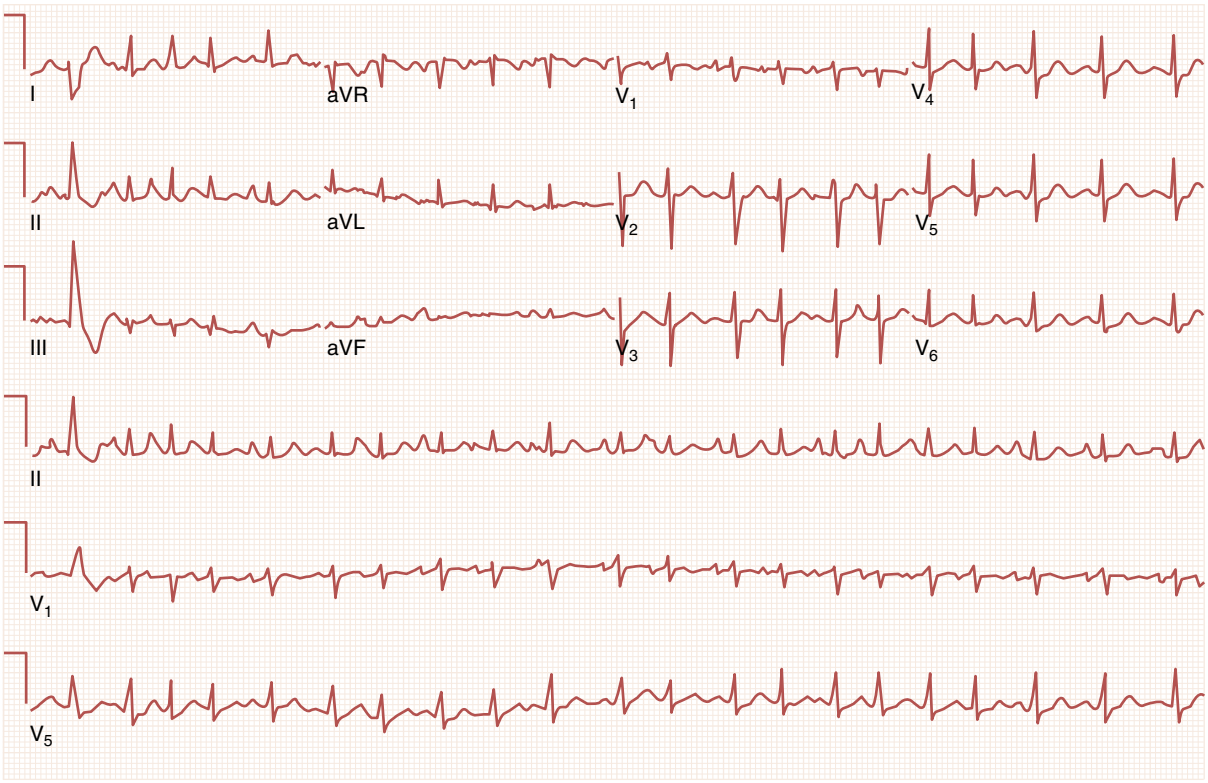

Figure 97-7 Multifocal atrial tachycardia. P-wave morphology varies across the tracing. Each QRS complex is preceded by a single P wave.

ment choices. If cardioversion is chosen, the energy levels are identical to those used in unstable patients. If procainamide is chosen, a loading dose of 20 mg/min until the tachycardia is controlled or a total of 17 mg/kg has been injected. Systemic hypotension and QRS widening by more than 50% of control values are therapeutic end points. If procainamide fails to control the arrhythmia, amiodarone should be administered. In patients with evidence of or known impaired left ventricular function, amiodarone is the drug of choice. Amiodarone, 150 mg in 100 mL of sterile water injected over a 10-minute period, followed by a loading infusion of 1 mg/min for 6 hours and then a 0.5-mg/min maintenance infusion over an 18-hour period, may be effective.[165-168] The mechanism of action of amiodarone is unclear, but it probably includes antisympathetic and calcium channel–blocking actions. It exerts antiarrhythmic action within an hour of intravenous administration. If breakthrough VT/VF occurs, supplemental 150-mg infusions over a period of 10 minutes can be given. The major adverse effects of amiodarone are hypotension and bradycardia, both of which can be prevented by slowing the rate of infusion.

In unstable patients (e.g., in the presence of systemic hypotension, pulmonary edema, or clinical or electrocardiographic signs of acute myocardial ischemia or infarction), synchronized cardioversion is the treatment of choice with either monophasic energy doses of 360 J or biphasic, nonescalating, impedance-compensated energy doses of 120 J. An algorithm for cardioversion of a variety of tachyarrhythmias, including VT, is shown in Figure 97-6.

An atypical form of VT known as *torsades de pointes* ("twisting of the points") that was originally described in 1966 is characterized by twisting of the QRS axis around the baseline and a polymorphic appearance.[169-173] The underlying electrophysiologic derangement in this arrhythmia is a marked and nonuniform delay in repolarization manifested by a prolonged QT interval on the ECG. It typically begins with a characteristic long-short initiating sequence (Fig. 97-10). It can be induced by drugs such as quinidine, procainamide, disopyramide, and phenothiazine, as well as by bradycardia, hypokalemia, hypomagnesemia, or acute ischemia or infarction.[174] Even though amiodarone produces marked prolongation of repolarization, it rarely causes torsades de pointes, possibly because the drug-induced prolonged repolarization is uniform (nondispersed), in contrast to the repolarization abnormality induced by other drugs.[175] Closely related

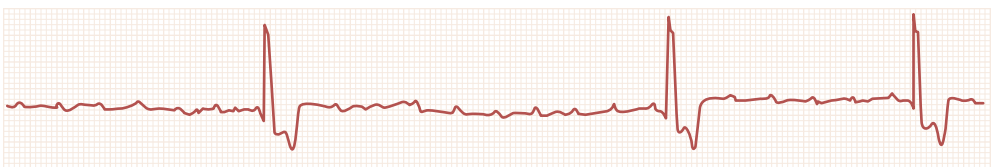

Figure 97-8 Slow (14 beats/min) idioventricular escape rhythm in a patient with carotid sinus hypersensitivity. External or transvenous pacing is the treatment of choice for bradyarrhythmias such as this.



Figure 97-9 Ventricular tachycardia. The rate is 280 beats/min, the QRS width is 160 msec, and three consecutive capture/fusion beats are seen.

to torsades de pointes is PVT (Fig. 97-11). Description of the tachycardia as PVT rather than torsades de pointes implies that there is no evident cause of prolonged repolarization and the QT interval is not prolonged.[176-179] Because both PVT and torsades de pointes can be life threatening, a correct diagnosis is required. The critical therapeutic distinction is based on the presence or absence of prolongation of the QT interval. If QT prolongation is present, therapy is directed toward shortening the repolarization time (after withdrawal of the offending drugs listed earlier or correction of abnormalities such as hypokalemia). In the past, drugs such as isoproterenol were used for this purpose, but definitive short-term therapy is overdrive ventricular or atrial pacing, preferably the latter, if AV conduction is intact. Magnesium sulfate has also been used successfully in the treatment of torsades de pointes, and some clinicians recommend it as the first line of emergency treatment.[180-183]

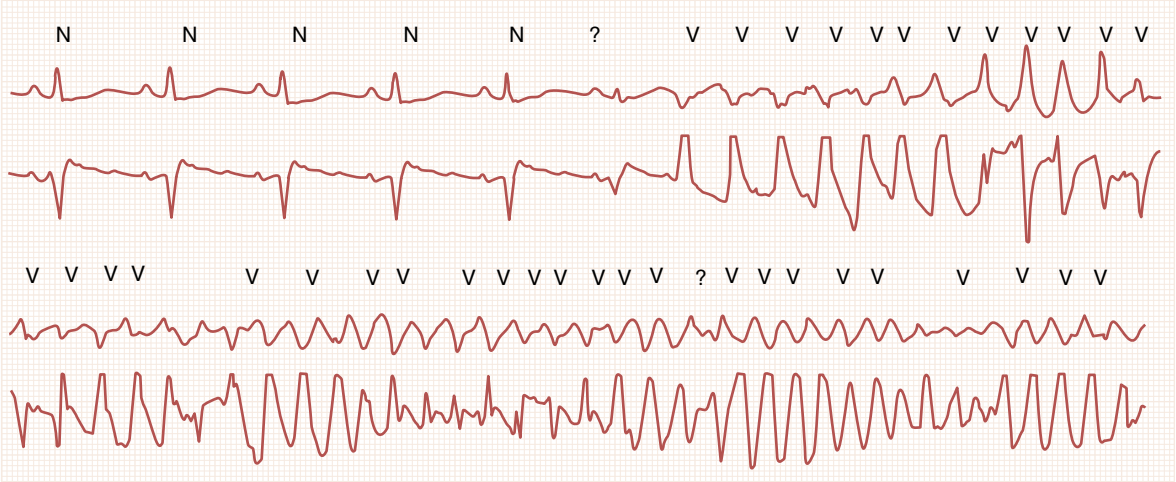

Figure 97-10 Polymorphic ventricular tachycardia. A prolonged QT interval during sinus rhythm suggests that the arrhythmia is torsades de pointes. This arrhythmia occurred in a patient after resuscitation from cardiac arrest.

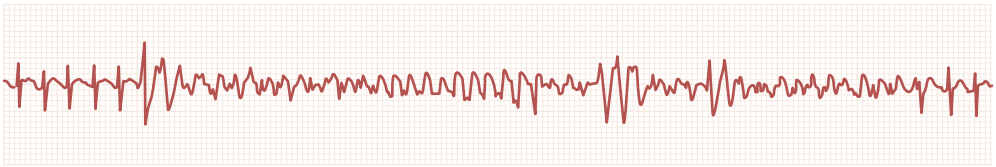

Figure 97-11 Polymorphic ventricular tachycardia. The QRS complexes have varying morphology, but without the "twisting of the points" torsades morphology seen in Fig. 97-10. The tachycardia terminated spontaneously. *(From White RD, Wood DL: Out-of-hospital pleomorphic ventricular tachycardia and resuscitation: Association with acute myocardial ischemia and infarction. Ann Emerg Med 21:1282, 1992.)*

If PVT is present (i.e., without evident QT prolongation), standard antiarrhythmic therapy as outlined earlier for VT can be tried, although magnesium sulfate should be considered early in the treatment of this form of PVT as well, particularly if torsades de pointes is suspected by history but QT prolongation cannot be confirmed on the ECG. In fact, a 12-lead ECG is often needed to identify QT lengthening. If hemodynamic deterioration occurs with PVT, defibrillation should be used as the initial treatment.

An algorithm for the treatment of tachyarrhythmias that encompasses those of both supraventricular and ventricular origin is shown in Figure 97-6. This algorithm makes provision for intervention in patients with wide–QRS complex tachycardia (Fig. 97-12) of indeterminate origin based on the patient's hemodynamic stability. In a hemodynamically stable patient, Guidelines 2005 emphasizes making a specific diagnosis and identifying the presence of a clinically significant reduction in ventricular function rather than attempting a diagnosis based on response to antiarrhythmic mediations.[9]

Verapamil should be avoided in any wide–QRS complex tachycardia unless it is known with certainty that the tachycardia is supraventricular in origin; if VT is present, verapamil can induce severe hypotension or cardiovascular collapse in as many as 87% of such misdiagnosed episodes (Fig. 97-13). Any wide-complex tachycardia of uncertain origin (despite careful scrutiny of the ECG for all helpful clues) should be assumed to be VT and be treated accordingly. If the patient is hemodynamically deteriorating, cardioversion should be used initially without a preceding trial of drug therapy.

Management of Cardiac Arrest

This section reviews the interventions, both electrical and pharmacologic, used for treatment of the various forms of cardiorespiratory arrest. Included is a discussion of the major beneficial and adverse actions of the drugs used in ACLS. The clinical applications of some of these drugs have already been presented in the review of recognition and management of "pre-arrest" or potentially life-threatening events.

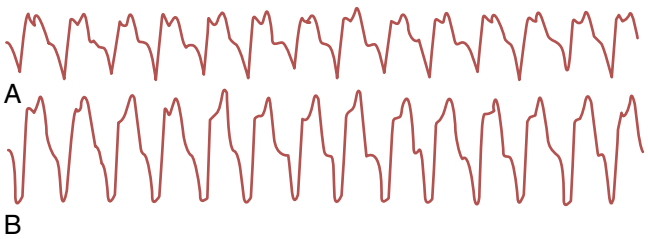

Figure 97-12 Wide–QRS complex tachycardia at a rate of 160 beats/min. **A,** Precordial lead 5. **B,** Lead 2. Atrioventricular dissociation is present, as evident by the P wave preceding the third QRS complex, thus confirming this to be ventricular tachycardia.

Pulseless Ventricular Tachycardia or Ventricular Fibrillation

For therapeutic purposes, pulseless VT and VF should be considered the same entity in need of the same interventions. It is fortunate that this is the most common form of cardiac arrest because it is the most treatable and it is the arrhythmia that yields the greatest likelihood of immediate and long-term survival, both in the hospital and out of the hospital.[184] This finding has accelerated the extension of early intervention in VF to levels of out-of-hospital emergency care lower than emergency medical technicians, even to first responders with minimal training. The likelihood of significant salvage by early defibrillation also accounts for the growing interest in and distribution of AEDs in public places and the rapid increase in implantation of cardioverter-defibrillators[185-190] in patients at risk for cardiac arrest from VF. It is obvious that physicians involved in caring for patients in the hospital are assumed to know now to intervene in the event of cardiac arrest, how to operate defibrillators, and how to administer drugs rationally, especially in the presence of VT/VF, when survival is likely with rapid and correct treatment. Unfortunately, retention of the knowledge and skills in resuscitative interventions learned in ACLS courses declines rapidly.[123] Periodic ACLS review courses may be indicated in the intervals between ACLS certification to ensure that current ACLS therapies and interventions are used. Making ACLS handbooks available to resuscitation teams may also improve performance of resuscitation events.

Despite rare reports of apparently spontaneous termination of VF, the required and definitive intervention is rapid defibrillation. Two practical and important considerations enter into every attempt to defibrillate patients in VF. The first is the energy output of the defibrillator.[191] Termination of VF is critically dependent on the amount of energy available from a defibrillator, and it is therefore necessary that output be checked at regular intervals. Guidelines for proper maintenance of defibrillators are available.[192]

The second practical consideration is resistance to flow of current during delivery of the shock. Current flow is inversely related to resistance; excessive resistance because of poor technique can impede the transthoracic flow of current adequate to induce defibrillation.[191] Guidelines 2005 recommends the use of self-adhesive defibrillation pads rather than paddles because the pads can be placed before cardiac arrest in patients at risk.[9] Preapplied electrode pads are particularly advantageous in the operating room when patient position precludes rapid access to the chest for standard paddle placement. Finally, defibrillation should

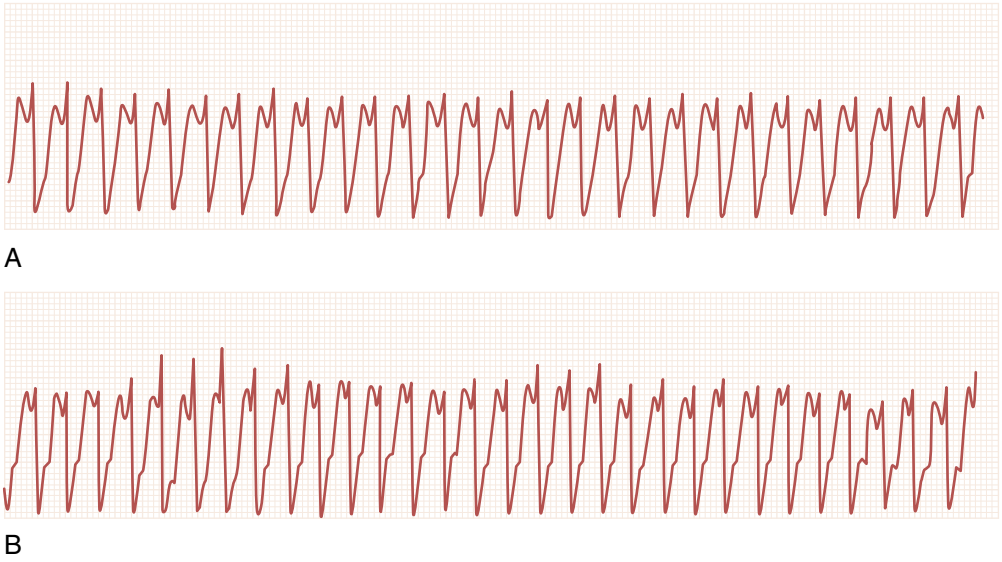

Figure 97-13 Adverse response to verapamil. Tachycardia thought to be atrial flutter was present initially (**A**). After injection of 5 mg verapamil, the rate accelerated and the patient became unresponsive, thus necessitating cardioversion (**B**). The first rhythm was ventricular tachycardia. Cardiovascular collapse is a potential complication of verapamil injection when the tachycardia is ventricular in origin.

occur at the end of expiration during rescue breathing to minimize impedance.

In the operating room or ICU, when cardiac arrest is witnessed and a monitor reveals the mechanism to be pulseless VT or VF, defibrillation should be performed immediately. If a monophasic defibrillator is available, 360 J should be delivered. Energy settings for biphasic defibrillators depend on the waveform. Biphasic truncated exponential waveforms should use 150 to 200 J for the first shock. Energy settings for rectilinear biphasic waveforms should use 120 J for the initial shock. If the rescuer is unfamiliar with the waveform used, 200 J should be used as a default energy.[9] All biphasic defibrillators available today are impedance compensated and adjust the delivered dose of energy in response to the impedance measured with each shock. If VF recurs, either the same or an escalating dose of energy can be used. At this time there is insufficient evidence that escalation of energy is superior to nonescalating energy shocks in terminating recurrent VF. In circumstances in which a cardiac arrest is witnessed but access to a defibrillator is delayed, chest compressions should be initiated immediately and continued until the defibrillator is available and charged. If at any time VF recurs after successful conversion, defibrillation should be repeated at the most recent successful energy level. If VF persists despite this initial treatment, pharmacologic therapy becomes necessary. It is assumed that the anesthesiologist has already controlled the airway and ventilation by endotracheal intubation and ventilation with 100% oxygen. In situations in which endotracheal intubation is not in place at the time of cardiac arrest, defibrillation takes precedence over endotracheal intubation if the defibrillator is immediately available.

If return of spontaneous circulation has not occurred after an initial attempt at defibrillation, five cycles of CPR consisting of 30 compressions to 2 ventilations, and then a second defibrillatory shock, pharmacologic interventions should accompany the resuscitative efforts. Currently, only two medications are recommended for use in cardiac arrest: epinephrine and vasopressin.[9] A peripheral intravenous line is recommended for resuscitation attempts because placement of a peripheral catheter does not interrupt chest compressions. Assuming that a peripheral intravenous line is present, initial drug injections can be given by this route, followed by a fluid bolus to propel the drug into the circulation. Peripherally administered drugs typically require 1 to 2 minutes to reach the central circulation in the setting of cardiac arrest. Two minutes of CPR should be performed after drug administration and before defibrillation is attempted. If peripheral venous access cannot be established, intraosseous or central venous cannulation should be considered.[9] Intraosseous cannulation will not interrupt chest compressions and will yield blood concentrations of drugs equivalent to those administered through a central line. In most circumstances a central line is not necessary for most resuscitation attempts and should not be pursued before peripheral or intraosseous attempts. Because of evidence that glucose administration during global cerebral ischemia can worsen neurologic outcome in survivors,[193-196] lactated Ringer's solution or normal saline should be used instead of glucose-containing solutions.

Previous clinical impressions regarding the beneficial effects of epinephrine during cardiac arrest, regardless of the underlying rhythm, have been substantiated.[197-201] The drug increases both cerebral and myocardial blood flow in experimental cardiac arrest.[197-199] The mechanisms responsible for enhanced cerebral and myocardial blood flow appear to be based on prevention of arterial collapse and intense vasoconstriction in other vascular beds, thus preventing runoff of blood into noncritical tissues and preferentially increasing cerebral and myocardial perfusion pressure and flow.[197] In human victims of cardiac arrest, epinephrine has been shown to produce increases in both peak aortic and coronary perfusion pressure, further attesting to its vasoconstrictive properties in a clinical setting.[202] The recommended dose of epinephrine is 1.0 mg (10 mL of a 1:10,000 solution). This dose should be repeated every 3 to 5 minutes as long as cardiac arrest persists to ensure sustained blood flow benefit.

If for some reason an intravenous line is not present or cannot be inserted promptly, endotracheal or intraosseous delivery of medication should be considered. Epinephrine can be injected into the tracheobronchial tree, a site from which it is rapidly absorbed to produce a prompt pharmacologic effect.[203-205] If this route is used, a dose of 2 to 2.5 times the intravenous dose is recommended.[126]

Because of the critical role of potent vasoconstriction in the beneficial action of epinephrine, phenylephrine has been studied as well.[198,206,207] Comparison of phenylephrine and epinephrine in experimental cardiac arrest has shown no evident benefit gained from using phenylephrine in terms of changes in blood flow,[197,207] somatosensory evoked potentials,[197] or neurologic or cardiovascular outcome.[199] Thus, epinephrine remains the drug of choice.

Based on experimental observations of apparent hemodynamic benefit from large doses of epinephrine (up to 0.2 mg/kg),[208,209] numerous clinical reports and studies have assessed the impact of high-dose epinephrine on such end points as restoration of spontaneous circulation and discharge from the hospital.[210-216] Although some investigators have observed an increased frequency of restoration of spontaneous circulation after high-dose epinephrine versus standard 1-mg doses,[214] most have not, and no study has yet confirmed benefit in terms of discharge and survival. Given the lack of conclusive evidence demonstrating benefit from high-dose epinephrine treatment, it is no longer accepted therapy for cardiac arrest.

Vasopressin was added to the treatment algorithm of VF and pulseless VT based on experimental and clinical data suggesting that it has beneficial effects on perfusion of vital organs during cardiac arrest.[217,218] Endogenous plasma vasopressin levels were noted to be significantly higher in patients successfully resuscitated from out-of-hospital cardiac arrest than in those who died, thus suggesting that the human body discharges this hormone under circumstances of physiologic stress.[219,220] Vasopressin acts by direct stimulation of smooth muscle V_1 receptors, and such stimulation results in prolonged smooth muscle constriction even in the presence of severe acidosis, which might maintain coronary perfusion pressure and contribute to improved success with resuscitation.[221,222] In one study, vasopressin administered to patients with refractory cardiac arrest led to increased blood pressure and, in some, return of spontaneous circulation.[223] However promising these results are in suggesting a potential benefit of vasopressin in cardiac arrest, no study has demonstrated significant benefit resulting in hospital discharge. In Guidelines 2005, the use of vasopressin is endorsed as an alternative to one dose of epinephrine during refractory VF.[9] Because of its long half-life (10 to 20 minutes) compared with that of epinephrine (3 to 5 minutes), vasopressin is administered in a one-time dose of 40 units intravenously or intraosseously.

If VF persists after initial defibrillation or injection of epinephrine or vasopressin (or both), a repeated defibrillation attempt at the maximal energy available for the device used should be initiated. If VF persists thereafter, mediations with antifibrillatory effects should be chosen. Amiodarone and lidocaine are acceptable choices. Lidocaine has not been shown in an evidence-based evaluation to have any demonstrable short-term or long-term benefit in patients with VF or pulseless VT. Amiodarone is the preferred antiarrhythmic agent in the presence of persistent VF. An initial amiodarone dose of 300 mg via the intravenous or intraosseous routes can be followed by a single dose of 150 mg.

Amiodarone produces prolongation of action potentials and refractoriness in all cardiac tissue. These effects may contribute to its potential use for refractory VF. In the study Amiodarone in Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachycardia (ARREST), Kudenchuk and colleagues[224] reported the results of a randomized, prospective study in which amiodarone, 300 mg intravenously, or placebo was administered to victims of out-of-hospital cardiac arrest with persistent VF after three attempts at defibrillation and 1 mg of intravenous epinephrine. The study demonstrated significant increases in survival to hospital admission in the amiodarone-treated group but was not able to demonstrate any difference in hospital discharge rates. In the study Amiodarone versus Lidocaine in Pre-hospital Ventricular Fibrillation Evaluation (ALIVE), Dorian and colleagues[225] reported the results of a double-blind, controlled clinical trial comparing amiodarone with lidocaine in patients experiencing out-of-hospital cardiac arrest in Toronto, Canada. Their results demonstrated that amiodarone was superior to lidocaine in terminating persistent VF in the out-of-hospital setting. Like the ARREST study, the ALIVE study was able to demonstrate the improvement induced by amiodarone only in survival to hospital admission, not to discharge, when compared with control or lidocaine therapy. Based on these studies, greater consideration for the use of amiodarone rather than lidocaine seems prudent in the management of patients experiencing persistent VF. However, given the current lack of evidence that survival to hospital discharge is improved with amiodarone versus lidocaine, there is no advantage in the use of either drug in the setting of refractory or persistent VF.

In cardiac arrest that does not respond to initial measures (intubation, ventilation with 100% oxygen, defibrillation, epinephrine, and antiarrhythmic drugs), sodium bicarbonate can be considered if specific conditions are present, such as preexisting metabolic acidosis, severe metabolic acidosis documented during resuscitation attempts, overdoses of tricyclic antidepressants, and hyperkalemia. If hyperkalemia is known or suspected to be present, sodium bicarbonate should be administered promptly (Fig. 97-14). Despite its long history of early and frequent administration in cardiac arrest, there is still no convincing evidence that it confers any benefit in survival from VF.[226,227] By contrast, its adverse effects are well documented, including severe plasma hyperosmolality,[228,229] paradoxical cerebrospinal fluid acidosis,[230] and generation of CO_2.[228,231] It is this last effect that has been primarily responsible for its infrequent role in cardiac arrest treatment algorithms.

During cardiac arrest with severely reduced pulmonary blood flow and therefore CO_2 transport and elimination, CO_2 is retained in mixed-venous blood and tissues, and a disparity between pH and P_{CO_2} in arterial and mixed-venous blood is produced.[231] Sodium bicarbonate is a rapid and potent generator of CO_2, which can be observed in arterial blood, as well as in expired air, after intravenous injection. Sodium bicarbonate would only add to the CO_2 load and could worsen mixed-venous (and presumably tissue) acidosis. Myocardial hypercapnic acidosis has been confirmed to exist during experimental cardiac arrest and resuscitation,[232] and it is not reversed with sodium bicarbonate or other buffer agents.[233] At least with regard to the heart, increases in tissue P_{CO_2} produce progressive decreases in the performance of ischemic myocardium. Clinically, one may infer that intractable pulseless electrical activity (PEA) could be a consequence, even if VF were eliminated. Myocardial hypercapnic

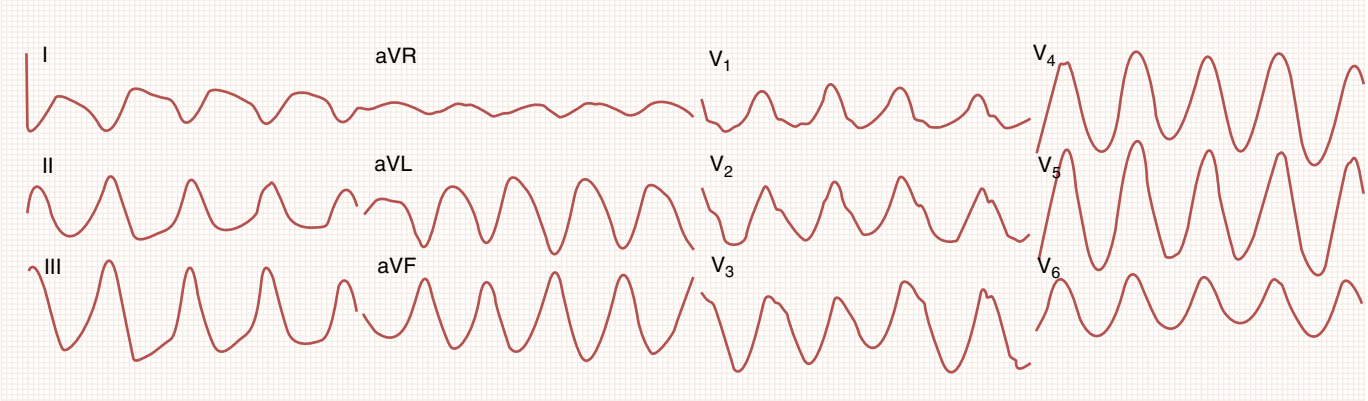

Figure 97-14 Hyperkalemic ventricular tachycardia with a sine-wave morphologic pattern.

acidosis decreases the success of restoration of spontaneous circulation and survival.[234]

In view of all these observations, sodium bicarbonate should not be used routinely in the treatment of cardiac arrest. It can be considered after the forgoing electrical and pharmacologic measures have been instituted, if preexisting metabolic acidosis is present, or if severe documented metabolic acidosis develops during the arrest.[235] A review of acid-base derangements during cardiac arrest[236,237] suggests that sodium bicarbonate may be beneficial in restoring spontaneous circulation after prolonged (15 minutes) VF cardiac arrest based on experimental observations. Clinically, if this drug is used, an initial dose of 1 mEq/kg can be given. When possible, bicarbonate therapy should be guided by bicarbonate concentrations or base deficits measured by blood gas analysis.

Pulseless Electrical Activity

PEA refers to a heterogeneous group of cardiac rhythm disorders, all characterized by pulselessness in the presence of some type of electrical activity other than VT or VF. Thus, included in this designation are traditional electromechanical dissociation, in which pulseless but organized electrical activity is present, idioventricular rhythms, ventricular escape rhythms, post-defibrillation idioventricular rhythms, and bradyasystole.

High priority must be given to identification of a possibly correctable cause of any form of PEA. For example, in a traumatized patient, hypovolemia, cardiac tamponade, and tension pneumothorax with hypoxemia are possible causes. Intraoperatively or postoperatively, acute massive pulmonary thromboembolism should be considered. Idioventricular rhythms may accompany such derangements as severe hyperkalemia, acidosis, hypothermia, or overdose with drugs such as digitalis, β-blockers, calcium channel blockers, and tricyclic antidepressants. In any of these forms of PEA, the most important point is that although initial temporizing measures such as injection of epinephrine or pacing may be needed to "tide the patient over," immediate diagnostic assessment and redirection of treatment in a disorder-specific direction may permit salvage of any patient with PEA. Figure 97-15 provides the PEA treatment algorithm with potentially reversible causes contributing to the condition.

Asystole

Complete and sustained absence of electrical activity is most often an irreversible and therefore terminal event caused by derangements such as uncorrected persistent hypoxia, severe hyperkalemia, massive drug overdose, myocardial infarction, or hypothermia. In most of these conditions, the asystole is irreversible and terminal, but at least a brief trial of interventions may be warranted in some patients. In specific instances such as hyperkalemia, known metabolic acidosis, or tricyclic antidepressant overdose, sodium bicarbonate should be administered early in the effort. Neither defibrillation nor pacing is indicated for the treatment of asystolic cardiac arrest.

Post–Cardiac Arrest–Induced Hypothermia

Therapeutic hypothermia is a new and significant intervention included in the Guidelines 2005 recommendations for patients who have experienced an out-of-hospital VF cardiac arrest, have been resuscitated, and are hemodynamically stable but unresponsive on hospital admission.[9,238,239] Hypothermia (32°C to 34°C) induced and maintained by external cooling techniques (cooling blankets, ice pack application) for 12 to 24 hours after resuscitation appears to be beneficial to neurologic outcome with minimal complications when compared with similar patients who were not cooled.[240] For patients with non-VF or in-hospital cardiac arrests, therapeutic hypothermia has not been studied. However, therapeutic hypothermia after resuscitation from cardiac arrest is given a class IIb recommendation, thus affording physicians the opportunity to use this intervention in the management of non-VF or in-hospital cardiac arrest occurring after resuscitation.

Outcome after In-Hospital Resuscitation

Discharge survival rates after in-hospital cardiac arrest and resuscitation range from 8% to 21%, with most reports demonstrating an average survival rate of approximately 14%.[241-251] These reports usually include cardiac arrests in both ICUs and general wards. In a retrospective review of 668 cardiac arrests over a 3-year period, the discharge survival rate was 3.3% in ICU patients and 14.0% in non-ICU patients.[249] In a small retrospective study of 24 consecutive patients who had an intraoperative cardiac arrest between 1986 and 1994, the survival rate was 38%.[252] A primary cardiac event was presumed to be causative in 50%. An accompanying invited commentary pointed out that much of the credit for these favorable outcomes is attributable to advances in intraoperative management by anesthesiologists. In any case, it is certain that anesthesiologists well trained in resuscitation can play a decisive role in the management of patients after intraoperative cardiac arrest.

The most favorable outcome, as in out-of-hospital cardiac arrest, is observed with VF or VT.[241,243,244,246-248] In a study compar-

ing CPR techniques in 143 hospitalized patients experiencing asystolic or PEA arrest, no patients survived to hospital discharge with intact neurologic function.[253] The duration of resuscitative attempts is a determinant of survival.[254-259] In one study, none of 179 patients in whom resuscitative effort lasted longer than 30 minutes survived to be discharged.[246] Other variables that limit survival from in-hospital cardiac arrest include unwitnessed arrest,[249] sepsis,[249] cancer,[246,249] renal failure,[246] and pre-arrest hypotension.[241,246] Age is a major determinant of outcome.[249] In one study no patients 70 years or older who experienced cardiac arrest and resuscitative attempts survived to discharge.[249] These data were obtained in a hospitalized population of relatively sick, aged male patients, and it is not possible to extrapolate these observations to a different hospital population. Nevertheless, these observations have provoked open and candid discussion and reappraisal in an attempt to define the appropriate application of CPR in hospitalized patients, as well as those in long-term care facilities.[260,261] Age alone should not preclude patients from receiving CPR.[246,261] At the same time, the presence of sepsis or cancer in an elderly patient who experiences an unwitnessed bradyarrhythmic cardiac arrest would be an example of a clinical circumstance in which resuscitative efforts would be unwarranted. As CPR and defibrillation become increasingly available, sophisticated clinical and ethical decision-making must assume a more dominant role in defining the appropriate application of resuscitation in hospitalized patients.

Resuscitation in the ICU is typically prompt and effective. Long delays in recognizing and treating cardiac arrest in general care areas of hospitals and outpatient medical facilities are common.[262] In an attempt to improve in-hospital resuscitation success rates in medical facilities (e.g., hospitals, outpatient clinics, and diagnostic centers), it is recommended that AEDs be made sufficiently available to ensure that defibrillation can occur within 3 minutes of collapse for most patients in medical facilities. Rather than identifying and training central resuscitation teams, general care nurses and other hospital employees should be trained in the use of AEDs and be authorized to initiate therapy when indicated. The Joint Commission on Accreditation of Heathcare Organizations, a U.S. regulatory agency working to improve patient care and safety, has included resuscitation response measures and procedures as an important area for review to ensure that victims of in-hospital cardiac arrest are provided prompt interventions by well-trained providers with appropriate systems for response, data collection, review, and tracking over several years.[262]

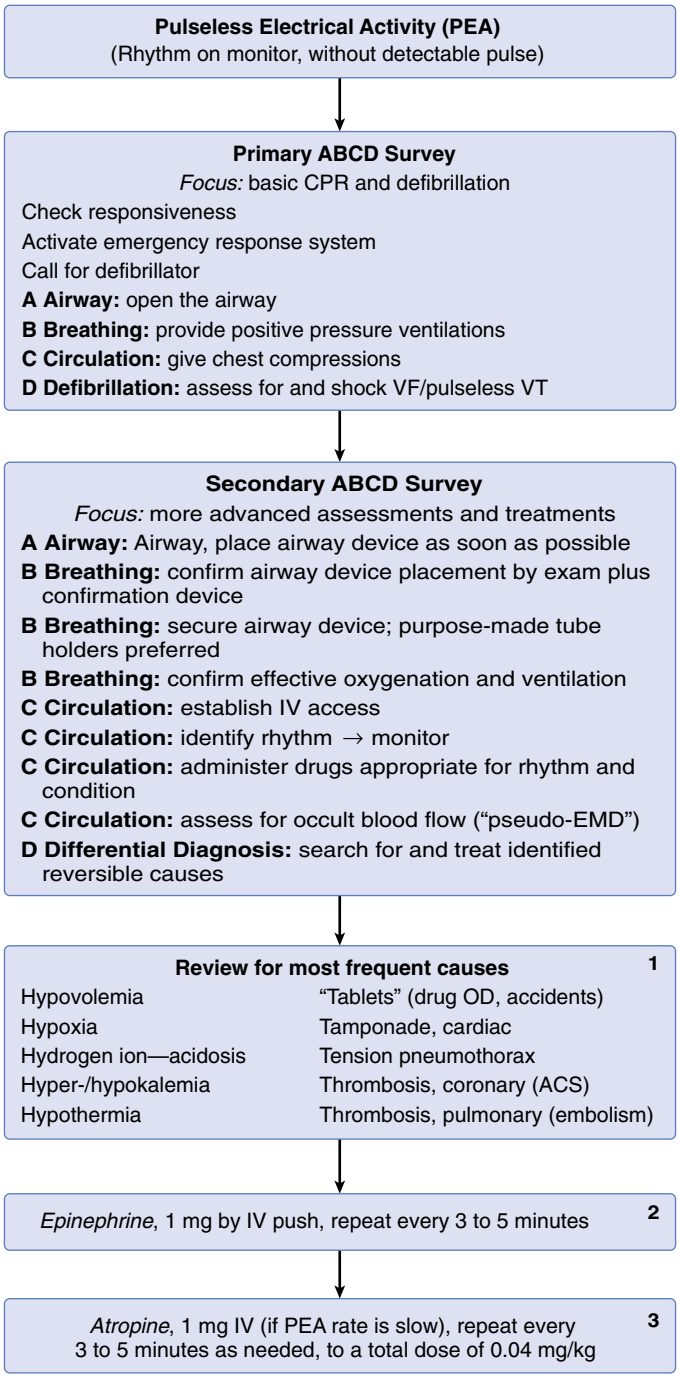

Figure 97-15 Pulseless electrical activity algorithm. ACS, acute coronary syndrome; CPR, cardiopulmonary resuscitation; EMD, electromechanical dissociation; IV, intravenous, OD, overdose; VF, ventricular fibrillation; VT, ventricular tachycardia. *(Redrawn with modification from American Heart Association in collaboration with the International Liaison Committee on Resuscitation: Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: International Consensus on Science, Parts 1-12. Circulation 102(Suppl I):I-1, 2000.)*

Do-Not-Resuscitate Orders

The increasing application of do-not-resuscitate (DNR) orders in hospitalized patients has necessitated the development of specific guidelines for the management of such patients. The CPR and emergency cardiac care guidelines addressed this issue in the section titled "Ethical Issues,"[9] and the American Medical Association Council on Ethical and Judicial Affairs developed guidelines for the use of DNR orders.[263] These documents provide helpful assistance in the use of DNR orders in hospitalized patients and should be consulted.

Pediatric Resuscitation (also see Chapters 82, 83, and 84)

It is now understood and accepted that pediatric resuscitation is an area of knowledge and skill with specific diagnostic and therapeutic considerations. Recognition of this perspective is evident in the current resuscitation guidelines.[9] However, health care providers must realize that the resuscitation recommendations intro-

duced in Guidelines 2005 for adult resuscitation apply to pediatric resuscitation as well. Like adults, pediatric chest compressions, when performed by a single rescuer, should be delivered at a rate of 100/min with two breaths interposed after every 30 compressions. Interruptions in chest compression during pediatric resuscitation should be kept to a minimum, even for airway management and defibrillation, just as in adult resuscitation. Like adults, prompt defibrillation rather than medications is most likely to be helpful to pediatric cardiac arrest victims. In light of this information, ACLS training provides sufficient consistencies in treatment recommendations extending from the young to the very old to be used effectively in the treatment of any cardiac arrest victim, young or old. AHA textbooks should be consulted for further specific details.

Basic Life Support

Primarily for convenience and uniformity in teaching, infants are considered to be 1 month to 1 year of age and children are 1 to 8 years old. Figure 97-16 depicts current recommendations for health care workers. In infants, detection of a brachial or femoral

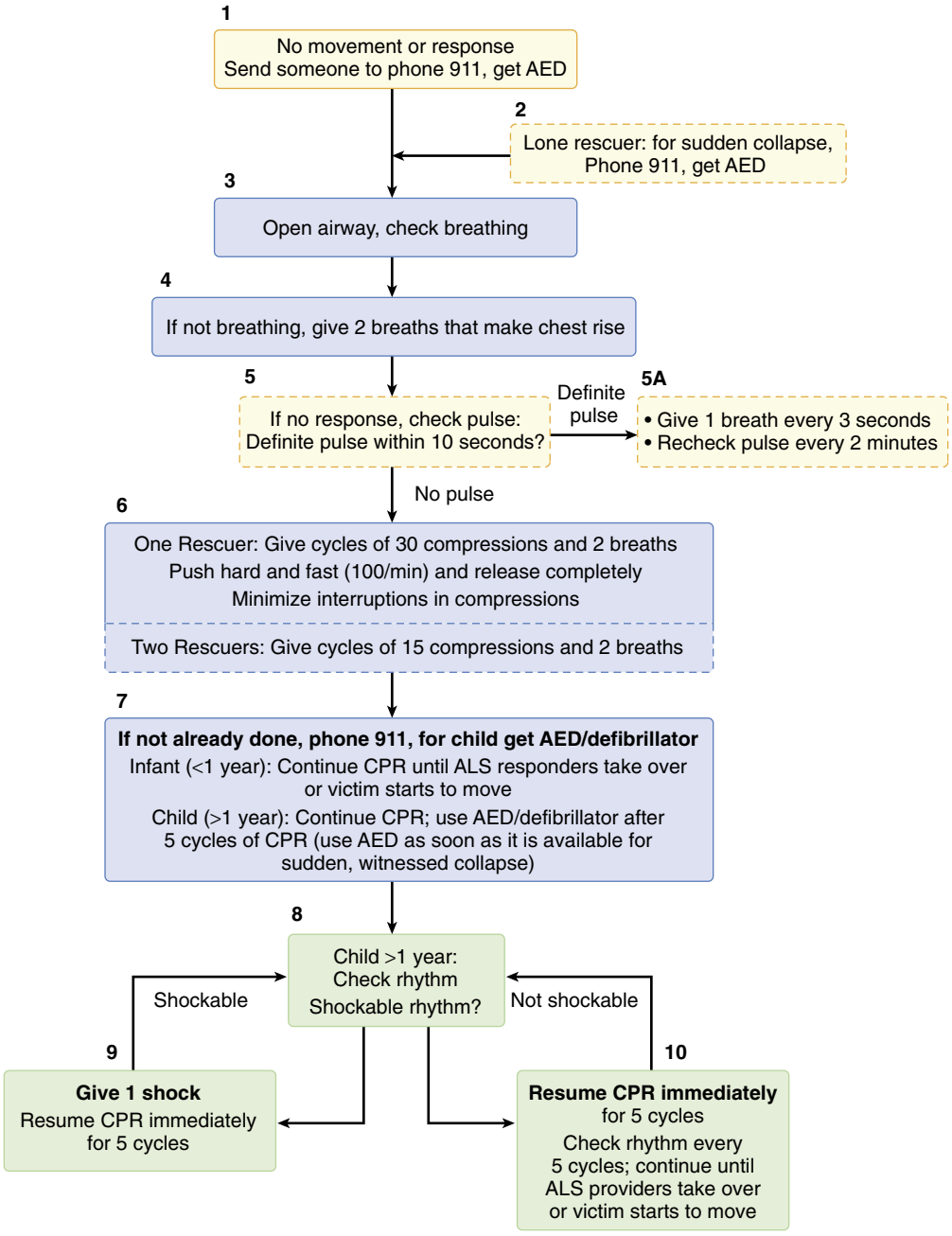

Figure 97-16 Pediatric health care provider BLS algorithm. Note that the *boxes* bordered by *dotted lines* are performed by health care providers and not by lay rescuers. AED, automated external defibrillator; CPR, cardiopulmonary resuscitation. *(From 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 112:IV-158, 2005.)*

pulse is often difficult for both health care and lay rescuers.[264,265] If a pulse cannot be palpated in 10 seconds, chest compressions should commence. If a pulse is palpated in a child with a rate of less than 60 beats/min and the child demonstrates signs of poor perfusion (i.e., pallor, cyanosis), chest compressions should be started. In infants, chest compressions are performed over the lower half of the patient's sternum, with the depth of compression being a third to half the depth of the chest (approximately 0.5 to 1.0 inch) and a compression rate of 100/min. Chest radiographs and right heart angiograms in infants, children, and young adults 1 day to 19 years old have confirmed that the heart lies under the lower part of the sternum in all age groups,[266,267] and thus this location is considered optimal for chest compressions in this age group.

Lone rescuers should perform 30 chest compressions with two interposed breaths. If two rescuers are present, a 15:1 compression-to-ventilation pattern should be used, with the breath being delivered during a short delay in chest compressions. If an advanced airway is in place, rescue breaths can be performed at a rate of 8 to 10/min without interruption in chest compression. The majority of cardiac arrests in infants and children are the result of asphyxia.[268,269] If a rescuer is alone in the presence of a child in need of resuscitation, two minutes of CPR (five cycles of 30 chest compressions and two ventilations) should be performed before activating emergency medical services.

Use of Automated External Defibrillators in Infants and Children

Since publication of the last AHA resuscitation guidelines in 2000, AEDs have been proved safe for use in infants and children.[270,271] However, there is currently insufficient evidence for or against the use of AEDs in infants younger than 1 year. It is recommended that a pediatric attenuator be used when applying AED technology to the treatment of pediatric patients. The attenuator decreases the delivered AED energy to a dose more suitable for children. If a pediatric AED is not available, a standard AED can be used.

Advanced Life Support

Unlike adults, infants and children experience cardiorespiratory arrest secondarily, rarely as a result of a primary cardiac event.[9,268,272-276] This observation is critical because ACLS interventions directed primarily toward restoration of cardiac function may cause the physician to delay properly directed therapy. For example, a progressive decline in cardiac rate leading to bradycardic arrest is likely to be an ominous sign of hypoxia in infants and children. Treatment with atropine in a futile attempt to increase the heart rate would be misdirected therapy. Furthermore, VF and VT, so common in adults, are uncommon cardiac arrest arrhythmias in infants and small children,[274,275] although some evidence indicates that VF is not rare in children and adolescents experiencing prehospital cardiac arrest.[277] Thus, application of ACLS is indeed different in these patient populations. Because the cause of cardiac arrest in children is most commonly respiratory and not cardiogenic, the ensuing pathophysiologic events and mode of manifestation of the cardiac arrest state are different, and the subsequent initial efforts at resuscitation must be directed toward respiratory support maneuvers. In addition, of course, equipment, techniques, and drug dosages are of necessity different. All these facts mandate that physicians caring for infants and children have a clear understanding of the role of ACLS interventions in these patients.

Airway Control and Ventilation

The foregoing discussion underscores what is well known to anesthesiologists: definitive control of the airway, as well as oxygenation and ventilation, is the most decisive, pivotal, and critical ACLS intervention in pediatric cardiac arrest. As in adults, anesthesiologists ordinarily intubate the trachea for this purpose and then ventilate with such devices as anesthesia bags or bag-valve units with supplemental oxygen.[278] It should be noted that the evolution of experience with LMAs should be viewed as an adjunct in this setting, with the airway secured by an endotracheal tube being the gold standard during resuscitation.

Monitoring and Recognition of Arrhythmia

ECG monitoring permits immediate recognition of the arrest rhythm or, more likely in infants and children, the "pre-arrest" rhythm. Prompt intervention and correction in the latter event prevent cardiac arrest that may be irreversible if induced by unrecognized hypoxia and manifested by progressive bradycardia. With this in mind, potentially life-threatening arrhythmias are discussed first, followed by cardiac arrest.

Supraventricular Bradyarrhythmia

As already discussed, the appearance and progression of slowing of the heart rate in infants and children demand immediate assessment of the cause, first by ruling out the most likely culprit—hypoxia. The bradycardia at this point (before cardiac arrest) is most commonly sinus or junctional in origin. Second- or third-degree heart block may ensue if corrective treatment is not applied. If hypoxia has been ruled out and the bradycardia is accompanied by clinical evidence of impaired perfusion, usually with systemic hypotension, the patient should be treated with chest compressions and epinephrine.

Epinephrine is the drug of choice for treating bradycardia in infants and children. The recommended dose is 0.01 mg/kg of a 1:10,000 dilution injected intravenously or intraosseously and can be repeated if necessary every 3 to 5 minutes. If the drug is injected into the tracheobronchial tree through an endotracheal tube, 0.1 mg/kg of a 1:1000 dilution is recommended. Chest compressions should continue until termination of the bradyarrhythmia.

If the heart rate does not increase with epinephrine, atropine can be used in a dose of 0.02 mg/kg and repeated once. An algorithm depicting interventions recommended for pediatric bradyarrhythmias is shown in Figure 97-17.

Supraventricular Tachyarrhythmia

In infants and children, supraventricular tachycardia (SVT) may represent ectopic atrial rhythms, atrial flutter or fibrillation, or paroxysmal reentrant tachycardia.[257] Standard pediatric cardiology texts should be referred to for specific diagnostic and therapeutic details. Although SVT is usually well tolerated in most infants and older children, immediate cardioversion may be necessary when heart rates in the range of 240 to 300 beats/min are reached—rates that may result in severe and rapid hemodynamic

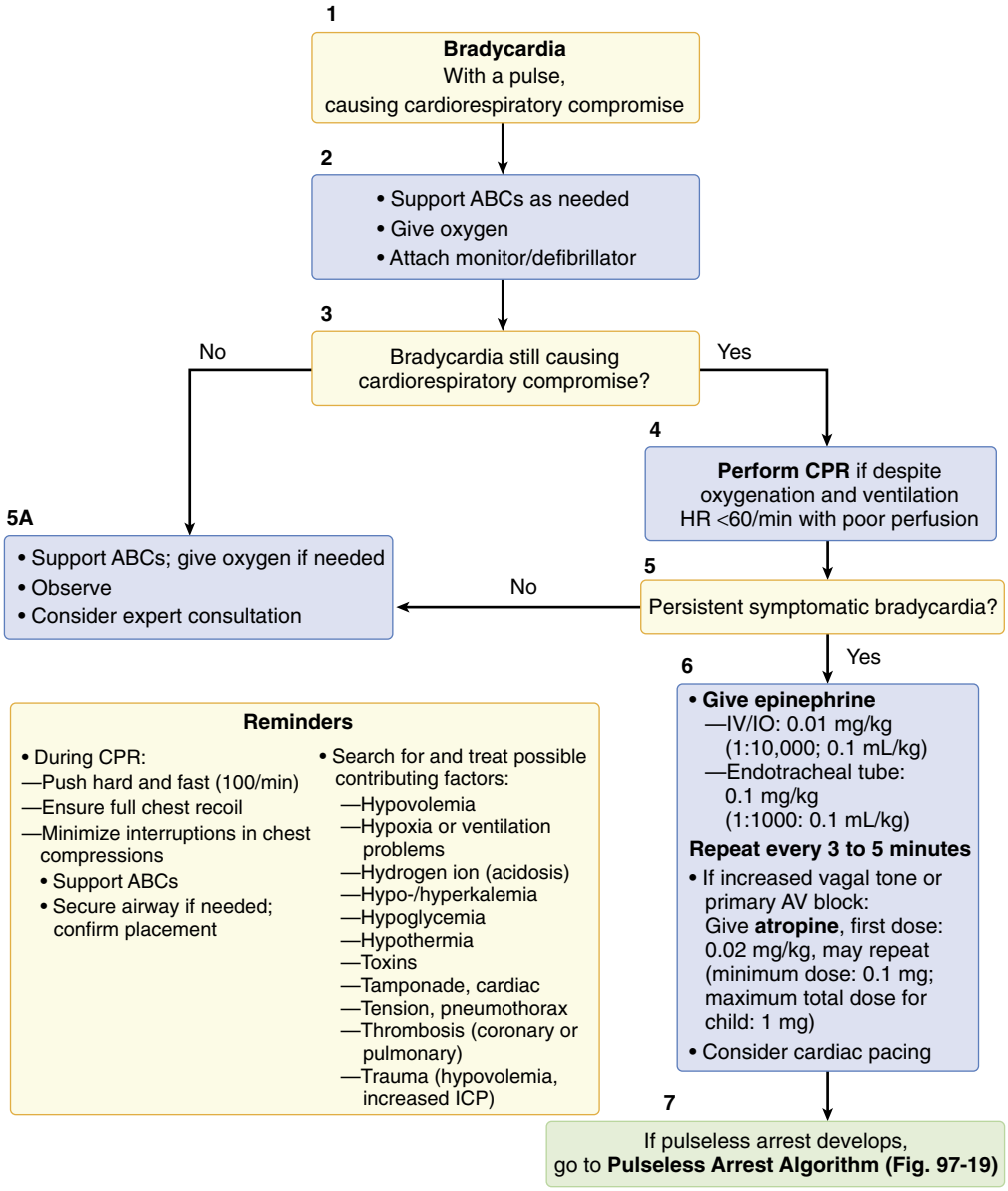

Figure 97-17 Bradycardia algorithm for pediatric advanced life support. ABC, airway, breathing, circulation; CPR, cardiopulmonary resuscitation; ICP, intracranial pressure; IO, intraosseous; IV, intravenous. *(From 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 112:IV-176, 2005.)*

compromise. In this emergency setting in which rapid SVT causes cardiovascular instability,[258] synchronized cardioversion is the treatment of choice. The initial energy dose is 0.5 J/kg body weight; if necessary, the energy dose is doubled.[279] If conversion to sinus rhythm still does not occur, the diagnosis of SVT should be reconsidered.

In hemodynamically stable children with SVT, vagal maneuvers are recommended before pharmacologic therapy. If vagal maneuvers are unsuccessful, adenosine is the drug of choice, as with adults. The drug can be given as a rapid bolus in a dose of 0.1 mg/kg intravenously or intraosseously, ideally injected into the closest port to the hub of the catheter and flushed with 2 to 3 mL of fluid. If the SVT persists or recurs, a second dose of 0.2 mg/kg intravenously or intraosseously can be given in 1 to 2 minutes.[9,259,279-281] The maximum single dose should not exceed 12 mg.

Verapamil is not recommended for pediatric SVT in an emergency setting because it may induce systemic hypotension and a state of depressed myocardial contractility.[282-284] Specifically, it is not recommended in this setting for infants younger than 1 year, children with congestive heart failure or myocardial depression, children receiving β-adrenergic–blocking drugs, or children who may have an accessory pathway between the atria and ventricles.[279]

In circumstances in which adenosine has been unsuccessful in converting hemodynamically stable SVT, procainamide and amiodarone can be considered ahead of cardioversion.[285,286] Procainamide, 15 mg/kg, can be delivered over a period of 30 to 60

minutes. Amiodarone, 5 mg/kg delivered over a 20- to 60-minute period, can also be considered. Procainamide and amiodarone should not be administered together.

The treatment algorithm for tachyarrhythmias in pediatric patients is presented in Figure 97-18.[9]

Ventricular Bradycardia

As with supraventricular bradyarrhythmias, a slow idioventricular rhythm that has not yet produced pulselessness must be considered indicative of severe hypoxia (see Fig. 97-17), and treatment must be directed accordingly. Only after this condition has been addressed should rate-accelerating therapy be invoked, as discussed for supraventricular bradycardia.

Ventricular Tachyarrhythmia

Despite a common misconception, VT is not always associated with severe hemodynamic compromise. Ventricular rates of 150 to 200 beats/min may be well tolerated, as defined as palpable pulses, but they should nonetheless be converted to a normal rhythm. Emphasis is placed on accurate diagnosis with 12-lead ECGs before treatment if the patient remains hemodynamically stable. In the setting of wide–QRS complex tachycardia, synchronized cardioversion is the indicated treatment, beginning at 0.5 J/kg and increasing to progressively higher doses up to 2 J/kg with either monophasic or biphasic waveform shocks. If pharmacologic therapy is undertaken, amiodarone is the drug of choice and is delivered as described for the treatment of SVT. Intravenous

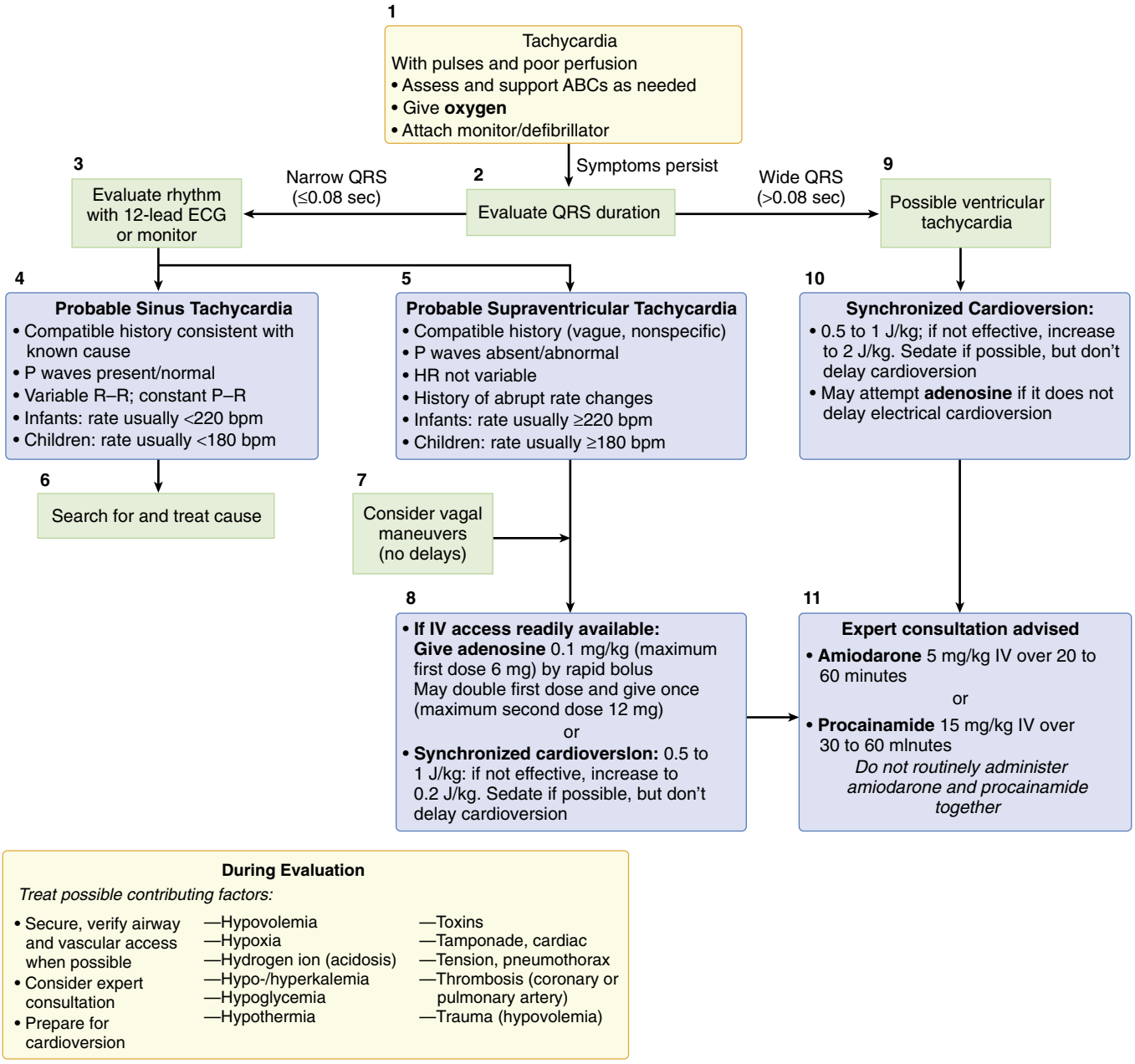

Figure 97-18 Tachycardia algorithm for pediatric advanced life support. ABCs, airway, breathing, circulation; ECG, electrocardiogram; HR, heart rate. *(From 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 112:IV-177, 2005.)*

procainamide (in doses identical for the treatment of SVT) can also be considered. The two drugs should not be administered together. If the tachycardia is very rapid (rates greater than 300/min) or cardiovascular collapse and loss of pulses occur, this situation should be treated like VF.

Management of Cardiac Arrest

Once pulselessness ensues, therapy must be directed not only at correcting the underlying rhythm disorder but also at maintaining organ viability during the period of cardiorespiratory arrest. Meticulous attention must be paid to ensuring proper chest compression rate and depth, avoidance of hyperventilation and interruption of chest compressions, and administration of medications that support perfusion pressure during resuscitation efforts. The pulseless arrest algorithm for pediatric advanced life support is shown in Figure 97-19.

In the great majority of pediatric cardiac arrests, bradyasystole is the terminal cardiac electrical activity (see Fig. 97-17).

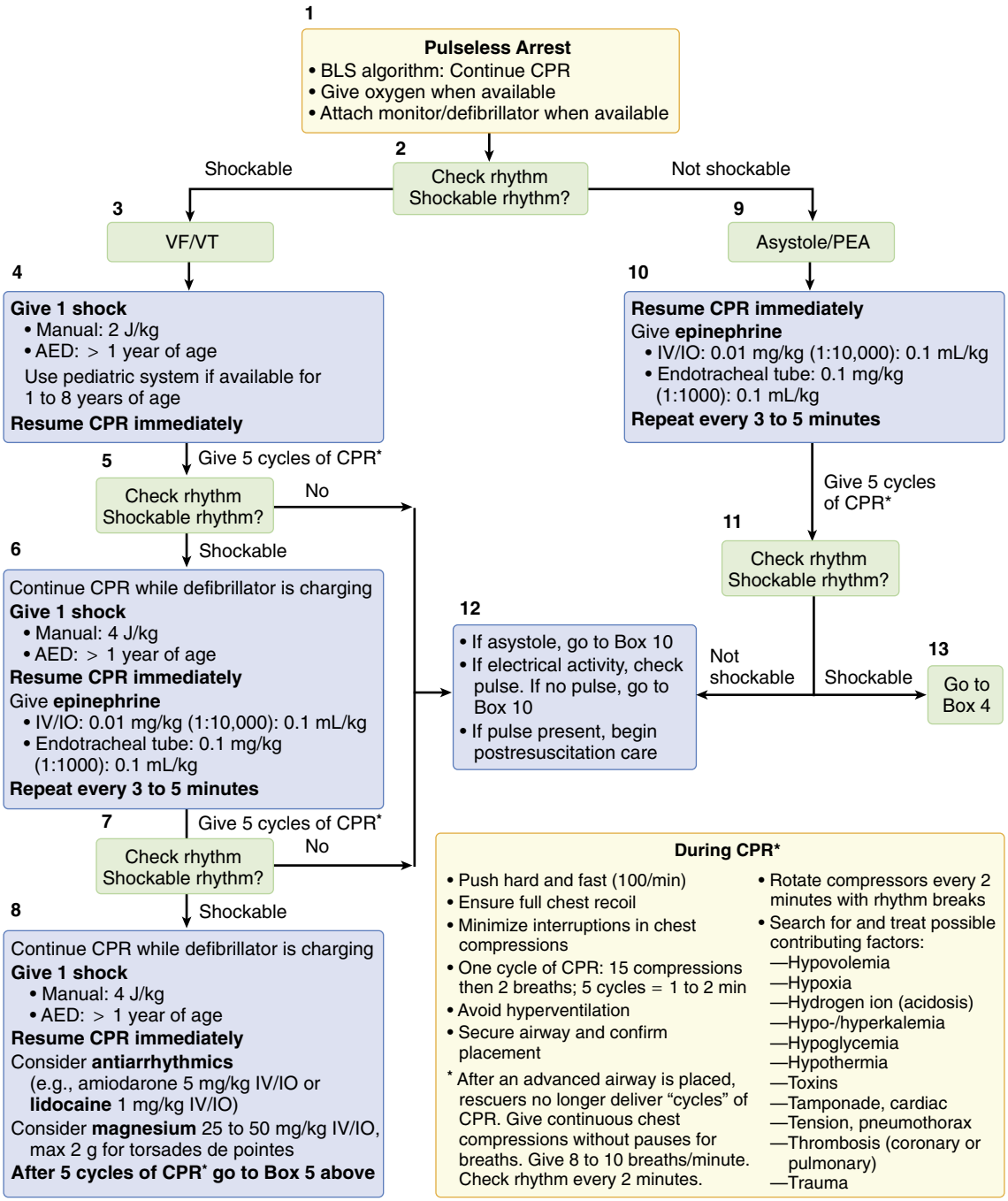

Figure 97-19 Pulseless arrest algorithm for pediatric advanced life support. AED, automated external defibrillator; BLS, basic life support; CPR, cardiopulmonary resuscitation; IO, intraosseous; IV, intravenous; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia. *(From 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 112:IV-173, 2005.)*

Early dominance of the parasympathetic nervous system and α-adrenergic activity may, in part, explain this dominance of brady-asystolic mechanisms as the terminal event in infants.[274] In addition, ventricular tachyarrhythmias (VT/VF) are most commonly seen in infants and children with congenital heart disease.[274] Such children may have cardiac hypertrophy and increased ventricular muscle mass sufficient to provide an anatomic substrate for reentrant wave fronts that initiate and sustain VT or VF.

Pulseless Electrical Activity and Asystole

PEA, as in adults, includes disorders in which some form of cardiac electrical activity is present, but without palpable pulses. In infants and children, this disorder is most commonly an idioventricular rhythm at a very slow and irregular rate (bradyasystole) and is the usual predecessor to ventricular asystole. When PEA is present, an immediate and aggressive effort should be made to identify treatable causes. As in adults, diagnoses to be considered immediately include hypovolemia, tension pneumothorax, cardiac tamponade, hypoxemia or acidosis (or both), or hypothermia. Immediate consideration of these possibilities and the corresponding direction of therapeutic effort may avoid administration of drugs for what will inevitably become a terminal situation if an underlying, potentially reversible catastrophe is present (see Fig. 97-18).

For both PEA and asystole, epinephrine is the drug of choice and is given initially at a dose of 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution) intravenously or intraosseously. Defibrillation is not associated with benefit in PEA or asystole. Emphasis is placed on correcting potentially reversible conditions.

If vascular access has not been achieved, initial treatment with epinephrine can be given through an intraosseous route or via an endotracheal tube. Intraosseous doses are equivalent to intravenous doses. Through the endotracheal route, 0.1 mg/kg of a 1:1000 solution is given. The dose can be repeated every 3 to 5 minutes, as long as the arrest persists. Epinephrine is presumed to have the same beneficial actions on elevating coronary and cerebral perfusion pressure discussed earlier in the adult resuscitation section. In an infant animal model (infant piglets), epinephrine increased cerebral and myocardial blood flow, a finding suggesting that it may have a similar beneficial action in infants and children.[287]

In pediatric cardiac arrest, if venous cannulation cannot be achieved in three attempts or 90 seconds, an intraosseous approach is now recommended and preferred for drug administration via the endotracheal tube route. Intraosseous access is a rapid, safe, and effective route for administering resuscitative fluids (including blood) and medications in both medical and traumatic emergencies. The needle is inserted perpendicular to the skin into the tibia approximately one fingerbreadth below the tubercle on the anteromedial surface. Loss of resistance will be felt as the needle passes through the bony cortex. Drug levels attained by intraosseous administration are nearly equivalent to those achieved with intravenous administration.[288] Fluid boluses are required to ensure that medications delivered intraosseously enter the circulation quickly.

In CPR of infants and children, it is recommended that a rapid glucose test be performed and glucose be injected if hypoglycemia is present.[9,279] For infants and children who do not respond to resuscitative therapy, glucose administration should also be considered. However, as expressed earlier in the discussion of adult cardiac arrest, routine use of glucose-containing solutions should be avoided because of a potentially adverse impact on neurologic outcome and because glucose administration may result in hyperglycemia and secondary osmotic diuresis. If glucose is necessary, the dose is 0.5 to 1.0 g/kg intravenously in a solution of 25% dextrose in water (2 to 4 mL/kg) for infants and children, preferably given as a continuous infusion rather than a bolus to avoid a sudden increase in serum osmolality.[9,279] The commercially available 50% dextrose in water solution can be diluted 1:1 with sterile water for this purpose. For neonates, in general, the concentration of glucose administered should not exceed 12.5%, thus necessitating further dilution of the 50% dextrose solution.

The same concerns discussed earlier regarding sodium bicarbonate therapy in adults also apply to pediatric patients. If it is used, 1 mEq/kg can be given initially and 0.5 mEq/kg at 10-minute intervals thereafter, unless arterial blood measurements of pH, $Paco_2$, and base deficit are available and indicate a different dosage scheme.[279] Likewise, no available evidence supports the continued use of calcium salts for cardiac arrest in infants and children. The use of calcium chloride should be reserved for the acute treatment of hyperkalemia, hypermagnesemia, hypocalcemia, or calcium channel–blocking drug toxicity. In these clinical situations, 0.2 to 0.25 mL/kg of 10% calcium chloride (5 to 7 mg/kg of elemental calcium) can be given and repeated once in 10 minutes.[277]

Pulseless Ventricular Tachycardia or Ventricular Fibrillation

VF occurs in 5% to 15% of all prehospital pediatric cardiac arrests[277,289] and in up to 20% of in-hospital pediatric cardiac arrests. VT and VF are relatively uncommon in infants and children, most likely to be seen with congenital heart disease. The increased cardiac muscle mass in congenital heart syndromes provide the anatomic electrophysiologic milieu for maintaining reentrant wave fronts. As in adults, the treatment of choice for VT/VF in children is defibrillation therapy, not medications.

Defibrillation can be accomplished with adult defibrillator pads for children weighing more than 10 kg, provided that more than 3 cm separates the pads. Infant paddles/pads should be used for patients younger than 1 year or those weighing less than 10 kg. Energy doses for safe and effective defibrillation in infants and children are not known. Guidelines 2005 recommends 2 J/kg for the first defibrillation attempt with either monophasic or biphasic defibrillators. Subsequent defibrillation attempts should use 4 J/kg.[9]

As long as the cardiac arrest persists, epinephrine should be given in the same concentrations, routes, and intervals as described for PEA-related cardiac arrest. There is insufficient evidence for using vasopressin in pediatric cardiac arrest. Amiodarone, 5 mg/kg intravenously or intraosseously, and lidocaine, 1 mg/kg intravenously or intraosseously, are also options for therapy in protracted VF unresponsive to defibrillation therapy. It must be remembered that fluid boluses must follow drug administration, as well as the need for uninterrupted chest compressions with avoidance of hyperventilation.

One of the most difficult aspects of pediatric resuscitation is determination of correct drug doses in the midst of a crisis, especially if one deals with cardiac arrest in infants and children infrequently. Various schemes have been proposed for simplifying this need. Table 97-3 incorporates a convenient scheme for selecting the proper dose of drug to be injected according to body

Table 97-3 Medications for Pediatric Resuscitation and Arrhythmias

Medication	Dose	Remarks
Adenosine	0.1 mg/kg (maximum: 6 mg) Repeat 0.2 mg/kg (maximum: 12 mg)	Monitor ECG Rapid IV/IO bolus
Amiodarone	5 mg/kg IV/IO; repeated up to 15 mg/kg Maximum: 300 mg	Monitor ECG and blood pressure Adjust administration rate to urgency (give more slowly when a perfusing rhythm is present) Use caution when administering with other drugs that prolong the QT interval (consider expert consultation)
Atropine	0.02 mg/kg IV/IO 0.03 mg/kg ET* Repeat once if needed Minimum dose: 0.1 mg Maximum single dose: Child: 0.5 mg Adolescent: 1 mg	Higher doses may be used with organophosphate poisoning
Calcium chloride (10%)	20 mg/kg IV/IO (0.2 mL/kg)	Slowly Adult dose: 5-10 mL
Epinephrine	0.01 mg/kg (0.1 mL/kg 1 : 10,000) IV/IO 0.1 mg/kg (0.1 mL/kg 1 : 1000) ET* Maximum dose: 1 mg IV/IO, 10 mg ET	May repeat q3-5 min
Glucose	0.5-1 g/kg IV/IO	$D_{10}W$: 5-10 mL/kg $D_{25}W$: 2-4 mL/kg $D_{50}W$:1-2 mL/kg
Lidocaine	Bolus: 1 mg/kg IV/IO Maximum dose: 100 mg Infusion: 20-50 µg/kg/min ET*: 2-3 mg	
Magnesium sulfate	25-50 mg/kg IV/IO over 10- to 20-min period; faster in torsades Maximum dose: 2 g	
Naloxone	<5 yr or ≤20 kg: 0.1 mg/kg IV/IO/ET* ≥5 yr or >20 kg: 2 mg IV/IO/ET*	Use lower doses to reverse respiratory depression associated with therapeutic opioid use (1-15 µg/kg)
Procainamide	15 mg/kg IV/IO over 30- to 60-min period Adult dose: 20-mg/min IV infusion up to total maximum dose of 17 mg/kg	Monitor ECG and blood pressure Use caution when administering with other drugs that prolong the QT interval (consider expert consultation)
Sodium bicarbonate	1 mEq/kg per dose IV/IO slowly	After adequate ventilation

$D_{10}W$, 10% dextrose in water; ECG, electrocardiogram; ET, via endotracheal tube; IO, intraosseous; IV, intravenous.
*Flush with 5 mL of normal saline and follow with five ventilations.

weight. It includes the major resuscitative drugs along with additional drugs that could be used in some cardiac arrests or other pediatric emergencies. The availability of a resuscitation team knowledgeable in pediatric resuscitation is critical for the proper management and resuscitation of a child victim of cardiac and near-cardiac arrest.

Termination of Pediatric Resuscitation Attempts

There are no clear clinical signs or reliable predictors indicating whether efforts made in resuscitating infants and children will be successful. Witnessed cardiac arrest, prompt effective chest compressions and ventilation, and rapid initiation of advanced resuscitative interventions improve the chance of a successful outcome but do not guarantee successful resuscitation. Prolonged resuscitation should be performed in infants and children with recurring or refractory VF or VT.[9] Emerging technologies (e.g., extracorporeal circulation and membrane oxygenation, ECMO) and their availability may influence decisions to terminate resuscitative events. The ethics of terminating resuscitative care have been addressed in Guidelines 2005, Part 2: "Ethical Issues."[9] Clinicians are encouraged to review these guidelines, as well as relevant guidelines developed in their local practice environment.

Educational Initiatives

As information has been thoroughly reviewed and considered in developing these most recent resuscitation guidelines, there is evidence that retention of resuscitation skills and knowledge

declines quickly, even in medical specialties where critical and timely interventions are the norm rather than exception,[123] thus suggesting a need for review at intervals within the period of advanced life support certification. Other avenues that must be addressed are the quality of resuscitation interventions (e.g., uninterrupted chest compressions, timely airway management, prompt defibrillation, accurate recognition of arrhythmias). Growing evidence suggests that health care providers are failing to provide effective BLS[16,65,66] and fail to deliver defibrillatory shocks in timely fashion.[290] It is likely that these issues will be scrutinized closely in the near future.

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98 Brain Death

Key Points

1. The first description of cessation of brain functions using a concept similar to the modern definition of brain death appeared in 1959, although the subject became more controversial after the development of organ transplantation. Criteria for brain death were first published in 1968, a year after the first heart transplantation. Although cultural and religious diversity may lead to great differences in attitudes toward brain death and there is no global consensus in diagnostic criteria, the concept of brain death as defining the death of the individual is widely accepted, and many countries have published recommendations or legal requirements for the diagnosis of brain death, in particular, as a necessary prerequisite for organ donation.
2. The traditional concept of death has used the cessation of cardiac and respiratory functions as its basis because of the acceptance of simple and nonmedical concepts: that life begins with the first inspiration after birth, that death comes with the last expiration, and that cardiac activity ceases within a few minutes of the last expiration. In contrast, the modern concept of brain death adopts the conclusions of modern biologic science (central integrator theory of the brain): that the central nervous system (CNS), including the brainstem, is the control center for the living organism; that cessation of CNS functions represents cessation of the harmony of life; and that without CNS control, the living organism is nothing more than an aggregation of living cells. However, this notion has become controversial, because not all brain-dead patients inevitably deteriorate to cardiovascular collapse in a short time and they can assimilate nutrients, fight infections, heal wounds, and carry out a pregnancy.
3. Trauma to the brain or cerebrovascular injury produces brain edema. Because the brain is covered by a rigid bony skull, edema is accompanied by an increase in intracranial pressure, which, if sufficiently high, exceeds arterial blood pressure. When cerebral circulation ceases, aseptic necrosis of the brain ensues. Within 3 to 5 days, the brain becomes a liquefied mass. Such increased intracranial pressure compresses the entire brain, including the brainstem, and total brain infarction follows.
4. Clinical studies indicate that hypothalamic and anterior pituitary functions are preserved to some degree for a certain period after the onset of brain death. The response of the immune system to stimulation is modified considerably after total and irreversible loss of CNS functions. Hormonal changes and inflammatory responses after brain death are the theoretical and scientific basis of hormonal therapy for hemodynamic stabilization of brain-dead organ donors.
5. During the process of brain death after head injury or intracranial bleeding, intracranial pressure increases and compression of the brainstem leads to marked hypertension and bradycardia (i.e., Cushing phenomenon). At the onset of brain death by tonsillar herniation, sudden decrease of arterial blood pressure occurs, but the arterial pressure gradually returns to normal with the spinal cord gaining automaticity.
6. Determination of brain death confirms the irreversible cessation of all functions of the entire brain, including the brainstem. Irreversibility means that no treatment may be reasonably expected to change the condition. Although testing all functions of the brain is conceptually impossible, the cessation of all functions of the brain is practically determined by loss of consciousness, loss of brainstem responses, apnea, and confirmatory tests.
7. Cerebral death, the so-called persistent vegetative state, refers to cessation of the functions of the cerebral cortices. It is not the equivalent of death.
8. It is true that cultural and religious diversities may affect the notion of death, but there is a significant variability in policies and practices for determining brain death internationally and even among states and hospitals.
9. Tests to confirm brain death include an electroencephalogram, evoked responses, and measurement of blood flow.
10. Because of their intact spinal cord and the presence of somatic and visceral reflexes, brain-dead patients require special anesthetic management, including use of muscle relaxants, vasodilators, and perhaps sedation and analgesia. Anesthesiologists should understand the medical and legal definitions of death, as well as the ethical concepts behind them.

Because advancements in medicine have changed the definition and concept of death, legislation must also change accordingly. This issue results from progress in organ transplantation and the increasing number of patients who have a living body but nonfunctioning brain, which is a consequence of discoveries in resuscitative and life support techniques. Such refinements in critical care medicine mean that neurologists, neurosurgeons, and anesthesiologists must be able to make an appropriate diagnosis of death. Although cultural and religious diversity may lead to great differences in attitudes toward brain death and there is no global consensus in diagnostic criteria, the concept of brain death as defining the death of the individual is widely accepted,[1,2] and many countries have published recommendations or legal requirements for the diagnosis of brain death as a necessary prerequisite for organ donation.[3,4]

History

In 1902, Cushing[5] first reported cessation of cerebral circulation when intracranial pressure exceeded arterial blood pressure in monkeys. He also described the use of artificial ventilation to prolong cardiac function for 23 hours after cessation of spontaneous respiration in a patient with a brain tumor. In 1959, Bertrand and colleagues[6] reported the maintenance of respiration by mechanical means for 3 days after death of a patient with otitis media who underwent circulatory collapse. Repeated convulsions had preceded a deep coma. Autopsy revealed extensive brain necrosis of the cerebral and cerebellar cortices, basal ganglia, and brainstem nuclei, which was attributed to cessation of cerebral circulation during artificial ventilation. Also in 1959 appeared the first description of cessation of brain functions using a concept similar to the modern definition of brain death (i.e., le coma dépassé) by Mollaret and coworkers.[7]

These historical reports support the argument that the concept of brain death is independent of and was established before the start of organ transplantation from brain-dead patients. However, there is still dispute about whether brain death is or is not directly related to organ transplantation. The heated discussion on brain death started after the first heart implantation by Barnard in 1967. One year later, the ad hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death published its criteria for brain death and defined "irreversible coma as a new criterion for death."[8] The committee deliberations focused on a whole-brain formulation to define brain death. In 1981 the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research[9] defined the brain as the "primary organ" and justified the application of a whole-brain definition for brain death in the United States. The whole-brain formulation of brain death was acknowledged by statute in the Uniform Determination of Death Act (UDDA)[10] by stating that "an individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead." This formulation is the one most commonly applied worldwide and forms the foundation for legal codification in many Western nations. Numerous criteria on brain death have been offered by institutions, state agencies, expert groups, and governments (Tables 98-1 and 98-2).[1,3,4,11,12]

In contrast, brainstem definition for brain death was first pronounced in 1976 by the Conference of Medical Royal Colleges and their Faculties in the United Kingdom.[13] The document in 1995 entitled "Criteria for the Diagnosis of Brain Stem Death"[14] encouraged the use of the more correct term *brainstem death* rather than *brain death* and gave a definition of death, stating that "death is defined as the irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe."

Traditional Concept of Death of an Organism

In Greek antiquity, two concepts existed regarding the body cavity, where "the principle of life," now known as "function of the brain," was housed. One is that of Plato, and another is Aristotle's. Plato first postulated the tripartite soul in the *Republic* and *Timaeus*. The first part is the reason, the second, emotion, and the third is appetite or desire. Reason, which we might today call "consciousness," is the reappearance of the God's soul (the divine), housed in the ideal shaped vessel, in which all distances from the center are the same (i.e., the head). The second soul, emotion, is located in the heart. It affects circulation, and its manifestations, such as pulse rate, are functions that correlate with what we think of as the autonomic nervous system. The neck is constructed as a kind of isthmus or boundary between the head and the chest to ensure that reason is not affected by emotion. The third part of the soul, that is, the appetite for food and drink or sexual desire, is the least noble part. It was housed in the stomach, separated from the heart by diaphragm, and thought to be punished by the bitterness of bile. However, we cannot interpret this too literally, because it was meant to be a sort of analogy for consumption by the ordinary citizen. Plato considered "death" to be the separation of reason from the mortal body, whereas Socrates, in his *Apology,* confessed that he did not know the fate of reason after death. The "vegetable state" in today's neurophysiology, is, according to Plato, the equivalent of death.

Unlike Plato, Aristotle, who is known as the founding father of genetics, stressed experience, or empirical knowledge, rather than abstract thinking. Aristotle postulated that all functions of the brain were housed in the heart, which he considered the most important organ of the body—the seat of the intelligence and the origin of motion and sensation. Other organs surrounding it, like the brain and the lungs, existed simply to cool the heart. Aristotle dissected dogs, horses, grasshoppers, crickets, and other living creatures to understand the reasons why, for instance, dogs cannot give birth to horses. He thought that animals "cook" foods in their digestive tracts and that blood transports nutrients to each organ from the heart. This transport corresponds to the electrical signals in the nerves in today's neurophysiology. According to Aristotle, the lungs cool the heart, and the cranium serves as a cooling apparatus for liquefying a transmitter, a kind of "pneuma."

In Aristotle's system, the vehicle that conveys commands from the control center to the peripheral organs and tissues, roughly equivalent to the electrical signals of the nervous system in today's neurophysiology, was assumed to be something like vapor or gas. This concept is the basis from which the idea of "pneuma" (breath or spirit) originates. God created man (Adam)

Table 98-1 Brain Death Survey in 80 Nations

Continent/Country	Law	Guideline	Apnea Test	No. of Physicians	Observation Time (hr)	Confirmatory Test
North America						
United States	P	P	Pco_2	2*	6	Optional
Canada	P	P	Pco_2	1	6	Optional
Caribbean						
Barbados	A	A	A	A	A	Optional
Cuba	A	P	Pco_2	2	6 (24)†	Optional
Jamaica	A	P	A	2	12	Mandatory
Trinidad and Tobago	A	P	Pco_2	2	A	Optional
Central and South America						
Argentina	P	P	DVO	1	6	Mandatory
Brazil	P	P	DVO	1	6	Optional
Chile	P	P	DVO	2	A	Mandatory
Colombia	P	P	A	2 (N)	A	Optional
Costa Rica	P	P	Pco_2	1	24	Optional
Ecuador	A	A	A	A	A	Optional
El Salvador	A	P	A	1	6 (24)†	Mandatory
Guatemala	A	A	A	A	A	Not known
Honduras	A	A	A	A	A	Not known
Mexico	P	P	A	A	24	Mandatory
Paraguay	A	P	Pco_2	1	24	Optional
Uruguay	P	P	Pco_2	1	A	Optional
Venezuela	P	P	Pco_2	2 (N)	12	Optional
Europe						
Austria	P	P	DVO	1	12	Optional
Belgium	P	P	DVO	3	A	Optional
Cyprus	P	P	DVO	2	A	Optional
Czech Republic	A	P	Pco_2	2	A	Mandatory
Denmark	P	P	DVO	2	2 (24)†	Optional
Estonia	P	P	Pco_2	1	12	Optional
Finland	P	P	DVO	1	A	Optional
France	P	P	Pco_2	2	A	Mandatory
Germany	P	P	Pco_2	2	12	Optional
Greece	P	P	DVO	3	6	Optional
Hungary	P	P	Pco_2	1	12 (72)†	Mandatory
Ireland	P	P	Pco_2	2	A	Optional
Italy	P	P	Pco_2	1	6 (24)†	Mandatory
Luxembourg	P	P	Pco_2	1	A	Mandatory
Malta	P	P	Pco_2	1	6	Optional
Netherlands	P	P	Pco_2	1	A	Mandatory
Norway	P	P	DVO	A	24	Mandatory
Poland	P	P	DVO	1	3	Optional
Portugal	P	P	Pco_2	1	2-24	Optional
Romania	P	P	Pco_2	2	6	Mandatory
Russia	P	P	Pco_2	2	6 (24)†	Optional
Slovak Republic	P	P	A	3	A	Mandatory
Spain	P	P	Pco_2	1	6 (24)†	Optional
Sweden	P	P	Pco_2	1	A	Mandatory
Switzerland	P	P	Pco_2	2	6 (48)†	Optional
Turkey	P	P	Pco_2	4	A	Mandatory
Ukraine	A	P	DVO	A	A	Optional
United Kingdom	P	P	Pco_2	2	6	Optional
Yugoslavia	A	P	DVO	3	A	Mandatory
Africa						
Egypt	A	A	A	A	A	Not known
Ghana	A	A	A	A	A	Not known
South Africa	P	P	Pco_2	2	A	Optional
Tanzania	A	P	A	1	A	Mandatory
Tunisia	P	P	DVO	1	A	Optional

Table 98-1 Brain Death Survey in 80 Nations—cont'd

Continent/Country	Law	Guideline	Apnea Test	No. of Physicians	Observation Time (hr)	Confirmatory Test
Middle East						
Iran	A	P	A	3	12, 24, 36	Mandatory
Israel	P	P	Pco_2	1	6 (24)†	Mandatory
Jordan	A	P	A	1	N/S	Mandatory
Lebanon	P	P	A	2	6	Mandatory
Oman	P	P	Pco_2	1	6	Optional
Qatar	P	P	Pco_2	1	N/S	Mandatory
Saudi Arabia	P	P	Pco_2	2	24†	Mandatory
Syria	A	A	A	N/S	N/S	Not known
United Arab Emirates	P	P	Pco_2	1	3	Optional
Asia						
Armenia	A	A	A	N/S	N/S	Optional
Bangladesh	P	P	DVO	3	N/S	Optional
China	A	A	A	N/S	N/S	Optional
Georgia	P	P	DVO	3	24	Mandatory
Hong Kong‡	P	P	Pco_2	1	N/S	Optional
India	P	P	DVO	4	N/S	Mandatory
Indonesia	A	P	Pco_2	3	24	Optional
Japan	P	P	Pco_2	1	N/S	Mandatory
Korea (South)	P	P	Pco_2	1	6	Optional
Malaysia	P	P	Pco_2	2	12	Mandatory
Pakistan	A	A	A	N/S	N/S	Not known
Philippines	A	P	DVO	1	24	Optional
Singapore	P	P	Pco_2	2	N/S	Optional
Taiwan	A	P	Pco_2	1	6	Optional
Thailand	P	P	DVO	3	6	Optional
Vietnam	A	A	DVO	N/S	N/S	Optional
Oceania						
Australia	P	P	Pco_2	2	2	Optional
New Zealand	A	P	Pco_2	2	2	Optional

Pco_2, target Pco_2 defined (50 or 60 mm Hg); A, absent; DVO, disconnection from ventilator only; N, neurologist; N/S, not specified; P, present; LAW, legal standard of organ donation.
*Eight US states only; time within parentheses indicates observation time in conditions due to anoxia.
†Observation time can be shortened or eliminated if one confirmatory test is positive for brain death.
‡China resumed control of Hong Kong in 1997.
From Wijdicks EF: Brain death worldwide. Neurology 58:20, 2002.

out of the dust of the earth and inspired the breath of life into his nostrils, and a man became a living soul. Later, Eve was created from Adam's rib and, with God's breath, became a living soul as well. This story might call to mind the first cry of the neonate, which is the first activity of life caused by the God's "inspiration." This creative breathing, or inspiration, is the subject of Botticelli's painting *The Birth of Venus*, in which Zephyr, the west wind, puffs vigorously as his wife Chloris gently blows her warm breath on Venus, who stands on a shell. Aristotle's idea postulating the heart as the principal seat of the spirit had a profound influence on Western scientific thought for a long period. William Harvey's discovery, described in his *Circulation of Blood* (1628) is considered as the final scientific development of Aristotle's ideas and Aristotle is the thinker most cited in Harvey's book.

In the time before the known history of the world, the loss of the upper limbs meant the loss of the ability to fight and, hence, the death of the individual. The concept of "limb death" could have developed during this prehistorical period. The same is true of the concept of "renal death," since, in the age before the advent of hemodialysis/renal transplantation, severe renal dysfunction caused uremia, and death was inevitable, just as the irreversible elimination of the immune functions could bring about "immune death." These examples are meant to illustrate that human understanding of death need not be uniform nor universal and has not been throughout history. It has changed with different periods, areas, ethics, and stages of advance of technologic and scientific advance. Brain death should be discussed separately from organ transplantation, although the latter is an important issue in considering the concepts of life and death.

All living organisms take in oxygen by respiration, distribute the oxygen to peripheral tissues through circulation, and then excrete metabolites by means of the circulation and through respiration. Respiration and circulation are vital to the living organism. Respiration is the functional expression of the brainstem, and cessation of brainstem functions leads to the cessation of respiration. Because the brainstem maintains its function through its supply of oxygen and nutrients, cessation of circulation ultimately leads to cessation of respiration. The functions of the

Table 98-2 Diagnostic Criteria for the Clinical Diagnosis of Brain Death

A. Prerequisites. Brain death is the absence of clinical brain function when the proximate cause is known and demonstrably irreversible.
   1. Clinical or neuroimaging evidence of an acute central nervous system catastrophe that is compatible with the clinical diagnosis of brain death
   2. Exclusion of complicating medical conditions that may confound clinical assessment (no severe electrolyte, acid-base, or endocrine disturbance)
   3. No drug intoxication or poisoning
   4. Core temperature ≥ 32°C (90°F)

B. The three cardinal findings in brain death are coma or unresponsiveness, absence of brainstem reflexes, and apnea.
   1. Coma or unresponsiveness—no cerebral motor response to pain in all extremities (nail-bed pressure and supraorbital pressure)
   2. Absence of brainstem reflexes
      a. Pupils
         i. No response to bright light
         ii. Size: midposition (4 mm) to dilated (9 mm)
      b. Ocular movement
         i. No oculocephalic reflex (testing only when no fracture or instability of the cervical spine is apparent)
         ii. No deviation of eyes to irrigation in each ear with 50 mL of cold water (allow 1 minute after injection and at least 5 minutes between testing on each side)
      c. Facial sensation and facial motor response
         i. No corneal reflex to touch with a throat swab
         ii. No jaw reflex
         iii. No grimacing to deep pressure on nail bed, supraorbital ridge, or temporomandibular joint
      d. Pharyngeal and tracheal reflexes
         i. No response after stimulation of the posterior pharynx with tongue blade
         ii. No cough response to bronchial suctioning
   3. Apnea testing performed as follows:
      a. Prerequisites
         i. Core temperature ≥ 36.5°C or 97°F
         ii. Systolic blood pressure ≥ 90 mm Hg
         iii. Euvolemia. *Option:* positive fluid balance in the previous 6 hours
         iv. Normal $Paco_2$. *Option:* $Paco_2$ ≥ 40 mm Hg
         v. Normal Pao_2. *Option:* preoxygenation to obtain arterial Pao_2 ≥ 200 mm Hg
      b. Connect a pulse oximeter and disconnect the ventilator.
      c. Deliver 100% O_2, 6 L/min, into the trachea. *Option:* place a cannula at the level of the carina.
      d. Look closely for respiratory movements (abdominal or chest excursions that produce adequate tidal volumes).
      e. Measure arterial Pao_2, Pco_2, and pH after approximately 8 minutes and reconnect the ventilator.
      f. If respiratory movements are absent and arterial Pco_2 is ≥ 60 mm Hg (*option:* 20 mm Hg increase in Pco_2 over a baseline normal Pco_2), the apnea test result is positive (i.e., it supports the diagnosis of brain death).
      g. If respiratory movements are observed, the apnea test result is negative (i.e., it does not support the clinical diagnosis of brain death), the test should be repeated.
      h. Connect the ventilator if, during testing, the systolic blood pressure becomes ≤ 90 mm Hg or the pulse oximeter indicates significant oxygen desaturation and cardiac arrhythmias are present; immediately draw an arterial blood sample and analyze arterial blood gas. If Pco_2 is ≥ 60 mm Hg or Pco_2 increase is ≥ 20 mm Hg over baseline normal Pco_2, the apnea test result is positive (it supports the clinical diagnosis of brain death); if Pco_2 is < 60 mm Hg or Pco_2 increase is < 20 mm Hg over baseline normal Pco_2, the result is indeterminate, and an additional confirmatory test can be considered.

From Practice Parameters for Determining Brain Death in Adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 45:1012, 1995.

brain, heart, and lungs are mutually dependent and share the basic role of maintaining life. An organism dies when one of these life-sustaining organ systems ceases to function. The traditional concept of death of an organism emphasized the cessation of respiration or circulation, without consideration of the role of the brain. This occurred because assessment of brain function was not easy to accomplish. When mechanical ventilation was not widely used, cessation of brain functions related directly to cessation of respiration and assessment of brainstem functions was unnecessary.

The Concept of Brain Death

Brain death represents death of the organism and not merely death or necrosis of the brain in a living body. The organism is an aggregation of living cells, although an aggregation of living cells does not necessarily constitute an organism. An organism exists only when the cell aggregation is under the control of modulating systems such as the central nervous system (CNS), the endocrine system, and the immune system. After any one of these systems ceases to function, death is inevitable unless artificial measures can be taken. The physiologic significance of brain death and cardiac death are essentially equal, and both represent an irreversible loss of communication between the control center and peripheral cells and tissues, as well as loss of modulation of an aggregation of cells. Without these systems, harmonious functioning of individual cells as constituents of the whole organism ceases. Because total and irreversible elimination of immune or endocrine function is not of practical significance, the concept of endocrine or immune death has not developed.

Previously, cessation of respiration was equivalent to immediate death of the organism, but artificial ventilation can

now prolong the life of a body for a certain period. Various functions are believed to reside in the hypothalamus and brainstem—the endocrine, autonomic, and immune functions, as well as others that are unknown. The brainstem also contains the main tracts for neural communication between the control center and peripheral tissues. All the motor outputs from the hemispheres have to travel through the brainstem, as do all the sensory inputs to the brain except sight and smell. Each of these functions of hypothalamus and brainstem can be monitored precisely and provided artificially. Autonomous respiratory function of the lower brainstem constitutes the border between life and death, and the need for mechanical devices to supply respiratory functions is defined as representing death of the individual. Possibly, most of the brain functions vital to life could be replaced with computers and drugs and the circulatory functions maintained for months or years. The only function advanced technology cannot provide is that constituting humanity or personality, both of which are possibly products of the telencephalon.

The traditional concept of death has used the cessation of cardiac and respiratory functions as its basis because of acceptance of simple and nonmedical concepts—that life begins with the first inspiration after birth, that death comes with the last expiration, and that cardiac activity ceases within a few minutes of the last expiration. In contrast, the current concept of brain death adopts the conclusions of modern biologic science—that the CNS, including the brainstem, is the control center for the living organism, that cessation of CNS functions represents cessation of the harmony of life, and that without CNS control, the living organism is nothing more than an aggregation of living cells.

Mechanism of Brain Death

Brain injury has a number of sources, such as traumatic or cerebrovascular injury and generalized hypoxia, all of which produce brain edema. Based on the pathologic mechanisms involved, brain edema is classified as vasogenic or cytotoxic.[15] Because it is rare that only one mechanism operates exclusively, the label of vasogenic or cytotoxic is only relative. Vasogenic edema is induced by an increase in cerebrovascular permeability after leaking of serum proteins into the brain parenchyma (i.e., after destruction of the blood-brain barrier). Chemical mediators such as histamine, serotonin, angiotensin, bradykinin, and prostaglandins can disrupt blood-brain barrier function.[16] Cytotoxic brain edema occurs in hypoxic and ischemic conditions and results from disturbance of cellular osmoregulation, a process that depends primarily on energy-dependent functioning of ionic pumps. The disturbance of osmoregulation increases entry of water into brain parenchyma. Although in a pure form of cytotoxic edema the blood-brain barrier would remain basically intact, cytotoxic edema would nevertheless disturb blood flow and induce hypoxia and vasogenic edema.

Brain edema may be focal at first, but it then spreads throughout the whole brain in a predictable sequence. Because the brain is covered by a rigid bony skull, its edema is accompanied by an increase in intracranial pressure, which, if sufficiently high, exceeds arterial blood pressure. When cerebral circulation ceases, aseptic necrosis of the brain ensues. Within 3 to 5 days, the brain becomes a liquefied mass, a condition known as respirator brain.[17] Such increased intracranial pressure compresses the entire brain, including the brainstem, and total brain infarction follows.[18]

Neurophysiologic Basis of Brain Death

Areas of the Brain Involved in Brain Death

By definition, brain death is a total irreversible cessation of functioning of the brain. However, "the whole brain" does not require the irreversible cessation of functioning of every brain neuron. Rather, it requires only the irreversible cessation of all clinical functions of the brain, namely, those measurable at the bedside by clinical examination.[2] The brain includes all the CNS structures except the spinal cord. It is generally agreed that brain death does not include lower portions of the spinal cord (caudal from C2), because their location outside the skull spares them from compression during brain edema. Histologic studies of human spinal cord in cases of brain death revealed divergent pathologic findings ranging from histologically intact tissues to complete destruction.[17]

The United Kingdom[13,14,19] and some other countries[3,4] supported a rather exceptional criterion for brain death, one that excludes involvement of the bilateral cerebral cortices. This state, known as "brainstem death," does not require recording of an electroencephalogram (EEG) for its diagnosis. In the United Kingdom, no confirmatory test (including an EEG) is required.[20] Grigg and colleagues reported that 11 of 56 clinically brainstem-dead patients (19.6%) had electroencephalographic activity and 2 patients (3.6%) even demonstrated sleeplike cortical electroencephalographic activity for as long as 168 hours, although none of the patients recovered.[21] The rationale for excluding the cerebral cortices is based on the facts that the brainstem, not the cerebral cortices, plays the major role in controlling whole-body vital activities such as respiration, circulation, and other homeostatic functions and that the reticular formation forms the basis of consciousness. However, some investigators strongly recommend confirmatory tests (EEG, transcranial Doppler, or brainstem auditory evoked potential) in supporting the diagnosis of brainstem death, especially when it is not possible to carry out all of the brainstem tests (e.g., in the presence of high spinal cord injury[22] or if the residual effect of sedative agents cannot be excluded[23]).

Consciousness and the Electroencephalogram

Moruzzi and Magoun[24] demonstrated the essential role of the brainstem reticular core in activating the cortical EEG. Segundo and associates[25] showed that destruction of the brainstem reticular core leads to a loss of consciousness in laboratory animals. These observations gave birth to the concept of the ascending reticular activating system (ARAS). Although the central insight of this concept, that structures in the brainstem regulate the state of consciousness, still holds true, the ARAS is no longer regarded

as a monolithic unit, nor is it restricted to the classically defined reticular nuclei of the brainstem. Maintenance of wakefulness or control of the sleep-wake cycle does not depend exclusively and unalterably on any single region of the brain.[26] In brain death, the patient is believed to have no consciousness, no intellectual activity, and therefore no true humanity. This state is defined as deep coma and is the basis for the concept of brainstem death.

Hockaday and colleagues[27] and Schwab and coworkers[28] studied the EEGs of 550 comatose patients, analyzed EEGs for 26 cases of sudden cardiac arrest and 13 cases of respiratory arrest, and classified abnormalities on EEGs into five grades according to final outcome. The prognosis for patients belonging to grade I was favorable. The determination of the prognosis for grade II and III patients required repeated recording of the EEG. When the EEG showed improvement on the day 2 or 3 recording session, the prognosis was favorable. When the EEG tended to deteriorate, the prognosis was poor. In this system, grade Vb, where there is no EEG at all, represented the EEG for brain death. Significant electroencephalographic changes occur when blood flow falls below 18 mL/100 g/min, and it becomes isoelectric when blood flow is in the range of 12 to 15 mL/100 g/min.[29] However, Paolin and associates[30] reported that 7 of 15 patients with clinical diagnosis of brain death showed persistent electrical activity, although cerebral blood flow measurements with xenon-133 and selective cerebral angiography showed intracranial circulatory arrest.

Respiration

The primary respiratory center, consisting of the inspiratory and expiratory neurons, is located in the reticular core of the medulla oblongata. Various abnormal patterns of respiration (e.g., gasping, apneusis, irregular shallow respirations) are observed in laboratory animals and humans with brainstem lesions. In brain death, spontaneous respiration does not occur in patients even when $Paco_2$ reaches 55 to 60 mm Hg. Mechanical stimulation of the carina to induce the cough reflex may be helpful in detecting residual functioning of the medullary respiratory neurons.

Cardiovascular Functions

The central neurons that control the circulatory system distribute diffusely in the pontine and medullary reticular core. Of these neurons, the vasomotor and cardioaccelerating neurons undergo negative-feedback control through the carotid and aortic sinus nerves, which relay at the nucleus tractus solitarius. Activation of these cells induces sympathetic nervous outflow, thereby increasing the heart rate and arterial blood pressure. Hypertension then suppresses these cells through the feedback mechanism, and circulation returns to preactivation levels.

During the process of brain death after head injury or intracranial bleeding, intracranial pressure increases, and compression of the brainstem leads to marked hypertension and bradycardia (i.e., the Cushing phenomenon). In an animal model of brain death, a precise mechanism of cardiovascular responses by the progression of CNS ischemia as a result of an expanding supratentorial mass was studied. When the entire cerebrum was ischemic, vagal activation with resultant decrease in heart rate, mean arterial pressure, and cardiac output was observed. As ischemia progresses rostrally to approach the pons, sympathetic stimulation was added to vagal stimulation, leading to bradycardia and hypertension (Cushing phenomenon). When the entire brainstem became ischemic, the vagal cardiomotor nucleus became ischemic, and there was unopposed sympathetic stimulation, leading to tachycardia, hypertension, and high blood levels of catecholamine (i.e., autonomic storm).[31,32] Some authorities think that myocardial damage may occur at this stage of autonomic storm, which may contribute to the early failure of some transplants and obscure or complicate the histologic manifestations of rejection in others.[31] However, in humans, this stage of tachycardia and hypertension may be brief, and attempts to reduce blood pressure may not be necessary or even not be recommended.[32]

When intracranial pressure is elevated, arterial blood pressure suddenly decreases (Fig. 98-1). This sudden decrease is the sign of tonsillar herniation (i.e., herniation of the cerebellar tonsils) through the foramen magnum on the cervical spinal cord, in which outflow of the cardioaccelerating and vasomotor neurons to the spinal cord suddenly ceases. This is one typical onset for brain death. Such dramatic changes in arterial blood pressure are not observed in other types of brain death such as that induced by hypoxia or those involving other intricate factors. Adequate volume replacement with balanced salt solution or colloid solution and, in some cases, blood transfusion is required. Inotropic agents, such as dopamine, epinephrine, and norepinephrine, are sometimes required to maintain an adequate blood pressure. The vasomotor and cardioaccelerating neurons of the spinal cord (located in the lateral horn) obtain automaticity within several days of disconnection from the supraspinal structures, and arterial blood pressure returns to normal without supplementation with vasopressors.[33] This situation is familiar to anesthesiologists because background arterial blood pressure is usually normal in tetraplegic patients.

After the establishment of brain death, different types of autonomic spinal cord reflexes develop, such as elevation of arterial blood pressure because of bladder distention. Surgical stimulation-induced hypertension and tachycardia are well known by anesthesiologists in tetraplegic patients. A similar phenomenon has been observed in brain-dead patients.[34] Vasodilators or general anesthesia, or both, should be used during the donation operation.[35] Although the cardioaccelerating and vasomotor neurons are located in the brainstem, changes in arterial blood pressure are not used as an index of brainstem function.

Regulation of Body Temperature

Rodbard[36] suggested that the neural mechanisms governing homeostatic temperature control developed in the hypothalamus from circulatory control neurons in the course of evolution from reptile to mammal. Body temperature is regulated when changes in blood temperature stimulate heat-sensitive receptors in the hypothalamus. Nerve impulses from cold receptors in the skin can also activate heat-producing neurons. The most important heat producers are the skeletal muscles, brain, liver, and heart. The greatest heat radiator is the skin, especially that on the hands. Local electrical stimulation of the heat-producing center induces shivering and constriction of blood vessels in the skin, activating vasomotor nerves and decreasing blood flow. Warming of the heat-loss center suppresses vasomotor nerve activity and in this way increases blood flow through the skin.

In brain death, the neural connection between the temperature-regulating center and peripheral body tissues is lost, and

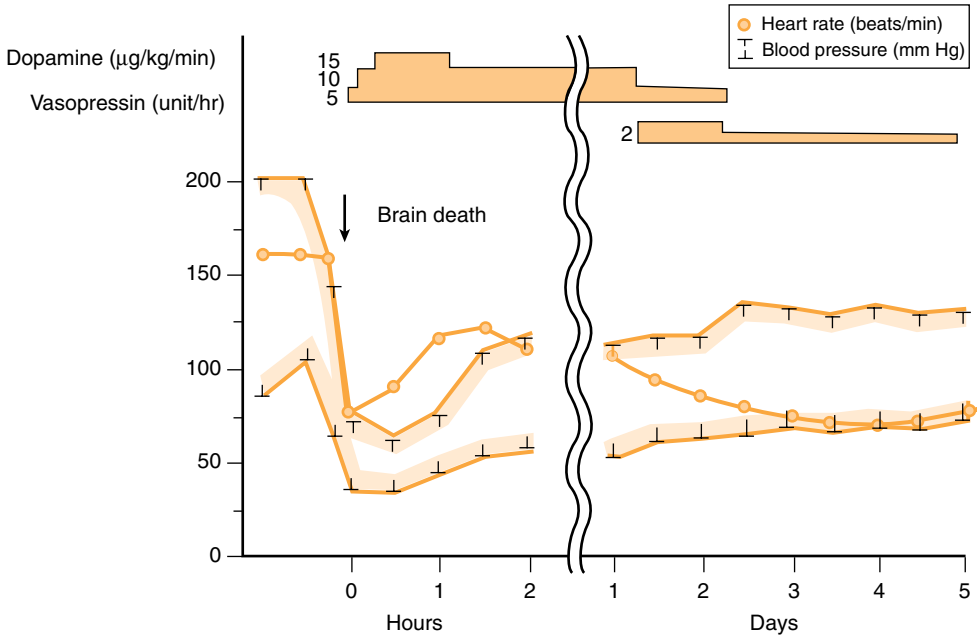

Figure 98-1 The representative time course of arterial blood pressure and heart rate before and after brain death. The 18-year-old male patient was involved in a traffic accident. Sustained hypertension was followed by a sudden and marked decrease in blood pressure. Dopamine was administered to increase blood pressure, which gradually became stable. Doses of dopamine were tapered and finally became unnecessary.

the patient becomes poikilothermic. When criteria from the National Institute of Neurological Diseases and Stroke (NINDS) were applied to establish brain death, such patients showed only a "tendency for the temperatures to be subnormal."[17] In contrast, when brain death was established using the criterion of cessation of all brainstem functions, "poikilothermia was found in all patients later than 24 hours after brain death."[37] Even if infection occurs, fever should not develop in cases of brain death, because the temperature-regulating centers no longer function. After brain death, body temperature tends to be hypothermic, even with vigorous application of external heat.

Hypothalamic-Pituitary Endocrine Functions

No criteria used to establish brain death attempt to determine whether functions of the hypothalamus are preserved. Clinical studies have indicated that hypothalamic and anterior pituitary functions are preserved to a certain degree for a certain period after the onset of brain death. Schrader and coworkers[38] reported normal levels of anterior pituitary hormones, the half-lives of which are less than 1 hour, such as thyroid-stimulating hormone, prolactin, growth hormone, and luteinizing hormone, as well as positive test results for the hypothalamic hormone luteinizing hormone–releasing hormone and thyrotropin-releasing hormone for 2 to 24 hours after determination of brain death. Sugimoto and associates[39] confirmed that concentrations of these hormones were normal for more than 1 week.

In contrast, the level of vasopressin, a hormone produced in the hypothalamus and stored in the posterior pituitary, decreased sharply after brain death.[39] However, the occurrence of diabetes insipidus is variable. In one study, many patients did not have diabetes insipidus after brain death.[40] Another study found that 24 (77%) of 31 patients with brain death had clinical diabetes insipidus.[41] When arginine vasopressin is added to the infusion in cases of brain death with diabetes insipidus, the heart beat can be maintained for several months.[42] It was reported that plasma levels of the thyroid hormones triiodothyronine (T_3) and thyroxin (T_4) were decreased markedly after brain death.[43]

The diaphragma sellae protects the pituitary gland from compression caused by swelling of the brain. Blood supply to the pituitary gland comes mostly from the superior, middle, and inferior hypophyseal arteries and the capsular arteries. The portal venous system is another source of blood supply to the anterior lobe. In brain death, blood supply through the superior hypophyseal artery and the portal vein can easily be blocked. However, blood supply through the cavernous portion of the internal carotid artery and its branches, such as the inferior hypophyseal artery and the capsular artery, may be spared.[44] Morphologic studies of brain death indicate that damage to the anterior lobe is incomplete but severe, whereas the posterior lobe is relatively preserved.[39] However, because vasopressin is synthesized in the hypothalamus and transferred to the posterior lobe of the pituitary through axoplasmic flow along the long axon, depletion of this hormone may be greater than would be expected from the slight morphologic damage seen in the posterior lobe.

In studies on brain death, the hypothalamic hormones, such as growth hormone–releasing hormone, corticotropin-releasing hormone, thyroxine-releasing hormone, and luteinizing hormone–releasing hormone were found in trace to subnormal levels.[39,45] Schrader and coworkers[38] reported a normal growth hormone response to hypoglycemic stimulation. Arita and associates[46] also demonstrated that insulin and arginine increased growth hormone levels in brain-dead patients. Hypoglycemia affects glucoreceptors in the ventromedial nucleus to stimulate growth hormone–releasing hormone and corticotropin-releasing hormone release and stimulates growth hormone or adrenocorticotropic hormone release, indicating that some hypothalamic function may be preserved. However, the origin of the hypothalamic hormones released in brain death cannot be identified. Results from morphologic studies on the hypothalamus are controversial. Walker and colleagues[17] reported that the neurons with lytic changes were intermingled with relatively normal cells, a result that may account for the sustained secretion of hypotha-

lamic hormones. In contrast, Sugimoto and coworkers[39] observed extensive necrosis of the hypothalamus after the sixth day of brain death and postulated a nonbrain supply of these hormones, such as the pancreas, intestine, or adrenal gland. As the hypothalamus receives its blood supply through the branches of the superior hypophyseal and posterior communicating arteries, blood flow to the hypothalamus, at least its basal part, may be preserved in relatively mild instances of intracranial hypertension.

Hormonal therapy for hemodynamic stabilization of brain-dead organ donors has been developed and recommended. The Cardiac Work Group of the Crystal City Conference led by United Network for Organ Sharing (UNOS) recommended a heart donor management algorithm that included four-drug hormonal resuscitation (T_3, vasopressin, methylprednisolone, and insulin) for donors with a left ventricular ejection fraction less than 45% or with unstable hemodynamics,[47] and Organ Procurement and Transplantation Network (OPTN)/UNOS multivariate studies on hormonal treatment of brain-dead donors (T_3/T_4, methylprednisolone, and arginine vasopressin) revealed significant increases in organs transplanted and in 1-year survival of kidneys and hearts.[48]

The Immune System

The CNS exerts significant influence over the immune system. Even if the immune system is intact, its response to stimulation is modified considerably after total and irreversible loss of CNS functions. Increased levels of inflammatory mediators, such as cytokines (IL-1β, IL-6, TNF-α)[49,50] and adhesion molecules (E-selectin, ICAM-1, VCAM-1)[51,52] in blood and in organs are observed in brain-dead patients, and it is thought that these cytokines are responsible for some of the endocrine and acute-phase reactant abnormalities found in these patients and for the low success rates after organ transplantation.

Brainstem Reflexes

Various brainstem reflexes are used to diagnose brain death, such as pupillary, oculocephalic, oculovestibular, and cough reflexes. Preservation of the cough reflex indicates preservation of the brainstem respiratory center. All the brainstem reflexes (except those of the respiratory centers) need not be present for the organism to be said to be alive, but they are tested to confirm preservation of brainstem functions.

Criteria and Tests for Determining Brain Death

Determination of brain death confirms the irreversible cessation of all functions of the entire brain, including the brainstem.[11] Irreversibility means that no treatment may be reasonably expected to change the condition. The responsible disorder may be thought of as structural, and it does not result from functional and potentially reversible causes such as drug intoxication, hypothermia, or metabolic or endocrine disturbance. The passage of time is also an essential component in determining that a lesion is irremediable. Although testing all functions of the brain is conceptually impossible, the cessation of all functions of the brain is practically determined by loss of consciousness, loss of brainstem responses, apnea, and confirmatory tests, including the lack of electroencephalographic activity.

Loss of Consciousness and Unresponsiveness

The patient should be in coma and scored as 3 on the Glasgow Coma Scale. Motor responses of the limbs or facial muscles to painful supraorbital pressure should be absent. Motor responses (i.e., the Lazarus sign) may occur spontaneously during apnea testing[53] and are considered to have a spinal origin. This sign is often observed during hypoxic or hypotensive episodes. Other spontaneous movements from spinal origin are observed.

Pupils

The shape of the pupils can be round, oval, or irregular. The size of the pupils may vary from 4 to 9 mm, but in most cases is 4 to 6 mm.[11,54] Sympathetic cervical pathways can be intact in the state of brain death, connect with the radially arranged fibers of the dilator muscle, and dilate the pupils.

Brainstem Responses

The tests for brainstem responses vary in different countries. The criteria of the American Academy of Neurology[11] include light reflex, oculocephalic reflex, caloric (vestibular) test, corneal reflex, jaw reflex, pharyngeal reflex, and cough reflex.

Apnea Test

Apnea testing is mandatory for the determination of brain death and considered as the most important testing, but there have been controversies about it. Its safety is a major issue. During the apnea test, marked hypotension or severe cardiac arrhythmias,[54] or both, and pneumothorax may occur[55] and the intracranial pressure can increase markedly. The apnea test should be performed as the last test after the other tests fulfill the criteria of brain death. Goudreau and coworkers[56] reported that, during the apnea test, complications such as a marked blood pressure decrease or the development of ventricular arrhythmia developed in 27 (39%) of 70 patients with pretest unfavorable factors but developed in only 11 (15%) of 74 patients without them. They pointed out that inadequate preoxygenation and acid-base or electrolyte abnormalities were the major unfavorable pretest factors. The American Academy of Neurology recommends preoxygenation with 100% oxygen for 10 minutes before apnea testing if Pa_{O_2} is 200 mm Hg or less and delivering 100% O_2, 6 L/min, into the trachea or administration of 100% O_2 through a catheter placed at the level of the carina during apnea testing (see Table 98-2).[11,54]

Another issue is the appropriate level of Pa_{CO_2} to be achieved. After equipment for analyzing blood gases became widespread, the importance of the value of Pa_{CO_2} rather than the

time for observation of apnea was confirmed. An increase in $Paco_2$ decreases pH in the cerebrospinal fluid, which stimulates the medullary respiratory chemical center. The normal ventilatory response to the increase in $Paco_2$ rises linearly to 80 mm Hg, and then the slope becomes less steep and peaks at about 150 mm Hg in dogs.[57] Damage in the medullary respiratory center may affect the level of $Paco_2$ for development of spontaneous respiration. The level of $Paco_2$ at which spontaneous respiration resumes is also modified by Pao_2. Wijdicks[4] reported that although most of all brain death guidelines in the world required apnea tests (71 of 80 nations), only 41 of 71 guidelines defined a definite $Paco_2$ target value (see Table 98-1), and he concluded that if the premise of documenting apnea using hypercarbia to maximally stimulate the respiratory centers was accepted, it could be concluded that in half of the countries the apnea test was not performed adequately. The exact level of $Paco_2$ to be achieved is still unknown, but the American Academy of Neurology criteria define various prerequisites and the procedure of apnea testing and adopt the level of $Paco_2$ greater than or equal to 60 mm Hg (see Table 98-2)[11,54] and the UK criteria requires a $Paco_2$ target of 6.65 kPa (50 mm Hg).[20]

Prerequisites for Diagnosing Brain Death

Several disorders mimic brain death and can lead to an erroneous diagnosis. The absence of these conditions must be confirmed and the following factors considered before the criteria for brain death are applied.

Deep Coma

The patient must be in a deep coma, and the cause of the coma must be identified. Organic brain damage must be confirmed as a prerequisite for diagnosing brain death. Drug intoxication, severe electrolyte, acid-base, or endocrine disturbance, hypothermia, and other common treatable disorders should be ruled out.

Body Temperature

After cessation of brainstem and hypothalamic functions and after complete disconnection of the spinal cord from supraspinal brain structures, the patient becomes poikilothermic, and body temperature tends to be hypothermic, even with vigorous warming. Because hypothermia suppresses CNS function and leads to misdiagnosis of brain death, body temperature must be within normal range (i.e., hypothermia must be corrected) before the criteria for brain death are applied.

Absence of Cardiovascular Collapse

When intracranial pressure increases, systemic hypertension occurs as a result of the Cushing phenomenon. This is followed by a sudden decrease in blood pressure because of sudden interruption of vasomotor output from the brainstem and hypothalamus to the spinal cord. Hypotension usually resolves spontaneously within several days because of restoration of spontaneous activity of the spinal cord's vasomotor neurons. Hypotension may result in compromised cerebral perfusion leading to loss of electroencephalographic activity, thus causing a spurious diagnosis. Therefore, administration of a vasopressor to achieve relative normotension should be considered; vasopressor therapy will occasionally restore electroencephalographic activity in the determination of brain death.

Clinical Diagnosis of Brain Death

The guidelines and clinical diagnosis for determining brain death differ in various countries[3,4] and among institutions in the United States and Canada. However, the principle seems similar,[1,3,4,11] and clinical diagnosis of brain death should be performed in three steps:

1. Establishing the cause of disease
2. Excluding certain potentially reversible syndromes that may produce signs similar to brain death
3. Demonstrating clinical signs of brain death: coma, brainstem areflexia, and apnea

Confirmatory tests in the determination of brain death are not always mandatory, but they are desirable, especially when the clinical picture is confusing. In general, two examinations separated by at least 6 hours are required to establish the diagnosis of brain death. Most codes mandate that the clinical diagnosis be confirmed by two or three physicians who are independent of the transplantation team, and at least one of the physicians is required to be a specialist in neurology, neurosurgery, or anesthesiology.

Special Considerations

Cerebral Death: Persistent Vegetative State

Cerebral death, the so-called persistent vegetative state, refers to cessation of the functions of the cerebral cortices. Brainstem functions governing the respiratory centers, autonomic nervous system, endocrine system, and immune system, which are vital for maintaining life, are preserved. Although the cortical EEG is flat, it is usually contaminated by electromyographic activity of the forehead, a sign of preservation of function of the facial nerve in the brainstem. The persistent vegetative state represents irreversible loss of consciousness but not irreversible loss of life or the mechanism of life; patients in this state can survive for months or years. The term *cerebral death* is occasionally used by mistake to indicate brain death, which includes the brainstem.

Cerebral death has not been accepted traditionally as equivalent to death.[58] However, some advocate that cerebral death should be accepted as the death of individuals because the critical elements of life are the organized cognition and "personhood" as the unique feature of human life, which originate from the cerebrum.[59] The problems with this notion are that the permanence of cerebral dysfunction cannot be easily predicted in most clinical

circumstances and threatens the severely senile and severely retarded, who may have severely damaged high-brain functions.[59,60] Of 40 patients referred to as being in the persistent vegetative state, 17 (43%) were considered to be misdiagnosed; they were aware of surroundings and able to communicate.[61]

The shortage of infant organs available for transplantation worldwide has promoted a growing recognition of the potential use of anencephalics, who are born without a forebrain and a cerebrum but with a rudimentary functional brainstem, as donors.[62,63] The natural course is that one half of the fetuses die in utero, and about 95% of live-born anencephalics usually die within 7 days.[63] In 1995, the American Medical Association Council on Ethical and Judicial Affairs supported the use of live anencephalic infants as organ donors,[62] although such a position opposes the legal and ethical application of the "dead-donor rule." It claimed that anencephalic neonates are definitely different from individuals who are in a persistent vegetative state, infants with profound neurologic injury, and elderly adults with severe dementia, because anencephalics have no history of consciousness and no possibility of ever being conscious. However, in 1996, it suspended its opinion because of concern about certain diagnoses of anencephaly and understanding of consciousness in these neonates.[64] In 1961, a kidney transplantation was first performed with an anencephalic newborn as a donor,[65] followed by some attempts of heart transplantation.[66] However, Western countries, with the exception of Germany, consider an anencephalic infant to be legally alive as long as the brainstem is functioning.[67]

Spinal Cord Reflexes and Surgery

The CNS structures essential to the definition of brain death do not include the spinal cord. Histologic studies have shown that the spinal cord is the best preserved part of the CNS in cases of brain death, and results have ranged from grossly normal histology to edema, neuronal loss, neurolysis, and, rarely, infarction.[17]

Spontaneous and reflex movements are found in brain-dead patients. Spontaneous body movements may be observed during the apnea test, while the body is being prepared for transport, at the time of a skin incision for the retrieval of organs, or in synchrony with the respirations produced by the mechanical ventilation.[1] In 5 of 60 cases of brain death after terminally turning off the ventilator or during apnea tests, Ropper[53] reported bizarre, seemingly purposeful movements of the upper extremities, called the Lazarus sign, in which the arms flexed quickly to the chest from the patient's side, the shoulders adducted, and in some patients, the hands crossed or opposed just below the chin. Saposnik and associates[68] reported that 15 (39%) of 38 patients who fulfilled criteria for brain death showed spontaneous or reflex movements; the most common movement was finger jerks, and the undulating toe flexion sign, triple flexion response, Lazarus sign, pronation-extension reflex, and facial myokymia also were seen. Health care staff should remember that a patient may move in response to noxious stimulation and that full curarization is required for surgical procedures involving brain death.

Considerations Regarding Children

The child's brain is a developing organ and it is believed that the anatomic neurodevelopment continues by 2 years of age or beyond the first decade of life. During this time, there are also changing patterns of vulnerability to injury and different responses to the injury itself.[69] Furthermore, the presence of open fontanelles and open sutures in young children makes the skull an expandable chamber. Intracranial pressure may not exceed mean arterial blood pressure, and cerebral blood flow continues. It is generally assumed that the child's brain is more resistant to insults leading to death, although this issue is controversial and lacks convincing clinical documentation.[70]

The need for facilitation of end-of-life decision and organ procurement in infants and children has increased. In 1987, the Task Force for the Determination of Brain Death in Children endorsed the Determination of Death Act and offered the Guidelines for the Determination of Brain Death in Children (Table 98-3).[70] The distinctions from the criteria for adults are three separate, longer observation periods, depending on the child's age, and the necessity for two corroborating EEGs or one EEG with corroborating radionuclide angiography. It is generally

Table 98-3 Brain Death Guidelines for Children

A. History: Determination of the proximate cause of coma to ensure absence of remediable or reversible conditions

B. Physical examination criteria:
   1. Coma and apnea
   2. Absence of brainstem function
      a. Midposition or fully dilated pupils
      b. Absence of spontaneous eye movements
      c. Absence of movement of bulbar musculature and corneal, gag, cough, sucking, and rooting reflexes
      d. Absence of respiratory movements with standardized testing for apnea
   3. Patient must not be hypothermic or hypotensive for age.
   4. Flaccid tone and absence of spontaneous or induced movements, excluding spinal cord events.
   5. The examination results should remain consistent with brain death throughout the observation and testing period.

C. Observation period according to age: the recommended observation period depends on the age of the patient and the laboratory test used.
   1. Seven days to 2 months: two examinations and electroencephalograms (EEGs) separated by at least 48 hours.
   2. Two months to 1 year: two examinations and EEGs separated by at least 24 hours.
   3. Older than 1 year: An observation period of at least 12 hours or, if it is difficult to assess the extent and reversibility of the brain damage, a more prolonged period of at least 24 hours. The observation period may be reduced in the presence of the electrocerebral silence of EEG or the lack of cerebral circulation.

D. Laboratory testing:
   1. EEG
      EEG to document electrocerebral silence should, if performed, be done throughout a 30-minute period using standardized techniques for brain death determination.
   2. Angiography
      Cerebral death is confirmed by a cerebral radionuclide angiogram by demonstrating the lack of visualization of cerebral circulation.
   3. Techniques being investigated:
      Xenon CT, digital subtraction angiography, visualization of cerebral arterial pulsations by real-time cranial ultrasound, Doppler determination of cerebral blood flow velocity, and evoked potential

From Task Force for the Determination of Brain Death in Children: Guidelines for the determination of brain death in children. Neurology 37:1077, 1987; and Ashwal S: Brain death in early infancy. J Heart Lung Transplant 12(pt 2):S176, 1993.

agreed that, except in very immature, preterm newborns, the same criteria of brain death can apply to term newborns, infants older than 7 days, children, and adults[71] if an observation period is prolonged for smaller children. However, there have been several reports arguing against this notion. For example, some investigators recommended that $Paco_2$ greater than 12.0 kPa in infants and children should be achieved for an apnea test, because the carbon dioxide threshold necessary to determine apnea is occasionally higher in children than in adults.[69,72]

Ashwal and Serna-Fonseca[73] stressed that brain death could be diagnosed in newborns (even when younger than 7 days) if an observation period to confirm the diagnosis was prolonged to 48 hours; and if an EEG was isoelectric or a cerebral blood flow study showed no flow, the observation period could be shortened to 24 hours. They also suggested that the same time frame would be applicable to preterm infants. However, the Special Task Force excluded infants younger than 7 days from its guideline.[70] There are several concerns about the diagnosis of brain death in newborns.[74]

1. If the injury occurred in utero, the duration of the insult and severity may be difficult to establish.
2. Normal systemic arterial pressure in the newborn is not determined.
3. The EEG and transcranial Doppler (TCD) ultrasonography may not be 100% reliable.
4. The clinical examinations cannot be reliable because of immaturity.

It was reported that a premature infant sustained an intraventricular hemorrhage on day 2 of life and showed the absence of brainstem reflexes, apnea, and flaccidity but was never clinically brain dead[75] and that 15 of 20 neonates who had isoelectric EEGs preserved partial clinical brain function.[76] Since these guidelines were issued, a wide variation in practices or violation of these guidelines has been reported.[77,78] Mejia and colleagues[77] investigated variability in the practices of determining brain death and organ procurement in pediatric intensive care units. Although apnea testing has been considered the most important criterion for brain death even in children, it was not carried out for 23 (25%) of 93 brain-dead patients, and the methods of apnea testing were not consistent with the Guideline for Determination of Brain Death in Children for 20 patients (22%). Four of 30 patients younger than 1 year did not have a confirmatory test. They concluded that the variability in brain death determination practices might reflect differences in documentation, lack of knowledge of the guidelines, or disagreement with the guidelines.

Central Integrator Theory of the Brain

The notion that brain death is equivalent to the death of the individual is mainly based on the theory of "the brain as the central integrator of the body." In brain death, the body is no more an integrated organism but a mere and rapidly disintegrating collection of organs that have lost forever the capacity of working as a coordinated whole.[79] Patients with brain death were once thought to inevitably have a cardiac arrest within a short period time (usually within 1 or 2 weeks), regardless of the intensity of life support.

However, it has been recognized that not all brain-dead patients inevitably deteriorate to cardiovascular collapse in a short time and some of them show an adequate level of biologic integration for weeks or months (up to more than 14 years in one case) if they are provided with an appropriate life support. Furthermore, brain-dead patients can assimilate nutrients, eliminate wastes, fight infections, heal wounds, carry out a pregnancy, and so on, without the control of the brain. Zapperetti and coworkers argue that the "central integrator" theory rests more on what we think should happen to brain-dead patients, according to the definition, than on what can be observed clinically.[80]

Variability in Policies and Practices for Determining Brain Death

Although the concept of brain death as defining the death of the individual is widely accepted, there is a significant variability in policies and practices for determining brain death among nations and even within a nation, that is, among states and hospitals. Wijdicks[4] reported that of 80 countries examined, legal standards on organ transplantation were present in 55 countries (69%) and practice guidelines for brain death for adults were present in 70 countries (88%). All guidelines specifically specified exclusion of confounders, irreversible coma, absent motor response, and absent brainstem reflexes, but there were significant differences in the method of apnea testing, in time of observation, in the number and required expertise of examining physicians, and in requirement of confirmatory tests (see Table 98-1). Furthermore, because brain death practices are largely determined by individual hospitals in the United States and Canada, significant variabilities among hospital policies and guidelines for brain death were found. Wijdicks and other investigators stressed the need to standardize the practice of the neurologic determination of death.[4,81,82] The wide variation in practices was also reported in the pediatric population[77,78] and in the brainstem death criteria in the United Kingdom,[23] despite the existence of clear guidelines for performing the test.

Confirmatory Tests for Brain Death

Tests that confirm the loss of bioelectrical activity of the brain or the cerebral circulatory arrest are not always mandatory for adults but strongly recommended for children, especially those younger than 1 year (Table 98-4).[1,3,4,70] In several European, Central American, South American, and Asian countries, confirmatory testing is required by law (see Table 98-1).[1,3,4] In the United States, the choice of tests is left to the discretion of the physician. Young and associates[83] proposed criteria for ideal confirmatory ancillary tests:

Table 98-4 Confirmatory Testing for Determination of Brain Death

Cerebral Angiography
- The contrast medium should be injected under high pressure in the anterior and posterior circulation.
- No intracerebral filling should be detected at the level of entry of the carotid or vertebral artery to the skull.
- The external carotid circulation should be patent.
- The filling of the superior longitudinal sinus may be delayed.

Electroencephalography
- A minimum of eight scalp electrodes should be used.
- Interelectrode impedance should be between 100 and 10,000 ohms.
- The integrity of the entire recording system should be tested.
- The distance between electrodes should be at least 10 cm.
- The sensitivity should be increased to at least 2 μV for 30 minutes with inclusion of appropriate calibrations.
- The high-frequency filter setting should not be set below 30 Hz, and the low-frequency setting should not be above 1 Hz.
- Electroencephalography should demonstrate a lack of reactivity to intense somatosensory or audiovisual stimuli.

Transcranial Doppler Ultrasonography
- There should be bilateral insonation. The probe should be placed at the temporal bone above the zygomatic arch or the vertebrobasilar arteries through the suboccipital transcranial window.
- The abnormalities should include a lack of diastolic or reverberating flow and documentation of small systolic peaks in early systole. A finding of a complete absence of flow may not be reliable because of inadequate transtemporal windows for insonation.

Cerebral Scintigraphy (^{99m}Tc-hexametazime)
- The isotope should be injected within 30 minutes after its reconstitution.
- A static image of 500,000 counts should be obtained at several time points: immediately, between 30 and 60 minutes later, and at 2 hours.
- A correct intravenous injection may be confirmed with additional images of the liver demonstrating uptake (optional).

From Wijdicks EF: The diagnosis of brain death. N Engl J Med 344:1215, 2001.

1. There should be no instances of a "false positive"; that is, when the test confirms "brain death" there should be none who recovers or who has the potential to recover.
2. The test should be independently sufficient to establish that brain death is or is not present.
3. The test should not be susceptible to "confounders" such as drug effects or metabolic disturbances.
4. The test should be standardized in technology, technique, and classification of results.
5. The test should be available, safe, and readily applied. Testing should not be restricted to only a few research centers; ideally it could be applied within any intensive care unit (ICU) and the technique should be reliable and mastered without difficulty.

In all cases, confirmatory tests should be used in conjunction with appropriate clinical judgment.

Electroencephalographic Recording

The EEG is the most widely available neurophysiologic test and is used in many countries and institutions as a confirmatory test for brain death (whole brain death).[1-4] Loss of bioelectrical brain activity as shown on the EEG (i.e., isoelectric EEG) is a reliable confirmatory test for brain death. However, several problems must be considered. An isoelectric EEG can be found after drug intoxication (false positive), such as occurs with barbiturates,[84] and, conversely, residual electrical activity may persist after brainstem death or even in some patients who met clinical criteria for brain death (false negative).[21,85]

Electrocerebral inactivity (ECI) or electrocerebral silence (ECS) is defined as no electroencephalographic activity above 2 μV/mm when recording from scalp electrode pairs placed 10 or more cm apart and with interelectrode impedances less than 10,000 ohms but more than 100 ohms. Ten guidelines for electroencephalographic recordings[86] follow:

1. A minimum of eight scalp electrodes should be used.
2. Interelectrode impedances should be less than 10,000 ohms but more than 100 ohms.
3. The integrity of the entire recording system should be tested.
4. Interelectrode distances should be at least 10 cm.
5. Sensitivity must be increased from 7 μV/mm to at least 2 μV/mm for at least 30 minutes of the recording, with inclusion of appropriate calibrations.
6. Filter settings should be appropriate for the assessment of ECS.
7. Additional monitoring techniques should be employed when necessary.
8. There should be no electroencephalographic reactivity to intense somatosensory, auditory, or visual stimuli.
9. Recordings should be made only by a qualified technologist.
10. A repeat EEG should be performed if there is doubt about ECS.

Evoked Responses

Brainstem auditory evoked potentials (BAEPs) and median nerve somatosensory evoked potentials (SSEPs) are used for the diagnosis of brain death. Unlike EEG signals, the early components of BAEPs and SSEPs are minimally affected by sedative drugs and anesthetics. However, drugs and metabolic derangements affect middle and late BAEPs and SSEPs.[83] BAEPs are signals generated in the auditory nerves and brainstem after an acoustic stimulus. BAEPs consist of five identifiable waves generated from specific brainstem structures along the auditory pathways. Wave I represents the eighth nerve compound action potential; wave II, the eighth nerve and cochlear nerves; wave III, the lower pons including the superior olive; and waves IV and V, the upper pons and the midbrain, as high as the inferior colliculus.[87] Brainstem abnormalities can be detected with BAEPs. The loss of waves III to V or II to V or no reproducible BAEP on both sides is usually regarded as brain death,[85] although wave I sometimes remains. Preexisting deafness or severe peripheral auditory system damage may lead to a false-positive diagnosis.

After electrical stimulation of a peripheral nerve, waves of SSEPs are generated from the neural structures along the afferent somatosensory pathways: the brachial plexus, the upper cervical cord, the dorsal column nuclei, the ventroposterior thalamus, and the sensory cortex.[87] "Practice Parameters for Determining Brain Death in Adults," published in *Neurology,* recommended bilateral absence of N20-P22 responses with median nerve stimulation as a confirmatory laboratory test.[11] Facco and coworkers[88] reported

that the absence of components later than N13, which represents postsynaptic activity in the central gray matter of the cervical cord, or N13/P13 dissociation, was reliable to confirm brain death. These investigators also recommended the combined use of BAEPs and SSEPs for determining brain death. Sonoo considered a loss of N18 potential, which is supposedly generated at the cuneate nucleus in the medulla oblongata, as reliable for the diagnosis of brain death.[89]

Demonstration of Brain Perfusion and Measurement of Cerebral Blood Flow

Possible mechanisms for brain death include an obstruction of circulation by cerebral swelling. The demonstration of absent intracranial circulation indicates irreversible cerebral damage. Adopting this concept, Scandinavian nations have taken the stance that total-brain infarction constitutes brain death.[3] The following methods are used to demonstrate perfusion of the brain or measure of cerebral blood flow.

Angiography

Contrast Catheter Angiography

Four-vessel cerebral angiography is a traditional "gold standard" modality among ancillary tests for brain death. This method is primarily an anatomic and not a physiologic demonstration of perfusion, although nonquantitative inferences about perfusion rates may be made. The greatest advantage of catheter angiography for the determination of brain death is that it is influenced neither by CNS depressant drugs nor by hypothermia. This method has been widely recommended to confirm brain death.[30,85,90] "Practice Parameters for Determining Brain Death in Adults" recommended conventional angiography as a confirmatory test, and the following criteria were identified[11]: There should be no intracerebral filling at the level of the carotid bifurcation or circle of Willis; the external carotid circulation is patent; and filling of the superior longitudinal sinus may be delayed. Drawbacks of this method are that the patients need to be transported to the radiology suite and it is an invasive examination that needs an experienced neuroradiologist and may yield severe complications, such as vasospasm, subintimal injection, arterial dissection, and thromboembolism, leading to a false image of absent flow and cerebral ischemia. Intra-arterial (aortic arch) or intravenous (vena cava) digital subtraction angiography has been shown to be as effective as conventional four-vessel angiography, is less invasive, and is easier to perform.[91]

Radionuclide Angiography

Confirmation of brain death using conventional dynamic radionuclide angiography with blood pool agents has been used for a long time.[92] Such investigations are less invasive than others and may be carried out at the bedside using a mobile scintillation camera, but they cannot image the posterior fossa well. Radioligands such as technetium 99m (^{99m}Tc) hexamethylpropyleneamine-oxime (HMPAO), which cross the blood-brain barrier and are picked up and held by viable cells for several hours, are recommended to confirm brain death.[93] The lack of uptake of isotope in brain parenchyma (i.e., hollow skull phenomenon) is characteristic for brain death.[11] ^{99m}Tc-HMPAO single-photon emission computed tomography (SPECT) provides much more precise regional information and has been proven effective in the diagnosis of brain death both in children and adults.[94,95] The lack of signal from the intracranial compartment and the normal uptake in other parts of the head produce the "empty light bulb" and "hot nose" signs.[94,95] Munari and coworkers confirmed the reliability of SPECT in the diagnosis of brain death and recommended that it should be a good candidate for the standard diagnostic modality.[96]

Computed Tomography

Computed tomography (CT) angiography has been useful as a noninvasive test to confirm brain death.[97] After intravenous injection of contrast media, time-density analysis of a specific area can be obtained with a CT scanner equipped with a special software program that can evaluate blood flow. CT angiography has several advantages[97]: (1) it is easily accessible around the clock and present in almost all hospitals with an ICU, (2) it is fairly inexpensive, (3) imaging requires only minutes, (4) it delivers conventional CT images at the same imaging session and can also be combined with CT perfusion imaging, (5) it is noninvasive except for intravenous injection of the contrast agent, and (6) the images are easy to interpret. However, significant divergence with catheter angiography was observed; CT angiography demonstrated some opacified proximal anterior cerebral artery segments, although there was an absence of intracranial flow with catheter angiography,[98] which may relate to contrast stasis with CT angiography.

The xenon-CT cerebral blood flow method has been applied to the confirmation of brain death.[30] This technique is quantitative and allows co-registration of flow data with CT anatomy. Pistoria and associates[99] suggested that an average global flow of less than 5 mL/dL/min confirms brain death.

Magnetic Resonance

Magnetic resonance (MR) imaging (MRI) and MR angiography have been used for the confirmation of brain death with the advent of MRI-compatible ventilators.[100,101] MRI allows an assessment of intracranial contents and is particularly helpful in defining abnormalities in the posterior fossa, which may be obscured by bone artifact inherent in CT. Although currently experimental and limited in spatial resolution, phosphorus (^{31}P) and proton (^{1}H) MR spectroscopy (MRS) has been proposed for the determination of brain death.[102,103] MRS can demonstrate the total absence of high-energy phosphorus compound (including ATP), leaving only one single peak of inorganic phosphate in ^{31}P MRS and massive lactate concentration in ^{1}H MRS. Diffusion-weighted MRI, which detects the molecular diffusion of water, has been proposed as an adjunct in the diagnosis of brain death, because it can identify widespread cerebral ischemia.[104]

Transcranial Doppler Ultrasonography

TCD is a safe, noninvasive, and inexpensive method that can be performed at the bedside. However, the test requires skill and knowledge in its application to insonate the major intracranial arteries. The Neurosonology Research Group (NRSG) of the World Federation of Neurology (WFN) created a Task Force Group to evaluate the role of TCD as a confirmatory test for determining brain death and offered the criteria for the diagnosis of cerebral circulatory arrest.[105] According to the criteria, cerebral circulatory arrest can be confirmed if the following extracranial

and intracranial Doppler sonographic findings have been recorded and documented both intracranially and extracranially and bilaterally on two examinations at an interval of at least 30 minutes:

1. "Systolic spikes" or "oscillating flow" in any cerebral artery can be recorded by bilateral transcranial insonation of the internal carotid artery (ICA) and middle cerebral artery (MCA), respectively any branch or other artery which can be recorded (anterior and posterior circulation).
2. The diagnosis established by the intracranial examination must be confirmed by the extracranial bilateral recording of the common carotid artery, ICA, and vertebral arteries.
3. The lack of a signal during transcranial insonation of the basal cerebral arteries is not a reliable finding because this can be due to transmission problems.
4. Ventricular drains or large openings of the skull as in decompressive craniotomy possibly interfering with the development of the intracranial pressure are not present.

According to the report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, the sensitivity of TCD for diagnosis of brain death ranges from 91% to 100%.[106] In a meta-analysis study of 10 studies concerning TCD examination, two high-quality studies showed a sensitivity of 95% and a specificity of 99% to detect brain death, and all 10 studies showed a sensitivity of 89% and a specificity of 99%.[107] Poularas and coworkers[108] reported that when they examined 40 clinically brain-dead patients by TCD and angiography the agreement between the TCD and angiography to confirm brain death was 100%. Young and coworkers,[83] however, strongly recommended that because of numerous caveats and lack of precise guidelines, TCD should not be, at this time, recommended as the sole test of brain perfusion in case of suspect brain death.

Positron Emission Tomography

Positron emission tomography (PET) imaging involves intravenous injection of radiotracers labeled with positron-emitting nuclides (e.g., oxygen 15 [^{15}O], carbon 11 [^{11}C], nitrogen 13 [^{13}N]). These radionuclides are incorporated into organic compounds that are chemically similar to those present in the body, and several physiologic parameters can be measured. A few of the reports about the use of PET in the setting of brain death indicated the utility of PET in the confirmation of brain death. No detectable glucose metabolism was reported using fluorine-18 fluorodeoxyglucose (^{18}F-FDG) in brain-dead patients.[109] On the other hand, Medlock and colleagues[110] reported a clinically brain-dead 2-month-old infant with no cerebral electrical activity who demonstrated the persistence of glucose metabolism by PET. These investigators speculated that the preservation of glucose metabolism was partly caused by glial cells, which are more resilient than neurons. The use of PET in the investigation of comatose or brain-dead patients is still in an early stage of development and limited by its high cost and need for special facilities. Laureys and associates[111] suggested that functional neuroimaging is providing new insights into cerebral activity in patients with severe brain damage and that measurements of cerebral metabolism and brain activations in response to sensory stimuli with PET, functional MRI, and electrophysiologic methods can provide information on the presence, degree, and location of any residual brain function.

Anesthesiologists in Organ Donation

The concept of brain death has been developed, at least in part, with the development of organ transplantation, and the main purpose of diagnosis of brain death is that it permits multiple vital organ procurement for transplantation. The "dead-donor rule,"[112] which requires that patients must be declared dead before the removal of any life-sustaining organs, is the ethical and legal axiom. Because of a critical shortage of organs for transplantation, various measures have been proposed to improve the rate of organ donation from brain-dead patients, such as "required request" and "presumed consent."[113,114] Furthermore, "non–heart beating organ donor" protocols, in which life-sustaining therapy is withheld on a imminently dying patient with the removal of the transplantable organs after the patient's cardiac arrest, have been introduced. Such protocols have gained popularity, especially after a qualified endorsement by the Institute of Medicine.[115,116]

Anesthesiologists should have ample knowledge about brain death and organ donation, because they would be involved not only in anesthetic management of a brain-dead patient for organ procurement but also in brain death diagnosis. In brain-dead patients, brainstem function with or without cortical functions is absent, and theoretically, the patients are unconscious. However, because their spinal cords are intact and somatic and visceral reflexes remain,[1,53] special care is required for anesthetic management. Muscle relaxants are necessary to suppress motor activity mediated by spinal reflexes. Vasodilators usually are employed to suppress hypertension and tachycardia by noxious stimuli. However, there is an opinion that sedation and analgesia should be given with muscle relaxation for organ donation, especially in cases of brainstem brain death,[35] although analgesic and anesthetic agents are theoretically unnecessary. Van Norman[113] stressed that anesthesiologists must have specific knowledge about the medical and legal definitions of death, as well as the ethical concepts behind them, and when anesthesiologists face anesthetic management for organ donation, they should consider the conditions of brain-dead patients and furthermore observe whether they are really brain dead.

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99 Operating Room Management

Key Points

1. Reorganizing the governance structure of the OR to consolidate control and authority into one position, such as the OR medical director, has many advantages in making the OR function at an optimal level.
2. Improvement in the OR scheduling process may lead to the biggest gains in OR efficiency. Block time scheduling allows better predictability and satisfaction for OR personnel.
3. On-time OR starts, surgical case performance benchmarks, and room turnover are all critical elements in making an OR run efficiently.
4. Traditional OR utilization assessments may not reflect how well an OR is working. Newer methods that focus on OR productivity are increasingly being used to determine allocation of OR resources.
5. Managing the daily surgical schedule requires careful planning, as well as frequent re-evaluation, to deal with the variability in case times, add-ons, and cancellations.
6. The OR director must create a professional environment in the OR and not allow disruptive behavior patterns to exist.
7. A detailed OR information system is essential in tracking OR activity and creating reports for assessment and improvement projects. OR cost accounting is essential to the OR director in guiding decisions for resource application.

The operating room (OR) is a major source of both revenues and expenses for hospitals.[1] Hospital chief executive officers must focus on the profitability of the OR service, and this emphasis has led to the rapid growth and development of OR management. The goal of current OR management is to replace the previously ill-defined structures for OR decision-making and administration with more formal and efficient structures. Over a decade ago, little information existed concerning OR direction and management, but as the focus on OR management has expanded, most hospitals now realize that clear-cut, scientific OR management is crucial to success. The discussion of OR management has expanded, as evidenced by the increasing number of journals including articles devoted to this subject. *Anesthesia and Analgesia* now includes a section on economics, education, and health systems research, with focused articles on OR management. The *Journal of the Association of Operating Room Nurses* (AORN J) also includes many articles on OR management issues. Another journal, *OR Manager,* is devoted to advancing knowledge in this field. Professional organizations have developed nationally and internationally to educate hospital staff on the concept of OR management. Examples include Anesthetists in Management in the United Kingdom and the American Association of Clinical Directors (AACD), which is a society formed in 1988 to lead the development of OR management expertise among anesthesiologists. The purpose of this chapter is to describe the development of OR management structure as well as offer information on identifying the complexities of OR function to improve OR productivity.

History

The role of the OR within the hospital has evolved. The organized structure and daily management of the OR are markedly different than they were 20 to 30 years ago.[2] In the past, ORs generated large profits. The priorities of the OR were to maximize convenience for surgeons and attract a greater market share, with little emphasis on controlling costs. Hospital administrators assumed that any new investment in the OR would lead to increased revenue. This mentality thrived in a period when revenues were plentiful, which allowed hospitals to provide new equipment or OR expansions upon request. Surgeons could schedule procedures as they desired, usually on a first-come/first-served basis. The authority for OR management was dispersed between hospital administrators, with little direct OR experience, and the OR nurse managers, who managed all the complex activities in the OR. Because the hospital administrators had responsibilities for several areas of the hospital, they left daily control to the OR head nurse, who became the de facto leader of the unit. Many of the

supporting services (housekeeping, admitting, materials management, and laundry) had separate administrative reporting structures. The low procedure complexity of ORs allowed for these simplified support services. Physicians often had a limited role in directing OR function.

As surgical procedures became more complex and competition for OR time increased, surgeons became dissatisfied with the control structure of OR management. Physicians formed OR committees to voice their thoughts to hospital leadership. The hospital and OR committees created rules and policies governing OR function. Dedicated rooms for complex procedures and increased scheduling demands led to the development of guaranteed reserved OR times called "blocks." These blocks allowed better predictability for surgeons to perform their procedures and allowed the hospital to provide the necessary support for the cases. The authority for daily OR management still resided primarily with nursing.

As Diagnosis-Related Group (DRG) reimbursement and capitative payment for care became more common, OR revenues declined. Hospital administrators noted that ORs were very expensive to furnish and run. The overall hospital operating margin (profit) declined from 6.3% in 1997 to 2.7% in 1999.[3] By 1999, 43% of not-for-profit hospitals actually lost money. Such losses forced hospital leaders to rethink how to run ORs. If the ORs consumed 9% to 10% of the institution's annual budget, the hospital needed to analyze and control the costs.[4] With the advent of general medical restructuring and primary care "gatekeepers," hospitals predicted reduced demand for specialists and surgical services. They reduced inpatient beds and limited OR growth. The net effect of these changes was increased frustration with OR function and management.

Predictions of reduced surgical caseload volume proved untrue. Surgical demand began to increase faster than the supply of OR infrastructure, OR nursing, and anesthesia services. Shortages of hospital beds, intensive care units (ICUs), and personnel have increased pressure to manage ORs with maximum efficiency while controlling costs. The hospitals expected all these OR changes to occur simultaneously while maintaining high OR customer and patient satisfaction. Hospital administrators realized that they needed more direct physician leadership in complex OR matters. As a result, they appointed medical directors to give more voice and authority to physicians in OR leadership roles. This physician leadership structure began in academic departments but has now expanded to many public and private organizations throughout the world. The focus on leadership structure and management techniques to improve OR function has led to the organized approach to OR management described in this chapter.

Medical Management in the Operating Room

Operating rooms are complex and expensive facilities that require a well-defined governance structure. As medical needs and regulatory requirements evolve, an OR governance structure must rapidly adapt to accommodate these changes. Traditionally, ORs followed a "top-down" management style. Hospital administrators were distant and unfamiliar with the daily work flow of the OR. They would often appoint the OR nursing director to serve as the unit manager. Often this nursing director was unfamiliar with the specific needs of surgeons and anesthesiologists. This unfamiliarity created a roadblock to rapidly addressing the evolving needs of the OR. In response to this problem, the original concept of an OR medical director was created. This concept involved creating an "OR czar" or single-handed decision maker. This approach was also flawed because it implied an authoritarian ruling style. That sort of management style is rarely successful in actual practice.

The most recent model for an OR medical director arose in response to the competing priorities of the diverse groups working within the OR (surgeons, anesthesiologists, nurses, and hospital administrators). For the OR to function effectively, the medical director must balance the priorities of each group while working cooperatively among the groups. Surgeons want maximum convenience and service, easy OR access, and state-of-the-art equipment. Nurses want predictable hours and standardization of cases. Anesthesiologists want high utilization during peak business hours and adequate support for starting procedures and turnovers. Hospital administrators want high utilization and low cost for personnel and equipment. These competing priorities may create conflict and inhibit productivity. The purpose of a medical director is to align the forces working in the OR in an efficient and productive manner. The most important advantage to this structure is that providing control and authority to one knowledgeable individual allows the OR to adapt to changes and make critical improvements. Creating an organizational structure with a medical director improves OR performance; increases physician, nursing, and patient satisfaction; permits rapid adaptability to changing market forces; improves communications throughout the system; and strengthens accountability and enforcement of OR rules and regulations. Figure 99-1 shows an organization structure that describes how the medical director may fit into the hierarchy of OR governance.

Anesthesiologists are good candidates for this position for several reasons. They have a global view of the OR and understand each component of the OR process. They share with the hospital administrators a desire for a smooth-running and cost-effective global OR. Because anesthesiologists are familiar with preoperative, intraoperative, and postanesthesia care unit (PACU) processes, they appreciate how to make the OR function as a unit. They are also familiar with the different surgical specialties and can balance the needs of these groups. Anesthesiologists are present in the OR daily and can intervene in urgent situations. Table 99-1 identifies personal characteristics that are beneficial for a medical director.

Another position that may complement the role of OR medical director is that of Director of Perioperative services. Responsibilities of this individual include managing the workflow of the anesthesia preoperative clinic and the PACU. This person works closely with the OR director because preoperative and postoperative problems have direct input on the flow of the operating room. Bottlenecks in throughput that occur before or after the surgical procedure will neutralize efficiencies developed within the OR.

Medical directors face many challenges. The position requires time away from clinical practice to attend meetings, plan projects, and coordinate OR productivity. The physicians' group or department chair must accommodate these scheduling demands to accomplish the OR's mission. The hospital should

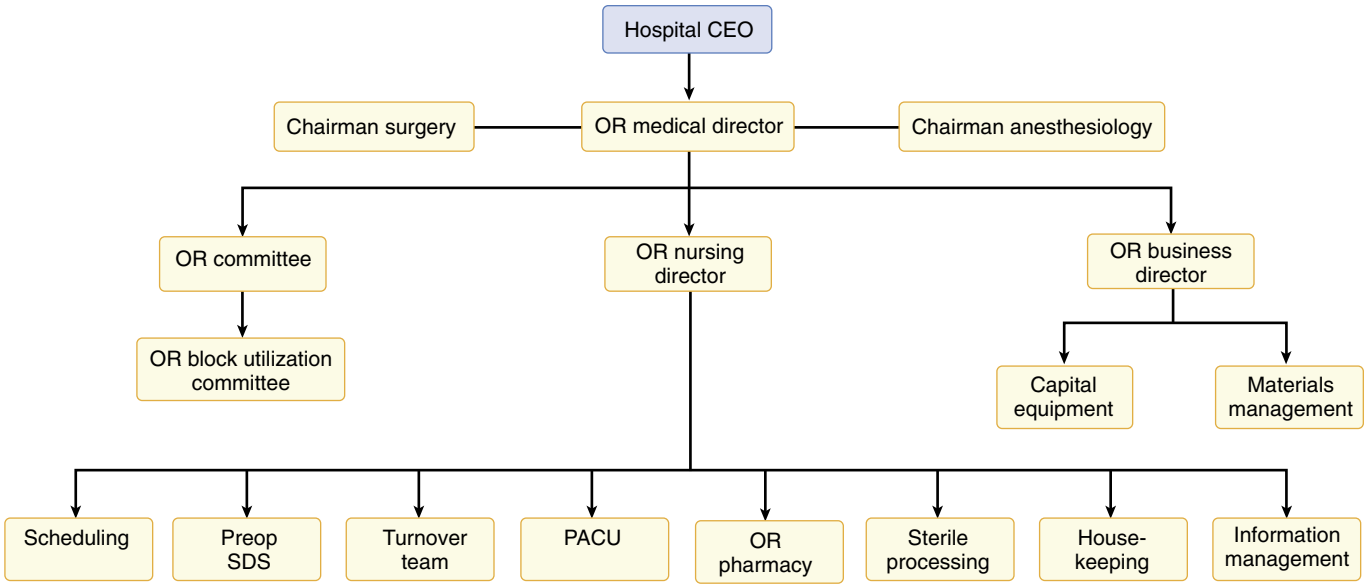

Figure 99-1 Organizational structure that describes how the medical director may fit into the operating room system. CEO, chief executive officer; OR, operating room; PACU, postanesthesia care unit; SDS, same-day surgery.

view the medical directorship as an investment and provide the appropriate financial support. Likewise, the chairs of surgery and anesthesia must cede some of their departmental control and authority involving OR matters. Time and energy demands may limit medical directors from advancing within their departments, organizations, or academic institutions. The medical director must make difficult decisions and be able to withstand criticism and challenges to his or her role. In addition, medical directors may require additional business training or data processing support.

Dealing with OR conflicts is another difficult aspect of management for OR directors, perhaps one of the least desirable roles of the position. With increased awareness of "culture" in the operating room, it is imperative to maintain a professional environment where staff members exhibit mutual respect for all parties.[5,6] The OR should develop performance policies including scheduling rules, surgeon presence in the OR, charting requirements, and behavioral expectations. The OR is one of the most common sites for disruptive physician behavior due to the high intensity and stress of the environment. The medical director should have a leading role in developing clear policies for addressing disruptive behavior. Table 99-2 lists steps for dealing with disruptive behavior.[7,8] Disruptive individuals or those who attempt to circumvent the established OR policies and rules create a dysfunctional system and dissatisfaction among the OR staff.[7] The medical director can set the tone for teamwork in the OR.

In 2002, AACD conducted a survey of its membership (Table 99-3).[9] The survey noted that the concept of a medical director, which began in academic organizations, has now spread to university-affiliated and private practice hospitals. Seventy-nine percent of OR medical directors served in hospitals with more than 200 beds. The survey disclosed that financial support varies, but most medical directors receive supplementation of less

Table 99-1 Characteristics of the Medical Director of an Operating Room

- Experienced individuals, usually in the middle of their careers
- Respected for clinical skills
- Strong interpersonal skills
- Integrity and trust by all groups
- Perceived neutrality and balanced views on issues
- Leadership style by consensus development
- Strong analytical and problem-solving skills
- Detailed data management traits
- Ability to commit significant time and focus to operating room
- Appreciation of hospital's goals
- Good long-range planning development
- Ability to address regulatory and oversight controls

Table 99-2 Dealing with Disruptive Behavior

- Educate the OR staff on hospital policies and definitions of disruptive behavior.
- Set a low threshold for identification and reporting.
- Respond immediately to an incident.
- Make the behavior the issue, not the individual.
- Focus on the acute behavior and not past frustrations.
- Do not accept excuses or explanations of justification.
- Set clear target goals for behavior modification and then follow up directly with the individual.
- Be sympathetic to the perspective of public humiliation of the individual. Deal with the individual in a quiet private setting with one or two witnesses.
- Seek out other issues in the physician's practice that may be the source of stress. Often, factors outside the OR lead to the disruptive behavior that is manifested in the OR.
- Be prepared to enforce your Disruptive Behavior Policy completely. If the physician does not reform or persists in the disruptive behavior, removal from the hospital staff may be the best solution.
- Enforce your policy evenly. Do not allow exceptions for behavior of high-profile individuals. Frequently, action against one physician will demonstrate the seriousness of your commitment to physician behavior standards and serve to deter others from acting out.

Table 99-3 American Association of Clinical Directors 2002 Survey of Operating Room Medical Directors

Hospital Type	
University teaching	44%
Community hospital	33%
University affiliated	33%
No. Hospital Beds	Size
<50	5%
50-100	4%
100-200	13%
200-500	54%
>500	25%
Hospital Compensation for Medical Director (per Year)	
None	40%
0-$10,000	25%
$10,000-$25,000	18%
$25,000-$50,000	13%
$>50,000	4%

than $10,000 per year. Appendix 99-1 provides the AACD guidelines for the role of medical director. Information is also available on the AACD website at www.AACDhq.org.

If an organization appoints an OR medical director, it should clearly define the director's responsibilities, expectations, and support. As stated earlier, the motivation for creating a medical director is often a result of frustration and low satisfaction among OR staff. Newly appointed medical directors can gain early success and acceptance by initially identifying issues that they can easily remedy. Coordination with the OR head nurse and OR business manager will unite the resources necessary for change. Regular communication with hospital superiors and OR staff will help define progress and identify future plans. Medical directors need to involve other physicians in setting goals and priorities. Success will require hospital administration and physicians to bring about change through compromise. The OR committee along with hospital administration should create reasonable rules and standards with equitable enforcement. While individual contributions should be rewarded, a team approach is essential. Alan Marco's "game theory" is a useful analogy for various situations a medical director may encounter in running the OR.[10,11] It should be emphasized that, albeit tedious at times, the position of medical director is often substantially rewarding.

Efficiency of Operation

Scheduling

Accurate scheduling in the OR is crucial to running an efficient surgical service. Poor scheduling causes delays and confusion on the day of surgery. It also results in dissatisfaction for patients, surgeons, and anesthesiologists. The process involves estimating, organizing, and assembling the necessary personnel, equipment, space, and time to perform a procedure.

Most ORs utilize a computerized scheduling system, and data integrity is paramount. Errors or omissions from documentation, including the patient's name, age, disposition (inpatient versus outpatient), procedure description, or surgical case duration, can have a major impact on how well the OR functions. Personnel who input these data should take precautions to reduce errors. Many computerized systems track posted cases to verify that available equipment matches resource needs. This prevents overbooking items with high demand including C-arm x-ray machines or microscopes.

Accurate prediction of surgical case times is also essential to scheduling. Errors in estimated times will affect the predicted start of every subsequent case. Gathering institution specific data is also important because operating times may significantly differ among hospitals.[12] Several authors have described how computer and statistical modeling can improve case duration estimates.[12-21]

Because there are wide differences among surgeons as well as multiple variations of a particular procedure, the potential times for a case may be difficult to predict. If the hospital has computerized historical data, it can base the surgical case time on a set number of similar performed cases. In our institution, the scheduling system will give the expected time for the procedure at the time it is posted. The surgeon may then increase or subtract time from this estimate based on his or her knowledge of the patient or predicted difficulty of the case. Based on this system, 50% of all cases in our ORs were completed within 30 minutes of the scheduled time. Fifteen percent of cases were 30 minutes longer than the scheduled time, whereas 35% of cases finished more than 30 minutes sooner than had been scheduled.

Historically, ORs were scheduled under an "open block" system. Surgeons scheduled cases in available rooms on a first-come-first-served basis. This system worked if there was little demand for OR time and each room was suited for all types of procedures. However, open block scheduling has many undesirable consequences. Surgeons with a short lead time in deciding to operate are unable to predict the availability of rooms. Personnel have to move complex equipment from room to room to accommodate demand from multiple types of surgeries. There is also marked variability between busy and light days resulting in poor overall OR efficiency and difficulty anticipating demand and allocating resources.

Because of the limitations of the "open block" system, ORs moved toward a system of "block" scheduling. Block scheduling guarantees a certain degree of OR availability. Under this system, the institution assigns a specific room on a specific day to a surgeon or surgical group. The surgeon or group may then schedule its cases for that room and day. This arrangement permitted the development of specialized ORs (i.e., rooms with heart-lung machines for cardiothoracic surgery, rooms with ophthalmologic fixed ceiling-mounted microscopes, and rooms with dedicated laparoscopic equipment).

The use of block scheduling has revealed several best practice standards. For example, block time works most effectively when it is granted to a surgical service (e.g., orthopedics or gynecology) rather than to an individual surgeon. In addition, full-day blocks (8 hours of OR availability) work better than half-day blocks because patient flow and case start times are more

Table 99-4 Guaranteed Room Starts

Service	Monday	Tuesday	Wednesday	Thursday	Friday
Cardiothoracic	3	3	3	3	3
General surgery	3	3	3	3	4
Orthopedics	4	3	4	3	3
Urology	2	2	2	2	2
Neurosurgery	1	2	2	2	2
Otolaryngology	2	2	3	3	2
Plastic surgery	1	1	1	2	1
Ophthalmology	0	1	0	0	1
Pediatric surgery	1	0	0	1	0
Gynecology	1	2	1	1	1
Nonoperating room cases	1	1	1	1	1
Open blocks	3	2	2	2	3

predictable. The reduced movement of personnel and equipment improves room setup and shortens turnover times. Tables 99-4 and 99-5 show examples of the block system at the University of Kansas Hospital.

In order for block scheduling to succeed, the institution should develop rules governing its use. For example, ORs may use measures of surgical demand, such as historical surgical hours per week, to grant the number of blocks to a surgical group. Key topics the rules should address include advance scheduling, turnover time,[21,22] and hold time or release time.[23,24] The release time, which varies among surgical specialties and institutions,[24] is the time when the block is no longer reserved for a particular service. Services performing procedures that have some urgency or a short lead time, such as heart or vascular surgery, have shorter times from release to the surgery date than services with a more elective practice, such as cosmetic plastic surgery or orthopedic joint replacement. Services with a high referral practice (cancer procedures or trauma) will also need shorter release periods for their blocks (Table 99-6). Once a release time is reached, remaining time (unused block time) is available to any surgeon on a first-come/first-served basis.

Table 99-6 Suggested Block Release Times

Service	Release Time
Cardiothoracic	1 day
Vascular surgery	2 days
Orthopedics	3 days
Neurosurgery	4 days
Pediatric surgery	1 wk
General surgery	1 wk
Gynecology	1 wk
Ophthalmology	1 wk
Otolaryngology	1 wk
Plastic surgery	2 wk

An institution should closely monitor block time utilization and adjust it as surgical practice changes within the hospital. For example, if a surgical service is filling more than 90% of its block time, it becomes difficult to perform additional cases or manage variability in the surgical referral base. On the other hand, if block utilization is low (60% to 70%), predictable OR time is not available to other surgeons who may need several days of advance planning to schedule cases. Each institution should set a threshold for block utilization to determine how services will gain or lose OR blocks.[25-28] A group with representatives from hospital administration, major surgeons, anesthesiology, and nursing should develop these thresholds. The institution should ensure it applies them equitably to avoid potential "games" to change OR availability.[10,11] The group should then monitor and enforce compliance with the rules.

Today, hospitals often schedule most of their ORs under a block system, reserving some ORs in open blocks to accommodate low volume surgeons and urgent add-ons.[26] The number and availability of open rooms will depend on the volume of urgent, emergency, and add-on cases. If the hospital has a significant number of elective cases, it may be appropriate to block schedule 80% of the ORs and leave the remaining 20% as "open" rooms. Several authors have described strategies to maximize surgical blocks and reduce variability to improve utilization.[29,30]

A final important aspect of scheduling is how to manage non-OR anesthesia cases such as endoscopy, radiology, computed

Table 99-5 Room Block Guarantees

	Operating Room No.																					
	1	2	3	4	5	6	7	8	9	10	11	12	14	15	16	17	18	19	20	21	22	23
Monday	Open	Uro	Open	Ort	Uro	CTS	Ort	Neu	Ort	Gen	Gen	Gen	Ped	Open	Pla	Ort	Gyn	Ent	Ent	Open	CTS	CTS
Tuesday	Open	Uro	Open	Ort	Uro	CTS	Ort	Neu	Ort	Neu	Gen	Gen	Open	Opt	Pla	Gyn	Gyn	Ent	Ent	Gen	CTS	CTS
Wednesday	Open	Uro	Open	Ort	Uro	CTS	Ort	Neu	Ort	Neu	Gen	Gen	Ort	Open	Pla	Ent	Gyn	Ent	Ent	Gen	CTS	CTS
Thursday	Open	Uro	Open	Ort	Uro	CTS	Ort	Neu	Ort	Neu	Gen	Gen	Ped	Ent	Pla	Pla	Gyn	Ent	Ent	Gen	CTS	CTS
Friday	Open	Uro	Open	Ort	Uro	CTS	Ort	Neu	Ort	Neu	Gen	Gen	Open	Opt	Pla	Gen	Gyn	Ent	Ent	Gen	CTS	CTS

CTS, cardiothoracic surgery; Ent, otolaryngology; Gen, general surgery; Gyn, gynecology; Neu, neurosurgery; Opt, ophthalmology; Ort, orthopedics; Pla, plastic surgery; Ped, pediatric surgery; Uro, urology.

tomography, and magnetic resonance imaging. These patients often require perioperative resources although they do not enter the OR. They often require a dedicated anesthesia team, spend recovery time in the PACU, and are processed through the preoperative unit. Institutions should include these patients and procedures in the OR scheduling system in order to assist the perioperative units and anesthesia schedule runner, assign appropriate resources, and track progress of the daily schedule.

On-Time Starts

It is crucial to start the first procedure of the day on time. An on-time start provides tangible (scheduling) and intangible (mood and tone) benefits. If there is a delay in starting the first case, it can negatively affect the overall mood and support for performing the remaining cases efficiently. It is important for everyone to agree on a definition of start time. Surgeons often define start time as when incision is made. Anesthesiologists define start time based on when they complete induction. Nurses associate start time with the completion of room preparation. Disagreements in what constitutes start time will result in misunderstandings and dissatisfaction with room starts.

In 1997, a group in the AACD published a procedure times glossary that created standards for OR events and time periods.[30] This glossary is accepted by the American Society of Anesthesiologists, Association of Operating Room Nurses, and the American College of Surgeons and serves as the standard for descriptive terms in the OR. Appendix 99-2 contains an excerpt of the glossary. The glossary describes *start time* as the time the patient enters the OR. This time has not proved to be useful in identifying cause for delay on a case-by-case basis. Furthermore, surgeons indicate that the time the patient enters the room has little bearing on when the patient will be ready for the surgical incision. The newer concepts of "anesthesia ready" (AR) or "anesthesia release time" (ART)[31] may be more helpful in determining surgical preparation and incision times. The AACD glossary describes *anesthesia ready* as the time at which the patient has a sufficient level of anesthesia established to begin surgical preparation of the patient, and remaining anesthetic procedures do not preclude positioning and prepping the patient. At our institution we reviewed times from the patient entering the OR to completion of preparation. In uncomplicated cases (patient supine with no invasive monitoring lines), staff completed preparation in 15 minutes in 78% of cases. If the case was complicated (position other than supine, invasive monitors), the duration from start time to completion of preparation averaged 30 minutes. These data are useful for surgeons to anticipate the time from room start (patient in room) until completion of preparation.

On-time starts depend on the completion of many factors. Patients must arrive on time and complete preoperative preparations including compliance with all preoperative instructions (NPO, medications, laboratory tests). The admitting process should be streamlined and organized to meet the needs of the surgical patient.[32] Preoperative testing clinics and assessment protocols have helped reduce delays on the day of surgery, as well as reduce costs.[33-36] The preoperative/admitting process should have sufficient personnel, organization, and space to process patients and make them available to surgeons and anesthesiologists. Operating room nurses must prepare the operating room and equipment. Anesthesia personnel must check the equipment in the room, prepare drugs, complete paperwork, place intravenous lines, and address special patient or surgical needs. Surgeons must be available to complete the patient's consent, history, and physical examination and to address any patient questions or needs.

Table 99-7 Delays in Start of First Case of the Day

Surgeon controlled	45%
Patient controlled	23%
Anesthesia controlled	17%
Nurse controlled	15%

A common misconception is that anesthesia factors result in the majority of room start delays. Many anecdotal reports by OR clinical directors do not support this concept. We recently studied reasons for all delayed room starts and grouped delays into factors controlled by patients, surgeons, anesthesiologists, and nurses. The results (Table 99-7) demonstrate that surgeons controlled the largest number of delays in first starts. Table 99-8 lists some of the most common reasons for delays.

Starting first cases on time is a complex and challenging process. When defining an on-time start as having the patient in the room by the start time, delays occur in 40% to 90% of first starts.[37,38] When defining an on-time start as having the patient in the room within 10 minutes of the scheduled start time, delays still occur in 5% to 50% of cases. Identifying causes of delays, removing barriers to smooth patient flow, improving communications between preoperative personnel, patients, surgeons, nurses, and anesthesiologists, and creating an atmosphere (culture) of shared ownership in starting on time will improve on-time starts. Table 99-9 lists other key factors for increasing the percentage of on-time starts.

Turnovers

The definition of *turnover* varies among OR personnel, leading to confusion. A surgeon may view surgical "down time" (the time between closing the incision on one patient and beginning the incision on the next patient) as turnover. Academic surgeons consider turnover to be the period between leaving the OR (before the incision is closed by a junior resident or medical student) and returning for the beginning of the next case. Thus, surgeons frequently complain that slow turnovers between cases cause significant delays in completing the surgery schedule. The OR nurse may treat turnover as the time from removing the used equipment from the first case until the equipment is in place for the next patient. Anesthesia personnel believe that turnover is the time between leaving the previous patient in PACU and bringing the next patient into the room. With varying definitions of turnover, it can be difficult to measure and create improvements in this area of OR function.[39] The AACD glossary (see Appendix

Table 99-8 Reasons for Surgeon-Controlled Delays

- No history and physical examination in chart
- No consent obtained
- Ordered new laboratory test; results not available
- Changed schedule order or procedure
- Surgeon not available

Table 99-9 Key Factors to Increasing On-Time Starts and Decreasing Turnover Times

Keys to Increasing On-Time Starts

- Do not require the surgeon to be present before the patient enters the operating room.
- Use guaranteed block time to allow for predictable operating room times and locations for surgeons.
- Have specialty teams dedicated to complex cases.
- Standardize preoperative orders and testing.
- Review the patient's chart the day before surgery to identify potential delays in getting the patient ready.
- Call patients the day before surgery to clarify instructions and answer questions.
- Triage personnel in the preoperative area to effectively manage patient needs before start of the procedure.

Keys to Decreasing Turnover Times

- Organize a turnover team to clean and prepare the room.
- Have the same surgeon follow in the same room with all their cases.
- Use specialty-specific nurses and anesthesiologists.
- Maintain an accurate surgery schedule and reduce changes in the surgical list (i.e., order changes, cancellations, add-ons).
- Streamline the preoperative process.
- Ensure that the communication process informs all personnel involved with case turnover in a timely manner.

99-2) defines *turnover* as the time from when one patient exits the OR until the succeeding patient enters. This turnover time applies only when the second case is scheduled to immediately follow the first case.

The period between patients occupying the OR is busy. The nurses must return used instruments to decontamination processing. A housekeeping service must clean the floors and sterilize all surfaces, including the OR table. Nurses must assemble and organize equipment for the next case. They must also check on the next patient and verify that the paperwork is complete and the procedure is correctly listed. Anesthesiologists must transport the previous patient to the PACU, assess vital signs, give report to the PACU nurse, and submit required paperwork. They must return unused drugs and prepare new drugs for the next case. They must also ensure that anesthesia equipment is replaced and prepared for the next patient. Finally, they must see the next patient, complete preoperative paperwork, obtain consent forms, discuss anesthesia plans with the patient, and answer questions.

Multiple system factors can affect turnover time, and several units must function efficiently together to be successful. Attention should be given to the preoperative process (see Chapter 34) to efficiently prepare patients for surgery and readily locate the required paperwork and preoperative test results. Hospital transportation services should allow patients to be reliably available when called for the OR. The drug management system must permit access to medications and manage controlled substances. A turnover team must organize, clean, and prepare the OR for the next case. The PACU must function well to allow efficient OR throughput.[40,41] Recently, problems with hospital floor and ICU bed availability have resulted in the PACU being filled to capacity, creating a back-up of patients in the OR. Chapter 85 further discusses ways to improve PACU function. Each of these individual factors contributes to the overall ability of the team to facilitate turnover.

There is no national standard for acceptable turnover time. In most facilities, turnover represents 10% to 20% of the total case time. When performing turnover between simple procedures, such as cataract extractions, it is reasonable to expect a turnover time of 10 minutes. However, when changing between heart bypass procedures or complex orthopedic cases, the turnover may require 45 minutes or longer. The complexity of room set-up and need for specialized patient preparation contribute to length of turnover. Table 99-10 illustrates average turnover times for various types of surgical procedures.[42] Some benchmarking data are available on turnover for specific procedures.[42-44] A review at four academic institutions indicated that turnover times ranged from 34 to 66 minutes.[44] Our academic institution averages turnover times of 33 to 38 minutes, whereas a private practice hospital may consider 20- to 30-minute turnovers more reasonable. An institution should consider this information when it looks at its specific turnover data to determine realistic goals for OR improvement.

Although reductions in turnover times may save 5 to 10 minutes per case, these time savings do not usually translate into large time reductions in a single OR's schedule. Reducing turnover time does improve efficiency and focus, which may translate to improvement in surgical preparation and case completion times. The intangible benefits of reducing turnover may be the most important. Reducing turnover can build teamwork and the institution's focus on achieving maximum OR efficiency. However, excessive focus on turnover time is counterproductive. Staff risk losing more time strategizing than can realistically be gained from the resulting changes.[43,44] Turnover time is also a favorite topic of consultants because it tends to strike an emotional chord with surgeons and hospital administrators. In reality, most efforts to reduce turnover times result in modest reductions in completion of the surgical schedule.[44] As an example, if an OR performs 4 cases in a day and can reduce turnovers by 10 minutes, the total time that can be saved is 30 minutes (3 turnovers × 10 minutes = 30 minutes). This small time savings may result in reduced overtime expenses and improved satisfaction measures, but it will not provide sufficient time to perform additional cases.[45]

OR of the Future

The increasing pressure on hospitals, surgeons, and anesthesiologists to improve throughput of patients has led to new concepts in streamlining cases. One area of discussion involves the use of dedicated anesthesia induction rooms and early recovery areas to minimize nonoperative time spent in the operating room. Induction rooms have been used in some European countries but are largely unknown in the United States. In attempting to apply new

Table 99-10 Average Turnover Times

Total-hip replacement	44 min
Total-knee replacement	46 min
Knee arthroscopy	38 min
Coronary artery bypass	52 min
Laparoscopic cholecystectomy	30 min
Cataract extraction	21 min

designs to optimize OR throughput, Sandberg described a concept known as the "Operating Room of the Future."[46] In addition, other investigators have described how this concept could be applied to their specific OR characteristics.[47,48]

By setting up processes to run in parallel instead of in series, nonsurgical time is reduced up to 40%. In Sandberg's 2005 study, parallel processes resulted in 30 fewer minutes of nonsurgical time. When anesthesia induction, line placement, and emergence from anesthesia take place in rooms adjacent to the OR, the time spent in the OR can be concentrated on performance of the procedure followed by simple OR housekeeping turnover. The advantage of this new process is more cases performed in the OR per day.

The disadvantage for this parallel process is the significant resource requirements. An additional 200 to 300 square feet of space in close proximity to the OR must be available for the induction and early recovery rooms. Capital equipment, including anesthesia machines and monitors, must be duplicated for these locations at a cost of $40,000 to $60,000 per room. The staffing requirements must be increased to allow nursing and physician coverage of the expanded patient care areas. Typically, because the net costs to the anesthesia team are increased, it is necessary for the facility to provide funding to offset these costs. This funding may be obtained by the additional revenue generated from the additional cases performed; however, additional cases do not completely offset the cost.

The applicability of this type of OR process has generated much debate and analysis.[46-52] Because complex variables such as OR procedure length, staffing plans, OR space availability, staff availability, patient demand, and hospital investment all have an impact on this type of process redesign, it is difficult to predict whether this concept will be applied to more OR locations in the future.

The Daily Schedule

The "running" of the daily schedule is a complex job.[53,54] An accurate and realistic schedule is one of the most important factors in a successful surgical day. Frequently, an anesthesiologist partners with an OR nursing leader to run the daily surgery schedule. The scheduler must be able to make fair decisions regarding moving cases, dealing with add-on cases, and using the nursing and anesthesia workforce to complete the surgical list efficiently.

Making the cases flow smoothly takes several steps (Table 99-11). The initial step is to review the schedule of cases the evening before and again the morning of surgery. These reviews should focus on identifying potential obstacles to patient flow and opportunities to deal with add-ons or changes. During the course of the day, the scheduler should frequently walk the "floor" in the OR to check on the status of room starts, case progression, and turnovers. Because surgical procedures have a high degree of variability, plans on how cases should proceed change frequently, and adaptation is paramount. The OR should create a tracking system to monitor the day's progress. This system does not need to be elaborate but should be available for people working in the OR to see schedule adjustments including starts, finishes, and add-ons.

Every OR has add-ons and case cancellations. As the number of add-ons and cancellations increases, so does the complexity of scheduling.[55-60] There are no national benchmarks for schedule changes, but planning measures to keep add-on rates less than 12% and cancellation rates less than 4% will help to effectively and efficiently manage the schedule. The cancellation rate varies based on patient population and surgical procedures but is generally in the range of 6% to 9%.[33,34] If an OR has higher rates, staff should assess why these changes are taking place. One strategy to reduce cancellations is to evaluate patients in an organized and efficient preoperative clinic with standardized algorithms for further testing and evaluation. These clinics reduce delays and cancellations on the day of surgery.[19,33-36] Table 99-12 shows some of the common issues in case cancellations.[61]

Table 99-11 Ten Steps to Completing the Daily Schedule

1. Recheck the schedule the afternoon before surgery to look for potential difficulties and to identify opportunities.
2. Review the schedule early in the morning on the day of surgery and note cancellations and add-ons.
3. Ensure that rooms are starting on time by walking through the operating room suites.
4. Set expectations for surgical case progress by using benchmark case times if available.
5. Organize the turnover process to manage peak room changes from midmorning until early afternoon.
6. Develop a well-understood policy for working add-on cases into the schedule.
7. Look for open room time to move cases from late-running rooms or to move add-on cases into.
8. Identify cancellations early and redeploy the room and personnel resources to complete other cases.
9. Set realistic staffing patterns to meet the surgical caseload demand. Use nonstandard shifts so that rooms do not have to be closed in the early afternoon.
10. Use a case-tracking system so that others can see where resources are needed to complete the caseload.

Table 99-12 Common Case Cancellation Issues

Patient
Self-cancellation or no-show
Desired second opinion
Patient not NPO
Preferred transfer to another institution
Surgeon
Not available; busy with an emergency or another case
Decided surgery was not indicated
Patient needed further workup
Anesthesiologist
Patient needed further workup
Hospital
Nursing staff not available
Lack required equipment or implants for case
Scheduling error; wrong date for surgery
Lack beds; ICU at capacity

Table 99-13 Add-on Case Management

Emergency	Urgent	Elective
Come to the OR within 30 min	Come to the OR within 2 hr	No time constraints
Example: gunshot to the abdomen	***Example:*** appendectomy or ectopic pregnancy	***Example:*** revision dialysis shunt
Place in any open room	Place in available staffed open block room or in room with cancellations. If no room is open, bump the posting surgeon's elective cases. If posting surgeon has no room, bump same surgical division. If no cases within same surgical division, bump room with the shortest surgical list.	Follow elective cases in first available room.

There should be a well-defined system for triage to improve the efficiency of performing add-on cases. Generally, the scheduled elective cases take precedence over add-on cases, but there are exceptions. Situations will arise in which an urgent or emergency case will delay or "bump" a planned elective case from the schedule. As a result, managing and scheduling urgent or emergency cases must also follow a well-understood system.[53] Table 99-13 shows one algorithm used to handle emergency cases.

Surgeons often help to control add-on placement by scheduling OR availability during specific days. If a group or division of surgeons is busy, they may have set OR days when they are available for surgical procedures and other days when they are committed to clinic visits and are unavailable. Often, the surgeons' add-on cases are self-channeled into days that they are already in the OR. In this situation, the add-ons should be scheduled into that surgeon's preexisting room. If a hospital system has a large number of add-ons that surgeons must perform at the end of the elective schedule late in the day, the OR should be scheduled to properly staff and support these times. Nursing shifts using the traditional 8-hour (7 AM to 3 PM) shift may need to be modified to cover late rooms by creating either 12-hour shifts (7 AM to 7 PM) or staggered shifts (10 AM to 6 PM). Anesthesiology departments must also address coverage of this off-peak OR time.

Despite the best planning, the daily schedule is challenging because cases are often unpredictable and surgeons are motivated to meet their own targets. A good rapport among schedulers and surgeons is helpful in diffusing potential scheduling conflicts. Alan Marco's articles on game theory create an interesting analogy of these interactions as they apply to the OR.[10,11] This perspective can be helpful in scheduling efficiently and seeking support for organizational success. Routine reviews of utilization reports and the daily schedule are important to identify opportunities for improvement, including decreasing unused OR time (Figs. 99-2 and 99-3). Regardless of goals to schedule efficiently, the quality of a patient's care should remain the top priority.

Operating Room Utilization

OR utilization is an important concept that guides the direction of OR management.[62] It is also a significant part of the OR medical director's job. To understand the concept of OR utilization, it is important to understand several definitions from the AACD glossary (see also Appendix 99-2):

- *Case time* is the time from the start of room setup to the end of room cleanup. It accounts for the entire time that the OR is dedicated to the performance of a procedure and cannot be used for any other purpose.
- *Resource hours* are the total number of hours that a room is staffed and available for the performance of procedures. Many ORs are staffed for 8 hours of regular resource hours (e.g., 7 AM to 3 PM). Resource hours do not include overtime or periods when on-call personnel are staffing the OR. Resource hours serve as the denominator in calculating utilization of the available blocked or open scheduled elective OR time.
- *Raw utilization* is the ratio of the time that patients are in the OR to the available resource hours. It does not include time spent preparing the OR or turnover time; therefore, it understates the actual time that the OR is committed to a case.
- *Adjusted percent utilization* is similar to raw utilization, but it includes case setup time and turnover time. This figure more accurately reflects the time that the OR is used for case performance and is unavailable for any other activity.

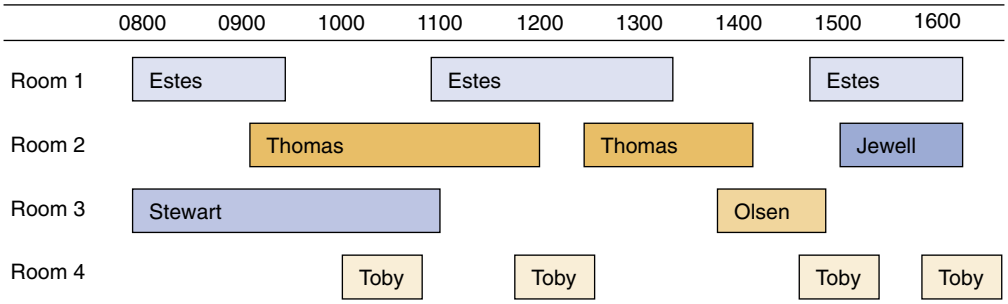

Figure 99-2 An example of schedule utilization.

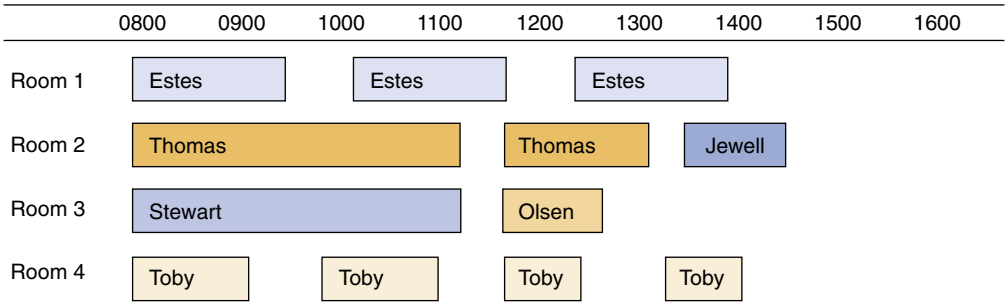

Figure 99-3 Improved schedule utilization.

Utilization is most commonly determined for a service or group of surgeons based on their set amount of block time. For example, if a group of orthopedic surgeons has block time in two rooms on Monday through Friday, their resource hours per week are 80 (2 rooms × 5 days per week × 8 hours per day). If their total case time (in-room time plus turnover) is 72 hours per week, the adjusted percent utilization is 90% (72 hours per week ÷ 80 hours per week).

Regularly tracking utilization is important. To achieve an efficient balance of available times for surgical divisions, hospitals should reassess block times based on utilization on a 3- to 6-month basis. For hospitals using utilization to track surgery performance and allocate block time, it is better to assign block time to a group of surgeons or a surgical division. Granting block time to individual surgeons produces more variability in use and may result in lower utilization. Table 99-14 contains an example of a raw utilization report from our institution.

There is no defined target for optimal utilization. Opinions of optimal utilization vary among entities involved in the OR (Table 99-15). As utilization increases above 80%, surgeons may have difficulty scheduling patients and the increased wait time may create patient dissatisfaction. Studies have shown that for elective procedures in the United States, most patients are willing to wait 1 week.[29] Waiting longer than this because of unavailable block time will lead to patient and surgeon dissatisfaction and possibly loss of the case to another institution. Utilization percentages that are very low represent lost opportunities to generate revenue. Anesthesiologists prefer to be busy during regular resource hours yet have some flexibility for covering urgent and emergent cases.

The exact break-even point for utilization is dependent on the OR's fixed versus variable costs and reimbursement mix. Consultants often quote 80% to 85% utilization as a target. This figure was used as a benchmark in the 1970s as hospitals were required to demonstrate a certificate of need prior to expansion of OR facilities. Most ORs seek a utilization of 70% to 85% to maximize benefits and reduce stress on the system. Trends have shown that with increasing surgical volume and reduction in OR availability, the overall raw utilization has been steadily increasing in hospitals (Fig. 99-4). Data from 1999 revealed that hospital-based ORs have higher utilization than ambulatory ORs (73% versus 55%).[63] Tracking overall OR utilization may be beneficial in demonstrating the need to expand OR capacity.

There are costs associated with both underutilization and overutilization. There are fixed costs for ORs regardless of utilization. Underutilization results in lower revenue generation to offset the fixed costs. Overutilization (cases running late) may require overtime pay for nurses or hiring temporary nurse services, which results in higher costs per minute of OR use. In addition, personnel who frequently must stay late may become dissatisfied and quit, increasing the costs associated with recruitment. Many recent studies have identified ways to maximize utilization or to assist with scheduling to improve percent utilization.[63-66] Because many ORs have frequent last-minute changes, cancellations, add-ons, and emergency cases, the ability to apply these simulations to actual OR practice may be limited.

Table 99-14 Operating Room Utilization: January-June

	% Utilization		
	Avg hr/wk	**Starts/wk**	**Block**
Orthopedics	125	17	92
General surgery	128	16	100
Urology	71	10	88
Cardiothoracic surgery	74	15	62
Otolaryngology	72	12	75
Plastic surgery	31	6	64
Neurosurgery	49	9	68
Ophthalmology	9	3	36
Pediatric surgery	6	2	40
Gynecology	45	6	93
Other	11	—	—
Total operating room hours used per week: 621			

Table 99-15 Utilization Comfort Zones

Utilization	Hospital Administration	Anesthesiology	OR Nursing	Surgeons
>100%	++	—	——	———
85%-100%	+++++	++	–	—
70%-85%	+++	++++	+	±
55%-70%	+	+++	+++	++
<55%	—	–	++	++++

From Mazzei W: AACD Workshop on Operating Room Management, 2003.

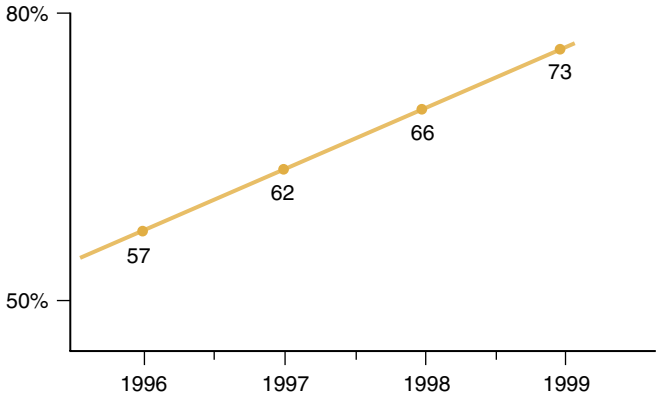

Figure 99-4 Raw utilization for operating rooms.

Table 99-16 Raw Utilization Calculations

	Case Time (hr)	No. Cases Performed	Total In-Room Time (hr)
Surgeon A	2.5	3	7.5
Surgeon B	1.0	6	6.0
Surgeon A	7.5 hr in room time ÷ 8.0-hr block available = 94% raw utilization		
Surgeon B	6.0 hr in room time ÷ 8.0-hr block available = 75% raw utilization		

Table 99-17 Operating Room Assessment Report

Surgeon	Cases	Collection	Avg Collection/Case	OR Minutes	Avg Minutes/Case	Collection per OR Minute
Green	53	$43,116	$813	1150	22	$37.49
Jones	17	$16,802	$988	989	58	$16.99
Smith	10	$17,179	$1718	588	59	$29.22
Rogers	19	$11,947	$629	800	42	$14.93
Wilson	12	$13,341	$1112	1052	88	$12.69
Lynch	13	$7,398	$569	883	68	$8.38

Utilization should not be used to assess how efficiently an OR is working. Utilization is only a measure of resource consumption. For example, if surgeon A takes 2.5 hours to perform a laparoscopic cholecystectomy and conducts three procedures in an 8-hour block, this results in a raw utilization of 94% (2.5 hours per case × 3 cases = 7.5 hours; 7.5 hours per 8-hour block = 94%). However, surgeon B, who completes laparoscopic cholecystectomies in 1 hour and is able to do six procedures during an 8-hour block, has a raw utilization of 75% (1.0 hour per case × 6 = 6 hours; 6 hours per 8-hour block = 75%). Even though surgeon A has higher utilization, surgeon B's financial margin is better. Table 99-16 illustrates these calculations.

Hospitals are becoming more refined at analyzing OR production. By looking at revenue generation and associated costs for each surgeon, they can determine the profit margin for each individual. Although studies have shown that nearly all surgeons contribute a positive profit margin for their OR cases, the range of profit margin is wide.[67] Table 99-17 shows an example of a report generated with this approach. OR managers and hospitals are increasingly using this type of information to make decisions concerning OR resources. Table 99-18 contains a list of key issues to improve OR utilization, throughput, and efficiency.

Anesthesia Service Management

It is important for OR directors to include anesthesia service management in the scope of OR management. If an OR director succeeds in streamlining and maximizing the efficiency of the OR, productivity within the anesthesia service will increase. Better OR scheduling, on-time starts, efficient turnovers, and proper management of add-ons and cancellations will result in concomitant improvement in anesthesia service utilization.

The two main components of anesthesia service management involve personnel issues and pharmaceutical costs. Anesthesia-related costs represent 3% to 5% of the total health care expenditures in the United States.[68] Although most of these costs involve personnel,[69] anesthesia-related drugs comprise the majority of the 20 most costly drugs used in the hospital.

Many authors have reviewed optimal staffing patterns for providing anesthesia coverage for the surgical schedule.[70-72] Staffing coverage depends on provider availability as well as local conditions. The benefits of physician-only versus concurrent supervision of multiple providers are not clear cut.[73] ORs must also consider the requirements for specialty teams to cover areas such as cardiac, organ transplant, obstetric, trauma, and pediatric

Table 99-18 Keys to Increasing Operating Room Throughput

- Schedule full-day blocks rather than half-day blocks.
- Surgeons should follow themselves in the same operating room.
- Verify schedule accuracy to decrease delays in case completion.
- Streamline preoperative processes and standardize testing.
- Use specialty teams of nurses and anesthesiologists.
- Organize supply and equipment needs for easy room setup.
- Focus attention on room starts and turnover to create a culture of timeliness and efficiency.
- If you have a significant number of add-on cases, plan for an open room or be able to move cases to available time slots.
- Ensure that the communication pattern throughout the perioperative area informs all necessary individuals of case progression.

cases, which may limit the ability to maximize staff utilization. Today, more anesthesia groups are negotiating financial support from hospitals for added call coverage for these specialty teams.

As a result of growing pressure to quantify anesthesia output, ORs have refined the measurement of anesthesia productivity.[74,75] Methods to track anesthesia output have evolved from simple availability to more sophisticated measurements of production and call coverage.[76] Clear differences exist between academic and private settings. Abouleish and colleagues showed that an anesthesiologist in an academic setting needed to work 30% longer than one in private practice to generate the same level of billable services (7.8 hours versus 6.0 hours).[75] Development of incentive plans can be useful to improve productivity and retain physicians.[77-82]

Anesthesia drugs are expensive and are a frequent focus for reducing hospital expenses.[83] Overall, pharmaceutical costs approximate 5.6% of a hospital's total operating costs.[84] Anesthesia drugs represent 22% of the total pharmacy costs.[85] Newly developed anesthesia drugs often have significantly higher costs (muscle relaxants, narcotics, antiemetics). Although these drugs may appear to be cost effective by improving patient throughput (decrease OR or PACU times) or increasing patient satisfaction (faster discharge, less postoperative nausea and vomiting), studies have been inconsistent in demonstrating those benefits.[86,87] Because there are many variables that contribute to change in resource utilization and drug cost, true assessment of the resulting changes from drug choices is difficult. It is also difficult to assess the fixed versus variable costs of those changes. If anesthesia-controlled costs represent 6% of the total cost for a surgical patient, it is likely that half of these costs are fixed. ORs can modify the remaining 3% of costs (drugs and supplies); however, experience has shown that intensive restructuring of anesthesia drug use only results in small reductions in overall pharmacy costs. In many cases, the savings are difficult to sustain and ORs return to previous drug choices.[85]

Operating Room Information Systems

ORs are the largest and most complex areas of the hospital and generate the greatest revenue (as well as expenses), yet OR use of information technology remains underdeveloped. Hospitals are 10 to 15 years behind industry in adopting and implementing information management systems. However, information systems are critical for today's OR director to manage effectively. A well-designed system can improve many processes, including OR scheduling, automated records, materials management, preoperative data, laboratory tracking, medication tracking, cost data, patient tracking, and quality improvement/quality assessment (QI/QA).[88-90] Most hospitals continue to use basic systems to manage scheduling, generate statistical reports, and create equipment lists.

Information systems are complex and expensive. It is a challenge for companies to create information systems that are able to integrate large volumes of information from many different sources. A single OR case can create over 1 million data bits in 3 hours.[90,91] Manual transcription of this information is problematic by creating difficulty for ORs to demonstrate regulatory compliance, to avoid legibility and medical errors, and to reduce the risk of legal concerns. Manual data entry also requires significant time; 30% to 40% of an anesthesia provider's time in the OR is spent as an information scribe.[92]

Hospitals have been slow to adopt information systems in the OR for many reasons. These systems are expensive, with an average cost of $1 million to $2 million for a medium-sized hospital. Hospitals frequently require a return-on-investment analysis to justify the expense. Integration of the new system into the OR also requires resources and the continual support of a systems manager. Hospitals are also concerned with vendor credibility in delivering the advertised benefits of the system.

The applicability of information systems must be carefully reviewed. Recently, Vigoda published an account of medicolegal concerns pertaining to time stamps for documentation of certain events.[93] Information systems are useful in tracking drug utilization and identifying discrepancies of controlled substances.[93-96] Information systems are a necessity for the OR director to maintain an efficient and competitive OR and to monitor and adjust the OR process. These systems can improve charge data and simplify managing equipment and personnel. Data on OR resources can also improve QI/QA assessment. Clear, accurate information allows the OR manager to focus on areas of improvement and create behavior changes in the system to remain efficient and competitive.

Cost Accounting in the Operating Room

Financially managing the OR is a difficult task for the OR director. Most physicians have not had a formal business education and are not familiar with OR financial management concepts. Health care is a complicated financial industry. In the United States, there was more than $2 trillion in health care spending in 2005, or 16% of the U.S. gross domestic product.[97] The health care industry provided 13.5 million jobs according to the 2004 Bureau of Labor Statistics.[98] It is essential to understand financial management theories of the OR because strong financial management within the hospital is essential for success.

The concept of management control in nonprofit organizations is becoming more sophisticated.[99] Financial management of the OR is analogous to running a business.[100,101] A hospital can classify an OR as an expense center or a profit center. If it is an expense center, attempts to improve the financial position of the hospital would focus on minimizing costs. If, however, the OR is a profit center, the OR director must pay attention to the margin between costs and revenues and attempt to maximize profit. It is reasonable for hospitals to focus on the financial performance of the OR. The OR averages 40% of the total costs of a hospital, but it is responsible for as much as 70% of the revenue.[1] As ambulatory health care activity has moved out of the hospital, many hospitals have become primarily tertiary care surgical facilities. Managing costs and increasing revenue in the OR will result in a hospital with strong profitability and the ability to expand its health care delivery.

The OR director needs a basic understanding of cost accounting to ensure effective OR decision-making. Cost accounting focuses on understanding the costs of running the OR to

Table 99-19 Operating Room Accounting Terminology

Charges	The fee listed for an item or procedure based on assumptions of resource consumption
Costs	The actual expenses incurred in delivery of a service
Fixed costs	Overhead. Costs that do not change up or down over a finite period, regardless of the volume of activity
Variable costs	Costs that change directly up or down with changes in volume of activity
Profit	Revenue–costs (both fixed and variable)
Contribution margin	Revenue–variable costs
Capacity	Maximum amount of activity that a facility can deliver without increasing fixed costs

determine an optimal price for services. Hospital management should use the information that cost accounting provides to plan and control activities, to make strategic decisions, and to improve the quality and efficiency of services in the OR. Table 99-19 contains a listing of certain accounting terms.

It is important to recognize the difference between costs and charges. Costs include all of the fixed and variable expenses associated with a specific procedure. Charges are the sum of all the costs plus the amount of profit over the costs that the hospital bills to insurers. In the 1970s and 1980s, most hospitals used the theory of cost-plus billing. In cost-plus billing, the hospital added an amount of money (profit) to the costs for a procedure. It submitted the resulting charge to insurers. However, as reimbursements declined, insurers began to contract services for a specific price, regardless of the hospital's costs for that service. The ratio of costs to charges varied widely for different services throughout the hospital.[1] For example, the cost-to-charge ratios at Stanford Hospital were 0.29 for anesthesia, 0.50 for laboratory, and 0.92 for the surgery admission unit.[1]

Because of the arbitrary nature of assigning charges to a service, as well as the variable reimbursement, decisions concerning OR management should use costs and not charges. Costs are either fixed or variable. Fixed costs (overhead) are costs that do not change in the short term regardless of the number of completed procedures. In the OR, these costs include rent or depreciation of the surgical suite, capital equipment in the OR, salaried employees, and administrative overhead (OR directors, medical records, admitting personnel). Fixed costs may change over longer periods if the hospital changes the number of OR suites or the budgeted number of OR staff. Variable costs will increase or decrease directly with the level of surgical activity. In the OR, variable costs include disposable supplies, sutures, linens, implants, and contracted labor. Fifty-six percent to 84% of operating room costs are fixed.[102,103] Short- and intermediate-term cost reductions will apply only to the variable portion of OR costs, representing a smaller part of the total OR costs as fixed costs remain unchanged.

The two methods to account for costs in the OR are either top-down or bottom-up. Top-down accounting uses cost-to-charge ratios to average and estimate the costs for a particular procedure. This is an easy and simplified calculation but has critical disadvantages. Top-down accounting is imprecise, and the ratio will vary because of changes in either costs or charges. This makes period to period comparisons difficult because it is difficult to isolate whether the cost-to-charge ratio trend is due to changes in costs, charges, or a combination of both. Bottom-up accounting (microcosting) is more precise, requiring a detailed measurement of all the expenses for a procedure. Bottom-up accounting also requires classifying costs as fixed or variable, which makes decision-making easier in OR planning.

Profit for the OR is equal to the total revenues minus the total costs. The OR must produce profit to pay for other areas within the hospital (e.g., emergency department) that operate at a loss. However, in assessing changes in surgical activity, the "contribution margin" is more important. Contribution margin is equal to the total revenues minus the variable costs. A larger contribution margin indicates that more money is available to pay the overall fixed costs of the institution.

A specific example of OR cost analysis is provided by the 1999 review of costs by Marcario. In the review, he found that the majority of costs for care of a patient undergoing laparoscopic cholecystectomy occurred in the OR.[103] The OR (37%), anesthesia (7%), PACU (6%), and OR-related laboratory and pharmacy costs accounted for more than 50% of the total hospital costs. For any OR procedure, most of the costs occur in the first hour of the case. These costs include room preparation, opening basic supplies, linens, and use of instruments or implants for the procedure. Subsequent time in the OR is less expensive and consists primarily of labor costs. Using a detailed analysis, Marcario established that the basic costs of an OR, exclusive of procedure-specific needs (e.g., trocars or implants) was $13.54 per minute.[103] Of this amount, 62% of the costs were fixed and 38% were variable. Cost-savings measures (i.e., changing physician practice) will affect only the variable costs of this expense. OR costs vary by institution, depending on labor and overhead costs.[104,105] Ambulatory surgical facilities, with reduced overhead, may have overall OR costs 20% less than hospital facilities have.

The potential benefit of cost analysis is illustrated by considering the amount of costs that can be reasonably reduced. For example, anesthesia costs, such as machine depreciation, supplies, and drugs, average 6% of the total hospital costs for a procedure.[1] Of these costs, approximately 50% are fixed and 50% are variable. To reduce overall anesthesia costs in the OR, a hospital can only modify the variable part of the anesthesia costs. Therefore, it is only possible to manage 3% of the total hospital costs when reviewing the anesthesia practice for cost savings.[106] The PACU is also an area with high fixed costs—up to 67% of the total PACU costs.[1] For this reason, opportunities for large cost reductions in the PACU by changing practice are difficult.

The largest variable costs associated with health care and the OR are personnel costs.[107] The unpredictable nature of the surgical volume, as well as late-running cases, may lead to increased labor costs. The Fair Labor Standards Act requires overtime wages of 150% of regular wages for hours worked over 40 per week. As a result, personnel costs increase significantly with poorly planned labor use in the OR. Strategies to minimize overtime including using 12-hour shifts, staggering nurse work times, and creating greater scheduling control will help reduce these labor costs. Careful analysis of nursing requirements and the creation of optimal staffing patterns can have a significant impact on OR costs.[108-110]

Studies on the contribution margin of individual surgeons to the hospital have shown that nearly all surgeons have a positive contribution margin.[67,111] However, the difference in the

contribution margin between surgeons varies greatly, in some cases by as much as 1,000%.[112] To improve profitability for the OR, efforts to increase the volume of highly profitable surgeons will have the greatest impact. However, before assigning more OR time to these surgeons, several questions must be addressed. Will the surgeon's utilization decrease if volume or OR time is increased? Do the surgeon's cases require hospital resources (ICU beds, specialty nursing) that have limited capacity? Does the system have enough overall capacity (OR rooms, nurses, anesthesia coverage) to increase volumes of services and hold fixed costs neutral? If additional volume of cases requires building more infrastructure (new rooms or more OR nurses), the fixed costs will increase and negate profit. Clear, accurate information is necessary for the OR director to track costs and make rational decisions to improve OR performance.

Regulatory Issues

OR activities are complex and critical to the delivery of health care. A large number of agencies and regulations oversee how an OR functions. The OR director must be familiar with these various agencies and regulations to ensure compliance within the OR. Table 99-20 lists these entities.

The OR director must focus on meeting the regulatory requirements for hospital accreditation. Patient and employee safety (infective agents, fire safety, laser safety, electrical safety), and proper use and tracking of drugs and medical devices are also important areas of focus. State and local regulations, as well as hospital policies, have specific requirements for the OR. Privileging and monitoring the quality of outcomes for physicians in the OR are paramount. Internal data collection and quality measures should be designed to demonstrate the performance of individual physicians and the OR. Initiatives brought forth by nongovernmental groups such as Leapfrog and the Institute for Healthcare Improvement (IHI) have challenged hospitals to apply best practice standards to the care delivered. Programs such as IHI's "100,000 Lives Campaign" have enlisted hospitals to adopt these standards to reduce morbidity, mortality, and health care costs. Recently, Medicare has begun to implement performance standards for best practice care relating to the OR. The Surgical Care Improvement Project (SCIP) was initially designed to reduce surgical infections by applying best practice standards to antibiotic use, hair removal, and temperature maintenance. Medicare has indicated tying hospital reimbursement to targeted performance standards. Pay-for-Performance (P4P) is a Medicare plan that ties reimbursement to specific physician activities.[113] Developing plans for insuring best practice, utilizing OR information systems, and partnering with the hospital leadership in meeting these requirements are a crucial part of the OR director's duties.[88,113-117]

Table 99-20 Operating Room Agencies and Regulators

- The Joint Commission
- Accreditation Association for Ambulatory Healthcare (AAAH)
- Drug Enforcement Administration (DEA)
- Food and Drug Administration (FDA)
- Centers for Disease Control and Prevention (CDC)
- Department of Health and Human Services (DHHS)
- Centers for Medicare and Medicaid Services (CMS)
- Occupational Safety and Health Administration (OSHA)
- American National Standards Institute (ANSI)
- National Fire Protection Association (NFPA)
- National Committee for Quality Assurance (NCQA)
- National Academy of Sciences/Institute of Medicine
- Safe Medical Devices Act
- Health Insurance Portability and Accountability Act (HIPAA)

Summary

Operating rooms are complex environments that are vital to the success of hospitals. Hospitals have re-evaluated OR management structure to improve efficiency while emphasizing quality and cost. Redesigning OR governance has been essential in addressing the changes required to make ORs run more effectively. Such redesign has resulted in an increasing trend to place overall responsibility in the hands of a single person, the OR director.

The OR director must understand OR economics and use sound strategies for cost control and revenue enhancement. A comprehensive OR information system that can capture and organize OR data is essential for the OR director. Hospitals set targets for performance, and regulatory organizations set quality measures for the OR. Information systems help to monitor whether the OR is meeting these targets and standards. Detailed data are required for instituting a successful business plan for the OR and implementing changes in how the OR functions.

The OR director's position has evolved into a broad and encompassing role as a manager of the perioperative process. The director must focus efforts on ensuring smooth, efficient throughput of patients in the perioperative area. Accurate scheduling, on-time OR starts, efficient turnover, and proper surgical case management are critical to the success of running the surgical schedule. OR directors must develop strategies to manage surgical schedule variability as a result of add-ons, emergency cases, and cancellations. They must also construct systems to control surgical and anesthesia costs. Although the challenges in making an OR function optimally are great, the benefits of an efficient and successful OR are critical to the hospital, to anesthesiologists, and to surgeons who work in this environment.

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APPENDIX 99-1

Guidelines for the Role of the Clinical Director of Anesthesiology and Director of the Operating Rooms

I. Responsibilities to the Department of Anesthesiology
  A. Personnel management
    1. Long-term faculty scheduling
    2. Daily faculty/resident/certified registered nurse anesthetist assignments; assurance of comprehensive resident case exposure/coordination with program director
    3. Staffing calculations and planning; recommendations to chairman
    4. Creation of management team representing all clinical aspects of the department
  B. Subspecialty coverage
    1. Develop appropriate faculty daily and on-call coverage
    2. Participate in resident subspecialty rotation development
  C. Daily operations
    1. Early morning review of schedule
    2. Morning clinical/staffing conference
    3. Assignment changes during the day
    4. Chief arbiter of clinical and interstaff disputes
  D. Participative roles (with significant institutional variations)
    1. Preoperative evaluation clinic/preadmission testing procedure
    2. Anesthesia equipment/monitoring
    3. Quality assurance/quality management process
    4. Disaster planning
  E. Evaluation and promotion of the clinical director
    1. Clinical management-oriented job may require special criteria
    2. Clinical tract appointment most appropriate
    3. Teaching time may be limited
    4. Research areas may exist in management and statistical and clinical studies

II. Responsibilities to the OR/Hospital/Medical Staff
  A. Scheduling and data collection
    1. Daily review/final arbiter of OR scheduling
    2. Supervisor of scheduling/data processing personnel
    3. Enforce scheduling policy
    4. Management of OR utilization data and submission of reports to appropriate governing body
  B. Communications center (OR desk)
    1. Establish practices that provide expeditious service
    2. Supervise OR desk personnel
  C. Clinical director's role with OR nurses, PACU nurses, and support staff (with significant institutional variation)
    1. Leadership and supervisory role for OR personnel
    2. Strong working relationship with nursing hierarchy and hospital administration
    3. May function as OR manager with budgetary, materials management, and quality assurance functions
  D. Chief liaison to:
    1. Hospital administration (formal position)
    2. Nursing administration
    3. OR committee (may serve as chairman of the committee). Authority must be delegated from surgical and anesthesiology departments and hospital administration
  E. Basic support from hospital administration
    1. Office, secretary, scheduler, and other personnel as necessary
    2. Financial subsidy may be appropriate
    3. Administrative authority

III. General Qualifications
  A. Seniority, appropriate academic rank—associate or professor level may facilitate the role
  B. Clinical proficiency/commitment—being respected for clinical abilities is a significant attribute
  C. Educational qualifications—formal training or experience in negotiation and interpersonal relationships and business administration may be desirable

APPENDIX 99-2

Selected Items from the Procedural Times Glossary of the American Association of Clinical Directors

Room ready: Time when the room is cleaned and supplies and equipment necessary for beginning of next case are present

Start time: Patient in room time

Preparation completed: Time at which prepping and draping have been completed and patient is ready for the procedure or surgery to start

Case time: Time from room setup start to room cleanup finished. This definition includes all the time for which a given procedure requires an OR. It allows for the different duration of room setup and room cleanup times that occur because of the varying supply and equipment needs for a particular procedure.

Turnover time: Time from prior patient out of room to succeeding patient in room for sequentially scheduled cases

Resource hours: Total number of hours scheduled to be available for performance of procedures (i.e., the sum of all available block time and open time)

Block time: Hours of OR time reserved for a given service or surgeon. Within a defined cutoff period (e.g., 72 hours prior to day of surgery), this is time into which only the given service may schedule.

Open time: Hours of OR time not reserved for any particular service, into which any service or surgeon may schedule according to the rules established by the given institution

Raw utilization: For the system as a whole, this is the percent of time that patients are in the room during resource hours. For an individual service, this is the percent of its block time during which it has a patient in the OR.

Adjusted percentage: (in-own block hours plus outside-own block hours × 100/block time)

Service utilization: This measures the percentage of time a service utilizes its block time during resource hours. It is adjusted compared to raw utilization, in that it gives a service "credit" for the time necessary to set up and clean up a room, during which time a patient cannot be in the room. It may exceed 100% because of the inclusion of cases performed during resource hours that are outside-own block hours.

Lawrence Litt

100 Electrical Safety in the Operating Room

Key Points

Fire Safety Issues

1. When setting up the anesthesia machine and drug cart before a case, be sure to know about the operation and the location of emergency equipment. Questions to ask oneself include the following
   - Where is the nearest fire extinguisher—there should be one in every operating room?
   - Where are the oxygen shut-off valves and how do I operate them to stop oxygen flow to the operating room?
   - Where is the nearest fire alarm should it be impractical to call the hospital's equivalent of "911" (fire alarms are often recessed in the wall near fire hoses)?
   - Where is the nearest escape passage?
   - Where is the nearest defibrillator and code cart?
2. Recall that electrical fires, particularly those that involve the electric panel, require a special approach. If possible, quickly cut all electric power that feeds an electrical fire (which then converts it into an ordinary fire). In fighting a fire, the proper type of fire extinguisher must be used. The most common type of fire extinguisher sprays water. However, water must never be thrown or sprayed onto an electrical fire or onto burning flammable liquids. Electrical fires require a dry chemical extinguisher, but CO_2 extinguishers, which are optimal for control of burning oils and liquids, may also be used.
3. Avoid use of high "blow-by" oxygen flow from an open facemask if after "blowing by" the patient, the flow ends up providing oxygen enrichment at a site of electrosurgery.

Macroshock Electrical Issues

1. All electrical equipment used in the operating room should be grounded (although internally such equipment can contain ungrounded circuits). If the power cord for a piece of equipment has a plug with only two prongs (i.e., no grounding prong to go in the third hole in the outlet), the equipment should not be in the operating room. When connecting or disconnecting plugs from outlets, do not yank the plug by the cord. Similarly, do not use equipment whose power plugs have been damaged, and do not let heavy equipment crush power cords by rolling over them.
2. Patients should not be directly connected to the operating room's electrical ground.
3. When electrosurgery is in use, a grounding pad should be used that connects the patient to the ground connection provided on the electrosurgery machine. The grounding pad should be well gelled and placed in contact with the patient across a large area. The grounding pad should be inspected during lengthy operations and gelled again or replaced if necessary. The electrosurgical grounding pad should be placed as near the operative site as reasonably possible and as far as possible from any pacemaker wires and ECG wires. When grounding pads are removed, the underlying skin should be inspected for burns.
4. The anesthesiologist should be concerned if increasing current levels are required for electrosurgery and take it as a cue to check for faulty connection of the electrosurgical grounding pad. In the event of very "wet" operations, with or without increasing current levels for electrical surgery, the physician should beware of errant current paths that include the grounding pad and other electrical contacts (e.g., ECG electrodes). For example, saline and body fluids in an abdominal procedure can extend under the drapes beyond the operative site and potentially form an electrical connection to a grounding pad or ECG electrodes.
5. If the line isolation monitor (LIM) sounds an alarm after someone activates equipment, the offending piece of equipment should be unplugged immediately. Plugging in that equipment has allowed the secondary side of the main isolation transformer to be coupled to the ground. It is also possible that so many items were plugged in simultaneously that the secondary side of the main transformer was coupled to ground by their combined capacitance. The anesthesiologist can try various combinations of unplugging one piece of equipment and plugging in another. However, if it is found that one piece of equipment causes the LIM to sound an alarm under several combinations, that piece of equipment should be removed from the operating room and examined for an unwanted connection to the ground contact.

6. All electrical equipment should be tested periodically by experienced personnel, usually a clinical bioengineering group associated with the operating rooms. Anesthesiologists should verify that equipment has been maintained properly, that standards of performance have been met, and that the entire electrical environment also meets National Fire Protection Association standards.[21,51-56]

Microshock Electrical Issues with Pacemakers

1. Patients with an automated implanted cardioverter-defibrillator (AICD) need to have the AICD turned off before surgery starts after first having established Zoll pad connections. Turning off the AICD feature is commonly done by magnet placement but can also be done by reprogramming. It should be appreciated that magnets do not change the pacing program that is in an AICD. Thus, preoperative cardiac electrophysiology consultation is essential for establishing appropriate pacing.
2. If possible, bipolar electrocautery units should be used instead of unipolar electrocautery.
3. All programmable pacemakers should be interrogated preoperatively to ensure proper function.
4. Pacemaker-dependent patients need to have asynchronous pacing programmed along with all rate-sensing features disabled. A conventional defibrillator should be available.
5. Other pacemaker patients should have a pacing strategy established by preoperative cardiac electrophysiology consultation.
6. A plan for pharmacologic treatment of complete heart block should be in place, particularly for pacemaker-dependent patients, and isoproterenol should be readily available on the anesthesia drug cart.
7. If electrophysiologic monitoring is being done, the anesthesiologist should review the locations of grounding pads that will be placed by the electrophysiologist.

MRI Issues

1. When using a pulse oximeter to monitor the oxygen saturation of patients in an MRI scanner, the connection between the oximeter console and the patient must take place through a long fiberoptic cable having no wires or conducting segments.
2. Items with internal wires should not be present during an MRI examination, including pulmonary artery catheters that have a wire for determination of temperature and certain epidural catheters with wires.
3. Because of missile danger, ferromagnetic anesthesia equipment may not be brought into the magnet room.
4. Essential anesthesia equipment that can be sucked into a magnet must be bolted to a wall and tested before entry of the patient into the scanner.
5. Anesthesiologists who stay in the magnet room during examinations must wear ear plugs to avoid permanent hearing loss from high-decibel acoustic noise.

Common to All Issues

If the cause of an electrical burn or incident is uncertain, the relevant equipment or areas should be secured until experienced biomedical personnel mount a thorough investigation that may include simulation of patient conditions.

Despite technologic advances that have increased the sophistication of operating room electrical equipment, three types of danger persist from the days of flammable anesthetics: fire, electrical burns, and electrical shocks (macroshocks and microshocks). Improved alarm systems and safeguards have accompanied the technologic progress, but there has also been an increase in the size and number of electrical devices used per case. The result is the introduction of new ways to create unsafe electrical configurations that can lead to severe injury during surgery and anesthesia. Inattention to electrical safety can have serious consequences. Tragic events continue to be reported in the medical literature, in some cases in which a moment of injury leads to a lifetime of patient suffering. Frequently, the culprit is unsafe surgical equipment or its unsafe use. However, disasters can also originate in damaged or misused anesthesia equipment, including physiologic monitoring devices.

Recently, there has been a surge in the number of important articles about intraoperative fires,[1-6] with cause analyses being based on the "fire triangle," or the three requirements for a fire: oxygen, fuel, and an ignition source.[6] Operating room fires fall into one of three basic categories: the patient or something in the patient is on fire, there is equipment with an electrical fire (i.e., one initiated and sustained by electric currents), or the surgical drapes or other operating room items are on fire. Inadvertent ignition is often involved and easily identified, for example, when burning of surgical drapes is initiated by electronically generated sparks or by high temperature. However, ignition sources can also be complex and not immediately understood, as in the case of an exploding expiratory valve in an anesthetic breathing circuit.[7] In the operating room, anesthesiologists need to be aware of fire safety concerns, do all they can to keep ignition sources away from fuel sources, and be safe about the use of supplemental oxygen. Apart from fires, severe burns have also been caused by electrical equipment with inadequate grounding or other faults and by induced currents from radiofrequency fields. One report described a neonate with third-degree burns after the application of an external cardiac pacing device for a prolonged period.[8] Another report described serious burns occurring from the direct electric current (DC) generated by a 9-V battery in a small neuromuscular stimulator.[9] Fortunately, patient electrocution is now uncommon, although it was once a well-recognized hazard of surgery and the operating room and even of hospitalization in general.[10-13]

Even though many types of modern equipment appear different from their ancestral counterparts, the injuries caused by electricity are similar or identical to those occurring generations

ago. Electrical malfunctions in the operating room continue to cause fires and explosions, central and peripheral nerve stimulation and damage, muscle stimulation and contracture, tissue burns, pacemaker interference, and sudden loss of power to important equipment. Safety standards for medical equipment have been improving, and most complications can be avoided by preventive maintenance of equipment, careful attention to the electrical contacts used on patients, and appropriate responses to alarm signals. Understanding electrical safety is an especially important responsibility for anesthesiologists because perioperative electrical dangers can often be identified before they lead to disruption of patient care or to injury.[14-18]

Having described the general situation, we now turn to the essential details of electrical safety. The "Key Points" provides guidelines for safe clinical practice.

Electrical Ground

What is "electrical ground"? This question is important because discussions of electrical safety often center on whether circuits are "grounded." To the clinician, an electrical ground is the wire connected to the third prong on plugs that are inserted into electrical wall outlets. With regard to circuits, an electrical ground is any object connected to a circuit that is capable of instantaneously supplying or receiving arbitrarily large amounts of electrical charge. The National Electrical Code of the National Fire Protection Association (NFPA*) defines electrical ground as a conducting connection, intentional or accidental, between an electrical circuit or equipment and earth or as a connection to some conducting body that serves in place of the earth. Because the earth can be taken as an infinite reservoir of electrical charge with a limitless ability to give up or receive electrons, any charged object connected to earth loses its charge and assumes the same potential as the earth.[14] Relative to earth and to each other, the voltage between two grounded objects is zero.

When a circuit is intentionally grounded, the physical objects chosen to serve as the electrical ground can vary. In a remotely located mobile army surgical hospital unit or recreational camping van, equipment may be grounded by connections to a spike that goes into the earth. In a large urban medical center, the ground may consist of a subterranean network of pipes. For a very small, hand-held radio, a human being may serve as the connection to ground.

In hospital settings, the clinician does not need to understand the details regarding the choice of ground. However, clinicians must often know whether they, their patients, or their pieces of equipment are grounded. Living organisms tolerate only limited amounts of electric current. Unintended new contacts with electrical ground can sometimes be injurious when they enable very small electric currents to reach the heart or neural tissue. However, they are always dangerous when they permit large electric currents to travel through the body. Fortunately, it is possible to design alarms for operating rooms and surgical equipment that provide danger signals before errant currents are established by a sudden, new, unwanted ground connection. If the operating room has a *line isolation monitor* (LIM), which is explained later, hearing its loud warning sound means that a faulty ground connection is one step away from establishing a large current in the patient. Human protection from large currents can be ensured if connections to ground always occur through a sizable resistance. The danger of being grounded through an electrical resistance that is too small can be illustrated by an unrealistic but vivid hypothetical example. Imagine a person standing on top of a giant copper cylinder that extended down to the molten core of the earth. This low-resistance connection to the largest imaginable electrical ground would be quite unsafe because the person would essentially be a fuse, poised to suffer whatever large electric current is applied. The safety that would be achieved by inserting very large electrical resistance between the person and the copper cylinder—but not so large a resistance that it causes perfect insulation—explains a requirement that was established long ago when explosive anesthetic gases such as cyclopropane were used. Operating rooms were then required to have conductive floors made of specific resistive materials. Such substances had high carbon content, making them neither as conductive as metal nor as insulating as rubber. The high carbon content imparted a dark black color, one that can commonly be found today in many operating room tables and cushions made of resistive material.

In the United States, electrical plugs have three prongs, with only two providing voltage or, equivalently, power. A special third prong serves only as a connection to ground (i.e., to an object that makes an electrical connection with the earth or with a metal network such as iron pipes.) Travelers to Europe and elsewhere may recall seeing electrical outlets for plugs that have only two prongs and no separate ground wire. A two-wire system becomes especially unsafe if three-pronged equipment is plugged into it with the third prong left unattached.

A ground fault current interrupter (GFCI) electrical outlet allows a person to test that the third connection in the outlet is connected to a functional ground. More significantly, GFCI outlets enhance electrical safety by serving as emergency circuit breakers that shut off power when one of the two power lines in the outlet is accidentally connected to ground. Thus, the GFCI is a "first fault" detector. GFCI outlets, found in hospitals and homes, have two buttons: "TEST" and "RESET." Pushing TEST causes a special resistor to be connected across the power and ground terminals in the receptacle. If the ground connection (i.e., the third wire) is in place and connected to the system ground, as it should be, current flows through the resistor and causes a circuit breaker in the outlet to open. No electricity can then be delivered by the outlet. Pushing RESET resets the circuit breaker and restores electrical power. Pushing TEST would not cause the circuit breaker to open if, for example, a contractor accidentally forgot to install the ground wire or if an earthquake or other mishap caused a break in an installed ground wire. Protection against accidental grounding of one power line in an outlet is required by the NFPA for wet environments such as operating rooms. Installation of GFCI electrical outlets is one way to satisfy NFPA protection requirements. As discussed later, a second way (the traditional but more expensive way) is to have power come from an isolation transformer equipped with an LIM.[19,20] In the operating room, if a power outlet is not part of an isolated system with a LIM, it should be a GFCI outlet.

Electrical engineers commonly choose the ground as a reference location where the voltage is defined to be zero. Therefore,

*National Fire Protection Association, 1 Batterymarch Park, P.O. Box 9146, Quincy, MA 02269-9959. http://www.nfpa.org. Standards are available for download at http://webstore.ansi.org.

the voltage at any point in a circuit is the difference between the voltage at that point and the voltage at the electrical ground. Because of this, ground connections in commercial circuits help professional personnel check for proper functioning. A technician connects one voltmeter probe to ground while touching different circuit elements with the other voltmeter probe. The manufacturer's table can be used to compare readings and, in this way, identify problems in the circuit. Specifying the location of the electrical ground helps people communicate standards for circuit performance.

Isolation of Electric Power from Ground

Electrical contacts with "ground" can cause injury if they occur in two different locations such that a circuit is completed and permits a large flow of current through "ground." One strategy for ensuring safety is to isolate all electric power sources from "ground," thus making it impossible for "ground" to be used as a path for injurious or damaging currents.

Traditionally, implementation of this strategy in the operating room has been accomplished by means of isolation transformers, which usually take the form of large wall panels that have outlets and meters. The term *isolation transformer* comes from the fact that power output is isolated from the electrical ground. Figure 100-1A shows a schematic diagram of an isolation transformer. A device built into the transformer constantly checks that all is well with this setup. It monitors the extent to which the output power lines are isolated from the ground and is called the LIM. Next we review how the LIM came into existence, why it can be important, and precisely what it is.

Electric power for an operating room comes from a primary hospital source that usually originates from a connection to an alternating electric current (AC) station of the local power company. (Sometimes an emergency, gasoline-powered electrical generator is the primary source.) In the traditional setup, after arriving at an operating room, electric power is modulated, isolated, and dispensed to electrical outlets in the room by the secondary coils of one or more large isolation transformers. Such transformers are very expensive, and the traditional setup is found less often in new hospitals. However, when there is a transformer, connections in three-hole power outlets in the operating rooms are somewhat different from connections in standard outlets found elsewhere in the hospital.[18] In such operating rooms, a circuit cannot be completed by connecting one of the two power contacts to the ground contact.

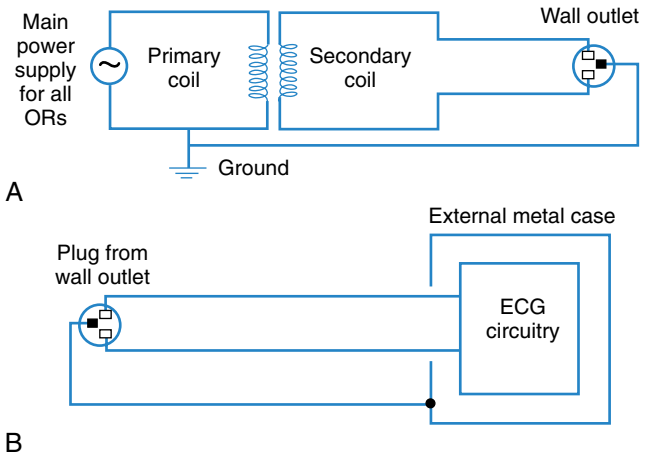

Figure 100-1 Schematic diagrams of an isolation transformer (**A**) and electric grounding (**B**) for an electrocardiographic (ECG) unit in the operating room (OR) (i.e., outlet to equipment).

The panel of each isolation transformer is required to have an LIM, which is an electric current meter that demonstrates isolation of the transformer's output power from ground. Large isolation transformers were originally required by the NFPA in all operating rooms because of the use of inflammable anesthetic.[19] It is permissible for operating rooms to be built without them as long as basic safety is maintained by otherwise isolating electrical circuits from ground. Such is now accomplished by a power transformer inside most electrical devices that isolates voltage applied to the device's circuits. Instead of there being one large isolation transformer for all equipment, each piece of electrical equipment has a small isolation transformer inside it. Such was not the case when large isolation transformers were initially required. It is therefore possible to argue for the total abolition of operating room isolation transformers and their LIMs. In support of such an argument is the observation that isolation transformers and LIMs have always been absent in intensive care units and postanesthesia care units, places where medical personnel use the same electrical instruments that are used in operating rooms. Should anesthesiologists advocate the elimination of future installations of isolation transformers and LIMs in operating rooms? The answer can be either yes nor no,[19,20] depending on the type of electrical equipment that is used and the surgical situation. Surgery can involve having very wet patients covered or soaked with fluids that conduct electricity and find pathways to "ground." In these situations, currents can be established through the errant pathways from electrosurgical tools, such as through saline solutions to electrocardiographic (ECG) electrodes or the operating room table. New operating rooms in ambulatory surgery centers would seem to not need isolation transformers, although they are well suited for operating rooms for liver transplants and other procedures involving a large amount of fluid.

The schematic diagram of an isolation transformer in Figure 100-1A shows what is presented by the power outlet to any power cord that gets plugged in. Each power outlet has two hot-wire contacts coming from the secondary coil of the transformer. The third contact in the power outlet is connected to the standard hospital ground and not to the isolation transformer. Note that the primary circuit of the transformer is attached to "ground" but the secondary circuit of the transformer is not.

When an ECG monitor is plugged into a power outlet in the operating room (see Fig. 100-1B), neither of the two hot wires from the secondary coil of the transformer is connected to the ground by the ECG circuitry. This demonstrates the general principle that electrical circuits within an apparatus need not be grounded, although the metal case that houses the circuits is always grounded. For many circuits, proper functioning depends on good isolation. The statement "all operating room equipment must be grounded" means that the "ground" connection on a power cord that comes from equipment must always end up in contact with the "ground" provided by the transformer. In the example given in Figure 100-1B, the electrocardiograph case is

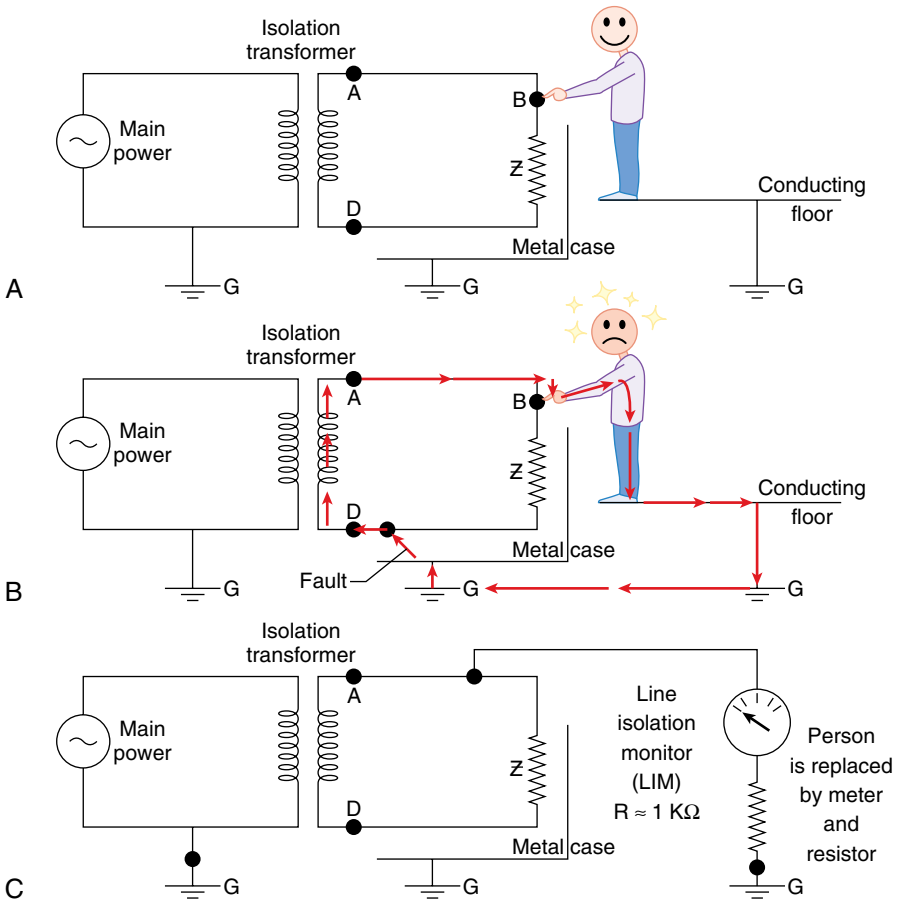

Figure 100-2 **A,** When the transformer output is ungrounded, no electric shock occurs to the person at the right if an isolated power line is touched. **B,** An electric shock does take place if the person touches the circuit after occurrence of the ground fault shown at the *bottom*. In the potentially injurious electricity path, shown in *red*, current comes up from ground through the fault, circles around, and returns to ground by traveling through the person's body. **C,** The person suffering the electric shock has been replaced by a current meter and a large resistance to ground. This is the basis for detection of the "first fault" by the line isolation monitor.

connected to the hospital's electrical ground, and the internal circuitry is connected to the output of the isolation transformer. This safe system is worthy of further discussion.

Let us suppose that mechanical or electrical damage causes concern about the electrical safety of an ECG monitor. Could a failure occur inside the ECG monitor that would place the patient or anesthesiologist in contact with the internal circuitry? If so, would electric current travel through the person from the ECG circuitry to the ground and cause injury or distress? If the ECG circuitry remains isolated from ground, the answer is no.

Figure 100-2A and B show how isolation provides safety. A grounded person is touching the internal circuitry at point B. The isolation transformer supplies current to pathways that connect the two hot leads in the outlet, indicated by points A and D. However, the only way for electric current to get from point A to D is through impedance Z. Because each of the hot points in the wall outlet are not grounded, the person in Figure 100-2B is safe from shock.

Figure 100-2C, however, shows that two inadvertent ground contacts could produce a dangerous situation, especially if one of those contacts is a human being. Suppose that a fault occurs near point D and causes the internal circuitry to come in contact with the external metal case. A dangerous shock would result from touching the circuit at point B. Because of the fault, current could complete a pathway through the person and ground (i.e., from point A to D). It is useful to isolate power lines from ground and know when isolation is compromised by a fault.

Every isolation transformer has an LIM that monitors isolation of the transformer's two power output lines from ground. Figure 100-2C shows how the LIM (an ammeter) replaces the smiling and frowning people in Figure 100-2A and B. When very low amperage is indicated, the LIM verifies that the power output lines of the transformer are isolated from the electrical ground, as in Figure 100-2A. The reality of the LIM connections is different because either of the hot wires could become grounded accidentally. The LIM is actually connected to both sides of the isolated power output (Fig. 100-3) and is set to sound an alarm when either side has an impedance to ground that is less than 25,000 Ω or when the maximum current that a short circuit could

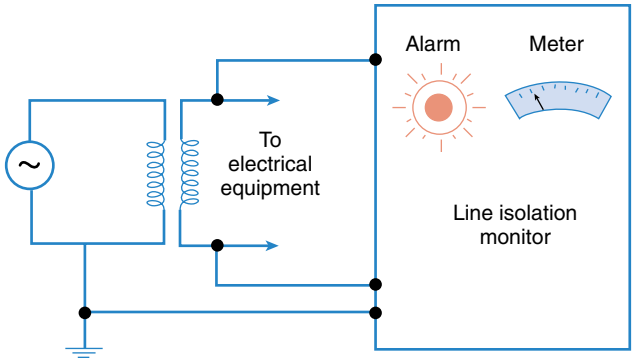

Figure 100-3 Schematic diagram shows the complete connections of the line isolation monitor (LIM). The alarm sounds a "first fault" if either isolated power line has less than 25,000 Ω of impedance, which corresponds to 2 mA or more being drawn through the LIM.

cause exceeds 2 mA. The LIM is insensitive to currents below 2 mA. As discussed later, the LIM provides no protection against microamp currents and microshock.

Many events that occur commonly in operating rooms can produce a short circuit between the power and ground and result in the LIM going off. For example, a short circuit can be produced by dripping or spilling saline, blood, or other conducting liquid into the receptacles of an electrical extension cord that is on the floor near the operating table. For this reason, NFPA and The Joint Commission (TJC) (formerly the Joint Commission on Accreditation of Hospital Organizations) rules have evolved to generally forbid the use of electrical extension cords in operating rooms and other clinical areas. Ideally, every piece of electrical equipment in the operating room is supposed to have a power cord that is safely routed to a wall outlet. In the rare circumstance when an exemption permits the use of an electrical extension cord, the cord must tolerate very high current and have watertight covers that flip into place over unused outlets. If wet receptacles on an extension cord appear to set off an LIM, the extension cord should be changed. If the LIM rings suddenly and unexpectedly or immediately after a new piece of equipment is plugged in, that equipment should be unplugged immediately. If plugging in a piece of equipment repeatedly causes the LIM to sound an alarm, the equipment should not be used until it is checked. Similarly, if use of a particular power outlet repeatedly causes an alarm, it should not be used until it has been checked. When an LIM alarm indicates a first fault (i.e., one power line is grounded), large, potentially damaging currents may subsequently occur through ground connections if there is a second ground fault. The path of damage may include the anesthesiologist, the patient, or an essential piece of equipment. An alarming LIM warns that someone in the operating room may receive an electrical shock or burn when touching connections to electrical equipment.

As noted earlier in the chapter, detection of a first fault in grounding is possible without the use of isolation transformers and LIMs. GFCI outlets provide protection against a first fault. However, they provide protection by suddenly shutting off all power from the outlet. An advantage of the LIM is that operating room personnel learn about a first fault without losing electric power. A disadvantage of the LIM is its susceptibility to newly developed artifactual causes of alarm. Certain devices used in operating rooms emit electrical radiation, intentionally or incidentally, that falsely causes LIMs to sound an alarm. Such devices include instruments that generate ultrasonic sound waves for disintegration of tumor and surgical navigation systems for stereotaxic surgery or anatomic localization, such as STEALTH and BRAINLAB. These systems use electromagnetic waves to track fiducial markers attached to patients so that locations on the patient can be linked to locations on three-dimensional magnetic resonance imaging (MRI) and computed tomography scans.

Capacitive Coupling

The direct connection of two circuit elements by a wire or resistor is known as resistive coupling. It is the easiest type of coupling for an anesthesiologist to recognize and understand. The connection is visible and the effects of the connection are apparent for circuits carrying DC or AC at all frequencies. More subtle and abstract is the concept of capacitive coupling, which applies only

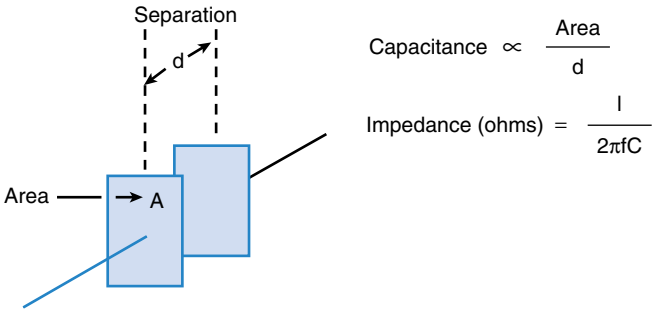

Figure 100-4 Schematic diagram of a parallel-plate capacitor. C, Capacitance in farads; f, frequency of alternating current.

to AC currents. This concept is relevant to anesthesiologists because it can account for electrical connections being present at high current frequencies. If the alarm of an LIM goes off only when the electrosurgical electrode delivers high-frequency current to the patient, the dangerous pathway to the ground may be caused by capacitive coupling, and there may be some power outlets that are safe for low-frequency currents but not for high-frequency currents. Grounding pads, connections to electrical plugs, and equipment may need to be separated even farther from each other before the problem is remedied. The rationale follows directly from the basic principles governing capacitive coupling.

The parallel-plate capacitor (Fig. 100-4) is a circuit element that permits temporary storage of electrical charge and the passage of AC. Parallel-plate capacitors, however, do not permit the passage of DC. The electrical impedance of an object is quantified by the total number of ohms that it has for obstructing AC or DC. This concept, which is a generalization of electrical resistance, permits frequency-dependent assignment of ohms to all circuit elements: capacitors, inductors, and resistors. For capacitors, the ohmic calculation is done with a simple formula. The impedance (Z, in ohms) of a pure parallel-plate capacitor is a function of the AC frequency (f):

$$Z = \frac{1}{2\pi fC}$$

In this instance, capacitance (C, in farads) is directly proportional to the area of the capacitor plates and inversely proportional to the space between the plates. As frequency (f) increases, impedance to the flow of current decreases. For DC, f equals 0, and impedance becomes infinitely large.

At very high frequencies, capacitive coupling to the ground occurs through fewer ohms of impedance than at low frequencies. Because any two conducting objects in a room have surface area and an average distance of separation, they form a kind of capacitor. Any two objects have a capacitive coupling, which means that each of the two output lines of an isolation transformer is always coupled to the ground at AC frequencies.

Although such capacitive coupling is usually insignificant, it can sometimes be significant at frequencies of 60 cycles/sec (i.e., 60 Hz). More commonly, capacitive coupling becomes a problem during electrosurgery performed at higher frequencies, typically hundreds to thousands of kilocycles per second. Capacitive coupling, which lets high-frequency currents pass easily, is commonly used by manufacturers in two connections: between the electrosurgical unit and the electrosurgical pencil (i.e., cutting or coagu-

lation tip) and between the electrosurgical unit and the large-area "grounding pad" that attaches to the patient. The formal term for this large-area conducting pad is *dispersive electrode*. Capacitive coupling gives high-frequency electrosurgery currents a low-impedance path to and from the patient. At the same time, by presenting high-impedance paths at low frequencies, capacitive coupling prevents the electrosurgical pencil and the large-area conducting pad from participating in dangerous low-frequency grounding of the patient.

Capacitive coupling in an electrosurgical unit might have prevented a serious burn caused by the DC of a 9.5-V battery within an anesthesiologist's damaged nerve stimulator.[9] An older electrosurgical unit was used in that case, and it was not capacitively coupled to the large-area grounding pad on the patient. The damaged nerve stimulator had a connection to the ground contact that permitted completion of a DC circuit (i.e., the patient through the faulty connection to ground and then ground through the large-area pad back to the patient). The DC persisted throughout the case, even when the stimulator was not pulsing. In laparoscopic and endoscopic surgery, it is important for surgeons to avoid unwanted capacitive coupling between the unipolar cautery tool and neighboring metal conductors such as trocar cannulas. Stray currents from unwanted capacitive coupling can involve and injure organs such as the bile duct and bowel.[21,22] Anesthesiologists need to be aware of such potential surgical complications, particularly if they may be erroneously attributed to anesthesia.

Capacitive coupling can be responsible for severe patient burns from conventional pulse oximetry (with nonfiberoptic cable) in patients anesthetized for MRI.[23-25] However, the possibility of being burned by a faulty pulse oximeter probe exists independently of capacitive coupling or radiofrequency currents induced by the MRI environment.[26,27] In the setting for such a burn, the patient is external to a malfunctioning electrical circuit that causes the probe (i.e., the unit that contains the photodiode and attaches to the patient) to overheat and burn tissue. Such a catastrophe can be caused by connecting the wrong kind of probe (e.g., one from another type of unit) to an oximeter console.

It has long been known that a perfectly safe conventional pulse oximeter (with nonfiberoptic cable) can be transformed into a dangerous, burn-causing device if it is attached to a patient being scanned in an MRI magnet. The problem arises from magnetic and electric fields that oscillate at megahertz frequencies (in radiofrequency coils) and at kilohertz frequencies (in gradient coils) during acquisition of MRI data. Capacitive coupling can connect a patient to wires in a pulse oximeter cable and to metal in a pulse oximeter probe. In such a situation, the patient becomes part of a high-frequency loop circuit, with currents entering and exiting at the points of capacitive coupling, particularly at the site of probe attachment.[28-31] Fortunately, anesthesiologists now know to use only pulse oximeter cables that have long, nonconducting fiberoptic connections between the photogenerating and photodetecting parts. Connections of the console to the cable are outside the magnet, distanced from pulsing MRI coils, and only nonconducting components are connected to the patient in the magnet. The absence of metal or conducting components of the cable or probe attachment eliminates the possibility of patient burns from induced currents during MRI.

Anesthesiologists monitoring patients with pulse oximetry in MRI magnets must use only units that are MRI safe and MRI compatible—those with a long fiberoptic cable as described previously. Severe burns can occur if for some reason the anesthesiologist decided to take a conventional pulse oximeter from an operating room to the MRI suite and attach it to a patient in an MRI magnet.

Electrical Shock

Macroshock

Macroshock refers to disturbances in neural or muscular function, or both, caused by the application of high voltage or current. Problems can arise if macroshocks occur near the heart, as in a fatal case when a patient's ECG leads were accidentally attached to a power cord.[10] However, macroshock can also cause injury if contact is made at locations remote from the heart.

If someone's hand or arm accidentally touches a voltage terminal, the response to electric current flowing through the arm will depend on the amplitude and frequency of the current. Sensation of a 60-cycle current occurs at approximately 300 μA, and pain occurs at approximately 1 mA. If the current exceeds a certain value, called the let-go current, the person is unable to release objects.[32] The value of the let-go current varies with frequency and among individuals. Figure 100-5 shows the range of average values as a function of AC frequency. The 50- and 60-cycle/sec currents have the lowest values and are therefore the most dangerous. The response of cardiac muscle to electroshock also depends on frequency. Electric current is more important than voltage when issues of safety arise. Table 100-1 indicates the physiologic responses to increasing total-body current.

Continuous, total-body currents that reach 0.1 to 2.5 A (approximately 10 times the let-go value) can cause ventricular fibrillation. The electric current generated by one pulse of an implanted cardiac pacemaker ranges from 0.1 to 50 μA. Only a small part of the total-body current needs to pass through the heart to affect cardiac function. An electrosurgical unit generates

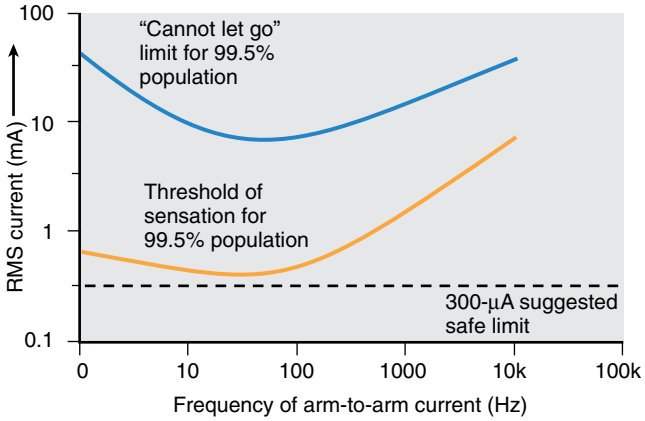

Figure 100-5 The response to electric current flowing through an arm when the hand accidentally touches a voltage terminal depends on the amplitude and the frequency of the current. Sensation of a 60-cycle current occurs at approximately 300 μA, and pain occurs at approximately 1 mA. If the current exceeds a certain value, called the "let go" current, the person is unable to release objects. The value of the let-go current varies with frequency and among individuals. RMS, root-mean-square average.

Table 100-1 Average Effects on Humans of 60-Hz Currents Applied at Body Surface and Passing through the Trunk

Current (mA) for 1-Second Contact	Effect
1	Threshold of perception
5	Accepted as maximum harmless current intensity
10-20	"Let-go" value is exceeded; sustained muscle contraction is next
50-100	Pain; possible fainting, exhaustion, mechanical injury; heart and respiratory function continue
100-2500	Ventricular fibrillation; respiratory center intact
≥6000	Sustained myocardial contraction followed by normal rhythm; temporary respiratory paralysis; burns if the current density is high (usually if current >100 mA/cm^2)

Adapted from Bruner JMR: Hazards of electrical apparatus. Anesthesiology 28:396, 1967.

so much power that it can induce microshock currents when it is used near implanted pacemaker wires. However, thanks to compliance with the safe grounding practices described earlier, the last convincing report of ventricular fibrillation induced by electrosurgery occurred in 1968.[33]

Defibrillation is often based on the same principle—that the skin is a good electrical insulator that requires large electric fields at its surface for the production of small electric fields internally. A jolt of 360 watt-seconds (or joules) during closed-chest cardiopulmonary resuscitation delivers energy to the body comparable to that produced by a large-caliber handgun. (A 0.45-caliber bullet weighs 250 grains and has a muzzle velocity of 860 ft/sec when fired. This corresponds to an energy of approximately 540 watt-seconds.) Only a very small portion of a defibrillator's energy dose is needed to depolarize the heart.

Microshock

The passage of even small amounts of electric current through the body can interfere with normal functioning of muscles and nerves. *Microshock* refers to the direct application of very low voltage or current to the heart, often intentionally, by means of external or internal cardiac pacemaker electrodes. Inadvertent microshock, however, is dangerous because it can produce ventricular fibrillation. Deaths from accidental microshock were caused by a faulty endoscope and by faulty dialysis equipment.[9,34] Before 1980, arterial and central venous pressure transducers were a potential source of microshock because they brought electrodes very close to heparinized saline in contact with the intravascular compartment.[35,36] However, in 1982, miniature disposable pressure transducers appeared that could be powered and operated with low-voltage telephone cables. They are now used exclusively, and their safety with respect to microshock has been demonstrated by years of frequent use without reported complications. Such systems, however, are vulnerable to more subtle dangers, as was reported when a faulty cable connection permitted precision pressure tracings but caused a substantially lower pressure reading.[37]

Electric current is the most appropriate variable to address when setting safety limits. Because investigators have reported that electric current passing through the human heart needs to be at least 50 μA before ventricular fibrillation occurs,[32,38,39] the American National Standards Institute (ANSI), on December 2, 1993, set 10 μA as the maximum leakage of current allowable through electrodes or catheters contacting the heart. This amount of current is considerably smaller than the peak electric current generated by an implanted pacemaker during a single pulse (0.1 to 10 μA). Because 2 mA is the LIM warning level, the LIM does not provide protection against microshock hazards.

ECG monitoring electrodes are electrically isolated from power circuits in the monitor by an isolation transformer in the main unit, a second level of isolation. However, an anesthesiologist who wishes to perform intravenous or intracardiac ECG monitoring, as occurs during p-wave guided brachial placement of a central venous pressure catheter, should have qualified personnel check the ECG monitor for current leaks. In some ECG and electroencephalographic (EEG) systems, electrode signals from the patient are translated into optical signals by a battery-powered amplifier with a photodiode output that is optically coupled to the main ECG or EEG unit, an even more thorough second level of isolation.

Endovascular procedures performed by interventional neuroradiologists include the placement of procoagulant coils inside certain types of intracranial aneurysms. The coils are placed directly in aneurysms with a considerable depth and a narrow neck. However, when the aneurysm has a wide entrance and a short depth, concern is high that a loose coil could get carried away and act as a thrombus wherever it lodged. Therefore, in such cases a detachable coil is generally used to completely occlude the unfilled region. After being convinced of the coil's location and stability, the angiographer sends a short electrical pulse through the coil, as though it were a unipolar surgical knife, which causes detachment at a known location. Although anesthesiologists should be aware of potential electrical hazards that come with new techniques,[40] they should feel comfortable about electrical issues in detachable coils inasmuch as they do not cause macroshock or microshock.

Electrosurgery

Most concerns with electrical safety in the operating room arise from the use of electrosurgical units because they are capable of causing electrical shock, burns, explosions, arrhythmias, and disturbances in pacemaker functioning.[41] Electrosurgical units operate at frequencies of approximately 300,000 to 2,000,000 cycles/sec (300 kHz to 2 MHz) to minimize the likelihood of ventricular fibrillation. During electrosurgery, high currents enter the patient through a small-area surface electrode at the tip of the cutting tool. The combination of high resistance (R), which is attributable to the small area, and high current (I) causes local tissue heating proportional to I^2R, which produces cutting or coagulation. The tip of the electrode is also designed to produce lower current densities (low I^2R) at points farther than a few millimeters from the electrode tip. Figure 100-6 shows fanning out of the electric current. Electrosurgery is therefore a form of highly controlled localized burning of tissue.

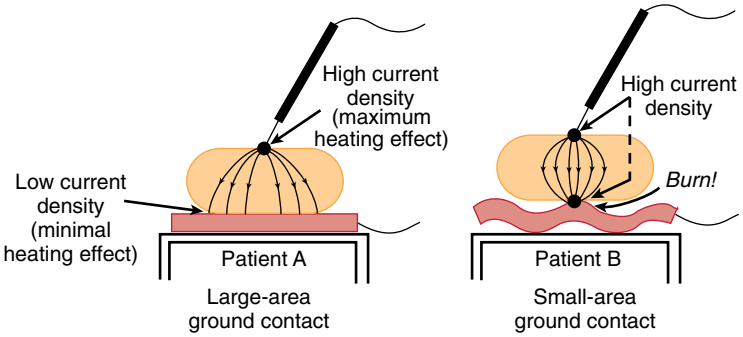

Figure 100-6 Flow of electric current through the body when small-area or large-area grounding pads are used.

Concern about suffering an unwanted electrosurgical burn is a legitimate issue for patients with metal jewelry that pierces the body, such as umbilical rings, nipple rings, earrings, tongue studs, etc. Obviously the best solution is to remove all metal jewelry prior to surgery, and this is highly recommended. However, there are times when removal of metal jewelry is cumbersome, burdensome, inconvenient, or simply unwanted by the patient. In such instances, it is reasonable to leave the jewelry in place if the site of electrosurgery is far from the jewelry, and if the jewelry is not directly within the path of the electrical current that travels from the cutting electrode to the grounding pad. For example, a nipple ring should be removed if there is surgery on the breast with the nipple, and if a nipple ring is allowed to remain on the opposite breast, the grounding pad should not also be on the patient's opposite side. We have just mentioned that in the case of no metal jewelry, electrical current fans out rapidly as it leaves the cutting electrode. The concern with metal jewelry is that it might re-concentrate electrical current that passes near it, and thereby cause a burn. Thus metal jewelry that is left in contact with the skin should be held with tape in as large a contact area as possible. For example, a metal umbilical ring would be taped flat against the abdomen. If instead of a grounding pad there is use of a capacitive coupled return electrode, all metal jewelry should be removed. Because all metal objects have a surface area that can form capacitive coupling with a capacitive coupled electrode, its use in certain circumstances can dangerously increase the risk of burns.

Because there is often smoke where there is fire, concern has been expressed regarding the safety of inhaling smoke from electrocautery. One group, assisted by the National Institute of Occupational Safety and Health, used the Ames test to examine the potential mutagenicity of electrocautery smoke collected during breast surgery.[42] Although the compounds collected were mutagenic, it is not known whether electrocautery smoke represents a serious health risk to operating room personnel. Nevertheless, the study recommended that surgeons minimize the production of electrocautery smoke and exposure of human beings to the smoke.

Because there is often fire where there is smoke, it is also important that nonflammable materials be used during electrosurgery. Fires have occurred in operating rooms because highly combustible surgical boundary drapes were placed close to electrosurgical units.[43] The smoke from such fires can contain toxic substances.

From the preceding discussion it is not surprising to find that electrosurgical units are powerful enough to provide excess electric currents capable of causing extensive tissue burns. Surgical patients who become wet with blood, saline, urine, or other conducting fluids can form electrical contacts with the operating table, the ground, or other conductors, including monitoring electrodes and surgical retractors. Such contacts can create potentially dangerous current pathways. For example, current from an electrosurgical unit may enter a patient through the grounding pad and return to the unit through one or more ECG electrodes. In this situation, the electrosurgical unit can provide current that burns the patient but never passes through the tip of the electrosurgical pencil used in the operative procedure.

The dangers of electrosurgery in a wet environment, especially the possibility of establishing ground faults through wet connections, account for the presence of an isolation transformer (and LIM) in modern operating rooms. As noted earlier, GFCI outlets protect against ground faults by causing sudden deprivation of power, whereas isolation transformer setups turn on an LIM alarm instead and thereby permit less disruption. Loss of electric power during cardiac surgery can be a very serious concern, which is one reason why anesthesiologists must know how to hand-crank cardiopulmonary bypass pumps.[44] Desflurane vaporizers require electricity for operation. The NFPA requires first ground fault detectors in operating rooms. However, anesthesiologists, surgical colleagues, and hospital administrators are free to choose GFCIs or isolation transformers with LIMs, whichever best suits local conditions and practices.[19,20]

Unipolar Electrosurgery

It is important to understand the difference between unipolar and bipolar electrosurgery. In both cases the surgeon applies electrodes directly to tissue to produce electric currents that burn and cut or burn and coagulate. In unipolar electrosurgery, the more common of the two, the electric current that enters the patient through one electrode travels throughout the body and is collected outside the surgical field by a large, wide-area, well-jelled grounding pad (i.e., the dispersive electrode). Skin burns can occur if the grounding pad is dry (i.e., most of the conducting gel is gone) or is otherwise in poor contact with the patient. In such situations, the electric current collected by the grounding pad is required to traverse small surface areas, and these inherently have high electrical resistance. Because I^2R can increase substantially at such small areas of grounding pad contact, increases in resistance can lead to electrical burns of the skin.[45] Electrical burns have also occurred at the site of ECG leads when the grounding pad was defective and the leads became an alternative path for returning high-frequency electrosurgery currents.[46,47]

A much more powerful unipolar electrosurgical tool, the argon beam coagulator (ABC), has become popular among surgeons who must cut or coagulate very vascular tissue.[48] Operating room personnel unfamiliar with the design and use of the ABC

can easily mistake it for an argon laser because a well-collimated, brightly colored beam of argon light glows at the tip of the electrosurgical pencil. The glow, which has the same color as light emitted from an argon laser, represents a continuous electrical discharge in a small, flowing column of argon gas having a density that supports electric current. The ABC was developed to solve a problem occurring with metal coagulation or cutting tips. In regions where there is a lot of blood, electrosurgical currents result in adherence of sticky, burned tissue to the tip of the cutting electrode, thus electrically insulating it and making further use impossible until the tissue is scraped off. Surgery must stop while the tip is scraped clean. When large areas of vascular tissue must be traversed (e.g., in hepatic resection or repair of traumatic lacerations of the liver), conventional metal tips become difficult surgical tools. With the ABC, no metal surface is present to attract sticky, burned tissue. The tip of the cutting electrode is a cushion of argon gas that can transmit current so long as it touches tissue.

The anesthesiologist must understand that use of the ABC means that much electrosurgery is taking place and that safety measures are more important than ever. As in conventional electrosurgery, surgical cutting and coagulation with the ABC come from local I^2R heating losses at the point where the electrosurgical pencil is applied—in this case, where the argon gas meets the tissue. ABC operation therefore resembles conventional arc welding. Because the ABC is perhaps the ultimate spark generator, its use illustrates the extent to which we have abandoned one safety concern that was prominent in the days of inflammable anesthetic gases.

Some body locations are never safe for unipolar electrosurgery. This situation is encountered frequently during neurosurgery and in patients with implanted cardiac pacemakers. The solution is bipolar electrosurgery.

Bipolar Electrosurgery

In bipolar electrosurgery, as in unipolar electrosurgery, current enters the patient through one electrode. However, instead of traversing the body to be collected by a dispersive electrode at a site remote from the surgery, injected current is collected millimeters away from the first electrode by a second electrode that appears identical to the first. Bipolar surgery is performed by two pencil-point electrodes arranged at the tips of a forceps. Electric current flows through patient tissue only at the site of surgery, where it is confined to the few millimeters between the electrodes. Bipolar devices are required when electrosurgery is performed on an ovary or a fallopian tube. Several cases of fatal bowel injury have occurred after female sterilization with unipolar devices.[49,50]

Patients with an implanted pacemaker or an automatic implanted cardioverter-defibrillator (AICD) frequently come to the operating room for procedures requiring electrosurgery (see Chapter 43). For such patients, bipolar devices should be used whenever possible. Nevertheless, on rare occasions in such cases, interference with the pacemaker can occur. Regardless of the type of electrosurgery being performed, an AICD should be turned off during surgery because unexpected intraoperative delivery of its 3- to 20-J defibrillation shock could result in injury not only to the patient but also to the surgeon and others near or in contact with the patient. People in contact with the patient at the moment of an AICD's defibrillation shock can also receive a dangerous, painful electrical shock. Placement of a magnet over an AICD turns off its defibrillation feature and converts it to pacemaker mode alone. However, magnet placement does not affect the pacing program of a programmable pacemaker. (All AICDs have pacemaker circuitry.) Zoll pads connecting the patient to an external defibrillator/pacer should be fully operational when the AICD's defibrillator is turned off, with the obvious exception being situations involving "code" resuscitation, such as when an advanced cardiac life support (ACLS) team has defibrillator pads ready for use. If anesthesiologists on ACLS teams arrive at a cardiac arrest situation and find that the patient has an implanted pacing device, they should immediately learn whether the device is an AICD so that precautions such as magnet placement can be taken to avoid shocking the "code blue" team during resuscitation.

Because so many different types of pacemakers are now in use, the plan for avoiding intraoperative pacemaker interference must be based on the details of each particular case.[51,52] In general, the likelihood of interference depends not only on patient factors, such as the type of pacing electrodes (i.e., unipolar or bipolar) and how well the pacemaker circuitry is shielded, but also on surgical factors, such as the proximity of the cutting electrode's discharge and the path of the electric current within the patient. In all such cases, grounding pads should be placed as far away as possible from the pacemaker and its wires. In addition, if possible, the path from the grounding pad to the surgeon's electrosurgical cutting electrode should not traverse the path from the pacemaker circuit to the heart. Because of capacitive coupling, it is potentially possible for electrosurgical noise to either affect the heart directly or disrupt processing by the pacer's program in a programmable pacemaker. Such interference can result in complete heart block and no pacing or in severe tachycardia. Descriptions of incidents can be found in numerous recent reports.[53-57]

Although anesthesiologists should always be prepared to reset a pacemaker to the asynchronous mode (i.e., regular, uninhibited pacing), it is no longer correct to assume that magnet placement always converts a pacemaker to asynchronous mode, which is the mode needed by pacemaker-dependent patients. Because of pacemaker diversity, preoperative consultation with an electrophysiology cardiologist is always appropriate and often essential, as is preoperative assurance that programmable pacemakers have recently been interrogated and found to have no faults and then properly reprogrammed. Although some precautions to take with programmable pacemakers can easily be understood, such as turning off rate-sensing features, consultation can often be the only way for many essential pacemaker details[51,52] to be reviewed by someone with the proper expertise. Most hospitals have a cardiologist on call who can be reached for an immediate electrophysiology consultation.

Finally, the anesthesiologist should be familiar with the use of isoproterenol, a pharmacologic pacer, which should be available on the anesthesiologist's drug cart. Concentrations of 1 μg/mL are appropriate for small bolus injections.

Safe Practice

One approach to safe practice involves having complete, efficient checklists to consult for each concern, such as fire safety or safety

for patients with pacemakers. The anesthesiologist should go through the checklists relevant to every case, just as the pilot and the copilot of a commercial airplane do for air travel. Years ago the word "vigilance" was used more commonly to describe how anesthesiologists' eyes and mind are repeatedly and systematically scanning everything in the operating room. "Vigilance" is now used more appropriately to describe the virtues of sophisticated electronic monitors and alarms in the operating room. However, there are no electronic monitors to direct the anesthesiologist's attention to issues "outside the alarms," to issues related to organization and planning, such as having enough electric power outlets in the operating room to accommodate all the equipment while also avoiding circuit overloads. Limitations of checklists include the danger of "finding only what one looks for and recognizing only what one knows."[58] Even though safe practice is boosted by checklists, anesthesiologists should also always be vigilant for new problems. Thus, the guidelines that the Key Points present should be seen as a minimal summary that directs safe electrical practice, with a natural assumption that many anesthesiologists will add refinements and elaborations.

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101 Environmental Safety Including Chemical Dependency

Key Points

1. Escape of anesthetic vapors into the operating room atmosphere is unavoidable. In the United States, the limits of exposure to atmospheric waste gases are set by NIOSH, which recommends a time-weighted average of 25 ppm for nitrous oxide and a ceiling of 2 ppm for volatile anesthetics.
2. No definitive evidence has shown that trace concentrations of anesthetics in the ambient air of the operating room present a health hazard.
3. Occupational exposure to radiation comes primarily from x-rays scattered by the patient and surrounding equipment. A distance of 6 feet from the patient provides the same protection as 2.5 mm of lead. A distance of 3 feet from the patient is recommended to minimize occupational exposure.
4. Occupational exposure to HIV is most often the result of a percutaneous injury. The risk of transmission is greatest from hollow-bore needles, needles contaminated with visible blood, and a source patient with high viral titer.
5. Post-exposure prophylaxis is recommended after occupational exposure to HIV or hepatitis B virus. The U.S. Public Health Service–recommended guidelines for post-exposure prophylaxis are available on the Centers for Disease Control and Prevention (CDC) website. The National Post-Exposure Prophylaxis Hotline is open 24 hours a day for expert advice (1-888-448-4911).
6. To minimize occupational exposure to blood-borne pathogens, standard precautions should be practiced at all times. The appropriate barrier precautions for anticipated contact with blood or body fluids are published by the CDC. Whenever possible, needleless systems should be used.
7. Sleep deprivation has an adverse effect on physician mood, cognitive function, reaction time, and vigilance. Although it is clear that sleep deprivation and fatigue adversely affect clinical performance, their full impact on patient outcome has not yet been determined.
8. Anesthesiologists are overrepresented in drug treatment centers. The preference for and access to potent opioids contribute to the prevalence of drug addiction among anesthesiologists.
9. The rate of drug-related deaths is more than twice as high in anesthesiologists as internists.
10. Although many recovered anesthesiologists return to the practice of anesthesia, there is a significant relapse rate. The chance of relapse is highest in physicians who become addicted to potent narcotics early in their career. Successful recovery requires a lifelong commitment to treatment. In some cases, a change in specialty is the only solution.

It is impossible to practice anesthesia without exposure to a number of potentially harmful environmental factors. Exposure to inhalation agents, transmissible diseases, and radiation are unavoidable in the operating room environment. Fortunately, the past several decades have produced a number of technical advancements and guidelines that serve to minimize the adverse effects of these occupational exposures. Efficient gas scavenger systems, needle-less systems, protect IVs, and post-exposure prophylaxis (PEP) protocols are now commonplace in contemporary anesthesia practice. But while these measures all serve to minimize occupational exposure and risk, they do not completely eliminate them.

In addition to environmental exposures, the access to potent opioids, the tradition of extended work hours, and the unique role the anesthesiologist plays in critical clinical situations contribute to the anesthesiologist's risk of chemical dependence, fatigue, and emotional distress. This chapter examines the relative risk of each of these environmental and situational hazards and reviews the measures one can take to avoid them. Awareness is essential to safe anesthesia practice.

Waste Gases

Trace amounts of waste gases enter the operating room atmosphere each time an inhaled anesthetic is delivered. Thus it is important to accurately detect, measure, and limit ambient anesthetic levels in order to minimize passive exposure of operating room personnel to waste gases.

Concentrations of waste gases are reported on a volume-per-volume basis in parts per million (ppm). For example, 100% halothane, such as in the saturated vapor above the liquid in a bottle or vaporizer, has a concentration of 1 million ppm. Similarly, 1% halothane represents 10,000 ppm. The National Institute for Occupational Safety and Health (NIOSH) recommends an exposure limit of 25 ppm for nitrous oxide (measured as a time weighted average over the duration of exposure) and a ceiling of 2 ppm for halogenated agents in the ambient air of the operating room.[1] When used in combination with nitrous oxide the ceiling for halogenated agents is reduced to 0.5 ppm.[2] To put these figures into perspective, assuming that 1 mL of a volatile liquid anesthetic produces 200 mL of vapor, that volume of liquid spilled in a closed room measuring 20 by 20 by 9 feet results in a concentration of vapor of nearly 2 ppm. The maximal concentration of halothane recommended by NIOSH is several-fold lower than the lowest concentration that humans can recognize. Only fifty percent of volunteers are able to detect halothane at concentrations as low as 33 ppm. The threshold of perception ranges from less than 3 to more than 100 ppm.[3] If the anesthetic can be smelled, its concentration is well above the maximum recommended level.

Waste nitrous oxide and halogenated anesthetics in the absence of scavenging may approach concentrations as high as 3000 and 50 ppm, respectively.[3] Although the concentration of waste gases can be well controlled with proper scavenging, in practice, the levels recommended by the NIOSH are not consistently met in the routine delivery of anesthesia. Mask inductions, circuit disconnects, the use of laryngeal mask airways and cuffless endotracheal tubes all contribute to operating room contamination. While the exposure to anesthetic gases is more common in pediatric anesthesia where mask inductions and uncuffed endotracheal tubes are the standard of care, the introduction of the laryngeal mask to anesthesia practice has increased operating room exposure to waste gases in adult cases as well. One study of inhaled induction of anesthesia and maintenance with sevoflurane and nitrous oxide in adults resulted in violations of NIOSH standards 50% of the time.[4]

The universal use of scavenging systems can lead to a false sense of security among operating room personnel. Kanmura and colleagues found abnormally high ambient concentrations of N_2O in 402 delivered anesthetics, of which 42% were the result of mask ventilation, 19.2% a disconnected scavenging system, 12.5% a leak around pediatric endotracheal tubes and 11.5% the result of equipment leakage. Although dysfunction of the scavenging system was not the most common cause of ambient contamination, scavenging system disconnects resulted in higher contamination levels than levels resulting from inhaled inductions. Furthermore, all of the scavenging system disconnects in this study were due to human error rather than equipment failure.[5] Because anesthesia machines are not equipped to recognize unconnected scavenging systems, a failure of the system may not be readily apparent. A thorough understanding and diligent maintenance of anesthesia scavenging systems is essential to comply with NIOSH standards and more importantly to minimize operating room exposure.

Simply transferring the patient from the operating room to the PACU does not eliminate the risk of exposure to waste gases, as patients continue to exhale trace amounts of N_2O for 5 to 8 hours after arrival in the PACU.[6] Sessler and Badgwell measured the concentrations of gases at the shoulder (and lapel) of recovery room nurses caring for patients who received inhalation anesthesia during their first hour in the PACU. In this study breathing zone anesthetic concentrations were in excess of NIOSH recommendations in 37% of patients who received isoflurane, 87% of patients who received desflurane and 53% of patients who received N_2O.[7] A more recent but similar study reported a much lower average concentration (3.1 ppm) of N_2O in the breathing zone of recovering patients in a Canadian PACU.[6] These studies demonstrate the importance of proper ventilation in postanesthesia care units. Both groups reported PACU room air exchanges of 8 vols/hr; however, much of the air in the Sessler study was recirculated. Nitrous oxide levels can be reduced to undetectable levels with air exchanges of 20 per hour with 25% of each exchange taken from fresh air.[8]

Although the Occupational Safety and Health Administration (OSHA) does not currently regulate exposure to N_2O and halogenated agents, the agency does provide guidelines designed to minimize workplace exposure. These include the appropriate assembly and monitoring of scavenging systems, detection and correction of machine leaks, and the installation of effective ventilation systems (American Institute of Architects, 2001).[1] In the operating room, the recommended air exchange rate is a minimum of 15 air exchanges per hour with at least 3 air exchanges of outdoor air per hour. In the recovery room at least 6 air changes are required with a minimum of two exchanges of outdoor air per hour. The agency recommends air sampling for anesthetic gases be done on a biannual basis in order to document the extent of worker exposure and the effectiveness of scavenging and ventilation systems.

Health Risks

The possibility that chronic exposure to anesthetic waste gases could result in adverse health effects was first appreciated in the late 1960s when a report of potential harm appeared in the Russian literature. In 1967, Vaisman reported an increased incidence of abortions among female anesthetists. Specifically, this study noted 18 spontaneous abortions in 31 pregnancies.[9] After this initial report a multitude of retrospective studies followed. Of these, three large studies conducted during the mid-1970s in the United States and the United Kingdom all concluded that the prevalence of abortion was substantially higher in female anesthesiologists than in female physicians working outside the operating room. Studies in this era also concluded that the incidence of congenital anomalies in children of male and female anesthesiologists was higher than in the control groups of physicians. In addition to these reproductive effects, meta-analysis of six of these early studies linked the exposure to anesthetic gases to hepatic disease in males[10] and cervical cancer, liver disease, and kidney disease in females.[11]

Subsequently, numerous reports appeared in the literature that criticized these original studies, citing faulty methodology as

a basis for erroneous conclusions; conclusions that were disproved when the data were reanalyzed. Biases may have arisen for many reasons, including inadequate response rates; lack of control for confounding variables, such as age, nutrition, obstetric history, drinking, smoking, exposure to methylmethacrylate, and radiation; lack of quantification of the exposure to anesthetic vapors; losses to follow-up; inappropriate comparison groups; and lack of independent verification of the reported data.[10,12,13] Even the titles of some questionnaires, such as "Effects of Waste Anesthetics on Health" and "Anesthetic Practice and Pregnancy," may have introduced selection and recall bias by stimulating respondents who work with anesthetics to over-report their past experiences.[14,15] Nevertheless, as late as 1997 a meta-analysis of over 19 studies completed between 1984 and 1992 reported an RR of abortion in females exposed to anesthetic gases to be 1.48 (CI 95%) 1.4-1.58.[16]

Given the persistence of this controversy, a Task Force on Trace Anesthetic Gases was convened by the American Society of Anesthesiologists (ASA) Committee on Occupational Health of Operating Room Personnel. The task force analyzed data from all of the available epidemiologic studies at the time and concluded that there was no proof of an association between occupational exposure to waste anesthetic gases and adverse health effects. In addition to the analysis of retrospective studies, their report, published in 1999, cited interim data from the only prospective survey in progress. This study monitored 11,500 female physicians in the United Kingdom and documented occupation, work practices, lifestyle, and medical and obstetric history, as well as hours of exposure and the use of scavenging equipment. This preliminary report showed the incidence of infertility, spontaneous abortion and children with congenital abnormalities in female anesthesiologists to be the same as that in other physicians.[17]

While there is no conclusive evidence to support the claim that current recommended levels of anesthetic waste gases present a health hazard, more recent studies suggest there remains a lingering concern among anesthesiologists. In 2003, Swedish investigators reported an increased incidence of multiple sclerosis among nurse anesthetists and proposed a link between waste gas exposure and the disease.[18] The nurse anesthetists were identified by "an appeal in monthly magazine(s)" and the incidence was based on questionnaires returned by respondents. The authors noted that volatile anesthetics are chemically similar to industrial solvents that have been linked to MS in the past. Once again, this study was soundly criticized for the method of data collection, the fact that dosage of exposure to waste anesthetic was not measured, and lack of control for possible confounding factors.[19] Concern may also have influenced anesthetic practice. In 2007, 59% of members of the Association of Paediatric Anesthetists in the UK reported a decreased use of N_2O over the last 5 years. Fifty-four percent considered occupational exposure to N_2O to be problematic, and 24% indicated that this concern for the possible harmful effect on operating room staff influenced their decision.[20]

Effect on Performance

The NIOSH recommendations arose from a study by Bruce and Bach in which healthy volunteers in the laboratory suffered a decrease in psychomotor performance when exposed to concentrations of nitrous oxide as low as 50 ppm, alone or in combination with 1 ppm of halothane. The same study showed that 25 ppm of nitrous oxide combined with 0.5 ppm of halothane had no effect.[1,21] Subsequently, three other groups of researchers studying volunteers in laboratories have been unable to confirm the findings of Bruce and Bach. The lack of agreement between investigators has led some to conclude "that there is no convincing evidence that anesthetic agents in concentrations equal to those found in unscavenged operating theatres have any effect on the psychomotor performance of healthy subjects in the laboratory."[22] A study conducted on volunteers in an operating room during normal clinical activities in which trace concentrations of nitrous oxide and halothane ranged from 0 to 2300 and 0 to 37 ppm, respectively, also failed to detect impairment in psychomotor performance.[23] These studies suggest there is no definitive cut-off above which psychomotor performance is depressed. Hence occupational limits vary among countries. The standards set by the regulating bodies in Canada, UK and Western Europe are often less stringent than the U.S. (Table 101-1).[3]

Radiation (also see Chapter 79)

The anesthesiologist is routinely exposed to both ionizing and nonionizing electromagnetic radiation. The former is primarily from x-rays and occasionally from radioactive isotopes that release gamma rays, and the latter is from lasers. Less common is contact with ionizing radiation from radioactive isotopes that release either alpha or beta particles. Ionizing radiation has enough energy to create both free radicals and ionized molecules in tissues by driving electrons completely out of their stable orbitals. If the radiation exposure is severe enough, tissues may be destroyed or chromosomal changes may cause malignant growth. Nonionizing radiation may excite electrons to move from the ground state to higher orbitals in molecules, but the electrons

Table 101-1 Occupational Exposure Standards (Time Weighted Average) in ppm in Different Countries with the Dates of Their Introduction

Country	Nitrous Oxide	Halothane	Enflurane	Isoflurane
UK (COSHH, 1996)	100	10	50	50
US (NIOSH, 1977)	25	2	2	2
Denmark (1988)	100	5	2	–
Germany (1995)	100	5	–	–
France (1985)	–	2	–	–
Italy (1989)	100	–	–	–
Netherlands (1989)	25	5	–	–
Norway (1991)	100	5	2	2
Sweden (1993)	100	5	10	10

Adapted from COSHH: The Control of Substances Hazardous to Health Regulations. NIOSH: The National Institute for Occupational Safety and Health. NIOSH confirmed by notice in Federal Register DOCID: fr21fe06-60, 2006, and Barker JP, Abdelatti MO: Anaesthetic pollution. Anaesthesia 52:1077-1083, 1997.

remain in the molecule. In this case, damage to tissues may result from the heat produced by the absorbed radiation.

Ionizing Radiation: X-rays

In the past, exposure to radiation occurred mostly in the operating room with the use of portable fluoroscopy and x-ray machines. Over the past several decades, however, anesthesiologists are increasingly exposed to radiation in remote locations. The advancement of endovascular surgery has led to an explosion of procedures performed in the radiology suite, significantly increasing exposure of anesthesia personnel to ionizing radiation. Because this type of radiation is undetectable with our normal senses, a basic understanding of its features will permit one to keep personal exposure to a minimum. Film badges, although not protective, provide a means of monitoring exposure.

Exposure is commonly reported in units of rem (roentgen equivalents man). A rem is essentially a measure of the biologic damage from radiation adjusted to apply to all tissues.[24] Estimates of radiation exposure from natural sources vary, depending on geographic location. The average in the United States ranges from 80 to 200 millirems (mrem) per year. Natural radiation comes primarily from cosmic rays (about 40 mrem at sea level, with an increase of 10 mrem/1000 ft), as well as from radioactive compounds found in soil, brick, and concrete. For most physicians, the additional radiation from occupational exposure is no greater than that from natural sources. Although the maximum yearly occupational exposure is mandated to be no more than 5 rem, radiology personnel rarely absorb more than 10% of this dose. Their greatest source of exposure is fluoroscopy. During pregnancy, radiograph personnel are advised to limit their exposure to a maximum of 500 mrem.[25]

Occupational exposure to radiation comes primarily from x-rays scattered by the patient and the surrounding equipment. One chest radiograph results in about 25 mrem of exposure to the patient; procedures requiring multiple films occasionally involve more than 1 rem. The amount of radiation generated during fluoroscopy depends on how long the x-ray beam is on. Just as light is reflected from surfaces, x-rays are reflected from the surfaces on which they impinge. This scattering accounts for most occupational exposure. Because the intensity of scattered radiation is inversely proportional to the square of the distance from the source, the best protection is physical separation. A distance of at least 3 feet from the patient is recommended. Six feet of air provides protection the equivalent of 9 inches of concrete or 2.5 mm of lead.[26] Although they are uncomfortable, aprons containing the equivalent of 0.25 to 0.5 mm of lead sheet are effective in blocking most scattered radiation and such devices are recommended to be worn whenever there is an exposure risk.[27] Uncovered areas, such as the lens of the eye, still bear the risk of injury. Intraoperative radiation measurements have shown that exposure is inversely related to the experience of the surgeon and the amount of radiation received by the anesthesiologist during orthopedic procedures is unmeasurable.[28]

Radiation physicists recommend adhering to the ALARA program: radiation exposure should be kept as low as reasonably achievable. The staff of departments of radiology have been extensively schooled in the safety of occupational exposure. Attention to recommended methods of protection will limit exposure to minimal levels.

Nonionizing Radiation: Lasers

Laser is an acronym for light amplification by stimulated emission of radiation. Lasers produce infrared, visible, or ultraviolet light. Although the radiation from lasers is nonionizing, it is potentially unsafe both because of its intensity and because of the matter released from tissues during treatment.

Lasers are used in many surgical specialties, including ophthalmology, plastic surgery, gynecology, neurosurgery, urology, head and neck surgery, and gastrointestinal surgery. A surgical laser produces intense focused electromagnetic radiation to cut or destroy tissues. The radiation is usually infrared or visible light and is created in a "laser medium" that is stimulated by high-intensity energy to release photons of identical wavelength (coherent or monochromatic light) from a laser chamber. The material in the medium (e.g., carbon dioxide, argon) is responsible for the wavelength produced by the laser. Of those in common clinical use, carbon dioxide and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers emit light in the far-infrared and near-infrared wavelengths, respectively; argon and tunable dye lasers produce visible light.[29]

Eye injuries are the greatest risk to personnel working near lasers (see also Chapter 77). Strict standards for protection have been developed on the basis of current understanding but are subject to periodic revision as more experience is gained with these instruments. Either direct exposure or reflected radiation may cause eye damage. Injuries include burns to the cornea and retina, destruction of the macula or optic nerve, and cataract formation. Protective eyewear is designed to filter out the radiation produced by a specific type of laser while still permitting vision. For example, clear plastic lenses block the far-infrared (10.6 μm) radiation from carbon dioxide lasers but provide no protection against the near-infrared (1060 nm) radiation emitted by Nd:YAG lasers. The type of protection provided by a given filter is marked on the frame of the goggles and should be checked before use. Filters that are scratched should not be used. Because certain filters block portions of the visible spectrum, it is prudent to confirm preoperatively that patient monitors can be seen and interpreted correctly with goggles in place. Protective eyewear is recommended for all personnel because reflected radiation can be as hazardous as direct radiation and the intensity is not diminished significantly in the distances traveled in the average operating room.[29]

Until recently, the plume—the vapor and cellular debris produced during laser surgery—was not considered to be harmful. Now, there is concern that the plume may present a significant risk. The median size of particles in plume samples obtained intraoperatively is 0.31 μm in diameter (range, 0.1 to 0.8 μm). Most surgical masks do not trap such small particles.[30] Even after filtration of particles greater than 0.5 μm in diameter, exhaust smoke from tissues treated with a carbon dioxide laser causes pulmonary lesions in laboratory animals. If all particles larger than 0.1 μm are scavenged, no lung damage occurs, thus pointing out the importance of scrupulous removal of the plume.[31] Under experimental conditions, viable bacteria have been recovered from the plume emanating from laser irradiation.[32] Intact DNA from human papillomavirus (HPV) has been detected in the vapor from both laser-treated plantar warts and genital condylomata.[33,34] Human immunodeficiency virus (HIV) proviral DNA has been found in laser smoke produced by vaporizing cultures

of HIV-positive cells. Although these experiments, which used tissue cultures, do not replicate the clinical situation, they stress the importance of strict attention to smoke removal.[35] With adequate evacuation and filtration using equipment specifically designed to scavenge such vapors, it is unlikely that operating room personnel will be contaminated by laser-dispersed HPV DNA.[34] However, a case report has documented the appearance of laryngeal papillomas in a laser surgeon who had previously treated several patients infected with anal condylomata without the benefit of a laser smoke evacuator. Tissue from the surgeon's laryngeal tumors contained HPV DNA types 6 and 11, the same viral types that are commonly harbored by anogenital condylomata. Though not conclusive, these findings suggest that the laryngeal papillomas may have been caused by inhaled virus particles.[36] Hence, it is prudent to scavenge all vaporized debris.

Infection

Transmission of Blood-Borne Pathogens

In March 1992, OSHA issued comprehensive, enforceable standards designed to minimize occupational exposure to blood-borne pathogens. These standards hold the employer responsible for the maintenance of an exposure control plan that protects all health care workers who have potential for contact with blood or blood products. Protective equipment, including gloves, gowns, and eye shields, must be supplied by the employer at no cost to the employee. The standard also provides for hand-washing facilities, proper receptacles for contaminated materials, methods for handling contaminated laundry, and management of waste, among many other things.[37] In the event of an exposure to infected blood or body fluid, health care workers should immediately contact their on-site Occupational Health Department and the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) at 1-888-448-4911 for expert advice. This hotline can be accessed 24 hours a day. Updated guidelines for the management of occupational exposures to blood-borne pathogens are available on the Centers for Disease Control and Prevention (CDC) website at http://www.cdc.gov/mmwr.

Contaminated Percutaneous Injuries

Despite the adoption of standard precautions, contaminated needlestick injuries in health care workers persisted at an unacceptable rate. In 2000, the CDC estimated that more than 380,000 contaminated percutaneous injuries occur in hospital workers in the United States on an annual basis.[38] As a result, Congress revised the blood-borne pathogen standard to include the "Needlestick Safety and Prevention Act" (H.R. S178).[39,40] This act emphasizes the use of safety devices and needle-less systems, in addition to requiring that employers establish an exposure control plan with records documenting each incident. Since the act was signed into law in November 2000, as part of a comprehensive program to prevent the transmission of blood-borne pathogens in health care workers, the National Institute for Occupational Safety and Health has called for the elimination of needle devices when "safe and effective alternatives are available." This recommendation was based on accumulating evidence in the 1990s showing that devices with safety features could reduce needlestick injuries.[41]

The risk of contaminated percutaneous injury correlates with medical specialty and clinical experience.The Duke Health and Safety Surveillance System tracked blood and body fluid (BBF) exposures among 24,425 health care workers over a 4-year period ending in 2002. They reported an average rate of 3.9 percutaneous injuries (PCI) per 100 full-time employees (FTE), with higher rates among persons employed less than 4 years. Anesthesia house staff reported among the highest rates at 19.1 PCI per 100 FTE.[42]

Extended work hours were implicated as a major causative factor in a recent study of PCIs in interns. In this study 498 percutaneous injuries were reported from a total of 17,003 monthly surveys. Whereas lapse in concentration (64%) and fatigue (34%) were the two most commonly reported contributing factors, PCIs were significantly more frequent during extended work hours (OR 1.61) and night time (OR 2.04).[43]

Hepatitis

Viral hepatitis may result from infection with any of several different pathogens. Of greatest interest to the anesthesiologist are hepatitis B (HBV) and C (HCV), the major cause of non-A, non-B (NANB) hepatitis. In contrast to these pathogens, hepatitis A is normally transmitted by the fecal-oral route and almost never by contact with blood. It is usually self-limited and rarely produces significant long-term sequelae. The appearance of antibodies to the virus several weeks after exposure confirms the diagnosis. Treatment is limited to one dose of gamma globulin.[44]

Hepatitis B

In the 1970s the prevalence of HBV infection in health care workers was 10 times higher than that in the general population. In the 1980s, it was estimated that 200 to 300 health care workers would die annually from the effects of hepatitis B. Fortunately, the introduction of an effective vaccine for hepatitis B has dramatically decreased the incidence, morbidity, and mortality of the disease.[45] Infection may be documented serologically by the appearance of HBV surface antigen (HBsAg), HBV surface antibody (anti-HBs), or HBV core antibody (anti-HBe) in serum. Before routine vaccination, the development of covert seropositivity for hepatitis B during residency was common. In a multicenter study involving hospitals in both rural and metropolitan areas, the overall prevalence of serologic indicators for hepatitis B in anesthesiology residents who had received neither hepatitis vaccine nor hepatitis B immune globulin (HBIG) was 17.8% in 267 tested. Most seropositive residents were unaware of having been exposed to hepatitis. No correlation was found between the incidence and geographic location, but the incidence of seropositivity increased in parallel with clinical experience. Thirty percent of residents with more than 11 total years of experience, including their current residency and previous work in other specialties, were seropositive for HBV. Routine use of gloves and attention to obtaining detailed histories from patients did not appear to decrease the incidence of infection.[46]

An estimated 200,000 new cases of HBV infection occur each year. Of these cases, jaundice will develop in 50,000 and 10,000 will require hospitalization. As many as 12,000 to 20,000 annually become asymptomatic carriers of HBsAg, with the total

Table 101-2 Risk of Contracting Hepatitis from Percutaneous Injury Related to Degree of Contact and HBeAg Status of Source

HBeAg Status of Source	Degree of Contact	Risk (%)
HBsAg+/HBeAg+	Clinical hepatitis	22-31
	Seroconversion	37-62
HBsAg+/HBeAg–	Clinical hepatitis	1-6
	Seroconversion	23-37

From CDC: 2001 MMWR US Public Health Service Guidelines for the Management of Occupational Transmission of HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. MMWR 50 (RR11):1-42, 2001.

number of carriers in the United States estimated to be nearly 800,000.[47] It is this group that most threatens nonimmunized anesthesiologists. While the incidence of seroconversion after parenteral inoculation with HBV can be as high as 40%, the rate conversion is proportional to the infectivity of the host and the magnitude of contact with the blood.[48] In addition to the degree of contact, the most recent CDC guidelines report that the risk of contraction of HBV from a percutaneous injury directly correlates the HbeAg status of the source (Table 101-2).[49]

Neither treatment at 60°C for 4 hours nor the use of disinfectants containing phenol or chlorine is sufficient to inactivate the hepatitis B particle with certainty. It remains viable on needles, environmental surfaces, and gloves for longer than 14 days.[50] Because gloves do not guarantee protection from accidental needlestick and because HBV is relatively resistant, accidental contact with live virus may occur in the course of patient management and also during cleaning of equipment.

Active immunization of seronegative health care workers with hepatitis B vaccine is imperative for prophylaxis against infection. The first vaccine was composed of inactivated particles of surface antigen prepared from the sera of HBsAg carriers. Ninety percent of recipients of the vaccine became seropositive and thus were protected against infection.[47] Despite the efficacy and the safety of the early vaccine, in the mid-1980s, substantial numbers of anesthesia personnel refused to be immunized.[46] Some were concerned that the vaccine for hepatitis B was prepared from sera obtained from patients at high risk for HIV. In the late 1980s, the vaccine was synthesized in yeast by the use of recombinant DNA.[51] The current OSHA standard on blood-borne pathogens mandates that employers make vaccination against HBV available at no cost to all employees who have a reasonable chance of exposure to the virus.[37]

Unvaccinated anesthesiologists who suspect HBV exposure with an HBsAg-positive source should be passively immunized with HBIG and begin a series of three injections of hepatitis B vaccine (Table 101-3).[45] The combination of HBIG and HBV vaccine prophylaxis is believed to be 85% to 90% effective, while either treatment alone is 70% to 75% effective.

The PEP protocol for previously vaccinated personnel is dependent upon the person's seroconversion or "responder"status. Nonresponders have mounted an inadequate response to vaccination with a measured serum HBsAg < 10 mIU/mL; while responders have adequate levels, HBsAg > 10 mIU/mL. Evidence of seroconversion in the health care worker eliminates the need for prophylaxis, while nonresponders are treated according to the protocol for unvaccinated workers. If responder status is unknown, the exposed person should be tested for HBs antibody, and if the level is unadequate, treated with HBIG and HBV vaccine (see Table 101-3).

Hepatitis C

HCV is the predominant source of hepatitis from transfusion. Chronic hepatitis develops in more than 85% of hepatitis C infections, with 20% of cases progressing to cirrhosis and 3% to hepatocellular carcinoma. It may also result in the development of a chronic carrier state.[52]

Important discoveries in the diagnosis of HCV were reported in 1989 when a segment of the genome of an NANB

Table 101-3 Recommended Post-exposure Prophylaxis for Exposure to Hepatitis B Virus

Vaccination and Antibody Response Status of Exposed Workers*	Treatment		
	Source HBsAg-Positive	Source HBsAg-Negative	Source Unknown or Not Available for Testing
Unvaccinated	HBIG† × 1 and initiate vaccine series	Initiate HBV vaccine series	Initiate HBV vaccine series
Previously vaccinated			
Known responder‡	No treatment	No treatment	No treatment
Known nonresponder§	HBIG × 1 and initiate revaccination or HBIG × 2‖	No treatment	If known high-risk source, treat as though source were HBsAg positive
Antibody response unknown	Test exposed person for anti-HBs 1. If adequate,‡ no treatment is necessary 2. If inadequate,§ administer HBIG × 1 and vaccine booster	No treatment	Test exposed person for anti-HBs 1. If adequate,‡ no treatment is necessary 2. If inadequate,§ administer vaccine booster and recheck titer in 1-2 mo

*Persons who have previously been infected with HBV are immune to reinfection and do not require postexposure prophylaxis.
†HBIG, 0.06 mL/kg intramuscularly.
‡A responder is a person with adequate levels of serum antibody to HBsAg (e.g., anti-HBs ≥10 mIU/mL).
§A nonresponder is a person with an inadequate response to vaccination (i.e., serum anti-HBs <10 mIU/mL).
‖The option of giving one dose of HBIG and reinitiating the vaccine series is preferred for nonresponders who have not completed a second three-dose vaccine series. For persons who previously completed a second vaccine series but failed to respond, two doses of HBIG are preferred.
Anti-HBs, HBV surface antibody; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.
From U.S. Public Health Service: Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. MMWR Recomm Rep 50(RR-11):1-42, 2001.

virus was isolated, cloned, and designated hepatitis C virus and when an assay for circulating anti-HCV antibodies was developed (see also Chapter 55).[53,54] Like HBV, HCV appears to be transmitted principally by infected blood. Studies using the anti-HCV assay have shown that HCV is responsible for up to 90% of transfusion-related NANB hepatitis.[55] With this assay, some have reported only a 1% to 2% incidence of antibody to HCV in health care workers (similar to that seen in volunteer donors), thus suggesting that HCV is not easily transmitted.[55,56] Reports based on the same assay indicate that transmission of HCV by contaminated needles occurs in less than 4% of these injuries.[57] More sensitive assays for HCV are currently under investigation. One of these assays, detection of HCV RNA by polymerase chain reaction, documented a 10% incidence of HCV infection in health care workers.[58] This method is limited to laboratory investigation, it is not licensed for clinical use, and its accuracy is widely variable.[49] At present, no effective postexposure treatment is available for HCV exposure. Instead, the recommendations for postexposure management are geared toward early recognition and intervention in chronic disease. Health care workers who are exposed to HCV should undergo baseline testing for anti-HCV and alanine aminotransferase activity as soon as possible after the injury, with follow-up testing 3 and 6 months after exposure.[49] Serum immune globulin prophylaxis is of little value because anti-HCV antibodies are not consistently found in production lots of immune globulin.[48]

Acquired Immunodeficiency Syndrome (see also Chapter 55)

Fortunately, HIV is a relatively fragile virus. To put it in perspective, the risk of becoming infected with a needle contaminated with HIV is approximately 0.3% as compared with 3% and 30% respectively for hepatitis C and hepatitis B. With proper attention to cleanliness and care in performing invasive procedures, the likelihood that the disease will develop in an anesthesiologist during the course of patient management is very low.

The human immunodeficiency viruses, HIV-1 and HIV-2, are retroviruses that attach to cells with $CD4^+$ surface antigen (predominantly helper T lymphocytes) and ultimately replicate by integrating virally produced DNA into the nucleus of the host cell.[59]

Initial infection with HIV follows within 2 to 10 weeks of inoculation. It is usually a self-limited, nonspecific, febrile viral syndrome lasting 1 or 2 weeks. An individual is considered to be both infected with HIV and infective if the results of both a serologic screening test, the enzyme-linked immunosorbent assay (ELISA), and a supplemental, more sensitive test, either Western blot or indirect fluorescent antibody, are positive. ELISA tests are relatively easy to perform in a clinical laboratory but may be subject to false-positive results. Supplemental tests are time consuming but necessary for confirmation. Results of the tests become positive within weeks of inoculation, but the median latency for the first opportunistic disease may be as long as 11 years.[59]

Epidemiology of AIDS

The apparent incidence, death rates, and other epidemiologic features of AIDS have been influenced over the years by the methods used to obtain these values. In 1993, the criteria for defining AIDS were expanded from those determined in 1987. Newer criteria included objective laboratory data and illnesses that were not previously used in confirming the diagnosis. With these changes, all HIV-infected patients with $CD4^+$ T-lymphocyte counts of less than 200/μL, as well as those with opportunistic infections, including pulmonary tuberculosis, recurrent pneumonia, and cervical cancer, were defined as having AIDS. The result was an apparent 200% increase in cases of the disease reported in early 1993.[60] At that time, nearly 900,000 persons in the United States were estimated to be infected with HIV. In spite of these methodologic changes, the proportional rate of the annual increase in cases of HIV continued to decline in the late 1990s.[61,62] Despite these overall declines, the incidence of AIDS increased in certain subpopulations, including black men and women and persons born after 1960.[61,62] The surveillance of AIDS in the United States continues to evolve. In January 2000, the surveillance case definition for HIV infection was revised again to include a single definition for adults, adolescents, and children older than 18 months. The revised criteria include positive results or reports of a detectable quantity of HIV nucleic acid or plasma HIV RNA.[63]

Regardless of these epidemiological statistics, health care workers will invariably care for unidentified carriers of the disease at some point during their career. The observation that more than 4% of 2300 patients treated in an urban emergency department had unrecognized HIV infection[64] underlines the need to treat all patients with universal precautions.

AIDS and Health Care Workers

Health care workers account for 5% of cases of AIDS in the United States. Although occupationally related infections have been reported, the vast majority of cases have been attributed to nonvocational contact.[65] By mid-2001, the CDC had documented 57 cases of occupationally acquired HIV infection in the United States.[66] Of these, 48 were due to percutaneous exposure. Of 1746 reported cases of AIDS in physicians, only 6 were directly linked to occupational exposure.

Because there is a latency period between infection with the virus and laboratory confirmation of the virus, health care workers may be unknowingly exposed if contact with the patient occurs during this time. It is reassuring that as late as 2002 there were no documented cases of HIV transmission to a U.S. health care worker from a patient who was in the window period for seroconversion.[67]

Injury from a needle is the most likely route of occupational related HIV infection for anesthesiologists. Of 493 anesthesia personnel surveyed in a multicenter study, 32% reported having been stuck with a contaminated needle at least once in the preceding 12 months. Of those, only half sought treatment.[68] The risk of infection is greater with hollow-bore than with solid needles and is further increased with large-bore needles and deep intramuscular injection.[59] In a study evaluating percutaneous injuries in anesthesia personnel, nearly 90% were from hollow-bore needles, were self-inflicted, most commonly involved the nondominant hand, and were deemed preventable. A significant number of the injuries occurred during disposal of contaminated needles.[69] Although the minimal dose of contaminated blood needed to infect humans is unknown,[70] the likelihood of development of antibodies to HIV is related to the volume of the inoculum and the concentration of viral particles.[45] Consequently, most

seroconversions have been associated with deep intramuscular injection of contaminated blood through large-bore needles.

The theoretical risk for occupational infection in anesthesiologists over a 30-year exposure period has been calculated to be 0.049% for HIV and 0.45% for HCV depending on the infectivity of the patient population.[71]

The CDC reports an overall risk of seroconversion in health care workers after a documented percutaneous exposure to HIV-infected body fluids of about 0.3%. Although seroconversion has been documented after nonintact skin has been in contact with infected blood, the incidence from this route is far lower than from needle injuries.[45]

The risk of transmission of HIV from health care workers to patients, with the exception of errors in technique, is extremely small. No infections were identified in more than 19,000 patients who had been treated by 57 infected health care workers, including 29 dentists, 12 surgeons, and 16 physicians in nonsurgical specialties. The only documented infections have been in 6 of 1100 patients treated by a dentist in Florida.[72]

With proper attention to routine methods of disinfection, sterilization, and housekeeping, the AIDS virus on instruments, surfaces, and laundry can be destroyed. At concentrations of 5 orders of magnitude greater than normally found clinically, HIV may survive for several days after being dried. This situation represents an extreme, however. Several hours of drying generally inactivates 90% to 99% of viable virus. The amount of HIV usually found on contaminated surgical instruments and equipment used in anesthetic management can be killed with "high-level disinfection." Such disinfection involves careful cleaning, followed by exposure either to one of the commercially available germicides or to a 1 : 10 to 1 : 100 dilution of sodium hypochlorite (household bleach). These methods annihilate bacteria and viruses but may not be effective against bacterial spores. If the instruments are to be sterilized, they should be thoroughly cleaned first. Contaminated hospital linen should not be washed or rinsed in the operating room or another patient care area; instead, it should be placed directly in sealed, water-impenetrable bags. It can safely be laundered by normal methods. Infective waste, including secretions, blood, and other body fluids, should be incinerated or autoclaved. Alternatively, large volumes of fluids may be discarded in a sanitary sewer.[73] Personal protection and protection of patients are afforded by standard precautions.

The best defense is a good offense, and there is no substitute for strict adherence to universal precautions. If in spite of these efforts you or a coworker are exposed to HIV, postexposure prophylaxis is available. Because most occupational exposures do not result in HIV transmission, the guidelines for postexposure prophylaxis weigh the relative risk of infection against the potential toxicity of treatment. The relative risk of infection depends on both the type and amount of blood exposure. The risk of transmission is increased by: (1) percutaneous exposure; (2) devices contaminated with visible blood; (3) hollow-bore needles; and (4) high viral titer (i.e., a patient late in the course of the disease). The three classes of antiretroviral agents recommended for prophylactic treatment include nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors. All are associated with a number of toxicities. A basic two-drug regimen is most often recommended, with an expanded three-drug regimen reserved for high-risk exposure (Table 101-4). The U.S. Public Health Service guidelines recommend that clinicians consider known drug resistance in their area or documented drug resistance in the source patient, or both, when selecting a prophylactic protocol.[49,74] The duration of treatment is 4 weeks.

Evaluation for postexposure prophylaxis and baseline HIV testing should be completed within hours of exposure. Prophylaxis should begin as soon as possible, because animal studies show that prophylaxis is less effective if begun more than 24 to

Table 101-4 Recommended HIV Post-exposure Prophylaxis (PEP) for Percutaneous Injuries

	Infection Status of Source				
Exposure Type	**HIV-Positive Class 1***	**HIV-Positive Class 2***	**Source of Unknown HIV Status†**	**Unknown Source‡**	**HIV Negative**
Less severe§	Recommend basic 2-drug PEP	Recommend expanded 3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP‖ for source with HIV risk factors¶	Generally, no PEP warranted; however, consider basic 2-drug PEP‖ in settings where exposure to HIV-infected persons is likely	No PEP warranted
More severe**	Recommend expanded 3-drug PEP	Recommend expanded 3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP‖ for source with HIV risk factors¶	Generally, no PEP warranted; however, consider basic 2-drug PEP‖ in settings where exposure to HIV-infected persons is likely	No PEP warranted

*HIV-positive, class 1—asymptomatic HIV infection or known low viral load (e.g., <1500 RNA copies/mL). HIV-positive, class 2— symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis (PEP) should not be delayed pending expert consultation, and because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

†Source of unknown HIV status (e.g., deceased source person with no samples available for HIV testing).

‡Unknown source (e.g., a needle from a sharps disposal container).

§Less severe (e.g., solid needle and superficial injury).

‖The designation "consider PEP" indicates that PEP is optional and should be based on an individualized decision between the exposed person and the treating clinician.

¶If PEP is offered and taken and the source is later determined to be HIV negative, PEP should be discontinued.

**More severe (e.g., large-bore hollow needle, deep puncture, blood visible on device, or needle used in a patient's artery or vein).

From U.S. Public Health Service: Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. MMWR Recomm Rep 50(RR-11):1-42, 2001.

36 hours after exposure. Because the time to no benefit in humans is unclear, the U.S. Public Health Service advises beginning prophylaxis up to 1 week after exposure. Four weeks of treatment is recommended if tolerated. Regardless of whether postexposure prophylaxis is initiated, follow-up should include counseling and HIV antibody testing at 6 and 12 weeks and again at 6 months after exposure.[74]

There are insufficient data on the efficacy of PEP in health care workers, primarily because seroconversion from occupational exposure in health care workers is rare. A single retrospective study of HIV PEP with ZDV in health care professionals after percutaneous injury showed a risk reduction of 81% (95% CI, 45% to 94%).[75]

Tuberculosis

Tuberculosis, the leading cause of death in the early 20th century, appeared to be steadily decreasing in incidence with the advent of streptomycin in 1946, isoniazid in 1952, and rifampin in 1970. However, in 1985, the incidence in the United States began to climb significantly. Between then and 1990, reported cases increased by 16%, with a 10% increase in 1990 alone. This increase was the largest since national reporting began in 1953.[76] Most cases were from reactivation of old infection in immigrants or in patients whose immune system had been compromised, and many cases involved multidrug-resistant strains of *Mycobacterium tuberculosis*. Epidemic transmission between hospitalized patients and from patients to health care workers also occurred.[77,78] Common to most of these cases was a low index of suspicion for tuberculosis, which was occasionally not confirmed before postmortem examination.[79]

In response to the resurgence of TB in the United States in the mid 1980s, the CDC published new guidelines for the prevention of transmission of TB in 1990. These guidelines were revised throughout the decade; first in 1992, and again in 1994. The 1992 guidelines targeted the prevention of transmission of tuberculosis in the hospital setting, and the 1994 guidelines added recommendations for the management of multidrug-resistant tuberculosis.[80,81] The updated guidelines in the 1990s included a comprehensive program for the prevention of multidrug-resistant tuberculosis in health care facilities.[82] The program places the responsibility for managing prevention of tuberculosis on individual health care facilities rather than requiring identical standards for all hospitals. Paramount are identification and treatment of patients with tuberculosis; development of engineering controls, including isolation rooms, filters, and ventilation; use of personal protective equipment; and implementation of educational programs for health care workers.

Since the implementation of CDC guidelines in the 1990s, the number of new cases of tuberculosis has steadily declined such that the number of cases now being reported is the lowest since 1953, the first year of reporting in the United States.

In 2004, the overall incidence of tuberculosis in the United States was 4.9 cases per 100,000 population. This was down from 8/100,000 reported in 1996. Despite this general decline, there remains a marked geographical variation in incidence. The highest incidence is found in the District of Columbia (14.6/100,000), followed by California (8.3/100,000) and New York (7.1/100,000). Previous studies found the rate to be highest among immigrants (31/100,000), most of whom were from Asia and the Caribbean. The lowest rate of infection is documented in Wyoming (1/100,000), while the highest rates are found in coastal areas of the country.[82] The risk to health care workers correlates with the region in which they practice.

The goal of the CDC is to decrease the rate of TB infection in the United States to less than 1 per million by 2010.[82] Accordingly, the CDC continually updates the guidelines to address the changing face of the disease, in regard to both emerging drug resistance and epidemiology. Acknowledging the success of the earlier guidelines in decreasing the incidence of TB throughout the 1990s, the most recent revision, drafted in 2005, emphasizes the measures needed to prevent another resurgence of the disease. To this end, the scope of the current recommendations are significantly broadened to include health care "settings." The term *health care settings* in this document encompasses all facilities in which health care is delivered, including clinics, correctional facilities, and so on.[82]

Tuberculosis spreads by small (1- to 5-μm) airborne droplets released when a person with pulmonary or laryngeal TB speaks, coughs, sneezes, or sings. The probability of transmission is directly related to the concentration of infectious droplets (up to 600,000 droplets may be expelled with each cough) and the duration of exposure. Droplets can travel up to 3 feet from the source and remain viable and airborne for several days.[76] Not surprisingly, intubation is second only to bronchoscopy as a risk for skin test conversion in health care workers. In healthy persons who have inhaled contaminated droplets, the resulting systemic infection is usually limited by the immune system within 2-10 weeks. In these individuals, the lifetime risk of developing active tuberculosis after infection is approximately 10%. The likelihood is higher in patients with HIV who have a 7% to 10% risk of converting per year.[82]

All health care workers at high risk for exposure to *M. tuberculosis* should be skin-tested at the time of employment. Those whose test results are negative should be retested annually. A positive test in a person who has not tested positive in the past suggests a new infection. A two-step test is recommended in anyone who tests negative more than a year after TB exposure or previous tuberculin testing. This is because latent infection can produce false negative results from waning over time of the delayed-type hypersensitivity response. The first test will "boost" the response, leading to a positive result. The second test, performed 1 to 3 weeks after the first, increases the predictive value of the test.

The commonly used tuberculin skin test (purified protein derivative) provides a qualitative measure of TB infection. A newer quantitative test for TB is now available, but requires a blood sample. This test can identify infection with atypical organisms.[82]

A newly positive skin test requires exclusion of active disease by chest x-ray and clinical evaluation. If TB is diagnosed, treatment according to recommended guidelines should begin immediately. Disease reporting laws generally require notification of local or state health departments within 24 hours. If active disease is excluded, a 6- to 9-month course of drug therapy for latent TB infection should be considered (Table 101-5). Treatment should be managed by a specialist in the area, given the documented liver toxicity of these drug regimens. Risks and benefits must be weighed carefully to identify persons who may not be candidates for prophylactic treatment (i.e., those with a history of excessive alcohol consumption, hepatitis, ESLD). Baseline and

Table 101-5 Standard Drug Regimens for Treatment of Latent TB Infection (LTBI)

Drug	Duration (months)	Interval	Minimum No. of Standard Doses
Isoniazid	9*	Daily	270
		Twice weekly	76
Isoniazid	6	Daily	180
		Twice weekly	52
Rifampin	4	Daily	120
Rifampin/ Pyrazinamide	†	†	†

*Nine months of isoniazid is preferred, but 6 months of isoniazid and 4 months of rifampin are acceptable alternatives.
†Generally should not be offered for treatment of LTBI.
From American Thoracic Society/CDC: Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep 49(RR-06):1, 2000; and Centers for Disease Control and Prevention: Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings. Available at http://www.cdc.gov/mmwR/preview/mmwrhtml/rr5417a1.htm, 2005.

follow up monitoring of aminotransferases are required. Asymptomatic conversion does not preclude the anesthesiologist from working.

OSHA standards to prevent airborne contamination include both environmental controls and respiratory protection. Environmental controls include engineering measures to manage exhaust ventilation and general ventilation. These include air exchange rates, HEPA filtration (high-frequency particulate air filters), and UVGI (irradiation of the air in the upper portion of a room, or within ducts and recirculating units). Respiratory protection requires masks with the ability to filter particles < 1 μm in size with a filter efficiency of 95%, at inspiratory flow rates up to 50 L/min. If worn properly, even with strenuous activity in the work setting, less than 5% of infectious particles will escape filtration. These masks are typically referred to as N95 masks. Essential to proper mask function are tight mask fit so as not to allow entrained air with inspiration, and a clean filter. To this end the NOISH requires the oversight of mask fit and maintenance by the employer.

SARS

SARS is caused by infection with a single-stranded RNA coronavirus, whose origins lie in an animal strain found in rural China. The first known case of SARS was identified in that country in November of 2002, and spread rapidly to Hong Kong, Vietnam, and Singapore, before finally appearing in North America. In all, more than 8000 cases were reported by July 2003. The overall mortality rate is 9.6%, with peak rates of 26.3% to 28% in patients older than 70.[83]

SARS is a clinical diagnosis based on exposure and clinical criteria prior to confirmatory laboratory tests, which are nonspecific and not widely or rapidly available. Initial flulike symptoms include fever, chills, headache, and myalgia that are followed by nonproductive cough (with or without fever). Individuals are not contagious for 4 to 6 days after infection (range 2 to 10 days) when they become symptomatic, and are no longer infective by 10 days after resolution of fever. The virus is transmitted through contact with respiratory secretions or bodily secretions. As with TB, strict environmental regulations are required. Negative pressure rooms, or HEPA filtration with a minimal of 12 air exchanges per hour are needed to decontaminate the atmosphere. Respiratory precautions are the same as with TB. An N95 mask is required. A surgical mask placed over the N95 can trap larger droplets.[83]

Creutzfeldt-Jakob Disease

In February 2004, British investigators published a study in *The Lancet* titled "Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion."[84] This report came on the heels of the first documented case of bovine spongiform encephalopathy, or "mad cow" disease, in the United States. It is only one of a number of studies on transmissible spongiform encephalopathies (TSEs) that have populated the British literature since the mid-1990s when the mad cow epidemic erupted in the United Kingdom.[85-87]

Although transmission of Creutzfeldt-Jakob disease (CJD) is extremely rare, a number of factors combine to make the disease particularly threatening to health care personnel. TSEs result in rapidly progressive and devastating neurologic deterioration and are uniformly fatal. The time from infection to clinical symptoms is a matter of years, during which time the disease may be unknowingly transmitted to others. To date, there is no reliable method to screen blood from an infected patient. Moreover, prions are resistant to the conventional means used to decontaminate medical devices.

TSEs have been transmitted from animal to animal, animal to human, and human to human. Until the mid-1990s, transmission among humans was thought to be dependent on the transmission of neurologic tissue, either by transplantation or by contaminated surgical instruments. In 1995, mad cow disease was linked to a new variant of CJD in England.[88] The new variant (vCJD) is thought to be the result of transmission of bovine spongiform encephalopathy from cattle to humans by the ingestion of infected beef products. Unlike CJD, vCJD is found in lymphoreticular tissue and can theoretically be transmitted by the transfusion of blood or blood products. This section focuses on the possibility of blood-borne transmission of this devastating disease.

Transmission

Pruisner coined the term prion in 1982 to describe the proteinaceous infectious agent responsible for the transmission of scrapie in sheep.[89] The equivalent disease in humans, CJD, was first described in the 1920s as a rapidly progressive dementia followed by ataxia and myoclonus.[90] Subsequent epidemiologic studies have shown that CJD can be sporadic, inherited, or acquired. Kuru is the most exotic example of the acquired form because of its transmission by ritualistic cannibalism among the natives of New Guinea.[90] The first iatrogenic transmission of CJD was documented in 1974. It was the first of three cases of CJD to result from corneal transplantation. Since then, over 300 cases of iatrogenic transmission have been documented in the literature. Most are the result of cadaveric pituitary–derived growth hormone used to treat children of short stature (162 cases). However, transmission by dura mater grafts (136 cases), human gonadotropin

(5 cases), stereotactic electrodes (2 cases), and neurosurgical instruments (4 cases) has been reported.[91]

A number of studies have demonstrated hematologic transmission of TSEs from animal to animal, and several studies have demonstrated transmission of CJD from humans to animals in the laboratory.[86] Whereas CJD is confined to neurologic tissue, the new variant is found in lymphatic tissue, including the tonsils, spleen, thymus, lymph nodes, and appendix.[85,92-94] vCJD resides in lymphatic tissue early in the incubation phase of the disease when the patient is asymptomatic.[85,95,96]

Despite reports of possible transmission of vCJD by blood products, to date there has been no definitive proof of transfusion-related transmission in humans. Even the most recent epidemiologic data are not conclusive.[84] In fact, reassuring evidence suggests that the disease is not transmitted by blood. Such evidence includes four epidemiologic case-control studies in the United States, Japan, and the United Kingdom in which it was found that the percentage of patients with CJD who had received blood transfusions was no higher than the percentage in matched controls.[86] Another study conducted by the CDC and the Red Cross monitored 178 recipients of transfusions from patients in whom CJD later developed; in no recipient did clinical disease develop up to 24 years after transfusion (although many died of other causes early on).[97] Additionally, no increase in the incidence of CJD has been reported in patients whose disease requires numerous transfusions of whole blood or blood products.[86,97]

In 2003, tonsillar biopsy was identified as a way to reliably diagnose vCJD antemortem.[92] The presence of vCJD in tonsillar tissue potentially puts anesthesia caregivers and ear, nose, and throat surgeons at increased risk of occupational exposure when performing routine tonsillectomies. Because of the prolonged incubation period during which infected patients remain asymptomatic, all adenotonsillectomies in the United Kingdom are performed with single-use disposable surgical and anesthesia equipment.[98]

Routine decontamination protocols do not inactivate prions. The proteins are resistant to proteases, and autoclaving alone is not effective. Attempts to clean instruments before autoclaving can result in further fixation of the protein to the instruments. Once the protein is allowed to dry, it becomes even more resistant to decontamination methods. As a result, the World Health Organization has developed guidelines for infection control when caring for patients with suspected CJD:

1. Disposable instruments should be used whenever possible.
2. Reusable surgical instruments should be kept moist until autoclaving.
3. Disinfection with 1N sodium hydroxide is to be used in combination with autoclaving at 134°C.[99]

By spring 2003, 135 cases of vCJD had been verified in the United Kingdom and 1 in the United States.[91] Because of the lack of an effective screen to identify vCJD in asymptomatic persons, the blood donor policy in the United States currently excludes donations from anyone who lived in or visited the United Kingdom for a cumulative period of more than 6 months between 1980 and 1996.[100] The United Kingdom currently imports all plasma for transfusion. All whole blood from U.K. donors is filtered to eliminate white blood cells.[101]

OSHA Standards

Universal Precautions

In the late 1980s, the CDC prepared a series of guidelines for health care workers who have contact with patients or body fluids.[73,102] They were subsequently incorporated into the OSHA standard on occupational exposure to blood-borne pathogens.[37] The recommendations can best be summarized by stating that because no symptoms or signs conclusively reflect the presence of blood-borne pathogens, all patients, blood, and body fluids should be considered potentially infective. The same safeguards should be used for all; hence, the guidelines were given the title "universal precautions."

In 1996, updated guidelines addressed isolation precautions in hospitals including transport and placement of infected patients, design and use of protective gear for medical personnel, equipment used in patient care, linen, laundry, and cleaning of spaces inhabited by infected patients.[103]

Standard Precautions

The guideline is composed of two tiers, standard precautions and transmission-based precautions. Standard precautions merge the principles of universal precautions and body substance isolation to reduce the risk of transmission of pathogens from moist body substances through the use of gloves. Standard precautions should be used during all encounters with patients. Transmission-based precautions are necessary in the management of patients known to be or suspected of being infected or colonized with epidemiologically important pathogens. The isolation methods used depend on the pathogen involved.[103] The following are taken almost verbatim from CDC publications.[37,102,103] Barrier precautions appropriate for the procedure being performed, including gloves, gowns, masks, and eye shields, should be worn when the potential for contact with blood or body fluids is present. Precautions apply to blood, all body fluids, secretions, and excretions except sweat, regardless of whether they contain visible blood; nonintact skin; and mucous membranes. Strict attention should be given to hand washing after gloves are removed, even if there has been no direct contact with blood or fluid. Needles should not be recapped, bent, or broken by hand but instead should be discarded in a puncture-resistant container. Resuscitation equipment that prevents the need for mouth-to-mouth contact should be available. All specimens sent to laboratories should be handled as though they are infected.

Transmission-Based Precautions

Transmission-based precautions should be followed when patients are known to be or are suspected of being infected with highly transmissible or epidemiologically important pathogens. These precautions are based on the properties of specific pathogens and are to be used in addition to standard precautions.

1. Airborne precautions are to be used when transmission of small particles or droplets (< 5 μm) is likely. Because these particles can be carried for long distances, special filtration and air handling are necessary. Diseases in this category include measles, varicella, and tuberculosis.

2. Droplet precautions apply to diseases transmitted by large particles (> 5 μm). Because of their size and because the droplets do not remain suspended in air, transmission is limited to short distances; a meter or less is the norm. Examples are invasive *Haemophilus influenzae* type b meningitis and epiglottitis, *Mycoplasma pneumoniae* pneumonia, streptococcal pharyngitis, and rubella.
3. Contact precautions apply to direct skin-to-skin contact, including hands. Indirect contact may also occur if surfaces in an infected patient's environment are contaminated. Included are colonies of antibiotic-resistant organisms, hepatitis A virus, herpes simplex virus, viral conjunctivitis, and major abscesses.[103]

Latex Allergy

Since 1992, health care workers who come in contact with infectious materials have been required to use barrier precautions, including protective gloves.[37] Coincidental with this mandate has been a progressively increasing number of allergic reactions to latex-containing products, especially in health care workers. Responses may be limited to irritant contact dermatitis, a delayed type IV reaction mediated by T cells, or they may be manifested by more serious IgE-mediated type I reactions. The latter include contact urticaria, rhinitis, conjunctivitis, asthma, and occasionally, full-blown anaphylactic shock.[104]

The prevalence appears to be more frequent in persons who have regular contact with latex-containing products. One report indicated that nearly 16% of the staff of a single anesthesia department had positive skin test results to latex, although of those tested, respiratory changes during work hours developed in far fewer.[105] Allergic responses to latex are also associated with a history of atopy and with allergies to certain foods such as avocado, potato, banana, tomato, chestnuts, kiwi fruit, and papaya. In some individuals, such a severe sensitivity developed that they are no longer able to work in areas containing airborne latex particles or to eat food that has come in contact with latex.

NIOSH has developed recommendations for the prevention of latex allergies as they currently exist. These recommendations include protection of workers from undue exposure to latex, hand washing after removing gloves, and educational programs for hospital workers.[106] Modifications of manufacturing processes for latex products, more accurate methods to assess allergies to latex, and perhaps the development of substitutes are additional goals of the recommendations. Up-to-date information concerning this dynamic area of interest is available on several Internet web sites.

Fatigue

Long and grueling work hours are a time-honored tradition in medical practice, especially for physicians in training. Although medical culture has historically considered overwork a virtue, this section will address the cultural evolution set into motion more than 20 years ago in response to the case of Libby Zion, an 18-year-old college freshman.[107,108] In March 1984, Libby Zion was taken to New York Hospital by her parents with a high fever, dehydration, and chills. She was admitted to the general medicine ward for observation. She was never examined by an attending physician; instead, she was cared for by an intern and a junior resident, both of whom had been up for 18 hours at the time of her admission. Throughout the night she became increasingly delirious and was placed in physical restraints without an interim examination by a physician. By morning, she was dead.

Over time Libby's death has been attributed to the inexperience and fatigue of resident physicians who lacked the direct supervision of an attending physician. The Bell Commission appointed to investigate the case cited inadequate supervision as the root cause of the outcome; a grand jury investigating the incident blamed too great a work assignment. At the time, neither body cited lack of sleep or long work hours as the primary cause of the incident. However, since Libby's death, addressing extended work hours and sleep deprivation have become central to the effort of the medical community to reduce medical errors.[109]

Fatigue and Clinical Performance

Well-defined periods of vulnerability to sleep have been identified in humans. The major peak occurs between 2 and 7 AM, and a smaller peak occurs in the midafternoon.[110] These peaks appear to be enhanced by irregular work schedules and sleep disruption, and they may also contribute to diurnal variation in the frequency of mishaps. For example, single-occupant motor vehicle accidents occur with alarming regularity in the early morning. Their timing is attributed in part to this cycle. Similar relationships have been observed in the timing of catastrophic industrial accidents. The nuclear reactor accidents at Three Mile Island, Chernobyl, and two other sites in the United States all began between 1 and 5 AM. Human error was a significant factor in each mishap. Critical errors in judgment involving the Challenger space shuttle accident were made in the early morning hours by personnel working irregular shifts. Again, human error was a contributing element. Although none of these accidents can be conclusively attributed to sleep-related processes, all involved a lack of proper response by well-trained personnel working to the best of their abilities at the time of the accident.[111] On the basis of these observations, the Committee on Catastrophes, Sleep, and Public Policy of the Association of Professional Sleep Societies has made the following recommendations:

1. Management should be made aware that performance errors are more common between 1 and 8 am.
2. Programs should be developed to identify signs of sleep-related error.
3. Because inadequate sleep or irregular sleep patterns enhance the tendency for error, work hours should be limited to permit adequate sleep.[111]

Despite mounting evidence regarding the detrimental effects of sleep deprivation on work performance, altered patterns of sleep continue to be a way of life for anesthesiologists.[112] Numerous studies have attempted to quantify the consequences of sleep deprivation on the practice of medicine. Many of these early studies measure clinical surrogates such as cognitive function, dexterity, and vigilance, whereas others focus on the effect of sleep deprivation and fatigue on physician well-being. Few have attempted to measure a direct effect on patient care.[113-115]

The chronic fatigue of being on call every third or fourth night has been shown to have a negative impact on the cognitive

function of university house staff on standardized tests.[116] In the practice of anesthesia, sleep deprivation may have subtle effects on vigilance in the operating room and may contribute to critical incidents.[117] However, when patient simulation was used to study the effects of sleep deprivation on the psychomotor and clinical performance of anesthesia residents, psychomotor performance and mood were found to suffer, whereas clinical performance did not.[118] This lack of correlation between psychomotor and cognitive testing and clinical performance has been noted in the surgical literature also.[119,120]

Although historically it has been difficult to link clinical performance with a documented decrease in cognitive and psychomotor function, there is accumulating evidence that fatigue does affect clinical outcome. For instance, resident physicians were found to make fewer medication errors after their work hours were adjusted to minimize sleep deprivation and fatigue. This study in a university-affiliated Veterans Affairs Medical Center also demonstrated a decrease in the length of patient stay and the number of laboratory tests ordered.[121] In another survey of 225 physicians, 48.8% blamed tiredness and 19.5% blamed the pressure of overwork to be a significant cause of clinical mistakes and suboptimal patient care.[122]

Regulation of Resident Work Hours

The sensationalism of the Libby Zion case has significantly influenced how medicine will be practiced in the future. The facts of the case suggest that insufficient attending physician supervision and excessive patient workload were major contributors to the adverse outcome. Subsequent reviews cited resident fatigue and sleep deprivation as contributing factors. As a result, in 1989 the state of New York limited resident work hours.[123] In July 2003, the Accreditation Council for Graduate Medical Education (ACGME) adopted similar resident work hour limitations for all accredited residency programs. The restrictions on resident duty hours for each of the ACGME-accredited specialties can be found at ftp://www.acgme.org/new/dutyhrequirem.pdf.

Although limitation of physician work hours is here to stay, some in the profession worry that patient care will suffer as a result. They fear that "shift work mentality," combined with increased transfer of patient care, will result in decreased professionalism and continuity of care. Although early studies suggest that patient care suffers from a discontinuity of care, recent studies suggest that limiting work hours may in fact decrease medical errors. In 2004 companion papers in the New England Journal of Medicine documented both fewer attentional failures and medical errors when intern work hours were reduced from 80 to 60 hours per week.[124,125] In an effort to determine the effect of work hour regulations on clinical outcome, two large-scale nationwide multicenter studies measured patient mortality within 30 days of hospital admission both two years before and after the rules went into effect in July of 2003.[126,127] They compared death rates between hospitals with a large number of residents (thought to be most affected by the rule change) to those with few residents. While they found no difference in mortality after the regulations went into effect among millions of Medicare recipients in both more and less teaching-intensive hospitals, a smaller scale VA study did suggest an improvement in patient outcome in a subset of medical patients. So while it is clear that sleep deprivation, overwork, and fatigue contribute to medical errors, patient outcome will depend on a delicate balance between discontinuity of care and the effects of fatigue on medical judgment.[128-131]

Physician Well-Being

Sleep deprivation has been shown to have an impact on physician well-being. The most obvious consequence of sleep deprivation on physician well-being is the well documented increased frequency of automobile accidents in post-call house staff.[132-134] More recent data indicate that percutaneous injury correlates with nighttime shifts and duration of time at work. Less obvious is the effect of sleep deprivation on physician mood. Interns in the United States report an increased incidence of fatigue and depression after a night on call,[135] and their incidence of major depression has been shown to be higher than that expected in an equivalent age group in the general population.[136] A study of house officers showed that sleep deprivation resulted in an adverse effect on mood, as well as cognitive testing of vigilance and reaction time.[137] Overwork played a significant role in the depressive illness suffered by 28% of preregistration house officers in Great Britain.[122,138]

Although significant attention has been placed on eliminating fatigue in resident physicians, inadequate supervision has yet to be vigorously addressed, and it continues to be a source of stress among physicians in training. When asked to describe a particularly stressful incident in their preregistration year, the number one stressor identified by house officers in the United Kingdom was the lack of supervision by superiors in situations where they were forced to take responsibility beyond their experience. Not surprisingly, these events occurred mostly at night. Only a small minority of house officers attributed stressful situations to fatigue alone, but fatigue together with work intensity combined to make "overwork" a significant factor.[139]

Additional Stressors

Stress in the workplace continues beyond the residency years. In a study conducted in Great Britain, the most significant source of stress for those beyond their training years was lack of control of circumstances at work.[140] Specific causes included professional relationships (especially with surgeons), work overload, threats of litigation, peer review, and increasing administrative responsibilities. It is not surprising, then, that a subsequent survey of retired members of the ASA identified similar stressors. Difficult anesthetic cases, the threat of professional liability, and the stress of night call were all considered to be significant causes of stress.[140]

Perhaps more than any other medical specialty, the practice of anesthesia requires uninterrupted vigilance with immediate reaction to life-threatening situations. An inappropriate response can prove to be acutely fatal to an otherwise healthy patient. It is reasonable, then, to ask whether the day-to-day practice of anesthesia produces episodes of significant physiologic stress in the practitioner. Studies to date do not support this hypothesis. In an investigation of 38 anesthesiologists over the course of 203 anesthetics, clinically significant changes in physiologic stress as measured by changes in heart rate, blood pressure, and cortisol levels could not be documented.[141]

Management of stress is rarely addressed in medical school or in continuing medical education seminars for anesthesiologists, but it should be. Stress is a universal phenomenon to which no one is immune. Vital to our interactions with others is the ability to recognize stressed behavior, not only in them but also in ourselves. Healthy means of coping with stress include an ability to communicate, appropriate assertiveness, interactive management of conflicts, adequate time with family, and time for recreational pastimes totally unrelated to professional activities.[142]

Chemical Dependence

Drug addiction has long been an occupational hazard in the practice of medicine (see also Chapters 27 and 30). In the late 19th century, Merck and Company began producing cocaine for commercial use. It was initially touted by Freud and others as a cure for alcoholism and morphine addiction, as well as an agent to increase endurance.[143] In 1884, Sir William Halstead successfully injected cocaine into a sensory nerve trunk to create the first regional anesthetic, a discovery that not only revolutionized the practice of surgery but also marked the beginning of his lifelong struggle with drug addiction.[144]

William Halstead attended Yale University and was captain of the football team before enrolling in the Columbia University College of Physicians and Surgeons. After graduation in 1877, he studied medicine abroad before returning to the United States, where he eventually became one of the founding members of the Johns Hopkins University School of Medicine. His contributions to modern-day surgery are legendary and include the introduction of antiseptic technique, surgical gloves, and vascular clamps into surgical practice. He performed the first total mastectomy for cancer and described the first hernia repair. Throughout his career, Halstead was addicted to morphine. At the peak of his career he is said to have used in excess of 180 mg/day, and despite numerous attempts to quit, he was believed to be addicted until the time of his death in 1922. By all accounts, Halstead became addicted to morphine in his effort to cure his addiction to cocaine.[144]

William Halstead's addiction to cocaine and morphine are mentioned here in order to illustrate the following characteristics that are often associated with drug addiction in anesthesiologists today. He was academically accomplished, his addiction began early in his career with an element of curiosity, he was a polydrug abuser, and he had easy access to potent drugs. His colleagues at work were the last to know.

The abuse potential of the psychotropic drugs used in the practice of anesthesia is well documented. Potent psychoactive drugs are readily available and familiar to anesthesiologists in the course of their daily practice. Even the inhaled drugs nitrous oxide and vapor anesthetics pose an abuse potential to health care workers with easy access to them. Zacny and Galinkin reported a case of an Air Force pharmacist court-marshaled during the 1991 Gulf War for abusing isoflurane.[145] More recently a fatality from sevoflurane abuse has been reported.[146] No doubt, familiarity and availability contribute to the increase in propofol abuse by anesthesia residents over the last 10 years.[147,148] Although abuse of ketamine by anesthesiologists is not new, its recent increased recreational use at rave parties may contribute to increased occupational abuse in the future.[145]

Addiction

A growing body of scientific evidence indicates that addiction is a chronic, relapsing disease resulting from the long-term effects of drugs on the brain.[149] Acceptance of this fact is crucial for those dealing with chemically dependent physicians. This section provides information about chemical dependence in anesthesiologists and the steps required to help a colleague or yourself.

Prevalence

Numerous studies have attempted to estimate the prevalence of substance abuse among physicians,[150,151] interns and residents,[152-154] and medical students.[155] A national survey published in 1992 reported a 2.1% annual and a 7.9% lifetime prevalence of substance abuse among physicians. This rate was substantially lower than the corresponding rate of 16% reported for the general population and thus disproved the myth that physicians are more likely to become substance-addicted than the population in general.[153] Although physicians are less likely to use cigarettes and illicit substances such as marijuana, cocaine, and heroin, they are five times as likely to take sedatives and minor tranquilizers without medical supervision.[156] This tendency to self-prescribe begins in medical school with tranquilizers and continues in residency with benzodiazepines and prescription opioids. Alcohol abuse is of particular concern in physicians. In 1991, over 87% of medical students reported alcohol use within "the last month" versus 83% of matched controls.[155] Although heavy alcohol use is less in young physicians than in matched controls, the incidence increases with age in the physician population and decreases with age in the general population. By the mid-50s, heavy use of alcohol in physicians surpasses that of the general population.[157]

Three retrospective surveys suggest that the prevalence of drug abuse in anesthesiologists ranges from 1% to 2%.[158-160] These published percentages rely on the recall of directors of U.S. anesthesiology programs and the honesty of individual anesthesiologists responding to questionnaires. Nevertheless, the estimates from these surveys are remarkably similar, and the prevalence is in line with published studies of anesthesia trainees in Australia and New Zealand.[161] In 1993 it was estimated that approximately 2% of U.S. anesthesia residents would become addicted to a substance during their residency.[162]

When comparing the published incidence of substance abuse in physicians as a whole with that of anesthesiologists, it is apparent that the overall incidence of abuse is not consistently higher in the practice of anesthesia than in other specialties.[163] However, it is notable that anesthesiologists are consistently overrepresented in drug treatment centers.[164] Although anesthesiologists account for 12% to 14% of physicians treated in three well-known treatment programs, they constitute only 4% of physicians in the United States.[165-167] This 3:1 overrepresentation of anesthesiologists in drug treatment centers is relatively consistent across state lines and over time. For example, data from the California Physicians Diversion Program have anesthesiologists accounting for 17% of physicians in treatment and 5% of physicians in practice.[168] Although these statistics imply that the incidence of chemical dependence is significantly greater among anesthesiologists, these data may instead be a reflection of the potency of the drugs abused, the ability of anesthesiologists to

recognize the disease in their colleagues, and the diligence within the specialty to refer colleagues for treatment. Additionally, the referral pattern mandated by the individual state medical boards and their associated legal ramifications may influence the percentages of impaired physicians enrolled in treatment.

The time until detection of abuse is inversely proportional to the potency of the drug abused. Much of the overrepresentation of anesthesiologists in treatment centers may reflect their preference for and access to potent narcotics. For instance, abuse of sufentanil is typically detected within the first 1 to 6 months while the abuse of fentanyl is not detected until 6 to 12 months. In contrast, alcohol abuse may not be detected for more than 20 years.[169] In the intitial published reports from state-run impaired physician treatment programs that began in the 1980s,[167-169,171] all of the anesthesiologists were chemically dependent, whereas 10% of the remaining physicians had other forms of impairment, such as depression.[165,166,168] Nearly 50% of anesthesiologists were younger than 35 years, and a third were residents. Half used both drugs and alcohol, 40% used drugs alone, and a minority used only alcohol. Fentanyl was the most commonly abused narcotic, followed by sufentanil, meperidine, morphine, and oral drugs.

The ASA Task Force on Chemical Dependence[170] has identified the following characteristics of addicted anesthesiologists:

- 50% are younger than 35 years
- Residents are overrepresented
- Many are members of AOA
- 76-90% abuse opioids as their drug of choice
- 33-50% are polydrug abusers
- 33% have a family history of addictive disease
- 65% are associated with academic departments

Causes

Stress

Occupational stressors first surface in residency where long hours preclude much time for relaxation and certain patients may evoke negative emotions. The death of a patient under one's care may cause a sense of professional inadequacy to surface for the first time.[171] Without doubt, the practice of medicine can be stressful, and it is tempting to assume that stress is a major cause of drug addiction among physicians. Contrary to common belief, however, stress is not necessarily the precipitating factor in a physician's addiction to drugs. Preexisting personality traits, a family history of substance abuse, and previous recreational drug use have been associated with substance abuse among physicians.[157,163]

Availability

Anesthesiologists are unique among physicians in that they administer drugs directly rather than order their administration by others. Drugs are immediately available, which is perhaps the most important cause of addiction in the specialty. One report indicated that 85% of anesthesiology residents treated in one large program stated that having drugs within reach influenced their career choice.[165] Over the last 15 years anesthesia departments have introduced measures to closely monitor the use of controlled substances by staff and resident physicians.

It is discouraging that an increased level of accountability of controlled substances in U.S. residency programs has thus far not correlated with a decreased incidence of drug dependence.[172] In a 2002 survey of 123 academic anesthesia departments, measures were introduced to regulate the use of controlled substances including changes in drug dispensing, disposing, and accountability. The study covered a span of 7 years, during which time drug dispensing was shifted from nurses to satellite pharmacies (42%) or dispensing machines (31%). Opened, but unused drugs were either returned to the pharmacy (52%) or wasted in front of a witness (41%), and the amount of drug administered was compared with the amount dispensed (80%). Despite these changes in drug dispensing and accountability, the incidence of drug abuse did not decrease.[173]

In the future the direct monitoring of atypical drug transactions from automated dispensing systems may more accurately identify drug diversion.[174,175]Additionally, the use of linkage of anesthesia information management systems with medication dispensing systems has been proposed as a means to accurately detect medication discrepancies.[176]

Drug Potency

Abuse of drugs by physicians is much more common than addiction. Patterns of abuse differ by specialty and are influenced by familiarity and availability. Psychiatrists most frequently abuse oral benzodiazepines, whereas anesthesiologists preferentially abuse potent narcotics. Casual abuse of alcohol obviously does not always lead to addiction, and although exceedingly risky, neither does abuse of morphine, meperidine, or codeine.[150] In contrast, the addictive potential of fentanyl and other potent opioids is so great that anyone who experiments with these drugs is at enormous risk of becoming chemically dependent.[165] Rapidly developing tolerance stimulates the ever-increasing doses needed to attain the desired sensation. The use of 50 to 100 mL of fentanyl or 10 to 20 mL of sufentanil per day is common in an addicted physician. These doses are easily reached within a few months for fentanyl and a few weeks for sufentanil. The potency of these drugs is reflected in associated fatality statistics. Between 1990 and 1997, 18% of identified substance abusers in academic departments either died or required resuscitation before substance abuse was suspected.[161] Fentanyl was most often the drug of choice.

Other Factors

Chemical dependence is a complex disease influenced by multiple factors. To identify availability and potency as the only significant factors in chemical dependence in anesthesiologists risks overlooking other significant factors such as previous use of drugs and a family history of drug abuse. A history of experimental use of drugs is known to increase the risk of future addiction.[150] Genetic predisposition may contribute to the progression from abuse to addiction.

Intervention

Drug addiction in anesthesia can result in the loss of one's job, profession, and family. Sadly, loss of life may be the first indication that there is a problem. Numerous studies have examined the mortality risk of physicians in general[177,178] and anesthesiologists specifically[179-181] versus that of the general population. This research has shown that the death rate from all causes is lower among physicians than the public in general. This difference is attributed to lifestyle awareness among physicians that results in

decreased rates of destructive behavior such as smoking. The higher socioeconomic status of physicians and greater access to health care may also contribute to this advantage. Although the mortality risk for anesthesiologists is no higher than that for other medical specialties, their risk of drug-related death and suicide is alarmingly high. Studies have shown a twofold increase in suicide among U.S. white male anesthesiologists[179] and British (mostly female) anaesthetists when compared with appropriate population controls.[178] A recent study in the United States reported the relative risk of suicide in anesthesiologists to be 1.45 when compared to internists. The relative risk of a drug-related death was even higher at 2.79.[181] All these studies identify drug-related death as a significant occupational hazard in the practice of anesthesia.

Management

Management of physicians who are chemically dependent includes identification, intervention, referral for treatment, and help with reentry. Each department should have an established mechanism in place to deal with impaired physicians.

Identification

Identification of a chemically dependent physician does not usually occur until the disease is in its late phases, when performance at work becomes significantly impaired. Although none of its signs and symptoms are diagnostic, an awareness of the usual sequence of events may help identify an ill colleague in the earlier stages of the disease (Table 101-6).

Normally, withdrawal from outside interests is the first sign. Examples include giving up athletics, community activities, church, and getting together with friends. Next comes increased turmoil at home. Domestic arguments, sexual problems, and lack of interest in family matters are common. Third is the appearance of frequent unexplained illnesses, personality changes, multiple jobs, and frequent moves between cities. This progression, which may take years to become apparent, is common with addictions that develop slowly.

The last activity to be affected is usually job performance. Page operators and nurses may be the first to recognize behavioral changes. Record keeping may become sloppy. Excessive use of certain drugs becomes apparent, perhaps accompanied by an unusual compulsion to explain the need for these drugs in patient management. Colleagues may note similar changes. Direct observation of self-administration confirms the diagnosis, but it is not common.[182]

Impaired physicians disclaim their illness by using superficially logical reasons to explain their bizarre patterns of behavior. Colleagues, too, use denial. Typically, they would rather accept these explanations than consider that a friend is a drug addict. For these reasons, the diagnosis is not usually made until its manifestations are clear.

Table 101-6 Signs and Symptoms of Chemical Dependence

At Work	At Home
Unusual changes in behavior (e.g., wide mood swings, depression, anger, euphoria)	Withdrawal from family, friends, and leisure activities
Gossip by others	Changes in behavior (e.g., wide mood swings)
Progressive increase in apparent narcotic use for anesthetic management	Fights and arguments at home
Careless charting	Frequent unexplained illness (common in alcoholism)
Preference for working alone	Gambling
Frequent requests for bathroom breaks	Extramarital affairs
Unusual willingness to provide relief for others	Legal problems (e.g., arrests for driving while intoxicated)
Inappropriate willingness to take calls	Decrease in sexual drive
Often appears in the hospital when not on call	Drugs and syringes found in the home
Frequent unexplained absences	Seclusive behavior at home
Difficult to find when on call	Odor of alcohol on breath
Excessive postoperative pain in patients cared for by an individual	Weight loss
Commonly wears long-sleeved gowns (to prevent chills often seen in early withdrawal and to hide needle tracks)	Pinpoint pupils (in persons addicted to opioids)
Pinpoint pupils	Symptoms of withdrawal (e.g., diaphoresis, tremulousness)
Weight loss	Denial of drug or alcohol use if confronted
Found comatose	
Found dead	
Witnessed self-administration (the only pathognomonic sign)	

Intervention

The appropriate initial response to the discovery of chemical dependence in a colleague is to seek help. A call to a person experienced in managing chemically dependent physicians initiates the next steps.[168,183] Most state medical societies in the United States have committees on impaired physicians to act as advocates for sick physicians. Advocacy continues as long as the physician cooperates with the committee's recommendations. These committees serve as a buffer between the physician and the medical board or licensing agency. They also provide advisers to aid in confirmation of the diagnosis and to intervene and refer impaired physicians to appropriate treatment centers. Although laws vary, the committees are usually required to notify the board of a physician's recalcitrance at any stage of treatment. In many states, the board does not censure impaired physicians who comply with the committee's recommendations.

Intervention is the process of demonstrating to chemically dependent persons that they are ill and need treatment.[184] Interventions should never be attempted with less than two concerned persons and ideally should be directed by a person with previous experience. Prior to meeting, the group must collect documentation of drug usage including pharmacy records, anesthetic records, and other pertinent testimony. It is important to rehearse with members of the group (colleagues, psychiatrists, family members, etc.) prior to meeting with the patient. Many suggest

that each participant prepare written notes to be used for reference during the intervention. The objectives are to present irrefutable proof of the addict's symptoms in a compassionate manner and to begin an appropriate treatment regimen. A recovering physician at the intervention can be a valuable role model for the patient. Arrangements for in-patient treatment and travel, if anticipated, should be made prior to the intervention.

When all is in order, the patient is invited into a room in which the other participants are already seated. Each in turn should express concern for the colleague's well-being and, without passing judgment, should describe the aberrant behavior that has been seen personally. If necessary, the documents at hand can be shown. The basics of the disease and its treatment should be explained, and the patient should be urged to accept the proposed plan. If the patient refuses, as many do initially for fear of losing control, the patient should be told that the ultimate decision regarding therapy will not be made until after a thorough evaluation by a group of specialists at the facility.[183] If the evaluation does not confirm the diagnosis, the patient will be discharged. Otherwise, formal treatment, perhaps lasting several months, will start. If still reluctant, the individual should be advised that the interveners must, by law, report that person to both the medical board and the controlled substance authorities. Although acceptance of treatment does not provide legal immunity, it is looked on favorably by many courts.

After the intervention, someone should stay with the patient continuously, not only to prevent the possibility of self-inflicted injury but also to provide friendship. With adequate preparation, most interventions are successful.

Principles of Treatment

Treatment consists of an in-depth evaluation, which is usually followed by both inpatient and outpatient therapy. Formal therapy may last as long as several months,[166] but on the basis of the initial workup, some programs permit a recovering physician to continue practicing medicine during what may be several years of outpatient care.[168] Although this is debated by some, physicians often fare better if treated at a facility experienced in managing physicians. Philosophies of treatment vary between programs, but the common goal is to provide a recovering physician with the ability to remain sober. The physician is assisted in developing a strong relationship with peer support groups such as Alcoholics Anonymous and Narcotics Anonymous.

Reentry into the Workplace

Return from treatment is a difficult process for a recovering physician. The comprehensive treatment program has provided a structured environment that is much different from the workplace. For this reason, reentry is greatly facilitated by understanding, compassionate peers who are willing to provide emotional support to the recovering physician. Gradual return to work, perhaps with others initially managing narcotic administration, is important. Without this support, the likelihood of relapse may be much greater.

In many states, the committee on impaired physicians plays a vital role in recovery. At discharge from formal treatment, the committee prepares an "aftercare contract" with the physician, who agrees to be bound by the committee's recommendations. The contract usually stipulates the number and the type of meetings that the physician must attend, the name of a "monitoring physician," the requirement for random urine samples on demand, and the procedures to be used in the event of a relapse.[166,185,186] Many recovery programs insist on the use of naltrexone or disulfiram, or both, for 6 months or more after returning. Novel treatments for alcohol dependence include investigational drugs such as acamprosate, bromocriptine, selective serotonin reuptake inhibitors, and buspirone.[187] As long as physicians adhere to the contract, the committee continues to serve as their advocate.

Federal law in the United States (the Americans with Disabilities Act [ADA]) provides limited protection against employment discrimination for recovering individuals.[188] Although persons who are currently using drugs are not protected by this law, those who have been successfully treated and are otherwise capable of working are considered to be "qualified individuals with a disability." The ADA defines a history of chemical dependence as a disability. Although it does not require an employer to provide for treatment, the ADA may require that "reasonable accommodation" be made for a qualified individual who wants to return to practice. For a recovering physician, such accommodation might include a modified work schedule, such as no call for several months and assistance with administration of narcotics. An employer is not required to make accommodation if "undue hardship" for the employer would result. For example, it could be argued in court that the accommodations needed to permit a recovering physician to return might have a negative impact on other employees or could result in prohibitive costs for the employer. Whether the ADA can be used also depends on the type of employer-employee relationship between an individual and a hospital or group practice. Clearly, any person who seeks the support of the ADA needs competent legal guidance.

Prognosis

As indicated by reports from treatment programs, most recovering physicians are able to return to a productive professional life.[189] Successful outcomes are dependent on lifelong participation in aftercare programs, total abstinence from drugs and alcohol, and continual acknowledgment of one's disease. Some now believe that the prognosis for long-term sobriety in anesthesiologists depends on the age and the status of the physician at the time of identification. Residents who have been dependent on fentanyl appear to have a significant rate of relapse.[160] Although each case must be handled separately, strong consideration should be given to a change in specialty for junior residents who become addicted to potent opioids.

The American Board of Anesthesiology (ABA) permits a physician recovering from alcoholism or other drug dependence, who is otherwise qualified, to take both the written and oral examinations. After a candidate with this history has satisfied the requirements for certification, "the [board] will determine whether it should defer awarding its certification to the candidate for a period of time in order to avoid certification of a candidate who poses a direct threat to the health and safety of others."[190] If the ABA deems that such deferral is appropriate, "the [board] will determine the length of time the candidate's certification is deferred following an individual assessment of the specific circumstances of the candidate's history of alcoholism or illegal use of drugs." This practice is in keeping with the intent of the ADA.[190]

Summary

Despite the many occupational hazards in the operating room, the relative risk of each of the hazards discussed in this chapter has evolved with the times. The introduction of efficient scavenging systems has made anesthetic gas exposure less of a concern in recent years, whereas the AIDS epidemic of the 1980s and 1990s has placed an emphasis on infection control. In 2009 it is clear that substance abuse and drug-related death have emerged as prominent occupational hazards to be addressed in the future. Ongoing education and awareness within the specialty will continue to reduce these risks and improve the safety of our specialty.

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102 Statistical Methods in Anesthesia

Key Points

1. Always plot your data. Significant trends should be visible to the eye.
2. Know your statistics program well enough to be sure that it is calculating what you want.
3. Interval data should not be treated like categorical data—the mathematics is different.
4. Many statistical methods assume that the data are distributed "normally," that is, in a symmetric bell-shaped curve; these methods can be misleading if the data are not normally distributed.
5. Standard deviation (SD) is used to describe the spread of data, and standard error of the mean (SEM) is used to compare data sets.
6. Multivariate regression, which relates the outcome variable to more than one other factor, requires more data but will probably pick up correlations that may be missed if only univariate regression is used.
7. When using multivariate regression, if two variables correlate closely with each other, the statistical package may miss reporting one as correlating with the outcome.
8. In hypothesis testing, a negative result may indicate no real difference or may just mean that the study was underpowered to pick up a true, but small difference.
9. A *P* value is the probability that the observed result will occur, assuming no true difference between the tested hypotheses, which is not the same as the probability of the difference being true.
10. A bayesian approach to diagnostic testing recognizes the fact that the value of a test depends on the patient population: if the test is almost always truly positive in the population, false-negative results will outnumber true-negative ones and make the test less useful. This is also the situation if the test is almost always truly negative, in which case false-positive results cause the confusion.
11. Selection biases make many real-life clinical studies difficult to interpret. Randomized clinical trials are the best way to minimize this problem.
12. Beware of the error of "data dredging." Applying too many tests to insufficient data will probably find something that, misleadingly, seems significant.

The advance of scientific knowledge in the past half millennium has been closely related to the linkage between experimental results and mathematical assessment of empirical observations. It is the role of the branch of mathematics termed *statistics* to describe the results of experiments and analyze, as best as can be done mathematically, the causes and effects behind the experiments.

A serious problem for a clinician or clinical scientist who wishes to use statistical methodology is that it is a modern branch of mathematics, much of it developed in the past century. Its mathematical sophistication is often considerably beyond that of the university-level calculus that is the upper limit of conventional medical training. Furthermore, many statistical methods involve extremely long and tedious calculations that require computerized techniques to be practical. This drawback leads us to the quandary that although statistical methods are useful and often essential to the understanding of medical science, they may be subtle to comprehend and difficult to use.

It cannot be the role of a chapter in a book such as this to derive or even genuinely explain the mathematics behind statistical methods. Many accessible introductory texts give some of the reasoning and rough, cookbook approaches to practical usage (see Bibliography). In real life, almost no one ever does any sort of statistical calculations beyond the most simple with paper and pencil. Application programs for statistical calculations are widely available for personal computers. Many of them are reasonably well documented and simple enough to use without much preparation.

The problem we have with these statistical programs for personal computers is that the assumptions behind the statistics remain obscure. It is very easy to use the wrong method or approach and still have the program generate an output that,

although appearing to be correct, is simply wrong. The old computer adage of "garbage in (statistically misleading), garbage out" is very easy to achieve with a computer package and a data file.

It is the goal of this chapter to provide some of the correct language for describing statistics and to suggest the proper methodology for the use of statistics in some standard situations. Some of the classic errors common in medical statistics will be indicated. Of course, readers must be familiar with whatever program they actually use.

Statistical Approaches

Within the broad rubric of statistics, several distinct and valuable areas can be viewed separately. "Descriptive statistics" is the use of mathematical methods to describe or categorize a collection of data that result from a set of empirical observations. "Statistical testing" is the broad approach to the determination of conclusions from a set of observations. Within each of these categories are many separate techniques.

Types of Data

It must be remembered that behind every statistical methodology there are formal mathematical definitions and proofs. Although it may sometimes seem that a simple intuitive approach is sufficient to understand what is happening, mathematical statistics can be misleading and unforgiving. The mathematical proofs and calculations that are behind our statistical tables and computation programs make strict distinctions among the several types of data (Table 102-1).

One type of data, termed *interval* data, are simple *continuous* numerical measurements (e.g., 1.2, 33.4). Often, we describe *discrete* numerical measurements, such as counts or integral quantities in the same categorization. This approach is occasionally misleading: the claim that a "typical family has 2.3 children" is meaningful in a crude way, even though the quantification of children is obviously not a continuous numerical fraction. In practical use, both continuous and discrete data can be handled by techniques similar to those used for interval data.

The other major grouping of data is *categorical* data. One type of categorical data is *ordinal* data, which refers to the ordering or ranking of subjects (e.g., 1st, 3rd, 10th). It is important to be careful to resist the temptation to regard the number of the ranking as an interval number, that is, to confuse "first" with the number "1," and so on. Such grouping does not usually have much numerical meaning and is false to the mathematics if an attempt is then made to manipulate the number as though it were an interval value. The arithmetic manipulation of arbitrary numerical assignments may easily produce misleading results.

Another similar category is *binary* data (e.g., up versus down, greater versus lesser). The most general grouping is the simple *category* (e.g., red, green, blue; cancer, diabetes, ulcer). When using simple or binary categories it is incorrect to attach numbers to the groups and try to get numerical results—the mathematics are not appropriate and the results are not likely to mean much. Specific statistical techniques for categorical data are necessary.

Table 102-1 Types of Data

Data Type	Examples
Interval	1.1, 22
Ordinal	1st, 3rd
Categorical—binary	Male/female, alive/dead
Categorical—multiple	Red, green, blue

Descriptive Statistics

Our most general statistical goal is to describe our data set. The simplest method is to just present all the crude data. For small data sets, the actual measurements can be presented. For larger amounts of data, a graph or statistical plot of the data can be helpful. One can frequently see trends and groupings in a picture that are very difficult to describe numerically. It is often suggested that before any mathematical method is applied to data analysis, a graphic plot should be produced. If the data do not look "right" to the naked eye, the statistical analyst should be very careful to avoid erroneous results. The choice of the correct format for the statistical plot can be an art form, and special data manipulation computer programs can be useful to search for visual clues in a data set.

Normal Distribution

Perhaps the most powerful numerical concept of mathematical statistics is the *normal distribution,* often called the "bell-shaped curve." The idea of a most likely central value with other values scattered evenly to both sides is a classic statistical concept with deep mathematical roots. It fits in nicely with our intuitive idea of a "true" value with measurements distributed randomly around that true value such that more values are close to the center than are distant.

Many typical data sets follow a normal distribution around a center point. This distribution, sometimes also called a gaussian distribution, is derived from the assumption that there is a center, "true" value and that deviations from the center are random and diminish in likelihood the farther the values get from the center (Fig. 102-1).

The strict use of normal distribution implies very large amounts of continuous interval data. When, as is usual, our data set does not meet this criterion, approximations are needed. Fortunately, most computerized statistical programs can deal with this problem with good effect.

In general, the mathematical description of the placement of the values is termed the *distribution.* There are many, mostly uncommon distributions other than normal distribution. They yield different curves and have specific mathematical properties. Not all data sets, even if they look like a bell-shaped curve, are normal distributions. If the curve is too wide (i.e., many distant outlying points) or too narrow or uneven, the mathematics derived for normal distributions will not work well.

When data follow a normal distribution or, more generally, any specific mathematical distribution, the methods of *parametric statistics* can be used. The term *parametric* refers to the ability to

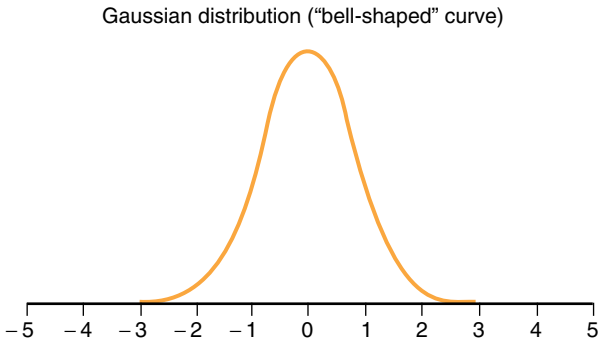

Figure 102-1 Gaussian distribution in a bell-shaped curve. The x-axis is in units of standard deviation.

describe the distribution with a specific set of values. Frequently, such is not possible, and *nonparametric* statistical methods are necessary. These methods make fewer mathematical assumptions about the distribution of the data, but they are more difficult and can be less robust in finding statistical distinctions. Conversely, if parametric statistical methods are applied to data that are not normally distributed, false or misleading results can be calculated. This type of error is common and can be prevented by using appropriate tests or checking the data for normality before applying tests that assume it.

In practical use, we often treat our data as though they follow a normal distribution. However, wise investigators will use the tests in their computer statistics packages to test for normality and recognize that if the data do not follow a normal distribution, other methods will be needed.

Measures of Central Tendency

In describing data, the first task is to give some indication of the approximate value, range, or size of what is being described. How this is done depends on the type of data involved (Table 102-2). For categorical or binary data, all that may be possible is to give the counts in each group. For categorical data with many groups, the most populous groups may be named and listed in order. For ordinal data, summary description may be difficult; often, first place or last place will be the most interesting.

The *median* is the center or middle data point if the data can be ordered from smallest to largest. This value would apply both to interval data and to ordinal types of categorical data. For interval data, many mathematical techniques can be applied. The simplest is the *mean,* or the simple average value of the numerical data, with each data point being counted equally. In a *weighted mean,* the individual points may be added in unequally, with some getting more credit (i.e., "weight") than others.

For interval data that can be analyzed mathematically, the data may be fitted to a curve, which means that a mathematical formula is computed that closely fits the measured data points, often by using a computer and sophisticated calculations. The relationship can be as simple as a straight line, or a complicated mathematical formula with exponentials, polynomials, or other functions included as may be needed. The various computed values in these formula would be the *parameters* of the curves. The data would thus be described by the parameters of the formula approximated to the observed data. For the simple case of a straight-line approximation to data, the parameters would be the slope and intercept of the line. For complex equations fitted to data, the parameters would be the various computed numbers that make up the equations.

Table 102-2 Measures of Central Tendency

Mean ± standard deviation
Mode
Median
Percentiles

The *mode* is the most common value in a set of data points. This concept can be misleading if the data are truly continuous because every data point would then probably be different (if only infinitesimally so) from every other point. Hence, to describe the mode of continuous data it makes the most sense to group the values into brief intervals. In this sense, the interval with the most points within it is the modal interval. The mode may also be a very misleading description of the central tendency of a data set because there may be no reason for the most common value to be anywhere near the middle.

Numerical data can be described by categorizing the values into *percentiles* or similar groups. The meaning here is that for the, say, 10th percentile, 10% of the data points are at or below that value. The 50th percentile corresponds to the median of the data set, and the 99th percentile is the value at or above 99% of the data points. Similarly, quartiles, quintiles, or other groups can be computed. With any method used to describe data, the choice of the description may subtly bias us in how we think about the result. In the simple data set [2, 2, 3, 7, 14], the mode = 2, the median = 3, and the mean = 5.6. Which, if any, of these representations is more accurate? The answer depends on how we want to use the data because no one representation is perfect.

Measures of Dispersion

Often we want to describe not only the values of our data but also how the data are spread out. For data that follow a normal distribution, the classic approach is to compute the *standard deviation* (SD) of the data. With this value, roughly 68% of the data fall within 1 SD of the mean and roughly 95% fall within 2 SD of the mean value. The larger the SD, the wider the "bell-shaped" curve, and the smaller the SD, the narrower the curve.

Another way of looking at this concept is to consider that if we were making measurements of an unknown value and our values were scattered in a random normal distribution around that value, it is likely that about 68% of the data points would be within 1 SD of the true value. Of course, this result is only the most probable outcome and in any real set of randomly distributed data we could be unlucky and have very atypical points.

For data that do not follow a normal distribution, it can be difficult to describe the dispersion of the data set in a standard fashion. Often, just the *range* of the data, from lowest to highest, is given. Occasionally, the data may be so scattered, with very distant extremes, that the range is not as useful as reporting the 25th to 75th percentiles of the data.

Caution

Because it is so easy to use a computer package to calculate the SD, we must be particularly cautious about using it. Frequently, data do not fit nicely into the normal distribution with a symmetric bell shape and unbounded tails out in both directions. As

an example, consider a data set of subjects with widely dispersed ages including many children. It would be easy to get a value of 10 for the mean age, with an SD of 15. Clearly, no values lie at the lower end of the distribution with ages of −5. In such situations, the SD has some merit in describing the spread of the data but is, by strict mathematics, being misapplied.

Standard Error of the Mean

Just as random numerical data can often be described by the SD, the means computed from multiple grouped determinations of the data set can be described by making a computation very similar to the SD but applied not to the measured data but to the computed means. This computed quantity is termed the *standard error of the mean* (SEM). As more data sets are gathered, with each data point being a measurement of what is a "true," but unknown, value, the means of the data sets will very probably get closer and closer to that true value. Hence, as more and more data are gathered, the SEM will get smaller and smaller. This concept is intuitively very reasonable—as we make more and more measurements of a value, we should be getting a mean value closer and closer to the "true" value, even if the data points themselves remain scattered.

The difference between SD and SEM is important. SD is used to describe the data, and SEM is used for computations about the certainty of the mean of the data. Because our computer packages can as easily provide either of these values and SEM is a smaller value, one is tempted to describe the data by the SEM. Although this is not dishonest if clearly labeled, it can certainly be misleading. If you have a very large number of data points, the SEM will be very small, but widely dispersed data will have a large SD no matter how many points are measured.

Graphing the Data

All experienced statisticians will stress that before statistical calculations are applied to a new data set, the data must be plotted in some graphic format. If the data are widely scattered, look asymmetric, or have a specific pattern, that information is useful in determining the statistical tools to be applied. Furthermore, noting the presence of extreme outlying points may be a clue to mathematical or experimental errors.

Regression Analysis

Data may often fit a mathematical formula, which may be a straight line (e.g., a linear relationship) or just about any sort of continuous mathematical formula. In *regression analysis,* we use the power of the computer program to determine the mathematical formula that best fits the data. To do this, we have to provide the program with the type of curve to use, for example, a straight line, quadratic equation, or exponential curve. The program will then provide us with the parameters within the selected equation that best fit the data points.

The art of regression is complex. The first problem is to pick the appropriate mathematical relationship to fit the data. Graphing the data is obviously very useful for this. There are also some mathematical subtleties in how to best fit the data to the curve, but by far, the most common method is a *least-squares* approach that minimizes the square of the distance of each data point from the proposed curve. Although this methodology is about 2 centuries old, it clearly benefits from the use of modern computerized calculations, without which it would be practically unusable.

The computer program for regression analysis will provide the parameters of the fitted equation, such as the slope and y intercept for a straight line, and also some information about how well these parameters fit the data. The user has to be cautious in using the fitted equation if the agreement is poor because almost any jumble of data can be fitted to some equation, albeit with terrible agreement. It is fair to stress that the human eye has real power to judge trends, so if a graph of the data does not look like it fits the curve, the wise user will be very skeptical of the result.

Univariate Versus Multivariate Regression

In fitting data in a regression analysis, the first step is to choose the variables that will be used as independent variables. In *univariate* analysis, only one variable is used for the data fit and the data are plotted and the computations are performed by using that one variable to describe the data. As an example, the weights of a group of subjects may be compared with their heights. However, in the real world, many possible variables can almost always be used to determine an outcome. In *multivariate* analysis, more than one variable is used to describe the observed results. In the weight example, the subjects' weights might be analyzed by using heights, ages, and gender. Note that in this multivariate example, the outcome is a continuous interval variable but is determined by a collection of interval variables (age, height) and a categorical variable (gender). The precise mathematical techniques that are used for multivariate analysis will depend on the nature of the variable used; in general, a mixed group of variables makes the most sense with real-world data.

On first approaching analysis of a data set, a simple univariate analysis may help in understanding the relationships involved. However, the data analyst must be cautioned that subtle relationships can be missed with only univariate analysis if the relevant variable is not used. As an example, heart rate may correlate with the dosage of pain medicine in an injured patient, but the causal relationship for both is likely to depend on the degree of pain.

With multivariate regression analysis, many potential pitfalls can readily be encountered with computerized calculations. One critical category of problems derives from the relationships that the various variables may have with one another, which is often described by indicating how *independent* these variables are in relation to one another. For an independent variable, the values of one variable do not tell what the values of the other would be. In the example of weight versus age and height, we would expect age and height to be independent in adults. Mathematically, it would be determined that age and height are *uncorrelated.* However, in children, age and height are correlated, so weight could be expressed as a function of weight versus age or weight versus height. In this last case, a multivariate analysis that focused on independent variables might just produce the result that weight is a function of height and throw out the relationship between weight and age. Hence, when many variables are involved, caution must be applied so that experimentally important relationships are not missed because they do not add mathematically to the results. Sophisticated statistical computer packages will look for these sorts of problems. Identification of significant correlation among the different variables would suggest that some information may be lost if only independent variables are reported. If a simpler statistical program is used, it would be wise to perform multivariate analyses with some of the variables left out to see whether other possible relevant relationships appear.

Another type of problem that can be misleading with multivariable relationships occurs in the situation in which the computer program produces a variable that correlates only weakly with the data but does so with high reliability. This situation would be expressed in linear analysis as a result with a small correlation coefficient but a very good "*P* value" (more about "*P*" later). The fact that the correlation likely is real (i.e., it is not a statistical fluke) does not offer much to the experimental analysis if the correlation is small—the data are not well explained by the relationship. Here, the confusion comes from the fact that although the correlation is weak and does not explain much, the calculation shows very high confidence in the presence of this weak correlation.

Hypothesis Testing

A very common use of statistical techniques is to test a question, called the *hypothesis*. Also often termed *significance testing,* this approach yields the valuable concept of the "*P* value." It is this *P* value that is often used to summarize the statistical strength of the data analysis in supporting or rejecting the hypothesis. If we were comparing groups, we often describe the test as a comparison of the *null hypothesis,* which states that there is no difference between two groups of data, and the *alternative hypothesis,* which states that there is a difference. If we were analyzing a single grouping of data and performing a comparison of two descriptions of the data, such as determining whether the mean value of the group as calculated from the data is different from 0, the two hypotheses would be "mean = 0" versus "mean = measured value ≠ 0."

The *P* value is computed from the observed data as the probability of obtaining this data set if in reality the null hypothesis were true. It is important to note that this calculation assumes the null hypothesis and is not the same as saying that *P* is the probability that the alternative hypothesis is true. If in reality the null hypothesis is true, it would be unlikely that we observe something else in our data. In actual experimental situations, all data have some randomness, so we can never be certain that our observation is not just chance and bad luck.

In hypothesis testing we choose a *level of significance,* termed the *alpha* value, and declare that if *P* is less than alpha, the result is statistically significant and accepted as true. If *P* is not less than alpha, we reject the hypothesis (equivalent to accepting the null hypothesis). Remember the logical sequence: we choose alpha in advance, then compute *P* from the data. If *P* is less than alpha, we agree to accept the hypothesis and we reject the null hypothesis. The *P* value is the chance that the null hypothesis was true but, through our bad luck, the data came out as observed anyhow. Typically, we set alpha equal to .05 and want *P* less than that. For that *P* value, it would mean that the chance of the data coming out this way was less than a probability of 5% ($P = .05$) if the null hypothesis were in fact true.

Choosing the level of significance is an arbitrary decision. We might want to be very sure that we did not erroneously reject the null hypothesis and set alpha at .01. It is common in biomedical studies to pick an alpha value of .05. Also be aware that a very small *P* value may lead us to reject the null hypothesis but may not give us much information about the exact nature of the alternative. As an example, tossing a coin and getting six heads in a row might lead us to reject the null hypothesis that the coin is a fair coin, but it is not enough information to convince us that the coin always comes up heads. We calculate the *P* value from the data assuming the null hypothesis and use a small value of *P* to allow us to reject the null hypothesis, yet that does not fully characterize the alternative hypothesis.

Power

It should seem intuitively obvious that the ability of a statistical test to make a valid determination depends on the amount of data available. With only a few observations or data points, we cannot be as certain about a conclusion as if we had large amounts of data. If our goal were determining the fairness of a coin, tossing it twice would not convince us of much; tossing it a thousand times, however, would give us a good idea about its nature. In statistical hypothesis testing, the *power* of a study is a description of the ability of the study to detect a true difference. A statistical hypothesis test may fail to achieve significance (fail to get $P <$ alpha) if either the data truly do not reflect a difference or if there are so few data points that the mathematics yields a poor *P* value. We define a *beta error* as the probability of falsely accepting the null hypothesis (calculated by assuming that the alternative hypothesis is true), and the *power* = 1 − beta. For the power to be good, that is, the beta value to be small, we want our study to have enough data points so that if a difference is observed between the null and alternative hypotheses, we can accept it with reliability.

A sample size calculation is often performed before an experiment is undertaken to determine how much data would be necessary to have a reasonable chance of observing what is guessed to be the observed result. Standard computer programs are available that will compute the number of data points necessary when the alpha and power values are provided and some estimate is made of the likely observed effect. It is important to be cautious about any study that is interpreted as "negative," that is, reports no significant difference between the study groups. It may be that no difference truly exists, but it may also be that the sample size was too small to determine a difference with statistical significance.

Confidence Intervals

It is becoming more common in reporting statistical measurements to use *confidence intervals* as a description of the statistical determination. A range of values may be given such that it is determined with some likelihood (often picked at 95%) that the true values lie within that range. For expressing simple results, the confidence interval is equivalent to providing a mean ± SD. This method becomes particularly useful for describing results when we want to describe "no difference" in correct statistical fashion. Here, the proper description would be that the true difference lies in an interval less than "x" with the given statistical confidence.

In sum, for hypothesis testing we want the following:

- Null hypothesis—e.g., mean = measure value "m"
- Alternative hypothesis—e.g., mean = 0
- Alpha value (chosen in advance)—e.g., alpha = .05
- Power (chosen in advance in conjunction with a sample size calculation so that we have enough data points)—e.g., power = 0.8
- P value—computed for data

We can say that we have a significant difference between the null and alternative hypotheses if P is less than alpha. If we are describing a value, we can give it as a confidence interval; and

if we are saying that there is "no difference," we can describe it as a difference (if any) in the interval less than some computed value.

Study Design

The essence of scientific study is generally some numerical determination of a result. It is this numerical analysis that we approach with our statistical calculations. However, without a careful design of the study in the way that the numerical data are generated, formal statistical analysis of the numbers will yield scant benefits and may even be very misleading. In the typical study we are usually attempting to either characterize some variable (e.g., mean or trend) or make a choice to accept or reject among various hypotheses. No matter what the question is in our minds, we must always be careful that the results genuinely answer the question and that we are not misleading ourselves with inappropriate conclusions.

Scientific studies may be *observational studies* in which we gather data without performing any specific intervention affecting the assignment of groups or effects on group members. Because in an observational study we have to take what we find as data, we are always very subject to other unrecognized factors that may distort our interpretation or limit our ability to ask questions about our data.

In an *interventional* study, we pick the group members, determine what is being done to them, and attempt to look out for and eliminate potential confusion before the data are collected. A *clinical trial* is a typical interventional study in which different therapies are compared.

In the design of a scientific study, one major fear is a statistical *bias,* which is a systematic effect in the study that produces an error in our interpretation of the results. When considering the various possible study designs, we need to beware of the potential biases that may creep in. A *selection bias* occurs when we are comparing groups with respect to some variable but do not realize that the groups are different in other (but important) ways. Because groups of subjects may differ in multiple ways, our assignment of subjects into groups may result, either from misdirected choice or just random "bad luck," in groups that are not fairly comparable. So although we think that our results are determined by the variable under study, it may really be that some other factor misleads us in our conclusion. As an example, consider a study that is comparing surgical and medical treatment of some illness and ends up with a grouping in which a higher proportion of men than women are undergoing surgical therapy. Any conclusion from this study about surgery versus medical therapy is biased and might be truly just reflecting a difference in the results of therapy on men versus women.

A *confounding bias* occurs when multiple variables are intimately intertwined so that although we may assume that the variable under study is important, the truth is that the confounding variable is more important. As an example, consider a study attempting to determine the effects of obesity on longevity. Because diabetes mellitus is very closely correlated to obesity, a result that purported to be about obesity might easily be more accurate about diabetes. When variables do not correlate with each other so that changes in one do not go along with changes in the other, we call them (in a rough nonmathematical sense) *independent variables.* Variables that are correlated with each other are not independent.

A *measurement* bias occurs if the methods used for making measurements when comparing different groups have different scales or sensitivities. As an example, consider attempting to get a history of chest pain in groups of patients with and without known coronary artery disease. Patients who know that they have heart disease might be imagined to remember brief pain more thoroughly than healthy patients do, or perhaps they might deny pain more in their wish to believe that they are healthy. Here the art of the experimenter is to predict and avoid such biases.

In a *blinded* study (more properly called a *masked* study), measurement bias may be avoided if the person performing the measurement does not know which group is being measured so that subtle bias in approaching or determining the data can be avoided. As an example, consider an active drug being compared with an inactive placebo. A researcher who knew which patient was taking the active drug might be more diligent in pursuing benefits or side effects. In a *double-blind* clinical study, neither the patients nor the experimenters obtaining the data should know which subjects are in which group to avoid subtle measurement bias.

Observational studies may be categorized as case, case-control, or cohort studies. In a simple *case study,* an individual case or group of cases is reported. Such reports may demonstrate the existence of some observation or effect, provide the presumably typical character of the observation, and suggest a therapy or natural history. These types of studies do not have the nature of a proof because it is always a possibility that some other hidden effect is producing the observation or that the observed characteristics are atypical in some fashion. Nevertheless, often "seeing is believing," so much of what is reported in medicine is in the form of case observations.

The distinction between cohort and case-control studies is important but often misinterpreted. In both categories, groups of subjects are compared, usually in regard to the effects of some intervention. In a *case-control* study, the factor separating the groups is determined *after* the intervention. Typically, a comparison is made of some outcome in one group, the case group, versus a similar group that does not have the outcome and functions as the control group. Because the groups are separated after the intervention, selection biases or unappreciated confounding variables can mislead the investigators. As an example, consider a study investigating the effects of hypertension on surgical mortality. If the groups are divided into patients with and without perioperative cardiac events, it may well be that one group will be different from the other. However, such a result may be misleading; perhaps it is really the renal disease that is associated with the hypertension that is significant (a confounding bias). Alternatively, perhaps patients with hypertension are sent to surgery by their physicians only when they have worse surgical problems, so the groups are not fairly compared (a selection bias).

In a cohort study, the study group is monitored before the intervention occurs. The group is assembled to be as similar as possible and then monitored forward in time. Such studies are useful for describing the natural history of disease and may be helpful in suggesting causes. However, as with the other observational studies, selection and confounding bias may occur and lead to misleading results.

A case-control study is sometimes termed a *retrospective* study because the analysis can only be done after the subjects

complete the study (so that it can be determined to which group they belong). In this sense, a cohort study is a *prospective* study inasmuch as the data must be gathered before the intervention. Unfortunately, these terms may be misused because, obviously, a case-control study can be planned in advance ("prospectively"). In addition, no matter how truly prospective a study is, once the data are gathered, the analyses are performed after the fact ("retrospectively"). These terms are best avoided.

After considering the nature of observational trials we can see the strength of the interventional clinical trial, where the investigators determine the membership of the groups to be compared in advance and attempt to make the groups as alike as possible. In a *randomized clinical trial,* the subjects are assigned by chance to the groups so that if there are some fluctuations in the subjects or some subtle selection bias, the effect will be the same in each group (and presumably cancel out in the result). Such a study is necessarily prospective in nature.

Randomized clinical trials are the idealized standard in medical research because they give the best chance to minimize biases. However, the effort and expense in setting up a clinical trial may be very considerable. Recognize that such a trial requires patients to be enrolled before the medical intervention is performed. Patients give up choice of the therapy that they receive and allow their therapy to be randomly selected among various options. Such trials (even if they involve standard therapies) require full ethical board clearance and explicit patient consent.

Even with the best clinical trial methodology, potential difficulties include dealing with subtle selection biases regarding who is entered into the trial. Studies that are actively watched by investigators and their highly motivated associates may result in atypical practices that cannot be generalized into standard clinical practice. The patients in clinical trials are themselves mostly motivated by the search for personal benefit and cannot be depended on to follow protocols strictly or to stay with a program that does not appear to be successful to them.

Data Dredging and the Problem of Multiple Comparisons

In all our statistical interpretations regarding the acceptance of data-determined conclusions, we always recognize that there is the random chance of a highly unlikely statistical result being misinterpreted as the typical true conclusion. A coin tossed six times and coming up all heads might lead us to conclude the coin was not fairly balanced, yet that will happen every $2^6 = 64$ times that it is attempted even with an entirely fair coin. When we pick an alpha value of .05, we are roughly saying that about 5% of the time we will accept misleading random errors as though they were true. This is roughly equivalent to recognizing that for every 20 experiments we do, perhaps 1 will be wrongly accepted as true based solely on bad luck and random chance. If we analyze a large set of data in many ways, some random results may appear statistically significant just based on this sort of chance. This is the error of *data dredging* and typically occurs when too many variables are examined for correlations within a single data set—by random chance something will be found that appears significant.

In a similar manner, if a very large number of independent comparisons are made between two groups of subjects and we accept an error rate of 5%, we might get a false, but statistically "significant" result about once for every 20 comparisons made. This is the error of *multiple comparisons.* Mathematical methods are available to correct for these errors—what is most relevant for the consumer of the statistical analysis is to recognize the presence of the error and look for the correction.

Choice of Tests

Nonparametric Statistics

When calculating the random distribution of some variable it is easy to visualize the values as clustered around some center value in the well-known bell-shaped (termed *normal*) distribution. However, as noted earlier, not all data have such a nice distribution. Data that are not in interval format, such as nominal data (e.g., red, black; male, female) or ordinal data (first, third), cannot be described by mathematical distributions with parameters such as the mean or SD. Such a situation calls for nonparametric statistics. Nonparametric statistical methods are typically used for the analysis of nominal or ordinal data. Data that are distributed in a very atypical skewed fashion (a *non-normal* distribution) will not be properly handled by analyses that have the mathematical assumptions of normality; such data will need nonparametric analysis.

The first step in considering the choice of a statistical test is to decide whether statistical methods that assume a normal distribution are appropriate or whether nonparametric methods are needed (Table 102-3). A test for normality is included in typical statistical computer packages. Often simple inspection of frequencies in tabular or graphic form will convey much information.

Contingency Tables

A very common nonparametric statistical problem is the analysis of a table of data in which each cell in the table is a count in a particular category. The question is to determine whether the groups are statistically different from one another. As an example, consider the question of men versus women and their political affiliation, Republican versus Democrat, in which a 2×2 table is generated. If additional political groups are added, say Green and Undeclared, we then have a 2×4 table. If we wished to analyze these data to determine whether men and women differ in political affiliation or whether Democrats versus Greens differ in gender distribution, we would apply nonparametric statistical methods appropriate to a contingency table.

Paired Versus Unpaired Data

If statistical methods are applied to analyze data from multiple groups and each individual data point comes from a separate and distinct source, the mathematics behind the statistics assumes an independence and randomness that would not be the same if the sources are highly related. As an example, consider a study of blood pressure in two groups of subjects, one treated with medication and the other untreated. Because blood pressure measurements can be widely scattered in distribution, depending on the subjects' previous medical condition, a small drug effect might be difficult to notice. However, if the same individuals were studied before and after therapy, the wide initial variations might cancel out and small effects would be noticed. In this latter study, the data points can be paired, one in each group, to detect these small

Table 102-3 Choice of Tests

Comparison Goal	Normally Distributed (Parametric) Interval Data	Nonparametric Interval Data	Categorical Data
Describe group	Mean ± SD	Median, mode, percentile	Counts and proportions
Compare group with value	t-Test	Wilcoxon	Chi-square
Compare two groups	Unpaired t-test	Mann-Whitney	Chi-square, Fisher
Two paired groups	Paired t-test	Wilcoxon	McNemar
Three or more groups	ANOVA	Kruskal-Wallis	Chi-square
Multiple matched groups	Repeated-measures ANOVA	Friedman	—
Regression	Linear regression	Nonparametric regression	Logistic regression

ANOVA, analysis of variance; SD, standard deviation.

effects. A study in which the data can be paired can be very sensitive in picking out small changes. Conversely, the erroneous use of paired statistics might suggest a statistically significant result when one does not exist.

Two-Group versus Multiple-Group Analysis

In a simple statistical analysis we may be characterizing one group of data or comparing that group with a standard value. It is slightly more intricate to compare two groups when we want to characterize each group and determine whether the groups are statistically different. Much more concern must be applied to the situation when we have three or more groups. In this case of multiple groups, two distinct types of questions can be asked. First, we might wish to know whether the groups are significantly different or whether they are all the same (with any numerical differences attributed solely to random fluctuations). Second, if we do conclude that the groups are statistically not all the same, we might want to know which groups are different from one another—that is, are they all distinct or are just one or a few different whereas the rest are similar to each other.

In summary, three questions should be asked when choosing between tests (see Table 102-3):

1. One group, two groups, or many groups?
2. Paired or unpaired groups?
3. Parametric (interval data following a normal distribution) or nonparametric methods?

Bayesian Approach to Probability

The commonsense meaning of the term *probability* can readily become confusing within the mathematical morass of formal statistics. In practice, we commonly use and interchange two definitions for probability. In the *frequentist* approach, we view the probability of an occurrence as the fraction of occasions that the selected event would occur if the trial were repeated many times. So we say that the probability of a fair coin coming up heads is .5 because if we toss it many times, we would get about 50% heads.

However, in many real-life situations we cannot repeat the trials many times to get a frequency of occurrence for an event. In the *subjectivist* approach, we assign a probability to an event based on our best guess or opinion. Such subjective assessments are very similar to what we do in medicine when we make an interpretation based on opinion and experience. This approach is often termed *bayesian* statistics because of a mathematical formula, Bayes' equation, that is used to manipulate subjective probabilities.

The powerful practical insight that comes from bayesian statistics lies in the requirement that we start statistical calculations with an initial probability of an event. This very much matches the real-life situation in which any test or prediction depends on the patient under study. It is generally medically unwise to consider a diagnosis for a patient unless we take the patient's own characteristics into account. It is obvious to any clinician that an abnormal cardiogram suggesting myocardial ischemia would not mean the same thing in a healthy 30-year-old as it would in his obese hypertensive grandfather. In a similar argument, a negative exercise stress test does not give us great confidence that a very high-risk patient is free of cardiac disease (because the chance of disease is so high and stress tests are notorious for missing disease in some patients).

In medical situations, bayesian statistics are mostly used for the interpretation of diagnostic or predictive data. The term *bayesian* is often an indication that the patients' or population's a priori chances of disease should be considered when applying a predictive test.

When using diagnostic or predictive tests, the concepts of sensitivity and specificity are very useful because they are not dependent on the population. *Sensitivity* is, roughly, the ability of the test to detect the disease when truly present, and *specificity* indicates the ability of the test to avoid a false indication of the disease when truly absent. To use these terms we define four possible situations:

True positive (TP): The patient has disease and the test is positive.
False positive (FP): The patient does not have disease and the test is positive.
True negative (TN): The patient does not have disease and the test is negative.
False negative (FN): The patient has disease and the test is negative.

By definition,

$$\text{Sensitivity} = \text{TP}/(\text{TP}+\text{FN})$$

$$\text{Specificity} = \text{TN}/(\text{TN}+\text{FP})$$

The ideal test has a sensitivity of 1, which indicates that the test picks up all the patients with the disease, and a specificity of 1, which indicates that the test never falsely claims that a healthy patient is diseased.

It is also sometimes useful to define the following:

$$\text{Positive predictive value (PPV)} = \text{TP}/(\text{TP}+\text{FP})$$

$$\text{Negaive predictive value (NPV)} = \text{TN}/(\text{TN}+\text{FN})$$

Remember that although the sensitivity and specificity of a test do not depend on the characteristics of the population, they certainly do depend on the quality of the test. However, PPV and NPV are dependent on the tested population—this situation is where our comment about "bayesian" is relevant. (Although it is not the goal of this chapter to prove these claims, the reader may be convinced by considering what happens to sensitivity, specificity, PPV, and NPV in situations in which the test is applied to a population in whom the disease is absent so that only TN and FP are nonzero: PPV is vanishingly small and NPV approaches 1. Similarly, for a population with almost all patients having disease, PPV goes to 1 and NPV vanishes.)

The bayesian insight can now be stated that we apply diagnostic or predictive tests only to populations of subjects who are somewhat likely to test positive, but not "excessively" so. If we test subjects who are very likely to test positive, a positive test is confirmatory and a negative may be more likely to be a false-negative than a true-negative result. Similarly, if the tested population is very unlikely to have the specified disease, a negative test is only confirmatory and a positive test is more likely to be a false-positive than a true result.

Evidence-Based Medicine

Making judgments in science is an intricate process. Our decisions are formed by theoretical reasoning, extrapolation from empirical data, traditional conventions, and, often, local authorities. Most modern philosophers of science recognize that the old view of the scientific method as a totally unbiased approach to the interpretation of raw data is naive. All the data we collect in any experiment is created, selected, and interpreted within the context of our theory-based view of the world. Science is the derivation of a set of generalized laws, consistent with each other, based on empirical data and able to predict or explain further data. Often, more than one theoretical explanation can generally be given for any one set of data. The choice of a scientific explanation, similar to the choice of a statistical test, is always based on our prior understanding of the data and experimental situation.

All this being the case, it must still be stressed that modern medicine has passed from the era when "practice" and "art" were sufficient justification for medical decision making. *Evidence-based medicine* is the fashionable term for the approach to medical decision making in which careful use is made of the applicable experimental scientific data. Controlled clinical trials and large-scale observational studies are important methods for this approach. A *meta-analysis* is a report of data that combines results from multiple similar studies to create a statistically more powerful study with many more data points and a better opportunity to come to a statistically significant conclusion.

The practicing clinician has many sources that analyze empirical evidence and provide guidance for medical decisions. Governmental groups and private medical organizations have produced many guidelines and clinical practice documents that assess the quality of available evidence and make suggestions. To give further guidance, these suggestions may also be ranked by confidence. The most reliable data backed by well-established theories would give recommendations with the greatest weight. Reports that are backed by weaker data such as uncontrolled studies give recommendations with less confidence in the evidence.

Summary

Clinicians use statistical methodology both to analyze their own data and to assess the value of others' scientific reports. Because data analysis is generally the application of one of a number of commercial computer packages, each with its own menus, formatting, and subtle caveats, the most valuable suggestion to the budding statistician is to know the program, read the manual, and plot the data. The human visual system is well adapted to see groups and trends—if the conclusions do not look like they fit the data, caution and skepticism are prudent.

When assessing the value of a scientific report, a careful clinician reads the "methods" section and asks the questions suggested earlier: Are the subjects selected to minimize bias? Are the statistical methods appropriate? Is the study large enough to be statistically powerful? Are the conclusions warranted by the evidence? Can the conclusions from this study be extended to cover more general cases or do they apply only to the limited situation under study?

Finally, despite the best statistical approaches and the most careful experimental procedures, a wise clinician recognizes that even some apparently well done experiments can yield erroneous conclusions. A study that produces an important clinical conclusion, especially one that seems to change tradition or violate previous theoretical understanding, bears confirmation by another group using different patients in a different setting. Healthy skepticism is the basis of good statistics and good science.

Bibliography

Standard Statistical Computer Packages

Instat, GraphPad Software, San Diego, California.
A simple, very user-friendly program with good built-in help.

JMP, SAS Institute, Cary, North Carolina.
The SAS group's simple stand-alone program. Although relatively simple when compared with the full SAS program, its completeness leads to some complexity for the beginner.

SPSS, SPSS Inc., Chicago, Illinois.
A full featured, expensive, and very powerful program that is accessible to the nonprofessional statistics user. The help files are usable and exhaustive.

SAS, SAS Institute, Cary, North Carolina.
Expensive, very complex, very powerful. This standard package of programs is the one most commonly used by professional biomedical statisticians. Not for the amateur.

(*Note:* there are many simple and midlevel statistical programs available, all of which require careful reading of the manual to be reliable!!)

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Well organized and complete. A good course textbook.

Dawson B, Trapp RG: Basic & Clinical Biostatistics. New York, McGraw-Hill, 2004.
Suitable for self-study, fairly complete.

Feinstein A: Clinical Epidemiology. Philadelphia, WB Saunders, 1985.
Enormously insightful about the structure and problems of clinical research.

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Very clear, very popular; also has a very simple-to-use statistics program that may be purchased with the book.

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